Application of Transition Metal Catalyzed Aldehyde-Alkyne-Amine Coupling Reactions to Tandem Reaction Sequences: A Greener Approach to the Preparation of Useful Organic Compounds

By

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A thesis submitted to McGill University in partial fulfillment of the requirements for the degree of Master of Science.

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Dedication

I dedicate this thesis to my wife Samantha E. Pranteau. Her support was unwavering from the first day of undergraduate school to the final days of writing this thesis. It is also dedicated to my sister, Candace Bonfield, who inspired me to be more socially responsible with respect to sustainability issues. Improving efficiency and atom economy of reactions and eliminating entire steps along with their associated waste became the central theme of my research. I know my sister is partially responsible for this ultimate direction.

“A pessimist finds problems in every opportunity, while an optimist finds opportunity in every problem”

Winston Churchill

Abstract

Application of Transition Metal Catalyzed Aldehyde-Alkyne-Amine Coupling Reactions to Tandem Reaction Sequences: A Greener Approach to the Preparation of Useful Organic Compounds

Tandem reactions are multiple reactions occurring simultaneously in one-pot, where the product of each reaction is the substrate for the next. The hallmark of tandem reactions is a considerable increase in molecular complexity resulting from a single synthetic step. As this represents a substantial gain in efficiency and step-economy, all tandem reaction methodology represents a more sustainable, “Greener,” approach to preparing more complex organic molecules from simple precursors.

The aim of this study was to expand the two-step tandem reaction, aldehyde-alkyne-amine coupling, to include two to three additional intermolecular steps. The goal of green chemistry is for the means to justify the end, but for a proof a principle the end should also justify the means. We chose dipropargyl amines and isoindolines due to their well documented importance as synthetic precursors and biologically active compounds. We outline the development of methodology for the preparation of dipropargyl amines (**Chapter 2**) and isoindolines (**Chapter 3**) starting from simple amines, alkynes, and aldehydes in one-pot and a single synthetic operation.

Résumé

Application du couplage entre les aldéhydes, les alcynes et les amines à des réactions tandem catalysé par des métaux de transition : une approche environnementalement durable pour la préparation de composés organiques.

Les réactions tandem sont des réactions multiples qui se produisent de façon consécutive dans un seul milieu réactionnel. Le produit de chaque réaction est en fait un réactif pour la réaction suivante. Par le biais des réactions tandem, il est possible d'accéder à des molécules complexes en une seule étape synthétique. Comme elle représente un gain significatif en termes d'efficacité et d'économie synthétique, ce type de réaction représente une approche environnementalement durable pour la préparation de molécules complexes à partir de simples précurseurs.

Le but de cette thèse consiste à augmenter la complexité de la réaction tandem entre les aldéhydes, les alcynes et les amines et d'y ajouter d'autres réactifs pour augmenter le nombre d'étapes synthétiques. Le but ultime de la chimie pour le développement durable est pour les moyens de justifier la fin. Par contre, comme preuve de principe, la fin doit aussi justifier les moyens. Nous avons choisi de synthétiser des amines dipropargyliques et des isoindolines en raison de leur

importance bien documentée comme précurseurs synthétiques et comme composés biologiquement actifs. La méthodologie pour la préparation des amines dipropargyliques est développée dans le Chapitre 2 alors que la synthèse des isoindolines à partir d'aldéhydes, d'alcynes et d'amines simples (dans un seul milieu réactionnel et en une étape synthétique) est développée dans le Chapitre 3.

Acknowledgements

I would like to thank Professor Chao-Jun Li for accepting me into his group and for providing first rate guidance during my project. Also his insight and instruction during many personal meetings, in a classroom setting, and during our weekly group meetings was invaluable.

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I would also like to thank Dr. Gleason, Dr. Moitessier, Dr. Arndtsen, Dr. Damha, Dr. Perepichka, and Dr. Moores for their instruction during valuable courses and for feedback during yearly evaluations. Last, but not least I owe a debt of gratitude to all staff members in the Department of Chemistry at McGill. I especially thank Chantal Marotte, the graduate studies coordinator for her guidance and assistance in a great number of matters.

Contribution of Authors

I am the primary author of the two published manuscripts that this thesis is based on. I conducted all the experiments myself and played the major role in experimental design. I also wrote the papers. The co-author was my supervisor Chao-Jun Li. Chao-Jun Li contributed by providing feedback, advice and suggestions throughout the research project.

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With kind regards

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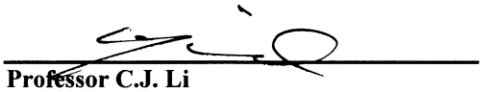

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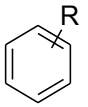
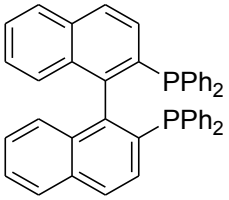
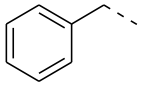
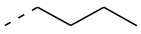
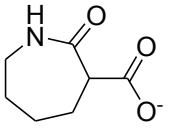
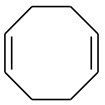
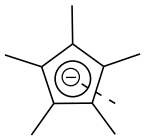
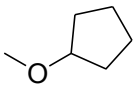
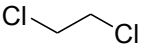
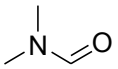
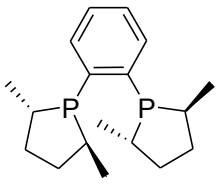
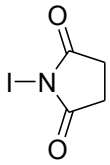
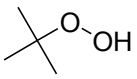
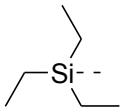
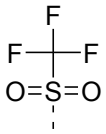
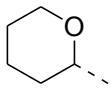
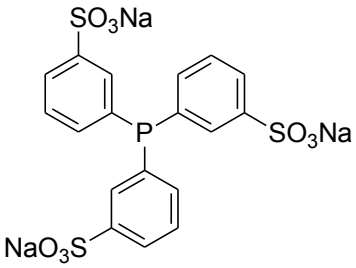
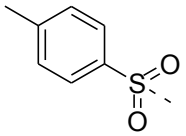
A^3	aldehyde-amine-alkyne
Ac	acetyl 
Ar	aryl (substituted aromatic ring) 
atm	atmosphere
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl 
Bn	benzyl 
Bu (^{n}Bu)	n-butyl 
◦C	degrees celcius
calcd	calculated
cap	caprolactamate 
cat.	catalytic
cm	centimetres

cod	1,5-cyclooctadiene	
Cp	cyclopentadienyl	
Cp*	pentamethylcyclopentadienyl	
CPME	cyclopentyl methyl ether	
δ	chemical shift	
DCE	dichloroethane	
DCM	dichloromethane	
DMF	dimethylformamide	
DMSO	dimethylsulfoxide	
dm	doublet of multiplets	
dt	doublet of triplets	
ddt	doublet of doublet of triplets	
MeDUPHOS	1,2-Bis[(2S,5S)-2,5-dimethylphopholano]ethane	
ee	enantiomeric excess	
equiv.	equivalents	

Et	ethyl	
h	hours	
J	coupling constant	
L	litre or ligand	
M	molecular ion, molar, or metal	
m	multiplet	
MAO	monoamine oxidases	
Me	methyl	--CH_3
MHz	megahertz	
min	minutes	
mmol	milimole	
m/z	mass/charge ratio	
NIS	N-iodosuccinimide	
NMR	nuclear magnetic resonance	
O.N.	over night	
PEA	2-phenylethylamine	
q	quartet	
rac	racemic	
Rf	retention factor	

r.t.	room temperature
s	singlet
t	triplet
tt	triplet of triplets
TBHP	tert-butyl hydrogen peroxide 
TES	triethylsilyl 
Tf	trifluoromethanesulfonyl 
THF	tetrahydrofuran 
THP	2-tetrahydropyranyl 
tppts	3,3',3''-phosphinidynetris(benzene sulfonic acid) trisodium salt 
Ts	p-toluenefulfonyl 
μL	micro litres

ν_{max} frequency of maximum absorption

Chapter 1

Introduction

1.0 Perspective: Green Chemistry

The term Green Chemistry is synonymous to sustainable chemistry. Industrial chemistry has been and continues to be a significant source of environmental damage.[1] While one important goal is to reverse the damage already done as much as possible, the aim of Green Chemistry is to significantly reduce or eliminate any further pollution. This is exemplified by methodologies that demonstrate an improvement in one or more of the twelve main principles of Green Chemistry (**Figure 1.1**).[2] A paradigm shift is already underway in the chemistry profession. Today most professionals in all branches of chemistry have some or all of the principles of Green Chemistry in mind when they develop new methodologies.[3]

This thesis describes the preparation of a couple classes of complex alkaloids starting from simple precursors such as primary amines, aldehydes, and terminal alkynes in a single step. The more obvious Green features of the synthesis to be described are the use of catalytic reagents (Principle 5, **Figure 1.1**), the avoidance of chemical derivatives (Principles 6-7, **Figure 1.1**), and the avoidance of solvent (Principle 8, **Figure 1.1**). Less obvious is how Principles 1 (waste

prevention) and 2 (increased energy efficiency) are satisfied by preparing these more complex molecules from the simple precursors via one-pot reaction cascades.

1. Prevent waste
2. Design safer chemicals and products
3. Design less hazardous chemical syntheses
4. Use renewable feedstocks
5. Use catalysts, not stoichiometric reagents
6. Avoid chemical derivatives
7. Maximize atom economy
8. Use safer solvents and reaction conditions
9. Increase energy efficiency
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

Figure 3.1: Twelve principles of green chemistry (Adapted from Anastas, P.; Warner, J. Green Chemistry: Theory And Practice, Oxford University Press, New York, 1998).

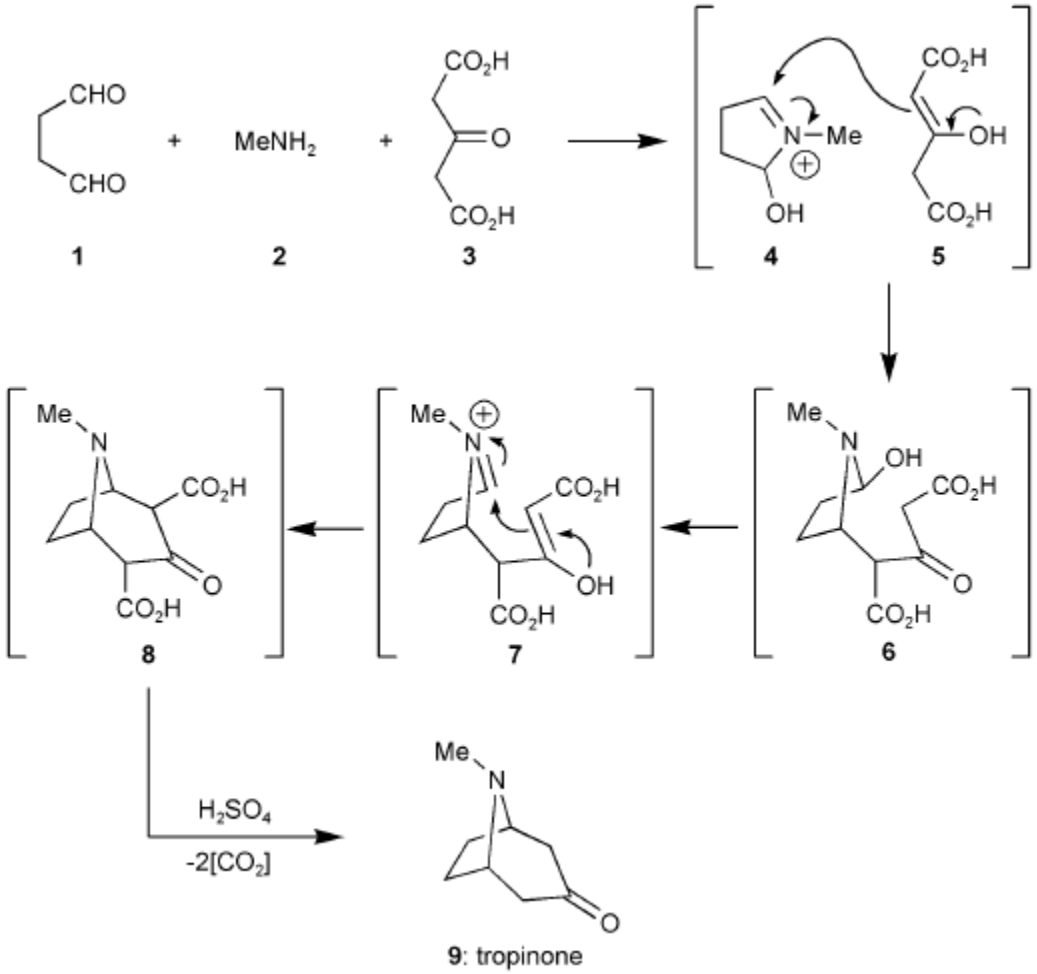
1.1 Tandem Reactions

The hallmark of tandem reactions is a considerable increase in molecular complexity resulting from a single synthetic step. Tandem reaction processes, also known as cascade or domino reactions, are defined by at least two reactions occurring in the same pot where the product of each reaction is the substrate for

the subsequent reaction. Furthermore, the conditions of a true tandem reaction process allow for the subsequent reactions to begin as soon as products of the initial reactions begin to accumulate. The reaction sequences which best lend themselves to tandem processes involve intramolecular reactions (**Scheme 1.1**), as there is no reliance on intermolecular collisions which are reduced in frequency as the reactions progress and concentrations decrease. So it is no surprise that the sequence shown in **Scheme 1.1** was one of the first demonstrations of a true tandem reaction sequence.[4] Tandem reaction methodology has received a good deal of attention over the last decade due to its inherent efficiency and step-economy.[5] The step-economy translates to reduced waste, since isolation and purification steps are avoided. Tandem reaction sequences are also time efficient and thus energy efficient. Nearly all reactions require an input of energy such as heat, ultra-violet light, microwave irradiation, and physical stirring. On industrial scales, saving even just one hour or less of reaction time can translate to substantial energy savings.

A less efficient variation of a tandem reaction is a one-pot sequential reaction. These sequential reactions are still often misnamed as tandem reactions[6]. The critical difference is that with one-pot sequential reactions, reagents or conditions required for one or more reactions in the sequence interfere with the other reactions so much that the reactions cannot occur simultaneously. Therefore,

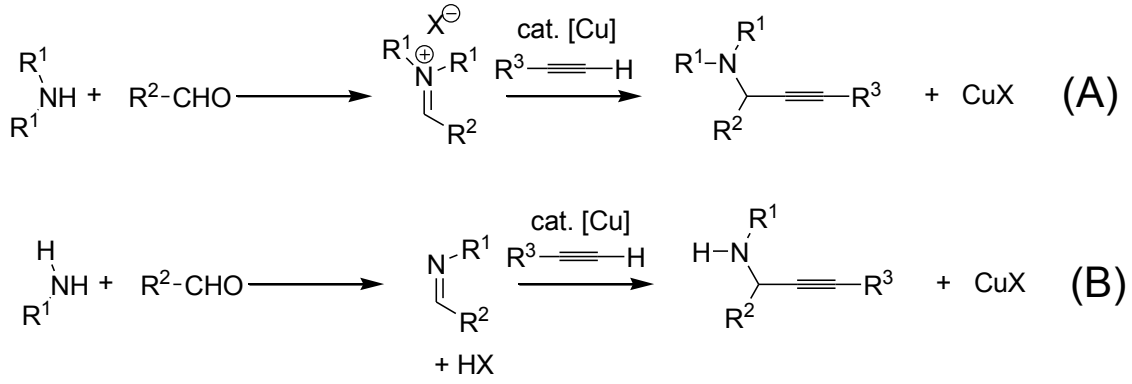
one-pot sequential reactions are more time and energy intensive. The methodologies presented in this thesis are examples of true tandem reaction sequences. Furthermore, all of these examples involve intermolecular tandem reactions with at least four individual intermolecular steps per sequence.



Scheme 1.1: Landmark tandem reaction sequence generating tropinone (**9**) from succindialdehyde (**1**), methylamine (**2**) and acetonedicarboxylic acid (**3**). (Adapted from R. Robinson, *J. Chem. Soc.*, **1917**, 762.)

1.2 Aldehyde-Amine-Akyne Coupling Reactions (A^3-Couplings)

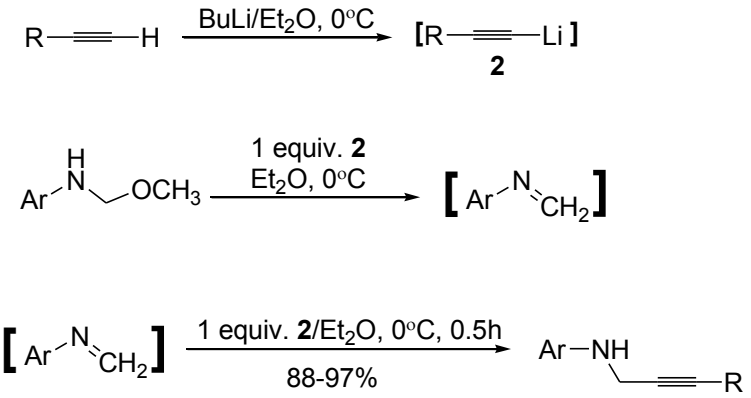
A^3-couplings are a class of reactions in which imines formed *in situ* are directly alkynylated to generate propargyl amines (**Scheme 1.2**).[7]



Scheme 1.2 : Aldehyde-amine-alkyne (A^3) coupling reactions with either secondary (A) or primary amines (B).

In this way one obtains a more complex alkaloid, a propargyl amine, from the simple precursor aldhydes, amines, and alkynes in one-pot and a single synthetic operation. Clearly A^3-couplings can be classified as tandem reactions on their own. The first step is the reaction of a primary or secondary amine with an aldehyde to form an imine or iminium ion respectively. This imine or iminium ion then serves as the substrate (electrophile) for the next step, which involves nucleophilic attack by an acetylide. The main feature of A^3-couplings that allow them to be tandem rather than one-pot sequential reactions is the use of transition metal catalysts to generate the metal acetylide *in situ*. Traditionally, reactive metal acetylides are prepared by deprotonation of terminal alkynes using

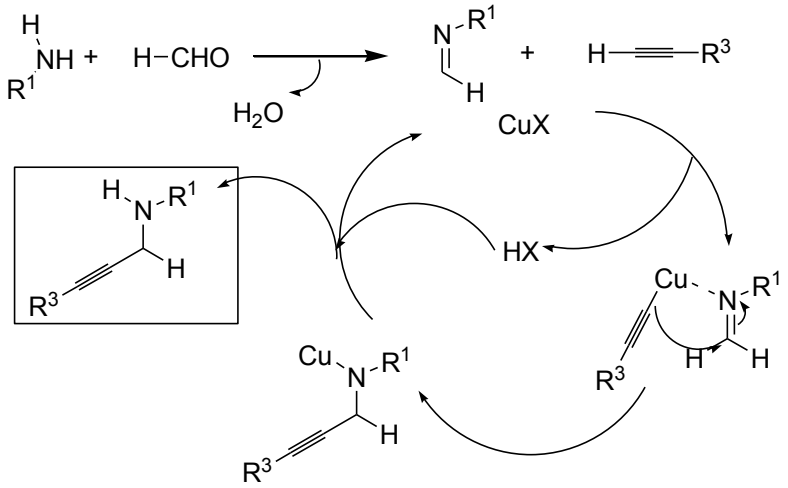
stoichiometric amounts of highly reactive organometallic reagents such as butyl lithium in a separate step (**Scheme 1.3**).[8] This alkali metal acetylide will readily react with an aldehyde or an imine and aldehydes are in fact more electrophilic than imines.[9] For this reason the imine must be pre-prepared in a separate step and then combined with the alkali metal acetylide (**Scheme 1.3**).



Scheme 1.3: Typical preparation of propargyl amine using stoichiometric alkali metal reagents and multiple steps.

Transition metal acetylides, such as copper acetylide, are much less reactive than the alkali metal acetylides and rely much more on catalytic activation of the imine.[10] Imines can be activated selectively over aldehydes and only catalytic quantities of transition metals are used, meaning no more than ten molar percent of the acetylide is present at any given time, and most often less than five molar percent. This allows for the entire process, including acetylide and imine formation, to occur simultaneously in one-pot as shown in **Scheme 1.4**. When the

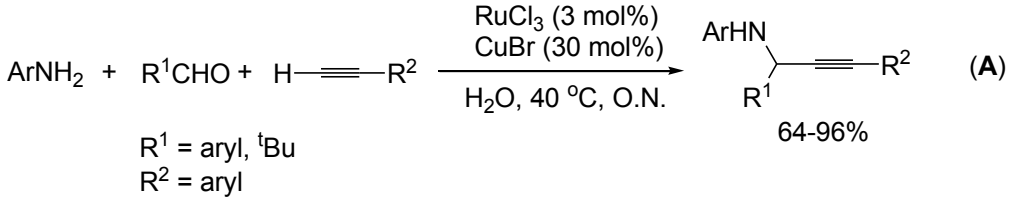
aldehyde is formaldehyde the imine is formed so rapidly and is so reactive that copper alone is sufficient to catalyze the A^3-coupling reaction (**Scheme 1.4**).[11] Likewise when secondary amines are used as substrates, a positively charged iminium ion is formed (**Scheme 1.2 (A)**) which is electrophilic enough to react with transition metal acetylides without any additional electrophilic activation.[12]

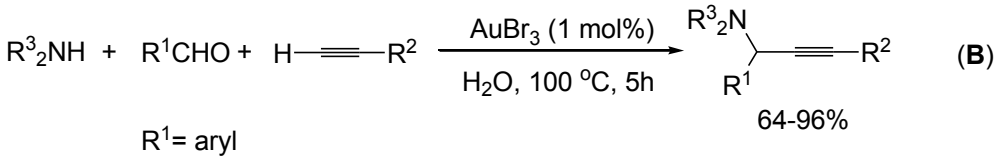


Scheme 1.4: General mechanism for aldehyde-alkyne-amine coupling reactions involving formaldehyde.

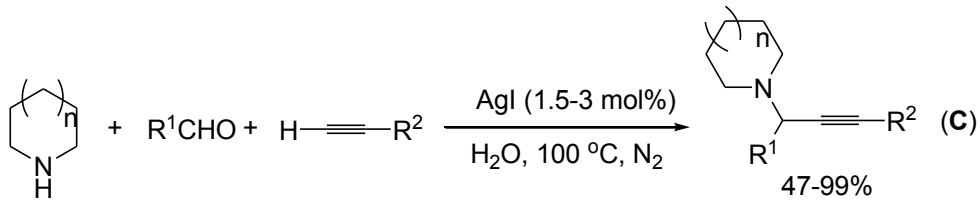
When primary amines are used with aromatic aldehydes, however, copper alone is insufficient to activate the imine and ruthenium (III) must be added as a co-catalyst for increased electrophilic activation (**Scheme 1.5A**).[13] When secondary amines were used as substrates with aliphatic or aromatic aldehydes it was found that gold (III) bromide could be used in quantities as low as 0.25mol% while still achieving yields as high as 99% (**Scheme 1.5B**).[14] With gold (III)

catalysis, yields were significantly lower when using aliphatic aldehydes due to trimerization. Silver (I) iodide was also effective for A^3-couplings involving secondary cyclic amines, but allowed for a wider range of aliphatic aldehydes to be added to the substrate scope (**Scheme 1.5C**).[15] Furthermore, the reactions were actually cleaner and more efficient with the aliphatic substrates. Since the gold catalysis showed improved reactivity with aryl aldehydes, the two catalysts complement one another. No product could be obtained using primary amines with gold or silver catalysis, making ruthenium and copper also a complementary system.





R^1= aryl
R^1 = alkyl (lower yield due to trimerization of aldehyde)
R^2 = aryl, alkyl, SiMe$_3$
R^3 = allyl, benzyl, or cyclic amine (piperidine)



R^1= aryl (longer reaction times and lower conversion and yield)
R^1 =alkyl (higher reactivity and cleaner reactions)
R^2= aryl, TES

Scheme 1.5: Complementary catalysts for a wide A^3-coupling substrate scope.

1.3 Overview of Thesis

The products of A^3-coupling reactions, propargyl amines, are themselves suitable substrates for a second A^3-coupling. The resulting products, dipropargyl amines, have demonstrated potential as biologically active molecules and have been extensively used as synthetic precursors. We first looked at the possibility of generating dipropargyl amines directly from aldehydes, amines, and alkynes via a four step tandem reaction sequence.[16] We examined the efficiency and scope of this reaction sequence. Once this first stage was established we considered the known uses of dipropargyl amines as substrate for additional reactions. A major example is in the area of [2 + 2 + 2] cycloaddition reactions. The isoindoline framework formed from a [2 + 2 + 2] cycloaddition reaction between a dipropargyl amine and an alkyne has demonstrated applications in pharmaceutical and other industrial settings. This seemed like a worthy target for a five step tandem reaction sequence. We examined whether tetra substituted isoindolines could be prepared from simple aldehydes, amines, and alkynes in one-pot and a single synthetic operation.[17] The scope and efficiency of this more complex, intermolecular tandem reaction sequence was examined in detail.

1.4 References

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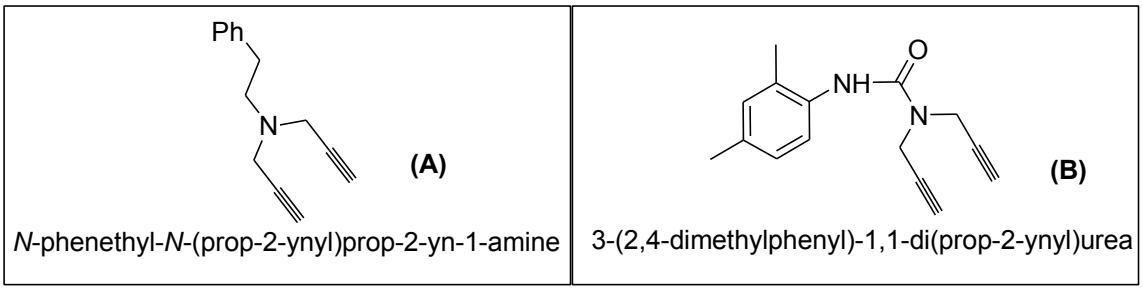
Chapter 2

Tandem Reaction Methodology Applied to the Preparation of Dipropargyl Amines

2.0 Introduction

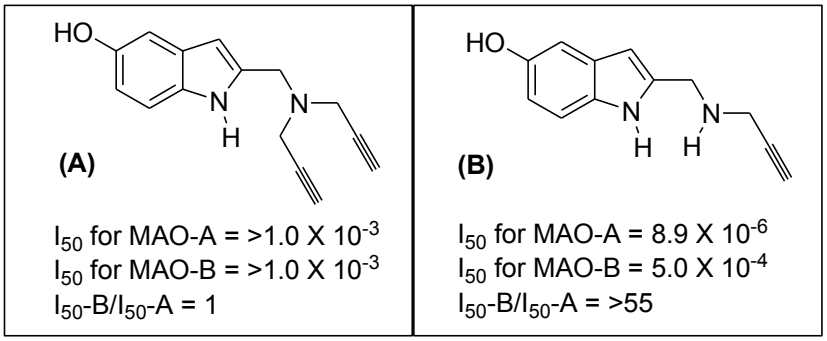
Propargyl amines are precursors of biologically active compounds. For example, N-phenethyl-N-(prop-2-ynyl)prop-2-yn-1-amine (**Figure 2.1 (A)**) is a prodrug of 2-phenylethylamine (PEA) which functions as a neuromodulator.[1] Monoamine oxidase inhibiting antidepressant drugs such as tranylcypromine and phenelzine cause marked elevations in PEA levels in experimental animals and in depressed patients.[2] Another example is a close derivative of a dipropargyl amine, 3-(2,4-dimethylphenyl)-1,1-di(prop-2-ynyl)urea (**Figure 2.1 (B)**), which inhibits acyl CoA:cholesterol 0-acyltransferase, thus reducing intracellular esterification of cholesterol.[3] Intracellular accumulation of esterified cholesterol is one of the distinctive features of an atherosclerotic plaque.[4]



N-phenethyl-*N*-(prop-2-ynyl)prop-2-yn-1-amine | 3-(2,4-dimethylphenyl)-1,1-di(prop-2-ynyl)urea

Figure 2.1: Dipropargyl amines are precursors to biologically active molecules.

The biological activity of a dipropargyl amine can differ significantly from the analogous compound with a monopropargyl amine substructure. For example the concentration of 2-((diprop-2-ynylamino)methyl)-1H-indol-5-ol (**Figure 2.2A**) required to inhibit fifty percent (I_{50}) of the monoamine oxidases A and B (MAO-A and MAO-B) is substantially different than the analogous monopropargyl amine (**Figure 2.2B**).[5] In this case the monopropargyl amine is more active and selective than the dipropargyl amine, but the proof of principle is demonstrated.

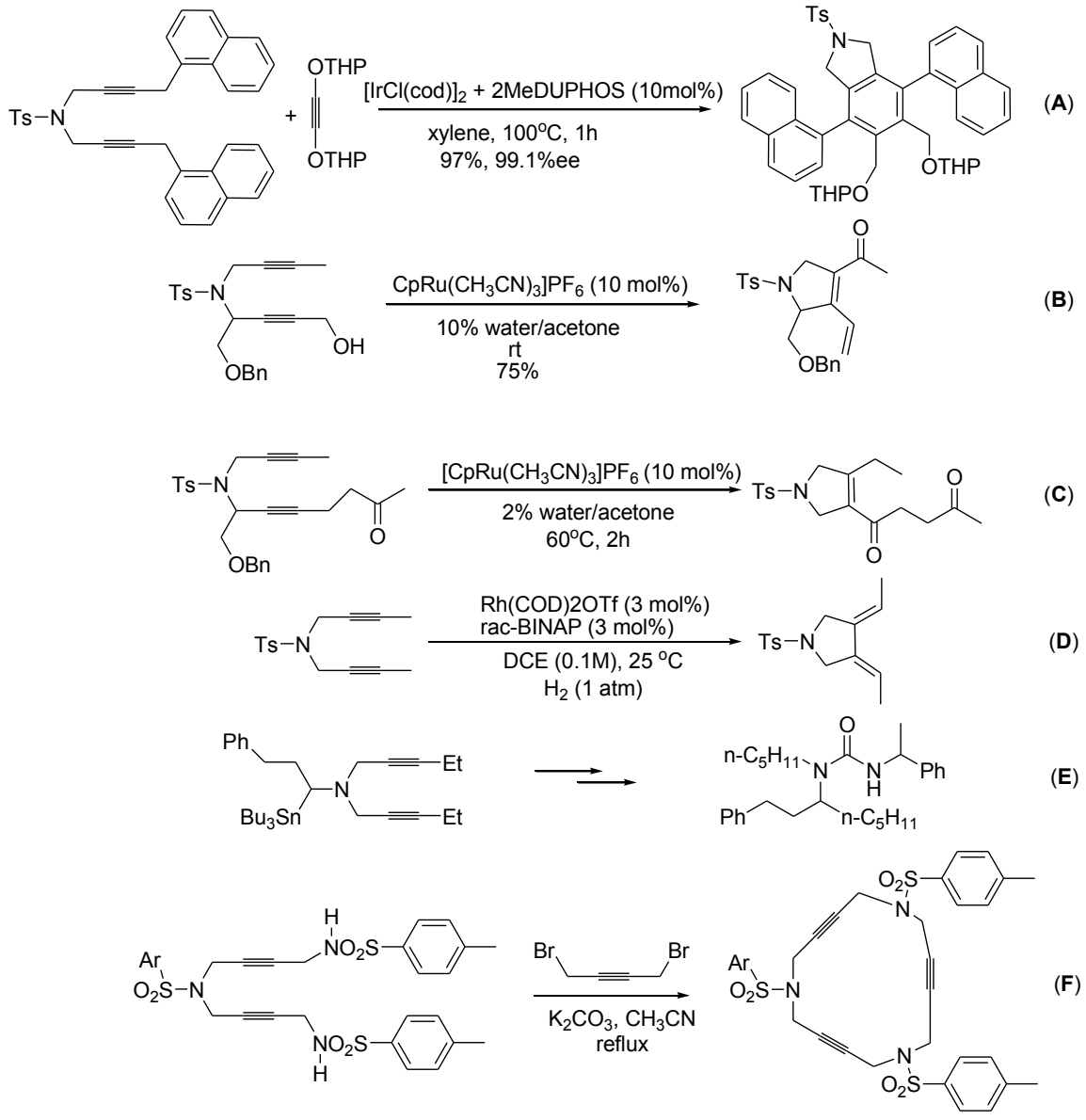


I_{50} for MAO-A = >1.0 X 10^{-3}
I_{50} for MAO-B = >1.0 X 10^{-3}
I_{50}-B/I_{50}-A = 1

I_{50} for MAO-A = 8.9 X 10^{-6}
I_{50} for MAO-B = 5.0 X 10^{-4}
I_{50}-B/I_{50}-A = >55

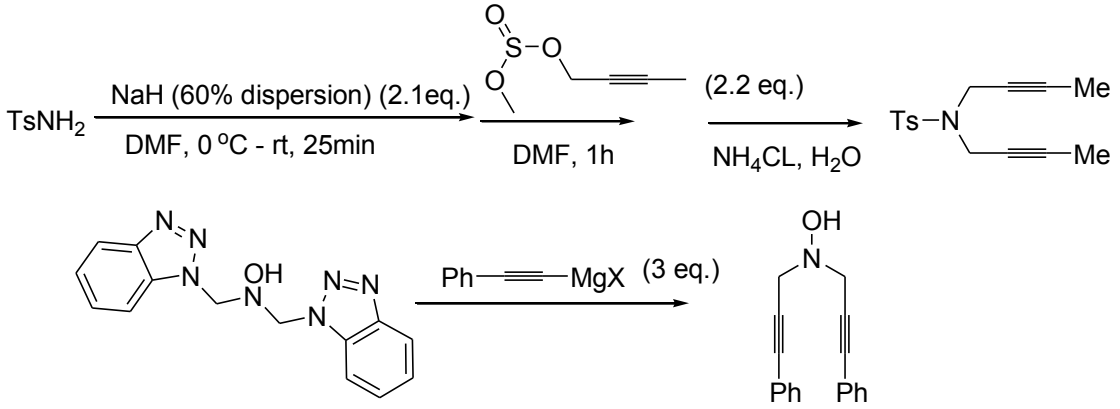
Figure 2.2: Example of a monopropargyl amine with substantially different activity and selectivity for biological targets than its dipropargyl amine counterpart.

Perhaps the most noteworthy feature of dipropargyl amines and their close derivatives are their potential use as substrates for a variety of synthetic transformations. For example, various types of cycloaddition (**Scheme 2.1A**)[6] and cycloisomerization (**Scheme 2.1B**)[7] reactions, hydrative (**Scheme 2.1C**)[8] and reductive (**Scheme 2.1D**)[9] cyclizations, aza-Wittig rearrangements (**Scheme 2.1E**)[10], and macrocycle synthesis (**Scheme 2.1F**)[11].



Scheme 2.1: Propargyl amines and their derivatives as synthetic precursors.

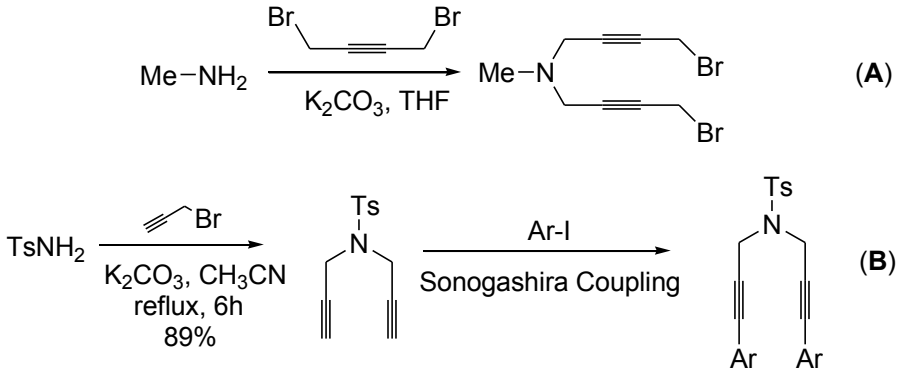
Yet, despite their widespread use, currently reported methods for the synthesis of dipropargyl amines have serious limitations. For example, the use of highly reactive bases such as sodium hydride or organometallic reagents in a separate step limits the efficiency (**Scheme 2.2**).[12]



Scheme 2.2: Conventional dipropargyl amine preparations using stoichiometric metal reagents.

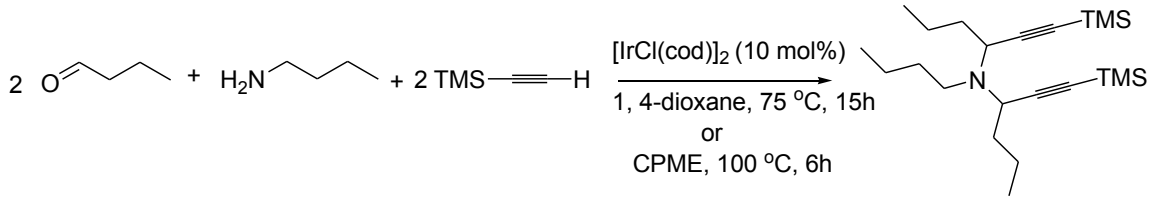
A more common alternative has been to use propargyl bromides directly (**Scheme 2.3**)[13], but most would also have to be pre-prepared in a separate step as few are commercially available. More common, commercially available, propargyl bromides have been used followed by a second step to further functionalize the dipropargyl amine (**Scheme 2.3B**).[14] Another problem with this

methodology is that the amine must be acidic enough to be deprotonated in order to react with a propargyl bromide. This explains why there is a prevalence of tosyl substituted dipropargyl amines being used as substrates in current literature (**Scheme 2.1**). The tosyl group is strongly electron withdrawing, imparting increased acidity to the amine group.



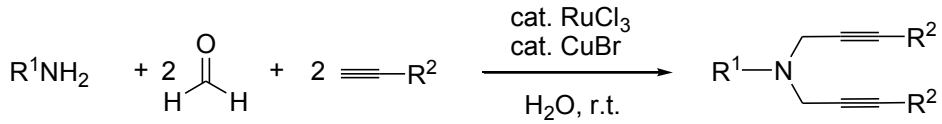
Scheme 2.3: Use of commercially available propargyl bromides for dipropargyl amine preparation.

Ishii *et al.* recently reported an iridium catalyzed five component coupling leading directly to dipropargyl amines (**Scheme 2.4**).[15] Yet, with this system the terminal alkyne is limited to trimethylsilylacetylene and 1,4-dioxane or cyclopentyl methyl ether were required as solvents at temperatures exceeding 75 ºC for up to 15 h to get satisfactory yields.



Scheme 2.4: Iridium catalyzed five component coupling leading directly to dipropargyl amines

We developed the use of a ruthenium–copper cocatalyzed five component double A^3-coupling to synthesize dipropargyl amines from a range of simple amines, aldehydes, and alkynes in one pot under mild conditions in water (**Scheme 2.6**).



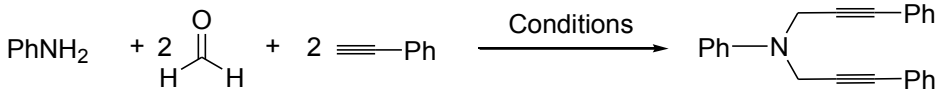
Scheme 2.5: Double A^3-coupling in one pot under mild conditions in water.

2.1 Results and Discussion

Initial screening of reaction conditions showed that increasing the reaction temperature can substantially decrease the yield (**Table 2.1, entries 1–2, 4–6**), indicating that side reactions are a problem. At 60 ºC the yield is slightly better in toluene compared to water, whereas at room temperature, with increased reaction time, the opposite is true (**Table 2.1, entries 4, 7, 10–11**). This could

indicate that hydrolysis of one or both of the imine intermediates is a major side reaction in water, which is enhanced by temperature substantially more than the desired A^3-coupling. The exclusion of oxygen from the reaction did not improve the yield (Table 2.1, entry 3) indicating that the Glaser-type alkyne coupling was not an important side reaction. When the reaction was performed neat at room temperature, the yield was increased considerably (**Table 2.1, entries 1–2**). This could indicate that even at room temperature imine hydrolysis is still a problem. The water in the neat examples comes from the formaldehyde solution, yet the A^3-coupling becomes more competitive over imine hydrolysis because there is now almost double the number of equivalents of alkyne relative to water. Increased temperature under these pseudo-neat conditions substantially decreased the yield (**Table 2.1, entry 2**). The conditions of entry 7 were used in preference to the neat conditions since it was not practical to perform the reaction neat with only 2.2 equivalents of alkyne due to insufficient mixing/stirring. Increasing the ruthenium catalyst loading to almost double can give an appreciable increase in yield, but whether or not this increased expense is worth an increase in yield of 8% is questionable. Optimum yield was obtained after reacting between 24–36 h at room temperature (**Table 2.1, entries 6–8**), and therefore lower temperatures were not attempted.

Table 2.1 Optimization of conditions for the double A3-coupling[a]



Entry	Catalyst Loading	Solvent	Temp/time	Yield (%)[b]
1	$RuCl_3$ (6%), CuBr (15%)	Neat[c]	rt / 20 h	82
2	$RuCl_3$ (7%), CuBr (18%)	Neat[c]	60 ∘C / 20 h	62
3	$RuCl_3$ (6%), CuBr (15%)	H_2O[d]	60 ∘C / 20 h	54
4	$RuCl_3$ (5%), CuBr (15%)	H_2O	60 ∘C / 19 h	53
5	$RuCl_3$ (6%), CuBr (17%)	H_2O	100 ∘C / 19 h	30
6	$RuCl_3$ (7%), CuBr (15%)	H_2O	rt / 24 h	61
7	$RuCl_3$ (5%), CuBr (16%)	H_2O	rt / 36 h	70
8	$RuCl_3$ (5%), CuBr (15%)	H_2O	rt / 61 h	60
9	$RuCl_3$ (10%), CuBr (17%)	H_2O	rt / 20 h	78
10	$RuCl_3$ (6%), CuBr (15%)	Toluene	rt / 36 h	64
11	$RuCl_3$ (6%), CuBr (18%)	Toluene	60 ∘C / 20 h	60

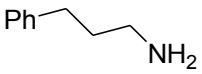
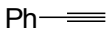
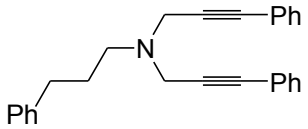
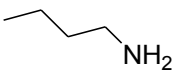
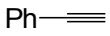
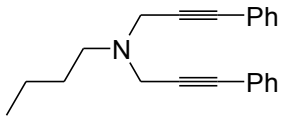
[a] 75 μL (0.82 mmol) aniline, 200 μL (1.8 mmol) phenylacetylene, 135 μL (1.8 mmol at 37 wt% in H_2O) formaldehyde, and 500 μL water were sealed in a tube containing the specified mol% of $RuCl_3$ and CuBr based on the moles of aniline

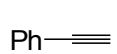
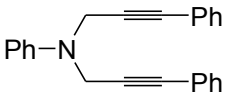
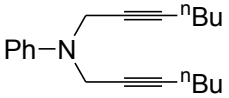
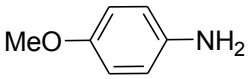
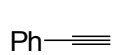
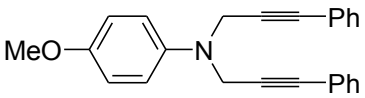
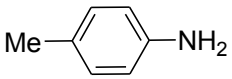
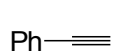
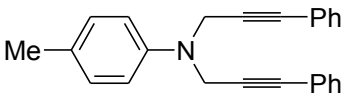
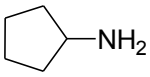
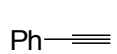
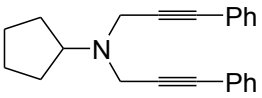
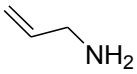
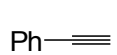
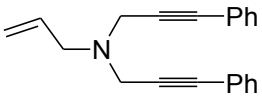
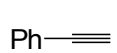
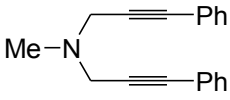
and agitated for the time specified. [b] Yields based on NMR internal standard mesitylene. [c] 10 equivalents (900 μL) phenylacetylene used (reaction not strictly neat since 93 μL H_2O present from the 37 wt% formaldehyde).[d] Solids were sealed in a tube which was subsequently purged with nitrogen (liquids were degassed together by three freeze–pump–thaw cycles before transferring to solids under nitrogen by cannula).

With optimized conditions (**Table 2.1, entry 7**) various substrates were examined. The yield was only modestly reduced upon using an aliphatic alkyne instead of phenylacetylene (Table **2.2, entries 3–4**). The yield, however, was highly dependent upon the nature of the primary amine used. This substantiates the possibility that imine stability/hydrolysis is a critical factor influencing the yields. The linear aliphatic amines used gave the best yields (**Table 2.2, entries 1–2**). However, methyl amine gave the lowest yield (**Table 2.2, entry 9**), which could indicate that all or part of the reaction cycle occurs on the water surface since the propargyl amine/imine intermediates as well as methyl amine itself would be more soluble in water than any of the other corresponding amines/imines. The concept of “on water” reactions is well documented.[16] The lower yield seen with cyclopentylamine (**Table 2.2, entry 7**) is likely the result of steric effects; whereas, allylamine could have undergone side reactions specific to the alkene

functionality. Solid amines can be used directly even though the system was heterogeneous for all the reactions (**Table 2.2, entries 5–6**). A direct comparison of *para*-anisidine and *para*-toluidine shows that electron donation to the nitrogen improves the yield. Whether this is due to increased stability of the imine to hydrolysis is unclear. When formaldehyde was substituted with benzaldehyde in the reaction shown in **Table 2, entry 3**, only the monopropargyl amine coupling product was observed. This is likely, due to the increased steric bulk of the monopropargyl amine product. Increasing the temperature could possibly lead to the formation of product, but it would be a mixture of diastereomers. For this reason we made no exhaustive attempts to develop this methodology for use with more complex aldehydes.

Table 2.2: Synthesis of bis-propargyl amines via [Ru]-[Cu] catalyzed double A^3-coupling[a]

Entry	Amine	Alkyne	Product	Yield (%)[b]
1				84 (82)
2				79 (78)

3	$PhNH_2$			70 (62)
4	$PhNH_2$			63 (53)
5				63 (51)
6				47 (44)
7				45 (45)
8				60 (59)
9	$MeNH_2$			15

[a] Conditions used based on entry 7 in Table 1. All reactions were performed at 0.82 mmol scale with 2.2 equiv. alkyne, 2.2 equiv. formaldehyde, 5 mol% $RuCl_3$, 15 mol% CuBr, 500 μL H_2O, agitated at room temperature (22 ◦C) for 36 h; [b] Yields based on NMR with an internal standard (mesitylene) and isolated yields after column chromatography (50:1 hexanes : EtOAC) in parentheses.

2.2 Conclusion

We demonstrated a substantial improvement upon the current methodology for the preparation of dipropargyl amines. The usual two-three steps have been reduced to a single synthetic operation and the avoidance of alkali metal reagents has allowed for the reaction to be carried out in water. Additionally, the application of tandem A^3-couplings to the preparation of dipropargyl amines has significantly expanded the scope. To date, tosyl-substituted dipropargyl amines have been prevalent due the amenability of the highly electron withdrawing tosyl group to conventional methodology. Tandem A^3-couplings extend the scope to include a wide range of aliphatic and aromatic substitutions on the nitrogen and alkyne moiety of the dipropargyl amine. The use of dipropargyl amines as substrates in current synthetic research efforts is widespread. This methodology should greatly facilitate these efforts.

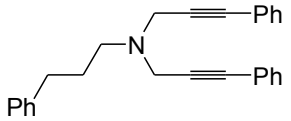
2.3 Experimental Section

All reactions were done on a 0.82 mmol scale with 2.2 equivalents alkyne, 2.2 equivalents formaldehyde, 5 mol% $RuCl_3$, 15mol% CuBr, and 500μL H_2O. The reagents were manipulated open to air and agitated at room temperature (22°C) for 36 hours. The reaction was considered complete when a spot corresponding

to the monopropargyl amine was no longer visible by TLC. The NMR spectra were recorded with a Varian spectrometer (400 and 100MHz for ^{1}H and ^{13}C respectively). IR spectra were recorded by an ABB Bomem MB100 spectrometer. High resolution mass spectra were obtained by a Kratos MS25RFA Mass Spectrometer at McGill University.

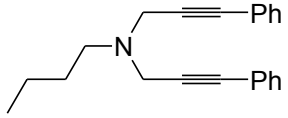
Spectral Data

3-Phenyl-N-(3-phenylprop-2-ynyl)-N-(3-phenylpropyl)prop-2-yn-1-amine (Table 2.2 entry 1)



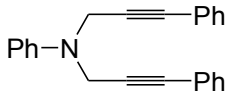
Purification by column chromatography (0-5% EtOAC gradient, R_f 0.3 in 9:1 hexanes:EtOAC) to get pale yellow oil; IR (neat) ν_{max} 3026, 2942, 2246, 1598, 1489, 1453, 1442, 1350, 1324cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42-7.40 (m, 4H), 7.27-7.13 (m, 11H), 3.71 (s, 4H), 2.72-2.67 (m, 4H), 1.89 (tt, J = 7.5, 7.5Hz, 2H); ^{13}C NMR (400MHz, $CDCl_3$) δ 141.9, 131. 6, 128.3, 128.2, 128.1, 128.0, 125.7, 123.0, 85.1, 84.6, 52.3, 43.2, 33.4, 29.0; HRMS *m/z* calcd for $C_{27}H_{24}N$ ($M-H^{+}$) 362.19087, found 362.19010

N,N-Bis(3-phenylprop-2-ynyl)butan-1-amine (Table 2.2, entry 2)



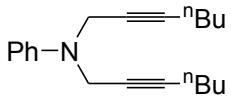
Purification by column chromatography (99:1 hexanes:EtOAC, R_f 0.4 in 9:1 hexanes:EtOAC) to get pale yellow oil; IR (neat) ν_{max} 3033, 2956, 2931, 2059, 1598, 1489, 1442, 1359, 1324cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.49-7.44 (m, 4H), 7.32-7.29 (m, 6H), 3.74 (s, 4H), 2.70 (t, J = 7.4Hz, 2H), 1.62-1.54 (m, 2H), 1.43 (tt, J = 7.4, 7.4Hz 2H), 0.98 (t, J = 7.2Hz, 3H); ^{13}C NMR (400MHz, $CDCl_3$) δ 131.8, 128.3, 128.1, 123.3, 85.1, 84.9, 53.0, 43.4, 29.8, 20.7, 14.1; HRMS *m/z* calcd for $C_{22}H_{22}N$ (M-H$^+$) 300.17522, found 300.17502.

N,N-Bis(3-phenylprop-2-ynyl)benzenamine (Table 2.2, entry 3)



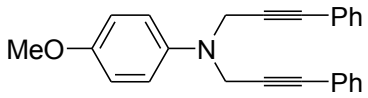
Purification by column chromatography (0-1% EtOAC gradient, R_f 0.5 in 9:1 hexanes:EtOAC) to get pale yellow oil; IR (neat) ν_{max} 3060, 2235, 1682, 1597, 1504, 1489, 1442, 1346, 1224cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.40-7.36 (m, 4H), 7.33-7.20 (m, 8H), 7.07-7.04 (m, 2H), 6.88 (tt, J = 7.2, 1.0Hz, 1H), 4.38 (s, 4H); ^{13}C NMR (400MHz, $CDCl_3$) δ 148.3, 131.9, 129.2, 128.3, 128.3, 123.1, 119.6, 116.0, 85.2, 84.7, 41.5; HRMS *m/z* calcd for $C_{24}H_{18}N$ (M-H$^+$) 320.14392, found 320.14360.

N,N-Di(hept-2-ynyl)benzenamine (Table 2.2, entry 4)



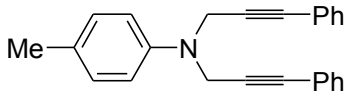
Purification by column chromatography (0-1% EtOAC gradient, R_f 0.7 in 9:1 hexanes:EtOAC) to get colourless oil; IR (neat) ν_{max} 2957, 2932, 2230, 1600, 1504, 1456, 1366, 1328, 1221cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.27-7.23 (m, 2H), 6.95 (d, J = 6.6, 2H), 6.83 (t, J = 7.2Hz, 1H), 4.06 (t, J = 2.0Hz, 4H), 2.18-2.14 (m, 4H), 1.49-1.32 (m, 8H), 0.88 (t, J = 7.4Hz, 6H); ^{13}C NMR (400MHz, $CDCl_3$) δ 148.5, 128.9, 119.0, 115.8, 84.7, 75.5, 40.7, 30.8, 21.9, 18.4, 13.6; HRMS *m/z* calcd for $C_{20}H_{26}N$ (M-H$^+$) 280.20652, found 280.20633.

4-Methoxy-N,N-bis(3-phenylprop-2-ynyl)benzenamine (Table 2.2, entry 5)



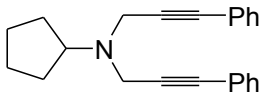
Purification by column chromatography (0-2% EtOAC gradient, R_f 0.3 in 9:1 hexanes:EtOAC) to get pale yellow oil; IR (neat) ν_{max} 3055, 2932, 2833, 2189, 1735, 1598, 1511, 1489, 1442, 1246, 1028cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.40-7.34 (m, 4H), 7.29-7.22 (m, 6H), 7.09-7.05 (m, 2H), 6.90-6.84 (m, 2H), 4.30 (s, 4H), 3.76 (s, 3H); ^{13}C NMR (400MHz, $CDCl_3$) δ 154.2, 142.7, 131.8, 128.2, 128.1, 123.0, 119.3, 114.4, 85.1, 84.9, 55.5, 42.6; HRMS *m/z* calcd for $C_{25}H_{21}NO$ (M$^+$) 351.16231, found 351.16095, for $C_{25}H_{20}NO$ (M-H$^+$) 350.15449, found 350.15396.

4-Methyl-N,N-bis(3-phenylprop-2-ynyl)benzenamine (Table 2.2, entry 6)



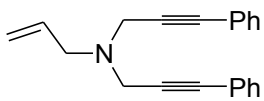
Purification by column chromatography (0-1% EtOAC gradient, R_f 0.4 in 9:1 hexanes:EtOAC) to get yellow oil; IR (neat) ν_{max} 3032, 2920, 2233, 1616, 1598, 1519, 1489, 1442, 1366, 1335, 1233, 1207, 1155, 1070, 1028cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39-7.34 (m, 4H), 7.26-7.20 (m, 6H), 7.11-7.08 (m, 2H), 6.98 (dt, J = 8.4, 2.2Hz, 2H), 4.34 (s, 4H), 2.27 (s, 3H); ^{13}C NMR (400MHz, $CDCl_3$) δ 146.0, 131.7, 129.6, 129.1, 128.1, 128.0, 123.0, 116.5, 85.1, 84.5, 41.7, 20.4; HRMS *m/z* calcd for $C_{25}H_{21}NO$ (M-H$^+$) 334.15957, found 334.15913.

N,N-Bis(3-phenylprop-2-ynyl)cyclopentanamine (Table 2.2, entry 7)



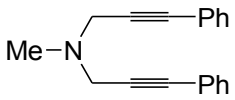
Purification by column chromatography (1-2% EtOAC gradient, R_f 0.3 in 9:1 hexanes:EtOAC) to get colourless oil; IR (neat) ν_{max} 3055, 2956, 2869, 2805, 2246, 1598, 1489, 1442, 1349, 1324, cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43 (s, 4H), 7.28 (d, J = 2.8Hz, 6H), 3.82 (s, 4H), 3.03 (tt, J = 8.0, 8.0Hz, 1H), 2.04-1.93 (m, 2H), 1.8-1.72 (m, 2H), 1.66-1.44 (m, 4H); ^{13}C NMR (400MHz, $CDCl_3$) δ 131.7, 128.1, 127.9, 123.2, 84.9, 84.8, 62.9, 42.1, 31.4, 24.0; HRMS *m/z* calcd for $C_{23}H_{22}N$ (M-H$^+$) 312.17522, found 312.17495.

N,N-Bis(3-phenylprop-2-ynyl)prop-2-en-1-amine (Table 2.2, entry 8)



Purification by column chromatography (0-1% EtOAC gradient, R_f 0.2 in 9:1 hexanes:EtOAC) to get colourless oil; IR (neat) ν_{max} 3079, 2918, 2813, 2228 1598, 1489, 1442, 1363, 1326, 1252, 1108 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.47-7.42 (m, 4H), 7.30-7.27 (m, 6H), 5.92 (ddt, J = 17.2, 10.4, 6.8Hz, 1H), 5.35 (ddt, J = 17.2, 1.6, 1.6Hz, 1H), 5.22 (dm, J = 10.0Hz, 1H), 3.72 (s, 4H), 3.32 (dt, J = 6.8, 1.2Hz, 2H); ^{13}C NMR (400MHz, $CDCl_3$) δ 135.0, 131.8, 128.3, 128.1, 123.1, 118.8, 85.3, 84.6, 56.5, 42.9; HRMS *m/z* calcd for $C_{21}H_{18}N$ ($M\text{-}H^+$) 284.14392, found 284.14370.

N-Methyl-3-phenyl-N-(3-phenylprop-2-ynyl)prop-2-yn-1-amine (Table 2.2, entry 9)



Purification by column chromatography (0-5% EtOAC gradient, R_f 0.5 in 7:3 hexanes:EtOAC) to get orange oil; IR (neat) ν_{max} 3056, 2944, 2866, 2790, 2195, 1598, 1489, 1442, 1361, 1326 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$) δ 7.48-7.46 (m, 4H), 7.33-7.30 (m, 6H), 3.67 (s, 4H), 2.53 (s, 3H); ^{13}C NMR (400MHz, $CDCl_3$) δ 131.7, 128.3, 128.1, 123.1, 85.3, 84.5, 45.6, 41.5; HRMS *m/z* calcd for $C_{19}H_{16}N$ ($M\text{-}H^+$) 258.12827, found 258.12850.

2.4 References

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Chapter 3

One-Pot Six-Component Synthesis of Tetrasubstituted Isoindolines

3.0 Introduction

The conversion of primary amines, aldehydes, and alkynes to isoindolines in a single synthetic operation is without precedent. This methodology has potential for application to the efficient and economical preparation of compounds with industrial and pharmaceutical importance. The ability of an isoindoline to act as a diuretic 100 times more active than chlorothiazide was reported over four decades ago (**Figure 3.1**).[1]

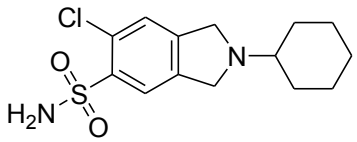


Figure 3.1: Isoindoline discovered in 1963 with diuretic activity.

The first anti-tumour activity for an isoindoline derivative was discovered nearly three decades ago (**Figure 3.2**).[2]

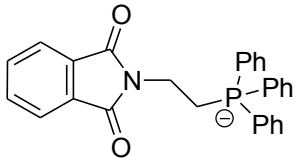


Figure 3.2: Isoindoline derivative discovered in 1977 with substantial activity in a P-388 lymphocytic leukemia screen.

In the decades to follow so many reports of various biological activities of isoindolines emerged that a comprehensive summary is beyond the scope of this thesis. The most recent reports show herbicidal activity (**Figure 3.3A**),[3] dipeptidyl peptidase inhibition (**Figure 3.3B**),[4] antagonism of the 5-HT_{2C} receptor (**Figure 3.3C**),[5] treatment of cutaneous lupus (**Figure 3.3D**),[6] metabotropic glutamate receptor potentiator activity (**Figure 3.3E**),[7] and treatment of cancer (**Figure 3.3F**),[8] or abnormal cell growth (**Figure 3.3G**).[9]

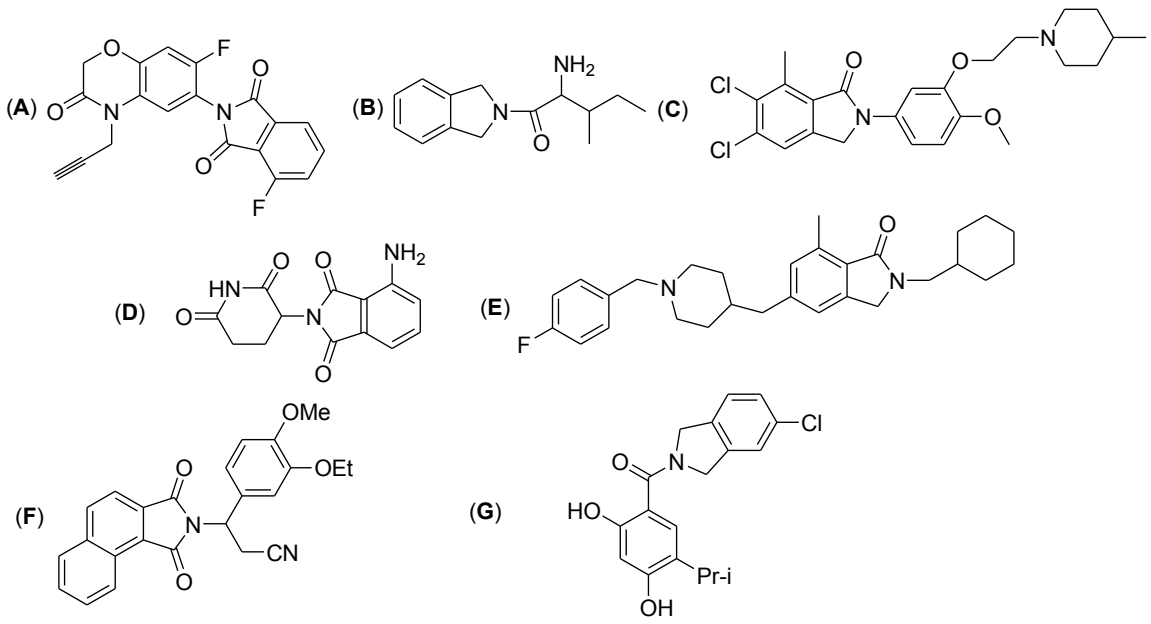
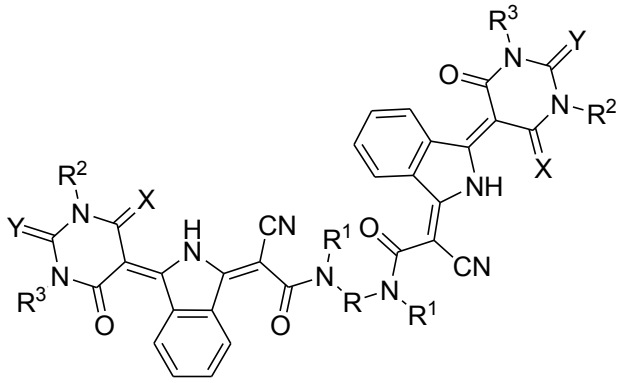


Figure 3.3: Biologically active isoindoline derivatives.

Reports of the use of isoindolines as key components of pigment compositions also continue to emerge (**Figure 3.4**).[10] Isoindolines have been recently shown to be active ingredients in the natural commercial drug ant lion (**Figure 3.5**).[11] Isoindolines have also found use as novel spin probes useful for studying cancer (**Figure 3.6**).[12] A number of the active compounds shown here are isoindoline 1-ones or 1,3-diones, which can be generated by oxidation of the benzylic positions (**Scheme 3.1**).[13]



R = linking group; R1 = H, C1-4 alkyl, Ph, Me- or halo-substituted Ph; X = O, NH; Y = O, S, NH

Figure 3.4: Recently patented pigment with isoindoline cores.

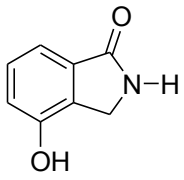


Figure 3.5: Natural, biologically active isoindoline-1-one derivative isolated from ant lion

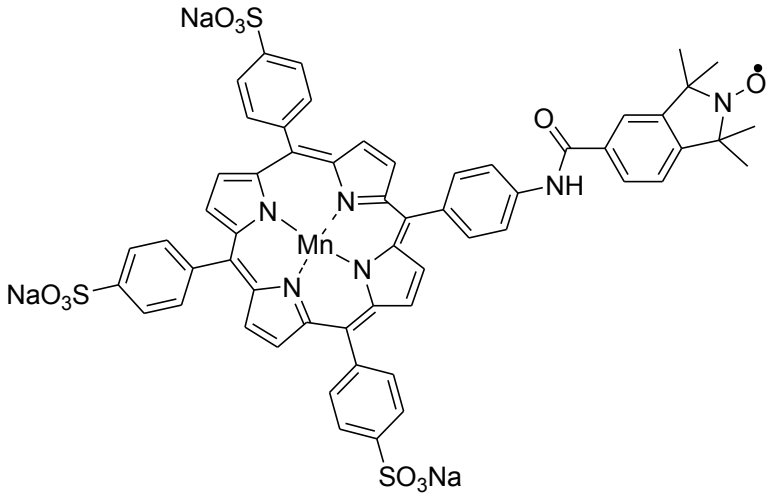
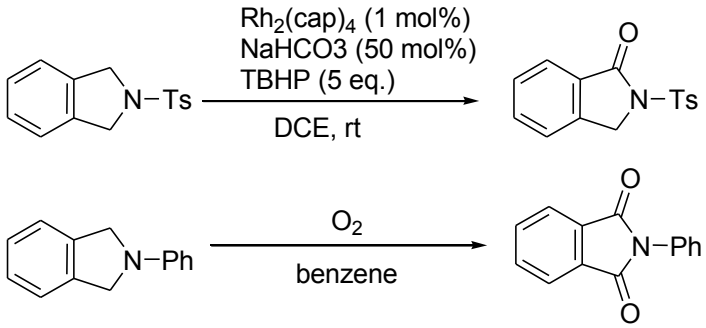
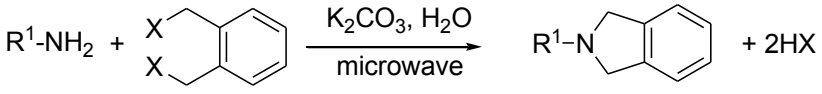


Figure 3.6: Spin-labelled porphyrins containing isoindoline nitroxide

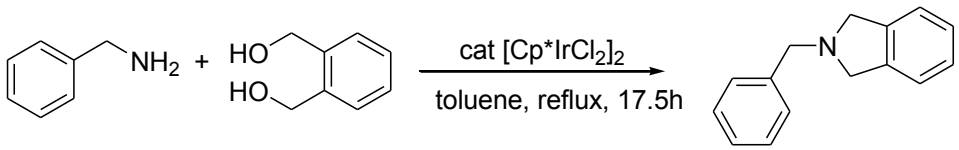


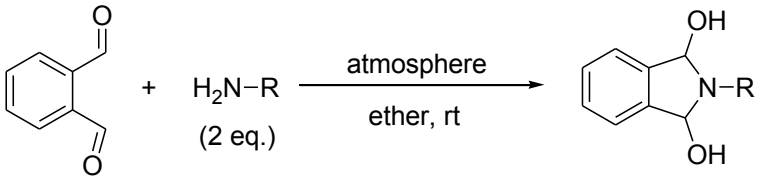
Scheme 3.1: Oxidation of the benzylic position on isoindolines.

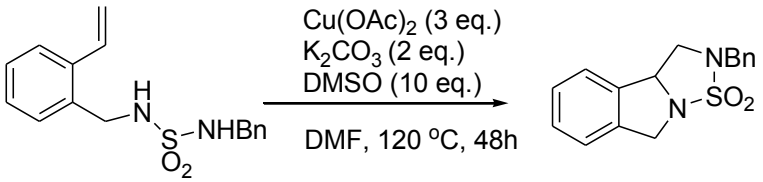
Previously reported preparations of isoindolines begin with a relatively complex starting material. Either the aromatic ring is already in place and needs to have appropriately placed functional groups to construct the dihydropyrrole skeleton of the isoindoline (**Scheme 3.2**),[14] or a dipropargylamine is used as the starting material (**Scheme 3.3**).[15] The second example of synthesizing isoindolines by [2+2+2] cycloaddition starting with dipropargylamines has been limited largely to tosylamines.[16] This is because the methodology for synthesizing those dipropargyl amines requires a highly electron-deficient amine, as discussed in detail in Chapter 2.



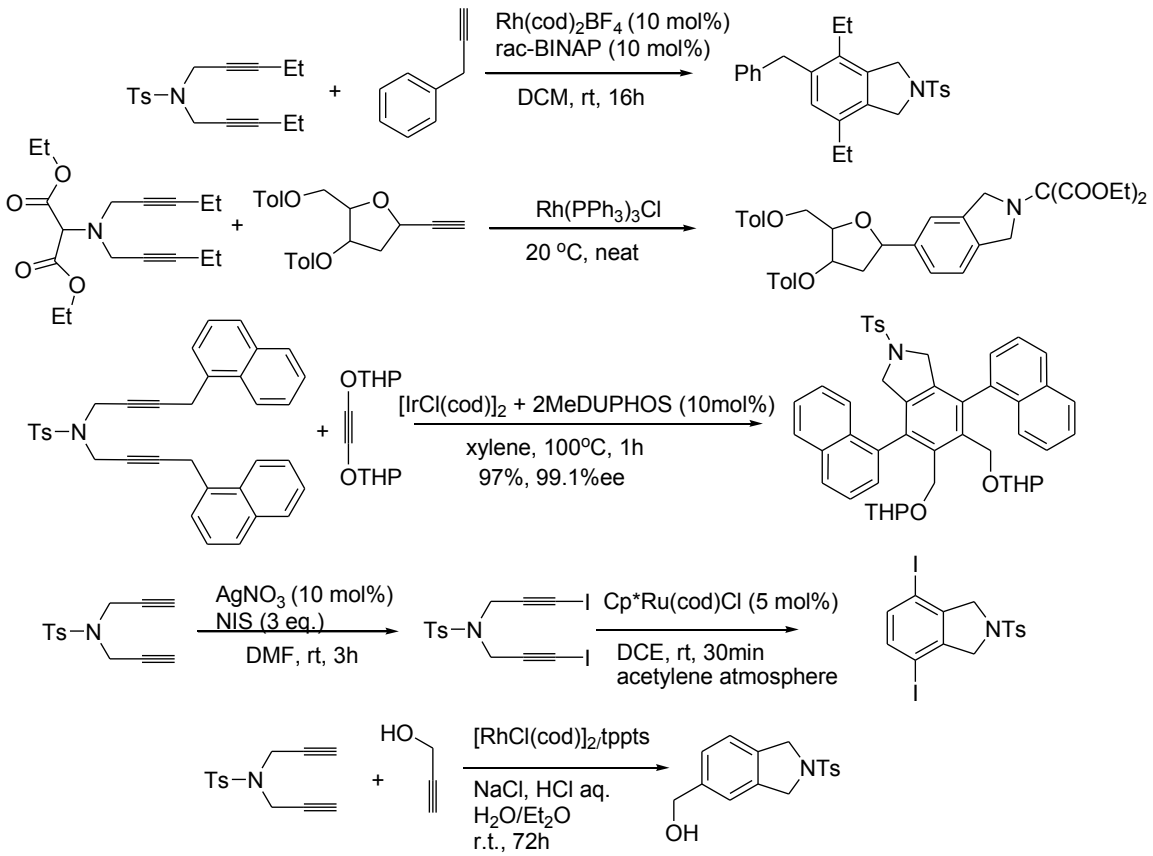
R^1 = H, alkyl, aryl; X = Cl, Br, I, TsO







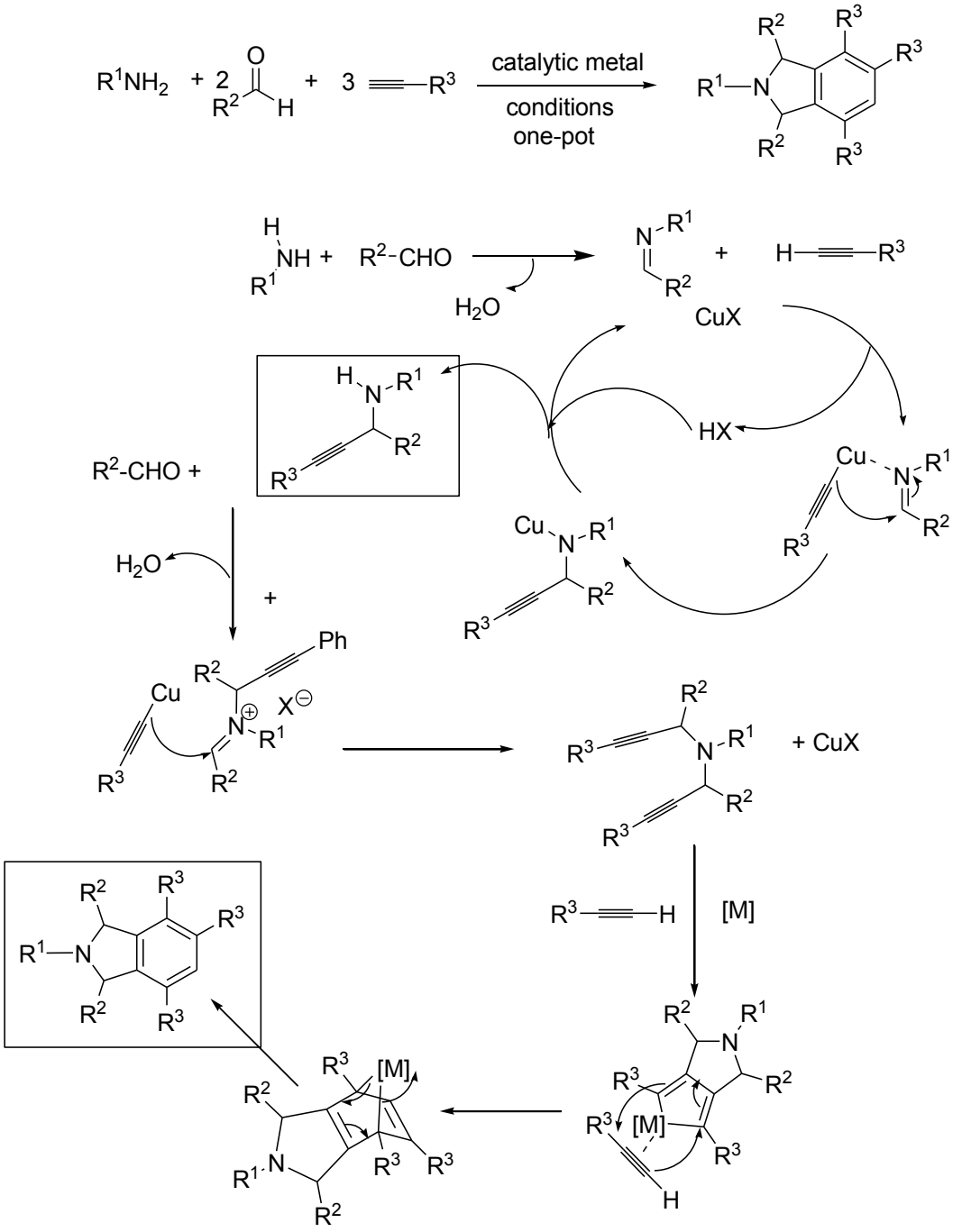
Scheme 3.2: Preparation of isoindolines from pre-functionalized benzene derivatives



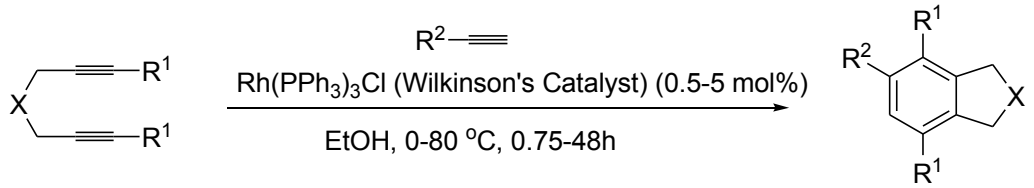
Scheme 3.3: Synthesis of isoindolines from pre-prepared dipropargyl amines.

While working on the tandem reaction methodology applied to the preparation of dipropargyl amines (**Chapter 2**) we envisioned adding an appropriate catalyst for a [2+2+2] cycloaddition so the dipropargylamines required for the isoindoline synthesis could be generated in situ and then react immediately to form the isoindoline in the same pot (**Scheme 3.4**). Ruthenium, cobalt, rhodium, and nickel

are the most common transition metals used to catalyze [2+2+2] cycloadditions.[17] Wilkinson's catalyst is well known for being efficient at catalyzing intermolecular [2+2+2] cycloadditions between 1,6-diynes, including dipropargyl amines, and monoalkynes (**Scheme 3.5**).[18]



Scheme 3.4: One-pot, six-component, 5-step tandem reaction sequence to generate the isoindoline framework.



X = CAc_2, $C(CO_2Et)_2$, CH_2, SO, SO_2, S, NAc, O
R^1 = H, Me
R^2 = H, CH_2OH, CH_2OMe, CH_2OAc, CH_2CH_2OH, Pr, $(CH_2)_2CCCH$, Ph, Me_3Si, Bu,

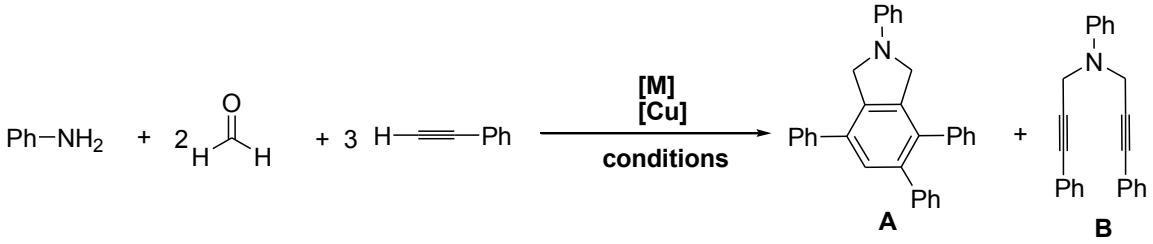
Scheme 3.5: Wilkinson's catalyst ($Rh(PPh_3)_3Cl$) is effective for intermolecular [2+2+2] cycloadditions between a range of 1,6-diynes and monoalkynes.

3.1 Results and Discussion

From **Table 3.1, entries 1 and 2** it is apparent that copper bromide[19] alone is sufficient to generate the dipropargylamine in good yield under the conditions used, whereas Wilkinson's catalyst does not catalyze the A^3-couplings. However, Wilkinson's catalyst seems to interfere with the initial A^3-couplings since the overall yield of dipropargylamine and isoindoline increases with decreased loading of Wilkinson's catalyst, although this also causes lower conversion of dipropargylamine to isoindoline (**Table 3.1, entries 4–6**). Ruthenium is known to be an efficient co-catalyst with copper for A^3-couplings[20] and the complexes listed in Table 1, entries 9[21] and 11[22] are known to be excellent catalysts for [2+2+2] cycloadditions. For this reason we expected a ruthenium catalyst to be most suitable for the overall tandem reaction sequence. The highest expectations were for Cp*RuCl-(cod) based on the literature examples that include electron-

deficient and relatively electron-rich dipropargylamines,[23] yet this catalyst gave no trace of isoindoline even with a number of variations in reaction time, temperature, and solvent. As a control the corresponding dipropargylamines were isolated and then combined with Cp*RuCl(cod) again under identical conditions and isoindoline product was detected in moderate yield by NMR (**Scheme 3.6**). From this we concluded that the catalyst is altered in the early stage of the cascade reaction processes in a way that renders it ineffective for the final cycloaddition. The ruthenium triphenylphosphine and p-cymene complexes gave isoindoline in low yield under the cascade conditions only if the temperature was raised to over 100 ◦C for over 24 h and no isoindoline was observed with moderate temperature and time (**Table 3.1, entries 8 and 10**). The nickel[24] and cobalt[25] catalysts used are also quite common and well known for efficient [2+2+2] cycloadditions (**Table 3.1, entries 12 and 13**). However, copper-catalyzed A^3-couplings did not occur in their presence so that the potential for efficient cycloadditions under the tandem reaction conditions could not be evaluated.

Table 3.1 Screening of catalysts for tandem, one-pot double A3-coupling and [2 + 2 + 2] cycloaddition using aniline as primary amine[a]



Entry	CuBr[b] [mol%]	[M] [mol%]	T [◦C]	Time [h]	Solvent	Yield[c] A [%]	Yield[c] B [%]
1	30	none	40-80	8	neat	0	81
2	none	$RhCl(PPh_3)_3$ (3)	40-80	8	neat	0	0
3	15	$RhCl(PPh_3)_3$ (3)	40-80	8	neat	39	23
4	30	$RhCl(PPh_3)_3$ (5)	60	17	neat	53	3
5	30	$RhCl(PPh_3)_3$ (3)	60	18	neat	47	17
6	30	$RhCl(PPh_3)_3$ (1)	60	26	neat	29	47
7[d]	30	$RhCl(PPh_3)_3$ (3)	40-80	8	neat	76	5
8[f]	30	$[Ru_2(p\text{-cynene})Cl_2]_2$ (2.5)	24-80	9	H_2O:MeOH, 9:1	0	78
9[e]	30	$Ru_2Cl_4(C_{10}H_{16})_2$ (2.5)	24-80	9	H_2O:MeOH, 9:1	0	66
10[f]	30	$RuCl_2(PPh_3)_3$ (5)	57	25	toluene	0	73

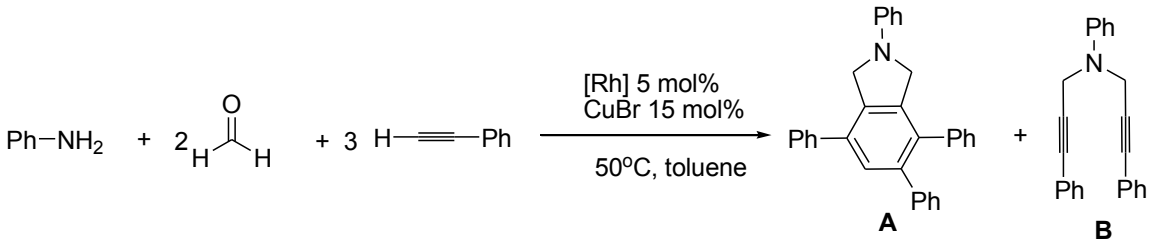
11	15	Cp*RuCl(cod) (5)	55	19	toluene	0	51
12	3	$CpCo(CO)_2$ (6)	27-100	21	toluene	0	0
13	15	$Ni(cod)_2$(5)/PPh_3 (20)	60	21	THF	0	0

[a]Reaction scale varied from 0.2–0.6 mmol aniline, but always 3 equivs. formaldehyde (37 wt% in H_2O) and 5 equivs. phenylacetylene. Neat reactions were run with 9 equivs. phenylacetylene. All reactions were degassed and run under inert atmosphere. [b]CuCl, CuI, and CuOTf gave inferior yields. [c]Yields determined by integrating methylene protons using 400 MHz ^{1}H NMR and mesitylene as quantitative internal standard. [d] Information for detailed screening of various conditions using Wilkinson's catalyst is below. [e]Catalyst was dichlorobis(m-chloro)bis[(1,2,3,6,7,8-η)-2,7-dimethyl-2,6-octadien-1,8-diyl]diruthenium(IV) CAS: [34801-97-3]. [f]Increasing the temperature to 100 °C for over 40 h will produce up to a 1:1 ratio of A:B but results in significant degradation of A even under N_2.

Variations in counter ion and ligand were then explored for rhodium complexes (**Table 3.2, entries 1–8**). Electron-rich phosphine ligands rendered the rhodium complex incapable of catalyzing the cycloaddition reaction (**Table 3.2, entries 3 and 4).** Chlorine proved to be the best counter ion when compared to other

commonly used counter ions for the cycloaddition step (**Table 3.2, entries 1 and 2, 5–8**) although all were capable of producing isoindoline under the tandem reaction conditions.

Table 3.2 Screening of rhodium complexes for tandem, one-pot double A3-coupling and [2 + 2 + 2] cycloaddition using aniline as primary amine[a]



Entry	[Rh]	Time [h]	Yield[c] **A** [%]	Yield[c] **B** [%]
1	$Rh(PPh_3)_3Cl/AgBF_4$	23	6	0
2	$Rh(PPh_3)_3Cl/AgOTf$	22	14	0
3	$[Rh(cod)Cl]_2/P(Me)_3$	18	0	45
4	$[Rh(cod)Cl]_2/P(Cy)_3$	26	0	34
5	$Rh(PPh_3)_3Cl$	29	29	0
6	$Rh(cod)(PPh_3)_2PF_6$	40	3	0
7	$Rh(cod)_2BF_4$	41	14	21

8	$Rh(cod)_2BF_4/PPh_3$	21	21	13

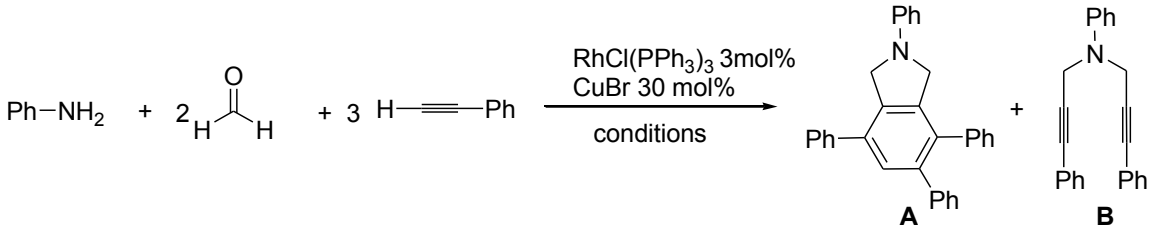
[a]Reaction scale was 0.4 mmol aniline, with 3 equivs. formaldehyde (37 wt% in H_2O) and 5 equivs. phenylacetylene in 0.25 mL solvent. [b]Paraformaldehyde providing 3 equivs. of formaldehyde was used in place of the regular aqueous formaldehyde solution and the reaction was carried out under anhydrous conditions. [c]Yields determined by integrating methylene protons using 400 MHz ^1H NMR and mesitylene as quantitative internal standard.

Optimization of the general reaction conditions proved to be the greatest challenge as the requirements for the cycloaddition and the A^3-couplings were disparate in many ways. Increasing the loading of Wilkinson's Catalyst always increased the conversion of dipropargylamine (**B**) to isoindoline (**A**) but lowered the overall yield, indicating that the $RhCl(PPh_3)_3$ interferes with the efficiency of the A^3 couplings at higher loadings (**Table 3.3, entries 1-2, 5-7**). Lowering the $RhCl(PPh_3)_3$ loading to 1% gave the best overall yield of **A** + **B**, but only 38% of **B** was converted to **A** even after 26 hours (**Table 3.3, entry 6**). The reaction takes several days to near completion with this loading of $RhCl(PPh_3)_3$ and the yield of **A** is then compromised due to gradual decomposition of **A** in solution. Hexanes and toluene provided similar results indicating an apolar environment favors the tandem reaction procedure overall (**Table 3.3, entries 1-4**). Many other more

polar solvents such as ethanol, isopropanol, butanol, methanol, water, methylene chloride, chloroform, dichloroethane, THF, DMSO, dioxane, and ether were tried and gave significant although inferior yields. DMSO was unique in that it provided the best yield of **B**, but 0% conversion to **A**. So it seems that the inferior yields in polar solvents are related to the cycloaddition step. The best yields were obtained when the only solvent was excess phenylacetylene and a small amount of water from the formaldehyde solution (**Table 3.3, entries 5-10**).

The reactions can be done at a single temperature and in an air atmosphere albeit in lower yields (**Table 3.3, entries 5 and 8**). Starting the reaction 20 ℃ lower favours the yield of **A,** likely by allowing a higher initial yield of **B** since water is present and the imines formed in situ are vulnerable to hydrolysis (**Table 3.3, entry 8**). The advantage of raising the temperature to 80 ℃ is a substantial increase in the rate of the [2 + 2 + 2] cycloaddition, which is acceptable after 6 h at 40 ℃ since there should be no primary imine and very little secondary imine in solution at this point (**Table 3.3, entries 8-10**). It is at temperatures over 60 ℃ that degassed reaction medium and inert atmosphere become important as it prevents decomposition of the final isoindoline product (**A**) (**Table 3.3, entries 8-9**). However, it is still important to keep the time at 80 ℃ minimal as the yield does get lower with increased time once the reaction is near completion (**Table 3.3, entries 9-10**).

Table 3.3: Optimization of general reaction conditions using Wilkinson's Catalyst[a]



Entry	Conditions[b]	Yield[c] A (%)	Yield[c] B (%)	Total Yield[c] A + B (%)
1	3% [Rh], hexanes, 50 ◦C, 15h	16	51	67
2	5% [Rh], hexanes, 50 ◦C, 15h	19	38	57
3	5% [Rh], toluene, 50 ◦C, 15h	20	32	52
4	5% [Rh], hexanes (0.3ml), 50 ◦C, 15h	11	36	47
5	3% [Rh], neat (10 eq. alkyne) 60 ºC, 18h	47	17	64
6	1% [Rh], neat (10 eq. alkyne) 60 ºC, 26h	29	47	76

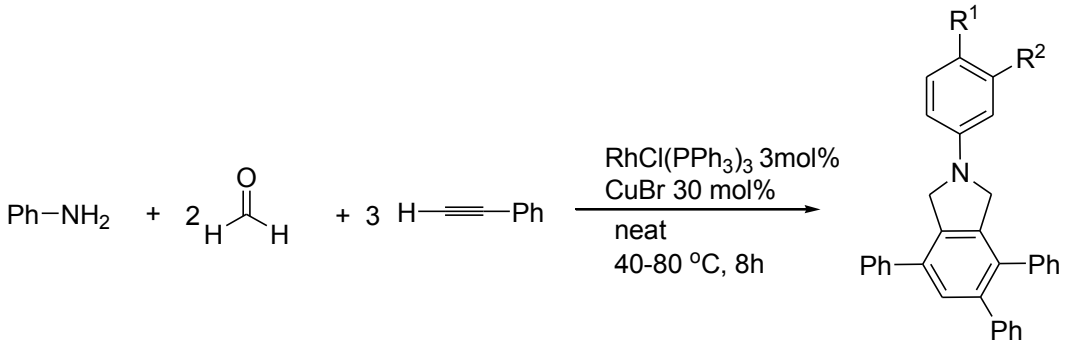
7	5% [Rh], neat (10 eq. alkyne) 60 ºC, 17h	53	3	56
8	3% [Rh], neat (10 eq. alkyne) 40 ºC, 6h, 80 ºC 2h	43	12	55
9[d]	3% [Rh], neat (10 eq. alkyne) 40 ºC, 6h, 80 ºC 2h	76	5	81
10[d]	3% [Rh], neat (10 eq. alkyne) 40 ºC, 6h, 80 ºC 4h	68	0	68

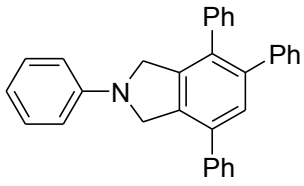
[a]Conditions: Used 0.2 mmoles aniline with 3 equiv. formaldehyde (37 wt. % in H_2O) and 5 equiv. phenylacetylene in 0.10 mL of solvent unless otherwise noted. [b]Yields were determined by integrating methylene protons using 400 MHz ^1H NMR and mesitylene as quantitative internal standard. [c]Reaction was sealed, but was not degassed nor purged with inert atmosphere. [d]Degassed and ran under N_2 atmosphere.

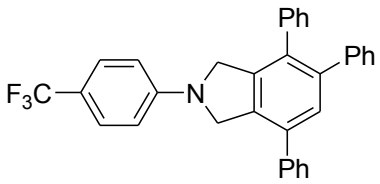
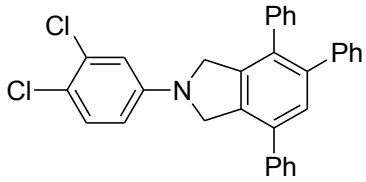
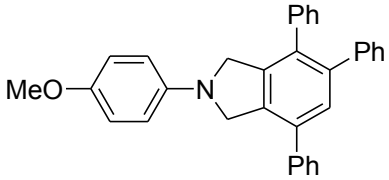
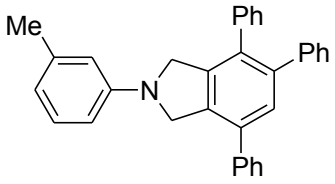
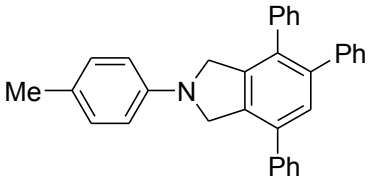
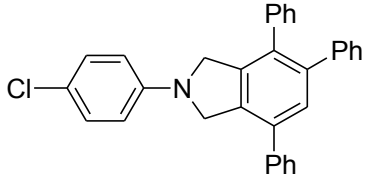
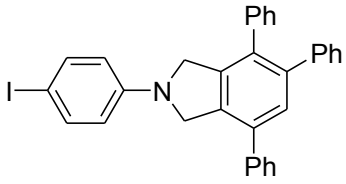
Clearly the most electron-rich amines gave the worst results (**Table 3.4, entries 4 and 6**). A methyl group in the meta position provides less inductive electron donation than either a methyl or a methoxy group in the para position, (Hammett substituent parameters of σ = -0.06, -0.14, and -0.12, respectively)[26], which could

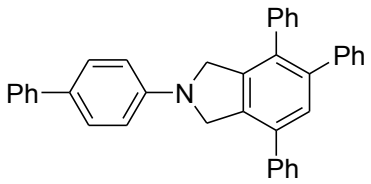
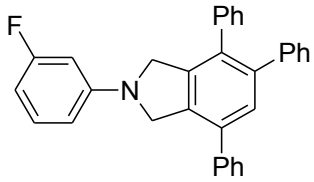
help to explain the difference between **entries 5 and 6 in Table 3.4**. Electron deficiency, on the other hand, impairs the A^3-couplings since highly electron-deficient amines such as tosylamines are incapable of undergoing this reaction. Thus, although there appears to be an advantage to electron withdrawing substituents (**Table 3.4, entries 1, 7, 8, 10 and 11**) there is an upper limit as seen by the decrease in yield when p-trifluoromethane or two chloro substituents are present (**Table 3.4, entries 2 and 3**). When either aliphatic alkynes or amines were used under the optimal conditions (**Table 3.4**) isoindoline could be detected by mass spectroscopy, but conversion was too low to isolate the product.

Table 3.4 Tandem, one-pot double A^3-coupling and [2 + 2 + 2] cycloaddition for various primary amines[a]



Entry	Product	Yield[b] [%]
1		78 (69)

2		62 (58)
3		66 (57)
4		33 (24)
5		60 (51)
6		15 (13)
7		86 (78)
8		85 (76)

9		76 (69)
10		84 (70)

[a]Reactions were run neat with 0.56 mmol primary amine, 3 equivs. formaldehyde (135 μL, 37 wt % in H_2O) and 9 equivs. phenylacetylene; Reaction mixture was degassed and agitated for 2 h at 40 ºC and 6 h at 80 ºC. [b]Yields determined by integrating methylene protons using 400 MHz ^1H NMR and mesitylene as quantitative internal standard. Isolated yields after flash chromatography shown in parenthesis.

3.2 Conclusion

We have demonstrated the first one-pot, six-component synthesis of the isoindoline framework. Furthermore, excellent yields were observed using only catalytic amounts of copper and rhodium under mild conditions with modest reaction times. Many challenges were presented due to the disparate reaction requirements of the A^3-coupling reactions and the cycloaddition. We have shown

that a middle ground can be found with respect to conditions and catalyst selection that allows for the two reaction types to occur in tandem. It was impossible to find conditions that were simultaneously optimal for both types of reactions. Yet, any loss in efficiency and yield due to tandem reaction conditions is more than made up for by the benefit of not having to isolate and purify the intermediate dipropargyl amine. This reaction worked well with electron rich aromatic primary amines, leading to unique isoindoline derivatives that have never before been isolated. The convenience and efficiency of this methodology as well as the complementary substrate scope will lift some barriers to renewed exploration of applications for isoindoline derivatives.

3.3 Experimental Section

General Remarks

Amines, phenylacetylene, formaldehyde solution (37 wt. % in water) and copper bromide were purchased from Aldrich and used without further purification. Wilkinson's catalyst was purchased from Strem and kept under inert atmosphere until ready for use. Slightly impure isoindoline products were isolated by flash chromatography using Silicycle ultrapure silica gel (40–63μm, 230–400 mesh) eluting with EMD™ ACS grade hexanes/ethyl acetate (0–2% ethyl acetate). Extra

high purity could be achieved by further dissolving in the minimal volume of Fisher ACS grade dichloromethane, adding 10–80 parts Fisher HPLC grade n-pentane and leaving at -20°C overnight to complete crystallization. TLC analysis was done on Silicycle preloaded Ultra Pure Silica Gel (extra hard 0.25 mm layer) glass backed plates; visualization of compounds was by UV light. The NMR spectra were recorded with a Varian Unity spectrometer (500 and 125 MHz for ^{1}H and ^{13}C respectively). Multiplicity is given as *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, and *m* = multiplet. Chemical shifts (δ) are reported in ppm downfield from TMS as internal standard. All coupling constants (*J*) are given in Hz. IR spectra were obtained for the isoindolines pressed in KBr discs and were recorded by an ABB Bomem MB100 spectrometer. High resolution mass spectra were obtained by a Kratos MS25RFA Mass Spectrometer at McGill University.

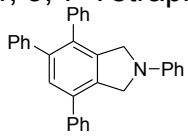
Optimal Conditions

Copper bromide and Wilkinson's catalyst were combined in a screw cap tube open to air. Phenylacetylene, formaldehyde solution (37 wt. % in water), and primary amine were then added in that order in open air via syringe. Solid amines were also added last for consistency. The tube was then sealed with a cap fitted with a valve connected to a schlenk line and after a five minute initial stir the reaction mixture was degassed by freeze-pump-thaw three times using liquid

nitrogen and then left with an overpressure of nitrogen gas at 40 °C for 6 h. After 6 h the temperature was increased to 80 °C for two additional hours and then the reaction mixture was filtered open to air through ~1–2 cm of silica with ethyl acetate. Ethyl acetate was removed with rotary evaporation followed by high vacuum for 1 h before dissolving in 1 ml of $CDCl_3$ for NMR analysis of the crude reaction mixture.

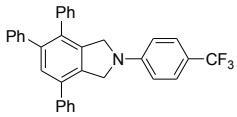
Spectral Data

2, 4, 5, 7-Tetraphenylisoindoline (**Table 3.4, entry 1**)



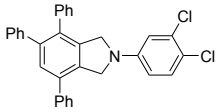
Yellow crystals (small needles). IR (KBr): V_{max} = 3056, 3024, 2831, 1597, 1505, 1462, 1374, 773, 746, 703cm^{-1}; ^1H NMR ($CDCl_3$, 500MHz, ppm): δ= 7.59-7.55(m, 2H), 7.49 (t, 2H, 7.5Hz), 7.45-7.37 (m, 2H), 7.30-7.14 (m, 13H), 6.71 (t, 1H, 7.2Hz), 6.60 (d, 2H, 8.0Hz), 4.81 (s, 2H), 4.55 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ= 147.0, 140.9, 140.8, 140.0, 138.9, 138.3, 136.3, 135.1, 134.8, 130.2, 129.9, 129.7, 129.2, 128.7, 128.22, 128.16, 127.7, 127.6, 126.9, 126.5, 116.3, 111.6, 54.1, 54.0; HRMS *m/z*: calc'd for $C_{32}H_{25}N$ (M^+): 423.1987; found, 423.1975. calc'd for $C_{32}H_{24}N$ ($M\text{-}1^+$): 422.1909; found, 422.1900. calc'd for $C_{32}H_{23}N$ ($M\text{-}2^+$): 421.1830; found, 421.1829.

2, 5, 7-Triphenyl-2-(4-trifluoromethyl)phenyl)isoindoline (**Table 3.4, entry 2**)



Light yellow powder. IR (KBr): V_{max} = 3058, 3024, 2932, 2828, 1618, 1532, 1464, 1379, 1328, 1194, 1162, 1105, 1068, 815, 701cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ= 7.58-7.55(m, 2H), 7.51(t, 2H, 7.0Hz), 7.45-742 (m, 4H), 7.33-7.27 (m, 3H), 7.22-7.15 (m, 7H), 6.58 (d, 2H, 8.0Hz), 4.84 (s, 2H), 4.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 148.9, 141.2, 140.6, 139.8, 138.8, 137.5, 136.4, 134.9, 134.3, 130.5, 129.9, 129.6, 128.8, 128.3, 128.2, 127.8, 127.7, 127.1, 126.6, 126.5 (q, 3.6Hz), 117.8 (q, 32.4Hz), 110.9, 54.1, 54.0; HRMS *m/z*: calc'd for $C_{33}H_{24}F_3N$ (M^+): 491.1861; found, 491.1834. calc'd for $C_{33}H_{23}F_3N$ ($M\text{-}1^+$): 490.1783; found, 490.1767. calc'd for $C_{33}H_{22}F_3N$ ($M\text{-}2^+$): 489.1704; found, 489.1699.

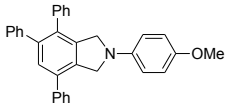
2-(3,4-Dichlorophenyl)-4,5,7-triphenylisoindoline (**Table 3.4, entry 3**)



Dark yellow powder. IR (KBr): V_{max} = 3057, 3026, 2829, 1599, 1490, 1460, 1376, 1135, 773, 702cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ= 7.58-7.46 (m, 4H), 7.46-7.39 (m, 2H), 7.34-7.24 (m, 3H), 7.24-7.12 (m, 8H), 6.61 (s, 1H), 6.38 (d, 1H, 8.0Hz), 4.74 (s, 2H), 4.49 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 146.3, 141.1, 140.6, 139.8, 138.7, 137.5, 136.4, 134.8, 134.3, 132.8, 130.53, 130.47, 129.9, 129.6, 128.8, 128.3, 128.1, 127.8, 127.7, 127.1, 126.6, 119.0, 112.7, 111.2, 54.2, 54.1; HRMS *m/z*: calc'd for $C_{32}H_{23}{}^{37}Cl_2N$ (M^+): 495.1149; found, 495.1166. calc'd for $C_{32}H_{23}{}^{35}Cl^{37}ClN$ (M^+): 493.1178; found,

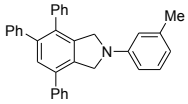
493.1156. calc'd for $C_{32}H_{22}{}^{35}Cl_2N$ (M-1$^+$): 490.1129; found, 490.1117. calc'd for $C_{32}H_{21}{}^{35}Cl_2N$ (M-2+): 489.1051; found, 489.1047.

2-(4-Methoxyphenyl)-4,5,7-triphenylisoindoline (**Table 3.4, entry 4**)



Light yellow crystalline fluff. IR (KBr): V_{max} = 3057, 3039, 3023, 2995, 2936, 2832, 2804, 1512, 1463, 1440, 1369, 1241,1039, 814, 703cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ= 7.64-7.56 (m, 2H), 7.54-7.40 (m, 4H), 7.35-7.16 (m, 10H), 6.88 (d, 2H, 7.0Hz), 6.59 (d, 2H, 7.0Hz), 4.79 (s, 2H), 4.54 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ =151.3, 142.0, 140.9, 140.7, 140.1, 139.0, 138.6, 136.2, 135.4, 134.7, 130.1, 129.9, 129.7, 128.7, 128.2, 128.1, 127.7, 127.5, 126.9, 126.4, 115.0, 112.5, 55.8, 54.66, 54.58; HRMS *m/z*: calc'd for $C_{33}H_{27}NO$ (M$^+$): 453.2093; found, 453.2071. calc'd for $C_{33}H_{26}NO$ (M-1$^+$): 452.2014; found, 452.1979. calc'd for $C_{33}H_{25}NO$ (M-2$^+$): 451.1936; found, 451.1931.

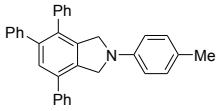
4,5,7-Triphenyl-2-*m*-tolylisoindoline (**Table 3.4, entry 5**)



Pale yellow powder. IR (KBr): V_{max} = 3057, 3023, 2936, 2844, 2795, 1601, 1579, 1495, 1465, 1369, 764, 755, 699cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ= 7.58-7.53 (m, 2H), 7.50-7.35 (m, 4H), 7.32-7.07 (m, 11H), 6.53 (s, 1H), 6.40 (s, 2H), 4.78 (s, 2H), 4.53 (s, 2H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ =147.1, 140.8, 140.0, 139.0, 138.9, 138.3, 136.3, 135.1, 134.8, 130.24, 130.21, 129.9, 129.7, 129.1, 128.7, 128.23, 128.16, 127.7, 127.5, 126.9,

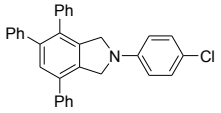
126.4, 117.3, 112.2, 108.9, 54.1, 54.0, 21.8; HRMS *m/z*: calc'd for $C_{33}H_{27}N$ (M^+): 437.2143; found, 437.2126. calc'd for $C_{33}H_{26}N$ ($M\text{-}1^+$): 436.2065; found, 436.2053. calc'd for $C_{33}H_{25}N$ ($M\text{-}2^+$): 435.1987; found, 435.1976.

4,5,7-Triphenyl-2-*p*-tolylisoindoline (**Table 3.4, entry 6**)



Yellow flakes. IR (KBr): V_{max} = 3054, 3019, 2920, 2863, 2814, 1620, 1521, 1463, 1368, 806, 773, 702cm^{-1}; ^{1}H NMR ($CDCl_3$, 500MHz, ppm): δ = 7.60-7.56 (m, 2H), 7.49 (t, 2H, 7.5Hz), 7.45-7.39 (m, 2H), 7.30-7.23 (m, 3H), 7.21-7.14 (m, 7H), 7.05 (d, 2H, 8.0MHz), 6.53 (d, 2H, 8.5MHz), 4.78 (s, 2H), 4.53 (s, 2H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 145.1, 140.9, 140.8, 140.1, 139.0, 138.5, 136.3, 135.3, 134.8, 130.2, 129.9, 129.8, 129.7, 128.7, 128.2, 128.1, 127.7, 127.5, 126.9, 126.4, 125.4, 111.7, 54.3, 54.2, 20.3; HRMS *m/z*: calc'd for $C_{33}H_{27}N$: 437.2143 (M^+); found, 437.2125. calc'd for $C_{33}H_{26}N$ ($M\text{-}1^+$): 436.2065; found, 436.2050. calc'd for $C_{33}H_{25}N$ ($M\text{-}2^+$): 435.1987; found, 435.1983.

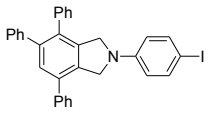
2-(4-Chlorophenyl)-4,5,7-triphenylisoindoline (**Table 3.4, entry 7**)



Pale yellow powder. IR (KBr): V_{max} = 3055, 3021, 2820, 1600, 1497, 1463, 1369, 808, 773, 702cm^{-1}; ^{1}H NMR($CDCl_3$, 500MHz, ppm): δ= 7.60-7.56 (m, 2H), 7.52 (t, 2H, 7.0Hz), 7.48-7.42 (m, 2H), 7.34-7.26 (m, 4H), 7.24-7.16 (m, 8H), 6.52 (d, 7.5Hz), 4.79 (s, 2H), 4.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 145.6, 141.0, 140.7, 139.9, 138.8, 138.0, 136.3, 134.82, 134.78, 130.4, 130.3, 129.9, 129.6, 129.0, 128.7, 128.2, 127.8, 127.6, 127.0, 126.5,121.2, 112.6, 54.3, 54.2;

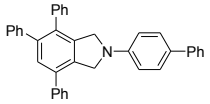
HRMS *m/z*: calc'd for $C_{32}H_{23}ClN$ ($M\text{-}1^+$): 456.1519; found, 456.1508. calc'd for $C_{32}H_{22}ClN$ ($M\text{-}2^+$): 455.1441; found, 455.1446.

2-(4-Iodoophenyl)-4,5,7-triphenylisoindoline (**Table 3.4, entry 8**)



Yellow powder. IR (KBr): V_{max} = 3055, 3023, 2819, 1586, 1498, 1462, 1372, 799, 778, 757, 739, 700cm^{-1} ^1H NMR ($CDCl_3$, 500MHz, ppm): δ= 7.53 (d, 2H, 7.5Hz), 7.47 (t, 2H, 7.3Hz), 7.44-7.37 (m, 4H), 7.28-7.22 (m, 3H), 7.18-7.12 (m, 7H), 6.32 (d, 2H, 8.5Hz) 4.72 (s, 2H), 4.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 146.3, 141.0, 140.6, 139.9, 138.8, 137.8, 137.7, 136.3, 134.8, 134.6, 130.4, 130.3, 129.9, 129.6, 128.7, 128.2, 128.1, 127.7, 127.6, 127.0, 126.5, 113.9, 54.0, 53.9; HRMS *m/z*: calc'd for $C_{32}H_{24}IN$ (M^+): 549.0953; found, 549.0946. calc'd for $C_{32}H_{23}IN$ ($M\text{-}1^+$): 548.0875; found, 548.0870. calc'd for $C_{32}H_{22}IN$ ($M\text{-}2^+$): 547.0797; found, 547.0798.

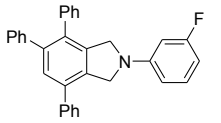
2-Biphenylyl-4,5,7-triphenylisoindoline (**Table 3.4, entry 9**)



Pale yellow flakes. IR (KBr): V_{max} = 3054, 3022, 2798, 2774, 1600, 1500, 1482, 1462, 1435, 773, 765, 756, 730, 698cm^{-1} ; ^1H NMR ($CDCl_3$, 500MHz, ppm): δ= 7.38-7.16 (m, 12H), 7.16-7.05 (m, 9H), 6.97-6.90 (m, 2H), 6.83 (d, 1H, 8.0Hz), 6.82 (t, 1H, 7.0Hz), 4.39 (s, 2H), 4.15 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 146.2, 142.9, 140.9, 140.3, 139.7, 138.8, 138.7, 135.6, 135.5, 134.1, 132.1, 130.6, 129.8, 129.7, 129.5, 129.1, 128.4, 128.05, 127.97, 127.9, 127.7, 127.2, 126.6, 126.4, 126.3, 118.7, 115.2, 56.2, 56.1; HRMS *m/z*: calc'd for

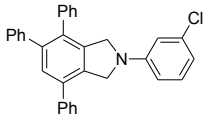
$C_{38}H_{29}N$ (M^+): 499.2300; found, 499.2266. calc'd for $C_{38}H_{28}N$ ($M\text{-}1^+$): 498.2222; found, 498.2202. calc'd for $C_{38}H_{27}N$ ($M\text{-}2^+$): 497.2143; found, 497.2136.

2-(3-Fluorophenyl)-4,5,7-triphenylisoindoline (**Table 3.4, entry 10**)



White crystalline fluff. IR (KBr): V_{max} = 3057, 3024, 2831, 1616, 1576, 1501, 1463, 1440, 1376, 1183, 1153, 1023, 892, 810, 753, 736, 703, 680cm^{-1} ; ^1H NMR ($CDCl_3$, 500MHz, ppm): δ = 7.55 (d, 2H, 7.5Hz), 7.49 (t, 2H, 7.5Hz), 7.45-7.39 (m, 2H), 7.31-7.24 (m, 3H), 7.20-7.11 (m, 8H), 6.38 (td, 1H, 8.2Hz, 2.0Hz), 6.33 (dd, 1H, 8.2Hz, 1Hz), 6.27 (d, 1H, 12Hz), 4.78 (s, 2H), 4.52 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 164.1 (d, 240Hz), 148.6 (d, 10.6Hz), 141.0, 140.7, 139.9, 138.8, 137.8, 136.3, 134.8, 134.6, 130.4, 130.3, 130.2, 129.9, 129.6, 128.7, 128.2 (d, 6Hz), 127.8, 127.6, 127.0, 126.5, 107.3, 102.8 (d, 22Hz), 98.6 (dd, 26Hz, 8.4Hz), 54.2, 54.1; HRMS *m/z*: calc'd for $C_{32}H_{24}FN$ (M^+): 441.1893; found, 441.1865. calc'd for $C_{32}H_{23}FN$ ($M\text{-}1^+$): 440.1814; found, 440.1800. calc'd for $C_{32}H_{22}FN$ ($M\text{-}2^+$): 439.1736; found, 439.1732

2-(3-Chlorophenyl)-4,5,7-triphenylisoindoline (**Table 3.4, entry 11**)



Dark yellow amorphous powder. IR (KBr): V_{max} = 3058, 3026, 2840, 1591, 1493, 1465, 1438, 1371, 1005, 758, 700cm^{-1} ; ^1H NMR ($CDCl_3$, 500MHz, ppm): δ =7.51 (d, 2H, 7.5Hz), 7.48-7.41 (m, 3H), 7.40-7.35 (m, 1H), 7.28-7.21 (m, 3H), 7.18-7.10 (m, 7H), 7.04 (t, 1H, 8.0Hz), 6.61 (d, 1H, 8.0Hz), 6.52 (s, 1H), 6.37 (d, 1H, 8.0Hz), 4.72 (s, 2H), 4.48 (s, 2H); ^{13}C NMR ($CDCl_3$, 125MHz, ppm): δ = 147.9, 141.0, 140.6, 139.8, 138.7, 137.7, 136.3, 135.0, 134.8, 134.5, 130.3,

130.1, 129.9, 129.6, 128.7, 128.2, 128.1, 127.7, 127.6, 127.0, 126.5, 116.1, 111.3, 109.8, 54.1, 54.0; HRMS *m/z* : calc'd for $C_{32}H_{23}ClN$ ($M\text{-}1^{+}$): 456.1519; found, 456.1496. for $C_{32}H_{22}ClN$ ($M\text{-}2^{+}$): 455.1441; found, 455.1435.

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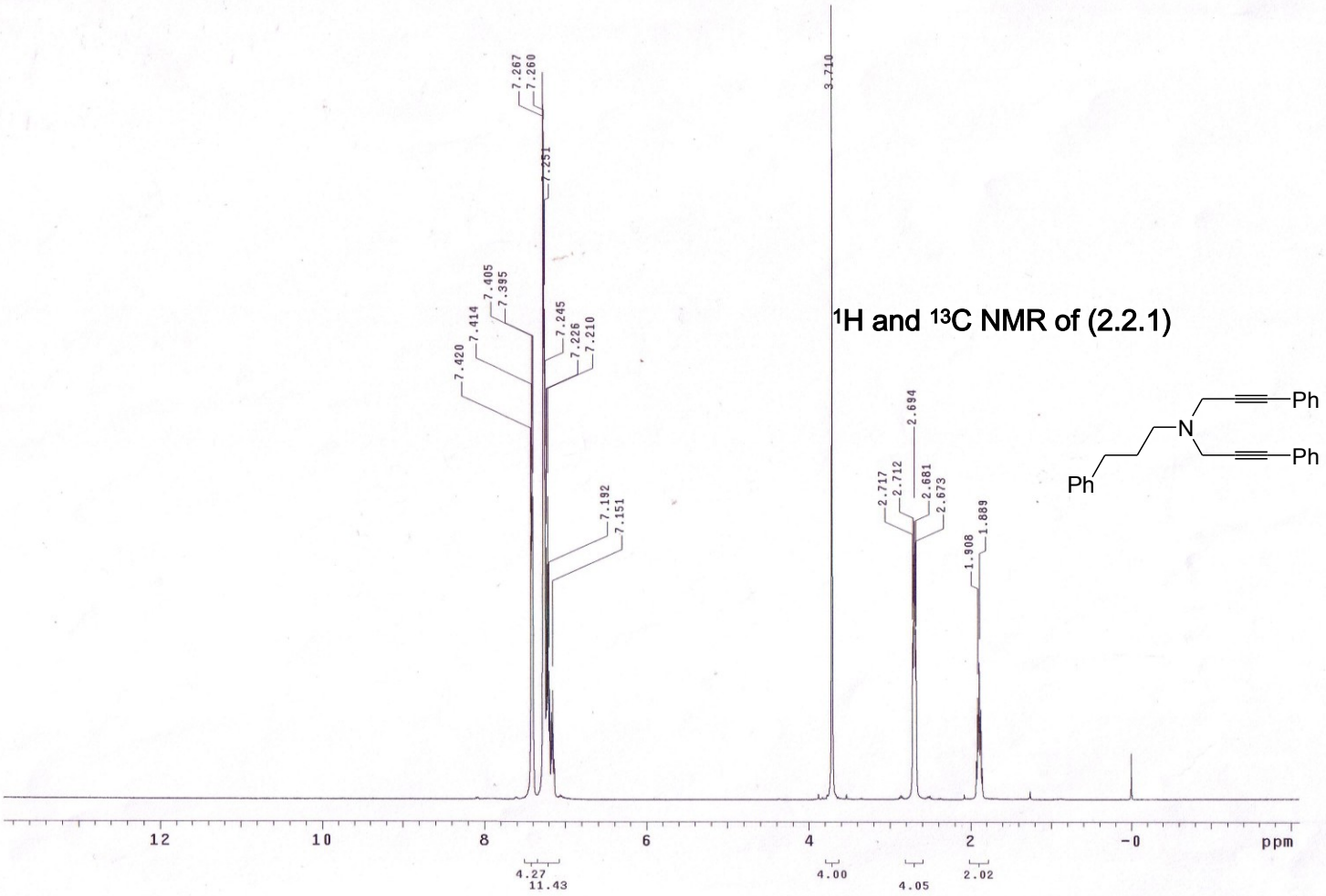
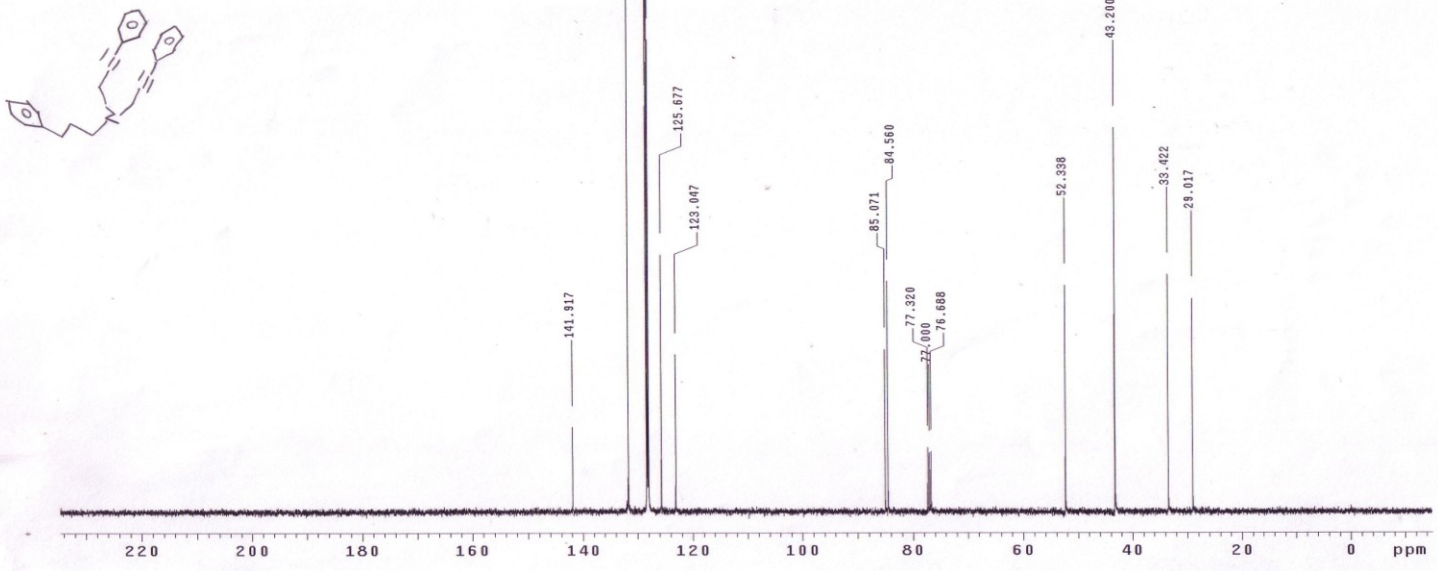
Appendix A

^{1}H and ^{13}C NMR Spectra for Chapter 2 Compounds 2.2.1-2.2.9



^{1}H and ^{13}C NMR of (2.2.1)



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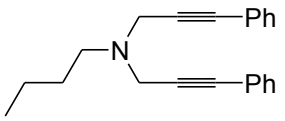

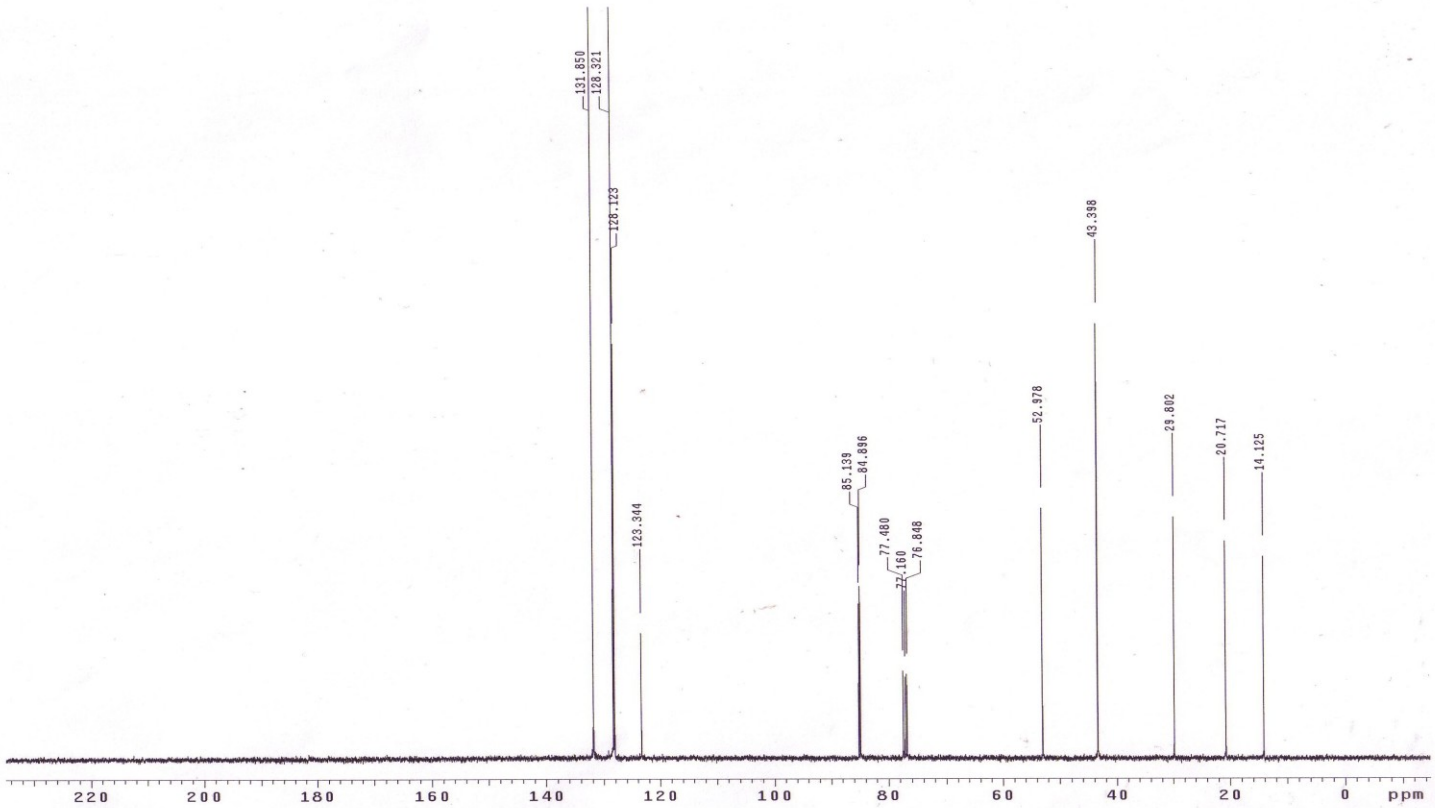

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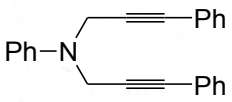
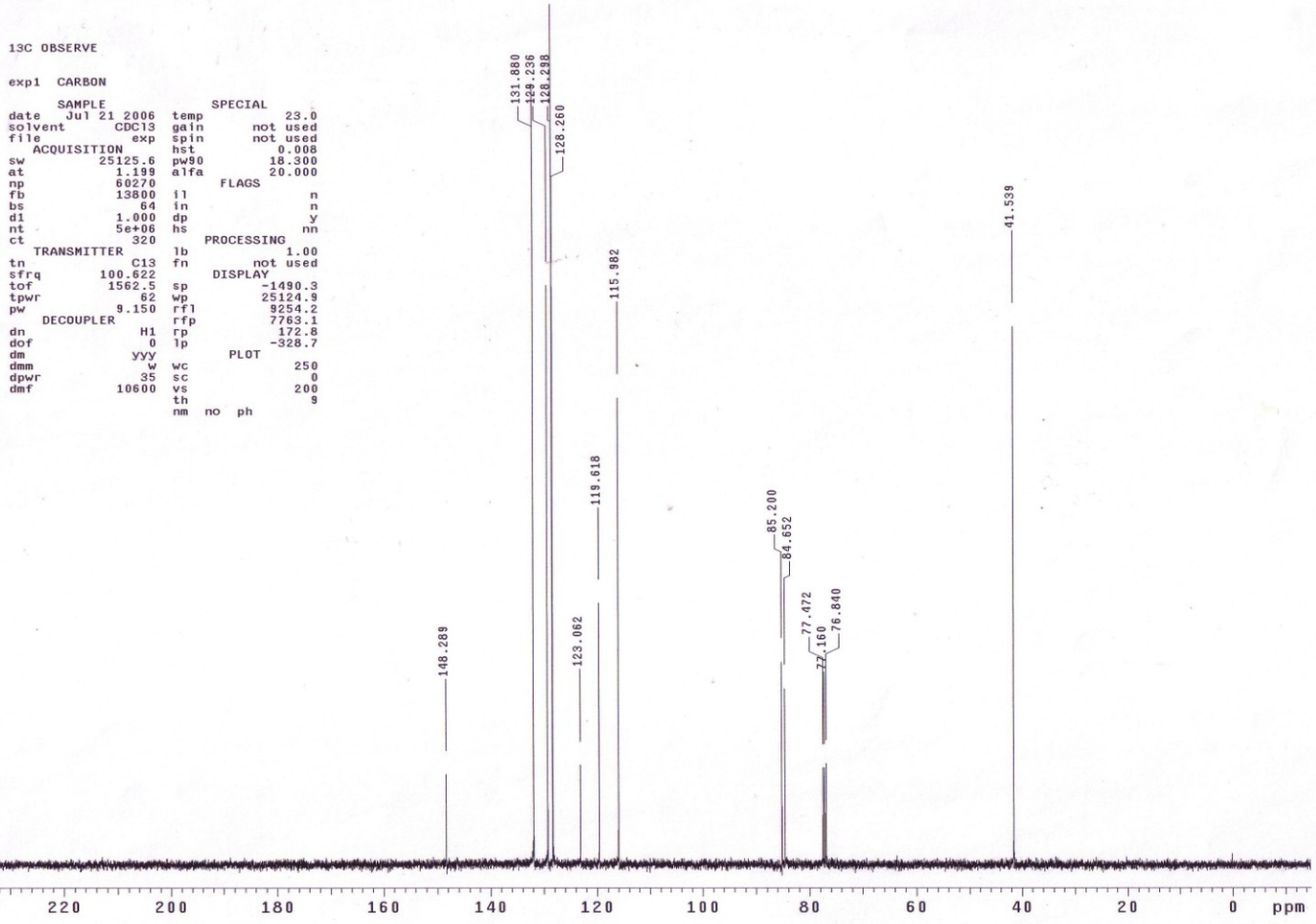
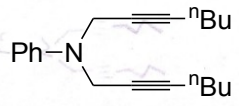
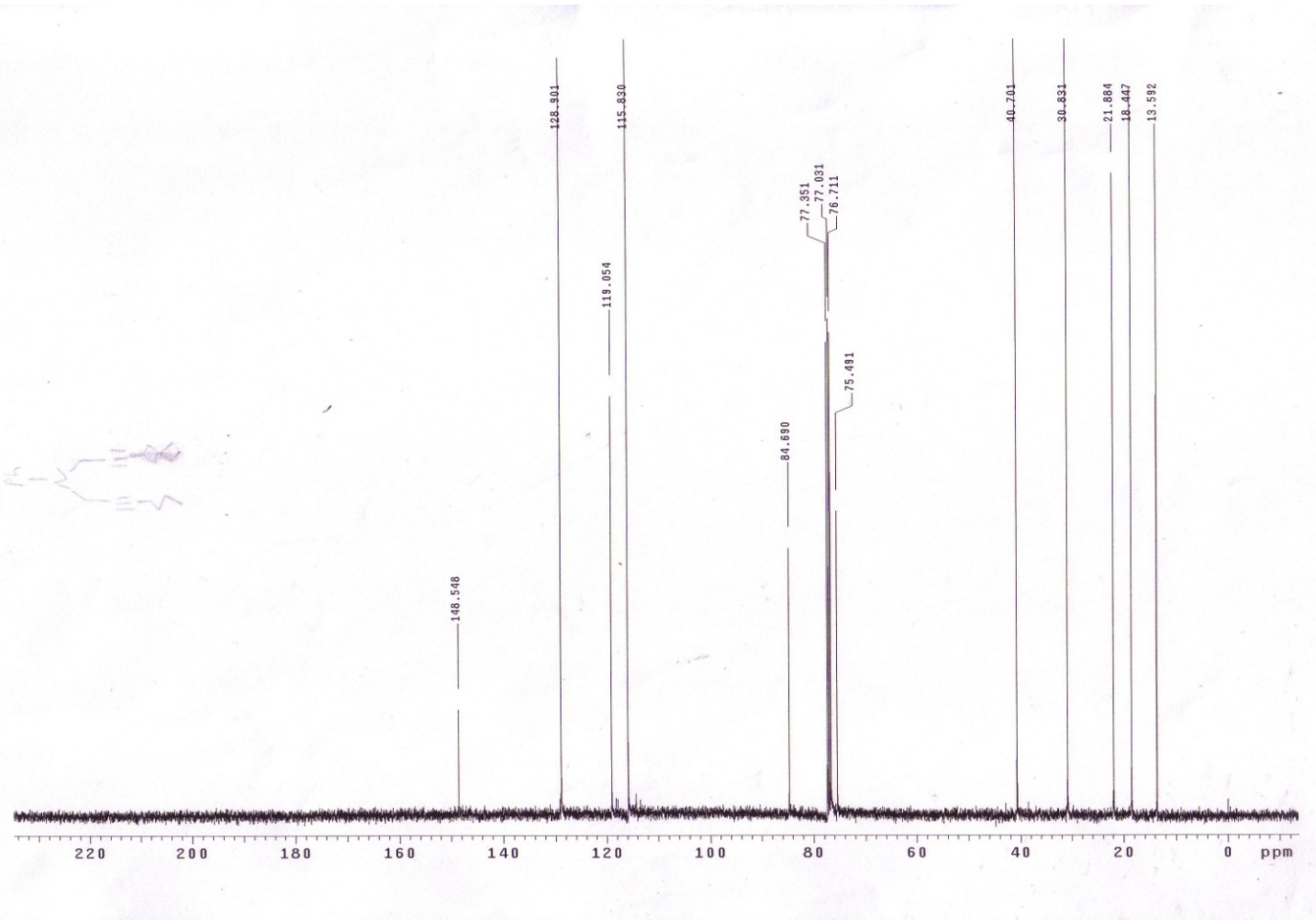


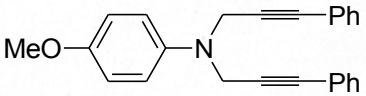


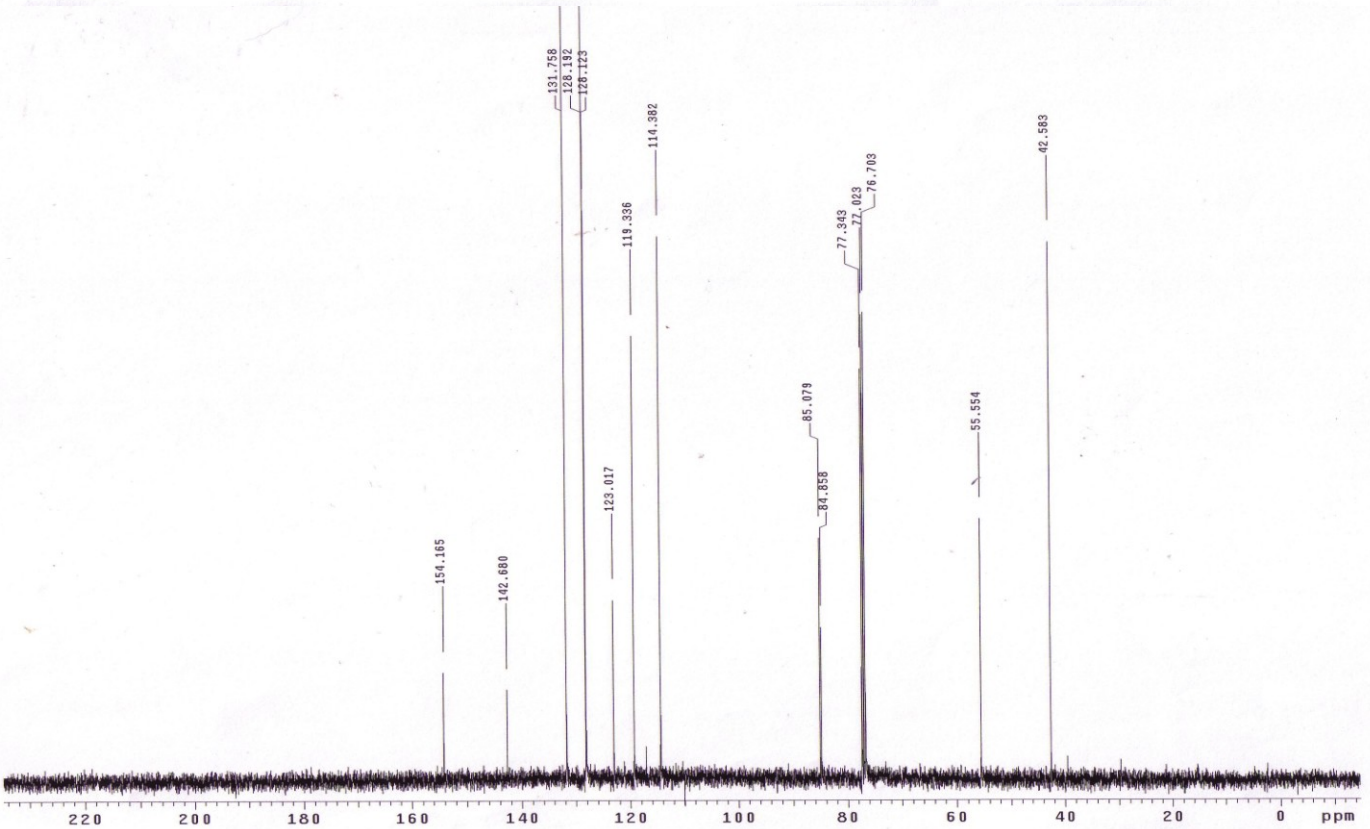
^{1}H and ^{13}C NMR of (2.2.4)



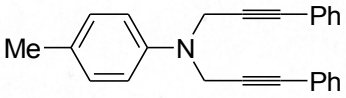


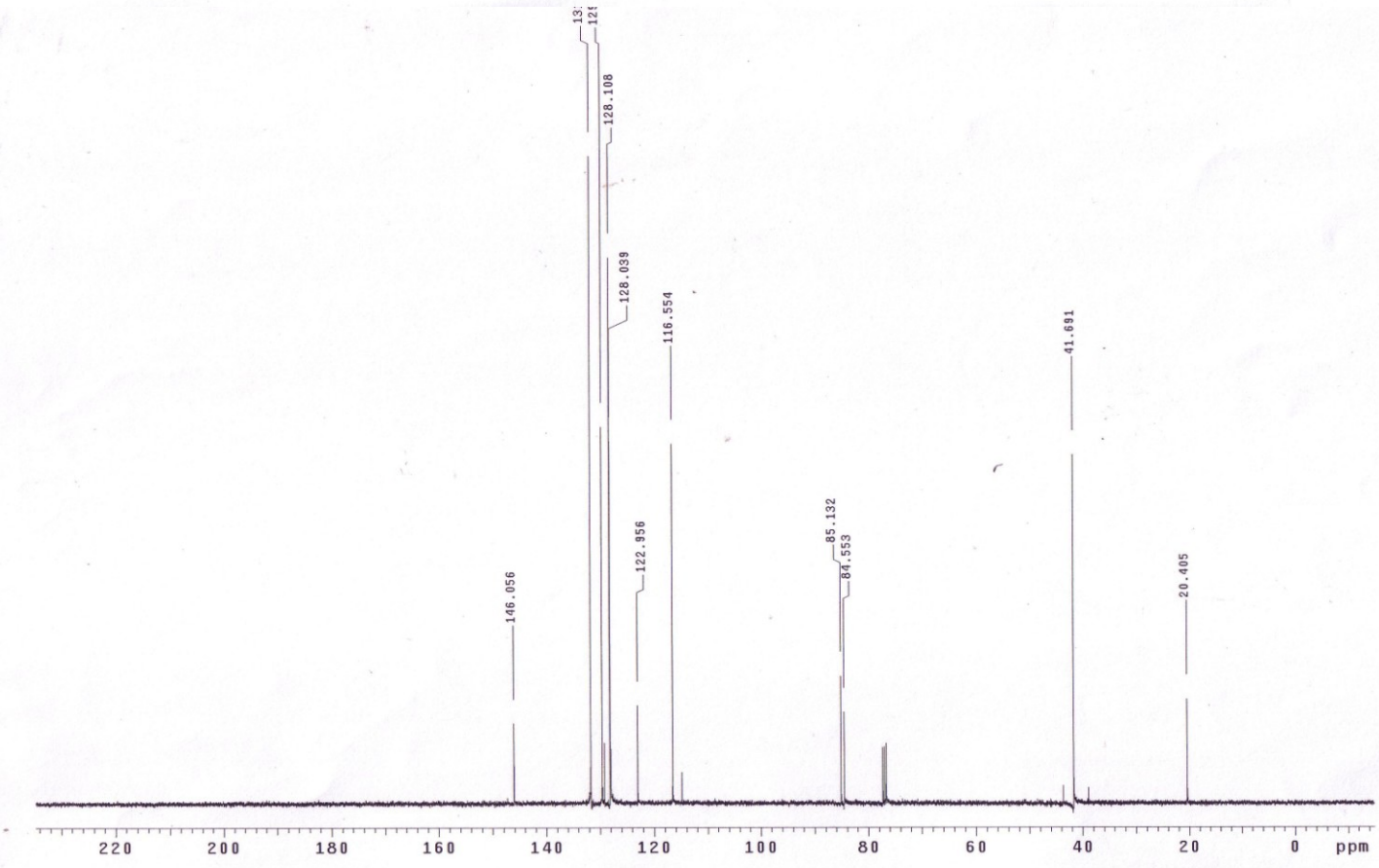
^{1}H and ^{13}C NMR of (2.2.5)



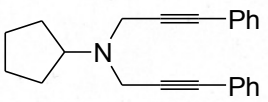


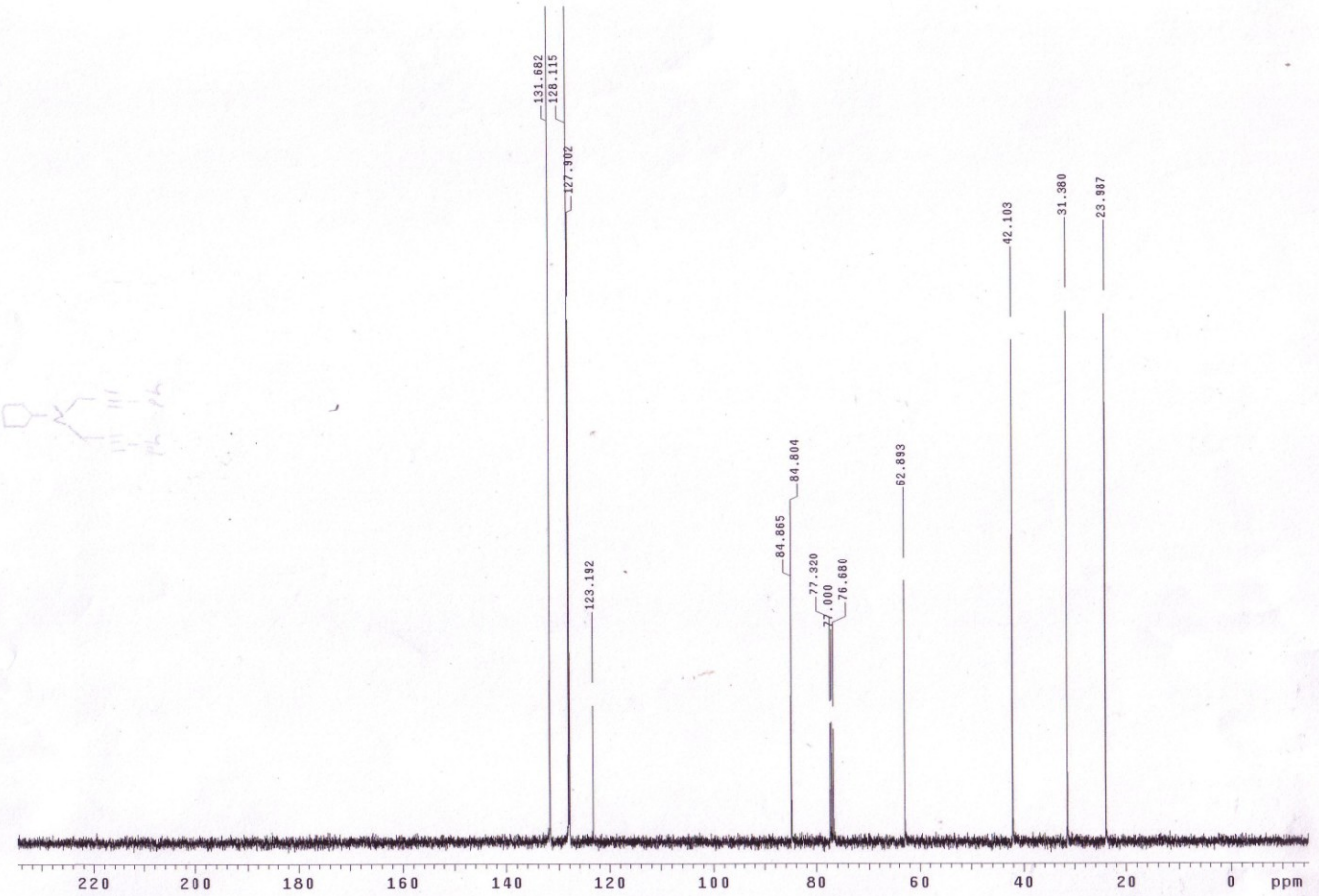
^{1}H and ^{13}C NMR of (2.2.6)





^{1}H and ^{13}C NMR of (2.2.7)





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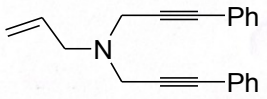

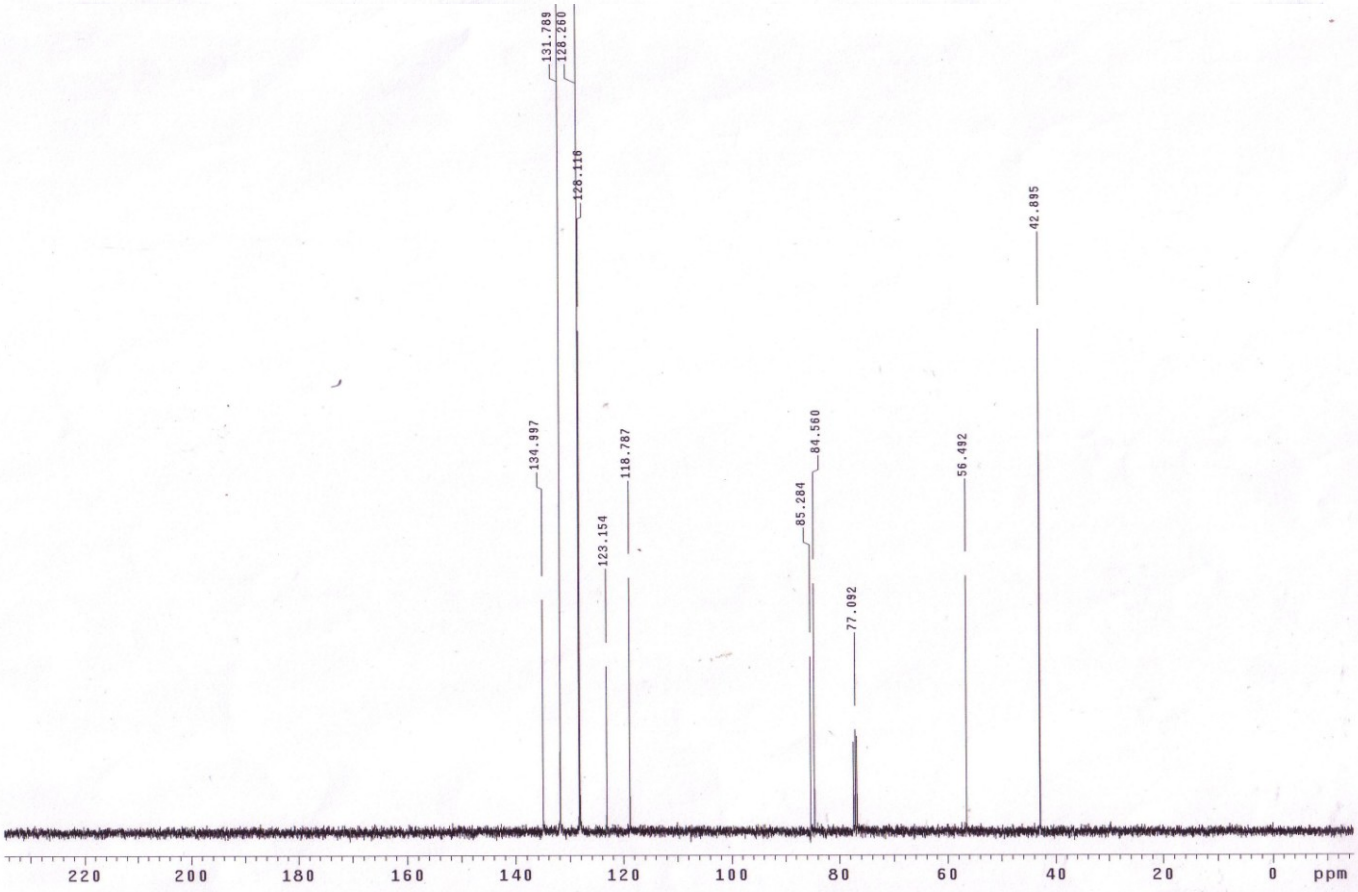

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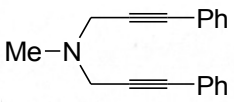
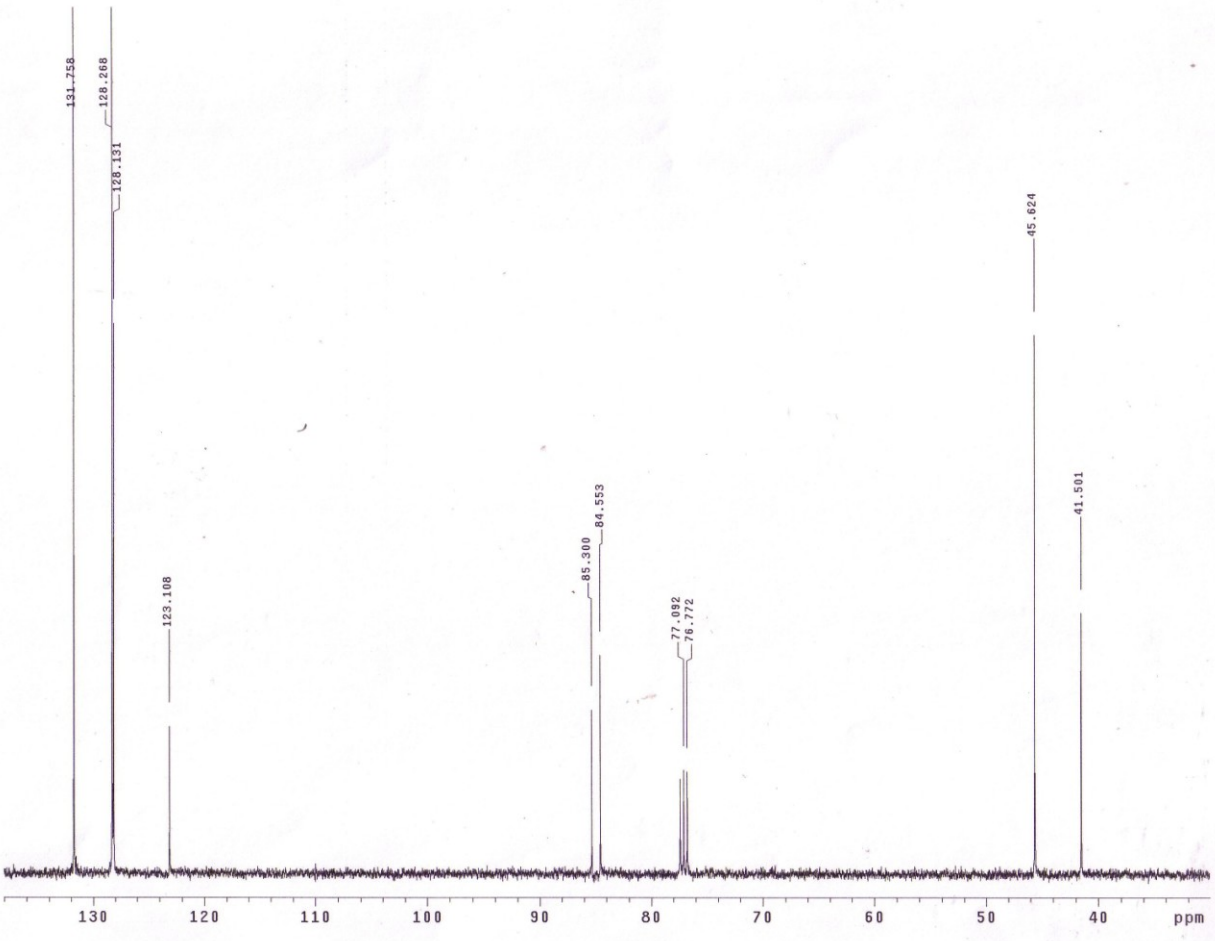
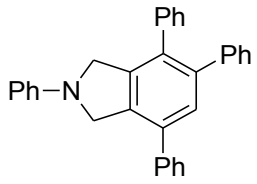


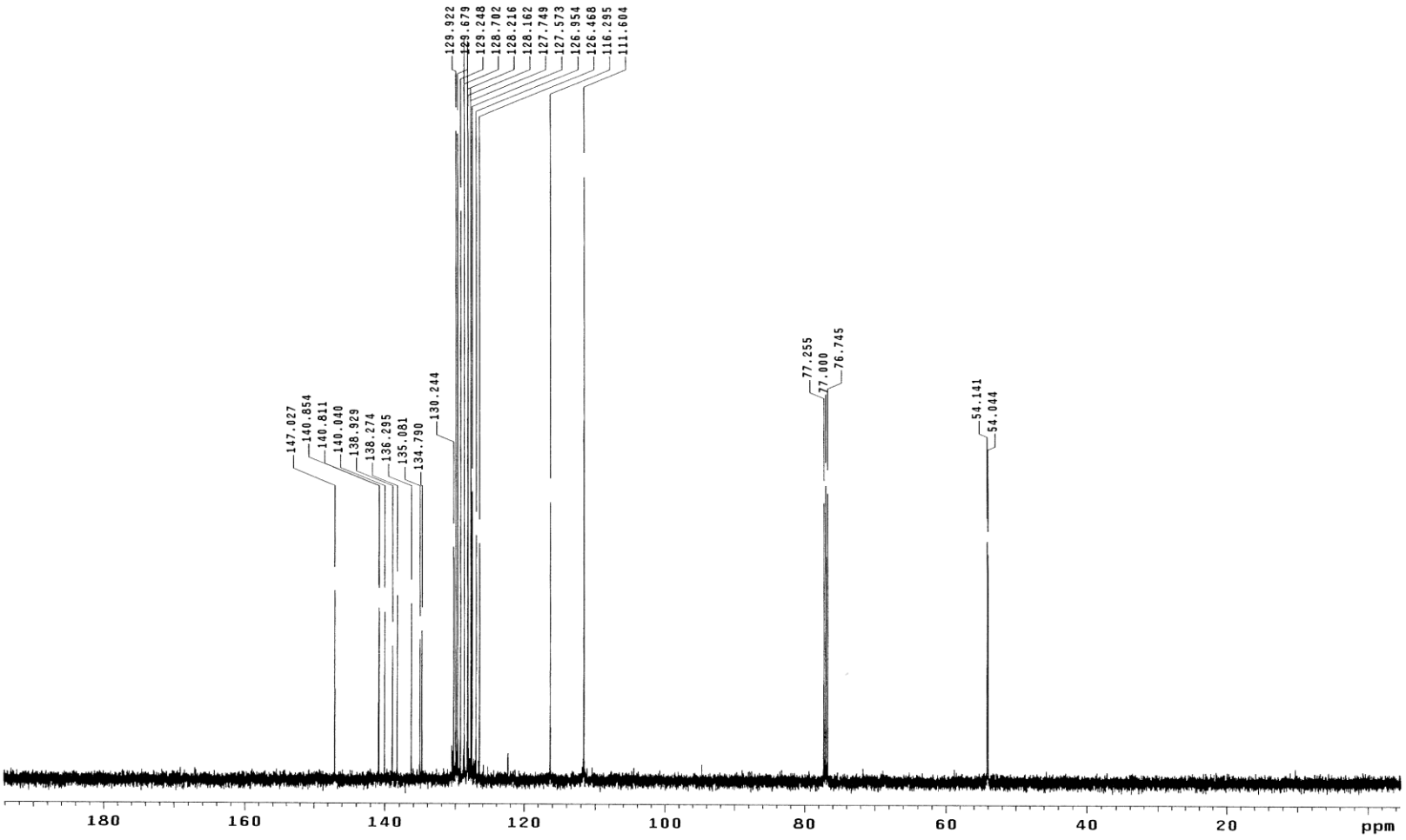


Appendix B

^{1}H and ^{13}C NMR Spectra for Chapter 3 Compounds 3.4.1-3.4.11

^{1}H and ^{13}C NMR of (3.4.1)





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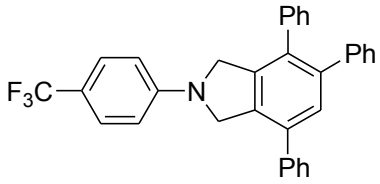
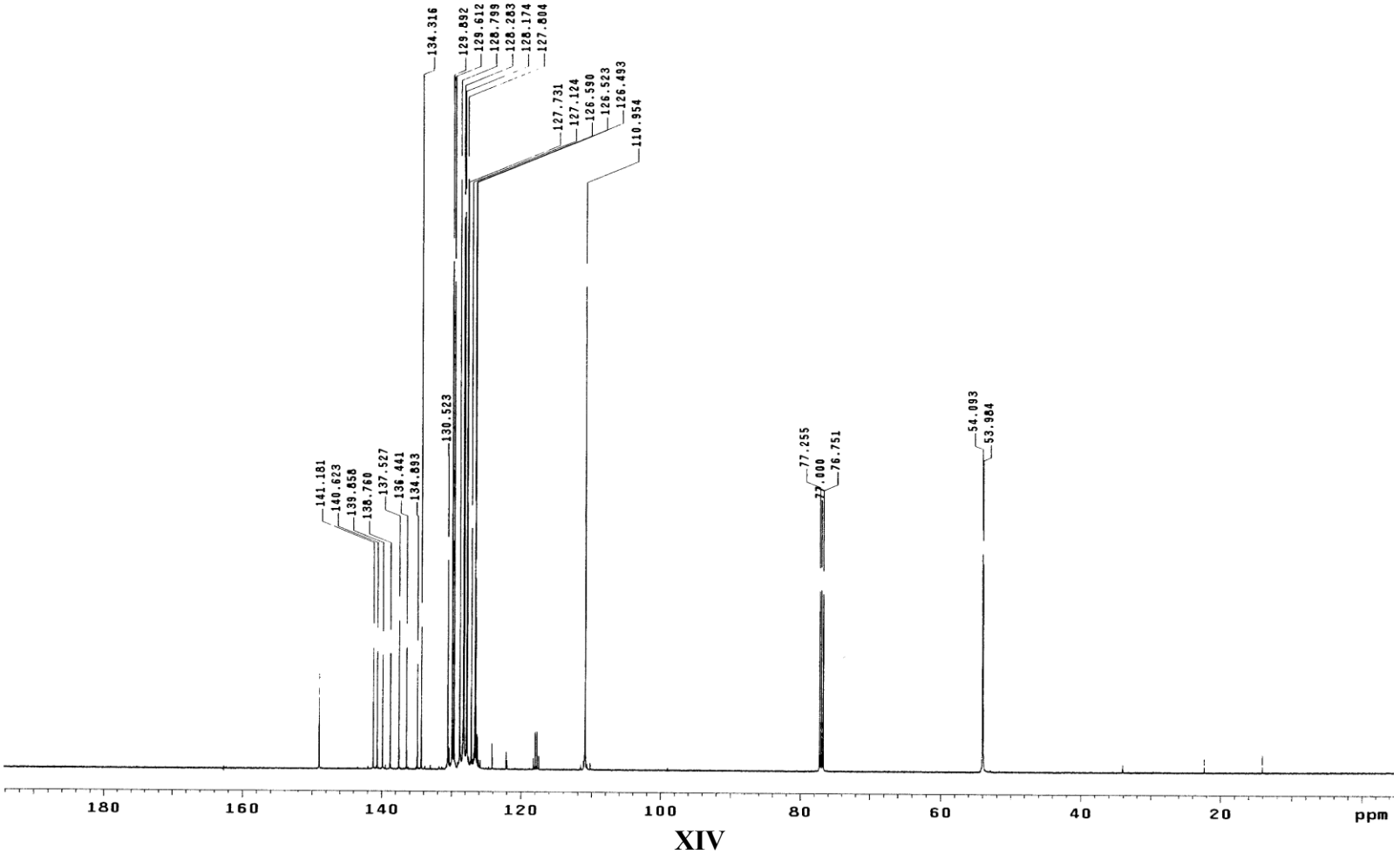
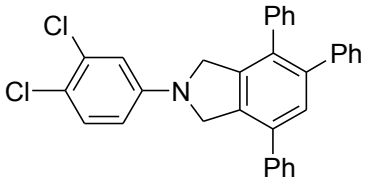
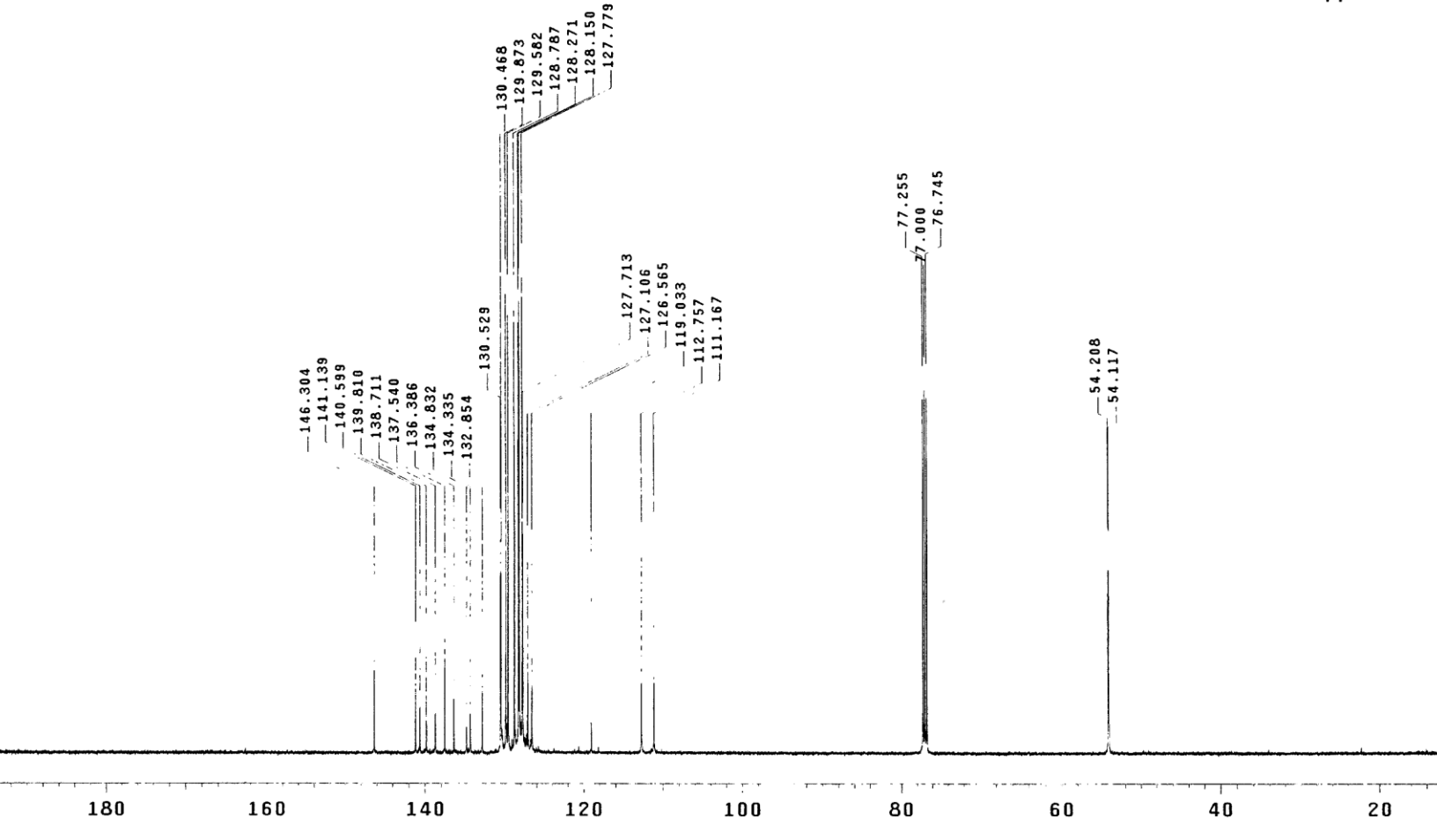


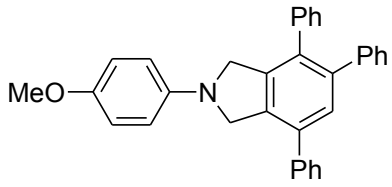


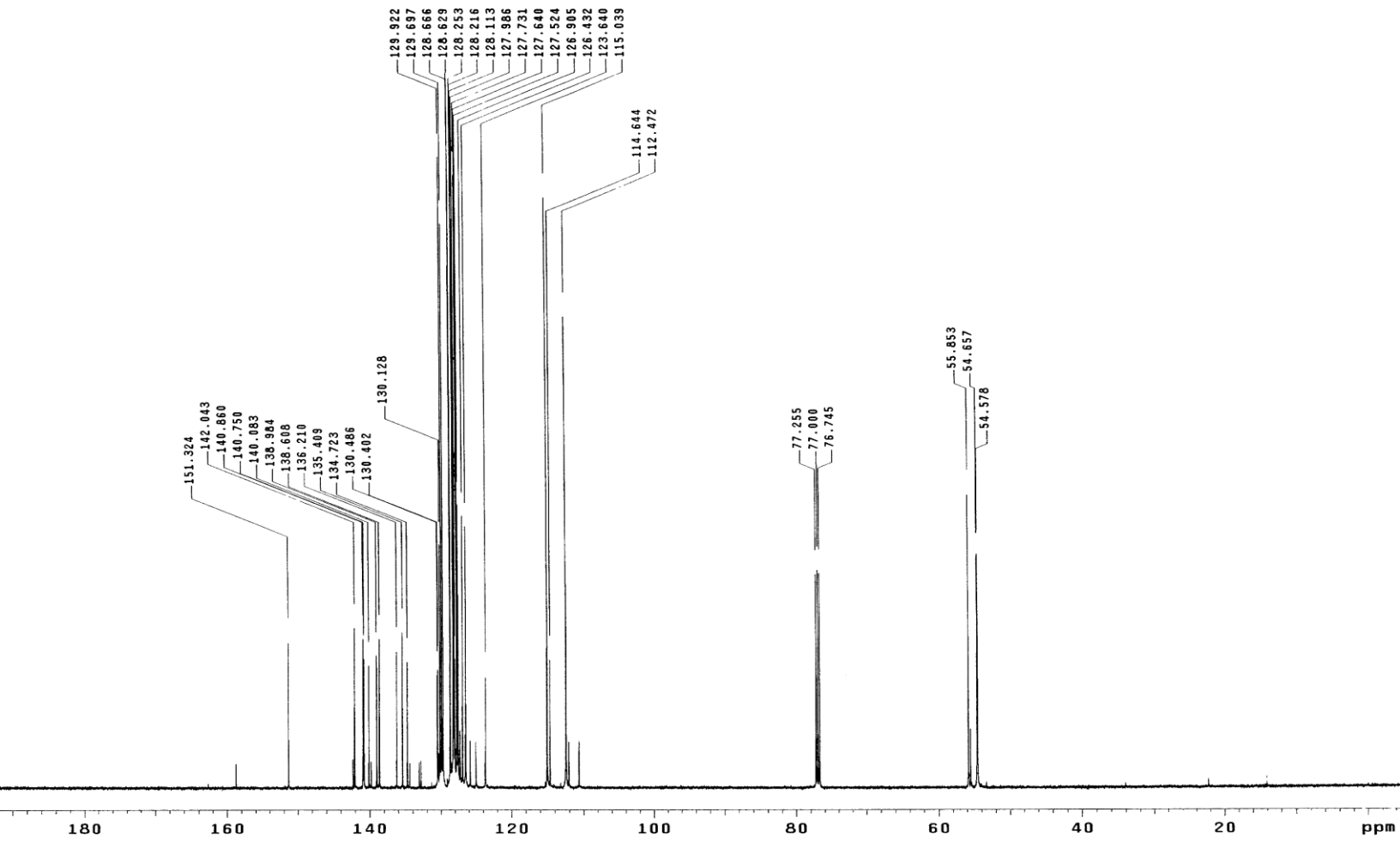
^{1}H and ^{13}C NMR of (3.4.3)





^{1}H and ^{13}C NMR of (3.4.4)





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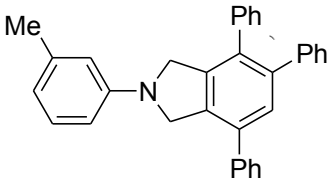
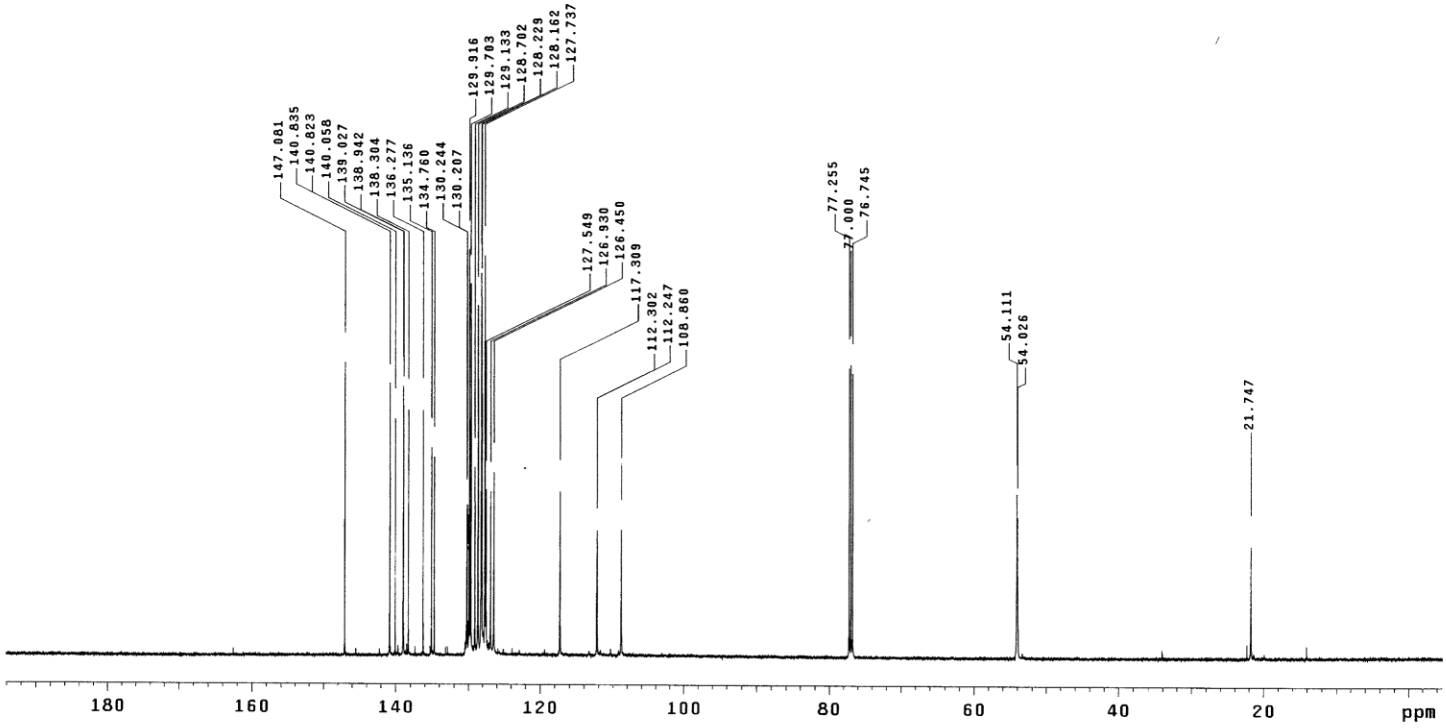
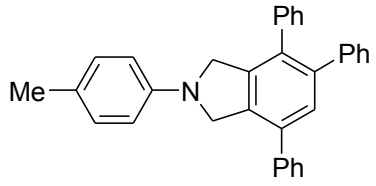
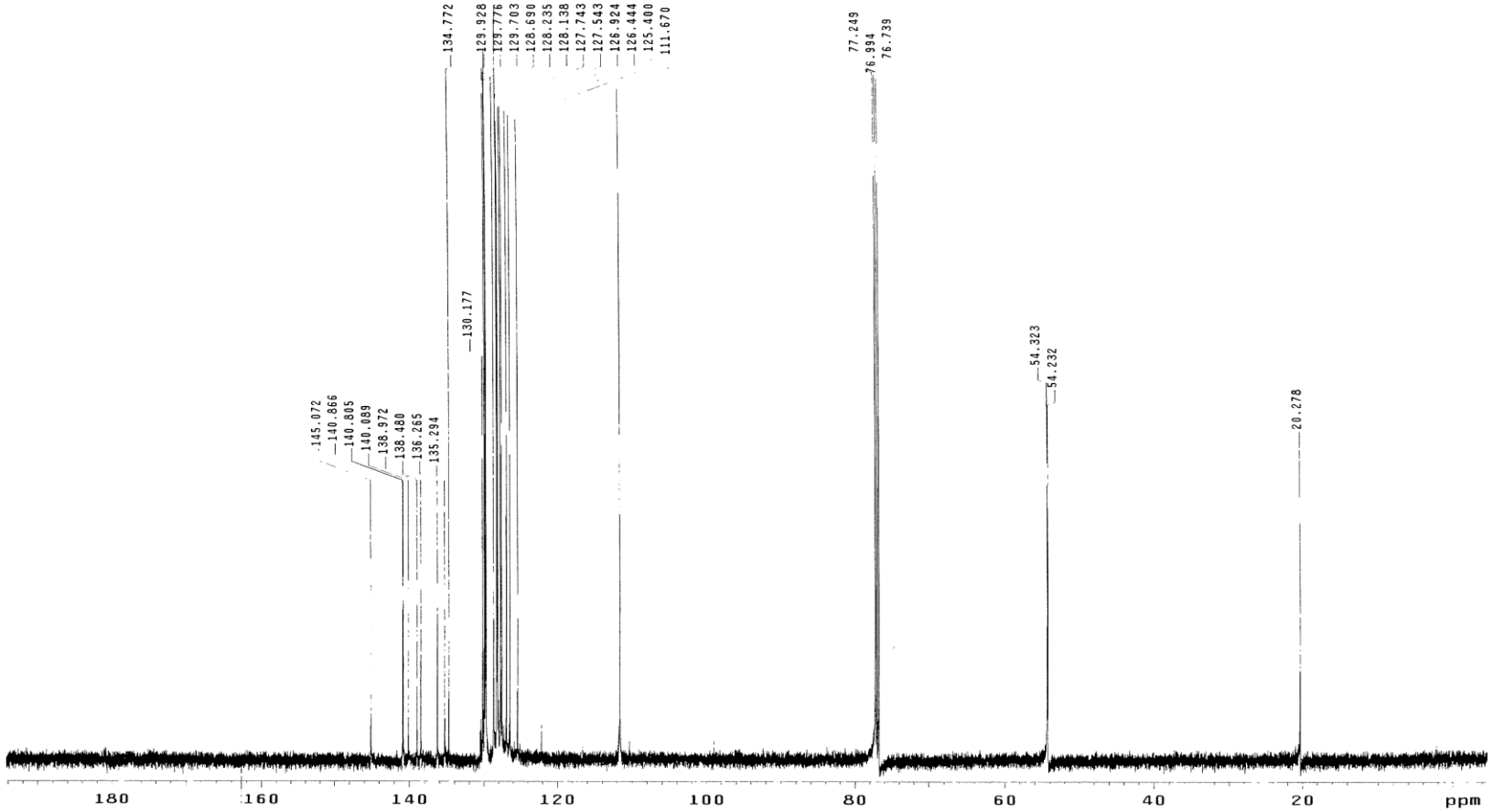




^{1}H and ^{13}C NMR of (3.4.6)





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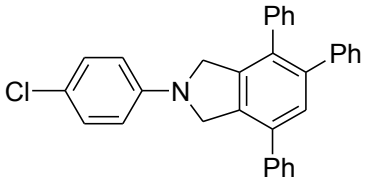

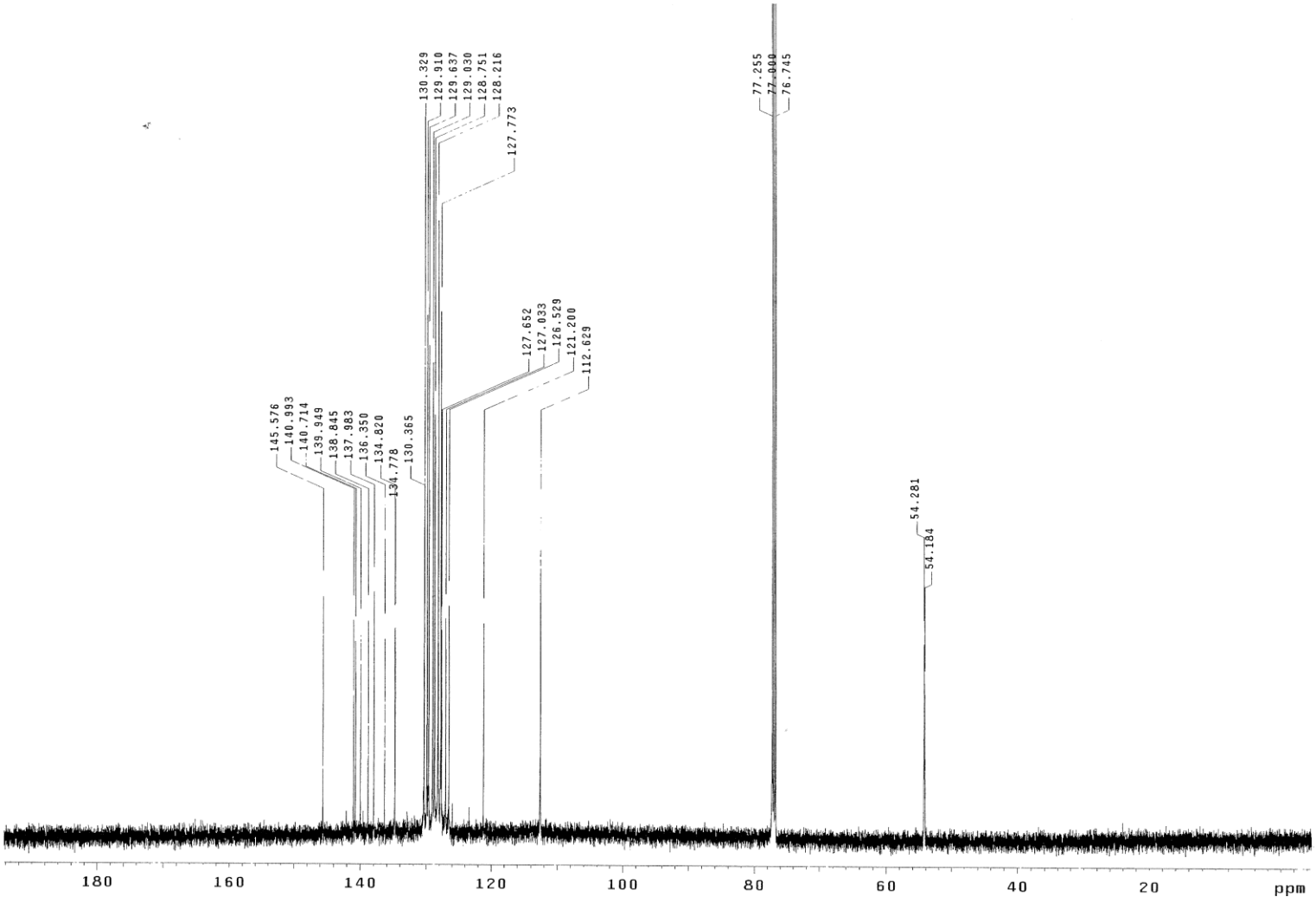

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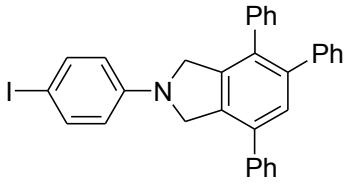
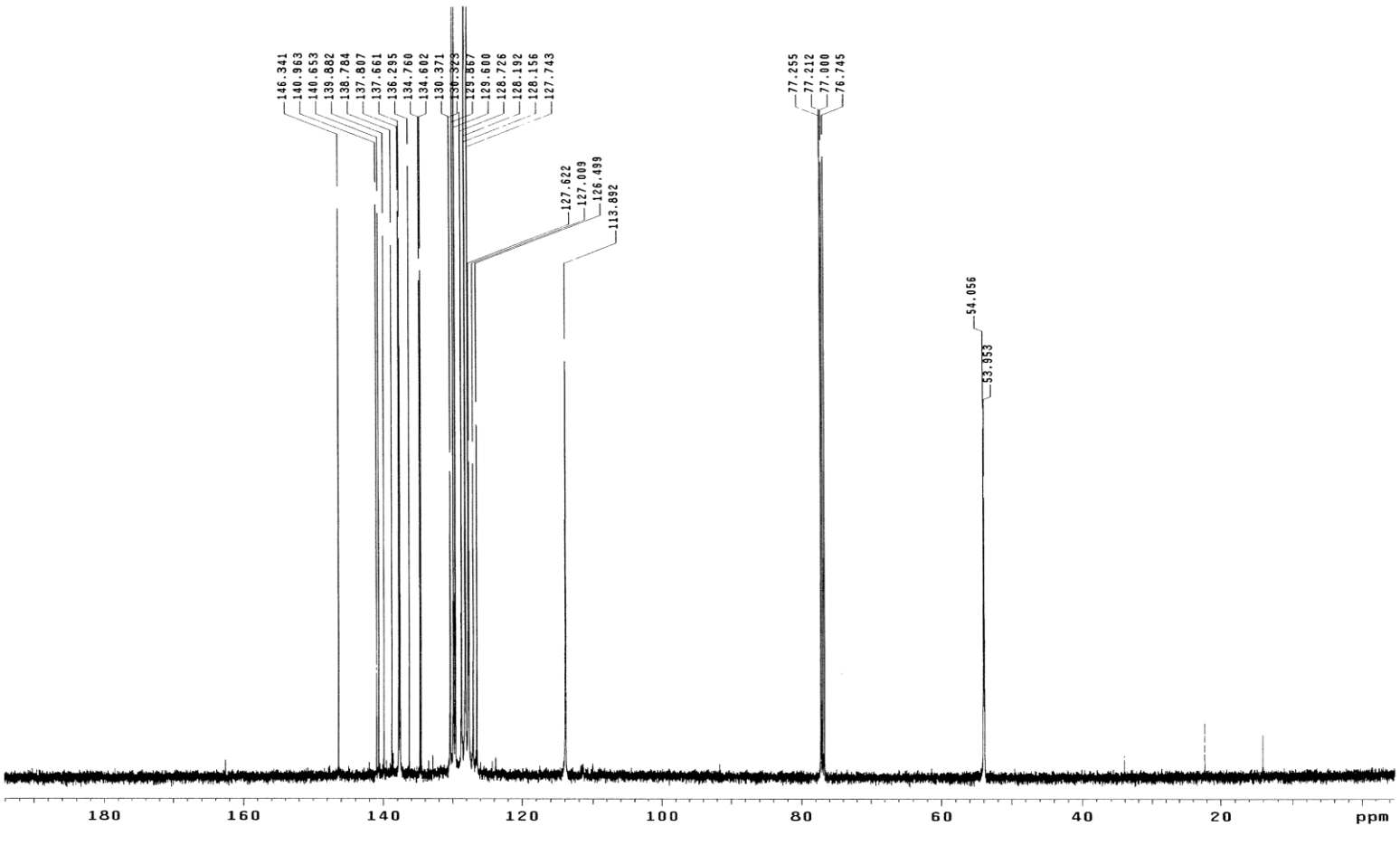
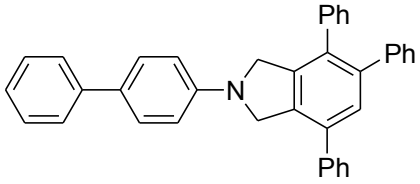
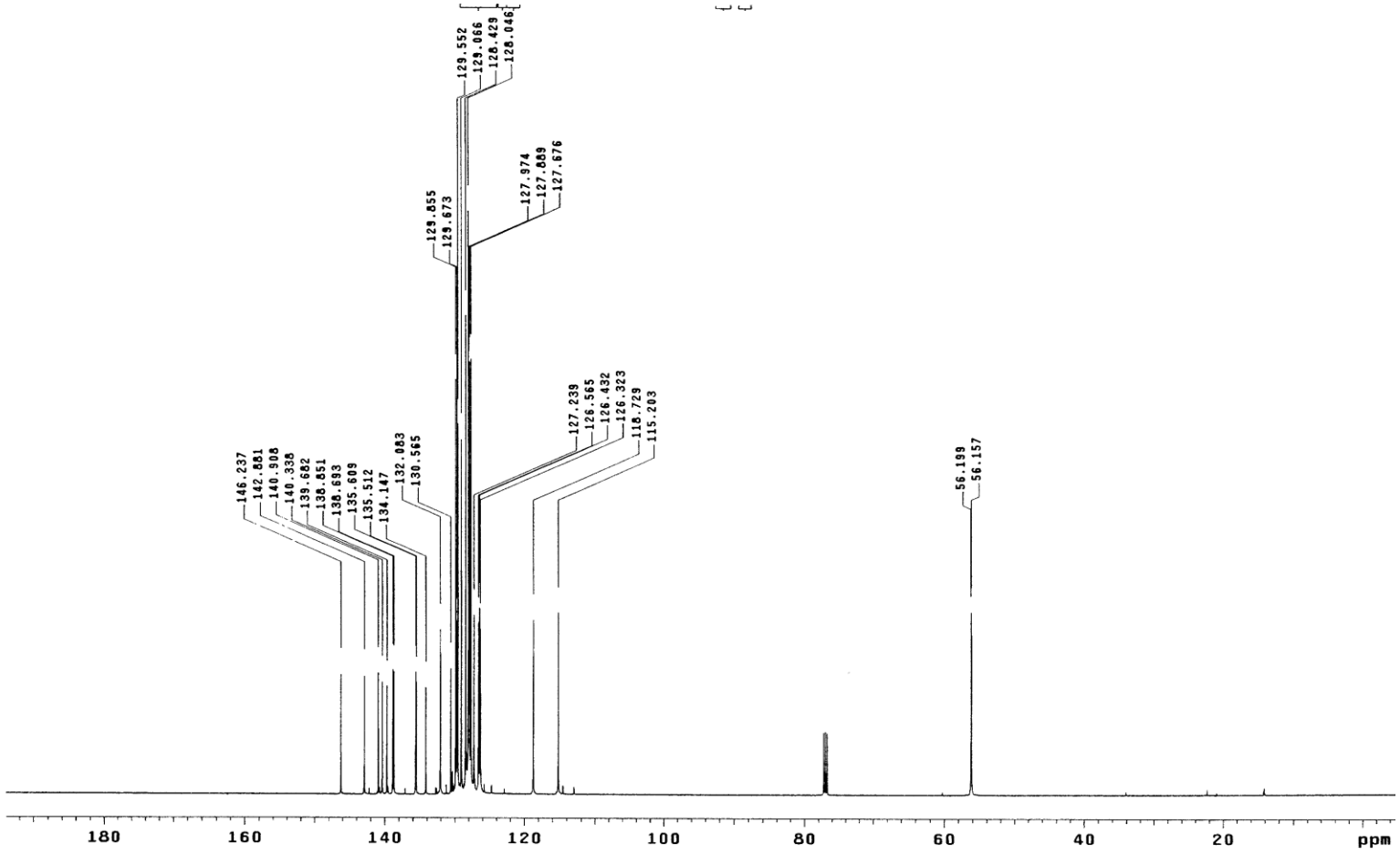




^{1}H and ^{13}C NMR of (3.4.9)





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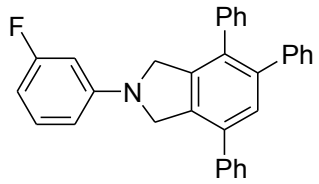

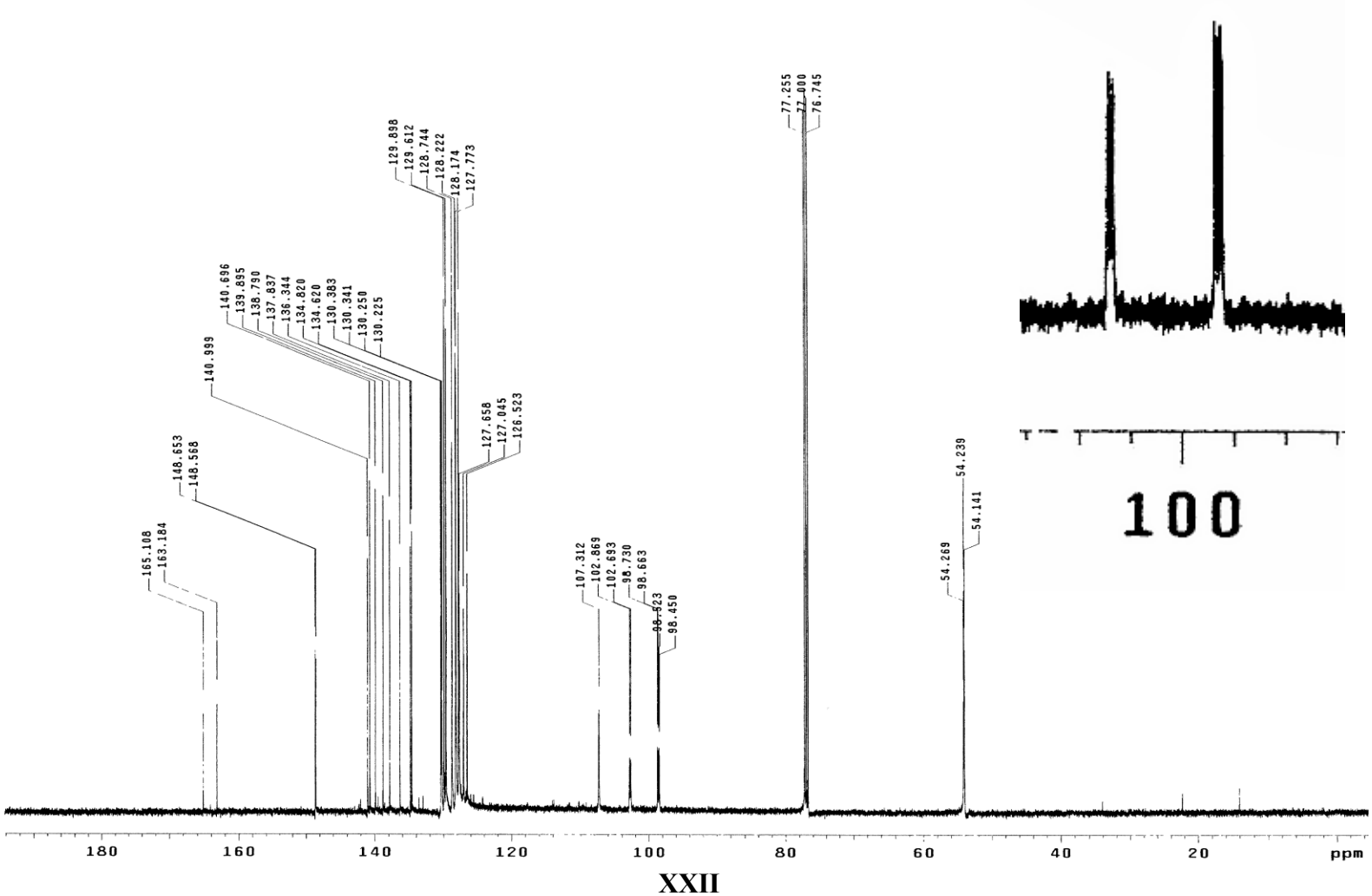

^{1}H and ^{13}C NMR of (3.4.11)