Towards a Metal-Catalyzed Annulation Route to Pyridines and *N*-Hydroxy Pyrroles

by

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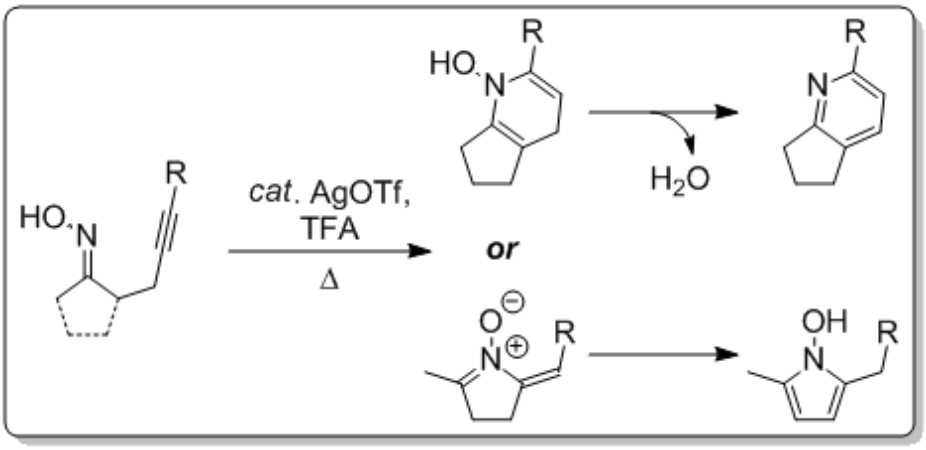
Abstract



Despite progress in the metal-catalyzed synthesis of aromatic heterocycles, annulation routes towards 6-membered heterocycles remain underdeveloped. Specifically, routes towards pyridines are rare in spite of the prevalence of this moiety in novel drug candidates. Our initial efforts towards pyridines featured oximes as competent nucleophiles in the intramolecular, *6-exo dig* annulation of alkynes using Brønsted acid catalysis. Two of the oxidation states required for subsequent aromatization are contained within the oxime via loss of water. An extension of this chemistry is presented and discussed, and involves the intramolecular metal-catalyzed *6-endo dig* annulation of analagous alkynyl-oximes. Additionally, the discovery of a *5-exo dig* annulation of related systems is discussed.

“What I hear, I forget.

What I see, I remember.

What I do, I understand.”

-Confucius

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Finally I would like to thank my parents who have always helped me when I needed it and for supporting me throughout my Master's and my entire life.

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List of Abbreviations

Ac	acetate
Bp	boiling point
Bn	benzyl
Br	broad
cat.	catalytic
Cy	cycloheyxl
Cp	cyclopentadiene
Cp*	cyclopentadienyl anion
CSA	(+) Camphorsulfonic acid
D	doublet
DCM	dichloromethane
DCE or 1,2-DCE	1,2-dichloroethane
DMB	1,4-dimethoxybenzene
DMF	*N, N*-dimethylformamide
DMSO	dimethylsulfoxide
EI	electron ionization
equiv.	equivalents
Et	ethyl
Et_3N	triethylamine
EtOAc	ethyl acetate
HRMS	high-resolution mass spectrometry
IR	infra-red

IMes	1,3-dimesityl-2,3-dihydro-1H-imidazole
I-Pr	isopropyl
I-PrOH	isopropanol
MeOH	methanol
J	coupling constant
LDA	lithium diisopropylamide
M	molar
M^+	molecular ion
Me	methyl
MS	mass spectrometry
n-BuLi	*n*-butyllithium
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
Nu	nucleophile
Ph	phenyl
p-TsOH	*para*-toluenesulfonic acid
PPh_3	triphenylphosphine
$PySO_3$	pyridine-sulfur trioxide
q	quartet
quint	quintet
R_f	retention factor
R_L	large substituent
R_s	small substituent
S.M.	starting material
sept	septet

sext	sextet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	toluene sulfonyl
TMS	trimethyl silane
Tf	trifluoromethane sulfonic
μw	microwave irradiation

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Chapter 2: Formation of Pyridines Via 6-endo-dig Annulation

1

Introduction

1.1. Pyridines and Other Unsaturated Nitrogen Heterocycles

The pyridine moiety is a heterocycle that is structurally analogous to benzene, and is ubiquitous in both natural products and synthetic targets (Figure 1.1). It is a particularly valuable structure in the pharmaceutical industry and the prevalence of pyridines in medicinal chemistry is well recognized.

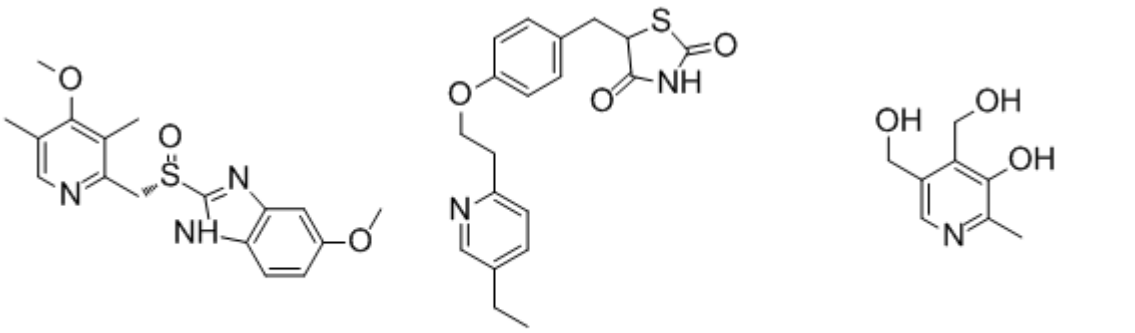


Figure 1.1. *Drugs and natural products containing pyridine motifs*

As an example, in 2006 Carey *et al.* surveyed this in the evaluation of drug candidates being developed at AstraZenica, GlaxoSmithKline and Pfizer.[1] An initial screening of "small molecules" synthesized in these major pharmaceutical companies with a molecular weight below 550 revealed that more than 90% contained at least one nitrogen atom, and again more than 90% contained an aromatic ring. Of these, 128 novel drug candidates were analyzed with the result that 24% contained substituted pyridines. Furthermore, it was found that 89% of pyridines utilized in the synthesis of these candidates were purchased from external companies rather than synthesized as required, which illustrates the need for an industrially applicable route for diverse pyridine synthesis.

Dugger *et al.* have also reviewed trends in the pharmaceutical industry from 1985 to 2002 and found that of all reactions performed in medicinal chemistry laboratories, 15% were C-N bond forming reactions.[2] A further 22% of these reactions were simple heterocycle formation. These two reviews of trends in pharmaceutical laboratories show that the demand for reliable C-N bond forming reactions is significant but general synthetic routes towards heterocycles are underdeveloped in drug synthesis.

The heterocycles often found in drug targets including pyridine and other related 6-membered heterocycles are similar to benzene in that they have π-electrons which are stabilized by aromaticity. Aromatic structures as defined by Huckel contain 4n+2 π electrons in alternating single and double bonds

[1] Carey, J. S.; Lafflan, D.; Thomson, C.; Williams, M.T. *Org. Biomol. Chem.* **2006**, *4*, 2337.
[2] Dugger, R. W.; Ragan, J. A.; Ripin, D. H. B. *Org. Proc. Res. Dev.* **2005**, *9*, 253.

(conjugation) and distributed throughout a cyclic structure.[3] In the case of pyridine there is a permanent dipole present due to nitrogen's high electronegativity relative to carbon, and resonance structures place positive charges on carbon atoms (Figure 1.2).

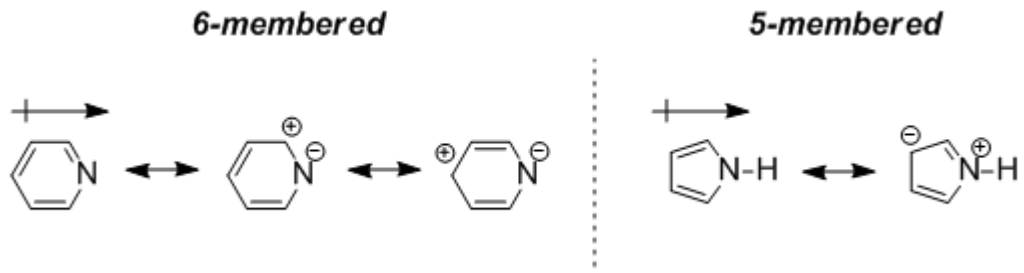


Figure 1.2. *Resonance structures for 5 and 6-membered N-heterocycles*

Before synthesizing any aromatic heterocycle, an understanding of oxidation state management is crucial since the requisite number of unsaturations, or equivalent functionality, must be present in any precursor (Figure 1.3).

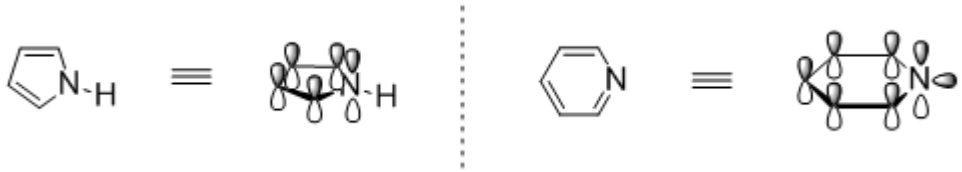


Figure 1.3. *Unsaturations in 5- and 6-membered N-heterocycles*

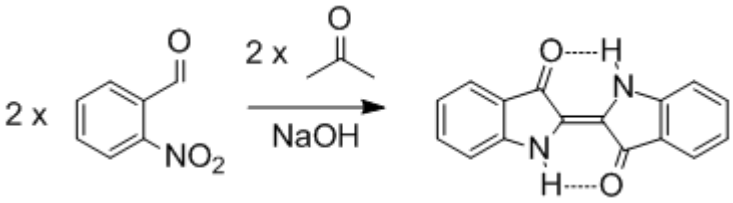
There is a long history of heterocycle synthesis in organic chemistry. Any introductory course involving heterocycles begins with a discussion of the methodologies developed over the past 100 years. Often the concepts previously presented that focus on conditions for aromaticity and oxidation state management

[3] Hückel, R. Z. *für Physik* **1931**, *70*, 204.

are addressed. The next sections will attempt to give an overview of the synthesis of 6-membered heterocycles, illustrate the limitations and subsequent improvements to these methods, and discuss specific details which are essential for each reaction to proceed to heterocyclic products.

1.1.1 Classic Heterocycle Syntheses

Early attempts to reproduce the small molecules that were being isolated from human and animal specimens naturally led to the synthesis of heterocyclic structures. The synthesis of indigo by Baeyer and Drewsen[4] via two aldol condensations on 2-nitrobenzaldehyde with acetone is an early example of a synthesis towards a natural heteroaromatic product (eq 1.1).

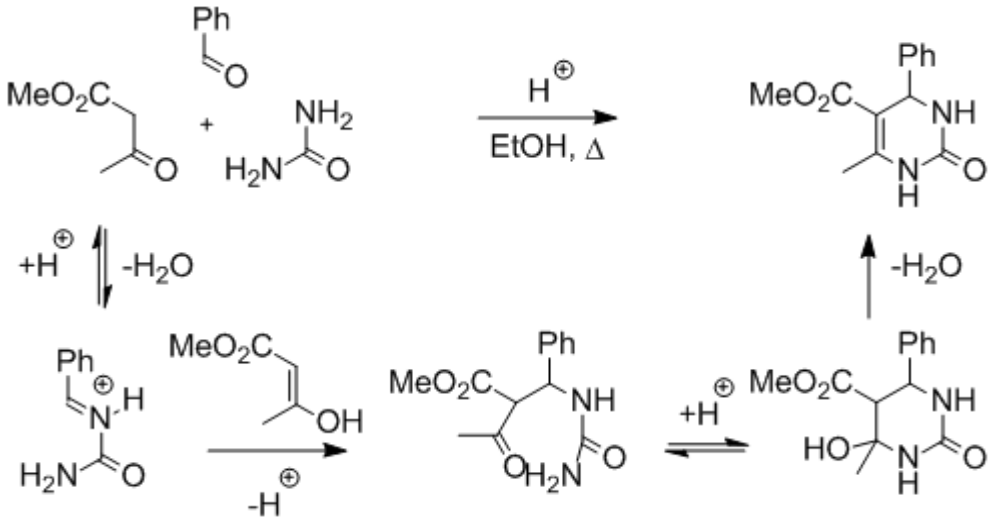


(1.1)

It is important to note that the methodologies that were being developed towards indigo and other heterocycles early in the history of synthetic chemistry required a basic understanding of functional group transformations.

[4] Baeyer, A.; Drewsen, V. *Chem. Ber.* **1882** *15*, 2856.

The realization that the carbonyl functionality may act as a surrogate for a single unsaturation via a dehydration mechanism was a key concept and utilized throughout early attempts towards heterocycles including the Biginelli reaction (Scheme 1.1). Additionally many early strategies rely upon either Lewis or Brønsted acid additives to form stable or transient intermediates which may lose one equivalent of water per unsaturation to aromatize to heterocyclic products.

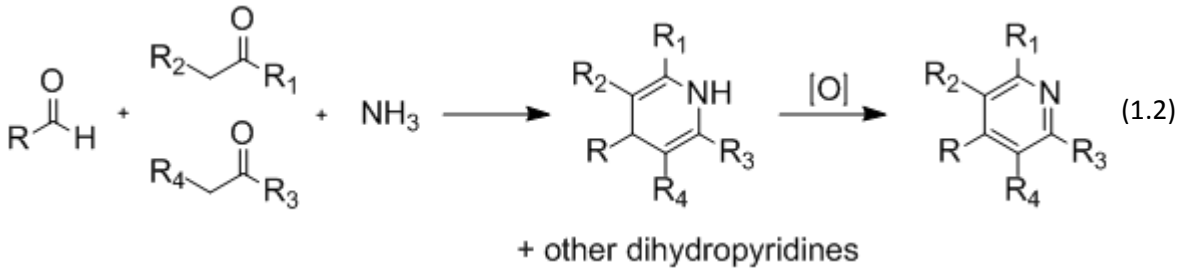


Scheme 1.1. *Biginelli reaction with ketone dehydration to an alkene*

1.1.2 Pyridine Syntheses

1.1.2a Hantzsch Synthesis

An introduction to the synthesis of heterocyclic products is often initiated with a discussion of the Hantzsch pyridine synthesis because it exemplifies the concept of oxidation state management and ketones as substitutes for alkenes. Hantzsch utilized substituted ketones in the presence of an aldehyde and ammonia to obtain dihydropyridine products. These may be further oxidized to the desired pyridine using nitrous acid (eq 1.2).[5] A significant issue is illustrated by the observation that three possible products may arise unless one is restricted to using a single ketone to access symmetrical dihydropyridines.



(1.2)

Homo and heterocoupling routes are possible with 2 different ketones, and controlling the distribution of products requires the use of specific reactions like the Knoevenagel condensation. A key finding by Hantzsch was that under basic conditions, an electron withdrawing group alpha to the carbonyl (R_2 and R_4) facilitates the ring formation. This may be in part due to the fact that the alpha-protons of all imine intermediates are more acidic.

[5] Hantzsch, A. *Chem. Ber.* **1881**, *14*, 1637.

1.1.2b Guareschi-Thorpe Pyridone Synthesis

Pyridones are 6-membered nitrogen-containing heterocycles and are the major constituent in polar solutions when the oxygen is in the 2- or 4-position in relation to nitrogen. Conversely, 3-hydroxypyridines are able to tautomerize to the protonated ketone equivalent but the equilibrium favours the OH tautomer in all solvents (Figure 1.4).[6]

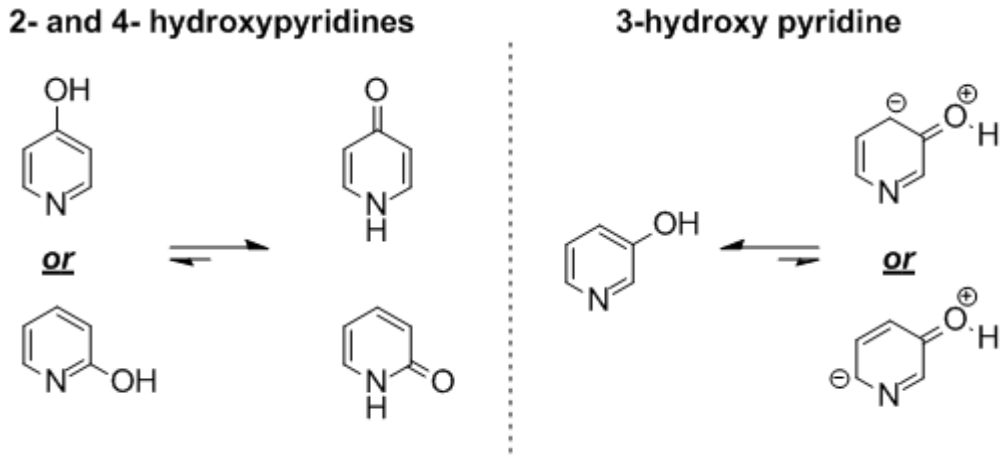
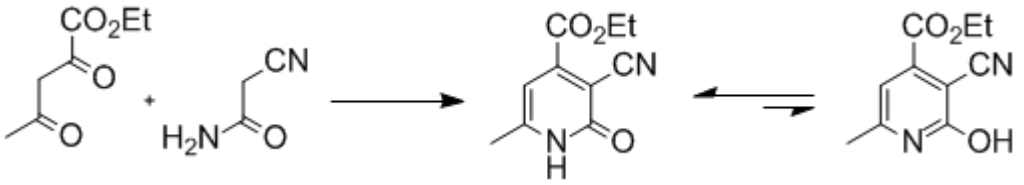


Figure 1.4. *Pyridone tautomerization*

With knowledge of this structural feature of pyridones, the products of the Guareschi-Thorpe synthesis can be predicted. This pyridone synthesis relies upon a primary cyanoacetamide functionality in conjunction with a 1,3-ketoester to provide the pyridone scaffold via initial imine formation between the methyl ketone and amide nitrogen (eq 1.3).[7]

[6] Forlani, L.; Cristoni, G.; Boga, C.; Todesco. P. E.; Del Vicchio, E.; Selva, S.; Monari, M.; *Arkivoc* **2002**, *XI*, 198.
[7] Guareschi, I. *Mem. Reale Accad. Sci. Torino* **1896**, *II*, 7, 11, 25.



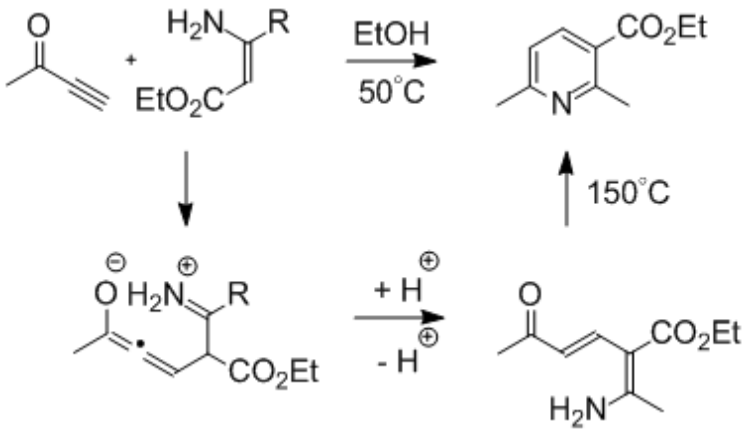
(1.3)

Following enamine formation and nucleophilic attack on the second ketone, dehydration leads to the pyridone structure shown above. In this example only 2 unsaturations are installed via dehydration mechanisms while the third comes from the conjugated amide π-system.[8] A variety of diketone reagents may be employed using this methodology, however being limited to using cyanoacetamide to form pyridones is the major restriction of this synthetic route. An additional two steps involving an α-chlorination, and hydrogenation of the 2-chloropyridine are required to obtain pyridines.

1.1.2c Bohlmann-Rahtz Synthesis

The development of the Bohlmann-Rahtz methodology allowed chemists to utilize enamines formed *in-situ* along with terminal ynones as a way to synthesize 2, 3, 6-trisubstituted pyridines in two synthetic manipulations. Similar to the examples given above, an initial condensation of ammonia on a ketone accesses an enamine intermediate. This enamine formed *in-situ* then undergoes a conjugate addition onto the terminal ynone (Scheme 1.2).[9]

[8] Cox, R. H.; Bothner-By A. A. *J. Phys. Chem.* **1969**, *73*, 2465.
[9] Bohlmann, F.; Rahtz, D. *Chem*. *Ber*. **1957**, *90*, 2265.



Scheme 1.2. *Bohlmann-Rahtz pyridine synthesis*

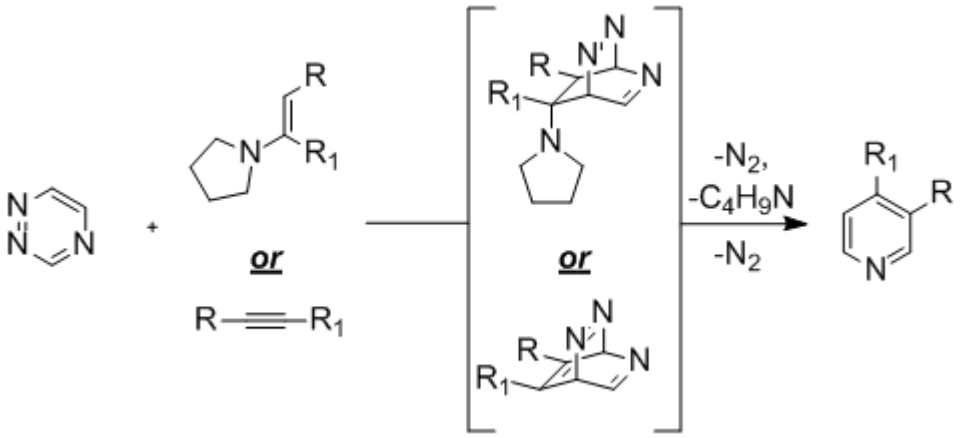
The resulting allenic enolate captures a proton to generate an *(E)*-enone. Upon heating the sample under vacuum the newly formed alkene isomerizes to the *(Z)*-configuration. A condensation of the enamine nitrogen to the ketone then results in substituted pyridines. Modifications have been developed to reduce the thermal requirements during the final ring formation including the addition of acetic acid to assist in the imine condensation steps.[10]

1.1.2d Boger Synthesis

The approach Boger (eq 1.4) developed during the 1980s is similar to the Kondrat'eva pyridine synthesis (eq 1.5),[11] the latter of which revealed that alkenes and oxazoles can undergo a 4 + 2 cycloaddition with dehydration to yield pyridines.

[10] Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett* **2001**, 1149.
[11] Kondrat'eva, L. V.; Chekuleva, I. A. *Russ. Chem. Rev.* **1965**, *34*, 669.

Boger's approach relies on an inverse electron-demand Diels-Alder and retro Diels-Alder sequence starting from either enamines or alkynes and severely electron-deficient tri- and tetrazines.[12]



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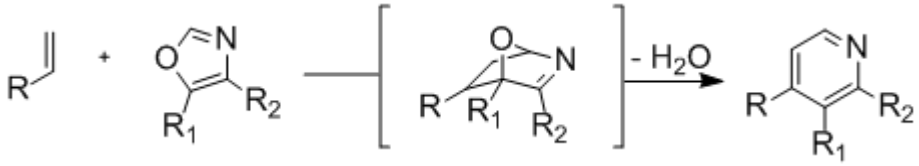


(1.5)

Both the Kondrat'Eva and Boger approach suffer from the fact that a heteroaromatic diene must be formed as a precursor to the desired reaction. While the loss of either water or nitrogen gas is environmentally benign and a strong driving force, these extrusions do not outweigh the synthetically difficult (and elegant) transformations needed to form the starting heterocycles.

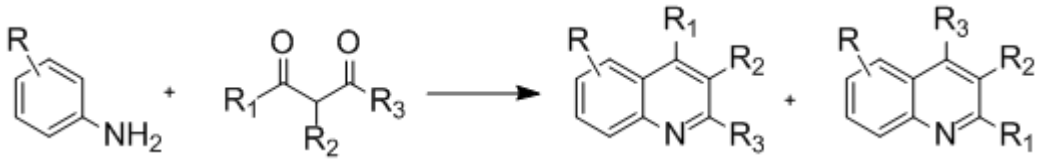
[12] a) Boger, D. L.; Panek, J. S. *J. Org. Chem*. **1981**, *46*, 2179.; b) Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem*. **1982**, *47*, 895.; c) Boger, D. L.; Panek, J. S.; Yasuda, M. *Org. Synth*. **1987**, *66*, 142.

Pyridines are only one class of heterocycle that were initial heterocyclic targets for early synthetic organic chemists. Routes towards the fused quinoline and isoquinoline systems are also common in literature from the 19th and early 20th century and a variety of precursors leading to synthetic analogues of these systems exist.

1.1.3 Quinoline Syntheses

1.1.3a Combes Synthesis

The Combes quinolone synthesis is one of the oldest and simplest ways to obtain substituted quinolones from simple and readily available starting materials, namely anilines and 1,3-diketones (eq 1.6).



(1.6)

Initial formation of an imine on one of the ketones, with tautomerization to form an enamine places the second ketone in proximity to the aromatic ring of the aniline. This second ketone can act as an electrophile to the aniline's aromatic ring when closing a 6-membered heterocycle. This ring closure provides access to an alcoholic intermediate that dehydrates to aromatize to a mixture of quinolone products.[13] A downside to this method is the possibility of a distribution of regioisomeric products depending on which ketone initially interacts with the aniline.

[13] Combes, A. *Bull. Chim. Soc. Fr.* **1888**, *49*, 89.

Control of the condensation was addressed by using 1,3-ketoesters rather than diketones, and is known as the Conrad-Limpach quinolone synthesis.[14] In the Combes synthesis it was found that anilines bearing electron withdrawing substituents severely reduce the speed of the reaction. The aniline must use electron density to attack the carbonyl functionality, disrupting aromaticity. With electron withdrawing substituents the positively charged Wheland intermediate is destabilized (Figure 1.5). Finally, it is important to note that in this example it is only necessary to install 2 unsaturations via ketone dehydration. The additional π-bond required for aromaticity of the full system (10 electrons) is already present in the aniline.

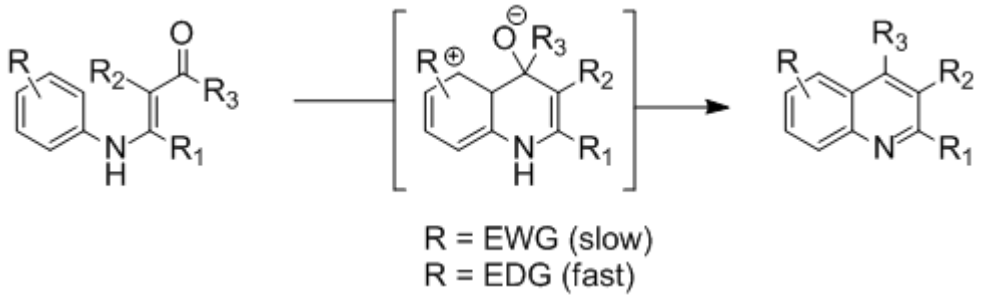


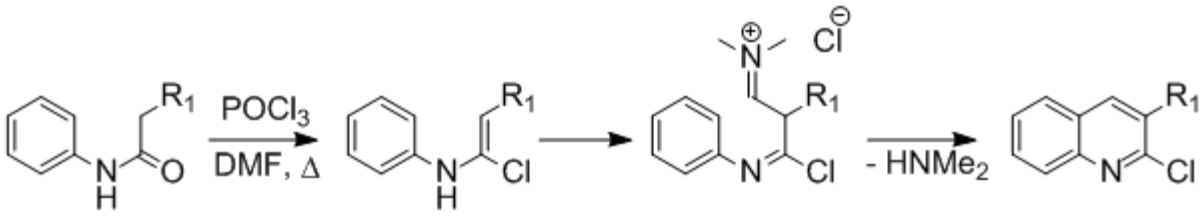
Figure 1.5. *Effect of substituents on reaction rate in Combes synthesis*

1.1.3c Meth-Cohn Synthesis

The method of converting acylanilides into chloroquinolines is known as the Meth-Cohn quinolone synthesis.[15] Initial formation of the Vilsmeyer-Hack reagent using DMF and $POCl_3$ allows for chlorination of the amide carbonyl.

[14] Conrad, M.; Limpach L. *Ber.* **1887**, *20*, 944.
[15] Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans.* **1981**, 1520.

The α-chloro enamine intermediate resulting from tautomerization of the imine then undergoes for a single carbon homologation producing the iminium ion shown in scheme 1.3. This iminium ion is attacked by the aromatic ring and closes the 6-membered ring. The system re-aromatizes the carbocyclic portion by deprotonation, and following the loss of dimethylamine the heterocyclic portion is formed.

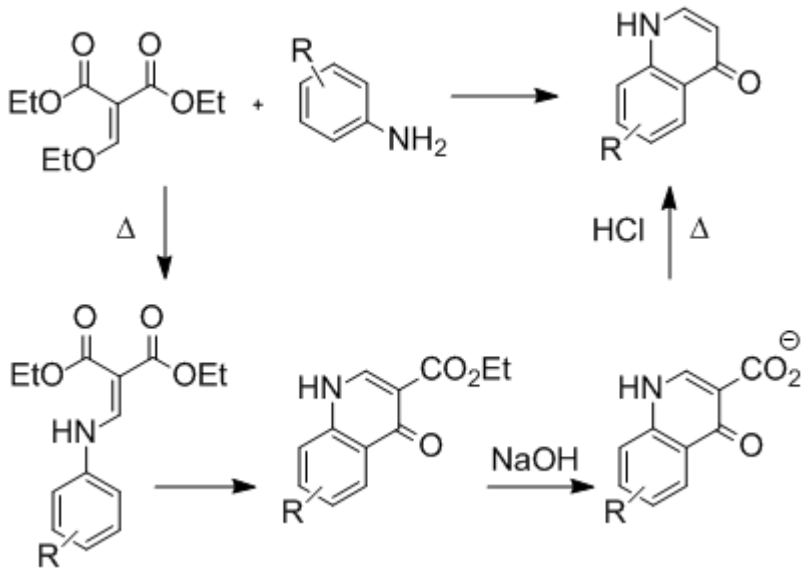


Scheme 1.3. *Meth-Cohn chloroquinoline synthesis*

The restriction of using acylanilides as starting materials is the main deterrent to the broad applicability of the Meth-Cohn methodology. Additionally, subsequent functionalization steps are required if a 4-substituted quinoline is the desired product. Indeed, only monosubstitution of the heterocyclic portion is tolerated using the Meth-Cohn approach to quinolones. Advantageously this route allows for further elaboration of the resulting chloroquinoline via nucleophilic aromatic substitution.

1.1.3d Gould-Jacobs Quinolone Synthesis

Substituted quinolones are present in medicinally relevant cores and the Gould-Jacobs route was developed during the 1930s towards the synthesis of these structures.[16] Substituted anilines and diethyl ethoxymethylenemalonate are used as the precursors to 4-quinolones via an initial conjugate addition to the malonate unit by the aniline. The loss of 2 equivalents of ethanol and a saponification step to the carboxylate salt provide an intermediate that can undergo a heat-assisted decarboxylation step. Quinolones are then obtained with the potential for further elaboration (Scheme 1.4). Anilines with electron withdrawing groups or sensitive functionalities are incompatible with the Gould-Jacobs approach because of the severely acidic and basic conditions employed in addition to the high temperatures needed for the decarboxylation step.



Scheme 1.4. *Gould-Jacobs quinolone synthesis*

[16] Gould, G.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890.

As can be seen from the previous examples of heterocycle syntheses, many methods involve harsh reactions conditions which are not compatible with sensitive substrates. In order to circumvent these issues innovative procedures have been developed as alternative routes to access pyridines and other heterocycles. Selected metal-free advances in heterocyclic syntheses from 2006 and onwards are presented in the following section. Additionally, metal-catalyzed discoveries in heterocyclic synthesis post-2006 are reviewed with the aim of illustrating improvements over prior classical methodologies.

1.2.1 Modern Heterocycle Syntheses

Heterocycles are found in a majority of new pharmaceuticals and while the classical cases described above provide access to a large number of heterocyclic derivatives, a large number of projects in both academic and commercial sectors focus on advancing routes towards these heterocycles. Progress in our understanding of how drugs function in the body has paved the road towards the current research climate for heterocycle synthesis. Indeed, the demand for heterocycles has exploded and the number of new publications have increased, which supply medicinal chemists with routes to novel precursors and heterocycles.

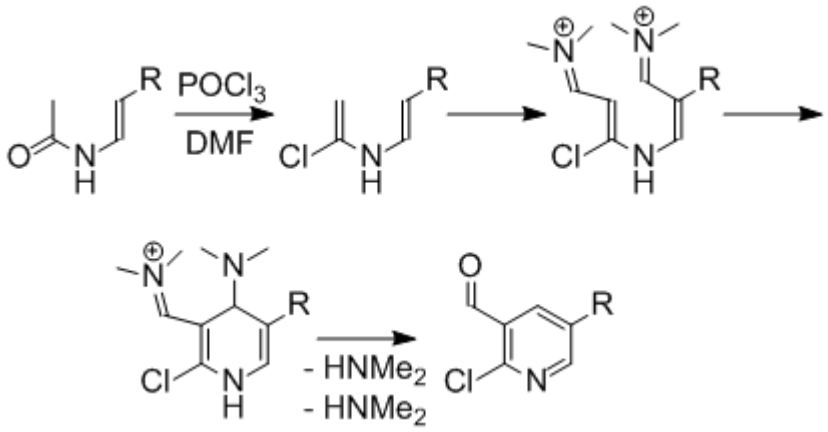
1.2.2 Metal-free Reactions

Utilizing solely non-d-block elements in order to effect the transformation of organic precursors into heterocyclic products can be a daunting task due to highly reactive intermediates and large activation barriers. Nonetheless, solutions to these issues require chemical ingenuity and are part of an ongoing effort to understand how organic molecules behave on a fundamental level.

1.2.2a Rao Pyridine Synthesis

From the recent literature on new routes towards heterocyclic structures comes the work of the Rao group and their approach to the conversion of enamides to chloronicotinamides.[17] In a similar vein to the Meth-Cohn quinolone synthesis, the Vilsmeyer-Hack salt is proposed to act as a dually functional reagent. Initially a dehydration and chlorination of the amide carbonyl provides a α-chloro enamine. The additional $POCl_3$ and DMF are used to perform a one-carbon homologation of the enamine, which then closes a 6-membered ring by attacking an iminium intermediate. Finally there is installation of an aldehyde at the 3-position of the resulting pyridine via hydrolysis of a second iminium ion (Scheme 1.5).

[17] Gangadasu, B.; Narender, S.; Kumar, S. B.; Ravinder, M.; Rao, A.; Ramesh, C.; Raju, B. C.; Rao, V. J. *Tetrahedron* **2006**, *62*, 8398.



Scheme 1.5. *Rao chloropyridine synthesis*

The reactions conditions developed avoid the use of any strong acids or bases, and mild heating at 75°C is required to aromatize the intermediate di-iminium species. This is a dramatic improvement over classic dehydrative aromatization, and both the chloropyridine and aldehyde can be further elaborated to attach additional groups to a pyridine core. The primary limitation of the scope presented is that fully functionalized pyridines cannot be accessed in a single step with both the 4- and 6-position of the product being unsubstituted.

Barring the Bohlman-Rahtz and Boger approaches, the classic heterocycle synthesis examples previously presented rely on alkenes, and ketones with dehydrative conditions for oxidation state management. When an alkene is used in a ring forming reaction these unsaturations are displaced by an incoming nucleophile and often must isomerize in order to provide an unsaturation needed for aromaticity. The use of alkynes in the synthesis of heterocycles is advantageous since for a 2-carbon subunit it can provide one unsaturation towards aromatic compounds without relying on additional isomerizations within the newly formed ring system (Figure 1.6).

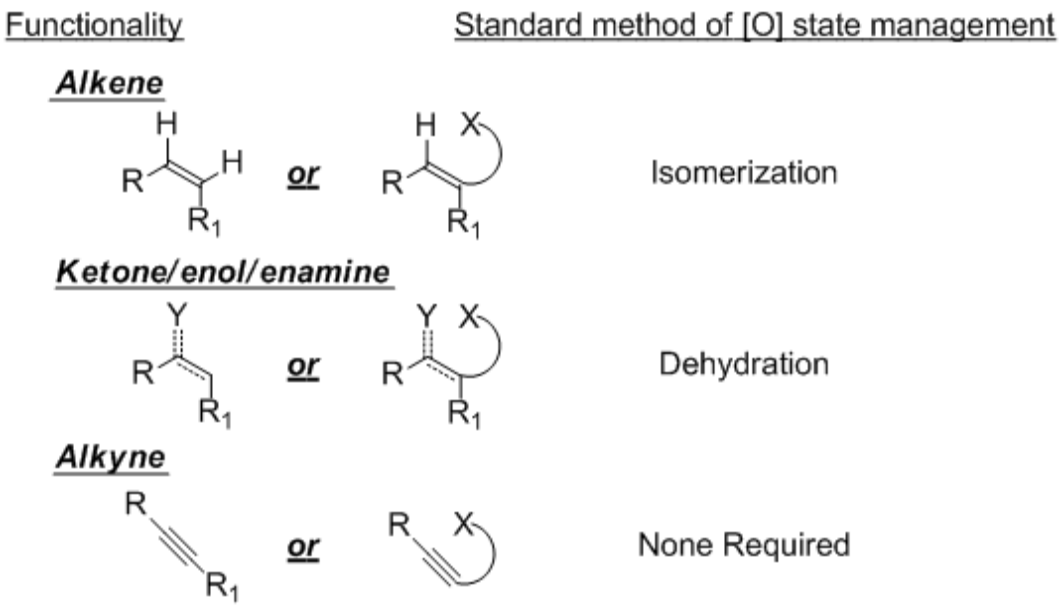


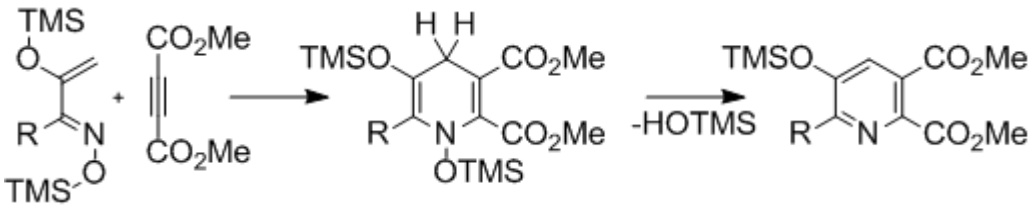
Figure 1.6. *Comparison of alkene, ketone and alkyne 2-carbon subunits*

Additionally, if a regiospecific intermolecular reaction can be utilized with an unsymmetrically substituted internal alkyne, densely functionalized pyridines are obtained as a result. The following examples of heterocyclic syntheses all take advantage of alkynes as precursors and illustrate the versatility of alkynes in heterocyclic synthesis.

1.2.2b Moody Pyridine Synthesis

The first example presented that takes advantage of the alkyne functionality is the work by Moody and co-workers. An intermolecular hetero-Diels-Alder approach from α-β-unsaturated oxime or hydrazine precursors was proposed as a route to densely functionalized pyridine derivatives (eq 1.7).[18]

[18] Fletcher, M. F.; Hurst, T. E.; Miles, T. J.; Moody, C. J. *Tetrahedron* **2006**, *62*, 5454.



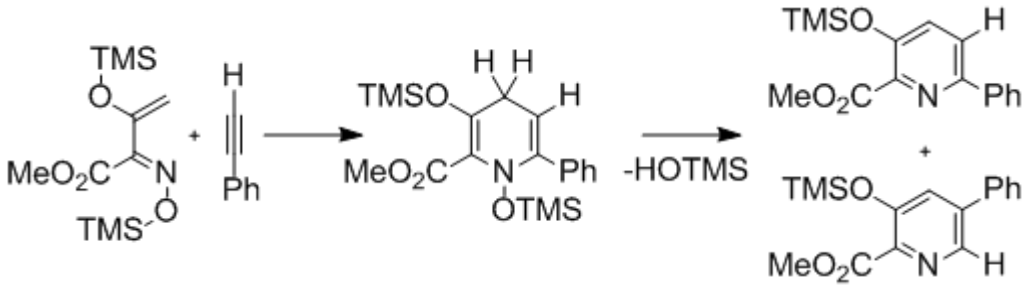
(1.7)

Following 4 + 2 cycloaddition, the alkyne provides a single unsaturation, while the oxime functionality allows for the aromatization step to occur. Deprotonation of the intermediate di-enamine and loss of trimethylsilyl alcohol causes aromatization and affords a tetra-substituted pyridine.

This microwave-assisted Diels-Alder route requires that the alkyne be substituted with ester groups, which can lead to mixtures of products. In making the requisite diene precursor an *O*-silyl protected ketone is formed, leading to a protected alcohol following cycloaddition. This protecting group must then be removed if subsequent manipulations are to be performed and requires an extra synthetic step.

1.2.2c Arndt Pyridine Synthesis

The group of Arndt utilized similar diene-dienophile systems to the same end but with a variety of unsymmetrically substituted alkynes (eq 1.8).[19]



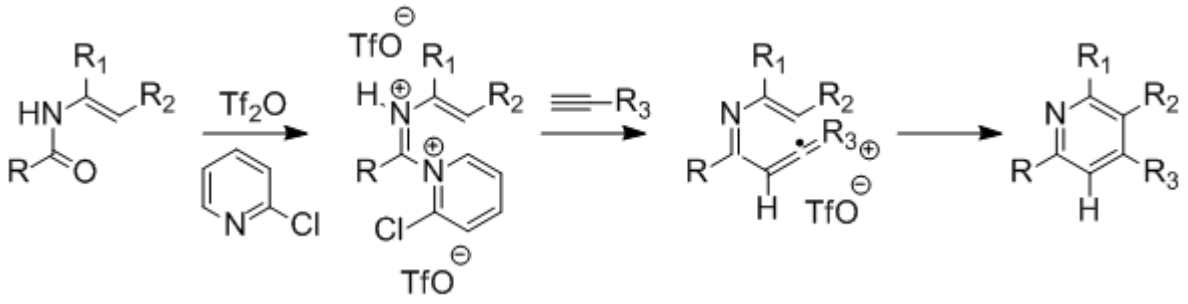
(1.8)

[19] Lu, J.; Arndt, H.-D. *J. Org. Chem.* **2007**, *72*, 4205.

The best regiochemistry and yields were highly dependent on the alkyne, with aryl- or ester substitutions providing the best results. Halogens and terminal alkynes proved to be tolerated, which expands upon the previous work of Moody.

1.2.2d Movassaghi Pyridine Synthesis

Movassaghi's approach to pyridines is dramatically different from the previous examples and treats the added alkyne as a source of a π-nucleophile.[20] Upon treating an amide with trifluoromethanesulfonic anhydride and 2-chloropyridine, an intermediate salt containing an iminium and pyridinium is attacked by an alkyne. Following this, an alkenyl carbocation can undergo annulation directly to the pyridine (Scheme 1.6).



Scheme 1.6. *Movassaghi 4 + 2 cycloaddition route to pyridines*

[20] Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *127*, 10096.

The focus of the reactions previously discussed has been on transformations of purely organic molecules using acid or base catalysis, organocatalysis and heat towards heterocyclic products. Metal catalysis leading to heterocycles can provide a significant improvement to the reaction efficiency and the aim of the following short section is to outline the impact that metal catalyzed heterocyclic syntheses have had on the availability of these aromatic motifs for use in medicinal chemistry.

1.2.3 Metal-catalyzed Reactions

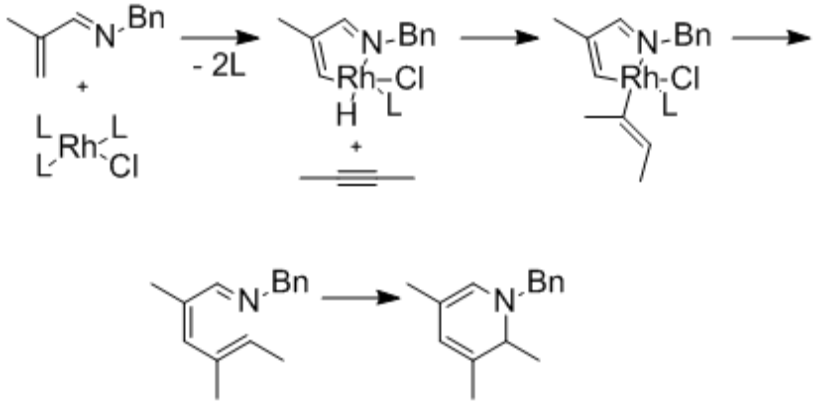
Transition metals have a ubiquitous presence in organic synthesis and have maintained this position due to their unique ability to enable reactions that are difficult or currently impossible with conventional catalysis. The factors which allow metals to facilitate these reactions are covered in many courses and textbooks and obtaining a complete understanding these is not the goal of this section. Instead, a selection of metal-catalyzed heterocyclic syntheses will be discussed with a focus on pyridines and indoles, and with the intent that the reader becomes familiar with a variety of the chemical transformations possible and mechanisms using metal catalysis. Additionally this will put the results of chapters 2 and 3 in context.

1.2.3a Ellman Pyridine Synthesis

C-H activation of sp^2 hybridized protons is a common practice in the field of aromatic heterocycle functionalization but its application to their synthesis has been expanded upon by Bergman and Ellman.[21] Starting with β-unsaturated imines and internal alkynes an initial C-H activation of the distal imine proton by a rhodium(I)

[21] Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 3645.

catalyst generates a rhodium(III) metallacycle. Migratory insertion of the metal onto the alkyne was proposed as a route to generate a vinyl rhodium species, which can reductively eliminate to form a diene. A 3+3 sigmatropic rearrangement produces the dihydropyridine shown below (Scheme 1.7).



Scheme 1.7. *Ellman pyridine synthesis and metallated intermediates*

1.2.3b Hartwig Indole Synthesis

Similar to Ellman's approach, Hartwig also takes advantage of C-H functionalization but using palladium(0) catalysis and oxime *O*-acetates as precursors for intramolecular reactions to form indoles.[22] The proposed mechanism involves an N-O bond insertion with tautomerization to yield an enamine intermediate (Figure 1.7). From this structure, C-H functionalization and reductive elimination of palladium(0) regenerates the catalyst and provides the product. Proof of the N-O bond insertion comes from isolation and characterization of an intermediate, which upon treatment using their standard reaction conditions gives the expected indole (Figure 1.8).

[22] Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

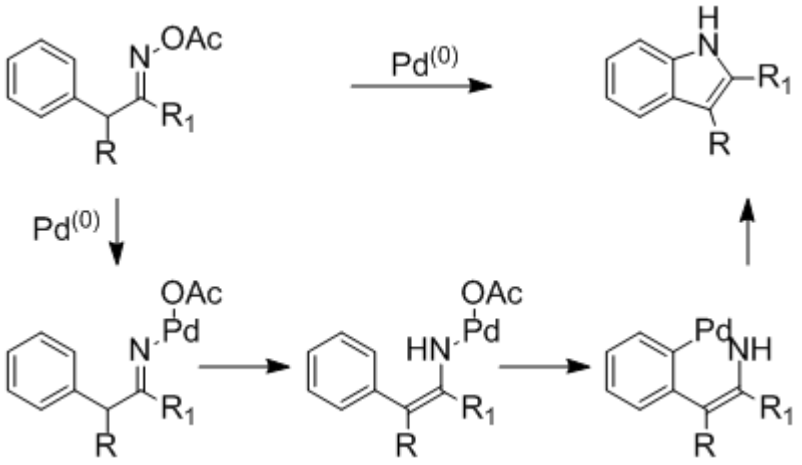


Figure 1.7. *Hartwig indole synthesis and intermediates*

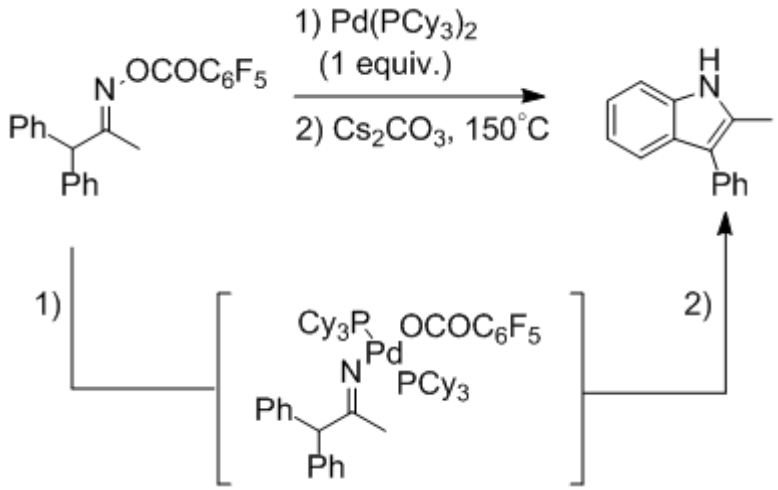
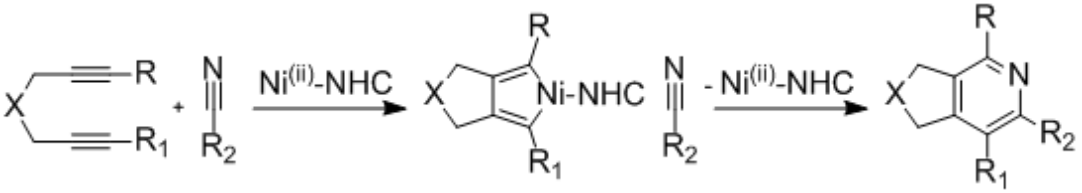


Figure 1.8. *Isolated intermediate in Hartwig indole synthesis*

1.2.3c Louie Pyridine Synthesis

Nickel catalysts are often found within the field of alkyne trimerization chemistry, producing mixtures of highly functionalized benzene derivatives. The Louie group has been responsible for developing the chemistry where one alkyne has been replaced by a nitrile to form pyridines and a variety of other nitrogen-

containing heterocycle via similar intermediates.[23] Initially the diyne is stitched together to yield a metallocyclopentadiene, which may react with a third alkyne in a Diels-Alder reaction. The resulting metal-bridged norbornadiene structure aromatizes with loss of the nickel catalyst and the cycle begins again (eq 1.9).



(1.9)

Unfortunately generation of the catalyst initially requires *n*-BuLi as both a reductant and base, and makes this route to pyridines very specific to substrates without acidic protons or sensitivity to strongly basic conditions.

1.2.3d Trost Pyridine Synthesis

Using similar precursors with a ruthenium catalyst, the research of the Trost group has led to an understanding of alternative mechanisms and intermediates for an alkyne dimerization and 3 + 3 rearrangement sequence.[24] An intermediate metallacycle analogous to using nickel is proposed as the initiating step, followed by loss of water on one side of the cycle and re-incorporation on the opposite. Oxidation of the alcohol forms a carbonyl and a vinyl-ruthenium species, which then eliminates to yield a dienone (Scheme 1.8). Upon treatment with hydroxylamine hydrochloride, followed by heating the crude mixture, a sigmatropic rearrangement occurs with the loss of water, giving a substituted pyridine.

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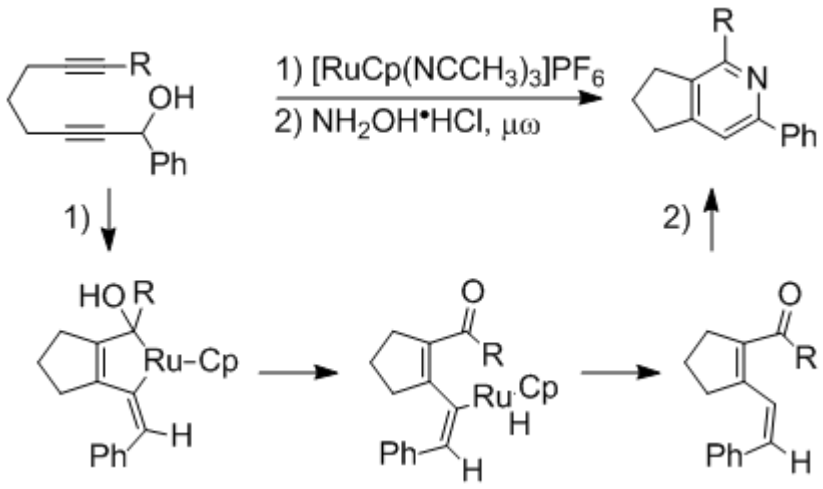
[23] Tekavec, T. N.; Zuo, G.; Simon, K.; Louie, J. *J. Org. Chem.* **2006**, *71*, 5834.
[24] a) Gutierrez, A. C.; Trost, B. M. *Org. Lett.* **2007**, *9*, 1473.; b) Rudd, M. T.; Trost, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 4178.



Scheme 1.8. *Trost pyridine synthesis and vinyl ruthenium intermediates*

The examples of metal catalysis leading to heterocyclic products discussed so far have all involved C-H activation or cycloaddition reactions with alkenes and alkynes. In the latter case, the concept of regiochemical control during ring-forming reactions has been overlooked to this point, or presented with substituents that can control the regiochemistry of the reaction. This viewpoint is inaccurate for many intramolecular heterocyclic syntheses with alkenes and alkynes, and the placement of atoms in space rather than substitution patterns can have an enormous effect on the product distribution. The aim of the next section is to provide a brief background of the stereoelectronic factors which can control the products of alkyne annulation leading to aromatic heterocycles.

1.2.4 Baldwin's Rules

In 1976 Jack Baldwin published a set of rules that help predict the ease of ring forming reactions based on an understanding of the molecular orbitals involved in these closures.[25] The simple rule that an incoming nucleophile must donate electron density into an unoccupied anti-bonding orbital at a trajectory corresponding to the position of the new C-X bond was proposed, and the "rules" he postulated were simply experimental observations of this principle guiding fact (Figure 1.9). If Baldwin's rules are applied to the synthesis of aromatic heterocycles using an alkyne, the regiochemistry of the ring-closing reaction is an essential factor to consider. The presence of an alkyne in aromatic heterocycle synthesis is advantageous since it acts as a pre-installed unsaturation towards aromaticity.

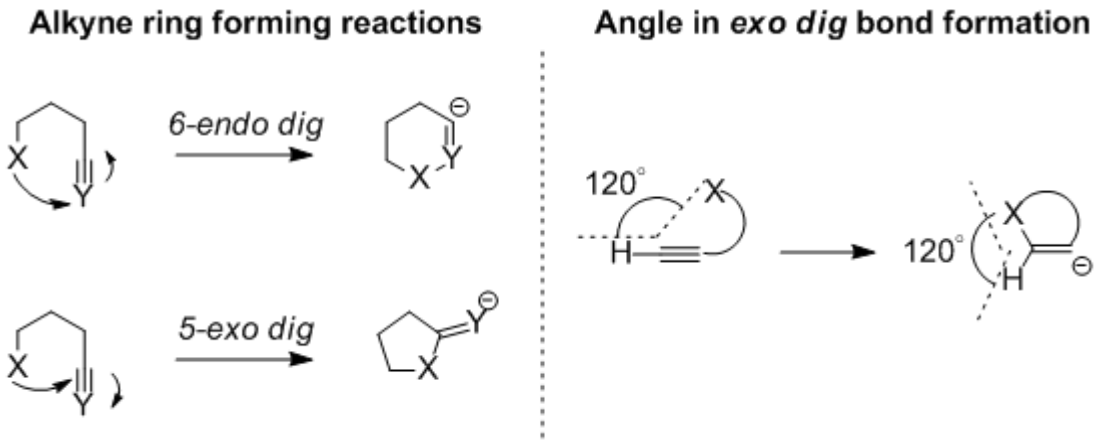


Figure 1.9. *Baldwin's rules for alkyne annulation reactions*

[25] a) Baldwin, J. E. *J. Chem. Soc., Chem. Comm.* **1976**, 734.; b) Baldwin. J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846.

Both *6-endo dig* and *5-exo dig* annulation pathways are favourable ring-closing reactions and will often compete with one another during annulation. In both cases activation of the alkyne towards an intramolecular nucleophilic attack is possible by initial coordination to the unsaturation. The following section includes examples of alkyne activation by an electrophile where multiple possible products are possible upon annulation. Currently a rationale for the selectivities observed is not given.

1.2.5 Selected Metal-catalyzed Alkyne Annulation Heterocycle Syntheses

The use of the alkyne functionality as a π-electrophile is not a new concept and both Lewis and Brønsted acid activation of the π-bond towards nucleophilic attack has long been exploited as a way to convert alkynes into partially unsaturated (alkene) or fully saturated (alkane) systems. In most high-valent states, metals are electron-poor, or Lewis acidic. In conjunction with the proper nucleophilic functional groups, annulation reactions producing heterocycles can be greatly accelerated by the presence of soft π-acid metals including copper,[26] silver[27] and gold[28] (Figure 1.10). There is a wealth of information describing the unique ability of these coinage metals, and palladium, to promote alkyne annulation reactions, both intra- and intermolecularly.

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[26] For copper catalysis and alkynes leading to *N*-heterocycles see: Vaslievsky, S; Mshvidobadze, E.V.; Mamatyuk, V.I.; Romanenko, G.V.; Elguero, J *Tetrahedron Lett.* **2005**, *46*, 4457.

[27] For silver catalysis and alkynes leading to *N*-heterocycles see: a) Patil, N. T.; Yamamoto, Y. *Che. Rev.* **2008**, *108*, 3395.; b) Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525.

[28] For gold catalysis and alkynes leading to *N*-heterocycles see a) Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Comm.* **2009**, 5075.; b) Qian, J.; Liu, Y.; Zhu, J.; Jiang, B.; Xu, Z. *Org. Lett.* **2011**, 13, 4220.; c) Gouault, N.; Le Roch, M.; Cheignon, A.; Uriac, P.; David, M. *Org. Lett.* **2011**, 13, 4371.; d) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2.; e) Hashmi, A. S. K.; Schuster, A. M.; Rominger, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 8247.; f) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, 6, 4391.

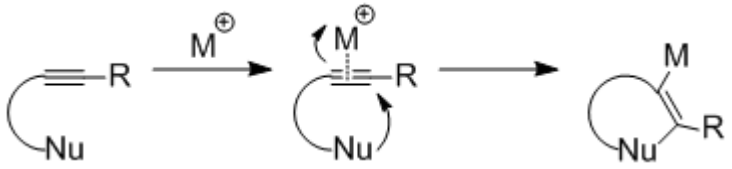
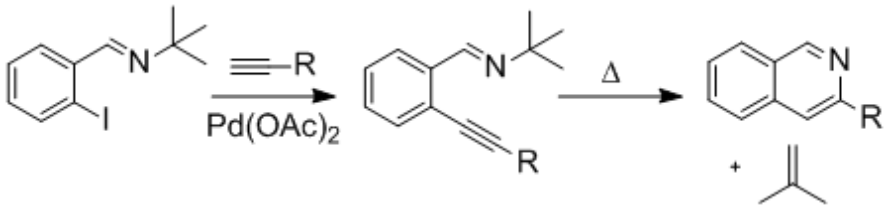


Figure 1.10. *Activation of an alkyne by a π-acid and intramolecular endo dig annulation*

1.2.5a Larock Isoquinoline Synthesis

The work of Larock relies on an alkyne acting as a π-electrophile during annulation reactions in the presence of *t*-butyl imines to obtain substituted isoquinolines (eq 1.10). There is a conjugated sp - sp^2(aryl) - sp^2(imine) system, with the aryl π-bond playing the role of a pre-installed unsaturation for the desired heterocycle. Both the imine and alkyne provide the additional unsaturations required for aromaticity.

In the area of isoquinoline synthesis Larock has two approaches, the first being a Sonogashira cross-coupling strategy between the halo-benzene and a terminal alkyne. This is followed by a 6-*endo dig* cyclization to the isoquinoline under thermal conditions.[29,30]



(1.10)

[29] a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.; b) Roesch, K. R.; Larock, R. C. *Org. Lett,*. **1999**, *1*, 553.

[30] For 5-membered imine-based annulations also see: Harrison, T. J.; Kozak, J. A.; Corbella-Pané, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525.; For 6-membered imine-based annulations also see: a) Numata, A.; Kondo, Y.; Sakamoto, T. *Chem. Pharm. Bull.* **2004**, *48*, 669.; b) Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, 306.

While palladium plays a key role in the cross-coupling reaction, there is no suggestion or evidence that it may actually facilitate the annulation step by activation of the alkyne towards nucleophilic attack by the imine nitrogen. Indeed, the annulation proceeds in highest yield without the presence of palladium, suggesting its role is exclusively limited to the cross-coupling step. Additional investigations by Larock's group into effective π-acids to promote heterocycle annulation have led to the addition of iodine, rather than a d-block metal, to activate the triple bond of an *o*-iminoalkyne towards the nucleophilic attack of an imine nitrogen (eq 1.11). The electrophile is incorporated into the product and no further reactions are possible.[31]

(1.11)

The alternative mechanism proposed by Larock in the presence of Palladium is an insertion route, whereby a palladium(II) intermediate is formed after oxidative insertion into an aromatic carbon-iodine bond. Coordination of the alkyne to the palladium intermediate followed by migratory insertion forms a 7-membered palladacycle (Figure 1.11). This metallacycle undergoes reductive elimination to yield an aromatic isoquinolinium ion, and following treatment with a base the isoquinoline is formed with release of 2-methylpropene.

[31] Huang. Q; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.

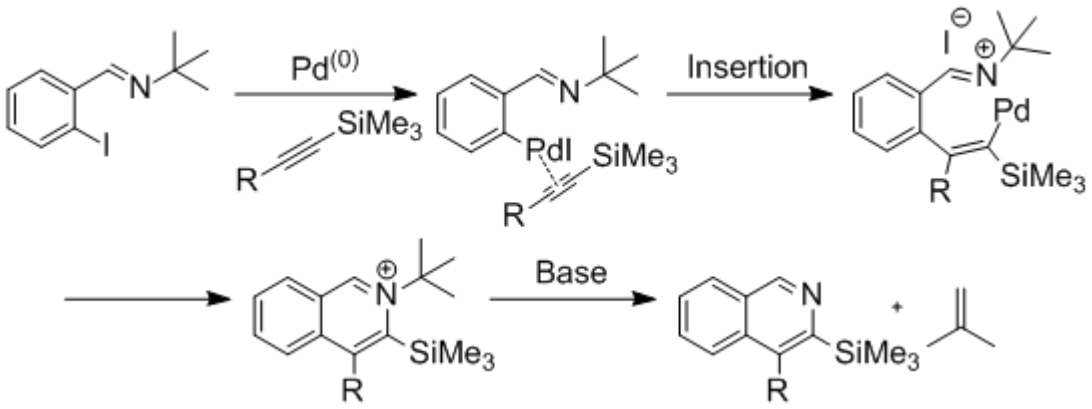


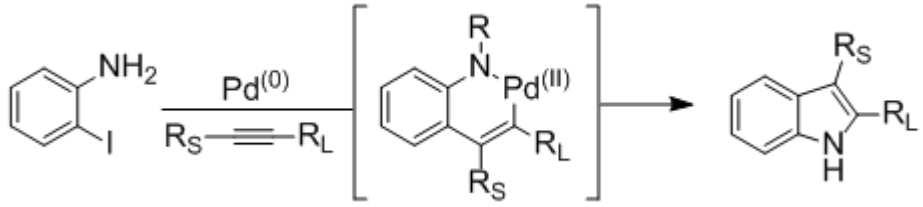
Figure 1.11. *Larock isoquinoline proposed palladium insertion intermediates*

One key feature present in these systems is that the nucleophile involved in the annulation step is either attached to the sp^2 hybridized carbon atoms (or in conjugation with those) of an unsaturation; either an alkene or benzene moiety. This is doubly beneficial as it not only restricts the alkyne and the nucleophile to be in the same plane, but reduces the conformational degrees of freedom in the starting material. Additionally, the presence of an alkene or benzene ring acts as a pre-installed unsaturation for the heterocycle being formed as previously mentioned.

It is unknown whether these structural advantages have any bearing upon the possible mechanisms at play in the annulation reactions, but with the proper conditions both 5 and 6-membered rings may be accessible from similar starting materials.

1.2.5b Larock Indole Synthesis

The Larock indole synthesis is a precursor to the isoquinoline synthesis presented above, and uses a variety of alkynes with 2-iodoanilines to prepare 2,3-disubstituted indoles with palladium catalysis.[32] In order to obtain the correct oxidation state for the indole upon annulation, only a single unsaturation must be added to the aniline via the alkyne since two of the necessary ten aromatic electrons come from rehybridization of the aniline nitrogen and six from the aryl system (eq 1.11). Initial insertion into the C-I bond by palladium(0) and migratory insertion of the alkyne provide the intermediate palladacycle shown, while reductive elimination forms the C-N bond and regenerates the catalyst.



(1.12)

Note that the intermediate 6-membered palladacycle which forms in the reaction closely resembles that of the Larock isoquinoline synthesis and that the reaction is regiospecific with unsymmetrical alkynes. The larger substitution was predominantly found to end up alpha to the nitrogen, which was proposed to be a result of an unfavourable steric repulsion between the aryl ring and the large substituent rather than palladium and the large substituent (Figure 1.12).

[32] Larock. R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

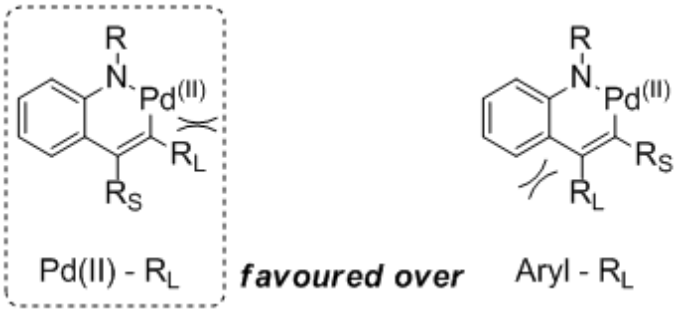


Figure 1.12. *Effect of steric interactions in the Larock indole synthesis*

1.2.5c Fagnou Indole Synthesis

Building on the work of Larock is the work of the Fagnou group, who had uncovered a method for the synthesis of indoles via a directed C-H functionalization of acetanilides with a rhodium(III) catalyst.[33] Initial coordination of the metal to the amide oxygen followed by aromatic C-H insertion leads to the metallacycle shown in Figure 1.13. Migratory insertion with an alkyne gives a 6-membered metallacycle resembling Larock's proposed intermediate using palladium.

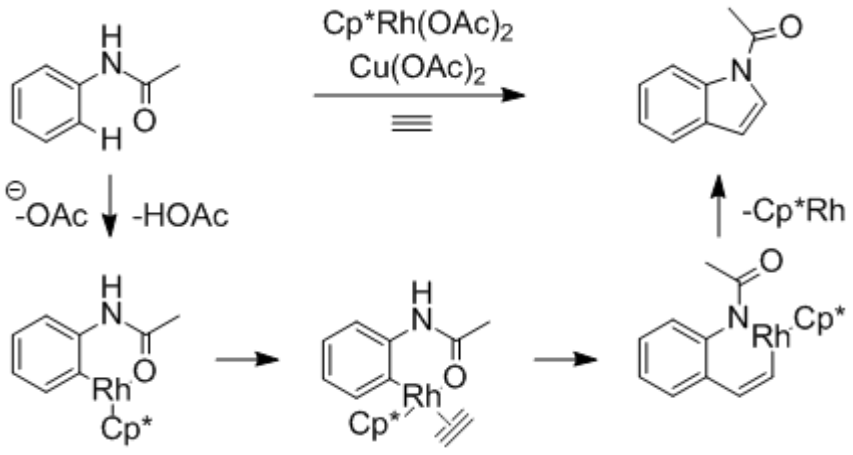


Figure 1.13. *Fagnou C-H functionalization towards indoles*

[33] Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326.

A C-N reductive elimination generates the indoles and a rhodium (I) species, which is re-oxidized to the active rhodium (III) catalyst using a copper and oxygen co-catalyst cycle. The conditions employed allow for the annulation of a variety of internal alkynes to the corresponding indoles.

1.2.5d Shin isoquinoline *N*-oxide and isoquinoline syntheses

An oxime is a functionality that differs from imines in terms of electronics and reactivity. They are less basic than the parent imine due to electron-rich oxygen being in close proximity to nitrogen, drawing electron density from nitrogen. The pK_a (DMSO) of 5.1 for the protonated oxime[34] versus 5.5 for the iminium[35] is representative of this. Additionally, while the nitrogen is the only nucleophilic atom in an imine, an oxime has both a nucleophilic oxygen and nitrogen and can cause chemoselectivity issues in the presence of electrophiles. With intramolecular alkyne annulation reactions, both *6-endo dig* and *5-exo dig* ring closures are allowed based on Baldwin's findings, and with the appropriate systems an oxime may give a mixture of these products.

Similar to the work of Larock previously discussed is that of both the Shin [36] and Wu [37] groups, who have used the oxime functionality to perform intramolecular annulation reactions with alkynes giving isoquinoline *N*-oxides (eq 1.13).

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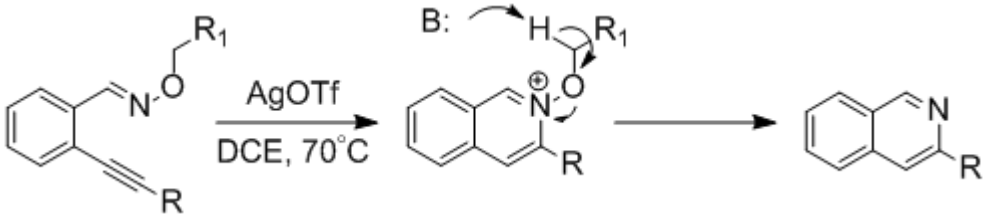
[34] Politzer, P.; Murray, J. S. Some intrinsic features of hydroxylamines, oximes and hydroxamic acids: Integration of theory and experiment. In *The Chemistry of Hydroxlamines, Oximes and Hydroxamic Acids: Part 2*; Pappoport, Z; Liebman, J. F., Eds.; Wiley: West Sussex, **2009**; p.23.
[35] Brown, H. C.; Braude, E. A. Nachod, F. C. in *Determination of Organic Structures by Physical Methods*, Academic Press, New York; **1955**.
[36] a) Yeom, H-S.; Kim, S.; Shin, S. *Synlett*. **2008**, *6*, 924.; b) Hwang, S.; Lee, S.; Lee, P. H.; Shin, S. *Tet .Lett.*, **2009**, 2305.

Shin has utilized both silver(I) and gold(I) sources to promote a chemoselective, *6-endo dig* annulation with an oxime nitrogen. Depending on whether a free OH-oxime or oxime ether is used, the isoquinoline *N*-oxide or isoquinoline may be isolated.

(1.13)

Following aromatization in the latter systems, an acidic α-proton on the oxime ether may be deprotonated by an added base to generate either an aldehyde or ketone and the free isoquinoline (eq 1.14). This route is impossible with a free-OH oxime unless further manipulations are employed to remove the oxygen.



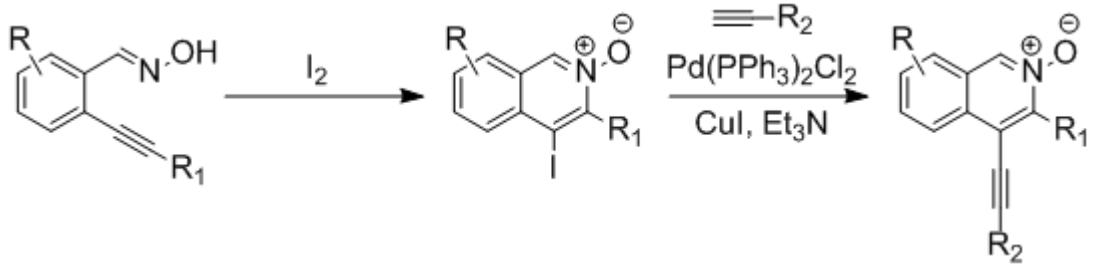
(1.14)

1.2.5e Yamamoto & Wu Isoquinoline Syntheses

The Yamamoto[38] and Wu[39] groups independently used identical precursors to Shin but rather than a metal-catalyzed alkyne activation they used halogens such as iodine just as Larock**Error! Bookmark not defined.**,[31] had done with imine systems. The added benefit to the inclusion of an aromatic halogen is the potential to do further cross-coupling reactions, rapidly increasing structural complexity (eq 1.15).

---

[37] a) Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850.; b) Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702.
[38] Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531.
[39] Ding, Q.; Wu, J. *Adv. Synth. Catal* **2008**, *350*, 1850.



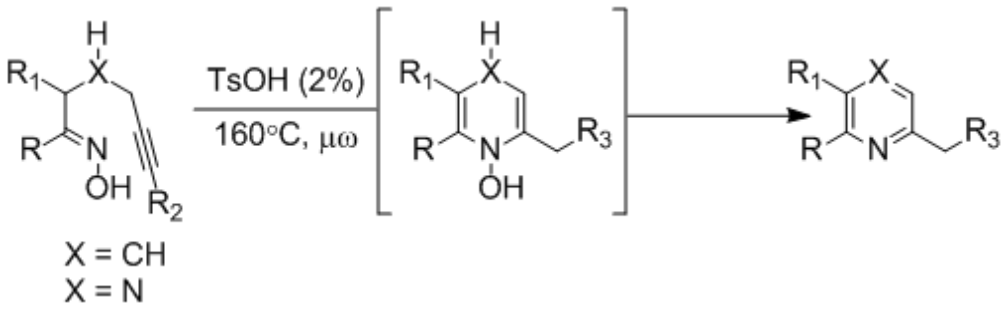
(1.15)

These examples all indicate that oximes are stable systems, but with the appropriate conditions they can be coaxed to react in an intramolecular fashion with an alkyne providing nitrogen heterocycles including a variety of fused heteroaromatic systems like isoquinolines. Despite the advances in heterocycle synthesis that have been highlighted within the recent literature, there are no examples of annulations towards pyridines using oximes and alkynes using metal catalysis.

1.3.1 Aim of the Project

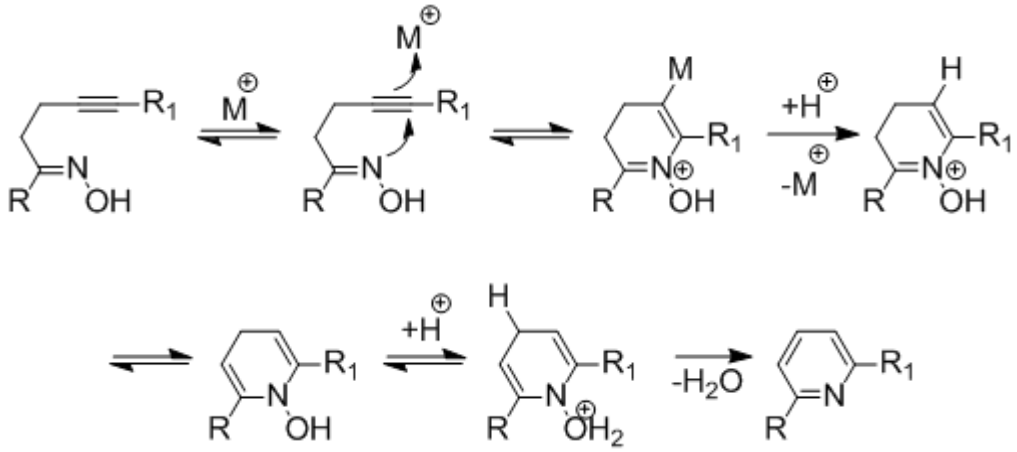
Our primary goal for heterocyclic synthesis was to be able to access 6-membered aromatic, nitrogen-containing heterocycles (pyridines specifically) using intramolecular, metal-catalyzed annulations of oximes onto alkynes. Initial efforts towards these heterocycles were intended to expand upon the previous work done by Mr.Toni Rizk, which involved the intramolecular microwave-assisted hydroamination of alkynes under Bronsted acid catalysis (eq 1.16).[40]

[40] Rizk, T.; Bilodeau. E. J. -F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8325.



(1.16)

In contrast, with π-acids it was envisioned that a metal-promoted nucleophilic attack of the oxime nitrogen onto the alkyne would close the desired 6-membered ring via a *6-endo dig* annulation (eq 1.17). With this intermediate two of the required unsaturations for aromaticity would already be present from the parent oxime precursor. Following protodemetalation of the vinyl-metal species and isomerization of the *N*-oxide to a di-enamine, the final aromatization step should occur following protonation of the oxygen and the loss of one equivalent of water. The driving force which would allow for the desired pyridines to be accessed would then be the loss of water to provide the final unsaturation needed for aromaticity.



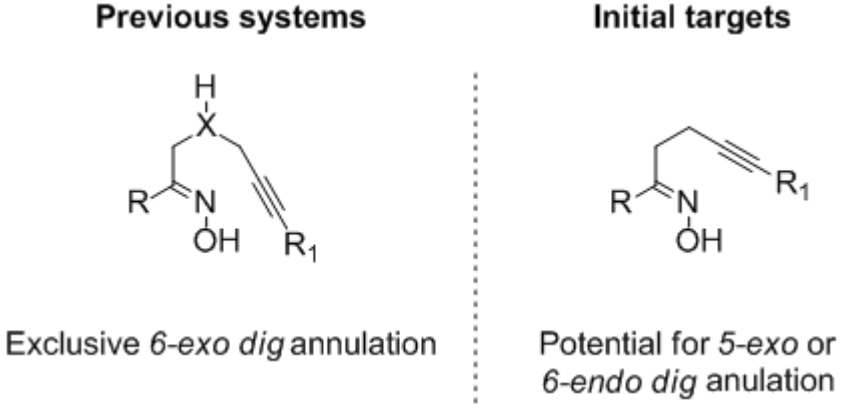
(1.17)

2

Formation of Pyridines Via 6-endo-dig Annulation

2.1. The *6-endo dig*, Metal-catalyzed Synthesis of Pyridines

The primary goal of this project has been to expand upon the research done by Mr.Toni Rizk involving the microwave assisted *6-exo dig* annulation of oximes onto alkynes to yield pyridines and pyrimidines. The new route would ideally provide alternative and mild reaction conditions towards the synthesis of pyridines. Metal catalysis was considered as a method to accomplish this and the main objective was to access a *6-endo dig* annulation process. To this end 1,4-alkynyl oximes were initial synthetic targets and are analogous to those previously synthesized (eq 2.1).



(2.1)

Competition between these pathways was expected, however the ability to guide the nucleophilic attack of the oxime onto the alkyne with good regiocontrol was considered to be a worthwhile area of investigation. In addition, the initial substrate targets could be accessed more readily than the parent 1, 5- systems.

As discussed previously, the metal-free route to pyridines and pyrazines went through a *6-exo dig* route exclusively and identification of a model substrate was the first aim of the project. Initial synthetic efforts were guided towards the synthesis of the simplest linear oxime-alkyne systems.

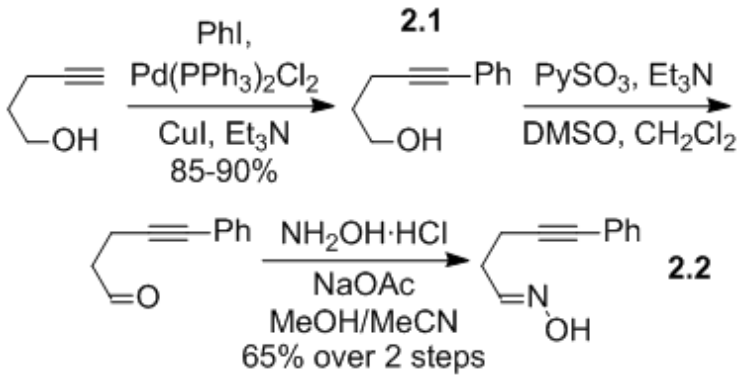
2.2. Preparation of Substrates

An initial investigation into the synthesis of simple pyridine derivatives began with the synthesis of precursor **2.2** (Scheme 2.1). This substrate was chosen as a target because Mr.Toni Rizk found that the analogous aldehydes with terminal alkynes attached were volatile, but substitution reduced the volatility of these compounds. Also 2-phenylpyridine resulting from a successful *6-endo dig* annulation of this precursor would be easy to identify due to the commercial availability of this heterocycle.

The synthetic pathway that we developed utilized 4-pentyn-1-ol as a starting point, which was readily converted into 5-phenyl-4-pentyn-1-ol (**2.1**) by a Sonogashira cross-coupling reaction with iodobenzene.[41]

[41] Lin, G.; Yang, C.; Liu, R. *J. Org. Chem*. **2007**, *72*, 6753.

Conversion of the resulting primary alcohol to the aldehyde via a Parikh-Doering oxidation with pyridine-sulfur trioxide, followed by oxime condensation using the crude aldehyde and hydroxylamine hydrochloride afforded the desired precursor oxime **2.2.**



Scheme 2.1. *Synthesis of aldoxime precursor **2.2***

2.3 Results and Discussion

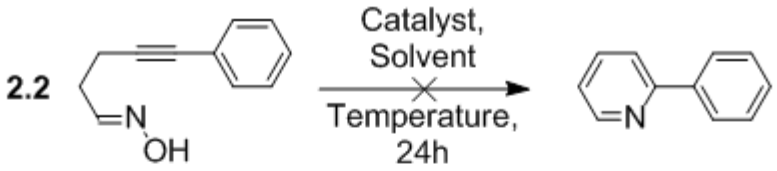
A good starting point for the π-acid catalyzed annulation of precursor **2.2** came from previous reports on the use of soft π-acids $AgNO_3$ and CuI, which have been shown to be ideal candidates for the activation of the internal alkyne towards *6-endo dig* annulation.[42] The cyclization reaction was attempted by refluxing solvent in a sealed tube with the respective potential catalysts.

Sodium tetrachloroaurate dihydrate was tested for its use as a source of gold(III), which is known for its ability to act as a soft π-acid.[43] At the same time $AgNO_3$ was tested again in refluxing dichloromethane. After 24 hours at reflux the starting oxime

[42] Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Comm.* **2009**, 5075., b) Patil, N. T.; Yamamoto, Y. *Arkivoc* **2007**, 6.
[43] Nieto-Oberhuber, C.; Paz Munoz, M.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402.

was recovered from all of these mixtures, suggesting that the thermal conditions were not sufficient to promote the annulation reaction. Higher temperatures were avoided to minimize any potential decomposition pathways. A third set of conditions using either palladium(II) acetate or palladium(II) chloride in dimethylformamide were tested (Table 2.1) with no success.

Table 2.1. *Attempts to cyclize aldoxime precursor* ***2.2***



Entry	Catalyst	Solvent	Temperature (°C)	NMR Yield (%)
1	$AgNO_3$ (5 mol%)	CH_2Cl_2	52	0
2	$AgNO_3$ (5 mol%)	$CHCl_3$	100	0
3	CuI (10 mol%)	DMF	130	0
4	$NaAuCl_4 \cdot 2H_2O$ (5 mol%)	CH_2Cl_2	52	0
5	$Pd(OAc)_2$ (5 mol%)	DMF	130	0
6	$PdCl_2$ (5 mol%)	DMF	130	0
7	Au-NHC	CH_2Cl_2	40	0
8	$[Cp^*RhCl_2]_2$	CH_2Cl_2	40	0

Finally, the Au-NHC and cyclopentadienyl rhodium(III) chloride catalysts (Figure 2.1) were employed to take advantage of either gold(I)'s special ability to coordinate to alkynes,[44] or rhodium(III)'s ability to allow for the migratory insertion of

[44] Rasika Dias, H .V.; Flores, J. A.; Wu, J.; Kroll, P. *J. Am. Chem. Soc.* **2009**, *131*, 11249.

an internal alkyne to give 2,3-substituted indoles.[45] These conditions did not provide 2-phenylpyridine at 40°C in CH_2Cl_2. Our attention was directed towards the use of silver catalysts as these were seen to be effective at promoting both *5-exo dig* and *6-endo dig* annulations.[46]

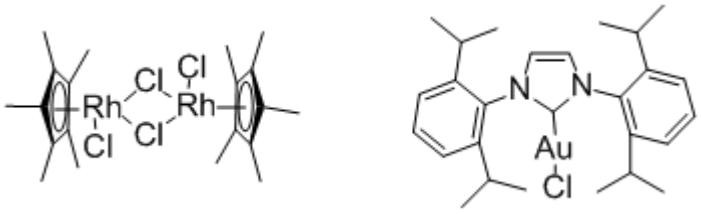
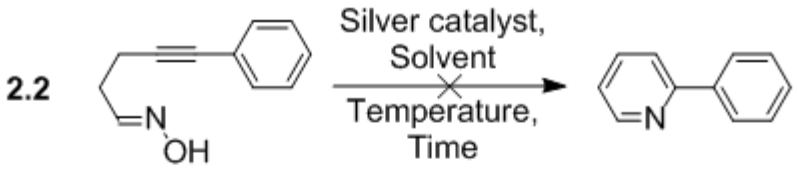


Figure 2.1. *Gold and rhodium catalysts employed for annulation attempts*

Our annulation attempts were initiated with silver catalysts including silver(I) trifluoromethansulfonate, tetrafluoroborate and hexafluoroantimonate (Table 2.2). Several catalysts were screened, however by TLC only AgOTf showed transformation of the starting material. Upon further inspection by proton NMR a mixture of unidentifiable products was obtained. Despite efforts to obtain 2-phenylpyridine after five days at reflux the product was not observed in the crude NMR or recovered following column chromatography.

[45] Huestis, M. P.; Chan, L.; Stuart, D. L.; Fagnou, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 1338.
[46] For annulations utilizing gold(I) catalysts see and references therein: a) Hashmi, A. S. K. *Gold Bulletin* **2003**, *1*, 3.; b) Hashmi, A. S. K. *Gold Bulletin* **2009**, *42*, 275.; c) Hashmi, A. S. K.; Ata, F.; Bats, J. W.; Blanco, M. C. *Gold Bulletin* **2007**, *40*, 31. d) Hashmi, A. S. K. *Gold Bulletin* **2004**, *37*, 51.

Table 2.2. *Screening of silver catalysts on oxime* ***2.2***



Entry	Catalyst (5 mol%)	Solvent	Temperature (°C)	Time	NMR Yield (%)
1	AgOTf	CH_2Cl_2	50	5d	0
2	$AgBF_4$	CH_2Cl_2	50	5d	0
3	$AgSbF_6$	CH_2Cl_2	50	5d	0
4	AgOTf	Acetone	r.t.	24h	0
5	AgOTf	Et_2O	40	24h	0
6	AgOTf	$CHCl_3$	40	24h	0
7	AgOTf	DMF	130	24h	0
8	AgOTf	DMSO	130	24h	0

The lack of conversion to the desired pyridine product and decomposition of the oxime **2.2** was believed to be due to the formation of stable intermediates that may be misdirecting the desired reaction. Microwave irradiation has been shown to be an efficient direct heating method compared to heating a sample in an oil or wax bath,[47] and it was believed that irradiation may allow for avoidance of substrate decomposition without deactivating the metal catalyst. Additionally, previous attempts by Mr.Toni Rizk to cyclize oxime **2.3** via a *6-exo dig* annulation (Figure 2.2) using Brønsted acids under microwave-assisted heating have been successful, and the use of a microwave was essential for these reactions.

[47] Alcázar, J., Diels, G.; Schoentjes, B. *Mini-Reviews in Medicinal Chemistry* **2007**, 7, 345.

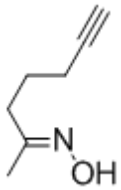
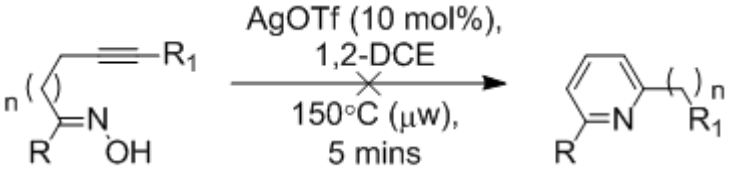


Figure 2.2. *Oxime precursor **2.3***

This led to an investigation whereby both precursors **2.2** and **2.3** were subjected to microwave heating at 150°C with 10 mol% of AgOTf. Oxime **2.3** was originally synthesized by Mr.Toni Rizk and purified prior to use. We were pleased to see complete conversion of substrate **2.2** to a new product in just 5 minutes, but unfortunately this product could not be isolated from the crude reaction mixture (Table 2.3).

Table 2.3. *Microwave-assisted annulation attempts of oximes **2.2** and **2.3***



Entry	n =	Oxime	R = , R_1 = , n =	NMR Yield (%)
1	1	**2.2**	H, Ph, 0	0
2	2	**2.3**	Me, H, 1	0

Oxime **2.3** simply decomposed using microwave heating with AgOTf rather than undergoing a *6-exo dig* annulation. When both reaction mixtures were spotted on TLC against 2-phenylpyridine and 2-methylpyridine the stain colour with *p*-anisaldehyde, UV illumination pattern (long- and short-wave) and R_f implied that we had not in fact formed the desired pyridines in either case.

Thus, the use of microwave heating was abandoned for the time due to unsuccessful attempts to isolate annulation products. The results at this time indicated that the annulation attempts thus far were unsuccessful, and decomposition pathways were the primary course of these reactions. While the conditions described above are taken directly from the literature, the structurally biased substrates used in the previously reported cyclizations do not allow the oxime and alkyne functionalities to have as many degrees of rotational freedom as oximes **2.2** and **2.3**. Also, the lack of conversion from substrate **2.2** to 2-phenylpyridine at various temperatures using catalysts that are well known to promote the intramolecular annulation of an alkynyl-oxime suggested that precursor **2.2** was not an optimal test substrate. 2-(3-Phenylprop-2-ynyl)cyclohexanone oxime was considered as a preliminary biased cyclic system for further annulation attempts because it causes the alkyne and oxime to reside in close proximity, similar to the systems of Larock and Shin (Figure 2.3).

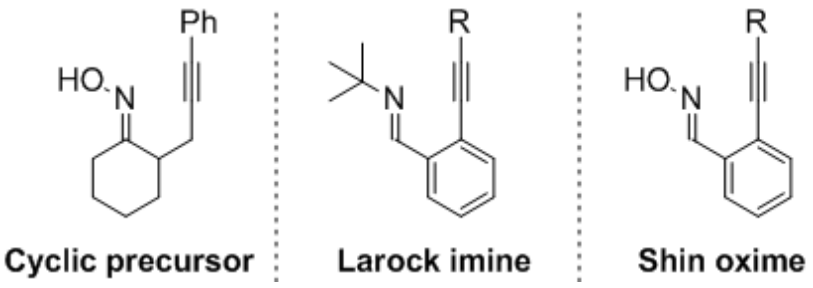


Figure 2.3. *Comparison of cyclic oxime to Larock and Shin's systems*

2.4. Preparation of Substrates

The initial route we envisioned to prepare the ketone precursor of oxime **2.6** involved an alkylation of cyclopentanone. The use of the Stork enamine approach with bromide **2.4** was used rather than alkylation via LDA and propargyl bromide in order to avoid polyalkylation and possible deprotonation of the alkyne under strongly basic conditions (Figure 2.4).[48]

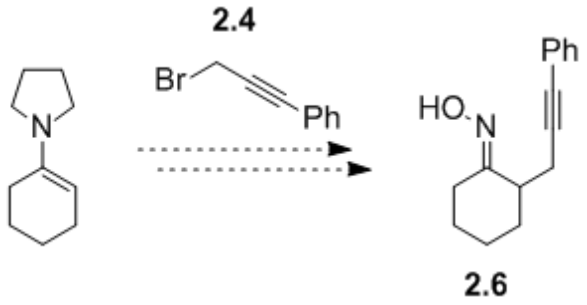
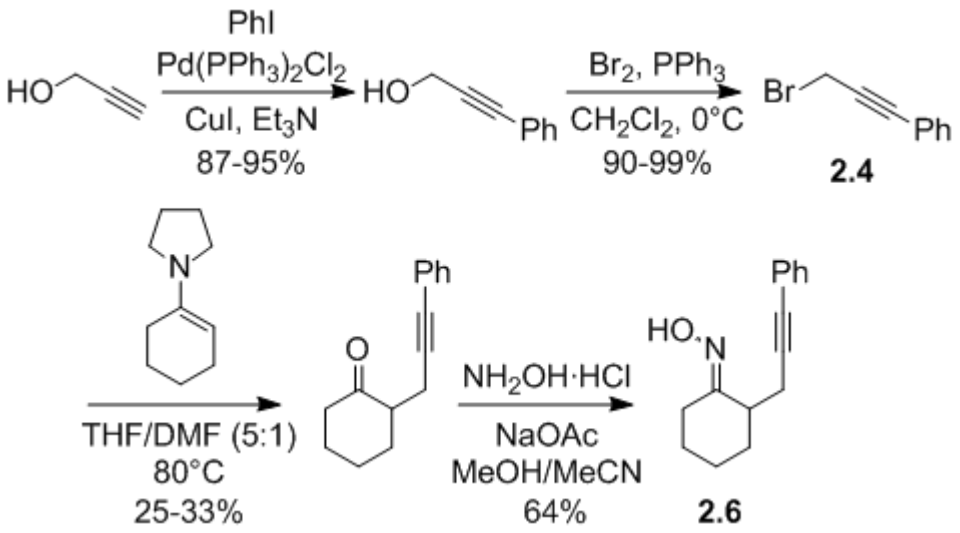


Figure 2.4. *Enamine alkylation route towards oxime **2.6***

For the alkyne substrate, propargyl alcohol was converted to the internal alkyne by a Sonogashira cross-coupling reaction. Conversion to the corresponding bromide using bromine and triphenylphosphine occurred without issue in a respectable 78% yield. A known procedure was used to generate the desired enamine derived from cyclohexanone.[49] however purification of this substrate by distillation proved to be difficult and did not work as outlined. In order to avoid hydrolysis of the enamine during workup, the alkylation step was performed using the crude enamine and pure (3-bromoprop-1-ynyl)benzene in a mixture of 5:1 THF and DMF.

[48] Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.
[49] Hayakawa, K.; Takewaki, M.; Fujimoto, I.; Kanematsu, K. *J. Org. Chem.* **1986**, *51*, 5100.

We were pleased to obtain the desired ketone **2.5**, albeit in 25% yield following purification. Oxime formation with hydroxylamine hydrochloride and NaOAc led to the oxime **2.6** in 64% yield (Scheme 2.2).

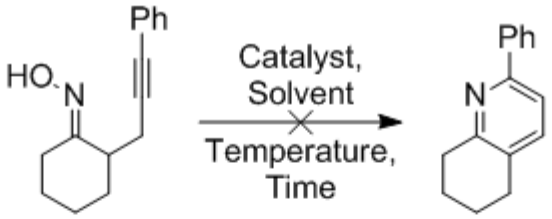


Scheme 2.2. *Synthesis of oxime precursor **2.6***

2.5. Annulation Attempts Using Cyclohexanone Oxime Derivative

With this structurally biased system in hand, the cyclohexanone oxime derivative was subjected to some literature-supported Lewis and Brønsted acids that had been previously tested on the acyclic oximes **2.2** and **2.3** (Table 2.4).

Table 2.4. *Annulation attempts for oxime* ***2.6***



2.6

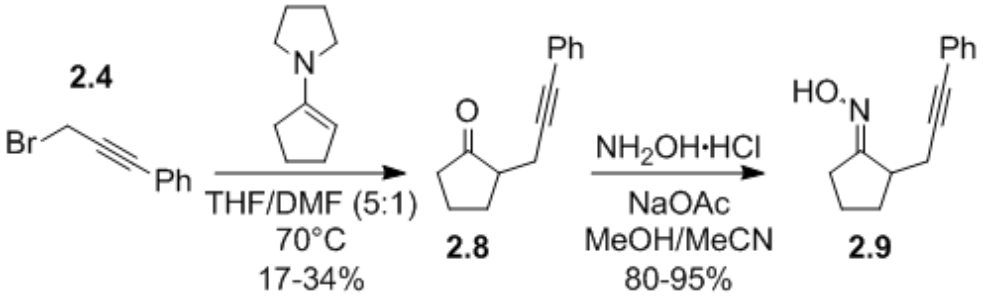
Entry	Catalyst (10 mol%)	Solvent	Temperature (°C)	Time	NMR Yield (%)
1	AgOTf	1,2-DCE	130	10h	0
2	CuI	DMF	100	24h	0
3	AuCl	CH_2Cl_2	70	18h	0
4	$Pd(OAc)_2$	DMF	100	18h	0
5	None	EtOH	100	22h	0
6	None	*i*-PrOH	160 (μw)	4h	0
7	TsOH	*i*-PrOH	160 (μw)	4h	0

Unfortunately none of the metal catalysts yielded any trace of the desired pyridine by TLC or NMR analysis, and precursor **2.6** was recovered in each instance. To better understand the results, molecular models were built to compare the cyclohexanone oxime derivative to the benzene derivative used by Larock, as well as precursor **2.2**. In the case of both 6-membered precursor **2.6** and acyclic oxime **2.2** the distil (*6-endo dig route*) alkyne carbon and oxime nitrogen atom are much closer in space than in Larock's system.

The transition state for this cyclization appeared to be too congested and the oxime nitrogen appeared to have a poor angle of attack on either of the anti-bonding π-orbitals of the alkyne (120°). This poor trajectory for nucleophilic attack may raise the barrier for cyclization such that annulation cannot occur.

2.6. Synthesis of Cyclopentanone Oxime Derivative

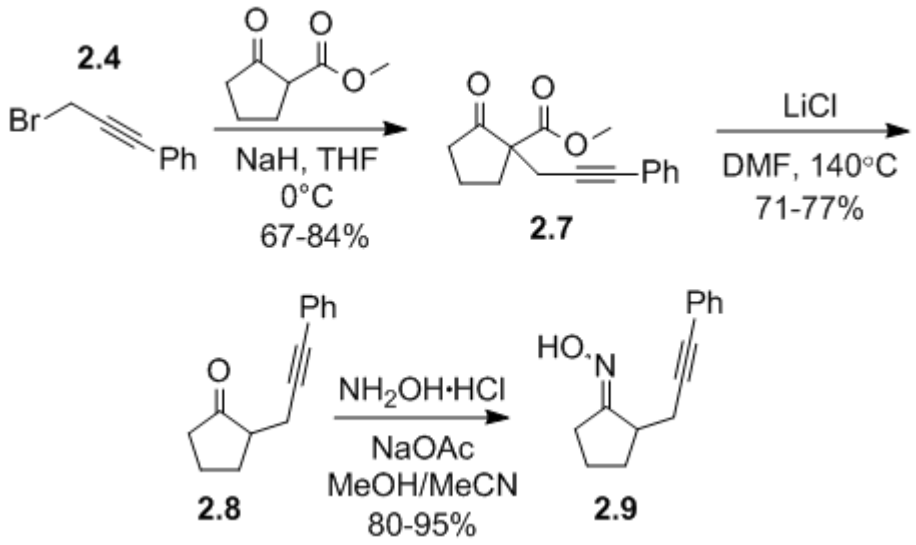
In an attempt to reduce steric strain in the transition state a molecular model of the homologous cyclopentanone oxime **2.9** was built and compared to precursors **2.2** and **2.6**. The alkyne and oxime positionings of **2.9** aligned almost perfectly with Larock's system, and the issues of crowding and poor angle-of-attack appeared to be solved on paper. Oxime precursor **2.9** was originally synthesized in a similar fashion to precursor **2.6** in 39% overall yield over 4 steps (Scheme 2.3).



Scheme 2.3. *1st route to oxime **2.9***

Alternatively a new alkylation-decarboxylation sequence was developed to access this oxime derivative. Alkylation of Methyl 2-cyclopentanonecarboxylate using a suspension of NaH in THF accessed Methyl 2-oxo-1-(3-phenylprop-2-yn-1-yl)cyclopentanecarboxylate **2.7** following chromatography.

Following Krapcho decarboxylation to provide ketone **2.8** and oxime condensation precursor **2.9** was obtained in 61% overall yield over three steps (Scheme 2.4).



Scheme 2.4. *2nd route to oxime **2.9***

2.7. Annulation of Cyclopentanone Oxime Derivative

Gratifyingly the cycolpentanone oxime underwent annulation to pyridine **2.10** with 5 mol% of AgOTf catalyst and mild heating in 65% NMR yield with the unreacted starting material accounting for the remaining mass. Other catalysts were screened and the results of this preliminary work are presented in Table 2.5.

Table 2.5. *Annulation results using oxime* ***2.9***

Entry	Metal	NMR Yield (%)
	Silver	
1	None	0
2	AgOTf (5 mol%)	65
3	AgOTf (10 mol%)	75
4	AgOTf (5 mol%) + 10 equiv. H_2O	25
5	AgOTf (5 mol%) + 4Å MS	50
6	AgOTf (5 mol%) + $MgSO_4$	28
7	AgOTf (5 mol%) + 1 equiv. product	27
8	AgOTf (5 mol%) + 1 equiv. K_2CO_3	3
9	$AgNO_3$ (5 mol%)	39
10	AgOTf (5 mol%)/ AuCl (5 mol%)	43
11	$AgBF_4$	55
12	$AgSbF_6$	55
	Gold	
13	AuCl (5 mol%)	34
14	$AuCl_3$ (10 mol%)	51
15	Au-NHC (5 mol%)	0
	Palladium	
16	$Pd(OAc)_2$ (10 mol%)	50
17	$Pd(OAc)_2$ (10 mol%) [a]	0
18	$PdCl_2$	0

Conditions: 0.5 mmol oxime, 1,2-DCE, 70°C, 0.2M
[a] Solvent: 1) DMF, 2) DMSO, 3) Benzene or 4) EtOH
Note: 5 mol% of CuI, CuBr, $PtCl_2$, $Rh_2(OAc)_4$, $Hg(OAc)_2$ or 1.1 equiv. TFA, HOTf, CSA did not promote annulation

initial results revealed that silver (Table 2.5, entry 1) and gold (Table 2.5, entry 13) sources as well as $Pd(OAc)_2$ (Table 2.5, entry 16) were all competent catalysts that were able to affect the *6-endo dig* annulation. Other metal additives and sources of acid were unable to promote the annulation reaction. No traces of the alternative *5-exo dig* annulation were detected by NMR and the lack of complete conversion of oxime **2.9** to pyridine **2.10** using silver and gold was attributed to catalyst decomposition over time via reduction of the metal. After one hour of heating with silver and gold catalysts visible traces of the elemental metals were observed coating the walls of the reaction flask. Palladium did not suffer from this this issue but appeared to be dependent on the counter anion and highly solvent dependent (Table 2.5, entry 17)

The moderate improvement in yield when going from 5 to 10 mol% AgOTf (Table 2.5, entry 3) suggested that product inhibition of the catalyst was occurring. Significantly, addition of one equivalent of the desired pyridine prior to heating the reaction (Table 2.5, entry 7) lowered the number of catalyst turnovers and may be due to coordination of the pyridine nitrogen to silver. The effect of water on the reaction was also investigated with 10 equivalents of water added to the standard reaction mixture and AgOTf as the catalyst (Table 2.5, entry 4). It was observed that water inhibits the reaction and within one hour there was significantly more deposition of the silver catalyst.

After 4 hours the annulation was unable to proceed any further and to counteract the effect of water either molecular sieves (Table 2.5, entry 5) or $MgSO_4$ (Table 2.5, entry 6) were added separately. While molecular sieves increased the NMR yield compared to the trial using water, silver plating on the sieves was accelerated. Similarly $MgSO_4$ accelerated decomposition of the silver catalyst and cause little improvement in NMR yield compared adding water. Both of these results may be due to the increased surface area available for the catalyst to deposit onto. Finally, K_2CO_3 stalled the reaction completely and may be a result of an increased oxime isomerization rate (Table 2.5, entry 3).

As catalyst inhibition by the product was occurring, a hypothesis was that an added acid would protonate the Lewis basic nitrogen of the pyridine and prevent coordination to the catalyst. Additionally, an acid was thought to be able to facilitate the proposed protodemetallation step (Figure 2.5).

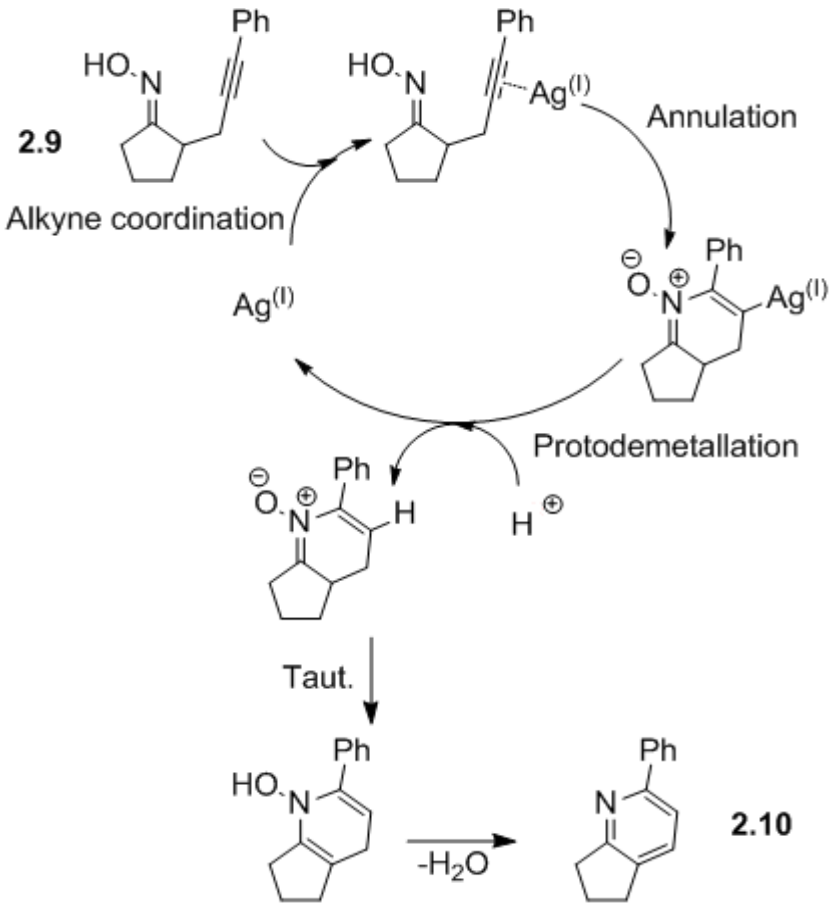
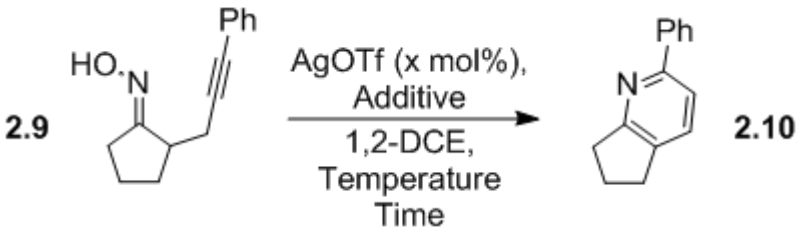


Figure 2.5. *Proposed catalytic cycle leading to pyridine **2.10***

An initial coordination of silver to the alkyne activates the alkyne towards nucleophilic attack by the oxime nitrogen in a *6-endo dig* annulation. A proton source is then used in a protodemetallation step of the vinyligous nitrone, regenerating silver(I) for use in the catalyst cycle. Following tautomerization of the vinyligous nitrone and loss of one equivalent of water the pyridine is formed. Trifluoroacetic acid was tested as an additive to assist in the protodemetallation step and found to significantly improve NMR yields for silver catalysts (Table 2.6). Indeed, 1.25 and even catalytic amounts (0.1 equivalents) of TFA were able to minimize catalyst inhibition and provide excellent yields. Further studies using other

substrates were performed using an excess of the acid in order to insure that issues of catalyst inhibition by the pyridine products was minimized. Despite the presence of high catalyst activity silver deposition was still observed.

Table 2.6. *Screen of additive, temperature and time conditions*



Entry	Additive	Conditions	NMR Yield (%)
1	None (5 mol% AgOTf)	70°C, 17h	67
2	None (10 mol% AgOTf)	70°C, 17h	75
3	1.25 equiv TFA	70°C, 17h	97
4	1.1 equiv TFA	70°C, 17h	89
5	0.1 equiv TFA	70°C, 17h	90
6	0.1 equiv TFA	50°C, 17h	50
7	0.1 equiv TFA	70°C, 5h	23

The decomposition pathway for the catalyst has not been explored but may occur via initial tautomerization of the oxime to a vinyl hydroxylamine (Figure 2.6). Silver(I) catalysts in the presence of hydroxylamines have been shown to be reduced to the elemental metal,[50] releasing nitrogen gas and water. This may

[50] a) Nichols, M. L. *J. Am. Chem. Soc.* **1934**, *56*, 841.; b) James, T. H. *J. Am. Chem. Soc.* **1939**, *61*, 2379.

account for the silver deposition seen during annulation attempts, although the mechanism is not well understood.

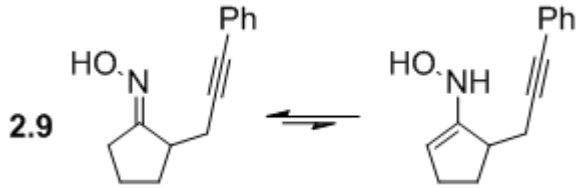
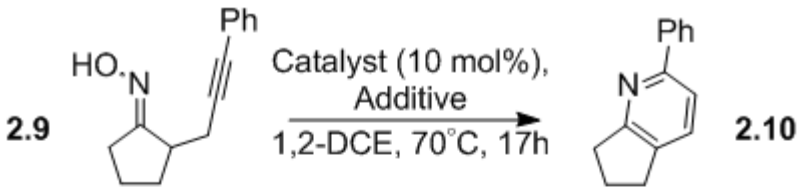


Figure 2.6. *Enamine of oxime **2.9***

When acid is added to the reaction, it is proposed that the amount of vinyl hydroxylamine present in solution is increased. Thus, under acidic conditions both the decomposition pathway for silver and the protodemetallation steps are enhanced, but the latter rate is thought to be accelerated to a greater extent than decomposition via the vinyl hydroxylamine. Both the temperature and reaction time were lowered from 70°C and 17h respectively but with significantly reduced NMR yield. using 1.1 equivalents of TFA as an additive the silver, gold, palladium and mercury catalysts were re-tested and appear in Table 2.7.

Table 2.7. *Effect of TFA additive on catalysts*



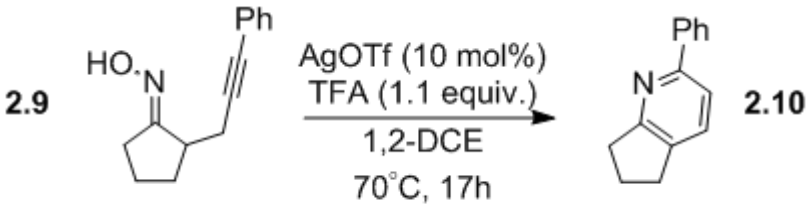
2.9 **2.10**

Entry	Catalyst	Additive	NMR Yield (%)
1	AgOTf	None	65
2	AgOTf	TFA (1.1 equiv.)	89
3	AuCl	None	34
4	AuCl	TFA (1.1 equiv.)	76
5	$Pd(OAc)_2$	None	50
6	$Pd(OAc)_2$	TFA (1.1 equiv.)	0
7	$Hg(OAc)_2$	None	0
8	$Hg(OAc)_2$	TFA (1.1 equiv.)	89

Encouragingly the NMR yield using AuCl as a catalyst increased significantly with TFA present, but the catalyst still decomposed to the pure metal over time. Both palladium and mercury were found to be highly dependent on the presence of TFA. Palladium acetate was completely deactivated with TFA present, whereas mercury acetate required TFA to provide any of the desired pyridine. Despite the optimistic results found with gold, palladium and mercury, AgOTf was ultimately chosen as a catalyst to continue optimization of annulation conditions using oxime **2.9** since it was able to provide good yields of the corresponding pyridine with or without TFA.

A solvent scan was conducted and appears in Table 2.8. DCE and $CDCl_3$ give comparable yields but EtOH was found to be superior at promoting annulation. Proton transfer may be facilitated with EtOH and the trend in yields supports this hypothesis.

Table 2.8. *Solvent scan*

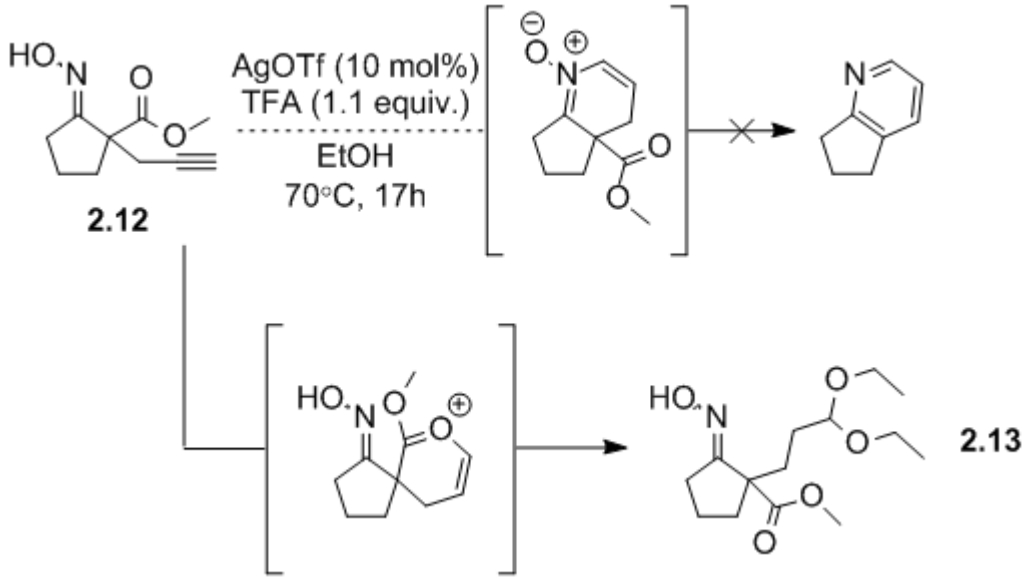


Entry	Solvent	NMR Yield (%)
1	1,2-DCE	89
2	Benzene	65
3	MeCN	50
4	$CDCl_3$	89
5	EtOH	95

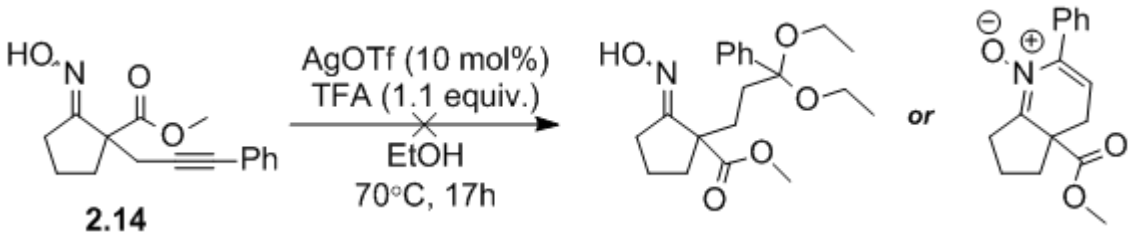
Protic solvents in the presence of acid and π-acids (Au and Hg) are known to promote alkyne hydration, which is not a novel annulation transformation.[51] Evidence that this mechanism may be assisting the annulation was observed following attempts to trap a proposed vinyl nitrone reaction intermediate using oxime **2.12** with EtOH as a solvent. Instead the product resulting from the anti-Markovnikov hydration product (**2.13**) was obtained (Scheme 2.5).

[51] Nun, P.; Dupuy, S.; Gaillard, S.; Poater, A.; Cavallo, L.; Nolan, S. P. *Catal. Sci. Technol.* **2011**, *1*, 58.

When oxime **2.14** was subjected to the same conditions the alkyne remained untouched and may be due to the increased steric bulk of a phenyl alkyne versus a terminal alkyne (Scheme 2.6). From this point DCE was used as a solvent for further test reactions.



Scheme 2.5. *Attempt to isolate a vinyl nitrone intermediate*



Scheme 2.6. *Oxime **2.14** hydrolysis attempt*

The substituent on the alkyne was varied since the stereoelectronics of the alkyne have been shown to influence the type of annulation possible, with *5-exo dig* preferred when alkyl groups are present.[52] Terminal (**2.19**) and methyl (**2.20**) oximes were synthesized according to the alkylation-decarboxylation route previously discussed. The ketones **2.17** and **2.18** were obtained following decarboxylation from ketoesters **2.11** and **2.16** in 29% and 42% yield overall respectively (Figure 2.7 & 2.8).

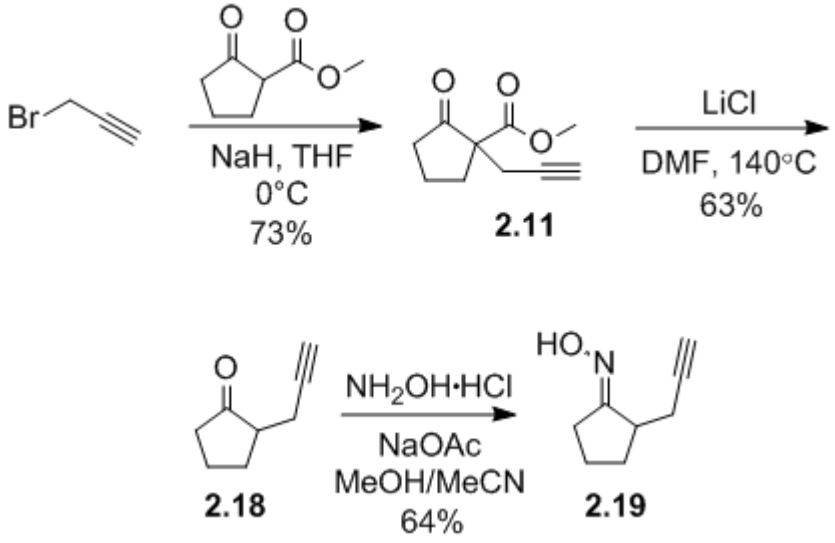


Figure 2.7. *Route to oxime **2.19***

[52] Hashmi, A. S. K.; Schuster, A. M.; Schmuck, M.; Rominger, F. *Eur. J. Org. Chem.* **2011**, 4595.

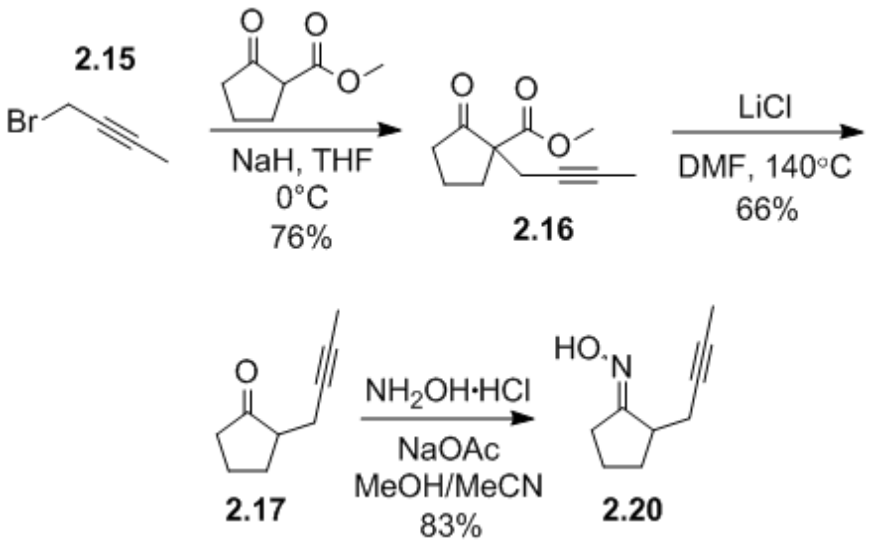


Figure 2.8. *Route to oxime **2.20***

Additionally, the 7-membered oxime **2.22** (Figure 2.9) was synthesized via the pyrrolidine enamine route originally developed in 24% yield overall.

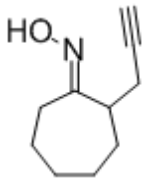
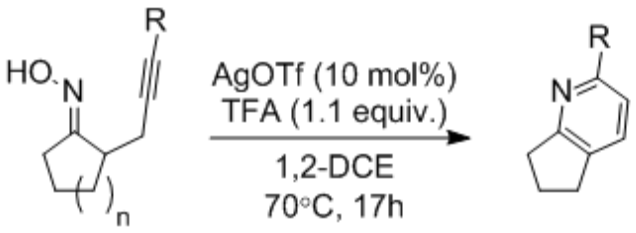


Figure 2.9. *Oxime **2.22***

All of oximes **2.19**, **2.20** and **2.22** were subjected to the conditions previously developed and the results appear in Table 2.9 below. The substitution of the alkyne was shown only to have an effect on the yield of the reaction but not on the type of ring closure (*endo* vs. *exo*). The low isolated yields for these systems were likely due to the volatility of the methyl and unsubstituted pyridines, as well as the polarity of these products due to a lack of steric bulk near the pyridine nitrogen.

The pyridines **2.23** and **2.24** from *6-endo dig* annulation were the only products detected by crude NMR following isolation by column chromatography. Neither 6- or 7-membered oxime precursors showed successful annulation and only decomposition occurred under these conditions. The specificity of these conditions to promote annulation exclusively in 5-membered oxime precursors was evidence supporting the hypothesis of crowding in the transition state of the annulation reaction.

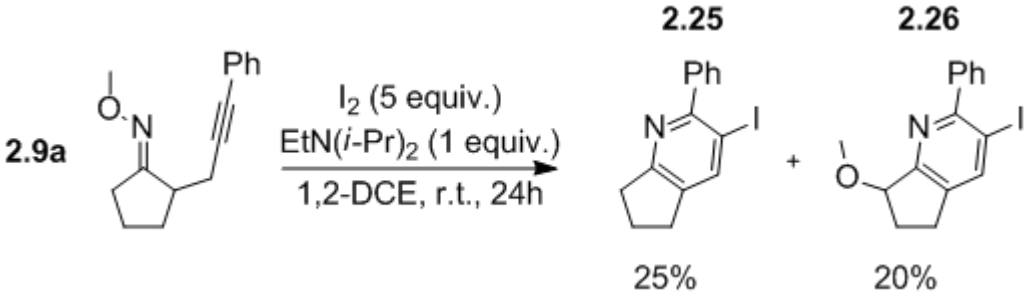
Table 2.9. *Annulation results using oximes **2.6**, **2.19**, **2.20** and **2.22***



Entry	n =	Oxime	Substitution (R=)	NMR yield (%) (isolated yield)	Pyridine
1	1	**2.19**	H	81 (50)	**2.23**
2	1	**2.20**	Me	50 (29)	**2.24**
3	2	**2.6**	Ph	0	x
4	3	**2.22**	H	0	x

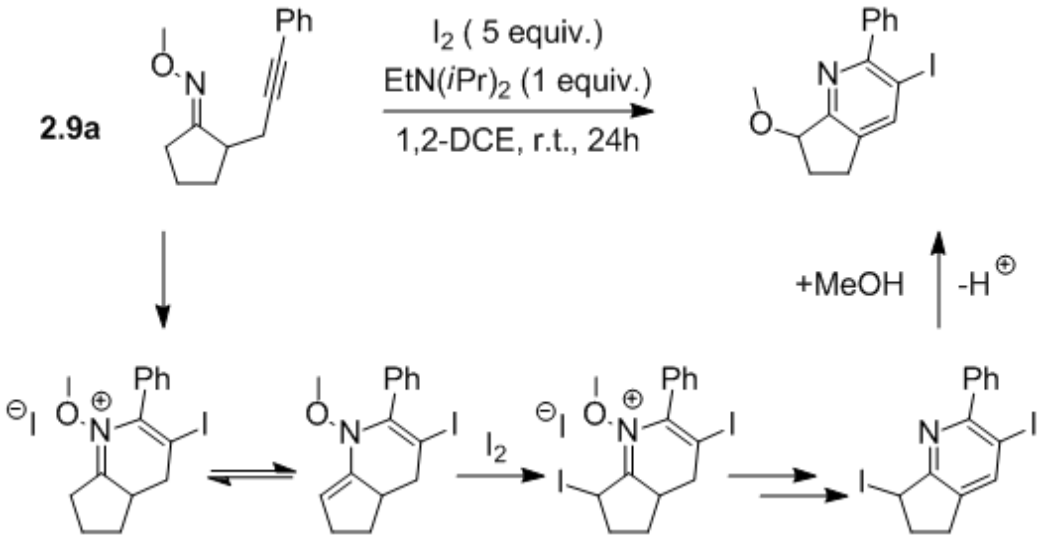
Finally, annulation reactions initiated by stoichiometric amounts of electrophiles such as ICl and iodine performed by Larock led us to believe that iodine may activate the alkyne towards nucleophilic attack by the oxime nitrogen in a similar fashion to metal catalysis. The products of a successful annulation are ideal substrates for further elaboration via cross-coupling reactions.

Oxime **2.9a** was synthesized from the corresponding ketone **2.8** using *O*-methyl hydroxylamine hydrochloride in 85% yield. This substrate was then treated with 5 equivalents of iodine and EtN(*i*-Pr)$_2$ at room temperature in DCE, giving a mixture of products shown in Scheme 2.7.



Scheme 2.7. *Iodine-promoted annulation of oxime* ***2.9a***

The expected pyridine **2.25** incorporating one iodine was isolated in 25% yield, but the side product pyridine **2.26** was also obtained in 20% yield following column chromatography. This product may be the result of the excess iodine in solution and is proposed to form via iodination of an intermediate enamine, followed by nucleophilic attack of methanol generated *in situ* following aromatization (Scheme 2.8). When the reaction was performed using 1 equivalent of iodine no aromatization products were obtained and an excess of the electrophile seems to be necessary.



Scheme 2.8. *Proposed mechanism leading to pyridine **2.26***

The mixture of products obtained following annulation with iodine as a method of alkyne activation was not encouraging and metal catalysis was used for further annulation experiments.

To summarize this chapter, the failure to promote annulation of the initial acyclic (**2.0** and **2.1**) and cyclic (**2.6** and **2.22**) oxime precursors using metal catalysis via either a *5-exo dig* or *6-endo dig* route coupled with the successful *6-endo dig* annulation of 5-membered precursors (**2.9**, **2.19**, **2.20**) revealed a substrate specificity towards cyclic (5-membered) systems. In order to see if the scope of the reaction could be broadened using the conditions developed for these conformationally restricted systems, the preparation of acyclic oxime-alkyne analogues was the next step toward developing a synthetically useful methodology leading to pyridines. The next chapter expands upon the research previously discussed and reintroduces oxime-alkyne systems lacking a ring system with the results of these annulation attempts.

3

Formation of N-hydroxy Pyrroles Via 5-exo-dig Annulation

3.1. Introduction

The ability to predict and control the outcome of a reaction is the major goal of chemistry. When considering metal-catalyzed intramolecular alkyne annulations all of the factors leading to a reaction's regioselectivity can be a major roadblock in understanding how to control the product distribution. Often a catalyst screen is performed to determine the optimal procedure to a desired product. It is not only the catalyst that can control which product is obtained from a reaction. Previous reports have shown that changing the solvent can alter the product distribution to favour one annulation product over another, although traces of side-products are common (Figure 3.1).[53]

[53] a) Hessian, K.O. ; Flynn, B. L. *Org. Lett.* **2006**, 8, 243.; b) Halim, R.; Scammells, P.J.; Flynn, B.L. *Org. Lett.* **2008**, 10, 1967.

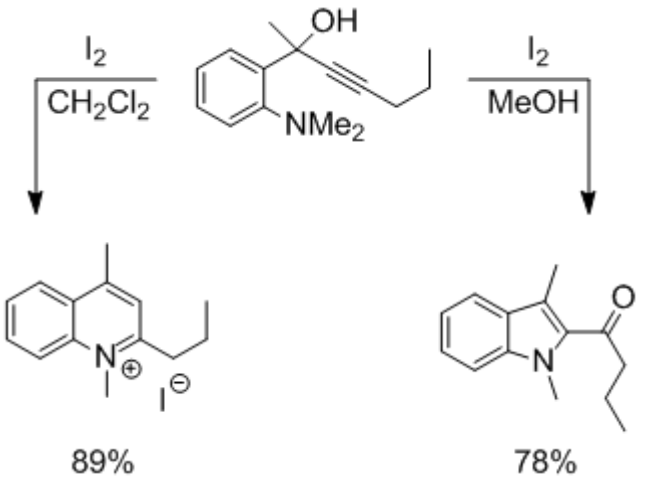


Figure 3.1. *Product control by modification of solvent*

When regiochemical control of a reaction is desired it is important to consider the required geometry leading to the transition state. With an understanding of these factors control of the necessary molecular conformation may be favoured with an appropriate catalyst. Even when a catalyst provides regioselectivity, regiospecificity is difficult to obtain.

In a recent review that focused on revising Baldwin's rules for alkyne annulation reactions leading to *N*-heterocyclic structures suggested that the orbital alignment requirements for ring closure can be substrate-dependent. Despite this finding, regiospecificity in alkyne annulation reactions may be obtained through an understanding of the reaction mechanism. Thus for alkyne annulations choosing appropriate catalysts to force the required geometry may provide either of the favoured *5-exo* or *6-endo-dig* pathways.[54]

[54] Gilmore, K.; Alabugin, I.V. *Chem. Rev.* **2011**, DOI: 10.1021/cr200164y

With the alkynyl-oxime systems used in this project the revised Baldwin rules for alkyne annulation reactions predicts that *5-exo* and *6-endo dig* ring closures are favourable with electrophilic activation of the alkyne by a metal (Figure 3.2).

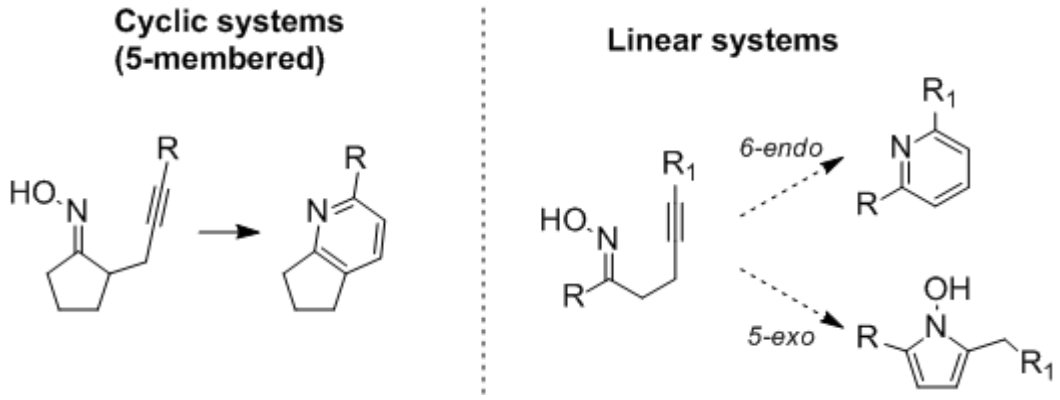


Figure 3.2. *Potential divergent reactivity of acyclic oximes*

The correct number of unsaturations are present to provide pyridines via a *6-endo dig* annulation with the loss of water allowing for aromatization. Alternatively, a *5-exo dig* annulation route does not require installation of a third unsaturation. The product of the reaction is then an *N*-hydroxy pyrrole, which are uncommon aromatic heterocycles found in two general structures: 1) fused to a second aromatic ring, 2) heavily substituted on the ring with at least one electron-withdrawing group (Figure 3.3).

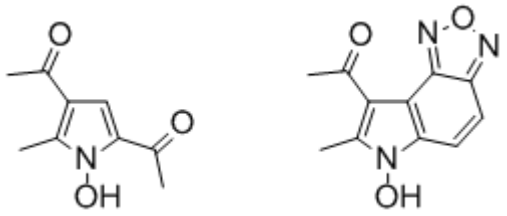


Figure 3.3. *Two selected N-hydroxy pyrrole motifs*

Currently there are fewer than 30 commercially available *N*-hydroxy pyrroles. A few examples of known natural products and drug targets contain this heterocyclic structure (Figure 3.4).[55]

If access to a mixture of *5-exo* and *6-endo dig* products can be obtained, then the hope was that regiocontrol of the ring closure could be provided by variation of the metal catalyst or ligand used as discussed previously.

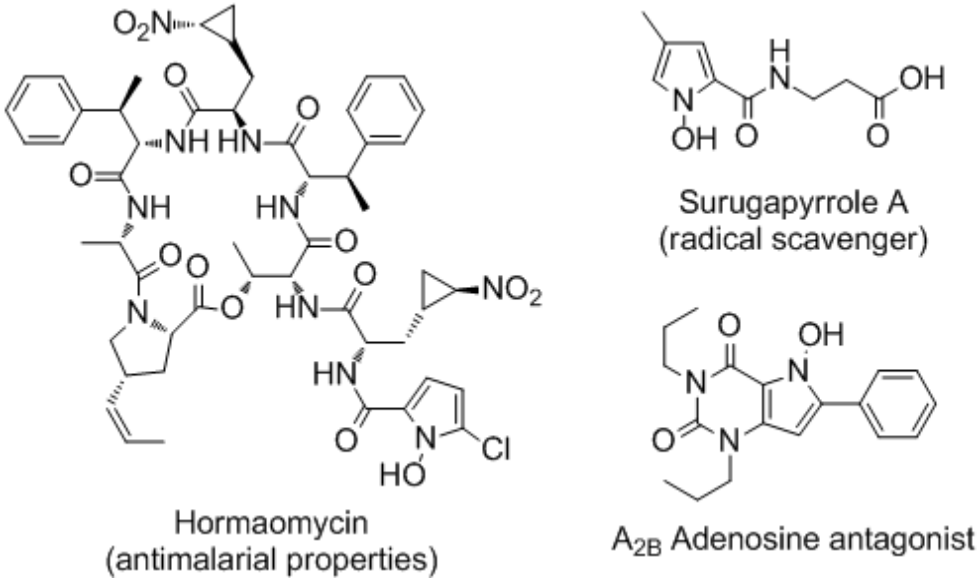


Figure 3.4. *Natural products and drug targets containing N-hydroxy pyrrole moiety*

[55] a) Reinscheid,U. M.; Zlatopolskiy, B.D.; Griesinger, C; Zeeck, A.; de Meijere, A. *Chem. Eur. J.* **2005**, *11*, 2929. b) Sugiyama, Y.; Watanabe, K.; Hirota, A. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 230; c) Carotti, A.; Stefanachi, A.; Raviña, E.; Sotelo, E.; Loza, M.I.; Cadavid, M.I.; Centeno, N.B.; Nicolotti, O. *Eur. J. Med. Chem.* **2004**, *39*, 879.

3.2. Goals

With the discovery of a regioselective *6-endo dig* annulation performed using conformationally locked 5-membered "cyclic" oximes with adjacent alkynes leading to pyridines, the focus of the project was then steered towards precursors without a pre-installed ring. The aim was to test whether the substrate specificity observed for the annulation of 5-membered ring precursors observed in chapter 2 was specific, and if "linear" systems were also able to cyclize. A major difference in geometry and conformational (rotational) freedom exists between unstrained linear systems and the majority of substrates used in Chapter 2 (Figure 3.5).

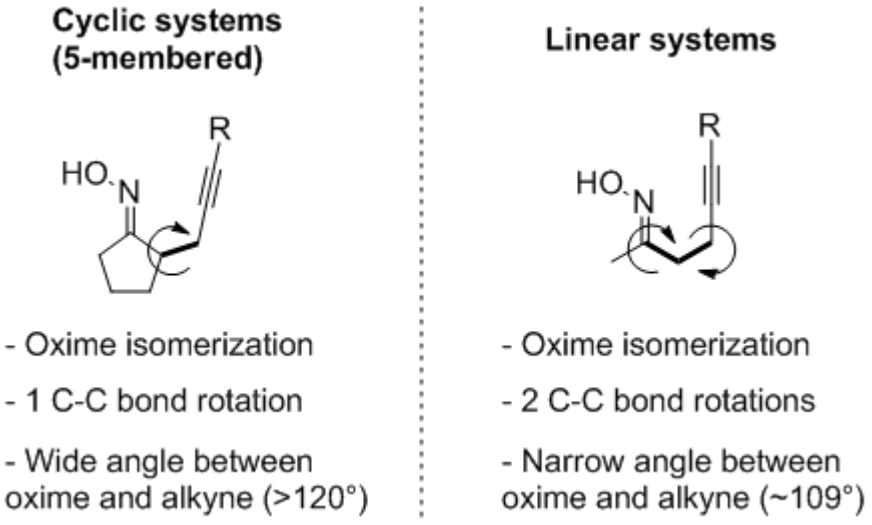


Figure 3.5. *Comparison of cyclic and linear oxime precursors*

Our expectation was that these "linear" oxime systems would follow either one of the *5-exo* or *6-endo* reaction pathways providing a mixture of products.

3.3. Preparation of Substrates

Initially, the alkylation-decarboxylation route (2nd route) that was previously developed (Scheme 2.3) was used as a way to access the desired oxime precursor **3.5** (Figure 3.6), as there were no known alkylation reactions involving enamine formation using acetone and an appropriate propargylic bromide.

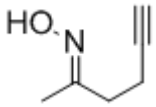
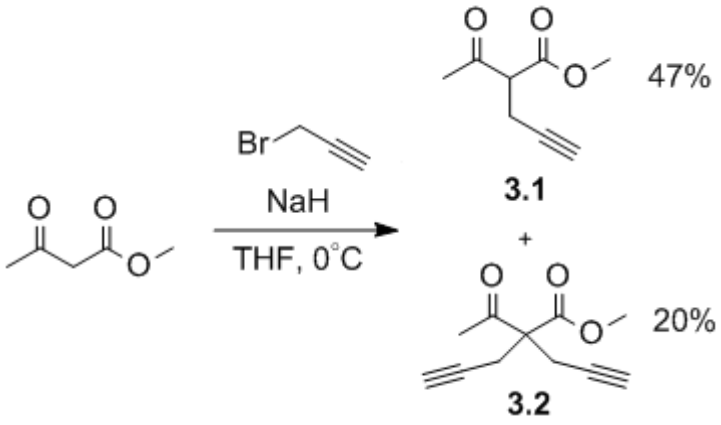


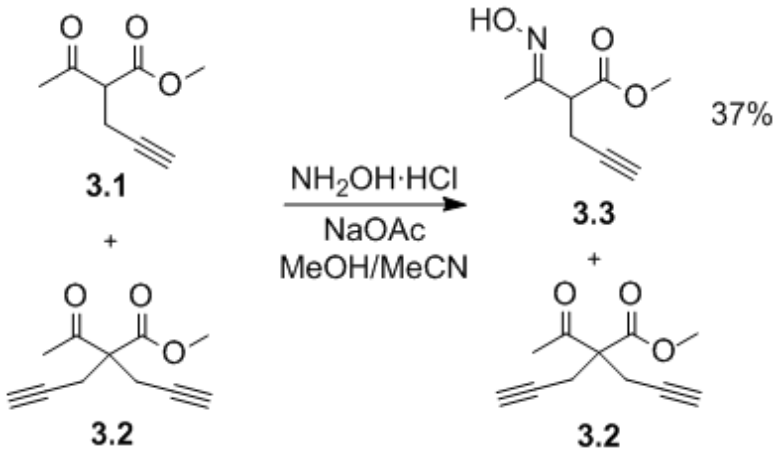
Figure 3.6. *Oxime precursor **3.5***

The synthesis began by alkylation of methyl acetoacetate with propargyl bromide using NaH. Ketoester **3.1** was obtained following chromatography, but a significant amount of the dialkylation product **3.2** was also collected and proved to be very difficult to separate from the desired monoalkylation product (eq 3.1).



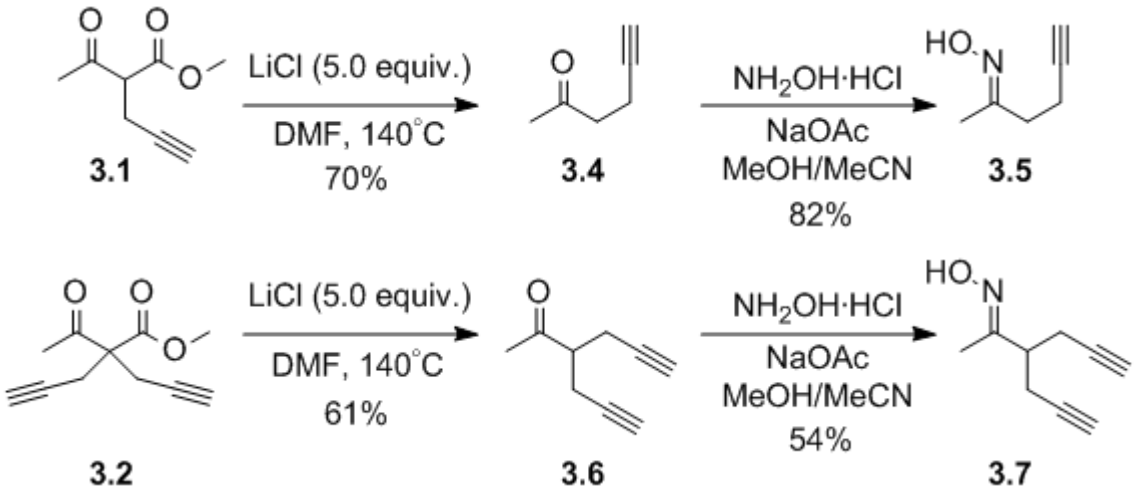
(3.1)

Thankfully when a mixture of mono- and dialkylation products was subjected to an oxime condensation the unreacted dialkyl product **3.2** was obtained with oxime **3.3** (eq 3.2). This result is likely due to steric hinderance alpha to the carbonyl.



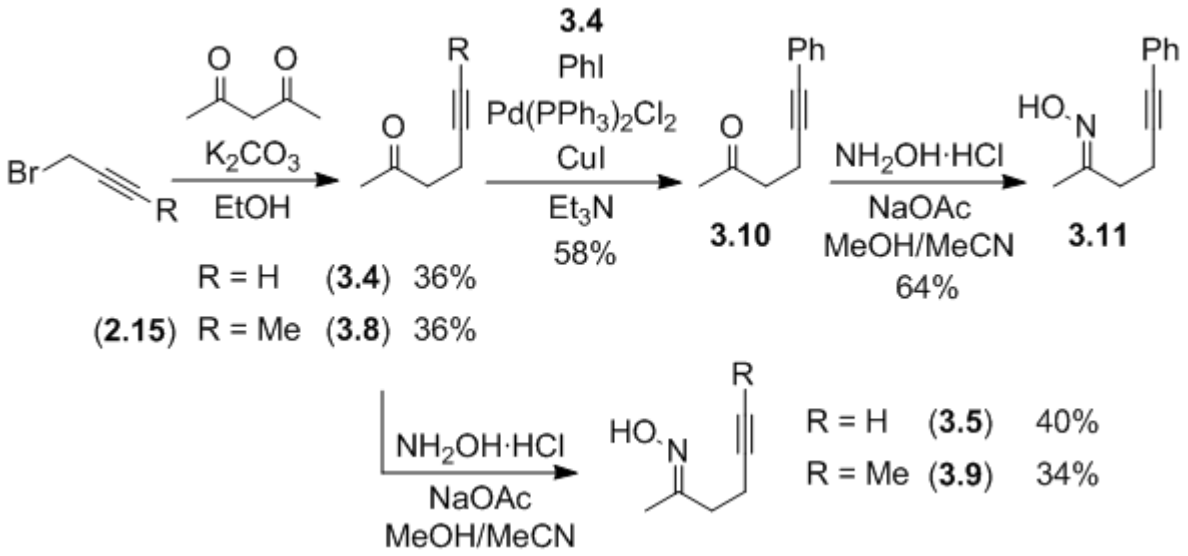
(3.2)

Decarboxylation of a pure sample of **3.1** using Krapcho conditions (LiCl in DMF at reflux) gave hex-5-yn-2-one **3.4** and the subsequent oxime **3.5** under standard condensation conditions. The same two-step sequence was performed for ketoester **3.2** to obtain the dialkylated oxime **3.7**, and intermediate ketone **3.5** (Scheme 3.1).



Scheme 3.1. *Synthesis of oxime precursors **3.5** and **3.7** via 2nd route method*

The two-step alkylation-decarboxylation route towards these linear systems was superseded by a one-step route involving alkylation and decarbonylation in one pot (Scheme 3.2).



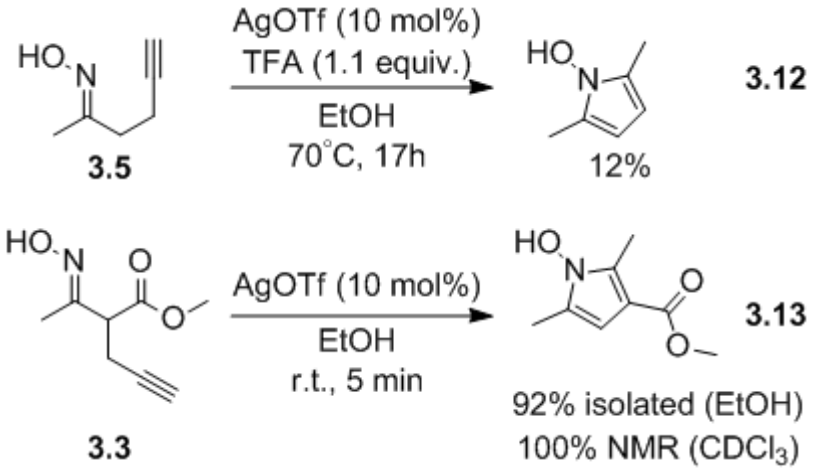
Scheme 3.2. *Synthesis of oximes **3.5**, **3.9** and **3.11** via 3rd route*

Following alkylation of acetoacetate by an appropriate propargylic bromide under basic conditions, attack of EtOH on a carbonyl and collapse of the tetrahedral intermediate with loss of EtOAc provided ketones **3.4** and **3.8**.[56] Purification of the crude reaction mixtures by distillation gave the resulting monoalkylated ketones for oxime condensation to afford precursors **3.5** and **3.9**. Sonogashira cross-coupling of ketone **3.4** provided ketone **3.10**, which led to oxime **3.11** under standard condensation conditions. With the completed synthesis of five new linear oxime precursors we could not focus on attempting the annulation using the same metal-catalysts that were found to promote annulation in the cyclic systems presented in Chapter 2.

[56] Görl, C.; Alt, H.G. *J.Organomet. Chem.* **2007**, *692*, 5727.

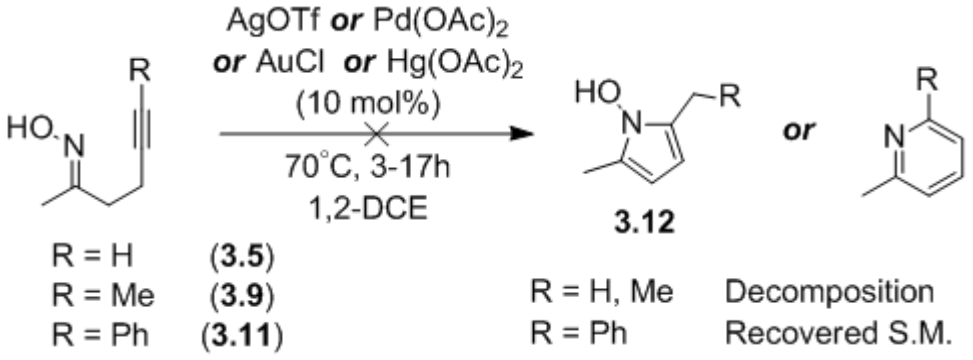
3.4. Results and Discussion

The oxime precursors **3.0**, and **3.3** were the first of the new substrates that were subjected to previous annulation conditions, although EtOH was used as a solvent initially. The initial tests for these first reactions were performed using EtOH since they were done following the solvent scan that revealed it as a superior reaction solvent, but before understanding that alkyne hydration was a possibility.[51] Under standard reaction conditions using AgOTf and TFA with EtOH as solvent, both **3.5** and **3.3** underwent annulation exclusively to the *5-exo* products **3.12** and **3.13** respectively (equations 3.3 and 3.4). In the case of substrate **3.3** this transformation was complete at room temperature before the acid could be added to the flask. With the understanding that alkyne hydration may be promoting the annulation of these precursors, cyclizations of substrates **3.5**, **3.7**, **3.9** and **3.11** were investigated using DCE as a solvent.

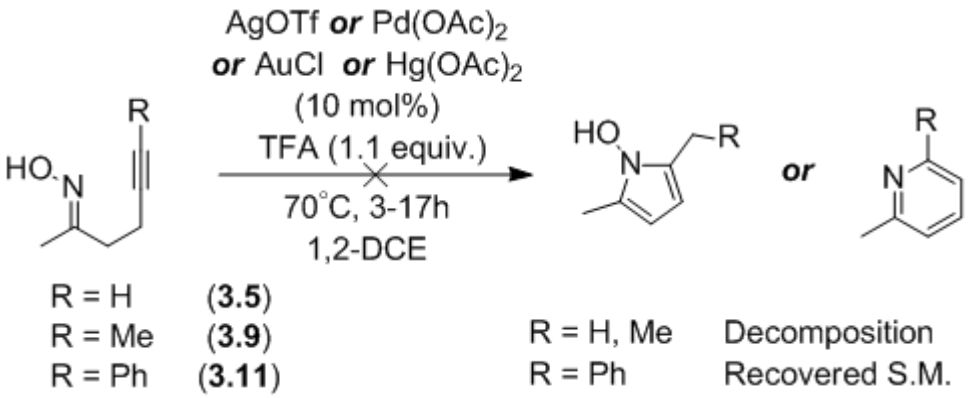


When returning to DCE as a solvent the control experiments had to be re-run with these oxime systems. To this end experiments with only TFA present were set up to insure that these systems were not able to undergo annulation promoted by Brønsted acid. NMR analysis showed that these attempts were all unsuccessful. While the pyrrole and pyridine products were not obtained, some transformation was observed by both NMR and TLCs stained with *p*-anisaldehyde. The new products were attributed to decomposition of the starting material to unidentified by-products.

With the control experiments indicating that TFA was unable to promote annulation on its own, a screen of each substrate with AgOTf, $Pd(OAc)_2$, AuCl or $Hg(OAc)_2$ was performed and Scheme 3.3 summarizes these results. Additional tests with these same four metals and 1.1 equivalents of TFA were performed and appear in Scheme 3.4. Substrate **3.7** was only tested using AgOTf and TFA rather than a complete re-screening of metal catalysts.



Scheme 3.3. *Annulation trials without TFA*

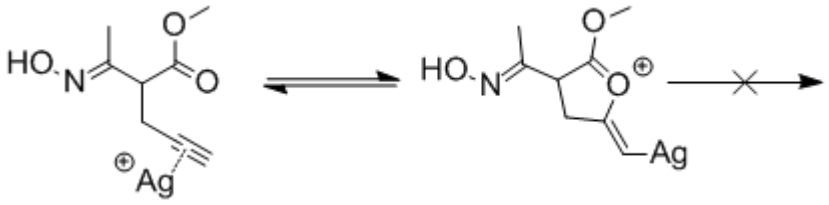


Scheme 3.4. *Annulation trials with TFA*

The terminal alkynly-oxime was completely consumed with and without added acid in 1 hour whereas starting material remained for the methyl- and phenyl-substituted precursors even after 17 hours. Unfortunately, none of the π-acids that afforded *6-endo dig* products in the cyclic systems of chapter 2 was able to provide isolable amounts of the desired pyrroles or pyridines. Traces (<5%) of the *5-exo* product were always seen as indicated by the pyrrole protons near 5.60ppm ($CDCl_3$) in crude proton NMRs. Purification of these pyrroles were unsuccessful and we proposed that product decomposition and volatility were the main factors that may be hindering our isolation efforts. Additionally, deposition of elemental silver and gold was still observed on the walls of the sealed tube even though annulation was largely unsuccessful showing that the proposed catalyst decomposition pathway shown in Chapter 2 (Scheme 2.6) may be faster than annulation.

Using DCE for these annulation attempts was unsuccessful and the inability of these substrates to provide aromatic products appeared to support the hypothesis that alkyne hydration was the mechanism that allowed annulation of **3.5** and **3.3** in EtOH. Despite this, the rapid conversion of precursor **3.3** to the *N*-hydroxy pyrrole **3.13** did not require acid and contradicts this proposition. In an attempt to determine if hydration was acting to promote annulation of **3.3** an NMR experiment was set up using this precursor in $CDCl_3$. A proton spectrum of the pure oxime was obtained. Afterwards and a small amount of AgOTf was added to the NMR tube. Within five minutes, a second proton spectrum of the mixture was taken and 100% NMR yield of the pyrrole was found. This result could not be replicated with any of the other oximes lacking the ester moiety, and it points to a mechanism of annulation involving the ester rather than alkyne hydration.

Analagous to the hydration mechanism proposed in Chapter 2 (Scheme 2.5) for oxime **2.12** to acetal **2.13** the ester may interact with the alkyne following activation by silver (eq 3.5). If this process does occur it is likely reversible since no stable products may be formed under these reaction conditions and no side products were observed via proton NMR.



(3.5)

The same interaction cannot be drawn using terminal oxime **3.5**, which lacks the ester moiety and suggests that conversion to this pyrrole using AgOTf, EtOH and TFA may be assisted by alkyne hydration. The low isolated yield is attributed to decomposition of the pyrrole under acidic conditions as outlined below.

The *N*-hydroxy pyrroles resulting from *5-exo dig* annulation are π-excessive systems and the presence of electrophiles or acid may promote decomposition of these products. Additionally it has been shown that when these pyrrole systems do not have 2,5-disubstitution either dimerization or polymerization may occur (Figure 3.7),[57] and may have been responsible for what occurred with initial annulation attempts from Chapter 2 (Tables 2.1 and 2.2).

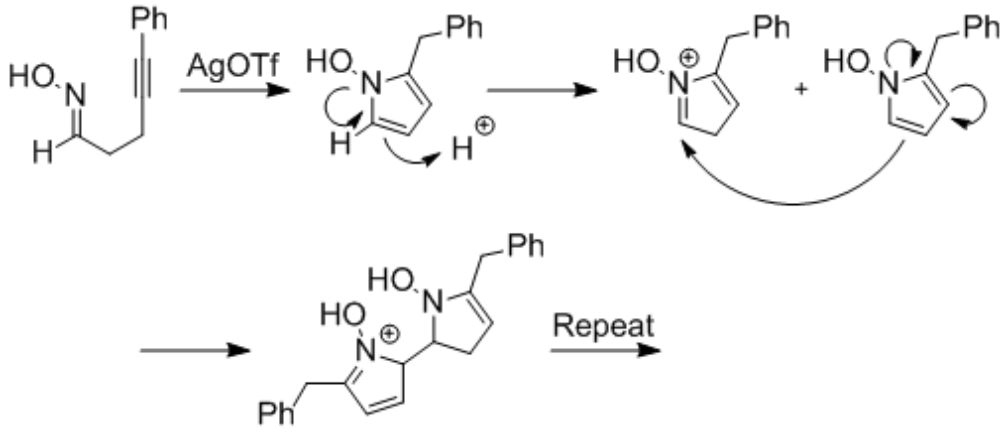
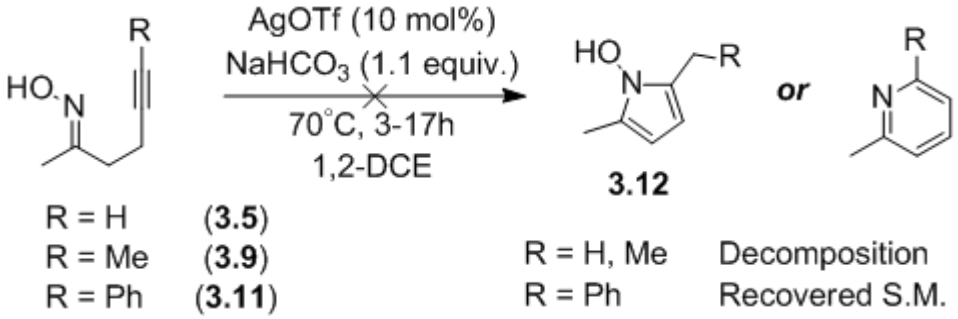


Figure 3.7. *Oxime polymerization*

[57] Hawkins, S.J.; Radcliffe, N.M. *J. Mat. Chem.* **2000**, *10*, 2057.

With electron withdrawing groups present or a high degree of substitution these pyrroles may be less reactive towards acids and polymerization respectively. An example is the rapid conversion of **3.3** to the pyrrole (which should have difficulty polymerizing due to 2,5-disubstitution) without evidence of decomposition in the presence of TFA. The inability of oximes lacking the ester functionality to undergo annulation in DCE with TFA and the significantly lower yield of pyrrole **3.12** in EtOH with TFA support this claim as well.

With the hypothesis that acid may be responsible for the decomposition of any *N*-hydroxy pyrrole formed, experiments were done using oximes **3.5**, **3.9** and **3.11** with AgOTf in DCE and $NaHCO_3$ to determine if this weak base could also facilitate proton transfers (Scheme 3.5). If these precursors undergo *5-exo* annulation the resulting pyrroles are all 2,5-disubstituted and the issue of polymerization is unlikely to be a potential problem, especially with the bulkier phenyl alkyne.



Scheme 3.5. *Annulation attempts of linear systems with weak base*

Again, decomposition to unidentifiable products was observed for all of these reactions and only trace amounts of the previously characterized pyrrole **3.12** were seen via proton NMR.

The current findings indicate that both the conditions developed, and the *6-endo-dig* annulation observed in chapter 2 are substrate specific to precursors containing a 5-membered ring. The exception is with the use of the standard reaction conditions for *6-endo* annulation but with EtOH as solvent.

This solvent is likely promoting annulation of **3.5** to the pyrrole **3.12** through a hydration mechanism. Conversely the annulation of oxime **3.3** with AgOTf seems to be dependent on the presence of the ester moiety since this can provide the pyrrole without a protic solvent and added acid.

These results showed that the oximes which were synthesized to test the *5-exo-dig* annulation were not compatible with the conditions we had developed for promoting a *6-endo-dig* ring closure, and alternative metal catalysts will be needed to progress this chemistry.

4

Conclusions

4.1. Summary and Future Work

In our attempts to extend the annulation chemistry of oximes to alkynes within acyclic systems, only one oxime proved to be a suitable precursor that was able to rapidly provide the corresponding *N*-hydroxy pyrrole in EtOH with TFA and DCE without TFA. Oximes without the ester functionality show issues of decomposition of the starting materials as well as both silver and gold catalysts. The pyrroles lacking the ester functionality are likely to be very sensitive to acidic conditions and prone to polymerization.

With the extended reaction times required to see consumption of the oxime precursors these unproductive pathways are amplified. Additionally with all of the data collected on these linear oxime systems it was hypothesized that there may be subtle conformational and electronic factors controlling the desired annulation that are not fully understood yet. The primary goal of future work should be to understand these factors and choose appropriate metal catalysts to promote annulations.

With an understanding that these linear systems may have a preference for the *5-exo* pathway the next goal would be to find a catalyst that could be selective for the *6-endo* route. Additionally, the cyclic oximes of Chapter 2 exclusively form pyridines, and development of catalysts that promote the *5-exo* route in those systems would be a great extension to the work presented here. Finally the issue of catalyst decomposition by reduction to the elemental metal is a problem that must be solved and may be possible with co-catalysts or radical inhibitors.

4.2. Claims to Original Research

1. Developed the first examples of a metal-catalyzed *6-endo dig* alkyne annulation route towards pyridines using the oxime functionality.

2. Discovered a silver-catalyzed *5-exo dig* annulation pathway leading to two new *N*-hydroxy pyrroles.

4.3. Poster Presentations

Whitmore, K. M.; Beauchemin, A. M. "*Towards a Metal-Catalyzed Route to Pyridines*",

1. June 6, 2011, 94th Canadian Chemistry Conference and Exhibition, Palais Des Congrés De Montréal, Montréal, Québec, Canada.

2. May 27, 2011, Ottawa-Carleton Chemistry Institute Day, University of Ottawa, Ottawa, Ontario, Canada.

3. November 12, 2010, Québec and Ontario Mini-symposium on Biological and Organic Chemistry, Brock University, St.Catharines, Ontario, Canada.

5

Experimental

Instrumentation. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 μm), unless noted otherwise. Thin layer chromatography (TLC) was performed on aluminum plates cut to size. Visualization was accomplished with a UV lamp and staining with a potassium permanganate solution unless otherwise noted.

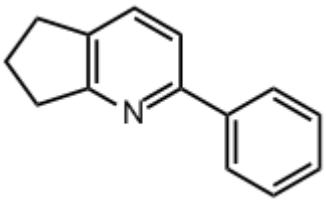
^{1}H NMR and ^{13}C NMR spectra were recorded on a Brüker AVANCE spectrometer at 300 MHz and 75 MHz respectively, or on a Brüker AVANCE spectrometer at 400 MHz and 100 MHz respectively, at room temperature. Spectra are reported in ppm using $CDCl_3$ (7.26 in ^{1}H NMR, 77.0 in ^{13}C NMR) as the reference. ^{1}H NMR multiplicity data reported as: (s = singlet, d = doublet, t = triplet, quartet = q, quint = quintet, sext = sextet, sept = septet, m = multiplet, br = broad), integration and coupling constant(s) in Hz. Infrared (IR) spectra were prepared as neat thin films on a sodium chloride disks and recorded on an AB Bomem, MB Series 100 Fourier Transform Infrared spectrometer. High resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70ev at the Ottawa-Carleton Mass Spectrometry Centre.

Materials. Unless otherwise noted all commercially available materials were purchased from commercial sources and used without prior purification. The solvents used were freshly distilled prior to use unless otherwise noted: THF over sodium; triethylamine, dichloromethane, toluene and 1,2-DCE over CaH_2; DMF and DMSO over 4Å molecular sieves.

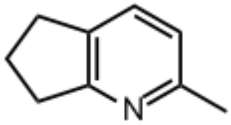
General Procedure for Alkyne Annulations

Typical experimental procedure (Table 2.5, 2.9; Scheme 3.2, 3.3, 3.4, 3.5): A modified procedure developed by Shin was used.[58] A sealed tube containing a stir bar was flame-dried under argon and charged with a metal salt (0.050 mmol, 0.10 equiv.) from a glove box. The precursor oxime (0.50 mmol, 1.0 equiv.) was dissolved in an appropriate solvent (1,2-DCE or 95% EtOH) and added to the sealed tube via syringe. The tube was wrapped in aluminum foil and stirred at 70°C for 3-24h. The reaction was cooled to room temperature and the mixture was treated with saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc, washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. Following concentration under reduced pressure, the reaction conversion was analyzed by ^1H NMR using 1,4-dimethoxybenzene (DMB) (0.25 mmol) as an internal standard and purified by flash column chromatography on silica gel. The resulting pyridine derivatives were analyzed by ^1H NMR.

[58] Hwang, S; Lee, Y; lee, P.H.; Shin, S *Tetrahedron Lett.* **2009**, *50*, 2305.

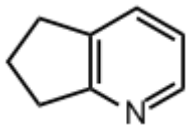


2-Phenyl-6,7-dihydro-5H-[1]pyrindine (2.10, Table 2.6, Entry 3): Synthesized using the general alkyne cyclization procedure using 2-(3-phenyl-prop-ynyl)-cyclopentanone oxime (0.50 mmol, 0.11 g) and columned using 20% EtOAc:Hexanes to give 0.090g (92%) of the desired pyridine. The spectral data was in agreement with the literature.[59]

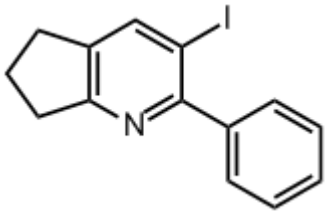


2-Methyl-6,7-dihydro-5H-cyclopenta[b]pyridine (2.24, Table 2.9, Entry 2): Synthesized using the general alkyne cyclization procedure using (*E/Z*)-2-(but-2-yn-1-yl)cyclopentanone oxime (0.50 mmol, 0.076 g) and columned using 20% EtOAc:Hexanes to afford 0.033 g (50%) of the pyridine. The spectral data was in agreement with the literature.[60]

[59] Kaiser, S.; Smidt, S. P.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5194.
[60] Rougeot, E.; Moskowitz, H.; Miocque, M. *J. Het. Chem.* **1983**, *20*, 1407.



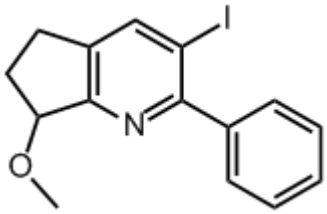
6,7-Dihydro-5H-cyclopenta[b]pyridine (2.23, Table 2.9, Entry 1): Synthesized using the general alkyne cyclization procedure using 2-(prop-2-yn-1-yl)cyclopentanone oxime (0.50 mmol, 0.067 g) and columned using 20% EtOAc:Hexanes to afford 0.017 g (29%) of the desired pyridine. The spectral data was in agreement with the literature.[61]



3-Iodo-2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (2.25, Scheme 2.7): To a flame dried flask under argon and charged with a stir bar was added Iodine (2.5 mmol, 0.64 g) in 1,2-DCE (1.0mL) and diisopropylethylamine (0.50 mmol, 0.087 mL). 2-(3-phenyl-prop-2-ynyl)-cyclopentanone *O*-methyl-oxime (0.50 mmol, 0.11 g) was added to the mixture via syringe in 1,2-DCE (1.5 mL) and the mixture was stirred for 24 hours at room temperature. A saturated solution of $Na_2S_2O_3$ was added and the mixture was stirred for 30 minutes. The mixture was extracted with CH_2Cl_2, washed twice with $Na_2S_2O_3$ and brine and dried over Na_2SO_4 before concentration under reduced pressure.

[61] Anderson, E. D.; Boger, D. L. *Org. Lett.* **2011**, *13*, 2492.

The crude mixture was purified by flash column chromatography using 20% EtOAc:Hexanes as eluent to afford 0.040 g (25%) of the pyridine. TLC R_f = 0.62 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.55 - 7.51 (m, 2H), 7.46 - 7.38 (m, 3H), 2.99 (dt, *J* = 19.2, 7.9 Hz, 4H), 2.17 (quint, *J* = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5 (C), 159.3 (C), 143.1 (CH), 142.5 (C), 137.9 (C), 129.3 (CH), 128.2 (CH), 127.9 (CH), 91.1 (C), 33.9 (CH_2), 30.0 (CH_2), 23.5 (CH_2).; IR (film, cm^{-1}); 2960, 2920, 2848, 1779, 1701, 1538, 1408, 1198, 992.; HRMS: Exact mass calculated for $C_{14}H_{12}NI$ $[M]^+$ = 321.0014, $[M+1]^+$ found = 321.0031.



3-Iodo-7-methoxy-2-phenyl-6,7-dihydro-5H-cyclopenta[b]pyridine (2.26, Scheme 2.7): To a flame dried flask under argon and charged with a stir bar was added Iodine (2.5 mmol, 0.64 g) in 1,2-DCE (1.0 mL) and diisopropylethylamine (0.50 mmol, 0.087 mL). 2-(3-phenyl-prop-2-ynyl)-cyclopentanone *O*-methyl-oxime (0.50 mmol, 0.11 g) was added to the mixture via syringe in 1,2-DCE (1.50mL) and the mixture was stirred for 24 hours at room temperature. A saturated solution of $Na_2S_2O_3$ was added and the mixture was stirred for 30 minutes. The mixture was extracted with CH_2Cl_2, washed twice with $Na_2S_2O_3$ and brine and dried over Na_2SO_4 before concentration under reduced pressure.

The crude mixture was purified by flash column chromatography using 20% EtOAc:Hexanes as eluent to afford 0.035 g (20%) of the pyridine. TLC R_f = 0.52 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (s, 1H), 7.57-7.54 (m, 2H), 7.46-7.37 (m, 3H), 4.72 (dd, *J* = 6.7, 3.4 Hz, 1H), 3.53 (s, 3H), 3.16 - 3.08 (m, 1H), 2.85 (dddd, *J* = 16.5, 8.7, 4.3, 0.9 Hz, 1H), 2.40 (tdd, *J* = 13.6, 8.7, 6.7 Hz, 1H), 2.18 (dddd, 16.2, 8.3, 4.3, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.6 (C), 160.0 (C), 144.4 (CH), 142.3 (C), 137.9 (C), 129.4 (CH), 128.4 (CH), 127.9 (CH), 82.8 (CH), 57.1 (CH_3), 30.7 (CH_2), 27.3 (CH_2). IR (film, cm^{-1}); 2955, 2929, 2844, 1694, 1564, 1408, 1189; HRMS: Exact mass calculated for $C_{15}H_{14}NOI$ $[M]^+$ = 351.0120 not found, exact mass calculated for $C_{14}H_{11}NI$ $[M\text{-}OMe]^+$ = 319.9936, $[M\text{-}OMe]^+$ found = 319.9959.

General Procedures for Substrate Preparation

General procedure A: A modified procedure developed by Roscini[62] was used. *p*-Toluenesulfonic acid (0.10 equiv.) was added to a flame-dried flask charged with a stir bar and under argon. Anhydrous toluene (0.90 M) was added to the acid along with the desired ketone (1.0 equiv) and pyrrolidine (1.7 equiv.). The flask was equipped with a Dean-Stark apparatus containing anhydrous toluene. The mixture was brought to reflux at 130ºC and stirred for 6 hours, cooled to room temperature and the contents were concentrated under reduced pressure.

[62] Roscini, C; Cubbage, K.L.; Berry, M; Orr-Ewing, A.J.; Booker-Milburn, K.I. *Angew. Chem. Int. Ed*. **2009**, *48*, 8716.

To this was added a 5:1 mixture of THF and DMF (0.70 M) and the flask was equipped with a reflux condenser. The propargylic bromide (0.50 equiv.) was added down the condenser and the mixture was heated at 80ºC for 4 hours before cooling to room temperature. Water was added and the solution was extracted using EtOAc, acidified to pH 7 and washed with brine before drying over $MgSO_4$. The crude mixture was purified on silica using flash column chromatography and analyzed by ^1H NMR.

General procedure B: A procedure developed by Hayashi was used.[63] To a flame dried flask under argon and charged with a stir bar was added a solution of THF (0.30 M) followed by NaH (1.1 equiv.) at 0°C. The ketoester (1.0 equiv.) was added dropwise at 0°C and the resulting solution was stirred for 30 minutes until the solution became yellow. The desired propargylic bromide (1.1 equiv.) was added dropwise over 15 minutes and the solution was allowed to warm to room temperature over 2 hours. The reaction was quenched at 0°C with water, extracted with Et_2O and washed with brine twice before drying over $MgSO_4$ and concentration under reduced pressure. The crude mixture was purified on silica gel using flash column chromatography and analyzed by ^1H NMR.

[63] Shintani, R; Duan, W; Park, S; Hayashi, T *Chem. Comm.* **2006**, 3646.

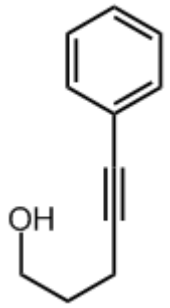
General procedure C: A procedure developed by Miginiac was used.[64] To a flame dried flask under argon and charged with a stir bar was added K_2CO_3 (1.1 equiv.) in EtOH (1.2 M). Acetylacetone (1.1 equiv.) and the desired propargylic bromide (1.0 equiv.) were added via syringe and the mixture was refluxed overnight. EtOH was removed by concentration under reduced pressure and the mixture was extracted twice with methyl *t*-butyl ether, washed with water and brine and dried over $MgSO_4$. Following concentration under reduced pressure the mixture was distilled under vacuum and analyzed by ^{1}H NMR.

General Procedure for Oxime Formation

Typical experimental procedure: A procedure developed by Beauchemin was used.[40] To a flame-dried flask under argon and charged with a stir bar was added the ketone (1.0 equiv.). A 10:1 mix of MeOH and MeCN was added and the ketone was stirred until fully dissolved. Hydroxylamine hydrochloride (1.1 equiv.) and NaOAc (3.0 equiv.) were added and the mixture was stirred for 1 hour at room temperature. The mixture was treated with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with saturated NaCl solution and dried over anhydrous Na_2SO_4. Following concentration under reduced pressure, the desired oxime was purified by flash column chromatography and analyzed by ^{1}H NMR.

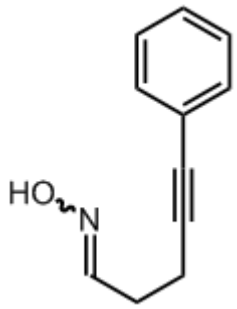
[64] Barbot, F; Mesnard, D; Miginiac, L *Org. Prep. Proc. Int.* **1978**, *10*, 261.

Preparation of Substrates:



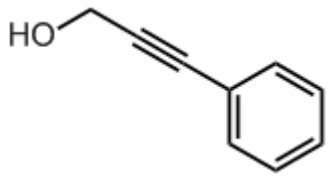
5-Phenylpent-4-yn-1-ol (2.1, Scheme 2.1): A procedure developed by Liu was used.[65] To a flame-dried flask under argon was added triethylamine (53 mL) and iodobenzene (22 mmol, 2.4 mL). Bis(triphenylphosphine)palladium(II)chloride (0.18 mmol, 0.13 g) and copper(I)iodide (0.36 mmol, 0.068 g) were added and the mixture was stirred for 5 minutes. 4-pentyn-1-ol (18 mmol, 1.7 mL) was added via syringe and the mixture was stirred for 18h, washed twice with sodium bicarbonate, once with brine and dried over Na_2SO_4 before concentration under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel using 15% EtOAc:Hexanes and 1% added Et_3N to yield 2.3 g (79%) of the desired compound as a red-orange oil. The spectral data was in agreement with the literature.[65]

[65] Lin, G.; Yang, C.; Liu, R *J. Org. Chem.* **2007**, *72*, 6753.



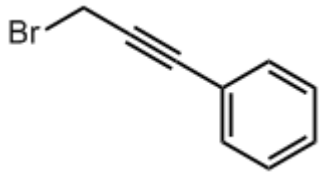
(*E/Z*)-5-Phenylpeny-4-ynal oxime (2.2, Scheme 2.1): A procedure developed by Beauchemin was used.[40] To a flame dried flask under argon was added dry CH_2Cl_2 (64 mL) and placed in an ice bath. 5-phenylpent-4-yn-1-ol (14 mmol, 2.3 g) was added via syringe with DMSO (45 mmol, 3.2 mL) and stirred while dry triethylamine (46 mmol, 6.4 mL) was added to the flask. Pyridine-sulfurtrioxide complex (42 mmol, 6.7 g) was quickly added and the mixture was stirred on ice for 5 minutes before stirring at room temperature for 3 hours, after which the reaction was quenched by NH_4Cl, washed with water and brine and dried over $MgSO_4$. Concentration under reduced pressure gave a yellow oil, which was used as a crude in the following step. MeOH (28 mL) and MeCN (2.8 mL) were added to the crude oil under argon along with sodium acetate (42 mmol, 3.5 g) and hydroxylamine hydrochloride (15 mmol, 1.1 g). The mixture was stirred for 12h then washed with brine, water and $NaHCO_3$, then 3 times with CH_2Cl_2 before drying over $MgSO_4$. The mixture was concentrated under reduced pressure and the crude oil was purified by flash column chromatography on silica gel using 20% EtOAc:Hexanes to yield 1.3 g (53% over two steps) of the desired compound. TLC R_f 0.22 and 0.27 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.58 (t, *J* = 5.6Hz, 1H), 7.42-7.35 (m, 2H), 7.32-7.27 (m, 2H), 6.94 (t, *J* = 4.8Hz, 1H), 2.80-2.60 (m, 3H), 2.55-2.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 150.6 (C), 131.6 (CH), 128.2 (2 x CH), 127.8 (2 x

CH), 123.4 (2 x C), 87.9 (C), 81.7 (C), 28.9 (CH_2), 24.3 (CH_2), 17.0 (CH_2)16.3 (CH_2); IR (film, cm^{-1}); 3260, 3085, 2914, 2230, 1595, 1562, 915; HRMS (EI): HRMS (EI): Exact mass calculated for $C_{11}H_{11}NO$ $[M]^+$ 173.0841; found: 173.0817.



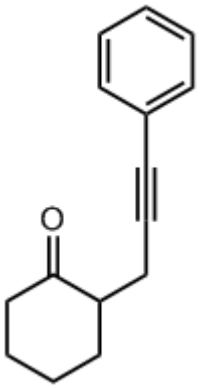
3-Phenylprop-2-yn-1-ol (2.4a, Scheme 2.2): A procedure developed by Liu was used.[65] To a flame-dried flask under argon was added triethylamine (31 mL) and iodobenzene (1.4 mL, 13 mmol). Bis(triphenylphosphine)palladium(II)chloride (0.11 mmol, 0.075 g) and copper(I)iodide (0.22 mmol, 0.041 g) were added and the mixture was stirred for 5 minutes. Propargyl alcohol (11 mmol, 0.63 mL) was added via syringe and the mixture was stirred for 18h, washed with $NaHCO_3$, brine and dried over Na_2SO_4 before concentration under reduced pressure. The crude oil was purified by flash column chromatography on silica gel using 20% EtOAc:Hexanes with 0.5% Et_3N added to yield 1.4 g (99%) of the desired compound as an orange oil. The spectral data was in agreement with the literature.[66]

[66] Kim, I. S.; Dong, R. G.; Jung, Y. H. *J. Org. Chem.* **2007**, *72*, 5424.

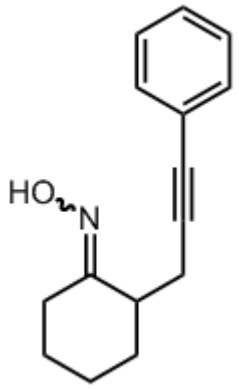


(3-Bromoprop-1-yn-1-yl)benzene (2.4, Scheme 2.2): A modified procedure developed by Toste[67] was used. A To a solution of PPh_3 (42 mmol, 11 g) in CH_2Cl_2 (150 mL) at 0°C was added bromine (42 mmol, 2.1 mL) over 10 minutes. The solution was stirred for 30 minutes or until a solid yellow precipitate had formed. A solution of 3-phenylprop-2-yn-1-ol (38 mmol, 5.0 g) was added dropwise over 5 minutes until the solid had disappeared. The solution was stirred for 30 minutes, slowly warming to room temperature. Petroleum ether (300mL) was added, forming a precipitate, which was stirred for an additional 30 minutes at room temperature. The mixture was filtered through a plug of silica under a water aspirator vacuum and washed with petroleum ether before concentration under reduced pressure. 6.6 g (90%) of the bromide was obtained and was determined to be pure enough by ^1H NMR to be used in subsequent manipulations. The spectral data was in agreement with the literature.[67]

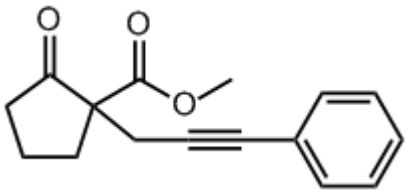
[67] Kleinbeck, F; Toste, D.F. *J. Am. Chem. Soc.* **2009**, *131*, 9178.



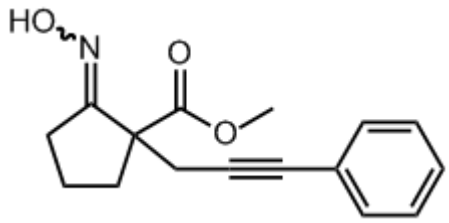
2-(3-Phenylprop-2-ynyl)cyclohexanone (2.5, Scheme 2.2): Synthesized according to general procedure A using cyclohexanone (23 mmol, 2.1 mL). 1.7 g (33%) of the desired alkynyl ketone was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f 0.33 (10% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.42-7.37 (m, 2H), 7.30-7.26 (m, 3H), 2.89 (dd, *J* = 4.4Hz, 16.8Hz, 1H), 2.63-2.55 (m,1H), 2.54-2.47 (m, 1H), 2.46-2.42 (m,1H), 2.40-2.31 (m, 2H), 2.14-2.08(m, 1H), 1.97-1.91 (m, 1H), 1.75-1.68 (m, 2H), 1.52-1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 211.1 (C), 131.6 (CH), 128.2 (CH), 127.6 (CH), 123.7 (C), 88.2 (C), 81.7 (C), 49.8 (CH), 42.0 (CH_2), 33.4 (CH_2), 27.9 (CH_2), 25.1 (CH_2), 19.7 (CH_2).; IR (film, cm^{-1}): 3071, 2884, 2815, 2215, 1734, 1488.; HRMS (EI): Exact mass calculated for $C_{14}H_{16}O$ $[M]^+$ = 212.1201, [M+1] found = 212.1207.



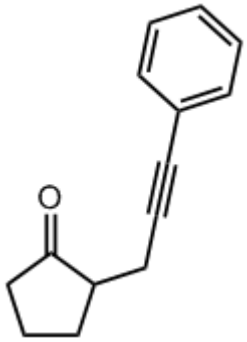
(*E*/*Z*)-2-(3-Phenylprop-2-ynyl)cyclohexanone oxime (2.6, Scheme 2.2): Synthesized according to the general procedure for oxime condensation using 2-(3-phenylprop-2-ynyl)cyclohexanone (7.8 mmol, 1.7 g). The crude mixture was purified by flash column chromatography on silica gel using 10% EtOAc:Hexanes to yield 1.1 g (64%) of the desired compound as a white powder. TLC R_f = 0.10 and 0.25 (10% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.42-7.40 (m, 2H), 7.29-7.26 (m, 3H), 3.11 (dt, *J* = 14.4Hz, 4.8Hz, 1H), 2.81 (dt, *J* = 11.6Hz , 8.4Hz, 1H), 2.56-2.47 (m, 2H), 2.27-2.18 (m, 1H), 2.03-1.99 (m, 1H), 1.86-1.78 (m, 2H), 1.57-1.45 (m, 2H), 1.32-1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 161.3 (C), 131.6 (CH), 128.1 (CH), 127.5 (CH), 123.9 (C), 88.5 (C), 81.8 (C), 41.8 (CH_2), 32.7 (CH_2), 31.7 (CH), 26.0 (CH_2), 24.6 (CH_2), 24.0 (CH_2), 21.5 (CH_2); IR (film, cm^{-1}); 3321, 2930, 2853, 2226, 1490, 1443, 937; HRMS (EI): Exact mass calculated for $C_{15}H_{17}NO$ $[M]^+$ = 227.1310 not found, exact mass calculated for $C_{14}H_{14}N$ $[M\text{-}OH]^+$ = 210.1283 , $[M\text{-}OH]^+$ found = 210.1279.



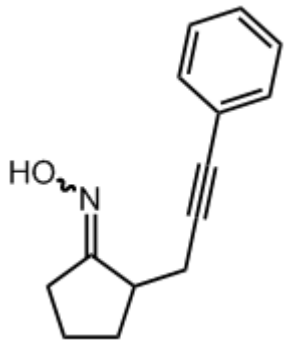
Methyl 2-oxo-1-(3-phenylprop-2-yn-1-yl)cyclopentanecarboxylate (2.7, Scheme 2.4): Synthesized according to general procedure B using methyl 2-cyclopentanonecarboxylate (17 mmol, 2.3 mL). The crude mixture was purified by flash column chromatography on silica gel using 20% EtOAc:Hexanes to yield 3.6 g (84%) of the desired ketoester as a yellow oil. TLC R_f 0.69 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 - 7.33 (m, 2H), 7.28 - 7.26 (m, 3H), 3.73 (s, 3H), 2.95 (s, 2H), 2.60 - 2.47 (m, 2H), 2.42 - 2.27 (m, 2H), 2.17 - 2.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.8 (C), 170.9 (C), 131.6 (CH), 128.2 (CH), 128.0 (CH), 123.1 (C), 85.1 (C), 82.8 (C), 59.1 (C), 52.8 (CH_2), 38.4 (CH_2), 32.7 (CH_2), 24.3 (CH_2), 19.8 (CH_2).; IR (film, cm^{-1}): 3084, 2953, 2914, 2884, 2843, 2231, 1741, 1602, 1481, 1091. HRMS (EI): Exact mass calculated for $C_{16}H_{16}O_3$ $[M]^+$ = 256.2964 not found, exact mass calculated for $C_{14}H_{14}O$ $[M\text{-}CO_2Me]^+$ = 197.0966, $[M\text{-}CO_2Me]^+$ found = 197.0951.



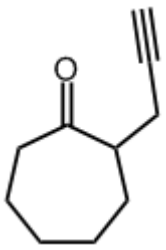
(*E/Z*)-Methyl-2-(hydroxyimino)-1-(3-phenylprop-2-yn-1-yl) cyclopentanecarboxylate (2.14, Scheme 2.6): Synthesized according to the general procedure for oxime condensation using methyl 2-oxo-1-(3-phenylprop-2-yn-1-yl)cyclopentanecarboxylate (2.0 mmol, 0.50 g) and 0.48 g (91%) of the product was obtained following recrystallization of the crude mixture from 20% EtOAc:Petroleum Ether. TLC R_f = 0.36 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (br s, 1H), 7.38 – 7.35 (m, 2H), 7.29 – 7.26 (m, 3H), 3.76 (s, 3H), 3.08 (d, *J* = 12.6 Hz, 1H), 2.85 (d, *J* = 12.6 Hz, 1H), 2.72 – 2.44 (m, 3H), 2.15 (dt, *J* = 9.9, 6.0 Hz, 1H), 2.01 – 1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9 (C), 165.5 (C), 131.7 (CH), 128.2 (CH), 127.9 (CH), 123.4 (C), 86.0 (C), 82.4 (C), 55.6 (C), 52.7 (CH_3), 34.9 (CH_2), 27.6 (CH_2), 27.0 (CH_2), 22.0 (CH_2).; IR (film, cm^{-1}): 3439, 3321, 2953, 2879, 2839, 2235, 1734, 1600, 1485.; HRMS (EI): Exact mass calculated for $C_{16}H_{17}NO_3$ $[M]^+$ = 271.1208, $[M+1]^+$ found = 271.1207.



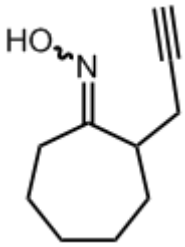
2-(3-Phenylprop-2-ynyl)cyclopentanone (2.8, Scheme 2.4): To a flame dried flask under argon and charged with a magnetic stir bar was added LiCl (60 mmol, 2.5 g) and DMF (8.0 mL). Methyl 2-oxo-1-(3-phenylprop-2-yn-1-yl)cyclopentanecarboxylate (12 mmol, 3.1 g) was added via syringe in DMF (8.0 mL) and the flask was attached with a reflux condenser. The mixture was refluxed at 140°C for 2h and cooled to room temperature before a 10% HCl solution was added down the condenser. The resulting solution was stirred for 10 minutes, extracted with EtOAc and washed 10 times with a 1:1 brine and distilled water solution. The crude mixture was concentrated under reduced pressure and columned using 100% toluene to afford 1.8 g (77%) of the desired ketone. TLC R_f = 0.21 (100% Toluene); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.36 (m, 2H), 7.29-7.26 (m, 3H), 2.78 (dd, *J* = 16.8, 4.0 Hz, 1H), 2.57 (dd, *J* = 17.2, 7.2 Hz, 1H), 2.41-2.31 (m, 3H), 2.20-2.04 (m, 2H), 1.94-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 219.0 (C), 131.6 (CH), 128.2 (CH), 127.7 (CH), 123.5 (C), 87.3 (C), 81.7 (C), 47.9 (CH), 38.1 (CH_2), 28.8 (CH_2), 20.5 (CH_2), 19.5 (CH_2).; IR (film, cm^{-1}): 3085, 2932, 2229, 1722, 1484, 1163.; HRMS (EI): Exact mass calculated for $C_{13}H_{14}O$ $[M]^+$ = 198.1045, [M+1] found = 198.1051.



(*E/Z*)-2-(3-Phenyl-prop-ynyl)-cyclopentanone oxime (2.9, Scheme 2.4): Synthesized according to the general procedure for oxime condensation using 2-(3-phenylprop-2-ynyl)cyclopentanone (9.2 mmol, 1.8 g). 1.7 g (84%) of the oxime was obtained as a white powder following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.23 and 0.35 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (br s, 1H), 7.41 – 7.37 (m, 2H), 7.30-7.27 (m, 3H), 2.83-2.75 (m, 2H), 2.66-2.40 (m, 3H), 2.20-2.12 (m, 1H), 1.97-1.88 (m, 1H), 1.74-1.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4 (C), 131.6 (CH), 128.1 (CH), 127.6 (CH), 123.8 (C), 88.1 (C), 81.4 (C), 42.4 (CH), 31.4 (CH_2), 27.4 (CH_2), 22.4 (CH_2), 22.2 (CH_2); IR (film, cm^{-1}): 3279, 2963, 2872, 2245, 1489, 1439; HRMS (EI): Exact mass calculated for $C_{14}H_{14}NO$ $[M]^+$ = 213.1154, [M+1] found = 213.1142.



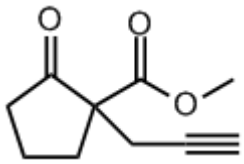
2-(Prop-2-yn-1-yl)cycloheptanone (2.21): Synthesized according to general procedure A using cycloheptanone (9.6 mmol, 1.1 mL) and columned using 20% EtOAc:Hexanes to give 0.49 g (34%) of the desired ketone. The spectral data was in agreement with the literature.[68]



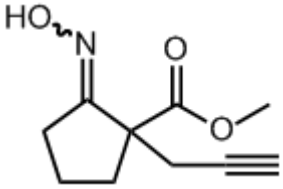
(*E/Z*)-2-(Prop-2-yn-1-yl)cycloheptanone oxime (2.22, Figure 2.9): Synthesized according to the general procedure for oxime condensation using 2-(prop-2-yn-1-yl)cycloheptanone (3.2 mmol, 0.49 g). 0.38 g (71%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.50 and 0.38 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.88 (br s, 1H), 2.81 – 2.73 (m, 1H), 2.66 – 2.57 (m, 1H), 2.46 (ddd, *J* = 16.5, 5.7, 2.4 Hz, 1H), 2.32 (dd, *J* = 8.7, 2.7 Hz, 1H), 2.28 - 2.21 (m, 1H), 2.14 - 2.04 (m, 1H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.88 - 1.77 (m, 3H), 1.57 - 1.26 (m, 4H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ =164.0 (C), 82.6 (C), 69.6 (CH), 42.9 (CH), 32.3 (CH_2), 30.3 (CH_2), 27.1 (CH_2), 26.3 (CH_2), 25.0 (CH_2), 23.3 (CH_2).; IR (film, cm^{-1}): 3296, 2927, 2854, 2120, 1645, 1335, 1326, 1265;

[68] Boltukhina, E. V.; Sheshenev, A. E.; Laypkalo, I. M. *Tetrahedron* **2011**, *67*, 5382.

HRMS (EI): Exact mass calculated for $C_{10}H_{15}NO$ $[M]^+$ = 165.1154, [M+1] found = 165.1142.



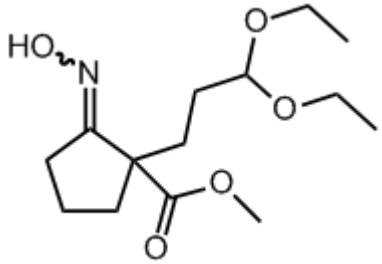
Methyl 2-oxo-1-(prop-2-yn-1-yl)cyclopentanecarboxylate (2.11, Scheme 2.5): Synthesized according to general procedure B using methyl 2-cyclopentanonecarboxylate (50 mmol, 6.2 mL). 6.58g (73%) of the desired ketoester was obtained following concentration under reduced pressure and was pure enough to be used in subsequent manipulations. The spectral data was in agreement with the literature.[69]



(*E/Z*)-Methyl 2-(hydroxyimino)-1-(prop-2-yn-1-yl)cyclopentanecarboxylate (2.14, Scheme 2.5): Synthesized according to the general procedure for oxime condensation using methyl 2-oxo-1-(prop-2-yn-1-yl)cyclopentanecarboxylate (20 mmol, 3.6 g). 3.5 g (89%) of the product as a 3:2 mixture of oxime isomers was obtained as a white solid following recrystallization of the crude mixture from 20% EtOAc:Petroleum Ether. TLC R_f 0.33 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): 3:2 mixture of oxime isomers: δ = 8.08 (br s, 1H) 7.98 (br s, 1H), 3.74 (s,

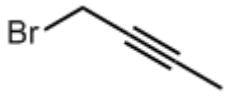
[69] Teixeira, L. H. P.; Barreiro, E. J.; Fraga, C. A. M. *Synth. Comm.* **1997**, *27*, 3241.

3H), 2.88 (d, *J* = 2.7 Hz, 1H), 2.83 (d, *J* = 2.4 Hz, 1H), 2.72-2.37 (m, 4H), 2.12-2.03 (m, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.94-1.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8 (C), 165.4 (C), 80.4 (C), 70.3 (CH), 55.3 (C), 52.7 (CH_3), 34.8 (CH_2), 27.5 (CH_2), 25.8 (CH_2), 21.9 (CH_2).; IR (film, cm^{-1}): 3447, 3295, 2956, 2892, 2120, 1733, 1432, 1152.; HRMS (EI): Exact mass calculated for $C_{10}H_{13}NO_3$ $[M]^+$ = 195.0895 not found, exact mass calculated for $C_{10}H_{12}NO_2$ $[M\text{-}OH]^+$ found = 178.0868, $[M\text{-}OH]^+$ found = 178.0867.

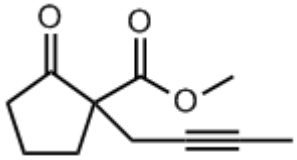


(*E/Z*)-Methyl 1-(3,3-diethoxypropyl)-2-(hydroxyimino)cyclopentanecarboxylate (2.13, Scheme 2.5): Synthesized using the general alkyne cyclization procedure using methyl 2-(hydroxyimino)-1-(prop-2-yn-1-yl)cyclopentanecarboxylate (2.5 mmol, 0.49 g) in EtOH (13 mL) and columned using a gradient from 5-30% EtOAc:Hexanes to afford 0.079 g (14%) of the acetal. TLC R_f = 0.07 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ =; 8.54 (br s, 1H), 4.45 (t, *J* = 5.8 Hz, 1H), 3.69 (s, 3H), 3.64 - 3.57 (m, 2H), 3.50 (dqd, *J* = 9.2, 7.1, 2.1 Hz, 2H), 2.61 (dt, *J* = 18.6, 6.5 Hz, 1H), 2.48 (dt, *J* = 18.6, 8.1 Hz, 1H), 2.37 (dt, *J* = 12.3, 6.0 Hz, 1H), 1.85 - 1.55 (m, 6H), 1.17 (dt, *J* = 7.1, 1.5 Hz, 6H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6 (C), 166.0 (C), 102.7 (CH), 61.1 (CH_2), 60.8 (CH_2), 56.0 (C), 52.4 (CH), 34.8 (CH_2), 31.4 (CH_2), 29.4 (CH_2), 27.3 (CH_2), 21.7 (CH_2), 15.2 (CH_3).; IR (film, cm^{-1}):

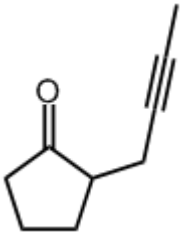
3356, 2973, 2883, 1732, 1446, 1376, 1343, 1207, 1128, 1063, 1001.; HRMS (EI): Exact mass calculated for $C_{14}H_{25}NO_5$ $[M]^+$ = 287.1733 not found, Exact mass calculated for $C_{12}H_{20}NO_4$ $[M\text{-}OEt]^+$ = 242.1392, $[M\text{-}OEt]^+$ found = 242.1384.



1-Bromobut-2-yne (2.15, Scheme 3.2): A modified procedure developed by Toste was used.[67] A To a solution of PPh_3 (49 mmol, 13 g) in CH_2Cl_2 (130 mL) at 0°C was added Br_2 (49 mmol, 2.5 mL) over 10 minutes. The solution was stirred for 30 minutes until a yellow solid had formed. A solution of 2-butyn-1-ol (45 mmol, 3.3 mL) was added dropwise over 10 minutes until the solid had disappeared. The solution was stirred for 10 minutes, while warming to room temperature. Petroleum ether (200mL) was added, forming a precipitate, which was stirred for an additional 30 minutes at room temperature. The mixture was filtered through a plug of silica under a water aspirator vacuum and washed with petroleum ether and concentrated under reduced pressure to afford 3.5 g (59%) of the desired bromide, which was used crude in subsequent manipulations.

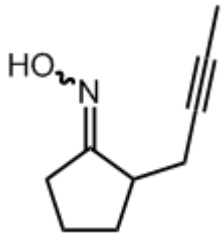


Methyl 1-(but-2-yn-1-yl)-2-oxocyclopentanecarboxylate (2.16, Figure 2.8): Synthesized according to general procedure B using methyl 2-oxocyclopentanecarboxylate (16 mmol, 2.1 mL). 2.4 g (76%) of the desired ketoester was obtained following column chromatography using a 5-20% gradient of EtOAc:Hexanes. TLC R_f = 0.60 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.62 (s, 3H), 2.56 (t, *J* = 2.4Hz, 2H), 2;45-2.34 (m, 2H), 2.26-2.15 (m, 2H), 2.03-1.91 (m, 2H), 1.66 (t, *J* = 2.4Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.8 (C), 170.9 (C), 77.9 (C), 74.1 (C), 58.9 (C), 52.4 (C), 38.2 (CH_2), 32.3 (CH_2), 23.4 (CH_2), 19.6 (CH_2)., 3.2 (CH_3).; IR (film, cm^{-1}): 2964, 2926, 2892, 2230, 1755, 1728, 1432, 1406, 1223.; HRMS (EI): Exact mass calculated for $C_{11}H_{14}O_3$ $[M]^+$ = 194.0943 not found, Exact mass calculated for $C_9H_{11}O$ $[M\text{-}CO_2Me]^+$ = 135.0810, $[M\text{-}CO_2Me]^+$ found = 135.0784.



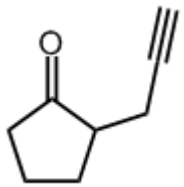
2-(But-2-yn-1-yl)cyclopentanone (2.17, Figure 2.7): To a flame dried flask under argon and charged with a magnetic stir bar was added LiCl (26 mmol, 1.1 g). Methyl 1-(but-2-yn-1-yl)-2-oxocyclopentanecarboxylate (5.2 mmol, 1.0 g) was added via syringe in DMF (6.9 mL) and the flask was equipped with a reflux condenser. The

mixture was refluxed at 140°C for 2h and cooled to room temperature before a 10% HCl solution was added down the condenser. The resulting solution was stirred for 10 minutes, extracted with EtOAc and washed 10 times with a 1:1 brine and distilled water solution. The crude mixture was concentrated under reduced pressure and columned using a gradient from 5-20% EtOAc:Hexanes to afford 0.46 g (66%) of the ketone. TLC R_f = 0.66 (20% EtOAc/Hexanes).; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.51 - 2.45 (m, 1H), 2.36 – 2.17 (m, 4H), 2.15 – 2.00 (m, 2H), 1.84 – 1.17 (m, 4H), 1.75 (t, *J* = 4.0 Hz, 1H) ;^{13}C NMR (100 MHz, $CDCl_3$): δ = 219.3 (C), 76.8 (C), 76.6 (C), 48.1 (CH), 38.2 (CH_2), 28.7 (CH_2), 20.5 (CH_2), 18.8 (CH_2), 3.4 (CH_3).; IR (film, cm^{-1}): 3079, 2946, 2234, 1719, 1484, 1159, 1074.; HRMS (EI): Exact mass calculated for $C_9H_{12}O$ $[M]^+$ = 136.0888, $[M-H]^+$ found = 136.0853.



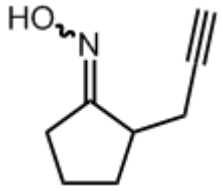
(*E/Z*)-2-(But-2-yn-1-yl)cyclopentanone oxime (2.20, Figure 2.7): Synthesized according to the general procedure for oxime condensation using 2-(but-2-yn-1-yl)cyclopentanone (3.4 mmol, 0.46 g). 0.43 g (83%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.38 and 0.32 (20% EtOAc/Hexanes).; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (br s, 1H), 2.69 - 2.34 (m, 4H), 2.31 – 2.20 (m, 1H), 2.11 - 2.01 (m, 1H), 1.93 - 1.84 (m, 1H), 1.77 (t, *J* = 2.4 Hz, 1H), 1.71 - 1.51 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5 (C), 77.1 (C), 76.4 (C), 42.6 (CH), 38.9 (CH_2), 31.4 (CH_2), 30.5 (CH_2), 27.4 (CH_2), 23.2 (CH_2),

22.3 (CH_2), 21.6 (CH_2), 20.1 (CH_2), 3.5 (CH_3); IR (film, cm^{-1}): 3282, 3116, 2964, 2915, 2866, 2240, 1676, 1435, 1207.; HRMS (EI): Exact mass calculated for $C_9H_{13}NO$ $[M]^+$ = 151.0997 not found, exact mass calculated for $C_9H_{12}NO$ $[M-H]^+$ = 150.0919, $[M-H]^+$ found = 150.0926.

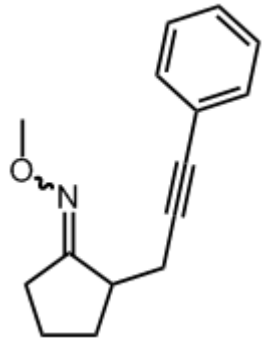


2-(Prop-2-yn-1-yl)cyclopentanone (2.18, Figure 2.8): To a flame dried flask under argon and charged with a magnetic stir bar was added LiCl (42 mmol, 1.8 g) and DMF (8.1 mL). Methyl 2-oxo-1-(prop-2-yn-1-yl)cyclopentanecarboxylate (8.3 mmol, 1.5 g) was added via syringe in DMF (3.0 mL) and the flask was attached with a reflux condenser. The mixture was refluxed at 140°C for 2h and cooled to room temperature before a 10% HCl solution was added down the condenser. The resulting solution was stirred for 10 minutes, extracted with EtOAc and washed 10 times with a 1:1 brine and distilled water solution. The crude mixture was concentrated under reduced pressure and columned using 20% EtOAc:Hexanes to afford 0.64 g (63%) of the desired ketone. The spectral data was in agreement with the literature.[70]

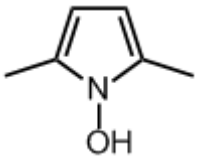
[70] Ovaska, T. V.; Reisman, S. E.; Flynn, M. A. *Org. Lett.* **2001**, *3*, 115.



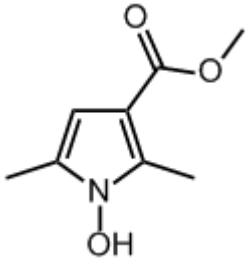
2-(Prop-2-yn-1-yl)cyclopentanone oxime (2.19, Figure 2.8): Synthesized according to the general procedure for oxime condensation using 2-(prop-2-yn-1-yl)cyclopentanone (1.9 mmol, 0.64 g). 0.46 g (64%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.20 and 0.16 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.58 (br s, 1H), 2.73-2.66 (m, 1H), 2.64-2.54 (m, 2H), 2.46-2.39 (m, 1H), 2.33 (ddd, *J* = 16.8, 8.4, 2.8Hz, 1H), 2.15-2.07 (m, 1H), 1.97 (d, J = 2.8Hz, 1H), 1.94-1.86 (m, 1H), 1.71-1.57 (m, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 167.2 (C), 82.4 (C), 69.1 (CH), 42.0 (CH), 31.3 (CH_2), 27.3 (CH_2), 22.3 (CH_2), 21.1 (CH_2).; IR (film, cm^{-1}): 3276, 3127, 2943, 2903, 2249, 1668, 1442.; HRMS (EI): Exact mass calculated for $C_8H_{11}NO$ $[M]^+$ = 137.0841, $[M-H]^+$ found = 137.0834.



(*E/Z*)-2-(3-Phenyl-prop-2-ynyl)-cyclopentanone *O*-methyl-oxime (2.9a, Figure 2.7): Synthesized according to the general procedure for oxime condensation using 2-(3-Phenylprop-2-ynyl)cyclopentanone (1.5 mmol, 0.29 g) and *O*-methyl hydroxylamine hydrochloride (1.6 mmol, 0.14 g). 0.28 g (85%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.38 (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.38 (m, 2H), 7.29-7.26 (m, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 2.88 - 2.65 (m, 2H), 2.57 - 2.33 (m, 3H), 2.33-2.18 (m, 1H), 1.94 - 1.85 (m, 1H), 1.73 - 1.62 (m, 2H), 1.91-1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6 (C), 166.1 (C), 131.6 (2 x CH), 128.2 (2 x CH), 127.6 (2 x CH), 123.8 (C), 88.3 (C), 81.3 (C), 61.5 (2 x CH_3), 42.3 (CH), 39.1 (CH), 31.6 (CH_2), 31.3 (CH_2), 30.7 (CH_2), 27.8 (CH_2), 23.3 (CH_2), 22.6(CH_2), 22.5 (CH_2), 21.0 (CH_2).; IR (film, cm^{-1}): 3048, 2991, 2974, 2867 2242, 1474, 1184; HRMS: Exact mass calculated for $C_{15}H_{17}NO$ $[M]^+$ = 227.1310 not found, exact mass calculated for $C_{14}H_{14}N$ $[M\text{-}OMe]^+$ = 196.1126, $[M\text{-}OMe]^+$ found = 197.0614.

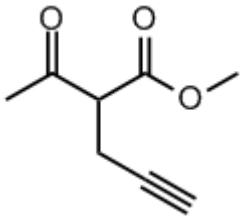


2,5-Dimethyl-1H-pyrrol-1-ol (3.12, eq. 3.3): Synthesized using the general alkyne cyclization procedure using hex-5-yn-2-one oxime (0.50 mmol, 0.056 g) in EtOH (2.5 mL). The crude was columned using 20% EtOAc:Hexanes to afford 0.012 g (22%) of the desired pyrrole. TLC R_f = 0.58 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.07 (br s, 1H), 5.62 (s, 2H), 2.21 (S, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 124.2 (C), 100.2 (CH), 10.6 (CH_3).; IR (film, cm^{-1}): 3447, 3295, 2956, 2892, 1433, 1227, 1153, 999.; HRMS (EI): Exact mass calculated for C_6H_9NO $[M]^+$ = 111.0684, $[M+1]^+$ found = 111.0688.

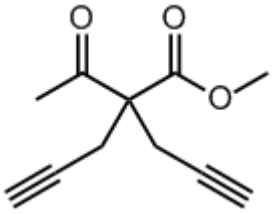


Methyl 1-hydroxy-2,5-dimethyl-1H-pyrrole-3-carboxylate (3.13, eq 3.4): Synthesized using the general alkyne cyclization procedure using methyl 2-(1-(hydroxyimino)ethyl)pent-4-ynoate (0.50 mmol, 0.085 g) in EtOH (2.5 mL). The crude was columned directly using 20% EtOAc:Hexanes to give 0.078 g (92%) of the hydroxy pyrrole. TLC R_f = 0.28 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): 8.23 (br s, 1H), 6.00 (s, 1H), 3.72 (s, 3H), 2.34 (s, 3H), 2.16 (s, 3H).; δ =; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2 (C), 132.2 (C), 125.3 (C), 104.9 (C), 102.6 (CH), 51.0 (CH_3), 10.3 (CH_3), 9.9 (CH_3).;IR (film, cm^{-1}): 3205, 2960, 2919, 2853,

1659, 1524, 1443, 1349, 1242, 1086.; HRMS (EI): Exact mass calculated for $C_8H_{11}NO_3$ $[M]^+$ = 169.0739, [M+1] found = 169.0738.



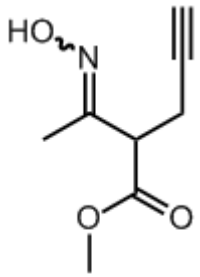
Methyl 2-acetylpent-4-ynoate (3.1, Scheme 3.1): Synthesized according to general procedure B using methyl acetoacetate (25 mmol, 2.7 mL) and columned using 20% EtOAc:Hexanes to give 1.8 g (47%) of the alkylated ketoester. The spectral data was in agreement with the literature.[71]



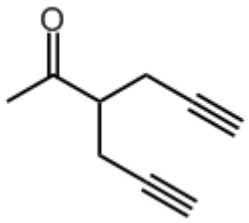
Methyl 2-acetyl-2-(prop-2-yn-1-yl)pent-4-ynoate (3.2, eq 3.2): Synthesized according to general procedure B using methyl acetoacetate (25 mmol, 2.7 mL) and columned using 20% EtOAc:Hexanes to give 0.95 g (20%) of the dialkylated ketoester as a side product. TLC R_f = 0.62 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ =; 3.78 (s, 3H), 2.96 (dq, *J* = 17.4, 2.7 Hz, 4H), 2.21 (s, 3H), 2.03 (t, *J* = 2.7 Hz, 2H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.7 (C), 169.7 (C), 78.4 (C), 72.0 (C), 62.4 (C), 53.2 (C_3), 26.1 (C_3), 21.8 (CH_2).; IR (film, cm^{-1}): 3282, 2960, 2920,

[71] Chen, Y-F.; Wang, H-F.; Wang, Y.; Luo, Y-C.; Zhu, H-L.; Xu, P-F. *Adv. Synth. Catal.* **2010**, *352*, 1163.

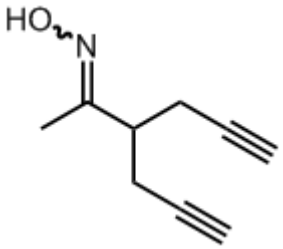
2852, 2118, 1744, 1717, 1435, 1358, 1278.; HRMS (EI): Exact mass calculated for $C_{11}H_{12}O_3$ $[M]^+$ = 192.0786 not found, Exact mass calculated for $C_{10}H_9O_3$ $[M\text{-}Me]^+$ = 177.0552, $[M\text{-}Me]^+$ found = 177.0555.



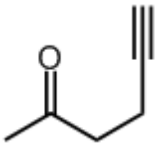
Methyl 2-(1-(hydroxyimino)ethyl)pent-4-ynoate (3.3, eq. 3.2): Synthesized according to the general procedure for oxime condensation using methyl 2-acetylpent-4-ynoate (2.1 mmol, 0.33 g). 0.13 g (37%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.59 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (br s, 1H), 3.75 (s, 3H), 3.49 (dd, *J* = 8.4, 7.2 Hz, 1H), 2.77 (ddd, *J* = 16.8, 8.7, 2.7 Hz, 1H), 2.64 (ddd, *J* = 17.1, 8.1, 2.7 Hz, 1H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.93 (s, 3H): ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8 (C), 154.6 (C), 80.4 (C), 70.5 (CH), 52.5 (CH_3), 50.4 (CH), 18.9 (CH_2), 12.0 (CH_3).; IR (film, cm^{-1}): 3341, 3251, 2934, 2888, 2205, 1718, 1489, 1439, 1391; HRMS (EI): Exact mass calculated for $C_8H_{11}NO_3$ $[M]^+$ = 169.0739, [M+1] found = 169.0743.



3-(Prop-2-yn-1-yl)hex-5-yn-2-one (3.6, eq. 3.2): To a flame dried flask under argon and charged with a magnetic stir bar was added LiCl (11 mmol, 0.46 g) and DMF (1.0 mL). Methyl 2-acetyl-2-(prop-2-yn-1-yl)pent-4-ynoate (2.2 mmol, 0.42 g) was added via syringe in DMF (1.9 mL) and the flask was attached with a reflux condenser. The mixture was refluxed at 120°C for 2h and cooled to room temperature before a 10% HCl solution was added down the condenser. The resulting solution was stirred for 10 minutes, extracted with EtOAc and washed 10 times with a 1:1 brine and distilled water solution. The crude mixture was concentrated under reduced pressure and columned using 20% EtOAc:Hexanes to give 0.18 g (61%) of the desired ketone. TLC R_f 0.64 (20% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.84 (quint, *J* = 6.9 Hz, 1H), 2.64 - 2.47 (m, 4H), 2.27 (s, 3H), 2.02 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 131.9 (CH), 128.9 (CH), 128.3 (CH), 122.1 (C), 86.7 (C), 84.2 (C), 15.3 (CH_2).; IR (film, cm^{-1}): 3080, 2917, 2238, 1718, 1490, 1442, 1163.; HRMS (EI): Exact mass calculated for $C_9H_{10}O$ $[M]^+$ = 134.0732, [M+1] found = 134.0735.

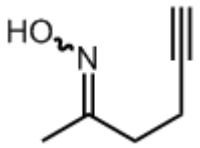


(*E/Z*)-3-(Prop-2-yn-1-yl)hex-5-yn-2-one oxime (3.7 eq. 3.2): Synthesized according to the general procedure for oxime condensation using 3-(prop-2-yn-1-yl)hex-5-yn-2-one (1.3 mmol, 0.18 g). 0.11 g (54%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.54 and 0.37 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ =; 8.59 (br s, 1H), 2.67 (q, *J* = 6.3 Hz, 1H), 2.53 (2 x d, *J* = 2.7 Hz, 2.4 Hz, 1H + 1H), 2.04 (t, *J* = 2.7 Hz, 2H), 1.93 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9 (C), 81.0 (C), 70.6 (CH), 43.1 (CH), 20.9 (CH), 12.2 (CH_3).; IR (film, cm^{-1}) 3295, 2920, 2842, 2119, 1653, 1430, 1204 ;HRMS (EI): Exact mass calculated for $C_9H_{11}NO$ $[M]^+$ = 149.0841, $[M+1]^+$ found = 149.0820.

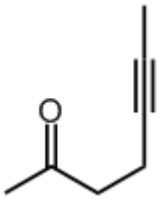


Hex-5-yn-2-one (3.4, Scheme 3.1): Synthesized according to general procedure C using acetoacetate (200 mmol, 20 mL) and distilled under reduced pressure (26mmHg) to give 6.3 g (36%) of the desired ketone as a colourless oil. The spectral data was in agreement with the literature.[72]

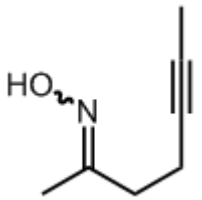
[72] Görl, C.; Alt, H. G. *J. Organomet. Chem.* **2007**, *692*, 5727.



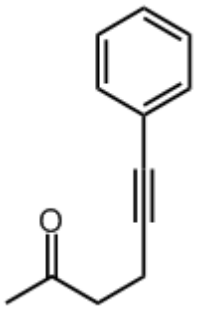
Hex-5-yn-2-one oxime (3.5, Scheme 3.1): Synthesized according to the general procedure for oxime condensation using hex-5-yn-2-one (21 mmol, 2.0 g). 0.90 g (40%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.33 and 0.44 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (br s, 1H), 2.59 (dt, *J* = 7.2, 1.5 Hz, 2H), 2.45 (dt, *J* = 7.2, 2.7 Hz, 2H), 1.99 (t, *J* = 2.4 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (C), 83.2 (C), 69.0 (CH), 27.8 (CH_2), 20.4 (CH_3), 14.7 (CH_3).; IR (film, cm^{-1}) 3268, 2937, 2918, 2823, 2120, 1691, 1436, 1371, 1276; HRMS (EI): Exact mass calculated for C_6H_9NO $[M]^+$ = 111.0684, [M+1] found = 111.0668.



Hept-5-yn-2-one (3.8, Scheme 3.1): Synthesized according to general procedure C using acetoacetate (120 mmol, 13 mL) and distilled under reduced pressure (22mmHg) to give 4.5 g (36%) of the desired ketone as a yellow oil. The spectral data was in agreement with the literature.**Error! Bookmark not defined.**[b)]

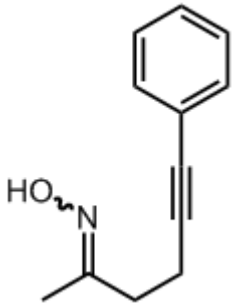


(*E*/*Z*)-Hept-5-yn-2-one oxime (3.9): Synthesized according to the general procedure for oxime condensation using hept-5-yn-2-one (18 mmol, 2.0g). 0.78 g (34%) of a 2:1 mixture of oxime isomers was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.44 and 0.31 (20% EtOAc:Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ =; 2.54 (t, *J* = 8.4Hz, 1H) (A), 2.40-2.31 (m, 4H + 1H), 1.93 (s, 3H) (A), 1.90 (s, 3H) (B), 1.77-1.76 (m, 3H).' ^{13}C NMR (100 MHz, $CDCl_3$): δ =; 157.8 (C), 157.1 (C), 77.7 (C), 76.5 (C), 35.3 (CH_3), 28.3 (CH_3), 20.3 (CH_2), 16.1 (CH_2), 15.1 (CH_2), 13.6 (CH_2), 3.5 (CH_3), 3.4 (CH_3).; IR (film, cm^{-1}): 3216, 2915, 2858, 2736, 2230, 1668, 1444, 1371, 1345; HRMS (EI): Exact mass calculated for $C_7H_{11}NO$ $[M]^+$ = 125.0841, [M+1] found = 125.0814.



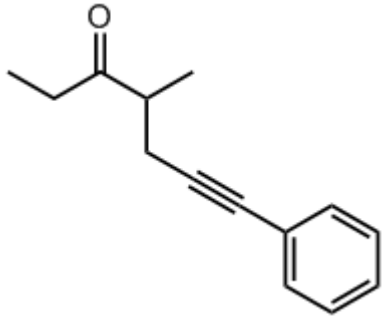
6-Phenylhex-5-yn-2-one (3.10, Scheme 3.1): To a flame-dried flask under argon was added triethylamine (62 mL) and iodobenzene (25 mmol, 2.8 mL). Bis(triphenylphosphine)palladium(II) chloride (0.21 mmol, 0.15 g) and copper(I)iodide (0.42 mmol, 0.079 g) were added and the mixture was stirred for 5 minutes. Hex-5-yn-2-one (20.8mmol, 2.00g) was added via syringe and the mixture

was stirred for 18h, washed twice with sodium bicarbonate, once with brine and dried over sodium sulfate before concentration under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel using 20% EtOAc:Hexanes to yield 2.1 g (58%) of the desired ketone. The spectral data was in agreement with the literature.[73]

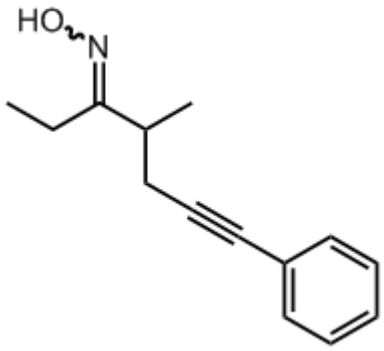


(*E/Z*)-6-Phenylhex-5-yn-2-one oxime (3.11, Scheme 3.1): Synthesized according to the general procedure for oxime condensation using 6-phenylhex-5-yn-2-one (12 mmol, 2.1 g). 1.5 g (64%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.39 and 0.25 (20% EtOAc:Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41- 7.37 (m, 2H), 7.29-7.25 (m, 3H), (A) 2.65 (t, *J* = 6.8 Hz, 2H), (B) 2.65 (t, *J* = 8.2 Hz, 2H), (B) 2.52 (t, *J* = 8.2 Hz, 2H), (A) 2.51 (t, *J* = 6.9 Hz, 2H), (A) 2.01 (s, 3H), (B) 1.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0 (C), 131.5 (CH), 131.5 (CH), 128.2 (CH), 128.1 (CH), 127.8 (CH), 127.7 (CH), 123.6 (C), 88.6 (C), 81.4 (C), 35.0 (CH_2), 28.1 (CH_2), 20.5 (CH_3), 16.7 (CH_2), 15.8 (CH), 13.7 (CH); IR (film, cm^{-1}): 3272, 2960, 2911, 2842, 2238, 1603, 1491, 1444, 1369; HRMS (EI): Exact mass calculated for $C_{12}H_{13}NO$ $[M]^+$ = 187.0997, [M+1] found = 187.0984.

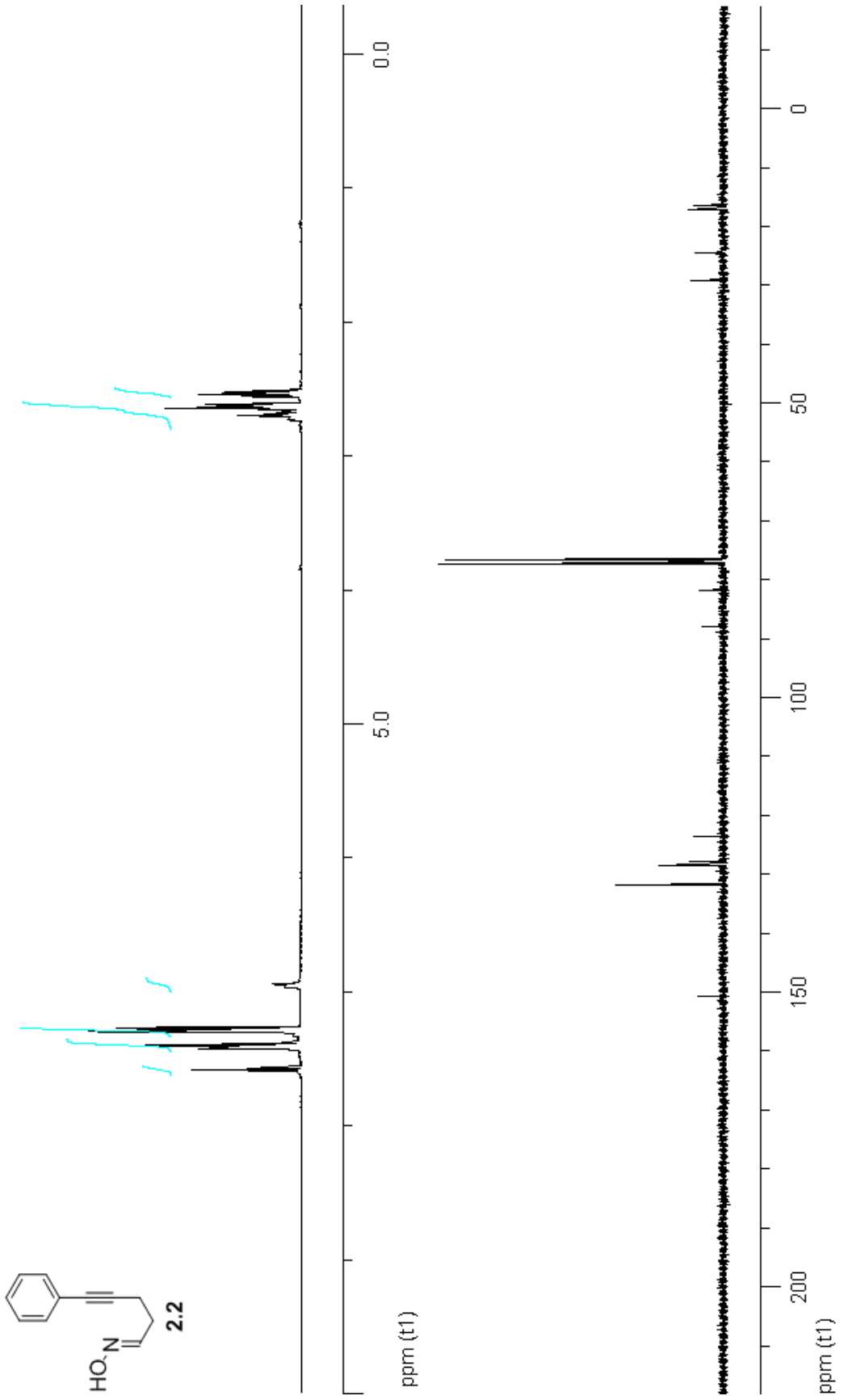
[73] Matsuda, I.; Komori, K-I.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 9072.



4-Methyl-7-phenyl-hept-6-yn-3-one: Synthesized according to general procedure A using 3-pentanone (22 mmol, 2.3 mL) and purified using flash column chromatography (100% toluene) to afford 0.33 g (11%) of the desired ketone. TLC R_f = 0.34 (100% toluene); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38-7.36 (m, 2H), 7.29-7.27 (m, 3H), 2.83 (sextet, *J* = 7.2 Hz, 1H), 2.68 (dd, *J* = 16.8, 6.4 Hz, 1H), 2.56 (dq, *J* = 7.2 ,3.6 Hz, 2H), 2.50 (dd, *J* = 16.8, 7.2 Hz, 1H), 1.25 (d, *J* = 7.2Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.3 (C), 131.5 (CH), 128.2 (CH), 127.8 (CH), 123.5 (C), 87.6 (C), 82.0 (C), 45.3 (CH), 34.7 (CH_2), 22.9 (CH_2), 16.4 (CH_3), 7.7 (CH_3).; IR (film, cm^{-1}): 3094, 2974, 2897, 2843, 2218, 1744, 1472, 1163.; HRMS: Exact mass calculated for $C_{14}H_{16}O$ $[M]^+$ = 200.1201, $[M+1]^+$ found = 200.1225.



(*E/Z*)-4-Methyl-7-phenyl-hept-6-yn-3-one oxime (3.15): Synthesized according to the general procedure for oxime condensation using 4-methyl-7-phenyl-hept-6-yn-3-one (1.7 mmol, 0.33 g). 0.24 g (67%) of the oxime was obtained following column chromatography using 20% EtOAc:Hexanes. TLC R_f = 0.37 and 0.44 (20% EtOAc/Hexanes); 1:1 mixture of oxime isomers ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (br s, 1H), 8.61 (br s, 1H), 7.41-7.37 (m, 2 x 2H), 3.51 (sextet, *J* = 7.2 Hz, 1H), 2.73-2.25 (m, 2 x 4H + 1H), 1.26 (dd, *J* = 10.9, 6.8 Hz, 2 x 3H), 1.15 (dt, *J* = 7.6Hz, 7.3 Hz, 2 x 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6 (C), 163.8 (C), 131.6 (CH), 131.5 (CH), 128.2 (CH), 128.1 (CH), 127.6 (2 x CH), 123.8 (C), 123.7 (C), 88.1 (C), 87.9 (C), 82.1 (C), 81.9 (C), 38.3 (CH), 31.9 (CH), 24.5 (CH_2), 24.4 (CH_2), 23.3 (CH_2), 20.3 (CH_2), 17.7 (CH_3), 16.1 (CH_3), 10.4 (2 x CH_3); IR (film, cm^{-1}): 3268, 2960, 2913, 2840, 2239, 1600, 1490, 1444, 1367; HRMS (EI): Exact mass calculated for $C_{14}H_{16}NO$ $[M]^+$ = 215.1310, [M+1] found = 215.1297.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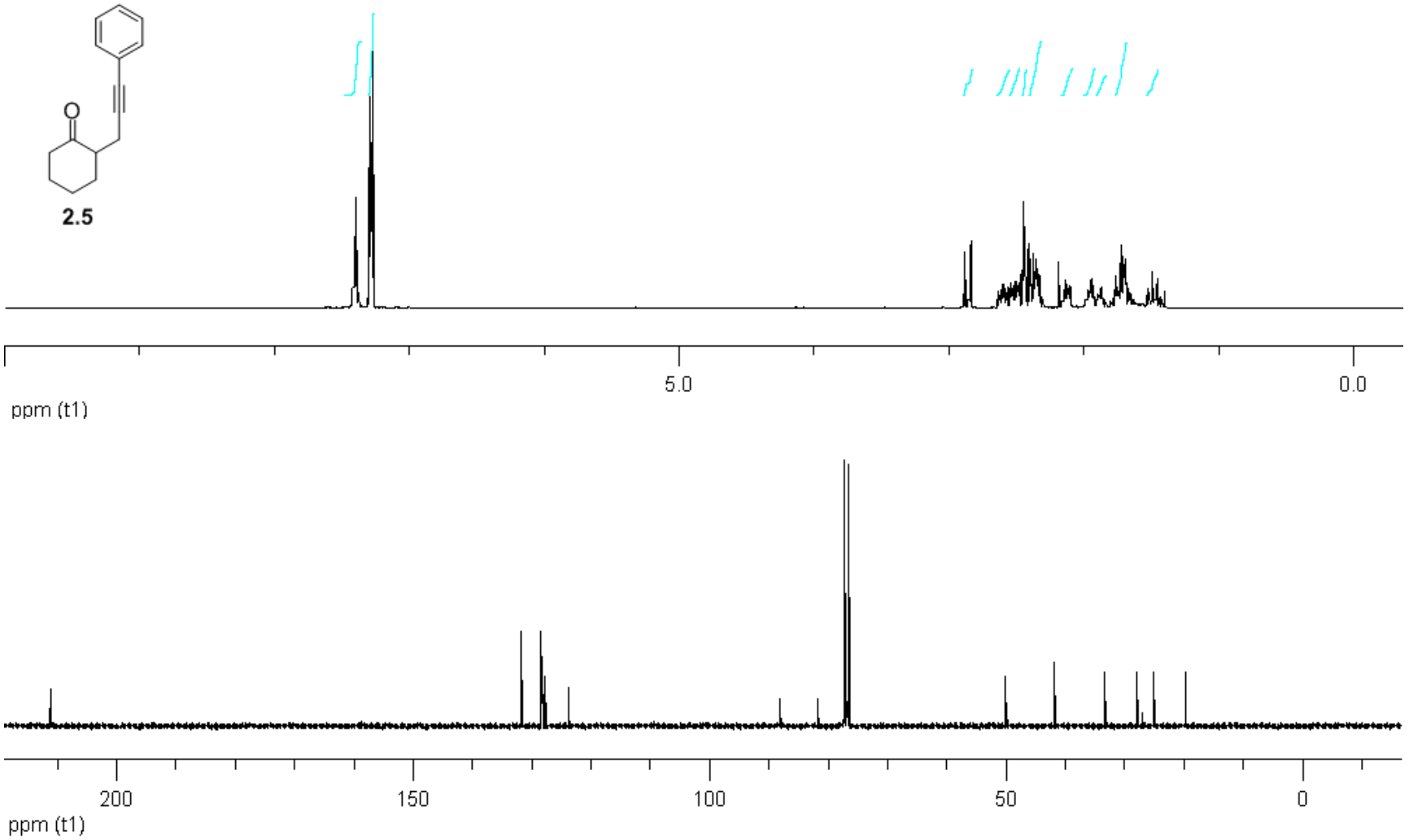
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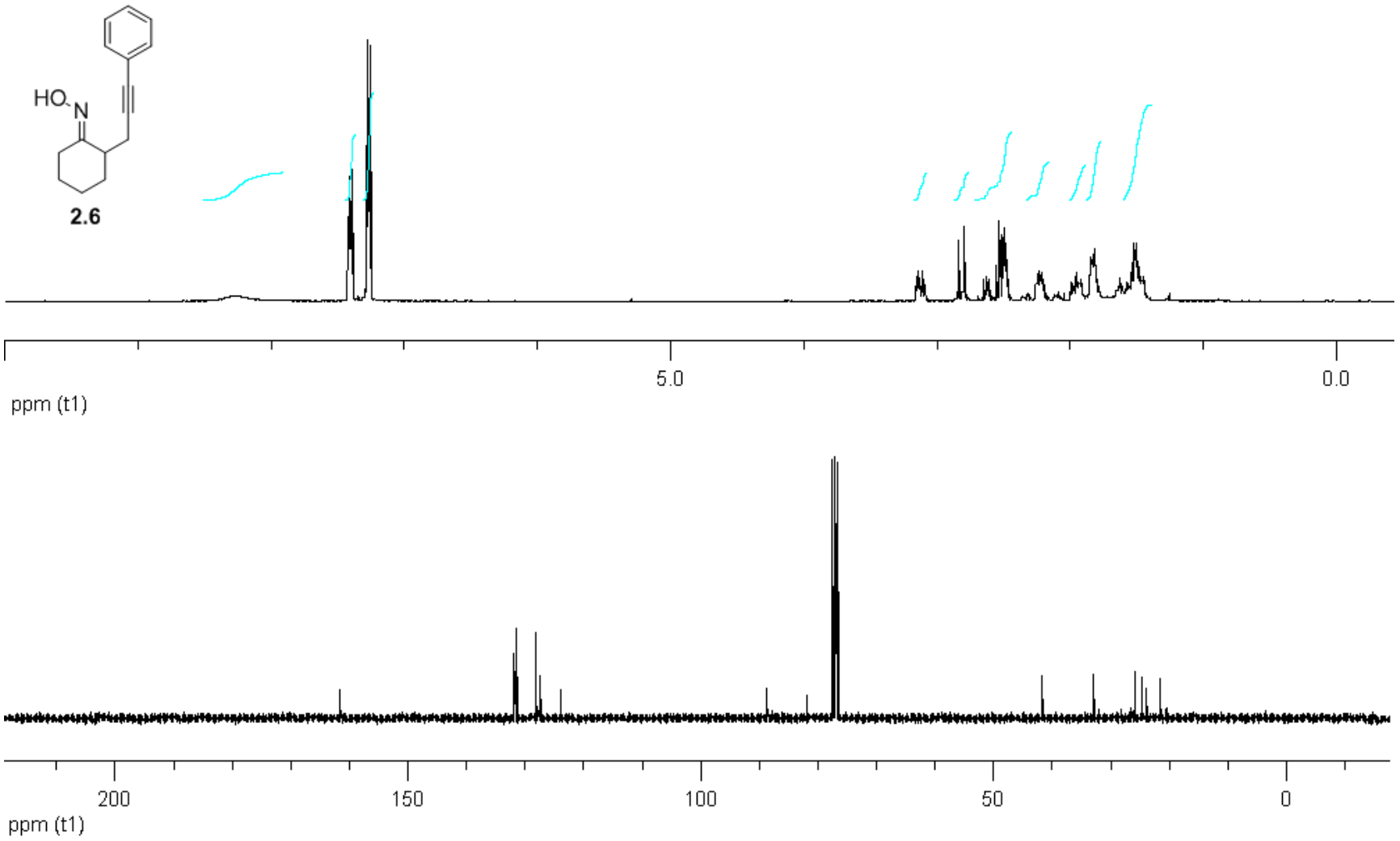
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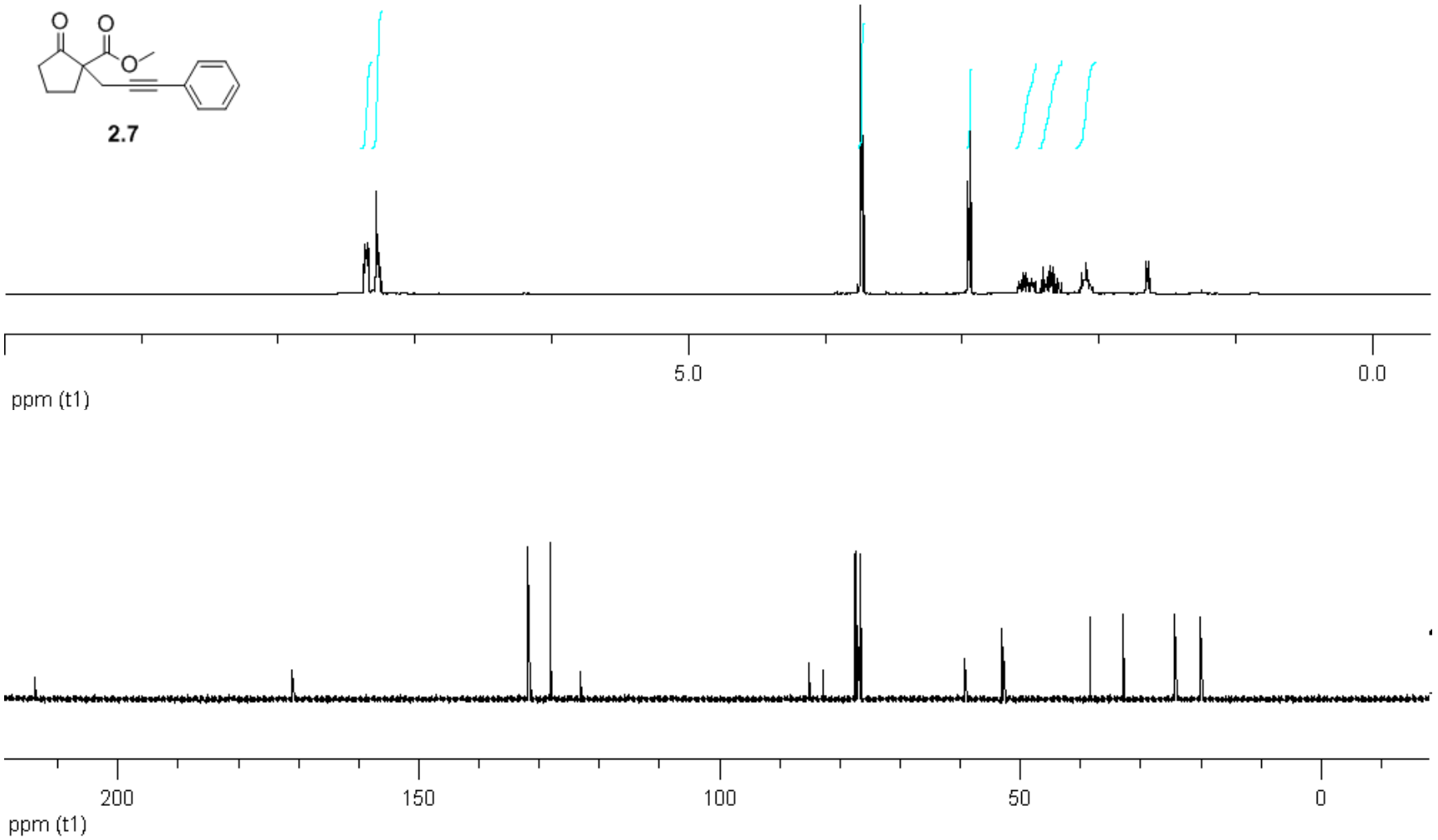
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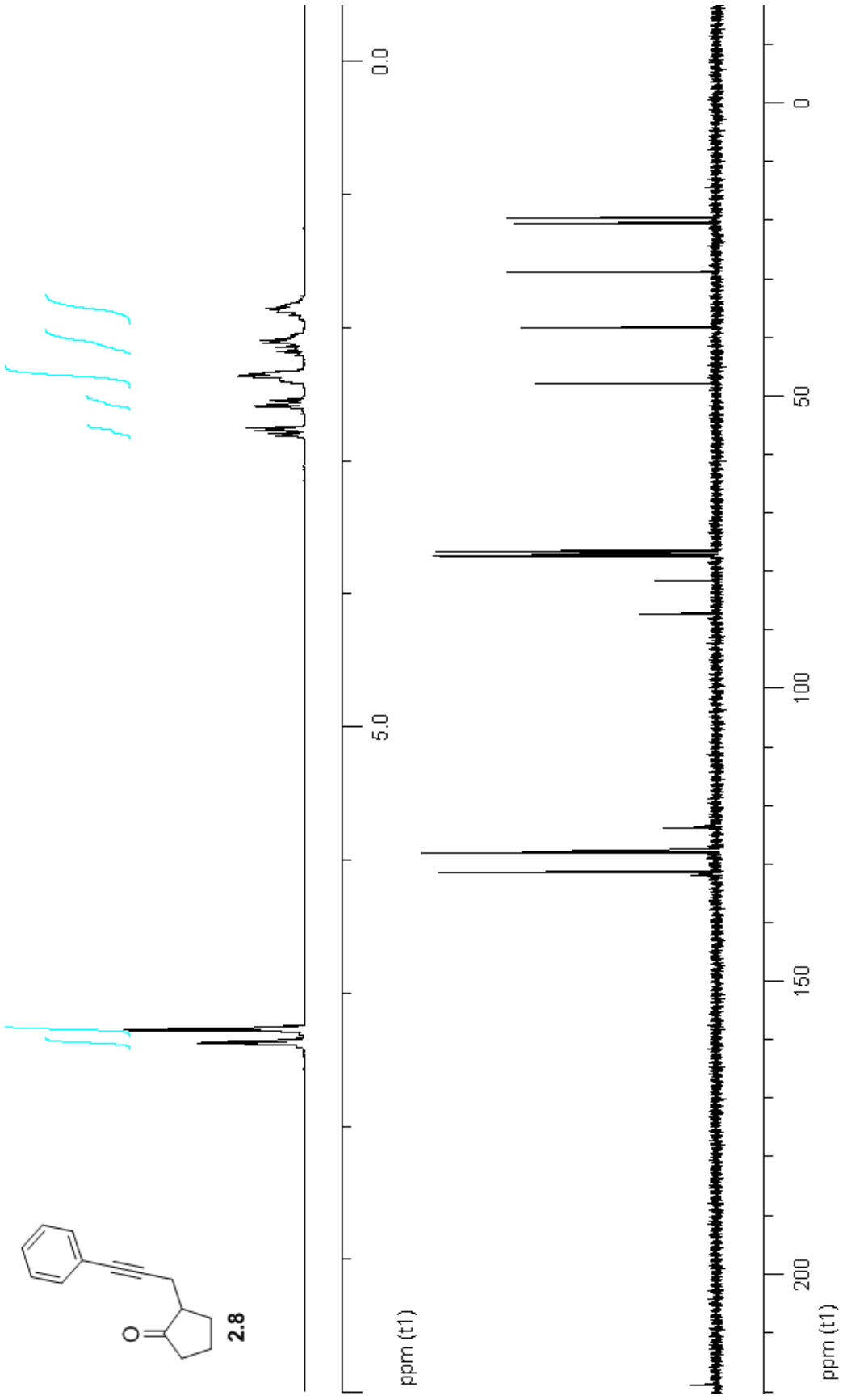
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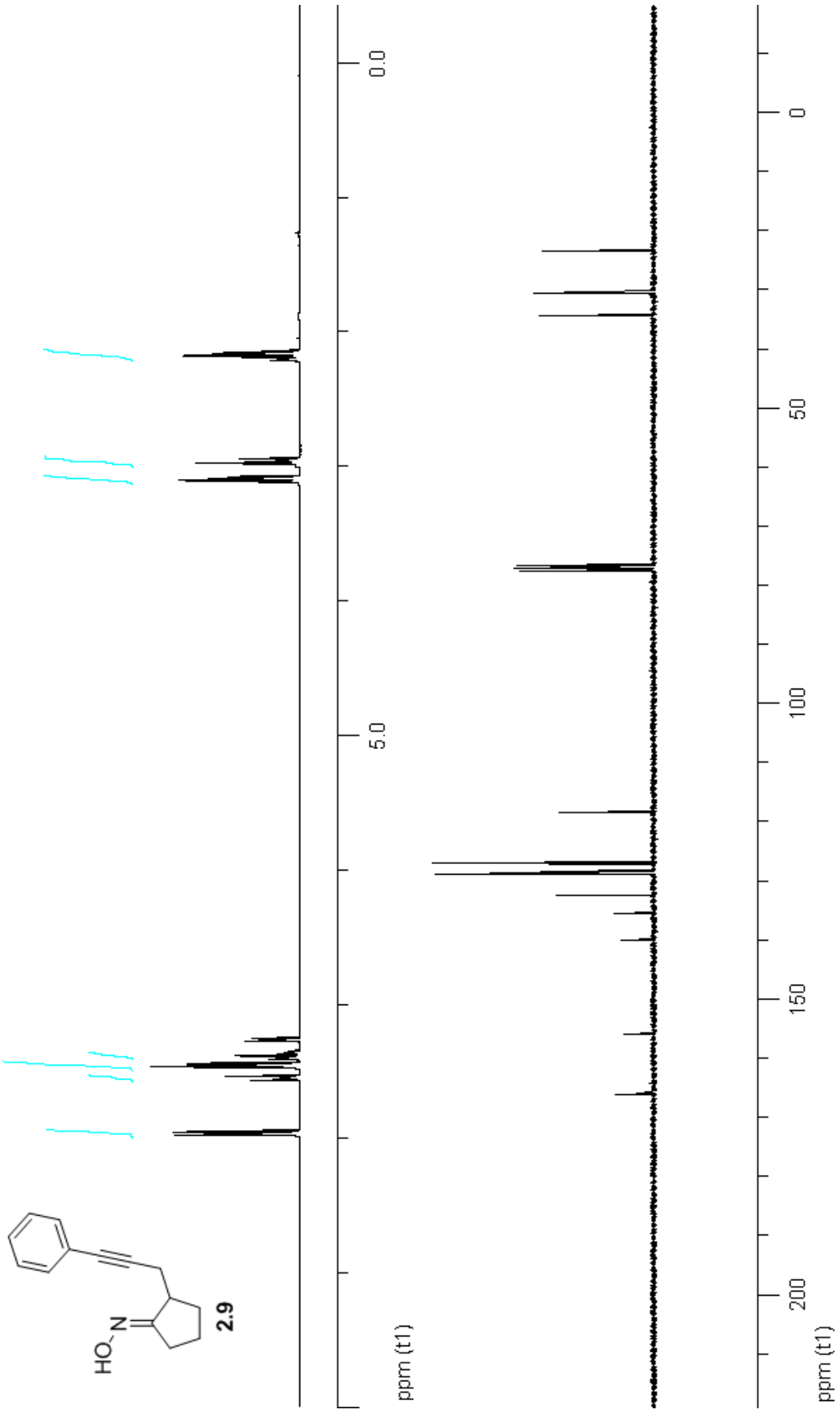
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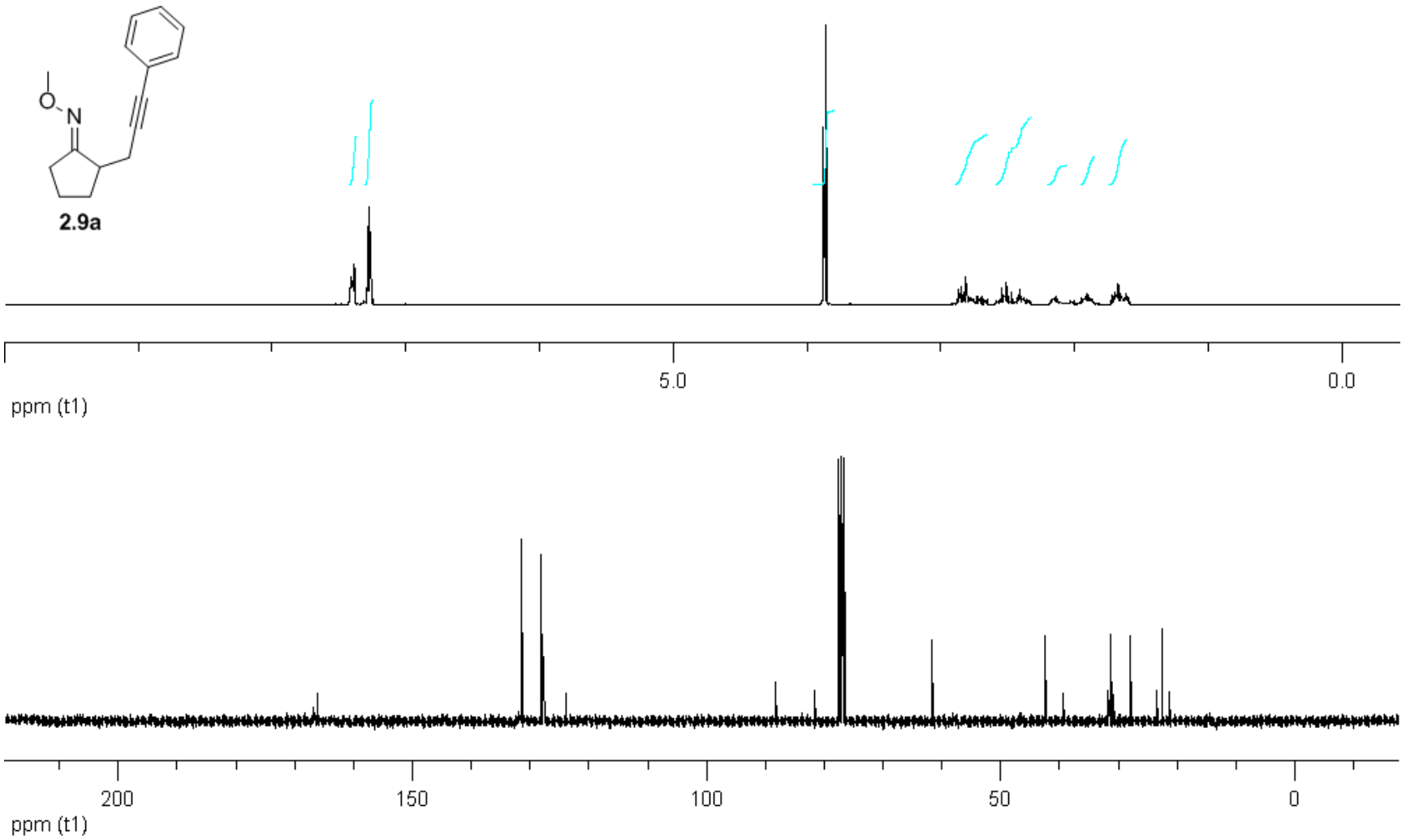
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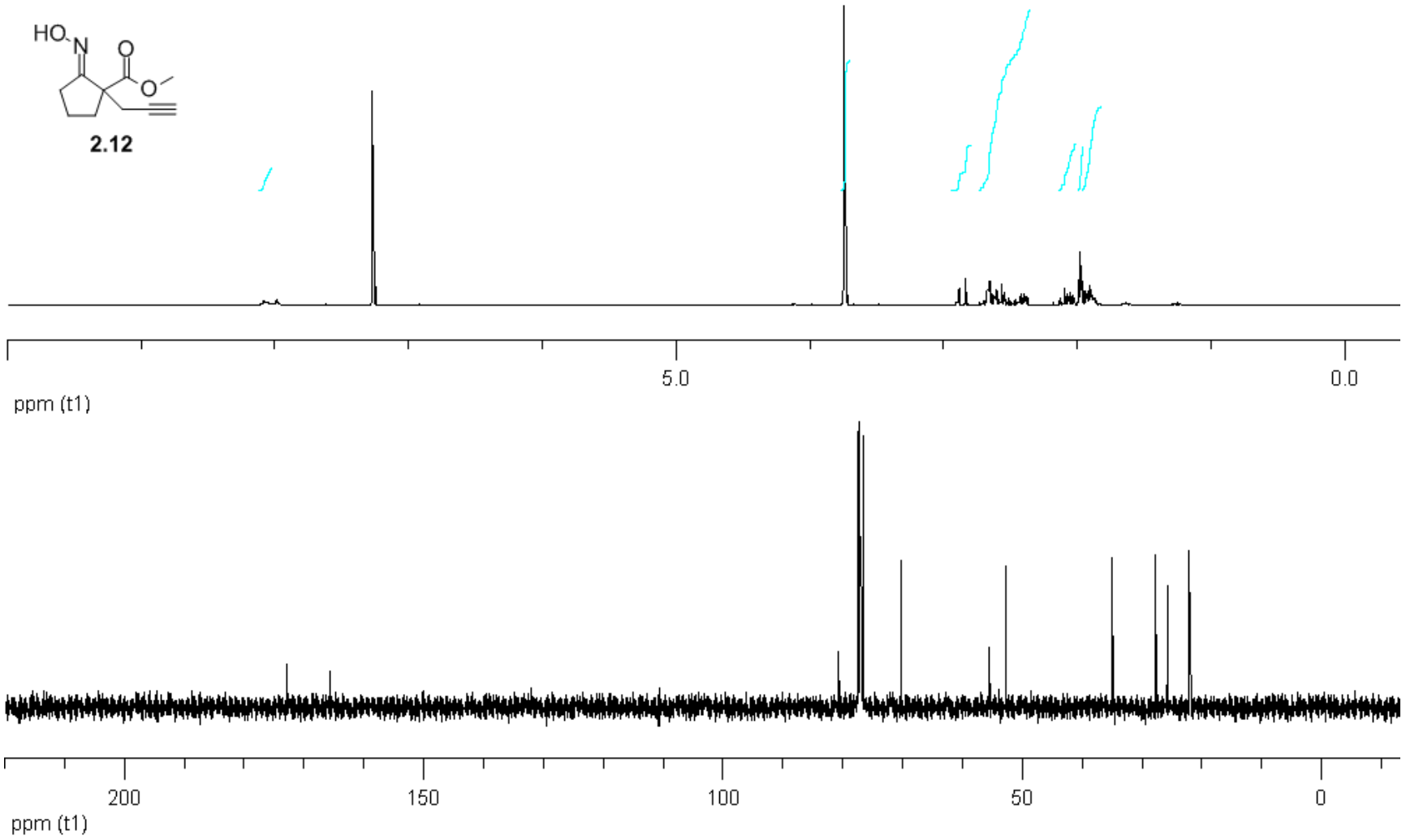
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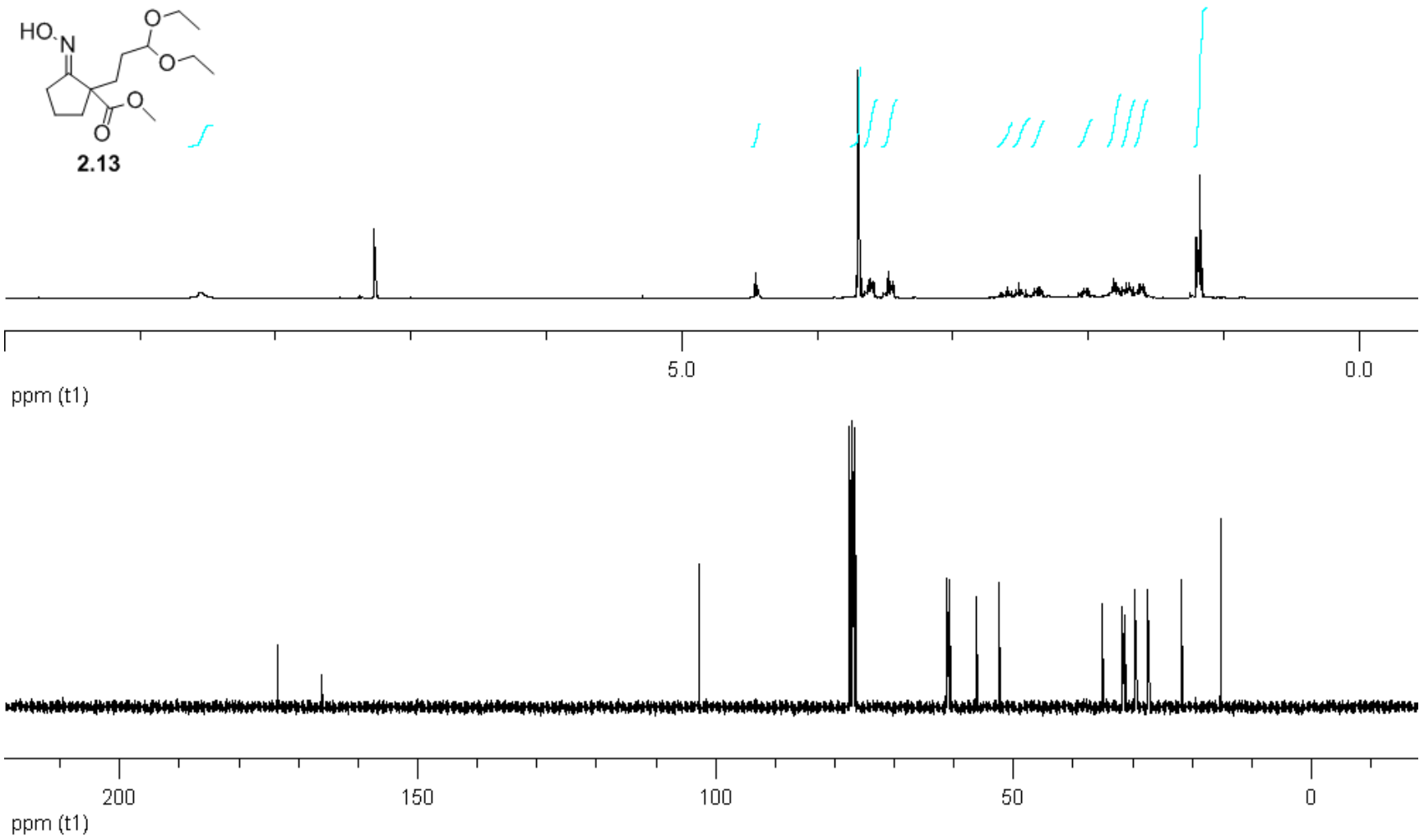
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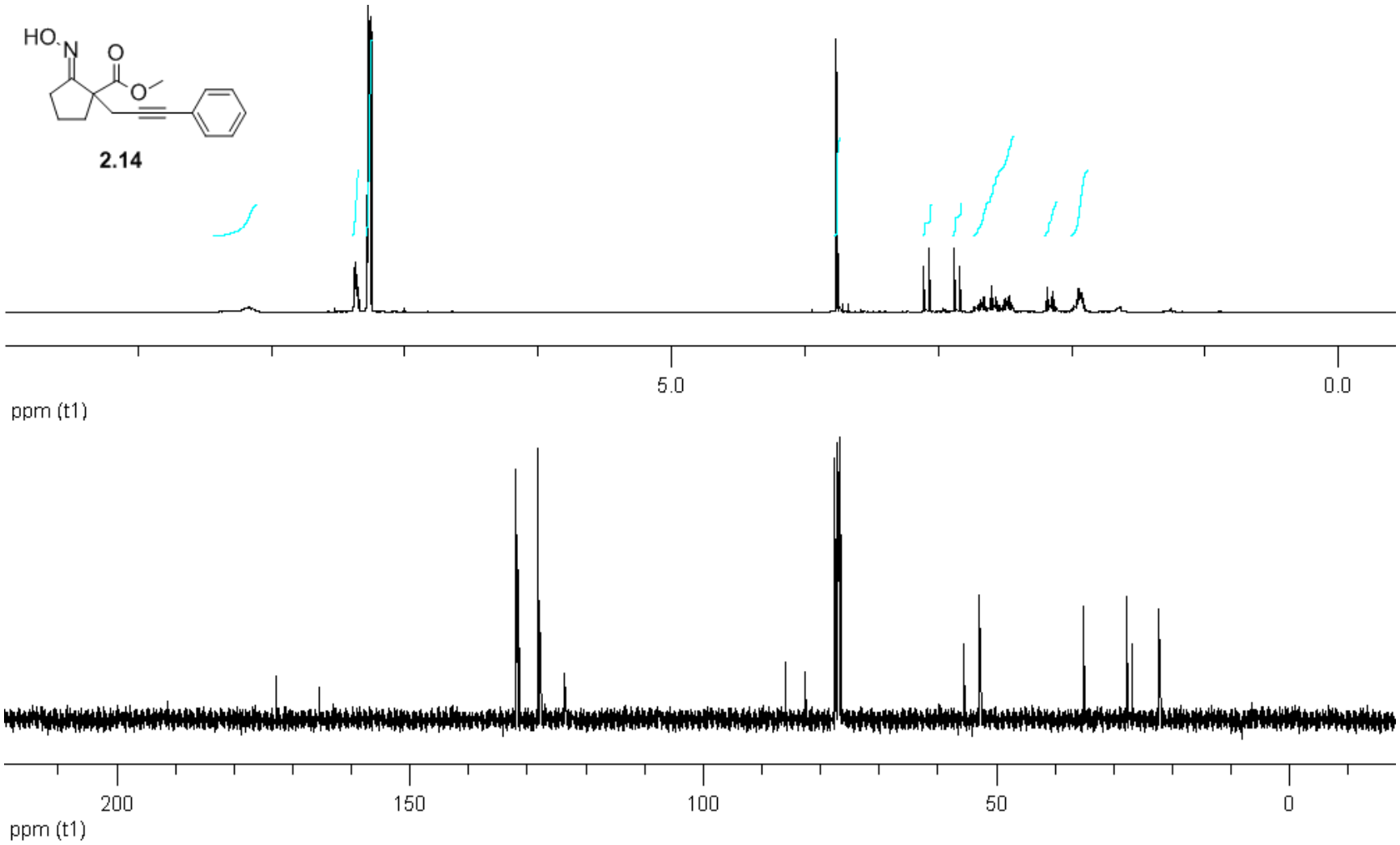
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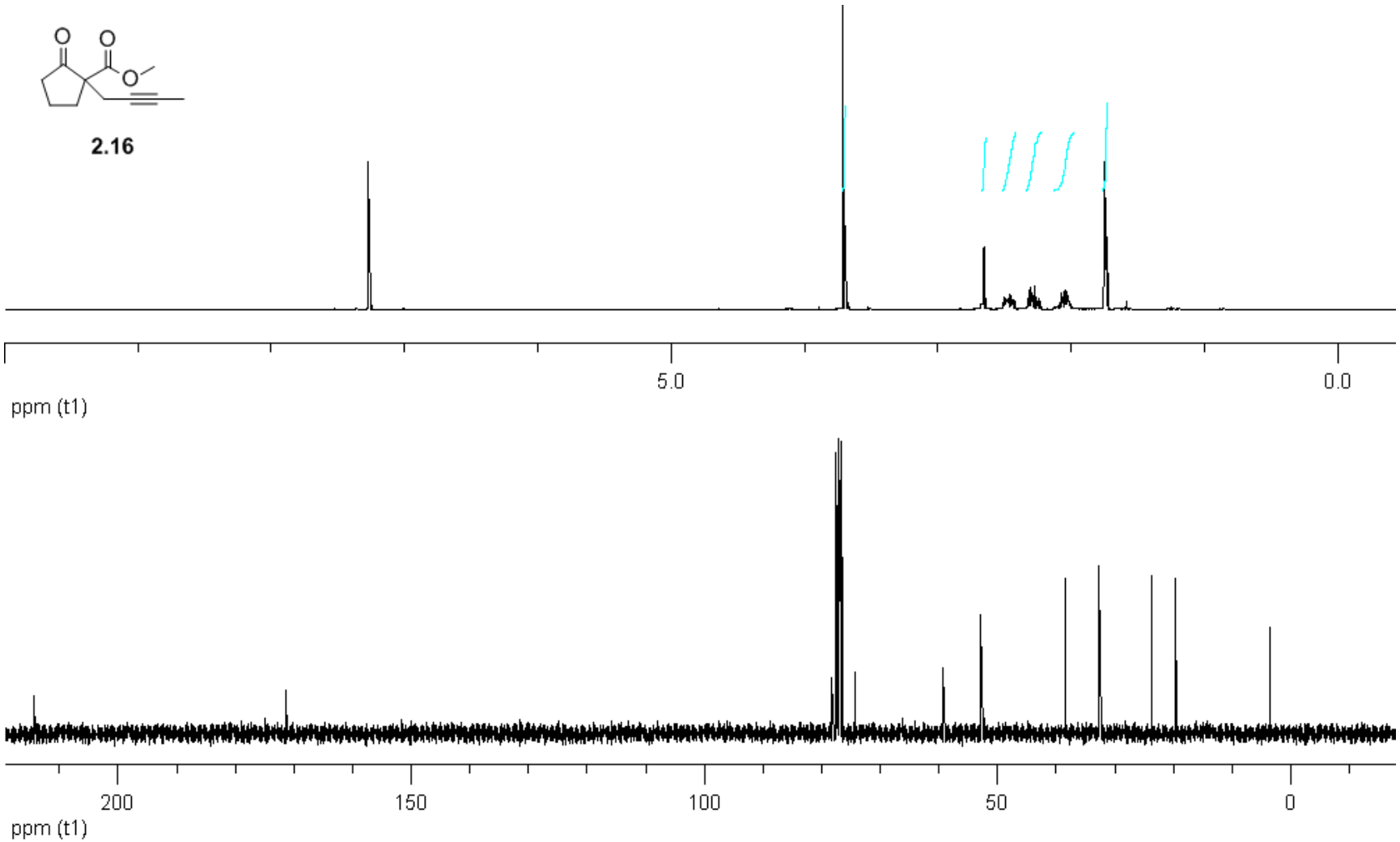
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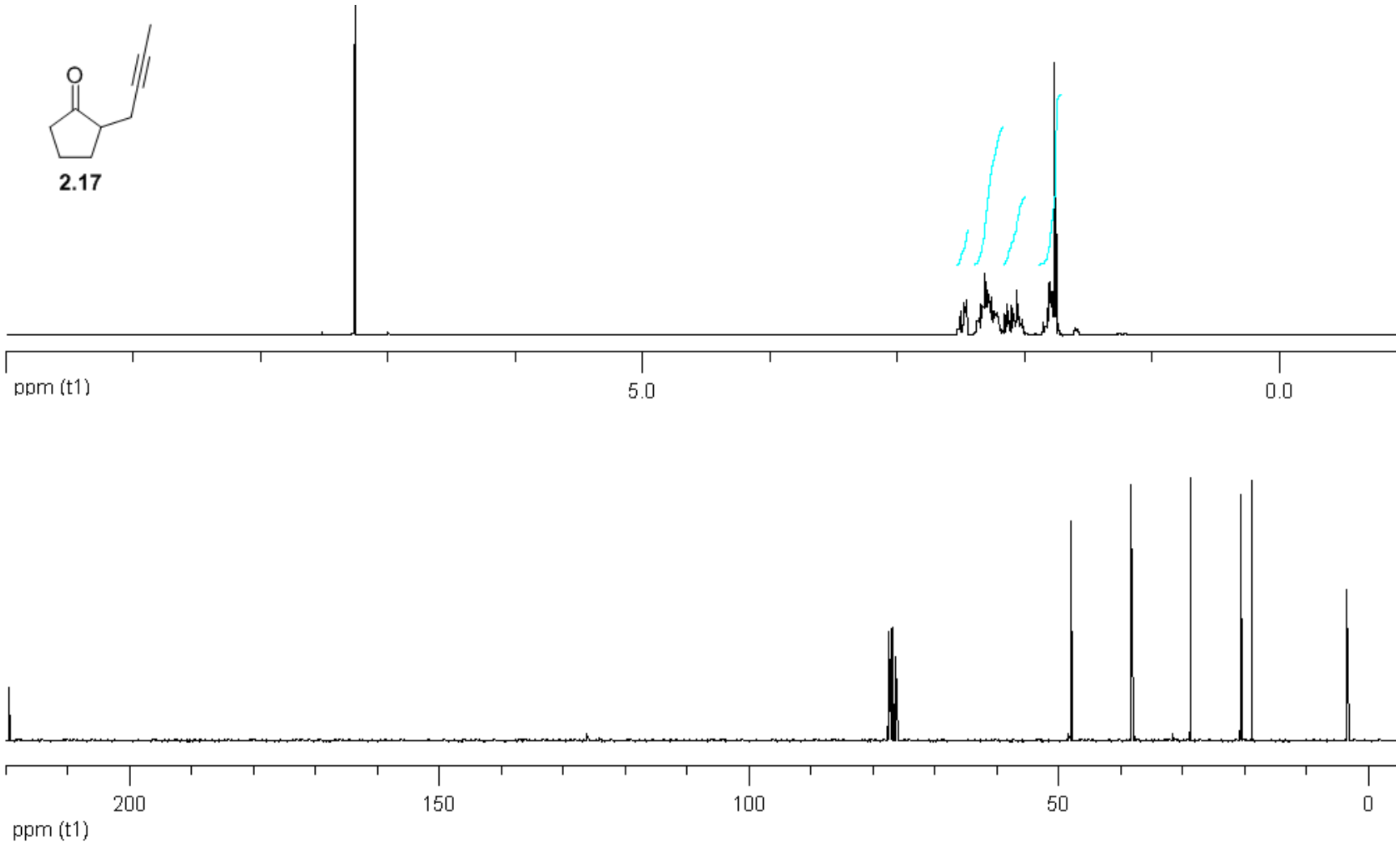
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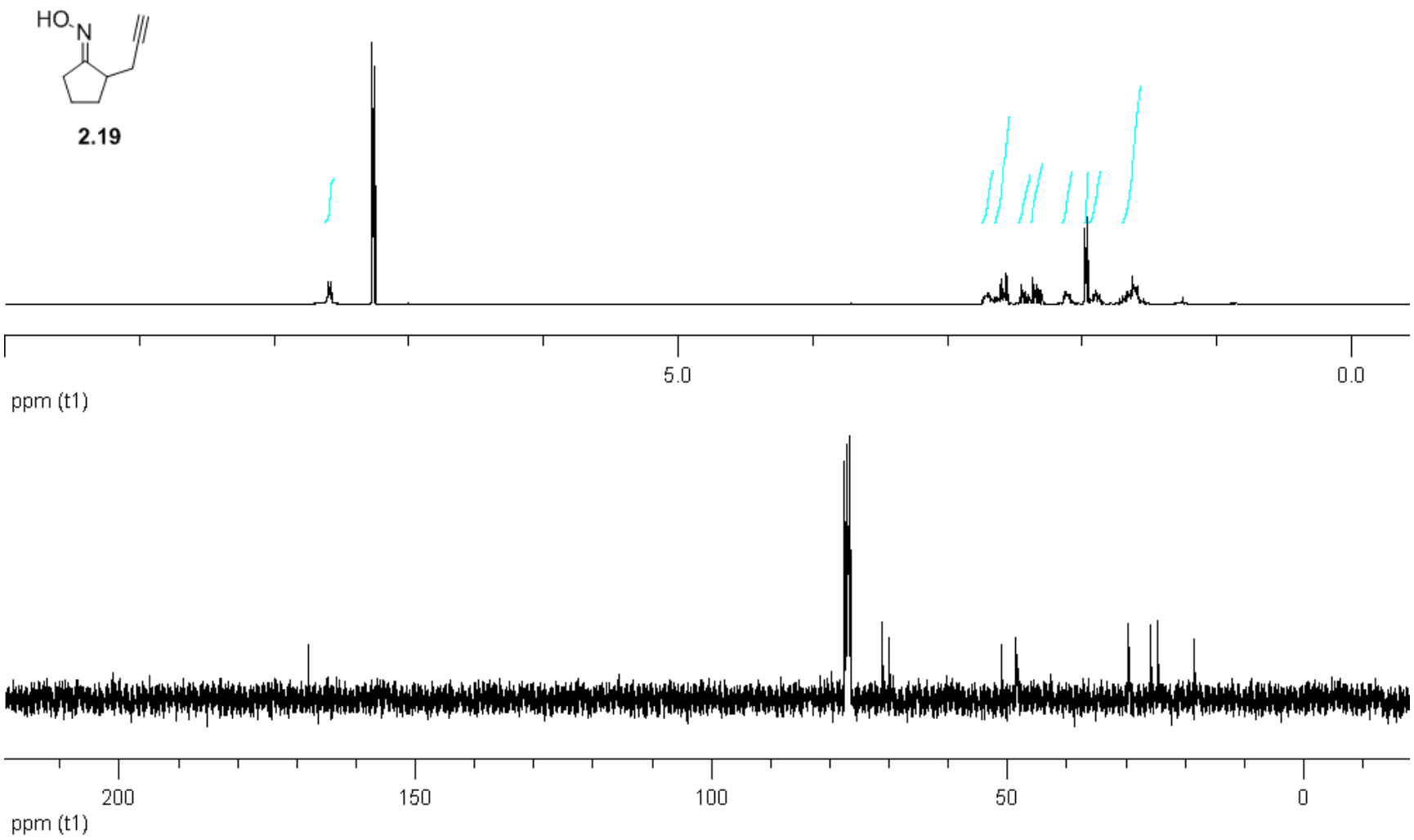
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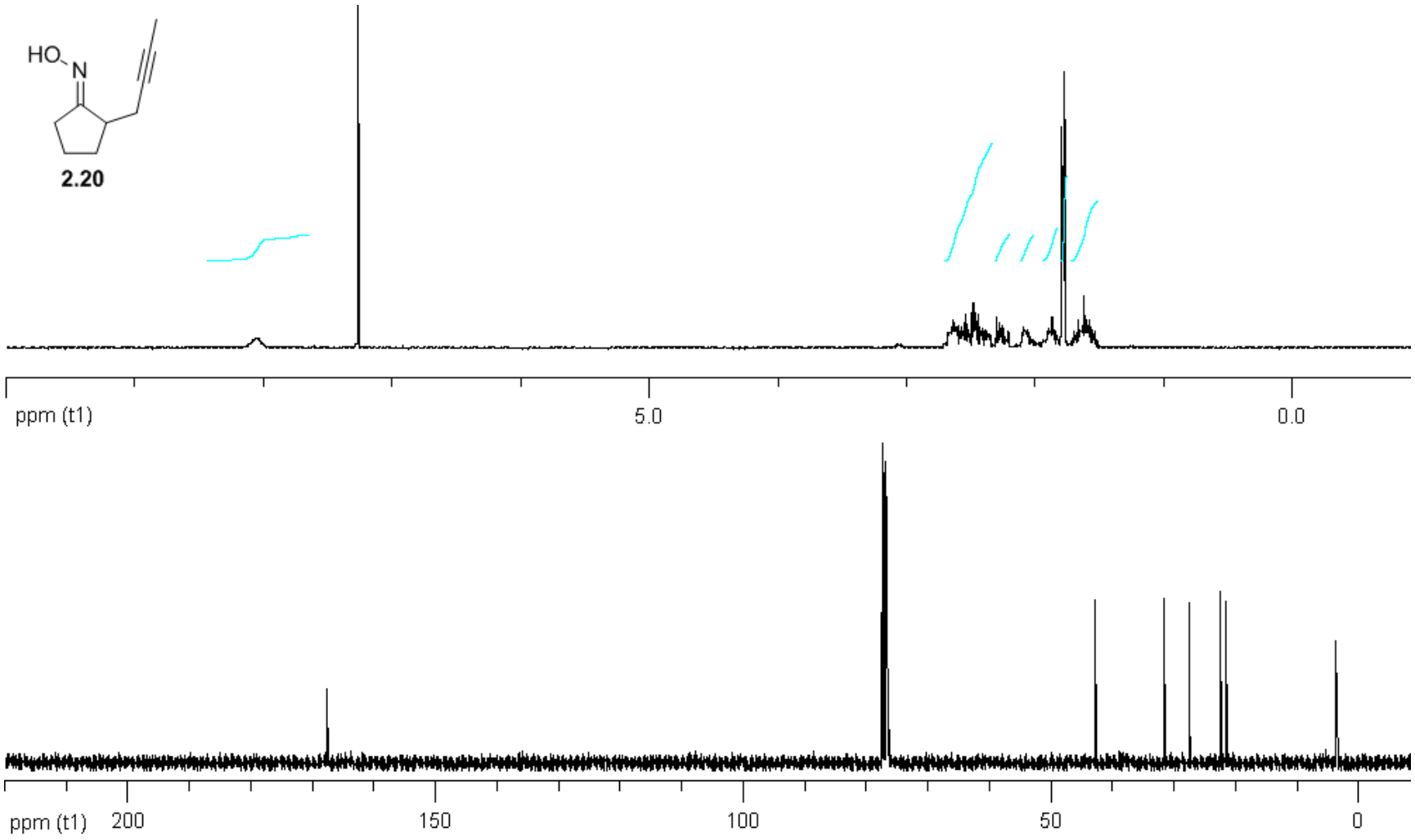
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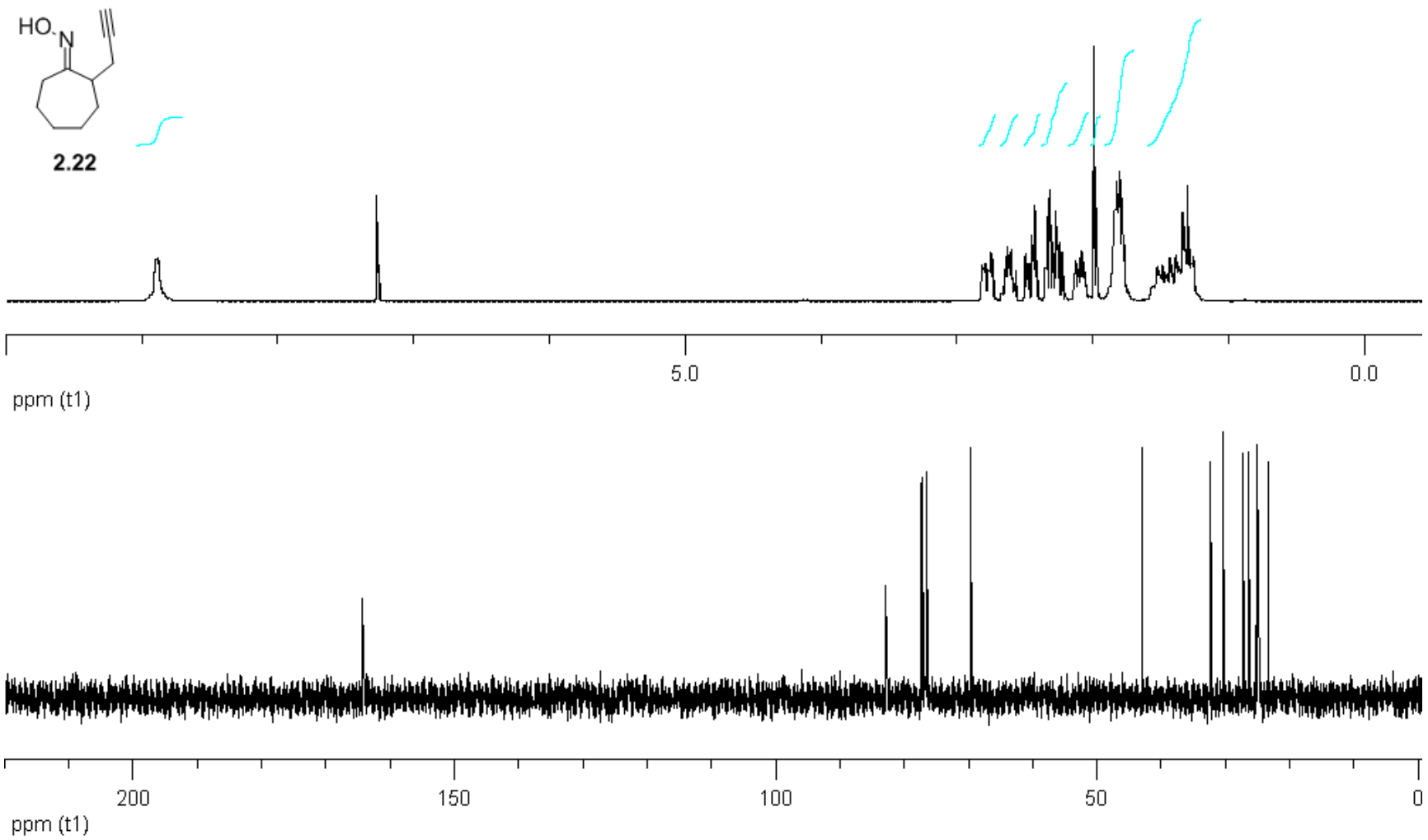
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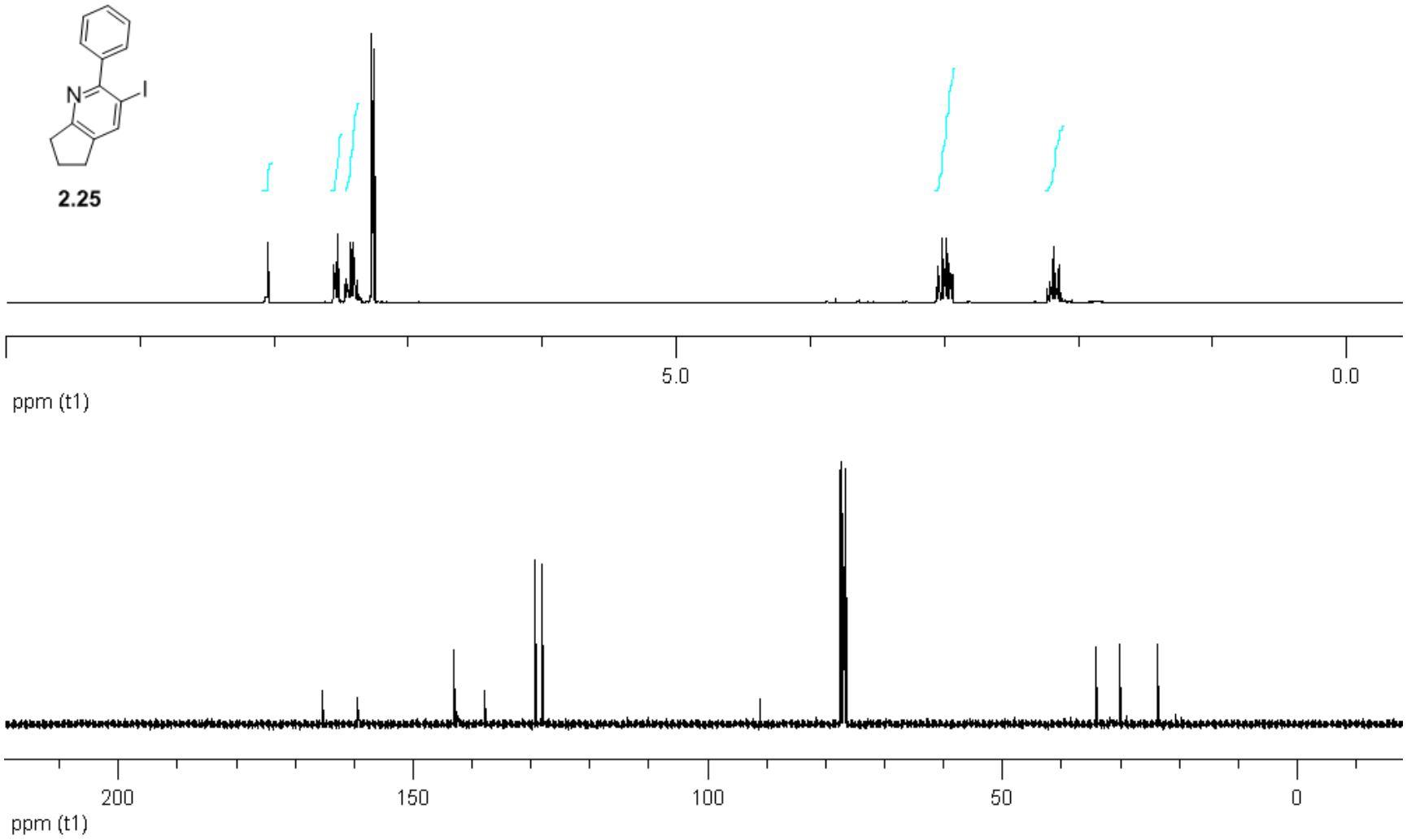
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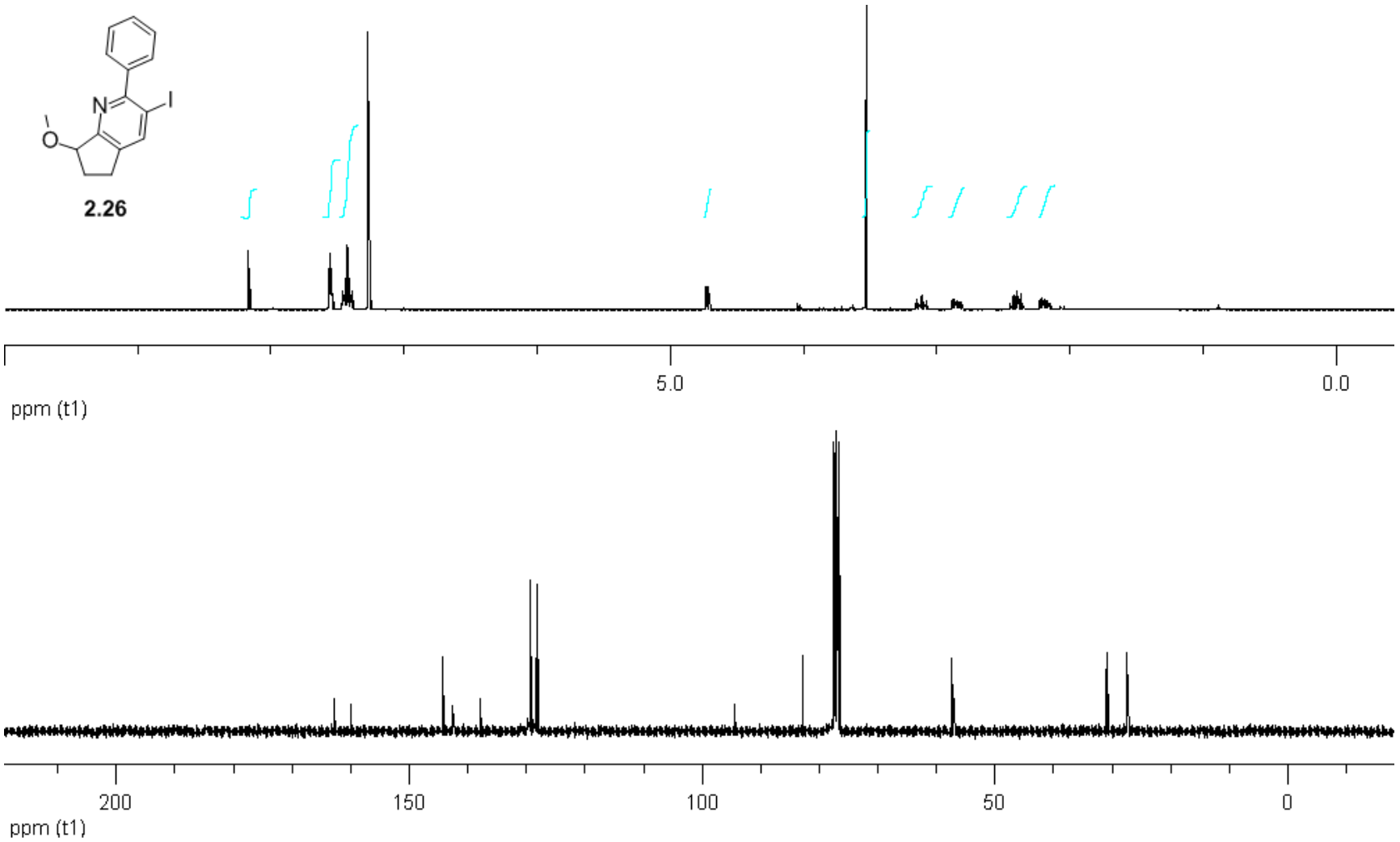
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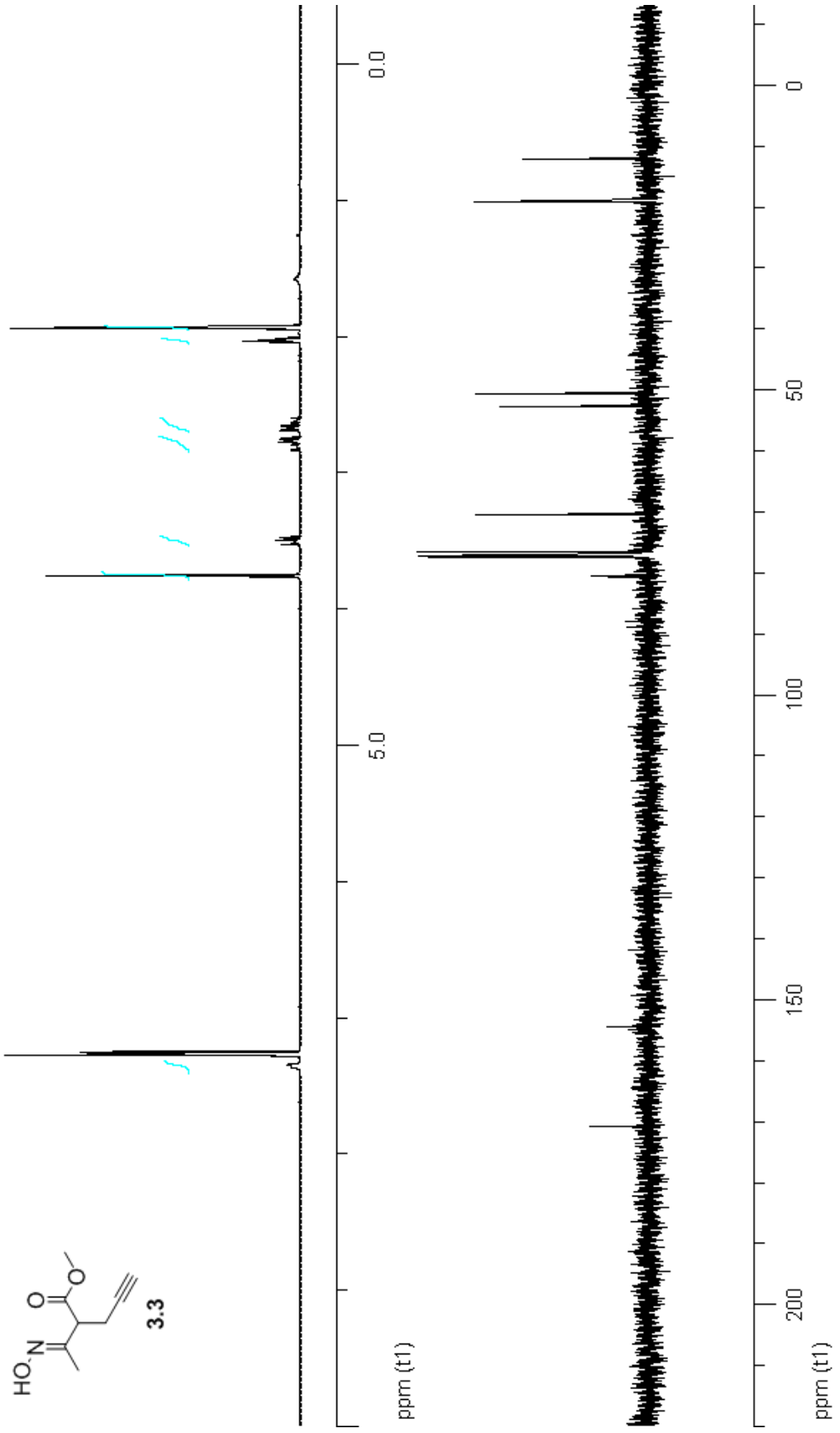
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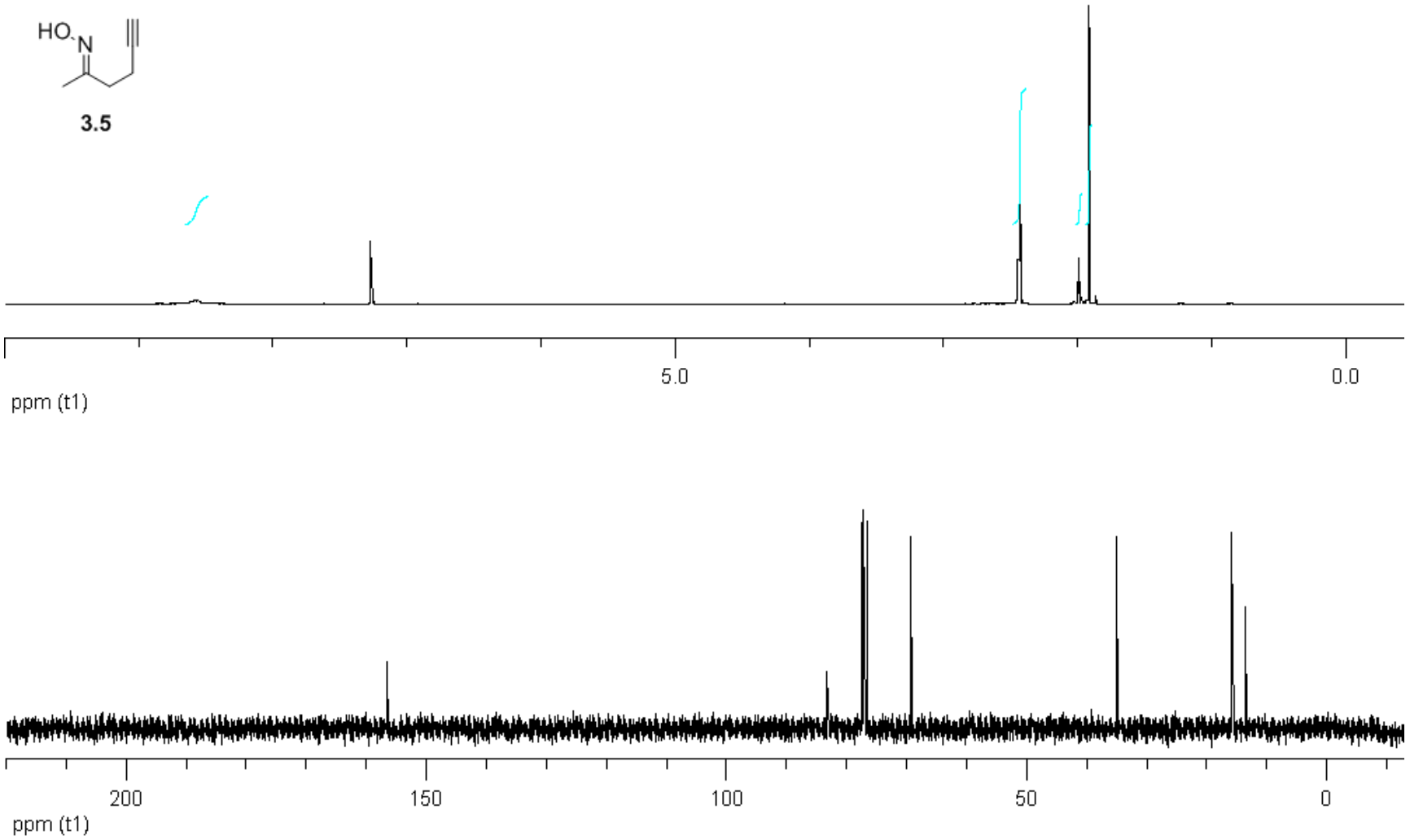
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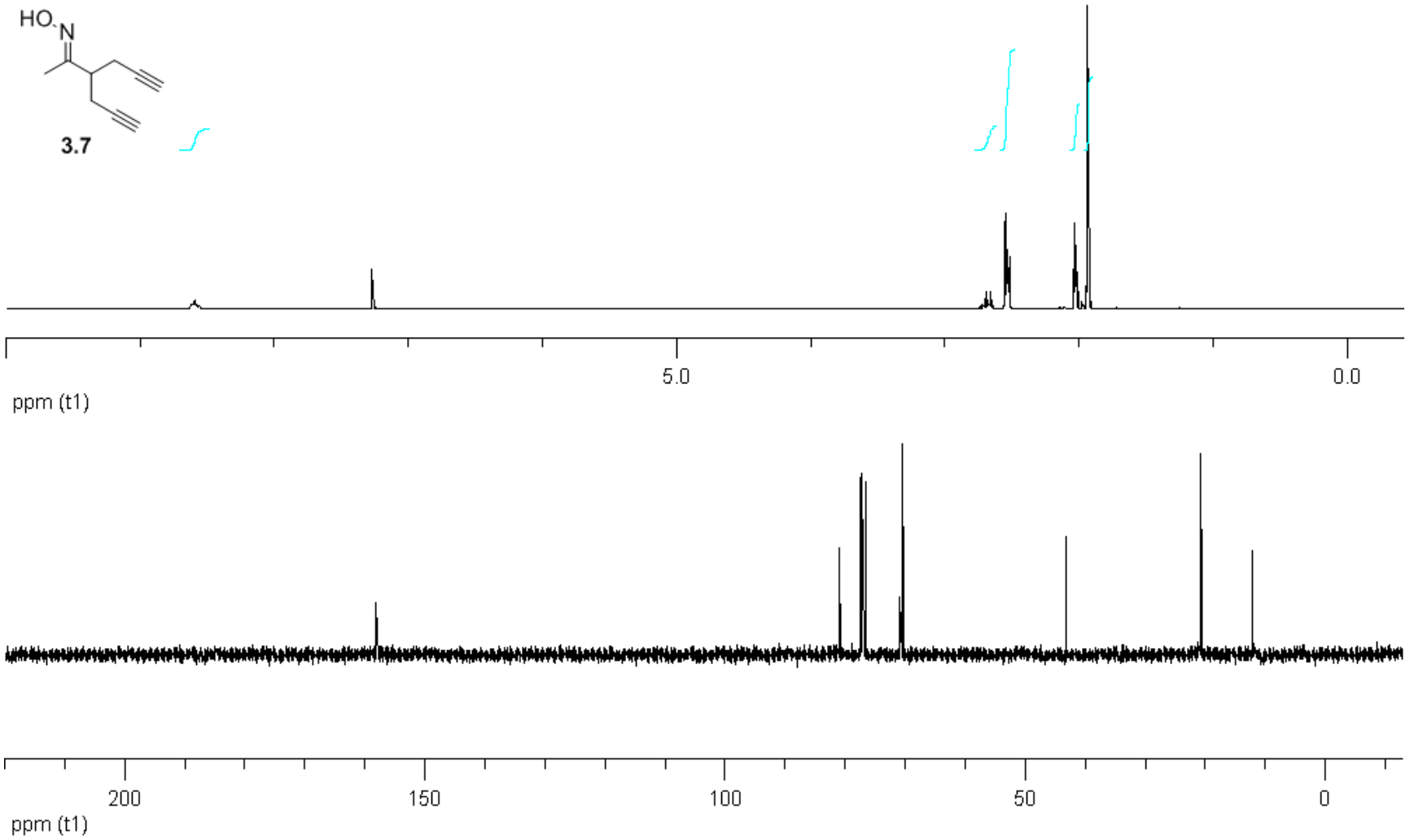
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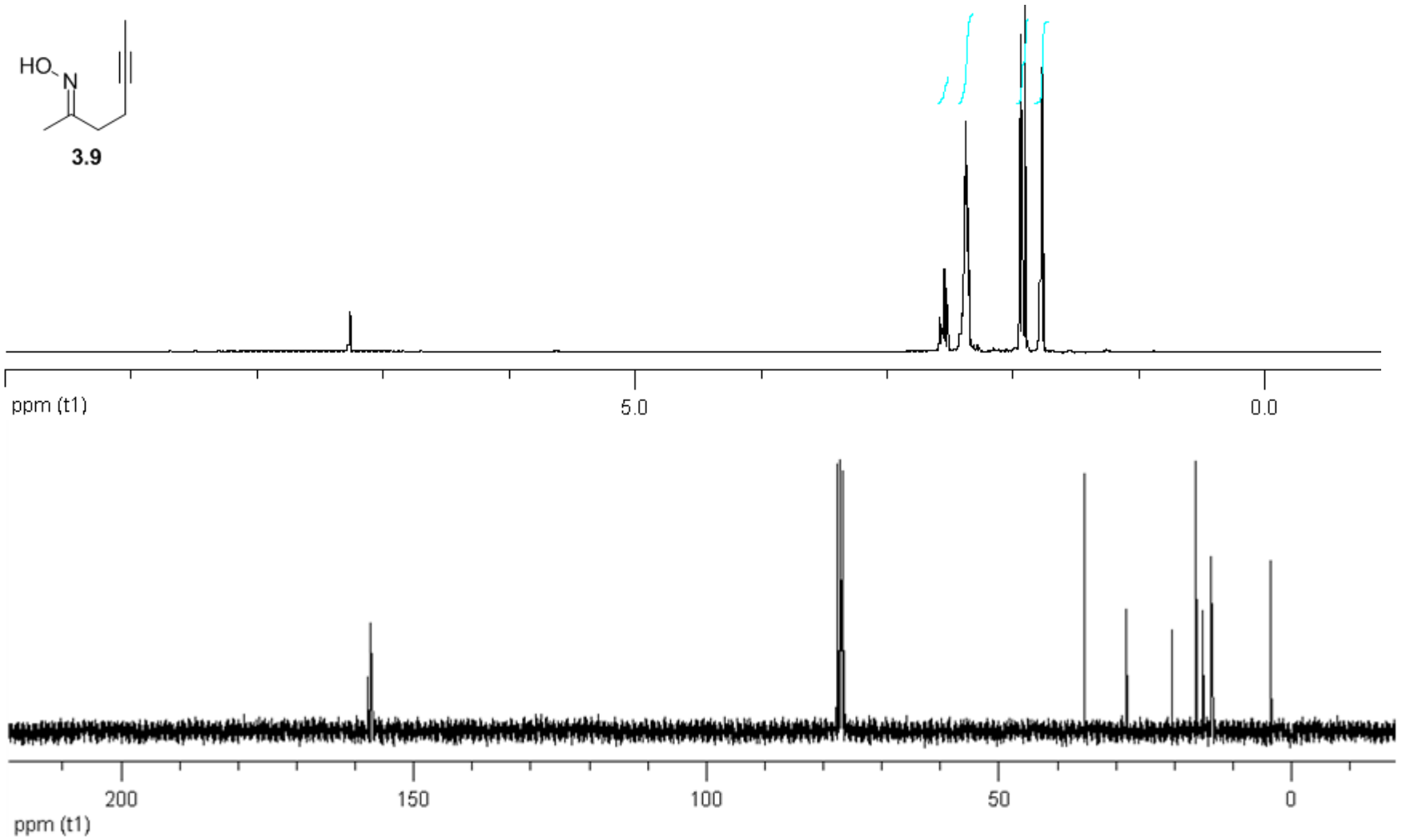
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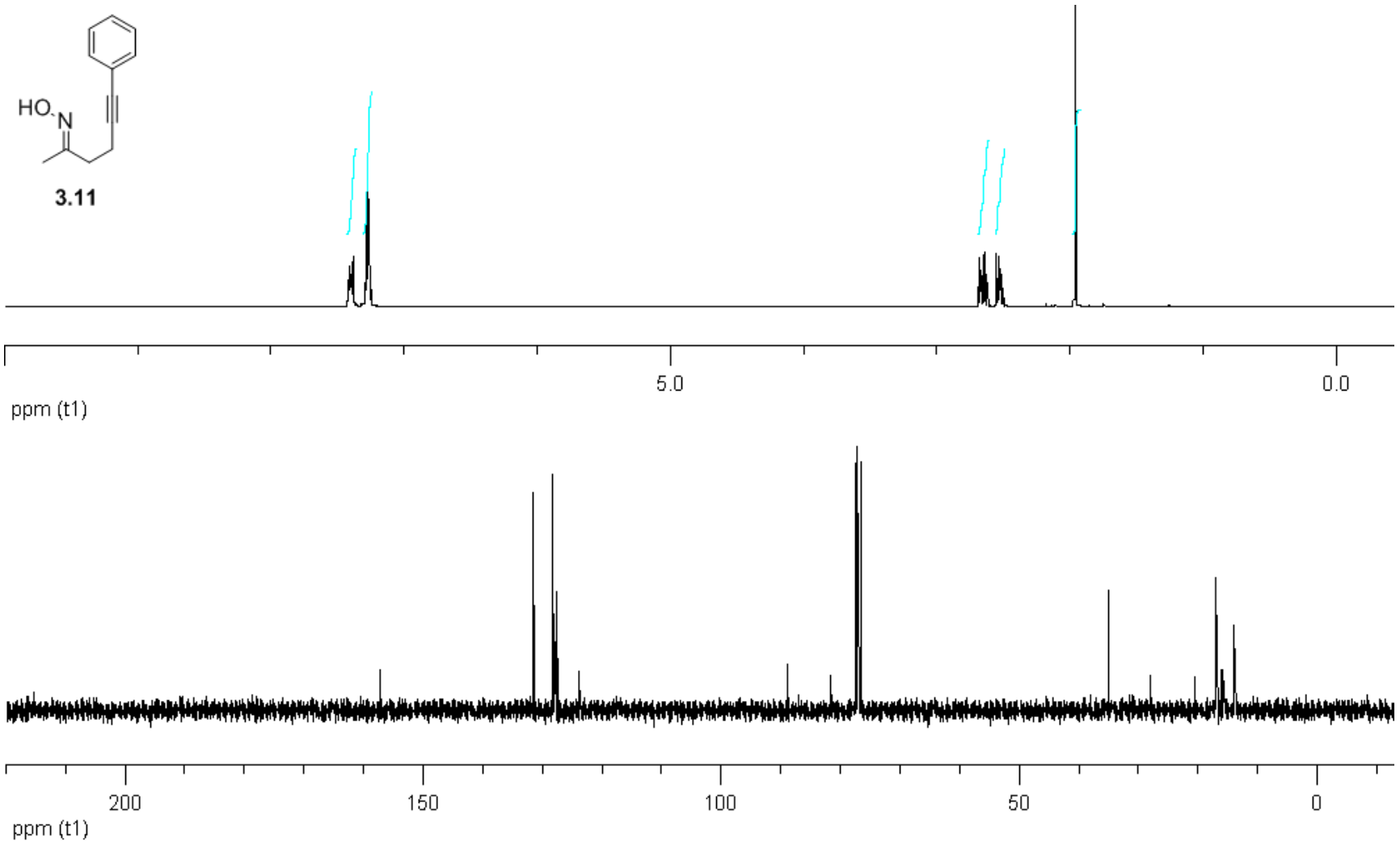
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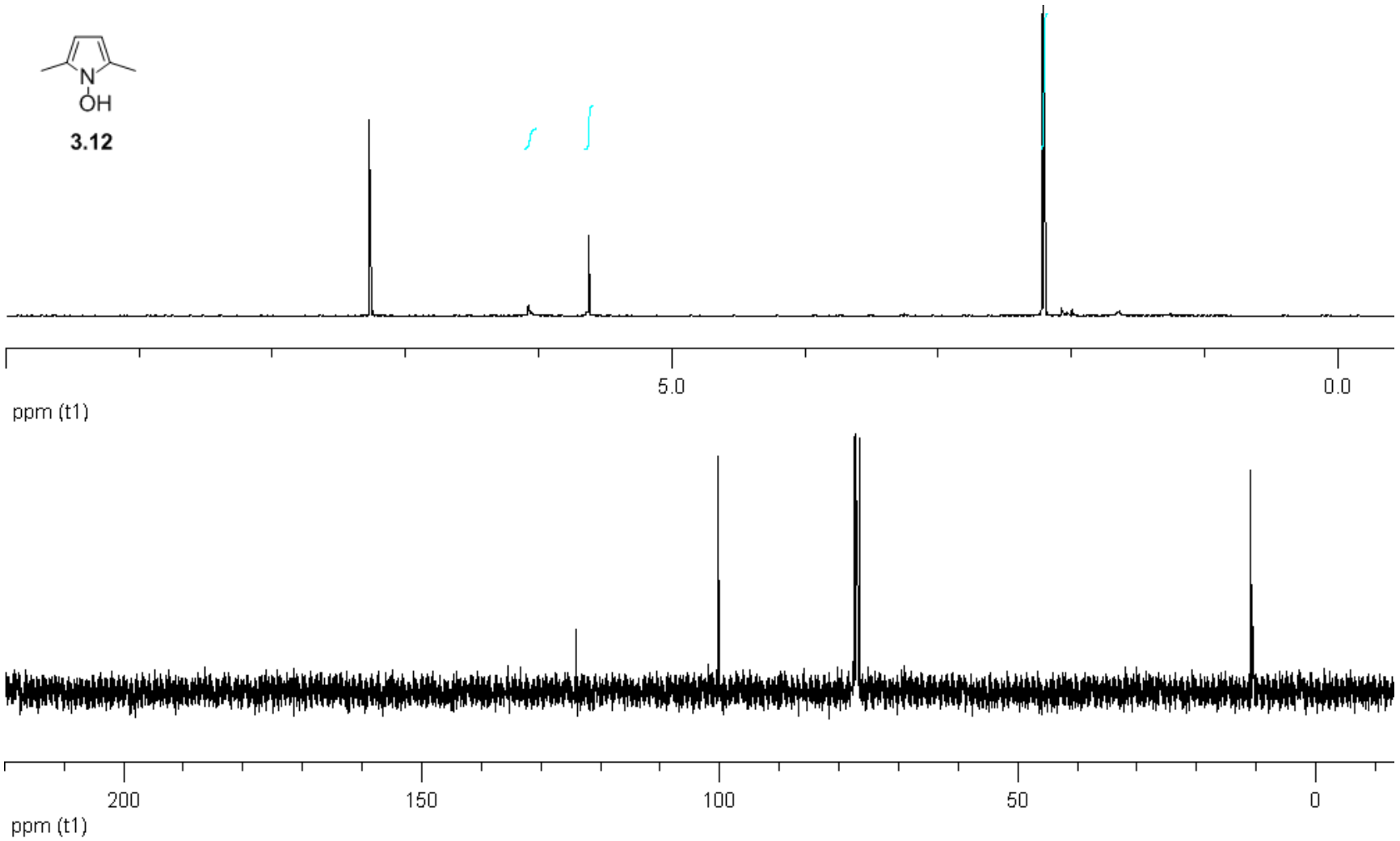
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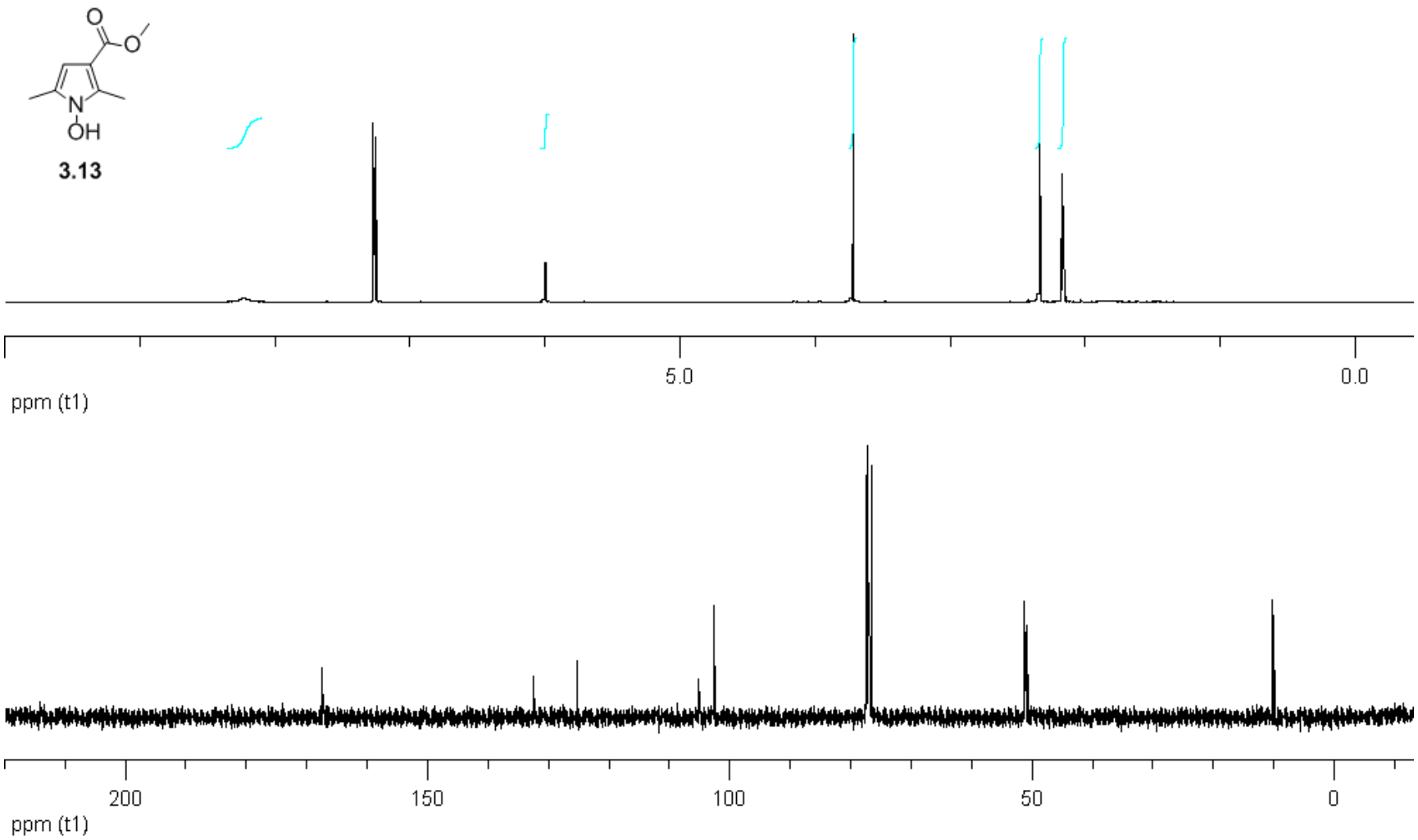
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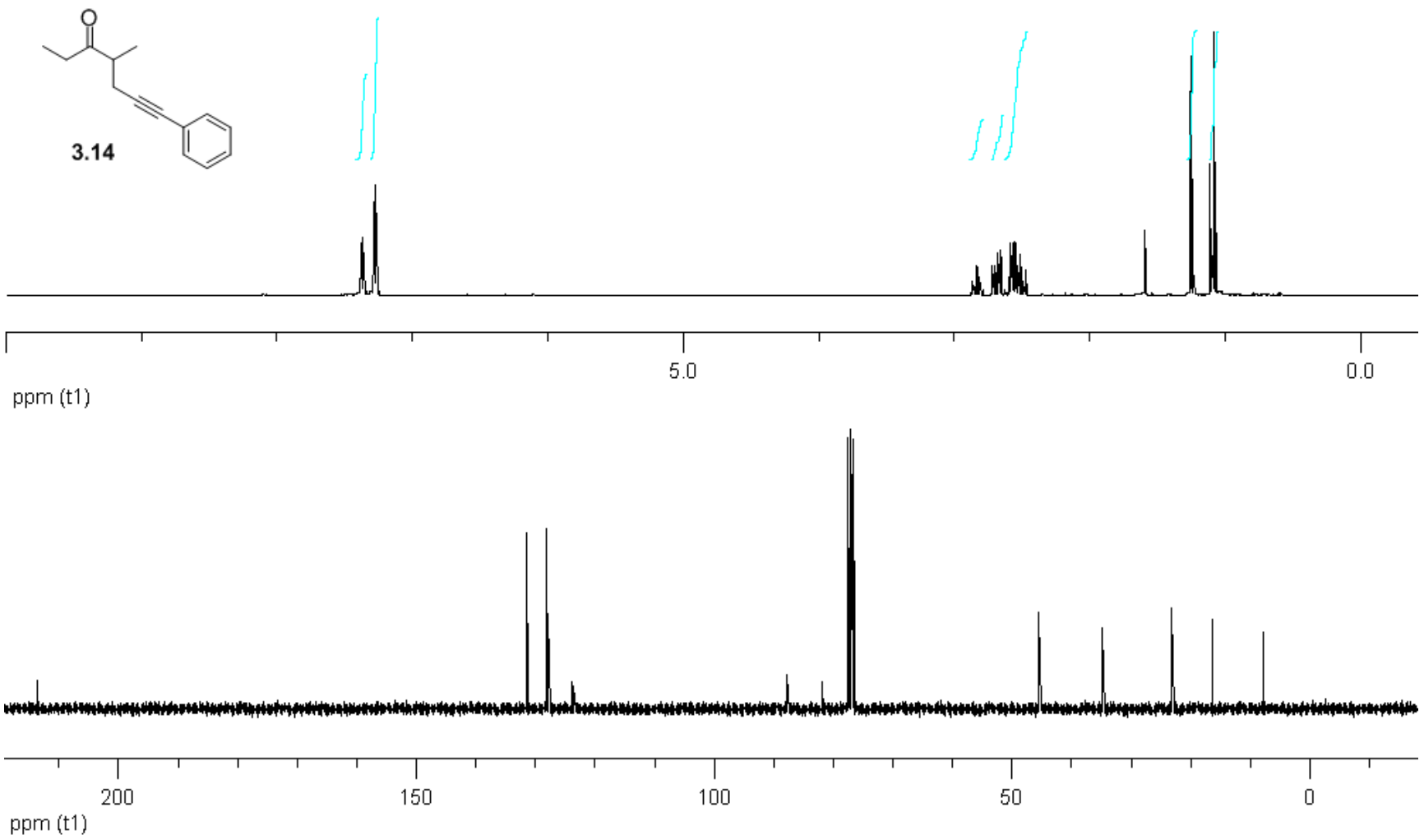
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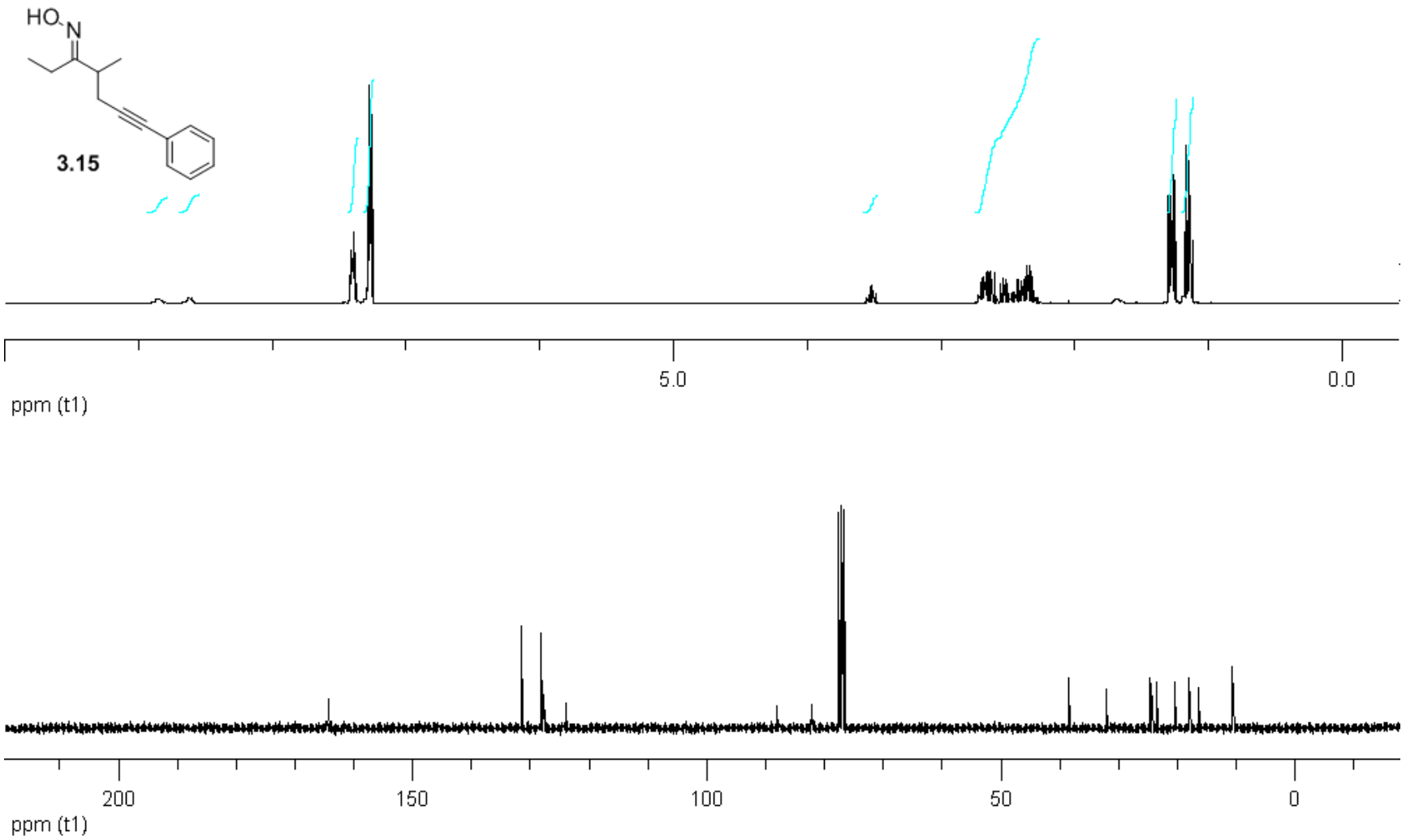
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