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Halogen–deuterium exchange reaction mediated by tributyltin hydride using THF-d_8 as the deuterium source

Tomonobu Mutsumi [a,b,*], Hiroki Iwata [b], Kazuo Maruhashi [a], Yasunari Monguchi [b], Hironao Sajiki [b,*]

[a] *Chemical Technology Laboratory, Taiho Pharmaceutical Co., Ltd., 200-22 Motohara, Kamikawa-machi, Kodama-gun, Saitama 367-0241, Japan*
[b] *Laboratory of Organic Chemistry, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan*

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ABSTRACT

A regioselective deuteration method for a wide variety of aromatic compounds using the halogen–deuterium exchange reaction initiated by Bu_3SnH using THF-d_8 as the deuterium source was developed.

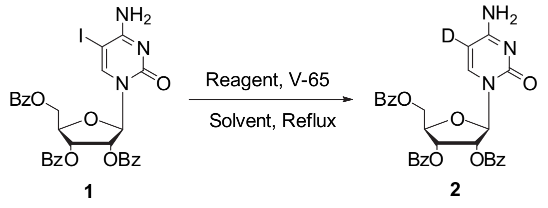
1. Introduction

Deuterium (D)-labeled compounds are widely used in many fields, such as the structural studies of biological materials, elucidation of reaction mechanisms and microanalyses of metabolites, residual agrochemicals, environmental pollutants, etc.[1] Recently, deuterated-drugs (heavy-drugs, such as deuterated venlafaxine) have also created an area of active research,[2] since C–D bonds vibrate at lower frequencies and are more stable than C–H bonds. Because of these factors, the need for the development of efficient, convenient, and selective D-labeling methods has been increasing.[3] Many D incorporation methods, such as the use of transition-metal catalysts,[4] supercritical conditions,[5] microwave irradiation,[4q–s,6] etc.,[7] are reported in the literature. One of the more useful labeling methods already reported is the radical-mediated halogen–D exchange using Bu_3SnD as the D source.[8] In this paper, we report a novel and radical method based on the Bu_3SnH-mediated halogen–D exchange reaction of aromatic nuclei using THF-d_8 as the D source.[9]

2. Results and discussion

When 2′,3′,5′-tri-*O*-benzoyl-5-iodocytidine was treated with Bu_3SnD (98 atm % D) and 2,2′-azobis(2,4-dimethylvaleronitrile) (V-65) in boiled THF, the iodine(I)–D exchange reaction at the 5-position proceeded with only 4% D efficiency (Table 1, entry 1). Low D efficiencies (<22%) were also obtained by the use of other non-deuterium-labeled solvents, such as EtOAc, acetone, MeOH, EtOH, and MeCN, while use of THF-d_8 as the solvent led to a quantitative D incorporation (entry 2). Furthermore, a nearly quantitative D efficiency was achieved using even non-labeled Bu_3SnH with THF-d_8

Table 1
Verification of the deuterium source



Entry	Reagent (equiv)	V-65 (equiv)	Solvent[a] (v/w)	Time (h)	Yield[b] (%)	D Content[c] (%)
1	Bu_3SnD (1.7)	0.3	THF (20)	4	68	4
2	Bu_3SnD (1.2)	0.2	THF-d_8 (100)	1	64	99
3	Bu_3SnH (2.4)	0.4	THF-d_8 (100)	2.5	42	96

[a] The usage (mL) of the solvent based on the weight (g) of 2′,3′,5′-tri-*O*-benzoyl-5-iodocytidine.
[b] Isolated yield.
[c] Determined by ^1H NMR.

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* Corresponding authors. Tel.: +81 495 77 2601; fax: +81 495 77 3799 (T.M.); tel./fax: +81 58 230 8109 (H.S.); e-mail addresses: t-mutsumi@taiho.co.jp (T. Mutsumi), sajiki@gifu-pu.ac.jp (H. Sajiki).

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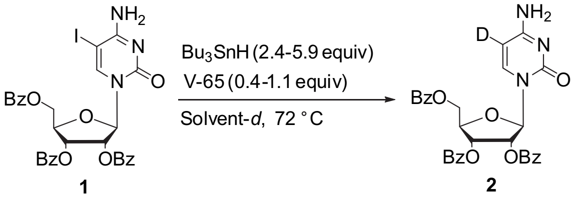
(96% D efficiency, entry 3). These results indicated that THF-d_8 can work as a D source in the present deuteration.

The I–D exchange reactions of 2′,3′,5′-tri-*O*-benzoyl-5-iodocytidine using various deuterated solvents as D sources were performed (Table 2). THF-d_8 was the most preferable D source to achieve the nearly quantitative D efficiency (entry 1). Although the use of fully deuterated methanol, CD_3OD, led to an excellent D efficiency (92%, entry 4), the D content decreased to 33% in MeOD (entry 5), indicating that the CD_3 of methanol-d_4 plays a crucial role as the D source. Furthermore, CH_3CD_2OH was a better D source (entry 7) compared to other deuterated ethanols possessing different labeling patterns, such as CD_3CH_2OH and CH_3CH_2OD (entries 6 and 8). These results indicated that deuteriums on the carbon adjacent to the oxygen atom effectively work as the D sources.

Table 2

Deuterium incorporation efficiency of various deuterated solvents



Entry	Solvent[a] (v/w)	Time (h)	Yield[b] (%)	D content[c] (%)
1	THF-d_8 (100)	5	60	96
2	THF-d_8 (40)	6	68	80
3	THF-d_8(20)	5.5	65	78
4	CD_3OD (100)	5	83	92
5	MeOD (100)	6	76	33
6	CD_3CH_2OH (100)	5	69	7
7	CH_3CD_2OH (100)	5	71	79
8	CH_3CH_2OD (100)	5	67	32
9	Acetone-d_6 (200)	7	76	71
10	Acetone-d_6 (100)	6	61	59
11	Acetone-d_6 (40)	6	60	29
12	EtOAc-d_8 (100)	9	52	59
13	CD_3CN (100)	10	quant.	22
14	EtOAc/THF-d_8, 9:1 (100)	7.5	68	49
15	MeCN/THF-d_8, 9:1 (100)	6	quant.	78
16	THF/THF-d_8, 1:1 (100)	5	70	9

[a] The usage (mL) of the solvent based on the weight (g) of 2′,3′,5′-tri-*O*-benzoyl-5-iodocytidine.

[b] Isolated yield.

[c] Determined by ^1H NMR.

The I–D exchange reaction of iodobenzene using the combination of Bu_3SnH and THF-d_8 has been reported as the only example to trace the reaction of aryl radicals with Bu_3SnH, although the actual D source was not specified.[10] To confirm the details of the D source, we further carried out the deuteration reaction of 5-iodo-1,3-dimethyluracil, and compared the peak intensities of each residual proton of THF-d_8 by ^1H NMR. The peak intensity of the 2- and 5-positions of the THF, which are adjacent to the oxygen atom, significantly increased, indicating that the deuterium atoms at the 2- and 5-positions of the THF-d_8 were preferably abstracted (Fig. 1). According to the relative bond dissociation energy values of THF C(2)–H and C(3)–H given by the semiempirical molecular orbital calculations applying the Austin Model 1 (AM1), the 2-yl radical of THF is approximately 3.87 kcal/mol stable when compared to the 3-yl radical.[11] This fact might also support our results that the D atoms at the 2- and 5-positions of THF-d_8 are more easily removed as the D sources.

We next examined the relation between the D efficiency and the substrate weight-for-volume of THF-d_8. Decreasing the ratio of THF-d_8 led to the lower D content (Table 2, entries 1–3). A similar tendency was observed in the reaction using deuterated acetone (entries 9–11).

The I–D exchange reactions in diluted THF-d_8 with MeCN or EtOAc were further investigated. The deuterium efficiency in 10% THF-d_8 in MeCN was better than that in 10% THF-d_8 in EtOAc (Table 2, entries 14 and 15) since the I–H exchange reaction in MeCN is more unfavorable than in EtOAc, similar to the I–D exchange reactions in the corresponding deuterated solvents (entries 12 and 13). Furthermore, only a 9% D content was obtained in one-to-one mixture of THF-d_8 and THF due to the more preferable introduction of the H atom of THF into the cytosine ring compared with the deuterium atom of THF-d_8 based on the deuterium isotope effect (entry 16).

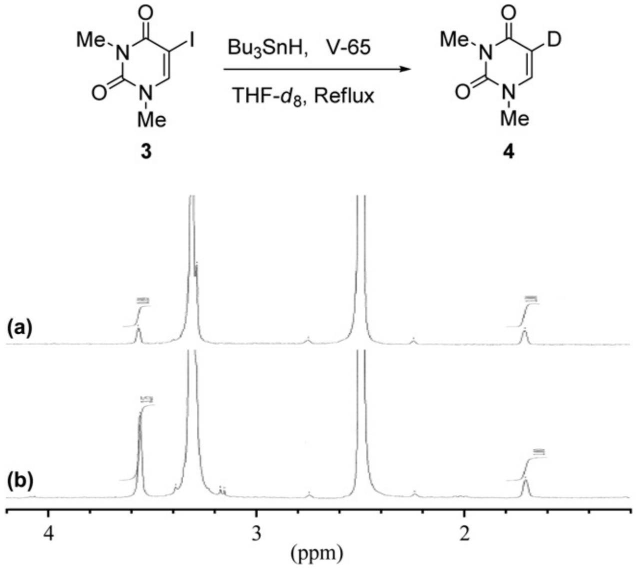
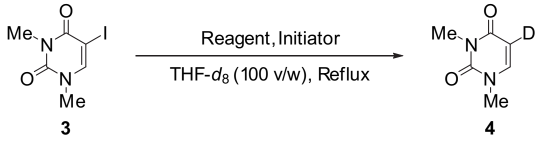


Fig. 1. ^1H NMR (DMSO-d_6) spectra of residual proton peaks in THF-d_8 before (a) and after (b) the reaction of 5-iodo-1,3-dimethyluracil using Bu_3SnH and V-65 in THF-d_8.

Next, the effects of other reagents, such as $(Bu_3Sn)_2$, Bu_3GeH, $Ph_4Si_2H_2$ (TPDS), and $(Me_3Si)_3SiH$ (TTMSS), instead of Bu_3SnH were examined. $(Bu_3Sn)_2$, Bu_3GeH, and TPDS also gave quite high deuteration ratios (Table 3, entries 2-4), while TTMSS was not very good as a reagent (65% D content). It is noteworthy that the deuteration using $(Bu_3Sn)_2$ possessing no Sn–H moiety within the molecule also smoothly proceeded with a high D content (entry 2).[12]

Table 3

D efficiency of the reaction using various reagents



Entry	Reagent (equiv)	Initiator (equiv)	Time (h)	Yield[a] (%)	D content[b] (%)
1	Bu_3SnH (1.2)	V-65 (0.2)	2	62	90
2	$(Bu_3Sn)_2$ (1.2)	Light	8.5	73	90
3	Bu_3GeH (3.6)	V-65 (0.6)	6	43	93
4	TPDS[c] (7.2)	V-65 (3.8)	37.5	54	92
5	TTMSS[d] (1.8)	V-65 (0.3)	5	74	65

[a] Isolated yield.

[b] Determined by ^1H NMR.

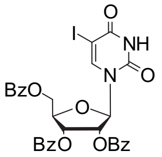
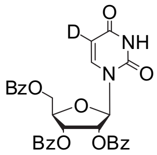
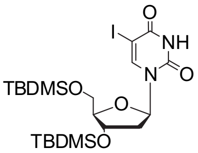
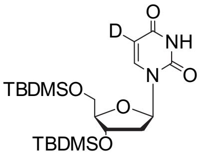
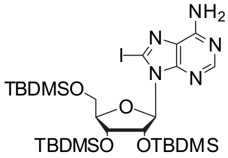
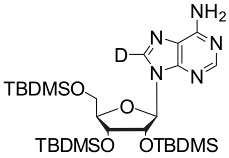
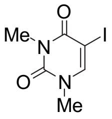
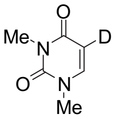
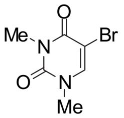
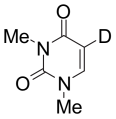
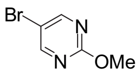
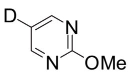
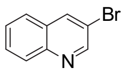
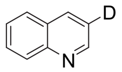
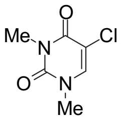
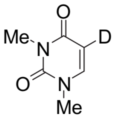
[c] $Ph_4Si_2H_2$.

[d] $(Me_3Si)_3SiH$.

The halogen–D exchange reactions of various heterocyclic halides are summarized in Table 4. The reactions of 2′,3′,5′-tri-*O*-benzoyl-5-iodouridine[13] (entry 1), 3′,5′-di-*O*-*tert*-butyldimethylsilyl-2′-deoxy-5-iodouridine (entry 2), 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-8-iodoadenosine[14] (entry 3), and 5-iodo-1,3-dimethyluracil (entry 4) also provided regioselectively deuterated products with efficient D contents (90–92%). The deuteration reaction using heterocyclic

Table 4
Deuteration of heterocyclic aromatic substrates

$$\text{Substrate} \xrightarrow[\text{THF-}d_8\text{ (100 v/w), Reflux}]{\text{Bu}_3\text{SnH, V-65}} \text{Substrate-}d$$

Entry	Substrate	Bu_3SnH (equiv)	V-65 (equiv)	Time (h)	Substrate-*d*	Yield[a] (%)	D content[b] (%)
1	 **5**	2.4	0.4	5	 **6**	67	90
2	 **7**	1.2	0.2	3	 **8**	97	92
3	 **9**	2.4	0.4	5	 **10**	91	92
4	 **3**	1.2	0.2	2	 **4**	62	90
5	 **11**	2.4	0.4	6	 **4**	55	89
6	 **12**	3.6	0.6	6	 **13**	78	92
7	 **14**	3.6	0.6	6	 **15**	95	84
8	 **16**	3.6	0.6	8	 **4**	32	10

[a] Isolated yield unless otherwise noted.

[b] Determined by ^{1}H NMR.

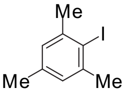
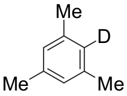
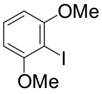
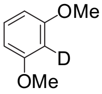
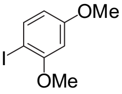
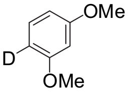
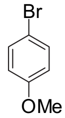
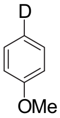
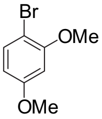
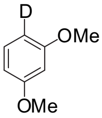
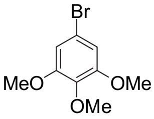
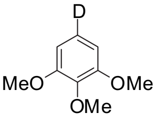
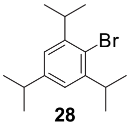
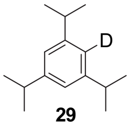
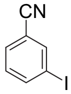
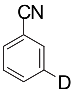
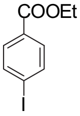
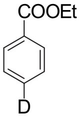
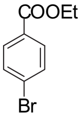
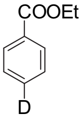
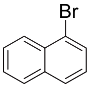
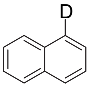
bromides, such as 5-bromo-1,3-dimethyluracil, 5-bromo-2-methoxypyrimidine, and 3-bromoquinoline, also successfully proceeded (entries 5–7). Furthermore, the present protocol was applicable to the deuteration of 5-chloro-1,3-dimethyluracil while the incorporation efficiency of D was not satisfactory (entry 8).

The deuteration of non-heterocyclic aromatic compounds was next carried out. Halogenated benzenes bearing electron-donating and -withdrawing substituents were both well-deuterated (entries 1–6 and 8–12, Table 5), although a significantly lower D efficiency (17%) was observed in the case of 1-bromo-2,4,6-triisopropylbenzene, a sterically-hindered substrate (entry 7). Furthermore, the present method was also applicable for the deuteration of fused aromatic substrates, such as naphthalene derivatives (entries 11–13, see also Table 4, entry 7).

We next explored the reaction mechanism. These included the I–D exchange reactions using 2′,3′,5′-tri-*O*-benzoyl-5-iodocytidine as a substrate under three different reaction conditions, i.e., (1) with V-65 [2,2′-azobis(2,4-dimethylvaleronitrile)] as a radical initiator, (2) without V-65, and (3) with V-65 and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl)[15] as a radical scavenger. The reaction was

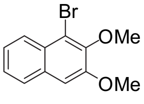
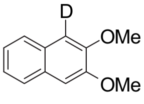
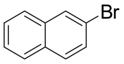
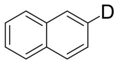
Table 5
Deuteration of non-heterocyclic aromatic substrates

$$\text{Substrate} \xrightarrow[\text{THF-}d_8\text{ (100 v/w), Reflux}]{\text{Bu}_3\text{SnH, V-65}} \text{Substrate-}d$$

Entry	Substrate	Bu_3SnH (equiv)	V-65 (equiv)	Time (h)	Substrate-*d*	Yield[a] (%)	D content[b] (%)
1	 **17**	2.4	0.4	5	 **18**	72 (93)[c]	90
2	 **19**	2.4	0.4	5	 **20**	100	85
3	 **21**	2.4	0.4	5	 **22**	100	69
4	 **23**	2.4	0.4	5	 **24**	94	61
5	 **25**	3.6	0.6	6	 **22**	77	91
6	 **26**	3.0	0.5	6	 **27**	94	71
7	 **28**	1.2	0.2	3	 **29**	98	17
8	 **30**	2.4	0.4	5	 **31**	70	54
9	 **32**	3.6	0.6	6	 **33**	78	80
10	 **34**	3.6	0.6	6	 **33**	71	78
11	 **35**	2.4	0.4	6	 **36**	68	57

(*continued on next page*)

Table 5 (*continued*)

Entry	Substrate	Bu_3SnH (equiv)	V-65 (equiv)	Time (h)	Substrate-*d*	Yield[a] (%)	D content[b] (%)
12	 **37**	4.8	0.8	12	 **38**	90	75
13	 **39**	1.2	0.2	3	 **40**	88	72

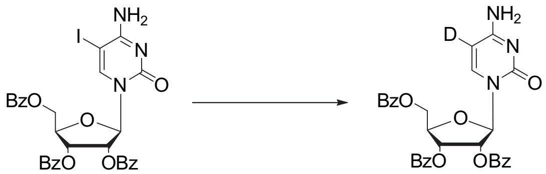
[a] Isolated yield unless otherwise noted.

[b] Determined by ^1H NMR.

[c] The yield in the parentheses was determined by ^1H NMR using CH_2Cl_2 as an internal standard.

Table 6

The effect of radical initiator (V-65) and radical scavenger (TEMPO) on the deuteration reaction of 2′,3′,5′-tri-*O*-benzoyl-5-iodocytidine


1 **2**

Entry	Bu_3SnH (equiv)	V-65 (equiv)	TEMPO (equiv)	Time (h)	Residual SM[a]	D content[b] (%)
1	2.4	0.4	0	5	No	96
2	3.6	0	0	6	No	98
3	3.6	0.6	18	8.5	Yes	—[c]

[a] The residual starting material in the reaction mixture by TLC analysis.

[b] Determined by ^1H NMR.

[c] The product was not isolated.

slightly accelerated by the addition of V-65 (Table 6, entry 1) and the starting material (**1**) disappeared faster in comparison to the reaction without V-65 (entry 2) in spite of the low use of Bu_3SnH (2.4 equiv vs 3.6 equiv). Furthermore, the addition of TEMPO significantly suppressed the reaction progress. These results suggest that the present deuteration reaction was initiated by a radical mechanism.

The proposed reaction mechanism of the halogen–D exchange reaction is postulated in Fig. 2. The tributyltin radical species formed in the initiation step removes a halogen atom (X) from the substrate, forming Bu_3SnX and an aryl radical intermediate (R•), which removes a D radical from the carbon adjacent to the oxygen atom of the deuterated solvent to afford the corresponding D-labeled product (R–D).[16]

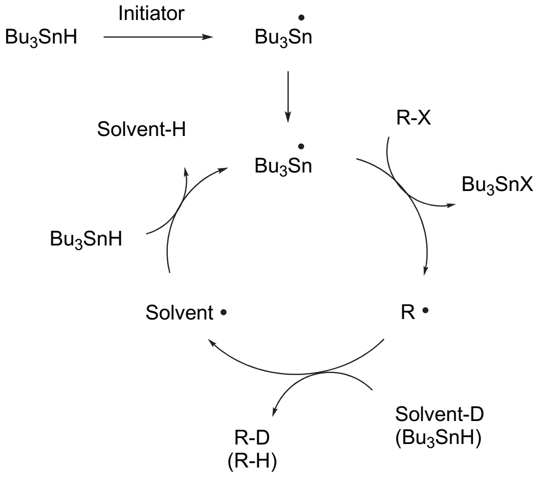


Fig. 2. The plausible reaction mechanism.

3. Conclusion

A general method for the halogen–deuterium exchange reaction on aromatic nuclei using THF-d_8 as the D source to achieve a complete regioselectivity and sufficient D efficiency was established. The present reaction efficiently proceeded in the presence of V-65 as the radical initiator. The broad substrate applicability will significantly contribute to the preparation of regioselectively-labeled compounds that play useful roles in a variety of scientific fields.

4. Experimental

4.1. General methods

Bu_3SnH, V-65, and THF-d_8 were obtained from Kanto Chemical Co., Inc., Wako Pure Chemical Industries, Ltd., and Cambridge Isotope Laboratories Inc., respectively. Flash column chromatography was accomplished using Kanto Silica Gel 60 N (sphere, neutral), and the pre-treated silica gel with KF (Nacalai Tesque, Inc.) was used for **4.8**, **4.9**, **4.11**–**4.15**, **4.19**, **4.20**, and **4.23**.[17] IR spectra were recorded by attenuated total refection (ATR) measurement with a Bruker FT-IR ALPHA spectrometer. The internal refection element (IRE) was diamond crystal. The ^1H NMR spectra were recorded on a JEOL JNM-EX270 (270 MHz) or JNM-AL400 (400 MHz). The ^2H NMR spectra were recorded on a JEOL JNM-AL400 (61 MHz) or JNM-ECA500 (77 MHz). The chemical shifts (δ) are expressed in parts per million and are internally referenced. [0.00 ppm for tetramethylsilane for DMSO-d_6 (**4.2**–**4.7**, **4.16**–**4.19**, **4.22**, **4.23**) or 2.49 ppm for DMSO-d_6 (**4.8**–**4.15**, **4.20**, **4.21**, **4.24**)]. The MS spectra were measured by a JEOL JMS-700, and the HRMS spectra were taken by a JEOL JMS-SX102A.

*4.1.1. 2′,3′,5′-Tri-O-benzoyl-5-deuterocytidine (**2**, Table 1, entry 3).* To a solution of 2′,3′,5′-tri-*O*-benzoyl-5-iodocytidine (20.0 mg, 29.4 μmol) and 2,2′-azobis(2,4-dimethylvaleronitrile) (V-65, 1.5 mg, 6.04 μmol) in THF-d_8 (2 mL) was added tri-*n*-butyltin hydride (Bu_3SnH, 9.4 μL, 34.9 μmol), and the mixture was stirred at reflux for 2.5 h. After the completion of the reaction, the reaction mixture was cooled to rt, then hexane (8 mL) was added. The precipitate was collected on filter paper and washed with hexane to give 2′,3′,5′-tri-*O*-benzoyl-5-deuterocytidine (6.8 mg, 42%). IR (ATR) cm^{-1}; 3063, 2962, 1721, 1631, 1486, 1451, 1350, 1316, 1259, 1177, 1090, 1067, 1024;

^{1}H NMR (270 MHz): 4.58–4.72 (m, 3H, 4′-H, 5′-H), 5.74 (d, J=7.3 Hz, 0.04H, 5-H), 5.89–5.98 (m, 2H, 2′-H, 3′-H), 6.07 (d, J=3.1 Hz, 1H, 1′-H), 7.35–8.02 (m, 18H, 6-H, benzoyl, and NH$_2$); ^{2}H NMR: 5.77 (br); MS (FAB$^+$): m/z 557 [M+H]$^+$; HRMS (FAB$^+$): calcd for $\mathrm{C_{30}H_{25}{}^{2}HN_3O_8}$ [M+H]$^+$: 557.17825, found: 557.17861.

*4.1.2. 5-Deutero-1,3-dimethyluracil (**4**, Table 3, entry 1).* A mixture of 1,3-dimethyl-5-iodouracil (40.0 mg, 150 μmol), Bu$_3$SnH (48.0 μL, 178 μmol), and V-65 (7.5 mg, 30.2 μmol) in THF-d_8 (4 mL) was stirred at reflux for 2 h. The reaction mixture was concentrated, then hexane (16 mL) was added to the residue. The precipitate was collected on filter paper to give 5-deutero-1,3-dimethyluracil (13.2 mg, 62%). IR (ATR) cm^{-1}; 3082, 2966, 1693, 1660, 1620, 1518, 1450, 1361, 1341, 1226, 1135, 1011; ^{1}H NMR (270 MHz): 3.15 (s, 3H, N–CH$_3$), 3.29 (s, 3H, N–CH$_3$), 5.66 (d, J=7.9 Hz, 0.10H, 5-H), 7.67 (t, 1H, 6-H); ^{2}H NMR: 5.67 (s); MS (EI$^+$): m/z 141 [M]$^+$; HRMS (EI$^+$): calcd for $\mathrm{C_6H_7{}^{2}HN_2O_2}$: 141.06486, found: 141.06518 [M]$^+$.

*4.1.3. 2′,3′,5′-Tri-O-benzoyl-5-deuterouridine (**6**, Table 4, entry 1).* A mixture of 2′,3′,5′-tri-*O*-benzoyl-5-iodouridine (40.0 mg, 58.6 μmol), Bu$_3$SnH (18.8 μL, 69.9 μmol), and V-65 (3.1 mg, 12.5 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu$_3$SnH (18.8 μL, 69.9 μmol) and V-65 (3.2 mg, 12.9 μmol) were added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane→hexane/ethyl acetate=2:1) to give 2′,3′,5′-tri-*O*-benzoyl-5-deuterouridine (22.0 mg, 67%). IR (ATR) cm^{-1}; 3063, 1722, 1688, 1621, 1601, 1452, 1360, 1352, 1265, 1178, 1121, 1095, 1070, 1025; ^{1}H NMR (270 MHz): 4.60–4.75 (m, 3H, 4′-H, 5′-H), 5.68 (d, J=8.1 Hz, 0.10H, 5-H), 5.89–5.96 (m, 2H, 2′-H, 3′-H), 6.16 (d, J=3.6 Hz, 1H, 1′-H), 7.42–8.02 (m, 16H, 6-H, benzoyl) 11.51 (s, 1H, NH); MS (FAB$^+$): m/z 558 [M+H]$^+$; HRMS (FAB$^+$): calcd for $\mathrm{C_{30}H_{24}{}^{2}HN_2O_9}$ [M+H]$^+$: 558.16225, found: 558.16294.

*4.1.4. 3′,5′-Di-O-tert-butyldimethylsilyl-2′-deoxy-5-deuterouridine (**8**, Table 4, entry 2).* A mixture of 3′,5′-di-*O*-*tert*-butyldimethylsilyl-2′-deoxy-5-iodouridine (40.2 mg, 69.0 μmol), Bu$_3$SnH (22.3 μL, 82.9 μmol), and V-65 (3.5 mg, 14.1 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane→hexane/ethyl acetate=2:1) to give 3′,5′-di-*O*-*tert*-butyldimethylsilyl-2′-deoxy-5-deuterouridine (30.5 mg, 97%). IR (ATR) cm^{-1}; 3177, 3056, 2954, 2885, 2867, 1681, 1620, 1460, 1389, 1361, 1275, 1255, 1196, 1121, 1066, 1031; ^{1}H NMR (270 MHz): 0.07 and 0.09 (each as s, 12H, SiMe), 0.88 and 0.89 (each as s, 18H, SiBu-*t*), 2.08–2.26 (m, 2H, 2′-H), 3.68–3.80 (m, 3H, 4′-H, 5′-H), 4.26–4.31 (m, 1H, 3′-H), 5.50 (d, J=8.2 Hz, 0.08H, 5-H), 6.13 (t, 1H, 1′-H), 7.70 (t, 1H, 6-H), 11.32 (s, 1H, NH); ^{2}H NMR: 5.59 (br); MS (FAB$^+$): m/z 458 [M+H]$^+$; HRMS (FAB$^+$): calcd for $\mathrm{C_{21}H_{40}{}^{2}HN_2O_5Si_2}$ [M+H]$^+$: 458.26168, found: 458.26276.

*4.1.5. 2′,3′,5′-Tri-O-tert-butyldimethylsilyl-8-deuteroadenosine (**10**, Table 4, entry 3).* A mixture of 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-8-iodoadenosine (40.1 mg, 54.5 μmol), Bu$_3$SnH (17.4 μL, 64.7 μmol), and V-65 (2.8 mg, 11.3 μmol) in THF-d_8 (4 mL) was stirred under reflux for 3 h. Bu$_3$SnH (17.4 μL, 64.7 μmol) and V-65 (2.7 mg, 10.9 μmol) were then added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane→hexane/ethyl acetate=2:1) to give 2′,3′,5′-tri-*O*-*tert*-butyldimethylsilyl-8-deuteroadenosine (30.2 mg, 91%). IR (ATR) cm^{-1}; 3318, 3165, 2964, 2930, 2896, 2868, 1646, 1557, 1462, 1406, 1361, 1321, 1284, 1264, 1158, 1128, 1074, 1044; ^{1}H NMR (270 MHz): -0.35, -0.10, 0.09, 0.12, and 0.14 (each as s, 18H, SiMe), 0.72, 0.90, and 0.93 (each as s, 27H, SiBu-*t*), 3.71–3.79 (m, 1H, 4′-H), 4.00–4.05 (m, 2H, 5′-H), 4.33 (br, 1H, 3′-H), 4.90–4.94 (m, 1H, 2′-H), 5.94 (d, J=6.3 Hz, 1H, 1′-H), 7.30 (s, 2H, NH$_2$), 8.13 (s, 1H, 2-H), 8.34 (s, 0.08H, 8-H); ^{2}H NMR: 8.26 (br); MS (FAB$^+$): m/z 611 [M+H]$^+$; HRMS (FAB$^+$): calcd for $\mathrm{C_{28}H_{55}{}^{2}HN_5O_4Si_3}$ [M+H]$^+$: 611.37030, found: 611.37079.

*4.1.6. 5-Deutero-1,3-dimethyluracil (**4**, Table 4, entry 5).* A mixture of 5-bromo-1,3-dimethyluracil (40.0 mg, 183 μmol), Bu$_3$SnH (59.0 μL, 219 μmol), and V-65 (9.2 mg, 37.0 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu$_3$SnH (59.0 μL, 219 μmol) and V-65 (9.2 mg, 37.0 μmol) were then added, and the mixture was stirred at reflux for 3 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane→hexane/ethyl acetate=1:1) and subsequent suspension with hexane (8 mL) to give 5-deutero-1,3-dimethyluracil (14.1 mg, 55%). ^{1}H NMR (270 MHz): 3.15 (s, 3H, N–CH$_3$), 3.29 (s, 3H, N–CH$_3$), 5.66 (d, J=7.7 Hz, 0.11H, 5-H), 7.67 (t, 1H, 6-H); ^{2}H NMR: 5.67 (s); MS (EI$^+$): m/z 141 [M]$^+$; HRMS (EI$^+$): calcd for $\mathrm{C_6H_7{}^{2}HN_2O_2}$: 141.06486, found: 141.06518 [M]$^+$.

*4.1.7. 5-Deutero-2-methoxypyrimidine (**13**, Table 4, entry 6).* A mixture of 5-bromo-2-methoxypyrimidine (60.1 mg, 318 μmol), Bu$_3$SnH (103 μL, 382 μmol), and V-65 (15.9 mg, 63.2 μmol) in THF-d_8 (6 mL) was stirred at reflux for 3 h. Bu$_3$SnH (103 μL, 382 μmol) and V-65 (15.9 mg, 63.2 μmol) were added, and the mixture was stirred at reflux for 2 h. More Bu$_3$SnH (103 μL, 382 μmol) and V-65 (15.9 mg, 63.2 μmol) were added, and the mixture was stirred at reflux for 1 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=10:1) to give 5-deutero-2-methoxypyrimidine (27.7 mg, 78%). ^{1}H NMR (400 MHz): 3.89 (s, 3H, *O*–CH$_3$), 7.13 (t, J=5.0 Hz, 0.08H, 5-H), 8.60 (s, 2H, 4-H, 6-H); ^{2}H NMR: 7.16 (br); MS (FAB$^+$): m/z 112 [M+H]$^+$; HRMS (FAB$^+$): calcd for $\mathrm{C_5H_6{}^{2}HN_2O}$ [M+H]$^+$: 112.06212, found: 112.06303.

*4.1.8. 3-Deuteroquinoline (**15**, Table 4, entry 7).* A mixture of 3-bromoquinoline (60.1 mg, 289 μmol), Bu$_3$SnH (93.3 μL, 347 μmol) and V-65 (14.4 mg, 58.0 μmol) in THF-d_8 (6 mL) was stirred at reflux for 3 h. Bu$_3$SnH (93.3 μL, 347 μmol) and V-65 (14.4 mg, 58.0 μmol) were added, and the mixture was stirred at reflux for 2 h. More Bu$_3$SnH (93.3 μL, 347 μmol) and V-65 (14.4 mg, 58.0 μmol) were added, and the mixture was stirred at reflux for 1 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=5:1) to give 3-deuteroquinoline (35.6 mg, 95%). ^{1}H NMR (400 MHz): 7.52–7.55 (m, 0.16H, 3-H), 7.61 (t, J=7.4 Hz, 1H, 6-H), 7.76 (t, J=7.0 Hz, 1H, 7-H), 7.97–8.03 (m, 2H, 5-H, 8-H), 8.34 (s, 1H, 4-H), 8.91 (s, 1H, 2-H); ^{2}H NMR: 7.56 (br); MS (FAB$^+$): m/z 131 [M+H]$^+$; HRMS (FAB$^+$): calcd for $\mathrm{C_9H_7{}^{2}HN}$ [M+H]$^+$: 131.07195, found: 131.07154.

*4.1.9. 5-Deutero-1,3-dimethyluracil (**4**, Table 4, entry 8).* A mixture of 5-chloro-1,3-dimethyluracil (40.1 mg, 230 μmol), Bu$_3$SnH (74.0 μL, 275 μmol), and V-65 (11.4 mg, 45.9 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu$_3$SnH (74.0 μL, 275 μmol) and V-65 (11.4 mg, 45.9 μmol) were added, and the mixture was stirred at reflux for 3 h. More Bu$_3$SnH (74.0 μL, 275 μmol) and V-65 (11.4 mg, 45.9 μmol) were added and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane→hexane/ethyl acetate=2:1) to give 5-deutero-1,3-dimethyluracil (10.4 mg, 32%). ^{1}H NMR (270 MHz): 3.15 (s, 3H, N–CH$_3$), 3.29 (s, 3H, N–CH$_3$), 5.66 (d, J=7.7 Hz, 0.90H, 5-H), 7.67 (d, J=7.8 Hz, 1H, 6-H); ^{2}H NMR: 5.67 (s); MS (EI$^+$): m/z 141 [M]$^+$; HRMS (EI$^+$): calcd for $\mathrm{C_6H_7{}^{2}HN_2O_2}$: 141.06486, found: 141.06518 [M]$^+$.

*4.1.10. 2-Deutero-1,3,5-trimethylbenzene (**18**, Table 5, entry 1).* A mixture of 2-iodo-1,3,5-trimethylbenzene (40.1 mg, 163 μmol), Bu$_3$SnH (52.6 μL, 196 μmol), and V-65 (8.1 mg, 32.6 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu$_3$SnH (52.6 μL, 196 μmol) and V-65 (8.2 mg, 33.0 μmol) were added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo. The ^{1}H NMR of the residue in DMSO-d_6 was measured in the presence of CH_2Cl_2 (5.22 μL, 81.5 μmol) as an internal standard. The ^{1}H NMR sample was diluted with CH_2Cl_2 (10 mL) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane) to give 2-deutero-1,3,5-trimethylbenzene (14.2 mg, 72%). ^{1}H NMR (400 MHz): 2.20 (s, 9H, CH_3), 6.76 (s, 2.10H, 2-H, 4-H, 6-H); ^{2}H NMR: 6.78 (br); MS (EI$^+$): *m*/*z* 121 [M]$^+$; HRMS (EI$^+$): calcd for $C_9H_{11}^2H$ [M]$^+$: 121.10018, found: 121.09992.

*4.1.11. 2-Deutero-1,3-dimethoxybenzene (**20**, Table 5, entry 2).* A mixture of 2,6-dimethoxyiodobenzene (40.1 mg, 151 μmol), Bu_3SnH (48.7 μL, 181 μmol), and V-65 (7.5 mg, 30.2 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu_3SnH (48.7 μL, 181 μmol) and V-65 (7.5 mg, 30.2 μmol) were added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (pentane/Et_2O=40:1) to give 2-deutero-1,3-dimethoxybenzene (21.1 mg, 100%). ^{1}H NMR (400 MHz): 3.72 (s, 6H, *O*—CH_3), 6.46–6.51 (m, 2.15H, 2-H, 4-H, 6-H), 7.17 (t, *J*=8.1 Hz, 1H, 5-H); ^{2}H NMR: 6.50 (br); MS(EI$^+$): *m*/*z* 139 [M]$^+$; HRMS (EI$^+$): calcd for $C_8H_9{}^2HO_2$ [M]$^+$: 139.07436, found: 139.07515.

*4.1.12. 4-Deutero-1,3-dimethoxybenzene (**22**, Table 5, entry 3).* A mixture of 2,4-dimethoxyiodobenzene (40.0 mg, 152 μmol), Bu_3SnH (48.7 μL, 181 μmol), and V-65 (7.5 mg, 30.2 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu_3SnH (48.7 μL, 181 μmol) and V-65 (7.5 mg, 30.2 μmol) were added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (pentane/Et_2O=40:1) to give 4-deutero-1,3-dimethoxybenzene (21.1 mg, 100%). ^{1}H NMR (400 MHz): 3.72 (s, 6H, *O*—CH_3), 6.47–6.51 (m, 2.31H, 2-H, 4-H, 6-H), 7.17 (m, 1H, 5-H); ^{2}H NMR: 6.52 (br); MS (EI$^+$): *m*/*z* 139 [M]$^+$; HRMS (EI$^+$): calcd for $C_8H_9{}^2HO_2$ [M]$^+$: 139.07436, found: 139.07451.

*4.1.13. 4-Deuteromethoxybenzene (**24**, Table 5, entry 4).* A mixture of 1-bromo-4-methoxybenzene (40.0 mg, 214 μmol), Bu_3SnH (69.1 μL, 257 μmol), and V-65 (10.6 mg, 42.7 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu_3SnH (69.1 μL, 257 μmol) and V-65 (10.6 mg, 42.7 μmol) were added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (pentane) to give 4-deuteromethoxybenzene (22.2 mg, 94%). ^{1}H NMR (400 MHz): 3.73 (s, 3H, *O*—CH_3), 6.91–6.93 (m, 2.39H, 2-H, 4-H, 6-H), 7.26–7.30 (m, 2H, 3-H, 5-H); ^{2}H NMR: 6.94 (br); MS (EI$^+$): *m*/*z* 109 [M]$^+$; HRMS (EI$^+$): calcd for $C_7H_7{}^2HO$ [M]$^+$: 109.06380, found: 109.06445.

*4.1.14. 4-Deutero-1,3-dimethoxybenzene (**22**, Table 5, entry 5).* A mixture of 1-bromo-2,4-dimethoxybenzene (80.1 mg, 369 μmol), Bu_3SnH (119 μL, 442 μmol), and V-65 (18.3 mg, 73.7 μmol) in THF-d_8 (8 mL) was stirred at reflux for 3 h. Bu_3SnH (119 μL, 442 μmol) and V-65 (18.3 mg, 73.7 μmol) were added, and the mixture was stirred at reflux for 2 h. Further Bu_3SnH (119 μL, 442 μmol) and V-65 (918 mg, 73.7 μmol) were added, and the mixture was stirred at reflux for 1 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography twice on silica gel (hexane/ethyl acetate=10:1 and hexane/ethyl acetate=20:1) to give 4-deutero-1,3-dimethoxybenzene (39.4 mg, 77%). ^{1}H NMR (400 MHz): 3.73 (s, 6H, *O*—CH_3), 6.47–6.53 (m, 2.09H, 2-H, 4-H, 6-H), 7.15–7.21 (m, 1H, 5-H); ^{2}H NMR: 6.53 (br); MS (EI$^+$): *m*/*z* 139 [M]$^+$; HRMS (EI$^+$): calcd for $C_8H_9{}^2HO_2$ [M]$^+$: 139.07436, found: 139.07469.

*4.1.15. 5-Deutero-1,2,3-trimethoxybenzene (**27**, Table 5, entry 6).* A mixture of 1-bromo-3,4,5-trimethoxybenzene (80.0 mg, 324 μmol), Bu_3SnH (105 μL, 390 μmol), and V-65 (16.1 mg, 64.8 μmol) in THF-d_8 (8 mL) was stirred at reflux for 3 h. Bu_3SnH (105 μL, 390 μmol) and V-65 (16.2 mg, 65.2 μmol) were added, and the reaction mixture was stirred at reflux for 2 h. More Bu_3SnH (52.3 μL, 194 μmol) and V-65 (8.1 mg, 32.6 μmol) were added, and the mixture was stirred at reflux for 1 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=4:1) to give 5-deutero-1,2,3-trimethoxybenzene (51.3 mg, 94%). IR (ATR) cm^{-1}; 2997, 2937, 2834, 1590, 1493, 1478, 1457, 1418, 1292, 1240, 1174, 1126, 1112, 1034, 1008; ^{1}H NMR (270 MHz): 3.65 (s, 3H, *O*—CH_3), 3.76 (s, 6H, *O*—CH_3), 6.65 (t, 2H, 4-H, 6-H), 6.99 (t, *J*=8.3 Hz, 0.29H, 5-H); ^{2}H NMR: 7.00 (br); MS (EI$^+$): *m*/*z* 169 [M]$^+$; HRMS (EI$^+$): calcd for $C_9H_{11}{}^2HO_3$ [M]$^+$: 169.08493, found: 169.08578.

*4.1.16. 2-Deutero-1,3,5-triisopropylbenzene (**29**, Table 5, entry 7).* A mixture of 2-bromo-1,3,5-triisopropylbenzene (60.1 mg, 212 μmol), Bu_3SnH (68.3 μL, 254 μmol), and V-65 (10.5 mg, 42.3 μmol) in THF-d_8 (6 mL) was stirred at reflux for 3 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane) to give 2-deutero-1,3,5-triisopropylbenzene (42.9 mg, 98%). ^{1}H NMR (270 MHz): 1.17 and 1.20 (each as s, 18H, CH_3), 2.77–2.88 (m, 3H, CH), 6.89 (s, 2.83H, 2-H, 4-H, 6-H).

*4.1.17. 1-Cyano-3-deuterobenzene (**31**, Table 5, entry 8).* A mixture of 1-cyano-3-iodobenzene (40.1 mg, 175 μmol), Bu_3SnH (56.5 μL, 210 μmol), and V-65 (8.7 mg, 35.0 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. Bu_3SnH (56.5 μL, 210 μmol) and V-65 (8.8 mg, 35.4 μmol) were added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane→hexane/ethyl acetate=20:1) to give 1-cyano-3-deuterobenzene (12.8 mg, 70%). IR (ATR) cm^{-1}; 3438, 2998, 2914, 1662, 1436, 1407, 1311, 1018; ^{1}H NMR (270 MHz,): 7.56–7.62 (m, 1.46H, 3-H, 5-H), 7.70–7.77 (m, 1H, 4-H), 7.83–7.86 (m, 2H, 2-H, 6-H); ^{2}H NMR: 7.61 (br); MS (EI$^+$): *m*/*z* 104 [M]$^+$; HRMS (EI$^+$): calcd for $C_7H_4{}^2HN$ [M]$^+$: 104.04847, found: 104.04930.

*4.1.18. Ethyl 4-deuterobenzoate (**33**, Table 5, entry 9).* A mixture of ethyl 4-iodobenzoate (60.2 mg, 218 μmol), Bu_3SnH (70.0 μL, 260 μmol), and V-65 (10.8 mg, 43.5 μmol) in THF-d_8 (6 mL) was stirred at reflux for 3 h. Bu_3SnH (70.0 μL, 260 μmol) and V-65 (10.8 mg, 43.5 μmol) were added, and the mixture was stirred at reflux for 2 h. More Bu_3SnH (70.0 μL, 260 μmol) and V-65 (10.8 mg, 43.5 μmol) were added, and the mixture was stirred at reflux for 1 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=20:1) to give ethyl 4-deuterobenzoate (25.7 mg, 78%). IR (ATR) cm^{-1}; 3088, 3066, 3032, 2982, 2950, 2926, 2868, 2850, 1716, 1559, 1450, 1408, 1391, 1367, 1311, 1271, 1174, 1105, 1071, 1026; ^{1}H NMR (400 MHz): 1.33 (t, *J*=7.1 Hz, 3H, CH_3), 4.28–4.36 (dd, *J*=7.1 Hz, 2H, CH_2), 7.50–7.56 (m, 2H, 3-H, 5-H), 7.66 (t, *J*=7.3 Hz, 0.20H, 4-H), 7.97 (d, *J*=7.9 Hz, 2H, 2-H, 6-H); ^{2}H NMR: 7.66 (br); MS (EI$^+$): *m*/*z* 151 [M]$^+$; HRMS (EI$^+$): calcd for $C_9H_9{}^2HO_2$ [M]$^+$: 151.07436, found: 151.07510.

*4.1.19. Ethyl 4-deuterobenzoate (**33**, Table 5, entry 10).* A mixture of ethyl 4-bromobenzoate (60.1 mg, 262 μmol), Bu_3SnH (84.6 μL, 314 μmol), and V-65 (13.0 mg, 52.3 μmol) in THF-d_8 (6 mL) was stirred at reflux for 3 h. Bu_3SnH (84.6 μL, 314 μmol) and V-65 (13.0 mg, 52.3 μmol) were added, and the mixture was stirred at reflux for 2 h. More Bu_3SnH (84.6 μL, 314 μmol) and V-65 (13.0 mg, 52.3 μmol) were added, and the mixture was stirred at reflux for 1 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=20:1) to give ethyl 4-deuterobenzoate (28.3 mg, 71%). ^{1}H NMR (400 MHz): 1.32 (t, *J*=6.8 Hz, 3H, CH_3), 4.28–4.36 (dd,

J=7.1 Hz, 2H, CH_2), 7.50–7.56 (m, 2H, 3-H, 5-H), 7.66 (t, J=7.3 Hz, 0.22H, 4-H), 7.97 (d, J=7.9 Hz, 2H, 2-H, 6-H); ^2H NMR: 7.67 (br); MS (EI$^+$): m/z 151 [M]$^+$; HRMS (EI$^+$): calcd for $C_9H_9{}^2HO_2$ [M]$^+$: 151.07436, found: 151.07344.

*4.1.20. 1-Deuteronaphthalene (**36**, Table 5, entry 11).* A mixture of 1-bromonaphthalene (60.0 mg, 290 μmol), Bu_3SnH (93.6 μL, 348 μmol), and V-65 (14.4 mg, 58.0 μmol) in THF-d_8 (6 mL) was stirred at reflux for 3 h. Bu_3SnH (93.6 μL, 348 μmol) and V-65 (14.4 mg, 58.0 μmol) were added, and the mixture was stirred at reflux for 2 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (hexane) to give 1-deuteronaphthalene (25.6 mg, 68%). IR (ATR) cm^{-1}; 3054, 1593, 1504, 1381, 1346, 1265, 1214, 1127, 1011; ^1H NMR (270 MHz,): 7.49–7.55 (m, 4H, 2-H, 3-H, 6-H, 7-H), 7.89–7.95 (m, 3.43H, 1-H, 4-H, 5-H, 8-H); ^2H NMR: 7.93 (br); MS (EI$^+$): m/z 129 [M]$^+$; HRMS (EI$^+$): calcd for $C_{10}H_7^2H$ [M]$^+$: 129.06888, found: 129.06915.

*4.1.21. 1-Deutero-2,3-dimethoxynaphthalene (**38**, Table 5, entry 12).* A mixture of 1-bromo-2,3-dimethoxynaphthalene (60.1 mg, 225 μmol), Bu_3SnH (72.6 μL, 270 μmol), and V-65 (11.2 mg, 45.1 μmol) in THF-d_8 (6 mL) was stirred at reflux for 3 h. Bu_3SnH (72.6 μL, 270 μmol) and V-65 (11.2 mg, 45.1 μmol) were added three times every 3 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel twice (hexane → hexane/ethyl acetate=20:1 → hexane/ethyl acetate=4:1, and hexane/ethyl acetate=4:1) to give 1-deutero-2,3-dimethoxynaphthalene (38.3 mg, 90%). IR (ATR) cm^{-1}; 3057, 3015, 2999, 2970, 2937, 2833, 1619, 1598, 1503, 1486, 1465, 1431, 1326, 1260, 1219, 1197, 1165, 1114, 1052, 1003; ^1H NMR (270 MHz): 3.88 (s, 6H, O–CH_3), 7.29–7.34 (m, 3.25H, 1-H, 4-H, 6-H, 7-H), 7.72–7.77 (m, 2H, 5-H, 8-H); ^2H NMR: 7.32 (br); MS (EI$^+$): m/z 189 [M]$^+$; HRMS (EI$^+$): calcd for $C_{12}H_{11}{}^2HO_2$ [M]$^+$: 189.09001, found: 189.09094.

*4.1.22. 2-Deuteronaphthalene (**40**, Table 5, entry 13).* A mixture of 2-bromonaphthalene (40.0 mg, 193 μmol), Bu_3SnH (62.4 μL, 232 μmol), and V-65 (9.6 mg, 38.7 μmol) in THF-d_8 (4 mL) was stirred at reflux for 3 h. The mixture was concentrated in vacuo, and the residue was purified by column chromatography on silica gel (pentane) to give 2-deuteronaphthalene (22.1 mg, 88%). ^1H NMR (400 MHz,): 7.49–7.52 (m, 3.28H, 2-H, 3-H, 6-H, 7-H), 7.89–7.91 (m, 4H, 1-H, 4-H, 5-H, 8-H); ^2H NMR: 7.53 (br); MS (EI$^+$): m/z 129 [M]$^+$; HRMS (EI$^+$): calcd for $C_{10}H_7^2H$ [M]$^+$: 129.06888, found: 129.06937.

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