Easy-to-implement Hydrogen Isotope Exchange for the labeling of N-heterocycles, alkylamines, benzylic scaffolds and pharmaceuticals

Supporting information

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I. Materials and Methods

I-1. Materials

All substrates were purchased and used without further purification. When substrates have been received as salts (dextromethorphan hydrochloride or chloroquine hydrochloride for instance), they were solubilized in water and free bases were recovered by addition of $\text{K}_2\text{CO}_3$ until basic pH and extracted with $\text{CH}_2\text{Cl}_2$. $\text{THF}$ was dried by distillation over sodium and benzophenone. Anhydrous and inhibitor-free $\text{2-MeTHF}$ and a solution of $\text{HCl}$/Diethyl ether (1M) were purchased from Sigma-Aldrich. $^1\text{H}$ NMR (400 MHz), $^2\text{H}$ NMR (61 MHz) and $^3\text{H}$ NMR (427 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in Hertz (Hz). Splitting patterns are designated as singlet (s), doublet (d), triplet (t), broad signal (brs). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Electrospray mass spectra were recorded using either an ESI/TOF Mariner Mass Spectrometer or a Q-TOF Premier Waters Mass Spectrometer. LC-MS analyses for tritium experiments were performed using a Waters Alliance 2695 system (Column: Waters BEH XBridge C18 100 x 4.6 mm, 3.5 µm). Liquid scintillation countings were performed using a PerkinElmer Tricarb 2910 TR Liquid Scintillation analyser equipped with automatic external standardization. The samples for liquid scintillation counting were prepared with a 9 mL Ultima Gold™ LLT scintillator in 10 mL PerkinElmer super polyethylene vials. For each measurement, 3 countings have been realized and the results given correspond to an average of these 3 values. Electron microscopy observations were carried out on a Philips CM12 microscope operated at 80 kV. [α]$^\text{D}_{20}$ measurements were realized on a Jasco P-2000 polarimeter equipped with sodium lamp (589 nm) at 20 °C and using a 1.5 mL cell. Centrifugations were performed on a VWR Mini Star Silverline.

I-2. H/D exchange quantification

Deuterium incorporation was quantified by the decrease of $^1\text{H}$ NMR integral intensities at the specified positions compared to the starting material. Integral intensities were calibrated against hydrogen signals that do not undergo H/D-exchange. Mass spectrometry quantification was performed by subtraction of the mean molecular masses of the product and substrate isotopologue clusters in order to eliminate the contribution of the natural isotope abundance to the total mass. When all positions are deuterated, the isotopic enrichment was evaluated by $^1\text{H}$ NMR and corrected either with an internal standard (for compound 10) or using mass spectrometry analysis (for compound 17).

I-3. General Procedure for H/D exchanges

A 100 mL Fischer–Porter glassware equipped with a magnetic stirrer was charged with the corresponding substrate (0.02 mmol, 1 equiv.) and [Rh(COD)OME]$_2$ (2.5 or 5 mol%). Then, distilled THF or 2-MeTHF (C = 0.1 M) was added under argon. The solution was stirred under vacuum until bubbling and then pressurized with $\text{D}_2$ gas (1 bar) for 5 min. This operation was repeated twice. The reaction mixture was stirred at the corresponding temperature under pressure of $\text{D}_2$ (1 bar) for 24 h or 48 h. The final black solution was cooled down to room temperature and filtered through a nylon syringe filter (0.2 µm) before being evaporated under reduced pressure to give the desired product.
II. Description of compounds

II-1. Description of the deuterated products

Indole 1

Following general procedure with indole (23.4 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 1 as a white solid with a quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 8.16 (bs, 1H, NH), 7.66 (d, J = 8 Hz, 1H), 7.41 (d, J = 7.6 Hz, 0.07H), 7.23–7.17 (m, 1.03H), 7.16–7.08 (m, 1H), 6.56 (d, J = 2 Hz, 0.53H) ppm.

²H-{¹H} NMR (61 MHz, CHCl₃) δ 7.41, 7.20, 6.57 ppm.

Mass: not detected (n.d)

Figure S1. ¹H NMR spectrum of 1 (starting material)
Figure S2. $^1$H NMR spectrum of 1

Figure S3. $^2$H-$^1$H NMR spectrum of 1
Harmane 2

Following general procedure with harmane (36.4 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 2 as a yellow oil with a quantitative yield.

¹H NMR (400 MHz, DMSO-d₆) δ 11.56 (bs, 1H), 8.22–8.15 (m, 1.12H), 7.91 (d, J = 5.2 Hz, 1H), 7.63–7.56 (m, 1H), 7.55–7.50 (m, 1H), 7.26–7.19 (m, 1H), 2.77 (s, 3H) ppm.

²H-{¹H} NMR (61 MHz, DMSO) δ 8.23 ppm.

Mass: M+1(0D) 0%, M+2(1D) 77.7%, M+3(2D) 7.4%, M+4(3D) 1.1%: 1.0D.

Figure S4. Mass spectrum of 2
Figure S5. $^1$H NMR spectrum of 2 (starting material)

Figure S6. $^1$H NMR spectrum of 2
Figure S7. 2H-{1H} NMR spectrum of 2. The sharp peak visible at 2.50 ppm corresponds to the residual signal of DMSO-d6.

Optimization studies for easily reducible compounds 3 & 4

| Entry | Substrate | Catalyst loading (mol%) | Additive (mol%) | Number of D atoms incorporated | Reduction observed |
|-------|-----------|-------------------------|-----------------|-------------------------------|-------------------|
| 1     | 2-(4-methoxyphenyl)pyridine 3 | 1.25 | / | 4.5 | Yes |
| 2     | 2-(4-methoxyphenyl)pyridine 3 | 1.25 | ICyCl (2.5 mol%) | 2.5 | No |
| 3     | 2-benzylpyridine 4 | 2.5 | / | / | Full |
| 4     | 2-benzylpyridine 4 | 1.25 | / | 4.6 | Yes |
| 5     | 2-benzylpyridine 4 | 2.5 | ICyCl (5 mol%) | 1.4 | Yes |
| 6     | 2-benzylpyridine 4 | 1.25 | ICyCl (2.5 mol%) | 1.2 | No |

Table S1. Optimization studies for 3 and 4. ICyCl: Dicyclohexylimidazolium chloride
2-(4-methoxyphenyl)pyridine 3

Following general procedure with 2-(4-methoxyphenyl)pyridine (37 mg, 0.2 mmol, 1 equiv.), [Rh(COD)OME]₂ (1.2 mg, 0.0025 mmol, 1.25 mol%), ICyCl (1.3 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 3 as a white solid with a quantitative yield.

\(^{1}\text{H NMR (400 MHz, acetone-d₆)}\ δ 8.61 (s, 0.44H), 8.15-8.00 (m, 0.48H), 7.90–7.70 (m, 1.67H), 7.22 (s, 0.89H), 7.03 (s, 2H), 3.86 (s, 3H) ppm.\)

\(^{2}\text{H-[¹H] NMR (61 MHz, acetone)}\ δ 8.61, 8.08, 7.79, 7.24 ppm.\)

Mass: M₊1(0D) 0%, M₊2(1D) 14.3%, M₊3(2D) 25.1%, M₊4(3D) 28.5%, M₊5(4D) 18.8%, M₊6(5D) 5.0%: 2.5D.
Figure S9. $^1$H NMR spectrum of 3 (starting material)

Figure S10. $^1$H NMR spectrum of 3
Following general procedure with 2-benzylpyridine (34 mg, 0.2 mmol, 1 equiv.), [Rh(COD)OMe]₂ (1.2 mg, 0.0025 mmol, 1.25 mol%), ICyCl (1.3 mg, 0.005 mmol, 2.5 mol%) in 2 mL of THF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 4 as a colorless oil with a quantitative yield.

\[
{^1}H \text{ NMR (400 MHz, CDCl}_3\) \delta 8.58 (dd, } J = 5.5, 1.7 \text{ Hz, 0.02H}), 7.60 (dd, } J = 9.5, 5.9 \text{ Hz, 0.90H}), 7.36–7.27 (m, 4H), \]
\[
7.26–7.21 (m, 1H), 7.13 (d, } J = 7.7 \text{ Hz, 2H), 4.19 (s, 2H) ppm.}
\]

\[
{^2}H-\{^1}H\} \text{ NMR (61 MHz, CHCl}_3\) \delta 8.58, 7.62, 7.32, 7.16 \text{ ppm.}
\]

Mass: M+1(0D) 0%, M+2(1D) 74.5%, M+3(2D) 16.8%, M+4(3D) 3.5%, M+5(4D) 0.8%: 1.2D.
Figure S12. Mass spectrum of 4

Figure S13. $^1$H NMR spectrum of 4 (starting material)
Figure S14. $^1H$ NMR spectrum of 4

Figure S15. $^2H-^1H$ NMR spectrum of 4
Following general procedure with 3,6-dimethylcarbazole (39 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was filtered and the desired product 5 was obtained from precipitation in cold CH₂Cl₂ as a white solid with 38% yield.

¹H NMR (400 MHz, acetone-d₆) δ 10.04 (bs, 1H), 7.86 (s, 2H), 7.35 (d, J = 8.2 Hz, 0.23H), 7.18 (s, 1.52H), 2.47 (s, 1.06H) ppm.

²H-{¹H} NMR (61 MHz, acetone) δ 7.36, 7.18, 2.40 ppm.

Mass: not detected (n.d)

Figure S16. ¹H NMR spectrum of 5 (starting material)
Figure S17. $^1$H NMR spectrum of 5

$^2$H-$^1$H NMR (81 MHz, acetone)
Following general procedure with 2,4-dimethylaniline (25 µL, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 6 as a colorless oil with a quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 6.92–6.81 (m, 3H), 6.59 (d, J = 7.6 Hz, 0.12H), 3.39 (bs, 2H), 2.26–2.18 (m, 1.61H (isotopologues)), 2.18–2.10 (m, 2.30H (isotopologues)) ppm.

²H-(¹H) NMR (61 MHz, CHCl₃) δ 6.64, 2.19, 2.13 ppm.

Mass: M+1(0D) 0%, M+2(1D) 20.6%, M+3(2D) 7.5%, M+4(3D) 6.8%, M+5(4D) 15.2%, M+6 (5D) 4.3%, M+7 (6D) 4.8%, M+8 (7D) 5.2%, M+9 (8D) 13.0%: 3.1D.

Figure S19. Mass spectrum of 6
Figure S20. $^1$H NMR spectrum of 6 (starting material)

Figure S21. $^1$H NMR spectrum of 6
Figure S22. $^2\text{H}-^1\text{H}$ NMR spectrum of 6. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$.

4-butylaniline 7

Following general procedure with 4-butylaniline (29.4 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 7 as a brown liquid with a quantitative yield.

$^1\text{H}$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.00–6.94 (m, 2H), 6.66–6.59 (m, 0.54H), 2.50 (t, $J = 7.6$ Hz, 1.39H), 1.59–1.48 (m, 2H), 1.42–1.28 (m, 2H), 0.95–0.86 (t, $J = 7.2$ Hz, 3H) ppm.

$^2\text{H}-^1\text{H}$ NMR (61 MHz, CHCl$_3$) $\delta$ 6.70, 2.50 ppm.

Mass: M+1(OD) 0%, M+2(1D) 24.3%, M+3(2D) 40.6%, M+4(3D) 16.0%, M+5(4D) 8.7%, M+6(5D) 0.9%, M+7(6D) 0.4%: 2.0D.
Figure S23. Mass spectrum of 7

Figure S24. $^1$H NMR spectrum of 7 (starting material)
Figure S25. $^1$H NMR spectrum of 7

Figure S26. $^2$H-$^1$H NMR spectrum of 7
Following general procedure with spinol ((R)-2,2',3,3'-tetrahydro-1,1'-spirobi[indene]-7,7'-dilin) (50.4 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was filtrated through a nylon syringe filter (0.2 µm) and the Fisher Porter was washed with 2 × 3 mL of dichloromethane. The combined organic phases were concentrated under vacuum. The product was purified via crystallization (in cold hexane) to give 8 as a white crystalline solid (34 mg, 67%).

¹H NMR (400 MHz, CDCl₃) δ 7.21–7.15 (m, 1.62H), 6.92–6.87 (m, 1.75H), 6.71–6.65 (m, 1.11H), 4.60 (s, 1.63H, OH), 3.12–2.95 (m, 2.28H), 2.36–2.26 (m, 1.77H), 2.26–2.14 (m, 2H) ppm.

²H-{¹H} NMR (61 MHz, CHCl₃) δ 7.19, 6.92, 6.71, 3.05, 2.29 ppm.

Mass: M-1 (0D) 0%, [M-1]+1 (1D) 10.8%, [M-1]+2(2D) 25.9%, [M-1]+3(3D) 30.1%, [M-1]+4(4D) 19.1%, [M-1]+5(5D) 8.8%, [M-1]+6(6D) 3.4%; 2.9D.

Figure S27. Mass spectrum of 8
Figure S28. $^1$H NMR spectrum of 8 (starting material)

Figure S29. $^1$H NMR spectrum of 8
Figure S30. $^2$H-$^1$H NMR spectrum of 8. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$.

3,4-dimethoxyltoluene 9

Following general procedure with 3,4-dimethoxytoluene (21.6 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 9 as a colorless liquid with a quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ 6.79–6.74 (m, 1H), 6.72–6.67 (m, 2H), 2.86 (s, 3H), 2.85 (s, 3H), 2.30 (s, 0.14H (isotopologues)) ppm.

$^2$H-$^1$H NMR (61 MHz, CHCl$_3$) δ 2.30 ppm.

Mass: not detected (n.d)
Figure S31. $^1$H NMR spectrum of 9 (starting material)

Figure S32. $^1$H NMR spectrum of 9
3,4-dimethoxytoluene 9(Ir)

Following general procedure with 3,4-dimethoxytoluene (21.6 mg, 0.2 mmol, 1 equiv.) and [Ir(COD)OMe]₂ (3.3 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 9(Ir) as a colorless liquid with a quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 6.79–6.74 (m, 1H), 6.72–6.67 (m, 2H), 2.86 (s, 3H), 2.85 (s, 3H), 2.30 (s, 2.86H (isotopologues)) ppm.
Following general procedure with diphenylmethane (33.6 mg, 0.2 mmol, 1 equiv.), diethylamine (0.4 mmol, 2 equiv.) and [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified by flash chromatography using cyclohexane as the eluent to give the pure desired product 19 as a colorless oil (14.5 mg, 43%). NMR was realized with 1 equivalent of 1,3,5-trimethoxybenzene as internal standard (1.3 mg of product and 1.3 mg of 1,3,5-trimethoxybenzene)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32–7.27 (m, 3.59H), 7.23–7.16 (m, 5.41H), 4.02–3.92 (m, 0.62H (isotopologues)) ppm.

$^2$H-$^1$H NMR (61 MHz, CHCl$_3$) $\delta$ 7.30, 7.21, 3.94 ppm.

Mass: not detected (n.d)
Figure S35. $^1H$ NMR spectrum of 10 (starting material)

Figure S36. $^1H$ NMR spectrum of 10 (with 1 equiv. of 1,3,5-trimethoxybenzene as internal standard)
Figure S37. $^2$H-$^1$H NMR spectrum of 10

Figure S38. $^1$H NMR spectrum of 10 (in blue with 2 equiv. of diethylamine; in red with 1 equiv. of diethylamine)
Table S2. Optimization studies for 11

| Entry | Substrate | Catalyst loading (mol%) | Additive (equiv.) | Reduction observed |
|-------|-----------|-------------------------|------------------|--------------------|
| 1     | Tetralin 11 | 2.5         | /                | Full reduction     |
| 2     | Tetralin 11 | 2.5         | Diethylamine (0.3 equiv.) | yes               |
| 3     | Tetralin 11 | 2.5         | Diethylamine (2 equiv.)  | < 5%               |

Figure S39. $^1$H NMR spectrum of 11 with 2.0 (blue) and 0.3 equiv. (red) of diethylamine

Following general procedure with tetralin (27 µL, 0.2 mmol, 1 equiv.), [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) and diethylamine (6.2 µL, 0.06 mmol, 0.3 equiv) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at room temperature under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure (washing with 2 × 10 mL of Et$_2$O instead of dichloromethane). The
solvent was removed *in vacuo* to give the pure product 11 as a colorless oil. It should be noted that the product and the reduced product are volatile. Thus, the reduced product was removed thanks to concentration under vacuum.

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ 7.15–7.04 \ (m, 4\text{H}), \ 2.80–2.68 \ (m, 0.35\text{H}), \ 1.86–1.70 \ (m, 3.63\text{H}) \ \text{ppm.} \]

\[ ^2\text{H-}[^1\text{H}] \text{NMR} \ (61 \text{ MHz, CHCl}_3) \delta \ 7.13, \ 2.74, \ 1.77 \ \text{ppm.} \]

Mass: not detected (n.d)

![Figure S40. 1H NMR spectrum of 11 (starting material)](image-url)
Figure S41. $^1$H NMR spectrum of 11

$^1$H NMR (400 MHz, CDCl$_3$)

chloroform

Figure S42. $^2$H-$^1$H NMR spectrum of 11

$^2$H-$^1$H NMR (81 MHz, CHCl$_3$)
Dodecylamine 12

Following general procedure with dodecylamine (37 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80 °C under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 12 as a pale yellow oil with a quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$) δ 2.64 (q, $J$ = 7.2 Hz, 0.10H), 1.44–1.36 (m, 1.52H), 1.34–1.20 (m, 18H), 1.13 (bs, 2H, NH$_2$), 0.87 (t, $J$ = 6.8 Hz, 3H) ppm.

$^2$H-$^1$H NMR (61 MHz, CHCl$_3$) δ 2.64, 1.41, 1.06 ppm.

Mass: M+1(OD) 0%, M+2(1D) 7.0%, M+3(2D) 60.6%, M+4(3D) 14.0%, M+5(4D) 14.0%, M+6(5D) 2.1%, M+7(6D) 1.2%, M+8(7D) 0.4%, M+9(8D) 0.3%: 2.5D.

Figure S43. Mass spectrum of 12
Figure S44. $^1$H NMR spectrum of 12 (starting material)

Figure S45. $^1$H NMR spectrum of 12
Figure S46. $^2\text{H}$-$^1\text{H}$ NMR spectrum of 12. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$.

Dioctylamine 13

Following general procedure with dioctylamine (60 µL, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80°C under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 13 as a colorless oil with a quantitative yield.

$^1\text{H}$ NMR (400 MHz, CDCl$_3$) δ 2.55 (t, $J = 7.2$ Hz, 0.29H), 1.53–1.37 (m, 3.62H), 1.36–1.14 (m, 20H), 0.87 (t, $J = 6.8$ Hz, 3H) ppm.

$^2\text{H}$-$^1\text{H}$ NMR (61 MHz, CHCl$_3$) δ 2.53, 1.42 ppm.

Mass: M+1(0D) 0%, M+2(1D) 0.5%, M+3(2D) 2.4%, M+4(3D) 18.2%, M+5(4D) 56.3%, M+6 (5D) 11.0%, M+7 (6D) 8.8%: 3.9D.
Figure S47. Mass spectrum of 13

Figure S48. $^1$H NMR spectrum of 13 (starting material)
Figure S49. $^1$H NMR spectrum of 13

Figure S50. $^2$H-$^1$H NMR spectrum of 13. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$. 
Pyrrolidine 14

Following general procedure with pyrrolidine (16.4 µL, 0.2 mmol, 1 equiv.) and \([\text{Rh(COD)OMe}]_2\) (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80°C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was filtered over a nylon syringe filter (0.2 µm) and 0.5 mL of an HCl/Et₂O (1 M) solution were added. The solvent was removed under vacuum and the desired product 14 was obtained as a white solid (hydrochloride salt, 14 mg, yield = 65%).

\(^1\)H NMR (400 MHz, D₂O) δ 3.32–3.20 (m, 0.11H), 2.02–1.92 (m, 4H) ppm.

\(^2\)H-(\(^1\)H) NMR (61 MHz, H₂O) δ 3.24 ppm.

Mass: M+1(0D) 0%, M+2(1D) 0.6%, M+3(2D) 3.9%, M+4(3D) 14.1%, M+5(4D) 69.6%; M+6(5D) 9.2%, M+7(6D) 1.9%, M+8(7D) 0.4%: 3.9D.

Figure S51. Mass spectrum of 14
Figure S52. $^1$H NMR spectrum of 14 (starting material)

Figure S53. $^1$H NMR spectrum of 14
Following general procedure with (R)-(−)-2-(methoxymethyl)pyrrolidine (24.7 µL, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80°C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was filtered over a nylon syringe filter (0.2 µm) and 0.5 mL of an HCl/Et₂O (1 M) solution were added. The solvent was removed under vacuum and the desired product 15 was obtained as a white solid (27.9 mg, 92%). No racemization was observed.

¹H NMR (400 MHz, CDCl₃) δ 9.91 (bs, 1H), 9.19 (bs, 1H), 3.88–3.78 (m, 0.08H), 3.73–3.60 (m, 1.48H), 3.40 (s, 3H), 3.39–3.37 (m, 0.21H), 2.11–2.01 (m, 1.97H), 2.01–1.90 (m, 0.93H), 1.85–1.73 (m, 1H) ppm.

²H-{¹H} NMR (61 MHz, CHCl₃) δ 3.83, 3.65, 3.34, 2.06, 1.97 ppm.

Mass: M+1(0D) 0%, M+2(1D) 0.3%, M+3(2D) 5.1%, M+4(3D) 40.1%, M+5(4D) 35.2%; M+6(5D) 12.4%, M+7(6D) 5.1%: 3.6D.

[α]D²⁰ = +14.8 (C = 1.0, CHCl₃) (starting material)

[α]D²⁰ = +17.7 (C = 1.0, CHCl₃) (product)
Figure S55. Mass spectrum of 15

Figure S56. $^1$H NMR spectrum of 15 (starting material)
Figure S57. $^1$H NMR spectrum of 15

Figure S58. $^2$H-$^1$H NMR spectrum of 15. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$. 
Piperidine 16

Following general procedure with piperidine (19.8 µL, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (4.8 mg, 0.01 mmol, 5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80°C under pressure of D₂ (1 bar) for 48 h. Then the crude reaction mixture was filtered over a nylon syringe filter (0.2 µm) and 0.5 mL of an HCl/Et₂O (1 M) solution were added. The solvent was removed under vacuum and the desired product 16 was obtained as a white solid (hydrochloride salt) with a quantitative yield.

¹H NMR (400 MHz, D₂O) δ 3.09 (t, J = 5.7 Hz, 0.32H), 1.71 (dt, J = 11.1, 5.7 Hz, 3.43H), 1.62–1.58 (m, 2H) ppm.

²H-{¹H} NMR (61 MHz, H₂O) δ 3.09, 1.70 ppm.

Mass: M+1(0D) 0%, M+2(1D) 0.4%, M+3(2D) 3.3%, M+4(3D) 21.1%, M+5(4D) 56.0%; M+6(5D) 13.3%, M+7(6D) 4.2%, M+8(7D) 0.9%, M+9(8D) 0.3%: 4.0D.

Figure S59. Mass spectrum of 16
Figure S60. $^1$H NMR spectrum of 16 (starting material)

Figure S61. $^1$H NMR spectrum of 16
Figure S62. $^2$H-$^1$H NMR spectrum of 16. The sharp peak visible at 4.79 ppm corresponds to the residual signal of D$_2$O.

Morpholine 17

Following general procedure with morpholine (17.4 $\mu$L, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (4.8 mg, 0.01 mmol, 5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80 °C under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was filtered over a nylon syringe filter (0.2 $\mu$m) and 0.5 mL of an HCl/Et$_2$O (1 M) solution were added. The solvent was removed under vacuum and the desired product 17 was obtained as a white solid (hydrochloride salt, 22.3 mg, yield = 91%).

$^1$H NMR (400 MHz, D$_2$O) $\delta$ 4.02–3.84 (m, 2.74), 3.36–3.19 (m, 0.24H) ppm.

$^2$H-$^1$H NMR (61 MHz, H$_2$O) $\delta$ 3.90, 3.23 ppm.

Mass: M+1(0D) 0%, M+2(1D) 0%, M+3(2D) 0%, M+4(3D) 4.9%, M+5(4D) 23.8%; M+6(5D) 32.3%, M+7(6D) 25.6%; 5.0D.
Figure S63. Mass spectrum of 17

Figure S64. $^1$H NMR spectrum of 17 (starting material)
Figure S65. $^1$H NMR spectrum of 17

$^1$H NMR (400 MHz, D$_2$O)

solvent peak from D2O

Figure S66. $^2$H-$^1$H NMR spectrum of 17. The sharp peak visible at 4.79 ppm corresponds to the residual signal of D$_2$O.
Nicotine 18

Following general procedure with nicotine (32.4 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 18 as a yellow oil with a quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, J = 2.0 Hz, 0.02H), 8.49 (dd, J = 4.8, 1.7 Hz, 0.02H), 7.69 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 3.27–3.21 (m, 1H), 3.08 (t, J = 8.3 Hz, 1H), 2.35–2.26 (m, 1H), 2.25–2.10 (m, 4H), 2.03–1.90 (m, 1H), 1.87–1.77 (m, 1H), 1.77–1.66 (m, 1H) ppm.

²H-{¹H} NMR (61 MHz, CHCl₃) δ 8.54, 8.50 ppm.

Mass: M+1(0D) 0%, M+2(1D) 5.0%, M+3(2D) 85.7%, M+4(3D) 7.2%, M+5(4D) 1.2%, M+6 (5D) 0.5%: 2.1D.

Figure S67. Mass spectrum of 18
Figure S68. $^1$H NMR spectrum of 18 (starting material)

Figure S69. $^1$H NMR spectrum of 18
Figure S70. $^2$H-$^1$H NMR spectrum of 18. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$.

**Chloroquine 19**

Following general procedure with chloroquine (69.9 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 19 as a white solid with a quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.49 (d, $J$ = 5.2 Hz, 0.07H), 7.91 (d, $J$ = 2 Hz, 0.72H), 7.72 (d, $J$ = 8.8 Hz, 1H), 7.31 (dd, $J$ = 9.2, 2.0 Hz, 1H), 6.40 (bs, 1H), 5.40 (d, $J$ = 7.2 Hz, 1H), 3.76–3.64 (m, 1H), 2.54 (q, $J$ = 7.2 Hz, 4H), 2.46 (t, $J$ = 6.8 Hz, 2H), 1.80–1.55 (m 3H), 1.30 (d, $J$ = 6.4 Hz, 3H), 1.01 (t, $J$ = 7.2 Hz, 6H) ppm.

$^2$H-$^1$H NMR (61 MHz, CHCl$_3$) $\delta$ 8.49, 7.92 ppm.

Mass: M+1(OD) 0%, M+2(1D) 75.1%, M+3(2D) 18.4%: 1.1D.
Figure S71. Mass spectrum of 19

Figure S72. $^1$H NMR spectrum of 19 (starting material)
Figure S73. $^1$H NMR spectrum of 19

Figure S74. $^2$H-$^1$H NMR spectrum of 19. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$. 

$^1$H NMR (400 MHz, CDCl$_3$)

$^2$H-$^1$H NMR (61 MHz, CHCl$_3$)
Following general procedure with papaverine (67.9 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 20 as a white solid with a quantitative yield.

\[
\text{H NMR (400 MHz, CDCl₃) } \delta 8.36 (d, J = 5.6 Hz, 0.04H), 7.41 (s, 0.83H), 7.33 (s, 1H), 7.04 (s, 1H), 6.84–6.78 (m, 1.43H), 6.78–6.72 (m, 1H), 4.52 (s, 1.74H) 3.99 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H) ppm.
\]

\[
\text{H-{¹}H NMR (61 MHz, CHCl₃) } \delta 8.45, 7.33, 6.90, 4.56 ppm.
\]

Mass: M+1(0D) 0%, M+2(1D) 38.7%, M+3(2D) 45.9%, M+4(3D) 12.0%, M+5(4D) 1.7%, M+6(5D) 0.2%: 1.7D.

Figure S75. Mass spectrum of 20
Figure S76. $^1$H NMR spectrum of 20 (starting material)

Figure S77. $^1$H NMR spectrum of 20
Following general procedure with pindolol (48.6 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 21 as a yellow oil with a quantitative yield.

^1H NMR (400 MHz, Acetone-d₆) δ 7.20–7.17 (m, 0.09H), 7.06–6.95 (m, 1H), 6.58–6.52 (m, 0.72H), 6.52–6.47 (m, 1H), 4.14–4.08 (m, 2H), 4.08–4.01 (m, 1H), 2.95–2.87 (dd, J = 12, 4.4 Hz, 1H), 2.84–2.70 (m, 2H), 1.04 (dd, J = 6.0, 0.8 Hz, 6H) ppm.

^2H-{^1H} NMR (61 MHz, Acetone) δ 7.20, 7.03, 6.56 ppm.

Mass: M+1(0D) 0%, M+2(1D) 10.7%, M+3(2D) 49.3%, M+4(3D) 24.1%, M+5(4D) 6.5%, M+6(5D) 2.0%, M+7(6D) 1.0%: 2.2D.
Figure S79. Mass spectrum of 21

Figure S80. $^1$H NMR spectrum of 21 (starting material)
Figure S81. $^1$H NMR spectrum of 21

$^1$H NMR (400 MHz, acetone-d$_6$)

Figure S82. $^2$H-$^1$H NMR spectrum of 21. The sharp peak visible at 2.05 ppm corresponds to the residual signal of acetone-d$_6$. 

$^2$H-$^1$H NMR (61 MHz, acetone)
Following general procedure with zolmitriptan (57.4 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at room temperature under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product **22** as a yellow oil with a quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.22 (bs, 1H), 7.38 (s, 1H), 7.31 (d, $J = 8.4$ Hz, 0.82H), 7.04 (d, $J = 2.4$ Hz, 0.45H), 6.97 (dd, $J = 8$, 7.6 Hz, 1H), 5.26 (bs, 1H), 4.47 (t, $J = 8.4$ Hz, 1H), 4.22–4.16 (m, 1H), 4.15–4.06 (m, 1H), 3.03–2.86 (m, 4H), 2.67–2.58 (m, 2H), 2.34 (s, 6H) ppm.

$^2$H-{$^1$H} NMR (61 MHz, CHCl$_3$) $\delta$ 7.31, 7.14 ppm.

Mass: M+1(0D) 0%, M+2(1D) 40.0%, M+3(2D) 18.1%, M+4(3D) 1.1%, M+5(4D) 0.6%, M+6(5D) 0.5%: 0.8D.

**Figure S83. Mass spectrum of 22**
Figure S84. \(^1\)H NMR spectrum of 22 (starting material)

Figure S85. \(^1\)H NMR spectrum of 22
Atropine 23

Following general procedure with atropine (68.2 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]$_2$ (4.8 mg, 0.01 mmol, 5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80 °C under pressure of D$_2$ (1 bar) for 48 h. Then the crude reaction mixture was purified by HPLC (C18-HDO Interchim, 100×4.6 mm, 3 µm, Flow: 1 mL/min, Room temperature) to give the formiate salt of 23 (20 mg, yield = 29%). Extraction with a solution of K$_2$CO$_3$ and dichloromethane gives the product 23 as the free base (white solid).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34–7.12 (m, 5H), 5.02–4.89 (m, 1H), 4.19–4.05 (m, 1H), 3.81–3.80 (m, 1H), 3.76–3.73 (m, 0.28H), 3.00 (bs, 1H), 2.87 (bs, 1H), 2.12–1.91 (m, 2H), 1.87–1.73 (m, 1H), 1.73–1.55 (m, 3H), 1.47–1.37 (m, 1H), 1.16–1.05 (m, 1H) ppm.

$^2$H-$^1$H NMR (61 MHz, CHCl$_3$) $\delta$ 3.79, 2.15 ppm.

Mass: M+1(0D) 0%, M+2(1D) 1.5%, M+3(2D) 6.1%, M+4(3D) 29.6%, M+5(4D) 37.6%, M+6(5D) 15.6%, M+7(6D) 6.1%, M+8(7D) 2.0%, M+9(8D) 0.6%: 3.9D.

HPLC: $t_R$ 8.25 min
HPLC program:

A/ H$_2$O +0.1%HCOOH

B/ CH$_3$CN +0.1%HCOOH

| t (min) | A (%) | B (%) |
|---------|-------|-------|
| 0       | 95    | 5     |
| 24      | 50    | 50    |
| 24.1    | 0     | 100   |
| 30      | 0     | 100   |
| 30.1    | 95    | 5     |
| 35      | 95    | 5     |

Figure S87. Mass spectrum of 23
Figure S88. $^1$H NMR spectrum of 23 (starting material)

Figure S89. $^1$H NMR spectrum of 23
Following general procedure with ibuprofen (45.6 mg, 0.2 mmol, 1 equiv.), diethylamine (27 µL, 0.26 mmol, 1.3 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was extracted with a solution of 0.5 M HCl in water and dichloromethane (3 × 10 mL). The combined organic phases were dried over MgSO₄ and concentrated under vacuum to give the desired product 24 as a colorless oil with a quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 3.71 (q, J = 7.2 Hz, 0.70H), 2.49–2.38 (m, 1.24H), 1.92–1.78 (m, 1H), 1.50 (d, J = 7.2 Hz, 2.82H), 0.90 (d, J = 6.4 Hz, 6H) ppm.

²H-{¹H} NMR (61 MHz, CHCl₃) δ 3.69, 2.43, 1.48 ppm.

Mass: M-1(0D) 0%, [M-1]+1(1D) 22.0%, [M-1]+2(2D) 18.2%, [M-1]+3(3D) 12.4%, [M-1]+4(4D) 6.0%: 1.2D.
Figure S91. Mass spectrum of 24

Figure S92. $^1$H NMR spectrum of 24 (starting material)
Figure S93. $^1$H NMR spectrum of 24

$^1$H NMR (400 MHz, CDCl$_3$)

Figure S94. $^2$H-$^1$H NMR spectrum of 24. The peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$. 
Nefiracetam 25

Following general procedure with nefiracetam (49.2 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of distilled THF. The reaction mixture was stirred at 55 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was filtered through a nylon syringe filter (0.2 µm) before being evaporated under reduced pressure. Further purification was performed by HPLC (HSSC18, 4.6×100 mm, 3.5 µm, Flow: 1mL/min; Room temperature) to give the labelled product 25 as a white solid (yield = 31%).

\[ ^1\text{H NMR (400 MHz, CDCl}_3 \] \( \delta \) 7.67 (bs, 1H), 7.20–7.00 (m, 3H), 4.11 (s, 2H), 3.61 (t, \( J = 7.1 \) Hz, 2H), 2.48 (t, \( J = 8.1 \) Hz, 2H), 2.22–2.18 (m, 0.45H), 2.17–2.08 (m, 2H) ppm.

\[ ^2\text{H-}{^1}\text{H} \text{ NMR (61 MHz, CHCl}_3 \] \( \delta \) 2.21 ppm.

Mass: M+1(0D) 0%, M+2(1D) 0%, M+3(2D) 0%, M+4(3D) 1.1%, M+5(4D) 5.7%, M+6(5D) 23.7%, M+7(6D) 49.7%, M+8(7D) 16.5%, M+9(8D) 2.9%, M+10(9D) 0.5%: 5.9D.

HPLC: t\(_R\) 14.97 min

HPLC program:

A/ H₂O +0.1%HCOOH
B/ CH₃CN +0.1%HCOOH

| t (min) | A (%) | B (%) |
|---------|-------|-------|
| 0       | 95    | 5     |
| 24      | 60    | 40    |
| 30      | 0     | 100   |
| 35      | 95    | 5     |
Figure S95. Mass spectrum of 25

Figure S96. $^1$H NMR spectrum of 25 (starting material)
Figure S97. $^1$H NMR spectrum of 25

Figure S98. $^2$H-$^1$H NMR spectrum of 25
Lidocaïne 26

Following general procedure with lidocaine (46.9 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80°C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 26 as a white solid with a quantitative yield.

¹H NMR (400 MHz, CDCl₃) δ 8.94 (bs, 1H, NH), 7.13–7.00 (m, 3H), 3.32–3.14 (m, 2H), 2.77–2.59 (m, 3.77H), 2.24–2.14 (m, 0.63H (isotopologues)), 1.19–1.08 (t, J = 7.2 Hz, 6H) ppm.

²H-{¹H} NMR (61 MHz, CHCl₃) δ 2.69, 2.19 ppm.

Mass: M+1(OD) 0%, M+2(1D) 0.1%, M+3(2D) 0.4%, M+4(3D) 1.8%, M+5(4D) 8.6%, M+6(5D) 29.4%, M+7(6D) 43.3%, M+8(7D) 12.2%, M+9(8D) 3.6%, M+10(9D) 2.1%, M+11(10D) 1.3%: 5.9D.

Figure S99. Mass spectrum of 26
Figure S100. $^1$H NMR spectrum of 26 (starting material)

Figure S101. $^1$H NMR spectrum of 26
Lidocaïne 26(Ir)

Following general procedure with lidocaine (46.9 mg, 0.2 mmol, 1 equiv.) and [Ir(COD)OMe]$_2$ (3.3 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80°C under pressure of D$_2$ (1 bar) for 24 h. Then the crude reaction mixture was filtered according to the general procedure, then filtered through a short pad of silica (1g) eluted with CH$_2$Cl$_2$ and finally concentrated under reduced pressure to give the desired product 26(Ir) as a white solid with a quantitative yield.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.93 (bs, 1H, NH), 7.13–7.00 (m, 3H), 3.32–3.14 (m, 2H), 2.77–2.59 (m, 3.54H), 2.23 (s, 6H), 1.19–1.08 (t, $J$ = 7.2 Hz, 6H) ppm.

Mass: M+1(0D) 0%, M+2(1D) 34%, M+3(2D) 10.4%, M+4(3D) 3.4%: 0.6 D.
Figure S103. Mass spectrum of 26(Ir)

Figure S104. $^1$H NMR spectrum of 26(Ir)
Letrozole 27

Following general procedure with letrozole (57.0 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 27 as a white solid with a quantitative yield.

\(^1\)H NMR (400 MHz, CDCl₃) δ 8.08 (s, 0.88H), 8.06 (s, 1H), 7.74–7.66 (m, 4H), 7.32–7.27 (m, 4H), 6.80 (s, 0.13H) ppm.

\(^2\)H-{\(^1\)H} NMR (61 MHz, CHCl₃) δ 8.08, 6.77 ppm.

Mass: M+1(0D) 0%, M+2(1D) 78.8%, M+3(2D) 6.7%, M+4(3D) 0.2%; 0.9D.

Figure S105. Mass spectrum of 27
Figure S106. $^{1}$H NMR spectrum of 27 (starting material)

Figure S107. $^{1}$H NMR spectrum of 27
Following general procedure with dextromethorphan (54.3 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product **28** as a white solid with a quantitative yield.

**¹H NMR** (400 MHz, CDCl₃) δ 7.03 (d, J = 8.4 Hz, 0.85H), 6.80 (d, J = 3.0 Hz, 1H), 6.69 (dd, J = 8.4, 2.8 Hz, 1H), 3.78 (s, 3H), 2.97 (d, J = 18 Hz, 1H), 2.83–2.76 (m, 1H), 2.57 (dd, J = 18, 6 Hz, 1H), 2.46–2.38 (m, 1H), 2.36–2.31 (m, 1H), 2.14–2.01 (m, 1H), 1.87–1.75 (m, 1H), 1.75–1.67 (m, 1H), 1.67–1.59 (m, 1H), 1.55–1.48 (m, 1H), 1.41–1.22 (m, 4H), 1.19–1.03 (m, 1H) ppm.

**²H-{¹H} NMR** (61 MHz, CHCl₃) δ 7.05, 2.34 ppm.

Mass: M+1(0D) 0%, M+2(1D) 0.5%, M+3(2D) 10.0%, M+4(3D) 68.5%, M+5(4D) 17.1%, M+6(5D) 3.1%, M+7(6D) 0.5%, M+8(7D) 0.2%: 3.1D.
Figure S109. Mass spectrum of 28

Figure S110. $^1H$ NMR spectrum of 28 (starting material)
Figure S111. $^1$H NMR spectrum of 28

$^1$H NMR (400 MHz, CDCl$_3$)

Figure S112. $^2$H-$^1$H NMR spectrum of 28. The sharp peak visible at 7.26 ppm corresponds to the residual signal of CDCl$_3$. 

$^2$H-$^1$H NMR (61 MHz, CHCl$_3$)
Dextromethorphan 28(Ir)

Following general procedure with dextromethorphan (54.3 mg, 0.2 mmol, 1 equiv.) and [Ir(COD)OMe]₂ (3.3 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified according to the general procedure and gave the desired product 28(Ir) as a white solid with a quantitative yield.

$^1$H NMR (400 MHz, CDCl₃) δ 7.03 (d, $J = 8.4$ Hz, 0.92H), 6.80 (d, $J = 3.0$ Hz, 1H), 6.69 (dd, $J = 8.4$, 2.8 Hz, 1H), 3.78 (s, 3H), 2.97 (d, $J = 18$ Hz, 1H), 2.83–2.76 (m, 1H), 2.27 (dd, $J = 18$, 6 Hz, 1H), 2.46–2.38 (m, 1H), 2.38 (s, 2.72H), 2.36–2.31 (m, 1H), 2.14–2.01 (m, 1H), 1.87–1.75 (m, 1H), 1.75–1.67 (m, 1H), 1.67–1.59 (m, 1H), 1.55–1.48 (m, 1H), 1.41–1.22 (m, 4H), 1.19–1.03 (m, 1H) ppm.

Mass: M+1(0D) 0%, M+2(1D) 20.6%, M+3(2D) 5.7%, M+4(3D) 3.8%: 0.4 D.

Figure S113. $^1$H NMR spectrum of 28(Ir)
Following general procedure with maprotiline (55.5 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80°C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was purified by HPLC (C18-HDO Interchim, 100x4.6 mm, 3 µm, Flow: 1 mL/min, Room temperature) to give the formiate salt of 23. Extraction with a solution of K₂CO₃ and dichloromethane gives the product 23 as the free base (white solid).

¹H NMR (400 MHz, CDCl₃) δ 7.29–7.21 (m, 4H), 7.17–7.02 (m, 3H), 4.33–4.21 (m, 1H), 2.98–2.81 (m, 1H), 2.58–2.43 (m, 2H), 2.09–1.92 (m, 2H), 1.91–1.76 (m, 2H), 1.65–1.52 (m, 2H) ppm.

²H-{¹H} NMR (61 MHz, CHCl₃) δ 7.15, 2.90, 2.53 ppm.

Mass: M+1(OD) 0%, M+2(1D) 3.6%, M+3(2D) 11.7%, M+4(3D) 23.1%, M+5(4D) 26.5%, M+6(5D) 20.4%, M+7(6D) 10.0%, M+8(7D) 3.1%; M+9(8D) 0.7%, M+10(9D) 0.3%; 3.9D.

HPLC: tᵣ 13.80 min
HPLC program:

A/ H$_2$O +0.1%HCOOH

B/ CH$_3$CN +0.1%HCOOH

| t (min) | A (%) | B (%) |
|---------|-------|-------|
| 0       | 80    | 20    |
| 24      | 60    | 40    |
| 24.1    | 0     | 100   |
| 30      | 0     | 100   |
| 30.1    | 80    | 20    |
| 35      | 80    | 20    |

Figure S115. Mass spectrum of 29
Figure S116. $^1$H NMR spectrum of 29 (starting material)

Figure S117. $^1$H NMR spectrum of 29
Figure S118. $^2\text{H-}^1\text{H}$ NMR spectrum of 29

$^2\text{H-}^1\text{H}$ NMR (61 MHz, CHCl$_3$)

0.96 D on aromatics
Data for mass analyses and comparison with NMR analyses:

| Compound | M_{1+} (0D) | M_{2+} (1D) | M_{3+} (2D) | M_{4+} (3D) | M_{5+} (4D) | M_{6+} (5D) | M_{7+} (6D) | M_{8+} (7D) | M_{9+} (8D) | M_{10+} (9D) | M_{11+} (10D) | Total D | NMR Total D |
|----------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|---------|-------------|
| 1        | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | n.d     | 2.4         |
| 2        | 0           | 77.7        | 7.4         | 1.1         | -           | -           | -           | -           | -           | -           | -           | 1.0     | 0.9         |
| 3        | 0           | 14.3        | 25.1        | 28.5        | 18.8        | 5.0         | -           | -           | -           | -           | -           | 2.5     | 2.2         |
| 4        | 0           | 74.5        | 16.8        | 3.5         | 0.8         | -           | -           | -           | -           | -           | -           | 1.2     | 1.1         |
| 5        | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | n.d     | 7.2         |
| 6        | 0           | 20.6        | 7.5         | 6.8         | 15.2        | 4.3         | 4.8         | 5.2         | 13.0        | -           | -           | 3.1     | 3.0         |
| 7        | 0           | 24.3        | 40.6        | 16.0        | 8.7         | 0.9         | 0.4         | -           | -           | -           | -           | 2.0     | 1.9         |
| 9        | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | n.d     | 2.9         |
| 9(lr)    | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | n.d     | 0.1         |
| 10       | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | n.d     | 2.4         |
| 11       | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | -           | n.d     | 4.0         |
| 12       | 0           | 7           | 60.6        | 14.0        | 14.0        | 2.1         | 1.2         | 0.4         | 0.3         | -           | -           | 2.5     | 2.4         |
| 13       | 0           | 0.5         | 2.4         | 18.2        | 56.3        | 11.0        | 8.8         | -           | -           | -           | -           | 3.9     | 4.0         |
| 14       | 0           | 0.6         | 3.9         | 14.1        | 69.6        | 9.2         | 1.9         | 0.4         | -           | -           | -           | 3.9     | 3.9         |
| 15       | 0           | 0.3         | 5.1         | 40.1        | 35.2        | 12.4        | 5.1         | -           | -           | -           | -           | 3.6     | 3.6         |
| 16       | 0           | 0.4         | 3.3         | 21.1        | 56.0        | 13.3        | 4.2         | 0.9         | 0.3         | -           | -           | 4.0     | 4.2         |
| 17       | 0           | 0           | 0           | 4.9         | 23.8        | 32.3        | 25.6        | -           | -           | -           | -           | 5.0     | 5.0         |
| 18       | 0           | 5.0         | 85.7        | 7.2         | 1.2         | 0.5         | -           | -           | -           | -           | -           | 2.1     | 2.0         |
| 19       | 0           | 75.1        | 18.4        | -           | -           | -           | -           | -           | -           | -           | -           | 1.1     | 1.2         |
| 20       | 0           | 38.7        | 45.9        | 12.0        | 1.7         | 0.2         | -           | -           | -           | -           | -           | 1.7     | 2.0         |
| 21       | 0           | 10.7        | 49.3        | 24.1        | 6.5         | 2.0         | 1.0         | -           | -           | -           | -           | 2.2     | 2.1         |
| 22       | 0           | 40.0        | 18.1        | 1.1         | 0.6         | 0.5         | -           | -           | -           | -           | -           | 0.8     | 0.7         |
| 23       | 0           | 1.5         | 6.1         | 29.6        | 37.6        | 15.6        | 6.1         | 2.0         | 0.6         | -           | -           | 3.9     | 3.7         |
| 25       | 0           | 0           | 0           | 1.1         | 5.7         | 23.7        | 49.7        | 16.5        | 2.9         | 0.5         | -           | 5.9     | 5.5         |
| 26       | 0           | 0.1         | 0.4         | 1.8         | 8.6         | 29.4        | 43.3        | 12.2        | 3.6         | 2.1         | 1.3         | 5.9     | 5.7         |
| 26(lr)   | 0           | 34          | 10.4        | 3.4         | -           | -           | -           | -           | -           | -           | -           | 0.6     | 0.6         |
| 27       | 0           | 78.8        | 6.7         | 0.2         | -           | -           | -           | -           | -           | -           | -           | 0.9     | 1.0         |
| 28       | 0           | 0.5         | 10.0        | 68.5        | 17.1        | 3.1         | 0.5         | 0.2         | -           | -           | -           | 3.1     | 3.2         |
| 28(lr)   | 0           | 20.6        | 5.7         | 3.8         | -           | -           | -           | -           | -           | -           | -           | 0.4     | 0.4         |

*Table S3. Relative amount in percent of the non-deuterated (M_{9+}) and deuterated (M_{10+}) isotopologues in ESI* mode*

| Compound | M_{1+} (0D) | M_{2+} (1D) | M_{3+} (2D) | M_{4+} (3D) | M_{5+} (4D) | M_{6+} (5D) | M_{7+} (6D) | M_{8+} (7D) | M_{9+} (8D) | M_{10+} (9D) | M_{11+} (10D) | Total D | NMR D |
|----------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|---------|-------|
| 8        | 0           | 10.8        | 25.9        | 30.1        | 19.1        | 8.8         | 3.4         | -           | -           | -           | -           | 2.9     | 3.2   |
| 24       | 0           | 22.0        | 18.2        | 12.4        | 6.0         | -           | -           | -           | -           | -           | -           | 1.2     | 1.2   |

*Table S4. Relative amount in percent of the non-deuterated (M_{9+}) and deuterated (M_{10+}) isotopologues in ESI* mode*
II-2. Description of the tritiated products

**Dextromethorphan-T**

A 5 mL Fischer–Porter glassware was equipped with a magnetic stirrer and charged with dextromethorphan (0.02 mmol, 5.4 mg, 1 equiv.) and 0.96 mg of [Rh(COD)OMe]₂ (10 mol%) in distilled THF (0.2 mL). The solution was frozen in liquid nitrogen at the liquid/gas interface and the reaction vessel was evacuated. The Fisher Porter tube was maintained under static vacuum for 5 min to check for leaks. Then the Fisher Porter tube was charged with tritium gas, \( P_{\text{frozen}} = 458 \text{ mbar} \). The reaction mixture was then warmed to room temperature, \( P_{\text{rt}} = 637 \text{ mbar} \). As soon as the gas pressure achieved a stable value, the stirring was launched and the mixture was heated to 55 °C for 3 h. The final black solution was cooled down to room temperature and the solution was filtered through a nylon syringe filter (0.2 µm). The Fisher-Porter tube was washed with dichloromethane (3 × 0.5 mL) and the filtrate was evaporated under reduced pressure. 2 × 20 mL of MeOH were added and the solution was then evaporated. The desired product was obtained with a molar activity of 40.4 Ci mmol⁻¹ and a total activity of 496 mCi.

\(^3\)H-\(^1\)H NMR (427 MHz, CDCl₃) \( \delta 2.49, 2.46, 2.43 \text{ ppm} \).

Mass: M+3 (1T) 29%, M+5 (2T) 28.5%, M+7 (3T), 16.6%: 1.4T.
Figure S119. $^3$H-$^1$H NMR spectrum of dextrometorphan-T

Figure S120. Mass spectrum of dextromethorphan-T
Figure S121. HPLC chromatogram for dextromethorphan-T

Nefiracetam-T

A 5 mL Fischer–Porter glassware equipped with a magnetic stirrer was charged with nefiracetam (0.02 mmol, 4.9 mg, 1 equiv.) and 0.96 mg of [Rh(COD)OMe]₂ (10 mol%) in distilled THF (0.2 mL). The solution was frozen in liquid nitrogen at the liquid/gas interface and the reaction vessel was evacuated. The Fisher Porter tube was maintained under static vacuum for 5 min to check for leaks. Then the Fisher Porter tube was charged with tritium gas, \( P_{\text{tr}} = 542 \text{ mbar} \). The reaction mixture was warmed to room temperature, \( P_{\text{rt}} = 710 \text{ mbar} \). As soon as the gas pressure achieved a stable value, the stirring was launched and the mixture was heated to 55 °C for 2 h. The final black solution was cooled down to room temperature and the solution was filtered through a nylon syringe filter (0.2 µm). The Fisher-Porter tube was washed with dichloromethane (3 × 0.5 mL) and the filtrate was evaporated under reduced pressure. 2 × 20 mL of MeOH was added and the solution was
then evaporated. The crude product was dissolved in 350 mL of MeOH and analysed by liquid scintillation counting and mass. Total activity = 1380 mCi. 100 mL (= 395 mCi) of the crude product was purified by HPLC (Column long HDO-150×100 Interchim N°: 1928218, D = 4 mL/min, UV detection: 210 & 262 nm, with a cell Berthold Z1000-SM). The desired product was obtained with a molar activity of 113.0 Ci mmol\(^{-1}\) and a total activity of 251 mCi.

\(^{3}\text{H}-\{^{1}\text{H}\} \text{NMR (427 MHz, CDCl}_3) \delta 2.31, 2.28, 2.26 \text{ ppm.}

Mass: M+3 (1T) 3.9%, M+5 (2T) 11.3%, M+7 (3T) 20.2%, M+9 (4T) 20.2%, M+11 (5T) 23.1%, M+13 (6T) 11.4%: 3.9T.

HPLC: t\(_R\) 10.55-11.22 min

Figure S122. \(^{3}\text{H}-\{^{1}\text{H}\} \text{NMR spectrum of nefiracetam-T} \)
Figure S123. Mass spectrum of nefiracetam-T

HPLC program
A/ H$_2$O +0.1%HCOOH
B/ MeCN +0.1%HCOOH

| t (min) | A (%) | B (%) |
|--------|------|------|
| 0      | 95   | 5    |
| 24     | 0    | 100  |
| 24.1   | 0    | 100  |
| 30     | 0    | 100  |
| 30.1   | 95   | 5    |
| 35     | 95   | 5    |
II-3. TEM analyses

Procedure for TEM grids preparation: 4 μL of the corresponding solution was deposited on a carbon film 200 Mesh Copper (50) and analyzed by TEM (samples containing substrates 3 and 13 were diluted 10 times).

| Substrate | T(°C) | Catalyst loading (mo%) | Solvent | Nps size | Histogram | TEM image |
|-----------|-------|------------------------|---------|----------|-----------|-----------|
| [Rh(COD)OMe] / No substrate | 25 | - | THF | 3.2 ± 0.6 nm | | |
| Compound                          | Temp | Solvent     | Diameter (nm) |
|---------------------------------|------|-------------|---------------|
| [Rh(COD)OMe]₂ / No substrate    | 25   | DMF         | 3.1 ± 0.4 nm  |
| [Rh(COD)OMe]₂ / No substrate    | 25   | Cyclohexane | 4.7 ± 0.8 nm  |
| indole 1                         | 25   | THF         | 3.0 ± 0.4 nm  |
| 2-(4-methoxyphenyl)pyridine 3    | 25   | THF         | 3.1 ± 0.6 nm  |
| System                        | Temp | pH  | Solvent          | Average Dm (nm) |
|-------------------------------|------|-----|------------------|-----------------|
| Diphenylmethane 10           | 25   | 2.5 | THF              | 3.2 ± 0.5 nm    |
| Diphenylmethane 10 + diethylamine (2 equiv.) | 25   | 2.5 | THF              | 3.2 ± 0.4 nm    |
| Diphenylmethane 10 + 1,3-dicyclohexylimidazolium chloride (5 mol%) | 25   | 2.5 | THF              | 3.0 ± 0.5 nm    |
| Dodecylamine 12              | 80   | 2.5 | 2-MeTHF          | 3.3 ± 0.5 nm    |
| Compound    | Temp | Dilv | Solvent   | Diameter (nm) |
|-------------|------|------|-----------|---------------|
| Dodecylamine 12 | 80   | 2,5  | Cyclohexane | 5.0 ± 0.7 nm  |
| Dodecylamine 12 | 80   | 2,5  | DMF       | 3.1 ± 0.4 nm  |
| Dioctylamine 13 | 80   | 2,5  | 2-MeTHF   | 3.1 ± 0.5 nm  |
| Pyrrolidine 14  | 80   | 2,5  | 2-MeTHF   | 3.3 ± 0.5 nm  |
|                   | Size | Condition          | Size | Condition          |
|-------------------|------|--------------------|------|--------------------|
| **Lidocaine 26**  | 80   | 2.5                | 2-MeTHF | 3.1 ± 0.5 nm |
| **Lidocaine 26**  | 80 (48h) | 5 | 2-MeTHF | 3.2 ± 0.3 nm |
| **Dextromethorphan 28** | 55 (650 mbar, 3h) | 10 | THF | 2.8 ± 0.6 nm |
| **Dextromethorphan 28** | 80 | 2.5 | 2-MeTHF | 3.1 ± 0.5 nm |

Table S5. Representative TEM images of RhNps in different conditions
III. Recyclability studies

III-1. General procedure

Following general procedure with dodecylamine (37 mg, 0.2 mmol, 1 equiv.) and [Rh(COD)OMe]₂ (2.4 mg, 0.005 mmol, 2.5 mol%) in 2 mL of dry 2-MeTHF. The reaction mixture was stirred at 80 °C under pressure of D₂ (1 bar) for 24 h. Then the crude reaction mixture was concentrated under vacuum and distilled THF and water were added followed by addition of the additive (for DANTA: 1.5 mL of dry THF, 0.5 mL H₂O and 40 mg of DANTA; for PDAMAC: 2 mL of dry THF, 0.5 mL of H₂O, 0.1 mL of PDAMAC 20 wt% in water; for sodium oleate: 2 mL of a stock solution (0.441 mL of oleic acid in 10.2 mL of THF with 55.99 mg of NaOH in 3.4 mL of H₂O)). The solution was centrifuged and the supernatant was removed and analyzed. The black solid obtained was reused for a new run on dodecylamine or lidocaine.

III-2. Results obtained

| Additive          | 1st run | 2nd run | 3rd run | 4th run | 5th run |
|-------------------|---------|---------|---------|---------|---------|
| DANTA (0.32 equiv.) | 2.0     | 2.0     | 1.8     | 2.0     | 2.1     |
| PDAMAC (0.65 equiv.) | 1.6     | 1.4     | 1.3     | 0.4     | -       |
| Sodium oleate (1 equiv.) | 2.0     | 1.9     | 0.9     | 0.3     | -       |

*Table S6. Recycling of RhNps using different additives. Numbers represent the total number of deuterium atoms incorporated*
Figure S126. Recycling of RhNps using DANTA as the additive

Figure S127. Recycling of RhNps using PDAMAC as the additive

Figure S128. Recycling of RhNps using sodium oleate as the additive
### III-3. TEM analyses

| Substrate             | Run number | T(°C) | Solvent     | Nps size    | Histogram | TEM image |
|-----------------------|------------|-------|-------------|-------------|-----------|-----------|
| dodecylamine 12 + DANTA | 5          | 80    | 2-MeTHF     | 3.0 ± 0.5 nm | ![Histogram](image1.png) | ![TEM image](image2.png) |
| lidocaine 26 + RhNPs/DANTA (with RhNPs/DANTA used in five runs with 12) | 6          | 80    | 2-MeTHF     | 3.4 ± 0.4 nm | ![Histogram](image3.png) | ![TEM image](image4.png) |