

Supplementary Information

Radiolabeling of Oligopeptides by Selective Hydrogen Isotope Exchange with Deuterium and Tritium in Aqueous Buffers

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1 Materials and Equipment

All chemicals and solvents commercially received were used without any further purification. Deuterium (99.8%) in 25/45 L gas cylinders was purchased from Sigma-Aldrich.

1.1 Used catalysts

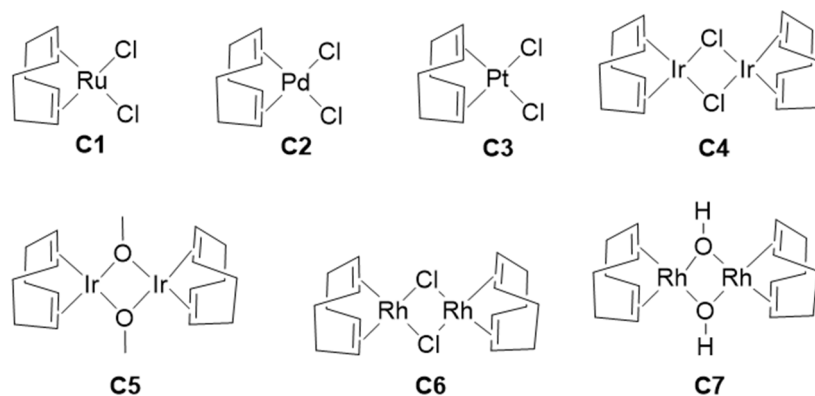


Figure S1: Structures of used commercially available catalysts **C1-7**.

Commercially available catalysts and suppliers are displayed in Table S1 below.

Table S1: Used commercially available catalysts with CAS number and supplier.

Catalyst	CAS	Supplier
$\text{Ru}(\text{COD})\text{Cl}_2$ C1	50982-12-2	BLD
$\text{Pd}(\text{COD})\text{Cl}_2$ C2	12107-56-1	Abcr GmbH
$\text{Pt}(\text{COD})\text{Cl}_2$ C3	12080-32-9	Thermo Fisher
$[\text{Ir}(\text{COD})\text{Cl}]_2$ C4	12112-67-3	Aldrich
$[\text{Ir}(\text{COD})(\text{OMe})]_2$ C5	12148-71-9	Abcr GmbH
$[\text{Rh}(\text{COD})\text{Cl}]_2$ C6	12098-47-6	Aldrich
$[\text{Rh}(\text{COD})(\text{OH})]_2$ C7	73468-85-6	Abcr GmbH

1.2 Used ligands

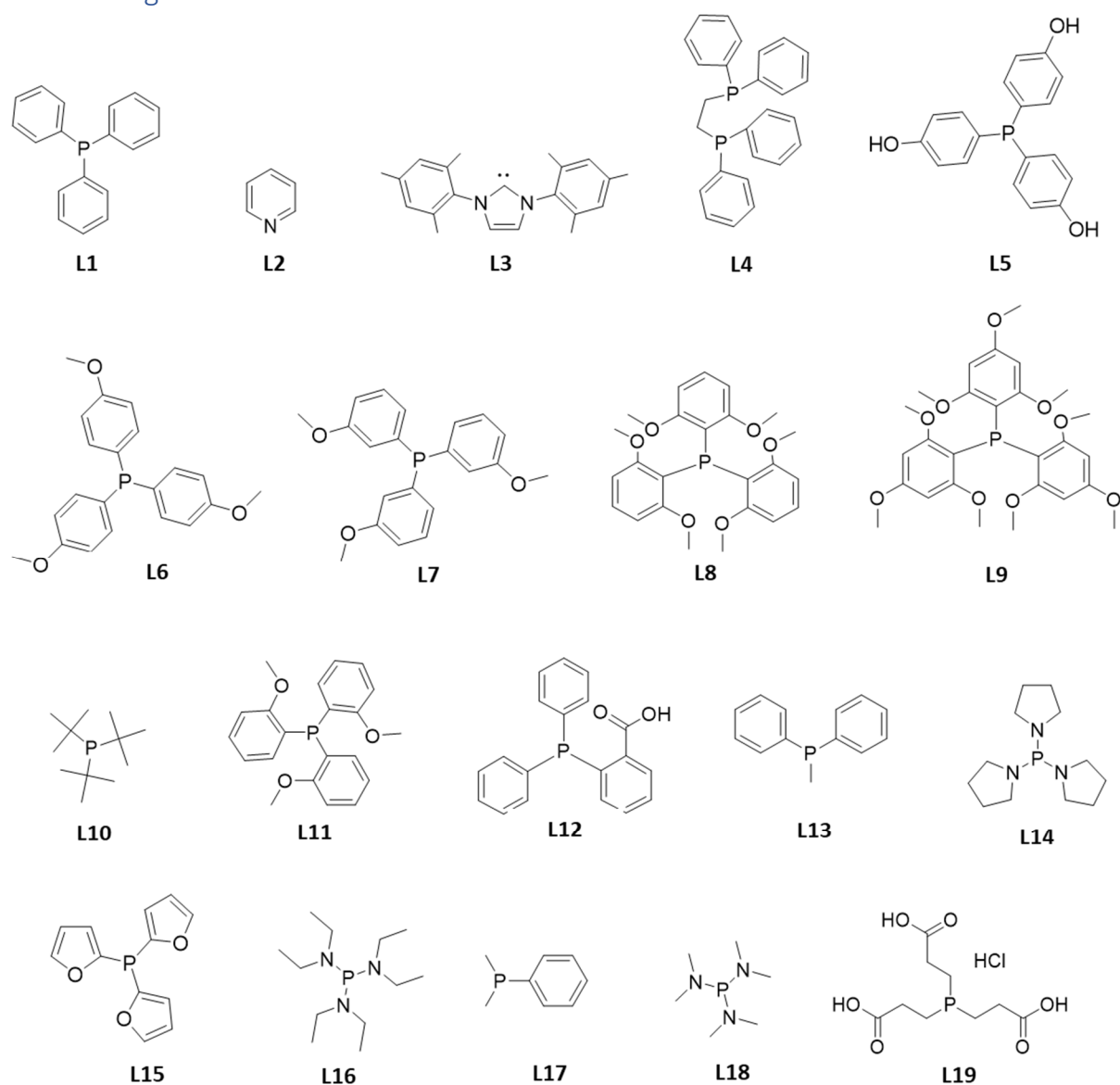


Figure S2: Structures of used commercially available ligands **L1-19**.

1.3 Analytical methods

LC-MS spectra were obtained on Agilent 1200 Series (Agilent Technologies).

Column: Luna C18(2) 10x2 mm, particle size: 5 μm

Mobile phase A: H_2O + 0.05% TFA

Mobile phase B: ACN + 0.05% TFA

Flow rate: 0.5 mL/min

Detection: UV 254 nm and UV 210 nm

HR-MS spectra were obtained on a Vanquish (Thermo Fisher) couple with a Bruker Compact QTOF.

Column: CSH Peptide C18-N11, 150x2.1 mm, particle size: 1.7 μm

Mobile phase A: H₂O/ACN/TFA 900:100:0.5
Mobile phase B: H₂O/ACN/TFA 100:900:0.375
Flow rate: 0.25 mL/min
Detection: UV 10 nm, UV 220 nm, UV 254 nm and UV 280 nm

Purification of peptides done by RP-HPLC.
Column: HyPURITY C18 150x21.2 mm, particle size: 5 µm
Mobile phase A: H₂O + 0.05% TFA
Mobile phase B: ACN + 0.05% TFA
Detection: UV 210 nm

Stability test run by UHPLC.
UHPLC spectra were obtained on a Vanquish instrument from Thermo Fischer Scientific.
Column: Waters Acquity Peptide CSH 130 C18 150x2.1 mm, particle size: 1.7 µm
Mobile phase A: H₂O/ACN/TFA 900:100:0.5
Mobile phase B: H₂O/ACN/TFA 100:900:0.375
Flow rate: 0.5 mL/min
Detection: UV 220 nm and radiodetection

¹H-NMR, ³¹P-NMR, deuterium (²H)-NMR and tritium (³H)-NMR spectra were obtained on Bruker 300 UltraShieldTM spectrometer (Bruker BioSpin AG). The chemical shifts (δ) are expressed in ppm and are adapted to the proton signal the respective solvent. The blue dots reported in the chemical structures as well as the blue arrows reported in the NMR spectra indicate the position(s) of hydrogen-deuterium exchange and are determined by ²H-NMR run in non-deuterated solvent. All spectra were recorded at room temperature.

For determination of NMR yields, a 39 mM stock solution of maleic acid (purchased from Sigma-Aldrich) in D₂O was prepared. Each sample was solubilized in 0.7 mL of the prepared solution and analyzed by ¹H-NMR.

pH was measured using the Orion Star A211 pH meter (Thermo Fisher Scientific) and the pH meter was calibrated with pH 4/7/10 technical pH buffer solutions (VWR Chemicals).

1.4 Buffers

1.4.1 Sorensen's Phosphate Buffer (SPB)¹

Two stock solutions were prepared for SPB. 4.5 g of KH₂PO₄ were solubilized in 500 mL of deionized water to obtain Stock A. 5.9 g of Na₂HPO₄ • 2H₂O were solubilized in 500 mL of deionized water to obtain Stock B.

- Buffer pH 5.9: 43.95 mL of Stock A + 6.05 mL of Stock B
- Buffer pH 6.9: 19.40 mL of Stock A + 30.60 mL of Stock B

1.4.2 Borax/HCl Buffer¹

Borax buffer was obtained by dissolving 125.8 mg of anhydrous borax in different HCl (0.1 M) volumes according to the desired pH and filled up to 50 mL with deionized water.

- Buffer pH 8: 10.25 mL of HCl (0.1 M)
- Buffer pH 9: 2.3 mL of HCl (0.1 M)

1.4.3 PBS Buffer

PBS buffer was obtained by dissolving 400 mg of NaCl, 10 mg of KCl, 72 mg of Na₂HPO₄ and 12.25 of NaH₂PO₄ in 40 mL of deionized water, adjusting the pH at 7.4. The solution was added with water until 50 mL.

2 Analysis of deuterium incorporation

Analysis of deuterium incorporation by LC-MS was performed using IsoPat2 evaluation in Excel (Excel sheet: Excel-Worksheet for deconvolution of MS-patterns (D, ¹⁷O, ¹³C, ¹⁵N) by GRUBER and KROUTIL).³ This calculation method compares the ratios of the peaks in the mass spectrum of the isotopically labeled compound with those of the unlabeled starting material. By considering the isotope distribution of the unlabeled molecule, this method allows the determination of the deuterium incorporation.

Analysis of deuterium incorporation into a molecule by ¹H-NMR was performed using MestReNova 15.0.03 software. The ¹H-NMR spectra were adjusted to the respective solvent after the measurement. The comparison of the peak area of the signal to be analyzed before and after isotope labeling was done according to the following equation 1.

$$\text{Deuterium incorporation} = \text{Peak intensity before labeling} - \text{Peak intensity after labeling} \quad (1)$$

3 Identification of active catalytic system for aliphatic Hydrogen Isotope Exchange (HIE)

3.1 Screening of *in situ* catalytic systems

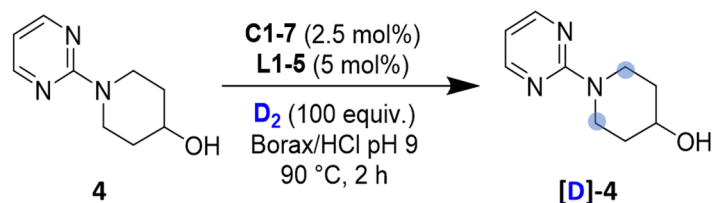
All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

Catalysts **C1-7** in combination with ligands **L1-5** were screened with compound **4** at 90 °C for 2h in 3 mL of Borax/HCl buffer pH 9.

A 6 mM stock solution of each catalyst and a 30 mM stock solution of each ligand were prepared using dioxane as solvent.

Compound **4** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl buffer pH 9 and the amount of the selected catalyst (2.5 mol%, 0.025 equiv.) and ligand (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to the reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D₂ atmosphere (100 equiv.) for 2 h at 90 °C. The reaction mixture was filtered through a syringe filter (0.45 µm) and one aliquot was analyzed by LC-MS.

Table S2: Catalytic system screening for the HIE of compound **4**, deuterium content reported as D/molecule as an average of three reactions analyzed by LC-MS (red < 0.20 D/molecule, orange 0.20 – 0.75 D/molecule, green > 0.75 D/molecule).



Entry	Catalyst	L1	L2	L3	L4	L5
1	Ru(COD)Cl ₂ C1	0.26	0	0	0	0
2	Pd(COD)Cl ₂ C2	0.13	0.20	0	0.20	0.20
3	Pt(COD)Cl ₂ C3	0.18	0.39	0.15	0.10	0.10
4	[Ir(COD)Cl] ₂ C4	0.17	0.25	0.10	0.20	1.24
5	[Ir(COD)(OMe)] ₂ C5	0.12	0.10	0	0.12	2.36
6	[Rh(COD)Cl] ₂ C6	0.38	0	0.68	0.34	0.47
7	[Rh(COD)(OH)] ₂ C7	0.51	0	0.80	0.24	0

a) average of three reactions, analyzed by LC-MS

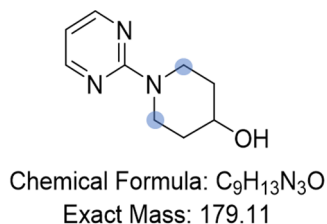


Figure S3: Structure of 1-(pyrimidin-2-yl)piperidin-4-ol **4**.

¹H-NMR (300 MHz, MeOD): δ [ppm] = 8.31 (d, *J* = 4.8 Hz, 2H), 6.57 (t, *J* = 4.8 Hz, 1H), 4.45-4.37 (m, 2H), 3.91-3.85 (m, 1H), 3.29-3.23 (m, 2H), 1.96-1.87 (m, 2H), 1.53-1.41 (m, 2H). Analytical data compared to literature.⁴

Incorporation expected at δ 4.45-4.37 and δ 3.29-3.23. (blue arrows, blue dots in the structure). Determined against integral at δ 6.57 (grey arrow). As reported in literature.⁵

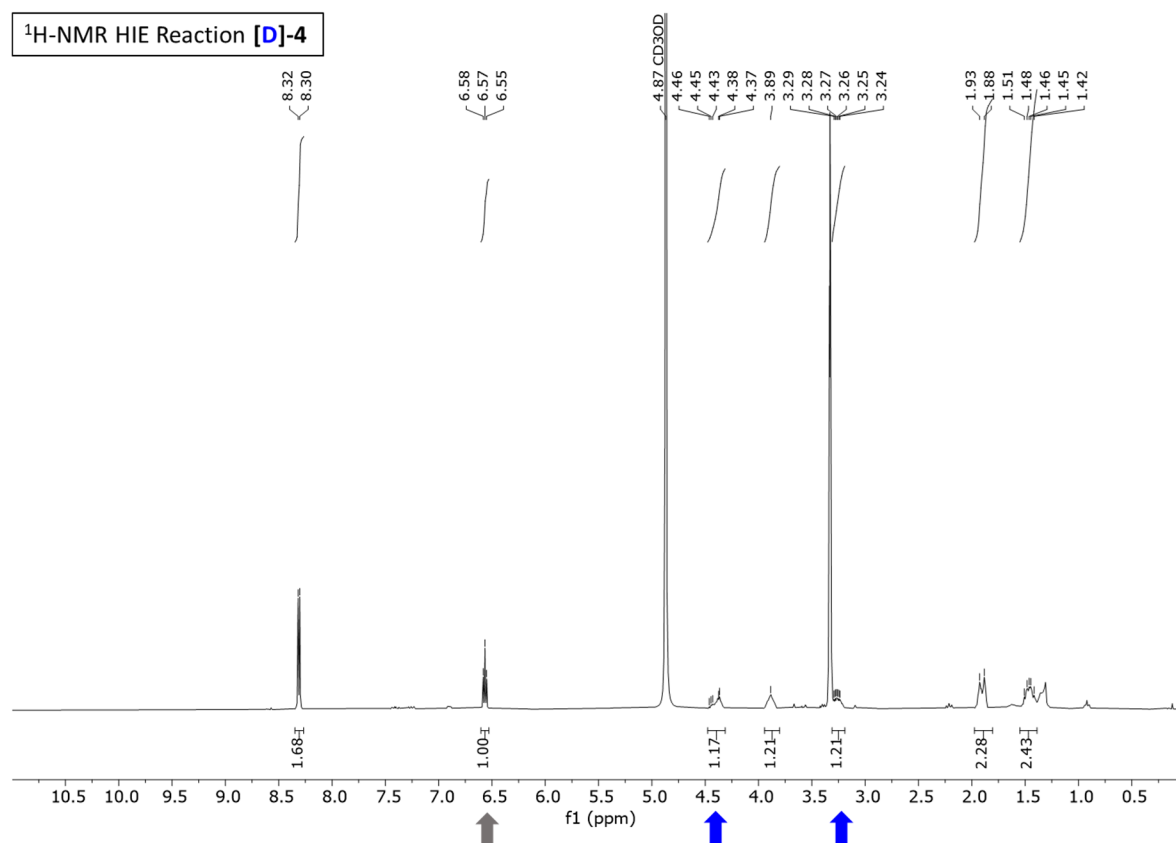
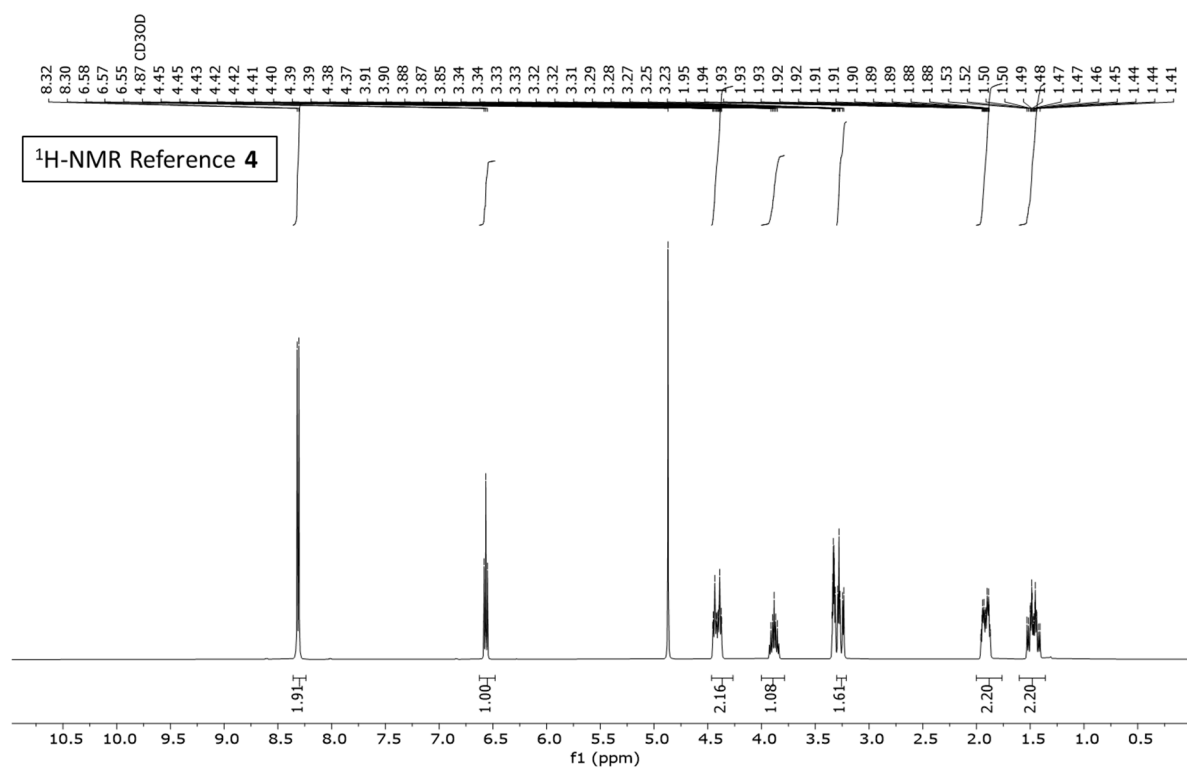


Figure S4: ¹H-NMR spectra of reference compound 4 and the crude of the deuteration reaction yielding [D]-4.

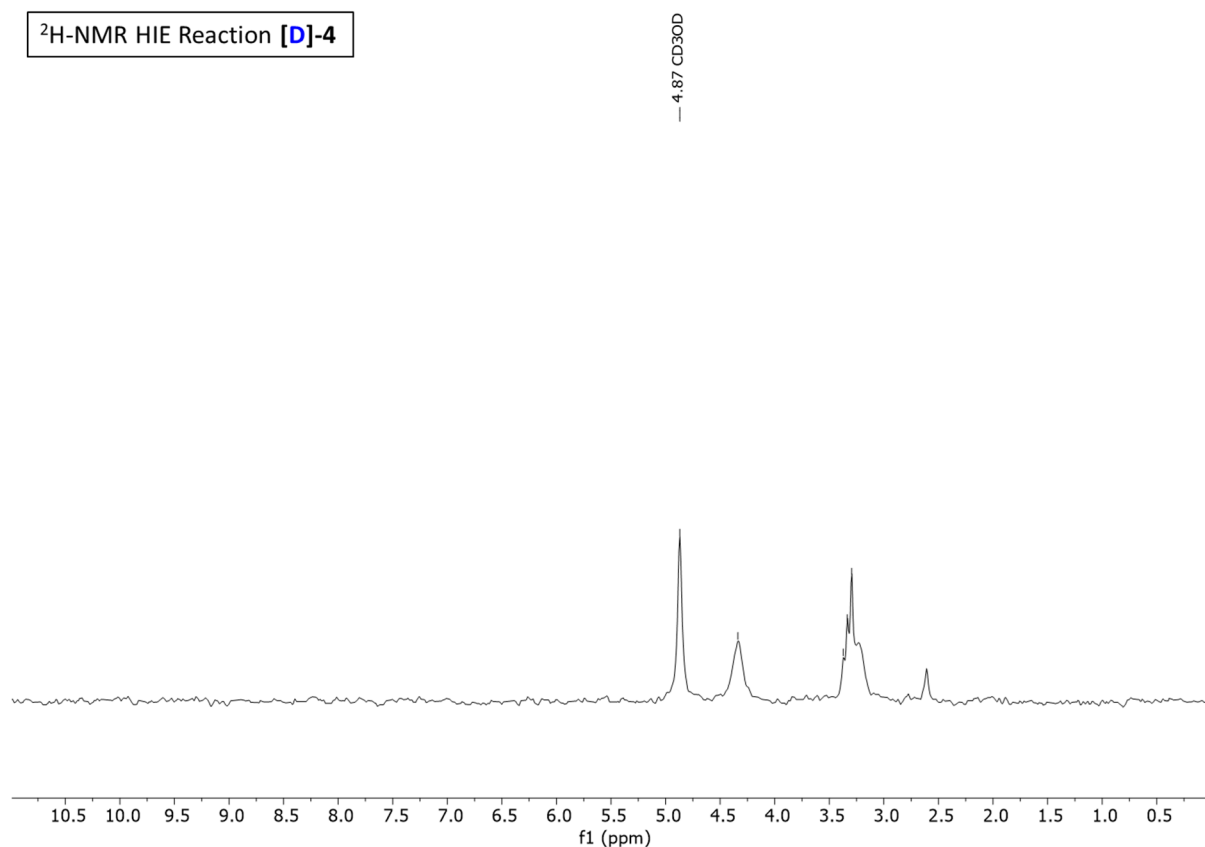


Figure S5: ²H-NMR spectra of the deuteration crude reaction yielding [D]-4.

The reduction of the pyrimidine ring is occurring when rhodium is used, especially in combination with pyridine. In a few cases the saturation of the pyrimidine is the prevalent reaction. The conditions used for the screening with [Rh(COD)Cl]₂ and pyridine have been repeated using H₂ instead of D₂. As shown here below, all the aromatic peaks have disappeared in comparison with the starting material. The reported product is consistent with literature.⁶

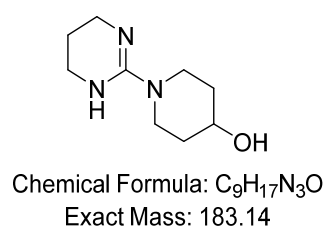


Figure S6: 1-(1,4,5,6-tetrahydropyrimidin-2-yl)piperidin-4-ol **4a**.

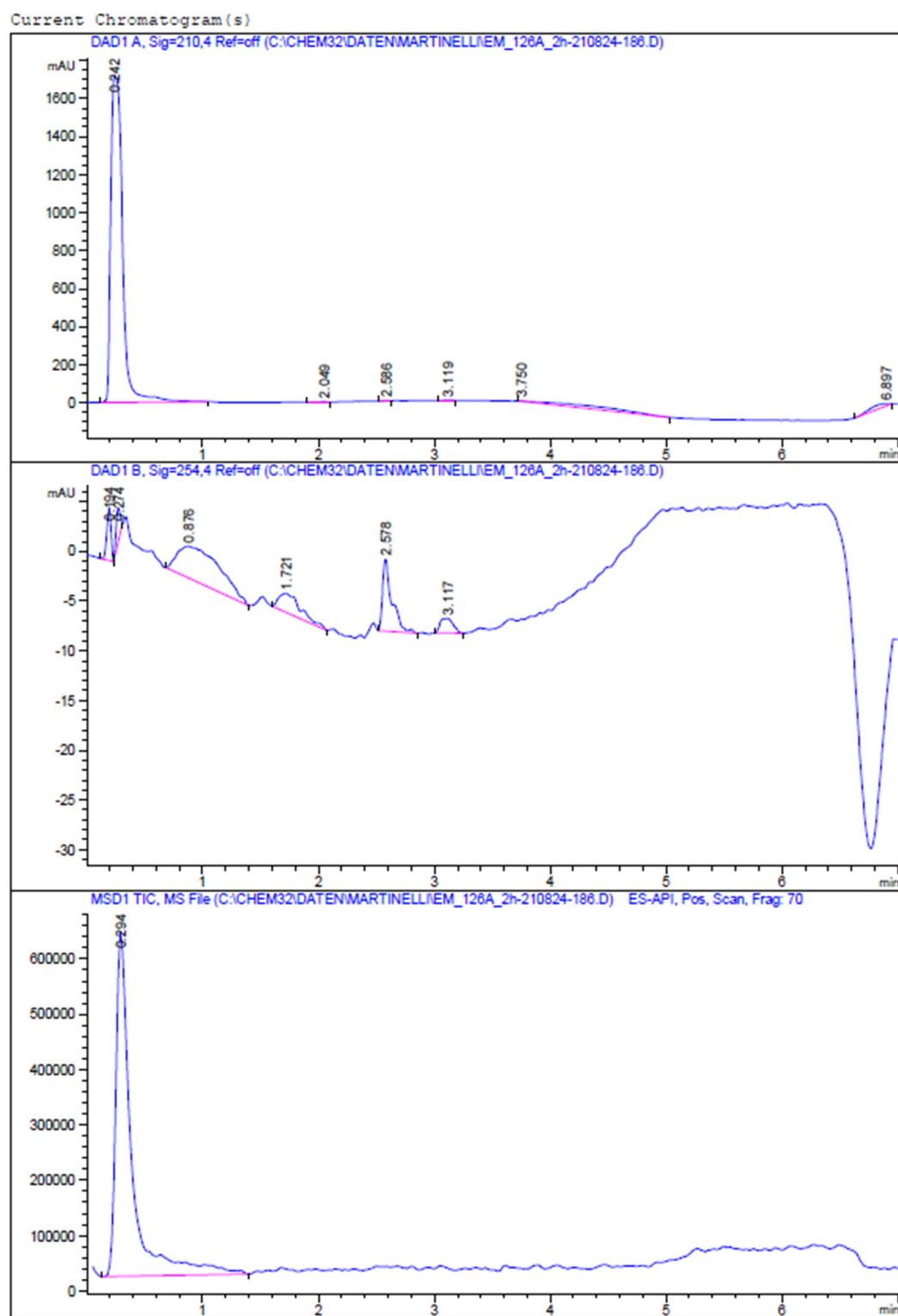


Figure S7: LC-MS spectra of hydrogenated product **4a**.

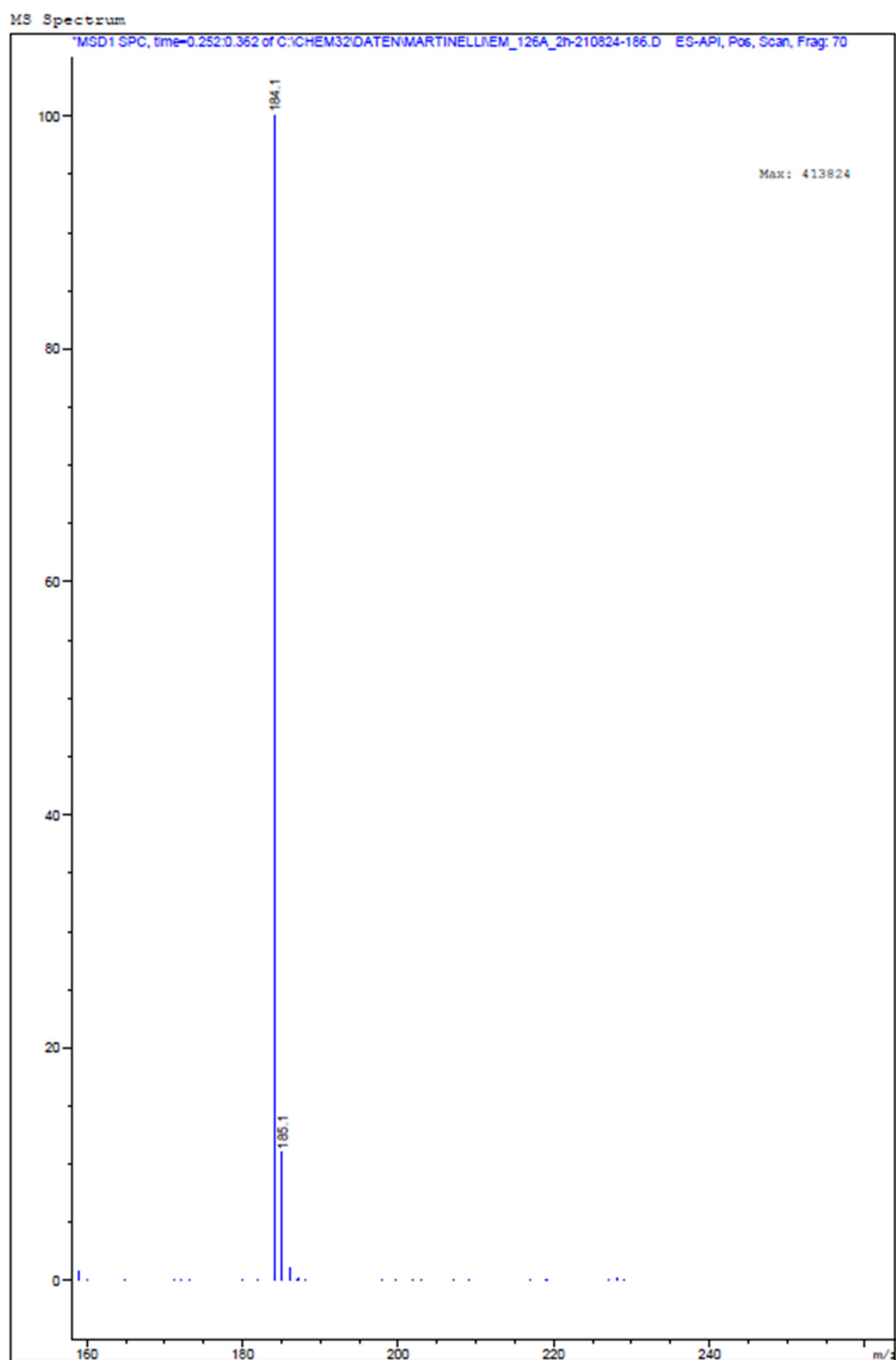


Figure S8: MS spectrum of hydrogenated product **4a**.

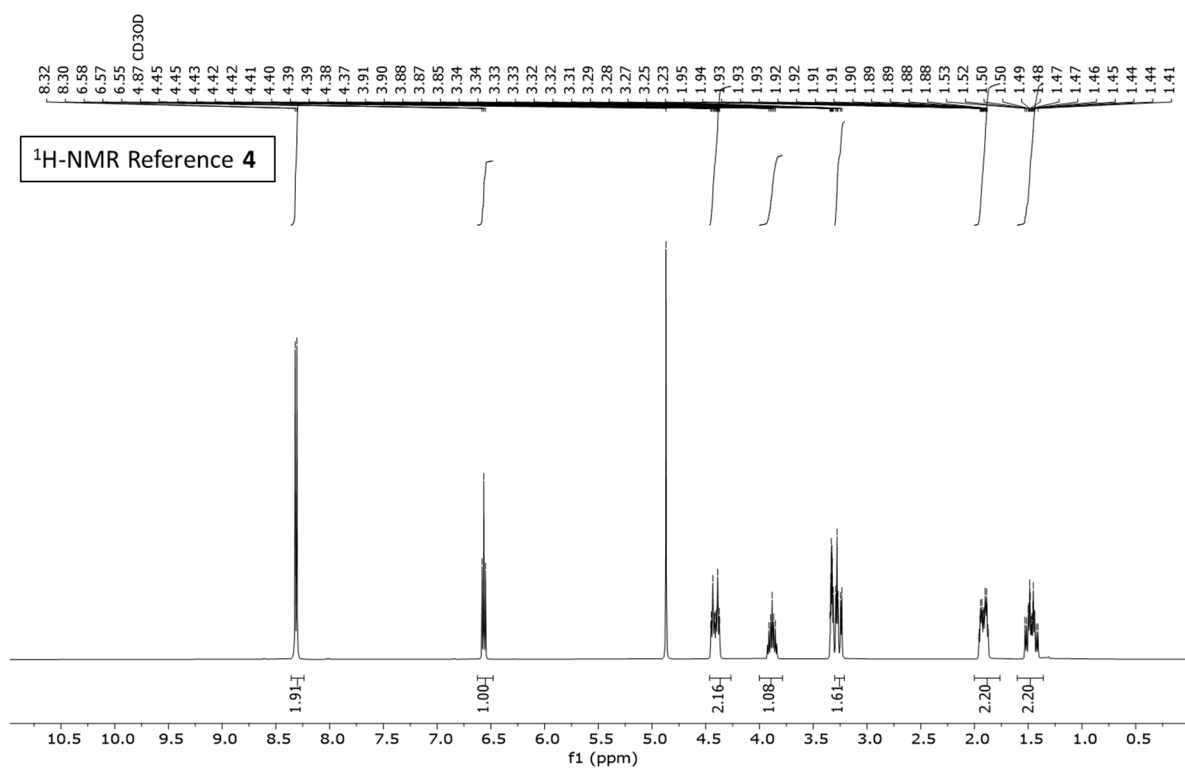


Figure S9: ¹H-NMR spectrum of reference compound **4**.

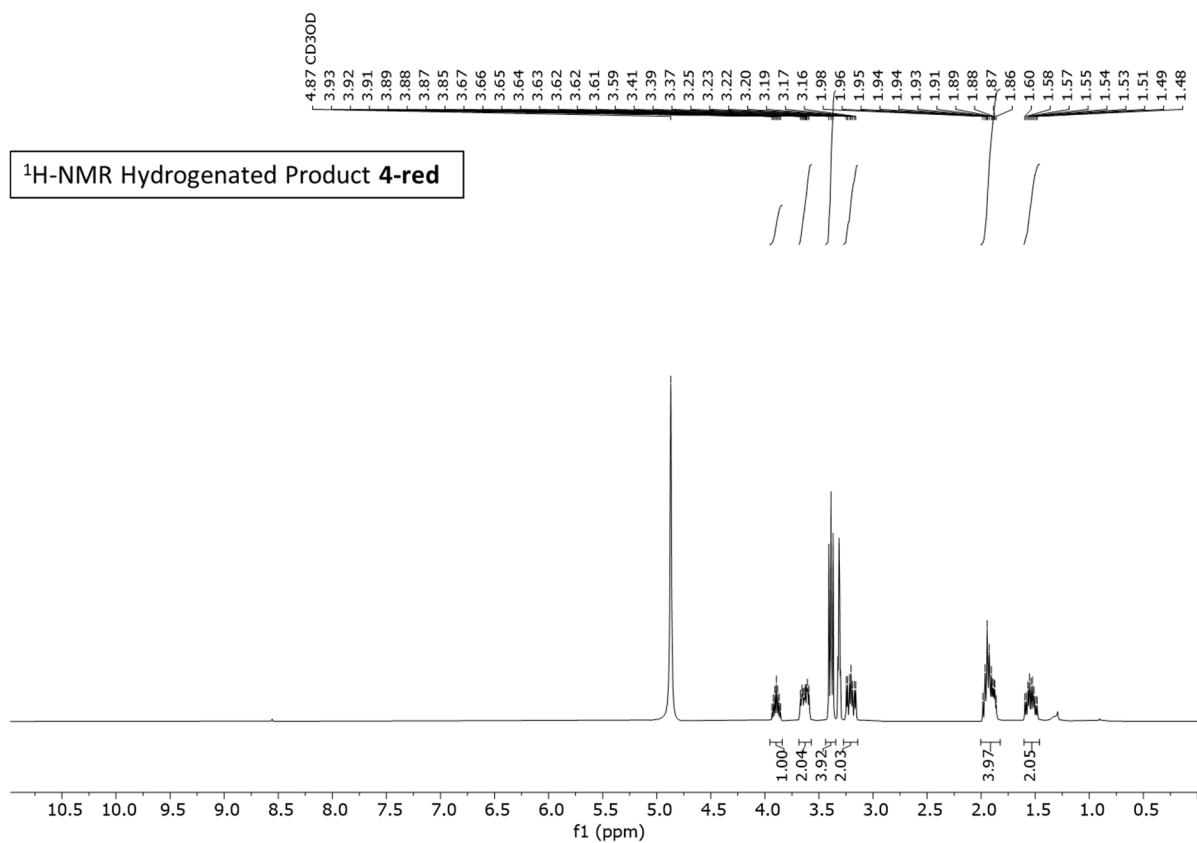


Figure S10: ¹H-NMR spectrum of hydrogenated product **4a**.

3.2 *In situ* formation of catalytic systems

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

Catalyst **C4** was tested with ligands **L1-3** with compound **4** as substrate in 3 mL of Borax/HCl buffer pH 9 at 90 °C for 2h.

A 6 mM stock solution of each catalyst and a 30 mM stock solution of each ligand were prepared using dioxane as solvent.

Compound **4** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl buffer pH 9 and the amount of catalyst **C4** (2.5 mol%, 0.025 equiv.) was dispensed as the previously prepared stock solution and added to the solution. Ligand **L1** (5 mol%, 0.025 equiv.) for entry 1, ligand **L1** (2.5 mol%, 0.025 equiv.) and **L2** (2.5 mol%, 0.025 equiv.) for entry 2, and ligands **L1** (2.5 mol%, 0.025 equiv.) and **L3** (2.5 mol%, 0.025 equiv.) for entry 3 were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D₂ atmosphere (100 equiv.) for 2 h at 90 °C. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS.

Table S3: *In situ* formation of common catalytic systems, deuterium content for compound **4** reported as D/molecule as an average of three reactions analyzed by LC-MS (red < 0.20 D/molecule, orange 0.20 – 0.75 D/molecule, green > 0.75 D/molecule).

Entry	Catalytic system	D/molecule
1	[Ir(COD)Cl] ₂ C4 + L1 + L1	0.17
2	[Ir(COD)Cl] ₂ C4 + L1 + L2	0.14
3	[Ir(COD)Cl] ₂ C4 + L1 + L3	0.22

a) average of three reactions, analyzed by LC-MS

3.3 Screening of amino acids

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

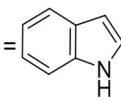
Catalysts **C4**, **C5** or **C7** were tested in combination with ligands **L3** (for **C7**) or **L5** (for **C4** and **C5**) with five different amino acids in 3 mL of Borax/HCl buffer pH 9 at 90 °C for 2h.

A 6 mM stock solution of each catalyst and a 30 mM stock solution of each ligand were prepared using dioxane as solvent.

Each amino acid (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl buffer pH 9 and the amount of the selected catalyst (2.5 mol%, 0.025 equiv.) and ligand (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to the reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was

stirred under D₂ atmosphere (100 equiv.) for 2 h at 90 °C. The reaction mixture was filtered through a syringe filter (0.45 µm) and one aliquot was analyzed by LC-MS.

Table S4: Screening of the three best catalytic systems with five different amino acids (AAs), deuterium incorporation reported as D/molecule as an average of three reactions analyzed by LC-MS (red < 0.20 D/molecule, orange 0.20 – 0.75 D/molecule, green > 0.75 D/molecule).

$ \begin{array}{c} \text{R-CH(NH}_2\text{)-COOH} \\ \text{AA} \end{array} \xrightarrow[\text{D}_2 \text{ (100 equiv.)}]{\text{C4 or C5 or C7 (2.5 mol\%)} \\ \text{L3 or L5 (5 mol\%)}} \begin{array}{c} \text{R-CH(NH}_2\text{)-COOH} \\ \text{[Dx]-AA} \end{array} $ Borax/HCl pH 9 90 °C, 2 h						
		L-Ser 5 , R = OH	L-Glu 6 , R = CH ₂ COOH	L-Lys 1 , R = (CH ₂) ₃ NH ₂	L-His 7 , R = 	L-Trp 8 , R = 
Entry	Catalytic system	L-Ser	L-Glu	L-Lys	L-His	L-Trp
1	[Ir(COD)(OMe)] ₂ C5 + L5	0	0	0.17	0	0
2	[Ir(COD)Cl] ₂ C4 + L5	0	0	1.10	0	0
3	[Rh(COD)(OH)] ₂ C7 + L3	0	0	0	0	0

3.4 Screening of phosphine ligands

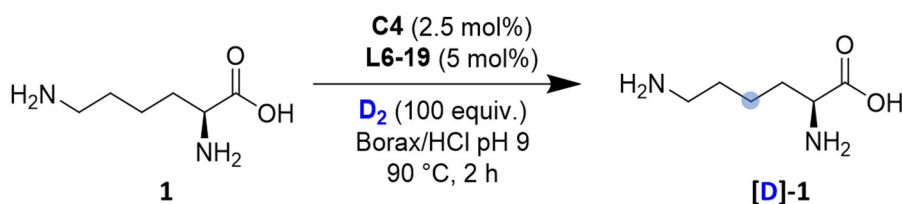
All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

Catalyst [Ir(COD)Cl]₂ **C4** was tested in combination with ligands **L6-19** with L-Lys **1** in 3 mL of Borax/HCl buffer pH 9 at 90 °C for 2h.

A 6 mM stock solution of catalyst [Ir(COD)Cl]₂ **C4** and a 30 mM stock solution of each ligand were prepared using dioxane as solvent.

Compound L-Lys **1** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl buffer pH 9, catalyst [Ir(COD)Cl]₂ **C4** (2.5 mol%, 0.025 equiv.) and the selected ligand (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D₂ atmosphere (100 equiv.) for 2 h at 90 °C. The reaction mixture was filtered through a syringe filter (0.45 µm) and one aliquot was analyzed by LC-MS.

Table S5: Ligand screening for the HIE reaction of L-Lys **1** with catalyst [Ir(COD)Cl]₂ **C4**.



Entry	Ligand	LogP	D/molecule ^a
1	L6	-4.4	0.36
2	L7	-4.4	0.16
3	L8	-4.4	0.19
4	L9	-4.3	0.14
5	L10	-4.3	0.10
6	L11	-4.2	1.49
7	L12	-4.2	0.29
8	L13	-4.0	1.08
9	L14	-3.8	0.10
10	L15	-3.7	0.32
11	L16	-3.6	0
12	L17	-3.6	1.16
13	L18	-3.5	0
14	L19	-3.1	0

a) average of three reactions, analyzed by LC-MS

4 Reaction optimization

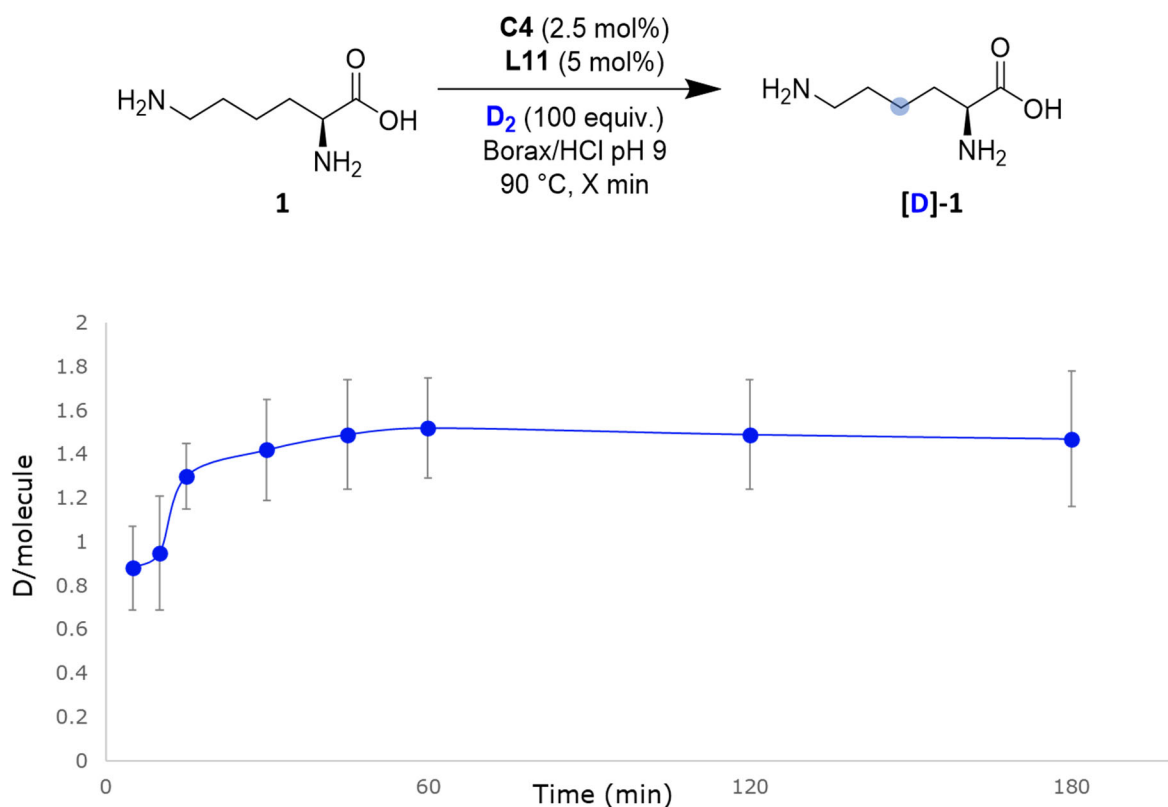
4.1 Screening of reaction time

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

A 6 mM stock solution of catalyst [Ir(COD)Cl]₂ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

Compound L-Lys **1** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl buffer pH 9, catalyst [Ir(COD)Cl]₂ **C4** (2.5 mol%, 0.025 equiv.) and the ligand **L11** (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D_2 atmosphere (100 equiv.) at 90 °C. At different time points, an aliquot of the reaction mixture was filtered through a syringe filter (0.45 μ m) and analyzed by LC-MS.

Table S6: Screening of reaction time for the HIE reaction with L-Lys **1**.



Entry	Time (min)	D/molecule ^a	Standard deviation
1	5	0.88	0.19
2	10	0.95	0.26
3	15	1.30	0.15
4	30	1.42	0.23
5	45	1.49	0.25
6	60	1.52	0.23
7	120	1.49	0.25
8	180	1.47	0.31

a) average of three reactions, analyzed by LC-MS

4.2 Screening of catalyst load

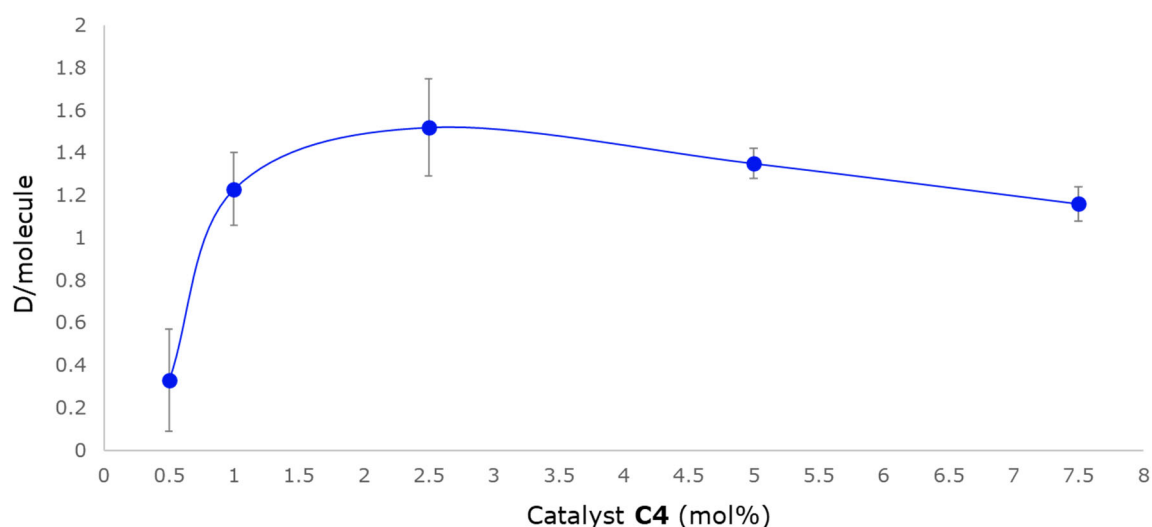
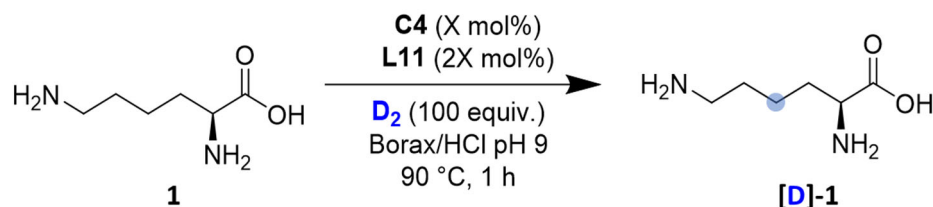
All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

A 6 mM stock solution of catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

Compound L-Lys **1** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl buffer pH 9, catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** (X mol%) and the ligand **L11** (2X mol%) were dispensed as the previously prepared stock

solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D₂ atmosphere (100 equiv.) at 90 °C for 1 h using the cooling system of the synthesis station. The reaction mixture was filtered through a syringe filter (0.45 µm) and one aliquot was analyzed by LC-MS.

Table S7: Screening of catalyst load in the HIE reaction with L-Lys **1**.



Entry	C4 (mol%)	D/molecule ^a	Standard deviation
1	0.5	0.33	0.24
2	1	1.23	0.17
3	2.5	1.52	0.23
4	5	1.35	0.07
5	7.5	1.16	0.08

a) average of three reactions, analyzed by LC-MS

To analyze the particles present in the reaction mixture, 10 µmol of the unfiltered crude mixture were analyzed on a A. Krüss – Optronic MBL2100 230VAC 20 W microscope with a 10x zoom. To calculate the amount of deuterium present in the solvent ²H-NMR analysis was performed. The crude reaction mixture was filtered through a syringe filter (0.45 µm) and 0.1 mL of the filtered reaction mixture were diluted with 0.4 mL of a solution of Borax/HCl buffer pH 9 containing 0.05% *d*₈-THF (corresponding to 2.5 µmol) as reference and analyzed by ²H-NMR. A 0.5 mL sample of the Borax/HCl buffer containing

0.05% d_8 -THF was prepared to control the natural abundance of the deuterium present in 0.5 mL of the solution.

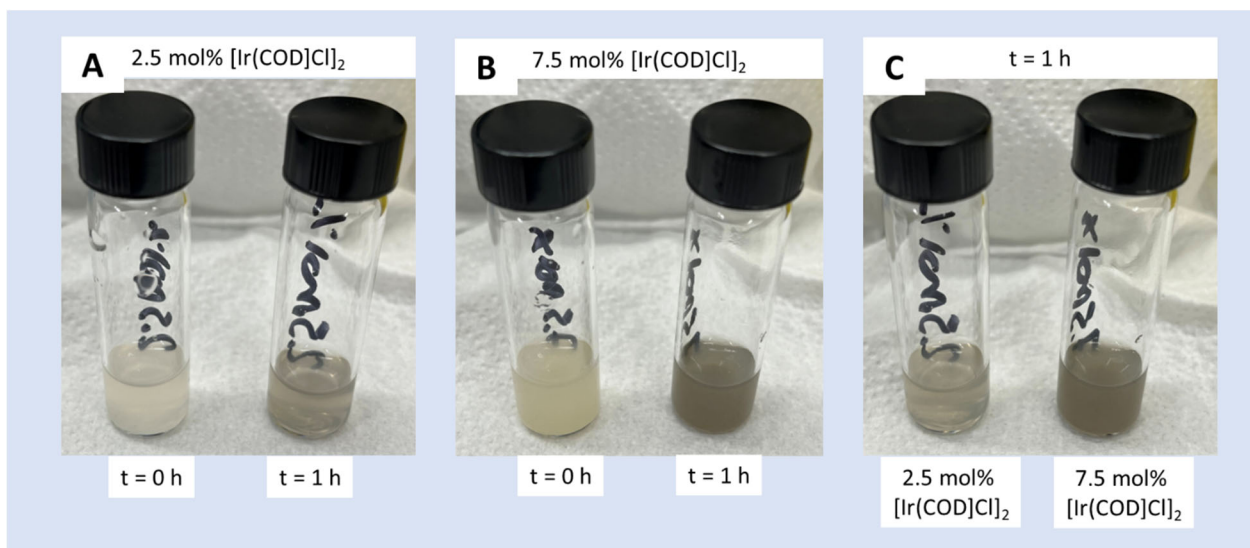


Figure S11: Crude reaction mixtures. A. Crude reaction mixtures using 2.5 mol% of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ before the reaction ($t = 0$ h, left) and after the reaction ($t = 1$ h). B. Crude reaction mixtures using 7.5 mol% of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ before the reaction ($t = 0$ h, left) and after the reaction ($t = 1$ h). C. Crude reaction mixtures after the reaction ($t = 1$ h) using 2.5 mol% (left) and a 7.5 mol% (right) of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$. Conditions: 0.02 mmol substrate, X mol% $[\text{Ir}(\text{COD})\text{Cl}]_2$, 2X mol% ligand **L11**, Borax/HCl buffer pH 9, 90 °C, 1 h.

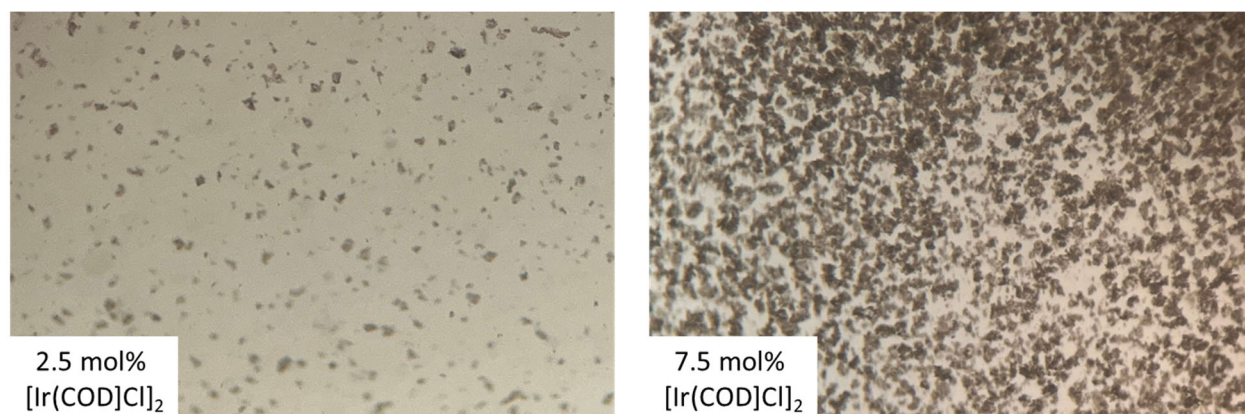


Figure S12: Microscope analysis (10x zoom) of the crude reaction mixtures with 2.5 mol% (left) and 7.5 mol% (right) content of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$.

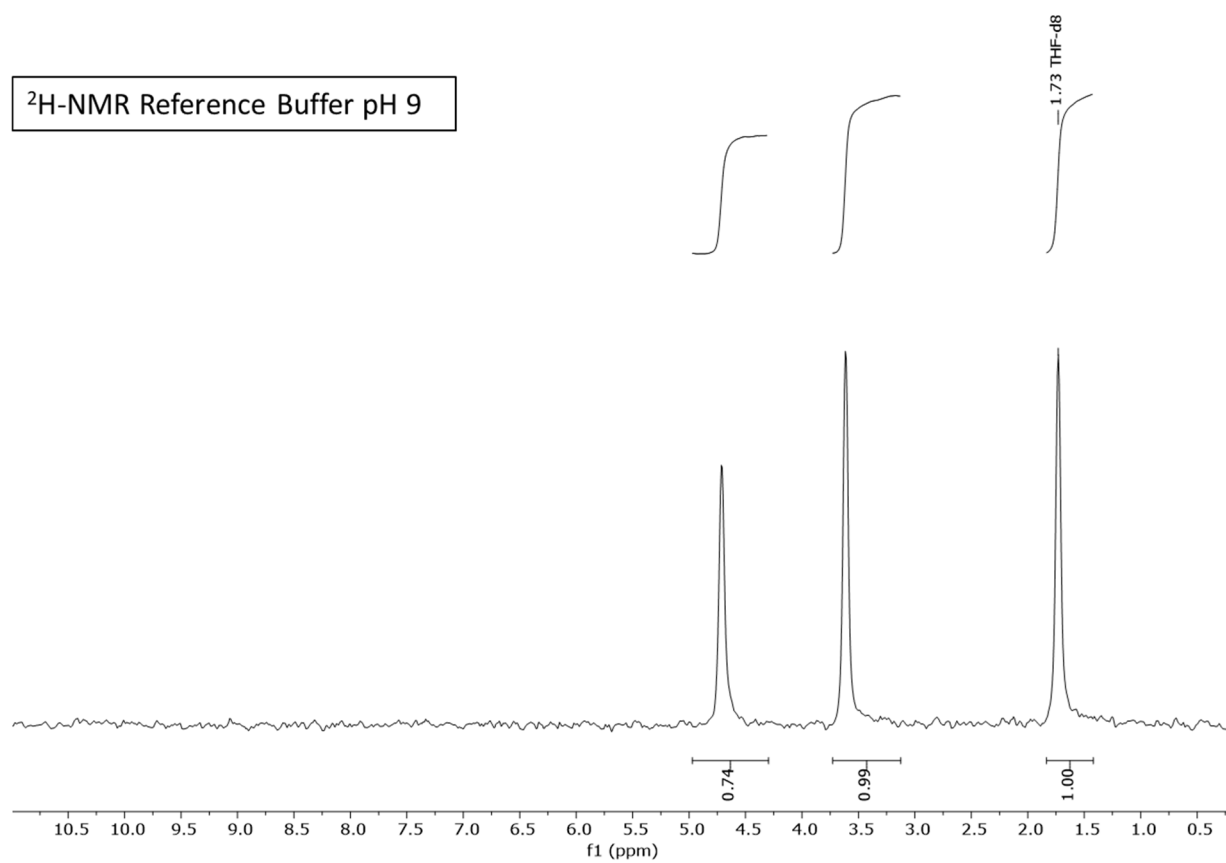


Figure S13: ²H-NMR spectrum of Buffer pH 9 as reference.

D₂O in 0.5mL buffer: $n = 4.4 \mu\text{mol}$ (baseline amount)

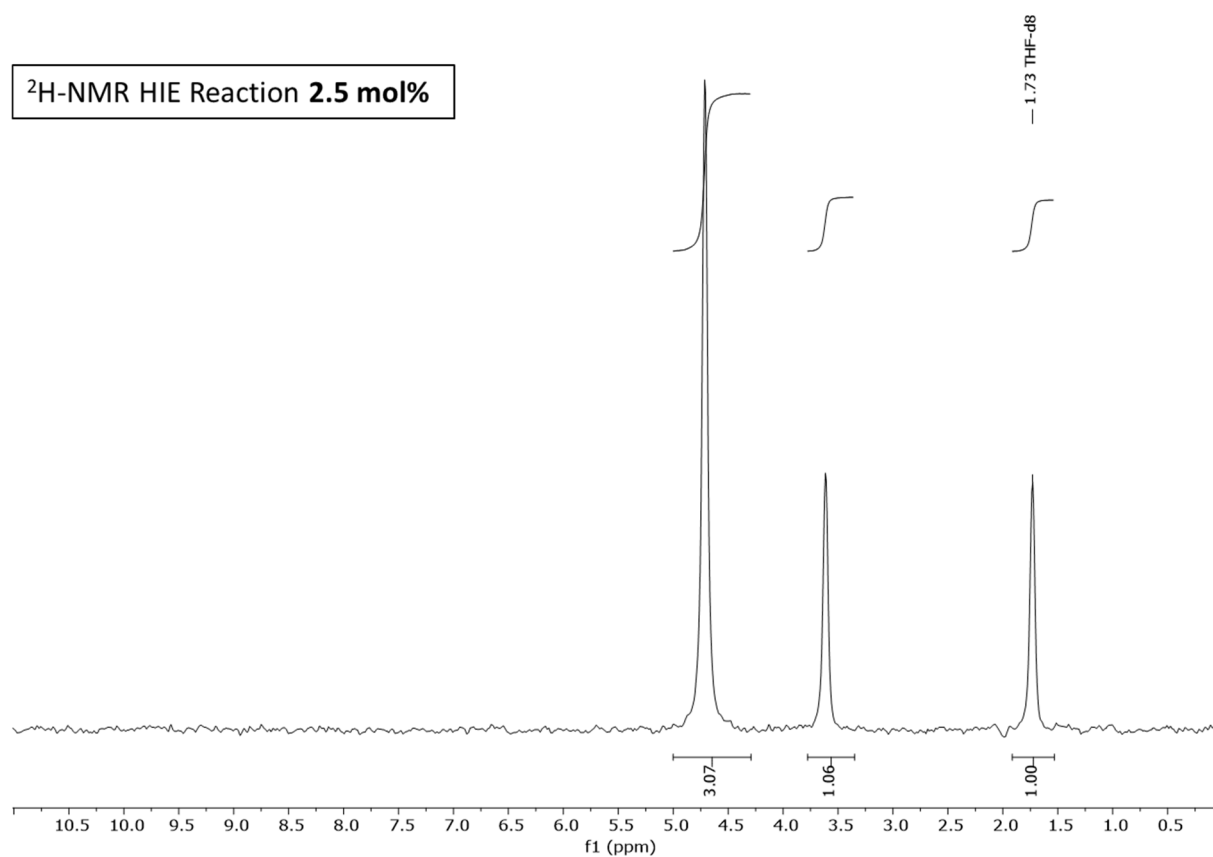


Figure S14: ²H-NMR spectrum of the deuteration crude reaction of L-Lys **1** using 2.5 mol% of pre-catalysts [Ir(COD)Cl]₂.

D₂O in 0.5 mL sample: $n = 15 \mu\text{mol}$

D₂O in 0.1 mL reaction: $n = 10.6 \mu\text{mol}$ (by baseline subtraction) $\rightarrow 318 \mu\text{mol}$ in 3.0 mL $\rightarrow 16$ equiv.
D₂ in the solvent.

²H-NMR HIE Reaction 7.5 mol%

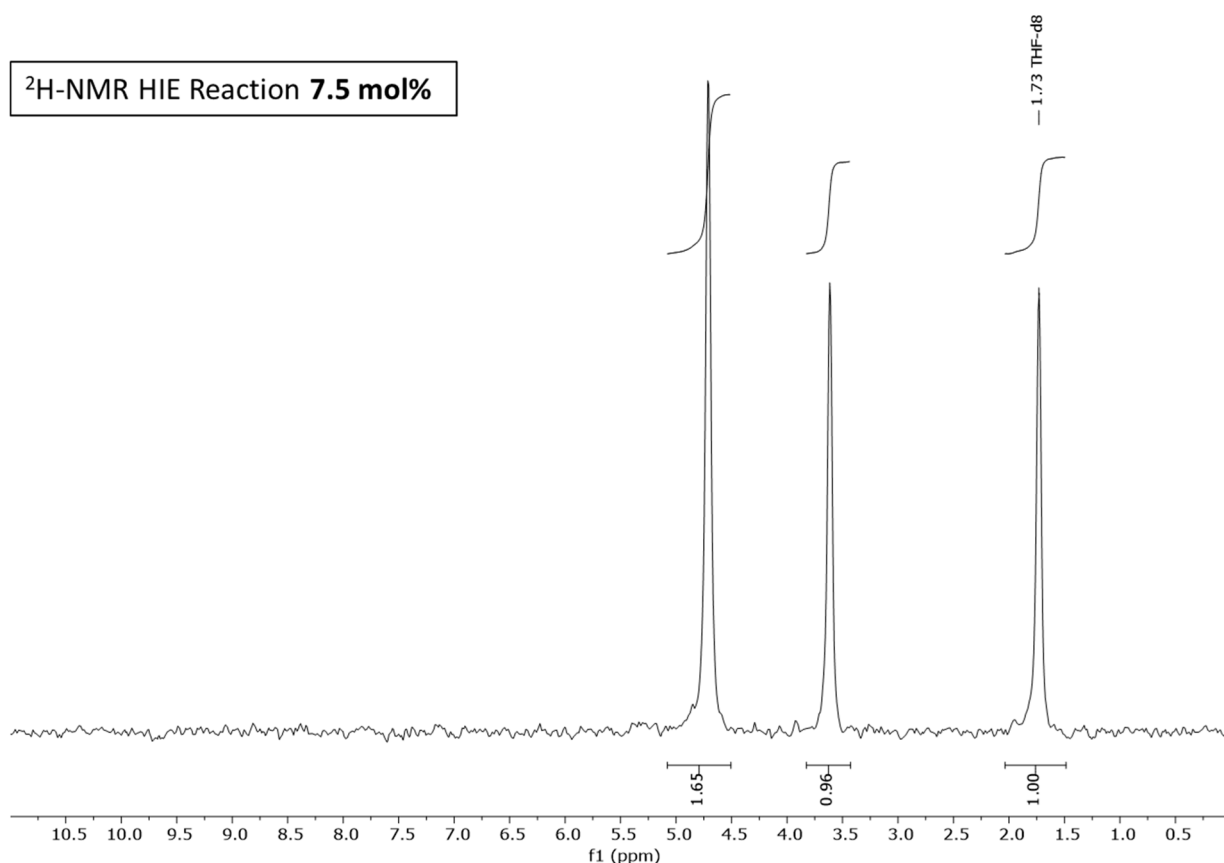


Figure S15: ²H-NMR spectrum of the deuteration crude reaction of L-Lys **1** using 7.5 mol% of pre-catalysts [Ir(COD)Cl]₂.

D₂O in 0.5 mL sample: $n = 8.3 \mu\text{mol}$

D₂O in 0.1 mL reaction: $n = 3.9 \mu\text{mol}$ (by baseline subtraction) $\rightarrow 117 \mu\text{mol}$ in 3.0 mL $\rightarrow 6$ equiv. D₂ in the solvent.

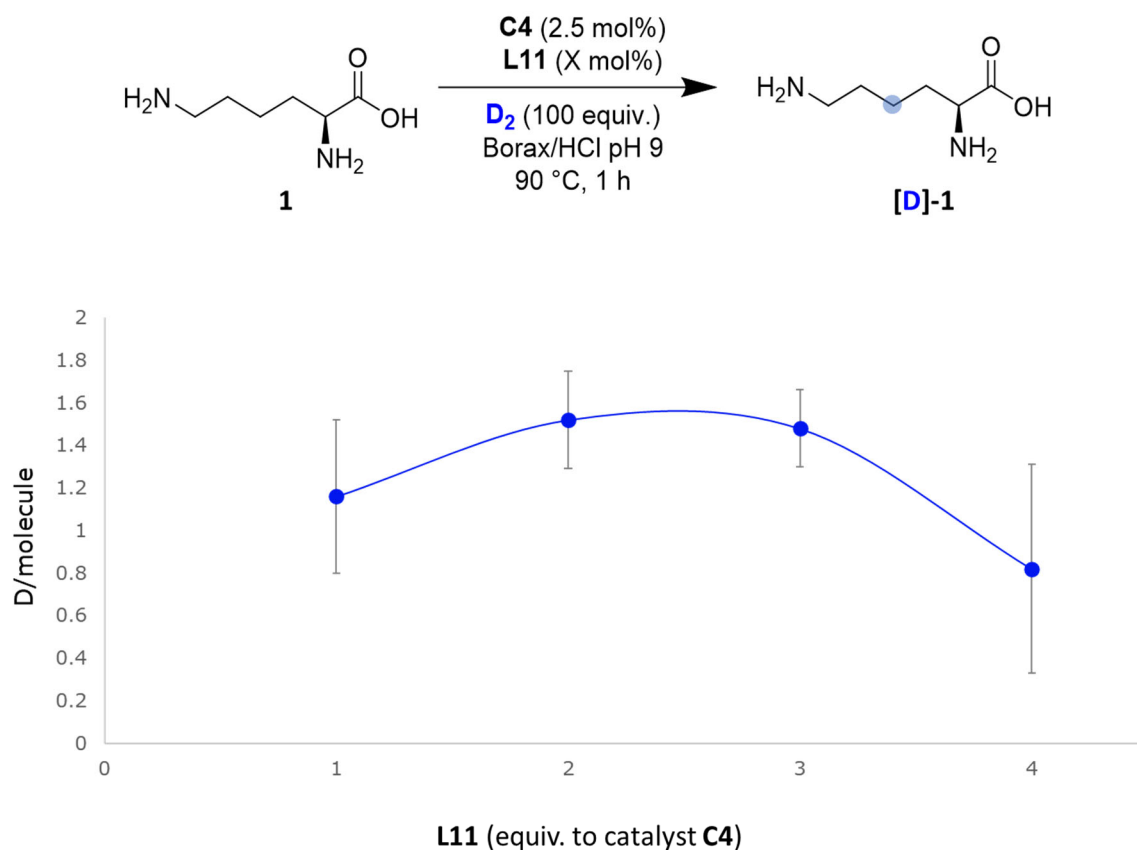
It is possible to postulate two simultaneous processes happening in the reaction conditions. The Ir metal present in the mixture can form an Ir-complex with the phosphine ligand and substrate as well as metal particles, detected visually at the end of the reaction and by microscope analysis. When the amount of pre-catalyst is increased from 2.5 mol% to 7.5 mol%, the amount of metal clusters is also augmented, reducing the amount of Ir available for interaction with the ligand and the substrate and, therefore, for the formation of the active catalytic species. This results in a lower deuterium incorporation on the substrate.

4.3 Screening of phosphine load

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

A 6 mM stock solution of catalyst [Ir(COD)Cl]₂ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

Compound L-Lys **1** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl buffer pH 9, catalyst [Ir(COD)Cl]₂ **C4** (2.5 mol%, 0.025 equiv.) and ligand **L11** (X mol%) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D₂ atmosphere (100 equiv.) at 90 °C for 1 h. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS.

Table S8: Screening of phosphine load in the HIE reaction with L-Lys **1**.

Entry	Equiv. to C4	L11 (mol%)	D/molecule ^a	Standard deviation
1	1	2.5	1.16	0.36
2	2	5	1.52	0.23
3	3	7.5	1.48	0.18
4	4	10	0.82	0.49

a) average of three reactions, analyzed by LC-MS

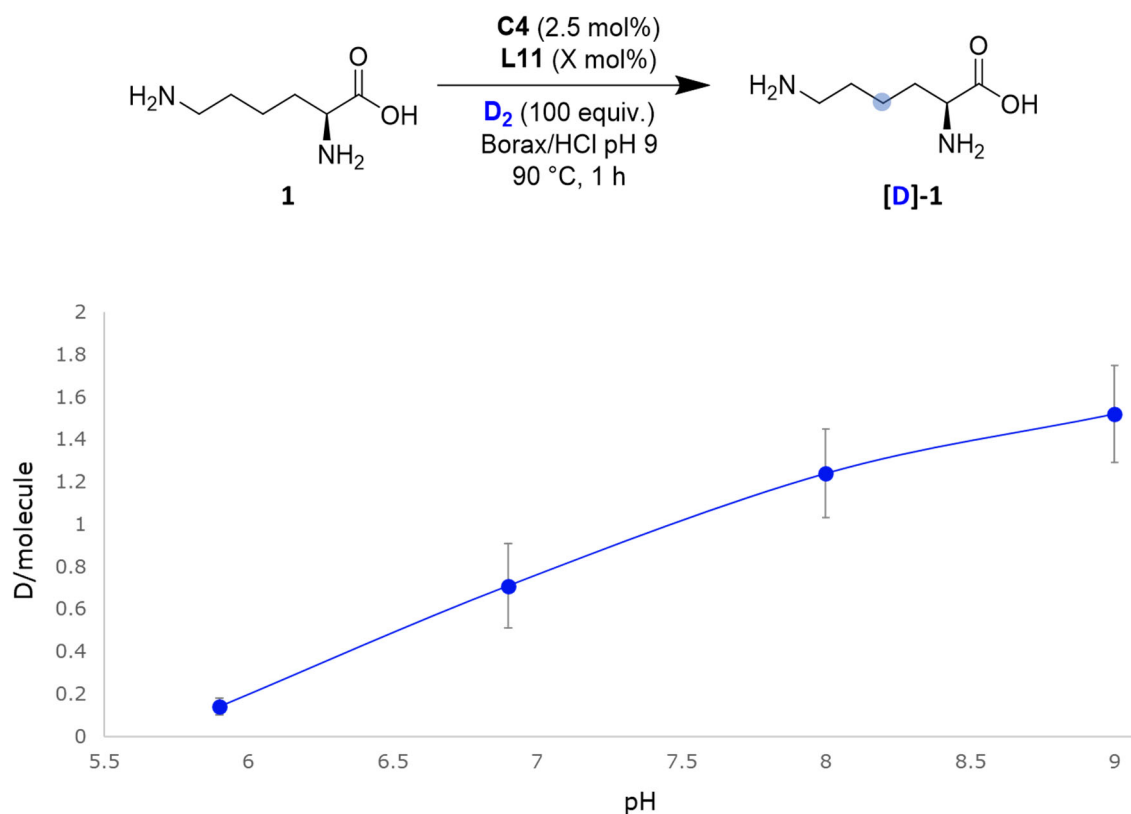
4.4 Screening of pH

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

A 6 mM stock solution of catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

Compound L-Lys **1** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of buffer, catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** (2.5 mol%, 0.025 equiv.) and ligand **L11** (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D_2 atmosphere (100 equiv.) at 90 °C for 1 h. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS.

Table S9: Screening of pH in the HIE reaction with L-Lys **1**.



Entry	Buffer (pH)	D/molecule ^a	Standard deviation
1	6	0.14	0.04
2	7	0.71	0.20
3	8	1.24	0.21
4	9	1.52	0.23

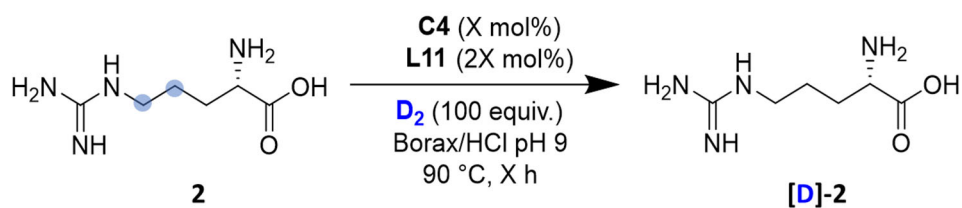
a) average of three reactions, analyzed by LC-MS

4.5 L-Arginine optimization

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

A 6 mM stock solution of catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

Compound L-Arg **2** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of of Borax/HCl buffer pH 9, catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** (X mol%) and ligand **L11** (2X mol%) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D_2 atmosphere (100 equiv.) at 90 °C for X h. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS.

Table S10: Reaction optimization for L-Arg **2**.

Entry	C4 (mol%)	L11 (mol%)	Time (h)	D/molecule ^a
1	2.5	5	1	0.15
2	2.5	5	3	0.35
3	2.5	5	5	0.40
4	2.5	5	17	0.46
5	5	10	1	0.49
6	5	10	3	0.59
7	5	10	5	0.59
8	5	10	17	0.64

a) average of three reactions, analyzed by LC-MS

5 Control reactions

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

A 6 mM stock solution of catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

Compound L-Lys **1** (0.02 mmol) was used as substrate and solubilized in 3 mL of buffer pH 9.

The reaction was stirred at 90 °C for 1 h. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS.

Table S11: Control reactions for the optimized HIE reaction conditions with L-Lys **1**.

Entry	C4 (mol%)	L11 (mol%)	D ₂ (equiv.)	D/molecule ^a
1	-	5	100	0
2	2.5	-	100	0.10
3	2.5	5	-	0
4 ^b	2.5	5	100	1.70
5 ^{b,c}	2.5	5	-	1.15

a) average of three reactions, analyzed by LC-MS, b) Borax/DCl buffer pH 9 prepared with D₂O, c) use of H₂ gas instead of D₂

To analyze the particles present in the reaction mixture, 10 µmol of the unfiltered crude mixture were analyzed on a A. Krüss – Optronic MBL2100 230VAC 20 W microscope with a 10x zoom. To calculate the amount of deuterium present in the solvent ²H-NMR analysis was performed. The crude reaction mixture was filtered through a syringe filter (0.45 µm) and 0.1 mL of the filtered reaction mixture were diluted with 0.4 mL of a solution of Borax/HCl buffer pH 9 containing 0.05% *d*₈-THF (corresponding to 2.5 µmol) as reference and analyzed by ²H-NMR. A 0.5 mL sample of the Borax/HCl buffer containing 0.05% *d*₈-THF was prepared to control the natural abundance of the deuterium present in 0.5 mL of the solution.

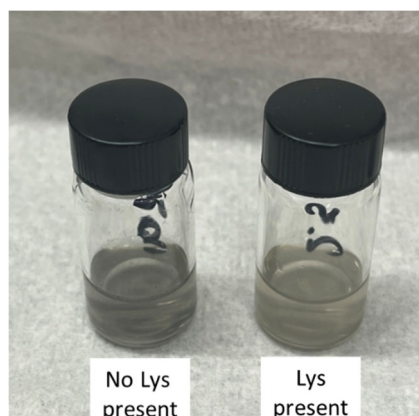


Figure S16: Crude reaction mixtures after the reaction with no Lys (left) and Lys (right) present. Conditions: 0.02 mmol substrate, 2.5 mol% [IrCODCl]₂, 5 mol% ligand **L11**, 3 mL Borax/HCl buffer pH 9, 90 °C, 1 h.

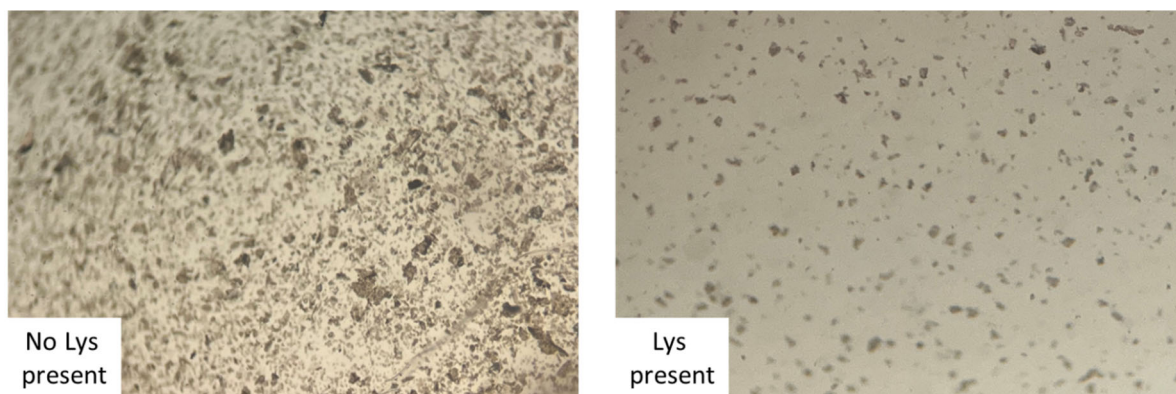


Figure S17: Microscope analysis (10x zoom) of the crude reaction mixtures without (left) and with (right) substrate.

²H-NMR HIE Reaction **no substrate**

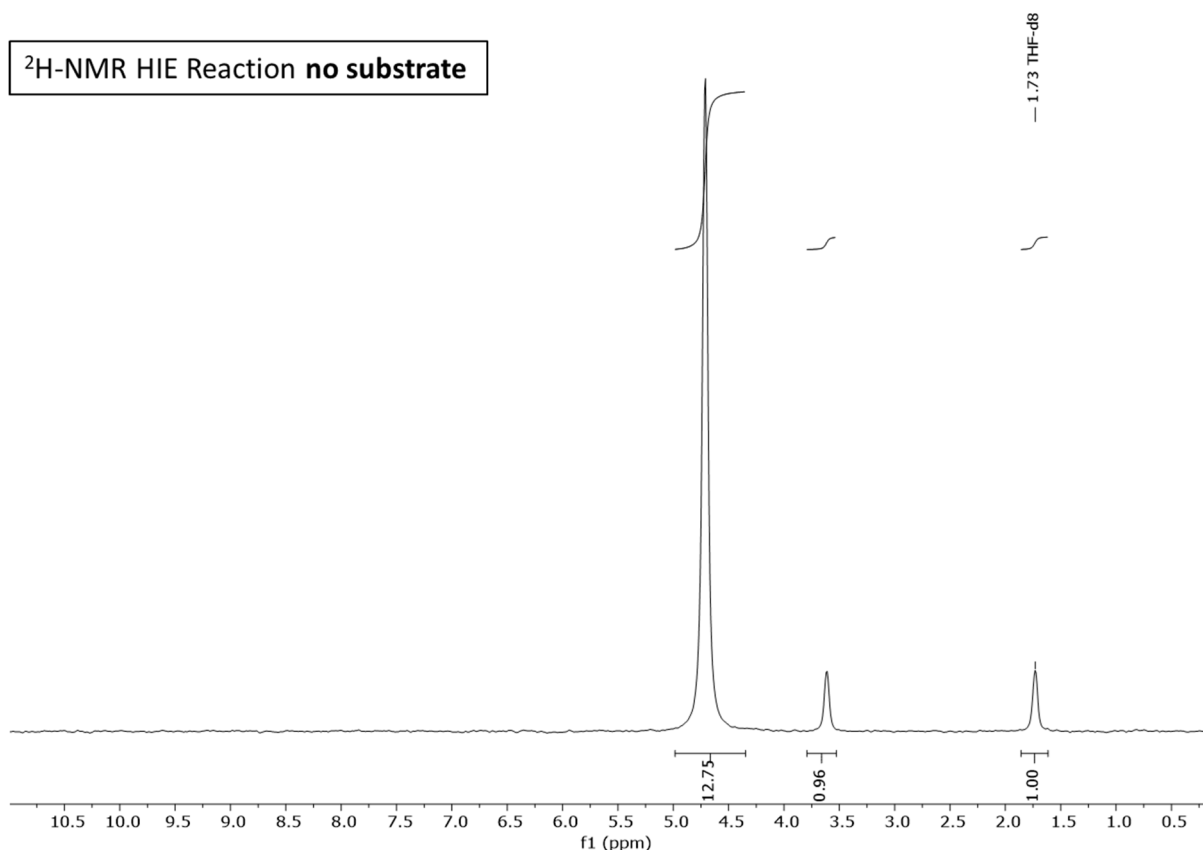


Figure S18: ²H-NMR spectrum of the deuteration crude reaction without substrate (L-Lys **1**).

D₂O in 0.5 mL sample: $n = 63.8 \mu\text{mol}$

D₂O in 0.1 mL reaction: $n = 59.4 \mu\text{mol}$ (by baseline subtraction) $\rightarrow 1.8 \text{ mmol in } 3.0 \text{ mL} \rightarrow 90 \text{ equiv. D}_2$ in the solvent.

6 General HIE protocols

All reactions were performed using a Radleys synthesis station for parallel solution phase chemistry.

6.1 Method A

A 6 mM stock solution of catalyst [Ir(COD)Cl]₂ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

The substrate (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl Buffer pH 9, catalyst [Ir(COD)Cl]₂ **C4** (2.5 mol%, 0.025 equiv.) and ligand **L11** (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D₂ atmosphere (100 equiv.) at 90 °C for 1 h. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS. Additionally, water was removed by using a lyophilizer. The filtered or purified sample was analyzed by ¹H- and ²H-NMR.

As mentioned above, in each reaction workup the crude was filtered by a 0.45 μm syringe filter to remove the insoluble residues prior purifying by RP-HPLC. Although metal traces can remain in the deuterated or tritiated product, the amount of the tritiated compound (μg) is so low that it plays no role in suitable biological testing. This can be different if the deuterated compound would be used.

6.2 Method B

A 6 mM stock solution of catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

The substrate (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl Buffer pH 9, catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** (2.5 mol%, 0.025 equiv.) and ligand **L11** (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D_2 atmosphere (100 equiv.) at 90 °C for 1 h. After 1 h, catalyst **C4** (2.5 mol%) and ligand **L11** (5 mol%, 0.05 equiv.) were dispensed in 0.5 mL of dioxane and added to the reaction mixture, which was left stirring for another 1 h. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS. Additionally, water was removed by using a lyophilizer. The purified sample was analyzed by ^1H - and ^2H -NMR.

As mentioned above, in each reaction workup the crude was filtered by a 0.45 μm syringe filter to remove the insoluble residues prior purifying by RP-HPLC. Although metal traces can remain in the deuterated or tritiated product, the amount of the tritiated compound (μg) is so low that it plays no role in suitable biological testing. This can be different if the deuterated compound would be used.

6.3 Method C

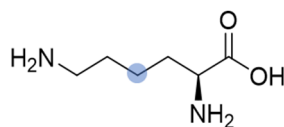
A 6 mM stock solution of catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and a 30 mM stock solution of ligand **L11** were prepared using dioxane as solvent.

The substrate (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl Buffer pH 9, catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** (5 mol%, 0.05 equiv.) and ligand **L11** (10 mol%, 0.10 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D_2 atmosphere (100 equiv.) at 90 °C for 17 h. The reaction mixture was filtered through a syringe filter (0.45 μm) and one aliquot was analyzed by LC-MS. Additionally, water was removed by using a lyophilizer. The filtered or purified sample was analyzed by ^1H - and ^2H -NMR.

7 Screening of compounds

7.1 Initial scope

7.1.1 L-Lysine **1**



1

Chemical Formula: C₆H₁₄N₂O₂

Exact Mass: 146.11

Figure S19: Structure of L-Lys **1**.

Method A: 3.0 mg, 0.02 mmol **1**, 0.5 μ mol catalyst **C4** (2.5 mol%), 1 μ mol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 3.34 (t, J = 6.2 Hz, 1H), 2.96 (t, J = 7.3 Hz, 2H), 1.75-1.56 (m, 4H), 1.49-1.32 (m, 2H). Analytical data compared to literature.⁷

Incorporation expected at δ 1.49-1.32. (blue arrow, blue dot in the structure). Determined against integral at δ 3.34 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 1.52 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 1.71 D/molecule for δ 1.49-1.32.

Yield: 30%, NMR yield.

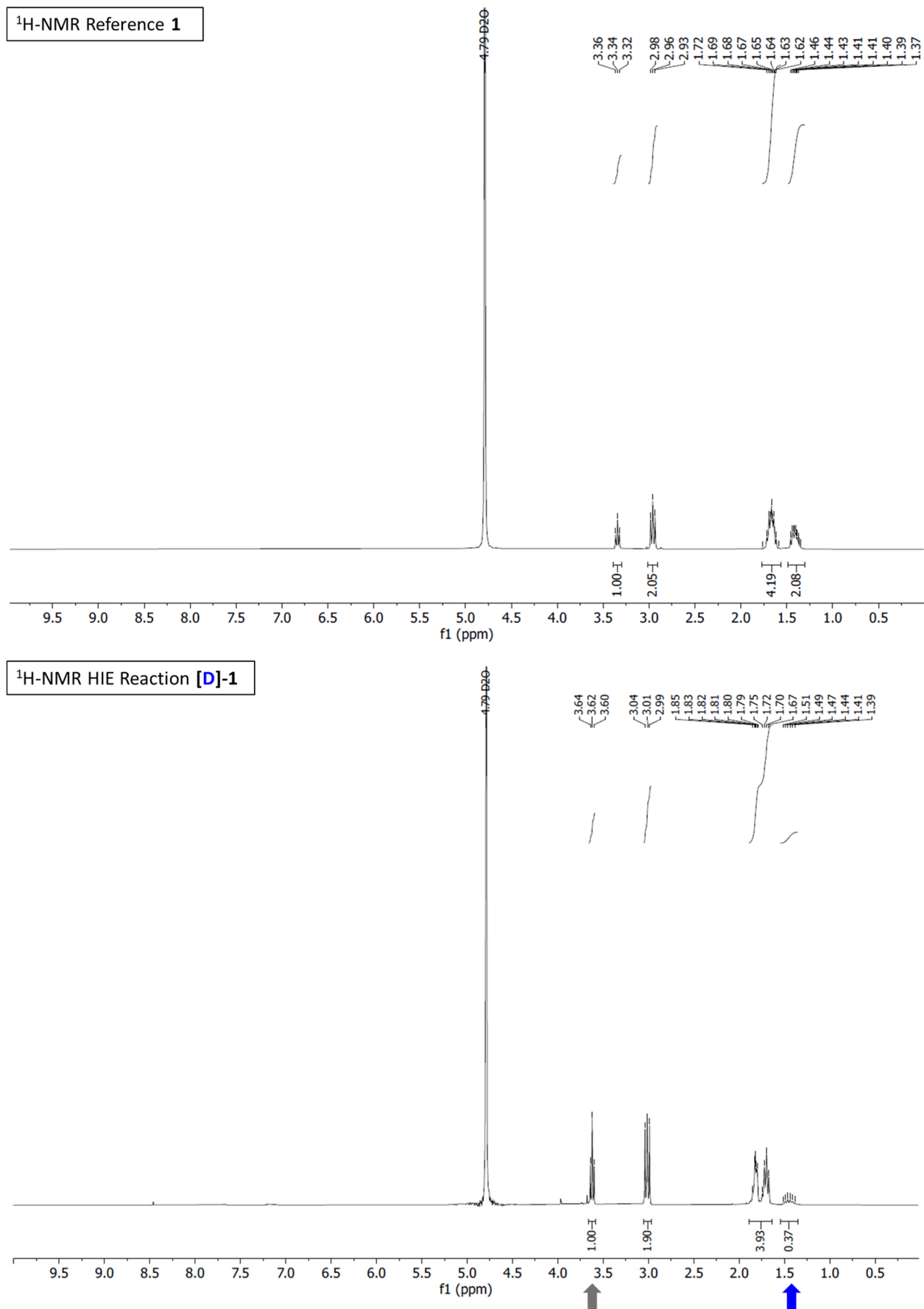


Figure S20: ¹H-NMR spectra of the HIE reaction of compound **1** to yield the deuterated product **[D]-1**.

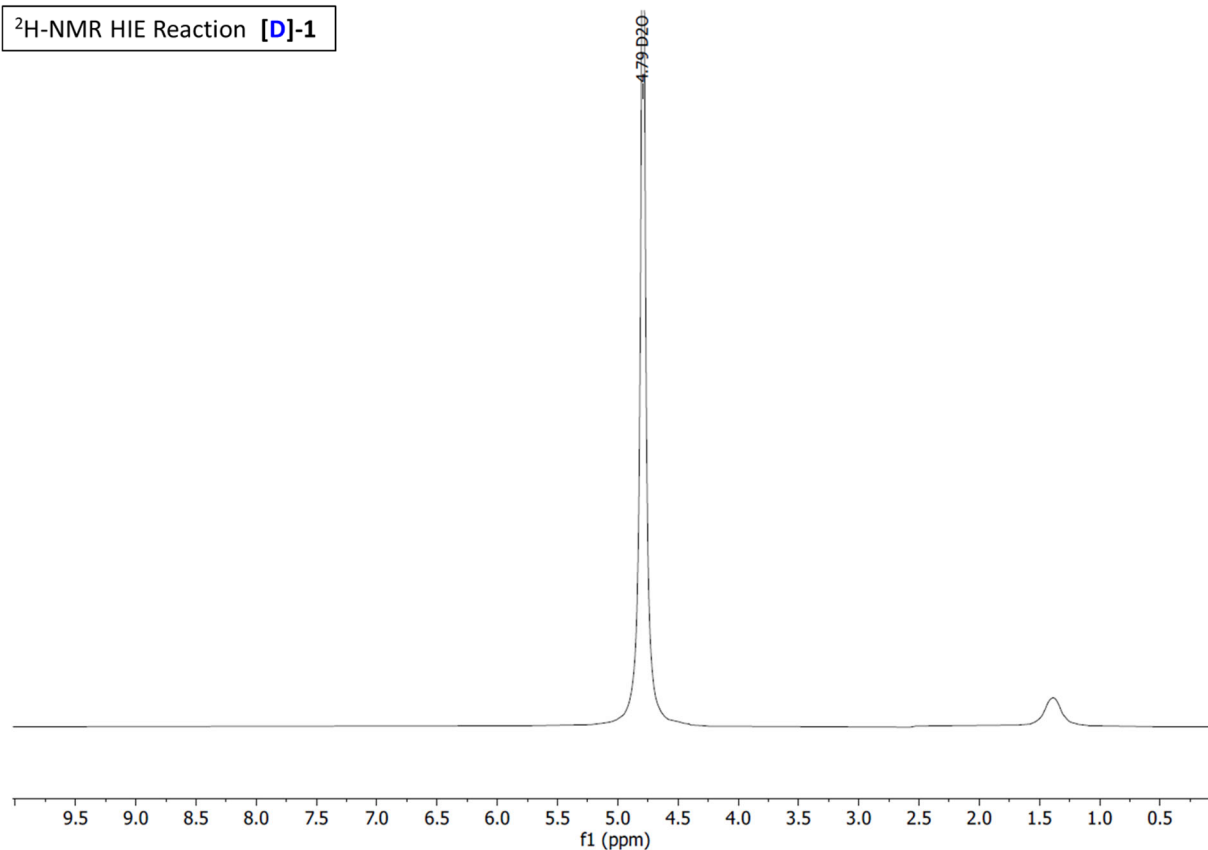


Figure S21: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-1.

To confirm the variation in the chemical shift of some of the signals was due to the pH and possible remaining buffer salts, both the reference and the yielded HIE product were analyzed as HCl salt by ¹H-NMR.

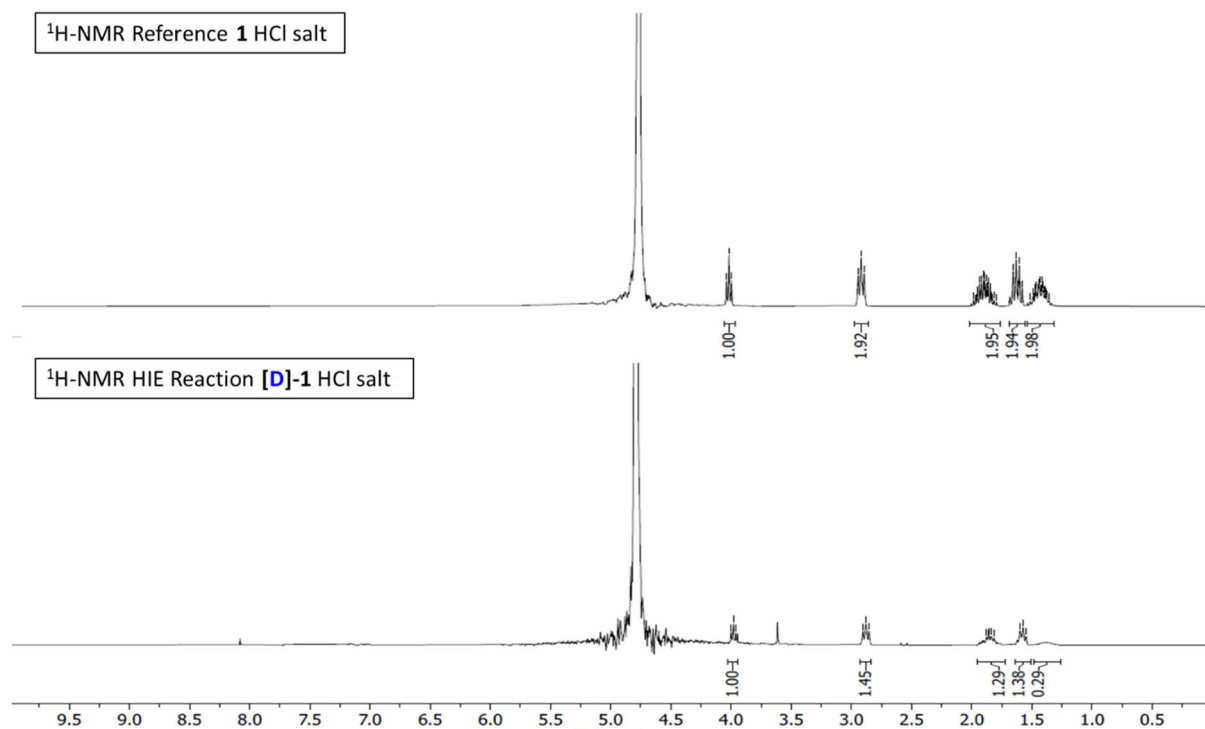


Figure S22: Overlay of ¹H-NMR spectra of the HCl salts of the reference compound 1 and the HIE reaction of deuterated product [D]-1.

7.1.2 L-Arginine 2

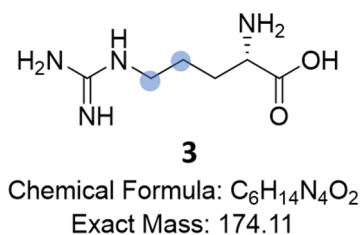


Figure S23: Structure of L-Arginine **3** with ²H labeling positions.

Method C: 3.5 mg, 0.02 mmol **2**, 1 μmol catalyst **C4** (5 mol%), 2 μmol ligand **L8** (10 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 4.08 (t, *J* = 6.3 Hz, 1H), 3.26 (t, *J* = 6.8 Hz, 2H), 2.11-1.87 (m, 2H), 1.86-1.61 (m, 2H). Analytical data compared to literature.⁸

Incorporation expected at δ 3.26 and 1.86-1.61. (blue arrow, blue dot in the structure). Determined against integral at δ 4.08 (grey arrow).

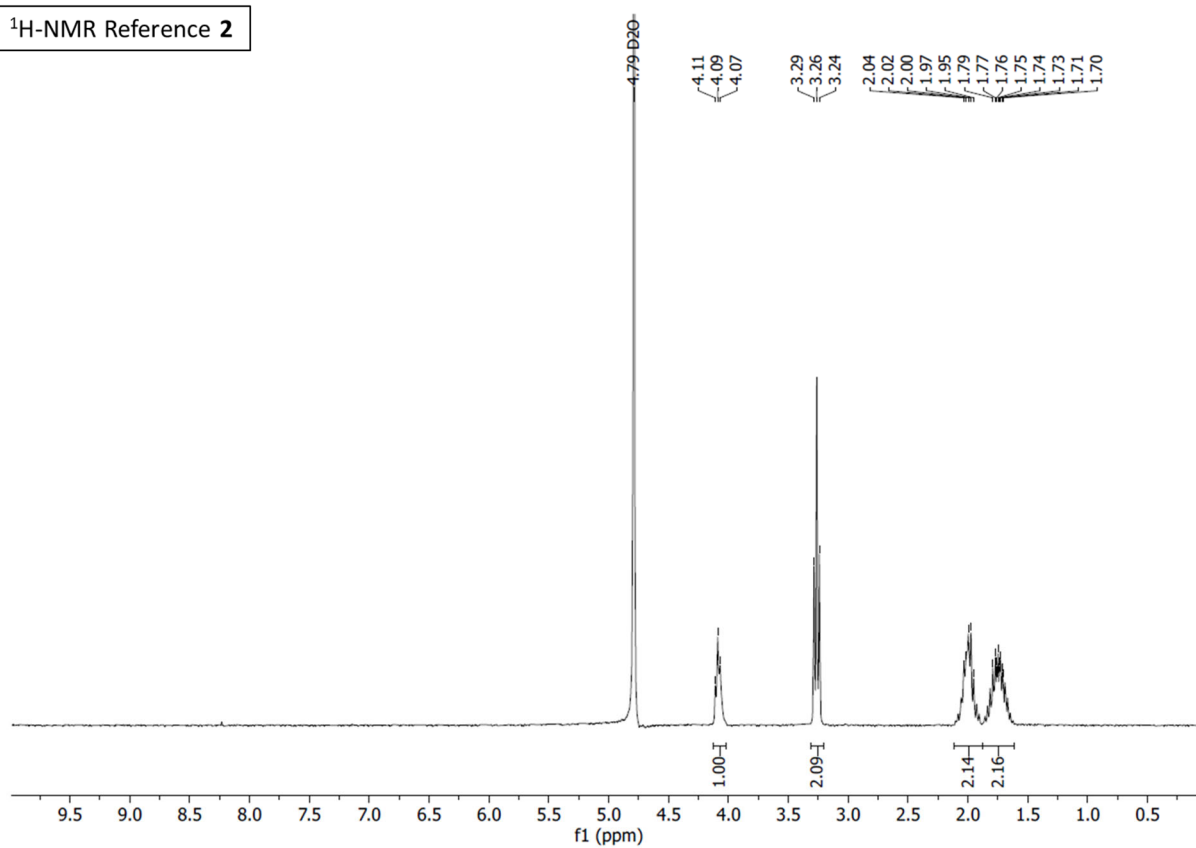
Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.64 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.39 D/molecule for δ 3.26 and 0.38 D/molecule for δ 1.86-1.61.

Yield: 34%, NMR yield.

¹H-NMR Reference **2**



¹H-NMR HIE Reaction **[D]-2**

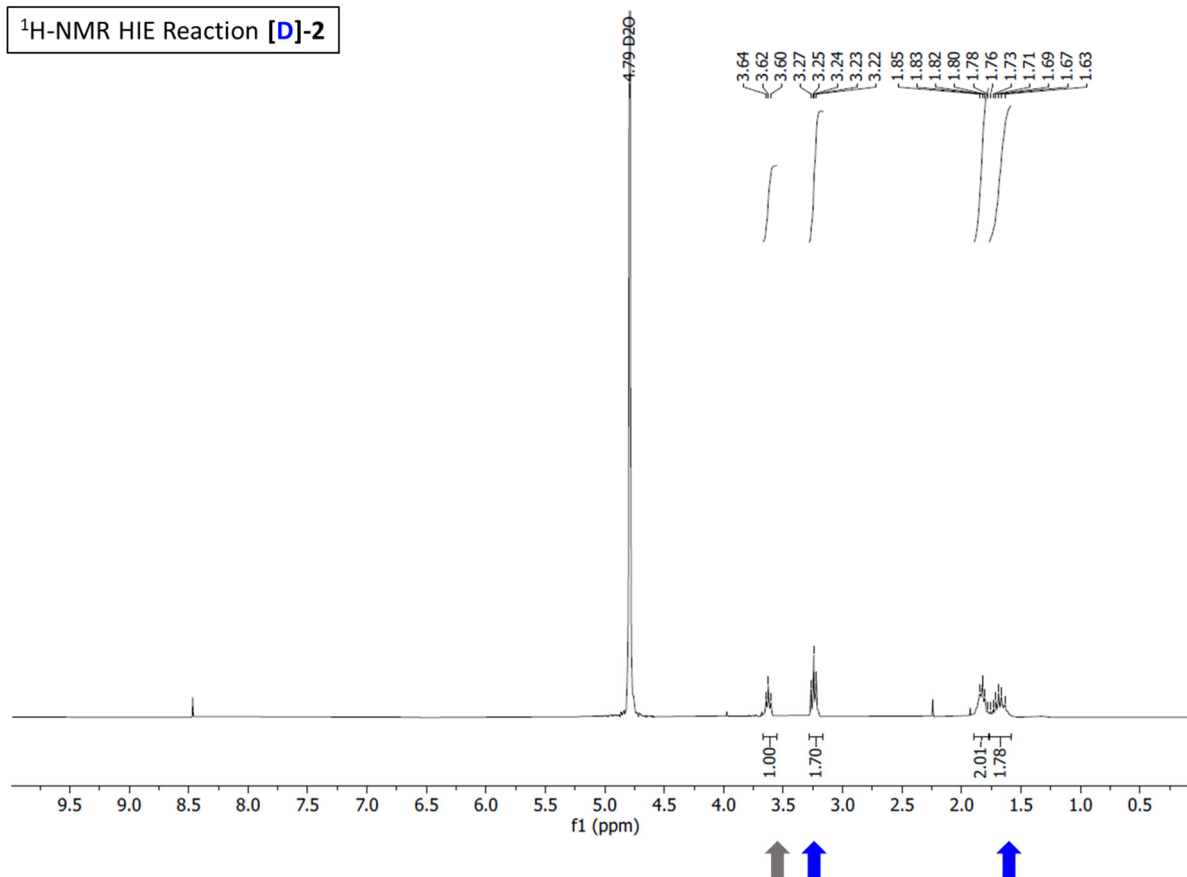


Figure S24: ¹H-NMR spectra of the HIE reaction of compound **2** to yield the deuterated product **[D]-2**.

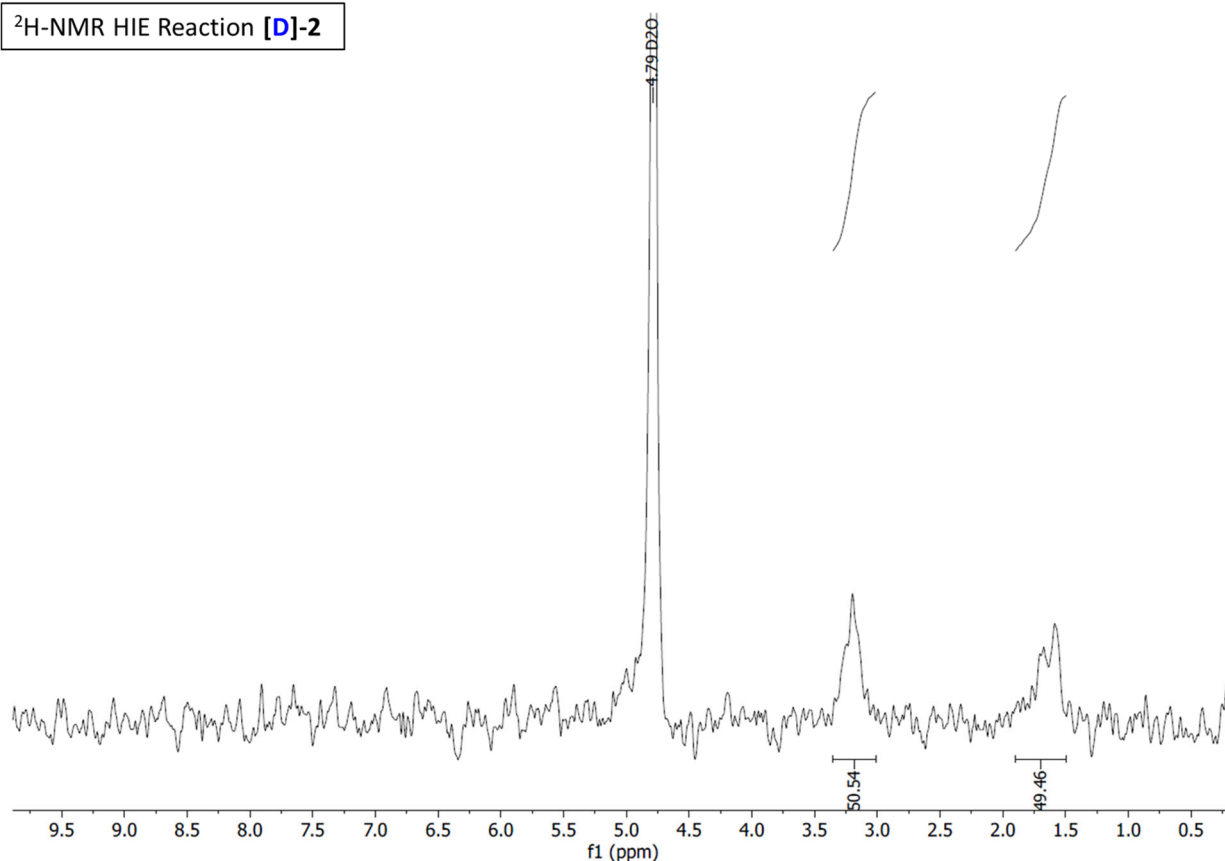


Figure S25: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-3.

7.1.3 1,4-diaminobutane **9**



Figure S26: Structure of 1,4-diaminobutane **9**.

Method A: 2 mg, 0.02 mmol **9**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

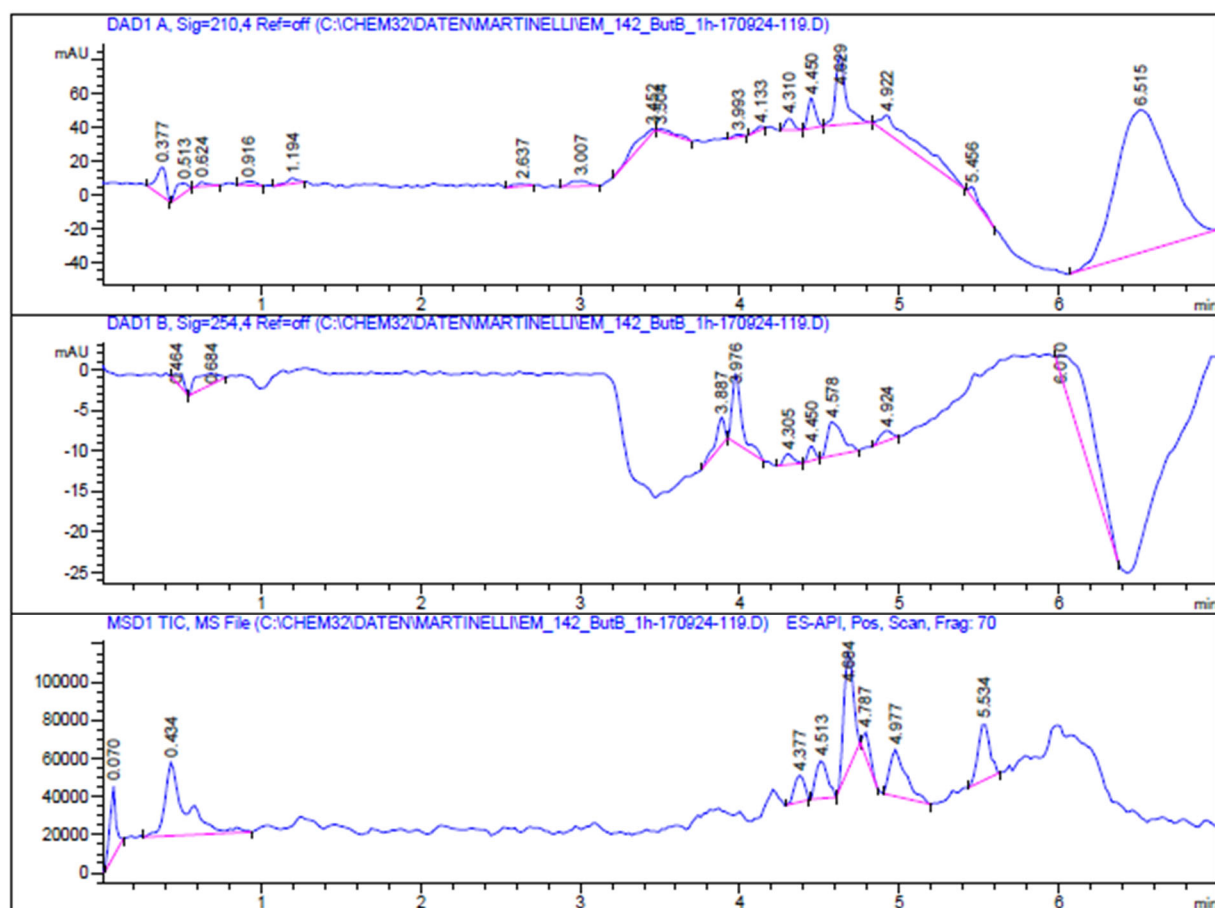
¹H-NMR (300 MHz, D₂O): δ [ppm] = 2.73-2.53 (m, 4H), 1.52-1.41 (m, 4H). Analytical data compared to literature.⁹

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.36 D/molecule.

Deuterium incorporation determined by ²H-NMR: 77%D (0.28 D/molecule) for δ 2.73-2.53 and 23%D (0.08 D/molecule) for δ 1.52-1.41 (blue arrows).

Yield: 14%, NMR yield.



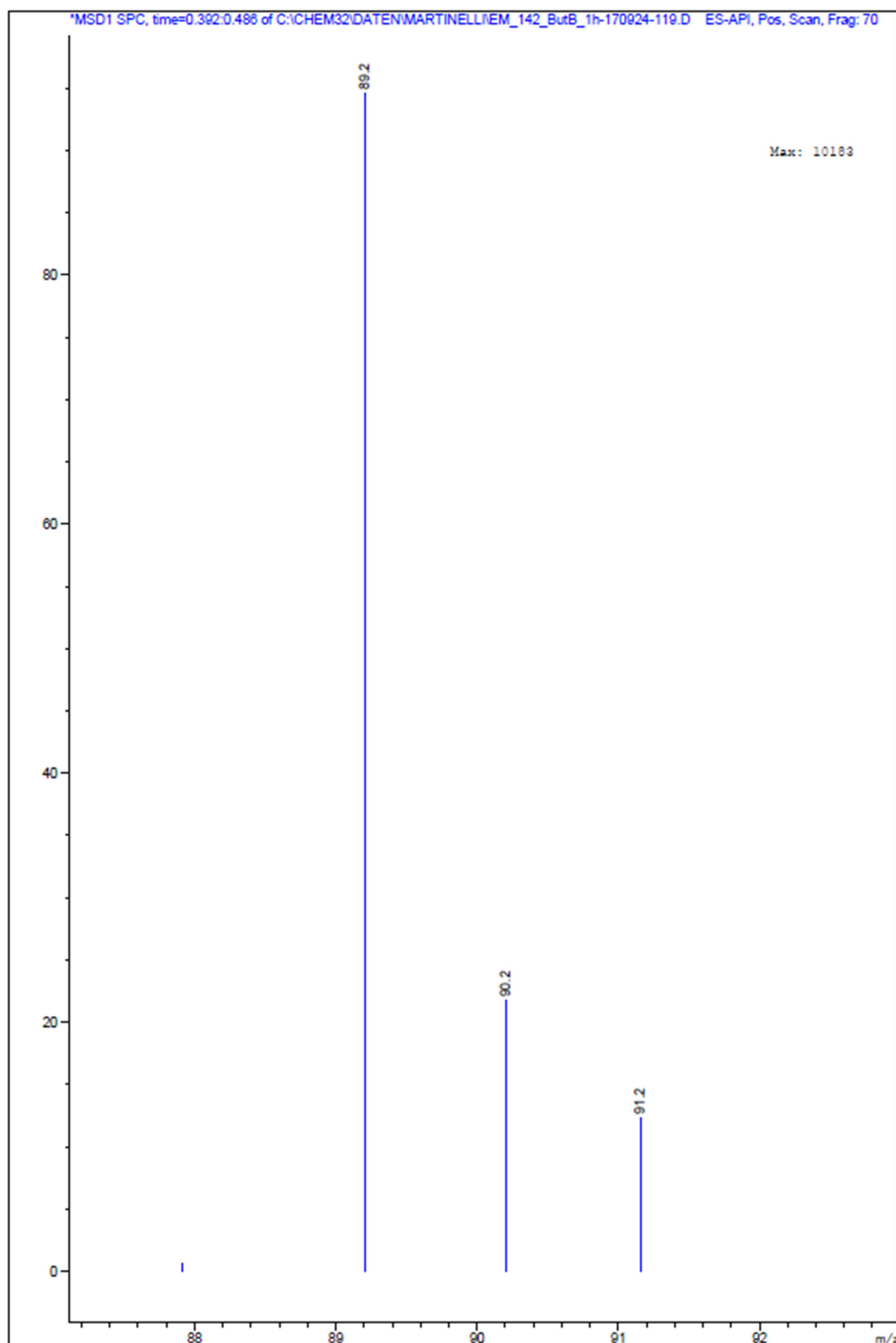


Figure S27: LC-MS analysis of representative HIE reaction of 1,4-diaminobutane **9**.

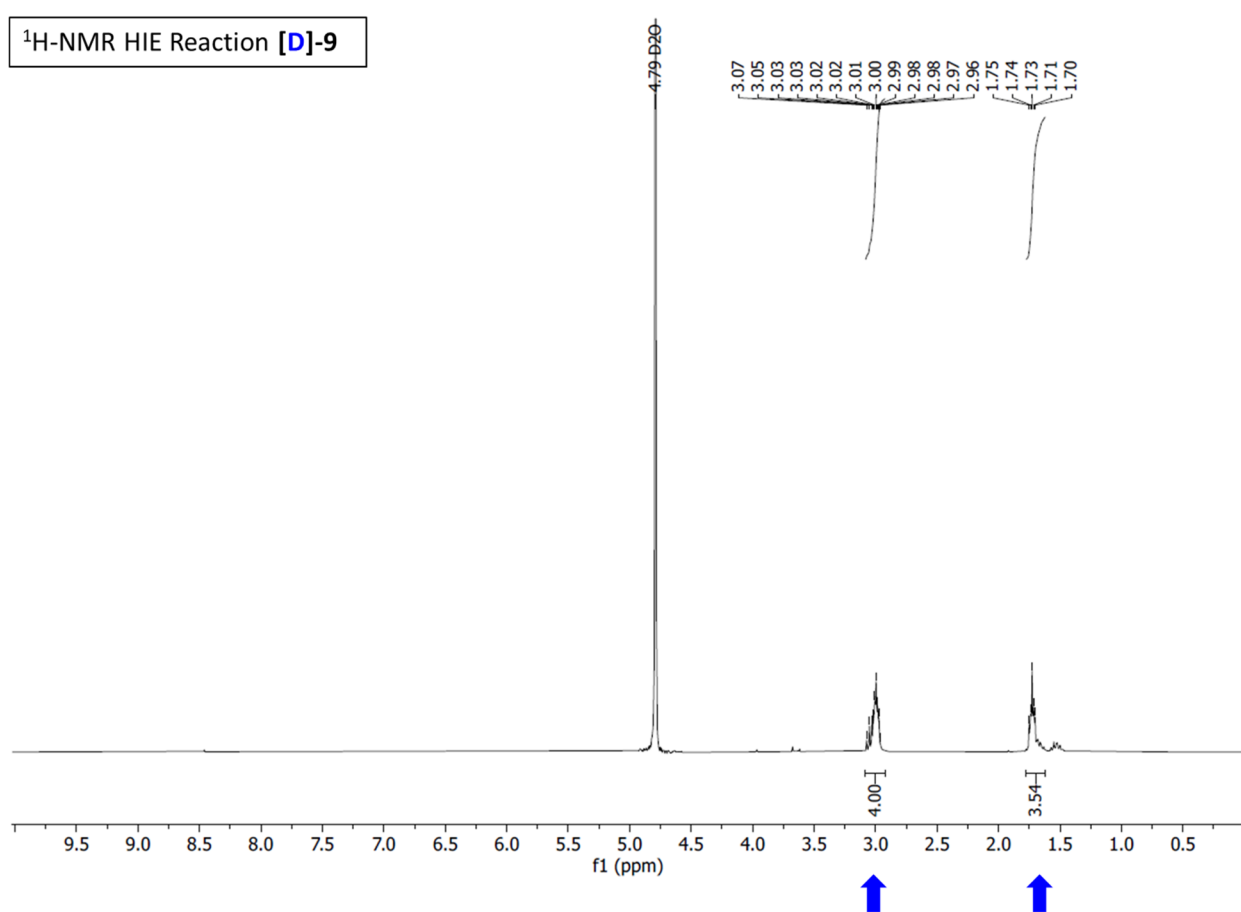
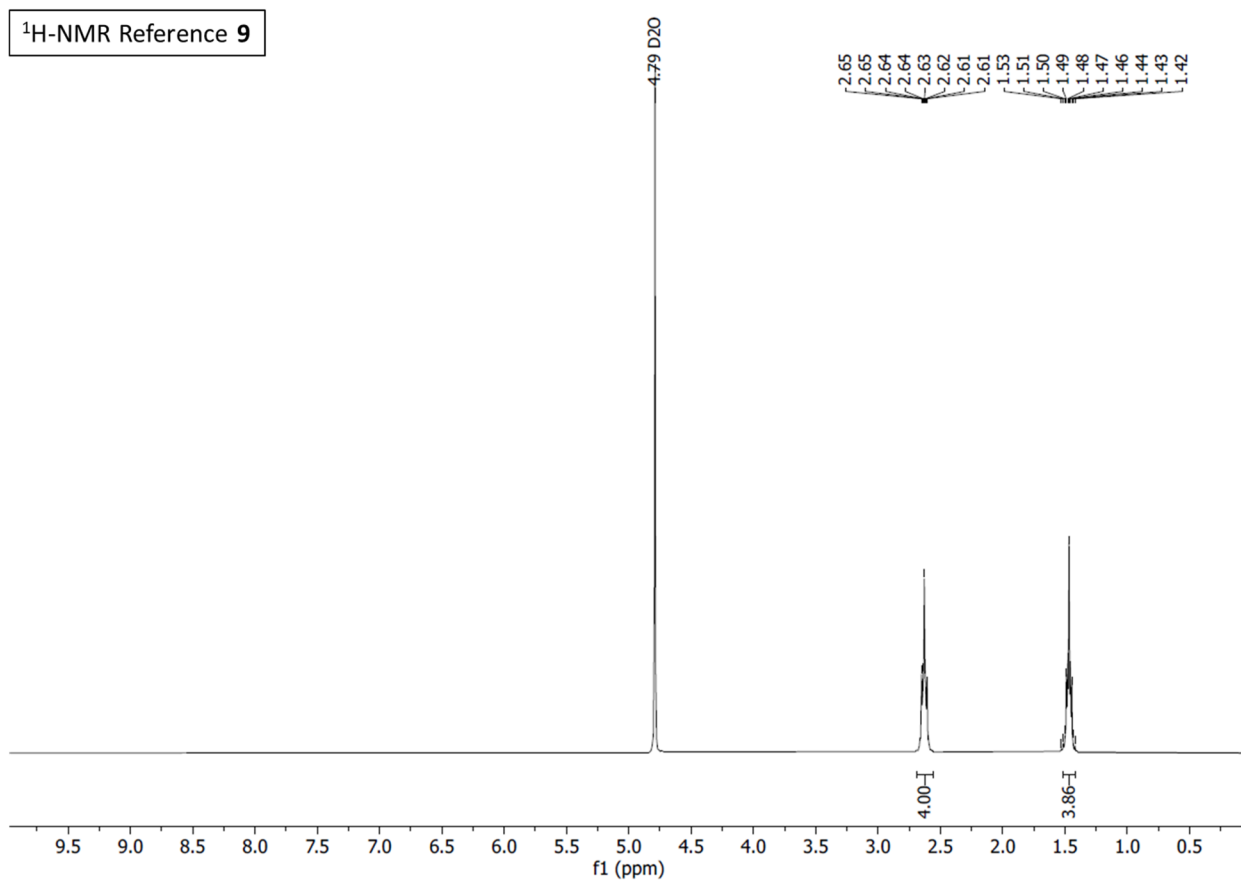


Figure S28: ¹H-NMR spectra of the HIE reaction of compound **9** to yield the deuterated product **[D]-9**.

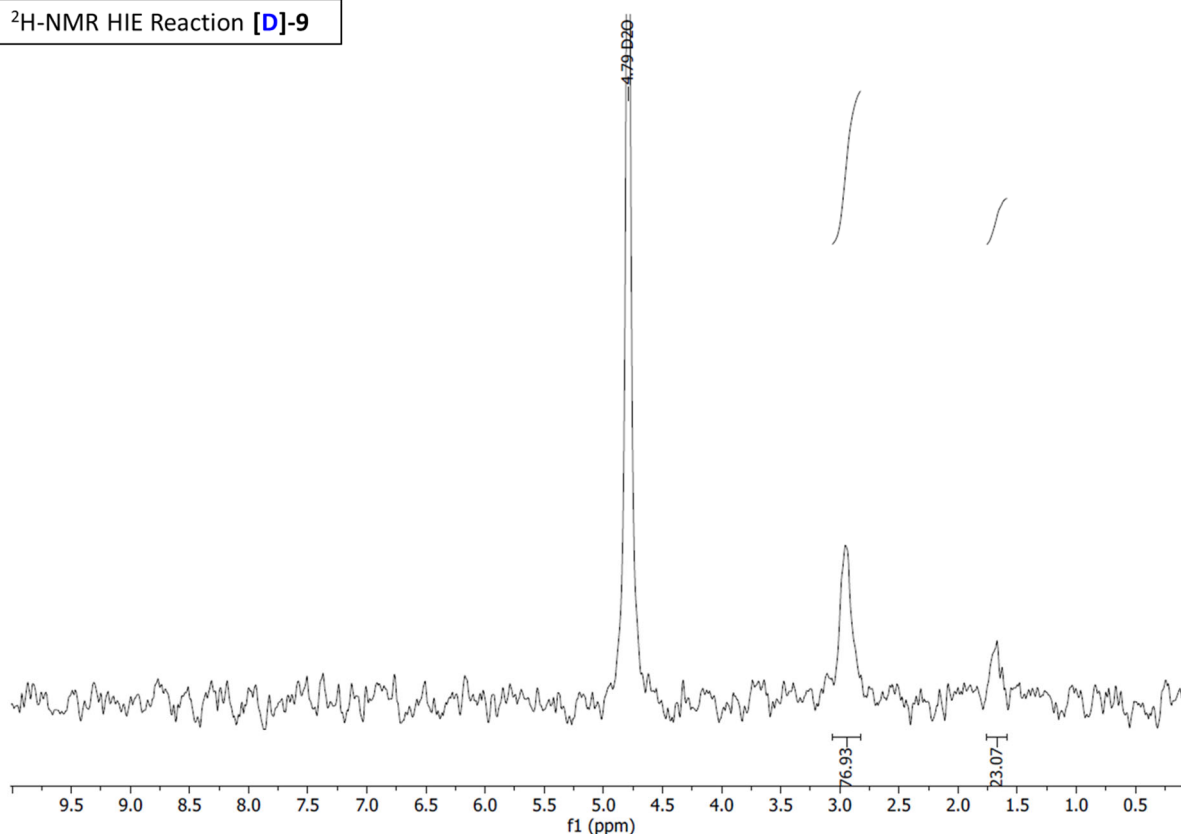
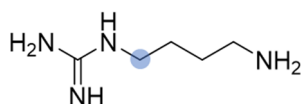


Figure S29: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-9.

7.1.4 Agmatine **10**



10

Chemical Formula: C₅H₁₄N₄

Exact Mass: 130.12

Figure S30: Structure of agmatine **10**.

Method A: 4.5 mg, 0.02 mmol **10**·H₂SO₄, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 3.25 (t, *J* = 6.4 Hz, 2H), 3.05 (t, *J* = 7.2 Hz, 2H), 1.83-1.61 (m, 4H).
Analytical data compared to literature.¹⁰

Incorporation expected at δ 3.25. (blue arrow, blue dot in the structure). Determined against integral at δ 3.05 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.27 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.16 D/molecule for δ 3.25.

Yield: 33%, NMR yield.

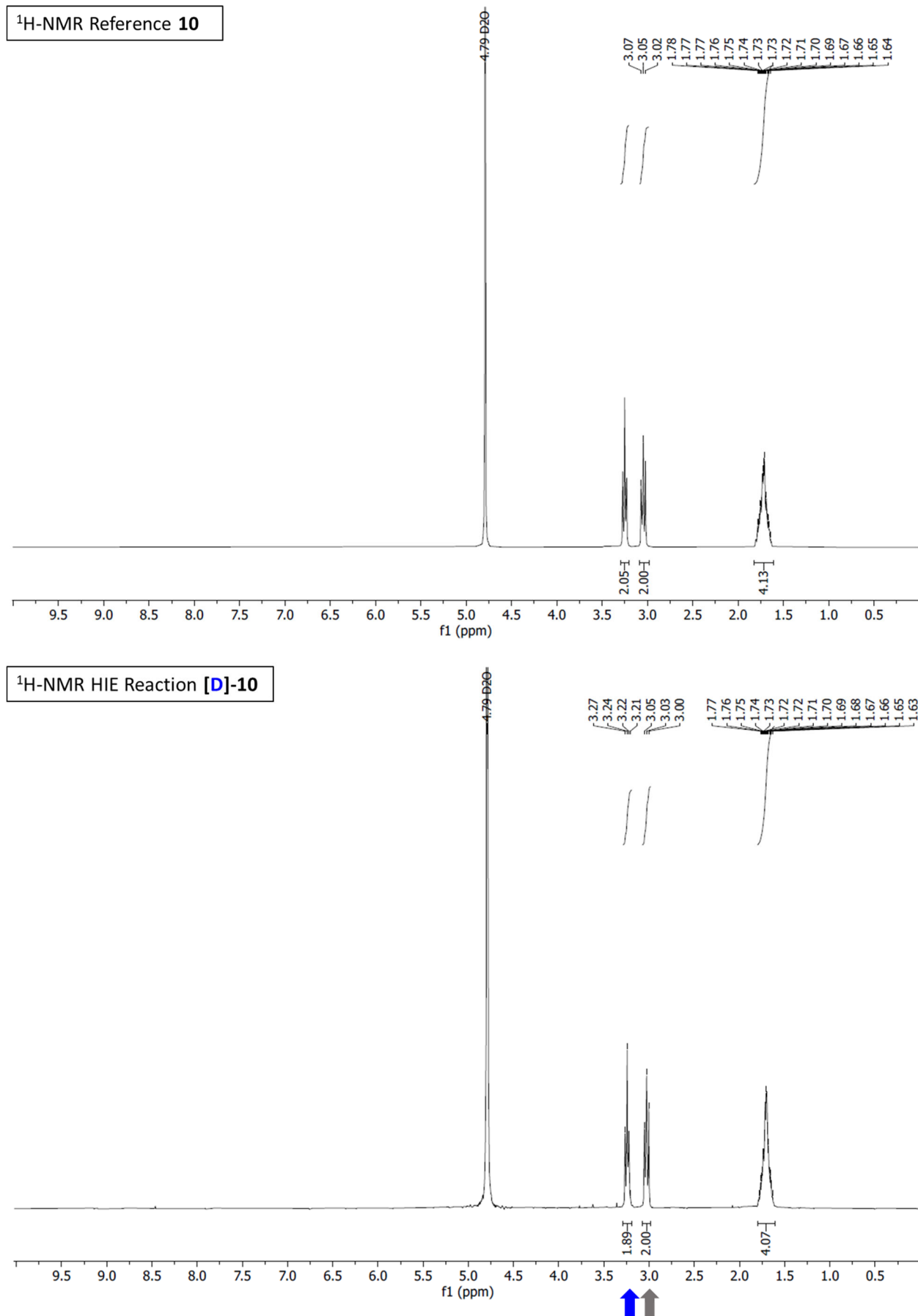


Figure S31: ¹H-NMR spectra of the HIE reaction of compound **10** to yield the deuterated product **[D]-10**.

²H-NMR HIE Reaction [D]-10

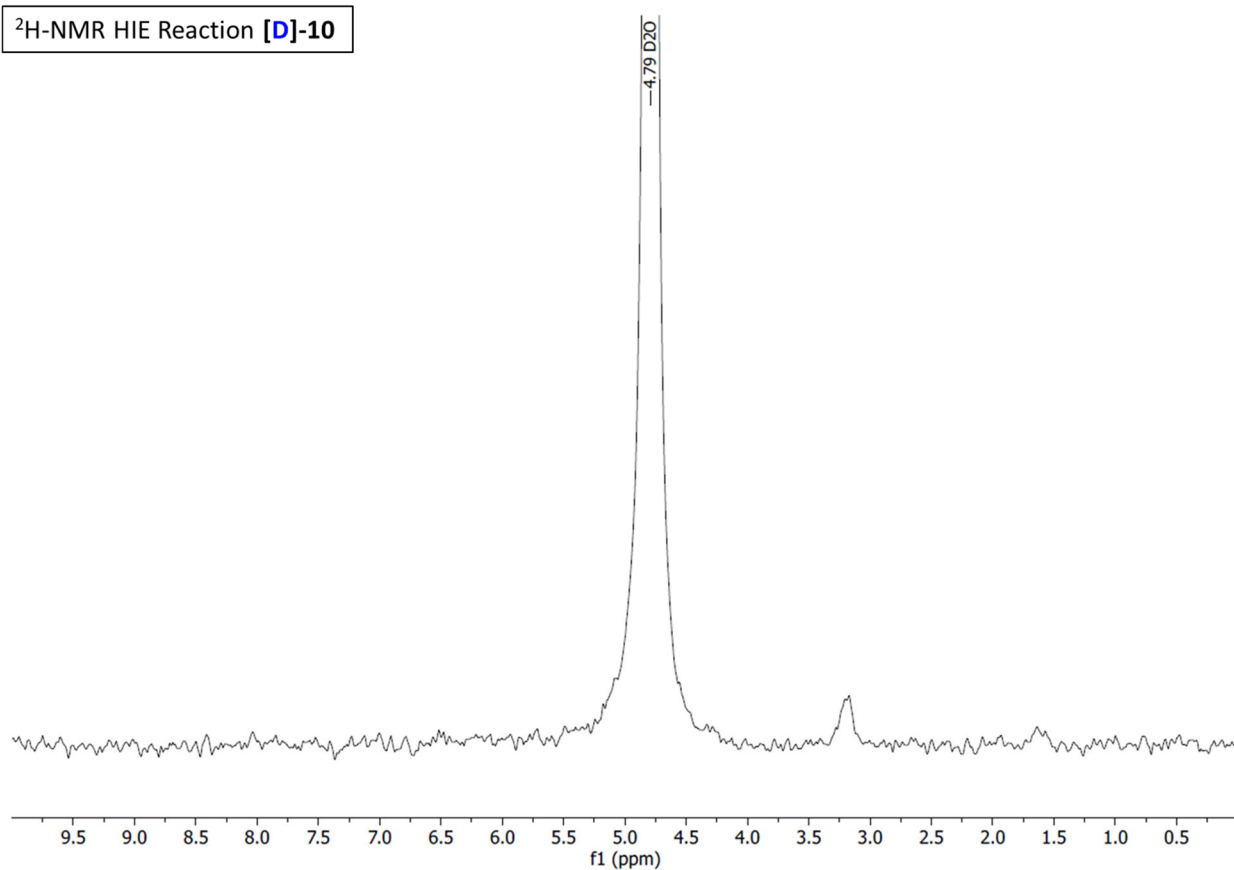
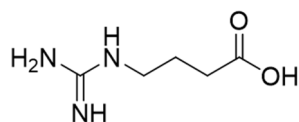


Figure S32: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-10.

7.1.5 4-guanidinobutyric acid **11**



11

Chemical Formula: C₅H₁₁N₃O₂

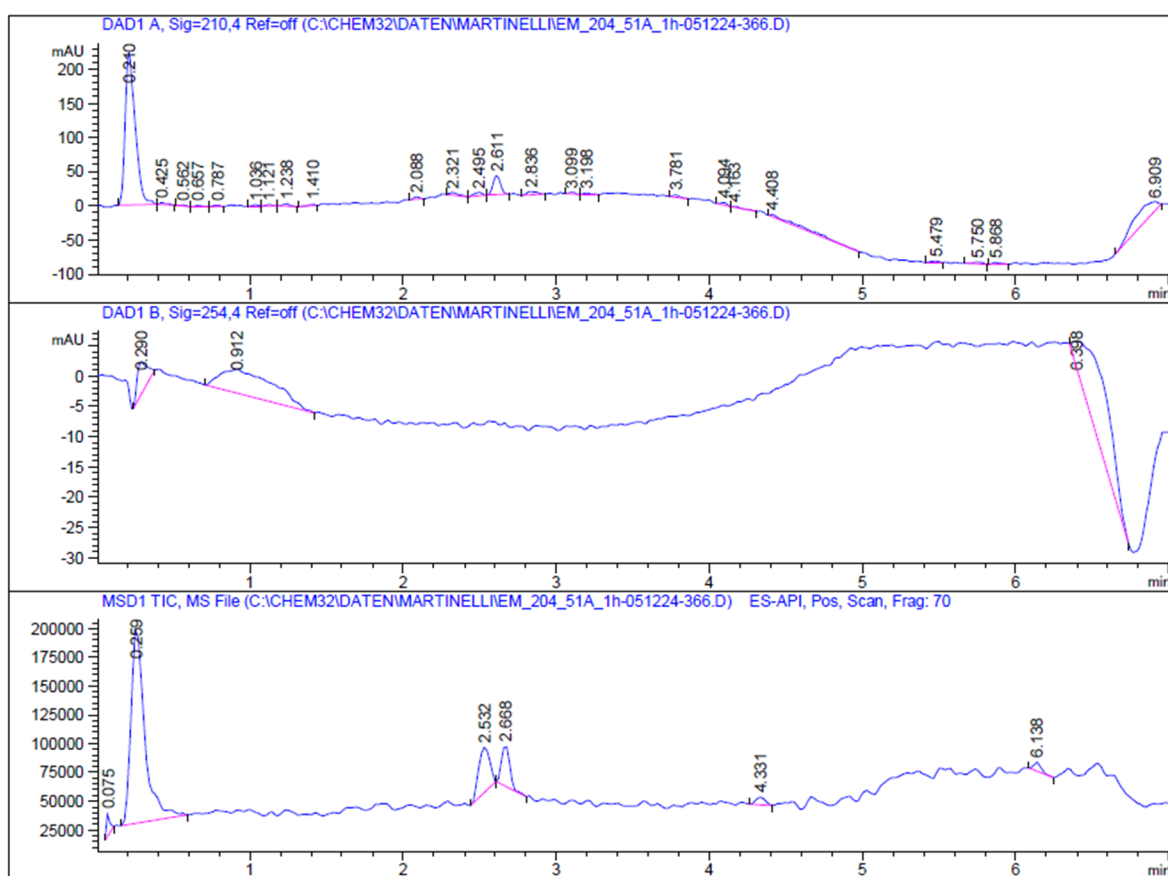
Exact Mass: 145.09

Figure S33: Structure of 4-guanidinobutyric acid **11**.

Method C: 3 mg, 0.02 mmol **11**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0 D/molecule.



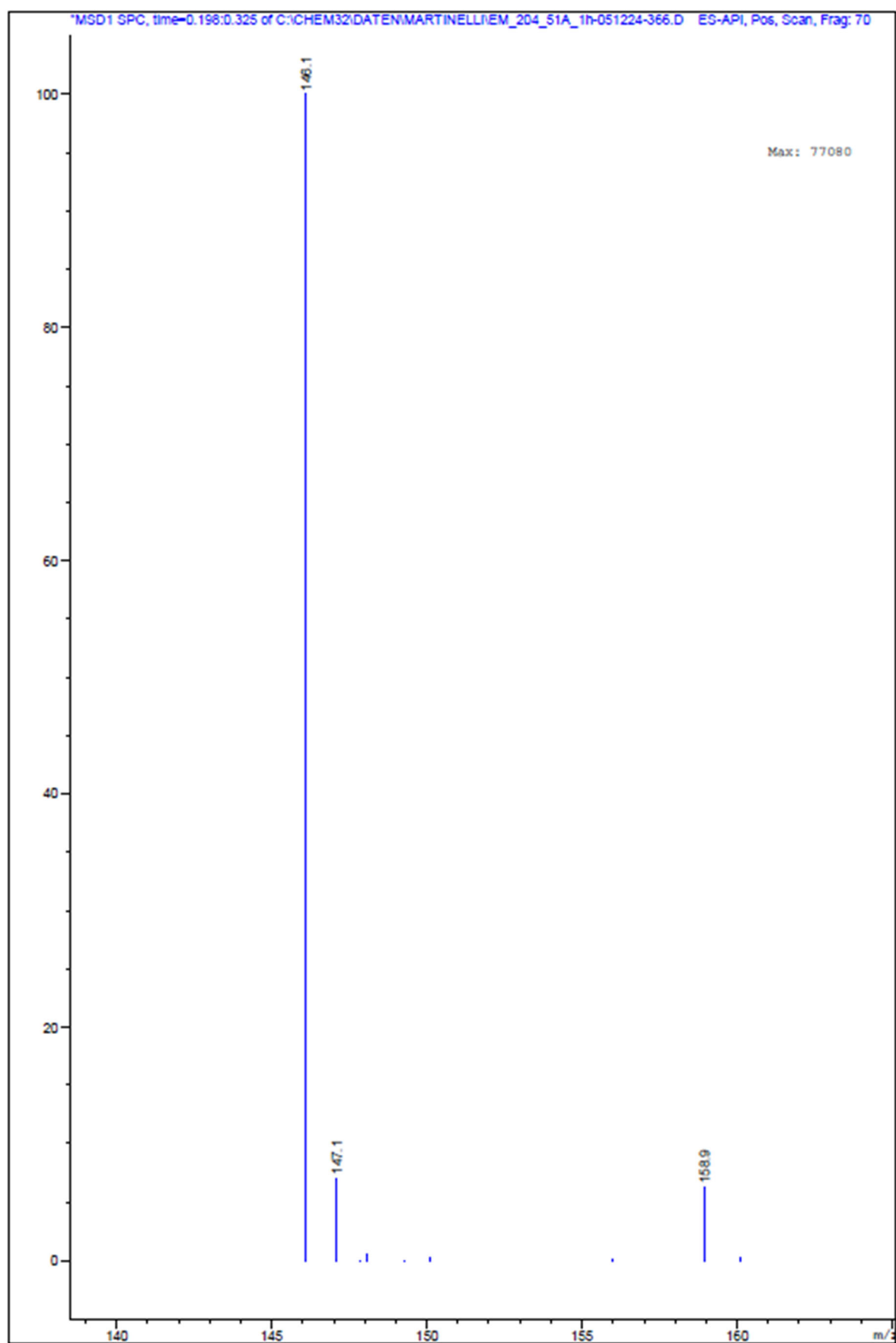
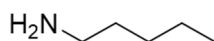


Figure S34: LC-MS analysis of representative HIE reaction of 4-guanidinobutyric acid **11**.

7.1.6 Amylamine 12



12

Chemical Formula: $\text{C}_5\text{H}_{13}\text{N}$

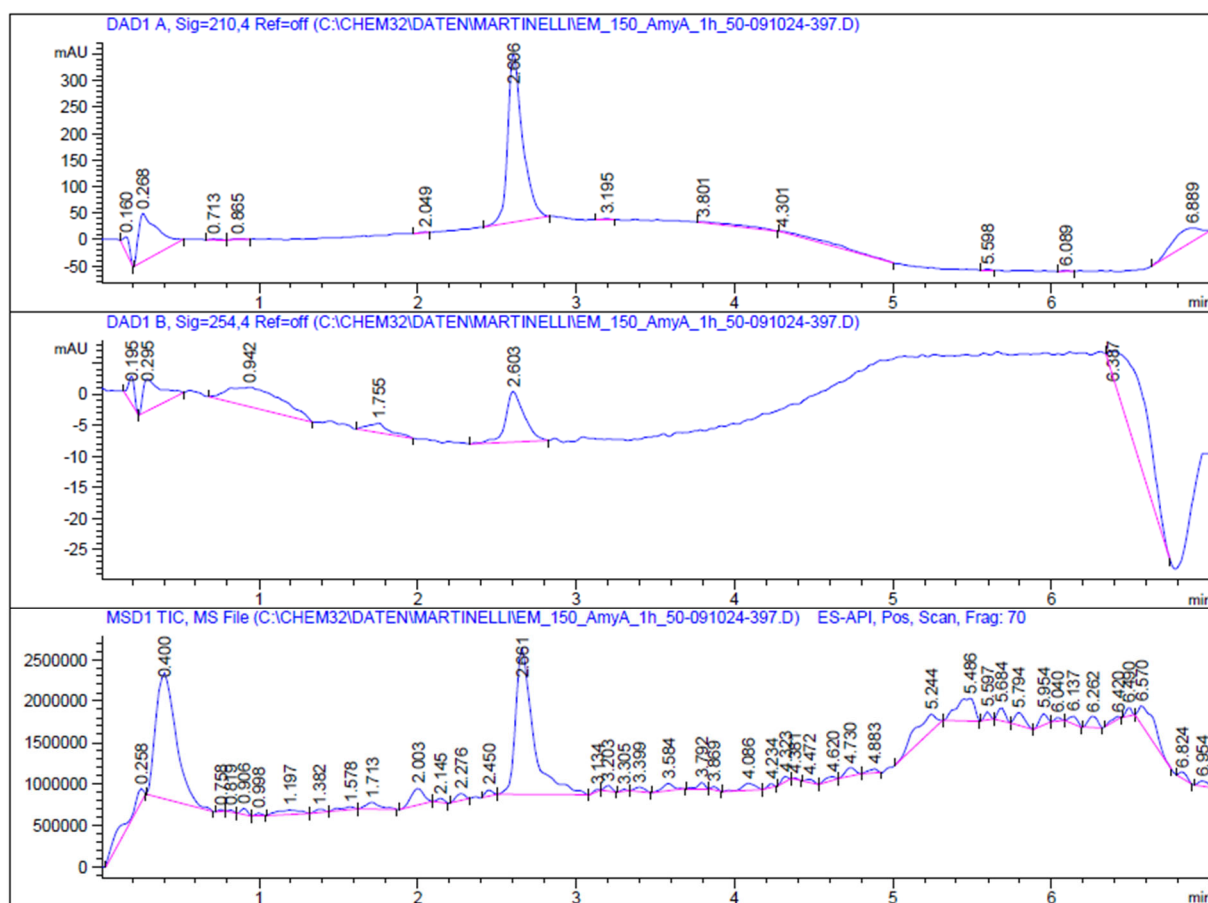
Exact Mass: 87.10

Figure S35: Structure of amylamine **12**.

Method A: 2 mg, 0.02 mmol **12**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0 D/molecule.



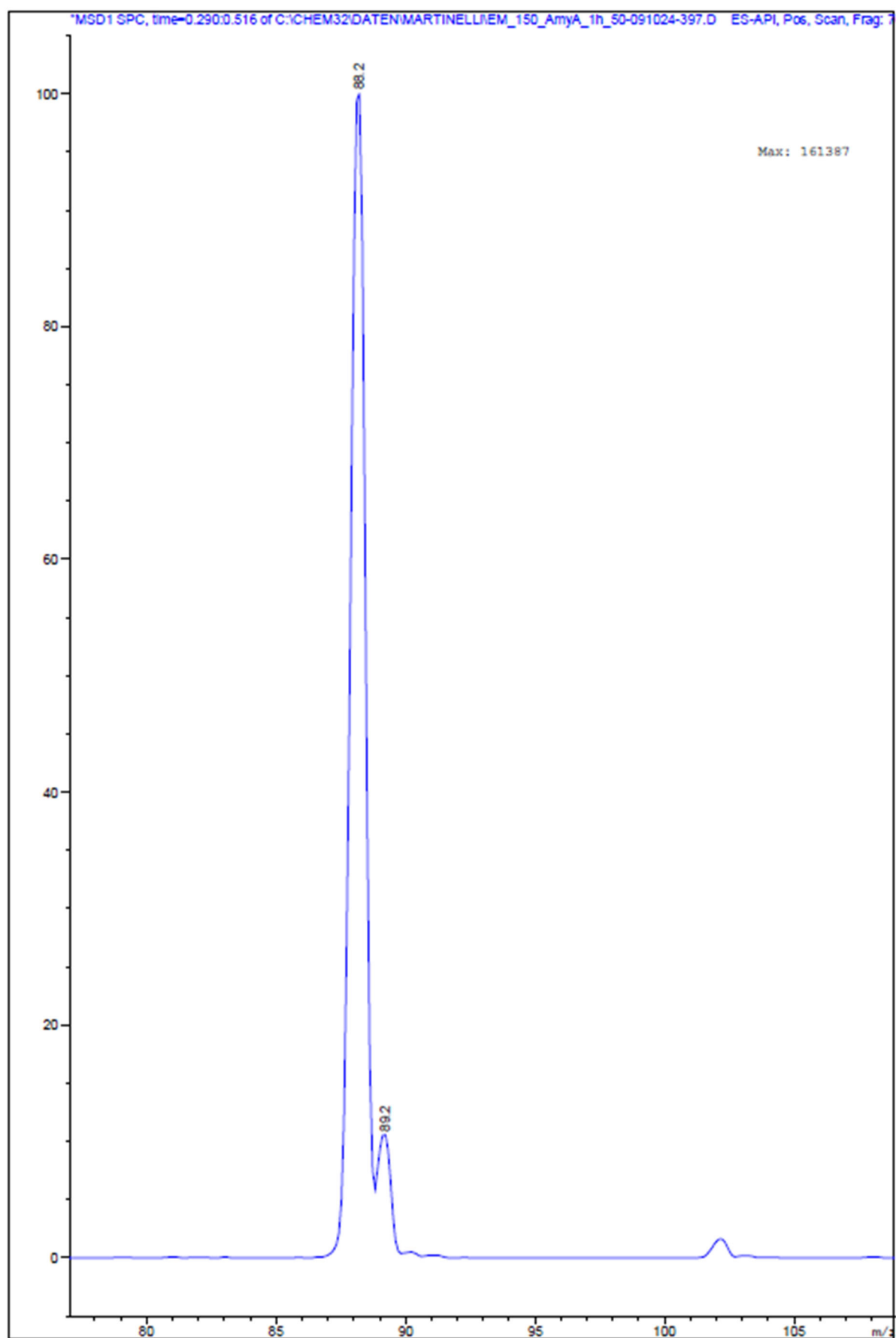


Figure S36: LC-MS analysis of representative HIE reaction of amylamine **12**.

7.1.7 1,5-diaminopentane **13**

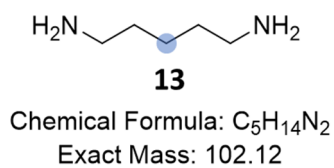


Figure S37: Structure of 1,5-diaminopentane **13**.

Method A: 2 mg, 0.02 mmol **13**, 0.5 μ mol catalyst **C4** (2.5 mol%), 1 μ mol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 2.64 (t, J = 6.9 Hz, 4H), 1.54-1.42 (m, 4H), 1.41-1.36 (m, 2H).
Analytical data compared to literature.¹¹

Incorporation expected at δ 1.41-1.36. (blue arrow, blue dot in the structure). Determined against integral at δ 2.64 (grey arrow).

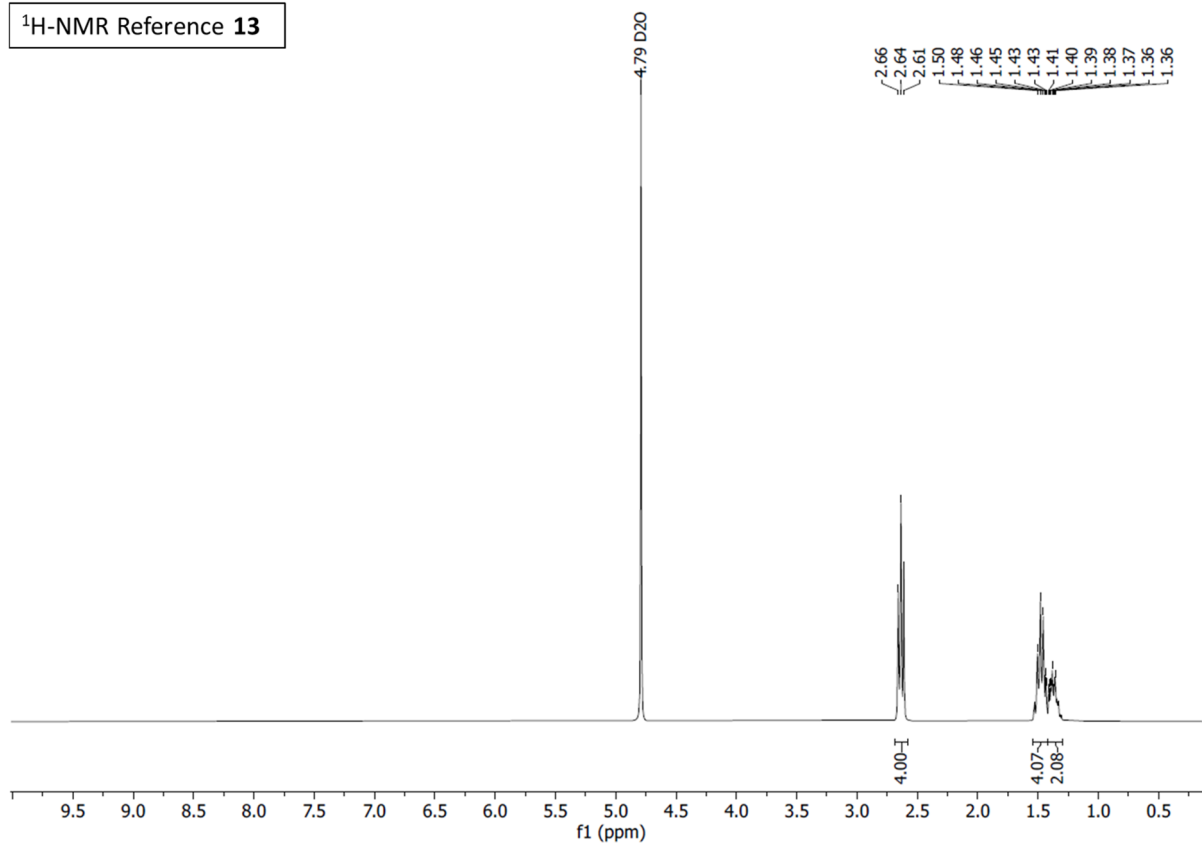
Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 1.40 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 1.11 D/molecule for δ 1.41-1.36.

Yield: 63%, NMR yield.

¹H-NMR Reference **13**



¹H-NMR HIE Reaction **[D]-13**

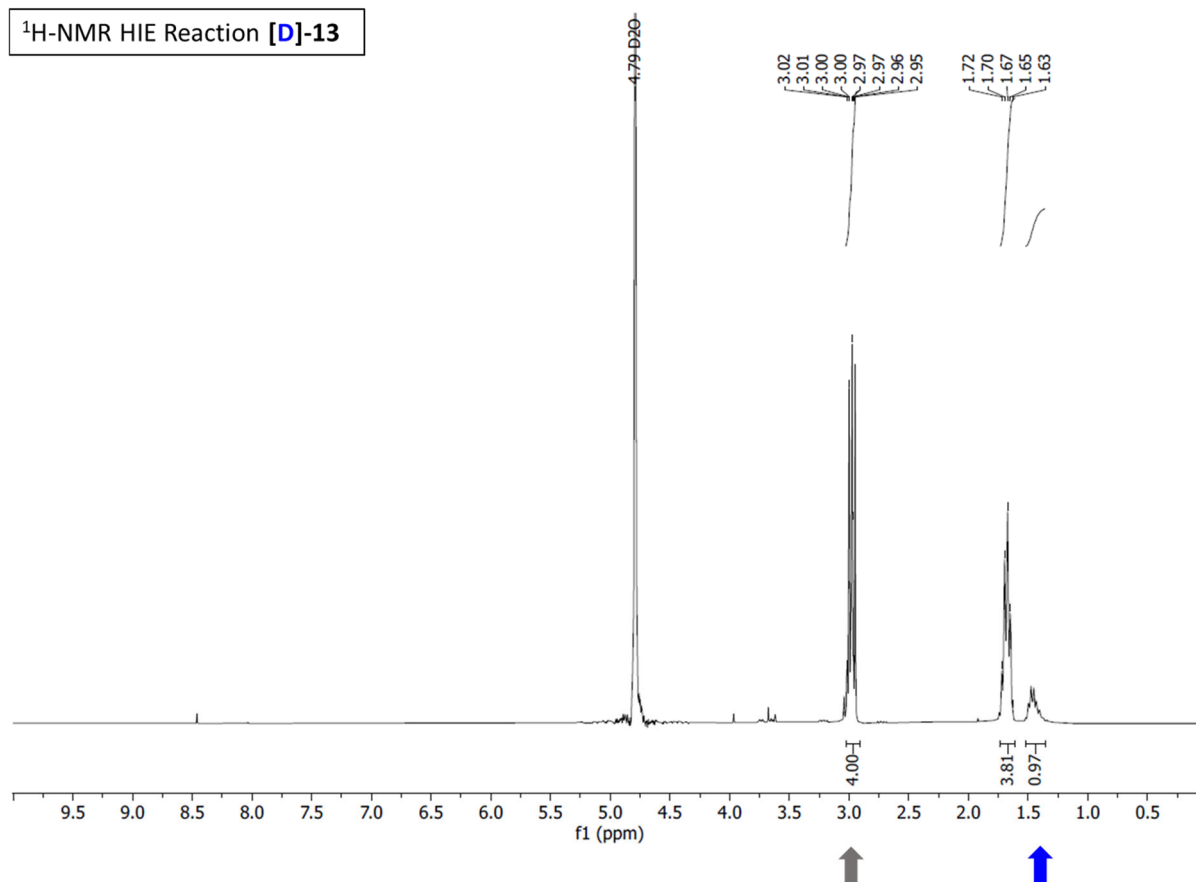


Figure S38: ¹H-NMR spectra of the HIE reaction of compound **13** to yield the deuterated product **[D]-13**.

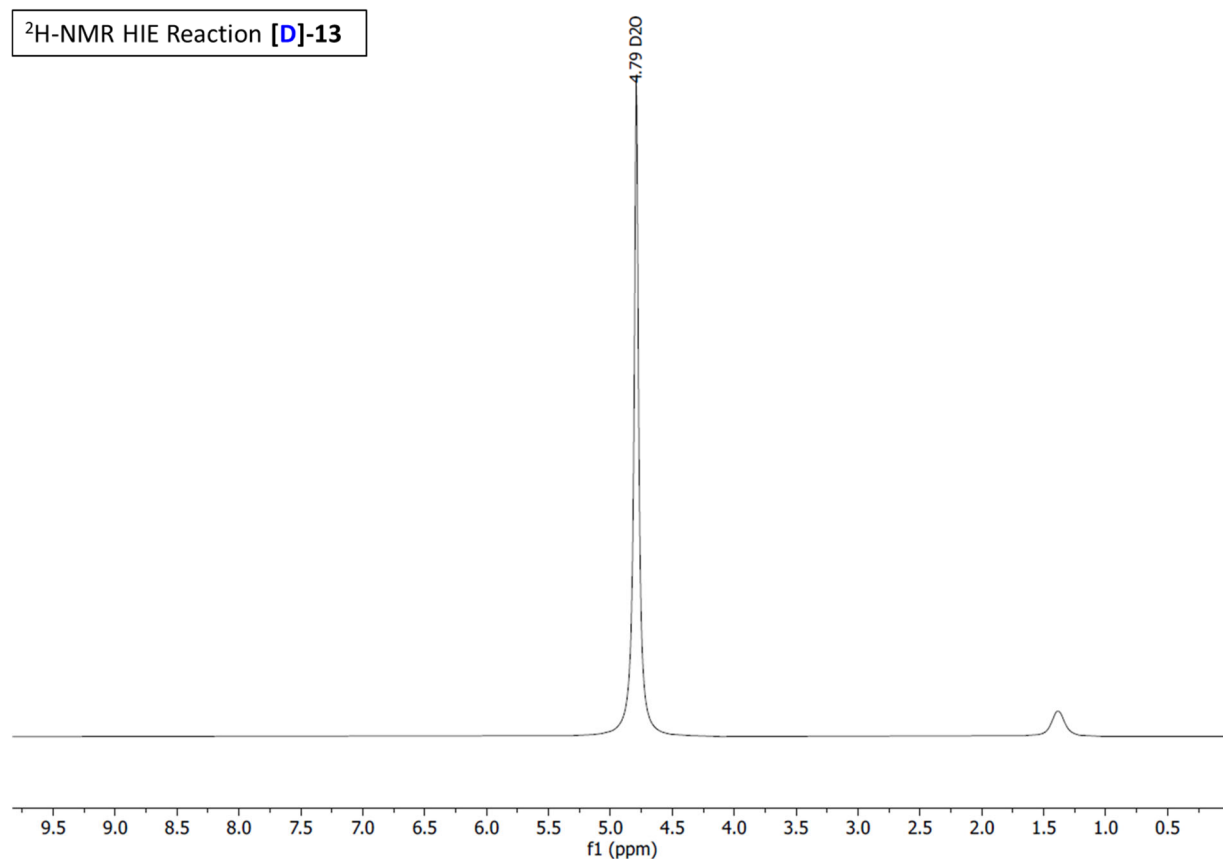


Figure S39: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-13.

7.1.8 1-methyl-1,5-diaminopentane **14**

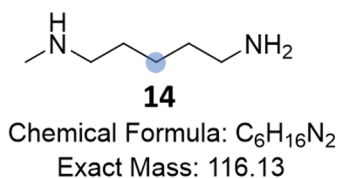


Figure S40: Structure of 1-methyl-1,5-diaminopentane **14**.

Method A: 2 mg, 0.02 mmol **14**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 2.60 (t, *J* = 6.9 Hz, 2H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.30 (s, 3H), 1.56-1.39 (m, 4H), 1.38-1.24 (m, 2H). Analytical data compared to literature.¹²

Incorporation expected at δ 1.38-1.24. (blue arrow, blue dot in the structure). Determined against integral at δ 2.30 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 1.11 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.96 D/molecule for δ 1.38-1.24

Yield: 54%, NMR yield.

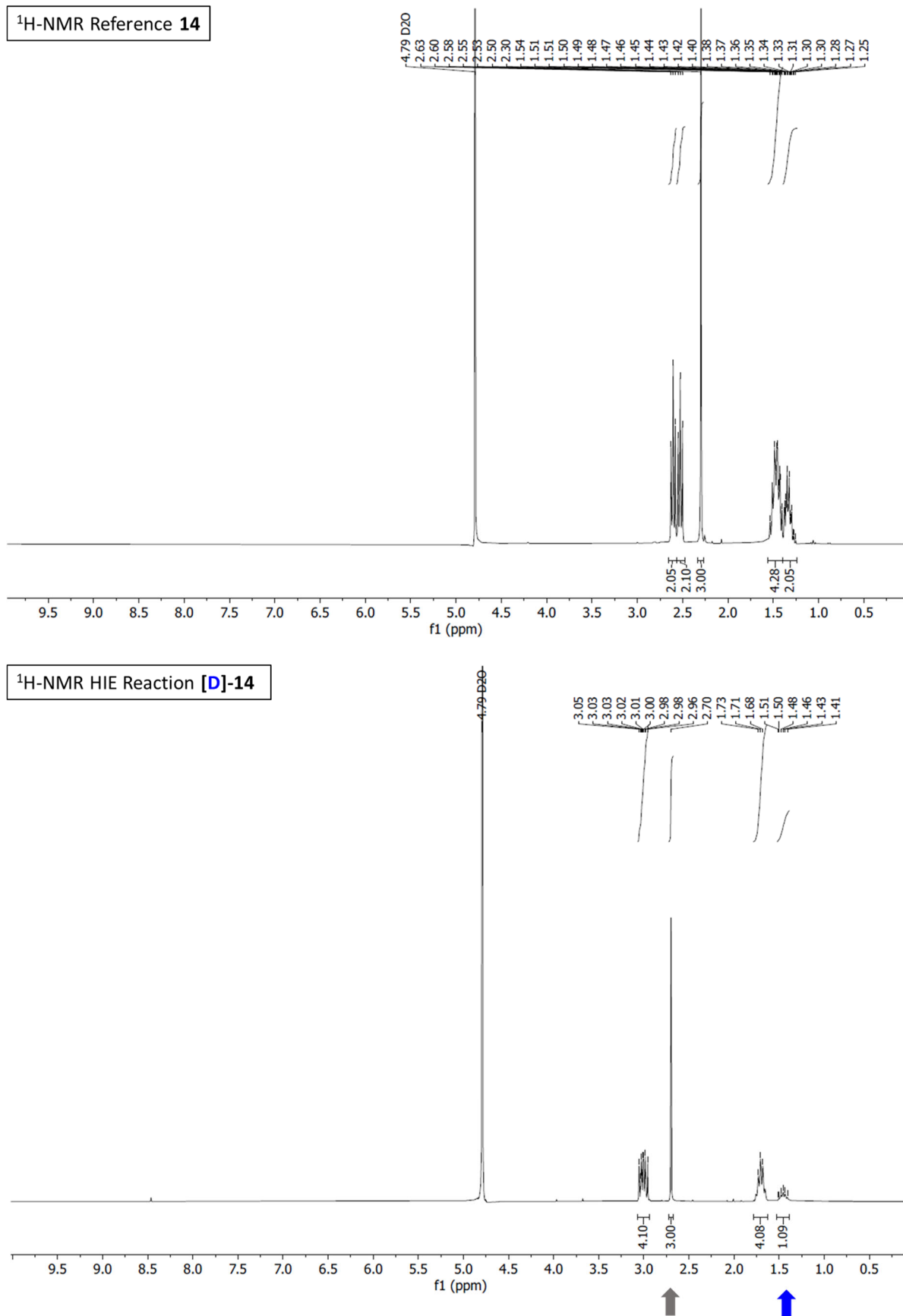


Figure S41: ¹H-NMR spectra of the HIE reaction of compound **14** to yield the deuterated product **[D]-14**.

²H-NMR HIE Reaction [D]-14

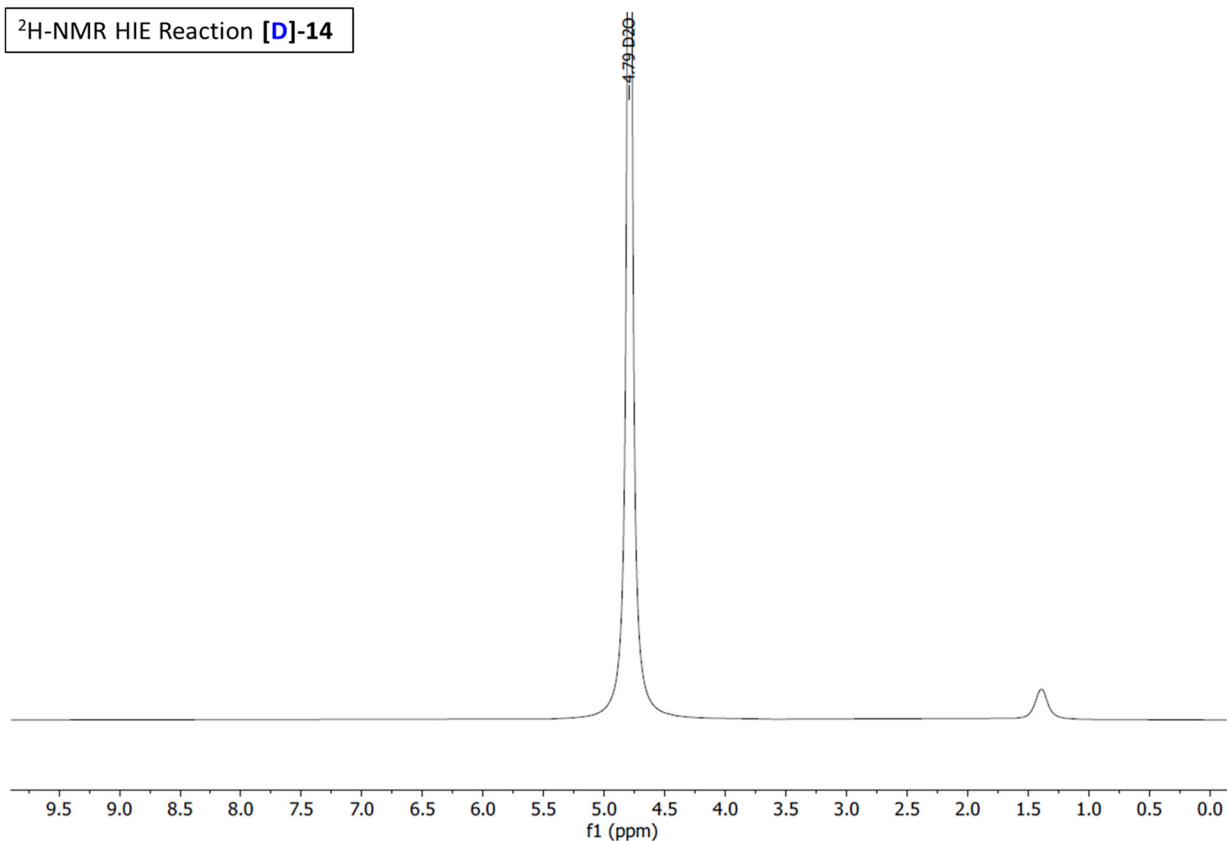
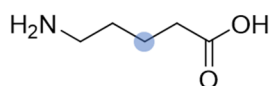


Figure S42: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-14.

7.1.9 5-aminopentanoic acid **15**



15

Chemical Formula: C₅H₁₁NO₂

Exact Mass: 117.08

Figure S43: Structure of 5-aminopentanoic acid **15**.

Method A: 2 mg, 0.02 mmol **15**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 3.02 (t, *J* = 7.1 Hz, 2H), 2.28-2.19 (t, *J* = 7.1 Hz, 2H), 1.70-1.62 (m, 4H). Analytical data compared to literature.¹³

Incorporation expected at δ 1.70-1.62. (blue arrow, blue dot in the structure, uncertainty due to overlapping signals, position assigned as indicated by postulated mechanism). Determined against integral at δ 3.02 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.24 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.19 D/molecule for δ 1.70-1.62

Yield: 35%, NMR yield.

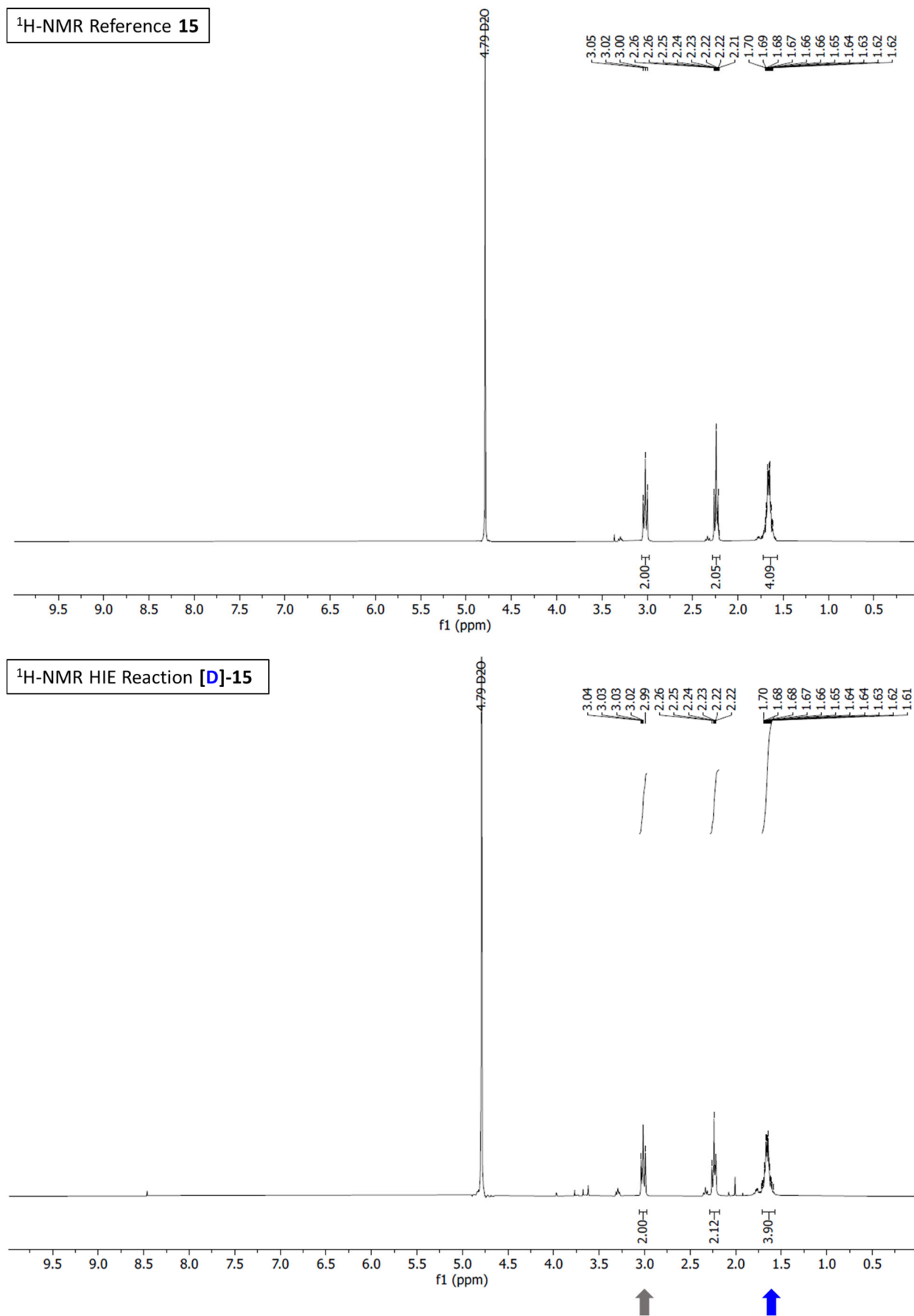


Figure S44: ¹H-NMR spectra of the HIE reaction of compound **15** to yield the deuterated product **[D]-15**.

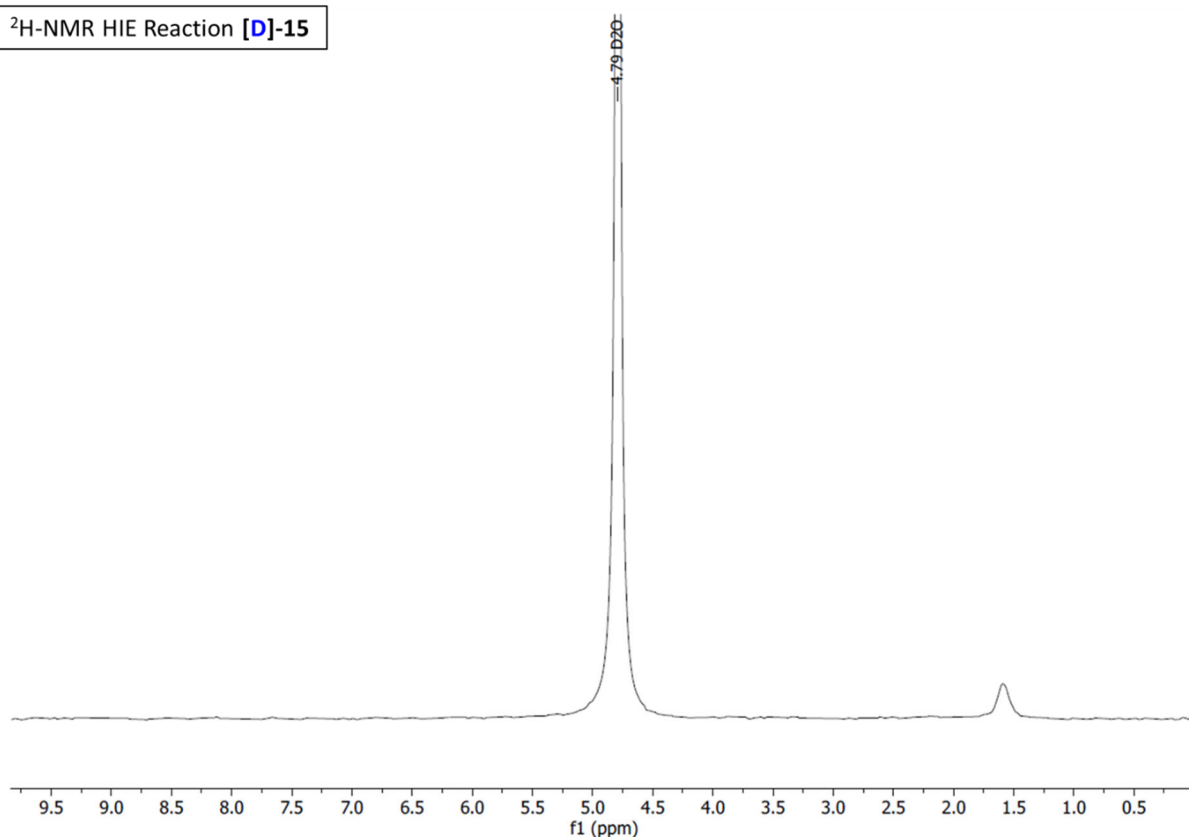
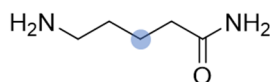


Figure S45: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-15.

7.1.10 5-aminopentamide **16**



16

Chemical Formula: C₅H₁₁NO₂

Exact Mass: 117.08

Figure S46: Structure of 5-aminopentamide **16**.

Method A: 3 mg, 0.02 mmol **16**·HCl, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 3.04 (t, *J* = 6.8 Hz, 2H), 2.28-2.19 (t, *J* = 6.4 Hz, 2H), 1.80-1.60 (m, 4H). Analytical data compared to literature.¹⁴

Incorporation expected at δ 1.80-1.60. (blue arrow, blue dot in the structure, uncertainty due to overlapping signals, position assigned as indicated by postulated mechanism). Determined against integral at δ 3.04 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.32 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.32 D/molecule for δ 1.80-1.60

Yield: 21%, NMR yield.

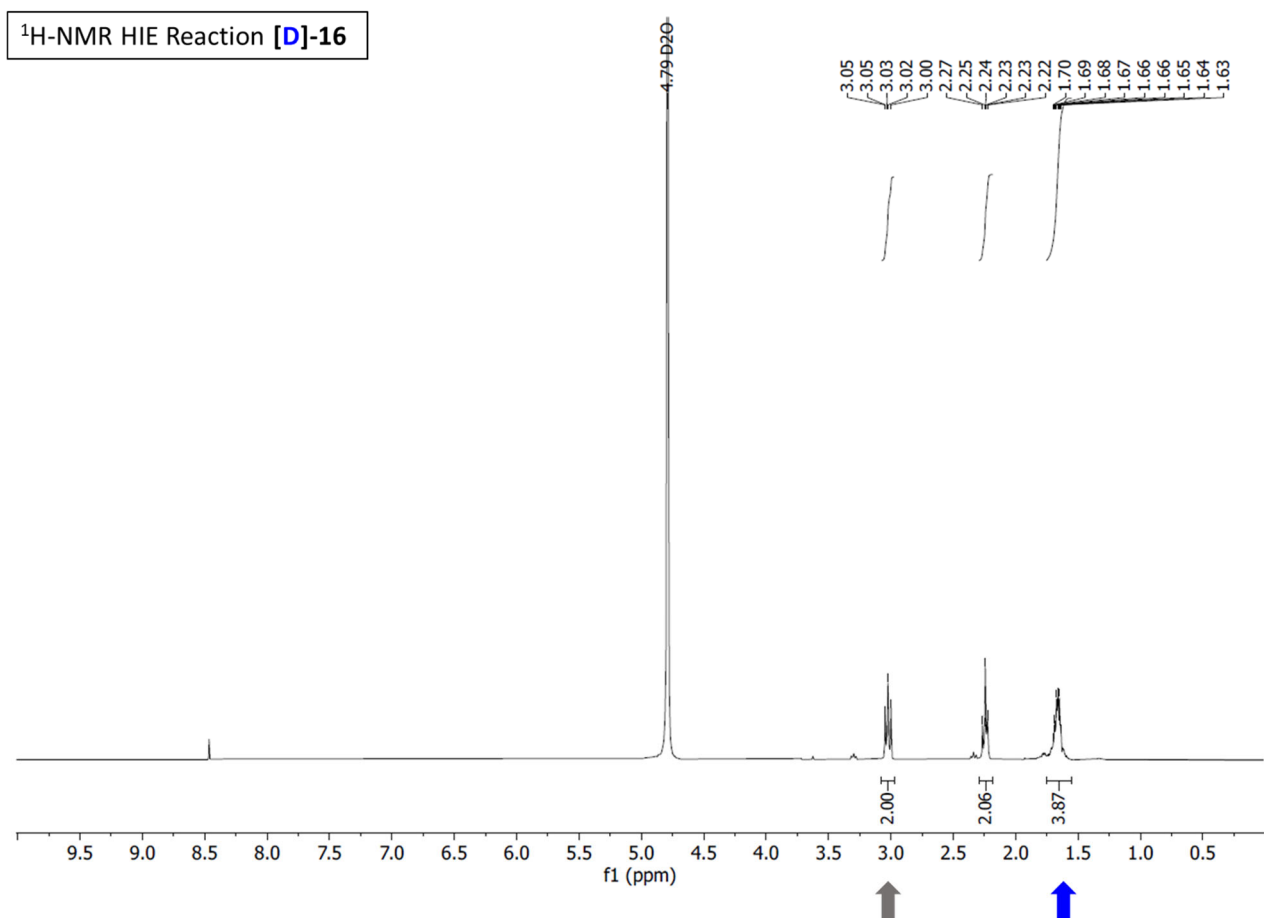
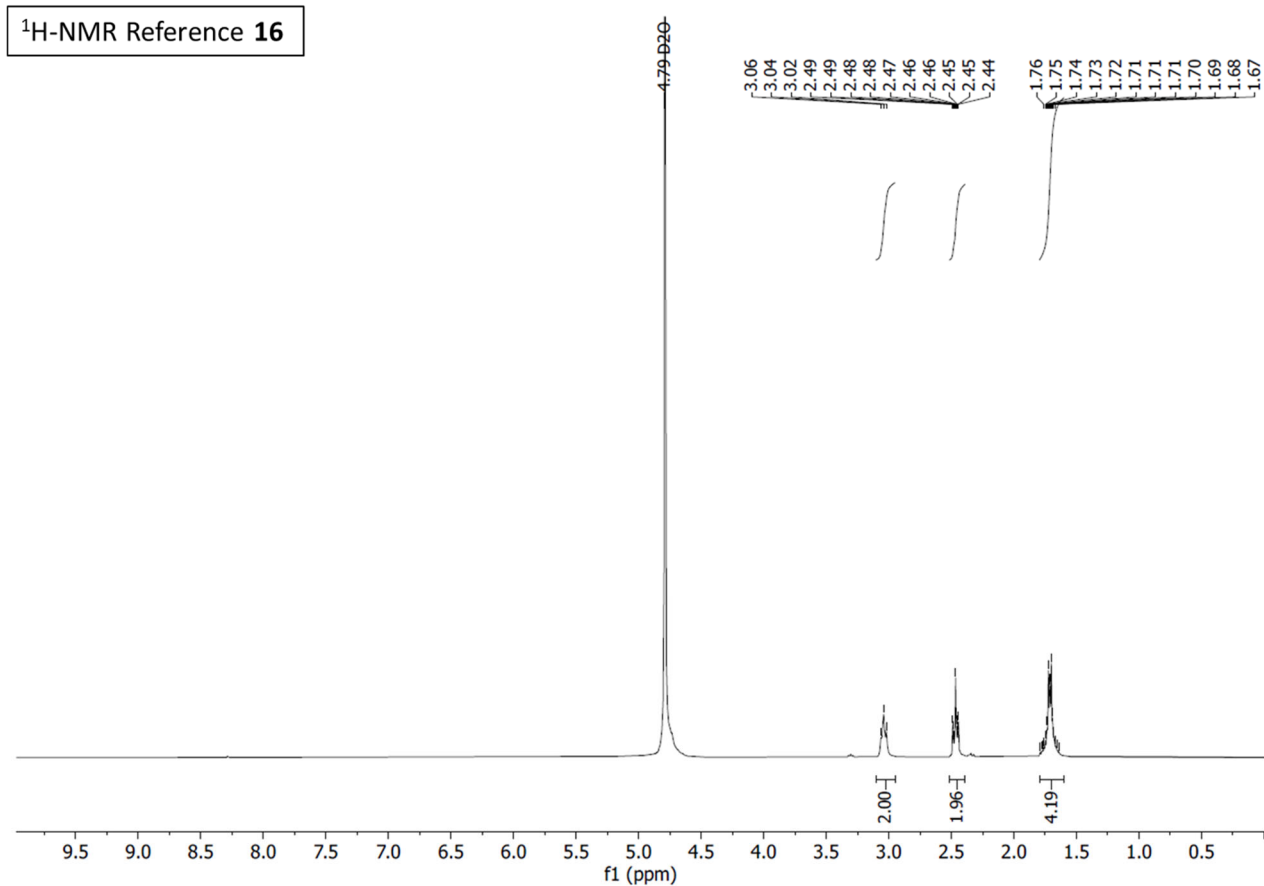


Figure S47: ¹H-NMR spectra of the HIE reaction of compound **16** to yield the deuterated product **[D]-16**.

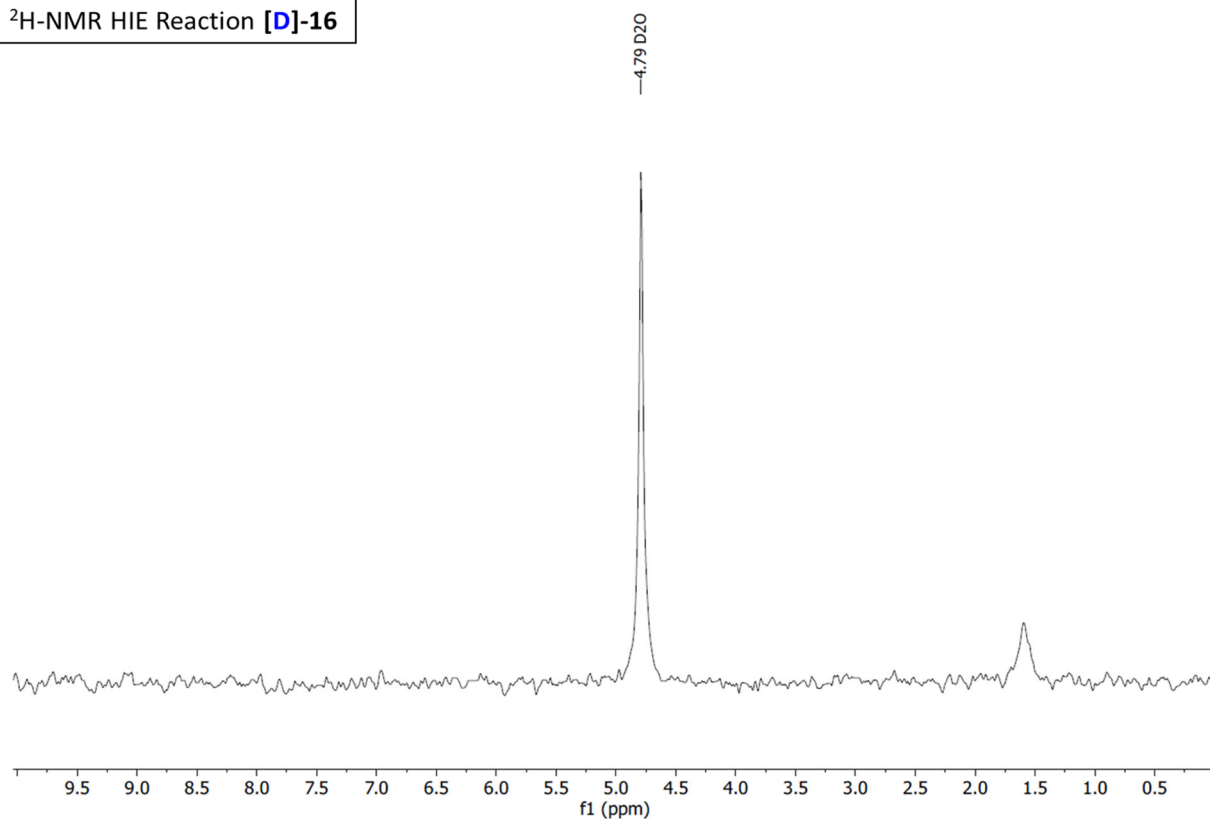
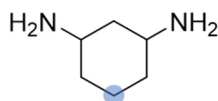


Figure S48: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-16.

7.1.11 1,3-cyclohexanediamine **17**



17

Chemical Formula: C₆H₁₄N₂

Exact Mass: 114.12

Figure S49: Structure of 1,3-cyclohexanediamine **17**.

Method A: 2 mg, 0.02 mmol **17**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 2.72-2.62 (m, 2H), 2.01-1.93 (m, 1H), 1.89-1.68 (m, 3H), 1.68-1.51 (m, 1H), 1.39-1.22 (m, 2H), 1.06-0.83 (m, 3H). Analytical data compared to literature.¹⁵

Incorporation expected at δ 1.89-1.68. (blue arrow, blue dot in the structure). Determined against integral at δ 2.72-2.62 (grey arrow).

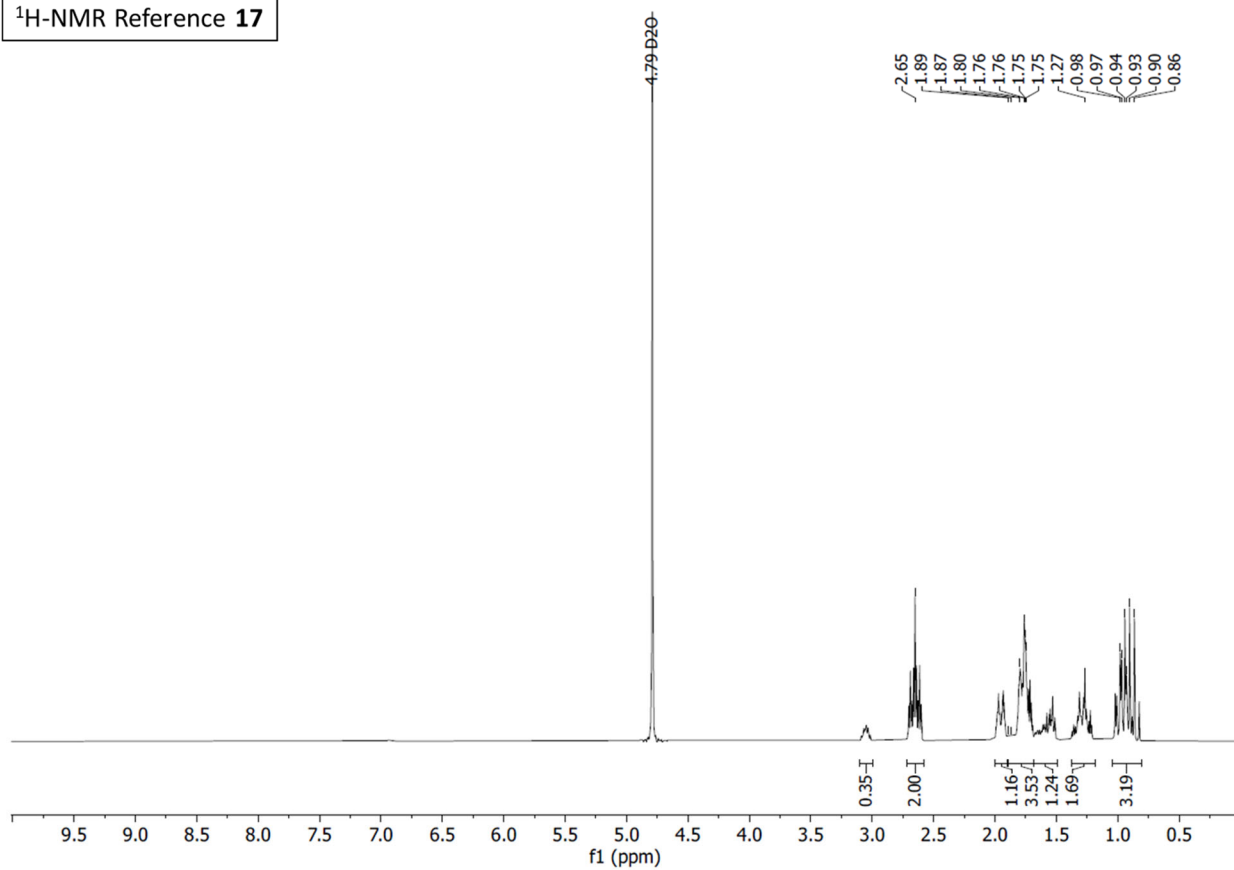
Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.44 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.31 D/molecule for δ 1.89-1.68

Yield: 74%, NMR yield.

¹H-NMR Reference **17**



¹H-NMR HIE Reaction **[D]-17**

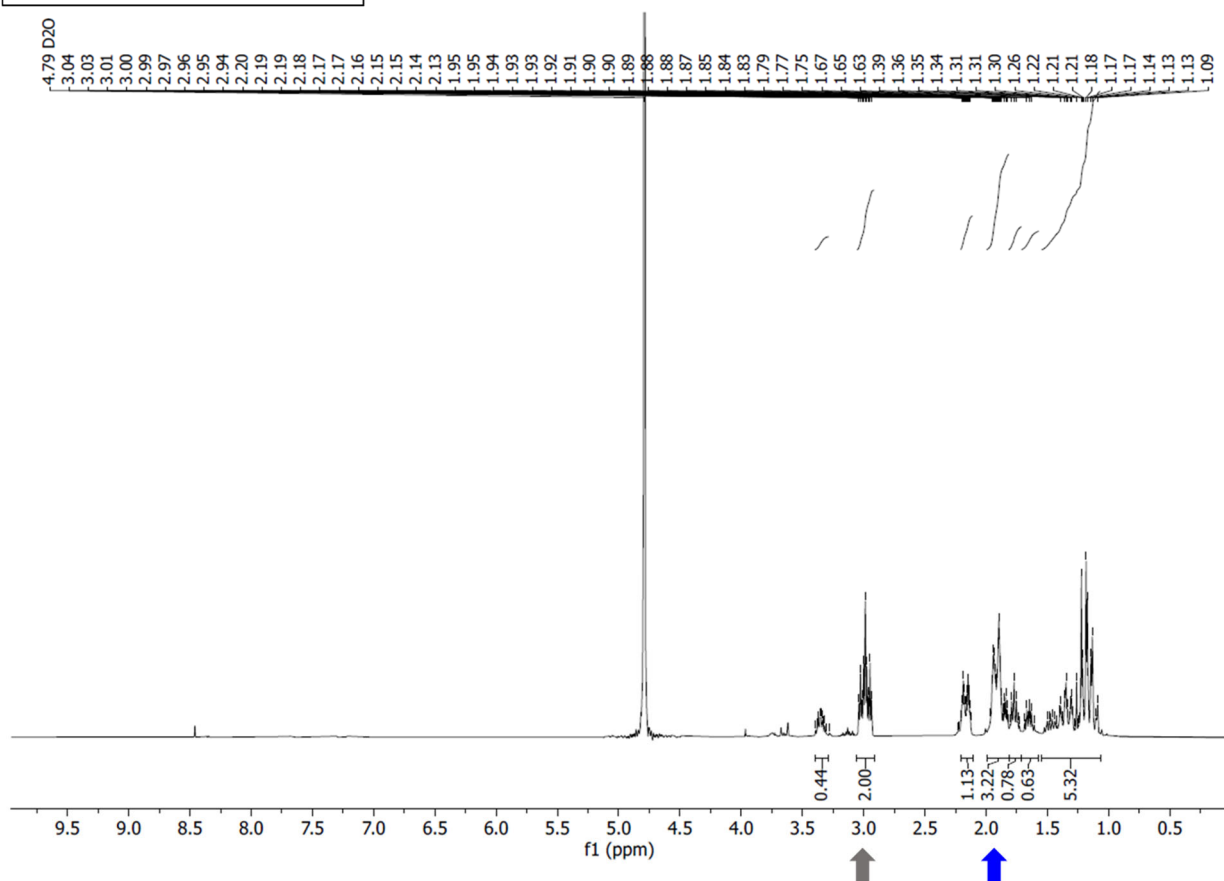


Figure S50: ¹H-NMR spectra of the HIE reaction of compound **17** to yield the deuterated product **[D]-17**.

^2H -NMR HIE Reaction [D]-17

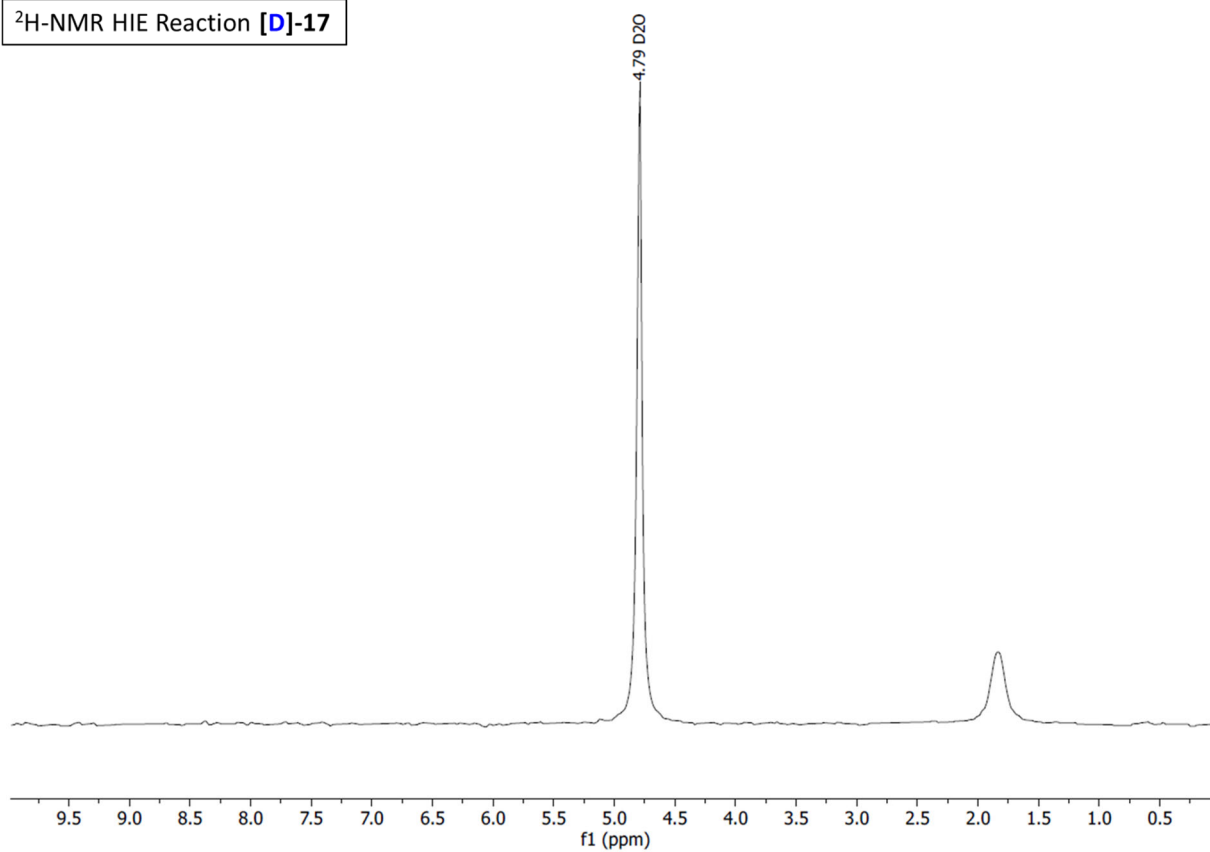


Figure S51: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-17.

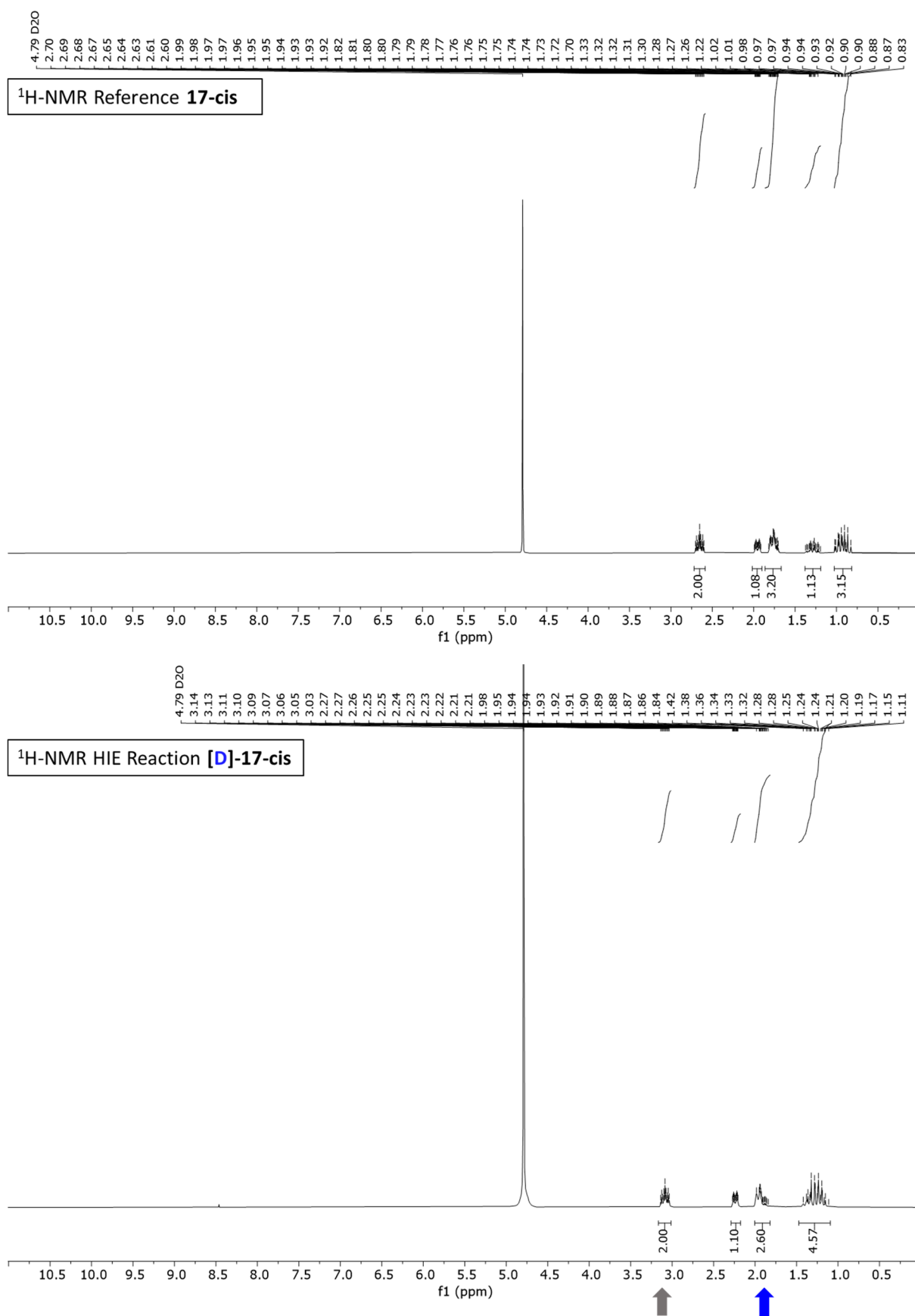


Figure S52: ¹H-NMR spectra of reference compound **17** and the crude of the deuteration crude reaction yielding **[D]-17-cis**.

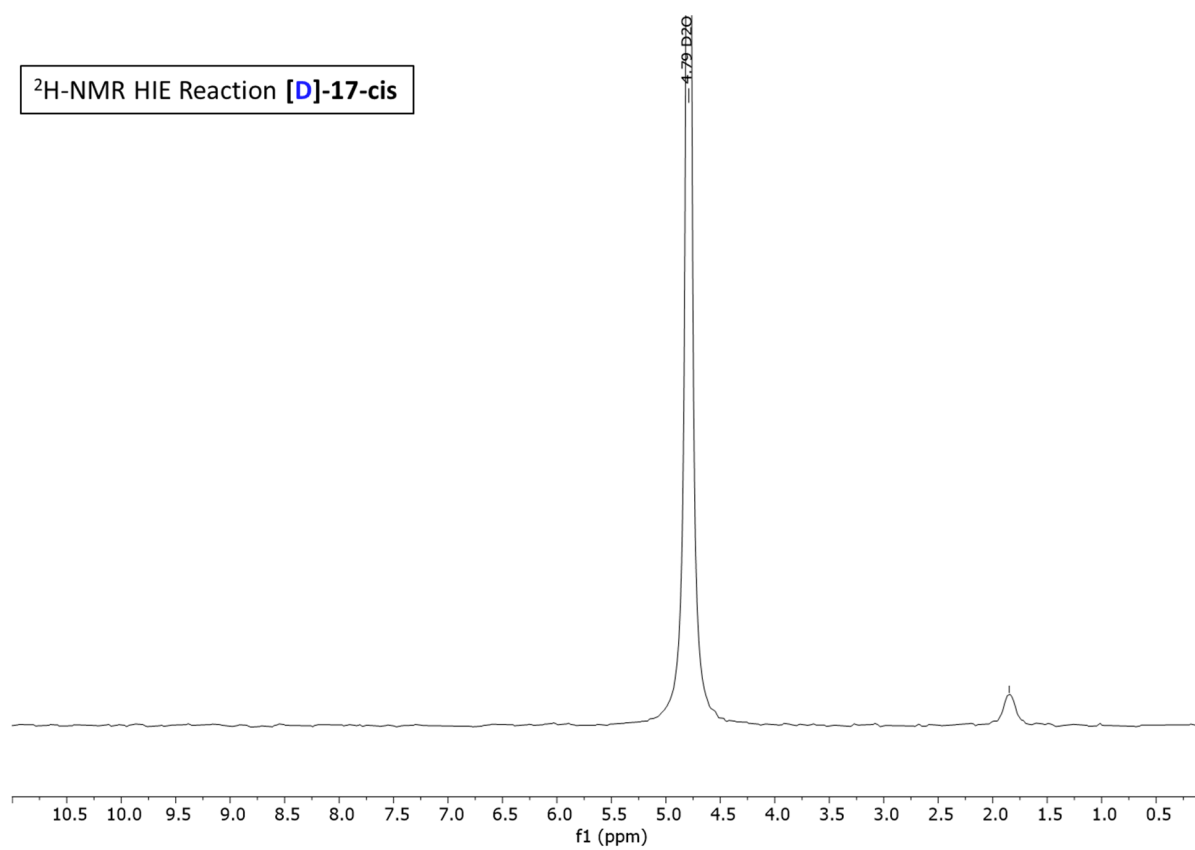


Figure S53: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-17-cis.

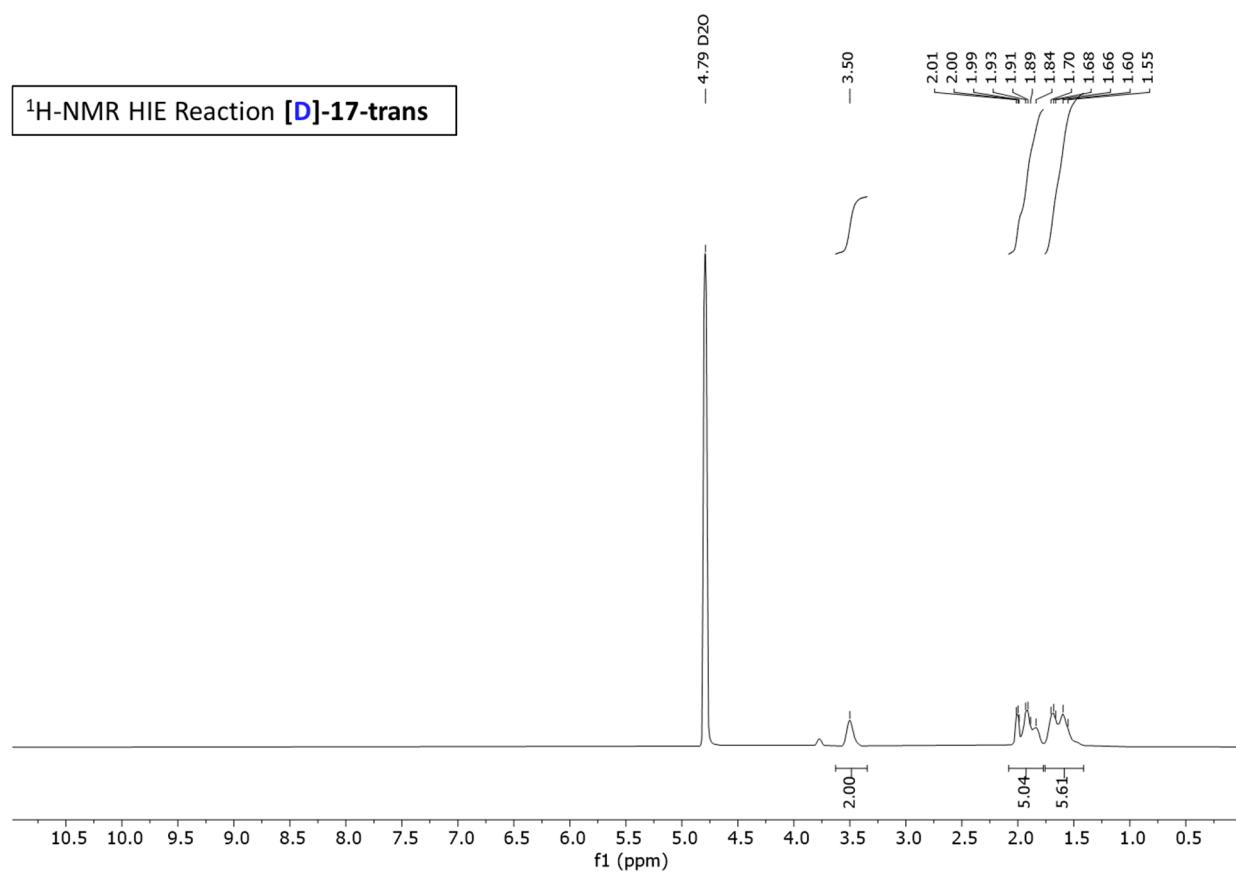
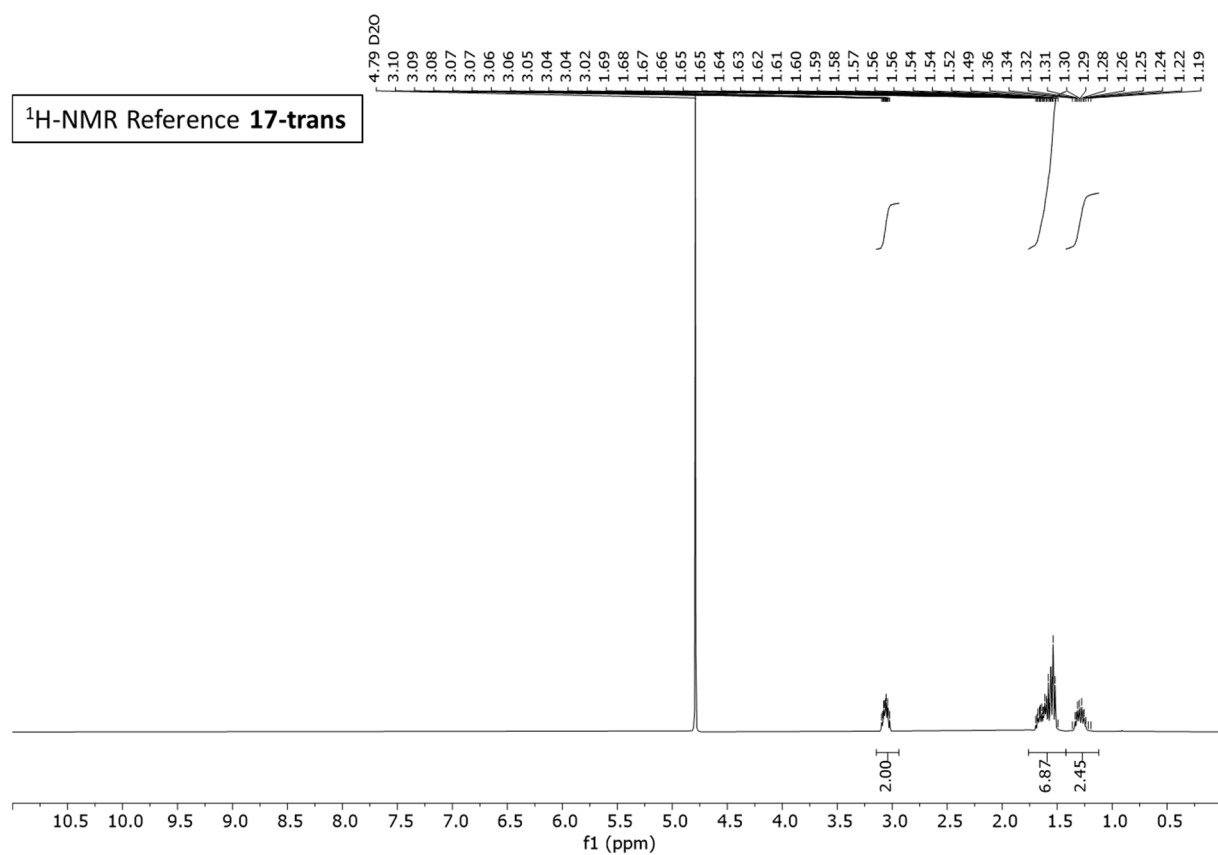


Figure S54: ¹H-NMR spectra of reference compound **17** and the crude of the deuteration crude reaction yielding [**D**]-**17-trans**.

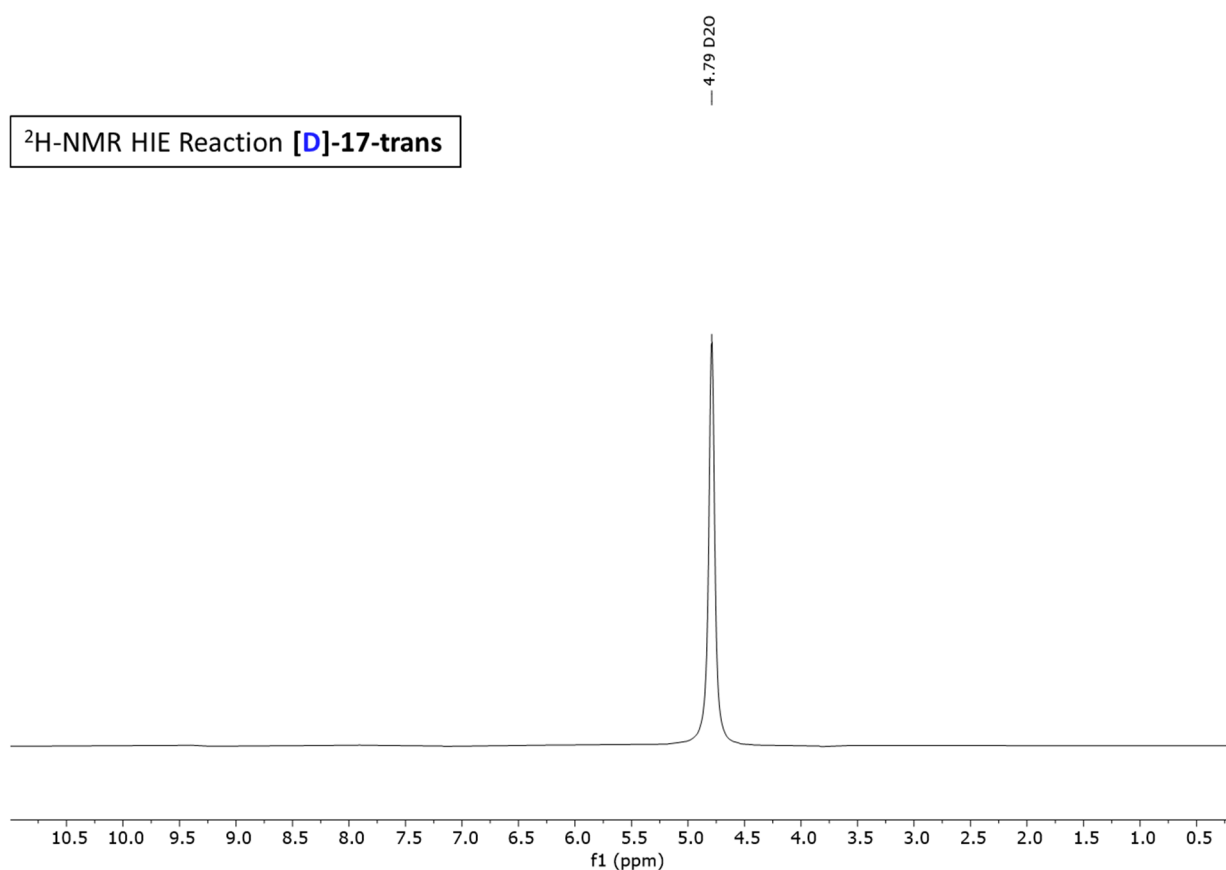


Figure S55: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [**D**]-**17-trans**.

7.1.12 1,6-diaminohexane **18**

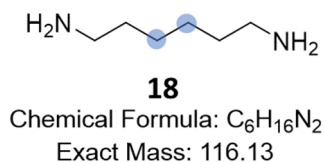


Figure S56: Structure of 1,6-diaminohexane **18**.

Method A: 2 mg, 0.02 mmol **18**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

¹H-NMR (300 MHz, D₂O): δ [ppm] = 2.62 (t, *J* = 6.9 Hz, 4H), 1.54-1.39 (m, 4H), 1.39-1.28 (m, 4H).
Analytical data compared to literature.¹⁶

Incorporation expected at δ 1.39-1.28. (blue arrow, blue dot in the structure). Determined against integral at δ 2.62 (grey arrow).

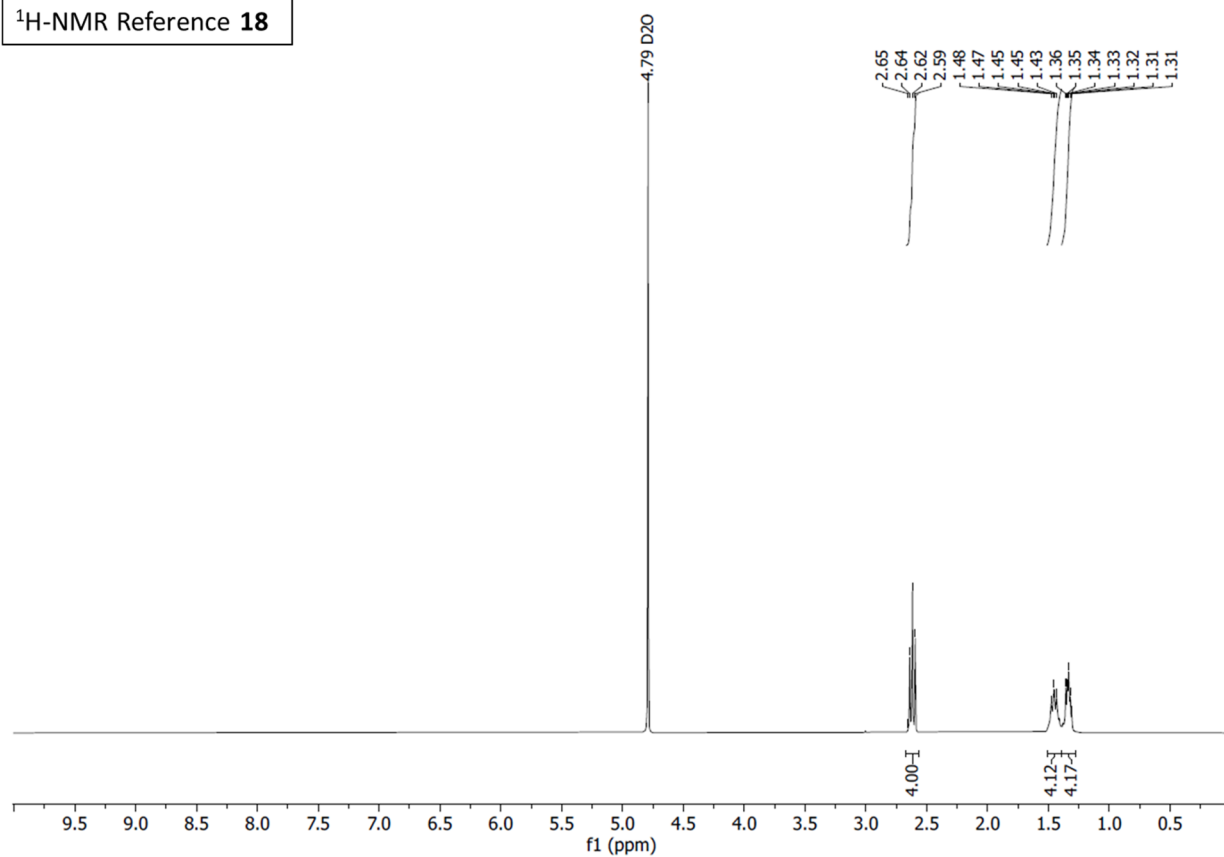
Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.45 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.47 D/molecule for δ 1.39-1.28

Yield: 40%, NMR yield.

¹H-NMR Reference **18**



¹H-NMR HIE Reaction **[D]-18**

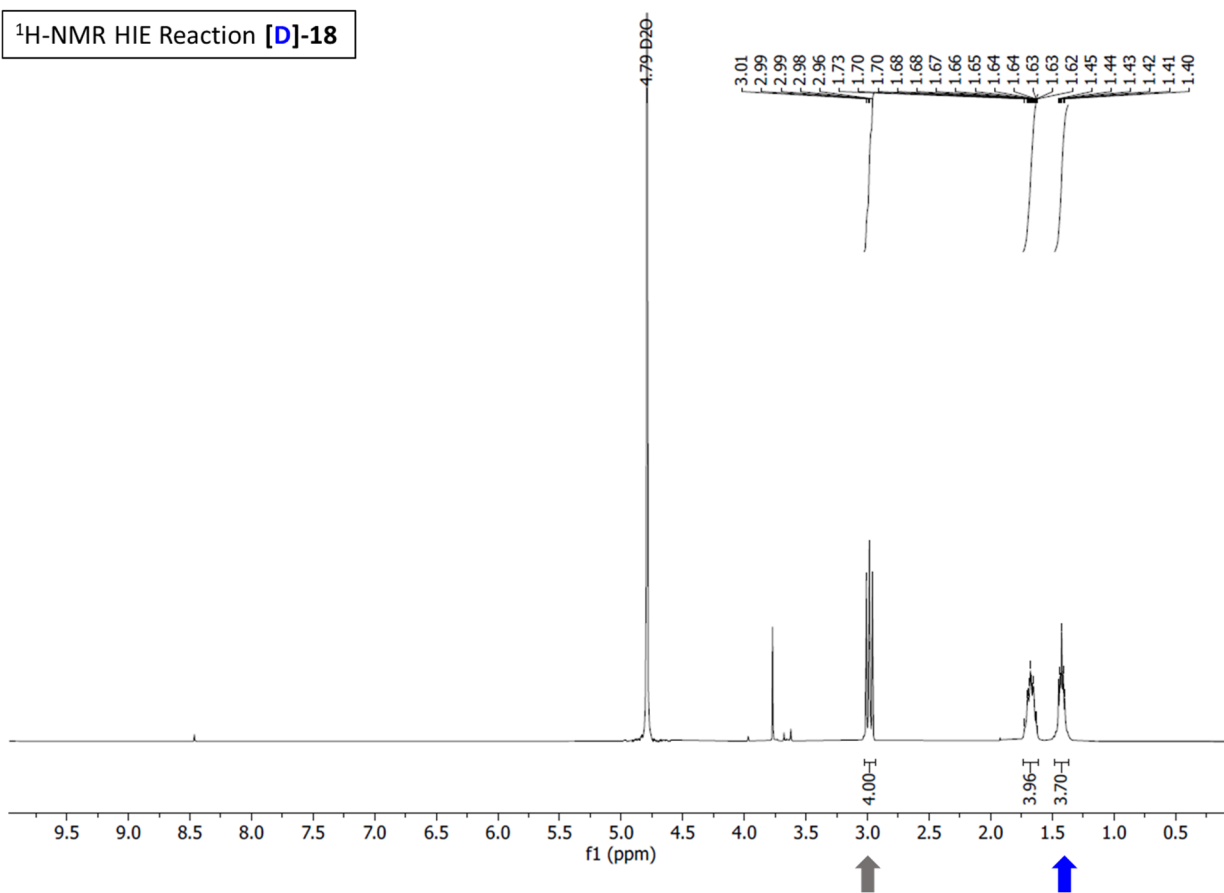


Figure S57: ¹H-NMR spectra of the HIE reaction of compound **18** to yield the deuterated product **[D]-18**.

^2H -NMR HIE Reaction [D]-18

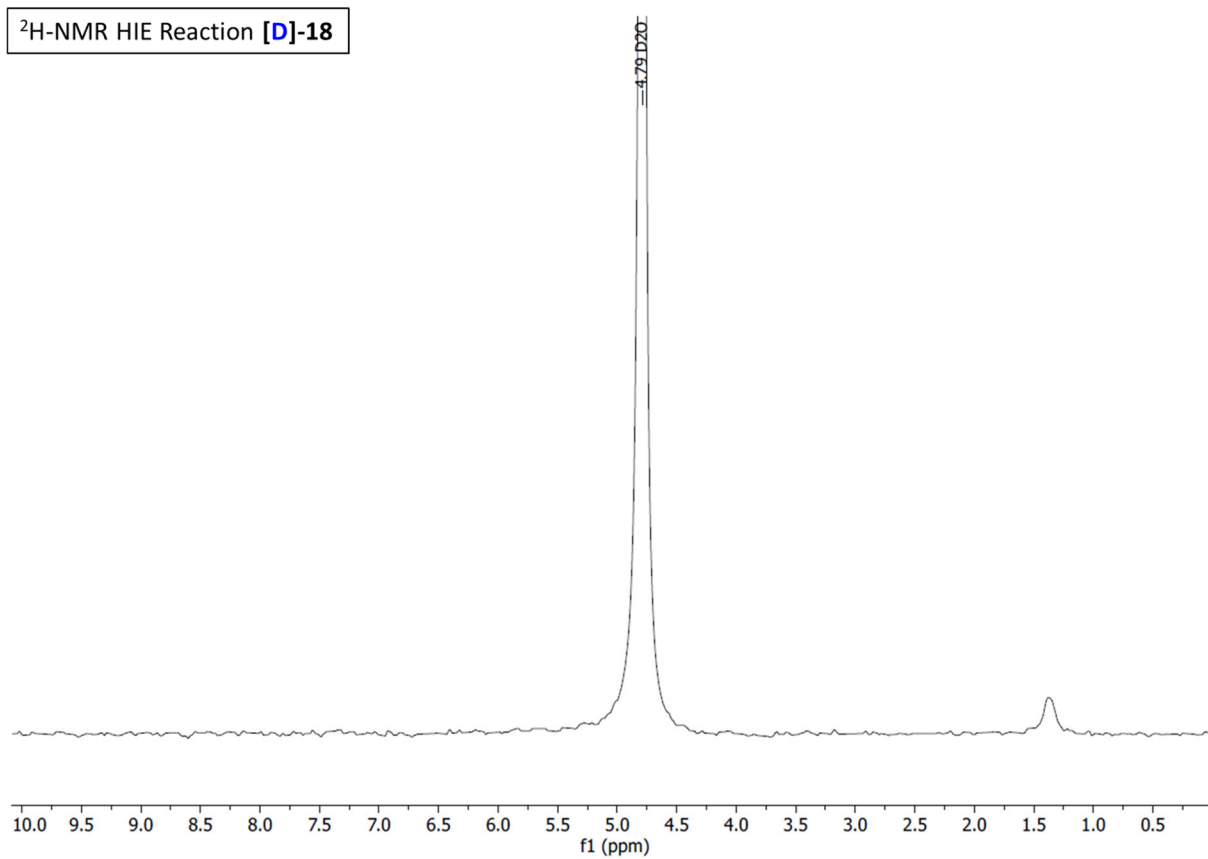
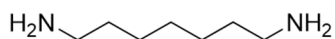


Figure S58: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-18.

7.1.13 1,7-diaminoheptane **19**



19

Chemical Formula: $\text{C}_7\text{H}_{18}\text{N}_2$

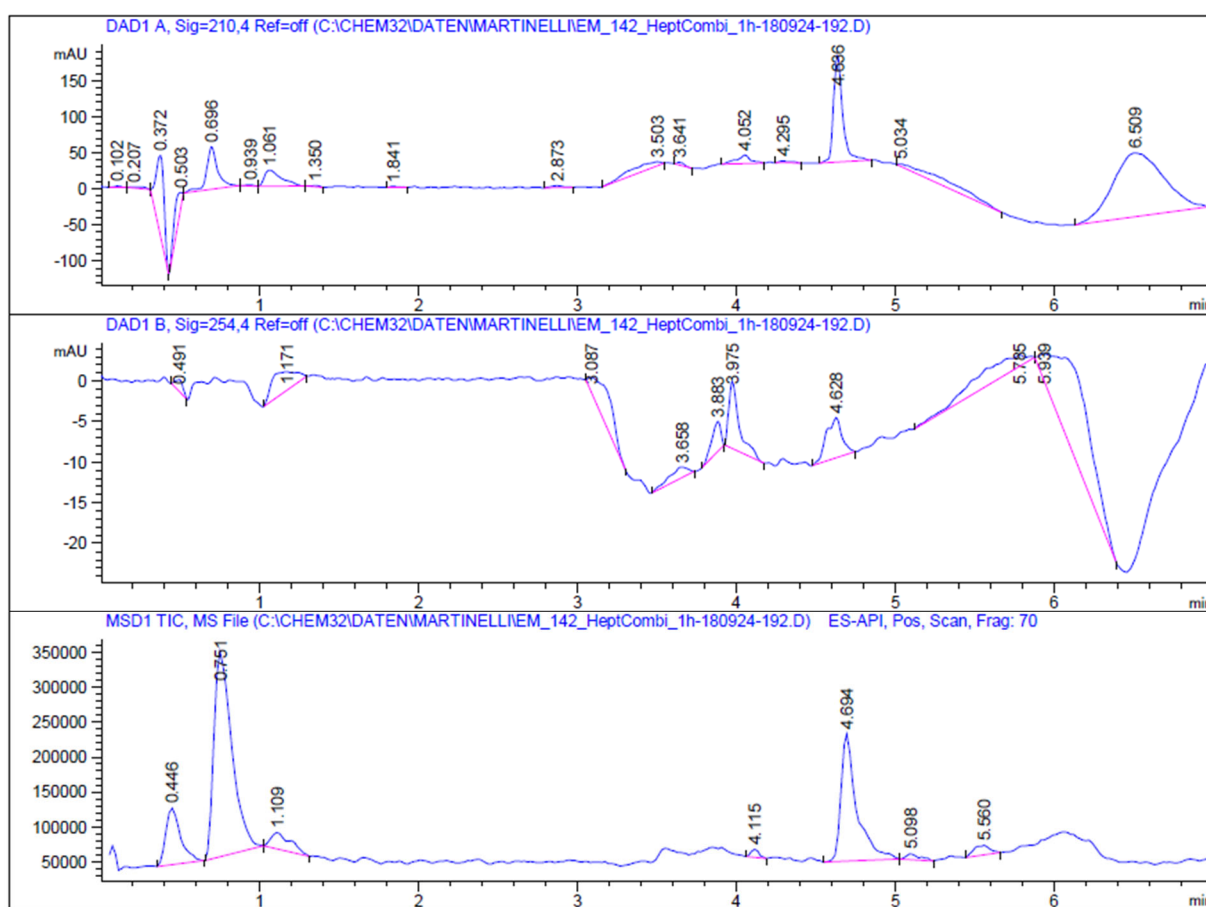
Exact Mass: 130.15

Figure S59: Structure of 1,7-diaminoheptane **19**.

Method A: 2.5 mg, 0.02 mmol **19**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0 D/molecule.



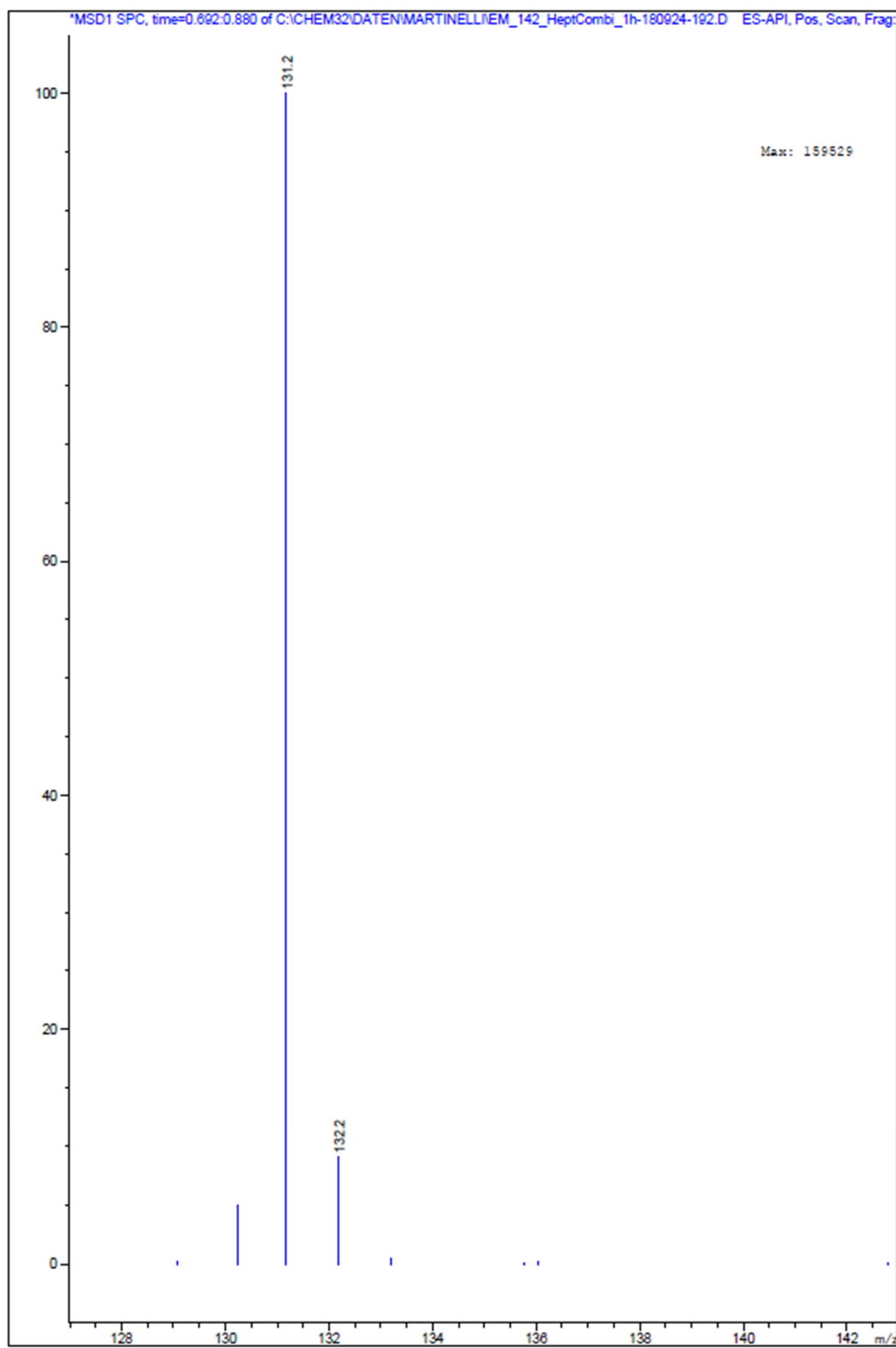
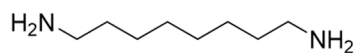


Figure S60: LC-MS analysis of representative HIE reaction of 1,7-diaminoheptane **19**.

7.1.14 1,8-diaminooctane **20**



20

Chemical Formula: C₈H₂₀N₂

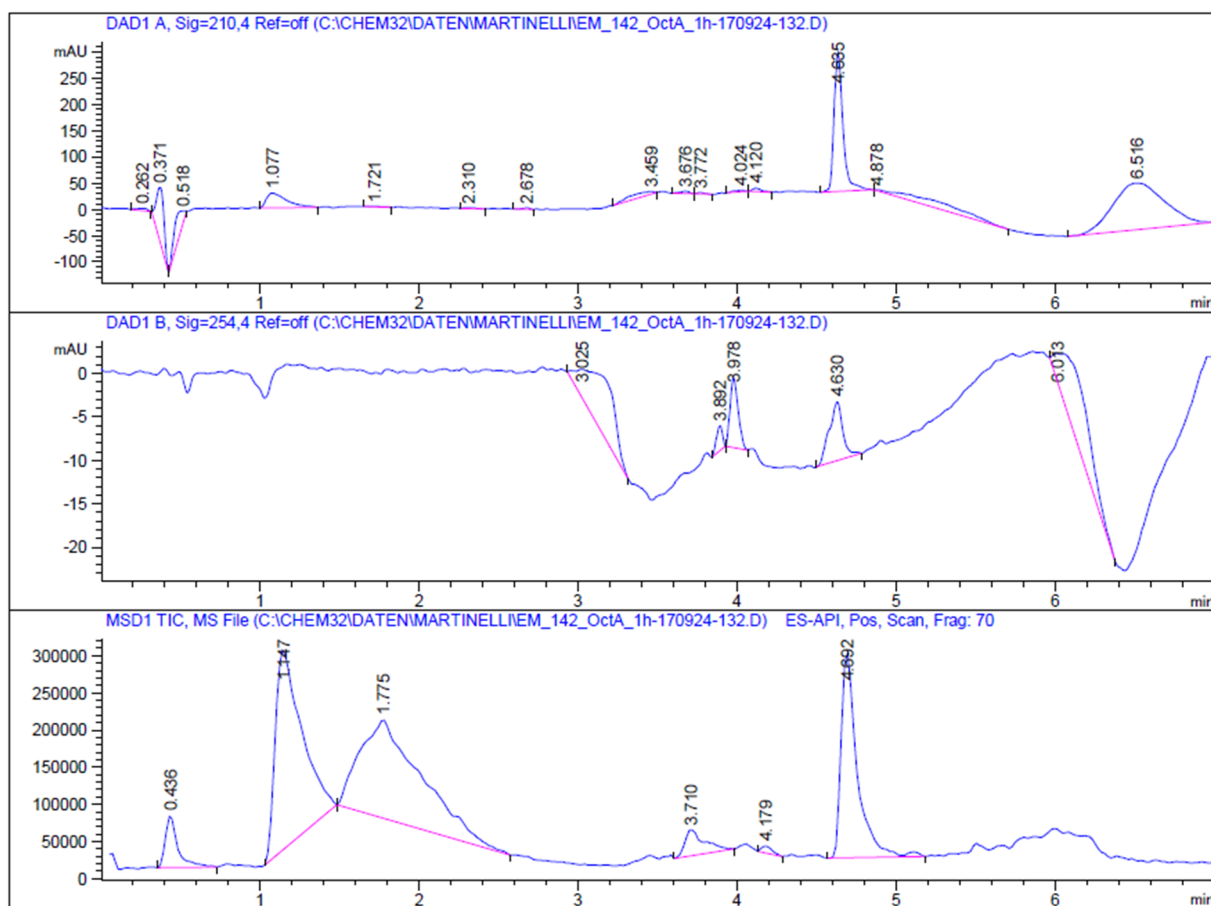
Exact Mass: 144.16

Figure S61: Structure of 1,8-diaminooctane **20**.

Method A: 3 mg, 0.02 mmol **20**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%)

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0 D/molecule.



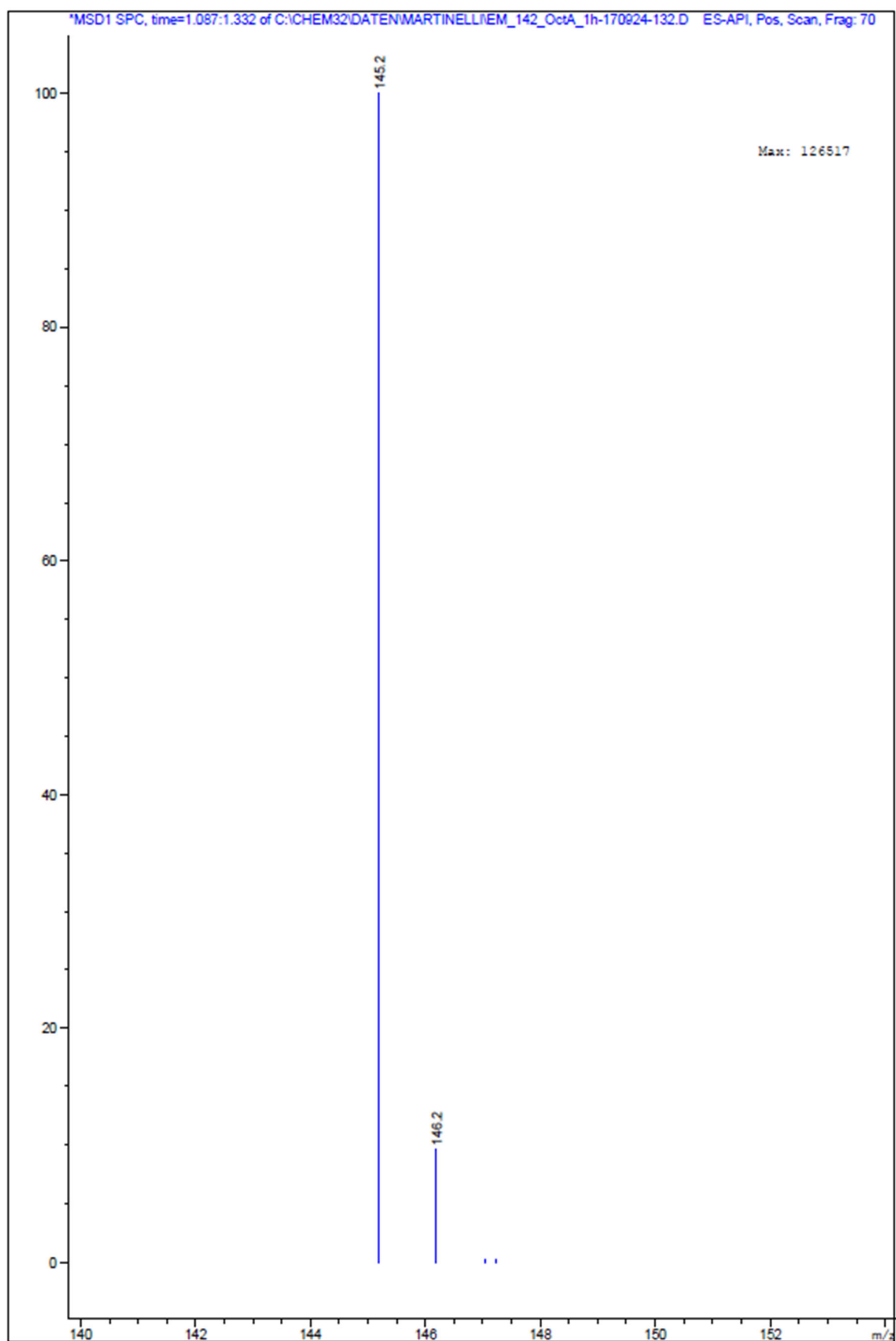


Figure S62: LC-MS analysis of representative HIE reaction of 1,8-diaminoheptane **20**.

7.2 Peptides

7.2.1 Bradykinin 3

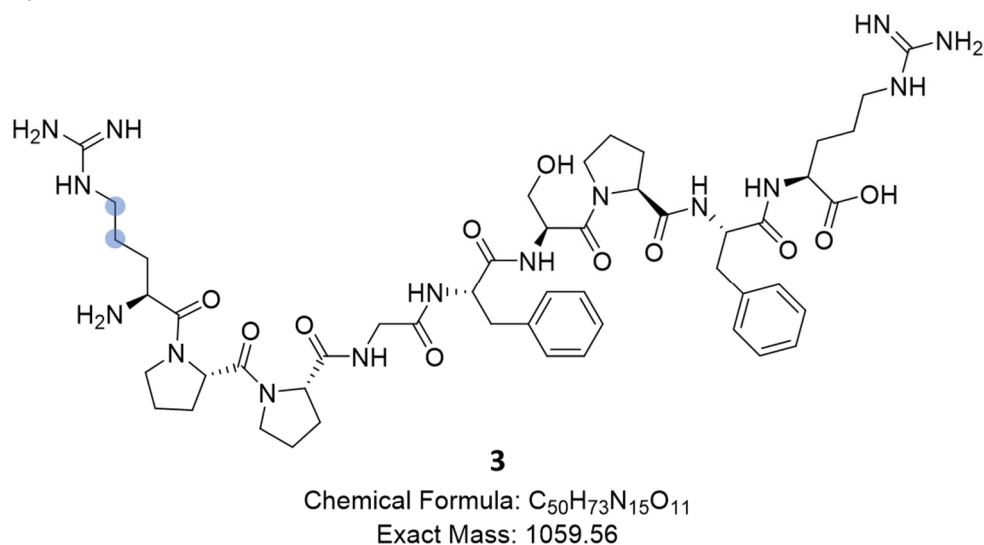


Figure S63: Structure of Bradykinin **3**.

Method C: 25 mg, 0.02 mmol **3**•CH₃COOH, 1 μmol catalyst **C4** (5 mol%), 2 μmol ligand **L11** (10 mol%).

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.44-7.19 (m, 10H), 4.74-4.56 (m, 5H), 4.52-4.20 (m, 5H), 3.97-3.45 (m, 11H), 3.28-2.95 (m, 8H), 2.55-2.14 (m, 4H), 2.14-1.81 (m, 15H), 1.81-1.57 (m, 7H).
Analytical data compared to literature.¹⁷

Incorporation expected at δ 3.28-2.95 and δ 1.81-1.63 (blue arrows, blue dots in the structures, position assigned as indicated by postulated mechanism). Determined against integral at δ 7.44-7.19 (grey arrow).

Results are determined as single reaction.

Deuterium incorporation determined by HR-MS: 0.72 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.74 D/molecule for δ 3.28-2.95 and 0.77 D/molecule for δ 1.81-1.57

Yield: 2.5 mg, 1.9 μmol, 10%, isolated yield.

To investigate degradation of complex compounds, bradykinin was analyzed. The chromatograms of the starting material and the crude mixture of reacted bradykinin **3** are shown below. Minor degradation is present in the crude reaction, the deuterated compound elutes at retention time 4.1 min and represents the major product of the reaction.

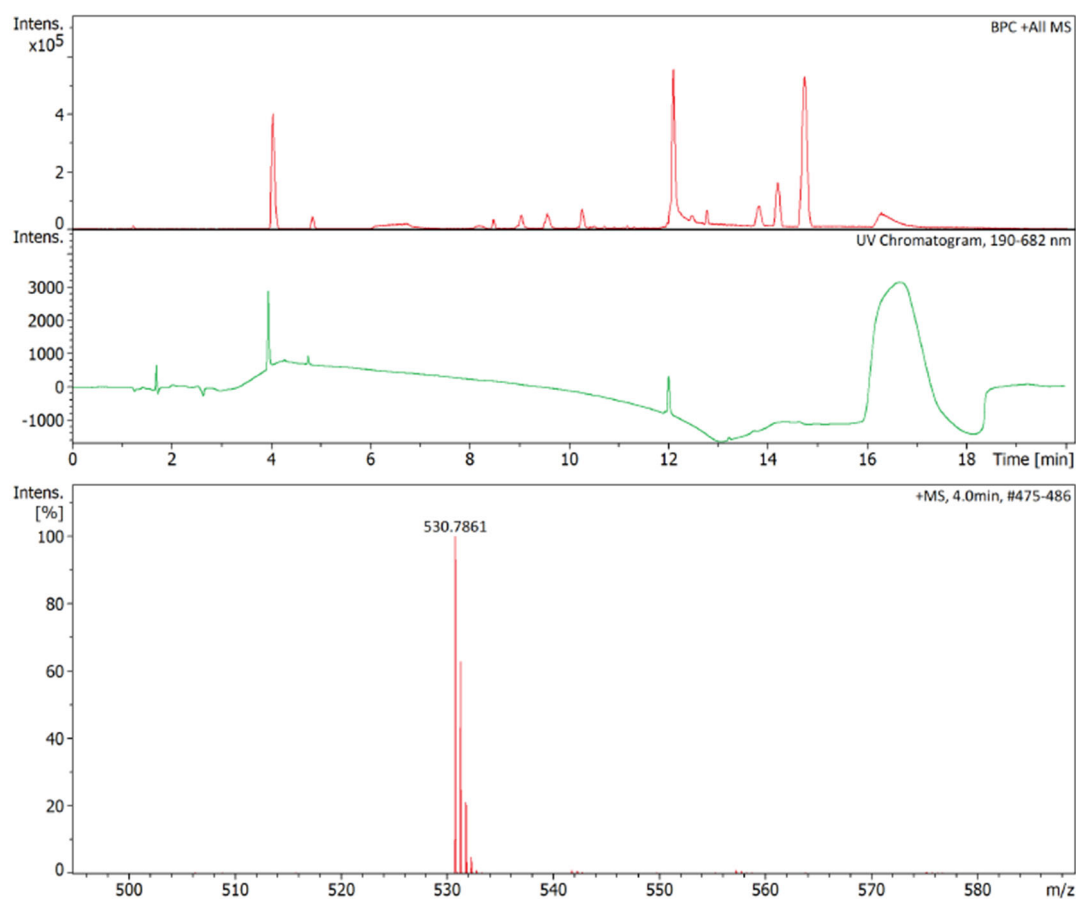


Figure S64: HR-MS analysis of reference compound bradykinin **3**.

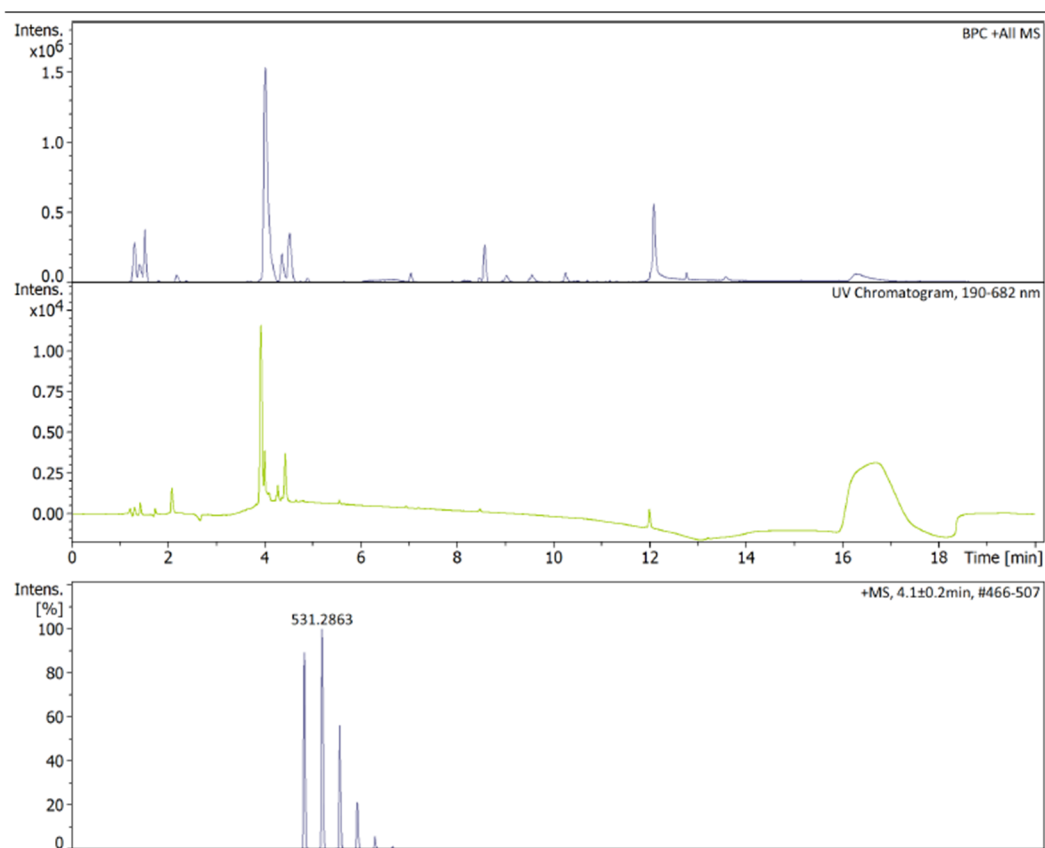
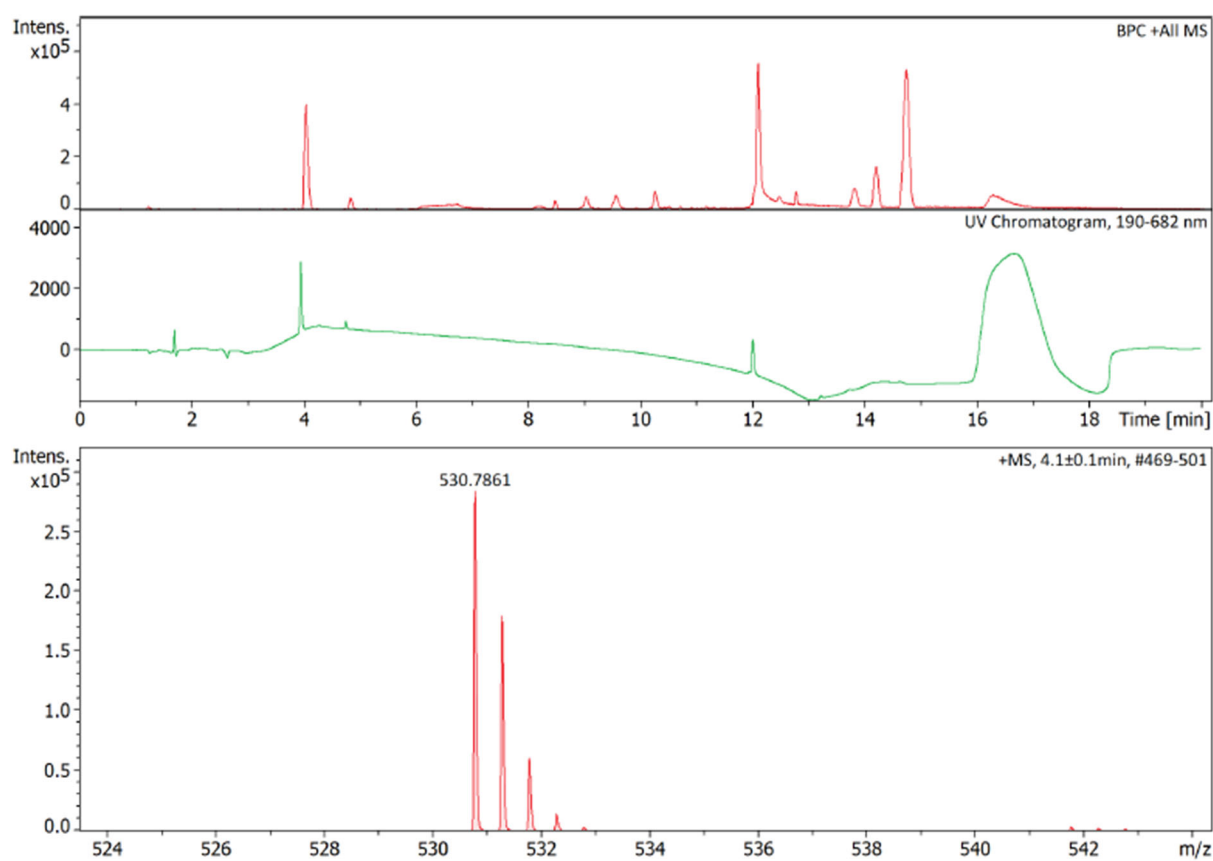


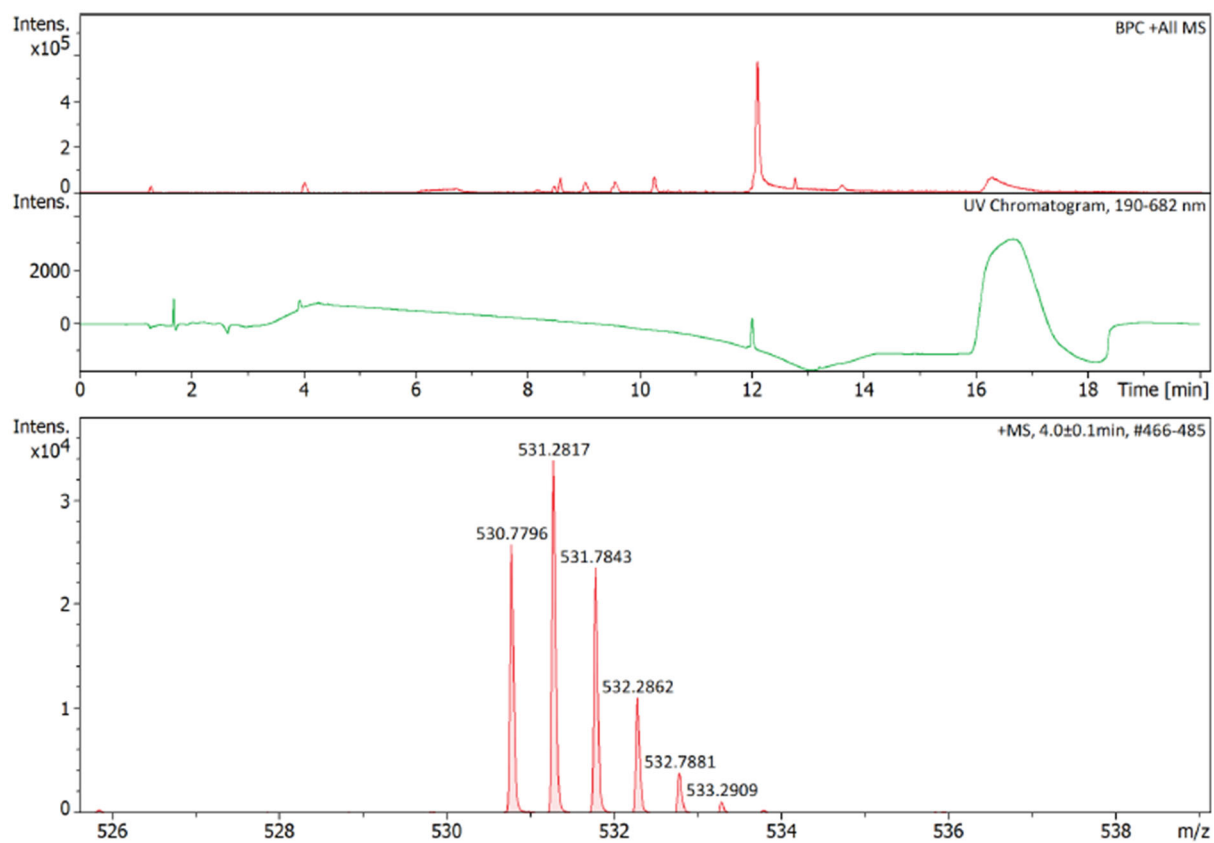
Figure S65: HR-MS analysis of the crude reaction mixture yielding bradykinin **[D]-3**.



#	m/z	Res.	S/N	I	I %	FWHM
1	60.0457	6943	47.6	1170	0.4	0.0086
2	114.0912	8386	31.5	748	0.3	0.0136
3	118.0862	8304	35.3	833	0.3	0.0142
4	122.0961	8953	139.4	3280	1.2	0.0136
5	132.9615	8634	27.3	633	0.2	0.0154
6	149.0231	8949	56.1	1264	0.4	0.0167
7	155.1539	9089	38.6	857	0.3	0.0171
8	205.0855	9825	39.8	800	0.3	0.0209
9	210.1231	10814	67.3	1341	0.5	0.0194
10	226.9479	10083	111.6	2150	0.8	0.0225
11	244.9581	9371	30.9	575	0.2	0.0261
12	252.9725	9647	33.0	603	0.2	0.0262
13	253.6394	10732	75.5	1376	0.5	0.0236
14	278.1545	10508	41.2	710	0.2	0.0265
15	279.1582	10273	50.5	870	0.3	0.0272
16	321.6708	10804	255.6	4202	1.5	0.0298
17	322.1737	10035	91.4	1502	0.5	0.0321
18	348.1900	11280	262.5	4254	1.5	0.0309
19	348.5241	10913	156.0	2529	0.9	0.0319
20	348.8592	10515	57.4	930	0.3	0.0332
21	354.1938	11093	3400.9	55068	19.4	0.0319
22	354.5283	11092	2138.2	34635	12.2	0.0320
23	354.8629	11028	688.9	11162	3.9	0.0322
24	355.1967	11320	183.3	2970	1.0	0.0314
25	419.2389	9977	121.8	1939	0.7	0.0420
26	506.2698	11117	40.0	701	0.2	0.0455
27	515.7817	11056	34.6	615	0.2	0.0467
28	530.7861	11239	15675.8	284555	100.0	0.0472
29	531.2876	11025	9856.7	178964	62.9	0.0482
30	531.7893	11008	3314.4	60176	21.1	0.0483
31	532.2906	10707	747.1	13569	4.8	0.0497
32	532.7917	10130	145.6	2646	0.9	0.0526
33	541.7766	11396	163.6	2999	1.1	0.0475

#	m/z	Res.	S/N	I	I %	FWHM
34	542.2787	11270	101.2	1856	0.7	0.0481
35	542.7741	11424	55.5	1019	0.4	0.0475
36	549.7663	10558	32.8	603	0.2	0.0521
37	555.2983	9439	32.1	592	0.2	0.0588
38	557.2426	11081	163.7	3027	1.1	0.0503
39	557.7423	11165	118.0	2183	0.8	0.0500
40	558.2434	11054	43.1	798	0.3	0.0505
41	558.7445	12805	39.4	729	0.3	0.0436
42	563.7835	11097	35.3	653	0.2	0.0508
43	575.2294	11086	54.0	1002	0.4	0.0519
44	575.7343	10315	39.6	735	0.3	0.0558
45	576.2308	11917	34.7	644	0.2	0.0484
46	1060.5621	11126	995.6	12886	4.5	0.0953
47	1061.0658	11127	512.7	6635	2.3	0.0954
48	1061.5660	11243	692.8	8967	3.2	0.0944
49	1062.0703	11294	141.4	1830	0.6	0.0940
50	1062.5677	10996	164.0	2123	0.7	0.0966

Figure S66: HR-MS analysis of Bradykinin **3** (double charged, reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	60.0460	7098	49.6	1316	3.9	0.0085
2	112.9552	8801	21.0	553	1.6	0.0128
3	114.0902	8288	33.5	881	2.6	0.0138
4	115.9586	8009	17.9	471	1.4	0.0145
5	118.0859	8733	41.4	1087	3.2	0.0135
6	122.0956	8792	135.2	3543	10.5	0.0139
7	129.0515	8435	17.7	461	1.4	0.0153
8	130.9654	9202	20.0	520	1.5	0.0142
9	132.9607	8739	42.0	1093	3.2	0.0152
10	134.9565	9145	35.3	917	2.7	0.0148
11	149.0222	8569	36.8	944	2.8	0.0174
12	153.0895	9031	25.3	645	1.9	0.0170
13	155.1528	8681	35.3	897	2.6	0.0179
14	171.0993	9517	41.8	1043	3.1	0.0180
15	205.0837	9554	32.3	772	2.3	0.0215
16	226.9460	9968	175.7	4095	12.1	0.0228
17	244.9568	9406	42.6	975	2.9	0.0260
18	252.9701	9715	36.8	833	2.5	0.0260
19	267.9724	9476	49.1	1094	3.2	0.0283
20	279.1558	10091	32.5	714	2.1	0.0277
21	285.9812	9858	28.5	625	1.8	0.0290
22	322.9292	9816	22.3	481	1.4	0.0329
23	348.5214	10639	23.8	514	1.5	0.0328
24	354.1902	10870	221.7	4804	14.2	0.0326
25	354.5249	11139	290.7	6302	18.6	0.0318
26	354.8591	10781	199.2	4316	12.7	0.0329
27	355.1939	10840	94.5	2047	6.0	0.0328
28	355.5299	9949	31.9	692	2.0	0.0357
29	399.9729	10231	52.8	1169	3.5	0.0391
30	471.9498	9406	20.0	474	1.4	0.0502
31	530.7796	10800	1026.3	25790	76.1	0.0491
32	531.2817	11069	1347.1	33874	100.0	0.0480
33	531.7843	10724	937.3	23565	69.6	0.0496

#	m/z	Res.	S/N	I	I %	FWHM
34	532.2862	10777	437.9	11016	32.5	0.0494
35	532.7881	10978	151.3	3810	11.2	0.0485
36	533.2909	10405	41.8	1054	3.1	0.0513
37	541.7706	10870	28.8	732	2.2	0.0498
38	542.2728	11080	37.7	959	2.8	0.0489
39	542.7739	9838	27.8	708	2.1	0.0552
40	557.2333	10253	35.5	915	2.7	0.0544
41	557.7363	11268	47.1	1214	3.6	0.0495
42	558.2388	11055	34.2	882	2.6	0.0505
43	558.7412	10842	20.5	529	1.6	0.0515
44	575.7271	9172	23.2	603	1.8	0.0628
45	576.2280	10528	22.8	595	1.8	0.0547
46	576.7266	10397	19.0	495	1.5	0.0555
47	584.8830	10527	19.6	514	1.5	0.0556
48	1060.5476	10053	42.2	752	2.2	0.1055
49	1061.5532	10554	60.1	1071	3.2	0.1006
50	1062.5561	10805	43.5	775	2.3	0.0983

Figure S67: HR-MS analysis of Bradykinin [D]-3 (double charged).

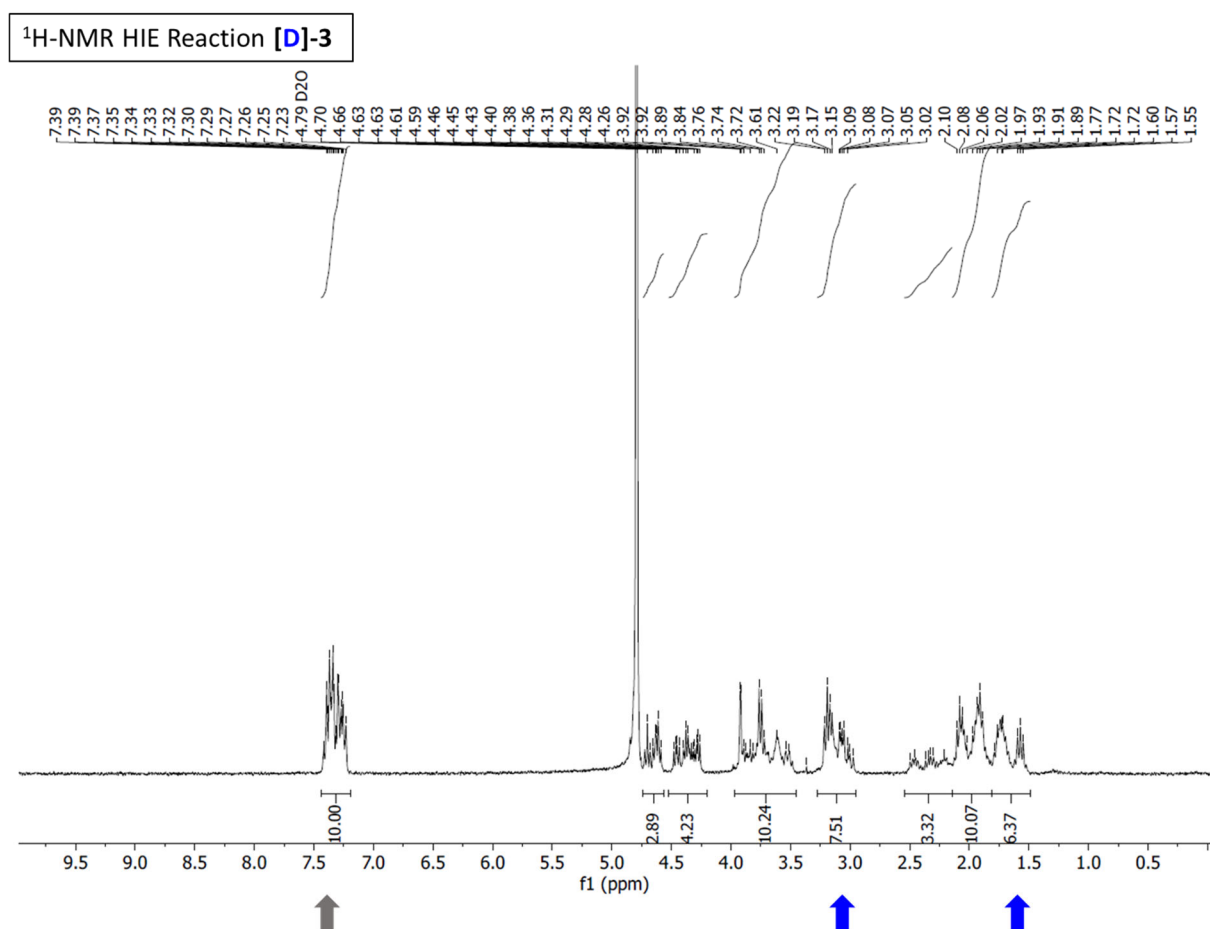
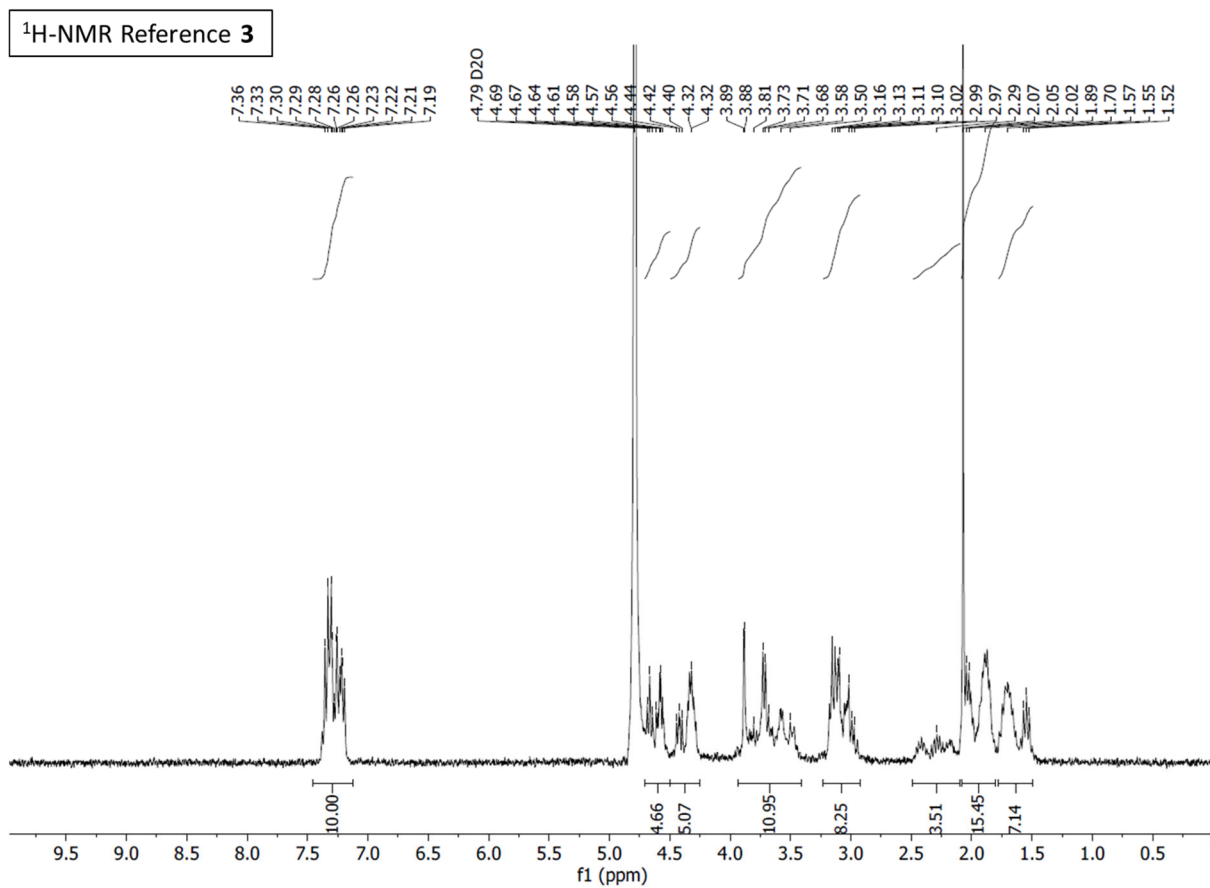


Figure S69: ¹H-NMR spectra of the HIE reaction of compound **3** to yield the deuterated product **[D]-3**.

^2H -NMR HIE Reaction [D]-3

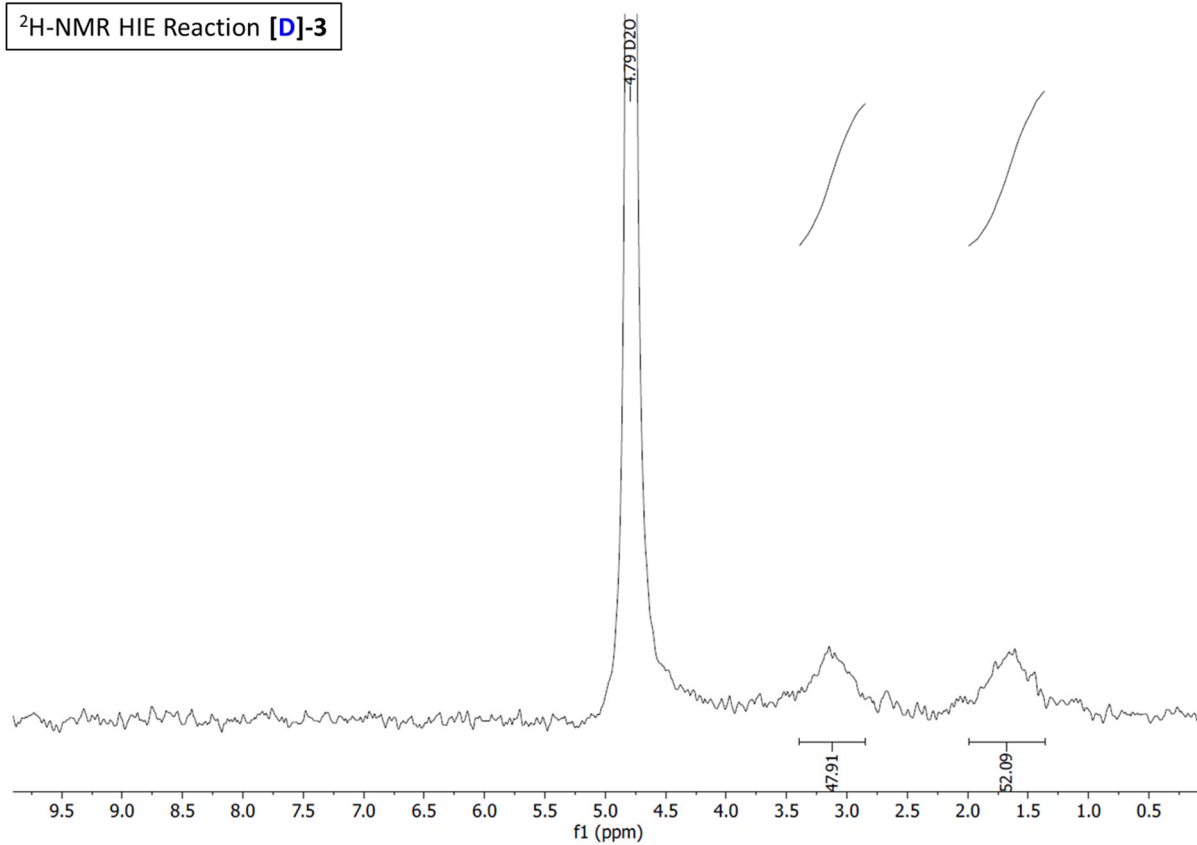
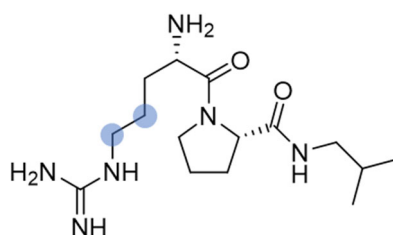


Figure S70: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-3.

7.2.2 Arg-Pro-NH-*i*Bu **21**



21

Chemical Formula: C₁₅H₃₀N₆O₂

Exact Mass: 326.24

Figure S71: Structure of Arg-Pro-NH-*i*Bu **21**.

Method C: 13.5 mg, 0.02 mmol **21**•TsOH, 1 μmol catalyst **C4** (5 mol%), 2 μmol ligand **L11** (10 mol%).

HR-MS (ESI⁺): *m/z* [M+H]⁺ mass calc. for C₁₅H₃₀N₆O₂: 327.2503; found: 327.2457.

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.64 (d, *J* = 8.0 Hz, 5H), 7.32 (d, *J* = 8.0 Hz, 5H), 4.43-4.31 (m, 2H), 3.78-3.65 (m, 1H), 3.60-3.49 (q, 1H), 3.19 (t, *J* = 6.9 Hz, 2H), 3.10-3.01 (m, 1H), 2.95-2.84 (m, 1H), 2.34 (s, 7H), 2.31-2.21 (m, 1H), 2.09-1.80 (m, 5H), 1.79-1.56 (m, 3H), 0.83 (d, *J* = 6.6 Hz, 6H). Peaks at δ 7.64, 7.32 and 2.34 belonging to TsOH.

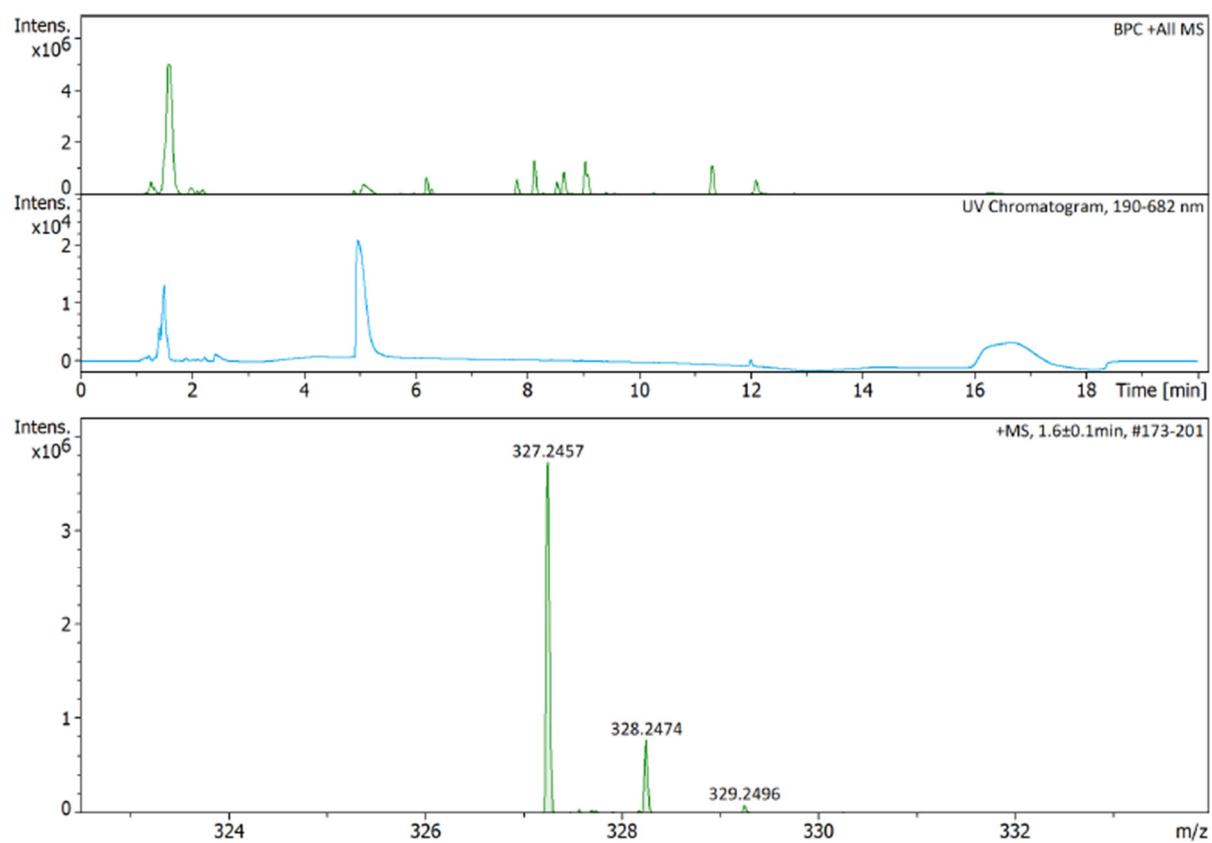
Incorporation expected at δ 3.19 and 1.79-1.56 (blue arrows, blue dots in the structure, positions assigned as indicated by postulated mechanism). Determined against integral at δ 0.83 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by HR-MS: 1.04 D/molecule.

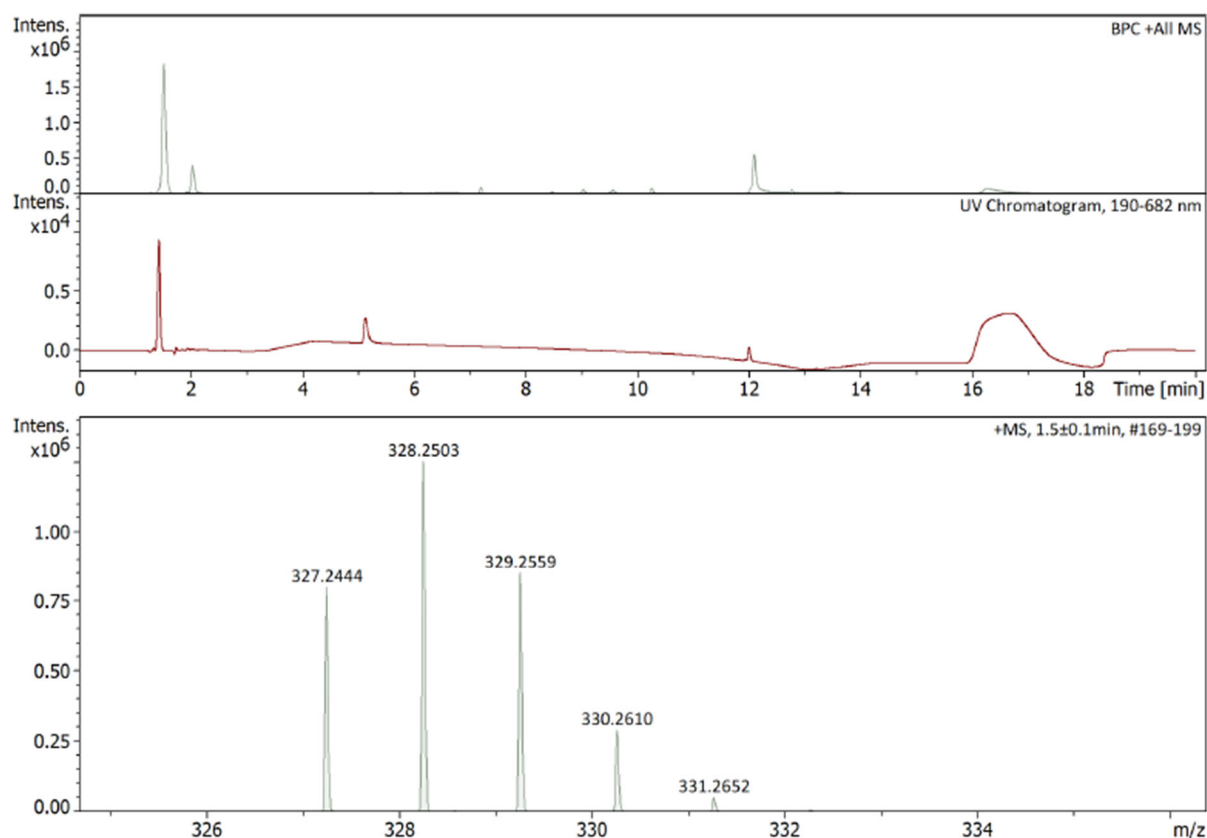
Deuterium incorporation determined by ¹H-NMR: 0.52 D/molecule for δ 3.19 and 0.73 D/molecule for δ 1.79-1.56

Yield: obtained as TsOH salt, 6 mg, 9 μmol, 15%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	70.0657	7231	11610.5	414471	11.1	0.0097
2	71.0687	7402	542.5	19342	0.5	0.0096
3	74.0969	7593	2649.8	94209	2.5	0.0098
4	112.0860	8485	2389.9	81849	2.2	0.0132
5	113.5858	8618	9869.8	337892	9.0	0.0132
6	114.0873	8465	1282.9	43873	1.2	0.0135
7	116.0696	8735	240.7	8187	0.2	0.0133
8	121.0912	9207	793.3	26545	0.7	0.0132
9	127.0965	8830	297.8	9816	0.3	0.0144
10	127.5830	9283	899.9	29631	0.8	0.0137
11	129.1122	9119	246.5	8077	0.2	0.0142
12	157.1074	8470	311.1	9767	0.3	0.0185
13	164.1268	9372	34718.7	1081014	28.9	0.0175
14	164.6282	9257	6808.9	211827	5.7	0.0178
15	165.1295	9718	793.0	24645	0.7	0.0170
16	171.1470	9113	5539.2	168615	4.5	0.0188
17	171.6322	9799	2301.7	69957	1.9	0.0175
18	172.1443	5451	686.6	20833	0.6	0.0316
19	175.1166	9164	20762.0	622723	16.7	0.0191
20	176.1191	9058	1683.8	50319	1.3	0.0194
21	190.1272	9407	985.3	27980	0.7	0.0202
22	193.1421	9613	374.3	10608	0.3	0.0201
23	195.1108	9104	345.5	9776	0.3	0.0214
24	210.1686	9557	351.4	9787	0.3	0.0220
25	226.1628	9810	546.3	14914	0.4	0.0231
26	237.1312	9713	395.1	10618	0.3	0.0244
27	254.1573	9846	4864.0	125953	3.4	0.0258
28	255.1600	9698	658.4	17018	0.5	0.0263
29	312.2344	10220	2026.3	47781	1.3	0.0306
30	313.2371	10428	380.2	8949	0.2	0.0300
31	327.2457	8917	162752.3	3737059	100.0	0.0367
32	327.5656	14376	1623.1	37252	1.0	0.0228
33	327.6957	11279	1168.4	26814	0.7	0.0291
#	m/z	Res.	S/N	I	I %	FWHM
34	327.7305	10377	1047.0	24027	0.6	0.0316
35	327.9156	11081	503.0	11540	0.3	0.0296
36	328.1773	9997	813.5	18661	0.5	0.0328
37	328.2474	9909	33507.8	768639	20.6	0.0331
38	329.2496	10157	3637.5	83386	2.2	0.0324
39	342.2555	10161	17240.2	382892	10.2	0.0337
40	343.2579	10263	3413.4	75592	2.0	0.0334
41	344.2600	10038	363.3	8013	0.2	0.0343
42	370.2499	10512	397.2	8088	0.2	0.0352
43	653.4806	10668	1404.6	16572	0.4	0.0613
44	767.4696	10871	21394.2	271132	7.3	0.0706
45	768.4724	10896	8898.3	112822	3.0	0.0705
46	769.4750	10792	1909.9	24223	0.6	0.0713
47	782.4807	10861	1967.2	25212	0.7	0.0720
48	783.4837	10681	772.0	9901	0.3	0.0734
49	1207.6928	11179	1556.7	21304	0.6	0.1080
50	1208.6967	10731	910.6	12467	0.3	0.1126

Figure S72: HR-MS analysis of Arg-Pro-NH-*i*Bu **21** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	70.0657	7296	6328.8	238722	19.0	0.0096
2	71.0700	6952	458.9	17310	1.4	0.0102
3	72.0778	7472	126.8	4780	0.4	0.0096
4	74.0968	7619	1537.1	57959	4.6	0.0097
5	112.0859	8669	418.7	15394	1.2	0.0129
6	113.0920	8486	603.2	22196	1.8	0.0133
7	113.5857	8798	1759.7	64800	5.2	0.0129
8	114.0895	7870	2766.1	101917	8.1	0.0145
9	114.5916	8796	1741.1	64158	5.1	0.0130
10	115.0955	7515	556.7	20514	1.6	0.0153
11	127.5830	9147	155.9	5679	0.5	0.0139
12	128.0859	9318	238.1	8667	0.7	0.0137
13	128.5888	8971	154.6	5624	0.4	0.0143
14	130.1576	8796	99.6	3618	0.3	0.0148
15	164.1267	9478	6037.4	214156	17.1	0.0173
16	164.6296	9429	9897.3	350716	28.0	0.0175
17	165.1325	9386	6962.5	246628	19.7	0.0176
18	165.6351	9443	2474.9	87599	7.0	0.0175
19	166.1371	9274	425.7	15056	1.2	0.0179
20	169.1310	9264	159.8	5606	0.4	0.0183
21	171.1468	9117	2818.0	98314	7.8	0.0188
22	172.1495	9079	301.0	10441	0.8	0.0190
23	175.1165	9213	3436.0	118089	9.4	0.0190
24	176.1225	9065	5019.3	172105	13.7	0.0194
25	177.1285	8919	3053.0	104400	8.3	0.0199
26	178.1342	9037	870.3	29655	2.4	0.0197
27	179.1382	8794	106.8	3628	0.3	0.0204
28	227.1684	9688	136.2	4322	0.3	0.0234
29	254.1571	9844	770.5	23120	1.8	0.0258
30	255.1629	9752	1196.2	35818	2.9	0.0262
31	256.1688	9617	768.1	22949	1.8	0.0266
32	257.1743	9125	231.3	6903	0.6	0.0282
33	327.2444	9988	29434.8	798952	63.7	0.0328

#	m/z	Res.	S/N	I	I %	FWHM
34	328.2503	9838	46234.1	1253981	100.0	0.0334
35	329.2559	9807	31445.7	851980	67.9	0.0336
36	330.2610	9831	10727.7	290403	23.2	0.0336
37	331.2652	9884	1871.6	50581	4.0	0.0335
38	332.2689	9224	207.0	5574	0.4	0.0360
39	342.2572	9341	150.7	3854	0.3	0.0366
40	655.4907	10706	340.0	4296	0.3	0.0612
41	656.4972	10418	274.1	3462	0.3	0.0630
42	767.4702	10563	974.3	13185	1.1	0.0727
43	768.4749	11036	3419.9	46340	3.7	0.0696
44	769.4800	10893	5129.8	69541	5.5	0.0706
45	770.4863	10923	4646.2	62986	5.0	0.0705
46	771.4919	10727	2754.3	37341	3.0	0.0719
47	772.4969	10729	1143.9	15513	1.2	0.0720
48	773.5017	10491	330.9	4489	0.4	0.0737
49	1210.7084	10811	293.4	4135	0.3	0.1120
50	1211.7178	9947	279.1	3936	0.3	0.1218

Figure S73: HR-MS analysis of Arg-Pro-NH-iBu [D]-21.

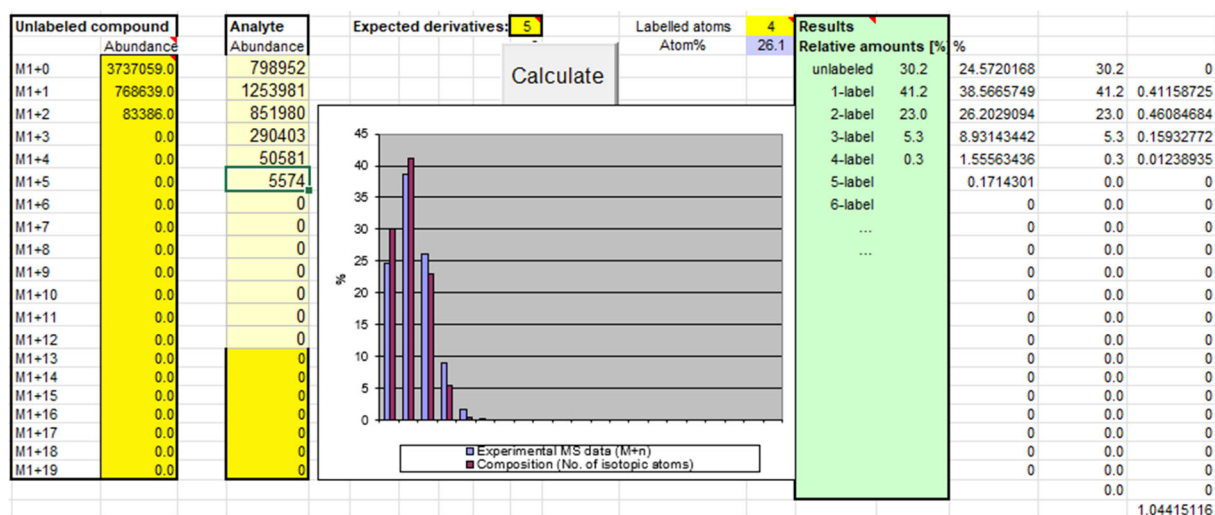
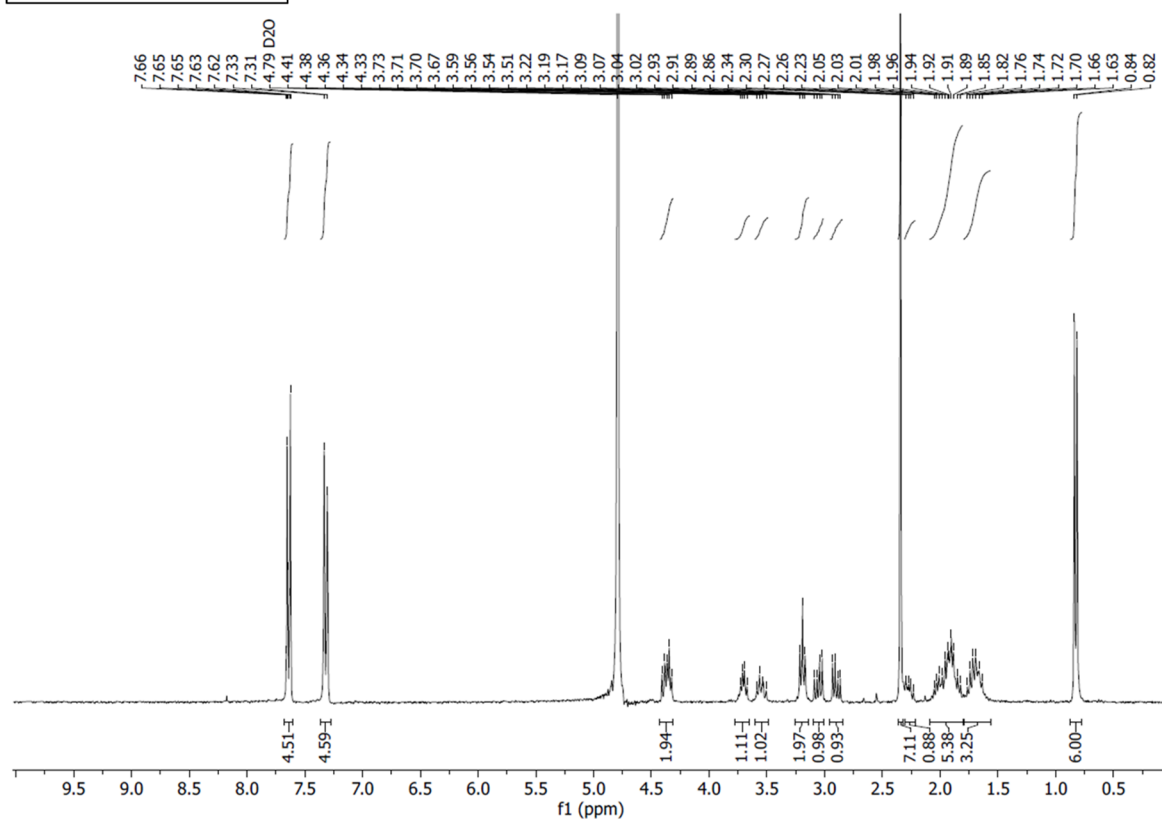


Figure S74: Calculation of deuterium content in Arg-Pro-NH-iBu [D]-21.

¹H-NMR Reference 21



¹H-NMR HIE Reaction [D]-21

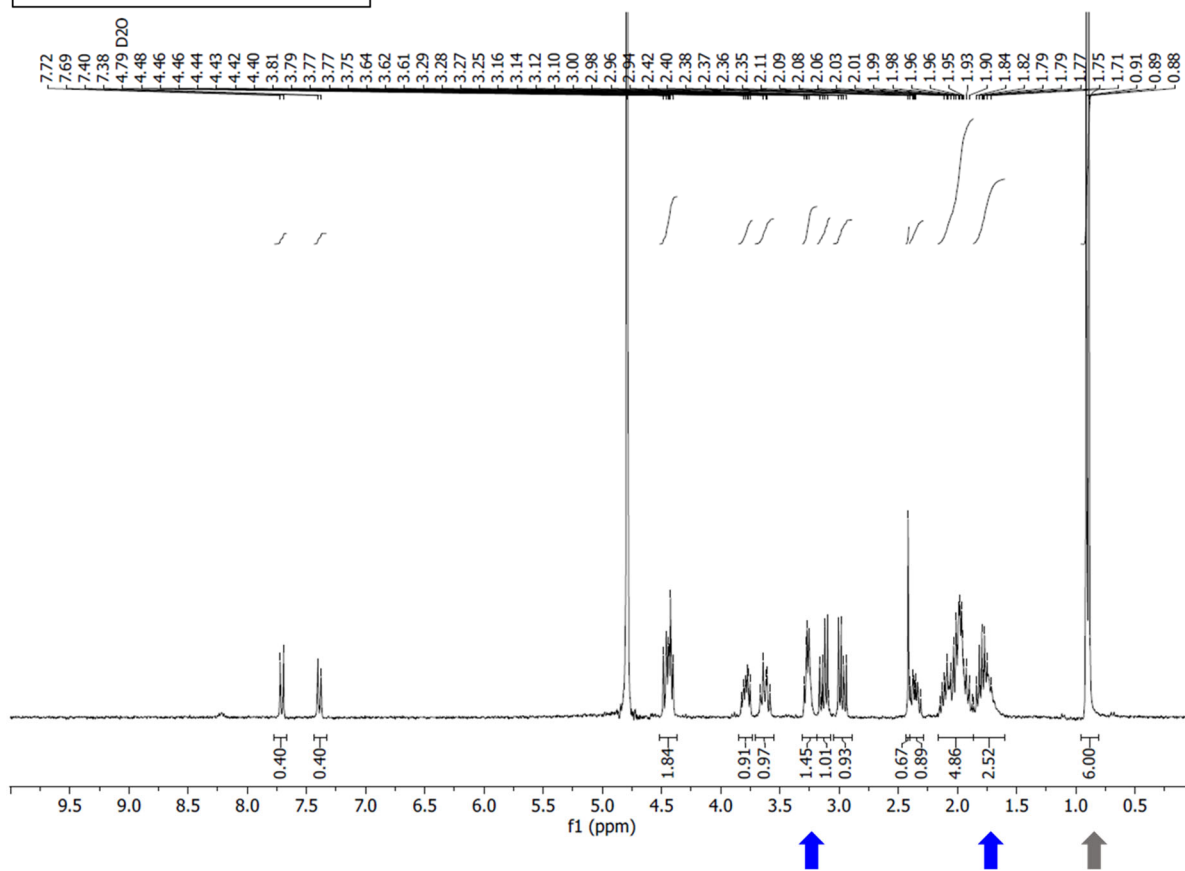


Figure S75: ¹H-NMR spectra of the HIE reaction of compound **21** to yield the deuterated product [D]-**21**.

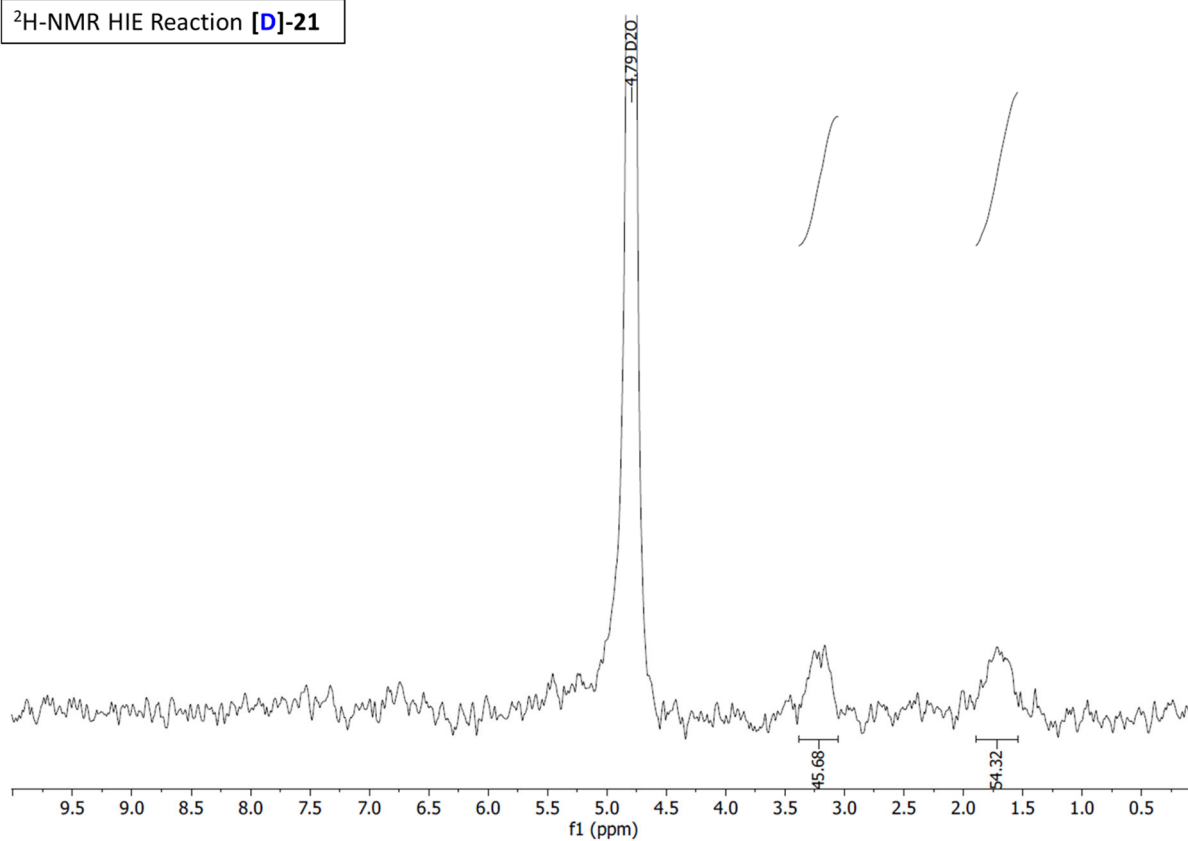
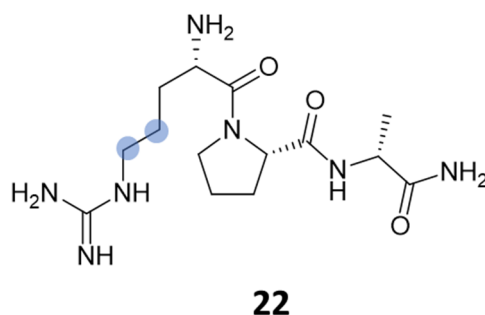


Figure S76: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-21.

7.2.3 Arg-Pro-D-Ala-NH₂ **22**



Chemical Formula: C₁₄H₂₇N₇O₃
Exact Mass: 341.22

Figure S77: Structure of Arg-Pro-D-Ala-NH₂ **22**.

Method C: 14 mg, 0.02 mmol **22**•TsOH, 1 μmol catalyst **C4** (5 mol%), 2 μmol ligand **L11** (10 mol%).

HR-MS (ESI⁺): *m/z* [M+H]⁺ mass calc. for C₁₄H₂₇N₇O₃: 342.2248; found: 342.2219.

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.68 (d, *J* = 8.0, 3H), 7.35 (d, *J* = 8.0 Hz, 3H), 4.48 (t, *J* = 7.2 Hz, 1H), 4.43-4.31 (m, 1H), 4.30-4.21 (m, 2H), 3.81-3.68 (m, 1H), 3.63-3.48 (m, 2H), 3.26-3.13 (m, 3H), 2.42-2.25 (m, 5H), 2.14-1.78 (m, 7H), 1.75-1.61 (m, 2H), 1.55 (t, *J* = 6.9 Hz, 2H), 1.50-1.35 (m, 3H). Peaks at δ 7.68, 7.35 and partially 2.42-2.25 belonging to TsOH.

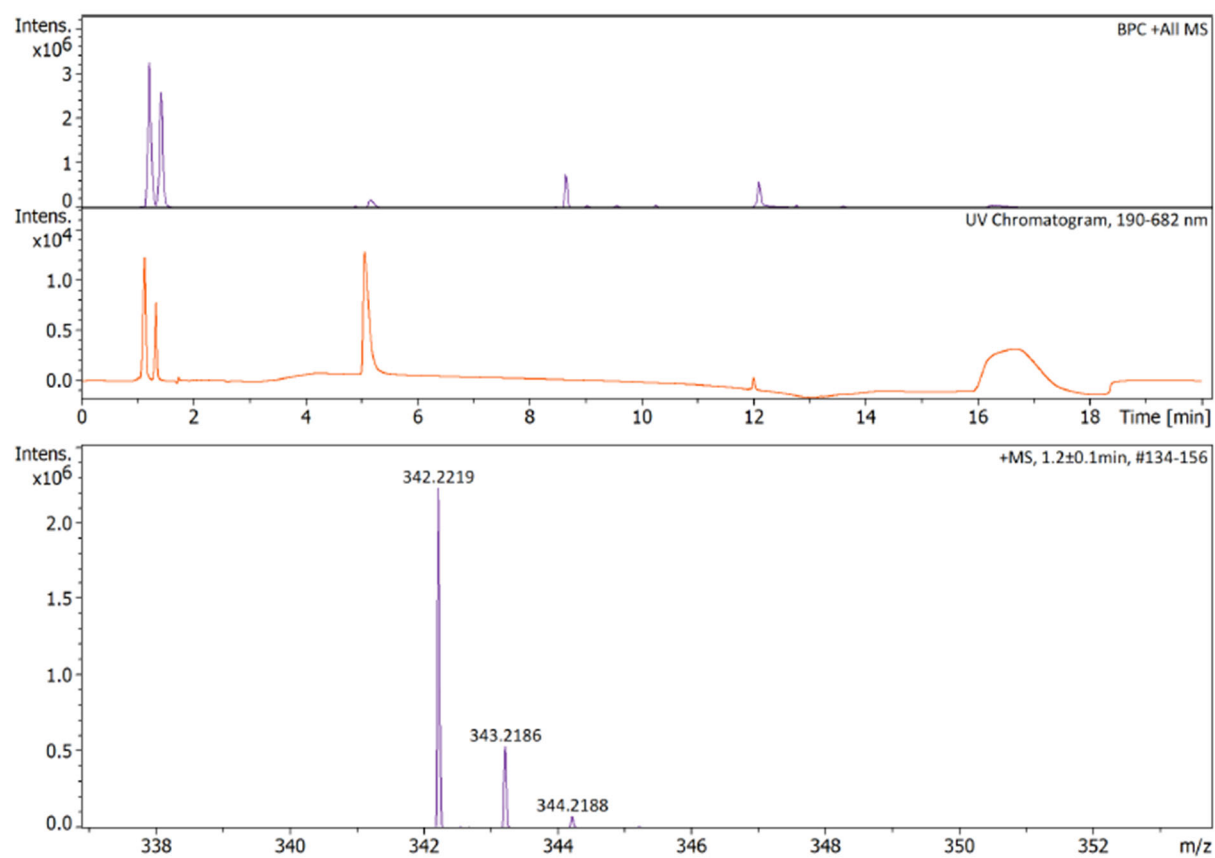
Incorporation expected at δ 3.26-3.13 and 1.75-1.61 (blue arrow, blue dot in the structure). Determined against integral at δ 1.50-1.35 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 0.41 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.60 D/molecule at δ 3.26-3.13 and 0.44 D/molecule at δ 1.75-1.61

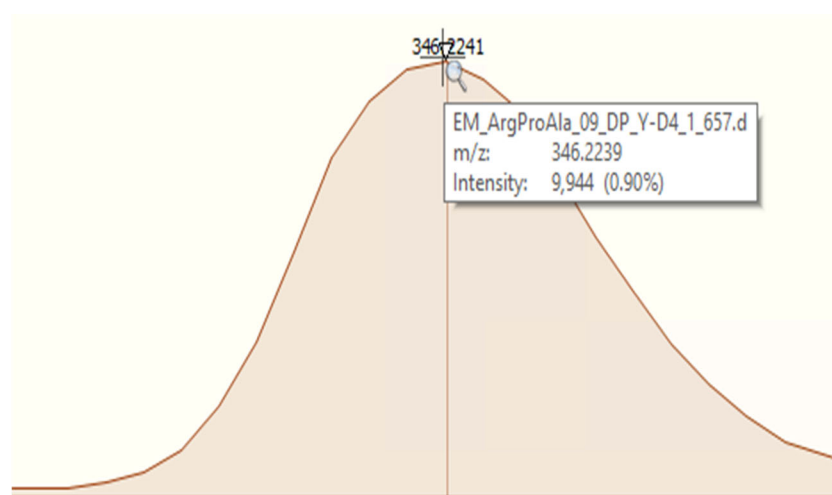
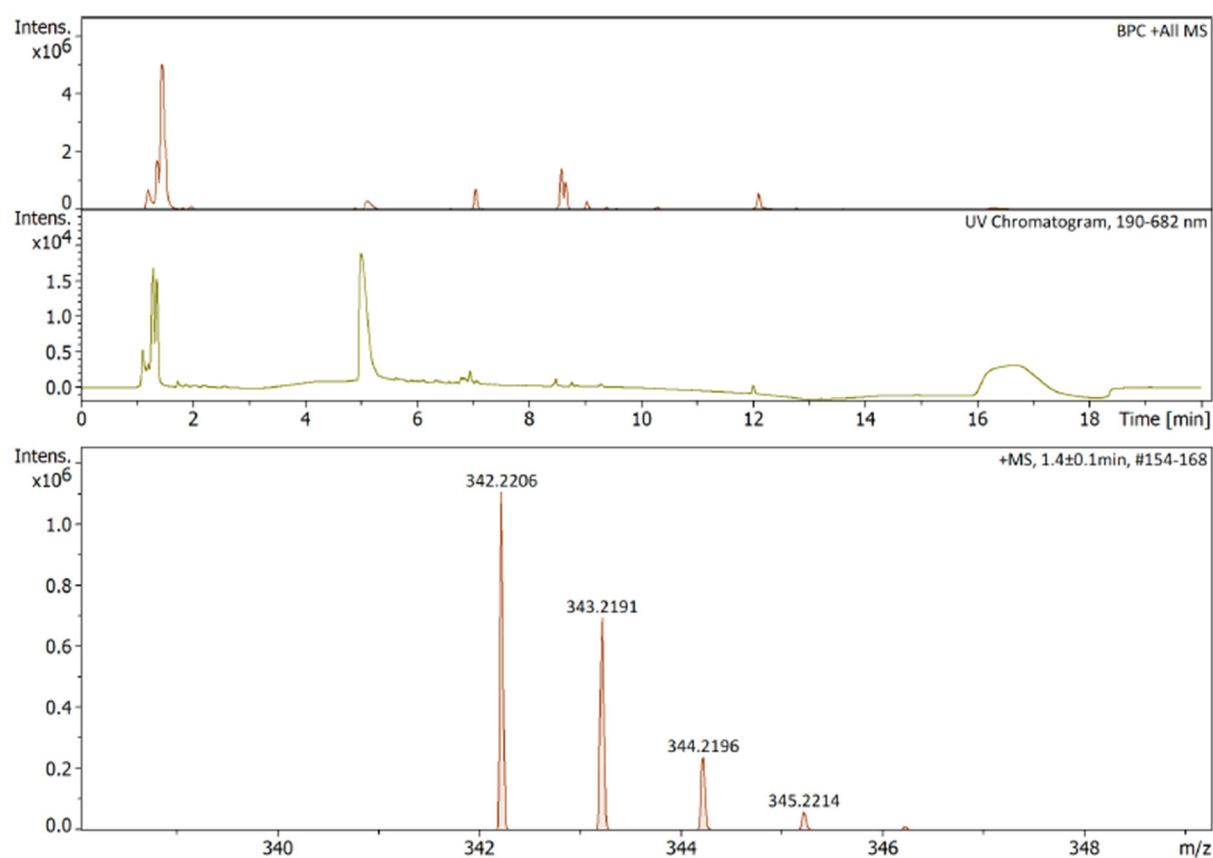
Yield: obtained as TsOH salt, 18 mg, 26 μmol, 43%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	70.0658	7785	894.2	28515	1.3	0.0090
2	89.0709	8042	2494.3	79036	3.5	0.0111
3	90.0557	7995	202.3	6410	0.3	0.0113
4	112.0863	8799	611.1	19297	0.9	0.0127
5	113.5862	8791	4456.7	140979	6.3	0.0129
6	114.0878	8841	588.4	18610	0.8	0.0129
7	127.5836	9216	4303.7	135278	6.1	0.0138
8	128.0850	9163	631.4	19831	0.9	0.0140
9	149.1044	9661	2971.4	92782	4.2	0.0154
10	149.6057	9547	484.7	15143	0.7	0.0157
11	162.6098	9990	382.3	11976	0.5	0.0163
12	163.1019	9642	2382.0	74546	3.3	0.0169
13	163.6032	9398	429.5	13426	0.6	0.0174
14	171.6148	10096	1298.0	40223	1.8	0.0170
15	172.1080	8766	1517.8	47013	2.1	0.0196
16	172.6089	9306	274.9	8509	0.4	0.0185
17	174.1338	9333	232.4	7196	0.3	0.0187
18	175.1183	8073	190.6	5898	0.3	0.0217
19	186.1228	9095	160.6	4999	0.2	0.0205
20	187.1065	8950	246.1	7662	0.3	0.0209
21	195.1116	9412	353.7	11109	0.5	0.0207
22	202.1647	9674	3193.8	100765	4.5	0.0209
23	203.1671	9320	332.2	10483	0.5	0.0218
24	226.1643	9794	510.6	16223	0.7	0.0231
25	244.1748	9477	189.0	5968	0.3	0.0258
26	254.1588	9851	15650.6	491886	22.0	0.0258
27	255.1615	9868	2240.5	70396	3.1	0.0259
28	256.1636	9225	208.3	6549	0.3	0.0278
29	300.2006	9877	550.4	17167	0.8	0.0304
30	325.1952	10320	2886.4	89545	4.0	0.0315
31	326.1979	10223	493.6	15298	0.7	0.0319
32	334.2023	10741	242.2	7490	0.3	0.0311
33	342.2219	10009	72556.7	2234883	100.0	0.0342

#	m/z	Res.	S/N	I	I %	FWHM
34	342.5493	14793	235.3	7245	0.3	0.0232
35	342.6840	17572	179.7	5533	0.2	0.0195
36	343.2186	8431	17205.0	529535	23.7	0.0407
37	344.2188	8236	2404.4	73952	3.3	0.0418
38	345.2196	7866	239.3	7350	0.3	0.0439
39	356.2373	10175	425.8	12806	0.6	0.0350
40	370.2523	10383	242.8	7127	0.3	0.0357
41	413.2580	10533	712.5	19125	0.9	0.0392
42	414.2530	8403	259.4	6937	0.3	0.0493
43	683.4351	10707	362.5	6048	0.3	0.0638
44	684.4197	10769	1945.2	32464	1.5	0.0636
45	685.4164	10263	944.5	15757	0.7	0.0668
46	797.4249	11298	6364.3	103827	4.6	0.0706
47	798.4278	11273	2486.1	40548	1.8	0.0708
48	799.4302	11181	525.1	8561	0.4	0.0715
49	1252.6287	11156	497.5	7314	0.3	0.1123
50	1253.6307	10960	296.9	4362	0.2	0.1144

Figure S78: HR-MS analysis of Arg-Pro-D-Ala-NH₂ **22** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	64.9781	7532	1075.5	24235	2.2	0.0086
2	70.0657	7614	1803.0	40279	3.6	0.0092
3	89.0708	7944	2602.1	58096	5.2	0.0112
4	90.0549	8175	715.9	15980	1.4	0.0110
5	112.0860	8718	1176.8	26685	2.4	0.0129
6	113.5860	8770	6498.7	147956	13.4	0.0130
7	114.0889	8618	2849.0	64952	5.9	0.0132
8	114.5914	8928	752.5	17157	1.5	0.0128
9	127.5832	9197	4117.1	94996	8.6	0.0139
10	128.0858	8945	1901.0	43881	4.0	0.0143
11	149.1040	9550	2421.4	57091	5.2	0.0156
12	149.6064	9475	1188.6	28062	2.5	0.0158
13	157.1685	9183	833.3	20026	1.8	0.0171
14	158.9624	9115	5773.4	139158	12.6	0.0174
15	163.1019	9162	1828.7	44202	4.0	0.0178
16	163.6041	9350	916.0	22150	2.0	0.0175
17	171.6144	10031	892.7	21723	2.0	0.0171
18	172.1075	8755	3184.3	77571	7.0	0.0197
19	172.6096	9194	1595.7	38929	3.5	0.0188
20	187.1059	9122	1124.9	28015	2.5	0.0205
21	195.1109	9279	687.9	17521	1.6	0.0210
22	212.1369	9686	1481.3	39235	3.5	0.0219
23	226.1634	9958	516.8	14124	1.3	0.0227
24	254.1581	9725	32456.8	909451	82.1	0.0261
25	255.1625	9624	9682.2	270978	24.5	0.0265
26	256.1677	9636	2142.9	59950	5.4	0.0266
27	272.1685	9912	3177.8	91367	8.2	0.0275
28	273.1728	9443	810.7	23387	2.1	0.0289
29	294.9354	10207	857.3	25913	2.3	0.0289
30	300.2133	6891	550.5	16899	1.5	0.0436
31	325.1942	10223	1506.9	48439	4.4	0.0318
32	326.1991	10077	722.4	23272	2.1	0.0324
33	342.2206	10155	33293.3	1107751	100.0	0.0337

#	m/z	Res.	S/N	I	I %	FWHM
34	343.2191	7975	20826.8	693864	62.6	0.0430
35	344.2196	7407	7144.7	238380	21.5	0.0465
36	345.2214	7573	1736.4	57991	5.2	0.0456
37	364.2022	10328	5605.6	189911	17.1	0.0353
38	365.1974	7799	4189.2	142082	12.8	0.0468
39	366.1983	7855	1628.1	55262	5.0	0.0466
40	367.2010	8054	415.6	14100	1.3	0.0456
41	430.9084	10557	1745.1	62908	5.7	0.0408
42	478.1933	10492	1703.4	62386	5.6	0.0456
43	479.1947	9853	1028.8	37675	3.4	0.0486
44	501.1601	10150	651.2	24070	2.2	0.0494
45	566.8814	10661	507.2	18532	1.7	0.0532
46	614.1656	10986	994.4	35135	3.2	0.0559
47	615.1708	10655	521.4	18414	1.7	0.0577
48	685.4163	10110	500.5	16827	1.5	0.0678
49	750.1379	11142	817.5	25659	2.3	0.0673
50	751.1430	10698	443.5	13914	1.3	0.0702

Figure S79: HR-MS analysis of Arg-Pro-D-Ala-NH₂ [D]-22.

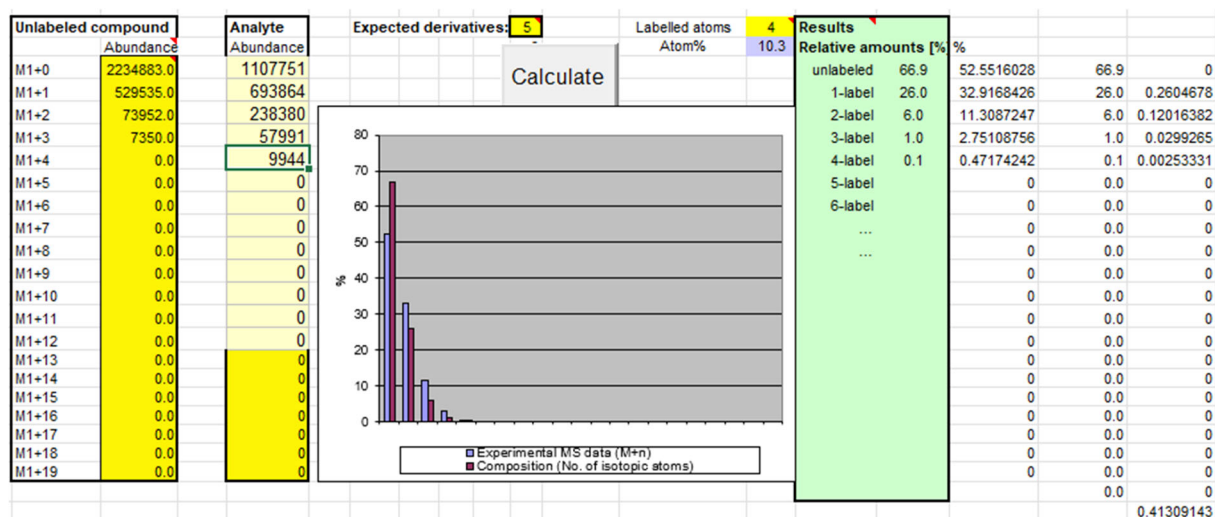
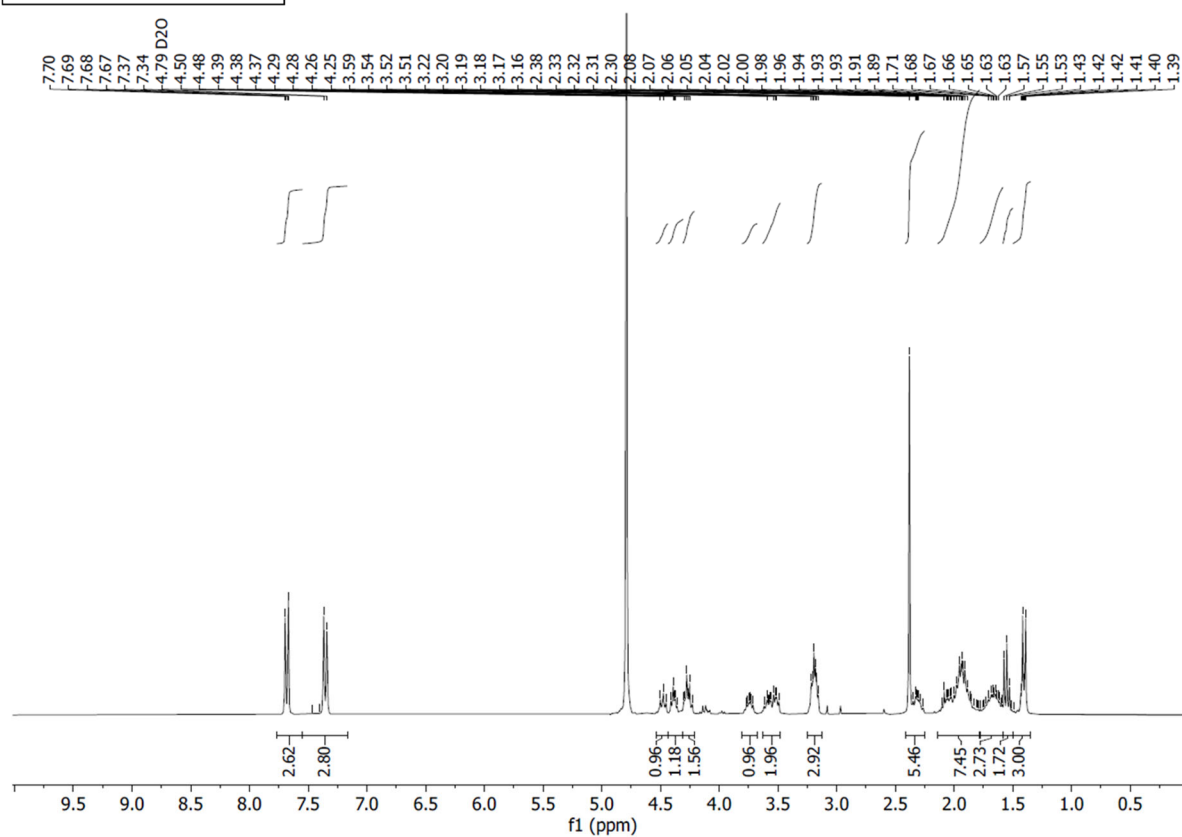


Figure S80: Calculation of deuterium content in Arg-Pro-D-Ala-NH₂ [D]-22.

¹H-NMR Reference 22



¹H-NMR HIE Reaction [D]-22

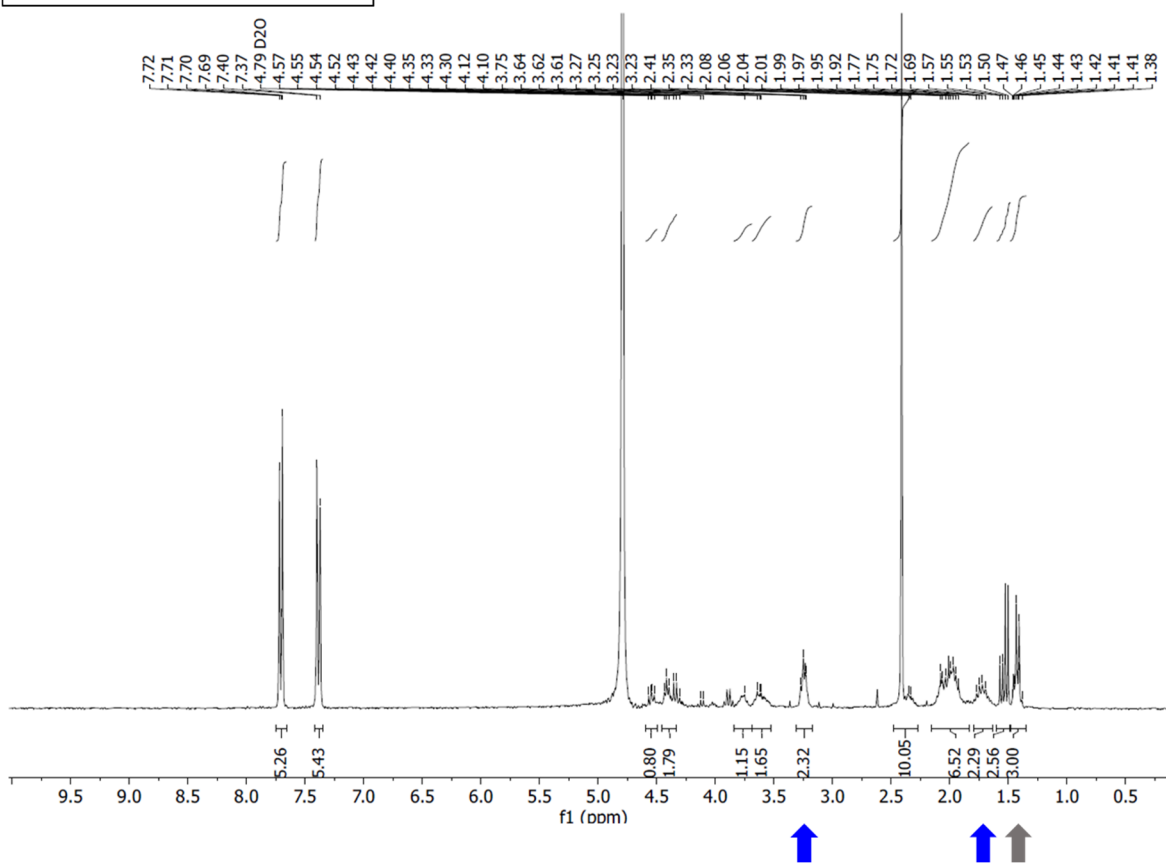


Figure S81: ¹H-NMR spectra of the HIE reaction of compound **22** to yield the deuterated product **[D]-22**.

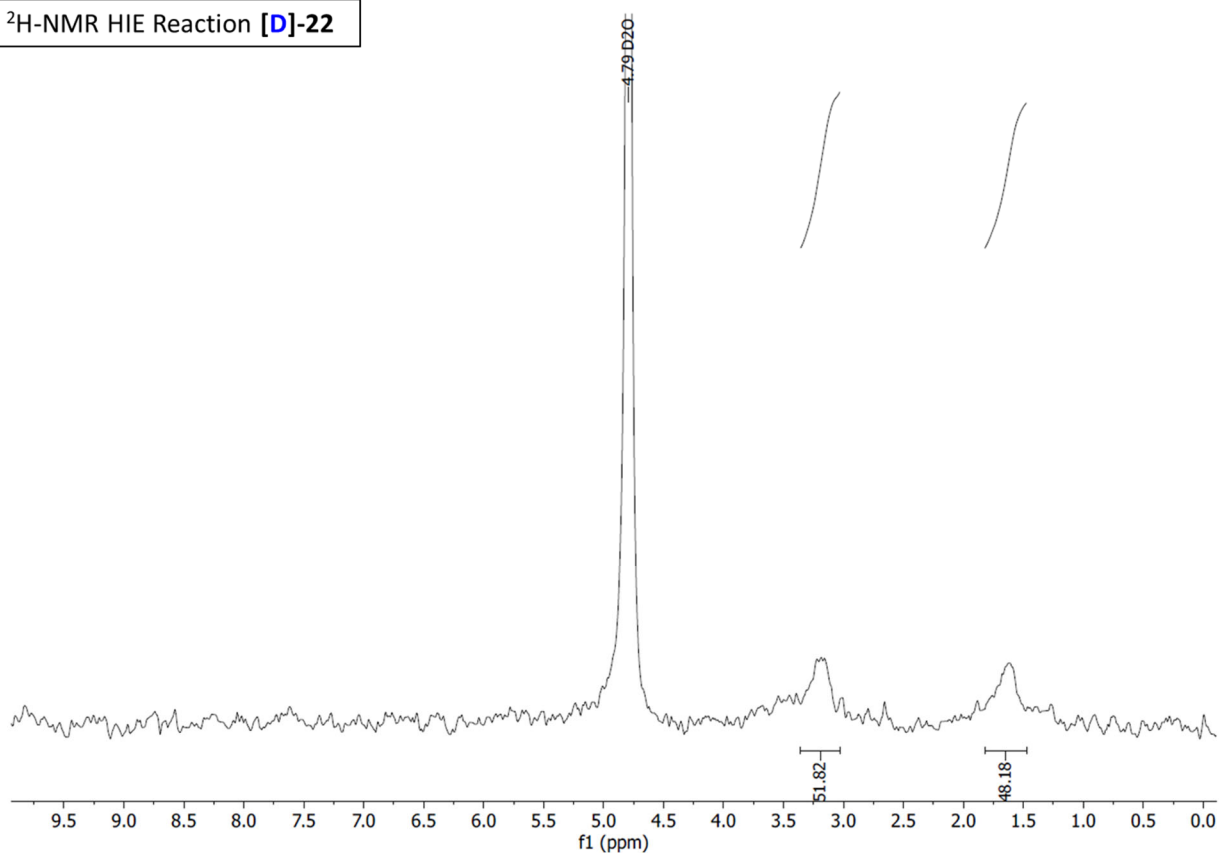
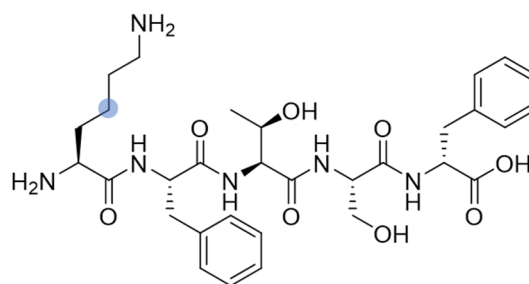


Figure S82: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-22.

7.2.4 Lys-Phe-Thr-Ser-D-Phe **23**



23

Chemical Formula: C₃₁H₄₄N₆O₈

Exact Mass: 628.32

Figure S83: Structure of Lys-Phe-Thr-Ser-D-Phe **23** with ²H labeling position.

Method B: 15 mg, 0.02 mmol **23**•CH₃COOH, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%).

HR-MS (ESI⁺): *m/z* [M+H]⁺ mass calc. for C₃₁H₄₄N₆O₈: 629.3293; found: 629.3175.

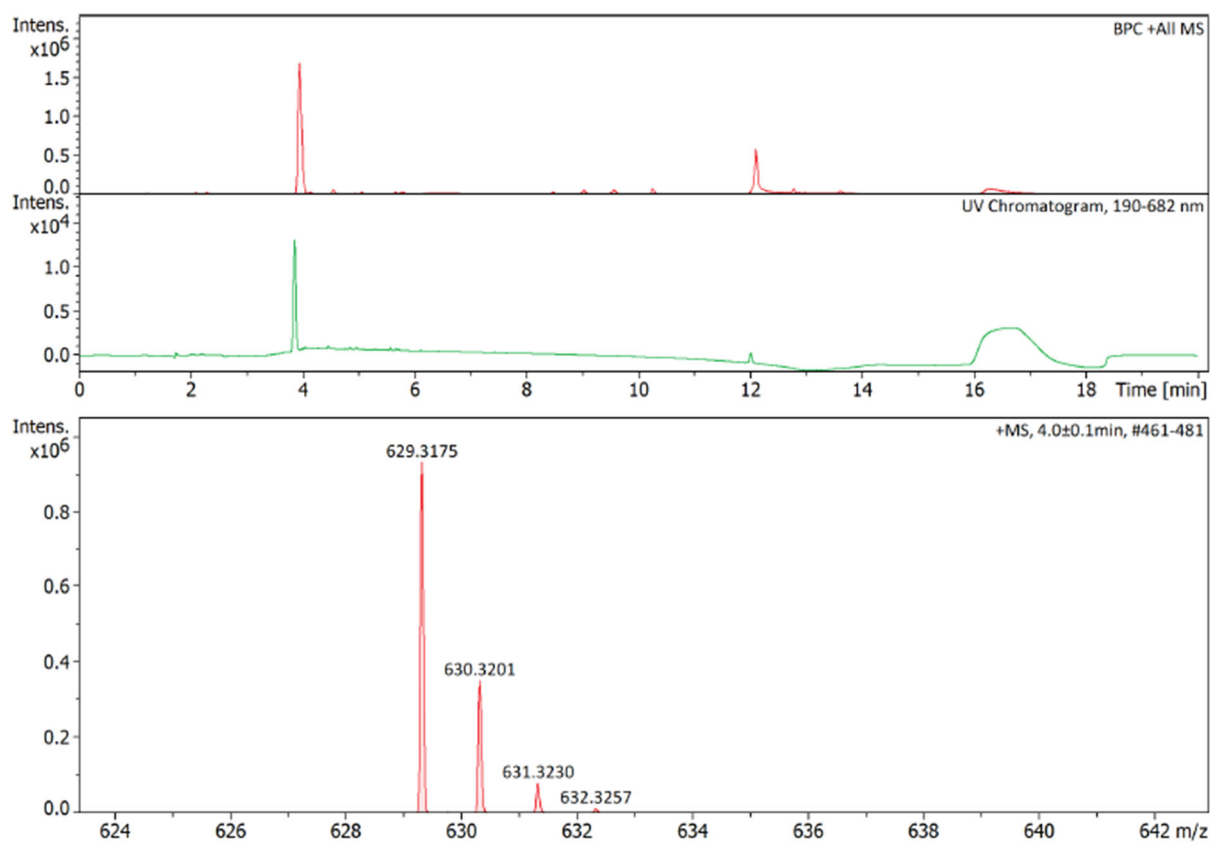
¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.40-7.20 (m, 10H), 4.75-4.65 (m, 2H), 4.36-4.24 (m, 2H), 4.05 (dd, *J* = 6.5, 5.1 Hz, 1H), 3.95 (t, *J* = 6.5 Hz, 1H), 3.65-3.55 (m, 2H), 3.25 (dd, *J* = 14.1, 5.5 Hz, 1H), 3.14-2.87 (m, 5H), 1.90-1.77 (m, 2H), 1.70-1.56 (m, 2H), 1.41-1.30 (m, 2H), 1.08 (d, *J* = 6.4 Hz, 3H). Incorporation expected at δ 1.41-1.30 (blue arrow, blue dot in the structure). Determined against integral at δ 7.40-7.20 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by HR-MS: 0.47 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.46 D/molecule for δ 1.41-1.30

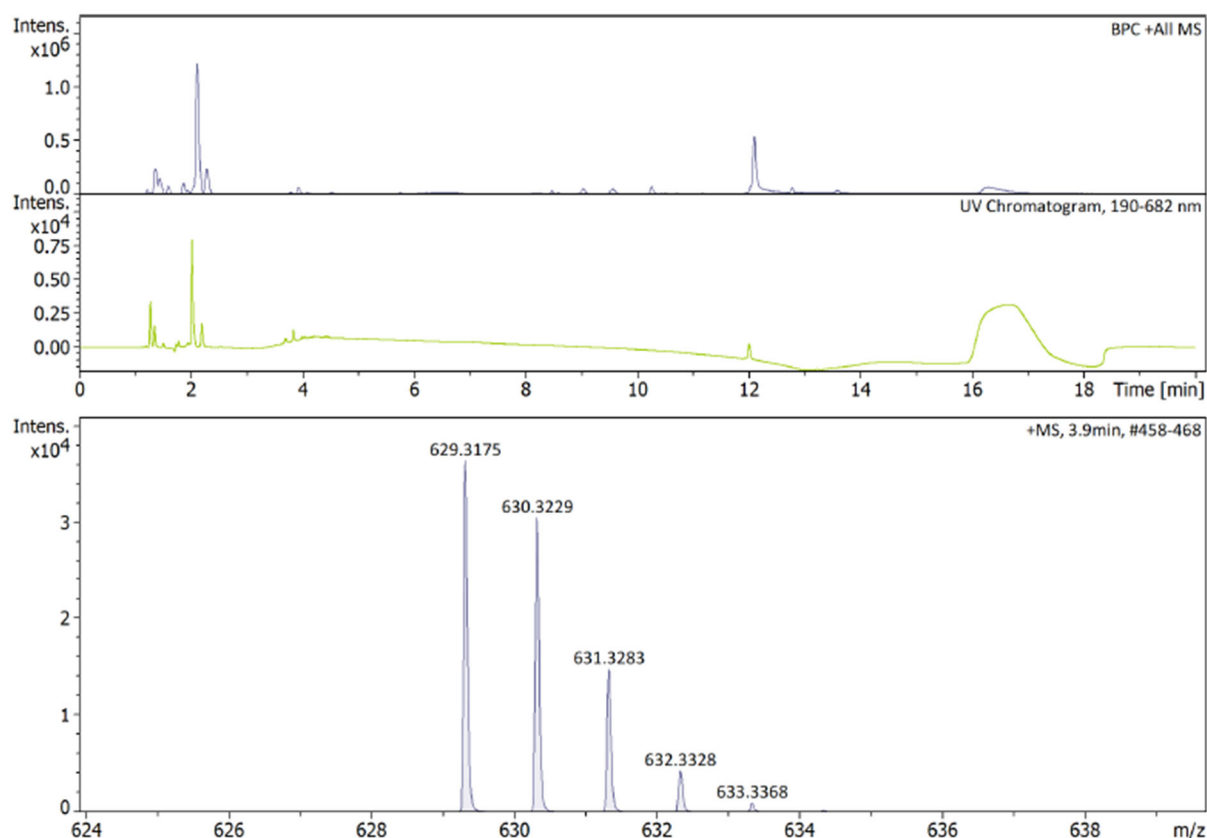
Yield: obtained as TFA salt, 5 mg, 6 μmol, 10%, isolated yield over two purification steps.



#	m/z	Res.	S/N	I	I %	FWHM
1	84.0810	7919	347.5	10801	0.9	0.0106
2	120.0800	8549	920.3	26660	2.2	0.0140
3	121.0830	8676	82.9	2395	0.2	0.0140
4	122.0954	8885	88.9	2562	0.2	0.0137
5	129.1015	8418	97.2	2767	0.2	0.0153
6	166.0845	9070	2307.5	64790	5.4	0.0183
7	167.0880	8973	236.4	6625	0.6	0.0186
8	171.1099	8536	59.3	1656	0.1	0.0200
9	226.9460	9357	72.5	1925	0.2	0.0243
10	253.1150	9630	420.0	10967	0.9	0.0263
11	276.1670	9685	182.8	4740	0.4	0.0285
12	284.1467	10073	78.7	2031	0.2	0.0282
13	292.1620	10468	542.3	13966	1.2	0.0279
14	292.6634	10194	188.7	4858	0.4	0.0287
15	293.1578	7890	118.3	3044	0.3	0.0372
16	297.1540	10296	409.2	10514	0.9	0.0289
17	297.6551	10438	150.4	3865	0.3	0.0285
18	306.1590	10445	1791.2	45818	3.8	0.0293
19	306.6601	10329	680.3	17395	1.4	0.0297
20	307.1609	10371	157.0	4016	0.3	0.0296
21	315.1641	10266	47192.9	1199942	100.0	0.0307
22	315.4779	8905	89.6	2276	0.2	0.0354
23	315.6655	10266	17966.8	456543	38.0	0.0308
24	316.1669	10424	4059.8	103079	8.6	0.0303
25	316.6683	10410	662.0	16800	1.4	0.0304
26	317.1705	9906	97.1	2463	0.2	0.0320
27	341.6199	9902	105.2	2460	0.2	0.0345
28	354.1607	9823	198.4	4477	0.4	0.0361
29	377.2130	10139	488.7	10576	0.9	0.0372
30	378.2162	9623	105.1	2268	0.2	0.0393
31	446.2324	10573	360.7	7300	0.6	0.0422
32	447.2336	9800	107.9	2182	0.2	0.0456
33	464.2427	10455	3158.5	63043	5.3	0.0444

#	m/z	Res.	S/N	I	I %	FWHM
34	465.2459	10966	840.1	16749	1.4	0.0424
35	466.2485	10153	137.6	2737	0.2	0.0459
36	509.2631	10554	146.3	2733	0.2	0.0483
37	599.3076	10468	117.0	2027	0.2	0.0572
38	629.3175	10374	52710.2	934271	77.9	0.0607
39	629.7588	43016	154.4	2737	0.2	0.0146
40	630.3201	10385	19750.7	350071	29.2	0.0607
41	631.3230	10478	4380.1	77646	6.5	0.0602
42	632.3257	10360	667.8	11843	1.0	0.0610
43	655.7741	11064	142.3	2478	0.2	0.0593
44	656.2745	11255	126.1	2194	0.2	0.0583
45	1257.6215	10793	1639.6	24190	2.0	0.1165
46	1258.1276	11272	487.4	7191	0.6	0.1116
47	1258.6258	11133	1402.2	20687	1.7	0.1131
48	1259.1304	11071	203.3	2999	0.2	0.1137
49	1259.6300	10557	451.8	6665	0.6	0.1193
50	1260.6324	10634	114.6	1692	0.1	0.1185

Figure S84: HR-MS analysis of Lys-Phe-Thr-Ser-D-Phe **23** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	60.0458	7034	44.3	1299	2.4	0.0085
2	114.0902	8274	27.4	791	1.5	0.0138
3	118.0859	8299	38.4	1105	2.0	0.0142
4	120.0801	8683	39.8	1145	2.1	0.0138
5	122.0956	8351	116.2	3332	6.1	0.0146
6	132.9607	9581	39.7	1123	2.1	0.0139
7	134.9565	9851	28.4	800	1.5	0.0137
8	149.0220	8778	33.4	927	1.7	0.0170
9	155.1531	10127	32.2	888	1.6	0.0153
10	166.0847	9078	114.7	3120	5.8	0.0183
11	171.0990	9860	32.8	884	1.6	0.0174
12	205.0834	10736	29.6	756	1.4	0.0191
13	226.9460	9465	155.8	3824	7.1	0.0240
14	244.9562	9624	41.3	979	1.8	0.0255
15	252.9706	9925	33.0	771	1.4	0.0255
16	253.1149	9551	32.9	769	1.4	0.0265
17	267.9713	10472	42.6	969	1.8	0.0256
18	276.1665	10129	29.9	670	1.2	0.0273
19	279.1555	11126	28.4	633	1.2	0.0251
20	306.1587	10106	61.0	1292	2.4	0.0303
21	306.6616	10722	47.9	1014	1.9	0.0286
22	315.1642	10623	2598.8	54193	100.0	0.0297
23	315.6666	10714	2124.6	44294	81.7	0.0295
24	316.1690	10904	1112.0	23156	42.7	0.0290
25	316.6714	9919	312.9	6508	12.0	0.0319
26	317.1728	10498	68.7	1426	2.6	0.0302
27	354.1603	9968	53.7	1029	1.9	0.0355
28	399.9720	11201	39.9	723	1.3	0.0357
29	464.2435	10840	102.4	1796	3.3	0.0428
30	465.2476	10888	74.3	1302	2.4	0.0427
31	466.2521	10920	32.6	572	1.1	0.0427
32	509.2623	11083	40.5	698	1.3	0.0459
33	629.3175	10834	2018.1	36417	67.2	0.0581

#	m/z	Res.	S/N	I	I %	FWHM
34	630.3229	10953	1687.5	30469	56.2	0.0575
35	631.3283	10479	816.8	14756	27.2	0.0602
36	632.3328	10456	232.5	4203	7.8	0.0605
37	633.3368	11363	50.7	917	1.7	0.0557
38	651.3001	10552	93.2	1708	3.2	0.0617
39	652.3028	10260	76.4	1399	2.6	0.0636
40	653.3098	10249	39.0	715	1.3	0.0637
41	655.7708	12732	30.2	555	1.0	0.0515
42	656.2745	11861	46.3	851	1.6	0.0553
43	656.7800	12677	43.6	802	1.5	0.0518
44	657.2801	9994	32.8	604	1.1	0.0658
45	667.2719	10498	31.2	577	1.1	0.0636
46	682.2274	9970	30.9	579	1.1	0.0684
47	683.2357	10011	30.6	574	1.1	0.0683
48	718.2046	9859	35.1	671	1.2	0.0728
49	796.2185	9817	39.3	762	1.4	0.0811
50	797.2241	10829	37.4	725	1.3	0.0736

Figure S85: HR-MS analysis of Lys-Phe-Thr-Ser-D-Phe [D]-23.

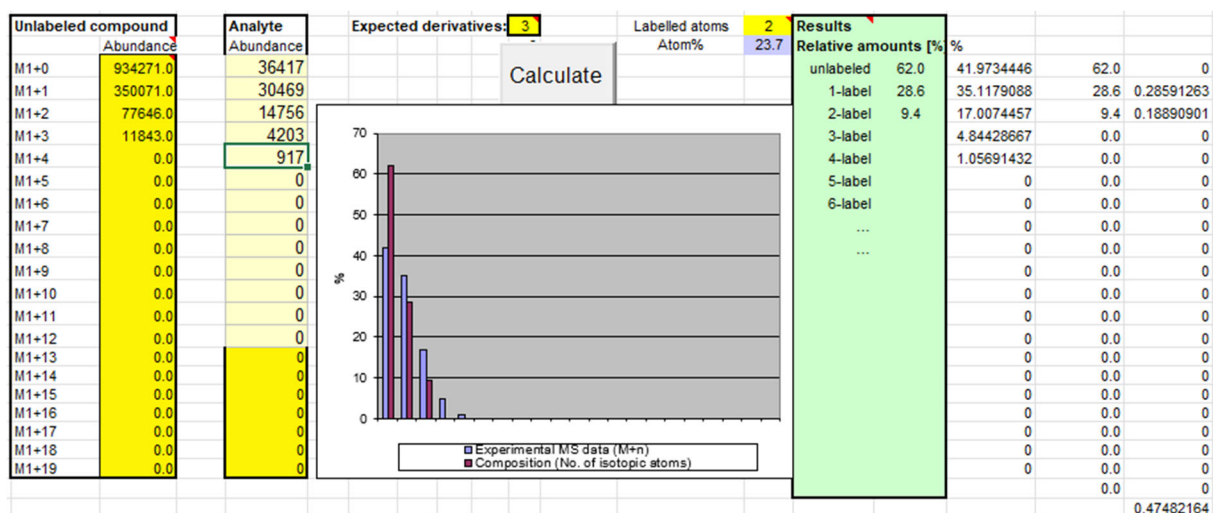


Figure S86: Calculation of deuterium content in Lys-Phe-Thr-Ser-D-Phe **[D]-23**.

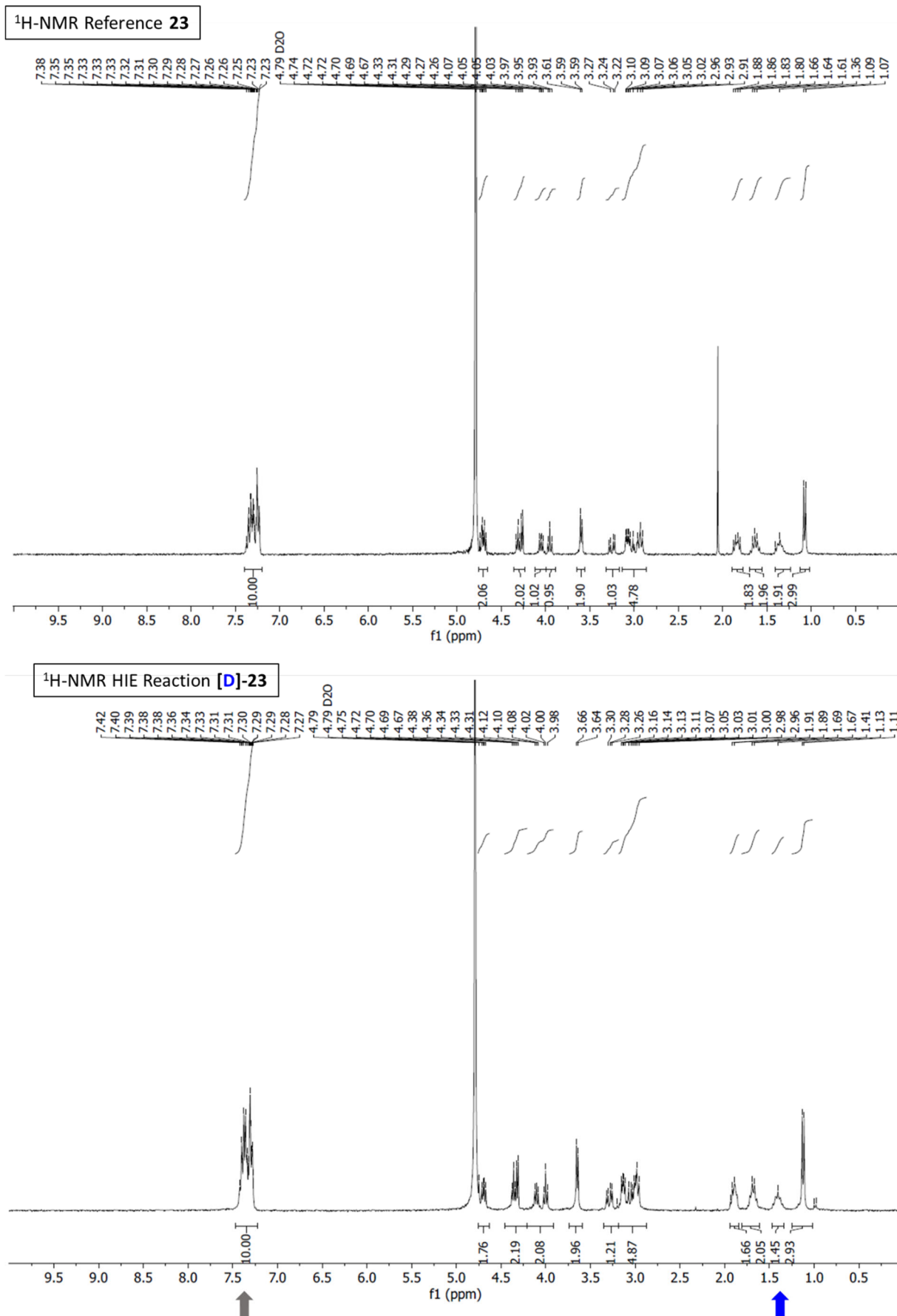


Figure S87: ¹H-NMR spectra of the HIE reaction of compound **23** to yield the deuterated product **[D]-23**.

^2H -NMR HIE Reaction [D]-23

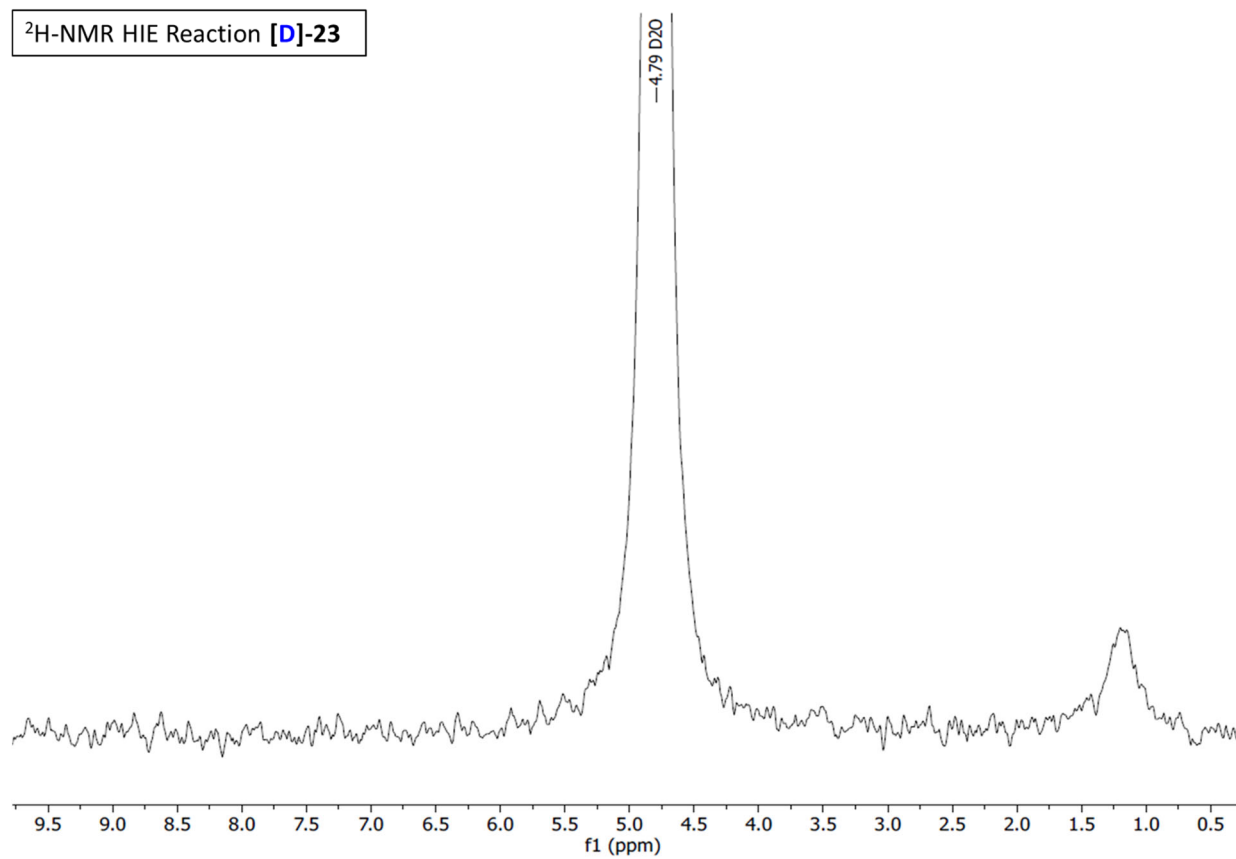
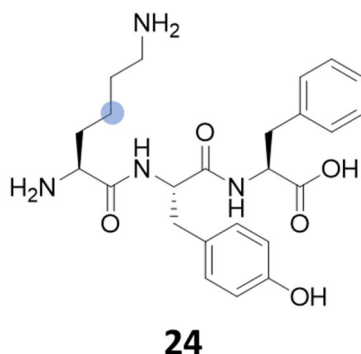


Figure S88: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-23.

7.2.5 Lys-Tyr-Phe **24**



Chemical Formula: C₂₄H₃₂N₄O₅
Exact Mass: 456.24

Figure S89: Structure of Lys-Tyr-Phe **24**.

Method B: 9 mg, 0.02 mmol **24**, 0.5 μ mol catalyst **C4** (2.5 mol%), 1 μ mol ligand **L11** (5 mol%).

HR-MS (ESI⁺): m/z [M+H]⁺ mass calc. for C₂₄H₃₂N₄O₅: 457.2445; found: 457.2367.

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.48-7.19 (m, 6H), 7.11 (d, J = 8.3, 2H), 6.83 (d, J = 8.8, 2H), 4.63-4.47 (m, 2H), 3.93 (t, J = 6.6, 1H), 3.75 (d, J = 2.1 Hz, 1H), 3.71-3.61 (m, 1H), 3.17 (dd, J = 13.7, 5.2 Hz, 1H), 3.03-2.85 (m, 5H), 1.88-1.72 (m, 2H), 1.72-1.54 (m, 2H), 1.35-1.18 (m, 2H).

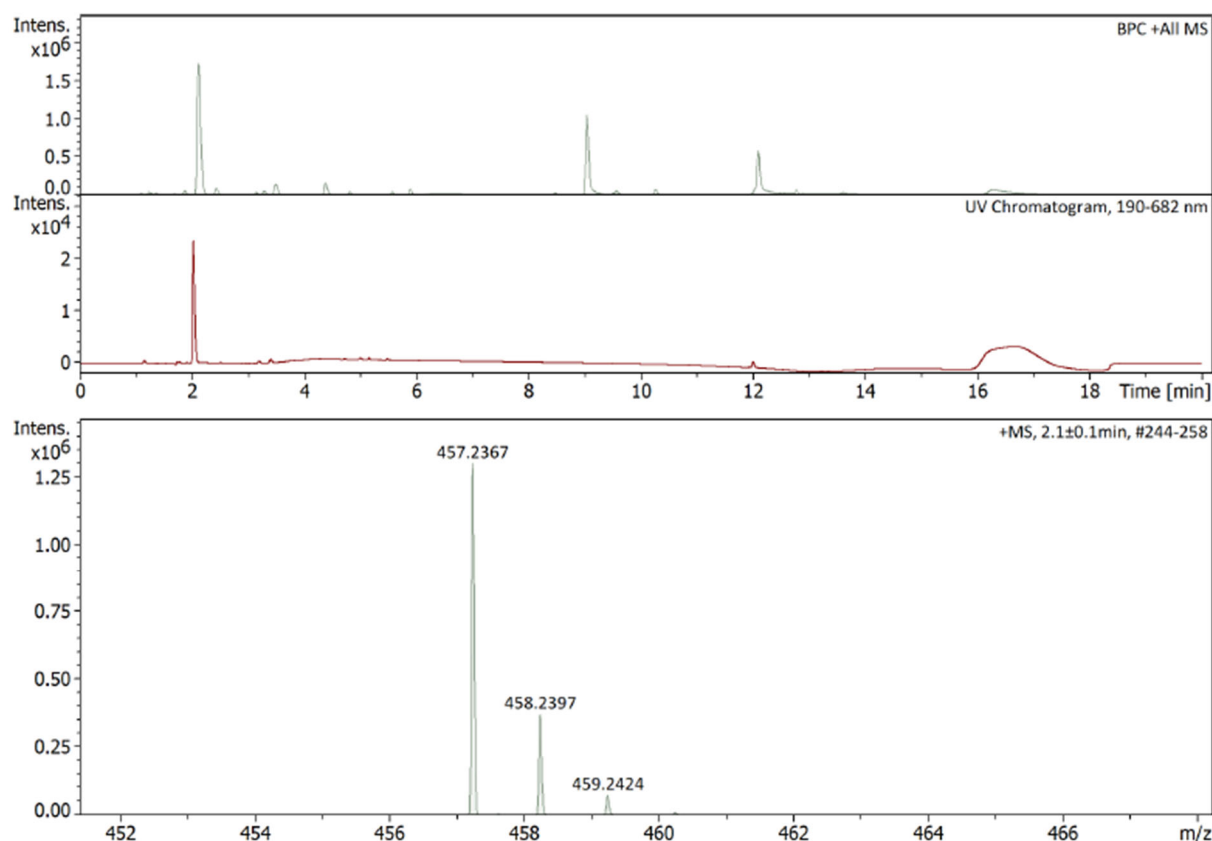
Incorporation expected at δ 1.35-1.18. (blue arrow, blue dot in the structure). Determined against integral at δ 6.83 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by HR-MS: 0.61 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.79 D/molecule for δ 1.35-1.18

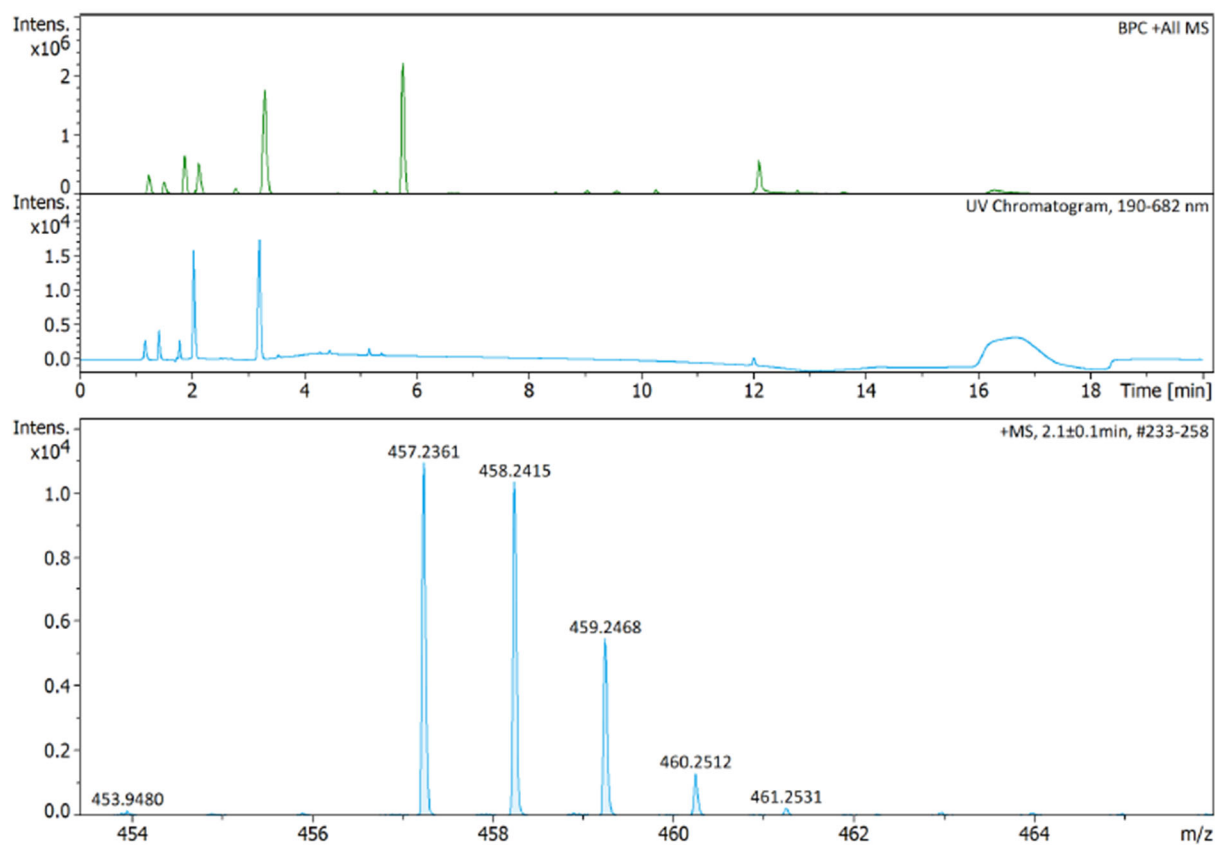
Yield: obtained as TFA salt, 8 mg, 12 μ mol, 20%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	84.0810	8064	767.8	20375	1.6	0.0104
2	101.1068	8520	110.5	2924	0.2	0.0119
3	103.0537	8908	140.9	3727	0.3	0.0116
4	120.0799	8375	8523.2	223724	17.2	0.0143
5	121.0828	8591	782.4	20498	1.6	0.0141
6	122.0938	7963	101.1	2642	0.2	0.0153
7	129.1012	8644	4167.9	107770	8.3	0.0149
8	130.1040	8890	305.5	7889	0.6	0.0146
9	132.5880	9746	103.2	2655	0.2	0.0136
10	136.0745	9010	632.0	16193	1.2	0.0151
11	166.0845	9291	4785.7	119693	9.2	0.0179
12	167.0878	9223	485.1	12113	0.9	0.0181
13	197.6078	10063	299.7	7266	0.6	0.0196
14	198.1097	10445	81.1	1964	0.2	0.0190
15	206.1208	10043	10259.6	249376	19.2	0.0205
16	206.6224	10324	2879.6	69986	5.4	0.0200
17	207.1239	10108	433.4	10533	0.8	0.0205
18	220.1181	10167	531.3	12742	1.0	0.0216
19	220.6190	10112	157.0	3761	0.3	0.0218
20	226.9458	9775	84.7	2019	0.2	0.0232
21	229.1231	10148	21287.1	507124	39.0	0.0226
22	229.6247	10159	6171.4	147155	11.3	0.0226
23	230.1259	10095	1182.9	28212	2.2	0.0228
24	230.6269	10404	173.5	4136	0.3	0.0222
25	238.1284	10219	138.1	3249	0.2	0.0233
26	247.1409	9846	822.3	19150	1.5	0.0251
27	248.1441	9457	127.2	2960	0.2	0.0262
28	264.1671	9941	713.3	16453	1.3	0.0266
29	265.1704	9865	117.8	2717	0.2	0.0269
30	274.1510	10256	507.7	11636	0.9	0.0267
31	275.1376	8108	394.0	9027	0.7	0.0339
32	292.1612	10037	7525.7	170623	13.1	0.0291
33	293.1644	9836	1292.3	29241	2.2	0.0298

#	m/z	Res.	S/N	I	I %	FWHM
34	294.1665	10077	156.2	3526	0.3	0.0292
35	329.1446	10204	654.2	14501	1.1	0.0323
36	330.1478	10812	143.1	3171	0.2	0.0305
37	440.2115	10487	96.4	2067	0.2	0.0420
38	457.2367	10357	60685.5	1300221	100.0	0.0441
39	457.6119	50610	223.4	4786	0.4	0.0090
40	458.2397	10356	17311.6	370850	28.5	0.0442
41	459.2424	10451	3377.4	72338	5.6	0.0439
42	460.2448	10382	461.5	9881	0.8	0.0443
43	483.6923	10825	118.0	2422	0.2	0.0447
44	913.4600	11185	10524.2	165664	12.7	0.0817
45	914.4635	11200	5992.1	94346	7.3	0.0816
46	915.4666	10794	1888.4	29741	2.3	0.0848
47	916.4688	10741	436.2	6879	0.5	0.0853
48	1369.6894	10606	285.4	4328	0.3	0.1291
49	1370.1921	10511	127.0	1926	0.1	0.1304
50	1370.6934	10355	277.3	4205	0.3	0.1324

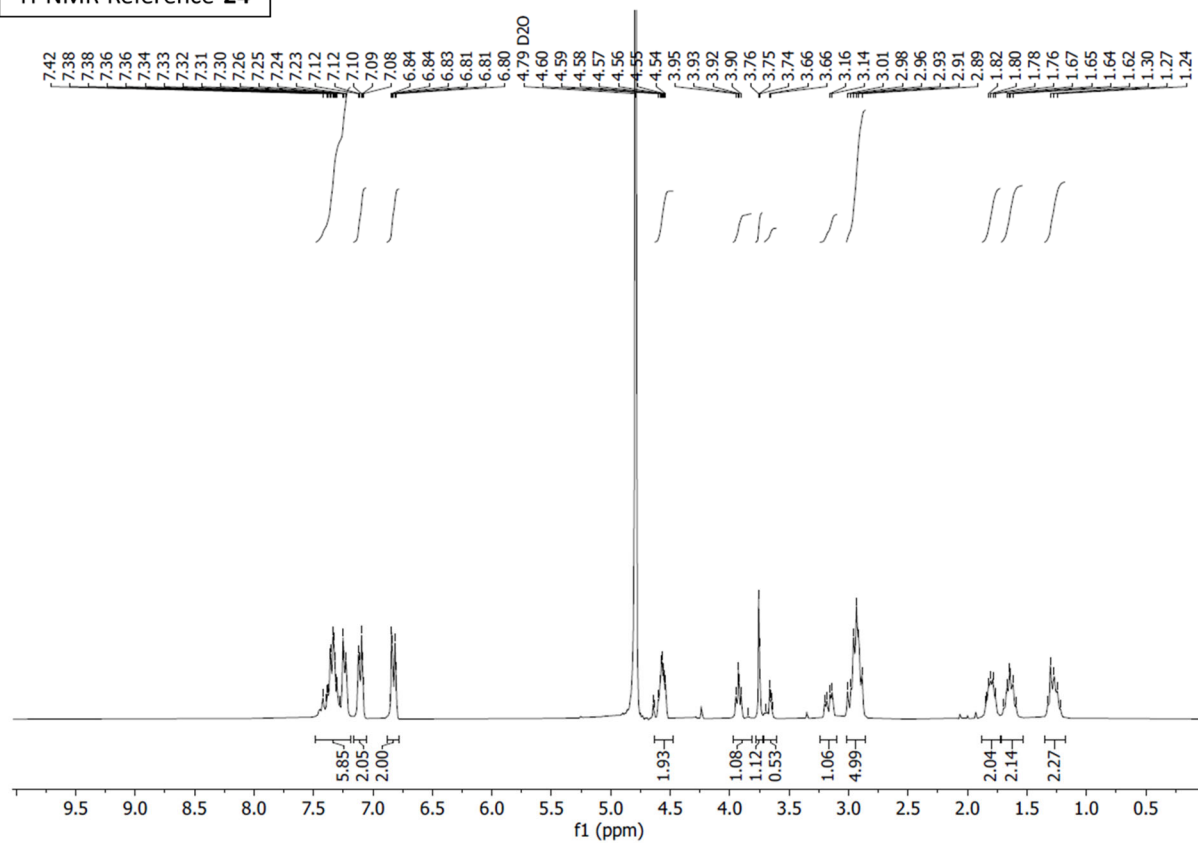
Figure S90: HR-MS analysis of Lys-Tyr-Phe **24** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	60.0460	7363	47.4	1348	6.2	0.0082
2	100.0754	8506	758.4	21806	100.0	0.0118
3	101.0815	8327	601.9	17309	79.4	0.0121
4	102.0875	8135	280.1	8066	37.0	0.0125
5	114.0906	8876	22.9	662	3.0	0.0129
6	118.0856	9018	50.7	1469	6.7	0.0131
7	120.0799	8427	139.5	4041	18.5	0.0143
8	122.0954	8973	120.9	3507	16.1	0.0136
9	129.1012	8354	32.6	943	4.3	0.0155
10	132.9610	8302	42.6	1232	5.7	0.0160
11	134.9563	9112	38.9	1124	5.2	0.0148
12	142.0851	8767	155.4	4477	20.5	0.0162
13	143.0910	8795	127.7	3677	16.9	0.0163
14	144.0963	8492	61.0	1754	8.0	0.0170
15	149.0220	8897	43.1	1236	5.7	0.0168
16	160.0951	9236	600.8	17141	78.6	0.0173
17	161.1009	9355	493.4	14076	64.5	0.0172
18	162.1070	8816	235.0	6705	30.7	0.0184
19	163.1164	6342	29.9	850	3.9	0.0257
20	166.0843	9631	111.4	3169	14.5	0.0172
21	171.0991	9720	24.8	705	3.2	0.0176
22	180.1107	9260	37.9	1072	4.9	0.0195
23	181.1165	9671	28.7	811	3.7	0.0187
24	182.0765	9547	198.3	5613	25.7	0.0191
25	183.0829	9142	158.0	4471	20.5	0.0200
26	184.0883	9250	78.2	2208	10.1	0.0199
27	205.0821	10574	28.8	807	3.7	0.0194
28	206.1209	9883	71.0	1985	9.1	0.0209
29	206.6235	10038	63.1	1764	8.1	0.0206
30	207.1262	9869	34.0	951	4.4	0.0210
31	226.9452	10179	182.4	5034	23.1	0.0223
32	229.1231	10016	147.7	4069	18.7	0.0229
33	229.6258	10039	137.5	3788	17.4	0.0229
#	m/z	Res.	S/N	I	I %	FWHM
34	230.1287	10138	78.8	2170	10.0	0.0227
35	244.9553	10784	43.3	1185	5.4	0.0227
36	252.9702	9782	33.1	901	4.1	0.0259
37	267.9716	9966	47.9	1292	5.9	0.0269
38	279.1556	9106	27.7	742	3.4	0.0307
39	292.1612	9905	49.7	1319	6.0	0.0295
40	293.1669	9979	41.0	1087	5.0	0.0294
41	320.1875	9803	35.0	913	4.2	0.0327
42	321.1929	9911	30.8	805	3.7	0.0324
43	342.1688	10451	30.4	786	3.6	0.0327
44	399.9715	11966	40.8	1024	4.7	0.0334
45	457.2361	10494	452.3	10971	50.3	0.0436
46	458.2415	10466	428.3	10380	47.6	0.0438
47	459.2468	10331	225.9	5469	25.1	0.0445
48	460.2512	10227	53.6	1296	5.9	0.0450
49	914.4650	10866	67.7	967	4.4	0.0842
50	915.4713	10981	68.4	977	4.5	0.0834

Figure S91: HR-MS analysis of Lys-Tyr-Phe [D]-24.

¹H-NMR Reference 24



¹H-NMR HIE Reaction [D]-24

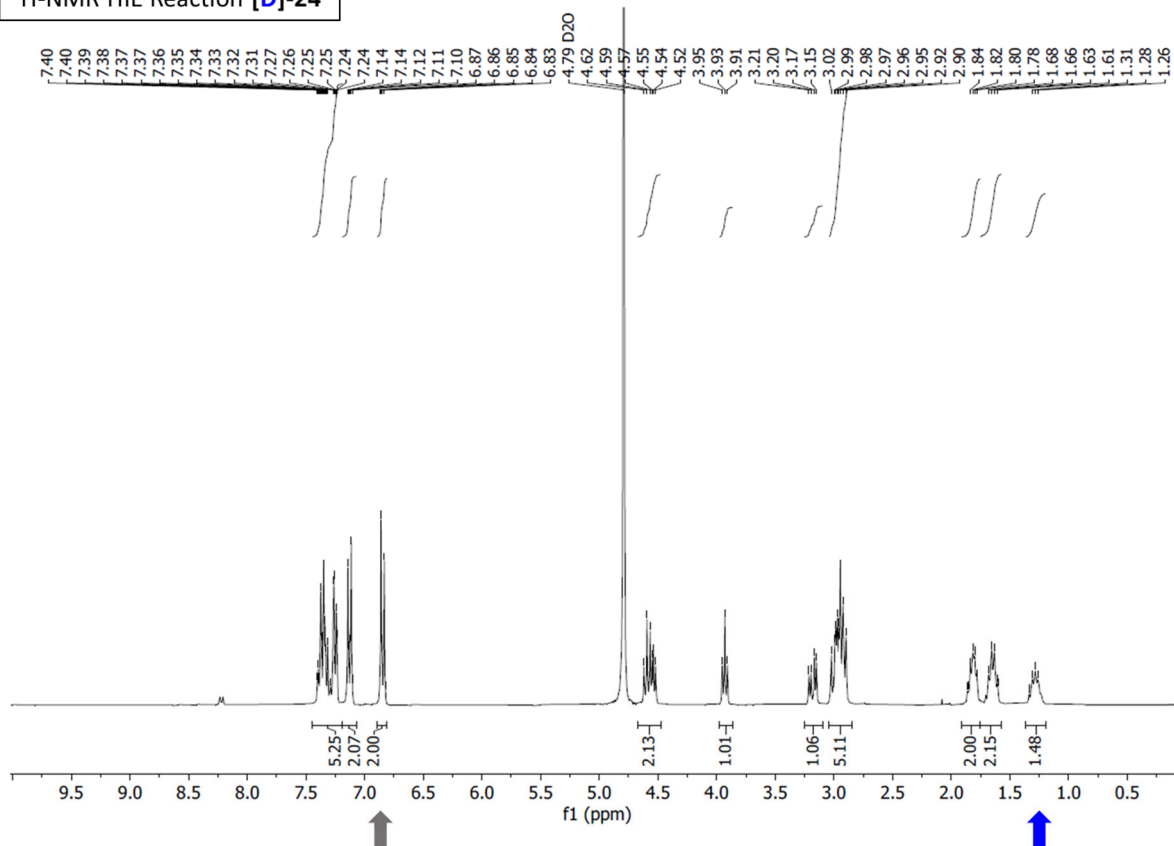


Figure S93: ¹H-NMR spectra of the HIE reaction of compound **24** to yield the deuterated product **[D]-24**.

^2H -NMR HIE Reaction [D]-24

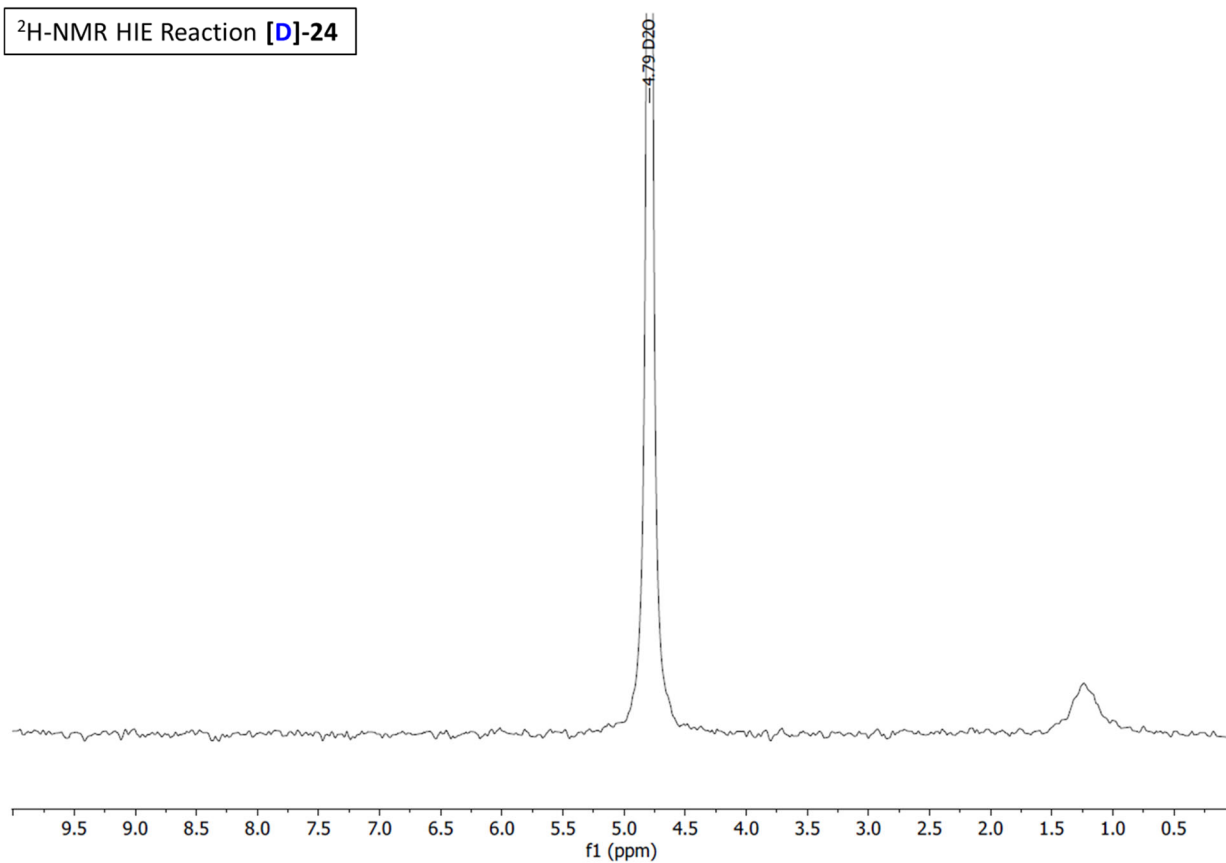
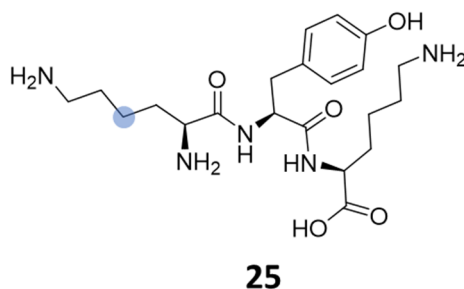


Figure S94: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-24.

7.2.6 Lys-Tyr-Lys **25**



Chemical Formula: C₂₁H₃₅N₅O₅
Exact Mass: 437.26

Figure S95: Structure of Lys-Tyr-Lys **25**.

Method B: 12 mg, 0.02 mmol **25**•CH₃COOH, 0.5 μmol catalyst **C4** (2.5 mol%), 2 μmol ligand **L11** (5 mol%), reaction run for 3h.

HR-MS (ESI⁺): *m/z* [M+H]⁺ mass calc. for C₂₁H₃₅N₅O₅: 438.2711; found: 438.2638.

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.14 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 4.57 (t, *J* = 7.7 Hz, 1H), 4.14 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.92 (t, *J* = 6.6 Hz, 1H), 3.01-2.91 (m, 6H), 2.06 (s, 6H), 1.88-1.56 (m, 8H), 1.43-1.22 (m, 4H).

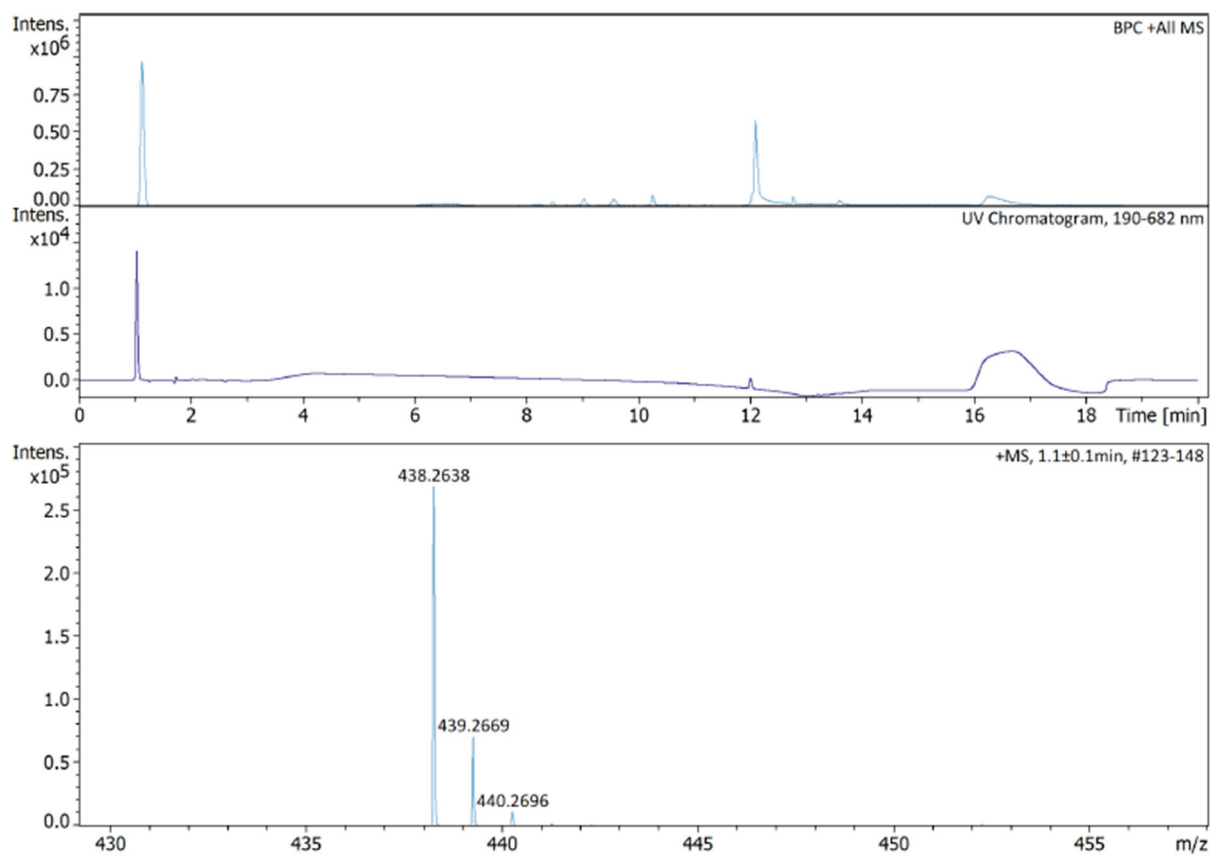
Incorporation expected at δ 1.43-1.22. (blue arrow, blue dot in the structure, position assigned as indicated by postulated mechanism). Determined against integral at δ 7.14 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by HR-MS: 0.61 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.68 D/molecule for δ 1.43-1.22

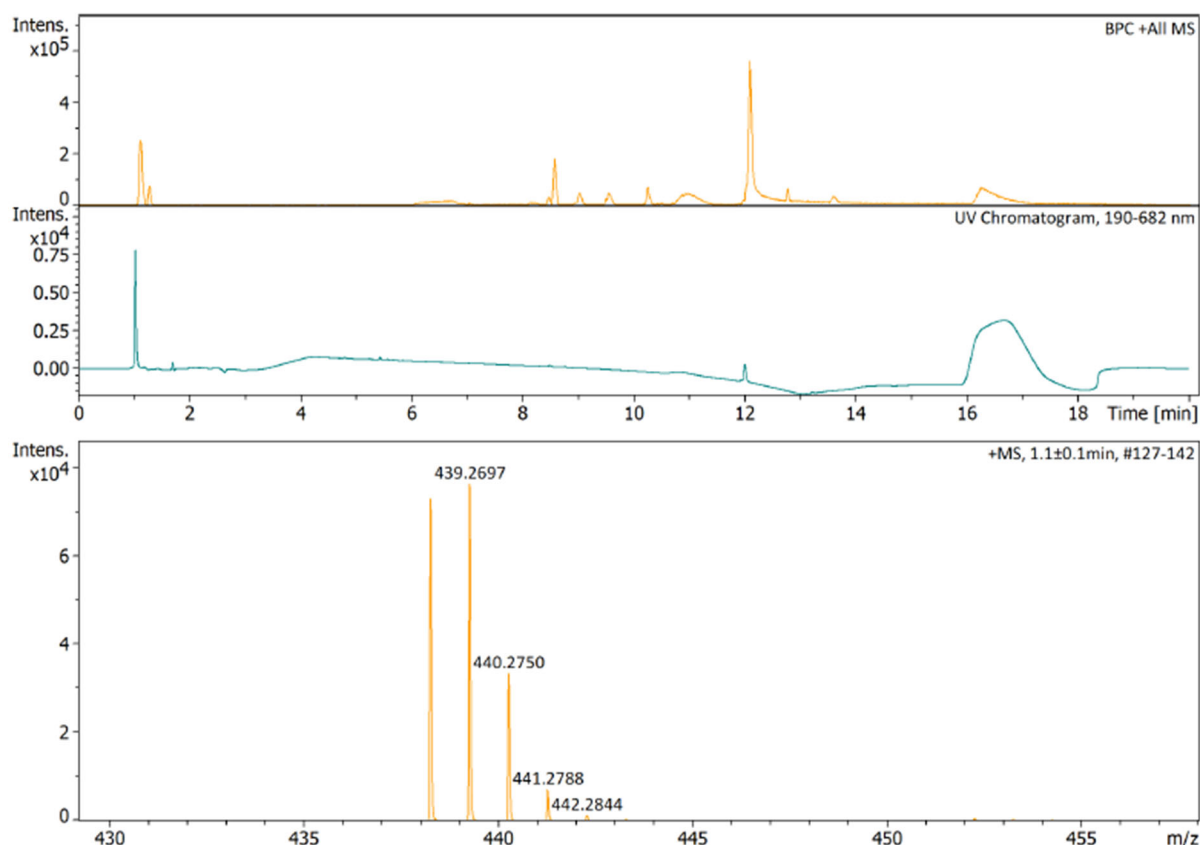
Yield: obtained as TFA salt, 14 mg, 18 μmol, 30%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	84.0808	7648	508.9	10349	1.5	0.0110
2	118.0854	8287	45.6	926	0.1	0.0142
3	121.0633	8575	48.7	989	0.1	0.0141
4	122.0954	8566	117.1	2374	0.3	0.0143
5	124.0750	8442	48.3	979	0.1	0.0147
6	129.1008	8786	178.5	3605	0.5	0.0147
7	130.0852	8877	347.5	7007	1.0	0.0147
8	132.5879	9048	396.2	7959	1.1	0.0147
9	133.0892	8995	62.2	1247	0.2	0.0148
10	135.0665	8974	63.6	1276	0.2	0.0151
11	136.0742	8612	501.8	10073	1.4	0.0158
12	137.0772	8833	47.4	952	0.1	0.0155
13	147.0773	9248	52.9	1058	0.2	0.0159
14	147.1109	8899	400.9	8011	1.1	0.0165
15	155.5902	9815	94.1	1876	0.3	0.0159
16	211.1234	10036	4430.6	86805	12.4	0.0210
17	211.6250	9892	1077.1	21100	3.0	0.0214
18	212.1262	9510	168.7	3303	0.5	0.0223
19	219.6364	9804	35887.2	700731	100.0	0.0224
20	220.1381	9668	9265.6	180873	25.8	0.0228
21	220.6392	9840	1502.8	29334	4.2	0.0224
22	221.1402	10017	186.8	3646	0.5	0.0221
23	221.6505	9131	79.2	1546	0.2	0.0243
24	226.6353	6315	103.3	2001	0.3	0.0359
25	226.9459	9474	135.5	2621	0.4	0.0240
26	233.6512	9888	64.3	1227	0.2	0.0236
27	246.0916	9724	54.6	1025	0.1	0.0253
28	283.6822	10164	82.5	1474	0.2	0.0279
29	292.1605	10331	55.9	986	0.1	0.0283
30	303.0878	10102	74.0	1286	0.2	0.0300
31	310.1719	9637	521.9	8973	1.3	0.0322
32	311.1740	10498	96.1	1648	0.2	0.0296
33	438.2638	10151	17783.1	268698	38.3	0.0432

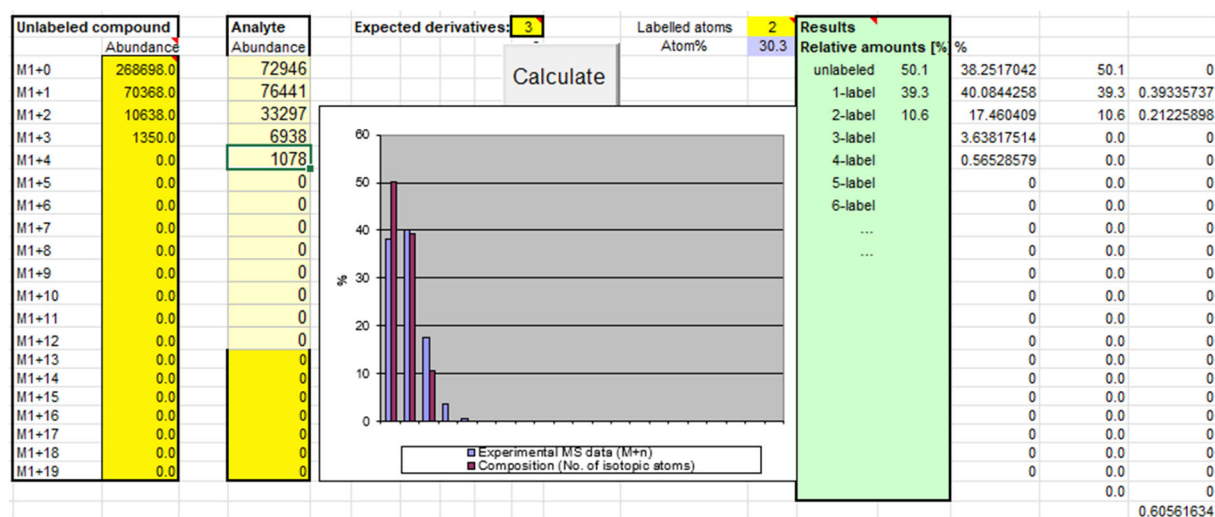
#	m/z	Res.	S/N	I	I %	FWHM
34	439.2669	10222	4657.5	70368	10.0	0.0430
35	440.2696	10102	705.1	10638	1.5	0.0436
36	441.2724	9873	89.7	1350	0.2	0.0447
37	464.7205	10177	119.2	1707	0.2	0.0457
38	465.2218	11539	67.9	973	0.1	0.0403
39	683.3491	11024	67.1	868	0.1	0.0620
40	875.5169	10754	2192.2	28113	4.0	0.0814
41	876.0205	11667	107.7	1381	0.2	0.0751
42	876.5207	10714	1106.1	14181	2.0	0.0818
43	877.5233	10288	304.8	3908	0.6	0.0853
44	901.9754	10857	76.3	979	0.1	0.0831
45	902.4754	10978	80.9	1038	0.1	0.0822
46	1094.1476	11699	258.4	3342	0.5	0.0935
47	1094.6478	10554	315.7	4084	0.6	0.1037
48	1095.1490	11279	221.6	2867	0.4	0.0971
49	1095.6501	10579	101.6	1314	0.2	0.1036
50	1313.7795	10025	71.1	903	0.1	0.1311

Figure S96: HR-MS analysis of Lys-Tyr-Lys **25** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	60.0456	7182	29.3	711	0.4	0.0084
2	84.0810	7841	158.0	3757	2.0	0.0107
3	85.0866	7915	50.4	1198	0.6	0.0107
4	118.0853	8141	35.3	827	0.4	0.0145
5	122.0953	8796	110.9	2585	1.4	0.0139
6	129.1008	8866	64.5	1492	0.8	0.0146
7	130.0855	8699	141.3	3260	1.8	0.0150
8	132.5882	9039	75.9	1747	0.9	0.0147
9	132.9609	9145	37.8	869	0.5	0.0145
10	133.0908	9526	74.7	1716	0.9	0.0140
11	134.9564	9220	32.1	735	0.4	0.0146
12	136.0744	8745	204.0	4681	2.5	0.0156
13	147.1108	8837	177.2	4016	2.2	0.0166
14	155.5904	10363	36.4	819	0.4	0.0150
15	211.1236	10080	1014.7	21596	11.6	0.0209
16	211.6264	9977	1027.6	21839	11.8	0.0212
17	212.1290	9870	437.7	9294	5.0	0.0215
18	212.6307	9816	86.4	1833	1.0	0.0217
19	219.6368	9871	8409.9	176505	95.2	0.0223
20	220.1395	9806	8837.3	185413	100.0	0.0225
21	220.6420	9856	3922.8	82293	44.4	0.0224
22	221.1438	9880	812.3	17039	9.2	0.0224
23	221.6458	9859	140.0	2933	1.6	0.0225
24	226.6388	6704	46.8	969	0.5	0.0338
25	226.9461	9421	146.6	3036	1.6	0.0241
26	227.1363	5307	34.3	709	0.4	0.0428
27	244.9563	9595	34.8	704	0.4	0.0255
28	267.9720	9721	39.3	769	0.4	0.0276
29	310.1724	8909	216.7	4020	2.2	0.0348
30	311.1764	8886	48.3	896	0.5	0.0350
31	438.2645	10228	4224.2	72946	39.3	0.0428
32	439.2697	10192	4428.6	76441	41.2	0.0431
33	440.2750	10080	1930.4	33297	18.0	0.0437

#	m/z	Res.	S/N	I	I %	FWHM
34	441.2788	10562	402.4	6938	3.7	0.0418
35	442.2844	9564	62.6	1078	0.6	0.0462
36	465.2221	11125	54.4	924	0.5	0.0418
37	465.7249	10164	51.0	866	0.5	0.0458
38	875.5175	10915	329.9	4623	2.5	0.0802
39	876.5237	10410	686.4	9614	5.2	0.0842
40	877.5290	10194	664.8	9309	5.0	0.0861
41	878.5335	10765	391.0	5473	3.0	0.0816
42	879.5387	10210	138.3	1935	1.0	0.0861
43	902.9797	12433	55.1	763	0.4	0.0726
44	903.4819	10152	64.2	889	0.5	0.0890
45	903.9846	12216	64.1	886	0.5	0.0740
46	1095.1502	11420	64.6	861	0.5	0.0959
47	1095.6541	10567	102.3	1364	0.7	0.1037
48	1096.1576	10646	116.9	1559	0.8	0.1030
49	1096.6609	11361	112.2	1496	0.8	0.0965
50	1097.1626	10842	76.6	1022	0.6	0.1012



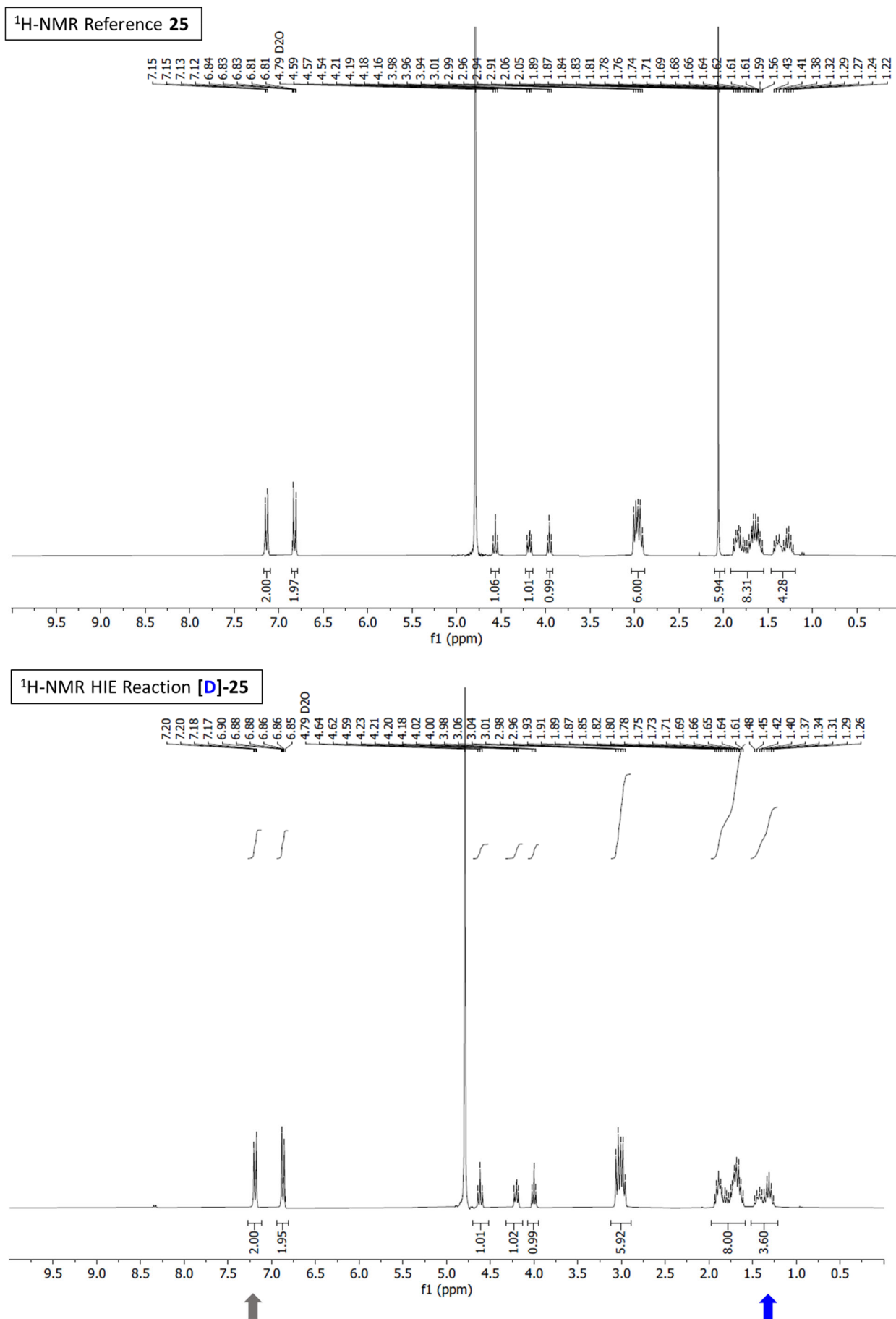


Figure S99: ¹H-NMR spectra of the HIE reaction of compound **25** to yield the deuterated product **[D]-25**.

^2H -NMR HIE Reaction [D]-25

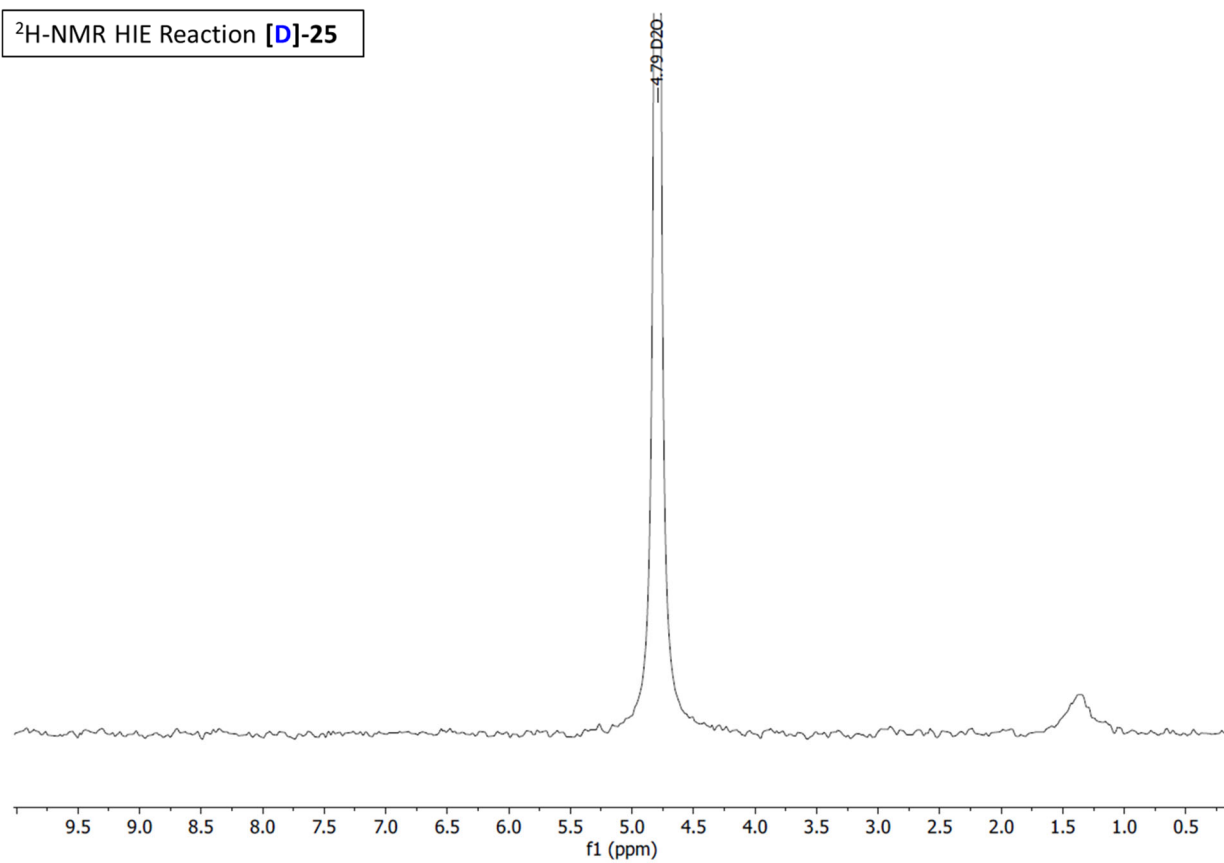


Figure S100: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-25.

7.2.7 Lys-D-Pro-Phe-Ile-Leu **26**

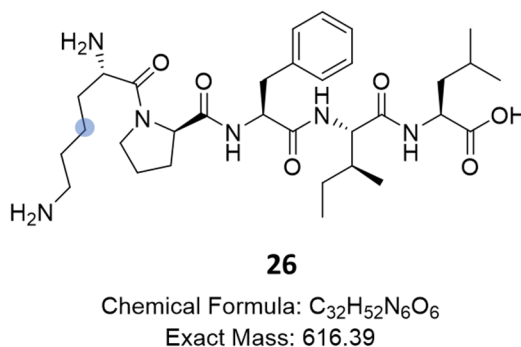


Figure S101: Structure of Lys-D-Pro-Phe-Ile-Leu **26**.

Method B: 12 mg, 0.02 mmol **26**, 0.5 μ mol catalyst **C4** (2.5 mol%), 1 μ mol ligand **L11** (5 mol%).

HR-MS (ESI⁺): m/z [M+H]⁺ mass calc. for C₃₂H₅₂N₆O₆: 617.4021; found: 617.3901.

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.46-7.23 (m, 5H), 4.62 (t, J = 7.6 Hz, 1H), 4.50 (dd, J = 8.2, 6.2 Hz, 1H), 4.37 (t, J = 6.2 Hz, 1H), 4.32-4.23 (m, J = 7.9 Hz, 1H), 4.21-4.09 (m, 1H), 3.82-3.70 (m, 1H), 3.68-3.55 (m, 1H), 3.16-2.96 (m, 4H), 2.40-2.25 (m, 1H), 2.14-1.61 (m, 11H), 1.61-1.36 (m, 3H), 1.24-1.04 (m, 1H), 1.05-0.75 (m, 12H).

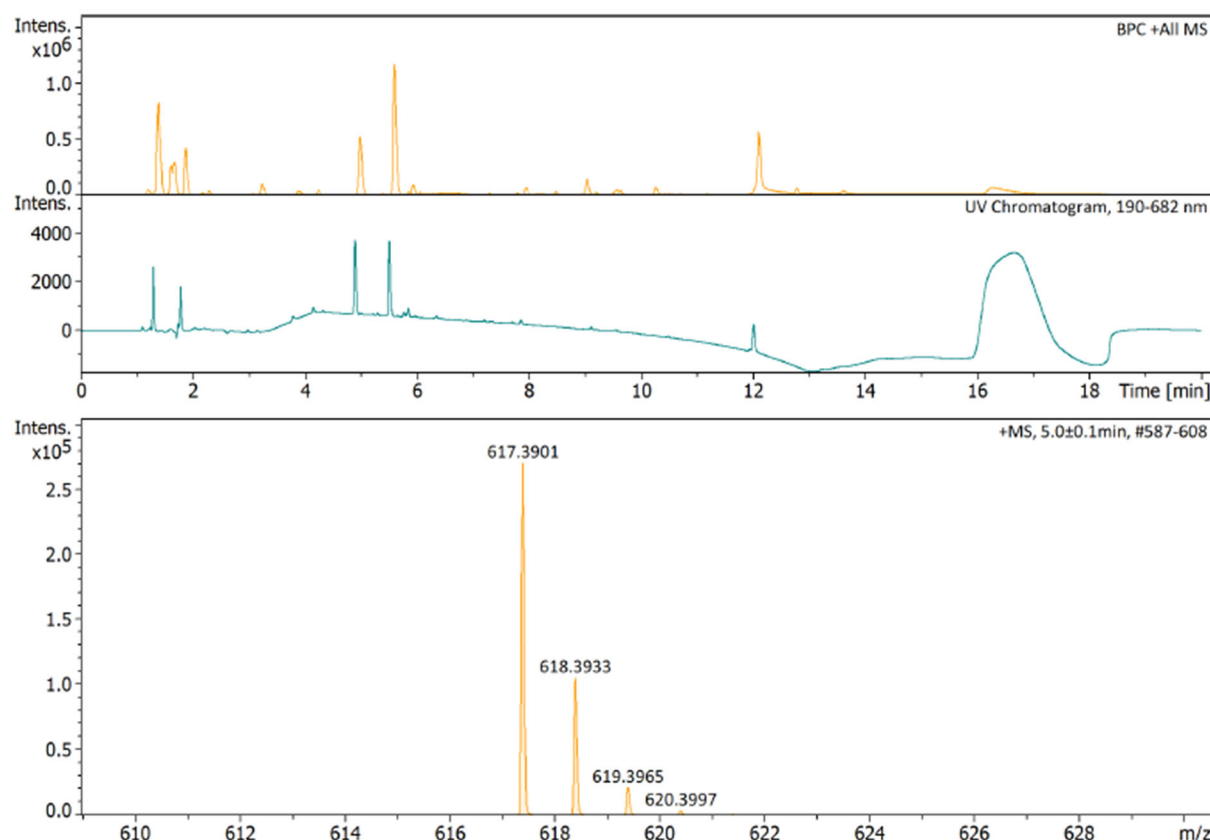
Incorporation expected at δ 1.61-1.36 (blue arrow, blue dot in the structure, position assigned as indicated by postulated mechanism). Determined against integral at δ 7.46-7.23 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by HR-MS: 1.22 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 1.44 D/molecule for δ 1.61-1.36

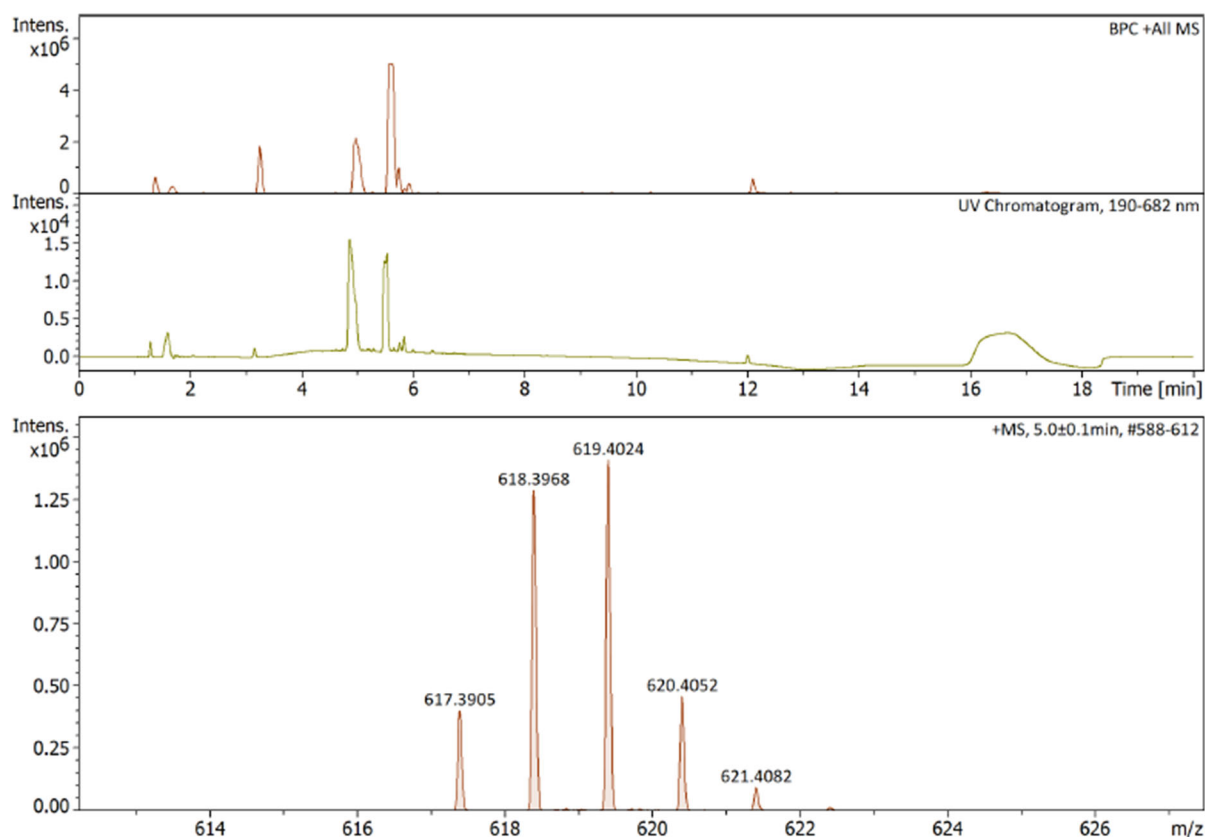
Yield: obtained as TFA salt, 17 mg, 20 μ mol, 33%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	70.0660	7895	54.9	1383	0.4	0.0089
2	84.0811	7735	86.0	2149	0.6	0.0109
3	86.0968	8159	410.0	10233	2.7	0.0106
4	122.0956	8921	125.4	3016	0.8	0.0137
5	132.1011	8967	1538.4	36616	9.8	0.0147
6	133.1042	8734	104.9	2493	0.7	0.0152
7	217.1306	9540	63.4	1361	0.4	0.0228
8	226.1525	9775	385.8	8171	2.2	0.0231
9	226.9460	10319	155.9	3297	0.9	0.0220
10	227.1557	9355	50.0	1058	0.3	0.0243
11	229.6572	10727	119.4	2516	0.7	0.0214
12	243.6543	11358	61.6	1270	0.3	0.0215
13	245.1254	9931	76.8	1579	0.4	0.0247
14	245.1825	9709	83.5	1715	0.5	0.0253
15	261.1564	9617	71.2	1427	0.4	0.0272
16	286.1976	11277	90.2	1746	0.5	0.0254
17	300.1957	10584	1047.2	19865	5.3	0.0284
18	300.6968	10557	420.6	7970	2.1	0.0285
19	301.1980	11244	95.2	1802	0.5	0.0268
20	308.1931	10247	56.2	1051	0.3	0.0301
21	309.2007	10606	20020.6	374123	100.0	0.0292
22	309.7022	10496	7685.0	143562	38.4	0.0295
23	310.2036	10372	1706.2	31859	8.5	0.0299
24	310.7048	10828	275.2	5137	1.4	0.0287
25	316.2075	10340	63.3	1163	0.3	0.0306
26	355.2076	10565	89.2	1507	0.4	0.0336
27	373.2185	9960	259.3	4249	1.1	0.0375
28	392.2485	10246	262.8	4207	1.1	0.0383
29	392.6510	11276	121.4	1942	0.5	0.0348
30	393.2525	9565	65.0	1038	0.3	0.0411
31	395.2411	11368	94.5	1505	0.4	0.0348
32	486.2995	10526	2583.6	38343	10.2	0.0462
33	487.3020	10507	783.2	11609	3.1	0.0464

#	m/z	Res.	S/N	I	I %	FWHM
34	488.3057	10139	142.4	2108	0.6	0.0482
35	617.3901	10734	17901.3	271089	72.5	0.0575
36	618.3933	10796	6913.4	104731	28.0	0.0573
37	619.3965	10401	1385.2	20989	5.6	0.0596
38	620.3997	10749	228.6	3464	0.9	0.0577
39	633.3863	10517	68.5	1045	0.3	0.0602
40	639.3724	10392	159.7	2437	0.7	0.0615
41	643.8466	11134	199.7	3055	0.8	0.0578
42	644.3485	10987	169.1	2587	0.7	0.0586
43	644.8494	10951	82.9	1268	0.3	0.0589
44	898.2806	10496	93.0	1311	0.4	0.0856
45	952.0361	11311	105.6	1411	0.4	0.0842
46	952.5360	11952	131.4	1756	0.5	0.0797
47	953.0394	11214	80.7	1078	0.3	0.0850
48	1233.7666	11106	962.3	11258	3.0	0.1111
49	1234.7698	10911	686.0	8026	2.1	0.1132
50	1235.7741	10012	264.0	3089	0.8	0.1234

Figure S102: HR-MS analysis of Lys-D-Pro-Phe-Ile-Leu **26** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	70.0662	7387	380.2	11082	0.7	0.0095
2	85.0874	7792	298.0	8435	0.5	0.0109
3	86.0966	7601	3139.9	88749	5.3	0.0113
4	132.1010	8443	10968.4	300253	17.8	0.0156
5	133.1042	8393	745.9	20357	1.2	0.0159
6	217.1312	9158	417.7	10335	0.6	0.0237
7	226.1524	9435	445.7	11001	0.7	0.0240
8	227.1586	9338	1293.8	31907	1.9	0.0243
9	228.1645	9356	1178.8	29057	1.7	0.0244
10	230.1608	9663	394.8	9714	0.6	0.0238
11	230.6633	10093	404.5	9945	0.6	0.0229
12	245.1257	9232	500.1	12251	0.7	0.0266
13	245.1815	9372	482.6	11821	0.7	0.0262
14	261.1564	9593	503.9	12410	0.7	0.0272
15	300.1958	10038	1067.8	26437	1.6	0.0299
16	300.6986	10094	3458.3	85641	5.1	0.0298
17	301.2012	9981	3754.5	93008	5.5	0.0302
18	301.7026	9914	1227.5	30409	1.8	0.0304
19	309.2008	10108	19155.1	474462	28.1	0.0306
20	309.7039	10013	62158.1	1540071	91.2	0.0309
21	310.0152	9783	408.3	10115	0.6	0.0317
22	310.2066	9896	68146.3	1688898	100.0	0.0313
23	310.5207	10947	387.7	9609	0.6	0.0284
24	310.6332	11606	569.9	14127	0.8	0.0268
25	310.7081	9925	22368.0	554467	32.8	0.0313
26	311.2095	9860	4635.7	114918	6.8	0.0316
27	311.7112	10067	698.2	17307	1.0	0.0310
28	358.2090	8941	319.6	7809	0.5	0.0401
29	374.2247	9562	698.7	16984	1.0	0.0391
30	375.2295	9926	674.4	16390	1.0	0.0378
31	392.2486	10090	1430.0	34845	2.1	0.0389
32	393.2519	9566	336.8	8211	0.5	0.0411
33	408.2430	9739	416.0	10130	0.6	0.0419
#	m/z	Res.	S/N	I	I %	FWHM
34	486.2995	10176	2114.6	50440	3.0	0.0478
35	487.3051	10065	6742.5	160672	9.5	0.0484
36	488.3108	10109	6990.0	166362	9.9	0.0483
37	489.3142	9896	1878.3	44660	2.6	0.0494
38	617.3905	10246	19423.6	401223	23.8	0.0603
39	618.3968	10060	62460.0	1289429	76.3	0.0615
40	618.8336	18751	509.8	10520	0.6	0.0330
41	619.4024	10015	68368.7	1410356	83.5	0.0618
42	620.4052	10141	22236.6	458363	27.1	0.0612
43	621.4082	10266	4495.5	92611	5.5	0.0605
44	622.4114	9973	635.9	13093	0.8	0.0624
45	1234.7722	10390	1750.2	23643	1.4	0.1188
46	1235.7764	10716	5192.4	70145	4.2	0.1153
47	1236.7818	10758	7573.3	102316	6.1	0.1150
48	1237.7866	10685	6123.0	82729	4.9	0.1158
49	1238.7902	10652	2893.5	39095	2.3	0.1163
50	1239.7952	10171	820.8	11091	0.7	0.1219

Figure S103: HR-MS analysis of Lys-D-Pro-Phe-Ile-Leu [D]-26.

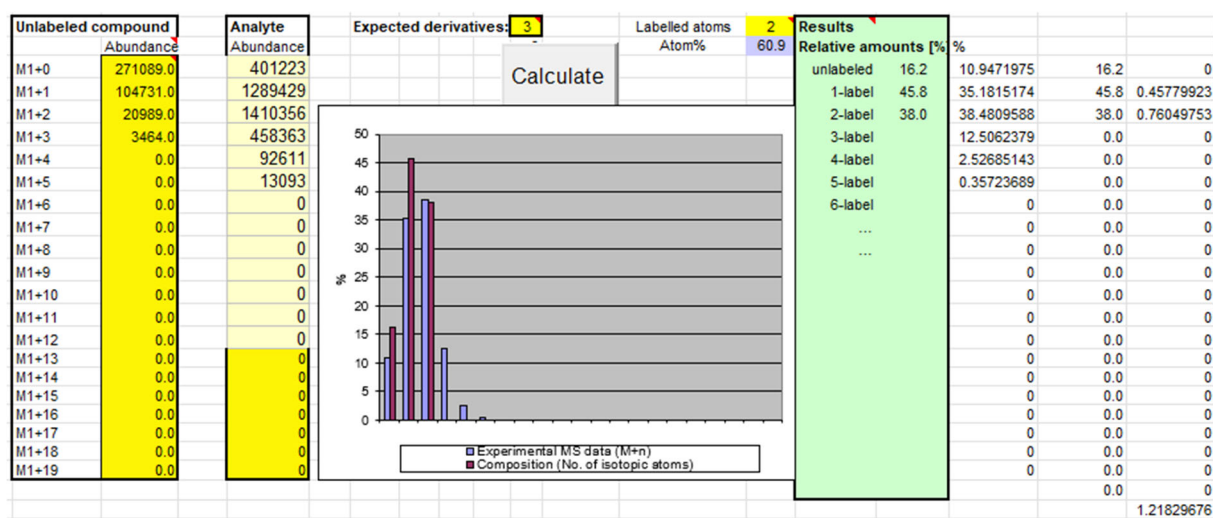
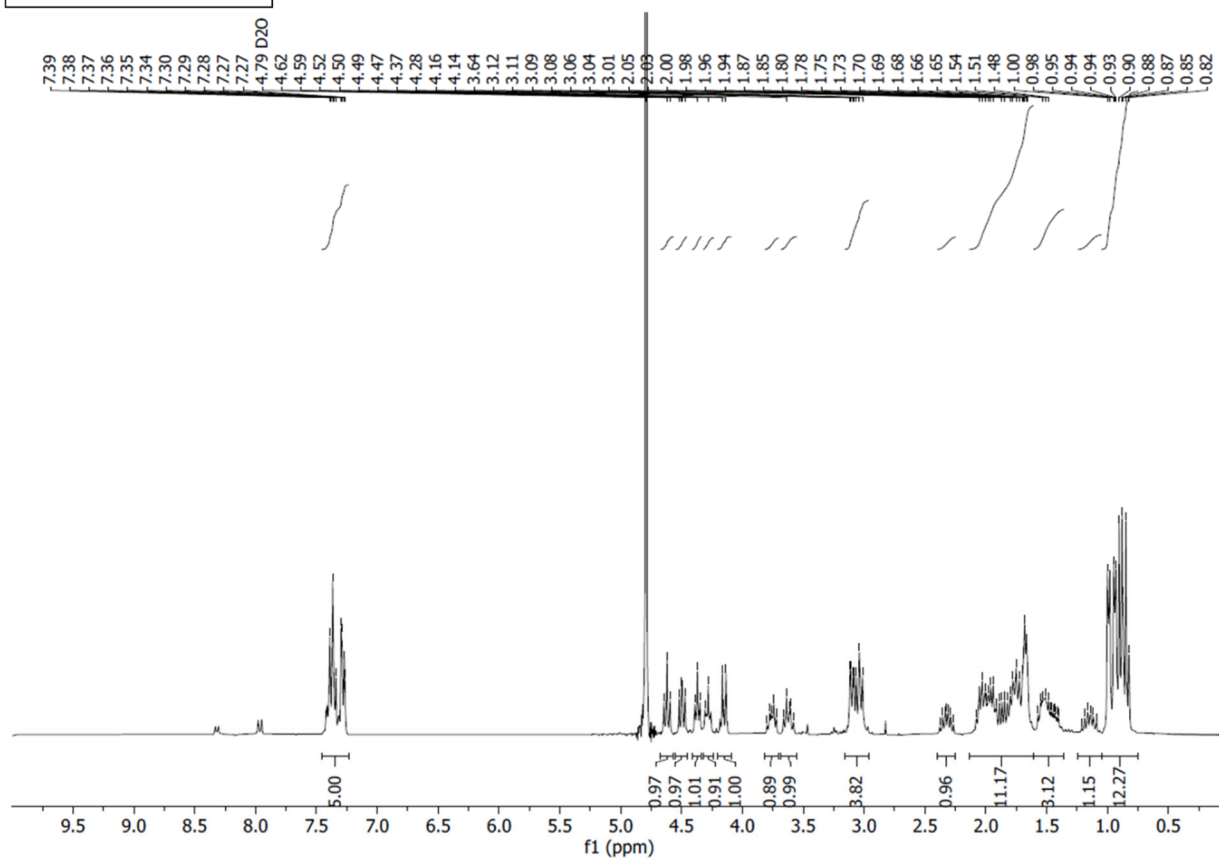


Figure S104: Calculation of deuterium content in Lys-D-Pro-Phe-Ile-Leu 26.

¹H-NMR Reference 26



¹H-NMR HIE Reaction [D]-26

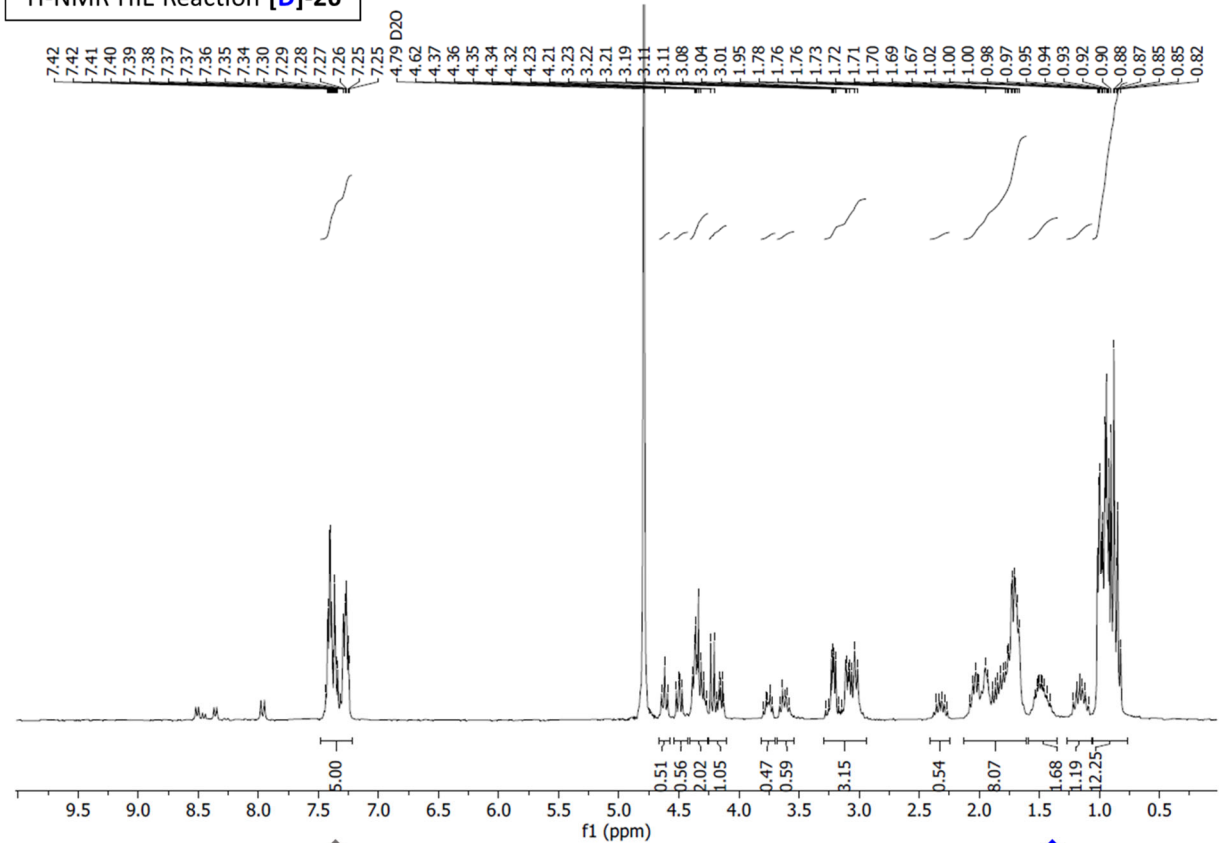


Figure S105: ¹H-NMR spectra of the HIE reaction of compound 26 to yield the deuterated product [D]-26.

^2H -NMR HIE Reaction [D]-26

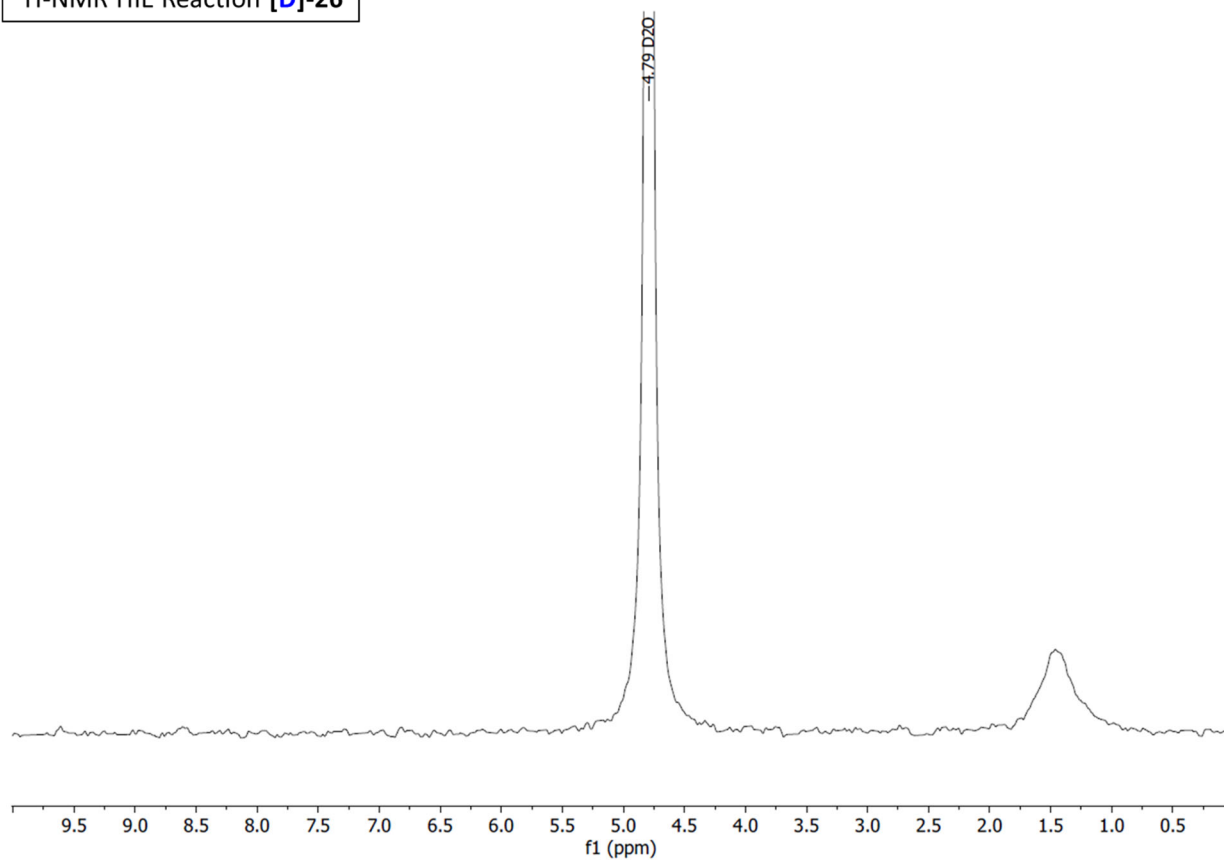
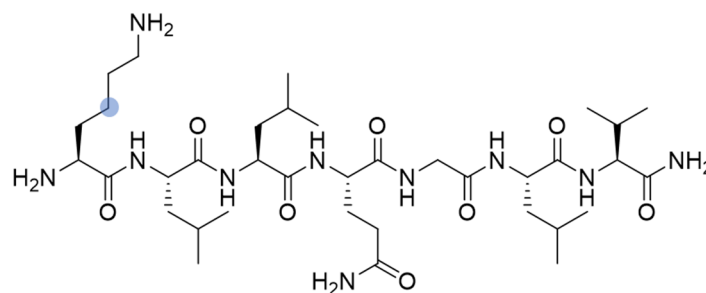


Figure S106: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-26.

7.2.8 Lys-Leu-Leu-Gln-Gly-Leu-Val-NH₂ **27**



27

Chemical Formula: C₃₆H₆₈N₁₀O₈
Exact Mass: 768.52

Figure S107: Structure of Lys-Leu-Leu-Gln-Gly-Leu-Val-NH₂ **27**.

Method B: 15 mg, 0.02 mmol **27**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%).

HR-MS (ESI⁺): *m/z* [M+H⁺] mass calc. for C₃₂H₅₂N₆O₆: 769.5294; found: 769.5142.

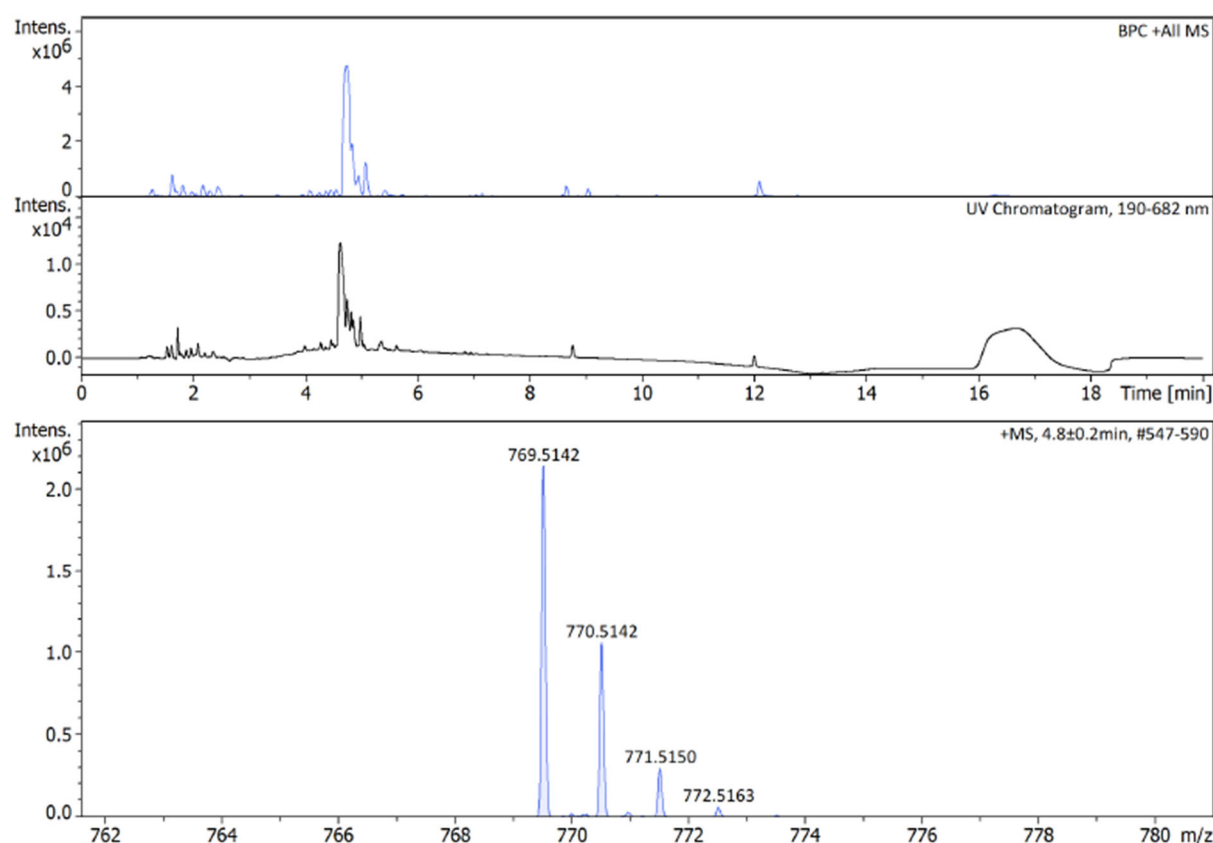
¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 4.43-4.34 (m, 3H), 4.14-4.10 (m, 1H), 4.03 (t, *J* = 6.5 Hz, 1H), 4.01-3.96 (s, 1H), 3.02 (t, *J* = 7.7 Hz, 1H), 2.38 (t, *J* = 7.5 Hz, 1H), 2.20-1.84 (m, 4H), 1.80-1.53 (m, 7H), 1.49-1.42 (m, 2H), 1.05-0.81 (m, 15H). Incorporation expected at δ 1.49-1.42 (blue arrow, blue dot in the structure). Determined against integral at δ 1.05-0.81 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by HR-MS: 0.46 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 0.39 D/molecule for δ 1.49-1.42

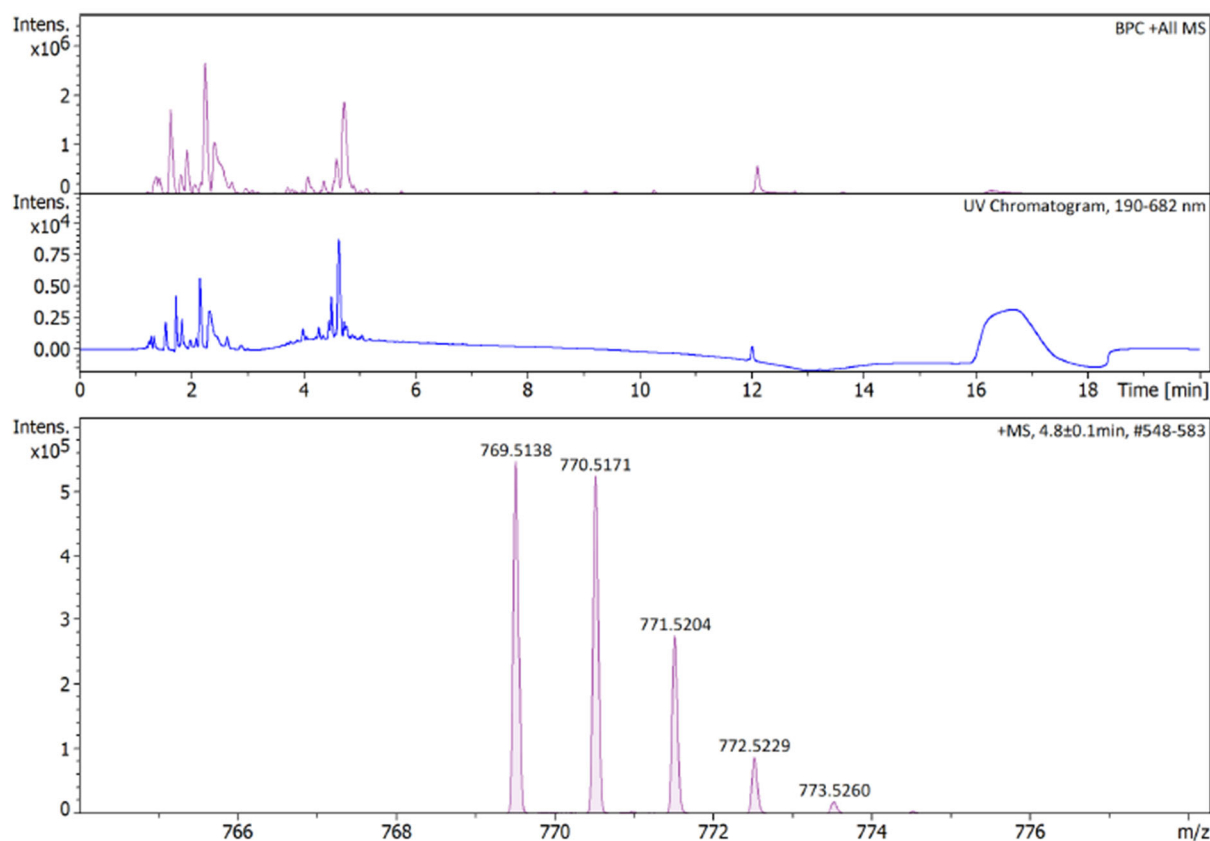
Yield: obtained as TFA salt, 20 mg, 20 μmol, 34%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	72.0816	7754	699.0	20566	0.6	0.0093
2	84.0812	7959	848.8	24267	0.7	0.0106
3	86.0967	8177	340.2	9675	0.3	0.0105
4	117.1017	8451	2359.1	64951	2.0	0.0139
5	327.2165	10495	307.7	13279	0.4	0.0312
6	362.7524	10705	298.7	14856	0.5	0.0339
7	368.2367	10395	176.6	8925	0.3	0.0354
8	376.7497	10539	10367.3	535889	16.3	0.0357
9	377.2497	10129	5453.5	281906	8.6	0.0372
10	377.7504	10207	1613.8	83438	2.5	0.0370
11	378.2509	10082	312.0	16146	0.5	0.0375
12	383.7570	10694	176.5	9240	0.3	0.0359
13	385.2636	9923	62871.1	3295634	100.0	0.0388
14	385.5126	19310	289.9	15196	0.5	0.0200
15	385.6102	12737	702.9	36847	1.1	0.0303
16	385.7632	10134	33522.7	1757424	53.3	0.0381
17	386.0112	13560	413.9	21699	0.7	0.0285
18	386.2640	9727	9868.4	517339	15.7	0.0397
19	386.7646	9959	2083.5	109222	3.3	0.0388
20	387.2654	9856	303.6	15915	0.5	0.0393
21	391.2622	10685	163.0	8574	0.3	0.0366
22	392.2705	10659	3668.3	193118	5.9	0.0368
23	392.7707	10387	1959.7	103157	3.1	0.0378
24	393.2701	10105	625.6	32940	1.0	0.0389
25	393.7666	9027	165.7	8727	0.3	0.0436
26	399.2761	9799	239.4	12639	0.4	0.0407
27	400.2687	9702	223.6	11809	0.4	0.0413
28	407.7677	10953	268.2	14179	0.4	0.0372
29	540.3410	10134	165.0	9121	0.3	0.0533
30	543.3401	10193	239.3	13238	0.4	0.0533
31	653.4215	10873	1518.7	74218	2.3	0.0601
32	654.4212	10227	682.7	33336	1.0	0.0640
33	752.4859	10837	339.3	14829	0.4	0.0694

#	m/z	Res.	S/N	I	I %	FWHM
34	769.5142	10182	50032.7	2145700	65.1	0.0756
35	770.0010	15235	489.5	20986	0.6	0.0505
36	770.2427	7823	351.8	15082	0.5	0.0985
37	770.5142	10305	24726.6	1059724	32.2	0.0748
38	770.9735	8115	620.7	26590	0.8	0.0950
39	771.5150	10314	6940.9	297201	9.0	0.0748
40	772.5163	10578	1385.9	59306	1.8	0.0730
41	783.5277	10936	2244.4	94433	2.9	0.0716
42	784.5293	10812	1119.9	47044	1.4	0.0726
43	785.5281	10333	332.2	13930	0.4	0.0760
44	1153.7629	11637	1859.9	41490	1.3	0.0991
45	1154.2645	11612	2600.8	58012	1.8	0.0994
46	1154.7649	11530	1911.4	42634	1.3	0.1002
47	1155.2641	11360	1029.9	22969	0.7	0.1017
48	1155.7621	10955	457.1	10193	0.3	0.1055
49	1538.0121	11375	722.2	12873	0.4	0.1352
50	1539.0147	11175	776.3	13837	0.4	0.1377

Figure S108: HR-MS analysis of Lys-Leu-Leu-Gln-Gly-Leu-Val-NH₂ **27** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	72.0817	7575	416.1	9716	0.8	0.0095
2	84.0812	7775	386.6	8835	0.8	0.0108
3	86.0963	7399	269.5	6126	0.5	0.0116
4	117.1018	8352	1516.8	32656	2.8	0.0140
5	182.1884	9258	316.3	6194	0.5	0.0197
6	243.6830	10102	216.1	3979	0.3	0.0241
7	299.1680	9149	265.1	4601	0.4	0.0327
8	327.2168	10403	260.5	4540	0.4	0.0315
9	362.7535	10497	272.5	4913	0.4	0.0346
10	363.2545	9804	251.8	4543	0.4	0.0371
11	376.7502	10231	9495.1	173679	15.1	0.0368
12	377.2519	10050	9134.4	167025	14.5	0.0375
13	377.7535	9950	4814.0	88006	7.6	0.0380
14	378.2546	9980	1491.5	27261	2.4	0.0379
15	378.7557	9682	335.3	6131	0.5	0.0391
16	383.7573	9963	456.4	8384	0.7	0.0385
17	384.2576	9599	352.2	6474	0.6	0.0400
18	385.2635	10096	62592.2	1151237	100.0	0.0382
19	385.6101	7662	272.9	5019	0.4	0.0503
20	385.7650	9883	62006.8	1140372	99.1	0.0390
21	386.0146	12075	242.6	4461	0.4	0.0320
22	386.2666	9674	33150.7	609439	52.9	0.0399
23	386.7677	9587	11052.9	203176	17.6	0.0403
24	387.2690	9740	2492.6	45819	4.0	0.0398
25	387.7696	9687	420.5	7736	0.7	0.0400
26	391.2628	10659	518.3	9541	0.8	0.0367
27	391.7608	10044	482.4	8881	0.8	0.0390
28	392.2708	10293	11624.6	214139	18.6	0.0381
29	392.7709	9914	7331.6	135087	11.7	0.0396
30	393.2717	9780	2492.3	45933	4.0	0.0402
31	393.7720	9493	592.5	10918	0.9	0.0415
32	399.2788	10101	715.5	13193	1.1	0.0395
33	399.7772	9987	464.2	8556	0.7	0.0400

#	m/z	Res.	S/N	I	I %	FWHM
34	400.2735	9378	291.4	5368	0.5	0.0427
35	653.4226	10284	1353.6	23568	2.0	0.0635
36	654.4258	10044	1217.2	21176	1.8	0.0652
37	655.4294	9592	569.5	9902	0.9	0.0683
38	769.5138	10340	34088.8	547611	47.6	0.0744
39	770.5171	10084	32686.5	524729	45.6	0.0764
40	771.5204	10086	17155.6	275247	23.9	0.0765
41	772.5229	10000	5418.4	86869	7.5	0.0773
42	773.5260	10178	1114.9	17866	1.6	0.0760
43	783.5281	10600	5462.1	87170	7.6	0.0739
44	784.5298	10294	3185.0	50797	4.4	0.0762
45	785.5317	9982	978.9	15602	1.4	0.0787
46	797.5438	10036	257.9	4052	0.4	0.0795
47	1154.2694	10776	545.1	6352	0.6	0.1071
48	1154.7707	10946	788.3	9187	0.8	0.1055
49	1155.2730	11182	764.7	8912	0.8	0.1033
50	1155.7734	10747	538.5	6276	0.5	0.1075

Figure S109: HR-MS analysis of Lys-Leu-Leu-Gln-Gly-Leu-Val-NH₂ [D]-27.

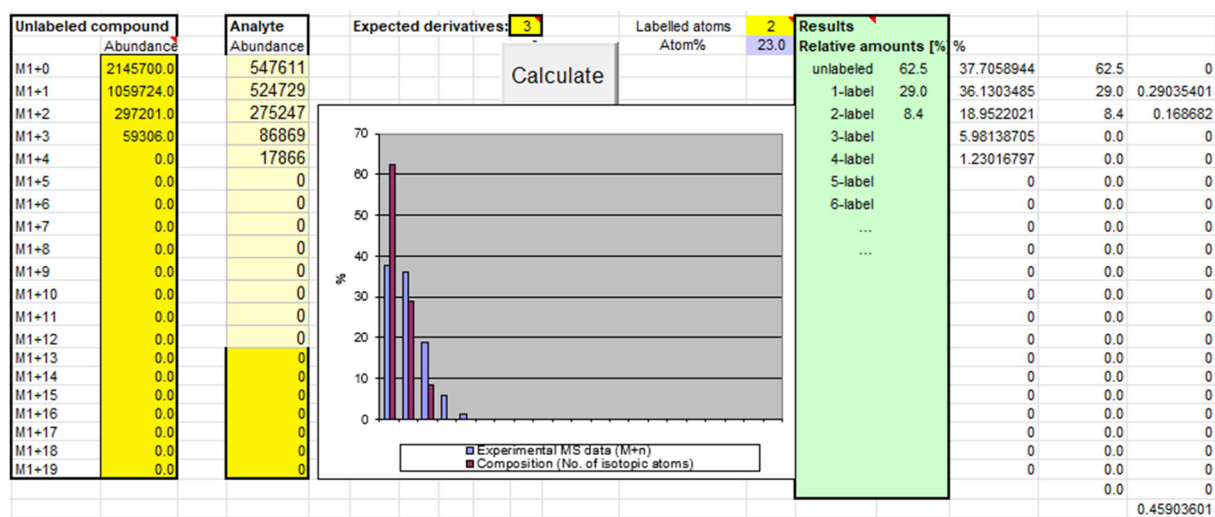


Figure S110: Calculation of deuterium content in Lys-Leu-Leu-Gln-Gly-Leu-Val-NH₂ [D]-27.

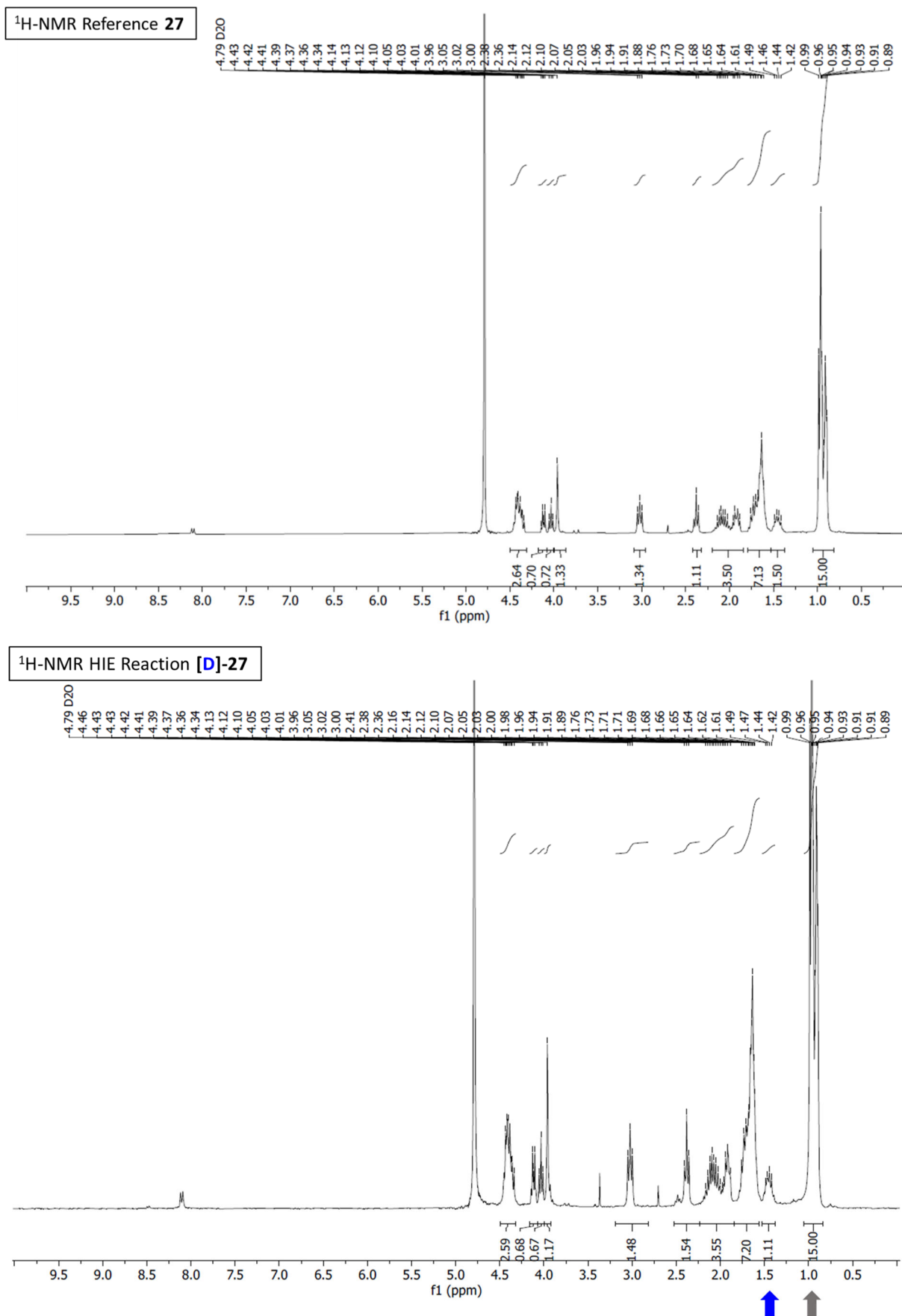


Figure S111: ¹H-NMR spectra of the HIE reaction of compound **27** to yield the deuterated product **[D]-27**.

^2H -NMR HIE Reaction [D]-27

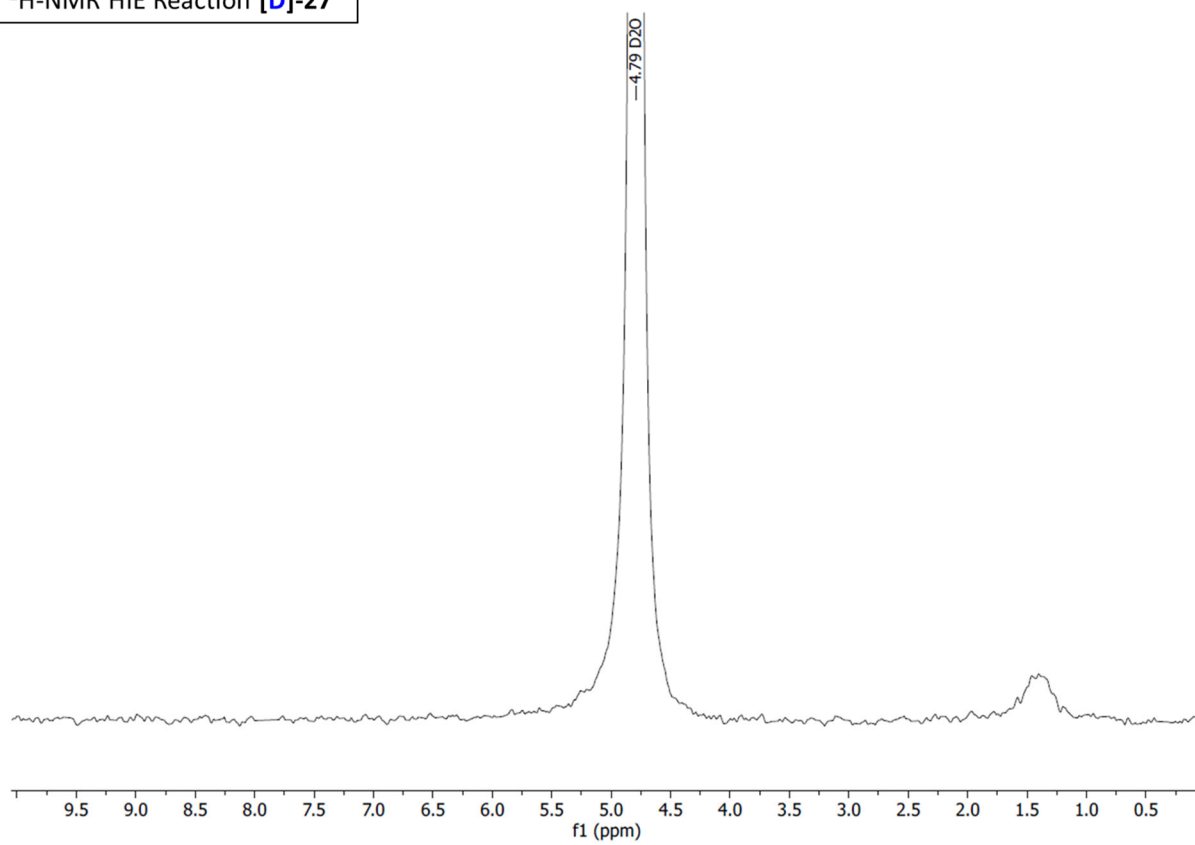


Figure S112: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-27.

7.2.9 Lys-Pro-Ile-Thr-Val **28**

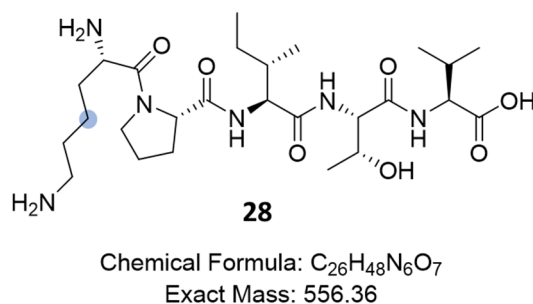


Figure S113: Structure of Lys-Pro-Ile-Thr-Val **28**.

Method A: 11 mg, 0.02 mmol **28**, 0.5 μ mol catalyst **C4** (2.5 mol%), 1 μ mol ligand **L11** (5 mol%).

HR-MS (ESI⁺): m/z [M+H]⁺ mass calc. for C₂₆H₄₈N₆O₇: 557.3657; found: 557.3563.

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 4.51 (t, J = 7.1 Hz, 1H), 4.41-4.30 (m, 2H), 4.25 (d, J = 5.9 Hz, 1H), 4.20-4.08 (m, 2H), 3.76-3.68 (m, 1H), 3.62-3.50 (m, 1H), 2.99 (t, J = 7.7 Hz, 2H), 2.37-2.10 (m, 2H), 2.06-1.76 (m, 6H), 1.75-1.62 (m, 2H), 1.60-1.42 (m, 3H), 1.17 (d, J = 6.3 Hz, 4H), 0.96-0.78 (m, 12H).

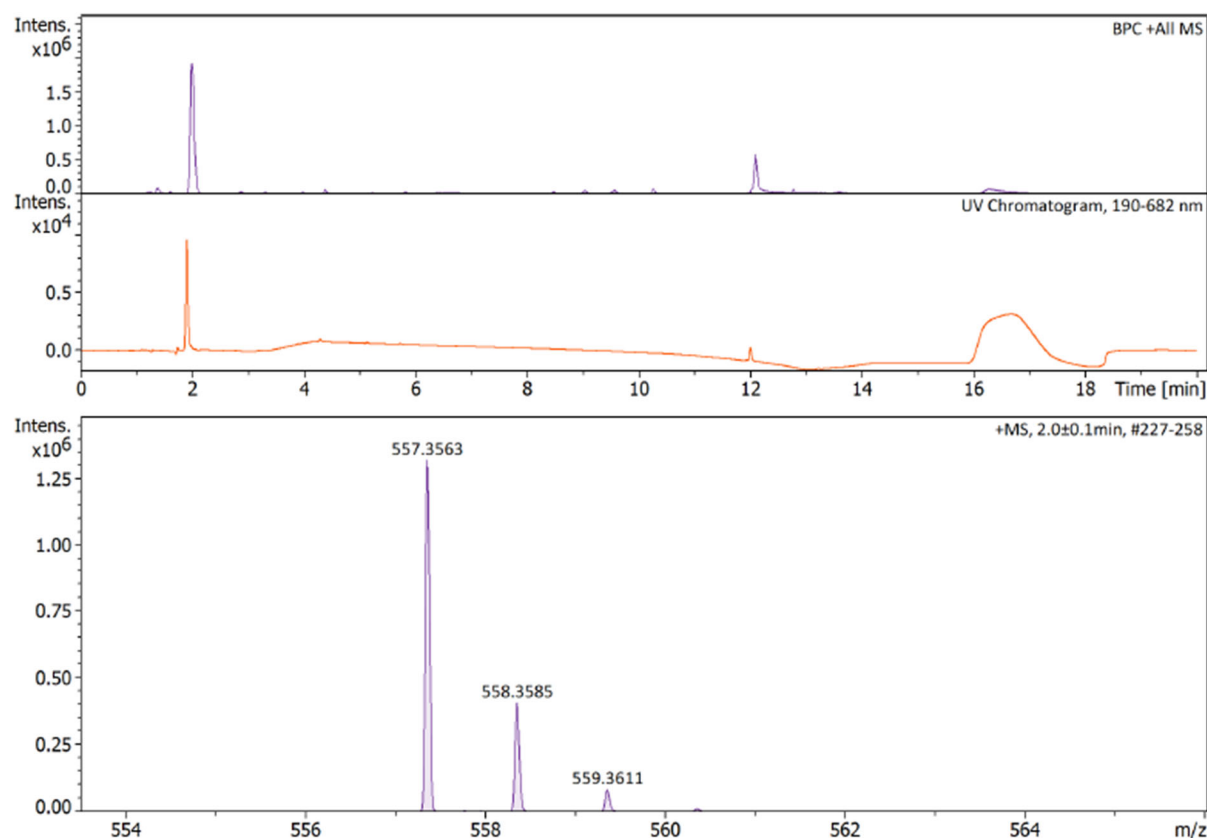
Incorporation expected at δ 1.60-1.42 (blue arrow, blue dot in the structure). Determined against integral at δ 0.96-0.78 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by LC-MS: 1.15 D/molecule.

Deuterium incorporation determined by ¹H-NMR: 1.06 D/molecule for δ 1.60-1.42

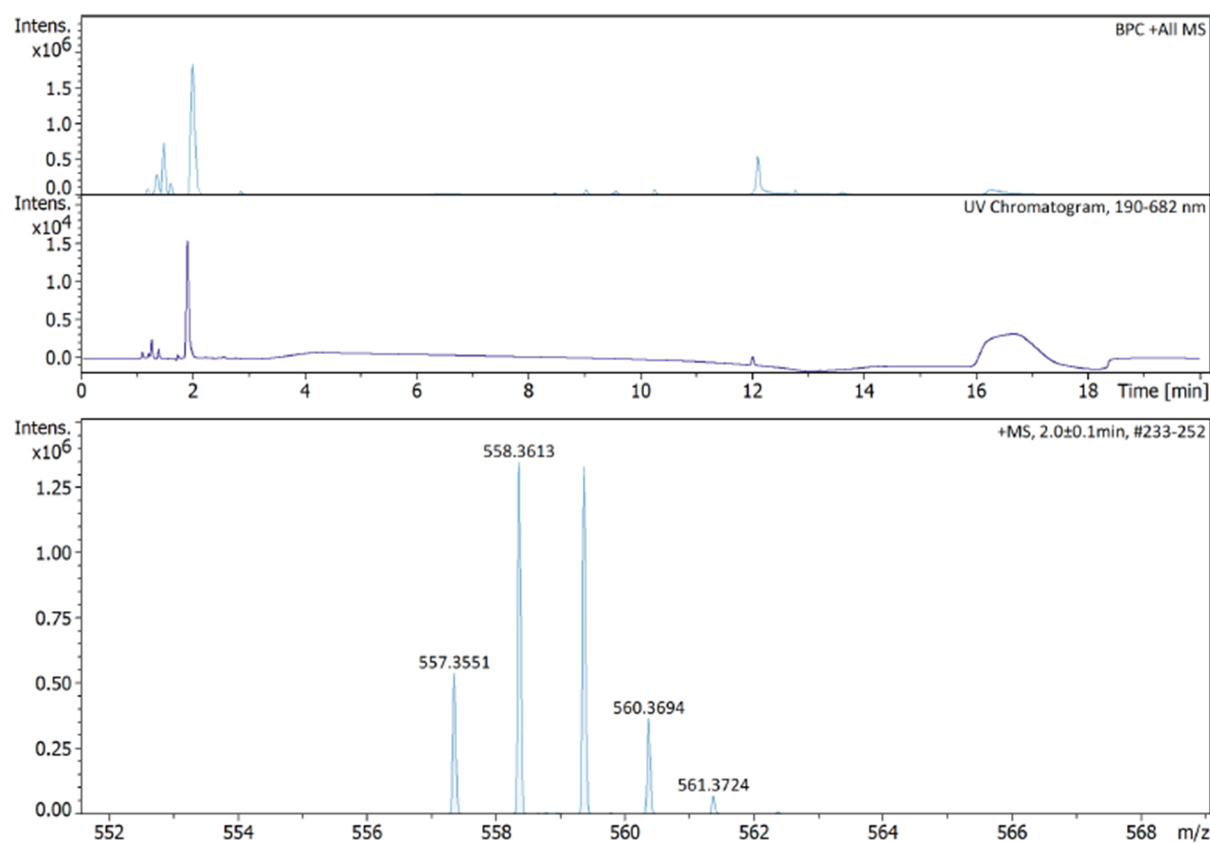
Yield: obtained as TFA salt, 12 mg, 15 μ mol, 25%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	70.0660	7321	223.8	6595	0.5	0.0096
2	72.0816	7697	1420.1	41747	3.0	0.0094
3	84.0811	7836	342.7	9951	0.7	0.0107
4	86.0969	8117	95.3	2760	0.2	0.0106
5	118.0856	8576	3928.3	114275	8.2	0.0138
6	119.0887	8465	234.6	6823	0.5	0.0141
7	129.1012	9000	101.5	2956	0.2	0.0143
8	183.1474	8944	148.3	4138	0.3	0.0205
9	215.1366	9685	198.8	5439	0.4	0.0222
10	219.1315	9568	1070.0	29218	2.1	0.0229
11	220.1406	6056	126.7	3460	0.2	0.0364
12	220.6454	10054	401.9	10969	0.8	0.0219
13	221.1455	9366	107.5	2932	0.2	0.0236
14	226.1524	9797	1092.2	29702	2.1	0.0231
15	227.1550	9609	142.2	3866	0.3	0.0236
16	256.1810	10247	856.6	22994	1.6	0.0250
17	256.6824	10068	253.6	6803	0.5	0.0255
18	257.1777	7519	108.5	2910	0.2	0.0342
19	261.1729	10440	1185.3	31727	2.3	0.0250
20	261.6734	10033	410.5	10988	0.8	0.0261
21	270.1781	10460	2457.8	65326	4.7	0.0258
22	270.6786	10144	868.8	23079	1.7	0.0267
23	271.1784	9946	186.7	4958	0.4	0.0273
24	279.1832	10246	53057.5	1394942	100.0	0.0272
25	279.4788	8314	106.0	2787	0.2	0.0336
26	279.6847	10159	16962.8	445796	32.0	0.0275
27	280.1862	10194	3430.5	90115	6.5	0.0275
28	280.6874	10343	478.8	12569	0.9	0.0271
29	286.1909	10511	466.0	12062	0.9	0.0272
30	286.6924	10245	148.3	3832	0.3	0.0280
31	321.2243	9728	198.3	4660	0.3	0.0330
32	332.2134	10128	749.0	17370	1.2	0.0328
33	333.2164	10150	130.3	3018	0.2	0.0328

#	m/z	Res.	S/N	I	I%	FWHM
34	339.2344	10081	1581.9	36489	2.6	0.0337
35	340.2375	9754	307.7	7091	0.5	0.0349
36	422.2701	10382	568.1	12111	0.9	0.0407
37	423.2670	8740	199.4	4249	0.3	0.0484
38	440.2797	10390	6888.7	143581	10.3	0.0424
39	441.2827	10218	1707.2	35531	2.5	0.0432
40	442.2861	10210	274.4	5703	0.4	0.0433
41	557.3563	10351	72852.9	1321423	94.7	0.0538
42	557.7697	12538	164.4	2981	0.2	0.0445
43	558.3585	10416	22433.4	406791	29.2	0.0536
44	559.3611	10548	4486.5	81332	5.8	0.0530
45	560.3640	10522	640.0	11597	0.8	0.0533
46	571.3716	10396	436.2	7863	0.6	0.0550
47	1113.6972	11078	6256.9	89190	6.4	0.1005
48	1114.7000	10958	3953.4	56355	4.0	0.1017
49	1115.7051	11041	1305.9	18616	1.3	0.1011
50	1116.7070	10018	294.4	4199	0.3	0.1115

Figure S114: HR-MS analysis of Lys-Pro-Ile-Thr-Val **28** (reference).



#	m/z	Res.	S/N	I	I %	FWHM
1	70.0660	7440	414.4	12235	0.9	0.0094
2	72.0816	7640	2601.5	76574	5.7	0.0094
3	86.0947	7554	394.8	11530	0.9	0.0114
4	118.0855	8428	6908.1	206337	15.3	0.0140
5	119.0886	8441	411.7	12304	0.9	0.0141
6	215.1365	9822	355.8	10004	0.7	0.0219
7	219.1312	9710	1903.4	53531	4.0	0.0226
8	221.1484	9064	376.0	10586	0.8	0.0244
9	226.1523	9852	395.7	11124	0.8	0.0230
10	227.1582	9620	887.5	24936	1.9	0.0236
11	228.1641	9594	791.7	22224	1.6	0.0238
12	256.6834	10545	787.1	21836	1.6	0.0243
13	257.1858	10526	781.8	21677	1.6	0.0244
14	261.1725	10863	446.5	12353	0.9	0.0240
15	261.6751	10455	1054.0	29151	2.2	0.0250
16	262.1778	10317	1054.8	29162	2.2	0.0254
17	270.1777	10798	887.8	24389	1.8	0.0250
18	270.6804	10551	2250.1	61785	4.6	0.0257
19	271.1829	10243	2215.4	60804	4.5	0.0265
20	271.6837	10025	679.3	18635	1.4	0.0271
21	279.1827	10428	19062.6	516910	38.4	0.0268
22	279.6857	10307	47971.5	1300142	96.5	0.0271
23	280.1886	10286	47996.3	1300210	96.5	0.0272
24	280.6903	10169	13474.6	364958	27.1	0.0276
25	281.1917	10323	2527.2	68409	5.1	0.0272
26	286.1905	10569	892.6	23957	1.8	0.0271
27	286.6928	10644	603.1	16163	1.2	0.0269
28	332.2128	10160	1326.7	32184	2.4	0.0327
29	339.2340	10220	566.2	13673	1.0	0.0332
30	340.2398	10266	1322.7	31916	2.4	0.0331
31	341.2455	10095	1160.2	27972	2.1	0.0338
32	423.2744	10578	514.0	11654	0.9	0.0400
33	424.2792	9686	474.0	10742	0.8	0.0438
#	m/z	Res.	S/N	I	I %	FWHM
34	440.2792	10497	2381.8	52985	3.9	0.0419
35	441.2851	10504	5835.1	129626	9.6	0.0420
36	442.2907	10495	5498.3	121945	9.1	0.0421
37	443.2940	10357	1226.8	27168	2.0	0.0428
38	557.3551	10574	29166.1	539198	40.0	0.0527
39	558.3613	10402	72918.2	1347237	100.0	0.0537
40	559.3668	10395	72074.2	1330838	98.8	0.0538
41	560.3694	10437	19720.2	363983	27.0	0.0537
42	561.3724	10735	3697.0	68234	5.1	0.0523
43	571.3703	10803	906.5	16695	1.2	0.0529
44	572.3752	10708	624.0	11487	0.9	0.0535
45	1114.7010	11044	3394.2	53971	4.0	0.1009
46	1115.7067	11310	8028.0	127681	9.5	0.0986
47	1116.7122	10991	9920.2	157771	11.7	0.1016
48	1117.7171	11004	7046.1	112104	8.3	0.1016
49	1118.7215	11309	2810.1	44722	3.3	0.0989
50	1119.7243	10929	735.0	11701	0.9	0.1025

Figure S115: HR-MS analysis of Lys-Pro-Ile-Thr-Val [D]-28.

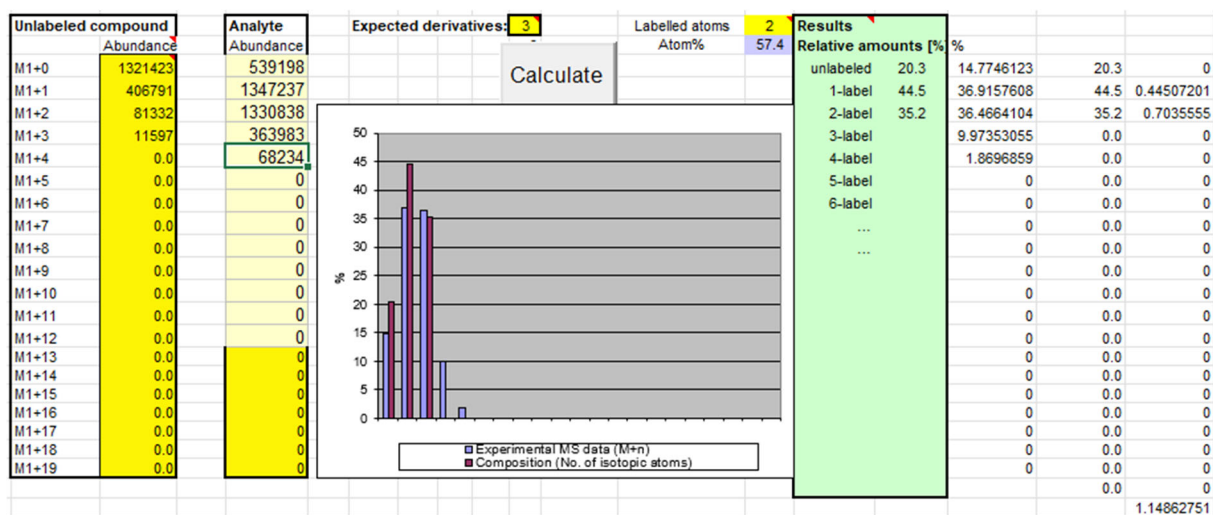
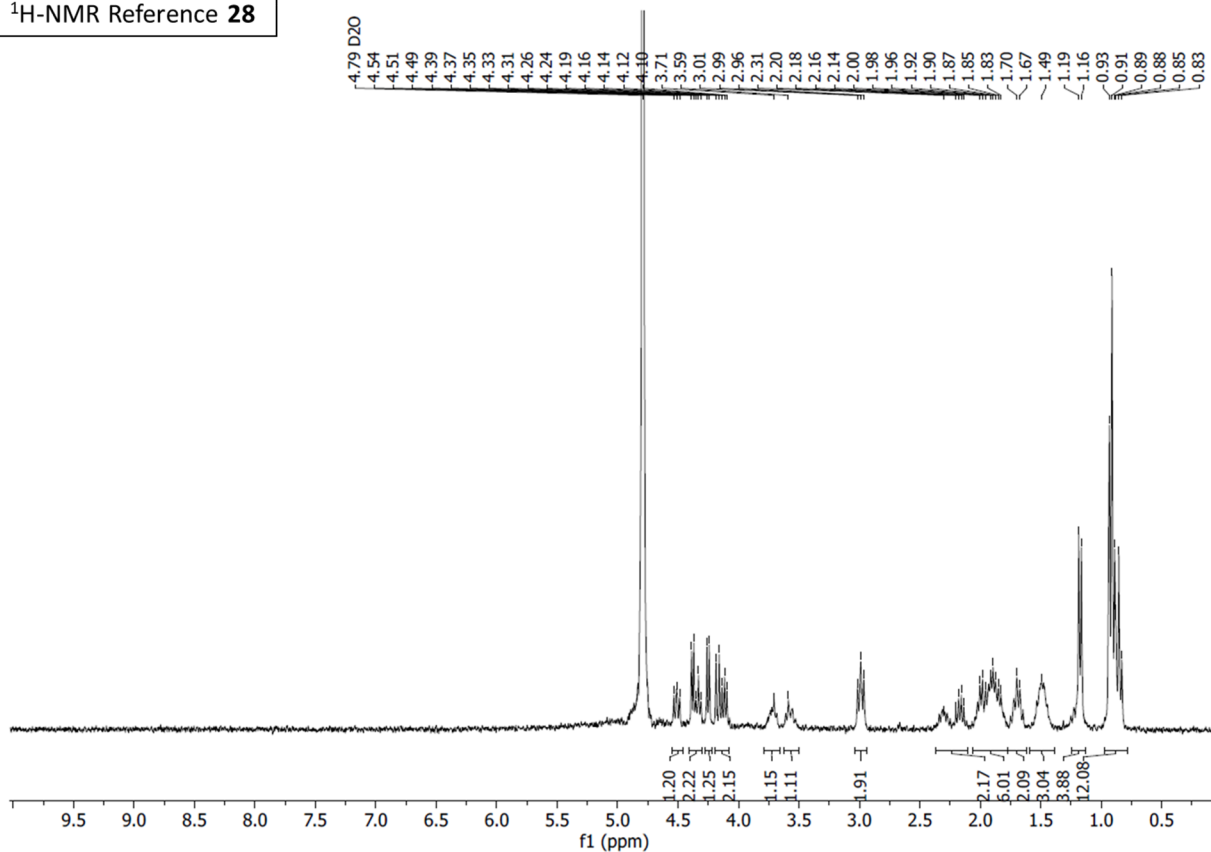


Figure S116: Calculation of deuterium content in Lys-Pro-Ile-Thr-Val [D]-28.

¹H-NMR Reference **28**



¹H-NMR HIE Reaction [**D**]-**28**

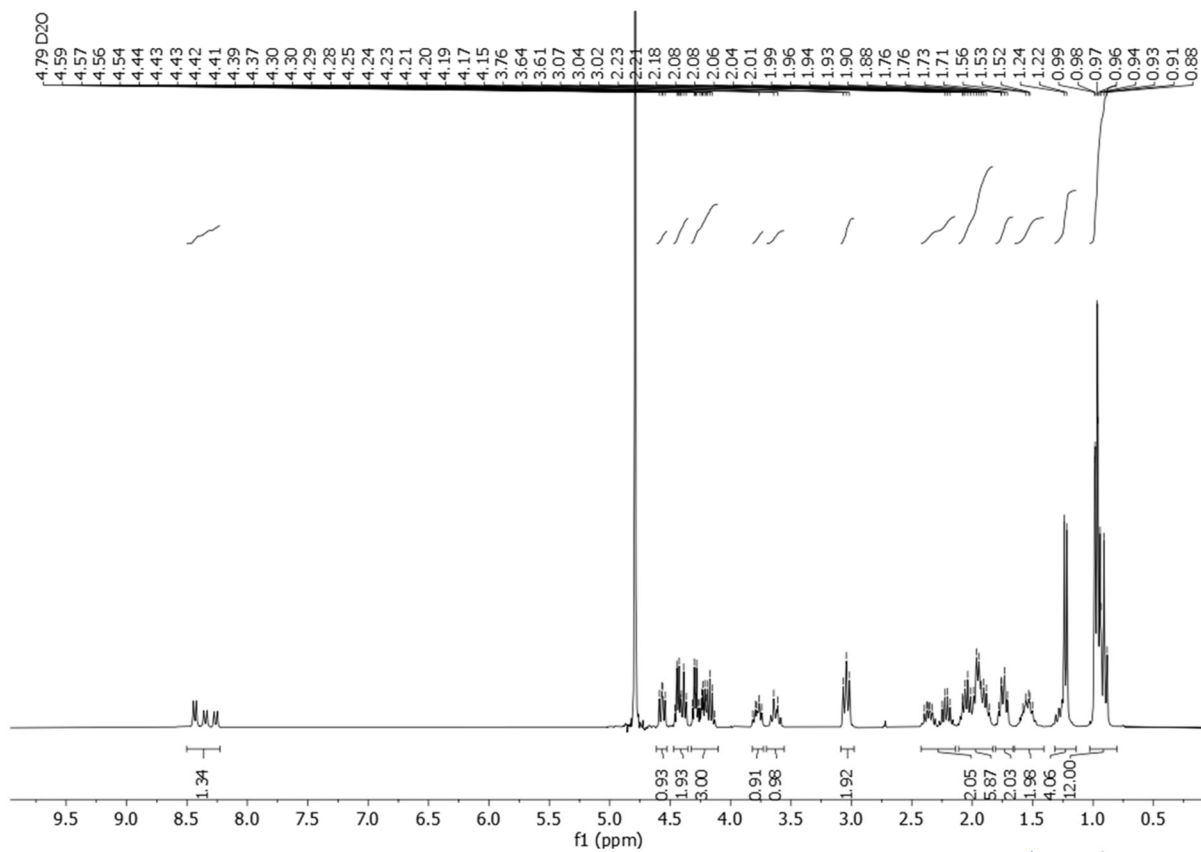


Figure S117: ¹H-NMR spectra of the HIE reaction of compound **28** to yield the deuterated product [**D**]-**28**.

^2H -NMR HIE Reaction [D]-28

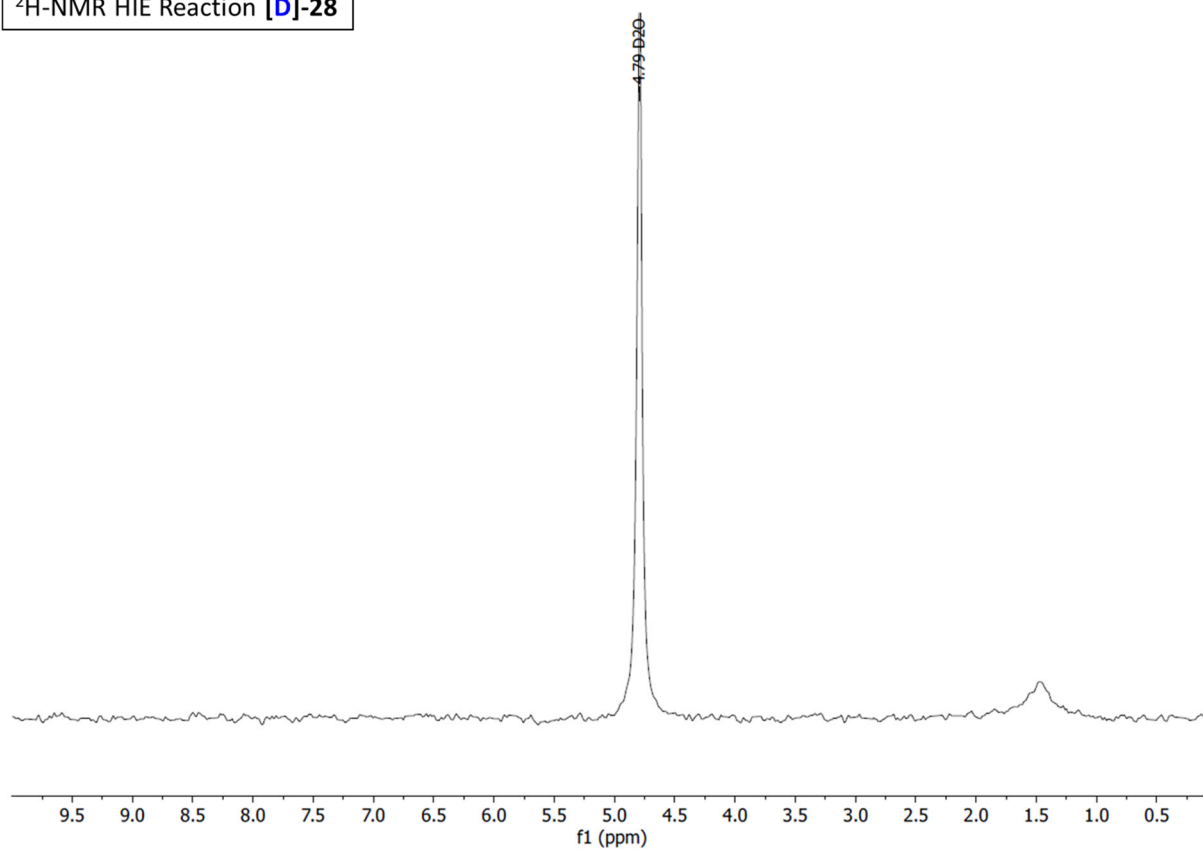
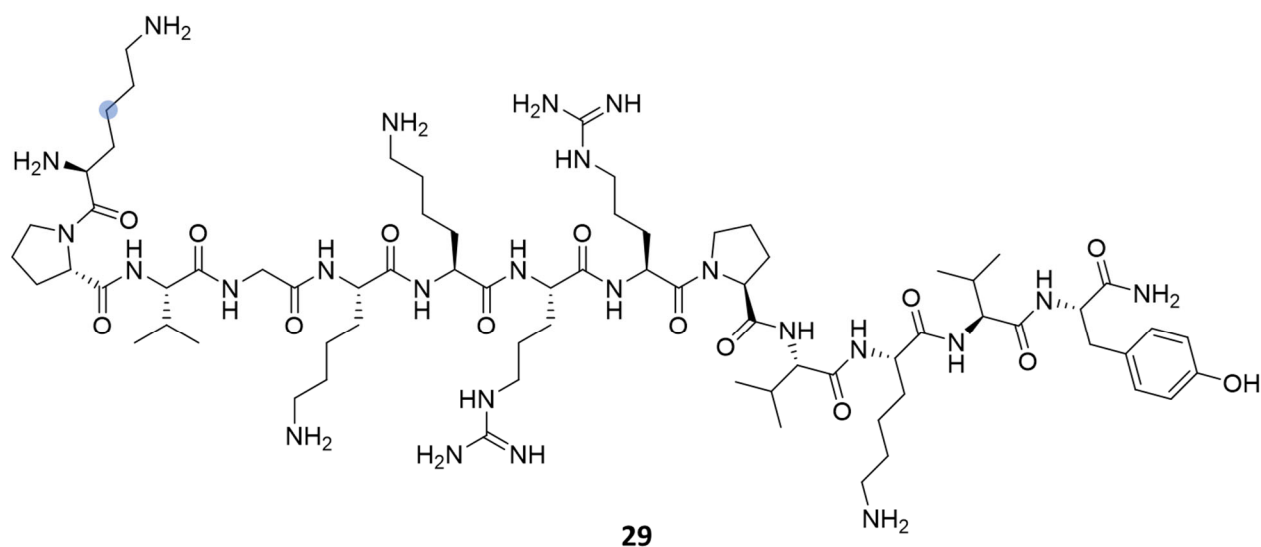


Figure S118: ^2H -NMR spectrum of the HIE reaction yielding the deuterated product [D]-28.

7.2.10 Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29**



Chemical Formula: C₇₂H₁₂₈N₂₄O₁₄
Exact Mass: 1553.00

Figure S119: Structure of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29**.

Method B: 23 mg, 0.02 mmol **29**, 0.5 μmol catalyst **C4** (2.5 mol%), 1 μmol ligand **L11** (5 mol%).

HR-MS (ESI⁺): m/z [M+2H]²⁺ mass calc. for C₇₂H₁₂₈N₂₄O₁₄: 777.5093; found: 777.4957.

¹H-NMR (300 MHz, D₂O+TFA): δ [ppm] = 7.22-7.11 (m, 2H), 6.90-6.78 (m, 2H), 4.67-4.42 (m, 6H), 4.42-4.24 (m, 9H), 4.17-3.71 (m, 14H), 3.71-3.56 (m, 4H), 3.29-3.17 (m, 4H), 3.09-2.86 (m, 16H), 2.44-2.23 (m, 4H), 2.21-1.17 (m, 71H), 1.09-0.77 (m, 26H).

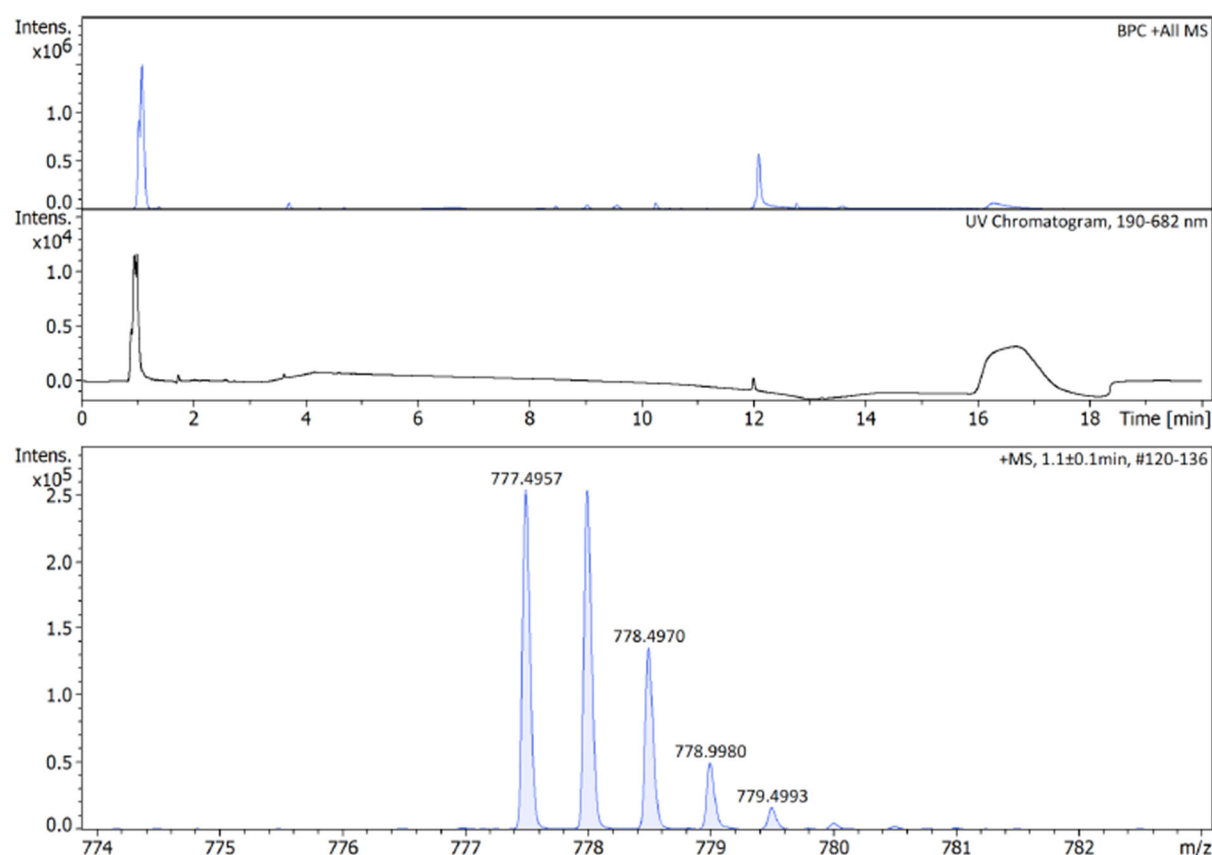
Incorporation expected at δ 2.21-1.17 (blue arrow, blue dot in the structure, position assigned as indicated by postulated mechanism). Determined against integral at δ 6.90-6.78 (grey arrow).

Results are determined as the average of three reactions.

Deuterium incorporation determined by HR-MS: 0.31 D/molecule.

Deuterium incorporation determined by ¹H-NMR: impossible to determine.

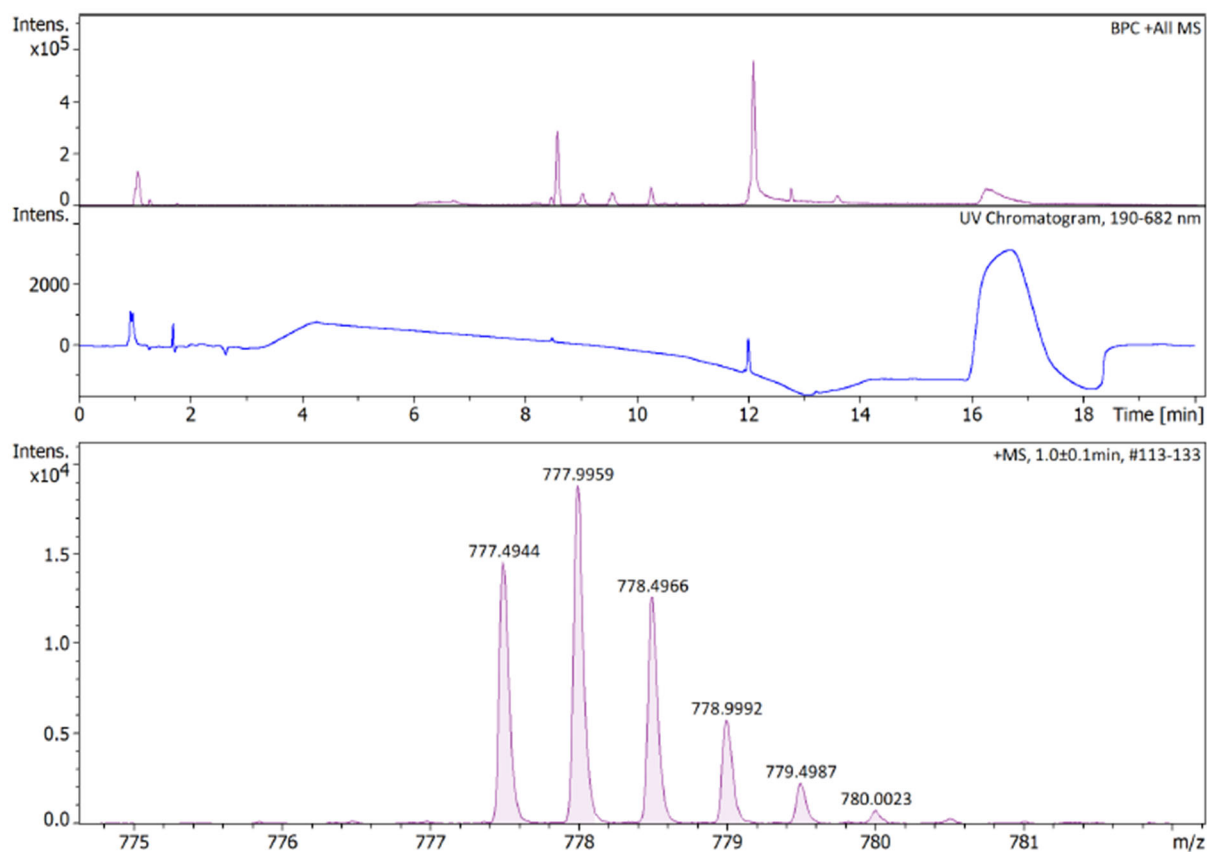
Yield: obtained as TFA salt, 13 mg, 6 μmol, 10%, isolated yield.



#	m/z	Res.	S/N	I	I %	FWHM
1	213.8089	10410	2799.4	84426	9.3	0.0205
2	214.1431	10430	1030.9	31112	3.4	0.0205
3	219.4843	10321	6649.3	203257	22.4	0.0213
4	219.8186	10374	2518.7	76985	8.5	0.0212
5	224.1560	10376	953.5	29308	3.2	0.0216
6	252.1749	10562	906.9	30081	3.3	0.0239
7	328.7223	10547	20848.3	908934	100.0	0.0312
8	329.2235	10382	7870.7	343187	37.8	0.0317
9	329.7246	10447	1727.4	75506	8.3	0.0316
10	335.7298	10740	2035.7	91730	10.1	0.0313
11	336.2312	10692	784.8	35433	3.9	0.0314
12	342.7218	9380	1332.6	61976	6.8	0.0365
13	343.2234	9162	511.7	23881	2.6	0.0375
14	356.7528	10820	463.0	23095	2.5	0.0330
15	377.7582	10817	1262.4	68960	7.6	0.0349
16	378.2593	10837	569.2	31101	3.4	0.0349
17	389.2539	11282	1286.5	71500	7.9	0.0345
18	389.5041	11291	1234.6	68620	7.5	0.0345
19	389.7545	11294	636.9	35407	3.9	0.0345
20	434.2853	11223	1076.7	65475	7.2	0.0387
21	434.6191	11002	889.3	54121	6.0	0.0395
22	434.9530	11114	388.8	23663	2.6	0.0391
23	518.6683	11231	5661.2	425925	46.9	0.0462
24	519.0022	11040	5550.5	417988	46.0	0.0470
25	519.3360	10818	2895.7	218034	24.0	0.0480
26	519.6698	10751	1030.2	77590	8.5	0.0483
27	520.0049	10682	326.0	24613	2.7	0.0487
28	528.0014	10815	316.8	24380	2.7	0.0488
29	528.3367	10631	344.5	26559	2.9	0.0497
30	533.6631	11516	739.0	57918	6.4	0.0463
31	533.9977	11311	659.1	51707	5.7	0.0472
32	534.3317	11179	328.2	25754	2.8	0.0478
33	551.3582	11207	441.3	35882	3.9	0.0492

#	m/z	Res.	S/N	I	I %	FWHM
34	551.6922	11279	507.6	41275	4.5	0.0489
35	552.0231	10788	357.6	29092	3.2	0.0512
36	572.8731	11275	290.5	24220	2.7	0.0508
37	573.3744	11032	211.1	17615	1.9	0.0520
38	650.9220	11336	883.8	77684	8.5	0.0574
39	651.4227	11379	758.8	66693	7.3	0.0572
40	651.9233	11082	323.4	28429	3.1	0.0588
41	656.4340	10738	1917.6	168680	18.6	0.0611
42	657.4365	10929	731.3	64268	7.1	0.0602
43	670.4492	10842	331.1	29217	3.2	0.0618
44	777.4957	11477	2914.6	254563	28.0	0.0677
45	777.9964	11235	2910.1	254178	28.0	0.0692
46	778.4970	11136	1552.8	135558	14.9	0.0699
47	778.9980	11263	570.1	49770	5.5	0.0692
48	791.4946	11452	193.9	16827	1.9	0.0691
49	799.9881	11428	365.5	31541	3.5	0.0700
50	800.4894	11528	337.1	29089	3.2	0.0694

Figure S120: HR-MS analysis of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29** (double charged, reference).

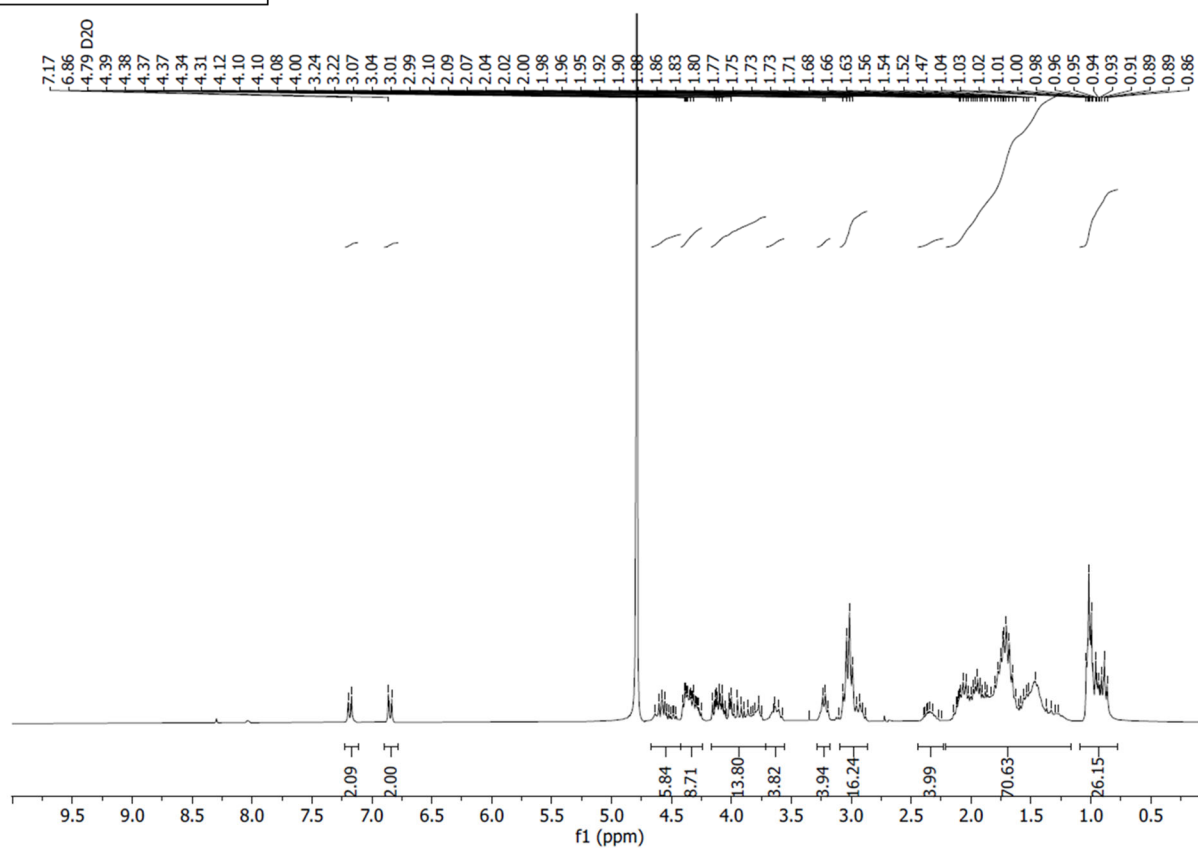


#	m/z	Res.	S/N	I	I %	FWHM
1	122.0951	8568	134.1	2850	3.6	0.0142
2	213.8084	10199	292.8	5661	7.1	0.0210
3	214.1428	10463	168.9	3263	4.1	0.0205
4	219.4838	10101	695.4	13383	16.8	0.0217
5	219.8185	10076	396.7	7629	9.6	0.0218
6	220.1534	9666	142.1	2732	3.4	0.0228
7	226.9456	9444	185.4	3528	4.4	0.0240
8	252.1746	10361	126.2	2357	3.0	0.0243
9	328.7215	10413	4385.9	79516	100.0	0.0316
10	329.2236	10215	2456.7	44537	56.0	0.0322
11	329.7261	10294	877.7	15912	20.0	0.0320
12	330.2274	10194	205.6	3728	4.7	0.0324
13	335.7296	10011	166.1	3009	3.8	0.0335
14	342.7230	8438	176.8	3196	4.0	0.0406
15	343.2241	8690	91.7	1658	2.1	0.0395
16	377.7575	10187	371.1	6741	8.5	0.0371
17	378.2584	10627	166.1	3016	3.8	0.0356
18	389.2531	11127	198.2	3589	4.5	0.0350
19	389.5038	11362	244.4	4426	5.6	0.0343
20	389.7543	11080	166.4	3014	3.8	0.0352
21	390.0036	11443	81.9	1483	1.9	0.0341
22	434.2842	11371	206.4	3730	4.7	0.0382
23	434.6183	10706	228.9	4139	5.2	0.0406
24	434.9523	10940	136.2	2463	3.1	0.0398
25	518.6673	11257	1433.2	26989	33.9	0.0461
26	519.0013	11313	1813.5	34159	43.0	0.0459
27	519.3356	10939	1233.3	23229	29.2	0.0475
28	519.6701	10763	567.0	10681	13.4	0.0483
29	520.0044	10897	212.4	4001	5.0	0.0477
30	520.3406	10412	80.0	1508	1.9	0.0500
31	528.0017	10794	100.3	1900	2.4	0.0489
32	528.3369	10450	124.6	2361	3.0	0.0506
33	533.6637	10002	100.2	1912	2.4	0.0534

#	m/z	Res.	S/N	I	I %	FWHM
34	533.9981	11521	125.9	2404	3.0	0.0464
35	534.3333	10290	78.7	1503	1.9	0.0519
36	551.3575	10711	162.1	3132	3.9	0.0515
37	551.6909	10724	180.4	3486	4.4	0.0514
38	552.0222	11174	131.1	2533	3.2	0.0494
39	572.8718	10501	74.5	1466	1.8	0.0546
40	650.9204	10921	234.6	4853	6.1	0.0596
41	651.4229	10860	270.2	5590	7.0	0.0600
42	651.9238	10584	168.5	3487	4.4	0.0616
43	656.4331	10291	642.1	13302	16.7	0.0638
44	657.4371	10551	366.2	7589	9.5	0.0623
45	658.4413	10043	129.6	2685	3.4	0.0656
46	777.4944	11240	679.0	14583	18.3	0.0692
47	777.9959	11092	879.2	18881	23.7	0.0701
48	778.4966	10915	587.0	12599	15.8	0.0713
49	778.9992	10436	268.8	5767	7.3	0.0746
50	779.4987	11027	105.7	2268	2.9	0.0707

Figure S121: HR-MS analysis of deuterate Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ [D]-29 (double charged).

¹H-NMR Reference 29



¹H-NMR HIE Reaction [D]-29

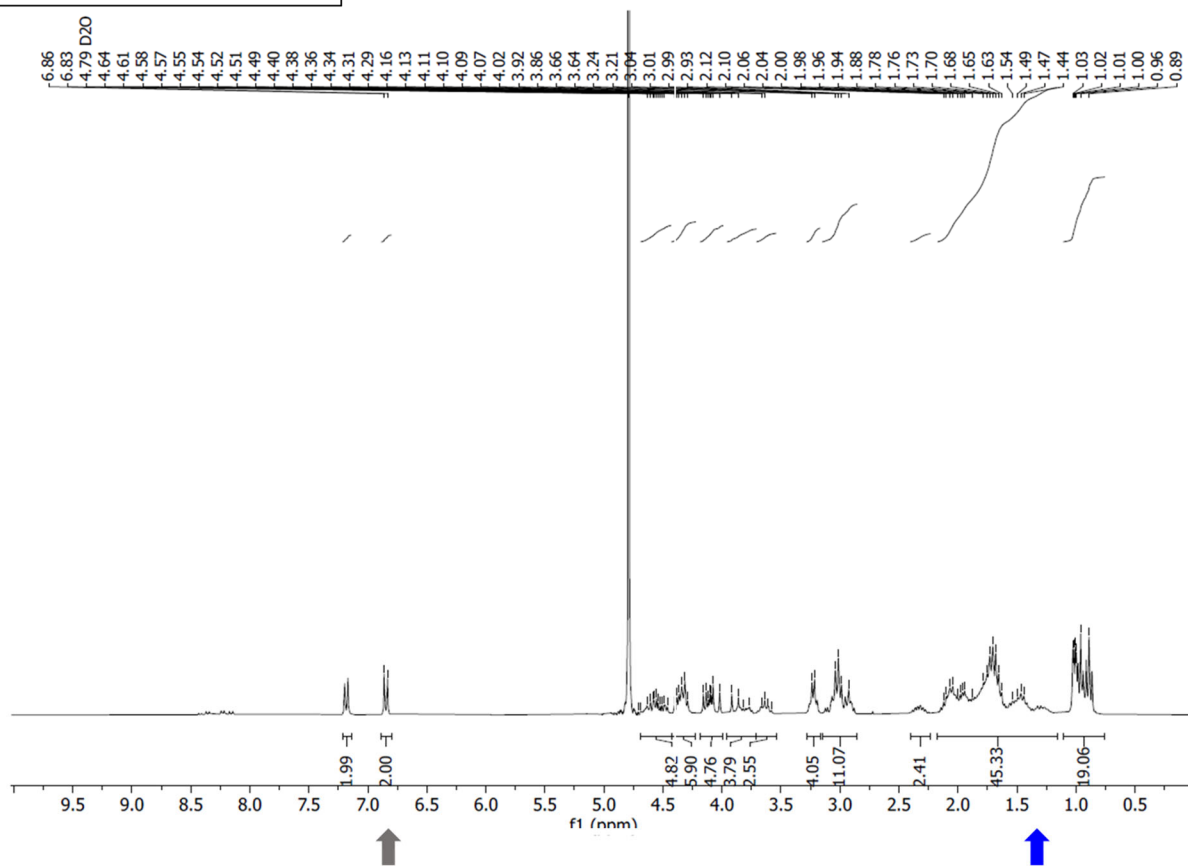


Figure S123: ¹H-NMR spectra of the HIE reaction of compound 29 to yield the deuterated product [D]-29.

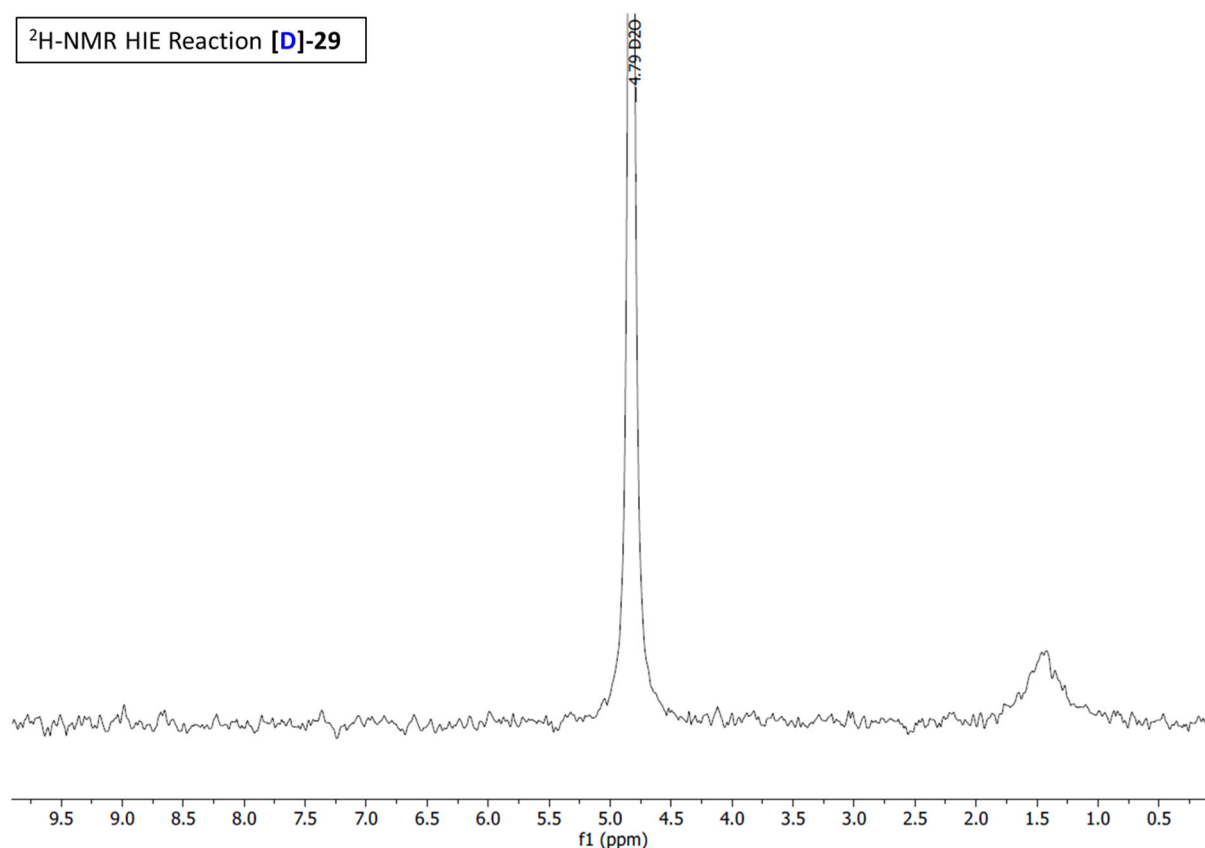


Figure S124: ²H-NMR spectrum of the HIE reaction yielding the deuterated product [D]-29.

8 Reactions under reduced pressure

As preparation for the transfer of the method to T₂ gas, the deuterium manifold was used to examine the HIE reaction of the selected compounds for deuteration at low pressures with a defined equivalent of D₂.

A deuterium manifold from RC TRITEC (Figure S103) was used for the HIE reactions under reduced pressure. The selected substrate and catalyst [Ir(COD)Cl]₂ **C4** were dissolved in 1.5 mL of Borax/HCl buffer pH 9 in the manifold reaction flask **A** and connected to the manifold. The apparatus was purged 3 times with deuterium using the deuterium balloon **C**. Using the pressure difference of the deuterium gas in the cross (apparatus with closed taps **B1** and **B2**) and in the branch (tap **B2** is opened), the amount of deuterium in the reaction was calculated using the following equation 2.

$$n_{D2} = + \frac{p_2 \left(\frac{p_1 \cdot V}{p_2} - V \right)}{RT} \quad (2)$$

n_{D2}	D ₂ amount	[mol]
p_1	Pressure before opening tap to the reaction flask	[bar]
p_2	Pressure after opening tap to the reaction flask	[bar]
V	Volume of apparatus + reaction flask	[L]
R	Ideal gas constant	8.31 bar L mol ⁻¹ K ⁻¹
T	Temperature	[K]

The tap to the reaction flask was closed, and the reaction was heated to 90 °C for X h. The reaction mixture was analyzed by LC-MS.



Figure S125: Deuterium manifold set up for HIE reaction.

Table S12: HIE reactions under reduced pressure.

Entry	Substrate	Amount (mmol)	Branch pressure (mbar)	D ₂ (eq.)	HIE1 (D/molecule)
1 ^{a,b}	1	0.01	245	9.8	1.01 ^f
2 ^{c,d}	3	0.002	72	9.0	1.02 ^g
3 ^{a,e}	28	0.01	272	9.0	1.38 ^f
4 ^{b,e}	29	0.005	95	8.4	0.86 ^g

a) catalyst **C4** (2.5 mol%), ligand **L11** (5 mol%).

b) 30 min.

c) catalyst **C4** (5 mol%), ligand **L11** (10 mol%).

d) 18 h.

e) 1 h.

f) determined by LC-MS.

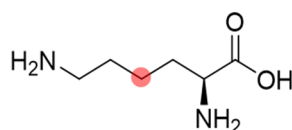
g) determined by HR-MS.

9 Tritium reactions



Figure S126: Tritium reaction set up.

9.1 L-Lysine **1**



1

Chemical Formula: $C_6H_{14}N_2O_2$

Exact Mass: 146.11

Figure S127: Structure of L-Lysine **1**.

1.5 mg (10.27 μmol) of L-Lysine **1**, 2.5 mol% (0.025 equiv.) of catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and 5 mol% (0.05 equiv.) of ligand **L11** (each dispensed as stock solution in dioxane) were added to the reaction flask. 1.5 mL of Borax/HCl buffer pH 9 and a stirring bar were added to the flask. The reaction flask was adapted to a TRITEC tritium manifold and the solution was frozen in liquid nitrogen (-196°C). The flask was evacuated and charged with tritium (159.4 GBq, 73.46 μmol T_2 , 7.15 equiv., pressure 150 mbar). The reaction mixture was then allowed to warm to room temperature before stirring at 90°C for 30 min. Then all volatile components were distilled into an ampoule in vacuo at -196°C . The labile tritium

was exchanged and removed by addition of MeOH and a freeze-drying process (repeated three times, then one time with CH₃CN).

The residue was dissolved in 1 mL 0.1M NaOH solution. 17 mg (120.94 µmol) of benzoyl chloride were added and the reaction mixture was stirred at room temperature for 17h. 1 mL of MeOH was added to the crude and the mixture was directly purified.

Purification and isolation of the product was done *via* HPLC (Waters CSH C18 10x150 mm, 5 µm, 6 mL/min flow, ACN/water + 0.1% TFA gradient program) and gave 1.36 mg, 5453.4 MBq, 3.4 % RCY, 37% CY (2 steps), 1420.8 GBq/mmol (38.4 Ci/mmol) of the desired labelled compound **[T]-1** (isolated as dibenzoyl derivative). This corresponds to 1.32 T/molecule.

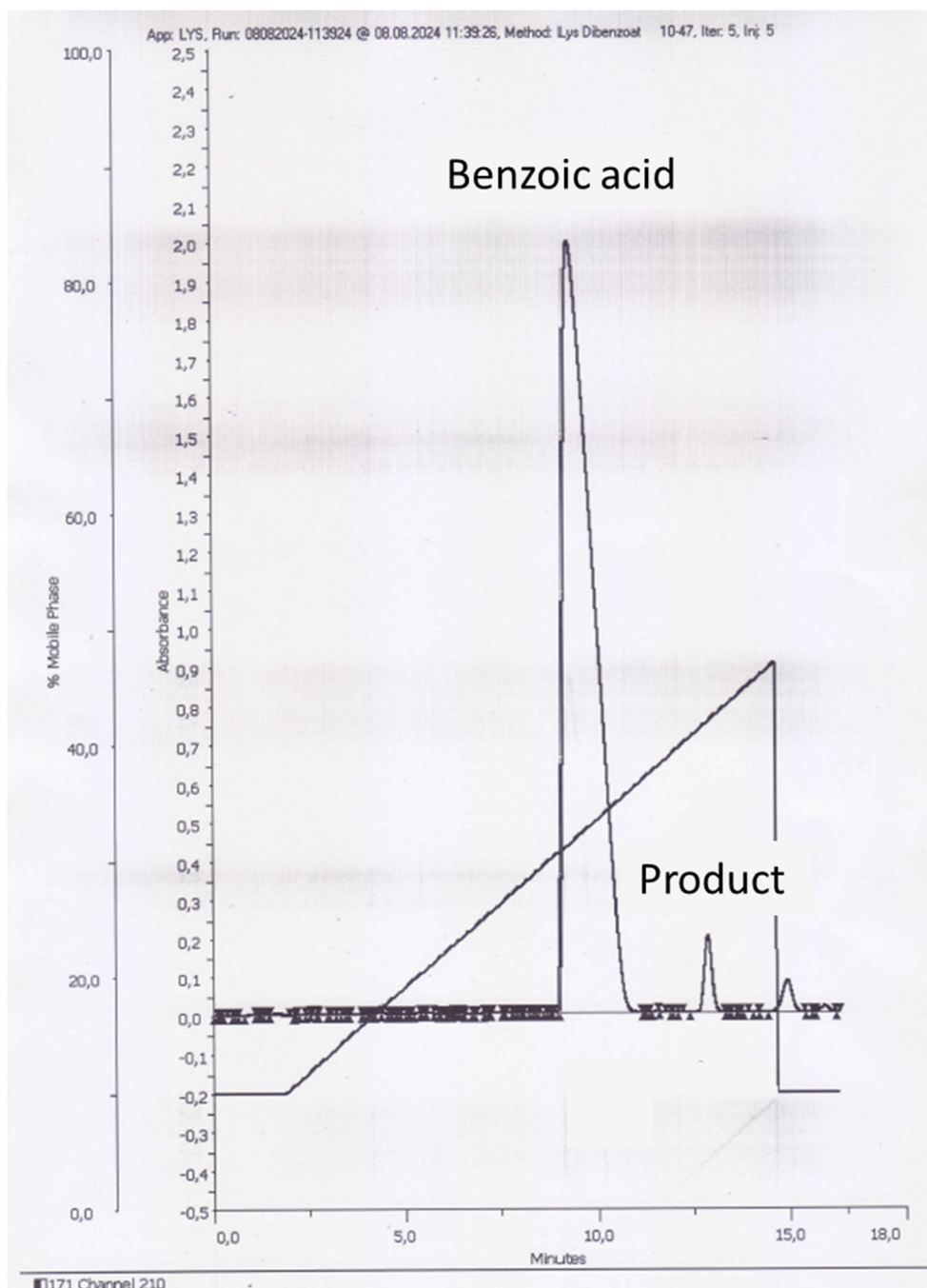


Figure S128: Purification chromatogram of L-Lys **[T]-1** as dibenzoyl derivative (UV spectrum 210 nm).

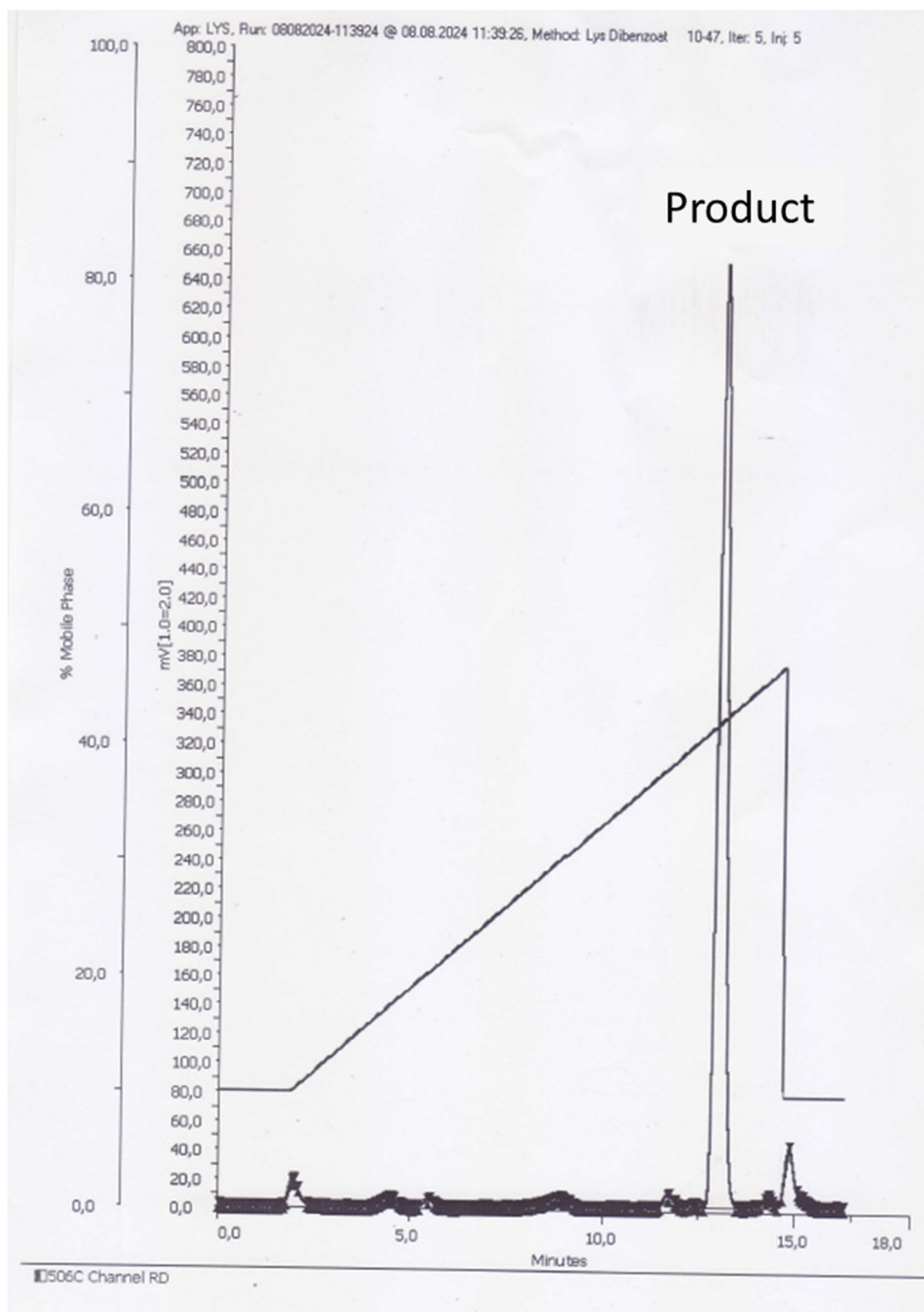
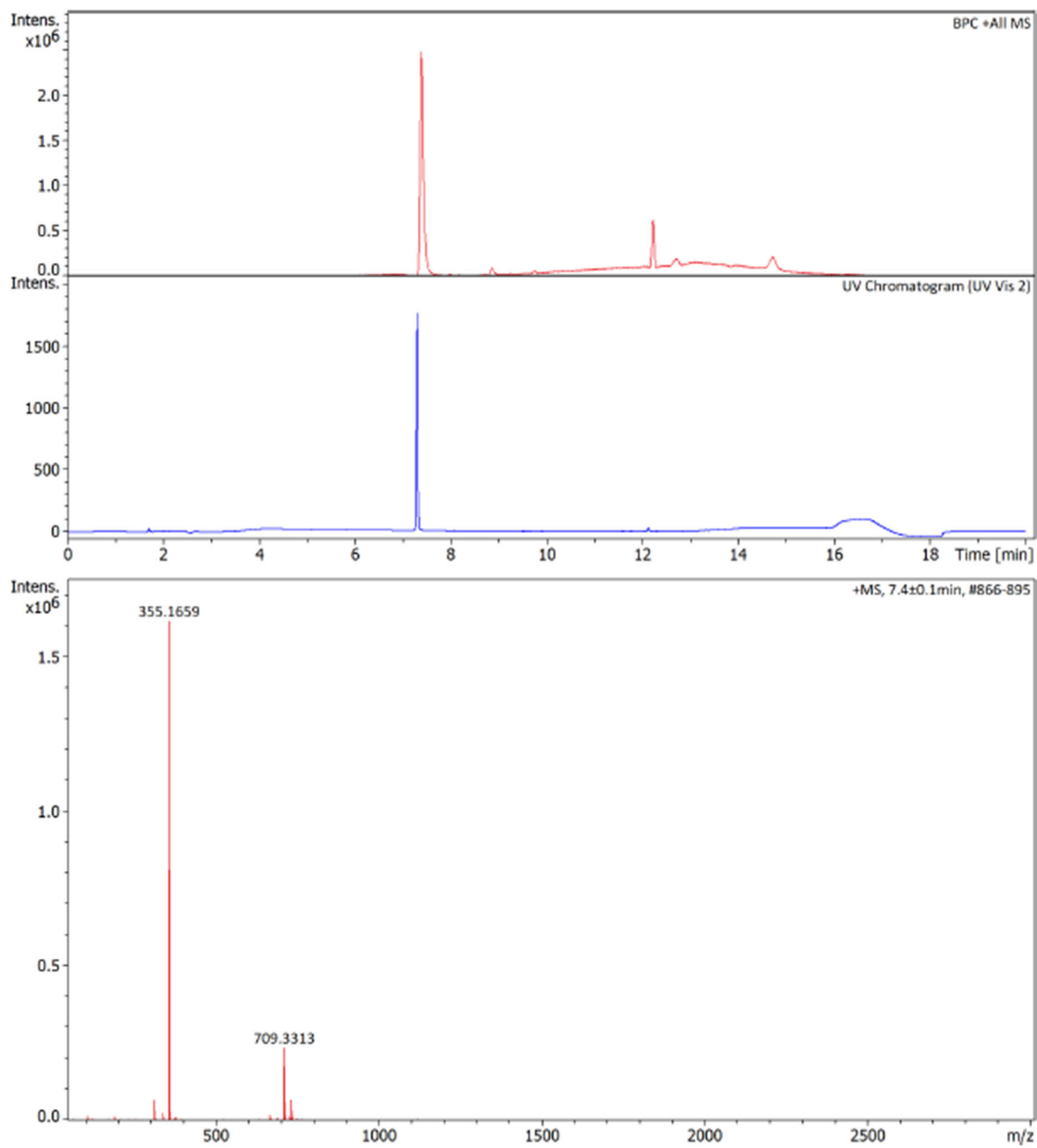
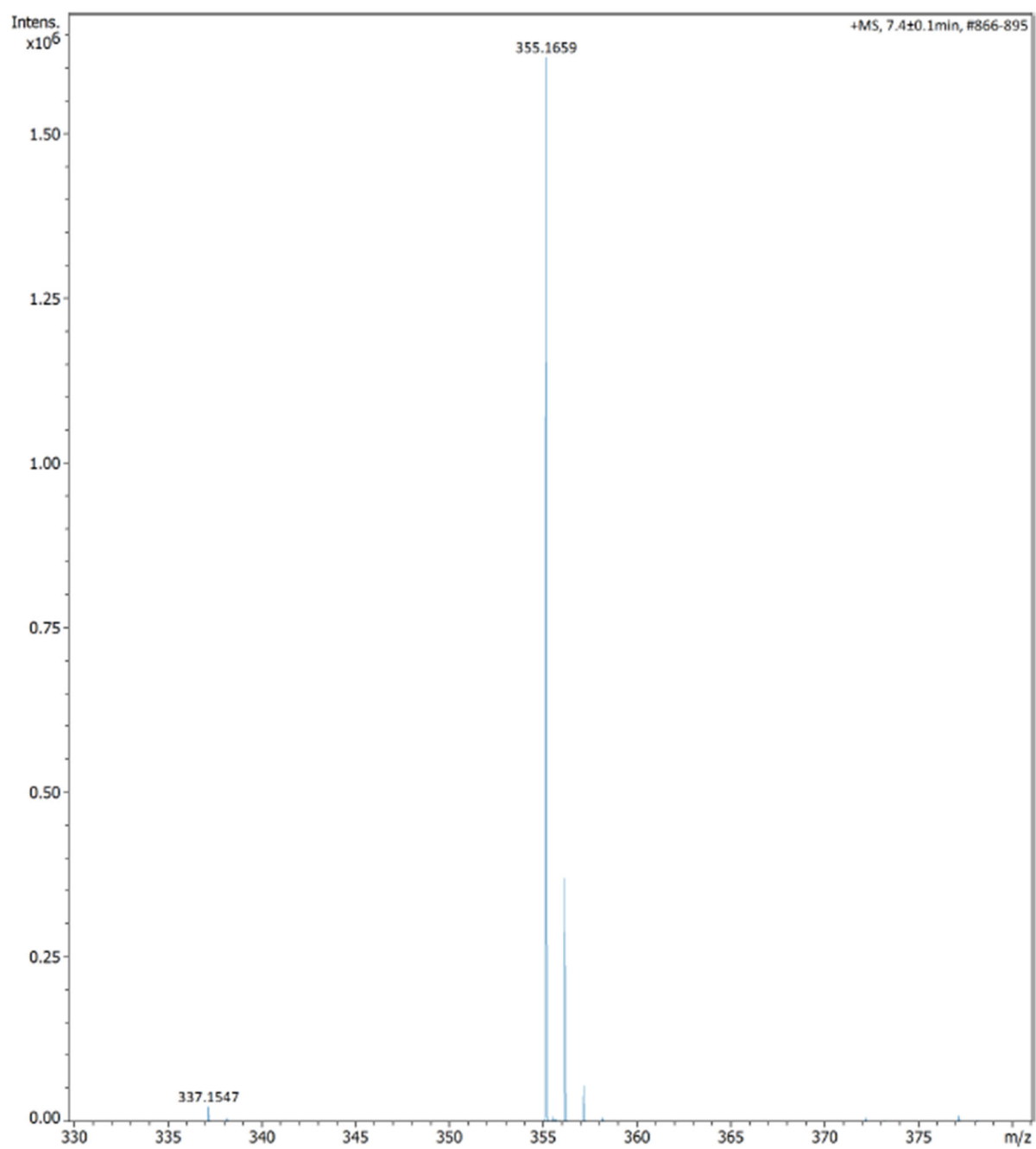


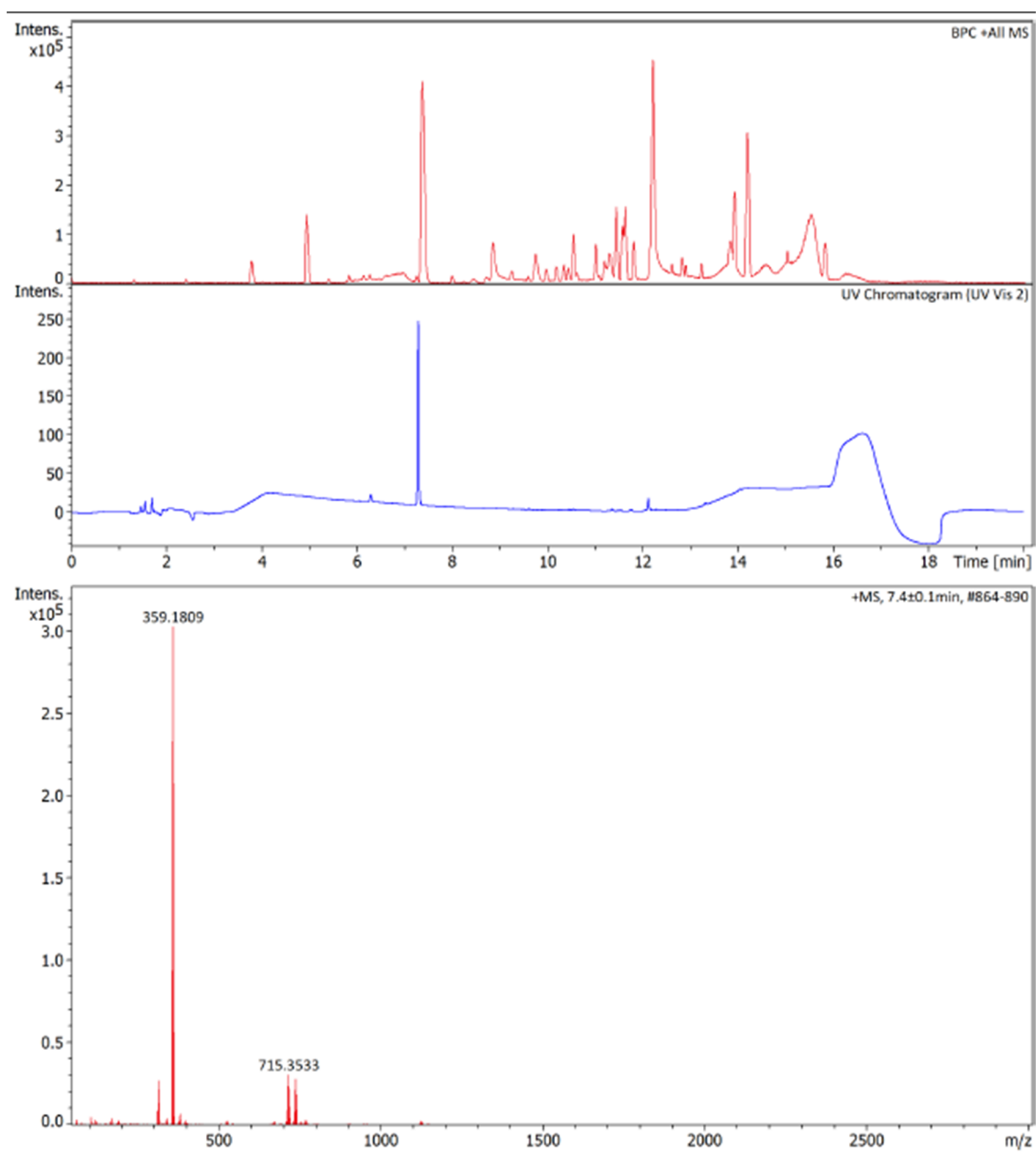
Figure S129: Radiochromatogram of L-Lys [T]-1 as dibenzoyl derivative.

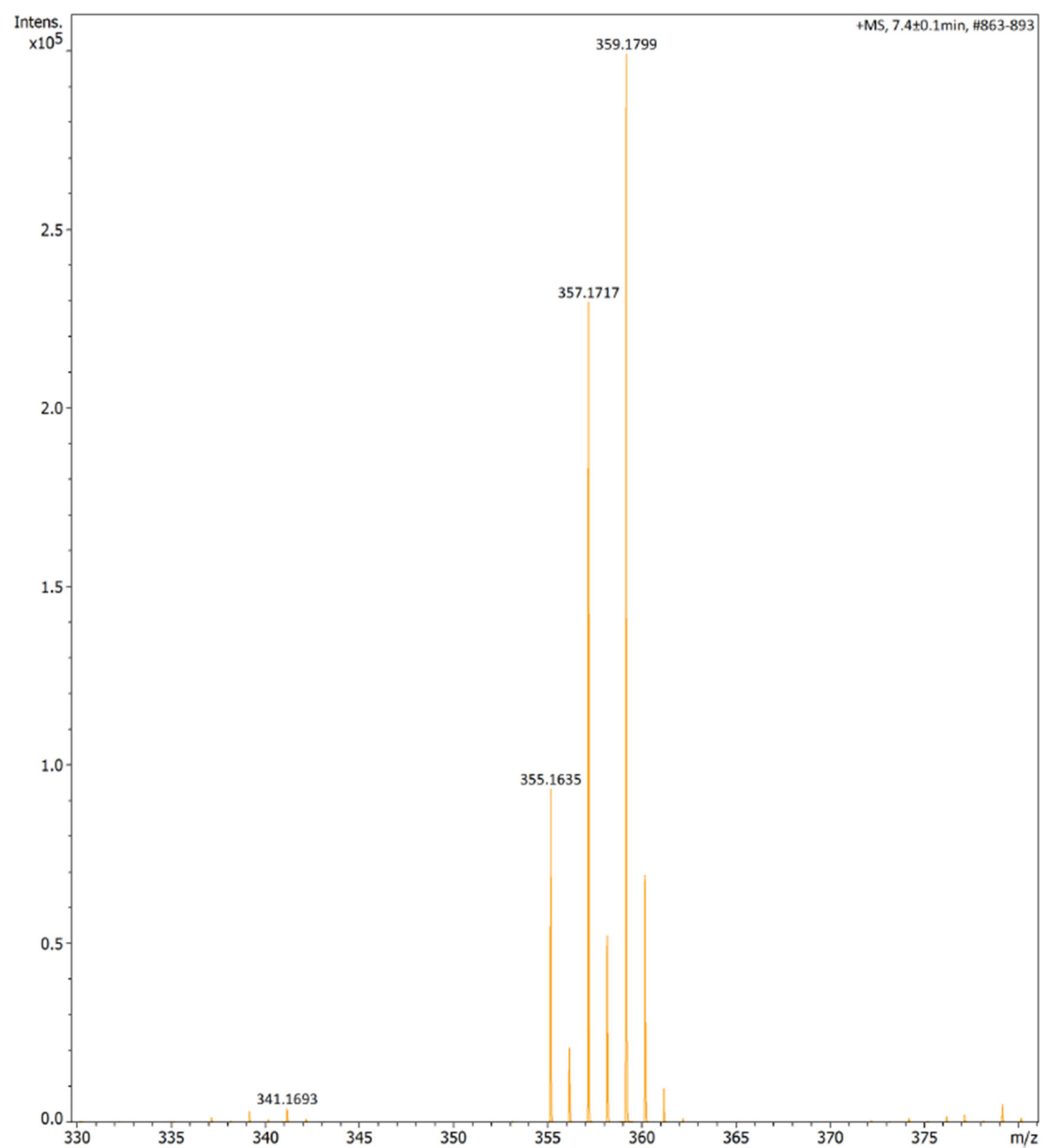




#	m/z	Res.	S/N	I	I %	FWHM
1	105.0143	8356	503.1	13970	0.9	0.0126
2	118.0689	8509	127.1	3489	0.2	0.0139
3	188.0975	9457	503.1	12543	0.8	0.0199
4	311.1741	10195	3095.7	63859	3.9	0.0305
5	312.1776	9950	644.6	13276	0.8	0.0314
6	337.1547	10276	1118.0	22268	1.4	0.0328
7	338.1580	10074	257.7	5124	0.3	0.0336
8	355.1659	10197	83410.7	1617207	100.0	0.0348
9	355.4989	34462	412.3	7993	0.5	0.0103
10	355.6352	25892	179.7	3482	0.2	0.0137
11	356.1688	10105	19098.2	370064	22.9	0.0352
12	357.1719	10275	2793.3	54095	3.3	0.0348
13	358.1752	10031	287.4	5561	0.3	0.0357
14	372.1933	10136	337.9	6320	0.4	0.0367
15	377.1487	10544	455.0	8409	0.5	0.0358
16	631.2841	10221	275.3	3571	0.2	0.0618
17	665.3417	10902	1374.1	17074	1.1	0.0610
18	666.3452	10599	600.1	7448	0.5	0.0629
19	687.3234	11194	622.4	7589	0.5	0.0614
20	709.3313	11125	19453.1	234297	14.5	0.0638
21	710.3345	11048	9085.6	109416	6.8	0.0643
22	711.3378	11120	2266.6	27286	1.7	0.0640
23	712.3406	10829	402.9	4849	0.3	0.0658
24	726.3592	10489	1043.9	12387	0.8	0.0692
25	727.3622	10796	491.6	5836	0.4	0.0674
26	731.3136	11183	5543.8	65659	4.1	0.0654
27	732.3179	10992	2508.5	29690	1.8	0.0666
28	733.3203	10905	653.3	7730	0.5	0.0672
29	747.2887	10427	423.0	4945	0.3	0.0717
30	1116.4074	10402	430.2	4180	0.3	0.1073

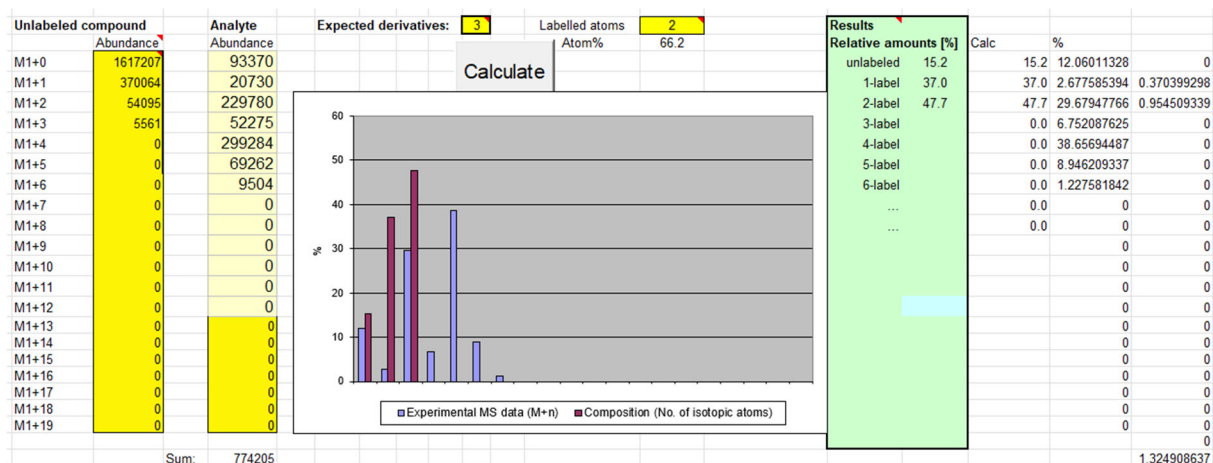
Figure S130: HR-MS analysis of L-Lys **1** as dibenzoyl derivative (reference).





#	m/z	Res.	S/N	I	I %	FWHM
1	105.0137	7894	155.7	4264	1.4	0.0133
2	311.1722	9958	368.5	8346	2.8	0.0312
3	313.1805	10049	921.4	20823	7.0	0.0312
4	314.1836	10063	201.6	4551	1.5	0.0312
5	315.1889	10074	1180.3	26619	8.9	0.0313
6	316.1920	10060	251.8	5677	1.9	0.0314
7	355.1635	10489	4270.8	93370	31.2	0.0339
8	356.1671	10155	948.8	20730	6.9	0.0351
9	357.1717	10307	10521.4	229780	76.8	0.0347
10	358.1751	10176	2394.2	52275	17.5	0.0352
11	359.1799	10248	13712.5	299284	100.0	0.0350
12	360.1834	10297	3175.0	69262	23.1	0.0350
13	361.1862	10163	436.1	9504	3.2	0.0355
14	379.1545	10173	234.1	5010	1.7	0.0373
15	381.1633	10059	302.1	6459	2.2	0.0379
16	711.3356	10720	445.4	8455	2.8	0.0664
17	712.3389	10777	208.3	3953	1.3	0.0661
18	713.3435	10909	1201.3	22801	7.6	0.0654
19	714.3469	11109	531.9	10093	3.4	0.0643
20	715.3516	11003	1592.5	30207	10.1	0.0650
21	716.3551	11094	697.9	13230	4.4	0.0646
22	717.3600	10772	1112.5	21083	7.0	0.0666
23	718.3636	10646	448.6	8499	2.8	0.0675
24	733.3190	10046	409.9	7731	2.6	0.0730
25	735.3264	10619	1032.8	19499	6.5	0.0692
26	736.3301	10684	468.8	8857	3.0	0.0689
27	737.3337	10881	1400.8	26469	8.8	0.0678
28	738.3374	10936	602.3	11376	3.8	0.0675
29	739.3420	10711	955.4	18045	6.0	0.0690
30	740.3456	10569	394.3	7453	2.5	0.0701

Figure S131: HR-MS analysis of L-Lys [T]-1 purified as dibenzoyl derivative.



15,3 % T0	→	I	29 Ci/mmol	→	10,7 Ci/mmol
37,1 % T1	→	I	58 Ci/mmol	→	27,7 Ci/mmol
47,7 % T2	→	I	87 Ci/mmol	→	0,0 Ci/mmol
0,0 % T3	→	I	116 Ci/mmol	→	0,0 Ci/mmol
0,0 % T4	→	I	145 Ci/mmol	→	0,0 Ci/mmol
0,0 % T5	→	I	174 Ci/mmol	→	0,0 Ci/mmol
0,0 % T6	→	I	203 Ci/mmol	→	0,0 Ci/mmol
0,0 % T7	→	I	232 Ci/mmol	→	0,0 Ci/mmol
0,0 % T8	→	I	261 Ci/mmol	→	0,0 Ci/mmol
0,0 % T9	→	I	290 Ci/mmol	→	0,0 Ci/mmol
0,0 % T10	→	I		→	0,0 Ci/mmol

100,0 % 38,383 Ci/mmol 38,4 Ci/mmol

Figure S132: Calculation of tritium content in L-Lys [T]-1.

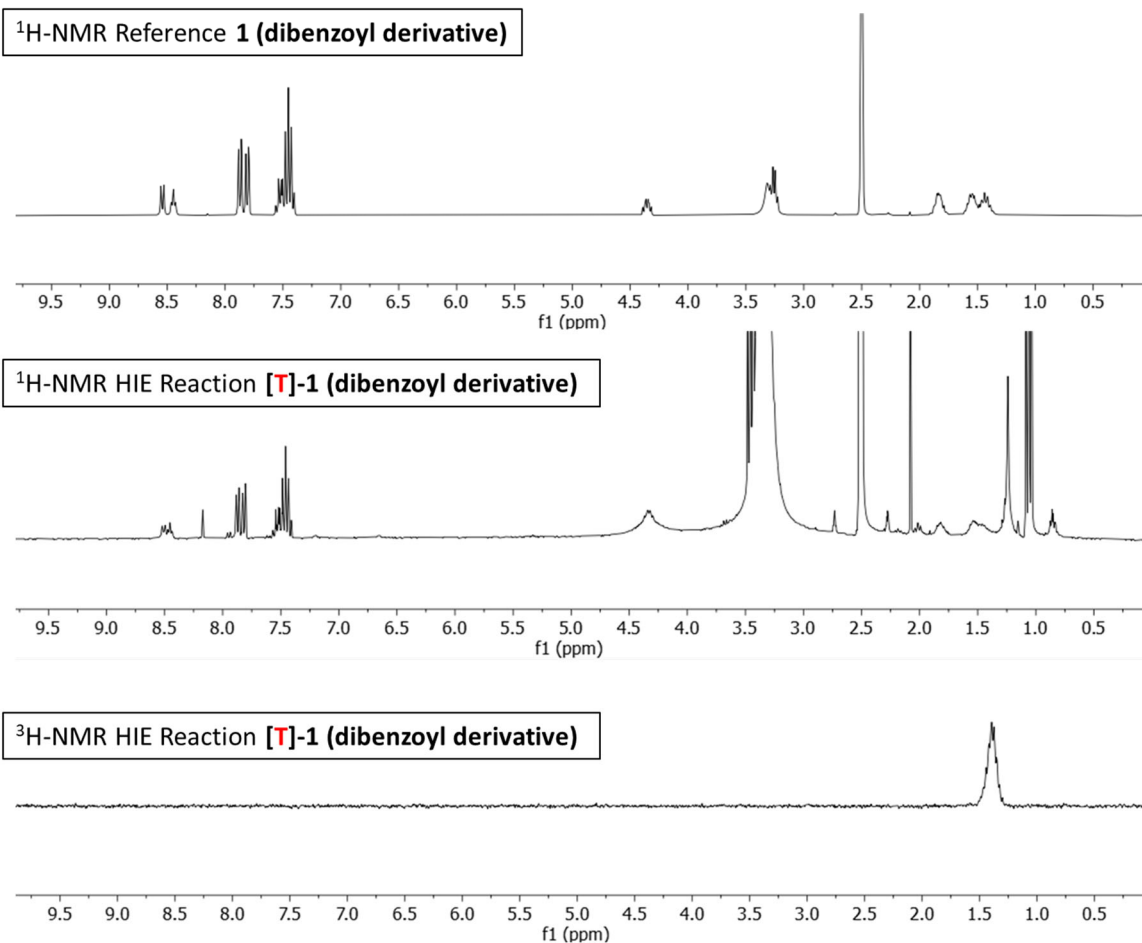


Figure S133: Overlay and comparison between ¹H-NMR spectrum of L-Lys 1 as benzoyl derivative and ¹H/³H-NMR spectra of L-Lys [T]-1 purified as dibenzoyl derivative.

Stability tests have been performed in PBS buffer and rat plasma (Sprague Dawley Rat LiHep plasma, gender pooled from Neo Biotech) to check the stability of tritiated dibenzoyl derivate of L-Lys [T]-1.

For the PBS tests at r. t. and 37 °C two samples of the substrate in PBS buffer were prepared. A stock solution of 7 µg/mL of tritiated dibenzoyl derivate of L-Lys [T]-1 was prepared. The two samples (one at r. t. and one at 37 °C) for the UHPLC analysis have been prepared in a 1.5 mL HPLC vial taking with

50 μ l of the stock solution and adding 950 μ l of PBS buffer. One aliquot of the sample at $t = 0$ has been analyzed as starting point for the test. After 24 h one aliquot of test sample at r. t. and one at 37 $^{\circ}$ C have been analyzed. The samples were analyzed on the UHPLC, with both UV and RD detectors.

For the plasma tests at r. t. and 37 $^{\circ}$ C two samples of the substrate in the rat plasma were prepared. A stock solution of 7 μ g/mL of tritiated dibenzoyl derivate of L-Lys [T]-1 was prepared. The two samples (one at r. t. and one at 37 $^{\circ}$ C) for the UHPLC analysis have been prepared in a 1.5 mL HPLC vial taking with 50 μ l of the stock solution and adding 950 μ l of plasma. One aliquot of the sample at $t = 0$ has been analyzed as starting point for the test. Another sample with no tritiated substrate in plasma was prepared and analyzed as a blank reference. After 24 h one aliquot of test sample at r. t. and one at 37 $^{\circ}$ C have been analyzed. The samples for the data points are prepared as follows: a 100 μ l aliquot of the sample has been added to an Eppendorf vial and diluted with two volumes of ACN. After the addition the sample was mixed and then centrifuged in a Minispin Eppendorf Centrifuge at 6708 x g for 15 min. The samples were incubated in the fridge for 10 minutes. 50 μ l of the supernatant were transferred to a HPLC vial and diluted it with 50 μ l of water. The samples were analyzed on the UHPLC, with both UV and RD detectors.

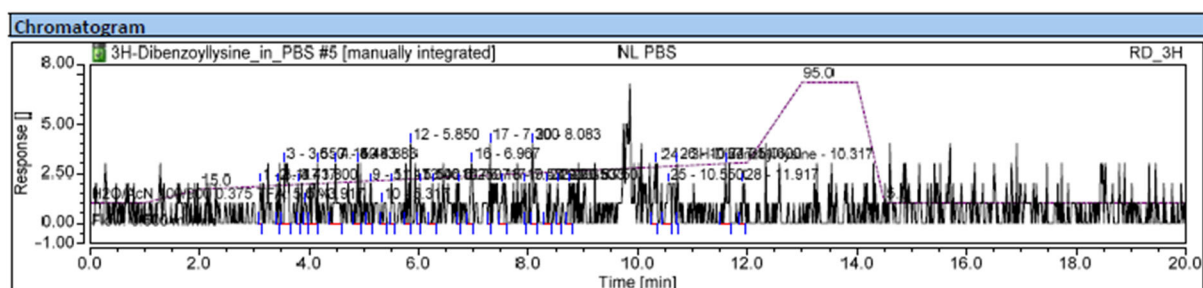


Figure S134: RD chromatogram of the blank reference not containing any tritiated substrate.

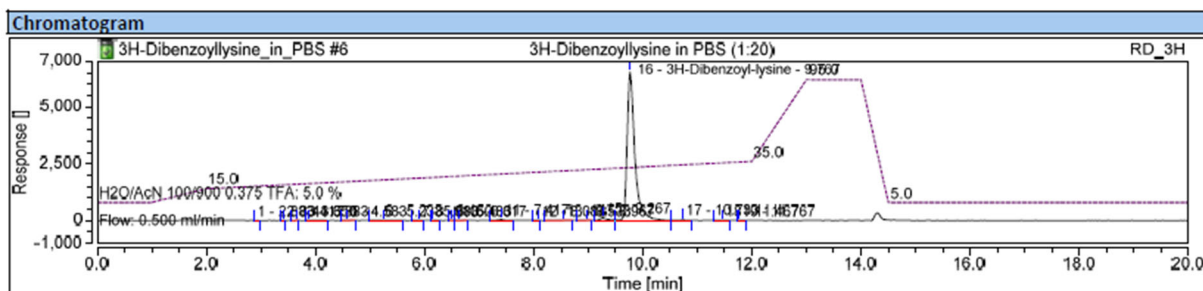


Figure S135: RD chromatogram of one aliquot of the sample at $t = 0$ h in PBS.

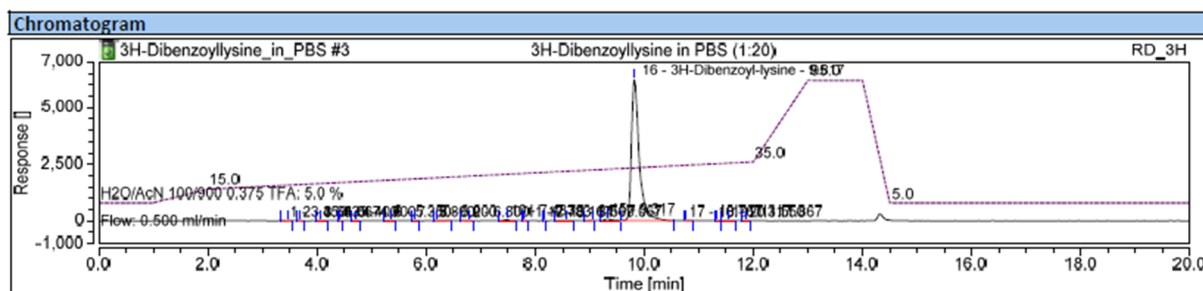


Figure S136: RD chromatogram of one aliquot of the sample at r. t. at $t = 24$ h in PBS.

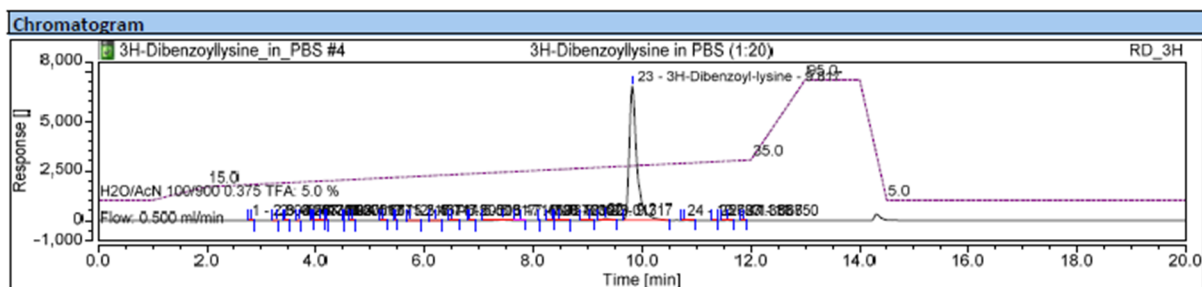


Figure S137: RD chromatogram of one aliquot of the sample at 37 °C at t = 24 h in PBS.

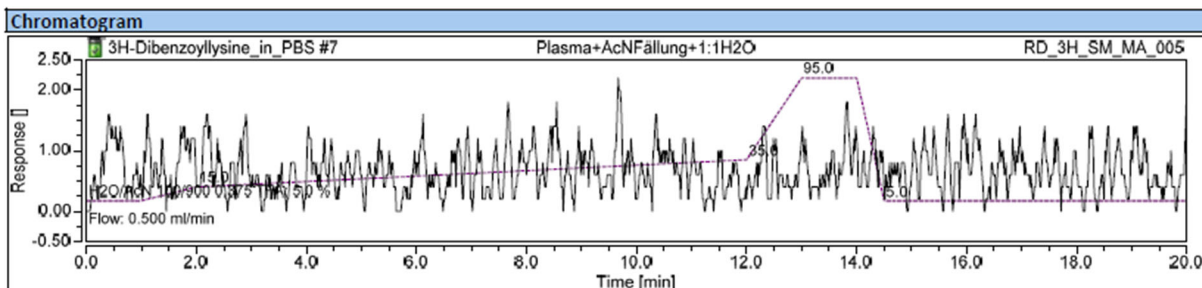


Figure S138: RD chromatogram of the blank reference not containing any tritiated substrate.

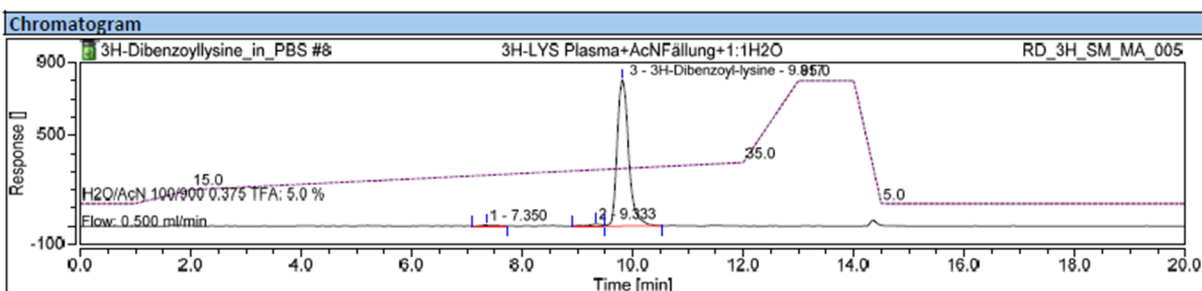


Figure S139: RD chromatogram of one aliquot of the sample at t = 0 h in rat plasma.

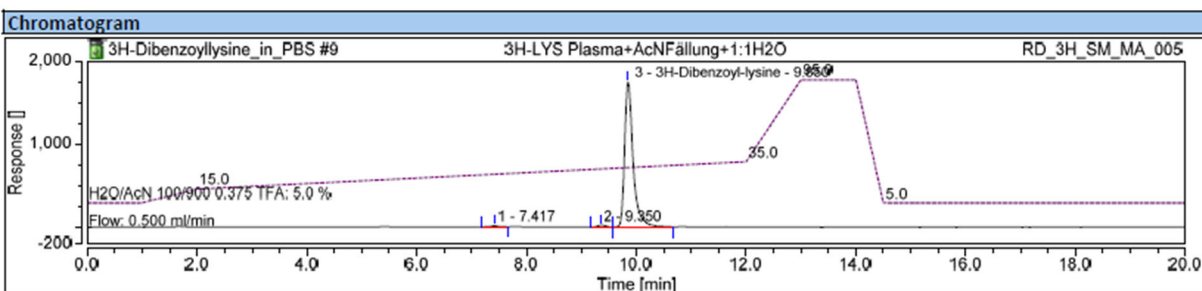


Figure S140: RD chromatogram of one aliquot of the sample at r. t. at t = 24 h in rat plasma.

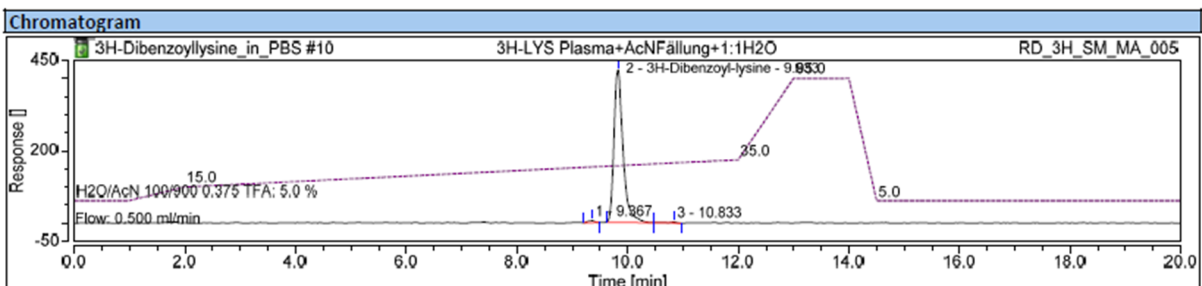


Figure S141: RD chromatogram of one aliquot of the sample at 37 °C at t = 24 h in rat plasma.

9.2 Bradykinin 3

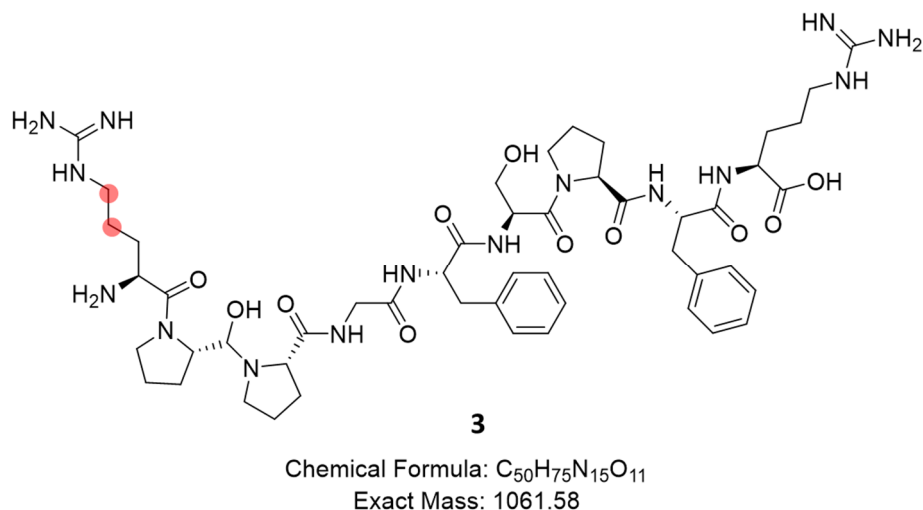


Figure S142: Structure of Bradykinin **3**.

4.0 mg (3.77 μ mol) of bradykinin **3**, 5 mol% (0.05 equiv.) of catalyst [Ir(COD)Cl]₂ **C4** and 10 mol% (0.1 equiv.) of ligand **L11** (each dispensed as stock solution in dioxane, each in 0.08 mL) were added to the reaction flask. 1.5 mL of Borax/HCl buffer pH 9 and a stirring bar were added to the flask. The reaction flask was adapted to a TRITEC tritium manifold and the solution was frozen in liquid nitrogen (-196°C). The flask was evacuated and charged with tritium (130.02 GBq, 60.15 μ mol T₂, 15.55 equiv., pressure 105 mbar). The reaction mixture was then allowed to warm to room temperature before stirring at 90°C for 21h. Then all volatile components were distilled into an ampoule in vacuo at -196°C. The labile tritium was exchanged and removed by addition of MeOH and a freeze-drying process (repeated four times, then one time with CH₃CN).

The residue was dissolved in 2 mL CH₃CN/water, followed by purification and isolation *via* HPLC (Waters CSH C18 10x150 mm, 5 μ m, 6 mL/min flow, ACN/water + 0.1% TFA gradient program) that gave 1.29 mg, 1422 MBq, 1.1 % RCY, 32% CY, 1169.2 GBq/mmol (31.6 Ci/mmol) of the desired labelled compound [**T**]-**3**. This corresponds to 1.09 T/molecule.

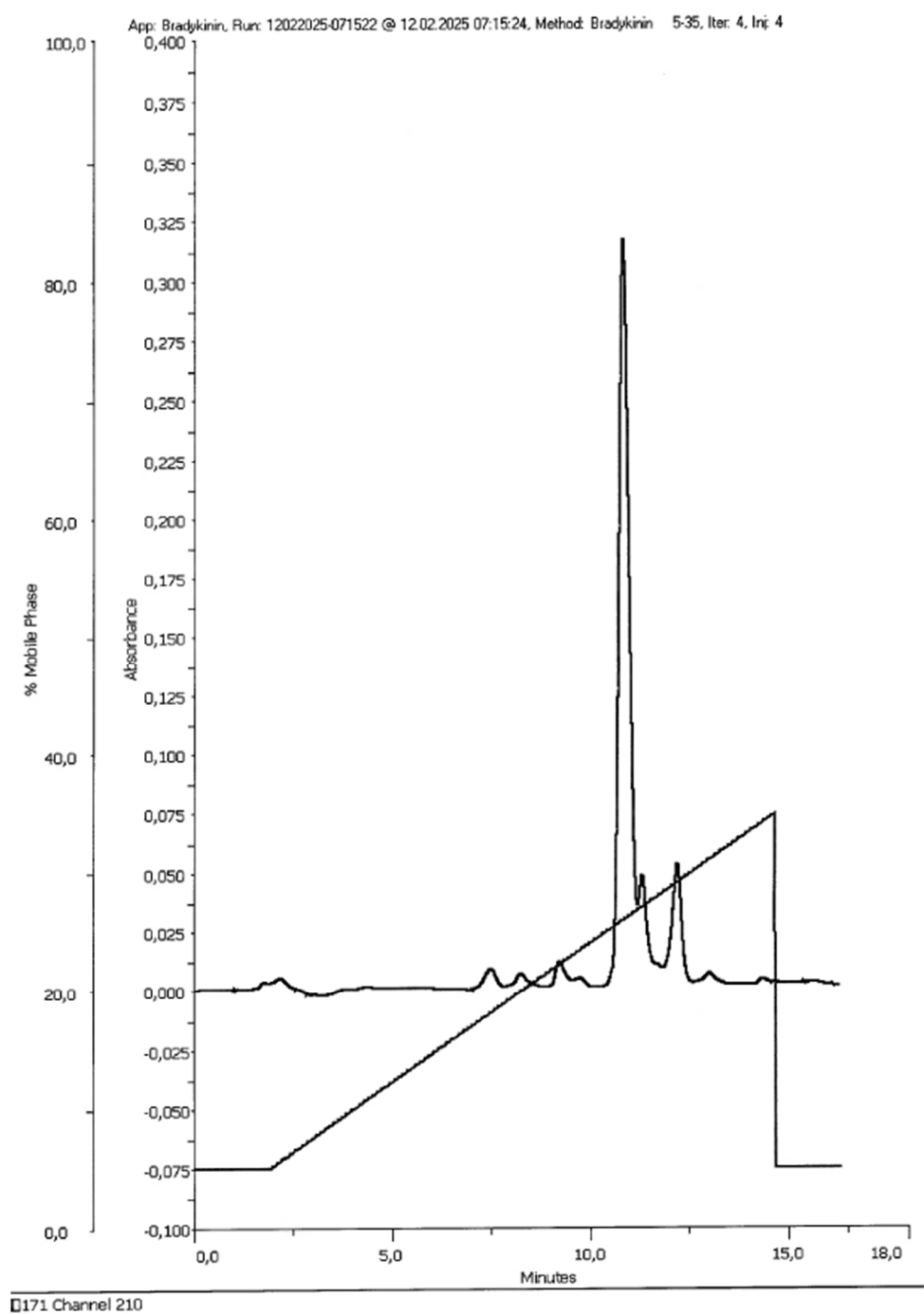


Figure S143: Purification chromatogram of Bradykinin [T]-3 (UV spectrum 210 nm).

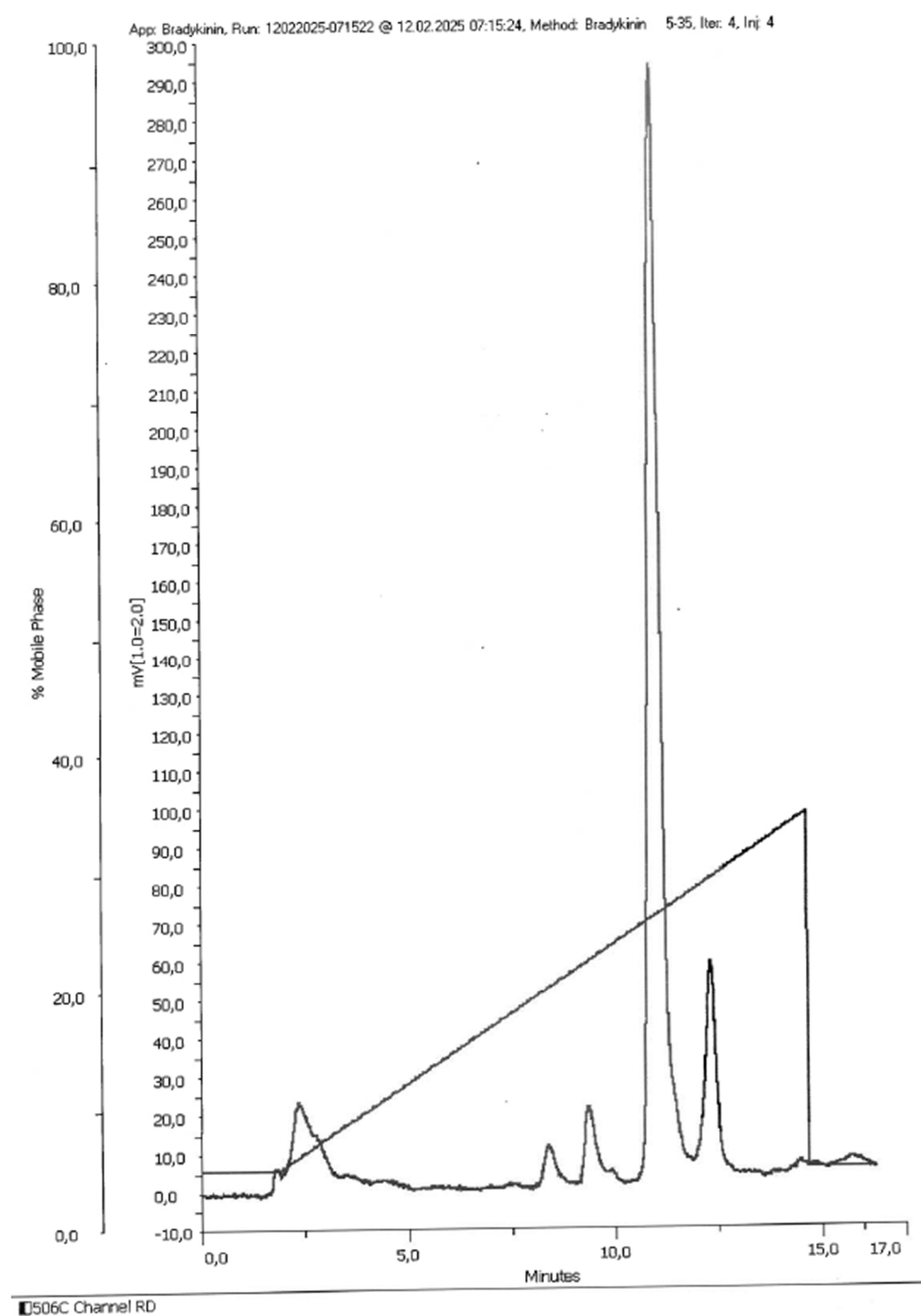
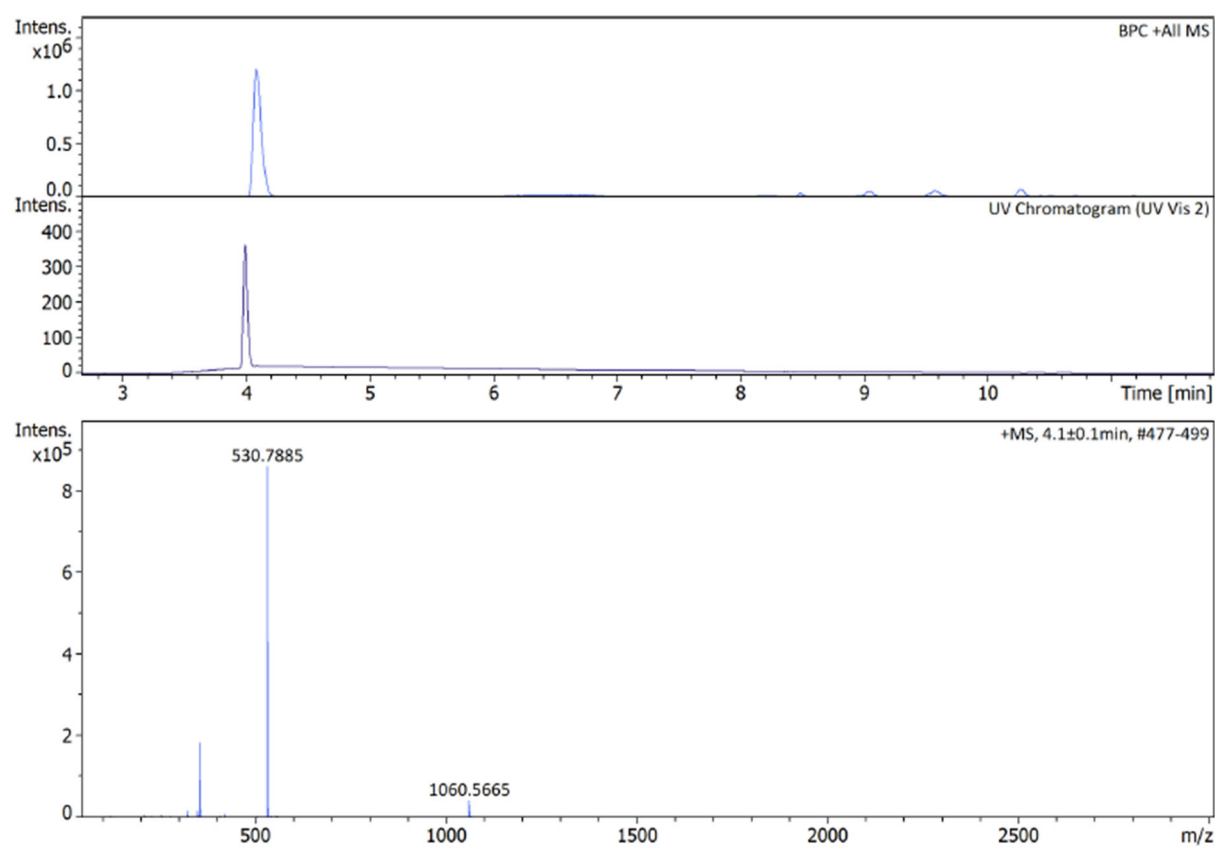
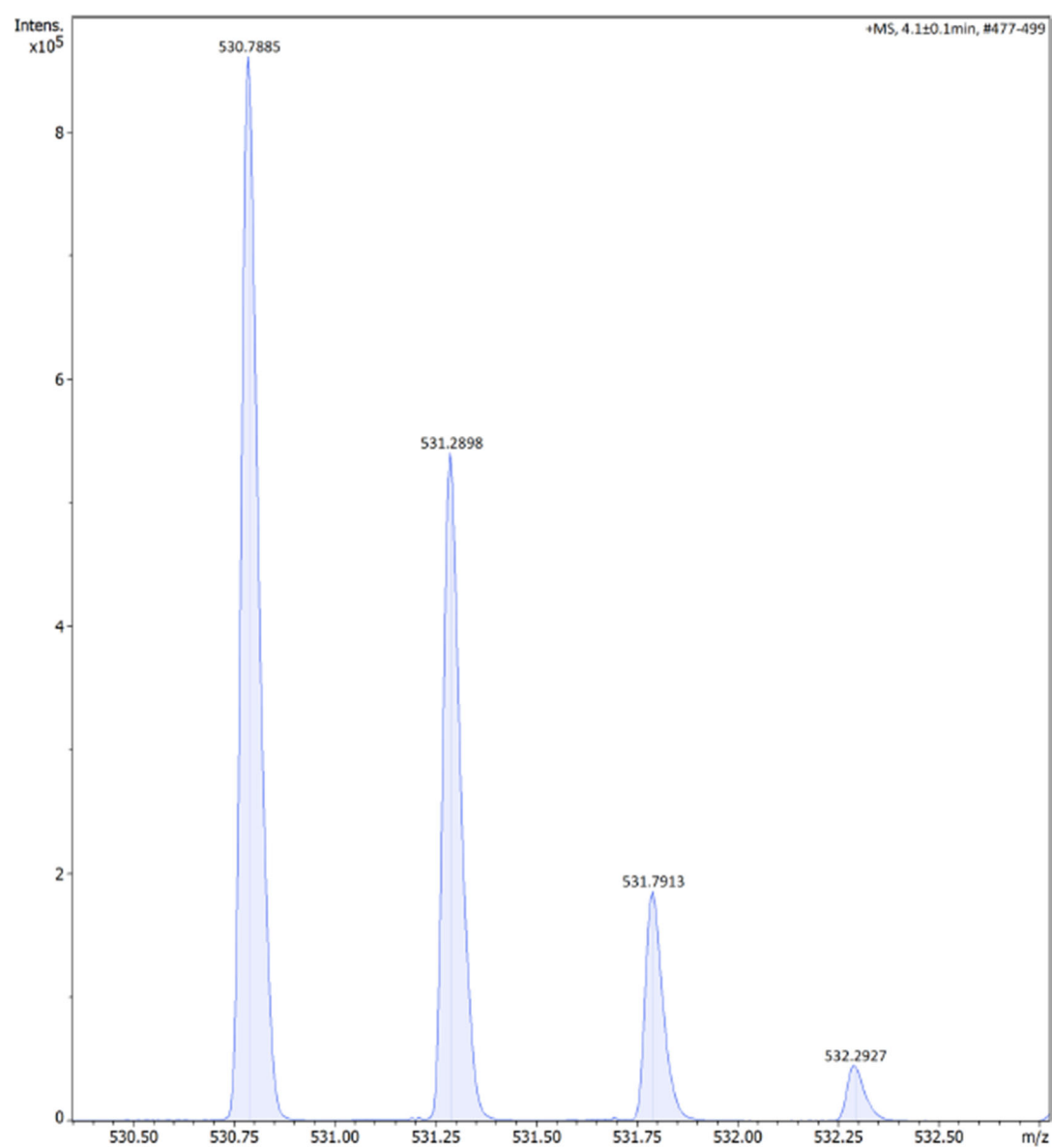


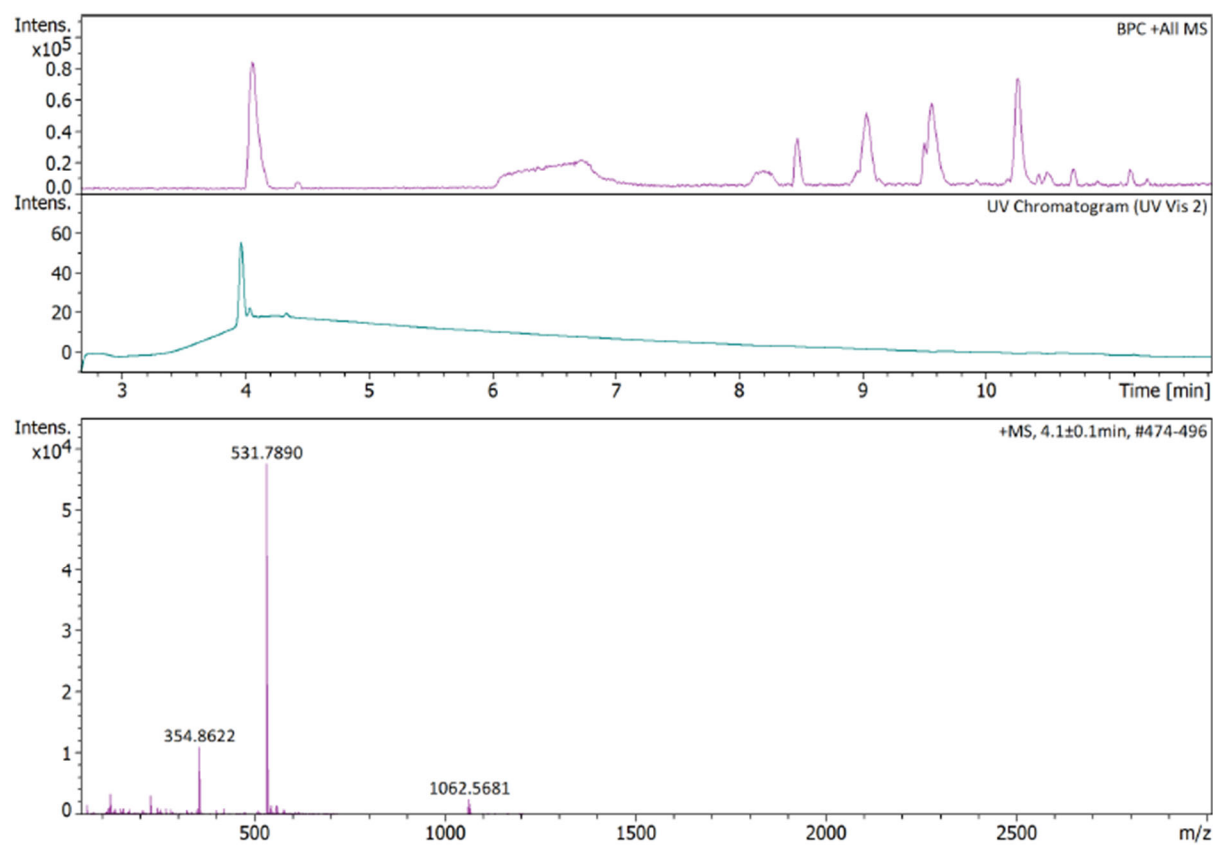
Figure S144: Radiochromatogram of Bradykinin [T]-3.

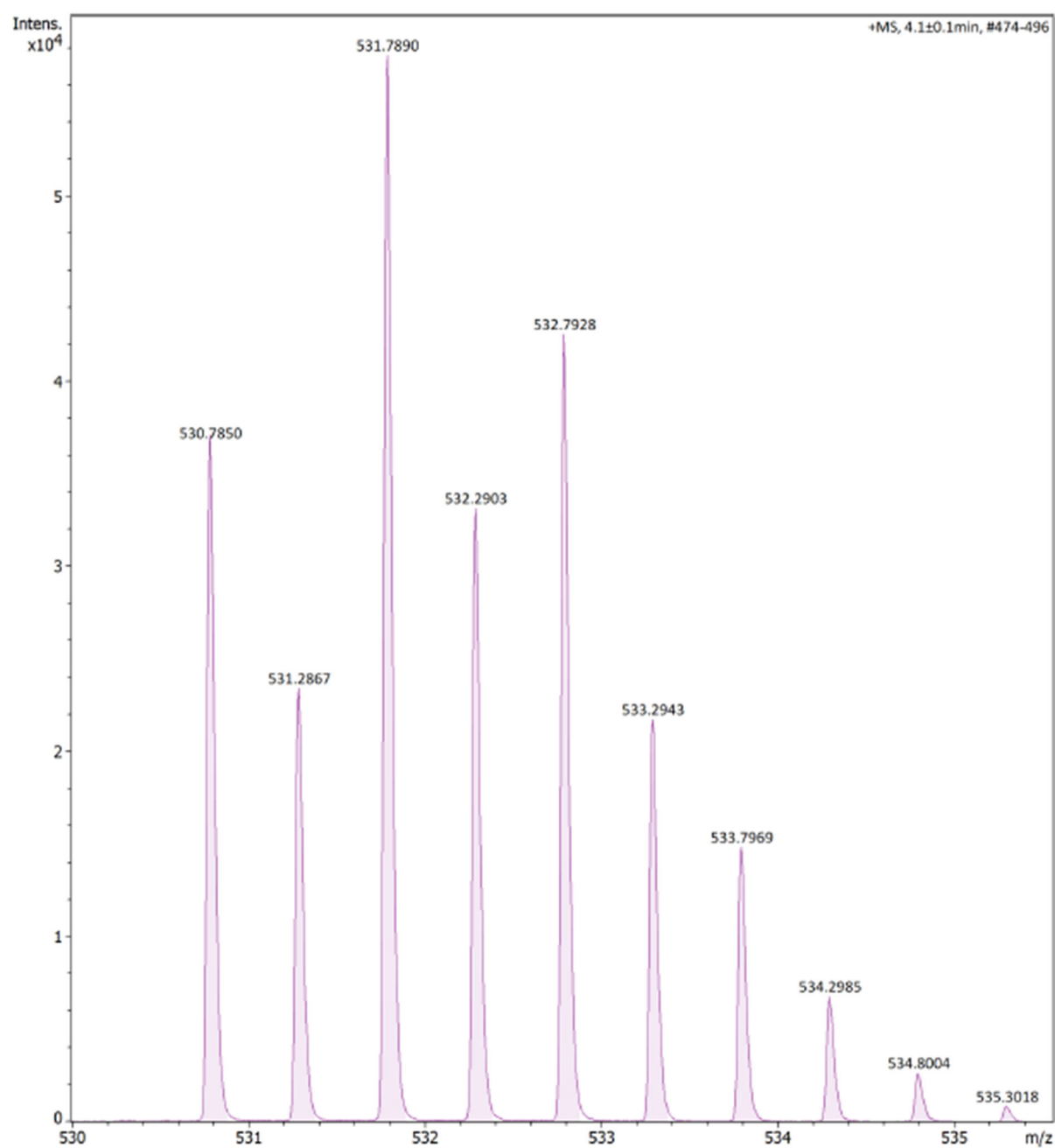




#	m/z	Res.	S/N	I	I %	FWHM
1	60.0461	7379	108.1	1306	0.2	0.0081
2	120.0811	9402	93.8	1254	0.1	0.0128
3	122.0968	8528	213.6	2862	0.3	0.0143
4	210.1244	10176	302.8	4233	0.5	0.0206
5	226.9493	10369	108.4	1504	0.2	0.0219
6	253.6404	10385	337.8	4642	0.5	0.0244
7	254.1478	6356	95.1	1305	0.2	0.0400
8	264.1581	11016	95.2	1294	0.2	0.0240
9	265.8989	11148	90.2	1225	0.1	0.0239
10	278.1558	11118	186.4	2523	0.3	0.0250
11	321.6725	10953	1044.5	14183	1.6	0.0294
12	322.1742	10501	389.3	5286	0.6	0.0307
13	322.6752	9984	85.0	1154	0.1	0.0323
14	348.1918	11385	1037.4	14190	1.6	0.0306
15	348.5262	11330	665.4	9105	1.1	0.0308
16	348.8604	10858	217.1	2971	0.3	0.0321
17	354.1952	11478	13263.2	181762	21.1	0.0309
18	354.5295	11414	8447.5	115743	13.4	0.0311
19	354.8637	11215	2873.8	39373	4.6	0.0316
20	355.1980	11499	726.4	9953	1.2	0.0309
21	355.5328	10726	141.4	1938	0.2	0.0331
22	404.2114	10427	92.5	1239	0.1	0.0388
23	408.2365	10873	129.9	1735	0.2	0.0375
24	419.2409	10628	529.4	7011	0.8	0.0394
25	420.2440	10697	128.8	1704	0.2	0.0393
26	506.2733	9968	147.5	2045	0.2	0.0508
27	515.7835	11776	94.1	1313	0.2	0.0438
28	530.7885	11587	61441.6	861448	100.0	0.0458
29	531.0830	7743	94.2	1321	0.2	0.0686
30	531.2898	11462	38545.7	540561	62.8	0.0464
31	531.5934	10386	97.1	1361	0.2	0.0512
32	531.6935	15559	219.1	3072	0.4	0.0342
33	531.7913	11334	13265.0	185963	21.6	0.0469
#	m/z	Res.	S/N	I	I %	FWHM
34	532.2927	11473	3210.8	45011	5.2	0.0464
35	532.7936	11487	629.8	8829	1.0	0.0464
36	533.2943	10700	109.8	1540	0.2	0.0498
37	541.7799	11338	179.9	2524	0.3	0.0478
38	542.2804	11113	112.4	1577	0.2	0.0488
39	555.3018	10133	153.9	2155	0.3	0.0548
40	557.2442	11466	216.8	3033	0.4	0.0486
41	557.7456	11552	148.7	2080	0.2	0.0483
42	563.7861	11402	91.6	1281	0.1	0.0494
43	1060.5665	11927	3317.3	39505	4.6	0.0889
44	1060.9038	11477	351.1	4182	0.5	0.0924
45	1061.0686	11660	1794.0	21363	2.5	0.0910
46	1061.2298	9222	361.8	4308	0.5	0.1151
47	1061.5694	11477	2370.7	28229	3.3	0.0925
48	1061.9051	11643	123.0	1465	0.2	0.0912
49	1062.0725	11835	543.8	6475	0.8	0.0897
50	1062.5740	11512	542.3	6458	0.7	0.0923

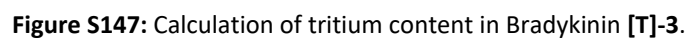
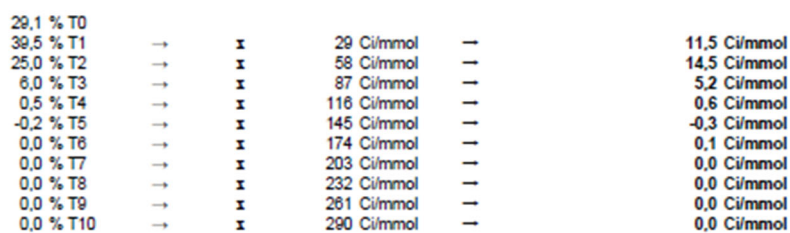
Figure S145: HR-MS analysis of Bradykinin **3** (reference).





#	m/z	Res.	S/N	I	I %	FWHM
1	60.0453	7719	138.1	1504	2.6	0.0078
2	114.0909	9080	73.9	918	1.6	0.0126
3	118.0861	8480	82.6	1036	1.8	0.0139
4	122.0959	8705	264.2	3348	5.8	0.0140
5	132.9616	8780	67.9	882	1.5	0.0151
6	149.0226	8898	68.6	922	1.6	0.0167
7	155.1537	9088	68.2	928	1.6	0.0171
8	171.1008	9436	57.7	807	1.4	0.0181
9	226.9474	9597	209.3	3073	5.3	0.0236
10	244.9577	9704	67.1	993	1.7	0.0252
11	252.9722	9683	50.7	749	1.3	0.0261
12	267.9739	10399	61.6	913	1.6	0.0258
13	279.1579	10659	52.7	783	1.4	0.0262
14	348.8584	10736	56.5	881	1.5	0.0325
15	354.1928	11799	452.4	7077	12.3	0.0300
16	354.5279	10861	258.4	4044	7.0	0.0326
17	354.8622	11617	702.6	10991	19.1	0.0305
18	355.1966	11196	383.4	6001	10.4	0.0317
19	355.5312	11546	512.1	8017	13.9	0.0308
20	355.8663	11559	253.4	3967	6.9	0.0308
21	356.2006	12015	190.5	2984	5.2	0.0296
22	356.5347	12342	86.5	1355	2.4	0.0289
23	419.2380	9888	54.7	885	1.5	0.0424
24	530.7850	11239	1958.1	36669	63.6	0.0472
25	531.2867	11306	1250.3	23431	40.6	0.0470
26	531.7890	11414	3076.6	57643	100.0	0.0466
27	532.2903	11621	1768.1	33148	57.5	0.0458
28	532.7928	11565	2269.2	42546	73.8	0.0461
29	533.2943	11347	1160.0	21751	37.7	0.0470
30	533.7969	11257	790.5	14835	25.7	0.0474
31	534.2985	11660	361.1	6781	11.8	0.0458
32	534.8004	11196	139.8	2627	4.6	0.0478
33	535.3018	10571	42.8	804	1.4	0.0506
#	m/z	Res.	S/N	I	I %	FWHM
34	541.7766	11133	46.4	879	1.5	0.0487
35	542.7789	11677	76.9	1460	2.5	0.0465
36	543.2809	11370	40.8	774	1.3	0.0478
37	543.7823	11627	55.1	1047	1.8	0.0468
38	557.2419	11805	55.4	1070	1.9	0.0472
39	558.2453	10420	74.7	1444	2.5	0.0536
40	558.7458	10728	54.7	1058	1.8	0.0521
41	559.2484	10952	61.5	1189	2.1	0.0511
42	559.7512	11350	45.0	872	1.5	0.0493
43	576.2324	11282	39.1	768	1.3	0.0511
44	1060.5600	10315	79.1	1158	2.0	0.1028
45	1061.5652	10431	75.7	1108	1.9	0.1018
46	1062.5681	11126	167.2	2445	4.2	0.0955
47	1063.0697	11199	53.8	787	1.4	0.0949
48	1063.5725	11510	120.3	1758	3.1	0.0924
49	1064.5752	10948	119.6	1747	3.0	0.0972
50	1065.5823	10997	62.3	910	1.6	0.0969

Figure S146: HR-MS analysis of Bradykinin [T]-3.



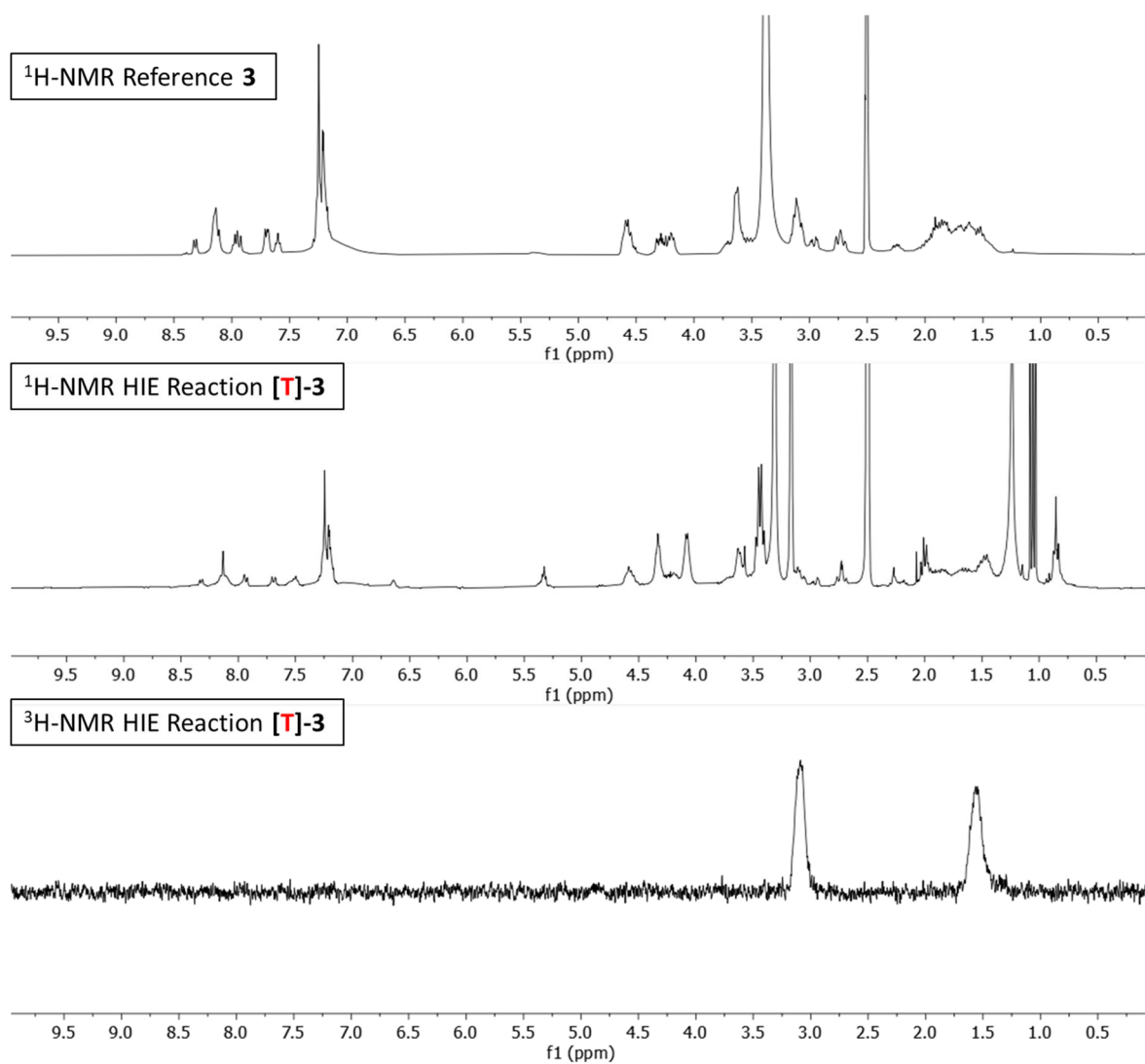


Figure S148: Overlay and comparison between ¹H-NMR spectrum of Bradykinin **3** and ¹H/³H-NMR spectra of Bradykinin **[T]-3**.

9.3 Lys-Pro-Ile-Thr-Val **28**

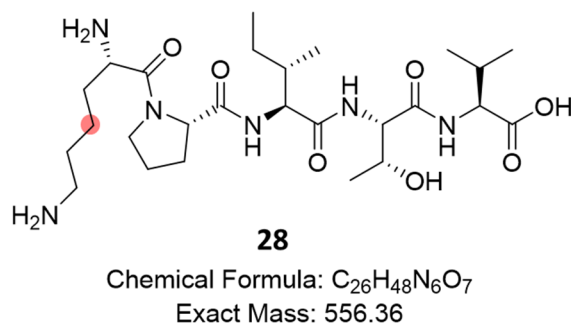


Figure S149: Structure of Lys-Pro-Ile-Thr-Val **28** with ³H labeling positions.

4.4 mg (7.91 μmol) of Lys-Pro-Ile-Thr-Val **28**, 2.5 mol% (0.025 equiv.) of catalyst [Ir(COD)Cl]₂ **C4** and 5 mol% (0.05 equiv.) of ligand **L11** (each dispensed as stock solution in dioxane) were added to the reaction flask. 1.5 mL of Borax/HCl buffer pH 9 and a stirring bar were added to the flask. The reaction flask was adapted to a TRITEC tritium manifold and the solution was frozen in liquid nitrogen (-196°C). The flask was evacuated and charged with tritium (149.03 GBq, 68.96 μmol T₂, 8.71 equiv., pressure 120 mbar). The reaction mixture was then allowed to warm to room temperature before stirring at 90°C for 1h. Then all volatile components were distilled into an ampule in vacuo at -196°C. The labile tritium was exchanged and removed by addition of MeOH and a freeze-drying process (repeated three times, then one time with CH₃CN).

The residue was dissolved in 1 mL CH₃CN/water, followed by purification and isolation *via* HPLC (Waters CSH C18 10x150 mm, 5 μm, 6 mL/min flow, ACN/water + 0.1% TFA gradient program) that gave 1.58 mg, 5300 MBq, 3.5 % RCY, 36% CY, 1864.8 GBq/mmol (50.4 Ci/mmol) of the desired labelled compound [**T**]-**28**. This corresponds to 1.73 T/molecule.

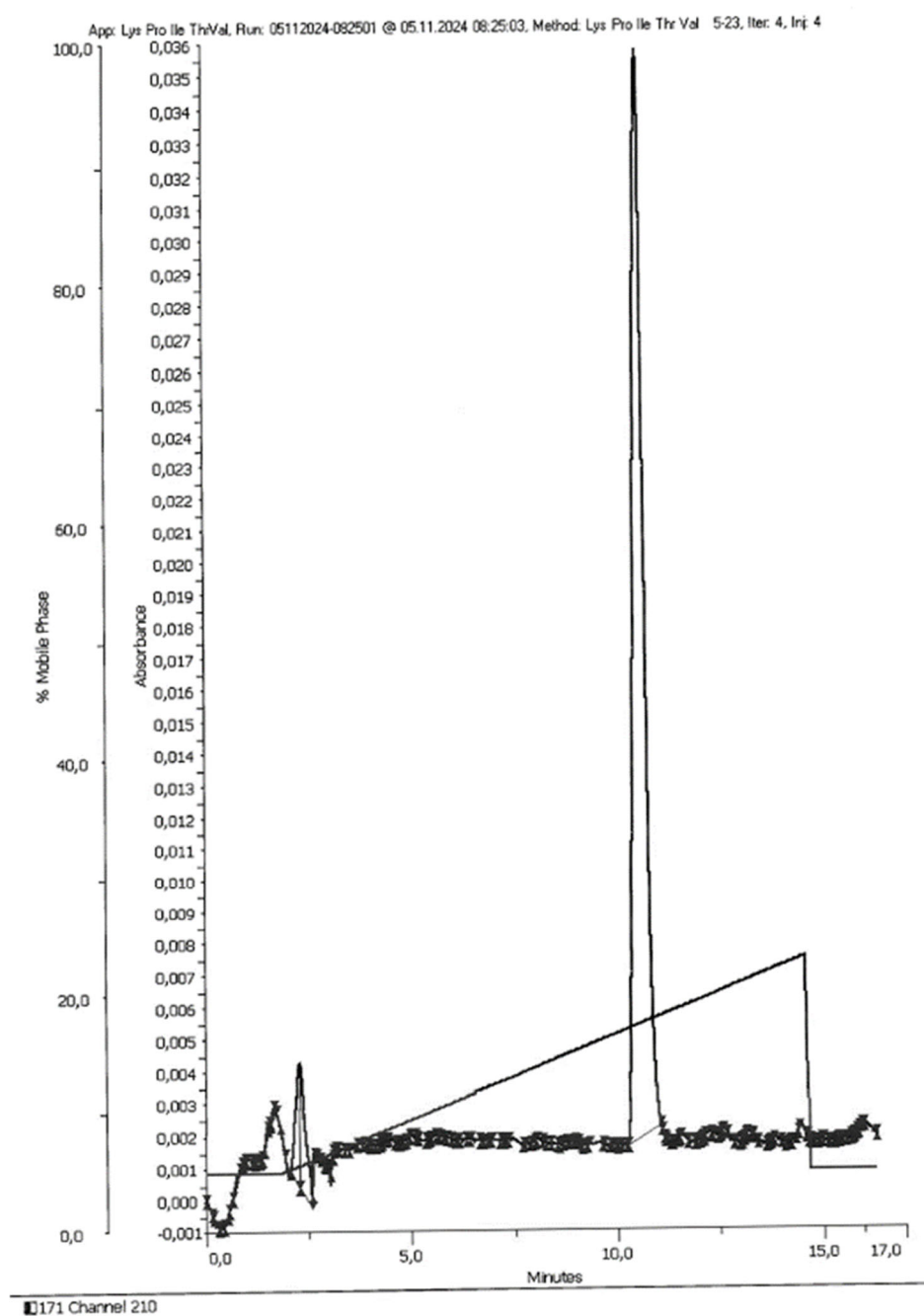


Figure S150: Purification chromatogram of Lys-Pro-Ile-Thr-Val [T]-28 (UV spectrum 210 nm).

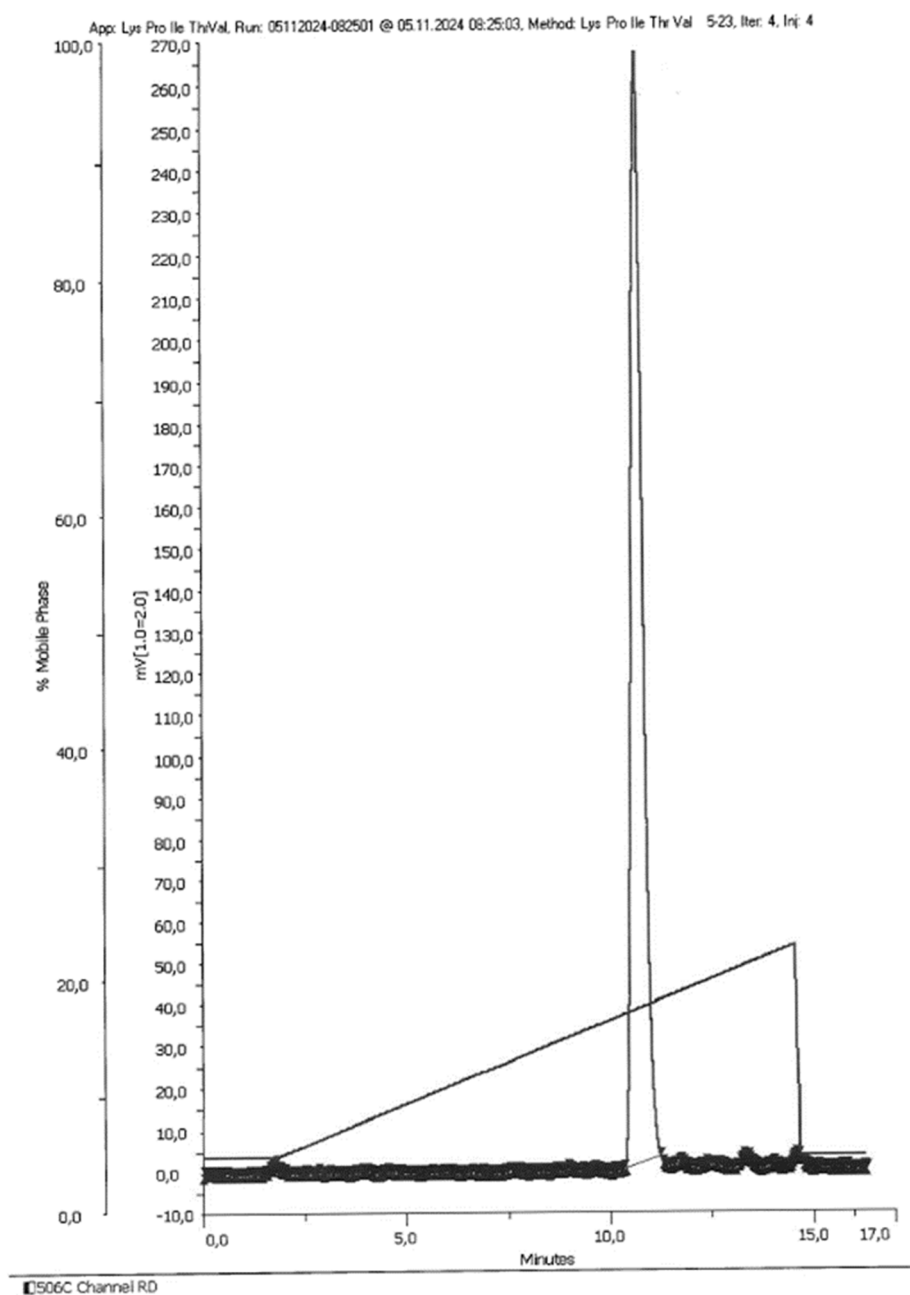
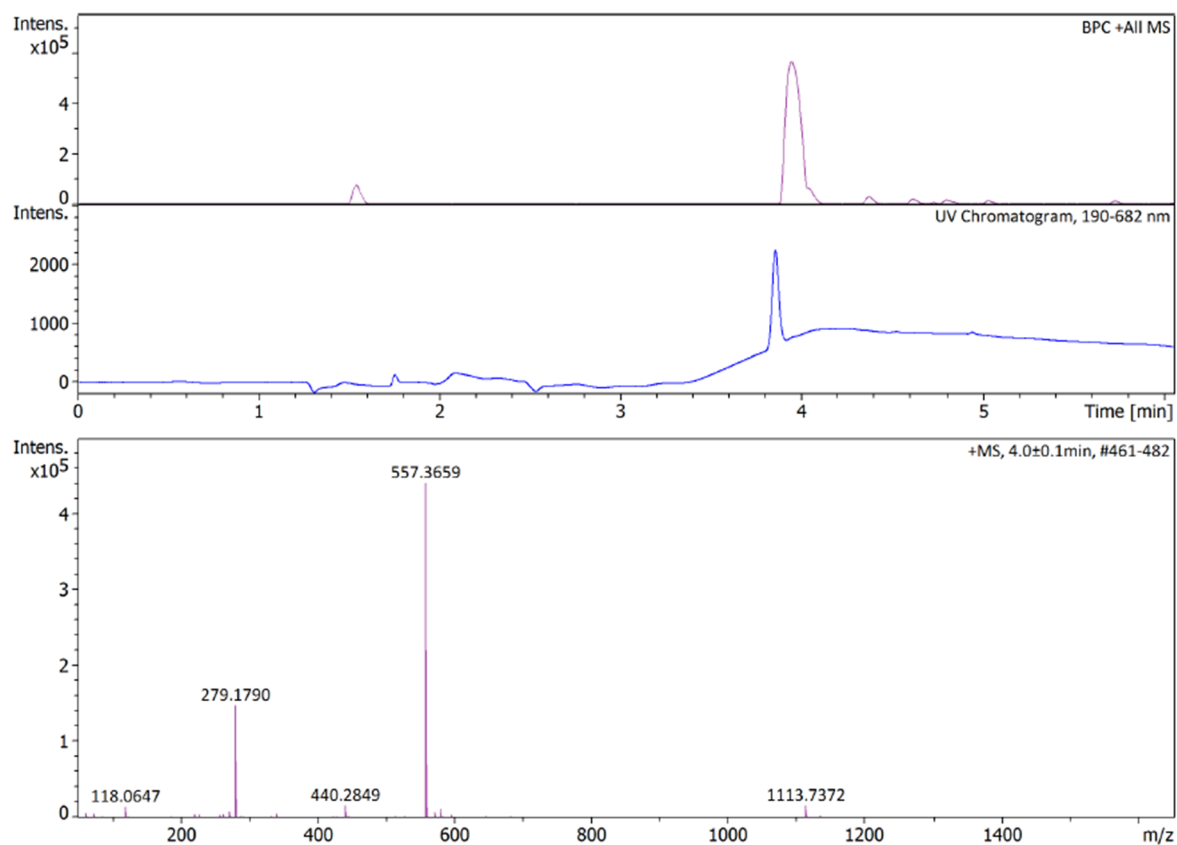
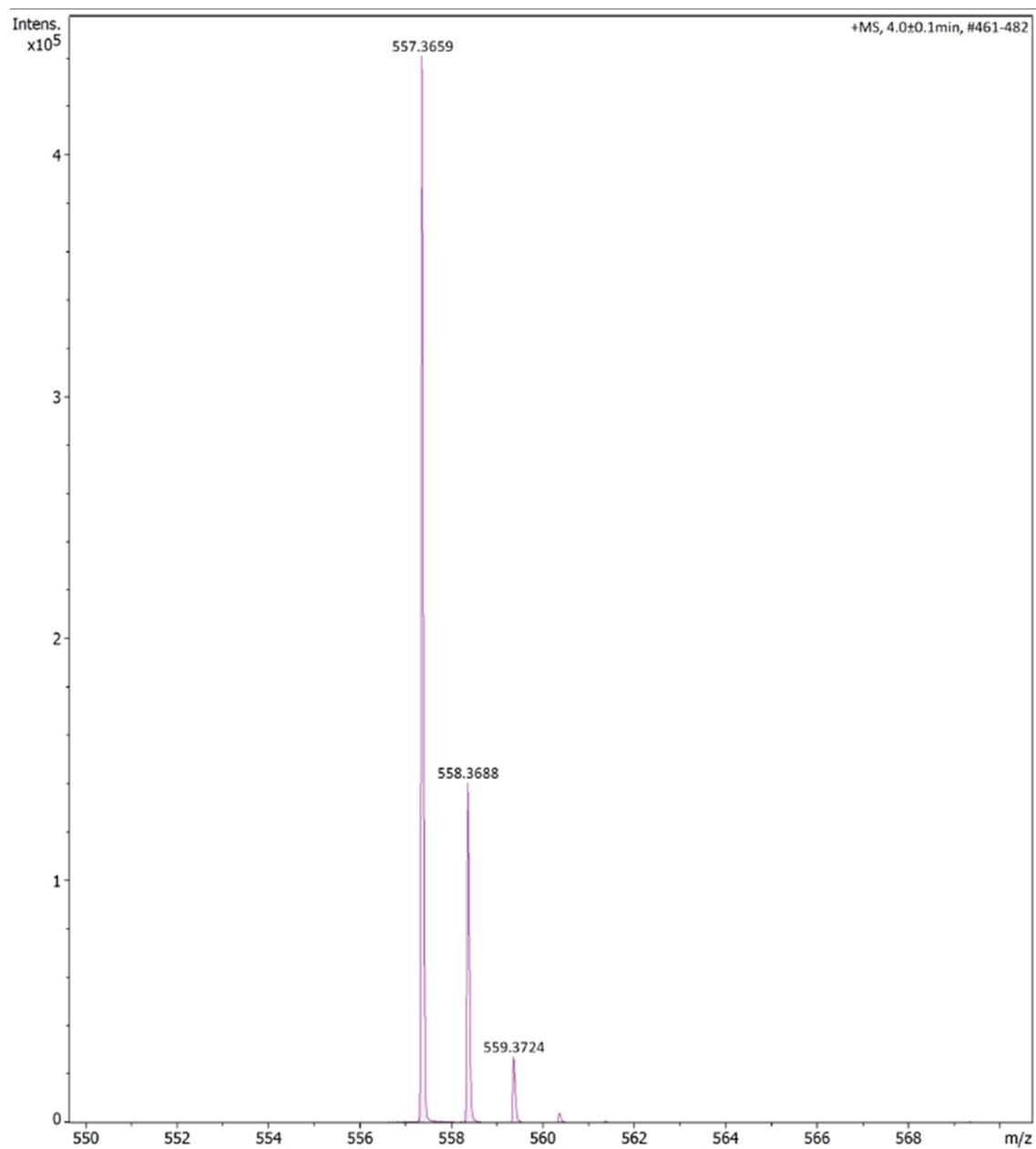


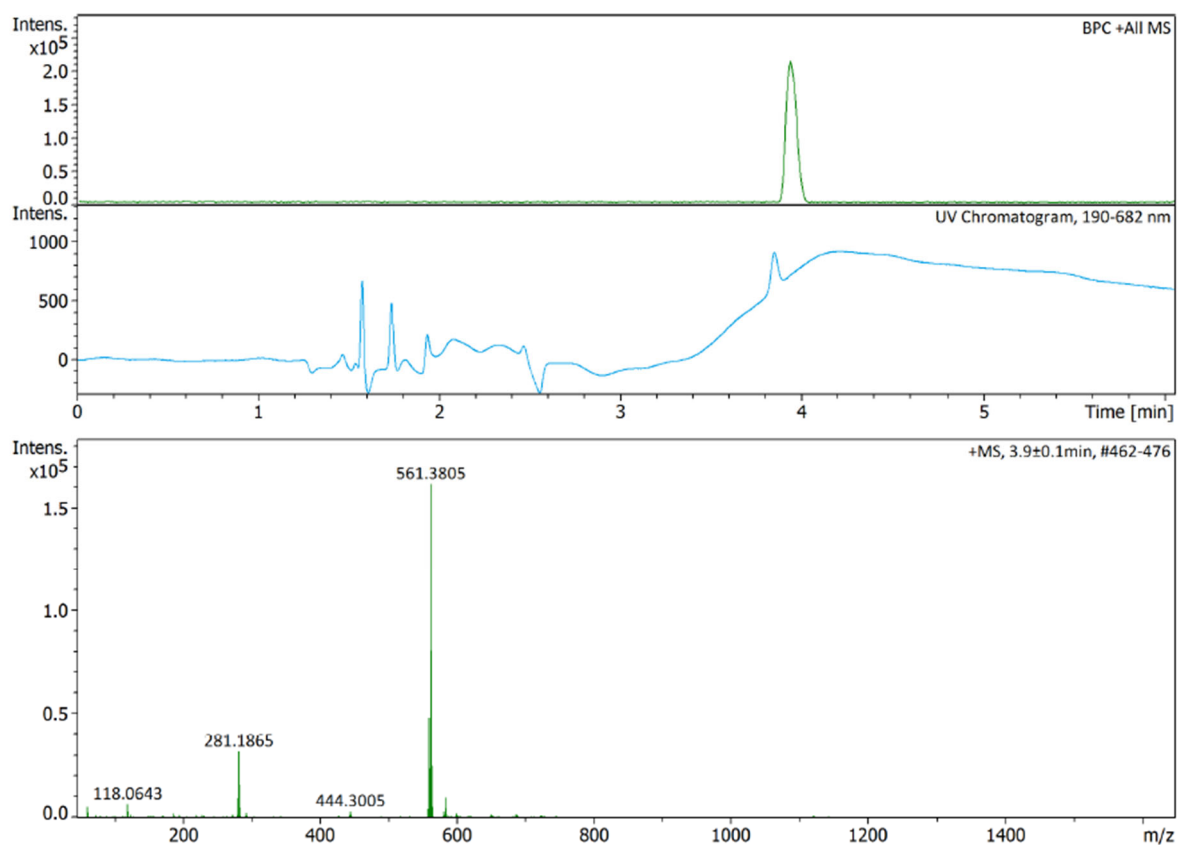
Figure S151: Radiochromatogram of Lys-Pro-Ile-Thr-Val [T]-28.

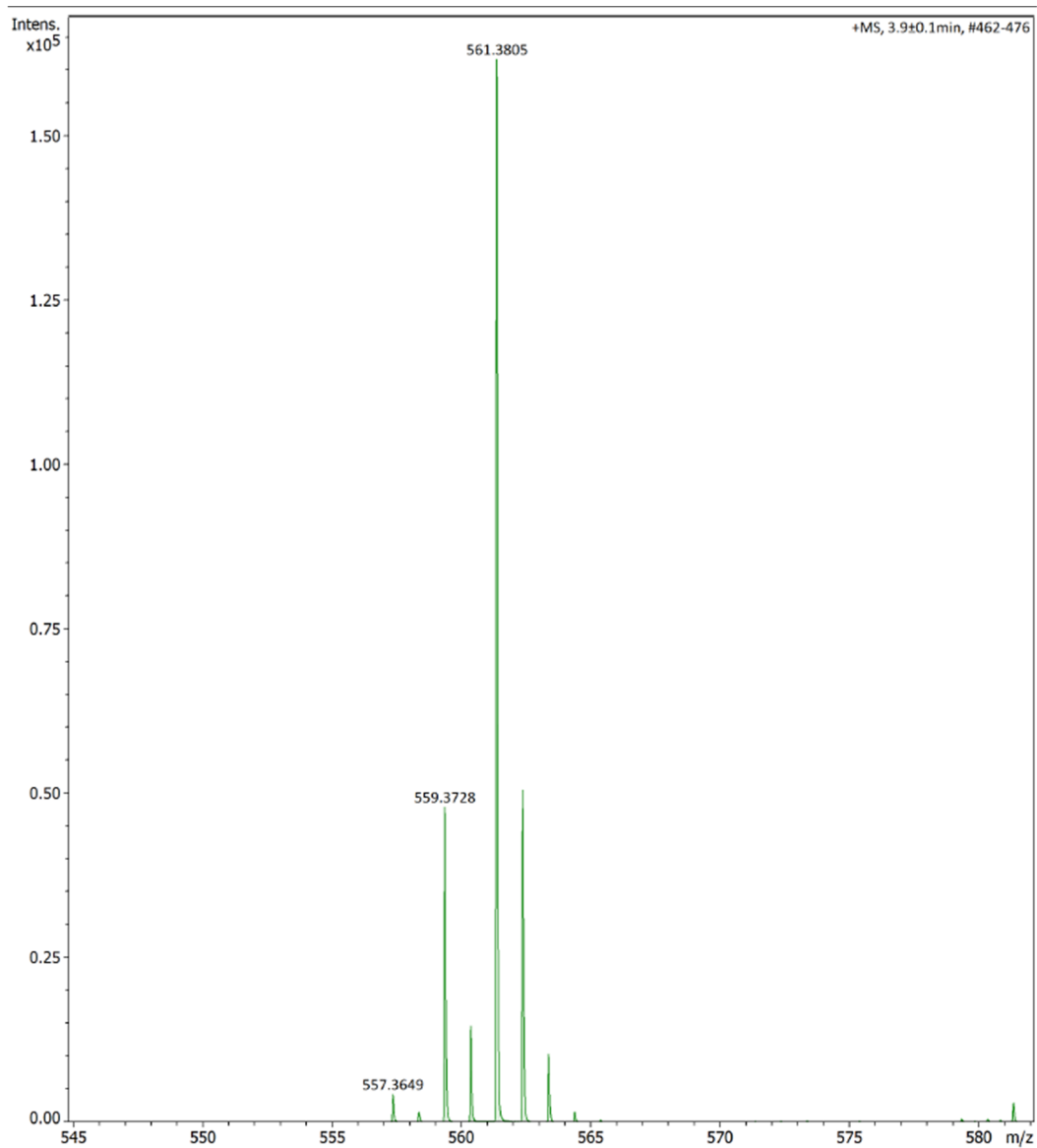




#	m/z	Res.	S/N	I	I %	FWHM
1	60.0134	6419	263.6	4475	1.0	0.0093
2	72.0522	7111	236.8	4066	0.9	0.0101
3	118.0647	7930	748.8	13464	3.1	0.0149
4	219.1218	9281	180.8	3052	0.7	0.0236
5	226.1438	9002	185.2	3101	0.7	0.0251
6	256.1743	9668	145.6	2337	0.5	0.0265
7	261.1679	9476	198.5	3157	0.7	0.0276
8	270.1736	9216	428.9	6700	1.5	0.0293
9	270.6733	9566	161.5	2519	0.6	0.0283
10	279.1790	9443	9627.3	147537	33.5	0.0296
11	279.6807	9585	3133.5	47993	10.9	0.0292
12	280.1826	9242	611.3	9356	2.1	0.0303
13	286.1875	9490	101.6	1527	0.3	0.0302
14	332.2119	9280	139.3	1905	0.4	0.0358
15	339.2337	9579	296.4	4010	0.9	0.0354
16	440.2849	9770	1222.1	14813	3.4	0.0451
17	441.2888	9502	310.9	3761	0.9	0.0464
18	557.3659	10169	34774.1	440958	100.0	0.0548
19	558.3688	10183	11072.5	140513	31.9	0.0548
20	559.3724	9899	2134.9	27109	6.1	0.0565
21	560.3749	9596	304.8	3873	0.9	0.0584
22	571.3823	10098	496.8	6391	1.4	0.0566
23	572.3857	9885	158.9	2046	0.5	0.0579
24	579.3489	10011	812.0	10529	2.4	0.0579
25	580.3519	9723	247.2	3209	0.7	0.0597
26	595.3234	9971	181.2	2386	0.5	0.0597
27	1113.7372	10253	1167.7	14666	3.3	0.1086
28	1114.7401	10211	733.7	9212	2.1	0.1092
29	1115.7439	10169	246.6	3097	0.7	0.1097
30	1135.7210	10122	143.5	1796	0.4	0.1122

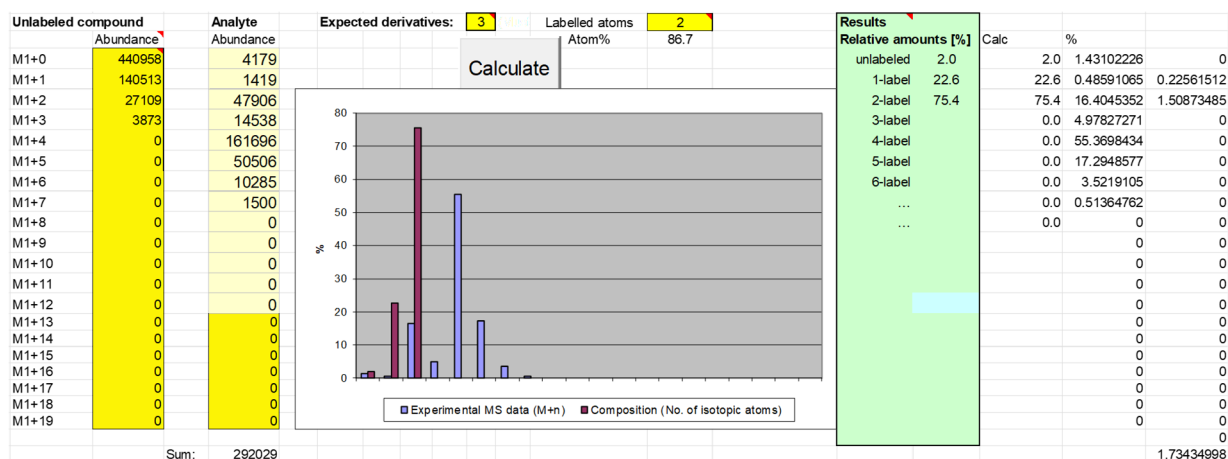
Figure S152: HR-MS analysis of Lys-Pro-Ile-Thr-Val **28** (reference).





#	m/z	Res.	S/N	I	I %	FWHM
1	60.0132	6591	276.3	4837	3.0	0.0091
2	72.0519	6957	56.8	1008	0.6	0.0104
3	118.0643	8036	340.0	6405	4.0	0.0147
4	122.0745	8131	60.8	1150	0.7	0.0150
5	186.0432	8515	90.0	1683	1.0	0.0218
6	272.1806	9103	78.2	1329	0.8	0.0299
7	279.1748	7861	54.5	916	0.6	0.0355
8	280.1824	9259	555.2	9326	5.8	0.0303
9	280.6835	9647	177.0	2970	1.8	0.0291
10	281.1865	9436	1898.1	31833	19.7	0.0298
11	281.6880	9377	595.3	9978	6.2	0.0300
12	282.1897	8942	116.7	1955	1.2	0.0316
13	292.1779	9370	120.7	1989	1.2	0.0312
14	444.3005	9471	199.2	2900	1.8	0.0469
15	445.2915	6901	60.8	885	0.5	0.0645
16	557.3649	9672	277.2	4179	2.6	0.0576
17	558.3675	9288	94.0	1419	0.9	0.0601
18	559.3728	9924	3174.2	47906	29.6	0.0564
19	560.3759	9797	963.2	14538	9.0	0.0572
20	561.3805	9989	10706.6	161696	100.0	0.0562
21	562.3841	9895	3341.3	50506	31.2	0.0568
22	563.3870	10034	680.1	10285	6.4	0.0561
23	564.3919	9757	99.1	1500	0.9	0.0578
24	581.3558	9377	182.8	2819	1.7	0.0620
25	582.3597	8922	62.9	970	0.6	0.0653
26	583.3633	9831	620.5	9570	5.9	0.0593
27	584.3659	9187	188.9	2917	1.8	0.0636
28	599.3380	9360	115.9	1825	1.1	0.0640
29	650.2714	9005	77.4	1285	0.8	0.0722
30	686.2459	10462	82.0	1410	0.9	0.0656

Figure S153: HR-MS analysis of Lys-Pro-Ile-Thr-Val [T]-28.



2,0 % T0					
22,6 % T1	→	x	29 Ci/mmol	→	6,5 Ci/mmol
75,2 % T2	→	x	58 Ci/mmol	→	43,6 Ci/mmol
0,2 % T3	→	x	87 Ci/mmol	→	0,2 Ci/mmol
0,0 % T4	→	x	116 Ci/mmol	→	0,0 Ci/mmol
0,0 % T5	→	x	145 Ci/mmol	→	0,0 Ci/mmol
0,0 % T6	→	x	174 Ci/mmol	→	0,0 Ci/mmol
0,0 % T7	→	x	203 Ci/mmol	→	0,0 Ci/mmol
0,0 % T8	→	x	232 Ci/mmol	→	0,0 Ci/mmol
0,0 % T9	→	x	261 Ci/mmol	→	0,0 Ci/mmol
0,0 % T10	→	x	290 Ci/mmol	→	0,0 Ci/mmol

100,0 %		50,370 Ci/mmol	→	50,4 Ci/mmol
		558,7		3,34 GBq/mg
		α/mol		

Figure S154: Calculation of tritium content in Lys-Pro-Ile-Thr-Val [T]-28.

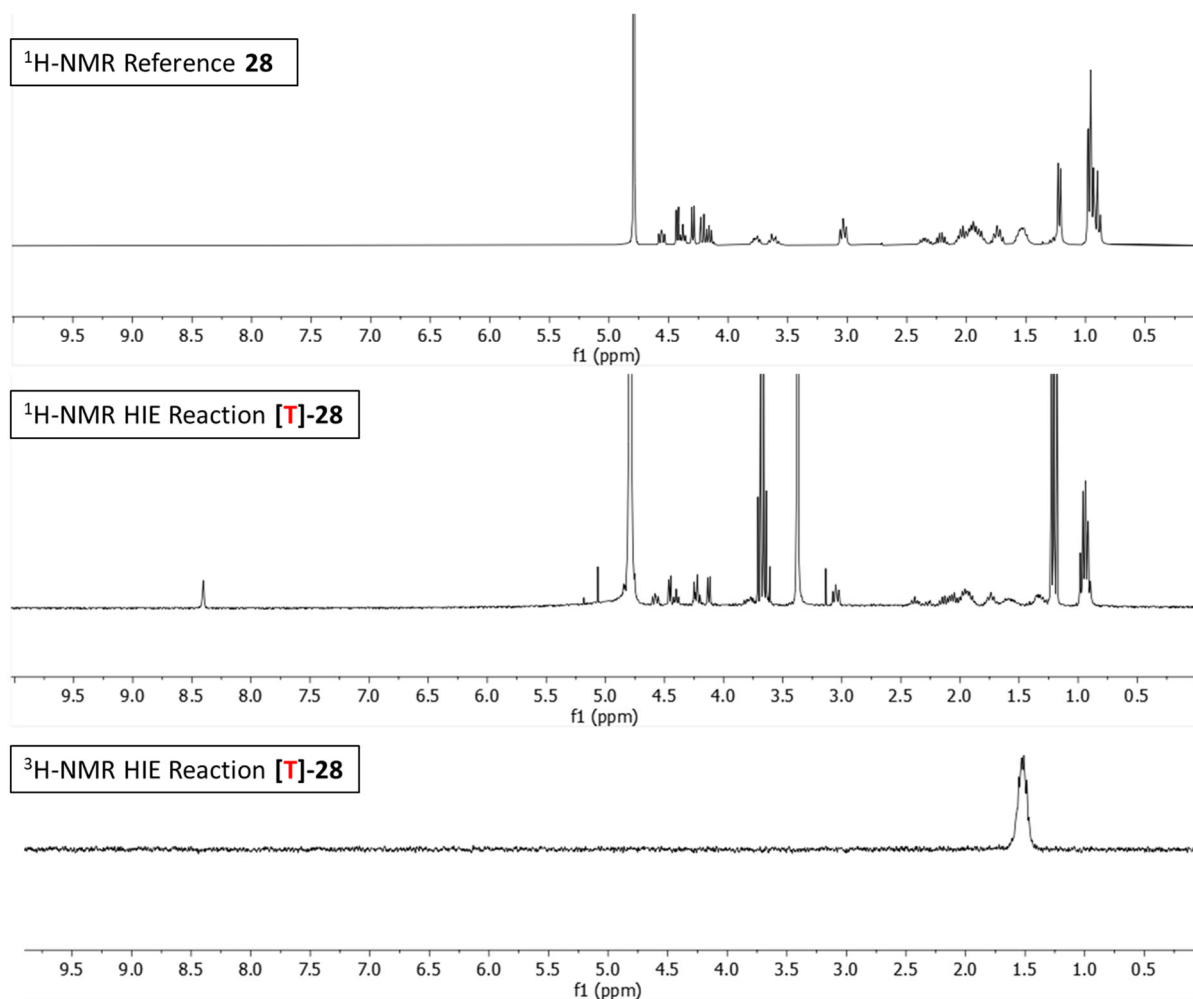


Figure S155: Overlay and comparison between ¹H-NMR spectrum of Lys-Pro-Ile-Thr-Val **28** and ¹H/³H-NMR spectra Lys-Pro-Ile-Thr-Val [T]-28.

9.4 Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29**

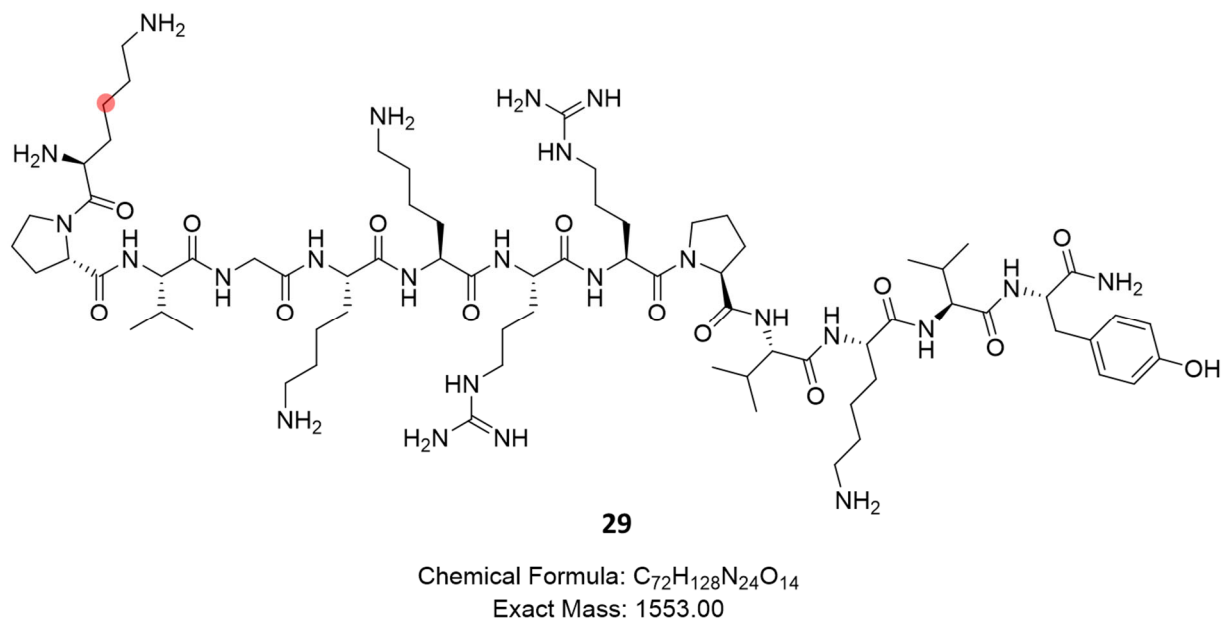


Figure S156: Structure of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29**.

8.0 mg (5.13 μ mol) of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29**, 5 mol% (0.05 equiv.) of catalyst [Ir(COD)Cl]₂ **C4** and 10 mol% (0.1 equiv.) of ligand **L11** (each dispensed as stock solution in dioxane, each in 0.03 mL) were added to the reaction flask. 1.5 mL of Borax/HCl buffer pH 9 and a stirring bar were added to the flask. The reaction flask was adapted to a TRITEC tritium manifold and the solution was frozen in liquid nitrogen (-196°C). The flask was evacuated and charged with tritium (140.03 GBq, 64.79 μ mol T₂, 12.63 equiv., pressure 110 mbar). The reaction mixture was then allowed to warm to room temperature before stirring at 90°C for 1h. Then all volatile components were distilled into an ampule in vacuo at -196°C. The labile tritium was exchanged and removed by addition of MeOH and a freeze-drying process (repeated three times, then one time with CH₃CN).

The residue was dissolved in 2 mL CH₃CN/water/TFA (10/100/1), followed by purification and isolation *via* HPLC (Waters CSH C18 10x150 mm, 5 μ m, 6 mL/min flow, ACN/water + 0.1% TFA gradient program) that gave 0.75 mg, 220 MBq, 0.16 % RCY, 9.3% CY, 455.1 GBq/mmol (12.3 Ci/mmol) of the desired labelled compound [**T**]-**29**. This corresponds to 0.42 T/molecule.

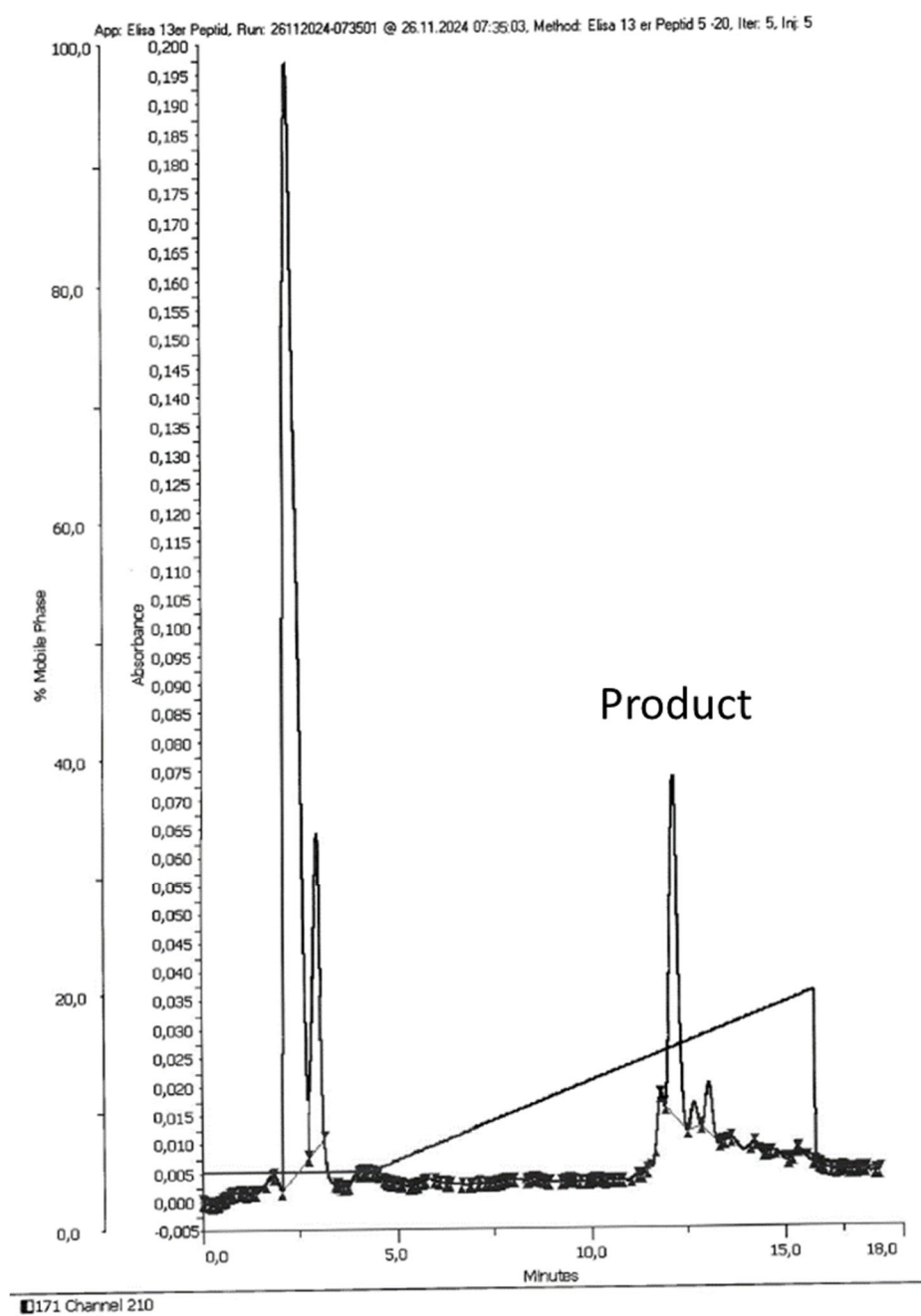


Figure S157: Purification chromatogram of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ [T]-29 (UV spectrum 210 nm).

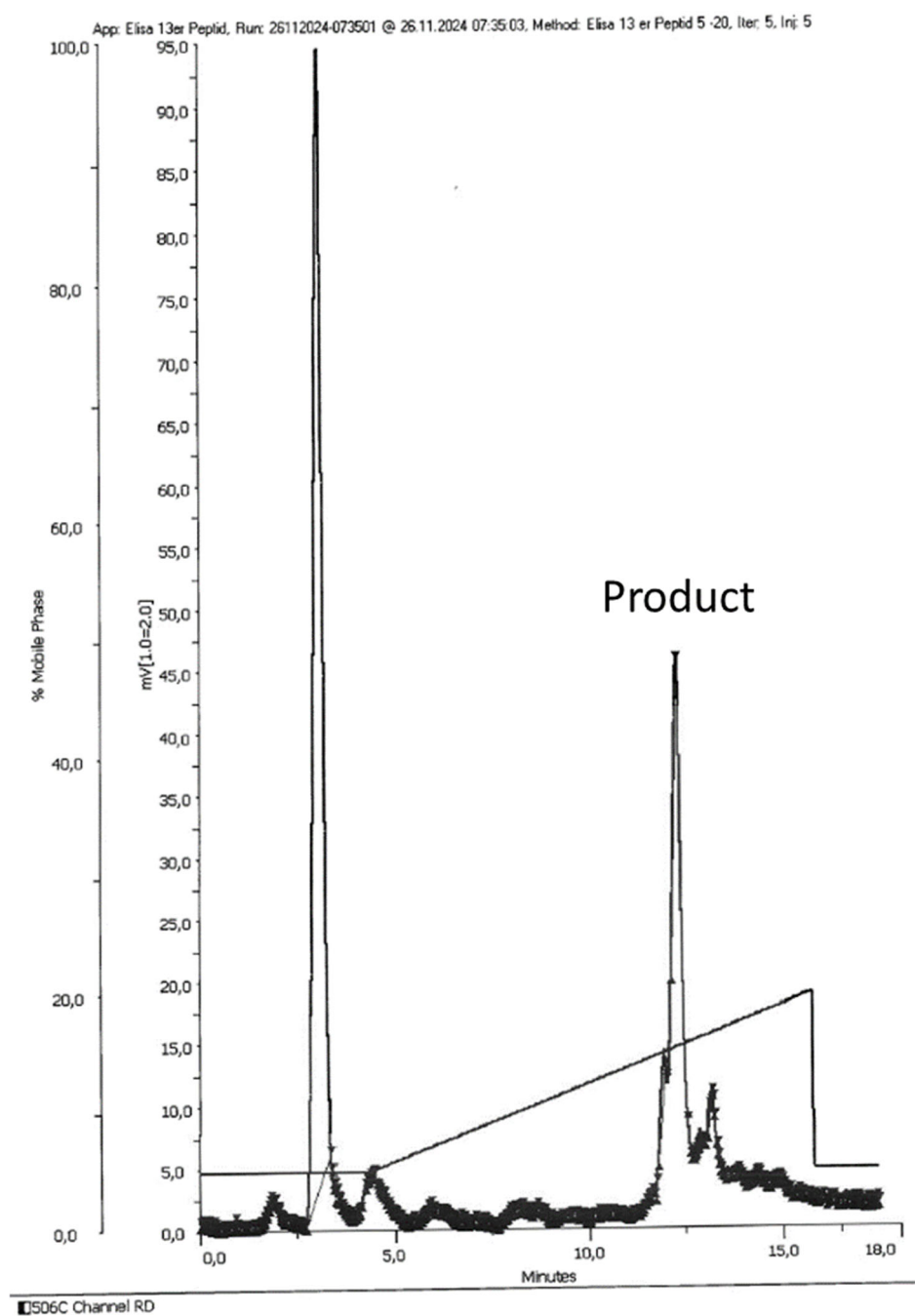
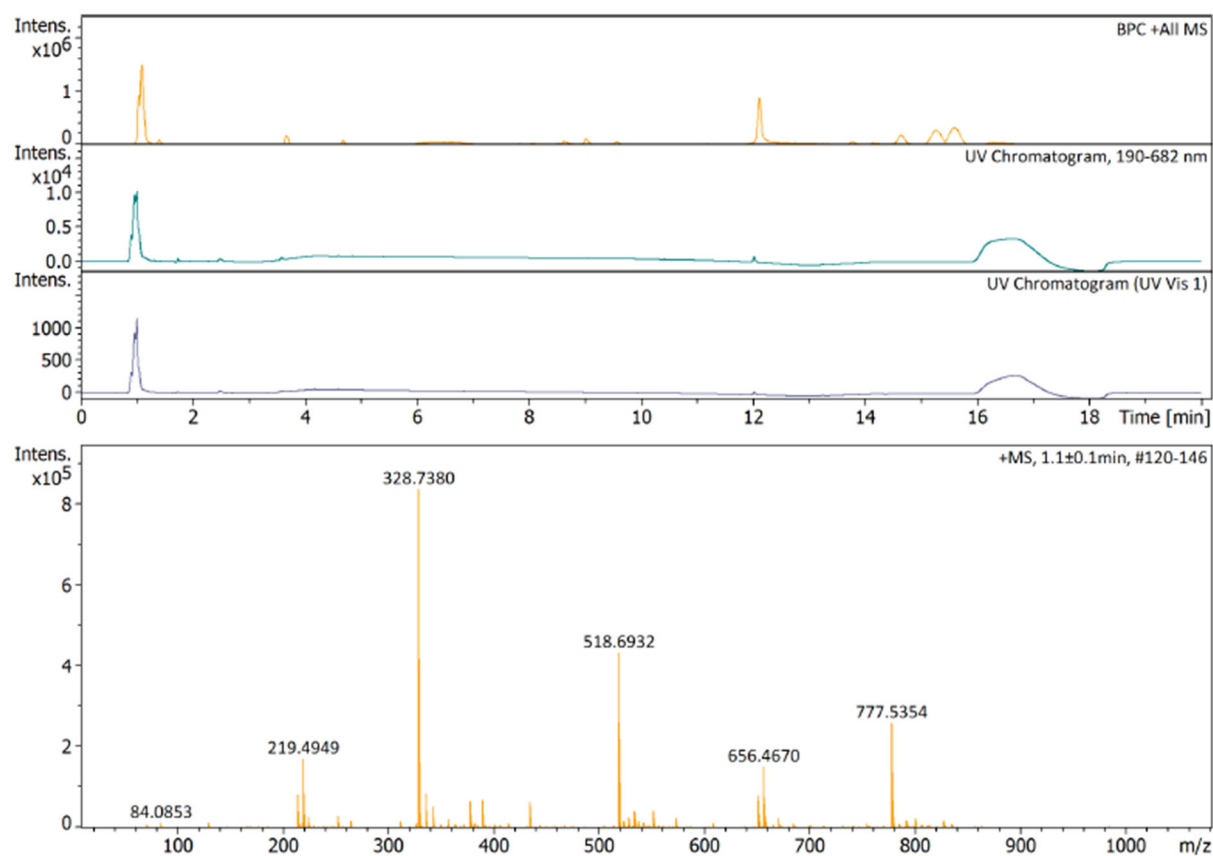
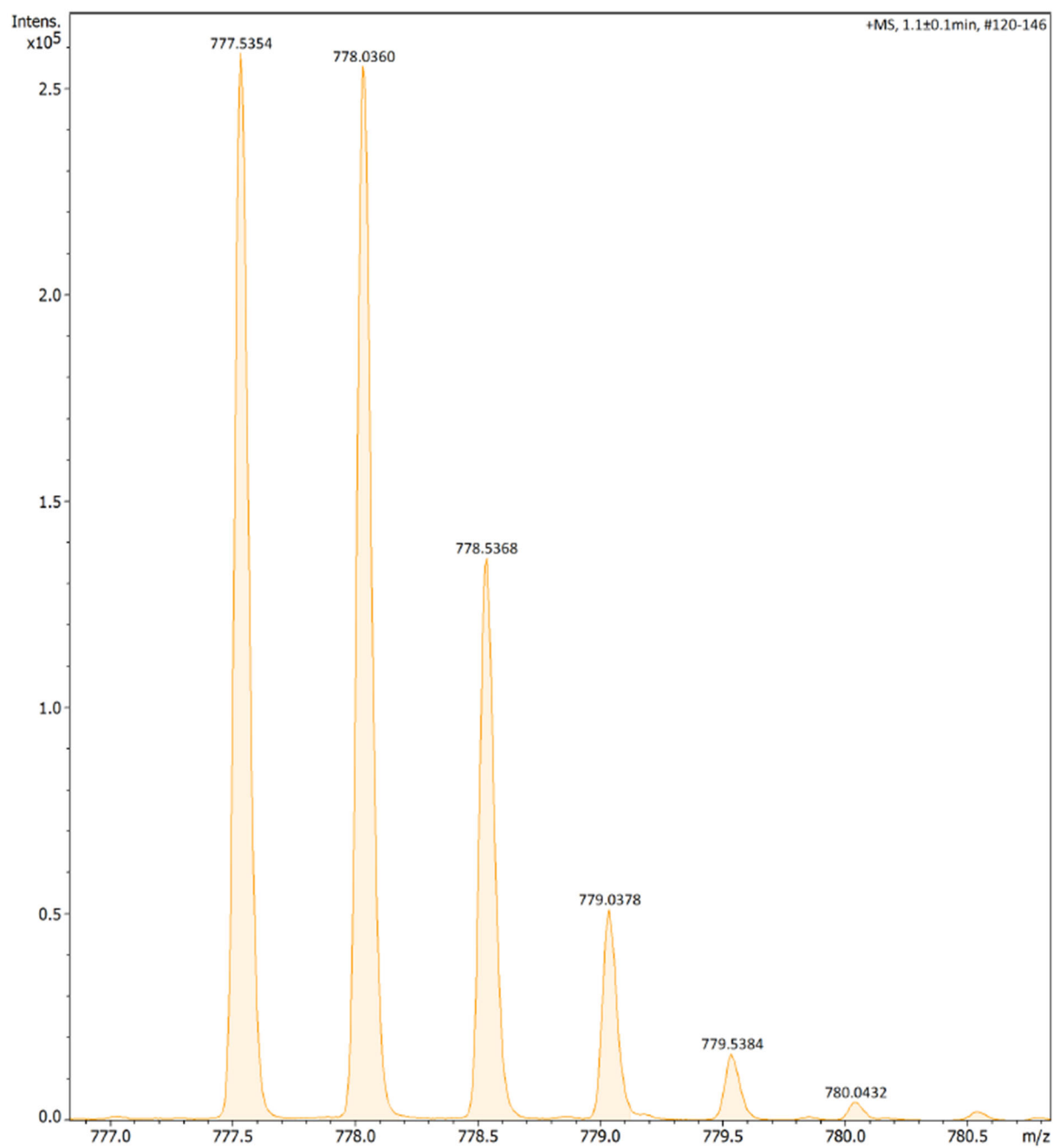


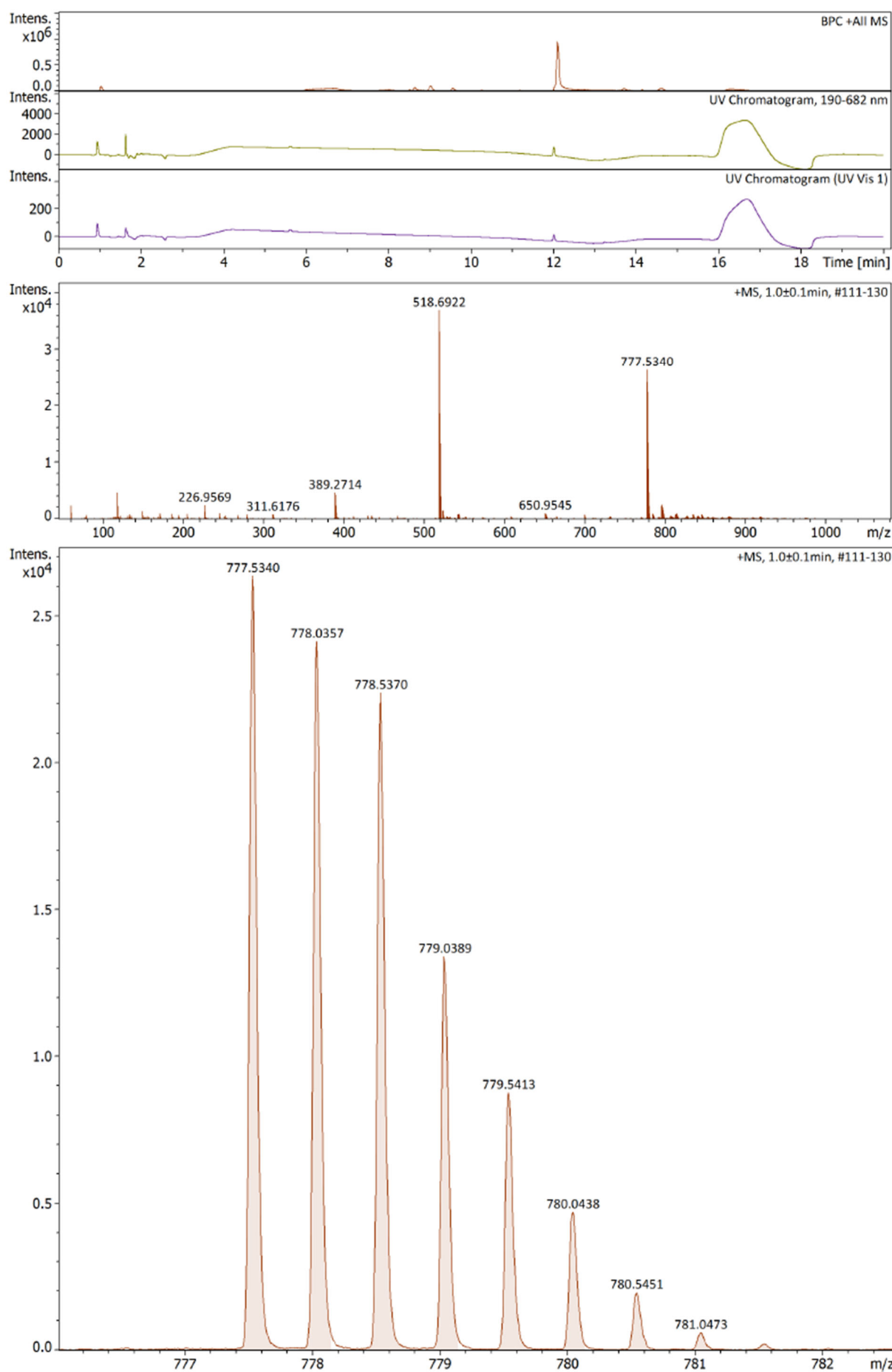
Figure S158: Radiochromatogram of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ [T]-29.





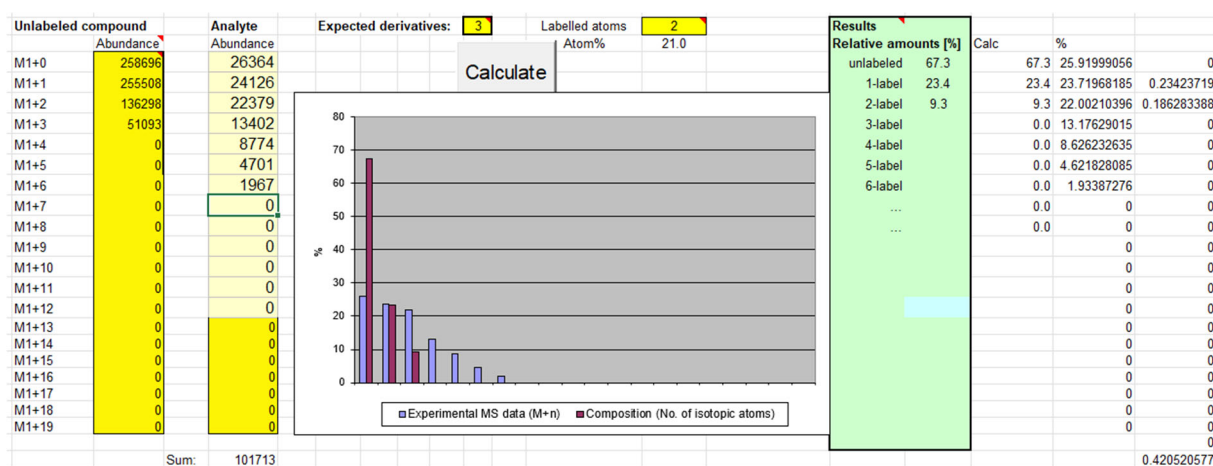
#	m/z	Res.	S/N	I	I %	FWHM
1	213.8192	11055	3379.7	80730	9.6	0.0193
2	219.4949	10902	6957.4	168890	20.2	0.0201
3	219.8293	10975	2629.5	63835	7.6	0.0200
4	328.7380	11142	22975.6	837182	100.0	0.0295
5	329.2393	11114	8828.0	321777	38.4	0.0296
6	329.7406	11246	1971.0	72082	8.6	0.0293
7	335.7460	11187	2244.5	84176	10.1	0.0300
8	342.7386	9747	1318.1	51083	6.1	0.0352
9	377.7763	11522	1401.0	63917	7.6	0.0328
10	389.2723	12211	1475.0	68551	8.2	0.0319
11	389.5224	12186	1396.4	64896	7.8	0.0320
12	389.7730	12295	722.5	33576	4.0	0.0317
13	434.3059	12201	1247.0	63030	7.5	0.0356
14	434.6397	11975	1017.5	51452	6.1	0.0363
15	518.6932	12361	6846.4	432332	51.6	0.0420
16	519.0272	12129	6627.7	419102	50.1	0.0428
17	519.3611	11879	3450.1	218179	26.1	0.0437
18	519.6951	11788	1227.3	77664	9.3	0.0441
19	533.6894	12254	606.6	39930	4.8	0.0436
20	534.0234	12228	553.5	36458	4.4	0.0437
21	551.3851	12323	538.2	36838	4.4	0.0447
22	551.7189	12304	596.6	40839	4.9	0.0448
23	650.9546	12045	1060.4	77945	9.3	0.0540
24	651.4554	11911	881.9	64821	7.7	0.0547
25	656.4670	11304	2041.6	150219	17.9	0.0581
26	657.4698	11299	773.5	56861	6.8	0.0582
27	777.5354	12212	3524.5	258696	30.9	0.0637
28	778.0360	11994	3481.6	255508	30.5	0.0649
29	778.5368	11868	1858.1	136298	16.3	0.0656
30	779.0378	12201	696.6	51093	6.1	0.0639

Figure S159: HR-MS analysis of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29** (reference).



#	m/z	Res.	S/N	I	I%	FWHM
1	60.0487	7207	131.6	2333	6.3	0.0083
2	118.0913	8899	254.3	4621	12.5	0.0133
3	149.0294	9300	72.6	1301	3.5	0.0160
4	226.9569	10387	146.3	2422	6.6	0.0218
5	389.2714	12393	274.4	4613	12.5	0.0314
6	389.5224	12440	247.4	4158	11.3	0.0313
7	389.7731	12484	230.2	3869	10.5	0.0312
8	390.0244	12202	139.9	2351	6.4	0.0320
9	390.2755	12602	99.4	1671	4.5	0.0310
10	518.6922	12603	1969.9	36882	100.0	0.0412
11	519.0265	12610	1771.4	33157	89.9	0.0412
12	519.3613	12435	1628.7	30495	82.7	0.0418
13	519.6958	12513	993.3	18594	50.4	0.0415
14	520.0306	12634	679.1	12708	34.5	0.0412
15	520.3656	12353	357.2	6688	18.1	0.0421
16	520.6994	13080	156.0	2920	7.9	0.0398
17	523.3621	11252	78.0	1462	4.0	0.0465
18	523.6971	11357	77.7	1458	4.0	0.0461
19	777.5340	12259	1501.9	26364	71.5	0.0634
20	778.0357	12312	1374.5	24126	65.4	0.0632
21	778.5370	12579	1275.4	22379	60.7	0.0619
22	779.0389	12455	764.0	13402	36.3	0.0626
23	779.5413	12246	500.2	8774	23.8	0.0637
24	780.0438	11661	268.1	4701	12.7	0.0669
25	780.5451	11779	112.2	1967	5.3	0.0663
26	795.5234	11987	132.1	2278	6.2	0.0664
27	796.0249	11752	117.3	2022	5.5	0.0677
28	796.5257	11760	142.7	2460	6.7	0.0677
29	797.0283	12122	110.7	1908	5.2	0.0657
30	797.5286	12477	89.8	1546	4.2	0.0639

Figure S160: HR-MS analysis of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ [T]-29.



67,7 % T0	→	x	29 Ci/mmol	—	6,3 Ci/mmol
21,8 % T1	→	x	58 Ci/mmol	—	6,4 Ci/mmol
11,0 % T2	→	x	87 Ci/mmol	—	-0,7 Ci/mmol
-0,8 % T3	→	x	116 Ci/mmol	—	0,5 Ci/mmol
0,4 % T4	→	x	145 Ci/mmol	—	-0,3 Ci/mmol
-0,2 % T5	→	x	174 Ci/mmol	—	0,2 Ci/mmol
0,1 % T6	→	x	203 Ci/mmol	—	-0,1 Ci/mmol
-0,1 % T7	→	x	232 Ci/mmol	—	0,1 Ci/mmol
0,0 % T8	→	x	261 Ci/mmol	—	0,0 Ci/mmol
0,0 % T9	→	x	290 Ci/mmol	—	0,0 Ci/mmol
0,0 % T10	→	x			



Figure S161: Calculation of tritium content in Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **[T]-29**.

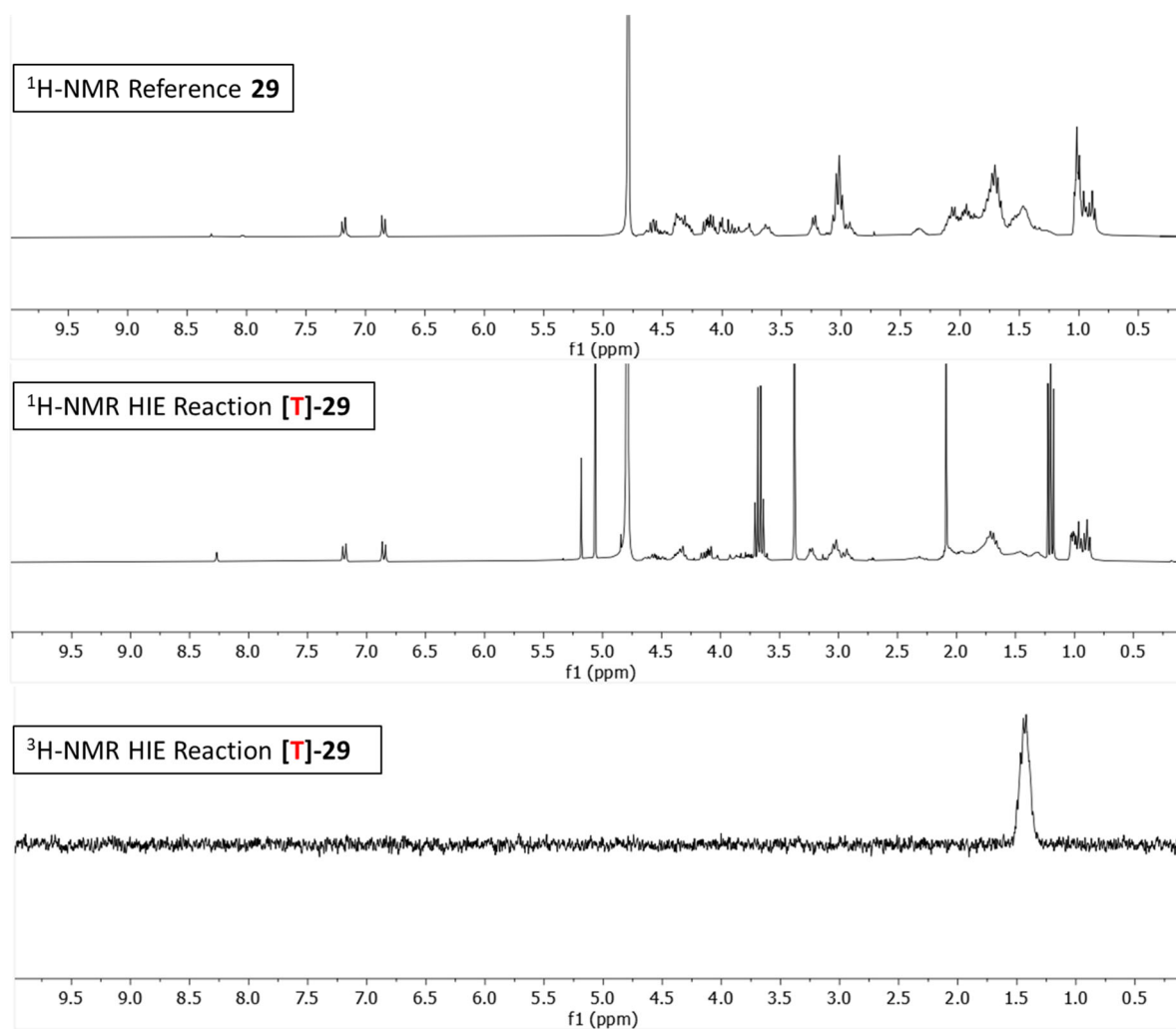


Figure S162: Overlay and comparison between ¹H-NMR spectrum of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **29** and ¹H/³H-NMR spectra of Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-NH₂ **[T]-29**.

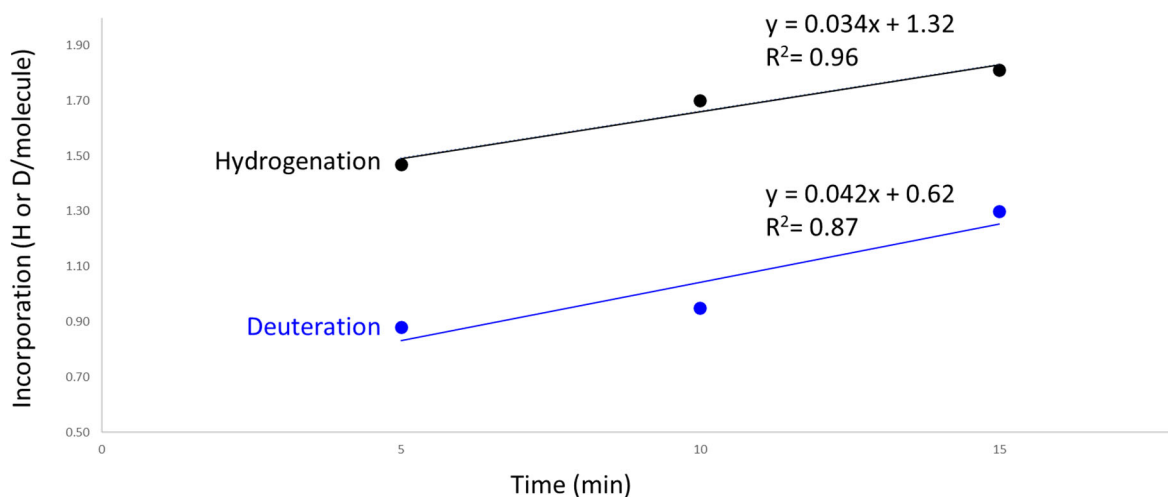
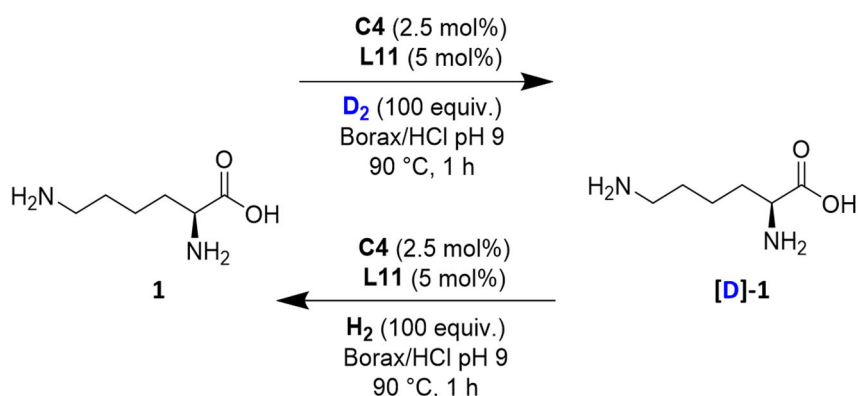
10 Kinetic Isotope Effect (KIE) studies

A 6 mM stock solution catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** and a 30 mM stock solution of **L11** are prepared using dioxane as solvent.

Reactions to incorporate deuterium are prepared as follows: L-Lys **1** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl Buffer pH 9, catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** (2.5 mol%, 0.025 equiv.) and ligand **L11** (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with deuterium gas. This procedure was repeated three times. The reaction was stirred under D_2 atmosphere (100 equiv.) at 90 °C. At different time points, an aliquot of the reaction mixture was filtered through a syringe filter (0.45 μm) and analyzed by LC-MS

Reactions to incorporate hydrogen are prepared as follows: deuterated L-Lys **[D]-1** (0.02 mmol, 1 equiv.) was dissolved in 3 mL of Borax/HCl Buffer pH 9, catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ **C4** (2.5 mol%, 0.025 equiv.) and ligand **L11** (5 mol%, 0.05 equiv.) were dispensed as the previously prepared stock solution. A stirring bar was added to each reaction flask, which was closed properly and connected to the gas inlet. The flask was evacuated until slight bubbling of the solution and then refilled with hydrogen gas. This procedure was repeated three times. The reaction was stirred under H_2 atmosphere (100 equiv.) at 90 °C. At different time points, an aliquot of the reaction mixture was filtered through a syringe filter (0.45 μm) and analyzed by LC-MS

Table S13: Reactions carried out for KIE studies.



Entry	Time (min)	Isotope Incorporated	Incorporation ^a
1	5	H	1.47
2	5	D	0.88
3	10	H	1.70
4	10	D	0.95
5	15	H	1.81
6	15	D	1.30

a) average of three reactions, analyzed by LC-MS

Equation for Hydrogenation: $y = 0.034x + 1.32$

Equation for Deuteration: $y = 0.042x + 0.62$

The resulting KIE constant is calculated as $k_i = k_H/k_D = 0.042/0.034 = 1.24$

11 Computational Studies

11.1 General details of quantum chemical calculations

All calculations have been performed using the quantum chemistry software program Jaguar version 12.4, release 134.¹⁸

Geometry optimization and subsequent frequency calculations were performed with density functional theory (DFT)¹⁹ employing the M06- 2X functional²⁰ in combination with the def2-SVP basis set.²¹ Default parameters were used throughout except for the following: The grid density for DFT calculations was set to 'Fine', SCF settings were set to accuracy level 'Ultrafine' and the initial guess was taken from ligand field theory. 'Tight' convergence criteria were employed for optimization.

The effects of solvation by water were treated with the polarizable continuum model (PCM) by using the C-PCM variant²² using Bondi radii²³ for water. Transition states were located at the same level of theory. Harmonic vibrational frequencies have been calculated at the same level of theory to characterize the respective minima (i.e.) and first order saddle points (TS). Thermal energies have been calculated at 363.15K corresponding to experimental conditions. Atomic coordinates for Iridium, Deuterium, Tris(p-methoxyphenyl)phosphine ligand (**L11**) as well as substrates were taken from our previous studies,^{1,2,24,25} as starting point of the calculations. The orientation of the methoxy groups of the ligand **L11** was carefully analysed for insertion products, which constitute the highest energy minimum of the catalytic cycle. For that a systematic conformational search of the ligand atoms was performed at force field level in Maestro²⁶ while all other atoms were kept frozen. Conformations were ranked by single point energies at the M06-2X/def2-SVP/CPCM level. Finally, the three lowest energy conformers were fully optimized at the same level of theory.

In general, input structures were generated by modification from results obtained earlier and the modified parts were preoptimized at force field level in Maestro.²²

11.4 Calculations on the postulated HIE mechanism (Fig. 4)

Our computational investigations for the HIE mechanism for the case of ligand **L11** and substrate **13** are based on results of previous studies by us and others.^{1,2,24,25} There, it was found that the actual H/D exchange starts by forming a reactant complex that is comprised of an d^{10} octahedral Ir(I) complex that is formed by COD reduction and deuterium coordination in the presence of two ligand moieties and one monodentate substrate moiety. We investigated that route at first but found that the corresponding reaction free energies are highly unfavorable (see below). As experimental results show that the HIE reaction works only for bi- or tridentate substrates, we decided to investigate the case where one ligand moiety is present and both *N*-atoms of substrate **13** would coordinate at the Ir(I) center. This corresponds to structures **E** and **E'** where one water moiety coordinates to complete the Ir(I) coordination sphere. Displacing this water by alkyl-H coordination in γ -position leads to an energetically favorable reactant complex **F** that is comprised of one ligand and one substrate. Analogously to previous studies,^{1,2,24,25} the insertion product **G** is reached via transition state **FG***. H/D scrambling at the Ir(I) center converts insertion product **G** to **G'** from which deuterium is transferred on to the substrate by going to **E'** via transition state **FG''** and reactant complex **E'**. We suggest that closing of the catalytic cycle from **E'** to **E** happens via **C**, that is originally formed from **B**, via deuteration and hydration. In **C** the deuterated substrate is coordinated only by one *N*-atom, enabling to form **D** by binding of a new, non-deuterated, substrate moiety. By leaving of the deuterated substrate and bidentate coordination of non-deuterated substrate, **E** is formed again and the catalytic cycle closed.

The cartesian coordinates and energies of all species involved are given below. The corresponding reaction free energies were obtained in a canonical fashion based on the difference of the sum of the free energies of products and educts.

11.5 Calculations on alternative reaction pathways – formation of single dentate insertion products

The mechanism for the HIE reaction that we propose in this manuscript for the case of substrate **13** and ligand **L11** is the result of numerous calculations where alternative reaction pathways were investigated. From this and previous studies by us and others^{1,2,24,25} we know that formation of the insertion product (IP), in which Ir(I) inserts into a C-H bond, is the key step of the HIE reaction. As this is a high energy intermediate, we were looking for low energy pathways for its formation. In Figure S164 pathways for the formation of insertion products are shown.

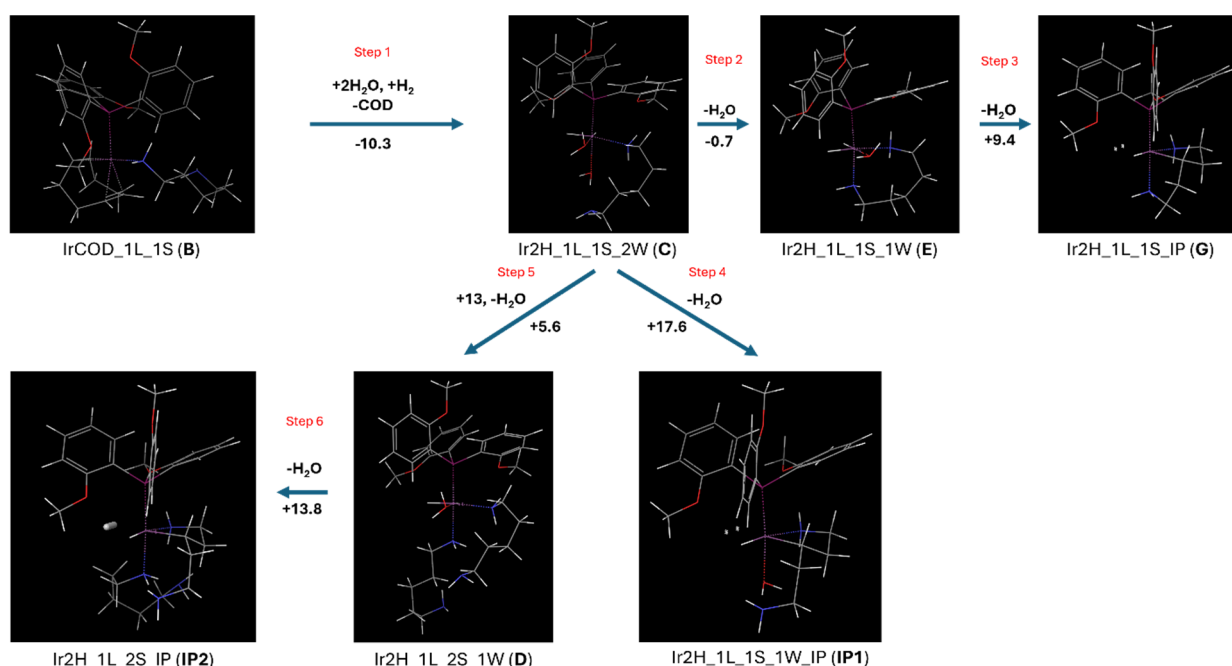


Figure S164: Pathways for the formation of insertion products via single-dentate substrates. The following designation was used for distinguishing the different species: Ir2H_nX(_mY), where X,Y is L for ligand, S for substrate and W for water. The number of ligand, substrate and water molecules present are specified by n,m where n,m can be 1 or 2. Number on the arrows correspond to the respective reaction free energies ΔG_r (kcal/mol).

Alternative pathways originate from species in which one (**IP1**) or two moieties (**IP2**) of substrate **13** are coordinated in a single dentate fashion to Ir(I) in the presence of a displaceable water molecule. Specifically, we found that formation of **IP1** from **C** (Step 4) requires $+17.6$ kcal/mol and formation of **IP2** from **D** (Step 6) requires $+13.8$ kcal/mol. In contrast the formation of insertion product **G** from **E** (Step 3) requires less energy ($+9.4$ kcal/mol) and is hence favored.

The cartesian coordinates and energies of all species involved are given below. The corresponding reaction free energies were obtained in a canonical fashion based on the difference of the sum of the free energies of products and educts.

11.6 Calculations on alternative reaction pathways – absence of ligand

Experimental results show that the HIE reaction does not work in the absence of a phosphine ligand such as **L11**. In order to confirm this with our DFT calculations, different reaction pathways were calculated starting from the Ir(COD) complex with moieties of substrate **13** bound (Fig.3B, **IV**). The results are reported in Figure S165.

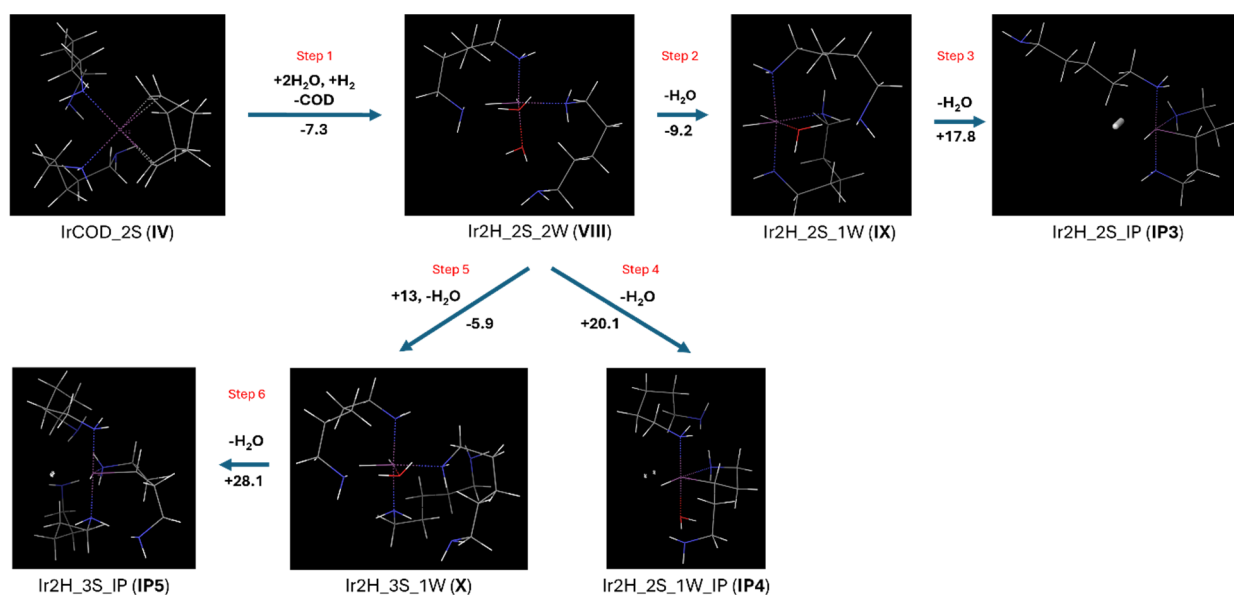


Figure S165: Pathways for the formation of insertion products in the absence of ligands. The following designation was used for distinguishing the different species: Ir2H_nX(_mY), where X,Y is L for ligand, S for substrate and W for water. The number of ligand, substrate and water molecules present are specified by n,m where n,m can be 1 or 2. Number on the arrows correspond to the respective reaction free energies ΔG_r (kcal/mol).

We found that hydrogenation and hydration of **IV** to **VIII** is slightly less exergonic ($\Delta G_r = -7.3$ kcal/mol) compared to the reaction with one moiety of **L11** present. All further *N*-coordination however, either by bidentate coordination of substrate (Step2, $\Delta G_r = -9.2$ kcal/mol) or single dentate coordination of a third substrate moiety (Step 5, $\Delta G_r = -5.9$ kcal/mol) lead to further stabilization of the Ir(I) complex. This contrasts with the corresponding reactions with a ligand present that are either neutral or slightly endergonic. Furthermore, we conclude that substrate coordination does not translate into stabilization of the insertion product in the same way, as we found the formation of insertion products **IP3-IP5** to be highly endergonic.

The cartesian coordinates and energies of all species involved are given below. The corresponding reaction free energies were obtained in a canonical fashion based on the difference of the sum of the free energies of products and educts.

11.7 Calculations on alternative reaction pathways – two ligands

In previous studies by us and others^{1,2,24,25} the catalytic systems studies comprised two ligands, one phosphine ligand and a NHC ligand, typically. Therefore, it cannot be ruled out a priori that alternative reaction pathways play a role in which species with two coordinating phosphine ligands play a role. From our calculations we found that hydrogenation and hydration of **B** and binding of two ligands **L11** to form species **XI** (Figure S166, Step 2) is strongly endergonic ($\Delta G_r = +17.7$ kcal/mol), but still within reach considering that the reaction is run at 90°C.

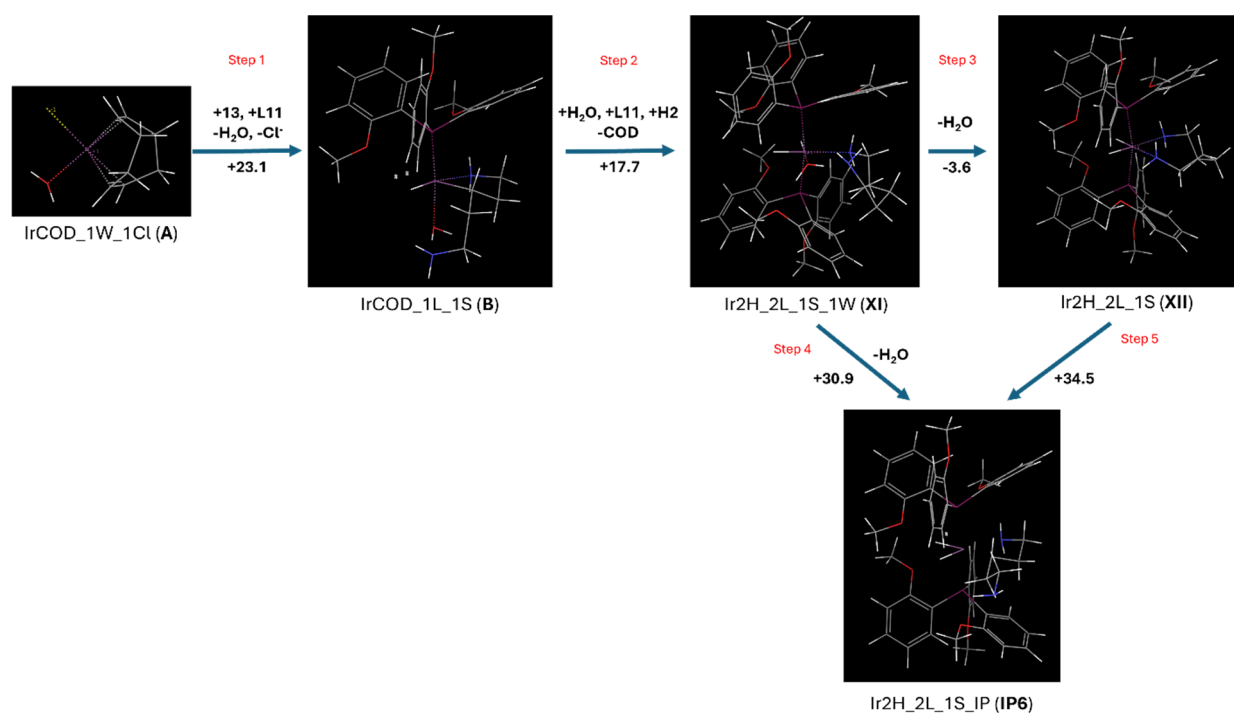


Figure S166: Pathway for the formation of insertion products in the presence of two ligands. The following designation was used for distinguishing the different species: Ir2H_nX(_mY), where X,Y is L for ligand, S for substrate, W for water and Cl for chloride. The number of ligand, substrate and water molecules present are specified by n,m where n,m can be 1 or 2. Number on the arrows correspond to the respective reaction free energies ΔG_r (kcal/mol).

Going from single dentated substrate (species **XI**) to a bidentate one (species **XII**) is exergonic (Step 3). However, the energy required for reaching the corresponding insertion product **IP6** from both species **XI** and **XII** (Steps 4 and 5) is higher than those of all other alternative pathways we considered.

The cartesian coordinates and energies of all species involved are given below. The corresponding reaction free energies were obtained in a canonical fashion based on the difference of the sum of the free energies of products and educts.

11.8 Calculations on HIE selectivity

In order to investigate the selectivity in deuteration, model substrate diaminopentane (**13**) was used to compare the relative energies of insertion products for iridium insertion into the CH bond in the beta, gamma and delta positions. We found that the energy of the beta-insertion product to be 7.4 kcal/mol higher and the energy of the delta-insertion product to be 11.3 kcal/mol higher than the gamma-Insertion product.

The cartesian coordinates and energies of all species involved are given below. The corresponding relative energies given above were obtained in a canonical fashion based on the difference of the free energies of beta and delta insertion products and the corresponding gamma insertion product.

11.9 Calculations on the postulated HIE mechanism for 1,5-dihydropentane

In order to further study the role of the coordinating ability of the amino group relative to others, we followed suggestions by reviewers and added DFT calculations on 1,5-dihydropentane for our postulated mechanism as well as further calculations on pincer-type reactant complexes and insertion products to study the regioselectivity. Overall, we found similar results for 1,5-diaminopentane (Fig. 137A) and 1,5-dihydropentane (Figure S167B). One striking difference was identified however, and

this concerns the elimination of water from **E** to form the reactant complex **F**. While this step is exergonic (-4.1 kcal/mol) for amino, it is endergonic (+3.0 kcal/mol) for hydroxy. We explain this with a stronger coordinating ability for NH₂ compared to OH where excess of electrons makes water leaving more feasible. Furthermore, this is supported further by the finding that the formation of insertion products **G** requires more energy for NH₂ (+13.7 kcal/mol) compared to hydroxy (+12.2 kcal/mol).

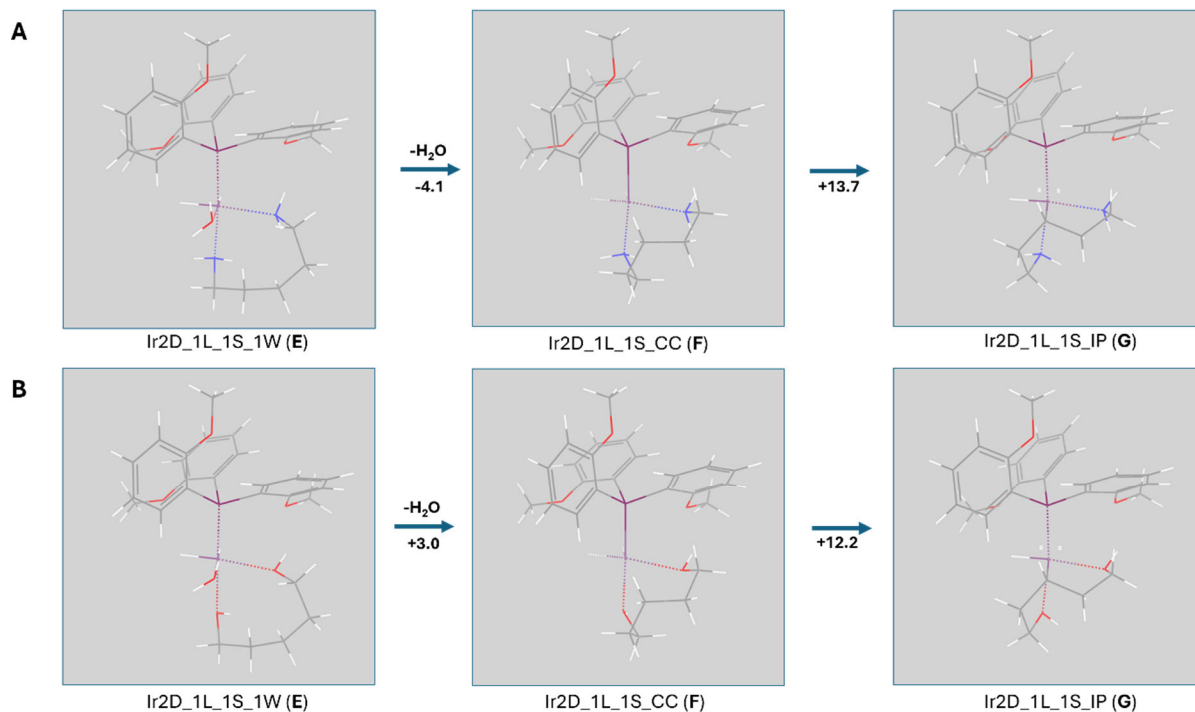


Figure S167: Comparison of results of calculations for 1,5-diaminopentane (**A**) and 1,5dihydroxypentane (**B**).

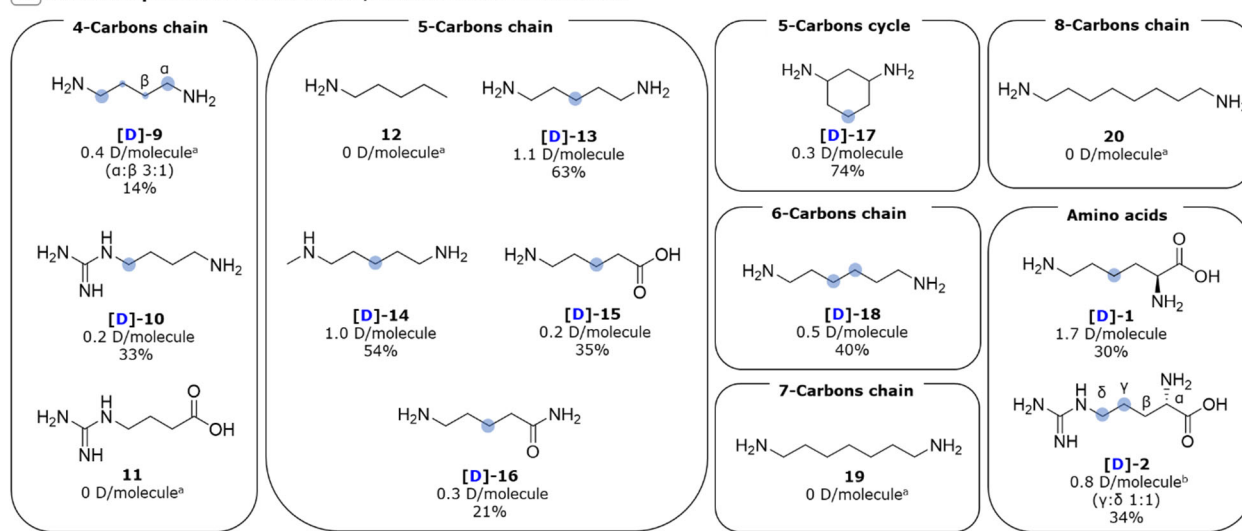
On the other hand, we found that the regioselectivity in pincer-type species is not affected. Deuteration in gamma position is most favorable for both reactant complexes and insertion products as well as amino and hydroxy. From that we conclude that regioselectivity is driven to a large degree by steric constraints.

Table S14: Free energies for the mechanistic steps calculated on diaminopentane **13** and dihydroxypentane.

Mechanistic step	ΔG_r diaminopentane 13 (kcal/mmol)	ΔG_r dihydroxypentane (kcal/mmol)
A $\rightarrow$ B	23.1	28.6
B $\rightarrow$ C	-10.5	-9.2
C $\rightarrow$ D	-0.8	3.3
D $\rightarrow$ E	-0.7	0.4
E $\rightarrow$ F	-4.1	3.0
F $\rightarrow$ G	13.7	12.2
G $\rightarrow$ H	-0.1	-0.2
H $\rightarrow$ I	-13.9	-12.6
I $\rightarrow$ J	4.0	-2.8
J $\rightarrow$ C	3.0	-4.5

11.10 Schemes of full postulated mechanism

A Initial scope studies with amines, diamines and amino acids



B Active species formation path

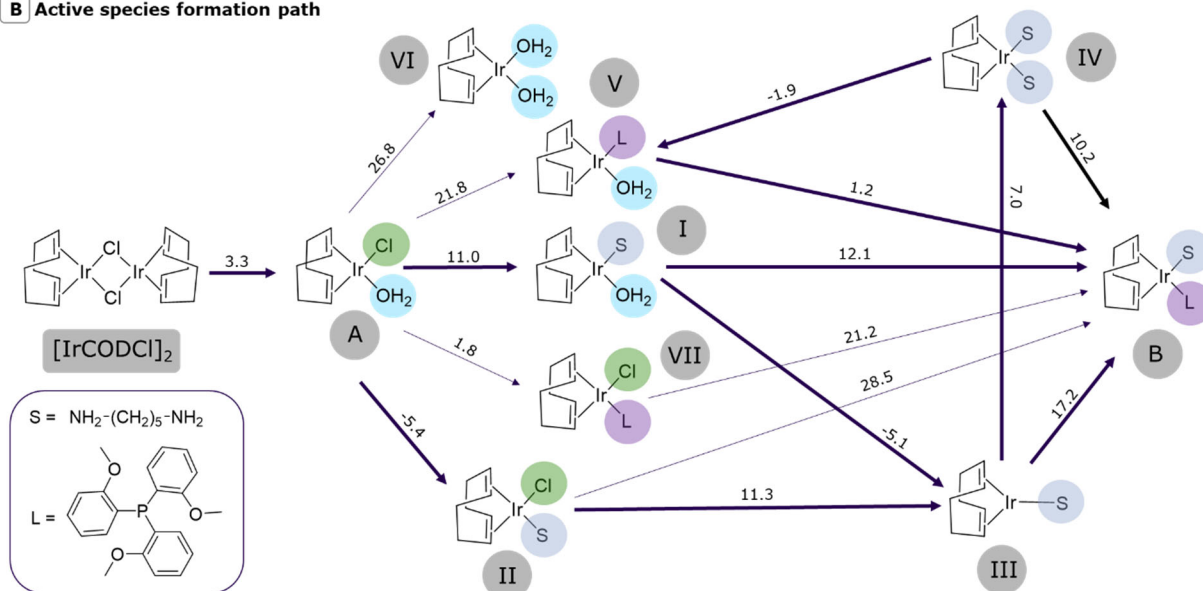


Figure S168: Full mechanism scheme for Fig.3B in the manuscript.

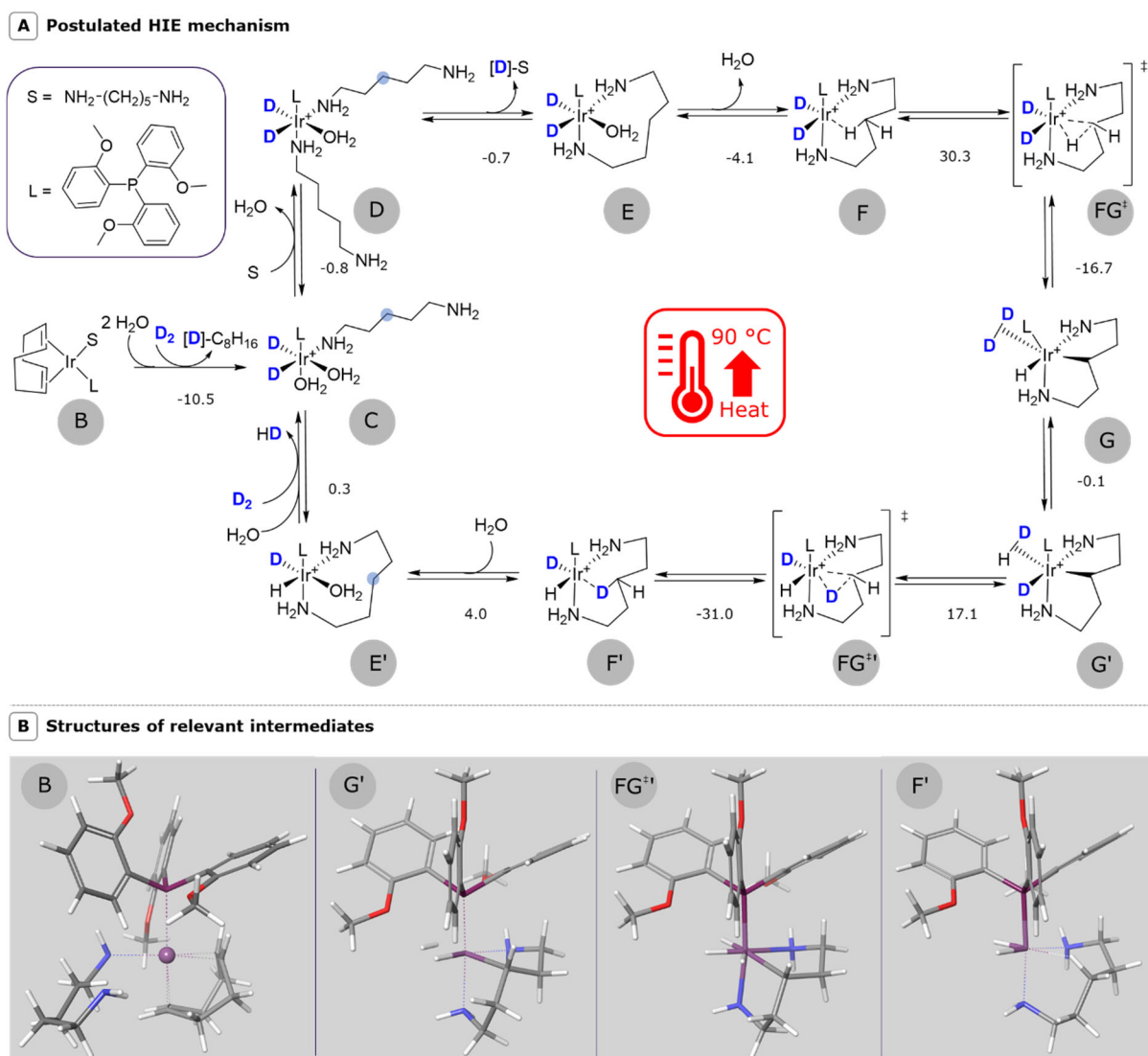


Figure S169: Full mechanism scheme for Fig.4A and relevant intermediates of Fig.4B in the manuscript.

12 NMR studies on the catalytic species formation

Stock solutions of $[\text{Ir}(\text{COD})\text{Cl}]_2$ (15 mM), phosphine ligand **L11** (35 mM), and 1,5-diaminopentane **13** (100 mM) were prepared in CDCl_3 .

Step 1:

0.3 mL of the $[\text{Ir}(\text{COD})\text{Cl}]_2$ stock solution (corresponding to 5 μmol) and 0.3 mL of the **L11** stock solution (corresponding to 10 μmol , 2 equiv.) were added to an NMR tube under Ar atmosphere. After vigorously shaking the solution for two minutes the sample was analyzed by ^1H -NMR (300 MHz, CDCl_3) and ^{31}P -NMR (121 MHz, CDCl_3). Compared to the starting materials it is possible to see a shift in the COD olefinic protons of the $[\text{Ir}(\text{COD})\text{Cl}]_2$ in ^1H -NMR (Figure S172) and the formation of a second peak in the ^{31}P -NMR spectrum, correlating with the formation of a complex between the metal and the phosphorus of **L11** (Figure S174).

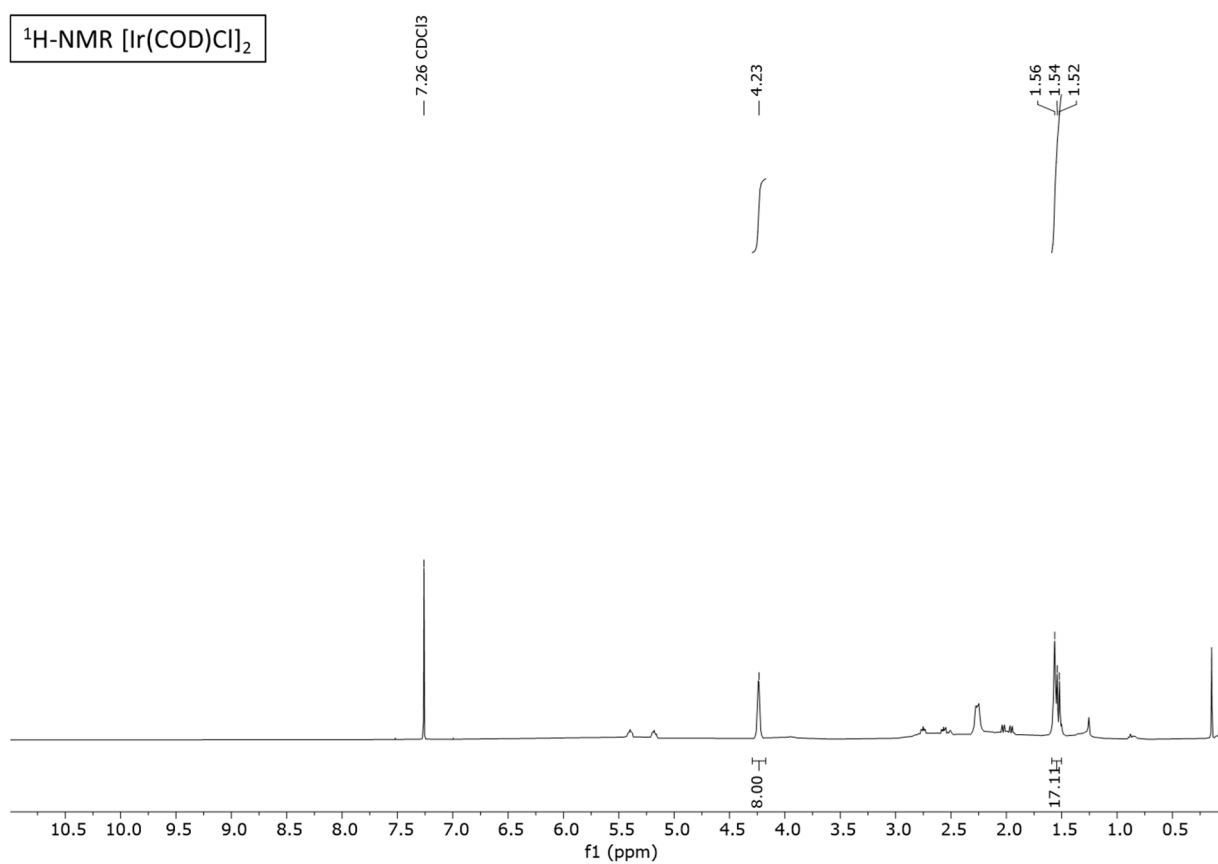


Figure S170: $^1\text{H-NMR}$ spectrum of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$.

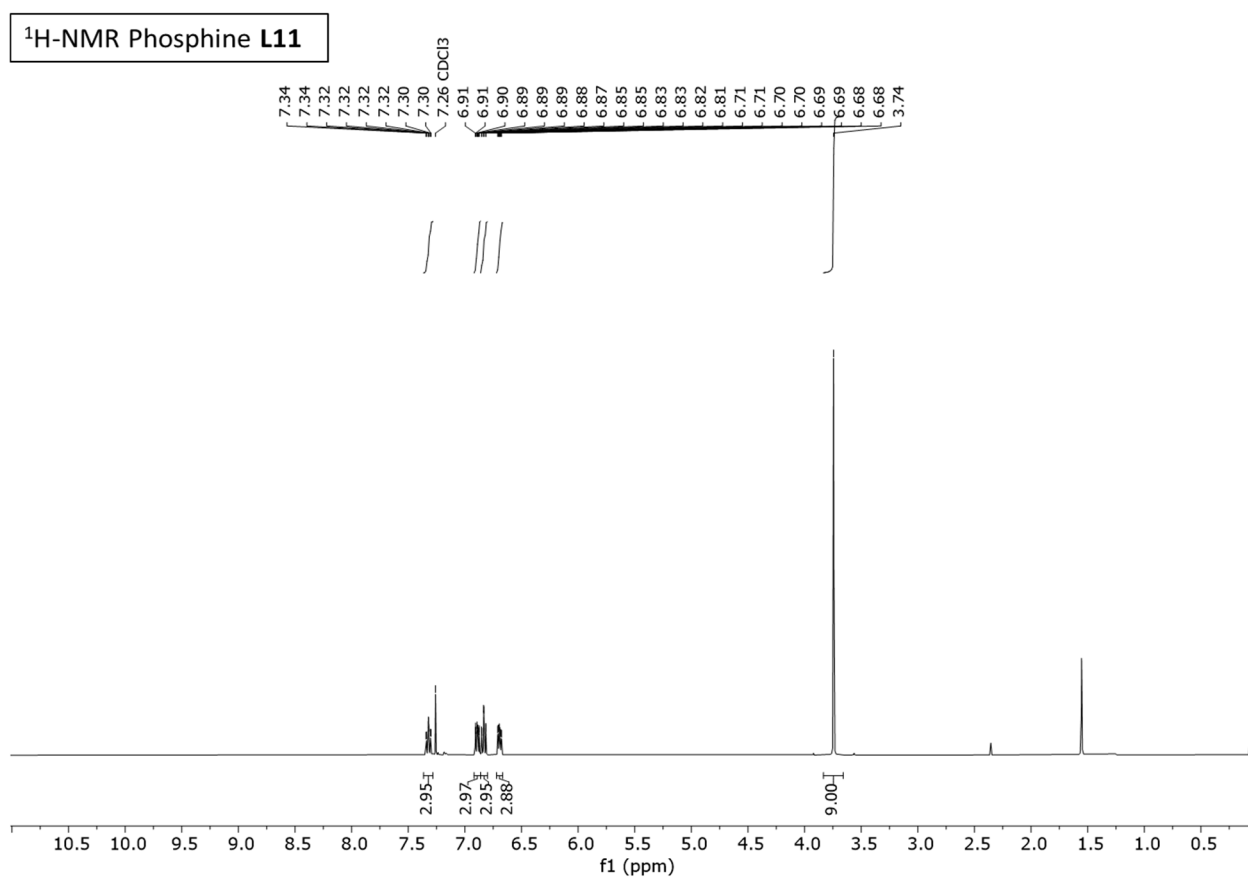


Figure S171: $^1\text{H-NMR}$ spectrum of phosphine ligand **L11**.

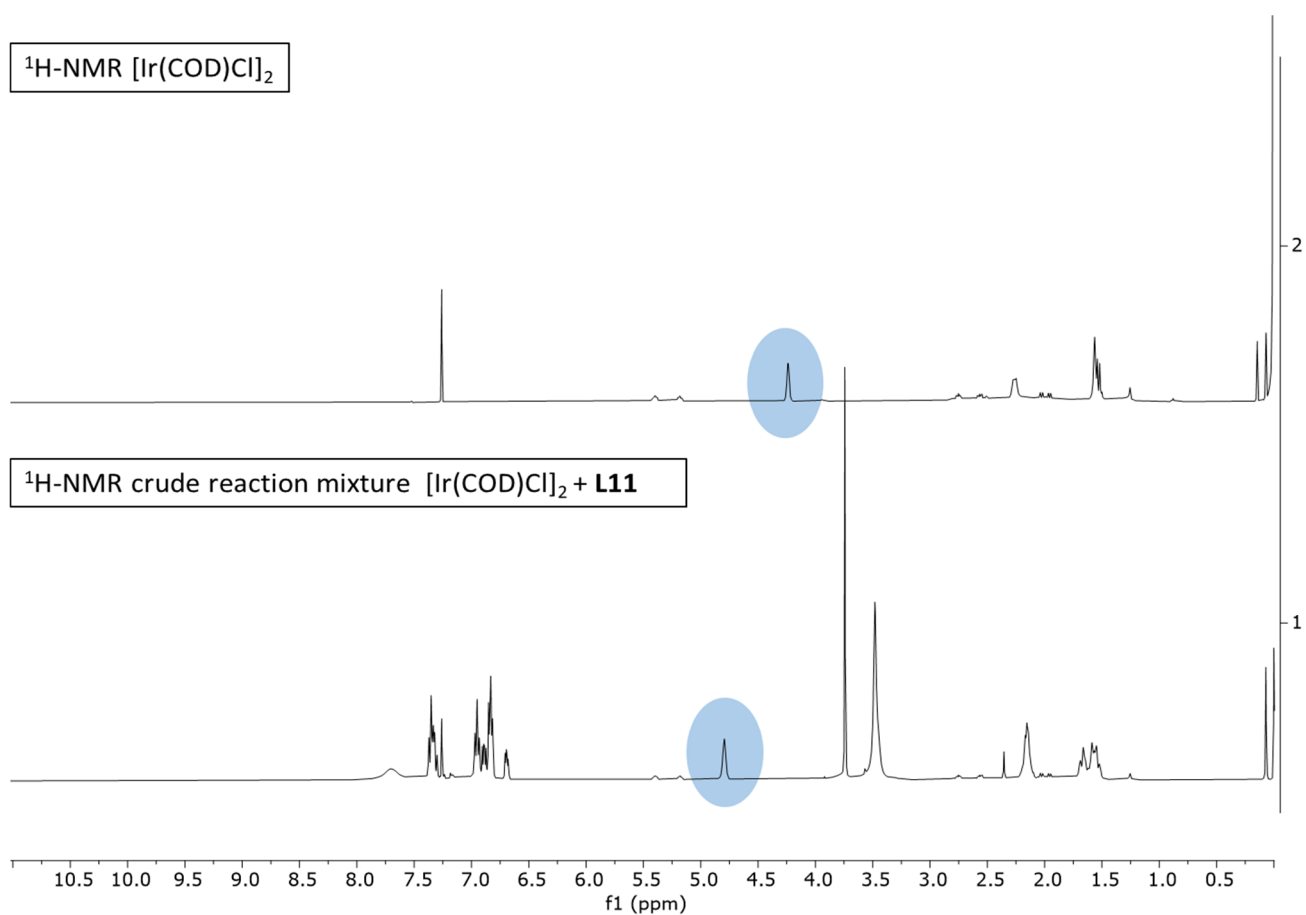


Figure S172: Overlay of the ¹H-NMR spectra of pre-catalyst [Ir(COD)Cl]₂ and of the crude reaction mixture upon addition of **L11** (2 equiv.). The COD olefinic protons peak is highlighted in blue.

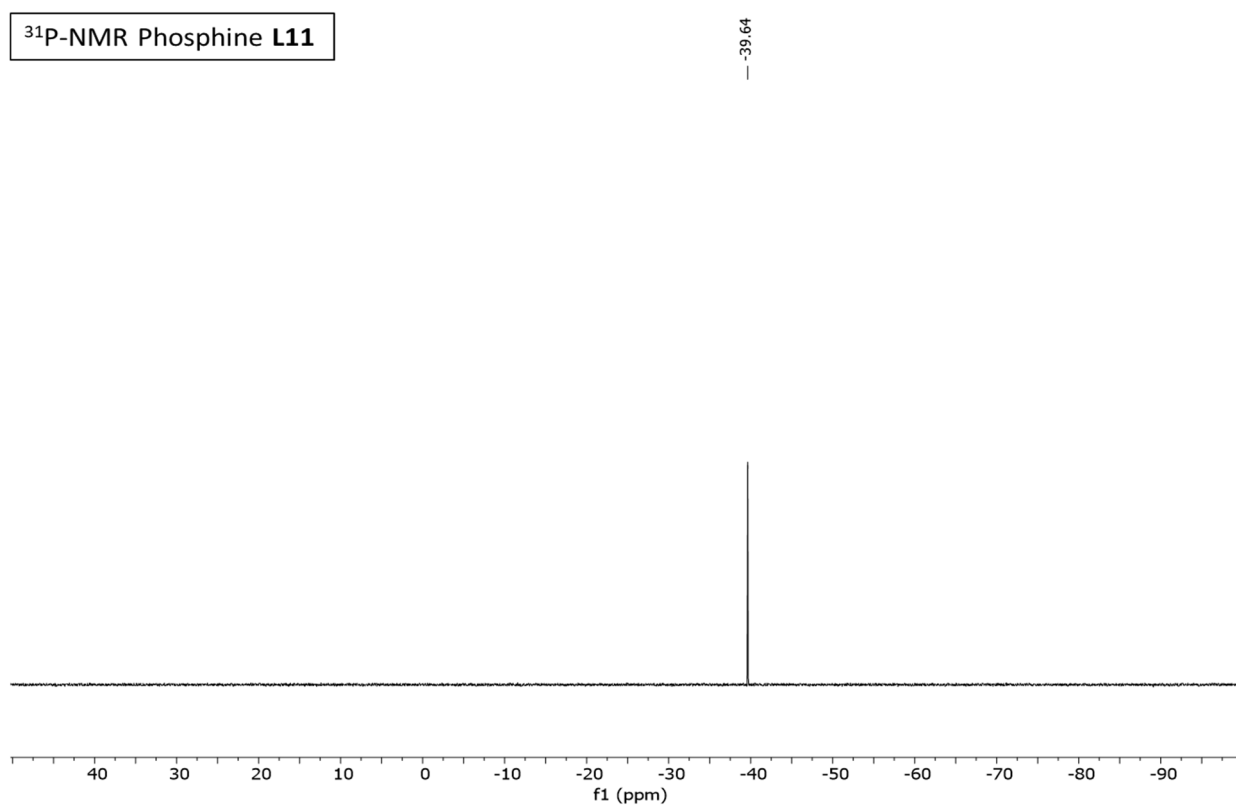


Figure S173: ³¹P-NMR spectrum of phosphine ligand **L11**.

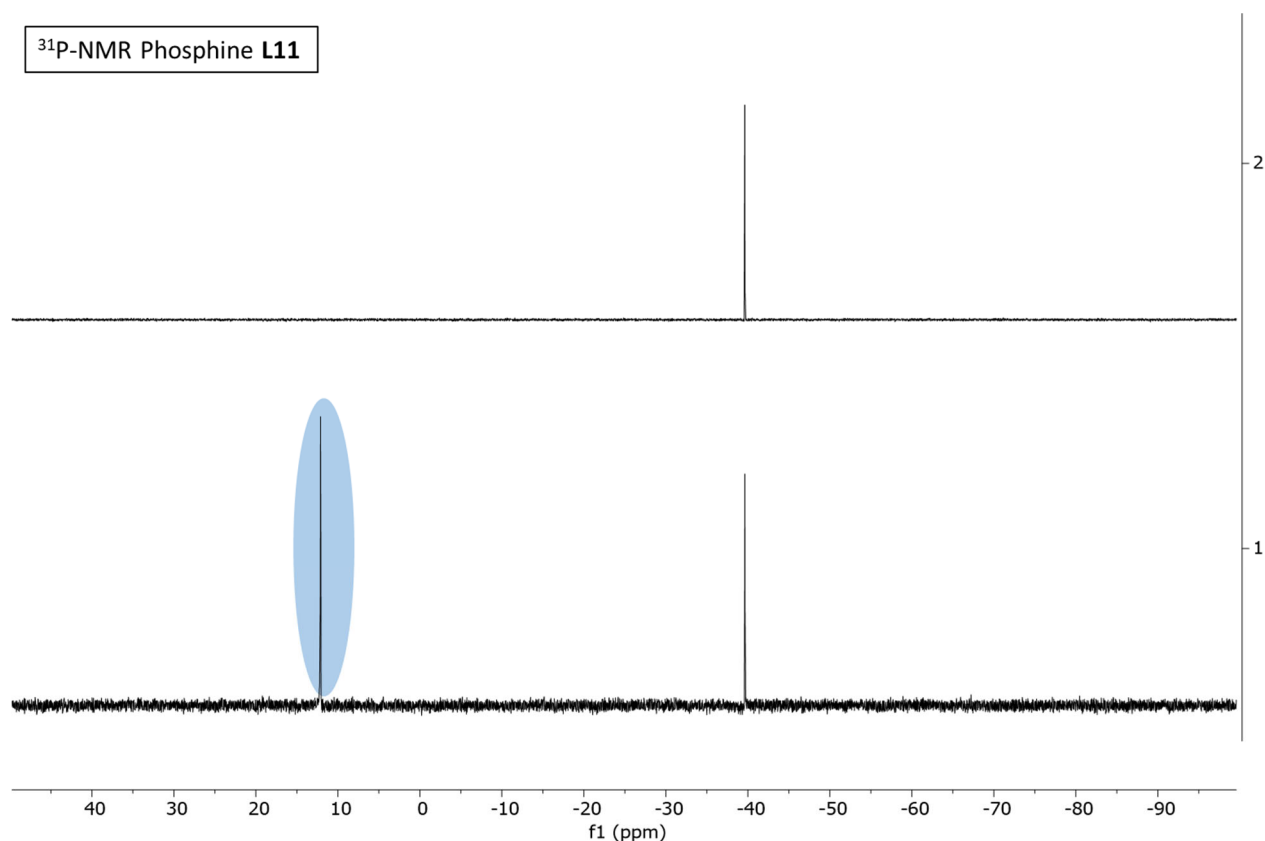


Figure S174: Overlay of the ^{31}P -NMR spectra of ligand **L11** and of the crude reaction mixture of the pre-catalyst and **L11**. The complex peak is highlighted in blue.

Step 2:

0.1 mL of the 1,5-diaminopentane **13** stock solution (corresponding to 10 μmol , 2 equiv.) were added to the reaction mixture under Ar atmosphere. After vigorously shaking the solution for two minutes the sample was analyzed by ^1H -NMR (300 MHz, CDCl_3) and ^{31}P -NMR (121 MHz, CDCl_3). The reaction is then heated at 60 $^\circ\text{C}$ for 1 h and analyzed again by ^1H -NMR and ^{31}P -NMR. For both samples there was no change compared to step 1 (Figures S175 and S176).

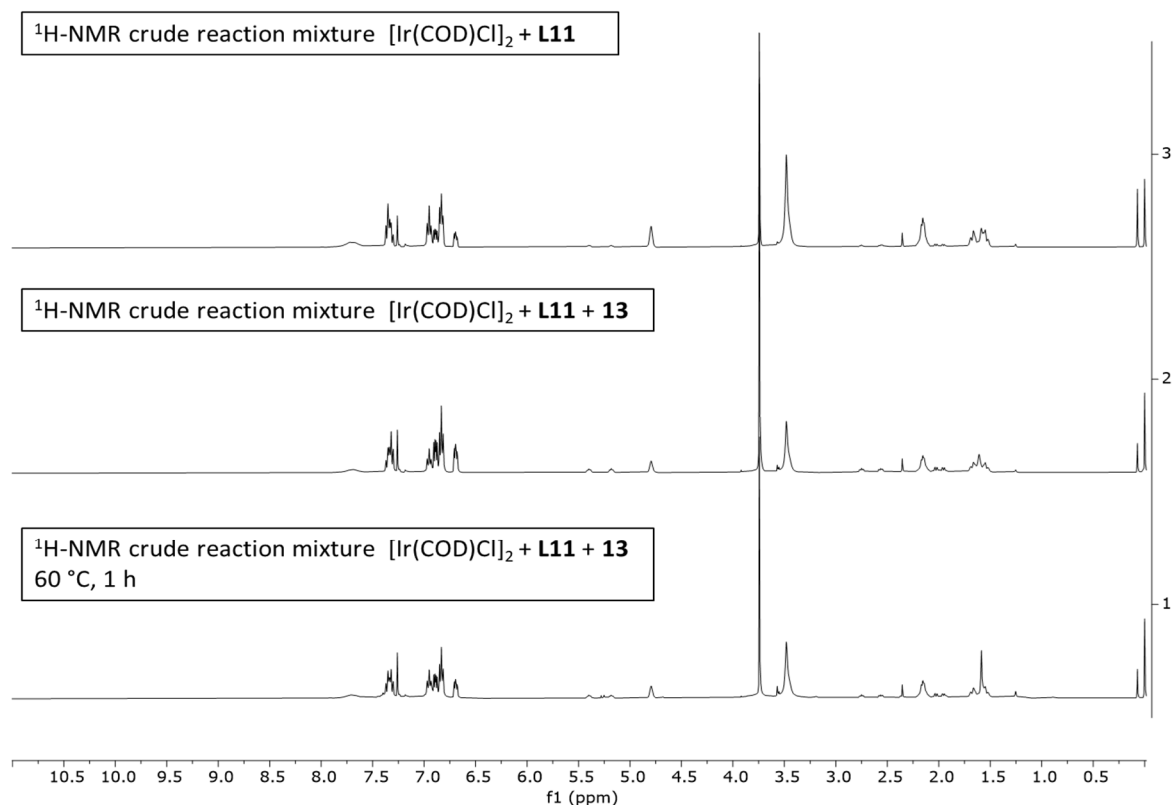


Figure S175: Overlay of the ^1H -NMR spectra of reaction mixture of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ and **L11** (2 equiv.), reaction mixture upon addition of **13** (2 equiv.), and reaction mixture with all components upon heating at 60 °C for 1 h.

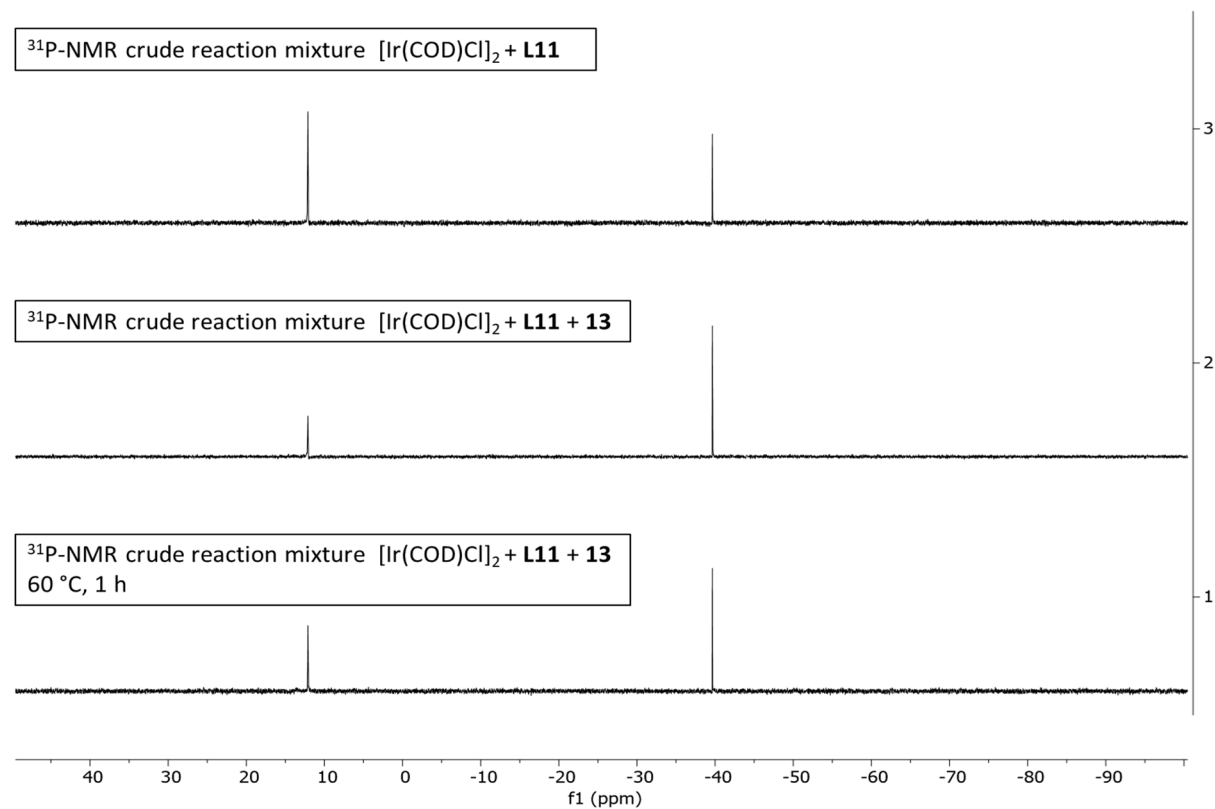


Figure S176: Overlay of the ^{31}P -NMR spectra of reaction mixture of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ and **L11** (2 equiv.), reaction mixture upon addition of **13** (2 equiv.), and reaction mixture with all components upon heating at 60 °C for 1 h.

Step 3:

An additional 1 equiv. of substrate **13** was added to the reaction mixture, having therefore an excess of substrate in the solution. This experiment was carried out to simulate the excess of substrate **13** present in the developed HIE reaction conditions. After vigorously shaking the solution for two minutes the sample was analyzed by ^1H -NMR (300 MHz, CDCl_3) and ^{31}P -NMR (121 MHz, CDCl_3). Compared to the previous sample, the peak of the COD olefinic protons in ^1H -NMR (Figure S177) and the complex peak in ^{31}P -NMR (Figure S178) were absent. It is postulated that the excess of 1,5-diaminopentane **13** can displace both the phosphine and the COD ligands. The COD has been reported to be displaced by different solvents or ligands depending on the reaction conditions in organic media.²⁷

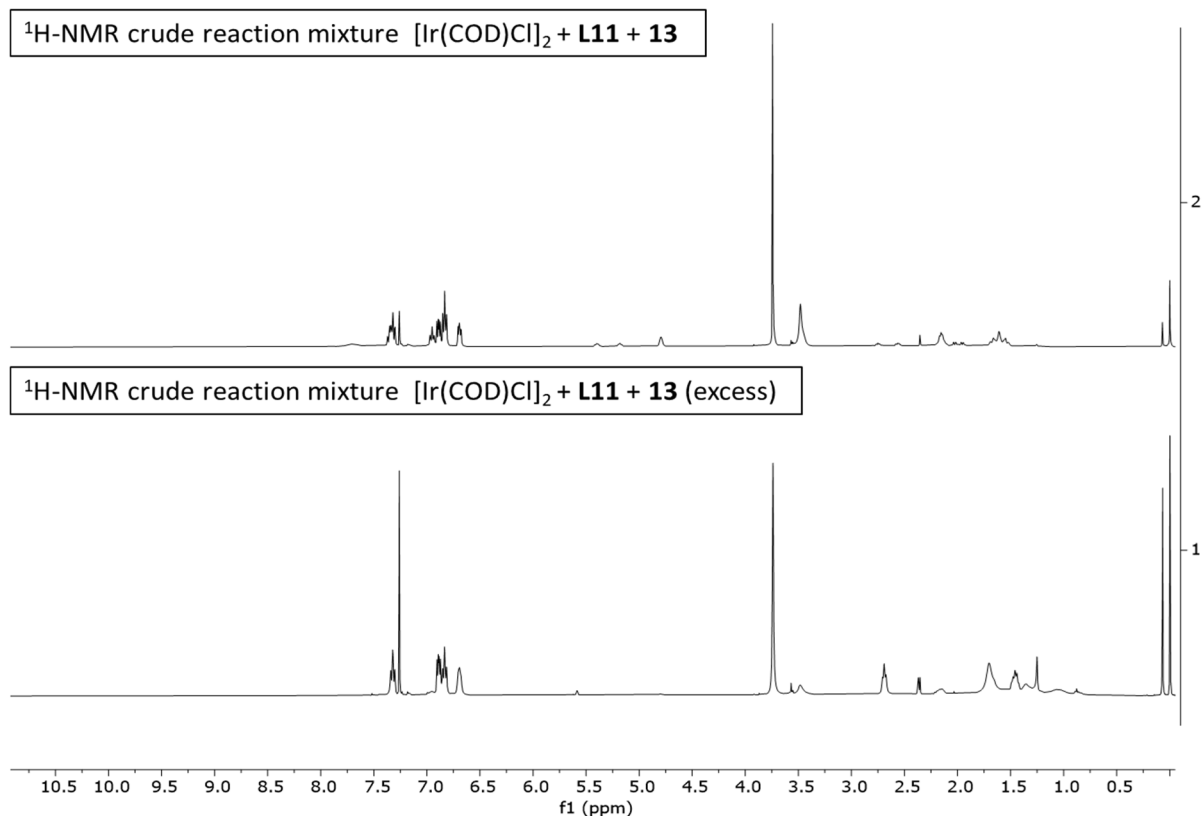


Figure S177: Overlay of the ^1H -NMR spectra of reaction mixture of pre-catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ and **L11** (2 equiv.), reaction mixture upon addition of **13** (2 equiv.), and with an excess of **13** (3 equiv. in total).

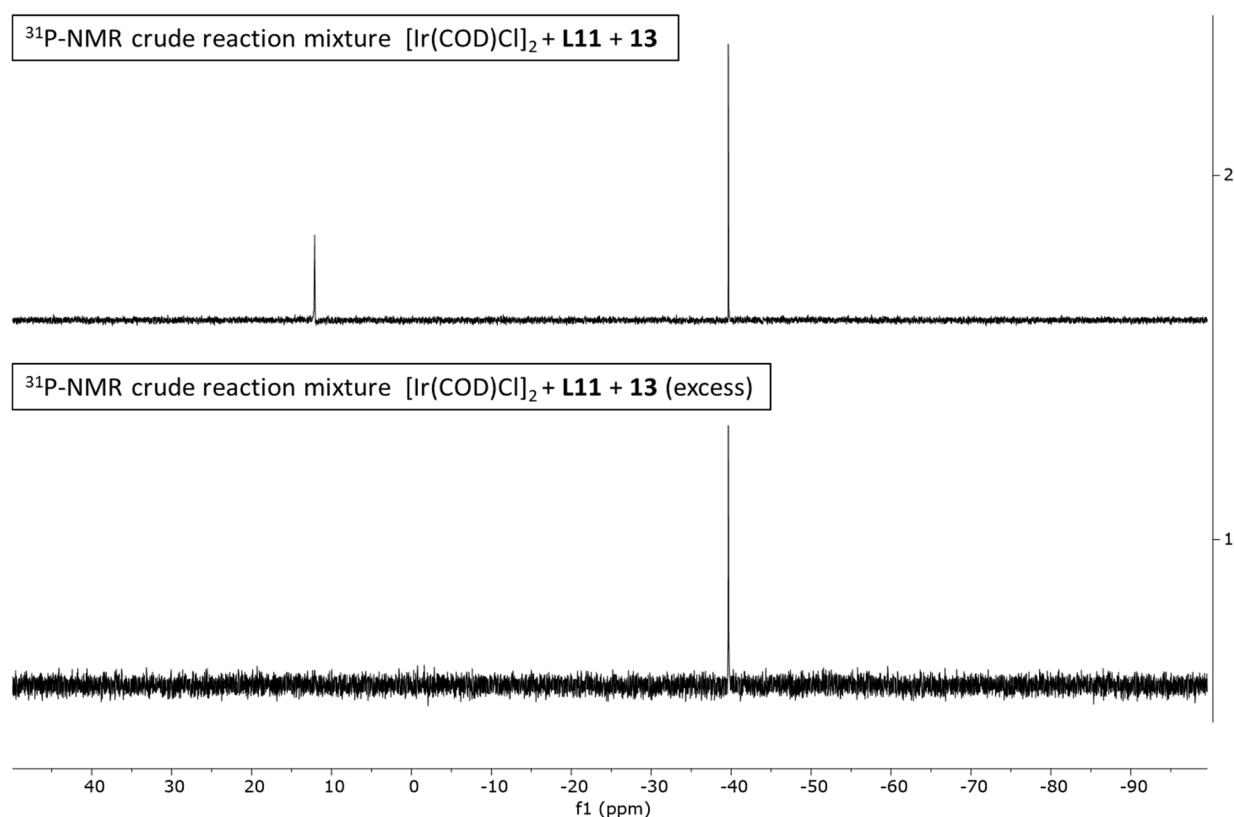


Figure S178: Overlay of the ³¹P-NMR spectra of reaction mixture of pre-catalyst [Ir(COD)Cl]₂ and **L11** (2 equiv.), reaction mixture upon addition of **13** (2 equiv.), and with an excess of **13** (3 equiv. in total).

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