Fall 2013

Metal mediated intramolecular transformations of pyridine substrates

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METAL MEDIATED INTRAMOLECULAR TRANSFORMATIONS OF PYRIDINE SUBSTRATES

by

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A thesis submitted in partial fulfillment
of the requirements for the Doctor of
Philosophy degree in Chemistry
in the Graduate College of
The University of Iowa

December 2013

Thesis Supervisor: Associate Professor. F. Christopher Pigge

Graduate College
The University of Iowa
Iowa City, Iowa

CERTIFICATE OF APPROVAL

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PH.D. THESIS

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This is to certify that the Ph.D. thesis of

Lokesh Pawar

has been approved by the Examining Committee
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To my parents

To my wife Niveditha

To my sons Akshat and Aryansh

We should not give up and we should not allow the problem to defeat us.

Dr. A. P. J. Kalam

ACKNOWLEDGMENTS

First and foremost, I would like to thank my Ph.D research advisor Dr. F. Christopher Pigge for supporting me during these past six years. I am grateful to him for his guidance, patience and his support to pursue various projects during this journey and writing of this thesis. Dr. Pigge is lively, enthusiastic and very energetic and I hope that I could be like him some day. I would like to thank the members of my Ph. D committee Dr. James Gloer, Dr. Daniel Quinn, Dr. Amanda Haes, and Dr. Horacio Olivo for being on my committee and providing the needed guidance and sparing their valuable time.

For this research, characterization of the synthesized compound was very important and this would have not been possible without the help of Dr. Santhana Velupillai (NMR facility), Lynn Teesch and Vic Parcell (Mass spectrometry facility). I would like to thank them for their timely help and guidance in solving the problems. I would like to thank Tim Koon and Andy for being a good support throughout my program.

When I first came to Iowa, first persons to meet in the department were Janet Kugley and Sharon Robertson. They were always available for any problem I had and I would like to thank them for all the support and help they provided to make me feel at home away from home. I would like to thank all my professors for being such good teachers. I would like to thank the department of chemistry and University of Iowa for providing me the opportunity to be a part of the institution and providing the needed learning experience.

A good support system is important to surviving and staying sane in grad school. I was lucky to be part of one such group. I would also like to thank past members of Pigge

group, Sharu and Pradeep and the present members Ashaba, Chris, Dan for all the help and support. Sharu, Pradeep and myself have always been there for one another and taught ourselves and each other many tools in chemistry and had a lot of fun time. I would like to thank Ashish for being there with me whenever I needed him and making life easy. I would like to thank all my friends Nisarga, Abhinaba and Suman for their support and encouragement. I would like to specially thank Sampada for helping me for formatting this thesis.

This would have not been possible without the support and blessings of my parents Shri. Shiwaji and Smt. Sumadevi, I cannot thank my wife and kids enough for being supportive and making my life wonderful and keep me working towards my goal. In the end I would like to thank all the people I have missed and who have directly or indirectly helped me in achieving my dream.

ABSTRACT

Nature continuously provides fascinating and complicated structures which offer synthetic chemists amazing opportunities for the design of new methods for the natural product synthesis. Nitrogen containing aza-heterocycles are of unparalleled importance in natural product, bioorganic and medicinal chemistry. Pyridine in particular is one of the most common aza-heterocycles encountered in natural products, medicinal and materials chemistry. Pyridine derivatives also serve as precursors to functionalized piperidines, which are likewise common structural motifs in bioactive and functionalized materials. Thus, developing synthetic methods suitable for the manipulation of pyridine ring systems remains an important objective in the organic chemistry community.

We approached this objective by two different routes. In the first method, we used the nucleophilicity of the benzylic position of the 4-alkyl pyridine substrates to engage in gold (I) catalyzed 5 or 6-*endo dig* cyclizations with attached alkynyl amide groups. Processing of the resulting cycloadducts under hydrolytic conditions then afforded substituted pyridines with functionalized lactams.

In the second approach, we investigated the feasibility of Pd-catalyzed cyclization of 3-substituted pyridines. It was envisioned that Pd(0) catalysts could react with alkyne substituents positioned along the pyridine periphery such that a nucleophilic alkynyl moiety would be generated. Activation of the pyridine by N-alkylation or acylation would then result in intramolecular cyclization. Rather than the desired reaction pathway, however, only products of alkyne hydroarylation were observed.

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CHAPTER 1

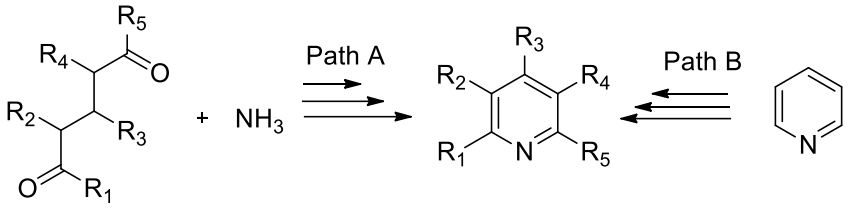
INTERMOLECULAR AND INTRAMOLECULAR NUCLEOPHILIC ADDITION TO PYRIDINES AND ACTIVATED PYRIDINES

1.1 Introduction

Heterocycles are structural motifs that are ubiquitous in marine and terrestrial natural products. Among the large number of heterocyclic compounds, nitrogen containing compounds (called aza-heterocycles) are the most common family of heterocycles. Many of these aza-heterocycles exhibit potent biological activity and are frequently found in pharmaceuticals and other pharmacologically active compounds.[1] Heterocyclic frameworks are also important in agrochemicals, as ligands in organo-transition metal complexes and catalysts, and in organic and metal-organic materials.[2] Prominent sub-families of aza-heterocycles possess either pyridine or piperdine rings as part of their structures. Accordingly, efficient methods for the synthesis of pyridine and piperidine derivatives are extremely important in organic synthesis as these ring systems often serve as synthetic building blocks in construction of more elaborate organic architectures.[3]

There are currently two main general synthetic pathways available to access pyridine derivatives. One is through construction of an aromatic ring with an sp^2 hybridized nitrogen atom through inter- and intramolecular condensation reactions between substituted carbonyl compounds and ammonia as shown in scheme 1.1, path A.[4] The second involves introducing functionality onto pre-formed pyridine or partly substituted pyridines as shown in scheme 1.1, path B. The research described in this

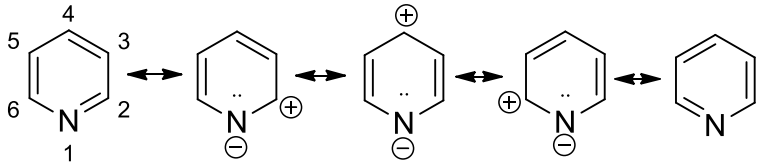
dissertation describes new approaches to functionalizing pyridine derivatives, thus the reminder of this chapter summarizes existing methods for pyridine derivatization.



Scheme 1.1 General synthetic pathways to access pyridine substrates.

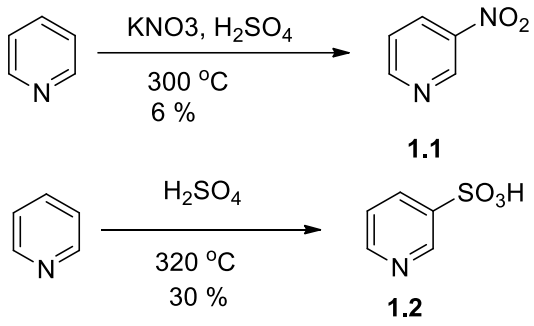
1.2 Substitution reactions of pyridine

Because of the presence of an electronegative nitrogen atom, the pyridine π-system exhibits a lower degree of aromatic stabilization compared to benzene.[5] Consequently, pyridine and pyridine derivatives exhibit partial positive charge at the 2, 4 and 6 positions, as shown in scheme 1.2. In turn, this results in lower reactivity of the pyridine ring towards electrophilic substitution reactions (commonly used to functionalize benzenes) such as Friedel-Crafts alkylation or acylation. Often these reactions result in addition to the nitrogen atom. When electrophilic substitution does take place, the C-3 position of the pyridine ring is the preferred site of reactivity, as this is the least deactivated position in the ring. Exceptions to this regioselectivity can occur depending on additional substituents to activate the pyridine ring.[6]



Scheme 1.2 Resonance structures of pyridine.

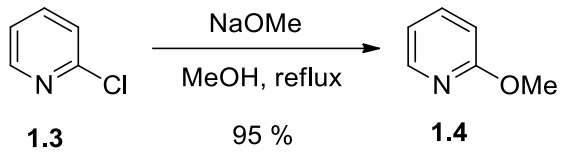
Examples of successful electrophilic substitution reactions of pyridine are shown in scheme 1.3. Pyridine, on reaction with dinitrogen pentoxide and sulfuric acid, gives 3-nitropyridine (although yields are not high). However, pyridine-3-sulfonic acid was obtained by boiling pyridine in excess sulfuric acid at 320 °C.[7]



Scheme 1.3 Examples of electrophilic substitution reactions

In contrast to reactions with electrophiles, and unlike benzene, pyridines do undergo nucleophilic substitution reactions when they have a good leaving group attached. Nucleophilic substitution reactions occur easily with pyridines modified with bromide, chloride, fluoride, or sulfonic acid fragments as good leaving groups. Generally used nucleophiles are alkoxides, thiolates, amines, and ammonia as shown in scheme 1.4.

Organometallic nucleophiles can also attack the pyridine ring directly, but these reactions often are low yielding in the absence of an external oxidant.[8]



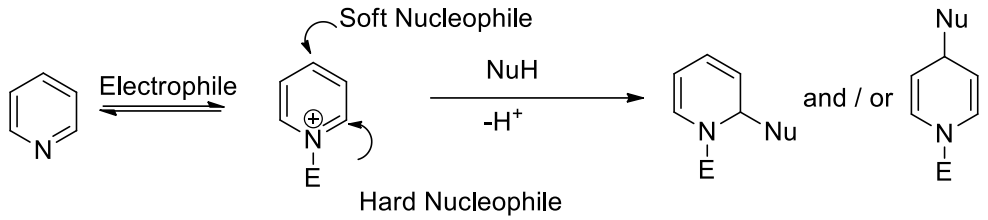
1.3 **1.4**

Scheme 1.4 Nucleophilic aromatic substitution reaction of 2-chloropyridine.

1.3 Intermolecular nucleophilic addition reactions to acyl pyridinium salts

The lower reactivity of pyridine due to the basic nitrogen atom in the ring has led to the use of pyridines functionalized at nitrogen to generate cationic pyridinium salts, or neutral activated pyridinium ylides, which can be more electrophilic or more nucleophilic than the parent pyridine compound. In addition to this, the acidity of α-C-H bonds is increased in the pyridinium reagents, enabling facile deprotonation at these sites compared to direct treatment of pyridine substrates with strong bases.[9]

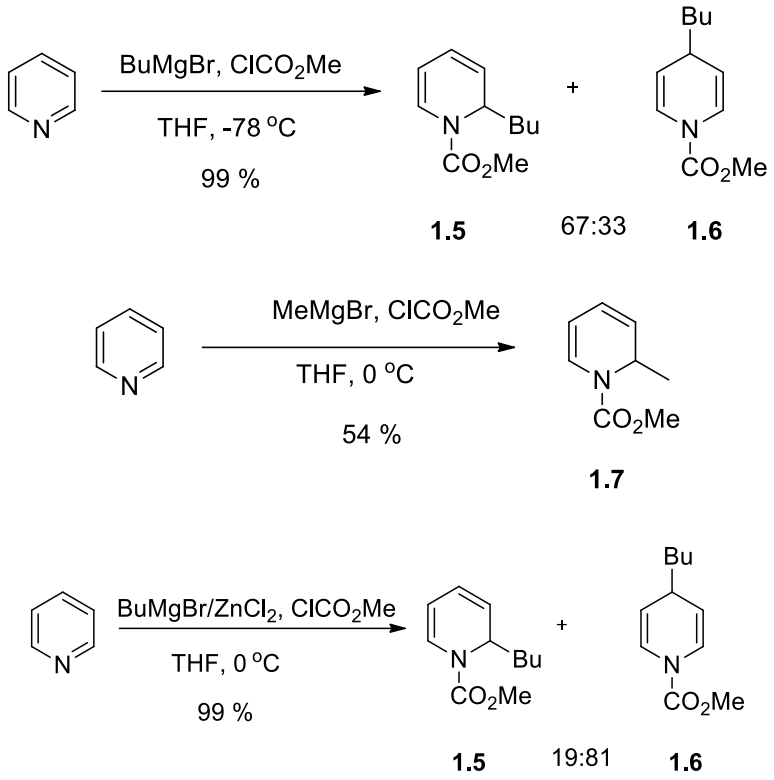
Pyridines react with nucleophiles more readily when converted to the corresponding pyridinium salts upon treatment with either alkylating or acylating reagents. N-acyl pyridinium salts are more electrophilic than N-alkyl pyridinium salts due to increased activation of the π system, in addition to giving more stable dihydropyridine products.[10] The so-formed pyridinium salt contains reactive electrophilic sites at the 2, 4 and 6 positions of the heterocyclic ring as shown in scheme 1.5.



Scheme 1.5 General representation of nucleophilic additions to activated pyridines.

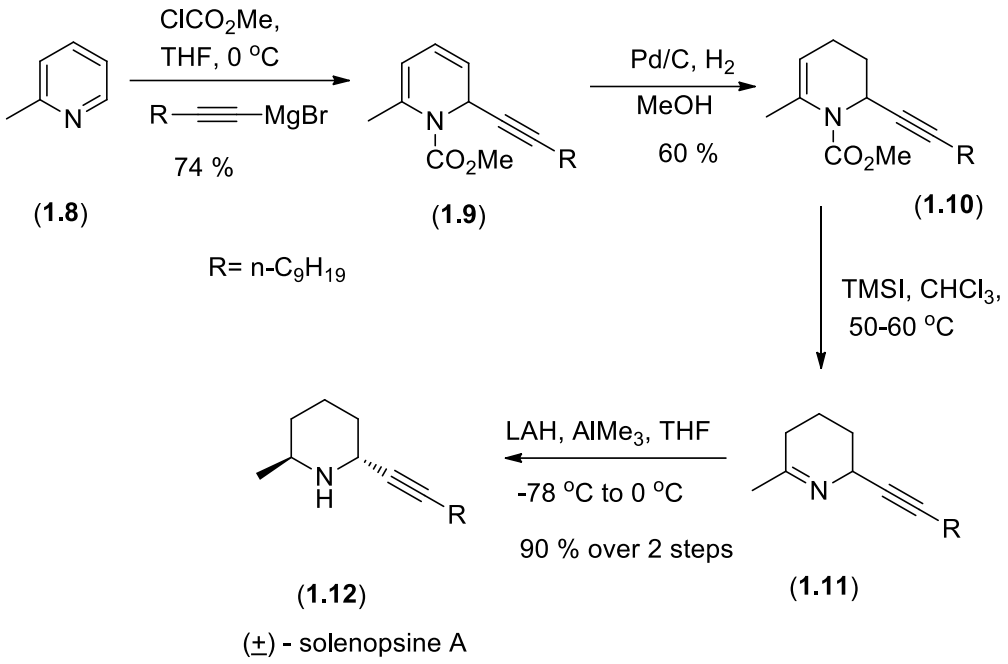
In general, it is observed that hard nucleophiles, like organolithium and organomagnesium reagents, add to pyridinium salts at C-2 to give 1, 2-dihydropyridines while soft nucleophiles like organocuprates, enolates and enol ethers, add to the C-4 position of pyridinium salts to give the corresponding 1, 4-dihydropyridines.

Yamaguchi and co-workers investigated the regioselectivity of addition to pyridines activated by methyl chloroformate as a function of the nature of the nucleophile. Alkyl Grignard reagents like butyl magnesium bromide gave a mixture of 1, 2 and 1,4- dihydropyridines (**1.5** and **1.6**) , whereas harder nucleophiles like MeMgBr and alkynyl Grignard reagents afforded higher selectivity for the 1, 2-dihydropyridine (**1.7**) as shown in scheme 1.6.[11, 12] When the organometallic reagent was varied to the softer butylzinc chloride, increased 1, 4- dihydropyridine product (**1.6**) was observed.



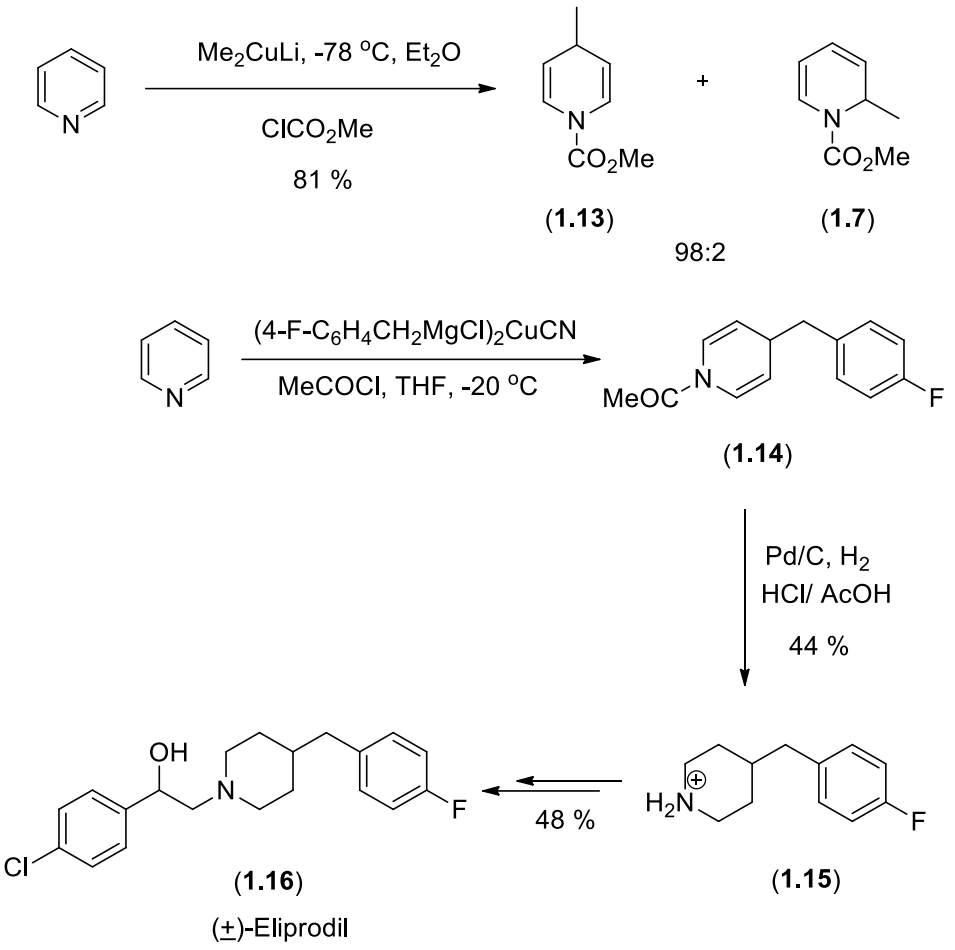
Scheme 1.6 1, 2- and 1, 4-dihydropyridine synthesis.

This methodology was used in the total synthesis of the piperidine alkaloid (±)-solenopsine A as shown in scheme 1.7.[11] 2-Methylpyridine (**1.8**) was treated with methyl chloroformate followed by the addition of an alkynyl Grignard reagent to provide dihydropyridine **1.9**. Further careful hydrogenation using 5 mol % palladium on carbon gave the 1, 2, 3, 4- tetrahydropyridine compound (**1.10**). Demethoxycarbonylation of **1.10** followed by reduction using LAH in the presence of trimethyl aluminum provided the natural product (±)-solenopsine A with 40 % overall yield in 4 steps.



Scheme 1.7 Total synthesis of (±)-solenopsine A.

Piers and Soucy demonstrated the use of organocopper reagents as soft nucleophiles for the synthesis of 1, 4-dihydropyridine derivatives with reliable 4-selectivity and high yields.[13] This methodology was used by Pable *et al.* in the synthesis of Eliprodil, which is an N-methyl-D-aspartate (NMDA) receptor antagonist, as shown in scheme 1.8.[14]

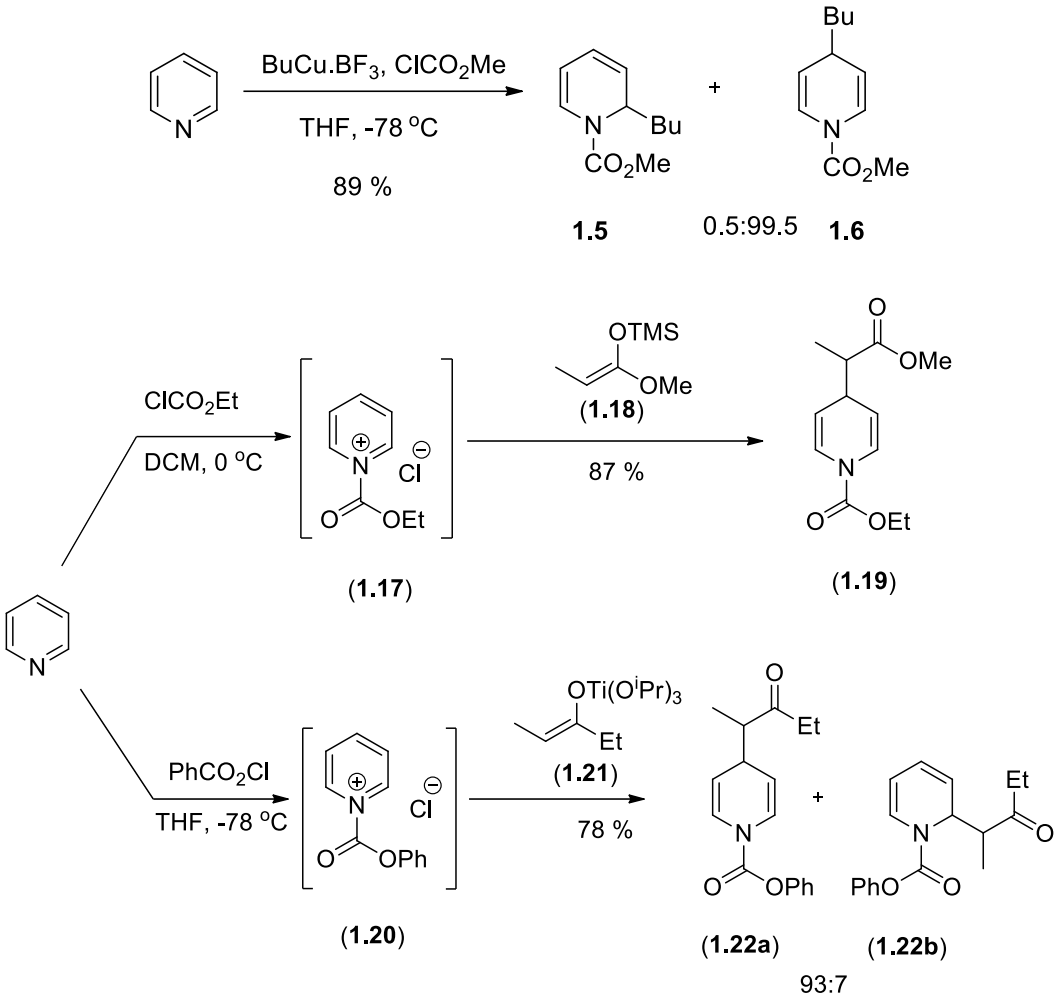


Scheme 1.8 C4-selective cuprate addition and synthesis of (±)-Eliprodil.

A suspension of CuCN and 4-fluorobenzylmagnesium chloride in THF, was added to a stirred solution of pyridine and acetyl chloride gave the dihydropyridine compound (**1.14**), which on further reduction gave **1.15**, and ultimately the desired product (±)-Eliprodil (**1.16**).

Akiba and coworkers have achieved high selectivity and yields in forming 1, 4-dihydropyridines by using $RCuBF_3$ reagents.[15] This same group also reported that silyl ketene acetals (**1.18**) acts as soft nucleophile and add with high regioselectivity to the 4-

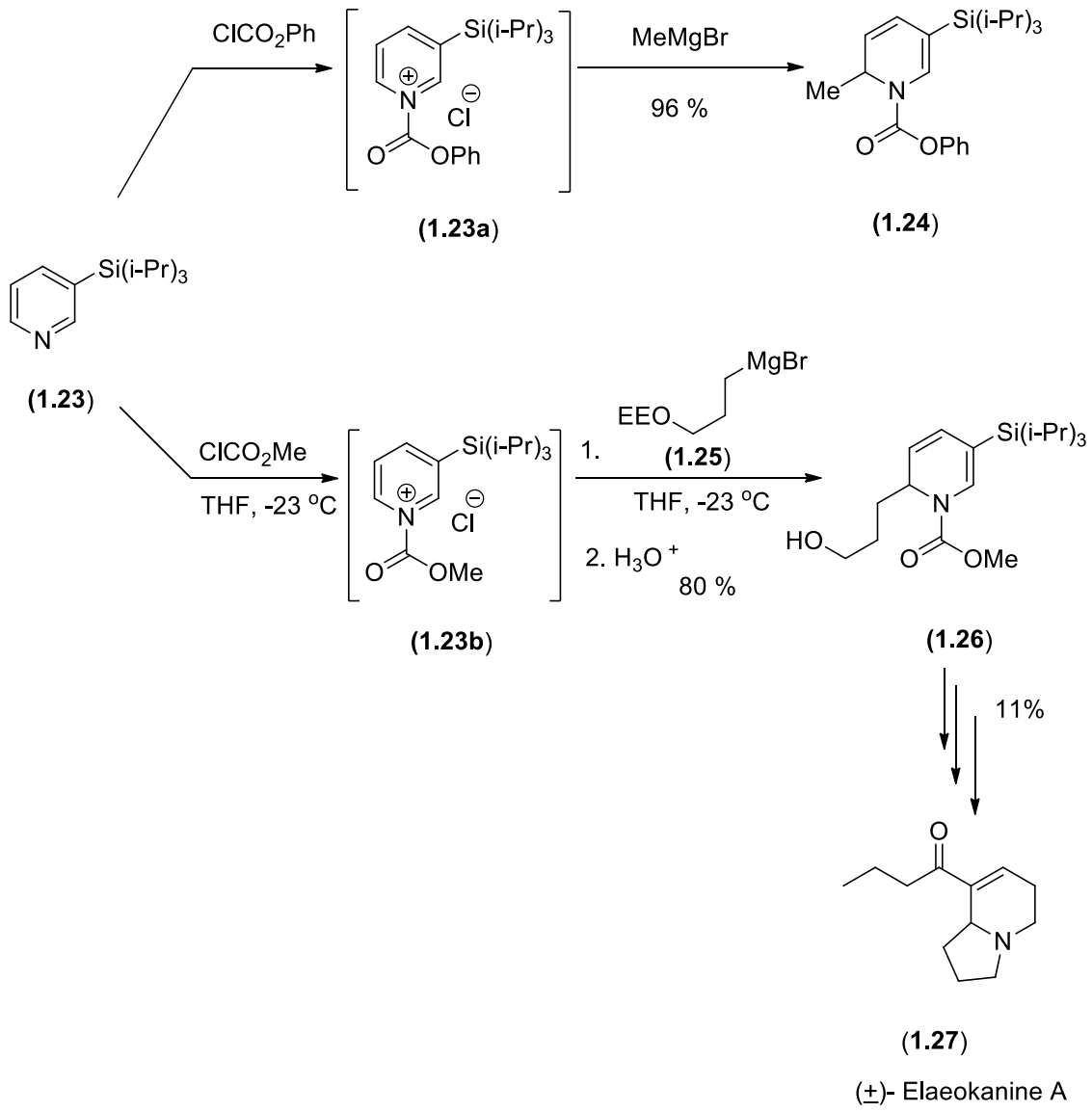
position of pyridinium salt **1.17** to give 1, 4-dihydropyridine regioisomer (**1.19**) in good yield.[16] Comins also reported the addition of titanium enolates **1.21** to the intermediate pyridinium salt (**1.20**). The 1, 4-dihydropyridine **1.22a** was obtained as the major isomer along with the 1, 2-dihydropyridine (**1.22b)** as shown in scheme 1.9.[17]



Scheme 1.9 Regioselectivity in nucleophilic additions to pyridinium salts.

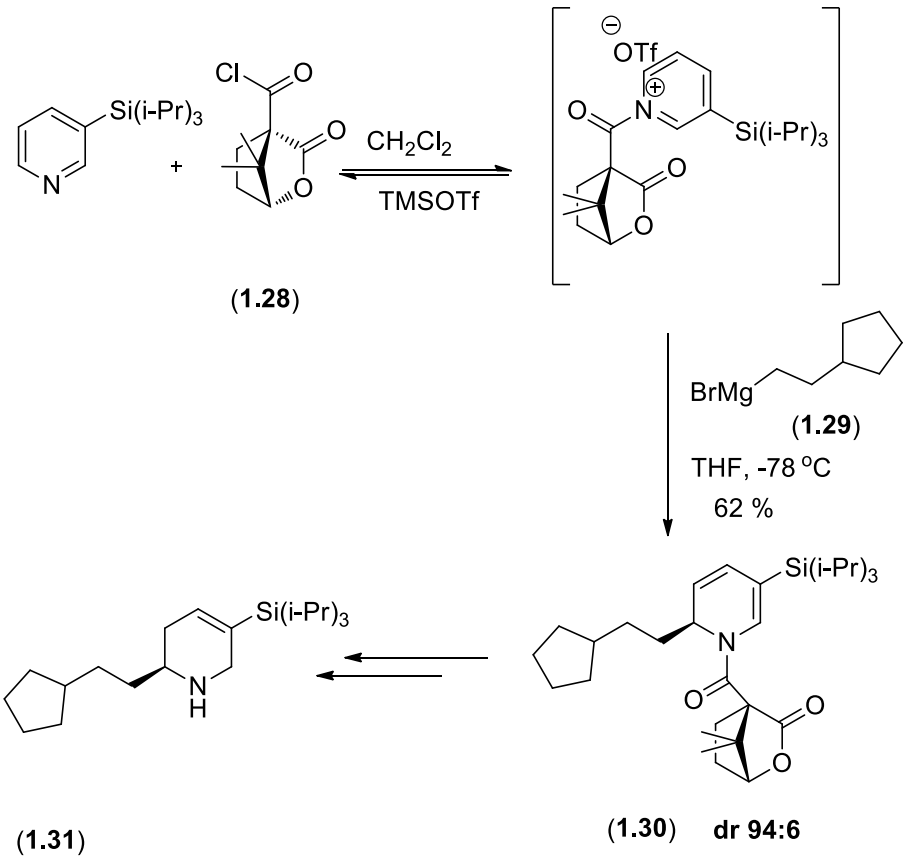
Comins and coworkers have used bulkier substituents like trialkyl tin and trialkyl silyl groups at the 3-position as blocking groups to afford 6-substituted 1, 2-dihydropyridines regioselectively.[18] 3-Triisopropylsilyl pyridine (**1.23**) in combination with phenyl chloroformate results in the addition of alkyl or aryl Grignard reagents (e.g., MeMgBr) exclusively at the 6-position to give the 1,6-dihydropyridine (**1.24**).[19] This methodology was further utilized by Comins and coworkers for the synthesis of the indolizidine alkaloid (±)-elaeokanine A. The Grignard reagent (**1.25**) added selectively to

the 6-position of the triisopropylsilyl pyridine (**1.23**) in the presence of methyl chloroformate to give 1, 6-dihydropyridine (**1.26**) which, on further modification, yielded (±)-elaeokanine A (**1.27**) as shown in scheme 1.10.



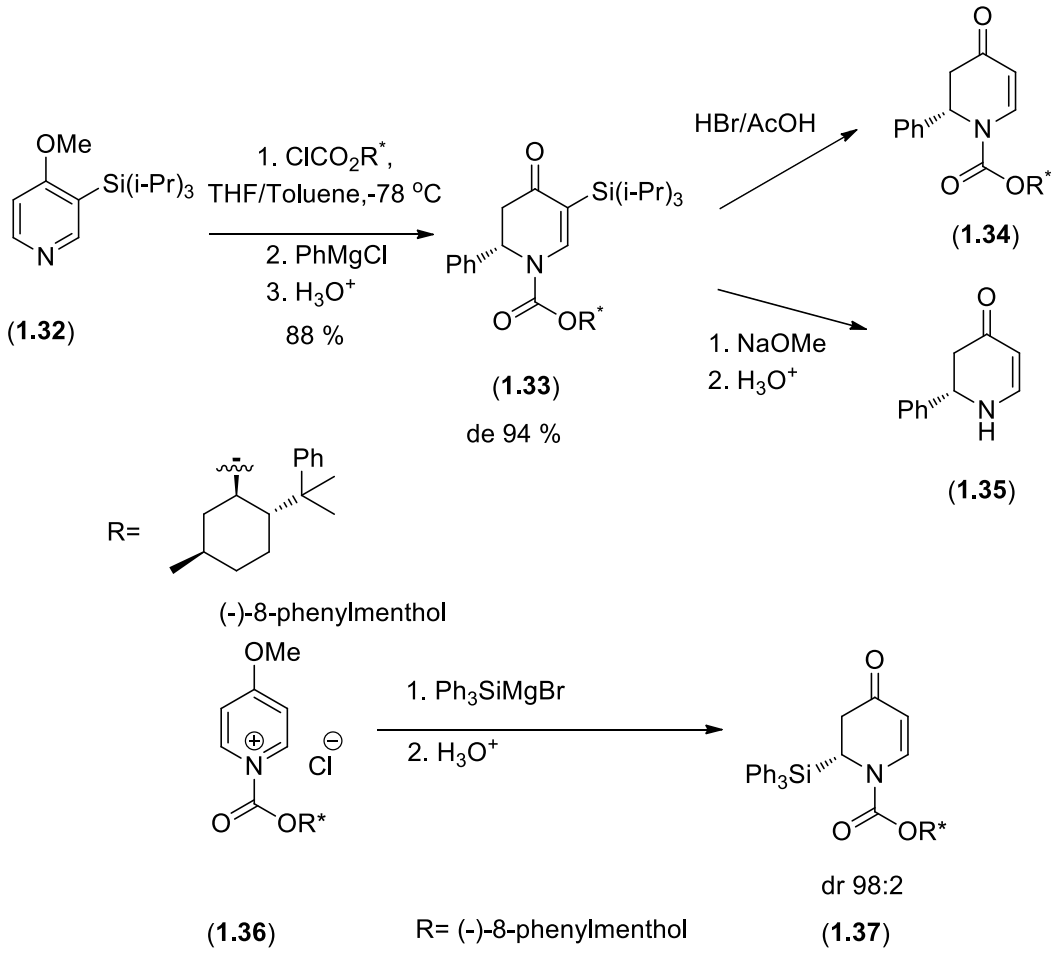
Scheme 1.10 Total synthesis of (±)-Elaeokanine A.

Asymmetric versions of nucleophilic addition to pyridines are powerful tools for stereo-controlled synthesis of heterocyclic compounds. The use of chiral auxiliaries to mediate diastereoselective additions to pyridine has been widely used in organic synthesis. Wanner and coworkers developed a chiral acyl group (**1.28**) to allow diastereoselective addition of Grignard reagent (**1.29**) to 3-trialkylsilyl pyridine providing a chiral N-acyl-1, 2-dihydropyridine (**1.30**) in very high regio- and diastereoselectivity. Further reduction and removal of the chiral auxiliary provided the 1, 2, 3, 6-tetrahydropyridine (**1.31**) in enantiomerically pure form as shown in scheme 1.11.[20]



Scheme 1.11 Diastereoselective addition to 3-alkylsilylpyridine.

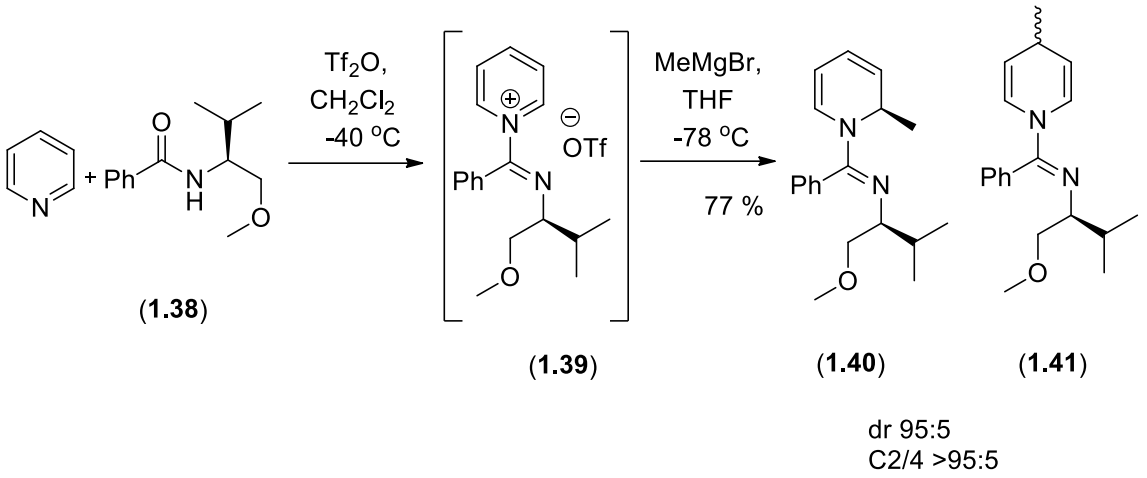
Comins and coworkers developed a robust methodology for preparation of dihydropyridones with high stereoselectivity. This involved the addition of Grignard reagent to the chiral N-acyl pyridinium salts formed from 4-methoxy-3-(triisopropylsilyl) pyridine (**1.32**) and the chloroformate of an 8-phenyl menthol derivative to give dihydropyridine (**1.33**) with high diastereoselectivity as shown in scheme 1.12. Further hydrolysis of the dihydropyridine (**1.33**) provided compounds **1.34** and **1.35**.[21]



Scheme 1.12 Comin's diastereoselective addition to 4-methoxy-3-(triisopropylsilyl) pyridine.

When Comins and coworkers used a bulky silyl nucleophile such as (triphenylsilyl)magnesium bromide, the large blocking group was not required at the 3-position to achieve high selectivity and addition to 4-methoxypyridine **1.36** occurred with 98:2 diastereomeric ratio (dr).[22] These strategies have been utilized by Comins and coworkers in the stereoselective synthesis of numerous alkaloid natural products.[23]

In addition to the above methods Charette and coworkers have developed a conceptually similar approach for selective addition of nucleophiles to the C-2 position of unsubstituted pyridines. Their methodology relies on the formation of N-imidoyl pyridinium salts formed by treating pyridines with in situ-activated amides in the presence of triflic anhydride. By employing chiral non-racemic amides (**1.38**), chrial pyridinium salts such as (**1.39**) could be obtained. These pyridinium salts then participate in chelation controlled regioselective and diastereoselective addition of carbon nuclephiles to produce 1, 2-dihydropyridines. For example, addition of Grignard reagent (MeMgBr) to the chiral pyridinium salt (**1.39**) gave 1, 2-dihydropyridine (**1.40**) in good yield with high regioselectivity and excellent stereocontrol (scheme 1.13).[24]

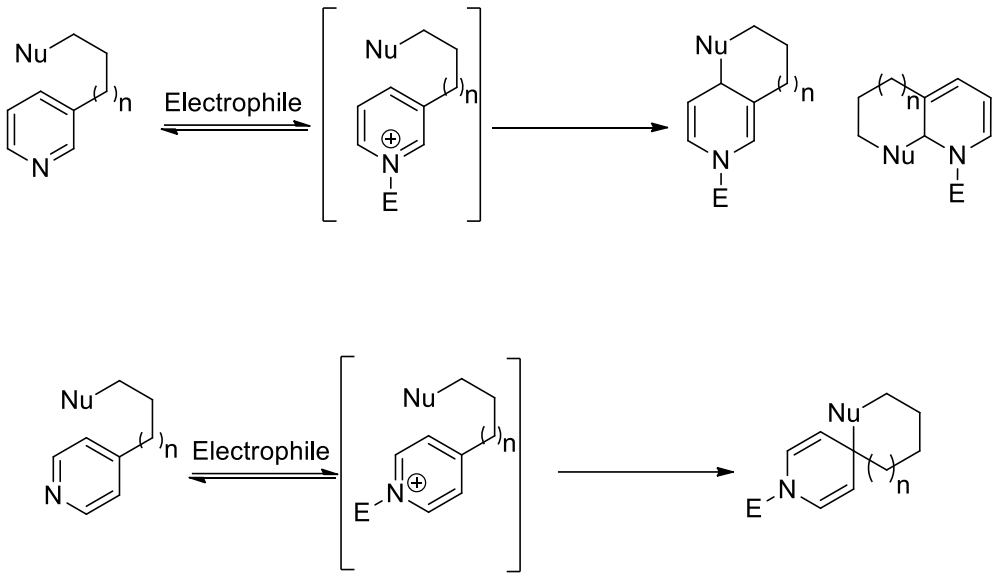


Scheme 1.13 Diastereoselective addition to chiral pyridinium N-imidate salts.

1.4 Intramolecular nucleophilic addition reactions of acyl pyridinium salts

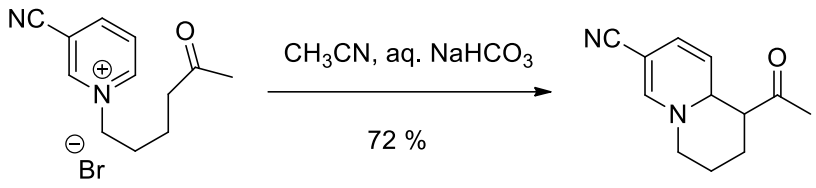
Elaboration of the pyridine ring system offers convenient access to a large class of substituted aza-heterocyclic derivatives. Intramolecular nucleophilic addition to pyridine is an excellent synthetic tool for the construction of polycyclic heterocyclic frameworks. Surprisingly, intramolecular additions of nucleophiles to pyridine substrates are less common relative to intermolecular nucleophilic additions (as discussed in the preceding section). Importantly, intramolecular additions to pyridinium salts provide concise entry to spirocyclic dihydropyridine derivatives and/or fused ring systems that are well suited for synthetic manipulation. Most intramolecular reactions involving pyridine substrates are initiated by alkylation or acylation of the pyridyl nitrogen to afford electrophilic pyridinium cation intermediates. Prior attachment of the nucleophilic group to the C-3 position provides fused ring 1, 2-dihydropyridines or 1, 4-dihydropyridines, whereas a

nucleophilic group at the C-4 position may result in the cyclization to afford spirodihydropyridines, as shown in scheme 1.14.



Scheme 1.14 General representation of intramolecular nucleophilic additions to pyridine.

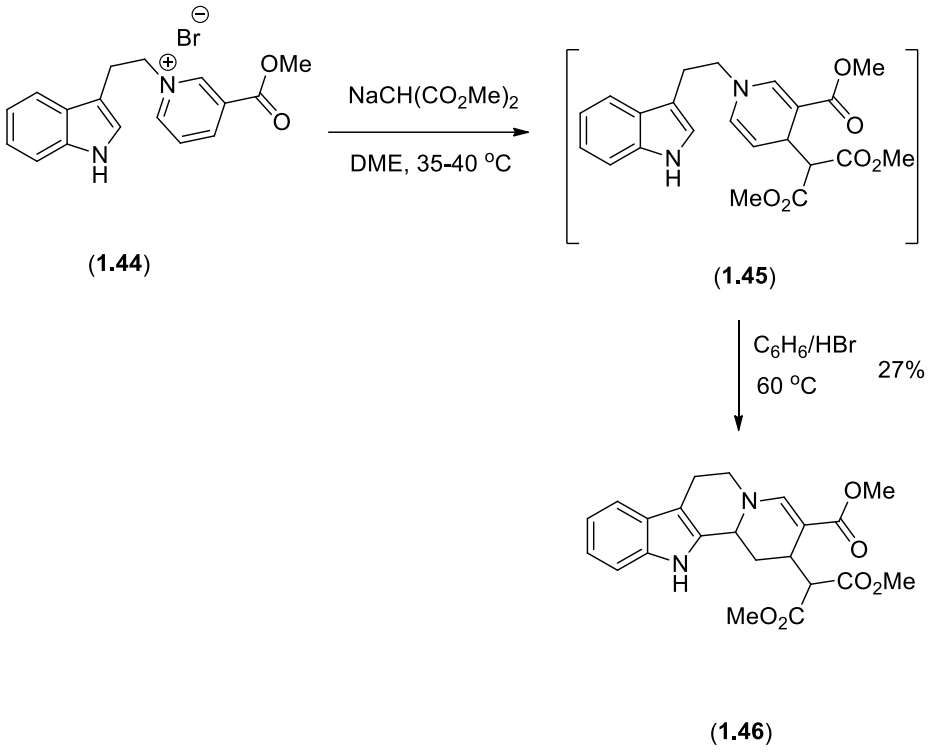
Reactive nucleophiles can also be generated from functional groups introduced to the pyridine N-atom. For example, Wilson and Dininno synthesized the pyridinium salt (**1.42**) by reacting neat 6-bromo-2-hexanone with 3-cyanopyridine at room temperature. The so formed pyridinium salt undergoes cyclization in the presence of weak bases like sodium bicarbonate to give 1,6-dihydropyridine (**1.43**) (scheme 1.15).[25]



(**1.42**) (**1.43**)

Scheme 1.15 1, 6-Dihydropyridine synthesis.

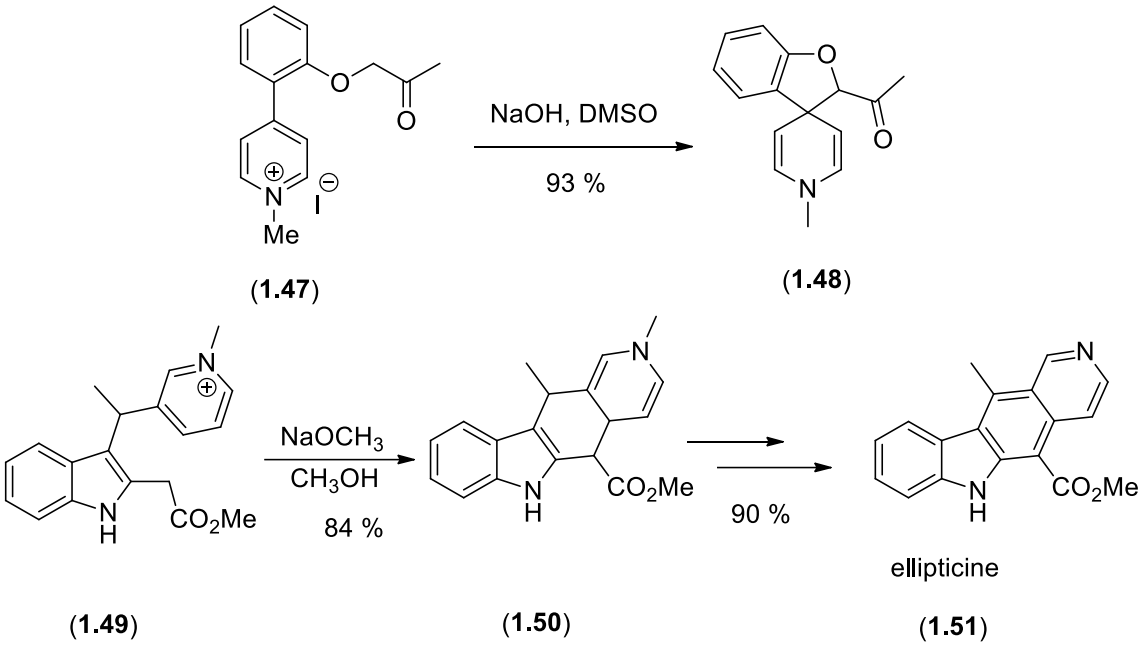
Wenkert *et al.* introduced a new scheme for synthesis of yohimboid ring systems via addition of the sodium salt of dimethyl malonate to the pyridinium salt (**1.44**), followed by acid catalyzed intramolecular addition to afford the yohimboid ring system (**1.46**) (scheme 1.16).[26]



(**1.44**) (**1.45**) (**1.46**)

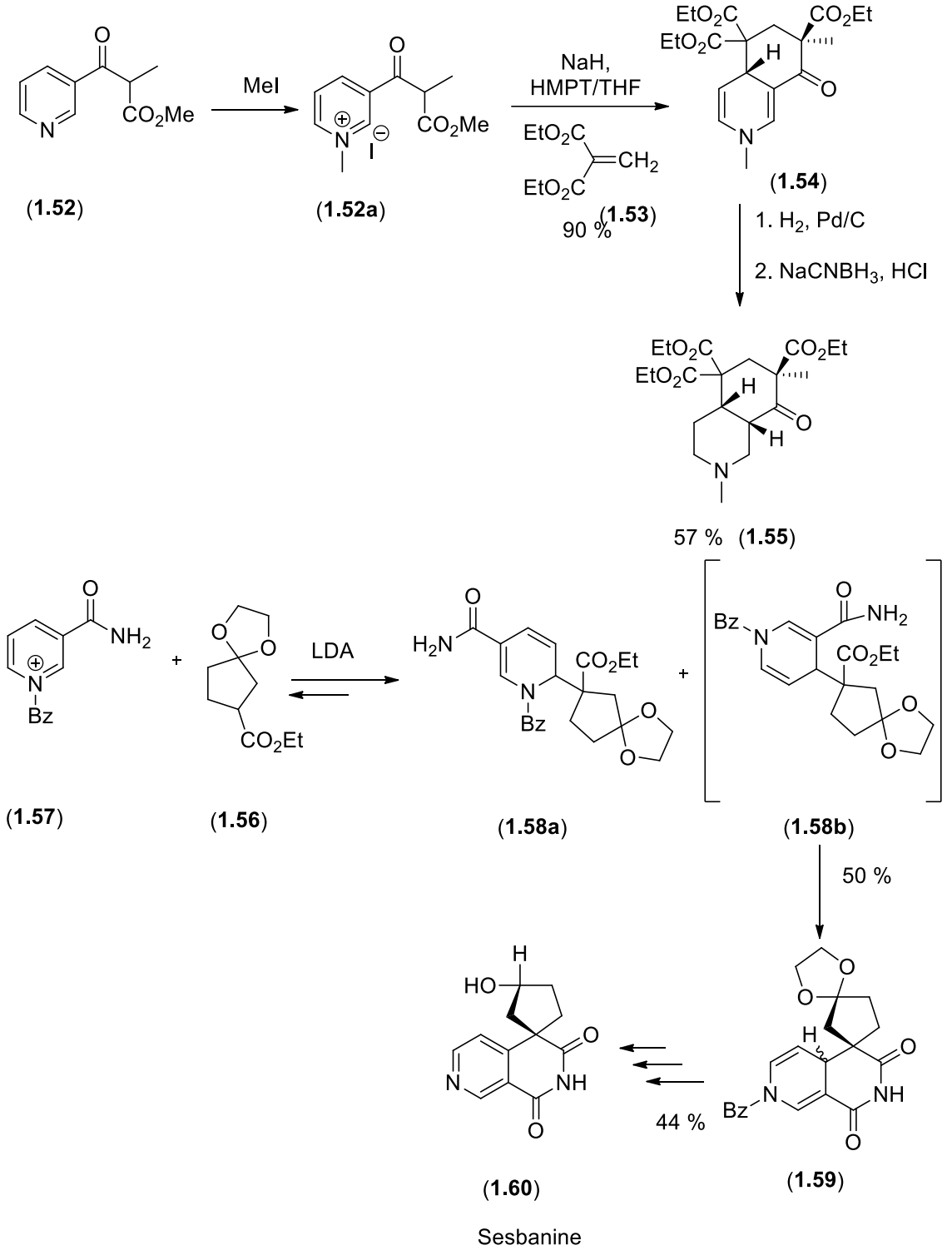
Scheme 1.16 Yohimboid ring system synthesis (Wenkert approach).

Weller *et al.* prepared both 4- and 3-substituted pyridine derivatives with carbon nucleophiles in their side chains (scheme 1.17). Treatment of the alkyl pyridinium salt (**1.47**) with NaOH in DMSO provided somewhat unstable (at room temperature) spirocyclic product (**1.48**) in good yield.[27] Intramolecular addition to pyridine was utilized in the synthesis of ellipticine. Base mediated intramolecular attack of a tethered ester side chain to the pyridinium salt (**1.49**) to the C-4 position gave intermediate (**1.50**), which, on further modification, gave the natural product ellipticine (**1.51**). [28]



Scheme 1.17 Synthesis of ellipticine.

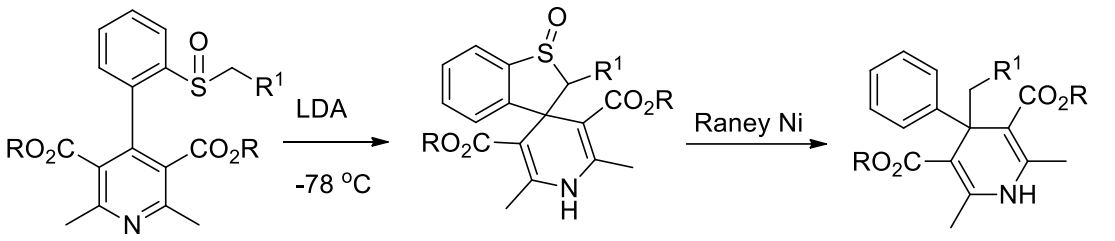
Pandit *et al.* has successfully developed a one-pot base mediated reaction of pyridinium salts of N-alkylated-3-pyridylketone (**1.52**) with diethylmethylene malonate (**1.53)** to give fused ring product (**1.54**) which on further reduction and modification provided hexahydroisoquinoline derivative (**1.55**) (scheme 1.18).[29] Pandit *et al.* have also successfully demonstrated the use of their methodology in the total synthesis of sesbanine. The α-ester carbanion generated by treating the ester (**1.56**) with LDA adds to the N-benzylnicotinamide salt (**1.57**) to give the C-6 and C-4 substituted primary products (**1.58a** and **1.58b**). The C-4 substituted dihydropyridine undergoes further reaction involving nucleophilic attack of the amide nitrogen to the carbonyl group of the ester to give polycyclic ring system (**1.59**). Further manipulation provided the final natural product sesbanine (**1.60**) (scheme 1.18).[30]



(**1.52**) (**1.52a**) (**1.53**) (**1.54**) (**1.55**) (**1.57**) (**1.56**) (**1.58a**) (**1.58b**) (**1.59**) (**1.60**)

Scheme 1.18 Pandit *et al.* methodology and total synthesis of sesbanine.

Goldmann *et al.* also demonstrated the direct intramolecular addition of sulfinyl carbanions generated by the treatment of **1.61** with LDA to the 4-position of an unactivated pyridine ring to afford spiro-1, 4-dihydropyridine (**1.62**), which was further reduced to obtain **1.63**. These compounds were screened for their antihypertension activity (scheme 1.19).[31]



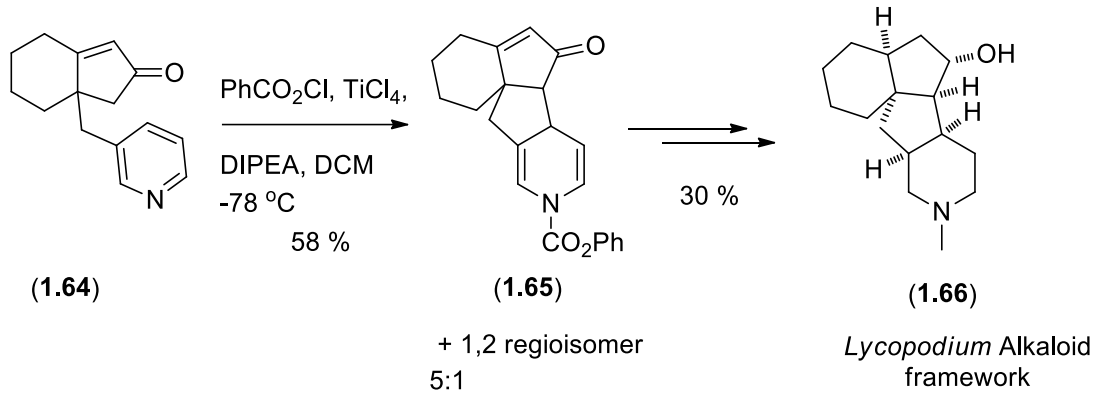
(**1.61**) (**1.62**) (**1.63**)

R=H, R^1=Me, 80%
R=Me, R^1=Me, 41%

R=H, R^1=Me, 74%
R=Me, R^1=Me, 11%

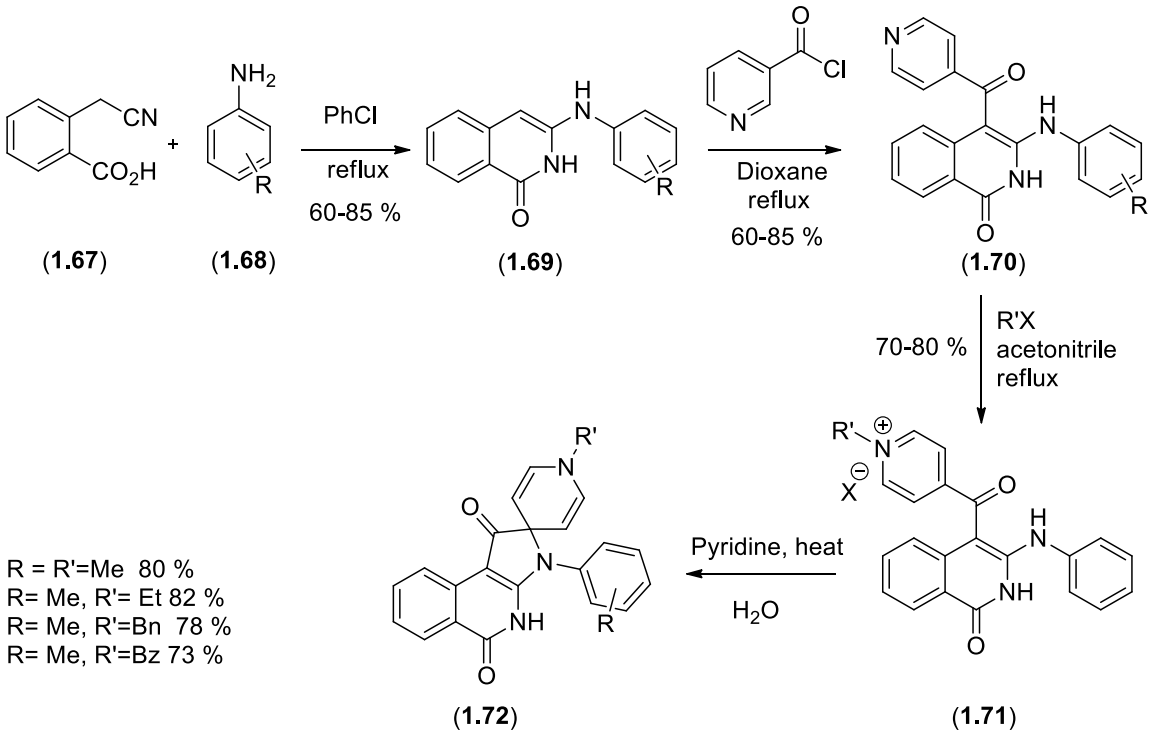
Scheme 1.19 Example of intramolecular addition to unactivated pyridine.

Sandham and Meyers have developed a method for addition of titanium enolates to the 4-position of pyridinium salts generated by the treatment of phenylchloroformate to **1.64** in the presence of organic base DIPEA (N, N-diisopropyl ethyl amine) to afford a 5:1 mixture of regioisomers **1.65** (desired 3,4-isomer being major and 2,3-regioisomer minor). Further manipulation provided the tetracyclic framework of *Lycopodium* alkaloids (**1.66**) (scheme 1.20).[32]



Scheme 1.20 Examples of intramolecular addition to pyridinium salt.

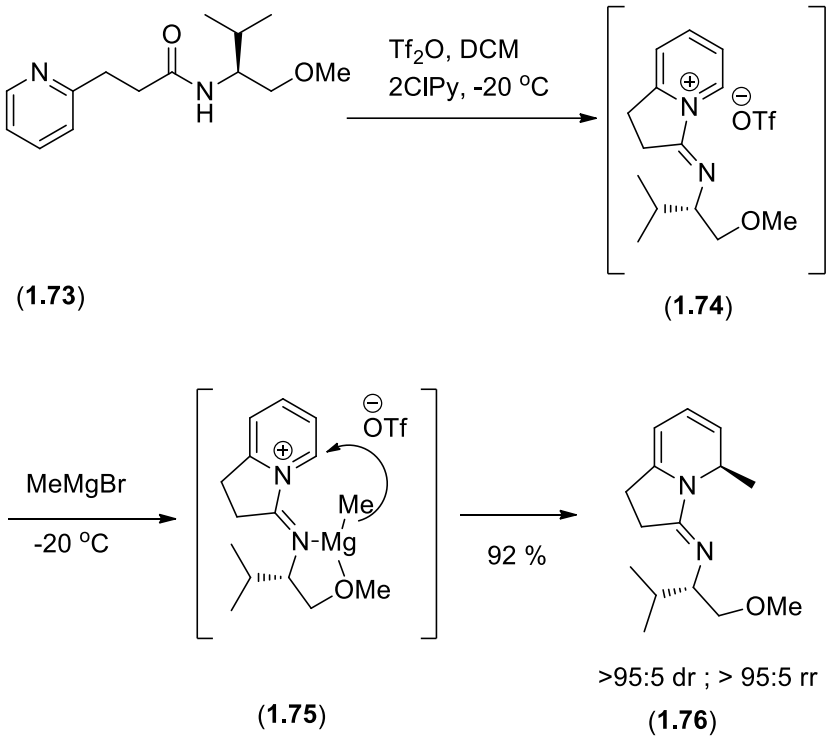
Kucherenko *et al.* utilized the intramolecuar nucleophilic addition to pyridinium salts strategy very well to synthesize fused isoquinoline derivatives (scheme 1.21).[33] The condensation of 2-cyanomethyl benzoic acid (**1.67**) with the aryl amine (**1.68**) provided the intermediate **1.69**. Isonicotinoylation of **1.69** proceeded at C-4 carbon atom to give the corresponding pyridine compound (**1.70**). Reaction with alkyl halide generated the pyridinum salt (**1.71**), which under basic conditions, gave the spirocyclic isoquinoline (**1.72**) in good yield.



Scheme 1.21 Synthesis of isoquinoline derivatives (Kucherenko *et al.*).

Asymmetric versions of intramolecular activation of pyridine followed by addition of nucleophiles were performed by Charette and coworkers to obtain 5-substituted indolizidines and 6-quinolizidines in excellent yields with high regio- and stereoselectivity (scheme 1.22). [34] After extensive optimization of reaction conditions, they found that treating pyridine **1.73** with trifluoromethane sulfonic anhydride in the presence of 2-chloropyridine smoothly generated pyridinium salt **1.74** as a transient intermediate. The use of 2-chloropyridine as a non-nucleophilic and slightly basic additive proved crucial for efficient intramolecular pyridine activation. Then, treatment of the intermediate pyridinium salt with Grignard reagent resulted in the formation of the unsaturated indolizidine (**1.75**) with excellent yield as a single regio- and diastereomer. The stereo- and regio-control is thought to arise from precomplexation (**1.75**) of the

Grignard reagent with the E-imidate lone pair and the ether functionality, thereby directing the nucleophilic addition to the 6-position by minimizing the 1, 3-allylic strain with the chiral auxiliary. This chelation of Grignard with the ether moiety shifts the Grignard reagent towards the β-face of the pyridinium ring to provide the desired diastereomer **1.76**.

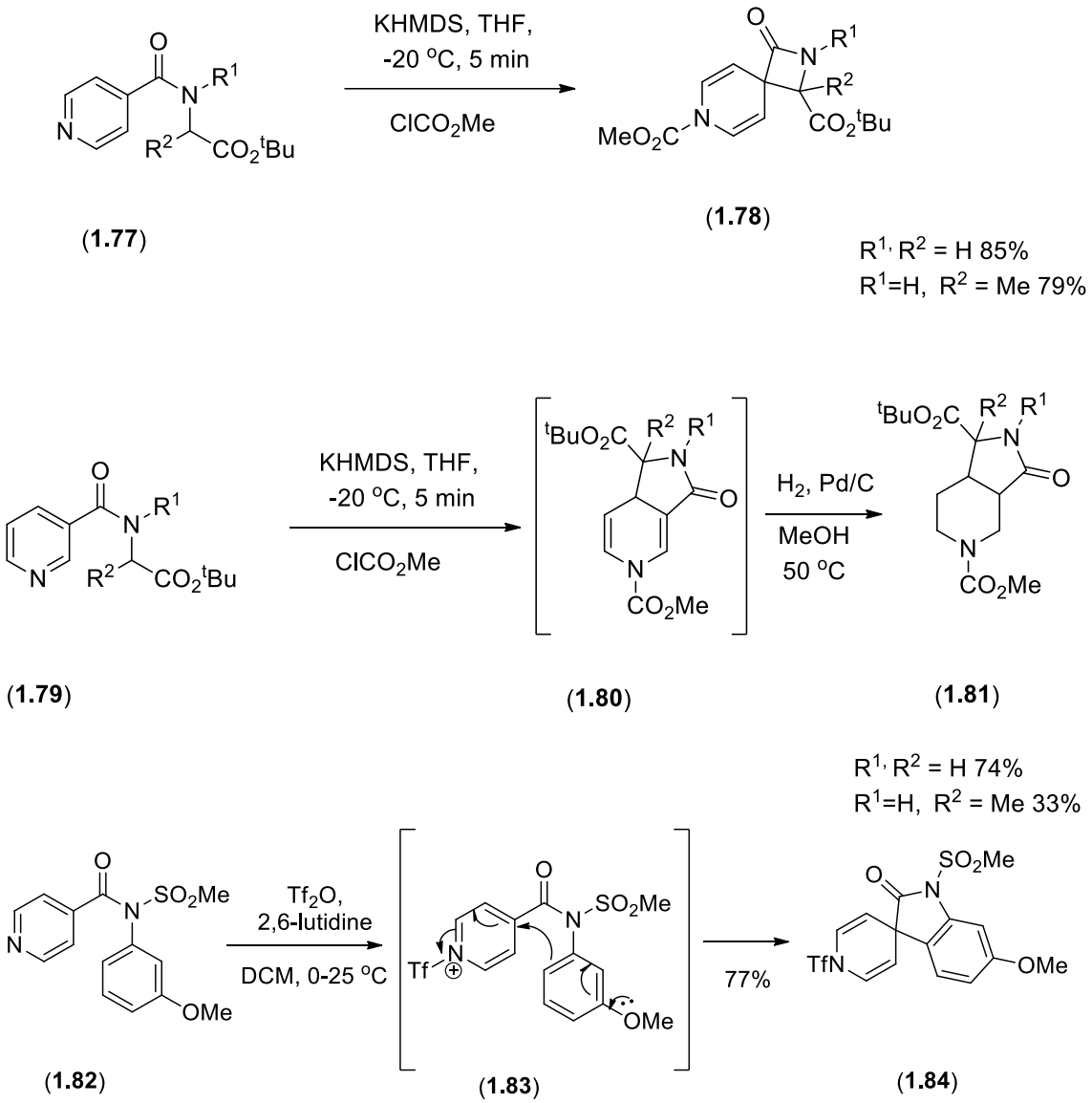


(**1.73**) (**1.74**) (**1.75**) (**1.76**)

Scheme 1.22 Intramolecular activation and asymmetric induction (Charette *et al.*).

Clayden and coworkers have extensively utilized intramolecular nucleophilic addition strategies on pyridine and quinoline substrates to access 4-, 5- or 6- membered ring containing compounds, which then can be further manipulated to polycyclic heterocycles such as pyrrolopyridines, pyrroloquinolines, benzonaphthridines etc. For

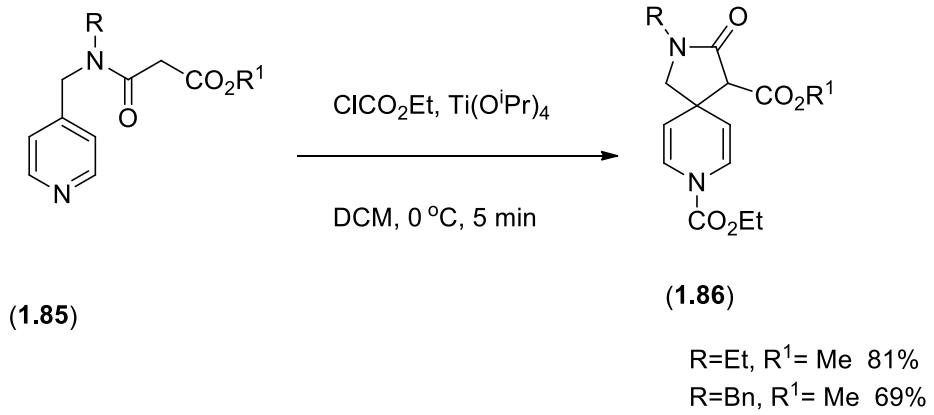
example, the enolate generated by treatment of isonicotinamide derivative **1.77** with LDA reacts in an intramolecular fashion with the pyridine ring in the presence of methyl chloroformate to give the spirocyclic dihydropyridine (**1.78**).[35] Similarly, the enolate of the nicotinamide derivative (**1.79**) added in an intramolecular manner to the pyridine ring also in the presence of methyl chloroformate to give the rather unstable fused ring dihydropyridine **1.80**, which is then readily reduced to give bicyclic ϒ-lactam **1.81** as shown in scheme 1.23.[36] The same group demonstrated that N-arylisonicotinamides undergo tandem intramolecular nucleophilic attack of the aryl ring on the 4-position of pyridine intermediate in the presence of trifluoromethane sulfonic anhydride to give spirocyclic dihydropyridines, which can be further converted to valuable spirocyclic piperidines.[37] The pyridine derivative (**1.82**) was activated by acylation using Tf_2O, the resulting triflate underwent immediate attack from the arene nucleophile resulting in formation of spirocycle (**1.84**).



Scheme 1.23 Intramolecular addition examples from the Clayden group.

Notably, all the transformations discussed so far have utilized pyridine derivatives that do not contain benzylic hydrogens. While this removes concerns of unwanted deprotonation arising from the increased acidity exhibited by C-4 benzylic hydrogens upon the acylation or alkylation of pyridine, it also narrows the scope of spirocyclization processes. Recently, however, Pigge and coworkers have successfully developed tandem

spirocyclization reactions of pyridines substituted at the 4-position with alkyl tethers containing β-dicarbonyl moieties under acidic or neutral reaction conditions to afford functionalized spirocyclic dihydropyridines.[38] The pyridine derivative (**1.85**) was converted to the acylated pyridinium salt in situ by treating with ethyl chloroformate. In the presence of titanium isopropoxide the spirodihydropyridine product (**1.86**) was formed virtually instantaneously and in good to excellent yields (scheme 1.24).



(**1.85**)

(**1.86**)

R=Et, R^1= Me 81%
R=Bn, R^1= Me 69%

Scheme 1.24 Spirodihydropyridines from 4-alkyl substituted pyridines.

1.5 Conclusion

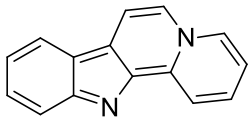
As it can be seen from the examples discussed in this chapter, inter- and intramolecular nucleophilic addition reactions to pyridines provide powerful synthetic methodology to access complex heteroatom-containing molecular frameworks in concise and direct fashion. The products of these reactions can be further manipulated and functionalized to achieve the total synthesis of natural products containing aza-heterocyclic ring systems in their cores. It also gives a handle for the synthesis of small heterocyclic molecules which can be of biological significance. Challenges remain in this area, particularly with respect to catalytic asymmetric transformations of pyridines. Additionally, the manipulation of activated pyridines at benzylic positions (e.g., via anhydrobase intermediates) has not been explored, and this topic is the subject of the next chapter.

CHAPTER 2

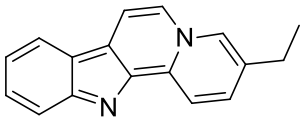
ANHYDROBASES OF PYRIDINE AND OTHER HETEROCYCLIC ARENES AS SYNTHETIC INTERMEDIATES

2.1 Introduction

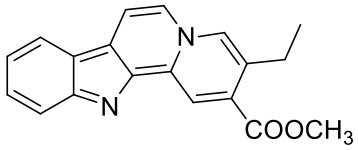
Heterocyclic ring systems, particularly aza-hetereocycles, are well recognized as important structural motifs in numerous bio-active compounds. Anhydrobases are a class of organic compounds that are generated from heterocyclic cations that have hydrogen containing substituents. Anhydrobases have been of interest to researchers because of their diverse chemical and physical properties. They display high reactivity and are used as starting materials in the construction of various heterocyclic ring systems such as indolizines, pyridazine, and substituted pyridines.[39, 40] Anhydrobases are also of importance because they are found as a part of the skeletal framework of many alkaloids such as semepervirine, flavopereirine, flavocarpine, alstonine, serpentine, and alstonine (Figure 2.1).[41] Anhydrobases have also been used in the preparation of pharmaceutically active compounds displaying hypotensive, antiphlogistic, analgesic action and anticoagulant properties.[42]



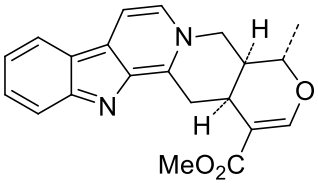
Sempervirine



Flavopereirine



Flavocarpine

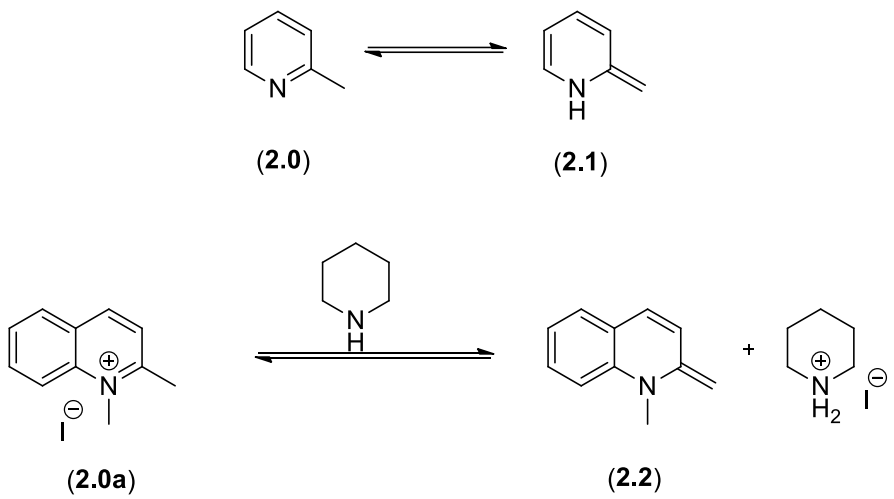


Alstonine

Figure 2.1 Anhydrobases in skeletal frameworks of alkaloids.

2.2 Structure, characteristics and synthesis of anhydrobases

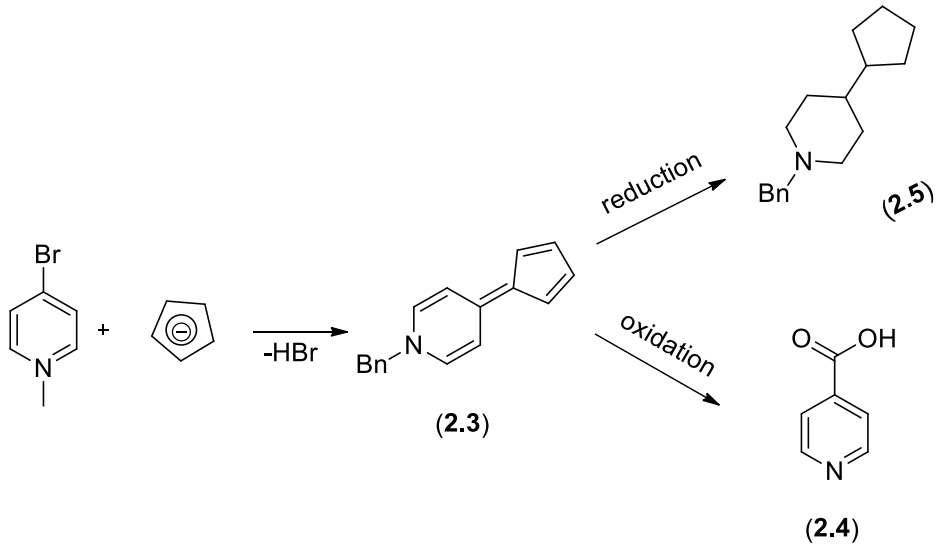
Pyridine anhydrobases are generally unstable, highly colored compounds. Some simple anhydrobases may exist in equilibrium with their aromatic counterparts. For example, Chichibabin proposed that 2-picoline exists as a tautomeric mixture of **2.0** and **2.1**.[43] A similar structure (**2.2**) was proposed to explain the role of piperidine as the catalyst in the condensation of a quarternary salt of quinaldine (**2.0a**) with aromatic aldehydes.[44]



Scheme 2.1 Proposed structure of 2-picoline by Chichibabin.

Katritzy and coworkers successfully demonstrated the apparent structures of anhydrobases **2.1** and **2.2** are similar to the structure of pyridone by means of IR spectroscopy. The IR absorptions at 1637-1651, 1530-1583, 1511-1550 and 1438-1449 and the intensities of these bands for anhydrobase **2.1** are virtually same as the absorption and intensities of pyridones and pyridinethiones.[45]

The anhydrobase structure has been established most accurately in the case of 1-benzyl-4-cyclopentadienylidene-1, 4-dihydropyridine (**2.3**). The oxidation of this anhydrobase leads to pyridine-4-carboxylic acid while reduction gives the corresponding piperidine (**2.5**).[46]



Scheme 2.2 Example of stable anhydrobase of pyridine.

Quantum chemical calculations of N-methyl picolinium salts show significant separation of charge between the nitrogen atom and the exocyclic methylene group, hence pronounced alteration in the bonds of the anhydrobase molecule.[47] The later fact explains the relative lower stability of the anhydrobases. Additionally, the greater local π-surplus on the exocyclic methylene carbon atom renders this site nucleophilic and susceptible to reaction with electrophiles (Figure 2.0).

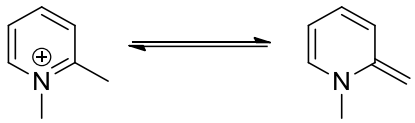
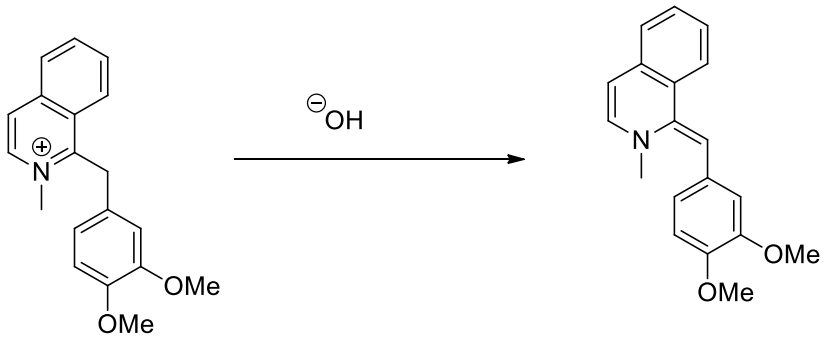


Figure 2.2 Anhydrobase of N-methyl picolinium salt.

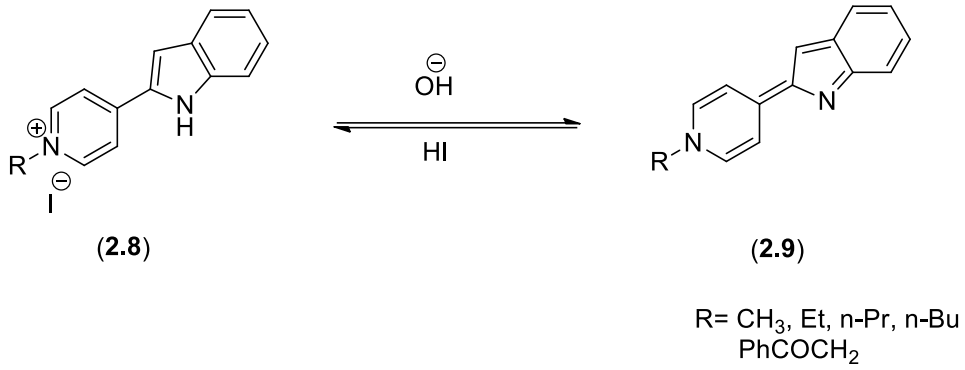
The anhydrobase (**2.7**) of isoquinoline was obtained by the treatment of papaverine methiodide (**2.6**) with an alkali as shown in scheme 2.3. A systematic study of reactions of quaternary pyridinium salts that contain a substituent with labile hydrogen at 2 or 4 positions with a base showed formation of extremely unstable anhydrobases that decompose readily. [48] Annelation of the pyridine ring (as in scheme 2.3) provided somewhat more stable anhydrobases.



(**2.6**) (**2.7**)

Scheme 2.3 Example of anhydrobase.

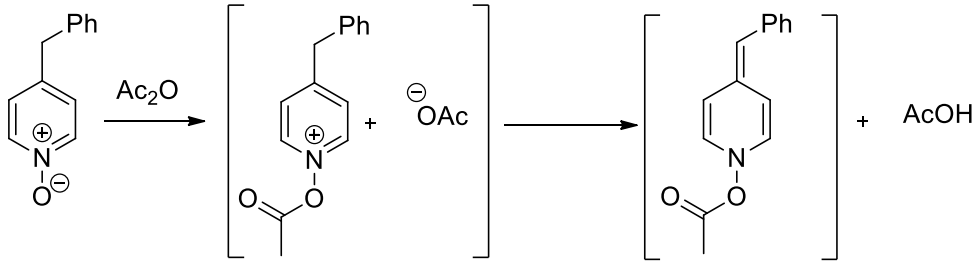
Stable anhydrobase (**2.9**) is formed in the reaction of quaternary salts of 3-(4-pyridyl) indole (**2.8**) with alkali; various structural factors viz., annelation, aza substitution, the presence of vinyl grouping between the rings and the character of the substituents in both pyridine and indole rings have an effect on the formation of corresponding anhydrobases (scheme 2.4).[49]



(**2.8**) (**2.9**)

Scheme 2.4 Example of stable anhydrobase.

Anhydrobase **2.11** is generated in situ by the treatment of 4-alkyl pyridine N-oxide (**2.10**) with acid anhydrides.[50] The intermediacy of anhydrobase was ascertained by the spectral study of the reaction (scheme 2.5).



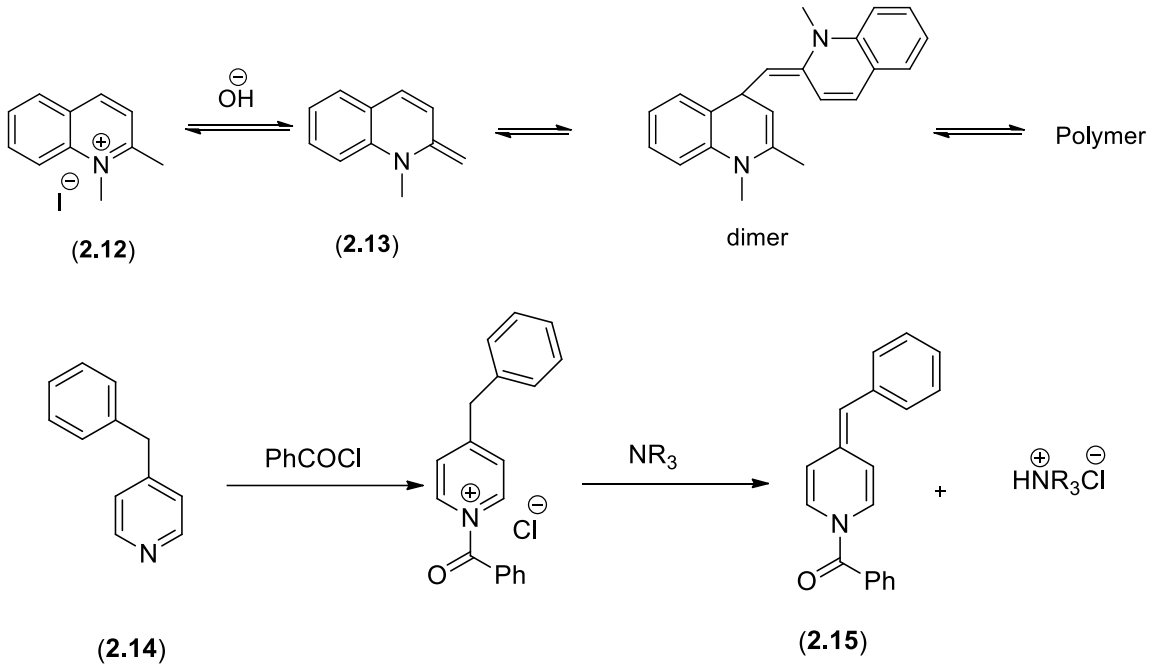
(**2.10**) (**2.11**)

Scheme 2.5 Examples of anhydrobase from a pyridine-N-oxide.

Decker and coworker have found that the anhydrobase (**2.13**) obtained from quinaldine methiodide (**2.12**) is quite stable and could be recrystallized from benzene-

petroleum ether; however, it also forms dimers and polymers in solution depending on the solvent concentration, and temperature.

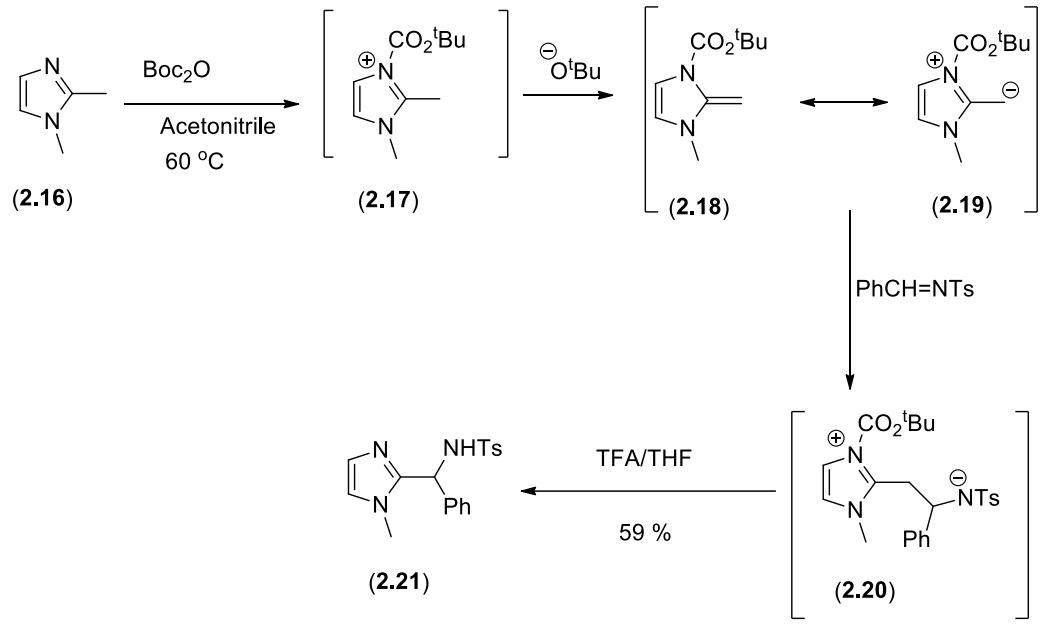
The stability of anhydrobases generated from quaternary pyridinium salts is increased by the presence of electron withdrawing groups. For example, Ernst Anders and co-workers have synthesized the relatively stable anhydrobase (**2.15**) by acylation of the 4-benzyl pyridine (**2.14**) with acyl chloride followed by treatment with trialkyl amine as base. [51]



Scheme 2.6 Examples of stable anhydrobases.

Other hetero-aromatic compounds like imidazoles, benzothiazoles, and benzimidazoles also exhibit the ability to form anhydrobase intermediates on treatment of their corresponding salts with strong bases.[52, 53] For example, Hlasta and co-workers

successfully demonstrated that 2-substituted azole (**2.21**) was formed when N-methyl-2-methyl imidazole (**2.16**) was treated with benzaldehyde in the presence of Boc_2O via the intermediate azolium ylide (**2.18**) (scheme 2.7).

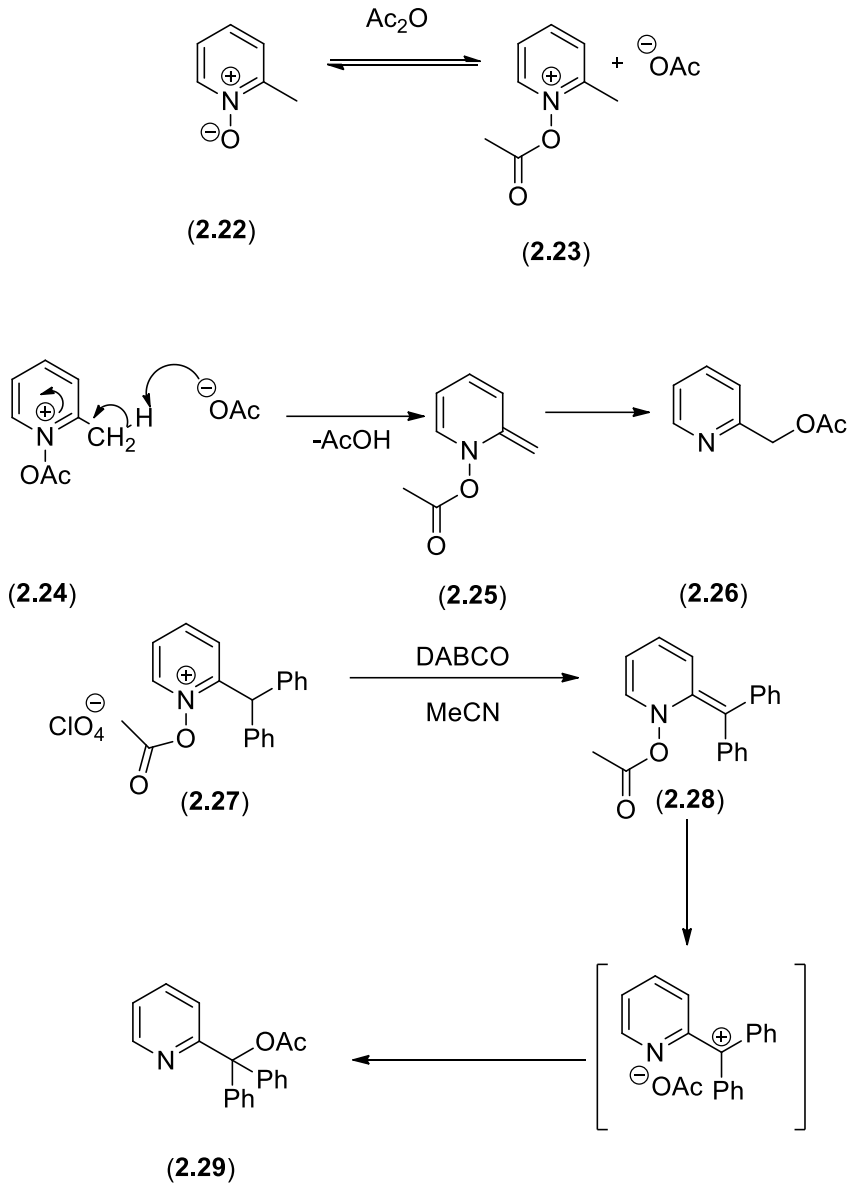


Scheme 2.7 Synthesis of 2-substituted azoles from imidazole.

2.3 Reactivity and synthetic applications of anhydrobases

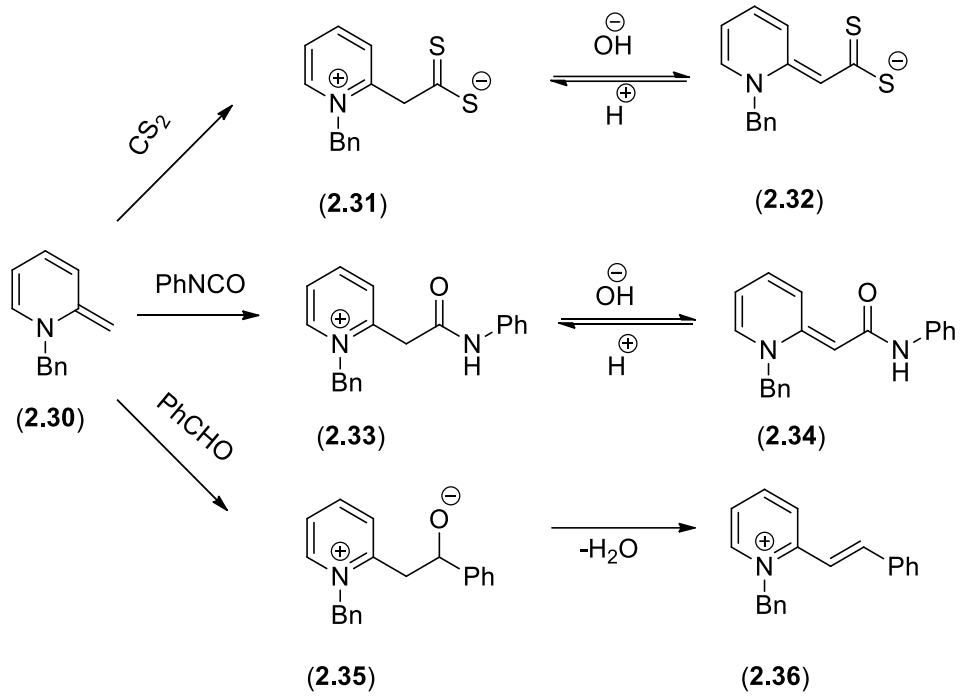
As determined from quantum mechanical model studies, anhydrobases can act as good electrophiles or nucleophiles. Kozuka and coworkers have extensively studied the kinetics of reaction of N-oxides of pyridine and quinolines with acylating agents like acetic anhydride leading to substitution at the α-carbon atom. Pyridine-N-oxide (**2.22**) was converted to 2-pyridyl acetate (**2.26**) when heated in acetic anhydride. Acetic anhydride reacts with pyridine N-oxide to give the corresponding pyridinium salt (**2.23**),

which then loses a proton to generate the intermediate anhydrobase (**2.25**). Further heterolytic cleavage of the N-O bond and intramolecular attack of the acetate ion provides the desired product (**2.26**).[54] The intramolecular attack of acetate ion was also supported by Markgraf and coworkers, where in they elucidated the pathway by a combination of ^{18}O labeling studies and the conversion of 1-acetoxy-2-benzhydrylpyridinium perchlorate (**2.27**) to the desired acetylated product (**2.29**) by a base (DABCO) other than added acetate ion.[55]



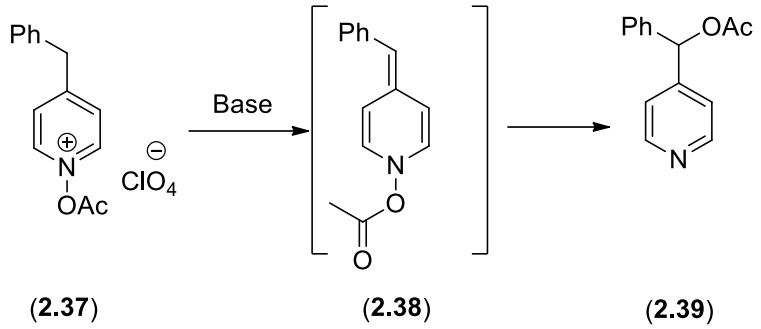
Scheme 2.8 Mechanism of α-acylation of picoline-N-oxide derivatives.

Electrophilic reagents like isocyanates, isothiocyanates, carbon disulfide, and aromatic aldehydes add to the methylene group of the anhydrobase (**2.30**) in inert solvents to give the corresponding adducts (**2.32, 2.34, 2.36**) (scheme 2.9).[56]



Scheme 2.9 Reactions of anhydrobase with electrophilic reagents.

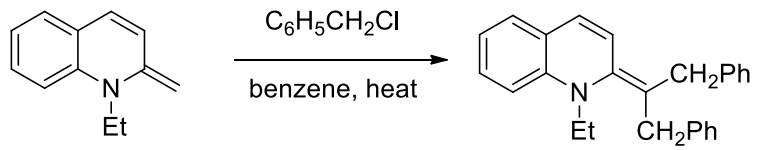
Traynelis and coworkers have examined the reaction of 1-acetoxy-4-benzylpyridinium perchlorate (**2.37**) and triethylamine spectroscopically and provided UV evidence for the intermediate anhydrobase, 1-acetoxy-4-benzal-1, 4-dihydropyridine (**2.38**) to give acylated product (**2.39**). The UV visible spectrum of the anhydrobase intermediate (**2.38**) in acetonitrile showed an absorption maximum at 352 nm (absorbance 0.780) and remained constant for 10 min, but by 25 min it had decreased markedly due to its lower stability in solution.[50]



(**2.37**) (**2.38**) (**2.39**)

Scheme 2.10 UV support for anhydrobase formation.

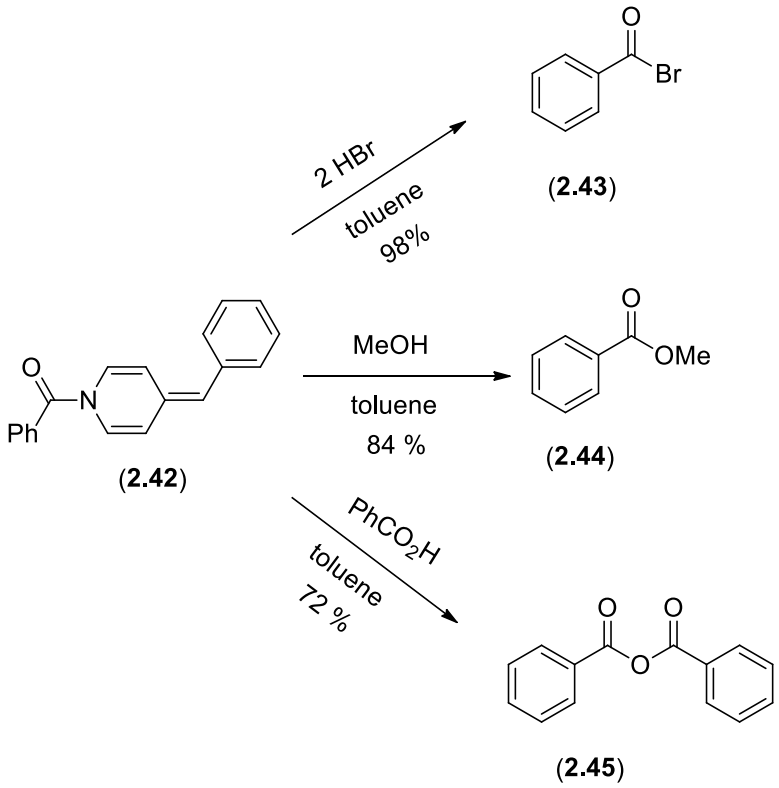
It has been noted that, like acylation, alkylation of the anhydrobase takes place at the carbon atom. Chichibabin observed that treatment of the anhydrobase 1-ethyl-2-methylene-1, 2-dihydroquinoline (**2.40**) with benzyl chloride in benzene resulted in formation of dibenzylated anhydrobase (**2.41**) immediately as shown in scheme 2.11.



(**2.40**) (**2.41**)

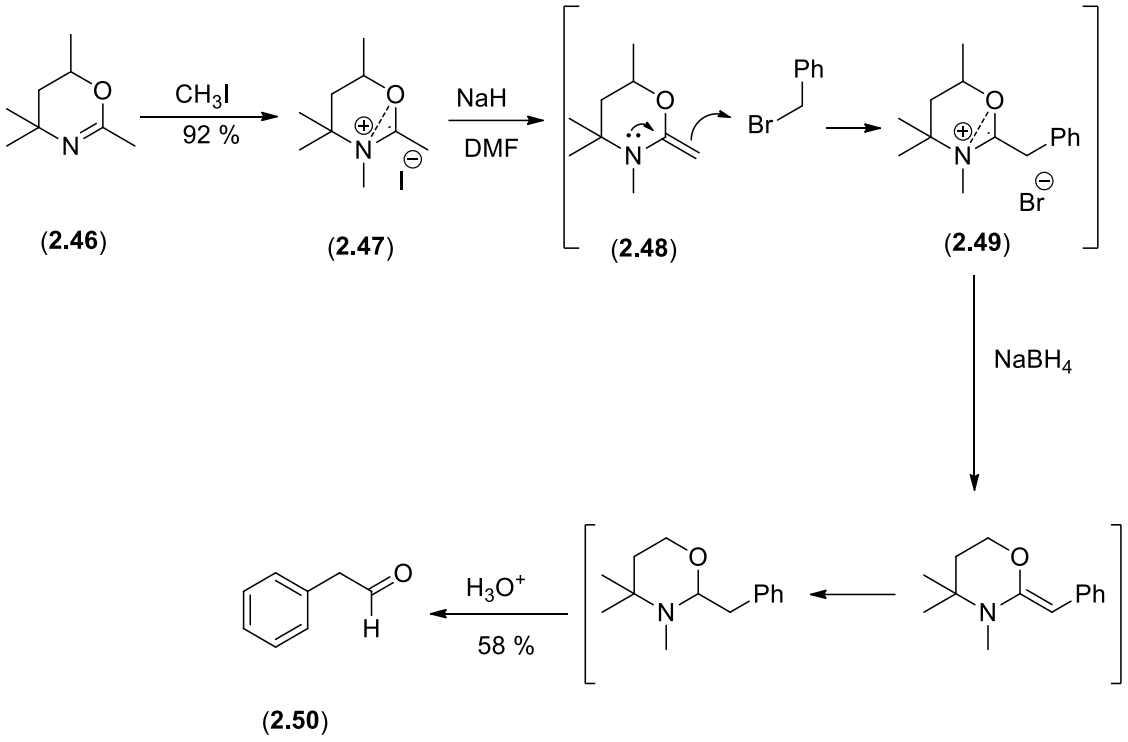
Scheme 2.11 Alkylation of anhydrobase.

On the other hand anhydrobase (**2.42**) reacts with nucleophiles through transfer of the N-benzoyl group. Thus, reaction with HBr gengerates the corresponding acyl bromide (**2.43**), reaction with an alcohol gives the ester (**2.44**) and reaction with acids gives the corresponding anhydride (**2.45**) (scheme 2.12).[51]



Scheme 2.12 Examples of reactions of anhydrobase.

Meyers and co-workers have successfully demonstrated the use of an oxazine anhydrobase intermediate in the two carbon homologation of alkyl halides to give the corresponding aldehyde. 2-Methyldihydro-1, 3-oxazine (**2.46**), on reaction with methyl iodide, gives the salt (**2.47**). Addition of NaH gives the unstable intermediate anhydrobase (**2.48**). This anhydrobase undergoes reaction with added alkyl halide to give (**2.49**), which, on further reduction and hydrolysis, provides the homologated aldehyde (**2.50**) (scheme 2.13).[57]

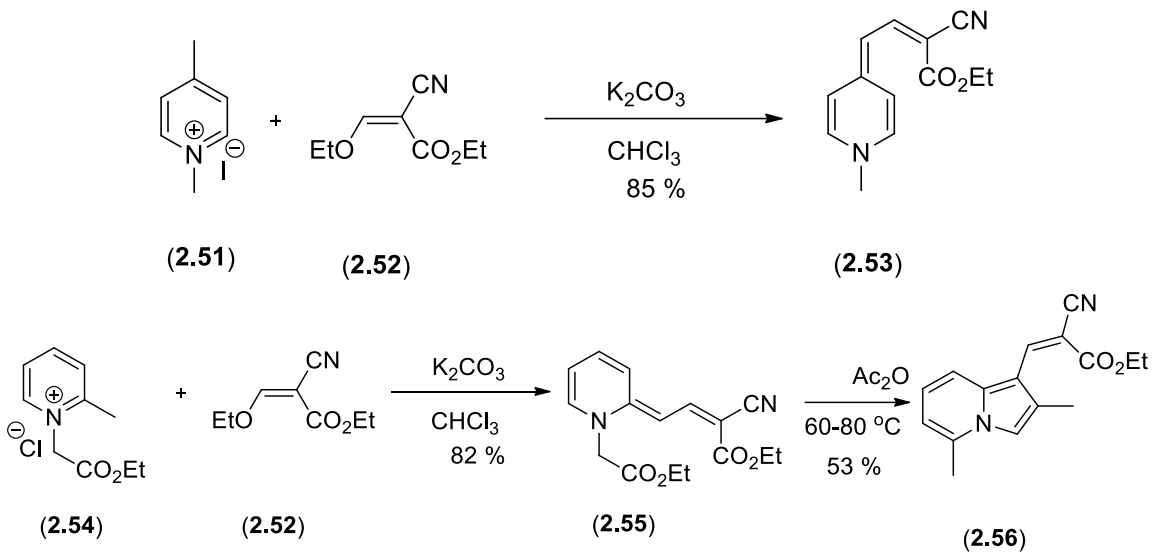


(**2.46**) (**2.47**) (**2.48**) (**2.49**) (**2.50**)

Scheme 2.13 Homologation of alkyl halide to aldehyde via oxazine anhydrobase.

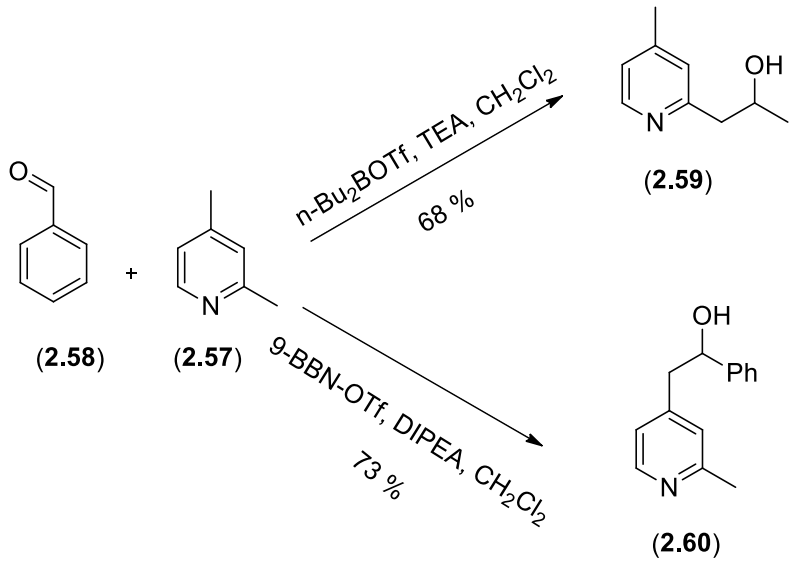
Kakehi and coworkers investigated the reactions of 1-alkylpyridinium salts carrying a 2- or 4-methyl or amino substituent with ethoxymethylene compounds activated by electron withdrawing groups. In the presence of alkali these reactants gave 2 or 4-allylidenedihydropyridine derivatives in fairly good yield.[58] Pyridinium salt (**2.51**) was prepared by treating 4-picoline with the methyl iodide and was used without purification. The mixture of pyridinium salt (**2.51**) and ethyl ethoxymethylenecyanoacetate (**2.52**) when treated with potassium carbonate in chloroform provided allylidene-1, 4-dihydropyridine (**2.53**). Similarly, when a mixture of 1-(ethoxycarbonylmethyl)-2-picolinium bromide (**2.54**) and ethyl ethoxymethylenecyanoacetate (**2.52**) was treated with postassium carbonate in chloroform at room temperature the allylidene-1, 4-dihydropyridine (**2.55**) was obtained

as a crystalline compound in 57% yield. Further elaboration of this dihydropyridine provided the indolizine derivative (**2.56**) in good yield (scheme 2.14).[39]



Scheme 2.14 Novel synthetic methods for indolizine derivatives.

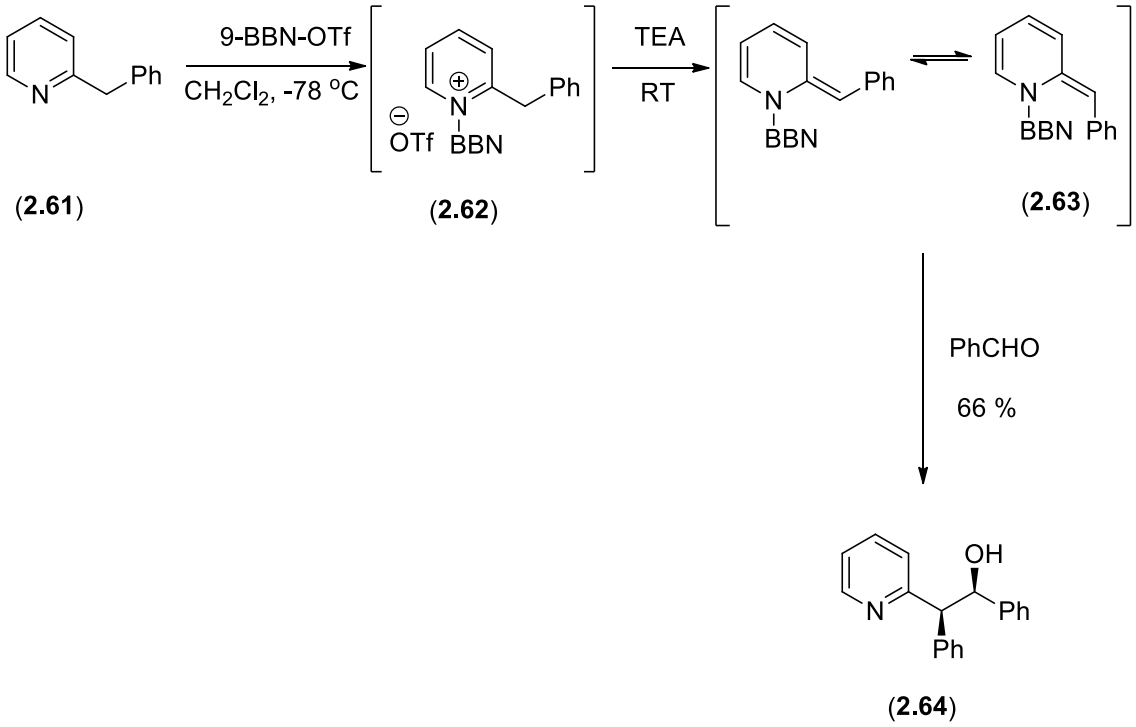
Hamana and coworkers have explored stero- and regio-selectivity in the reaction of alkylpyridines with benzaldehyde in presence of Lewis acid (alkyl boranes) and organic amine bases. They have successfully demonstrated that substitution at the 2- or 4-position of 2, 4-lutidine could be controlled by the combination of dialkylboryl triflate and an aliphatic tertiary amine. In the presence of di-n-butylboryl triflate and triethyl amine, the 2-methyl group of 2, 4-lutidine (**2.57**) exclusively reacted with benzaldehyde (**2.58**) giving compound (**2.59**) (scheme 2.15).



Scheme 2.15 Regio-selective addition to aldehyde.

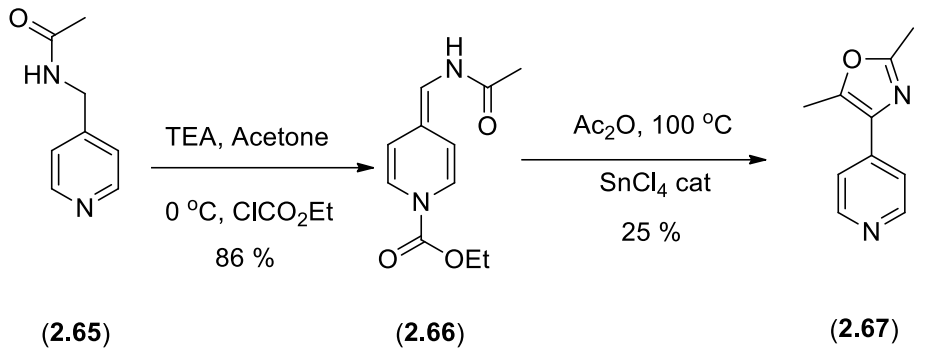
In the presence of 9-BBN-OTf and DIPEA, however, the reaction only took place at the 4-methyl group, giving compound (**2.60**) (scheme 2.15).[59] The reason for the sharp difference in reactivity was not fully elucidated, but it may be due to the fact that the selection of deprotonation from 2- or 4-methyl group is influenced by the mutual bulkiness of attacking tertiary amine and the alkyl group attached to the boron atom.

The erythro-selectivity was observed when the alkylpyridine (**2.61**) was treated with 9-BBN-OTf to provide the pyridinium salt (**2.62**). In the presence of triethylamine anhydrobase (**2.63**) is formed, which then adds to benzaldehyde via the z-form to give the erythro isomer (**2.64**) (scheme 2.16).



Scheme 2.16 Stereo-selective anhydrobase addition to benzaldehyde.

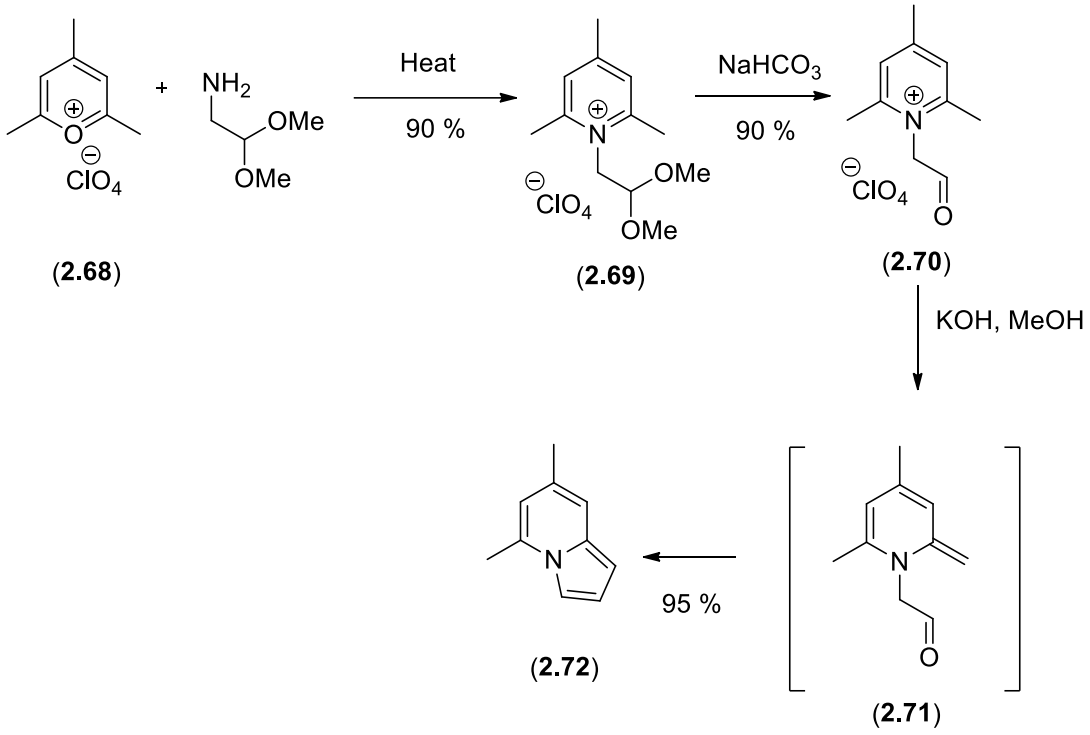
Brana and coworkers successfully demonstrated that 4-acylaminomethyl-1-alkylpyridinium salts on heating with acetic anhydride, give dimerized products or oxazoles via the formation of anhydrobase intermediates. Hence they prepared a series of stable anhydrobases and achieved a good synthetic procedure to obtain 4-(4-pyridyl)oxazoles.[60] Anhydrobase (**2.66**) was synthesized by the reaction of 4-(acetylaminomethyl)pyridine (**2.65**) with ethyl chloroformate and TEA in acetone. Heating **2.66** with acetic anhydride at 100 °C in the presence of a Lewis acid ($SnCl_4$) as catalyst gave the corresponding oxazole (**2.67**) in decent yield (scheme 2.17). Some of these oxazoles have shown interesting antitumoral activity.[61]



(**2.65**) (**2.66**) (**2.67**)

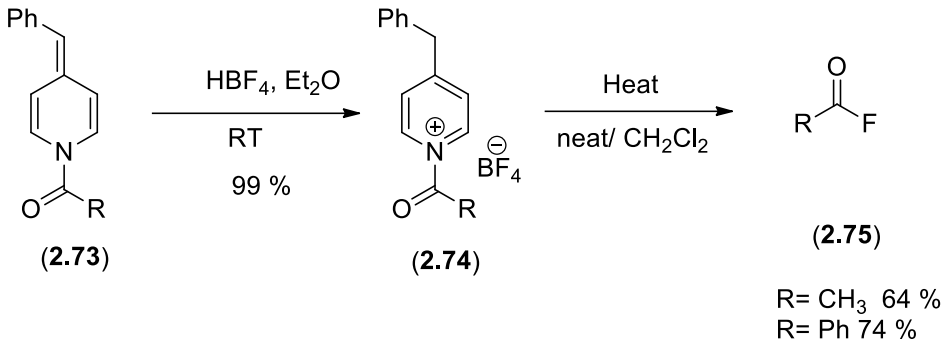
Scheme 2.17 Synthesis of oxazoles.

Anotnie and coworkers have successfully used anhydrobase intermediates in an intramolecular reaction for the synthesis of indolizine derivatives. The pyridinium salt (**2.69**) formed from the reaction of pyrilium salt (**2.68**) and aminoacetaldehyde dimethylacetal was hydrolysed to the corresponding aldehyde (**2.70**). Intramolecular dehydrating condensation with a 2-methylene group in the presence of alkali affords the indolizine derivative (**2.72**) (scheme 2.18).[62]



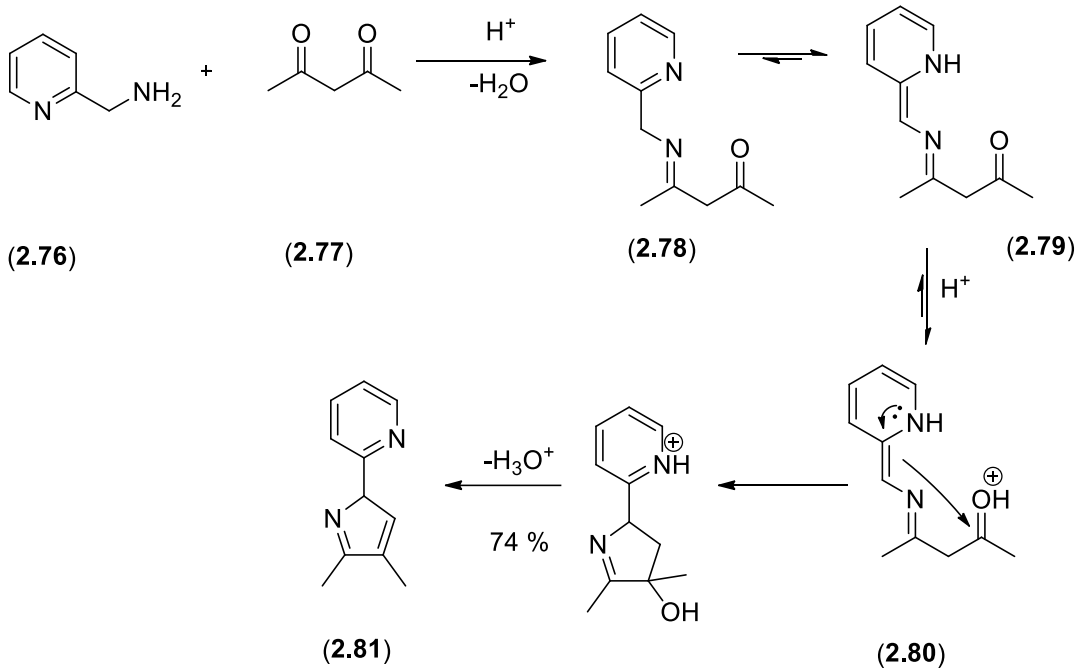
Scheme 2.18 Indolizine synthesis from pyrilium salt.

Wagner and coworkers have demonstrated that 1-acyl-4-benzylpyridinium tetrafluoroborates (**2.74**) generated quantitatively in situ from 1-acyl-4-alkylidene-1, 4-dihydropyridine (**2.73**) and HBF_4 exhibit an interesting unexpected thermal instability which allows the convenient synthesis of carboxylic acid fluorides (**2.75**).[63]



Scheme 2.19 Synthesis of acid fluorides from anhydrobases.

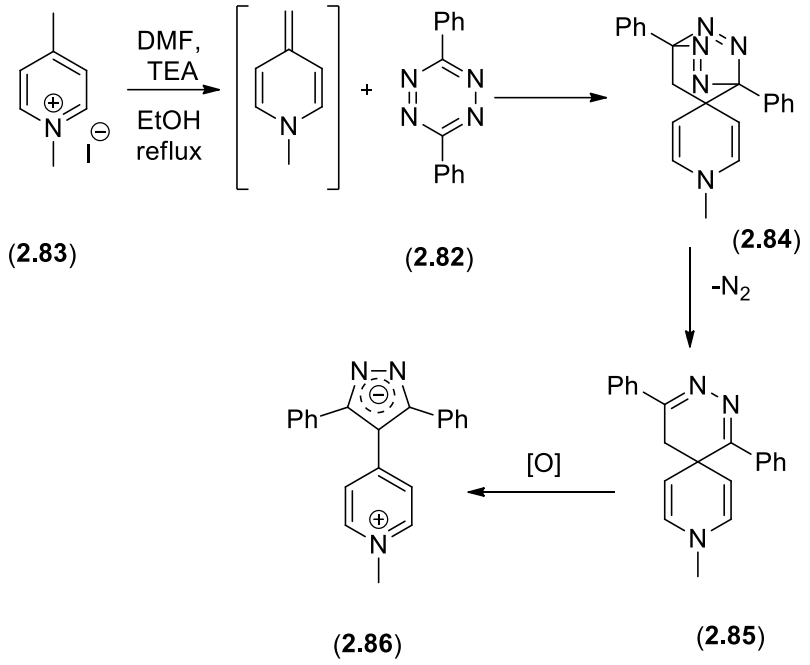
McNeill and coworkers have shown that anhydrobases can be used as synthetic intermediates in the synthesis of substituted pyridylpyrroles during the novel condensation of 2-(aminomethyl) pyridine and 1, 3-diones. A solution of 2-(aminomethyl) pyridine (**2.76**) and the diketone (**2.77**) in the presence of catalytic *p*-toluene sulfonic acid gave the β-iminoketone intermediate (**2.78**) which is in equilibrium with the enamine tautomer (**2.79**). The enamine tautomer (anhydrobase) intermediate attacks the ketone carbonyl to give the intermediate (**2.80**), which undergoes loss of water to give the pyridylpyrrole compound (**2.81**).[64]



(**2.76**) (**2.77**) (**2.78**) (**2.79**) (**2.80**) (**2.81**)

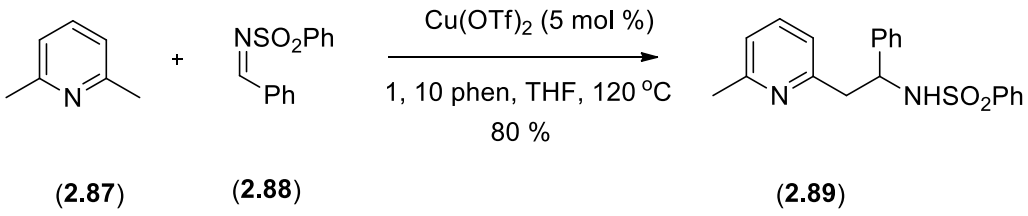
Scheme 2.20 Synthesis of pyridylpyrrole derivatives.

Zhou and coworkers have presented an alternative route for the Carboni-Lindsey reaction by the C, C-cycloaddition of an alkene to s-tetrazine instead of N-N cycloaddition to form 1, 2, 4-triazole derivatives as shown in scheme 2.21. When a mixture of s-tetrazine (**2.82**) and 1, 4-dimethyl pyridinium iodide (**2.83**) and TEA were reacted in DMF, the major product obtained was the pyrazole derivative (**2.86**).[65]



Scheme 2.21 Cycloaddition of anhydrobase to tetrazine.

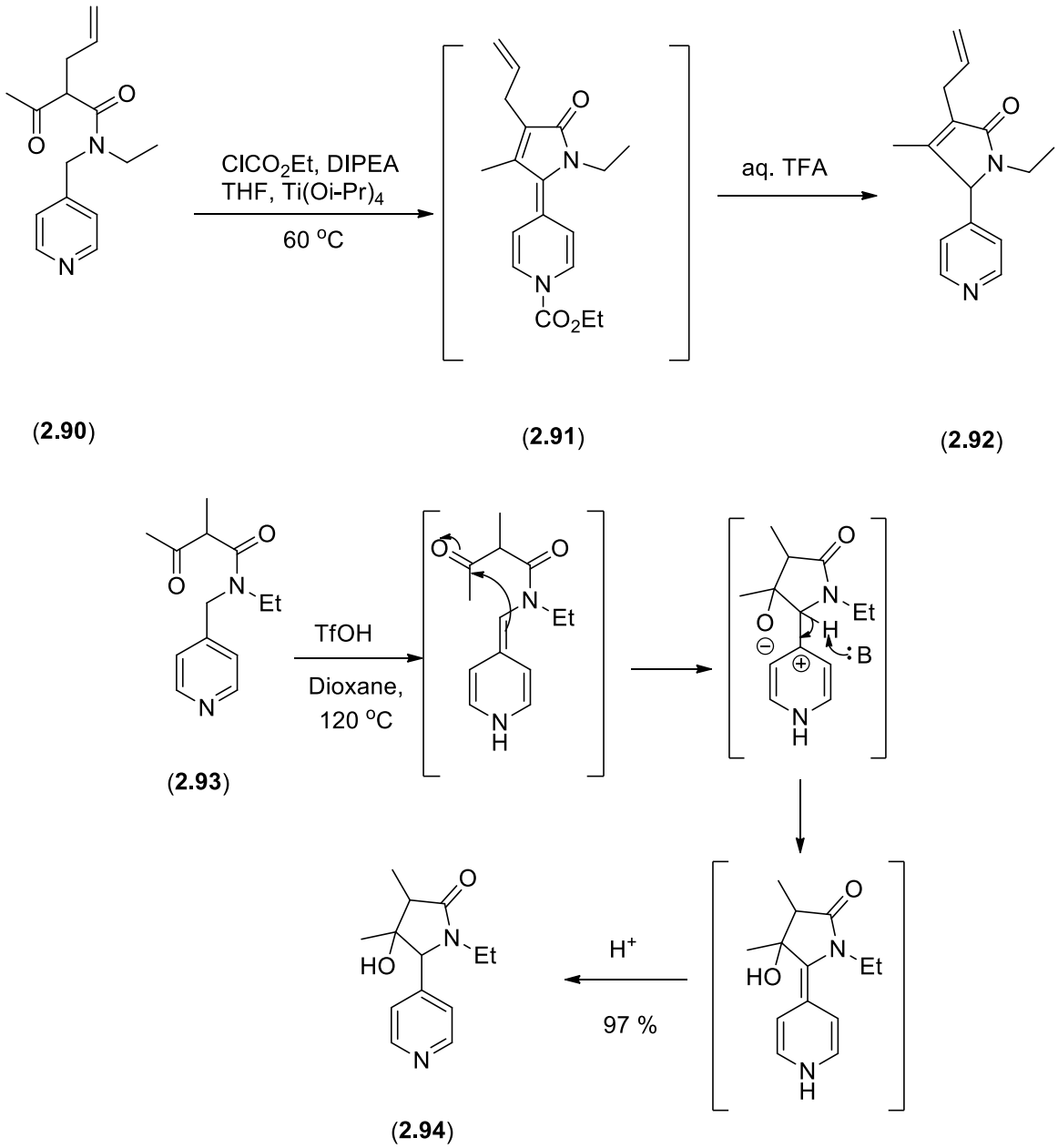
Rueping and coworkers have developed a novel protocol for Mannich type addition of α and ϒ alkyl pyridines to activated imines in the presence of a Lewis acid for the synthesis of various functionalized heterocycles. These transformations relied on the ability of the Lewis acid reagents to convert the α or ϒ-methyl group in the pyridine to a reactive nucleophile. The reaction of 2, 6-dimethyl pyridine (**2.87**) with the N-sulfonyl aldimine (**2.88**) in presence of $Cu(OTf)_2$ as Lewis acid and 1, 10- phenanthroline in THF gave the addition product (**2.89**) (scheme 2.22).[66]



(**2.87**) (**2.88**) (**2.89**)

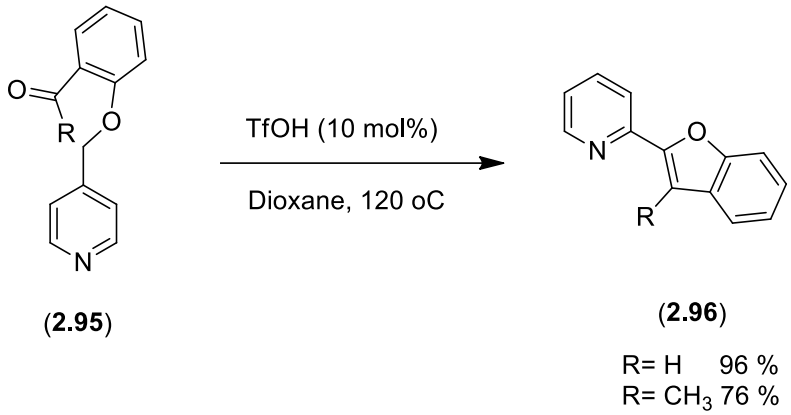
Scheme 2.22 Lewis acid catalyzed addition.

Pigge and coworkers uncovered a novel beneficial effect of the added Lewis acid in presence of Hunig's base in promoting intramolecular reactions of 4-alkylpyridines possessing an electrophile in the side chain. These substrates underwent intramolecular addition via anhydrobase intermediates, which on further manipulation gave functionalized pyridyl lactams. In particular the treatment of 4-alkylpyridine (**2.90**) with titanium isopropoxide, along with DIPEA and ethyl chloroformate in THF cleanly gave rise to putative anhydrobase intermediate (**2.91**). Treatment with aqueous trifluoroacetic acid (TFA) and heating resulted in the formation of pyridyl lactam (**2.92**) in high yields (scheme 2.23).[67] Pigge and coworkers have also demonstrated that 4-alkylpyridine substrates such as (**2.93**) react in an intramolecular fashion in the presence of Bronsted acid catalyst to give pyridyl lactam compound (**2.94**) in 97% yield (as a mixture of diastereomers).



Scheme 2.23 Intramolecular anhydrobase addition.

This work has been extended to include the synthesis of benzofuran compounds (**2.96**) as shown in scheme 2.24.

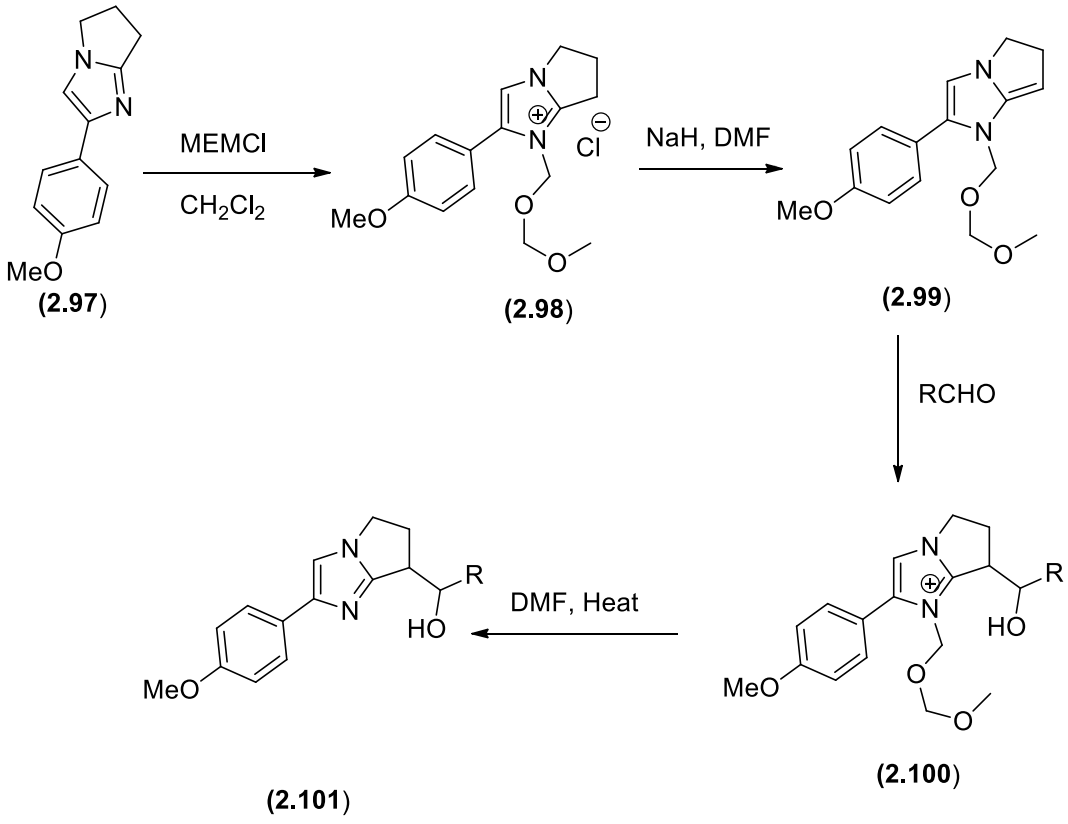


(**2.95**) (**2.96**)

R= H 96 %
R= CH_3 76 %

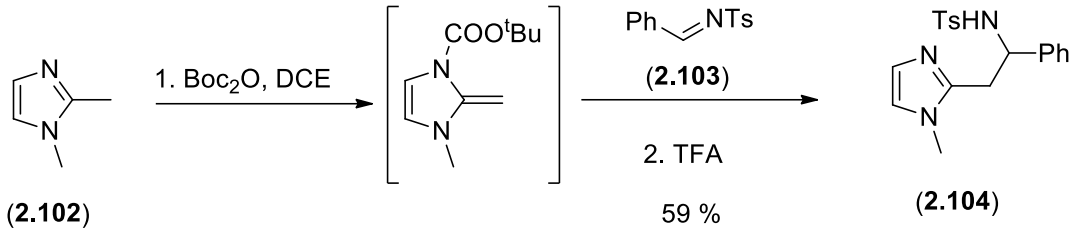
Scheme 2.24 Benzofuran synthesis (unpublished work from Pigge group).

Anhydrobase chemistry has also been extended to other heterocyclic compounds. Gallagher and coworkers have successfully functionalized the C-7 position of dihydropyrolo[1, 2, a]imidazole. Imidazole (**2.97**) is converted to quaternary imidazolium salt (**2.98**) using MEMCl. This imidazolium salt, on treatment with base, reacted with aldehydes via anhydrobase intermediate (**2.99**) to give the corresponding products (**2.101**) (scheme 2.25).[53]



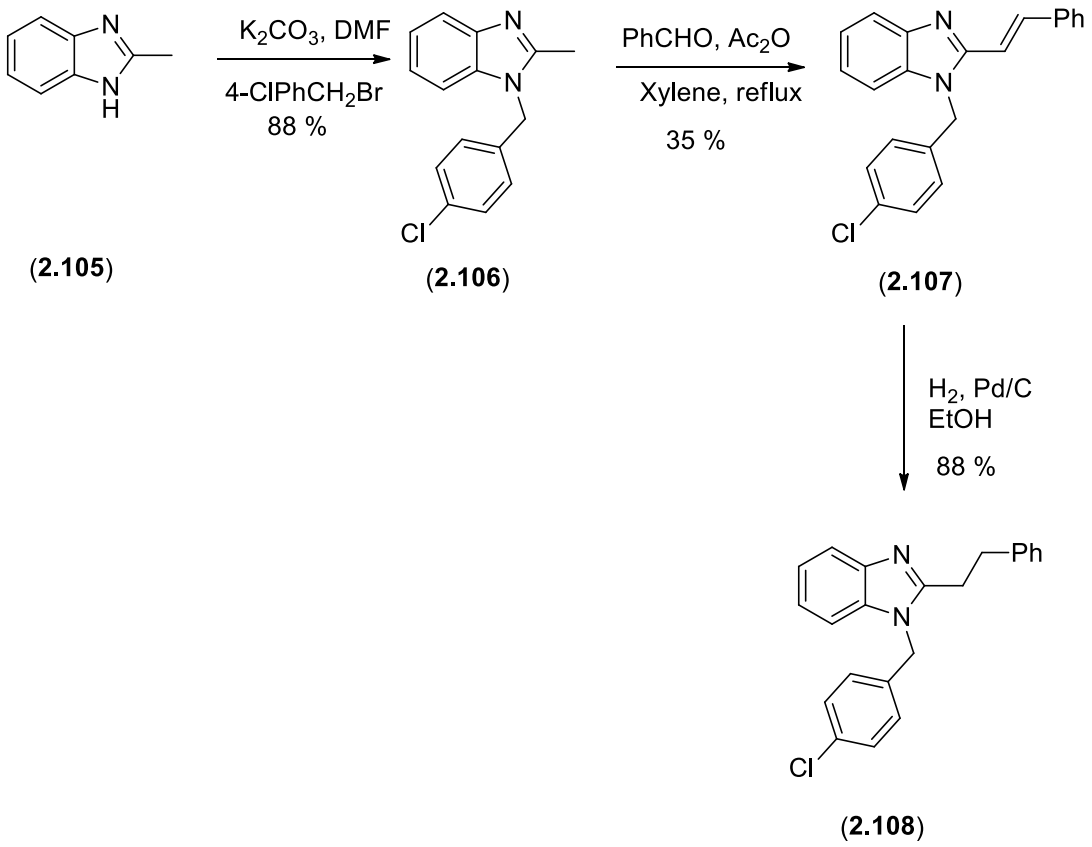
Scheme 2.25 Anhydrobase of imidazolium salt.

Hlasta *et al.* have successfully obtained homologated 2-alkylimidazole adduct (**2.104**) by treating 1, 2-dimethylimidazole (**2.102**) with benzaldehyde sulfonylimine (**2.103**) and $(Boc)_2O$ under microwave conditions (scheme 2.26).[68]



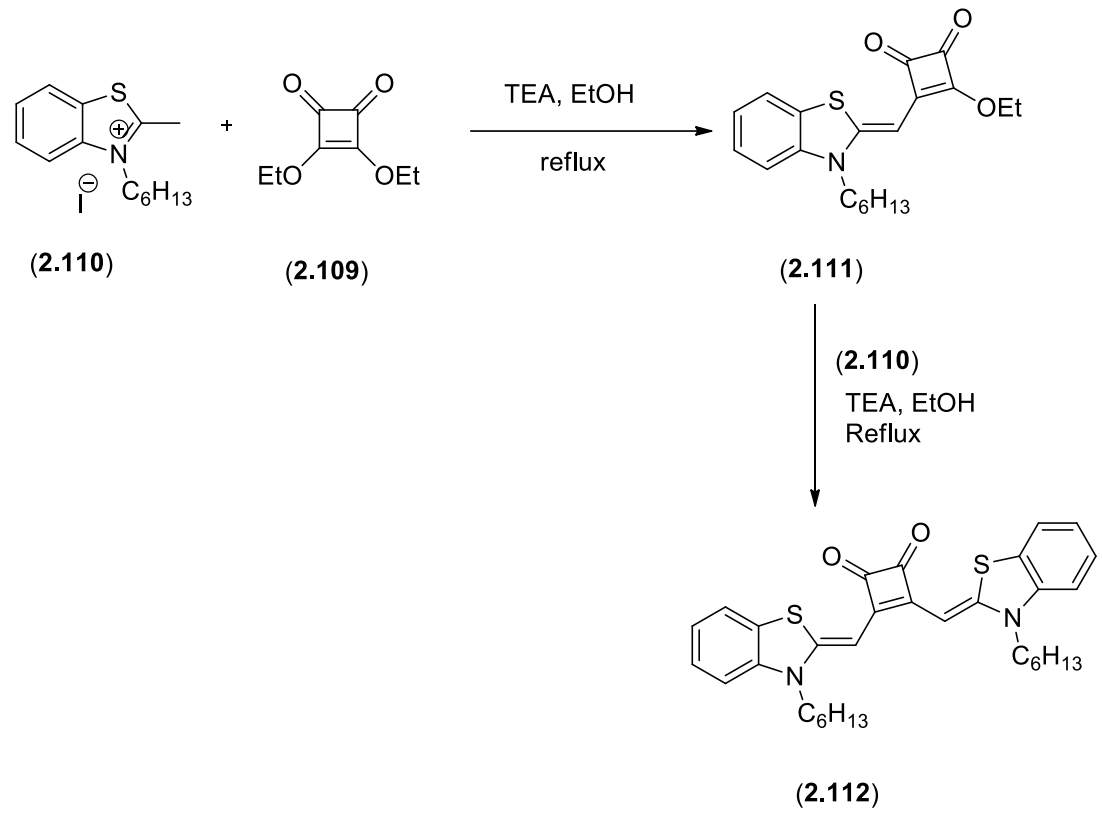
Scheme 2.26 Anhydrobase of imidazolium salt.

Similarly, Beaulieu and coworkers have synthesized various benzimidazoles for the treatment of allergic rhinitis using the nucleophilicity of an intermediate anhydrobase. The 2-phenethyl benzimidazole (**2.107)** was prepared from the 2-methylbenzimidazole (**2.105**) by alkyation followed by condensation with a benzaldehyde in the presence of acetic anhydride. Further reduction gave the benzimidazole substrate (**2.108**).



Scheme 2.27 Example of benzimidazole derivative.

Rizzato and coworkers have developed a facile direct synthesis of 1, 2-squaraines by the reaction of ethyl squarate (**2.109**) with the benzothiazole salt (**2.110**) in presence of TEA to give compound (**2.112**).[69] The benzothiazole anhydrobase is formed by deprotonation of the methyl group. Nucleophilic addition of this species to the vinylogous ester (**2.109**) and a second deprotonation gives **2.111**. A second substitution on the squaraine affords the bis(benzothiazole) (**2.112**) (scheme 2.28).



Scheme 2.28 1, 2-Squaraine synthesis via anhydrobase intermediates.

2.4 Conclusion

Anhydrobases of heteroaromatic rings provide an array of reactions as summarized in the examples above. This chemistry has been used for the synthesis of building blocks used for natural product synthesis, as well as for the preparation of small molecules, ligands and functional materials. This powerful methodology of engaging anhydrobases in new bond-forming events gives chemists access to complex molecular frameworks in a direct and concise manner. There remains ample opportunity for the further development of anhydrobase chemistry, particularly in metal-mediated synthesis. Developing new procedures for harnessing the reactivity of anhydrobases may ultimately facilitate construction of novel medicinally relevant small molecules and natural products. The next chapter in this dissertation describes an approach to achieving this goal.

CHAPTER 3

GOLD CATALYZED INTRAMOLECULAR CYCLIZATION OF PYRIDINE ANHYDROBASES

3.1 Introduction

Substituted pyridines and their reduced analogues (e.g., dihydropyridines and piperidines) are privileged and important structural motifs encountered in pharmacophores in medicinal chemistry, natural products, pharmaceuticals and other pharmacologically active compounds (Figure 3.1).[70] Highly conjugated heterocycles provide the molecular basis for many synthetic dyes and fluorescent (or colorimetric) indicators and biological probes.[71] The structural complexity of aza-heterocycles is interesting from a synthetic standpoint as they often serve as synthetic building blocks in the construction of more elaborate organic architectures. Hence, methods for the synthesis of pyridine derivatives along with strategies for elaboration of readily available pyridines are valuable preparative tools.[4, 72]

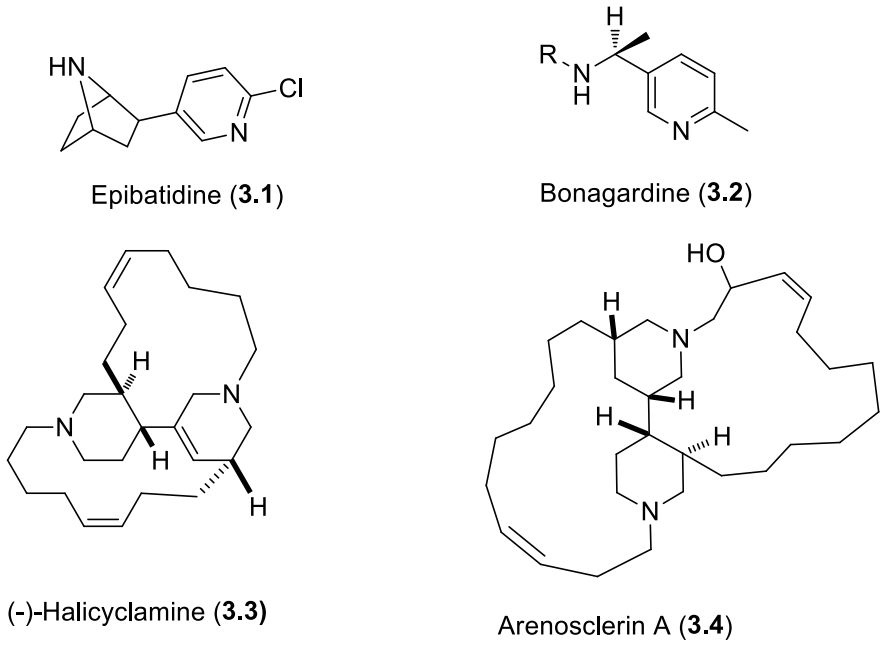


Figure 3.1 Selected aza-heterocycles of biological importance.

As described in chapter 2, activation of 2- and 4-alkylpyridines by N-acylation or alkylation will yield the corresponding anhydrobase under basic conditions by loss of a proton from the alkyl substituent as illustrated in Figure 3.2. Developing new methods to manipulate pyridine anhydrobase intermediates would then provide another means for construction of complex heterocyclic molecules of biological or pharmaceutical importance.[61] The proceeding chapter provided an overview of this topic, and additional examples are summarized below.

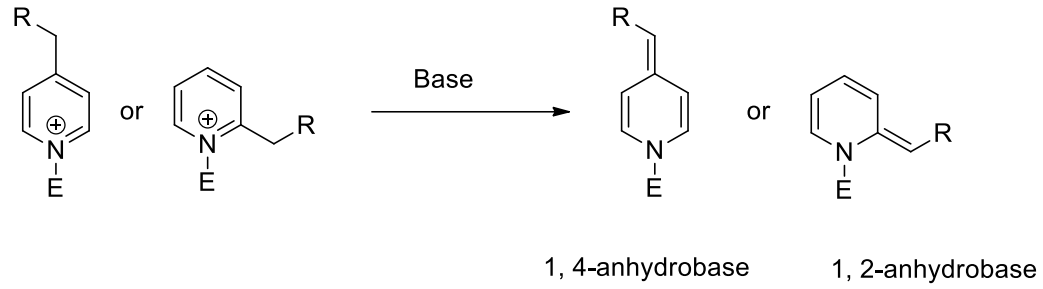
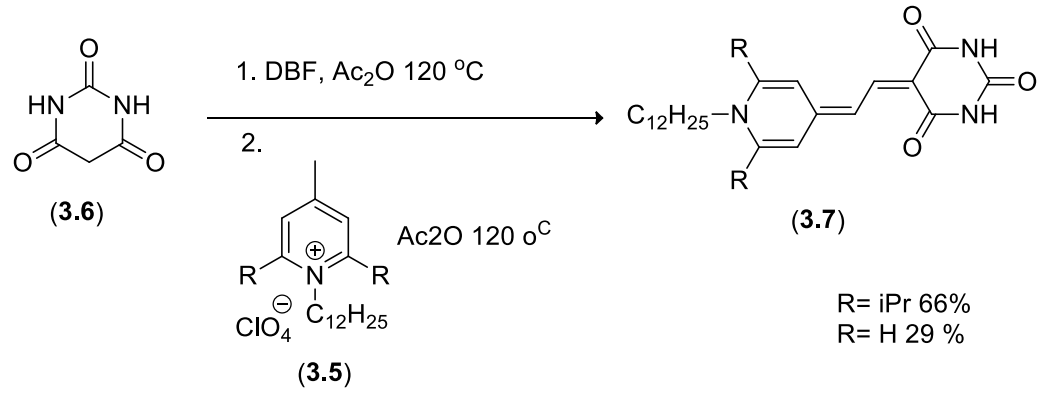


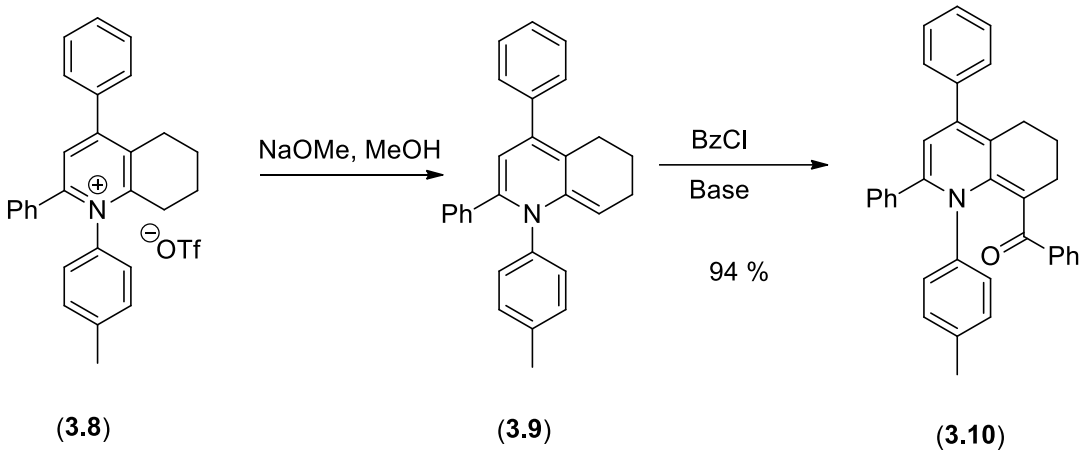
Figure 3.2 Anhydrobases of pyridinium salts.

Wurthner and coworkers reported the synthesis of merocyanine dyes containing imide functional groups to study hydrogen bonding to melamine receptors.[73] The activated pyridinium salt (**3.5**) reacted with barbituric acid (**3.6**) in presence of dibutylformamide (DBF) and acetic acid at 120 ^{o}C to give the merocyanine dye (**3.7**) in good yield (scheme 3.1).



Scheme 3.1 Synthesis of merocyanine dye.

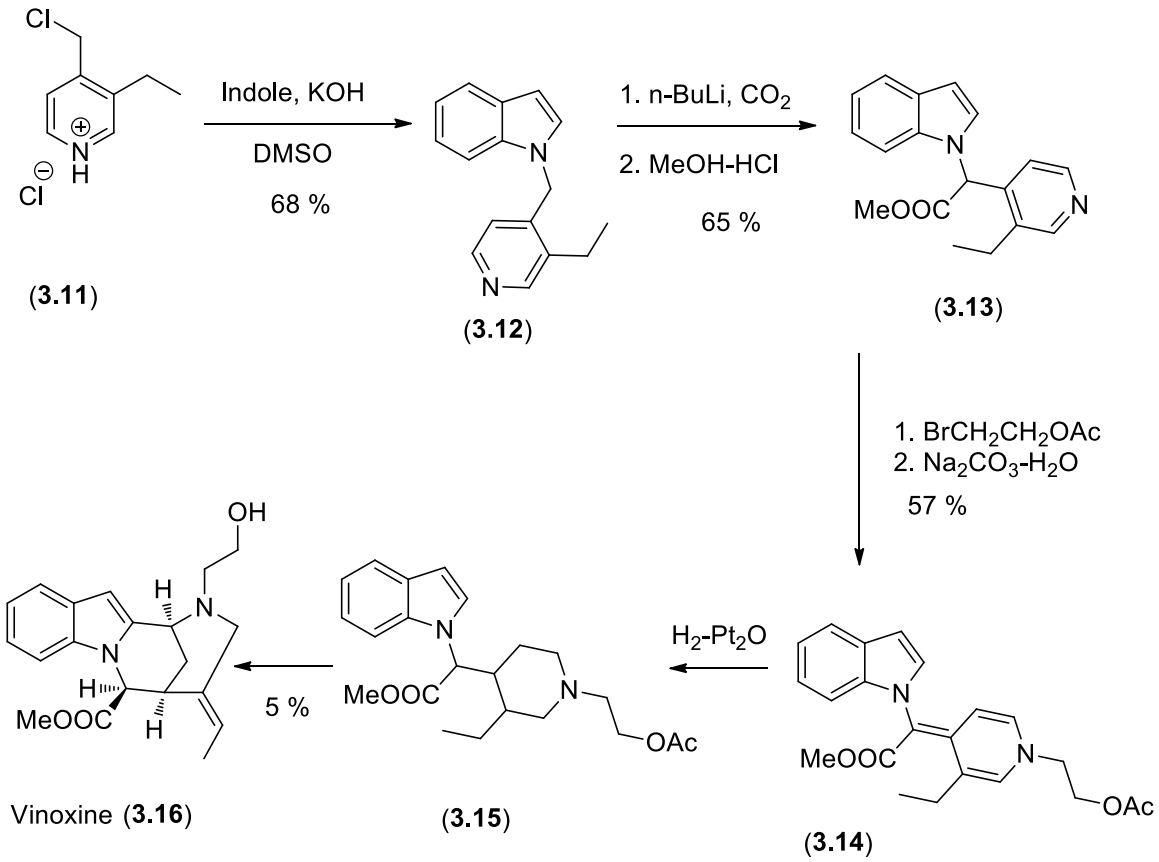
Katritzky and coworkers treated quinolinium salt **3.8** with sodium methoxide in methanol at room temperature to obtain an orange colored anhydrobase intermediate **3.9**, which, on further treatment with electrophiles such as benzoyl chloride under Schotten-Baumann conditions, generated the corresponding acylated anhydrobase **3.10** as represented in scheme 3.2. However it was found that very few of the so formed anhydrobases were stable and would rearrange back to the starting materials.[74]



(**3.8**) (**3.9**) (**3.10**)

Scheme 3.2 Acylated anhydrobase synthesis.

Bosch and coworkers utilized an anhydrobase intermediate in their attempt to synthesize vinoxine, a tetracyclic indole alkaloid (**3.16**). Starting from 3-ethyl-4-picolylchloride hydrochloride (**3.11**), the anhydrobase intermediate (**3.14**) was obtained as shown in scheme 3.3.[75] Anhydrobase **3.14** was then converted to the reduced intermediate **3.15** in the presence of H_2-Pt_2O. Further manipulation then provided the alkaloid vinoxine (**3.16**).

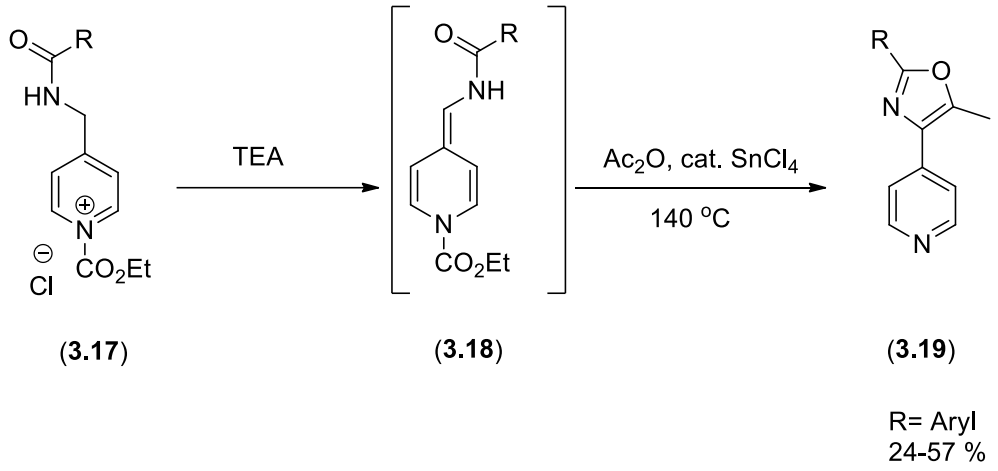


Scheme 3.3 Total synthesis of vinoxine.

In general, reports of anhydrobase intermediates in the synthesis of natural products are less common. Nonetheless, such compounds are intriguing potential nucleophiles and may offer new preparative routes for pyridine functionalization. Along these lines, we initiated a project aimed at uncovering new reactions of pyridine anhydrobases. We were interested in utilizing these anhydrobase intermediates as nucleophiles towards electrophilic substitution or Michael addition reagents.

3.2 Background

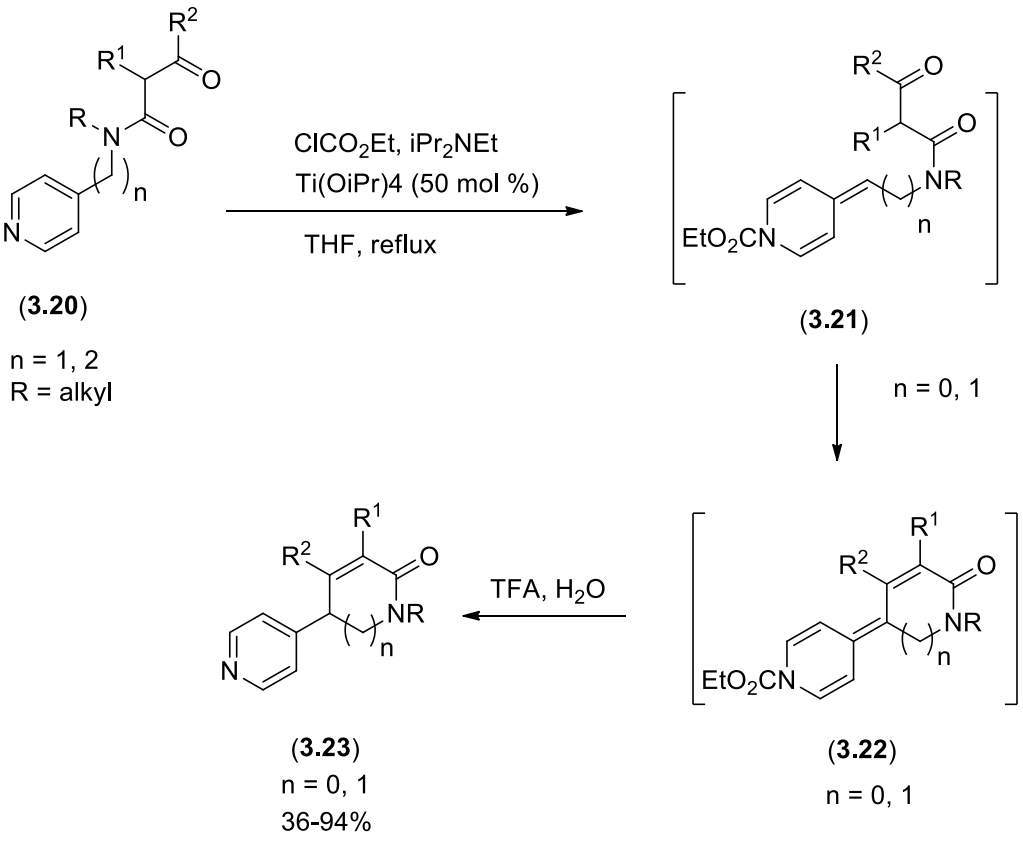
As discussed in chapter 2, Brana and coworkers found that treatment of 4-acylaminomethyl-1-alkyl pyridinium salts (**3.17**) with triethylamine (TEA) gave the anhydrobase (**3.18**), which on heating with acetic anhydride in the presence of tin tetrachloride ($SnCl_4$) provided the 4-(4-pyridyl)oxazole (**3.19**) in decent yields (scheme 3.4).[61]



(**3.17**) (**3.18**) (**3.19**)

Scheme 3.4 Synthesis of oxazoles.

Pigge and coworkers observed that carbonyl electrophiles tethered to 4-alkyl pyridine substrates underwent aldol like condensation involving the C-4 alkyl carbon, resulting in net cyclization at the pyridine benzylic position (scheme 3.5). This reaction is believed to proceed via the initial formation of anhydrobase intermediates **3.21** generated by the deprotonation of acylated pyridine species. Cyclization and loss of water affords a second anhydrobase **3.22** which is then re-aromatized upon exposure to aqueous acid to give the pyridyl substituted lactams **3.23** in moderate to good yields.[67]



Scheme 3.5 4-Pyridyl lactams via anhydrobase intermediate.

Recently, several groups have reported the ability of simple methyl pyridines (2- and 4-picoline) and related heterocycles (e.g., imidazole) to participate in intermolecular alodol and Mannich reactions in the presence of both Bronsted and Lewis acids, as well as by thermal activation.[76] However, the range of electrophiles engaged in these reactions are limited to functional groups like C=O or C=N only. Intrigued by the direct means that substituted pyridines might be obtained by engaging the intermeditae anhydrobases, we sought to expand the scope of these intramolecular cyclization reactions to include

alternate electrophiles. One class of alternative electrophile identified as potential participants in these reactions includes alkynes and alkynones (figure 3.3).

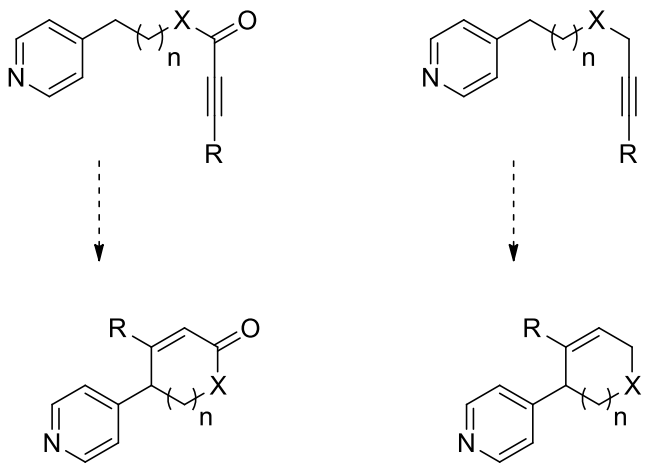
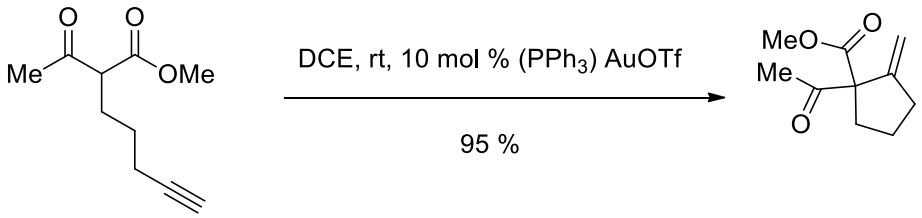


Figure 3.3 Proposed scheme for cyclization reactions.

There are many examples of nucleophilic addition to alkynes in the presence of transition metal catalysts (especially gold and platinum complexes). For example, shown in scheme 3.6, Toste and coworker engaged the acyclic β-ketoester (**3.24**) in a Conia-Ene reaction to obtain exocyclic compound **3.25** in good yield using a gold (I) catalyst.[77]



(**3.24**) (**3.25**)

Scheme 3.6 Gold catalyzed carbocyclization.

Given the resonance stabilization available to anhydrobase nucleophiles, we thought that these might serve as viable participants in metal catalyzed alkyne functionalization. During the reaction, we envisioned the formation of anhydrobase (**3.32**) which could be then reduced to get bis(piperidine) core. In this context, we became interested in investigating routes to bis(piperidines) and related substrates via intermolecular condensation of anhydrobase intermediates. Interestingly, the bis(piperidine) ring system is encountered in macrocyclic marine alkaloids such as halicyclamine A and B (**3.26** and **3.27**), arenosclerin A (**3.28**), haliclonacyclamine C (**3.29**), neopetrosiamine A (**3.30**) and saraines (**3.31**) (figure 3.4).[78] These macrocycles exhibit a wide range of biological activities such as anticancer, antibacterial, antiviral and antimalarial properties. Reports of their synthesis are less common because of their complex nature and the requirement for lengthy synthetic sequences.[79]

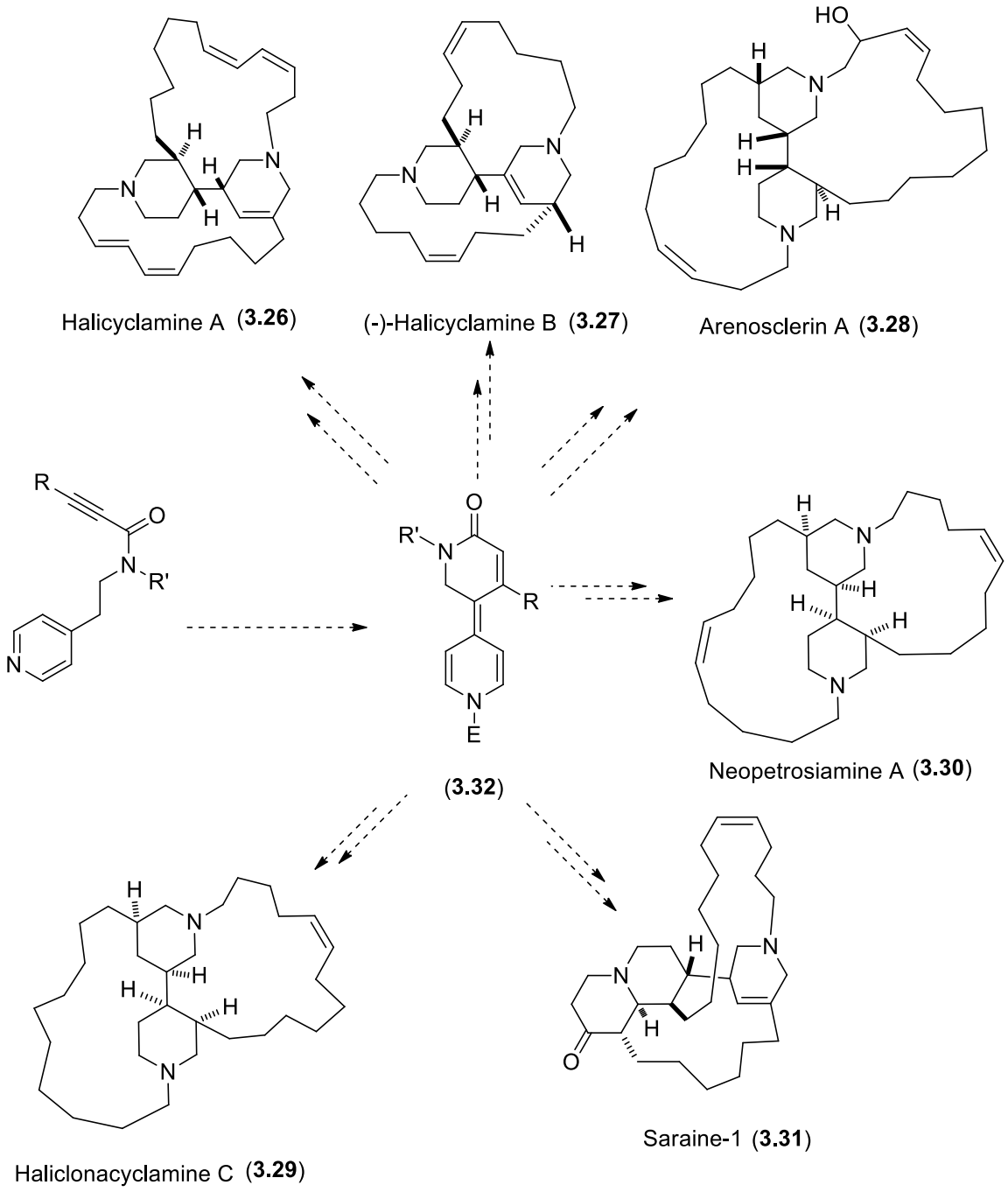
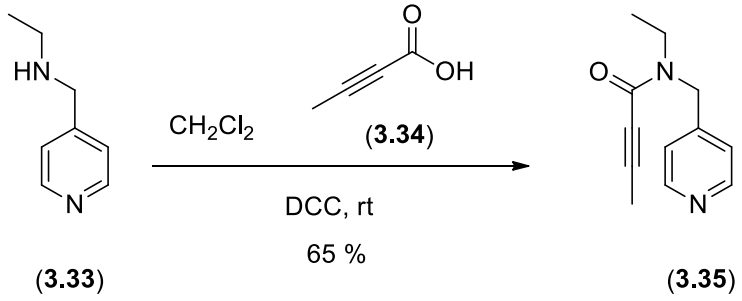


Figure 3.4 Marine alkaloids bearing bis(piperidine) core.

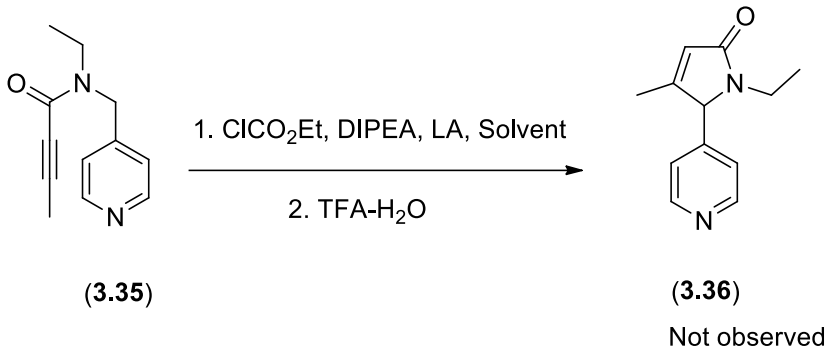
3.3 Results and Discussion

Considering the information available on carbocyclization reactions, we needed to carefully design substrates that would undergo either endo or exo cylclization according to Baldwin's rules. In this context, we envisioned that the tertiary amide **3.35** would be a good substrate to start with, as this material is easily prepared from commercially available N-ethyl aminomethylpyridine (**3.33**) as shown in scheme 3.7. It is set to undergo *endo-dig* cyclization following Baldwin's rules for ring closure.[80]



Scheme 3.7 Synthesis of tertiary amide.

It was envisoned that alkynone **3.35** on exposure to the conditions as outlined in scheme 3.5 would lead to the corresponding anhydrobase intermediate that is set to undergo 5-*endo-dig* cyclization with the attached electrophilic alkynone side chain (scheme 3.8). Several attempts were made to carry out this transformation in the presence of DIPEA and $ClCO_2Et$ with varying Lewis acids as listed in table 3.1. The reactions were also tried using different solvents (THF, dioxane, toluene), followed by workup under acidic conditions, but this resulted only in recovery of the starting material or decomposition of the substrate.



(**3.35**) (**3.36**)
Not observed

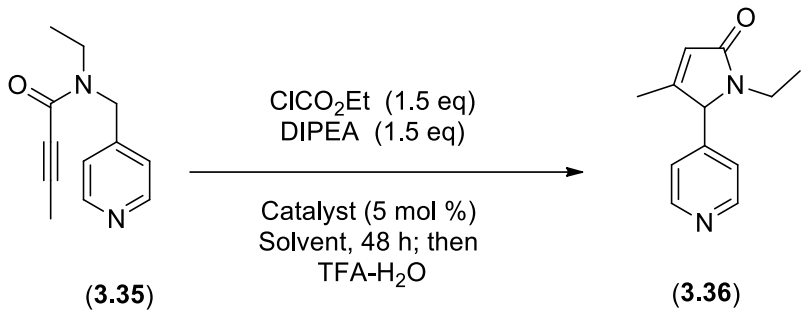
Scheme 3.8 Attempted Lewis acid catalyzed cyclization.

Table 3.1 Attempted Lewis acid conditions for cyclization.

Entry	Catalyst (10 mol %)	electrophile	Base	Solvent	Temperature (°C)	% Recovery of SM
1	Tf_2O	None	None	Dioxane	110-120	None
2	$Ti(O^i\text{-}Pr)_4$	$ClCO_2Et$	DIPEA	THF	60-65	50 %
3	TMSOTf	$ClCO_2Et$	DIPEA	Toluene	70-80	40 %
4	$Mg(OTf)_2$	$ClCO_2Et$	DIPEA	Dioxane	100-110	None
5	$Mg(OTf)_2$	--	DIPEA	Dioxane	100-110	50 %
6	$InCl_3$	$ClCO_2Et$	DIPEA	Dioxane	100-110	35 %
7	$InCl_3$	--	DIPEA	Dioxane	100-110	50 %
8	AgOTf	$ClCO_2Et$	DIPEA	Dioxane	100-110	None
9	AgOTf	--	DIPEA	Dioxane	100-110	40 %
10	$Cu(OTf)_2$	$ClCO_2Et$	DIPEA	Dioxane	100-110	None
11	$Cu(OTf)_2$	--	DIPEA	Dioxane	100-110	25 %
12	TMSOTf	$ClCO_2Et$	DIPEA	Dioxane	100-110	30 %
13	TMSOTf	--	DIPEA	Dioxane	100-110	45 %

As the attempts to perform Lewis acid-promoted cyclizations failed, we shifted our attention towards using transition metal catalysts (especially gold and platinum complexes) to further activate the alkyne electrophile. Gold and platinum catalyzed reactions of alkynes have gathered a great deal of attention in recent years.[81] Typically, stabilized or "soft" nucleophiles exhibit good reactivity toward electrophilic (alkynyl) gold or platinum complexes.[82] Considering the resonance stabilization available to anhydrobase nucleophiles, it was postulated that these species may also serve as "soft" nucleophiles and participate in metal-catalyzed alkyne functionalization. The initial efforts to engage the alkynone amide in metal catalyzed cyclization are summarized in table 3.2.

Table 3.2 Initial conditions for metal-catalyzed cyclization.

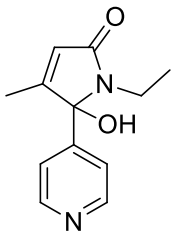


(**3.35**) (**3.36**)

Entry	catalyst[a]	solvent	temp. (°C)	% yield **3.36**[b]
1	A	PhMe	90	20
2	A	THF	reflux	20
3	A	MeCN	reflux	0
4	A	dioxane	reflux	0
5	B	PhMe	reflux	9
6	A	PhMe	rt[c]	20
7	A	THF	rt	30
8	A	DCE[d]	rt	15
9	A	MeCN	rt	0
10	A	dioxane	rt	12
11	A	CH_2Cl_2	rt	48
12	B	CH_2Cl_2	rt	9

[a]Catalyst A: 5 mol% $AuCl(PPh_3)$ + 5 mol% AgOTf; Catalyst B: 5 mol% $PtCl_2$ + 5 mol% AgOTf. [b]isolated yield. [c]Room temperature. [d]1,2-Dichloroethane.

Initially, the effect of in-situ generated gold(I) and platinum(II) triflate from reaction of the corresponding metal chlorides and silver triflate (AgOTf) was examined in different solvents (THF, toluene, acetonitrile, dioxane) under elevated temperatures (table 3.2, entries 1-5). It was observed that the yields were low at elevated temperature, which can be attributed in part to the instability of the alkynone **3.35** at elevated temperatures. Consequently, cyclization reactions were next performed at ambient temperature. Reactions were monitored by TLC, and in the cases where product **3.36** was ultimately obtained, a relatively non-polar intermediate assigned a structure analogous to **3.22** (scheme 3.5) was observed. All the reactions were quenched with the addition of TFA and H_2O after 48 h, and the product was isolated by flash column chromatography (SiO_2). Even though we isolated the cyclized product in most of the reactions, the yields remained disappointing, although the cyclization does appear to be slightly more efficient compared to reactions at higher temperature. The best results were obtained in CH_2Cl_2 as solvent (table 3.2, entry 11). In a few cases we also observed an oxidized product **3.37** (figure 3.5), which was isolated and completely characterized by ^{1}H-NMR, ^{13}C-NMR , ^{13}C-DEPT 135 NMR and HRMS. We speculate that the formation of **3.37** might be due to Ag_2O present as an impurity in the AgOTf salt. When fresh AgOTf was used for the reaction, no **3.37** was observed.

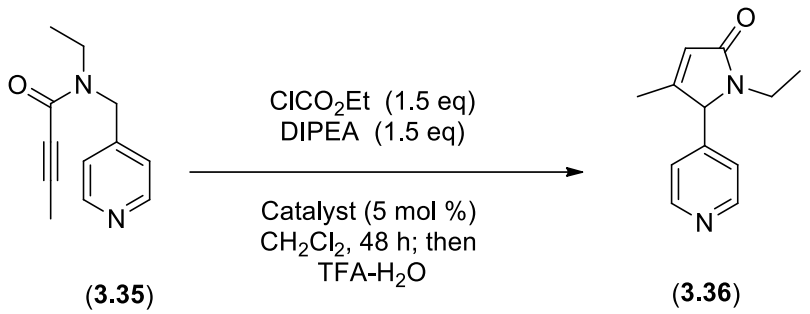


(**3.37**)

Figure 3.5 Oxidized product.

Based on the moderately successful results of benzylic cyclization summarized in table 3.2, gold catalysts appear to give better results compared to platinum catalysts. It is well known that the electronic features of gold complexes can be modified through changes in the attached ligands.[83, 84] Initially, we hypothesized that electron withdrawing ligands on the gold catalyst would make it more alkynophilic and would speed up the reaction to give better yields. So, several different catalysts and catalyst precursors with electron-withdrawing as well as electron-donating ancillary ligands were screened in the conversion of **3.35** to **3.36** as summarized in Table 3.3.

Table 3.3 Catalyst Screening.



(**3.35**) (**3.36**)

Entry	Catalyst	% yield **3.36**[a]
1	$AuCl(PPh_3)$	0
2	AgOTf	0
3	$AuCl_3$	0
4	$AuCl(P(OPh)_3)$ + AgOTf	0
5	(JohnPhos)AuCl + AgOTf	10
6	(JohnPhos)Au(MeCN)SbF_6	0
7	(Bt)AuCl + AgOTf	10
8	$AuCl(PPh_3)$ + $AgBF_4$	32
9	$AuCl(PPh_3)$ + $AgPF_6$	18
10	$AuCl(PPh_3)$ + $AgSbF_6$	Trace
11	$AuCl(P(C_6F_5)_3)$ + AgOTf	0

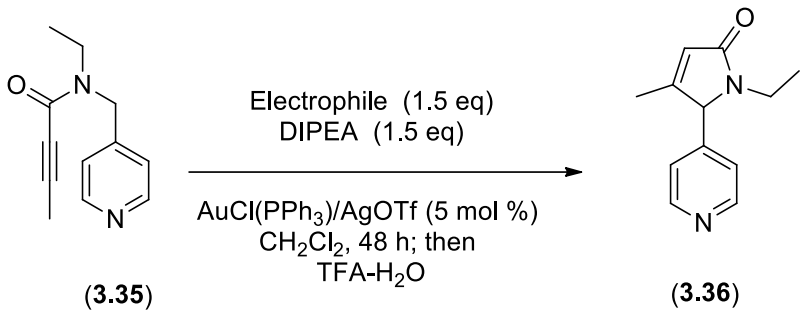
[a]Isolated yield, Bt = Benzotriazole

The entries 1 and 2 in Table 3.3 were control reactions which show that both $AuCl(PPh_3)$ and AgOTf were needed for the carbocyclization reaction to occur. Gold (III) chloride as catalyst resulted in no reaction (entry 3). Other gold (I) catalysts possessing a

phosphite ligand (entry 4), bulky biphenylphosphine ligand (entries 5-6), thermally stable benzotriazole ligand (entry 7)[85] and electron deficient gold(I)tris(pentafluorophenyl)phosphine chloride (entry 11) were largely ineffective. Changing the counter ion (entries 8-10) did not have much impact on the yield of the reaction either.

In attempting to further refine the reaction conditions, we examined varying the electrophiles used for anhydrobase formation (table 3.4). It was observed that chloroformates (entries 1-4) were the best electrophiles for this reaction, whereas use of anhydrides (entries 5 and 6), Bronsted acid (entry 7) or sulfonylchloride (entry 8) did not give any cyclized product.

Table 3.4 Screening of electrophiles.



(**3.35**) (**3.36**)

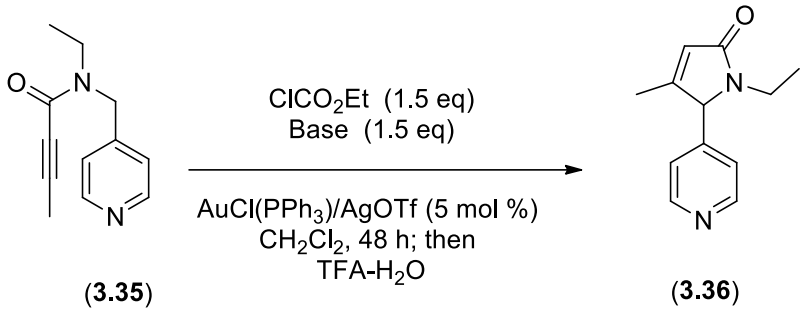
entry	Catalyst	% yield **3.36**[a]
1	$ClCO_2Et$	48
2	$ClCO_2iPr$	20
3	$ClCO_2Me$	40
4	$ClCO_2Bn$	20
5	Ac_2O	0
6	Tf_2O	0
7	TfOH	0
8	$PhSO_2Cl$	0

[a]Isolated yield.

Since the base plays an important role in the generation of the proposed anhydrobase intermediate, bases other than DIPEA were examined and the results are summarized in Table 3.5. As seen in entries 1 and 2, amine bases diisopropylethylamine and triethylamine were equally effective. The inorganic base K_2CO_3 and the stronger

organic bases DBU and KO^{t}Bu, however, were incompatible with the cyclization (entries 3-5).

Table 3.5 Screening of Bases



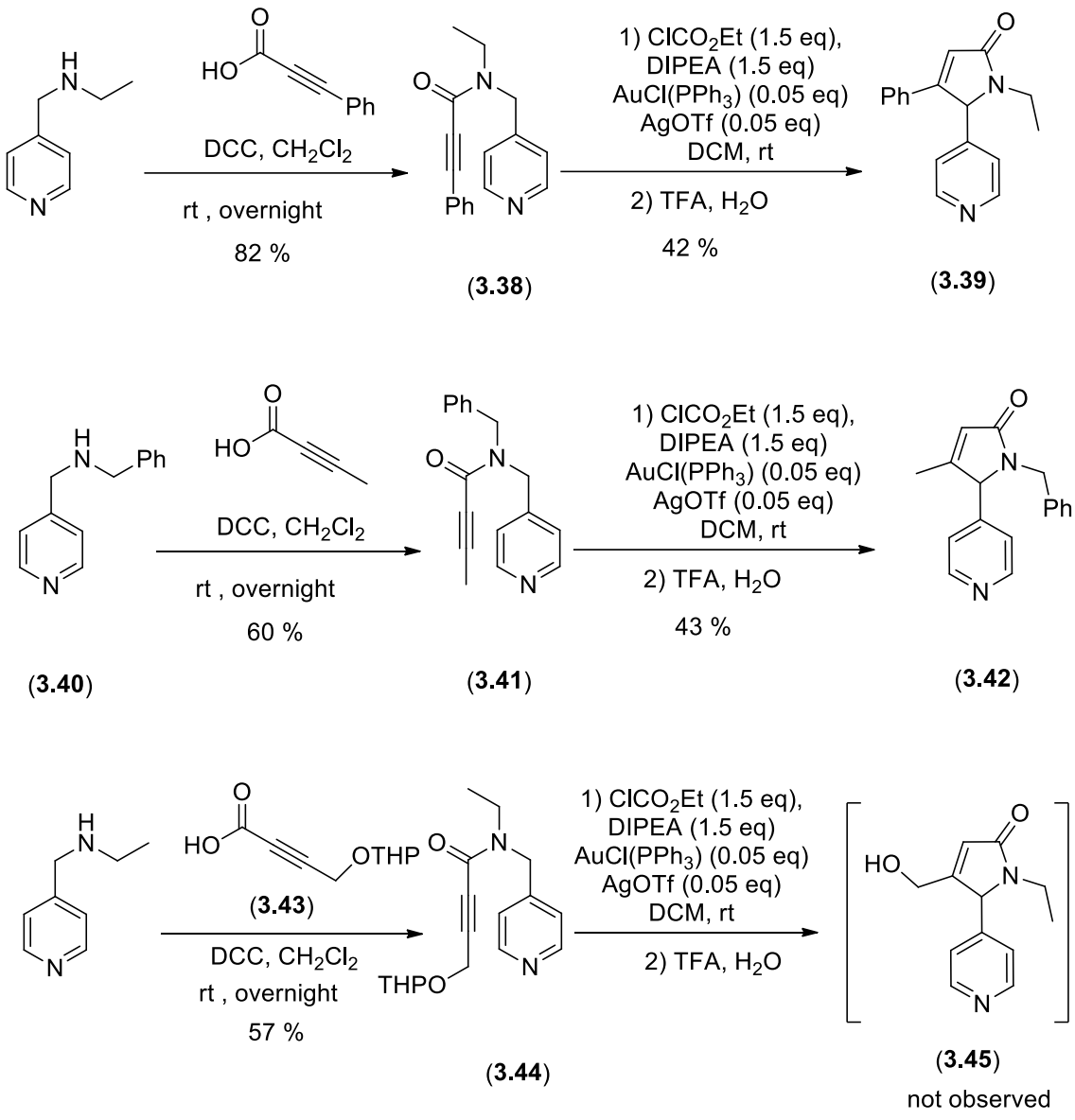
(**3.35**) (**3.36**)

entry	Catalyst	% yield **3.36**[a]
1	DIPEA	48
2	TEA	45
3	K_2CO_3	0
4	DBU	0
5	KO-^{t}Bu	0

[a]Isolated yield

Next, the generality of the reaction was investigated by varying the substitution at the amide nitrogen, changing the alkyne side chain, and moving the side chain to the C-2 position of the pyridine ring, as shown in scheme 3.9. The reaction conditions entailed treatment of the substrates with 1.5 equivalent DIPEA and 1.5 equivalent $ClCO_2Et$, followed by the addition of a suspension of $AuCl(PPh_3)$ (5 mol %) and AgOTf (5 mol %)

in DCM at room temperature. As was the case with **3.35**, isolated yields of cyclized products **3.39** and **3.42** were modest, whereas we did not observe the product **3.45**.



Scheme 3.9 Additional examples of benzylic cyclization.

Moreover, several other substrates, such as secondary amides, 4-aminoethylpyridine derivatives, 2-alkylpyridine analogues and 4-alkylpyridines with no conjugated alkyne substituents failed to react under the specified conditions (figure 3.6).

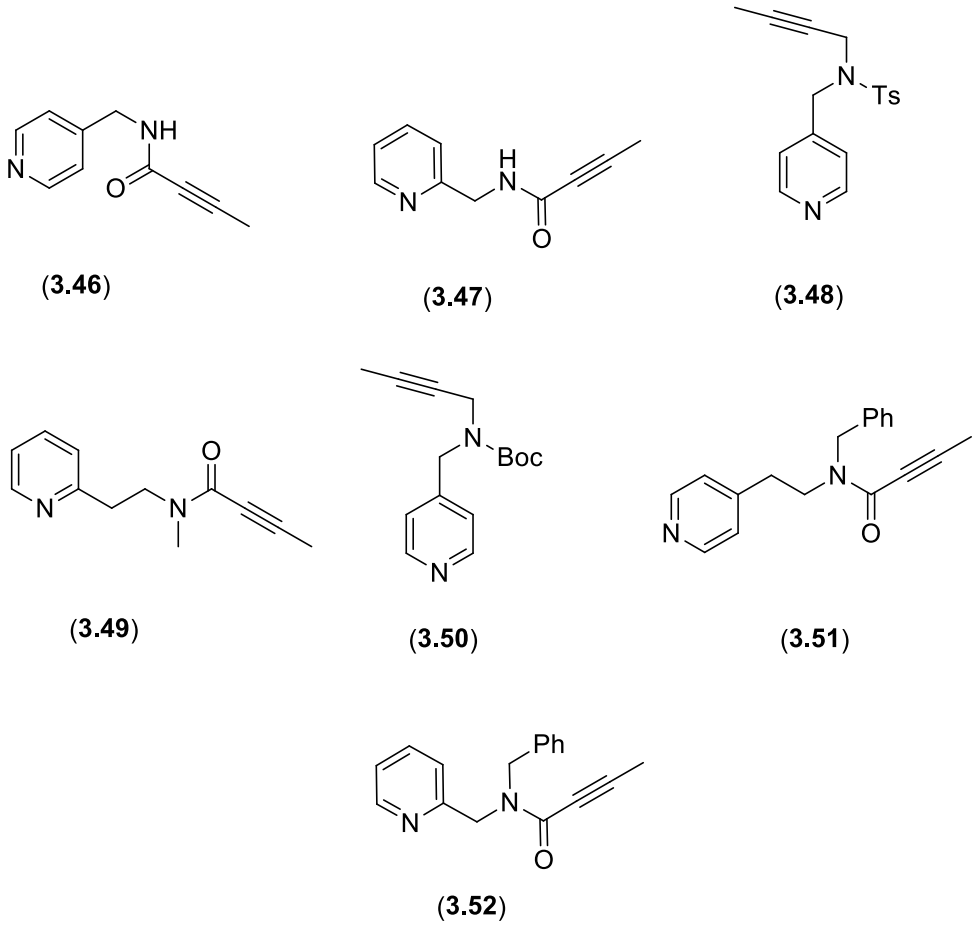


Figure 3.6 Substrates that failed to undergo cyclization.

Attention was next directed towards further modifying the substrate structure in order to possibly increase both the scope and efficiency of the cyclization. When examined carefully, we noted that substrates **3.35**, **3.38** and **3.41** all exist as distinct

alkynyl side chain rotamers that interconvert only slowly at room temperature on the NMR time scale. The spectrum of **3.35** is representative (figure 3.7), and two sets of peaks for each equivalent signal are apparent in almost equal intensities.

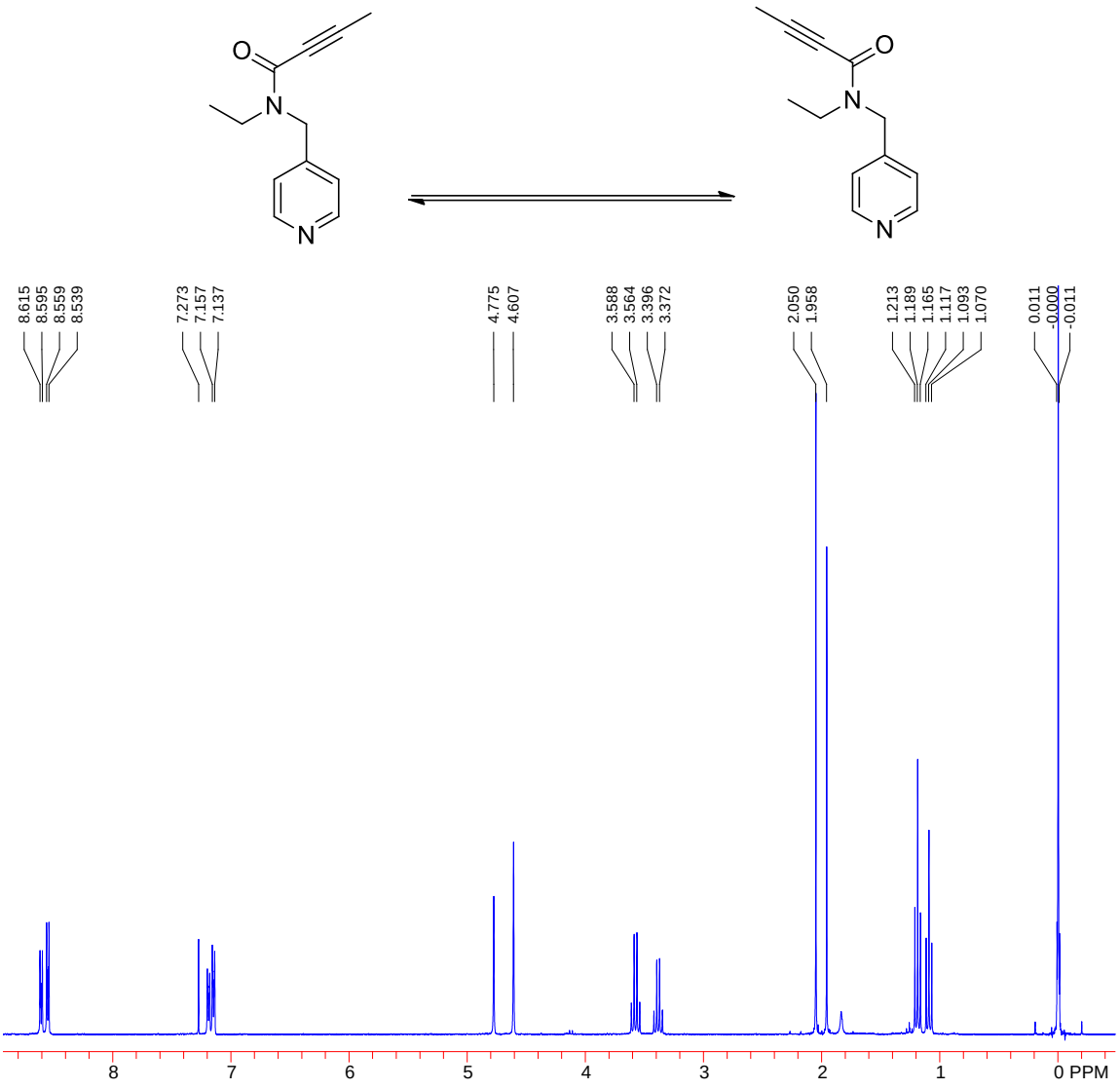
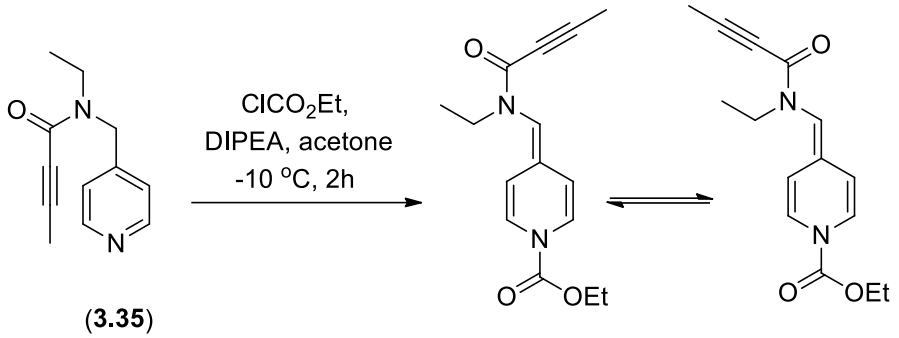


Figure 3.7 ^{1}H-NMR spectrum of **3.35** showing distinct rotamer populations.

The presence of distinct rotamers was also evident in the anhydrobase generated from **3.35**. In this experiment, the anhydrobase of **3.35** was formed using Brana's conditions (scheme 3.10)[61], which involved treatment of **3.35** with ethylchloroformate (2.0 equivalent) and DIPEA (2.0 equivalent) in acetone at -10 ^{o}C for 2 h. While the anhydrobase of **3.35** is unstable to isolation, performing the reaction in deuterated acetone allowed the NMR spectrum of the anhydrobase intermediate **3.53**, to be measured, again revealing the presence of distinct rotamers on the NMR time scale (figure 3.8).



(**3.35**) (**3.53**)

Scheme 3.10 Anhydrobase synthesis.

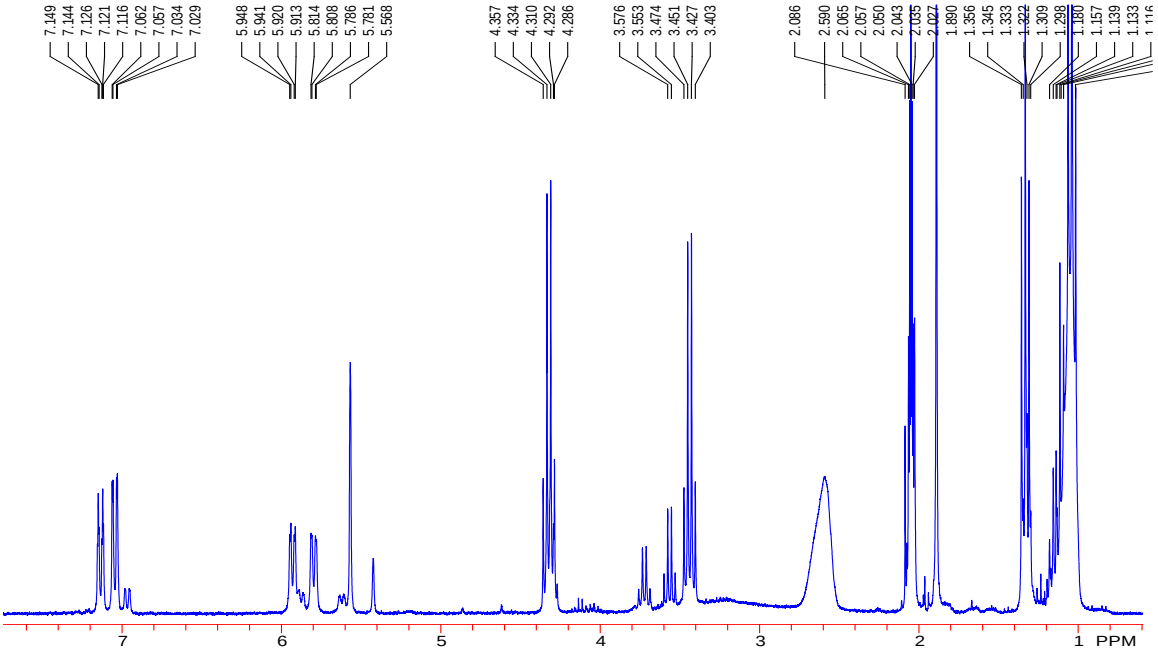
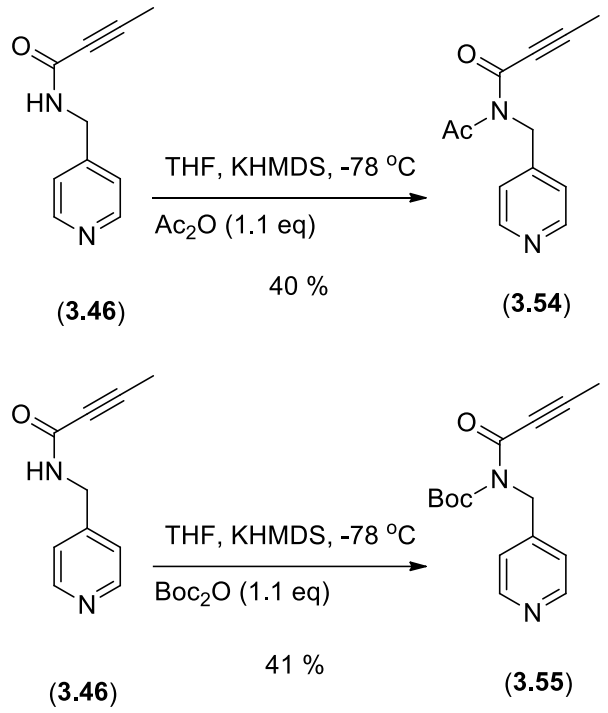


Figure 3.8 ^{1}H-NMR of anhydrobase **3.53**.

As a result of observing these rotamers, we speculated that stereoelectronic factors in the alkynone side chain may play a critical role in the cyclization event. To

investigate this notion, we prepared substrates in which N-alkyl groups were replaced with an acyl group (**3.54**) and t-butoxycarbonyl group (**3.55**) as shown in scheme 3.11.



Scheme 3.11 Imide and carbamate derivatives.

The room temperature ^{1}H NMR spectra of **3.54** and **3.55** did not show any evidence for distinct rotamers, indicating that the presence of an acyl or BOC protecting group resulted in the formation of either a single rotamer or caused rotamer inter-conversion to become rapid on the NMR time scale (figure 3.9). Exposure of the compound **3.54** to our standard anhydrobase cyclization reaction conditions, however, did not show any improvement in the yield of the cyclized product **3.56**. Gratifyingly,

substrate **3.55**, on exposure to Au-catalyzed cyclization conditions, afforded the cyclized product **3.57** in much improved 74 % isolated yield (scheme 3.12).

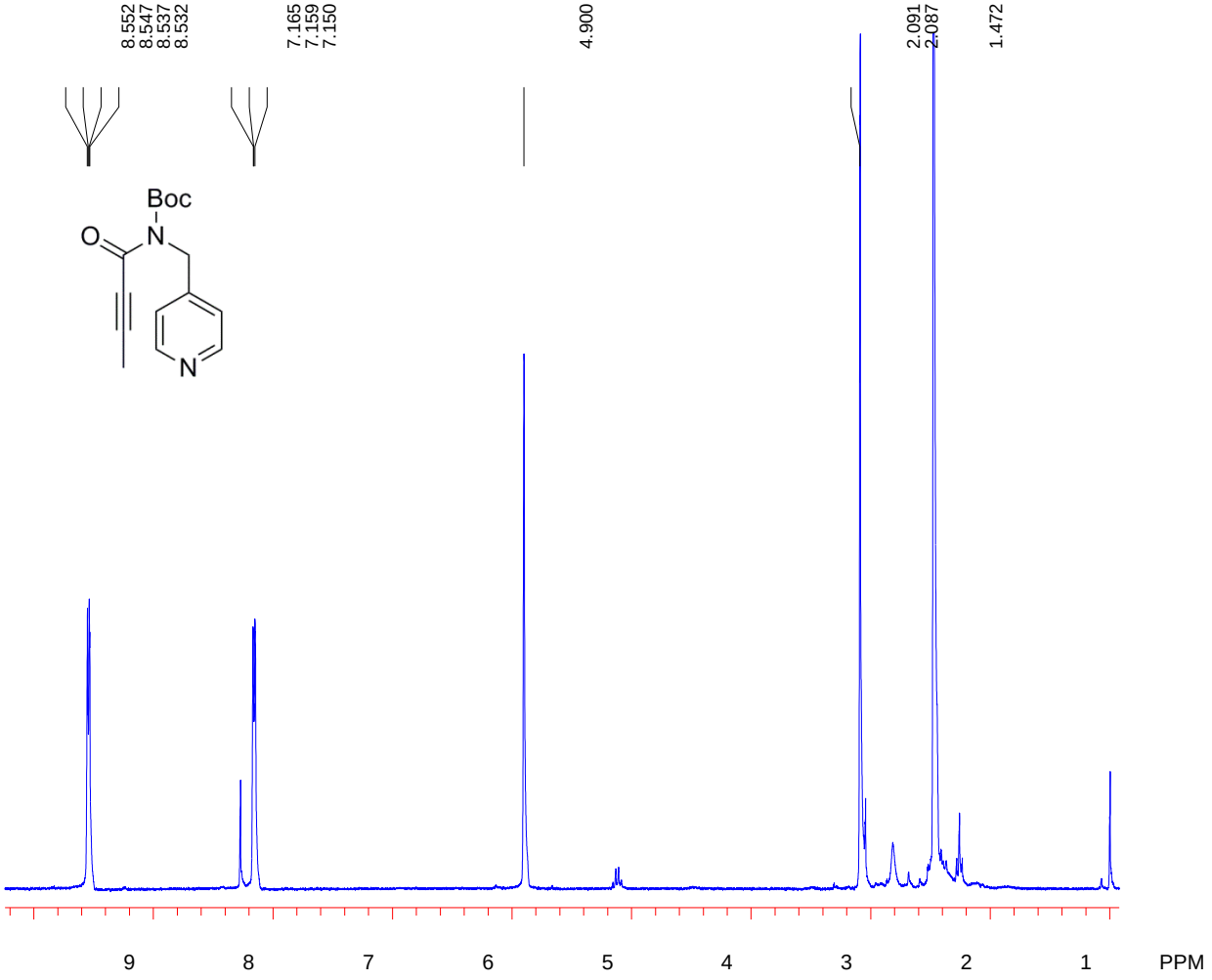
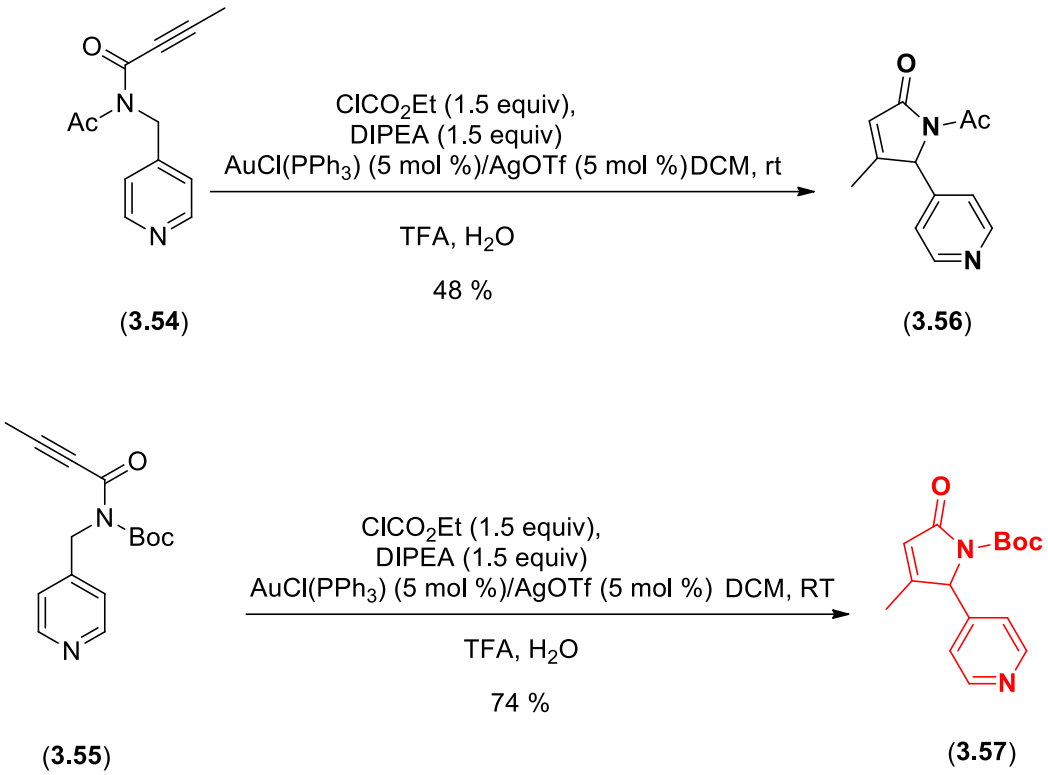
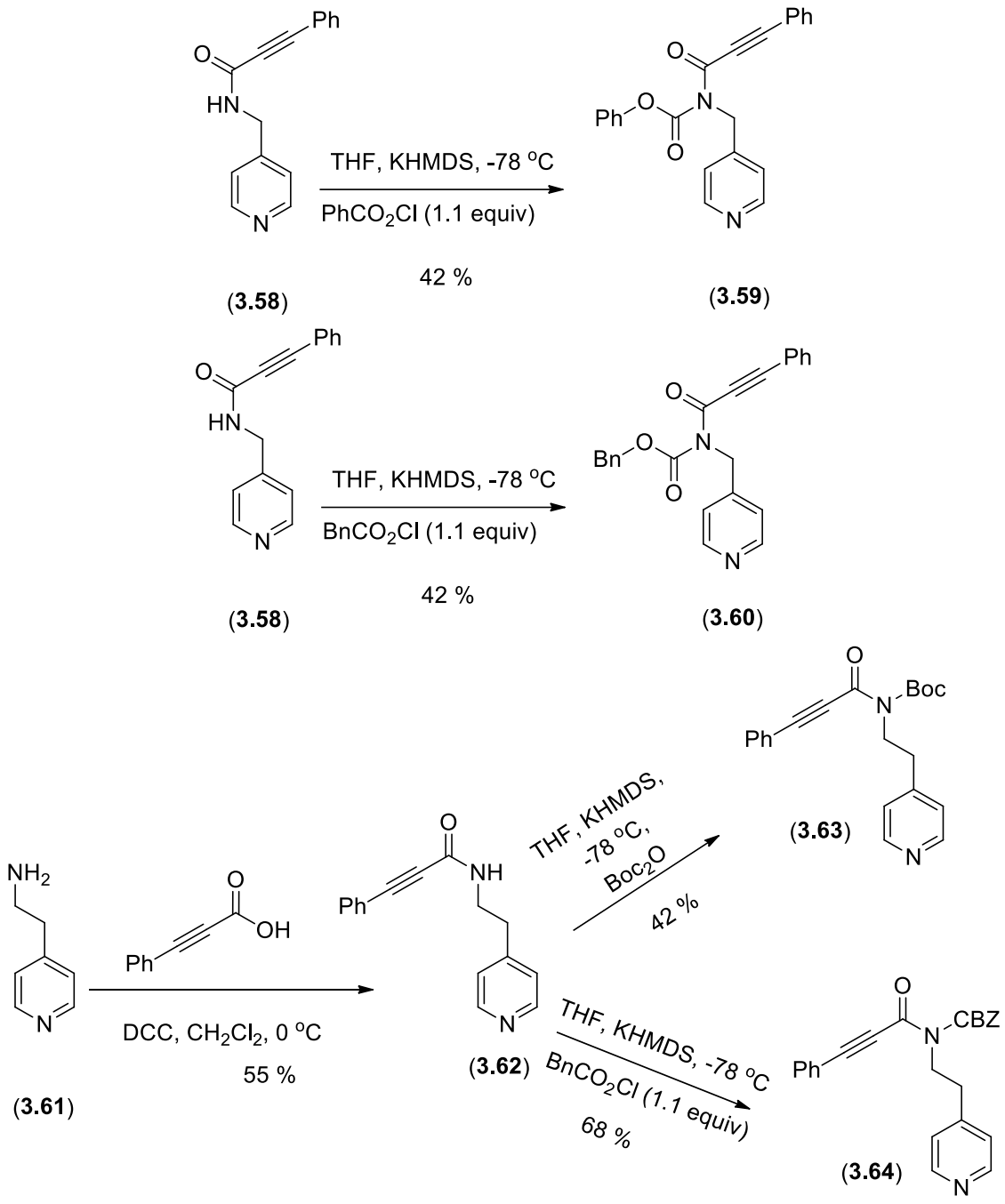


Figure 3.9 ^{1}H NMR Spectrum of **3.55**.



Scheme 3.12 Au-catalyzed reactions.

Given the improvement in yield for the cyclization of **3.55**, other pyridine substrates with BOC, phenoxycarbonyl and CBZ groups were synthesized as shown in scheme 3.13.

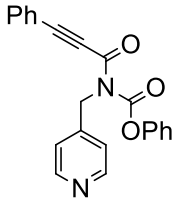
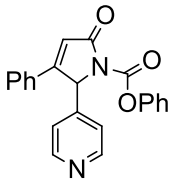
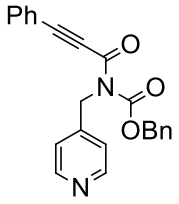
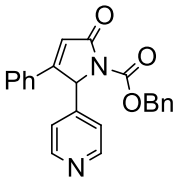
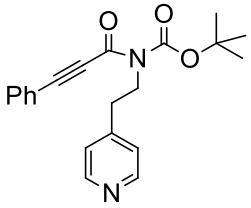
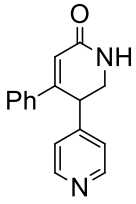
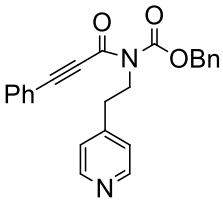
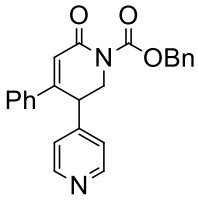


Scheme 3.13 Synthesis of carbamate substrate.

All these carbamates were then converted to the corresponding cyclized products in much higher yields than their N-ethyl analogues discussed earlier (see scheme 3.9).

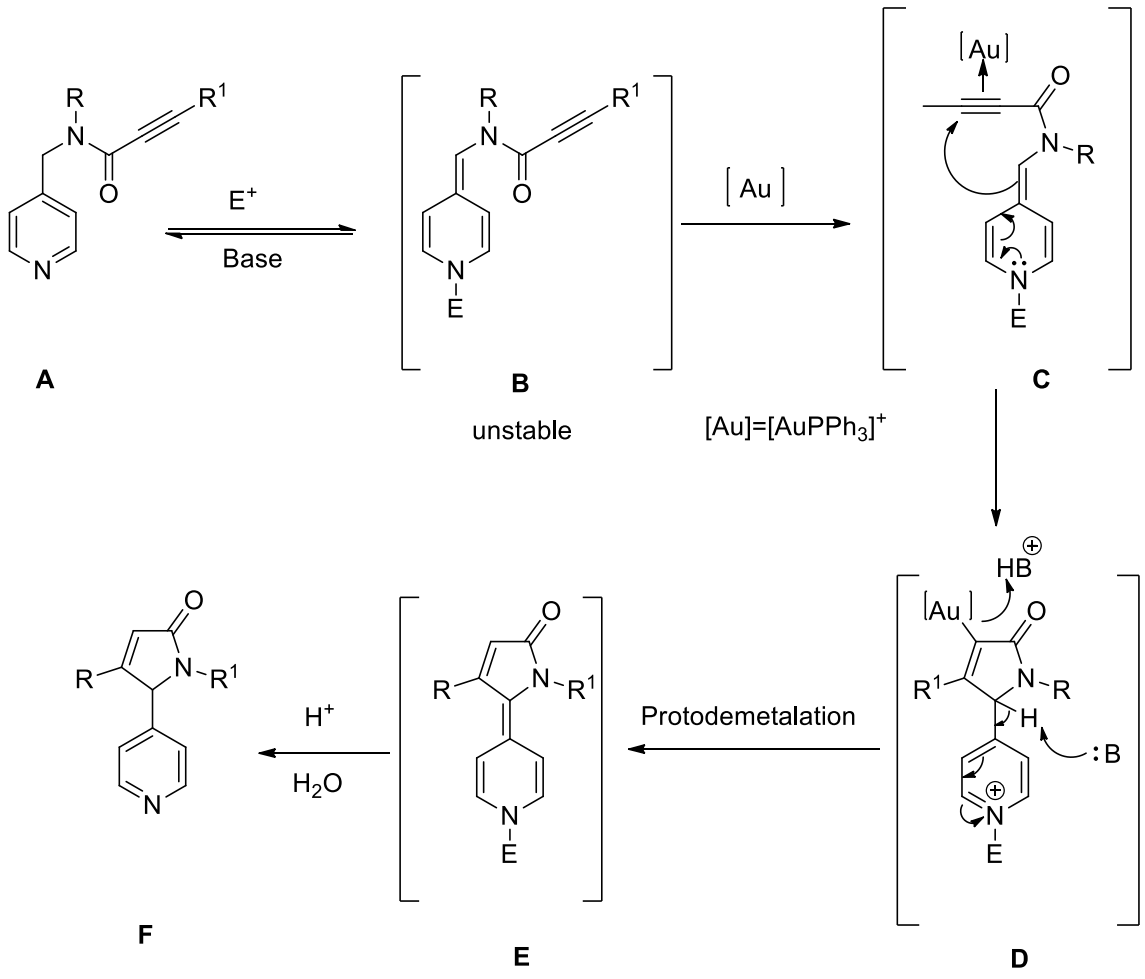
The results of cyclizations with substrates **3.59**, **3.60** and **3.63**, **3.64** are summarized in table 3.6. In addition to 5-*endo dig* cyclizations to give **3.65** and **3.66** (entries 1-2), a 6-*endo dig* reaction manifold is also operative to afford δ-lactam products **3.67**-**3.68** (entries3-4). However, the BOC group in **3.63** is lost during this transformation, presumably during the acid hydrolysis phase of the reaction that takes place after cyclization. Based on the results obtained with moderately improved yields, we can say that both the electronic and steric effects exerted by the carbamate groups might be important in facilitating the anhydrobase cyclization.

Table 3.6 Cyclization of carbamate-protected alkynones[a].

Entry	Substrate	Product	% yield[b]
1	 (**3.59**)	 (**3.65**)	58
2	 (**3.60**)	 (**3.66**)	62
3	 (**3.63**)	 (**3.67**)	58
4	 (**3.64**)	 (**3.68**)	64[c]

[a]Reaction conditions: $ClCO_2Et$ (1.5 equiv), DIPEA (1.5 equiv), $AuCl(PPh_3)$ (5 mol%), AgOTf (5 mol%), CH_2Cl_2, rt, 48 h; then TFA, H_2O, rt. [b]Isolated yield. [c]Yield calculated based on 10% recovered starting material.

A plausible mechanism to account for these benzylic cyclizations is illustrated in scheme 3.14.

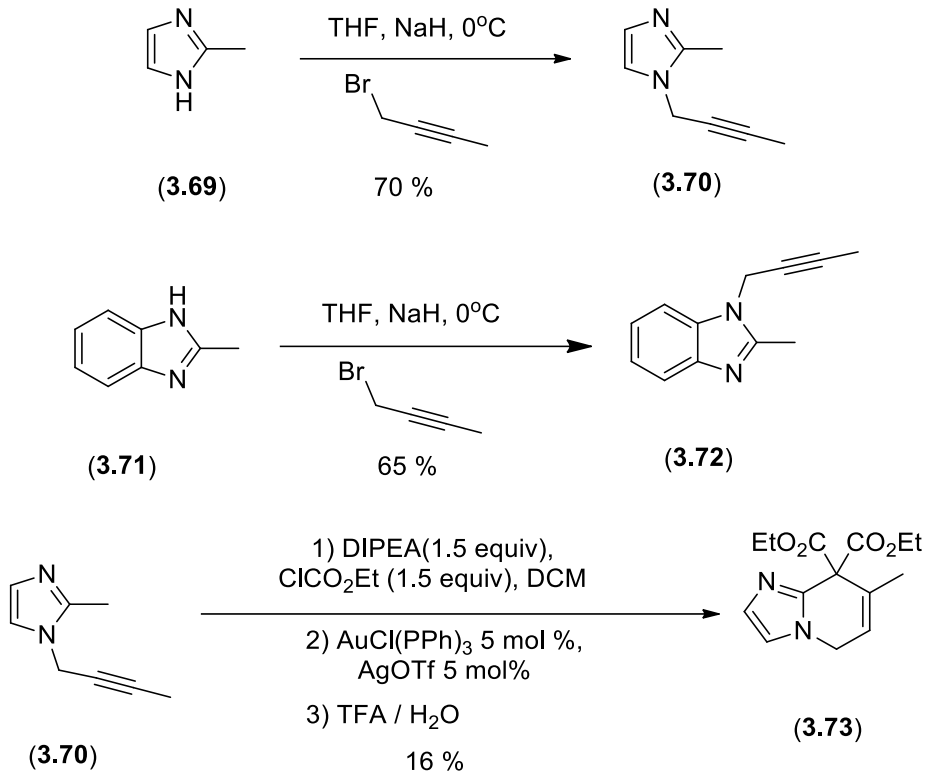


Scheme 3.14 Proposed mechanism for cyclization.

Acylation of the general pyridine substrate **A** with an electrophile (E^+), followed by benzylic deprotonation by a base generates the unstable anhydrobase **B**. Activation of the alkynone unit by coordination of Au(PPh_3) and *endo-dig* cyclization affords **D**. A second benzylic deprotonation and proto-demetalation of the vinyl gold intermediate then

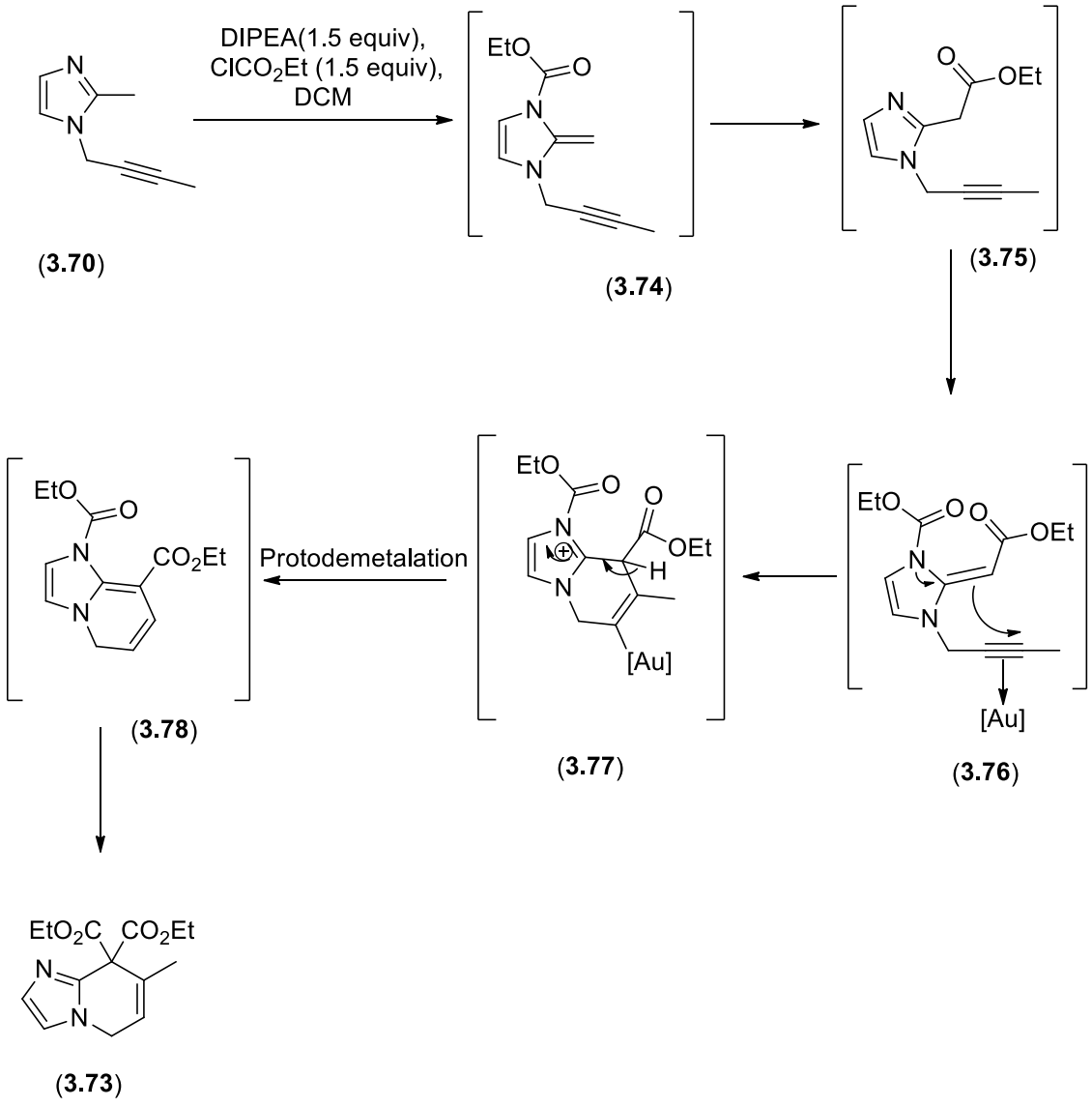
gives rise to anhydrobase **E**. Quenching the reaction with TFA re-protonates **E** and promotes hydrolysis of the acyl pyridinium group upon addition of H_2O to give the 4-pyridyl lactam product **F**. The rate of reaction depends on two factors, 1) the alkynophilicity of the gold (I) catalyst and 2) the ease with which the vinyl gold intermediate undergoes protodeauration to regenerate the cationic gold species that resumes the catalytic cycle. The ligand effect is well reported in literature.[83, 86] Xu and coworkers found that the electronic properties of the ligand has a major influence on protodeauration: electron-withdrawing groups decreased the rate of reaction, whereas electron-donating groups increased the rate of reaction. Sterically more demanding ligands slowed down the reactions. This might be one of the reasons for the failure of reactions where gold (I) catalyst with electron-deficient ligands and bulkier Buchwald ligands were used for the cyclization reaction.

With the results from pyridine anhydrobase cyclizations in hand, attempts were made to extend this methodology to other heterocyclic ring systems, like imidazoles and benzimidazoles. The imidazole substrate **3.70** and benzimidazole substrate **3.72** were synthesized as shown in scheme 3.15.



Scheme 3.15 Imidazole and benzimidazole derivatives for Au catalyzed reactions.

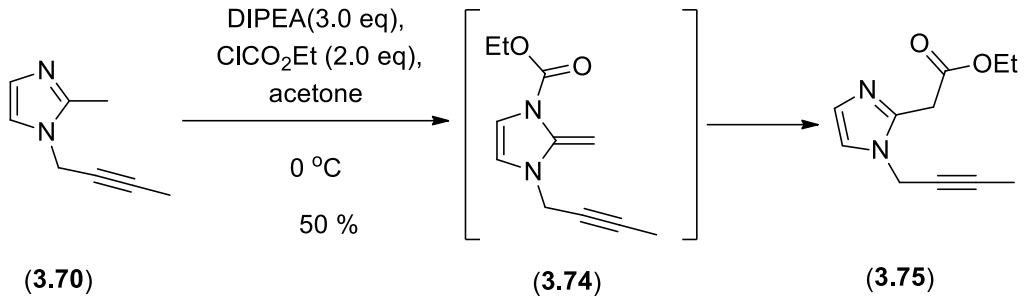
When subjected to the Au-catalyzed carbocyclization reaction condition, the imidazole substrate gave an unexpected cyclized product **3.73** in low yield which was completely characterized by NMR and mass spectrometry. The benzimidazole derivative failed to give any cyclized product under these same conditions. The formation of the product **3.73** is rationalized by the proposed mechanism in scheme 3.16.



Scheme 3.16 Proposed mechanism for formation of **3.73**.

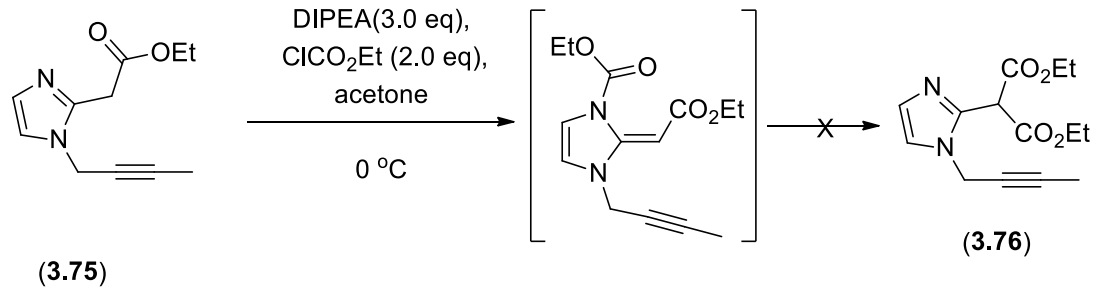
It has been reported in the literature that N-alkylimidazole substrates, when treated with acylating agents, give acylated product **3.75** via the anhydrobase intermediate **3.74**. A second acylation of **3.75** may generate the anhydrobase **3.76**, which, on activation with Au –catalyst, undergoes *endo-dig* cyclization. Another deprotonation,

followed by protodemetallation, may afford the anhydrobase **3.78**, which then undergoes acylation of the anhydrobase carbon to give the final product **3.73** in 16 % isolated yield. Several attempts were made to improve the yield of this intriguing transformation by changing the solvent, reagent ratios, and gold catalyst, but no improvement was observed. So we thought if we could make the acylated imidazole substrate **3.75**, it could help in improving the reaction. Substrate **3.75** was synthesized by treating **3.70** with DIPEA (3.0 equiv) and $ClCO_2Et$ (2.0 equiv) in CH_2Cl_2 at 0 ^oC (scheme 3.17).



Scheme 3.17 Synthesis of **3.75**.

Attempts to engage substrate **3.75** in Au-catalyzed cyclization did not give the corresponding product **3.73**. Consequently, we next considered the possibility that doubly acylated substrate **3.79** might be the immediate precursor to **3.73**. Attempts to prepare **3.79** from **3.75** as outlined in scheme 3.18, however, were unsuccessful.



Scheme 3.18 Acylation attempts for synthesis of **3.76**.

Several reactions were screened in an effort to synthesize substrate **3.79** by acylation of **3.75** using $ClCO_2Et$ with various bases like DIPEA, TEA, KHMDS and NaH. In each case, no **3.79** was observed and **3.75** was recovered in 50-80%. Failure to obtain **3.79** indicates that it is not an intermediate during the course of gold catalyzed cyclization. Currently, the sequence of events leading to bicyclic diazaheterocycle 3.73 are unknown. Future work should be directed towards developing a better understanding of this transformation and increasing the scope/efficiency of the reaction.

3.4 Conclusion

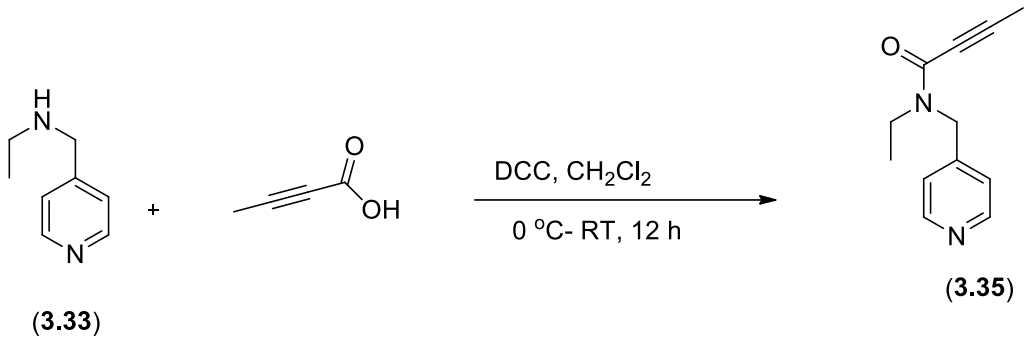
We successfully demonstrated the ability to utilize transiently generated anhydrobase intermediates in Au-catalyzed additions to alkynyl amide electrophiles. This gives us a useful tool to convert 4-alkylpyridine substrates to pyridyl substituted ϒ- and δ-lactams. The amide side-chains in the 4-alkyl pyridine substrates show the presence of distinct rotamers in their ^{1}H-NMR spectra and changing the electronics around the amide nitrogen atom significantly affected the rotamer population and/or rate of rotamer interconversion on the NMR time scale. Importantly, the change in the electronics around

the nitrogen atom resulted in improved yields of cyclized products. The ability to observe anhydrobase intermediates may bode well for manipulating these compounds in other organo-transition metal-catalyzed reactions, and this aspect of anhydrobase chemistry has not been previously explored.

3.5 Experimental

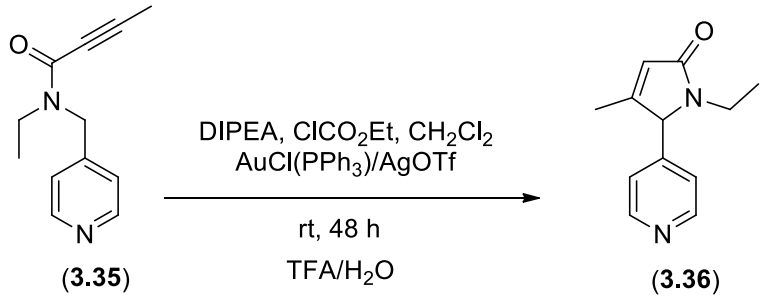
3.5.1 General experimental:

All commercially available starting materials and the reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz/500 MHz and 75 MHz/125 MHz respectively. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for ^{1}H-NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds used in this study reveal the presence of amide rotomers. Resonances corresponding to major and minor rotamers are identified when appropriate. IR spectra was recorded on a FT-IR spectrometer as thin films on sodium chloride discs. High resolution mass spectra were obtained using electrospray ionization (ESI). Melting points were recorded using a capillary melting point apparatus and are uncorrected.



(**3.33**) (**3.35**)

N-Ethyl-N-(pyridin-4-ylmethyl)but-2-ynamide (3.35): To a solution of N-ethyl (4-aminomethyl) pyridine (2.01 g, 14.7 mmol, 1.0 equiv) and 2-butynoic acid (1.23 g, 14.7 mmol, 1.0 equiv) in dichloromethane (50 mL) was added a solution of DCC (3.64 g, 17.6 mmol, 1.2 equiv) in dichloromethane (25 mL) at 0 ^{o}C. The reaction was allowed to warm to room temperature and stirred for 14 h, during which time a white precipitate formed. The reaction was filtered through a bed of Celite® which was then washed with additional dichloromethane (50 mL). The filtrate was concentrated under reduced pressure to yield a brown liquid. Purification by silica gel flash column chromatography using 70-80 % ethyl acetate in hexanes gave **3.35** (2.13 g, 71%) as a dark brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) Major rotamer: δ 8.55 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.21–7.17 (m, 2H), 4.61 (s, 2H), 3.58 (q, *J* = 7.2 Hz, 2H), 2.05 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). Minor rotamer: δ 8.61 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.21–7.17 (m, 2H), 4.77 (s, 2H), 3.38 (q, *J* = 7.2 Hz, 2H), 1.96 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 150.3, 146.5, 146.3, 126.7, 122.7, 122.2, 89.8, 80.1, 72.0, 51.4, 50.5, 46.5, 43.9, 40.9, 39.8, 14.1, 12.8, 12.5, 11.9, 4.3, 4.1. IR (film): 2976, 2240, 1701, 1620 cm^{-1}. HRMS (ESI) $C_{12}H_{15}N_2O$ [M + H] $^{+}$, 203.1184; found 203.1197.

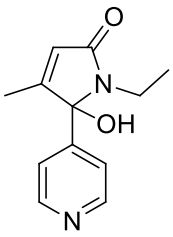


(**3.35**) (**3.36**)

1-Ethyl-4-methyl-5-(pyridin-4-yl)-1H-pyrrol-2(5H)-one (3.36): A catalyst suspension was prepared by combining $AuCl(PPh_3)$ (6.10 mg, 0.012 mmol, 5 mol %) and AgOTf (3.10 mg, 0.012 mmol, 5 mol %) in dichloromethane (1.0 mL) at room temperature.

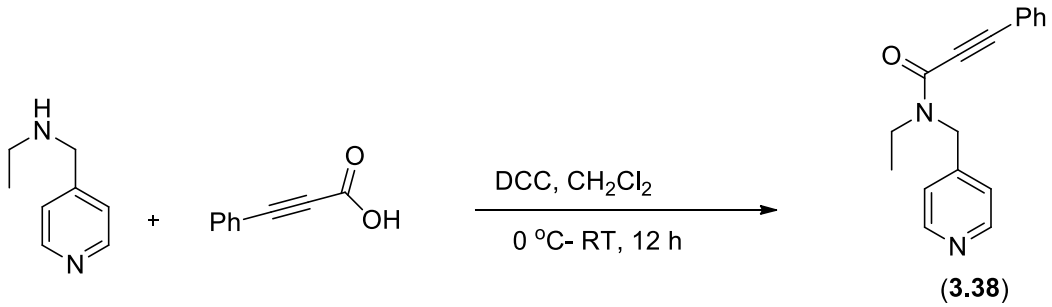
In a separate reaction flask was combined compound **3.35** (0.0501 g, 0.247 mmol, 1.0 equiv), DIPEA (61.2 µL, 0.371 mmol, 1.5 equiv) and ethyl chloroformate (35.0 µL, 0.371 mmol, 1.5 equiv) in 3 mL dichloromethane. The catalyst suspension was added to this solution at room temperature and the reaction was stirred for 48 h. After this time, trifluoroacetic acid (TFA, 0.190 mL, 2.47 mmol, 10 equiv) was added at room temperature, followed by addition of water (2 mL). After stirring for 4 h, the reaction mixture was adjusted to pH 8-9 by addition of saturated aqueous Na_2CO_3 solution. The reaction mixture was then diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with additional aliquots of ethyl acetate (2 x 5 mL), and the combined organic layer was washed with water (5 mL) and brine (5 mL), and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent gave a dark residue that was purified by silica gel flash column chromatography using 70-80% ethyl acetate in hexanes to afford **3.36** (0.024 g, 48%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.8 Hz, 2H), 7.15–7.06 (m, 2H), 5.96 (d, *J* = 1.4 Hz, 1H), 4.83 (s, 1H), 3.80 (dq, *J* = 14.6, 7.4 Hz, 1H), 2.78 (dq, *J* = 14.5, 7.4 Hz, 1H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.10–0.99 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 157.6, 150.9, 145.3, 123.3, 122.6, 68.1,

35.3, 14.5, 14.0. IR (film): 3021, 1705, 1602 cm^{-1}. HRMS (ESI) $C_{12}H_{15}N_2O$ $[M + H]^+$, 203.1184; found 203.1189.



(**3.37**)

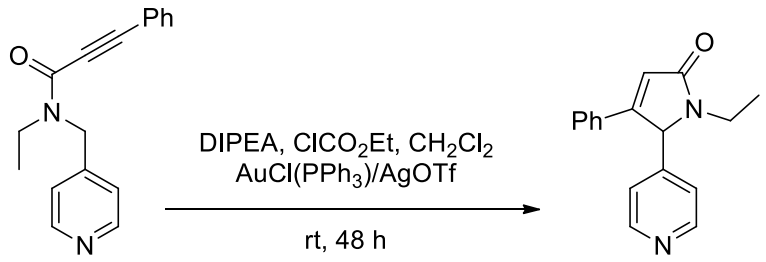
3.37, brown oil, (5.1 mg, 10 %), ^1H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, *J* = 6.0 Hz, 2H), 7.36 (d, *J* = 5.6 Hz, 2H), 5.87 (q, *J* = 1.6 Hz, 1H), 4.63 (s, 1H), 3.41 (dq, *J* = 14.5, 7.3 Hz, 1H), 3.01 (dq, *J* = 14.3, 7.2 Hz, 1H), 1.77 (d, *J* = 1.6 Hz, 3H), 1.07 – 0.90 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6(C), 160.9 (C), 150.2 (CH), 146.5 (C), 122.3 (CH), 121.3 (CH), 92.8 (C), 34.5 (CH_2), 14.7 (CH_3), 12.2 (CH_3). IR (film): 3119, 2984, 1699 cm^{-1}. HRMS (ESI) $C_{12}H_{15}N_2O$ $[M + H]^+$, 219.1133; found 219.1129.



(**3.38**)

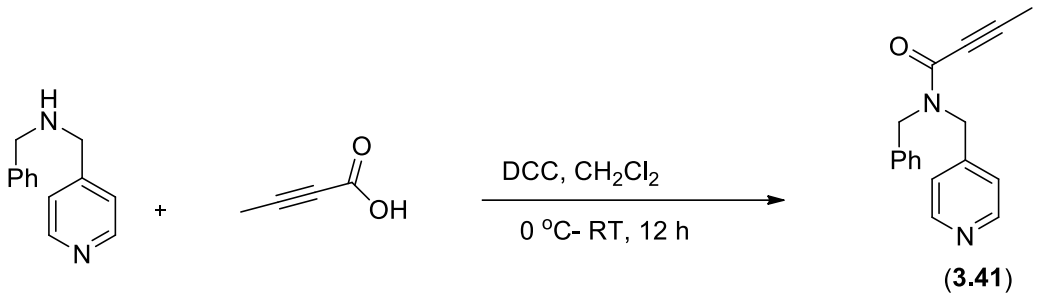
N-Ethyl-3-phenyl-N-(pyridin-4-ylmethyl)propiolamide (3.38): Using the procedure described for the preparation of **3.35**, 0.372 g (2.74 mmol) of N-ethyl (4-aminomethyl) pyridine and 0.406 g (2.74 mmol) of 3-phenyl-2-propynoic acid were coupled to give **3.38** (0.602 g, 82%) as a pale yellow solid. Mp. 68-71 °C. ^1H NMR (300 MHz, $CDCl_3$)

Major rotamer δ 8.57 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.56 (t, *J* = 1.8 Hz, 1H), 7.46–7.37 (m, 4H), 7.20 (d, *J* = 6.0 Hz, 2H), 4.68 (s, 2H), 3.68 (q, *J* = 7.1 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H). Minor rotamer δ 8.62 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.58 (t, *J* = 1.2 Hz, 1H), 7.35–7.30 (m, 4H), 7.25 (d, *J* = 6.0 Hz, 2H), 4.86 (s, 2H), 3.47 (q, *J* = 7.2 Hz, 2H), 1.15 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 154.7, 150.3, 150.1, 146.1, 146.0, 132.5, 132.4, 130.3, 128.6, 128.6, 122.6, 122.0, 120.3, 120.1, 90.6, 90.4, 81.5, 81.2, 51.4, 46.6, 44.0, 40.0, 14.0, 12.4. IR (film): 2973, 2212, 1622 cm^{-1}. HRMS (ESI) $C_{17}H_{17}N_2O$ [M + H]$^+$, 265.1341; found 265.1353.



(**3.38**) (**3.39**)

1-Ethyl-4-phenyl-5-(pyridin-4-yl)-1H-pyrrol-2(5H)-one (3.39): Using the procedure described in the preparation of **3.36**, 0.100 g of **3.38** was cyclized to give **3.39 (**0.042 g, 42%) as Brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.8 Hz, 2H), 7.38–7.28 (m, 5H), 7.19 (dd, *J* = 4.5, 1.6 Hz, 2H), 6.58 (d, *J* = 1.2 Hz, 1H), 5.48 (s, 1H), 3.80 (dq, *J* = 14.6, 7.4 Hz, 1H), 2.79 (dq, *J* = 14.2, 7.1 Hz, 1H), 2.11–2.06 (m, 1H), 1.11 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 157.7, 150.7, 145.6, 131.1, 130.4, 129.2, 126.9, 123.1, 122.1, 65.3, 35.2, 14.0. IR (film): 3082, 1692 cm^{-1}. HRMS (ESI) $C_{17}H_{17}N_2O$ [M + H]$^+$, 265.1341; found 265.1329.



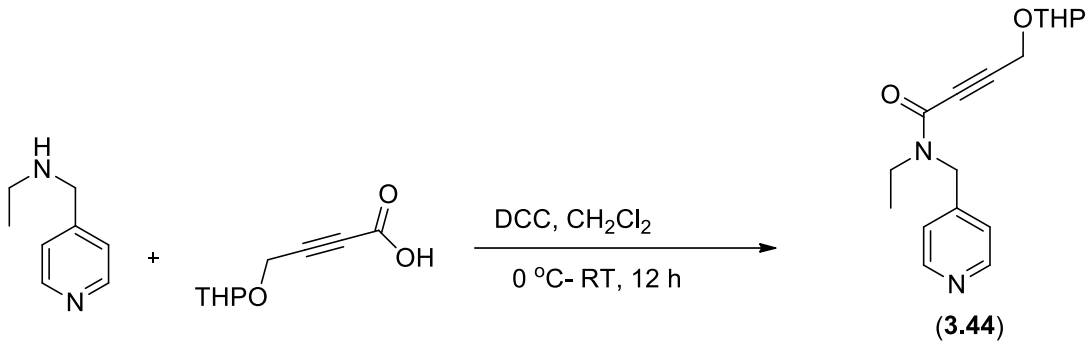
(**3.41**)

N-Benzyl-N-(pyridin-4-ylmethyl)but-2-ynamide (3.41): Using the procedure described for the preparation of **3.35**, 1.50 g (7.56 mmol) of N-benzyl (4-aminomethyl) pyridine and 0.643 g (7.56 mmol) of 2-butynoic acid were coupled to give **3.41** (1.21 g, 60%) as brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) Major rotamer δ 8.60 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.40–7.28 (m, 3H), 7.24–7.21 (m, 2H), 7.14 (dd, J= 4.4, 1.6, 2H), 4.72 (s, 2H), 4.54 (s, 2H), 2.04 (s, 3H). Minor rotamer δ 8.54 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.40–7.28 (m, 3H), 7.19–7.17 (m, 2H), 7.09 (dd, J= 4.4, 1.6, 2H), 4.67 (s, 2H), 4.49 (s, 2H), 1.99 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.5, 150.5, 150.3, 145.8, 145.6, 136.0, 135.9, 129.2, 129.0, 128.6, 128.4, 128.1, 127.9, 123.1, 122.4, 90.8, 90.6, 73.2, 52.3, 50.6, 47.1, 45.8, 4.4, 4.3. IR (film): 3029, 2931, 2246, 1704, 1630 cm^{-1}. HRMS (ESI) $C_{17}H_{17}N_2O$ [M + H] $^+$, 265.1341; found 265.1354.

(**3.41**) (**3.42**)

1-Benzyl-4-methyl-5-(pyridin-4-yl)-1H-pyrrol-2(5H)-one (3.42): Using the procedure for the preparation of **3.36**, 0.050 g of **3.41** was cyclized to give **3.42** (0.026 g, 43%) as a

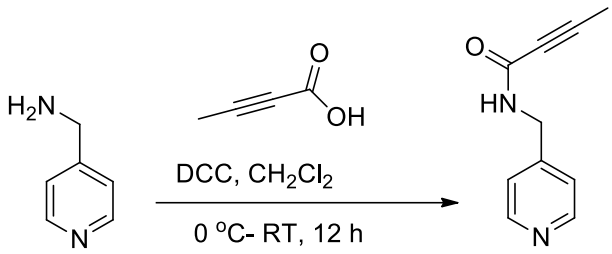
pale yellow solid, Mp. 91-94 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 5.6 Hz, 2H), 7.31–7.26 (m, 3H), 7.11–7.05 (m, 2H), 7.01 (d, *J* = 5.9 Hz, 2H), 6.01 (s, 1H), 5.19 (d, *J* = 15.0 Hz, 1H), 4.59 (d, *J* = 7.4 Hz, 1H), 3.58 (d, *J* = 15.0 Hz, 1H), 1.76 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 158.3, 150.9, 144.8, 137.1, 129.0, 128.5, 127.9, 122.8, 122.7, 67.5, 44.1, 14.5. IR (film): 3030, 1682 cm^{-1}. HRMS (ESI) $C_{17}H_{17}N_2O$ $[M + H]^+$, 265.1341; found 265.1348.



(**3.44**)

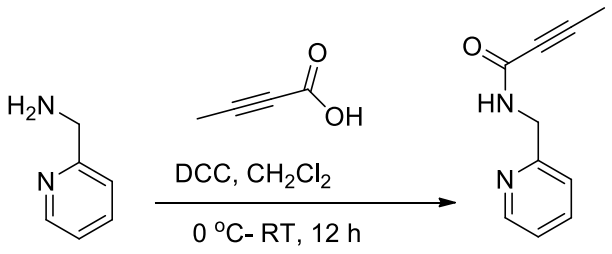
N-ethyl-N-(pyridin-4-ylmethyl)-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-ynamide (3.44): Using the procedure for the preparation of **3.35**, 0.530 g (3.91 mmol) of N-ethyl (4-aminomethyl) pyridine and 0.720 g (3.91 mmol) of 4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-ynoic acid were coupled to give **3.44** (0.670 g, 57 %) as brown oil. ^{1}H NMR (500 MHz, $CDCl_3$), Major rotamer: δ 8.56 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.16 – 7.14 (m, 2H), 4.82 (t, *J* = 3.4 Hz, 1H), 4.61 (s, 2H), 4.45 (s, 2H), 3.87 – 3.82 (m, 2H), 3.62 – 3.53 (m, 2H), 1.67 – 1.41 (m, 6H), 1.20 (t, *J* = 7.2 Hz, 3H). Minor rotamer: δ 8.61 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.20 – 7.19 (m, 2H), 4.78 (s, 2H), 4.64 (t, *J* = 3.3 Hz, 1H), 4.36 (s, 2H), 3.76-3.72 (m, 2H), 3.47 – 3.38 (m, 2H), 1.87 – 1.70 (m, 6H), 1.13 – 1.08 (t, *J*= 7.2, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 154.2, 150.5, 150.3, 146.1, 146.00, 122.7, 122.2, 97.4, 97.4, 88.2, 88.0, 78.5, 78.2, 62.3, 62.3, 60.6, 54.2, 54.1, 51.4, 46.6, 44.0, 40.0, 34.1, 30.3,

30.3, 25.8, 25.4, 25.4, 25.1, 21.2, 19.1, 19.1, 14.4, 14.1, 12.5. IR (film): 3009, 2980, 2262, 1645 cm^{-1}. HRMS (ESI) $C_{17}H_{23}N_2O_3$ $[M + H]^+$, 303.1709; found 303.1728.



(**3.46**)

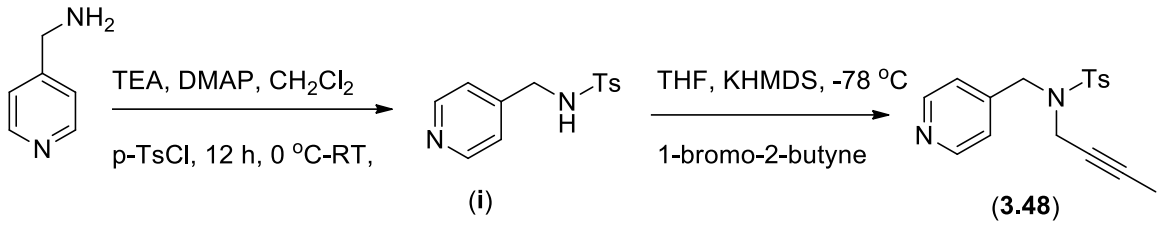
N-(Pyridin-4-ylmethyl)but-2-ynamide (3.46): Using the procedure described for the preparation of 3.**35**, 2.50 g (23.1 mmol) of 4-aminomethyl pyridine and 1.94 g (23.1 mmol) of 2-butynoic acid were coupled to give substrate (**3.46**) (1.93 g, 48%) as pale yellow solid. Mp.78-82 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 4.6, 1.4 Hz, 2H), 7.20 (d, *J* = 5.9 Hz, 2H), 6.33 (bs, 1H), 4.49 (d, *J* = 6.3 Hz, 2H), 1.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 150.3, 146.8, 122.4, 84.8, 74.6, 42.7, 3.9. IR (film): 3234, 2256, 1639 cm^{-1}. HRMS (ESI) $C_{10}H_{11}N_2O$ $[M + H]^+$, 175.0871; found 175.0883.



(**3.47**)

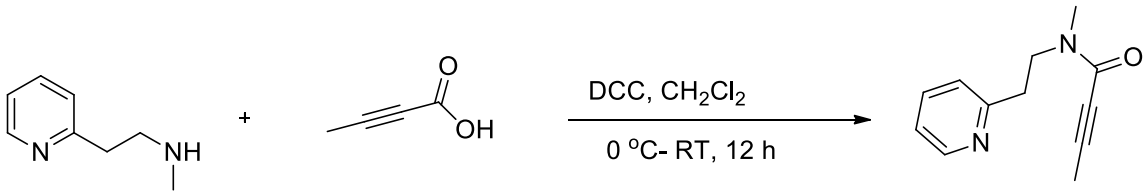
N-(Pyridin-2-ylmethyl)but-2-ynamide (3.47): Using the procedure described for the preparation of **3.35**, 2.50 g (23.1 mmol) of 2-aminomethyl pyridine and 1.94 g (23.1 mmol) of 2-butynoic acid were coupled to give substrate (**3.47**) (1.93 g, 48%) as yellow

oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.9 Hz, 1H), 7.68 (m, 1H), 7.32 – 7.17 (m, 3H), 4.59 (d, *J* = 5.2 Hz, 2H), 1.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 153.67, 149.2, 137.0, 122.7, 122.2, 83.8, 75.0, 44.7, 3.8. IR (film): 2978, 2221, 1651 cm^{-1}. HRMS (ESI) $C_{10}H_{11}N_2O$ $[M + H]^+$, 175.0871; found 175.0884.



4-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (i): To a solution of 4-picolylamine (2.01 g, 18.5 mmol, 1.0 eq), TEA (3.96 mL, 27.7 mmol, 1.5 eq), and DMAP (0.225 g, 1.85 mmol, 0.1 eq) in 100 mL dichloromethane was added a solution of p-TsCl (3.87 g, 20.3 mmol, 1.1 eq) in 50 mL dichloromethane at 0 °C and then slowly allowed to attain room temperature. The reaction was stirred at room temperature for 12 h. The reaction was quenched with H_2O (50 mL) and the organic layer was separated. The aqueous layer was extracted (2 x 50 mL) with dichloromethane and the combined organic layer was washed with saturated aq. $NaHCO_3$ (50mL), water (50 mL), brine (50 mL), dried over anhydrous Na_2SO_4. Fitration and removal of the solvent gave the residue that was then purified by silica gel flash column chromatography using ethyl acetate:hexanes (7:3) to get a pale yellow solid (2.4 g, 50%). Melting point: 158-161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, *J* = 6.0 Hz, 2H), 7.75 (d, *J* = 8 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 6.0 Hz, 2H), 5.28 (br, 1H), 4.16 (d, *J* = 6.0 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 145.7, 143.9, 138.3, 130.1, 127.3, 122.5, 46.1, 21.5. IR (film): 3190, 1642 cm^{-1}.

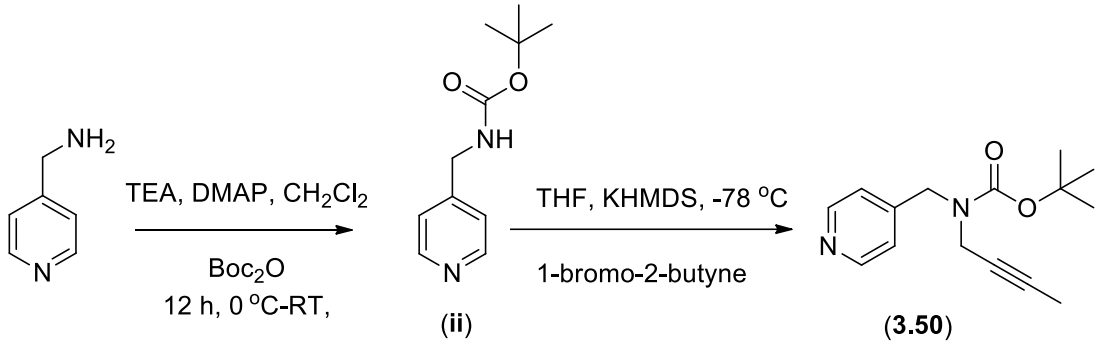
N-(but-2-yn-1-yl)-4-methyl-N-(pyridin-4-ylmethyl)benzenesulfonamide (3.48): To a solution of N-tosyl compound (**i**) (0.251 g, 0.951 mmol, 1.0 eq) in 5.00 mL THF was added KHMDS (0.500 M in toluene), (3.81 mL, 1.90 mmol, 2.0 eq) at -78 ^{o}C and stirred for 2 h. 1-Bromo-2-butyne (0.100 mL, 1.14 mmol, 1.3 eq) was added dropwise at -78 ^{o}C, and the reaction was allowed to warm to room temperature. The reaction was quenched after 12 h, with dil. NH_4OH solution (10. 0 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with water (25 mL), brine (25 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated to get a brown liquid. The crude product was then purified by silica gel flash column chromatography using 50-60 % ethyl aceate in hexanes to afford compound **3.48** (0.126 g, 42 %) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.83 – 7.71 (m, 2H), 7.34 (dd, *J* = 8.6, 0.6 Hz, 2H), 7.30 (dd, *J* = 4.4, 1.6 Hz, 2H), 4.34 (s, 2H), 3.92 (q, *J* = 2.3 Hz, 2H), 2.45 (s, 3H), 1.54 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 145.1, 143.9, 136.0, 131.0, 129.7, 128.1, 123.4, 120.5, 82.7, 71.3, 49.3, 37.2, 33.8, 21.8, 3.4. IR (film): 3019, 2895, 2256, 1567 $^{-1}$cm. HRMS (ESI) $C_{17}H_{19}N_2O_2S$ $[M + H]^+$, 315.1167; found 315.1164.



(**3.49**)

N-methyl-N-(2-(pyridin-2-yl)ethyl)but-2-ynamide (3.49): Using the procedure described for the preparation of **3.35**, 0.500 g of N-methyl-2-(pyridin-2-yl)ethanamine was coupled with 0.335 g of 2-butynoic acid to give **3.49** (0.371 g, 51 %) as pale yellow

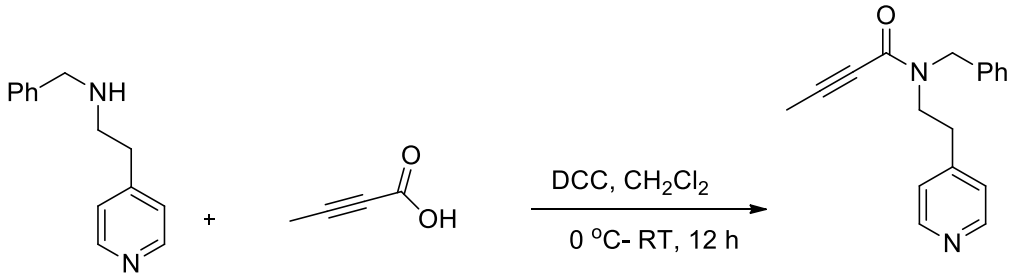
oil. (Mixture of rotamers) ^{1}H NMR (300 MHz, $CDCl_3$) Major rotamer δ 8.59 – 8.51 (m, 1H), 7.62 (m, 1H), 7.24 – 7.10 (m, 2H), 3.96 (t, *J* = 7.1 Hz, 2H), 3.08 – 2.99 (m, 2H), 2.93 (s, 3H), 2.00 (s, 7H), 1.95 (s, 3H). Minor rotamer δ 8.59 – 8.51 (m, 1H), 7.62 (m, 1H), 7.24 – 7.10 (m, 2H), 3.83 – 3.72 (m, 2H)), 3.09 (s, 3H), 3.08 – 2.99 (m, 2H), 2.00 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.4, 154.8, 154.7, 149.6, 149.4, 136.7, 136.7, 123.7, 123.6, 121.8, 121.7, 89.1, 88.6, 73.6, 73.2, 51.1, 47.0, 37.3, 37.1, 35.7, 34.0, 32.6, 25.1, 4.1, 4.1. IR (film), 2998, 2263, 1674 cm^{-1}. HRMS (ESI) $C_{12}H_{15}N_2O$ $[M + H]^+$, 203.1184; found 203.1178.



tert-butyl (pyridin-4-ylmethyl)carbamate (ii): Using the procedure described for the preparation of (**i**), 3.0 g of 4-picolylamine was acylated with 6.65 g of Boc_2O to get compound **ii** as a yellow solid (2.5 g, 43 %) . Mp. 84-86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.25 – 7.13 (m, 2H), 5.17 (s, 1H), 4.33 (d, *J* = 6.1 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.8, 149.7, 122.6, 122.3, 74.1, 49.1, 48.5, 28.3. IR (film): 3206, 3012, 2983, 1690 cm^{-1}.

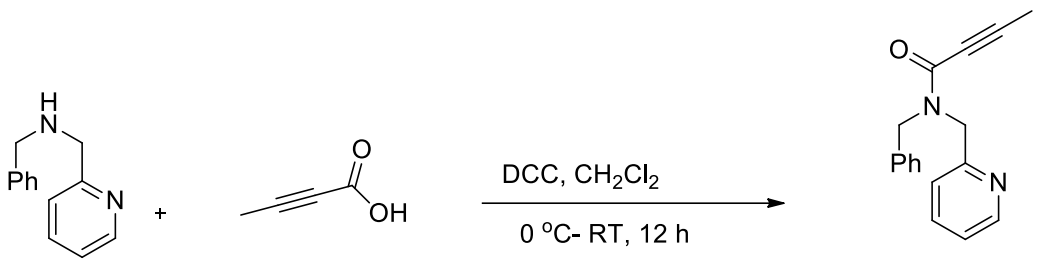
tert-butyl but-2-yn-1-yl(pyridin-4-ylmethyl)carbamate (3.50): Using the procedure described for the preparation of **3.48**, 0.250 g of compound **ii** was alkylated with 126 µL of 1-bromo-2-butyne to get compound **3.50** (0.115 g, 37 %) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.9 Hz, 2H), 7.19 (d, *J* = 5.1 Hz, 2H), 4.53 (s, 2H), 4.02 (d, *J*

= 71.0 Hz, 2H), 1.79 (t, *J* = 2.4 Hz, 3H), 1.47 (dd, *J* = 30.7, 13.9 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 149.8, 122.7, 122.3, 85.1, 81.0, 74.2, 49.0, 48.5, 36.8, 28.4, 3.6. IR (film): 3102, 2976, 2225, 1696 cm^{-1}. HRMS (ESI) $C_{15}H_{21}N_2O_2$ $[M + H]^+$, 261.1603; found 261.1621.



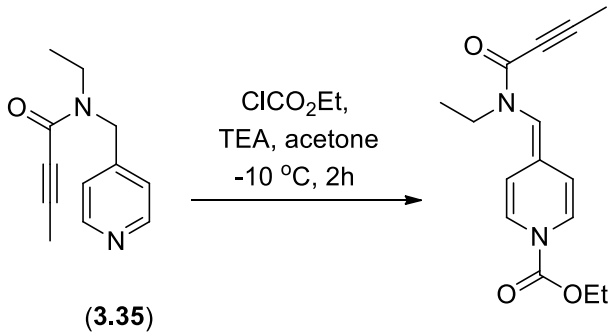
(**3.51**)

N-Benzyl-N-(2-(pyridin-4-yl)ethyl)but-2-ynamide (3.51): Using the procedure described for the preparation of **3.35**, 1.00 g (4.71 mmol) of N-benzyl-2-(pyridin-4-yl)ethanamine and 0.402 g (4.71 mmol) of 2-butynoic acid were coupled to give **3.51** (0.66 g, 50%) as yellow semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$) Major rotamer δ 8.49 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.38–7.28 (m, 5H), 7.07 (dd, *J* = 4.4, 1.6 Hz, 2H), 4.65 (s, 2H), 3.51 (dt, *J* = 16.9, 7.7 Hz, 2H), 2.80–2.76 (m, 2H), 2.00 (s, 3H). Minor rotamer δ 8.52 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.25–7.19 (m, 5H), 7.04 (dd, *J* = 4.4, 1.6 Hz, 2H), 4.61 (s, 2H), 3.73–3.67 (m, 2H), 2.84–2.80 (m, 2H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 150.2, 150.1, 148.0, 147.4, 136.7, 136.5, 129.1, 129.0, 128.4, 128.3, 128.0, 127.7, 124.3, 124.3, 89.7, 73.6, 73.5, 53.6, 49.0, 48.0, 45.3, 34.8, 34.2, 33.0, 25.2, 4.3, 4.2. IR (film): 2930, 2242, 1714, 1625 cm^{-1}. HRMS (ESI) $C_{18}H_{19}N_2O$ $[M + H]^+$, 279.1497; found 279.1517.



(**3.52**)

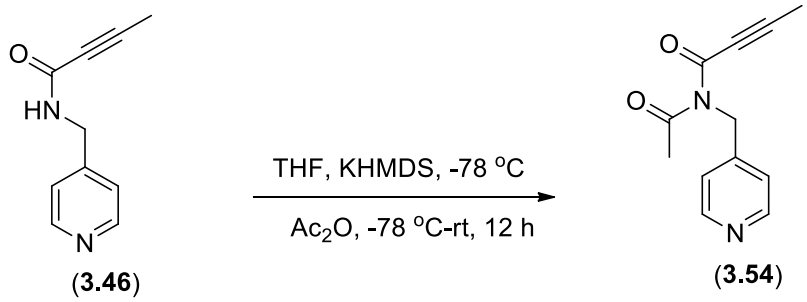
N-Benzyl-N-(pyridin-2-ylmethyl)but-2-ynamide (3.52): Using the procedure described for the preparation of **3.35**, 1.00 g (6.05 mmol) of N-benzyl (2-aminomethyl) pyridine and 0.510 g (6.05 mmol) of 2-butynoic acid were coupled to give **3.52** (0.94 g, 59%) as pale brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) Major rotamer δ 8.52 (dd, *J* = 4.9, 0.8 Hz, 1H), 7.65–7.58 (m, 1H), 7.39–7.14 (m, 7H), 4.85 (s, 2H), 4.62 (s, 2H), 2.02 (s, 3H). Minor rotamer δ 8.58 (dd, *J* = 3.2, 1.0 Hz, 1H), 7.72–7.65 (m, 1H), 7.39–7.14 (m, 7H), 4.82 (s, 2H), 4.61 (s, 2H), 1.97 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 156.7, 155.5, 155.3, 149.8, 149.5, 137.1, 136.9, 136.4, 128.9, 128.8, 128.8, 128.0, 127.8, 122.7, 122.7, 122.6, 121.5, 90.1, 89.9, 73.6, 53.6, 52.7, 48.8, 47.5, 4.3. IR (film): 2927, 2246, 1623 cm^{-1}. HRMS (ESI) $C_{17}H_{17}N_2O$ $[M + H]^+$, 265.1341; found 265.1360.



(**3.35**) (**3.53**)

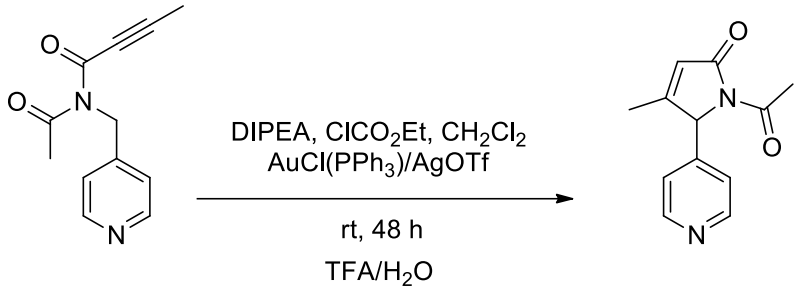
Ethyl-4-((N-ethylbut-2-ynamido)methylene)pyridine-1(4H)-carboxylate (3.53): A solution of ethyl chloroformate (47 µl, 0.049 mmol, 1.0 equiv) in deuterated acetone (2.0 mL) was added dropwise with magnetic stirring to a mixture of tertiary amide **3.35** (0.100

g, 0.49 mmol, 1.0 equiv) and TEA (137 µl, 0.98 mmol, 2.0 equiv) in deuterated acetone at -10 ^{o}C. The resulting suspension was stirred at -10 ^{o}C for 2 h, then allowed to warm to room temperature. The white precipitate was filtered off and washed with deuterated acetone (5 mL). The combined filtrate was concentrated under reduced pressure to afford a pale yellow semi-solid (**3.53**, 0.129 g, 95%) which was characterized by (Mixture of rotamers).^{1}H NMR (300 MHz, acetone-d_6) Major rotamer; δ 7.05 (dd, *J* = 8.3, 1.5 Hz, 2H), 5.93 (dd, *J* = 8.3, 2.1 Hz, 2H), 5.57 (s, 1H), 4.38 – 4.24 (m, 2H), 3.44 (q, *J* = 7.1 Hz, 2H), 1.89 (s, 3H), 1.33 (td, *J* = 7.1, 3.3 Hz, 3H), 1.04 (t, *J* = 7.1, 3.3 Hz, 3H). Minor rotamer; δ 7.13 (dd, *J* = 8.4, 1.4 Hz, 2H), 5.80 (d, *J* = 8.3 Hz, 2H), 5.42 (s, 1H), 4.38 – 4.24 (m, 2H), 3.62 – 3.51 (m, 2H), 1.89 (s, 3H), 1.33 (td, *J* = 7.1, 3.3 Hz, 3H), 1.04 (t, *J* = 7.1, 3.3 Hz, 3H).



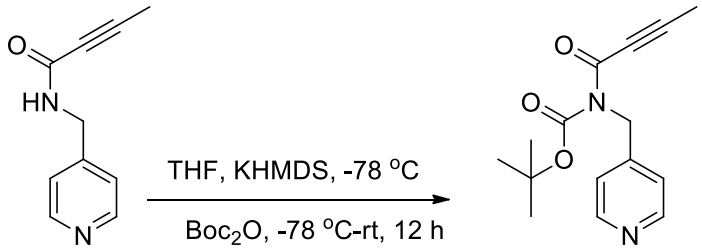
(**3.46**) (**3.54**)

N-Acetyl-N-(pyridin-4-ylmethyl)but-2-ynamide (3.54): Using the procedure described for the preparation of **3.55**, 0.150 g (0.862 mmol) of compound **3.46** was acylated with 97.6 µL (1.03 mmol) of acetic anhydride to give substrate **3.54** (0.075 g, 40%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58–8.55 (m, 2H), 7.16 (d, *J* = 4.6 Hz, 2H), 5.13 (s, 2H), 2.61 (d, *J* = 1.2 Hz, 3H), 2.06–2.00 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 150.3, 146.3, 122.0, 94.8, 74.6, 48.0, 27.7, 4.5. IR (film): 2909, 2241, 1728, 1699 cm^{-1}. HRMS (ESI) $C_{12}H_{13}N_2O_2$ $[M + H]^+$, 217.0977; found 217.0995.



(**3.54**) (**3.56**)

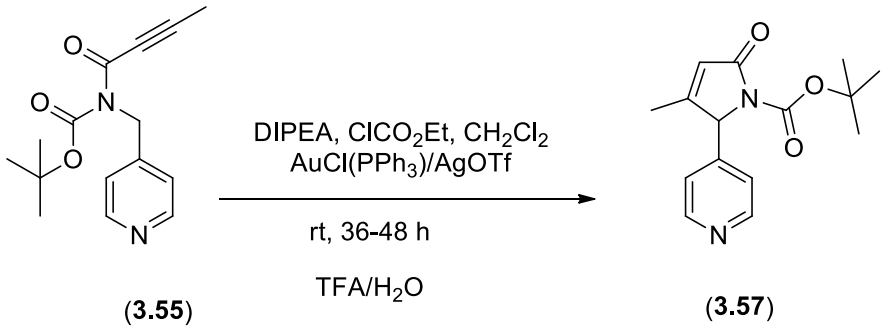
1-Acetyl-4-methyl-5-(pyridin-4-yl)-1H-pyrrol-2(5H)-one (3.56): Using the procedure for the preparation of **3.36**, 0.050 g of **3.54** was cyclized to give **3.56** (0.024 g, 48%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64–8.58 (m, 2H), 7.15 (dd, *J* = 4.5, 1.6 Hz, 2H), 6.01–5.96 (m, 1H), 5.41 (s, 1H), 2.51 (s, 3H), 1.85 (dd, *J* = 5.3, 1.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.3, 162.5, 150.8, 145.3, 122.4, 121.9, 66.7, 24.9, 15.0. IR (film): 3085, 2217, 1732, 1697 cm $^{-1}$. HRMS (ESI) $C_{12}H_{13}N_2O_2$ [M + H] $^{+}$, 217.0977; found 217.0972.



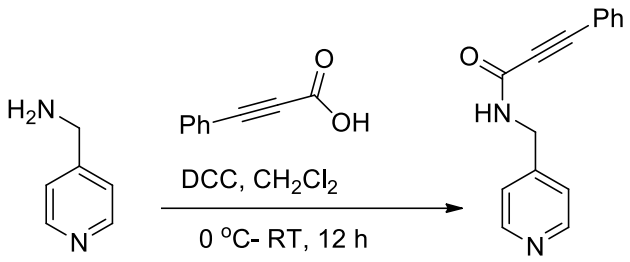
(**3.46**) (**3.55**)

tert-Butyl-but-2-ynoyl(pyridin-4-ylmethyl)carbamate (3.55): To a solution of compound **3.46** (0.331 g, 1.89 mmol, 1.0 equiv) in THF (3.0 mL) was added KHMDS (0.500 M in toluene, 5.70 mL, 2.84 mmol, 1.5 equiv) at -78 °C. After stirring for 2 h at -78 °C, a solution of Boc_2O (0.492 g, 2.27 mmol, 1.2 equiv) in THF (2.0 mL) was added dropwise. The reaction was allowed to warm to room temperature and maintained overnight. The reaction was quenched with dilute aq. NH_4OH solution and the layers

were separated. The aqueous layer was extracted with ethyl acetate (2 x 25 mL), and the combined organic layer was washed with water (25 mL) and brine (25 mL), and dried over anhydrous Na_2SO_4. Filtration and removal of the solvent gave a brown oil that was purified by silica gel column chromatography using 60-70 % ethyl aceate in hexanes to afford **3.55** (0.21 g, 40%) as brown semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.4, 1.5 Hz, 2H), 7.16 (d, *J* = 4.5 Hz, 2H), 4.90 (s, 2H), 2.07 (s, 3H), 1.47 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.9, 151.7, 150.2, 146.5, 122.4, 94.0, 84.7, 75.0, 46.4, 28.1, 4.8. IR (film): 2980, 2226, 1772, 1726, 1645 cm^{-1}. HRMS (ESI) $C_{15}H_{19}N_2O_3$ [M + H] $^+$, 275.1396; found 275.1413.

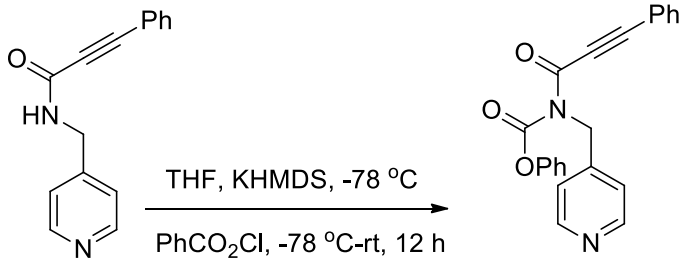


tert-Butyl 3-methyl-5-oxo-2-(pyridin-4-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (12): Using the procedure for the preparation of **3.36**, 0.050 g of **3.55** was cyclized to give **3.57** (0.037 g, 74 %) as a pale pink solid. Mp. 82-86 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.8 Hz, 2H), 7.16 (d, *J* = 5.8 Hz, 2H), 5.96 (s, 1H), 5.25 (s, 1H), 1.83 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 160.3, 150.5, 148.4, 146.0, 122.5, 121.5, 83.3, 67.6, 27.8, 14.7. IR (film): 2985, 1776, 1716, 1645 cm^{-1}. HRMS (ESI) $C_{15}H_{19}N_2O_3$ [M + H] $^+$, 275.1396; found 275.1402.



(**3.58**)

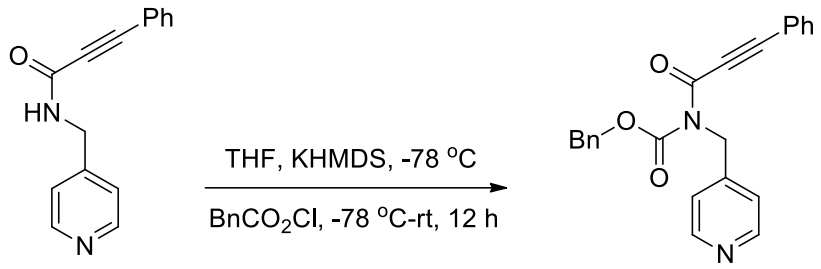
3-Phenyl-N-(pyridin-4-ylmethyl)propiolamide (3.58): Using the procedure described for the preparation of **3.35**, 1.00 g (9.25 mmol) of 4-aminomethyl pyridine and 1.35 g (9.25 mmol) of 3-phenyl-2-propynoic acid were coupled to give substrate (**3.58**) (1.39 g, 61%) as brown solid. Mp. 75-77 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.52 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.46–7.31 (m, 3H), 7.26 (dd, *J* = 12.6, 4.8 Hz, 2H), 6.69 (s, 1H), 4.56 (d, *J* = 6.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 150.3, 150.1, 146.5, 132.6, 130.3, 128.6, 122.4, 119.9, 85.9, 82.6, 42.6. IR (film): 3227, 2222, 1633 cm^{-1}. HRMS (ESI) $C_{15}H_{13}N_2O$ [M + H] $^{+}$, 237.1028; found 237.1046.



(**3.58**) (**3.59**)

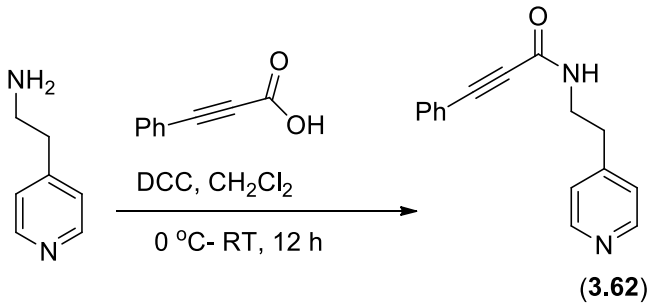
Phenyl (3-phenylpropioloyl)(pyridin-4-ylmethyl)carbamate (3.59): Using the procedure described for the preparation of **3.55**, 0.160 g (0.676 mmol) of compound **3.58** was acylated with 100 µL (0.813 mmol) of phenyl chloroformate to give substrate **3.59** (0.101 g, 42%) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.57–7.48 (m, 2H), 7.48–7.25 (m, 8H), 7.09 (dd, *J* = 4.5, 1.6 Hz, 2H), 5.15 (d, *J* =

5.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 150.1, 145.7, 133.4, 131.2, 130.0, 128.8, 126.9, 122.8, 121.4, 120.0, 95.4, 82.7, 46.8. IR (film): 3061, 2998, 2211, 1747, 1659 $^{-1}$cm. HRMS (ESI) $C_{22}H_{17}N_2O_3$ $[M + H]^+$, 357.1239; found 357.1259.



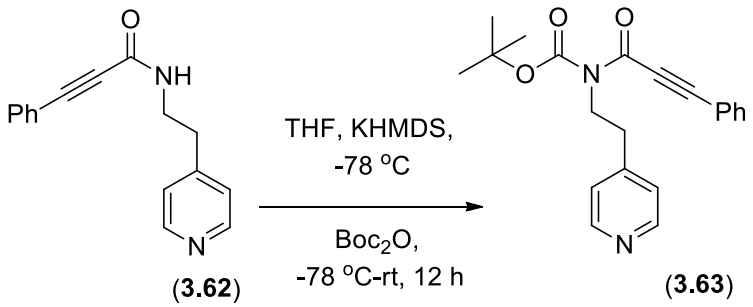
(**3.58**) (**3.60**)

Benzyl (3-phenylpropioloyl) (pyridin-4-ylmethyl) carbamate (3.60): Using the procedure described for the preparation of **3.55**, 0.160 g (0.676 mmol) of compound (**3.58**) was acylated with 116 µL (0.813 mmol) of benzyl chloroformate to give **3.60** (0.105 g, 42%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.49 – 7.39 (m, 2H), 7.38 – 7.22 (m, 8H), 7.12 (dd, *J* = 4.6, 1.6 Hz, 2), 5.26 (s, 2H), 4.95 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 153.1, 150.3, 150.2, 145.8, 135.1, 134.5, 133.1, 130.9, 129.1, 129.0, 128.84, 128.80, 128.7, 128.5, 122.6, 122.3, 120.3, 94.9, 82.9, 69.7, 69.4, 49.1, 46.6. IR (film): 2993, 2223, 1740, 1701 cm^{-1}. HRMS (ESI) $C_{23}H_{19}N_2O_3$ $[M + H]^+$, 371.1396; found 371.1408.



(**3.62**)

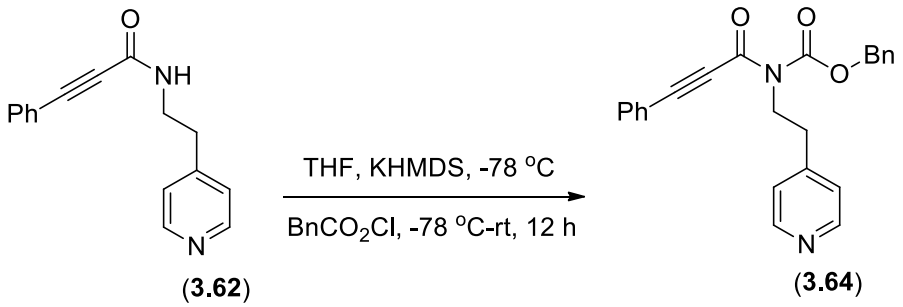
3-Phenyl-N-(2-(pyridin-4-yl) ethyl)propiolamide (3.62): Using the procedure described for the preparation of **3.35**, 1.00 g (8.18 mmol) of 4-(2-aminoethyl) pyridine and 2.02 g (8.18 mmol) of 3-phenyl-2-propynoic acid were coupled to give substrate (**3.62**) (0.75 g, 55%) as an off white solid. Mp. 88-90 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54–8.50 (m, 2H), 7.50 (dd, *J* = 5.2, 3.2 Hz, 2H), 7.41 (ddd, *J* = 6.6, 3.9, 1.3 Hz, 1H), 7.34 (dd, *J* = 10.3, 4.5 Hz, 2H), 7.16 (t, *J* = 5.2 Hz, 2H), 6.30 (s, 1H), 3.64 (q, *J* = 6.9 Hz, 2H), 2.91 (dt, *J* = 13.9, 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 150.0, 147.7, 132.5, 130.2, 128.6, 124.2, 120.1, 85.0, 82.8, 40.1, 34.8. IR (film): 3236, 2215, 1645 cm^{-1}. HRMS (ESI) $C_{16}H_{15}N_2O$ $[M + H]^+$, 251.1184; found 251.1204.



(**3.62**) (**3.63**)

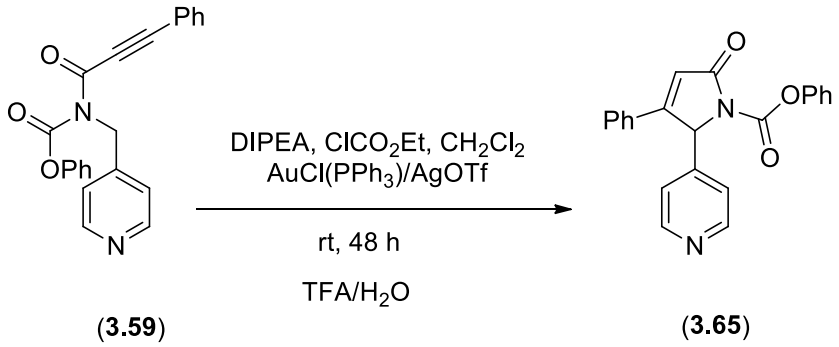
tert-Butyl (3-phenylpropioloyl)(2-(pyridin-4-yl)ethyl)carbamate (3.63): Using the procedure described for the preparation of **3.55**, 0.250 g (0.99 mmol) of compound **3.62** was acylated with 0.239 g (0.99 mmol) of Boc_2O to give substrate **3.63** (0.240 g, 42%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.60–7.56

(m, 2H), 7.44 (dd, *J*= 6.0, 3.8 Hz, 1H), 7.42 (dd, *J* = 11.1, 6.0 Hz, 2H), 7.18 (t, *J* = 5.9 Hz, 2H), 4.00 (dd, *J* = 8.3, 6.8 Hz, 2H), 2.91 (dd, *J* = 16.8, 9.1 Hz, 2H), 1.51 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 151.7, 150.1, 147.6, 132.7, 130.6, 128.8, 124.6, 120.7, 93.3, 84.5, 83.6, 44.9, 34.2, 28.1. IR (film): 3001, 2301, 1725, 1700 cm^{-1}. HRMS (ESI) $C_{21}H_{23}N_2O_3$ [M + H] $^+$, 351.1709; found 351.1717.



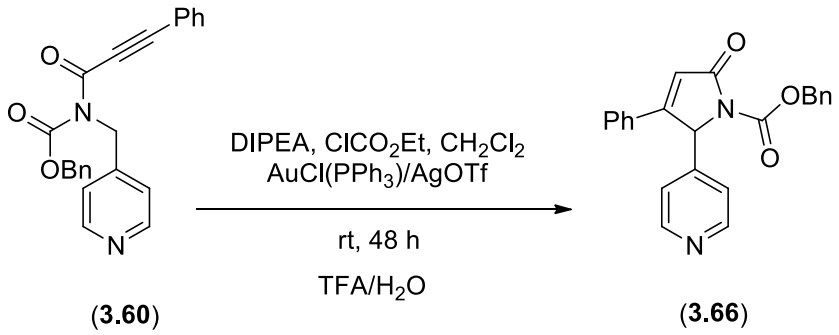
(**3.62**) (**3.64**)

Benzyl (3-phenylpropioloyl) (2-(pyridin-4-yl)ethyl)carbamate (3.64): Using the procedure described for the preparation of **3.55**, 0.190 g (0.759 mmol) of compound **3.62** was acylated with 130 µL (0.911 mmol) of benzyl chloroformate to give substrate **3.64** (0.140 g, 68%) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.5, 1.5, 2H), 7.49–7.40 (m, 2H), 7.40–7.29 (m, 8H), 7.09 (dd, *J* = 4.5, 1.4 Hz, 2H), 5.25 (s, 2H), 4.07–4.01 (m, 2H), 2.87 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 153.2, 150.2, 147.3, 134.7, 133.1, 130.8, 129.1, 129.0, 128.8, 128.7, 124.5, 120.4, 93.9, 83.2, 69.5, 45.0, 34.2. IR (film): 2987, 2241, 1735, 1701 cm^{-1}. HRMS (ESI) $C_{24}H_{21}N_2O_3$ [M + H] $^+$, 385.1552; found 385.1546.



(**3.59**) (**3.65**)

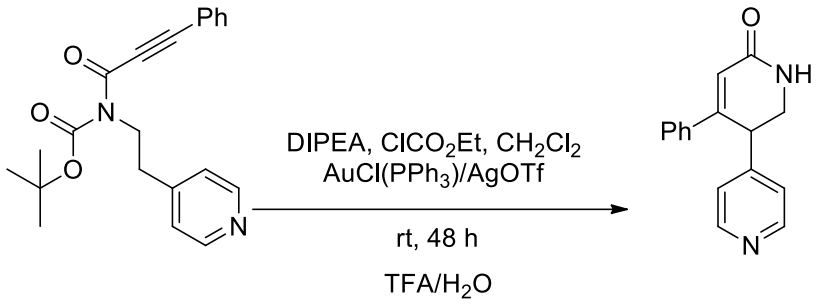
Phenyl 3-phenyl-5-oxo-2-(pyridin-4-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (3.65): Using the procedure for the preparation of **3.36**, 0.050 g of **3.59** was cyclized to give **3.65** (0.029 g, 58 %) as light orange solid. Mp. 178-181 ^{o}C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.49–7.19 (m, 12H), 7.03–6.96 (m, 2H), 6.64 (d, *J* = 1.2 Hz, 1H), 6.15 (d, *J* = 1.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 160.7, 150.8, 150.2, 145.2, 131.8, 129.9, 129.7, 129.5, 127.5, 126.6, 123.0, 121.6, 120.4, 64.8. IR (film): 2957, 1788, 1732, 1648 cm^{-1}. HRMS (ESI) $C_{22}H_{17}N_2O_3$ [M + H] $^{+}$, 357.1239; found 357.1233.



(**3.60**) (**3.66**)

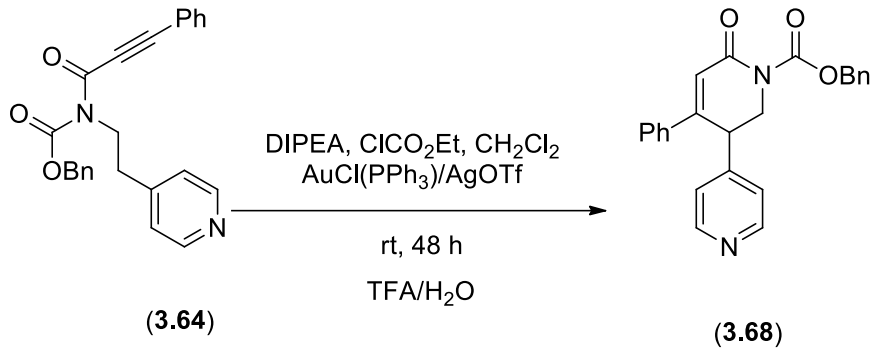
Benzyl 3-phenyl-5-oxo-2-(pyridin-4-yl)-2, 5-dihydro-1H-pyrrole-1-carboxylate (3.66): Using the procedure for the preparation of **3.36**, 0.050 g of **3.60** was cyclized to give **3.66** (0.031 g, 62%) as yellow solid. Mp. 185-190 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, *J* = 5.7 Hz, 2H), 7.41–7.29 (m, 8H), 7.25 (d, *J* = 6.7 Hz, 2H), 7.18 (d, *J* = 5.7 Hz,

2H), 6.54 (s, 1H), 5.99 (s, 1H), 5.28–5.19 (m, 1H), 5.14 (d, *J* = 12.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 160.4, 150.6, 150.4, 145.4, 135.0, 131.6, 129.4, 128.8, 128.8, 128.5, 127.4, 122.8, 120.4, 68.6, 64.6. IR (film): 3057, 1779, 1734, 1650 cm^{-1}. HRMS (ESI) $C_{23}H_{19}N_2O_3$ [M + H] $^+$, 371.1396; found 371.1389.



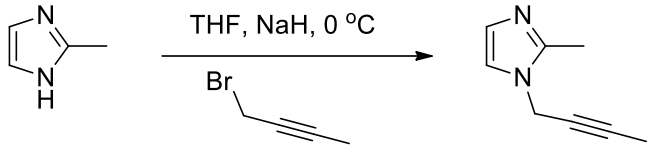
(**3.63**) (**3.67**)

4-Phenyl-2, 3-dihydro-[3,4'-bipyridin]-6(1H)-one (3.67): Using the procedure for the preparation of **3.36**, 0.050 g of **3.63** was cyclized to give **3.67** (0.021 g, 58%) as a pale yellow semi-solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.67 (d, *J* = 2.1 Hz, 1H), 7.26 (d, *J* = 6.2 Hz, 5H), 7.18 (t, *J* = 8.8 Hz, 2H), 6.34 (s, 1H), 4.58 (d, *J* = 8.2 Hz, 1H), 4.01 (dd, *J* = 17.4, 8.1 Hz, 1H), 3.34 (dd, *J* = 9.7, 1.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 151.3, 150.7, 134.7, 134.2, 130.8, 130.0, 129.5, 129.0, 128.8, 122.5, 48.7, 42.9. IR (film): 2997, 1718 cm^{-1}. HRMS (ESI) $C_{16}H_{15}N_2O$ [M + H] $^+$, 251.1184; found 251.1181.



(**3.64**) (**3.68**)

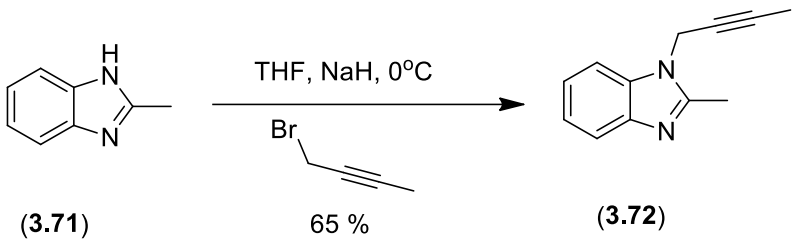
Benzyl 6-oxo-4-phenyl-2,3-dihydro-[3,4'-bipyridine]-1(6H)-carboxylate (3.68): Using the procedure for the preparation of **3.36**, 0.050 g of **3.64** was cyclized to give **3.68** (0.032 g, 64 %) as pale yellow oil. (Mixture of rotamer) ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.51–7.23 (m, 10H), 7.18–7.13 (m, 2H), 5.33–5.28 (m, 2H), 4.49 (d, *J* = 8.6 Hz, 1H), 4.24 (dd, *J* = 10.9, 8.6 Hz, 1H), 3.79 (dd, *J* = 10.9, 2.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 151.9, 150.9, 150.3, 138.7, 135.34, 135.28, 133.6, 130.5, 130.4, 130.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 127.90, 122.4, 121.8, 68.6, 68.6, 52.1, 51.0, 39.9, 30.3. IR (film): 3058, 1776, 1718 cm^{-1}. HRMS (ESI) $C_{24}H_{21}N_2O_3$ [M + H] $^{+}$, 385.1552; found 385.1561.



(**3.70**)

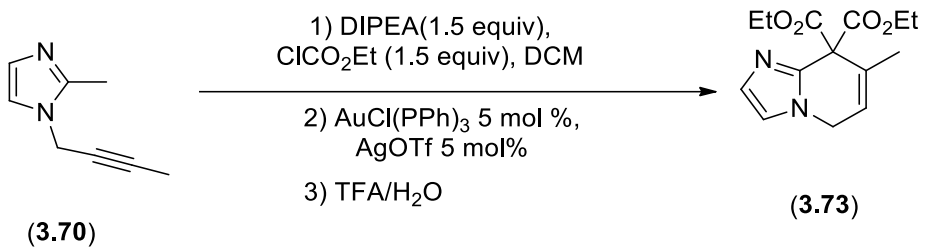
1-(but-2-yn-1-yl)-2-methyl-1H-imidazole (3.70): To a solution of 2-methyl imidazole (0.50 g, 6.09 mmol, 1.0 eq) in THF, 60 % NaH (0.16 g, 6.70 mmol, 1.1 eq) was added at 0 °C. After 1 h, 1-bromo-2-butyne (0.640 mL, 7.31 mmol, 1.2 eq) was added at 0 °C and this reaction was allowed to warm to room temperature and stirred for 4-5 h. The reaction was quenched with water (10.0 mL) and extracted with ethyl acetate (25 mL x 2). The

combined organic layer was washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get a brown residue. This residue was then purified by silica gel flash column chromatography using ethyl acetate: hexanes 80-90 % to get **3.70** (0.57 g, 70 %) as a brown liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 12.1, 1.3 Hz, 2H), 4.54 (q, *J* = 2.4 Hz, 2H), 2.40 (s, 3H), 1.83 (t, *J* = 2.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 127.90, 121.4, 77.5, 69.2, 29.7, 4.0. IR (film): 3110, 2275 cm^{-1}. HRMS (ESI) $C_8H_{11}N_2$ [M + H] $^+$, 135.0922; found 135.0926.



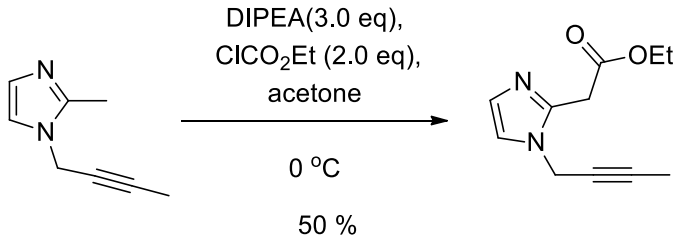
(**3.71**) 65 % (**3.72**)

1-(but-2-yn-1-yl)-2-methyl-1H-benzimidazole (3.72): Using the procedure described for the preparation of **3.70**, 1.00 g of 2-methyl benzimidazole was alkylated with 1.05 g of 1-bromo-2-butyne to give **3.72** (0.81 g, 58 %) as pale brown solid. Mp. 58-62 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 – 7.55 (m, 1H), 7.34 – 7.24 (m, 1H), 7.21 – 7.06 (m, 2H), 4.65 (q, *J* = 2.4 Hz, 2H), 2.54 (s, 2H), 1.68 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 142.7, 134.9, 122.3, 122.14, 119.3, 109.4, 81.4, 72.4, 33.6, 14.0, 3.6. IR (film): 3055, 2229, 1615 cm^{-1}. HRMS (ESI) $C_{12}H_{13}N_2$ [M + H] $^+$, 185.1079; found 185.1079.



(**3.70**) (**3.73**)

Diethyl 7-methylimidazo[1,2-a]pyridine-8,8(5H)-dicarboxylate (3.73): Using the procedure for the preparation of **3.36**, 0.100 g of **3.70** was cyclized to afford **3.73** (0.033 g, 16 %) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 1.2 Hz, 1H), 6.93 (d, *J* = 1.2 Hz, 1H), 5.94 (td, *J* = 3.3, 1.6 Hz, 1H), 4.61 – 4.51 (m, 2H), 4.32 – 4.21 (m, 4H), 2.06 (dd, *J* = 3.4, 1.9 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.17, 140.24, 130.58, 129.85, 120.82, 118.10, 62.50, 44.42, 20.22, 14.17. IR (film): 3009, 1739, 1605 cm^{-1}. HRMS (ESI) $C_{14}H_{19}N_2O_4$ [M + H] $^{+}$, 279.1345; found 279.1318.



(**3.70**) (**3.75**)

Ethyl 2-(1-(but-2-yn-1-yl)-1H-imidazol-2-yl)acetate (3.75): To a solution of **3.70** (0.100 g, 0.746 mmol, 1.0 eq) and DIPEA (0.370 mL, 2.24 mmol, 3.0 eq) in 5.0 mL acetone was added $ClCO_2Et$ (0.142 mL, 1.5 mmol, 2.0 eq) in 3.0 mL acetone at 0 °C. Stirred the reaction mixture overnight at room temperature. Concentrated the reaction mixture under reduced pressure and then purified the crude residue by silica gel flash column chromatography using 75-80 % ethyl acetate:hexanes to give **3.75** (0.077 g, 50 %) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 0.9 Hz, 2H), 4.70 (q, *J* =

2.4 Hz, 2H), 4.15 (q, *J* =7.1 Hz, 2H), 3.98 (s, 2H), 1.85 (t, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.1Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.58, 140.79, 126.18, 120.79, 83.17, 71.77, 61.88, 37.07, 33.46, 14.28, 3.68. IR (film): 3019, 2253, 1713 cm^{-1}. HRMS (ESI) $C_{11}H_{15}N_2O_2$ $[M + H]^+$, 207.1134; found 207.1137.

CHAPTER 4

APPROACHES TO INTRAMOLECULAR METAL CATALYZED ADDITION TO PYRIDINE DERIVATIVES

4.1 Introduction

As has been emphasized in previous chapters, nitrogen containing heterocycles occupy positions of unparalleled importance in natural product, bioorganic and medicinal chemistry. In particular, the nitrogen containing derivatives of pyridine and piperidine ring systems are among the most common. Pyridine and pyridine derived structures are privileged pharmacophores in medicinal chemistry.[87] The presence of these ring systems in bioactive materials of pharmaceutical significance mandates the availability of synthetic methods for accessing a wide range of structural analogues. Several pharmacologically active pyridine/piperidine compounds are illustrated in figure 4.1.

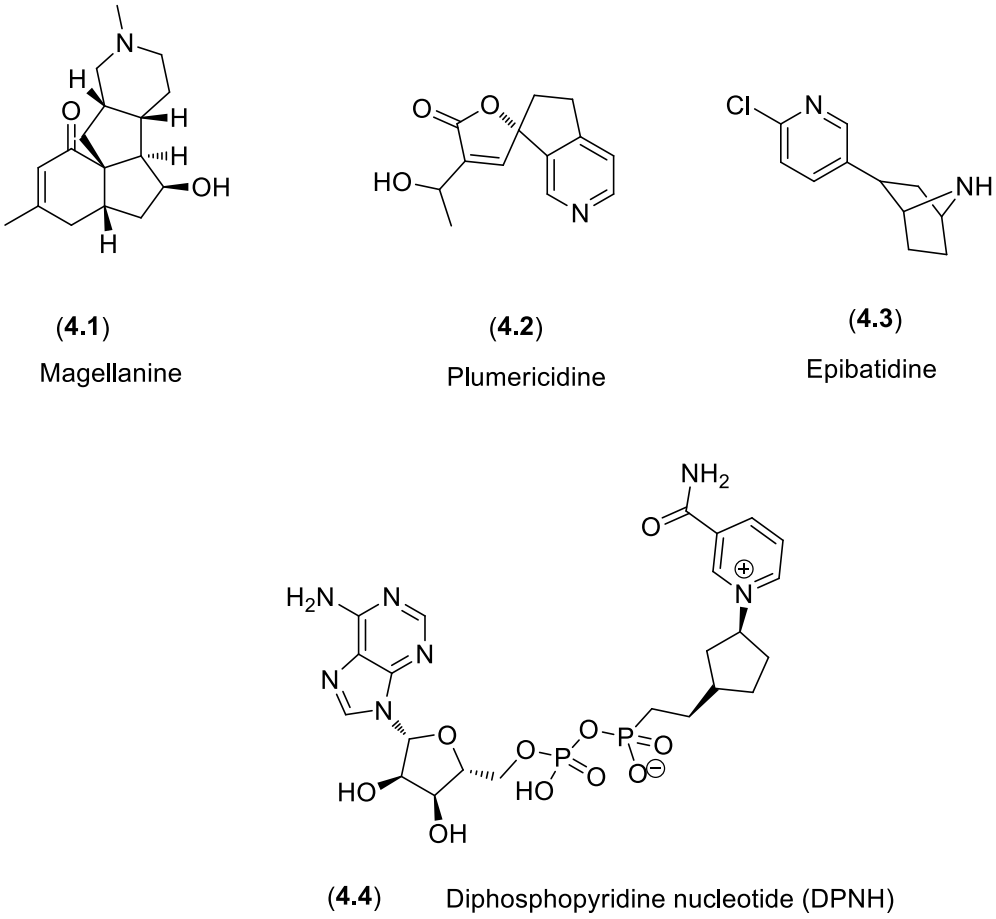
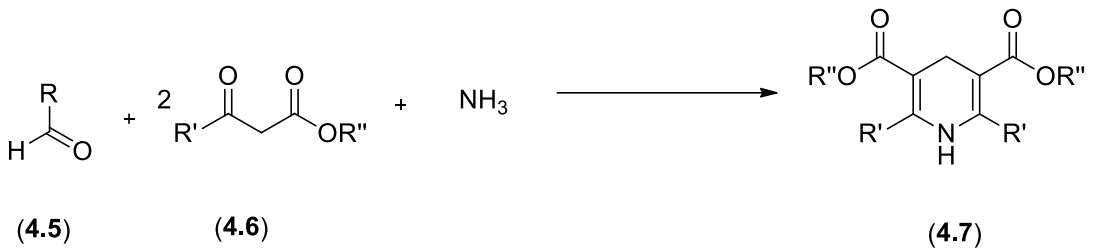


Figure 4.1 Selected pyridine and piperidine-based natural products.

Magellanine (**4.1**) a *Lycopodium* alkaloid has a characteristic tetracyclic core that consists of six contiguous stereocenters, one of which is quaternary. Hence, this framework presented formidable synthetic challenge, which is further heightened by the presence of highly basic tertiary amine group.[88] Plumericidine (**4.2**) a recently isolated alkaloid with anticancer activity is obtained from the flowers of *Plumeria rubra* L. *cv*. *Acutifolia*.[89] Epibatidine (**4.3**) is an alkaloid obtained from the skin of the endangered Ecuadorian frog *Epipedobates tricolor*. It turned out to be a very powerful analgesic, but

due to its gastrointestinal side effects it could not appear on the medicinal market.[90] The dihydropyridine ring systems are of considerable interest because of their presence in the coenzymes. In metabolism, diphosphopyridine nucleotide (DPNH) (**4.4**) is involved in redox reactions and acts as an electron carrier from one reaction to other.[91]

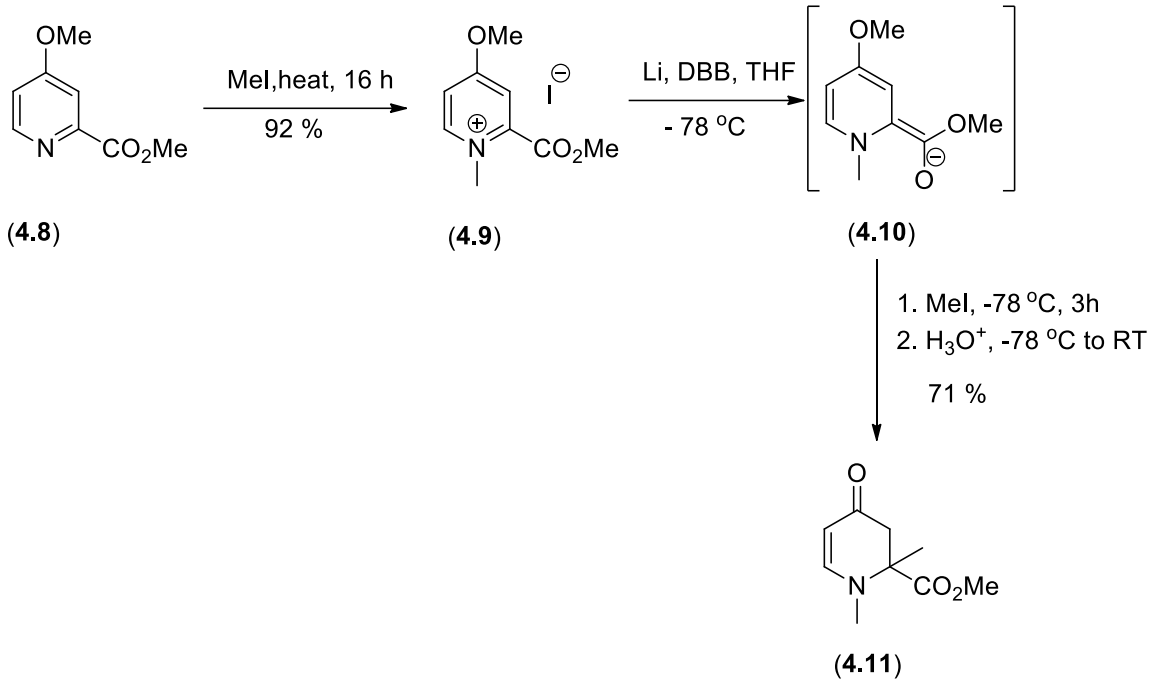
Given the presence of these aza-heterocyclic ring systems in various natural products, bioactive materials and pharmaceutically important compounds, it is not surprising that considerable amounts of time and energy have been devoted towards developing viable synthetic methodologies for their construction. Various groups have reported the synthesis of dihydropyridines which can serve as versatile intermediates in the synthesis of natural products. There are three general routes for the synthesis of these dihydropyridines: a) Synthesis from ring opened precursors. For example, one of the most common and well established methods is the three component condensation reaction involving an aldehyde, a β-ketoester and ammonium acetate, popularly known as the Hantzsch pyridine synthesis.[92] This procedure leads to 1, 4-dihydropyridines as indicated in scheme 4.1.[93]



(**4.5**) (**4.6**) (**4.7**)

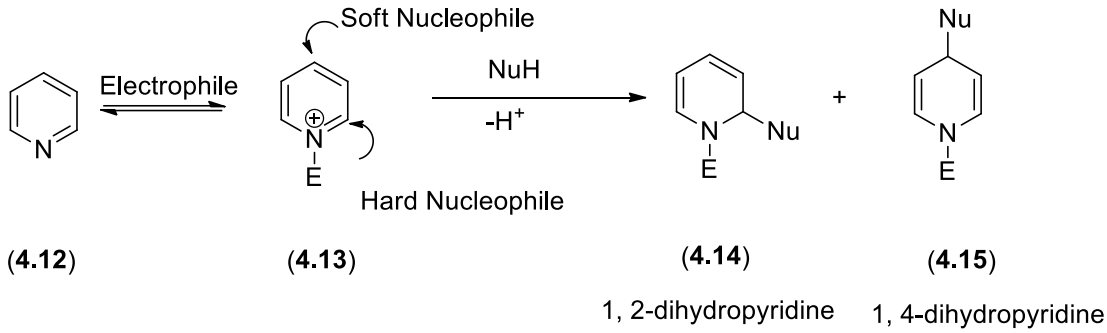
Scheme 4.1 Hantzsch synthesis.

b) The partial reduction of pyridines or their salts: Pyridinium salts are reduced to the corresponding dihydropyridine intermediates on treatment with reducing agents like sodium dithionate, lithium di-tert-butylbiphenyl (Li-DBB), Na-naphthalene, and $NaBH_4$ (scheme 4.2).[94]



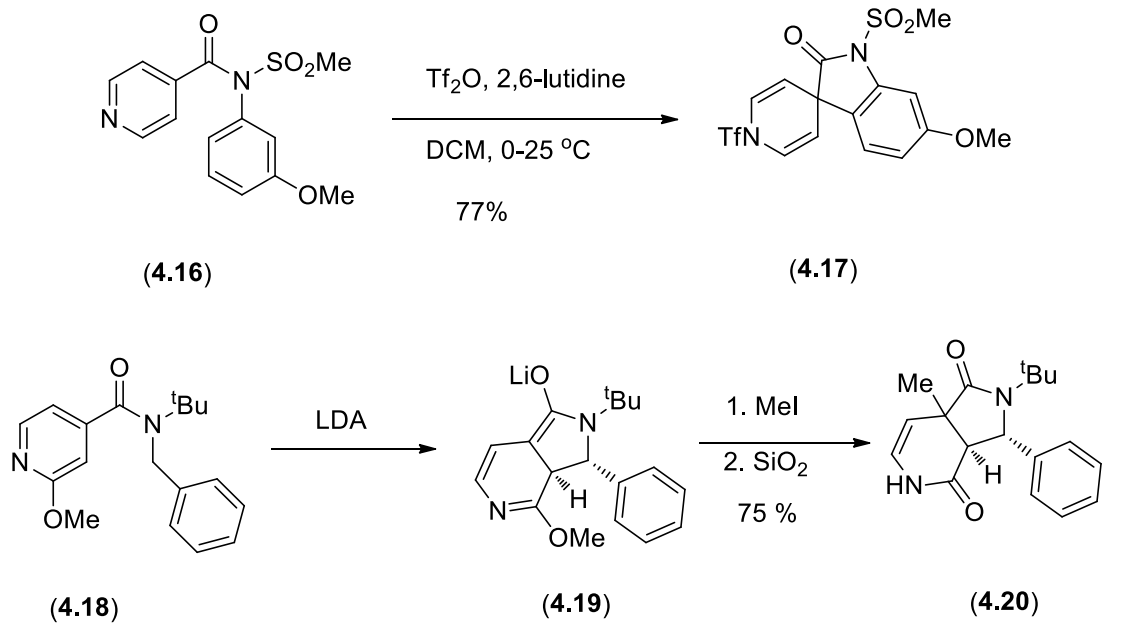
Scheme 4.2 Example of pyridinium salt reduction.

c) Reaction of pyridines or their salts with nucleophiles: As discussed in chapter 1, pyridines participate in regioselective reactions with nucleophiles after conversion to pyridinium salts upon treatment with alkylating or acylating reagents. Both inter- and intramolecular nucleophilic additions to pyridinium salts have been reported. Particularly, intermolecular nucleophilic additions are extensively studied for the synthesis of functionalized heterocycles.[10] In general, hard nucleophiles like organomagnesium and organolithium reagents preferentially add to the C-2 position of pyridinium salts to give 1, 2- dihydropyridines.[95] In contrast, soft nucleophiles like organocuprates, metal-enolates and enol ethers add preferentially to the C-4 position of pyridinium salts to give 1, 4-dihydropyridines (scheme 4.3). [96]



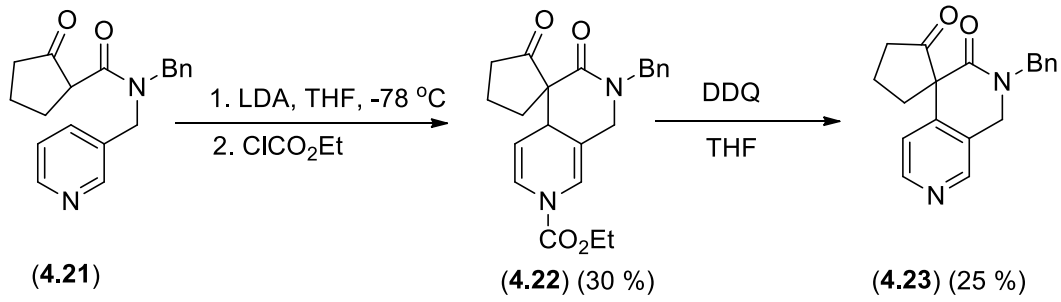
Scheme 4.3 General representation of nucleophilic additions to pyridinium salts.

Intramolecular nucleophilic addition to pyridinium salts also has been reported in the literature. The further manipulation of the so formed dihydropyridines can help in accessing more complex molecular frameworks. For example, Clayden and coworkers reported that N-arylisonicotinamide (**4.16**) afforded the benzofused spiro 1, 4-dihydropyridine (**4.17**) on reaction with triflic anhydride in the presence of a hindered base in CH_2Cl_2 (scheme 4.4).[37] The same group also showed that when lithiated isonicotinamide derivative (**4.18**) added in an intramolecular fashion to the unactivated pyridine ring, the resulting dihydropyridine (**4.19**) could be further alkylated or acylated to give (**4.20**) in good yield as a single diastereomer (scheme 4.4).[36]



Scheme 4.4 Intramolecular reaction examples.

In related transformations, Pigge and co-workers have successfully shown that derivatives of aminomethylated pyridine (**4.21**) undergo intramolecular cyclization in the presence of base and electrophile to give diazadecaline ring system (**4.22**). Oxidation of **4.22** affords fused ring pyridine product **4.23** (scheme 4.5).[97]

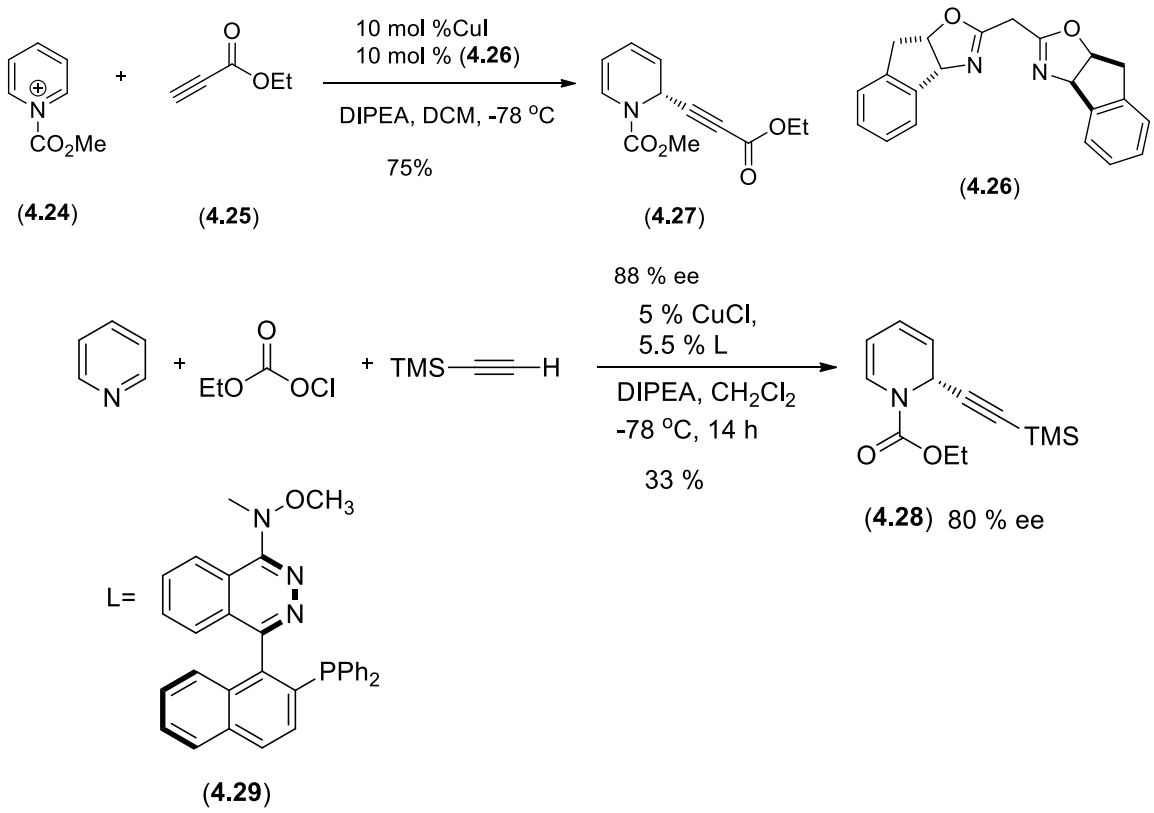


Scheme 4.5 Diazadecaline ring system.

Although there are numerous reports of inter- and intramolecualr nucleophilic additions to pyridinium, very few of these examples entail metal catalyzed transformations. Importantly, metal catalyzed additions to pyridine ring systems may open new and potentially asymmetric routes to functionalized heterocycles. This chapter describes our attempts to develop palladium catalyzed intramolecular additions to activated pyridines.

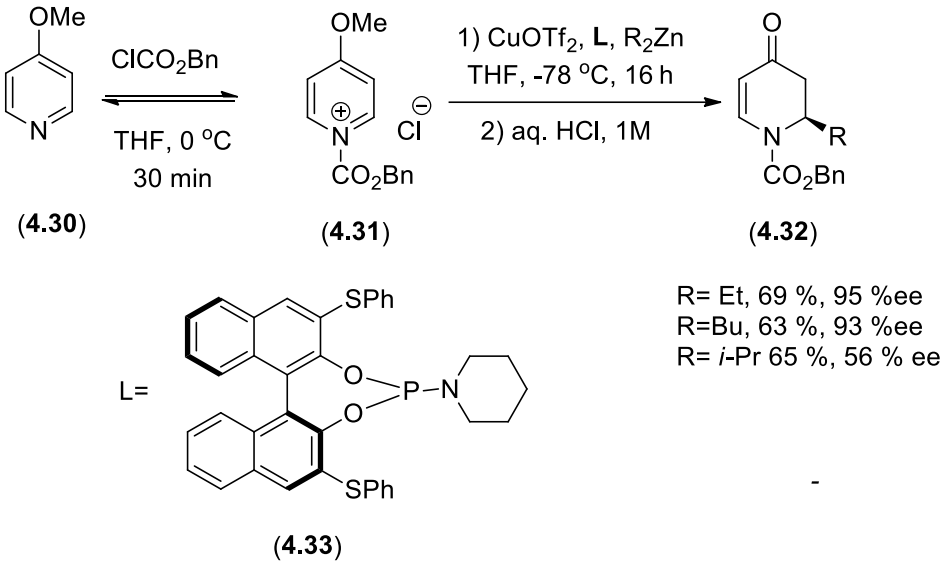
4.2 Background

Ma and coworkers reported the asymmetric addition of activated terminal alkynes (**4.25**) to acylpyridinium salts (**4.24**) in the presence of copper complexes with bis(oxazoline) ligands (**4.26**) to give 1, 2-dihydropyridine (**4.27**) in good yield and in decent ee (scheme 4.6).[98] Similarly, Arndtsen and coworkers reported that various terminal alkynyl reagents (like TMS acetylene) without electron withdrawing groups as substituents could be added to the C-2 position of pyridinium salts using copper catalysts and (R)-QUINAP ligands.[99]



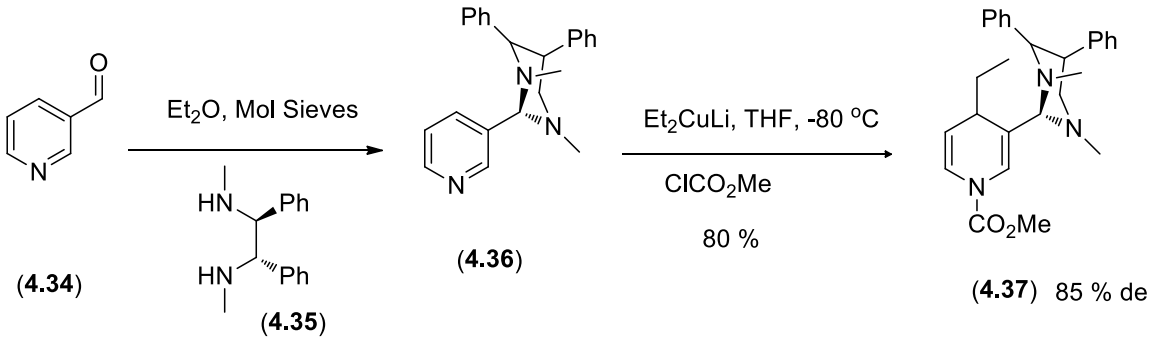
Scheme 4.6 Asymmetric addition to pyridinium salts.

Similarly Feringa *et al.* successfully demonstrated the use of dialkyl zinc in enantioselective addition to N-acylpyridinium salts in the presence of phosphoramidite ligands. The pyridinum salt **4.31**, obtained from the acylation of **4.30**, when treated with the corresponding dialkyl zinc reagent and phosporamidite ligand **4.33** provided the corresponding dihyropyridine compounds **4.32** in good yield with high enantioselectivity as shown in scheme 4.7.[100]



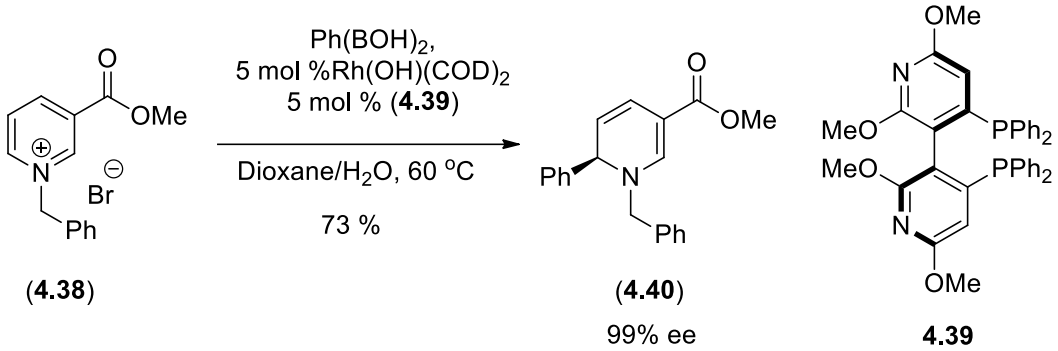
Scheme 4.7 Addition of dialkyl zinc reagents to the pyridinium salts.

Alexakis and coworkers developed method for asymmetric synthesis of 3-formyl-1, 4-dihydropyridines involving addition of organocopper reagents, to activated 3-imidazolidinylpyridine synthesized from the reaction of pyridine-3-carboxaldehyde and chiral amine as shown in scheme 4.8.[101]



Scheme 4.8 Use of chiral amines in asymmetric synthesis.

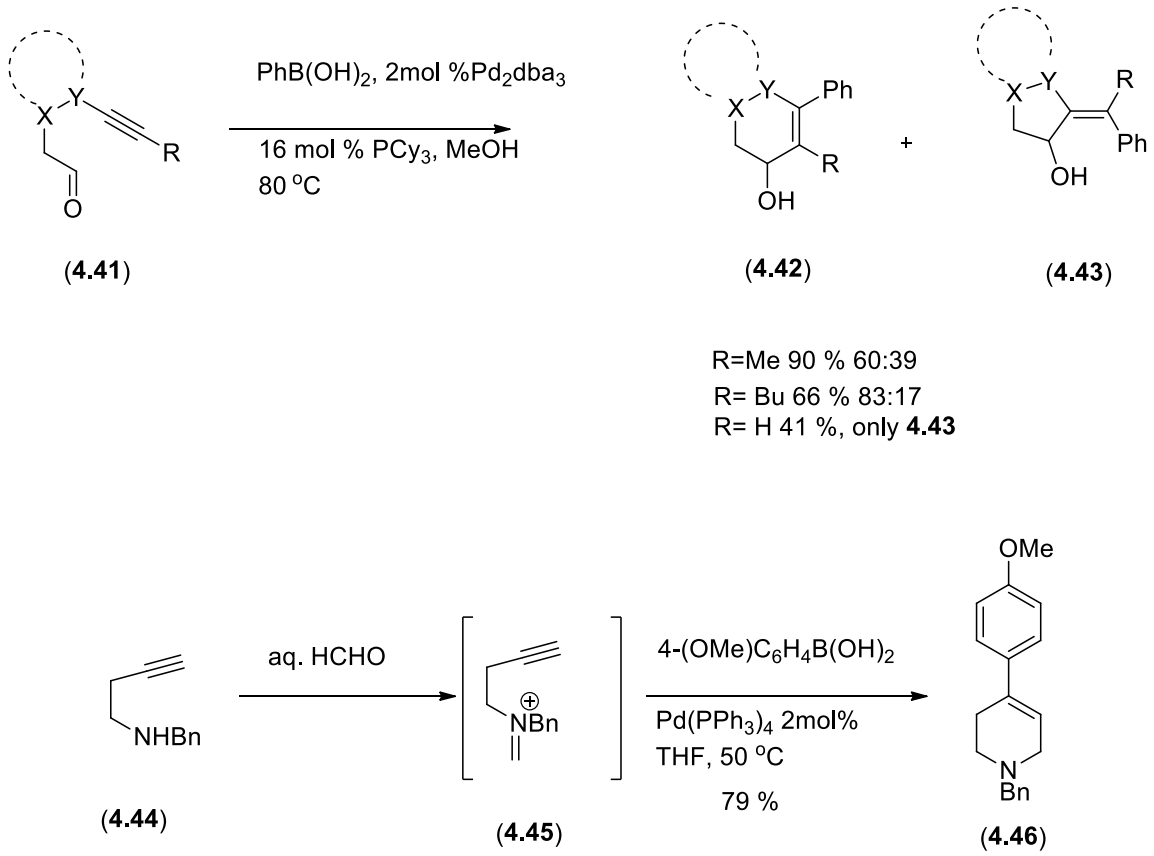
Belyk and coworker developed a highly enantioselective catalytic asymmetric addition of aryl and alkenylboronic acids (eg $Ph(BOH)_2$) to N-benzylnicotinate salt (**4.38**) to yield dihydropyridine (**4.40**) with good enantiopurity using rhodium complexes with (R)-CTH-P-Phos (**4.39**) as ligand (scheme 4.9).[102]



Scheme 4.9 Rhodium catalyzed asymmetric addition to activated nicotinoyl esters.

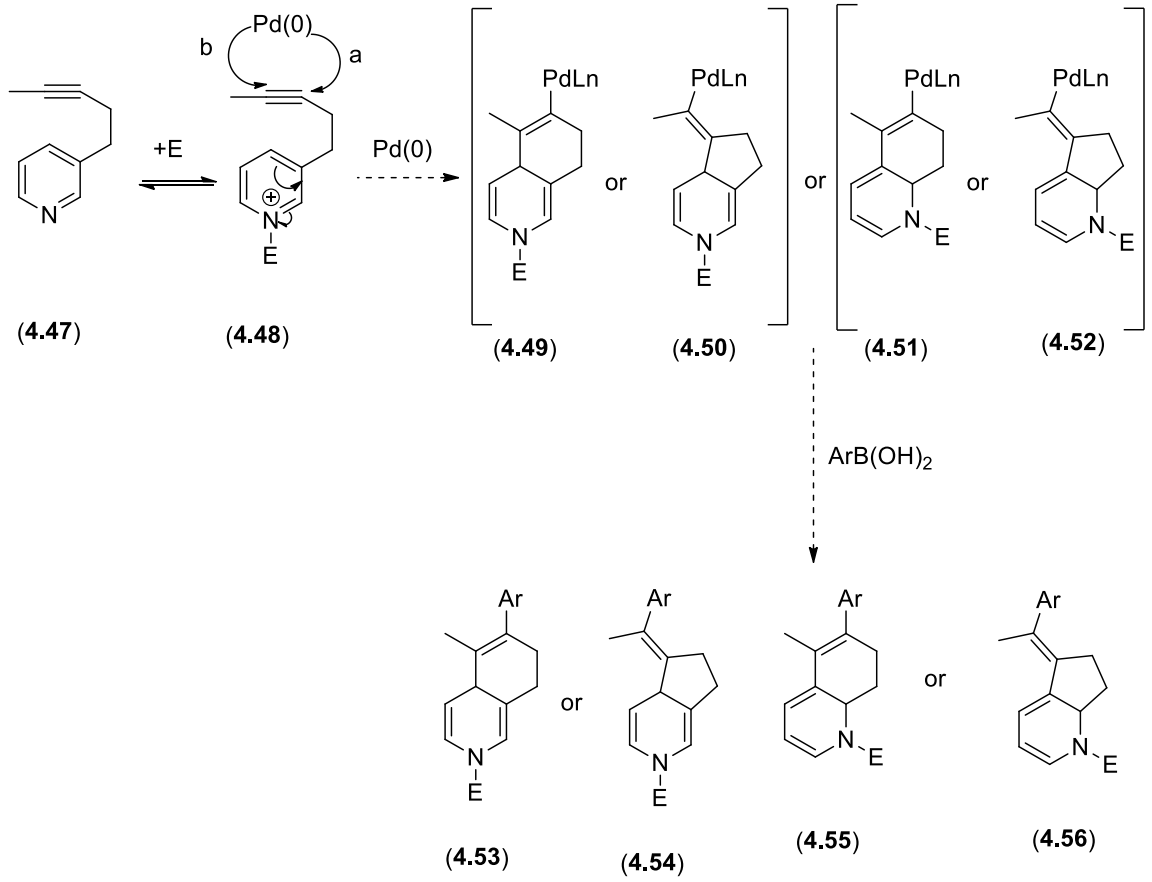
Aside from these contributions, the elaboration of pyridinium electrophiles via metal mediated pathways has not been extensively investigated. In particular, there are no reports of engaging properly substituted pyridinium salts in metal catalyzed cylizations to yield fused 1, 2 or 1, 4-dihydropyridine compounds. However, Tsukamoto and coworkers have demonstrated that aldehydes containing terminal alkyne groups undergo cyclization upon heating with phenylboronic acid and catalytic $Pd(PPh_3)_4$.[103] Internal alkynes (such as **4.41**) also underwent arylative cyclization when treated with phenylboronic acid in the presence of Pd_2dba_3 as catalyst and tricyclohexylphosphine as ligand, yielding a mixture of trans-addition products (**4.42** and **4.43**). The same group extended the arylative cyclization reaction manifold to palladium mediated alkynyl and allenyl iminium ion cyclizations leading to the synthesis of 1, 4-disubstituted 1, 2, 3, 6-tetrahydropyridines. They developed a three-component synthesis of (**4.46**) based on anti-Wacker type

cyclization of an alkynyl imminium ion (**4.45**), generated in-situ with phenylboronic acid as shown in scheme 4.10.



Scheme 4.10 Palladium catalyzed arylative cyclizations

Given this precedent, we wondered if an activated pyridine could take the place of the aldehyde/iminium ion electrophile in similar cyclizations. That is, if an alkyne were suitably positioned within the side-chain of a pyridine derivative, then would metal mediated alkylative or arylative cyclizations of the corresponding pyridinium salts be feasible? A general scheme for the proposed work is presented in scheme 4.11.



Scheme 4.11 Our approach to metal catalyzed cyclization

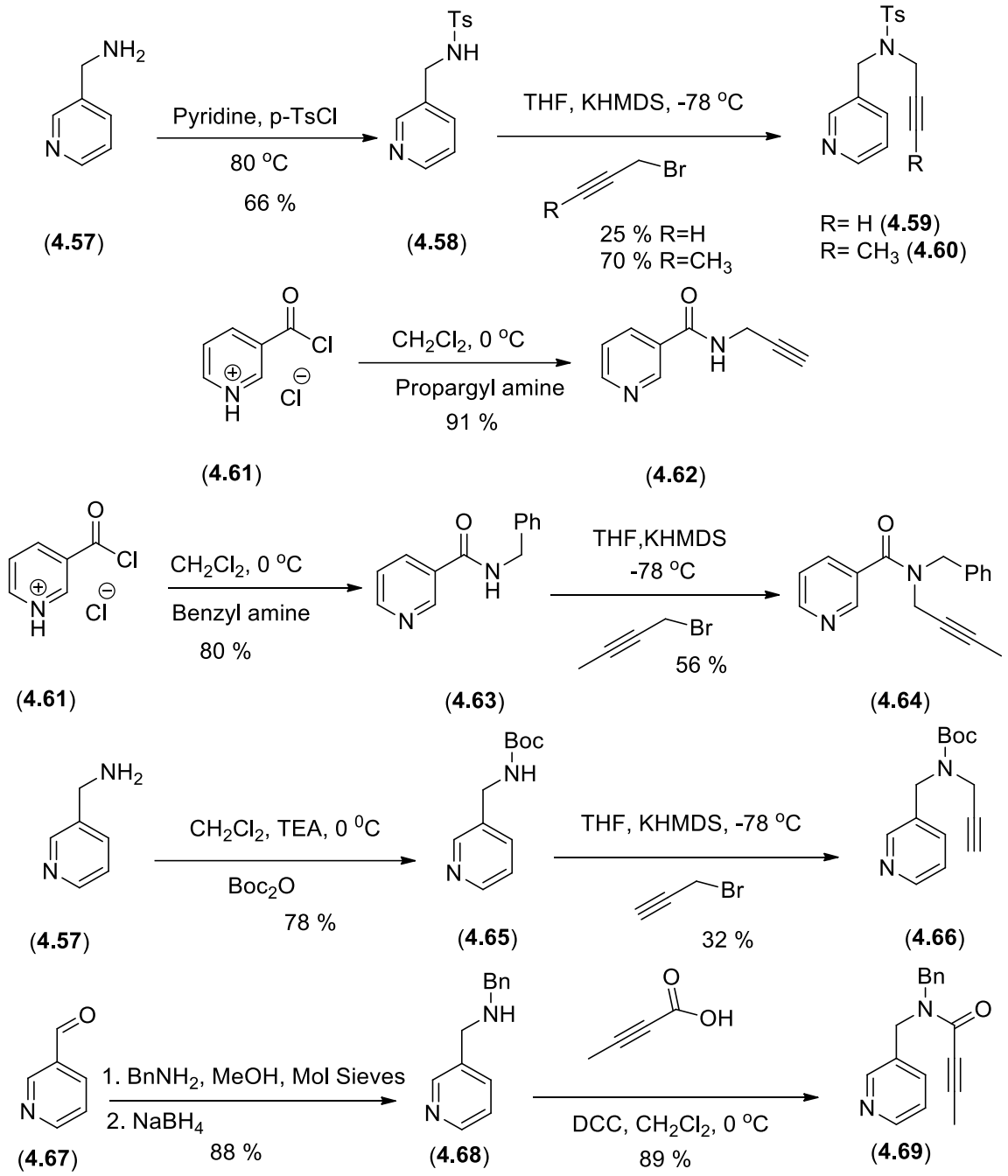
A pyridinium substrate possessing an alkynyl side chain at C3 could be treated with a Pd(0)-phosphine catalyst. It is envisoned that the Pd will function as a nucleophile and the electronic properties of the metal center will be subject to tuning via added phosphine ligands. Hence it is anticipated that strong σ-donor phosphines will be the best ligands for this reaction (e.g., Cy_3P, $^tBu_3P$). Addition of the Pd catalyst to the alkyne can potentially occur via two pathways (a and b). These manifolds would then afford the alkenyl palladium intermediates, 1, 4- dihydropyridines **4.49** and **4.50** or 1, 2-dihydropyridines **4.51** and **4.52**. Further transmetalation with arylboronic acid followed by subsequent reductive elimination would then afford one or more dihydropyridine

products **4.53**, **4.54**, **4.55** and **4.56**. These dihydropyridines could provide versatile building blocks for both total synthesis of natural products and also useful entry into pharmacologically interesting and important aza-heterocyclic scaffolds.

4.3 Results and Discussion

The pyridine substrates with attached alkynyl substituents were designed and synthesized are shown in scheme 4.12. While designing these substrates several factors were considered: 1) the alkyne should be positioned so that either 6-endo or 5-exo cyclizations may occur in keeping with Baldwin's rule, 2) The ability to vary substitution on nitrogen on the side chain would allow us to study the effect of different groups on the cyclization reaction.

The cyclization precursors **4.59** and **4.60** were prepared starting from the tosylation of 3-(aminomethyl) pyridine (**4.57**) with p-TsCl in pyridine to give N-tosyl compound (**4.58**). Further alkylation with propargyl bromide and 1-bromo-2-butyne gave the corresponding alkynyl pyridine substrates. Substrate (**4.62**) was obtained by the coupling of propargyl amine with nicotinoyl chloride hydrochloride (**4.61**).

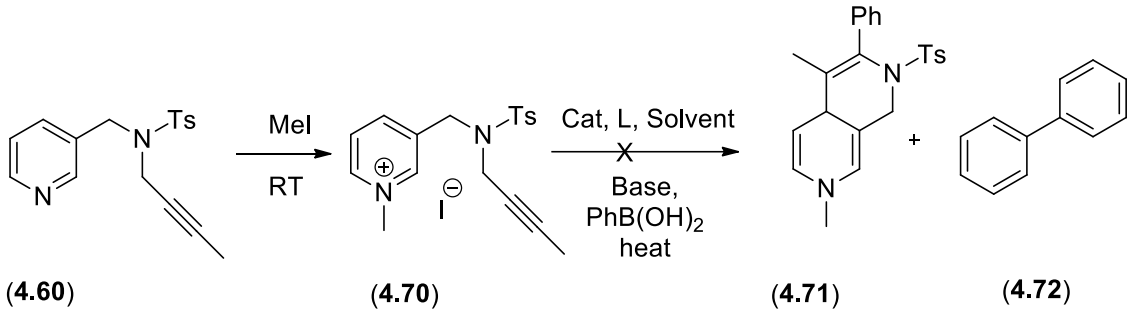


Scheme 4.12 Synthesis of 3-substituted pyridines

Nicotinoyl chloride (**4.61**) on treatment with benzylamine afforded the amide compound (**4.63**), which, on alkylation with 1-bromo-2-butyne, gave the alkynyl pyridine compound (**4.64**). Similarly, N-Boc compound (**4.65**) was obtained by the reaction of 3-

(aminomethyl) pyridine (**4.57**) with di-t-butylcarbonate. Further alkylation of **4.65** with propargyl bromide in the presence of strong base (KHMDS) gave the substituted pyridine **4.66**. Reductive amination of pyridine-3-carboxaldehyde with benzylamine forms the N-benzyl derivative (**4.68**), which is then coupled with 2-butynoic acid in presence of DCC to provide the pyridine substrate (**4.69**) (scheme 4.12). The substituted pyridines shown in scheme 4.12 were all obtained in moderate to good yield and all the precursors were stable to silica gel flash column chromatography. These substrates were characterized using NMR spectroscopy and mass spectrometry.

Pyridine derivative **4.60** was chosen as the model substrate for the initial palladium catalyzed cyclization studies. First the pyridine derivative was converted to the methylpyridinium salt (**4.70**) by treating with methyl iodide (scheme 4.13) and subjected to cyclization under two different general reaction conditions as described in table 4.1.



(**4.60**) (**4.70**) (**4.71**) (**4.72**)

Scheme 4.13 alkyl pyrdinium salt.

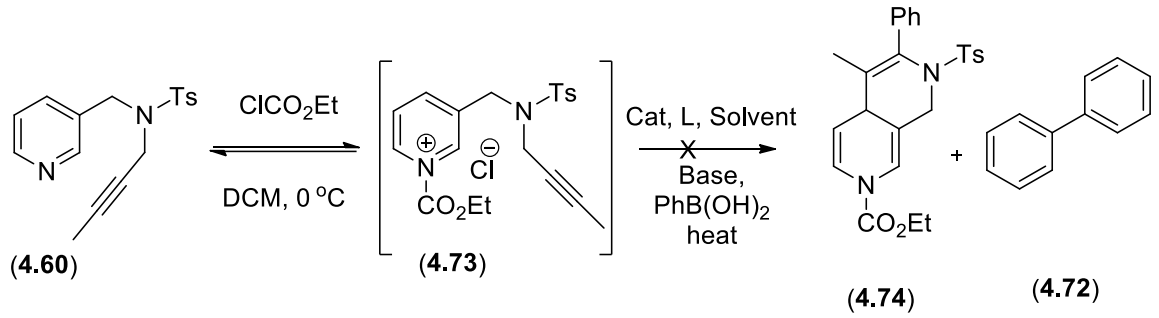
Table 4.1 General cyclization reactions.

Entry	Catalyst 5 mol %	Ligand 20 mol %	Base	Solvent	Temperature (^oC)	Result
1	$Pd(PPh_3)_4$	None	None	MeOH	60-70	No reaction
2	$Pd(PPh_3)_4$	None	K_2CO_3	MeOH	60-70	No reaction
3	$Pd(PPh_3)_4$	PCy_3	K_2CO_3	MeOH	60-70	No reaction
4	Pd_2dba_3	None	K_2CO_3	THF	60-70	No reaction
5	Pd_2dba_3	PCy_3	K_2CO_3	THF	60-70	No reaction

The initial reaction conditions used for attempted arylative cyclization of pyridinium salt (**4.70**) were those employed for cyclization of alkynals[104] (1.5 eq of $PhB(OH)_2$, 5 mol % $Pd(PPh_3)_4$, MeOH). The failure to observe any reaction prompted us to screen a catalyst comprised of Pd_2dba_3 and PCy_3 (entries 4-5). The desired cyclized product was not observed under either of these conditions. Instead NMR of the crude reaction mixture always showed only the starting pyridine substrate along with biphenyl, a product formed through homocoupling of phenyl boronic acid. Reactions performed using the related benzyl pyridinium salt also failed to give any of the product.

Next, we attempted to increase the electrophilicity of the activated pyridine by changing the substrate from an alkyl pyridinium salt to an acyl pyridinium salt. Hence, treatment of **4.60** with ethylchloroformate in DCM at 0 ^oC provided the corresponding acyl pyridinium salt (**4.73**), which was then subjected to arylative cyclization reaction conditions as summarized in table 4.2. This also failed to give the desired annelated

product. Instead, whenever base was used in the reaction we were able to isolate the free pyridine along with biphenyl **4.72**.

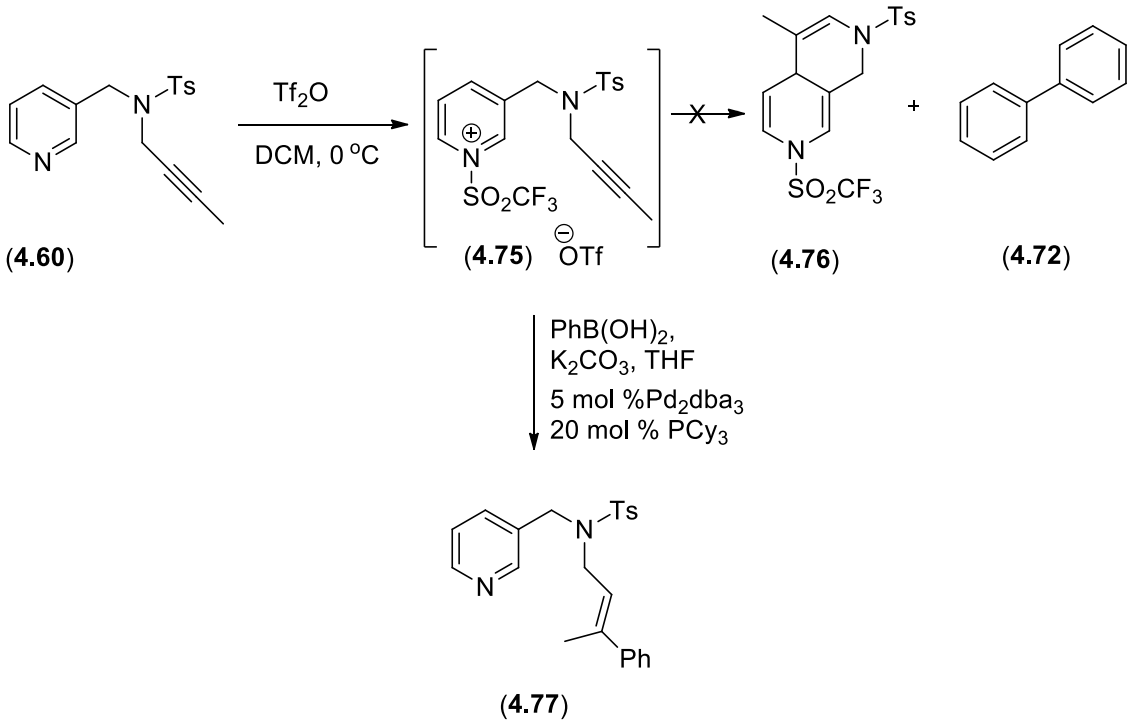


Scheme 4.14 acyl pyrdinium salt

Table 4.2 Reactions attempted with acylpyridinium salts.

Entry	Catalyst 5 mol %	Ligand 20 mol %	Base	Solvent	Temperature (°C)	Result
1	$Pd(PPh_3)_4$	None	None	THF	60-70	No Product
2	$Pd(PPh_3)_4$	None	K_2CO_3	THF	60-70	Recovered 50 % **4.60**
3	$Pd(PPh_3)_4$	PCy_3	K_2CO_3	THF	60-70	Recovered 36 % **4.60**
4	Pd_2dba_3	None	K_2CO_3	THF	60-70	Recovered 41 % **4.60**
5	Pd_2dba_3	PCy_3	K_2CO_3	THF	60-70	Recovered 35 % **4.60**

Since it is known that acylpyrdinium salts exist in equilibrium with the free base when in solution,[105] we thought this might be interfering with the carbocylization reaction manifold. Thus, a stronger acylating reagent (triflic anhydride) was used to form the pyridinium salt (**4.75**). Arylative cyclization reactions attempted on this substrate are summarized in table 4.3.

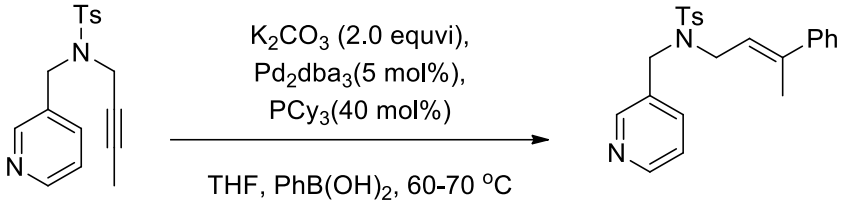


Scheme 4.15 Triflate salt of pyridine substrate

When the triflate salt (**4.75**) was subjected to the reaction conditions mentioned in table 4.3, we did not observe any cyclized product; instead we observed formation of hydroarylated product (**4.77**) in low yield. The formation of hydroarylated product is not seen in the absence of either palladium catalyst or the phosphine ligand. No hydroarylated product was observed when the base was absent. Interestingly, exposure of the free pyridine substrate (**4.60**) to these reaction conditions also afforded the hydroarylated product (**4.77**) as shown in scheme 4.16.

Table 4.3 Attempts for cyclization reaction with pyridinium triflate salt.

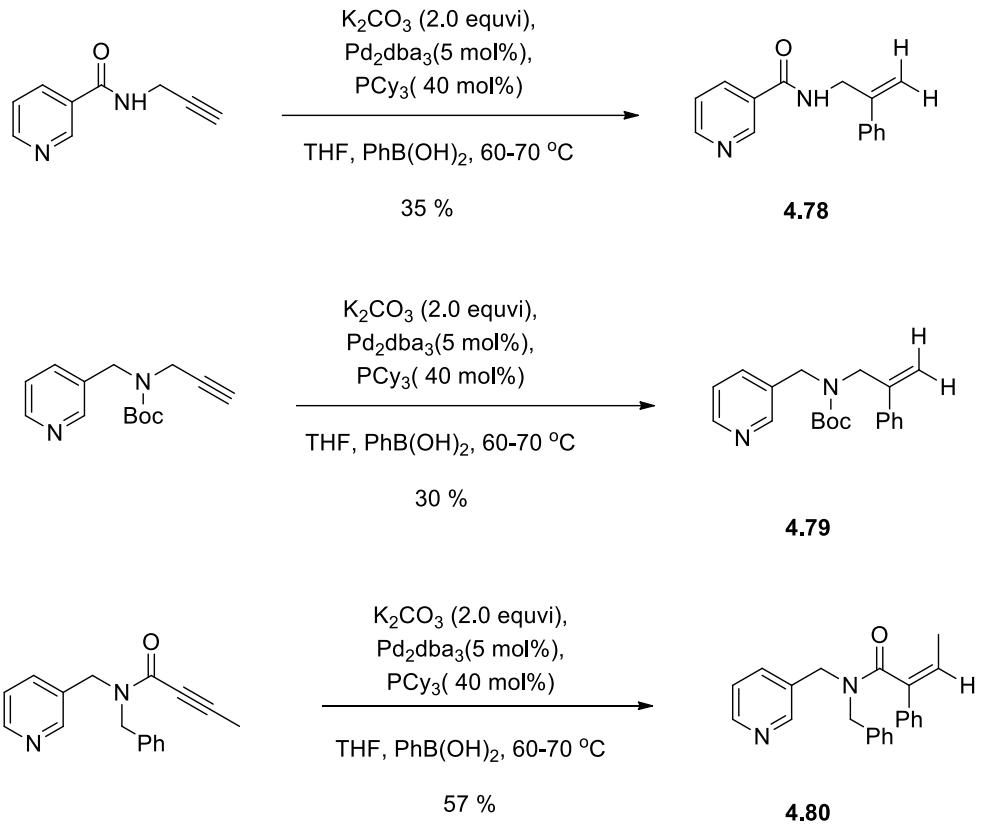
Entry	Pd catalyst (5 mol %)	Ligand (20 mol %)	Solvent	Temp (^oC)	Base	Result
1	Pd_2dba_3	None	THF	60-70	None	No Product
2	Pd_2dba_3	None	THF	60-70	K_2CO_3	50 % SM (**4.60**)
3	None	None	THF	60-70	K_2CO_3	No product
4	Pd_2dba_3	PCy_3	THF	60-70	K_2CO_3	34 % **4.77**
5	$Pd(OAc)_2$	PCy_3	THF	60-70	K_2CO_3	20 % **4.77**
6	Pd_2dba_3	PCy_3	MeOH	80	K_2CO_3	38 % SM (**4.60**)
7	Pd_2dba_3	PCy_3	Dioxane	90-100	K_2CO_3	43 % SM (**4.60**)



(**4.60**) (**4.77**)

Scheme 4.16 Hydroarylation reaction with free pyridine **4.60**.

Other pyridine substrates were then subjected to the conditions outlined in scheme 4.17, and they too, provided the corresponding hydroarylated products in low to moderate yield as shown in scheme 4.16.



Scheme 4.17 Additional examples of alkynyl pyridine hydroarylations

Upon observing hydroarylation products, we reviewed the literature to find typical procedures used to achieve alkyne hydroarylation. We found that various groups have reported hydroarylations of alkynes under acidic coditions, but Xu and coworkers provide the only examples of hydroarylation of alkynes under basic conditions in the presence of an N-P ancillary ligand.[106]

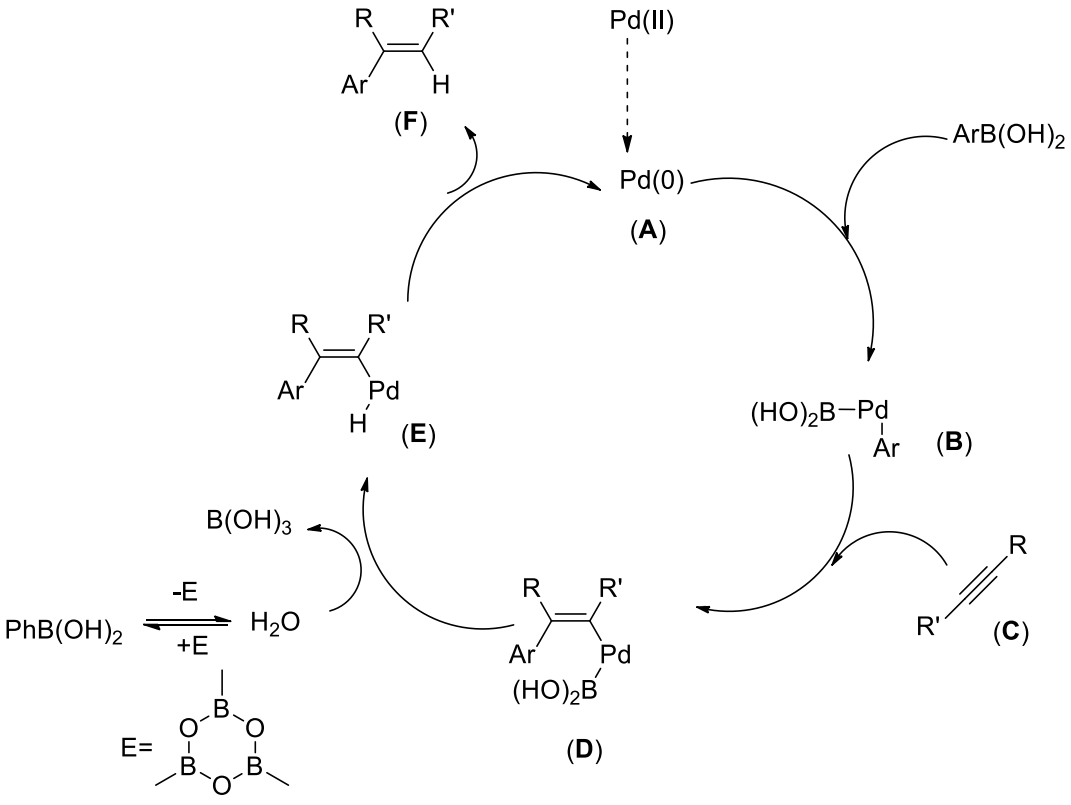
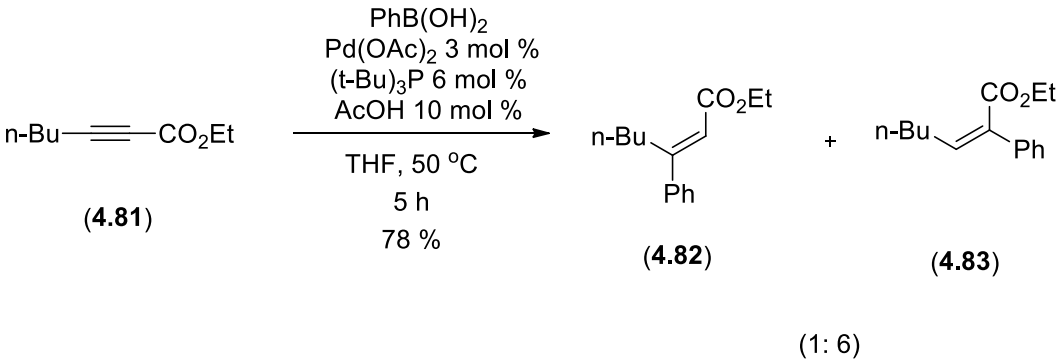


Figure 4.2 Proposed mechanism for hydroarylation.

The proposed mechanism for the hydroarylation is presented in figure 4.2. First, the oxidative addition of Pd(0) species (**A**) with the arylboronic acid may occur to afford intermediate (**B**). Subsequently, the selective insertion of the alkyne (**C)** into the Pd-C bond in a syn fashion takes place to give intermediate (**D**). Hydrolysis of (**D**) followed by the reductive elimination of (**E**) finally provides the hydroarylated product (**F**) and regenerates the active palladium species (**A**).

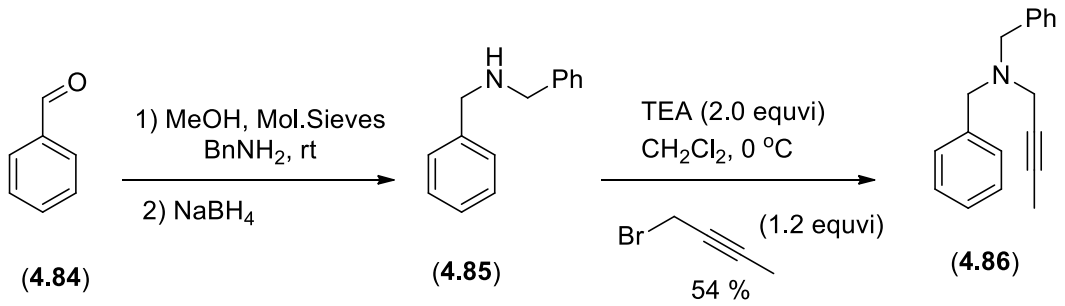
The regiochemistry for addition of the aryl group in products **4.78** and **4.79** was confirmed by the appearance of germinal coupling between the terminal alkene hydrogens and the presence of a secondary alkene carbon in the 13C-dept spectrum.

The structural assignment of compound **4.80** is consistent with the coupling constants between the allylic methyl group and the alkene hydrogen in the ^{1}H-NMR spectrum. The structure is also consistent with the regioselectivity for hydroarylation of conjugated alkynes. Specifically, Oh and coworkers reported the hydroarylations of alkyne ester **4.81** using the conditions shown in scheme 4.18 (note the need to use an acidic additive to promote the reaction).[107]



Scheme 4.18 Example of regioselective hydroarylation of an alkynecarboxylate.

As there were not many examples of palladium catalyzed hydroarylations under basic conditions, we thought to look at the generality of the reaction towards non-pyridine substrates. Reductive amination of benzaldehyde with benzylamine in MeOH provided the secondary amine **4.85**, which on further alkylation with 1-bromo-2-butyne gave the substrate **4.86** as shown in scheme 4.19.



(**4.84**) (**4.85**) (**4.86**)

Scheme 4.19 Synthesis of non-pyridine substrate.

The compound **4.86**, was then subjected to the conditions outlined in scheme 4.16. However, no hydroarylation product was observed. The failure of the reaction may indicate that the pyridine nitrogen is playing an important role in these hydroarylation reactions. Further research may shed light on the mechanistic details of these transformations. Additionally, there remains ample opportunities to improve and extend this work to include more examples of hydroarylations and to explore the use of other transition metal catalysts to bring about arylative cyclizations.

4.4 Conclusion

We successfully synthesized 3-substituted pyridine substrates bearing alkyne substituents for the purpose of investigating palladium catalyzed additions to pyridinium salts. While our efforts to effect Pd-catalyzed arylative cyclizations on these pyridine substrates were not successful, products of alkyne hydroarylation were observed. These hydroarylations occurred under unprecedentedly mild conditions, and the presence of a pyridine ring in the substrate seems to be important. This research may provide a basis for developing new methods for hydroarylation reactions of alkynes under mild basic conditions. It is hoped that future work will provide additional insight into mechanistic features of this process. Likewise, it is envisioned that the original goals of this study can

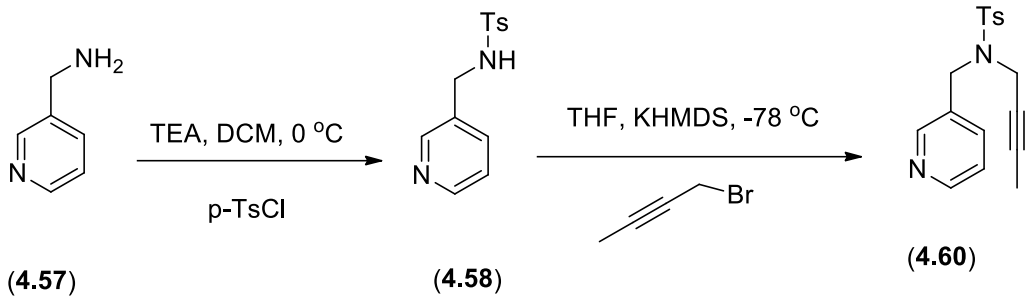
ultimately be achieved, perhaps through the use of alternative transition metal catalysts (e.g., Rh(I) or Pt(0)).

4.5 Experimental Section

4.5.1 General Experimental

All commercially available starting materials and reagents were used as received unless otherwise noted. All the reactions were performed under argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Proton nuclear mangetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C-NMR) spectra were recorded at 300 MHz and 75 MHz respectively. Chemical shifts are reported as δ-values in parts per million (ppm) relative to tetramethylsilane for ^{1}H-NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds used in this study reveal the presence of amide rotamers. Resonances corresponding to major and minor isomers were identified when appropriate. IR spectra were recorded on a FT-IR spectrometer as thin films on sodium chloride discs. High resolution mass spectra were obtained using positive ion electrospray ionization (ESI). Melting points were recorded using a capillary melting point apparatus and are uncorrected.

Experimental procedures and characterization of 3-alkynyl pyridine substrates:



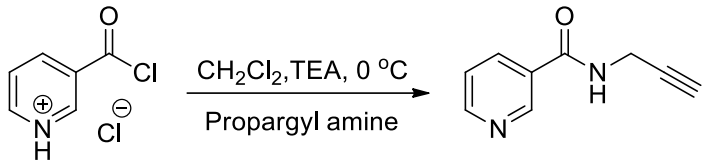
(**4.57**) (**4.58**) (**4.60**)

4-methyl-N-(pyridin-3-ylmethyl)benzenesulfonamide (4.58): To a solution of 3-(aminomethyl) pyridine (5.01 g, 46.2 mmol, 1.0 eq), TEA (9.60 mL, 69.4 mmol, 1.5 eq), DMAP (0.56 g, 4.62 mmol, 0.1 eq) in 100 mL dichloromethane was added a solution of p-TsCl (9.69 g, 50.9 mmol, 1.1 eq) in 50 mL dichloromethane at 0 ºC. The reaction was allowed to attain room temperature and stirred for 12 h. The reaction mixture was concentrated under reduced pressure and the residue was then purified by silica gel flash column chromatography using ethyl acetate:hexanes (6:4) to get a pale yellow solid (8.0 g, 66%). Mp. 145-147 ºC. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.39 (d, *J* = 2.0 Hz, 1H), 7.79 – 7.71 (m, 2H), 7.63 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.23 (dd, *J* = 7.7, 4.7 Hz, 1H), 5.20 (s, 1H), 4.15 (d, *J* = 3.5 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 149.3, 142.3, 137.8, 136.0, 133.2, 130.1, 127.3, 123.8, 44.9, 21.9.

N-(but-2-yn-1-yl)-4-methyl-N-(pyridin-3-ylmethyl)benzenesulfonamide (4.60): To a solution of hexamethyldisilane (HMDS) (1.78 mL, 8.38 mmol, 1.0 eq) in 5.0 mL THF was added n-BuLi (2.5 M in hexanes) (3.66 mL, 9.14 mmol, 1.1 eq) dropwise at -78 ºC and the resulting mixture was maintained at this temperature for 1.5 h.

In a separate reaction flask, to a solution of (**4.58**) (2.02 g, 7.62 mmol, 1.0 eq) in 20.0 mL THF was added the solution of LiHMDS prepared above at -78 ºC and stirred

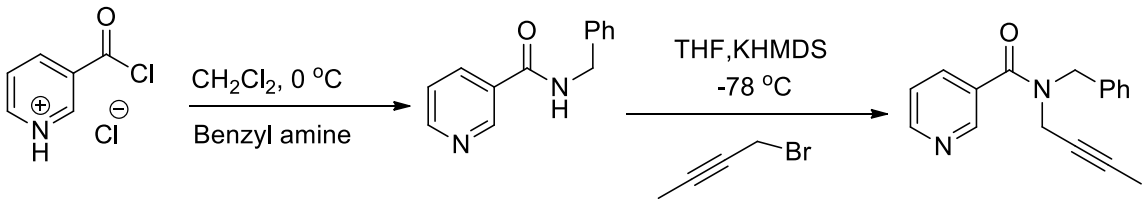
for 2 h. 1-Bromo-2-butyne (0.820 mL, 9.15 mmol, 1.2 eq) was then added dropwise at -78 ^{o}C. After the addition the reaction was allowed to warm to room temperature and maintained for 12 h. The reaction was quenched with dilute NH_4OH solution (10. 0 mL) and the aqueous layer was extracted with ethyl acetate (2 x 25 mL). The combined organic layer was washed with water (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to get a brown liquid. Crude product was then purified by silica gel flash column chromatography using 50-60 % ethyl acetate in hexane to give **4.60** (1.67 g, 70 %) as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 – 8.52 (m, 2H), 7.82 – 7.75 (m, 3H), 7.37 – 7.26 (m, 3H), 4.34 (s, 2H), 3.88 (q, *J* = 2.3 Hz, 2H), 2.45 (s, 3H), 1.55 (t, *J* = 2.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 149.8, 143.8, 136.7, 136.0, 131.4, 129.6, 128.1, 123.9, 82.7, 71.3, 47.6, 36.7, 21.7, 3.4. IR (film): 3032, 2224 cm $^{-1}$. HRMS (ESI) $C_{17}H_{19}N_2O_2S$ $[M + H]^+$, 315.1167; found 315.1164.



(**4.61**) (**4.62**)

N-(prop-2-yn-1-yl)nicotinamide (4.62): To a solution of nicotinoyl chloride hydrochloride (**4.61**) (2.04 g, 11.2 mmol, 1.0 eq) and TEA (4.68 mL, 33.7, 3.0 eq) in 50.0 mL dichloromethane was added propargylamine (0.850 mL, 12.4 mmol, 1.1 eq) at 0 ^{o}C. The reaction was allowed to warm to attain room temperature and stirred for 12 h. Water (50 mL) was added then the reaction mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (25 mL), brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced

pressure to give compound **4.62** (1.64 g, 91 %) as pale yellow semi-solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, *J* = 1.8 Hz, 1H), 8.75 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.22 – 8.12 (m, 1H), 7.42 (ddd, *J* = 7.9, 4.9, 0.7 Hz, 1H), 6.75 (s, 1H), 4.29 (dd, *J* = 5.2, 2.6 Hz, 2H), 2.31 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 151.4, 149.2, 135.7, 129.9, 125.3, 80.7, 73.0. 28.0. IR (film): 3032, 2253, 1704, 1596 cm $^{-1}$. HRMS (ESI) $C_9H_9N_2O$ $[M + H]^+$, 161.0715; found 161.0707.

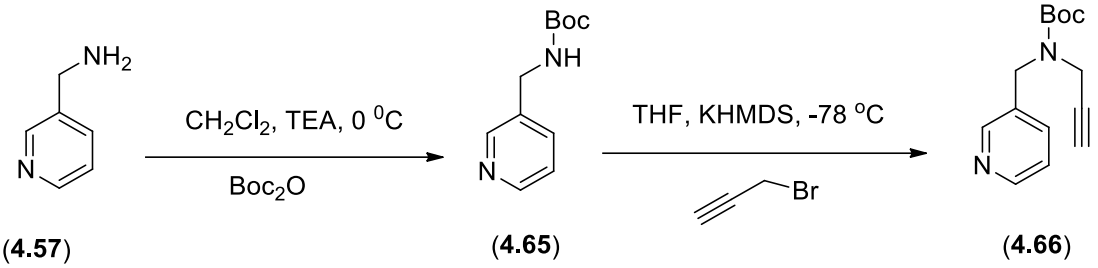


(**4.61**) (**4.63**) (**4.64**)

N-benzylnicotinamide (4.63): Using the procedure described for the preparation of **4.62**, 2.03 g (11.2 mmol, 1.0 eq) of nicotinoyl chloride hydrochloride (**4.61**) and 1.14 g (10.7 mmol, 0.95 eq) of benzyl amine were coupled to give N-benzylnicotinamide (**4.63**) as yellow oil (1.91 g, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.3 Hz, 1H), 8.71 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.19 – 8.11 (m, 1H), 7.43 – 7.29 (m, 5H), 6.61 (s, 1H), 4.67 (d, *J* = 5.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 152.4, 149.1, 137.7, 134.5, 130.1, 129.3, 128.7, 127.9, 123.5, 45.4.

N-benzyl-N-(but-2-yn-1-yl)nicotinamide (4.64): Using the procedure described for the preparation of **4.60**, 1.01 g (4.71 mmol, 1.0 eq) **4.63** was alkylated with 2.26 mL (6.12 mmol, 1.3 eq) 1-bromo-2-butyne to give **4.64** (0.70 g, 56 %) as dark brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) Major rotamer δ 8.87 (s, 1H), , 8.68 (s, 1H), 7.92 (s, 1H), , 7.35 (m, 5H), 7.18 (s, 1H), 4.86 (s, 2H), 3.82 (s, 2H), 1.85 (s, 3H). Minor rotamer 8.76 (s, 1H),

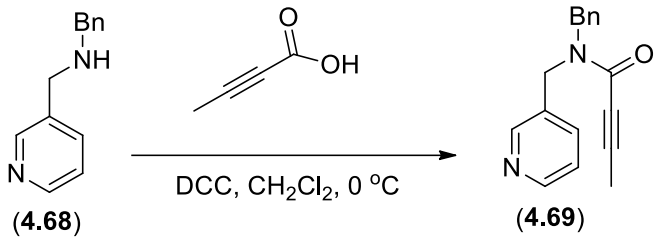
8.68 (s, 1H), 7.85 – 7.75 (m, 1H), 7.30 (m, 5H), 7.18 (s, 1H), 4.65 (s, 2H), 4.28 (s, 2H), 1.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 148.2, 136.5, 135.0, 131.8, 128.9, 128.0, 127.1, 123.5, 81.8, 73.5, 53.6, 51.9, 47.9, 38.9, 34.6, 3.8. IR (film): 2998, 2227, 1637 cm $^{-1}$. HRMS (ESI) $C_{17}H_{17}N_2O$ [M + H] $^+$, 265.1341; found 265.1348.



(**4.57**) (**4.65**) (**4.66**)

tert-butyl (pyridin-3-ylmethyl)carbamate (4.65): Using the procedure described for the preparation of **4.58**, 5.00 g (46.2 mmol) of 4-(aminomethyl) pyridine (**4.57**) was acylated with 11.1 g (50.9 mmol) Boc_2O to give compound **4.65** (7.50 g, 78 %) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.30 – 7.20 (m, 1H), 5.14 (s, 1H), 4.33 (s, 2H), 1.46 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 149.0, 148.8, 135.2, 134.5, 123.3, 79.9, 42.0, 28.5. IR (film): 3333, 1764 cm $^{-1}$.

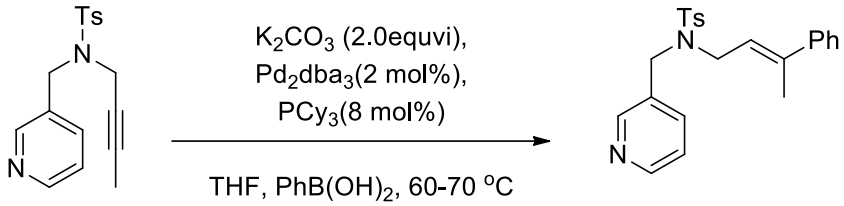
tert-butyl prop-2-yn-1-yl(pyridin-3-ylmethyl)carbamate (4.66): Using the procedure described for the preparation of **4.60**, 4.00 g (19.2 mmol) of **4.65**, was alkylated with 2.74 g (23.1 mmol) of propargyl bromide to give compound **4.66** (1.56 g, 32 %) as a brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 – 8.46 (m, 2H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.5 Hz, 1H), 4.56 (s, 2H), 4.01 (m, 2H), 2.24 (s, 1H), 1.49 (t, *J* = 7.3 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.7, 149.1, 133.4, 123.6, 81.2, 79.1, 66.3, 47.2, 36.0, 28.5, 19.3. IR (film): 2976, 2235, 1761 cm^{-1}. HRMS (ESI) $C_{14}H_{19}N_2O_2$ [M + H] $^+$, 247.1447; found 247.1446.



(**4.68**) (**4.69**)

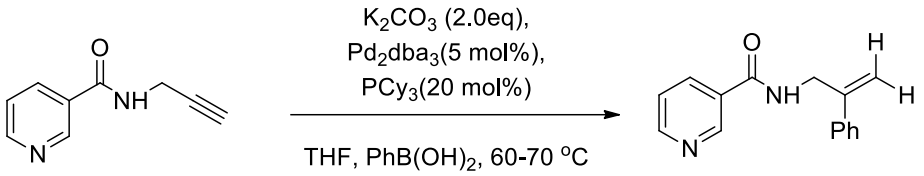
N-benzyl-N-(pyridin-3-ylmethyl)but-2-ynamide (4.69): To a solution of N-benzyl-1-(pyridin-3-yl)methanamine (1.61 g, 8.07 mmol, 1.0 eq) and 2-butynoic acid (0.710 g, 8.47 mmol, 1.05 eq) in dichloromethane (25 mL) was added a solution of DCC (1.83 g, 8.88 mmol, 1.1 eq) in dichloromethane (10 mL) at 0 ^{o}C. The reaction was allowed to stir at room temperature for 14 h. Filtered the reaction through celite bed, washed the bed with dichloromethane (20 mL) and concentrated the filtrate under reduced pressure to get brown liquid. Crude product was then purified by silica gel flash column chromatography using 70-80 % ethyl aceate in hexanes to get **4.69** (1.91 g, 89 %) as pale yellow solid. Mp. 45-47 ^{o}C. (Mixture of rotamers) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 – 8.37 (m, 2H), 7.63 – 7.56 (m, 1H), 7.42 – 7.16 (m, 6H), 4.69 (s, 2H), 4.50 (s, 2H), 1.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 155.2, 149.9, 149.6, 149.5, 149.3, 136.5, 136.1, 135.9, 135.4, 132.3, 132.1, 129.1, 129.0, 128.6, 128.3, 128.0, 127.8, 123.9, 90.5, 73.4, 73.3, 51.9, 50.9, 49.1, 46.6, 44.2, 4.3. IR (film): 3031, 2245, 1621 cm $^{-1}$. HRMS (ESI) $C_{17}H_{17}N_2O$ $[M + H]^+$, 265.1341; found 265.1337.

General experimental procedure of palladium catalyzed hydroarylation reactions:



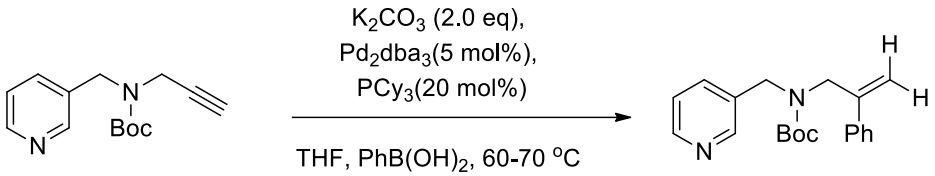
(**4.60**) (**4.77**)

Compound 4.77: To a solution of **4.60** (0.050 g, 0.084 mmol, 1.0 eq) in 2.00 mL degassed THF, (4.10 mg, 0.004 mmol, 0.05 eq) Pd_2dba_3, (8.90 mg, 0.033 mmol, 0.40 eq) PCy_3, (15.0 mg, 0.125 mmol, 1.5 eq) and (23.1 mg, 0.167 mmol, 2.0 eq) of K_2CO_3 were added at room temperature and heated at 60-70 ^oC for 14 h. Water (10.0 mL) was added. The reaction mixture extracted with ethyl acetate (10.0 mL x 2). The combined organic layer was then washed with brine (10.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get a brown liquid. The crude was then purified by silica gel flash column chromatography to give compound **4.77** (0.021 g, 34 %) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.7 Hz, 1H), 8.45 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.21 (m, 5H), 7.10 – 7.04 (m, 2H), 5.39 – 5.30 (m, 1H), 4.39 (s, 2H), 3.96 (d, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 149.6, 139.7, 137.4, 136.4, 132.3, 130.1, 128.4, 127.6, 127.5, 125.8, 123.9, 121.3, 48.7, 45.7, 21.7, 16.0. IR (film): 3126, 2998, 1596 cm^{-1}. HRMS (ESI) $C_{23}H_{25}N_2O_2S$ $[M + H]^+$, 393.1637; found 393.1640.



4.62 **4.78**

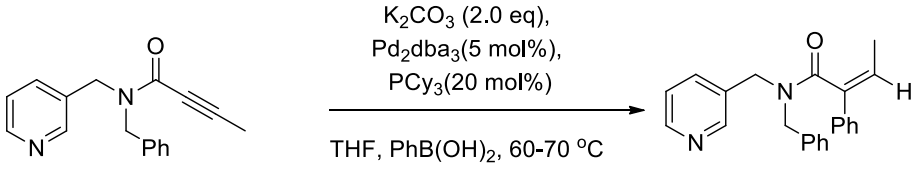
Compound 4.78: Using the procedure described for the preparation of **4.77**, 0.100 g of **4.62** was hydroarylated with 0.114 g of phenylboronic acid to give **4.78** (0.051 g, 35 %) as an off-white solid. Mp. 112-116 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, *J* = 1.7 Hz, 1H), 8.70 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.08 – 8.03 (m, 1H), 7.48 (dd, *J* = 5.3, 3.3 Hz, 2H), 7.39 – 7.30 (m, 4H), 6.19 (s, 1H), 5.54 (d, *J* = 0.5 Hz , 1H), 5.34 (d, *J* = 0.5 Hz, 1H), 4.57 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 148.0, 144.2, 138.5, 135.3, 130.3, 128.9, 128.5, 126.3, 123.7, 114.8, 44.1. IR (film): 3294, 2926, 1647 cm^{-1}. HRMS (ESI) $C_{15}H_{15}N_2O_2$ $[M + H]^+$, 239.1184; found 239.1190.



4.79

Compound 4.79: Using the procedure described for the preparation of **4.77**, 0.100 g of **4.66** was hydroarylated with 0.074 g of phenylboronic acid to give **4.79** (0.045 g, 30 %) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 – 8.40 (m, 2H), 7.46 (dd, *J* = 30.2, 25.0 Hz, 2H), 7.38 – 7.14 (m, 6H), 5.44 (d, *J* = 0.5 Hz, 1H), 5.12 (d, *J* = 0.5 Hz, 1H), 4.32 (d, *J* = 4.5 Hz, 2H), 4.25 (s, 2H), 1.36 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 148.3, 147.2, 146.6, 139.0, 135.6, 135.4, 128.7, 126.6, 123.1, 113.8, 79.5, 64.0, 54.3,

29.0. IR (film): 2977, 1689, 1598 cm^{-1}. HRMS (ESI) $C_{20}H_{25}N_2O_2$ $[M + H]^+$, 325.1916; found 325.1916.



4.80

Compound 4.80: Using the procedure described for the preparation of **4.77**, 0.075 g of **4.69** was hydroarylated with 0.052 g of phenylboronic acid to give **4.80** (0.055 g, 57 %) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, *J* = 8.7, 4.3 Hz, 1H), 8.47 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.42 – 7.24 (m, 10H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.39 (s, 1H), 4.68 – 4.62 (m, 2H), 4.52 (d, *J* = 16.9 Hz, 2H), 2.41 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 150.0, 149.2, 148.8, 142.1, 136.5, 136.3, 134.7, 133.3, 129.3, 129.0, 128.7, 128.7, 128.1, 127.1, 126.2, 126.2, 123.9, 123.9, 119.1, 51.1, 47.7, 18.5. IR (film): 3083, 1633 cm^{-1}. HRMS (ESI) $C_{23}H_{23}N_2O$ $[M + H]^+$, 343.1810; found 343.1809.

CHAPTER 5

SUMMARY AND FUTURE DIRECTIONS

5.1 Summary

The primary goal of the research described in chapter 3 was to develop new synthetic methodology for involving pyridine anhydrobases as nucleophiles in metal-catalyzed transformations to access architecturally sophisticated molecules. Specifically, our efforts were directed towards Au-catalyzed intramolecular cyclization reactions of pyridine substrates. For this purpose, 4-alkylpyridine substrates with tethered alkynones and alkynes were synthesized and subjected to the Au-catalyzed intramolecular cyclization under various conditions to afford the 4-pyridyl lactam products in moderate yields. We successfully demonstrated that the alkynone derivatives underwent gold(I) catalyzed cyclization, but with lower yields initially. While probing the reason for the lower yield, we found that the amides show distinct rotamer populations on the NMR time-scale and the same was observed for the corresponding anhydrobase intermediates. This drove us to change the electronics around the nitrogen atom, which proved beneficial in improving the yield of the cyclization reaction. Specifically, when these imide–like substrates were subjected to Au-catalyzed reactions, anticipated products were obtained in much improved yields. In contrast, non-conjugated alkyne substituents appear to be unreactive toward Au-catalyzed cyclization. Moreover, these substrates proved to be resistant to the anhydrobase formation in general. The pyridine substituted lactams obtained by successful benzylic cyclization should be amenable to further synthetic manipulations leading to more complex systems. Expanding the scope of these reaction manifolds by introducing other transition metal-catalysts may provide additional valuable

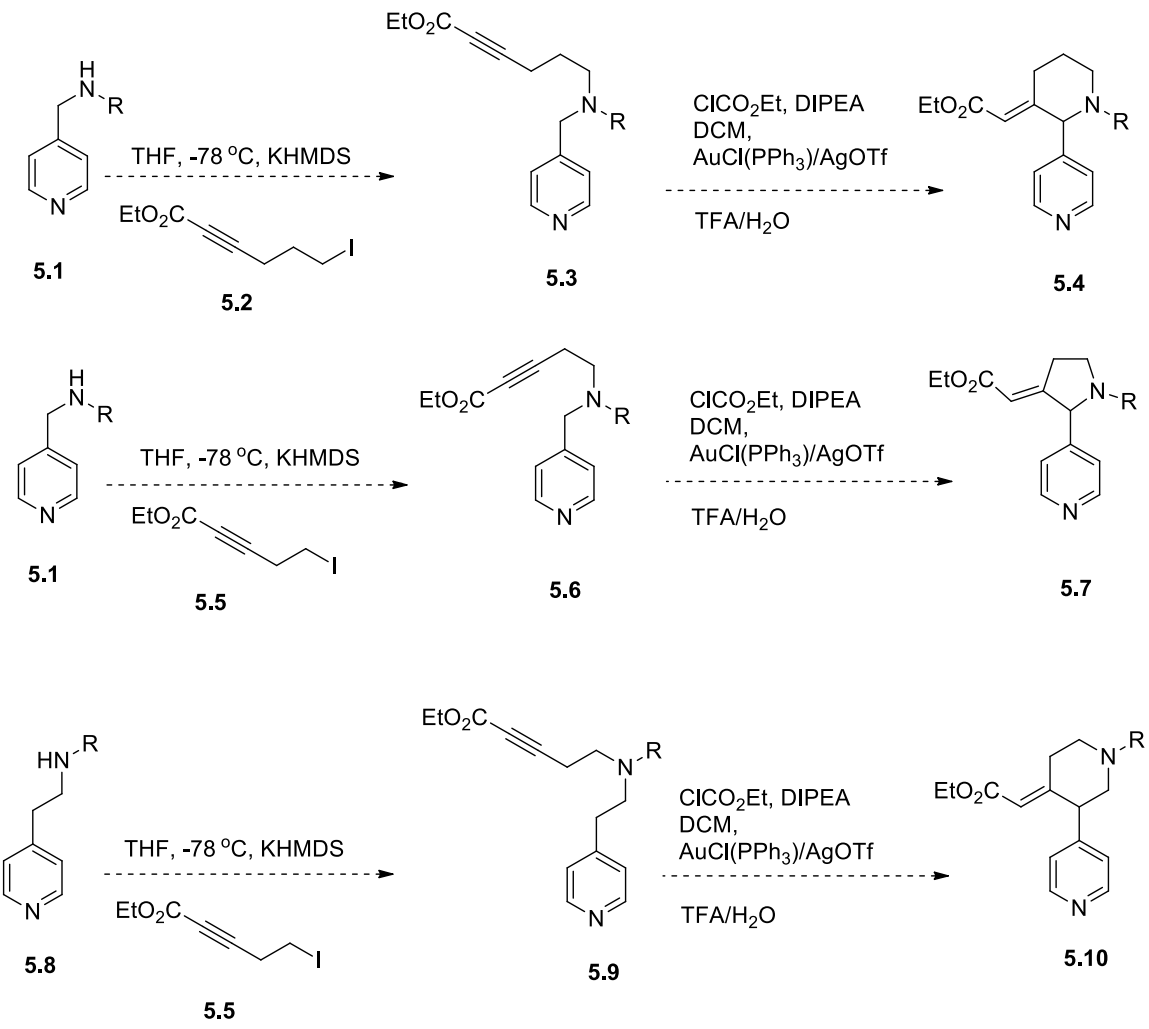
new synthetic procedures for the construction of complex molecular frameworks leading to the synthesis of natural products and their analogues of biological importance.

The objective of the research described in chapter 4 was to explore the use of pyridine rings as electrophiles towards metal-catalyzed nucleophilic additions. 3-Alkylpyridine substrates with tethered alkyne or alkynone side-chains were synthesized. Attempts to engage the corresponding acyl or alkyl pyridinium salts in palladium catalyzed arylative additions did not provide the desired results. During the course of this study, however, it was found that the alkynyl pyridine substrates underwent hydroarylation under mildly basic conditions, in contrast to literature reports of similar reactions in which acidic additives were required. Interestingly, the reaction failed when the pyridine ring in the substituent was replaced with a phenyl ring. Thus, it appears that the pyridine group is important and needed for these hydroarylation reactions. The mechanistic details of this reaction have not been fully established with respect to the original objective of this study, the substrate/catalysts combination examined clearly did not afford the envisioned products. Other nucleophilic transition metal complexes based on metals such as Rh(I) or Pt(0) may exhibit a different reactivity profile in this system, and investigations along these lines provide a starting point for future work.

5.2 Future directions

4-alkylpyridine substrates in Au-catalyzed exo-dig cyclization: We have successfully demonstrated in chapter 3 that anhydrobases generated from the 4-alkylpyridines with appropriately placed alkynone side-chain undergo gold(I) catalyzed *endo-dig* cyclizations to give pyridyl lactam products. One direction for future work entails the synthesis of substrates shown in scheme 5.1. These pyridine derivatives should

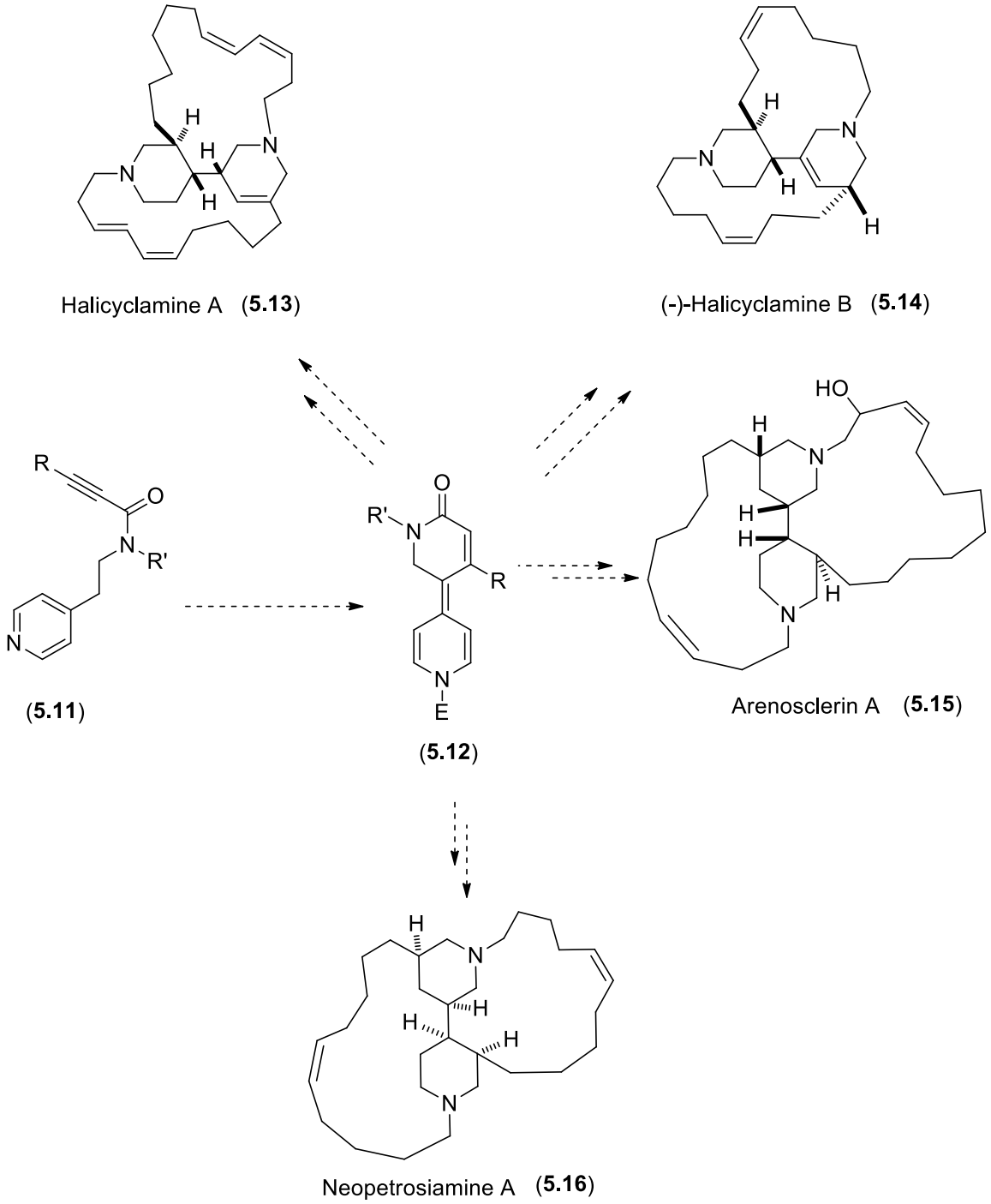
be amenable to gold(I) catalyzed cyclizations via anhydrobase intermediate to give the 5 or 6-*exo-dig* cyclized products as shown in scheme 5.1.



Scheme 5.1 Proposed scheme.

4-alkyl pyridine substrates in natural product synthesis: We have successfully demonstrated that properly tethered alkynone derivative of 4-alkylpyridines can act as electrophilic centers for gold (I) catalyzed reactions via anhydrobase intermediates. The

cyclized anhydrobase intermediate may act as a potential synthetic building block in an efficient way. This methodology can be used as an approach towards the synthesis of natural products like halicyclamine as shown in scheme 5.2. These natural products are polycyclic alkaloids having a bis-piperidine core. Pyridine derivatives **5.11** can be transformed to their corresponding anhydrobases **5.12** by subjecting them to the gold (I) catalyzed cyclization conditions as discussed in chapter 3. Reduction of these anhydrobase intermediates will then provide the bis-piperidine framework, which then can be further manipulated to yield the corresponding natural products **5.13**-**5.16**.

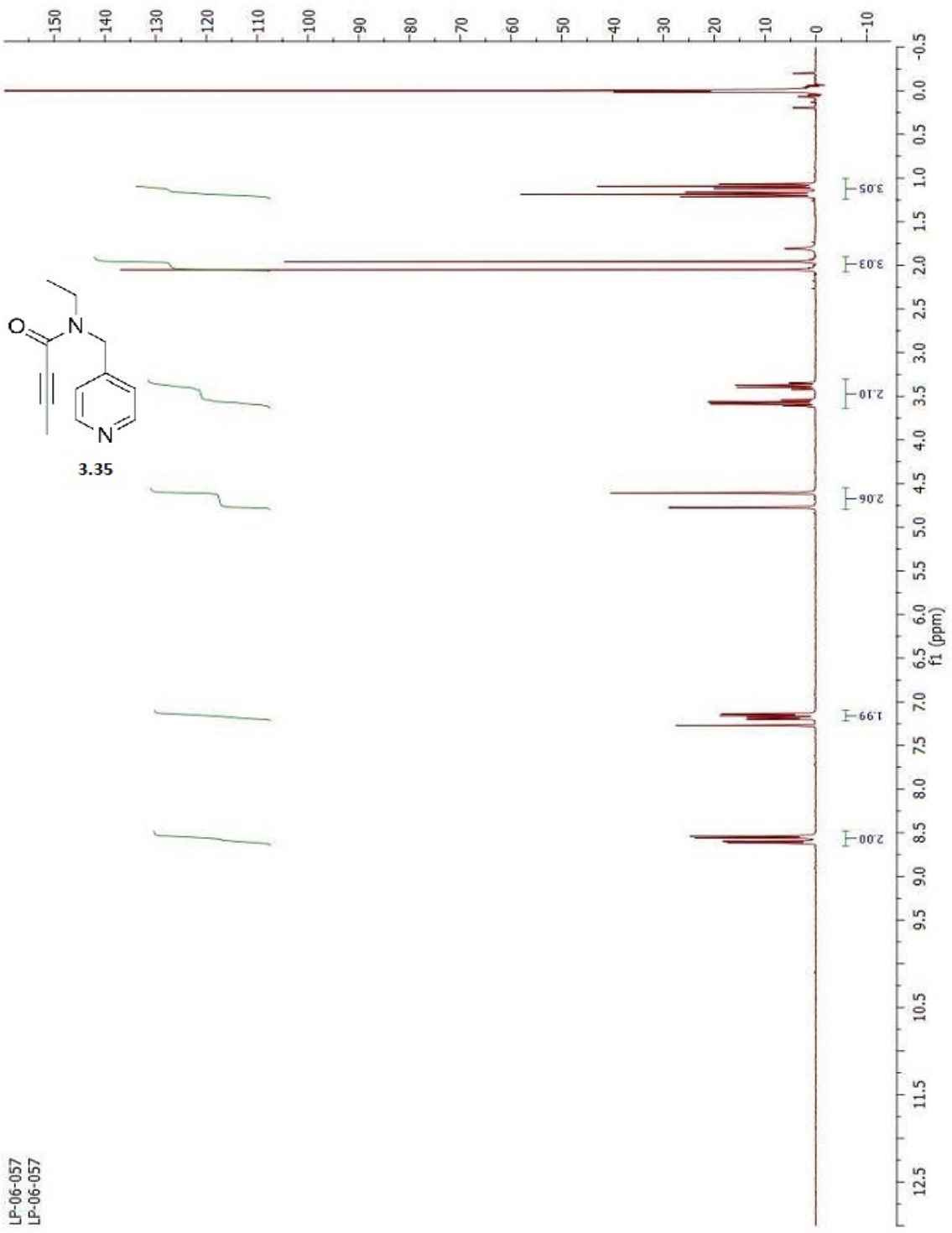


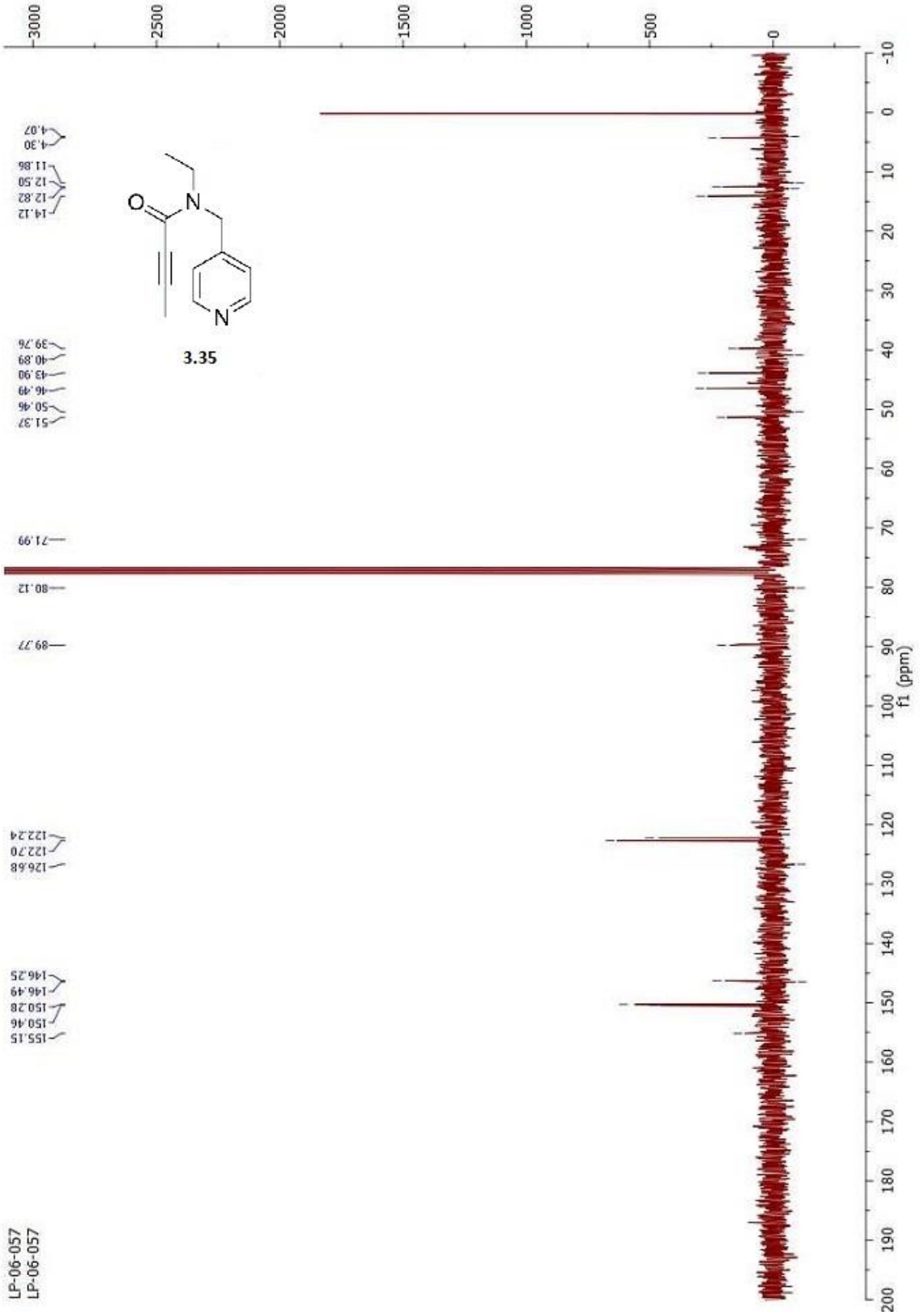
Scheme 5.2 Anhydrobase in natural product synthesis.

In conclusion, we have demonstrated that transiently generated 4-alkylidene dihydropyridines can be engaged in metal-catalyzed transformations to synthesize

substituted heterocycles. These methodologies provide a novel route for the synthesis of valuable biologically important manifolds. More importantly, this work shows the feasibility of capturing pyridine anhydrobases in metal-catalyzed transformations. The use of anhydrobase derivatives in other metal-promoted bond forming reactions (including asymmetric transformations) may emerge as an exciting area of future investigation.

APPENDIX

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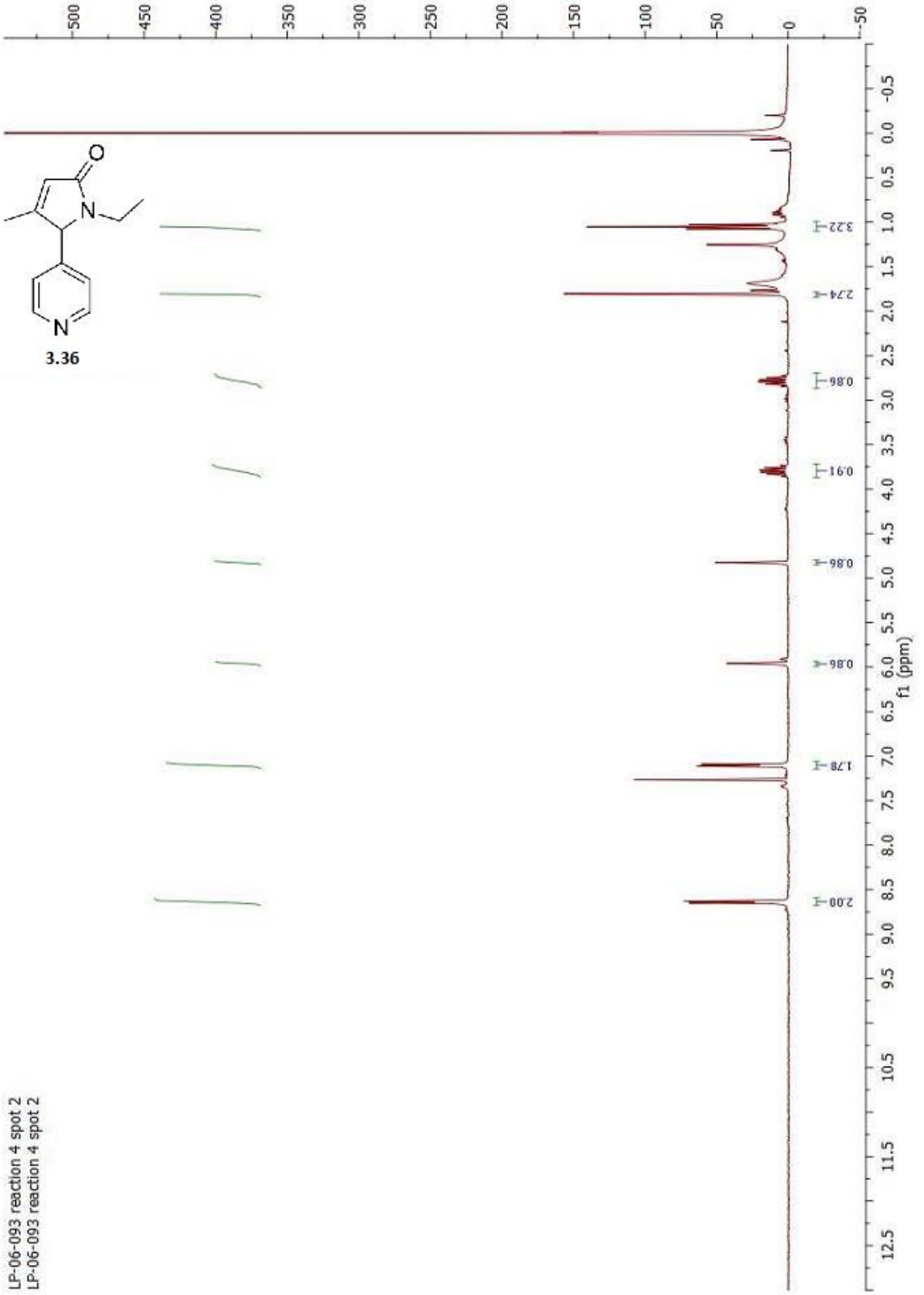
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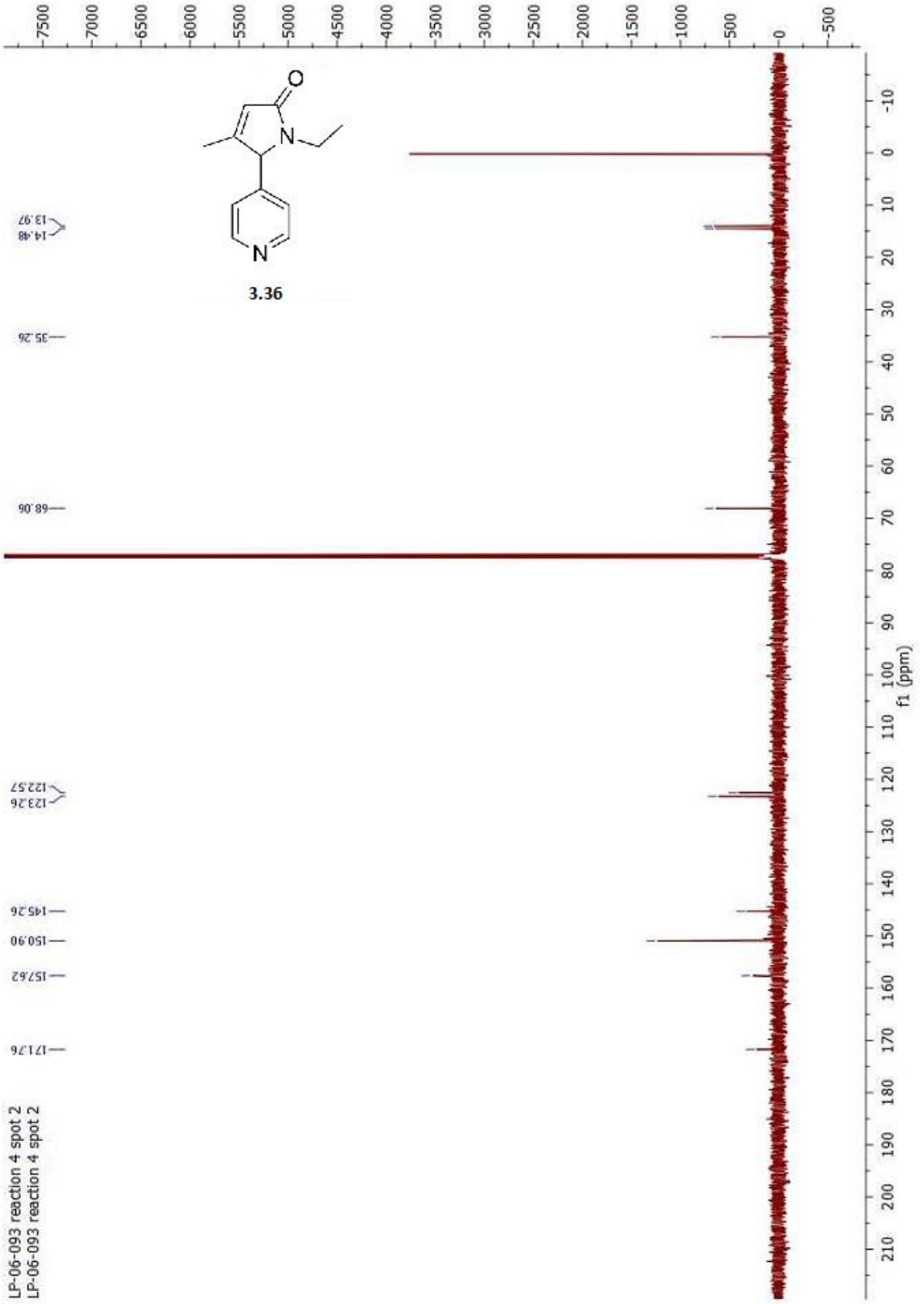
LP-06-093 reaction 4 spot 2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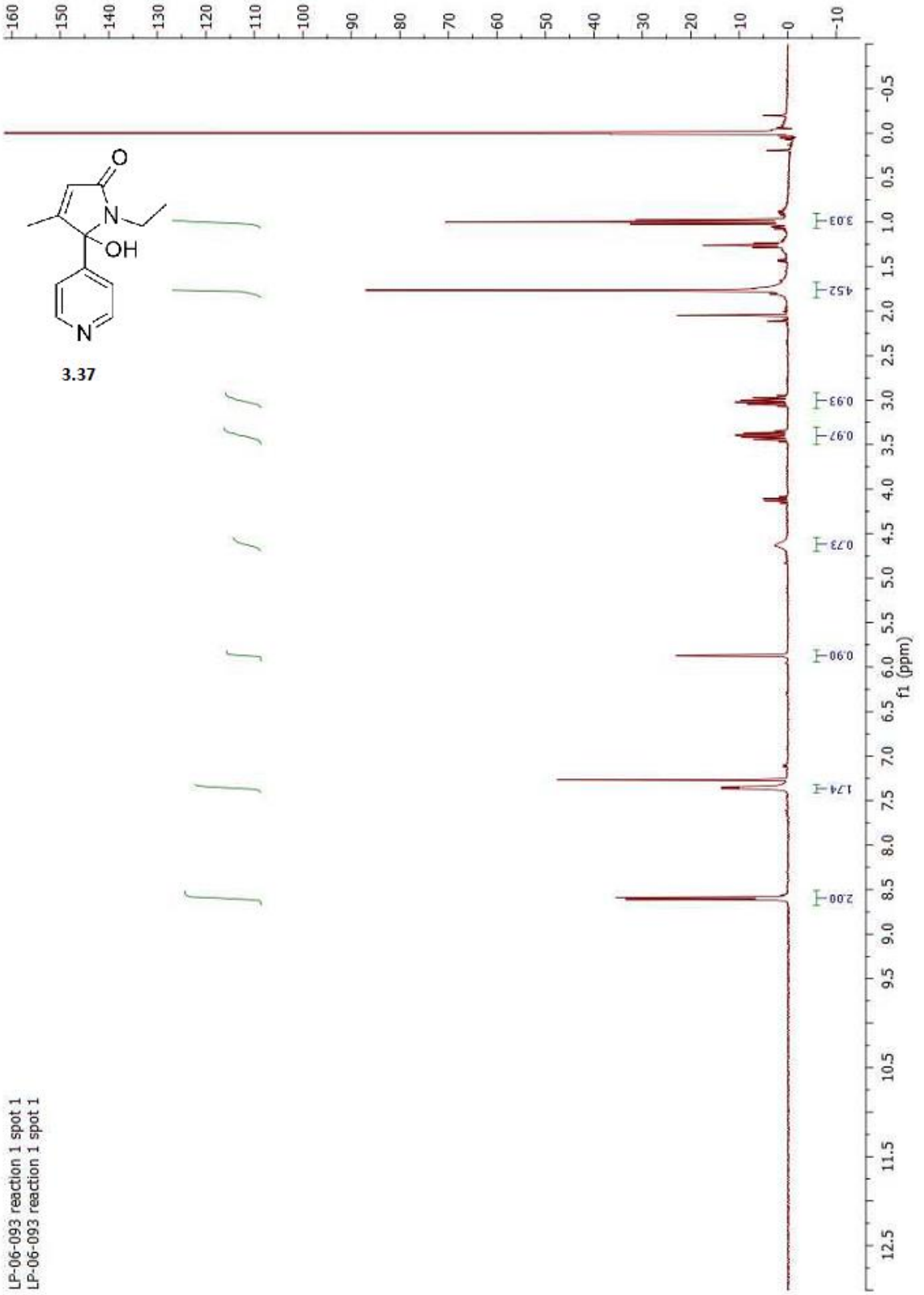
LP-06-093 reaction 4 spot 2
f1 (ppm)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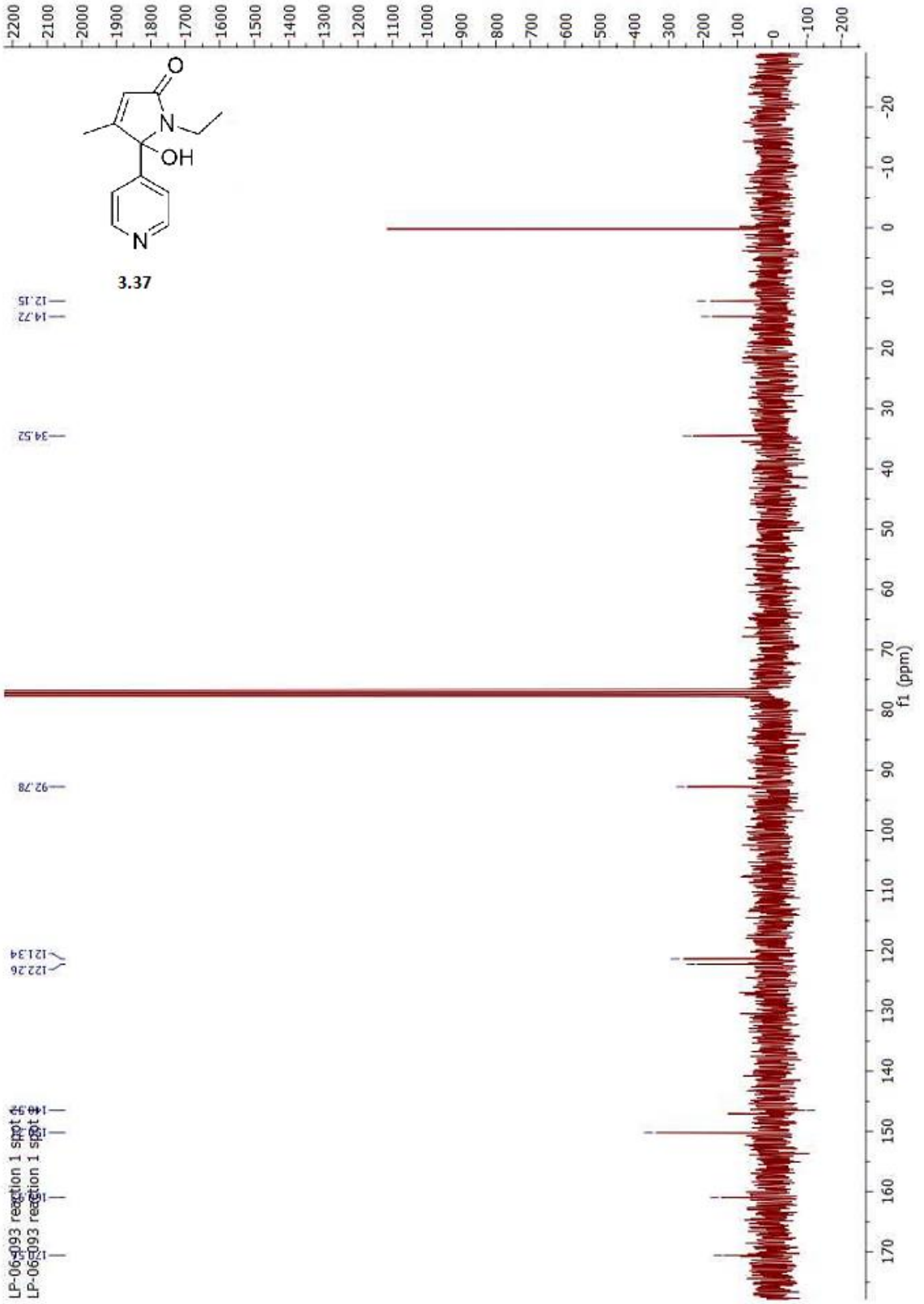
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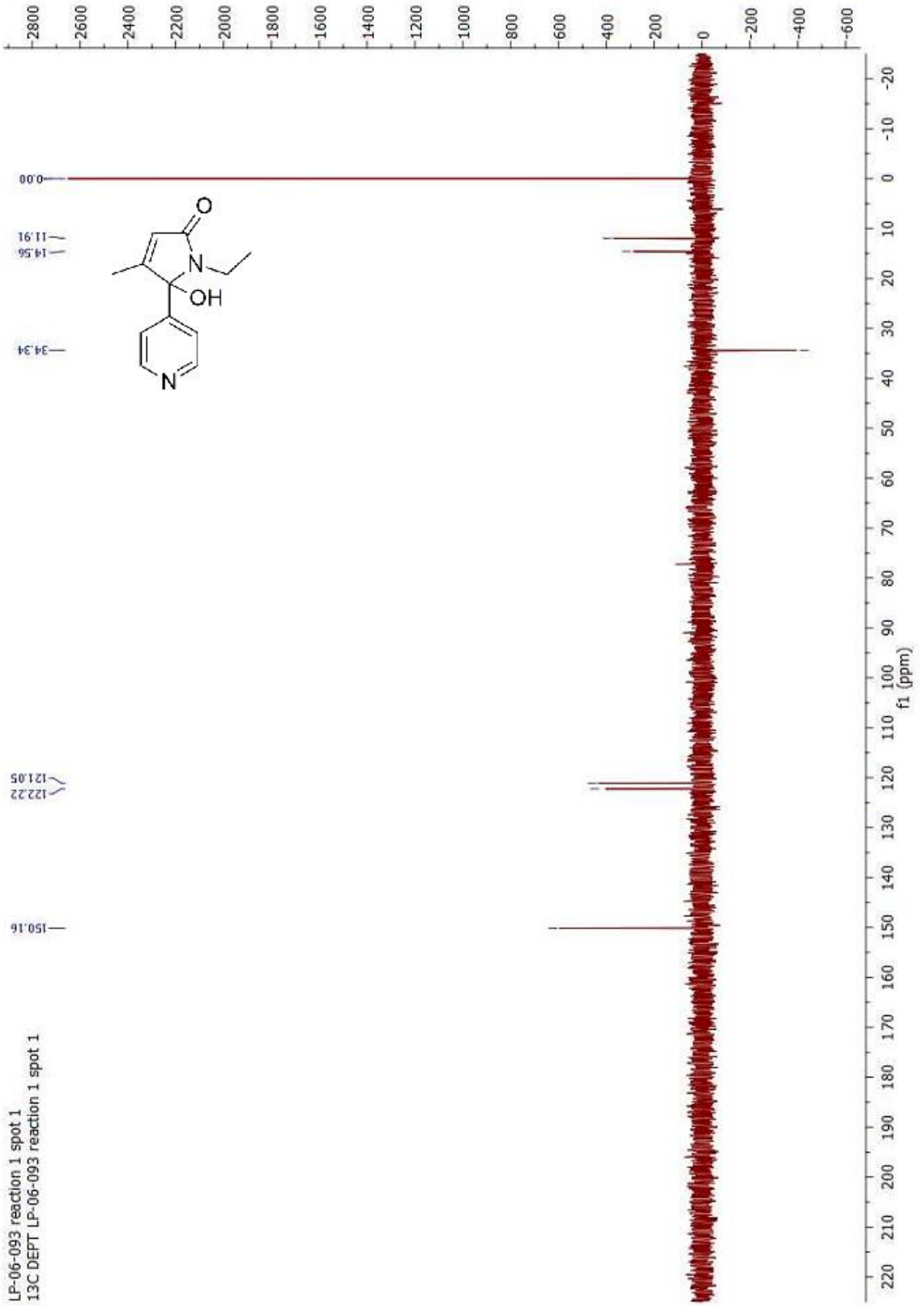
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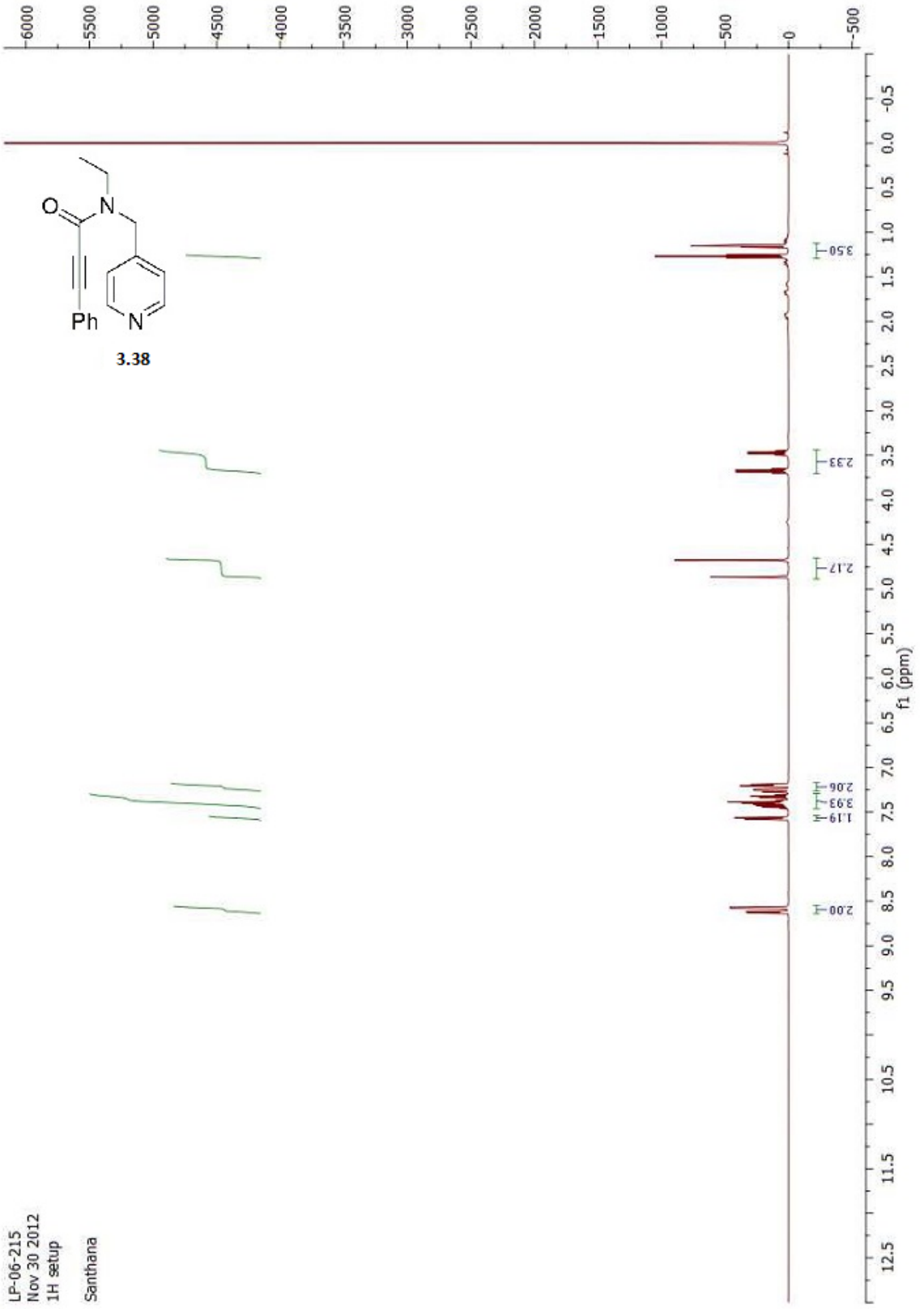
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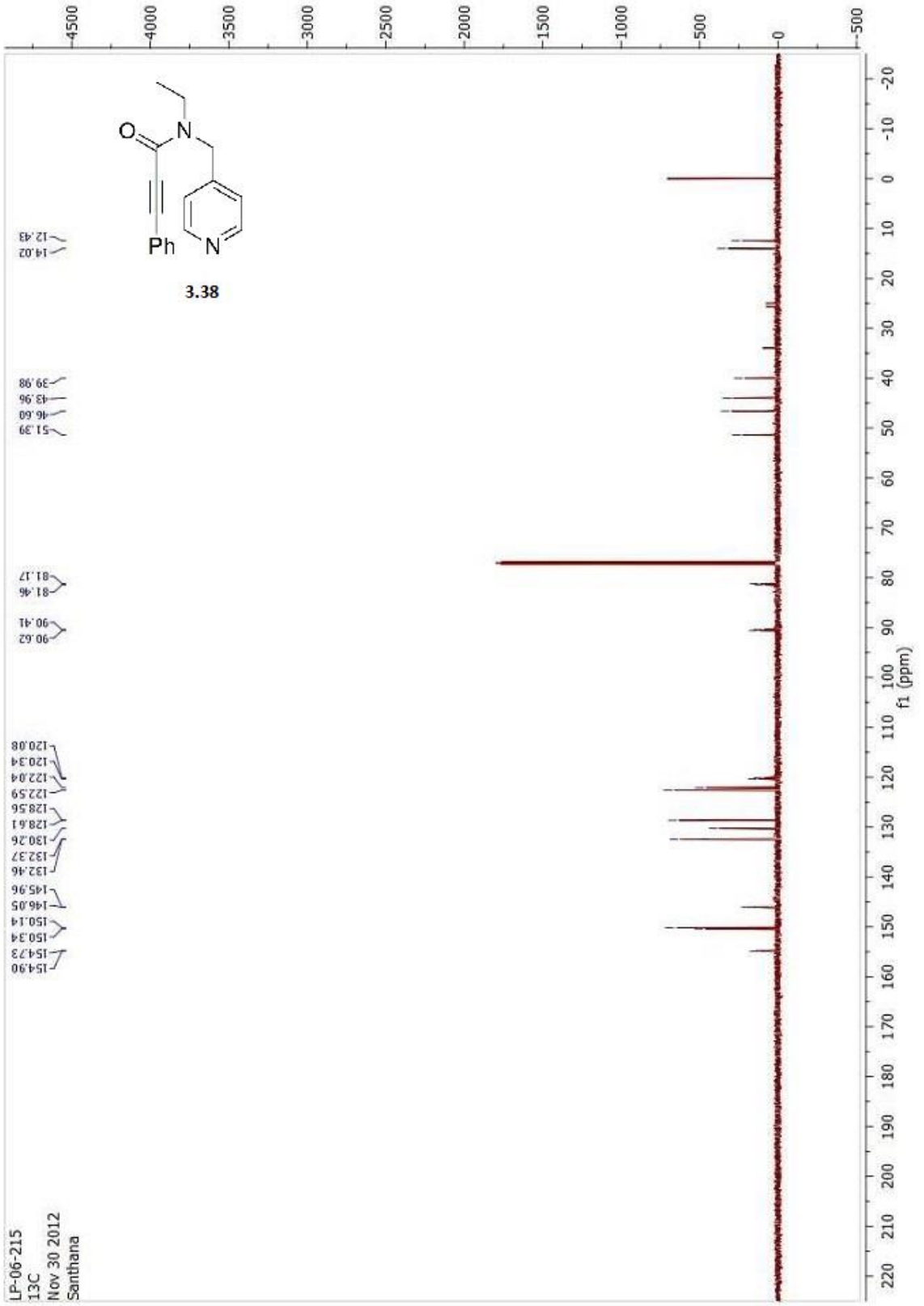
Nov 30 2012
1H setup
Santhana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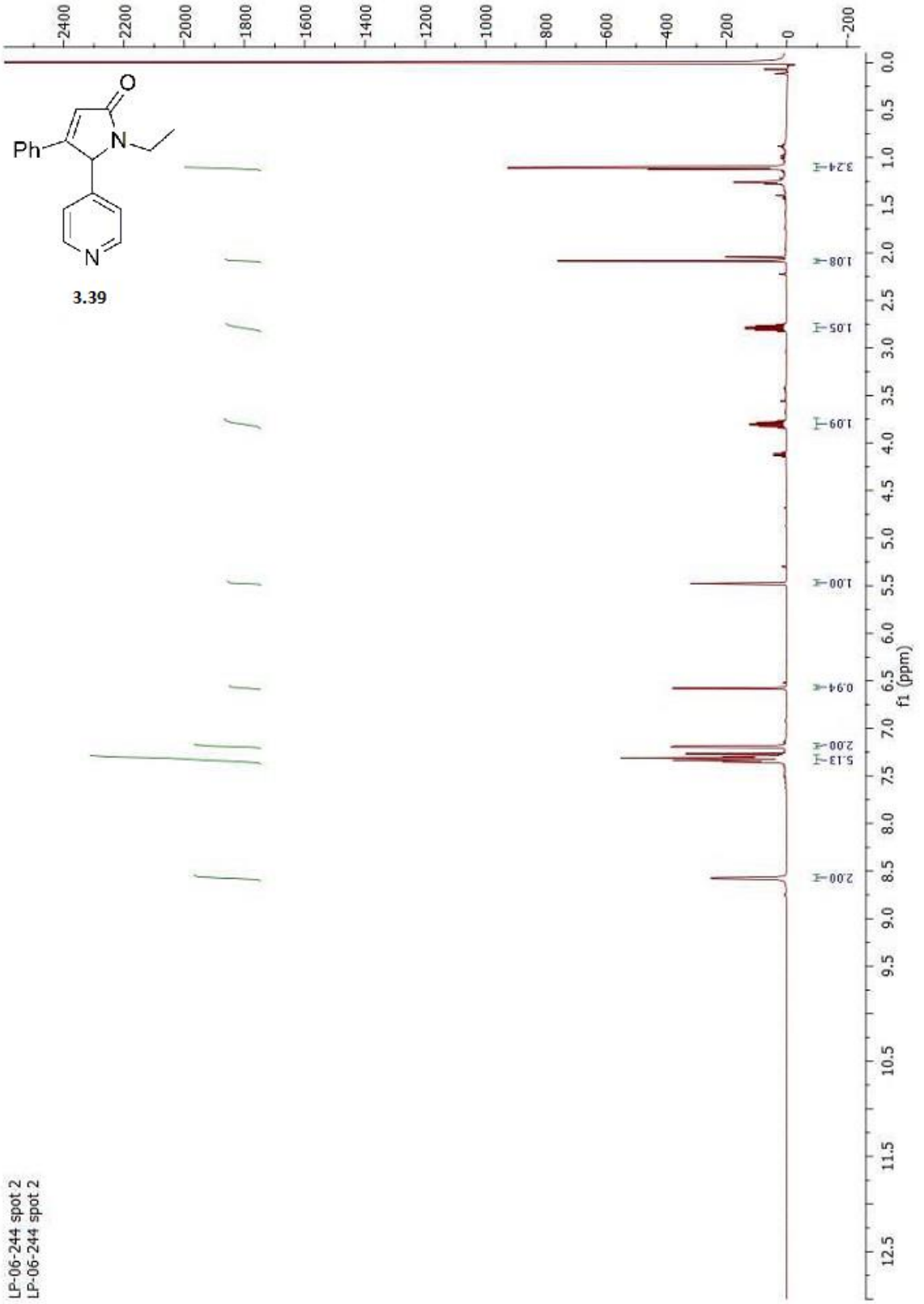
f1 (ppm)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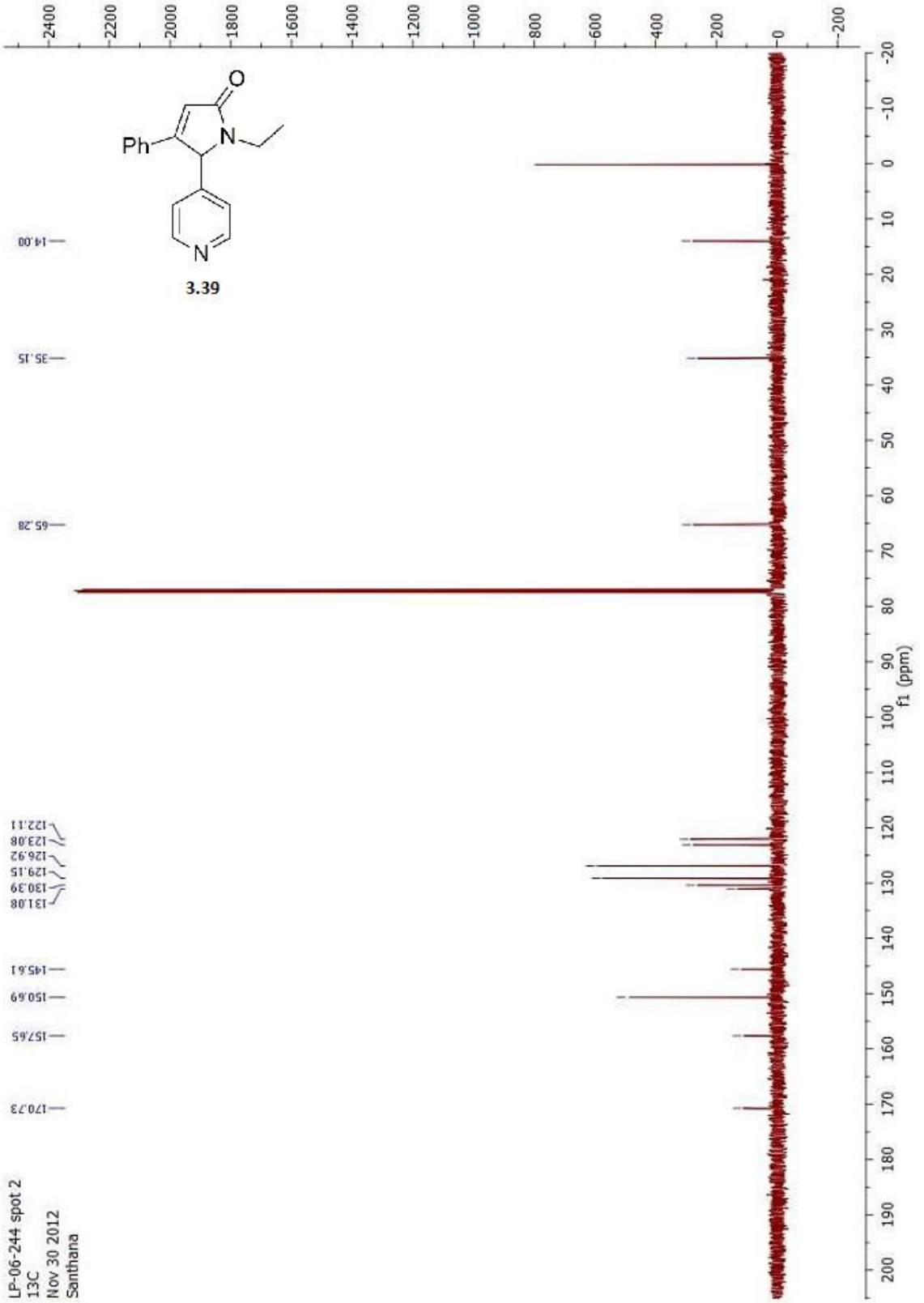
LP-06-244 spot 2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Ph
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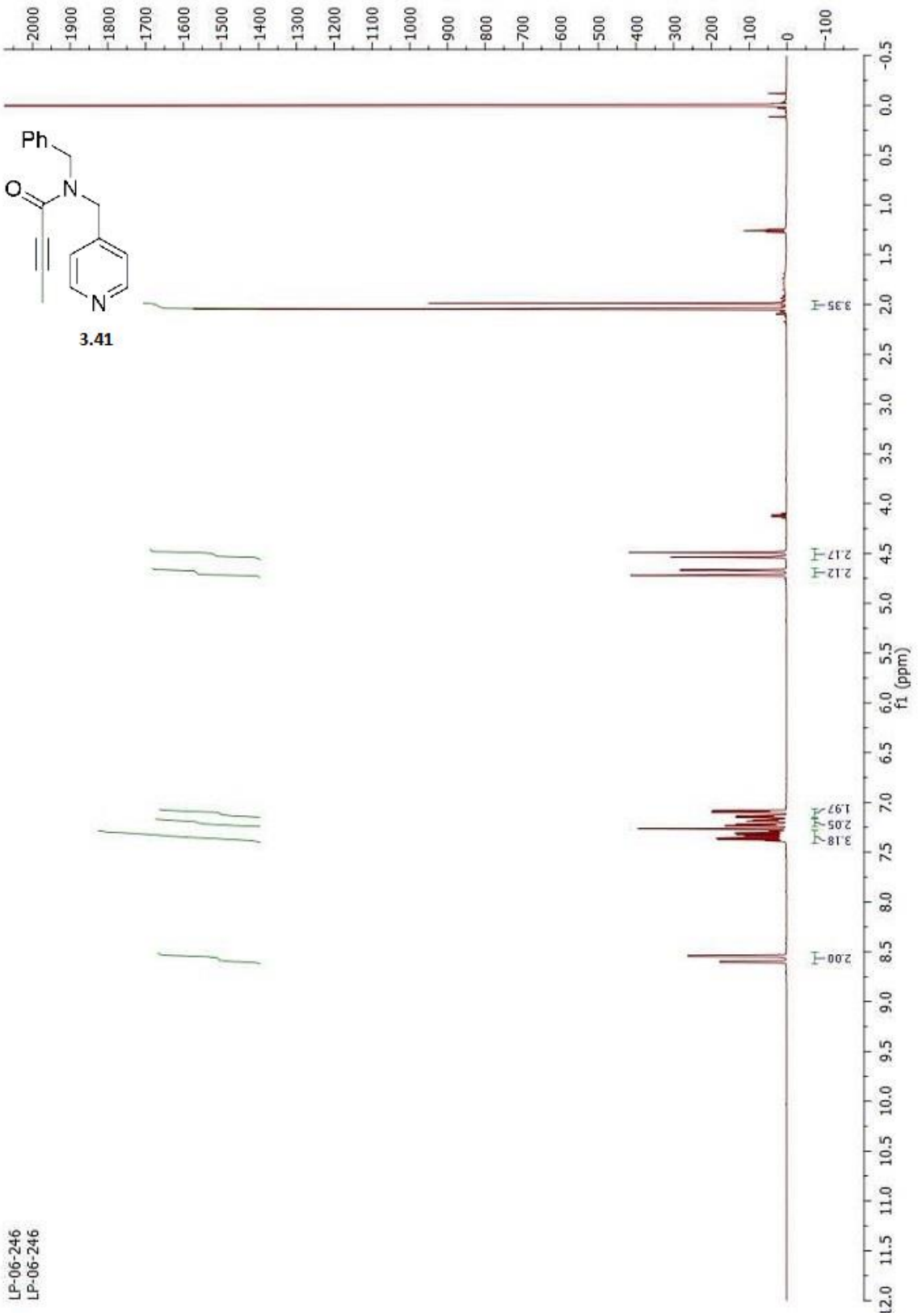
13C
Nov 30 2012
Santhana
f1 (ppm)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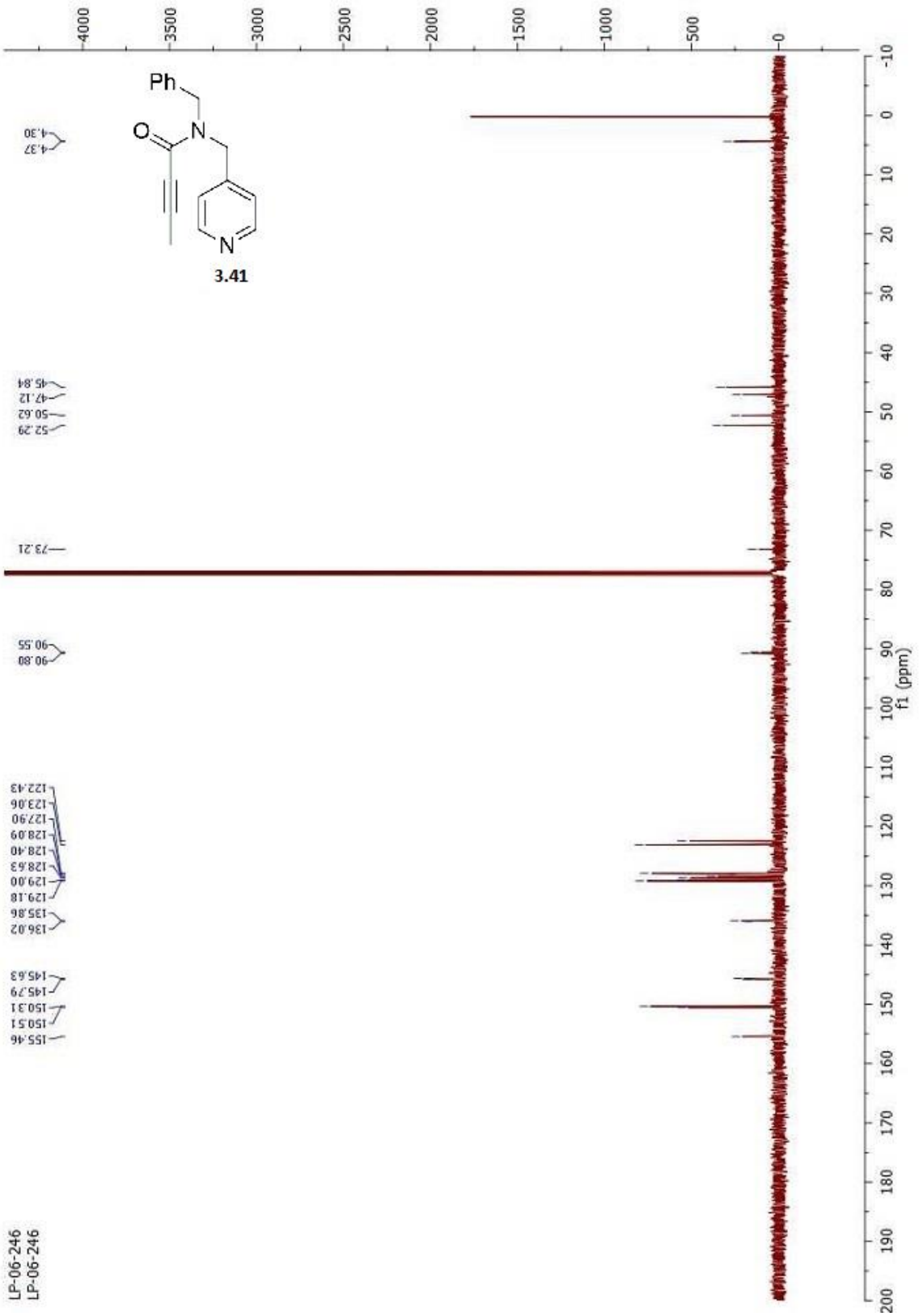
LP-06-246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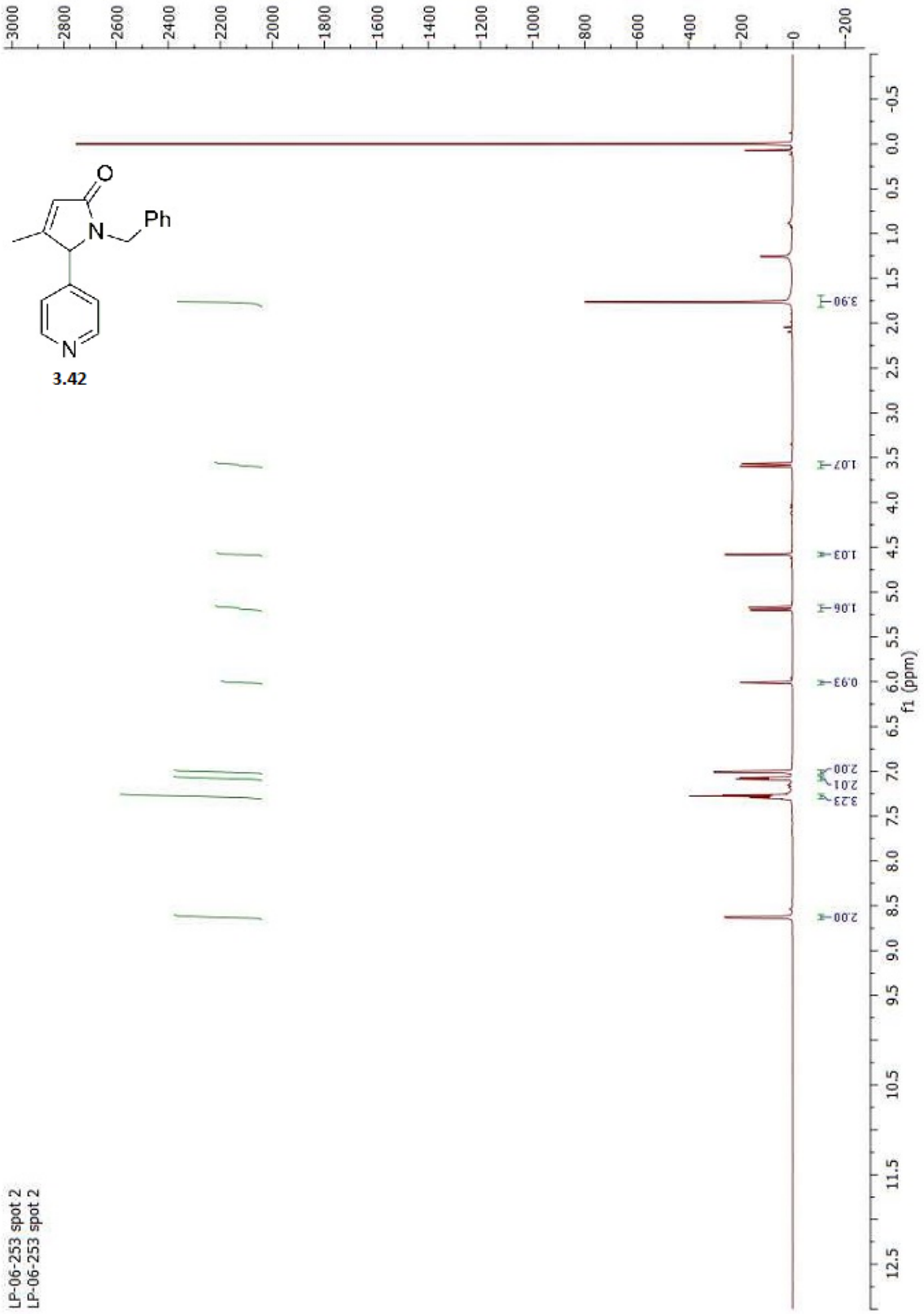
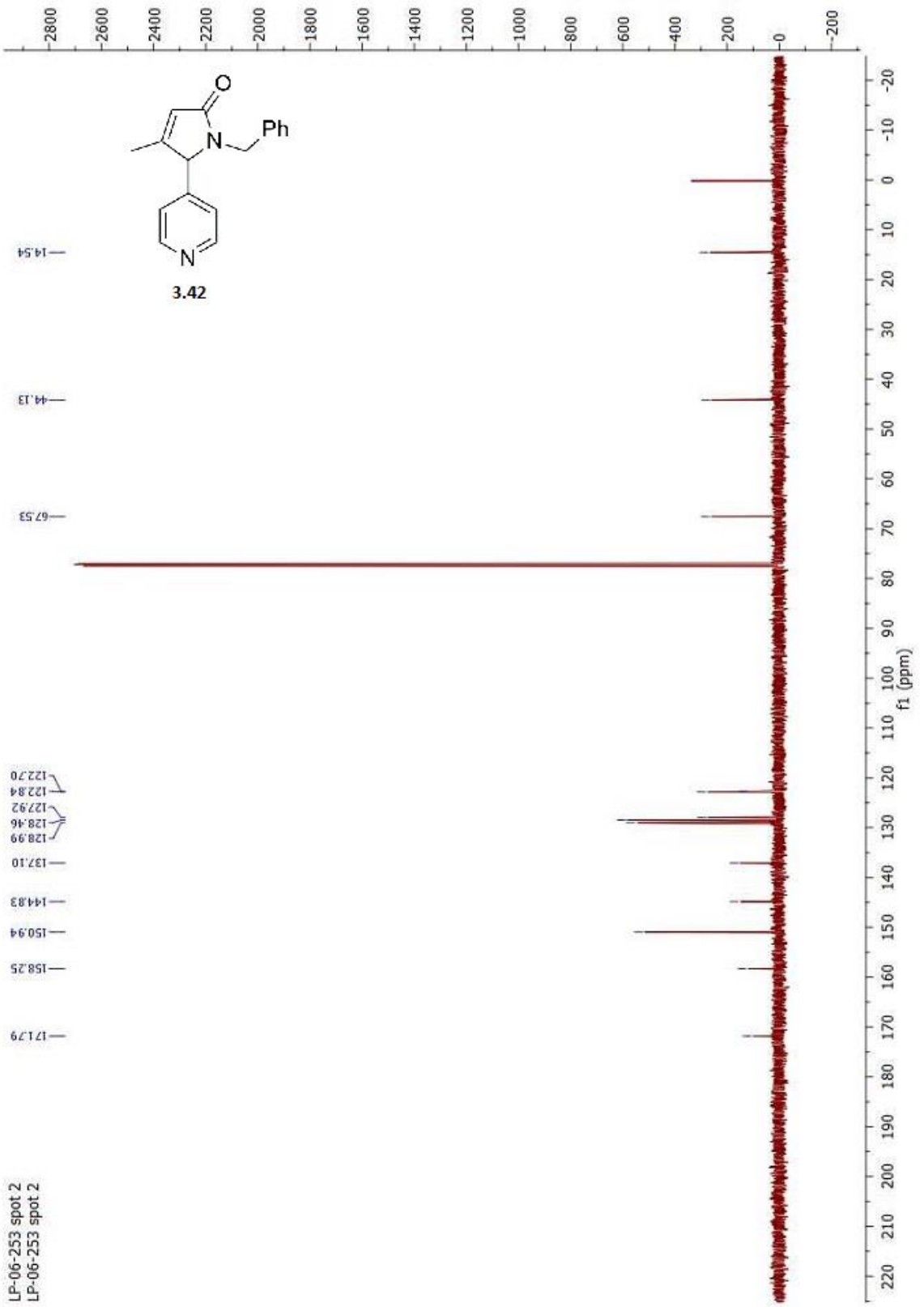
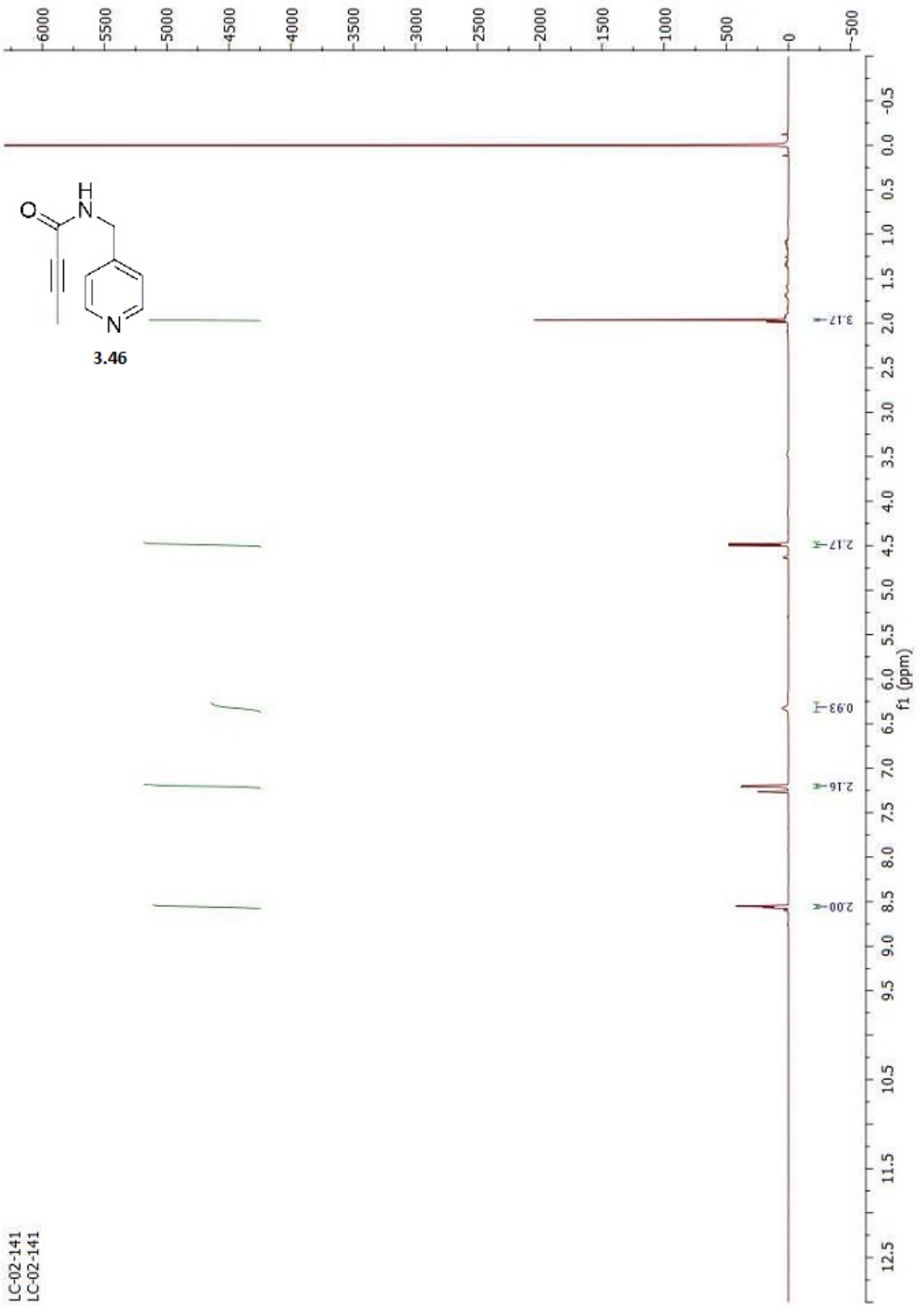
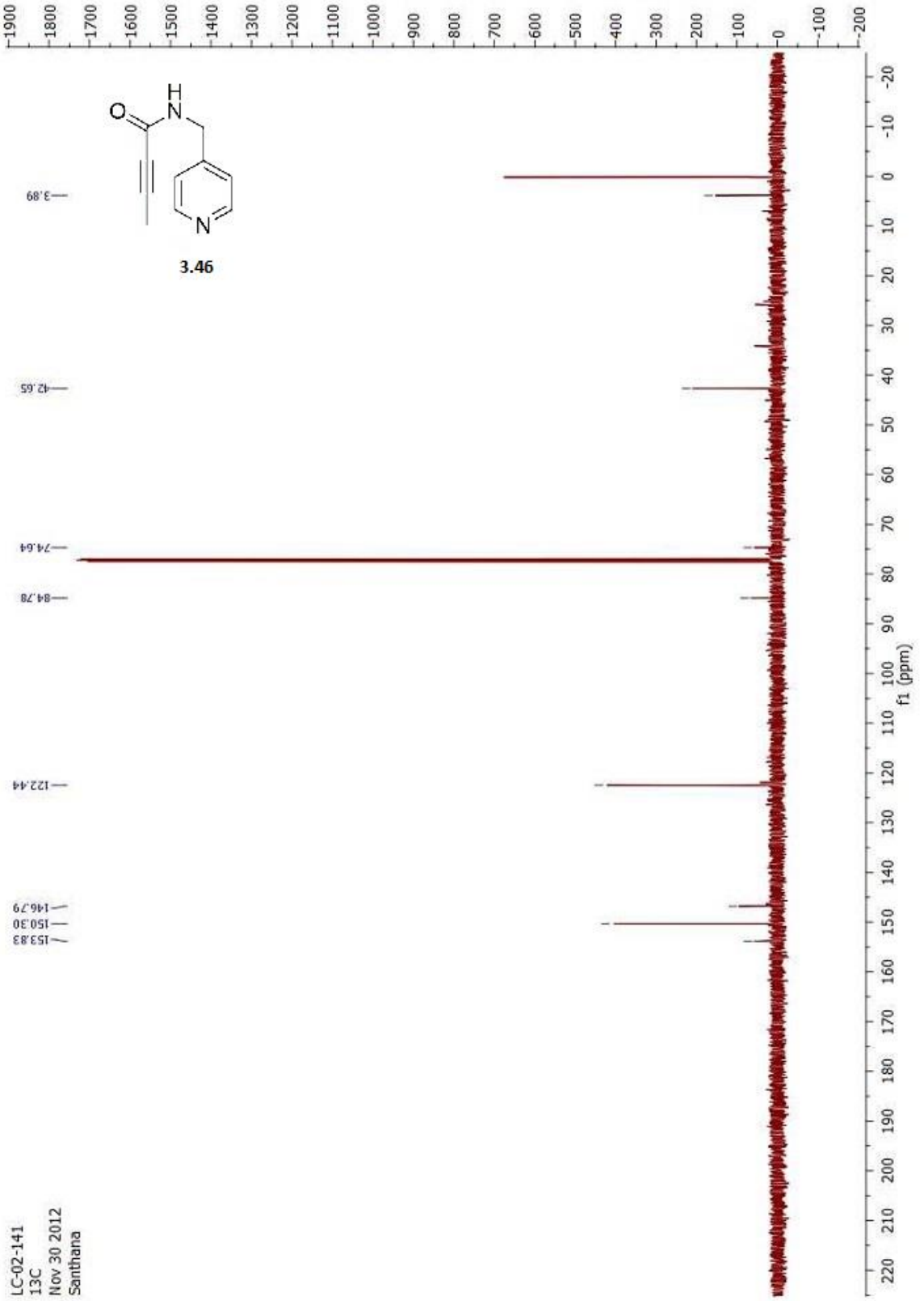
123.06
127.90
128.09
128.40
128.63
129.00
129.18
135.86
136.02
145.63
145.79
150.31
150.51
155.46
LP-06-246
LP-06-246
f1 (ppm)


O
N
Ph
N
3.42
f1 (ppm)
LP-06-253 spot 2
LP-06-253 spot 2


O
N
Ph
N
3.42
14.54
44.13
67.53
122.70
122.84
127.92
128.46
128.99
137.10
144.83
150.94
158.25
171.79
LP-06-253 spot 2
LP-06-253 spot 2
f1 (ppm)


3.46
LC-02-141
LC-02-141
f1 (ppm)


3.46
3.89
42.65
74.64
84.78
122.44
146.79
150.30
153.83
LC-02-141
13C
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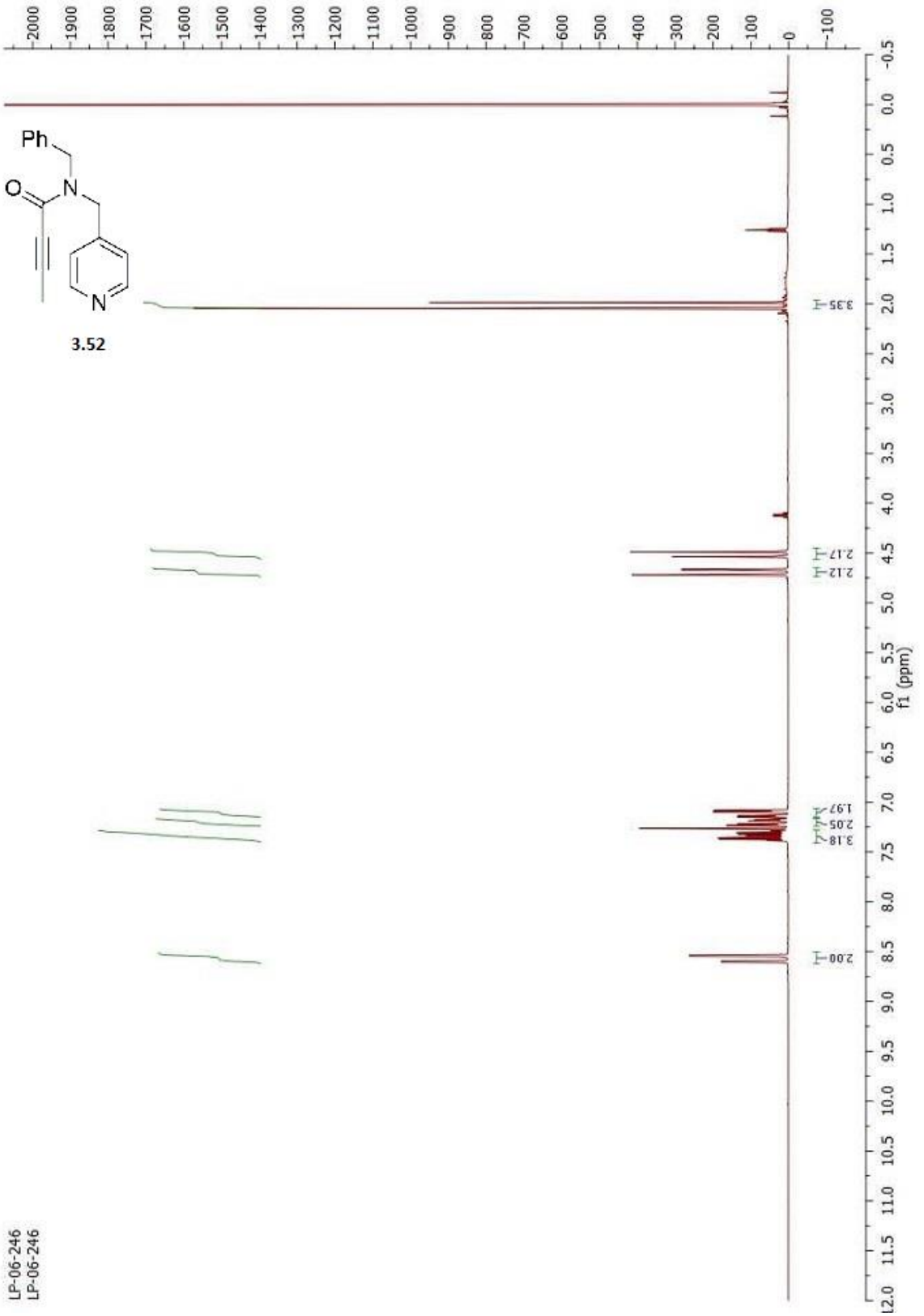
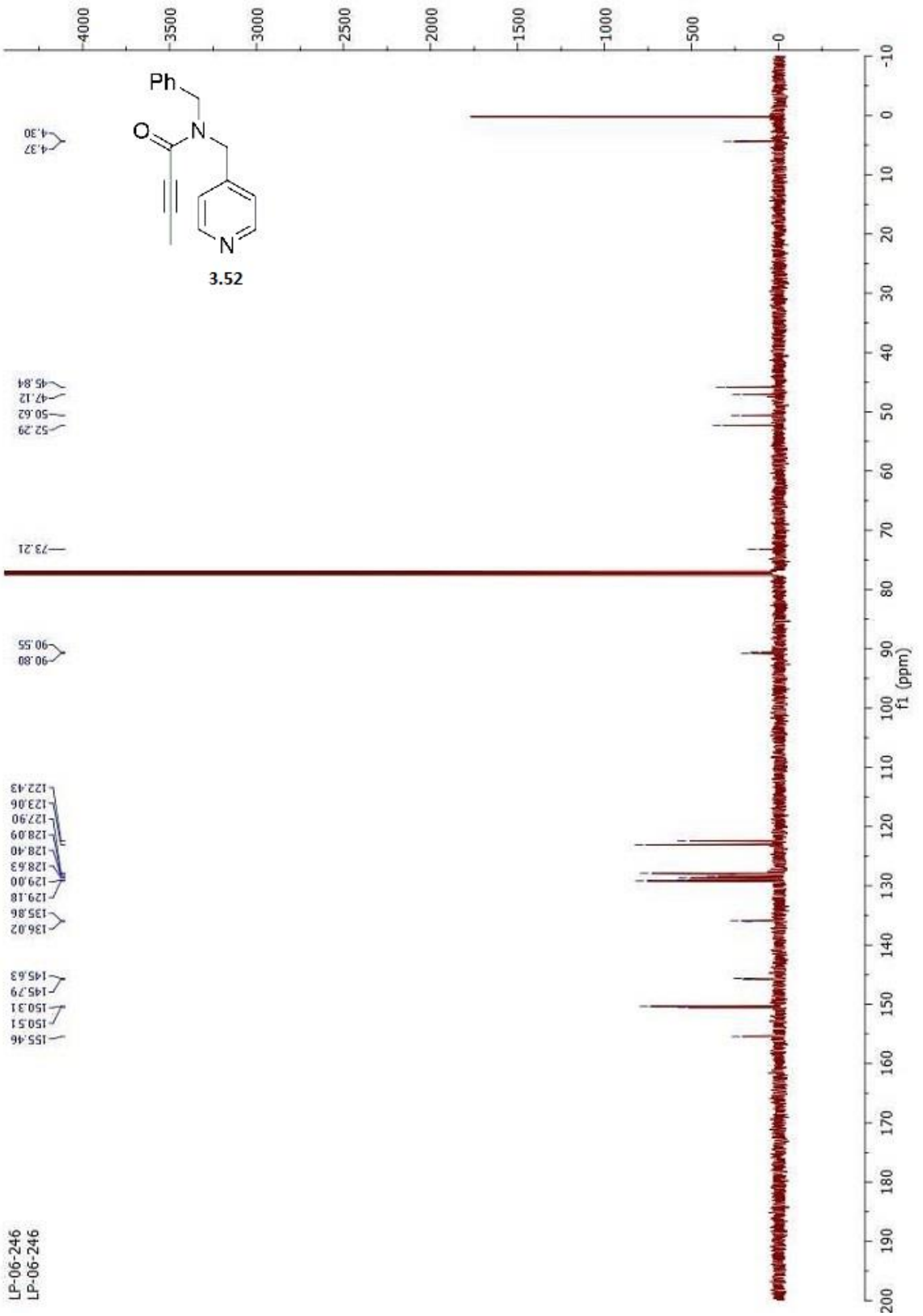
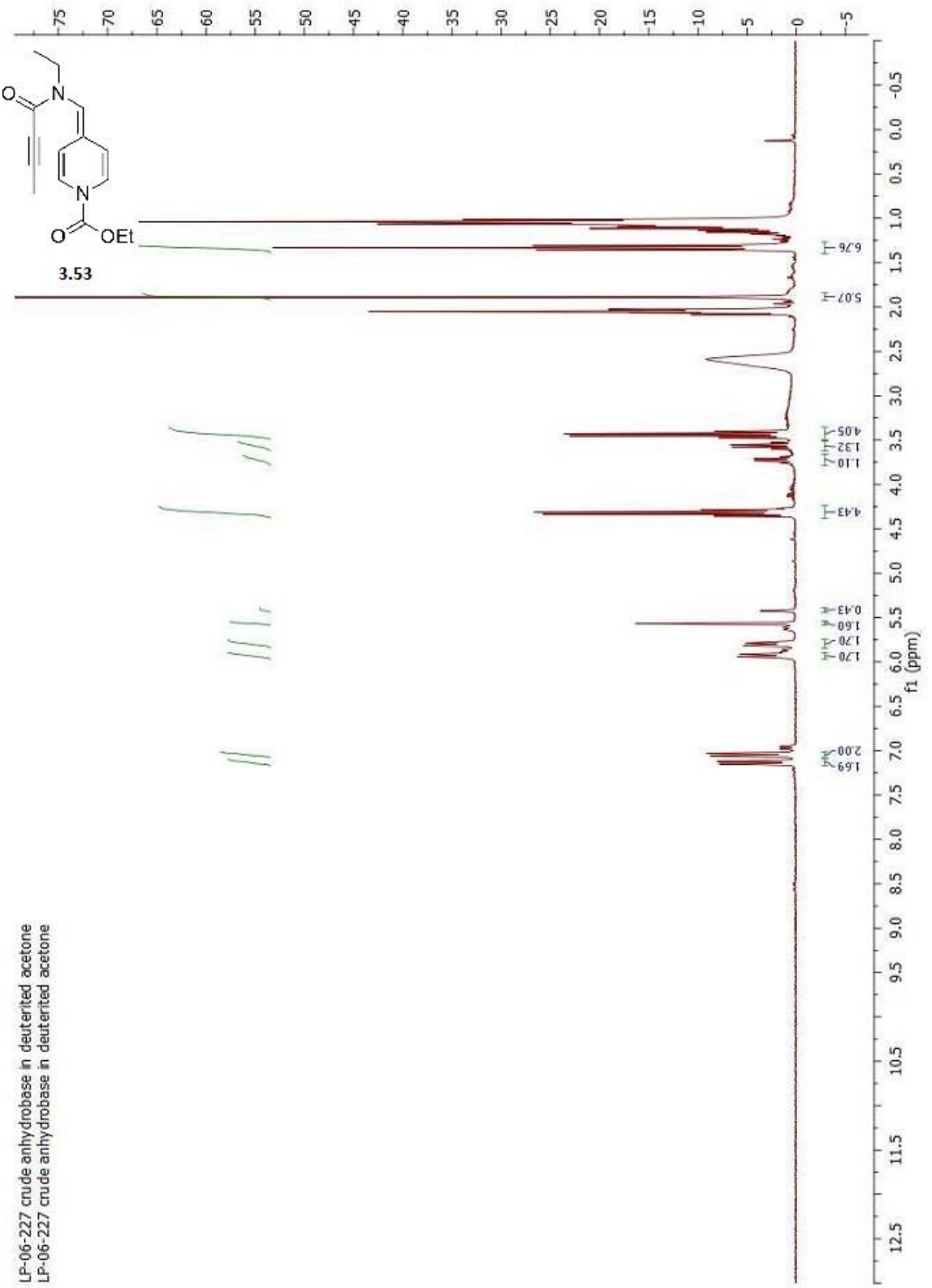
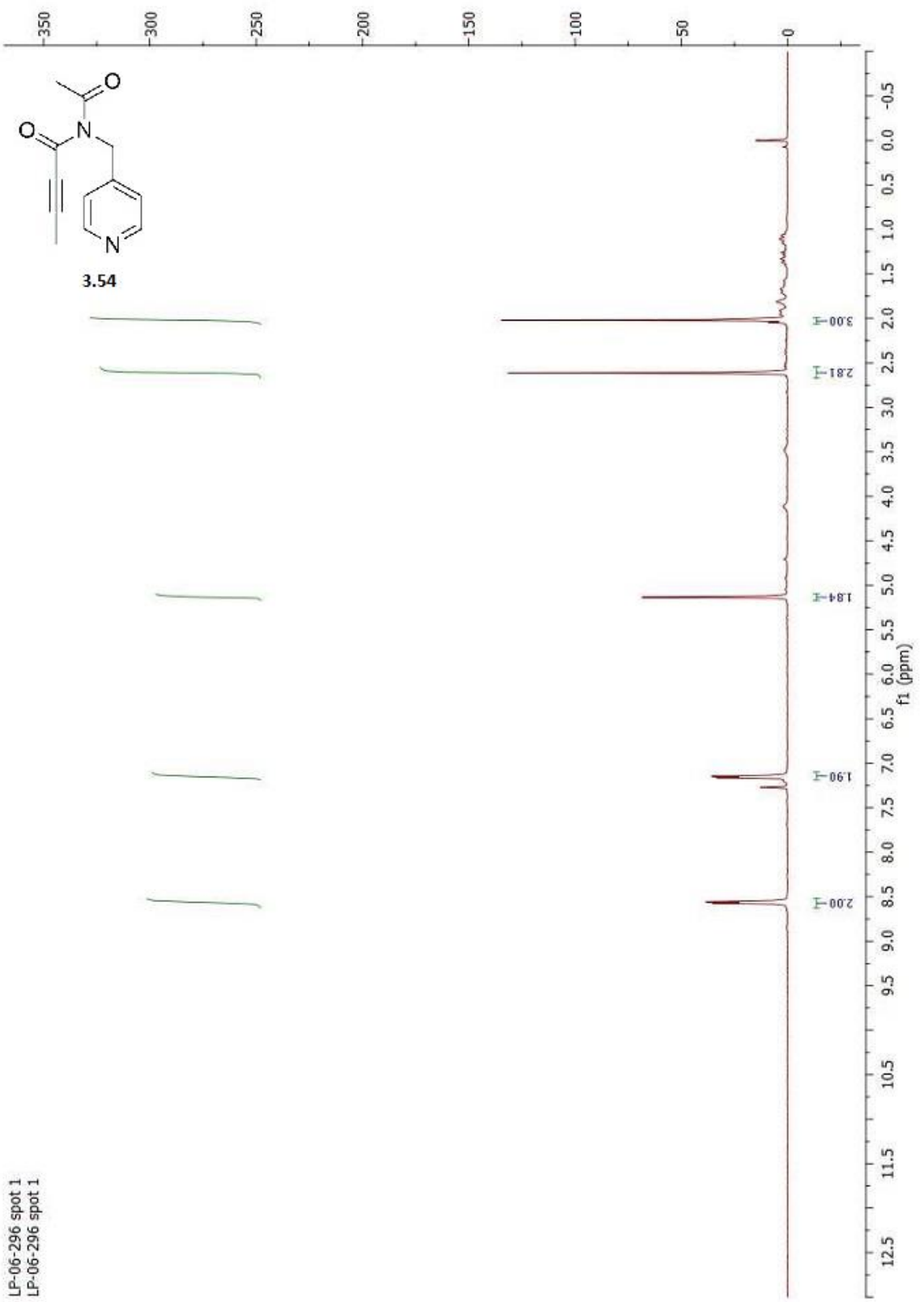
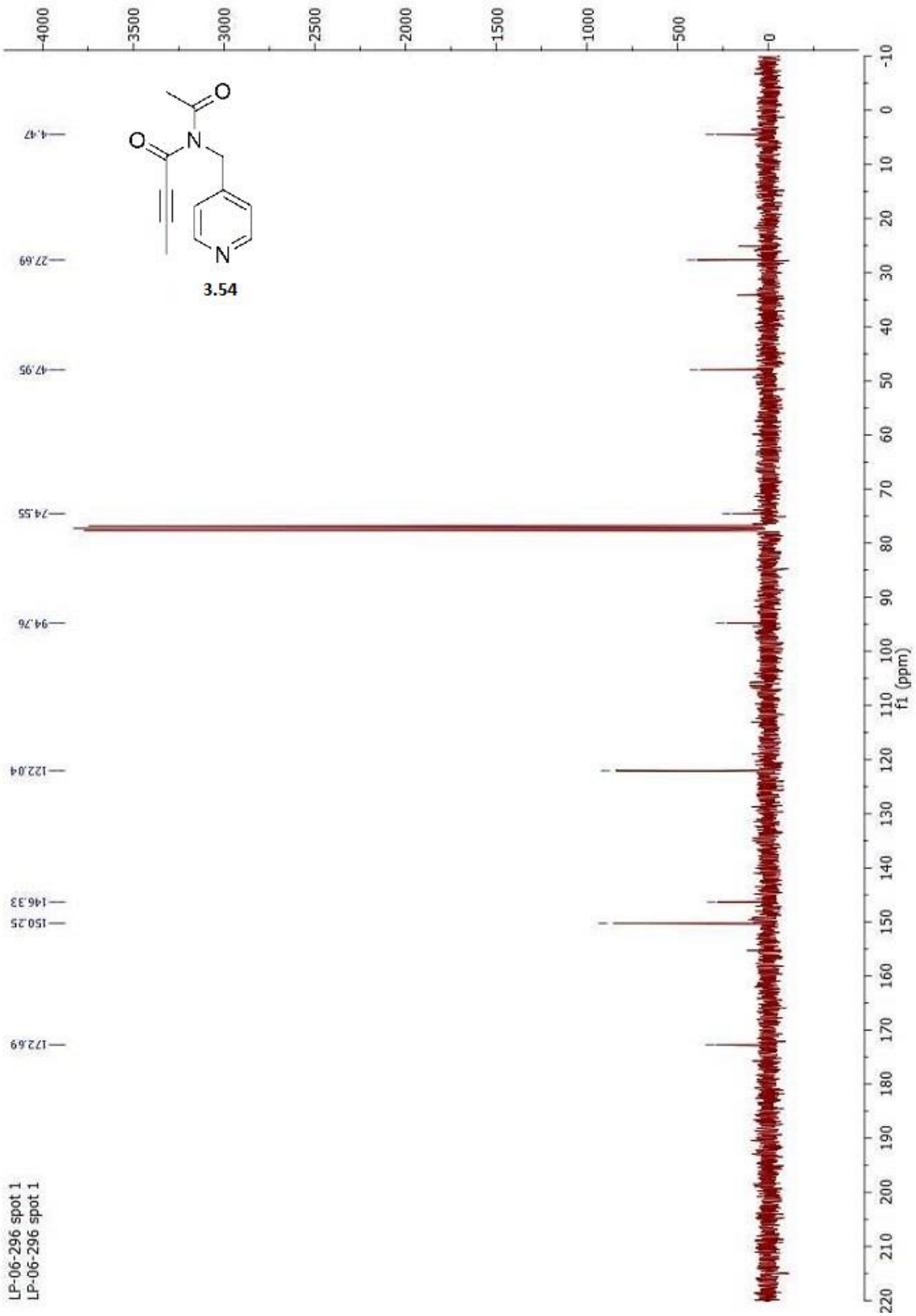
Santhana
f1 (ppm)

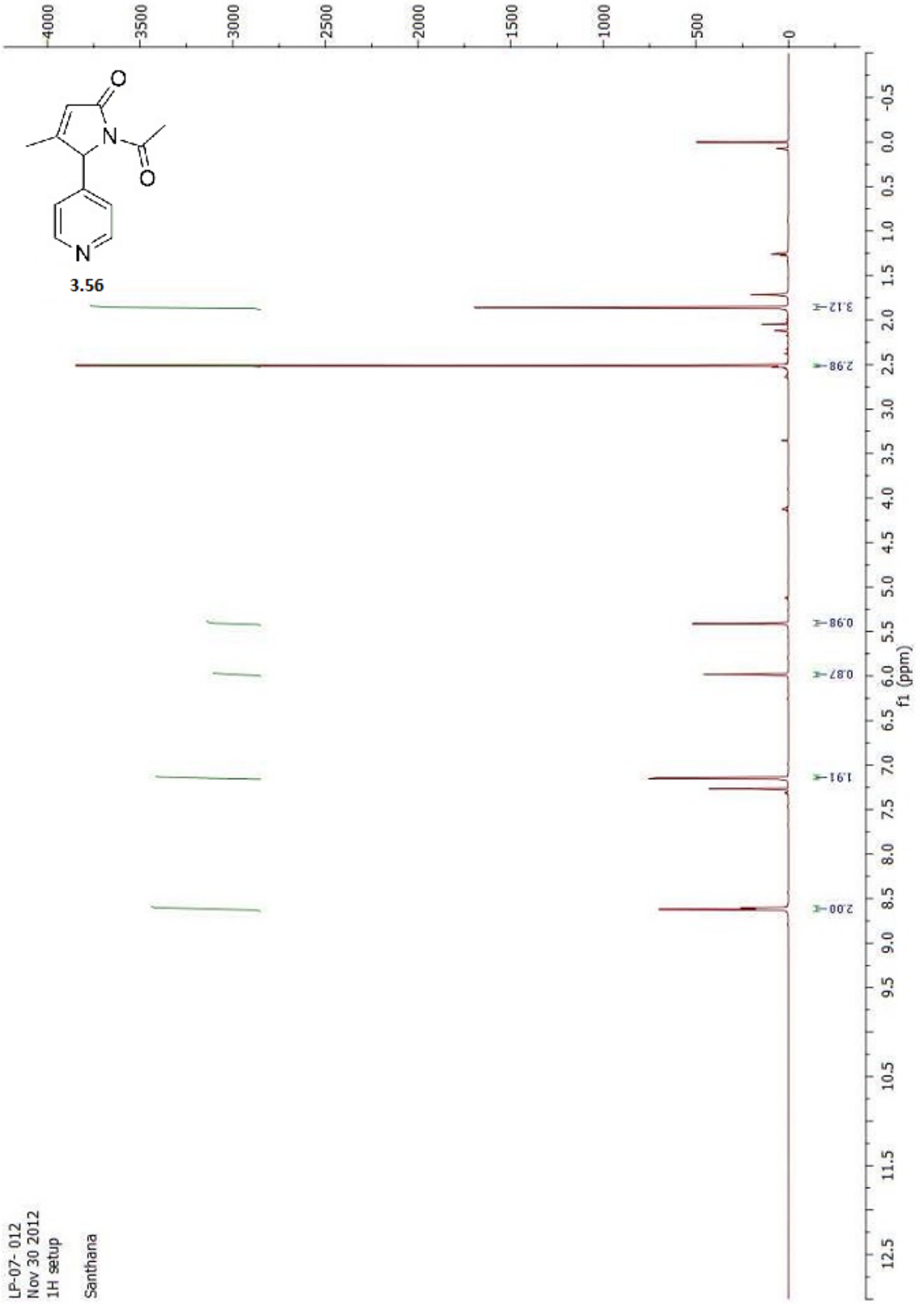

Ph
O
N
N
3.52
3.35
2.17
2.12
1.97
2.05
3.18
2.00
f1 (ppm)
LP-06-246
LP-06-246


Ph
O
N
N
3.52
4.30
4.37
45.84
47.12
50.62
52.29
73.21
90.55
90.80
122.43
123.06
127.90
128.09
128.40
128.63
129.00
129.18
135.86
136.02
145.63
145.79
150.31
150.51
155.46
LP-06-246
LP-06-246
f1 (ppm)


3.53
LP-06-227 crude anhydrobase in deuterited acetone
LP-06-227 crude anhydrobase in deuterited acetone
f1 (ppm)


3.54
LP-06-296 spot 1
LP-06-296 spot 1
f1 (ppm)


3.54
4.47
27.69
47.95
74.55
94.76
122.04
146.33
150.25
172.69
LP-06-296 spot 1
LP-06-296 spot 1
f1 (ppm)


3.56
3.12
2.98
0.98
0.87
1.91
2.00
f1 (ppm)
LP-07- 012
Nov 30 2012
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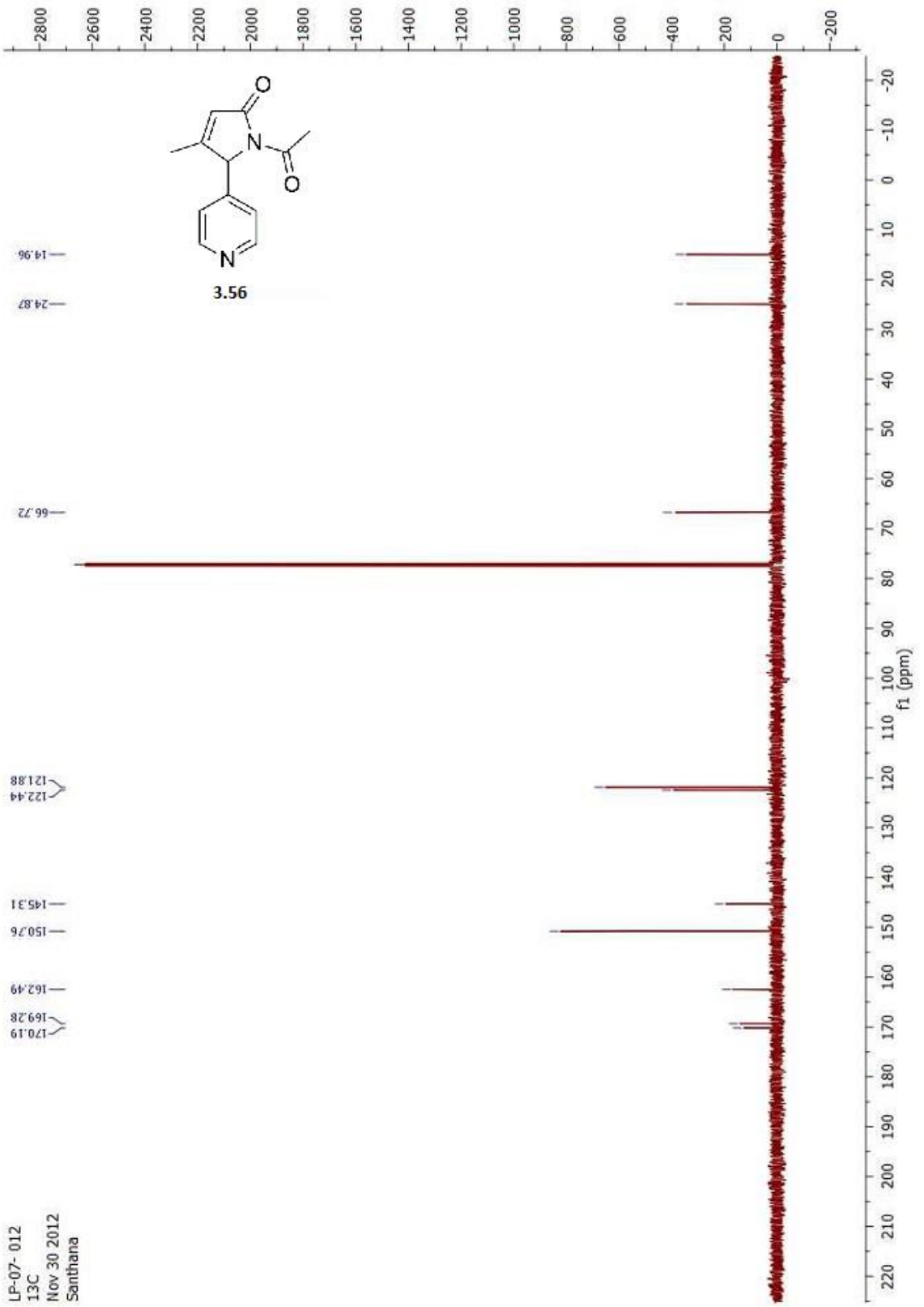
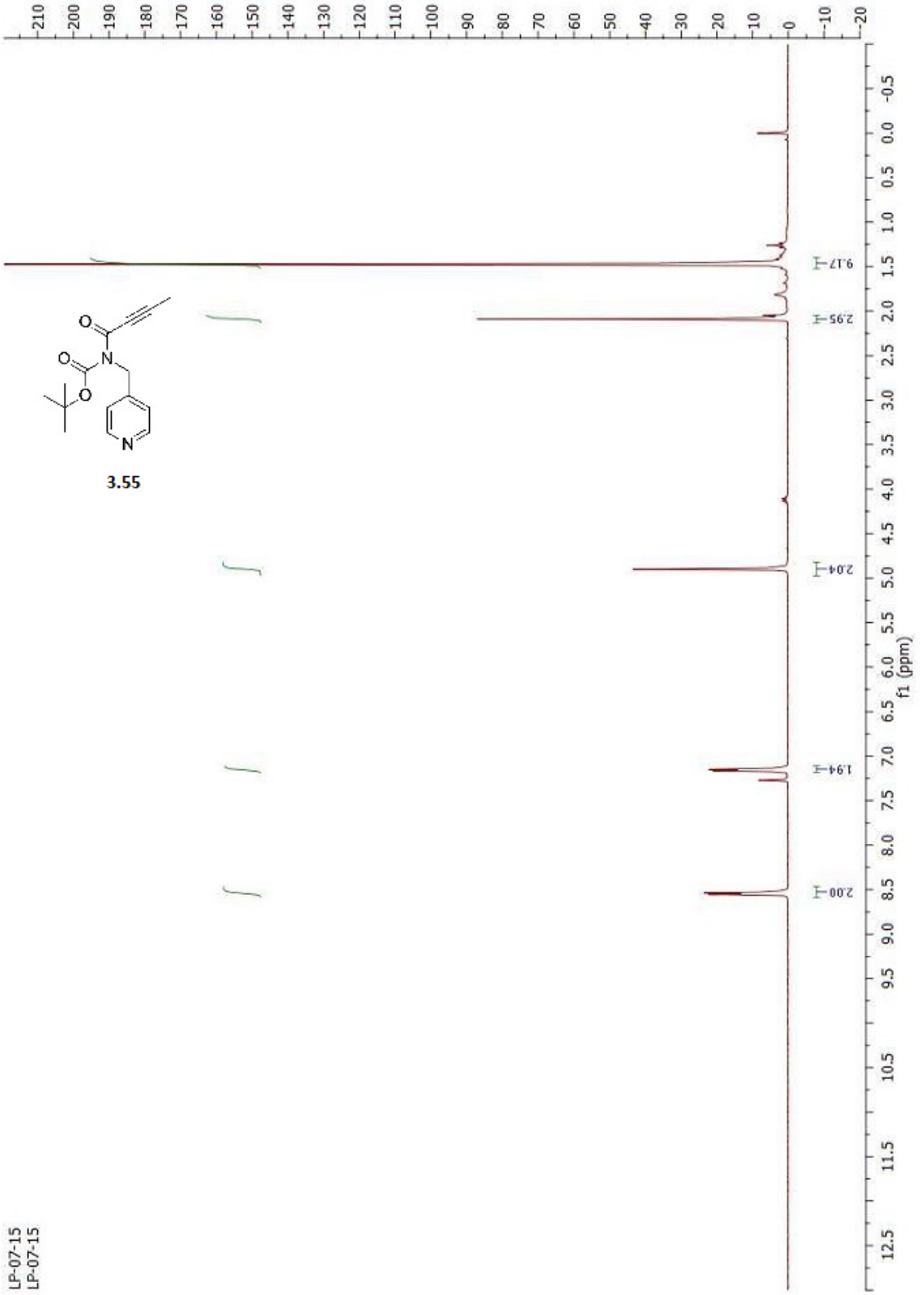
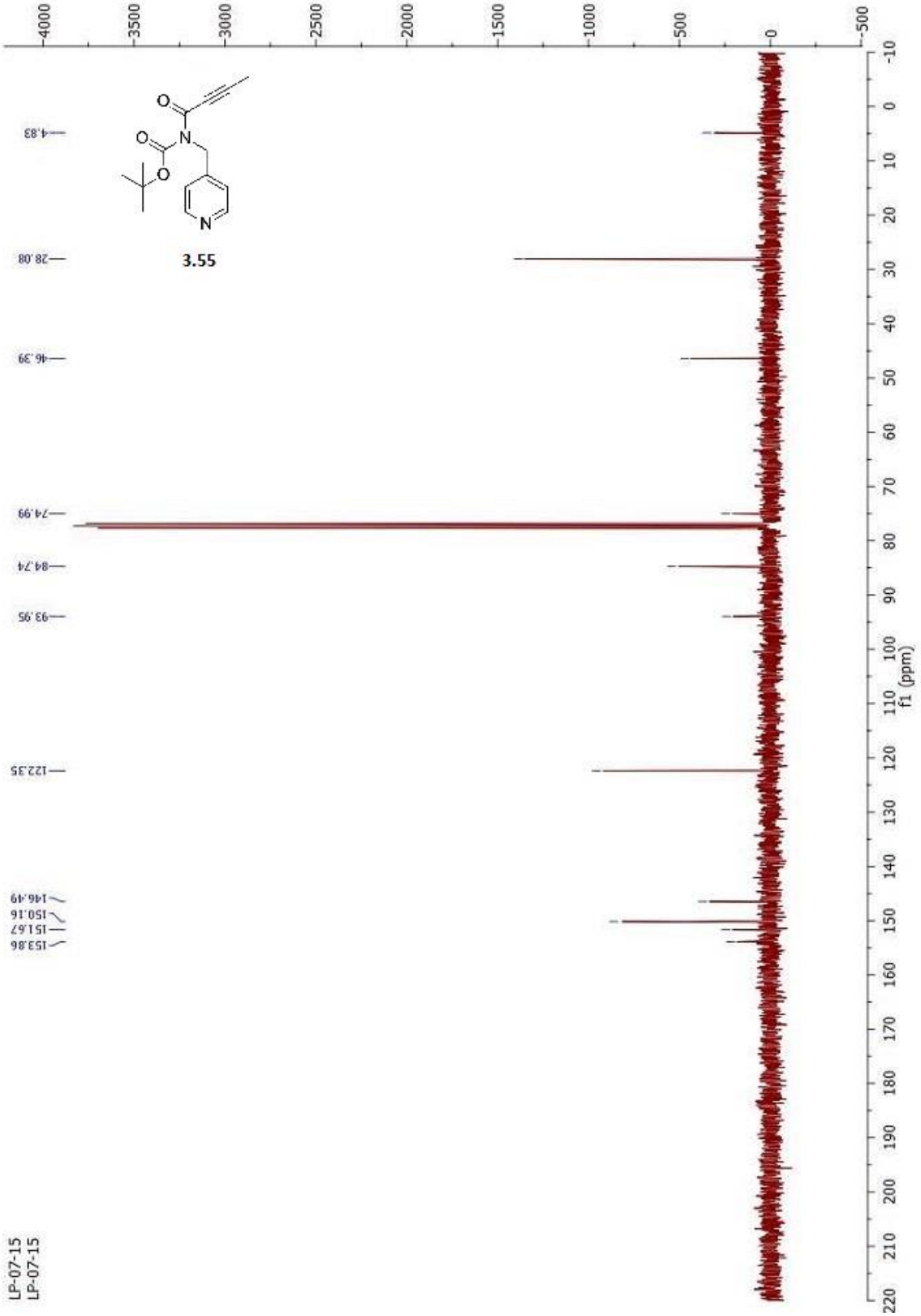
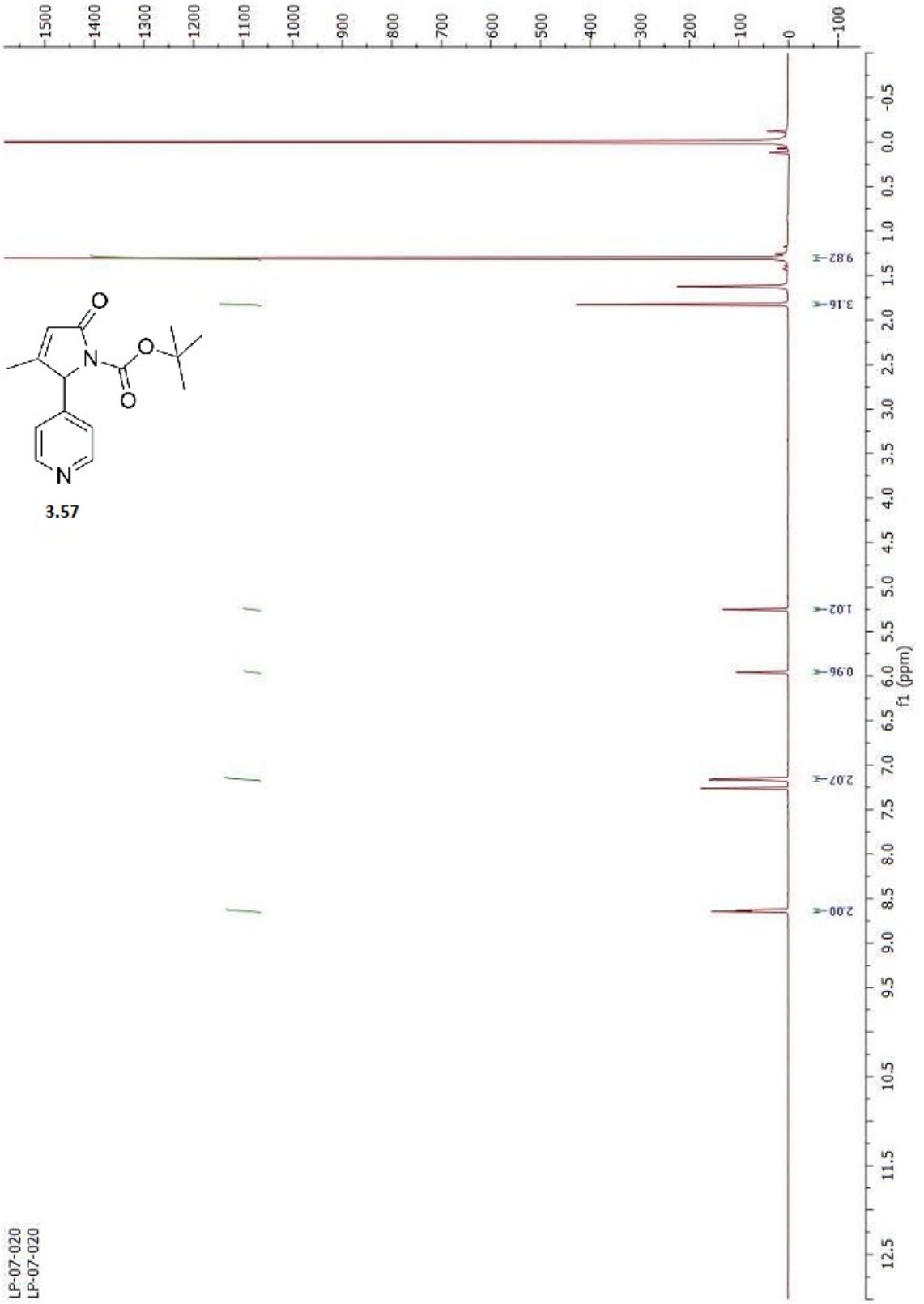
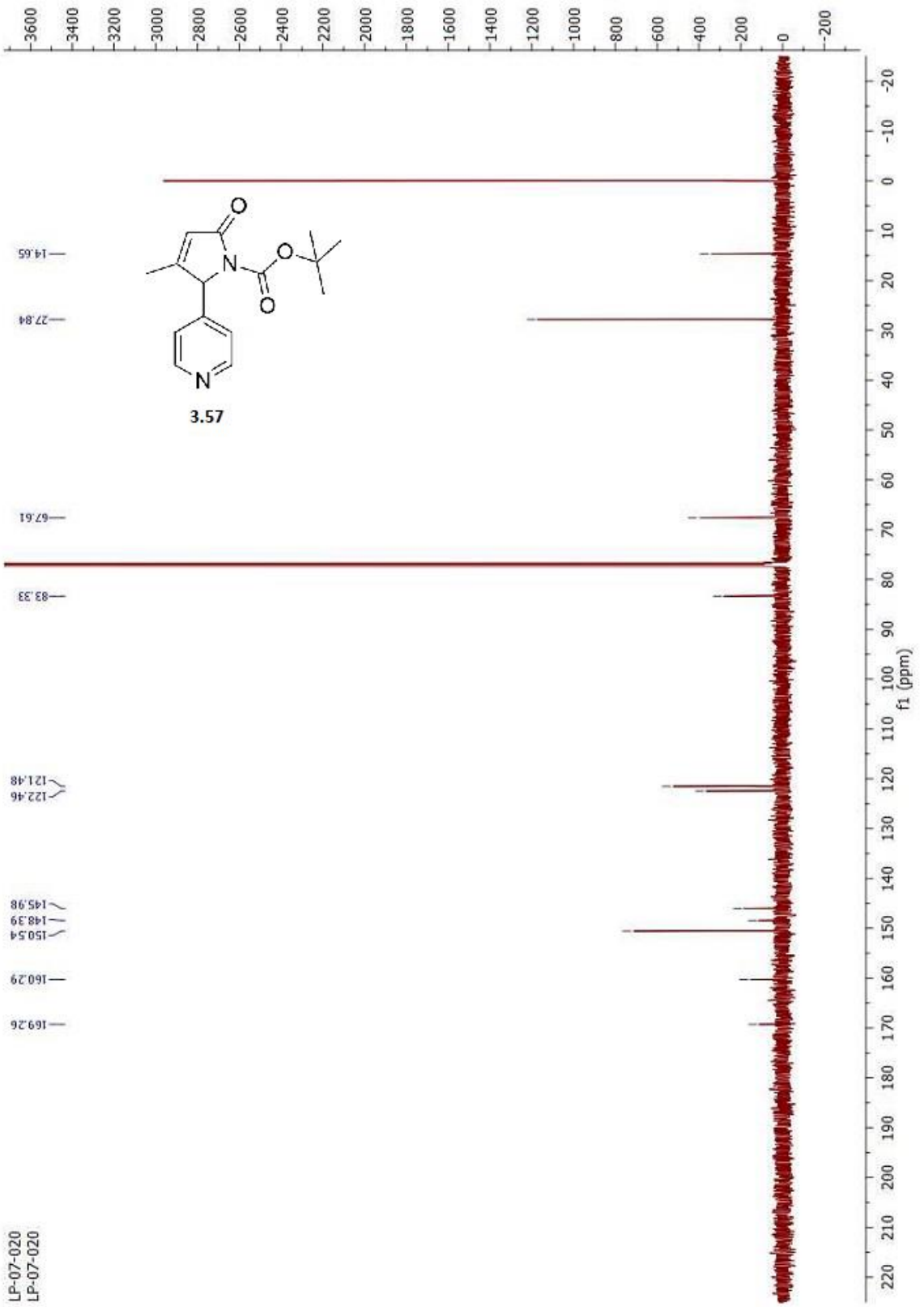
Santhana


3.56
14.96
24.87
66.72
121.88
122.44
145.31
150.76
162.49
169.28
170.19
f1 (ppm)
LP-07- 012
13C
Nov 30 2012
Santhana

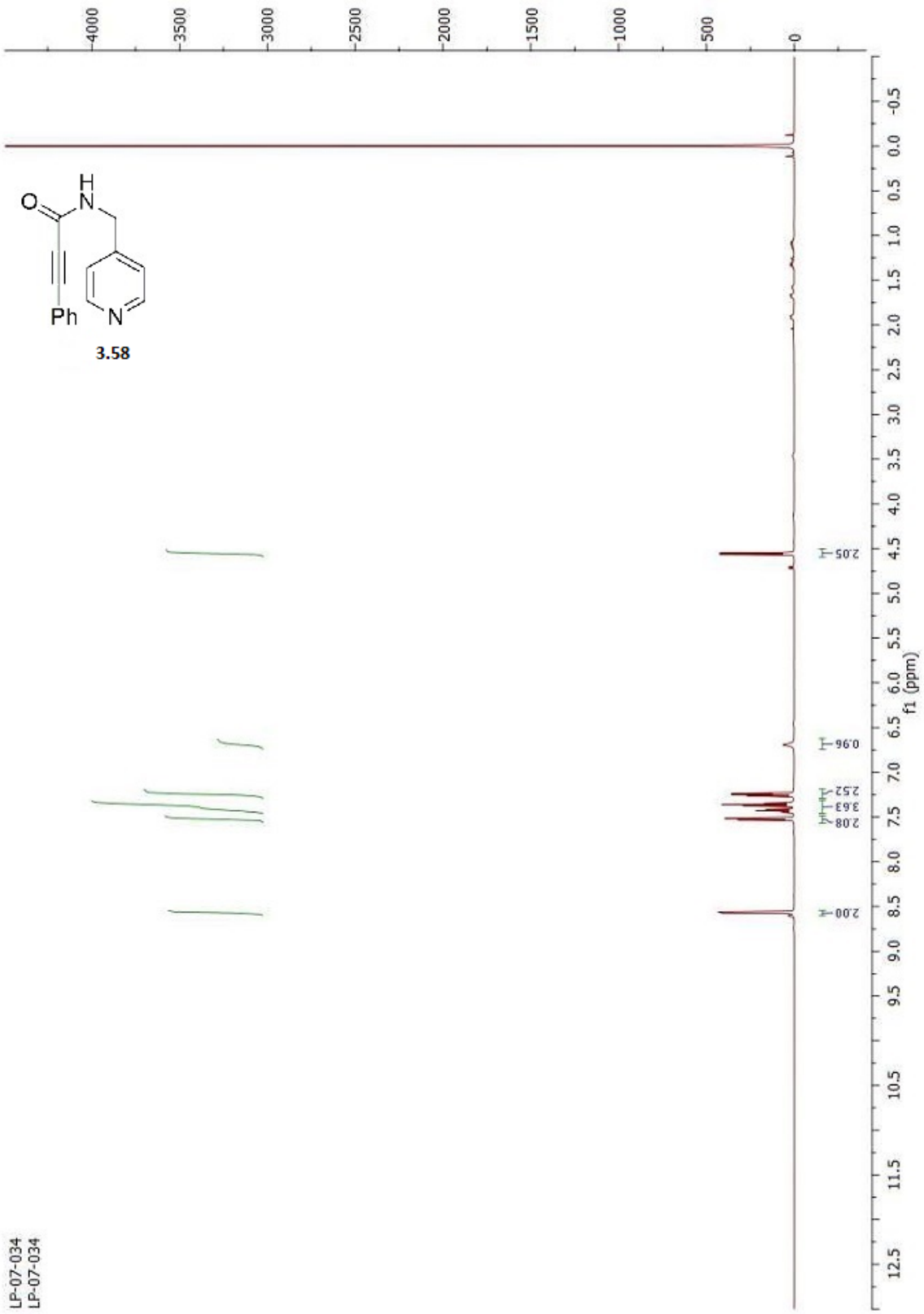

3.55
9.17
2.95
2.04
1.94
2.00
f1 (ppm)
LP-07-15
LP-07-15

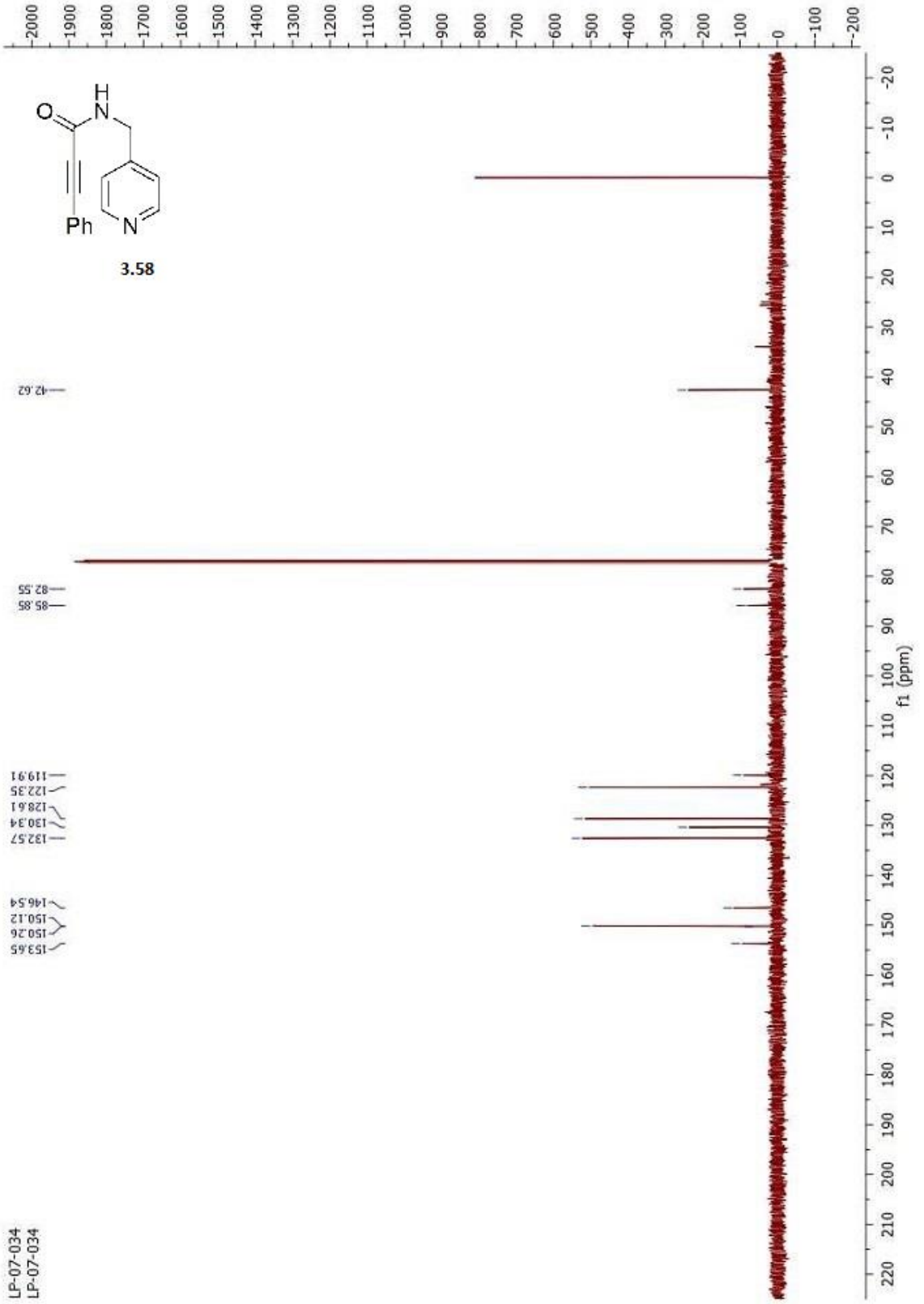

3.55
LP-07-15
LP-07-15
f1 (ppm)

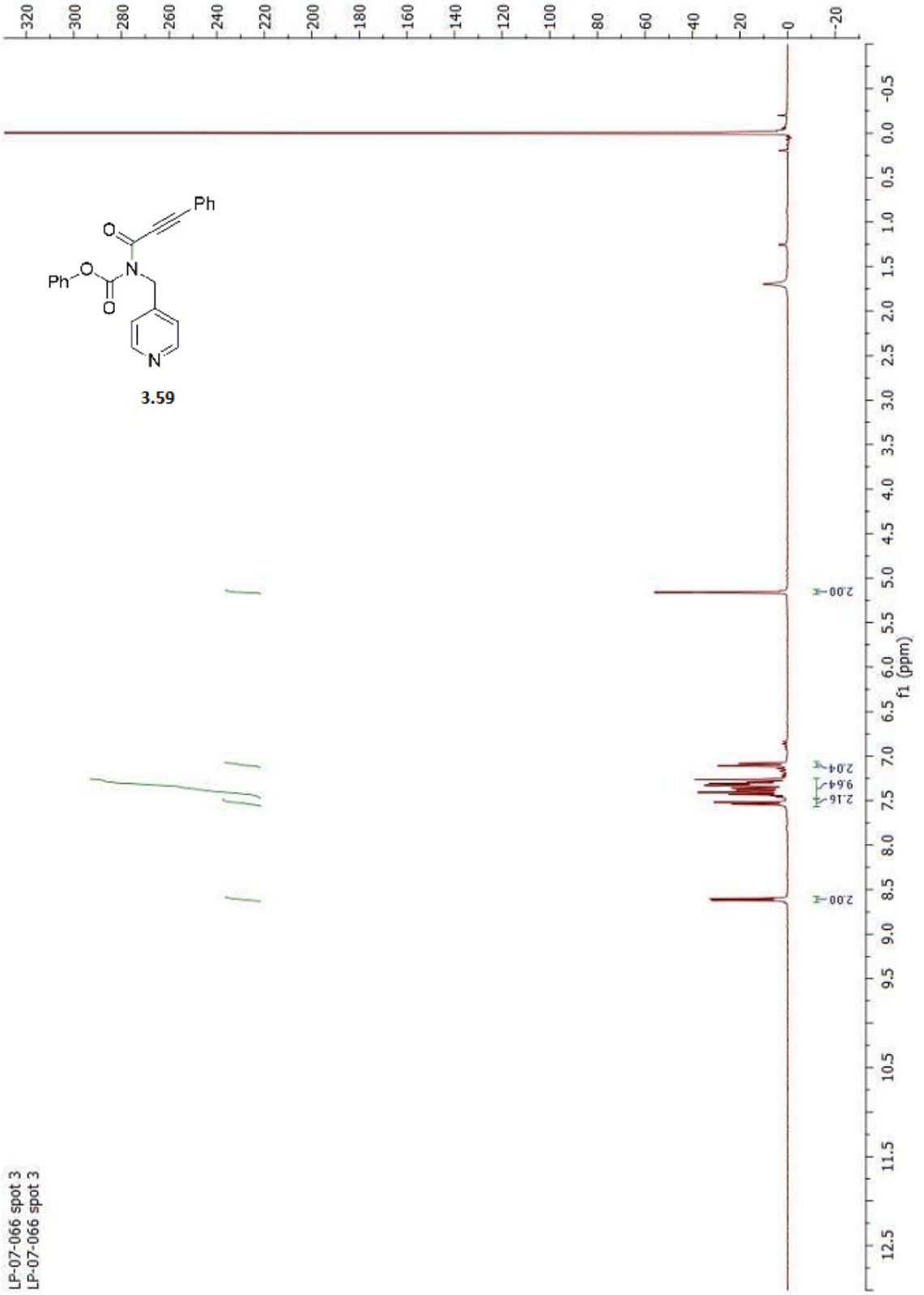

3.57
9.82
3.16
1.02
0.96
2.07
2.00
f1 (ppm)
LP-07-020
LP-07-020

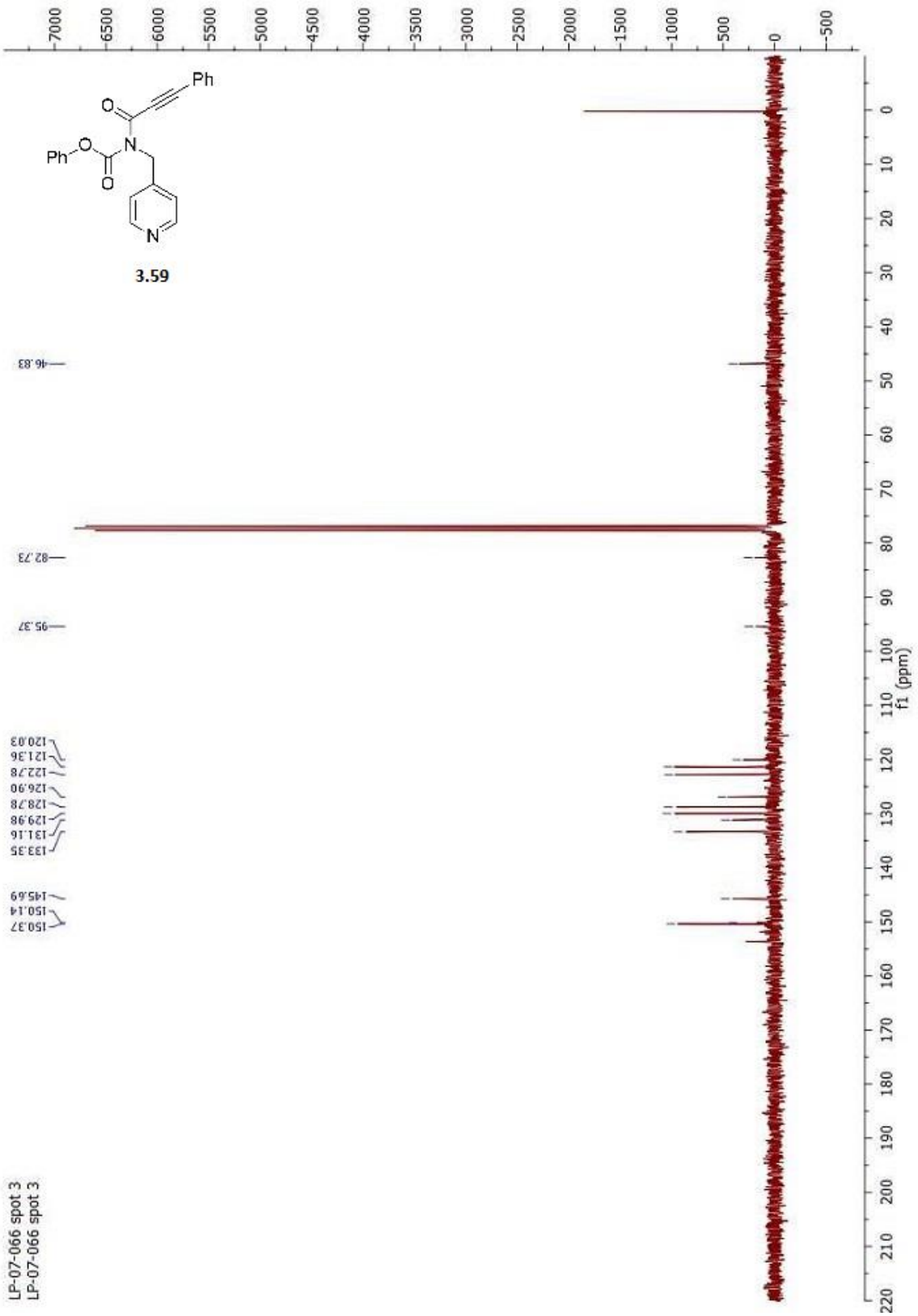

14.65
27.84
67.61
83.33
121.48
122.46
145.98
148.39
150.54
160.29
169.26
LP-07-020
LP-07-020
f1 (ppm)

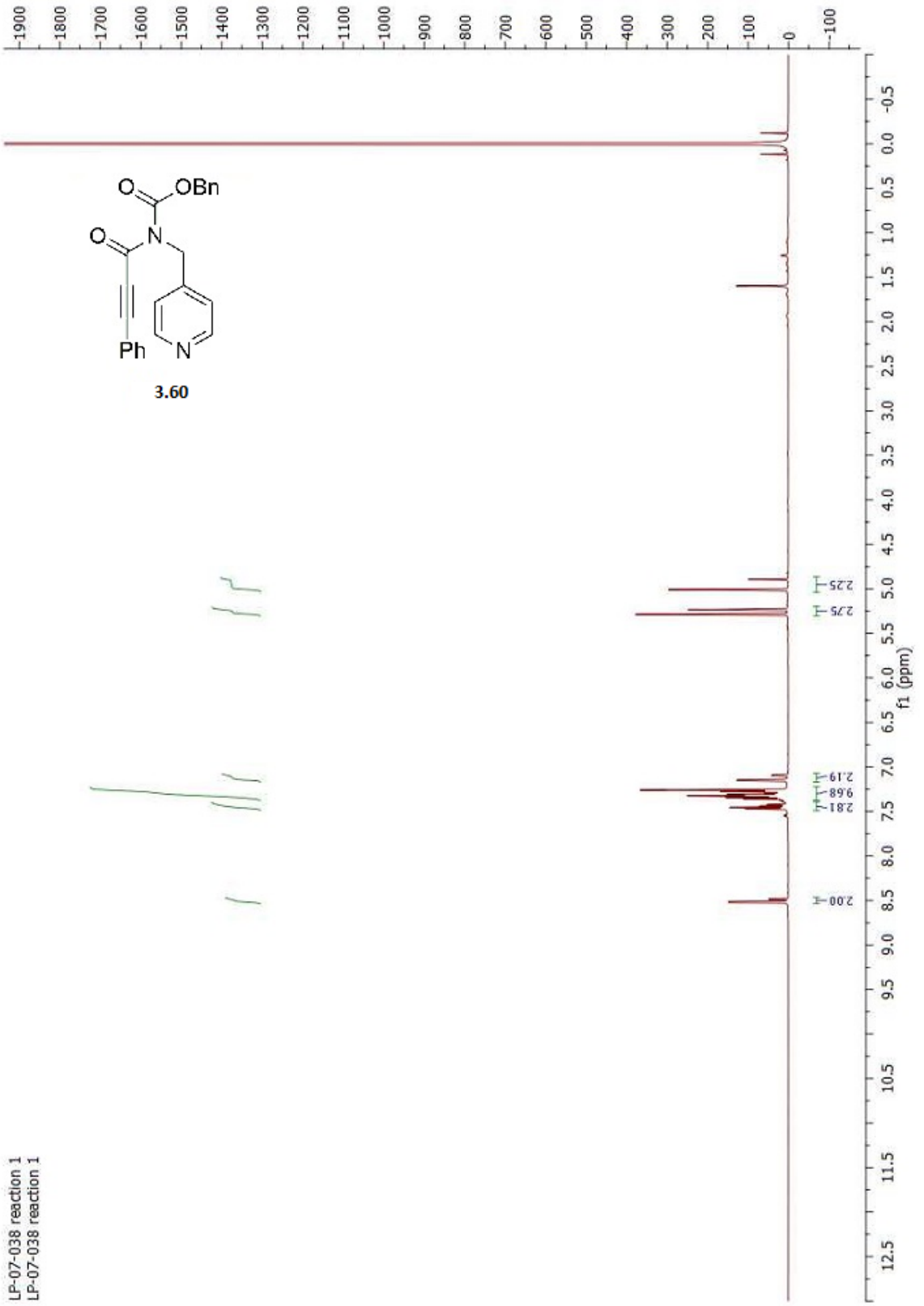
3.57

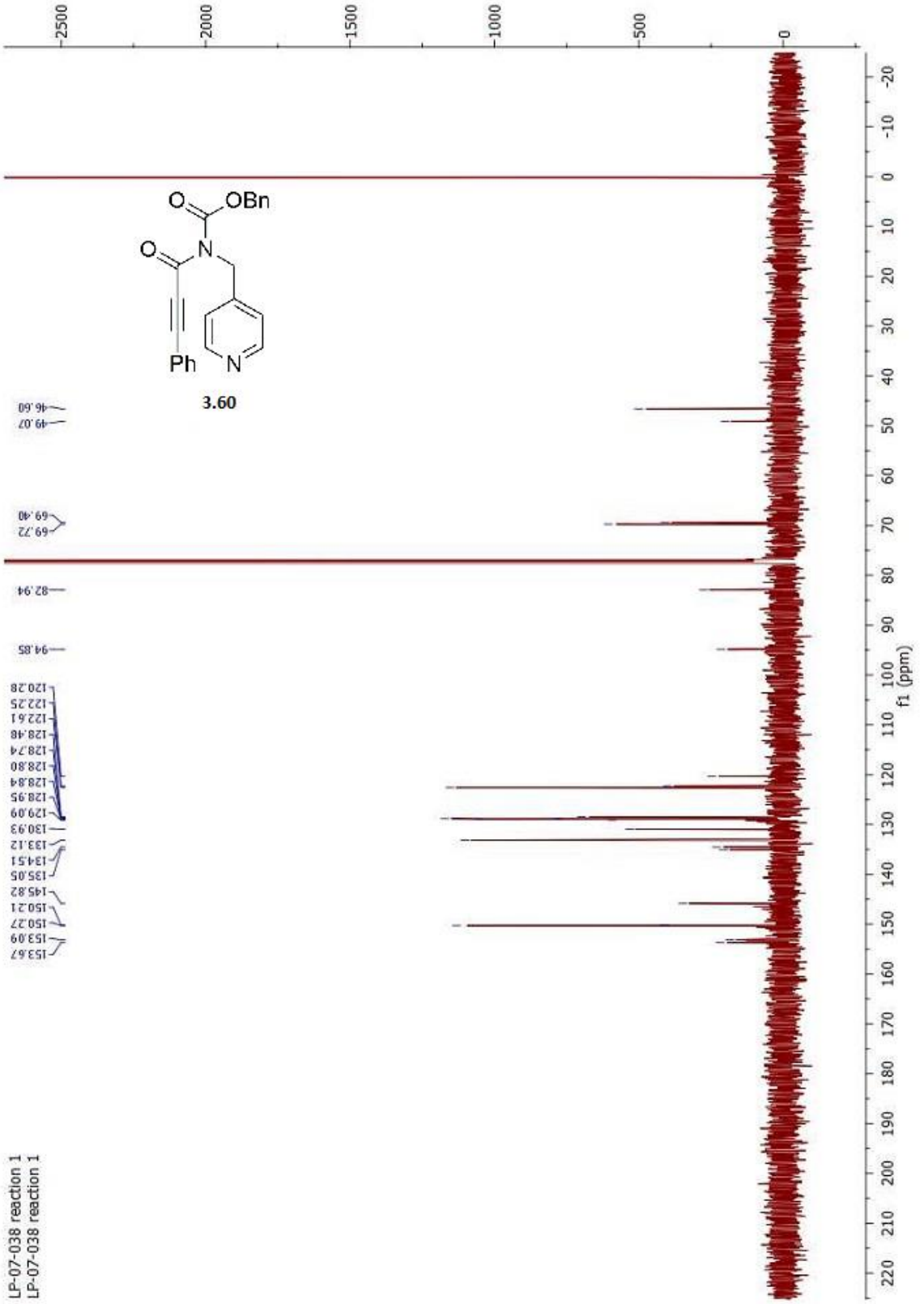

O
H
N
Ph
N
3.58
LP-07-034
LP-07-034
f1 (ppm)

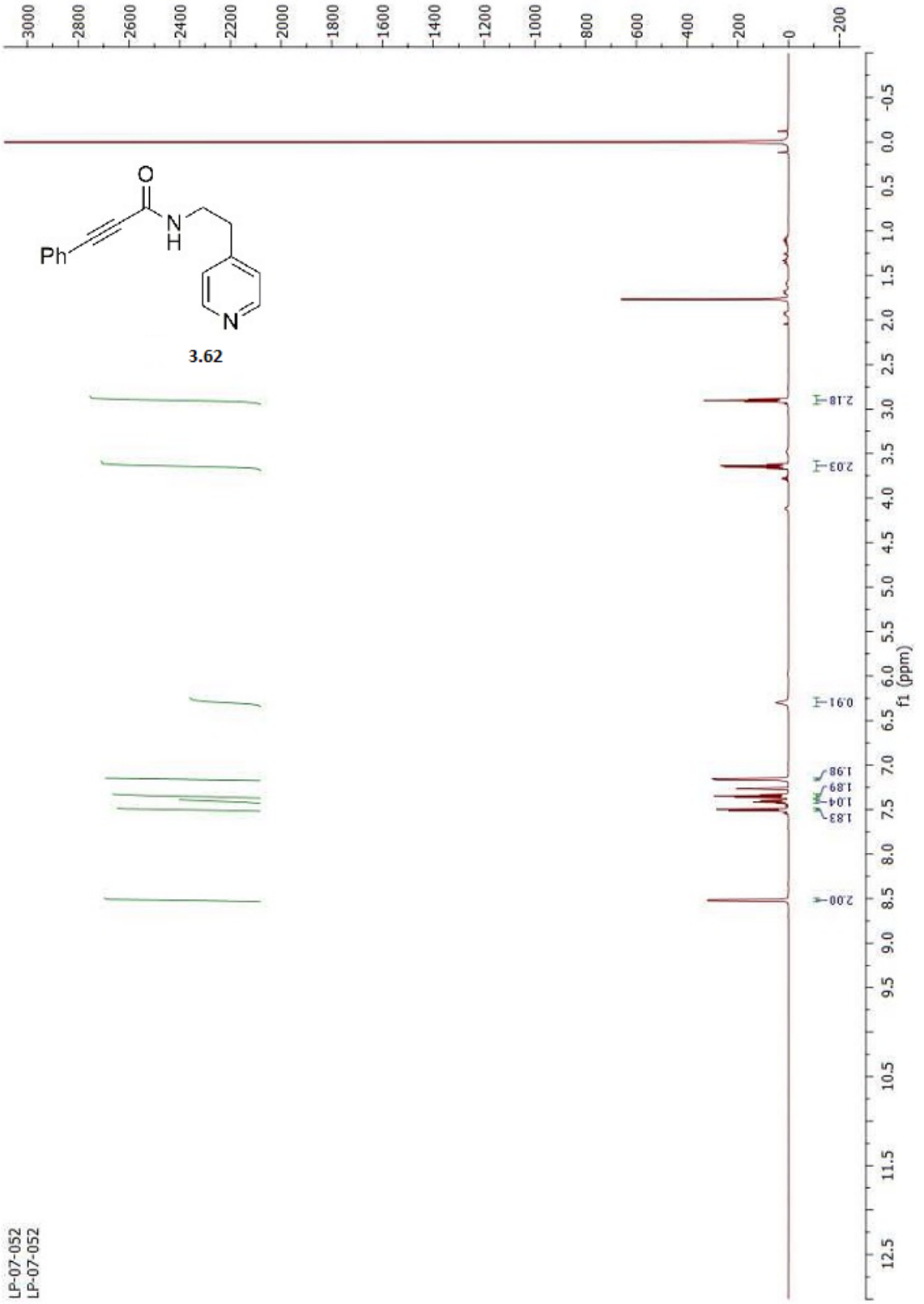

3.58
42.62
82.55
85.85
119.91
122.35
128.61
130.34
132.57
146.54
150.12
150.26
153.65
LP-07-034
LP-07-034
f1 (ppm)

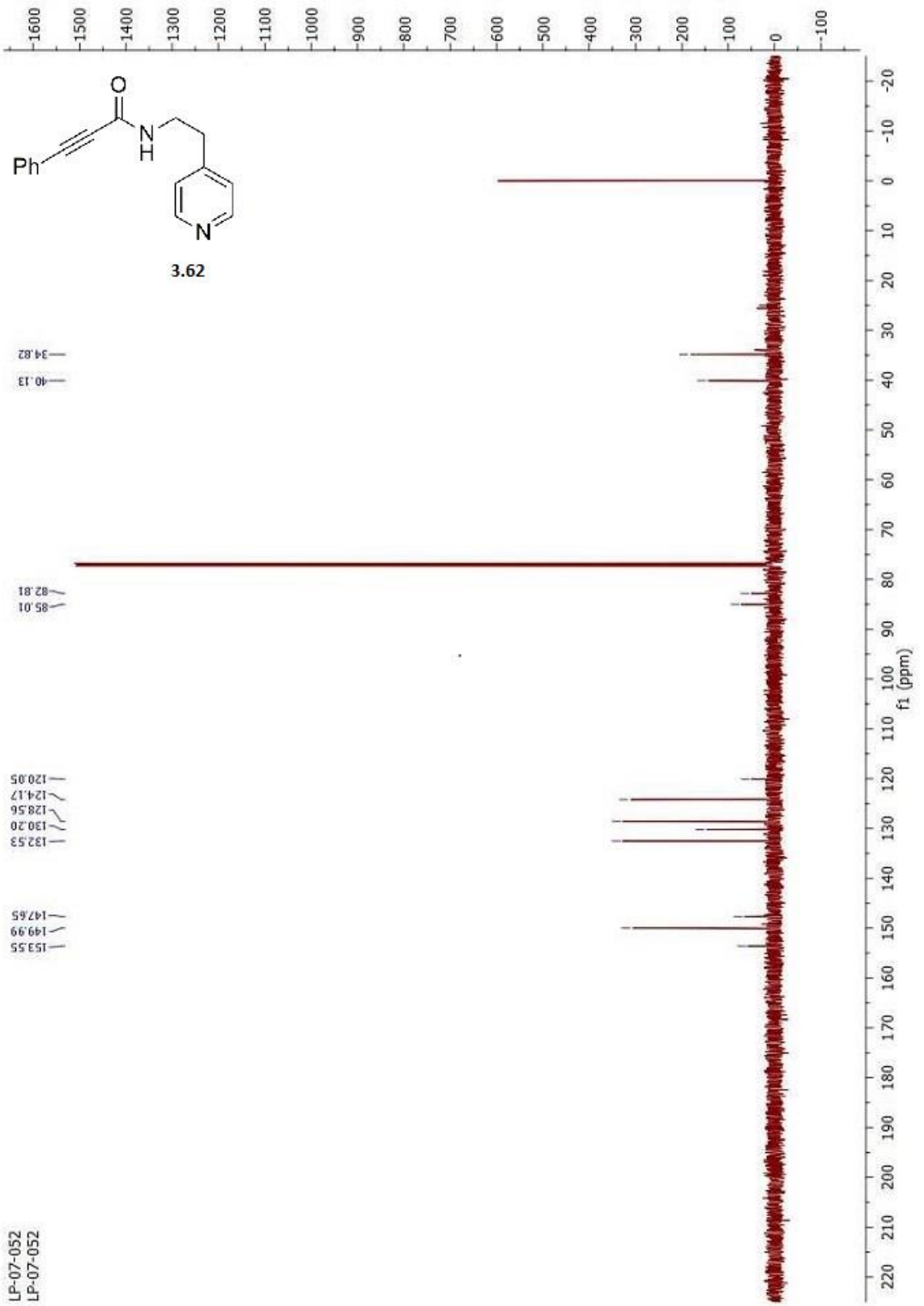

Ph
O
N
Ph
O
O
N
3.59
LP-07-066 spot 3
LP-07-066 spot 3
f1 (ppm)
2.00
9.64
2.16
2.04
2.00

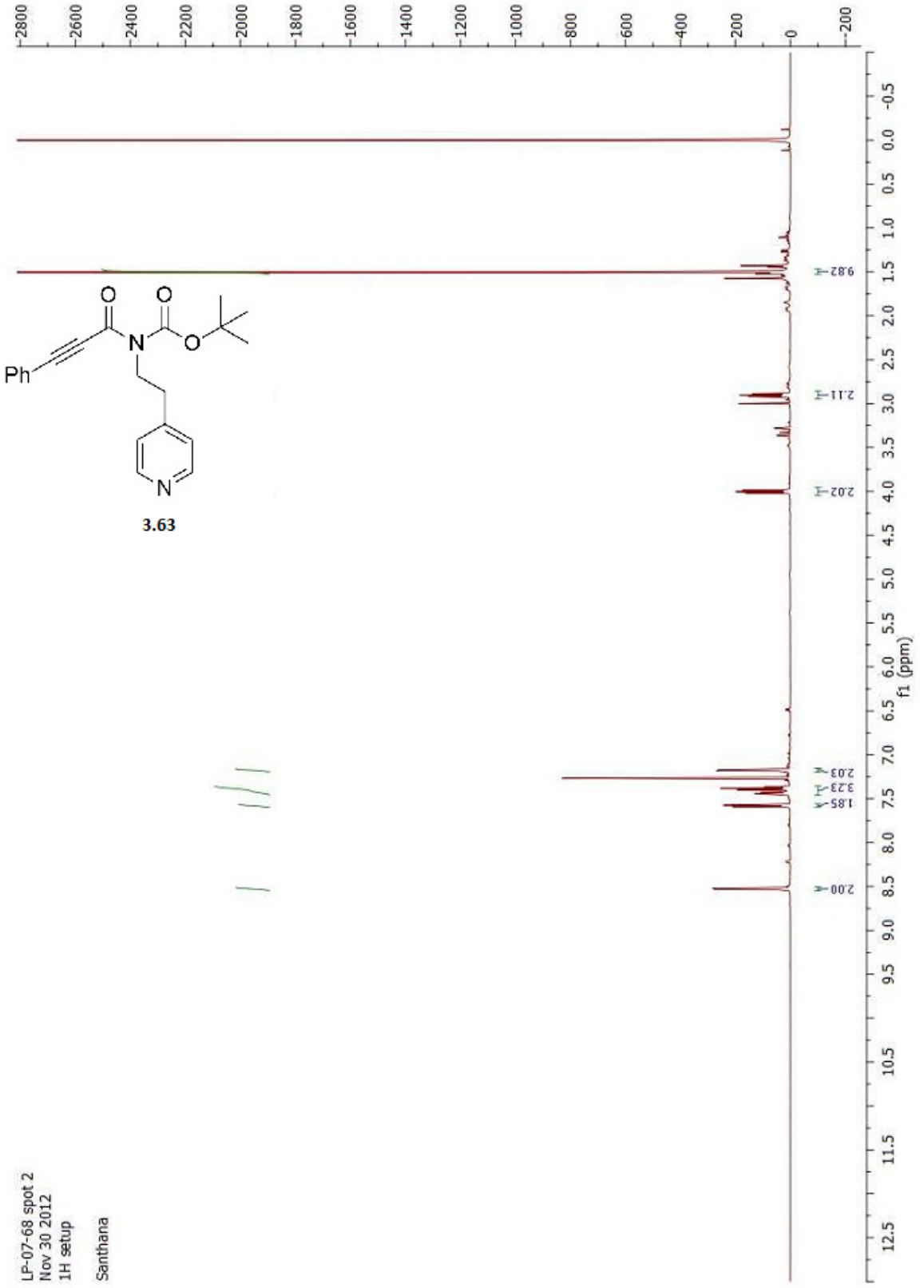

Ph
O
N
Ph
O
O
N
3.59
46.83
82.73
95.37
120.03
121.36
122.78
126.90
128.78
129.98
131.16
133.35
145.69
150.14
150.37
f1 (ppm)
LP-07-066 spot 3
LP-07-066 spot 3


OBn
O
N
Ph
N
3.60
LP-07-038 reaction 1
LP-07-038 reaction 1
f1 (ppm)
2.25
2.75
2.19
9.68
2.81
2.00


O
OBn
N
O
Ph
N
3.60
f1 (ppm)
LP-07-038 reaction 1
LP-07-038 reaction 1


Ph
O
N
H
N
3.62
LP-07-052
LP-07-052
f1 (ppm)


O
N
H
Ph
N
3.62
34.82
40.13
82.81
85.01
120.05
124.17
128.56
130.20
132.53
147.65
149.99
153.55
f1 (ppm)
LP-07-052
LP-07-052


Ph
O
O
N
O
N
3.63
LP-07-68 spot 2
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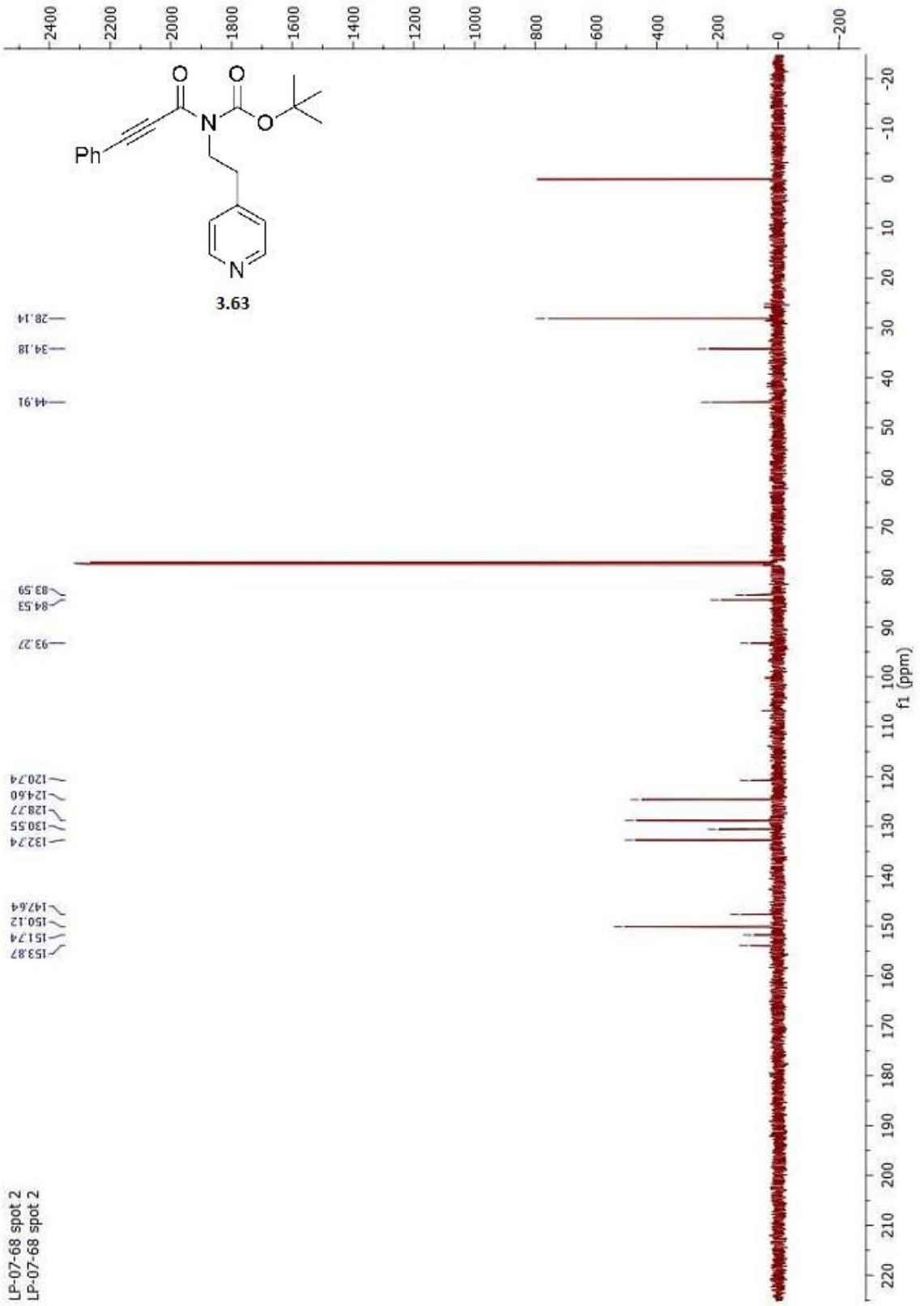
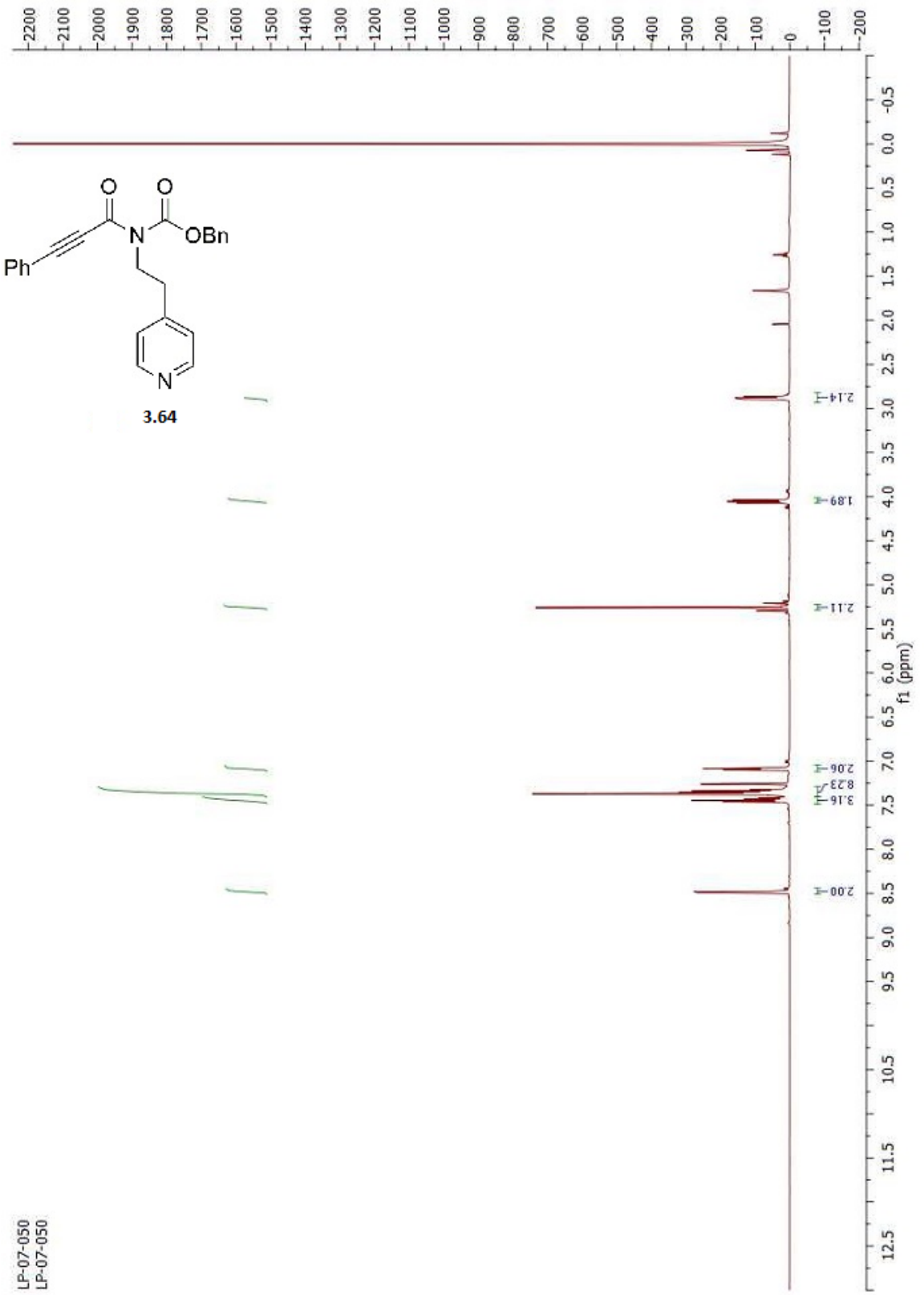
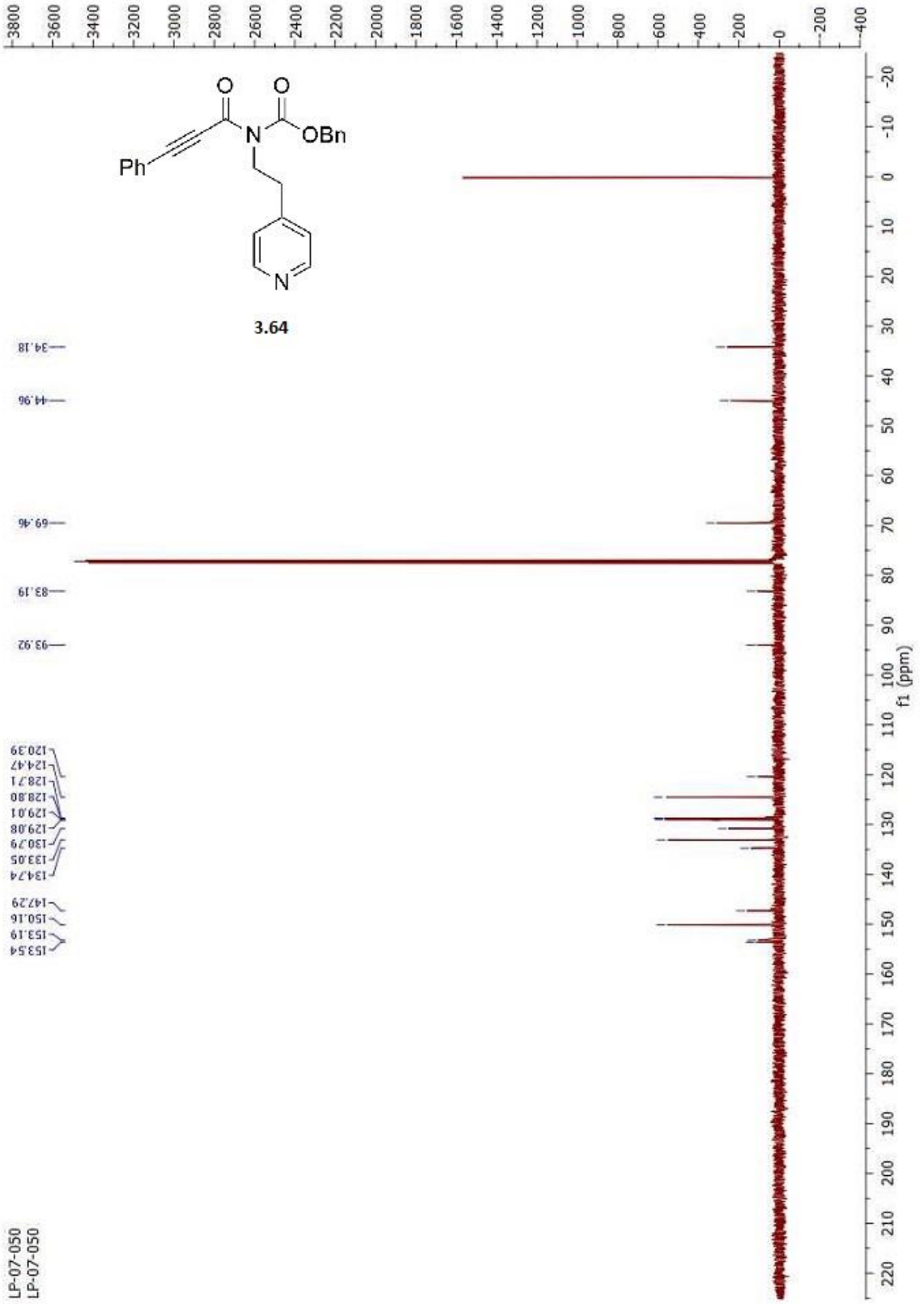
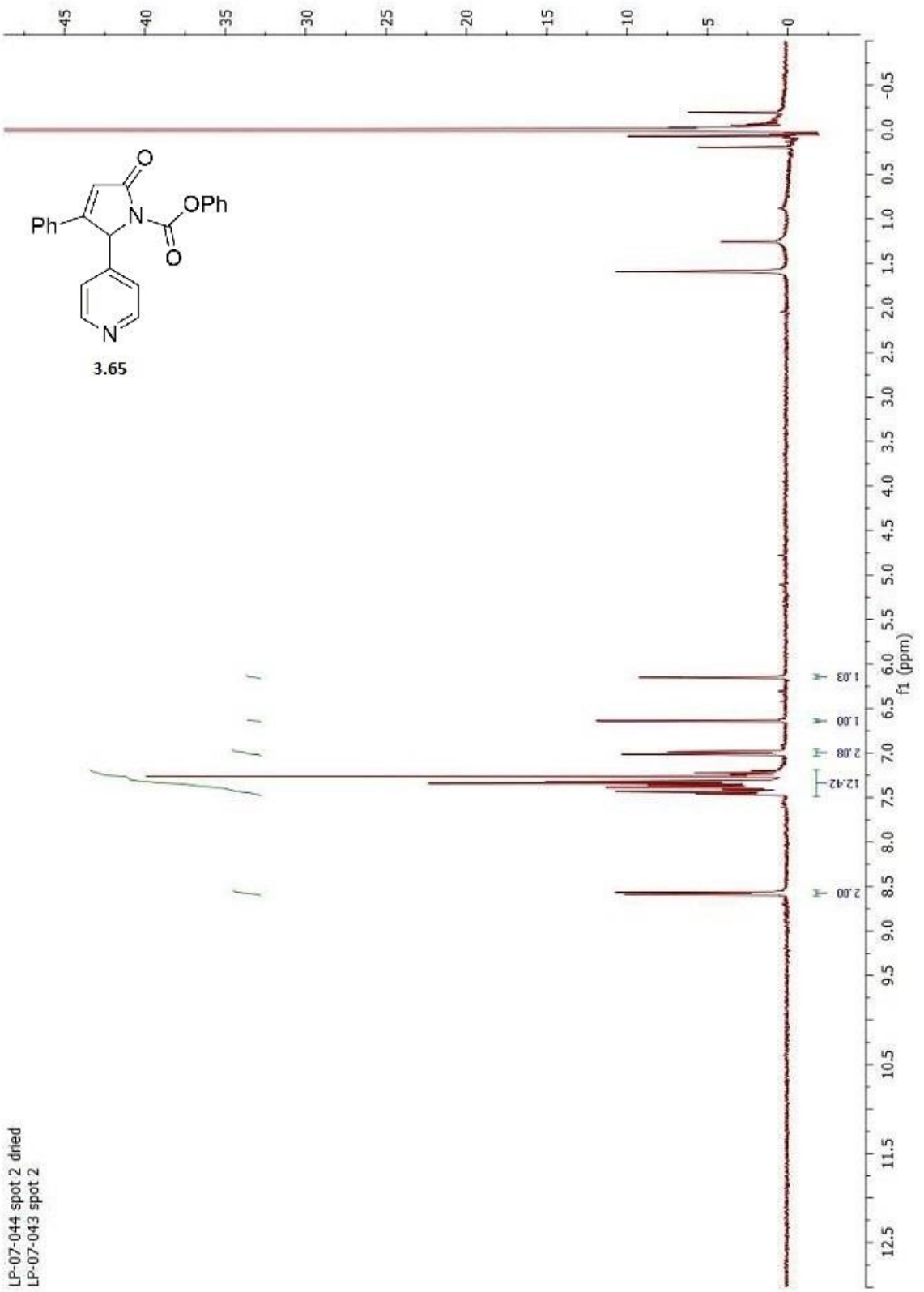
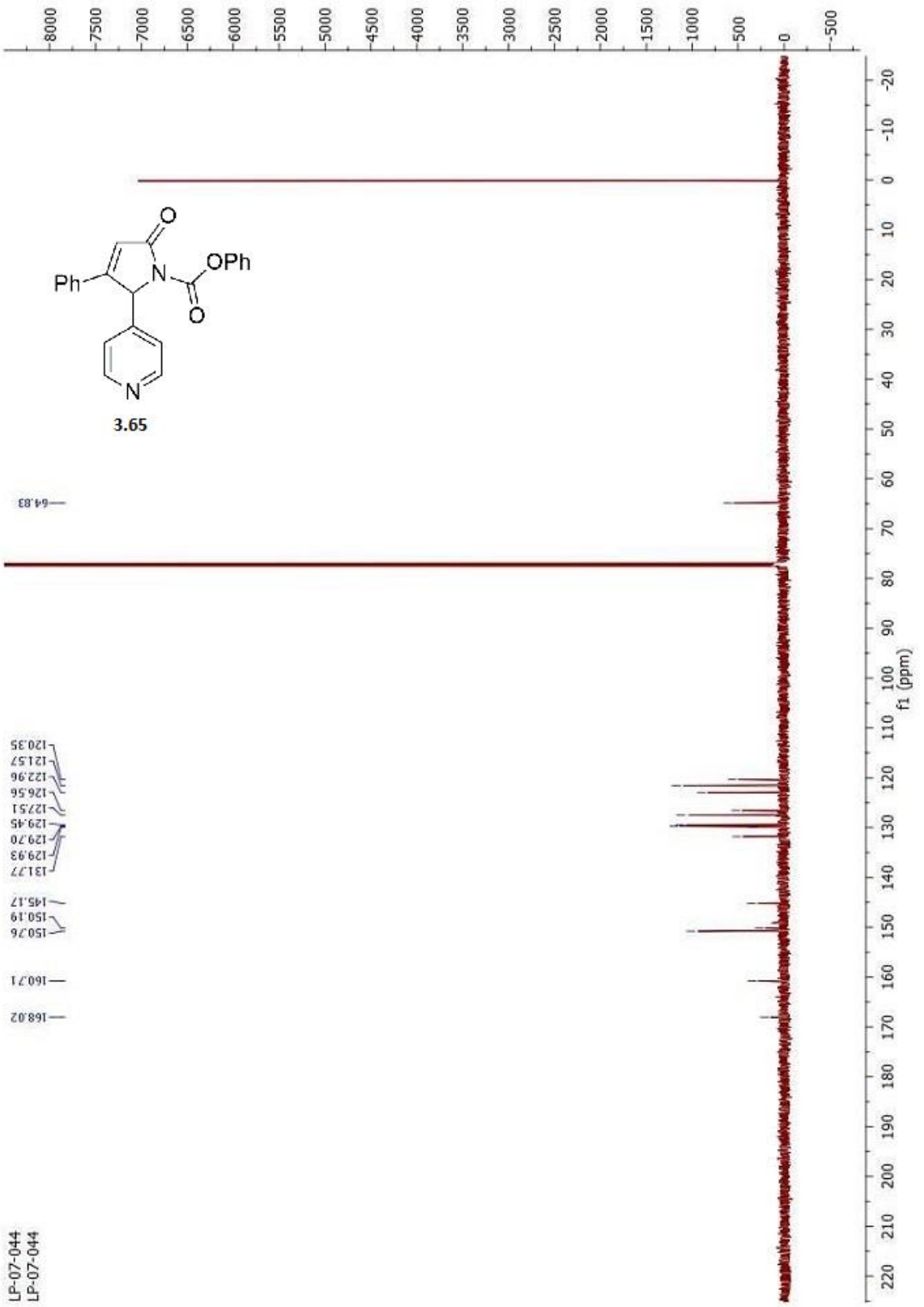
f1 (ppm)

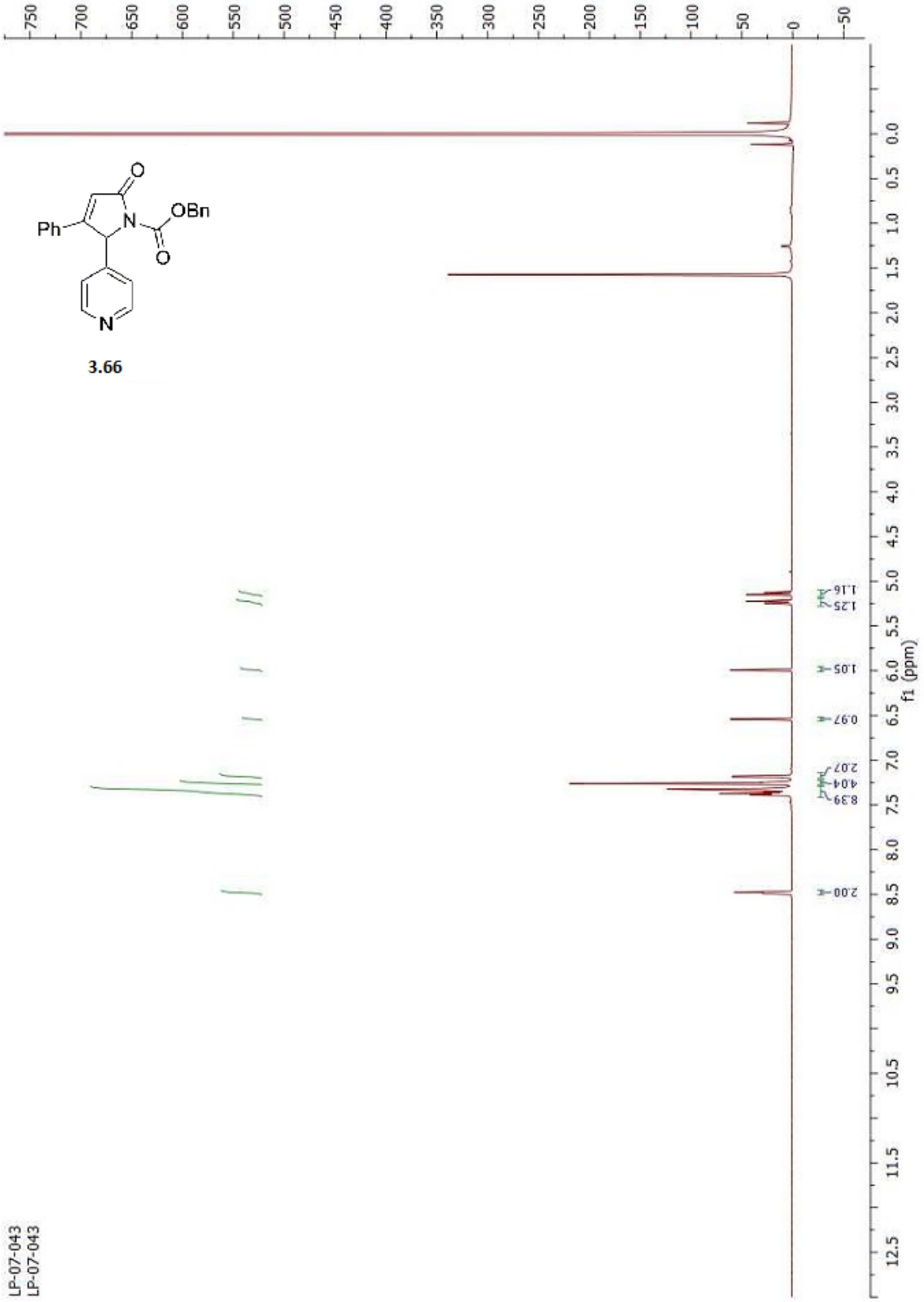

Ph
O
O
N
O
N
3.63
28.14
34.18
44.91
83.59
84.53
93.27
120.74
124.60
128.77
130.55
132.74
147.64
150.12
151.74
153.87
LP-07-68 spot 2
LP-07-68 spot 2
f1 (ppm)

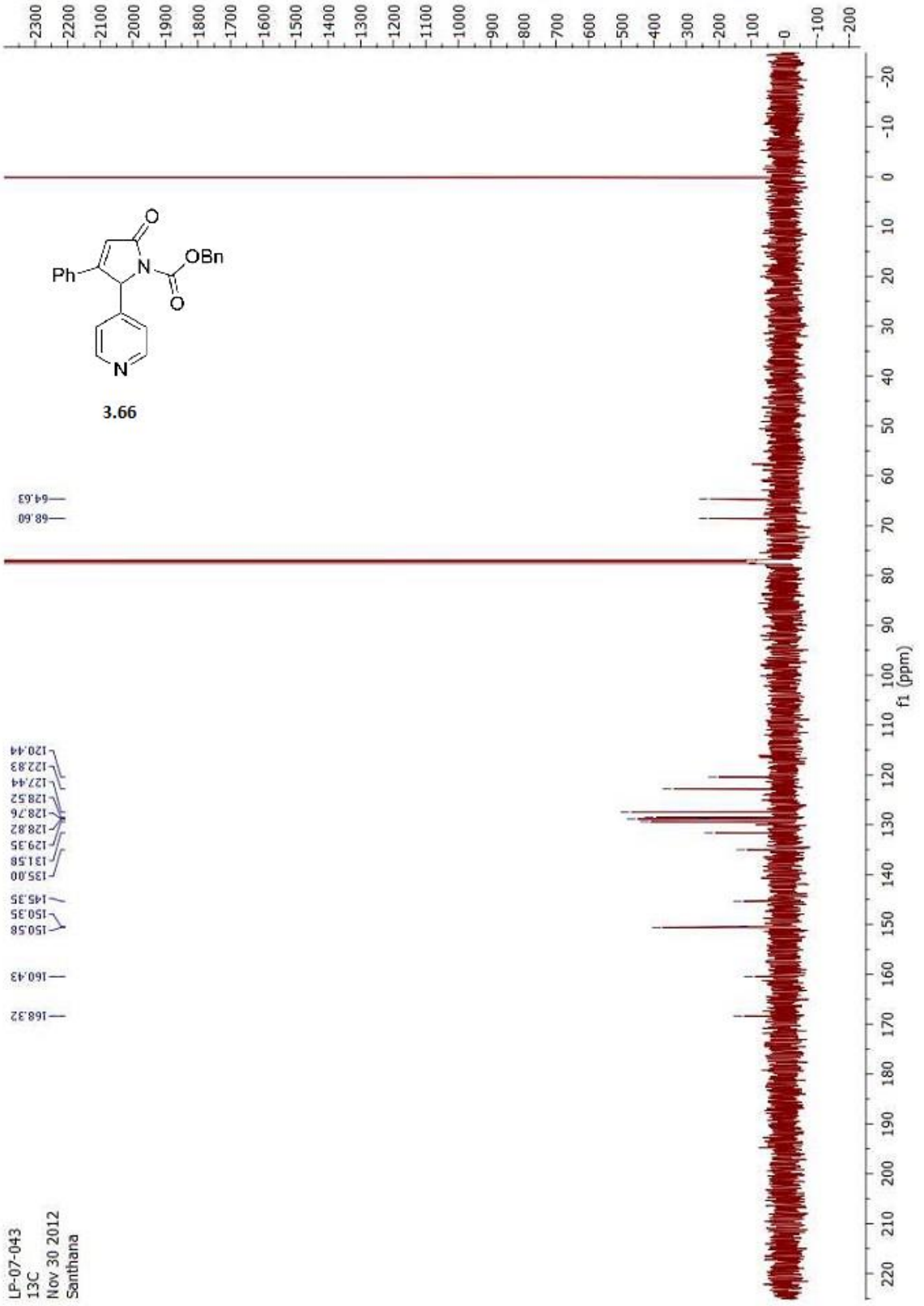

Ph
O
O
N
OBn
N
3.64
2.14
1.89
2.11
2.06
8.23
3.16
2.00
f1 (ppm)
LP-07-050
LP-07-050

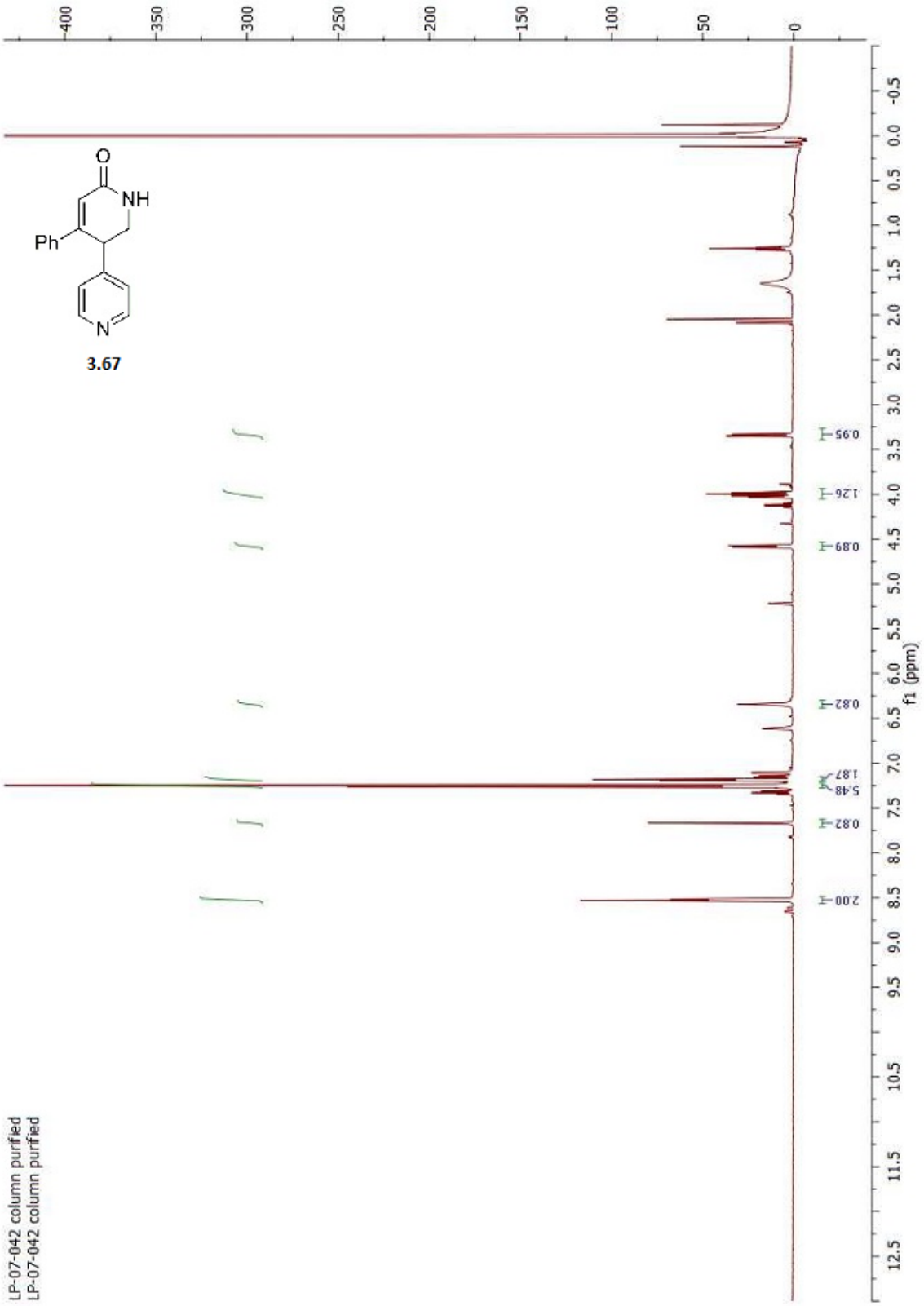

Ph
N
OBn
O
O
N
3.64
34.18
44.96
69.46
83.19
93.92
120.39
124.47
128.71
128.80
129.01
129.08
130.79
133.05
134.74
147.29
150.16
153.19
153.54
f1 (ppm)
LP-07-050
LP-07-050

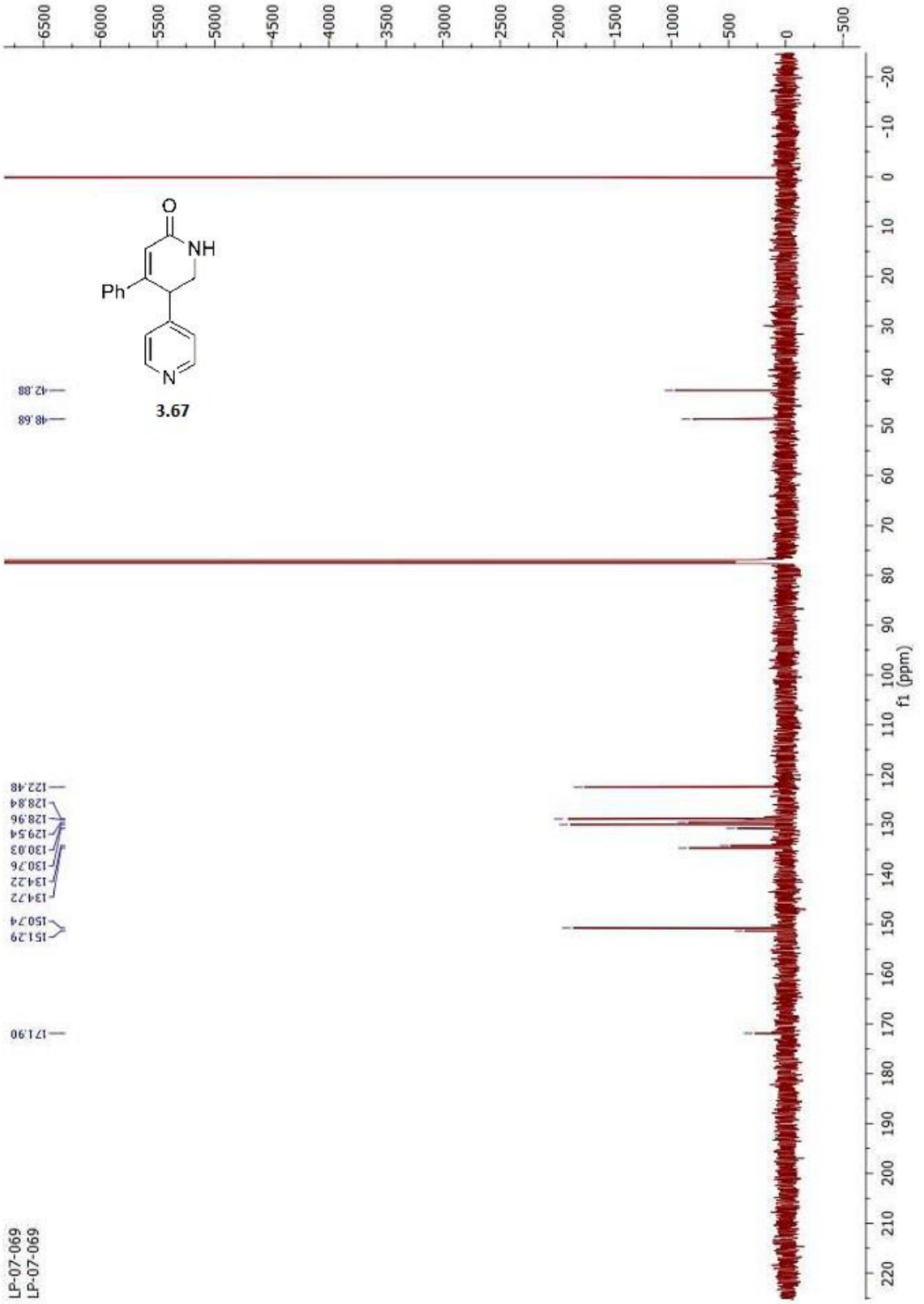

Ph
OPh
O
N
O
N
3.65
LP-07-044 spot 2 dried
LP-07-043 spot 2
f1 (ppm)
1.03
1.00
2.08
12.42
2.00

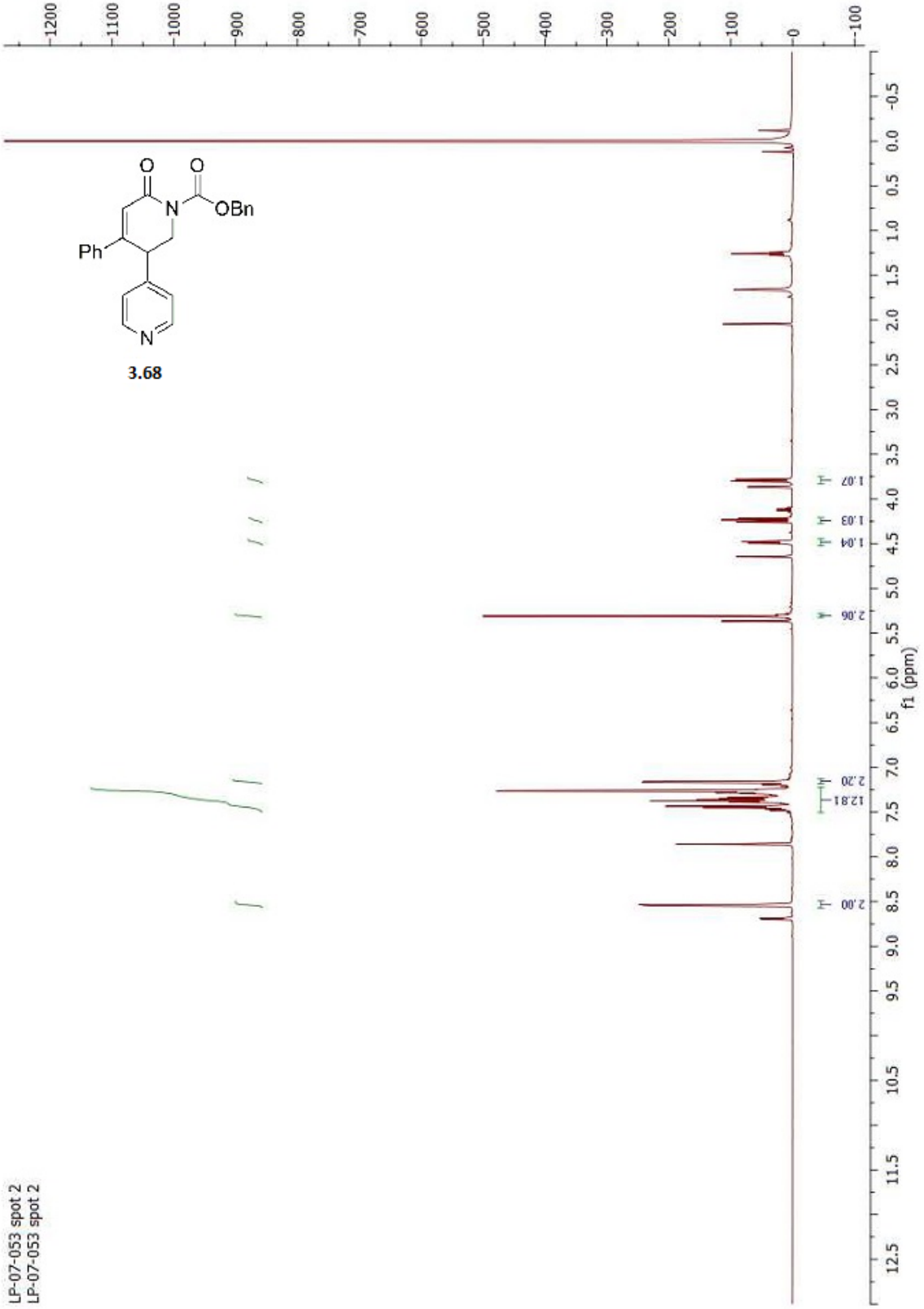

Ph
OPh
O
O
N
N
3.65
64.83
120.35
121.57
122.96
126.56
127.51
129.45
129.70
129.93
131.77
145.17
150.19
150.76
160.71
168.02
LP-07-044
LP-07-044
f1 (ppm)

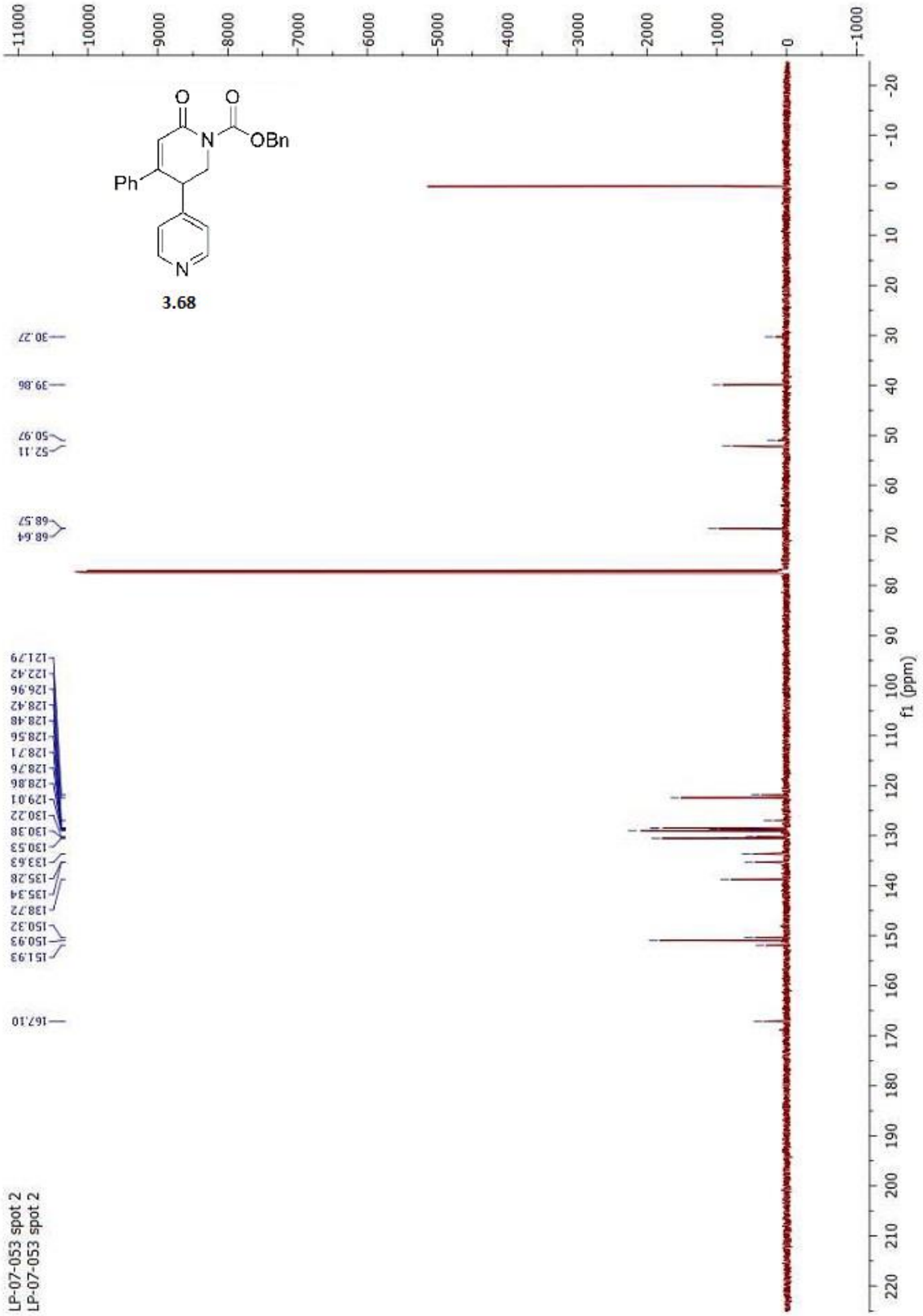

Ph
N
O
OBn
O
N
3.66
f1 (ppm)
LP-07-043
LP-07-043


Ph
OBn
O
N
O
N
3.66
64.63
68.60
120.44
122.83
127.44
128.52
128.76
128.82
129.35
131.58
135.00
145.35
150.35
150.58
160.43
168.32
LP-07-043
13C
Nov 30 2012
Santhana
f1 (ppm)


O
NH
Ph
N
3.67
LP-07-042 column purified
LP-07-042 column purified
f1 (ppm)
0.95
1.26
0.89
0.82
1.87
5.48
0.82
2.00


O
NH
Ph
N
3.67
42.88
48.68
122.48
128.84
128.96
129.54
130.03
130.76
134.22
134.72
150.74
151.29
171.90
LP-07-069
LP-07-069
f1 (ppm)


O
O
N
OBn
Ph
N
3.68
1.07
1.03
1.04
2.06
2.20
12.81
2.00
f1 (ppm)
LP-07-053 spot 2
LP-07-053 spot 2


O
O
N
OBn
Ph
N
3.68
LP-07-053 spot 2
LP-07-053 spot 2
f1 (ppm)

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1. Gribble, G. W. J. J. A. Prog. Heterocycl. Chem.. Vol. 21 Vol. 21. http://www.sciencedirect.com/science/book/9780080965154; Katritzky, A. R. R. C. W., *Comprehensive heterocyclic chemistry : the structure, reactions, synthesis, and uses of heterocyclic compounds*. Pergamon Press: Oxford [Oxfordshire]; New York, 1984.

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