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Efforts toward novel methods for the synthesis of stereochemically-dense pharmacologically relevant scaffolds

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EFFORTS TOWARD NOVEL METHODS FOR THE SYNTHESIS OF STEREOCHEMICALLY-DENSE PHARMACOLOGICALLY RELEVANT SCAFFOLDS

by

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A Thesis

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Subash Jonnalagadda Ph.D.
James Grinias Ph.D.

Dedication

To my family, who have sculpted me into the person I am today, I will continue to push the boundaries of what I can accomplish to reach my full potential and make you proud.

Acknowledgments

The faculty and staff of Rowan University's Department of Chemistry and Biochemistry have established a community that encourages scientific creativity. For this I am genuinely thankful. This department has provided me with the technology, resources and inspiration to become the scientist I am today.

I would like to personally thank Dylan Quinn for mentoring me during the beginning stages of my research, Brooke Austin for her collaboration and support in the lab as well as everyone in the Moura-Letts group.

Lastly, I would like to show my appreciation for Dr. Gustavo Moura-Letts who envisioned and provided me with the resources to discover my potential as an organic chemist. I am honored to have had the opportunity to conduct research under his guidance.

Abstract

Lauren N. Tumbelty
EFFORTS TOWARD NOVEL METHODS FOR THE SYNTHESIS OF STEREOCHEMICALLY-DENSE PHARMACOLOGICALLY RELEVANT SCAFFOLDS
2016-2018
Gustavo Moura-Letts Ph.D.
Master of Science in Pharmaceutical Sciences

Nitrogen is the most common pure element, present in nearly all relevant chemical compounds. It is an essential component of the building blocks of life such as proteins, nucleic acids, amino acids and adenosine tri-phosphate. There is a naturally occurring exchange between living organisms and the atmosphere which begins with the process of fixation. Although nitrogen is naturally abundant, the strength of the triple bond in atmospheric nitrogen prevents its applicability in organic synthesis. Therefore, the development of methods to place synthetic nitrogen into heteroatomic compounds plays an important role in the development of pharmacologically relevant scaffolds.

Contained within this manuscript are novel methods which utilize nitrones for various synthetic methods in order to incorporate nitrogen into a variety of heterocycles. The transfer agents used within this methodology are a variety of N-Substituted Hydroxylamines. This work highlights the value of these nitrogen transfer agents as well as their chemoselectivity in synthesis. Herein is reported the methodological development of vinylisoxazolidines and isoxazolooxazines from vinylnitrones

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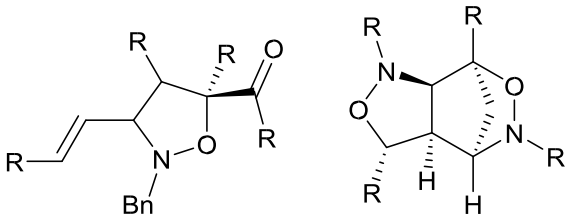
Chapter 1

Nitrones

The early works of the Moura Letts Group have explored possible avenues for the utilization of substituted hydroxylamines as nitrogen transfer agents. With interests in the synthesis of small heterocycles, the GML group aimed to investigate the synthesis of five-membered heterocycles with varying functionality. Isoxazolidines are fivemembered heterocycles containing an adjacent nitrogen and oxygen within the ring. These compounds have been isolated from a variety of natural sources, serve as intermediates in the synthesis current antibiotics, and have been recognized as therapeutic agents (Berthet et *al.* 2016). Furthermore, Isoxazolooxazines are bridged bicycles containing two isoxazolidine rings with an interconnected five-membered carbon bridge. The synthesis of these desired five-membered heterocycles (Figure 1) were synthesized by utilizing nitrone substrates during their synthesis.

Figure 1

Heteroatomic Differences: Isoxazolidine (left), Isoxazolooxazines (right)

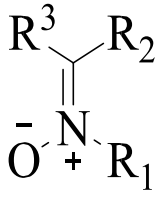


. Previous members of the Moura Letts' Group were in pursuit of a novel synthetic method to produce oxaziridines when the 1,3-Dipole, Nitrone was synthesized. This methodology utilized a condensation reaction of N-substituted hydroxylamines with

simple aldehydes in polar aprotic solvents. There were no indications that the desired Oxaziridine was produced in this reaction. After characterization, it was determined that the major product obtained from these experiments was the 1,3-Dipole, Nitrone.

Figure 2

General Structure of a 1,3 Dipole, Nitrone



Structurally, nitrones contain a positively charged nitrogen that makes four bonds. Most importantly, this nitrogen is bound to a negatively charged oxygen atom (Figure 2). The nitrogen-oxygen bond dipole has been identified as valuable synthetic intermediate as it allows for a broad range of chemical transformations (Macaluso & Hamer, 1964). These compounds have also been found to have value in other disciplines of chemistry besides organic such as analytical and pharmaceutical chemistry.

1.1 The Pharmaceutical Significance of Nitrones

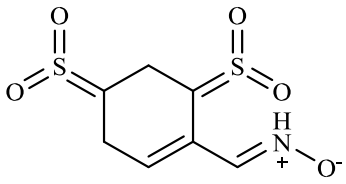
Oxidative stress is characterized by an imbalance between free-radical production and the body's ability to neutralize them with antioxidants. This can have very grave effects on the body as free radicals are extremely reactive. The consequences associated

with oxidative stress can result in disruptions in cellular signaling, DNA mutations and even widespread apoptosis (Lennon, Martin & Cotter, 1991). The health effects associated with these disturbances in cellular function have been reported consistently from various different research groups (Lobo, Phatak & Chandra, 2010). Due to their ability to spin trap, it has been determined that nitrones neutralize free radicals providing a less reactive and thus less harmful compound. Since there is evidence supporting that nitrones can be potential therapeutic agents, current research efforts have been made toward determining their potential in the pharmaceutical industry.

Phenyl tert-butylnitrone (PBN) and its derivatives have been identified in the literature as spin traps since the 1960's. Studies involving their ability to spin trap superoxide, hydrogen peroxide and hydroxyl free radicals that are responsible for oxygen-derived free radical damage in the body have been investigated. Radical damage particularly has been identified in causing an increase in the permeability of the bloodbrain barrier (Chan, Schmidley, Fishman & Longar, 1984). Initially commercial efforts were made to determine the efficiency of the 2,4-disulfonyl-phenylnitrone PBN derivative for the treatment acute ischemic strokes (Figure 3). Although the preclinical trials displayed evidence that this could be a viable treatment option, it was determined after Phase 3 of clinical trials that this PBN derivative was ineffective in the treatment of acute ischemic strokes. More recently, this derivative has been utilized as an anti-cancer agent in preclinical glioma models and has shown great promise alone and in combination with lanthionines as a therapeutic agent (Floyd, Castro Faria Neto, Zimmerman, Hensley & Towner, 2014).

Figure 3

2,4-Disulfonyl-phenylnitrone (PBN)

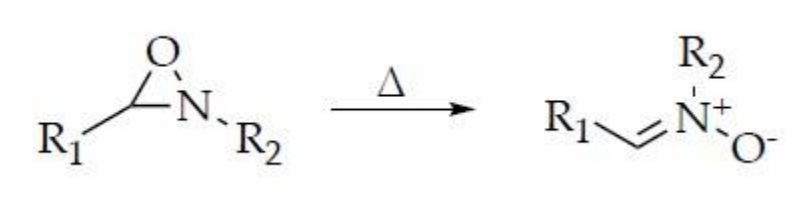


1.2 Methods for the Synthesis of Nitrones

Previously, nitrones have been synthesized from oxaziridines under thermal conditions. Due to the strain on the three-membered heterocycle containing a labile nitrogen-oxygen bond, the rearrangement to nitrone was made possible (Figure 4). Since this transformation can be accelerated by an increasing the thermal conditions, there was an observed direct conversion in high yields to nitrone with no need of additives or workup. Although this synthetic methodology was known, the construction of the starting oxaziridine was a major drawback, as we sought to develop a method that would be applicable for a library of compounds. The strained three-membered ring would not be able to tolerate a broad scope, which was the objective going forward.

Figure 4

Thermal Oxaziridine Rearrangement to Nitrone

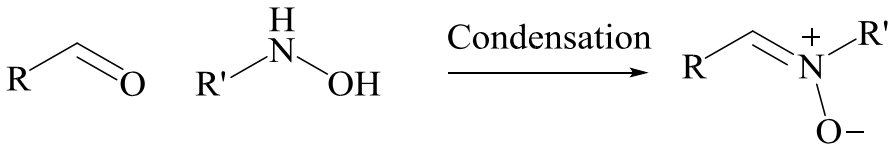


Additionally, it was noted in the literature that nitrones could be yielded via the mild oxidation of a tertiary hydroxylamine (Colladon, Scarso, & Strukul, 2008). This method has been proven to be valuable in a variety of different synthetic approaches as it allows the nitrone functional group to be introduced into a sterically hindered scaffold. The Moura Letts' Group has utilized this synthetic methodology, however when applied to the target library of molecular scaffolds, this synthetic method was low yielding and involved tedious work-up and purification.

In order to make the desired nitrone synthesis high-yielding, robust and applicable to the desired library of compounds, the Moura Letts' Group hypothesized that a conjugated-carbonyl condensation reaction with a hydroxylamine could be the most efficient synthetic route. In this methodology both R and R' are able to be functionalized by altering both the conjugated-carbonyl as well as the hydroxylamine source (Figure 5). After evaluating several literary sources, it was determined that this methodology would yield the desired vinyl-nitrones that were desired to carry out various different reactions.

Figure 5

Selective Carbonyl Condensation with a Hydroxylamine

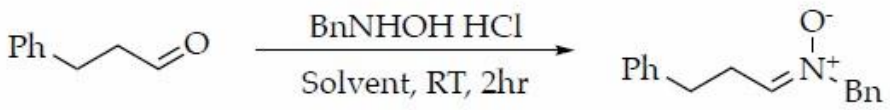


1.3 Results and Discussion

Since the Moura Letts' Group had previous experience in the realm of hydroxylamine chemistry, we sought to optimize a robust, high-yielding synthetic method for nitrones. This reaction was first optimized by employing various solvents and it was determined that polar-aprotic solvents were optimal for yielding the desired product (Table 1). The highest yields were seen utilizing acetonitrile and was therefore determined to be the most suitable solvent to perform this condensation reaction.

Table 1

Optimization of Nitrone Condensation Reaction



Entry	Solvent	Eq. Hydoxylmine	% Conversion*
1	DCM	1.0	65
2	Chloroform	1.0	59
3	THF	1.0	60
4	Ethyl Ether	1.0	24
5	MeCN	1.0	71
6	Benzene	1.0	15
7	Toluene	1.0	22
8	MeCN	1.5	80
9	MeCN	2.0	92
10	MeCN	3.0	96

*Determined by crude NMR

With the objective of utilizing these nitrones for the synthesis of a library of isoxazolidines as well as isoxazoloxazines, this work focuses primarily on the synthetic

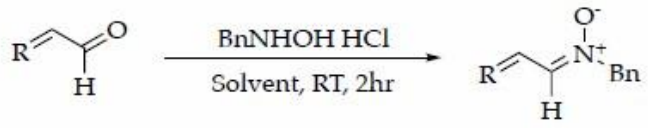
methods to produce nitrones from alpha-beta unsaturated carbonyls. Therefore going forward we employed a variety of both aliphatic and aromatic enals as the carbonyl source. In comparison to aromatic enals, the aliphatic enals displayed significantly lower yields. Since these results were consistent across all of the aliphatic enals, it was determined that this reaction needed to be re-optimized with the objective being to increase the yields for aliphatic enal substrates.

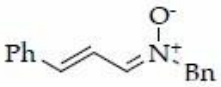
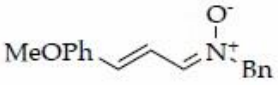
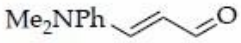
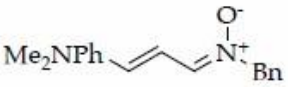
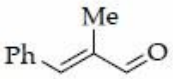
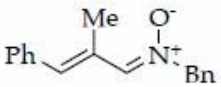
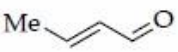
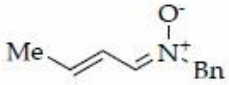
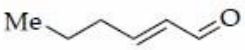
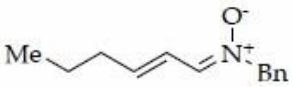
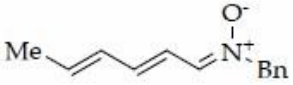
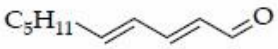
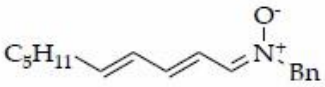
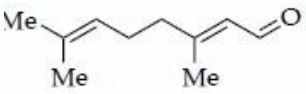
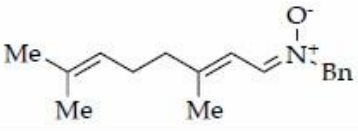
Acetonitrile is considered to be a polar organic solvent which allows for high solubility of the organic carbonyl. However, since the hydroxylamine is an inorganic salt, it is only slightly soluble in acetonitrile. Therefore during optimization an aqueous media was employed for aliphatic carbonyl sources to allow for a slow introduction of the starting aliphatic carbonyl to the aqueous hydroxylamine layer upon vigorous stirring. This methodology afforded significantly higher yields for aliphatic nitrones (Table 2).

All in all the rates of reactions we observed were significantly faster than the previously reported reactions with unsaturated or aromatic enals. When monitored by thin layer chromatography, the alpha-beta unsaturated nitrones showed full conversion in one hour (Table 2).

Table 2

Alpha-Beta Unsaturated Carbonyls to Nitrones



Enal	α-β unsaturated aldonitrone	Solvent	% Yield
		MeCN	82
		MeCN	95
		MeCN	56
		MeCN	62
		H_2O	68
		H_2O	70
		H_2O	85
		H_2O	90
		H_2O	92

1.4 Conclusion

Alpha-beta unsaturated aliphatic and aromatic enals were converted to their corresponding nitrones displaying a broad scope. Aromatic nitrones were afforded from aromatic alpha-beta unsaturated aldehydes through the use of acetonitrile as the solvent. Aliphatic nitrones were afforded from aliphatic alpha-beta unsaturated aldehydes by running the condensation on water, which allowed for the slow introduction of the organic carbonyl to the hydroxylamine. All in all, the chemoselectivity in this reaction can be of use to the industry as these reaction conditions are robust, high-yielding and can be applied to a broad scope of substrates.

1.5 Experimental

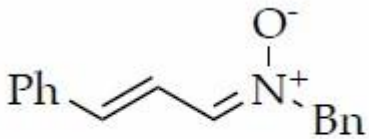
All of the reagents utilized in this experimentation were acquired from Aldrich Chemical, Acros Organics or Alfa Aesar and did not require further purification. All of the solvents used were obtained from EMD Miliphore DrySol and degassed with nitrogen to maintain inert reaction conditions. Reactions were performed in 4-ml glass vials with magnetic stirring. Thin layer chromatography analyses were performed on 0.25 mm E. Merck silica gel 60 F254 plates and observed under UV light (254 nm) and through staining with potassium permanganate (KMnO4). Silica flash chromatography analyses were performed on E. Merck 230–400 mesh silica gel 60. Automated chromatography was performed on an ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0–46100% EtOAc in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in CDCl3 unless otherwise indicated. Chemical shifts are denoted in ppm relative to solvent signals:

$CDCl_3$ (1H, 7.23 ppm; 13C, 77.0 ppm; coupling constants are expressed in Hz.

1.5.1. General Method for the Synthesis of Nitrones

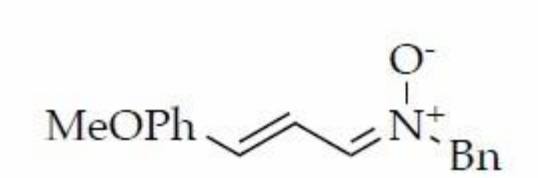
In a 4-mL reaction vial, the alpha-beta unsaturated carbonyl (1.0 mmol, 1.0 equivalent) and the Nbenzylhydroxylamine (1.1 mmol, 1.1 equivalent) were dissolved in 3 mL of acetonitrile. The reaction was stirred at RT for 2 hours or until complete conversion of starting material was confirmed by thin layer chromatography. The organic was extracted with diethyl ether, 3-50 mL aliquots. The organic layer was washed with 3-10 mL aliquots of aqueous (10%) sodium bicarbonate. The organic layer was dried with 3-10 mL aliquots of saturated aqueous brine solution (NaCl). The organic layer was isolated and dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford the crude product. The product was directly characterized unless traces of impurities required purification by automated silica gel flash chromatography.

1.5.2. Synthesis of Nitrones from Table 2



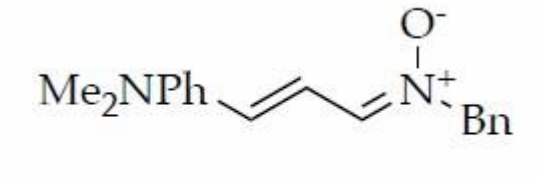
(T3A) DJQ-393

(1*Z*,2*E*)-*N*-benzyl-3-phenylprop-2-en-1-imine oxide (T3A) Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone **3a (**82% yield) as a white solid. **1H NMR** (400 MHz, Chloroform-*d*) δ 7.49 – 7.38 (m, 8H), 7.35 – 7.29 (m, 3H), 7.21 (dd, *J* = 9.5, 0.7 Hz, 1H), 6.94 (d, *J* = 16.3 Hz, 1H), 4.95 (s, 2H). **13C NMR** (101 MHz, Chloroform-*d*) δ 138.37 , 136.46 , 129.25 , 129.17 , 128.99, 128.97 , 128.81 , 127.28 , 118.40 , 69.29 .



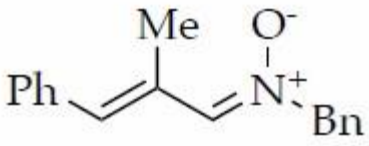
(T3B) DJQ-394

(1*Z*,2*E*)-*N*-benzyl-3-(4-methoxyphenyl)prop-2-en-1-imine oxide (T3A)
Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone **3b (**95% yield) as a white solid. **1H NMR** (400 MHz, Chloroform-*d*) δ 7.49 – 7.38 (m, 6H), 7.33 – 7.24 (m, 1H), 7.17 (dd, *J* = 9.5, 0.6 Hz, 1H), 7.00 – 6.77 (m, 3H), 4.93 (s, 2H), 3.80 (s, 3H). **13C NMR** (101 MHz, Chloroform-*d*) δ 160.53 , 138.20 , 136.80, 129.20 , 128.95 , 128.91 , 128.88 , 128.80 , 116.36 , 114.31 , 69.06 , 55.32 .



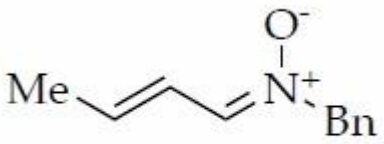
(T3C) DJQ-416

(1*Z*,2*E*)-*N*-benzyl-3-(4-(dimethylamino)phenyl)prop-2-en-1-imine oxide (T3C)
Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone **3c (**56% yield) as an orange solid. **1H NMR** (400 MHz, Chloroform-*d*) δ 7.44 – 7.36 (m, 6H), 7.29 – 7.22 (m, 1H), 7.14 (d, *J* = 9.6 Hz, 1H), 6.84 (d, *J* = 16.0 Hz, 1H), 6.66 – 6.60 (m, 2H), 4.91 (s, 2H), 2.97 (s, 6H). **13C NMR** (101 MHz, Chloroform-*d*) δ139.33 , 137.49 , 133.40 , 129.16 , 128.89 , 128.86 , 128.73 , 113.90 , 111.98 , 68.72 , 40.15



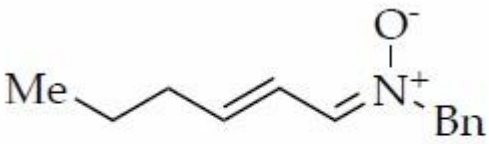
(T3D) DJQ-500

(1*Z*,2*E*)-N-benzyl-2-methyl-3-phenylprop-2-en-1-imine oxide (T3D) Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone 3c (56% yield) as an orange solid.



(T3E) DJQ-537

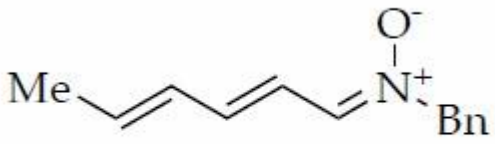
(1*Z*,2*E*)-*N*-benzylbut-2-en-1-imine oxide (T3C) Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone **3e (**68% yield) as pale oil. **1H NMR** (400 MHz, Chloroform-*d*) δ 7.37 (dtt, *J* = 5.2, 3.3, 2.0 Hz, 5H), 6.98 (d, *J* = 9.4 Hz, 1H), 6.81 – 6.70 (m, 1H), 6.20 (dq, *J* = 16.0, 7.0 Hz, 1H), 4.86 (s, 2H), 1.86 (dd, *J*= 6.9, 1.7 Hz, 3H). **13C NMR** (101 MHz, Chloroform-*d*) δ 138.21 , 136.08 , 129.17 ,128.89 , 128.83 , 122.35 , 68.90 , 19.01 .



(T3F) DJQ-421

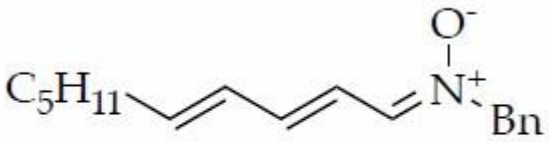
(1*Z*,2*E*)-*N*-benzylhex-2-en-1-imine oxide (T3F) Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone **3f (**70% yield) as a pale oil. **1H NMR** (400 MHz, Chloroform-*d*) δ 7.40 (dtd, *J* = 5.6, 2.7, 1.3 Hz, 4H), 6.98 (d, *J* = 9.4Hz, 1H), 6.76 (ddt, *J* = 15.9, 9.5, 1.6 Hz, 1H), 6.19 (dt, *J* = 15.6, 7.1 Hz, 1H), 4.88 (s,2H), 2.17 (qd, *J* = 7.2, 1.6 Hz, 2H), 1.49 – 1.41 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). **13CNMR** (101

MHz, Chloroform-*d*) δ 143.37 , 136.29 , 129.25 , 128.91 , 128.86 , 121.13 ,68.93 , 35.34 , 21.81 , 13.67 .



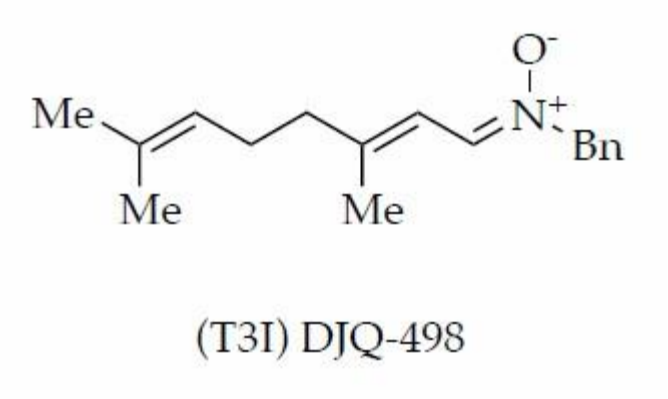
(T3G) DJQ-421

(1Z,2E,4E)-N-benzylhexa-2,4-dien-1-imine oxide (T3G) Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone 3g (85% yield) as a white solid.



(T3H) DJQ-586

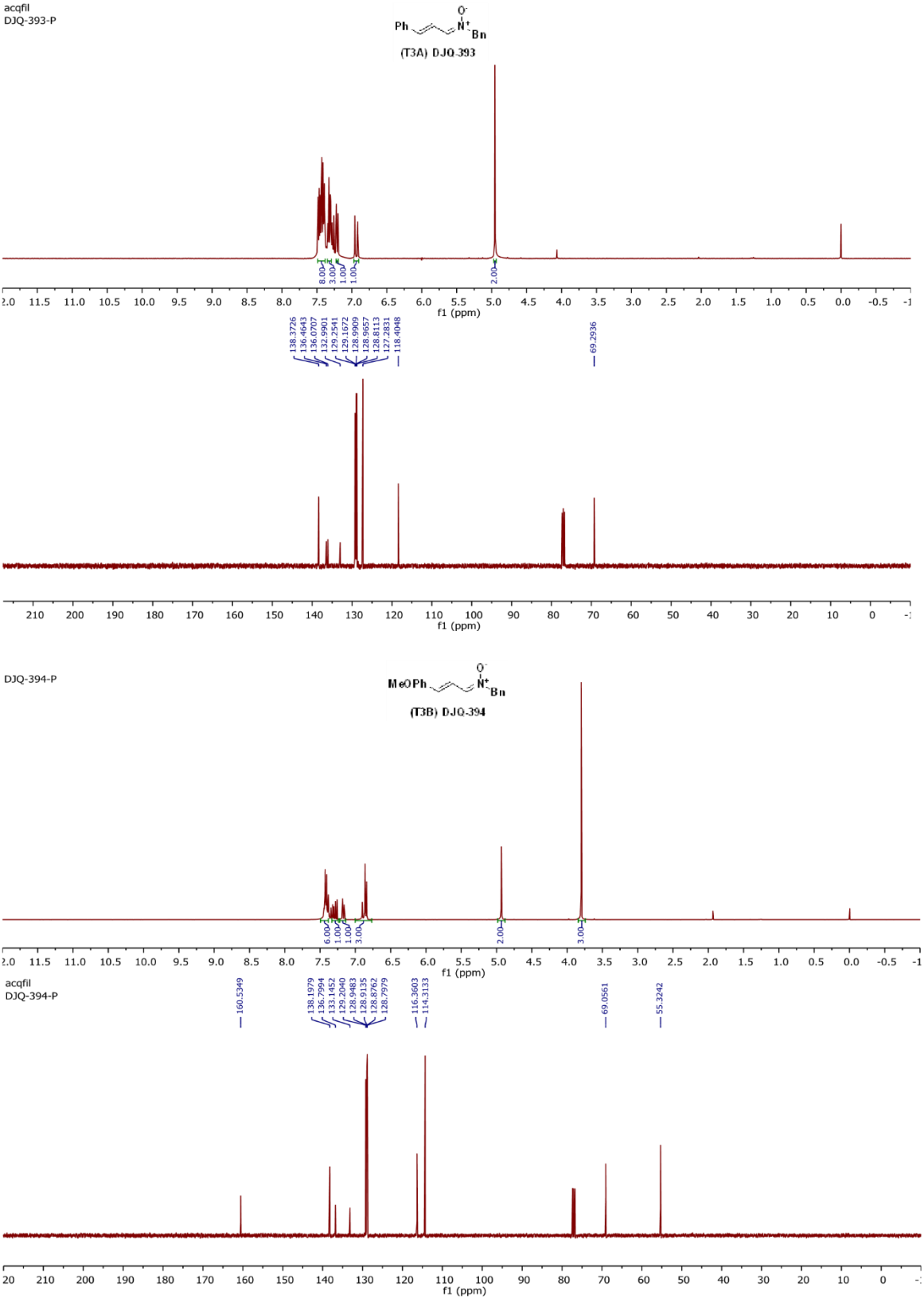
(1*Z*,2*E*,4*E*)-*N*-benzyldeca-2,4-dien-1-imine oxide (T3H) Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone **3h (**90% yield) as a white solid.

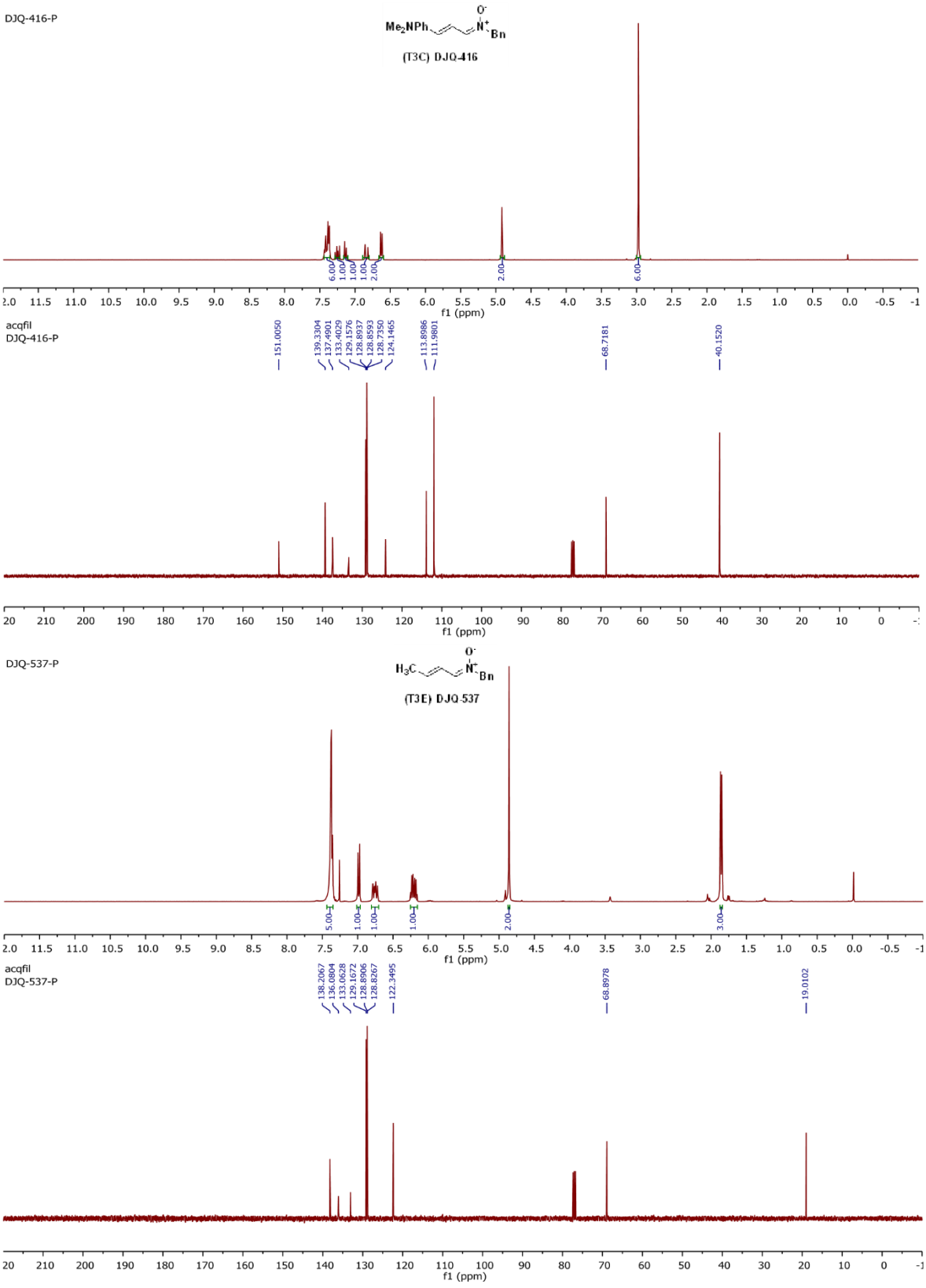


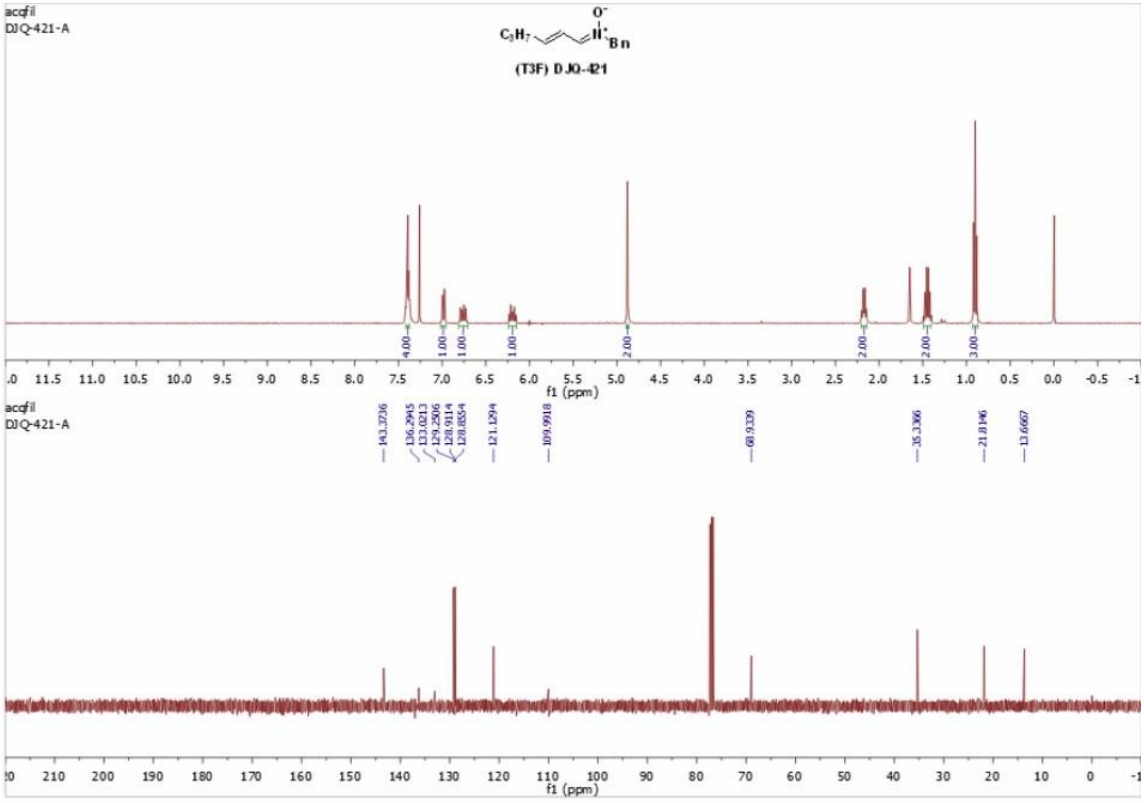
(T3I) DJQ-498

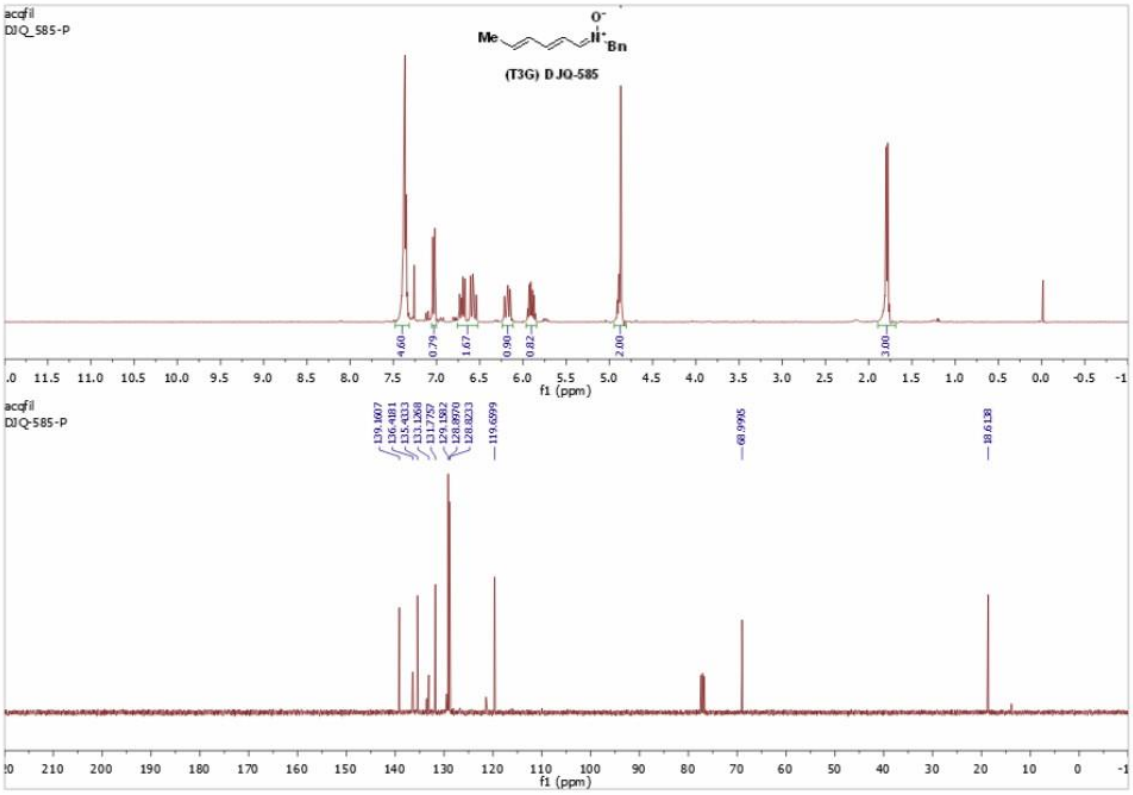
(1*Z*,2*E*)-*N*-benzyl-3,7-dimethylocta-2,6-dien-1-imine oxide (T3I) Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 Heptanes/EtOAc over 12 min) afforded the nitrone **3i (**92%yield) as a yellow oil. **1H NMR** (400 MHz, Chloroform-*d*) δ 7.43 – 7.37 (m, 4H), 7.22(d, *J* = 10.0 Hz, 1H), 6.60 (dq, *J* = 10.0, 1.3 Hz, 1H), 5.06 (ddtd, *J* = 5.6, 4.3, 2.7, 1.3Hz, 1H), 4.90 (s, 2H), 2.16 (q, *J* = 5.8, 4.2 Hz, 4H), 1.76 (d, *J* = 1.2 Hz, 3H), 1.68 – 1.65(m, 3H), 1.58 (d, *J* = 1.3 Hz, 3H). **13C NMR** (101 MHz, Chloroform-*d*) δ 149.91 ,133.81 , 133.34 , 129.05 , 128.85 , 128.74 , 123.18 , 115.87 , 69.11 , 40.37 , 26.28 , 25.64, 17.93 , 17.68.

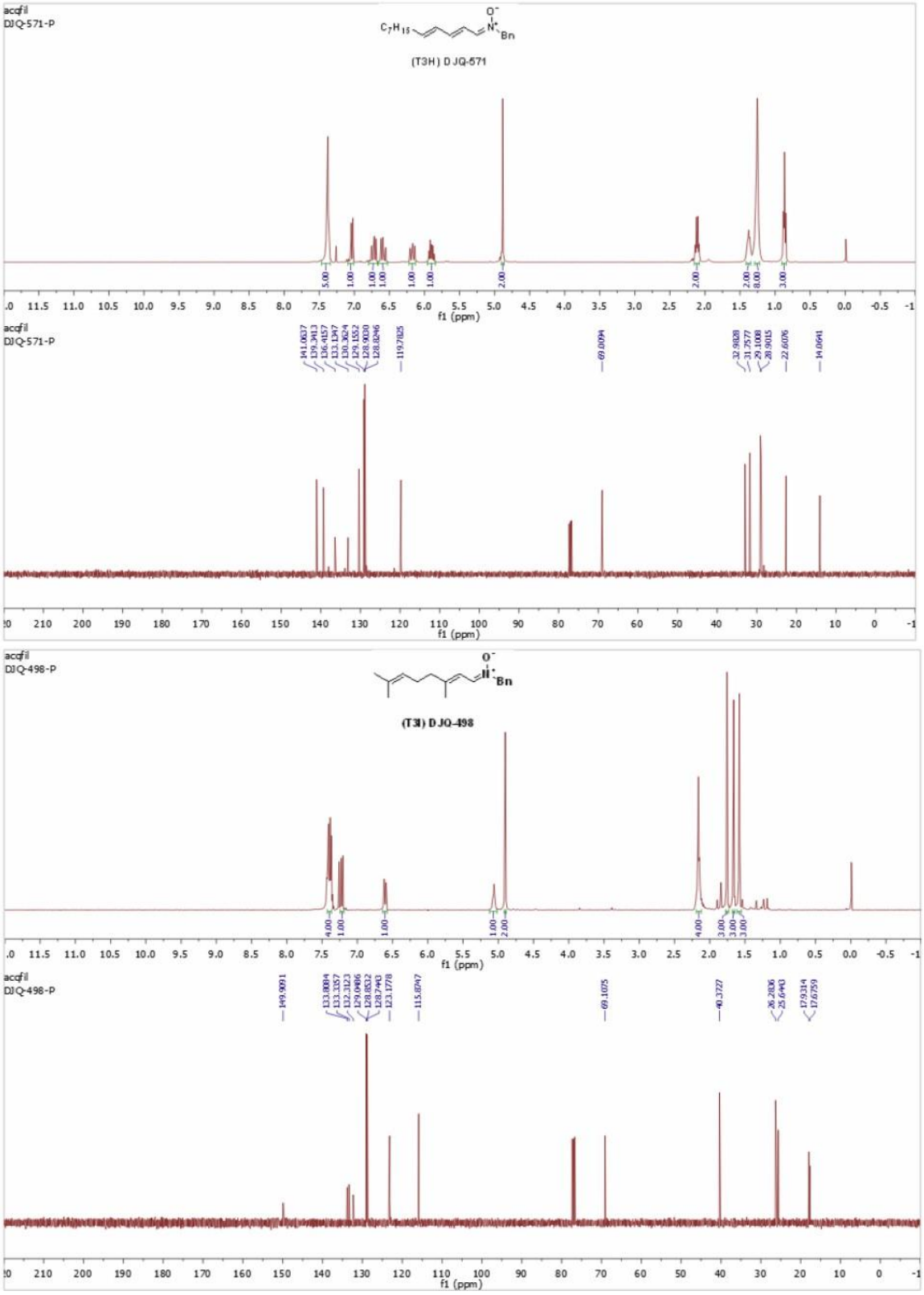
1.5.3. ^{1}H NMR and ^{13}C NMR of Nitrones











Chapter 2

The Dipolar Cycloaddition of Nitrones to Isoxazolidines

Isoxazolidines have been isolated as natural products, identified as important synthetic intermediates and resemble natural biological compounds. The potential value that isoxazolidines have as therapeutic agents has been recognized in multiple literary sources (Section 2.2). The isoxazolidine moiety consists of a 5-membered heterocylic ring containing a nitrogen-oxygen bond. These compounds have been synthesized from nitrones through a dipolar cycloaddition with various dipolarophiles (Ricci, Gioia, Fini, Mazzanti, & Bernardi, 2009). This synthetic methodology is known to be one of the most essential synthetic methods for the nitrone moeity (Hashimoto & Maruoka, 2015). There have been limitations recorded in the literature for this synthetic method, therefore we sought to develop a robust, regioselective synthesis to create a library of isoxazolidines from nitrones.

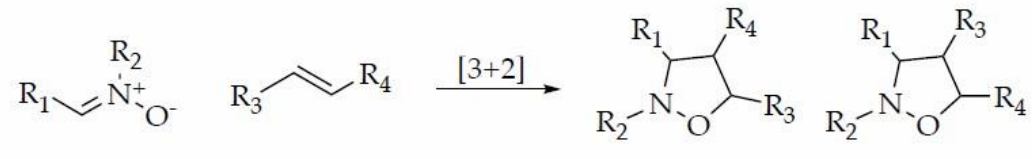
2.1 Limitations of the Dipolar Cycloaddition

The 1,3-dipolar cycloaddition of nitrones with a variety of alpha-beta unsaturated aldehydes has been identified as a successful mechanism for the synthesis of highly functionalized isoxazolidines. Although these methods have been explored, there was not an existing mechanism that could predict which regioisomers and diastereomers would be formed from these reactions. There are several different factors contributing to misconceptions in the regioselectivity of these reactions. The most significant contributing

factor influencing the regioselectivity are the electronic effects of both the dipole and the dipolarophile utilized in the cycloaddition (Figure 6).

Figure 6

Possible Regioisomers Produced by the 1,3-Dipolar Cycloaddition



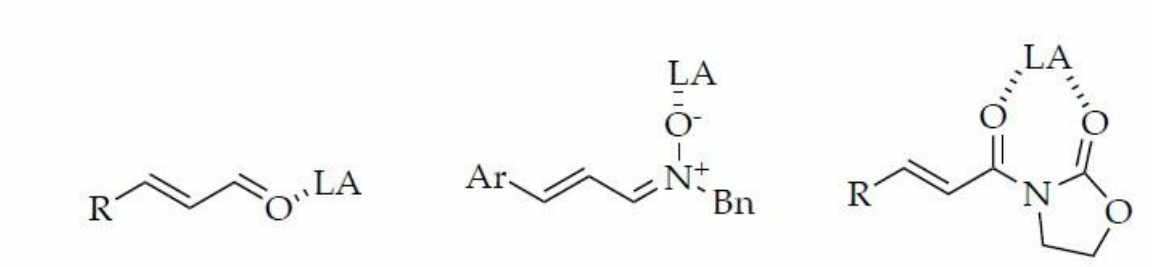
There have been contradicting arguments within the literature about the regioselectivity of the dipole-dipolarophile interaction (Barba, C., Carmona, D., Garcia, J. I., *et al.* 2006). One of the major contributing factors to regioselectivity of this reaction is the electronic interactions between the nitrone dipole and the dipolarophile. The effects of asymmetric dipolarophiles with varying electronic directionality results in a mixture of regioisomers, the 3,4-isoxazolidine and the 3,5-isoxazolidine. Computational efforts have displayed a bias for the 3,5-isoxazolidine with carbonyls and cyano groups as the dipolarophile while the 3,4-isoxazolidine product is typically in produced in higher yields when employing an electron withdrawing group (Barba, C., Carmona, D., Garcia, J. I., *et al.* 2006).

Efforts to improve the regioselectivity of this reaction include the utilization of Lewis Acid catalysts. The major challenge of reactions employing Lewis Acid promoters for dipolar cycloadditions is that the oxygen of the nitrone dipole has the ability to react

as a strong base and thus has a high binding affinity for the catalyst. Therefore, the nitrone competes with the dipolarophile causing reduced yields for the desired product. In order to increase binding affinity for the dipolarophile to the Lewis Acid catalyst, alpha-beta unsaturated aldehydes and ketones having bidentate or tridentate structures have been utilized (Figure 7). In the presence of bidentate or tridentate dipolarophiles, nitrones are unable to compete to bind to the catalyst which can increase yields for the desired isozaxolidines (Barroso, S., Blay, G., Munoz, M. C., *et al.* 2011).

Figure 7

Dipolarophile (left), Nitrone (center), Bidentate Dipolarophile (left) with Increasing Binding Affinity from Left to Right



Essentially, reviewing the techniques that researchers have utilized to overcome the limitations of this reaction is essential for improving the methodology. The demand for a robust synthesis which allows for the prediction of regioselectivity still remains due to the pharmaceuticalrelevance of the isoxazolidine scaffold.

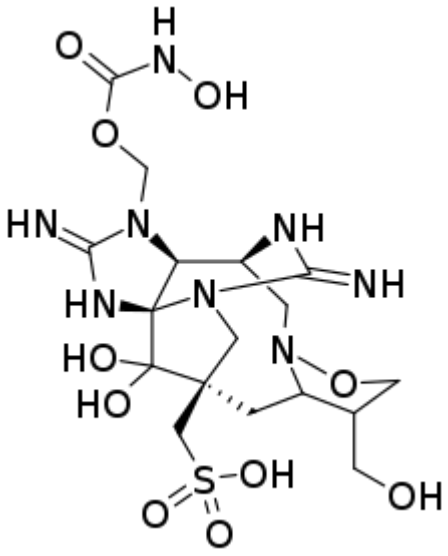
2.2 Biological Significance of Isoxazolidine Scaffolds

Isoxazolidines have been recognized as privileged scaffolds in the fields of both organic chemistry and medicinal chemistry. The isoxazolidine moiety has been isolated from several natural products, has been utilized in the synthesis of antimicrobial agents and shows potential for biological activity as it mimics the natural structures of nucleosides, carbohydrates, amino acids as well as some steroid analogs.

The isoxazolidine scaffold has been extremely useful in the synthesis of natural products as it has been isolated from a variety of different species. Zetekitoxin AB was the first alkaloid containing the isoxazolidine moiety extracted from a natural source; the *Atelopus Zetecki* a Panamanian frog species (Figure 8). This guanidine alkaloid functions as a neurotoxin as it blocks voltage-gated sodium channels (Yotsu-Yamashita, M., Kim, Y. H., Dudley, S. C. *et al.* 2004). The five-membered heterocycle has also been extracted from the *Alstonia pneumatophore* as Alsmaphorazin A; identified as an inhibitor of nitric oxide production by lipopolysaccharide stimulated macrophages (Koyama, K., Hirasawa, Y., Nugroho, A. E., Hosoya, T., Hoe, T. C., Chan, K.-L., Morita, H. 2010).

Figure 8

Zetekitoxin AB



Beta-Lactams have been synthesized utilizing the isoxazolidine scaffold as an important synthetic intermediate. Van Berkon *et al.* first developed the method to transform the isoxazolidine moiety through a base-induced ring contraction of nitrosoacetal, a 5,6,5-fused heterocyclic ring system. The mechanism then involved the base-indeucd lactam deprotonation followed by the reductive cleavage of the nitrogen oxygen bond to afford the desired beta-lactam (van Berkom, L. W. A., Kuster, G. J. T., de Gelder, R., Scheeren, H. W. 2004). Several other synthetic approaches to antimicrobial agents have been furthermore developed utilizing the isoxazolidine moiety contributing to its pharmaceutical relevance.

2.3 Results and Discussion

The development of a library of 3-vinyl-4-formylisoxazolidines as well as 3vinyl-5-formylisoxazolidines utilizing a 1,3-dipolar cycloaddition was an objective of high importance to the Moura Letts' Group due to the pharmaceutical relevance of the isoxazolidine scaffold. The nitrones utilized as the dipoles for the 1,3-dipolar cycloadditions were formed through the selective condensation of alpha-beta unsaturated carbonyls. Since these nitrones have been fully isolated and characterized throughout the works of this paper, their usage as a reaction intermediate in the development of this method is strongly referenced.

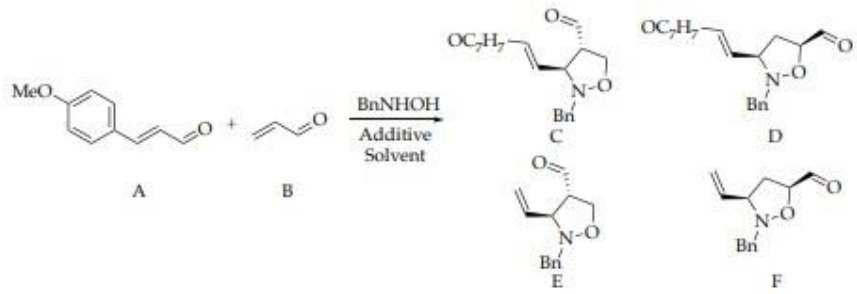
In our beginning reactions we observed that hydroxylamines undergo selective condensation with alpha-beta unsaturated carbonyls without the need for troublesome purifications. We envisioned that by introducing a more reactive alpha-beta unsaturated carbonyl in excess, we could utilize the steric effects of the dipolarophile and electronic effects of the nitrone to develop a method to determine which product would be produced. Therefore, during the initial optimization studies we reacted Nbenzylhydroxylamine with excess acrolein in attempt to perform both the selective condensation and 1,3-dipolar cycloaddition in one-pot. All in all we found that the 3vinyl-4-formylisoxazolidine was produced in a 20% yield and the 3-vinyl-5formylisoxazolidine was produced in a 2% yield (Table 3-Entry-1). Furthermore, we hypothesized that by first allowing a more bulky enal (Table 3-A) to undergo selective condensation with N-benzylhydroxylamine and then introducing the more reactive dipolarophile acrolein (Table 3-B), we could achieve the desirable chemeoselectivity (Table 3- Entry 4).

Once the optimal enal-dipolarophile pair was discovered, we wanted to determine what conditions would promote better conversions while increasing diastereoselectivity. First we explored the thermal activation of this cycloaddition and found that by increasing the temperature to 80°C resulted in both increased reactivity and increased diastereoselectivity (Table 3, Entry 7). Additionally, we employed several polar aprotic solvents and determined that acetonitrile was optimal for these reaction conditions (Table 7, Entries 7 and 9-11).

In an attempt to lower the thermal conditions required for this reaction, we investigated some Lewis Acid metal catalysts. Although the reaction proceeded at an accelerated rate by utilizing 20 molar percent copper triflate, there was a decrease in regioselectivity and percent yield (Table 3-Entries 12-16). Since regioselectivity and increased yield were the main objectives in optimizing these reactions, the thermal conditions remained the most practical approach.

Table 3

Optimization of the One-Pot Condensation-Cyclization



Entry[a]	Enal	Dipolarophile	Additive[e]	Solvent	Time	Temperature	%Yield of C:D:E:F[b]	d.r[c]
1	B	B	none	Acetonitrile	48h	rt	0:0:20:2	8:1
2	B[d]	A	none	Acetonitrile	48h	rt	5:1:10:2	8:1
3	B	A	none	Acetonitrile	48h	rt	8:2:6:2	6:1
4	A	B	none	Acetonitrile	48h	rt	40:4:0:0	10:1
5	A	B	none	Acetonitrile	48h	40 °C	53:6:0:0	15:1
6	A	B	none	Acetonitrile	16h	60 °C	64:9:0:0	15:1
7	A	B	none	Acetonitrile	16h	80 °C	88:4:0:0	15:1
8	A	B	none	Acetonitrile	18h	90 °C	80:16:0:0	10:1
9	A	B	none	dioxane	16h	80 °C	80:4:0:0	15:1
10	A	B	none	DCE	16h	80 °C	73:8:0:0	15:1
11	A	B	none	DMF	16h	80 °C	64:12:0:0	15:1
12	A	B	$Cu(OTf)_2$	Acetonitrile	6h	rt	64:28:0:0	20:1
13	A	B	$Cu(OAc)_2$	Acetonitrile	6h	rt	35:24:0:0	20:1
14	A	B	AgOTf	Acetonitrile	6h	rt	53:22:0:0	20:1
15	A	B	AuOTf	Acetonitrile	6h	rt	48:20:0:0	15:1
16	A	B	$Fe(OTf)_3$	Acetonitrile	6h	rt	46:32:0:0	15:1

a. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. b. Isolated yields. c. Ratio for the major isomer, measured by ^{1}H-NMR. d. ratio of enal:dipolarophile is 1:1. e. Lewis acid were added in 20 mol%.

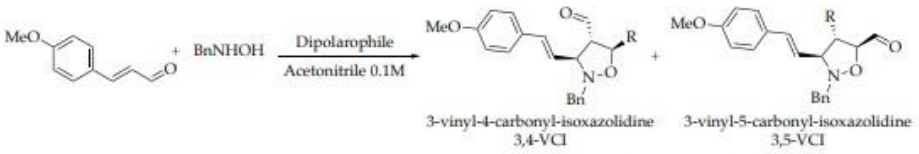
Once the reaction was optimized we sought to create a library of isoxazolidines employing various dipolarophiles to access the generality of the reaction. Trans-4methoxycinnamaldehyde afforded optimal yields for the cycloaddition therefore we utilized it as the enal for the cycloadditions. We were able to successfully react a variety of simple enals and enones as suitable dipolarophiles. The diplarophiles substituted at the beta position of the alphabeta unsaturated carbonyls provided the 3-vinyl-4-

formylisoxazolidine regioisomer with trace amounts of other regioisomer detected (Table 4, Entries 1-3). Oppositely, dipolarophiles substituted at the alpha position afforded the 3-vinyl-5-formylisoxazolidine regiosomer with complete selectivity. Although there was an increase in regioselectivity for these dipolarophiles, some diastereoselectivity was compromised (Table 4, Entries 4-7).

After we determined the generality of this reaction by employing simple enals and enones as the dipolarophile, we wanted to attempt cyclization with alternative carbonyl derivatives. Acrylonitrile; similarly to the unsubstituted carbonyl acrolein, displayed complete selectivity for the 3,4-isoxazolidine regioisomer (Table 5, Entry 1). Additionally, diesters adopted the 3,4isoxazolidine regiosomer with complete selectivity and increase diastereoselectivity due to their symmetric structure (Table 5, Entries 4 and 5). Esters methyl methacrylate and tert-butyl acrylate showed complete selectivity for the 3,5-isoxazolidine regioisomer similar to the alpha substituted dipolarophiles utilized previously (Table 5, Entries 2 and 3).

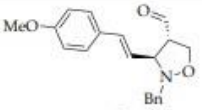
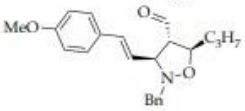
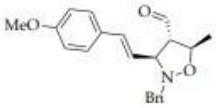
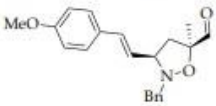
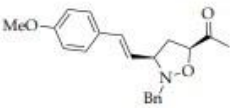
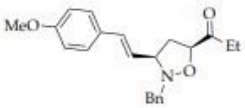
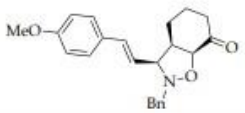
Table 4

Dipolarophile Scope: Simple Enals and Enones



3-vinyl-4-carbonyl-isoxazolidine 3,4-VCI

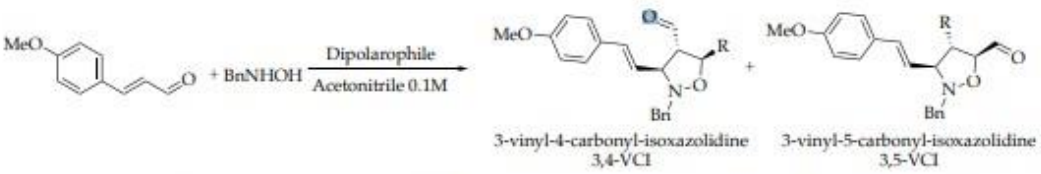
3-vinyl-5-carbonyl-isoxazolidine 3,5-VCI

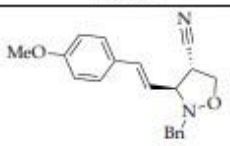
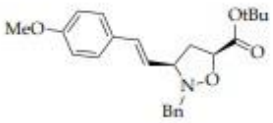
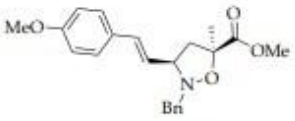
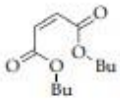
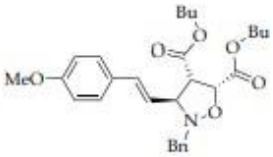
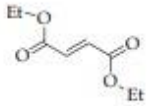
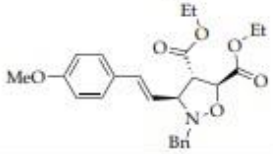
Dipolarophile	Product	%Yield of 3,4-VCI[2]	%Yield of 3,5-VCI[2]	d.r.[3]
		88	4	15:1
		90	2	16:1
		84	4	15:1
		0	91	12:1
		0	90	12:1
		0	92	12:1
		0	73	12:1

1. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. 2. Isolated yields. 3. Ratio for the major isomer, measured by ^{1}H-NMR.

Table 5

Dipolarophile Scope: Nitriles and Esters



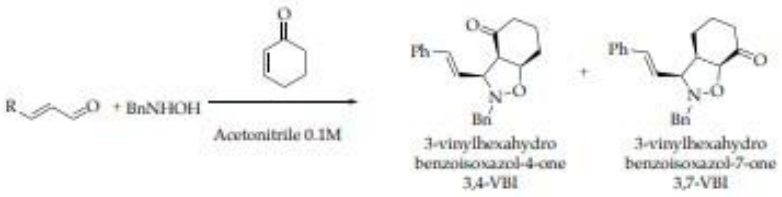
Dipolarophile	Product	%Yield of 3,4-VCI[2]	%Yield of 3,5-VCI[2]	d.r.[3]
		95	0	15:1
		0	91	16:1
		0	84	15:1
		88	0	18:1
		89	0	18:1

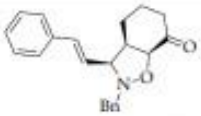
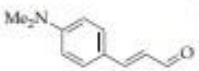
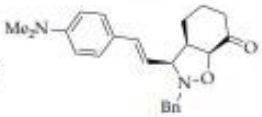
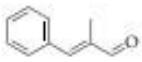
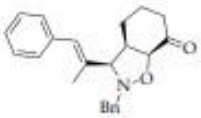
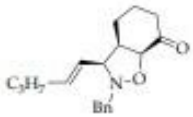
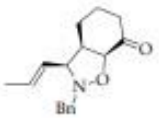
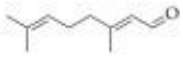
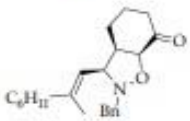
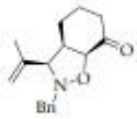
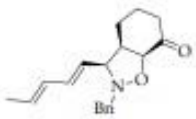
1. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. 2. Isolated yields. 3. Measured by ^{1}H-NMR.

We next sought to broaden the scope by employing different enals to assess the electronic effects of the nitrone during cyclization. Upon employing cyclohexenone as the dipolarophile for these reactions, we saw complete selectivity for the 3,7-VBI confirmation (Table 6).

Table 6

Enal Scope



Enal	Product	% of 3,4-VBI[2]	% of 3,7-VBI[2]	d.r.[3]
		0	73	15:1
		0	79	16:1
		0	69	15:1
		0	84	12:1
		0	86	12:1
		0	79	12:1
		0	84	16:1
		0	80	14:1

1. Ratio of enal:dipolarophile:hydroxylamine, 1:2:1. 2. Isolated yields. 3. Measured by ^{1}H-NMR.

2.4 Conclusion

A one-pot synthetic method was developed for the condensation and cyclization of nitrones from alpha-beta unsaturated carbonyls. This method is significant because the scope applies to a variety of enals, enones, nitriles and esters. Additionally, this method is appealing because it does not require troublesome purifications. Ultimately it was determined that the regioselectivity could be predicted based upon the substitution pattern of the dipolarophile used in excess for the 1,3-dipolar cycloaddition.

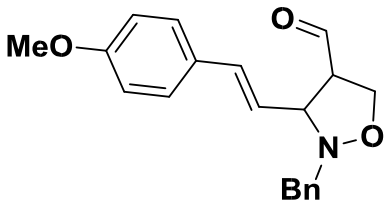
2.5 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Solvents were obtained from EMD Miliphore DrySol and degassed with nitrogen. Reactions were performed in 4-mL glass vials with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate (KMnO4). Silica flash chromatography was performed on E. Merck 230–400 mesh silica gel 60. Automated chromatography was performed on a ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0–20% EtOAc in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in CDCl3 unless otherwise indicated. Chemical shifts are expressed in ppm 74 relative to solvent signals: CDCl3 (1H, 7.23 ppm; 13C, 77.0 ppm; coupling constants are expressed in Hz).

2.5.1. General Method for the Synthesis of Vinyl-Isoxazolidines

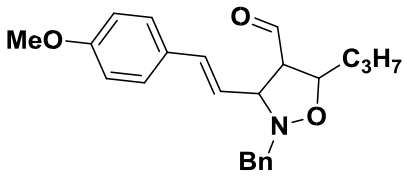
In a 4- mL glass vial, 1 mMol enal and 1.1 eq. hydroxylamine were dissolved in 1 mL acetonitrile. The mixture was stirred at room temperature for five minutes after which 3 molar equivalents dipolarphile was added. The reaction was stirred vigorously at 80°C for 16hours. The organic was extracted with 150 mL diethyl ether. The organic layer was washed with 3-25 mL aliquots of (10%) aqueous sodium bicarbonate. The organic layer was dried with 3-25 mL aliquots of saturated aqueous brine solution (NaCl). The organic layer is finally isolated and dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation to afford the crude product. The crude product is filtered through silica gel over a gradient of 4:1 Heptanes/EtOAc over 12 column volumes to obtain the respective isoxazolidine in good to excellent yields.

2.5.2. Synthesis of Vinyl-Isoxazolidines from Table 4



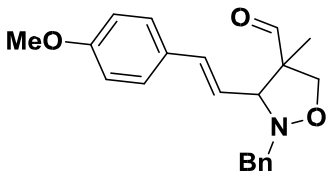
(T2A) DJQ-605

(E)-2-benzyl-3-(4-methoxystyryl)isoxazolidine-4-carbaldehyde(T2A): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2a** (115 mg, 90%) as a yellow oil. **TLC**: R_f 0.20 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 9.76 (dd, J = 2.4, 0.6 Hz, 1H), 7.38 – 7.32 (m, 6H), 7.29 (d, J = 10.0 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.61 (d, J = 15.8 Hz, 1H), 6.09 (dd, J = 15.8, 8.5 Hz, 1H), 4.24 (dd, J = 8.9, 4.0 Hz, 1H), 4.16 – 4.09 (m, 2H), 3.82 (d, J = 0.6 Hz, 3H), 3.78 (d, J = 14.1 Hz, 1H), 3.63 (d, J = 7.4 Hz, 1H), 3.35 – 3.29 (m, 1H). **13C NMR** (101 MHz, CDCl3) δ 198.86, 134.58, 128.81, 128.29, 127.85, 127.71, 127.33, 114.06, 65.49, 61.65, 55.30, 30.89.



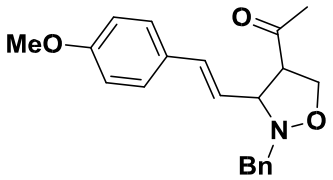
(T2B) DJQ-407

(E)-2-benzyl-3-(4-methoxystyryl)-5-propylisoxazolidine-4-carbaldehyde (T2B): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2b** (100 mg, 70%) as a yellow oil. **TLC**: Rf 0.38 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 9.75 (dd, J = 2.7, 0.7 Hz, 1H), 7.52 – 7.24 (m, 7H), 6.96 – 6.84 (m, 2H), 6.54 (d, J = 15.8 Hz, 1H), 6.06 (dd, J = 15.7, 8.5 Hz, 1H), 4.51 – 4.17 (m, 1H), 4.13 (d, J = 14.3 Hz, 1H), 3.81 (d, J = 0.7 Hz, 3H), 3.77 – 3.61 (m, 1H), 3.01 (ddd, J = 7.8, 5.4, 2.7 Hz, 1H), 1.87 (dddd, J = 13.4, 9.7, 7.8, 5.6 Hz, 1H), 1.60 (ddt, J = 13.5, 9.6, 5.9 Hz, 1H), 1.47 – 1.30 (m, 2H), 0.93 (td, J = 7.4, 3.1 Hz, 3H). **13C NMR** (101 MHz, CDCl3) δ 198.89, 133.85, 128.55, 128.16, 127.81, 127.08, 123.69, 114.03, 76.92, 67.75, 55.30, 37.26, 19.16, 13.87.



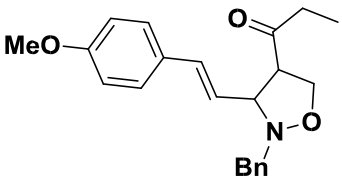
(T2C) DJQ-415

(E)-2-benzyl-3-(4-methoxystyryl)-4-methylisoxazolidine-4-carbaldehyde (T2C): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2c** (165 mg, 90%) as a yellow oil. **TLC**: Rf 0.35 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 9.59 (s, 1H), 7.39 (d, *J* = 7.1 Hz, 2H), 7.35 – 7.29 (m, 4H), 7.25 (tt, *J* = 6.0, 1.6 Hz, 1H), 6.93 – 6.78 (m, 2H), 6.53 (d, *J* = 15.8 Hz, 1H), 5.89 (ddd, *J* = 15.8, 8.8, 0.6 Hz, 1H), 4.19 (d, *J* = 14.8 Hz, 1H), 3.81 (d, *J* = 0.6 Hz, 3H), 3.76 (d, *J* = 14.8 Hz, 1H), 3.43 (q, *J* = 8.3 Hz, 1H), 2.52 (dd, *J* = 12.7, 7.8 Hz, 1H), 2.25 (dd, *J* = 12.7, 8.4 Hz, 1H), 1.30 (s, 3H). **13C NMR** (101 MHz, CDCl3) δ 205.12, 133.59, 128.35, 128.18, 127.72, 127.08, 124.71, 114.02, 69.67, 59.15, 55.30, 44.00, 19.07.



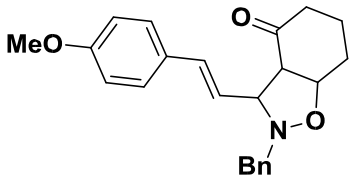
(T2D) DJQ-410

(E)-1-(2-benzyl-3-(4-methoxystyryl)isoxazolidin-4-yl)ethan-1-one (T2D): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2d** (180 mg, 80%) as a yellow oil. **TLC**: Rf 0.45 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.39 (d, *J* = 7.1 Hz, 2H), 7.34 (ddd, *J* = 4.3, 2.5, 1.3 Hz, 4H), 7.29 – 7.23 (m, 1H), 6.92 – 6.82 (m, 2H), 6.56 (d, *J* = 15.8 Hz, 1H), 5.92 (dd, *J* = 15.8, 8.6 Hz, 1H), 4.29 (dd, *J* = 9.5, 4.7 Hz, 1H), 4.18 (d, *J* = 14.1 Hz, 1H), 3.81 (d, *J* = 0.8 Hz, 3H), 3.70 (d, *J* = 14.1 Hz, 1H), 3.35 (q, *J* = 8.3 Hz, 1H), 2.72 (ddd, *J* = 12.8, 9.4, 7.8 Hz, 1H), 2.39 (ddd, *J* = 13.0, 8.5, 4.7 Hz, 1H), 2.11 (d, *J* = 0.8 Hz, 3H). **13C NMR** (101 MHz, CDCl3) δ 133.80, 128.91, 128.14, 127.71, 127.21, 124.54, 114.04, 80.49, 69.42, 59.76, 55.30, 39.01, 25.38.



(T2E) DJQ-464

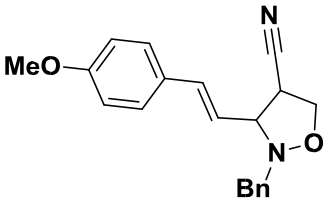
(E)-1-(2-benzyl-3-(4-methoxystyryl)isoxazolidin-4-yl)propan-1-one (T2E): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2e** (105 mg, 70%) as a pale oil. **TLC**: Rf 0.50 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.41 – 7.22 (m, 8H), 6.89 – 6.83 (m, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 5.91 (dd, *J* = 15.9, 8.5 Hz, 1H), 4.33 (dd, *J* = 9.4, 4.9 Hz, 1H), 4.16 (d, *J* = 14.1 Hz, 1H), 3.81 (d, *J* = 0.7 Hz, 3H), 3.70 (d, *J* = 14.1 Hz, 1H), 3.35 (q, *J* = 8.3 Hz, 1H), 2.76 – 2.68 (m, 1H), 2.65 – 2.56 (m, 1H), 2.47 (ddd, *J* = 11.5, 7.2, 4.4 Hz, 1H), 2.42 – 2.36 (m, 1H), 0.95 (td, *J* = 7.3, 0.6 Hz, 3H). **13C NMR** (101 MHz, CDCl3) δ 159.51, 137.57, 133.73, 128.89, 128.10, 127.69, 127.19, 124.59, 114.01, 69.45, 59.76, 55.30, 39.09, 30.54, 7.13.



(T2F) DJQ-397

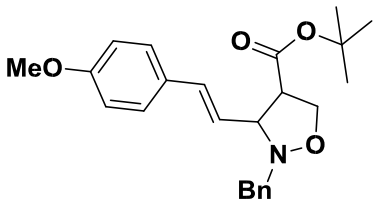
(E)-2-benzyl-3-(4-methoxystyryl)hexahydrobenzo[d]isoxazol-4(2H)-one (T2F): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2f** (110 mg, 65%) as a yellow oil. **TLC**: Rf 0.15 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.41 – 7.35 (m, 2H), 7.35 – 7.27 (m, 4H), 7.25 – 7.21 (m, 1H), 6.88 – 6.82 (m, 2H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.10 – 6.01 (m, 1H), 4.57 (dt, *J* = 7.7, 4.3 Hz, 1H), 4.10 (d, *J* = 14.1 Hz, 1H), 3.88 – 3.79 (m, 5H), 3.00 (t, *J* = 6.7 Hz, 1H), 2.51 (dt, *J* = 17.0, 5.1 Hz, 1H), 2.34 (ddd, *J* = 16.6, 10.2, 6.1 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.96 – 1.88 (m, 2H), 1.87 – 1.79 (m, 1H). **13C NMR** (101 MHz, CDCl3) δ 137.48, 133.11, 128.95, 128.20, 127.74, 127.19, 125.05, 113.94, 70.51, 60.81, 55.28, 39.92, 26.47, 19.05.

2.5.3. Synthesis of Vinyl-Isoxazolidines from Table 5



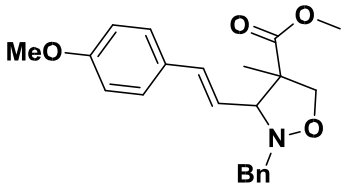
(T3A) DJQ-462

(E)-2-benzyl-3-(4-methoxystyryl)isoxazolidine-4-carbonitrile (T3A): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2g** (80 mg, 90%) as a pale oil. **TLC**: Rf 0.20 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.42 – 7.38 (m, 2H), 7.36 – 7.24 (m, 5H), 6.95 – 6.83 (m, 2H), 6.68 (d, *J* = 15.8
Hz, 1H), 6.20 (dd, *J* = 15.8, 8.9 Hz, 1H), 4.30 (t, *J* = 8.6 Hz, 1H), 4.18 (d, *J* = 14.3 Hz, 1H), 4.08 (dd, *J* = 8.4, 6.7 Hz, 1H), 3.82 (d, *J* = 0.5 Hz, 3H), 3.71 (d, *J* = 14.3 Hz, 1H), 3.61 (td, *J* = 8.5, 6.7 Hz, 1H), 3.51 (t, *J* = 8.2 Hz, 1H). **13C NMR** (101 MHz, CDCl3) δ 136.95, 136.61, 128.74, 128.44, 128.30, 128.22, 127.46, 119.86, 114.09, 69.99, 68.68, 55.33, 38.48.



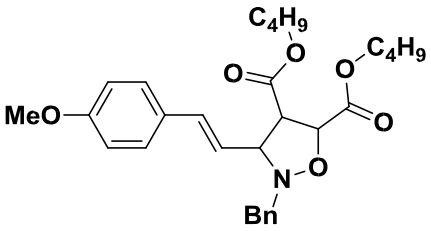
(T3B) DJQ-463

Tert-butyl (E)-2-benzyl-3-(4-methoxystyryl)isoxazolidine-4-carboxylate (T3B): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2h** (90 mg, 90%) as a pale oil. **TLC**: Rf 0.56 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.44 – 7.40 (m, 2H), 7.31 (dd, *J* = 8.3, 6.0 Hz, 4H), 7.26 – 7.22 (m, 1H), 6.89 – 6.84 (m, 2H), 6.56 (d, *J* = 15.9 Hz, 1H), 5.99 (dd, *J* = 15.8, 8.2 Hz, 1H), 4.50 (dd, *J* = 8.2, 5.2 Hz, 1H), 4.14 – 4.01 (m, 2H), 3.81 (d, *J* = 0.8 Hz, 3H), 3.67 – 3.59 (m, 1H), 2.57 (t, *J* = 8.4 Hz, 2H), 1.51 (s, 9H). **13C NMR** (101 MHz, CDCl3) δ 137.79, 133.31, 128.98, 128.24, 127.67, 127.12, 124.40, 114.02, 75.64, 68.04, 55.29, 40.66, 28.04.



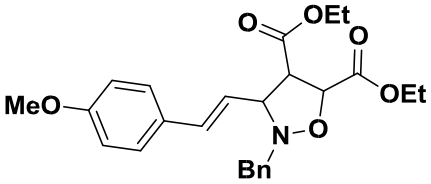
(T3C) LNT-29

Methyl (E)-2-benzyl-3-(4-methoxystyryl)-4-methylisoxazolidine-4-carboxylate (T3C): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2i** (105 mg, 90%) as a yellow oil. **TLC**: Rf 0.50 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.47 – 7.37 (m, 2H), 7.41 – 7.17 (m, 6H), 6.91 – 6.80 (m, 2H), 6.51 (d, *J* = 15.9 Hz, 1H), 5.95 (ddd, *J* = 15.8, 8.7, 1.3 Hz, 1H), 4.24 – 4.05 (m, 1H), 3.89 – 3.71 (m, 8H), 3.44 (q, *J* = 8.4 Hz, 1H), 2.83 (ddd, *J* = 12.8, 8.6, 1.3 Hz, 1H), 2.31 (ddd, *J* = 12.9, 8.0, 1.4 Hz, 1H), 1.57 (s, 1H), 1.50 (d, *J* = 1.3 Hz, 3H). **13C NMR** (101 MHz, Chloroform-d) δ 159.46, 137.53, 133.50, 128.19, 128.01, 127.69, 126.77, 124.72, 113.99, 81.10, 69.44, 58.71, 55.29, 52.32, 46.07, 23.71.



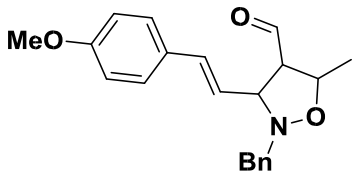
(T3D) DJQ-488

Dibutyl (E)-2-benzyl-3-(4-methoxystyryl)isoxazolidine-4,5-dicarboxylate (T3D): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2j** (120 mg, 90%) as a white solid. **TLC**: Rf 0.62 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.43 – 7.37 (m, 2H), 7.34 – 7.28 (m, 4H), 7.26 – 7.21 (m, 1H), 6.91 – 6.83 (m, 2H), 6.63 (d, *J* = 15.8 Hz, 1H), 5.97 (dd, *J* = 15.8, 8.5 Hz, 1H), 4.21 – 4.14 (m, 2H), 4.12 – 4.02 (m, 4H), 3.91 (t, *J* = 9.0 Hz, 1H), 3.81 (d, *J* = 0.6 Hz, 3H), 3.67 – 3.60 (m, 1H), 1.67 – 1.54 (m, 4H), 1.44 – 1.30 (m, 4H), 0.91 (ddd, *J* = 29.9, 7.6, 7.1 Hz, 6H). **13C NMR** (101 MHz, CDCl3) δ 137.34, 135.24, 128.99, 128.25, 127.87, 127.27, 122.01, 114.01, 72.19, 65.23, 60.25, 56.97, 55.31, 30.45, 19.07, 13.68.



(T3E) DJQ-489

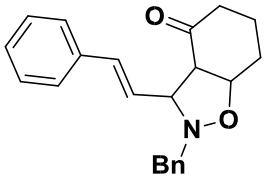
Diethyl (E)-2-benzyl-3-(4-methoxystyryl)isoxazolidine-4,5-dicarboxylate (T3E): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2k** (118 mg, 90%) as a white solid. **TLC:** Rf 0.35 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.46 – 7.43 (m, 2H), 7.33 (dq, *J* = 8.7, 2.3, 1.5 Hz, 4H), 7.29 (d, *J* = 1.5 Hz, 1H), 6.88 – 6.85 (m, 2H), 6.62 (d, *J* = 15.8 Hz, 1H), 6.02 (dd, *J* = 15.9, 8.6 Hz, 1H), 4.87 (d, *J* = 4.3 Hz, 1H), 4.24 (tdd, *J* = 15.0, 7.5, 3.7 Hz, 5H), 3.86 (d, *J* = 15.2 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, *J* = 8.2, 4.3 Hz, 1H), 3.65 – 3.58 (m, 1H), 1.31 (d, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 7.1 Hz, 3H). **13C NMR** (101 MHz, Chloroform-d) δ 135.12, 128.10, 128.08, 127.87, 126.96, 122.64, 114.02, 73.48, 61.59, 61.50, 58.74, 57.28, 55.30, 14.19, 14.12.



(T3F) DJQ-486

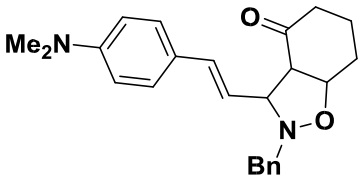
(E)-2-benzyl-3-(4-methoxystyryl)-5-methylisoxazolidine-4-carbaldehyde (T3F): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **2l** (85 mg, 70%) as a pale oil. **TLC**: Rf 0.31 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 9.76 (t, *J* = 2.0 Hz, 1H), 7.39 – 7.25 (m, 9H), 6.88 – 6.85 (m, 2H), 6.53 (d, *J* = 15.9 Hz, 1H), 6.13 – 6.05 (m, 1H), 4.52 – 4.47 (m, 1H), 4.13 (d, *J* = 14.2 Hz, 1H), 3.85 (d, *J* = 14.3 Hz, 1H), 3.81 (d, *J* = 1.5 Hz, 3H), 3.75 (d, *J* = 6.7 Hz, 1H), 2.97 (s, 1H), 1.43 (dd, *J* = 6.2, 1.5 Hz, 3H). **13C NMR** (101 MHz, CDCl3) δ 198.76, 133.80, 128.56, 128.23, 127.81, 127.15, 123.75, 114.04, 73.10, 68.94, 59.37, 55.30, 20.72.

2.5.4. Synthesis of Vinyl-Isoxazolidines from Table 6



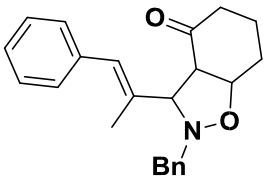
(T4A) DJQ-395

(E)-2-benzyl-3-styrylhexahydrobenzo[d]isoxazol-4(2H)-one (T4A): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **3a** (165 mg, 92%) as a white solid. **TLC**: Rf 0.25 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.39 (dd, *J* = 8.2, 6.5 Hz, 4H), 7.32 (t, *J* = 7.4 Hz, 4H), 7.28 – 7.23 (m, 2H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.22 (dd, *J* = 15.9, 7.9 Hz, 1H), 4.59 (dt, *J* = 7.8, 4.3 Hz, 1H), 4.10 (d, *J* = 14.0 Hz, 1H), 3.93 (dd, *J* = 7.9, 5.9 Hz, 1H), 3.87 (d, *J* = 14.0 Hz, 1H), 3.01 (t, *J* = 6.6 Hz, 1H), 2.52 (dt, *J* = 16.8, 5.0 Hz, 1H), 2.36 (ddd, *J* = 16.5, 10.2, 6.2 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.93 (dq, *J* = 9.8, 4.4 Hz, 2H), 1.84 (ddd, *J* = 14.0, 7.1, 3.7 Hz, 1H). **13C NMR** (101 MHz, CDCl3) δ 133.49, 128.99, 128.55, 128.23, 127.82, 127.49, 127.25, 126.54, 76.77, 70.16, 60.75, 60.50, 40.02, 26.42, 19.17.



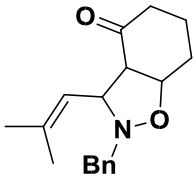
(T4B) DJQ-494

(E)-2-benzyl-3-(4-(dimethylamino)styryl)hexahydrobenzo[d]isoxazol-4(2H)-one (T4B): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **3b** (178 mg, 70%) as a red oil. TLC: Rf 0.19 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.40 – 7.28 (m, 6H), 7.25 – 7.22 (m, 1H), 6.67 (dd, *J* = 8.9, 2.6 Hz, 2H), 6.56 (d, *J* = 15.8 Hz, 1H), 5.98 (ddd, *J* = 15.7, 8.1, 1.0 Hz, 1H), 4.57 (dt, *J* = 7.6, 4.2 Hz, 1H), 4.12 (d, *J* = 14.1 Hz, 1H), 3.80 (d, *J* = 10.6 Hz, 1H), 3.01 (t, *J* = 6.9 Hz, 1H), 2.96 (d, *J* = 1.0 Hz, 6H), 2.54 – 2.30 (m, 3H), 2.09 – 1.92 (m, 2H), 1.91 – 1.82 (m, 2H). **13C NMR** (101 MHz, CDCl3) δ 128.98, 128.17, 127.56, 127.13, 122.53, 112.32, 70.95, 60.91, 60.13, 40.49, 39.81, 26.54, 18.96.



(T4C) DJQ-492

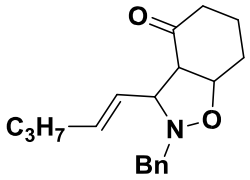
(E)-2-benzyl-3-(1-phenylprop-1-en-2-yl)hexahydrobenzo[d]isoxazol-4(2H)-one (T4C): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **3c** (105 mg, 72%) as a pale oil. TLC: Rf 0.33 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.42 – 7.20 (m, 10H), 6.94 – 6.53 (m, 1H), 4.57 – 4.47 (m, 1H), 4.25 – 4.02 (m, 1H), 3.93 – 3.63 (m, 2H), 3.48 – 2.92 (m, 1H), 2.53 – 2.02 (m, 3H), 1.89 (s, 3H), 1.89 – 1.78 (m, 2H). **13C NMR** (101 MHz, CDCl3) δ 209.40, 135.35, 132.30, 129.06, 128.99, 128.87, 128.16, 128.01, 127.17, 126.47, 75.19, 60.82, 59.16, 40.29, 26.29, 19.45, 14.86.



T4D (DJQ-596)

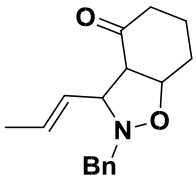
(3S,3aR,7aS)-2-benzyl-3-(2-methylprop-1-en-1-yl)hexahydrobenzo[d]isoxazol-7(4H)-one

(T4D): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4d** (mass, % yield) as a yellow oil. **TLC:** Rf 0.20 (3:1 heptanes/EtOAc). **1H NMR** (400 MHz, Chloroform-d) δ 7.36 – 7.28 (m, 4H), 7.25 – 7.21 (m, 1H),
5.19 (ddd, J = 9.4, 2.5, 1.3 Hz, 1H), 4.55 – 4.48 (m, 1H), 3.98 (d, J = 14.1 Hz, 1H), 3.87 (s, 1H), 3.76 (d, J = 14.1 Hz, 1H), 2.88 (t, J = 7.3 Hz, 1H), 2.47 (dt, J = 17.0, 5.1 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.08 – 1.98 (m, 1H), 1.88 – 1.78 (m, 3H), 1.71 (dd, J = 16.9, 1.3 Hz, 6H). **13C NMR** (101 MHz, cdcl3) δ 209.84, 137.68, 136.10, 128.81, 128.13, 127.08, 76.57, 66.73, 61.00, 39.49, 26.65, 26.05, 18.67, 18.47.



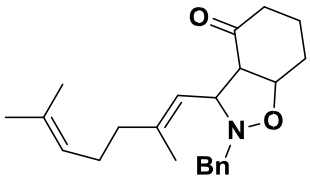
(T4E) DJQ-456

(E)-2-benzyl-3-(pent-1-en-1-yl)hexahydrobenzo[d]isoxazol-4(2H)-one (T4E): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **3d** (110 mg, 80%) as a yellow oil. **TLC**: Rf 0.42 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.36 (dd, *J* = 5.9, 1.9 Hz, 3H), 7.31 (d, *J* = 7.1 Hz, 2H), 5.70 (dt, *J* = 15.3, 6.8 Hz, 1H), 5.46 – 5.39 (m, 1H), 4.50 (dt, *J* = 8.0, 4.2 Hz, 1H), 4.05 (d, *J* = 14.1 Hz, 1H), 3.75 (d, *J* = 14.1 Hz, 1H), 3.58 (t, *J* = 7.6 Hz, 1H), 2.92 (t, *J* = 7.2 Hz, 1H), 2.50 – 2.45 (m, 1H), 2.31 (ddd, *J* = 16.7, 10.1, 6.2 Hz, 2H), 2.01 (d, *J* = 7.3 Hz, 2H), 1.90 – 1.81 (m, 3H), 1.38 (d, *J* = 7.3 Hz, 2H), 0.87 (d, *J* = 7.3 Hz, 3H). **13C NMR** (101 MHz, CDCl3) δ 135.84, 128.92, 128.16, 127.12, 70.71, 60.66, 39.64, 34.39, 26.56, 22.13, 18.77, 13.59.



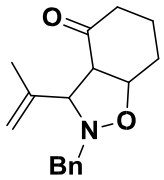
(T4F) DJQ-497

(E)-2-benzyl-3-(prop-1-en-1-yl)hexahydrobenzo[d]isoxazol-4(2H)-one (T4F): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 20:1 heptanes/EtOAc to 1:4 heptanes/EtOAc over 12 min) yielded the isoxazolidine **3e** (209 mg, 70%) as a yellow oil. TLC: Rf 0.38 (3:1 heptanes/EtOAc). **^{1}H NMR** (400 MHz, CDCl3) δ 7.38 – 7.24 (m, 5H), 5.80 – 5.66 (m, 1H), 5.46 (ddq, *J* = 15.2, 8.2, 1.5 Hz, 1H), 4.51 (ddt, *J* = 11.9, 8.1, 4.4 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.77 (dd, *J* = 19.9, 14.0 Hz, 1H), 3.63 – 3.41 (m, 1H), 2.90 (q, *J* = 8.8, 8.0 Hz, 1H), 2.47 (dt, *J* = 16.4, 5.0 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.00 (dddd, *J* = 15.7, 7.7, 3.6, 1.8 Hz, 1H), 1.89 – 1.75 (m, 3H), 1.70 (ddd, *J* = 6.3, 4.3, 1.6 Hz, 3H). **13C NMR** (101 MHz, CDCl3) δ 130.57, 128.91, 128.86, 128.15, 127.10, 76.35, 70.76, 60.52, 59.90, 39.63, 26.54, 18.73, 17.95.



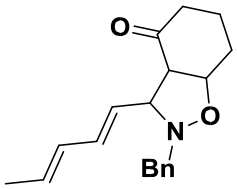
T4G (DJQ-619)

(3S,3aR,7aS)-2-benzyl-3-((E)-2,6-dimethylhepta-1,5-dien-1-yl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4G): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4g** (mass, % yield) as a yellow oil. **TLC:** Rf 0.20 (3:1 heptanes/EtOAc). **1H NMR** (400 MHz, Chloroform-d) δ 7.37 – 7.21 (m, 5H), 5.20 (dq, J = 9.2, 1.4 Hz, 1H), 5.13 – 4.96 (m, 1H), 4.52 (dt, J = 8.4, 4.4 Hz, 1H), 3.97 (d, J = 14.0 Hz, 1H), 3.89 (t, J = 8.7 Hz, 1H), 3.80 – 3.68 (m, 1H), 2.88 (t, J = 7.3 Hz, 1H), 2.47 (dt, J = 16.9, 5.2 Hz, 1H), 2.31 (ddd, J = 16.7, 9.7, 6.2 Hz, 1H), 2.20 – 1.91 (m, 6H), 1.87 – 1.75 (m, 3H), 1.72 – 1.56 (m, 9H). **13C NMR** (101 MHz, cdcl3) δ 209.64, 137.62, 131.61, 128.83, 128.63, 128.09, 127.05, 123.80, 76.68, 66.47, 61.07, 39.69, 39.48, 26.60, 26.24, 25.63, 18.69, 17.65, 16.78.



T4H (DJQ-418)

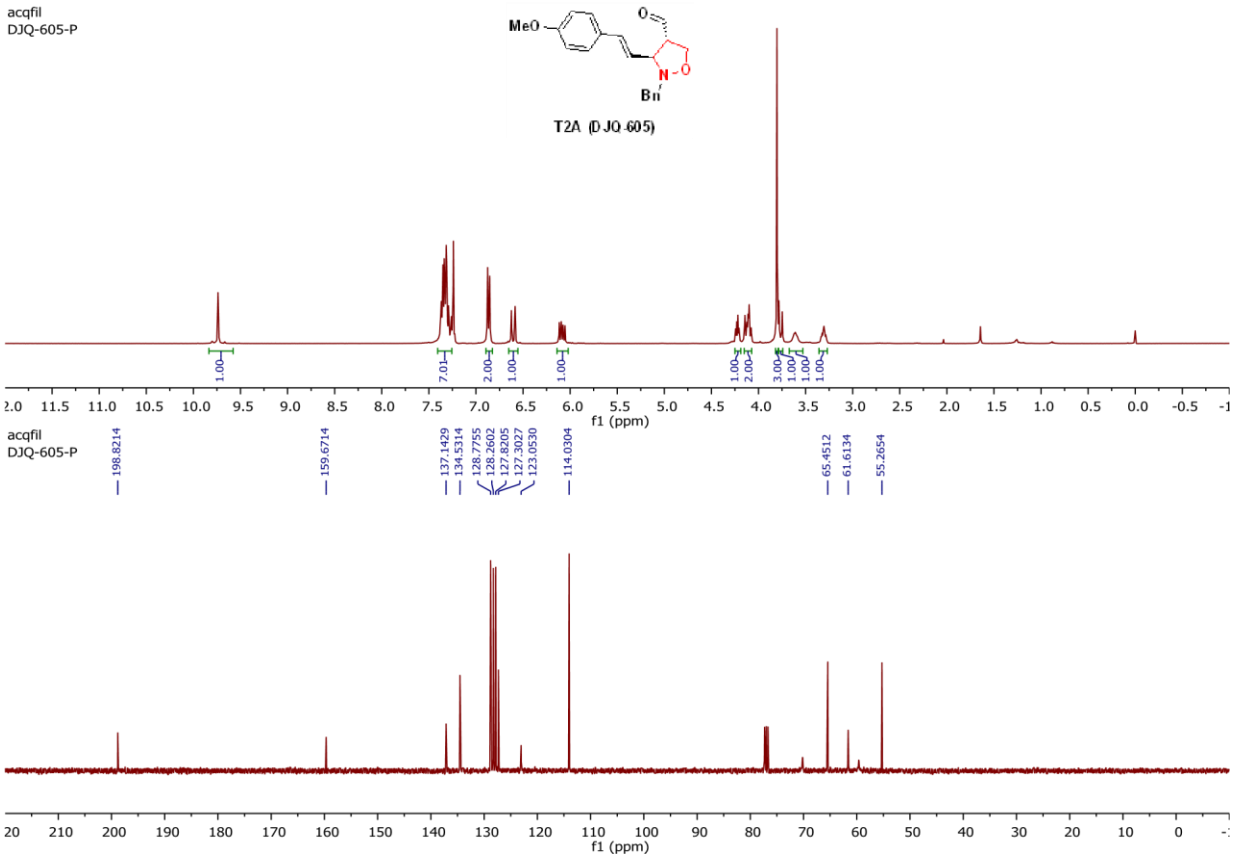
(3R,3aR,7aS)-2-benzyl-3-(prop-1-en-2-yl)hexahydrobenzo[d]isoxazol-7(4H)-one (T4H): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine 4h (mass, % yield) as a yellow oil. TLC: Rf 0.20 (3:1 heptanes/EtOAc). 1H NMR (400 MHz, Chloroform-d) δ 7.37 – 7.21 (m, 5H), 5.20 (dq, J = 9.2, 1.4 Hz, 1H), 5.13 – 4.96 (m, 1H), 4.52 (dt, J = 8.4, 4.4 Hz, 1H), 3.97 (d, J = 14.0 Hz, 1H), 3.89 (t, J = 8.7 Hz, 1H), 3.80 – 3.68 (m, 1H), 2.88 (t, J = 7.3 Hz, 1H), 2.47 (dt, J = 16.9, 5.2 Hz, 1H), 2.31 (ddd, J = 16.7, 9.7, 6.2 Hz, 1H), 2.20 – 1.91 (m, 6H), 1.87 – 1.75 (m, 3H), 1.72 – 1.56 (m, 9H). 13C NMR (101 MHz, cdcl3) δ 209.64, 137.62, 131.61, 128.83, 128.63, 128.09, 127.05, 123.80, 76.68, 66.47, 61.07, 39.69, 39.48, 26.60, 26.24, 25.63, 18.69, 17.65, 16.78.

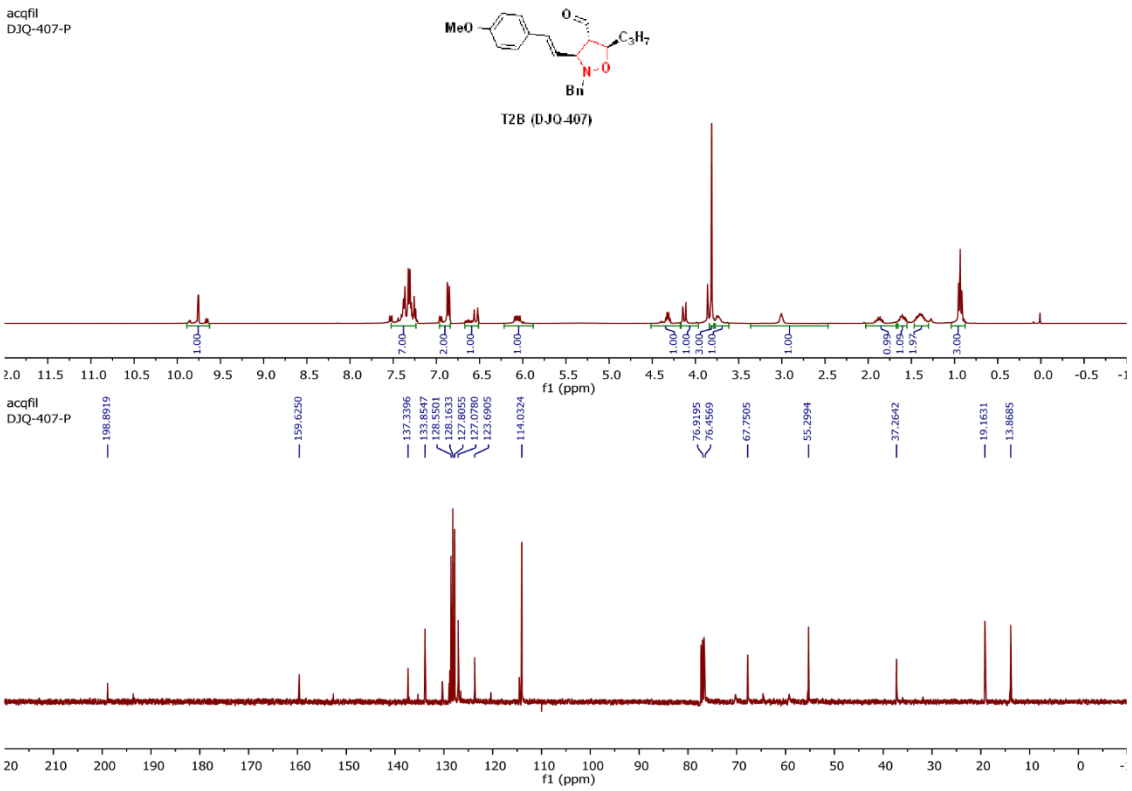


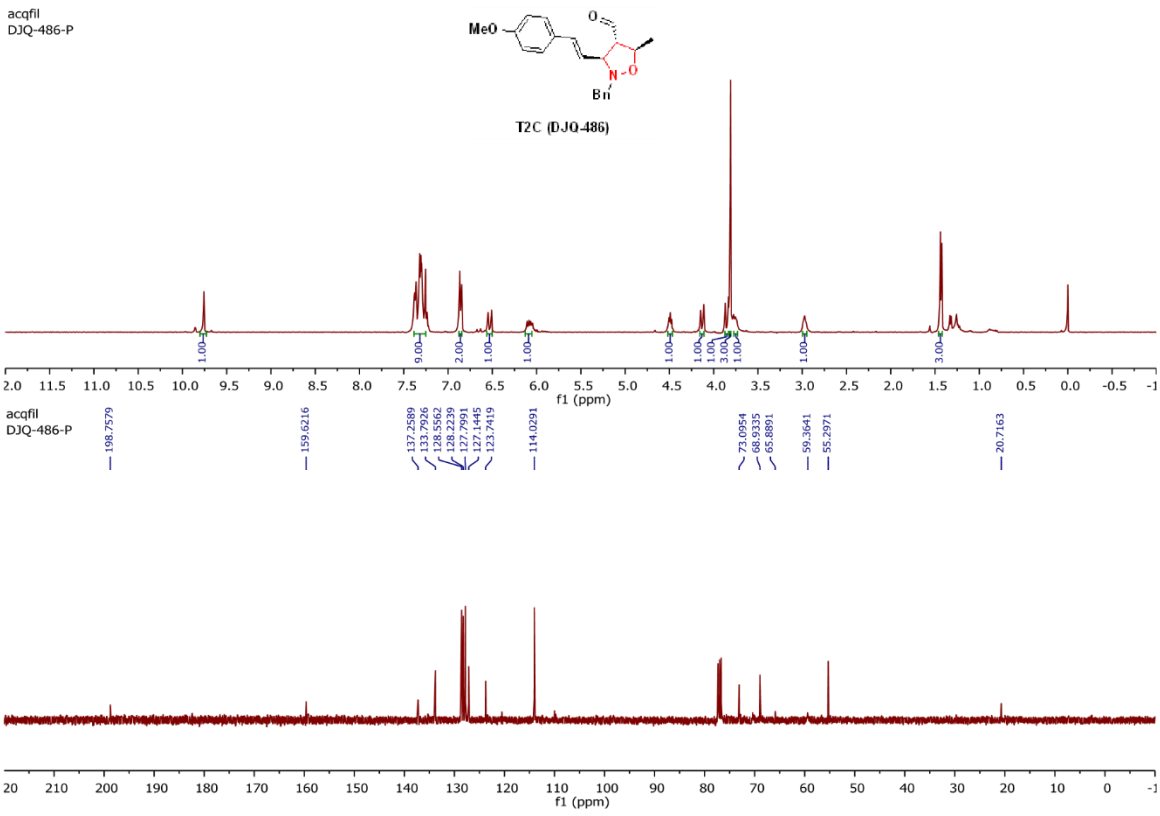
T4I (DJQ-615)

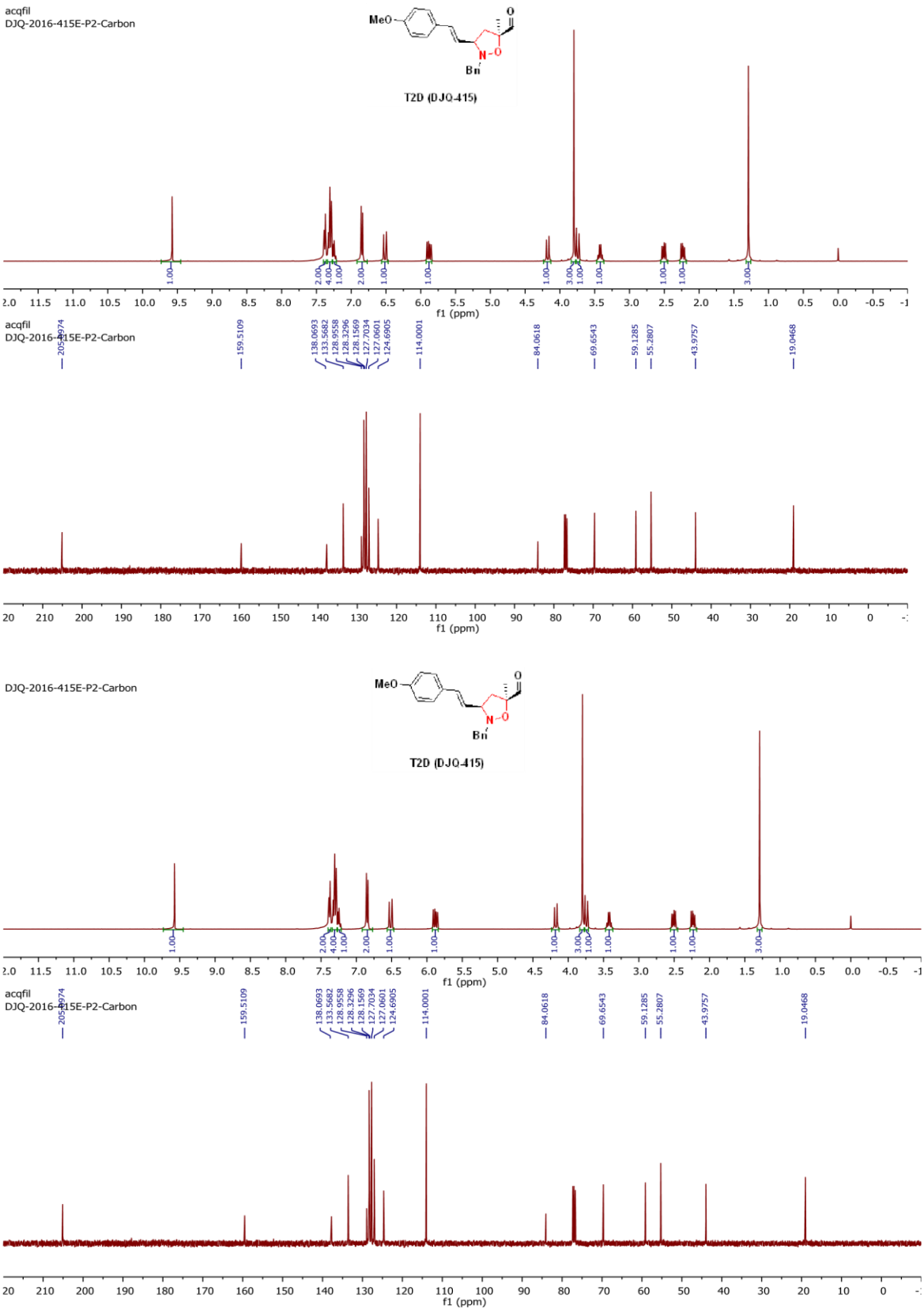
(3S,3aR,7aS)-2-benzyl-3-((1E,3E)-penta-1,3-dien-1-yl)hexahydrobenzo[d]isoxazol7(4H)-one (T4I): Purification by automated silica gel flash chromatography (10 g cartridge, 14 ml/min. 2 column volumes of 100% Heptanes followed by 0-33% EtOAc in Heptanes over 12 column volumes) yielded the isoxazolidine **4i** (mass, % yield) as a yellow oil. **TLC:** Rf 0.20 (3:1 heptanes/EtOAc). **1H NMR** (400 MHz, Chloroform-d) δ 7.37 – 7.23 (m, 5H), 6.25 (dd, J = 15.2, 10.4 Hz, 1H), 6.08 – 5.96 (m, 1H), 5.80 – 5.65
(m, 1H), 5.52 (dd, J = 15.2, 8.1 Hz, 1H), 4.51 (ddt, J = 11.5, 7.7, 4.2 Hz, 1H), 4.04 (d, J = 14.1 Hz, 1H), 3.74 (d, J = 14.1 Hz, 1H), 3.66 (t, J = 7.2 Hz, 1H), 2.92 (dd, J = 8.7, 5.2 Hz, 1H), 2.51 – 2.43 (m, 1H), 2.35 – 2.27 (m, 1H), 2.03 – 1.95 (m, 1H), 1.91 – 1.84 (m, 2H), 1.80 (ddd, J = 6.9, 5.4, 2.5 Hz, 1H), 1.77 – 1.73 (m, 3H). **13C NMR** (101 MHz, cdcl3) δ 209.31, 137.49, 134.26, 130.62, 130.53, 128.85, 128.13, 127.11, 76.49, 70.31, 60.74, 39.73, 26.46, 18.84, 18.07.

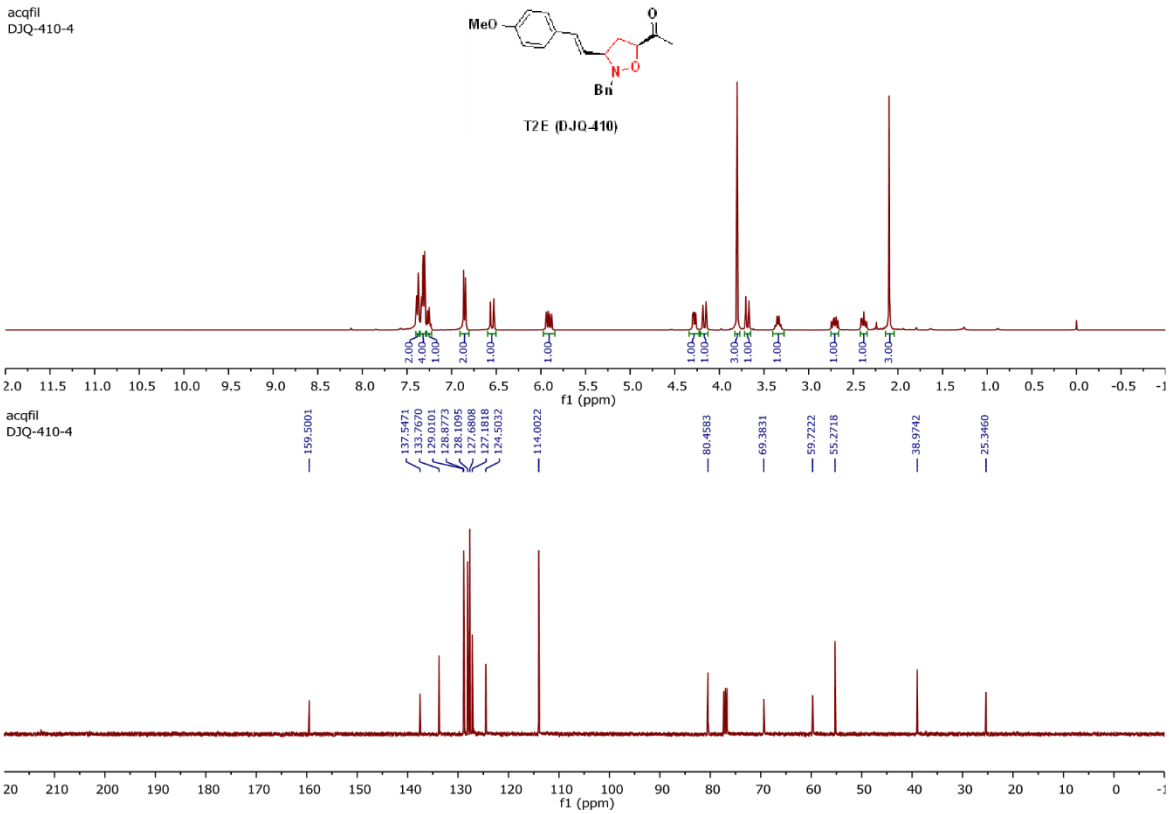
2.5.5. ^{1}H NMR and ^{13}C NMR of Vinyl-Isoxazolidines

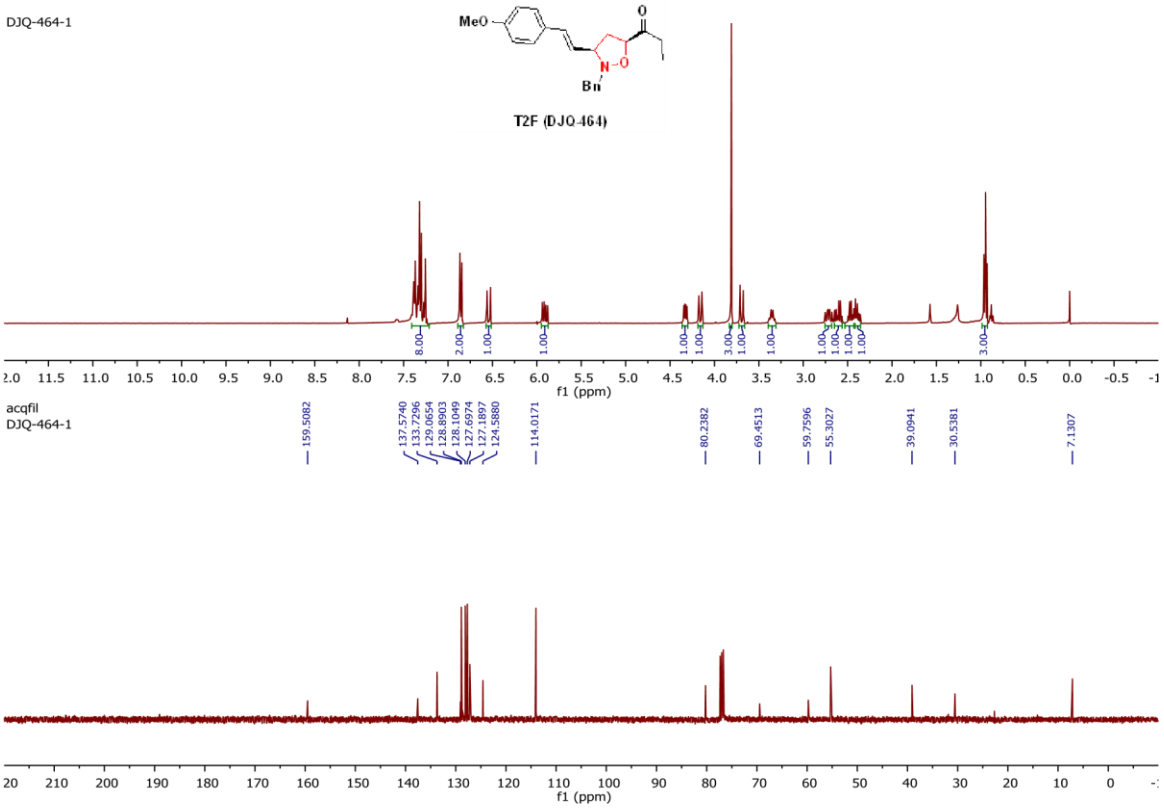


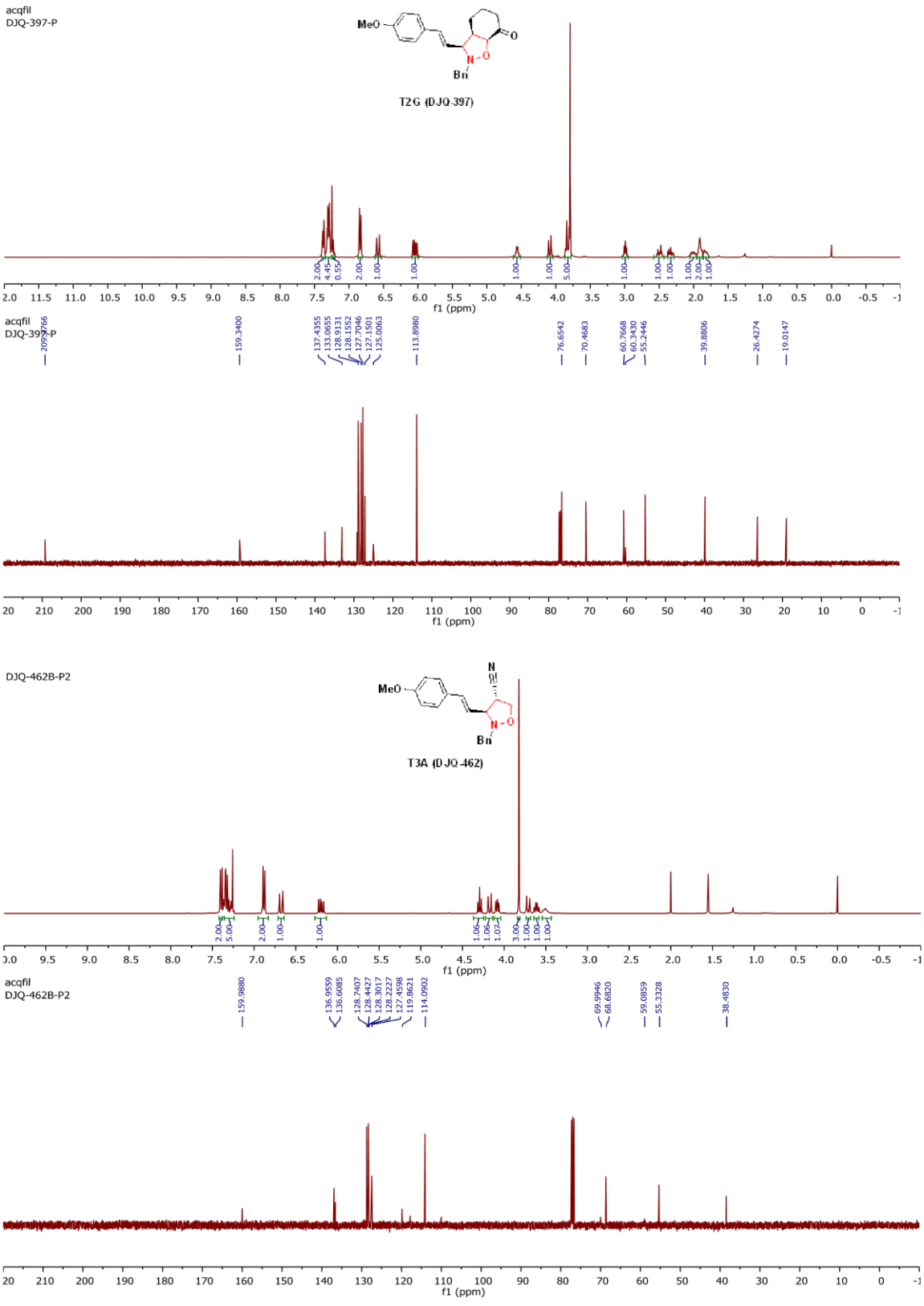


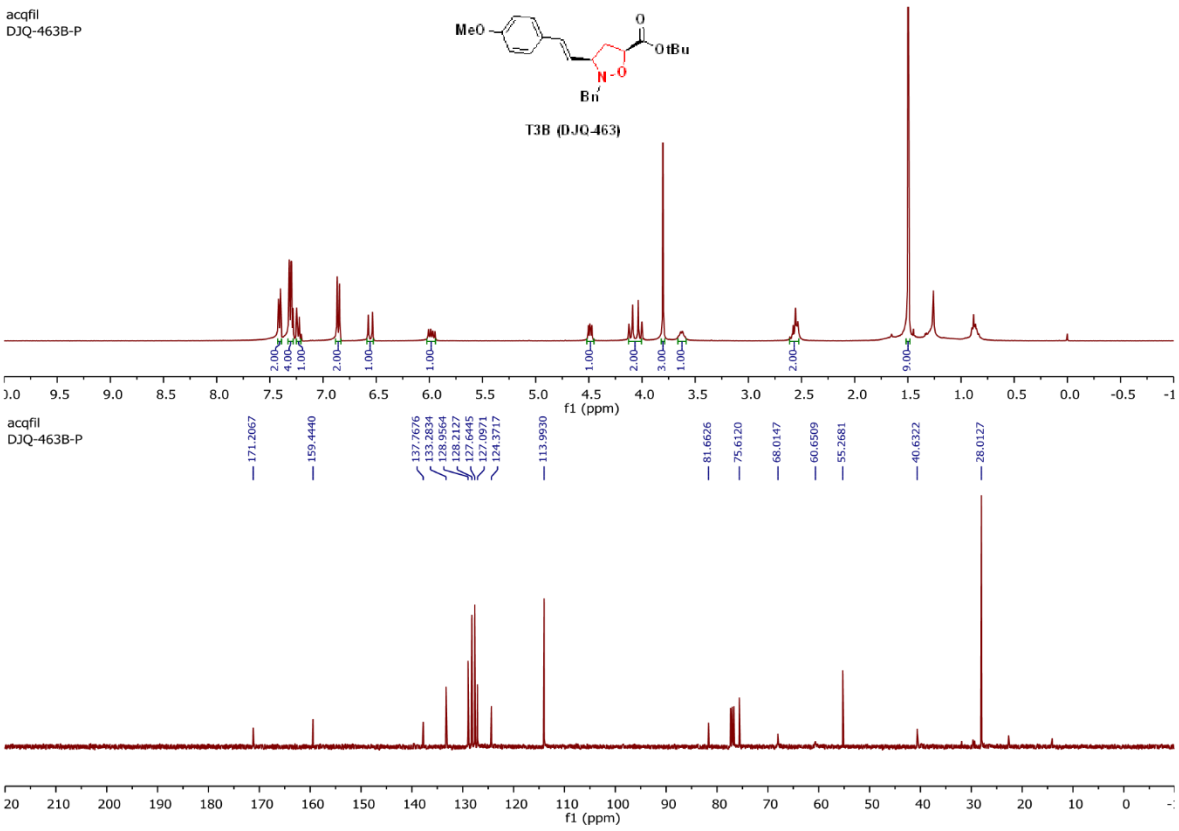


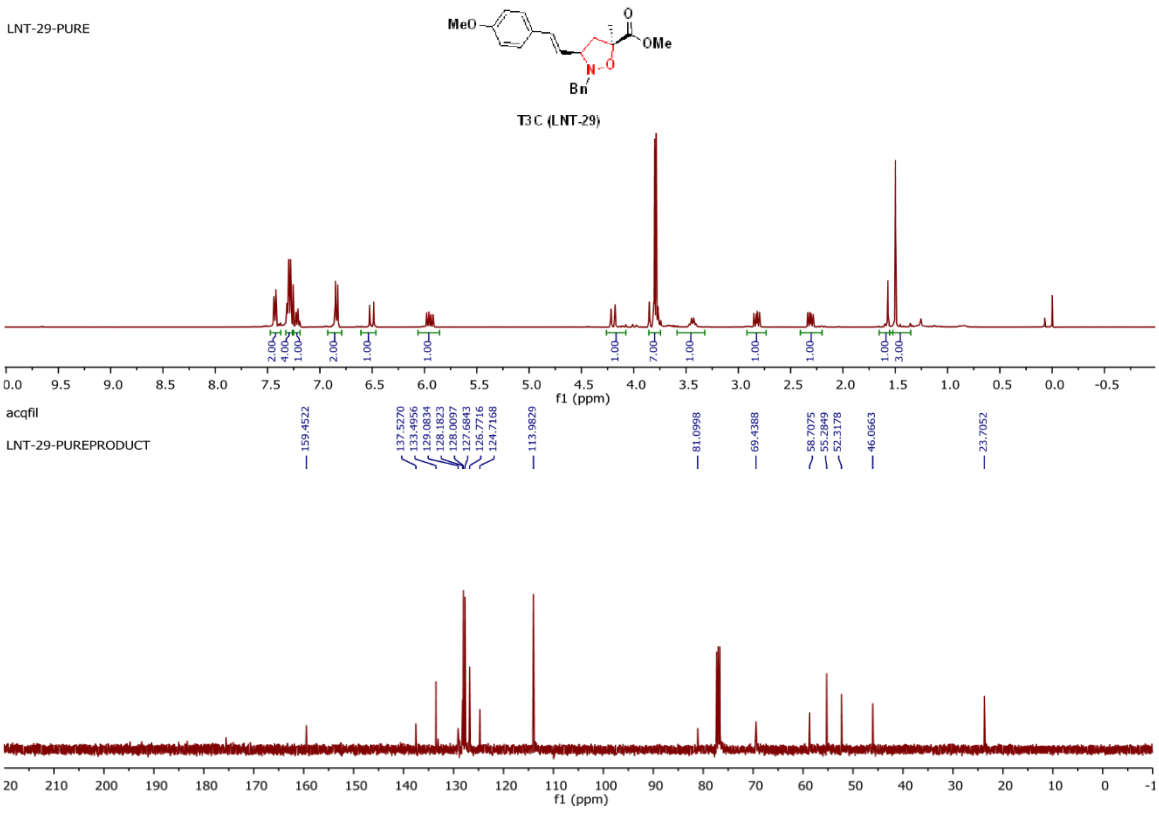


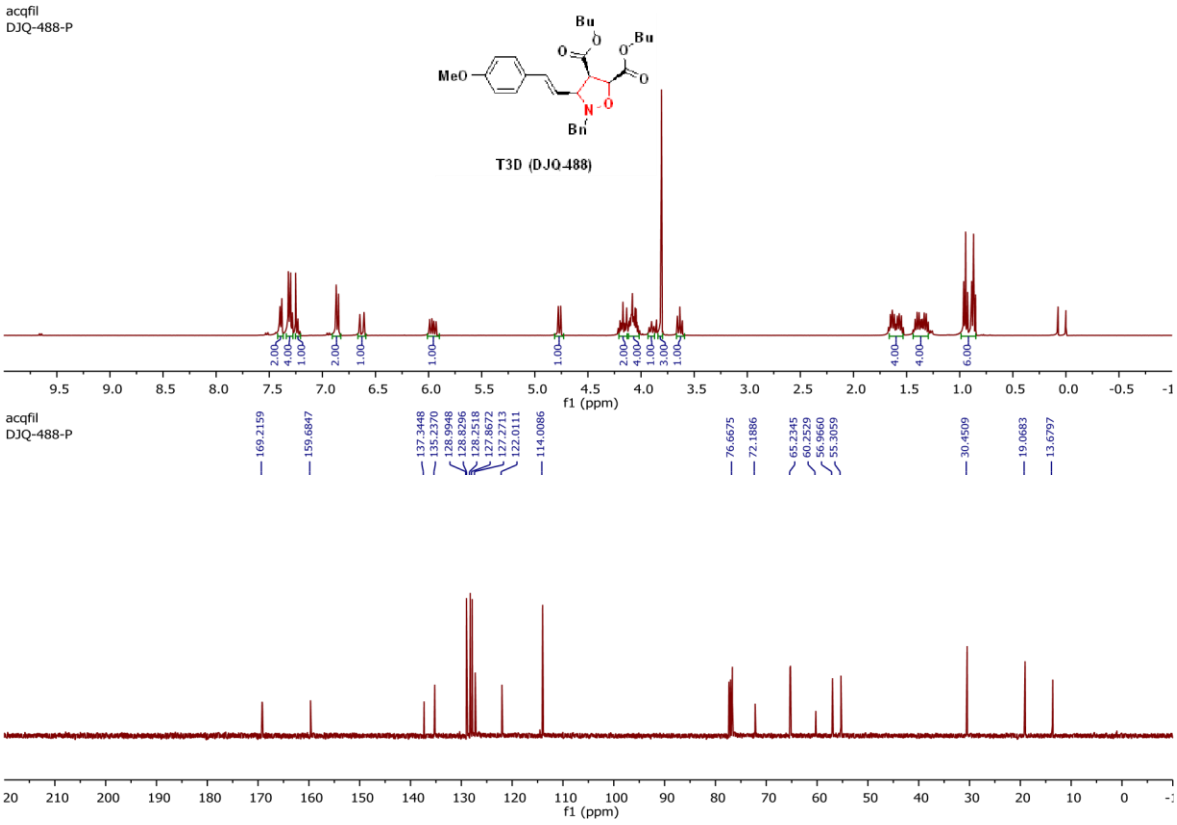


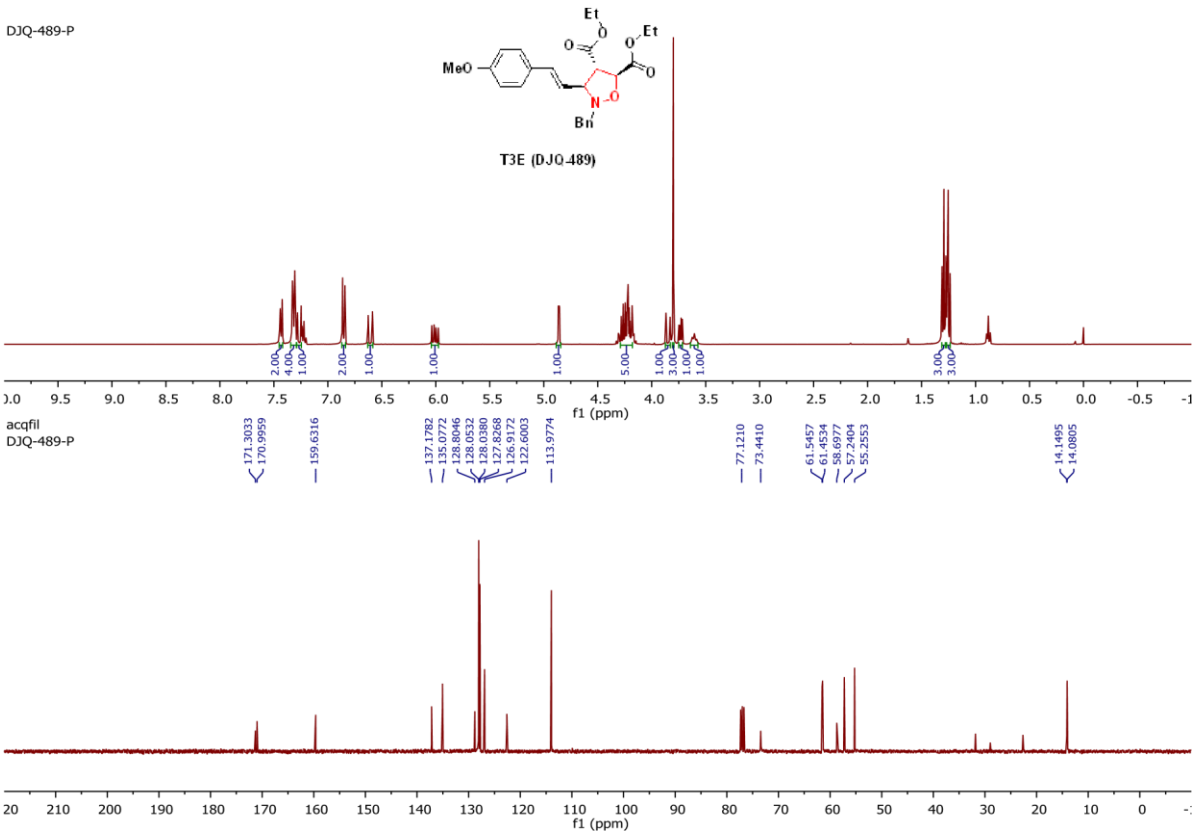


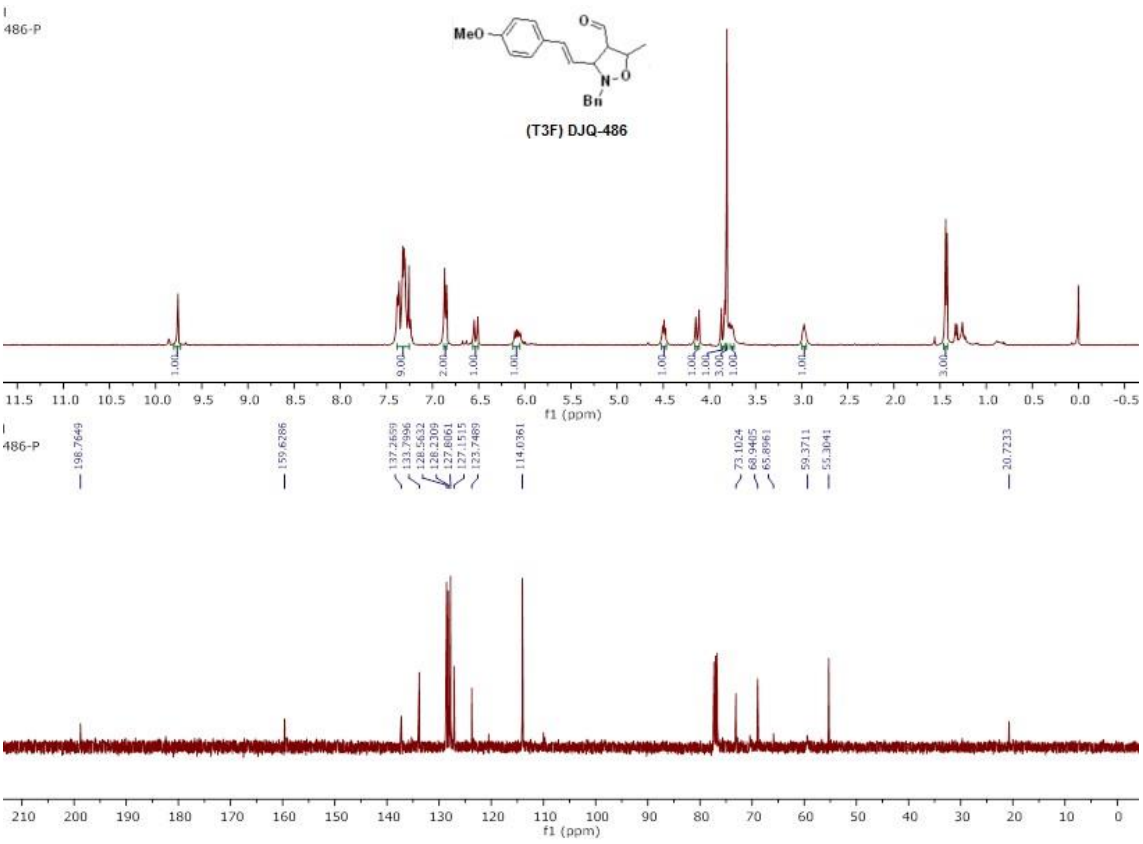


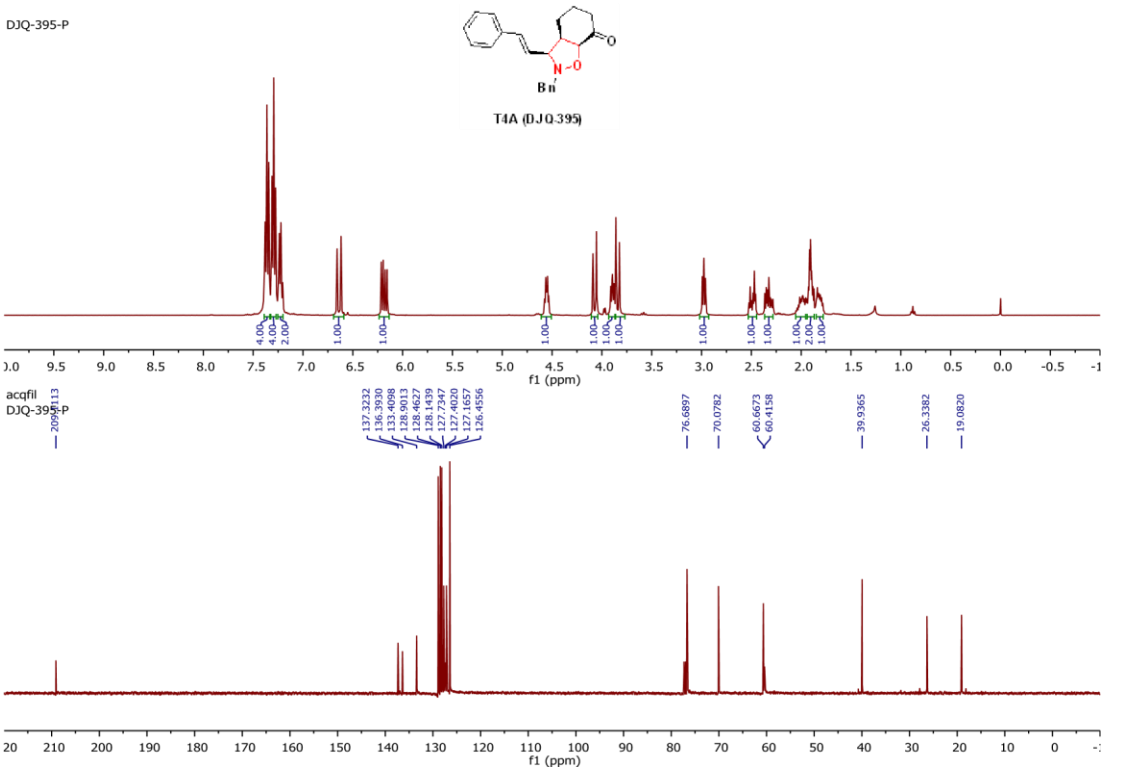


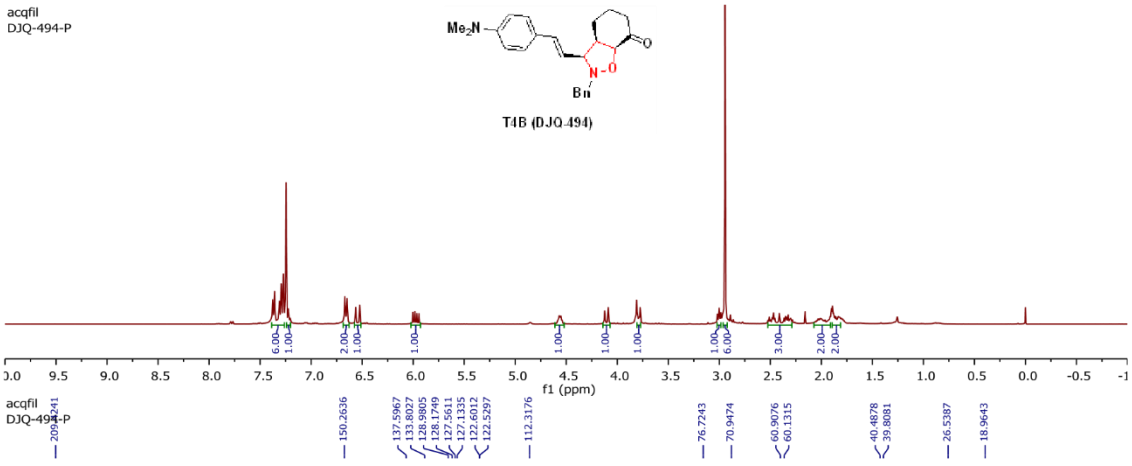


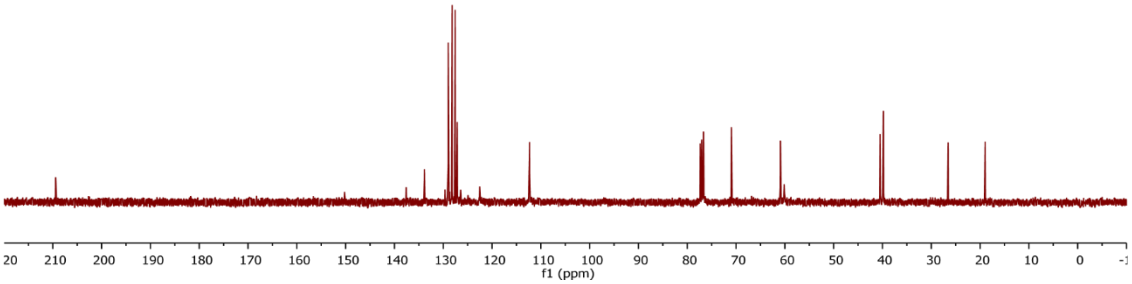


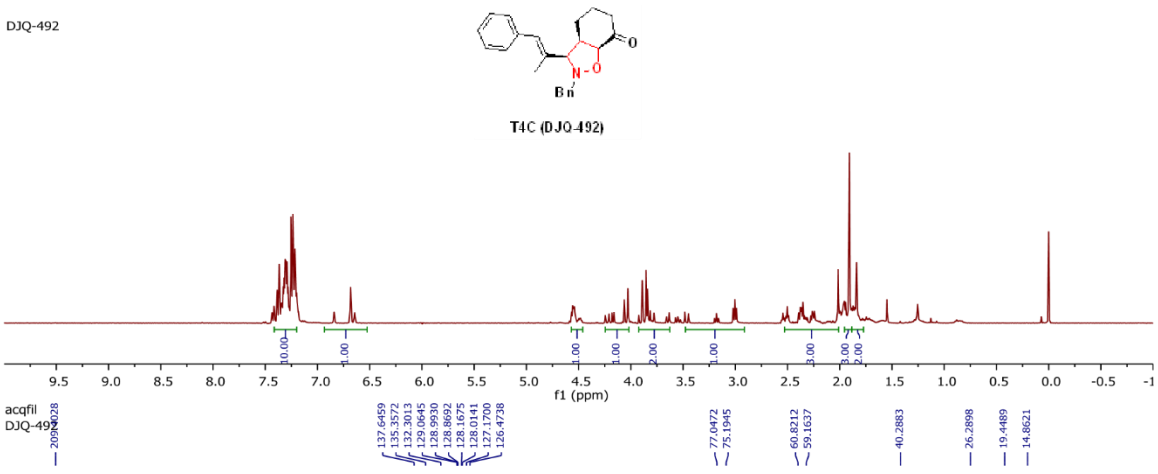


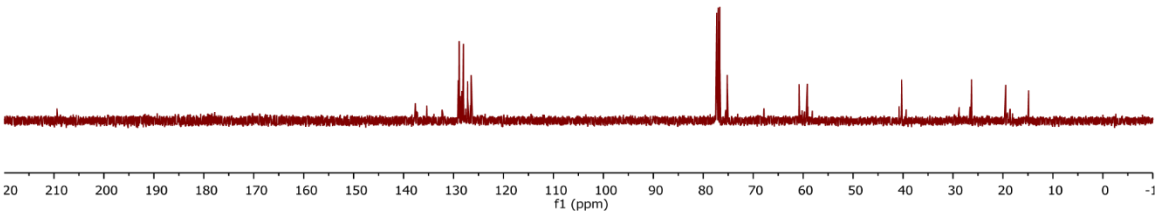


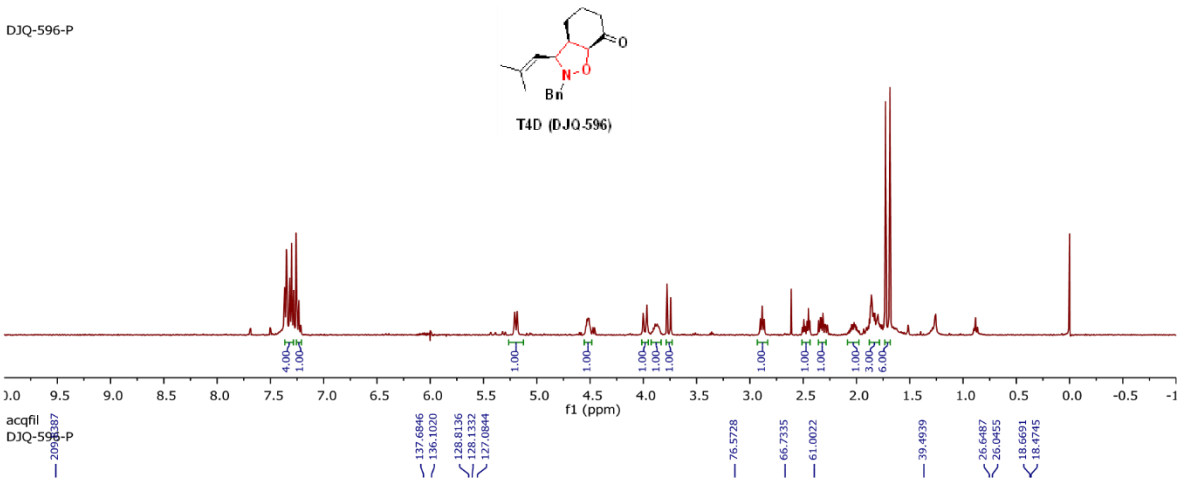


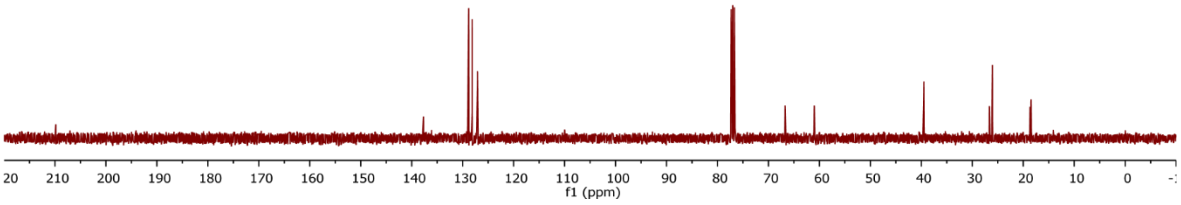


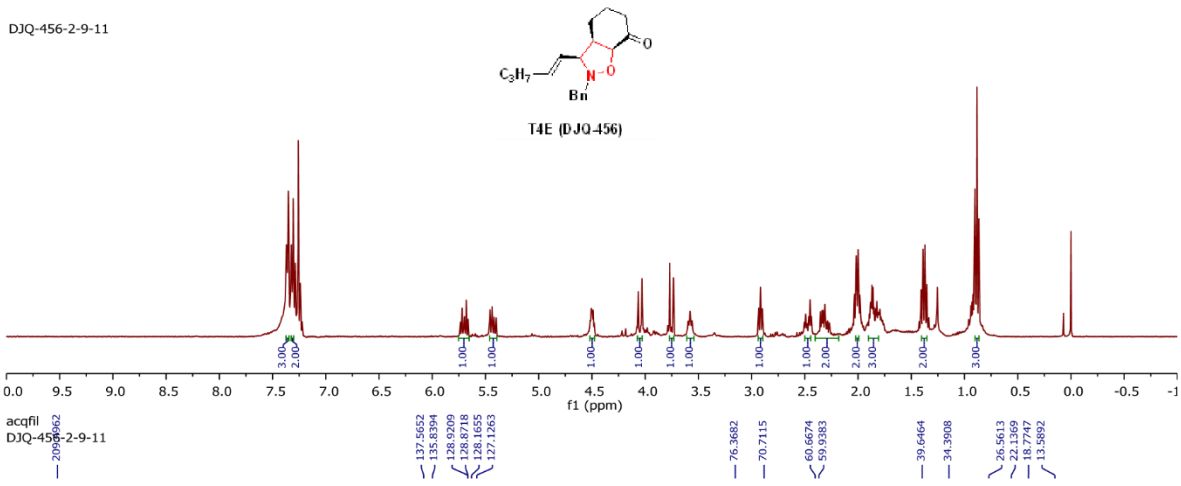


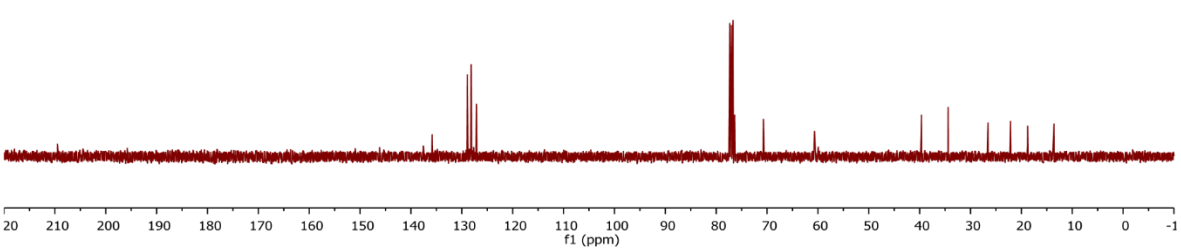


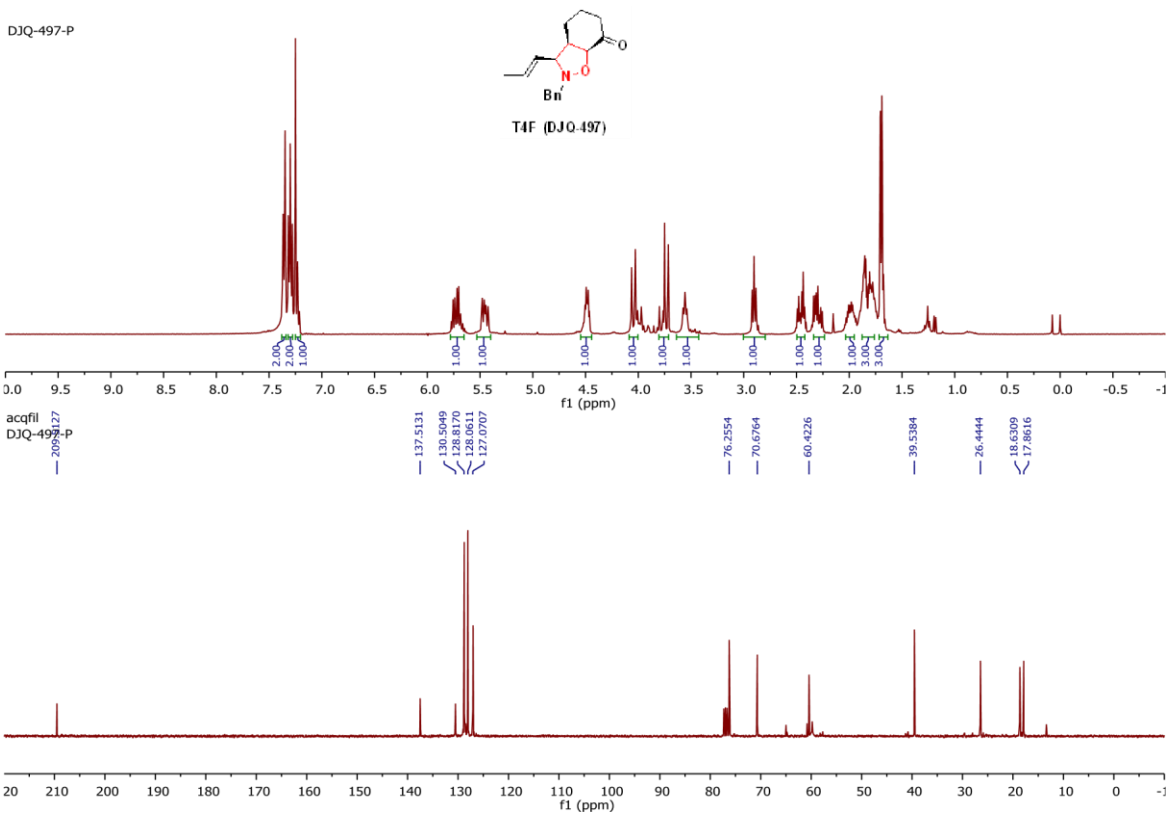


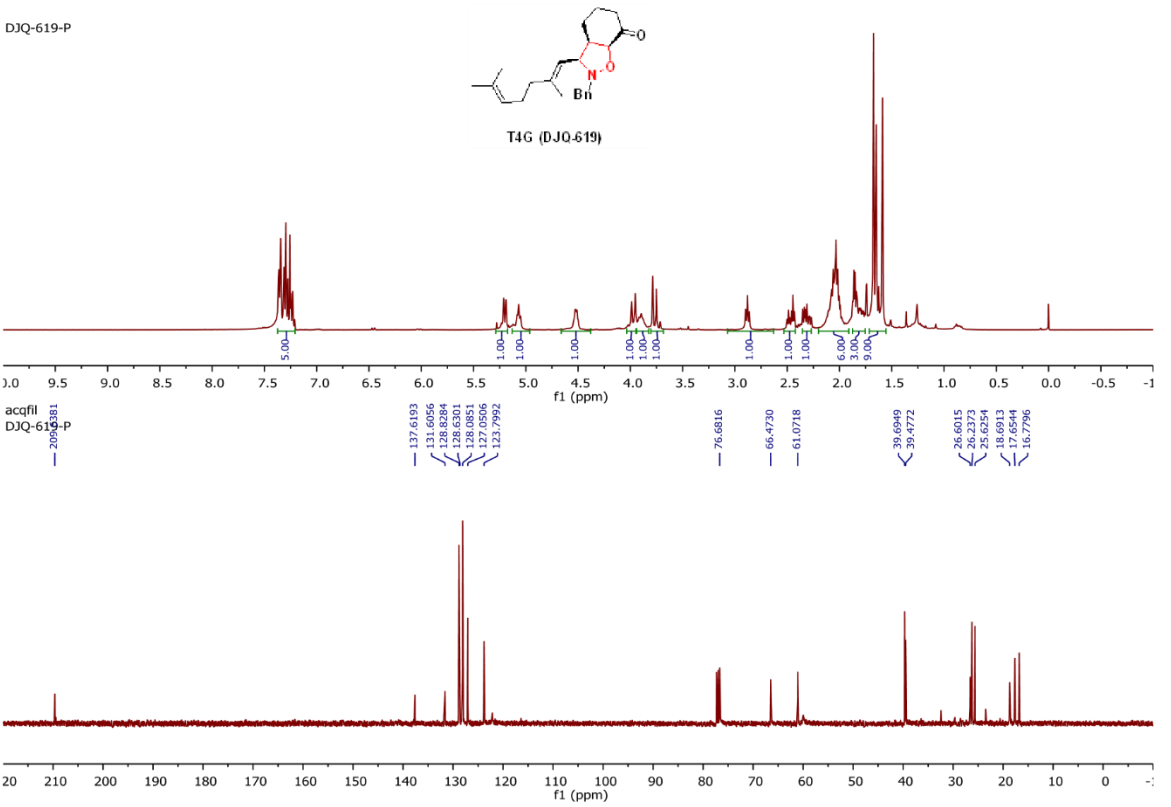


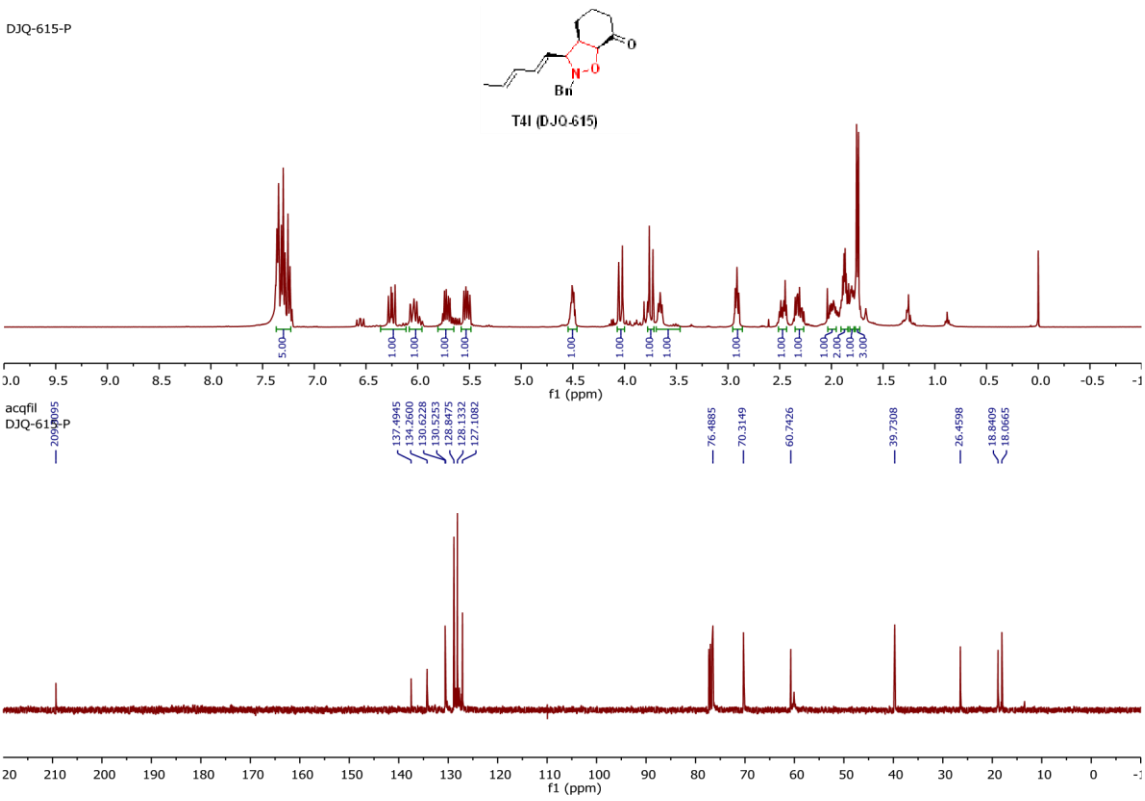












Chapter 3

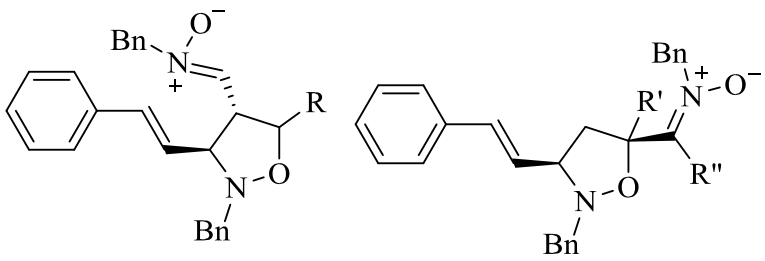
Synthesis of Isoxazolooxazines

3.1 Intermolecular Cycloadditions of Vinyl Isoxazolidines

Reported earlier in this document was the synthesis of nitrones from various enals utilizing a variety of hydroxylamines as nitrogen transfer agents. With this knowledge in mind, we attempted to form the cooresponding nitrone from both the 3vinyl-4-formylisoxazolidines (3,4-VFI) and 3-vinyl-5-formylisoxazolidines (3,5-VFI) reported in Chapter 2 (Figure 9).

Figure 9

Nitrones formed from 3,4-VFI (left) and 3,5-VFI (right)

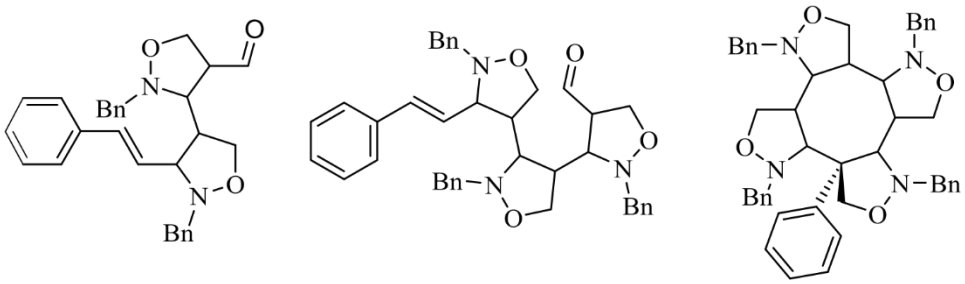


The further objective of creating these nitrones was to perform an intermolecular cycloadditon with various dipolarophiles in order to create biisoxazolidines, terisoxazolidines and eventually tetraisoxazoles. (Figure 10). The reactions would proceed by creating the cooresponding nitrone followed by an intermolecular cycloaddition utilizing an alpha-beta unsaturated aldehyde or ketone as a diploarophile to create biisoxazolidines and terisoxazolidines. To create the desired tetraisoxazoles, the last step would involve the intramolecular cycloaddition between the nitrone and double

bond of the terisoxazolidine. These reactions would be robust and would encompass a broad scope through the utilization of a variety of hydroxylamines, dipolarophiles and enals.

Figure 10

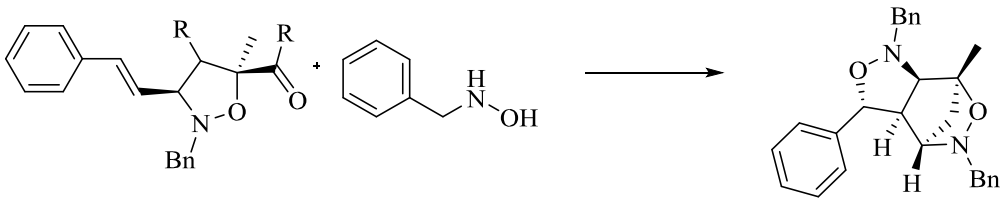
Scope Utilizing Acrolein as the Dipolarophile: Biisoxazolidines (left), Terisoxazolidine (center) and Tetraisoxazoles (right)



While attempting to create the nitrone of the 3-vinyl-5-formylisoxazolidine, we observed a different reaction was taking place. Instead of forming the expected nitrone, by analysis of the crude NMR the reaction was immediately performing an intermolecular cycloaddition once introduced to the hydroxylamine (Figure 11). Once seeing these consistent results among several of the 3-vinyl-5-formylisoxazoldine substrates, we saw an opportunity to pursue a synthetic approach to create carbacycles.

Figure 11

The Intermolecular Cycloaddition of the 3,5-VFI to the Isoxazolooxazine.



3.2 Synthetic Relevance

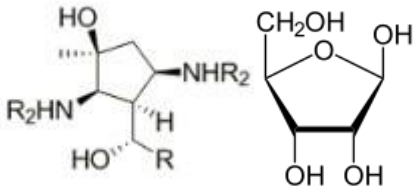
Upon the realization that the 3-vinyl-5-formylisoxazolidine regioisomer could undergo an intramolecular cycloaddition, we saw an opportunity to create carbacycles. By cleaving the two nitrogen oxygen bonds within the fused ring system of the isoxazolooxazine, we could obtain a stereochemically dense five-membered ring containing five stereocenters with electron rich substituents. Carbacycles hold significant pharmaceutical relevance as they resemble to molecular components of blockbuster drugs and natural products.

The structural motif we aimed to resemble was that of ribose (Figure 12). Ribose is pentose sugar that acts as an essential carbohydrate in biological systems and serves as part of the backbone of RNA. Additionally, phosphorylated derivatives of ribose that play critical roles in metabolism in biological systmes include ATP, NADH, cAMP and cGMP. Some of these biological molecules have the ability to participate as secondary messengers in signaling pathways for metabolic processes as well. D-ribose specifically holds pharmaceutical relevance as it is suggested to

manage congestive heart failure, myalgic encephalopmyelitis as well as some other forms of heart disease (Teitelbaum, J. E., Johnson, C., St Cyr, J. 2006).

Figure 12

Carbacycles (left) Resembling Ribose (right)



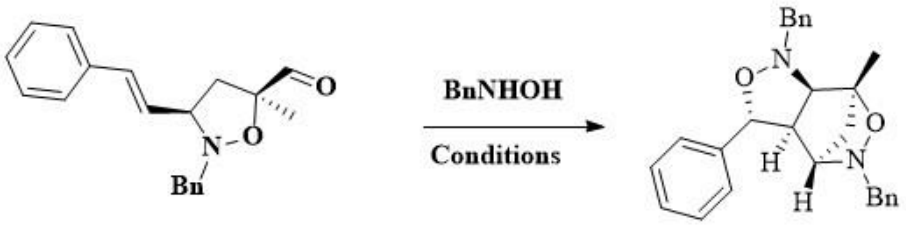
3.3 Results and Discussion

During optimization of this reaction we explored the thermal conditions, various polar aprotic solvents and concentrations that could be utilized to enhance the yields we obtained from these reactions. Initially we aimed to investigated the thermal conditions and found that by heating the reactions to 80°C we were able to increase the yield significantly (Table 7, Entry 3). Above this temperature we saw a decline in yield therefore exploring higher temperatures was not optimal for this reaction. Next, we explored the potential of utilizing different solvents for this reaction but found that acetonitrile gave the best yields at the optimal temperature (Table 7, Entries 3, 5 and 6). Lastly, we wanted to determine whether diluting the concentration would encourage the intramolecular cycloaddition and eliminate biproduct formation. In these studies, we found that employing a 0.01M concentration was ideal to promote the intramolecular cycloaddition.

We sought to expand the library of compounds by utilizing various enals for the intial nitrone formation. Both straight alkyl chain enals as well as aromatic enals were selected from previous studies to be utilized in this experimentation. We utilized N-Benzylhydroxylamine as the nitrogen transfer agent and methacrolein as the dipolarophile for these reactions. Overall the best yield was obtained utilizing aromatic enals with donating groups at the para position (Table 8, Entry 3). The straight alkyl-chain enals provided lower yields than that of the aromatic because water was not used during nitrone formation in an attempt to create a more robust synthesis (Table 8, Entries 4 and 5).

Table 7

Optimization Studies of the Intramolecular Cycloaddition



3-vinyl-5-formyl-isoxazolidine 3,5-VFI

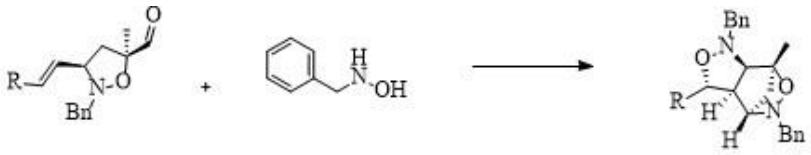
Methanoisoxazolooxazine

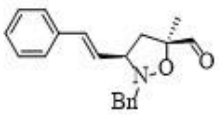
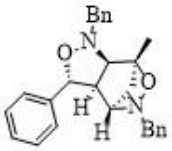
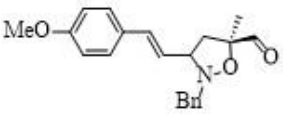
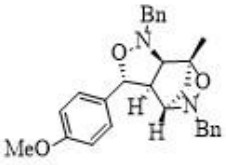
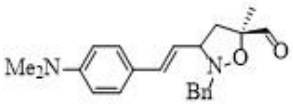
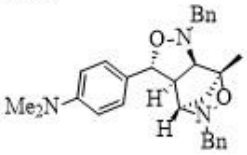
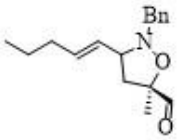
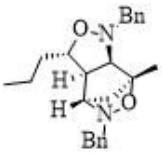
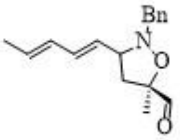
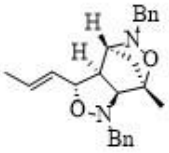
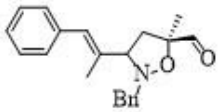
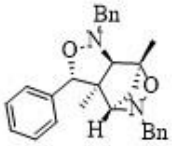
Entry	Solvent	Temperature	Concentration	Yield[a]
1	ACN	rt	0.01M	26%
2	ACN	60° C	0.01M	64%
3	ACN	80° C	0.01M	86%
4	ACN	90° C	0.01M	70%
5	CH_2Cl_2	80° C	0.01M	42%
6	DCE	80° C	0.01M	65%
7	ACN	80° C	0.02M	77%
8	ACN	80° C	0.03M	62%
9	ACN	80° C	0.05M	32%
10	ACN	80° C	0.005M	18%

a.Isolated yields.

Table 8

Enal Scope: Alkyl and Aromatic Enals



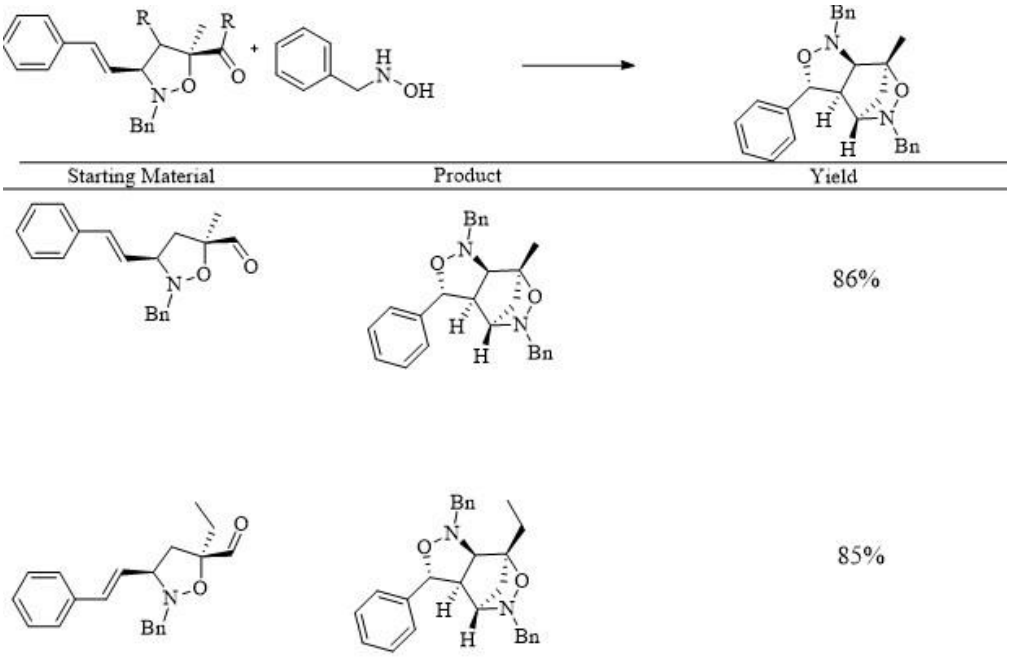
Starting Material	Product	Yield
		86%
		84%
		87%
		72%
		75%
		78%

The dipolarophiles utilized to broaden the scope of this reaction had to exhibit complete selectivity for the 3-vinyl-5-formylisoxazolidine. We attempted to utilize a variety of alpha-substituted alpha-beta unsaturated carbonyls, however the only two

substrates that provided the desired product for this reaction were methacrolein and ethylacrolein (Table 9).

Table 9

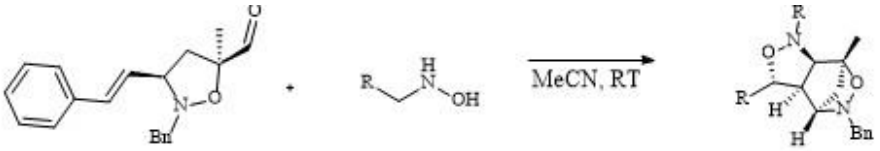
Dioplarophile Scope: Alpha-Substituted Carbonyls

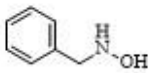
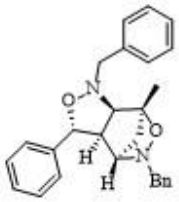
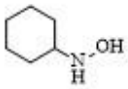
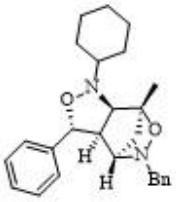
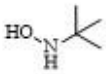
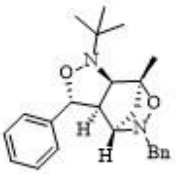
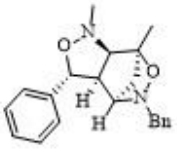


The intramolecular cycloaddition of isoxazolidines to isoxazolooxazines requires two nitrogen transfers agents to be employed. In attempt to increase reactivity and determine the steric effects of the hydroxylamine on the intramolecular cycloaddition, we reacted different hydroxylamines with the 3-vinyl-5formylisoxazolidine of cinnamaldehyde and methacrolein (Table 10).

Table 10

Hydroxylamine Scope



Hydroxylamine	Product	Yield
		86%
		76%
		80%
		78%

3.4 Conclusion

This method for the synthesis of isoxazolooxazines demonstrated the ability for N-Substituted hydroxylamine to build stereochemically dense molecules. Using simple enals similar structure, a regioselective and stereochemically rich fused ring system that incorporated two heterocyclic rings were achieved. Further research

efforts will be exploring how to cleave the nitrogen-oxygen bond of the two heterocyclic rings to yield the desired stereochemically dense carbacycle.

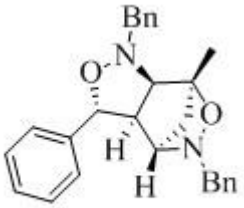
3.5 Experimental

Reagents were obtained from Aldrich Chemical, Acros Organics or Alfa Aesar and used without further purification. Solvents were obtained from EMD Miliphore DrySol and degassed with nitrogen. Reactions were performed in 4-mL glass vials with magnetic stirring. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light (254 nm) or by staining with potassium permanganate (KMnO4). Silica flash chromatography was performed on E. Merck 230–400 mesh silica gel 60. Automated chromatography was performed on a ISOLERA Prime instrument with 10 g. SNAP silica gel normal phase cartridges using a flow rate of 12.0 mL/min and a gradient of 0–25% Ethyl Acetate in Heptanes over 12 column volumes with UV detection at 254 nm. NMR spectra were recorded on Varian Mercury II 400 MHz Spectrometer at 24 °C in $CDCl_3$ unless otherwise indicated. Chemical shifts are expressed in ppm 74 relative to solvent signals: $CDCl_3$ (1H, 7.23 ppm; 13C, 77.0 ppm; coupling constants are expressed in Hz).

3.5.1. General Method for the Synthesis of Isoxazolooxazines

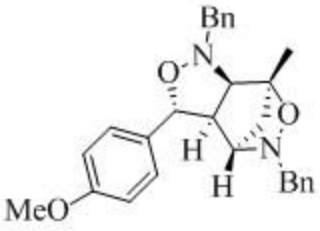
In a 4- mL glass vial, 1 mMol isoxazolidine and 1.5 equivalents hydroxylamine were dissolved in 100 mL anhydrous acetonitrile. The reaction was stirred vigorously at 80°C for 24 hours. The reaction contents were then concentrated by rotary evaporation to afford the crude product. The crude product is filtered through silica gel over a gradient of 3:1 Heptanes/Ethyl Acetate over 12 column volumes to obtain the respective isoxazolooxazine in excellent yields

3.5.2. Synthesis of Isoxazolooxazines from Table 8



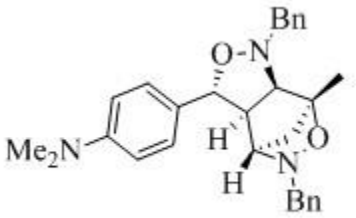
C1A (LNT-99P_8-9)

(3R,3aR,4R,7S,7aR)-1,5-dibenzyl-7-methyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C1A): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/ethyl acetate over 12 min) yielded the isoxazolooxazine **1A** (86%) as a white solid. **TLC:** Rf 0.32 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.25 – 7.22 (m, 10H), 7.19 (d, *J* = 4.4 Hz, 2H), 7.18 (d, *J* = 2.6 Hz, 2H), 4.49 (d, *J* = 7.0 Hz, 1H), 4.01 – 3.88 (m, 4H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.37 (s, 1H), 3.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 3.06 (t, *J* = 7.8 Hz, 1H), 2.41 (d, *J* = 11.3 Hz, 1H), 1.92 – 1.88 (m, 1H), 1.34 (s, 3H). **^{13}C NMR** (125 MHz, Common NMR Solvents) δ 137.94, 136.78, 136.35, 128.90, 128.60, 128.40, 127.99, 127.65, 81.20, 72.17, 64.93, 63.13, 62.24, 48.21, 42.84, 22.95.



C1B (DJQ-603-P2)

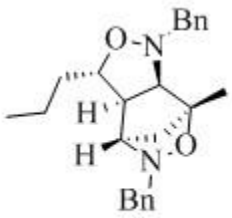
(3R,3aR,4R,7S,7aR)-1,5-dibenzyl-3-(4-methoxyphenyl)-7-methylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C1B): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/ethyl acetate over 12 min) yielded the isoxazolooxazine **1B** (84%) as a white solid. **TLC:** Rf 0.36 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.35 (d, J = 7.7 Hz, 3H), 7.32 – 7.21 (m, 7H), 6.85 (d, J = 8.1 Hz, 2H), 4.52 (d, J = 7.1 Hz, 1H), 4.09 – 3.94 (m, 3H), 3.78 (s, 3H), 3.72 (d, J = 12.9 Hz, 1H), 3.41 (s, 1H), 3.22 (d, J = 8.3 Hz, 1H), 3.11 (t, J = 7.7 Hz, 1H), 2.48 (d, J = 11.3 Hz, 1H), 1.97 (d, J = 11.3 Hz, 1H), 1.42 (s, 3H), 1.27 (s, 1H), 0.89 (t, J = 6.3 Hz, 1H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 159.48 , 137.28 , 136.85 , 131.17 , 129.25 , 128.45 , 128.34 , 128.21 , 127.40 , 127.30 , 113.85 , 85.47 , 81.85 , 63.55 , 63.07 , 62.45 , 60.97 , 55.27 , 34.14 , 31.88 , 22.69 , 14.84 , 14.12 .



C1C (BEA-145P_F1)

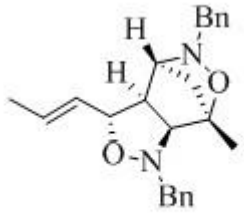
4-((3R,3aR,4R,7S,7aR)-1,5-dibenzyl-7-methylhexahydro-1H-4,7-methanoisoxazolo[4,3-d][1,2]oxazin-3-yl)-N,N-dimethylaniline (C1C): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/ethyl acetate over 12 min) yielded the isoxazolooxazine **1C** (87%) as a yellow solid. **TLC:** Rf 0.34 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 7.5 Hz, 3H), 7.33 (d, *J* = 7.9 Hz, 5H), 7.26 (s, 3H), 7.24 (s, 1H), 6.71 (d, *J* = 8.7 Hz, 2H), 4.54 (d, *J* = 6.9 Hz, 1H), 4.06 (q, *J* = 14.2 Hz, 3H), 3.74 (d, *J* = 12.9 Hz, 1H), 3.43 (s, 1H), 3.26 (d, *J* = 8.3 Hz, 1H), 3.19 (t, *J* = 7.7 Hz, 1H), 2.95 (s, 6H), 2.52 (d, *J* = 11.2 Hz, 1H), 1.99 (d, *J* = 11.2 Hz, 1H), 1.44 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-d) δ 150.61 , 137.44 , 136.92 , 129.45 ,

129.39 , 128.53 , 128.39 , 128.24 , 127.47 , 127.31 , 112.39 , 85.60 , 82.29 , 75.64 , 63.64 , 63.15 , 62.54 , 60.62 , 40.60 , 34.24 , 14.94 .



C1D (BEA-148P_F1)

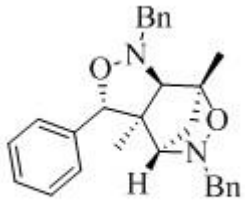
(3S,3aR,4R,7S,7aR)-1,5-dibenzyl-7-methyl-3-propylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C1D): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/ethyl acetate over 12 min) yielded the isoxazolooxazine **1D** (72%) as a yellow oil. **TLC:** Rf 0.39 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-d) δ 7.32 (dq, J = 24.9, 8.2 Hz, 10H), 4.04 (dd, J = 13.2, 6.8 Hz, 2H), 3.94 (d, J = 13.7 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H), 3.60 – 3.55 (m, 1H), 3.29 (s, 1H), 3.07 (d, J = 8.2 Hz, 1H), 2.73 (t, J = 7.1 Hz, 1H), 2.29 (d, J = 11.1 Hz, 1H), 1.88 (d, J = 11.1 Hz, 1H), 1.64 (ddd, J = 15.9, 10.0, 4.9 Hz, 1H), 1.35 (s, 4H), 0.90 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 137.53 , 136.90 , 129.61 , 129.14 , 129.08 , 128.38 , 128.14 , 127.32 , 127.19 , 85.32 , 80.50 , 75.08 , 63.72 , 63.58 , 62.23 , 59.59 , 36.88 , 34.00 , 29.63 , 19.52 , 14.74 , 14.02 .



C1E (BEA-146P_F1)

(3R,3aS,4S,7R,7aS)-1,5-dibenzyl-7-methyl-3-((E)-prop-1-en-1-yl)hexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C1E): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/ethyl acetate over 12 min) yielded the isoxazolooxazine **1E** (75%) as a yellow oil. **TLC:** Rf 0.37 (2:1 heptanes/ethyl acetate).**^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.39

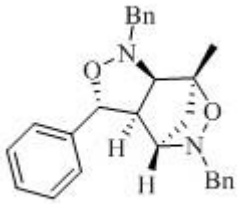
– 7.26 (m, 10H), 5.71 (dq, *J* = 13.6, 6.6 Hz, 1H), 5.52 (dd, *J* = 15.3, 7.6 Hz, 1H), 4.11 – 4.00 (m, 3H), 3.95 (d, *J* = 13.7 Hz, 1H), 3.73 (d, *J* = 12.9 Hz, 1H), 3.36 (s, 1H), 3.15 (d, *J* = 8.1 Hz, 1H), 2.90 (t, *J* = 7.0 Hz, 1H), 2.32 (d, *J* = 11.2 Hz, 1H), 1.93 (d, *J* = 11.2 Hz, 1H), 1.71 (d, *J* = 6.4 Hz, 3H), 1.37 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 137.51 , 136.97 , 130.48 , 129.82 , 129.34 , 129.12 , 128.49 , 128.29 , 127.44 , 127.33 , 85.45 , 82.07 , 75.58 , 63.74 , 63.43 , 62.42 , 59.40 , 34.14 , 17.88 , 14.84 .



C1F (LNT-237P_44-53)

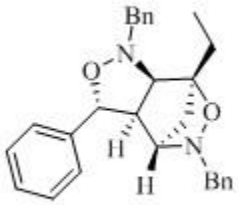
(3S,4R,7S,7aR)-1,5-dibenzyl-3a,7-dimethyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C1F): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/ethyl acetate over 12 min) yielded the isoxazolooxazine **1F** (78%) as a translucent oil. TLC: Rf 0.29 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 12.31 (s, 5H), 12.27 (s, 2H), 12.23 (d, *J* = 7.2 Hz, 4H), 12.16 (s, 3H), 11.68 (s, 1H), 11.45 (s, 1H), 9.77 (s, 3H), 9.03 (d, *J* = 14.7 Hz, 1H), 8.67 (d, *J* = 14.7 Hz, 1H), 8.32 (t, *J* = 8.5 Hz, 1H), 7.94 (dd, *J* = 13.1, 7.8 Hz, 1H), 7.34 (dd, *J* = 12.9, 9.3 Hz, 1H), 6.84 (s, 3H), 6.59 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 141.97 , 137.88 , 137.39 , 135.34 , 132.70 , 129.30 , 129.12 , 129.08 , 128.96 , 128.75 , 128.31 , 128.23 , 128.13 , 127.04 , 126.60 , 80.17 , 69.92 , 59.72 , 44.11 , 31.97 , 29.71 , 29.42 , 22.75 , 22.38 , 14.19 .

3.5.3. Synthesis of Isoxazolooxazines from Table 9



C2A (LNT-99P_8-9)

(3R,3aR,4R,7S,7aR)-1,5-dibenzyl-7-methyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C2A): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/EtOAc over 12 min) yielded the isoxazolooxazine **2A** (86%) as a white solid. **TLC:** Rf 0.32 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.25 – 7.22 (m, 10H), 7.19 (d, *J* = 4.4 Hz, 2H), 7.18 (d, *J* = 2.6 Hz, 2H), 4.49 (d, *J* = 7.0 Hz, 1H), 4.01 – 3.88 (m, 4H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.37 (s, 1H), 3.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 3.06 (t, *J* = 7.8 Hz, 1H), 2.41 (d, *J* = 11.3 Hz, 1H), 1.92 – 1.88 (m, 1H), 1.34 (s, 3H). **^{13}C NMR** (125 MHz, Common NMR Solvents) δ 137.94, 136.78, 136.35, 128.90, 128.60, 128.40, 127.99, 127.65, 81.20, 72.17, 64.93, 63.13, 62.24, 48.21, 42.84, 22.95.

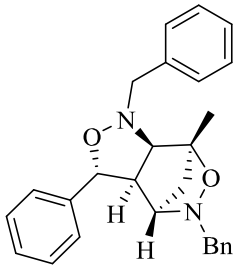


C2B (BEA-147P_F1)

(3R,3aR,4R,7S,7aR)-1,5-dibenzyl-7-ethyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C2B): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/EtOAc over 12 min) yielded the isoxazolooxazine **2B** (85%) as a yellow oil. **TLC:** Rf 0.33 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.41 – 7.33 (m, 13H), 7.30 – 7.25 (m, 2H), 4.62 (d, *J* = 6.8 Hz, 1H), 4.11 – 4.00 (m, 3H), 3.75

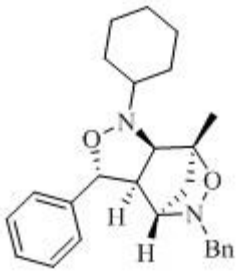
(d, *J* = 12.9 Hz, 1H), 3.50 (s, 1H), 3.33 (d, *J* = 8.3 Hz, 1H), 3.22 (t, *J* = 7.5 Hz, 1H), 2.40 (d, *J* = 11.3 Hz, 1H), 2.14 (d, *J* = 11.3 Hz, 1H), 1.97 (dd, *J* = 14.5, 7.3 Hz, 1H), 1.80 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.33 (s, 1H), 1.11 (td, *J* = 7.4, 1.4 Hz, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 139.47 , 137.28 , 136.78 , 129.26 , 129.05 , 128.37 , 128.34 , 128.11 , 127.89 , 127.32 , 127.18 , 126.72 , 88.79 , 82.12 , 74.71 , 63.47 , 62.94 , 62.12 , 60.64 , 30.81 , 29.62 , 21.21 , 8.77 .

3.5.4. Synthesis of Isoxazolooxazines from Table 10



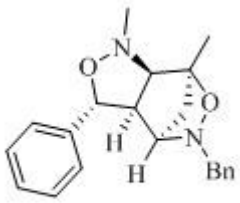
C3A (LNT-99P_8-9)

(3R,3aR,4R,7S,7aR)-1,5-dibenzyl-7-methyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C3A): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/EtOAc over 12 min) yielded the isoxazolooxazine **3A** (86%) as a white solid. **TLC**: Rf 0.32 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.25 – 7.22 (m, 10H), 7.19 (d, *J* = 4.4 Hz, 2H), 7.18 (d, *J* = 2.6 Hz, 2H), 4.49 (d, *J* = 7.0 Hz, 1H), 4.01 – 3.88 (m, 4H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.37 (s, 1H), 3.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 3.06 (t, *J* = 7.8 Hz, 1H), 2.41 (d, *J* = 11.3 Hz, 1H), 1.92 – 1.88 (m, 1H), 1.34 (s, 3H). **^{13}C NMR** (125 MHz, Common NMR Solvents) δ 137.94, 136.78, 136.35, 128.90, 128.60, 128.40, 127.99, 127.65, 81.20, 72.17, 64.93, 63.13, 62.24, 48.21, 42.84, 22.95.



C3B (LNT-196P_23-38)

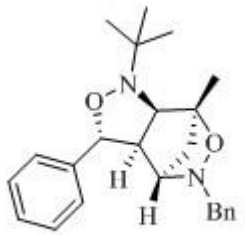
(3R,3aR,4R,7S,7aR)-5-benzyl-1-cyclohexyl-7-methyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C3B): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/EtOAc over 12 min) yielded the isoxazolooxazine **3B** (76%) as a white solid. **TLC**: Rf 0.34 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.33 – 7.24 (m, 10H), 4.53 (d, *J* = 6.4 Hz, 1H), 4.03 (d, *J* = 13.0 Hz, 1H), 3.72 (d, *J* = 12.9 Hz, 1H), 3.43 (d, *J* = 10.2 Hz, 2H), 3.15 (t, *J* = 7.5 Hz, 1H), 2.50 (s, 1H), 2.42 (s, 1H), 1.94 (s, 2H), 1.74 (s, 3H), 1.63 (s, 2H), 1.46 (s, 3H), 1.34 (s, 4H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 140.02 , 136.90 , 129.23 , 128.44 , 128.00 , 127.37 , 127.01 , 85.87 , 82.01 , 72.21 , 65.29 , 63.96 , 62.44 , 60.46 , 34.14 , 32.47 , 27.12 , 26.01 , 25.69 , 25.30 , 15.18 .



C3C (LNT-197P)

(3R,3aR,4R,7S,7aR)-5-benzyl-1,7-dimethyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (**C3C):** Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/EtOAc over 12 min) yielded the isoxazolooxazine **3C** (80%) as a white solid. **TLC**: Rf 0.36 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.33 (dd, *J* = 13.1, 5.1 Hz, 8H), 7.26 (s, 2H), 4.54 (d, *J* = 7.8 Hz, 1H), 4.05 (d, *J* = 12.9 Hz, 1H), 3.73 (d, *J* = 12.9 Hz, 1H), 3.43 (s, 1H), 3.13 (t, *J* = 7.9 Hz, 1H), 2.94 (d, *J* = 9.9 Hz, 1H), 2.80 (s, 4H), 2.47 (d, *J* = 11.2 Hz, 1H), 2.00 (d, *J* = 11.3 Hz, 1H), 1.48 (s, 3H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 138.41 , 136.74 , 129.15 , 128.52 , 128.40 ,

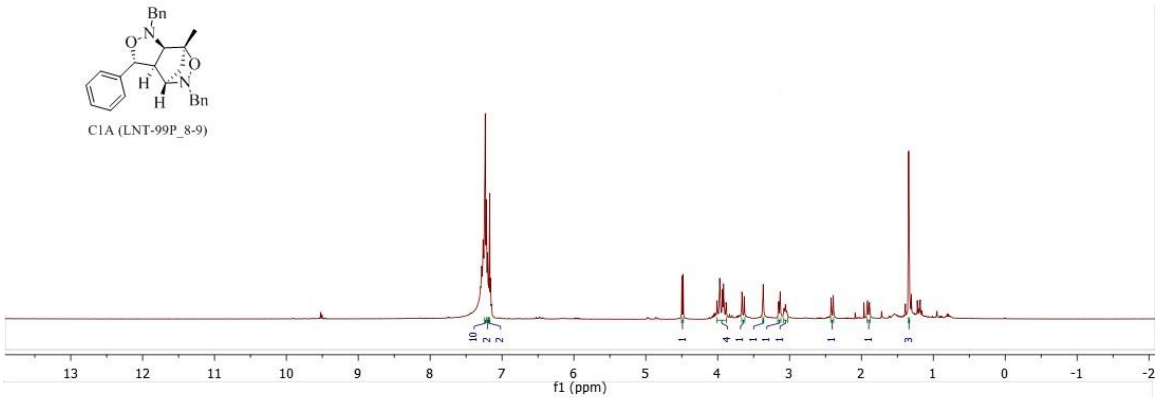
128.24 , 127.36 , 126.95 , 85.15 , 82.00 , 63.21 , 62.35 , 61.80 , 45.93 , 33.94 , 29.64 , 14.67 .

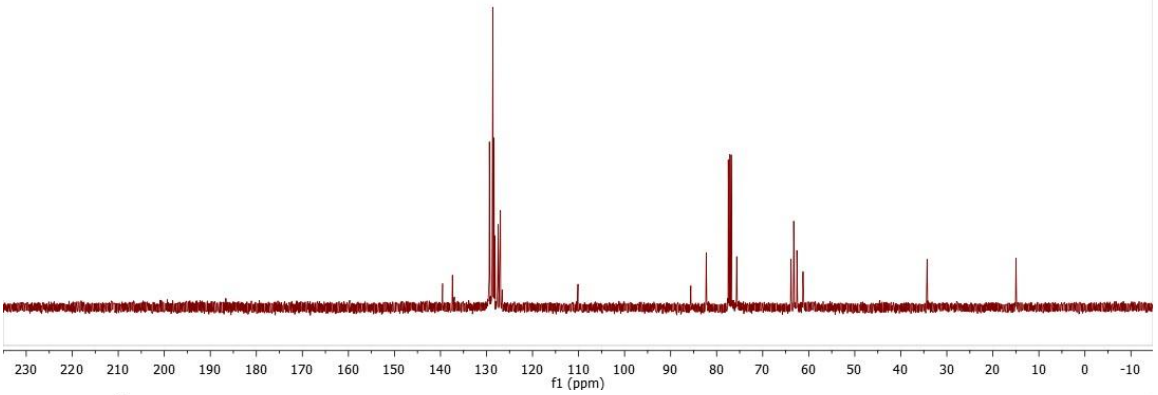


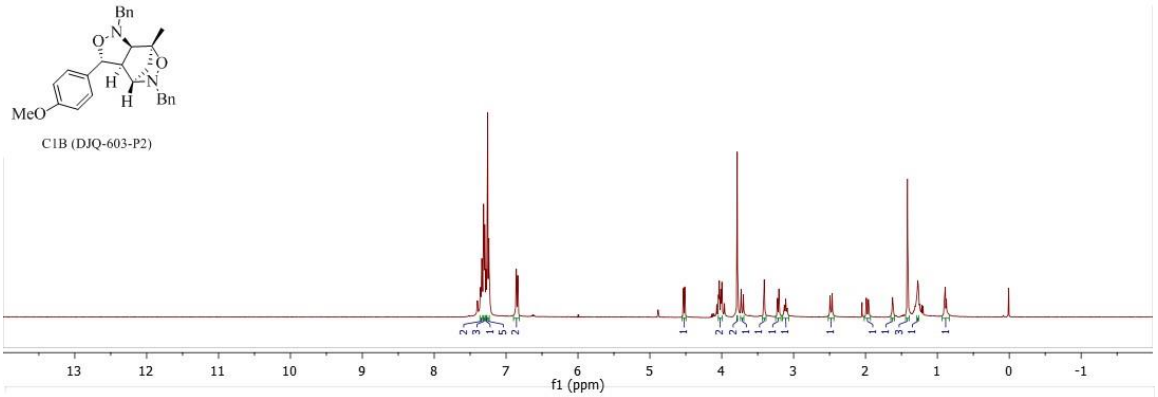
C3D (LNT-213P_29-37)

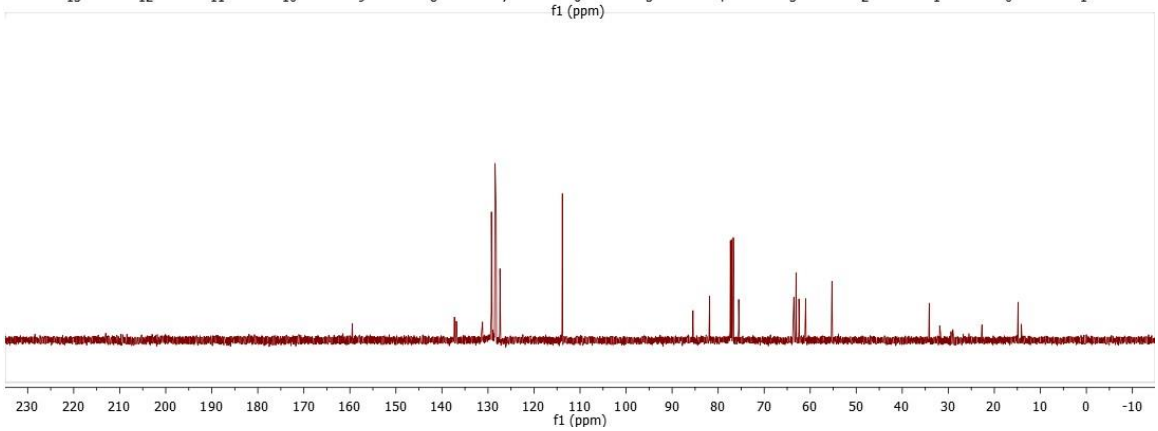
(3R,3aR,4R,7S,7aR)-5-benzyl-1-(tert-butyl)-7-methyl-3-phenylhexahydro-1H-4,7methanoisoxazolo[4,3-d][1,2]oxazine (C3D): Purification by automated silica gel flash chromatography (10 g cartridge, 14mL/min. 20:1 heptanes/ethyl acetate to 1:3 heptanes/EtOAc over 12 min) yielded the isoxazolooxazine **3C** (78%) as a white solid. **TLC**: Rf 0.35 (2:1 heptanes/ethyl acetate). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.35 (d, *J* = 5.2 Hz, 8H), 7.27 (d, *J* = 6.9 Hz, 2H), 4.57 (d, *J* = 7.6 Hz, 1H), 4.04 (d, *J* = 12.8 Hz, 1H), 3.74 (d, *J* = 12.9 Hz, 1H), 3.46 (d, *J* = 9.9 Hz, 2H), 3.17 (t, *J* = 8.2 Hz, 1H), 2.42 (d, *J* = 11.5 Hz, 1H), 1.99 (d, *J* = 11.5 Hz, 1H), 1.52 (s, 3H), 1.16 (s, 9H). **^{13}C NMR** (101 MHz, Chloroform-*d*) δ 139.74 , 136.73 , 129.22 , 128.41 , 127.88 , 127.37 , 126.72 , 86.11 , 81.55 , 69.79 , 63.83 , 62.57 , 61.96 , 59.40 , 34.75 , 26.52 , 16.27 .

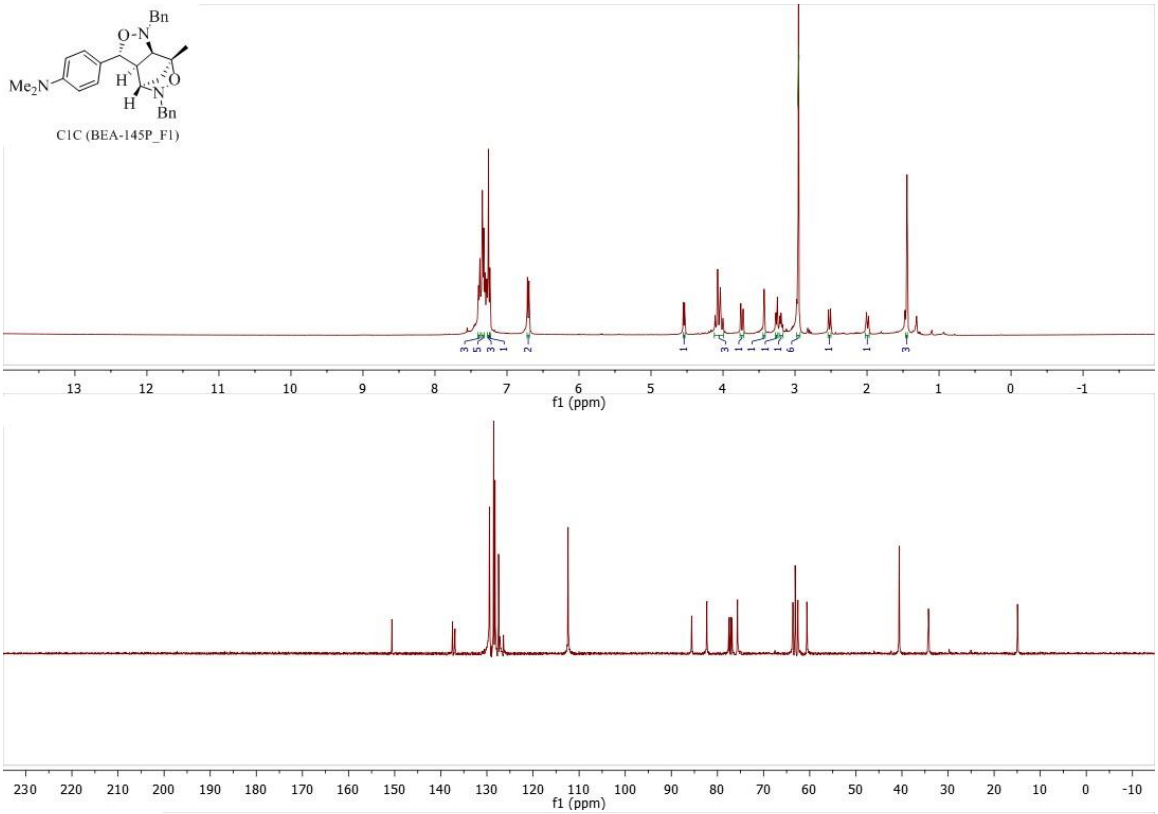
3.5.5. ^{1}H NMR and ^{13}C NMR of Isoxazolooxazines

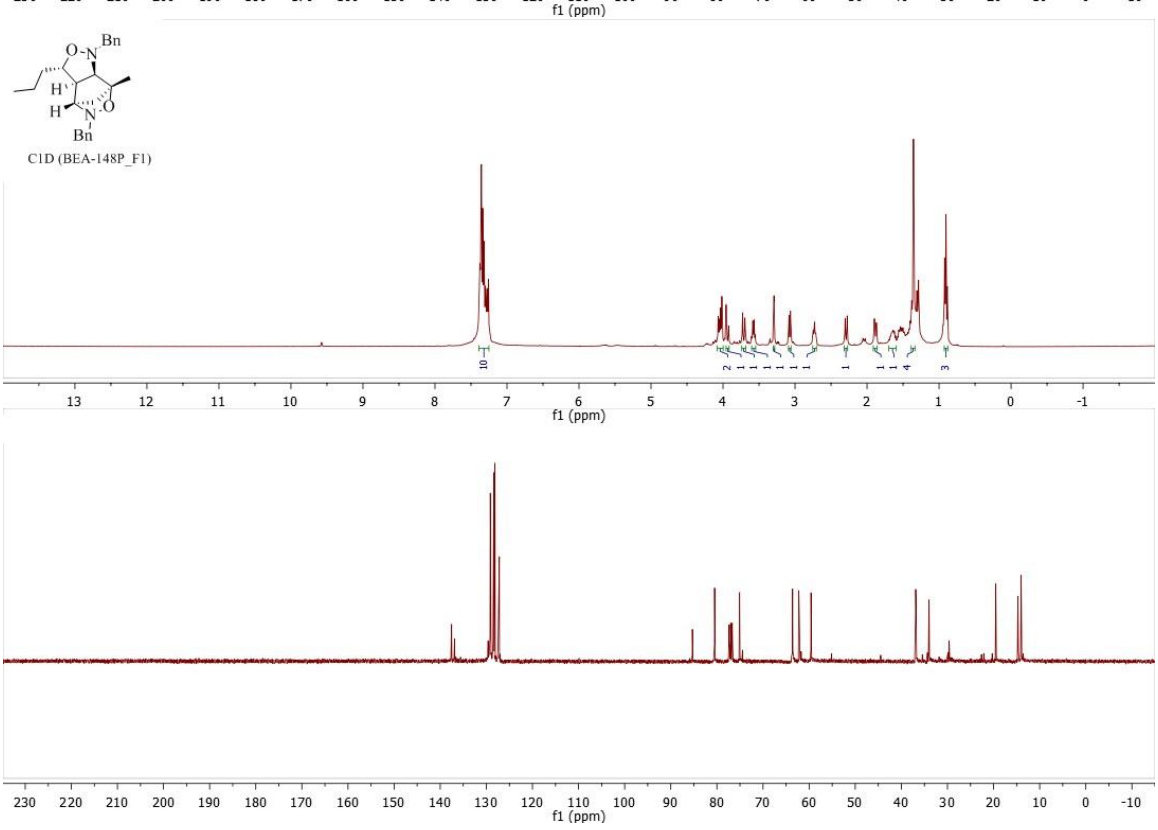


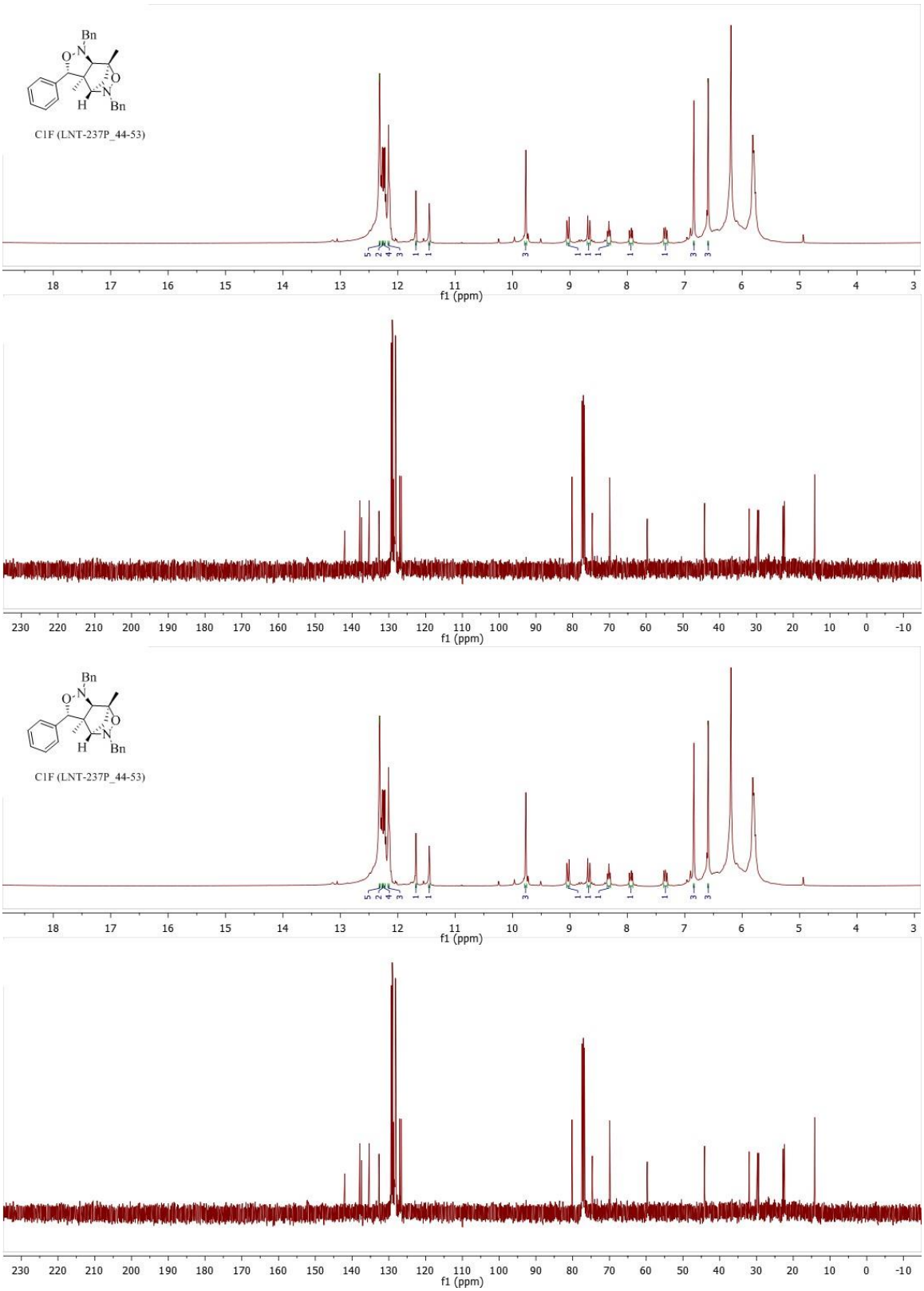


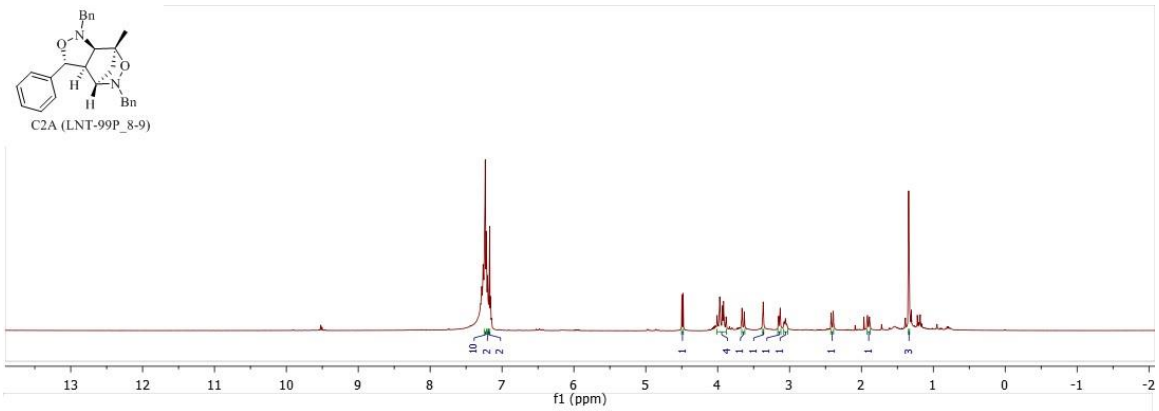


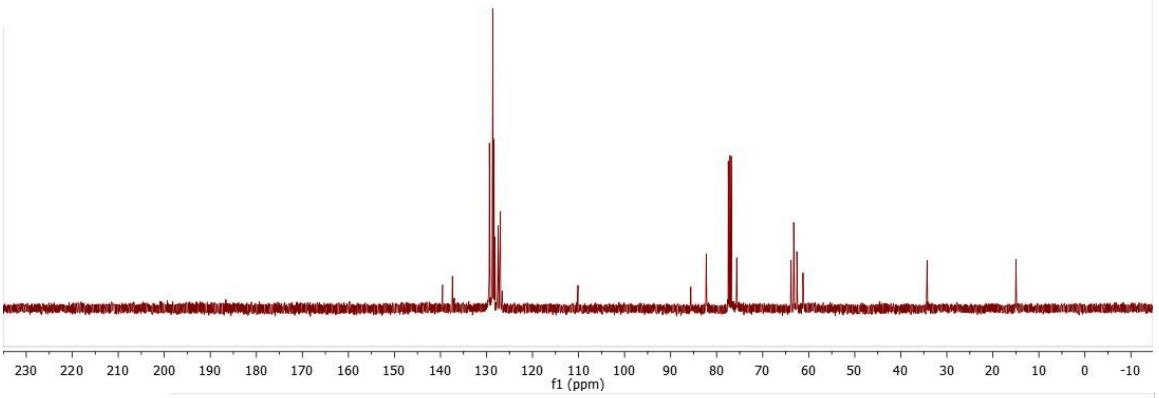


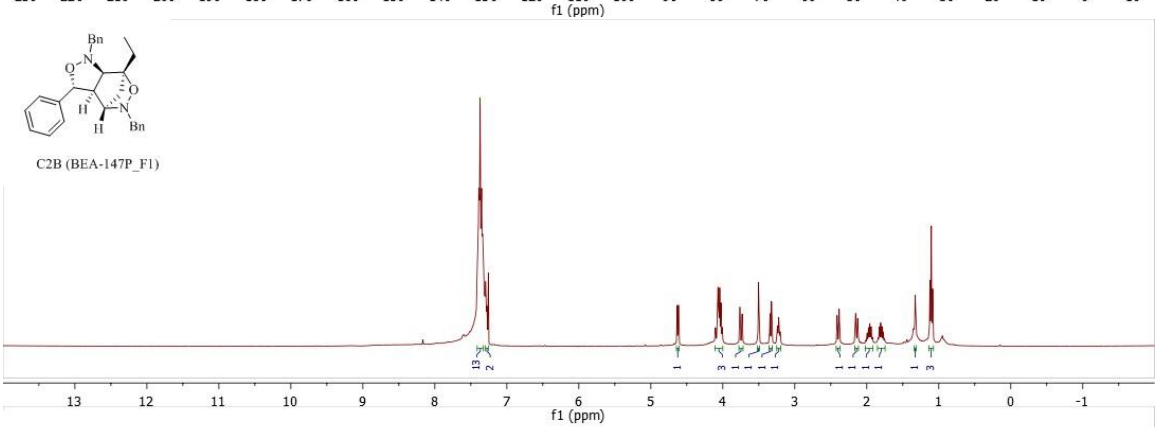


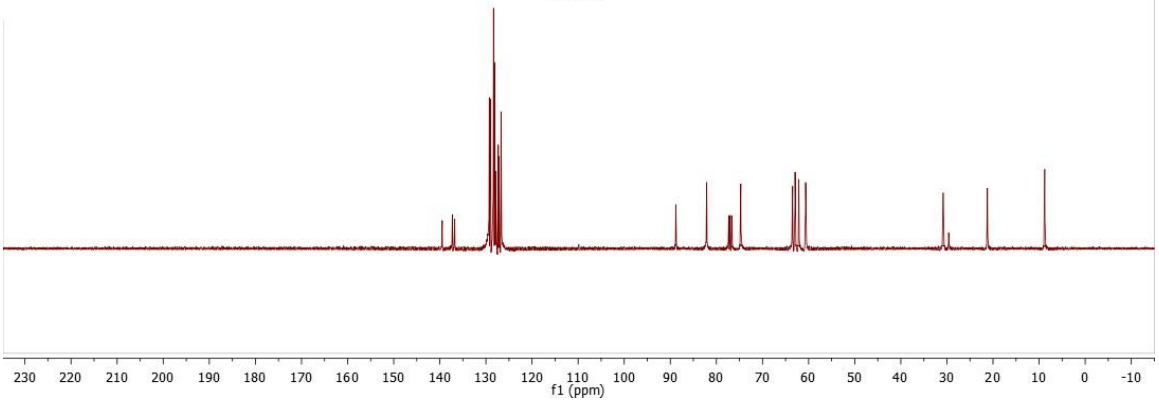


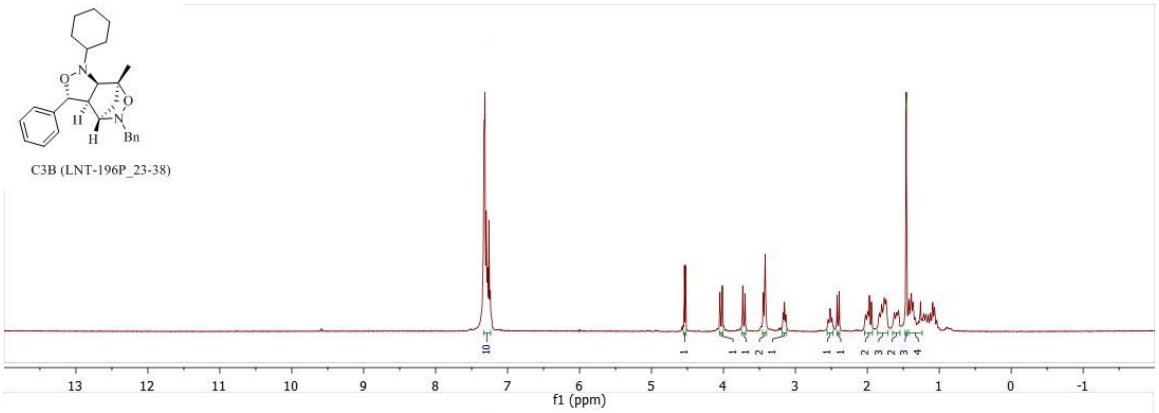


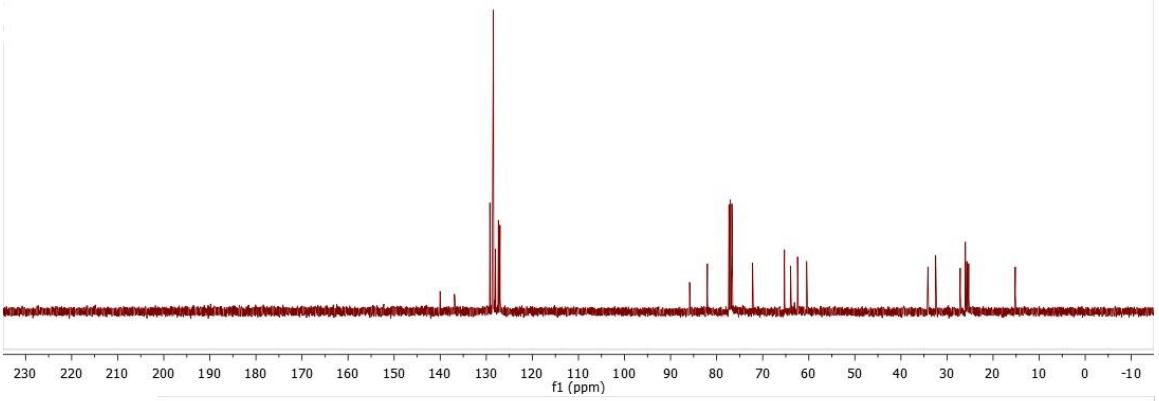


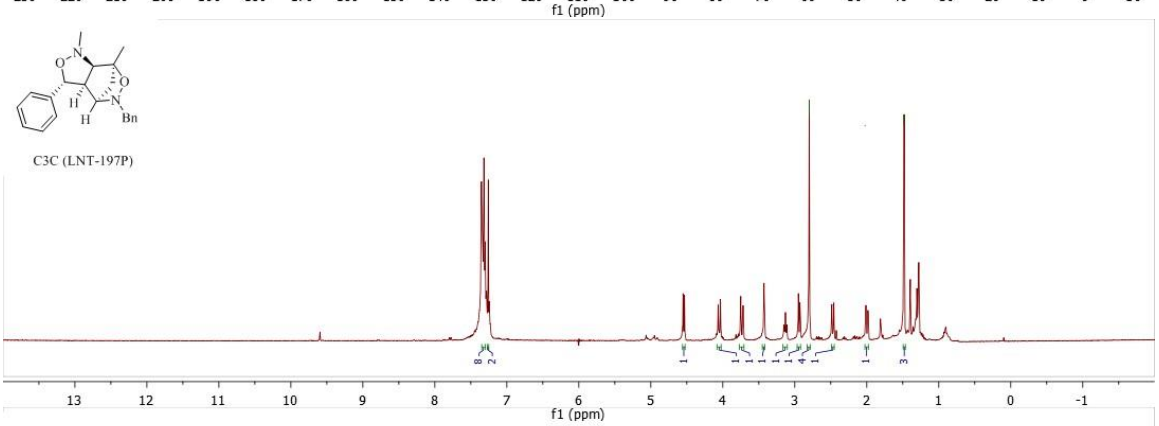


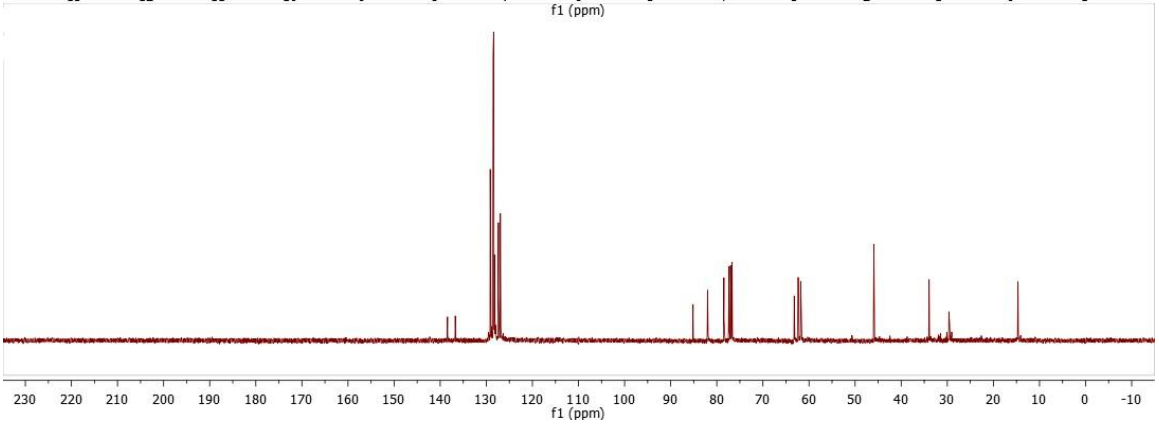


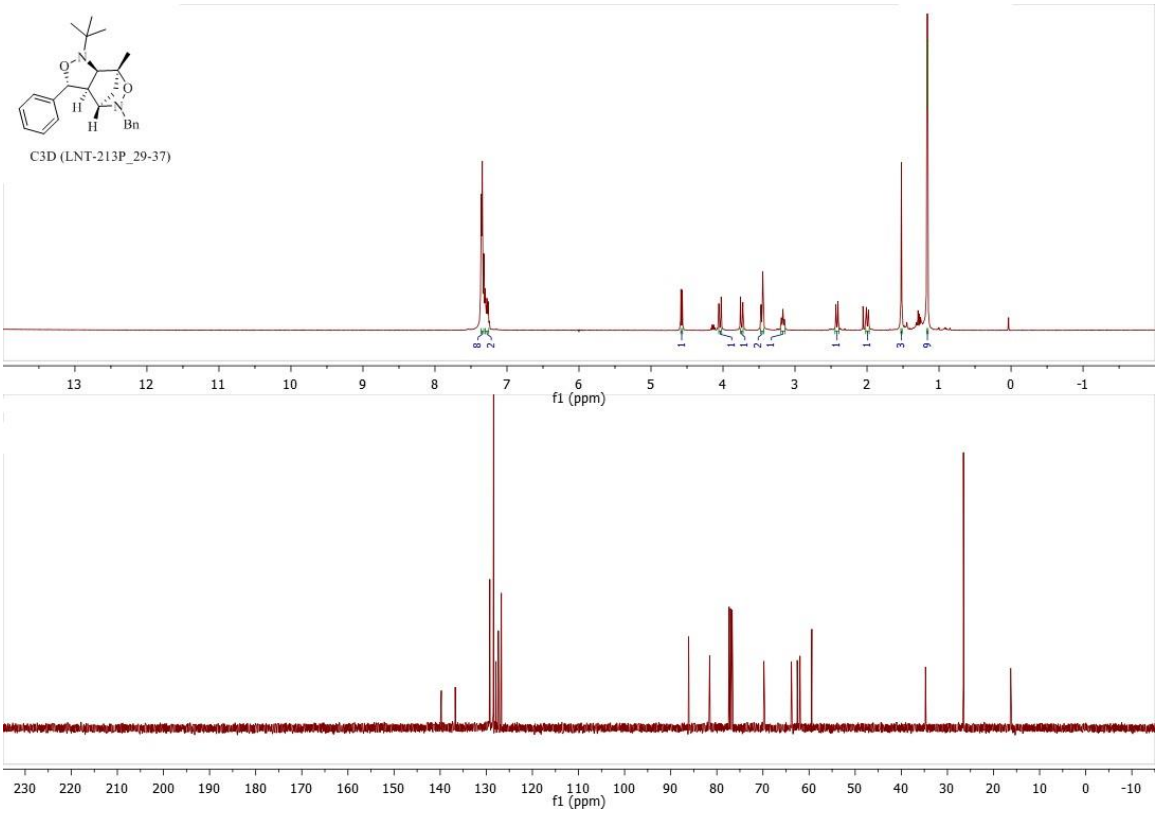












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