Fall 2023

Scandium Triflate-Catalyzed Aromatic Aldehydic C-H Activation

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Abstract

Herein described is a scandium triflate-catalyzed C-H activation of commercially available aromatic aldehydes achieved in low yields. The reaction occured in a one-pot synthesis over a two-hour duration and required minimal purification. Inclusion of a fluorine-tagged phenol allowed for reaction monitoring via ^{19}FNMR.

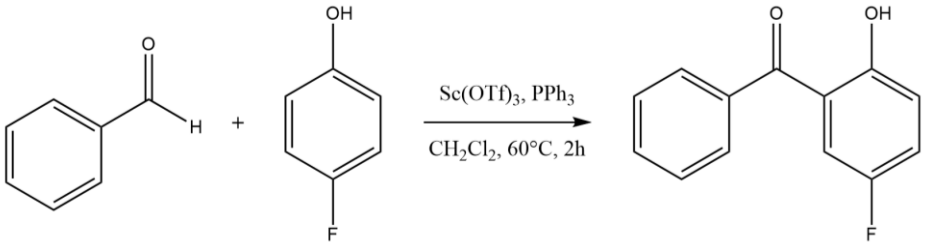
Introduction

C-H activation is a widely relevant field in organic chemistry research. The direct activation and functionalization of the C-H bond is sought after for its quick, efficient synthetic advantages. By avoiding intermediate functionalization C-H activation is atom economic, satisfying one of the "12 Principles of Green Chemistry."

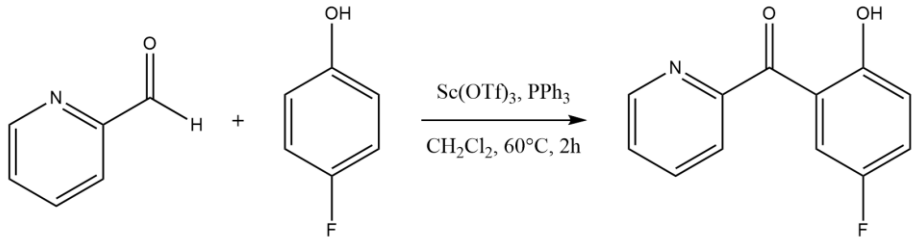
The activation of the C-H bond is much preferable than traditional cross-coupling reactions due to its efficiency. Therefore, sustainable and efficient C-H activation methodologies would find applications in numerous organic chemistry industries, such as the pharmaceutical industry. Palladium-catalyzed coupling reactions – such as Negishi, Stille, and Suzuki couplings – currently dominate the industry in generating carbon-carbon bonds. However, these palladium catalysts are expensive and the reagents require intermediate functionalization for the reaction to occur.

Aldehydic C-H activation is a challenging process due to the nonpolar nature of the carbon-hydrogen bond. Traditionally, catalysts have been used to weaken the bond in order to cleave the hydrogen. Current methods of aldehydic C-H activation utilize rhodium catalysts or a triple catalyst mechanism.[1,2] These catalysts work, however they are very expensive and not atom economic.

Herein described is a scandium triflate catalyzed C-H activation of commercially available aromatic aldehydes (Scheme 1 & 2). The reaction occurs in a one-pot synthesis over a short period of time (2h) and is purified via an acid-base extraction. The use of a fluorine-tagged phenol allows the reaction to be monitored via ^{19}FNMR.



Scheme 1. Scandium triflate catalyzed C-H activation of benzaldehyde.



Scheme 2. Scandium triflate catalyzed C-H activation of pyridine-2-carbaldehyde.

Experimental

1) General Procedures

All reactions were performed under inert nitrogen atmosphere. All reagents were used as received without further purification. The dichloromethane was dried via a PureSolv Micro Solvent Purification System. NMR spectra were obtained in $CDCl_3$ at 300 MHz (^{1}H & ^{13}C) and 60 MHz (^{19}F). GCMS analysis of products was performed using a single quadrupole mass spectrometer.

2) Benzaldehyde Reaction

Dichloromethane (10 mL) and benzaldehyde (0.31 mL, 3 mmol) were injected into a 100 mL round-bottom flask under an inert atmosphere. 4-flurophenol (0.4036 g, 3.6 mmol), scandium triflate (0.2953 g, 0.6 mmol), and triphenylphosphine (0.3150 g, 1.2 mmol) were subsequently added. A condenser was fitted to the flask and the contents were stirred for 2h in a 60°C water bath. An aliquot of the reaction mixture was then taken for crude ^{19}FNMR. The reaction mix was then added to a separatory funnel containing 2M NaOH. The aqueous layer was washed with dichloromethane, acidified with 6M HCl, and the organic product extracted using ether. Excess solvent was removed *in vacuo.*

The flask was placed under an inert atmosphere before methanol (10 mL) and methylamine (4mL, 4 mmol) were injected into the flask. The mixture was allowed to stir for 30 min at room temperature. The mixture was added to a separatory funnel containing 6M HCl. The mixture was then washed with ether. Following neutralization via saturated sodium bicarbonate, the organic product was extracted using ether before being dried by anhydrous sodium sulfate. Excess solvent was removed via rotary evaporator which gave a solid product. ^{1}H NMR (300 MHZ, $CDCl_3$) δ (ppm): 6.80 (m, 1H), 6.93 (t, 1H), 7.49 (t, 2H), 7.57 (t, 1H), 7.70 (m, 2H). ^{19}F NMR (300 MHZ, $CDCl_3$) δ (ppm): -124.64. M^+(m/z)=277.100.

3) Pyridine-2-Carbaldehye Reaction

Dichloromethane (10 mL) and pyridine-2-carbaldehyde (0.29 mL, 3 mmol) were injected into a 100 mL round-bottom flask under inert atmosphere. 4-flurophenol (0.4036 g, 3.6 mmol), scandium triflate (0.2953 g, 0.6 mmol), and triphenylphosphine (0.3147 g, 1.2 mmol) were subsequently added. A condenser was fitted to the flask and the contents were stirred for 2h in a 60°C water bath. An aliquot of the reaction mixture was then taken for crude ^{19}FNMR. The mixture was then poured into a separatory funnel containing 2M NaOH. The aqueous layer was washed twice with dichloromethane and

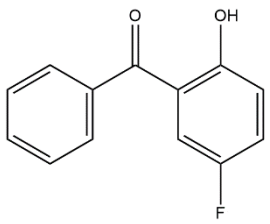
subsequently acidified using 6M HCl. The resulting aqueous mixture was washed twice with ether before being neutralized using saturated sodium bicarbonate. The organic product was then extracted using ether, dried using anhydrous sodium sulfate, and solvent removed via rotary evaporator, yielding a solid product. ^{1}H NMR (300 MHZ, $CDCl_3$) δ (ppm): 6.02 (s, 1H), 6.89 (d, 2H), 7.13 (d, 1H), 7.56 (d, 1H), 7.79 (t,1H), 8.50 (s, 1H). ^{13}C NMR (300 MHZ, $CDCl_3$) δ (ppm): 72.97, 112.88, 115.61, 119.48, 123.13, 130.08, 138.31, 147.54, 161.40. ^{19}F NMR (300 MHZ, $CDCl_3$) δ (ppm):-124.09. M^+(m/z)= 219.200.

4) Isobutyraldehyde Reaction

Dichloromethane (10 mL) and isobutyraldehyde (0.27 mL, 3 mmol) were injected into a 100 mL round-bottom flask under inert atmosphere. 4-flurophenol (0.4036 g, 3.6 mmol), scandium triflate (0.2953 g, 0.6 mmol), and triphenylphosphine (0.3150 g, 1.2 mmol) were subsequently added. A condenser was fitted to the flask and the contents were stirred for 2h in a 60°C water bath. An aliquot of the reaction mixture was then taken for crude ^{19}FNMR. The reaction mixture was then washed with deionized water, followed by another brine wash, and then dried using anhydrous sodium sulfate. Excess solvent and unreacted aldehyde was removed via rotary evaporator yielding a shiny brown solid.

Results and Discussion

Benzaldehyde was the first choice of substrate due to its availability as the most basic aromatic aldehyde. However, the use of benzaldehyde led to challenges of product purification. Column chromatography was not a viable option as the excess phenol and the product (Figure 1) were of similar polarity. Our solution was to use methylamine to convert the product to an imine, which could

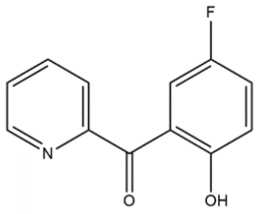


(5-fluoro-2-hydroxyphenyl)(phenyl)methanone
Exact Mass = 216.06

Figure 1. Structure of the product formed in the benzaldehyde reaction.

then be separated from the unreacted phenol via acid-base work up.

Pyridine-2-carbaldehyde was the next substrate tested. It offered an opportunity to test our methodology on the pyridine aromatic aldehydes. More importantly, it eliminated the need for the imine formation, as the product (Figure 2) could be separated via acid-base work up due to the pyridine ring.



(5-fluoro-2-hydroxyphenyl)(pyridin-2-yl)methanone
Exact Mass = 217.05

Figure 2. Structure of the product formed in the pyridine-2-carbaldehyde reaction.

Isobutyraldehyde was chosen next to determine if aromaticity was essential for the reaction to occur. Isobutyraldehyde was chosen over other aldehydes – such as pentanal, hexanal, etc. – due to its low boiling point, which would allow removal of the excess aldehyde via rotary evaporator. The reaction using isobutyraldehyde confirmed that the aromaticity was necessary, as the expected product (Figure 3) was not obtained. This was confirmed using IR spectroscopy, in which no carbonyl peak was observed.

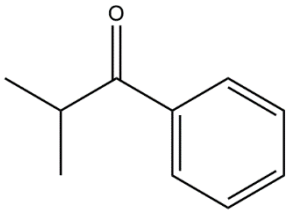


Figure 3. Structure of the expected product in the isobutyraldehyde reaction.

Although products have only been obtained in trace yields, this reaction has many opportunities for yield optimization. Future research will examine various solvents, catalyst percentage, reaction temperature, and reaction times in order to find the optimal conditions. Furthermore, we will study the effect of using a base to deprotonate the phenol before introduction to the aldehyde, with hopes that yield will increase.

Conclusion

In summary, a methodology for scandium triflate-catalyzed activation of the C-H bond of aromatic aldehydes has been reported. While initial yields are low, the reaction occurs via very simple

synthetic procedures and there has been minimal reaction optimization to date. The scandium triflate-catalyzed C-H activation is comparatively cheaper and more efficient than traditional palladium-catalyzed cross-coupling reactions, which suggests there are many potential industrial applications of this reaction.

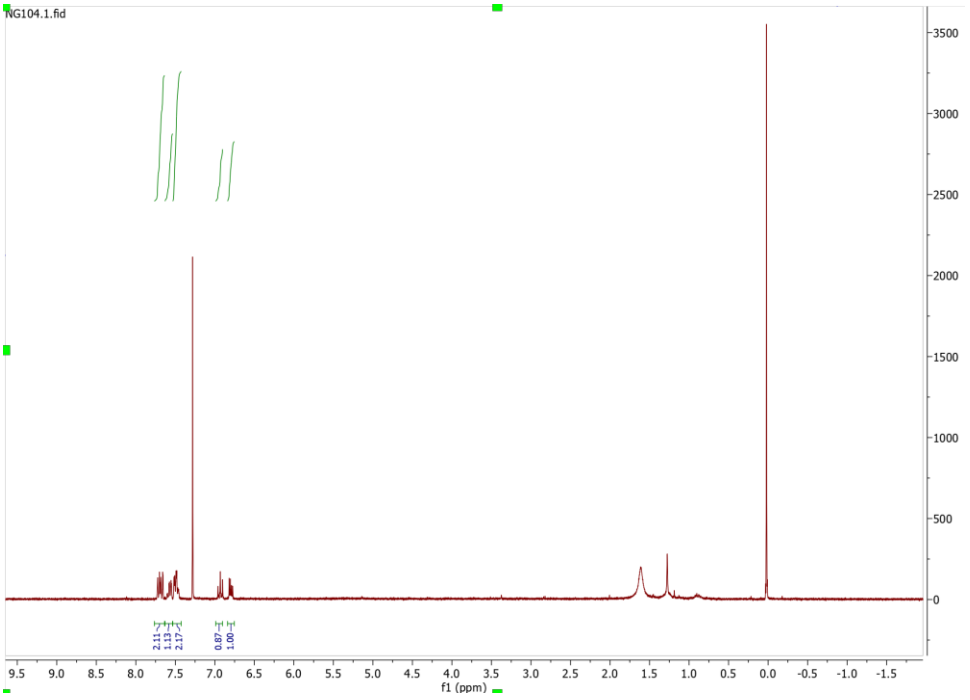
References

(1) Kumar, V.; Maayuri, R.; Mantry, L.; Gandeepan, P. Recent Advances in Rhodium-Catalyzed Electrochemical C-H Activation. *Chem Asian J* **2023**, *18* (9). https://doi.org/10.1002/ASIA.202300060.

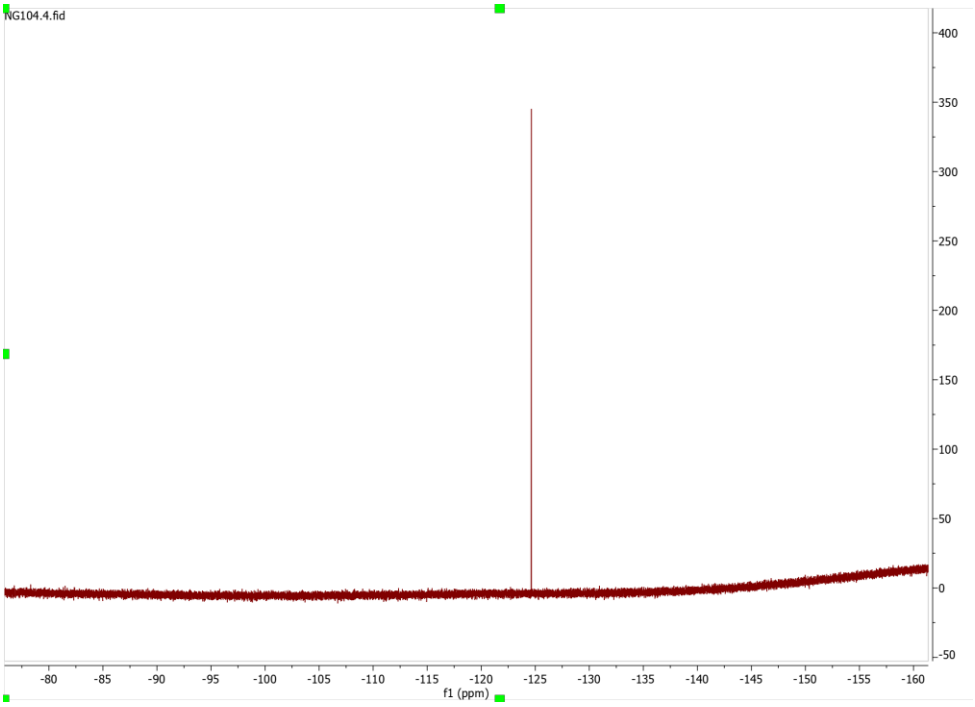
(2) Zhang, X.; MacMillan, D. W. C. Direct Aldehyde C-H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis. *J Am Chem Soc* **2017**, *139* (33), 11353–11356. https://doi.org/10.1021/JACS.7B07078/SUPPL_FILE/JA7B07078_SI_001.PDF.

Spectra

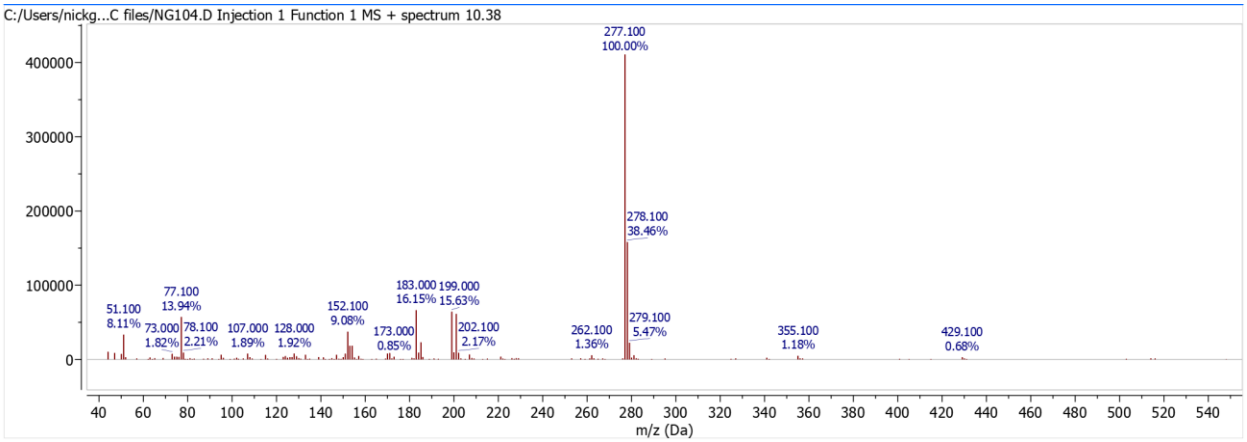
Benzaldehyde ^{1}H



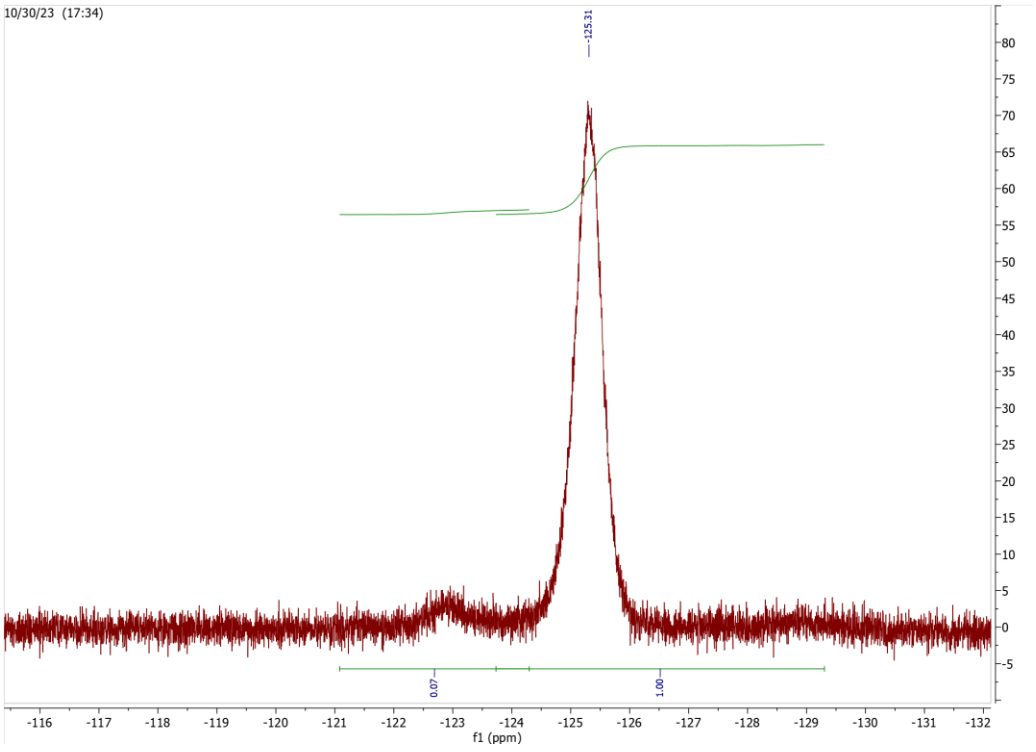
Benzaldehyde ^{19}F



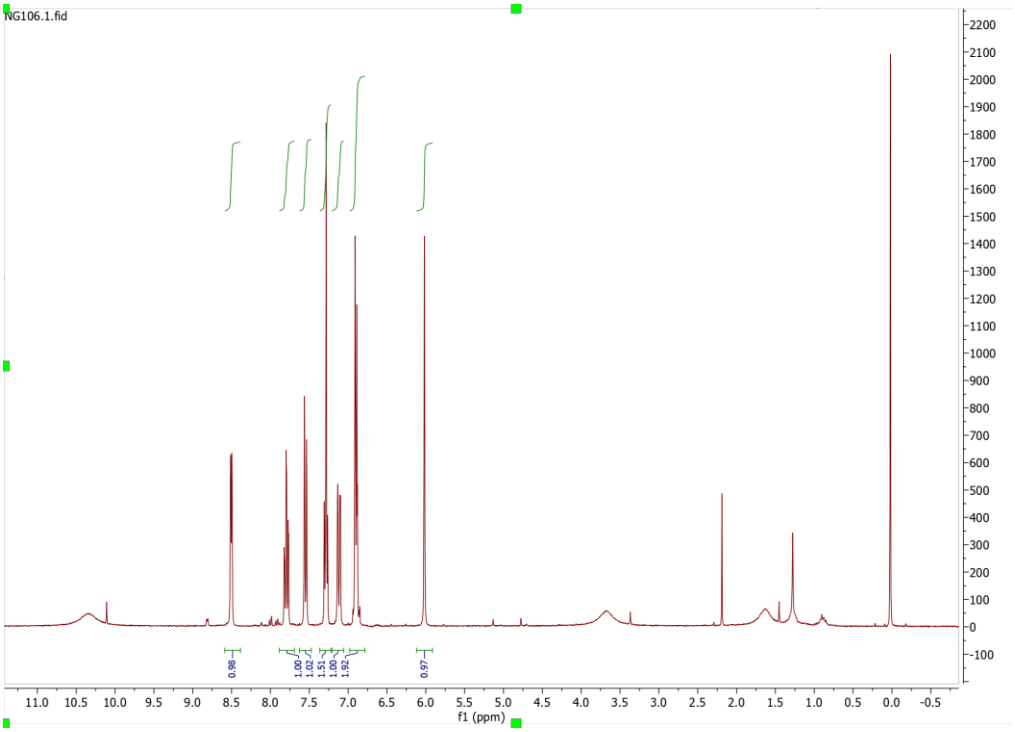
Benzaldehyde MS



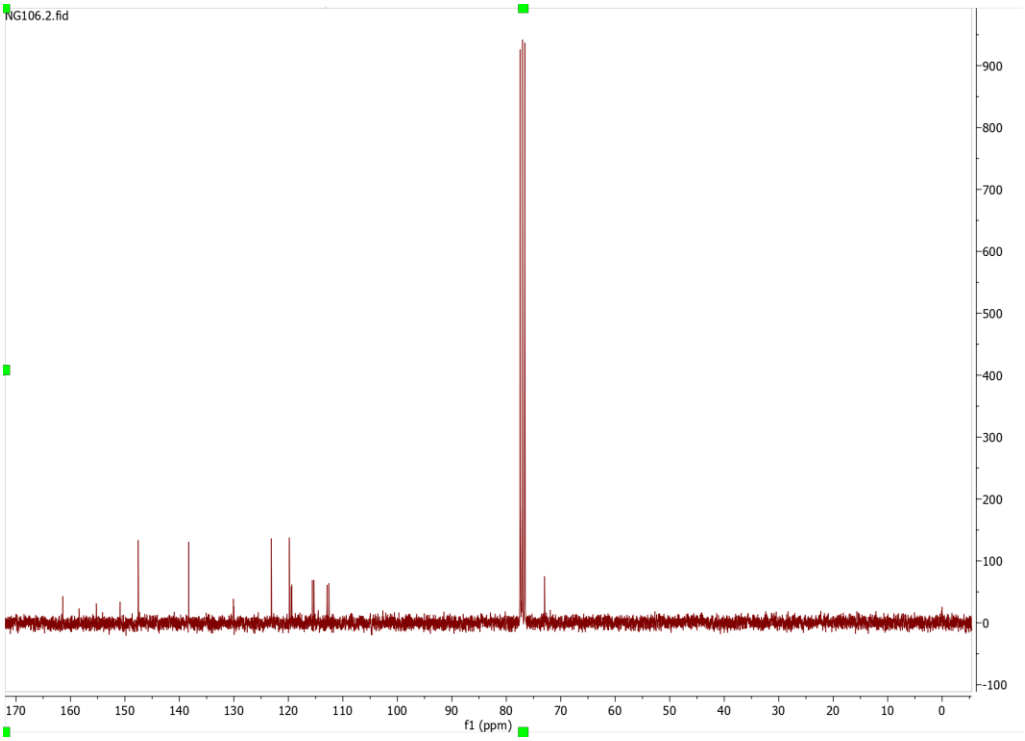
Pyridine-2-Carbaldehyde ^{19}F Crude



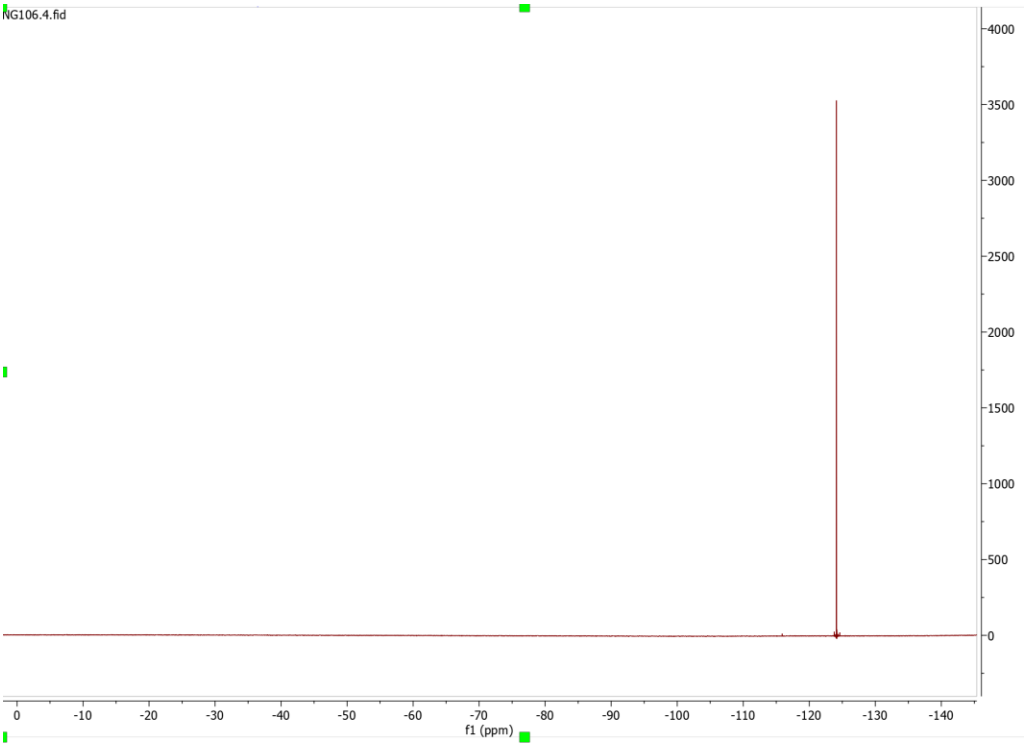
Pyridine-2-Carbaldehyde ^{1}H



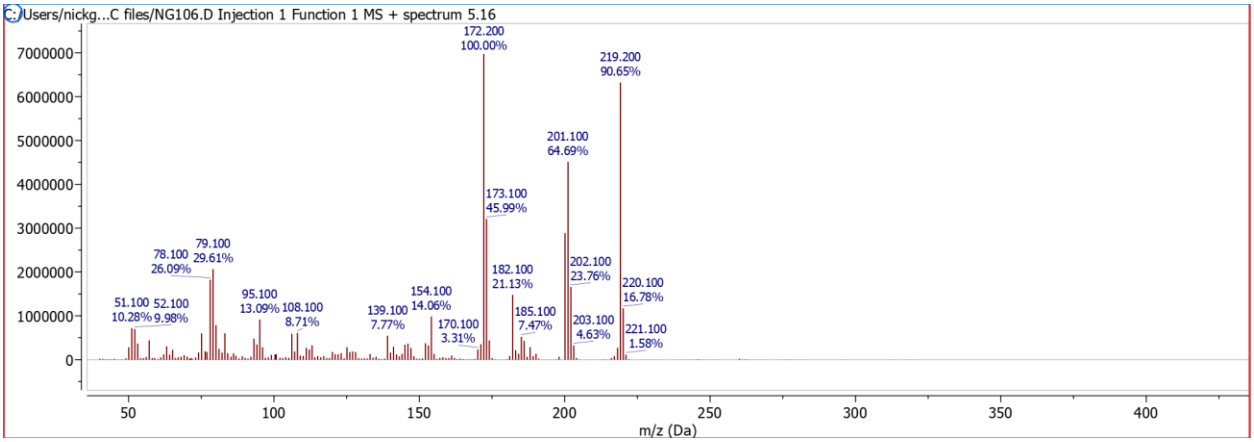
Pyridine-2-Carbaldehyde ^{13}C



Pyridine-2-Carbaldehyde ^{19}F



Pyridine-2-Carbaldehyde MS



Isobutyraldehyde IR