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Supporting Information

Diazirines as Potential Molecular Imaging Tags: Probing the Requirements for Efficient and Long-Lived SABRE-Induced Hyperpolarization

Kun Shen[+], Angus W. J. Logan[+], Johannes F. P. Colell[+], Junu Bae, Gerardo X. Ortiz, Jr., Thomas Theis, Warren S. Warren, Steven J. Malcolmson,* and Qiu Wang**

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Supporting Information

Table of Contents

I. Synthesis of Diazirine Compounds.

General Experiment Information.

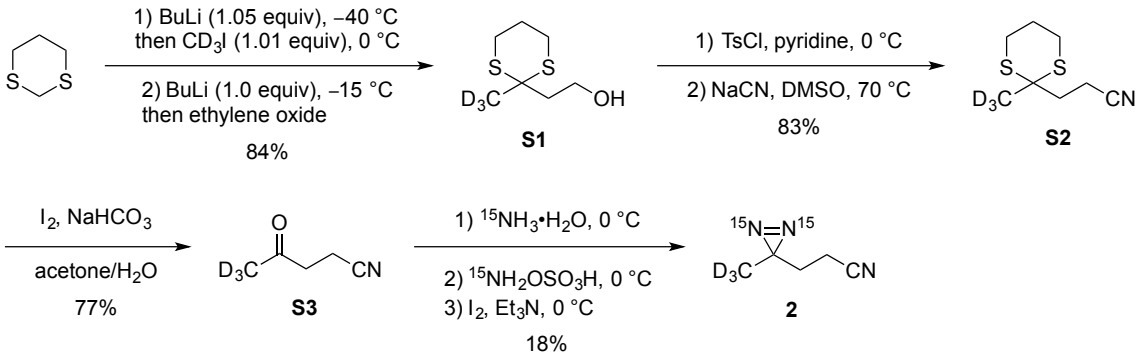
Unless otherwise noted, reactions were performed without exclusion of air or moisture. All commercially available reagents and solvents were used as received unless otherwise stated. THF was obtained from a DriSolve purification system when necessary. *n*-BuLi was titrated using 1,3-diphenyl-2-propanone tosylhydrazone directly before use. CD_3I was distilled under N_2 before use. ^{15}N-labeled hydroxylamine *O*-sulfonic acid ($^{15}NH_2OSO_3H$) was synthesized from ^{15}N-labeled hydroxylamine hydrochloride and chlorosulfonic acid directly before use.[1] Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with 0.25 mm of 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or various stains. Organic solutions were concentrated *in vacuo* using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade).

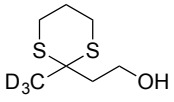
NMR spectra were recorded on Varian iNova 400 and 500 spectrometers. Proton and carbon chemical shifts (^1H, ^{13}C) are quoted in ppm and referenced to $SiMe_4$ with residual protonated solvent as internal standard. For chloroform-*d*, solvent residuals are 7.26 ppm and 77.00 ppm for ^1H and ^{13}C respectively. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet) and combinations thereof. Coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz. For diastereotopic protons, no particular stereochemistry is implied.

High resolution mass spectra were recorded by the Mass Spectrometry Facility at the Department of Chemistry, Duke University. High resolution *m*/*z* values are reported in Daltons, calculated to 4 decimal points from the molecular formula. All found values are within 5 ppm tolerance.

Infrared spectra were recorded on a ThermoScientific Nicolet 6700 FTIR equipped with a diamond ATR. Absorption maxima (υ_{max}) are described as s (strong), m (medium), w (weak), and br (broad) and are reported in wavenumbers (cm^{-1}). Only selected peaks are reported.

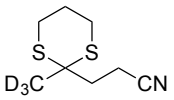
1. Synthesis of 3-(3'-(Methyl-d_3)-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile (2).[1]



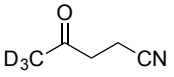


2-(2'-(Methyl-d_3)-1',3'-dithian-2'-yl)ethan-1-ol (S1). To a solution of 1,3-dithiane (3.97 g, 33 mmol, 1.0 equiv) in THF (60 mL) under a N_2 atmosphere at –40 °C, was added dropwise *n*-BuLi (13.9 mL, 2.5 M in hexanes, 34.65 mmol, 1.05 equiv) over 10 min. The reaction was slowly warmed to 0 °C, followed by the dropwise addition of CD_3I over 10 min. The reaction was allowed to stir at 0 °C for 4 h and at room temperature for 10 h, and then was cooled back down to –15 °C. To the reaction mixture, *n*-BuLi (13.2 mL, 33 mmol, 1.0 equiv, 2.5 M in hexanes) was added dropwise over 10 min. After 1 h at room temperature, a solution of ethylene oxide (11 mL, 2.5–3.3 M in THF, 27.5–36.3 mmol, 0.83–1.1 equiv) was added dropwise. The reaction was allowed to stir at room temperature overnight, and then quenched with aqueous HCl (2 M, 20 mL). The mixture was extracted with Et_2O (100 mL × 2). The organic extracts were combined, washed with saturated aqueous $NaHCO_3$ (100 mL), brine (50 mL × 2), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give **S1** as a light yellow liquid (4.97 g, 84%). $\mathbf{R}_f$ = 0.22 (25% ethyl acetate–hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 3.84 (t, *J* = 5.9 Hz, 2H), 2.99 (ddd, *J* = 14.7, 10.1, 3.0 Hz, 2H), 2.80 (ddd, *J* = 14.7, 6.6, 3.2 Hz,

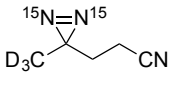
2H), 2.29 (s, br, 1H), 2.27 (t, J = 5.9 Hz, 2H), 2.04 (dtt, J = 14.0, 6.6, 3.0 Hz, 1H), 1.90 (dtt, J = 14.0, 10.1, 3.2 Hz, 1H). The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[1]



3-(2'-(Methyl-d_3)-1',3'-dithian-2'-yl)propanenitrile (S2). To a solution of alcohol **S1** (4.90 g, 27 mmol, 1.0 equiv) in pyridine (25 mL) at 0 °C, was added TsCl (5.40 g, 28.35 mmol, 1.05 equiv) portionwise over 15 min. The reaction was allowed to stir at 0 °C for 2 h then was placed in a –20 °C freezer for 24 h. The reaction was warmed to room temperature and added to a mixture of concentrated aqueous HCl (50 mL) and ice (200 g). The reaction mixture was extracted with Et_2O (250 mL). The organic layer was successively washed with cold aqueous HCl (0.5 M, 50 mL × 2), cold aqueous NaOH (0.5 M, 50 mL), saturated aqueous $NaHCO_3$ (25 mL), and brine (25 mL). The solvent was removed *in vacuo*. To the residue was added DMSO (60 mL) followed by NaCN (2.65 g, 54 mmol, 2.0 equiv), and the solution was heated to 70 °C for 4 h. The reaction mixture was cooled down to room temperature, followed by the addition of H_2O (75 mL), and then was extracted with Et_2O (60 mL × 3). The organic layers were combined, washed with aqueous NaOH (1 M, 40 mL × 2), brine (40 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% ethyl acetate–hexanes to 25% ethyl acetate–hexanes) to give **S2** as a clear liquid (4.26 g, 83%). $\mathbf{R}_f$ = 0.44 (25% ethyl acetate–hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 2.89 (ddd, J = 14.8, 10.2, 3.0 Hz, 2H), 2.77 (ddd, J = 14.8, 6.4, 3.3 Hz, 2H), 2.54 (t, J = 8.0 Hz, 2H), 2.33 (t, J = 8.0 Hz, 2H), 2.03 (dtt, J = 14.0, 6.4, 3.0 Hz, 1H), 1.89 (dtt, J = 14.0, 10.2, 3.3 Hz, 1H). The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[1]

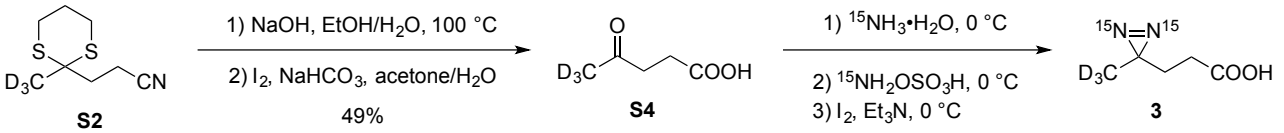


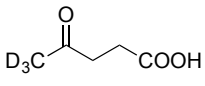
4-Oxopentanenitrile-5,5,5-d_3 (S3). To a solution of dithiane **S2** (4.00 g, 21 mmol, 1.0 equiv) in acetone/H_2O (75 mL/7.5 mL) at 0 °C was added solid $NaHCO_3$ (12.35 g, 147 mmol, 7 equiv) followed by I_2 (15.99 g, 63 mmol, 3 equiv). The reaction was allowed to stir at 0 °C for 2 h and then warmed to room temperature, followed by the addition of an extra amount of I_2 (5.33 g, 21 mmol, 1.0 equiv). The reaction was allowed to stir at room temperature for 1 h and quenched by the addition of aqueous $Na_2S_2O_3$ (10% w/v, 250 mL). The resulting solution was extracted with EtOAc (200 mL × 4). The combined organic extracts were washed with an aqueous $Na_2S_2O_3$ (10% w/v, 40 mL), an aqueous NaOH (1 M, 80 mL), brine (100 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give ketone **S3** as a light yellow liquid (1.62 g, 77%). $\mathbf{R}_f$ = 0.14 (25% ethyl acetate–hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 2.64 (t, J = 7.2 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H). The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[1]



3-(3'-(Methyl-d_3)-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile (2). To a solution of ketone **S3** (1.50 g, 15 mmol, 1.0 equiv) in aqueous $^{15}NH_4OH$ (14 M, 2.7 mL, 37.5 mmol, 2.5 equiv) at 0 °C, was added dropwise a solution of $^{15}NH_2OSO_3H$ (1.71 g, 15 mmol, 1.0 equiv) in MeOH (9 mL) over 5 min. The reaction was stirred at 0 °C for 40 min and then at room temperature for 1 h. The reaction was poured onto MeOH (60 mL), and filtered. The solvent was removed *in vacuo* (~20 mL residue). The concentrated solution was cooled down to 0 °C and Et_3N (1 mL) was added, followed by the addition of I_2 portion wise (until a brown color persisted). The reaction was allowed to stir at 0 °C for an additional 40 min and then at room temperature for 30 min, and was quenched by the addition of brine (50 mL). The mixture was extracted with Et_2O (25 mL × 2). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ (10% w/v, 25 mL × 2), aqueous HCl (0.25 M, 10 mL × 2), saturated aqueous $NaHCO_3$ (10 mL × 2), brine (10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (10% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give diazirine **2** as a clear liquid (0.303 g, 18%). $\mathbf{R}_f$ = 0.50 (25% ethyl acetate–hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 2.22 (t, J = 7.5 Hz, 2H), 1.73 (t, J = 7.5 Hz, 2H). The values of the ^{1}H NMR spectrum are in accordance with reported literature data.[1]

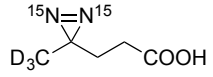
2. Synthesis of 3-(3'-(Methyl-d_3)-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanoic acid (3).[2,3]





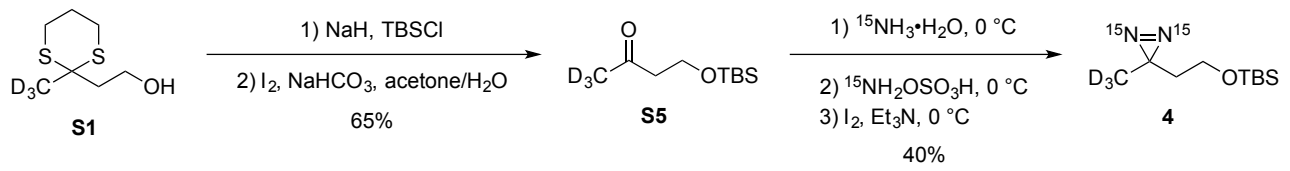
4-Oxopentanoic-5,5,5-d_3 acid (S4). A mixture of **S2** (1.9 g, 10 mmol, 1 equiv), EtOH (25 mL), and an aqueous NaOH solution (8 g in 10 mL of H_2O) was allowed to stir at 80 °C overnight. Then the mixture was concentrated *in vacuo* and the residue was dissolved in water. The aqueous solution was washed with Et_2O, acidified with concentrated HCl, and then extracted with Et_2O. The organic layers were combined and the solvent was removed *in vacuo*. The residue was dissolved in acetone/H_2O (25 mL/2.5 mL). Then $NaHCO_3$ (5.88 g, 70 mmol, 7 equiv) and I_2 (10.16 g, 40 mmol, 4 equiv) were added. The resulting mixture was stirred at room temperature for 2 h, and then acidified with aqueous HCl (2 M). The resulting solution was extracted with EtOAc (20 mL × 3). The organic layers were combined, washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and brine (20

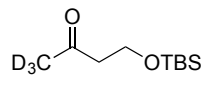
mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (20% ethyl acetate–hexanes to 50% ethyl acetate–hexanes) to give **S4** as a colorless liquid (663.9 mg, 49%). $\mathbf{R}_f$ = 0.10 (20% ethyl acetate–hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 10.5 (s, br, 1 H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.61 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): **δ** 206.7, 178.6, 37.6, 27.7, one carbon (CD_3) missing due to low signal-to-noise; **FTIR** (neat), cm^{-1} 2920, 1701, 1398, 1361, 1237, 1159; **HRMS-ESI** (m/z) calcd. for $C_5H_4D_3O_3$ ([M-H]$^-$): 118.0589; found: 118.0589.



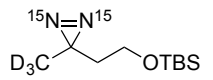
3-(3'-(Methyl-*d*$_3$)-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanoic acid (3). To a solution of **S4** (238 mg, 2 mmol, 1.0 equiv) in aqueous $^{15}NH_4OH$ (14 M, 0.44 mL, 6 mmol, 3 equiv) at 0 °C, was added dropwise a solution of $^{15}NH_2OSO_3H$ (226 mg, 2 mmol, 1.0 equiv) in MeOH (4 mL). The reaction was allowed to stir at 0 °C for 40 min and then at room temperature for 4 h. The solid was filtered off. The solvent was removed *in vacuo*. The concentrated solution was cooled down to 0 °C and MeOH/Et_3N (4 mL/1 mL) was added, followed by the addition of I_2 portion wise (until a brown color persisted). The reaction was stirred for an additional 40 min at 0 °C, then at room temperature for 30 min, and was quenched by the addition of brine (20 mL). The mixture was washed with Et_2O (20 mL). The aqueous layer were acidified to pH = 1, extracted with Et_2O (30 mL × 3). The organic layers were combined, washed with saturated aqueous $Na_2S_2O_3$ (20 mL × 2) and brine (20 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (50% diethyl ether–pentane) to give **3** as a yellow liquid (81.9 mg, 31%). $\mathbf{R}_f$ = 0.30 (20% ethyl acetate–hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$): **δ** 2.23 (t, *J* = 7.5 Hz, 2H), 1.72 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 177.6, 29.2, 28.3, two carbon (CD_3 and diazirine carbon) missing due to low signal-to-noise; **FTIR** (neat), cm^{-1} 2924, 1709, 1415, 1289, 1217, 932; **HRMS-ESI** (m/z) calcd. for $C_5H_4D_3{}^{15}N_2O_2$ ([M-H]$^-$): 132.0642; found: 132.0642.

3. Synthesis of 3-(2'-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(methyl-d$_3$)-3H-diazirine-1,2-$^{15}N_2$ (4).



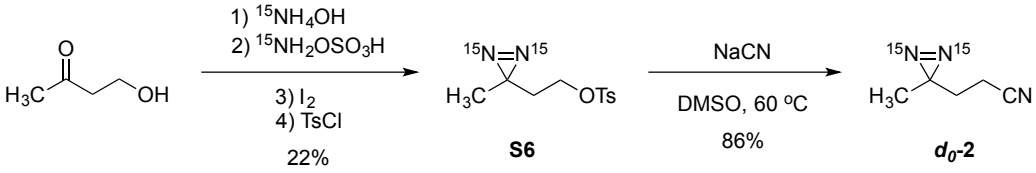


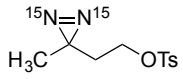
4-((*tert*-Butyldimethylsilyl)oxy)butan-2-one-1,1,1-*d*$_3$ (S5). To a suspension of NaH (336 mg, 60% dispersion in mineral oil, 8.4 mmol, 1.2 equiv) in THF (30 mL) was added **S1** (1.26 g, 7.0 mmol, 1 equiv) dropwise. The resulting mixture was allowed to stir at room temperature for 1 h. Then TBSCl (1.30 g, 8.4 mmol, 1.2 equiv) was added. After stirring for additional 3 h at room temperature, the mixture was partitioned between Et_2O (30 mL) and 10% aqueous solution of potassium carbonate (30 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (30 mL). The organic layers were combined and the solvent was removed *in vacuo*. The residue was dissolved in acetone/H_2O (25 mL/2.5 mL). Then $NaHCO_3$ (4.1 g, 49 mmol, 7 equiv) and I_2 (7.1 g, 28 mmol, 4 equiv) were added. The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL). The resulting solution was extracted with EtOAc (20 mL × 3). The organic layers were combined, washed with brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (hexanes to 5% ethyl acetate–hexanes) to give **S5** as a colorless liquid (932.6 mg, 65%). $\mathbf{R}_f$ = 0.70 (20% ethyl acetate–hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$): **δ** 3.85 (t, *J* = 6.5 Hz, 2H), 2.58 (t, *J* = 6.5 Hz, 2H), 0.84 (s, 9 H), 0.01 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 208.0, 58.8, 46.4, 25.8, 18.1, -5.5, one carbon (CD_3) missing due to low signal-to-noise; **FTIR** (neat), cm^{-1} 2954, 2928, 2884, 2856, 1711, 1252, 1096, 830, 774; **HRMS-ESI** (m/z) calcd. for $C_{10}H_{20}D_3O_2Si$ ([M+H]$^+$): 206.1650; found: 206.1650.



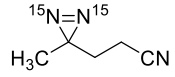
3-(2'-((*tert*-Butyldimethylsilyl)oxy)ethyl)-3-(methyl-d$_3$)-3*H*-diazirine-1,2-$^{15}N_2$ (4). To a solution of **S5** (615 mg, 3 mmol, 1.0 equiv) in aqueous $^{15}NH_4OH$ (14 M, 0.66 mL, 9 mmol, 3 equiv) at 0 °C, was added dropwise a solution of $^{15}NH_2OSO_3H$ (339 mg, 3 mmol, 1.0 equiv) in MeOH (6 mL). The reaction was allowed to stir at 0 °C for 40 min and then at room temperature for 4 h. The solid was filtered off. The solvent was removed *in vacuo*. To the concentrated solution, was added at 0 °C MeOH/Et_3N (12 mL/3 mL) followed by the addition of I_2 portion wise (until a brown color persisted). The reaction mixture was allowed to stir at 0 °C for 40 min and then at room temperature for 30 min, and was next quenched by the addition of brine (20 mL). The mixture was extracted with Et_2O (20 mL × 2). The organic layers were combined, washed with saturated aqueous $Na_2S_2O_3$ (20 mL × 2) and brine (20 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash column chromatography (5% diethyl ether–pentane) to give **4** as a yellow liquid (263.4 mg, 40%). $\mathbf{R}_f$ = 0.80 (10% ethyl acetate–hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$): **δ** 3.54 (t, *J* = 6.0 Hz, 2H), 1.50 (t, *J* = 6.0 Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 58.1, 37.6, 25.8, 18.2, -5.4, two carbon (CD_3 and diazirine carbon) missing due to low signal-to-noise; **FTIR** (neat), cm^{-1} 2953, 2928, 2856, 1254, 1100, 833, 744; **HRMS-ESI** (m/z) calcd. for $C_{10}H_{20}D_3{}^{15}N_2OSi$ ([M+H]$^+$): 220.1709; Satisfactory HRMS data could not be obtained.

4. Synthesis of 3-(3'-methyl-3'H-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile (d_0-2).



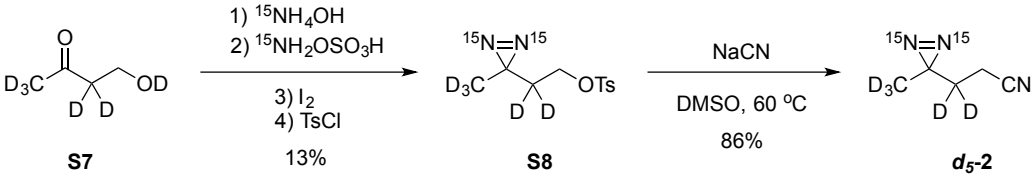


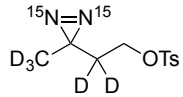
2'-(3''-Methyl-3''*H*-diazirin-3''-yl-1'',2''-$^{15}N_2$)ethyl-4-methylbenzenesulfonate (S6). To a solution of 4-hydroxybutan-2-one (0.44 g, 5 mmol) in aqueous $^{15}NH_4OH$ (14 M, 1.07 mL, 15 mmol, 3 equiv) was added dropwise a solution of $^{15}NH_2OSO_3H$ (0.57 g, 5 mmol, 1.0 equiv) in MeOH (10 mL). The reaction was stirred at room temperature for 5 h. The solid was filtered off. The solvent was removed *in vacuo*. The concentrated solution was cooled down to 0 °C and MeOH/Et_3N (10 mL/4 mL) was added, followed by the addition of I_2 portion wise (until a brown color persisted). The reaction was allowed to stir at room temperature for 1 h, and was quenched by the addition of brine (40 mL). The mixture was extracted with Et_2O (50 mL × 3). The organic layers were combined, washed with saturated aqueous $Na_2S_2O_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. To the crude residue was added pyridine (4 mL) and TsCl (1.15 g, 6 mmol, 1.2 equiv). The reaction mixture was allowed to stir overnight at room temperature and then was poured onto ice (60 g). The mixture was diluted with concentrated HCl (10 mL) and extracted with Et_2O (50 × 3 mL). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, and filtered. The crude residue was purified by flash silica column chromatography (10% ethyl acetate–hexanes) to give **S6** as a yellow liquid (282.5 mg, 22% yield). $\mathbf{R}_f$ = 0.53 (20% ethyl acetate–hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$): **δ** 7.74 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.90 (t, *J* = 6.0 Hz, 2H), 2.39 (s, 3H), 1.61 (t, *J* = 6.0 Hz, 2H), 0.93 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 144.8, 132.3, 129.7, 127.6, 65.0, 33.8, 23.1 (t, *J* = 9.0 Hz), 21.3, 19.4. **FTIR** (neat), cm^{-1} 1354, 1188, 1173, 967, 899, 814, 750, 660, 552; **HRMS-ESI** (m/z) calcd. for $C_{11}H_{14}{}^{15}N_2O_3S$ ($[M+Na]^+$): 279.0561; found: 279.0567.



3-(3'-Methyl-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile (d_0-2). To a solution of **S6** (52.4 mg, 0.2 mmol) in DMSO (1 mL) was added NaCN (11.8 mg, 0.24 mmol). The resulting mixture was allowed to stir at 60 °C for 5 h and then was quenched by the addition of H_2O (3 mL). The mixture was extracted with Et_2O (4 mL × 3). The organic layers were combined, washed with brine (4 mL), dried over Na_2SO_4, and filtered through a pale of silica gel. The filtrate was concentrated *in vacuo* to give ***d_0*-2** as a yellow liquid (18.9 mg, 86% yield). $\mathbf{R}_f$ = 0.50 (25% ethyl acetate–hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$): **δ** 2.22 (t, *J* = 7.5 Hz, 2H), 1.74 (t, *J* = 7.5 Hz, 2H) 1.10 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 118.4, 30.8, 24.4 (t, *J* = 9.0 Hz), 19.3, 12.1. **FTIR** (neat), cm^{-1} 2928, 2250, 1541, 1446, 1426, 913, 732; Satisfactory HRMS data could not be obtained.

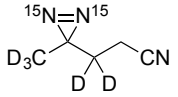
5. Synthesis of 3-(3'-(methyl-d_3)-3'H-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile-3,3-d_2 (d_5-2).





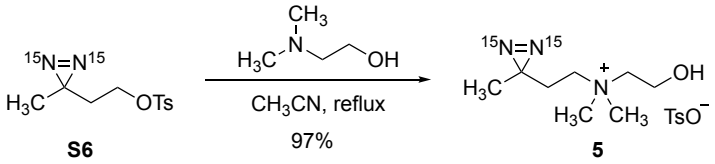
2'-(3''-(Methyl-d_3)-3''*H*-diazirin-3''-yl-1'',2''-$^{15}N_2$)ethyl-2',2'-d_2-4-methylbenzenesulfonate (S8). Compound **S7** was synthesized according to literature procedure (80%~86% deuteration by ^{1}H NMR).[4] To a solution of **S7** (1.28 g, 13.6 mmol) in aqueous $^{15}NH_4OH$ (14 M, 2.91 mL, 40.8 mmol, 3 equiv) was added dropwise a solution of $^{15}NH_2OSO_3H$ (1.54 g, 13.6 mmol, 1.0 equiv) in MeOH (30 mL). The reaction was stirred at room temperature for 5 h. The solid was filtered off. The solvent was removed *in vacuo*. The concentrated solution was cooled down to 0 °C and MeOH/Et_3N (40 mL/10 mL) was added, followed by the addition of I_2 portion wise (until a brown color persisted). The reaction was allowed to stir at room temperature for 1 h, and was quenched by the addition of brine (100 mL). The mixture was extracted with Et_2O (100 mL × 3). The organic layers were combined, washed with saturated aqueous $Na_2S_2O_3$ (25 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. To the crude residue was added pyridine (12 mL) and TsCl (3.11 g, 16.3 mmol, 1.2 equiv). The reaction mixture was allowed to stir overnight at room temperature and then was poured onto ice (120 g). The mixture was diluted with concentrated HCl (20 mL) and extracted with Et_2O (100 mL). The organic layer was washed with saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (25 mL). The organic layer was dried over Na_2SO_4, and filtered. The crude residue was purified by flash silica column chromatography (10% ethyl acetate–hexanes) to give **S8** as a yellow liquid (461.5 mg, 13% yield, 80% deuteration for CH_2, 86% deuteration for CH_3 by ^{1}H NMR). $\mathbf{R}_f$ = 0.53 (20% ethyl acetate–hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$): **δ** 7.71 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.86 (s, 2H), 2.36 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 145.0, 132.7, 129.9, 127.9, 65.0, 34.1–33.3 (m, 1C), 21.6, two carbon (CD_3 and diazirine carbon) missing

due to low signal-to-noise; **FTIR** (neat), cm^{-1} 1357, 1188, 1173, 976, 870, 813, 657, 552; **HRMS-ESI** (m/z) calcd. for $C_{11}H_9D_5{}^{15}N_2O_3SNa$ ([M+Na]$^+$): 284.0877; found: 283.0808.

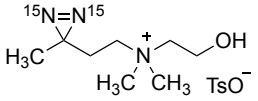


3-(3'-(Methyl-*d*$_3$)-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile-3,3-*d*$_2$ (*d*$_5$-2). To a solution of **S8** (104.8 mg, 0.4 mmol) in DMSO (1 mL) was added NaCN (23.5 mg, 0.48 mmol). The resulting mixture was allowed to stir at 60 °C for 5 h and then was quenched by the addition of H_2O (3 mL). The mixture was extracted with Et_2O (4 mL × 3). The organic layers were combined, washed with brine (4 mL), dried over Na_2SO_4, and filtered through a pale of silica gel. The filtrate was concentrated *in vacuo* to give ***d*$_5$-2** as a yellow liquid (40.0 mg, 86% yield, 80% deuteration for CH_2, 86% deuteration for CH_3 by ^{1}H NMR). $\mathbf{R}_f$ = 0.50 (25% ethyl acetate–hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$): **δ** 2.21 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 118.4, 30.8–29.9 (m, 1C), 19.2–18.2 (m, 1C), 12.1 (d, *J* = 10.0 Hz), one carbon (diazirine carbon) missing due to low signal-to-noise; **FTIR** (neat), cm^{-1} 2934, 2247, 1537, 1427, 1046, 714; Satisfactory HRMS data could not be obtained.

6. Synthesis of diazirine-labeled choline derivative (5).



S6 **5**



2-Hydroxy-*N*,*N*-dimethyl-*N*-(2'-(3''-methyl-3''*H*-diazirin-3''-yl-1'',2''-$^{15}N_2$)ethyl)ethan-1-ammonium 4-methylbenzenesulfonate (5). To a solution of **S6** (25.6 mg, 0.1 mmol) in MeCN (100 µL), was added 2-dimethylaminoethanol (10.1 µL, 0.1 mmol). The reaction was heated to 80 °C for 20 h. The solvent was removed *in vacuo* to give **5** as a yellow-brown semi-solid (33.5 mg, 97% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): **δ** 7.71 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.05–3.85 (m, 2H), 3.55–3.35 (m, 4H), 3.11 (s, 6H), 2.37 (s, 3H), 1.95–1.75 (m, 2H), 1.07 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$): **δ** 143.6, 141.7, 129.8, 126.9, 66.4, 61.3, 56.8, 52.2, 29.2, 24.3 (t, *J* = 8.8 Hz), 21.3, 19.3; **FTIR** (thin film), cm^{-1} 3348, 1491, 1220, 1182, 1120, 824, 684, 564; **HRMS-ESI** (m/z) calcd. for $C_{15}H_{25}N^{15}N_2O_4S$ ([M-OTs]$^+$): 174.1384; found: 174.1385.

II. Hyperpolarization Details

II.1 Experimental details

General Information
Measurments are carried out on a Magritek Spinsolve Nitrogen (1 T) or Bruker Avance DX 360 (8.45 T). Para-hydrogen was supplied from a commercially available Bruker BPHG090 (Conversion temperature 32.6 K, 92.6 % para-H_2).

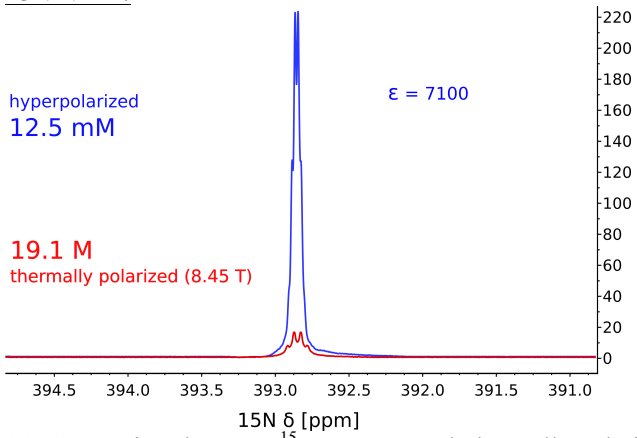
Sample preparation:
Stock solutions 5 mM in precatalyst (either [IrCl(COD)(IMes)] or [Ir(COD)(IMes)Pyr]PF_6), 100 mM in diazirine (**1 - 5**, and deuterated variants thereof) and 50 mM in Lewis-basic additives (CH_3CN, Pyridine) were added to a suitable volume of methanol-d4 to obtain desired concentrations in the respective compounds (c_{Cat} = 0.125 mM, c_{Sub} = 12.5 mM, $c_{Additive}$ = 1 mM). The D_2O additive could be added directly (c = 925 mM). Note that the water concentration was chosen to obtain conditions identical to those used in a previous study.[1] Samples prepared with [IrCl(COD)(IMes)] without additional Lewis basic additives turned dark red on exposure to hydrogen, no SABRE effect could be observed.

Hyperpolarization conditions:
Precatalysts were transformed to the catalytically active species under a hydrogen atmosphere (10 bar) species in presence of diazirine and Lewis-basic additives by bubbling *para*-H_2 through the solution (20 minutes, 20 sccm/min). Diazirine **3** is not indefinitely stable under the experimental conditions and the catalyst is activated in presence of LB additive only. Substrate is added under 1 bar of Ar and the sample subsequently pressurized with *para*-H_2.

The sample was transferred to a fixed magnetic evolution field of 0.5 µT and *para*-H_2 was supplied at a flow rate of 100 sccm/min for 150 s. The flow is stopped and the sample is transferred to a Magritek Spinsolve Nitrogen (1 T) or Bruker Avance DX 360 (8.45 T) for detection. Transfer time to 1 T is 4 s, to 8.45 T transfer time is 8 s.

Determination of enhancement/polarization
A single scan NMR spectrum on the hyperpolarized compound with a 90° excitation pulse is compared to a reference of neat ^{15}N acetonitrile (Cambridge Isotope Laboratories, 98 %+, 19.1 M, B = 8.45 T, see Figure S1) to determine enhancements. Absolute polarization is calculated from the recorded enhancements.

15N NMR:



S1. Comparison between ^{15}N spectra. Red: thermally polarized reference of ^{15}N-CH_3CN (c = 19.1 M, $^3J_{NH}$ = 1.7 Hz, 99.8%+, Cambridge Isotope Laboratories, B_0 = 8.45 T, shifted by 200 ppm for easier comparison). Blue: 12.5 mM diazirine ***d*$_0$-2** (observed is the average $^3J_{NH}$ = 0.75 Hz).

***T*$_1$ measurements**
T_1 measurements were carried out using sequential small tip angle excitation/acquisition methods. The time delay *d*t between individual acquisitions is 4.2 s at 8.45 T and 30 s at 1 T. The number of points is 16 at 8.45 T and eight at 1 T (see Figure S2). Data is processed with Mnova 8.0.1-10878 (baseline correction, line-broadening = 0.5 Hz (8.45 T) or 5 Hz (1 T)).

3-(3'-(Methyl-*d*$_3$)-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile (2).
^{15}N-NMR (36 MHz, [D4]MeOH, CD_2HOD, 22 °C): δ = 393.3 ppm (s).

3-(3'-methyl-3'H-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile (*d*$_0$-2).
^{15}N-NMR (36 MHz, [D4]MeOH, CD_2HOD, 22 °C): δ = 392.9 ppm (h, $^3J_{NH}$ = 0.75 Hz).

3-(3'-(methyl-d_3)-3'H-diazirin-3'-yl-1',2'-$^{15}N_2$)propanenitrile-3,3-d_2 (d_5-2)
^{15}N-NMR (36 MHz, [D4]MeOH, CD_2HOD, 22 °C): δ = 393.2 ppm (m).

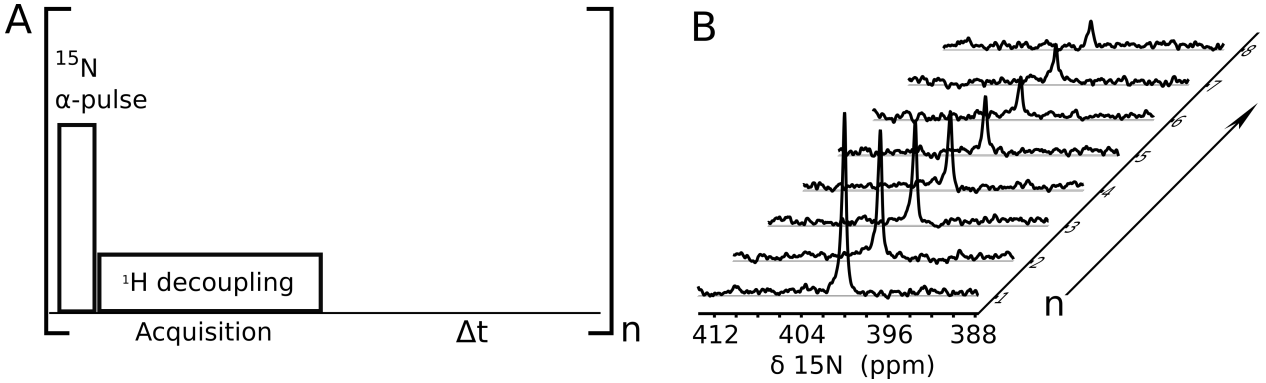
3-(3'-(Methyl-d_3)-3'*H*-diazirin-3'-yl-1',2'-$^{15}N_2$)propanoic acid (3).
^{15}N-NMR (36 MHz, [D4]MeOH, CD_2HOD, 22 °C): δ = 396.5 ppm (s).

3-(2'-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(methyl-d_3)-3H-diazirine-1,2-$^{15}N_2$ (4)
^{15}N-NMR (36 MHz, [D4]MeOH, CD_2HOD, 22 °C): δ = 400.0 ppm (s).

2-hydroxy-N,N-dimethyl-N-(2'-(3''-methyl-3''H-diazirin-3''-yl-1'',2''-$^{15}N_2$)ethyl)ethan-1-ammonium 4-methylbenzenesulfonate (5).
^{15}N-NMR (36 MHz, [D4]MeOH, CD_2HOD, 22 °C):): δ = 392.2 ppm (h, J= 0.76 Hz).

Note that J-couplings from ^{15}N to deuterium (I = 1) are characteristically smaller and multiplicity higher. Labeled substrates didn't allow to accurately determine the full set of coupling constants. Often only one line is resolved as a result of the field cycling process involved in SABRE SHEATH (vide infra).

II.2 T_1 measurements:



S2: A) Pulse sequence used for small pulse angle T_1 measurements, B) 1 T spectra at each individual time point. The first spectrum (n = 1) is acquired at t = 0 s, Δt is 30 s, ^{15}N pulse angle is 6°. Data in B) from Diazirine **4**, catalyst B.

The Signal to Noise Ratio (SNR) gets progressively worse for each successive time point in a T_1 experiment (see Figure S1B). For hyperpolarized studies, the experimental error of the T_1 values depends directly on the enhancement, which defines the initial signal intensity. T_1 in combination with S_0, defines the remaining signal intensity S(t) at increment i.

Furthermore, the signal to noise ratio depends on the magnetic field of detection. For a coil detected NMR experiment with thermal coil noise (Johnson-Noise) as dominant noise source the SNR is given as the product of polarization and induction (proportional to B_0) and the noise, which scales as $B_0^{1/4}$. For a hyperpolarized NMR sample, the polarization is independent of the magnetic field of detection. Accordingly, the SNR is proportional to $B_0^{3/4}$. The expected increase of the SNR, when changing the detection field from 1 T to 8.45 T is thus roughly a factor nine.

In low magnetic fields scalar relaxation of the second kind dominates relaxation. Here, polarization decays with a rate given by T_2 of the coupling partner. Our observation of the relaxation field dependence for deuterated compounds imply that ^{2}H has a much shorter T_2 at low fields than ^{1}H. Accordingly lower enhancements are observed for deuterated compounds, more generally nuclei with strong couplings to an adjacent qudrupole.

In the region from 3 G to 2 T relaxation times are almost field independent pointing to dipole-dipole relaxation as dominant relxation mechanism. At even higher field above 2 T significant shortening of T_1 is observed. Relaxation originating from chemical shift anisotropy (CSA) scales with B_0^2 and has been reported to be the major relaxation mechanism for ^{15}N in high field.

For determination and comparison of T_1 values reported in the main text resonances at the individual time points in a T_1 experiment are evaluated by Lorentzian line fitting. We find that line intensity yields the smallest systematic error, as shimming artifacts, and noise contribution to the integral (evaluation by direct integration) and noise contribution to the apparent area (line fitting) are most effectively suppressed, as exemplified in Figure S3. The resulting values are evaluated by fitting the first order exponential decay $f(t) = A_0 \exp(-t/T_1) + y_0$, with initial signal intensity A_0 and relaxation time constant T_1. The T_1 relaxation data for the different compunds is shown in Table S1.

In Table S2 the field dependence of T_1 for the isotopically differentiated compounds **d0-2**, **d3-2** and **d5-2** is shown. The individual points are acquired by subjecting the sample to the SABRE SHEATH procedure and storing it in the holding field B_{hold}.

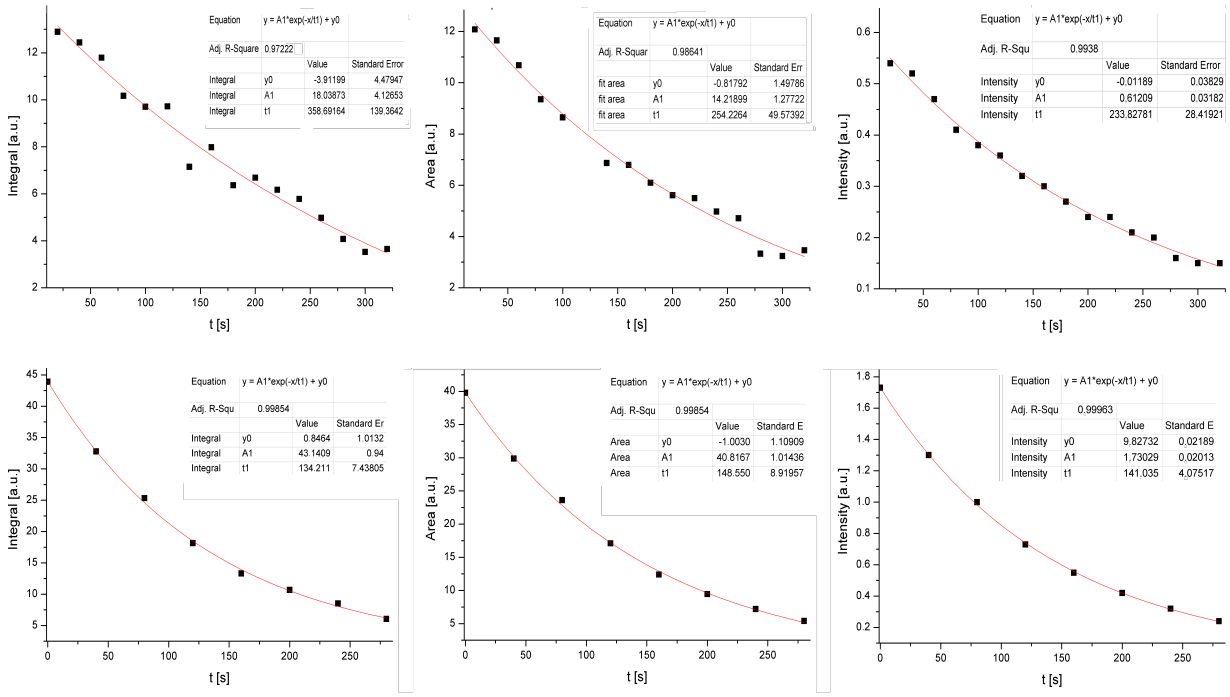
Table S1: ^{15}N-T_1 at two different magnetic fields for diazirines **2-4**.

	Additive	^{15}N-T_1 (1 T) [s][a]	^{15}N-T_1 (8.45 T) [s][b]
2	Pyridine	168 ± 18	34.6 ± 1.9
2	D_2O	176 ± 3	28.3 ± 0.3
2	CH_3CN	179 ± 16	n.a.[c]
4	Pyridine	141 ± 4	29.4 ± 0.6
4	D_2O	164 ± 25	27.3 ± 0.7
4	CH_3CN	263 ± 83	n.a.[c]
3	Pyridine	215 ± 22	17.7 ± 1.8
3	D_2O	234 ± 28	16.9 ± 1.7
3	CH_3CN	172 ± 17	n.a.[c]

[a] T_1 determined from line intensity, for details see text. [b] T_1 determined from integral data. [c] samples with CH_3CN additive are not long term stable.

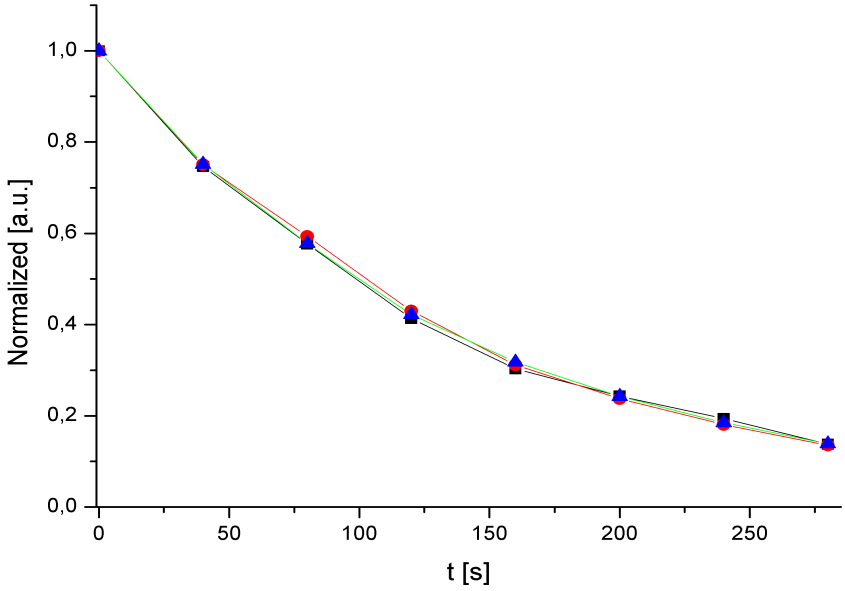
Table S2: Field dependence of ^{15}N-T_1 for different isotopic labeling.

B_{hold} [T]	**d0-2**, T_1 [s]	**d5-2**, T_1 [s]
$3\cdot10^{-4}$	210	190
$6.5\cdot10^{-3}$	210	290
0.1	155	200
0.25	140	210
0.5	173	198
1	187	160
2	180	146
8.45	34	31



S3. Comparison between different T_1 evaluation methods. From left to right: integral, area and the intensity for (top) diazirine-COOH **3**, additive D_2O, enhancement 1.900. Bottom: diazirine-OTBS **(4)**, additive pyridine, Enhancement 16.000.

As shown in Figure S4. for large enhancements, or equivalently large SNR at high fields, the choice of evaluation routine is irrelevant. Detection at 8.45 T or enhancements over 10.000 yield the same result within the fit error irrespective of the method.



S4. Comparison between normalized Integral (blue), area (red), and intensity (green) for diazirine-OTBS **(4)**. With large enhancements, equivalently.

III. References.

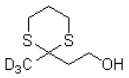
1. Theis, T.; Ortiz Jr., G. X.; Logan, A.; Claytor, K.; Feng, Y.; Kuhn, W.; Blum, V.; Malcolmson, S.; Chekmenev, E. Y.; Wang, Q.; Warren, W. S. *Sci. Adv.* **2016**, *2*, e1501438.

2. Vervacke, J. S.; Funk, A. L.; Wang, Y.; Strom, M.; Hrycyna, C. A.; Distefano, M. D. *J. Org. Chem.* **2014**, *79*, 1971–1978.

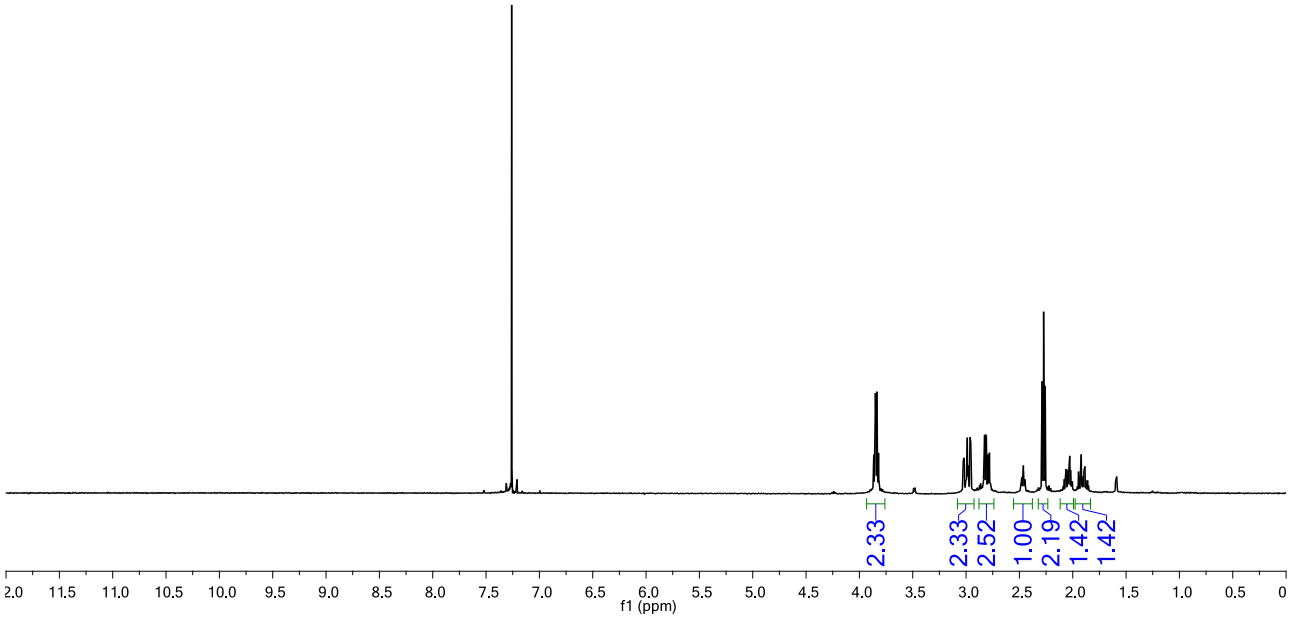
3. Bond, M. R.; Zhang, H.; Vu, P. D.; Kohler, J. J. *Nat. Protoc.* **2009**, *4*, 1044–1063.

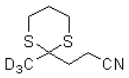
4. Kirst, D. T.; Statsyuk, A. V. *Biochemistry* **2015**, *54*, 4411–4414.

IV. ^{1}H and ^{13}C NMR Spectra.

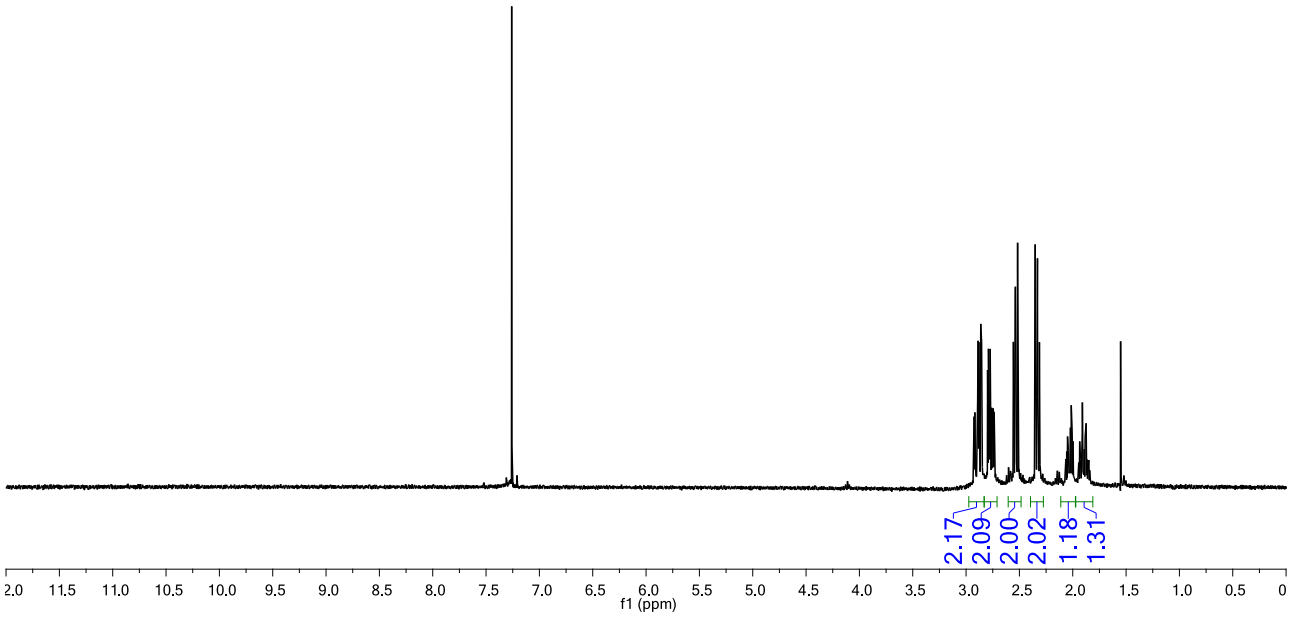


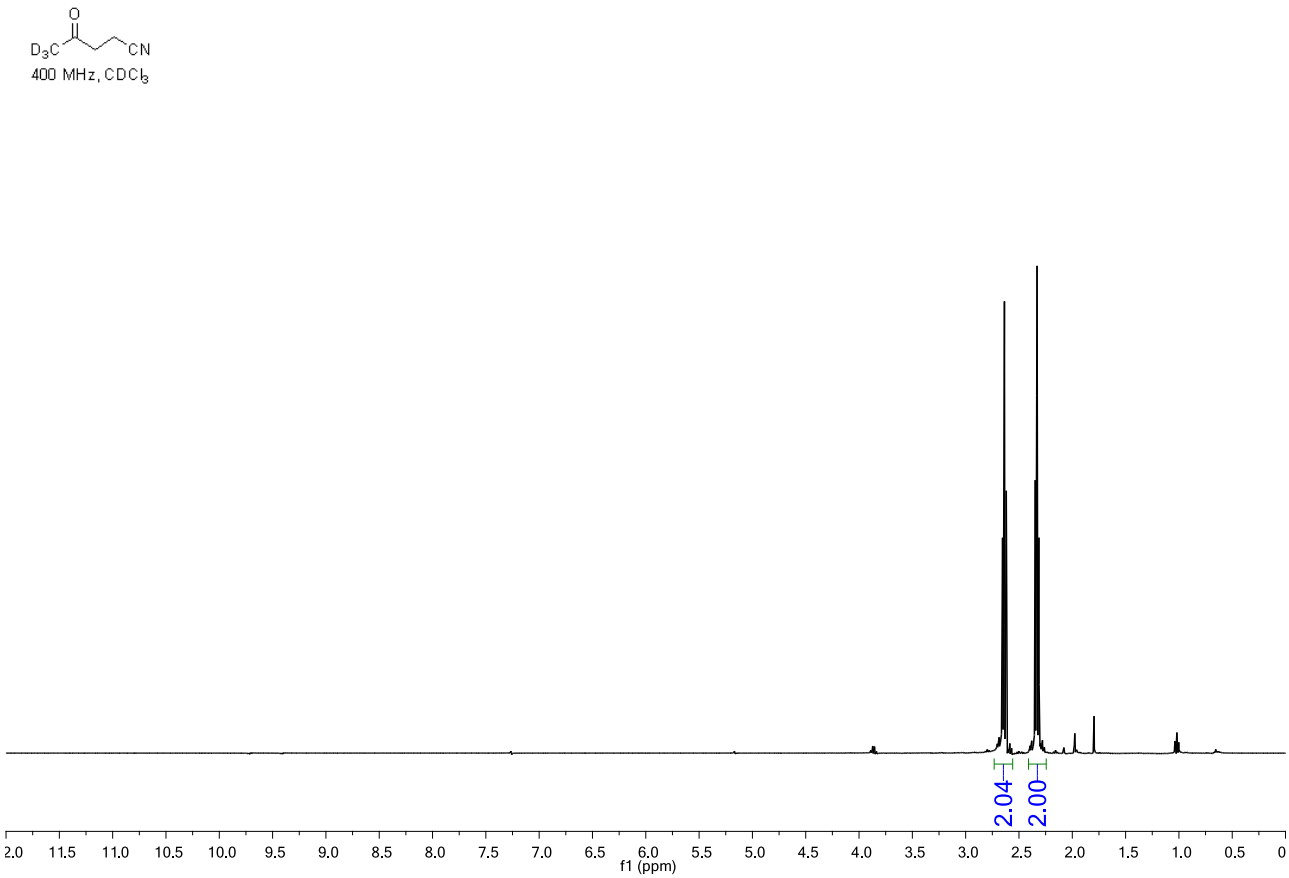
400 MHz, $CDCl_3$

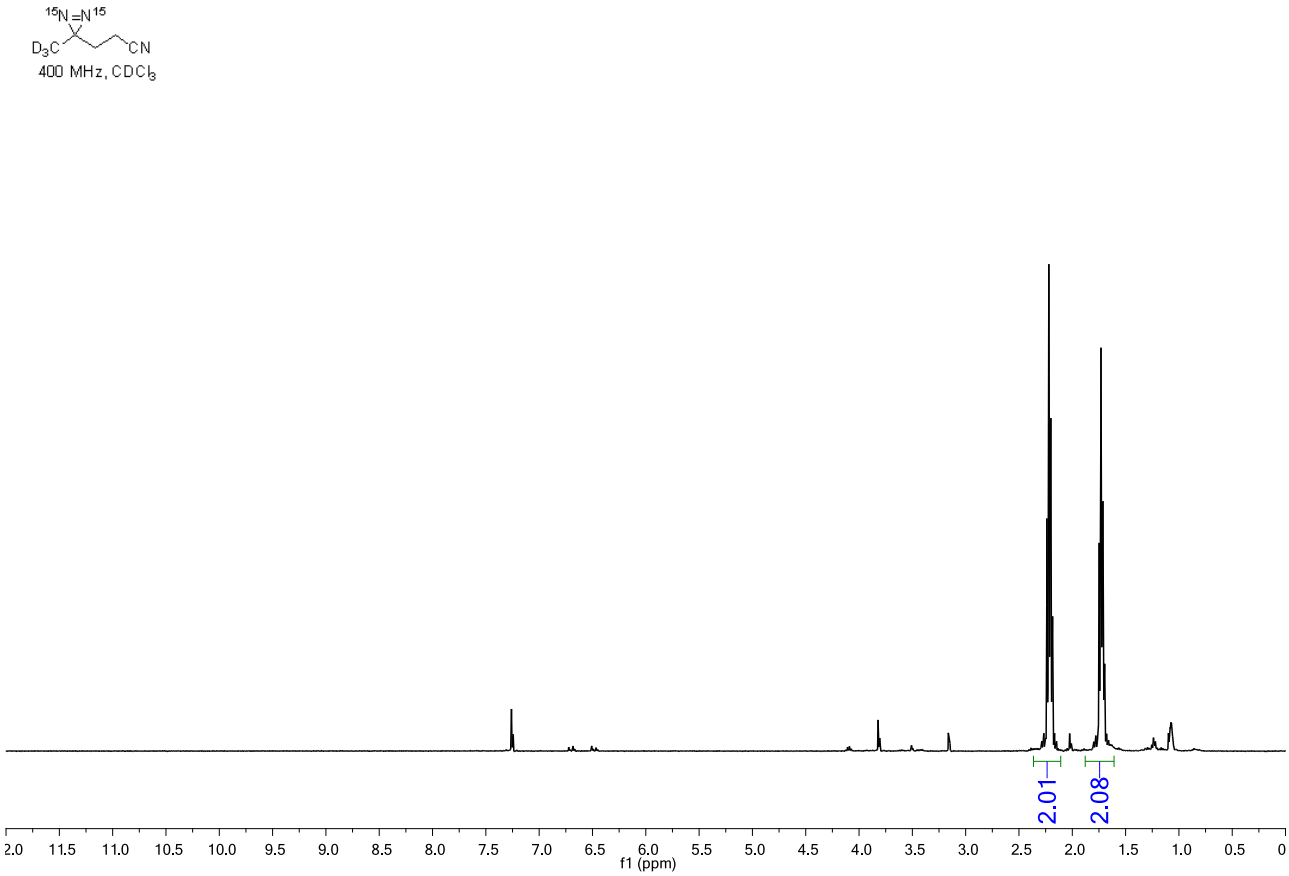


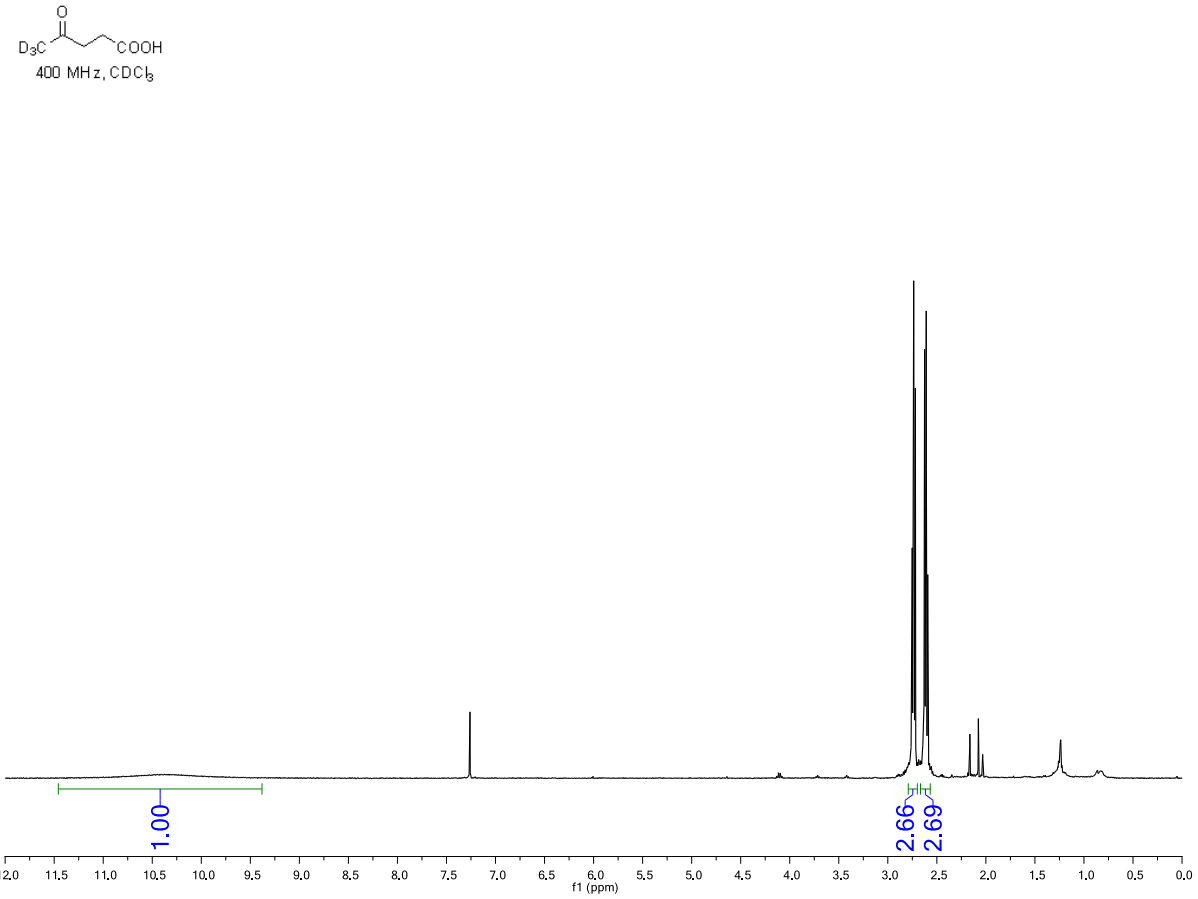


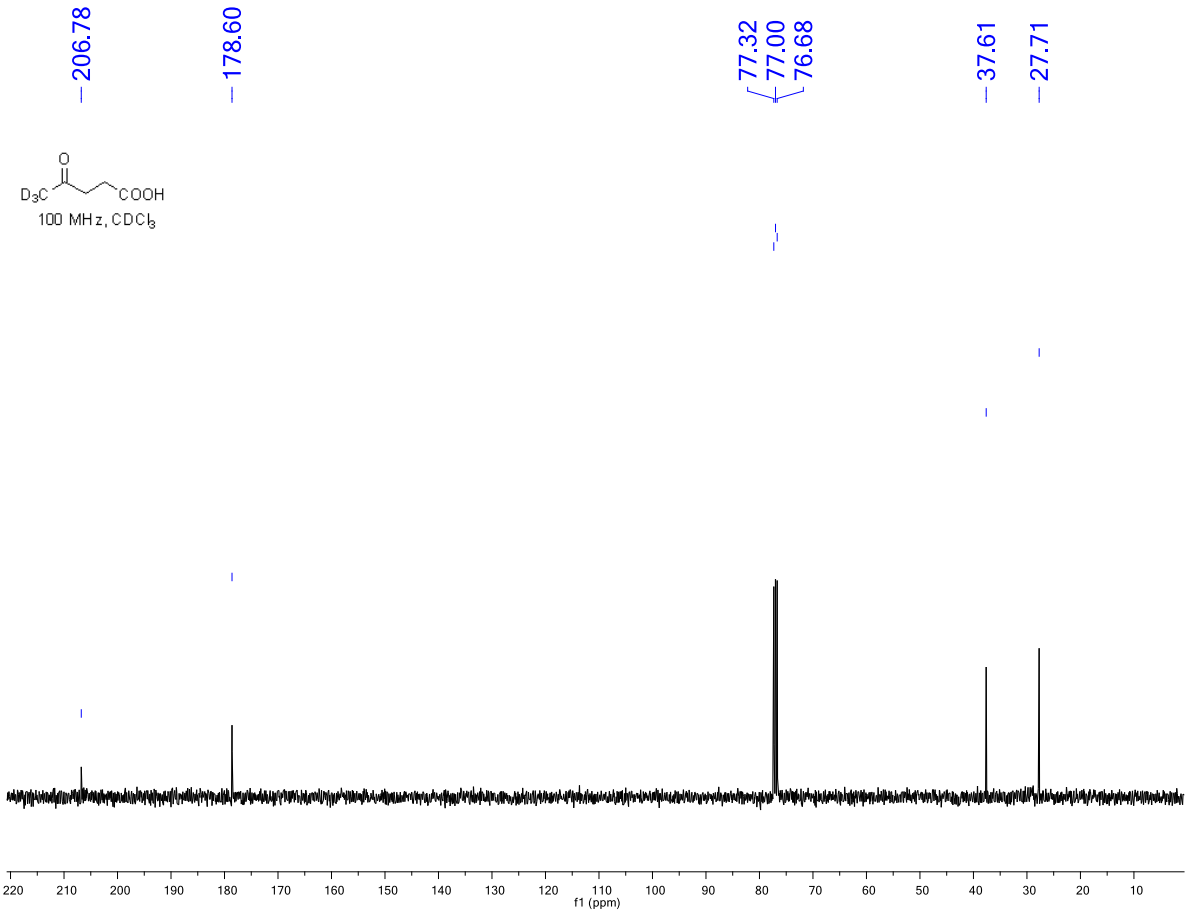
400 MHz, $CDCl_3$

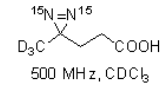



O
D3C
CN
400 MHz, CDCl3
2.04
2.00
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

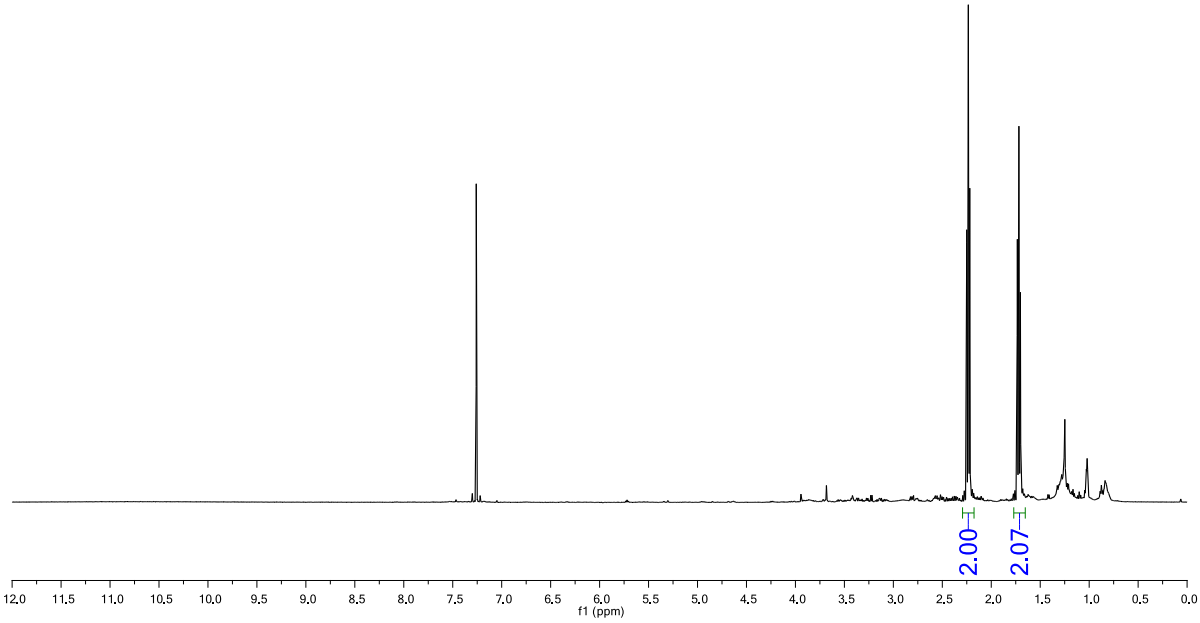

15N=N15
D3C
CN
400 MHz, CDCl3
2.01
2.08
2.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)

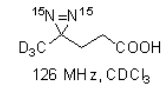

O
D3C
COOH
400 MHz, CDCl3
1.00
2.66
2.69
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


206.78
178.60
77.32
77.00
76.68
37.61
27.71
O
D3C
COOH
100 MHz, CDCl3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

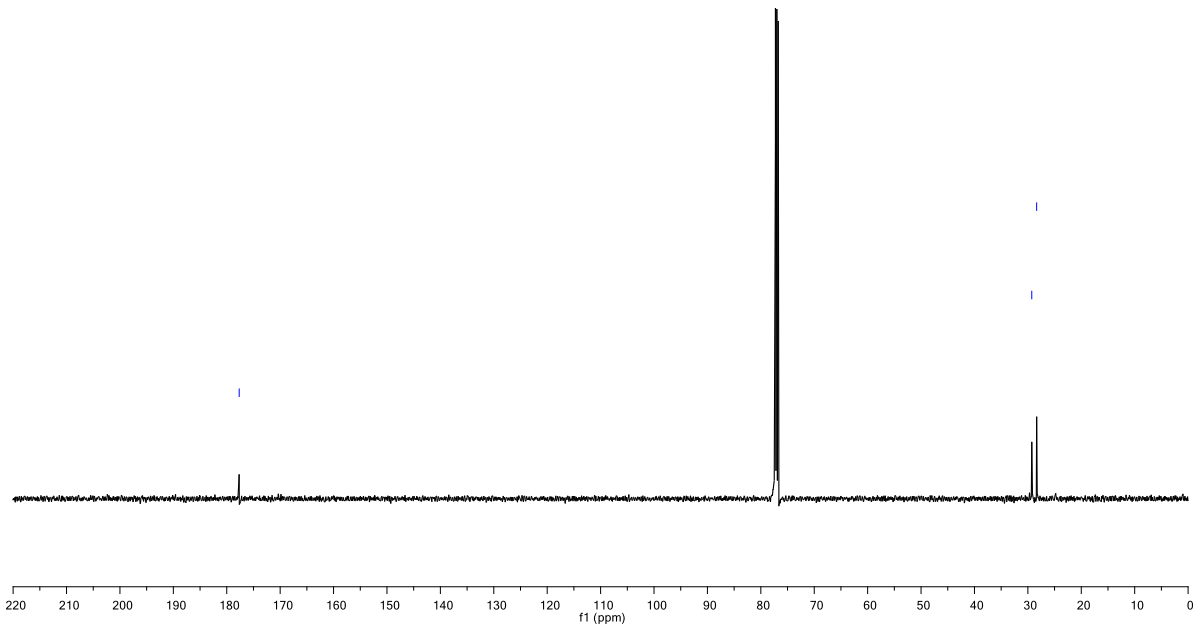


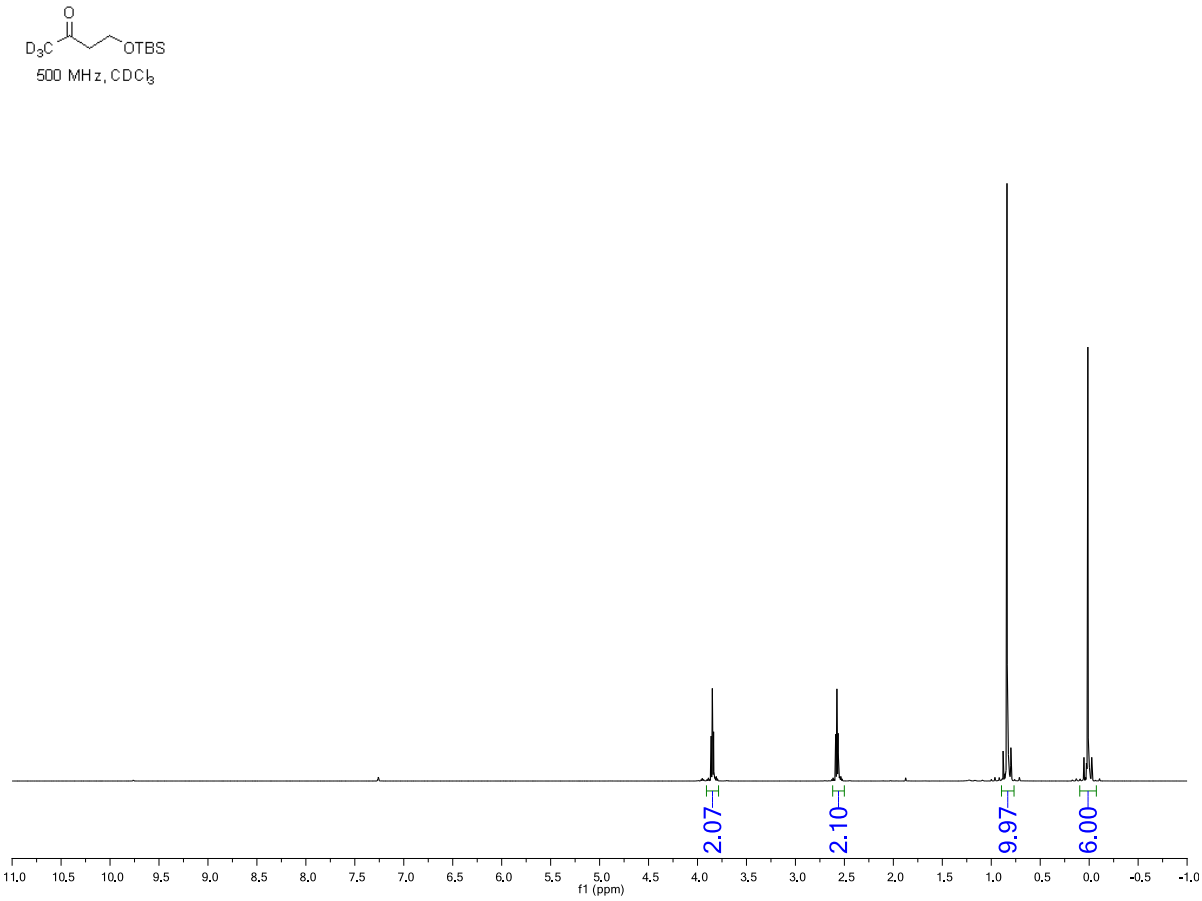
500 MHz, $CDCl_3$

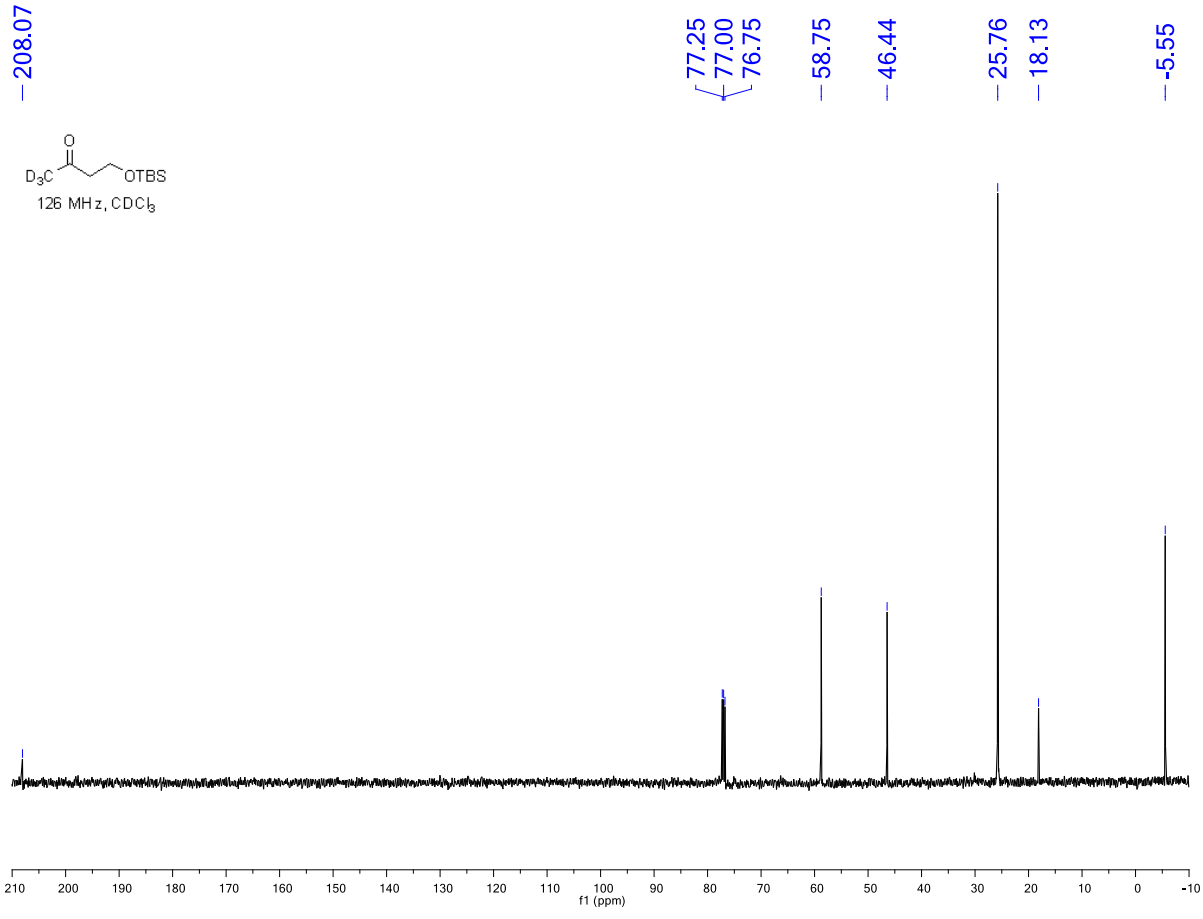


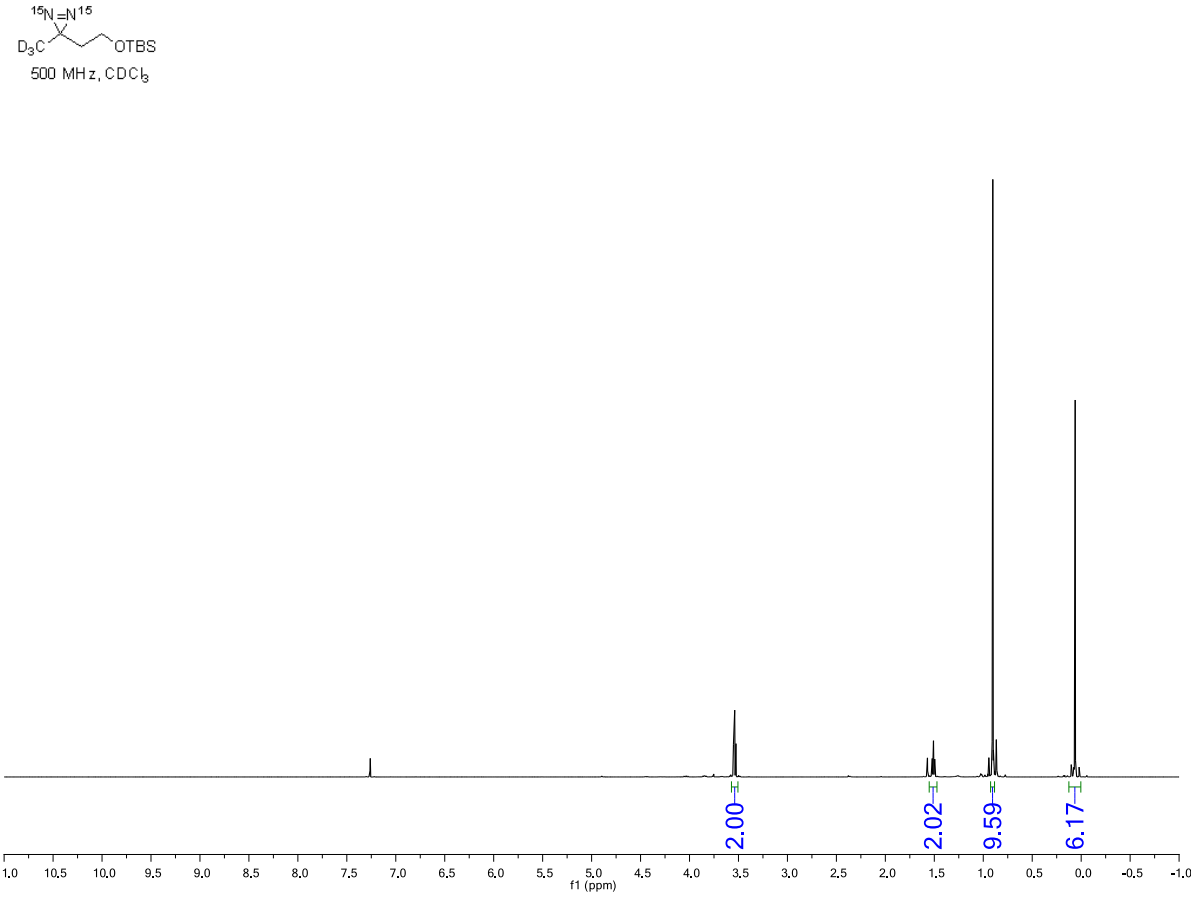


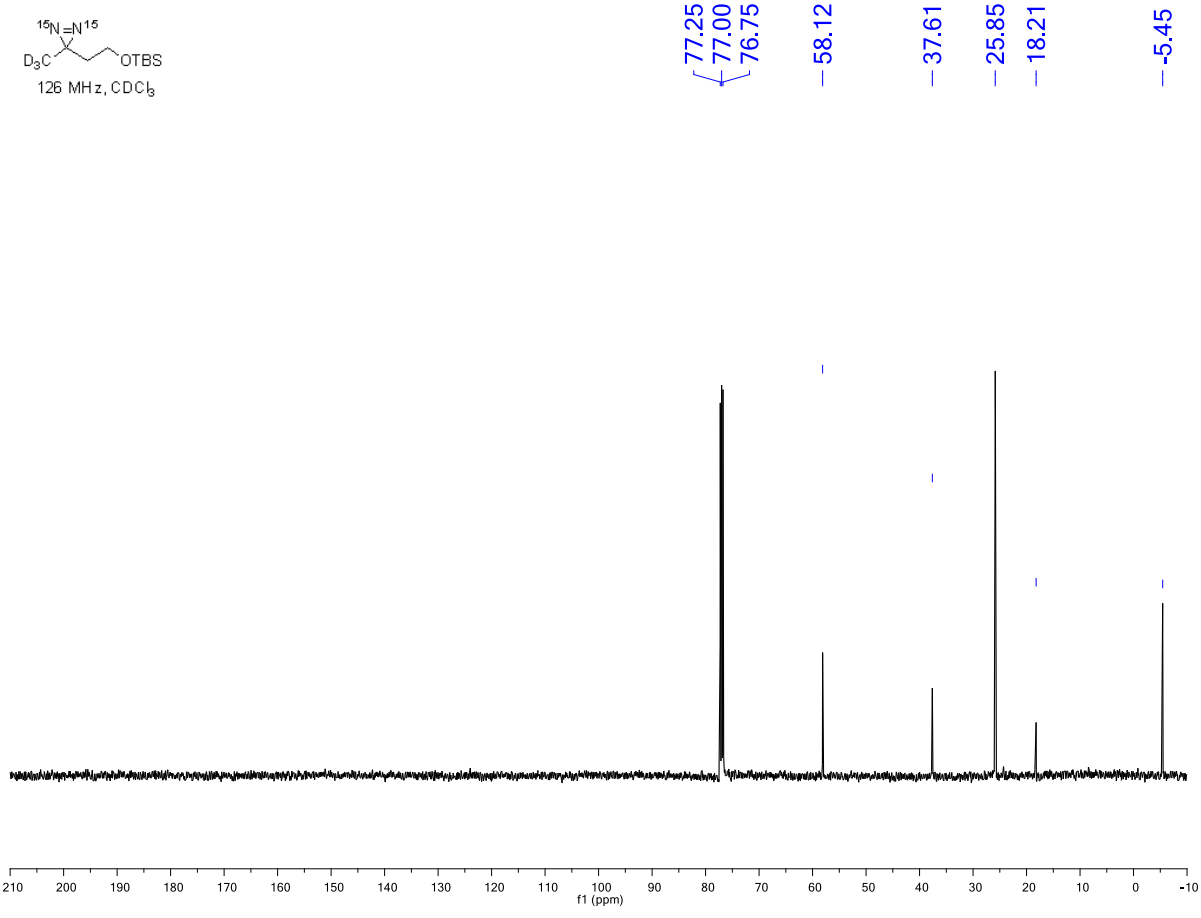
126 MHz, $CDCl_3$

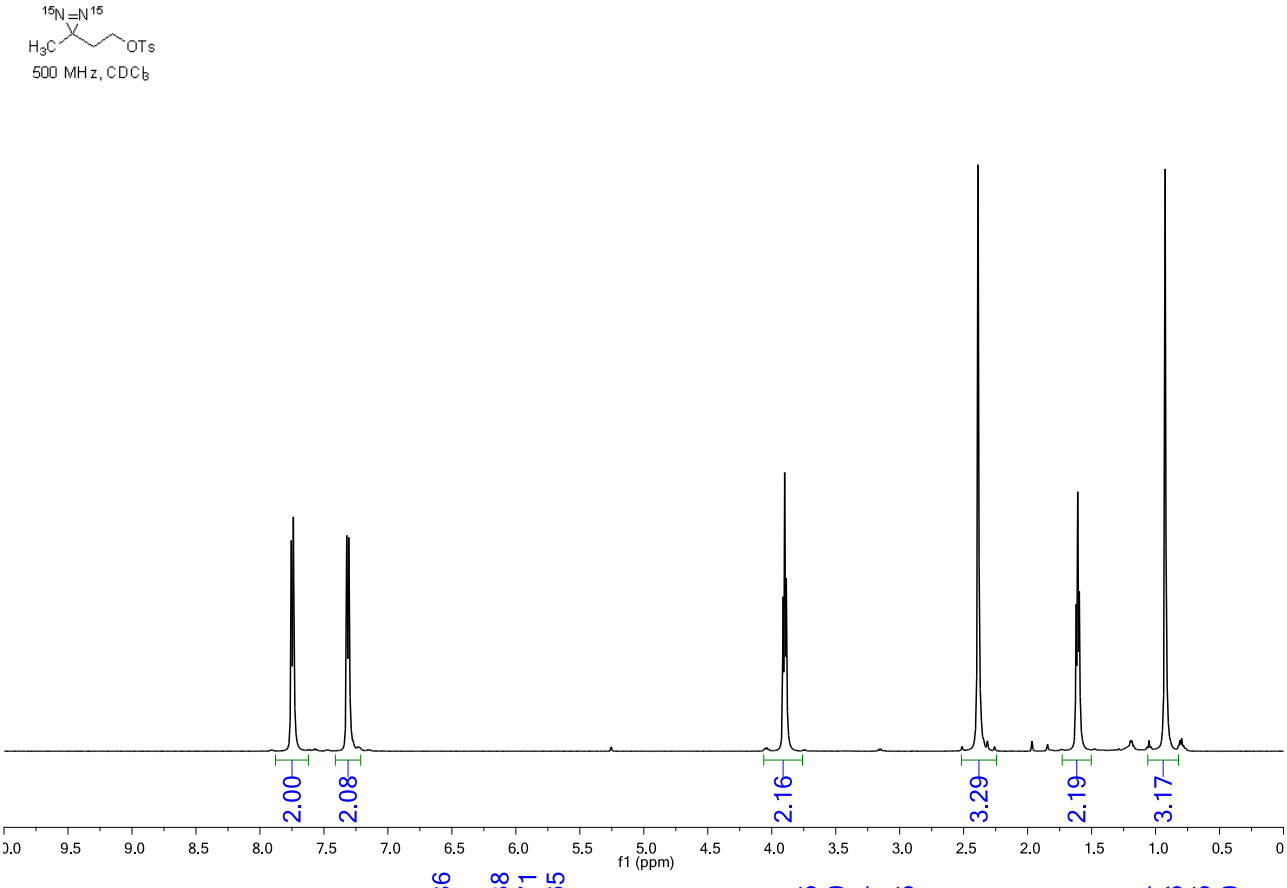


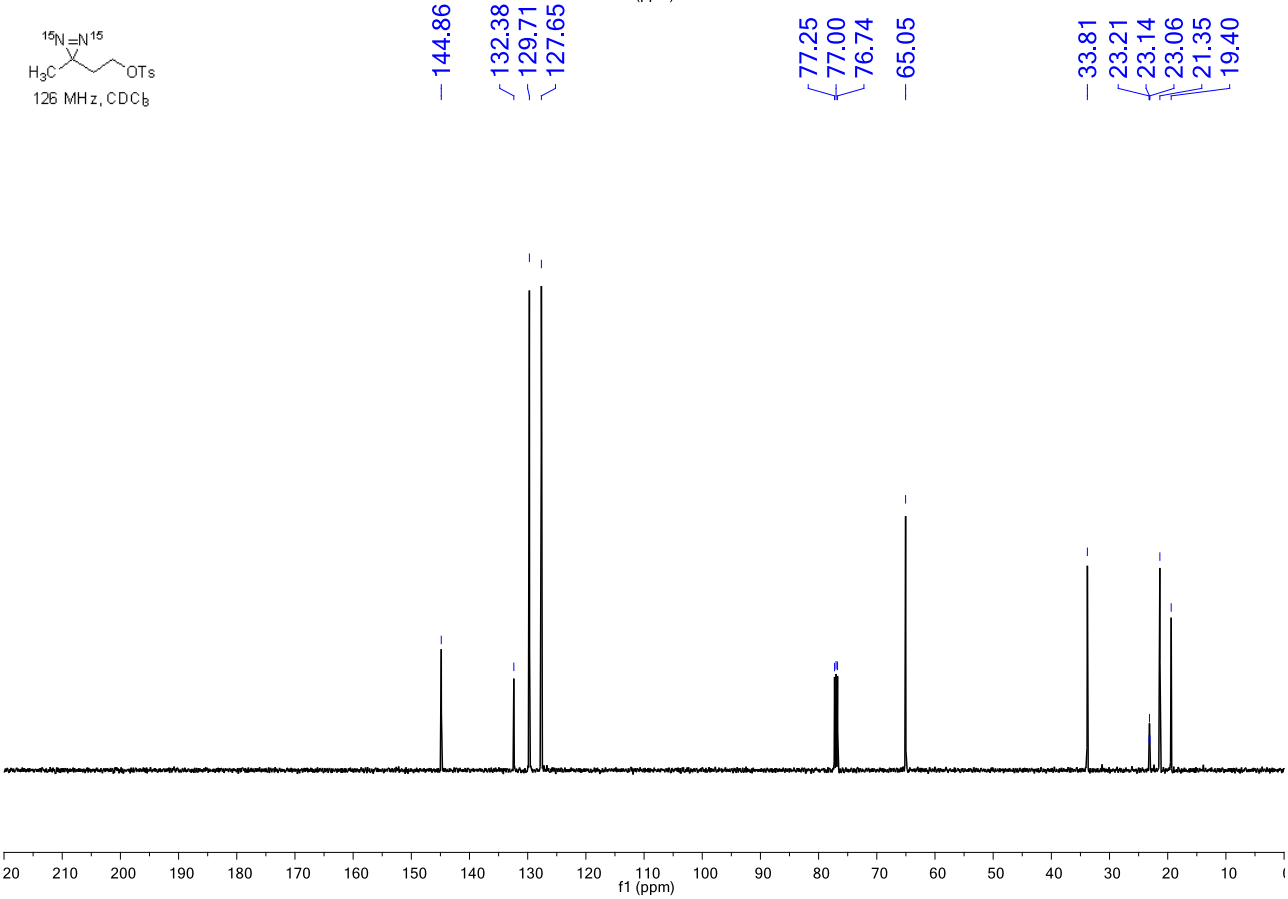

D3C
OTBS
500 MHz, CDCl3
2.07
2.10
9.97
6.00
f1 (ppm)

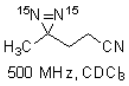

208.07
77.25
77.00
76.75
58.75
46.44
25.76
18.13
-5.55
D3C
OTBS
126 MHz, CDCl3
f1 (ppm)


15N=N15
D3C
OTBS
500 MHz, CDCl3
2.00
2.02
9.59
6.17
f1 (ppm)

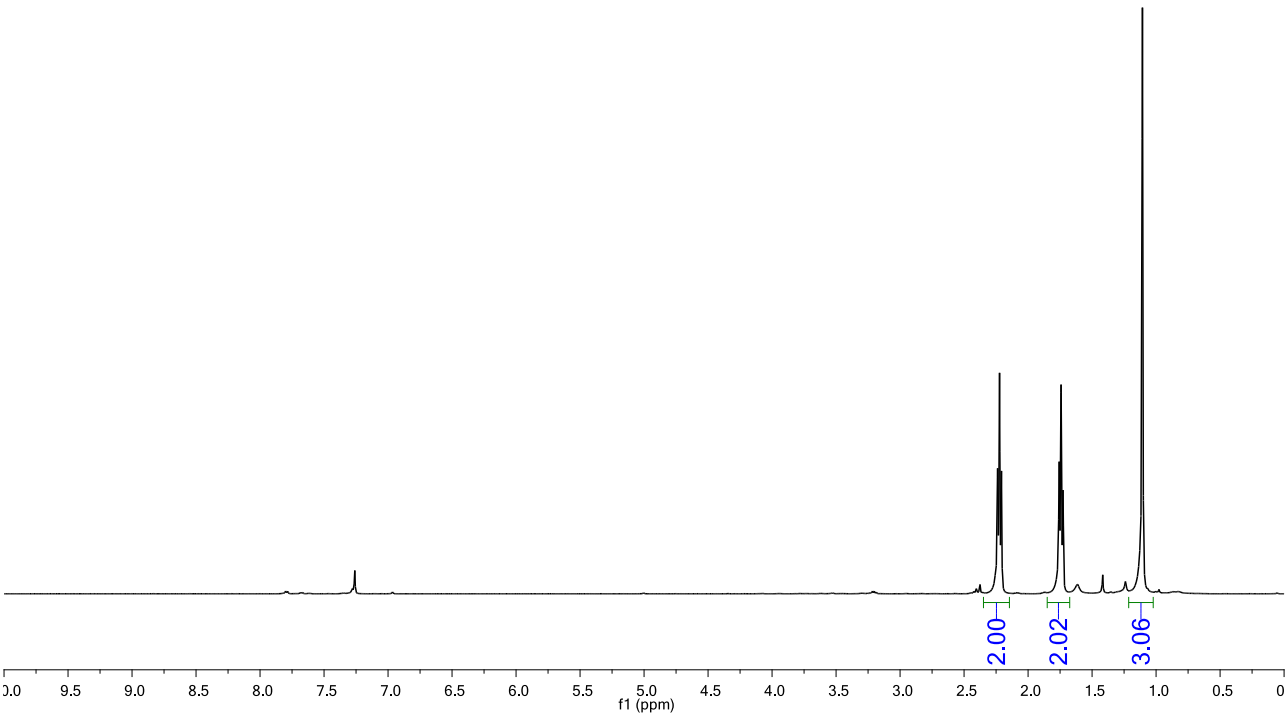

15N=N15
D3C
OTBS
126 MHz, CDCl3
77.25
77.00
76.75
58.12
37.61
25.85
18.21
-5.45
f1 (ppm)

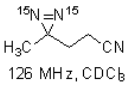

15N=N15
H3C
OTs
500 MHz, CDCl3
2.00
2.08
2.16
3.29
2.19
3.17
f1 (ppm)


15N=N15
H3C
OTs
126 MHz, CDCl3
144.86
132.38
129.71
127.65
77.25
77.00
76.74
65.05
33.81
23.21
23.14
23.06
21.35
19.40
f1 (ppm)



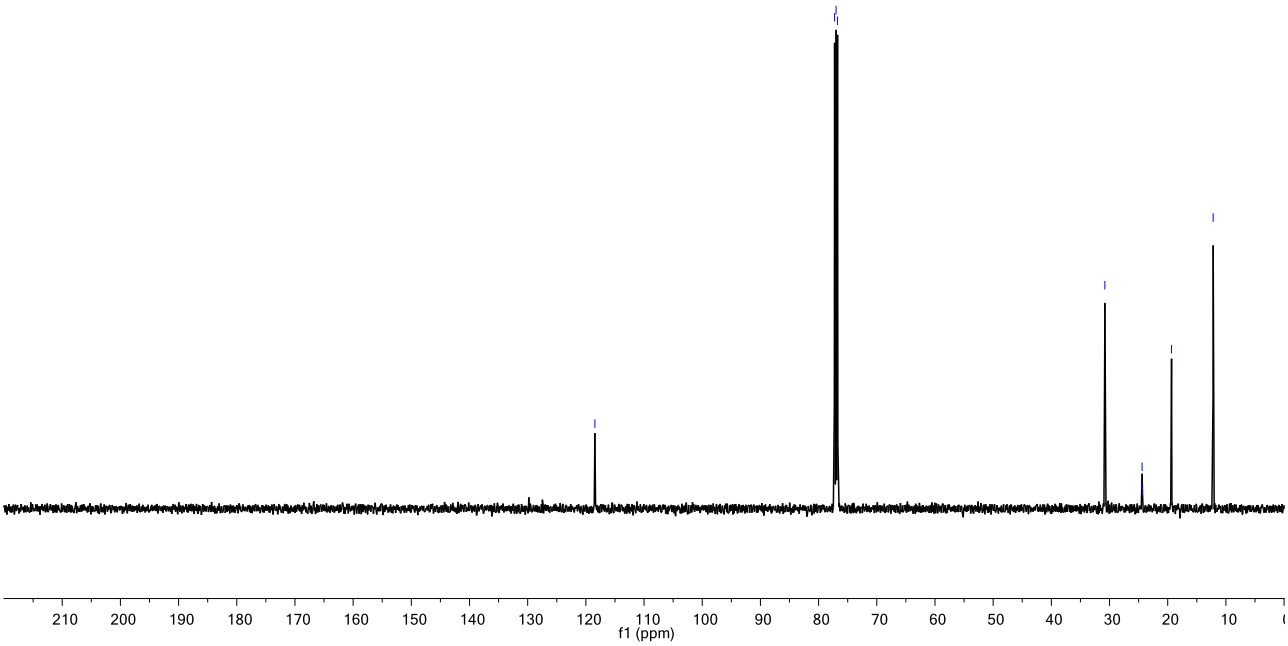
500 MHz, $CDCl_3$

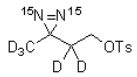




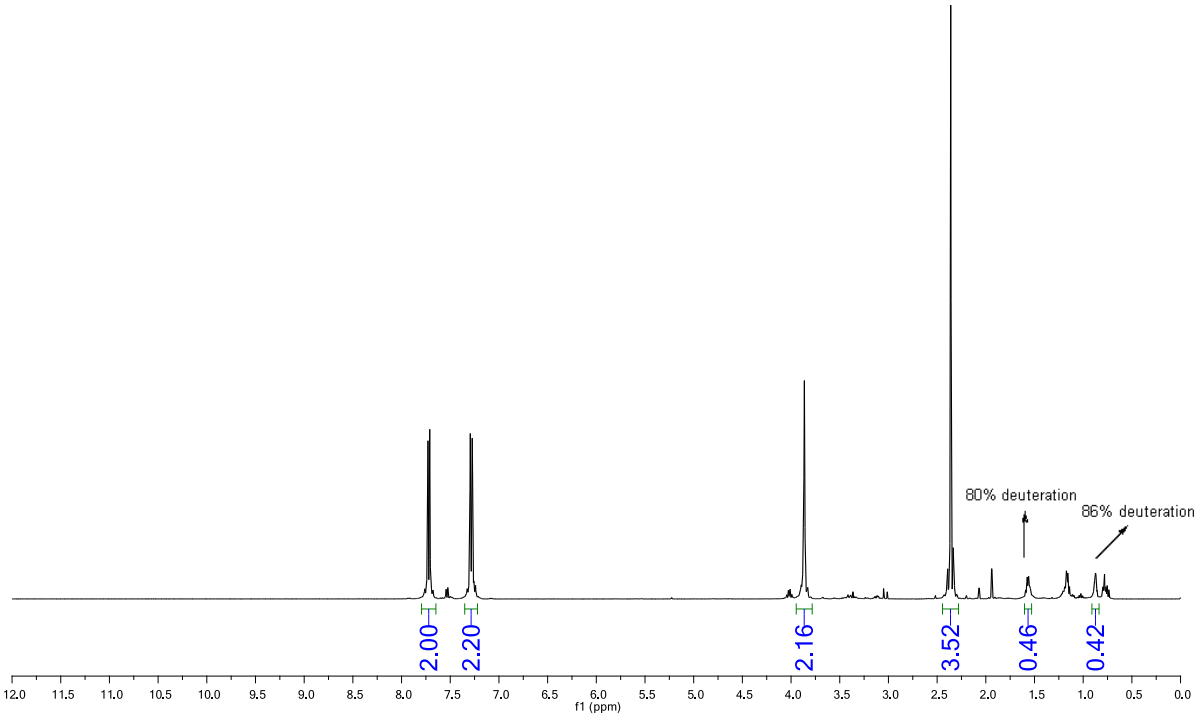
126 MHz, $CDCl_3$

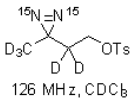
118.45
77.25
77.00
76.75
30.80
24.33
19.34
12.19





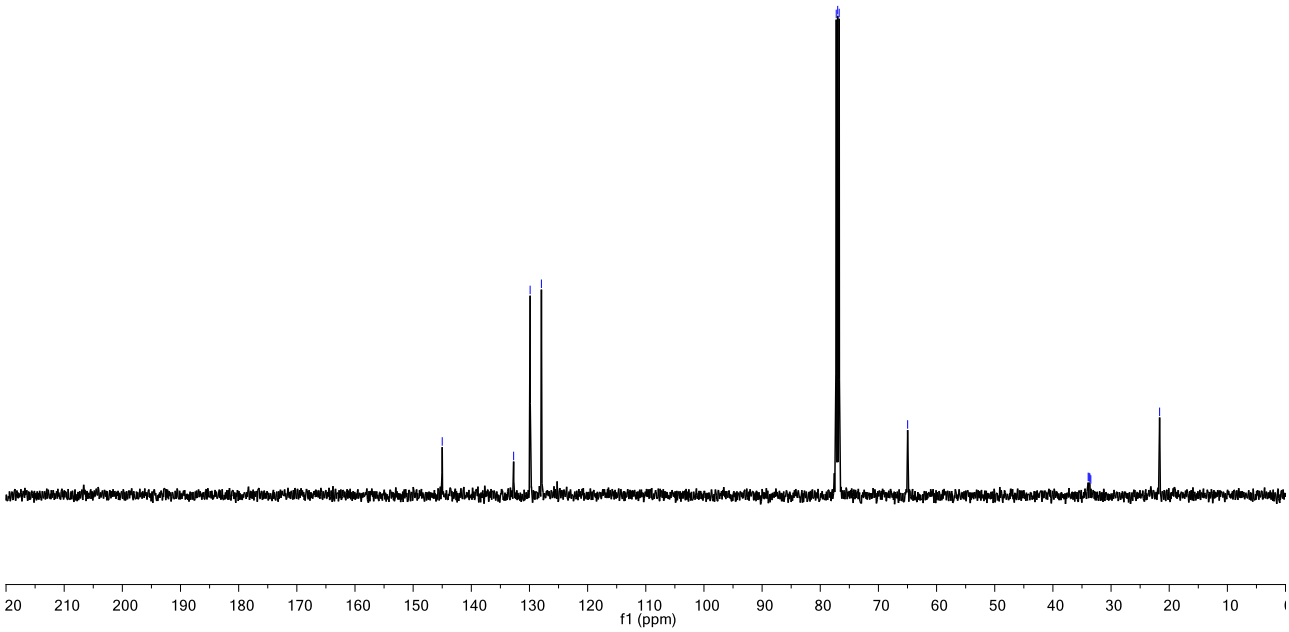
400 MHz, $CDCl_3$

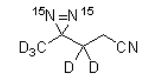




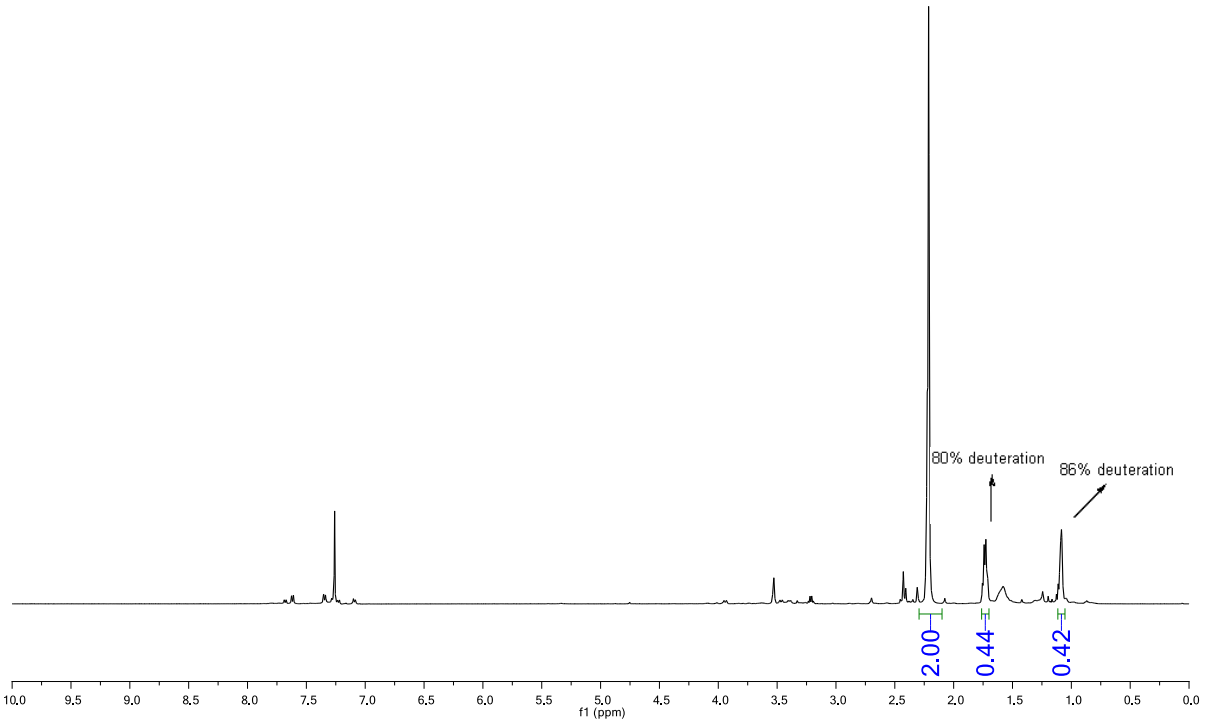
126 MHz, $CDCl_3$

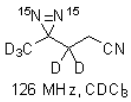
145.00
132.72
129.89
127.95
77.25
77.00
76.75
64.97
33.93
33.78
33.64
33.48
21.65



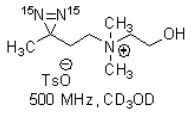


500 MHz, $CDCl_3$

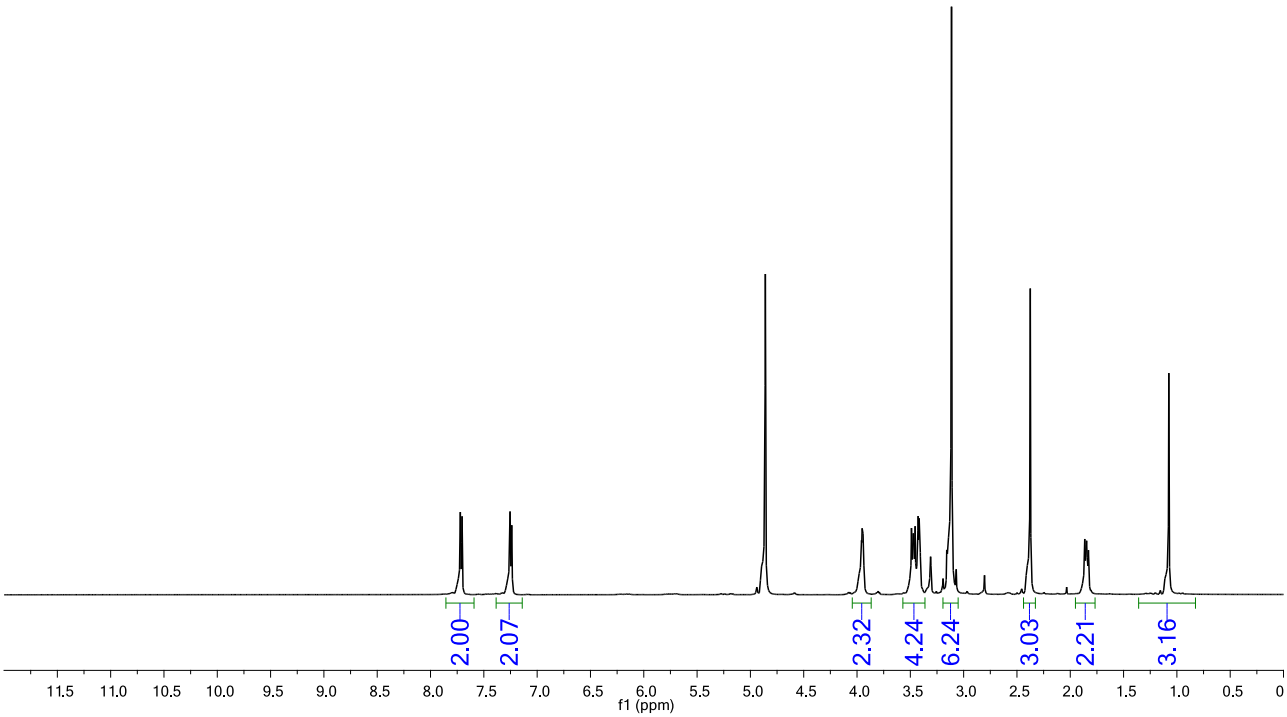


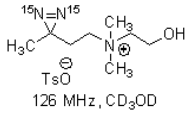


126 MHz, $CDCl_3$



500 MHz, CD_3OD





126 MHz, CD_3OD

143.63
141.72
129.87
126.91
66.43
56.82
49.51
49.17
48.83
48.49
29.27
24.46
24.39
24.32
21.31
19.35