Supporting Information: Hyperpolarization of ^{15}N in an amino acid derivative

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Abbreviations

DCM Dichloromethane

Dowex Dowex® 50WX8 (protonated form)

Et_2O Diethyl ether

EtOH Ethanol

Pd@C Palladium on carbon (5 %)

RT room temperature

MeOD Methanol-d_4

NaOH Sodium hydroxide

Ru@C Ruthenium on carbon (5 %)

Synthetic procedures

Materials and methods

Chemicals were purchased from commercial suppliers and were used without further purification. Allyl-d_5 bromide was purchased from CDN Isotopes Inc. NMR spectra have been recorded on BRUKER® 300 MHz NMR spectrometer. Analytical ^{13}C NMR spectra have been recorded on a BRUKER® 600 MHz NMR spectrometer. The solvent peaks have been used as reference for chemical shifts in NMR spectra. Mass spectrometry measurements were performed with an ESI-MS mass spectrometer (BRUKER®)

Synthesis of glycine-d_2-^{15}N

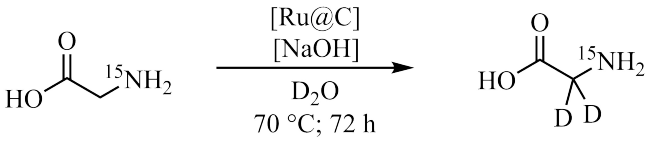
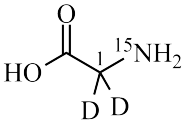


FIGURE S1: Synthesis of glycine-d_2-^{15}N.

Synthesis of glycine-d_2-^{15}N has been conducted according to a modified literature procedure.[1] To glycine-^{15}N (750 mg, 9.9 mmol), NaOH (1.2 g) and Ru@C (75 mg) were added under an N_2-atmosphere and dissolved in D_2O (20 mL). Afterwards the atmosphere was exchanged for H_2 and the reaction mixture was stirred for 72 h at 70 °C. The reaction mixture was filtrated over celite and the pH was adjusted to 6 with Dowex and subsequently filtrated again. The residue was washed with ammonia solution

(10 mL), the filtrates were unified and the solvent was removed under reduced pressure to obtain a slightly yellowish solid (809 mg, 10.4 mmol). The product was used without further purification.



^{2}H-NMR (46 MHz, D_2O, 25 °C): δ [ppm] = 3.25 (s, D-1)

^{13}C-NMR (150 MHz, D_2O, 25 °C): δ [ppm] = 41 (C1), 172

MS (ESI): m/z: 101.0 ($M + Na^+$)

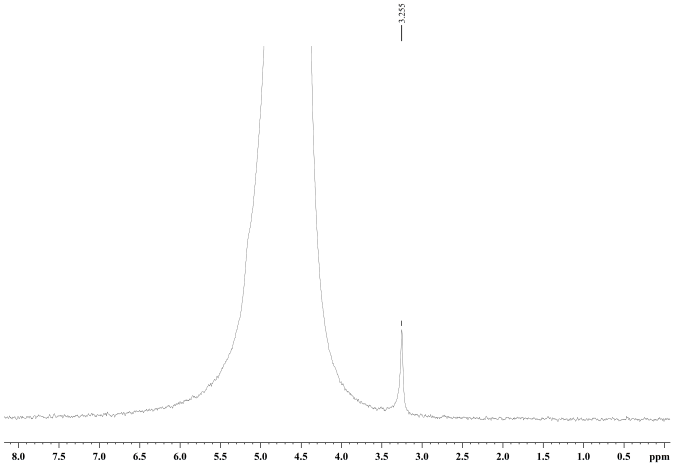


FIGURE S2: ^{2}H-NMR-spectrum of glycine-^{15}N-2,2-d_2.

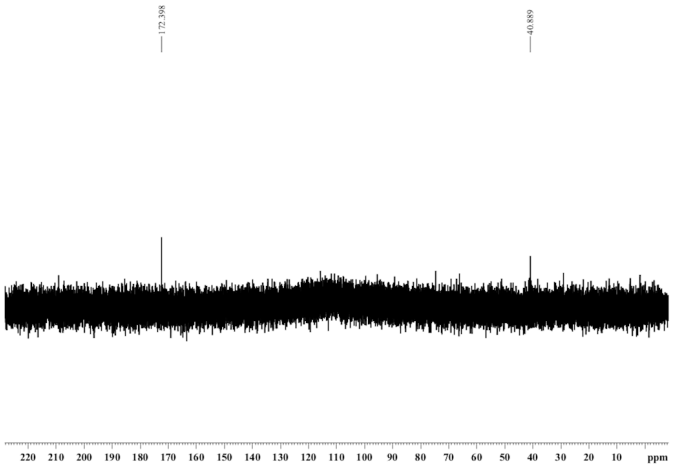


FIGURE S3: ^{13}C-NMR-spectrum of glycine-^{15}N-2,2-d$_2$.

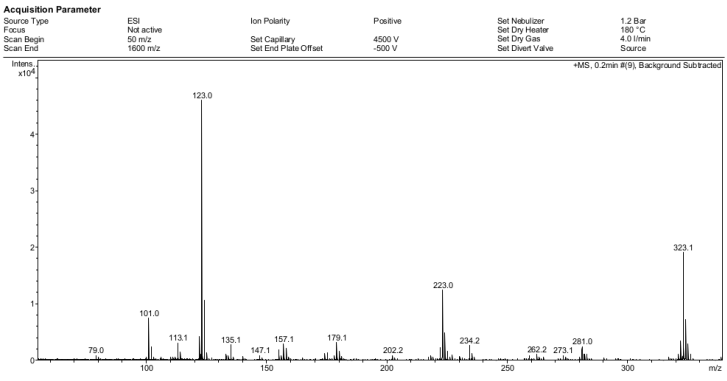


FIGURE S4: ESI mass spectrum of glycine-^{15}N-2,2-d$_2$.

Synthesis of *N*,*N*-bis(methyl-d_3)glycine-2,2-d_2-^{15}N

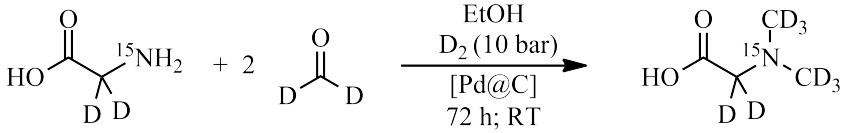
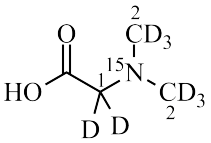


FIGURE S5: Synthesis of *N*,*N*-bis(methyl-d_3)glycine-2,2-d_2-^{15}N.

N,*N*-bis(methyl-d_3)glycine-2,2-d_2-^{15}N has been prepared with a modified procedure.[2] Glycine-d_2-^{15}N (771 mg, 9.88 mmol) and Pd@C (370 mg) were dissolved in EtOH

(15 mL) in a pressure reactor and a solution of formaldehyde-d_2 (20 % in D_2O w/w, 6.4 g, 40 mmol) was added. The reactor was pressurized with D_2 (10 bar) and the mixture was stirred for 72 h at room temperature. Afterwards the reaction mixture was filtrated over celite and the solvent was removed under reduced pressure. The remaining highly viscuous residue was taken up in EtOH and Et_2O was added. The product was precipitated from this solution at -25 °C to obtain 505 mg (4.5 mmol) of *N*,*N*-bis(methyl-d_3)glycine-2,2-d_2-^{15}N with a yield of 46 % over two steps from glycine-^{15}N.



^{2}H-NMR (46 MHz, D_2, 25 °C): δ [ppm] = 2.47 (s, D-2), 3.28 (s, D-1)

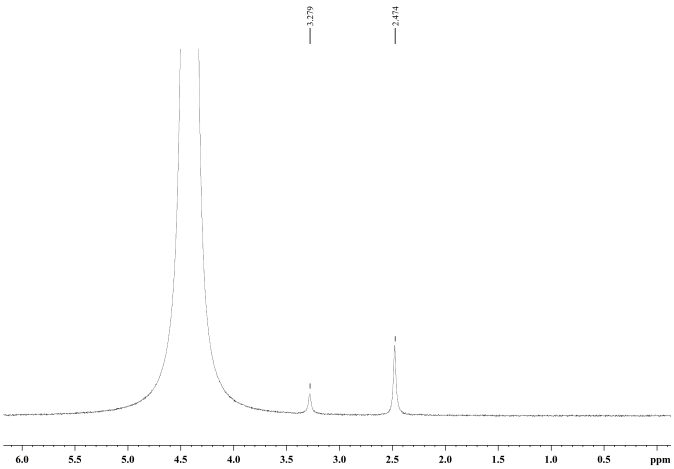


FIGURE S6: ^{2}H-NMR-spectrum of *N*,*N*-bis(methyl-d_3)glycine-2,2-d_2-^{15}N.

Synthesis of 2-(methoxy-d_3)-*N*,*N*-bis(methyl-d_3)-2-oxoethane-1,1-d_2-1-aminium-*d*-*N*-^{15}N chloride

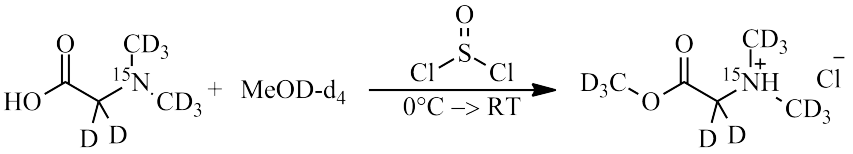
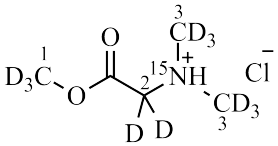


FIGURE S7: Synthesis of 2-(methoxy-d_3)-*N*,*N*-bis(methyl-d_3)-2-oxoethane-1,1-d_2-1-aminium-*d*-*N*-^{15}N chloride.

N,*N*-Bis(methyl-d_3)glycine-2,2-d_2-^{15}N (460 mg, 4.13 mmol) was dissolved in MeOD (10 mL) and cooled to 0 °C. Thionyl chloride (1.2 mL) was added dropwise and the reaction was stirred for 12 h at room temperature. Subsequently the solvent was removed under reduced pressure to obtain 2-(methoxy-d_3)-*N*,*N*-bis(methyl-d_3)-2-oxoethane-1,1-d_2-1-aminium-*d*-*N*-^{15}N chloride as a colorless solid (659 mg, 3.98 mmol) with a yield of 96 %.



^{2}H-NMR (46 MHz, D_2O, 25 °C): δ [ppm] = 3.00 (s, D-3), 3.86 (s, D-2), 4.17 (s, D-1)

^{13}C-NMR (150 MHz, D_2O, 25 °C): δ [ppm] = 43 (C3), 52 (C1), 56 (C2), 166

MS (ESI): m/z: 130.2 ($M - Cl^-$)

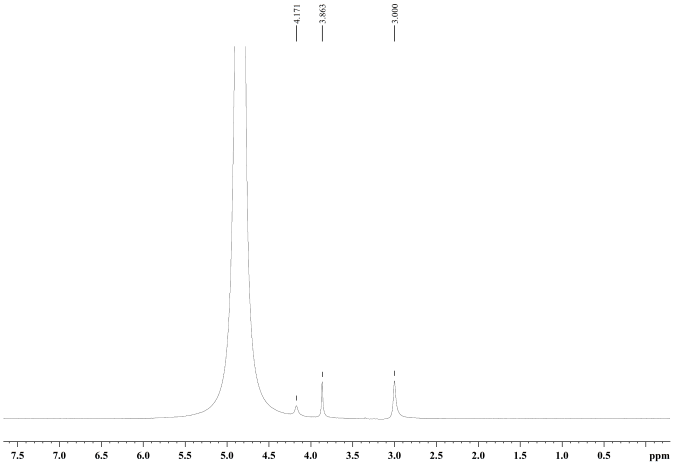


FIGURE S8: ^{2}H-NMR-spectrum of 2-(methoxy-d_3)-*N*,*N*-bis(methyl-d_3)-2-oxoethane-1,1-d_2-1-aminium-*d*-*N*-^{15}*N* chloride.

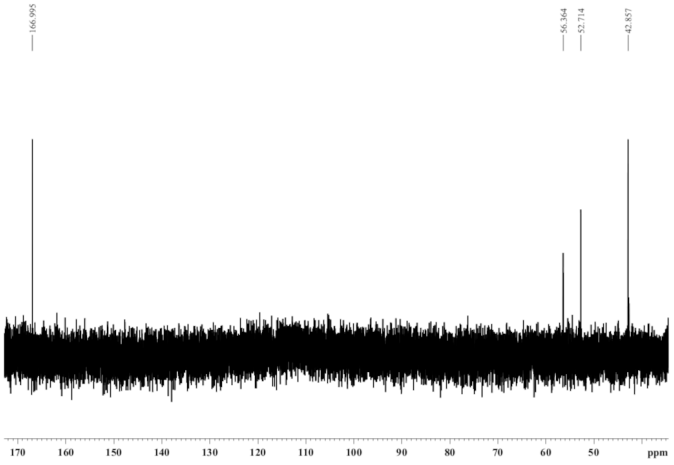


FIGURE S9: ^{13}C-NMR-spectrum of 2-(methoxy-d_3)-*N*,*N*-bis(methyl-d_3)-2-oxoethane-1,1-d_2-1-aminium-*d*-*N*-^{15}*N* chloride.

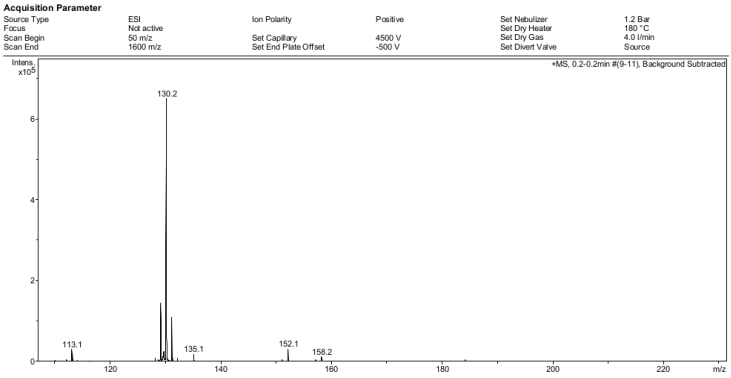


FIGURE S10: ESI-mass-spectrum of 2-(methoxy-d_3)-*N*,*N*-bis(methyl-d_3)-2-oxoethane-1,1-d_2-1-aminium-*d*-*N*-^{15}N chloride.

Synthesis of methyl-d_3-*N*,*N*-bis(methyl-d_3)glycinate-d_2-^{15}N

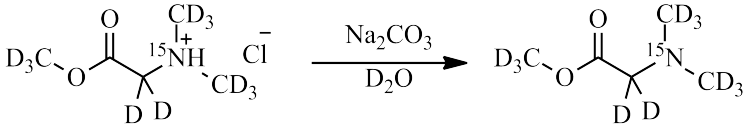
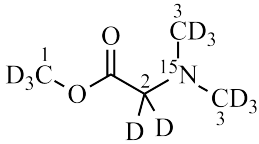


FIGURE S11: Synthesis of methyl-d_3-*N*,*N*-bis(methyl-d_3)glycinate-d_2-^{15}N.

2-(Methoxy-d_3)-*N*,*N*-bis(methyl-d_3)-2-oxoethane-1,1-d_2-1-aminium-*d*-*N*-^{15}N chloride (659 mg, 3.98 mmol) was suspended in DCM (10 mL) in a separating funnel. A saturated solution of Na_2CO_3 in D_2O (10 mL) was added and the mixture was shook over a period of several minutes. The aqueous phase was separated and the organic phase was washed with D_2O (3x5 mL). The unified aqueous phases were extracted with DCM and solvent of the unified organic phases was removed under reduced pressure (300 mbar, 40 °C) to obtain methyl-d_3-*N*,*N*-bis(methyl-d_3)glycinate-d_2-^{15}N as a colorless liquid (471 mg, 3.67 mmol) with a yield of 92 %.



^{2}H-NMR (46 MHz, $CDCl_3$, 25 °C): δ [ppm] = 2.36 (s, 6D, D-3), 3.19 (s, 2D, D-2), 3.74 (s, 3D, D-1)

^{13}C-NMR (150 MHz, $CDCl_3$, 25 °C): δ [ppm] = 44 (C3), 50 (C1), 59 (C2), 170

MS (ESI): m/z: 130.2 ($M + H^+$)

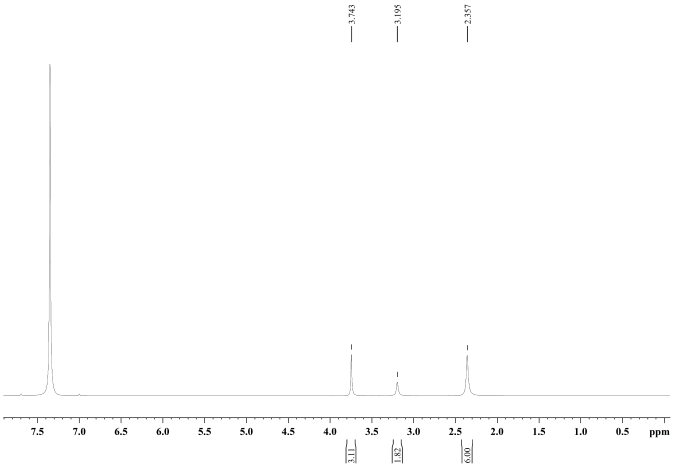


FIGURE S12: ^{2}H-NMR-spectrum of methyl-d_3-*N*,*N*-bis(methyl-d_3)glycinate-d_2-^{15}*N*.

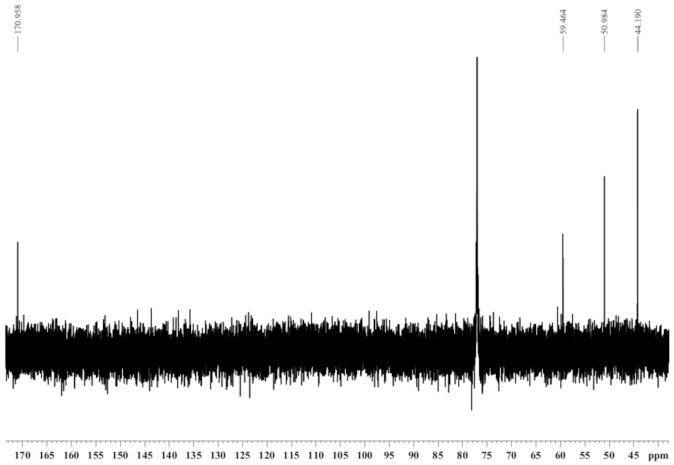


FIGURE S13: ^{13}C-NMR-spectrum of methyl-d_3-*N*,*N*-bis(methyl-d_3)glycinate-d_2-^{15}*N*.

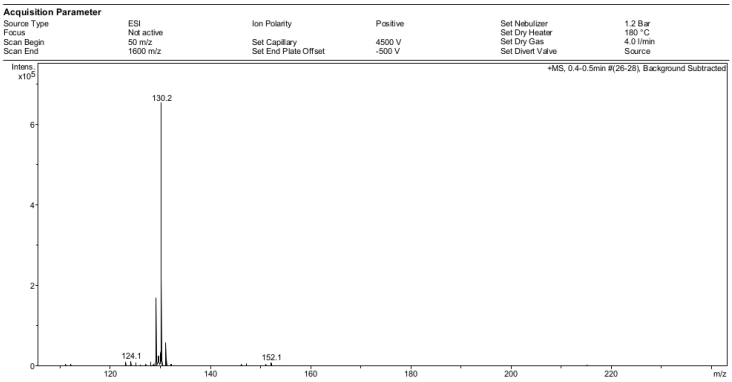


FIGURE S14: ESI-mass-spectrum of methyl-d_3-*N*,*N*-bis(methyl-d_3)glycinate-d_2-^{15}N.

Synthesis of *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}N bromide (1)

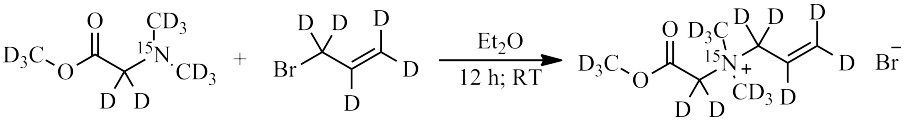
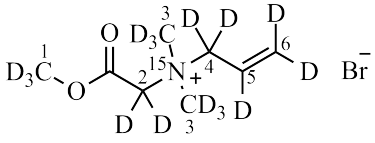


FIGURE S15: Synthesis of *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}N bromide.

The synthesis was conducted with a modified procedure.[3] methyl-d_3-*N*,*N*-bis(methyl-d_3)glycinate-d_2-^{15}N (471 mg, 3.67 mmol) was dissolved in Et_2O (5 mL) under the exclusion of light and N_2 athmosphere. Allyl-d_5 bromide (450 mL, 3.7 mmol) was added. The reaction mixture was stirred for 12 h and the solvent was removed under reduced pressure to give *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}N bromide as a colorless solid (217 mg, 0.85 mmol) with a yield of 23 %.



^{2}H-NMR (46 MHz, H_2O, 25 °C): δ [ppm] = 2.60 (s, 6D, D-3), 3.19 (s, 3D, D-1), 3.51-3.61 (m, 4D, D-2/D-4), 5.14 (m, 2D, D-6), 5.43 (s, 1D, D-5)

MS (ESI): m/z: 175.2 (M^+ - Br^-)

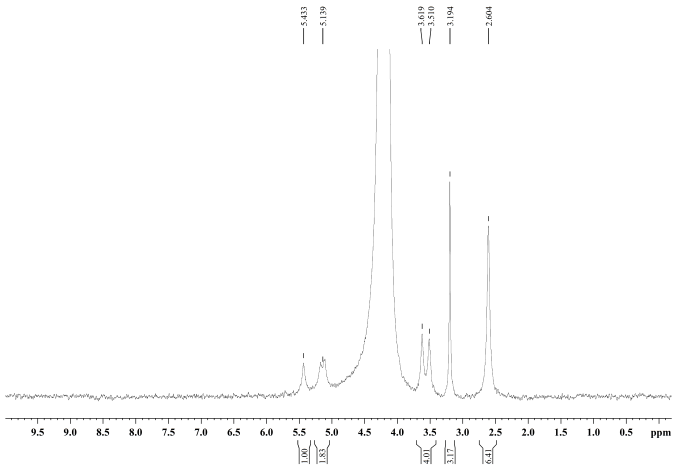


FIGURE S16: ^{2}H-NMR-spectrum of *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}*N* bromide.

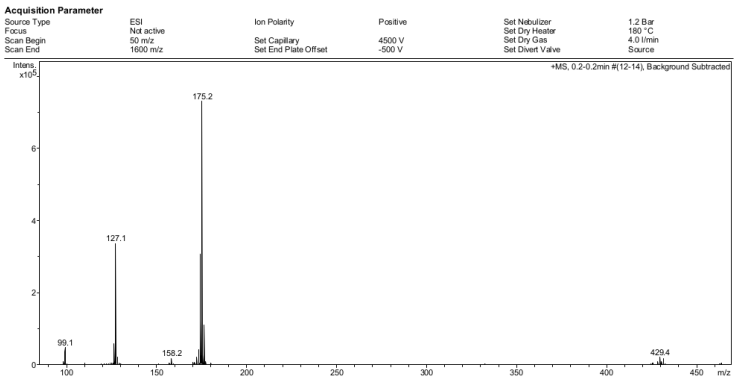


FIGURE S17: ESI-mass-spectrum of *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}*N* bromide.

PHIP experiments

The PHIP experiments have been performed at 7 T and 320 K on a BRUKER® 300 MHz NMR spectrometer. Samples have been prepared in MeOD with 2 mM of catalyst [Rh(dppb)(COD)][BF4] and 1 mM of **(1)**. Hydrogen gas was enriched in the *para* spin isomer at 99 % by using a custom ordered Sumitomo generator operating at 20 K. *Para*-hydrogen was bubbled for 10 s at 7 bar directly into the NMR tube via an automated console controlled delivery system.[4] For the ^{1}H NMR spectra, a 45 °-pulse has been applied. The polarization values have been determined by referencing the absolute signal intensity to a previously measured reference spectrum. ^{15}N polarization experiments

have been performed using the ESOTHERIC pulse sequence with ^{15}N instead of ^{13}C as the x-nucleus.[4] The delays used for heteronuclear and homonuclear decoupling were $\Delta_1 = 301.2$ ms and $\Delta_2 = 42.4$ ms. The ^{15}N T_1 of **(1)** has been determined by polarizing the molecule and afterwards recording spectra at 10°angles and different delays. Corrections for the loss in magnetization from the previous scans have been made.

Mass spectrometry measurements

For the mass spectrometry measurements on the samples before and after hydrogenation, two samples of 2 mM of the catalyst [Rh(dppb)(COD)][BF4] and 1 mM of substrate **(1)** have been prepared. One of those samples has been measured by ESI GC-MS directly. The other sample has been hydrogenated with *para*-hydrogen in an NMR tube at 7 bar, 320 K and 10 s bubbling time. Afterwards a mass spectrum has been recorded in the same manner as for the non-hydrogenated sample.

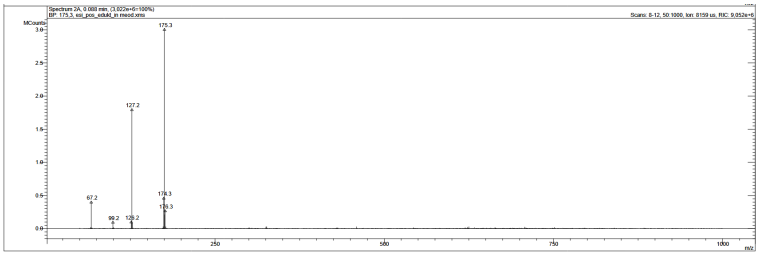


FIGURE S18: ESI-mass-spectrum of *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}N bromide **(1)** before hydrogenation.

From Figure S18 it can be seen that masses can be found for the *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}N ion (m/z = 175) as well as *N*,*N*-dimethyl glycine methyl ester (m/z = 127). This shows a fragmentation of the molecule by either cleaving of a methyl group or losing a allyl group.

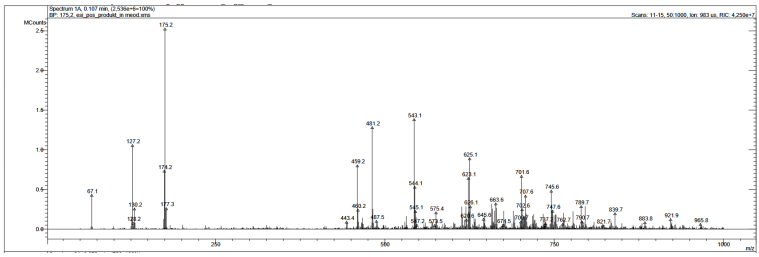


FIGURE S19: ESI-mass-spectrum of *N*-(2-(methoxy-d_3)-2-oxoethyl-1,1-d_2)-*N*,*N*-bis(methyl-d_3)prop-2-ene-1-aminium-d_5-*N*-^{15}N bromide **(1)** after hydrogenation.

The mass spectrum after hydrogenation (figure S19) shows the same pattern than the spectrum before hydrogenation. Especially the fact that the detected masses for the

quarternary ammonium compound are basically the same, in combination with the observation of hyperpolarized signal in the same sample during hydrogenation, hints to the hydrogenation-dehydrogenation mechanism referred to in the main article. Due to the fact that the masse spectrum of the starting material without hydrogenation displays masses that can be attributed to compounds in which a methyl or allyl function has been cleaved hints to a degradation during the ionization process.

References

[1] A. Michelotti, F. Rodrigues, M. Roche, *Org. Process Res. Dev.* **2017**, *21*, 1741–1744.

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[3] B. Biswas, S. C. Collins, D. A. Singleton, *J. Am. Chem. Soc.* **2014**, *136*, 3740–3743.

[4] S. Korchak, S. Yang, S. Mamone, S. Glöggler, *ChemistryOpen* **2018**, *7*, 344–348.