Supporting Information for

Investigating the Mechanism for the Metal-free Dehydrogenative Coupling of Acetone with 1,2,3,4-Tetrahydroisoquinoline

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General Experimental Information

Reactions were monitored by ^{1}H NMR. Components were visualised by UV and KMnO4 staining of thin layer chromatography (TLC) plates. NMR data was collected on a Varian MercuryPlus (^{1}H at 400 MHz; ^{13}C at 101 MHz) equipped with a 400 Autosw probe, a Varian 400MR (^{1}H at 400 MHz; ^{13}C at 101 MHz) equipped with a OneNMR probe and a Bruker NEO (^{1}H at 600 MHz; ^{13}C at 151 MHz) equipped with a SmartProbe BBFO. Chemical shifts are reported in parts per million (ppm) relative to residual solvent peak ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.16 ppm; Acetone-*d*6, ^{1}H: 2.05 ppm; ^{13}C: 206.26 ppm). Coupling constants are reported in Hertz (Hz). Multiplicity is reported with the usual abbreviations (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quadruplet, m: multiplet). Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI ionization.

Chemicals

Unless otherwise indicated, reagents and substrates were purchased from commercial sources and used as received. Solvents not required to be dry were purchased as technical grade and used as received. Dry solvents were freshly collected from a dry solvent purification system prior to use. Inert atmosphere experiments were performed with standard Schlenk techniques using dried (P_2O_5) nitrogen gas. All reported compounds were characterized by ^{1}H NMR and compared with literature data.

The following chemicals were purchased from Merck KGaA:

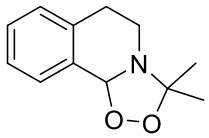
- 1,2,3,4-Tetrahydroisoquinoline
- 1,2,4-Triazole

The following chemicals were purchased from BLD Pharmatech Ltd.:

- 3,4-Dihydroisoquinolin-1(2H)-one
- Methyl 2-(bromomethyl)acrylate

Intermediate Isolation

Procedure for the synthesis and purification of 3,3-dimethyl-6,10b-dihydro-3H,5H-[1,2,4]dioxazolo[3,4-a]isoquinoline (5)



In a threaded Schlenk tube equipped with Teflon-covered stirring bar, THIQ (0.5 mmol, 1 equiv.), acetone (5 mL), 1,2,4-triazole (34.5 mg, 0.5 mmol, 1 equiv.) and oven-dried (120°C) molecular sieves (1 g, added at rt) were stirred under oxygen overpressure (300 mbar), at room temperature, for one day. The mixture was reduced to a new volume (evaporation under airflow) and filtered over a small plug of AlO_x (prepared using Et_2O). The filtrated solvent (acetone) was collected in a vial. Another vial was collected after column washing with 15-20 mL of Et_2O. The solvents of both vials were evaporated under airflow and 5 minutes on rotatory evaporator at room temperature (400 mbar pressure).

Product characterization

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.13 (m, 4H, CH_{AR}), 5.88 (s, 1H, NC$\underline{H}$OO), 3.03-2.74 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$N), 1.56 (d, J = 7.7 Hz, 6H, CC$\underline{H}_3$).

^{1}H NMR (Acetone-*d*6, 400 MHz): δ 7.46-7.01 (m, 4H, CH_{AR}), 5.86 (s, 1H, NC$\underline{H}$OO), 3.00-2.68 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$N), 1.52 (s, 6H, CC$\underline{H}_3$).

^{13}C NMR (Acetone-*d*6, 400 MHz): δ 137.04, 130.37, 129.96, 129.50, 128.97, 127.19, 100.94, 90.62, 41.57, 30.35, 28.21, 21.97.

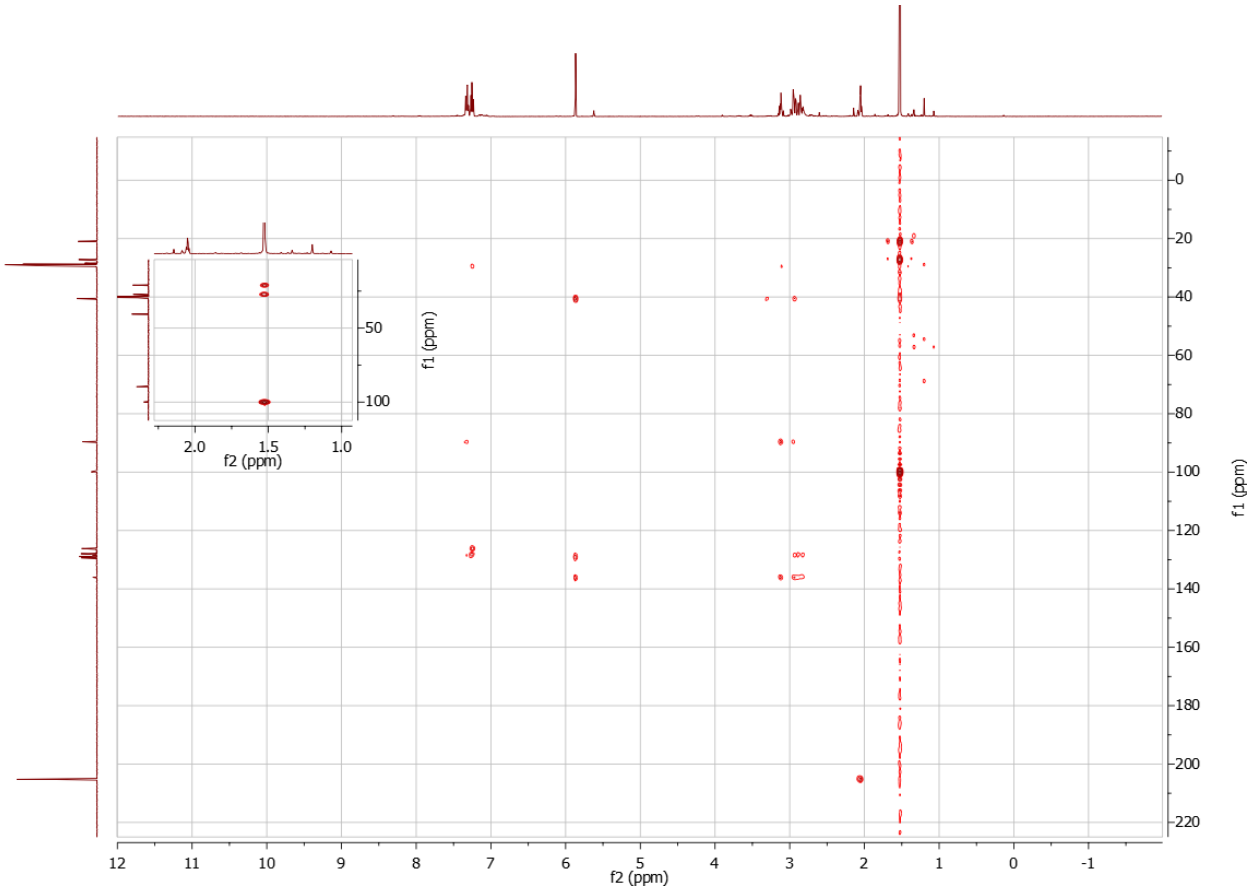


Figure S1. ^{1}H-^{13}C-gHMBC spectrum of the intermediate.

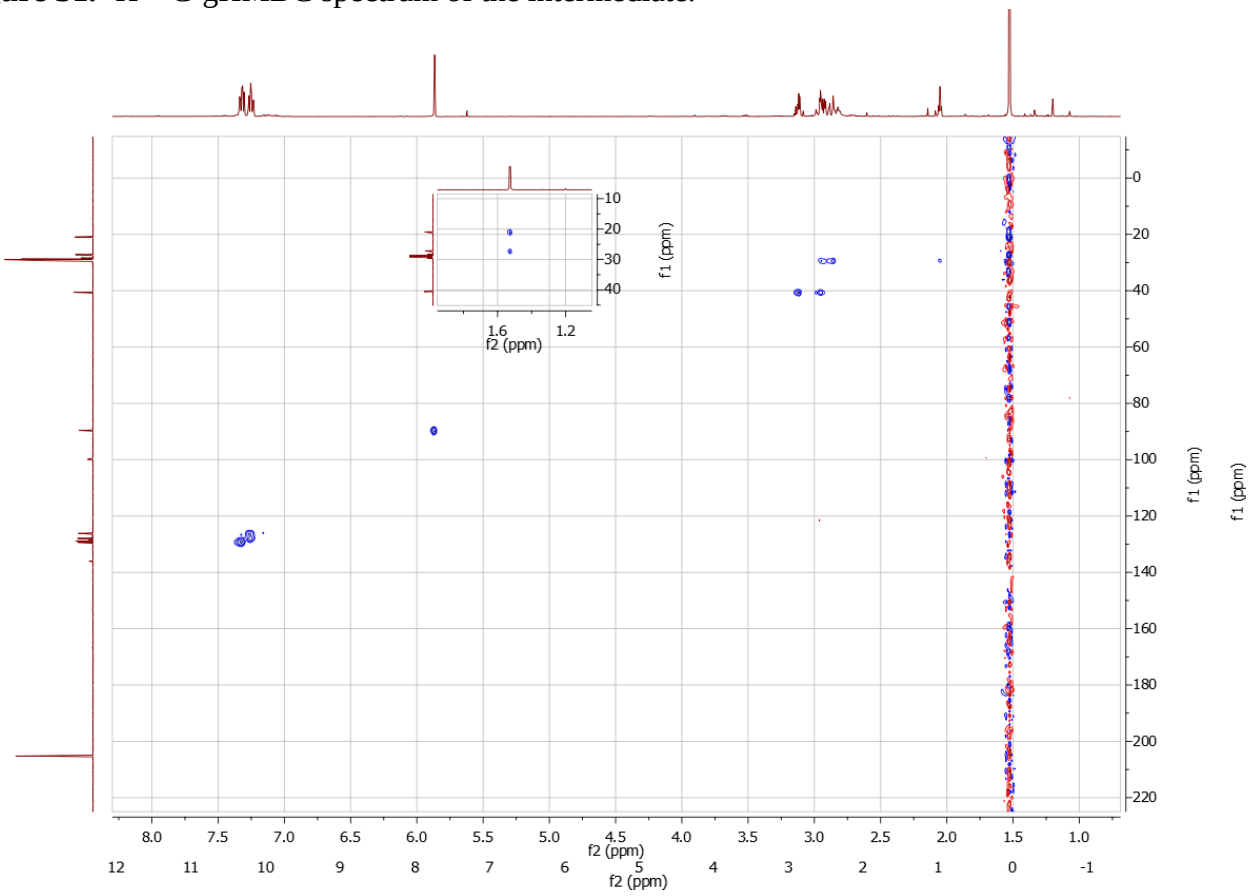
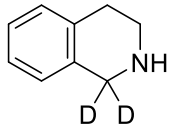


Figure S2. ^{1}H-^{13}C-HSQC spectrum of the intermediate.

Kinetic Isotope Effect

Procedure for the synthesis of

THIQ-*d*2 (9)[1,2]



A solution of 3,4-Dihydroisoquinolin-1(2H)-one (729 mg, 4.95 mmol, 1 equiv.) in anhydrous THF (5 mL, 1 M) was prepared and added to a three-neck reaction flask, containing $LiAlD_4$ (228.8 mg, 5.449 mmol, 1.1 equiv.), suspended in dry THF (1.5 mL) at 0 °C, under N_2. The mixture was stirred with a Teflon-covered stirring bar and heated to reflux. After 20 h, the mixture was let cool down to 0 °C. Water (20 mL) was then slowly added, together with NaOH (10-15 mL, 1M). The product was extracted with Et_2O (3×30 mL) and the combined organic layers were dried with Na_2SO_4. The solvent was removed on rotatory evaporator (45°C).

Product characterization

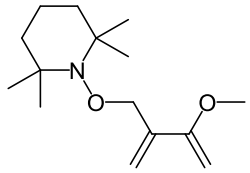
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16-7.07 (m, 3H, C*H*$_{AR}$), 3.14 (t, J = 6.0 Hz, 2H, $CH_2C\underline{H}_2$), 2.8 (t, J = 6.0 Hz, 2H, C$\underline{H}_2$N), 1.69 (s, 1H, $CH_2N\underline{H}$).

^{13}C NMR ($CDCl_3$, 600 MHz): δ 136.07, 135.01, 129.46, 126.35, 126.16, 125.85, 48.84-46.02 (dt, J = 41.3, 20.6 Hz), 44.03, 29.36.

Radical Trapping

Procedure for the synthesis of

Methyl 2-(TEMPOmethyl)acrylate (10)[3]



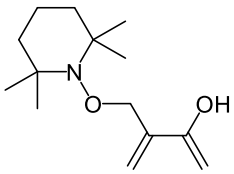
Methyl 2-(bromomethyl)acrylate (1.432 g, 8.0 mmol, 1.0 equiv.), (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 1.510 g, 9.6 mmol, 1.2 equiv.), NaI (2.398 g, 16.0 mmol, 2.0 equiv.) and Na_2SO_3 (3.025 g, 24.0 mmol, 3.0 equiv.) were dissolved in MeCN (80 mL). The mixture was stirred with a Teflon-covered stirring bar at 65 °C for 2 days under N_2. The solvent was removed in vacuo. H_2O (100 mL) was added and product extracted with EtOAc (3×100 mL). The organic phase was dried with $MgSO_4$ and filtered. The solvent was removed in vacuo, yielding crude orange oil. This was purified using flash silica column chromatography (visualised using $KMnO_4$ stain) yielding methyl 2- ([(2,2,6,6-tetramethylpiperidin-1-yl)oxyl]methyl)acrylate as yellow oil (methyl 2-(TEMPOmethyl)acrylate, 1.73 g, 85%).

Rf: 0.3 (2%Et_2O/DCM).

Product characterization

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.28 (q, J = 1.6 Hz, 1H, CCH*H*), 5.91 (q, J = 2 Hz, 1H, CCH*H*), 4.50 (t, J = 1.8, 2H, C*H*$_2$O), 3.75 (s, 3H, OC*H*$_3$), 1.63-1.49 (m, 1H, CH_2CH*H*CH_2), 1.49-1.36 (m, 4H, CC*H*$_2CH_2$) 1.35-1.25 (m, 1H, CH_2CH*H*CH_2), 1.16 (s, 6H, CC*H*$_3$), 1.12 (s, 6H, CC*H*$_3$).

Procedure for the synthesis of
2(TEMPOmethyl)acrylic acid (11)[3]



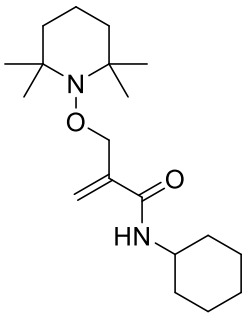
Methyl 2-(TEMPOmethyl)acrylate (1.730 g, 6.775 mmol, 1.0 equiv.) was dissolved in 1,4-dioxane (40 mL). Aqueous NaOH (1.0 M, 40 mL, 40 mmol, 5.9 equiv.) was added and the solution was stirred with a Teflon-covered stirring bar for 3.5 days. The mixture was then acidified (pH 5) with aqueous HCl (2.0 M, 20 mL, 40 mmol, 6.5 equiv.) and the product was extracted with EtOAc (3×40 mL). The organic phase was dried with $MgSO_4$ and filtered. The solvent was removed in vacuo, yielding crude golden oil, which was purified by raising the temperature to 65°C on rotatory evaporator (0 mbar), yielding pure 2- ([(2,2,6,6-tetramethylpiperidin-1-yl)oxyl]methyl)acrylic acid (2-(TEMPOmethyl)acrylic acid, 1.521g, 93%).

Product characterization

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.40 (s, 1H, CCH*H*), 5.96 (s, 1H, CCH*H*), 4.52 (s, 2H, C*H*$_2$O), 1.65-1.53 (m, 1H, CH_2CH*H*CH_2), 1.53-1.36 (m, 4H, CC*H*$_2CH_2$) 1.36-1.22 (m, 1H, CH_2CH*H*CH_2), 1.19 (s, 6H, CC*H*$_3$), 1.14 (s, 6H, CC*H*$_3$).

Procedure for the synthesis of

N-Cyclohexyl-2-(TEMPOmethyl)acrylamide (CHANT)[3]

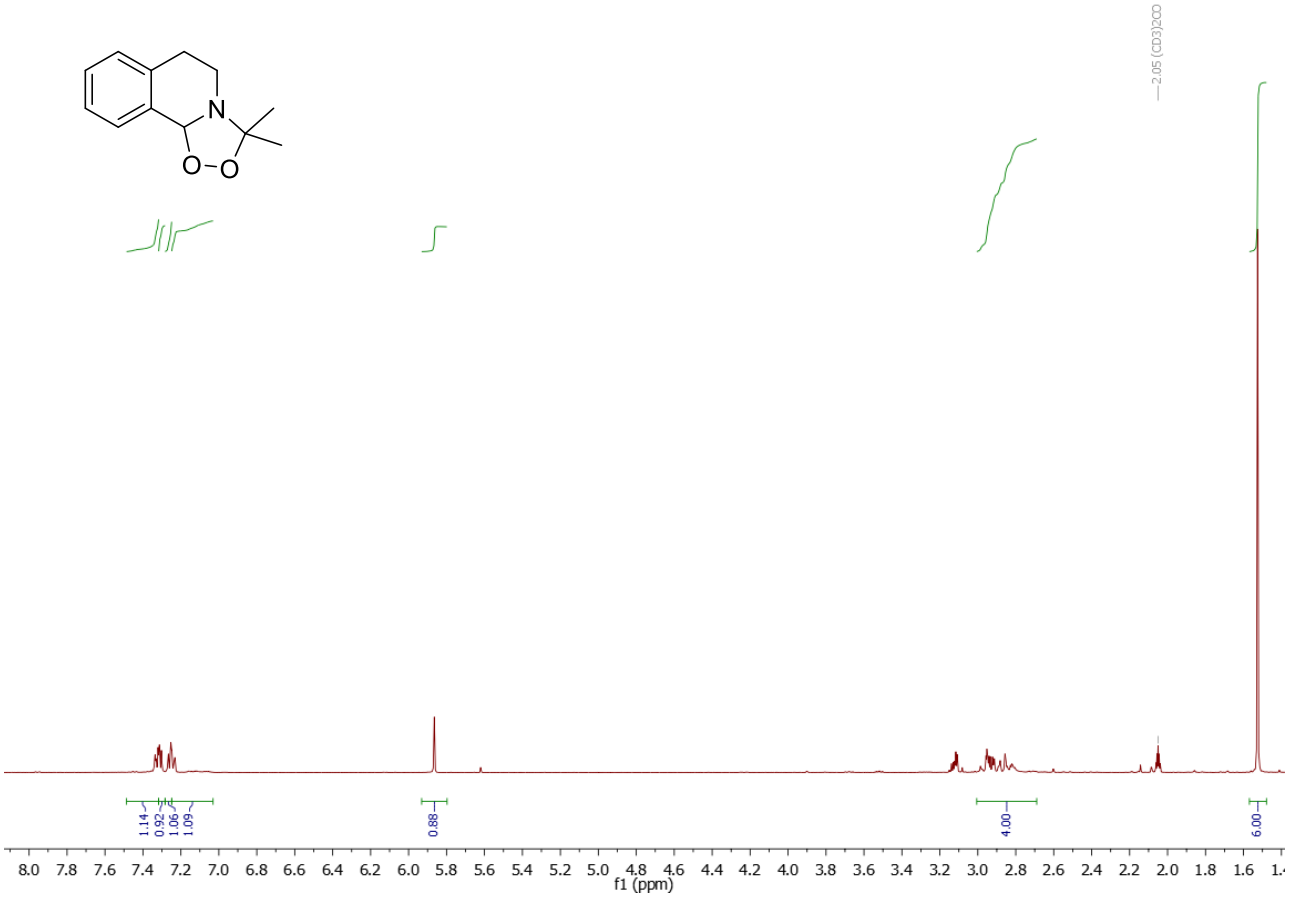


2-(TEMPOmethyl)acrylic acid (200.8 mg, 0,832 mmol, 1.0 equiv.), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU, 347.1 mg, 0.915 mmol, 1.1 equiv.), N,N-diisopropylethylamine (DIPEA, 290 µL, 1.66 mmol, 2.0 equiv.) and cyclohexylamine (95 µL, 0.832 mmol, 1.0 equiv.) were dissolved in N,N-dimethylformamide (DMF, 4.2 mL, 0.2 M) and stirred for 18 h. The solvent was then removed in vacuo. Saturated aqueous $NaHCO_3$ (8 mL) was added and product was extracted with EtOAc (3×8 mL). The combined organic layers dried with $MgSO_4$ and filtered. The solvent was removed in vacuo yielding crude product. This was purified using flash silica column chromatography (12%EtOAc/Pentane; visualised using KMnO4 stain) yielding pure white N-cyclohexyl-2-{[(2,2,6,6-tetramethylpiperidin-1-yl)oxy]methyl}acrylamide (CHANT, 174 mg, 64.8% or 51.2% overall).

Product characterization

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.59 (br s, 1H, OCN*H*), 6.08 (d, 1H, CCH*H*), 5.48 (s, 1H, CCH*H*), 4.48 (s, 2H, C*H*$_2$O), 3.89-3.79 (m, 1H, C*H*N), 2.05-1.95 (m, 2H, NCHCH*H*), 1.78-1.71 (m, 2H, CHCH$_2$CH*H*), 1.52-1.47 (m, 4H, NCC*H*$_2$), 1.47-1.44 (m, 1H, CCH$_2$CH*H*), 1.42-1.36 (m, 2H, CHCH$_2$CH*H*), 1.36-1.31 (m, 1H, CCH$_2$CH*H*), 1.20 (s, 6H, NCC*H*$_3$), 1.18-1.16 (m, 1H, CH$_2$CH*H*), 1.16-1.13 (m, 2H, NCHCH*H*), 1.11 (s, 6H, NCC*H*$_3$).

NMR Spectra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1.06
1.09
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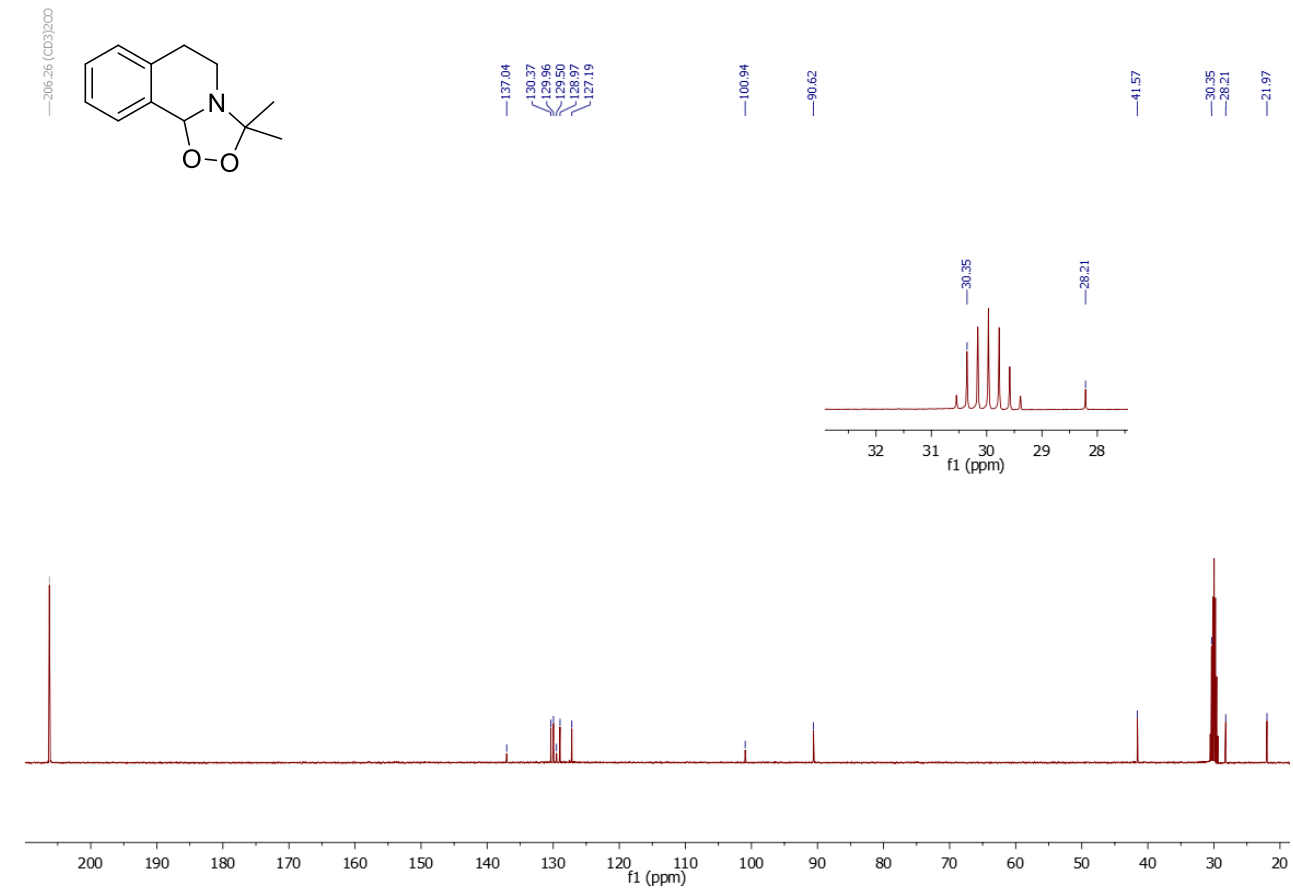
4.00
6.00
f1 (ppm)


206.26 (CD3)2CO
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130.37
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128.97
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100.94
90.62
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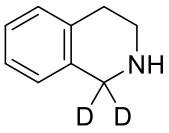
28.21
21.97
f1 (ppm)


NH
D D

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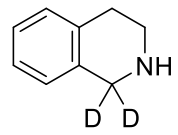
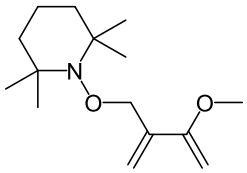
7.14
7.13
7.12
7.12
7.11
7.09
7.09
7.08
7.01
7.01
7.00
3.15
3.14
3.13
2.81
2.80
2.79
1.69
2.84
0.92
2.00
2.01
1.27
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
f1 (ppm)


NH
D D

136.07
135.01
129.46
126.35
126.16
125.85
77.16 CDCl3
48.03
47.89
47.76
47.62
47.48
44.03
29.36
48.03
47.89
47.76
47.62
47.48
49 48 47
f1 (ppm)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


N
O
O

7.26 CDCl3
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1.00
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2.94
6.85
12.88
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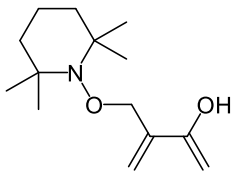
N
O
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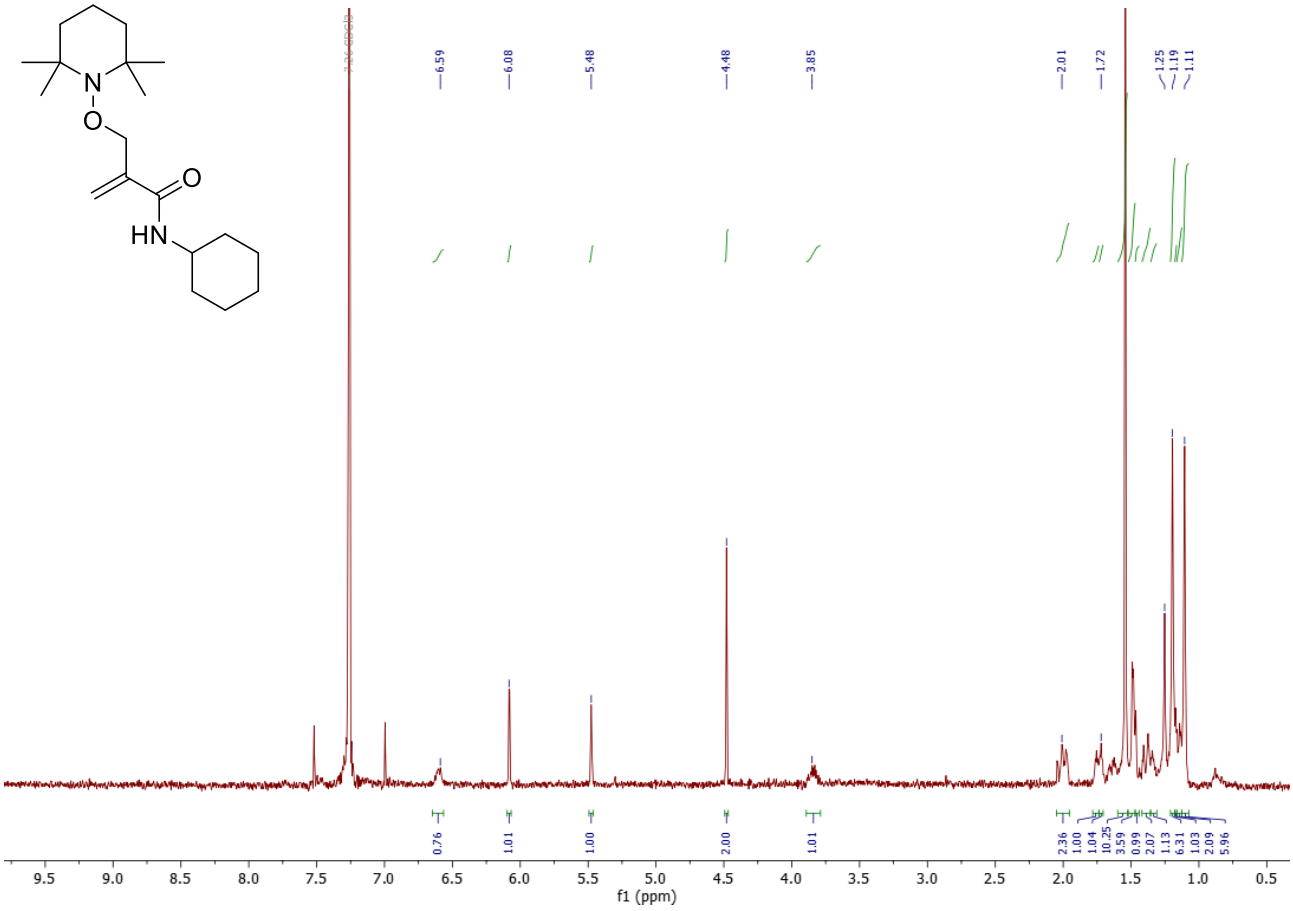
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O
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1.13
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1.03
2.09
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6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

References

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(3) *New Approach to the Detection of Short-Lived Radical Intermediates | Journal of the American Chemical Society*. https://pubs-acs-org.proxy-ub.rug.nl/doi/10.1021/jacs.2c03618 (accessed 2023-06-26).