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A simple method for α-position deuterated carbonyl compounds with pyrrolidine as catalyst†

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A simple, cost-effective method for deuteration of carbonyl compounds employing pyrrolidine as catalyst and D_2O as deuterium source was described. High degree of deuterium incorporation (up to 99%) and extensive functional group tolerance were achieved. It is the first time that secondary amines are used as catalysts for H/D exchange of carbonyl compounds, which also allow the deuteration of complex pharmaceutically interesting substrates. A possible catalytic mechanism, based on the hydrolysis of 1-pyrrolidino-1-cyclohexene, for this pyrrolidine-catalyzed H/D exchange reaction has been proposed.

Keywords: isotope exchange; deuterium; chemoselectivity; ketones; deuterium oxide; pyrrolidine

Introduction

Isotope-labeled compounds have been widely used in many areas. For example, they have been used as deuterated solvents,[1g] research tools in drug metabolism studies,[1a] structural elucidation of biological macromolecules,[1b,1h,1i] internal standard for validation of quantitative bioanalytical assays,[1l] reaction mechanism[1c,1k] and kinetic[1d] studies, quantitative analysis of environmental pollutants and residual pesticides,[1j] optical materials,[1e] and so forth. In addition, some deuterium-enriched compounds have been studied as drug candidates in recent years because of the kinetic isotopic effects.[2] The development of diverse and selective synthetic methods of deuterated materials is desired as the results of the new demands for suitably deuterated compounds.

For the preparation of deuterium-labeled carbonyl compounds, strong base catalyzed H–D exchange reactions provided a facile method for the exchange of acidic hydrogen atoms for deuterium by means of keto-enol equilibrium.[3] There was also an acid-catalyzed H–D exchange of α-proton of a carbonyl.[4] Mioskowski's group reported that 1,5,7-triazabicyclo [4.4.0]dec-5-ene (TBD) showed to be an isotope exchange catalyst in $CDCl_3$ at room temperature toward ketones and other acidic substrates.[3e] Although other methods for deuteration of ketones are available, such as using the Pd/C-H_2-D_2O system[5], other catalysts such as calcium vanadate apatite,[6] antibody 38C2,[7] cyclooctadieneiridium(I) acetylacetonate,[8] Ir-NHC complexes,[9] and Pd/C utilizing $NaBD_4$ for catalyst activation[10] were also used. Eames's group indicated that the regioselective *C*-deuteration of a series of related acyclic and exocyclic enolates derived from substituted aryl ketones.[11] It required two steps for deuteration of ketones; the first step was formation of enolate derivatives and then deuteration of them with [D_4]acetic acid.

In decades, significant efforts have been made to develop proline derived catalytic reactions, mainly based on enamine and/or iminium activation modes.[12] However, no attempts have been made for a secondary amine as catalyst for deuterium isotope exchange reactions on a preparative scale. The aim of the investigation was to seek a facile and efficient method to label aryl methyl ketones with deuterium, employing the secondary amine-pyrrolidine as catalyst. The first example that the secondary amine as catalyst for deuteration of α-proton of a carbonyl function was described here (Scheme 1), which may go through enamine and/or iminium modes.

Results and discussion

Initially, pyrrolidine (10 mol%) as catalyst, D_2O (75 eq) as deuterium source, and anhydrous THF as cosolvent were used for the deuteration of acetophenone at room temperature. The deuterium incorporation reached to 97% within 6 h. The total deuterium incorporation was confirmed by ^1H NMR spectroscopy. As THF was partially immiscible in the reaction system, the other cosolvents, such as 1,4-dioxane, acetonitrile and 1,2-dimethoxyethane were investigated at room temperature. As a result, all of them afforded 97% of deuterium incorporation within only 3 h. Without cosolvent, the system allowed 95.7% of deuterium incorporation after 12 h at room temperature. A two-phase reaction (D_2O/$CHCl_3$) gave only 10% of deuterium incorporation overnight because these two

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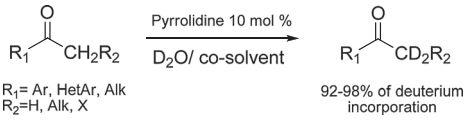


Scheme 1. Deuteration of various carbonyl compounds by pyrrolidine-D_2O/cosolvent system.

solvents were not miscible. Finally, 1,4-dioxane was chosen as cosolvent. For these substrates with poor solubility, acetonitrile was used as cosolvent.

With 1,4-dioxane as cosolvent and 75 eq (H : D = 1 : 50) of D_2O as deuterium source, pyrrolidine and other secondary amines were studied for deuteration of acetophenone within 3 h at room temperature (Table 1). Pyrrolidine (10 mol%) formed 97% of isotope incorporation after 3 h (Table 1, entry 1). Comparable deuterium incorporation was obtained with piperidine (93.3%, Table 1, entry 2). Whereas other secondary amines were less effective (entries 3–5), and isotope incorporation was unable to be observed without a catalyst (entry 6). Less amount of pyrrolidine resulted in a slow rate of incorporation (entries 7 and 8). Then, the optimized reaction conditions were obtained (10 mol% of pyrrolidine, 75 eq of D_2O, 1,4-dioxane as cosolvent, room temperature, 12 h).

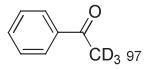
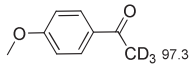
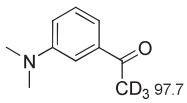
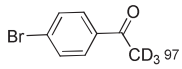
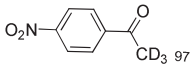
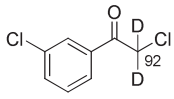
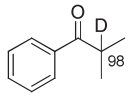
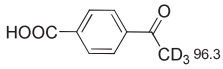
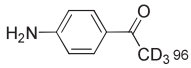
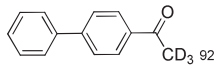
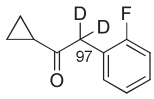
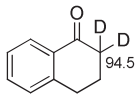
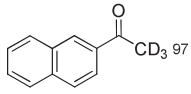
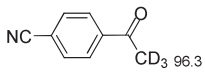
To investigate the scope of this H–D exchange method, various ketones were used as substrates (Table 2). Spectrographically pure labeled ketones were obtained through extraction, and no further purification was required. For acetophenone derivatives, it appeared that the nature of the substituent on the aromatic ring did not have significant effect on the deuterium incorporation after 12 h. Indeed, the 4′-methoxy gave high level of deuterium labeling (97.3%, Table 2, entry 2) as well as 3′-dimethylamino, 4′-nitro, 4′-bromo, 2,3′-dichloroacetophenone with 97.7, 97, 97 and 92% of deuterium incorporation after 12 h, respectively (Table 2, entries 3–6). An attempt to deuterate the isobutyrophenone at room temperature was unsuccessful probably because of steric hindrance. In contrast, 98% of deuterium incorporation was achieved at 100 °C (Table 2, entry 7). Substrates, such as 4-acetylbenzoic acid, which has carboxylic group, also could achieve 96% of deuterium

Table 1. Effect of the catalysts for deuteration of acetophenone [a]

Entry	Catalyst (mol %)	D content (%)
1	Pyrrolidine (10)	97
2	Piperidine (10)	93.3
3	Diethylamine(10)	85
4	1,4-Oxazinan (10)	12.7
5	Thiomorpholine (10)	9.3
6	None	0
7	Pyrrolidine (5)	88.7(96)[b]
8	Pyrrolidine (1)	44.7 (94.3)[c]

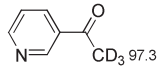
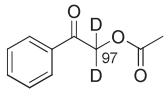
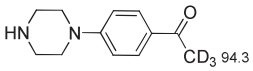
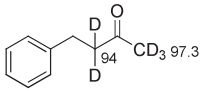
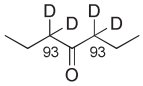
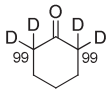
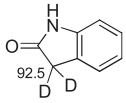
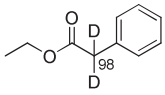
[a]The reaction was conducted with 1 mmol of the substrate in 1.5 mL of D_2O and 1.5 mL 1,4-dioxane at room temperature for 3 h. The D content was calculated on the basis of ^1H NMR spectrum.
[b]Prolonged to 6 h.
[c]Overnight.

Table 2. Deuteration of various substrates catalyzed by pyrrolidine in D_2O and cosolvent [a]

Entry	D content (%)	Yield (%)[b]
1		96
2		95
3		90
4		94
5		92
6[c]		93
7[d]		90
8[e]		91
9[f]		89
10[g]		94
11[g]		90
12		92
13		90
14		94

(Continues)

Table 2. (Continued)

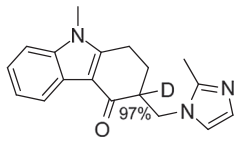
Entry	D content (%)	Yield (%)[b]
15		88
16[g]		93
17[g]		88
18[g]		91
19[g]		40[i]
20[j]		Not isolated
21[g]		90
22[g]		96

[a]Unless otherwise noted, the reaction was conducted with 1 mmol of the substrate and 10 mol% of pyrrolidine in 1.5 mL D_2O/1,4-dioxane at room temperature for 12 h. The D content was calculated on the basis of ^1H NMR spectrum.
[b]Isolated yield.
[c]45 °C, 36 h.
[d]100 °C, 12 h.
[e]1.2 eq of pyrrolidine.
[f]50 mol% of pyrrolidine.
[g]60 °C, 12 h.
[h]Acetonitrile as cosolvent.
[i]The low isolated yield of the deuteration is due to its low boiling point and volatile nature.
[j]Without cosolvent.

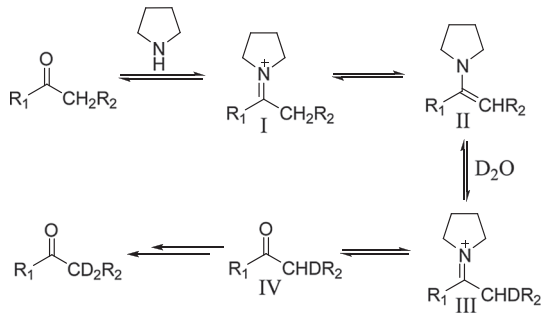
incorporation with 1.2 eq of pyrrolidine (Table 2, entry 8). With 10 mol% of pyrrolidine, 4-aminoacetophenone was deuterated at a slow rate probably because of the formation of imine intermediate of 4-aminoacetophenone itself. When the catalyst was up to 50 mol%, the 4-aminoacetophenone gave high level of deuterium labeling (96%, Table 2, entry 9) at room temperature after 12 h. The deuteration of cyclopropyl 2-fluorobenzyl ketone proceeded at the benzylic position selectively because no deuterium incorporation was detected ($^1H/^2H$ NMR) on the cyclopropyl group (Table 2, entry 11). Delightfully, strong base sensitive 4′-cyanoacetophenone afforded 96.3% of deuterium incorporation (Table 2, entry 14). Moreover, the reaction was also employed to heteroaromatic ketones, 3-acetylpyridine (97.3%, Table 2, entry 15). Additionally, the 2-acetoxyacetophenone was chemselectively deuterated at the α-carbon atom to the phenyl carbonyl group (98%, Table 2, entry 16) because no deuterium-incorporation was detected ($^1H/^2H$ NMR) on the acetyl group. Furthermore, the study from Sabot *et al.* implied deuterating 2-acetoxyacetophenone using usual base such as MeONa, NaOH, or TBD ended up in partial or complete deprotection of the substrate leading to 2-hydroxyacetophenone,[3e] which may suggest that the superiority of pyrrolidine over other strong base for the labeling of compounds bearing sensitive functional groups. 4′-Piperazinoacetophenone with piperidyl on acetophenone afforded 73% of deuteration incorporation without catalyst at 60 °C after 12 h through intermolecular catalytic reactions, and 94.3% of deuterium incorporation was achieved when 10 mol% of pyrrolidine was used (Table 2, entry 17). Finally, deuteration of several aliphatic ketones were successfully achieved (Table 2, entries 18–20).

These results prompted us to investigate the scope of our methodology to other substrates. Interestingly, oxindole underwent 92.5% of deuterium incorporation at the benzylic position (Table 2, entry 21). Previous exchange methods for oxindole analogs were D_2SO_4/D_2O system.[13] Moreover the ethyl-1-phenylacetate, a base-sensitive group, was efficiently deuterated with pyrrolidine (Table 2, entry 22), which may suggest that this method should be applicable to a variety of alkyl-1-phenylacetate derivatives. However, they are very substrate-limited, as common procedures for the deuteration of alkyl esters in protic solvents may lead to concomitant transesterification.[14]

To further evaluate the substrate scope of our novel catalytic deuteration procedure, FDA-approved drug ondansetron featuring a carbonyl moiety was chosen as a benchmark compound. Ondansetron is used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, and surgery.[15] Its deuterated fashion has been protected by the patent, but no implementations were introduced.[16] As



Scheme 2. Deuteration of ondansetron by pyrrolidine-D_2O/1,4-dioxane system.



Scheme 3. A possible mechanism for the H–D exchange reaction.

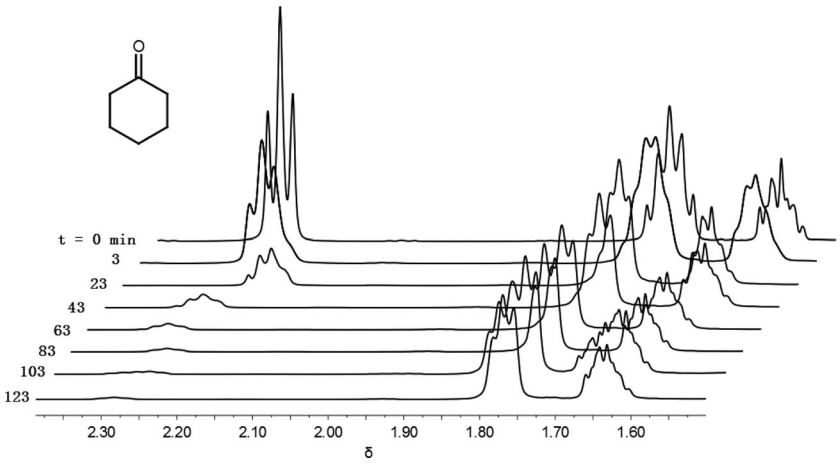


Figure 1. ^{1}H NMR trace of the pyrrolidine catalyzed deuteration of cyclohexanone (Table 2, entry 20).

expected, 97% of deuterium incorporation was achieved by our system (Scheme 2).

Outlined in Scheme 3 is a possible mechanism for the deuteration of carbonyl compounds. Reaction of pyrrolidine with carbonyl compounds results in the formation of the iminium I and tautomerization of the iminium to enamine II. With D_2O as solvent, the reversible tautomerization of enamine II to iminium III, and subsequent hydrolyzation could give the deuterium-labeled compound IV. IV goes through further deuteration as same as I to IV until the formation of a fully α-deuterated carbonyl product. However, the keto-enol equilibrium mechanism cannot be completely excluded.

To study the reaction process, cyclohexanone (38 mg), pyrrolidine (10 mol%) and D_2O (1 mL) was loaded into an NMR tube, which was monitored every 20 min (Figure 1). After 123 min, cyclohexanone was successfully achieved with 98% of deuterium incorporation.

To confirm the enamine and/or iminium mechanism, 20 mg of 1-pyrrolidino-1-cyclohexene was added to 1 mL of D_2O. At the beginning, 1-pyrrolidino-1-cyclohexene was not soluble in D_2O; after 2 h, the solution was clear because the hydrolyzates of 1-pyrrolidino-1-cyclohexene are water soluble. The ^{1}H NMR indicated that 1-pyrrolidino-1-cyclohexene had been hydrolysed completely, which confirmed the mechanism above to a certain extent (Figure 2).

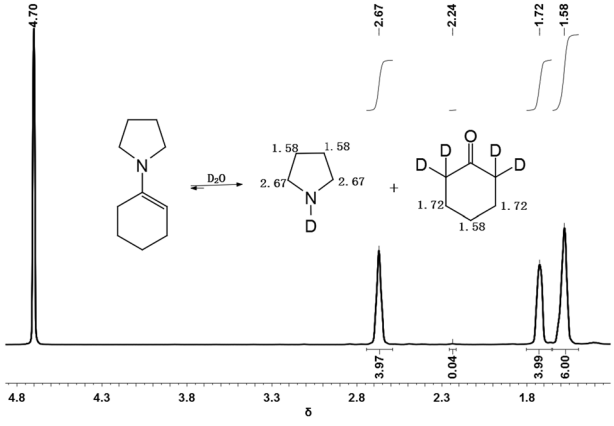


Figure 2. The hydrolysis of 1-pyrrolidino-1-cyclohexene in D_2O.

Conclusions

In summary, pyrrolidine has been shown to be an efficient isotope exchange catalyst in D_2O/1,4-dioxane at a mild condition toward a wide range of substrates. This synthetic method is compatible with sensitive functional groups. Finally, an easy workup provides spectrographically pure labeled ketones. To some extent, hydrolysis of 1-pyrrolidino-1-cyclohexene in D_2O supported the enamine and/or iminium mechanism. Further investigations to apply chiral catalysts for the deuterium reaction is underway.

Experimental section

General information

^{1}H NMR and ^{2}H NMR spectra were recorded on Bruker Avance III 400 (Bruker Corporation, Karlsruhe, Germany) (400 MHz for ^{1}H NMR and 61.4 MHz for ^{2}H NMR). Chemical shifts (δ) are expressed in ppm and are internally referenced (^{1}H NMR: 0.00 ppm for TMS in $CDCl_3$; 4.70 ppm for DSS in D_2O. ^{2}H NMR: 7.26 ppm for $CDCl_3$ in $CHCl_3$; 8.32 ppm for $CDCl_3$ in DMSO). Deuterium content was determined by comparison with the integration of deuterated position and nondeuterated position. Deuterium incorporation was assigned by ^{2}H NMR. The MS systems used were the Quattro Premier XE mass spectrometer and the Q-TOF premier mass spectrometer (Waters Micromass, Milford, Massachusetts, USA), which were used for LC/MS analysis and accurate mass detection, respectively. Both were equipped with a standard ESI source.

General procedure for the evaluation of catalysts (Table 1)

To a solution of catalyst in 1.5 mL of D_2O with 1.5 mL of cosolvent (if necessary) was added acetophenone (120.1 mg, 1 mmol). The reaction mixture was stirred for 3 h at room temperature, poured into 10 mL of water, and extracted with diethyl ether (2 × 10 mL). The organic layer was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. Filtrate was concentrated to afford acetophenone-d_3. The total incorporation yield was determined by ^{1}H NMR spectroscopy relative to the intensity of a nonexchangeable proton in the molecule.

Typical procedure for deuteration of acetophenone.

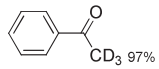
To a solution of 10 mol% of pyrrolidine (7.1 mg, 0.1 mmol) in 1.5 mL of D_2O with 1.5 mL anhydrous dioxane as cosolvent was added acetophenone (120.1 mg, 1 mmol). The reaction mixture was stirred at room temperature for 12 h, followed by water (10 mL), then extracted with diethyl ether (2 × 10 mL).The organic layer was washed with water

(5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to afford acetophenone-d_3.

The procedures for deuteration of the substrates in Table 2, entries 2, 3, 4, 5, 12, 13, 14, 15, and 20, were the same as acetophenone-d_3.

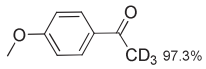
For substrates in Table 2, entries 10, 11, 16, 18, 19, 21, and 22 were similar to that for acetophenone-d_3, except that the room temperature was changed to 60 °C.

[^{2}H]-Acetophenone (Table 2, entry 1)



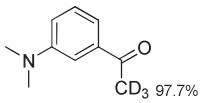
Colorless oil, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.45(t, *J* = 8 Hz, 2H), 2.58 (s, 0.09H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.59 (s) ppm.

[^{2}H]-4′-Methoxyacetophenone (Table 2, entry 2)



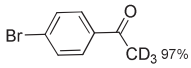
White solid, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.87(s, 3H), 2.52 (s, 0.08H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.53 (s) ppm.

[^{2}H]-3′-Dimethylaminoacetophenone (Table 2, entry 3)



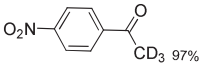
Light yellow solid, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 3H), 6.92 (m, 1H), 2.99(s, 6H), 2.55 (s, 0.07H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.58 (s) ppm. HRMS *m/z* 167.1263 $[M+H]^+$.

[^{2}H]-4′-Bromoacetophenone (Table 2, entry 4)



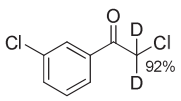
White solid, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 2.56 (s, 0.09H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.56 (s) ppm. HRMS *m/z* 201.9951 $[M+H]^+$.

[^{2}H]-4-Nitroacetophenone (Table 2, entry 5)



Light yellow solid, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 9.2 Hz, 2H), 2.66 (s, 0.09H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.67 (s) ppm.

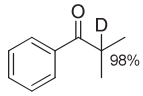
[^{2}H]-2,3′-Dichloroacetophenone (Table 2, entry 6)



Deuterated 2,3′-dichloroacetophenone was obtained at 45 °C for 36 h similarly to the procedure for acetophenone-d_3.

Light yellow solid, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 8 Hz, 1H), 4.66 (s, 0.15H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 4.65 (s) ppm. HRMS *m/z* 190.9997 $[M+H]^+$.

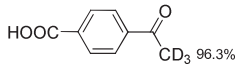
[^{2}H]-Isobutyrophenone (Table 2, entry 7)



Isobutyrophenone-d_3 was obtained similarly to that of acetophenone-d_3, except that the room temperature was changed to 100 °C.

Colorless oil, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 2H), 3.56 (s, 0.02H), 1.21 (s, 6H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 3.56 (s) ppm.

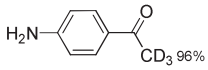
[^{2}H]-4-Acetylbenzoic acid (Table 2, entry 8)



To a solution of 1.2 eq of pyrrolidine (85.3 mg, 1.2 mmol) in 1.5 mL of D_2O was added 4-acetylbenzoic acid (120.1 mg, 1 mmol). The reaction mixture was stirred at room temperature for 12 h, followed by 2 eq of acetic acid glacial in water (10 mL), then extracted with dichloromethane (2 × 10 mL).The organic layer was washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated to afford 4-acetylbenzoic acid-d_3.

White solid, 91% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.32 (bs, 1H), 8.06 (s, 4H), 2.60 (s, 0.11H) ppm. ^{2}H NMR (61.4 MHz, DMSO-d_6): δ = 2.64 (s) ppm. HRMS *m/z* 190.0560 $[M+Na]^+$.

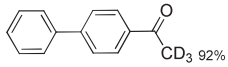
[^{2}H]-4-Aminoacetophenone (Table 2, entry 9)



The procedures for deuterated 4-aminoacetophenone was obtained similarly to that of acetophenone-d_3, except that the 10 mol% of pyrrolidine was changed to 50 mol%.

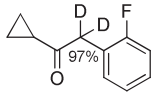
Light yellow solid, 89% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 4.15 (bs, 2H), 2.47 (s, 0.12H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.48 (s) ppm. HRMS *m/z* 161.0771 $[M+Na]^+$.

[^{2}H]-4′-Phenylacetophenone (Table 2, entry 10)



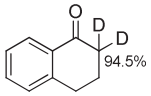
White solid, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, *J* = 7.2 Hz, 2H), 7.40 (t, 1H), 2.62 (s, 0.24H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.62 (s) ppm. HRMS *m/z* 222.0975 $[M+Na]^+$.

[^{2}H]-Cyclopropyl 2-fluorobenzyl ketone (Table 2, entry 11)



Colorless oil, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 2H), 7.08 (m, 2H), 3.85 (s, 0.06H), 1.99 (m, 1H), 1.06 (m, 2H), 0.87 (m, 2H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 3.87 (s) ppm. HRMS *m/z* 181.1490 $[M+H]^+$.

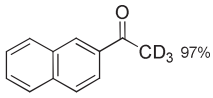
[^{2}H]-1-Tetralone (Table 2, entry 12)



Light yellow liquid, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.25

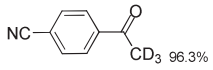
(d,J = 8.8 Hz, 1H), 2.97 (t, J = 6 Hz, 2H), 2.63 (s, 0.11H), 2.13 (t, J = 6 Hz, 2H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.64 (s) ppm. HRMS *m/z* 171.0755 $[M + Na]^+$.

[^{2}H]-2-Acetonaphthone (Table 2, entry 13)



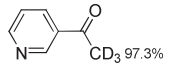
White solid, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.89 (m, 2H), 7.58 (dt, J = 19.6, 7.2 Hz, 2H), 2.70 (s, 0.09H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.70 (s) ppm. HRMS *m/z* 196.0819 $[M + Na]^+$.

[^{2}H]-4′-Cyanoacetophenone (Table 2, entry 14)



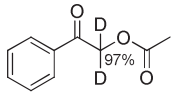
Brown solid, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 8 Hz, 2H), 7.79 (d, J = 8 Hz, 2H), 2.62 (s, 0.11H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.64 (s) ppm.

[^{2}H]-3-Acetylpyridine (Table 2, entry 15)



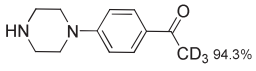
Light yellow liquid, 88% yield. ^{1}H NMR (400 , $CDCl_3$): δ = 9.18 (s, 1H), 8.80 (d, J = 4 Hz, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.44 (dd, J_1 = 7.6 Hz, J_2 = 4.8 Hz, 1H), 2.62 (s, 0.08H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.62 (d) ppm.

[^{2}H]-Phenacyl acetate (Table 2, entry 16)



Light yellow liquid, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 8 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 5.32 (s, 0.06H), 2.23 (s, 3H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 5.33 (s) ppm. HRMS *m/z* 203.0655 $[M + Na]^+$.

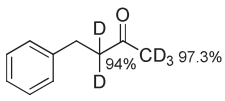
[^{2}H]-4′-Piperazinoacetophenone (Table 2, entry 17)



Deuterated 4′-piperazinoacetophenone was obtained using acetonitrile as cosolvent at 60 °C similarly to the procedure for acetophenone-d_3.

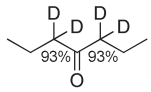
Light yellow solid, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 3.31 (m, 4H), 3.03 (m, 4H), 2.49 (s, 0.17H), 1.92 (bs, 1H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.50 (s) ppm. HRMS *m/z* 208.1547 $[M + H]^+$

[^{2}H]-Benzylacetone (Table 2, entry 18)



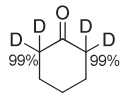
Colorless oil, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 8 Hz, 3H), 2.88 (s, 2H), 2.73 (s, 0.12H), 2.10 (s, 0.08H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.75 (s), 2.13 (d) ppm.

[^{2}H]-4-Heptanone (Table 2, entry 19)



Colorless liquid, 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 0.28H), 1.59 (q, J = 7.2 , 4H), 0.9 (t, J = 7.2 Hz, 6H) ppm. ^{2}H NMR (61.4 MHz, $CHCl_3$): δ = 2.35 (s) ppm.

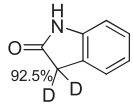
[^{2}H]-Cyclohexanone (Table 2, entry 20)



Cyclohexanone (38 mg), pyrrolidine (10 mol %, 2.8 mg) and D_2O (1 ml) was loaded into an NMR tube at room temperature. After 2 h, 97% of deuterium incorporation was achieved.

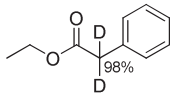
^{1}H NMR (400 MHz, D_2O): δ = 2.20 (s, 0.04H), 1.70 (m, 4H), 1.57 (m, 2H) ppm. ^{2}H NMR (61.4 MHz, $CDCl_3$): δ = 2.30 (s) ppm.

[^{2}H]-Oxindole (Table 2, entry 21)



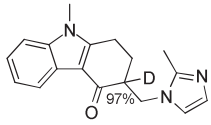
Light yellow solid, 90% yield. ^{1}H NMR (400vMHz, $CDCl_3$): δ = 8.98 (bs, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 3.52 (s, 0.15H) ppm. ^{2}H NMR (61.4 MHz, $CDCl_3$): δ = 3.54 (s) ppm. HRMS *m/z* 158.0551 $[M + Na]^+$.

[^{2}H]-Phenylacetic acid ethyl ester (Table 2, entry 22)



Colorless liquid, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 5H), 4.14 (q, J =7.2Hz, 2H), 3.59 (s, 0.04H), 1.25 (t, J = 7.6 Hz, 3H) ppm. ^{2}H NMR (61.4 MHz, $CDCl_3$): δ = 3.60 (s) ppm.

Procedure for regioselective deuteration of ondansetron



To a solution of 20 mol% pyrrolidine (4.3 mg) in 1.5 mL of D_2O with 1,4-dioxane as cosolvent was added ondansetron (100 mg). The reaction mixture was stirred at 80 °C for 12 h and then cooled to room temperature. Deuterated ondansetron was obtained through filtration. White solid, 98% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (m, 1H), 7.31 (m, 3H), 6.91 (d, J = 15.2 Hz, 2H), 4.63–4.67 (d, J = 14.4 Hz, 2H), 4.04–4.08 (d, J = 14.8 Hz, 2H), 3.68 (s, 3H), 2.96–3.00 (m, 1H), 2.82–2.88 (m, 1 + 0.03H), 2.15–2.18 (m, 1H), 1.87–1.90 (m, 1H) ppm. HRMS *m/z* 295.1664 $[M + H]^+$.

Conflict of Interest

The authors did not report any conflict of interest.

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