Intramolecular Cycloadditions of Allenes with Aminofurans and Aminooxazoles

by

Dishit P. Jhaveri

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This thesis was presented

by

Dishit P. Jhaveri

It was defended on

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and approved by

Dr. Alexander Deiters, Professor, Departmental of Chemistry

Dr. Dennis Curran, Distinguished Service Professor of Chemistry and Bayer Professor, Department of Chemistry

Thesis Advisor: Dr. Peter Wipf, Distinguished University Professor, Department of Chemistry

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A thermal cycloaddition of allenes tethered to an aminofuran provided good yields of substituted indoles. Allene-tethered 5-aminooxazoles were converted to 6-azaindoles, whereas 2-aminooxazoles lacked reactivity. The substrate scope and some limitations of this new reaction are discussed.

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LIST OF ABBREVIATIONS

aq……aqueous

Boc…….*tert*-butyloxycarbonyl

bs……broad singlet

DBN……...1,5-diazabicyclo[4.3.0]non-5-ene

DBU……...1,8-diazabicyclo[5.4.0]undec-7ene

DDQ……...2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DMAP……4-*N*,*N*-dimethylaminopyridine

DMF……...dimethylformamide

DPPA……..diphenylphosphoryl azide

dd……doublet of doublet

dt…….doublet of triplet

Et…….ethyl

HRMS…….high resolution mass spectroscopy

IMDAF……....intramolecular Diels-Alder furan reaction

IR…….infrared spectroscopy

LUMO…….lowest unoccupied molecular orbital

m…….multiplet

mp……...melting point

Ms……...mesyl

NMP……*N*-methyl pyrrolidione

NMR……nuclear magnetic resonance

o-DCB……..ortho dichlorobenzene

Pd……..palladium

PG…….protecting group

p……pentet

q……quartet

RBF……...round bottom flask

s…….singlet

SM…….starting material

t……..triplet

t-Bu……*tert*-butyl

THF……tetrahydrofuran

TLC……thin layer chromatography

PREFACE

I would like to thank Dr. Peter Wipf for mentoring me and providing the opportunity to conduct research in his lab. I would like to thank Dr. Alexander Deiters and Dr. Dennis Curran for serving on my committee and the University of Pittsburgh for its financial support.

It has been a joyful experience to work with members of the Wipf group and I thank all of them for their companionship and support. I would also like to thank all my friends in the Department of Chemistry for making my time in Pittsburgh memorable. Lastly, I would like to thank my family for all their love and encouragement. Thank you.

1.0 INTRAMOLECULAR CYCLOADDITIONS OF ALLENES WITH AMINOFURANS AND AMINOOXAZOLES

1.1 INTRAMOLECULAR CYCLOADDITIONS OF ALLENES WITH AMINOFURANS

1.1.1 Introduction

1.1.1.1 Intramolecular Diels Alder Reaction of Furans

The [4+2] cycloaddition of a diene with a dienophile has been well studied and synthetically exploited to form 6-membered rings and generally proceeds with high levels of regio- and diastereoselectivity. Several auxiliaries and chiral Lewis acids have been developed to attain a high level of enantioselectivity.[1] The initial report by Diels and Alder used furan as a 4π component.[2] Since then, the use of furan and its derivatives as dienes has been well documented and used to access useful synthetic intermediates.[3]

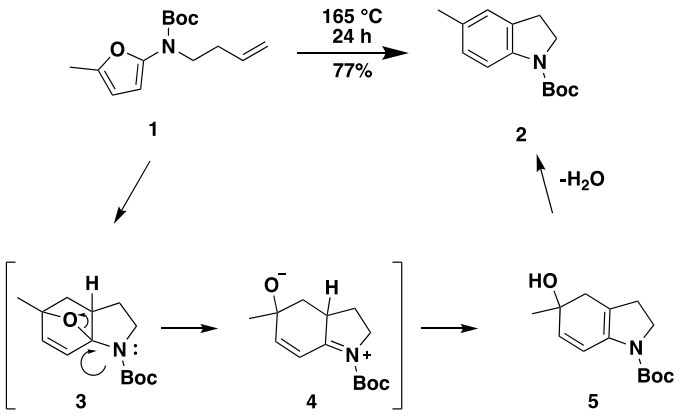
The intramolecular Diels-Alder reaction of furan (IMDAF) with a dienophile proceeds smoothly to give access to fused ring systems.[4] The scope of the reaction with respect to the substituents on the furan, the dienophile, and the tether length has been explored.[3] Studies of solvent effects on the rate of the reaction suggests that it proceeds via a polar transition state.[5] The

ease of reaction, high selectivity, and increased complexity of the products formed has rendered the IMDAF reaction useful for the synthesis of many natural products.[4]

1.1.1.2 IMDAF Reactions of Aminofurans

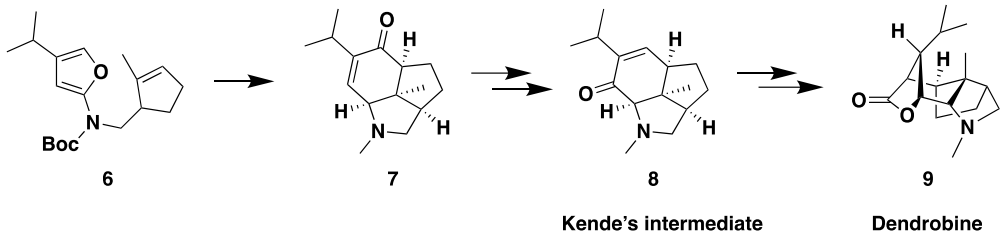
Aminofurans are unstable molecules and cannot be readily isolated since they are very electron rich and readily undergo oxidation.[6] The introduction of an electron withdrawing group on the amine increases the stability of the molecule by reducing the electron density in the ring and makes it amenable to further transformations.[7] The synthesis of 2-aminofurans is accomplished by the reaction of 2-furoic acid or its corresponding acyl halide with an azide source followed by a Curtius rearrangement in the presence of an alcoholic solvent.[8] The IMDAF reaction of 2-aminofuran derivatives has been examined by the Padwa group.[9]

The initial adducts formed after the IMDAF reaction using aminofurans are unstable and undergo aromatization to afford indolines. For example, heating aminofuran **1** at 165 °C gives indoline **2** in 77% yield (Scheme 1).[9] The reaction is proposed to proceed through the initial cycloadduct **3** which then undergoes ring opening and isomerization to give intermediate **5**. Dehydrative aromatization of **5** forms the indoline **2**.



Scheme 1. IMDAF reaction of 2-aminofuran

Many alkaloids have been targeted using the IMDAF reaction of 2-aminofurans.[4] For example, the key step in Padwa's synthesis[10] of dendrobine **9** involved an IMDAF reaction of aminofuran **6** to form the cycloadduct **7**, followed by a rearrangement to access **8**, an advanced intermediate that the Kende group used for the synthesis of dendrobine (Scheme 2).[11]



Scheme 2. Padwa's formal synthesis of dendrobine using IMDAF

1.1.1.3 Synthesis of Indoles using an IMDAF Reaction

Since its isolation by von Baeyer from coal tar with sulfuric acid, indole and its derivatives have been studied and synthesized for over a century.[12] Interest in the indole scaffold continues to grow because it is abundant in natural products and biologically active compounds.[13] Biologically important compounds that contain the indole motif include the amino acid tryptophan **10**, which is also the precursor to several indole alkaloids,[14] the neurotransmitter serotonin[15] **11** and the human hormone melatonin[16] **12**. The indole scaffold has important significance in medicinal chemistry. Several pharmaceuticals like pindolol **13**, indometacin **14**, etodolac **15**, sumitriptan **16** and indolmycin **17** contain indoles (Figure 1).[17]

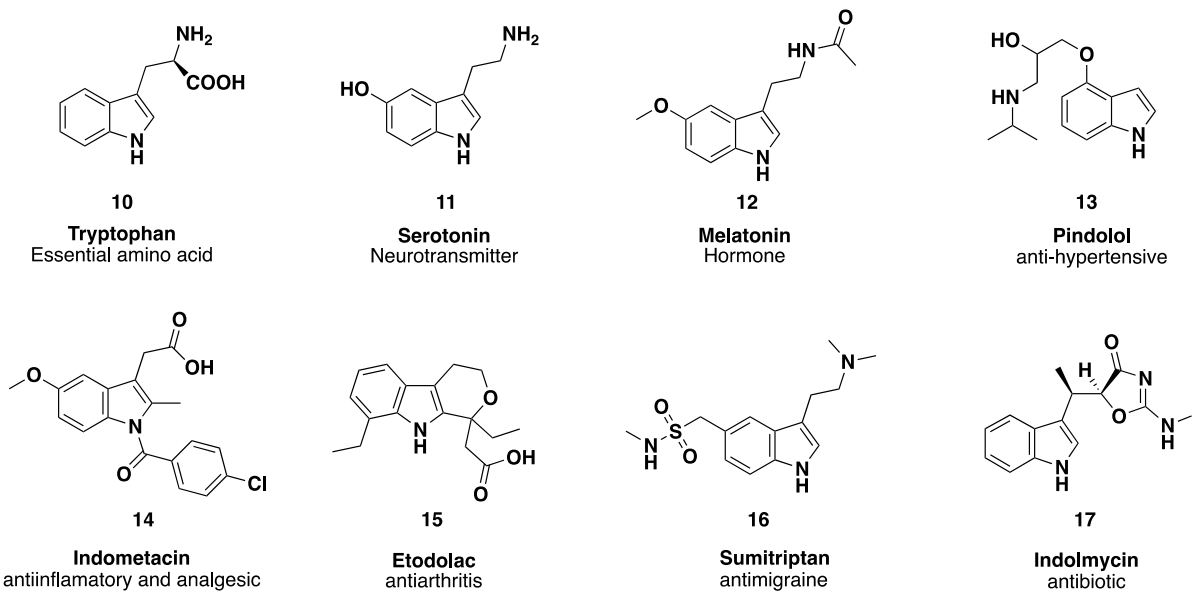


Figure 1. Biologically relevant compounds containing an indole ring

Alkaloid natural products that contain the indole core include the vinca alkaloids, ergot alkaloids and the strychnos alkaloids, among many others (Figure 2).

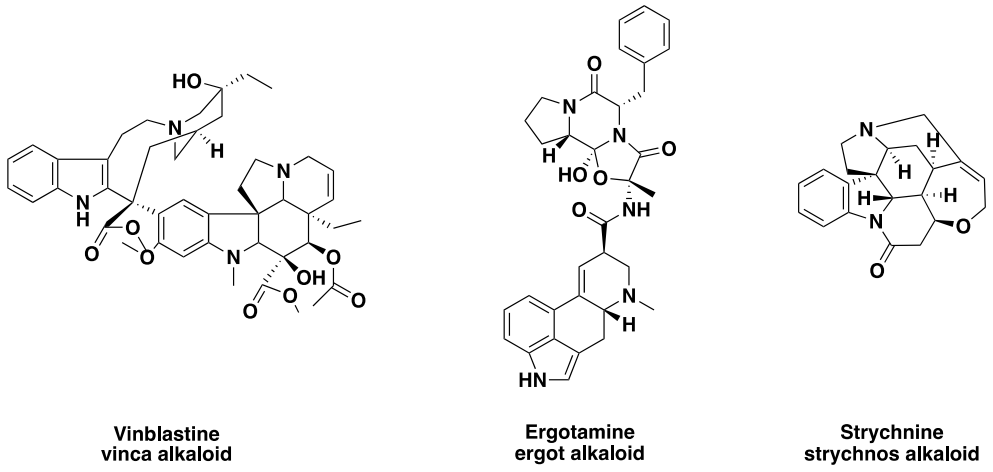
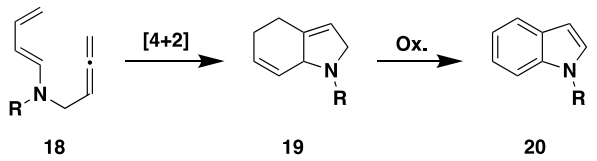


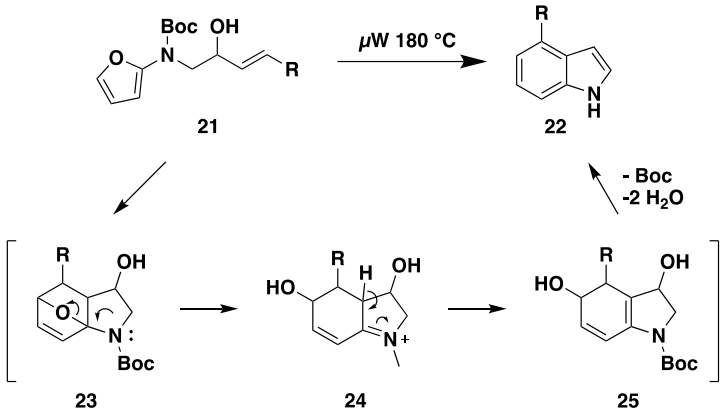
Figure 2. Representative natural products containing the indole nucleus

Subsequent to the Fischer indole synthesis, many methods and strategies have been developed for obtaining different indole substitution patterns.[18] In 1986, Kanematsu developed an intramolecular [4+2] cycloaddition of a diene with a tethered allene to form both rings of the indole core in one step.[19] Oxidative aromatization of the adducts gave the corresponding indoles.



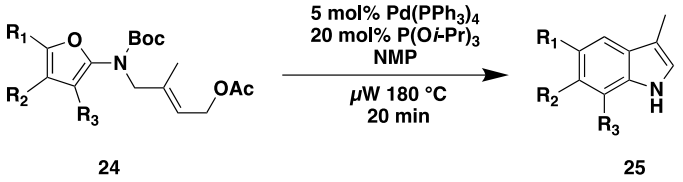
Scheme 3. Kanematsu's strategy for indole synthesis

Based on this work and Padwa's[9] indoline synthesis (vide supra), the Wipf group published a microwave assisted synthesis of 4-substituted indoles using the IMDAF reaction.[20] Heating homoallylic aminofuran **21** at 180 °C for 20 min in the microwave gave the indole **22** via an IMDAF reaction upon formation of the initial adduct **23**, followed by ring opening and elimination of water and the protecting group. The reaction gave good to moderate yields of several 4-substituted indoles[20] and was later used in the total synthesis of cycloclavine.[21, 22]



Scheme 4. Wipf's synthesis of 4-substituted indoles

In 2017, the Wipf group published a palladium-catalyzed cascade synthesis of indoles which utilized palladium π-allyl chemistry.[23] The optimized reaction conditions gave good to moderate yields for several substrates with different aryl and alkyl substituents on the 3-,4- and 5-position of the furan ring.

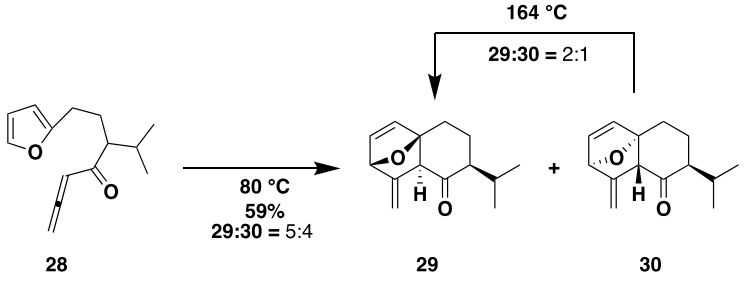


Scheme 5. Synthesis of indoles using a Pd-catalyzed IMDAF reaction

1.1.1.4 Intramolecular Cycloaddition of Allene with Furan

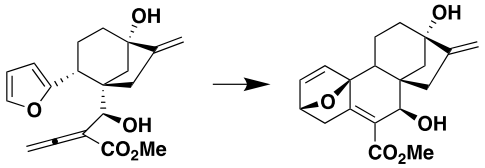
Allenes feature two adjacent π-bonds with orthogonal p-orbitals. They participate in [4+2] cycloadditions as a dienophile. The electron withdrawing sp^2 carbon of the double bond lowers the LUMO energy of the adjacent π-bond in an allene.[24] For a monosubstituted allene, the internal double bond has a lower LUMO energy and is more reactive.[24] Activated allenes react at room temperature in the presence of Lewis acids.[25] The reaction of allenic esters with furans has been studied.[26] The use of allenes in intramolecular cycloaddition reactions has been utilized for the synthesis of several natural products.[27-30] As described above, Kanematsu used this approach for the synthesis of indoles.[19]

Many examples of intramolecular cycloadditions between a furan and allene are known.[3] For example, heating **28** at 80 °C led to the formation of isomers **29** and **30** as a 5:4 mixture.[31] Further heating the mixture at 164 °C in mesitylene gave **29**:**30** in a 2:1 ratio. Compound **29** was used as an intermediate in the total synthesis of periplanone-b.[31]



Scheme 6. Intramolecular Diels-Alder reaction between furan and allene

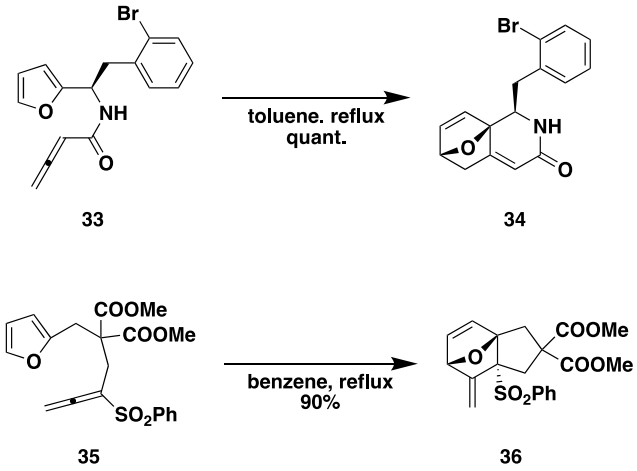
The intramolecular cycloadditions of furan **31** proceeded readily upon concentration of a pure HPLC fraction to give a single diastereomer which was confirmed by X-ray analysis.[32]



31 **32**

Scheme 7. Intramolecular cycloaddition of allene **31**

Examples of intramolecular cycloadditions of furan with allenic amides[33] and sulfonyl allenes[34] are known. Heating allenic amide **33** in toluene resulted in full conversion to **34** in less than 2 h. Similarly, heating sulfonyl allene **35** in benzene gave the adduct **36** in 90% yield.



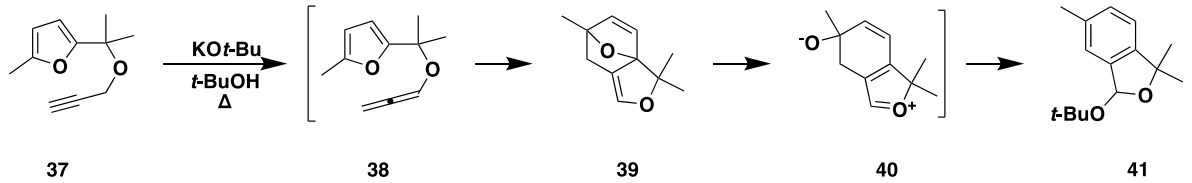
33 **34**

35 **36**

Scheme 8. Representative examples of intramolecular cycloadditions of furan with allenic amides and sulfonyl allenes

The intramolecular cycloadditions of furans with terminal alkynes in the presence of a base proceeds with isomerization of the alkyne to the corresponding allene, followed by a [4+2] cycloaddition. For example, heating furan **37** in the presence of a base initiated the isomerization of the terminal alkyne to the allene **38**. The furan then underwent an intramolecular Diels-Alder cyclization with the terminal double bond of the allene to give the cycloadduct **39**, which is

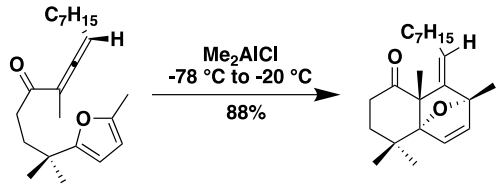
believed to undergo a fragmentation to obtain the zwitterionic species **40**. Subsequent trapping of the alkoxycarbenium ion with solvent and aromatization furnished the *tert*-butoxy derivative **41**.[35]



37 38 39 40 41

Scheme 9. Intramolecular cycloaddition of a terminal alkyne with furan in the presence of a base

Chirality transfer from the optically active allene to the cycloaddition adduct has been successfully achieved to yield an enantiomerically pure adduct.[36] Treatment of chiral allene **42** with dimethylaluminum chloride gave the Diels-Alder adduct **43** as a single enantiomer in 88% yield.



42 43

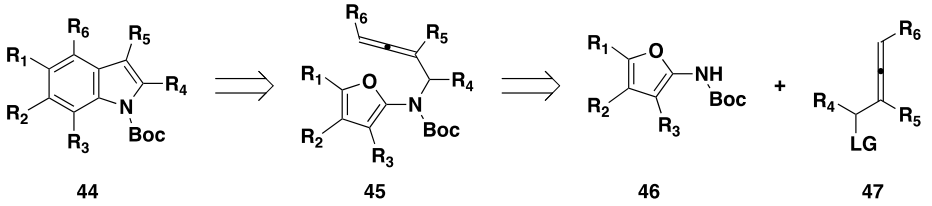
Scheme 10. Cycloaddition of chiral allene **42**

1.1.2 Results and Discussion

1.1.2.1 Introduction

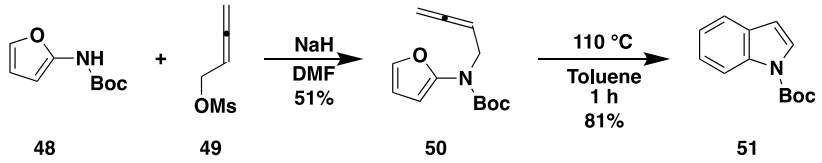
The Wipf group has an ongoing interest in the development of new methods to access indoles and has previously disclosed two methods for their synthesis using the IMDAF reaction.[20, 23] Both methods required the use of high reaction temperatures and relied on microwave heating (Scheme 4 and 5). We hypothesized that the use of allene in the IMDAF reaction with aminofurans could potentially provide access to indole and its derivatives. The substrate **45** could be prepared

by a nucleophilic displacement of a leaving group on the allene **47** using an appropriate aminofuran **46**.



Scheme 11. Proposed retrosynthesis of indoles employing an intramolecular cycloaddition between an allene and aminofuran

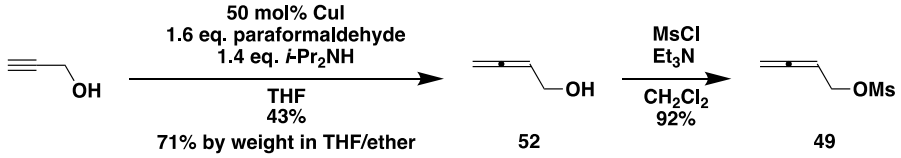
To test our hypothesis, we initially set out to synthesize allenyl furan **50**. To this end, aminofuran **48** was deprotonated with sodium hydride and then treated with mesylate **49** to form the required allenyl furan **50**.[9] To our delight, when allenyl furan **50** was heated in toluene at 110 °C in a sealed tube, indole **51** was obtained in 81% yield.



Scheme 12. Synthesis of an indole by an intramolecular cycloaddition between a tethered allene and an aminofuran

1.1.2.2 Synthesis of Substrates and their Cycloadditions

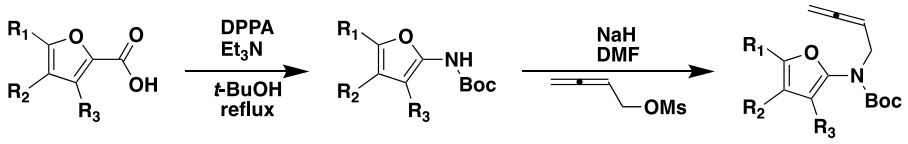
The synthesis of the allenyl alcohol **52** was accomplished by a literature protocol.[37] The copper-catalyzed homologation of propargyl alcohol gave access to allenyl alcohol **52** on gram scale. Treatment of alcohol **52** with mesyl chloride gave mesylate **49** in good overall yield which was then used for the alkylation of aminofuran derivatives.

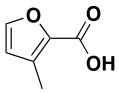
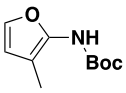
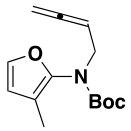
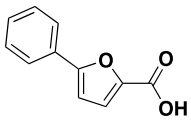
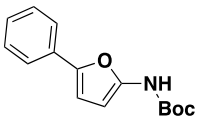
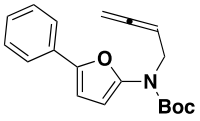
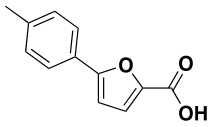
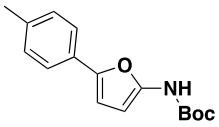
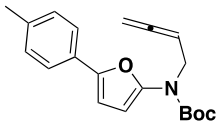
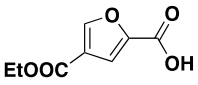
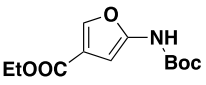
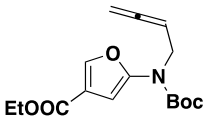


Scheme 13. Synthesis of allenyl alcohol **52** and mesylate **49**

The substrates were synthesized according to the general scheme outlined in Table 1. Reaction of the acid with DPPA followed by trapping of the intermediate isocyanate with the solvent *tert*-butanol gave the corresponding Boc-protected aminofurans. Treatment of the aminofuran with sodium hydride followed by the mesylate **49** gave the corresponding substrates. Upon alkylation, the 3-methyl derivative **57** (Table 1, entry 1) gave the allene **61**, which readily underwent cyclization upon workup to yield a mixture of both the allene **61** and the corresponding indole **65** in 16% yield after chromatography. Aryl-substituted substrates **62** and **63** (Table 1, entries 2 and 3) could be accessed from the corresponding carboxylic acids in good yields. The ethyl 4-carboxy derivative **64** (Table 1, entry 4) could be accessed in low yields from the corresponding acid **56**.

Table 1. Synthesis of the substrates for the intramolecular IMDAF reaction



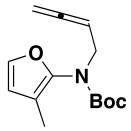
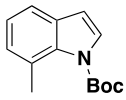
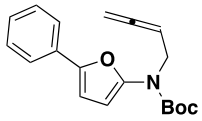
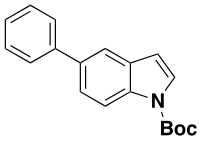
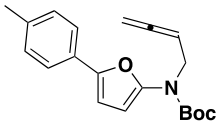
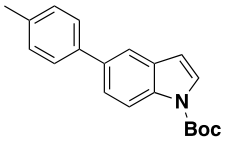
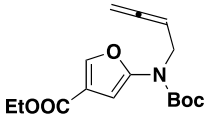
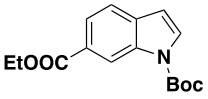
Entry	Acid	Aminofuran	Yield	Furanyl amine	Yield
1	 53	 57	81%	 61	16%[1]
2	 54	 58	76%	 62	51%
3	 55	 59	68%	 63	78%
4	 56	 60	36%	 64	31%

[1]The substrate obtained cyclized readily to obtain a mixture with the corresponting Boc-protected indole.

With several allenyl furans in hand, we next explored the key IMDAF reactions. We were pleased to find that the cycloaddition worked well with the 3-methyl substituted aminofuran **57** (Table 2, entry 1) to give the corresponding indole **61** in 90% yield when heated to just 50 °C in toluene. The methyl substituent makes the furan ring more electron rich and activates it for the Diels-Alder reaction. Aryl-substituted substrates **62** and **63** (Table 2, entries 2 and 3) formed the corresponding indoles **66** and **67** in 86% and 82% yield respectively when heated at 110 °C in

toluene. Introduction of an electron-withdrawing ester substituent at the 4-position (Table 2, entry 4) produced the indole **68** in 83% yield.

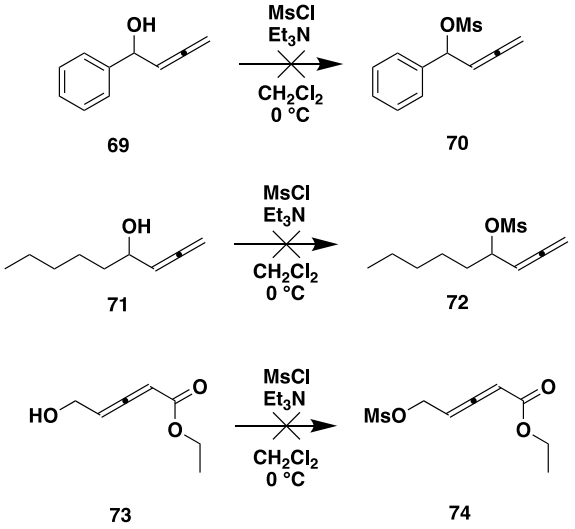
Table 2. Synthesis of 5,6,7-substituted indoles by an intramolecular cycloaddition between an allene and aminofuran

Entry	Substrate[1]	Indole	Yield[2]
1	 61	 65	90%[3]
2	 62	 66	86%
3	 63	 67	82%
4	 64	 68	83%

[1]Reaction conditions: 0.1 M in toluene at 110 °C untill TLC analysis showed complete conversion of SM. [2]Isolated yields.[3]Reaction was performed at 50 °C due to high reactivity.

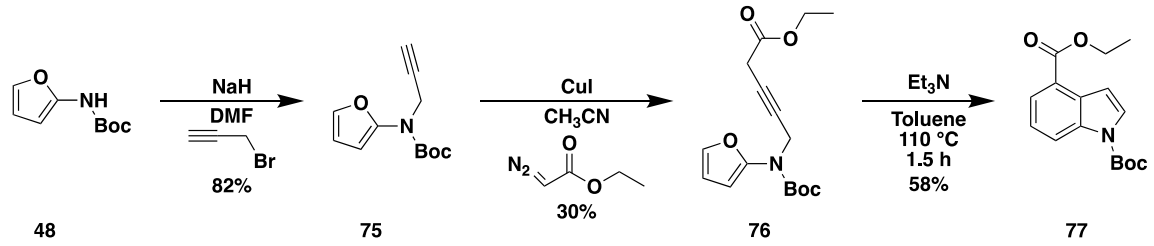
Having demonstrated the feasibility of the allenyl IMDAF reaction, we next sought to expand the scope of the reaction to allenes with additional substituents. However, the introduction of additional substituents on the allene proved to be extremely challenging. The mesylates of several substituted allenes were unstable or most likely underwent rearrangement to give the

corresponding diene. For example, treating allenes **69,**[37] **71**[37] and **73**[38] with mesyl chloride in the presence of triethylamine did not give the expected mesylate.



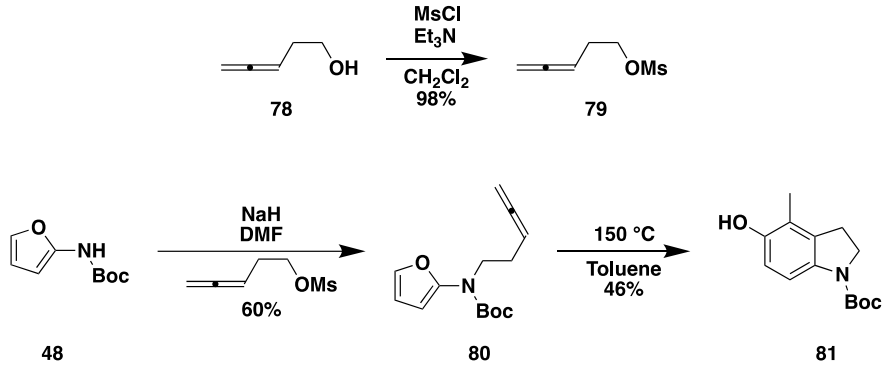
Scheme 14. Attempted synthesis of substituted allenyl mesylates

The synthesis of the terminal ester-substituted allene could be accomplished *in situ* by isomerization of the alkynyl ester **76**, which could be synthesized in two steps from the amino furan **48** in a moderate overall yield. Thus, when alkyne **76** was subjected to triethylamine in toluene at 110 °C, indole **77** was obtained in 58% yield.



Scheme 15. Synthesis of 4-substituted indole

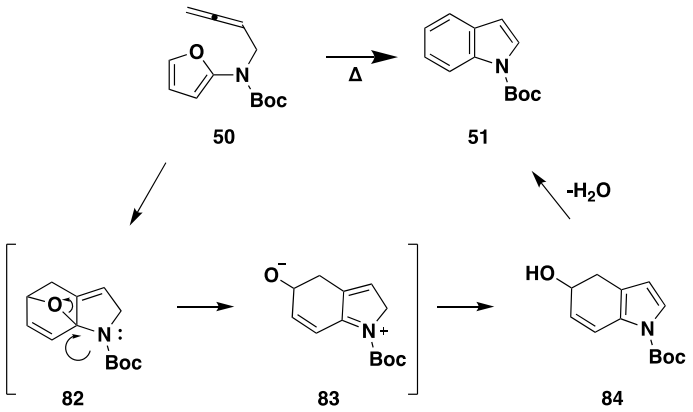
Not surprisingly, increasing the length of the tether gave the indoline **81** in 46% yield. The reaction temperature required to attain the transformation was much higher. The reaction most likely occurs via isomerization of the allene to the alkyne at elevated temperatures, the latter being known to react intramolecularly with aminofurans to produce indolines.[9]



Scheme 16. Synthesis of an indoline via an intramolecular cycloaddition

1.1.2.3 Proposed mechanism

A plausible mechanism for the conversion of **50** to **51** is outlined in Scheme 17. The initial cycloaddition of **50** gives Diels-Alder adduct **82** that immediately undergoes ring opening and isomerization to form intermediate **84**, which after dehydrative aromatization forms the desired indole **51**.



Scheme 17. Proposed mechanism for the IMDAF reaction with allene

1.1.3 Conclusions

The intramolecular cycloaddition of allenes with aminofurans gave good to excellent yields of several different substituted indoles. Moreover, the reaction temperatures are relatively mild as

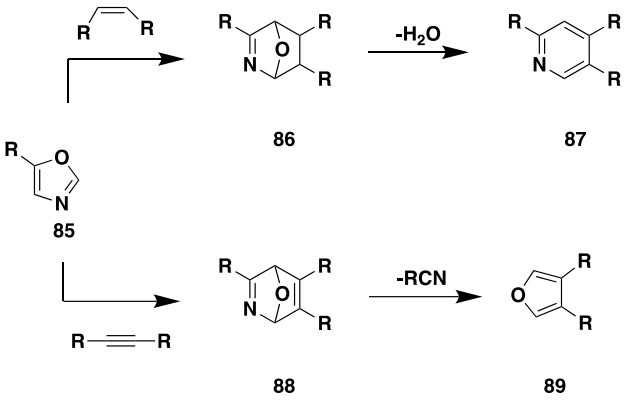
compared to the previously developed methodology which required microwave heating at 180 °C.[20, 23] The synthesis of substituted allenyl substrates proved to be more challenging than anticipated, thereby limiting the synthetic utility of the reaction. Future work can be directed towards introducing more substituents on the allene to access different 2-, 3- and 4-substituted indoles.

1.2 INTRAMOLECULAR CYCLOADDITIONS OF ALLENES WITH AMINOOXAZOLES

1.2.1 Introduction

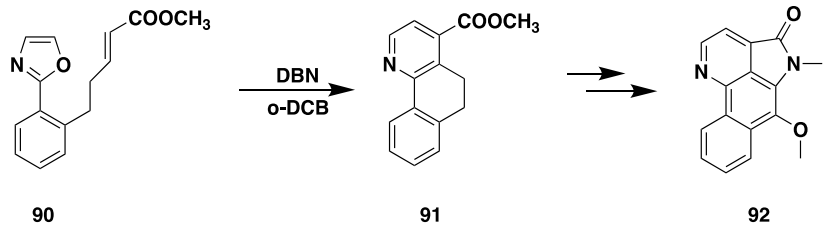
1.2.1.1 Intramolecular Cycloaddition Reactions of Oxazoles

The ability of oxazoles to participate in [4+2] cycloaddition reactions has been extensively studied.[39] The oxazole ring contains an electron deficient aza-diene which can participate in inverse-electron demand Diels-Alder reactions with electron-rich dienophiles. The introduction of electron-rich substituents on the ring allows for reactions with electron-poor dienophiles.[40] Cycloaddition of oxazoles with olefins and alkynes proceeds to give substituted pyridines **87** and furans **89**, respectively (Scheme 18).[41] The synthesis of substituted pyridines using this method has drawn considerable attention.[40] The synthesis of vitamin B6 (or pyridoxine) has been accomplished using the Diels-Alder reaction of an oxazole with several different dienophiles.[41]



Scheme 18. Diels-Alder chemistry of oxazole with olefins and alkynes

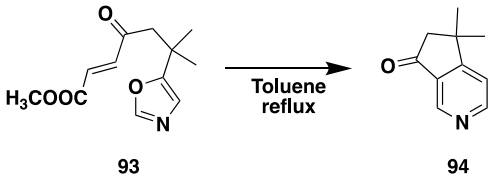
The first intramolecular cycloaddition between an alkene and an oxazole was reported by Weinreb[42] in 1983. The reaction was the key step to form the pyridine ring of the natural product eupolauramine **92** (Scheme 19). This method was later used for the synthesis of several other natural products.[43-45]



Scheme 19. Synthesis of eupolauramine using an intramolecular cycloaddition between an oxazole and alkene

The addition of Lewis acid catalysts like copper triflate[46] has been shown to catalyze the intramolecular reaction between oxazoles and olefins (Table 3).

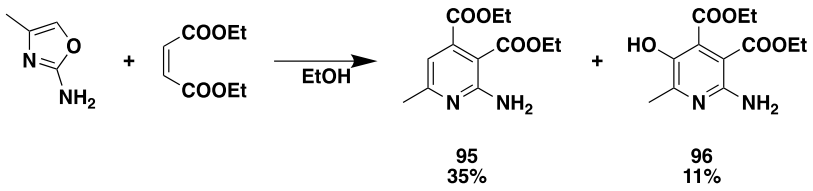
Table 3. Intramolecular Diels-Alder reaction of **93** in the presence of copper triflate



Catalyst	Time, h	% of recovered 93	% Yield of 94
-	24	88	3
10 mol% $Cu(OTf)_2$	3	0	93

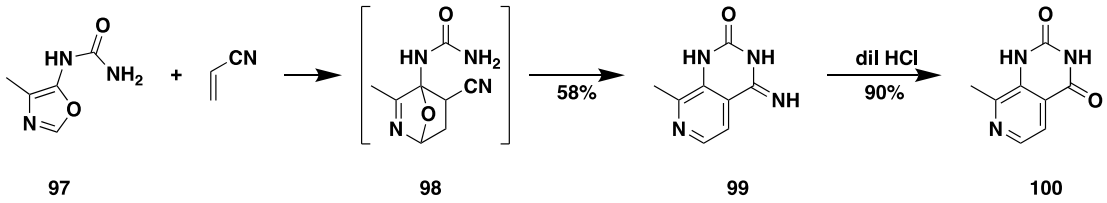
1.2.1.2 Cycloaddition Reactions of Aminooxazoles

The reaction of 5-aminooxazoles and its derivatives with maleimide and N-phenyl maleimide has been reported.[47, 48] The reaction of 4-methyl 2-aminooxazole with diethyl maleate proceeds at room temperature to give a 35% yield of pyridine **95** and a 11% yield of pyridine **96**.[49]



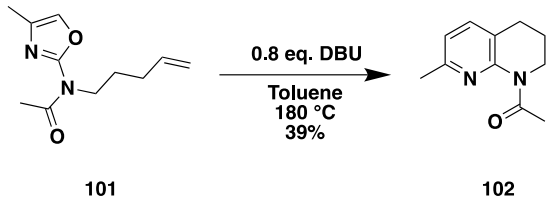
Scheme 20. Diels-Alder reaction of 4-methyl-2-aminooxazole with diethyl maleate

A novel synthesis of 1,2,3,4-tetrahydropyrido[3,4-*d*]-pyrimidine-2,4-diones has been accomplished by taking advantage of the intermolecular cycloaddition of oxazole ureas with substituted olefins.[50] For example, cycloaddition of oxazole urea **97** with acrylonitrile gave the pyridopyrimidine **99** in 58% yield. Upon hydrolysis, **99** afforded the desired pyrimidine dione **100** in 90% yield.



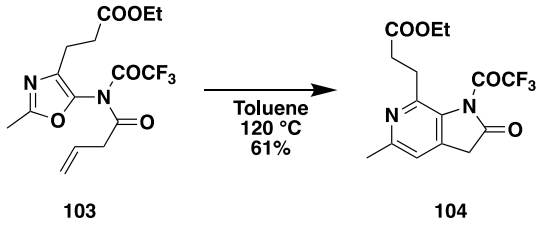
Scheme 21. Synthesis of 1,2,3,4-tetrahydropyrido[3,4-*d*]-pyrimidine-2,4-diones by intramolecular cycloaddition between oxazole urea and acrylonitrile

Very few examples of intramolecular cycloaddition reactions of aminooxazoles are known.[39] Treating aminooxazole **101** in toluene with 0.8 eq. of DBU at 180 °C in a sealed tube provided tetrahydronaphthyridine **102** in only 39% yield.



Scheme 22. Intramolecular cycloaddition of 2-aminooxazole with an olefin

The Padwa group has studied the intramolecular cycloaddition of substituted 5-aminooxazoles.[51] For example, heating oxazole **103** in toluene at 120 °C furnished the pyridine **104** in 61% yield.



Scheme 23. Intramolecular cycloaddition of 5-aminooxazole with an olefin

1.2.1.3 Synthesis of Azaindole-type Scaffolds using a [4+2] Cyclization

Pyrrolopyridines, more commonly referred to as azaindoles, contain a pyridine ring fused to a pyrrole ring. There are 4 positional isomers of azaindole based on the position of the nitrogen in the fused pyridine ring (Figure 3). The structural similarity to both indole and purine have made azaindoles a common bioisosteric replacement. Several kinase inhibitors,[52] HIV agents[53] and antihelminthic agents[54] have been designed by incorporating the azaindole scaffold. In nature, azaindoles are generally found in a fused polycyclic rings like the variolins.[55] Reviews detailing their chemistry and synthesis are available.[56, 57]

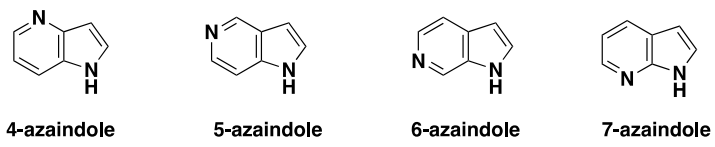
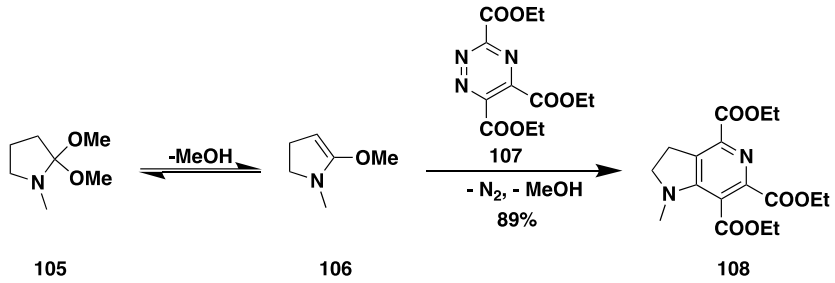


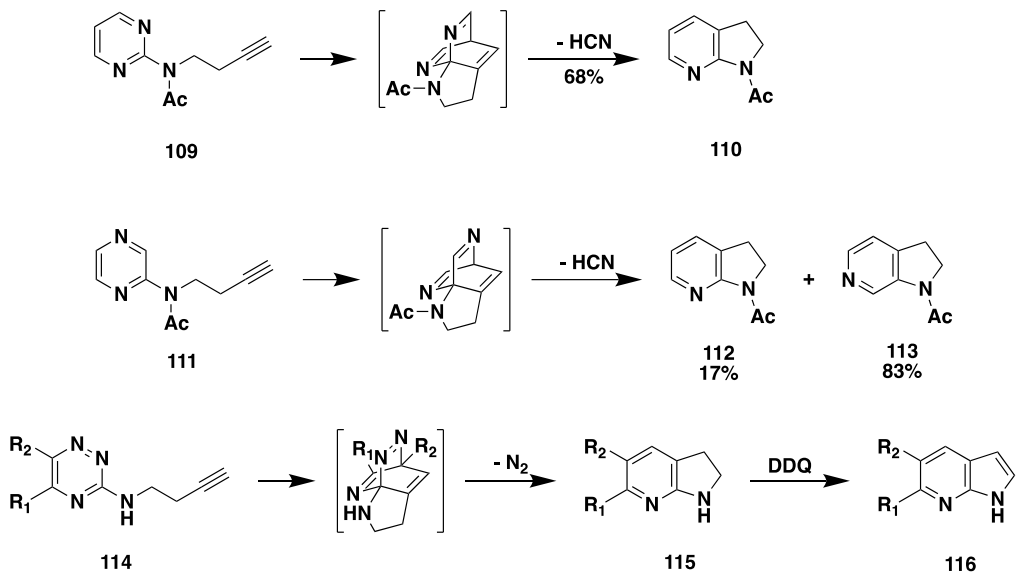
Figure 3. Chemical structures of different azaindole positional isomers

Cycloaddition reactions have been utilized for designing novel routes to synthesize heterocycles.[58] Interestingly, the reaction of electron-rich amide acetal **105** with triazine **107** gave the dihydro-azaindole **108** in 89% yield.[59]



Scheme 24. Synthesis of an azaindole using a cycloaddition reaction

The intramolecular cycloaddition of aminopyrimidine **109** with an alkyne tether gave the 2,3-dihydro 7-azaindole **110** in 68% yield.[60] An intramolecular reaction of pyrazines with alkynes on the other hand gave an isomeric mixture of 2,3-dihydro-6-azaindole **112** and 7-azaindole **113**.[61] Similarly, substituted butynylamino-1,2,4-triazines react with alkynes to give 7-azaindole derivatives after DDQ oxidation.[58]

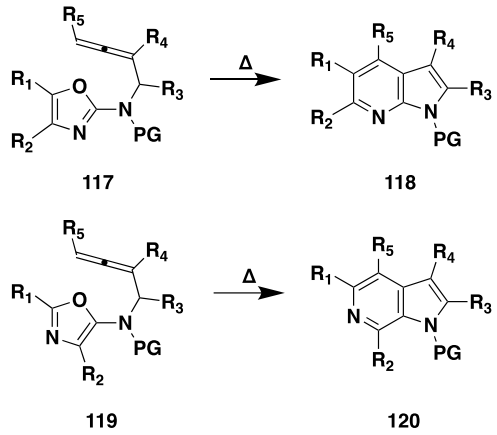


Scheme 25. Intramolecular cycloadditions of pyrimidine, pyrazines and 1,2,4-triazines with alkynes

1.2.2 Results and Discussion

1.2.2.1 Introduction

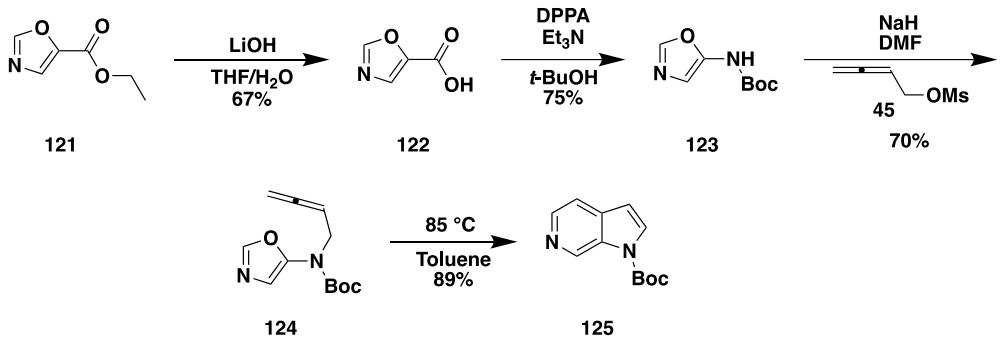
Since the intramolecular cycloaddition of allene with aminofuran gave good to excellent yields of indoles, we were interested in utilizing a similar approach for the synthesis of azaindoles. Using 2- or 5-amino oxazoles for the intramolecular cycloaddition with an allenyl tether could potentially give access to both 7- and 6-azaindoles, respectively.



Scheme 26. Proposed synthesis of 7- and 6-azaindoles using an intramolecular cycloaddition between an allene and aminooxazole

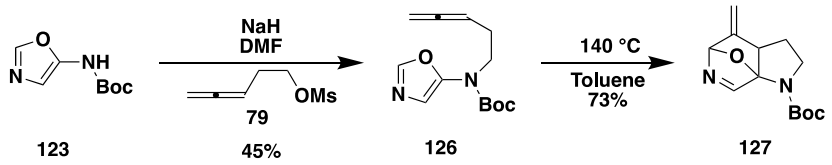
1.2.2.2 Cycloaddition of 5-Aminooxazoles with Allenes

The synthesis of Boc-protected 5-amino oxazole **123** was accomplished in two steps from the oxazole ester **121**. Saponification of the ester **121**, followed by treatment of the resulting acid **122** with DPPA gave the Boc-protected 5-aminooxazole **123** in good overall yield. Deprotonation of the carbamate using sodium hydride followed by addition of mesylate **49** gave the required substrate **124** for the synthesis of 6-azaindole. Heating **124** in toluene at 110 °C for 1.5 h furnished the Boc-protected 6-azaindole **125** in 68% yield. To improve the yield and further investigate the reaction conditions, it was found that heating **124** in toluene at 85 °C for 10 h gave the desired 6-azaindole **125** in 89% yield.



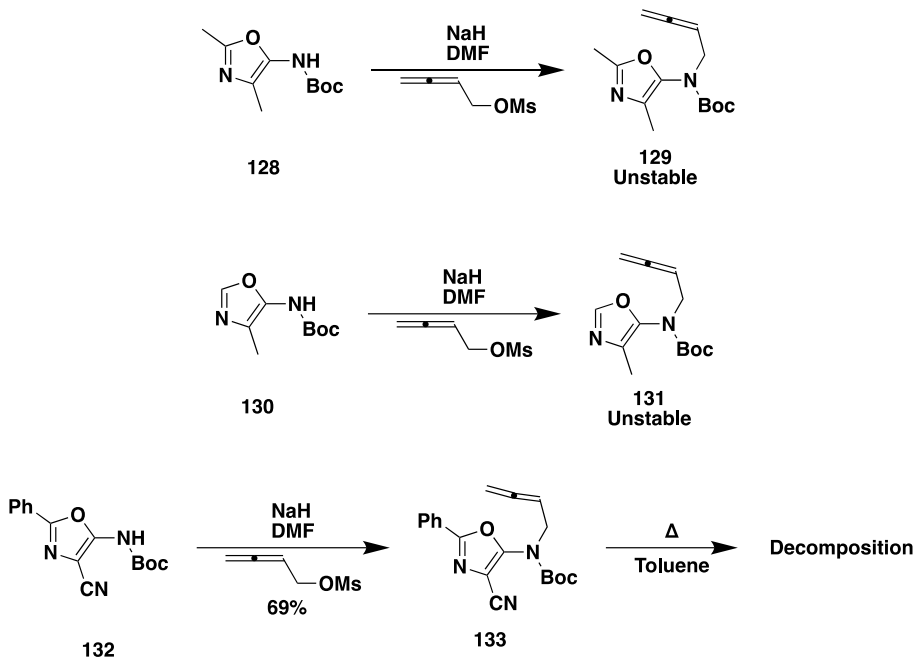
Scheme 27. Synthesis of 6-azaindole employing an intramolecular cycloaddition between an allene and aminooxazole

Increasing the length of the allene side chain resulted in isolation of the adduct **127** in 73% yield.



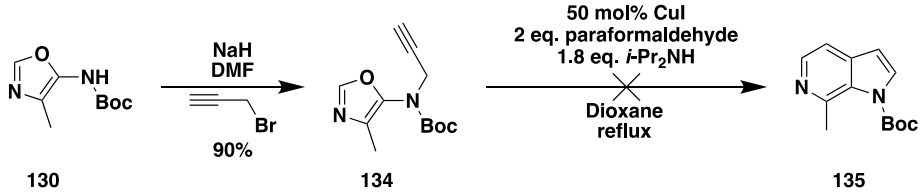
Scheme 28. Intramolecular cycloaddition of 5-aminooxazole with a homologated allene

Boc-protected aminooxazoles **128** and **130** were synthesized in a similar manner from the corresponding ethyl esters. Unfortunately, after alkylation, the allenyl oxazoles **129** and **131** were unstable and decomposed after isolation even when stored at -20 °C. Alkylation of Boc-protected aminooxazole **132** resulted in isolation of allenyl oxazole **133** in 69% yield which when heated in toluene decomposed to obtain a mixture of unidentifiable products.



Scheme 29. Synthesis of substituted allenyl oxazoles which were found to be unstable

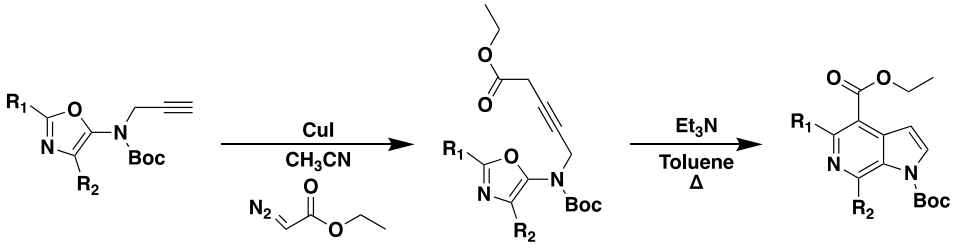
Synthesizing the allene *in situ* via the alkyne[37] **134** also resulted in decomposition of the substrate.

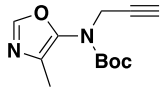
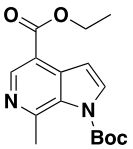
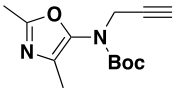
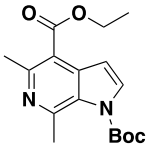


Scheme 30. Failed attempt for the synthesis of 6-azaindole derivatives by generating the allene *in situ*.

We next attempted to synthesize ethyl 4-carboxy substituted azaindoles by isomerization of the alkynyl ester to the corresponding allene *in situ* (Table 4). Mono methyl and dimethyl substituted azaindoles **137** and **138** were synthesized from the corresponding alkynes in 25% and 23% yield, respectively, over two steps.

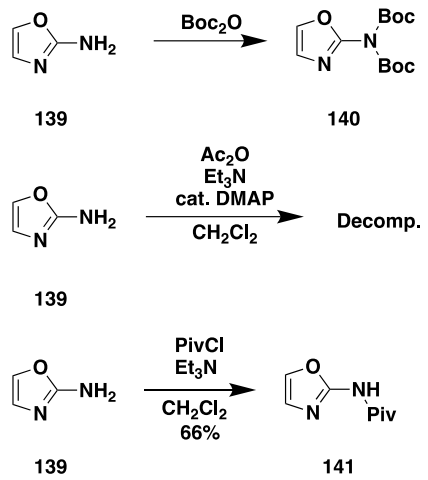
Table 4. Synthesis of ethyl 4-carboxyl substituted azaindoles



Entry	Alkyne	Azaindole	Yield over 2 steps
1	 134	 137	25%
2	 136	 138	23%

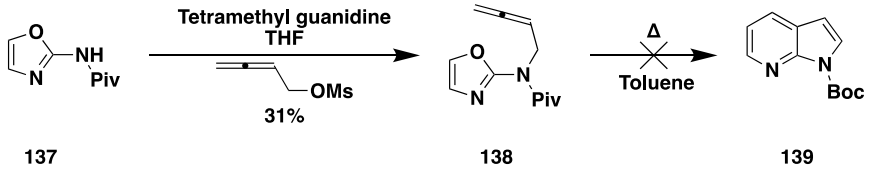
1.2.2.3 Cycloaddition of 2-Aminooxazoles with Allenes

Preparation of the substrate for the synthesis of 7-azaindoles proved to be more challenging than anticipated. Protection of 2-aminooxazole[62] **139** with Boc-anhydride resulted in the synthesis of the bis-Boc protected amine **140**. Protection with acetic anhydride resulted in decomposition, most likely via ring-opening.[63] Treatment with pivaloyl chloride on the other hand afforded the mono-protected 2-aminooxazole **141** in 66% yield.



Scheme 31. Synthesis of mono-protected 2-aminooxazoles

While alkylation of the amide **141** with sodium hydride as a base in DMF resulted only in recovery of starting material, using tetramethyl guanidine as a base in THF gave the oxazonyl allene **142** in 31% yield. To our disappointment, heating **142** in toluene at elevated temperatures of up to 150 °C resulted only in decomposition of the starting material. No traces of the desired 7-azaindole **143** could be seen by TLC or NMR analysis.



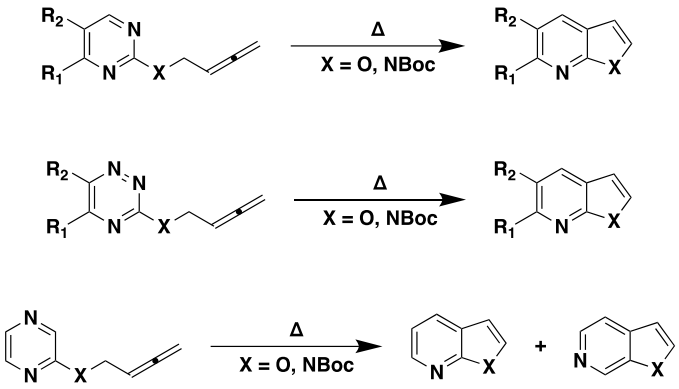
Scheme 32. Attempted synthesis of a 7-azaindole using the intramolecular cycloaddition between an allene and 2-aminooxazole

1.2.3 Conclusions

This work demonstrates the intramolecular cycloadditions of allenes tethered to an aminooxazole. Although some substituted 5-aminooxazole substrates were unstable or decomposed when heated at elevated temperatures, the reaction developed offers a new synthetic

strategy to synthesize 6-azaindole and its derivatives. The instability of the substrates and the lack of reactivity of 2-aminooxazole is not understood at this point. Further efforts are required to synthesize different substituted allenyl oxazoles to functionalize the azaindole core.

Future work can be directed towards extending the scope of the intramolecular allene cycloadditions to other heterocycles like pyrimidines,[60] 1,2,4-triazines[58] and pyrazines[61] to obtain substituted 6- and 7-azaindoles and aza-benzofurans (Scheme 33).



Scheme 33. Proposed extension of intramolecular cycloadditions of allenes to pyrimidines, 1,2,4-triazines and pyrazines

2.0 EXPERIMENTAL PART

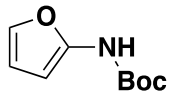
2.1 GENERAL

All glassware was oven dried and cooled in a desiccator prior to use. All moisture sensitive reactions were performed under an atmosphere of dry N_2 or Ar. Reactions carried out below 0 °C employed an acetone/dry ice bath. Reagents obtained from commercial sources were used as received unless otherwise specified. THF and Et_2O were distilled from sodium/benzophenone ketyl and CH_2Cl_2, triethylamine and toluene were distilled over CaH_2. DMF was distilled over CaH_2 under reduced pressure (1-1.5 torr) and stored under activated 3Å molecular sieves. *Tert*-butyl alcohol was distilled over Mg/I_2 and stored under activated 3Å molecular sieves. After purification by chromatography, unless otherwise stated, all samples were dried with the use of a rotary evaporator connected to a PIAB Lab Vac H40, followed by a 1–1.5 torr high vacuum pump to remove residual solvent.

Melting points were determined using a Laboratory Devices Mel-Temp II in open capillary tubes and are uncorrected. Infrared spectra were determined as neat solids or oils on a Smiths Detection IdentifyIR FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance 300 MHz, 400 MHz, or 500 MHz instruments. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) were reported in parts per million with the residual solvent peak used as an internal standard δ and are tabulated as follows: chemical shift, multiplicity (s = singlet, d = doublet, t =

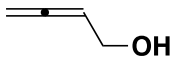
triplet, q = quartet, m = multiplet, p = pentet, dd = doublet of doublet, dt = doublet of triplet), number of protons, and coupling constant(s) (Hz). ^{13}C NMR spectra were obtained using a proton-decoupled pulse sequence and are tabulated by observed peak. Thin-layer chromatography was performed using precoated silica gel 60 F254 plates (EMD, 250 μm thickness) and visualization was accomplished with a 254 nm UV light and by staining with a $KMnO_4$ solution (1.5 g of $KMnO_4$ and 1.5 g of K_2CO_3 in 100 mL of a 0.1% NaOH solution). Flash chromatography on SiO_2 (Silicycle, Silia-P Flash Silica Gel or SiliaFlash® P60, 40-63 μm) was used to purify crude reaction mixtures.

2.2 EXPERIMENTAL PROCEDURES



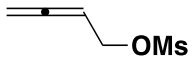
48

***tert*-Butyl furan-2-yl carbamate (48).** In a 50-mL RBF with a magnetic stirring bar was placed 2-furoyl chloride (1.99 g, 1.50 mL, 15.2 mmol), *tert*-butyl alcohol (15.0 mL), and sodium azide (1.00 g, 15.2 mmol). After the mixture was stirred at 25 °C for 16 h under an atmosphere of N_2, it was placed behind a protective shield and the solution was heated at reflux for 15 h under a constant flow of N_2. The solvent was removed under reduced pressure to provide a crude solid that was purified by chromatography on SiO_2 (10% EtOAc/hexane) to give **48** (2.32 g, 12.6 mmol, 83%) as a white solid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 1 H), 7.55 (br s, 1 H), 6.34 (t, 1 H, J = 2.5 Hz), 6.04 (br s, 1 H), 1.50 (s, 9 H). The spectroscopic data were consistent with those reported in the literature.[9]



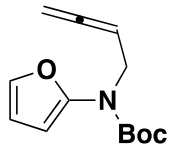
52

Buta-2,3-dien-1-ol (52). In a 500-mL RBF, paraformaldehyde (6.86 g, 228 mmol) and CuI (13.9 g, 71.4 mmol) was dissolved in dry THF (280 mL). The mixture was stirred at room temperature and subsequently diisopropylamine (20.4 g, 28.2 mL, 200 mmol) and propargyl alcohol (8.08 g, 8.40 mL, 143 mmol) was added dropwise. The mixture was refluxed for 24 h using a reflux condenser. After cooling the mixture to room temperature, the mixture was concentrated under reduced pressure (temperature not exceeding 25° C) and the crude was diluted with Et_2O (120 mL). The solution was passed through a plug of SiO_2 (7 cm, 5 x 60.0 mL of Et_2O). The solution was then transferred to an Erlenmeyer flask and an equal volume of sat. NaCl sol. (600 mL) was added to the mixture. Conc. HCl was then added dropwise with constant stirring till the pH reached 2-3. The mixture was then passed through a suction column containing sand/celite/sand/celite/sand. The two layers were then separated and the aq. layer was washed with Et_2O. The combined organic layers was dried (Na_2SO_4) and concentrated carefully under reduced pressure to obtain the crude material which was purified by bulb to bulb distillation to yield **52** (6.03 g, 61.5 mmol, 43%, 71% purity) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (p, 1 H, *J* = 6.5 Hz), 4.75 (dt, 2 H, *J* = 6.6, 3.3 Hz), 4.05 (dt, 2 H, *J* = 6.0, 3.0 Hz). The spectroscopic data were consistent with those reported in the literature.[37]



49

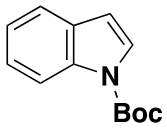
Buta-2,3-dien-1-yl methanesulfonate (49). In a 100-mL RBF with a magnetic stir bar, methanesulfonyl chloride (0.520 g, 0.350 mL, 4.49 mmol) was added slowly to a mixture containing buta-2,3-dien-1-ol **52** (0.400 g, 5.05 mmol, 71% purity) and triethylamine (0.830 g, 1.15 mL, 8.18 mmol) in dry CH_2Cl_2 (20.0 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred at 0°C for 1 h and then quenched with water (20.0 mL) and extracted with Et_2O (2 x 20.0 mL). The combined organic layers were washed with 5% aq. HCl (3 x 20.0 mL), brine (3 x 20.0 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure (temperature not exceeding 25 °C) to obtain **49** (0.552 g, 4.65 mmol, 92%) as a yellow oil which was used without further purification for the next reaction: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (p, 1 H, *J* = 7 Hz), 4.95 (dt, 2 H, *J* = 6.5 Hz, 2.0 Hz), 4.74 (dt, 2 H, *J* = 7.0 Hz, 2.0 Hz), 3.03 (s, 3 H). The spectroscopic data were consistent with those reported in the literature.[64]



50

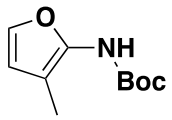
***tert*-Butyl buta-2,3-dien-1-yl(furan-2-yl)carbamate (50).** In a 25-mL RBF with a magnetic stir bar, NaH (0.105 g, 3.06 mmol) was added in 3 portions to a solution of *tert*-butyl furan-2-ylcarbamate **48** (0.500 g, 2.73 mmol) in dry DMF (8.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 1 h and then buta-2,3-dien-1-yl methanesulfonate **49** (0.45 g, 3.03 mmol) was added. The mixture was stirred at room temperature till TLC analysis showed complete conversion of the SM. The mixture was then diluted with sat. NH_4Cl sol. (10.0 mL) and

extracted with Et_2O (3 x 10.0 mL). The combined organic layers were washed with water (3 x 5.0 mL) and sat. NaCl sol. (3 x 5.0 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (5% EtOAc/hexane) gave **50** (0.330 g, 1.39 mmol, 51%) as a colorless oil: R_f 0.35 (5% EtOAc/hexane); IR (neat) 2978, 2933, 1956, 1709, 1613, 1147 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.43 (dd, 1 H, *J* = 2.0 Hz, 0.80 Hz), 6.42 (dd, 1 H, *J* = 3.2 Hz, 2.0 Hz), 6.09 (dd, 1 H, *J* = 2.8 Hz, 0.4 Hz), 5.24 (p, 1 H, *J* = 6.4 Hz), 4.87 (dt, 2 H, *J* = 6.0 Hz, 2.8 Hz), 4.06 (dt, 2H, *J* = 6.0 Hz, 2.8 Hz), 1.38 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) characteristic peaks δ 208.1, 152.7, 147.8, 138.8, 111.0, 86.8, 80.6, 77.0, 47.0, 27.7, 27.5; HRMS *m/z* calculated for $C_{13}H_{18}O_3N$ 236.1281, found 236.1282.



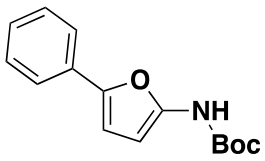
51

***tert*-Butyl 1H-indole-1-carboxylate (51).** *Tert*-butyl buta-2,3-dien-1-yl(furan-2-yl)carbamate **50** (0.0500 g, 0.212 mmol) was dissolved in dry toluene (2.10 mL) and heated in a sealed microwave tube at 110 °C for 3 h. The solvent was then evaporated under reduced pressure and purification by chromatography on SiO_2 (5% EtOAc/hexane) gave **51** (0.0375 g, 0.172 mmol, 81%) as a colorless oil: R_f 0.45 (5% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1 H, *J* = 8.0 Hz), 7.60 (d, 1 H, *J* = 3.6 Hz), 7.56 (d, 1 H, *J* = 7.6 Hz), 7.31 (ddd, 1 H, *J* = 7.4 Hz, 7.4 Hz, 1.2 Hz), 7.22 (ddd, 1 H, *J* = 7.6 Hz, 7.6 Hz, 1.2 Hz), 6.57 (d, 1 H, *J* = 4 Hz), 1.68 (s, 9 H). The spectroscopic data were consistent with those reported in the literature.[65]



57

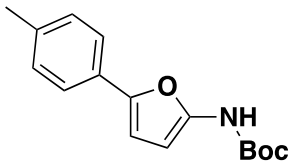
***tert*-Butyl (3-methylfuran-2-yl)carbamate (57).** In a 25-mL RBF with a magnetic stir bar and reflux condenser, DPPA (0.445 g, 0.350 mL, 1.60 mmol) was added to a solution of 3-methyl-2-furoic acid **53** (0.200 g, 1.54 mmol) and triethylamine (0.166 g, 0.230 mL, 1.64 mmol) in dry *t*-BuOH (4.00 mL) and refluxed for 16 h under an atmosphere of N_2. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The crude was then treated with sat. $NaHCO_3$ sol. (10.0 mL) at 0 °C and stirred for 2 h. The aq. layer was then extracted with EtOAc (3 x 10.0 mL). The combined organic layers were washed with sat. NaCl sol. and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and the crude was purified by chromatography on SiO_2 (10% EtOAc/hexane) to yield 7**5** (0.230 g, 1.16 mmol 76%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1 H, J = 2.1 Hz), 6.21 (d, 1 H, J = 2.1 Hz), 5.97 (br s, 1 H), 1.94 (s, 3 H), 1.48 (s, 9 H); HRMS *m/z* calculated for $C_{10}H_{16}O_3N$ 198.1125, found 198.1122. The spectroscopic data were consistent with those reported in the literature.[23]



58

***tert*-Butyl (5-(p-tolyl)furan-2-yl)carbamate (58).** In a dry 25-mL RBF with a magnetic stir bar and reflux condenser, DPPA (0.891 g, 0.700 mL, 3.21 mmol) was added to a mixture of 5-

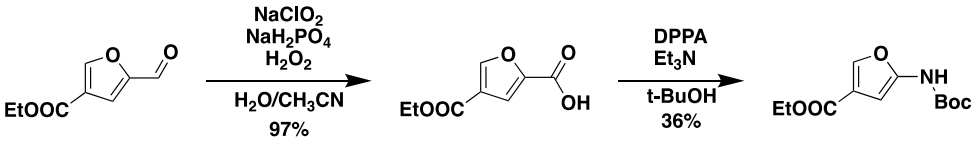
phenyl-2-furoic acid **54** (0.600 g, 3.09 mmol) and triethylamine (0.468 g, 0.650 mL, 4.63 mmol) in dry *t*-BuOH (15.0 mL). The mixture was refluxed for 16 h and then cooled to room temperature. The solvent was removed under reduced pressure and the crude obtained was treated with sat. $NaHCO_3$ sol. (10.0 mL) at 0 °C. The aq. sol. was then extracted with EtOAc (3 x 10.0 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and purification by chromatography on SiO_2 gave **58** (0.612 g, 2.36 mmol, 76%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2 H), 7.34 (m, 2 H), 7.20 (m, 1 H) 6.71 (br s, 1 H), 6.60 (d, 1 H, *J* = 3.3 Hz), 6.13 (s, 1 H), 1.53 (s, 9 H). HRMS *m/z* calculated for $C_{15}H_{18}O_3N$ 260.1287, found 260.1301. The spectroscopic data were consistent with those reported in the literature.[23]



59

***tert*-Butyl (5-(p-tolyl)furan-2-yl)carbamate (59).** In a dry 25-mL RBF with a magnetic stir bar and reflux condenser, DPPA (0.286 g, 0.230 mL, 1.03 mmol) was added to a mixture of 5-(p-tolyl)-2-furoic acid **55** (0.200 g, 0.990 mmol) and triethylamine (0.108 g, 0.150 mL, 1.06 mmol) in dry *t*-BuOH (4.00 mL). The mixture was refluxed for 16 h and then cooled to room temperature. The solvent was removed under reduced pressure and the crude obtained was treated with sat. $NaHCO_3$ sol. (10.0 mL) at 0 °C. The aq. sol. was then extracted with EtOAc (3 x 10.0 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and purification by chromatography on SiO_2 gave **59** (0.185 g, 0.677 mmol, 68%) as a white solid: R_f 0.21, 10% EtOAc/hexane); mp. 119.5-120.3 °C; IR (neat) 3259, 2980, 1699, 1629, 1504, 1250, 1155 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, 2 H, *J* = 8.4 Hz), 7.15 (d, 2 H, *J* = 8.4 Hz), 6.69

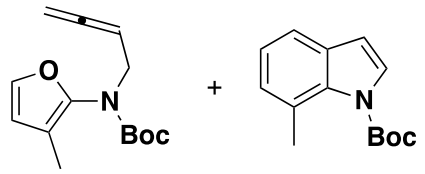
(br s, 1 H), 6.53 (d, 1 H, *J* = 3.3 Hz), 6.11 (s, 1 H), 2.34 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 147.6, 144.9, 136.8, 129.5, 128.1, 123.1, 106.1, 96.8, 81.6, 28.4, 21.3; HRMS *m/z* calculated for $C_{16}H_{20}O_3N$ 274.1438, found 274.1441.



4-(Ethoxycarbonyl)furan-2-carboxylic acid (E2). In a 100-mL RBF, a solution of $NaClO_2$ (5.71 g, 50.6 mmol) in H_2O (34.0 mL) was slowly added to a solution of ethyl 2-formyl-4-furoate[66] **E1** (1.70 g, 10.1 mmol), NaH_2PO_4 (8.34 g, 69.5 mmol) and 30% H_2O_2 (7.10 mL, 69.5 mmol) in acetonitrile/water (4:1, 19.0 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature (until no more oxygen evolved from the reaction). After acidification with 10% aq. HCl to pH 3, the solution was extracted with EtOAc (3 x 25.0 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield **E2** (1.77 g, 9.79 mmol 97%) as a white crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 1 H, *J* = 0.6 Hz), 7.60 (s, 1H), 4.34 (q, 2 H, *J* = 7.2 Hz), 1.37 (t, 1 H, *J* = 7.2 Hz). HRMS *m/z* calculated for $C_8H_9O_5$ 185.0445, found 185.0442.

Ethyl 2-((*tert*-butoxycarbonyl)amino)furan-4-carboxylate (60). 4-(Ethoxycarbonyl)furan-2-carboxylic acid **E2** (0.700 g, 3.80 mmol) was dissolved in dry *t*-BuOH (15.0 mL) and treated with triethylamine (0.540 g, 0.750 mL, 5.33 mmol) and DPPA (1.15 g, 0.900 mL, 4.12 mmol). The mixture was heated at reflux for 18 h under an atmosphere of N_2. After cooling the mixture to room temperature, the solvent was evaporated under reduced pressure. The crude obtained was treated with sat. $NaHCO_3$ (20.0 mL) and stirred at 0 °C for 2 h. The mixture was extracted with EtOAc (3 x 10.0 mL) and the combined organic layers were washed with brine

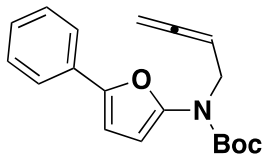
(3 x 10.0 mL), dried (Na_2SO_4), filtered and evaporated under reduced pressure. The crude solid obtained was purified by chromatography on SiO_2 (10% EtOAc/hexane) to yield **60** (0.350 g, 1.37 mmol, 36%) as a pale yellow solid: R_f 0.15 (10% EtOAc/hexane); mp. 98 °C; IR (neat) 3291, 3170, 2980, 1724, 1703, 1621, 1539, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 6.57 (br s, 1 H), 6.39 (br s, 1 H), 4.28 (q, 2 H, *J* = 7.2 Hz), 1.51 (s, 9 H), 1.32 (t, 3 H, *J* = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 151.6, 146.4, 141.3, 121.1, 95.2, 82.0, 60.6, 28.3, 14.4; HRMS *m/z* calculated for $C_{12}H_{18}O_5N$ 256.1180, found 256.1181.



61 **65**

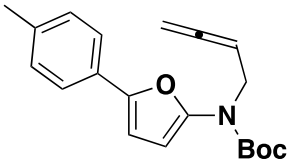
***tert*-Butyl buta-2,3-dien-1-yl(3-methylfuran-2-yl)carbamate (61) and *tert*-butyl 7-methyl-1*H*-indole-1-carboxylate[67] (65).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0500 g, 1.45 mmol) was added to a solution of *tert*-butyl (3-methylfuran-2-yl)carbamate **57** (0.230 g, 1.16 mmol) in dry DMF (5.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 30 mins at 0 °C and then buta-2,3-dien-1-yl methanesulfonate **49** (0.240 g, 1.62 mmol) was added. The mixture was stirred at room temperature for 16 h and then quenched with 10% NH_4Cl sol. (10.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic layers was washed with sat. NaCl sol. (3 x 10.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (4% EtOAc/hexane) to yield a mixture of **61** (0.0280 g, 0.112 mmol, 10%) and **65** (0.0170 g, 0.0730 mmol, 6%) as a colorless oil: Compound **61** ^1H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, 1 H, *J* = 2.4 Hz), 7.19 (d, 1 H, J = 2.1 Hz), 5.21 (p, 1 H, *J* = 6.9 Hz), 4.72 (dt, 2 H, *J* = 6.9 Hz, 2.4 Hz),

4.09 (m, 2 H), 1.89 (s, 3 H), 1.41 (s, 9 H); compound **65** ^{1}H NMR (300MHz, $CDCl_3$) δ 7.51 (d, 1 H, J = 3.6 Hz), 7.38 (d, 1 H, *J* = 7.2 Hz), 7.12 (m, 2 H), 6.53 (d, 1 H, *J* = 3.6 Hz), 2.64 (s, 3 H), 1.64 (s, 9 H). Note: The allene **61** cyclizes slowly to the indole **65** at room temperature.



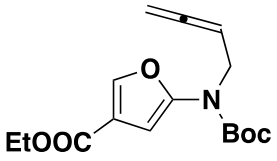
62

***tert*-Butyl buta-2,3-dien-1-yl(5-phenylfuran-2-yl)carbamate (62)**. In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0600 g, 1.75 mmol) was added to a solution of *tert*-butyl (5-phenylfuran-2-yl)carbamate **59** (0.400 g, 1.54 mmol) in dry DMF (5.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 45 min at 0 °C and then buta-2,3-dien-1-yl methanesulfonate **49** (0.340 g, 2.29 mmol) was added to the mixture. After stirring at room temperature for 16 h, the mixture was diluted with 10% NH_4Cl sol. (10.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic layers were washed with sat. NaCl sol. and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 to obtain **62** (0.243 g, 0.780 mmol, 51%) as a colorless oil: IR (neat) 2978, 2932, 1957, 1709, 1550, 1366, 1154 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 2 H), 7.36 (m, 2 H), 7.20 (m, 1 H), 6.60 (d, 1 H, *J* = 3.3 Hz), 6.11 (br s, 1 H), 5.29 (p, 1 H, *J* = 6.6 Hz), 4.79 (dt, 2 H, *J* = 6.3 Hz, 2.7 Hz), 4.27 (dt, 2 H, *J* = 6.3 Hz, 2.7 Hz), 1.49 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic peaks δ 209.3, 148.9, 148.0, 130.9, 128.9, 128.8, 127.5, 127.1, 123.4, 106.4, 102.6, 87.2, 81.7, 47.3, 28.4; HRMS *m/z* calculated for $C_{19}H_{20}O_3N$ 312.1594, found 312.1608.



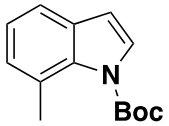
63

***tert*-Butyl buta-2,3-dien-1-yl(5-(p-tolyl)furan-2-yl)carbamate (63).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0270 g, 0.788 mmol) was added to a solution of *tert*-butyl (5-(p-tolyl)furan-2-yl)carbamate **59** (0.180 g, 0.658 mmol) in dry DMF (5.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred at 0 °C for 30 mins and then buta-2,3-dien-1-yl methanesulfonate **49** (0.240 g, 1.62 mmol) was added. The mixture was stirred at room temperature for 16 h and then quenched with 10% NH_4Cl sol. (10.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic layers were washed with sat. NaCl sol. (3 x 10.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (2-3% EtOAc/hexane) to give **63** (0.168 g, 0.516 mmol, 78%) as a colorless oil: IR (neat) 2977, 2932, 1957, 1710, 1553, 1366, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 2 H, 8.1 Hz), 7.17 (d, 2 H, *J* = 7.8 Hz), 7.53 (d, 1 H, *J* = 3.3 Hz), 6.09 (br s, 1 H), 5.28 (p, 1 H, *J* = 6.6 Hz), 4.78 (dt, 2 H, *J* = 6.6 Hz, 2.7 Hz), 4.25 (dt, 2 H, *J* = 6.6 Hz, 2.7 Hz), 2.35 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) characteristic peaks δ 209.3, 147.6, 136.9, 129.6, 129.4, 128.3, 127.3, 123.8, 123.4, 119.3, 115.4, 107.7, 105.6, 102.6, 87.2, 81.6, 47.4, 28.4, 21.4; HRMS *m/z* calculated for $C_{20}H_{24}O_3N$ 326.1751, found 326.1768.



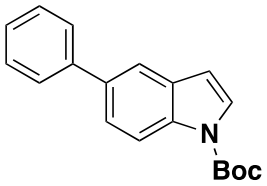
64

Ethyl 5-(buta-2,3-dien-1-yl(*tert*-butoxycarbonyl)amino)furan-3-carboxylate (64). In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0300 g, 0.875 mmol) was added in 2 portions to a solution of ethyl 5-((*tert*-butoxycarbonyl)amino)furan-3-carboxylate **60** (0.200 g, 0.784 mmol) in dry DMF (2.50 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 1 h and then buta-2,3-dien-1-yl methanesulfonate **49** (0.150 g, 1.01 mmol) was added and stirred at room temperature till TLC analysis showed complete conversion of the SM. The mixture was then diluted with sat. NH_4Cl sol. (5.0 mL) and extracted with Et_2O (3 x 5.0 mL). The combined organic layers were washed with water (3 x 5.0 mL) and sat. NaCl sol. (3 x 5.0 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated under reduced pressure and purified by chromatography on SiO_2 to obtain **64** (0.0740 g, 31%) as a colorless oil: IR (neat) 2980, 1957, 1713, 1620, 1550, 1135 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 1 H, *J* = 0.8 Hz), 6.38 (br s, 1 H), 5.20 (p, 1 H, *J* = 6.8 Hz), 4.78 (dt, 2 H, *J* = 6.4 Hz, 2.8 Hz), 4.29 (q, 2 H, *J* = 7.2 Hz), 4.15 (dt, 2 H, *J* = 7.2 Hz, 2.8 Hz), 1.46 (s, 9 H), 1.34 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 163.1, 153.3, 149.5, 143.2, 120.6, 101.4, 86.9, 82.0, 60.6, 47.6, 28.3, 14.5; HRMS *m/z* calculated for $C_{16}H_{22}O_5N$ 308.1493, found 308.1506.



65

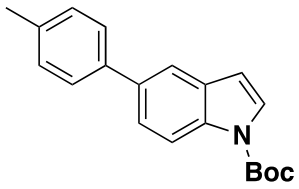
***tert*-Butyl 7-methyl-1H-indole-1-carboxylate (65).** In a sealed microwave tube, a mixture of **61** (0.0280 g, 0.112 mmol) and **65** (0.0170 g, 0.0730 mmol) was heated at 50 °C in dry toluene (1.80 mL). After TLC analysis showed complete conversion of the allene to the indole, the mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. Purification by passing the crude through a plug of SiO_2 (10% EtOAc/hexane) yielded **65** (0.0380 g, 0.163 mmol, 90%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 1 H, J = 3.6 Hz), 7.38 (d, 1 H, *J* = 7.2 Hz), 7.12 (m, 2 H), 6.53 (d, 1 H, *J* = 3.6 Hz), 2.64 (s, 3 H), 1.64 (s, 9 H). HRMS *m/z* calculated for $C_{14}H_{18}O_2N$ 232.1338, found 232.1333. The spectroscopic data were consistent with those reported in the literature.[67]



66

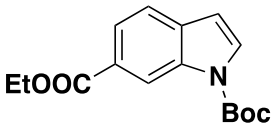
***tert*-Butyl 5-phenyl-1H-indole-1-carboxylate (66)**. In a sealed microwave tube, *tert*-butyl buta-2,3-dien-1-yl(5-phenylfuran-2-yl)carbamate **62** (0.0500 g, 0.161 mmol) was dissolved in dry toluene (1.60 mL) and heated at 110 °C for 1 h. The mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. The crude obtained was purified by chromatography on SiO_2 (10% EtOAc/hexane) to obtain **66** (0.0405 g, 0.138 mmol, 86%) as a white solid: R_f 0.20, 10% EtOAc/hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, 1 H, *J* = 9 Hz),

7.77 (d, 1H, *J* = 3 Hz), 7.63 (m, 3 H), 7.55 (dd, 1 H, *J* = 9 Hz, 2.1 Hz), 7.44 (m, 2 Hz), 7.34 (m, 1 H), 6.61 (d, 1 H, *J* = 3 Hz), 1.69 (s, 9 H); HRMS *m/z* calculated for $C_{19}H_{20}O_2N$ 294.1494, found 294.1519. The spectroscopic data were consistent with those reported in the literature.[68]



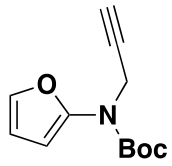
67

***tert*-Butyl 5-(p-tolyl)-1H-indole-1-carboxylate (67).** *Tert*-butyl buta-2,3-dien-1-yl(5-(p-tolyl)furan-2-yl)carbamate **63** (0.0500 g, 0.153 mmol) was dissolved in dry toluene (1.50 mL) and heated at 110 °C in a sealed microwave tube till TLC analysis showed complete conversion of SM. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (10% EtOAc/hexane) to yield **67** (0.0390 g, 0.127 mmol, 82%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, 1 H, *J* = 8.8 Hz), 7.87 (d, 1 H, *J* = 1.6 Hz), 7.69 (d, 1 H, *J* = 1.6 Hz), 7.60 (m, 4 H), 7.27 (d, 2 H, *J* = 8.0 Hz), 6.75 (d, 1 H, *J* = 4.0 Hz), 2.35 (s, 3 H), 1.65 (s, 9 H); HRMS *m/z* calculated for $C_{20}H_{22}O_2N$ 208.1651, found 208.1653. The spectroscopic data were consistent with those reported in the literature.[69]



68

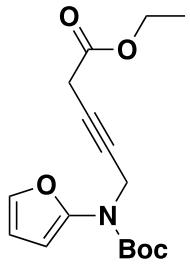
1-(*tert*-Butyl) 6-ethyl 1H-indole-1,6-dicarboxylate (68). Ethyl 5-(buta-2,3-dien-1-yl(*tert*-butoxycarbonyl)amino)furan-3-carboxylate **64** (0.0500 g, 0.163 mmol) was dissolved in dry toluene (1.60 mL) and heated at 110 °C for 1 h in a sealed microwave tube. The mixture was then concentrated under reduced pressure and purified by flash chromatography on SiO_2 (30% EtOAc/hexane) to obtain **68** (0.0391 g, 0.135 mmol, 83%) as a yellowish white solid: R_f 0.18, 30% EtOAc/hexane; mp. 98.9-100.3 °C; IR 3491, 2986, 1737, 1677, 1598, 1550, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 7.94 (dd, 1 H, *J* = 8.2 Hz, 1.2 Hz), 7.76 (d, 1 H, *J* = 3.6 Hz), 7.59 (d, 1 H, *J* = 8.4 Hz), 6.62 (d, 1 H, *J* = 3.2 Hz), 4.40 (q, 2 H, *J* = 7.2 Hz), 1.71 (s, 9 H), 1.42 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.4, 134.7, 134.4, 129.0, 126.5, 124.0, 120.7, 117.3, 107.3, 84.5, 61.0, 28.3, 14.6; HRMS *m/z* calculated for $C_{16}H_{20}O_4N$ 290.1387, found 290.1396.



75

***tert*-Butyl furan-2-yl(prop-2-yn-1-yl)carbamate (75).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0720 g, 2.10 mmol) was added to a solution of *tert*-butyl furan-2-ylcarbamate **48** (0.430 g, 2.35 mmol) in dry DMF (10.0 mL) at 0 °C under an atmosphere of N_2 and stirred for 30 mins. 80% Propargyl bromide in toluene (0.280 g, 0.200 mL, 2.36 mmol) was added to the

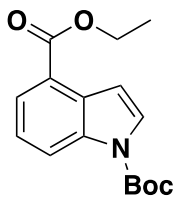
mixture and stirred at room temperature for 16 h. The mixture was then diluted with sat. NH_4Cl sol. (15.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic layers were washed with sat. NaCl sol. and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and purification by chromatography on SiO_2 (10% EtOAc/hexane) gave **75** (0.427 g, 1.93 mmol, 82%) as a colorless oil: R_f 0.34, 10% EtOAc/hexane; IR (neat) 3297, 2980, 1711, 1613, 1367 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, 1 H, *J* = 2.0 Hz, 0.8 Hz), 6.35 (dd, 1 H, *J* = 3.4 Hz, 2.4 Hz), 6.13 (br s, 1 H), 4.33 (d, 2 H, *J* = 2.4 Hz), 2.24 (t, 1 H, *J* = 2.4 Hz), 1.46 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 147.7, 138.7, 111.1, 101.9, 82.1, 79.3, 71.9, 38.5, 28.3; HRMS *m/z* calculated for $C_{12}H_{16}O_3N$ 222.1125, found 222.1125.



76

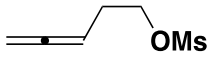
Ethyl 5-((*tert*-butoxycarbonyl)(furan-2-yl)amino)pent-3-ynoate (76). In a microwave tube, 87% ethyl diazoacetate in CH_2Cl_2 (0.0935 g, 0.085 mL, 0.713 mmol) was added to a solution containing *tert*-butyl furan-2-yl(prop-2-yn-1-yl) carbamate **75** (0.150 g, 0.681 mmol) and CuI (0.0100 g, 0.0510 mmol) in acetonitrile (3.00 mL) and stirred at room temperature for 16 h. The mixture was then filtered through a plug of celite (Et_2O wash) and the filtrate was concentrated under reduced pressure. The crude obtained was purified by chromatography on SiO_2 (10% EtOAc/hexane) to obtain **76** (0.0410 g, 0.136 mmol, 20%) as a colorless oil: R_f 0.36, 20% EtOAc/hexane; IR (neat) 2980, 2934, 1713, 1612, 1367, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$)

δ 7.19 (dd, 1 H, *J* = 2.1 Hz, 1.2 Hz), 6.34 (dd, 1 H, *J* = 2.1 Hz, 1.2 Hz), 6.14 (d, 1 H, *J* = 3.0 Hz), 4.34 (t, 2 H, *J* = 3.3 Hz), 4.17 (q, 2 H, *J* = 7.2 Hz), 3.26 (t, 2 H, *J* = 2.4 Hz); 1.45 (s, 9 H), 1.27 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 153.5, 147.8, 138.6, 111.0, 102.0, 81.9, 78.8, 75.6, 61.7, 38.8, 28.3, 26.2, 14.2; HRMS *m/z* calculated for $C_{16}H_{22}O_5N$ 308.1493, found 308.1504.



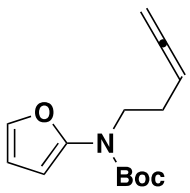
77

1-(*tert*-Butyl) 4-ethyl 1H-indole-1,4-dicarboxylate (77). In a sealed microwave tube, a solution of ethyl 5-((*tert*-butoxycarbonyl)(furan-2-yl)amino)pent-3-ynoate **76** (0.0350 g, 0.113 mmol) and triethylamine (0.0129 g, 0.0180 mL, 0.128 mmol) in dry toluene (1.50 mL) was heated at 110 °C till TLC analysis showed complete conversion of SM. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The crude obtained was purified by chromatography on SiO_2 (5% EtOAc/hexane) on silica to yield **77** (0.0190 g, 0.0657 mmol, 58%) as a yellow oil: IR (neat) 3936, 2980, 2932, 1734, 1712, 1264, 1141 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, 1 H, *J* = 8.1 Hz), 7.99 (dd, 1 H, *J* = 7.8 Hz, 0.9 Hz), 7.70 (d, 1 H, *J* = 3.9 Hz), 7.36 (t, 1 H, *J* = 8.1 Hz), 7.28 (dd, 1 H, *J* = 3.9 Hz, 0.6 Hz), 4.44 (q, 2 H, *J* = 7.2 Hz), 1.68 (s, 9 H), 1.46 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 149.6, 136.1, 130.7, 127.8, 125.6, 123.7, 122.4, 119.8, 108.1, 84.3, 60.9, 28.3, 14.6; HRMS *m/z* calculated for $C_{16}H_{20}O_4N$ 290.1387, found 290.1394.



79

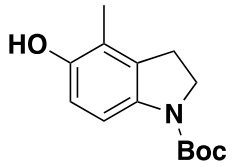
Penta-3,4-dien-1-yl methanesulfonate (79). Methanesulfonyl chloride (0.320 g, 0.220 mL, 2.82 mmol) was added to a solution containing penta-3,4-dien-1-ol[71] **78** (0.250 g, 2.52 mmol, 83%) and triethylamine (0.510 g, 0.710 mL, 5.05 mmol) in dry CH_2Cl_2 (10.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 2 h at 0 °C and then diluted with water (10.0 mL). The layers were separated and the aq. layer was extracted with Et_2O (2 x 10.0 mL). The combined organic layers were washed with 5% HCl. sol. (3 x 10.0 mL), sat. NaCl sol. (3 x 10.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure to give **79** (0.400 g, 98%) which was used for the next reaction without any further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (p, 1 H, *J* = 6.6 Hz), 4.77 (dt, 2 H, *J* = 6.6 Hz, 3.0 Hz), 4.28 (t, 2 H, *J* = 6.9 Hz), 3.02 (s, 3 H), 2.46 (m, 2 H). The spectroscopic data were consistent with those reported in the literature.[70]



80

***tert*-Butyl furan-2-yl(penta-3,4-dien-1-yl)carbamate (80).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0750 g, 2.19 mmol) was added in 3 portions to a solution of *tert*-butyl furan-2-ylcarbamate **48** (0.350 g, 1.91 mmol) in dry DMF (7.50 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred at 0 °C for 1 h after which penta-3,4-dien-1-yl methanesulfonate **75** (0.400 g, 1.29 mmol) was added to the mixture. The mixture was stirred for

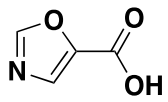
16 h and then quenched with sat. NH_4Cl sol. (2.0 mL) and water (5.0 mL). The mixture was extracted with Et_2O (3 x 10.0 mL) and the combined organic phases were collected and washed with sat. NaCl sol. (3 x 10.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and purification by chromatography on SiO_2 (5% EtOAc/hexane) gave **80** (0.288 g, 1.15 mmol, 60%) as a colorless oil: R_f 0.30, 5% EtOAc/hexane; IR (neat) 2978, 1956, 1709, 1613, 1156 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.44 (dd, 1 H, J = 1.2 Hz, 0.8 Hz), 6.43 (dd, 1 H, J = 3.2 Hz, 2.0 Hz), 6.11 Hz (dd, 1 H, J = 3.2 Hz, 0.4 Hz), 5.13 (p, 1 H, J = 7.2 Hz), 4.76 (dt, 2 H, J = 7.2 Hz, 3.2 Hz), 3.52 (t, 2 H, J = 7.2 Hz), 2.16 (m, 2 H), 1.38 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) characteristic peaks δ 208.3, 153.0, 147.8, 138.9, 111.1, 101.7, 86.4, 80.4, 75.4, 47.8, 27.7, 27.1; HRMS m/z calculated for $C_{14}H_{20}O_3N$ 250.1438, found 250.1446.



81

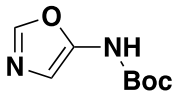
***tert*-Butyl 5-hydroxy-4-methylindoline-1-carboxylate (81).** *Tert*-butyl furan-2-yl(penta-3,4-dien-1-yl)carbamate **80** (0.0500 g, 0.200 mmol) was dissolved in dry toluene (2.00 mL) in a sealed microwave tube and heated at 150 °C till TLC analysis showed complete conversion of SM. The reaction mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. Purification by chromatography on SiO_2 (25% EtOAc/hexane) gave **81** (0.0230 g, 0.0923 mmol, 46%) as a yellow solid: R_f 0.20, 25% EtOAc/hexane; ^1H NMR (400 MHz, DMSO-d_6, 80 °C) δ 8.53 (s, 1 H), 7.22 (d, 1 H, J = 8.0 Hz), 6.56 (d, 1 H, J = 8.4 Hz), 3.87 (t, 2 H, J = 8.4 Hz), 2.93 (t, 2 H, J = 8.4 Hz), 2.03 (s, 3 H), 1.50 (s, 9 H); HRMS m/z calculated for

$C_{14}H_{20}O_3N$ 250.1438, found 250.1428. The spectroscopic data were consistent with those reported in the literature.[9]



122

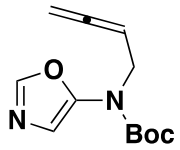
Oxazole-5-carboxylic acid (122). In a 100-mL RBF with a magnetic sir bar, a solution of lithium hydroxide (0.85 g, 35.49 mmol) in water (25.0 mL) was added to a solution of ethyl oxazole-5-carboxylate[72] (1.00 g, 7.08 mmol) in THF (25.0 mL) and the mixture was stirred for 16 h at room temperature. The mixture was then diluted with water (40.0 mL) and washed with Et_2O (2 x 30.0 mL). The aq. layer was then treated with 5 M HCl sol. till it turned to pH 2 and extracted with EtOAc (4 x 40.0 mL). The combined organic layers were washed with sat. NaCl sol. (3 x 30.0 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure to obtain **122** (0.536 g, 4.74 mmol, 67%) as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.74 (br s, 1 H), 8.62 (s, 1 H), 7.90 (s, 1 H).



123

***tert*-Butyl oxazol-5-ylcarbamate (123).** In a 50-mL RBF with a magnetic stir bar and reflux condenser, oxazole-5-carboxylic acid **122** (0.530 g, 4.68 mmol) was suspended in dry *t*-BuOH (14.0 mL) and treated with triethylamine (0.720 g, 1.00 mL, 7.11 mmol) and DPPA (1.40 g, 1.10 mL, 5.04 mmol). The mixture was refluxed for 18 h under an atmosphere of N_2 and then cooled to room temperature. The solvent was evaporated under reduced pressure and the crude

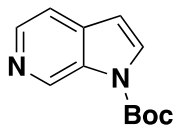
was stirred with sat. $NaHCO_3$ (20.0 mL) for 2 h at 0 °C. The mixture was then extracted using EtOAc (3 x 20.0 mL) and the combined organic layer was washed with sat. NaCl sol. and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (40% EtOAc/hexane) to yield **123** (0.650 g, 3.53 mmol, 75%) as a white solid: R_f 0.28, 40% EtOAc/hexane; mp. 81.5-82.8 °C; IR (neat) 3149, 2978, 1718, 1618, 1561, 1515, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 6.85 (br s, 1 H), 6.58 (br s, 1 H), 1.52 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 145.1, 144.8, 112.1, 82.4, 28.3; HRMS m/z calculated for $C_8H_{13}O_3N_2$ 185.0921, found 185.0916.



124

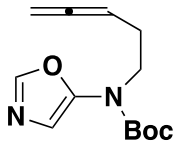
***tert*-Butyl oxazol-5-yl(propa-1,2-dien-1-yl) carbamate (124).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.045 g, 1.31 mmol) was added in 3 portions to a solution of *tert*-butyl oxazol-5-ylcarbamate **123** (0.235 g, 1.28 mmol) in dry DMF (7.50 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 1 h after which buta-2,3-dien-1-yl methanesulfonate **49** (0.294 g, 1.98 mmol) was added. The mixture was then stirred for 16 h at room temperature and then quenched with sat. NH_4Cl sol. (5.0 mL), water (10.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic layers was washed with sat. NaCl sol. (3 x 10.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (10% EtOAc/hexane) to obtain **124** (0.213 g, 0.899 mmol, 70%) as a yellow oil: R_f 0.20, 10% EtOAc/hexane; IR (neat) 3137, 2979, 1957, 1714, 1623, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 6.79 (br s, 1 H), 5.20 (p, 1 H, *J* =

6.4 Hz), 4.78 (dt, 2 H, *J* = 6.4 Hz, 2.8 Hz), 4.17 (dt, 2 H, *J* = 6.4 Hz, 2.8 Hz), 1.46 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 152.7, 147.7, 146.83, 116.65, 86.8, 82.4, 77.0, 47.2, 28.2; HRMS *m/z* calculated for $C_{12}H_{17}O_3N_2$ 237.1234, found 237.1228.



125

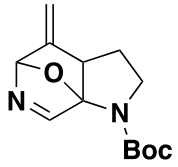
***tert*-Butyl 1H-pyrrolo[2,3-c]pyridine-1-carboxylate (125).** *Tert*-butyl buta-2,3-dien-1-yl(oxazol-5-yl)carbamate **124** (0.050 g, 0.211 mmol) was dissolved in dry toluene (2.10 mL) and the solution was heated at 85 °C in a sealed microwave tube till TLC analysis showed complete conversion of the SM (10 h). The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The crude obtained was purified by chromatography on SiO_2 (40% EtOAc/hexane) to obtain **125** (0.041 g, 89%) as a brownish yellow oil: R_f 0.20, 40% EtOAc/hexane; IR (neat) 2979, 2934, 1734, 1336, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br s, 1 H), 8.41 (br s, 1 H), 7.74 (d, 1 H, *J* = 3.2 Hz), 7.49 (d, 1 H, *J* = 5.2 Hz), 6.59 (d, 1 H, *J* = 3.6 Hz), 1.69 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 142.0, 137.6, 136.2, 129.6, 129.3, 115.7, 106.4, 85.1, 77.36, 28.3; HRMS m/z calculated for $C_{12}H_{15}O_2N_2$ 219.1128, found 219.1139.



126

***tert*-Butyl oxazol-5-yl(penta-3,4-dien-1-yl) carbamate (126).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0450 g, 1.31 mmol) was added in two portions to a solution of *tert*-

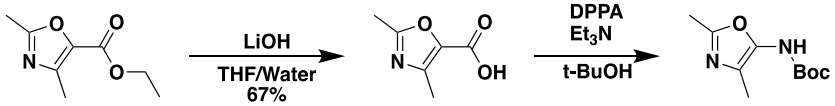
butyl oxazol-5-ylcarbamate **123** (0.180 g, 0.977 mmol) in dry DMF (5.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred at 0 °C for 1 h and then penta-3,4-dien-1-yl methanesulfonate **79** (0.330 g, 2.02 mmol) was added. The mixture was stirred at room temperature for 16 h and then quenched with water (3.00 mL) and sat. NH_4Cl sol. (2.00 mL) and extracted with Et_2O (3 x 7.00 mL). The combined organic layers were washed with sat. NaCl sol. (3 x 7.00 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (20% EtOAc/hexane) to obtain **126** (0.110 g, 0.439 mmol, 45%) as a colorless oil: R_f 0.26, 20% EtOAc/hexane; IR (neat) 3132, 2979, 1956, 1713, 1625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1 H), 6.80 (br s, 1 H), 5.06 (p, 1 H, *J* = 7.2 Hz), 4.68 (dt, 2 H, *J* = 7.2 Hz, 2.8 Hz), 3.67 (t, 2 H, *J* = 7.6 Hz), 2.28 (m, 2 H), 1.46 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 152.9, 147.8, 146.9, 86.4, 82.3, 77.4, 75.4, 47.8, 28.2, 27.7; HRMS m/z calculated for $C_{13}H_{19}O_3N_2$ 251.1390, found 251.1392.



127

***tert*-Butyl-4-methylene-3,3a,4,5-tetrahydro-5,7a-epoxypyrrolo[2,3-c]pyridine-1(2H)-carboxylate (127).** *Tert*-butyl oxazol-5-yl(penta-3,4-dien-1-yl)carbamate **126** (0.0500 g, 0.199 mmol) was dissolved in dry toluene (2.00 mL) and heated at 140 °C in a sealed microwave tube till TLC analysis showed complete consumption of SM (6.5 h). The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The crude obtained was purified by chromatography on SiO_2 (40% EtOAc/hexane) on silica to yield **127** (0.0365 g, 0.146 mmol, 73%) as a pink solid: R_f 0.28, 40% EtOAc/hexane; mp. 78-80 °C; IR (neat) 3385, 2976,

1693, 1368; ^{1}H NMR (400 MHz, DMSO-d_6, 80 °C) δ 8.25 (s, 1 H), 5.85 (s, 1 H), 5.26 (d, 1 H, J = 2.0 Hz), 5.01 (s, 1 H), 3.70 (m, 2 H), 2.57 (t, 1 H, J = 9.2 Hz), 2.25 (m, 1 H), 1.69 (m, 1 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 152.0, 144.7, 108.5, 103.1, 94.4, 80.5, 50.5, 44.2, 27.9, 27.8; HRMS m/z calculated for $C_{13}H_{19}O_3N_2$ 251.1390, found 251.1392.

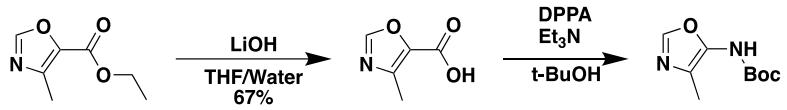


E3 **E4** **128**

2,4-Dimethyloxazole-5-carboxylic acid (E4). In a 100-mL RBF with a magnetic stir bar, a solution of lithium hydroxide (0.72 g, 29.76 mmol) in water (12.0 mL) was added to a solution of ethyl 2,4-dimethyloxazole-5-carboxylate[73] **E3** (1.0 g, 5.91 mmol) in THF (18.0 mL). The mixture was stirred for 2 h at room temperature and then diluted with water (30.0 ml) and washed with Et_2O (20.0 mL). The aq. layer was then acidified by adding 5 M HCl sol. to pH 2 and then extracted with EtOAc (3 x 40.0 mL). The combined organic layer was washed with sat. NaCl sol. (3 x 30.0 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure to obtain **E4** (0.412 g, 2.92 mmol, 50%) as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.28 (s, 1 H), 2.42 (s, 3 H), 2.31 (s, 3 H); HRMS *m/z* calculated for $C_6H_6O_3N$ 140.0342, found 140.0390.

***tert*-Butyl (2,4-dimethyloxazol-5-yl)carbamate (128).** In a 25-mL RBF with a magnetic stir bar and reflux condenser, DPPA (0.86 g, 0.68 mL, 3.11 mmol) was added to a solution containing 2,4-dimethyloxazole-5-carboxylic acid **E4** (0.400 g, 2.83 mmol) and triethylamine (0.400 g, 0.560 mL, 3.98 mmol) in dry *t*-BuOH (8.00 mL). The mixture was refluxed for 18 h under an atmosphere of N_2 and then cooled to room temperature. The solvent was evaporated under

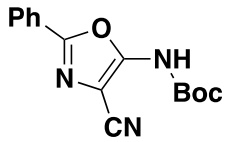
reduced pressure and the crude was treated with sat. $NaHCO_3$ sol. (10.0 mL) and water (5.0 mL) and stirred for 2 h. The mixture was extracted with EtOAc (3 x 10.0 mL) and the combined organic layers was washed with sat. NaCl sol. (3 x 10.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (50% EtOAc/hexane) to yield **128** (0.510 g, 2.40 mmol, 85%) as a white solid. R_f 0.22, 50% EtOAc/hexane; mp. 82-83 °C; IR (neat) 3145, 2942, 1730, 1676, 1572, 1511, 1250, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 6.08 (br s, 1 H), 2.35 (s, 3 H), 2.035 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.1, 153.5, 137.4, 129.9, 81.7, 28.3, 14.4, 11.0; HRMS *m/z* calculated for $C_{10}H_{17}O_3N_2$ 213.1234, found 213.1232.



E5 **E6** **129**

4-Methyl oxazole-5-carboxylic acid (E6). In a 250-mL RBF with a magnetic stir bar, a solution of lithium hydroxide (1.00 g, 41.3 mmol) in water (25.0 mL) was added to a solution of ethyl 4-methyloxazole-5-carboxylate[73] **E5** (1.30 g, 8.38 mmol) in THF (20.0 mL). The mixture was stirred for 18 h and then diluted with water (20.0 mL). The aq. layer was washed with Et_2O (2 x 25.0 mL) and then acidified with 5 M HCl sol. to pH 2. The aq. layer was then extracted using EtOAc (6 x 20.0 mL) and the combined organic layer was washed with sat. NaCl sol (3 x 30 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure to obtain **E6** (0.872 g, 6.85 mmol, 82%) as a white solid: ^1H NMR (300 MHz, acetone-d_6) δ 11.68 (br s, 1 H), 8.23 (s, 1 H), 2.43 (s, 3 H); HRMS *m/z* calculated for $C_7H_9O_3N$ 128.0342, found 128.0358.

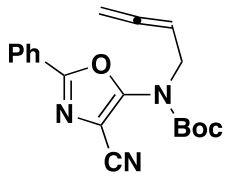
***tert*-Butyl (4-methyloxazol-5-yl)carbamate (129).** In a 50-mL RBF with a magnetic stir bar with a reflux condenser, 4-methyloxazole-5-carboxylic acid **E6** (0.400 g, 3.14 mmol) was suspended in dry *t*-BuOH (9.50 mL) and treated with triethylamine (0.468 g, 0.650 mL, 4.63 mmol) and DPPA (0.891 g, 0.700 mL, 3.21 mmol). The mixture was refluxed for 18 h under an atmosphere of N_2 and then cooled to room temperature. The solvent was evaporated under vacuum and the crude was stirred with sat. $NaHCO_3$ (15.0 mL) for 2 h at 0 °C. The mixture was then extracted using EtOAc (3 x 10.0 mL) and the combined organic layer was washed with sat. NaCl sol. (3 x 10.0 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and purification by chromatography on SiO_2 (40% EtOAc/hexane) gave **129** (0.462 g, 2.33 mmol, 74%) as a white solid: R_f 0.28, 40% EtOAc/hexane; mp. 98.1-99.5 °C; IR (neat) 3194, 2198, 1734, 1674, 1499, 1365, 1247, 1162, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1 H), 5.97 (br s, 1 H), 2.12 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 147.7, 138.5, 128.6, 81.9, 28.2, 11.1; HRMS *m/z* calculated for $C_9H_{14}O_3N_2$ 199.1077, found 199.1070.



132

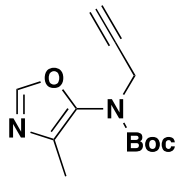
***tert*-Butyl (4-cyano-2-phenyloxazol-5-yl)carbamate (132).** In a 50-mL RBF with a magnetic sir bar, di-*tert*-butyl dicarbonate (0.300 g, 1.36 mmol) was added to a solution containing 5-amino-2-phenyloxazole-4-carbonitrile[74] (0.230 g, 1.24 mmol) and DMAP (0.0450 g) in dry THF (12.5 mL) and stirred at room temperature for 18 h under an atmosphere of N_2. The solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (20% EtOAc/hexane) to yield **132** (0.263 g, 0.922 mmol, 74%) as a white solid: R_f 0.30, 20%

EtOAc/hexane; mp. 142 °C (decomp); IR (neat) 3170, 2926, 2724, 2313, 1716, 1554, 1250, 1149 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.45 (s, 1 H), 7.88 (m, 2 H), 7.56 (m, 3 H), 1.51 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.3, 151.8, 150.4, 131.3, 129.3, 125.8, 125.1, 113.1, 98.2, 82.1, 27.7; HRMS *m/z* calculated for $C_{15}H_{16}O_3N_3$ 286.1186, found 286.1193.



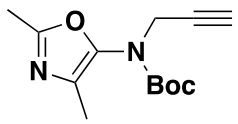
133

***tert*-Butyl buta-2,3-dien-1-yl(4-cyano-2-phenyloxazol-5-yl)carbamate (133).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0400 g, 1.16 mmol) was added to a solution containing *tert*-butyl (4-cyano-2-phenyloxazol-5-yl)carbamate **132** (0.250 g, 0.876 mmol) in dry DMF (5.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred at 0 °C for 1 h after which buta-2,3-dien-1-yl methanesulfonate **49** (0.156 g, 1.05 mmol) was added slowly. The mixture was then stirred at room temperature for 16 h and then quenched with 10% NH_4Cl sol. (7.00 mL). The product was extracted from the mixture using Et_2O (3 x 7.00 mL) and the combined organic layers were washed with sat. NaCl sol. (3 x 7.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and purification by chromatography on SiO_2 (10% EtOAc/hexane) gave **133** (0.203 g, 0.602 mmol, 69%) as a colorless oil: R_f 0.23, 10% EtOAc/hexane; IR (neat) 2981, 2937, 2240, 1958, 1727, 1620, 1310, 1148 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (m, 2 H), 7.50 (m, 3 H), 5.27 (p, 1 H, J = 6.4 Hz), 4.85 (dt, 2 H, J = 6.4 Hz, 2.8 Hz), 4.33 (dt, 2 H, J = 6.4 Hz, 2.8 Hz), 1.54 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 157.5, 153.2, 151.0, 131.7, 129.2, 126.5, 125.8, 112.5, 106.7, 86.2, 84.6, 77.9, 47.1, 28.1; HRMS *m/z* calculated for $C_{19}H_{20}O_3N_3$ 338.1499, found 338.1509.



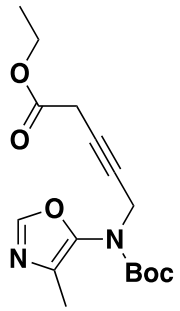
134

***tert*-Butyl (4-methyloxazol-5-yl) (prop-2-yn-1-yl)carbamate (134).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0400 g, 1.16 mmol) was added in 2 portions to a solution of *tert*-butyl (4-methyloxazol-5-yl) carbamate **130** (0.200 g, 1.01 mmol) in dry DMF (5.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred at 0 °C for 1 h and then 80% propargyl bromide in toluene (0.174 g, 0.130 mL, 1.16 mmol) was added. The mixture was stirred for 16 h at room temperature and then diluted with 10% NH_4Cl sol. (10.0 mL). The mixture was extracted with Et_2O (3 x 10.0 mL) and the combined organic layers were washed with sat. NaCl sol. (3 7.0 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by passing it through a plug of SiO_2 (30% EtOAc/hexane) to obtain **134** (0.214 g, 0.906 mmol, 90%) as a yellow oil: IR (neat) 3297, 3132, 2980, 2932, 2125, 1716, 1665, 1368, 1160 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.16 (s, 1 H), 4.26 (d, 2 H, J = 2.4 Hz), 3.27 (t, 1 H, J = 2.4 Hz), 2.00 (s, 3 H), 1.37 (s, 9 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.4, 148.9, 141.2, 128.0, 81.5, 79.0, 75.1, 37.9, 27.6, 10.7; HRMS *m/z* calculated for $C_{12}H_{17}O_3N_2$ 237.1234, found 237.1235.



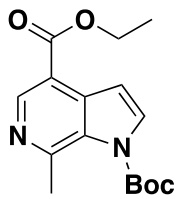
136

***tert*-Butyl (2,4-dimethyloxazol-5-yl)(prop-2-yn-1-yl)carbamate (136).** In a 25-mL RBF with a magnetic stir bar, 70% NaH (0.0700 g, 2.04 mmol) was added in two portions to a solution of *tert*-butyl oxazol-5-ylcarbamate **128** (0.330 g, 1.55 mmol) in dry DMF (5.00 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred for 30 mins and then 80% propargyl bromide in toluene (0.253 g, 0.190 mL, 1.71 mmol) was added. The solution was stirred for 16 h at room temperature and then quenched with 10% NH_4Cl sol. (10.0 mL) and extracted with Et_2O (3 x 10.0 mL). The combined organic layers were washed with sat. NaCl sol. (3 x 10.0 mL) and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (30% EtOAc/hexane) to yield **136** (0.327 g, 1.31 mmol, 84%) as a yellow solid: R_f 0.18, 30% EtOAc/hexane, mp. 53.6-55.2 °C; IR (neat) 3193, 2980, 2926, 2111, 1710, 1672, 1571, 1371, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27 (s, 2 H), 2.38 (s, 3 H), 2.24 (s, 1 H), 2.05 (s, 3 H), 1.42 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 153.3, 141.0, 129.6, 82.2, 78.7, 72.5, 38.3, 28.2, 14.5, 11.1; HRMS *m/z* calculated for $C_{19}H_{13}O_3N_2$ 151.1390, found 151.1393.



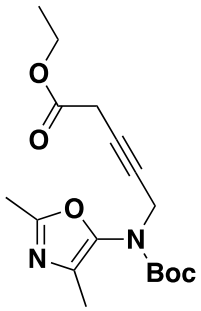
E7

Ethyl 5-((*tert*-butoxycarbonyl)(4-methyloxazol-5-yl)amino)pent-3-ynoate (E7). In an oven dried microwave tube, 87% ethyl diazoacetate in CH_2Cl_2 (0.0550 g, 0.0500 mL, 0.419 mmol) was added to a solution of *tert*-butyl (4-methyloxazol-5-yl)(prop-2-yn-1-yl)carbamate **134** (0.0800 g, 0.338 mmol) and copper iodide (0.00500 g, 0.0254 mmol) in acetonitrile (3.00 mL). The mixture was stirred at room temperature for 48 h after which it was filtered through a plug of celite (Et_2O wash). The solvent was then removed under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (20% EtOAc/hexane) to yield **E7** (0.0340 g, 0.105 mmol 31%) as a yellow oil: R_f 0.23, 40% EtOAc/hexane; IR (neat) 2980, 2934, 1718, 1665, 1506, 1368, 1321, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 1 H), 4.32 (s, 2 H), 4.17 (q, 2 H, *J* = 7.2 Hz), 3.23 (t, 2 H, *J* = 2.4 Hz), 2.11 (s, 3 H), 1.42 (s, 9 H), 1.27 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 153.2, 147.9, 141.9, 129.4, 82.3, 78.0, 77.4, 76.4, 61.7, 28.2, 26.1, 14.2, 11.1; HRMS *m/z* calculated for $C_{16}H_{23}O_5N_2$ 323.1602, found 323.1617.



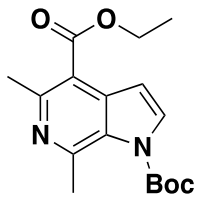
137

1-(*tert*-Butyl) 4-ethyl 7-methyl-1H-pyrrolo[2,3-c]pyridine-1,4-dicarboxylate (137). In a sealed microwave tube, a mixture of ethyl 5-((*tert*-butoxycarbonyl)(4-methyloxazol-5-yl)amino)pent-3-ynoate **E7** (0.0300 g, 0.0931 mmol) and triethylamine (0.0108 g, 0.0150 mL, 0.107 mmol) in dry toluene (1.00 mL) was heated at 60 °C for 19 h and then at 90 °C for 4 h. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. Purification by chromatography on SiO_2 (20% EtOAc/hexane) yielded **137** (0.0236 g, 0.0775 mmol, 83%, 23% over 2 steps) as a yellow oil: R_f 0.31, 20% EtOAc/hexane; IR (neat) 2981, 1752, 1713, 1583, 1369, 1317, 1302, 1215, 1150, 1078 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.86 (s, 1 H), 7.97 (d, 1 H, J = 3.5 Hz), 7.23 (d, 1 H, J = 3.5 Hz), 4.43 (q, 2 H, J = 7.0 Hz), 2.87 (s, 3 H), 1.69 (s, 9 H), 1.42 (t, 3 H, J = 7.0 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.4, 150.7, 149.4, 144.7, 137.5, 134.1, 132.1, 116.5, 107.2, 85.8, 61.4, 28.0, 26.1, 14.6; HRMS *m/z* calculated for $C_{16}H_{21}O_4N_2$ 305.1496, found 305.1503.



E8

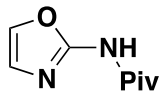
Ethyl 5-((*tert*-butoxycarbonyl)(2,4-dimethyloxazol-5-yl)amino)pent-3-ynoate (E8). In a 25-mL RBF with a magnetic stir bar, 87% ethyl diazoacetate in CH_2Cl_2 (0.0825 g, 0.0750 mL, 0.629 mmol) was added to a solution of *tert*-butyl (2,4-dimethyloxazol-5-yl)(prop-2-yn-1-yl)carbamate **136** (0.100 g, 0.399 mmol) and CuI (0.00500 g, 0.0257 mmol) in dry acetonitrile (4.00 mL) under an atmosphere of N_2. The mixture was stirred at room temperature for 18 h and then passed through a plug of celite (Et_2O wash). The solvent was evaporated under reduced pressure and the crude obtained was purified by chromatography on SiO_2 (40% EtOAc/hexane) to yield a mixture which was used for the next step without further purification.



138

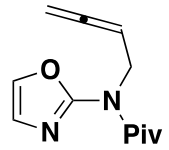
1-(*tert*-Butyl) 4-ethyl 5,7-dimethyl-1H-pyrrolo[2,3-c]pyridine-1,4-dicarboxylate (138). In a sealed microwave tube, **E8** (0.0600 g) and triethylamine (0.0180 g, 0.0250 mL, 0.178 mmol) was stirred at 70 °C for 16 h and then at 90 °C for 5 h. The mixture was cooled to room temperature and the solvent was evaporated under reduce pressure. The crude obtained was purified by chromatography on SiO_2 (10% EtOAc/hexane) to give **138** (0.0295 g, 0.0927 mmol,

25%) as a yellow oil: IR (neat) 2980, 2933, 1752, 1711, 1570, 1324, 1213, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1 H, *J* = 3.9 Hz), 6.96 (d, 1 H, *J* = 3.9 Hz), 4.45 (q, 2 H, *J* = 7.2 Hz), 2.87 (s, 3 H), 2.82 (s, 3 H), 1.65 (s, 9 H), 1.45 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 152.1, 148.7, 147.8, 138.3, 132.5, 130.1, 115.3, 107.1, 84.8, 61.1, 28.1, 25.9, 24.3, 14.5; HRMS *m/z* calculated for $C_{17}H_{23}O_4N_2$ 319.1652, found 319.1667.



141

N-(oxazol-2-yl)pivalamide (141). In a 250-mL RBF with a magnetic stir bar trimethyl acetyl chloride (0.970 g, 1.00 mL, 7.96 mmol) was added to a solution containing 2-aminooxazole[62] **139** (0.600 g, 7.13 mmol) and triethylamine (0.864 g, 1.20 mL, 8.53 mmol) in dry CH_2Cl_2 (70.0 mL) at 0 °C under an atmosphere of N_2. The mixture was stirred at room temperature for 16 h. The solvent was then evaporated under reduced pressure and purification by chromatography on SiO_2 (50% EtOAc/hexane) gave **141** (0.791 g, 4.70 mmol, 66%) as a pink solid: R_f 0.15, 50% EtOAc/hexane; mp. 101.5-102.8 °C; IR (neat) 3252, 3165, 2962, 2919, 1700, 1588, 1546, 1529, 1477, 1142 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.67 (br s, 1 H), 7.48 (s, 1 H), 6.96 (s, 1 H), 1.30 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 154.5, 135.8, 126.0, 40.0, 27.3; HRMS *m/z* calculated for $C_8H_{13}O_2N_2$ 169.098, found 169.0986.

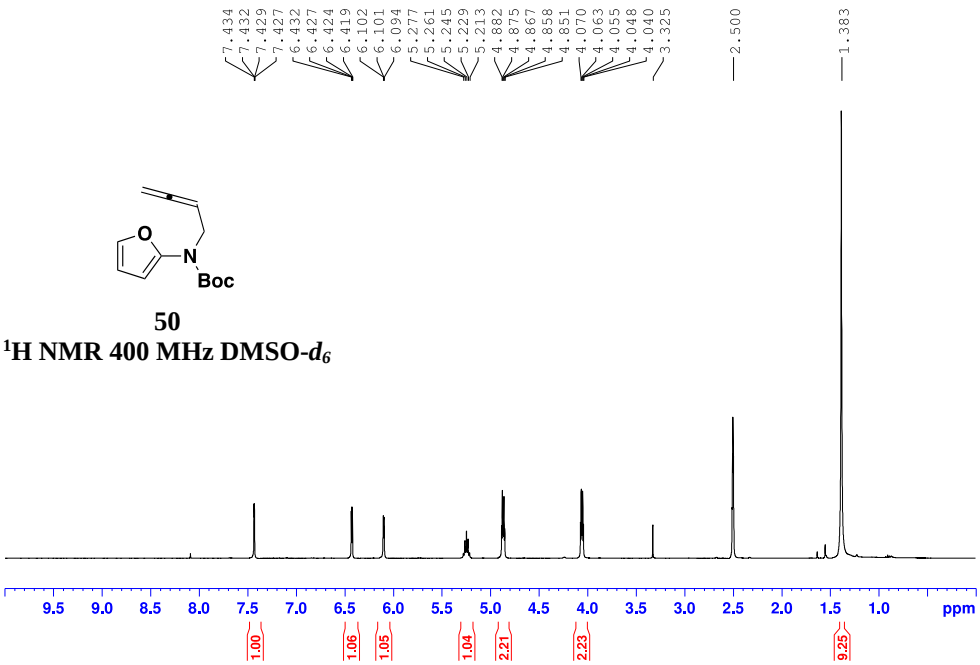


142

N-(buta-2,3-dien-1-yl)-N-(oxazol-2-yl)pivalamide (142). In a 25-mL RBF with a magnetic stir bar, buta-2,3-dien-1-yl methanesulfonate **49** (0.180 g, 1.21 mmol) was added to a solution of N-(oxazol-2-yl)pivalamide **141** (0.100 g, 0.595 mmol) and tetramethyl guanidine (0.0918 g, 0.100 mL, 0.797 mmol) in dry THF (6.00 mL). The mixture was stirred for 16 h at room temperature and then quenched with 10% NH_4Cl sol. (10.0 mL) and extracted with Et_2O (3 x 8.00 mL). The combined organic layers were washed with sat. NaCl sol. and dried (Na_2SO_4). After filtration, the solvent was evaporated under reduced pressure and purification by chromatography on SiO_2 (60% EtOAc/hexane) gave the **142** (0.0405 g, 0.184 mmol, 31%) as a white solid: R_f 0.18, 60% EtOAc/hexane; mp. 57.5-58.8 °C; IR (neat) 3133, 2952, 1958, 1633, 1600, 1580, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 1 H, *J* = 1.2 Hz), 6.70 (d, 1 H, *J* = 1.2 Hz), 5.27 (p, 1 H, *J* = 3.9 Hz), 4.89 (dt, 2 H, *J* = 3.9 Hz, 1.8 Hz), 4.33 (dt, 2 H, *J* = 3.9 Hz, 1.8 Hz), 1.22 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 187.9, 156.4, 131.0, 115.6, 85.5, 77.9, 44.0, 41.5, 28.0; HRMS *m/z* calculated for $C_{12}H_{17}O_2N_2$ 221.1290, found 221.1304.

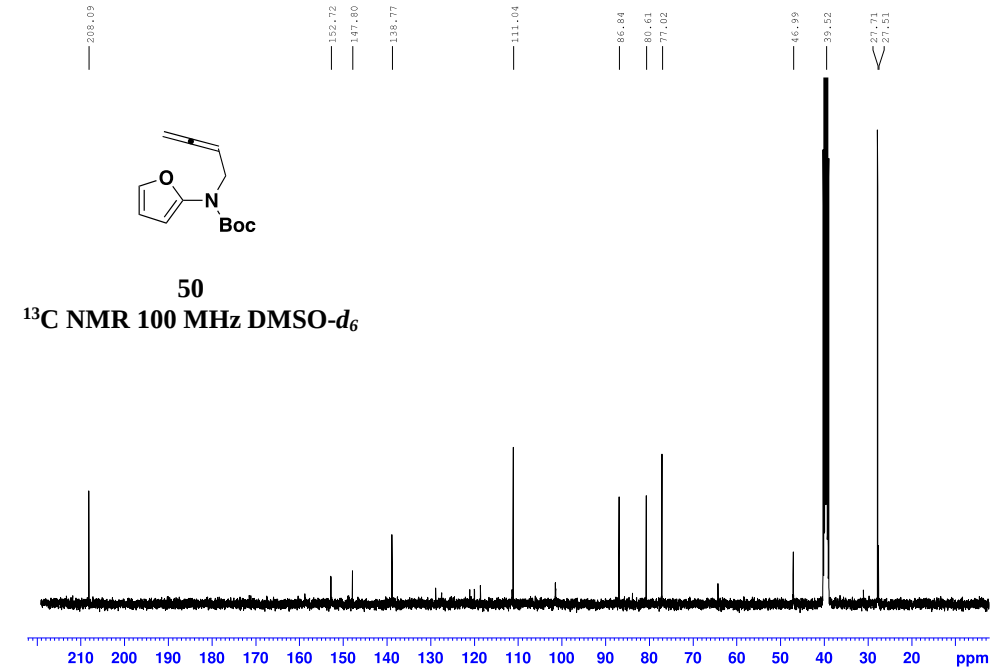
APPENDIX A

SELECTED NMR SPECTRA



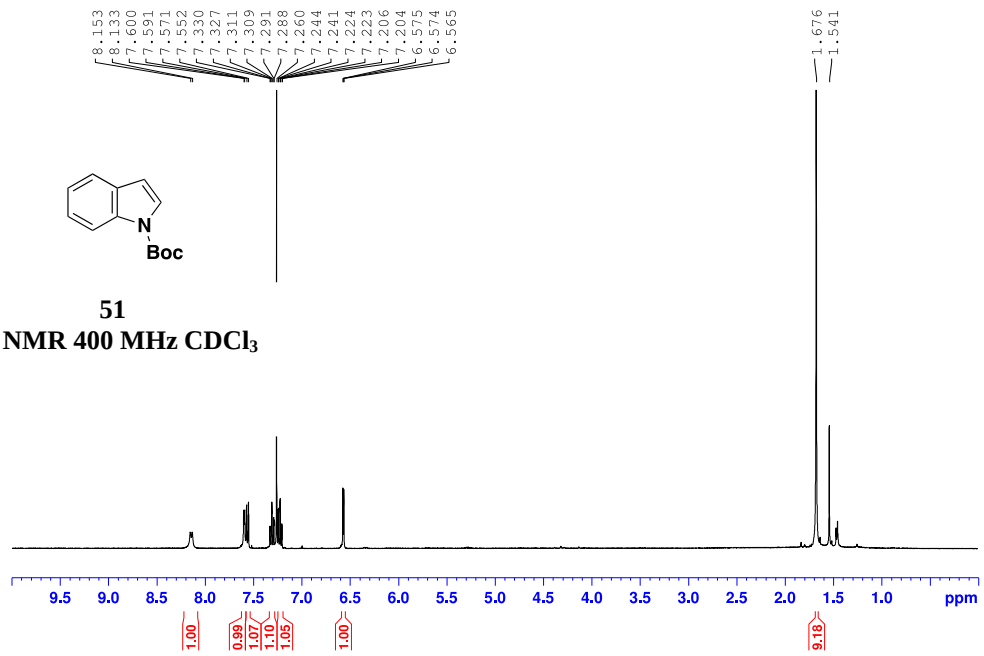
50

^{1}H NMR 400 MHz DMSO-*d*$_6$



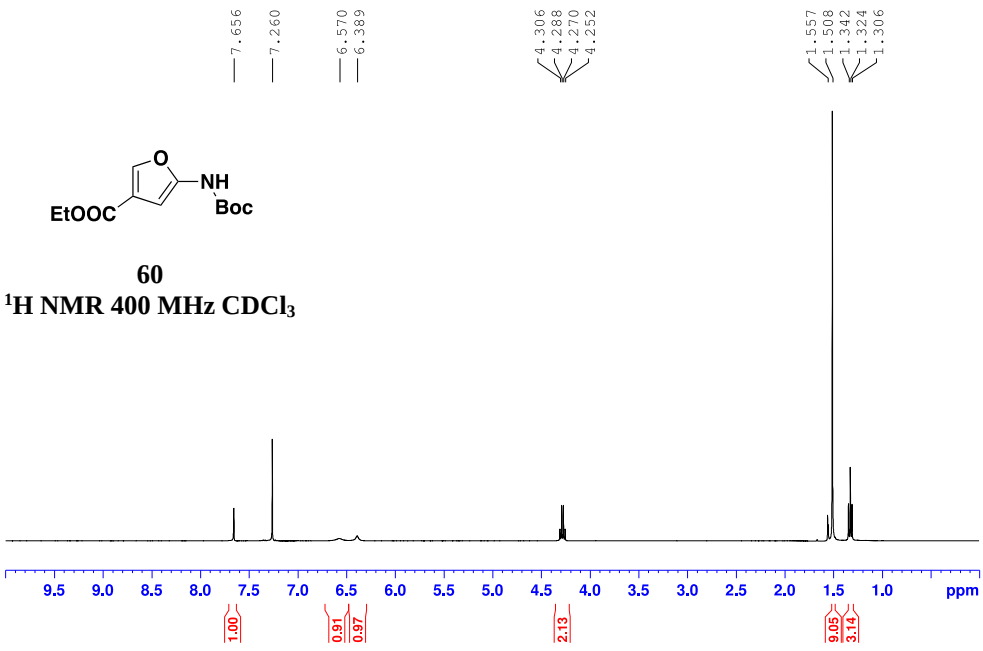
50

^{13}C NMR 100 MHz DMSO-*d*$_6$



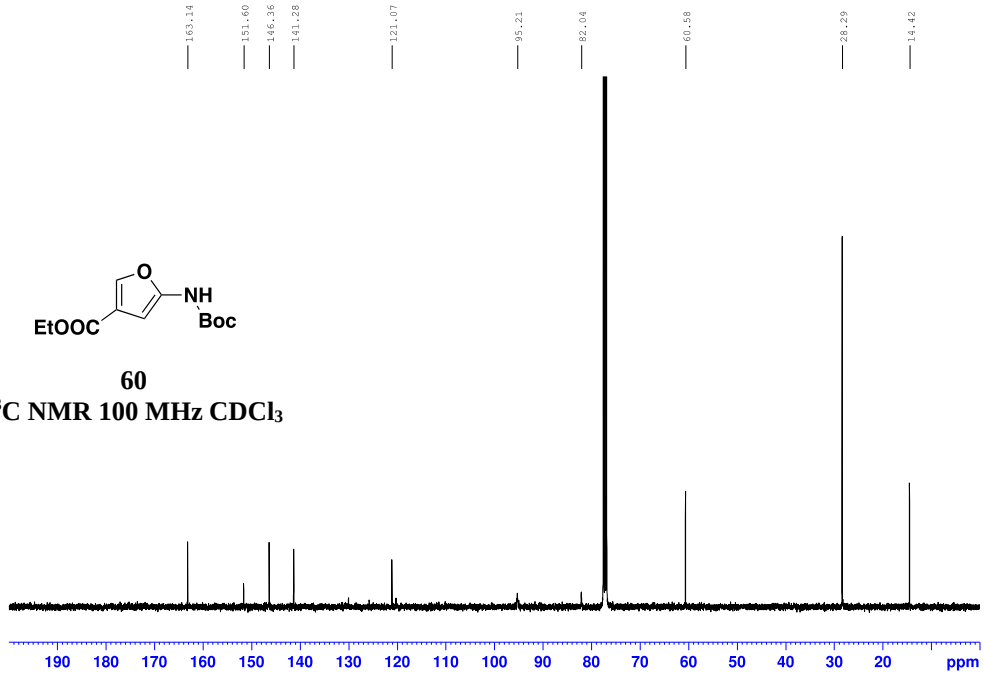
51

^{1}H NMR 400 MHz $CDCl_3$



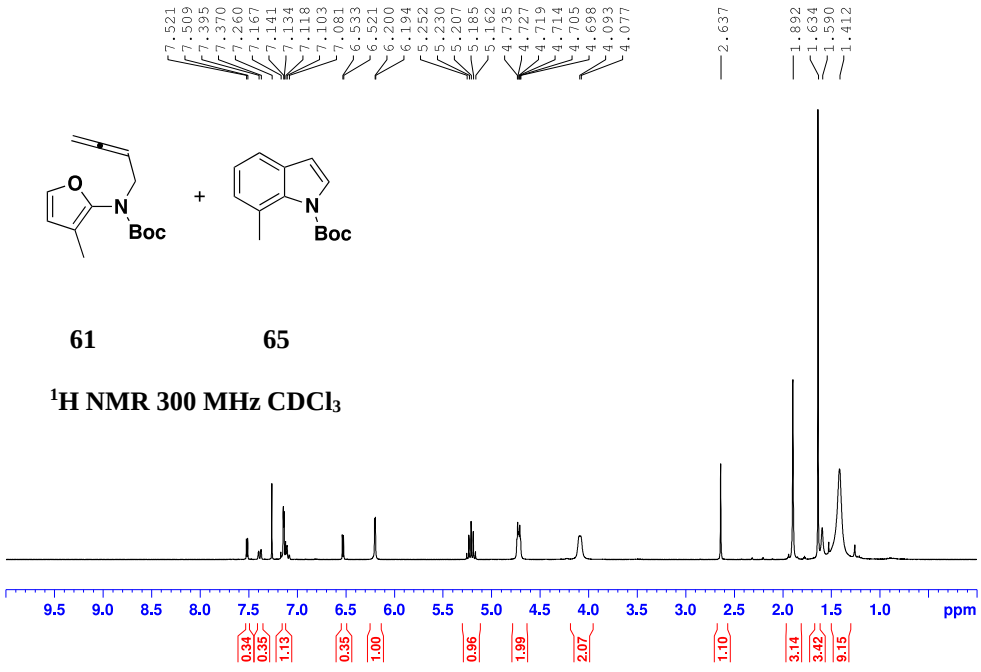
60

^{1}H NMR 400 MHz $CDCl_3$



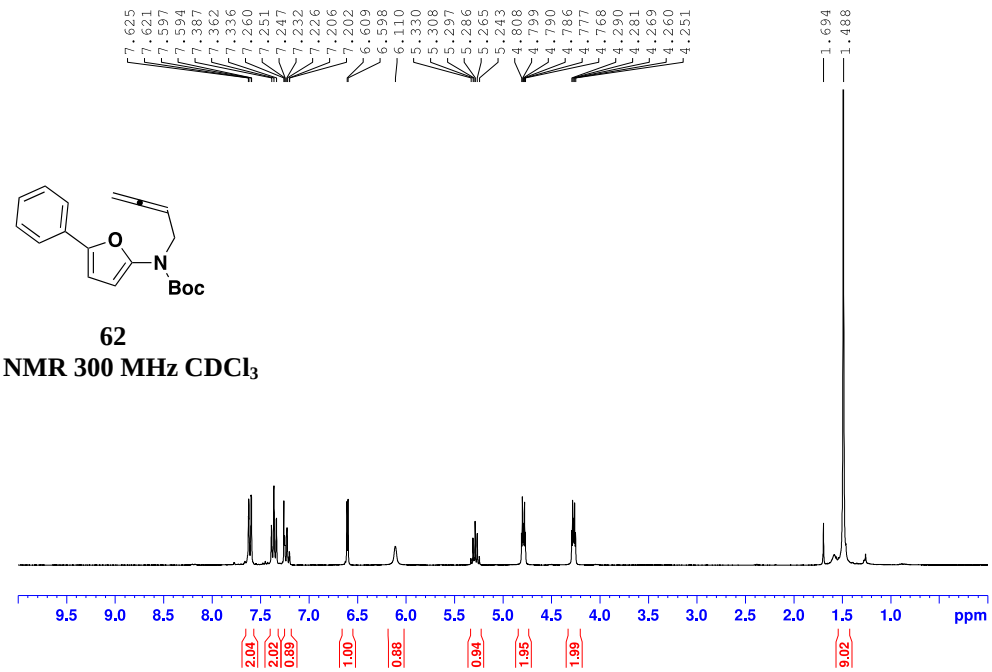
60

^{13}C NMR 100 MHz $CDCl_3$



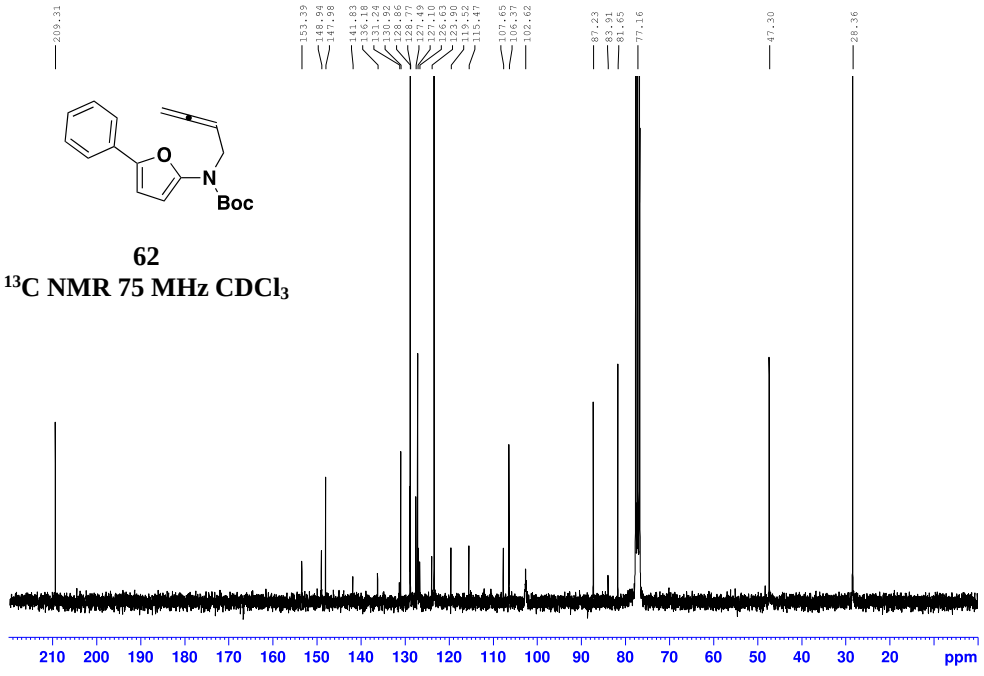
61 **65**

^{1}H NMR 300 MHz $CDCl_3$



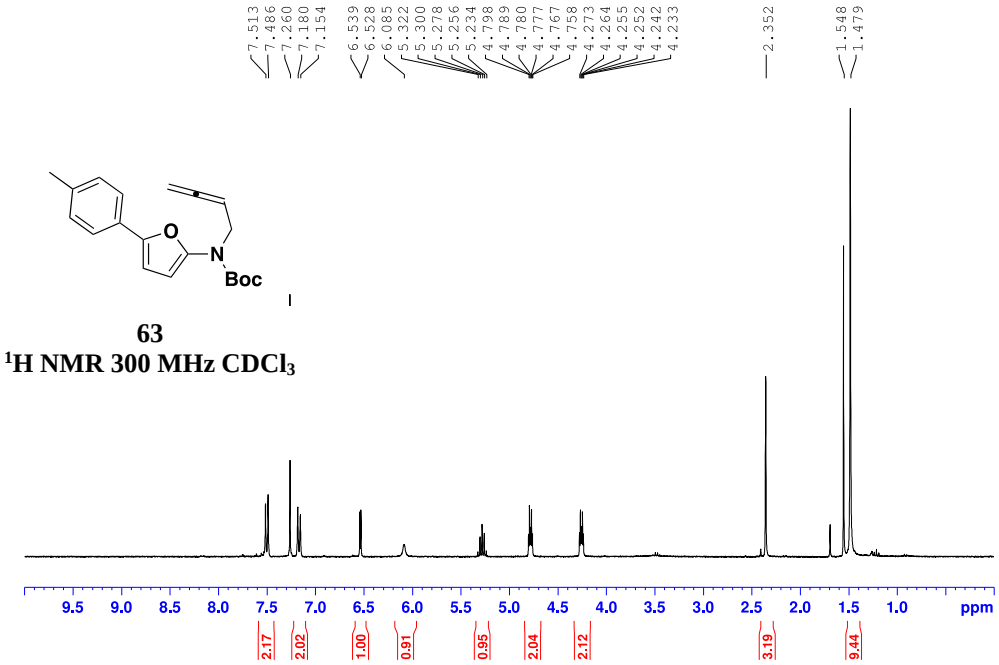
62

^{1}H NMR 300 MHz $CDCl_3$



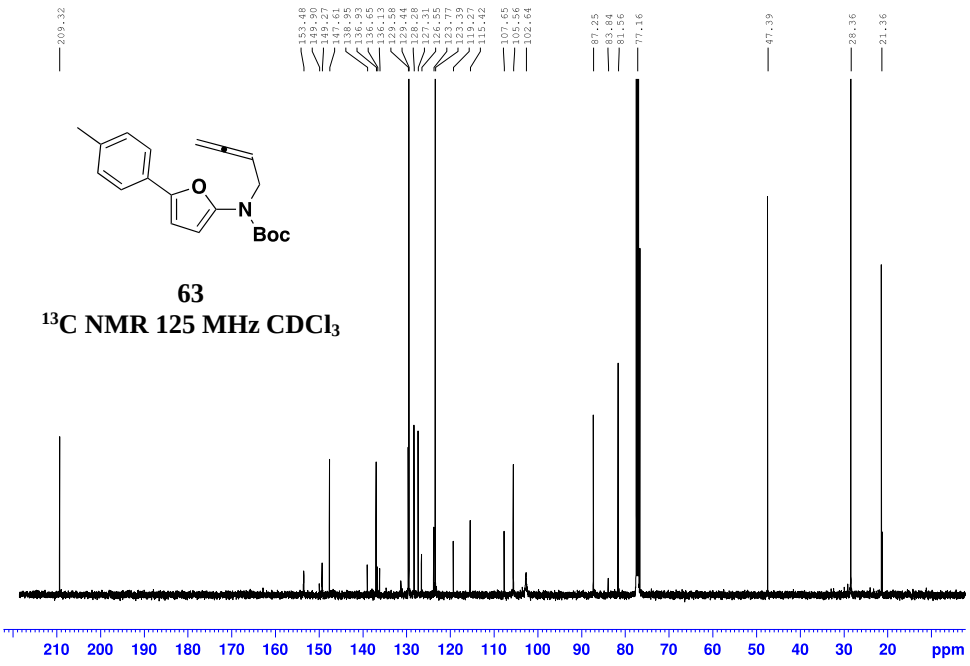
62

^{13}C NMR 75 MHz $CDCl_3$



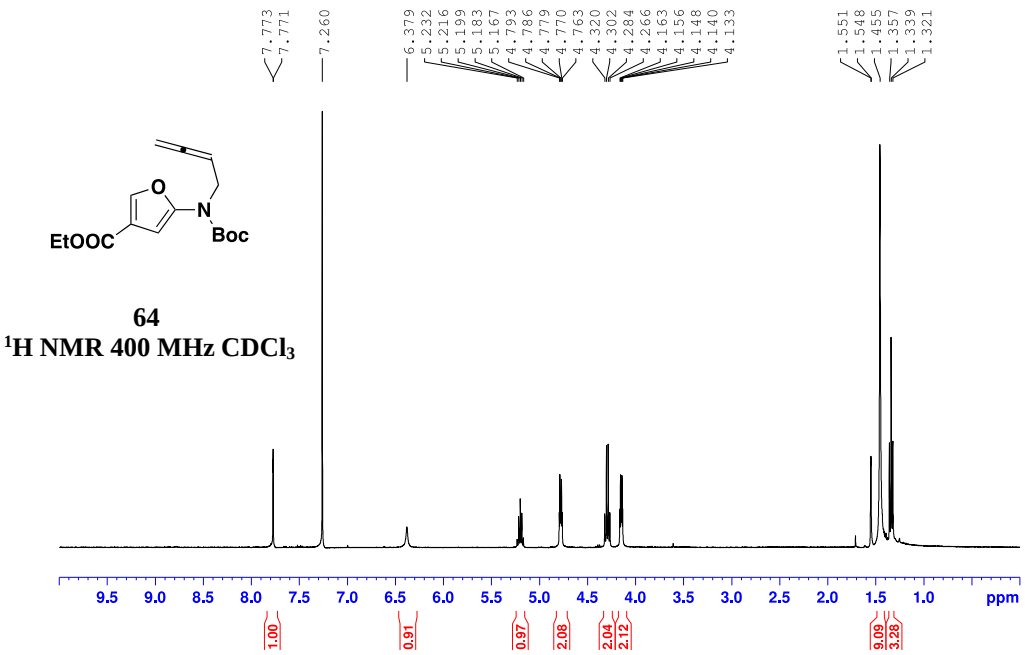
63

^{1}H NMR 300 MHz $CDCl_3$



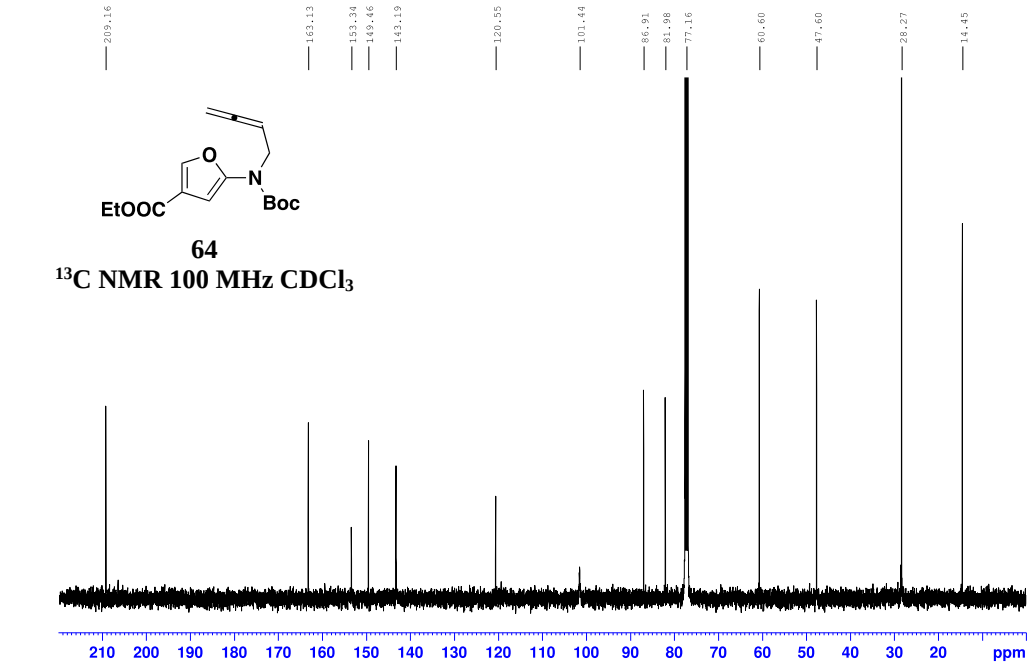
63

^{13}C NMR 125 MHz $CDCl_3$



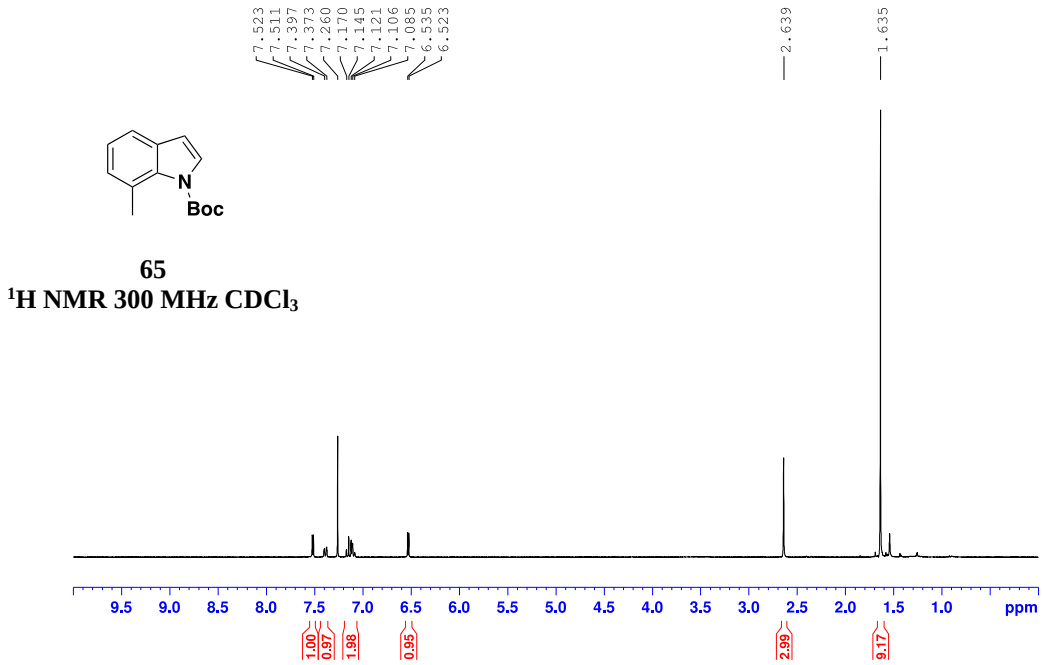
64

^{1}H NMR 400 MHz $CDCl_3$

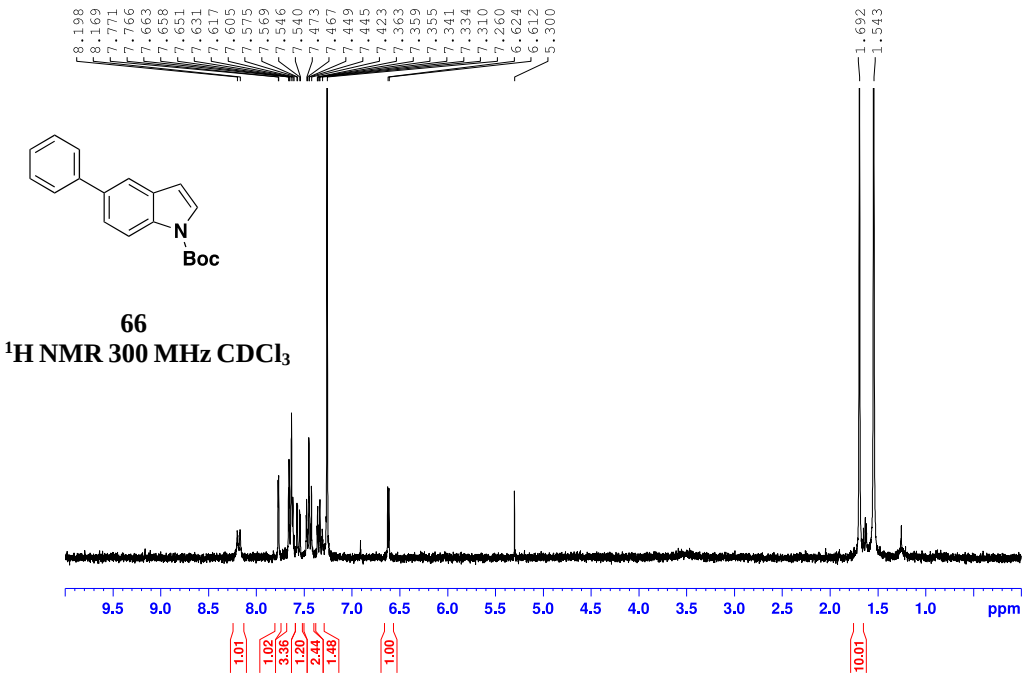


64

^{13}C NMR 100 MHz $CDCl_3$



65
^{1}H NMR 300 MHz $CDCl_3$



66
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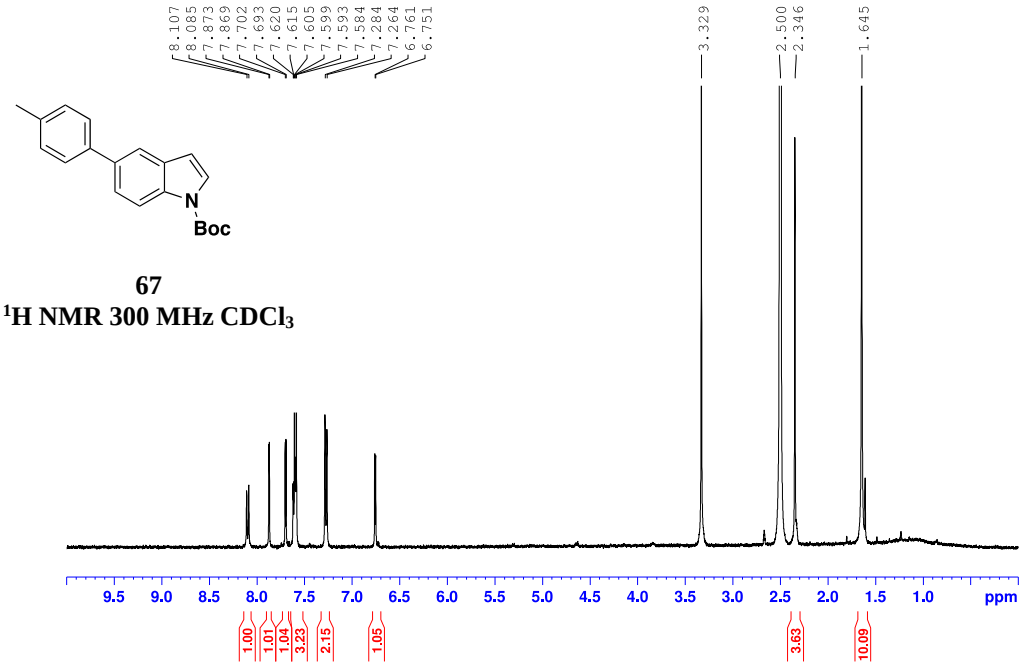
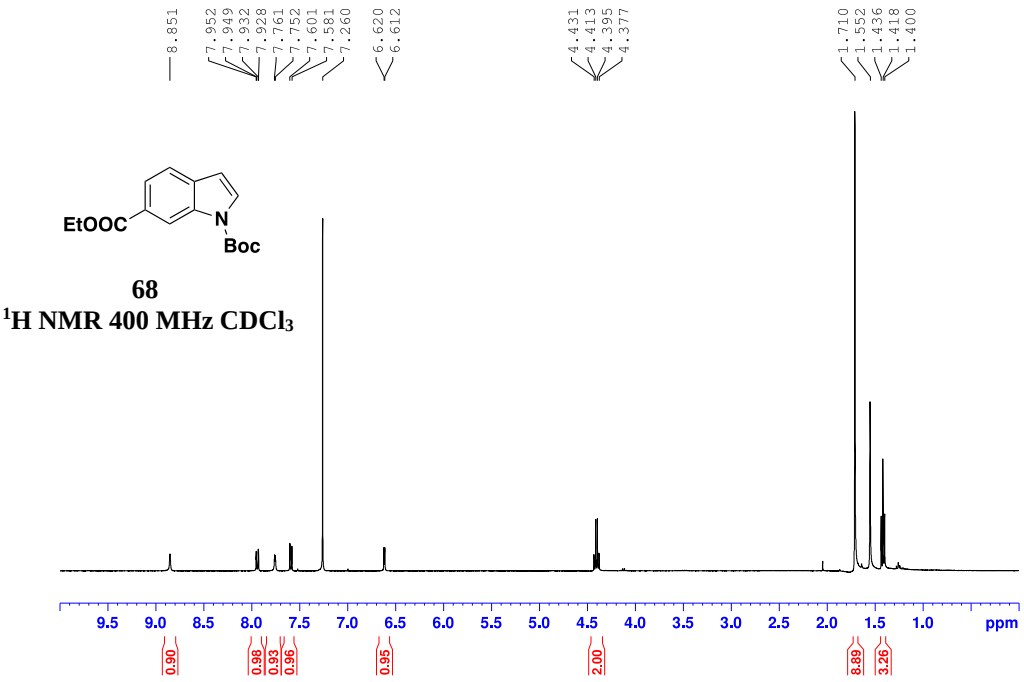
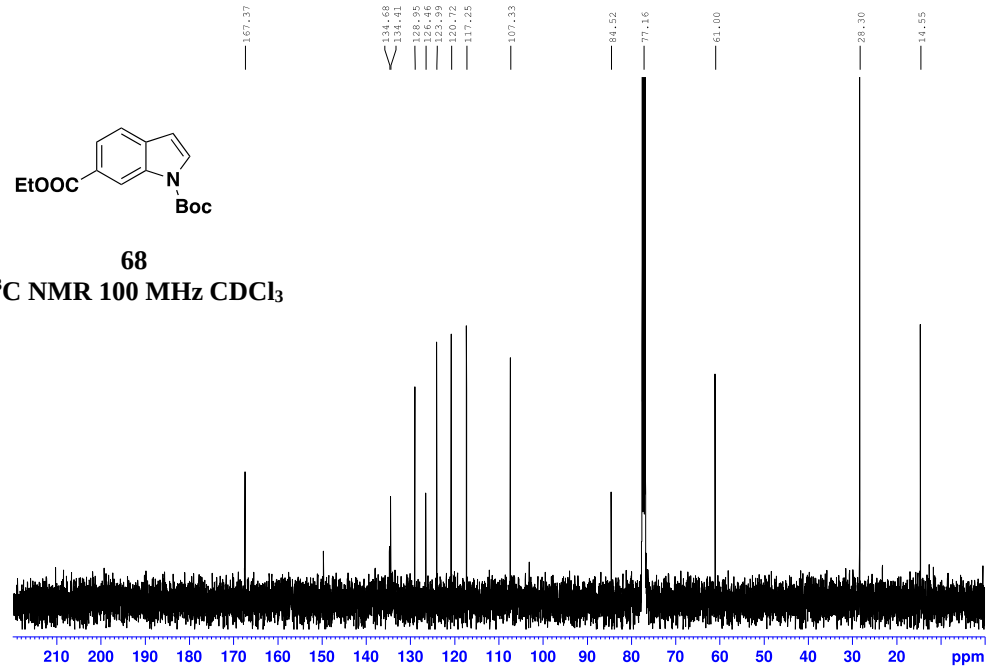


67
^{1}H NMR 300 MHz $CDCl_3$

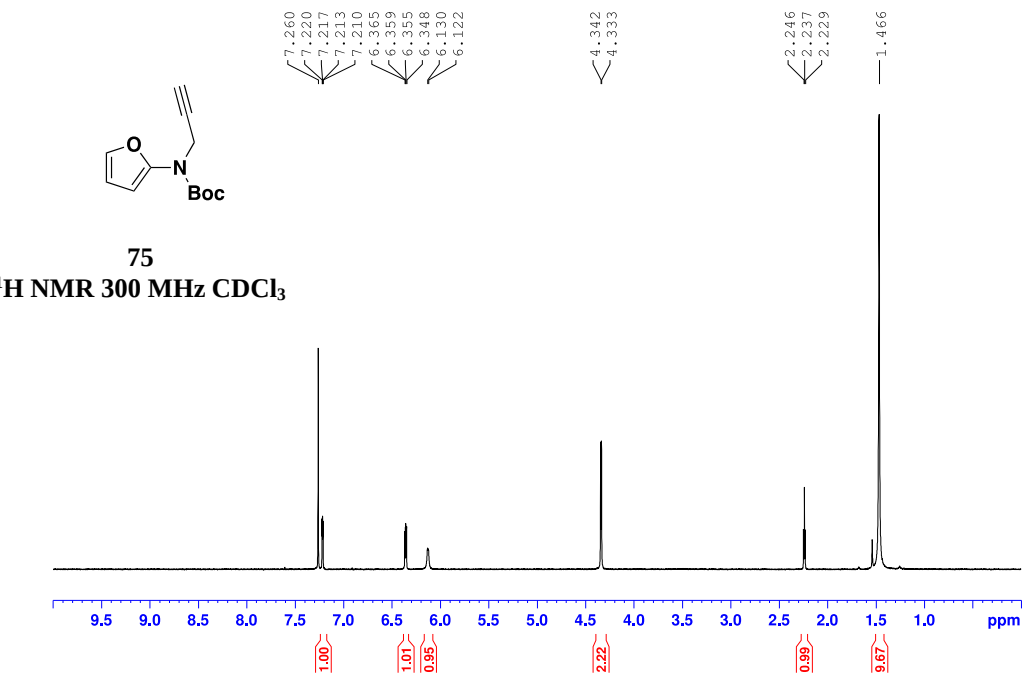


68
^{1}H NMR 400 MHz $CDCl_3$



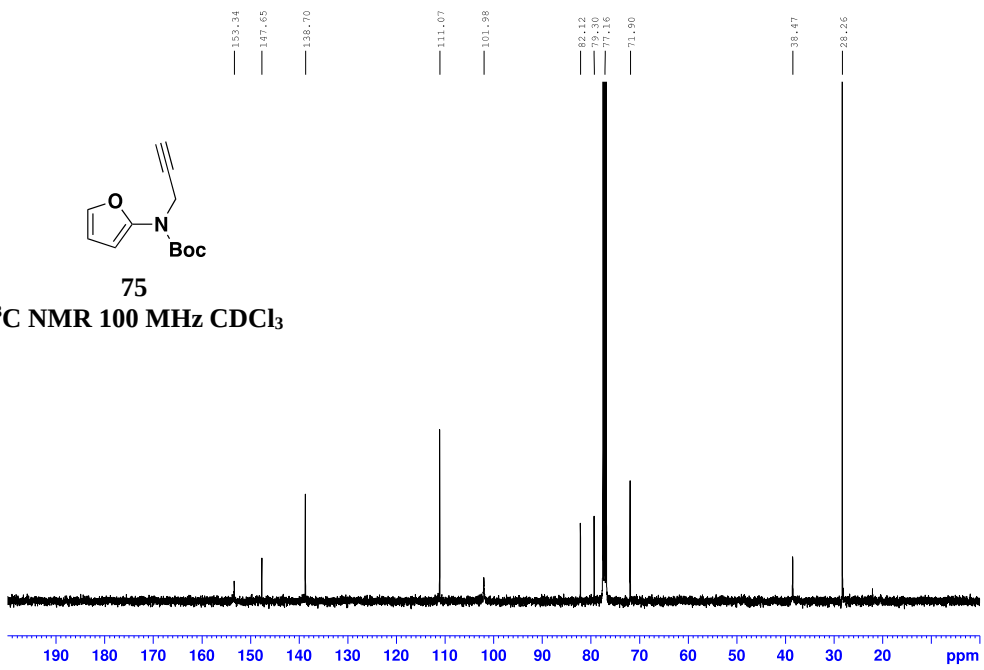
68

^{13}C NMR 100 MHz $CDCl_3$



75

^{1}H NMR 300 MHz $CDCl_3$



75

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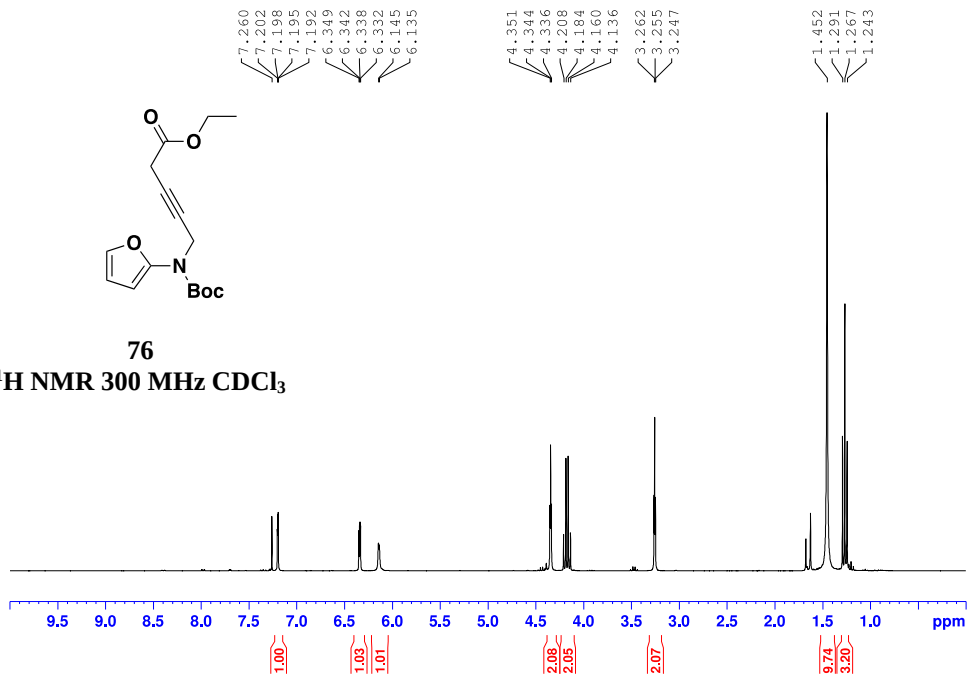
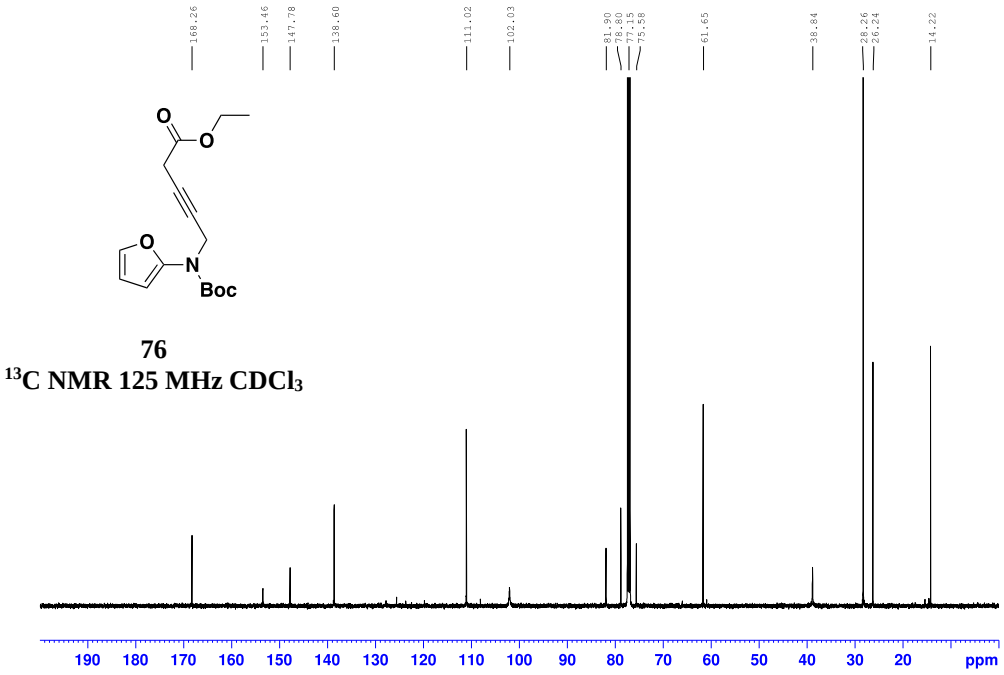


76

^{1}H NMR 300 MHz $CDCl_3$



76

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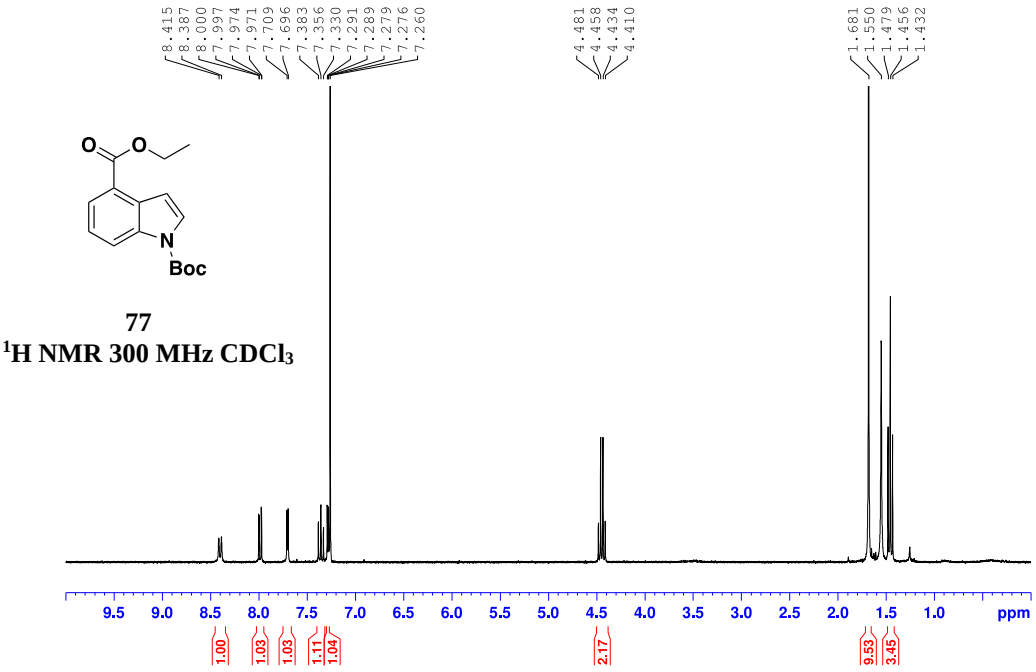
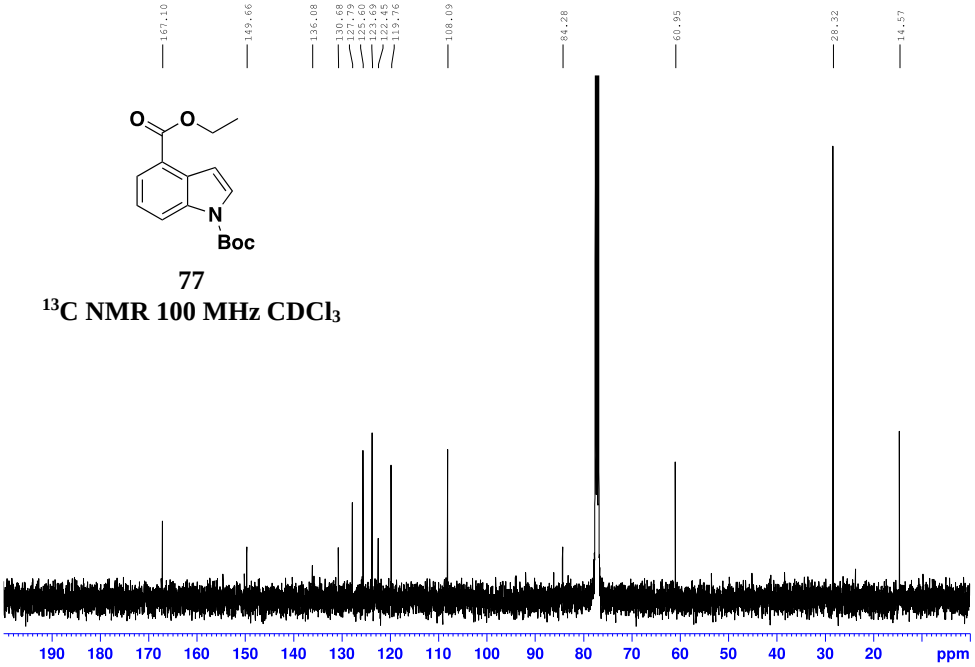


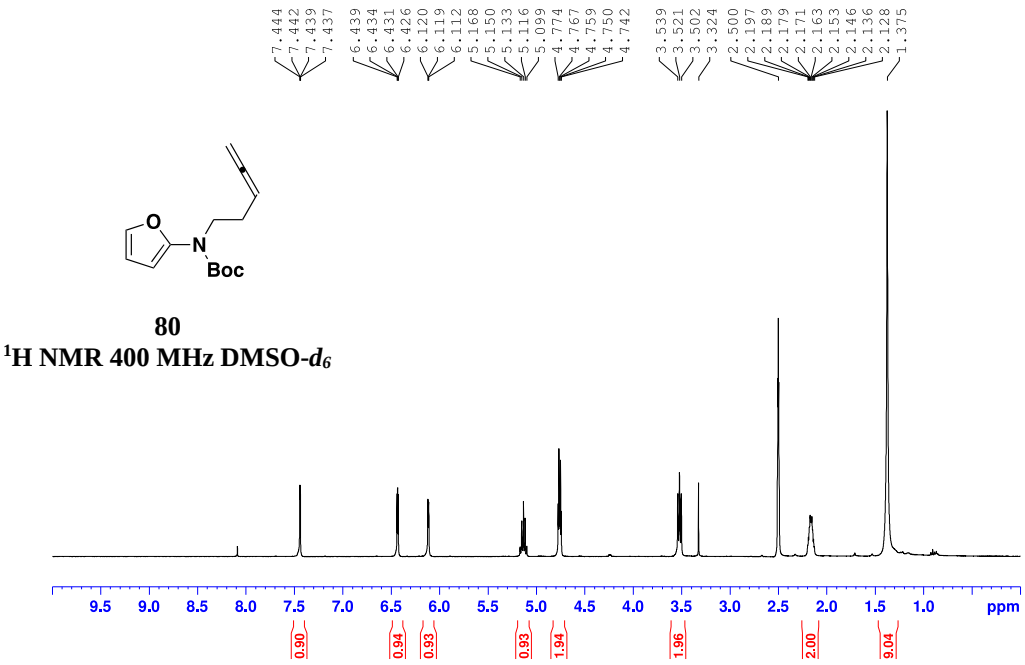
77

^{1}H NMR 300 MHz $CDCl_3$



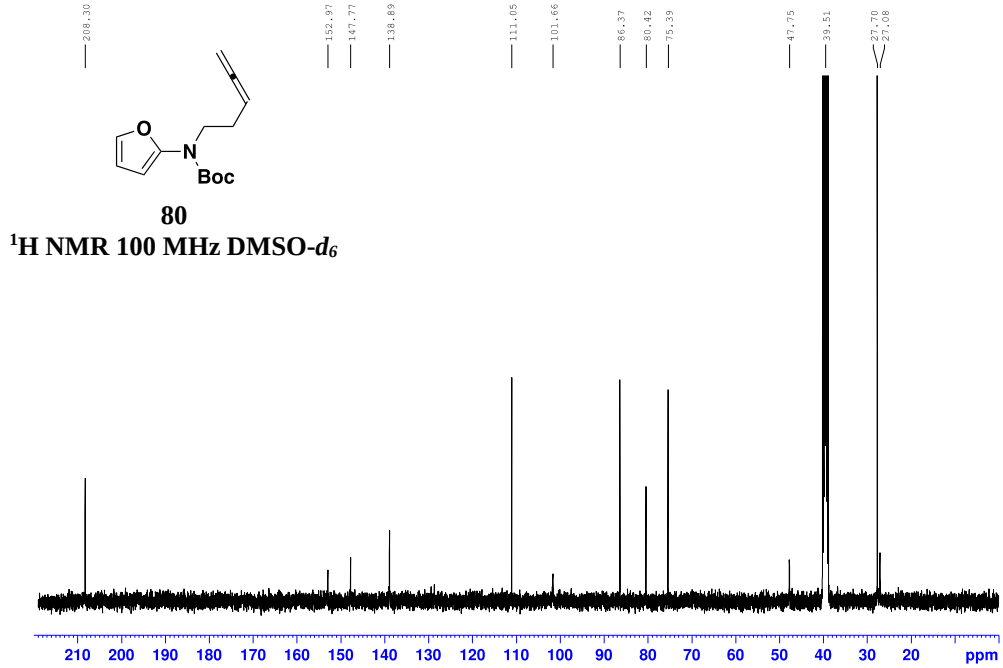
77

^{13}C NMR 100 MHz $CDCl_3$



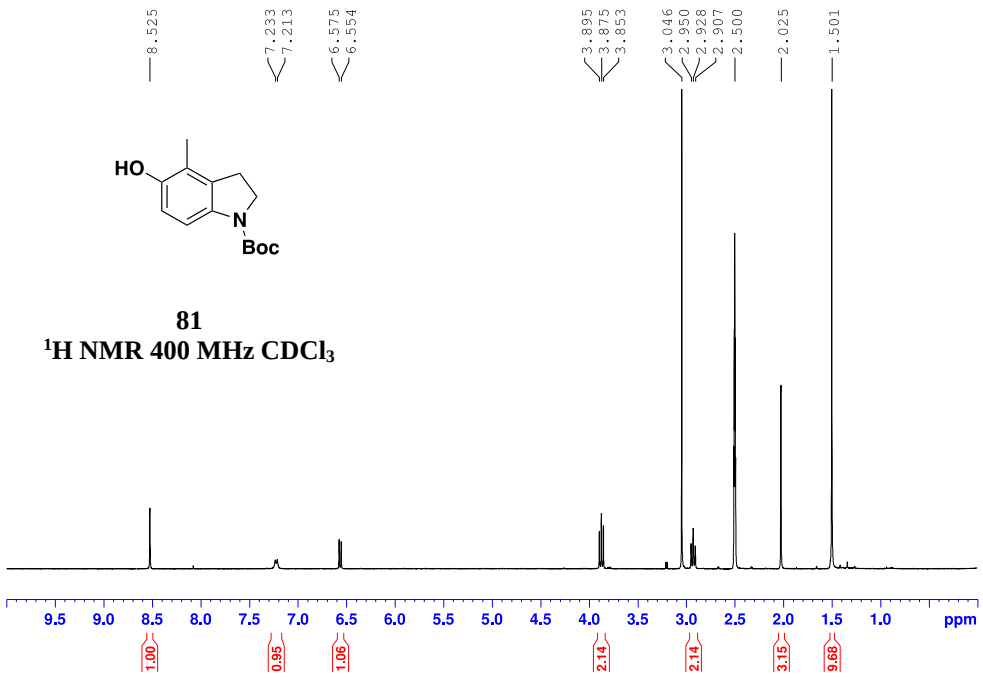
80

^{1}H NMR 400 MHz DMSO-*d_6*



80

^{1}H NMR 100 MHz DMSO-*d*$_6$



81

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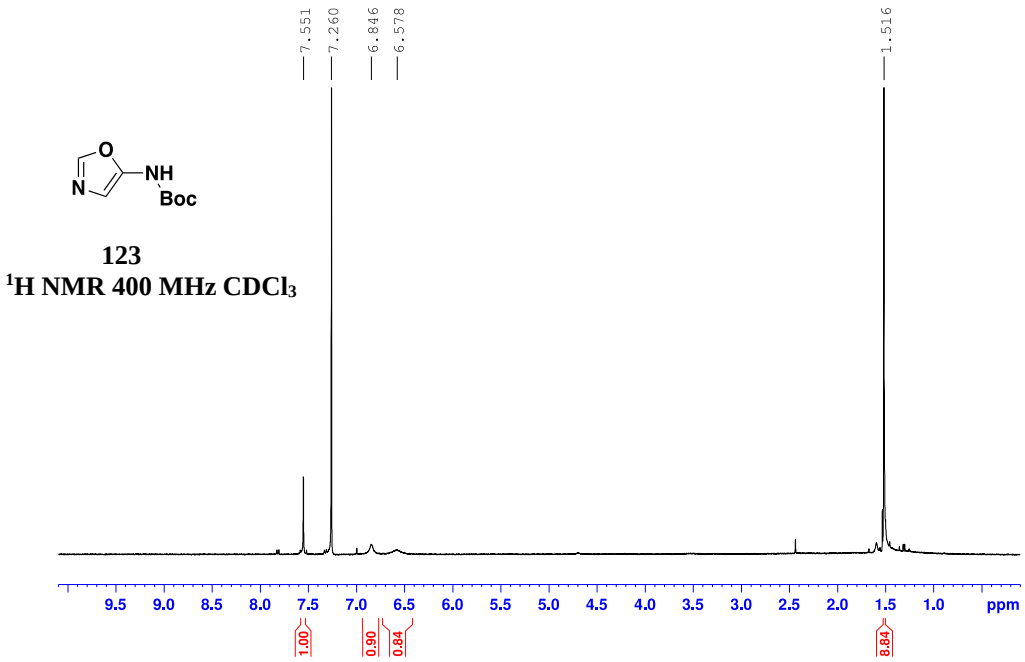

123
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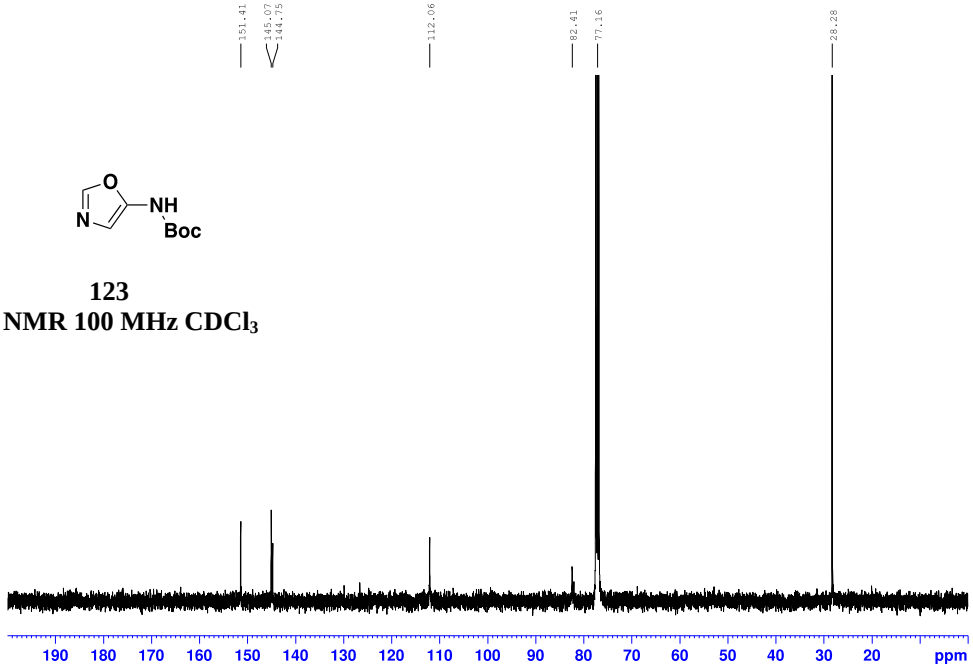

123
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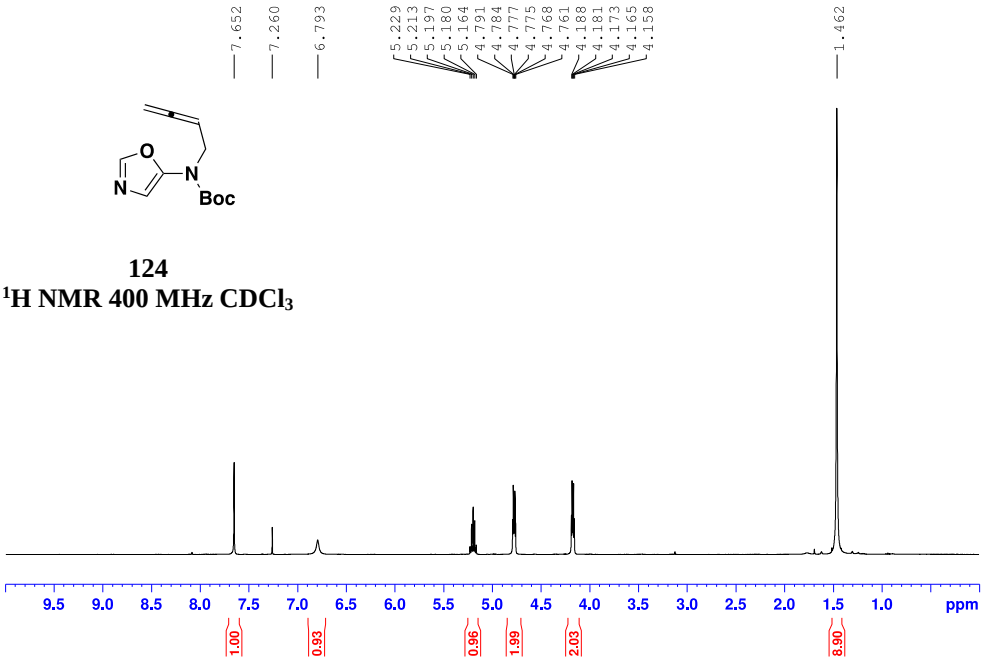

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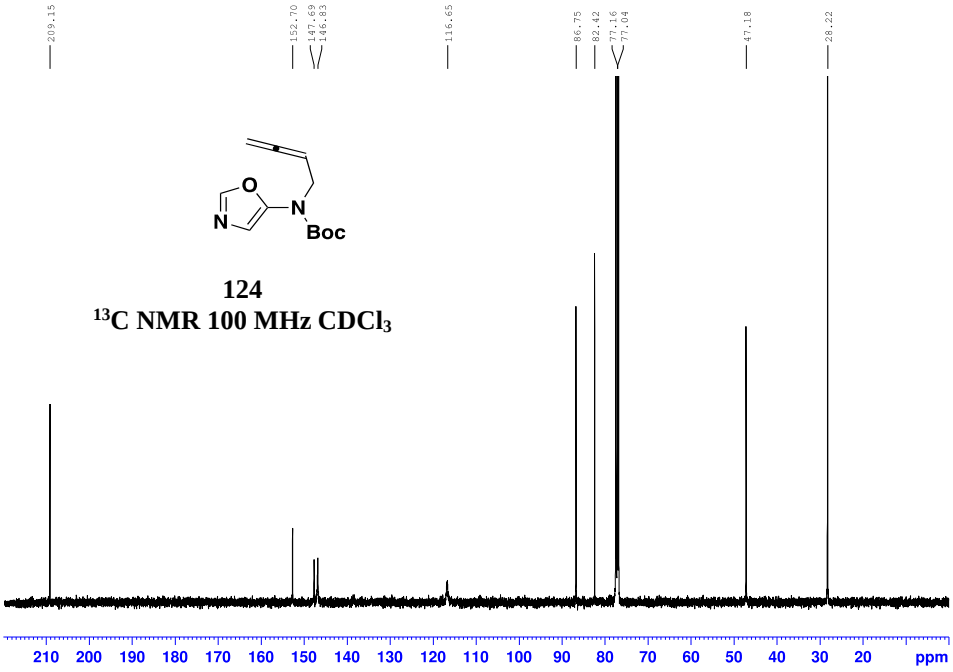

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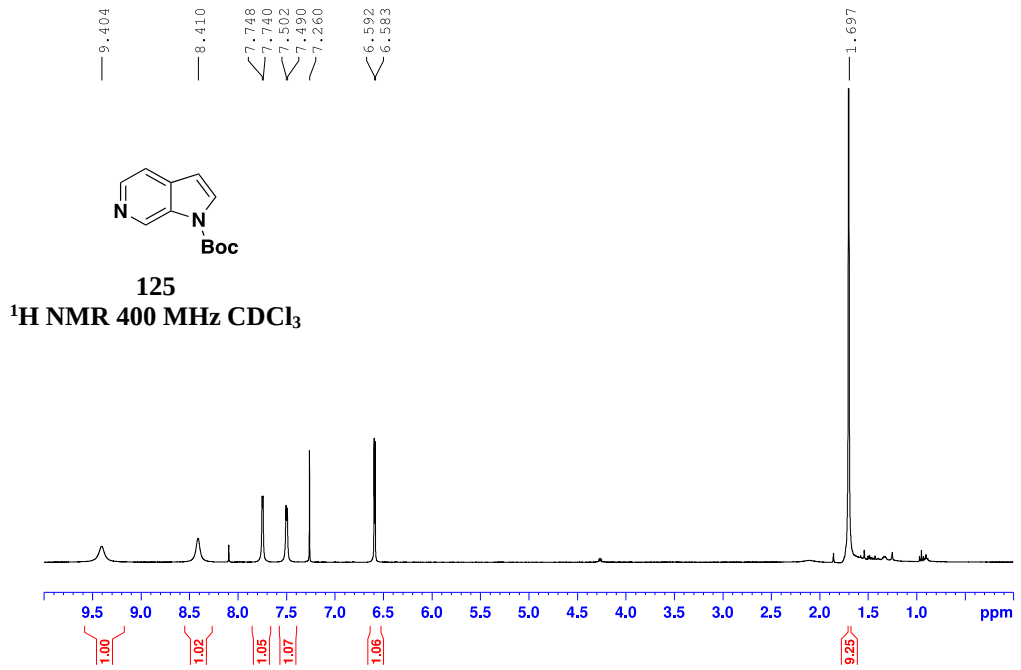
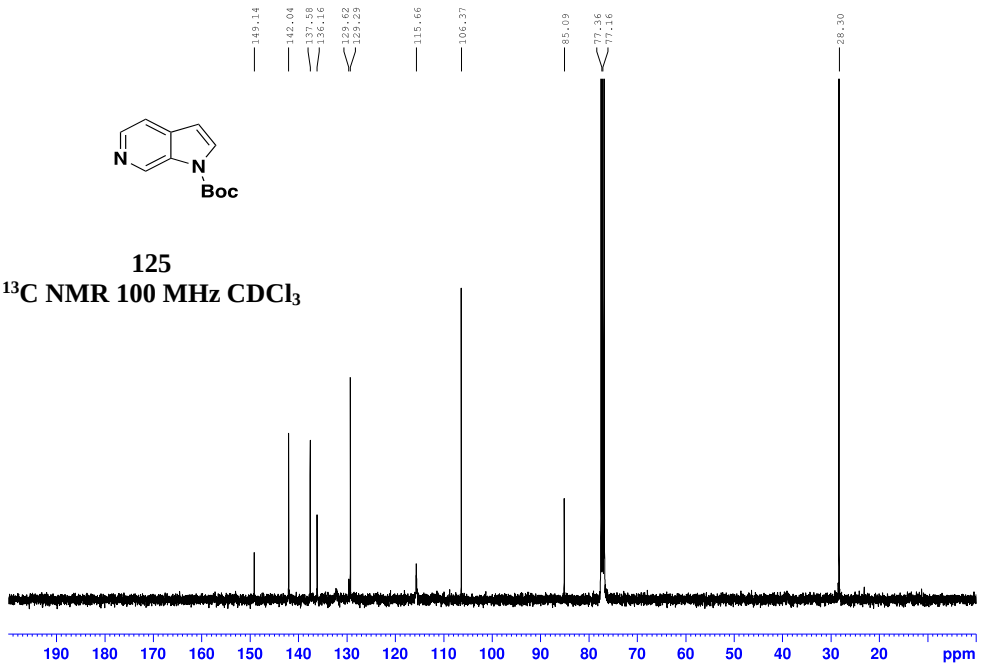


125

^{1}H NMR 400 MHz $CDCl_3$



125

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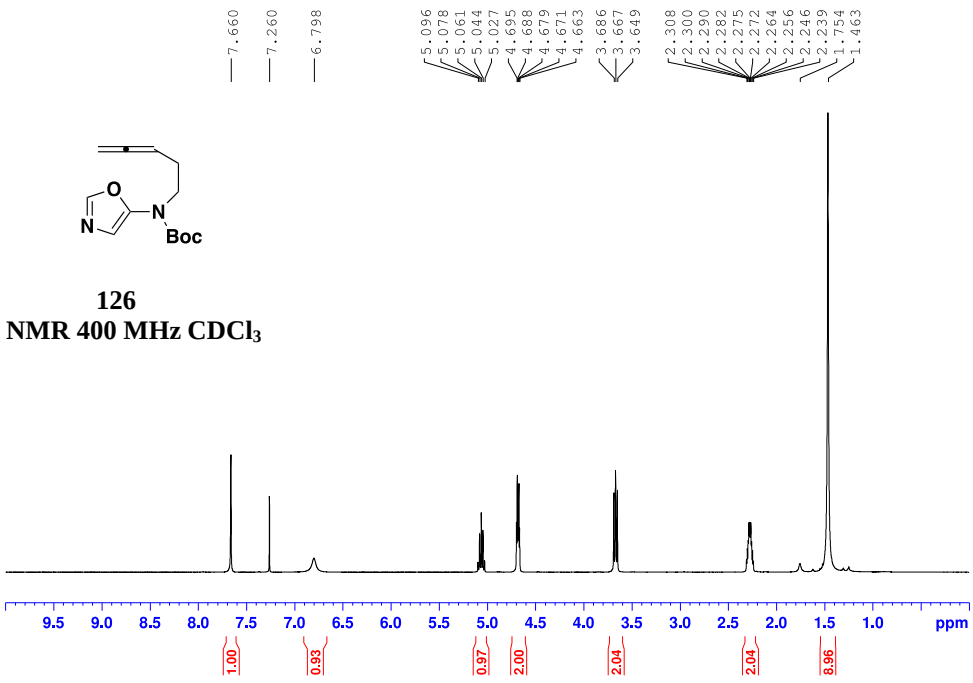
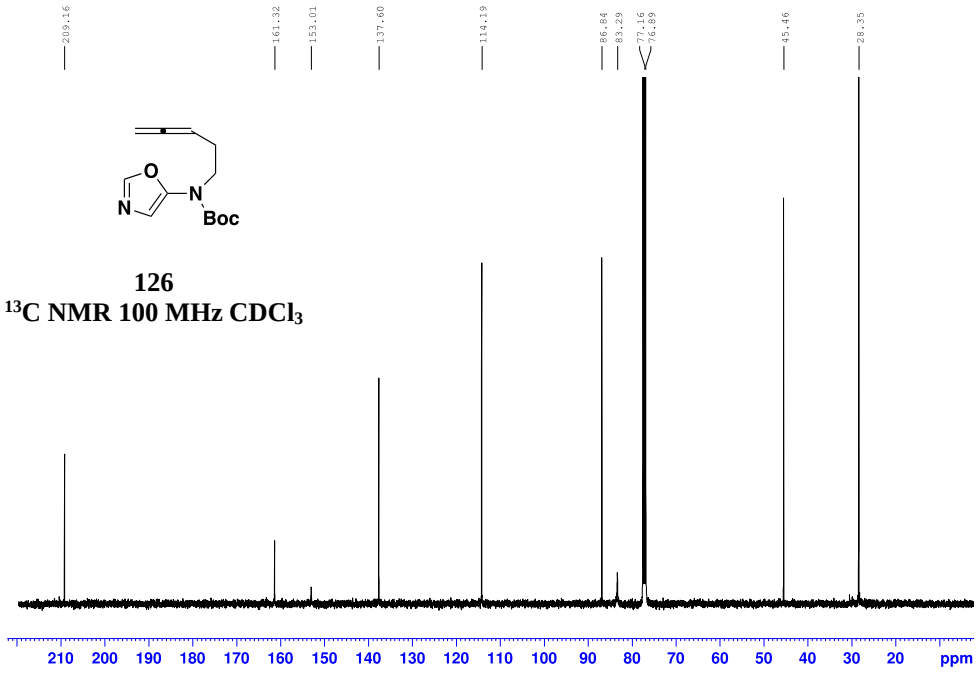
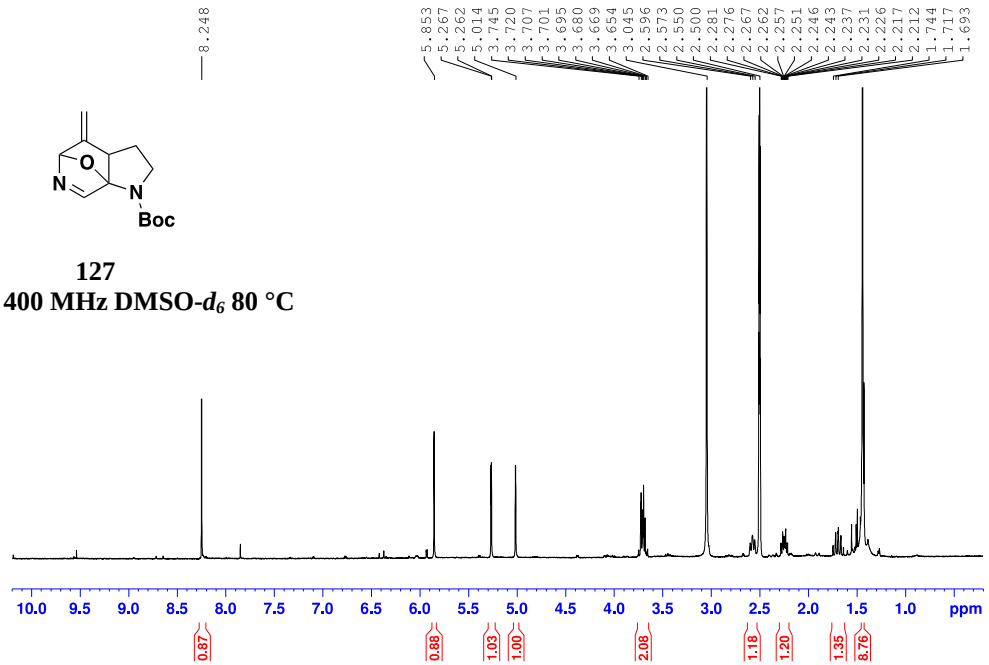


126
^{1}H NMR 400 MHz $CDCl_3$

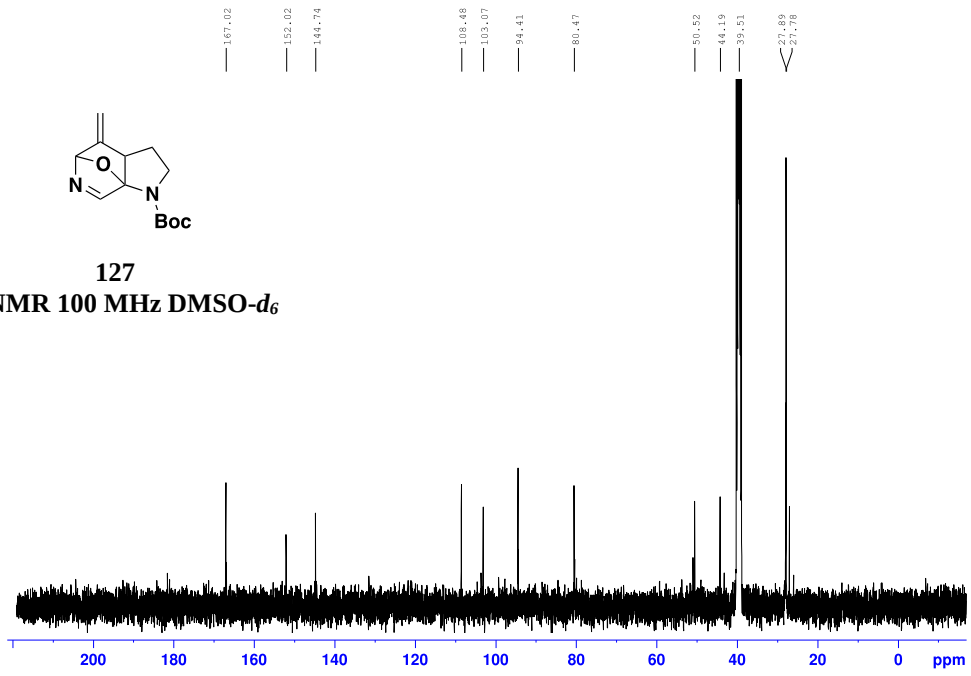


126
^{13}C NMR 100 MHz $CDCl_3$



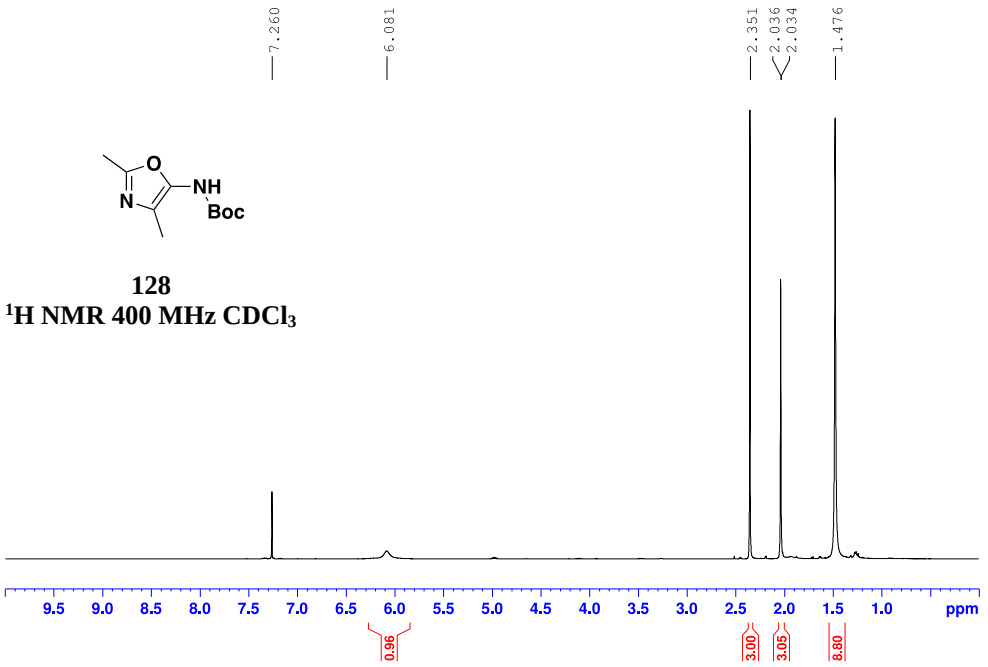
127

^{1}H NMR 400 MHz DMSO-d_6 80 °C

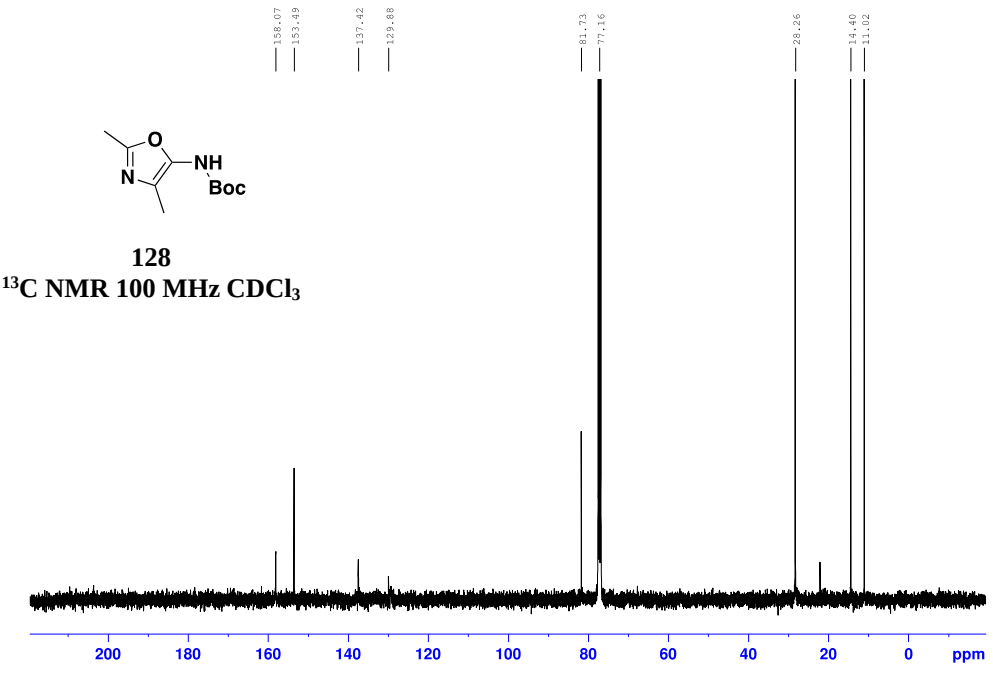


127

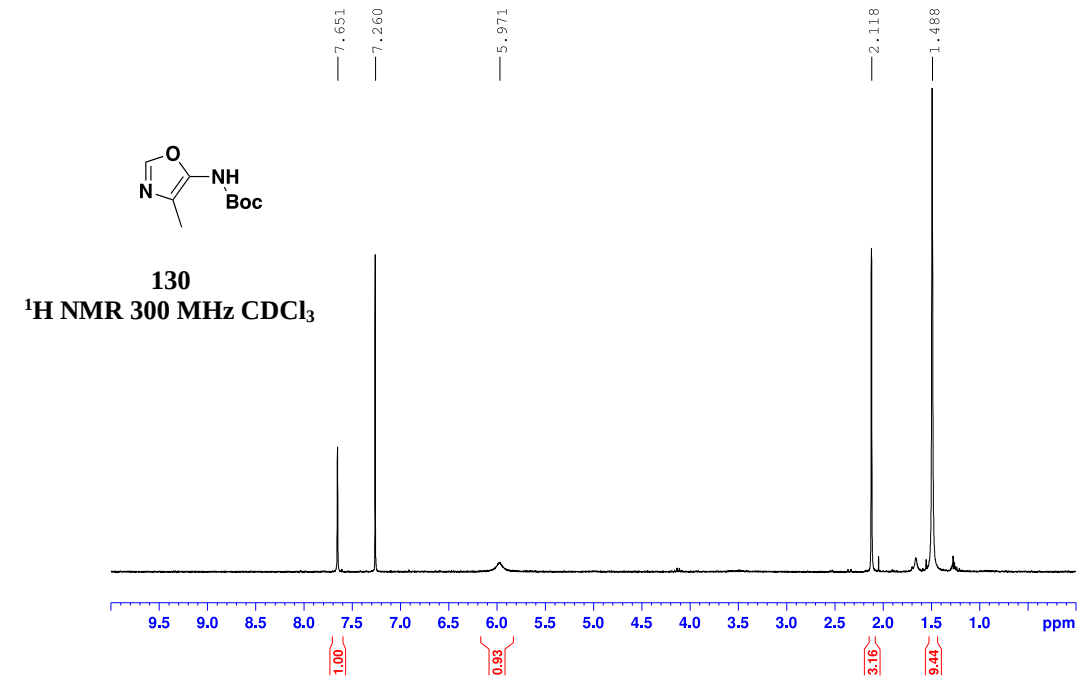
^{1}H NMR 100 MHz DMSO-d_6



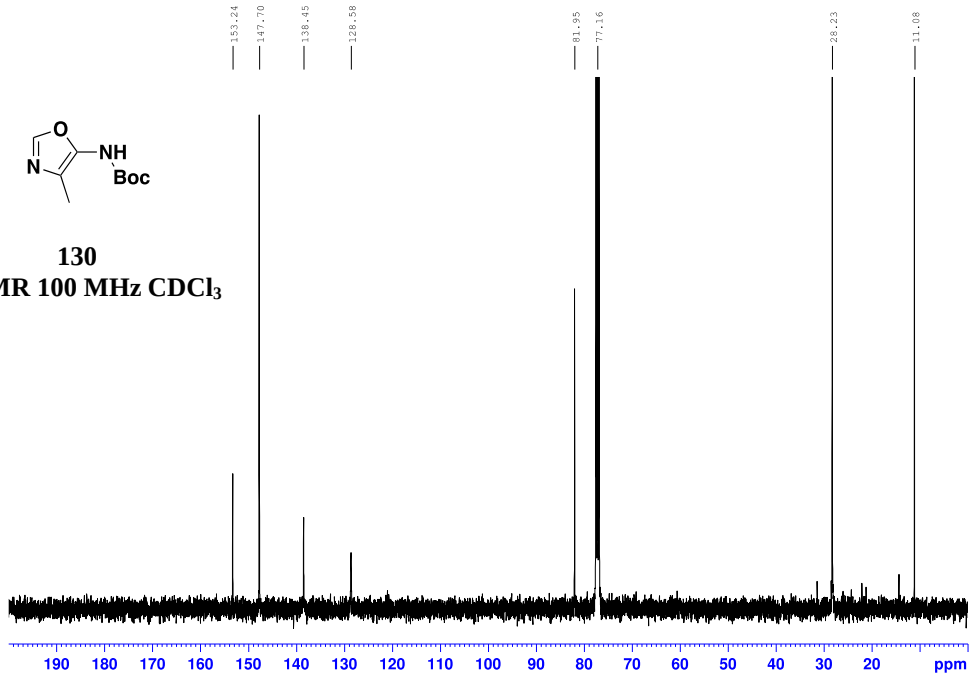
128
^{1}H NMR 400 MHz $CDCl_3$



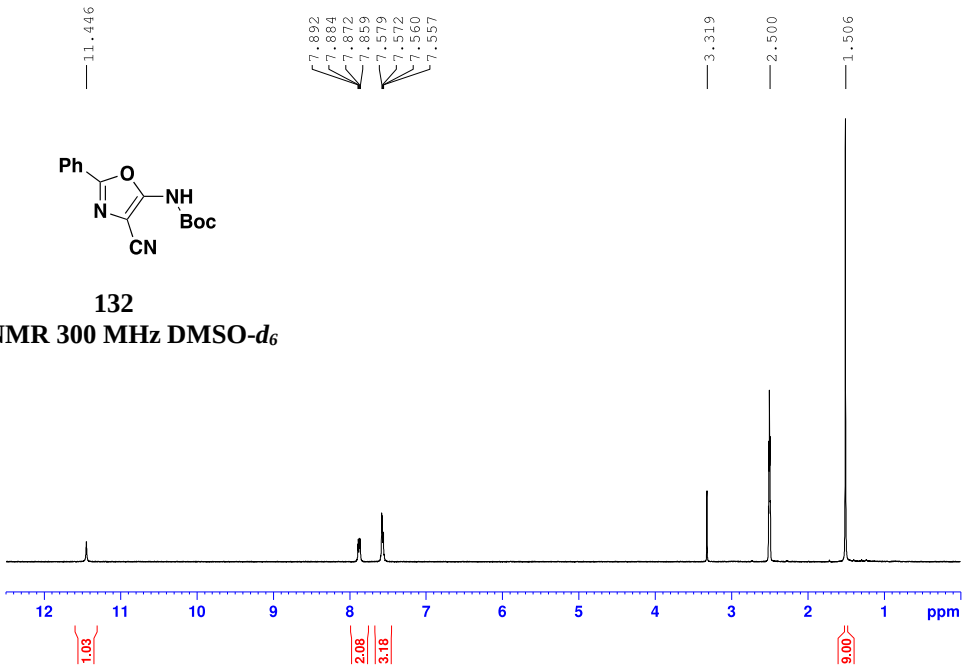
128
^{13}C NMR 100 MHz $CDCl_3$



130
^{1}H NMR 300 MHz $CDCl_3$

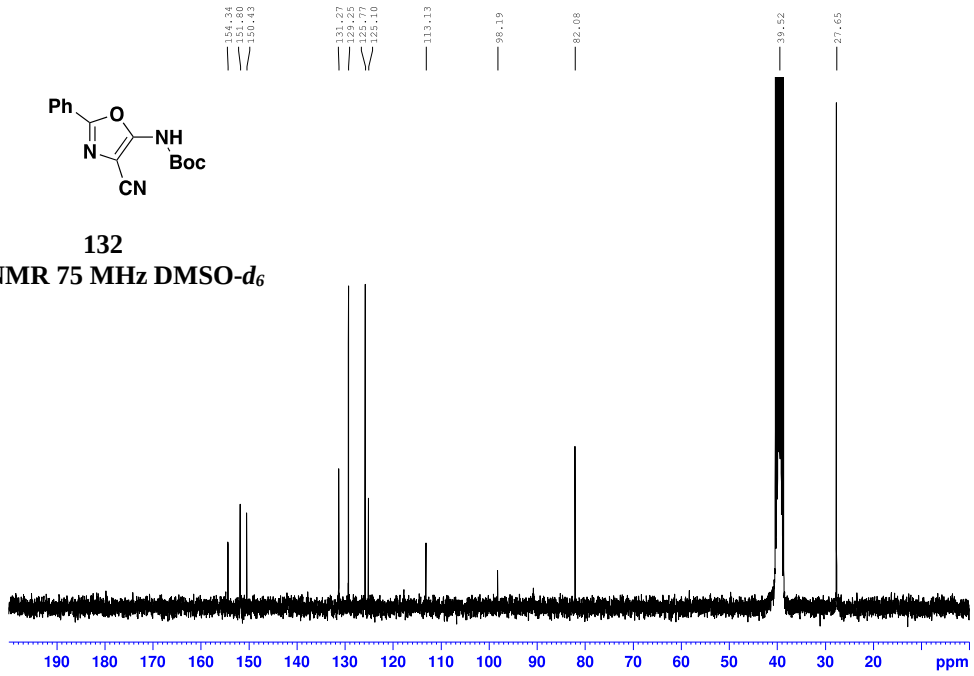


130
^{1}H NMR 100 MHz $CDCl_3$



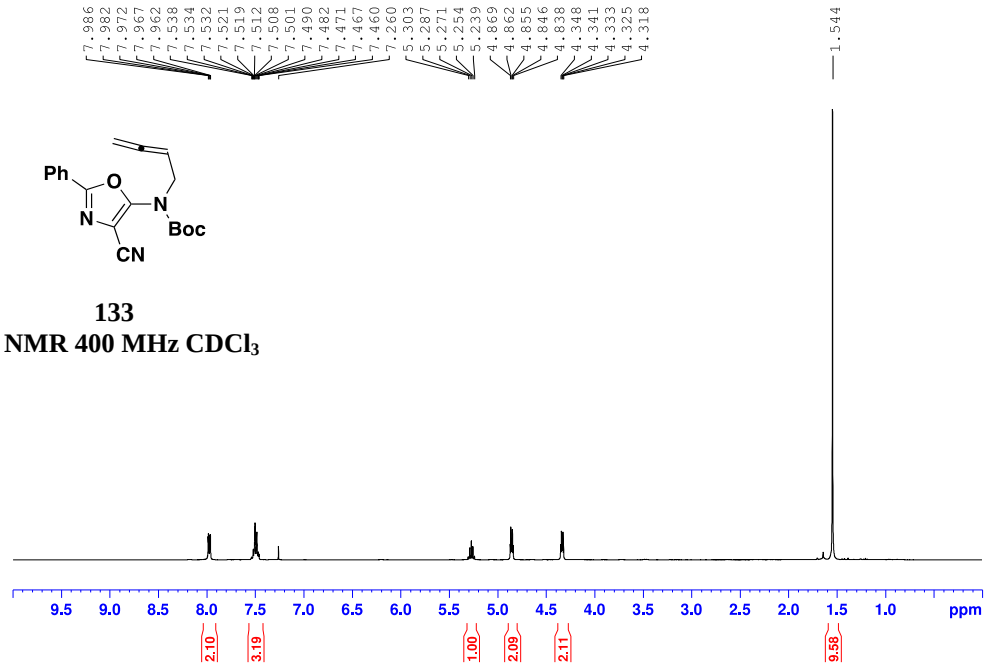
132

^{1}H NMR 300 MHz DMSO-*d*$_6$



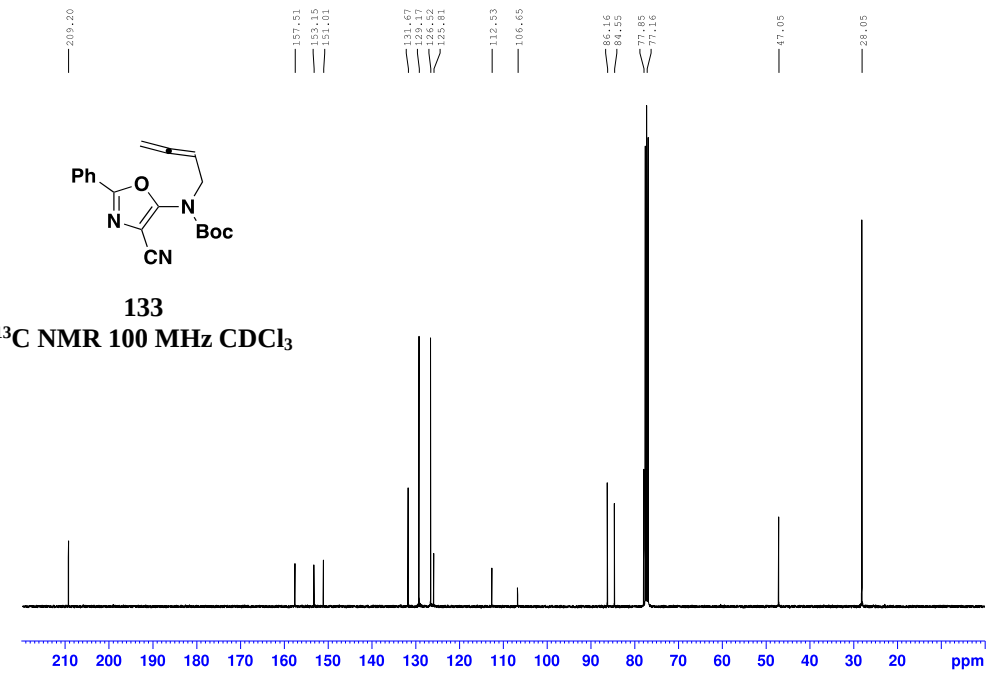
132

^{13}C NMR 75 MHz DMSO-*d*$_6$



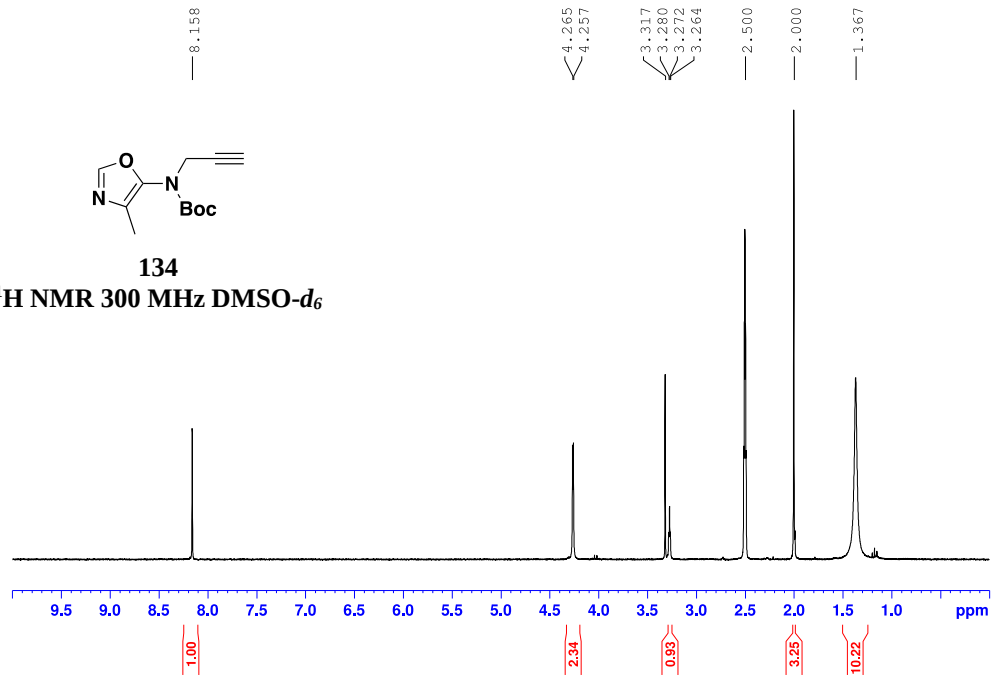
133

^{1}H NMR 400 MHz $CDCl_3$



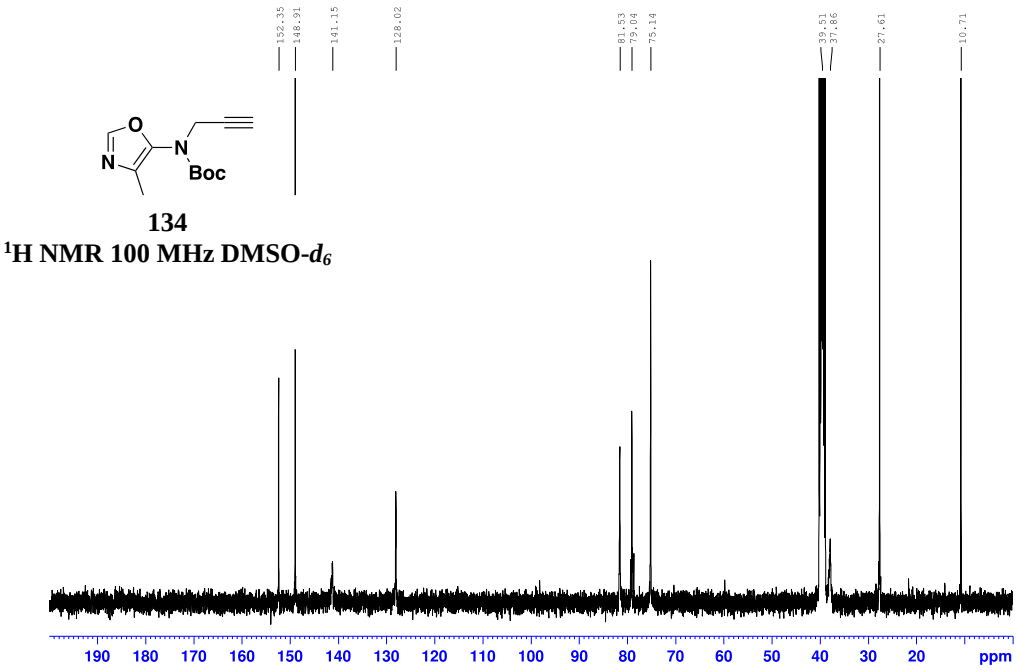
133

^{13}C NMR 100 MHz $CDCl_3$



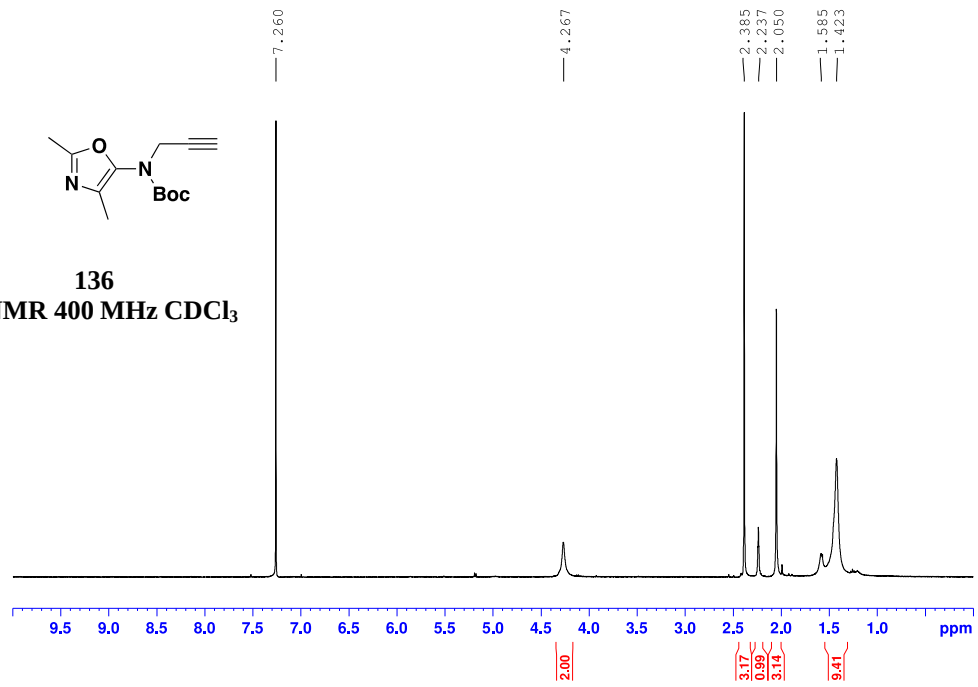
134

^{1}H NMR 300 MHz DMSO-*d*$_6$

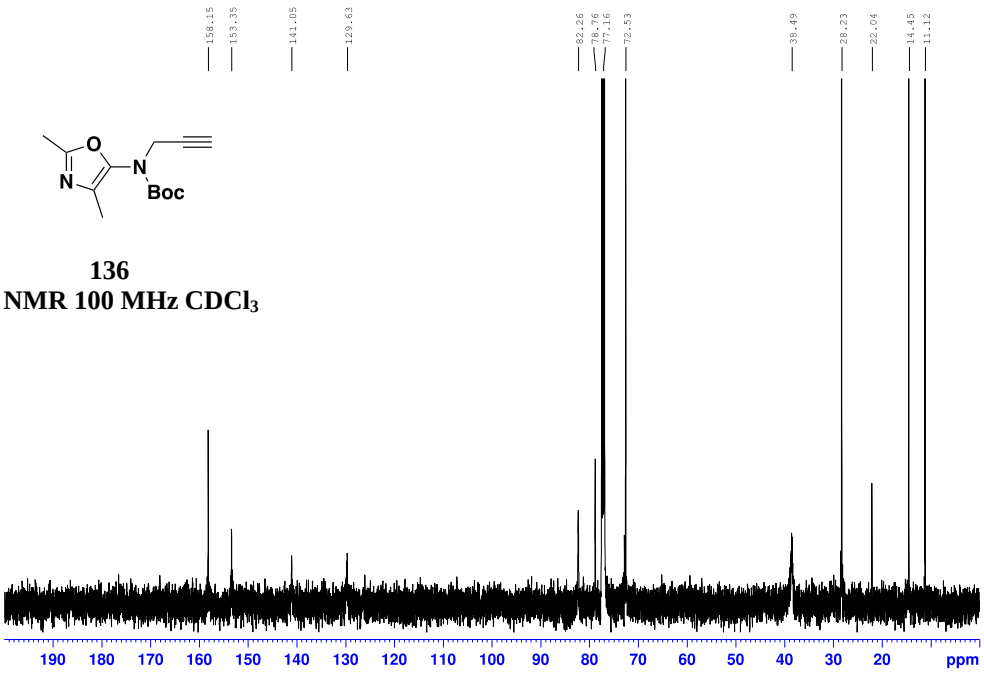


134

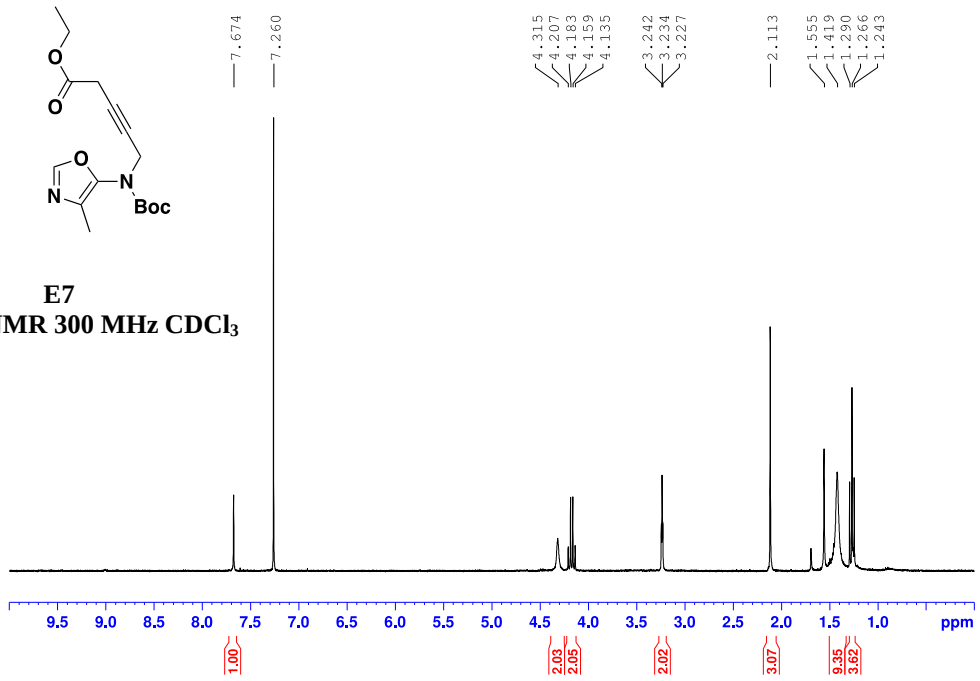
^{1}H NMR 100 MHz DMSO-*d*$_6$



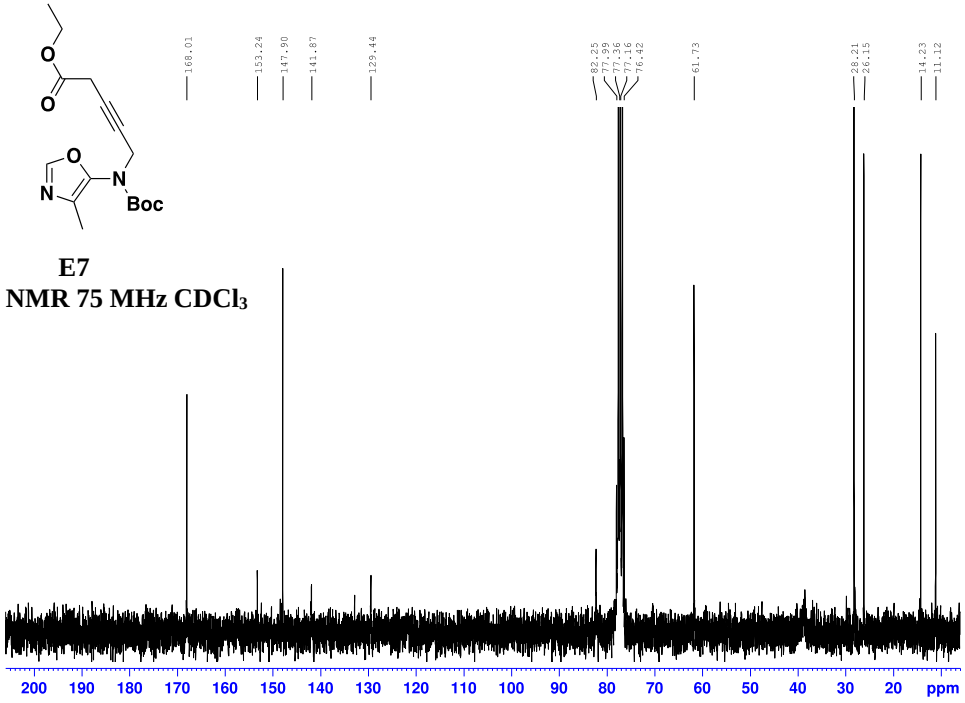
136
^{1}H NMR 400 MHz $CDCl_3$



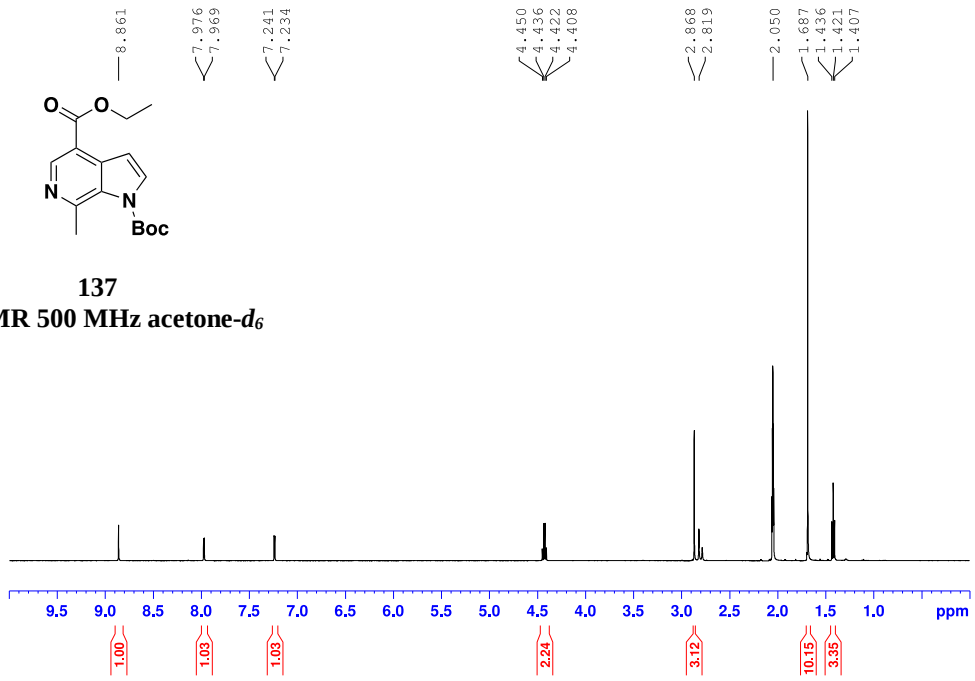
136
^{13}C NMR 100 MHz $CDCl_3$



E7
^{1}H NMR 300 MHz $CDCl_3$

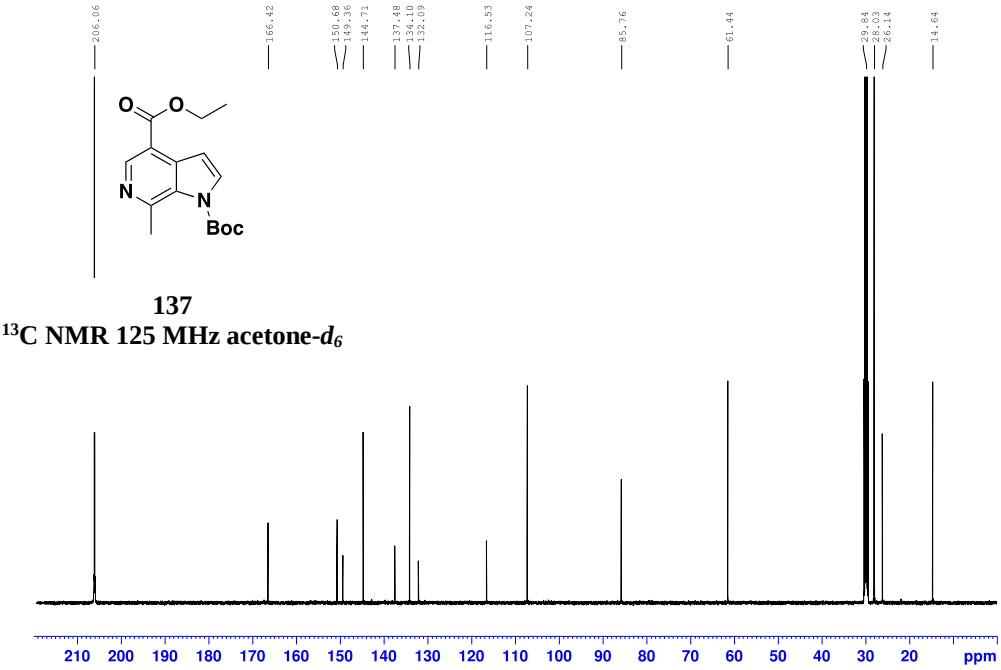


E7
^{13}C NMR 75 MHz $CDCl_3$



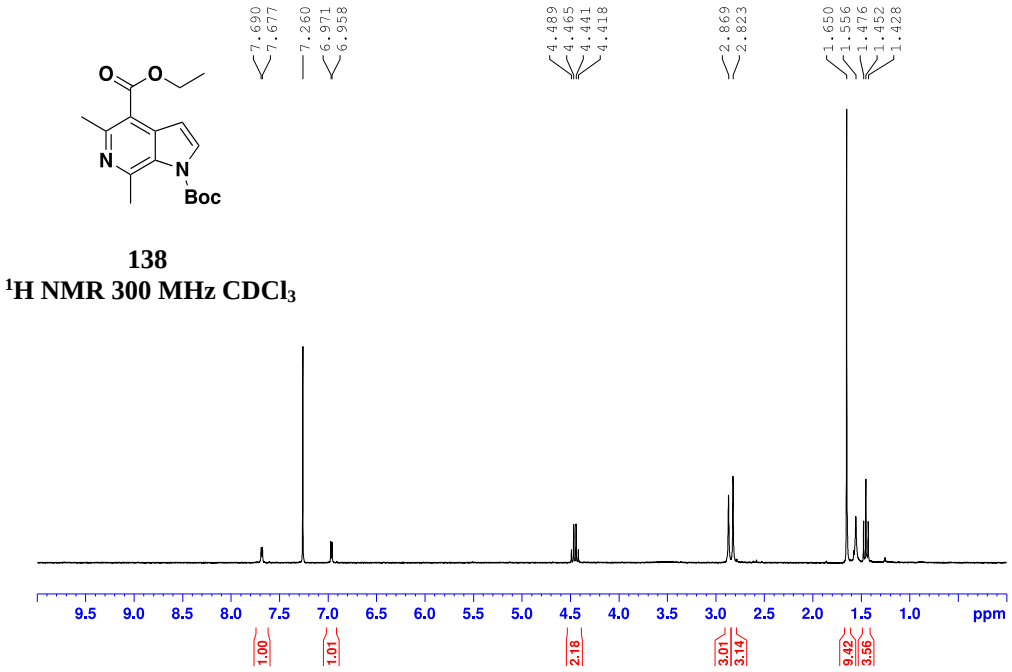
137

^{1}H NMR 500 MHz acetone-*d*$_6$



137

^{13}C NMR 125 MHz acetone-*d*$_6$



138
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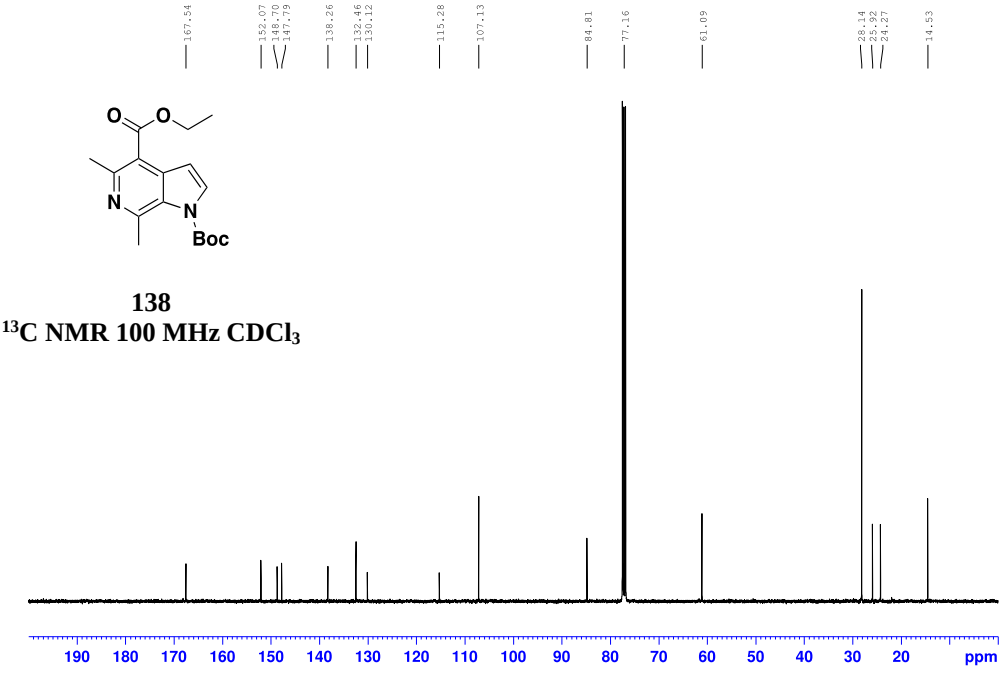
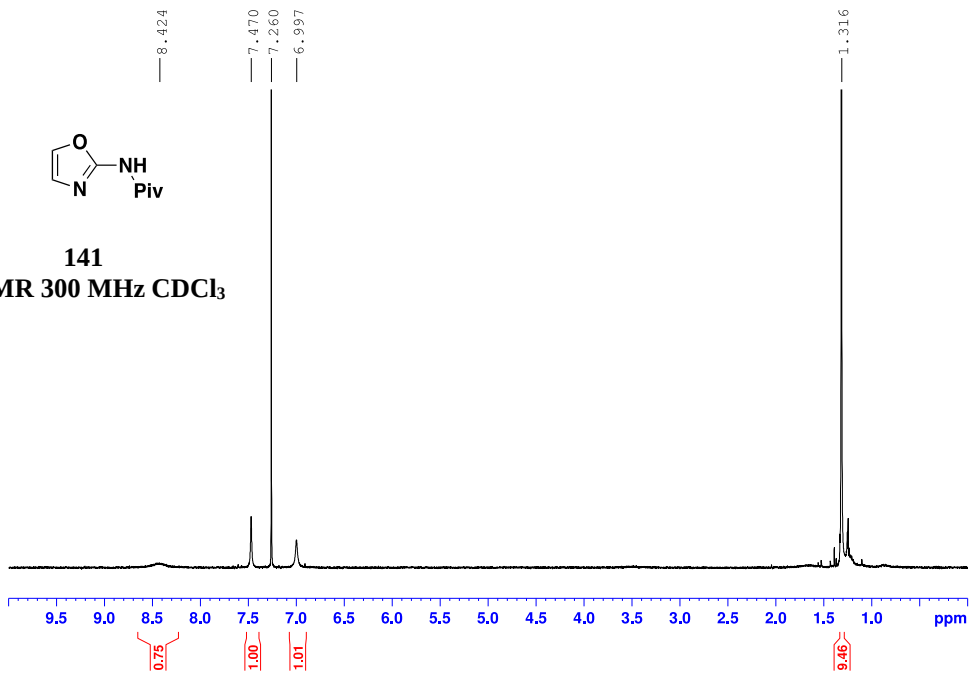
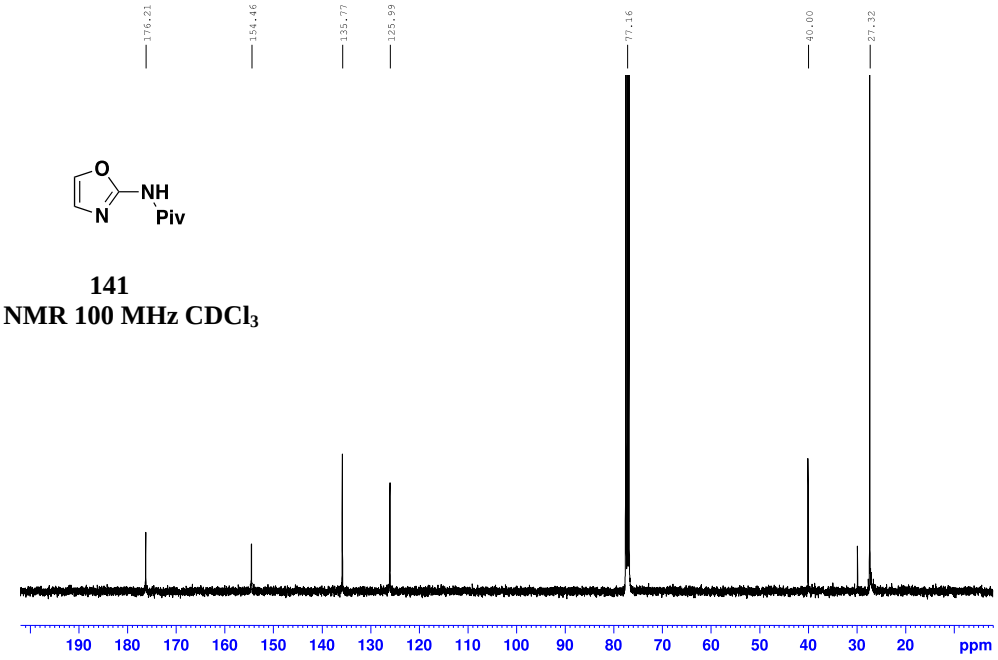


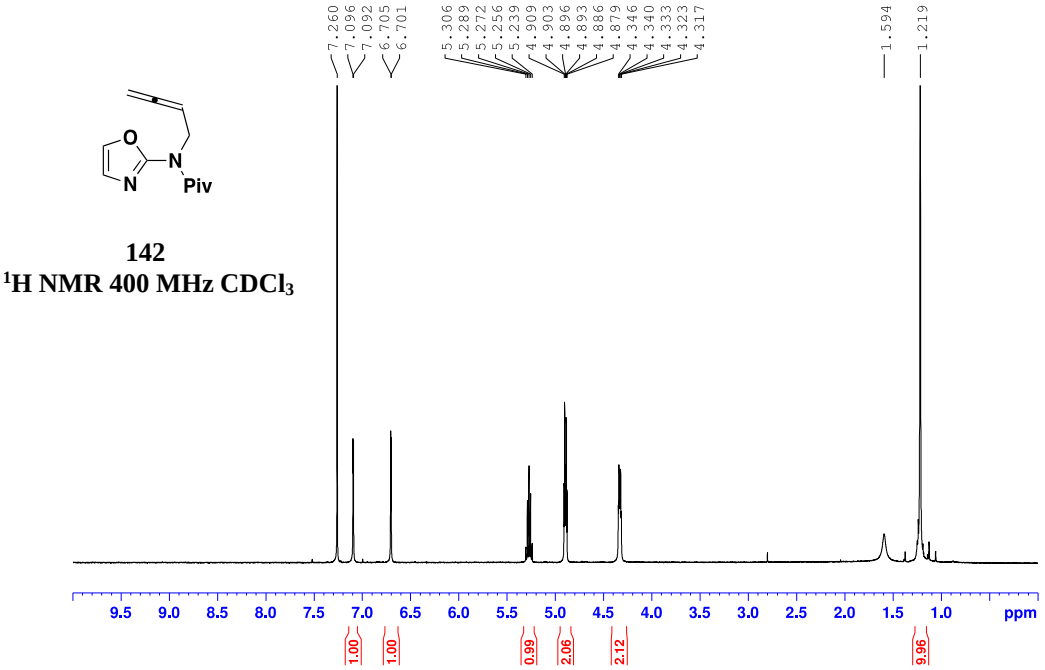
138
^{13}C NMR 100 MHz $CDCl_3$



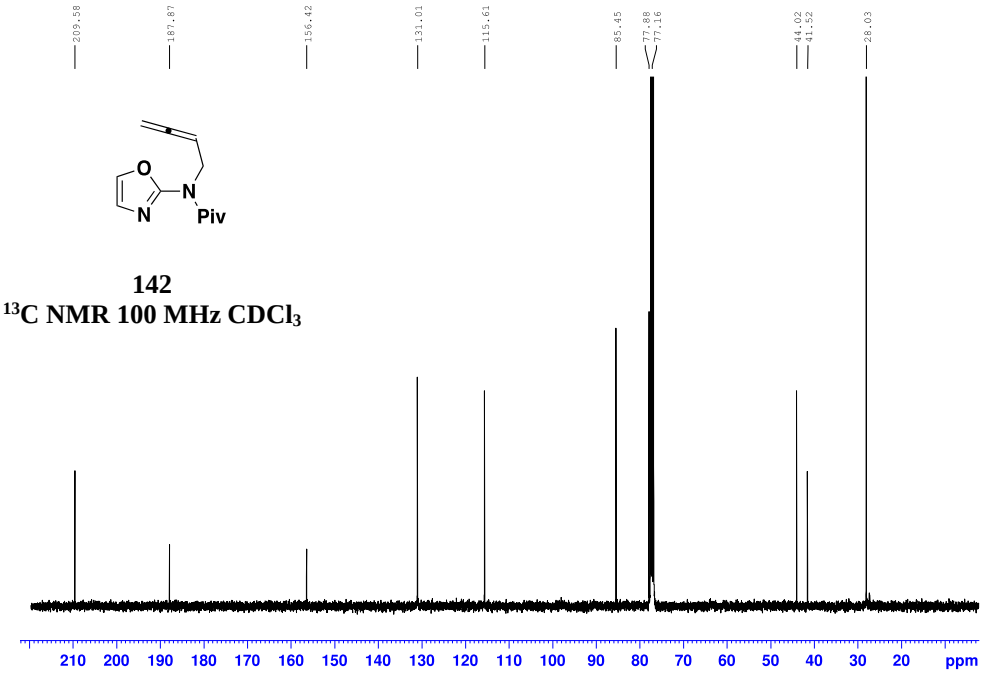
141
^{1}H NMR 300 MHz $CDCl_3$



141
^{13}C NMR 100 MHz $CDCl_3$



142
^{1}H NMR 400 MHz $CDCl_3$



142
^{13}C NMR 100 MHz $CDCl_3$

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