Supporting Information

General Information

All reagents were purchased from Sigma-Aldrich except for (+)-2,2-dimethyl-4,5-bis(diphenylphosphino)methyl-1,3-dioxolane ((+)diop) which was purchased from Alfa Aesar. NMR solvents and deuterated benzaldehyde were purchased from Cambridge Isotopes. All compounds were used without further purification. Synthesis was carried out using oven-dried (160°C) glassware. All compounds were analyzed by Bruker AC 400 (400 MHz) NMR, and determined to be pure when no extraneous peaks appeared in ^{1}H NMR spectra. Melting points were determined using Mel-Temp II. Elemental analyses were performed by Intertek Chemical and Pharmaceuticals using the Perkin-Elmer 2400 Elemental Analyzer. High resolution mass spectrometry experiments were performed using Agilent 6224 Accurate-Mass TOF LC/MS system in positive electrospray ionization mode.

In-situ hydrogenation with p-H_2

p-H_2 was generated by flowing H_2 gas through activated charcoal at 77 K. The gas was then bubbled through the reaction solution in an NMR tube for 15 s at a rate of 1 mL/s, after which the tube was inserted into the probe using a string to minimize the sample transfer time. Once lock signal was established the experiment was executed. The total time from the start of the bubbling to the start of the experiments was approximately 30 s.

General hydrogenation procedure

N-acetyl dehydro amino acid (14μmol) was dissolved in CD_3OD (0.35 mL). 0.7 μmol of catalyst: (1,5-cyclooctadiene)rhodium(I)((-/+)diop) tetrafluoroborate previously prepared in CD_3OD (0.35 mL) was added to the solution and p-H_2 was bubbled into the solution for 15 s at a time.

All PHIP NMR experiments were performed using a Bruker Avance Spectrometer operating at 11.76T ($\nu_0(^1H)$ = 500.20 MHz). The 90° pulses for both ^{1}H and ^{13}C spectra were calibrated each time before the experiment. The flip angle was 45° for the single pulse ^{1}H experiment when acquiring spectra with hyperpolarized signals. When the OPSY sequence was employed, the gradient strength was optimized to suppress the thermal peaks.[1] The typical gradient strength used was 8.4 G/cm for 1.2 ms. The OPSY spectra were acquired through the reaction at a 2s interval. The polarization transfer from the protons to the carbon atoms was achieved by applying the PH-INEPT+ sequence (Figure S1).[2] The delay t was set as 38.5 ms to obtain the strongest polarization transfer signal for the carbonyl carbon in phenylalanine. The spectrum was recorded with 1 scan, and the delay between two consecutive experiments was 5 s.

For the calculation of the enhancement factor for each compound's PHIP experiments, the integral of the hyperpolarized peak in each consecutive experiment was accumulated until the hyperpolarized signals decayed out. The sum of the integrals is divided by the integral of the thermal peak to give the enhancement factor. Magnitude spectra were used in the integration.

T_1 measurements were carried out using the inversion recovery pulse sequence at 11.76T.

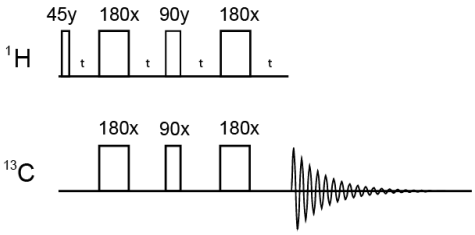

Figure S1. PH-INEPT+ pulse sequence.

Table S1. ^{1}H Enhancement factors (EF) of H_2* at 11.76T for hydrogenated products **1a** – **6a**

Product	EF	P%
1a	755	0.76%
2a	762	0.76%
3a	1075	1.1%
4a	367	0.37%
5a	396	0.40%
6a	605	0.61%

Synthesis of neurotransmitter precursors. The synthesis was performed according to literature procedure and NMR spectra agreed with reported data.

Synthesis of **1**:[3] ^{1}H NMR (400 MHz, d_6-DMSO) δ = 12.65 (s, 1H), 9.47 (s, 1H), 7.61 (d, J = 7.2, 2H), 7.42 – 7.36 (m, 3H), 7.21 (s, 1H), 1.98 (s, 3H).

Synthesis of **2**:[3] ^{1}H NMR (400 MHz, d_6-DMSO) δ = 12.40 (s, 1H), 9.90 (s, 1H), 9.28 (s, 1H), 7.48 (d, J = 8.4, 2H), 7.18 (s, 1H), 6.78 (d, J = 8.8, 2H), 1.98 (s, 3H).

Synthesis of **3**:[3] ^{1}H NMR (400 MHz, d_6-DMSO) δ = 12.34 (s, 1H), 9.39 (s, 1H), 9.22 (s, 1H), 9.11 (s, 1H), 7.35 (s, 1H), 7.23 (s, 1H), 6.91 (d, J = 8.4, 1H), 6.73 (d, J = 8.4, 1H), 1.99 (s, 3H).

Synthesis of **4**:[4] ^{1}H NMR (400 MHz, d_6-DMSO) δ = 12.21 (s, 1H), 11.69 (s, 1H), 9.18 (s, 1H), 7.79 (d, J = 2.8, 1H), 7.71 (d, J = 8, 1H), 7.63 (s, 1H) 7.45 (d, J = 8, 1H), 7.20 – 7.11 (m, 2H), 2.03 (s, 3H).

Synthesis of **5**:[4] ^{1}H NMR (400 MHz, d_6-DMSO) δ = 12.17 (s, 1H), 11.55 (s, 1H), 9.15 (s, 1H), 7.74 (d, J = 2.8, 1H), 7.63 (s, 1H), 7.33 (d, J = 8.8, 1H), 7.21 (d, J = 2.4, 1H), 6.80 (dd, J = 8.4, 2.4, 1H), 3.76 (s, 3H), 2.03 (s, 3H).

Synthesis of **6**:[5] ^{1}H NMR (400 MHz, CD_3OD) δ = 7.84 (s, 1H), 7.44 (s, 1H), 7.37 (s, 1H), 2.16 (s, 3H).

Synthesis of **7**: The reaction conditions and reagents were the same as **1** except that deuterated benzaldehye and deuterated acetic anhydride were used. Melting point: 188 – 190°C, lit.[6] (for **1**): 191 – 192°C; Elemental anal. calc (mass%)[7] for $C_{11}H_2D_9NO_3$: C 61.66; H(D) 5.17; N 6.54; Found C 61.32; H(D) 4.98; N 6.36; HRMS (ESI) calc. for [$C_{11}H_2D_9NO_3$+H^+] 215.13766, found 215.13724

Synthesis of **8**: The reaction conditions and reagents were the same as **1** except that deuterated benzaldehye was used. Melting point: 189 – 190 °C, lit.[6] (for **1**) 191 – 192°C; Elemental anal. calc (mass%) for $C_{11}H_5D_6NO_3$: C 62.54, H(D) 5.25, N 6.63; Found C 62.84; H(D) 5.04; N 6.52; HRMS (ESI) calc. for [$C_{11}H_5D_6NO_3$+H^+] 212.11883, found 212.11837

Synthesis of **9**: The reaction conditions and reagents were the same as **1** except that deuterated benzaldehye and N-acetyl-[1-^{13}C]glycine were used. Elemental anal. calc (mass%) for $C_{11}H_5D_6NO_3$: C 62.24, H(D) 5.23, N 6.60; Found C 62.19; H(D) 4.84; N 6.55.

General procedure for hydrogenation of N-acetyl dehydro-amino acids

N-acetyl dehydro-amino acid (14 μmol) was dissolved in CD_3OD (0.35 mL). 0.7 μmol of catalyst: (1,5-cyclooctadiene)rhodium(I)((-/+)diop) tetrafluoroborate previously prepared in CD_3OD (0.35 mL) were added to the solution and H_2 or p-H_2 was bubbled into the solution for 15 s until reaction was completed.

1a: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.29 – 7.2 (m, 5H), 4.85 (dd, J = 8, 4, 1H), 3.25 (dd, J = 14, 8, 1H), 2.95 (dd, J = 14, 8, 1H), 1.9 (s, 3H)

2a: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.03 (d, J = 8, 2H), 6.70 (d, J = 8, 2H), 4.58 (dd, J = 8, 4, 1H), 3.09 (dd, J = 14, 8, 1H), 2.84 (dd, J = 14, 8, 1H), 1.91 (s, 3H)

3a: ^{1}H NMR (400 MHz, CD_3OD) δ = 6.68 (d, J = 8, 1H), 6.66 (s, 1H), 6.54 (d, J = 8, 1H), 4.56 (dd, J = 8, 4, 1H), 3.03 (dd, J = 14, 8, 1H), 2.79 (dd, J = 14, 8, 1H), 1.92 (s, 3H)

4a: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.56 (d, J = 8, 1H), 7.32 (d, J = 8, 1H), 7.09 – 6.99 (m, 3H), 4.72 (dd, J = 8, 4, 1H), 3.34 (dd, J = 14, 8, 1H), 2.15 (dd, J = 14, 8, 1H), 1.90 (s, 3H)

5a: ^{1}H NMR (400 MHz, CD_3OD) δ = 7.21 (d, J = 8, 1H), 7.05 (s, 2H), 6.75 (d, J = 8, 1H), 4.71 (dd, J = 8, 4, 1H), 3.83 (s, 3H), 3.29 (dd, J = 14, 8, 1H), 3.12 (dd, J = 14, 8, 1H), 1.92 (s, 3H)

6a: SDS (2mg) in D_2O (0.7ml) was used instead of CD_3OD as the hydrogenation reaction solvent. ^{1}H NMR (400 MHz, D_2O) δ = 8.67 (s, 1H), 7.36 (s, 1H), 4.63 (dd, J = 8, 4, 1H), 3.35 (dd, J = 14, 8, 1H), 3.20 (dd, J = 14, 8, 1H), 2.01 (s, 3H)

7a: ^{1}H NMR (400 MHz, CD_3OD) δ = 4.66 (s, 1H), 3.18 (s, 1H)

8a: ^{1}H NMR (400 MHz, CD_3OD) δ = 4.66 (s, 1H), 3.18 (s, 1H), 1.9 (s, 3H)

9a: ^{1}H NMR (400 MHz, CD_3OD) δ = 4.66 (s, 1H), 3.18 (s, 1H), 1.9 (s, 3H)

^{1}H PHIP spectra of hyperpolarized N-acetyl amino acids 2a – 6a

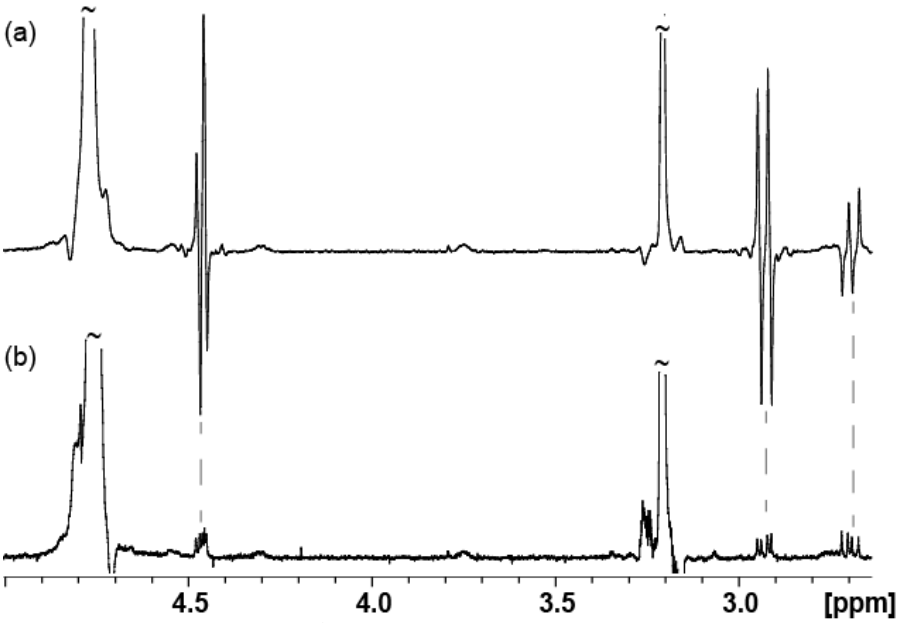

Figure S2. Single-scan ^{1}H NMR: (a) Spectrum recorded immediately after hydrogenation of **2**; (b) reference spectrum of **2** and **2a** after the hyperpolarization decay.

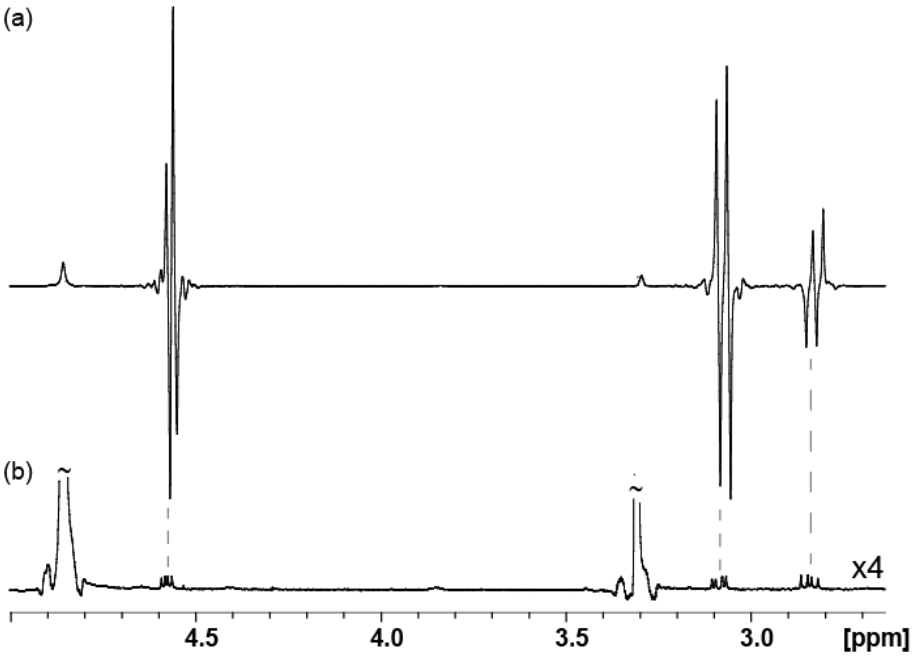

Figure S3. Single-scan ^{1}H NMR: (a) Spectrum recorded immediately after hydrogenation of **3**; (b) reference spectrum of **3** and **3a** after the hyperpolarization decay.

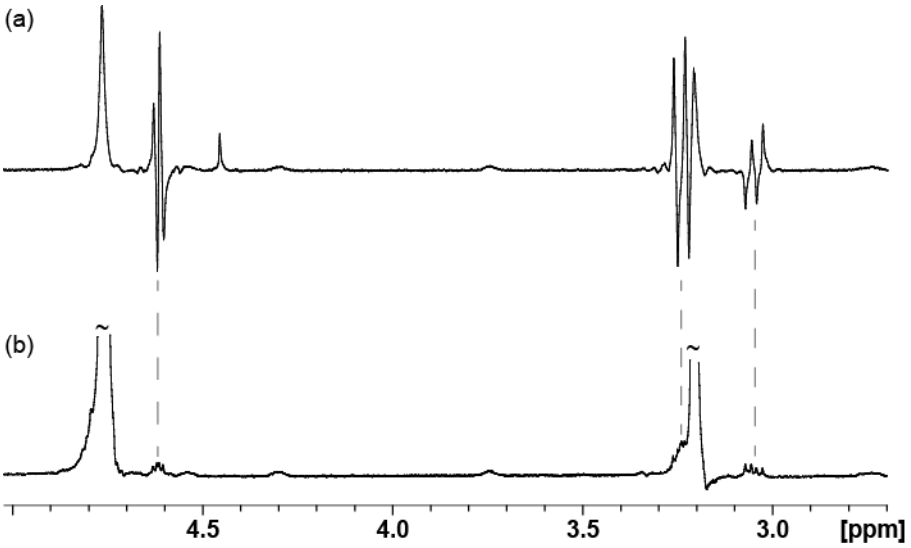

Figure S4. Single-scan ^{1}H NMR: (a) Spectrum recorded immediately after hydrogenation of **4**; (b) reference spectrum of **4** and **4a** after the hyperpolarization decay.

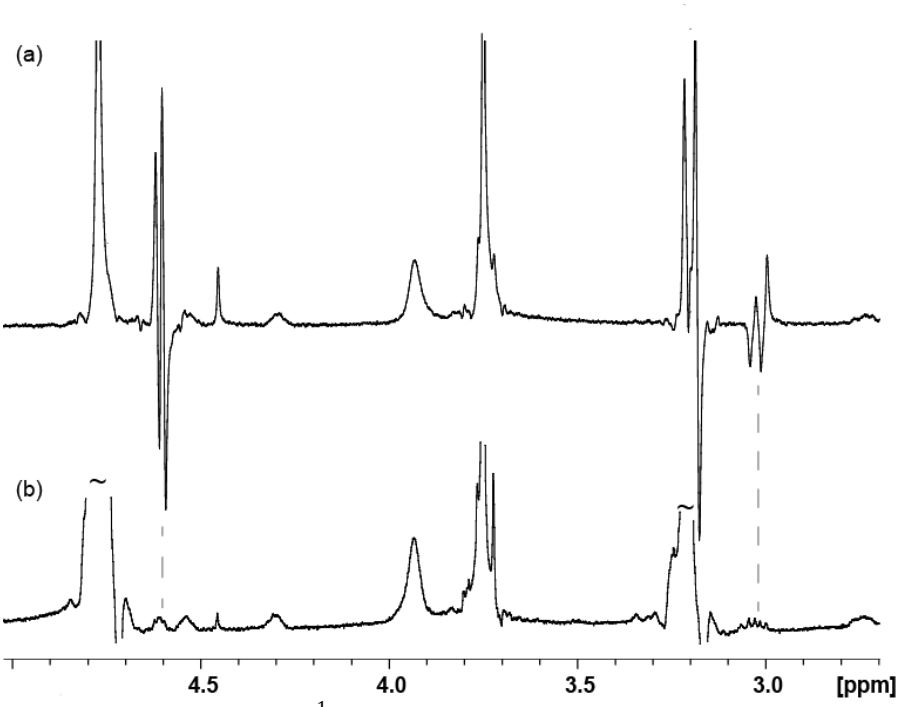

Figure S5. Single-scan ^{1}H NMR: (a) Spectrum recorded immediately after hydrogenation of **5**; (b) reference spectrum of **5** and **5a** after the hyperpolarization decay.

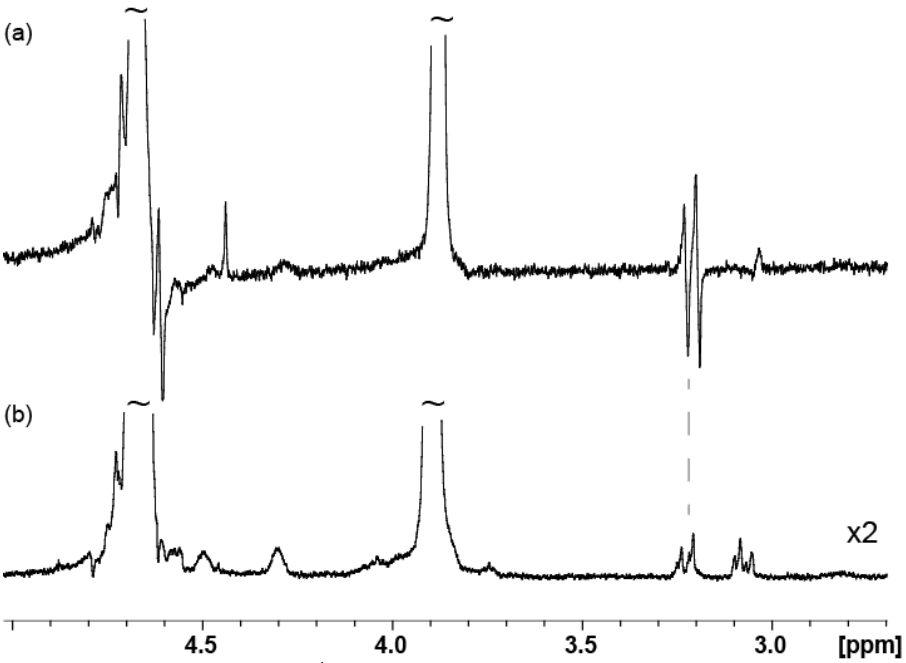

Figure S6. Single-scan ^{1}H NMR: (a) Spectrum recorded immediately after hydrogenation of **6**; (b) reference spectrum of **6** and **6a** after the hyperpolarization decay.

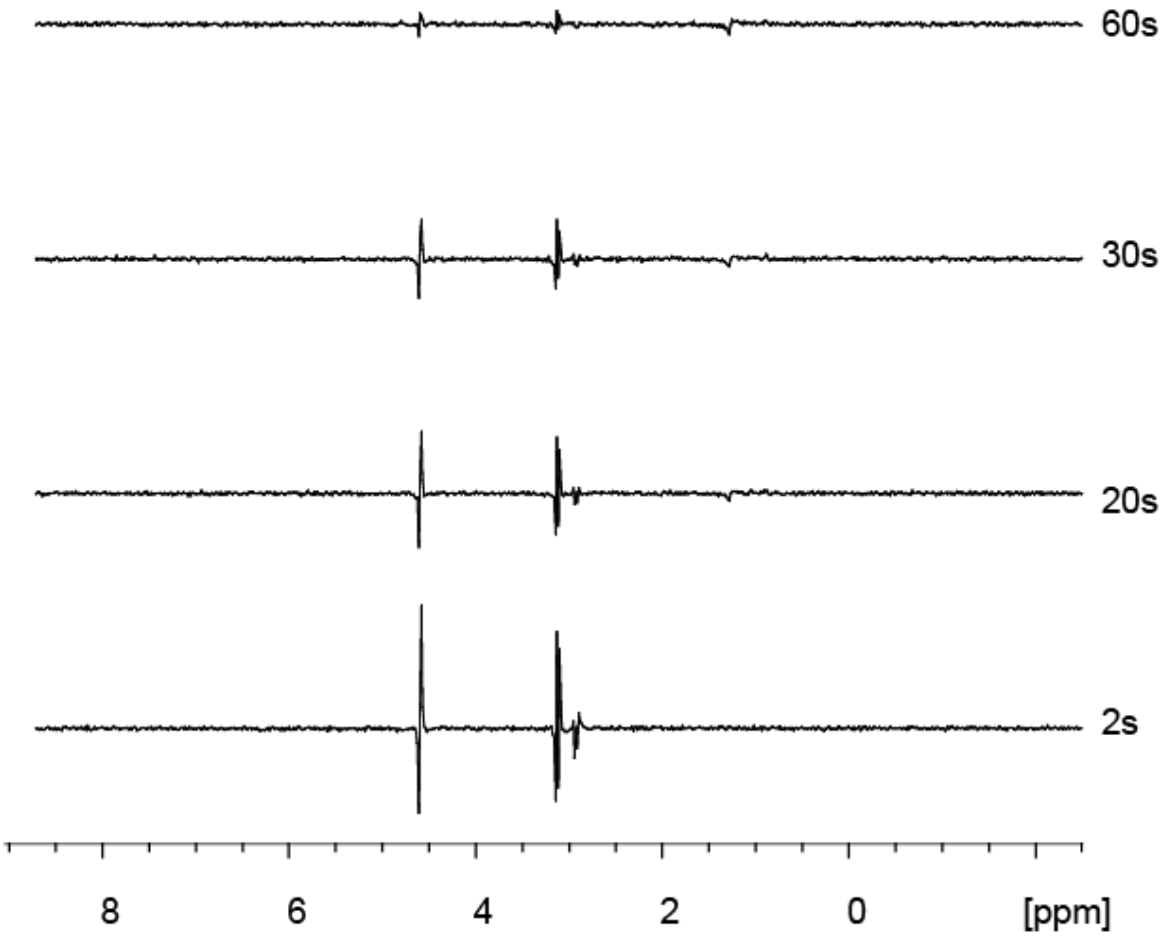

Figure S7. OPSY spectra of **2a** acquired during hydrogenation, showing slices from different reaction times.

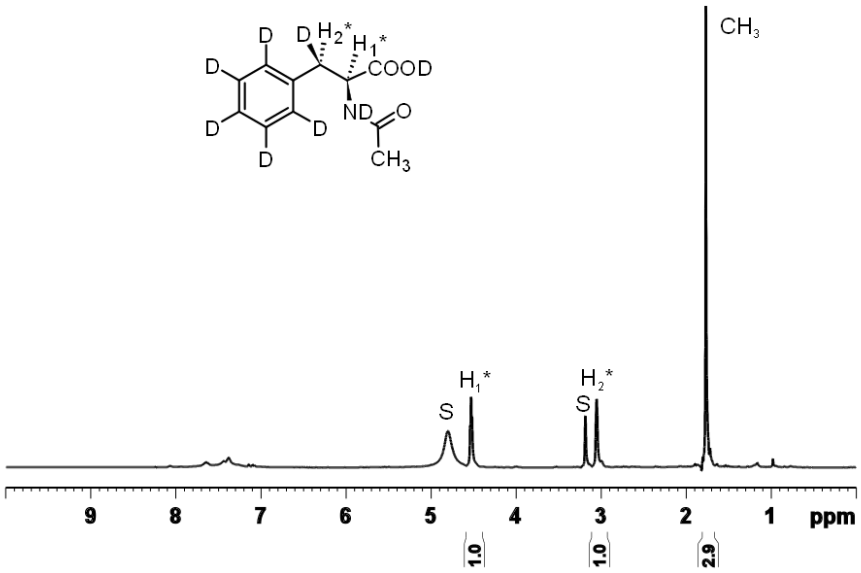

Figure S8. ^{1}H NMR spectrum of **8a** in CD_3OD. "S" denotes solvent peaks.

References

(1) Aguilar, J. A.; Elliott, P. I. P.; Lopez-Serrano, J.; Adams, R. W.; Duckett, S. B. *Chem. Commun.* **2007**, 1183.
(2) Haake, M.; Natterer, J.; Bargon, J. *J. Am. Chem. Soc.* **1996**, *118*, 8688.
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(4) Oba, M.; Ueno, R.; Fukuoka, M.; Kainosho, M.; Nishiyama, K. *J. Chem. Soc., Perk. Trans. 1* **1995**, 1603.
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(6) Herbst, R.M.; Shemin, D. *Org. Synth. Coll. Vol 2* **1943**, 1.
(7) http://www.atlanticmicrolab.com/faq.html#Q5 The elemenal analyzer detected all D atoms as if they were H. For example, in $C_{11}H_2D_9NO_3$, H_{11} was detected.