Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes

Florian Bourriquen, Kathrin Junge, Matthias Beller.
Affiliations below.
DOI: 10.1055/a-1992-6596

Please cite this article as: Bourriquen F, Junge K, Beller M. Homogenous iron-catalysed deuteration of electron-rich arenes and heteroa- renes. Synlett 2022. doi: 10.1055/a-1992-6596

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by European Unions Horizon 2020 research and innovation program, 862179

Abstract:
Deuterated organic molecules are of interest for many applications ranging from mechanistic investigations in basic organic and physical chemistry to the development of new pharmaceuticals. Thus, methodologies for isotope labelling reactions continue to be important. Here, a convenient methodology for hydrogen/deuterium exchange reactions in electron-rich arenes is reported using simple iron salts and deuterium oxide as isotope source.

Corresponding Author:
Matthias Beller, Leibniz Institut für Katalyse, Angewandte Homogene Katalyse, Albert-Einstein-Strasse 29a, 18059 Rostock, Germany, Matthias.Beller@catalysis.de

Affiliations:
Florian Bourriquen, Leibniz-Institut für Katalyse eV, Angewandte Homogenkatalyse, Rostock, Germany
Kathrin Junge, LIKAT, Catalysis, Rostock, Germany
Matthias Beller, Leibniz Institut für Katalyse, Angewandte Homogene Katalyse, Rostock, Germany
Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes

Florian Bourriquen
Kathrin Junge*
Matthias Beller*
Leibniz-Institut für Katalyse e.V. Albert-Einstein-Straße 29a, 18059 Rostock (Germany)
kathrin.junge@catalysis.de
matthias.beller@catalysis.de

Abstract Deuterated organic molecules are of interest for many applications ranging from mechanistic investigations in basic organic and physical chemistry to the development of new pharmaceuticals. Thus, methodologies for isotope labelling reactions continue to be important. Here, a convenient methodology for hydrogen/deuterium exchange reactions in electron-rich arenes is reported using simple iron salts and deuterium oxide as isotope source.

Key words catalysis, deuterium, heavy water, isotopic labelling, Lewis Acid.

Procedures for deuterium incorporation in organic molecules continue to attract the interest of many chemists. Indeed, deuterium labelled compounds are well known as standards in mass spectrometry\(^1\) and are of interest in materials sciences to improve properties of polymers.\(^2\) Organic Light-Emitting Diodes (OLEDs)\(^3\) and fluorophores.\(^4\) Regarding life science applications,\(^5\) in medicinal chemistry the exchange of hydrogen atoms by its stable isotope deuterium not only permits improved absorption, distribution, metabolism, and excretion (ADME) properties of potential drug candidates, but it is also a useful technique to follow metabolic pathways during the drug discovery process.\(^6\) Attesting the importance given to labelled compounds, three of them were recently authorised as medications for human use. Deuterabenazine has first been approved in 2017 by the American Food and Drug Administration (FDA) for the treatment of chorea associated with Huntington’s disease,\(^7\) followed by donafenib in China for the treatment of unresectable hepatocellular carcinoma (Figure 1).\(^8\) Earlier this year, the third one was deucravactinib, approved by the FDA for the treatment of plaque psoriasis.\(^9\)

In order to introduce deuterium atoms in organic molecules, numerous approaches are feasible.\(^10\) Simple by conception yet challenging by implementation, hydrogen-isotope exchange (HIE) reactions are among the most desirable techniques for the labelling of organic molecules. Prevalent for numerous years, iridium-catalysed HIE procedures are now supplemented by base-metal catalysis,\(^11\) notably with the use of iron\(^12\) and

![Diagram of deuterated compound](image-url)

**Figure 1** Selected applications of deuterated compounds: structures of marketed deuterated pharmaceuticals; SD-P3HT and poly-cyclooctene-d\(^{14}\) (poly-COE-d\(^{14}\)) as deuterated materials.
nickel\textsuperscript{13} molecularly defined complexes. Similarly, photocatalytic\textsuperscript{14} and electrocatalytic\textsuperscript{15} labelling reactions are on the rise. In addition, the use of supported catalysts becomes important in the field of HIE, with reports utilising ruthenium,\textsuperscript{16} iridium,\textsuperscript{17} palladium,\textsuperscript{18} rhodium,\textsuperscript{19} iron\textsuperscript{20} and manganese\textsuperscript{21} nanoparticles. Another trend in HIE reactions is the use of Frustrated Lewis Pairs (FLP) and Lewis acids (LA) for the incorporation of deuterium atoms in electron-rich arenes and heteroaranes. In this respect, Werner and co-workers showed the efficacy of tris(pentafluorophenyl)borane \((B(C_{6}F_{5}))_{3}\) for the labelling of electron-rich arenes and heteroarenes in 2017.\textsuperscript{22} More recently, Gong and Hao described a similar reactivity of Ag(O Tf))\textsuperscript{23}. Interestingly, both systems use CD\textsubscript{3}D and D\textsubscript{2}O as practical and -relatively- inexpensive solvent mixture and isotope source. Interested in the development of new methodologies for deuterium labelling, we envisioned the use of other Lewis Acids as practical and accessible catalysts to complement the already reported investigations\textsuperscript{24}. We initiated our investigations with the testing of several metal triflate salts for the labelling of 1,2,3,4-tetrahydroquinoline as model substrate. Surprisingly, except for Mg(O Tf)\textsubscript{2}, all the tested catalysts showed activity and allowed a deuterium content >70% at both the ortho- and para-position.

We applied the reaction conditions of our previous work\textsuperscript{2} (Table 1) to demonstrate the described activity. Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), Fe(O Tf)\textsubscript{3} (2.5–0.1 mol%), CH\textsubscript{3}CN (1 mL), 90°C, 18 h. \textsuperscript{4} D\textsubscript{2}O (1 mL) instead of CH\textsubscript{3}CN.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fe(O Tf)\textsubscript{3} (X eq.)</th>
<th>D\textsubscript{2}O (Y eq.)</th>
<th>ortho D (%)</th>
<th>para D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>20</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>50</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>10</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>1.25</td>
<td>10</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>1.25</td>
<td>20</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>1.25</td>
<td>50</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>10</td>
<td>83</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>0.5</td>
<td>20</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>0.5</td>
<td>50</td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>10\textsuperscript{a}</td>
<td>0.5</td>
<td>Solvent</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>0.1</td>
<td>20</td>
<td>33</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>0.1</td>
<td>50</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>13</td>
<td>0.1</td>
<td>100</td>
<td>30</td>
<td>54</td>
</tr>
<tr>
<td>14\textsuperscript{a}</td>
<td>0.1</td>
<td>Solvent</td>
<td>5</td>
<td>16</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), Fe(O Tf)\textsubscript{3} (2.5–0.1 mol%), CH\textsubscript{3}CN (1 mL), 90°C, 18 h. \textsuperscript{4} D\textsubscript{2}O (1 mL) instead of CH\textsubscript{3}CN.

In addition, both systems use CD\textsubscript{3}D and D\textsubscript{2}O as practical and relatively inexpensive solvent mixture and isotope source. Interested in the development of new methodologies for deuterium labelling, we envisioned the use of other Lewis Acids as practical and accessible catalysts to complement the already reported investigations\textsuperscript{24}. We initiated our investigations with the testing of several metal triflate salts for the labelling of 1,2,3,4-tetrahydroquinoline as model substrate. Surprisingly, except for Mg(O Tf)\textsubscript{2}, all the tested catalysts showed activity and allowed a deuterium content >70% at both the ortho- and para-position.

We applied the reaction conditions of our previous work\textsuperscript{2} (Table 1) to demonstrate the described activity. Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), Fe(O Tf)\textsubscript{3} (2.5–0.1 mol%), CH\textsubscript{3}CN (1 mL), 90°C, 18 h. \textsuperscript{4} D\textsubscript{2}O (1 mL) instead of CH\textsubscript{3}CN.

<table>
<thead>
<tr>
<th>Entry</th>
<th>D\textsubscript{2}O (X eq.)</th>
<th>ortho D (%)</th>
<th>para D (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>80</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>33</td>
<td>36</td>
</tr>
</tbody>
</table>

Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), Fe(O Tf)\textsubscript{3} (0.5 mol%), CH\textsubscript{3}CN (2 mL), 130°C, 1 h.

\textsuperscript{1} Relative to the nitrogen (Figure 2). In addition, in presence of D\textsubscript{2}O the labile N–H is exchanged to a N–D bond. However, aqueous work-up after the reaction the N–H bond is regenerated. Under the applied reaction conditions, Fe(O Tf)\textsubscript{3} was identified as the most active LA, which was also applied in different solvents and at various temperatures (see SI for details). In general, a reaction temperature of 90°C was crucial for the success of this methodology. Then, we examined the effect of the variation the catalyst loading and quantity of D\textsubscript{2}O for our model reaction. Using 2.5 mol% catalyst, the deuterium content is increased to >95% at both the ortho- and para-position with 50 eq. of deuterium oxide, highlighting the possibility to reach high deuterium incorporation using this methodology. On the opposite, using only 10 eq. of heavy water lowered the deuterium incorporation (Table 1, entries 1–3). Comparable results were obtained using half of this catalyst loading (Table 1, entries 4–6). The limit of our catalytic system was reached using 0.5 mol% Fe(O Tf)\textsubscript{3} (Table 1, entries 7–10). Applying this low catalyst loading, 92% and 93% deuterium incorporation are detected at the ortho- and para-positions, respectively (Table 1, entry 8), which are not increased by performing the reaction in CD\textsubscript{3}CN. Interestingly, the labelling is not increased with 50 eq. of D\textsubscript{2}O. Using 0.1 mol% of Fe(O Tf)\textsubscript{3} or D\textsubscript{2}O as solvent showed poor deuterium incorporation, possibly due to solubility issues. Considering the higher deuterium enrichment at the para-position compared to the ortho, we subsequently monitored a kinetic profile for our model reaction. As can be seen in Figure 3, the deuterium incorporation at the para-position takes place more rapidly than at the ortho-position.

![Figure 2](image_url) Evaluation of various Lewis Acids for the deuterium labelling of 1,2,3,4-tetrahydroquinoline. Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), Lewis Acid (2.5 mol%), D\textsubscript{2}O (20 eq. 180 μL), CH\textsubscript{3}CN (1 ml), 90°C, 18 h.

![Figure 3](image_url) Kinetic profile for the deuterium labelling of 1,2,3,4-tetrahydroquinoline.
This phenomenon can be explained by the higher stability of Wheland intermediates at the *para*-position of amines compared to the *ortho*-position.\(^{25}\) Furthermore, a reaction time of 18 h proved to be necessary to achieve high deuterium contents. Besides deuterium incorporation, tritium enrichment is a complementary subject of interest in isotopic labelling.\(^{5, 12a, 13-14, 26}\) Inherent to the radioactive nature of tritium, high reaction rates, short reaction times and the use of small quantities of the isotope source is highly desirable. Thus, we explored this methodology at higher temperature (130 °C) for one hour and observed a deuterium content superior to 80% using 20 eq. of deuterium oxide (Table 2). Pleasingly, only 2 equivalents of D\(_2\)O are sufficient to induce a labelling >50%.

The scope of this methodology was investigated under our optimal reaction conditions (Table 1, entry 8) and is represented in Scheme 1. Gratifyingly, high deuterium incorporation is achievable in a number of indoles substrates, preferentially but not limited to the C3 position. Electron-donating substituents such as methoxy (2c) or amine (2e) increase the overall labelling by permitting isotope incorporation on the benzene ring, whereas withdrawing ones such as the methyl ester in 2d allow high deuterium content specifically at C3. Under these conditions, other common N-containing heterocycles imidazole (2g) and benzimidazole (2h) provided a high deuterium content (97%) at the C2 position. Similarly, pyrrole 2i showed a D enrichment of 95%. When anilines were subjected to our methodology, good to high deuterium incorporation was observed (2j–2l). Deuterium content in natural terpenoid 2m is lower (19% in *ortho*, 41% in *para*), possibly due to the reduced electron-donating properties of phenols in comparison with anilines. Finally, 1,3,5-trimethoxybenzene 1n provided the corresponding deuterated product with 92% D. Besides model substrates, the applicability of this methodology is showcased with the labelling of natural products and pharmaceuticals (Figure 4). Pleasingly, under our standard reaction conditions, high deuterium incorporation was detected in resveratrol 2o. Moreover, human hormone melatonin (2p) is efficiently labelled at the 2-, 4- and 6-positions. Other relevant substrates labelled by this methodology are the dye coumarin 1 (2q), even though with a limited deuterium incorporation for this electron-deficient compound, and alkaloid papaverine (2r). In this latter case, the activated methylene group alpha to the nitrogen is the sole deuterated position as already reported in previous Lewis Acid-based methodologies.\(^{23}\)

In conclusion, we demonstrate that relatively simple, commercially available Lewis Acids can be used for deuterium incorporation in electron-rich positions of arenes and heteroarenes. In particular, Fe(OTf)\(_3\) shows good activity and allows for the labelling of a variety of model substrates as well
as natural products, dyes, and commercial medications. All these labelling reactions are possible using D₂O as the most available deuterium source.

**Funding Information**

This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 862179.

**Acknowledgment**

We thank the LIKAT analytical department for excellent service. We thank Sara Kopf (LIKAT) for constructive discussions.

**Supporting Information**

YES (this text will be updated with links prior to publication)

**Primary Data**

NO.

**Conflict of Interest**

The authors declare no conflict of interest.

**References and Notes**


Supporting Information

Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes

Florian Bourriquen, Kathrin Junge* and Matthias Beller*

Kathrin Junge – kathrin.junge@catalysis.de

Matthias Beller – matthias.beller@catalysis.de
1. General information

All reagents were purchased from various chemical suppliers and were used without previous purification.

$^1$H NMR and $^{13}$C NMR spectra were recorded on an AV-300, or Fourier-300 Bruker spectrometer. All chemical shifts (δ) are reported in parts per million (ppm) downfield of tetramethylsilane and coupling constants (J) in hertz (Hz). The residual solvent signals were used as references for $^1$H and $^{13}$C NMR spectra (CDCl$_3$: δH = 7.26 ppm, δC = 77.16 ppm or DMSO-d$_6$: δH = 2.50 ppm, δC = 39.52 ppm).

2. Determination of deuterium content

Starting material and deuterated product were analysed by NMR using the same deuterated solvent. The spectra were referenced using the residual solvent signal, then the integration of the signals was realised on the unlabelled starting material. Note that the calibration was performed against signals which do not undergo H/D exchange, typically methyl or methoxy signals. The same integration areas were applied to the deuterated product spectra, and calibration of the integration was carried out on the same signal.

Deuterium content was calculated by the decrease of the area of a specific signal, using the following formula, where $A_{substrate}$ is the area in the substrate spectra and $A_{product}$ is the area in the product spectra:

$$D = 1 - \frac{A_{product}}{A_{substrate}}$$

This calculated deuterium content for a given position is indicated in green circles.

Remarks:

- Overall deuterium incorporation in the product was verified by mass analysis.
- Position of the deuterium incorporation was confirmed by $^{13}$C NMR.
- Absence of deuterium incorporation at the position used as calibration was confirmed by $^{13}$C NMR.
3. General procedure

A flame-dried 25 mL Schlenk flask was charged in the glovebox with Fe(OTf)$_3$ (90%, 14 mg). The Schlenk was closed, and dry acetonitrile (10 mL) was added under inert atmosphere.

A 4 mL glass vial was charged with a Teflon-coated stir bar, the substrate (0.5 mmol), Fe(OTf)$_3$ (1 mL from the stock solution) and D$_2$O (180 μL, 20 eq.). The reaction mixture was stirred overnight at 90 °C in an aluminium bloc. After return to room temperature, the media was diluted with EtOAc (2 mL) and a saturated aqueous NaHCO$_3$ solution (1 mL). The aqueous phase was further extracted with EtOAc (3 x 2 mL). The combined organic phases were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Obtained products were submitted for NMR analyses to determine the deuterium content.

4. Optimisation of reaction conditions

Table S1. Solvent screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ortho D [%]</th>
<th>Para D [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,4-dioxane</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexane</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>CH$_2$Cl$_2$</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>CH$_3$CN</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>DCE</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>CHCl$_3$</td>
<td>88</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>PrOH</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>toluene</td>
<td>89</td>
<td>84</td>
</tr>
</tbody>
</table>

Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), Fe(OTf)$_3$ (2.5 mol%), solvent (1 mL), D$_2$O (20 eq., 180 μL), 90 °C, 18 h.

Table S2. Temperature screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature [°C]</th>
<th>Catalyst loading [mol %]</th>
<th>Ortho D [%]</th>
<th>Para D [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>0.5</td>
<td>26</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>1</td>
<td>45</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>0.5</td>
<td>49</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>1</td>
<td>74</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>0.5</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>1.25</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Reaction conditions: 1,2,3,4-tetrahydroquinoline (0.5 mmol), Fe(OTf)$_3$, CH$_3$CN (1 mL), D$_2$O (20 eq., 180 μL), 18 h.
5. Unreactive substrates

The Figure S1 presents a selection of substrates tested under our standard reaction conditions that did not lead to deuterium incorporation.

![Diagram of unreactive compounds](image)

**Figure S1.** Selected unreactive compounds.
6. Product characterisation

1,2,3,4-tetrahydroquinoline-6,8-d$_2$ 2a

The general deuteration procedure was followed with 1,2,3,4-tetrahydroquinoline (65.5 mg) as substrate. The title compound was isolated as a brown oil (73.5 mg, qt.).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.07 – 6.96 (m, 2H), 6.66 (t, $J = 7.4$ Hz, 7% $^1$H, 1H), 6.58 – 6.44 (m, 8% $^1$H, 1H), 3.81 (s, 1H), 3.38 – 3.29 (m, 2H), 2.82 (t, $J = 6.4$ Hz, 2H), 2.06 – 1.91 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 144.8, 129.4 (m), 126.5 (m), 121.5, 116.7 (m), 113.9 (m), 42.0, 27.0, 22.2.

ES-MS (m/z) calculated for C$_{9}$H$_{9}$D$_{2}$N: 135; observed: 135 (81), 134 (100), 133 (29), 132 (18), 131 (7), 120 (27), 106 (11), 93 (7), 79 (10), 66 (6).

1-methyl-1H-indole-2,3-d$_2$ 2b

The general deuteration procedure was followed with 1-methyl-1H-indole (65.4 mg) as substrate. The title compound was isolated as a brown oil (73.5 mg, qt.).

$^1$H NMR (300 MHz, DMSO) δ 7.55 (ddd, $J = 7.8$, 1.3, 0.8 Hz, 1H), 7.42 (dt, $J = 8.2$, 0.9 Hz, 1H), 7.30 (s, 1H), 7.14 (ddd, $J = 8.2$, 7.0, 1.3, 0.4 Hz, 1H), 7.02 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 1H), 6.42 (ddd, $J = 3.1$, 0.9 Hz, 3% $^1$H, 1H), 3.77 (s, 3H).

$^{13}$C NMR (75 MHz, DMSO) δ 136.4, 129.4, 127.9, 121.0, 120.3, 118.9, 109.6, 32.4.

ES-MS (m/z) calculated for C$_{9}$H$_{8}$DN: 132; observed: 132 (27), 131 (100), 130 (74), 116 (7), 103 (9), 89 (13), 77 (9).

4-methoxy-1H-indole-3,5,7-d$_3$ 2c

The general deuteration procedure was followed with 4-methoxy-1H-indole (73.8 mg) as substrate. The title compound was isolated as an off-white solid (78.3 mg, qt.).

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.13 (s, 1H), 7.17 (d, $J = 3.6$ Hz, 1H), 7.09 (q, $J = 1.5$ Hz, 1H), 7.03 (dt, $J = 8.2$, 0.5 Hz, 18% $^1$H, 1H), 6.83 – 6.65 (m, 54% $^1$H, 1H), 6.60 (d, $J = 7.8$ Hz, 18% $^1$H, 1H), 4.01 (s, 3H).

F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 153.4, 137.3, 122.7 (m), 122.6 (m), 118.6, 104.6, 99.8, 99.6 (m), 55.4.

ESI-HRMS (m/z) calculated for C\(_9\)H\(_9\)DO ([M+H]\(^+\)): 149.0825; observed: 149.0831.

(m/z) calculated for C\(_9\)H\(_8\)D\(_2\)NO ([M+H]\(^+\)): 150.0888; observed: 150.0887.

methyl 1H-indole-6-carboxylate-3-\(d\)2d

The general deuteration procedure was followed with methyl 1H-indole-6-carboxylate (87.7 mg) as substrate. The title compound was isolated as an off-white solid (94.8 mg, qt).

\(^1\)H NMR (300 MHz, DMSO) \(\delta\) 11.52 (s, 1H), 8.16 (dd, \(J = 1.4, 0.8\) Hz, 1H), 7.71 – 7.61 (m, 2H), 7.61 – 7.57 (m, 1H), 6.55 (dd, \(J = 3.0, 2.0, 1.0\) Hz, 5\% \(^1\)H, 1H), 3.86 (s, 3H).

\(^{13}\)C NMR (75 MHz, DMSO) \(\delta\) 167.4, 135.2 (m), 131.3 (m), 129.2 (m), 122.1, 119.8, 119.6, 113.6 (m), 101.4 (m), 51.7.

ES-MS (m/z) calculated for C\(_{10}\)H\(_8\)DN\(_2\) ([M+H]\(^+\)): 176; observed: 176 (23), 175 (75), 145 (31), 144 (100), 117 (16), 116 (52), 89 (20).

2-methyl-1H-indol-3,4,6-\(d\)3-5-amine 2e

The general deuteration procedure was followed with 2-methyl-1H-indol-5-amine (73.4 mg) as substrate. The title compound was isolated as a brown solid (62.5 mg, 85\%).

\(^1\)H NMR (300 MHz, DMSO) \(\delta\) 10.35 (s, 1H), 7.03 – 6.84 (m, 1H), 6.40 (d, \(J = 8.4\) Hz, 82\% \(^1\)H, 1H), 5.97 – 5.79 (m, 22\% \(^1\)H, 1H), 4.33 (s, 2H), 2.31 (s, 3H).

\(^{13}\)C NMR (75 MHz, DMSO) \(\delta\) 140.8, 140.7, 140.6, 135.0, 134.9, 130.0, 129.8, 129.5, 129.4, 110.5, 110.4, 102.9, 98.0, 13.5.

ESI-HRMS (m/z) calculated for C\(_{10}\)H\(_{10}\)DN\(_2\) ([M+H]\(^+\)): 148.0985; observed: 148.0982.

(m/z) calculated for C\(_{10}\)H\(_{10}\)D\(_2\)N\(_2\) ([M+H]\(^+\)): 149.1048; observed: 149.1040.

1-methyl-2-phenyl-1H-indole-3-\(d\)2f
The general deuteration procedure was followed with 1-methyl-2-phenyl-1H-indole (104.6 mg) as substrate. The title compound was isolated as an off-white solid (102.6 mg, 98%).

\( ^1H \) NMR (300 MHz, DMSO) \( \delta \) 7.69 – 7.37 (m, 7H), 7.20 (ddd, \( J = 8.3, 7.0, 1.3 \) Hz, 1H), 7.12 – 7.03 (m, 1H), 6.57 (d, \( J = 0.9 \) Hz, 3\% \( ^1H \), 1H), 3.73 (s, 3H).

\( ^{13}C \) NMR (75 MHz, DMSO) \( \delta \) 140.9, 138.1, 132.2, 129.0, 128.6, 127.9, 127.3, 121.4, 120.0, 119.6, 110.1, 31.1.

ESI-HRMS (m/z) calculated for C\(_{15}\)H\(_{11}\)DN ([M+H]\(^+\)): 207.10270; observed: 207.10341.

**1-(4-methoxyphenyl)-1H-imidazole-2-d\(_2\)g**

The general deuteration procedure was followed with 1-(4-methoxyphenyl)-1H-imidazole (87.3 mg) as substrate. The title compound was isolated as a white solid (96.9 mg, qt).

\( ^1H \) NMR (300 MHz, DMSO) \( \delta \) 8.13 (s, 3\% \( ^1H \), 1H), 7.62 (s, 1H), 7.59 – 7.49 (m, 2H), 7.19 – 6.95 (m, 3H), 3.78 (s, 3H).

\( ^{13}C \) NMR (75 MHz, DMSO) \( \delta \) 158.0, 130.3, 129.5, 122.0, 118.3, 114.9, 55.4.

ESI-HRMS (m/z) calculated for C\(_{10}\)H\(_{10}\)N\(_2\)O ([M+H]\(^+\)): 175.0871; observed: 175.0874. (m/z) calculated for C\(_{10}\)H\(_{9}\)D\(_{1}\)N\(_2\)O ([M+H]\(^+\)): 176.0934; observed: 176.0913.

**1-methyl-1H-benzo[\(d\)]imidazole-2-d\(_2\)h**

The general deuteration procedure was followed with 1-methyl-1H-benzo[\(d\)]imidazole (65.8 mg) as substrate. The title compound was isolated as a yellow oil (48.6 mg, 74\%).

\( ^1H \) NMR (300 MHz, DMSO) \( \delta \) 8.18 (s, 3\% \( ^1H \), 1H), 7.67 (ddd, \( J = 7.5, 1.5, 0.8 \) Hz, 1H), 7.54 (ddd, \( J = 7.9, 1.5, 0.8 \) Hz, 1H), 7.37 – 7.14 (m, 2H), 3.82 (s, 3H).

\( ^{13}C \) NMR (75 MHz, DMSO) \( \delta \) 144.3 (m), 143.4, 134.6, 122.2, 121.4, 119.3, 110.1, 30.6.

ESI-HRMS (m/z) calculated for C\(_8\)H\(_8\)N\(_2\) ([M+H]\(^+\)): 133.0765; observed: 133.0766. (m/z) calculated for C\(_8\)H\(_7\)DN\(_2\) ([M+H]\(^+\)): 134.0828; observed: 134.0796.

**2,5-dimethyl-1-phenyl-1H-pyrrole-3,4-d\(_2\)i**

F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
The general deuteration procedure was followed with 2,5-dimethyl-1-phenyl-1H-pyrrole (85.5 mg) as substrate. The title compound was isolated as a brown solid (86.5 mg, qt.).

$^1$H NMR (300 MHz, DMSO) δ 7.59 – 7.36 (m, 3H), 7.29 – 7.18 (m, 2H), 5.79 (s, 5% $^1$H, 2H), 1.95 (s, 6H).

$^13$C NMR (75 MHz, DMSO) δ 138.4, 129.2, 128.0, 127.6, 127.4, 105.8 (m), 12.8.

ESI-HRMS (m/z) calculated for C$_{12}$H$_{12}$D$_{2}$N ([M+H]$^+$): 174.1252; observed: 174.1252.

$^1$H NMR (300 MHz, DMSO) δ 8.29 – 8.07 (m, 1H), 7.85 – 7.66 (m, 1H), 7.50 – 7.33 (m, 2H), 7.29 (m, 1H), 7.11 (dt, $J$ = 8.0, 0.7 Hz, 11% $^1$H, 1H), 6.49 (d, $J$ = 7.7 Hz, 8% $^1$H, 1H), 6.05 (t, $J$ = 5.3 Hz, 1H), 3.23 (qd, $J$ = 7.1, 5.2 Hz, 2H), 1.31 (t, $J$ = 7.1 Hz, 3H).

$^13$C NMR (75 MHz, DMSO) δ 144.1 (m), 134.0 (m), 127.9 (m), 126.7 (m), 125.5, 123.8, 123.1, 121.7, 114.9 (m), 102.6 (m), 37.7, 14.1.

ESI-HRMS (m/z) calculated for C$_{12}$H$_{12}$D$_{2}$N ([M+H]$^+$): 173.1189; observed: 173.1187.

Remark: due to the impossible attribution of the signals at the C2 and C4 positions with respect to the amine, the average content is given, ie 6.32 (8% $^1$H), 6.25 (10% $^1$H): average 9% $^1$H.

$^1$H NMR (300 MHz, DMSO) δ 7.12 – 7.02 (m, 1H), 6.32 (d, $J$ = 8.3 Hz, 8% $^1$H, 1H), 6.25 (d, $J$ = 8.1 Hz, 10% $^1$H, 1H), 6.23 (s, 7% $^1$H, 1H), 3.71 (s, 3H), 2.86 (s, 6H).

$^13$C NMR (75 MHz, DMSO) δ 160.3 (m), 151.7 (m), 129.3 (m), 105.1 (m), 101.2 (m), 98.2 (m), 54.7, 40.1.

ESI-HRMS (m/z) calculated for C$_{9}$H$_{11}$D$_{3}$NO ([M+H]$^+$): 154.1201; observed: 154.1203.

Remark: due to the impossible attribution of the signals at the C2 and C4 positions with respect to the amine, the average content is given, ie 6.32 (8% $^1$H), 6.25 (10% $^1$H): average 9% $^1$H.
The general deuteriation procedure was followed with 4-methylbenzene-1,3-diamine (62.1 mg) as substrate. The title compound was isolated as a brown solid (60.3 mg, 97%).

\[ ^1H \text{ NMR (300 MHz, DMSO) } \delta 6.74 - 6.43 (m, 1H), 5.91 (s, 18\% ^1H, 1H), 5.79 (d, } J = 7.8 \text{ Hz, 24\% } ^1H, 1H), 4.43 (s, 4H), 1.91 (d, } J = 0.8 \text{ Hz, 3H).} \]

\[ ^{13}C \text{ NMR (75 MHz, DMSO) } \delta 146.9 (m), 146.6 (m), 130.1 (m), 109.4, 103.5 (m), 100.6 (m), 16.6. \]

ESI-HRMS (m/z) calculated for C\textsubscript{7}H\textsubscript{10}N\textsubscript{2} ([M+H]\textsuperscript{+}): 123.0922; observed: 123.0919.

ESI-HRMS (m/z) calculated for C\textsubscript{7}H\textsubscript{9}DN\textsubscript{2} ([M+H]\textsuperscript{+}): 124.0985; observed: 124.0986.

ESI-HRMS (m/z) calculated for C\textsubscript{7}H\textsubscript{8}D\textsubscript{2}N\textsubscript{2} ([M+H]\textsuperscript{+}): 125.1048; observed: 125.1048.

**Thymol-d\textsubscript{1}**

2-isopropyl-5-methylphen-4,6-d\textsubscript{1}-ol 2m

The general deuteriation procedure was followed with 2-isopropyl-5-methylphenol (75.9 mg) as substrate. The title compound was isolated as a colourless oil (62.5 mg, 82\%).

\[ ^1H \text{ NMR (300 MHz, DMSO) } \delta 9.07 (s, 1H), 7.04 - 6.89 (m, 1H), 6.58 (t, } J = 1.1 \text{ Hz, 81\% } ^1H, 1H), 6.54 (dd, } J = 7.7, 1.1, 0.6 \text{ Hz, 59\% } ^1H, 1H), 3.14 (hept, } J = 6.9 \text{ Hz, 1H), 2.16 (s, 3H), 1.12 (d, } J = 6.9 \text{ Hz, 6H).} \]

\[ ^{13}C \text{ NMR (75 MHz, DMSO) } \delta 154.2 (m), 135.3 (m), 131.2, 125.7 (m), 119.7, 115.6, 26.1, 22.7, 20.7 (m). \]

ES-MS (m/z) calculated for C\textsubscript{10}H\textsubscript{12}D\textsubscript{2}O: 152; observed: 152 (7), 151 (27), 150 (31), 137 (22), 136 (85), 135 (100), 115 (16), 91 (18).

**1,3,5-trimethoxybenzene-2,4,6-d\textsubscript{1}** 2n

The general deuteriation procedure was followed with 1,3,5-trimethoxybenzene (84.2 mg) as substrate. The title compound was isolated as a white solid (83.2 mg, 99\%).

\[ ^1H \text{ NMR (300 MHz, CDCl}3) \delta 6.10 (s, 8\% ^1H, 3H), 3.77 (s, 9H). \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}3) \delta 161.5 (m), 92.7 (m), 55.4. \]
Resveratrol-$d_3$

$(E)$-5-(4-hydroxystyryl)benzene-2,4,6-$d_3$-1,3-diol 2o

The general deuteration procedure was followed with $(E)$-5-(4-hydroxystyryl)benzene-1,3-diol (114.5 mg) as substrate. The title compound was isolated as an off-white solid (122.9 mg, q.t.).

$^1$H NMR (300 MHz, DMSO) $\delta$ 9.32 (s, 3H), 7.50 – 7.25 (m, 2H), 7.10 – 6.61 (m, 4H), 6.42 (s, 16% $^1$H, 2H), 6.15 (s, 16% $^1$H, 1H).

$^{13}$C NMR (75 MHz, DMSO) $\delta$ 158.5 (m), 157.3, 139.3 (m), 128.2, 127.9 (m), 125.7, 115.6, 104.4 (m), 101.6 (m).

ESI-HRMS (m/z) calculated for C$_{14}$H$_{10}$D$_2$O$_3$ ([M+H]$^+$): 231.0990; observed: 231.0987.

$^{13}$C NMR (75 MHz, DMSO) $\delta$ 158.5 (m), 157.3, 139.3 (m), 128.2, 127.9 (m), 125.7, 115.6, 104.4 (m), 101.6 (m).

ESI-HRMS (m/z) calculated for C$_{14}$H$_{10}$D$_3$O$_3$ ([M+H]$^+$): 232.1053; observed: 232.1052.

Melatonin-$d_3$

$N$-(2-(5-methoxy-1H-indol-3-yl)-2,4,6-$d_3$)ethyl)acetamide 2p

The general deuteration procedure was followed with $N$-(2-(5-methoxy-1H-indol-3-yl)ethyl)acetamide (116.2 mg) as substrate. The title compound was isolated as a yellow oil (120.3 mg, q.t.).

$^1$H NMR (300 MHz, DMSO) $\delta$ 10.64 (s, 1H), 7.95 (t, $J$ = 5.7 Hz, 1H), 7.29 – 7.18 (m, 1H), 7.10 (d, $J$ = 2.3 Hz, 16% $^1$H, 1H), 7.06 – 6.99 (m, 17% $^1$H, 1H), 6.72 (d, $J$ = 8.7 Hz, 65% $^1$H, 1H), 3.76 (s, 3H), 3.31 (ddd, $J$ = 7.8, 6.7, 5.5 Hz, 2H), 2.78 (dd, $J$ = 8.1, 6.8 Hz, 2H), 1.81 (s, 3H).

$^{13}$C NMR (75 MHz, DMSO) $\delta$ 169.2, 153.0 (m), 131.4, 127.6 (m), 123.3, 111.9, 111.7, 111.6 (m), 100.2, 55.4, 25.3, 22.8.

ESI-HRMS (m/z) calculated for C$_{13}$H$_{13}$D$_3$N$_2$O$_2$ ([M+H]$^+$): 235.13946; observed: 235.13880.

Coumarin 1-$d_2$

7-(diethylamino)-4-methyl-2$H$-chromen-2-one-3,8-$d_3$ 2q

F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
The general deuteration procedure was followed with 7-(diethylamino)-4-methyl-2H-chromen-2-one (115.2 mg) as substrate. The title compound was isolated as an off-white solid (117.6 mg, q.t.).

$^1$H NMR (300 MHz, DMSO) \(\delta\) 7.45 (d, \(J = 9.0\) Hz, 1H), 6.65 (dt, \(J = 9.0, 1.3\) Hz, 1H), 6.47 (d, \(J = 2.6\) Hz, 61% \(^1\)H, 1H), 5.90 (q, \(J = 1.1\) Hz, 84% \(^1\)H, 1H), 3.39 (q, \(J = 7.0\) Hz, 5H), 2.30 (d, \(J = 1.1\) Hz, 3H), 1.10 (t, \(J = 7.0\) Hz, 6H).

$^{13}$C NMR (75 MHz, DMSO) \(\delta\) 160.7, 155.6, 153.4, 150.3, 150.3, 126.1, 108.2 (m), 96.6, 43.9, 17.9, 12.3.

ES-MS (m/z) calculated for C_{14}H_{15}D_2NO_2: 233.0. Observed: 233 (6), 232 (28), 231 (40), 216 (100), 188 (25), 159 (11), 131 (7).

Papaverine-\(\Delta^2\)

1-((3,4-dimethoxyphenyl)methyl-\(\Delta^2\))-6,7-dimethoxyisoquinoline 2r

![Diagram of papaverine-\(\Delta^2\)]

The general deuteration procedure was followed with 1-((3,4-dimethoxybenzyl)-6,7-dimethoxy-isoquinoline (169.5 mg) as substrate. The title compound was isolated as a colourless oil (174.7 mg, q.t.).

$^1$H NMR (300 MHz, CDCl$_3$) \(\delta\) 8.40 (d, \(J = 5.6\) Hz, 1H), 7.44 (dd, \(J = 5.8, 0.8\) Hz, 1H), 7.36 (s, 1H), 7.05 (s, 1H), 6.89 – 6.74 (m, 3H), 4.54 (s, 5% \(^1\)H, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) \(\delta\) 157.6, 152.3, 149.6, 148.9, 147.4, 140.9, 133.3, 132.1, 132.0, 122.8, 120.4, 118.6, 111.7, 111.1, 105.1, 104.0, 55.8, 55.7, 55.6.

ESI-HRMS (m/z) calculated for C_{20}H_{20}D_2NO_4 ([M+H]^+): 341.1611; observed: 341.1614.

(m/z) calculated for C_{20}H_{19}D_2NO_4 ([M+H]^+): 342.1674; observed: 342.1671.
7. NMR spectra

F. Bourriquen et al., Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogeneous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteriation of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
8. MS traces
Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
### Elemental Composition Report

<table>
<thead>
<tr>
<th>Mass</th>
<th>RA</th>
<th>Calc. Mass</th>
<th>mDa</th>
<th>PPM</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>148.0982</td>
<td>100.00</td>
<td>148.0985</td>
<td>0.3</td>
<td>-2.0</td>
<td>C9H10D1N2</td>
</tr>
<tr>
<td>149.1040</td>
<td>45.03</td>
<td>149.1048</td>
<td>0.8</td>
<td>-5.4</td>
<td>C9H9D2N2</td>
</tr>
</tbody>
</table>

**Chemical Formula:** C9H9D2N2

**Exact Mass:** 149.1032

---

**File:** C:\Users\Lee\Desktop\Data\55950435143107pucw1w2.1.srm

<table>
<thead>
<tr>
<th>Mass</th>
<th>Intensity</th>
<th>Relative Abundance</th>
<th>Theoretical Mass</th>
<th>Relative Error</th>
<th>Delta</th>
<th>ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td>207.10135</td>
<td>60.6</td>
<td>50.0</td>
<td>207.10143</td>
<td>0.1</td>
<td>0.7</td>
<td>15.5</td>
</tr>
<tr>
<td>207.10294</td>
<td>92.7</td>
<td>92.5</td>
<td>207.10284</td>
<td>-0.5</td>
<td>0.5</td>
<td>15.5</td>
</tr>
<tr>
<td>207.10363</td>
<td>23.8</td>
<td>22.5</td>
<td>207.10358</td>
<td>-0.3</td>
<td>0.3</td>
<td>15.5</td>
</tr>
</tbody>
</table>

**Chemical Formula:** C9H9D2N2

**Exact Mass:** 207.1111

---

F. Bourriquen *et al.*, Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen *et al.*, Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”
F. Bourriquen et al., Supporting for "Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes"
F. Bourriquen et al., Supporting for “Homogenous iron-catalysed deuteration of electron-rich arenes and heteroarenes”