Supporting information for

Highly-selective H/D exchange reaction of 1,4-dihydropyridines

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1. General information

All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Reactions were monitored by thin-layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm and 365 nm). Column chromatography was performed using 200-300 mesh silica gels. $^1$H and $^{13}$C NMR spectra were acquired on 400 and 500 MHz Bruker NMR instruments. NMR chemical shifts were reported in ppm and were referenced to TMS ($\delta = 0.00$ ppm, $^1$H NMR) or the residual solvent peak for CDCl$_3$ ($\delta = 7.26$ ppm, $^1$H NMR; $\delta = 77.16$ ppm, $^{13}$C NMR). Following abbreviations are used for multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants ($J$) are reported in Hertz.

All analytical LC-MS were performed to determine the distribution of hydrogen isotopes of the products on a Shimadzu LC-MS 2020 system equipped with Hedera C18 column (2.1 x 100 mm, 3 $\mu$m; heater set on 40 °C) involved a mobile phase of 0.1% formic acid (FA) in water (solvent A) and 0.1% formic acid (FA) in acetonitrile (solvent B) at a flow rate of 0.3 mL/min. All of the samples were tested over the same gradient: from 15 to 55% B in 3 min, then from 55 to 95% B in 7 min, and 95% B for 5 min, 0.1% FA, $\lambda = 254$ nm.

2. Synthesis of substrates

Note: 1a, 2k, 2l, 2m, 2n and 2o was obtained in commercial source. 1b, 1c, 1d, 1e and 1f were synthesized according to reported literature.$^1$ 2a, 2b, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 2j, 3a and 3b were synthesized according to reported methods.$^{2-8}$ The oxidation procedure was performed according to reported literature.$^9$ Typical synthesis procedures were described as following examples.

$$\text{Diethyl 2,6-diisopropyl-1,4-dihydropyridine-3,5-dicarboxylate (1e): Ethyl 4-methyl-3-oxopentanoate (1.58 g, 10 mmol), paraformaldehyde (0.15 g, 5 mmol) and ammonium acetate (0.58 g, 7.5 mmol) were added to a 25 mL flask, the resulting mixture was heated to 80 °C and stirred for 4 h at this temperature. The mixture was then cooled to room temperature and diluted by ethyl acetate (EA), and washed with brine. The organic layer was dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure after filtration. A silica gel chromatography was performed with PE/EA = 20:1 to afford a pale yellow solid 1e (0.76g, 49%).}$^{1}$$

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.68 (s, 1H), 4.08 (q, $J = 7.1$ Hz, 4H), 4.02 (p, $J = 7.0$ Hz, 2H), 3.18 (s, 2H), 1.20 (t, $J = 7.1$ Hz, 6H).
Hz, 6H), 1.04 (d, J = 7.2 Hz, 12H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.5, 153.4, 97.5, 59.5, 27.5, 25.1, 20.2, 14.4. LRMS (ESI+) m/z: 310.3 [M+H$^+$].

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (2a): To a solution of ethyl 3-aminocrotonate (0.65 g, 5 mmol), ethyl acetoacetate (0.65 g, 5 mmol) and the corresponding benzaldehyde (0.53 g, 5 mmol) in ethylene glycol (2 mL) was added TBAHS (Bu$_4$NHSO$_4$, 0.2 g, 0.6 mmol). The mixture was heated to 80 °C and stirred for 4 h. After complete consumption of the aldehyde monitored by TLC, the reaction was cooled to room temperature and diluted with EA. The solution was poured into a separatory funnel containing brine and extracted three times with EA. After drying over anhydrous Na$_2$SO$_4$, it was filtered and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel chromatography using PE/EA=6:1 as eluent to give 2a as a pale yellow solid (0.86 g, 52%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29 – 7.26 (m, 2H), 7.22 – 7.17 (m, 2H), 7.14 – 7.09 (m, 1H), 6.07 (s, 1H), 4.99 (s, 1H), 2.29 (s, 6H), 2.63 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.9, 147.9, 144.3, 128.0, 127.9, 126.2, 104.0, 59.8, 39.7, 19.5, 14.3. LRMS (ESI+) m/z: 330.3 [M+H$^+$].

Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (3d): 2m (1.73 g, 5 mmol), 10% Pd/C (20% weight of 2m, 0.35 g) and acetic acid(15mL) were added to a 50 mL flask. The resulting mixture was heated to 80°C and stirred for 4h. After completion of the reaction determined by TLC analysis, Pd/C was filtered off by celite. The filtrate was poured into saturated NaHCO$_3$ and extracted with EA for three times. The combined organic layers were washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvents were removed under reduced pressure and the crude mixture was purified by silica gel chromatography with PE/EA = 10:1 as eluent to afford pure product 3d as a pale yellow solid (0.86 g, 50%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.18 (dq, J = 8.4, 1.8 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.58 – 7.53 (m, 1H), 7.21 – 7.16 (m, 1H), 3.48 (s, 6H), 2.63 (s, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.3, 157.1, 147.7, 145.3, 133.0, 132.1, 130.7, 129.7, 124.9, 124.4, 52.3, 23.7. LRMS (ESI+) m/z: 345.2 [M+H$^+$].

3. General procedure 1 for HIE reactions
To a 10 mL Schlenk tube with a magnetic bar was added 1,4-dihydropyridines (0.2 mmol), D$_2$O (10 mmol, 181 μL), TFA-d (23 μL, 0.3 mmol (or 154 μL, 2 mmol)) and NMP (2 mL). The solution was freeze-dried in liquid nitrogen, then the vessel was evacuated and backfilled with nitrogen following by being warmed to room temperature. The operation was repeated for 3 cycles. The resulting mixture was stirred at 50 °C (or 70 °C) for 24 h (or 48 h), cooled to room temperature, diluted with EA and then washed with saturated NaHCO$_3$ and brine. The organic layer was dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo. The crude product was further purified by silica gel chromatography. Hydrogen isotope distribution of the products was determined by LC-MS. $^1$H NMR was performed to determine deuterium incorporation.


4.1 Condition optimization for deuteration of Hantzsch ester 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variations</th>
<th>D Incorporation$^b$ (%)</th>
<th>Yield$^c$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none$^a$</td>
<td>85$^d$</td>
<td>53(71$^e$)</td>
</tr>
<tr>
<td>2</td>
<td>no TFA-d</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>3 eq. TFA-d</td>
<td>82</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>RT</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>70°C</td>
<td>75</td>
<td>68$^e$</td>
</tr>
<tr>
<td>7</td>
<td>Air</td>
<td>45</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>degassed by N$_2$ purging</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>DMF as solvent</td>
<td>74</td>
<td>26</td>
</tr>
<tr>
<td>10</td>
<td>DMA as solvent</td>
<td>83</td>
<td>31</td>
</tr>
<tr>
<td>11</td>
<td>MeOH as solvent</td>
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<td>46</td>
</tr>
<tr>
<td>12</td>
<td>MeOD as solvent</td>
<td>75</td>
<td>45</td>
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</table>

$^a$ standard condition: 1a (0.2 mmol, 50.7 mg), D$_2$O (10 mmol, 181 μL), TFA-d (0.3 mmol, 23 μL), NMP (N-Methyl pyrrolidone, 2 mL), N$_2$, 50 °C for 24 h. $^b$ D incorporation determined by $^1$H NMR spectroscopy. $^c$ crude yield determined by $^1$H NMR spectroscopy. $^d$ an average of two parallel reactions. $^e$ isolated yield.

Note: The isolated yield was much higher as all materials were exposed to air during purification process. Absolutely no deuteration and little oxidation occurred when TFA-d was omitted, showing acid to be critical for both the D incorporation and oxidation process. Only 5% oxidation product was obtained as no acid was added. No other byproduct was detected during the experiments. We also tested the pH value
of the reaction system under standard conditions. The pH value was 2.42 as all reagents were well mixed and after 24 hours reaction it was 2.43. To our best knowledge, the oxidation of 1a involved unknown hydrogen transfer under heating and acidic conditions. More deeper studies are needed to get approach to the detailed mechanism. D incorporation did not change even the product was immersed in chloroform-\textit{d} for 3 days longer. To confirm the relationship between oxidation and deuteration, we performed the experiment under standard conditions with 1a' prepared previously\textsuperscript{9}, whereupon 85% D incorporation showed the deuteration and oxidation processes to be independent of one another.

### 4.2 Condition optimization for deuteration of nifedipine 2m

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variations</th>
<th>D Incorporation\textsuperscript{b} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 eq. TFA-\textit{d}, 50 °C, 24 h</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>3 eq. TFA-\textit{d}, 50 °C, 48 h</td>
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</tr>
<tr>
<td>3</td>
<td>6 eq. TFA-\textit{d}</td>
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</tr>
<tr>
<td>4</td>
<td>none\textsuperscript{a}</td>
<td>80\textsuperscript{c}</td>
</tr>
<tr>
<td>5</td>
<td>12 eq. TFA-\textit{d}</td>
<td>80</td>
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<tr>
<td>6</td>
<td>no TFA-\textit{d}, 24 h</td>
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</tr>
<tr>
<td>7</td>
<td>no D\textsubscript{2}O</td>
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</tr>
<tr>
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<td>25 eq. D\textsubscript{2}O</td>
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</tr>
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<td>150 eq. D\textsubscript{2}O</td>
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</tr>
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<td>10 eq. TFA</td>
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<td>12</td>
<td>10 eq. TfOH</td>
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</tr>
<tr>
<td>13</td>
<td>10 eq. BF\textsubscript{3}·OEt\textsubscript{2}</td>
<td>76</td>
</tr>
<tr>
<td>14</td>
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<td>30 eq. BF\textsubscript{3}·OEt\textsubscript{2}</td>
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<tr>
<td>17</td>
<td>150 h</td>
<td>79</td>
</tr>
</tbody>
</table>

\textsuperscript{a} standard condition: 2m (0.2 mmol, 69.3 mg), D\textsubscript{2}O (10 mmol, 181 μL), TFA-\textit{d} (2 mmol, 154 μL), NMP (N-Methyl pyrrolidone, 2 mL), N\textsubscript{2}, 70 °C for 48 h. \textsuperscript{b} D incorporation determined by \textsuperscript{1}H NMR spectroscopy. \textsuperscript{c} an average of two parallel reactions.
5. Deuteration of 1,4-dihydropyridines and derivatives

All of the deuteration procedure was done according to general procedure 1 with or without some variations.

**Diethyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1a′-d₆).**

1a (50.7 mg, 0.2 mmol) and TFA-d (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain 1a′-d₆ as a white solid (36.5 mg, 0.142 mmol, 71%, 85% D). The same result was obtained as 1a′ (50.3 mg, 0.2 mmol) and TFA-d (23 μL, 0.3 mmol) were used according to general procedure 1.

1H NMR (500 MHz, CDCl₃) δ 8.64 (s, 1H), 4.37 (q, J = 7.2 Hz, 4H), 2.82 - 2.76 (m, 0.9H), 1.39 (t, J = 7.1 Hz, 6H).

13C NMR (126 MHz, CDCl₃) δ 166.0, 162.3, 141.0, 123.2, 61.5, 24.9, 24.8, 24.7, 24.5, 24.4, 24.3, 24.2, 24.1, 14.4.

**Diisopropyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1b′-d₆).**

1b (56.3 mg, 0.2 mmol) and TFA-d (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain 1b′-d₆ as a white solid (40.4 mg, 0.142 mmol, 71%, 77% D).

1H NMR (500 MHz, CDCl₃) δ 8.59 (s, 1H), 5.24 (hept, J = 6.3 Hz, 2H), 2.82 - 2.76 (m, 1.4H), 1.37 (d, J = 6.3 Hz, 12H).

13C NMR (126 MHz, CDCl₃) δ 165.8, 161.8, 140.9, 123.8, 69.2, 24.9, 24.8, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2, 22.0.

**Di-tert-butyl 2,6-bis(methyl-d3)pyridine-3,5-dicarboxylate (1c′-d₆).**

1c (61.8 mg, 0.2 mmol) and TFA-d (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain 1c′-d₆ as a white solid (44.8 mg, 0.144 mmol, 72%, 81% D).

1H NMR (500 MHz, CDCl₃) δ 8.51 (s, 1H), 2.79 - 2.74 (m, 1.2H), 1.59 (d, J = 1.1 Hz, 18H).

13C NMR (126 MHz, CDCl₃) δ 165.6, 161.2, 140.9, 124.8, 82.2, 28.3, 25.0, 24.9, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2.

**Diethyl 2,6-bis(ethyl-1,1-d₂)pyridine-3,5-dicarboxylate (1d′-d₄).**

1d (28.1 mg, 0.1 mmol) and TFA-d (12 μL, 0.150 mmol) were used according to general procedure 1 to obtain 1d′-d₄ as a white solid (23.2 mg, 0.082 mmol, 82%, 71% D).

1H NMR (500 MHz, CDCl₃) δ 8.60 (s, 1H), 4.39 (q, J = 7.1 Hz, 4H), 3.22-3.13 (m, 1.2H), 1.41 (t, J = 7.1 Hz, 6H), 1.29 (d, J = 8.5 Hz, 6H).

13C NMR (126 MHz, CDCl₃) δ 167.0, 166.2, 141.4, 122.8, 61.6, 30.5, 30.2, 14.4, 14.0, 14.0, 13.9.

**Diethyl 2,6-bis(propan-2-yl-2-d)pyridine-3,5-dicarboxylate (1e′-d₂).**

1e (61.9 mg, 0.2 mmol) and TFA-d (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain 1e′-d₂ as a white solid (46.1 mg, 0.150 mmol, 75%, 19% D).

1H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1H), 4.37 (q, J = 7.1 Hz, 4H), 3.22 (q, J = 7.1 Hz, 4H), 2.69 - 2.57 (m, 1.2H), 1.37 (t, J = 7.1 Hz, 6H).
Hz, 4H), 3.86 (hept, J = 6.7 Hz, 1.6H), 1.39 (t, J = 7.1 Hz, 6H), 1.28 (d, J = 6.7 Hz, 12H).

\[ \text{1,1'-}(2,6-	ext{bis(methyl-d3)pyridine-3,5-diyl)bis(ethan-1-one-2,2,2-d3)} \] (1f'-d\(_{12}\)). 1f (38.7 mg, 0.2 mmol) and TFA-d (23 μL, 0.3 mmol) were used according to general procedure 1 to obtain 1f'-d\(_{12}\) as a pale yellow solid (26.0 mg, 0.128 mmol, 64%, 71% D, 61% D).

\[ \text{1H NMR (500 MHz, CDCl}_3 \text{)} \delta 8.23 (s, 1H), 2.77 – 2.71 (m, 1.7H), 2.62 – 2.57 (m, 2.4H). \]

\[ \text{13C NMR (126 MHz, CDCl}_3 \text{)} \delta 199.4, 160.4, 138.0, 130.3, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 28.8, 24.9, 24.8, 24.7, 24.6, 24.5, 24.4, 24.2. \]

Diethyl 2,6-bis(methyl-d3)-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (2a-d\(_{6}\)). 2a (65.9 mg, 0.2 mmol) and TFA-d (46 μL, 0.6 mmol) were used according to general procedure 1 to obtain 2a-d\(_{6}\) as a white solid (65.1 mg, 0.194 mmol, 97%, 77% D).

\[ \text{1H NMR (500 MHz, CDCl}_3 \text{)} \delta 7.30 – 7.26 (m, 2H), 7.20 (t, J = 7.7 Hz, 2H), 7.11 (td, J = 7.0, 1.4 Hz, 1H), 5.88 (s, 1H), 4.12 – 4.04 (m, 4H), 2.32 – 2.25 (m, 1.4H), 1.21 (t, J = 7.1 Hz, 6H). \]

\[ \text{13C NMR (126 MHz, CDCl}_3 \text{)} \delta 167.8, 147.9, 144.1, 128.1, 127.9, 126.2, 104.2, 59.8, 39.7, 19.5, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.7, 14.4. \]

Diethyl 4-(2-bromophenyl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2b-d\(_{6}\)). 2b (81.7 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2b-d\(_{6}\) as a pale yellow solid (81.2 mg, 0.196 mmol, 98%, 77% D).

\[ \text{1H NMR (500 MHz, CDCl}_3 \text{)} \delta 7.41 (dd, J = 8.0, 1.3 Hz, 1H), 7.37 (dd, J = 7.8, 1.8 Hz, 1H), 7.15 (td, J = 7.5, 1.3 Hz, 1H), 6.93 (ddd, J = 7.9, 7.2, 1.7 Hz, 1H), 6.07 (s, 1H), 5.35 (s, 1H), 4.09 (qd, J = 7.1, 4.7 Hz, 4H), 2.25 – 2.19 (m, 1.4H), 1.19 (t, J = 7.1 Hz, 6H). \]

\[ \text{13C NMR (126 MHz, CDCl}_3 \text{)} \delta 167.9, 147.6, 143.9, 143.9, 132.8, 131.7, 127.9, 126.2, 104.2, 59.8, 39.8, 19.5, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.8, 18.7, 18.6, 14.5. \]

Diethyl 2,6-bis(methyl-d3)-1,4-dihydro-[4,4'-bipyridine]-3,5-dicarboxylate (2c-d\(_{6}\)). 2c (66.1 mg, 0.2 mmol) and BF\(_3\)·OEt\(_2\) (494 μL, 4 mmol) were used according to general procedure 1 to obtain 2c-d\(_{6}\) as a pale yellow solid (63.9 mg, 0.190 mmol, 95%, 70% D).

\[ \text{1H NMR (500 MHz, CDCl}_3 \text{)} \delta 8.42 (d, J = 5.1 Hz, 2H), 7.24 – 7.21 (m, 2H), 6.50 (s, 1H), 5.00 (s, 1H), 4.13 – 4.05 (m, 4H), 2.34 – 2.27 (m, 1.8H), 1.21 (t, J = 7.1 Hz, 6H). \]

\[ \text{13C NMR (126 MHz, CDCl}_3 \text{)} \delta 167.3, 156.7, 149.1, 145.3, 145.3, 123.6, 102.7, 102.7, 60.1, 39.6, 19.5, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 14.4. \]

Diethyl 4-(furan-2-yl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate-1-d (2d-d\(_{7}\)). 2d (63.9 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2d-d\(_{7}\),
as a white solid (63.5 mg, 0.196 mmol, 98%, 81% D, -ND, 67% D). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.19 (dd, J = 1.8, 0.9 Hz, 0.3H), 6.23 – 6.16 (m, 1H), 6.03 (s, 1H), 5.92 (d, J = 3.2 Hz, 1H), 5.19 (s, 1H), 4.21 – 4.09 (m, 4H), 2.31 – 2.25 (m, 1.1H), 1.25 (t, J = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.7, 158.8, 158.7, 145.3, 140.9, 110.1, 109.9, 104.5, 100.8, 59.9, 33.5, 19.5, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.8, 18.7, 18.5, 14.4.

Diethyl 2,6-bis(methyl-d3)-4-(thiophen-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (2e-d$_6$). 2e (67.1 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2e-d$_6$ as a pale yellow solid (67.3 mg, 0.197 mmol, 99%, 82% D). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.11 (dd, J = 5.0, 3.1 Hz, 1H), 6.98 (dd, J = 5.0, 1.3 Hz, 1H), 6.91 (dd, J = 3.3, 1.3 Hz, 1H), 5.96 (s, 1H), 5.13 (s, 1H), 4.19 – 4.07 (m, 4H), 2.30 – 2.24 (m, 1.1H), 1.24 (t, J = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.8, 148.0, 144.6, 144.6, 127.7, 124.7, 120.4, 103.5, 103.5, 77.4, 77.2, 76.9, 59.9, 34.7, 19.4, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.7, 18.6, 14.4.

Diethyl 4-(4-hydroxy-3-methoxyphenyl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2f-d$_6$). 2f (75.1 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2f-d$_6$ as a white solid (75.4 mg, 0.198 mmol, 99%, 80% D). $^1$H NMR (500 MHz, CDCl$_3$) δ 6.84 (d, J = 1.6 Hz, 1H), 6.75 – 6.70 (m, 2H), 5.88 (s, 1H), 5.63 – 5.52 (m, 1H), 4.91 (s, 1H), 4.13 – 4.05 (m, 4H), 3.81 (s, 3H), 2.31 – 2.24 (m, 1.2H), 1.23 (t, J = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 167.9, 145.9, 144.0, 143.9, 143.8, 140.2, 120.5, 114.0, 111.0, 104.3, 104.3, 59.8, 55.8, 39.2, 19.5, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.8, 18.7, 14.4.

Diethyl 4-methyl-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2g-d$_6$). 2g (53.5 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2g-d$_6$ as a pale yellow solid (50.8 mg, 0.186 mmol, 93%, 77% D). $^1$H NMR (500 MHz, CDCl$_3$) δ 5.74 (s, 1H), 4.27 – 4.13 (m, 4H), 3.84 (q, J = 6.5 Hz, 1H), 2.28 – 2.21 (m, 1.4H), 1.30 (t, J = 7.1 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 168.0, 144.4, 104.8, 22.4, 19.5, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.8, 18.7, 14.6.

Diethyl 4-cyclohexyl-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2h-d$_6$). 2h (67.1 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2h-d$_6$ as a pale yellow solid (58.7 mg, 0.172 mmol, 86%, 80% D). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.04 (s, 1H), 4.24 – 4.05 (m, 4H), 3.89 (d, J = 5.7 Hz, 1H), 2.28 – 2.20 (m, 1.2H), 1.65 – 1.58 (m, 2H), 1.57 – 1.46 (m, 3H), 1.26 (t, J = 7.1 Hz, 6H), 1.17 (dq, J = 6.0, 3.0 Hz, 1H), 1.09 – 0.98 (m, 3H), 0.88 (qd, J = 13.6, 12.6, 5.1 Hz, 2H). $^{13}$C NMR (101
Diethyl 4-isopropyl-2,6-bis(methyl-d₃)-1,4-dihydropyridine-3,5-dicarboxylate (2i-d₆). 2i (59.1 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2i-d₆ as a white solid (53.0 mg, 0.176 mmol, 88%, 77% D). ¹H NMR (500 MHz, CDCl₃) δ 5.92 (s, 1H), 4.15 (ddq, J = 39.2, 10.8, 7.1 Hz, 4H), 3.89 (d, J = 5.5 Hz, 1H), 2.28–2.22 (m, 1.4H), 1.56 (pd, J = 6.9, 5.4 Hz, 1H), 1.27 (t, J = 7.1 Hz, 6H), 0.72 (d, J = 6.9 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 168.9, 144.8, 101.8, 59.7, 39.9, 35.6, 19.3, 19.2, 19.2, 19.1, 19.0, 18.9, 18.8, 18.6, 14.5.

Diethyl 2,6-bis(methyl-d₃)-4-(pentan-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (2j-d₆). 2j (64.7 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2j-d₆ as a white solid (55.4 mg, 0.168 mmol, 84%, 77% D). ¹H NMR (500 MHz, CDCl₃) δ 5.70 (s, 1H), 4.21–4.09 (m, 5H), 2.27–2.21 (m, 1.4H), 1.29 (t, J = 7.1 Hz, 6H), 1.14 (ddq, J = 20.9, 13.8, 7.1 Hz, 4H), 1.03 (qd, J = 6.5, 4.5 Hz, 1H), 0.85 (t, J = 7.3 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 168.9, 144.7, 102.3, 59.7, 50.0, 34.6, 21.3, 19.4, 19.3, 19.2, 19.1, 19.0, 18.8, 18.7, 18.6, 14.4, 11.9.

3-isobutyl 5-methyl 2,6-bis(methyl-d₃)-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2k-d₆). 2k (77.7 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2k-d₆ as a yellow solid (74.9 mg, 0.190 mmol, 95%, 79% D). ¹H NMR (500 MHz, CDCl₃) δ 7.67 (dd, J = 8.1, 1.3 Hz, 1H), 7.51 (dd, J = 7.9, 1.5 Hz, 1H), 7.44 (td, J = 7.6, 1.3 Hz, 1H), 7.22 (ddd, J = 8.5, 7.2, 1.5 Hz, 1H), 6.14 (s, 1H), 5.76 (s, 1H), 3.83–3.75 (m, 2H), 3.56 (s, 3H), 2.34–2.27 (m, 0.6H), 2.27–2.20 (m, 0.6H), 1.87 (dt, J = 13.5, 6.7 Hz, 1H), 0.76 (d, J = 6.7 Hz, 3H), 0.71 (d, J = 6.7 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 167.8, 167.5, 147.9, 145.1, 145.0, 142.5, 132.9, 131.2, 127.1, 124.1, 103.9, 103.5, 70.5, 51.1, 34.7, 27.6, 19.1.

3-isopropyl 5-(2-methoxyethyl) 2,6-bis(methyl-d₃)-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2l-d₆). 2l (83.7 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2l-d₆ as a pale yellow solid (79.8 mg, 0.188 mmol, 94%, 68% D). ¹H NMR (400 MHz, CDCl₃) δ 8.12 (t, J = 2.0 Hz, 1H), 7.98 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 7.65 (dt, J = 7.7, 1.4 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 6.04 (s, 1H), 5.08 (s, 1H), 4.93 (p, J = 6.2 Hz, 1H), 4.22–4.10 (m, 2H), 3.59–3.47 (m, 2H), 3.33 (s, 3H), 2.35–2.28 (m, 2H), 1.24 (d, J = 6.2 Hz, 3H), 1.07 (d, J = 6.2 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 167.2, 166.7, 150.1, 148.2, 145.3, 144.5, 134.8, 128.7, 123.4, 121.4, 104.0, 103.1, 70.6, 67.4, 63.1, 59.0, 40.1, 22.2, 21.9, 19.6, 19.5, 19.4, 19.4, 19.3, 19.2, 19.1, 19.0.
Dimethyl 2,6-bis(methyl-d3)-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2m-d6). 2m (69.3 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2m-d6 as a yellow solid (67.7 mg, 0.192 mmol, 96%, 79% D). 1H NMR (500 MHz, CDCl3) δ 7.65 (dd, J = 8.1, 1.3 Hz, 1H), 7.50 (dd, J = 7.9, 1.5 Hz, 1H), 7.44 (td, J = 7.6, 1.4 Hz, 1H), 7.23 (ddd, J = 8.4, 7.2, 1.5 Hz, 1H), 6.15 (s, 1H), 5.70 (s, 1H), 3.57 (s, 6H), 2.32 – 2.23 (m, 1.3H).

13C NMR (126 MHz, CDCl3) δ 167.7, 147.9, 145.2, 145.2, 142.3, 132.9, 131.1, 127.1, 124.0, 103.6, 103.6, 51.1, 34.6, 19.4, 19.3, 19.2, 19.1, 19.0, 18.9, 18.8, 18.8, 18.7, 18.6.

3-ethyl 5-methyl 2-((2-aminoethoxy)methyl-d2)-4-(2-chlorophenyl)-6-(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2n-d5). Amlodipine besylate (113.4 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2n-d5 as a white solid (79.9 mg, 0.194 mmol, 97%, 80% D, 77% D). 1H NMR (500 MHz, CDCl3) δ 7.78 (s, 1H), 7.37 (dd, J = 7.8, 1.7 Hz, 1H), 7.20 (dd, J = 8.0, 1.4 Hz, 1H), 7.11 (td, J = 7.5, 1.4 Hz, 1H), 7.01 (td, J = 7.5, 1.7 Hz, 1H), 5.38 (s, 1H), 5.07 (s, 2H), 4.81 – 4.67 (m, 0.5H), 4.07 – 3.96 (m, 2H), 3.68 (hept, J = 5.2 Hz, 2H), 3.58 (s, 3H), 3.09 (t, J = 4.7 Hz, 2H), 2.33 (d, J = 11.0 Hz, 0.6H), 1.16 (t, J = 7.2 Hz, 3H). 13C NMR (126 MHz, CDCl3) δ 168.3, 167.4, 145.9, 145.2, 145.1, 145.1, 144.8, 132.4, 131.6, 129.3, 127.5, 127.0, 103.8, 102.2, 102.2, 102.1, 70.0, 68.2, 60.0, 50.9, 40.5, 37.3, 18.7, 14.3.

Diethyl (E)-4-(2-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)phenyl)-2,6-bis(methyl-d3)-1,4-dihydropyridine-3,5-dicarboxylate (2o-d6). 2o (91.1 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 2o-d6 as a white solid (89.5 mg, 0.194 mmol, 97%, 80% D). 1H NMR (500 MHz, CDCl3) δ 8.44 (d, J = 15.8 Hz, 1H), 7.46 (dd, J = 7.9, 1.4 Hz, 1H), 7.40 (dd, J = 7.9, 1.3 Hz, 1H), 7.23 (td, J = 7.6, 1.4 Hz, 1H), 7.10 (td, J = 7.6, 1.4 Hz, 1H), 6.25 (d, J = 15.9 Hz, 1H), 5.99 (s, 1H), 5.32 (s, 1H), 4.05 (dq, J = 10.8, 7.2 Hz, 2H), 3.93 (dq, J = 10.8, 7.1 Hz, 2H), 2.31 – 2.24 (m, 1.2H), 1.53 (s, 9H), 1.13 (t, J = 7.1 Hz, 6H). 13C NMR (126 MHz, CDCl3) δ 167.6, 166.8, 148.5, 144.3, 144.3, 143.9, 132.0, 130.6, 130.1, 126.5, 125.5, 120.2, 104.7, 104.6, 80.2, 59.8, 35.8, 28.4, 19.2, 19.1, 19.0, 18.9, 18.8, 18.6, 14.4.

6. Controlled experiments

3c and 3d were oxidated according to general procedure 3 and then deuterated according to general procedure 1 using 10 eq TFA-d. Deuteration of 3e, 3f, 3g and 3h were operated according to general procedure 1 in CH2Cl2 and 1.5eq TFA-d was used for each reaction. When CH2Cl2 was used as the solvent, the reaction mixture was degassed by N2 gently purging the vial for 3 minutes. After 24 h reaction under 50°C,
cool to RT. CDCl$_3$ was added to dilute the mixture and $^1$H NMR was done without further purification to determine D incorporation. 3e and 3f were rarely deuterated after reaction. 3g was deuterated in 17% D content.

2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarbonitrile (3a-d$_6$). 3a (47.1 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1. No D incorporation was found. 3a was 98% recovered.

Diethyl 4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (3b-d$_6$). 3b (60.3 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1. No D incorporation was found. 3b was 92% recovered.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36 – 7.33 (m, 2H), 7.29 – 7.23 (m, 4H), 7.18 – 7.11 (m, 2H), 4.89 (s, 1H), 4.14 – 4.00 (m, 5H), 1.19 (t, $J$ = 7.2 Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.5, 147.1, 134.2, 128.3, 128.0, 126.5, 108.1, 60.1, 37.7, 14.2.

Diethyl 2,4,6-tris(methyl-d3)pyridine-3,5-dicarboxylate (3c-d$_6$). 3c (53.1 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 3c-d$_6$ as a colorless oil (53.8 mg, 0.196 mmol, 98%, 70% D, 78% D). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.38 (q, $J$ = 7.1 Hz, 4H), 2.50 – 2.44 (m, 1.8H), 2.24 – 2.20 (m, 0.7H), 1.36 (t, $J$ = 7.1 Hz, 6H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.4, 155.0, 142.2, 127.7, 61.7, 23.0, 22.9, 22.8, 22.7, 22.6, 22.5, 22.4, 22.3, 22.2, 22.2, 17.0, 16.9, 16.8, 16.7, 16.7, 16.6, 16.4, 16.3, 16.3, 16.2, 14.3.

Dimethyl 2,6-bis(methyl-d3)-4-(2-nitrophenyl)pyridine-3,5-dicarboxylate (3d-d$_6$). 3d (68.9 mg, 0.2 mmol) and TFA-d (154 μL, 2 mmol) were used according to general procedure 1 to obtain 3d-d$_6$ as a white solid (68.0 mg, 0.194 mmol, 97%, 78% D). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.18 (dd, $J$ = 8.1, 1.3 Hz, 1H), 7.62 (td, $J$ = 7.5, 1.4 Hz, 1H), 7.55 (ddd, $J$ = 8.9, 7.6, 1.5 Hz, 1H), 7.18 (dd, $J$ = 7.5, 1.5 Hz, 1H), 3.48 (s, 6H), 2.64 – 2.59 (m, 1.3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 167.3, 157.1, 145.3, 133.0, 132.1, 130.7, 129.7, 124.9, 124.4, 52.3, 23.6, 23.5, 23.5, 23.4, 23.3, 23.2, 23.1, 23.1, 23.0, 22.9, 22.8.

Ethyl 3-iminobutanoate-2,2,4,4,4-d$_5$ (3h’-d$_5$). 3h (12.9 mg, 0.1 mmol), TFA-d (23 μL, 0.3 mmol), D$_2$O (90 μL, 5 mmol) and CH$_2$Cl$_2$ (1 mL) were added in a 10 mL schlenk tube. N$_2$ purged the headspace of the vial for 3 minutes following by tightly sealed. The reaction mixture was heated at 50°C for 24 h. Cool to room temperature and dilute with 1 mL CDCl$_3$ directly for $^1$H NMR. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 4.16 (q, $J$ = 7.1 Hz, 2H), 3.43 – 3.40 (m, 0.1H), 2.23 (s, 2.3H), 1.24 (t, $J$ = 7.1 Hz, 3H).

Research on reversibility of HIE reaction. 2m-d$_6$ (35.2 mg, 0.1 mmol), H$_2$O (90 μL, 5 mmol), TFA (75 μL, 1 mmol) and NMP were added in a 10 mL schlenk tube. The mixture
was then treated according to general procedure 1 and reacted at 70°C for 48 h. After general work-up and purification, $^1$H NMR was done to show the D incorporation decreased to 12% which meant the HIE reaction was reversible to a great extent. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.67 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.50 (dd, $J = 7.9, 1.5$ Hz, 1H), 7.45 (td, $J = 8.0, 7.6, 1.4$ Hz, 1H), 7.29 – 7.21 (m, 2H), 5.78 (s, 1H), 5.72 (s, 1H), 3.59 (s, 6H), 2.34 (s, 5.3H).

7. References

8. NMR spectra

1a’ (oxidative product of 1a)
1a'-d₆ (reaction for 36h, mixture, 1a'-d₆:1a-d₆=4:1)
$1b' \cdot d_6$
$1c'\text{-}d_6$
$1e'\cdot d_2$
2a-d6
2b-d$_6$
2d-d$_7$
2i-d$_6$

![Chemical Structure Image](image)

![NMR Spectra Image](image)
2k-d₆
21-d₆
$2n-d_5$
3g-d₁(crude)

3g
3h'-d₅ (crude)

3h + CH₂Cl₂ + TFA
$3h + \text{CH}_2\text{Cl}_2$
9. LC-MS spectra

1a'-d$_6$

1b'-d$_6$
**2i-d₆**

**2j-d₆**