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Palladium-Catalyzed Synthesis of Deuterated Alkenes through Deuterodechlorination of Alkenyl Chlorides

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Supporting Information

ABSTRACT: The palladium-catalyzed deuterodechlorination of alkenyl chlorides has been developed, and a variety of deuterated alkenes were synthesized with precise control of the deuterium incorporation. This catalytic process tolerates heterocyclic moieties and frameworks derived from bioactive agents. In addition to the double incorporation of deuterium, the gram-scale synthesis of a deuterated iminostilbene unit including a core substructure of carbamazepine was achieved in a high yield with an excellent degree of deuteration.

KEYWORDS: *deuteration, alkene, palladium, N-heterocyclic carbene*

INTRODUCTION

Deuterated molecules have been known to be highly useful because of their wide application, such as metabolic analyses of bioactive agents as well as mechanistic investigations of a variety of reactions.[1] In addition, site-specific incorporation of deuterium into pharmaceutical compounds has been of growing significance in drug development because of its beneficial effects to improve their therapeutic profiles through isotope-effect-based optimization of the metabolic stability and toxicity of drugs.[2] For example, deutetrabenazine was approved by the U.S. Food and Drug Administration in 2017 as a treatment agent for chorea associated with Huntington's disease.[3] Since alkenes are among the most fundamental and ubiquitous substructures in pharmaceutical and bioactive molecules,[4] catalytic synthetic processes for deuterated alkenes as building blocks are quite important. The Pd-catalyzed semideuterogenation of alkynes and metal-catalyzed H/D exchange for alkenes have been investigated as representative catalytic methods for the synthesis of deuterated alkenes, in which multiple introduction of deuterium basically proceeds depending on the respective reactivities of reactive sites in the presence of excess amounts of deuterium sources, such as deuterium gas, deuterated organic solvents, and deuterium oxide.[5,6] Although these processes make it possible to obtain multideuterated alkenes with high efficiency, achievement of precise site selectivity and high deuterium incorporation remains challenging despite its necessity and importance in production processes for pharmaceutical compounds. On the other hand, deuterodehalogenation is also a powerful transformation,[7] but this type of method for the catalytic preparation of deuterated alkenes is quite rare. While a few examples of Br/D exchange for alkenyl bromides were reported as catalytic processes with a radical initiator or transition metal,[8] no catalytic Cl/D exchange for alkenyl chlorides has been found in spite of the advantageous features of organochlorides, such as lower cost and higher stability.[9] Herein we report the palladium-catalyzed deuterodechlorination of alkenyl chlorides using an unsymmetrical N-heterocyclic carbene (NHC) ligand.

RESULTS AND DISCUSSION

At the beginning, unsymmetrical NHC ligands were examined in the palladium-catalyzed deuterodechlorination of alkenyl chloride **1a** with α-deuteriobenzhydrol as a stable, easy to handle solid deuterium source (Table 1). We recently found that this type of unsymmetrical NHC ligand precursor (Figure 1) was effective in transition-metal-catalyzed deuterodefunctionalization processes.[10] NHC ligand precursor **L2** was more suitable than imidazolium chloride **L1**, and methyl groups at the 4- and 5-positions proved to be important for catalytic efficiency (entries 1 and 2).[11] The bulkier aryl group in NHC precursor **L3** delivered a better yield with a high degree of deuteration (entry 3). On the other hand, the 2,4,6-triisopropylbenzyl unit in imidazolium chloride **L4** did not lead to further improvement (entry 4). A ligand precursor bearing benzhydryl moieties gave superior results, especially at 100 °C (92% yield and >99% D; entry 5). In the examination of metal complexes, neither a zero-valent palladium complex nor nickel complexes showed sufficient catalytic activity (entries 5−8). Subsequently, a series of bases were screened, and another option was found (entries 5 and 9−13). While tribasic potassium phosphate and cesium fluoride as well as inorganic carbonates except for cesium carbonate were less effective (entries 5, 9, 10, 12, and 13), the catalytic deuterodechlorination of **1a** proceeded efficiently with an excellent degree of deuteration in the presence of potassium *tert*-butoxide (entry 11). The influence of the solvent was also investigated (entries 5 and 14−17). The use of less polar

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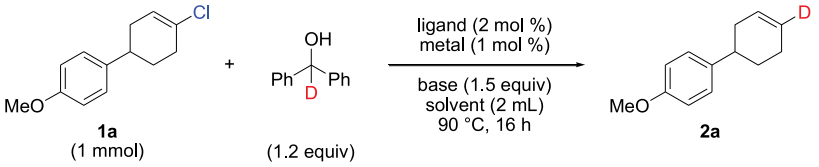
Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	metal	base	solvent	yield (%)	D content (% D)
1	**L1**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	toluene	12	>99
2	**L2**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	toluene	60	93
3	**L3**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	toluene	81	>99
4	**L4**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	toluene	80	>99
5	**L5**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	toluene	89 (92[b])	>99 (>99[b])
6	**L5**	$Pd_2(dba)_3$	Cs_2CO_3	toluene	3	>99
7	**L5**	$Ni(1\text{-naph})Cl(PPh_3)_2$	Cs_2CO_3	toluene	trace	ND
8	**L5**	$Ni(COD)_2$	Cs_2CO_3	toluene	trace	ND
9	**L5**	$[Pd(allyl)Cl]_2$	K_2CO_3	toluene	22	>99
10	**L5**	$[Pd(allyl)Cl]_2$	Na_2CO_3	toluene	0	ND
11	**L5**	$[Pd(allyl)Cl]_2$	KO*t*-Bu	toluene	87 (96[b])	>99 (>99[b])
12	**L5**	$[Pd(allyl)Cl]_2$	K_3PO_4	toluene	28	>99
13	**L5**	$[Pd(allyl)Cl]_2$	CsF	toluene	45	>99
14	**L5**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	dioxane	77	>99
15	**L5**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	DMA	64	>99
16	**L5**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	DMF	20	>99
17	**L5**	$[Pd(allyl)Cl]_2$	Cs_2CO_3	DMSO	0	ND

[a]Reaction conditions: **1a** (1 mmol), Ph_2CDOH (1.2 mmol), ligand (2 mol %), metal (1 mol %), base (1.5 mmol), solvent (2 mL), 90 °C, 16 h. [b]100 °C.

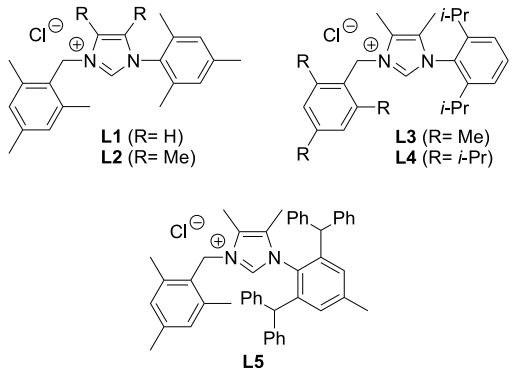


Figure 1. Unsymmetrical NHC ligand precursors

solvents had a tendency to lead to higher yields, and toluene proved to be suitable in this catalytic deuteration.

An investigation of a variety of alkenyl chlorides in the palladium-catalyzed deuterodechlorination process was conducted (Scheme 1). As well as a cycloalkenyl chloride with a simple aryl moiety (**1b**),[12] substrates bearing pyridyl and thienyl groups with high coordinating ability to metal centers were tolerated, giving the desired products in high yields with excellent degrees of deuteration (**2c** and **2d**). In the presence of a cyclic amine unit as an important substructure in bioactive compounds, deuterium incorporation was also achieved with high efficiency (**2e**). In addition to a simple acyclic alkenyl chloride bearing a naphthyl group (**1f**), a substrate with steric hindrance close to a reactive site proved to be a suitable reaction partner (**2g**). Neither an electron-donating group nor an electron-withdrawing group led to a significant decrease in yield and degree of deuteration (**2h** and **2i**). The catalytic preparation of a terminally deuterated alkene was also accomplished with this deuteration method (**2j**). The double incorporation of deuterium with a chromane-derived substrate proceeded smoothly with sufficient efficiency (**2k**). Additionally, an iminostilbene-based compound and an estrone derivative were examined, leading to high yields of the desired deuterated products (**2l** and **2m**). In most cases, excellent degrees of deuteration were observed with high selectivity. Moreover, this palladium-catalyzed deuterodechlorination was applied to cycloalkenyl chloride **1l** on a gram scale, and a deuterated iminostilbene unit constituting the core framework of carbamazepine was obtained in 82% yield with >99% D (Scheme 2).

To examine the possibility of single electron transfer processes, the palladium-catalyzed incorporation of deuterium was conducted with radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 9,10-dihydroanthracene (DHA) (Scheme 3). This catalytic deuteration reaction proceeded smoothly even in the presence of these radical trapping reagents, suggesting that single electron transfer processes might not be included.

On the basis of all of these results, a tentative reaction mechanism for the palladium-catalyzed deuterodechlorination of alkenyl chlorides is shown in Scheme 4. After oxidative addition of the alkenyl chloride to the Pd(0) complex, the alkenylpalladium chloride intermediate is converted to an α-deuterioalkoxypalladium species by displacement of the chloride anion. Then β-deuterium elimination proceeds with the formation of benzophenone to give the alkenylpalladium deuteride complex. Finally, the deuterated alkene is formed as the desired product through reductive elimination, leading to regeneration of the Pd(0) catalyst.

CONCLUSION

Precisely deuterated alkenes were successfully synthesized through the palladium-catalyzed deuterodechlorination reac-

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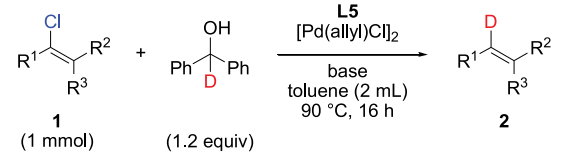
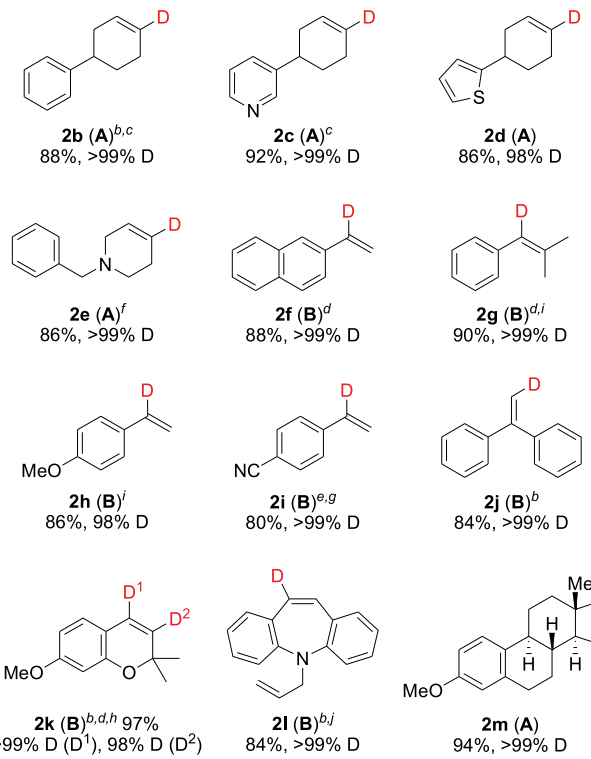
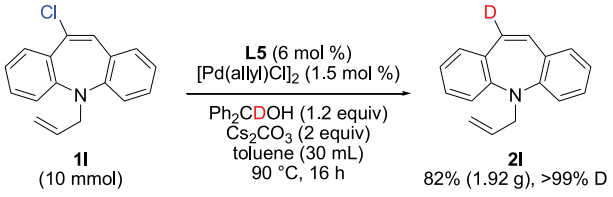
Scheme 1. Substrate Scope[a]



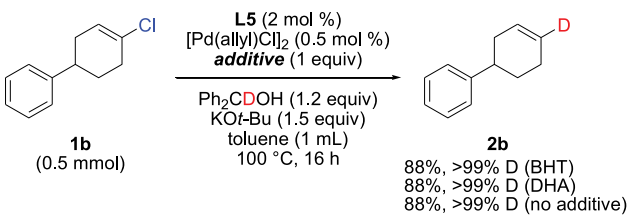


[a]Conditions A: **L5** (2 mol %), Pd (1 mol %), KO*t*-Bu (1.5 equiv). Conditions B: **L5** (6 mol %), Pd (3 mol %), Cs_2CO_3 (2 equiv). [b]0.5 mmol scale. [c]100 °C. [d]80 °C. [e]70 °C. [f]KO*t*-Bu (2 equiv). [g]Cs_2CO_3 (2.5 equiv). [h]Ph_2CDOH (2.4 equiv), KO*t*-Bu (2.25 equiv). [i]GC yield. [j]0.33 M.

Scheme 2. Gram-Scale Deuterodechlorination of 1l

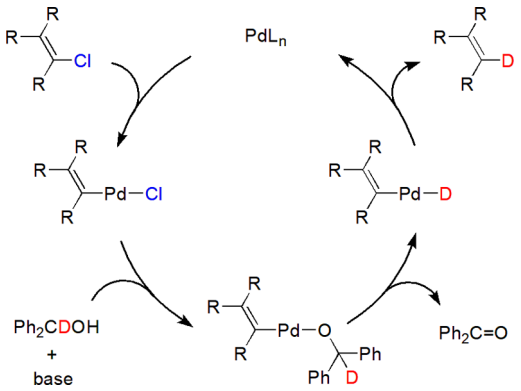


Scheme 3. Catalytic Deuterodechlorination in the Presence of Additives



tion of alkenyl chlorides. The adequate catalytic activity of the palladium/unsymmetrical NHC system led to the production of deuterated alkenes with excellent degrees of deuteration in high yields. In this process, a variety of substrates such as heterocycles were tolerated, as well as iminostilbene and estrone derivatives. In addition, the gram-scale synthesis of a deuterated iminostilbene unit constituting the core framework of carbamazepine was achieved with sufficient efficiency. We believe that this palladium-catalyzed deuterium incorporation method will contribute to the progress of catalytic production processes for pharmaceutical compounds.

Scheme 4. Plausible Reaction Mechanism



EXPERIMENTAL SECTION

General. All melting points are uncorrected. IR spectra are expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were taken at 500 and 100 MHz, respectively. Chemical shift values are expressed in parts per million relative to internal or external tetramethylsilane. Abbreviations for multiplicities are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectrometry (MS) and high-resolution mass spectrometry (HRMS) were performed using electron ionization (EI). The products were isolated by silica gel column chromatography. Degrees of deuteration were determined by ^1H NMR (500 MHz) analyses. All of the reactions were performed under an argon atmosphere unless otherwise specified. Toluene was distilled from sodium benzophenone ketyl under an argon atmosphere. Alkenyl chlorides **1a**, **1c–i**, and **1k–m** were synthesized as new chemical compounds. On the other hand, **1b**,[13] **1j**,[14] *α*-deuteriobenzhydrol,[10a] and the unsymmetrical NHC precursors[10a] were prepared as previously reported.

Typical Procedure for the Palladium-Catalyzed Deuterodechlorination of Alkenyl Chlorides. Under an argon atmosphere, a reaction tube was charged with ligand precursor **L5** (13.7 mg, 0.02 mmol), $[Pd(allyl)Cl]_2$ (1.83 mg, 0.005 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol). After toluene (2.0 mL) was added, the mixture was stirred for 15 min at 80 °C and cooled to room temperature. Then alkenyl chloride **1a** (223 mg, 1.0 mmol) and *α*-deuteriobenzhydrol (222 mg, 1.2 mmol) were added. The reaction mixture was stirred for 16 h at 100 °C and cooled to room temperature. Water was added, and then the resulting mixture was extracted with AcOEt. The combined organic layers were dried over Na_2SO_4. Concentration and purification through silica gel column chromatography gave the desired product **2a**.

1-(4-Deuteriocyclohex-3-enyl)-4-methoxybenzene (2a). Silica gel column chromatography (hexane/EtOAc = 100/1) gave 174 mg of the product (0.92 mmol, 92% yield) as a colorless oil with >99% D (the D content was judged by comparison of the peak at 5.76–5.77 ppm (a deuterated site)

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with the peak at 6.84−6.87 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.67−1.76 (m, 1H), 1.88−1.93 (m, 1H), 2.08−2.29 (m, 4H), 2.73−2.79 (m, 1H), 3.79 (s, 3H), 5.76−5.77 (m, 1H), 6.84−6.87 (m, 2H), 7.14−7.17 (m, 2H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.77 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7 (CH_2), 29.9 (CH_2), 33.5 (CH_2), 39.2 (CH), 55.2 (CH_3), 113.7 (CH), 126.66 (t, J_{C-D} = 23.2 Hz, C), 126.72 (CH), 127.7 (CH), 139.6 (C), 157.9 (C). IR (ATR): 1180, 1240, 2910, 3030 cm^{-1}. HRMS (EI) m/z: calcd for $C_{13}H_{15}DO$ (M^+) 189.1264, found 189.1268.

(4-Deuteriocyclohex-3-enyl)benzene (2b). This reaction was conducted on a 0.5 mmol scale. Silica gel column chromatography (hexane) gave 70 mg of the product (0.44 mmol, 88% yield) as a colorless oil with >99% D (the D content was judged by comparison of the peak at 5.75−5.76 ppm (a deuterated site) with the peak at 7.24−7.31 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.67−1.73 (m, 1H), 1.80−1.84 (m, 1H), 2.07−2.24 (m, 4H), 2.72−2.78 (m, 1H), 5.75−5.76 (m, 1H), 7.17−7.20 (m, 1H), 7.24−7.31 (m, 4H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.80 (br s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.3 (CH_2), 29.3 (CH_2), 32.9 (CH_2), 39.5 (CH), 126.0 (CH), 126.5 (t, J_{C-D} = 24.8 Hz, C), 126.6 (CH), 126.9 (CH), 128.4 (CH), 147.1 (C). IR (ATR): 700, 1500, 3030 cm^{-1}. HRMS (EI) m/z: calcd for $C_{12}H_{13}D$ (M^+) 159.1158, found 159.1156.

3-(4-Deuteriocyclohex-3-enyl)pyridine (2c). Silica gel column chromatography (hexane/AcOEt = 2/1) gave 148 mg of the product (0.92 mmol, 92% yield) as brown oil with >99% D (the D content was judged by comparison of the peak at 5.777−5.782 ppm (a deuterated site) with the peak at 8.45 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.73−1.81 (m, 1H), 1.92−1.97 (m, 1H), 2.12−2.26 (m, 3H), 2.28−2.33 (m, 1H), 2.82−2.88 (m, 1H), 5.777−5.782 (m, 1H), 7.23 (dd, J = 4.8, 7.8 Hz, 1H), 7.53 (dt, J = 2.2, 7.8 Hz, 1H), 8.45 (dd, J = 1.5, 4.8 Hz, 1H), 8.51 (d, J = 2.2 Hz, 1H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.78 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2 (CH_2), 29.2 (CH_2), 32.7 (CH_2), 37.5 (CH), 123.4 (CH), 126.1 (CH), 126.7 (t, J_{C-D} = 24.0 Hz, C), 134.2 (CH), 142.2 (C), 147.5 (CH), 149.0 (CH). IR (ATR): 710, 810, 1020, 3030 cm^{-1}. HRMS (EI) m/z: calcd for $C_{11}H_{12}DN$ (M^+) 160.1111, found 160.1117.

2-(4-Deuteriocyclohex-3-enyl)thiophene (2d). Silica gel column chromatography (hexane) gave 142 mg of the product (0.86 mmol, 86% yield) as a yellow oil with 98% D (the D content was judged by comparison of the peak at 5.740−5.744 ppm (a deuterated site) with the peak at 7.13 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.70−1.78 (m, 1H), 2.08−2.25 (m, 4H), 2.41−2.47 (m, 1H), 3.09−3.15 (m, 1H), 5.740−5.744 (m, 1H), 6.84 (dt, J = 1.0, 3.4 Hz, 1H), 6.93−6.95 (m, 1H), 7.13 (dd, J = 1.1, 5.1 Hz, 1H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.77 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2 (CH_2), 30.9 (CH_2), 33.8 (CH_2), 35.2 (CH), 122.2 (CH), 122.5 (CH), 125.9 (CH), 126.5 (CH), 126.6 (t, J_{C-D} = 24.0 Hz, C), 151.4 (C). IR (ATR): 690, 810, 2910, 3030 cm^{-1}. HRMS (EI) m/z: calcd for $C_{10}H_{11}DS$ (M^+) 165.0722, found 165.0725.

1-Benzyl-4-deuterio-1,2,3,6-tetrahydropyridine (2e). Silica gel column chromatography (hexane/benzene = 1/4) gave 149 mg of the product (0.86 mmol, 86% yield) as a brown oil with >99% D (the D content was judged by comparison of the peak at 5.74−5.78 ppm (a deuterated site) with the peak at 5.65−5.68 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.14−2.17 (m, 2H), 2.55−2.58 (m, 2H), 2.96−2.98 (m, 2H), 3.58−3.60 (m, 2H), 5.65−5.68 (m, 1H), 7.23−7.27 (m, 1H), 7.30−7.36 (m, 4H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.78 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.9 (CH_2), 49.5 (CH_2), 52.7 (CH_2), 62.9 (CH_2), 125.0 (t, J_{C-D} = 24.0 Hz, C), 125.3 (CH), 127.1 (CH), 128.2 (CH), 129.3 (CH), 138.4 (C). IR (ATR): 700, 1160, 3030 cm^{-1}. HRMS (EI) m/z: calcd for $C_{12}H_{14}DN$ (M^+) 174.1267, found 174.1269.

2-(1-Deuteriovinyl)naphthalene (2f). Silica gel column chromatography (hexane) gave 137 mg of the product (0.88 mmol, 88% yield) as a white solid with mp 66 °C and >99% D (the D content was judged by comparison of the peak at 6.93 ppm (a deuterated site) with the peak at 5.33−5.34 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.33−5.34 (m, 1H), 5.86−5.87 (m, 1H), 7.42−7.48 (m, 2H), 7.64 (dd, J = 1.7, 8.5 Hz, 1H), 7.75 (s, 1H), 7.79−7.82 (m, 3H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 6.92 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.0 (CH_2), 123.2 (CH), 125.9 (CH), 126.3 (CH), 126.4 (CH), 127.7 (CH), 128.1 (CH), 128.2 (CH), 133.2 (C), 133.6 (C), 135.0 (C), 136.7 (t, J = 23.2 Hz, C). IR (ATR): 890, 1510, 1680, 3080 cm^{-1}. HRMS (EI) m/z: calcd for $C_{12}H_9D$ (M^+) 155.0845, found 155.0844.

(1-Deuterio-2-methylprop-1-enyl)benzene (2g). The GC yield was 90%. Silica gel column chromatography (hexane/benzene = 10/1) gave 74.2 mg of the product (0.56 mmol, 56% yield) as a colorless oil with >99% D (the D content was judged by comparison of the peak at 6.24 ppm (a deuterated site) with the peak at 7.29−7.32 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.87 (s, 3H), 1.90 (s, 3H), 7.16−7.19 (m, 1H), 7.22−7.23 (m, 2H), 7.29−7.32 (m, 2H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 6.31 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2 (CH_3), 26.7 (CH_3), 124.8 (t, J = 23.2 Hz, C), 125.8 (CH), 128.1 (CH), 128.7 (CH), 135.4 (C), 138.7 (C). IR (ATR): 700, 1600, 1650 cm^{-1}. HRMS (EI) m/z: calcd for $C_{10}H_{11}D$ (M^+) 133.1002, found 133.1003.

1-(1-Deuteriovinyl)-4-methoxybenzene (2h). The GC yield was 86%. Silica gel column chromatography (hexane/AcOEt = 50/1) gave 97.6 mg of the product (0.72 mmol, 72% yield) as a colorless oil with 98% D (the D content was judged by comparison of the peak at 6.66 ppm (a deuterated site) with the peak at 5.10−5.11 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.75 (s, 3H), 5.10−5.11 (m, 1H), 5.65−5.66 (m, 1H), 6.89−6.92 (m, 2H), 7.39−7.42 (m, 2H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 6.69 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2 (CH_3), 111.4 (CH_2), 113.9 (CH), 127.4 (CH), 130.4 (C) 135.9 (t, J_{C-D} = 23.2 Hz, C), 159.4 (C). IR (ATR): 830, 1030, 1240, 3070 cm^{-1}. HRMS (EI) m/z: calcd for C_9H_9DO (M^+) 135.0794, found 135.0807.

4-(1-Deuteriovinyl)benzonitrile (2i). Silica gel column chromatography (benzene/AcOEt = 10/1) gave 104 mg of the product (0.80 mmol, 80% yield) as a colorless oil with >99% D (the D content was judged by comparison of the peak at 6.73 ppm (a deuterated site) with the peak at 5.45 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45 (t, J = 1.5 Hz, 1H), 5.87 (t, J = 2.6 Hz, 1H), 7.48−7.50 (m, 2H), 7.60−7.63 (m, 2H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 6.74 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.1 (C), 117.6 (CH_2), 118.9 (C), 126.7 (CH), 132.4 (CH), 135.0 (t, J_{C-D} = 24.0 Hz, C), 141.8 (C). IR (ATR): 840, 1500, 2230, 3090 cm^{-1}. HRMS (EI) m/z: calcd for C_9H_6DN (M^+) 130.0641, found 130.0638.

1,1′-(2-Deuterioethenylidene)bis(benzene) (2j). This reaction was conducted on a 0.5 mmol scale. Silica gel column chromatography (hexane) gave 76 mg of the product (0.46 mmol, 84% yield) as a colorless oil with >99% D (the D

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content was judged by comparison of the peak at 5.45 ppm (a deuterated site) with the peak at 7.29−7.35 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.45 (s, 1H), 7.29−7.35 (m, 10H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.50 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.0 (t, J_{C-D} = 24.0 Hz, CH), 127.7 (CH), 128.2 (CH), 128.3 (CH) 141.5 (C), 150.1 (C). IR (ATR): 690, 1080, 1490 cm^{-1}. HRMS (EI) *m*/*z*: calcd for $C_{14}H_{11}D$ (M^+) 181.1002, found 181.1002.

3,4-Dideuterio-7-methoxy-2,2-dimethyl-2*H*-chromene (2k). This reaction was conducted on a 0.5 mmol scale. Silica gel column chromatography (hexane/AcOEt = 20/1) gave 93 mg of the product (0.48 mmol, 97% yield) as a colorless oil with D^1 > 99% D (the D^1 content was judged by comparison of the peak at 6.27 ppm (a deuterated site) with the peaks at 6.37 and 6.40 ppm by ^{1}H NMR) and D^2 = 98% D (the D^2 content was judged by comparison of the peak at 5.47 ppm (a deuterated site) with the peaks at 6.37 and 6.40 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (s, 6H), 3.77 (s, 3H), 6.37 (d, *J* = 2.5 Hz, 1H), 6.40 (dd, *J* = 2.5, 8.2 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.49 (br s), 6.29 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9 (CH_3), 55.2 (CH_3), 76.2 (C), 102.0 (CH), 106.6 (CH), 114.5 (C), 121.5 (t, *J* = 24.8 Hz, C), 126.9 (CH), 127.4 (t, *J* = 24.8 Hz, C), 154.2 (C), 160.7 (C). IR (ATR): 810, 1030, 1190, 1270, 1500 cm^{-1}. HRMS (EI) *m*/*z*: calcd for $C_{12}H_{12}D_2O_2$ (M^+) 192.1119, found 192.1118.

5-Allyl-10-deuterio-5*H*-dibenzo[*b*,*f*]azepine (2l). This reaction was conducted on a 0.5 mmol scale. Silica gel column chromatography (hexane/AcOEt = 20/1) gave 98 mg of the product (0.42 mmol, 84% yield) as a yellow oil with >99% D (the D content was judged by comparison of the peak at 6.74 ppm (a deuterated site) with the peak at 5.74−5.82 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.39−4.40 (m, 2H), 5.08−5.11 (m, 1H), 5.27−5.31 (m, 1H), 5.74−5.82 (m, 1H), 6.74 (s, 1H), 6.96−6.99 (m, 4H), 7.05−7.07 (m, 2H), 7.22−7.25 (m, 2H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 6.77 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.5 (CH_2), 117.6 (CH_2), 120.6 (CH), 123.4 (CH), 128.7 (CH), 129.09 (CH), 129.13 (CH), 131.9 (t, J_{C-D} = 24.0 Hz, C), 132.1 (CH), 133.7 (C), 133.8 (C), 135.2 (CH), 150.7 (C). IR (ATR): 880, 1110, 1230, 1480 cm^{-1}. HRMS (EI) *m*/*z*: calcd for $C_{17}H_{14}DN$ (M^+) 234.1267, found 234.1267.

(8*S*,9*S*,13*R*,14*S*)-17-Deuterio-3-methoxy-13-methyl-7,8,9,11,12,13,14,15-octahydro-6*H*-cyclopenta[*a*]-phenanthrene (2m). Silica gel column chromatography (hexane/AcOEt = 50/1) gave 254 mg of the product (0.94 mmol, 94% yield) as white solid with >99% D (the D content was judged by comparison of the peak at 5.90−5.93 ppm (a deuterated site) with the peak at 5.74−5.75 ppm by ^{1}H NMR). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (s, 3H), 1.41−1.65 (m, 5H), 1.87−1.96 (m, 2H), 2.01 (ddd, *J* = 1.4, 11.2, 15.0 Hz, 1H), 2.21 (ddd, *J* = 3.0, 6.1, 15.0 Hz, 1H), 2.26−2.36 (m, 2H), 2.84−2.96 (m, 2H), 3.78 (s, 3H), 5.74−5.75 (m, 1H), 6.64 (d, *J* = 3.0 Hz, 1H), 6.71 (dd, *J* = 2.8, 8.6 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H). ^{2}H NMR (60 MHz, $CHCl_3$): δ 5.96 (br s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.0 (CH_3), 26.5 (CH_2), 27.9 (CH_2), 29.7 (CH_2), 31.7 (CH_2), 35.8 (CH_2), 37.3 (CH), 44.5 (CH), 45.6 (C), 55.1 (CH_3), 55.4 (CH), 111.4 (CH), 113.9 (CH), 126.1 (CH), 129.2 (CH), 133.2 (C), 138.0 (C), 143.7 (t, J_{C-D} = 24.0 Hz, C), 157.5 (C). IR (ATR): 670, 820, 1230, 1610, 3020 cm^{-1}. HRMS (EI) *m*/*z*: calcd for $C_{19}H_{23}DO$ (M^+) 269.1890, found 269.1881.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00193.

Synthetic details of alkenyl chlorides and ^{1}H, ^{13}C, and ^{2}H NMR spectra of products (PDF)

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