Supporting Information

69451 Weinheim, Germany

Catalytic Reduction of Alkyl and Aryl Bromides using Isopropanol

Michael C. Haibach, Brian M. Stoltz, and Rober H. Grubbs*

Abstract: Milstein's complex (PNN)RuHCl(CO) catalyzes the efficient reduction of aryl and alkyl halides under relatively mild conditions, using isopropanol and a base. Sterically hindered tertiary and neopentyl substrates are reduced efficiently, as well as more functionalized aryl and alkyl bromides. The reduction process is proposed to occur via radical abstraction/hydrodehalogenation steps at ruthenium. Our research represents a safer and more sustainable alternative to typical silane, lithium aluminium hydride, and tin-based conditions for these reductions.

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1. Additional Optimization Information

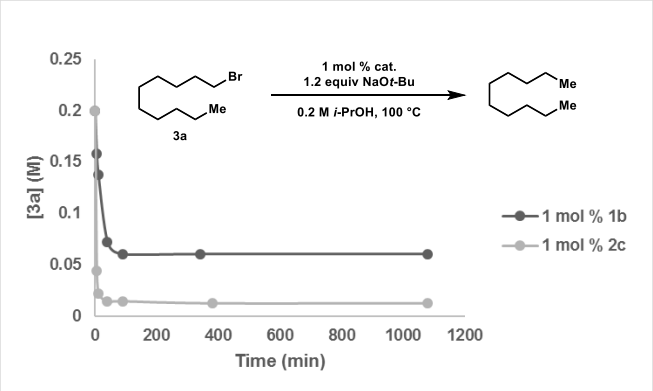


Figure S1. Comparison of the reaction kinetics for **1b** and **2c**

Given that **2c** resulted in ca. 30% higher conversion than the next best catalyst during optimization, **1b**, we compared the kinetic profiles of these two species. Under the optimized reaction conditions (1.00 mmol scale, 1.2 equiv NaO*t*-Bu, 1 mol % cat., 0.2 M *i*-PrOH), we monitored the reaction of **3a** with both **2c** and **1b** over time as shown in Figure 2. The reaction using **2c** is initially faster, and reaches a maximum conversion of 96% in ≤40 minutes at 100°C. The reaction using **1b** requires ~90 min to reach a maximum conversion of 70%. Hence the iridium complex **1b** is both initially slower and more readily deactivated than the ruthenium complex **2c**.

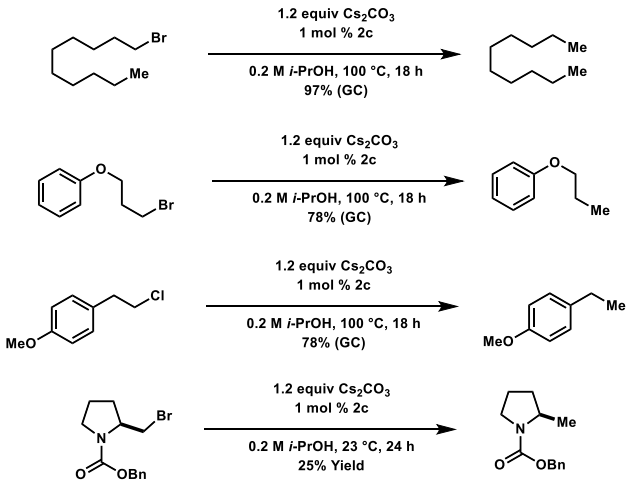


Figure S2. Results using Cs_2CO_3 as a base.

2. Experimental Procedures

General Information: All manipulations of metal complexes were carried out under atmospheres of N_2 or argon using standard airfree techniques. ^{1}H, ^{13}C and ^{31}P NMR were recorded on Varian and Bruker 300 and 400 MHz spectrometers. ^{1}H and ^{13}C NMR are reported in ppm (δ) and referenced[1] to residual solvents. ^{31}P NMR are referenced to 85% H_3PO_4 (0.00 ppm). GC analyses were conducted on an Agilent 6800 instrument with an Agilent HP-5 column. Column chromatography was carried out using silica gel F60, 230-400 mesh from Silicycle. CAM (cerium ammonium molbydate) and PMA (phosphomolybdic acid) stains were prepared according to Not Voodoo.[2] Isopropanol (anhydrous) was purchased from Sigma-Aldrich and sparged with argon before use. Iridium complexes **1a-e** were prepared according to the literature.[3] Ruthenium complexes **2a-c** were purchased from Sigma-Aldrich. Commercially available halide substrates were purchased in the highest available purity and used as received. Older substrates from existing chemical stock were purified by filtration through a plug of neutral alumina before use.

General procedure for reduction with 2c: Inside a N_2 glovebox, a 20 mL septum-capped vial was charged with 1.00 mmol organohalide (if solid), 115 mg NaOt-Bu (1.20 mmol) and 4.4 mg **2c** (0.01 mmol, 1 mol%). The vial was capped and removed from the glovebox. 5.0 mL anhydrous degassed *i*-PrOH was then added via syringe, followed by 1.00 mmol organohalide (if liquid). The vial was then stirred at 100 °C on a hotplate using an aluminum block, with the solvent level remaining above the top of the well. The reaction was monitored by GC or TLC.

Workup procedure A: After completion, the vial was cooled to room temperature and the reaction mixture diluted with pentane. The mixture was washed with H_2O and brine. The combined aqueous layers were extracted with pentane. The organic layers were dried over Na_2SO_4 and purified by column chromatography (SiO_2, pentane).

Workup procedure B: After completion, the vial was cooled to room temperature and the reaction mixture was concentrated in vacuo. The resulting crude product was dissolved in EtOAc and washed with H_2O and brine. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by column chromatography (SiO_2).

3. Characterization of Products

***n*-Decane**: Isolated as a colorless oil (134 mg, 0.93 mmol, 93% yield) from 1-bromodecane following the general procedure and workup procedure A. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.47 – 1.16 (m, 16H), 0.92 (t, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 31.97, 29.71, 29.41, 22.72, 14.10.[4]

1-Ethyl-4-methoxybenzene: Isolated as a colorless oil (129 mg, 0.95 mmol, 95% yield) from 1-(2-chloroethyl)-4-methoxybenzene following the general procedure and workup procedure A. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.17 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 2.86 – 2.49 (m, 2H), 1.28 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.67, 136.38, 128.71, 113.75, 55.20, 28.02, 15.93.[5]

Adamantane: Isolated as a colorless solid (128 mg, 0.94 mmol, 94% yield) from 1-bromoadamantane following the general procedure and workup procedure A. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.87 (s, 3H), 1.75 (t, *J* = 3.2 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 37.90, 28.48. mp 192-195°C (sublimed)[6]

Adamantane: Isolated as a colorless solid (131 mg, 0.95 mmol, 95% yield) from 2-bromoadamantane following the general procedure and workup procedure A. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 1.87 (s, 3H), 1.75 (t, *J* = 3.2 Hz, 9H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 37.90, 28.48.

***n*-Propoxybenzene:** Isolated as a colorless oil (120 mg, 0.88 mmol, 88% yield) from (3-bromopropoxy)benzene following the general procedure and workup procedure A. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.18 (m, 2H), 7.05 – 6.82 (m, 3H), 3.97 (t, *J* = 6.6 Hz, 2H), 1.87 (dtd, *J* = 13.9, 7.4, 6.5 Hz, 2H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.14, 129.44, 120.48, 114.51, 69.38, 22.66, 10.59.[7]

Naphthalene: Isolated as a colorless solid (122 mg, 0.95 mmol, 95% yield) from 1-bromonaphthalene following the general procedure and workup procedure A. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dq, *J* = 6.2, 2.8 Hz, 4H), 7.52 (dt, *J* = 6.3, 3.1 Hz, 4H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 133.46, 127.90, 125.83. mp 72-76 °C[8]

Isopropyl benzoate: Isolated as a colorless oil (148 mg, 0.90 mmol, 90% yield) from methyl 4-bromobenzoate and workup procedure B. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 7.99 (m, 2H), 7.63 – 7.51 (m, 1H), 7.51 – 7.35 (m, 2H), 5.26 (hept, *J* = 6.3 Hz, 1H), 1.37 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.13, 132.69, 130.90, 129.50, 128.26, 68.35, 21.97.[9]

1,3-Bis(trifluoromethyl)benzene: Isolated as a colorless oil (158 mg, 0.74 mmol, 74% yield) from 1,3-bis(trifluoromethyl)-5-bromobenzene following the general procedure and workup procedure A. Volatile product. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.64 (t, *J* = 7.9 Hz, 1H). ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.17.[10]

Mesitylene: Isolated as a colorless oil (107 mg, 0.89 mmol, 89% yield) from 2-bromomesitylene following the general procedure with 2 mol% **2c**, and 48 h reaction time. Workup procedure A was used. Spectral data matched the literature: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 6.86 (s, 1H), 2.34 (s, 3H).[1]

1,1-dimethylcyclohexane: Isolated as a colorless oil (78 mg, 0.70 mmol, 70% yield) from **3h** following the general procedure and workup procedure A. Volatile product. Spectral data matched the literature: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 1.47 – 1.40 (m, 5H), 1.24 (dt, *J* = 11.2, 6.1 Hz, 5H), 1.14 (s, 2H), 0.83 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 37.94, 32.22, 26.64, 22.13.[11]

Benzyl *(S)*-2-methylpyrrolidine-1-carboxylate: Inside an N_2 glovebox, a 20 mL septum-capped vial was charged with 115 mg NaOt-Bu (1.20 mmol) and 4.4 mg **2c** (0.01 mmol, 1 mol%). The vial was capped and removed from the glovebox. 5.0 mL anhydrous degassed i-PrOH was then added via syringe, followed by 298 mg **3n** (1.00 mmol). The reaction was stirred at room temperature. After 24 h, the reaction appeared complete by TLC (DCM, CAM stain). The reaction mixture was extracted with ether, washed with water, brine and dried over $MgSO_4$. The crude product was purified by column chromatography (SiO_2, DCM) to afford the title compound as a colorless oil (187 mg, 0.85 mmol, 85% yield). Spectral data matched the literature: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.42 – 7.20 (m, 5H), 5.14 (p, *J* = 12.0 Hz, 2H), 3.99 (s, 1H), 3.44 (s, 2H), 2.04 – 1.74 (m, 3H), 1.58 (s, 1H), 1.16 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*), observed as two rotamers, δ 128.40, 127.78, 66.58, 66.34, 53.43, 52.84, 46.63, 46.25, 33.25, 23.65, 22.91, 20.86, 20.00.[12] Enantiomeric excess was determined to be >99% by SFC (AD-H, 2% i-PrOH, 3.0 mL/min), using a racemic sample prepared by the reaction of *rac*-2-methylpyrrolidine with Cbz-Cl and i-Pr_2NEt in DCM.

Hexahydro-2H-3,5-methanocyclopenta[b]furan-2-one: Isolated as a colorless solid (99 mg, 0.72 mmol, 72% yield) from bromolactone **3r** following the general procedure, using 1.0 equiv NaO*t*-Bu at room temperature. Workup procedure B was used. Column condition: 50% hexanes/DCM. Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.76 (dd, *J* = 5.0, 7.9 Hz, 1H), 3.17 (tq, *J* = 4.9, 1.5 Hz, 1H), 2.51 (ddt, *J* = 11.3, 4.9, 1.5 Hz, 1H), 2.43 (ddp, *J* = 3.8, 2.9, 0.9 Hz, 1H), 1.94 (ddt, *J* = 13.0, 11.3, 3.4 Hz, 1H), 1.80 – 1.66 (m, 3H), 1.62 – 1.54 (m, 2H), 1.50 (ddd, *J* = 14.1, 2.3, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 181.58, 80.93, 46.50, 39.14, 38.16, 37.94, 36.52, 34.52.

4. Preparation of unreported compound 1-bromomethyl-1-methylcyclohexane

1-hydroxymethyl-1-methylcyclohexane: A solution of 2.84 g (20.0 mmol) 1-methylcyclohexane carboxylic acid in THF (40 mL, 0.2 M) was cooled with an ice-water bath and 3.8 mL (40 mmol) BH_3-DMS complex was added dropwise (gas evolves). The ice-water bath was removed and the reaction was stirred for 48 h at room temperature, then cooled again with an ice-water bath. H_2O was added carefully until no more gas evolved, then the mixture was extracted with 3 x 25 mL DCM. The DCM layers were washed with aq. $NaHCO_3$ and dried over $MgSO_4$. Concentration in vacuo afforded the title compound as a clear colorless oil: 2.40 g (18.8 mmol, 94% yield). Spectral data matched the literature: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.73 (s, 1H), 3.32 (s, 2H), 1.84 (s, 1H), 1.74 – 1.10 (m, 11H), 0.89 (s, 3H).[13]

1-bromomethyl-1-methylcyclohexane: A stirred solution of 614 mg (5.00 mmol) 1-hydroxymethyl-methylcyclohexane and 1.44 g (5.50 mmol) PPh_3 in 5.0 mL (1.0 M) DMF was cooled in a water bath under argon. Br_2 was added dropwise until an orange color persisted (ca. 0.13 mL). The reaction mixture was then heated to 150°C for 30 min, and cooled to room temperature. The resulting dark solution was diluted with 25 mL water and 25 mL pentane, stirred and filtered. The mixture was separated and extracted with 2 x 10 mL pentane. The pentane extracts were washed with 2 x 25 mL brine, then dried (Na_2SO_4) and filtered through a plug of SiO_2. Concentration afforded the title product as a clear colorless oil: 279 mg (1.46 mmol, 29% yield). This compound was previously reported in the literature but not fully characterized.[14] ^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.34 (s, 2H), 1.52 – 1.42 (m, 5H), 1.42 – 1.35 (m, 4H), 1.35 – 1.28 (m, 1H), 1.00 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 47.62, 35.89, 34.27, 26.10, 22.02. HRMS (EI+) for $C_8H_{15}Br$: calculated 190.0357, measured 190.0358.

References

[1] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176-2179.

[2] http://chem.chem.rochester.edu/~nvd/pages/magic_formulas.php?page=tlc_stains

[3] a) M. Gupta, C. Hagen, W. C. Kaska, R. E. Cramer, C. M. Jensen, *J. Am. Chem. Soc.* **1997**, *119*, 840-841; b) I. Göttker-Schnetmann, P. White, M. Brookhart, *J. Am. Chem. Soc.* **2004**, *126*, 1804-1811; c) M. Yamashita, Y. Moroe, T. Yano, K. Nozaki, *Inorganica Chimica Acta* **2011**, *369*, 15-18; d) R. Ahuja, B. Punji, M. Findlater, C. Supplee, W. Schinski, M. Brookhart, A. S. Goldman, *Nature chemistry* **2011**, *3*, 167-171; e) W. Yao, Y. Zhang, X. Jia, Z. Huang, *Angewandte Chemie International Edition* **2014**, *53*, 1390-1394.

[4] T. Ogoshi, Y. Shimada, Y. Sakata, S. Akine, T.-a. Yamagishi, *Journal of the American Chemical Society* **2017**, *139*, 5664-5667.

[5] D. Leow, Y.-H. Chen, T.-H. Hung, Y. Su, Y.-Z. Lin, *European Journal of Organic Chemistry* **2014**, *2014*, 7347-7352.

[6] A. Dewanji, C. Mück-Lichtenfeld, A. Studer, *Angewandte Chemie International Edition* **2016**, *55*, 6749-6752.

[7] Y.-W. Zheng, P. Ye, B. Chen, Q.-Y. Meng, K. Feng, W. Wang, L.-Z. Wu, C.-H. Tung, *Organic Letters* **2017**, *19*, 2206-2209.

[8] L. Liu, P. E. Floreancig, *Organic Letters* **2010**, *12*, 4686-4689.

[9] Q. Jiang, A. Zhao, B. Xu, J. Jia, X. Liu, C. Guo, *The Journal of Organic Chemistry* **2014**, *79*, 2709-2715.

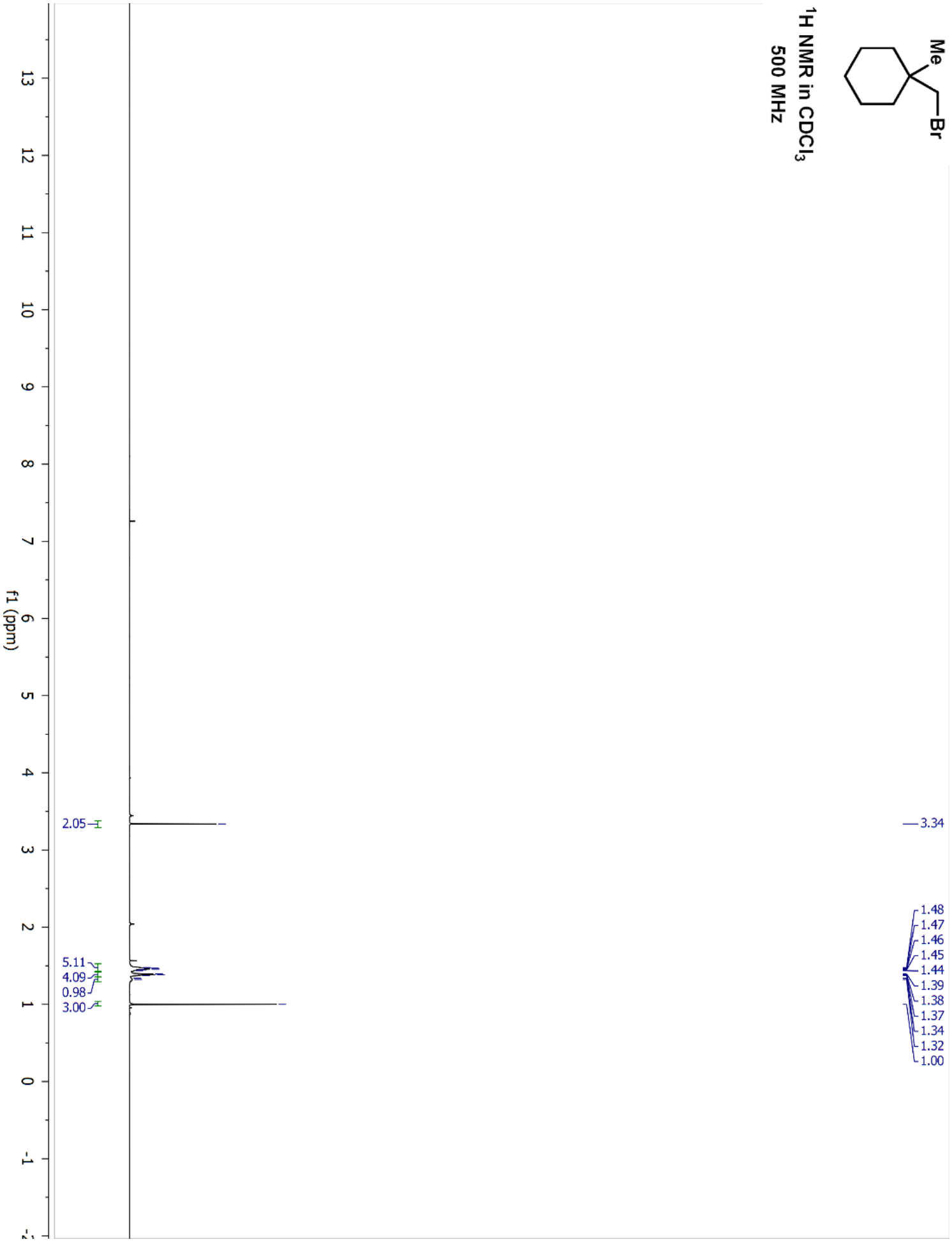
[10] K. A. Giffin, I. Korobkov, R. T. Baker, *Dalton Transactions* **2015**, *44*, 19587-19596.
[11] R. J. Abraham, M. A. Warne, L. Griffiths, *Journal of the Chemical Society, Perkin Transactions 2* **1997**, 31-40.
[12] W. H. Nijhuis, W. Verboom, A. Abu El-Fadl, G. J. Van Hummel, D. N. Reinhoudt, *The Journal of Organic Chemistry* **1989**, *54*, 209-216.
[13] V. Shiner Jr, J. J. Tai, *Journal of the American Chemical Society* **1981**, *103*, 436-442.
[14] W. Parker, R. A. Raphael, *Journal of the Chemical Society (Resumed)* **1955**, 1723-1727.

Author Contributions

M.C.H.: designed the project, carried out experiments, analysed the data, wrote the manuscript

B.M.S.: designed the project, analysed the data, contributed to writing the manuscript

R.H.G. designed the project, analysed the data, contributed to writing the manuscript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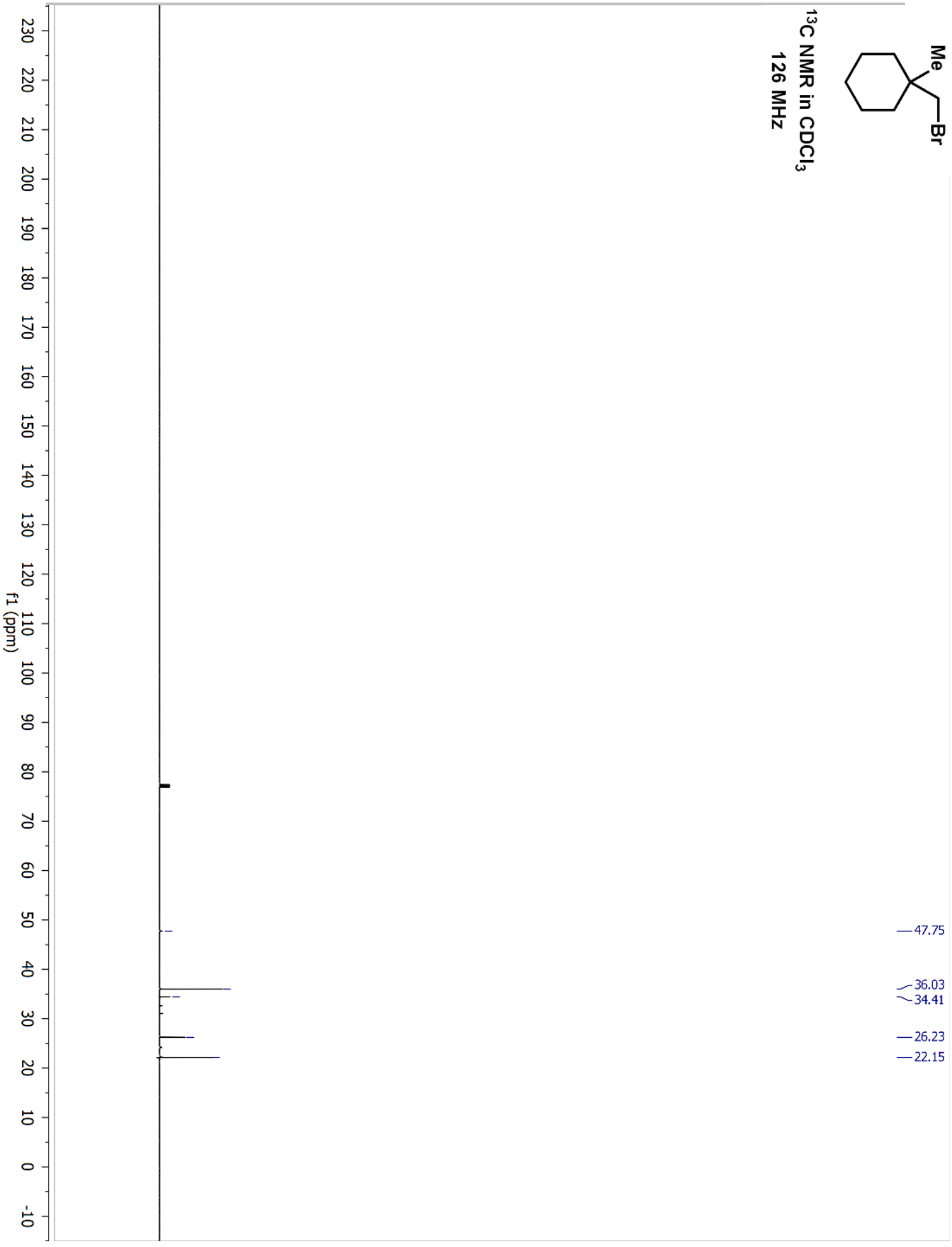
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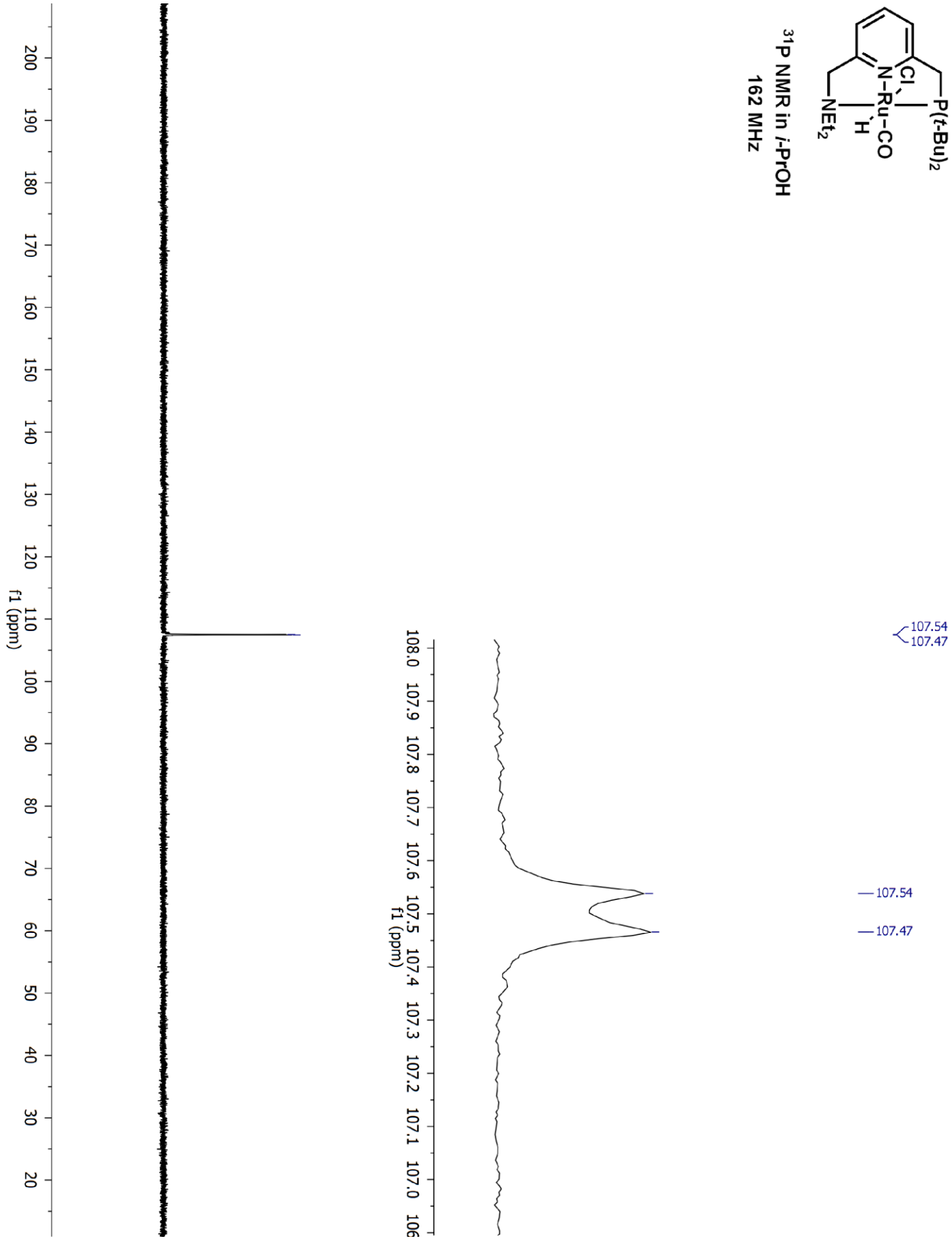
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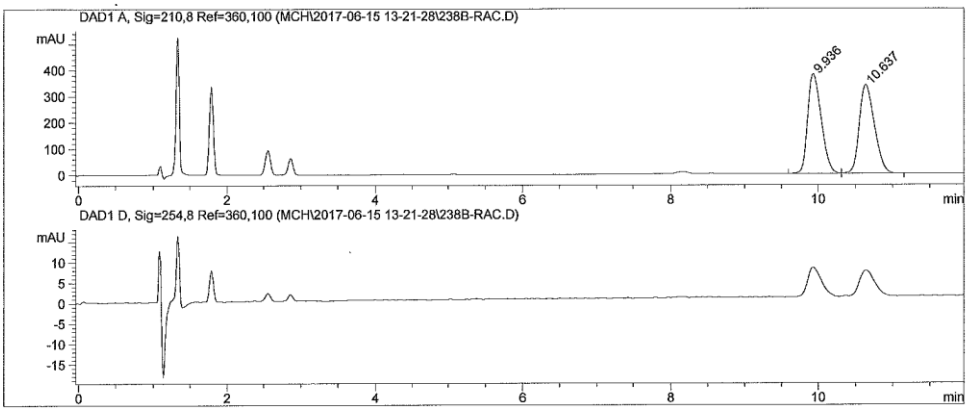

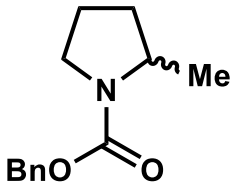


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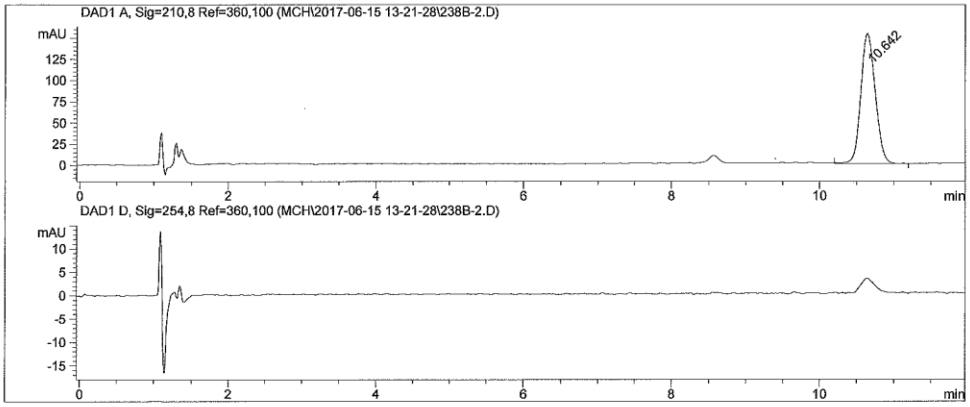

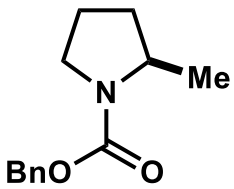


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