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Investigations Toward Metal-Free Hydroamination Approaches to Aromatic Nitrogen Heterocycles

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Investigations toward metal-free hydroamination approaches to aromatic nitrogen heterocycles

Hao Peng

Thesis submitted to the Faculty of Graduate & Postdoctoral Studies, University of Ottawa in partial fulfillment of the requirements for the M.Sc. degree in the Ottawa-Carleton Chemistry Institute

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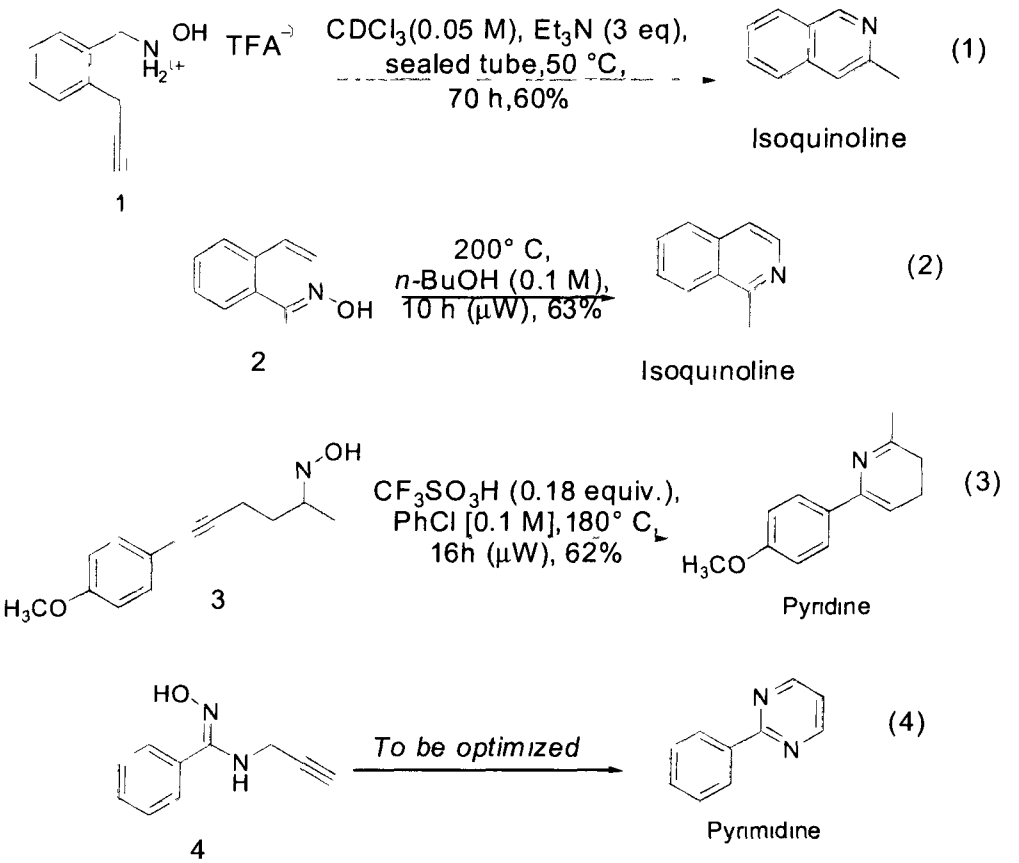
Abstract



Metal-free hydroamination approaches were investigated to afford aromatic nitrogen heterocycles. Several substrates were synthesized to test different sequences such as 6-endo-dig and 6-exo-dig cyclization. The desired reactivity was observed for each of the desired routes, which were discussed in Chapter 2. More research is needed for optimization in the future.

Acknowledgements

Finally, I come to the acknowledgement section. After working on this thesis one overnight after another, I am very tired now. Fortunately, I finished it today, which is the deadline of submission. Before I become unconscious, I really want to say something, which comes from my heart.

First and most I would like to thank my supervisor, Prof. André Beauchemin. He is a dynamic and dedicated scientist. But most of all, his enthusiasm to chemistry is the driving force in our lab. Everything should be perfect: knowledge, lab skills, ideas, and lab reports. Under this "kinetic control", we are pushed to make progress. Sometimes, I can not understand. But, when I am writing this page, I realize it's the principle of game, and it's good for all of us. However, I am a thermodynamic controlled person. As the consequence, probably I can not move over the energy barrier so quickly. I hope you will not be so disappointed. I think you won't since we have investigated our sequences toward aromatic nitrogen heterocycles for two years, and you never gave up. I will show my appreciation to you because you opened a door of heterocyclic chemistry to me, and it's very enjoyable. I hope you win Nobel Prize in the near future. But, please don't forget your family.

For sure I would like to thank all the guys in the lab. You helped me a

lot. All of you are friendly and ambitious. I am pleased you are friendly, but I felt stressful because you were ambitious. But now, I am also pleased you are ambitious. That forced me to be ambitious as well. Thank Joe for always be patient to "stupid" questions. Thank Joffré for training me though I did not understand totally sometimes. I wonder why not Pam or Isabelle instead? They were proved to be much better. I am sorry, Joffré... Jean, an easygoing man. I envy your publication. Frank is a very active "reagent" in the lab. Jenn, please don't always ask me the same question when you see me. Toni, congratulations to your heterocyclic publication. To Peter, Ashley, Melissa, Chris, and Matthew, good luck in the OU.

I also want to show my appreciation to my parents, relatives and friends. It was your supports that encourage me to go thus far.

Finally, thanks Tim hortons and Manchuwok at Rideau center for energy support, you guys know me well.

A good story was finished. It means another good beginning will start. Let's look forward to it.

Table of contents

Abbreviations

BHT	butylated hydroxytoluene
Ar	argon
CH_2Cl_2	dichloromethane
TEA	triethylamine
i-Pr	isopropyl
n-Bu	normal butyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
h	hours
TLC	thin-layer chromatogarphy
ppm	parts per million
mmol	millimolar
mL	millitres
M	molarity
MHz	megahertz
THF	tetrahydrofuran
Boc	*t*-butoxycarbonyl
CSA	camphorsufonic acid
DEAD	diethyl azodicarboxylate

DIAD	diisopropyl azodicarboxylate
DMAP	*N,N*-4-dimethylaminopyridine
NCS	*N*-chlorosuccinimide
Ph	phenyl
TFA	trifluoroacetic acid
Piv	pivaloyl
TMS	trimethylsilyl

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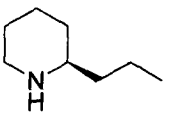
Introduction

1.1 Heterocyclic chemistry

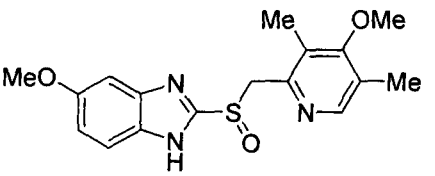
Of all currently registered chemical compounds, about half contain heterocyclic systems. Heterocyclic compounds are abundant in natural products, medicines and technical products, and are very important because of their chemical and biological significance. For these reasons, heterocyclic compounds are in great demand in the pharmaceutical industry and are widely synthesized every year.

Unlike isocyclic compounds, which have only carbon and hydrogen in their structures, heterocyclic compounds contain other elements such as nitrogen, oxygen, or sulfur. Other elements, such as selenium, phosphorus and boron, can be found but are less common.



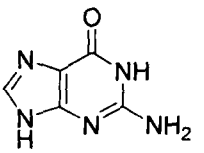
coniine **1.1**

a nature product in hemlock used to kill Socrates



Omeprazole **1.2**

a gastric pump inhibitor



guanine **1.3**

a purine base found in nucleic acids

Figure **1.1**. Some heterocyclic compounds

Of the first three heteroatoms, N is the most common. Consequently, nitrogen-carbon bond formation is a field of interest in research, and it has attracted much attention for many years.

1. 2 Aromatic heterocycles

1. 2. 1 Aromaticity and Hückel's rule

According to Hückel's rule, aromatic compounds have planar cyclic structures containing (4n+2) delocalized π-electrons, where n = 1, 2, 3.... This concept of "aromaticity" is evident in the structure of benzene. It has a planar 6-membered ring structure, and has 6 π-electrons "moving

through" the six carbon atoms. The aromaticity greatly decreases the energy of the structure and makes the molecule much more stable.

If one or more carbon atoms of benzene are replaced by heteroatoms such as N, O, and S, the aromaticity of the molecule is maintained, the new compounds are classified as aromatic heterocycles.

In fact, there are many basic types of aromatic heterocycles with various types of heteroatoms, ring sizes, and numbers of heteroatoms, as well as their relative positions in the structure. An aromatic heterocycle can also be fused with benzene or some other aromatic ring, forming a new, more complex aromatic compound.

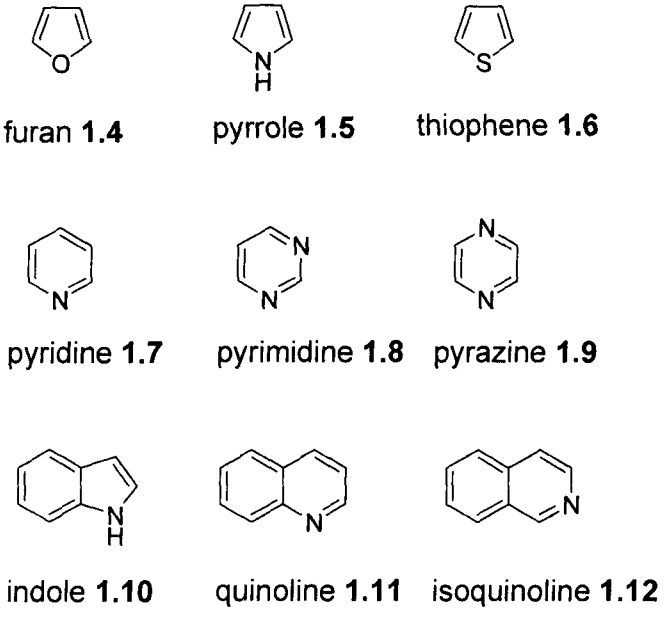


Figure **1.2**. Basic types of aromatic heterocycles

1. 2. 2 Electron-rich and electron-poor unsaturated heterocycles

In aromatic heterocycles (Figure 1.2), 5- and 6-membered rings are the most common. Both types of heterocycles contain 6 π -electrons. In 5-membered rings, such as such as furan **1.4**, pyrrole **1.5**, and thiophene **1.6**, the 6 π-electrons are shared between 5 atoms, making the aromatic system more electron-rich (π-excessive) compared to that of 6-membered rings, such as pyridine **1.7**, pyrimidine **1.8**, and pyrazine **1.9**. Six-membered rings with multiple heteroatoms are more electron-poor (π-deficient) than those with single heteroatoms.

In reactions, electron-rich heterocycles are good nucleophiles while electron-poor heterocycles are good electrophiles.

1. 3 Syntheses of heterocycles

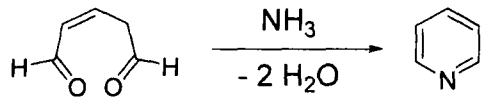
1. 3. 1 Unsaturation degrees in aromatic heterocycles

In both of 5- and 6-membered unsaturated heterocycles (Figure 1.2), 6 π-electrons are required to achieve aromaticity, and the unsaturation degree is 4 (including the cycle). If they are fused with benzene rings, the corresponding unsaturation degree is higher. For example, the unsaturation degree of quinoline **1.11** and isoquinoline **1.12** is 7 (including the cycle).

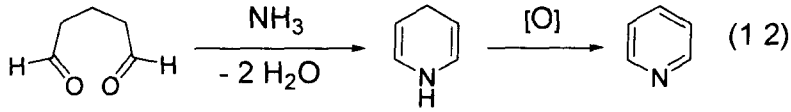
In 5-membered heterocycles, such as furan **1.4**, pyrrole **1.5**, and thiophene **1.6**, the heteroatom connects with Carbon atoms by C-X single bonds (X= O, N, S), and it can provide one pair of electrons for conjugation. Thus, only two unsaturations (C=C) are needed to make the structure aromatic. When the 5-membered ring is fused with a benzene ring, for example in indole, one C=C is needed along with the heteroatom. In contrast, there is a C=X bond (X= N) in 6-membered heterocycles. Thus, another two C=C bonds are needed to achieve aromaticity. In addition, when a 6-membered ring is fused with a benzene ring, such as in quinoline and isoquinoline, the whole system requires two unsaturations apart from (or) in addition to the benzene ring: one is a C=X bond and another is a C=C bond.

1. 3. 2 Strategies of oxidation state control

The retrosynthetic analysis of heterocycles provides many different assemblies of a diverse array of starting materials. While the synthetic method is not the most important aspect of a synthesis, the oxidation state of starting materials plays a key role in determining the unsaturation degree in final products.



1.13



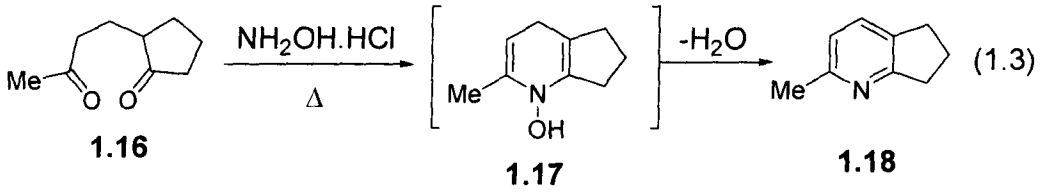
1.14 **1.15**

The oxidation state issue is apparent in the synthesis of pyridine. In dione **1.13** (eq. 1.1), the two carbonyl groups will produce two unsaturations in the corresponding target molecule, via loss of two water molecules. In addition, there is an alkene present. Thus, the 3 unsaturations of pyridine can be installed from **1.13**.

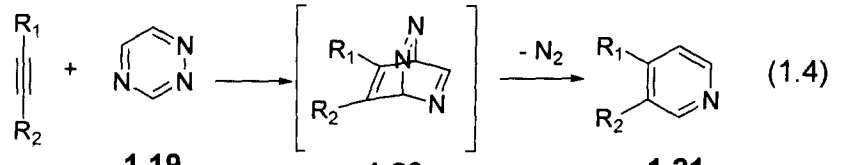
On the other hand, the situation is different beginning from dione **1.14** (eq. 1.2), since only amine **1.15** can be obtained after condensation. In contrast with pyridine, amine **1.15** is in a lower oxidation state (less unsaturation), and needs to be oxidized to achieve the same unsaturation degree. The oxidizing reagents can be $KMnO_4$, $POCl_3$, P_2O_5, etc.[1]

However, the control of oxidation states in starting materials is not limited to the use of oxidizing agents). The two most frequently used methods are the use of leaving groups and cycloaddition reactions.

[1] For a review see Manske, R. H. F., Kulka, M. *Org. React.* **1953**, *7*, 80.



1.16 **1.17** **1.18**



1.19 **1.20** **1.21**

The application of leaving groups can increase the unsaturation degree in target molecules. For example, dione **1.16** only has two carbonyl groups (eq. 1.3).[2] Thus, reaction (or) condensation with NH_3 will produce a degree of unsaturation of two in the corresponding product. However, reaction with hydroxylamine instead will produce intermediate **1.17**. Although the unsaturation degree in this intermediate is only two, the -OH group can be protonated to H_2O, which is a good leaving group. This leads to the third unsaturation in product **1.18**. Several other reagents possessing good leaving groups can be used, such as NH_2-NH_2, or NH_2TS, for example.

Cycloaddition followed by release of gas is another method of assembling starting materials into aromatic products. For example, 1,2,4-triazine **1.19** can undergo a [4+2]-cycloaddition with an alkyne (eq. 1.4)[3] to form the bicyclic product **1.20**, which can be regarded as an

[2] Knoevenagel, E. *Justus Liebigs Ann. Chem.* **1894**, *281*, 25.
[3] Sauer, J.; Heldmann, D. K. *Tetrahedron Lett.* **1998**, *39*, 2549.

intermediate to form pyridine. This intermediate has a strong tendency to release N_2 and form pyridine **1.21** due to the ring strain of intermediate **1.20**. Initially, the unsaturation degree of triazine **1.19** along with the alkyne is five. After reaction, N_2 removes two unsaturations, leaving pyridine with three. Similarly, the gas released can also be HCN and H_2O.[4]

In Beauchemin lab, an important branch of research is the application of Cope-type hydroamination in the synthesis of heterocycles, including the syntheses of isoquinolines, pyridines and pyrimidines. Before discussing new approaches to these heterocyclic systems, it is necessary to be familiar with the classical synthetic methods for these heterocycles.

1.4 Isoquinoline syntheses

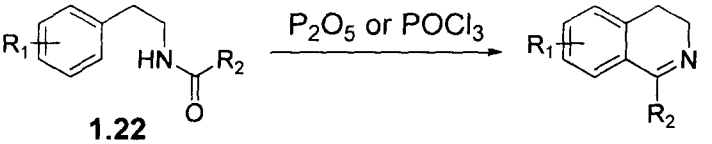
The framework of isoquinoline is found in the structures of many natural products. Thus, research into isoquinoline synthesis was of great interest in the last centuries, and several methods are highlighted below.

1.4.1 Bischler-Napieralski synthesis

In 1893, it was found that an acyl derivative of phenylethylamine **1.22**

[4] Naito, T., Yoshikawa, T., Ishikawa, F., Isoda, S., Omura, Y., Takamura, I. *Chem Pharm Bull* **1965**, *13*, 869

can undergo a cyclodehydration when treated with dehydrating agents (P_2O_5, Tf_2O etc), forming 3,4-dihydroisoquinoline derivative **1.23** (eq. 1.5). This reaction obtained a skeleton of isoquinoline in high yields (>80%). However, a catalyst was required to yield isoquinoline from its dihydro derivative. This is known as Bischler-Napieralski synthesis.[5]



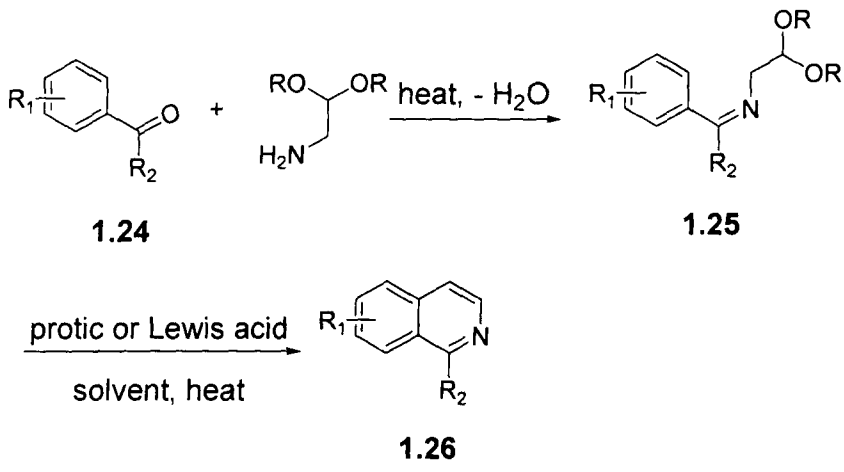
1.22 **1.23** (1 5)

The Bischler-Napieralski reaction is one of the most widely used methods of obtaining the dihydro- and tetrahydroisoquinoline frameworks in natural products.

1.4.2 Pomeranz-Fritsch reaction

In the end of the ninetenth century, Pomeranz and Fritsch independently reported a new method of isoquinoline synthesis[6] by heating a benzalaminoacetal under acidic conditions.

[5] Bischler, A ; Napieralski, B *Chem Ber* **1893**, *26*, 1903
[6] Bevis, M J , Forbes, E J Naik, N N , Ulf B C *Tetrahedron* **1971**, *27*, 1253

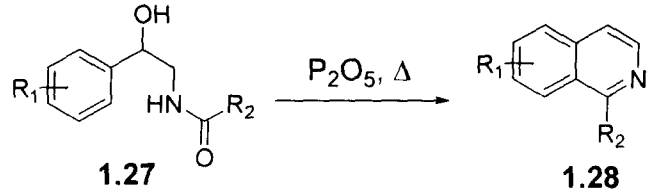


1.24 **1.25** **1.26**

Scheme 1.1. Pomeranz-Fritsch reaction

The Pomeranz-Fritsch reaction (Scheme 1.1) is the only direct and generally accepted method for unsaturated isoquinoline synthesis. The first step of the mechanism is the thermal condensation between aldehyde or ketone **1.24** and amine. Under acidic conditions, imine **1.25** can be converted to isoquinoline **1.26**. Usually, very strong acids, such as HCl and H_2SO_4, are used for the cyclization. This leads to low yields due to the instability of imine **1.25** in strong acidic conditions. Thus, Lewis acids are used instead.

1.4.3 Pictet-Gams reaction



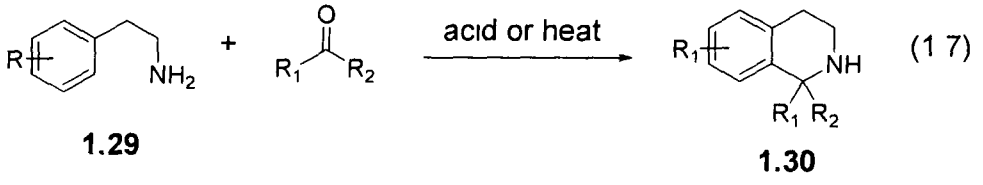
1.27 **1.28** (1.6)

This reaction can be regarded as a variation of Bischler-Napieralski reaction.[7] The hydroxyl group in starting material **1.27** can be removed as H_2O at high temperature (eq. 1.6), and consequently, the unsaturated isoquinoline **1.28** can be obtained.

The drawback of this reaction is low yield of products. In addition, the reaction affords several by-products.[8] As a result, its popularity as a synthetic tool diminished quickly.

1.4.4 Pictet-Spengler reaction

In 1911, Pictet and Spengler reported that tetrahydroisoquinolines can be generated via condensation between β-arylethylamines and aldehydes or ketones (eq. 1.7).[9]



1.29 **1.30** (1.7)

Although this method does not produce isoquinoline directly, it is widely used to build the skeleton, since tetrahydroisoquinoline units are

[7] Czerwinski, K. M., Cook, J. M. *Adv. Heterocycl. Nat. Prod. Synth.* **1996**, *3*, 217
[8] Bindra, A. A., Wdza, M. S., Dutta, N. C. *Tetrahedron Lett.* **1968**, *9*, 2677
[9] Pictet, A., Spengler, T. *Ber.* **1911**, *44*, 2030

also popular in natural products. The reaction is usually catalyzed by protic or Lewis acids and the yields are especially high when electron-donating groups are on the aromatic ring.

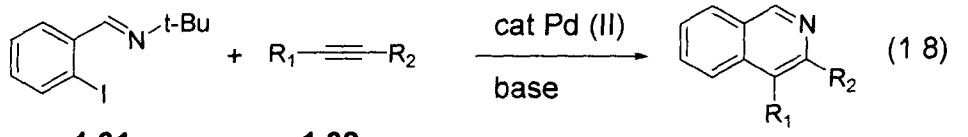
In conclusion, the conventional methods of isoquinoline have drawbacks. Either they require strong reaction conditions, as with the Pomeranz-Fritsch reaction[6], or yield of product is not high, as with the Pictet-Gams reaction[7]. Thus, the most widely used approaches to isoquinoline frameworks are the Bischler-Napieralski reaction[5] and Pictet-Spengler reaction[9]. However, they can only be used for dihydro- or tetrahydro- derivatives, and not directly for unsaturated isoquinoline synthesis.

1.4.5 Recent advances in isoquinolines chemistry

In addition to the classical approaches, newer methods of isoquinoline syntheses have been published. Usually these are metal-catalyzed methodologies.

In 1998, Larock reported a palladium-catalyzed annulation of internal alkynes to prepare 3, 4-disubstituted isoquinolines (eq. 1.8).[10]

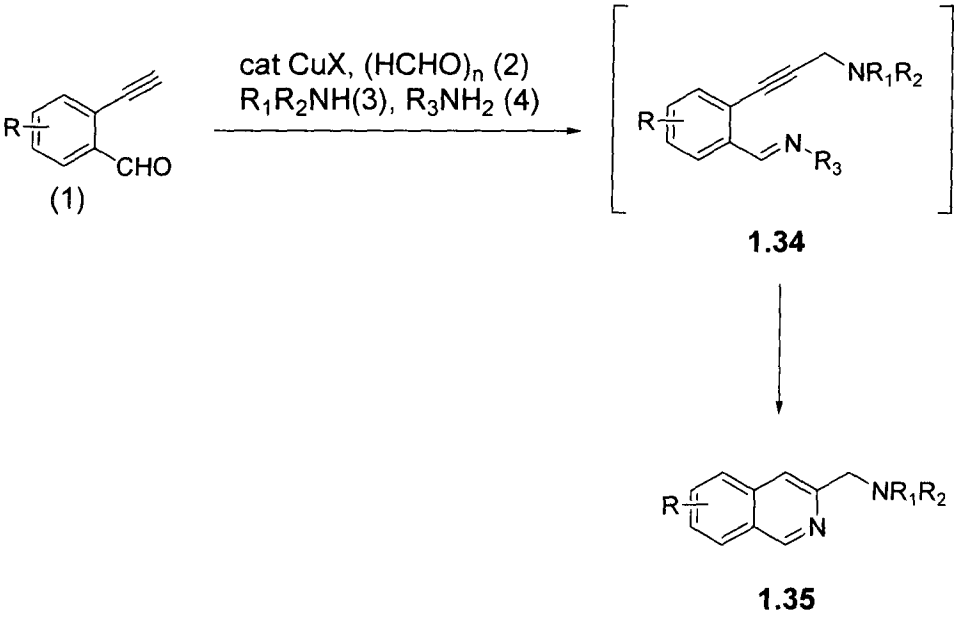
[10] Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.



1.31 **1.32** **1.33**

8 examples, 65-99%

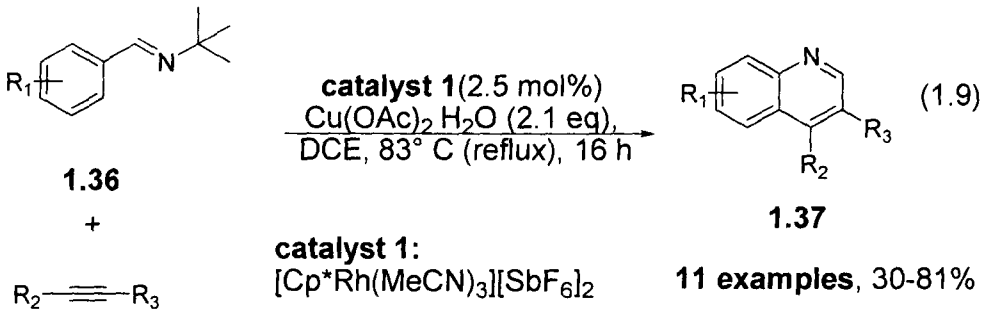
More recently, Nobutaka Fujii and Hiroaki Ohno reported a copper (I)-catalyzed method of isoquinoline synthesis (Scheme 1.2).[11] It is a four-component coupling reaction where 2-ethynylbenzaldehyde reacts with paraformaldehyde, a secondary amine and *t*-$BuNH_2$ to form intermediate **1.34**. This intermediate cyclizes to afford 3-(aminomethyl)isoquinolines efficiently.



Scheme 1 2 Copper-catalyzed coupling and cyclization

[11] Ohta, Y , Oishi S , Fujii, N , Ohno, H *Chem Comm* **2008**, 835

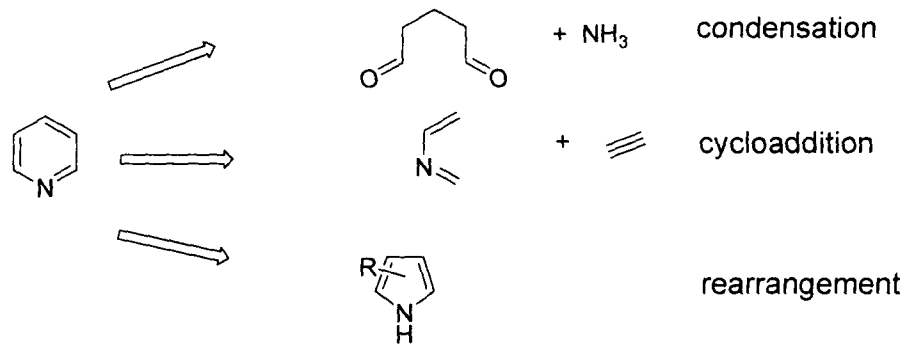
In 2009, Fagnous reported a new methodology of isoquinoline synthesis catalyzed by $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (eq. 1.9).[12] This method requires only readily available starting materials and mild reaction conditions. It can afford isoquinolines with various substituents in both good yield and high regioselectivity.



1.5 Pyridine syntheses

The nucleus pyridine is also an important motif in natural products and medicine chemicals. The conventional approaches to pyridines can be divided into three main types: condensation, cycloaddition, and rearrangement (Scheme 1.3). Each type includes several classical reactions.

[12] Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* ***2009****, In Press*



Scheme 1.3. Approaches to pyridines

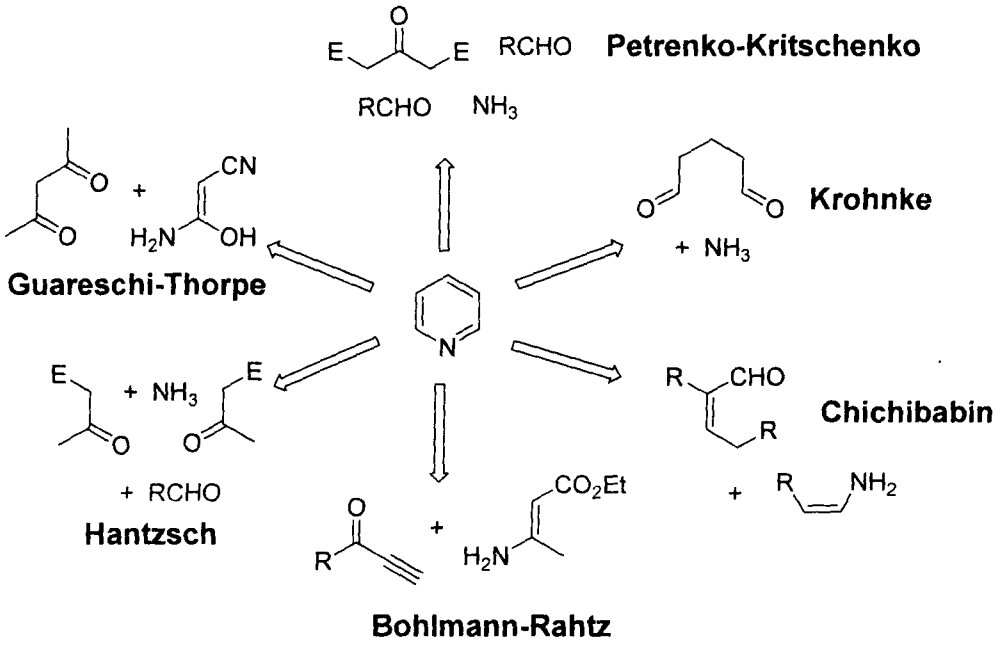
1.5.1 Condensation approaches to pyridines

In condensation approaches to pyridines (Scheme 1.4), C-N bonds are first formed through condensation between carbonyls and amines. This type of approach includes the Hantzsch, [13] Guareschi-Thorpe, [14] Chichibabin, [15] Bohlmann-Rahtz, [16] Krohnke, [17] and Petrenko -Kritschenko reactions. [18]

The condensation approaches are general methods for pyridine synthesis since a wide range of carbonyl compounds can be used, the source of N atom can be ammonia or amines, the starting materials are easily obtained, and reaction conditions are substrate specific.

---

[13] Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, 215, 1.
[14] Vogel, A. L. *J. Chem. Soc.* **1934**, 1758.
[15] Sprung, M. M. *Chem. Rev.* **1940**, *40*, 297.
[16] Bohlmann, F.; Rahtz, D. *Chem. Ber.* **1957**, *90*, 2265.
[17] Krohnke, F.; Zecher, W. *Angew. Chem. Intf. Ed.* **1962**, *1*, 626.
[18] Petrenko-Kritschenko, P.; Zoneff, N. *Ber.* **1906**, *39*, 1358.

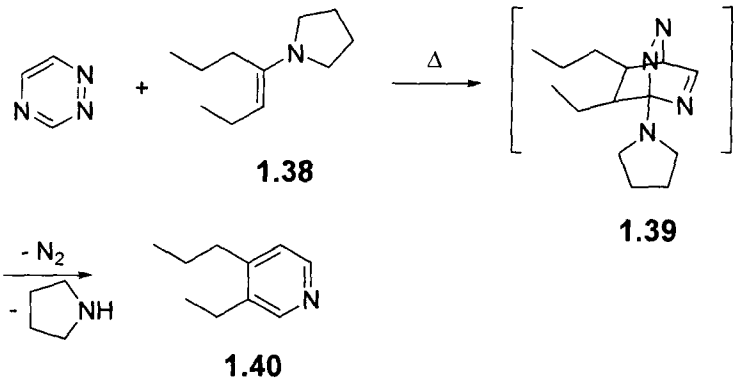


Scheme 1.4. Classical condensation appraoches to pyridines

1.5.2 Cycloaddition approaches to pyridines

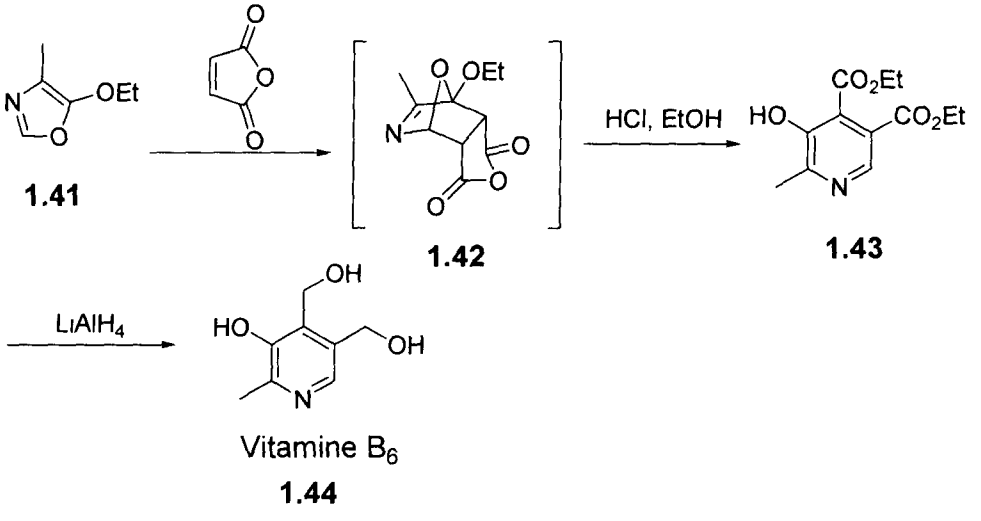
In cycloaddition approaches, the C-N bonds are formed through Diels-Alder type reactions. This is an efficient way of accessing pyridines and can be used to introduce substituents at specific positions on the ring. One classical reaction of this type is the Boger reaction (Scheme 1.5),[19] in which a triazine undergoes cycloaddition with the activated alkene **1.38**, providing intermediate **1.39**. This converts to the corresponding pyridine **1.40** by releasing N_2, thereby relieving ring strain.

[19] Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.



Scheme 1.5. Boger reaction to synthesize pyridine

In addition to triazines, oxazoles can undergo similar cycloadditions to obtain pyridines. This approach was successfully applied to the synthesis of Vitamin B_6.[20]



Scheme **1.6**. cycloaddition approach to Vitamine B_6

Vitamin B_6 has a highly substituted pyridine ring structure, which is

[20] Firestone, R. A., Harris, E. E., Reuter, W. *Tetrahedron* **1967**, *23*, 943

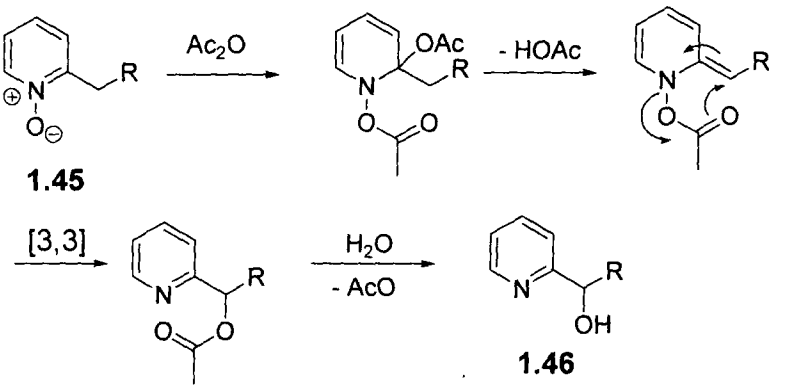
difficult to synthesize by conventional approaches. However, cycloaddition of oxazole **1.41** (Scheme 1.6) with furan-2, 5-dione affords intermediate **1.42** which can be converted to the pyridine framework **1.43** upon treatment with HCl and EtOH. Product **1.44** is then easily obtained by reduction of the esters to the corresponding alcohols.

1.5.3 Rearrangement approaches to pyridines

Rearrangement is also an efficient way to obtain the pyridine skeleton. There are two classical reactions in this type: the Boekelheide reaction and the Ciamician-Dennstedt reaction.

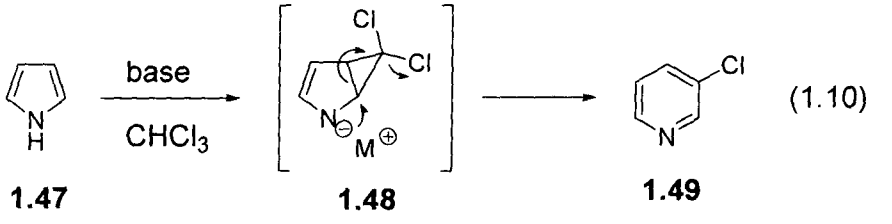
The Boekelheide reaction (Scheme 1.7) starts with a pyridine *N*-oxide **1.45**.[21] After *O*-acylation, the second acetoxy group is added at the α-position of the pyridine ring. Following deacetylation, which stores one unsaturation on the branch chain of the pyridine, rearrangement restores the aromaticity of the structure. Finally, hydration converts the intermediate to pyridine **1.46**, with a hydroxyl group on its α-substituent.

[21] Katritzky, A. R.; Lam, J. N. *Heterocycles* **1992**, *33*, 1011.



Scheme 1.7. Mechanism of Boekelheide reaction

On the other hand, the Ciamician-Dennstedt reaction starts with a pyrrole framework.[22] Under basic conditions, pyrrole can react with dichlorocarbene (generated from $CHCl_3$ in basic condition), and affording 3-chloropyridine as the product (eq. 1.10).



(1.10)

Pyrrole **1.47** is deprotonated and converted to its salt under basic conditions. Intermediate **1.48** forms through cyclopropanation of one C=C bond producing a highly strained [3,1,0] ring system. Rearrangement releases this strain, providing 3-chloropyridine **1.49**.

This reaction can also be used for quinoline synthesis if indoles are

[22] Wynberg, H. *Chem Rev* **1960**, *60*, 169.

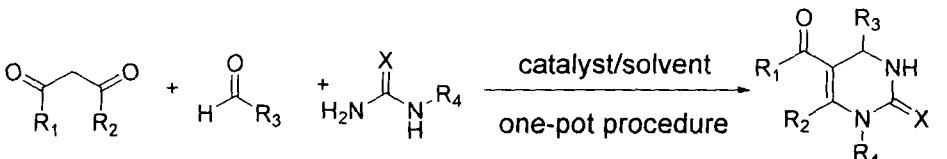
used as starting materials.[23]

In conclusion, there are many conventional approaches to pyridines. The basic strategies of C-N bond formation are condensation, cycloaddition, and rearrangement. For each type of approach, many classical reactions were developed, but many methods have limitations such as limited scope or low functional group compatibility.

1.6 Pyrimidine syntheses

Compared to the two previous heterocycles, not many classical approaches for pyrimidine have been reported. The general methodology of C-N bond formation in the pyrimidine structure is the condensation between carbonyl and amine functionalities. The two classical reactions of pyrimidine synthesis are the Biginelli reaction and the Pinner pyrimidine synthesis.

1.6.1 Biginelli reaction



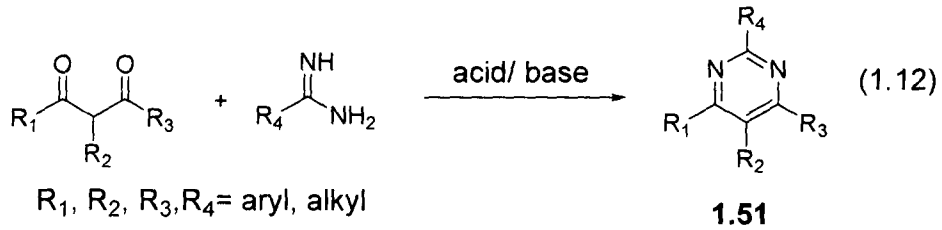
(1.11)

1.50

[23] Rees, C. W.; Smithen, C. E. *J Chem Soc* **1964**, 938.

This one-pot reaction (eq. 1.11) is a condensation between di-arbonyl functionality, an aldehyde and a urea or thiourea. By this method, 3, 4-dihydropyrimidin-2-one (DHPM) **1.50** can be easily obtained.[24] This reaction had increasing importance especially after the mid-1970s, when this DHPM framework was widely founded in biologically active natural products.[25-26]

1.6.2 Pinner pyrimidine synthesis



(1.12)

R_1, R_2, R_3,R_4= aryl, alkyl

1.51

The Pinner pyrimidine synthesis is a condensation between a dicarbonyl and an amidine. This process can be catalyzed by acid or base and produces the highly substituted pyrimidine **1.51** (eq. 1.12).

One drawback of classical Pinner pyrimidine synthesis is low yield. In 2002, Ghosh and Katzenellenbogen reported a modification of the classical approach by using tris-(trimethylsilyl) amidine. This new

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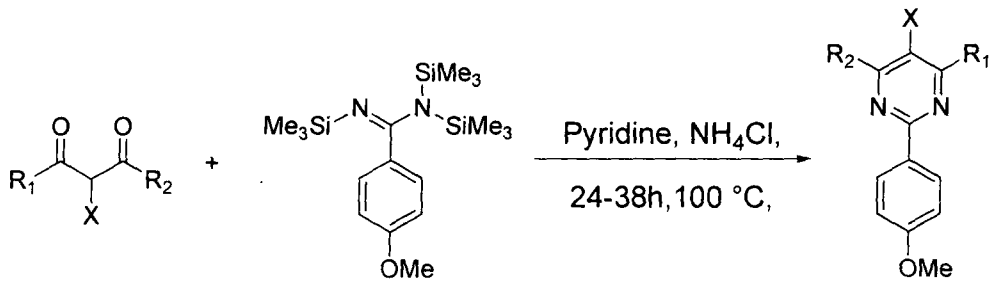
[24] Biginelli, P *Ber* **1893**, *26*, 447
[25] Kappe, C O *Tetrahedron* **1993**, *49*, 6937.
[26] Kappe, C O *Acc Chem Res* **2000**, *33*, 879

method led to much higher yields (Table 1.1).[27]

Table 1.1. Ghosh's modification of Pinner process



1.52 **1.53**

Entry	R1	R2	X	Yield
1	Me	Me	H	89
2	Ph	Ph	H	83
3	Me	Me	Et	78
4	Ar[a]	Ar	H	74

[a] Ar= *p*-(OMe)-C_6H_4

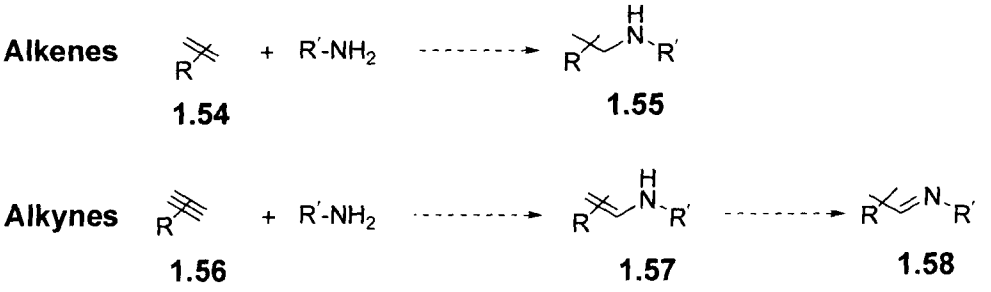
This modification solved the issue of low yields in highly substituted pyrimidine synthesis by the Pinner reaction. Both tri-substituted and tetra-substituted pyrimidines can be prepared.

1.7. Hydroamination

[27] Ghosh, U.; Katzenellenbogen, J. A. *J. Heterocyclic Chem.* **2002**, *39*, 1101.

In the previous sections, some classical approaches for heterocyclic synthesis have been discussed. The general strategies of C-N bond formation are condensation (between carbonyl functionalities and nitrogen species), cycloaddition (Diels-Alder type reactions), and rearrangement in heterocycles themselves. Other methods of nitrogen atom introduction into structures include substitution (e.g. Mitsunobu reaction), displacement of acyl or alkyl halides and reductive amination, among others. These approaches usually have disadvantages, either low yields, harsh reaction conditions, poor functionality tolerance, or long synthetic routes. Therefore, efforts towards more straightforward approaches to nitrogen-containing heterocycles are of great interest.

Hydroamination is a direct approach of forming a new C-N bond, which is N-H addition across unsaturated carbon-carbon bonds (alkenes and alkynes) (Scheme 1.8).



Scheme 1.8. Hydroamination of alkenes and alkynes

The hydroamination of alkenes **1.54** with primary amines will afford secondary amines **1.55** as products. Alternatively, alkynes **1.56** can

undergo similar reactions with primary amines to form an enamine product **1.57**, which will tautomerize to imines **1.58**.

Although both alkenes and alkynes have carbon-carbon unsaturated bonds, alkynes are more reactive under similar hydroamination reaction conditions,[28] due to the increased stability of alkenes. Consequently, alkynes are considered good substrates for hydroamination. Both internal and terminal alkynes are widely used as starting materials, since they are relatively inexpensive and readily available.

In addition to amines in C-N bond formation, hydroxylamines (R-NHOH) and oximes (C=N-OH) are widely used as sources of nitrogen atoms in hydroamination methodologies. They are especially powerful tools in the synthesis of unsaturated heterocycles, because these compounds are not only good reagents for carbon-carbon triple bonds, but also contain a built-in good leaving group. Through this strategy, installation of an unsaturation degree required in the product can be achieved (see section **1.3.1**). Therefore, in chapter 2, both hydroxylamines and oximes will be discussed in isoquinolines syntheses.

Although hydroamination provides an atom-efficient method for direct C-N bond formation, this addition of N-H across carbon-carbon bonds has a high energy barrier and is orbital-forbidden under thermal conditions.[29-30] Therefore, hydroamination usually requires catalysis. The

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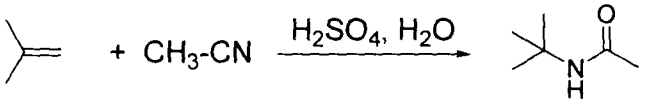
[28] Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104.

[29] Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

currently developed catalysts can be acids, base/alkali metals, and transition metals.

1.7.1. Acid-catalyzed hydroamination

Hydroamination of olefins can be catalyzed by Brønsted acids, and the general mechanism is similar to that of the Ritter reaction (eq. 1.13). The C=C bond of the olefin is activated by protonation, and then undergoes a nucleophilic attack by nitrogen-containing species. However, acid-catalyzed hydroamination has two problems. The first is the buffering issue of nitrogen-species under acidic conditions which results both in the reduction of acidity (which renders π-bond protonation more difficult) and sequestration of the nitrogen nucleophile (i.e. the doublet is not available for C-N bond formation). The second is the lack of tolerance of various functional groups under strongly acidic conditions.

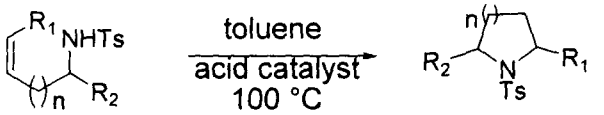


(1.13)

In 2002, Hartwig reported a Brønsted acid-catalyzed cyclization of protected alkenylamines to afford pyrrolidines and piperidines[31]. Hartwig used less basic tosylamides **1.59** as starting materials and obtained both

[30] Steinborn, R.; Taube, R. Z. *Chem.* **1986**, *26*, 349.
[31] Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

five- and six-membered heterocycles in good yields, through catalysis with triflic or sulfuric acid (eq. 1.14).



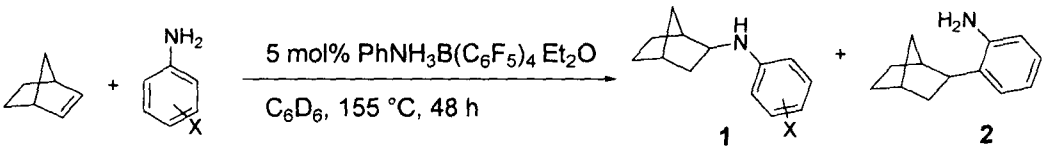
(1.14)

1.59 **9 examples**, 27-99%

In 2005, Bergman reported an acid-catalyzed intermolecular hydroamination of alkenes with anilines.[32] However, this method had hydroarylation as a competitive side reaction (Table 1.2), with the corresponding product distribution being acid counter-anion dependant. Finally $PhNH_3B(C_6F_5)_4 \cdot Et_2O$ was found to be the best catalyst to afford high yield. However, the product selectivity between hydroamination and hydroarylation is also affected by aniline substitution.

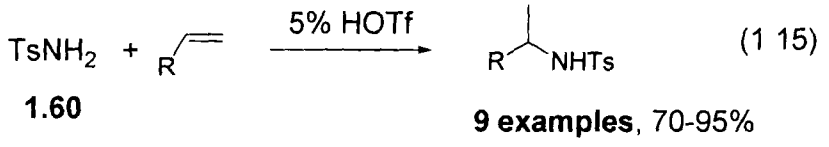
[32] Anderson, L. L.; Arnold, J.; Bergman, R. G. *J Am Chem Soc* **2005**, *127*, 14542.

Table 1.2. Effect of Aniline Substitution on Hydroamination and Hydroarylation Product Ratios



Entry	X	% Yield	1 2
1	H	84	1 1
2	4-Cl	56	only 1
3	4-OMe	34	1 2
4	2 6-Me_2	50	2 3
5	N-Me	55	1 4
6	3,5-CF_3	80	only 1

In 2006, He developed more general reaction conditions for the hydroamination of olefins.[33] Again, tosylamides **1.60** were used to react with different olefins (eq. 1.15). In order to have high yields and good substrate compatibility, the amount of acid was carefully controlled. He also found that a good control of temperature is important for this reaction.



(1 15)

Compared with transition metal-catalyzed processes, acid-catalyzed

[33] Li, Z., Zhang, J., Brouwer, C., Yang, C. G., Reich, N. W., He, C. *Org Lett* **2006**, *8*, 4175

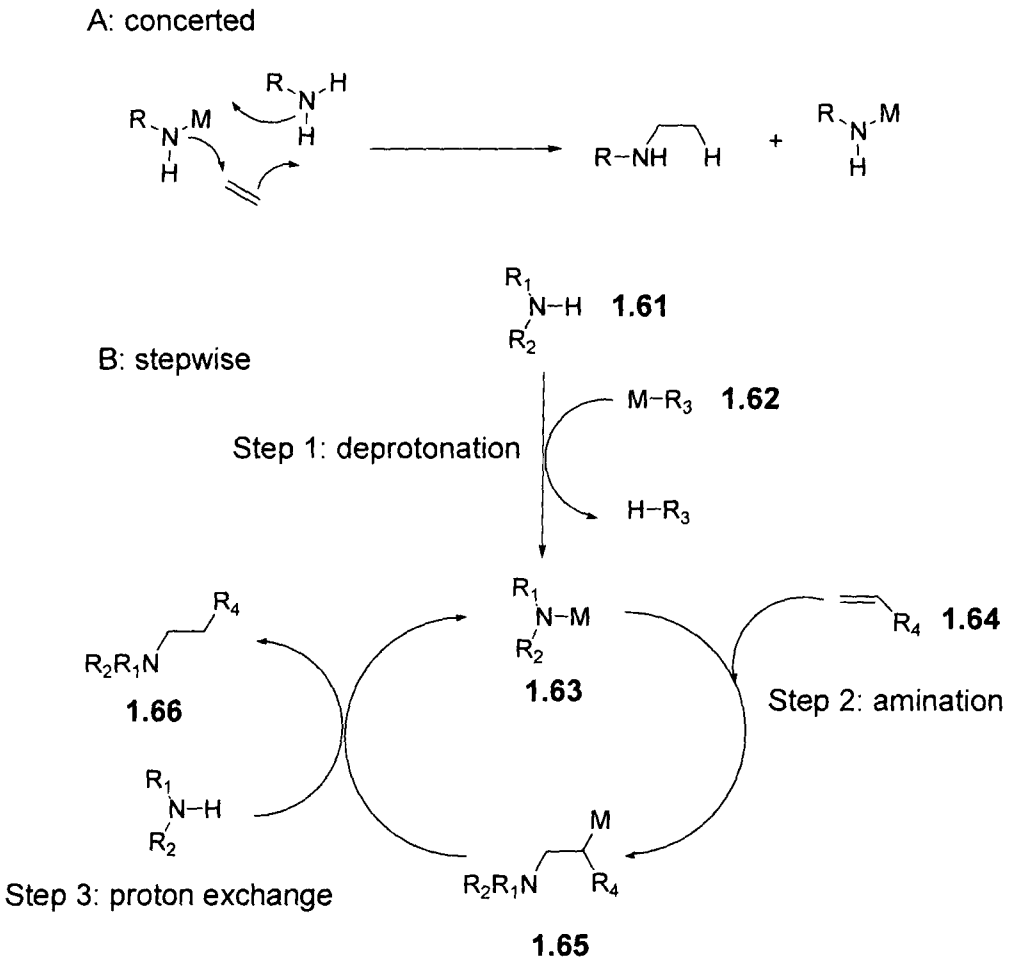
hydroamination is inexpensive and can be applied in a large scale, though the reaction conditions must be carefully controlled to ensure substrate compatibility.

1.7.2. Base/alkali metal-catalyzed hydroamination

Hydroamination of alkenes and alkynes can also be catalyzed by base and alkali metals. The general idea involves the deprotonation of amines using base or alkali metals, increasing their nucleophilicity. Usually alkyllithium reagents, lithium and sodium amides, NaH, KO-*t*-Bu, and alkali metals such as Li or Na can be used to activate amines. However, alkali metals are the focus in this field because of their low prices.

The stepwise mechanism of base-catalyzed hydroamination has been widely accepted, though this reaction can also be concerted in some cases.[34]

[34] Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal* **2002**, *344*, 795.

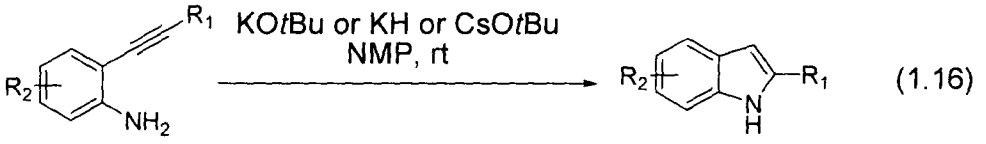


Scheme 1.9. Possible mechanism of base-catalyzed hydroamination

In the stepwise mechanism (Scheme 1.9), amines **1.61** are deprotonated by bases MR_3 **1.62** (M= alkali metal). This deprotonation is rapid and metal amides **1.63** are formed. Although these metal amides are very nucleophilic, the following amination is the rate-determining step. This is because of the repulsion between the activated complexes and electron-rich olefins **1.64**. In addition, the possible coordination between the alkali metals and the olefins also contributes to the low rate of the

step.[35] After the second step, aminoalkyl metal complexes **1.65** are formed, and rapid proton exchange with original amines **1.61** generates the final hydroamination product **1.66**. The metal amides **1.63** are regenerated, and the catalytic cycle continues.

The base-catalyzed hydroamination methodologies have been applied into heterocycle synthesis, and proved efficient. For example, Knochel reported a potassium or cesium base-catalyzed hydroamination to afford indoles in good yield (61-90%). [36] In polar solvent *N*-methyl-2-pyrrolidinone (NMP), substrates **1.67** underwent a hydroamination via a 5-endo-dig cyclization (eq. 1.16), catalyzed by bases, such as KO*t*Bu, KH, or CsO*t*Bu. At room temperature, indoles **1.68** were formed in good yield after 3-12 hours. This base-mediated method can also be used to synthesize azaindoles.



(1.16)

1.67 **1.68**

18 examples, 61-90%

Generally, base-catalyzed hydroaminations are less expensive methods compared with transition-metal catalyzed approaches. However,

[35] Pez, G. P., Galle, J. E. *Pure Appl. Chem.* **1985**, *57*, 1917.

[36] Rodriguez, A., Koradin, C., Dohle, W., Knochel, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488.

because these methods require harsh reaction conditions, they still have limitations on substrates compatibility. On the other hand, much milder reaction conditions can be obtained by transition-metal catalyzed approaches.

1.7.3. Transition metal-catalyzed hydroamination

In the last ten years, hydroamination methodologies became a widely popular field of research.[37] The main focus in this field is metal catalysis. This includes early transition metal catalysts (such as titanium, zirconium, and niobium), late transition metal catalysts (such as palladium, gold, copper and zinc), and catalysts in the lanthanide and actinide series.

Transition metal catalysts can decrease the energy barrier required in normal hydroamination, increasing reaction rates. In addition, the transition metal-catalyzed approaches usually only require mild reaction conditions, and have better functional group tolerance than either acid- or base-catalyzed methodologies. More importantly, transition metal-catalyzed approaches can lead to high selectivity of anti-Markovnikov products while normal hydroamination approaches favour Markovnikov products.[38]

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[37] Muller, T. E., Hultzsch, K. C., Yus, M., Foubelo, F., Tada, M. *Chem. Rev.* **2008**, *108*, 3795

[38] Nobis, M., Drießen-Holscher, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3983

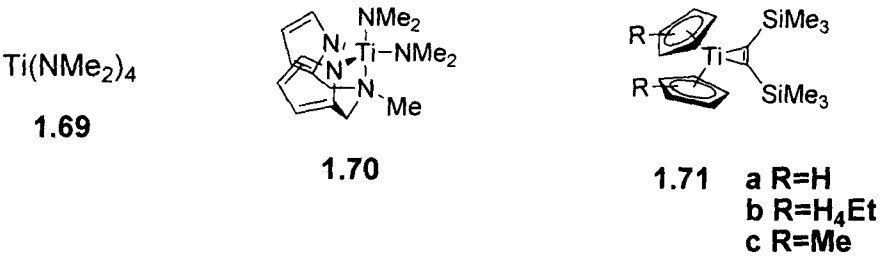
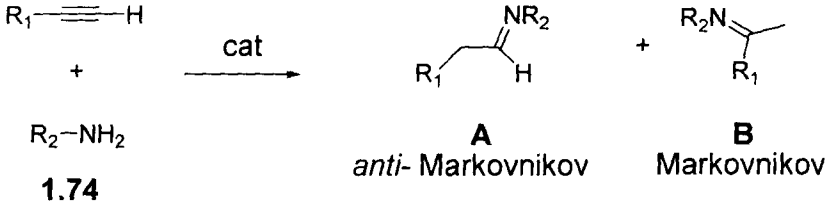


Figure 1.3. Titanium catalysts for hydroamiation

Table1.3. Intermolecular hydroamination of terminal alkynes

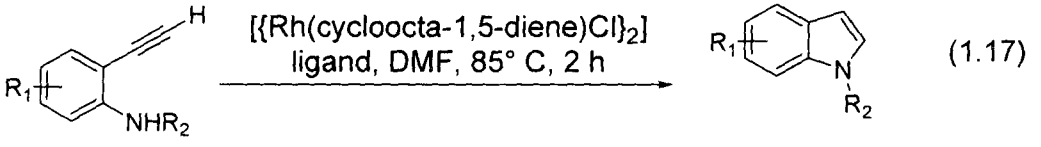


Entry	R_1	R_2	Catalyst	Time (h)	T,°C	yield, %	A/B
1	**1.72** *n*-Bu	*p*-Tol	**1.69**	10	75	87	1:4
2	*n*-Bu	*p*-Tol	**1.70**	10	75	94	1:>50
3	**1.73** *n*-Hex	*n*-Bu	**1.71 a**	10	120	48	72:28
4	*n*-Hex	*n*-Bu	**1.71 b**	10	100	62	44:56
5	*n*-Hex	*n*-Bu	**1.71 c**	10	120	48	22:78

An advantage of transition metal catalysts is the selectivity of *anti*-Markovnikov vs. Markovnikov products. For example (Table 1.3),[37] in intermolecular hydroamination of terminal alkynes, several titanium catalysts exhibited different selectivities between the two possible isomers. In the hydroamination of terminal alkyne **1.72**, both catalyst **1.69** and catalyst **1.70** favour the Markovnikov product. However, using catalyst **1.71**, the *anti*-Markovnikov product is favoured. On the other

hand, in the similar reaction of alkyne **1.73**, catalyst **1.71a** favoured the *anti*-Markovnikov product while **1.71c** favoured the Markovnikov product.

Hydroamination has been widely applied in the synthesis of saturated nitrogen heterocycles, while examples of approaches to aromatic nitrogen heterocycles are scarce. Many specific transition metal complexes were developed to have high yield reactions, provide mild reaction conditions, and increase chemoselectivity. In 2007, Trost reported a Rhodium-catalyzed cycloisomerization of alkynyl anilines **1.75** to afford indoles **1.76** (eq. 1.17)[39]. The process was short, chemoselective, efficient and atom-economical. In addition, it had high functional group tolerance. This methodology can also be applied to benzofuran synthesis.[39]



(1.17)

1.75 **1.76**

9 examples, 52-98%

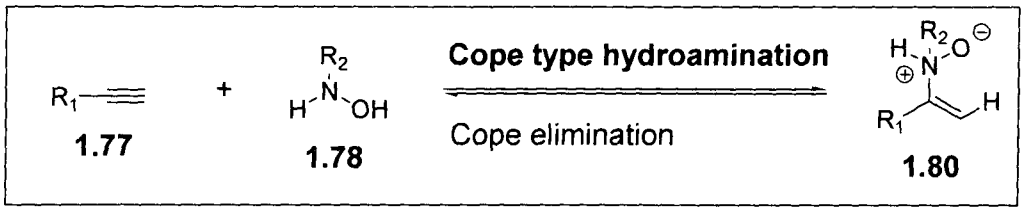
Transition metal catalyzed methodologies increased the rate, efficiency, selectivity and functional group compatibility of the hydroamination reaction. However, transition metals are usually

[39] Trost, B. M.; McClory, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 2074.

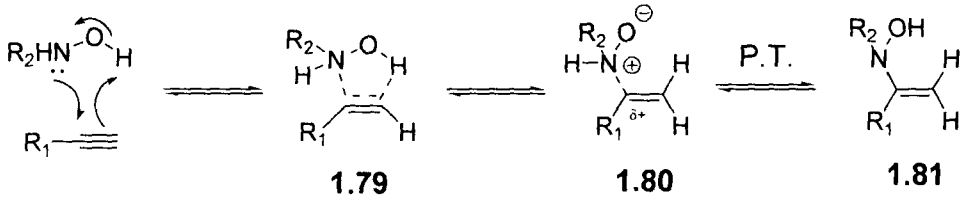
expensive, which limits the scale of the reaction. In addition, transition metal coupling methods can also introduce some toxic heavy metals into products, and these impurities are difficult to remove.[36]

1.7.4. Cope-type hydroamination

Cope-type hydroamination, also called reverse Cope elimination,[40] is another method of adding an N-H bond across alkenes and alkynes. Usually a bifunctional reagent, such as hydroxylamine and oxime, is required for Cope-type hydroamination. Such reactions are the microscopic reverse of the Cope elimination.



Mechanism:

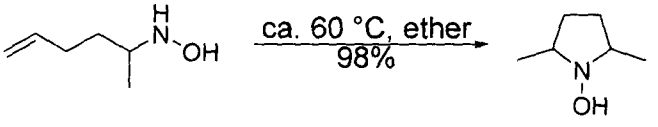


Scheme.1.10. Mechanism of Cope-type Hydroamination

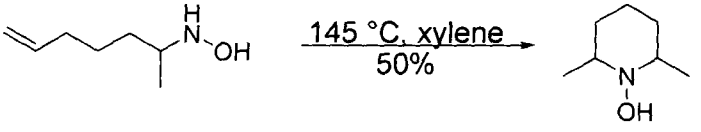
[40] For a review: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

It was found that terminal alkyne **1.77** reacted with hydroxylamine **1.78** through a 5-membered transition state **1.79** (Scheme 1.10), providing intermediate **1.80**. After proton transfer, product **1.81** is formed.[40]

The Cope-type hydroamination methodology has been applied in heterocyclic synthesis. In 1976, House used intramolecular hydroamination of alkenes to form 2-alkylpyrrolidines and 2-alkylpiperidines. [41] It was found that five-membered rings were easily formed under mild conditions by this methodology (eq. 1.18) while six-membered rings required higher temperatures (eq. 1. 19).



(1.18)



(1.19)

Although Cope-type hydroamination provides a metal-free and mild method C-N bond formation, publications of this methodology toward the synthesis of unsaturated nitrogen heterocycles are limited. This limitation attracted our interest.

Cope-type hydroamination is a focus of research in the Beauchemin

[41] House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.

research group. The research fields involved both intermolecular and intramolecular reaction types, and the principles of chemoselectivity and regioselectivity of alkenes and alkynes were well established. In addition, these basic principles were successfully applied in the syntheses of some nature products as well as some unsaturated heterocycles.

In 2008, our group reported intermolecular Cope-type hydroamination of both alkenes and alkynes using hydroxylamines.[42] The reaction parameters were optimized to control both regio- and chemoselectivity. The scope of the reaction and the functional group tolerance proved that Cope-type hydroamination could be used as a general method of C-N bond formation (eqs. 1.20, 1.21, and 1.22).

In non-symmetrical alkynes (eq. 1.20), the product distribution of intermolecular Cope-type hydroamination followed the Markovnikov principle, and product **1.82** was more favoured than product **1.83** (R_2=H, for example). In non-symmetrical alkenes (eq. 1.21), the reactions with both aqueous and *N*-benzylhydroxylamines also resulted in relatively stable product distributions (**1.84** vs. **1.85**, **1.86** vs.**1.87**). In addition, it was found that the incorporation of EWG substituents or increase steric hindrance can lead to a reverse product distribution (eq. 1.22).[42]

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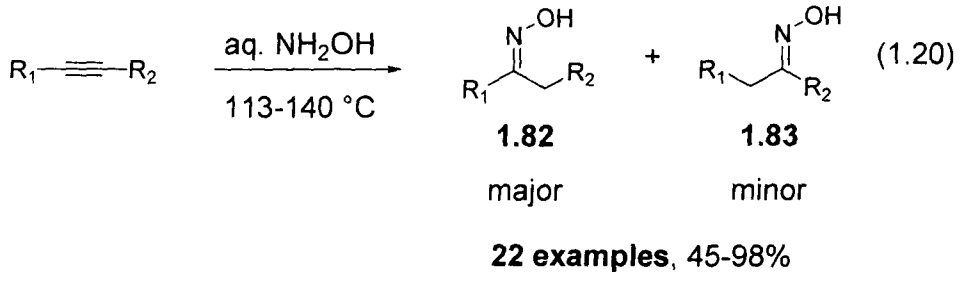
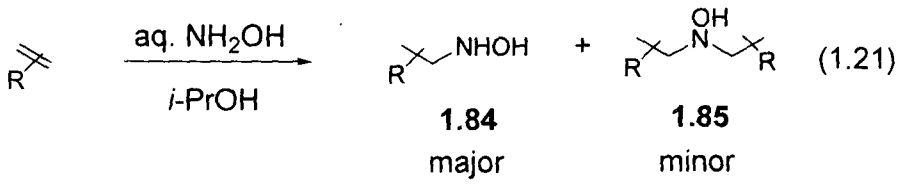
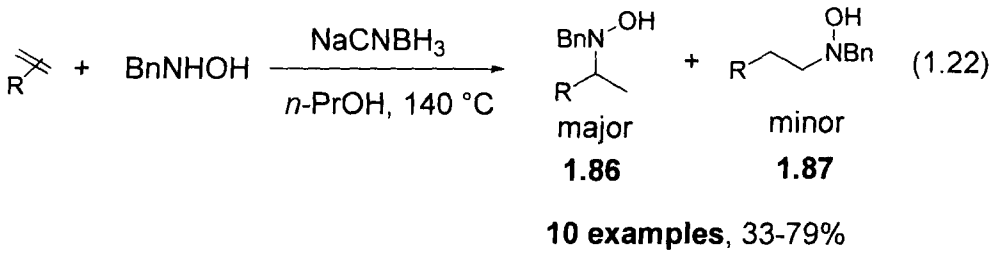
[42] Moran, J. Gorelsky, S. I., Dimitrijevic, E., Lebrun, M.-E. Bédard, A.-C. Seguin, C., Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.



(1.20)

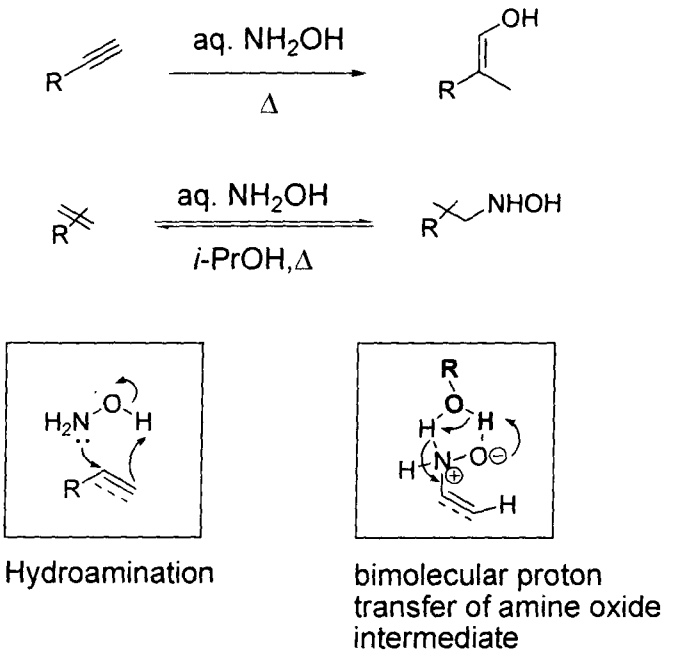


(1.21)



(1.22)

Solvent effect on reactivity of intermolecular Cope-type hydroamination was discussed as well. It was found that reactions of alkynes were more favourable in alcoholic solvents. On the other hand, the use of alcoholic solvents is essential to reactions of alkenes.[42]



Scheme **1.11**. Solvent effect on intermolecular Cope-type hydroamination

Intermolecular Cope-type hydroamination of alkenes and alkynes occurs through an amine oxide intermediate (Scheme 1.11).[43] It was found that the alcoholic solvent likely allowed a facile bimolecular proton transfer of the intermediate, which favoured the formation of the final product. The same solvent effect was also found in intramolecular Cope-type hydroamination. Consequently, in the second chapter, the reactions were mainly tested in alcoholic solvents.

The Beauchemin group also used intramolecular Cope-type hydroamination methods to synthesize natural products, trying to overcome the limitations of the method in challenging cyclizations.

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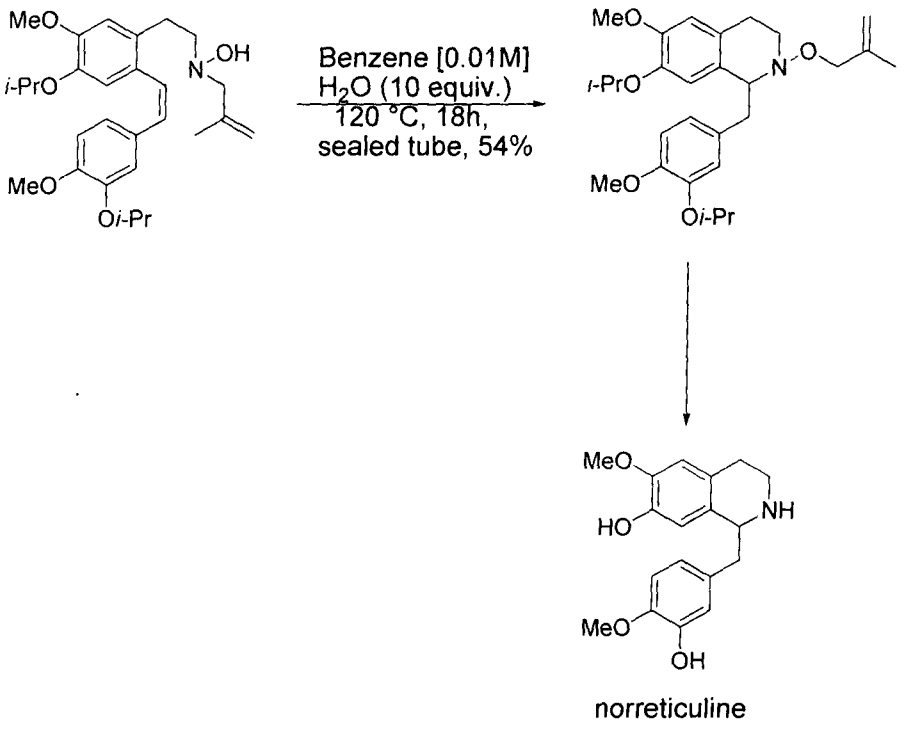
[43] Beauchemin, A. M. ; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem Int. Ed.* **2008**, *47*, 1410.



Scheme **1.12**. The key intramolecular Cope-type hydroamination step towards norreticuline

One key step in norreticuline synthesis can be easily achieved by intramolecular Cope-type hydroamination method (Scheme 1.12).[44] This methodology provided a shorter synthetic route, and afforded norreticuline in good yield. A related strategy was used in the synthesis of coniine and 2-epi-pumiliotoxin C.[45]

1.8. Hydroamination in the synthesis of unsaturated heterocycles

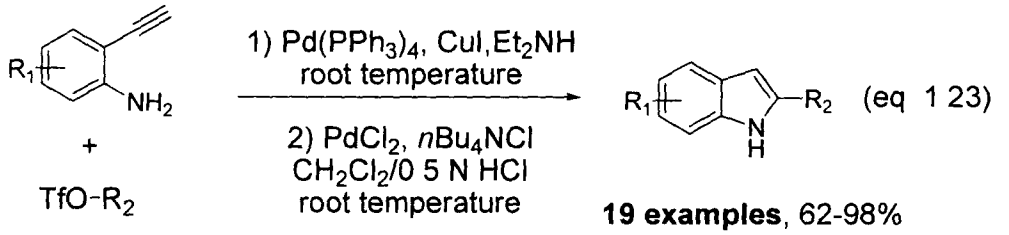
[44] Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem Soc* **2009**, *131*, 874.

[45] Lebrun, M.-E. ; Pfeiffer, J. Y. ; Beauchemin, A. M. *Synlett* **2009**, 1087.

Hydroamination methodology to afford unsaturated heterocycles had been studied for many years. Most of these approaches were transition-metal catalyzed; however, Cope-type hydroamination was seldom used.

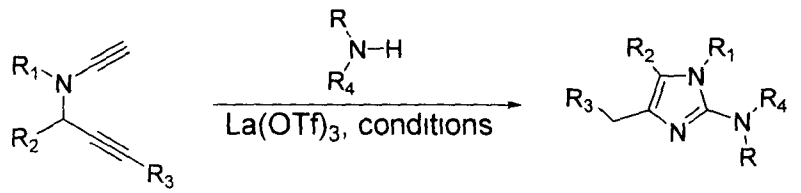
There are several examples demonstrating the wide use of transition metal catalyzed hydroamination/alkyne annulation to afford indoles (eq. 1.23),[46] imidazoles (eq. 1.24),[47] pyrroles (eq. 1.25),[48] pyridines and isoquinolines (eq. 1.26),[49] etc. However, such approaches are mostly used to build π-excessive, 5-membered nitrogen heterocycles.

Indoles:



(eq 1 23)

Imidazoles:



(eq 1 24)

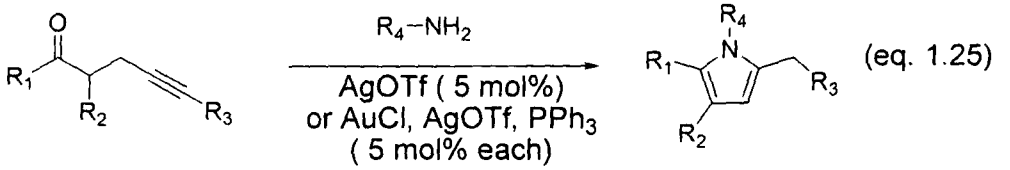
[46] Cacchi, S., Carnicelli, V., Marinelli, F. *J Organomet Chem* **1994**, *475*, 289

[47] Giles, R. L., Sullivan, J. D., Steiner, A. M., Looper R. E. *Angew Chem Int Ed* **2009**, *48*, 3116

[48] Harrison, T. J., Kozak, J. A., Corbella-Pane, M., Dake, G. R. *J Org Chem* **2006**, *71*, 4525

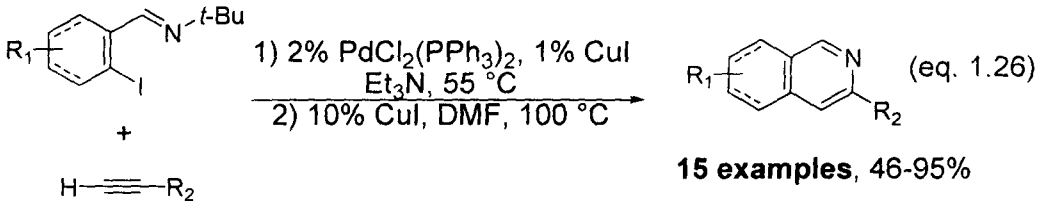
[49] Roesch, K. R., Larock, R. C. *J Org Chem* **2002**, *67*, 86

Pyrroles:



6 examples, 57-92%

Pyridines and isoquinolines:

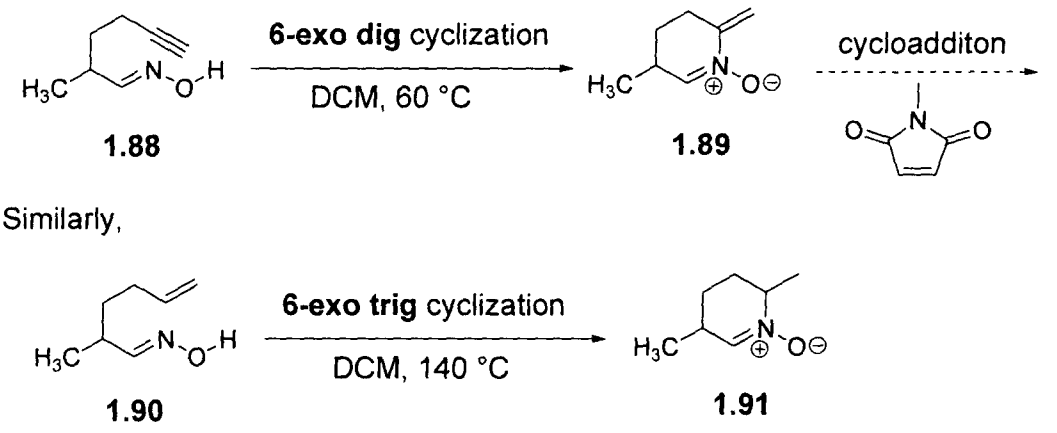


15 examples, 46-95%

1.9. Oximes in the synthesis of unsaturated heterocycles

Oximes are also bifunctional reagents and widely used in hydroamination. In the C=N-OH functionality, the proton of hydroxyl group can be transferred to and activate unsaturated carbon-carbon bonds. The lone pair electrons of the nitrogen atom can attack the activated bond, forming a new C-N bond. Grigg reported 1, 3-azaprotio cyclotransfer (APT) reaction of oximes with both alkenes and alkynes in 1993. The corresponding cyclic *N*-vinyl nitrones were obtained as products and were used for further cycloaddition reactions.[50]

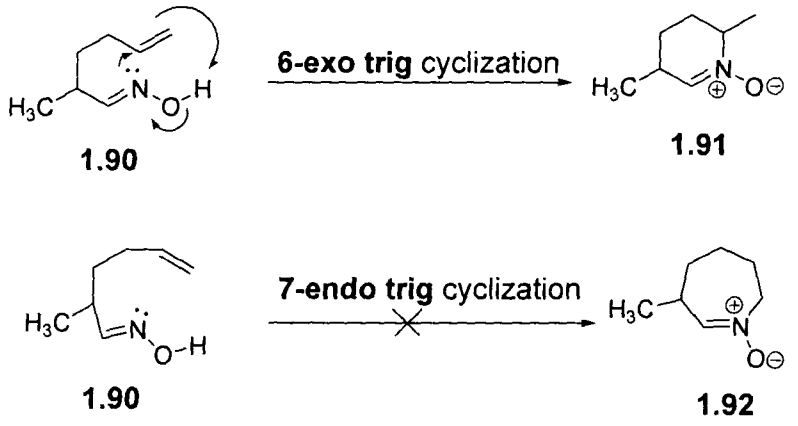
[50] Grigg, R.; Perrior, T. R.; Sexton, G. J.; Surendrakumar, S.; Suzuki, T. *J Chem. Soc. Chem. Commun.***1993**, 372.



Scheme **1.13**. 1, 3-azaprotio cyclotransfer (APT) reaction of oximes

Grigg claimed that oximes **1.88** (Scheme 1.13) undergo facile cyclizations to afford corresponding nitrones **1.89**, which were used for further cycloaddition with *N*-methylmaleimide (NMM). The intramolecular cyclization of oximes **1.90** was carried out at 60°C. Similarly, intramolecular oxime-alkene cyclizations of oximes **1.90** were also possible, but required higher temperatures (140°C).[50]

Grigg also pointed out that application of oximes in intramolecular cyclizations had less possibility of competitive products (Scheme 1.14). For example, though oximes **1.90** undergo 6-exo trig cyclization to afford 6-membered ring nitrones **1.91**, but 7-membered ring nitrones **1.92** were not detected.[50]



Scheme **1.14**. chemoselectivity of cyclotransfer (APT) reaction of oximes

Although oximes appear to be very useful synthetic tools for C-N bond formation, the direct applications of oximes in Cope-type hydroamination towards unsaturated heterocycles syntheses are rare. Therefore, in the following chapter, investigations toward the synthesis of isoquinolines, pyridines and pyrimidines via oxime hydroamination will be presented.

2

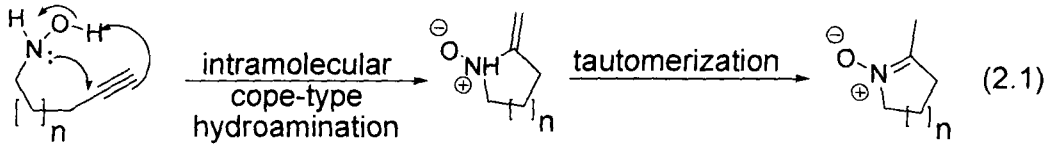
Investigations towards metal-free hydroamination approaches to aromatic nitrogen heterocycles

2.1 Research goals

Over the past 20 years, hydroamination approaches have been applied to the synthesis of various heterocyclic ring systems. While most examples focus on approaches to saturated heterocycles, some efforts have focused on aromatic nitrogen heterocycles, such as indoles,[45] pyrroles,[47] imidazoles,[46] pyridines and isoquinolines.[48] These hydroamination methods required the use of transition metals as catalysts, and have limitations preventing broad applicability. In addition, transition metal complexes are usually expensive. Due to these issues, there is a need for additional strategies and methods to synthesize aromatic nitrogen heterocycles.

Cope-type hydroamination requires milder reaction conditions, and

can be a cheap, efficient method for C-N bond formation. In 1976, House reported the intramolecular Cope-type hydroamination of alkenes to afford 5- and 6-membered heterocycles.[40] In 1992, Holmes reported the formation of pyrrolines (nitrones) **2.3** from the corresponding hydroxylamine precursors **2.1** through the intramolecular cyclization of alkynyl hydroxylamines followed by tautomerisation (eq. 2.1).[51]



2.1 **2.2** **2.3** (2.1)

Based on the results of Holmes' research, it was of interest whether the nitrones **2.3** could provide access to aromatic nitrogen heterocycles. To determine this experimentally, alkynes were chosen to try both intermolecular and intramolecular Cope-type hydroamination approaches. The alkyne functionality was used due to the fact that it is readily accessible and that alkynes are known to be more reactive than their alkene counterpart. Another intrinsic advantage is that the products are in a higher oxidation state, which is useful to access highly unsaturated (or aromatic) ring systems.

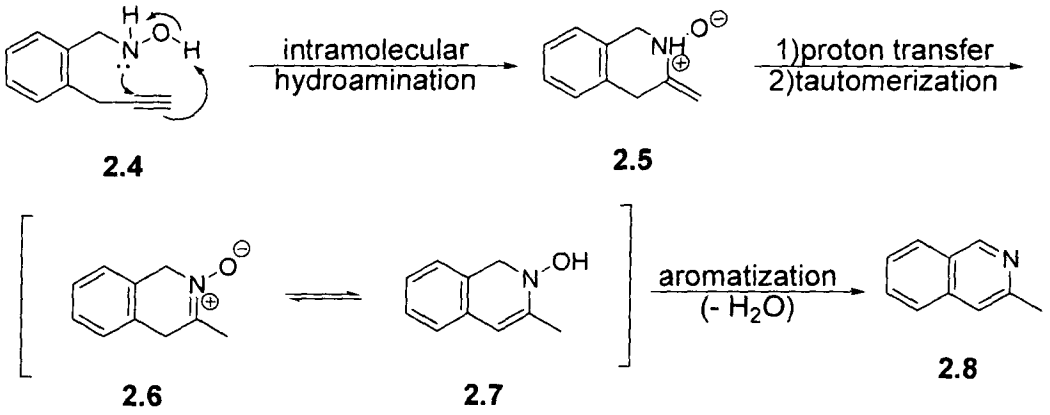
51 Fox, M.E.; Holmes, A.B.; Forbes, I. T.; Thompson, M. *Tetrahedron Lett*, **1992**, *33*, 7421

2.2 Toward an intramolecular hydroamination route to isoquinolines

Since the majority of the literature in this area involves the formation of 5-membered unsaturated heterocycles, the focus of our research became the less common 6-membered aromatic nitrogen heterocycles. Inherently, such ring systems are also challenging to form as the aromatization requires the presence and management of three unsaturations.

2.2.1 Proposed approach

In order to synthesize isoquinolines through hydroamination approaches, two degrees of unsaturation are required besides the existing benzene ring in the starting material. In our proposed strategy (Scheme 2.1), one unsaturation develops from tautomerization of the terminal alkene to an internal one after intramolecular hydroamination, and the other is formed upon the cleavage of the N-O bond of the hydroxylamine and loss of H_2O.



2.4 **2.5** **2.6** **2.7** **2.8**

Scheme **2.1**. Proposed hydroamination approach to isoquinolines

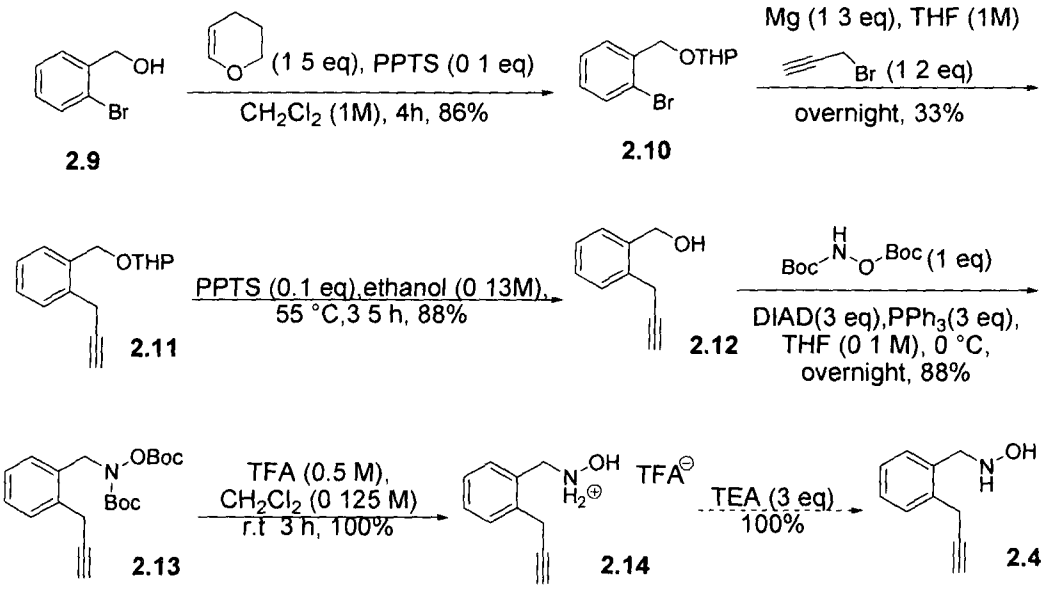
The alkynyl hydroxylamine **2.4** (Scheme 2.1) will be used to attempt intramolecular hydroamination. A Cope-type hydroamination would form intermediate **2.5**. The nitrone intermediate **2.6** (formed after a proton transfer step) would then tautomerize to intermediate **2.7**. Then, the formed hydroxylamine would be finally converted to isoquinoline **2.8** by dehydration.

2.2.2 Synthesis of substrates

In order to test the desired approach to isoquinolines, substrate **2.4** was prepared from commercially available alcohol **2.9** in 5 steps. The alkyne functionality was introduced through a Grignard reaction (Scheme 2.2).[52] The hydroxyl group in starting material **2.9** was protected using 3,4-dihydro-2H-pyran since the OH group was sensitive to basic Grignard

[52] Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034.

reagents.[53] The THP protected compound **2.10** was then reacted with magnesium to form a Grignard reagent. Following this, 3-bromoprop-1-yne was added dropwise as the electrophile, after which compound **2.11** was obtained. The THP protective group was removed with the weak acid pyridinium *p*-toluenesulfonate (PPTS) in ethanol, giving compound **2.12**.[54]



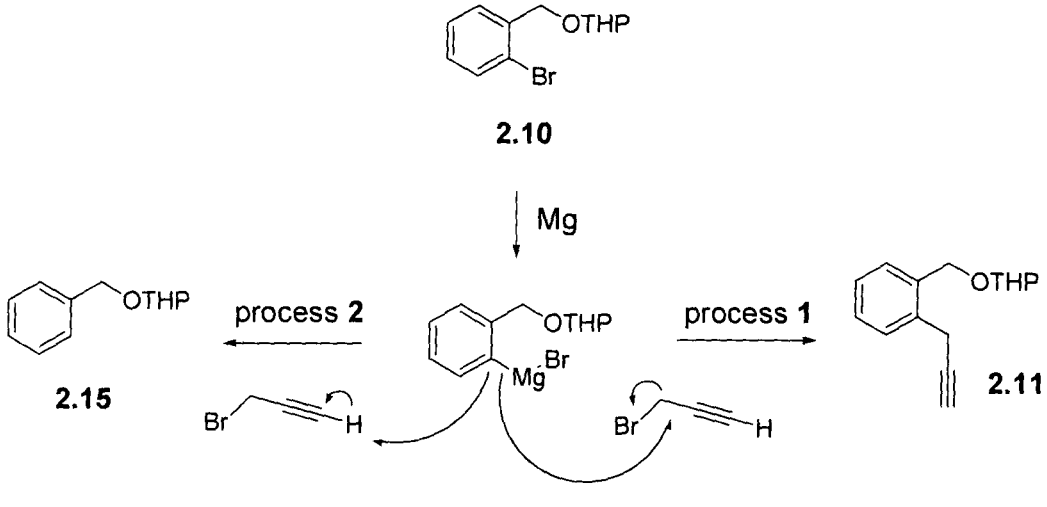
Scheme **2.2**. Synthesis of intramolecular hydroamination substrate **2.4**

While attempting to convert compound **2.10** to **2.11** via a Grignard reaction, problems were encountered (Scheme 2.3). Compound **2.11** was obtained after a nucleophilic attack of the formed Grignard reagent on

[53] Eric Marsault *J Med Chem* **2006**, *49* 7190-7197

[54] Miyashita, M , Yoshikoshi, A , Grieco, P *J Org Chem* **1977**, *42*, 3772

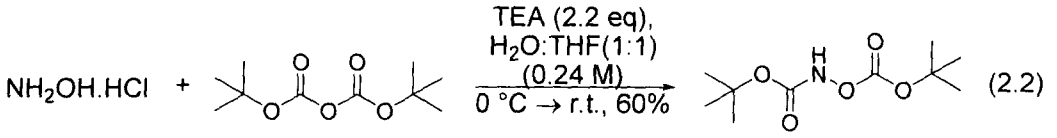
3-bromoprop-1-yne (process **1**). In this reaction, the Grignard reagent reacted as the nucleophile. However, Grignard reagents are not only good nucleophiles, but also strong bases (since $pKa_{R\text{-}H} > 40$). In the reaction system of Scheme 2.3, process **2** was also possible. Since both the reactant, 3-bromoprop-1-yne, and the product **2.11** had terminal alkyne functionality in their structures, the alkynylic protons are very acidic (pKa ~ 25) compared to the Grignard reagent. Therefore, the deprotonation of terminal alkyne in either reactant or product consumed the prepared Grignard reagent, and led to a by-product **2.15**. Consequently, the conversion from **2.10** to **2.11** had poor yield (~ 30%). To make the problem even worse, this by-product had similar polarity with **2.11**, making it difficult to purify the crude reaction mixture and led to a difficult separation by column chromatography.



Scheme **2.3**. Competitive processes of Grignard reaction

From compound **2.12** (Scheme 2.2), a Mitsunobu reaction was used to convert the hydroxyl group to the Boc-protected hydroxylamine (Boc-NH-OBoc).[55] Following this step, product **2.13** was purified by column chromatography and then the two Boc- groups in compound **2.13** were removed with trifluoroacetic acid (TFA). Substrate **2.4** was stored as its TFA salt **2.14**. This conversion was necessary in order to store substrate **2.4** for a longer period of time, since the hydroxylamine was sensitive in its unprotected form. Before compound **2.14** was used for intramolecular cyclization, triethylamine (TEA) was added to neutralize the TFA and convert compound **2.14** to substrate **2.4**.

There was also an issue associated with the Mitsunobu approach. The hydroxylamine was di-Boc protected in advance to avoid competition between the –OH and $–NH_2$ groups. Equation 2.2 shows the conditions for the Boc protection of hydroxylamine.



(2.2)

Substrate **2.17** (eq. 2.2) has two Boc groups in its structure, but it still has an active proton on nitrogen, which is necessary for the subsequent

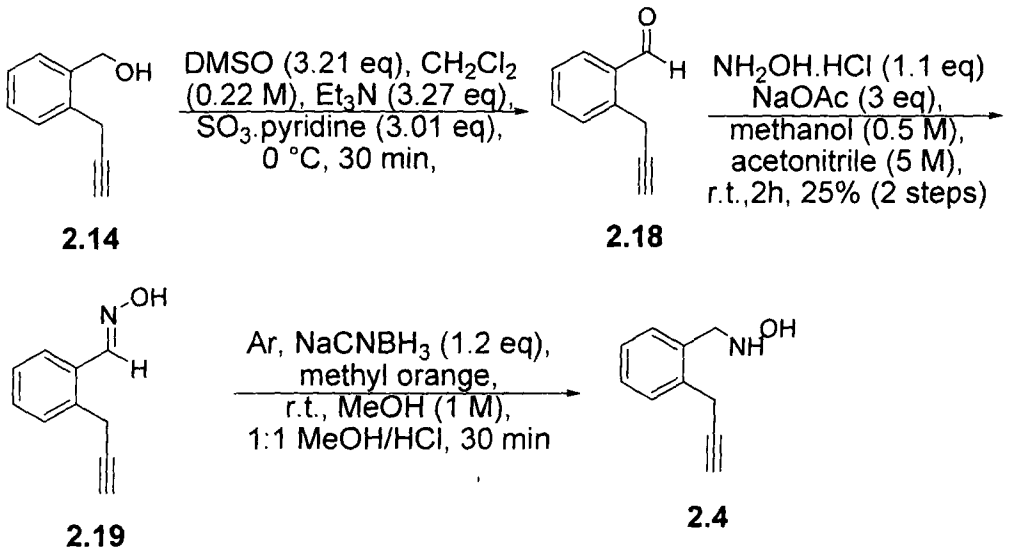
[55] Tao, T.; Alemany, L. B.; Parry, R. J. *Org. Lett.* **2003**, *5*, 1213.

Mitsunobu reaction. Unfortunately, formation of the tri Boc protected hydroxylamine derivative could also occur under the reaction conditions (due to the acidity of the proton present in **2.17**), typically at longer reaction times. A difficult, time-consuming column separation was required to get a complete separation, and the purity of di-Boc product **2.17** could be established by ^{1}H NMR.

To avoid the problems associated with the Mitsunobu reaction, Ms. Isabelle Dion developed a new strategy applicable towards the synthesis of substrate **2.4** (Scheme 2.4). Following her approach, a Parikh-Doering oxidation[56] was used to convert alcohol **2.12** to the corresponding aldehyde **2.18**. Due to the volatility of the aldehyde, it was used directly in the next step without purification.

After conversion of aldehyde **2.18** to corresponding oxime **2.19**,[57] $NaCNBH_3$ was used to reduce oxime **2.19** to the active substrate **2.4**. In order to evaluate the efficiency of the new route, a yield over 3 steps (from oxime **2.19** to isoquinoline) was calculated (Table 2.5).

[56] Mukai, C.; Nomura, I.; Kitagaki, S. *J. Org. Chem.* **2003**, *68*, 1376.
[57] Bialecki, J. B.; Ruzicka, J.; Attygalle, A. B. *J. Label. Compd. Radiopharm.* **2007**, *50*, 711.



Scheme **2.4**. synthesis of substrate **2.4** from oxime

In general, both synthetic routes suffered several disadvantages. In the first route, the low-yielding Grignard reaction was a major issue. Also, preparation of the TFA salt of substrate **2.4** (Scheme 2.3) and the synthesis of the di-Boc hydroxylamine was not easy. In addition, the excess PPh_3 made the following chromatographic purification difficult as well. On the other hand, preparation of the active hydroxylamine during the second route required (Scheme 2.5) an extraction. Therefore, if the active hydroxylamine is exposed to air for a long period of time, there will be a risk of oxidation and degradation.

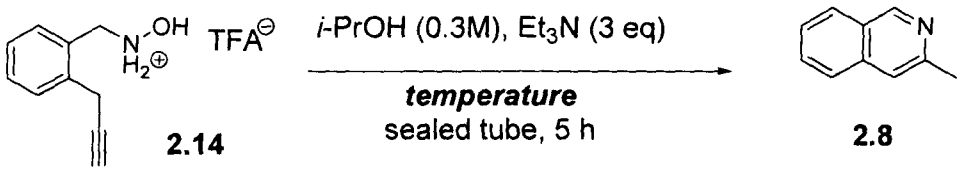
2.2.3 Results and discussion

From previous work performed in the Beauchemin lab,[42] it was found

that the optimum conditions for the intermolecular Cope-type hydroamination of alkynes was heating in *i*-PrOH (1M) at 140 °C in the microwave for 5 to 10 hours. Theoretically, intramolecular hydroamination will be easier than intermolecular hydroamination because the latter has a negative entropy change. Consequently, these optimized conditions for the intermolecular Cope-type hydroamination were used to attempt our intramolecular cyclization. Parameters such as temperature, reaction time, concentration of substrate, and solvent were tested to determine which would afford the best yield for isoquinolines.

The first optimization study involved looking at the efficiency of the proposed sequence at various temperatures. Although 140 °C was found to be the optimum temperature for intermolecular hydroamination, it was verified that this temperature would work for the intramolecular cyclization as well as the following aromatization.

Table2.1. Temperature optimization of intramolecular hydroamination



2.14 **2.8**

Entry	Temperature,(°C)	% conversion
1	140	42%
2	180	45%
3	100	33%

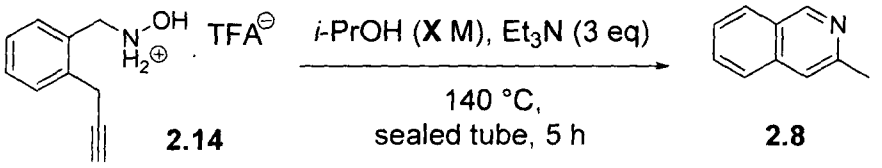
Calculated from result of ^{1}H NMR spectra using 1,4-dimethoxylbenzene as internal standard

From Table 2.1, the tandem cyclization and aromatization at 140 °C gave 42% conversion to the corresponding isoquinoline (Entry 1). On the basis of this result, the reaction was repeated at both higher and lower temperature. A higher temperature (180 °C) gave a similar result (45%, Entry 2) while a lower temperature (100 °C) led to a lower conversion (33%, Entry 3). This demonstrated that 140 °C was in the correct temperature range, even though the conversion was only moderate. At 180 °C, the crude mixture showed possible decomposition of the starting material. Therefore the reaction was not repeated at higher temperature. On the other hand, the result at 100 °C showed that this temperature was not high enough for this intramolecular cyclization.

It is believed that the low conversion can be attributed to an intermolecular side reaction of the starting material **2.14** (Table 2.1).

Therefore, the concentration of **2.14** was decreased in order to minimize this possible intermolecular side reaction (Table 2.2).

Table2.2. Concentration effect on intramolecular hydroamination



2.14 **2.8**

Entry	concentration [M]	% conversion
1	0.05	40%
2	0.1	41%
3	0.3	42%

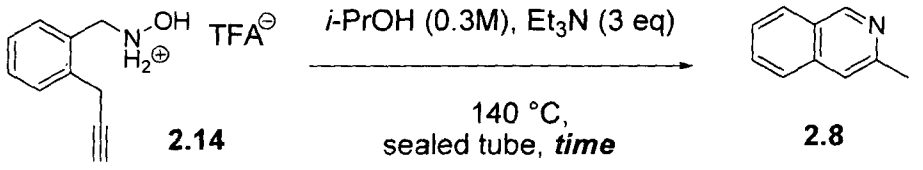
Calculated from result of ^{1}H NMR spectra using 1,4-dimethoxylbenzene as internal standard

Although it was known that 10 hours was the best reaction time for this intramolecular reaction, the concentration effect was surveyed a reaction time of 5 hours. As shown in Table 2.2, the concentration of substrate **2.14** was increased from 0.05 M to 0.3 M. It was shown that no significant change was observed upon varying the concentration. Using the best result obtained, the concentration of substrate **2.14** was chosen 0.05 M (Entry 1) in all of the following reactions.

Given the moderate conversion at 140 °C, it was decided to perform the reaction optimization considering that the reaction involved two steps. The first step, the intramolecular cyclization, should be fast while the

second step, the aromatization, may require a longer time to finish. This hypothesis led to the test on reaction time (Table 2.3).

Table2.3. Reaction time optimization of intramolecular hydroamination



2.14 **2.8**

Entry	Time,(hours)	% conversion
1	5	42%
2	10	51%
3	49	50%
4	24	48%
5	77	52%

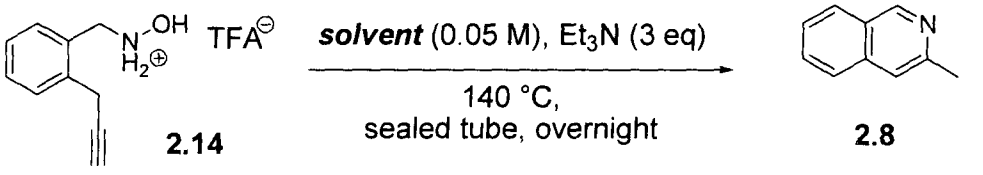
Calculated from result of ^{1}H NMR spectra using 1,4-dimethoxylbenzene as internal standard

As shown in Table 2.3, it was found that a longer reaction time (10 hours) did result in a higher conversion (Entry 2), but the increase was not dramatic (42% to 51%). After 10 hours (Entry 3, 4 and 5), the reaction appeared complete, and conversion would not increase even when allowing for longer reaction times. The reaction for a very long time (77 hours, Entry 4) was to ensure completion of the reaction.

Relying on the result of Table 2.3, it was thought that *i*-PrOH was not the best solvent for this cyclization. Therefore, the reaction was repeated

in different solvents in order to find a better alternative. Both protic and non-protic solvents were used in order to create a comparison.

Table2.4. Solvent effect on intramolecular hydroamination



2.14 **2.8**

Entry	solvent	% conversion [a]
1	benzene	42%
2	*n*-PrOH	37%
3	$CDCl_3$ [b]	60%

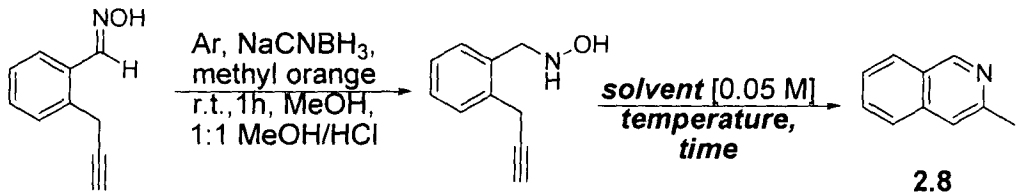
[a] Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard
[b] The reaction was run at 50 °C, and 70 hours was spent to monitor the process

As can be seen in Table 2.4, the conversion in non-protic benzene (Entry 1) was 10% less when compared with that of Entry 2 in Table 2.3 (51%). This result is reasonable because it has been well established that protic solvent helps the formation of intermediate in the Cope-type hydroamination. However, this in not the case as the conversion obtained in *n*-PrOH (Entry 2) was even lower than that in benzene. This bizarre result led us to investigate the reaction mechanism. In order to do so, the reaction was repeated in in $CDCl_3$ (Entry 3), so that the process could be monitored by ^1H NMR.

Also, instead of running the reaction in a sealed-tube, the reaction was repeated in a round bottom flask. A temperature of 50 °C was chosen because it was below the boiling point of $CDCl_3$. After the TEA was added, ^1H NMR showed only hydroxylamine **2.4** (Scheme 2.1). After stirring at room temperature for 1 hour, ^1H NMR showed the co-existence of the starting material **2.4** and intermediates (**2.6** and **2.7**) (Scheme 2.1). This result demonstrates that the intramolecular cyclization proceeded with ease. After the peaks corresponding to the starting material in the ^1H NMR spectra had disappeared, the reaction mixture was heated at 50 °C to allow for aromatization. The reaction mixture was tested by ^1H NMR from time to time until the peaks of the intermediates in the spectrum disappeared. Surprisingly, a conversion of 60% was obtained after 70 hours (Entry 3).

The same reaction conditions were also used for the conversion of the oxime **2.21** to isoquinoline **2.10** (Table 2.5). Unlike the previous reaction, the percent conversion reported was for 3 steps (oxime to isoquinoline). It was found that the reaction had the best conversion (35%) after 96 hours (Entry 2). Since reductions of oximes are typically efficient, these results highlight that there is either a problem with the isolation of hydroxylamine **2.14**, or an issue of reproducibility for the sequence that is associated with the method used to synthesize the precursor.

Table2.5. Optimization of conversion from oxime to isoquinoline



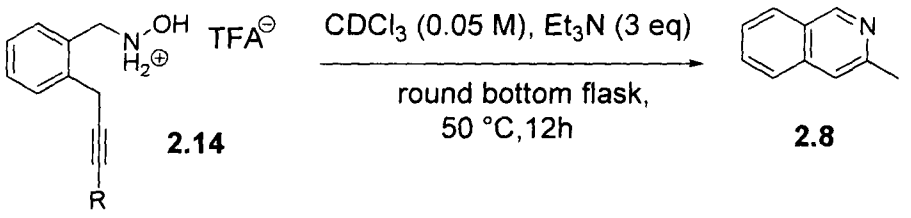
2.19 **2.4** **2.8**

Entry	Time (hours)	Temp (°C)	Solvent	% conversion [a,b]
1	24	55	$CDCl_3$	29%
2	96	60	$CDCl_3$	35%
3	96	60	$CHCl_3$	24%

[a] Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard
[b] The conversion was for 3 steps from oxime **2.19** to isoquinoline **2.8**

To extend the substrate scope of this intramolecular Cope-type hydroamination, two internal alkynes were reacted under the same reaction conditions (Table 2.6). Unfortunately, both the methyl and ethyl-substituted substrates did not afford the corresponding isoquinolines. This suggests that distal alkyne substitution made the hydroamination reaction more difficult.

Table2.6. Substrate scope of intramolecular hydroamination



2.14 **2.8**

Entry	R	% conversion
1	CH_3	no reaction
2	C_2H_5	no reaction

Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard

2.2.4 Conclusion

To conclude, an intramolecular Cope-type hydroamination approach the isoquinoline framework was developed. Several parameters such as temperature, reaction time, concentration of substrate, and solvent were scanned in order to determine the optimum conditions for this reaction.

It was found that the optimum conditions for the formation of isoquinolines using this approach were using $CDCl_3$ as solvent and allowing the reaction to run for 3 days (60 % conversion, Table 2.4, Entry 3). Temperatures higher than 50 °C resulted in decomposition of the substrate and lower conversion. However, a current limitation to this methodology is that it cannot be applied to internal alkynes. In addition to this problem, both methods (from TFA salt of hydroxylamine and from

oxime) suffered some synthetic issues, such as low yields for some steps, difficult purification, and long synthetic routes. Unfortunately, it was realized that this methodology may not be optimal to afford isoquinolines. Consequently, alternative methods, such as intermolecular Cope-type hydroamination strategies were also attempted in the hopes of obtaining better results (see section 2.3).

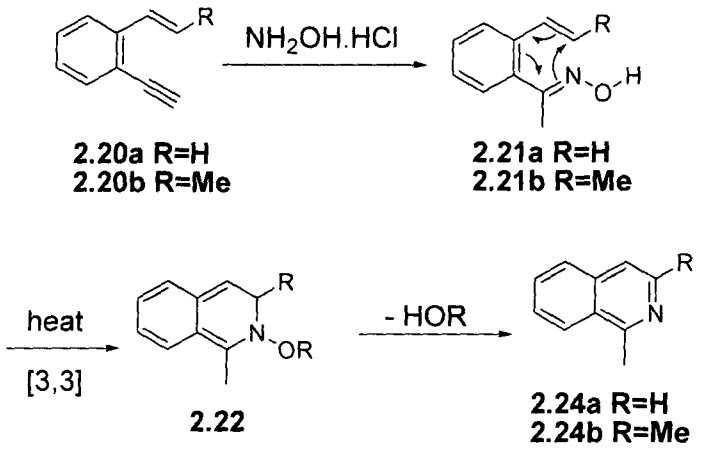
2.3 Progress toward an intermolecular hydroamination route to isoquinolines

Previous work in the Beauchemin research group extensively studied the intermolecular reaction of alkynes with aqueous hydroxylamine (NH_2OH) (eq. 1.20). Both reactivity and regioselectivity were well known for this reaction.[42]

Since this intermolecular reaction also results in new a C-N bond formation, it was wondered whether this method could be applied to in a sequence providing access to aromatic nitrogen heterocycles. Therefore, a new approach to isoquinolines was considered. It involved oxime formation by intermolecular Cope-type hydroamination, followed by an intramolecular rearrangement to afford the desired heterocycle. In this strategy, the two required unsaturation degrees (excluding the aromatic ring) in isoquinolines synthesis come from the use of the oxime functionality and loss of water.

Comparing with the previous intramolecular Cope-type hydroamination methods, this new method had a shorter synthetic route to the substrates. In addition, the new method used a microwave to replace conventional heating in order to improve heating efficiency and decrease heating time.

2.3.1 Proposed approach



Scheme **2.5**. Intermolecular Cope-type hydroamination approach to isoquinolines

The proposed sequence involving an intermolecular hydroamination step is shown in Scheme 2.5. The first step was an intermolecular Cope-type hydroamination of compound **2.20**. This compound had both alkene and alkyne functionality in the structure. However, alkynes have a higher reactivity towards Cope-type hydroamination than alkenes.[41] Therefore they should react first and in turn provide compound **2.21**

(Scheme 2.5). At high temperatures, substrate **2.21** should rearrange via a [3, 3] sigmatropic rearrangement to afford hydroxylamine **2.22**. Finally, loss of water would provide the isoquinoline nucleus.

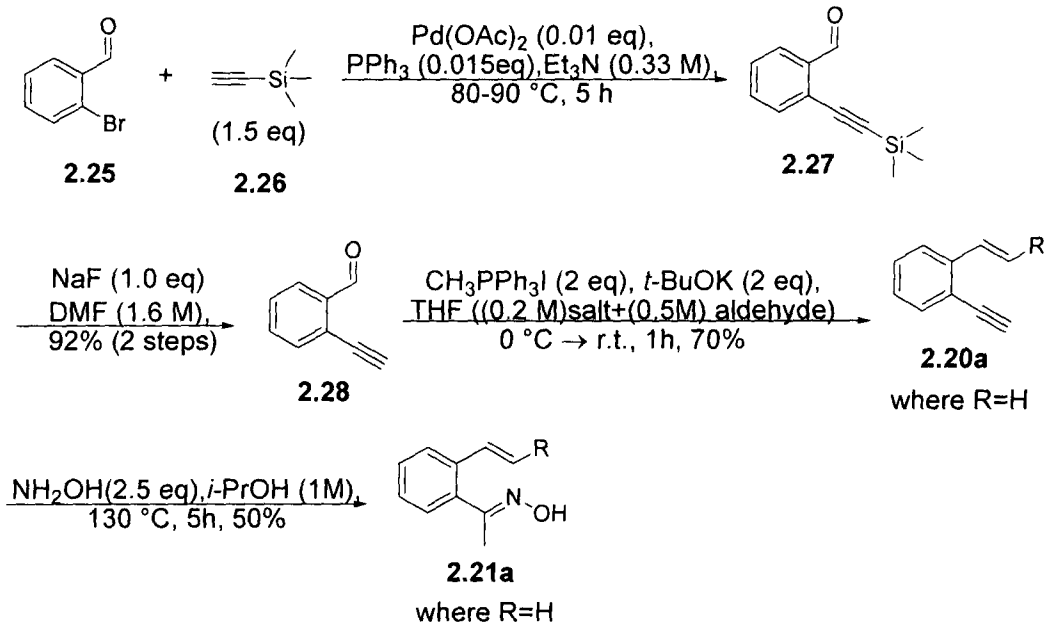
Compared with the intramolecular Cope-type hydroamination method, the intermolecular method has an advantage. Different substituents on the alkene functionality can be easily introduced, which could enlarge the scope of the reaction. To explore the contribution of leaving groups towards formation of isoquinolines, several moieties besides –OH could also be studied.

2.3.2 Synthesis of substrates

In order to explore the viability of the sequence, a route to the desired en-yne precursors was developed. The synthesis of oxime **2.21a** started from aldehyde **2.25** (Scheme 2.6). The first step was a coupling between aldehyde **2.25** and ethynyltrimethylsilane **2.26**.[58] The high yielding reaction (92% for 2 steps) introduced alkyne functionality into the molecule, and gave product **2.27**. The TMS group on the alkyne was removed by NaF,[59] and alkynyl aldehyde **2.28** was formed. Furthermore, a Wittig reaction was used to convert the aldehyde to the alkene,[60] and afforded compound **2.20a**. Finally, compound **2.20a** was submitted to an

[58] Ratovelomana, V.; Linstrumelle, G. *Synth Comm.* **1981**, *11*, 917.
[59] Cai, C.; Vasella, A. *Helv Chim. Acta*, **1995**, 78, 732
[60] McCortney, B. A.; Jacobson, B. M.; Vreeke, M.; Lewis, E. S. *J Am. Chem Soc.* **1990**, *112*, 3554

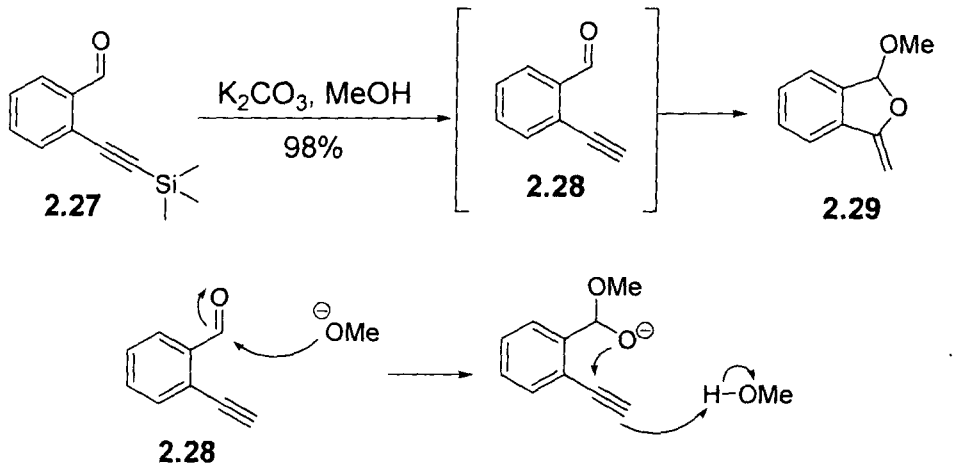
intermolecular Cope-hydroamination with NH_2OH.[42] The mixture was heated in the microwave and oxime **2.21a** was purified by column chromatography.



Scheme **2.6**. Synthetic route of subtrate **2.21a** for intramolecular rearrangement

The conversion from **2.27** to **2.28** was not as straightforward as anticipated. There are two possible methods to cleave the TMS group on the alkyne: K_2CO_3 in methanol[61] or NaF. Although both of these methods are efficient, only NaF could be used to treat compound **2.27**. On the other hand, using K_2CO_3 in methanol led to a side reaction creating product **2.29** (Scheme 2.7).

[61] Corey, E. J.; Kirst, H. A.; *Tetrahedron Lett.* **1968**, 5041



Scheme **2.7**. A side reaction in process of TMS group cleavage

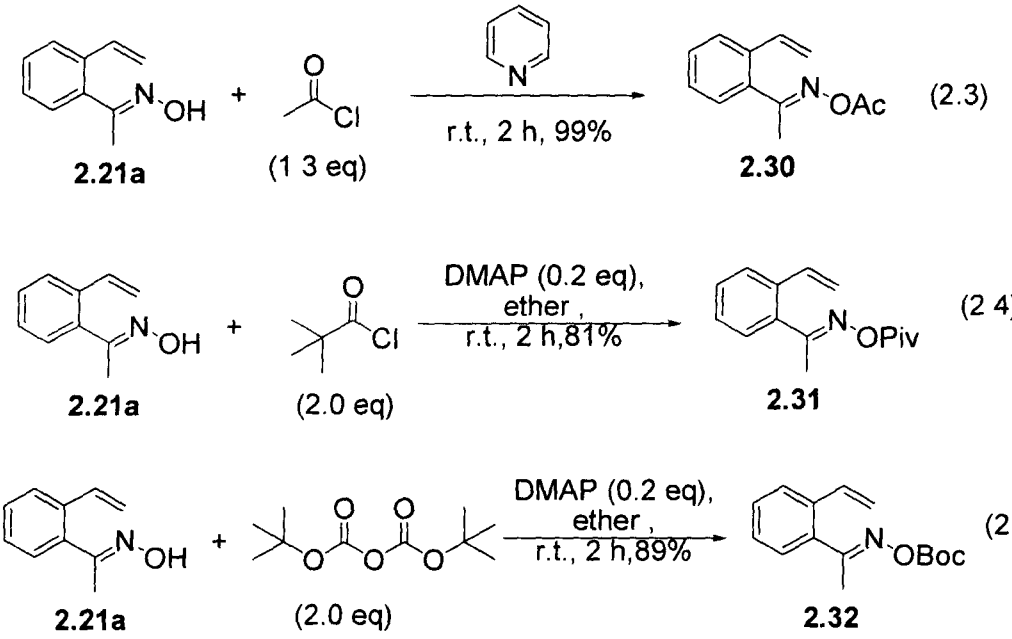
As shown in Scheme 2.7, K_2CO_3 in methanol did cleave the TMS group on the alkyne. However, the formed product **2.28** had another side reaction in the crude mixture. In basic conditions, the methoxyl group was a good nucleophile and attacked the aldehyde functionality in product **2.28**. This nucleophilic attack formed a new oxygen nucleophile, which added on the alkyne functionality. As the result, a side product **2.29** was formed after an intramolecular nucleophilic attack. The ^{1}H NMR showed the existence of compound **2.29** while product **2.28** was not detectable.

The substituted oximes can be obtained from corresponding oximes in a single step (eq. 2.3, 2.4 and 2.5). The reaction results with –OAc **2.30**,[62] -OPiv **2.31**,[63] and –OBoc **2.33** substituted[64] oximes will be discussed in

[62] Okamoto, T.; Kobayashi, K.; Oka, S.; Tanimoto, S. *J. Org Chem.* **1987**, *52*, 5089

[63] Marmer, W. N.; Maerker, G. *J Org Chem.* **1972**, *37*, 3520.

section 2.3.3.



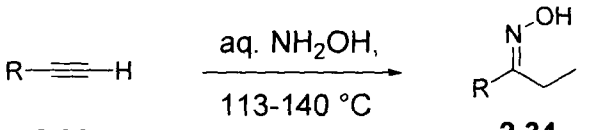
2.3.3 Results and discussion

Before optimizing the reaction of substrate **2.21a** to corresponding isoquinoline, it was essential to discover the best reaction conditions to synthesize substrate **2.21a**. Since the alkyne in compound **2.20a** was mono-substituted, there was a regioselectivity issue for this intermolecular hydroamination. Two types of hydroamination, such as acid-catalyzed, and Cope-type, favor the Markovnikov product over the

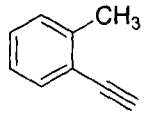
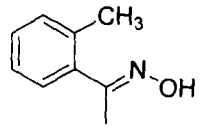
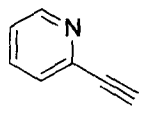
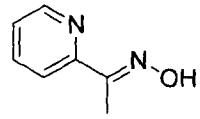
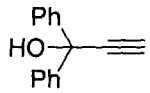
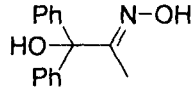
[64] Learmonth, D A , Benes, J., Parada, A , Hamzi, D , Beliaev, A , Bonifacio, M J., Matias, P M , Carrondo, M A , Garrett, J . Soares-da-Silva, P *Eur J Med Chem* **2001**, *36*, 227

anti- Markovnikov isomer. In our research group,[42] experiments showed that alkynes had a similar preference when reacting with hydroxylamine (Table 2.7). The Markovnikov products are more favorable even in some cases where the Markovnikov transition state could be destabilized by steric interactions.

Table2.7. Reaction of alkynes [a] with aqueous NH_2OH from previous experiments by Dr. Moran



2.33 **2.34**

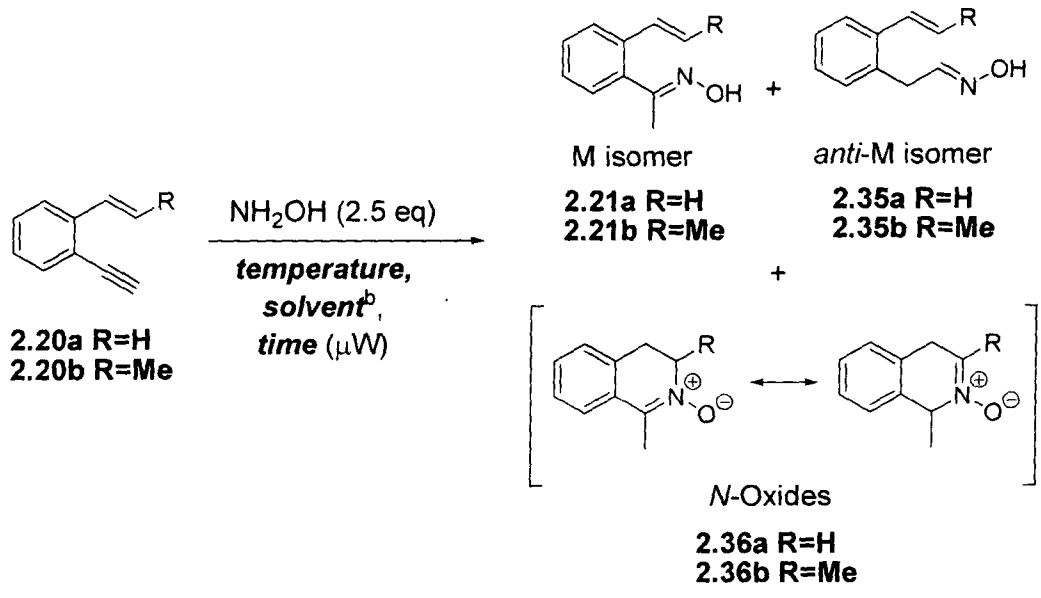
Entry	substrate	Major product	yield(s) [%] [b]
1			45 (11)
2			73 (15)
3			63

a A part of examples from literature are shown here.
b Yield of isolated product. Yield of regioisomer shown in parentheses.

In the synthesis of substrate **2.21a**, the same distribution of products was found. (Table 2.7) The optimization of the reaction from compound **2.20a** to oxime **2.21a** included tests of temperature, reaction time,

concentration of the starting material **2.20a**, and type of solvent. From our previous research,[42] two reaction conditions were optimized: 1) *i*-PrOH (1M), 140 °C, 5-10 hours; 2) Dioxane (2M), 140 °C, 38-40 hours. In the following experiment of substrate **2.22a**, condition one was chosen for tests because our overall sequence required high conversion. On the other hand, dioxane was also tried to offer a comparison. Table 2.8 shows the results of this optimization.

Table2.8. Optimization of hydroamination[a] of substrate **2.20a** with NH_2OH



Entry	Time (hours)	Temp (°C)	Solvent	**2.20**	**2.21**[c]	**2.36**
1	5	130	*i*-PrOH	**a** 18%	**a** 50%	**a** 20%
2	5	140	Dioxane	-----	**a** 26%	**a**18%
3	10	130	*i*-PrOH	**a** 20%	**a** 29%	**a** 28%
4	10	120	*i*-PrOH	**a** 80%	**a** 16%	**a** 3%
5	5	130	*i*-PrOH	**a** 31%	**a** 7%	**a** 1%
6	5	125	*i*-PrOH	**a** 10%	**a** 31%	**a** 9%
7	5	130	*i*-PrOH	**b** 18%	**b** 50%	**b** 20%
8	5	140	*i*-PrOH	-----	**b** 50%	**b** 32%
9	5	100	*i*-PrOH	**b** 80%	**b** 20%	-----

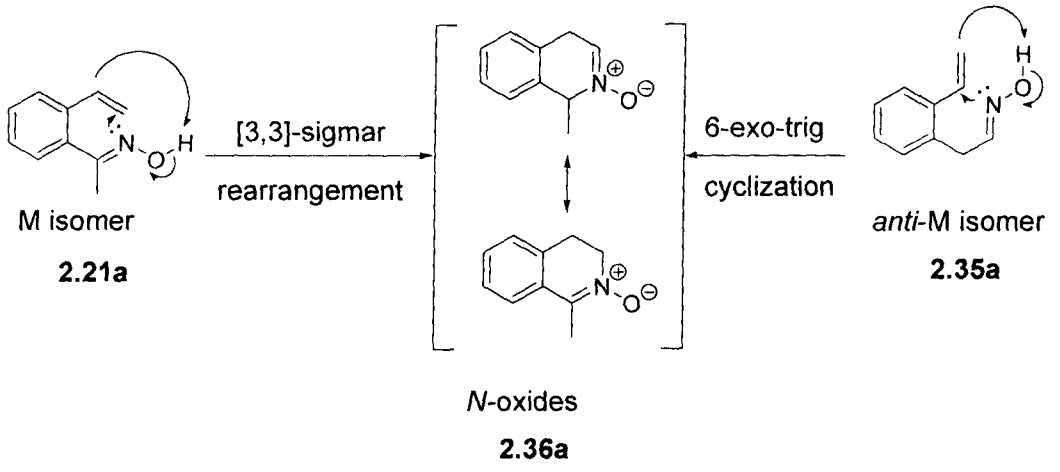
[a] Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard
[b] Only Entry 5 used [2M]
c In all Enties, anti-M isomer **2.35** only showed trace amount.

In Table 2.8, entries 1-6 show the results for substrate **2.20a** (R=H) and entries 7-9 show the results of methyl substituted oxime **2.20b**. Analysis of the unpurified reaction mixture by ^{1}H NMR, revealed that a mixture of compounds was present. It contained the product of interest **2.21**, the starting material **2.20**, *N*-oxides **2.36** as the main impurities, and the anti-Markovnikov isomer **2.35** in trace amounts. The use of dioxane (entry 2) had a lower conversion than the conditions using *i*-PrOH as solvent. When the concentration of **2.20a** was [2M] (entry 5), the result was worse than [1M] cases.

The intermolecular Cope-type hydroamination was performed using microwave irradiation at 120 °C for 10 hours (Entry 4). At this time, 80% of the alkyne **2.20a** remained in the mixture while only 16% of oxime **2.21a** was obtained. As a comparison, when the reaction was repeated at 130 °C for 5 hours (Entry 1), only 18% of the alkyne **2.20a** was left while 50% of oxime **2.21a** existed in the mixture. Therefore, 130 °C was the optimal temperature for the reaction. In addition, when the mixture was at 130 °C for a longer time (10 hours, entry 4), the amount of oxime **2.21a** decreased while the amount of *N*-oxides **2.36a** increased. Therefore, 5 hours was long enough for the reaction. As a result, the best conditions for the reaction of **2.20a** with aqueous NH_2OH were *i*-PrOH [1M], at 130 °C for 5 hours in the microwave (entry 1).

The results of Entry 1 and 4 in Table 2.8 gave a hint to explain the

formation of the main impurities **2.36**. As time went on, the amount of oxime **2.21a** decreased while that of *N*-oxides **2.36a** increased. We thought that *N*-oxides **2.36a** came from oxime **2.21a** through an intramolecular reaction.



Scheme **2.8**. Possible mechanisms of *N*-oxides **2.36a** formation

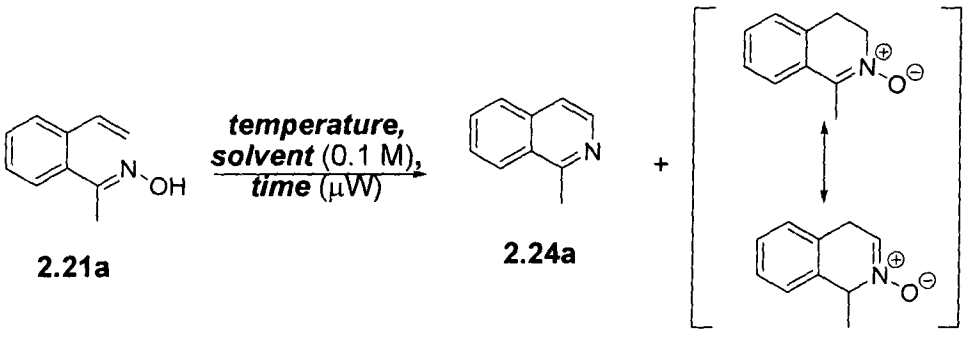
In 1993, Grigg reported nitrones forming cyclizations from both alkynes and alkenes when reacting with oximes.[50] He pointed out that oximes can react with alkenes to form nitrones using harsher conditions than those of alkynes (Scheme 1.13). In this publication, Grigg also mentioned a 6-exo trig cyclization between an oxime and alkene can happen in CH_2Cl_2 at 140 °C.[50]

We can imagine that the 6-exo trig cyclization of substrate **2.35a** can happen at 130° C (microwave). Consequently, the *N*-oxides **2.36a** could arise from the anti-Markovnikov product **2.35a** (Table 2.8). Another possible mechanism to form the *N*-oxides is a [3,3]-sigmatropic

rearrangement of substrate **2.21a** (Scheme 2.8). In our case, both of the two possible cyclizations afforded the same *N*-oxides **2.36a**. Although Grigg mentioned the possible competitive 7-endo-trig, this product was not detected. Based on previous results showing that the Markovnikov isomer was the major product, we believed that 6-endo trig cyclization was the mechanism involved. This can explain why the amount of substrate **2.21a** decreased while that of *N*-oxides **2.36a** increased.

After the optimization of the intermolecular hydroamination, the second step was intramolecular rearrangement of substrate **2.21a** to corresponding isoquinoline **2.24a (R=H)** (Scheme 2.6). Table 2.9 shows the optimization of the rearrangement reaction.

Table2.9. Conversion[a] of oxime **2.21a** to isoquinoline **2.24a** by rearrangement



2.21a **2.24a** *N*-oxides **2.36a**

Entry	Time (hours)	Temp (°C)	Solvent	**2.24a**	**2.36a**
1	5	150	*n*-BuOH	7%	16%
2	5	175	*i*-PrOH	32%	27%
3	10	180	*i*-PrOH	40%	42%
4	10	180	$PhCF_3$	23%	55%
5	10	200	*n*-BuOH	63%	28%
6 [b]	10	200	*n*-BuOH	61%	21%

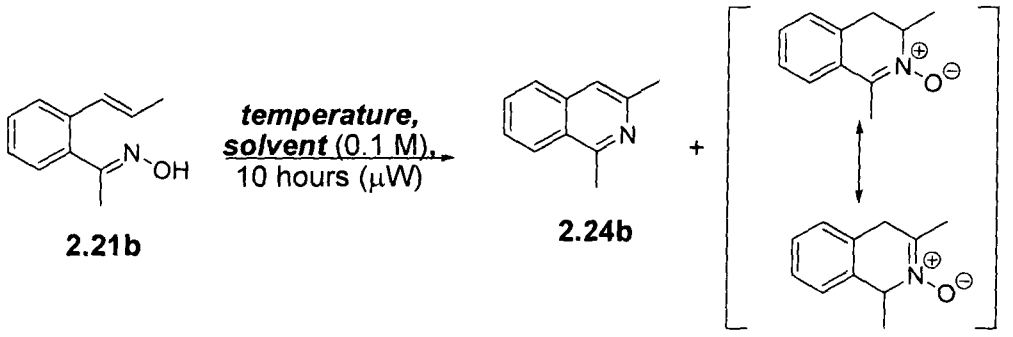
[a] Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard
[b] Entry 6 used H_2O/*n*-BuOH= 1:4 as solvent

The temperature survey started with microwave irradiation at 150 °C. It was found that both isoquinoline **2.24a** and *N*-oxide **2.36a** were formed with low conversion and a lot of starting material remained. The reaction was sequentially tried at 175 °C, 180 °C and 200 °C. It was found that the conversion of isoquinoline **2.24a** reached its highest point of 63% at 200 °C. In addition, $PhCF_3$ favored the formation of *N*-oxide **2.36a** (Entry

4). Therefore, only protic solvents were used to continue optimization. *n*-BuOH was used due to its high boiling point, and ability to support a higher temperature than *i*-PrOH. In Entry 6, water was added as a better proton source to test solvent effects on the cyclization (Scheme 1.11). However, this did not change the result.

To test the substitution effect on this rearrangement reaction, oxime **2.21b** was synthesized by using the reaction conditions developed for substrate **2.21a** (Table 2.10). It was found that the methyl substituent on the alkene decreased the efficiency of the rearrangement. Although the protic solvent *n*-BuOH led to a better result than aprotic $PhCF_3$, the conversion in *n*-BuOH at 200 °C (Entry 2) was low (30%). In addition, when temperature was increased to 210 °C (Entry 3), the NMR yield of isoquinoline **2.24b** decreased to 20%.

Table2.10. Substitution effect on rearrangement of alkenyl oxime **2.21**

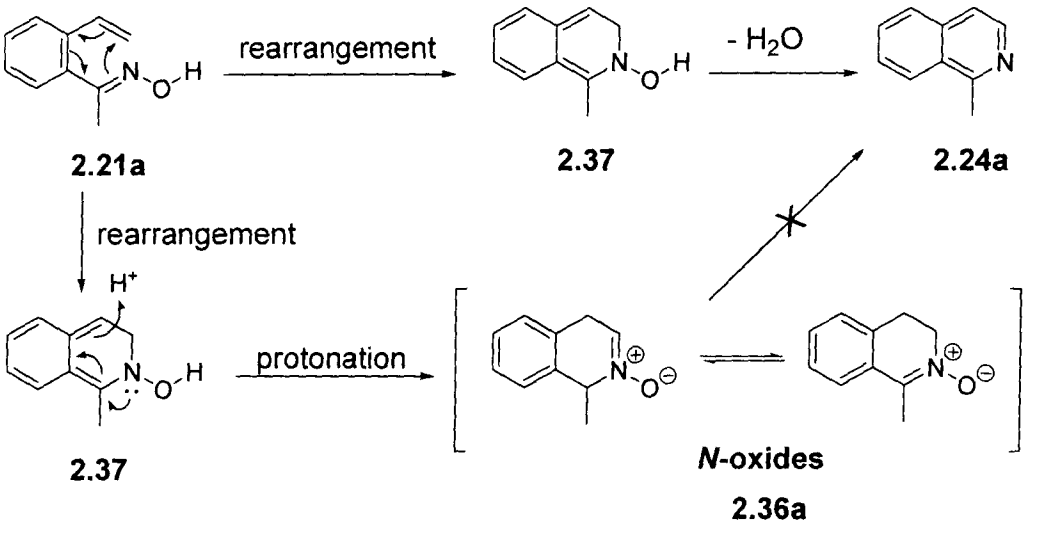


2.21b **2.24b** ***N*-oxides 2.36b**

Entry	Temp (°C)	Solvent	**2.24b**[a]	**2.36b**
1	200	$PhCF_3$	23%	32%
2	200	*n*-BuOH	30%	27%
3	210	*n*-BuOH	20%	42%

[a] Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard

According to the results, it was realized that this intramolecular rearrangement to afford isoquinolines competed with nitrone formation at high temperature (Scheme 2.10). The rearrangement resulted in hydroxylamine **2.39**, which was converted to isoquinoline **2.26a** by loss of water. On the other hand, 6-endo-trig cyclization via hydroamination of the same oxime **2.21a** at high temperature resulted in *N*-oxides **2.36a**. They had the right oxidation state to afford isoquinolines. Therefore they were isolated and heated at high temperature for 10 hours, in hope of conversion from the *N*-oxides to the corresponding isoquinoline **2.24a**.



Scheme **2.9**. Two competitive reactivities of oxime **2.21a**

Unfortunately, the conversion of isoquinoline **2.24a** was low, likely because the rearrangement reaction required to overcome the stability of the nitrone intermediates formed. This required a high temperature to overcome the energy barrier. From Table 2.10, in *i*-PrOH at 180 °C (Entry 3), the amounts of isoquinoline **2.24a** and *N*-oxides **2.36a** were almost the same. When the temperature increased to 200 °C (Entry 5), formation of isoquinoline was favored. This suggests that the rearrangement can compete with the nitrone formation at this temperature.

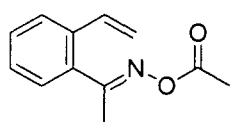
After realizing the competition issue of this methodology, several modifications were envisioned to avoid the problem and obtain higher yields of the isoquinoline. From Scheme 2.9, a proton-transfer step was required in the side reaction (from **2.21a** to **2.36a**). In addition, it seemed that the proton of -C=N-OH could be involved in side-reactions.

Therefore, we decided to use protected hydroxylamines to repeat the reaction and favor aromatization. The protecting groups used were –OAc, -OPiv, and –Boc groups (eq. 2.3, eq. 2.4, and eq. 2.5).

Our modification started with –OAc protected oxime **2.30**. The rearrangement was attempted at different temperatures and with some additives (Table 2.11). As predicted, the protected oxime resulted in less *N*-oxide by-products. However, the temperature of 180 °C only resulted in 36% conversion of the isoquinoline (Entry 2). It was lower than 40% for unprotected oxime under the same conditions (Table 2.9, Entry 3). There was the possible decomposition of oxime **2.30** in an acidic media, perhaps caused by formation of acetic acid as the by-product. Based on this hypothesis, Et_3N (Entry 3) and DIPEA (Entry 4) were added to neutralize acetic acid. DIPEA was used as a more hindered base to avoid nucleophilic side-reactions. After the reactions, no positive changes were noticed. It was also hypothesized that the decomposition of oxime **2.30** may have a radical mechanism.[65] Therefore, BHT (Entry 5) was added as a radical inhibitor. Unfortunately, similar results of the reaction were obtained.

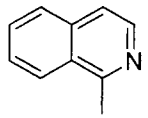
[65] House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863

Table 2.11. Rearrangement of acetyl-protected alkenyl oxime **2.30**



2.30

i-PrOH(0.1 M),
temperature
time(μW)



2.24a

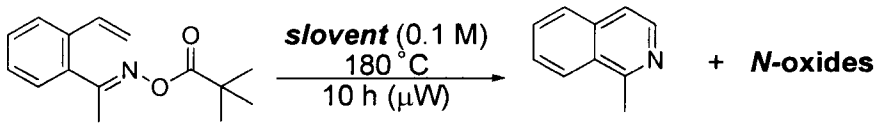
\+ ***N*-oxides**

Entry	Time (hours)	Temp (C°)	additive	% conversion [a]	***N*-oxides**
1	10	160	-----	32%	5%
2	10	180	-----	36%	4%
3	5	180	TEA	10%	-----
4	5	180	DIPEA	12%	-----
5	10	180	BHT	30%	-----

[a] Calculated from result of ^{1}H NMR spectra using 1,4-dimethoxylbenzene as internal standard

The –OPiv protected oxime **2.31** was used to replace –OAc protected oxime **2.30** since -Piv was a more hindered substituent (Table 2.12). This design was used to minimize the possible by-products.

Table2.12. Rearrangement of pivaloyl protected alkenyl oxime **2.31**



2.31 **2.24a**

Entry	solvent	% conversion [a]	***N*-oxides**
1	$PhCF_3$	23%	-----
2[b]	*i*-PrOH	22%	-----
3	*i*-PrOH	20%	-----

[a] Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard
[b] Et_3N was added

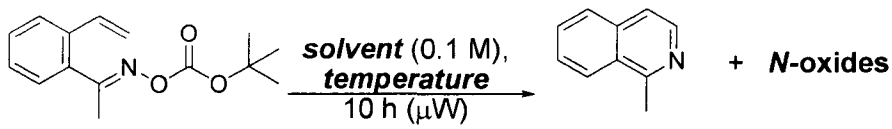
The best reaction conditions from the acetate protected oxime substrate were used to repeat the reaction (Entry 3). Unfortunately, the conversion was even lower (20%). $PhCF_3$ was attempted but showed a similar result (Entry 1). The addition of Et_3N did not improve the conversion (Entry 2), nor could starting material be recovered.

Since the side reactions may be caused by by-products in the system, we turned to –OBoc protected oxime **2.32** to continue the experiment. The reason for this modification was that all by-products of Boc deprotection are gas and as a result cannot affect the mixture. The results are listed in Table 2.13.

It was showed that using protic *i*-PrOH caused the formation of *N*-oxides. Consequently, non-protic $PhCF_3$ was attempted. At 180 °C, it

afforded 50% conversion of isoquinoline **2.24a** (Entry 3), which was 10% higher than that of active oxime **2.21a** (40%, Table 2.9, Entry 3). When the reaction was repeated at 200 °C in $PhCF_3$, 70% conversion was obtained (Entry 4). Another aprotic solvent, PhCl, provided only 50% even at 220 °C.

Table2.13. Rearrangement of -Boc protected alkenyl oxime **2.32**



2.32 **2.24a**

Entry	Temp (°C)	solvent	% conversion [a]	*N*-oxides
1	160	*i*-PrOH	33%	26%
2	180	*i*-PrOH	15%	40%
3	180	$PhCF_3$	50%	-----
4	200	$PhCF_3$	70%	-----
5	220	PhCl	50%	-----

[a] Calculated from result of ^1H NMR spectra using 1,4-dimethoxylbenzene as internal standard

Therefore, the optimized reaction conditions for –Boc protected oxime **2.32** to afford isoquinoline **2.24a** were microwave irradiation in $PhCF_3$, at 220° C for 10 hours. The best conversion by ^1H NMR calculation was 70%.

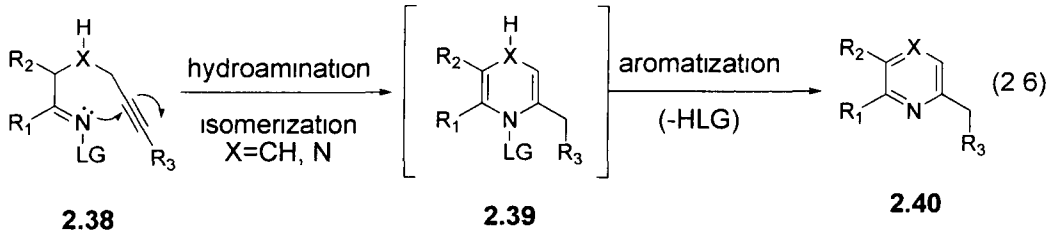
2.3.4 Conclusion

The intermolecular Cope-type hydroamination approach to isoquinoline had a short synthetic route. However, it also presented some challenges. First of all, the syntheses of oximes had only modest yields while a lot of *N*-oxides existed as impurities. Secondly, the following rearrangement to afford corresponding isoquinolines competed with an intramolecular hydroamination to afford stable *N*-oxides. Consequently, reaction conditions such as reaction time, temperature and type of solvent had to be optimized. Finally, the rearrangement of oximes to isoquinolines required a very high temperature obtain acceptable yields.

To conclude, the best reaction conditions for oxime **2.21a** formation from substrate **2.20a** with aqueous NH_2OH were *i*-PrOH [1M], at 130 °C for 5 hours in the microwave (Table 2.8, Entry 1). It afforded 50% conversion of **2.21a**. The best reaction conditions for the [3,3] rearrangement reaction of substrate **2.21a** to isoquinoline **2.24a** were *n*-BuOH [0.1M], at 200 °C for 10 hours (Table 2.9, Entry 5). This was done in the microwave and afforded 63% conversion. To the same rearrangement the best reaction conditions for Boc-protected oxime **2.32** were $PhCF_3$ [0.1M], at 200 °C for 10 hours in the microwave, which afforded 70% conversion.

2.4 6-endo-dig cyclization approach to pyridines and pyrimidines

Of interest to our research group was the application of the Cope-type hydroamination and related methodologies towards the synthesis of aromatic nitrogen heterocycles. From the work performed by Mr. Toni Rizk and Mr. Eric Bilodeau, it was determined that pyridines and pyrazines can be accessed through an acid-catalyzed 6-exo-dig cyclization of oximes. Two general reaction conditions were developed for this conversion, and both gave the desired products in moderate to excellent yields.[66]



This sequence involved a 6-exo-dig cyclization (hydroamination) of oxime **2.38**, followed by isomerization to afford intermediate **2.39**, which then formed the final unsaturated product **2.40** by aromatization. This sequence builds on the well known tendency intermediates such as **2.39** to aromatize,[67] and allows the formation of substituted pyridines and pyrazines from simple acyclic precursors.

This finding triggered our interest in a possible 6-endo-dig cyclization

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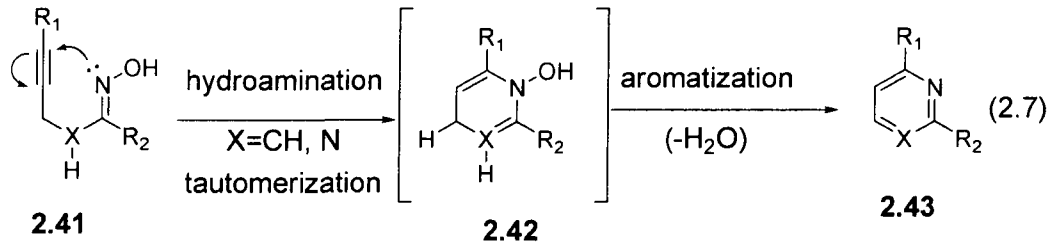
[66] Rizk,T Bilodeau, F , Beauchemin, A M *Angew Chem Int Ed* **2009** accepted

[67] J A Joule K Mills, In *Heterocyclic Chemistry*, 4th ed , Blackwell Oxford, UK, 2000

approach to aromatic heterocycles. According to Baldwin's rules, both 6-exo-dig and 6-endo-dig cyclizations are favored. The focus of our research therefore turned to oxime design and optimization of the reaction conditions towards unsaturated heterocycles.

2.4.1 Proposed approach

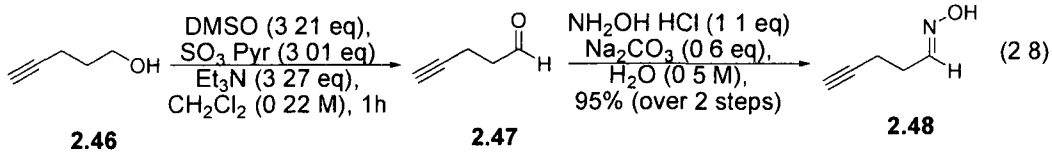


(2.7)

Thus, the proposed approach involved the parent 6-endo-dig variant of the sequence described above. The key difference is that following cyclization (hydroamination) of precursor **2.41**, a tautomerization event directly provides the intermediate **2.42** required for subsequent aromatization. Other advantages are that different products can be formed, and that the synthesis of some precursors could be simplified. On the other hand, different conditions may be needed for cyclization. Efforts to develop this sequence for the synthesis of pyridines and pyrimidines are presented below.

2.4.2 Synthesis of substrates

To probe the viability of the sequence, two oximes were synthesized: one possessing a terminal alkyne (**2.48**) and one possessing an internal alkyne (**2.51**).

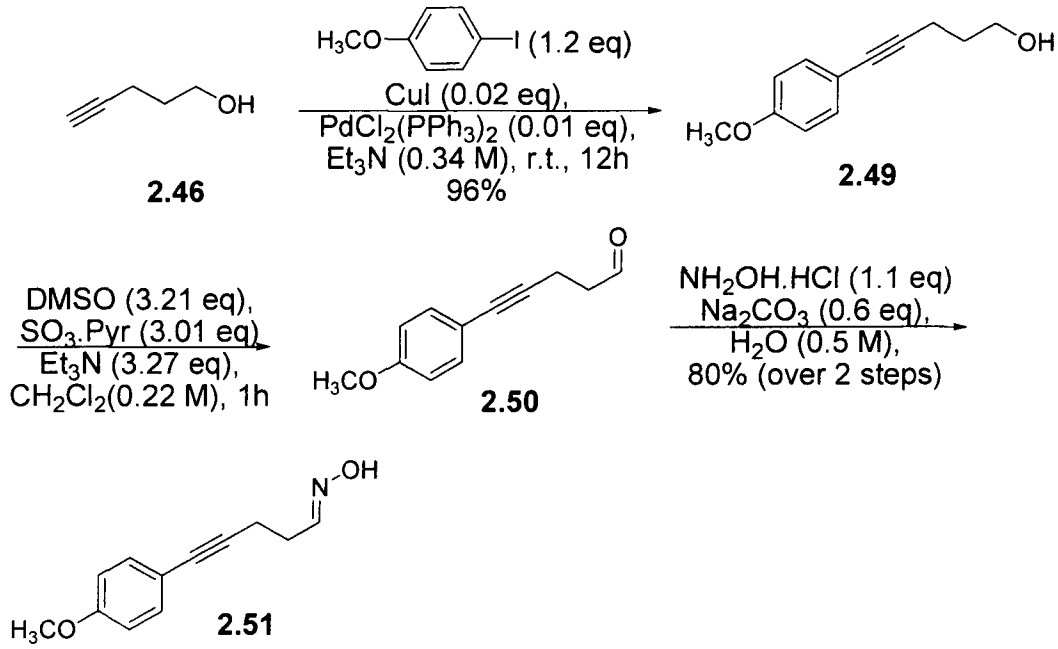


2.46 **2.47** **2.48** (2 8)

The research on the desired sequence started with the substrate **2.48** (eq. 2.8). To access it, alcohol **2.46** was oxidized to the corresponding aldehyde **2.47** by Parikh-Doering oxidation.[68] Compound **2.47** was then converted to oxime **2.48** by a condensation reaction between the aldehyde and aqueous hydroxylamine.[69]

[68] C. Mukai, I. Nomura and S. Kitagaki, *J. Org. Chem.*, 2003, **68**, 1376

[69] Bialecki, J. B., Ruzicka, J., Attygalle, and A. B. *J. Label Compd. Radiopharm* **2007**, *50*, 711

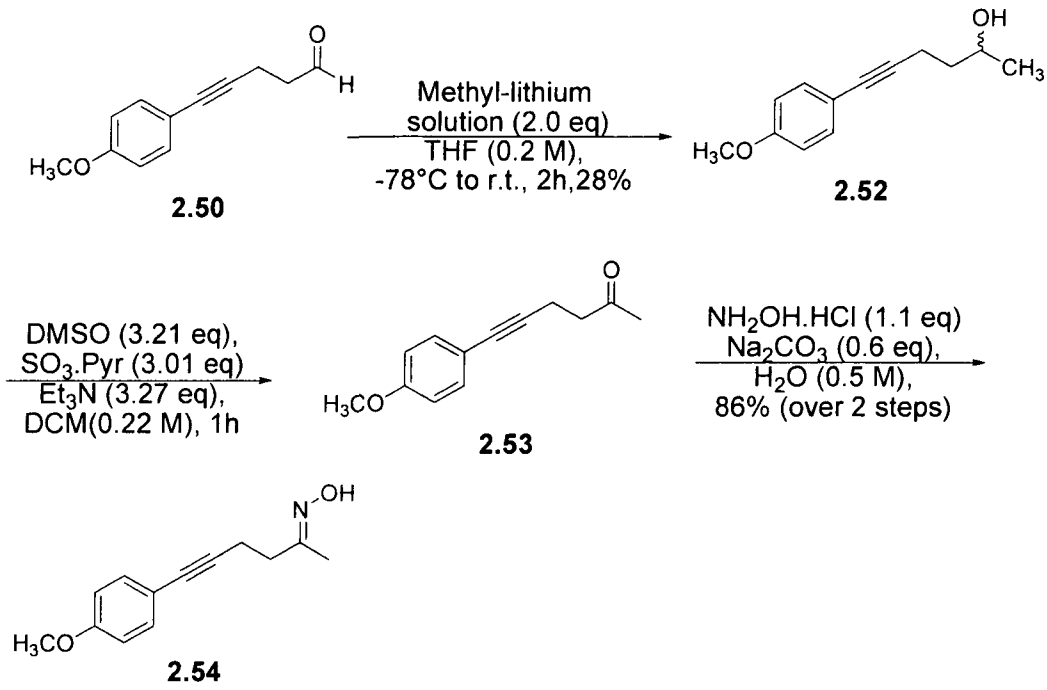


Scheme **2.9**. Synthetic routes of oxime **2.51**

In order to introduce substitution on the alkyne of substrate **2.46**, a Sonogashira cross-coupling was carried out (Scheme 2.9).[58] From alcohol **2.49**, oxime **2.50** was formed through the same route as that discussed previously for compound **2.48** (eq. 2.8)

In addition, ketoxime **2.54** was also synthesized to try the same 6-endo-trig cyclization because it should be more stable than corresponding aldehyde oxime **2.51**. A methyl-lithium addition to aldehyde **2.50** was used to introduce the methyl group into the structure of compound **2.52**.[70] After another two steps, ketoxime **2.54** was formed in 86% (Scheme 2.10).

[70] Fitt, J. J.; Gschwend, H. E. *J. Org. Chem.* **1984**, *49*, 209-210



Scheme **2.10**. Synthetic routes of oxime **2.54**

In order to access ketoximes with different substitution at the terminal position, a new synthetic route was designed (Scheme 2.11).[71] The advantage of the synthetic route for ketoximes was that the substitution on the alkyne (introduced by a Sonogashira cross-coupling reaction) was performed as the last step. Consequently, ketoximes with different substituents on the alkyne can be obtained using the same synthetic route.

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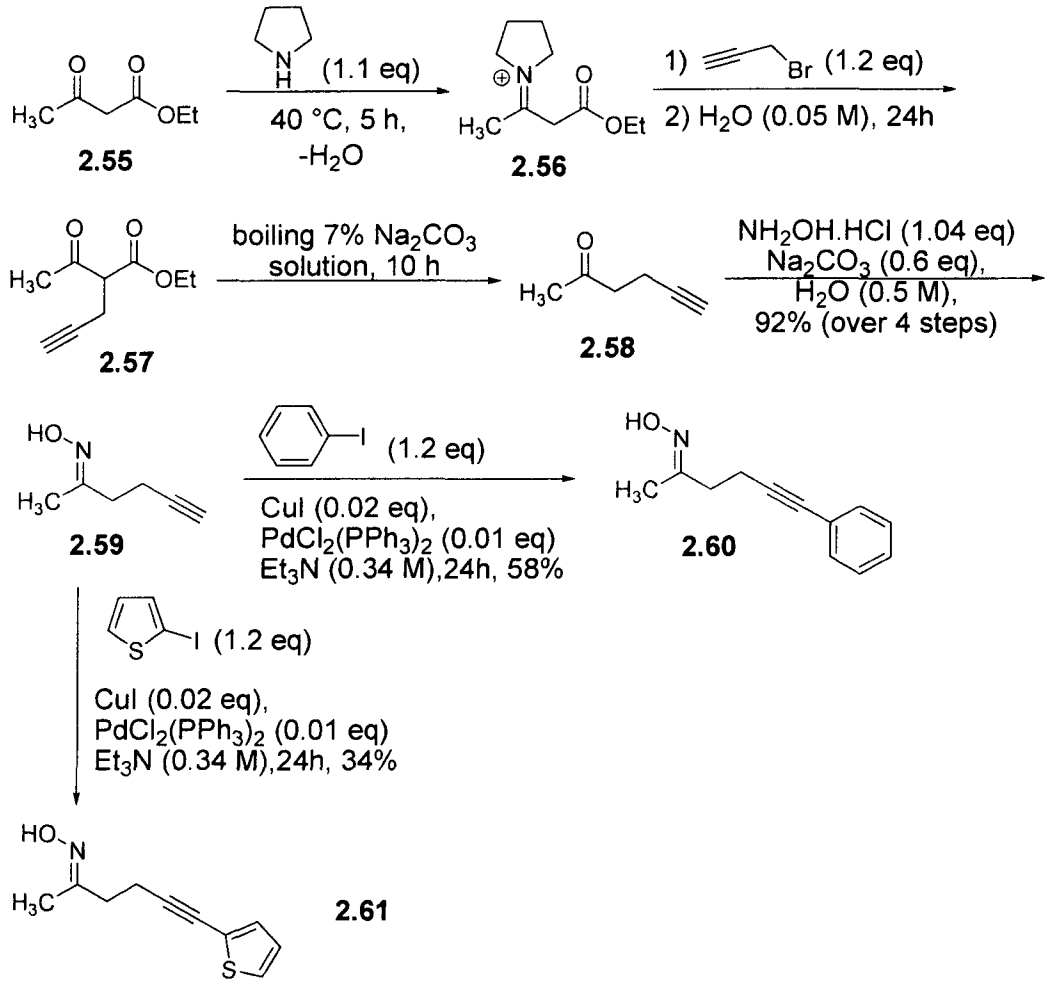
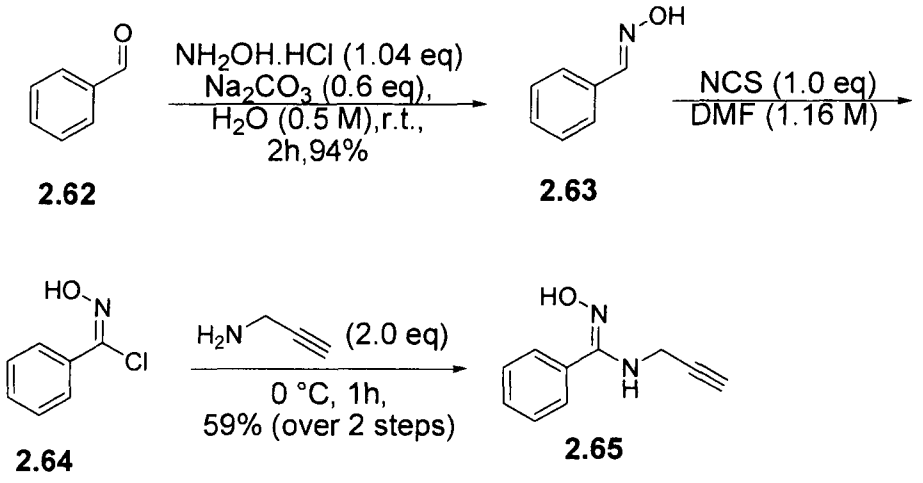
[71] Heather, J. B.; Sood, R.; Price, P.; Peruzzotti, G.-P.; Lee, S. S.; Lee, L. F.; Sih, C. J. *Tetrahedron*, **1973**, *25*, 2313.



Scheme **2.11**. General synthetic routes of ketoximes



Scheme **2.12**. Synthetic routes to potential pyrimidine precursor **2.65**

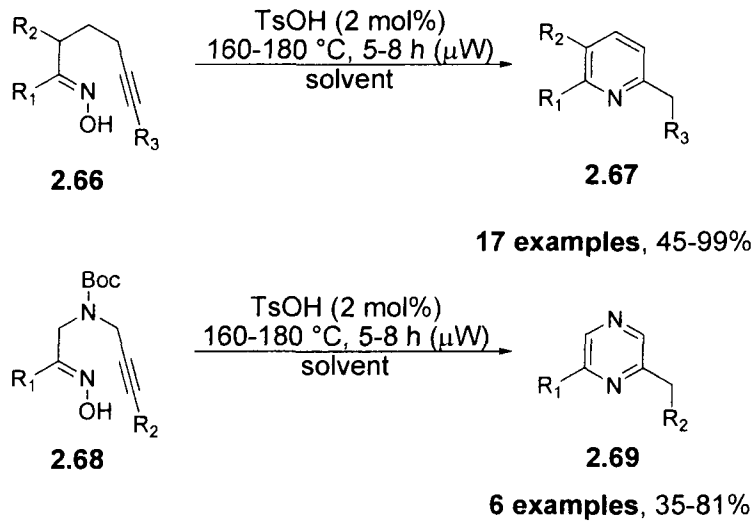
To test if the proposed sequence could be applied towards the synthesis of pyrimidines, substrate **2.65** was accessed through a short synthetic route. Benzaldehyde **2.62** was first condensed with aqueous hydroxylamine to afford oxime **2.63**. Then *N*-chlorosuccinimide was then used to convert the oxime to chloride **2.64**,[72] making it a good electrophile. Finally, prop-2-yn-1-amine was used as the nucleophile to afford substrate **2.65**.[72]

2.4.3 Results and discussion

In a previous publication outlining the synthesis of pyridines and pyrazines,[66] two conditions were developed by Mr. Toni Rizk and Mr. Eric Bilodeau to provide optimum results for the 6-exo-dig cyclization.

[72] Kost, D.; Raban, M. *J Am Chem Soc* **2003**, *125*, 15762.

Therefore, our first trials for the 6-endo-dig cyclization were performed under the same conditions (condition A and B in Scheme 2.13).

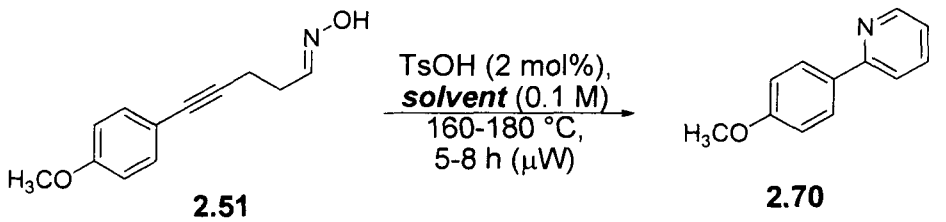


Condition A: in *i*-PrOH (0.1 M) at 160 °C for 5 h

Condition B: in PhCl (0.1 M) at 180 °C for 8 h

Scheme **2.13**. Conditions developed for the related 6-exo-dig hydroamination based sequence towards pyridines and pyrazines

Table **2.14**. Formation of pyridine **2.70** from oxime precusor **2.51**



2.51 **2.70**

Entry	Time (hours)	Temp (°C)	Solvent	**2.70** [a]	**2.51**
1	5	160	*i*-PrOH	10%	37%
2	8	180	PhCl	7%	40%
3	5	160	THF	4%	80%
4	5	160	$CDCl_3$	10%	70%
5	5	200	PhCl	10%	-----

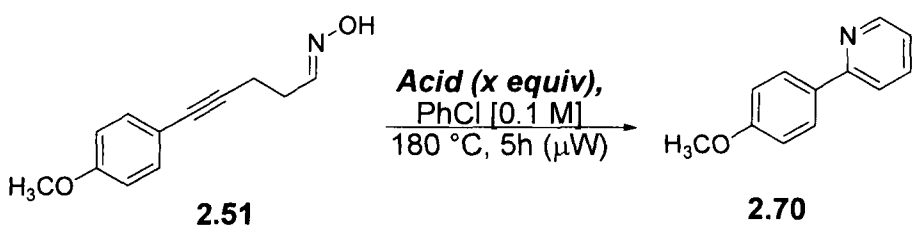
[a] Calculated from result of ^1H NMR spectra using mesitylene as internal standard

Table 2.14 shows the various trials performed using oxime **2.51** to give pyridine **2.70**. Entries 1 and 2 show the results of using the same conditions shown in Scheme 2.13 (conditions A and B). Both afforded only small amounts of the desired pyridine while a lot of starting material **2.51** still remained in the mixture. Therefore, the reaction parameters were modified in an attempt to improve the conversion. In the next trials, (entries 3 and 4) a different solvent was used, and unfortunately the results were worse. When heating the reaction at a higher temperature (entry 5), the conversion was still low. Based on these results, we suspected that either TsOH was not the appropriate catalyst or the

reaction time was not long enough.

Thus, the effect of the catalyst on the reaction was tested (Table 2.15). In order to do so, different types of acid were used and the results obtained were compared. Three different types of acid were tested while keeping all of the other conditions the same (180° C for 5 hours). It was found that use of trifluoromethanesulfonic acid (CF_3SO_3H) gave the best result.

Table **2.15**. Choice of acid in conversion of **2.51** to **2.70**



2.51 **2.70**

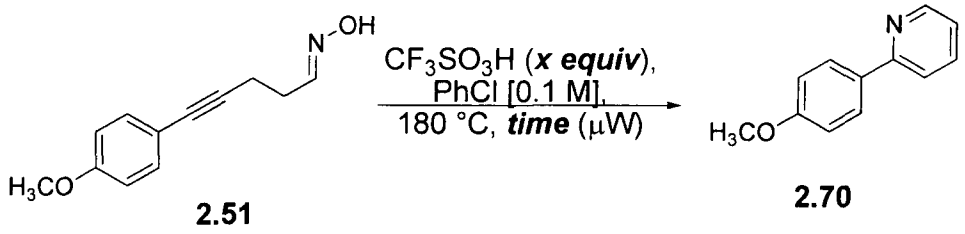
Entry	Acid (equiv)	% Conversion [a]
1	CSA (0.02)	6%
2	CF_3SO_3H (0.07)	30%
3	$(CF_3SO_3)_2NH$ (0.15)	25%

[a] Calculated from result of ^1H NMR spectra using mesitylene as internal standard

The third parameter of the reaction, the reaction time was also optimized. As shown in Table 2.14, times of 5 to 8 hours resulted in low conversions. Due to these results, it was questioned whether the

6-endo-dig reactions were perhaps more difficult than 6-exo-dig type, and thus required longer reaction times. There was also an issue with regards to the quantity of acid required. Consequently, the effect of changing the quantity of acid required was also investigated simultaneously (Table 2.16).

Table **2.16**. Optimization of parameters in conversion of **2.51** to **2.70**



2.51 **2.70**

Entry	Acid (eq)	Time (hours)	% Conversion [a]
1	0.15	8	22%
2	0.03	12	8%
3	0.13	16	42%
4	0.5	16	36%
5	0.13	24	30%

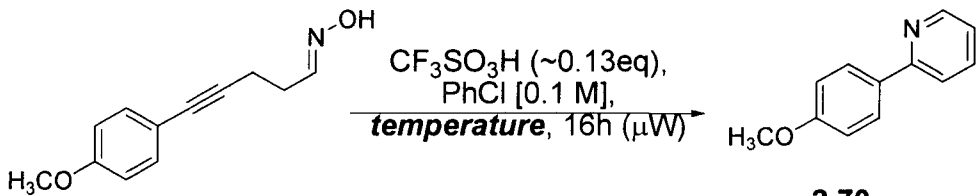
[a] Calculated from result of ^{1}H NMR spectra using mesitylene as internal standard

It was determined that the reaction had the best result when ~0.13 equivalents of TfOH was used and when the reaction was heated for 16 hours (Entry 3). If the reaction time was too long (Entry 5), the formed pyridine would decompose. If too much acid was used (Entry 4), it

resulted in a lower conversion, which may be caused by reduced thermal stability of oximes under a strong acid conditions.

Based on these findings, the final parameter that required optimization was temperature (Table 2.17). It was believed that a temperature higher than 180 °C may give a higher conversion. The reaction was repeated at both lower (Entry 1) and higher temperatures (Entry 3). It was determined that a higher temperature (200 °C) resulted in a similar conversion, and no significant change was observed. Therefore, the optimum conditions for this 6-endo-dig cyclization were using chlorobenzene (0.1M), heating at 180 °C for 16 hours with CF_3SO_3H (0.09-0.13 eq) as the catalyst.

Table **2.17**. Optimization of temperature in conversion of **2.51** to **2.70**



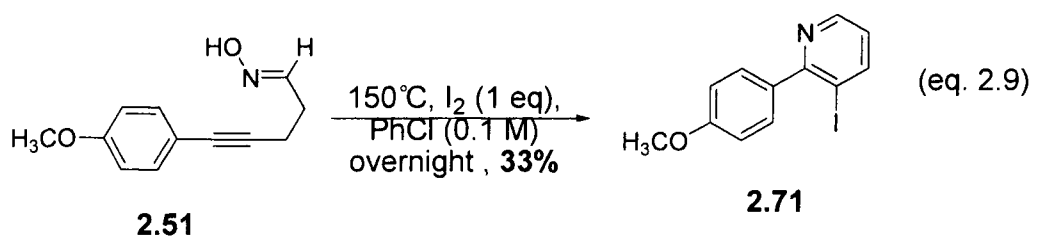
2.51 **2.70**

Entry	acid (eq)	Temp (°C)	% conversion [a]
1	0.1	160	22%
2	0.13	180	42%
3	0.09	200	43%

[a] Calculated from result of ^1H NMR spectra using mesitylene as internal standard

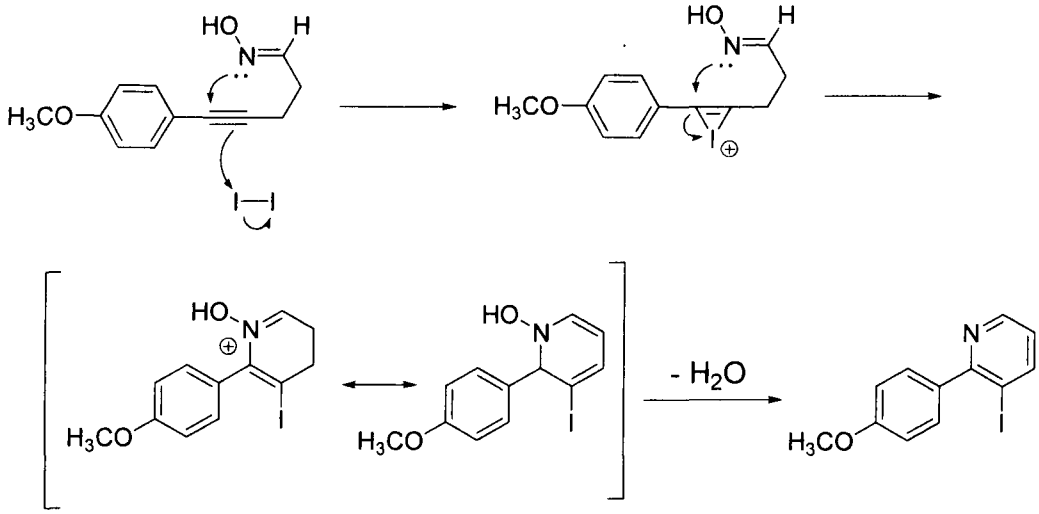
In addition to the optimization of reaction conditions, iodine was also used to activate the alkyne in order to promote the 6-endo-dig cyclization and make it more facile. The idea for this came from the fact that iodine is a good electrophile,[73] while the alkyne is a good nucleophile. The reaction of I_2 with the alkyne can be done at room temperature. Once the alkyne is activated by I_2 (Scheme 2.14), the cyclization of the oxime **2.51** should be possible at a lower temperature. This will hopefully limit the amount of oxime that decomposes, while increasing the conversion of the overall reaction.

[73] Huang, Q., Hunter, J. A., Larock, R. C. *Org Lett* **2001**, *3*, 2973



2.51 2.71 (eq. 2.9)

Proposed mechanism:



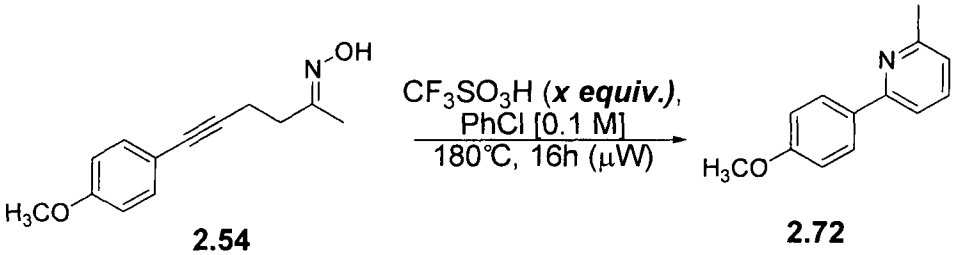
Scheme **2.14**. Iodine activation of alkynyl oxime **2.51** to afford pyridine

It was found that the reaction between the alkyne and iodine would run to completion at room temperature. The temperature was increased to 150 °C to complete aromatization. The crude mixture was heated overnight. However, upon observing the ^{1}H NMR spectrum, it was noted that the conversion to the desired isoquinoline was only 33%. In addition, a lot of insoluble black solid was present in the flask, which could be attributed to the decomposition of the intermediate.

The decomposition of starting material was observed frequently during the 6-endo-dig reactions. On the other hand, 6-exo-dig reactions

seldom had the same problem. This can be explained by the fact that 6-endo-dig reactions are slower than 6-exo-dig reactions. It was realized that the thermal stability of the oxime **2.51** was an issue and this has an effect on the rate of the reaction. Consequently, we used a more stable ketoxime to replace these less stable aldehyde oximes.

Table **2.18**. 6-endo-dig cyclization of ketoxime **2.54**



2.54 **2.72**

Entry	acid (eq)	% conversion [a]
1	0.05	43%
2	0.18	62%
3	0.3	60%

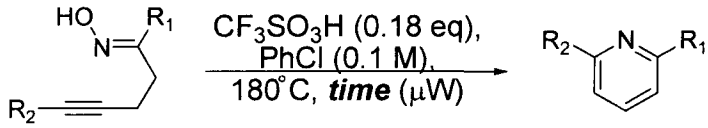
[a] Calculated from result of ^1H NMR spectra using mesitylene as internal standard

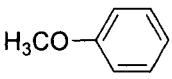
Ketoxime **2.54** was reacted using the optimized conditions (Table 2.18). The equivalence of CF_3SO_3H was the only parameter that was tested again in order to obtain the best result. It was found that 0.18 equivalents of the acid resulted in highest conversion, 62% (Entry 2). Due to time constraints, this optimization was not finished.

In order to probe the mechanism and scope of this 6-endo-dig

cyclization, different ketoximes were used under similar reaction conditions (Table 2.19). Different substituents on the alkyne were introduced in an attempt to gain information regarding the electronic effects of the reaction. Oximes **2.48** and **2.59** were also used under the same conditions to allow direct comparison.

Table **2.19**. Mechanism study of 6-endo-dig cyclization



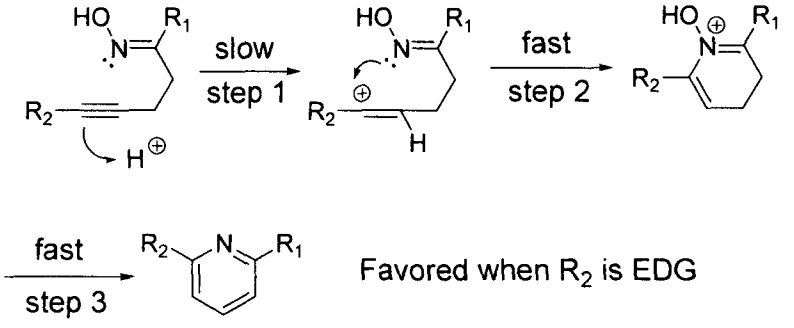
Entry	substrate	time (hours)	% conversion [a]
1	**2.48** R_1,R_2=H	16	decomposed
2	**2.59** R_1=Me,R_2=H	16	decomposed
3	**2.60** R_1=Me,R_2=Ph	16	11%
4	**2.61** R_1=Me, R_2= 	10	60%
5	**2.54** R_1=Me, R_2= 	16	62%

[a] Calculated from result of ^{1}H NMR spectra using mesitylene as internal standard

From Table 2.19 it can be seen that oximes with terminal alkyne functionality (substrate **2.48** and **2.59**) decomposed under the reaction

conditions. When the substitution on the alkyne was a phenyl group (Entry 3), the conversion when using the best reaction conditions was only 11% (Table 2.18, Entry 2). When there was a thiophene ring on the alkyne (Entry 4), the conversion increased to 60% in only 10 hours.

From these results, we can deduce that this 6-endo-dig reaction is very sensitive to substitution. Without any substituent on alkyne, the cyclization did not work. For those oximes with internal alkyne functionality, substituents having more electron donating effects favored the cyclization. For example, the phenyl group (substrate **2.60**) on the alkyne resulted in only 11% conversion (Entry 3). On the other hand, the 4-methoxyl phenyl substrate **2.54**, which is more electron rich, resulted in a 62% conversion (Entry 5). In addition, the thiophene ring, which is again an electron-rich substituent, resulted in a 60% conversion in a shorter amount of time (Entry 4). Given more reaction time, the conversion would be expected to be higher.

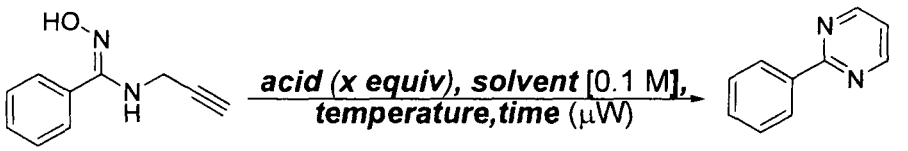


Scheme **2.15**. Electronic effect of 6-endo-dig cyclization

The proposed mechanism is shown in Scheme 2.15. The first step is likely slow and therefore the rate determining, and leads to the formation of carbocation, which was stabilized by R_2 as EDG. When R_2 is a hydrogen, the formed terminal carbocation would not stable and the aldoxime would decompose at high temperatures. In addition, R_1 contributed the substrate's thermal stability. This can explain the higher conversion of ketone oxime **2.54** over the corresponding aldehyde oxime **2.51**.

The 6-endo-dig cyclization methodology was also tested to synthesize pyrimidines. In work performed by Mr. Toni Rizk and Mr. Eric Bilodeau, the two basic reaction conditions for pyridines and pyrazines were optimized (see section 2.4.3). Due to time limits, investigations on this methodology for the synthesis of pyrimidines could not be completed. Nevertheless, basic conditions along with slight modifications were tried, as showed in Table 2.20.

Table **2.20**. 6-endo-dig cyclization towards pyrimidines



2.65 **2.73**

Entry	Time (h)	Temp (°C)	Solvent	Acid (eq)	Conversion [a]
1	8	160	PhCl	TsOH (0.02)	3%
2	8	160	PhCl	TFA (5)	3%
3	8	120	*i*-PrOH	TsOH (0.02)	no reaction [b]
4	8	120	*i*-PrOH	TFA (0.02)	no reaction [b]

[a] Calculated from result of ^{1}H NMR spectra using mesitylene as internal standard
[b] Substrate was decomposed by nucleophilic attack of *i*-PrOH

The results of the cyclization using the two basic reaction conditions described above were modest. When chlorobenzene was used as solvent, only trace amounts of pyrimidine **2.73** were detected by ^{1}H NMR spectrum. On the other hand, when *i*-PrOH was used as the solvent, the ^{1}H NMR spectrum showed strong peaks consistent with an *i*-PrOH substituted side product. Degradation of the starting material was also observed. The failure of this reaction may have been caused by the acid catalyst as it was realized that substrate **2.65** was acid-sensitive. More tests on the parameters of the reaction such as temperature, reaction time, and the amount and type of acid are still underway, and results from the

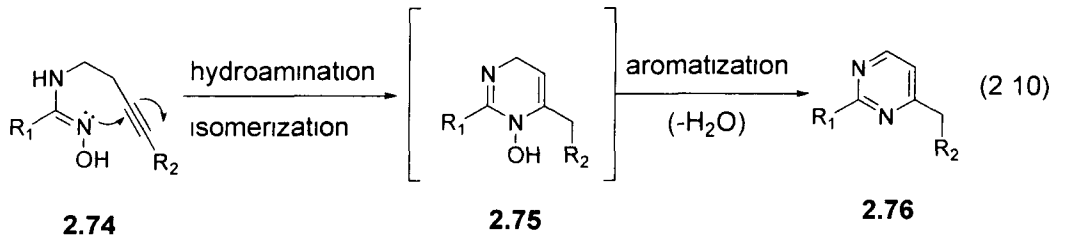
previous section suggest that alkyne substitution is required to achieve the desired sequence.

2.4.4 Conclusion

The reaction conditions determined for the 6-endo-dig cyclization were harsher than those of the 6-exo-dig cyclization. Increased reaction time was needed, and the type of acid as well as the amount of acid is of great importance. The conversions of oximes to corresponding pyridines or pyrimidines were moderate and substrates tended to decompose under harsh reactions. Modifications are needed to make the reaction conditions much milder.

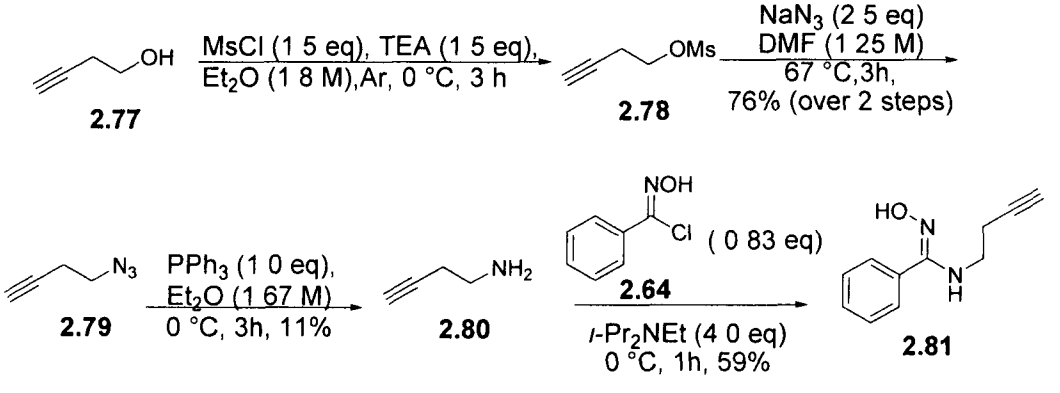
2.5 6-exo-dig cyclization approach to pyrimidines

It was found by Mr. Toni Rizk and Mr. Eric Bilodeau that 6-exo-dig cyclization methodology can afford pyridines and pyrazines.[66] Therefore, we wondered whether other unsaturated heterocycles, such as pyrimidines, could also be obtained.



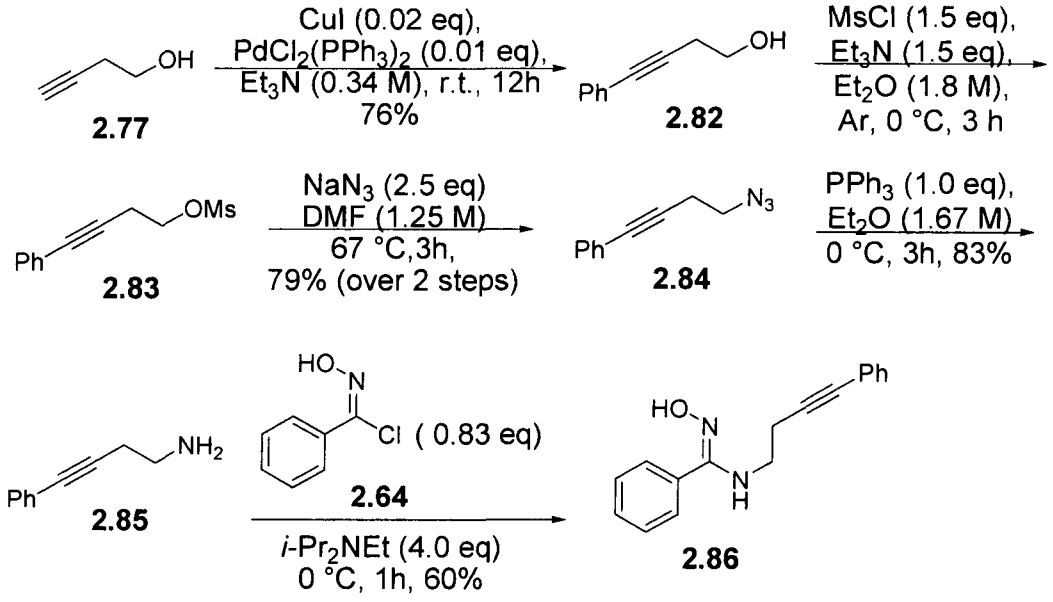
2.5.1 Synthesis of substrates

Three substrates (**2.81**, **2.86** and **2.91**) were synthesized to investigate the desired 6-exo-dig cyclization sequence. Investigation of this reactivity began with substrate **2.81**, prepared from but-3-yn-1-ol **2.77** in four steps (Scheme 2.16). Mesylation of the hydroxyl group provided intermediate substrate **2.78**, which was converted to azide **2.79**. This was converted to amine **2.80** via a Staudinger reaction, and then reacted with substrate **2.64**,[73] which was obtained through Scheme 2.12 to afford substrate **2.81**.



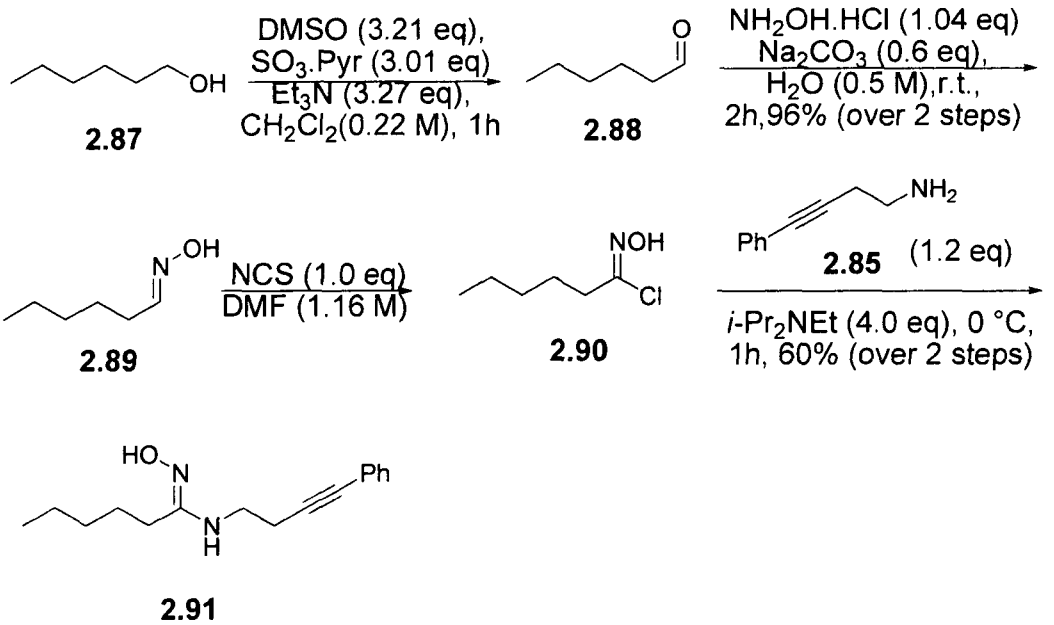
Scheme **2.16** Sythetic route of substrate **2.81**

However, the volatility of compounds **2.79** and **2.80** resulted in very low yields after the three steps, greatly reducing the yield of substrate **2.81**. After realizing this problem, substrate **2.80** was substituted for compound **2.85** in a similar sequence (Scheme 2.17). Sonagashira coupling between alcohol **2.77** and iodobenzene introduced a phenyl group, making the substrates much less volatile. Thus, substrate **2.86** was synthesized more efficiently.



Scheme **2.17.** Sythetic route of substrate **2.86**

Substrate **2.91** (Scheme 2.18) was also synthesized to test the same cyclization. This design depended on the fact that an alkyl group as R_1 substituent favoured the 6-exo-dig cyclization.[66]



2.87 **2.88** **2.89** **2.90** **2.85**

2.91

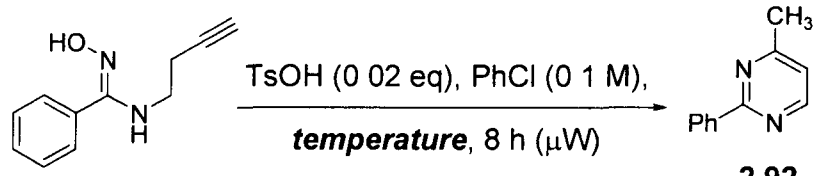
Scheme **2.18.** Sythetic route of substrate **2.91**

Alcohol **2.87** was oxidized to corresponding aldehyde **2.88** by Parikh-Doering oxidation. Aldehyde **2.88** was converted to corresponding oxime **2.89**, and then treated with *N*-chlorosuccinimide to afford compound **2.90**. This underwent nucleophilic attack by amine **2.85** to provide substrate **2.91**.

2.5.2 Results and discussion

Substrate **2.81** was first used to test the 6-exo-dig cyclization using two optimized reaction conditions found by Mr. Toni Rizk and Mr. Eric Bilodeau (Table 2.21). Because of the limited amount of substrate **2.81**, only these two reactions were examined.

Table **2.21** 6-exo-dig cyclization of substrate **2.81**



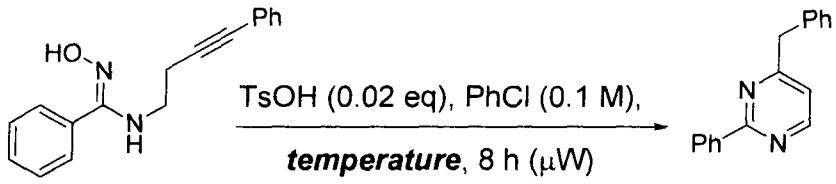
2.81 **2.92**

Entry	Temp (°C)	% conversion [a]
1	160	20%
2	180	15%

[a] Calculated from result of ^{1}H NMR spectra using mesitylene as internal standard

Based on the optimized conditions for 6-exo-dig cyclization (Scheme 2.14), the reactions were tried at 160 and 180 °C. Both of them resulted in modest conversion and suggested that more optimization was needed.

Table **2.22**. Temperature optimization of cyclization of substrate **2.86**



2.86 **2.93**

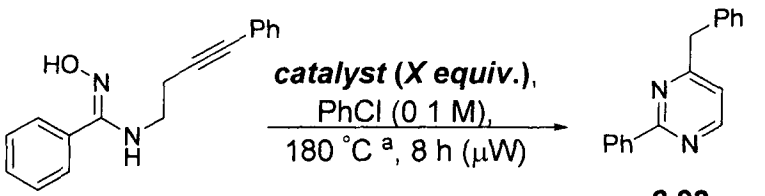
Entry	Temp (°C)	% conversion [a]
1	130	2%
2	140	4%
3	150	5%
4	180	10%

[a] Calculated from result of ^{1}H NMR spectra using mesitylene as internal standard

Further experiments were done on substrate **2.86**. From Table 2.22, the highest conversion of substrate **2.86** to **2.93** was obtained at 180 °C (10%). In all the four entries, only trace amount of starting material **2.86** was detected. Therefore, more optimization on the type and quantity of acid was needed.

Table 2.24 showed the result of acid catalyst optimization. We wondered if the cyclization proceeded without any catalyst. Entry 1 showed only 5% conversion under such conditions. Then the amount of TsOH as catalyst was also investigated. Again, the conversions were very low. When 5 eq TFA was used as catalyst (Entry 2), conversion was only 10% by ^{1}H NMR.

Table **2.23** Catalyst optimization of cyclization of substrate **2.86**



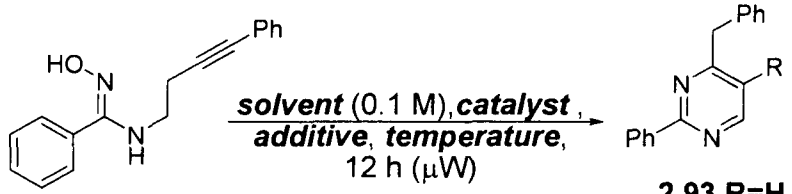
2.86 **2.93**

Entry	Catalyst (eq)	% conversion [b]
1	----	5%
2	TFA (5)	10%
3	TsOH (0 02)	10%
4	TsOH (0 05)	4%
5	TsOH (0 2)	6%

[a] Entry 3, 4 were tested at 160 °C
[b] Calculated from result of ^{1}H NMR spectra using mesitylene as internal standard

In addition, other methods were used to test the cyclization (Table 2.24). For example, the reaction was repeated at 50 °C with 5 equiv. TFA in $CDCl_3$. After stirring for 12 hours, no reaction occurred. Activation of the triple bond with iodine gave 5% conversion after stirring in C_6D_6 for 12 hours.

Table **2.24**. Other methods for cyclization of substrate **2.86**



2.86

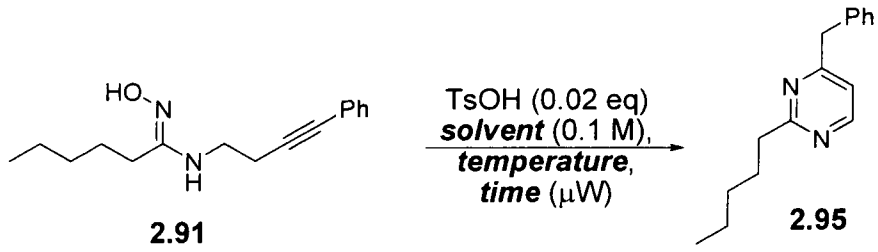
2.93 R=H
2.94 R=I

Entry	Solvent	Catalyst	Additive	Temp (°C)	% conversion [a]
1	$CDCl_3$	TFA (5 eq)	-----	50	**2.93** -----
2	C_6D_6	-----	I_2 (1 eq)	reflux	**2.94** 5%

[a] Calculated from result of ^1H NMR spectra using mesitylene as internal standard

Finally, substrate **2.91** was used to test the 6-exo-dig cyclization briefly. Only the two optimized reaction conditions were examined. However, the results were not good either.

Table **2.25**. Cyclization of substrate **2.91**



2.91 **2.95**

Entry	Solvent	Time (hours)	Temp (°C)	% conversion [a]	**2.91**
1	PhCl	8	180	5%	45%
2	*i*-PrOH	5	160	3%[b]	-----

[a] Calculated from result of ^{1}H NMR spectra using mesitylene as internal standard
[b] A large amount of by-product from *i*-PrOH substitution existed

2.5.3 Conclusion

The synthesis of pyrimidines was investigated using the optimized reaction conditions developed for pyridines and pyrazines. However, it was found that pyrimidines required harsher conditions to cyclize, resulting in issues associated with thermal and acid sensitivity of substrates. More optimization tests are required to uncover the best conditions for pyrimidine synthesis through the 6-exo-dig cyclization method.

2.6 Conclusion

Four different hydroamination based sequences to aromatic nitrogen heterocycles were tested, with the objective of providing reliable, novel routes to isoquinolines, pyridines and pyrimidines. While the desired reactivity was observed for each of the desired routes, issues such as inefficient substrate preparation, complex reactivity, substrate sensitivity and/or limited substrate scope remain associated with the sequences explored. However, increased understanding was gained and in particular the results presented in section 2.4 provide an excellent basis for further studies on 6-endo-dig approaches to pyridines and pyrimidines. A new graduate student, Mr. K. Matthew Whitmore recently started investigating metal-catalyzed variants, as the results presented herein suggest that the acid-catalyzed cyclization step is not reliable for 6-endo-dig cyclizations.

3

Experimental

3.1 General Information

All the precursors of Cope-type hydroamination tests were synthesized in oven-dried or flame-dried glass round-bottomed flasks. Cope-type hydroamination tests were performed in sealed tubes by oil bath or in sealed vials under microwave irradiation. The reactions were monitored by aluminum thin layer chromatographic sheets, and UV light or an aqueous $KMnO_4$ solution was used to show existence of substrates on TLC. Purification of reaction products was done by flash column chromatography.

Spectra. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a Bruker Avance300 (300 MHz) or Avance400 (400 MHz) spectrometer at ambient temperature, and peak positions are reported in parts per million (ppm) using solvent as the internal standard ($CDCl_3$ at 7.26 ppm and C_6D_6 at 7.15 ppm). Spectra which were recorded with off-resonance decoupling have peaks reported as singlets (s), doublets (d), triplets (t), quartets (q), broad (br) and multiplet (m). Carbon nuclear

magnetic resonance (^{13}C NMR) spectra were recorded with a Bruker Avance300 (75 MHz) or Avance400 (100 MHz) spectrometer using solvent as the internal standard ($CDCl_3$ at 77.0 ppm). Infrared (IR) spectra were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). High-resolution mass spectra were recorded on an Kratos-Concept IIH instrument.

3.2 Procedures and characterizations for section 2.2

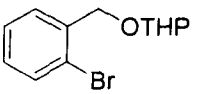
General procedure for the intramolecular hydroamination of substrate 2.14 (Tables 2.1, 2.2, 2.3 and 2.4). An oven-dried sealed tube was filled in TFA salt of *N*-hydroxy(2-(prop-2-ynyl)phenyl)methanamine **2.14** (80 mg, 0.29 mmol), Et_3N (0.15 mL, 0.93 mmol), and *i*-PrOH as solvent. A magnetic stir bar was charged too. Then the sealed tube was closed and heated to reach the required temperature. When the test was finished, the sealed tube was cooled to room temperature. The solvent was evaporated and the crude mixture was dissolved into deuterated solvent and analyzed by ^1H NMR.

General procedure for the intramolecular hydroamination of oxime 2.19 (Table 2.5).[74] An oven-dried round bottom flask was filled in a solution of oxime **2.19** (100 mg, 0.629 mmol), $NaBH_3CN$ (48.8 mg, 0.78

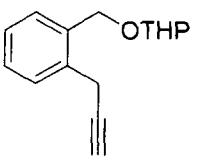
[74] Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc* **1971**, *93*, 2897.

mmol) in 0.629 mL of methanol. A trace of Methyl orange was added. A solution of 2 N HCl /methanol (1:1) was then added dropwise with stirring to maintain the yellow color. After ca. 30 min, the color changed very slowly. The solution was stirred for 3 hr, and the methanol was removed at reduced pressure. The residue was dissolved in 2 mL of water, raised to pH >9 with 6 N KOH, saturated with sodium chloride, and extracted with four 5-mL portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The crude product **2.4** (a brown solid) was diluted by $CDCl_3$ (13 mL) in a new RBF, and was heated to 55-60 °C. After the test was finished, the RBF was cooled to room temperature. The crude mixture was directly analyzed by ^1H NMR.

General procedure for the intramolecular hydroamination of substrate 2.16 (Table 2.6, Entry 1, R=Me). An oven-dried round bottom flask was filled in TFA salt **2.16** (161 mg, 0.56 mmol), Et_3N (0.27 mL, 1.67 mmol), and 11 mL $CDCl_3$ (0.05 M) as solvent. A magnetic stir bar was charged too. Then the RBF was under argon, and the mixture was stirred at room temperature. The solution was transferred by syringe into a NMR tube. ^1H NMR was used to check the composition of the mixture until no more **2.16** existed. Then the RBF was heated to 50 °C for 12 hours and was cooled to room temperature. The crude mixture was directly analyzed by ^1H NMR.



2-(2-Bromobenzyloxy)-tetrahydro-2H-pyran (2.10). (Scheme 2.2) The title compound was prepared according to the procedure by Grieco et al.[75] A solution of alcohol **2.9** (5 g, 26 mmol) and dihydropyran (3.3 g, 39 mmol) in dry methylene chloride (182 mL) containing PPTS (0.65 g, 2.6 mmol) is stirred for 4 h at room temperature. Then the solution is diluted with ether and washed once with half-saturated brine to remove the catalyst. After evaporation of the solvent, gives an essentially quantitative yield of THP ether (6.18 g, 86%). TLC R_f 0.3 (10% EtOAc/Hexanes); spectroscopic data corresponds with literature.[76]



2-(2-(Prop-2-ynyl)benzyloxy)-tetrahydro-2H-pyran (2.11) (Scheme 2.2). The title compound was prepared according to the procedure by Miyashita et al.[77] A solution of the tetrapyranyl ether of *o*-bromobenzyl alcohol (5.0 g, 18.4 mmol) in THF (15 mL) was added dropwise over 5 min to magnesium turnings (0.49 g, 20.2 mmol) in THF (5 mL) in a 40-mL round-bottom flask equipped with a reflux condenser and under

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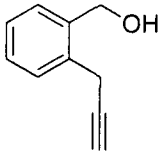
[75] Miyashita, M., Yoshikoshi, A., Grieco, P. *J. Org. Chem.* **1977**, *42*, 3772

[76] Lovey, R. G., Elliott, A. J., Kaminski, J. J., Loebenberg, D., Parmegiani, R. M., Rane, D. F., Girijavallabhan, V. M., Pike, R. L., Guzik, H., Antonacci, B., Tomaine, F. Y. *J. Med. Chem.* **1992**, *35*, 4221

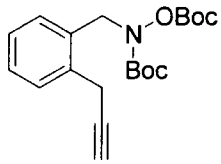
[77] Semmelhack, M. F., Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034

argon. The reaction mixture was briefly heated at reflux (5 min) and then cooled to 25 °C. Propargyl bromide (2.35 mL, 21 mmol) was then added dropwise over 5 min. After 6 h at 25 °C, the resulting suspension was diluted with ether, washed sequentially with 5% aqueous sodium bicarbonate (2x) and water (lx), dried over potassium carbonate, and rotary evaporated. The residual dark red oil (3.97 g) showed a single UV-active spot by TLC (hexanes: ether = 5:1), expected to be the tetrahydropyranyl ether of 2-(2-propyn-1-yl)benzyl alcohol. TLC R_f 0.3 (10% EtOAc/Hexanes); ^{1}H NMR (300 MHz, C_6D_6) δ ppm 7.56-7.04 (m, 4H), 4.76 (d, J = 12.23 Hz, 1H), 4.58 (t, J = 3.33, 3.33 Hz, 1H), 4.39 (d, J = 12.22 Hz, 1H), 3.75 (m, 1H), 3.53 (d, J = 2.69 Hz, 2H), 3.37 (m, 1H), 1.91 (t, J = 2.75, 2.75 Hz, 1H), 1.67 (m, 1H), 1.49 (m, 2H), 1.32 (m, 1H), 1.26 (m, 2H); ^{13}C NMR (300 MHz, C_6D_6) δ ppm 136.34 (C), 135.26 (C), 129.35 (CH), 128.90 (CH), 128.55 (CH), 127.04 (CH), 97.61 (CH), 81.80 (C), 71.29 (CH), 66.93 (CH_2), 61.64 (CH_2), 30.79 (CH_2), 25.82 (CH_2), 22.21 (CH_2), 19.44 (CH_2); IR (CH_2Cl_2/NaCl, cm^{-1}) 3294, 3066, 2941, 2871, 1605, 1454, 1441, 1077, 753; HRMS (EI) m/z $C_{15}H_{18}O_2$ (M^+) calcd 230.13, Not found with EI.



(2-(Prop-2-ynyl)phenyl)methanol (**2.12**). The title compound was

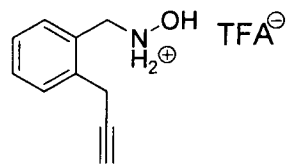
prepared according to the procedure by Miyashita et al.[75] A solution of THP ether **2.11** (0.2 g, 0.84 mmol) and PPTS (21.1 mg, 0.084 mmol) in ethanol (6.72 mL) was stirred at 55 °C (bath temperature) for 3.5 h. The solvent was evaporated in vacuo, and the residue was purified by flash column chromatography on silica gel with 20% EtOAc/hexanes to afford pure alcohol **2.12** (112 mg, 88%). TLC R_f 0.4 (20% EtOAc/Hexanes); spectroscopic data corresponds with literature.[78]



***N,O*-bis(*tert*-Butoxycarbonyl)-(2-(prop-2-ynyl)phenyl)methanamine (2.13) (Scheme 2.2).** The title compound was prepared according to the procedure by Tao et al.[55] To a cold solution of *N,O-di-t*-butoxycarbonyl-hydroxylamine (2.78 g, 11.9 mmol), pent-4-yn-1-ol **2.12** (1.10 mL, 11.9 mmol), and triphenylphosphine (9.37 g, 35.7 mmol, 3 equiv.) in anhydrous THF (119 mL), diisopropyl azodicarboxylate (6.93 mL, 35 mmol, 3 equiv.) was added. The mixture was then stirred at 0°C for 4 hours. After removal of the solvent in vacuo, the residue was purified by flash column chromatography on silica gel with 10% EtOAc/hexanes to yield 3.15 g (88%) of the product as a colourless oil. TLC R_f 0.3 (10% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.67-3.61 (m, 2H), 2.23 (dt, J = 7.02, 7.01, 2.46 Hz, 2H),

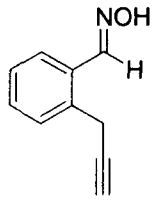
[79] Seo, S. Y.; Yu, X.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263.

1.91 (t, J = 2.58, 2.58 Hz, 1H), 1.76 (tt, J = 6.94, 6.94, 6.91, 6.91 Hz, 2H), 1.47 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 154.67 (C), 152.14 (C), 84.66 (C), 83.14 (CH), 82.20 (C), 68.80 (CH), 48.91 (CH_2), 27.99 (CH_3), 27.49 (CH_3), 26.01 (CH_2), 15.63 (CH_2); IR (CH_2Cl_2/NaCl, cm^{-1}) 3294, 3066, 2980, 2934, 1794, 1716, 1699, 1695, 1495, 840; HRMS (EI) m/z $C_{20}H_{27}NO_5$ (M^+) calcd 361.19. Not found with EI.



TFA salt of *N*-hydroxy(2-(prop-2-ynyl)phenyl)methanamine (2.14) (**Scheme 2.2**). The title compound was prepared according to the procedure by Hansen.[79] The substrate **2.13** (2.23 g, 6.86 mmol) was dissolved in CH_2Cl_2 (54 mL, 0.5 M) and treated with 13.5 mL (3 equiv.) of trifluoroacetic acid (TFA). The mixture was stirred at room temperature for 3 hours. Then mixture was partitioned between CH_2Cl_2 (50 mL) and aqueous $NaHCO_3$ (30 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford 1.75 g **2.14** (100%) as brown product. The characterization was impossible because of its instability. Therefore, the substrate **2.14** was freshly prepared for intramolecular Cope-type hydroamination tests.

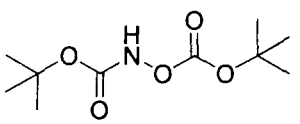
[79] Hansen, M.; Riggs, J. R. *Tetrahedron*, **1998**, *39*, *2705*



2-(Prop-2-ynyl)benzal-oxime (2.19) (Scheme 2.4). The title compound was prepared according to the procedure by Bialecki et al.[80] Aldehyde **2.14** was synthesized by Parikh-Doering oxidation.[81] To a solution of alcohol **2.12** (2.11 g, 14.4 mmol), DMSO (3.28 mL, 46.2 mmol), and Et_3N (6.57 mL, 47.1 mmol) in dry CH_2Cl_2 (65 mL) was added SO_3.pyridine (6.77 g, 43.3 mmol) at 0 °C. After the mixture was stirred for 6 h at room temperature, the reaction was quenched by addition of saturated aqueous NH_4Cl, and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness to afford the crude aldehyde **2.14**. A solution of sodium carbonate (0.28 g, 2.6 mmol in 5mL of H_2O) was slowly added to a solution of hydroxylamine hydrochloride (0.34 g, 4.8 mmol in 5 mL of H_2O) and benzaldehyde (0.50 g, 4.6 mmol), and the mixture was stirred at RT for 2 h. The reaction mixture was extracted with Et_2O (15 mL); the Et_2O layer was separated, dried over Na_2SO_4 and evaporated to give the crude product. After flash column chromatography on silica gel with 30% EtOAc/hexanes, 774 mg of **2.19** (25%, over 2 steps) was obtained as white powder. TLC R_f 0.3 (30% EtOAc/hexanes); ^1H NMR (300 MHz,

[80] Bialecki, J. B., Ruzicka, J., Attygalle, and A. B. *J. Label Compd. Radiopharm.* **2007**, *50*, 711.
[81] Nomura, M. J., Kitagaki, S. *J. Org. Chem.*, **2003**, *68*, 1376.

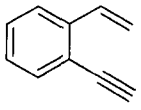
$CDCl_3$) δ ppm 8.44 (s, 1H), 7.65-7.29 (m, 4H), 3.75 (d, J = 2.66, 2H), 2.23 (t, J = 2.73, 2.73Hz, 1H), 1.57 (br, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 149.39 (CH), 134.76 (C), 130.01 (CH), 129.79 (C), 129.36 (CH), 128.06 (CH), 127.28 (CH), 81.31 (C), 71.39 (CH), 23.27 (CH_2); IR (CH_2Cl_2/NaCl, cm^{-1}) 3305, 2976, 2950, 1786, 1713; HRMS (EI) m/z $C_{10}H_9NO$ (M^+) calcd 159.07, found 159.10.



***N,O*-bis(*tert*-Butoxycarbonyl)hydroxylamine (2.17) (eq. 2.2).** The title compound was prepared according to the procedure by Tao et al.[55] To a cold solution of hydroxylamine hydrochloride (2.0g, 28.78 mmol) in THF:water (1:1, 120 mL) containing triethylamine (8.0mL, 57.56 mmol), di-tert-butyl-dicarbonate (12.57g, 57.56 mmol, 2.0 equiv.) was added. The mixture was warmed to room temperature and stirred for 8 hours. The THF was removed in vacuo, the residue extracted with methylene chloride (3x 20 mL), and the combined extracts were dried over sodium sulfate. After filtration, the CH_2Cl_2 was removed, and the residue was purified by flash column chromatography on silica gel with 2% EtOAc/hexanes to yield 4.0g (60%) of the product as a white solid. TLC R_f 0.3 (10% EtOAc/Hexanes); spectroscopic data corresponds with literature.[55]

3.3 Procedures and characterizations for section 2.3

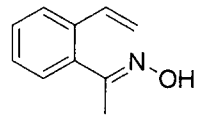
General procedure for rearrangement of oximes towards isoquninolines (Tables 2.9-2.13). A small vial of microwave was filled in oxime, solvent (molarity relative to the oxime), and a magnetic stir bar. Then the vial was closed and heated by microwave irradiation to reach the required temperature. When the test was finished, the vial was cooled to room temperature. The solvent was evaporated and the crude mixture was dissolved into deuterated solvent and analyzed by ^{1}H NMR.



1-Ethynyl-2-vinylbenzene (2.20a) (Scheme 2.6). The title compound was prepared according to the procedure by Beaulieu et al.[82] In a flame-dried round bottom flask (RBF, 500 mL), dissolve phosphonium salt ($MePPh_3I$, 12.4 g, 30.4 mmol) and potassium *t*-butoxide (3.4 g, 30.4 mmol) in 152 mL of THF. The mixture was stirred in ice bath for 30 minutes, and then it was warmed to room temperature. It was a yellow solution. In a second flamme-dried RBF (50 mL), dissolve 2-ethynylbenzaldehyde (1.95 g, 15.2 mmol) in 30.4 mL THF. After 30 minutes, 2-ethynylbenzaldehyde was transferred through niddle and

[82] Beaulieu, P. L.; Duceppe, J.-S.; Johnson, C. *J Org. Chem.* **1991**, *56*, 4197.

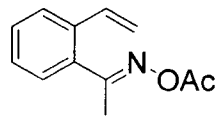
dropwised into the first RBF. The color of mixture turned brown. At the room temperature, the mixture was stirred for another 30 minutes, and then it was qunched by HCl solution (10%). After extraction in ether for 3 times, the organic phase was dried by Na_2SO_4, and ether was evaporated. The mixture was dark brown. It was separated by column chromatography in hexanes (100%) to yield 1.37 g (70%) of pure product as colorless oil. TLC R_f 0.5 (10% ether/Hexanes); spectroscopic data corresponds with literature.[83]



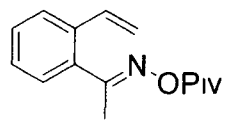
1-(2-Vinylphenyl)ethanone oxime (2.21a) (Scheme 2.6). The title compound was prepared according to the procedure by Moran et al.[42] In a small seal tube, 985 mg (6.12 mmol) of 1-ethynyl-2-vinylbenzene was dissolved into 7.7 mL of *i*-PrOH (1M). Then 0.58 mL of NH_2OH (50 wt% H_2O, 2.5 equiv.) was added. The air in the system was removed by Argon. Then the tube was sealed and was microwaved at 130 °C for 5 hours. 20% ether in hexanes was used to column separate the crude mixture. The pure product was white solid (617 mg, 50%). TLC R_f 0.4 (30% EtOAc/Hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.61-7.34 (m, 4H), 6.90 (dd, J = 17.57, 10.98 Hz, 1H), 5.72 (dd, J = 17.48, 1.09 Hz, 1H),

[83] Shen, H. C.; Pal, S.; Lian, J. J.; Liu, R. S. *J. Am. Chem. Soc.* **2003**, *125*, 15762.

5.32 (dd, J = 11.00, 1.12 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 158.22 (C), 136.72 (C), 136.48 (C), 135.44 (CH), 129.21 (CH), 128.83 (CH), 128.12 (CH), 126.57 (CH), 116.24 (CH_2), 16.66(CH_3); Spectroscopic data corresponds with literature.[84]



2-Vinylbenzaldehyde-*O*-acetyloxime (2.30) (eq. 2.3). The title compound was prepared according to the procedure by Alonso et al.[85] The oxime (5 mmol) was dissolved in 5 mL of pyridine. 1.3 equivalents of acetyl chloride were dropped, and the mixture was stirred for 2 h at room temperature. 50 mL of diethyl ether was then added and the resulting solution was washed with HCl (10% aq solution) and $NaHCO_3$ (5% aq solution). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The resulting acyloxime was purified by column chromatography (silica gel, hexane/EtOAc, 4:1). TLC R_f 0.3 (30% ether/Hexanes); spectroscopic data corresponds with literature.[86]

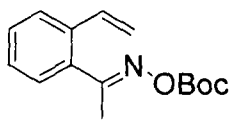


2-Vinylbenzaldehyde-*O*-pivyloxime (2.31) (eq. 2.4). The title compound was prepared according to the procedure by Marmer et al.[63] A round

[84] Okamoto, T., Kobayashi, K., Oka, S., Tanimoto, S. *J Org Chem* **1987**, *52*, 5089

[85] Alonso, R. Campos, P. J., Garcia, B., Rodriguez, M. A. *Org Lett* **2006**, *8*, 3521

bottom flask (25 mL) was flame-dried and protected by Argon. 150 mg (1 equiv.) of oxime **2.21a** was dissolved into 7.5 mL dry ether. Then 224mg of trimethyl acetyl chloride (2 equiv.) was added into the flask. Finally, 0.2 equiv. DMAP was added, and the mixture was stirred at room temperature for 4 hours. The crude mixture was purified by column (5% ether in toluene). The pure product was white powder (yield :81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.58-7.29 (m, 4H), 6.89 (dd, J = 17.49, 10.97 Hz, 1H), 5.71 (dd, J = 17.42, 1.05 Hz, 1H), 5.35 (dd, J = 10.98, 1.02 Hz, 1H), 2.3(s,3H), 1.35(s,9H) ; ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 136.16 (C), 134.54 (CH), 129.69 (CH), 129.57 (C), 128.68(CH), 128.59(C), 127.65(CH), 126.41(C), 126.21(CH), 116.77(CH_2), 38.85(C), 27.34(CH_3), 18.49 (CH_3); IR (CH_2Cl_2/NaCl, cm^{-1}): 2975, 2870, 1755, 1479, 1309, 1265, 1124, 914, 874, 778; HRMS (EI): Exact mass calcd for $C_{15}H_{17}NO_2$ (M^+) 245.32. Not found with EI.

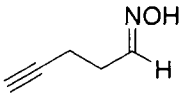


1-(2-vinylphenyl)ethanone-*O*-(*tert*-Butoxycarbonyl) oxime (2.32) (eq. 2.5). The title compound was prepared according to the procedure by Learmonth et al.[64] A round bottom flask (25 mL) was flammed and protected by argon. 100 mg (1 equiv.) of 2-vinyl phenyl-ethan-2-one oxime was dissolved into 5 mL dry ether. Then 271mg of *t*-Boc anhydride

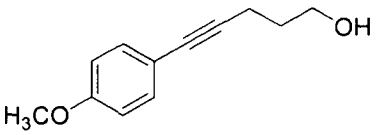
(2 equiv.) was added into the flask. Finally, 15 mg of DMAP (0.2 equiv.) was added, and the mixture was stirred at room temperature for overnight. The crude mixture was purified by column (20% ether in hexanes). The pure product was white powder (89%). TLC R_f 0.5 (30% Ether/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.56-7.30 (m, 4H), 6.86 (dd, J = 17.68, 11.02 Hz, 1H), 5.70 (dd, J = 17.43, 0.80 Hz, 1H), 5.33 (dd, J = 11.09, 0.80 Hz, 1H), 2.3(s,3H), 1.57(s,9H) ; 13C NMR (300 MHz, $CDCl_3$) δ ppm 164.31 (C), 151.96 (C), 136.16 (C), 134.66 (C), 129.48(CH), 128.68(CH), 127.61(CH), 126.19(CH), 116.76(CH_2), 83.52(C), 27.78(CH_3), 18.49(CH_3); IR (CH_2Cl_2/NaCl, cm^{-1}): 2983, 2921, 1769, 1363, 1237, 1149, 908, 831, 743; HRMS (EI): Exact mass calcd for $C_{15}H_{19}NO_3$ (M^+) 261.1. Not found with EI.

3.4 Procedures and characterizations for section 2.4

General procedure for 6-endo-dig cyclization of oximes (Tables 2.14-2.20). A small vial of microwave was filled in oxime, solvent (molarity relative to the oxime), acid catalysts, additives, and a magnetic stir bar. Then the vial was closed, purged with argon, and heated by microwave irradiation to reach the required temperature. When the test was finished, the vial was cooled to room temperature. The solvent was evaporated and the crude mixture was dissolved into deuterated solvent and analyzed by ^{1}H NMR.



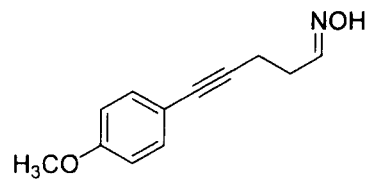
Pent-4-ynal oxime (2.48). (**eq. 2.7**) The title compound was prepared according to the general procedure of Parikh-Doering oxidation and oxime formation from commercial alcohol **2.46**. Spectroscopic data corresponds with literature.[86]



5-(4-Methoxyphenyl)pent-4-yn-1-ol (2.49) (Scheme 2.11) The title compound was prepared according to the general procedure of Sonogashira coupling from alcohol **2.46**.[58] To a 250 mL round bottom flask, CuI (68 mg, 2 mol %), $PdCl_2(PPh_3)_2$ (125 mg, 1 mol %) and 1-iodo-4-methoxybenzene (5.0 g, 1.2 mol%) was added to Et_3N (52 mL, 0.34M). The mixture was stirred for 5 min before alcohol **2.46** (1.5 g, 17.8 mmol) was added. The mixture was flushed with argon and stirred at room temperature for 12 h. EtOAc (100 mL) was added and the mixture was poured into sat. aq. $NaHCO_3$ (50 mL), and extracted with EtOAc. The combined organic extracts were washed with sat. aq. NH_4Cl (30 mL), H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), and filtered. The solvent was evaporated and the residue was purified on a silica gel column using

[86] Rossiter, J. T.; James, D. C. *J Chem Soc Perkin Trans 1*, **1990**, 1909.

30% EtOAc in hexanes to afford 3.25 g of **2.49** (96%) as a yellow oil isolated after column chromatography (40% EtOAc in hexanes).TLC R_f 0.3 (40% EtOAc/hexanes); spectroscopic data corresponds with literature.[87]



5-(4-Methoxyphenyl)pent-4-ynal-oxime (2.51) (Scheme 2.11) The title compound was prepared according to the general procedure of Parikh-Doering oxidation and oxime formation from substrate **2.49**. 1.60 g (80 %) of a 1.1:1 mixture of isomers as a brown solid was isolated after column chromatography (20% EtOAc in hexanes). TLC R_f 0.3 (20% EtOAc/hexanes); 1H NMR (300 MHz, $CDCl_3$) δ ppm 7.55 (t, J = 5.62, 5.62 Hz, 1H) (major), 7.33-7.29 (m, 4H) (major and minor), 7.55 (t, J = 4.95, 4.95 Hz, 1H) (minor), 6.82-6.76 (m, 4H) (major and minor), 3.77 (s, 3H) (major), 3.76 (s, 3H) (minor), 2.69-2.44 (m, 8H) (major and minor); 13C NMR (300 MHz, $CDCl_3$) δ ppm 159.22 (C), 159.20 (C), 151.10 (CH), 150.6 (CH), 132.93 (CH), 115.62 (C), 115.59(C), 113.84 (CH), 113.82 (CH), 86.53 (C), 86.34 (C), 81.44 (C), 81.36 (C), 55.24 (CH_3), 28.99 (CH_2), 24.44 (CH_2), 17.06 (CH_2), 16.35 (CH_2); IR (CH_2Cl_2/NaCl, cm^{-1}): 2845, 2034, 1568, 1289, 1243, 1172, 1089, 1023; HRMS (EI):

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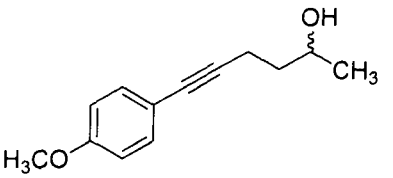
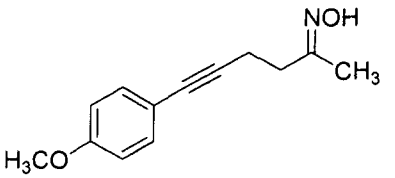
[87] Chong, J. M., Jackson, W. R., Van Der Schoot, M. *Tetrahedron*, **1994**, *50*, 2533

Exact mass calcd for $C_{12}H_{13}NO_2$ (M^+) 203.09. Found 203.1001.

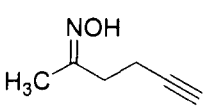


6-(4-Methoxyphenyl)hex-5-yn-2-ol (2.52)[70] **(Scheme 2.12)** At -78°C, methyl-lithium solution (1.6 M) (3.28 mL, 5.26 mmol) was dropwised to THF solution (13 mL) of substrate **2.50** (494 mg, 2.63 mmol). The mixture was stirred at -78°C for 2 hours and then was warmed to room temperature. NH_4Cl (sat.) solution (30 mL) was added to quench the reaction, and the mixture was extracted by EtOAc (60 mL). Wash the organic phase by $NaHCO_3$ (30 mL) and brine (30 mL). The solvent was dried by $MgSO_4$, and then it was evaporated. 150 mg (28 %) brown solid was Isolated after column chromatography (30% EtOAc in hexanes). TLC R_f 0.3 (30% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.29 (dd *J*=8.86, 1 Hz, 2H), 6.76 (dd *J*=8.86, 1 Hz, 2H), 3.96 (m, 1H), 3.74 (s, 3H), 2.22 (br, 1H), 2.52-2.43 (m, 2H), 1.69 (dd, *J* = 7.00, 6.85 Hz, 2H), 1.20 (d, *J* = 6.23 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 158.88 (C), 132.66 (CH), 115.69 (C), 113.64 (CH), 87.81 (C), 80.62 (C), 66.91 (CH_3), 55.02 (CH), 37.57 (CH_2), 23.16 (CH_3), 15.83 (CH_2); IR (CH_2Cl_2/NaCl, cm^{-1}): 3384, 2973, 2926, 2834, 1608, 1568, 1294, 1248, 1172, 1034, 831; HRMS (EI): Exact mass calcd for $C_{13}H16O_2$ (M^+) 204.12. Found 204.1153.



6-(4-Methoxyphenyl)hex-5-yn-2- one-oxime (2.54) (Scheme 2.12)

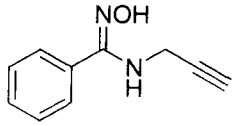
The title compound was prepared according to the general procedure of Parikh-Doering oxidation and oxime formation from substrate **2.52**. 520 mg (80 %) of a 2.6:1 mixture of isomers as a brown solid was Isolated after column chromatography (30% EtOAc in hexanes). TLC R_f 0.3 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.32 (m, 2H) (minor), 7.29 (m, 2H) (major),7.24 (br, 2H), 6.80 (m, 2H) (minor), 6.76 (m, 2H) (major), 3.77 (s, 3H) (minor), 3.65 (s, 3H) (major), 2.62 (m, 2H) (minor), 2.49 (m, 2H) (major), 1.98 (s, 3H) (minor), 1.94 (s, 3H) (major); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 159.08 (C), 157.59 (C), 156.98 (C), 132.85 (CH), 132.81 (CH), 115.74 (C), 113.78 (CH), 113.74 (CH), 87.14 (C), 86.87 (C), 81.16 (C), 80.92 (C), 55.16 (CH_3), 35.02 (CH_2), 28.23 (CH_2), 20.39 (CH_3), 16.80 (CH_2), 15.67 (CH_2), 13.74(CH_3); IR (CH_2Cl_2/NaCl, cm^{-1}): 2837, 2043, 1606, 1568, 1289, 1243, 1172, 1106, 1031, 830, 733; HRMS (EI): Exact mass calcd for $C_{13}H_{15}NO_2$ (M^+) 217.11. Found 217.1109.



Hex-5-yn-2-one oxime (2.59) (Scheme 2.13) The title compound was

prepared according to the procedure by Heather et al.[71] 13 g of substrate **2.55** (0.10 mmol) was mixed with pyrrolidine (8.0 g, 0.11 mmol), and heated at 40 °C for 5 hours. The formed water was removed by extraction, and the crude product **2.56** was sticky red oil. It was used directly for the next step. 3-bromoprop-1-yne (14.3 g, 0.121 mmol) was added slowly into ether solution (50 mL) of **2.56**. The mixture was stirred at room temperature overnight, and 50 mL distilled water was added to afford substrate **2.57**. The crude mixture was refluxed for 30 minutes, and then it was extracted by ether (3x 60 mL). The organic solvent was evaporated. The crude product was used for the next step. 150 mL of sodium carbonate solution (7%) was gently boiled, and the crude product **2.57** was added into the hot solution. The mixture was boiled and stirred for 10 hours. 120 mL of ether was used to extract crude **2.58**. The organic phase was dried by $MgSO_4$ and evaporated. The crude **2.58** was used to synthesize **2.59** according to the general procedure of oxime synthesis. 9.4 g (92 %) of a 1.2:1 mixture of isomers as a colorless oil was Isolated after column chromatography (20% EtOAc in hexanes). TLC R_f 0.4 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.33 (br, 2H) (major and minor), 2.56 (m, 2H) (major), 2.40 (m, 2H) (minor), 1.96 (t, J = 2.61, 2.61 Hz, 1H) (major), 1.95 (t, J = 2.61, 2.61 Hz, 1H) (minor), 1.92 (s, 3H) (major), 1.89 (s, 3H) (minor); 13C NMR (300 MHz, $CDCl_3$) δ ppm 157.15 (C), 156.60 (C), 83.19 (C), 82.95 (C), 69.13 (CH), 68.94

(CH), 34.65 (CH_2), 27.83 (CH_2), 20.30 (CH_3), 15.68 (CH_2), 14.67 (CH_2), 13.74(CH_3); IR (CH_2Cl_2/NaCl, cm^{-1}): 3293, 2920, 2120, 1664, 1370, 1051, 952, 648; HRMS (EI): Exact mass calcd for C_6H_9NO (M+) 111.07. Found 111.0672.



***(E)-N'*-Hydroxy-*N*-(prop-2-ynyl)benzamidine 2.65 (Scheme 2.14)** was prepared from oxime chloride **2.64** and commercial prop-2-yn-1-amine.[88]

Oxime chloride **2.64** was prepared according to the procedure by Johnson et al.[89] Benzaldoxime **2.63** (0.85g, 5.8 mmol) was freshly made from benzaldehyde according to general procedure of oxime formation, and was dissolved in *N,N*-dimethylformamide (5 mL) at room temperature and solid *N*-chlorosuccinimide (0.78g, 5.8 mmol) was slowly added with stirring in a 50-mL round bottom flask. The reaction was exothermic. Completion of the reaction was noted by the cessation of the exotherm to room temperature. The solution was poured into ice water (18 mL) and extracted with ether (2x 20 mL). The organic layer was dried over anhydrous $MgSO_4$ and the ether was removed using a rotary evaporator to give 0.93 g (86%) of benzohydroximoyl chloride **2.64** without further purification. Prop-2-yn-1-amine (0.41 g, 7.44 mmol) was

[88] Gennet, D., Zard, S.-Z., Zhang, H. *Chem Commun* **2003**, 1870
[89] Johnson, J. E., Nwoko, D., Hotema, M., Sanchez, N., Alderman, R. *J. Heterocyclic Chem.*, **1996**, *33*, 1583

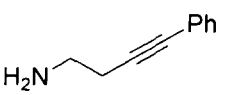
mixed with *N*-ethyl-*N*-isopropylpropan-2-amine (*i*-Pr_2NEt) (3 mL, 4 equiv.) in 50 mL dry ether in RBF. The solution was cooled by ice bath for 10 minutes, and then freshly prepared oximinoyl chloride **2.64** (0.50 g, 4.01 mmol) was slowly added to (**CAUTION:** oximinoyl chlorides can be harmful and allergenic) the solution. The mixture was stirred at 0 °C for 1 hour. Then it was diluted with water (30 mL) and extracted with ether (2x 50 mL). The organic layer was dried ($MgSO_4$) and concentrated. 380 mg (59%) of **2.65** as a yellow oil after column chromatography (50% ether/hexanes). TLC R_f 0.3 (50% ether/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ ppm 7.49-7.38 (m, 5H), 5.86 (br, 1H), 3.75 (d, J =2.43 Hz, 2H), 2.21 (t, J =2.43 Hz, 1H; ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 155.5 (C), 130.5 (C), 129.83 (CH), 128.52 (CH), 128.47(CH), 80.76(C), 71.71(CH), 33.35(CH_2); IR (CH_2Cl_2/NaCl, cm^{-1}): 2837, 2043, 1606, 1568, 1289, 1243, 1172, 1106, 1031, 830, 733; HRMS (EI): Exact mass calcd for $C_{13}H_{15}NO_2$ (M^+) 174.08. Found 174.0799.

3.5 Procedures and characterizations for section 2.5

General procedure for 6-exo-dig cyclization of oximes (Tables 2.21-2.23). A small vial of microwave was filled in oxime, solvent (molarity relative to the oxime), acid catalysts and additives, and a magnetic stir bar. Then the vial was closed and heated by microwave irradiation to reach the required temperature. When the test was finished,

the vial was cooled to room temperature. The solvent was evaporated and the crude mixture was dissolved into deuterated solvent and analyzed by ^{1}H NMR.

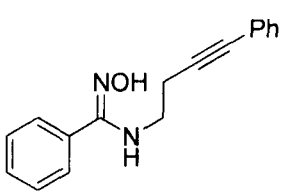
General procedure for 6-exo-dig cyclization of oxime 2.86 (Table 2.22). An oven-dried round bottom flask was filled in oxime **2.86**, deuterated solvent (molarity relative to the oxime), acid catalysts and additives, and a magnetic stir bar. Then the RBF was under argon, and the mixture was stirred at room temperature. The solution was transferred by syringe into a NMR tube. ^{1}H NMR was used to check the composition of the mixture until no more **2.86** existed. Then the RBF was heated to required temperature for 12 hours and was cooled to room temperature. The crude mixture was directly analyzed by ^{1}H NMR.



4-Phenylbut-3-yn-1-amine (**2.85**) (Scheme 2.19). The title compound was prepared by Staudinger reaction according to the procedure by Roychowdhury et al.[90] 4.0 g of alcohol **2.77** was used to afford 6.3 g **2.82** (76%) according to general procedure of Sonogashira coupling. Methanesulfonylchloride (4.0 g, 57.0 mmol) was added drop wise to a stirred solution of 4-phenylbut-3-yn-1-ol **2.82** (2.12 g, 13.7 mmol) and

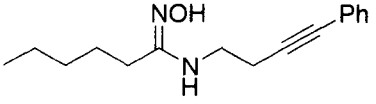
[90] Roychowdhury, A.; Illangkoon, H.; Hendrickson, C. L.; Benner, S. A. *Org Lett* **2004**, *6*, 489.

Et_3N (2.08 g, 20.6 mmol, 1.5 equiv.) in anhydrous ethyl ether (9.1 mL) at 0°C. After 3h, water (4.6 mL) was added to the reaction mixture. The organic layer was separated, washed with water (12 mL), dried with Na_2SO_4 and distilled in vacuo to yield crude **2.82** as dark yellow liquid. Sodium azide (2.22 g, 34.3 mmol) was added to a solution of **2.82** in anhydrous DMF (11 mL). The mixture was stirred for 3.5 h at 67 °C. The reaction mixture was poured over water (5 mL) and extracted with ethyl ether (3 x 12 mL). The solution was then dried over Na_2SO_4 and evaporated to yield 1.84 g (79.0%, over 2 steps) of **2.84** as yellow liquid. Then it was dissolved in ethyl ether (13 mL) at 0 °C, PPh_3 (2.81 g, 10.7 mmol) was added and allowed to stir for 1.5h. Water (3.0 mL) was then added to the reaction mixture and allowed to stir for another 16 h. The reaction mixture was poured over 10% aqueous HCl, extracted with ethyl ether (3x 12 mL). The aqueous layer was made basic (pH= 9.0) with 10% aqueous NaOH and extracted with ethyl ether (5x 30 mL). The solvent was dried over Na_2SO_4 and evaporated to yield 1.3 g (83.0 %) of **2.85** as light yellow liquid without column chromatographic purification. Spectroscopic data corresponds with literature.[90]



(E)-*N'*-Hydroxy-*N*-(4-phenylbut-3-ynyl)benzamidine (2.86) (Scheme

2.19). The title compound was prepared according to the general procedure of amidine syntheses. Amine **2.85** was prepared according to the general procedure of Staudinger reaction. Substrate **2.64** was prepared according to the general procedure of oximinoyl chloride synthesis. 1.3 g of substrate **2.85** (7.77 mmol) was used to afford 1.18g (60%) of **2.86** as a dark yellow oil after column chromatography (50% ether/hexanes). TLC R_f 0.3 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.52-7.27 (m, 10H), 5.62 (br, 1H), 3.29 (dt, J = 6.52, 6.30, 6.30 Hz, 2H), 2.21 (t, J =6.30 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 156.11 (C), 131.61 (C), 131.32 (CH), 129.59 (CH), 128.53 (CH), 128.47 (CH), 128.19 (CH), 127.85 (CH), 123.32 (C), 86.47 (C), 82.45 (C), 42.46 (CH_2), 22.27 (CH_2); IR (CH_2Cl_2/NaCl, cm^{-1}): 4051, 2232, 1959, 1722, 1703, 1699; HRMS (EI): Exact mass calcd for $C_{17}H_{16}N_2O$ (M^+) 264.13. Found 264.1289.

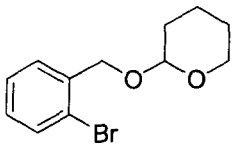


***(E)*-*N*'-Hydroxy-*N*-(4-phenylbut-3-ynyl)hexanamidine (2.91) (Scheme 2.20)**. The title compound was prepared according to the general procedure of amidine syntheses. Amine **2.85** was prepared according to the general procedure of Staudinger reaction. Substrate **2.90** was prepared according to the general procedure of Parikh-Doering oxidation, oxime formation and oximinoyl chloride synthesis from commercial substrate **2.87**. 0.55 g of substrate **2.90** (7.77 mmol) was used to afford 0.49g (60%)

of **2.91** as a yellow oil after column chromatography (50% EtOAc/hexanes). TLC R_f 0.3 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.79 (br, 1H), 7.40-7.24 (m, 5H), 5.57 (t, *J* = 6.52 , 6.52 Hz,1H), 3.32 (dt, J = 6.52, 6.30, 6.30 Hz, 2H), 2.58 (t, *J* = 6.77, 6.77 Hz, 2H), 2.21 (t, J =6.30, 6.30 Hz, 2H), 1.55 (m, 2H),1.29 (m, 4H), 0.86 (t, *J* = 6.77, 6.77 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ ppm 154.99 (C), 131.62 (CH), 128.23 (CH), 127.90 (CH), 123.33 (C), 86.54 (C), 82.49 (C), 41.16 (CH_2), 31.45 (CH_2), 28.63 (CH_2), 26.37 (CH_2), 22.37 (CH_2), 22.26 (CH_2), 13.99 (CH_3); IR (CH_2Cl_2/NaCl, cm^{-1}): 4047, 2218, 1962, 1721, 1699; HRMS (EI): Exact mass calcd for $C_{16}H_{22}N_2O$ (M^+) 258.17. Found 258.1733.

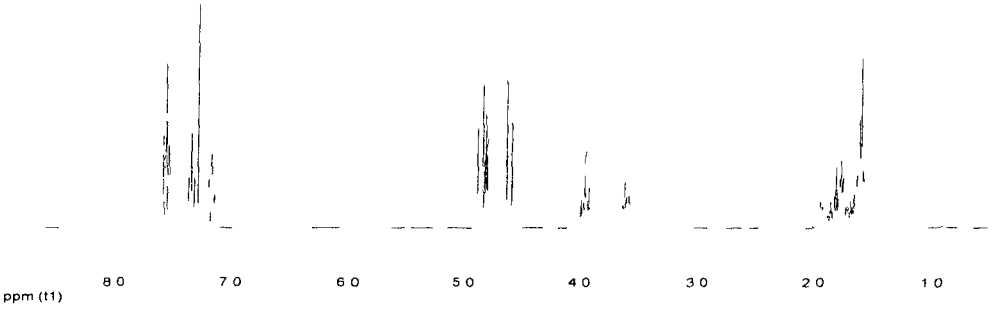
Appendix:

^{1}H and ^{13}C NMR spectra

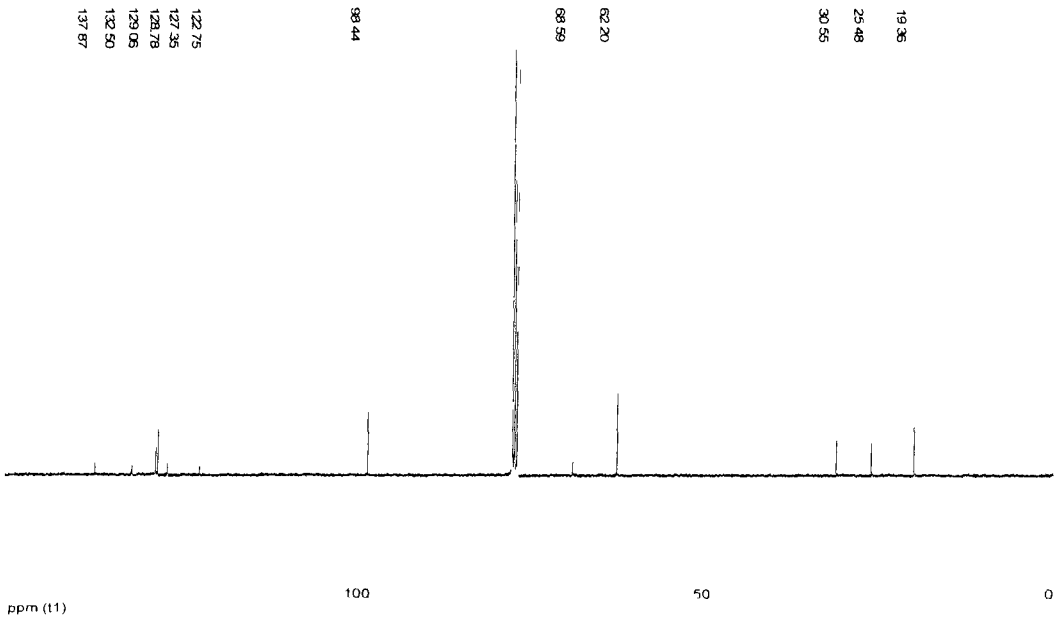


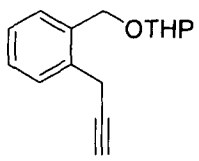
2.10, Scheme 2.2

^{1}H NMR (C_6D_6, 400 mHz)



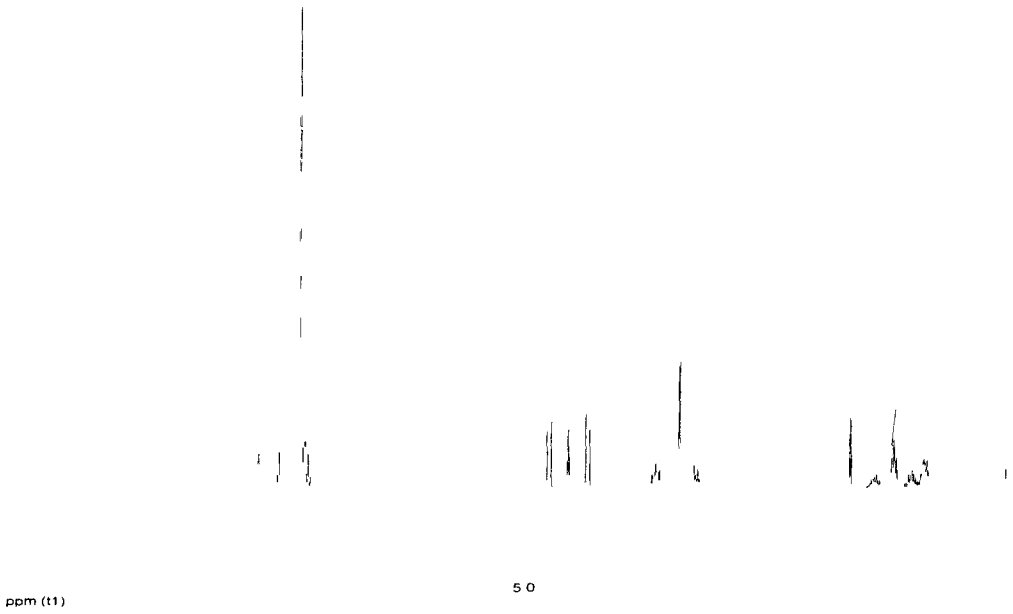
^{13}C NMR (C_6D_6, 400 mHz)



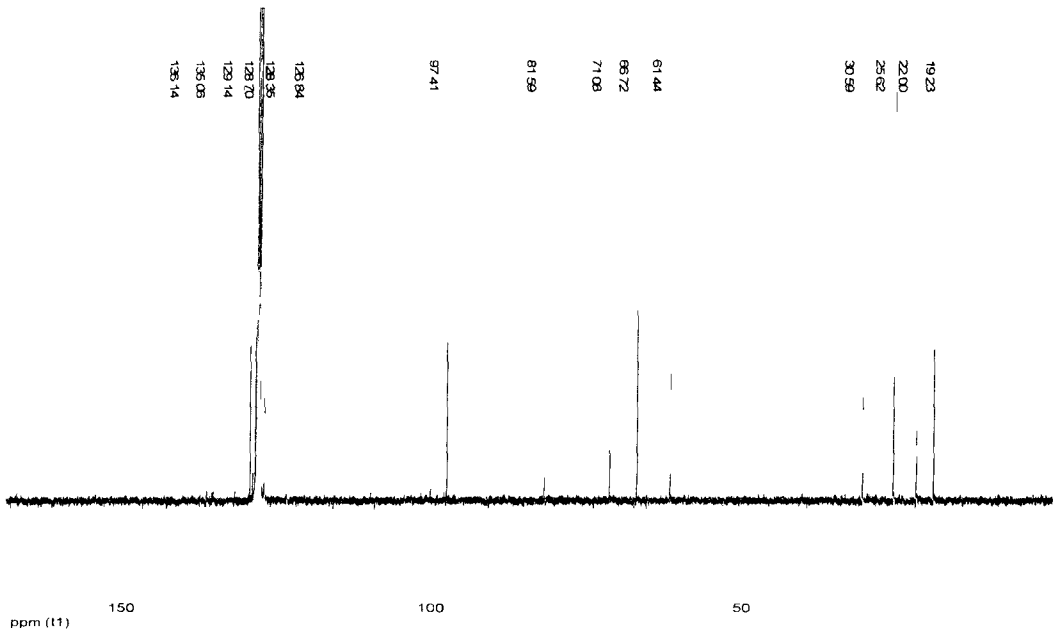


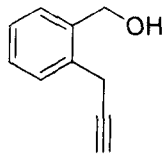
2.11, Scheme 2.2

^{1}H NMR (C_6D_6, 400 mHz)



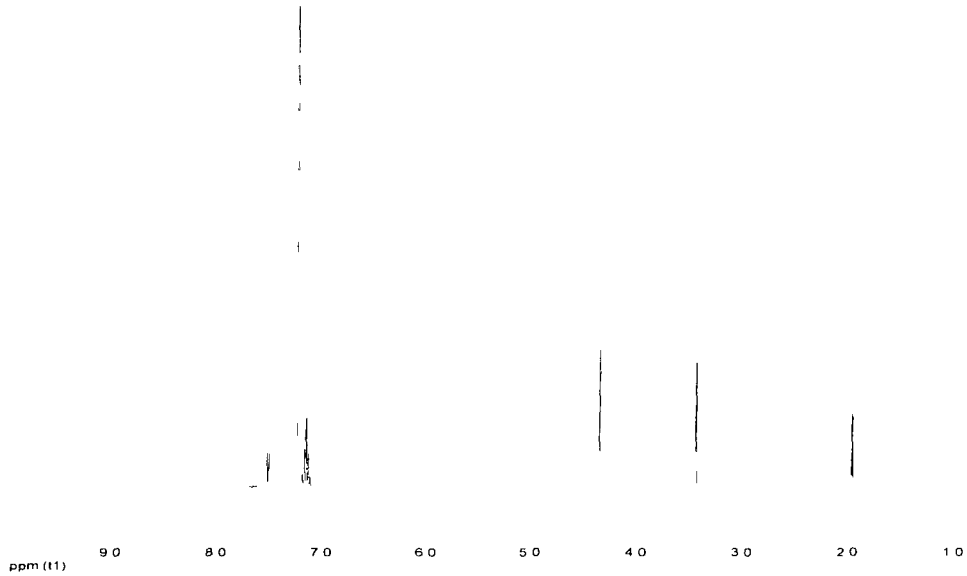
^{13}C NMR (C_6D_6, 400 mHz)



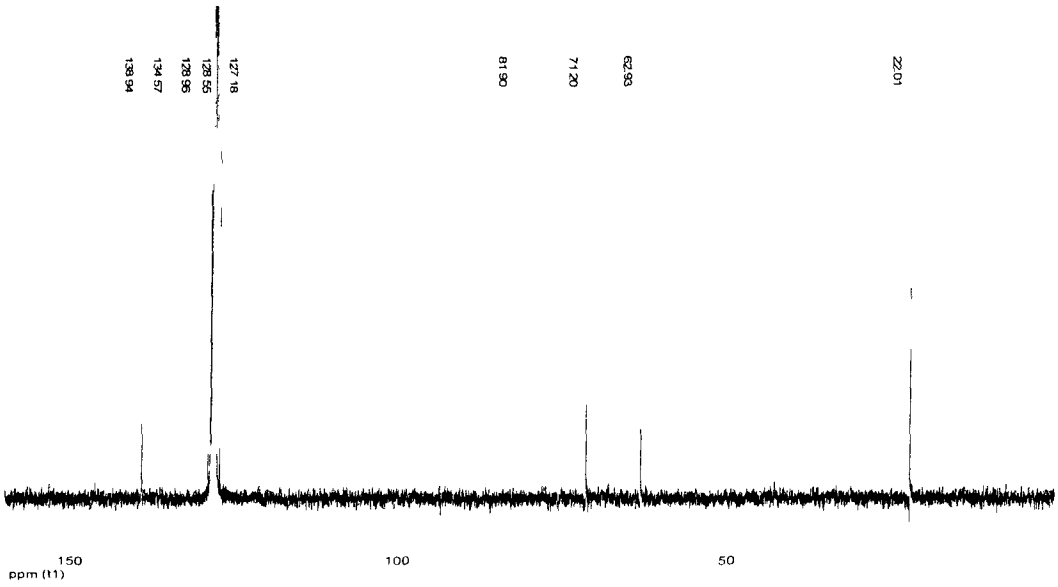


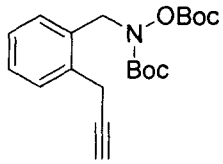
2.12, Scheme 2.2

^{1}H NMR (C_6D_6, 400 mHz)



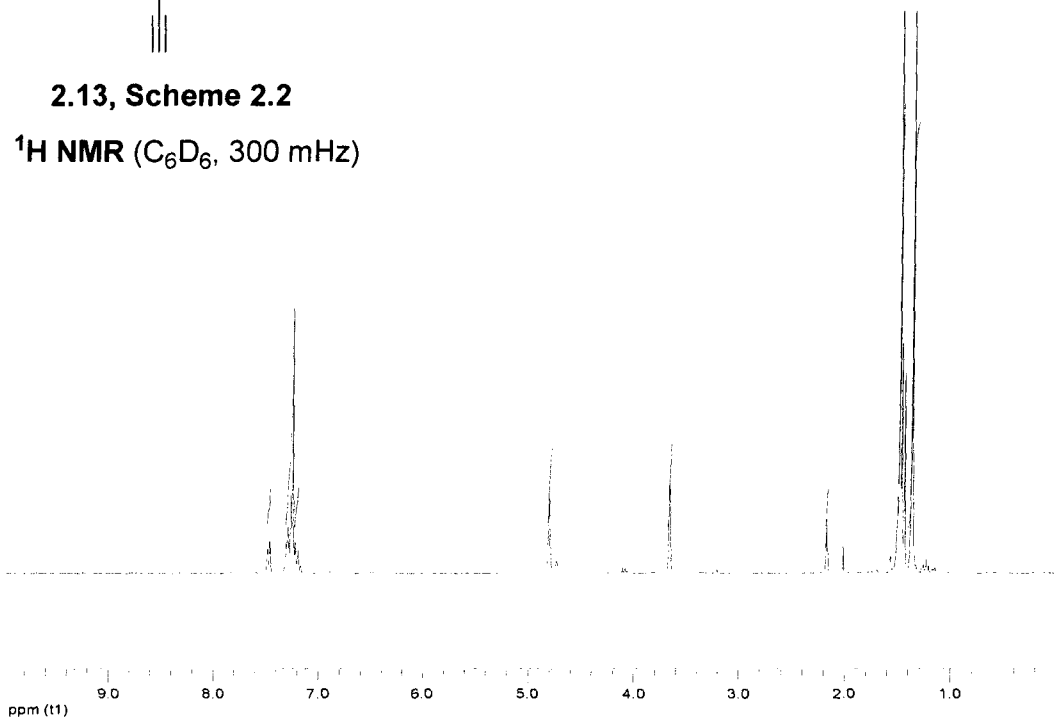
^{13}C NMR (C_6D_6, 400 mHz)



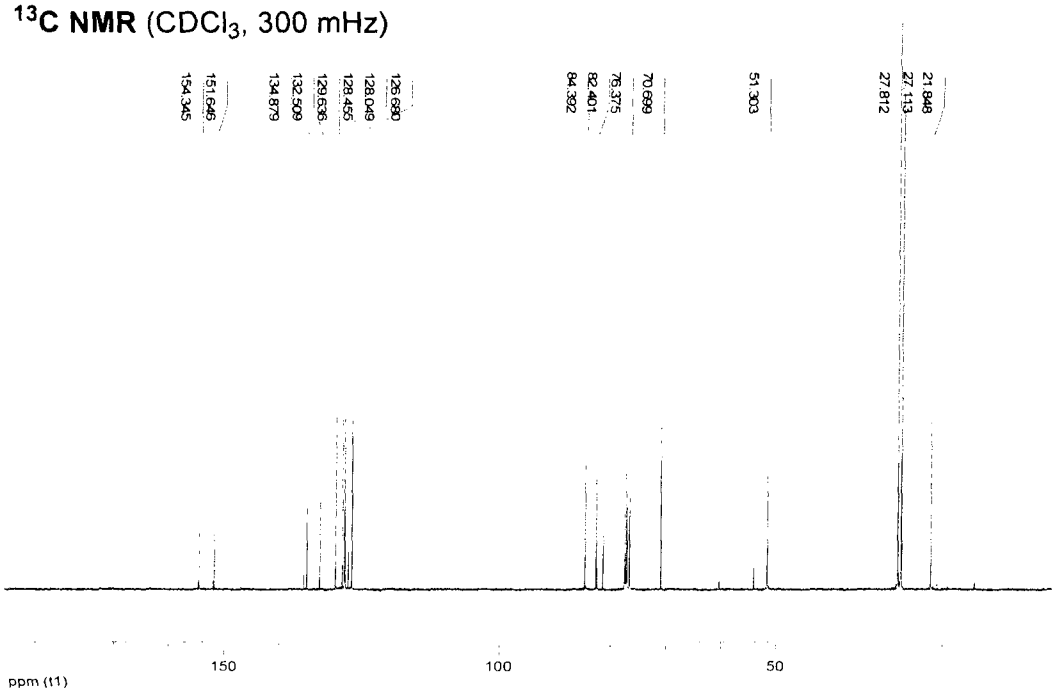


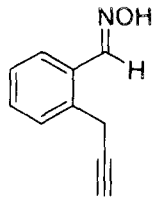
2.13, Scheme 2.2

^{1}H NMR (C_6D_6, 300 mHz)



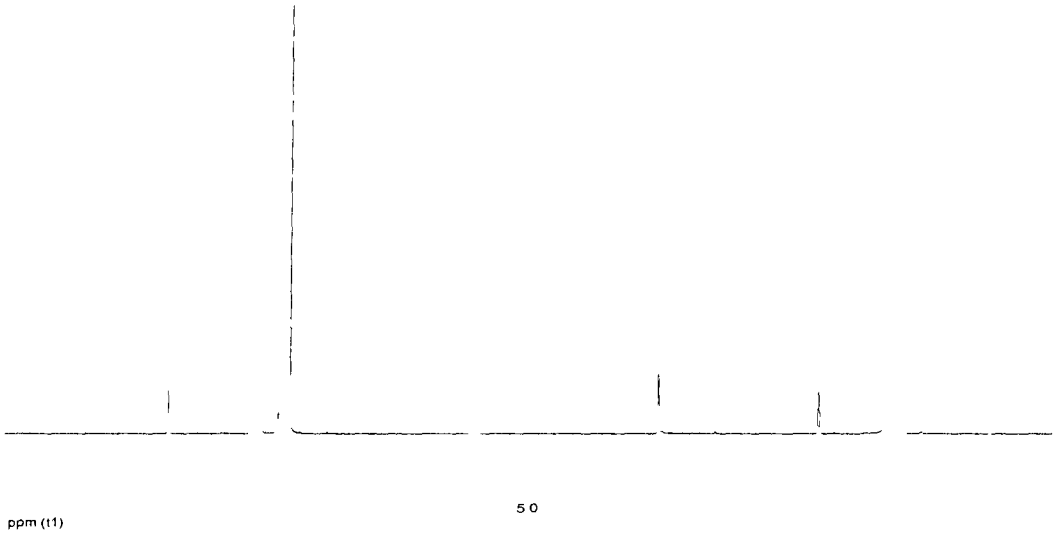
^{13}C NMR ($CDCl_3$, 300 mHz)



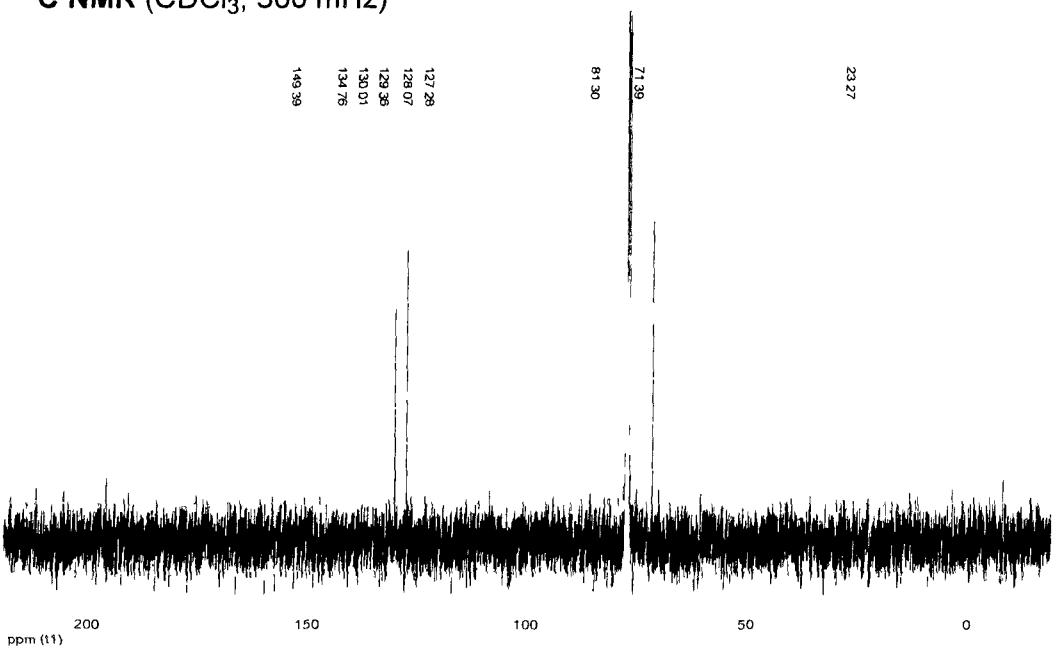


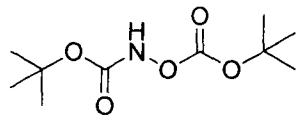
2.19, Table 2.5

^{1}H NMR ($CDCl_3$, 300 mHz)



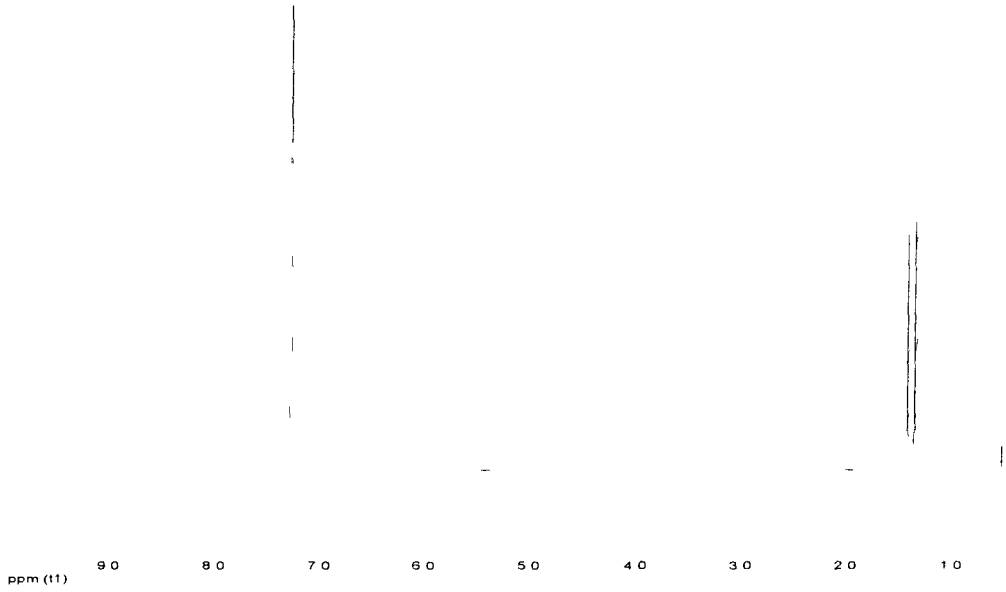
^{13}C NMR ($CDCl_3$, 300 mHz)



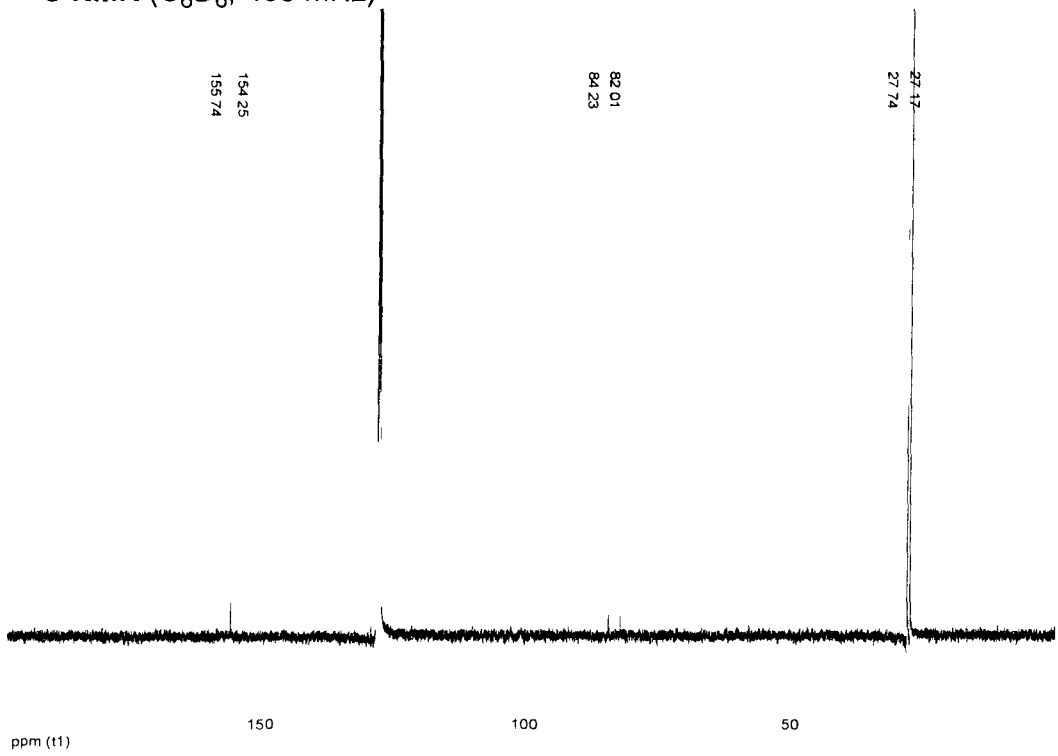


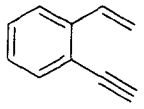
2.17, Equation 2.2

^{1}H NMR (C_6D_6, 300 mHz)



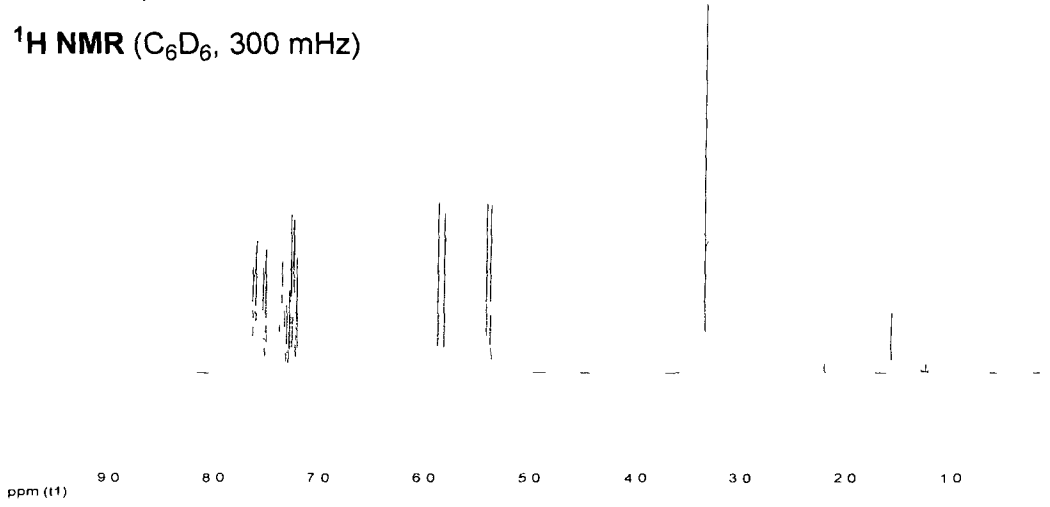
^{13}C NMR (C_6D_6, 400 mHz)



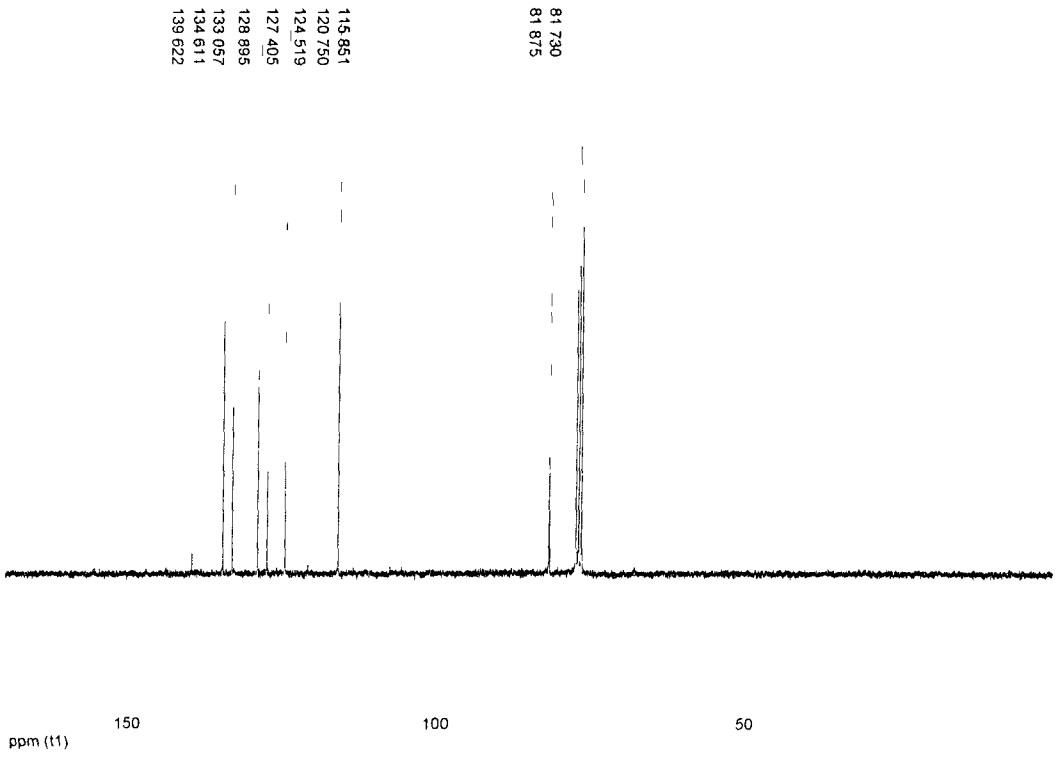


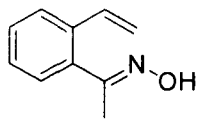
2.20a, Table 2.8

^{1}H NMR (C_6D_6, 300 mHz)



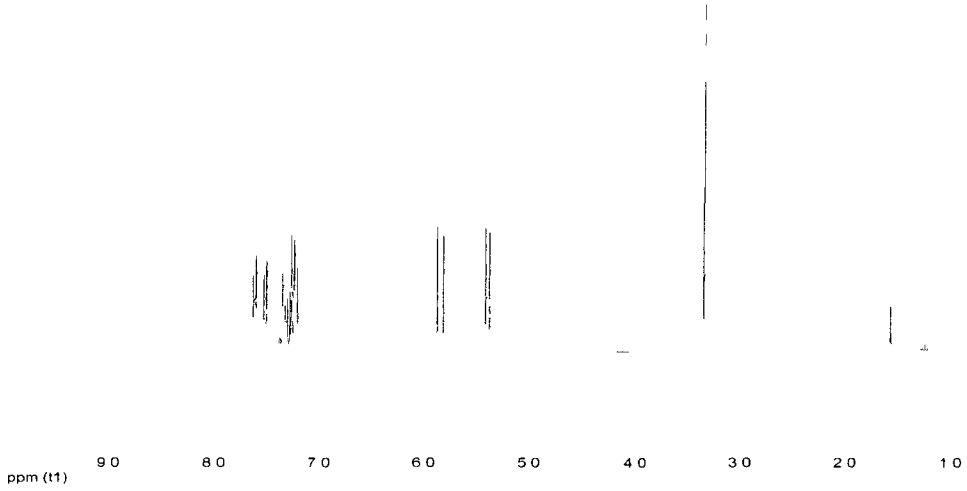
^{13}C NMR (C_6D_6, 300 mHz)



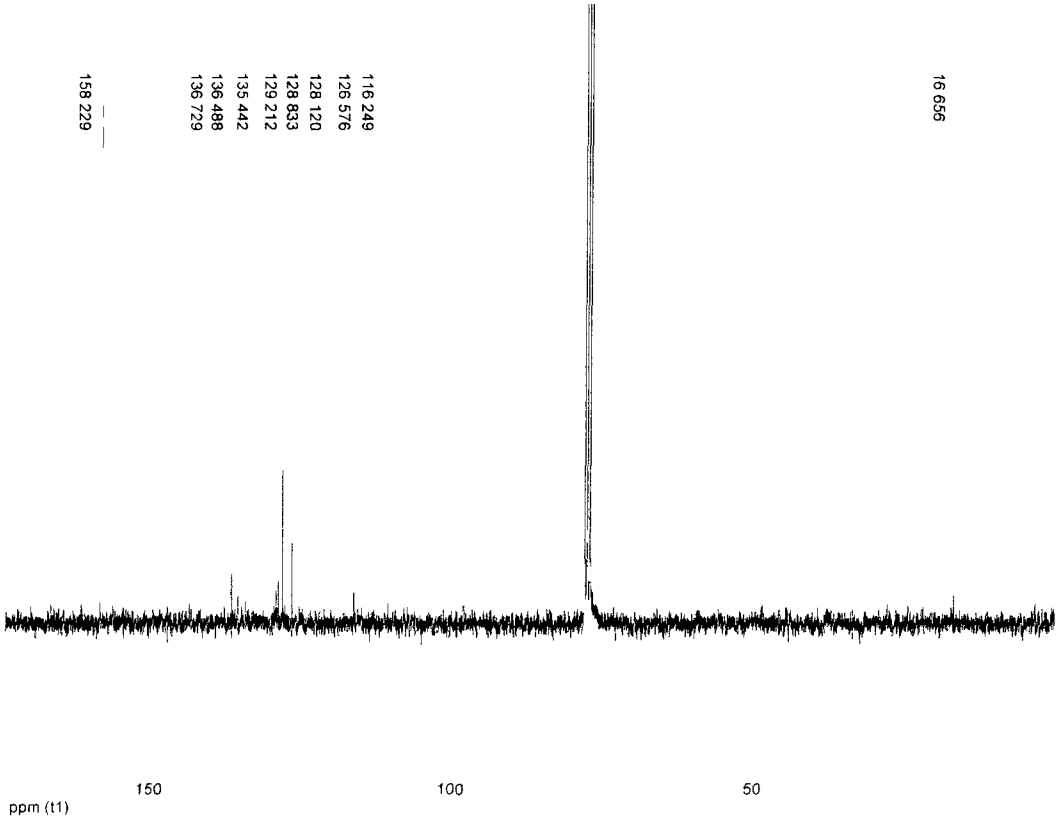


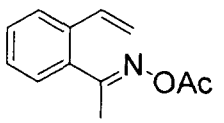
2.21a Table 2.9

^{1}H NMR ($CDCl_3$, 300 mHz)



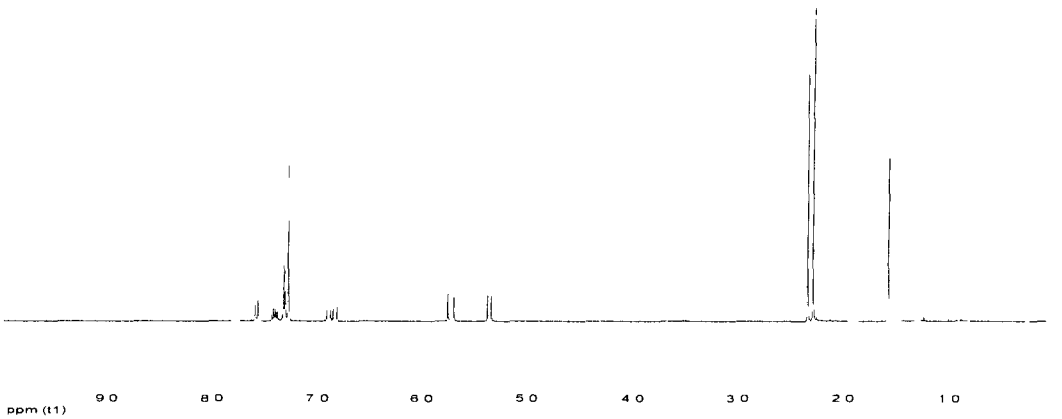
^{13}C NMR (C_6D_6, 300 mHz)





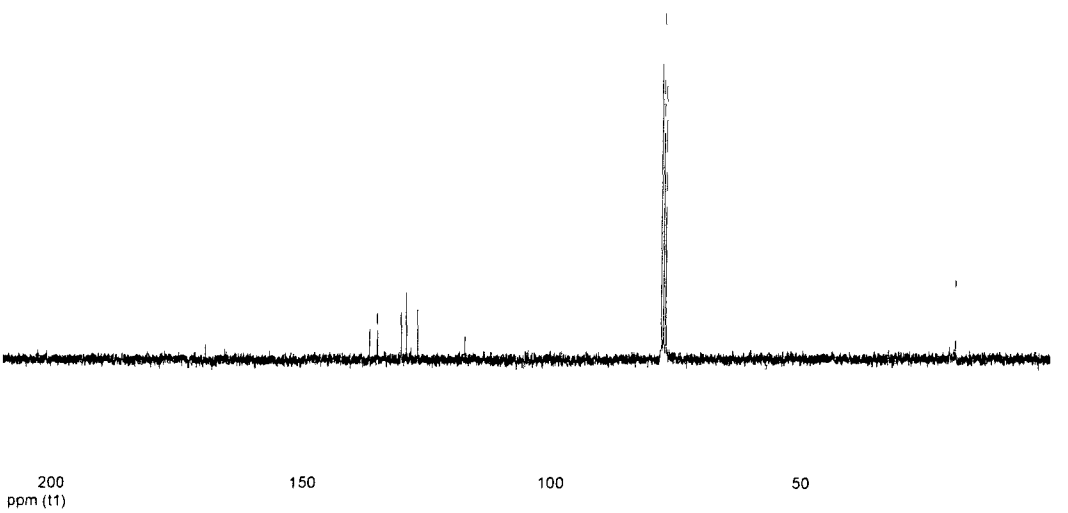
2.30 Table 2.11

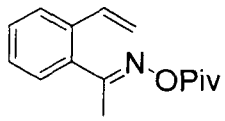
^{1}H NMR ($CDCl_3$, 300 mHz)



^{13}C NMR ($CDCl_3$, 300 mHz)

169.355
165.522
136.586
135.058
134.870
130.033
129.015
128.137
126.732
117.277
20.257
19.045

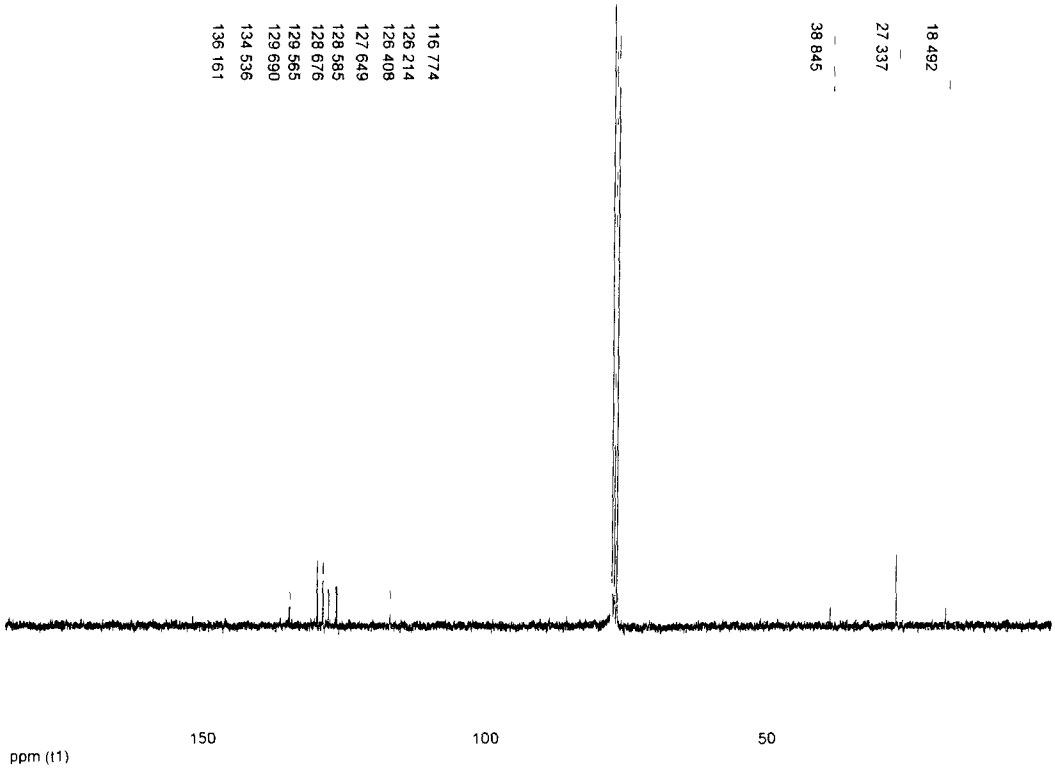


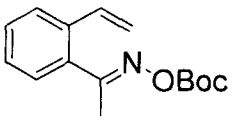


2.31, Table 2.12

^{1}H NMR ($CDCl_3$, 300 mHz)

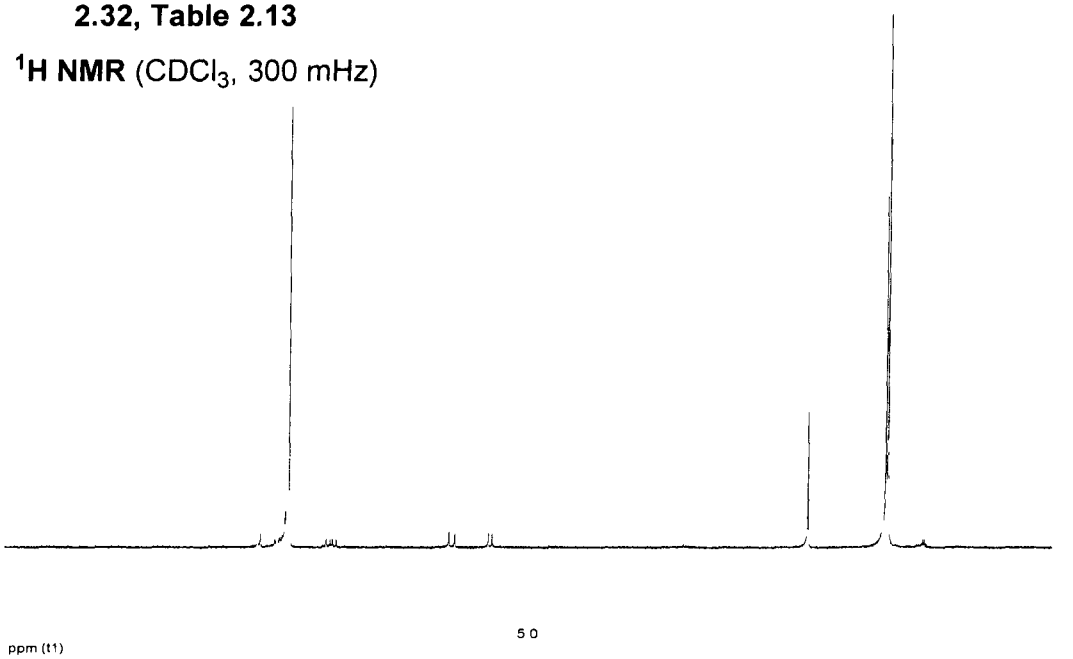
^{13}C NMR ($CDCl_3$, 300 mHz)



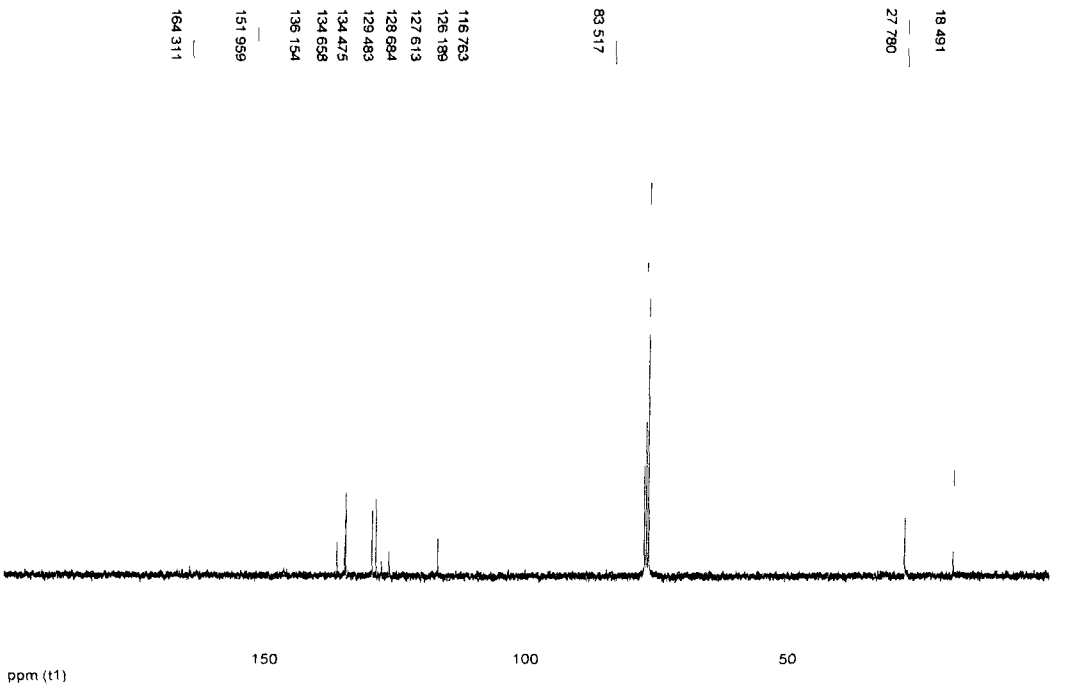


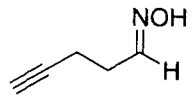
2.32, Table 2.13

^{1}H NMR ($CDCl_3$, 300 mHz)



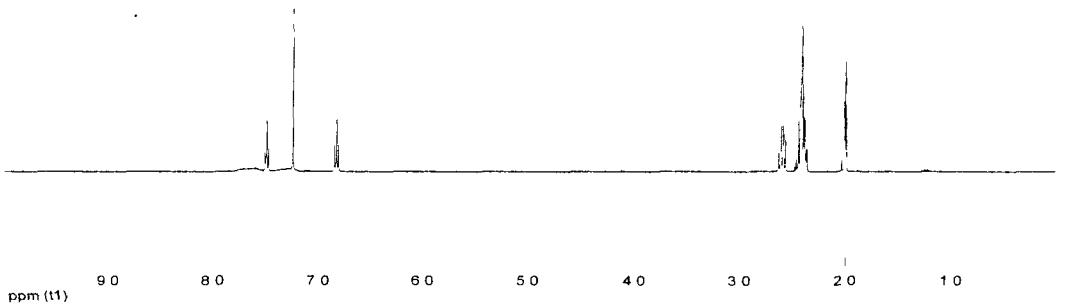
^{13}C NMR ($CDCl_3$, 300 mHz)



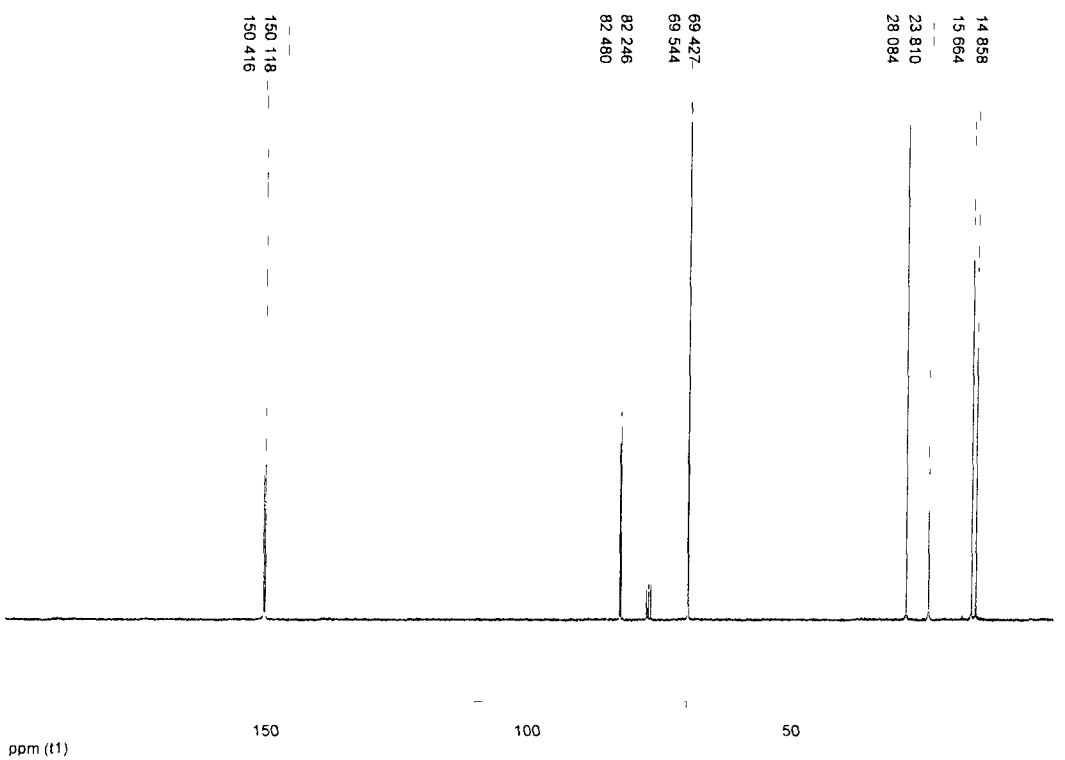


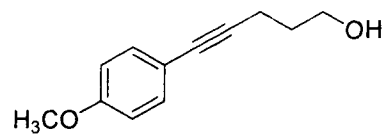
2.48, Equation 2.7

^{1}H NMR ($CDCl_3$, 300 mHz)



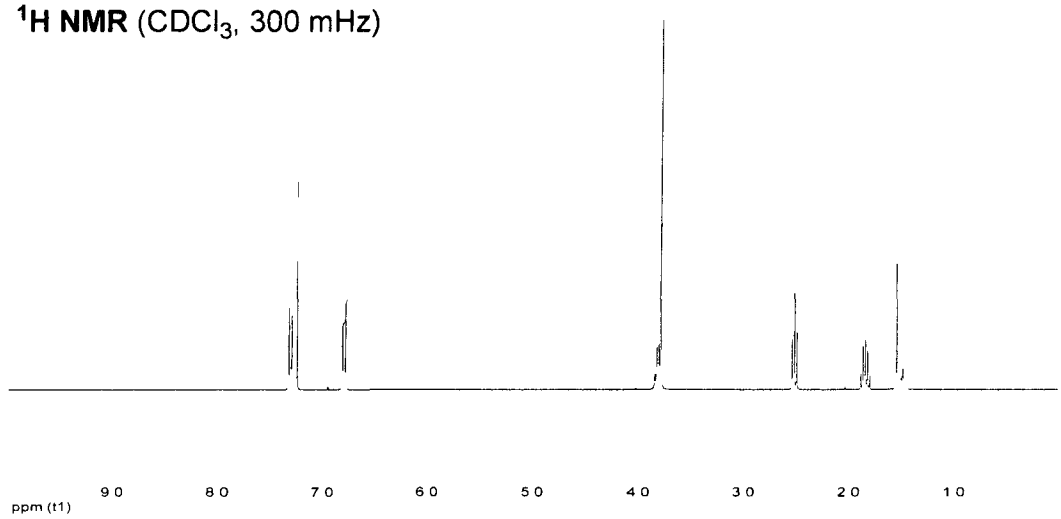
^{13}C NMR ($CDCl_3$, 300 mHz)



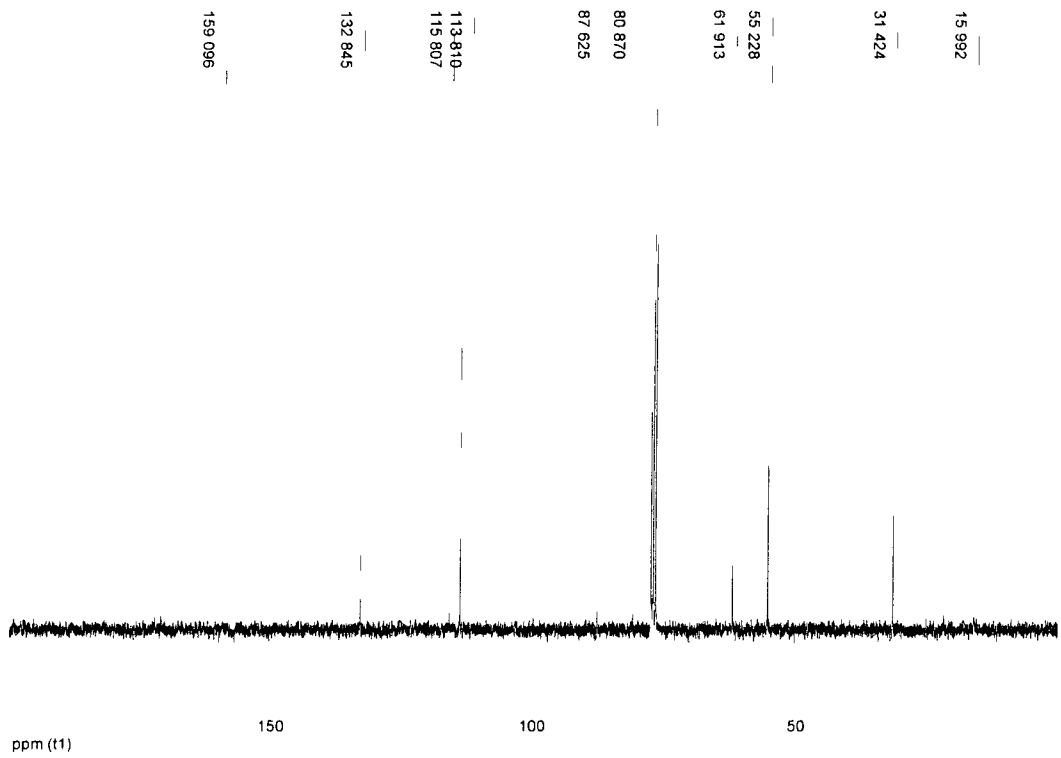


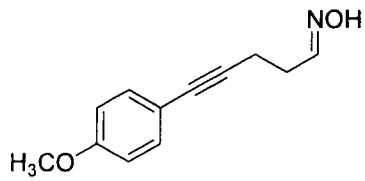
2.49, Scheme 2.11

^{1}H NMR ($CDCl_3$, 300 mHz)



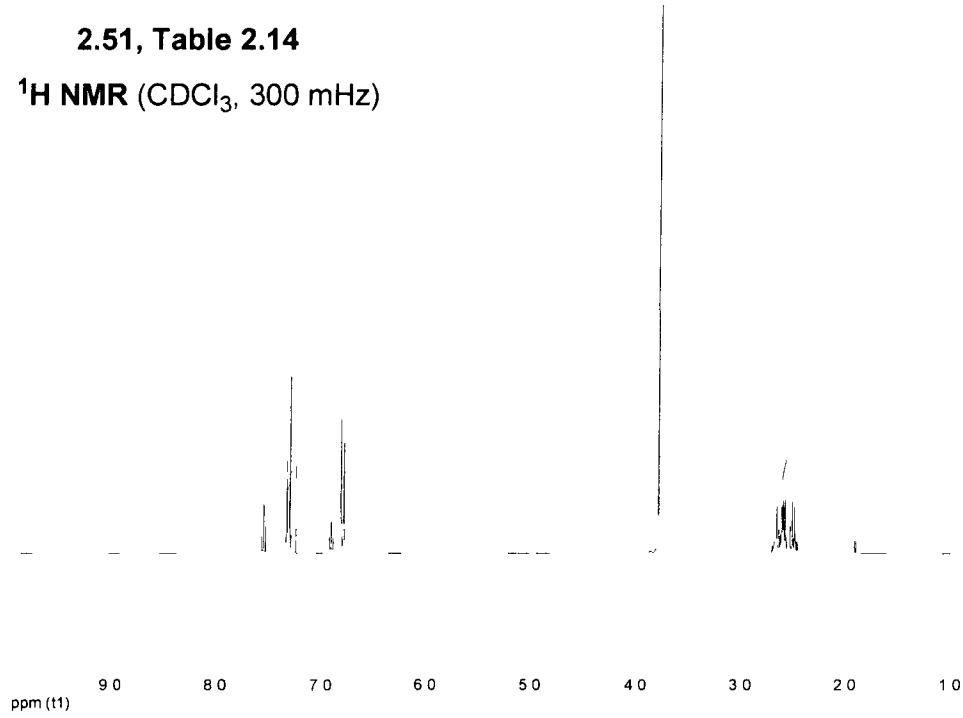
^{13}C NMR ($CDCl_3$, 300 mHz)



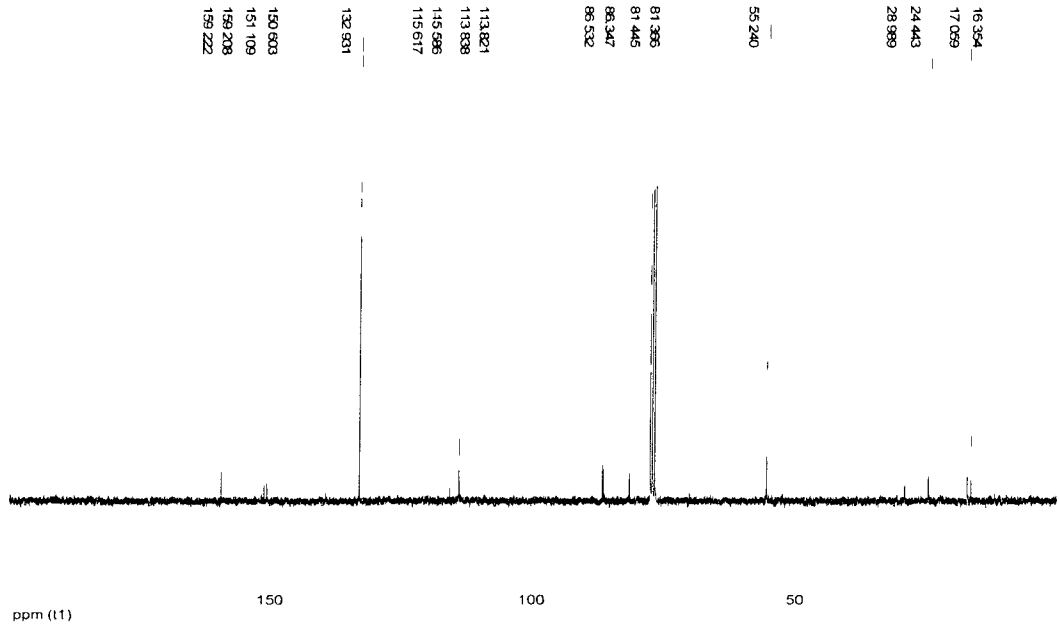


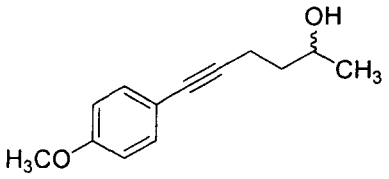
2.51, Table 2.14

^{1}H NMR ($CDCl_3$, 300 mHz)



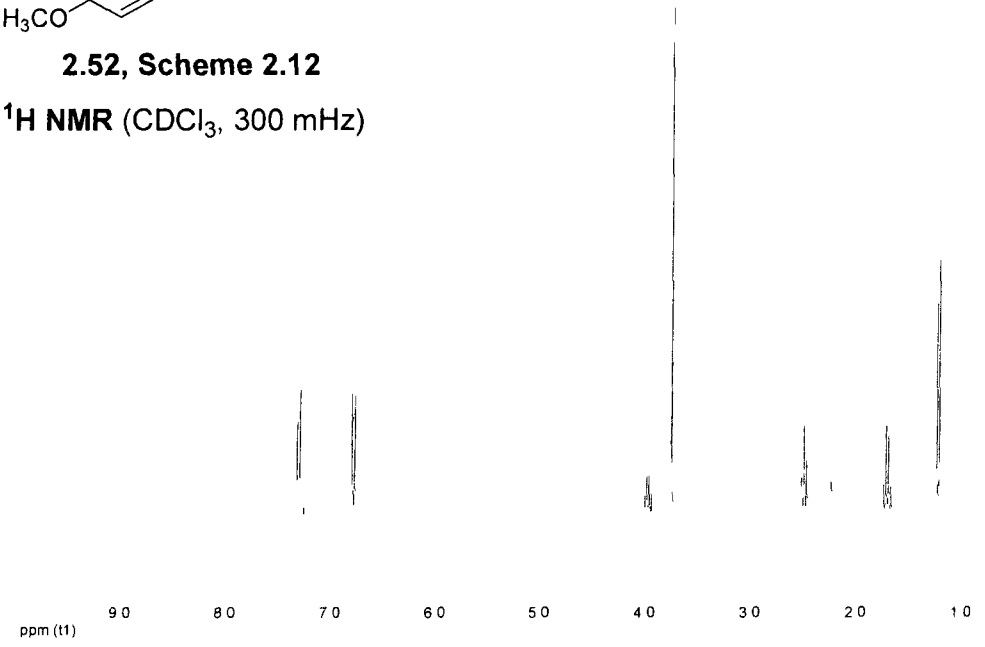
^{13}C NMR ($CDCl_3$, 300 mHz)



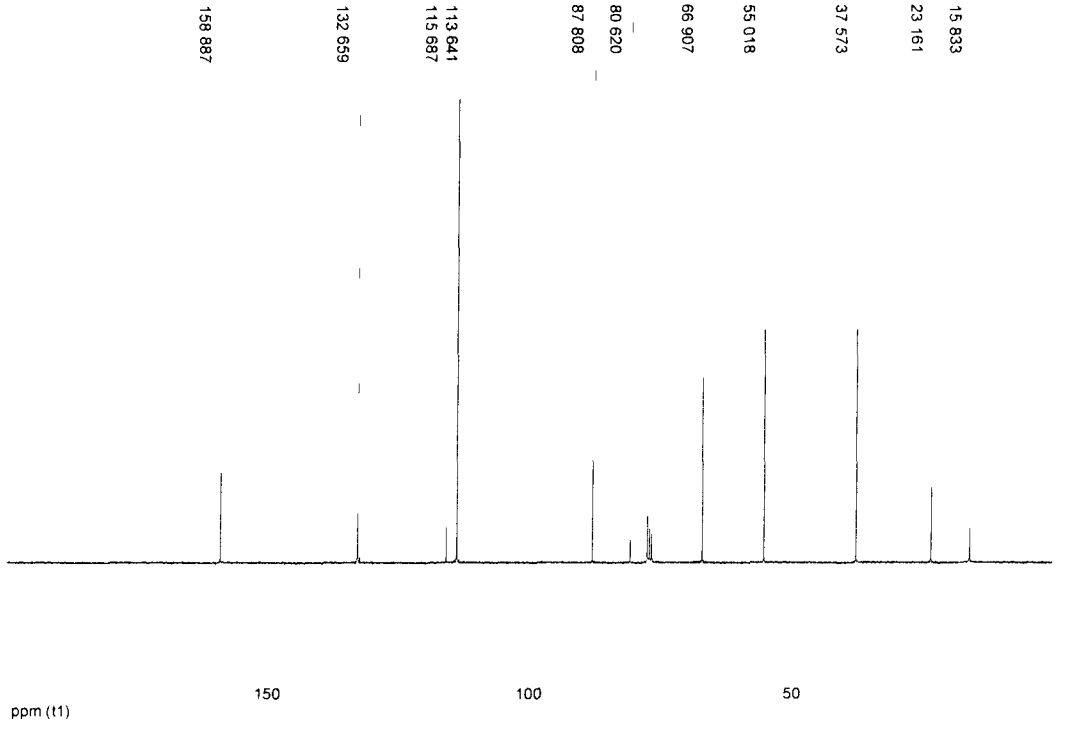


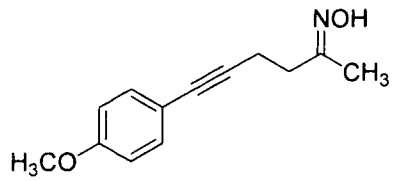
2.52, Scheme 2.12

^{1}H NMR ($CDCl_3$, 300 mHz)



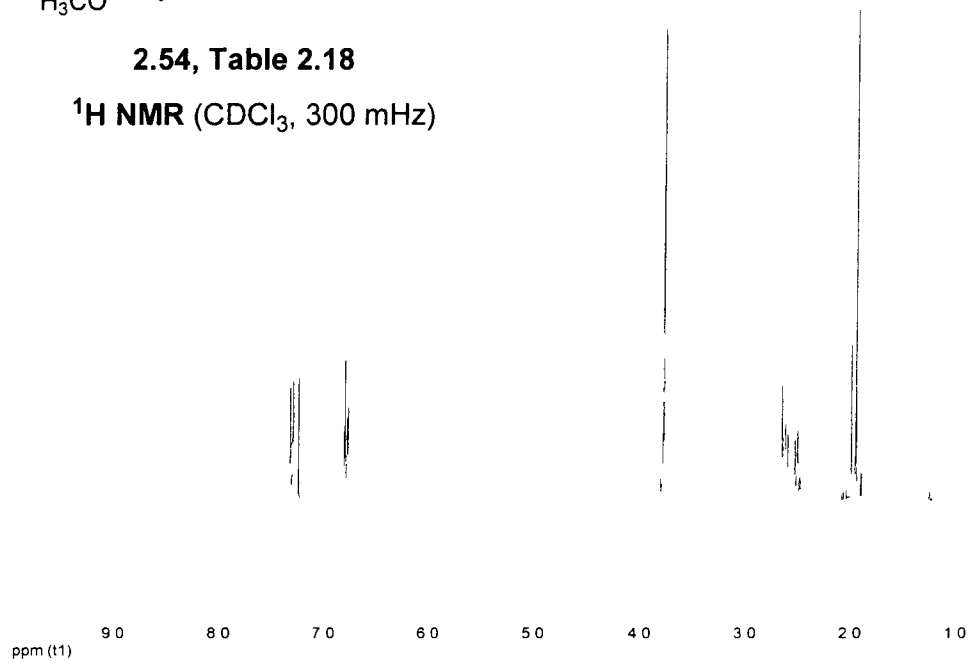
^{13}C NMR ($CDCl_3$, 300 mHz)



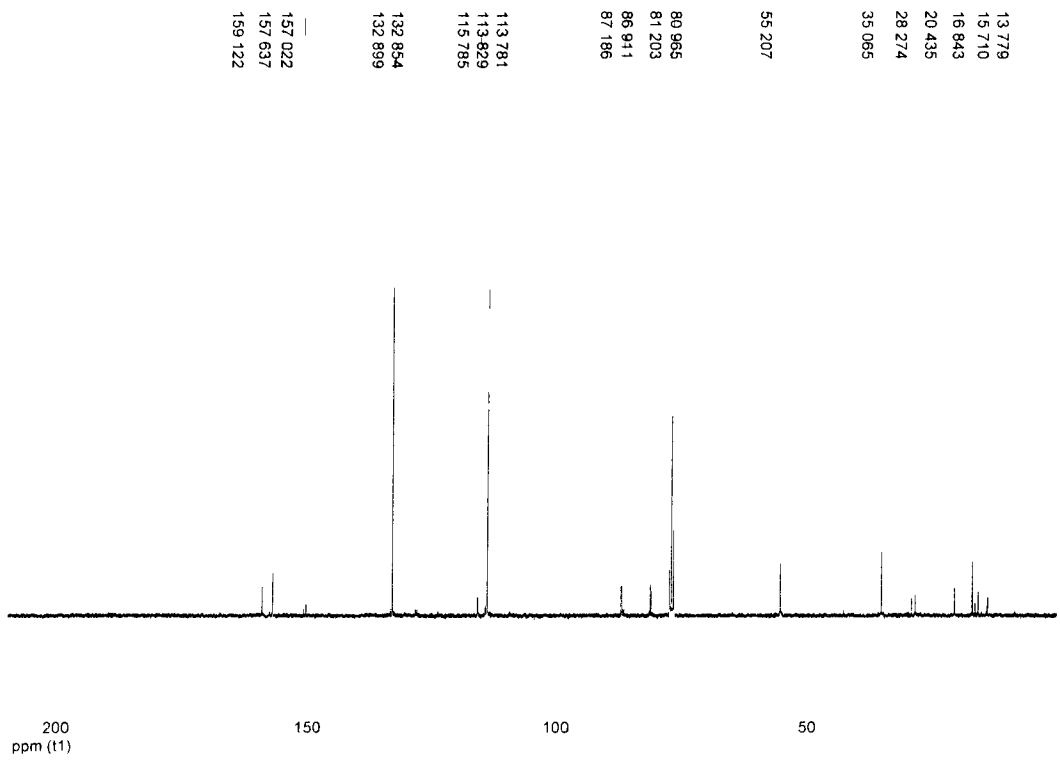


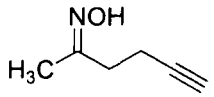
2.54, Table 2.18

^{1}H NMR ($CDCl_3$, 300 mHz)



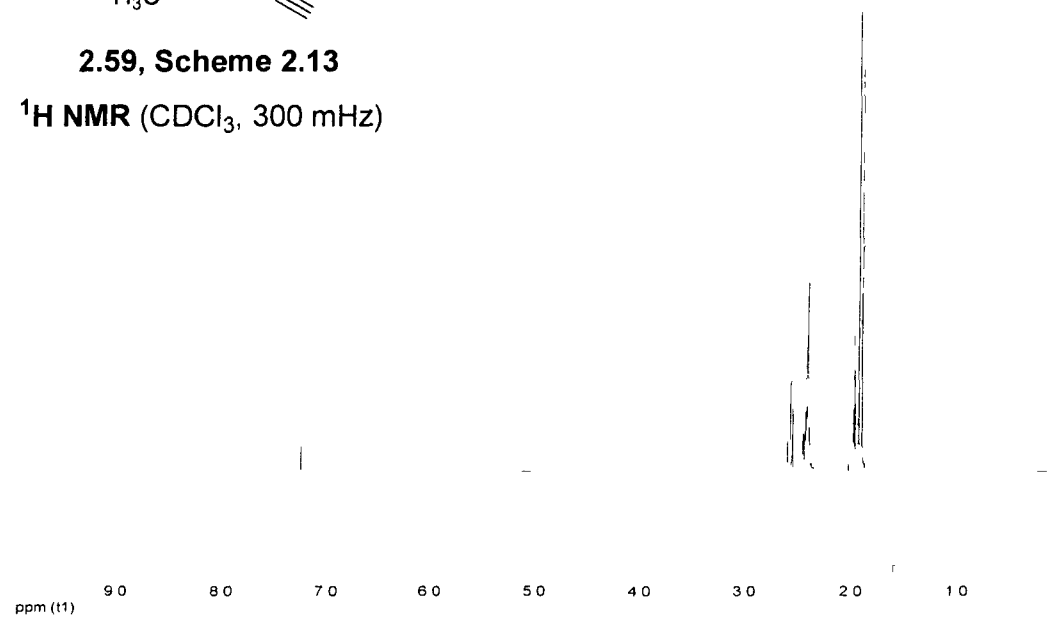
^{13}C NMR ($CDCl_3$, 300 mHz)



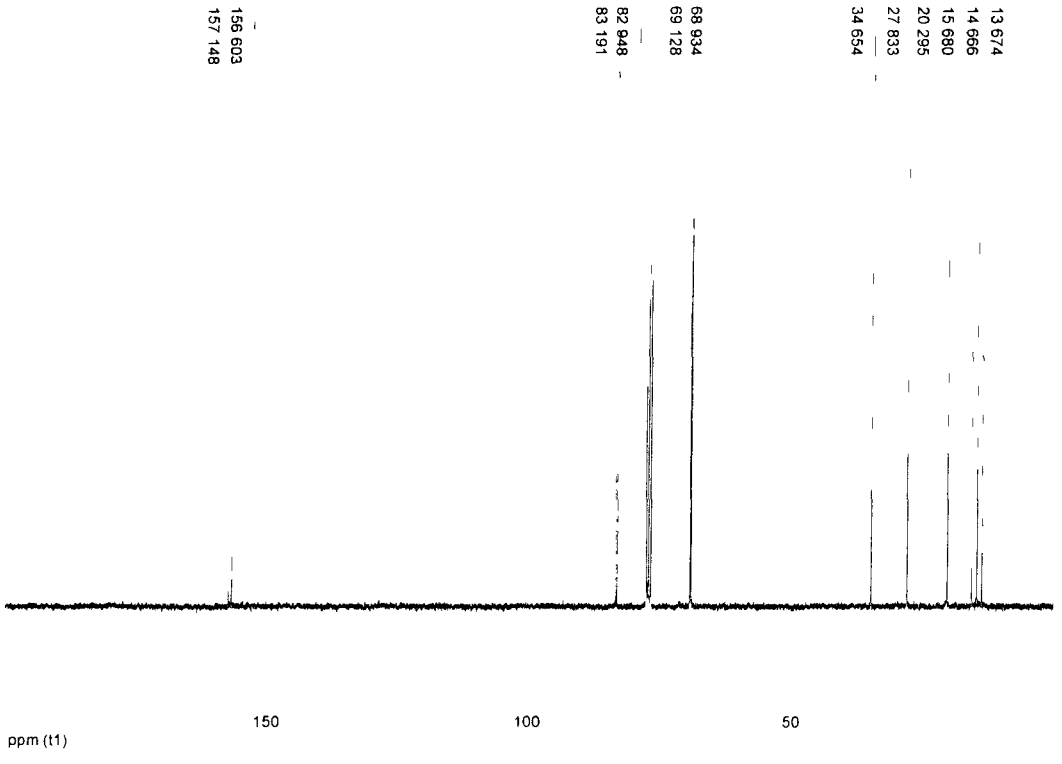


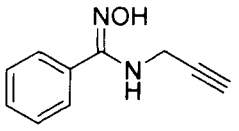
2.59, Scheme 2.13

^{1}H NMR ($CDCl_3$, 300 mHz)



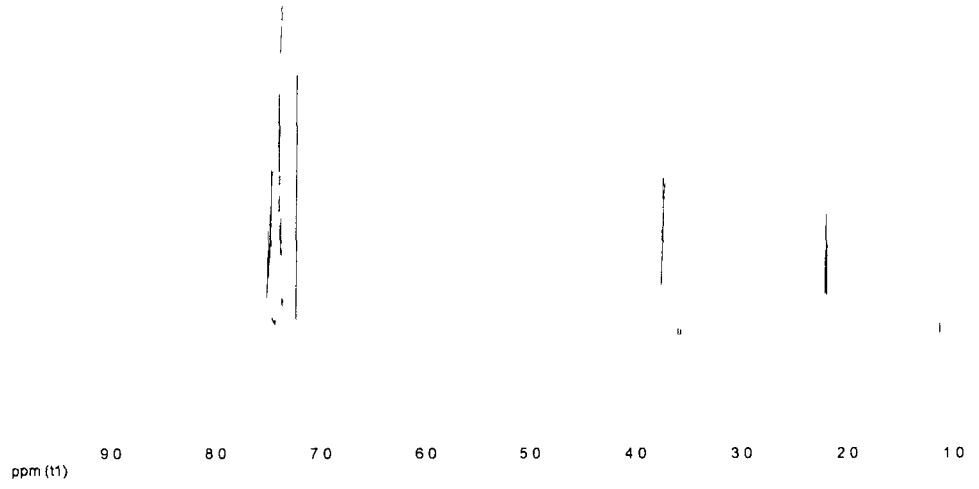
^{13}C NMR ($CDCl_3$, 300 mHz)



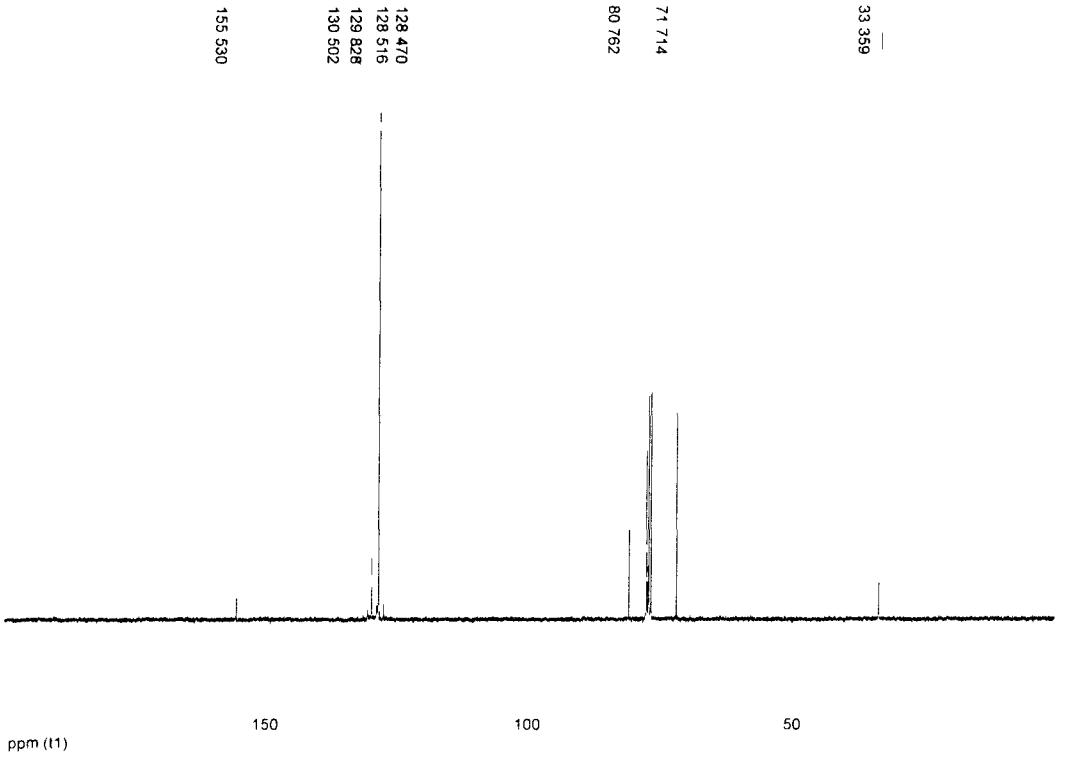


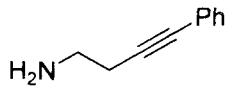
2.65, Table 2.20

^{1}H NMR ($CDCl_3$, 300 mHz)



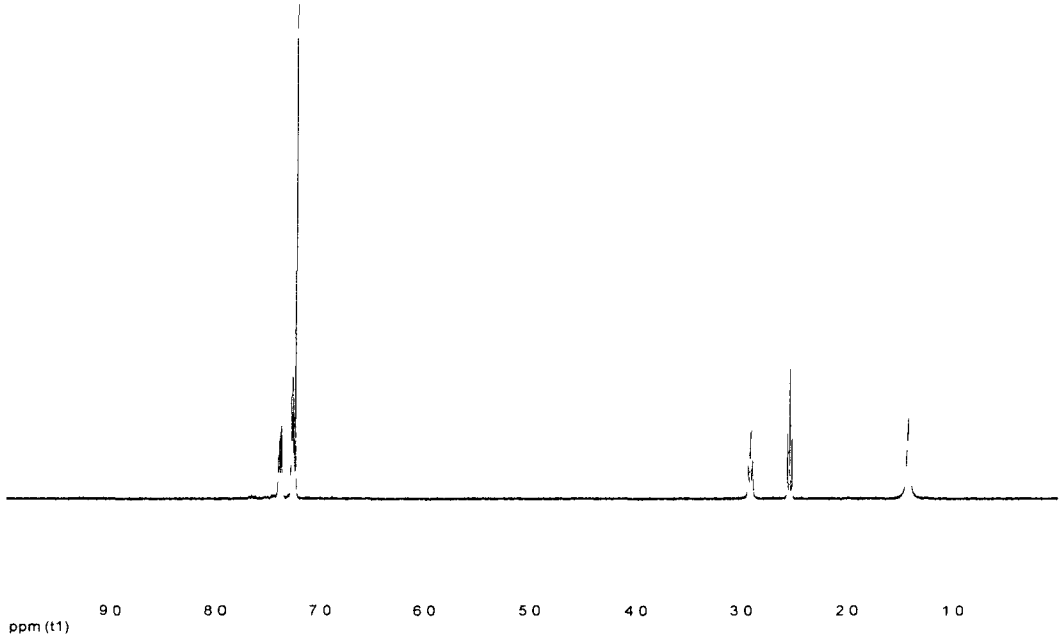
^{13}C NMR ($CDCl_3$, 300 mHz)



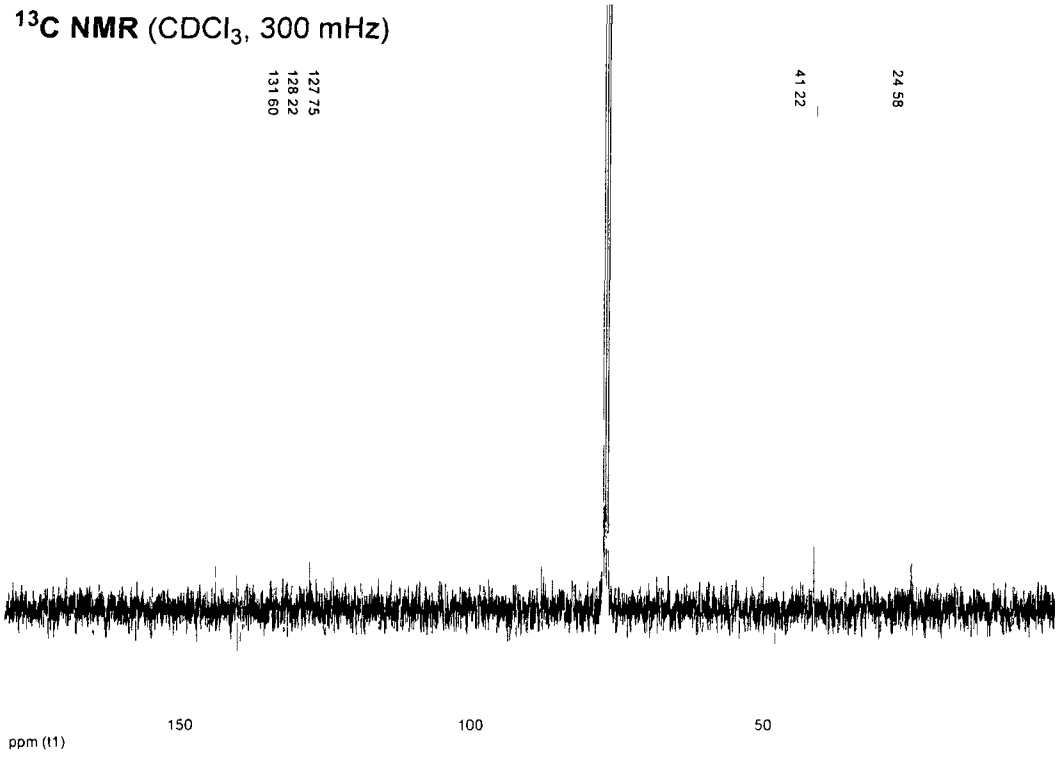


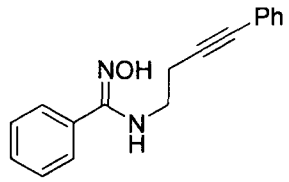
2.85, Scheme 2.19

^{1}H NMR ($CDCl_3$, 300 mHz)



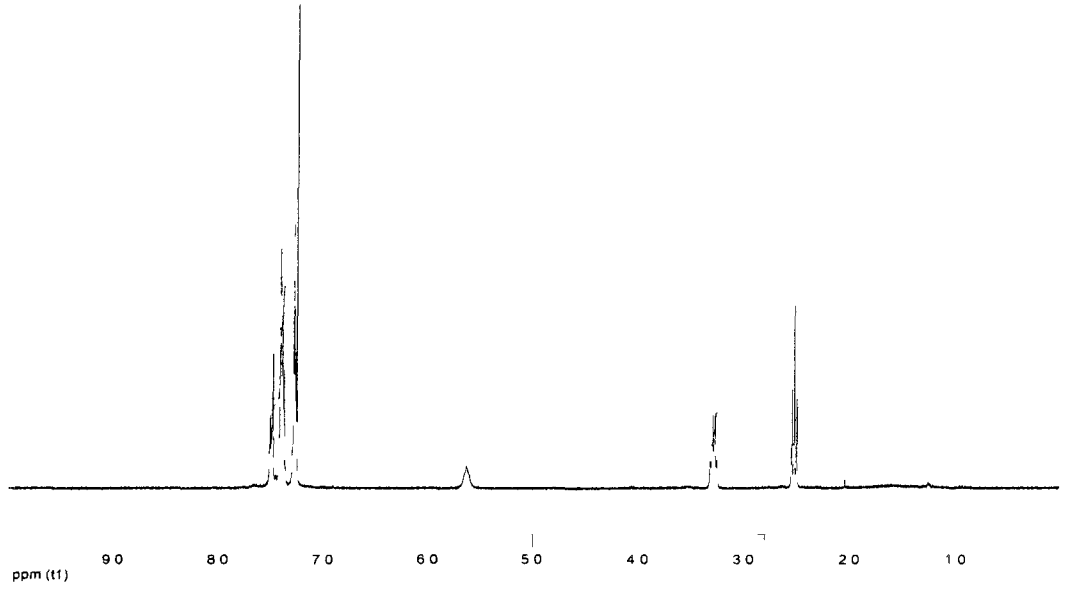
^{13}C NMR ($CDCl_3$, 300 mHz)



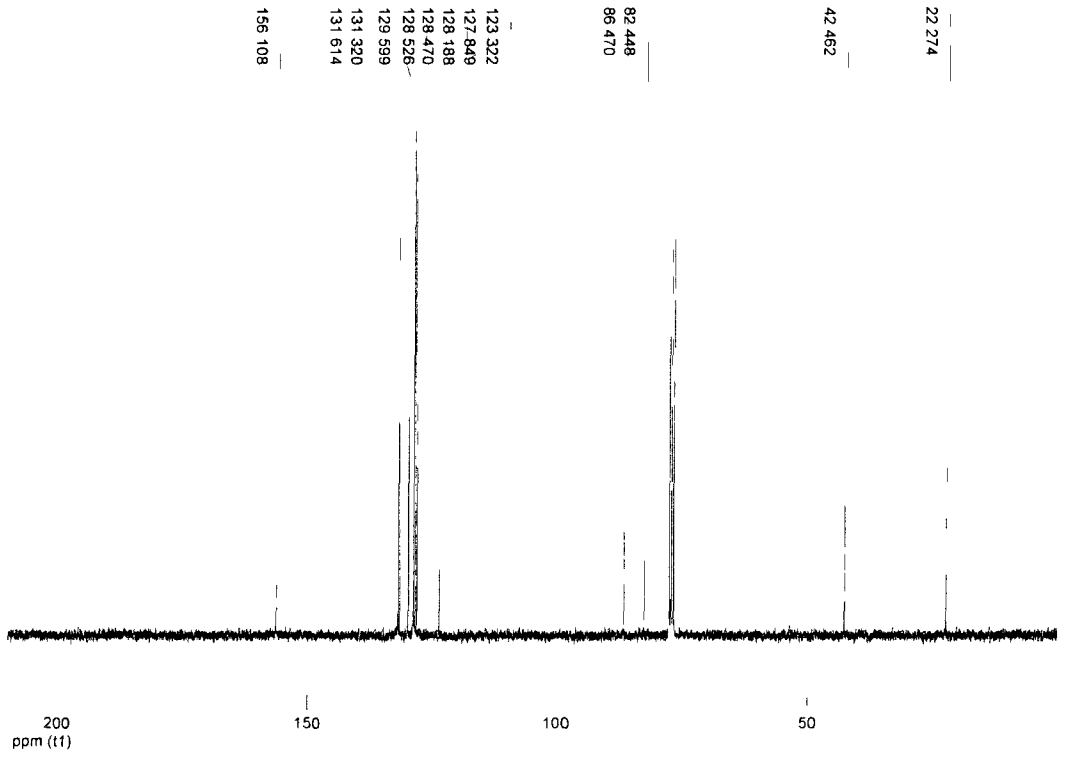


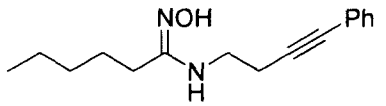
2.86, Table 2.22

^{1}H NMR ($CDCl_3$, 300 mHz)



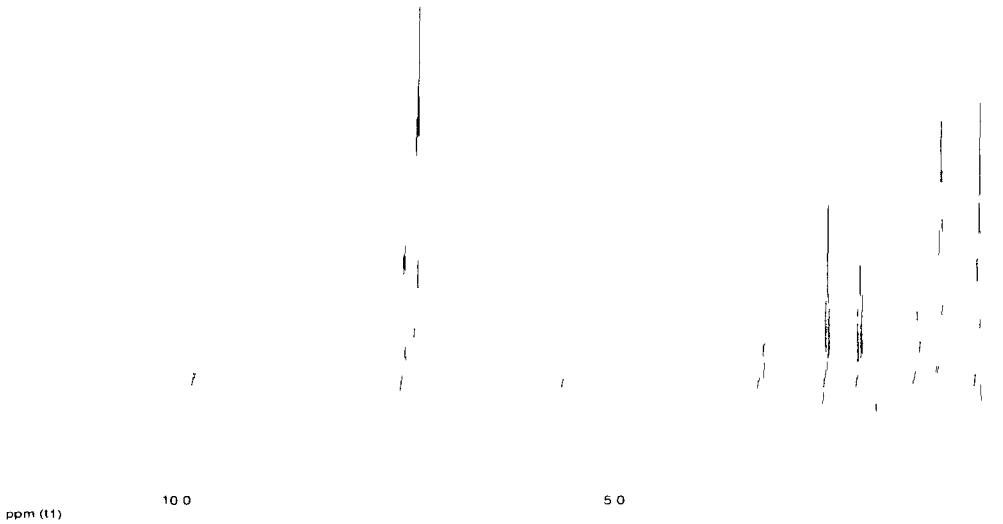
^{13}C NMR ($CDCl_3$, 300 mHz)





2.91, Table 2.25

^{1}H NMR ($CDCl_3$, 300 mHz)



^{13}C NMR ($CDCl_3$, 300 mHz)