SYNTHESIS OF ACRYLAMIDINES VIA THE INTRAMOLECULAR AMINO GROUP MIGRATION

Thesis submitted towards the partial fulfillment

of BS-MS dual degree programme

By

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Under the guidance of

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Certificate

This is to certify that the thesis titled "**Synthesis of acrylamidines via the intramolecular amino group migration**" towards the partial fulfilment of BS-MS Dual degree programme at Indian Institute of Science Education and Research (IISER), Pune represents original research carried out by **Sreejith J. Varma** at IISER Pune under the supervision of **Dr. Pinaki Talukdar**, Assistant Professor, Department of Chemistry during the academic year 2013-2014.

Declaration

I hereby declare that the matter embodied in the report titled " **Synthesis of acrylamidines via the intramolecular amino group migration** " are the results of the investigation carried out by me at the Department of Chemistry, IISER Pune, under the supervision of Dr. Pinaki Talukdar and the same has not been submitted elsewhere for any other degree.

Date of Submission:

Place: Sreejith J. Varma

Acknowledgement

It is my privilege to be a student of the Department of Chemistry, IISER Pune. I would like to thank Dr. Pinaki Talukdar for introducing me to this wonderful research environment in my first year and the several accomplishments that I was able to achieve thereafter under his guidance. His intense care as well as timely criticisms are what that has moulded the researcher in me. The various research opportunities he provided gave me a glimpse of the academic research and its ways.

I would like to thank Dnyaneshwar who has taught me the techniques and skills of the laboratory which I would cherish for the rest of my life.

I would like to thank Dinesh whose collaboration without which I couldn't have achieved this feat- my thesis. His extensive patience and encouragement helped me through the difficult times during this project.

I thank all my lab mates Sharad, Tanmoy, Arundhati, Sopan, Pratyush, Prashant, Aditi and Ajit for their help and making my study at the department pleasant and enjoyable.

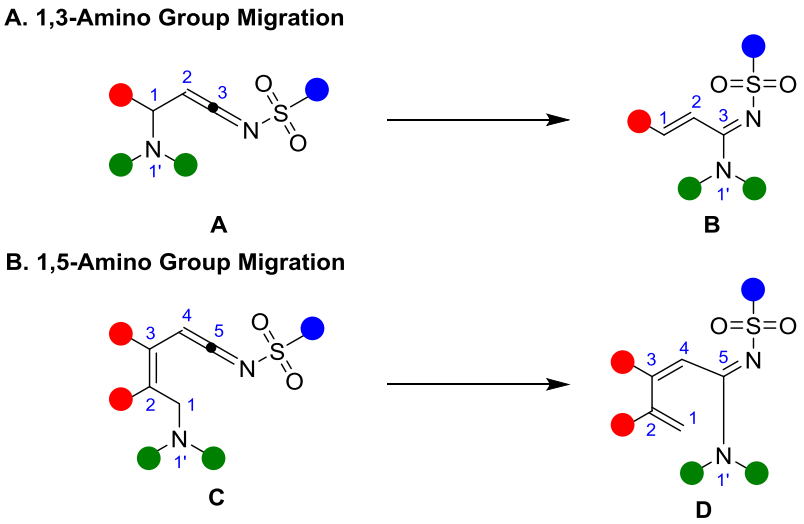
I would like to thank all my friends and batch mates for their support throughout my study. I would also like to thank Sonashree whose encouragement during my difficult times was a blessing.

- Sreejith

Contents

Abstract

Ketenimine is a synthetic intermediate that has been applied in wide ranges of reactions. Cu(I) catalyzed cycloaddition reaction of alkyne with sulfonylazide is reported to form ketenimine intermediate which participate in addition reactions with various external nucleophiles *e.g.* amine, alcohol, water, etc. In the present work, we demonstrate new types of reactions *i.e.* rearrangements of ketenimines involving a flanking amino group as an internal nucleophile. We report that propargylamine derivatives when reacted with sulfonylazides undergo a 1,3-amino group migration leading to acrylamidines. The methodology allows the formation of acrylamidines even in the presence of competing nucleophiles, such as H_2O, alcohol, amine and thiol. We further demonstrate that a flanked amino group also undergoes 1,5-migration when a C=C moiety is introduced between the alkyne and the aminomethylene group. *Cis*-stereochemistry of these groups around the C=C is important for the rearrangement to proceed.



Publication:

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Introduction

A. Amidines

Amidines are nitrogen analogues of carboxylic acid and ester functionalities. Attributing to the presence of two highly conjugated N atoms, this functionality is one of the strongest organic bases along with guanidine functionality (**Figure 1A**). Their p*K*a is in the range of 24 and protonation occurs on the imino nitrogen forming a conjugated amidinium ion.[1] Owing to their strong basicity, amidines *e.g.* 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN), etc. have been employed in organic synthesis (**Figure 1B**). For example, DBU is routinely used in dehydro-halogenation reactions to avoid the undesirable side-products due to its milder reaction conditions than when employing other nitrogen bases.[1] Amidine bases are also effective acyl transferring agents in organocatalysis.[1]

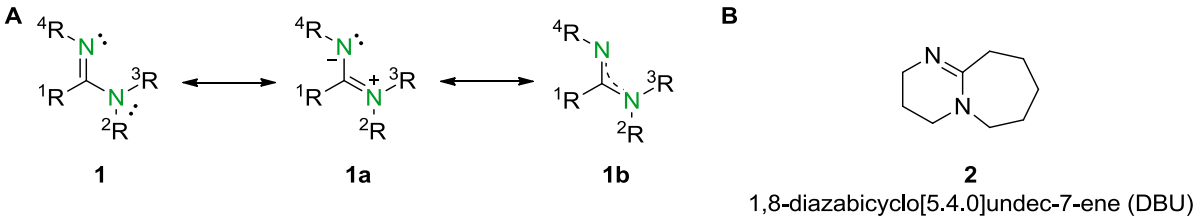


Figure 1: (**A**) Demonstration of resonance in amidine. (**B**) Structure of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

In nature, molecules such as norformycin (from actinobacteria) and pentamidine (used to treat protozoan infections) bear amidine moieties.[1] Furthermore, they serve as important lead compounds in pharmacology,[2] synthetic intermediates and efficient coordinating ligands.[3] This ubiquitous functionality is an integral component of several top selling medicines.[4] Some of the drugs that contain the amidine functionality are depicted in **Figure 2**. Noformycin **3** is inhibitor of human inducible-Nitric Oxide Synthase and is used in anti-cancer treatment. Another example is Quetiapine **4** which is used as anti-psychotic medication. Pentamidine **5** is an amidine containing drug which is prescribed for the treatment of pneumonia.

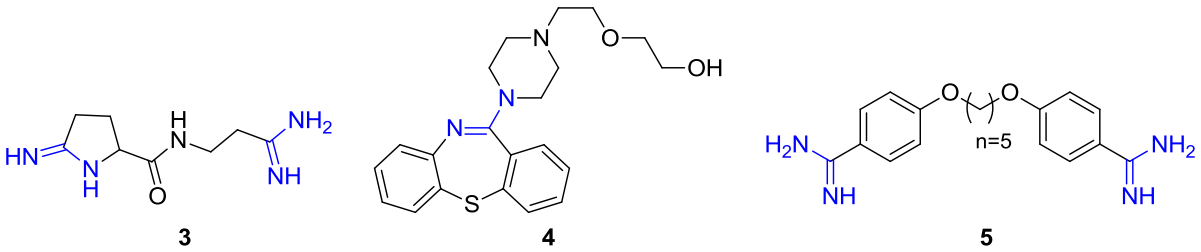
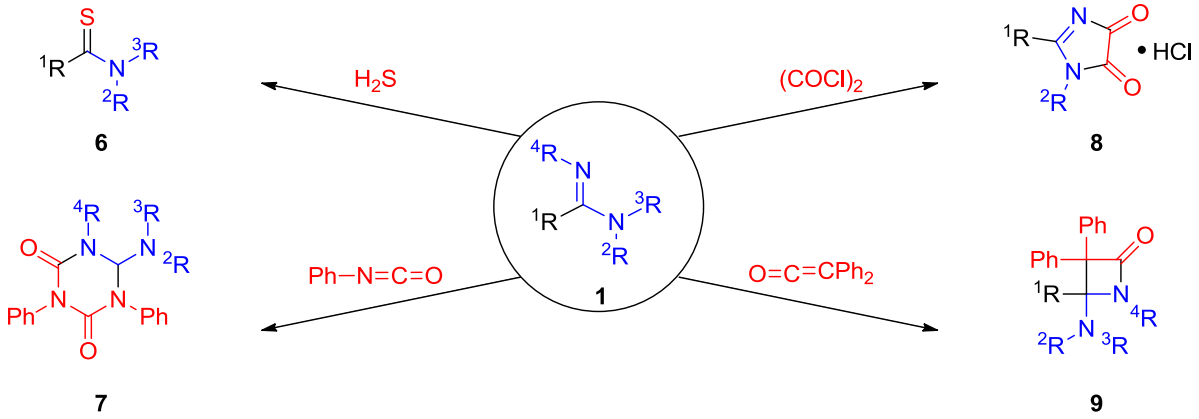


Figure 2: Selected examples of drugs bearing amidine functionality: Noformycin **3**, Quetiapine **4** and pentamidine **5**.

In addition to its direct utility in medicinal chemistry, amidines are considered as important synthetic precursors for the preparation of thioamides[5] and heterocycles like triazines,[6] azetidinones[7] and imidazolinediones.[8]



Scheme 1: Synthetic applications of amidines.

B. Acrylamidines

In 1968, Hamada and co-workers isolated colourless crystalline hydrochlorides from a culture of a streptomyces and the molecules displayed antibiotic activity.[9] Structural elucidation using spectroscopic methods depicted the structure as acrylamidine **10** (**Figure 3**). Since then, acrylamidine has been an essential component of various bioactive synthetic molecules. This motif is encountered as selective agonists for muscarinic receptors and other receptors belonging to NR2B subtype[10] and are used for selectively installing methylarginine modifications on

recombinant proteins.[11] In addition to ranges of biological activity, the additional α,β-unsaturation could provide access to a variety of synthetic transformations like epoxidation, cycloadditions, metathesis etc. The reactivity of acrylic functionality is determined by the functional group at allylic position. Hence a tuneable electron donating group like amidine can alter the reactivity of the functionality towards various polymerisation and Michael addition reactions.

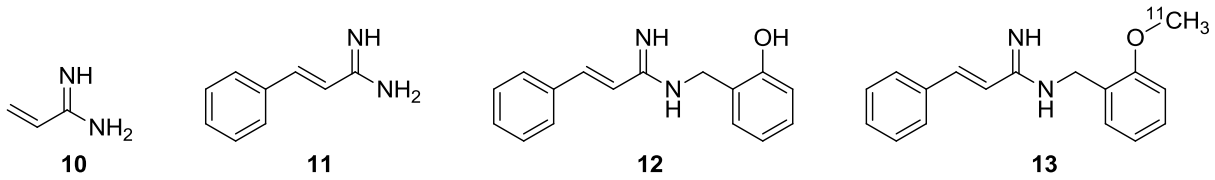


Figure 3: Biologically active acrylamidines: Anti-fungal agents **10** and **11**, NR2B subtype specific NMDA antagonist **12** and ^{11}C labelled antagonist **13** for target binding studies.

The applications of acrylamidines are not limited to synthetic chemistry. Possessing structural features like constrained rotations make them ideal for conformational studies in physical organic chemistry. When a steric strain barrier is introduced along an acyclic π system *e.g.* 1,3-butadiene (**15**), they can behave as a non-aromatic analogue of biaryls (**14**) that exhibit restricted rotation along the single bond, called atropisomerism (**Scheme 2**). Acrylamidines with bulky substituents on nitrogen (**16**), are used as tool for atropisomerism studies[12] and it is also employed in the study rotational modes of torquo-selective electrocyclic ring opening reactions.[13]

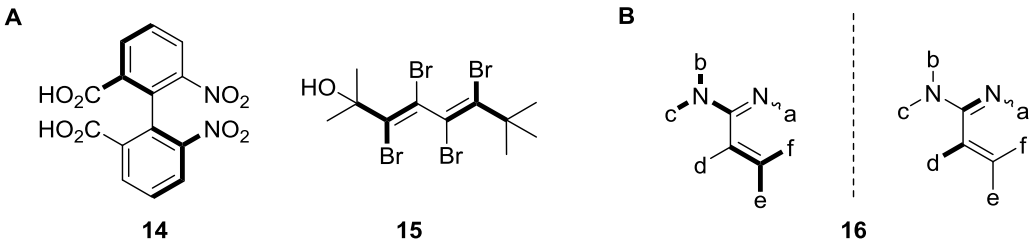
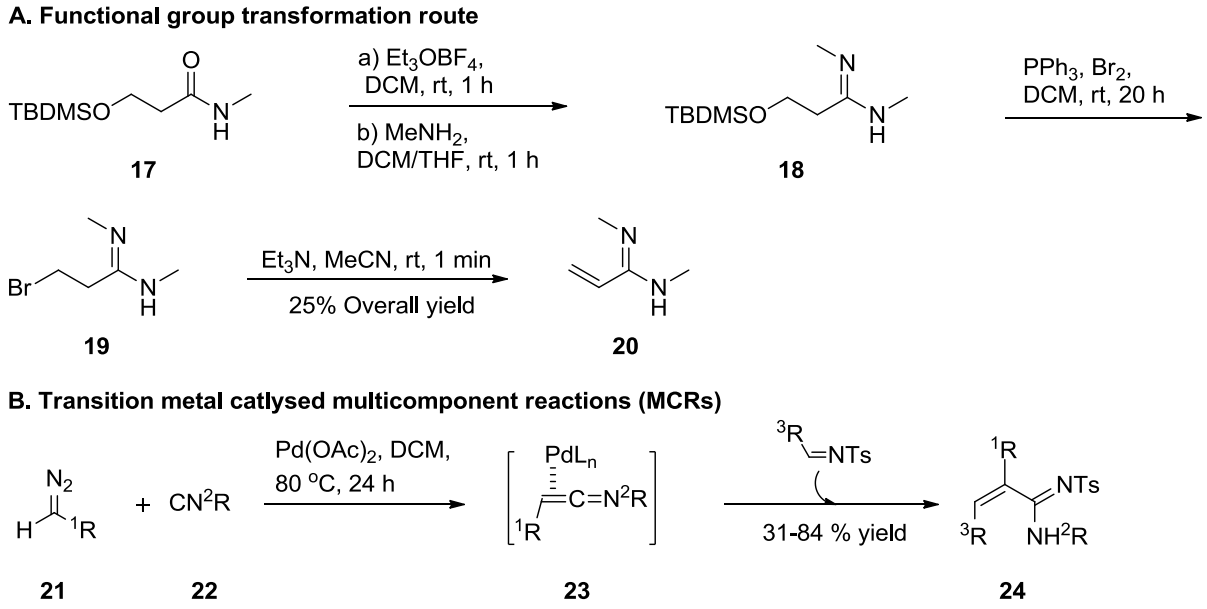


Figure 4: Examples of classical molecules (**A**) and acrylamidines (**B**) used in the atropisomerism studies.

Due to such diverse synthetic applicability of acrylamidines, there have been many reports in recent years for their preparation. Among the popular methods adopted for amidine synthesis, the most commonly encountered routes use either functional group transformation or multicomponent reactions (**Scheme 2A**). A major drawback of these methods is long reaction times and unsatisfactory yields.

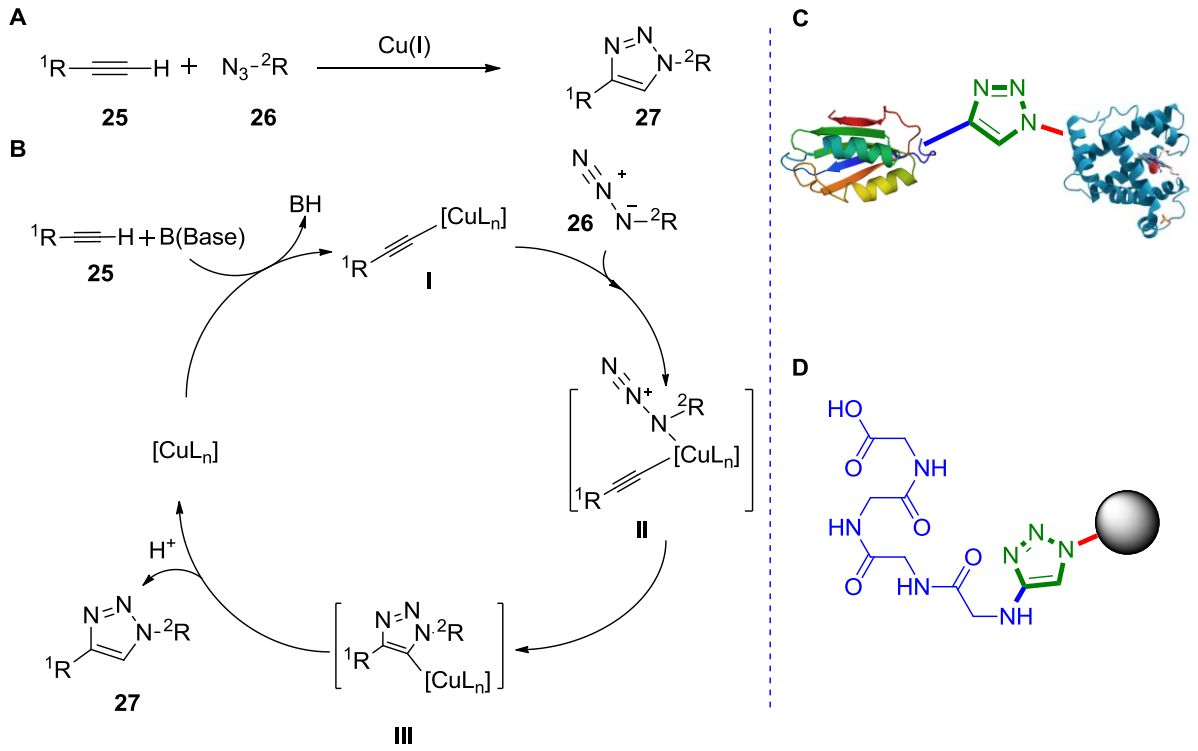


Scheme 2: Examples of reported acrylamidine synthesis.[13],[14]

C. Cu(I) Catalyzed Alkyne-Azide Huisgen Cycloaddition

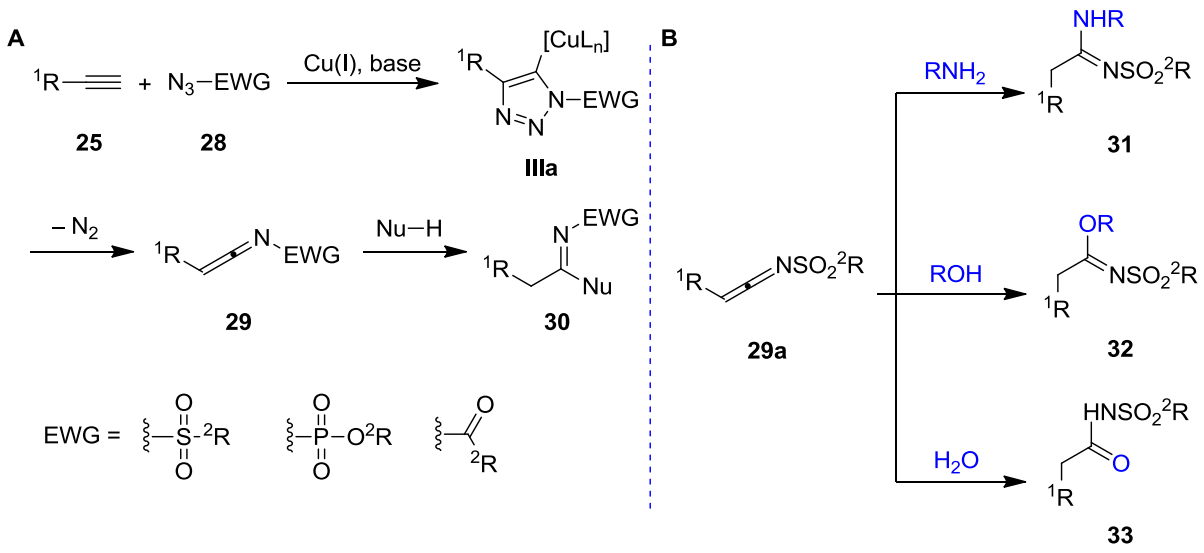
Although alkyne azide cycloaddition was discovered by Dimroth in early 20th century, its scope, generality and mechanism were not completely understood until recently.[15] The mixture of 1,4- and 1,5-disubstitued products the reaction generates as well as requirement of elevated temperatures hindered the wide spread use of this chemistry. In 2002, independent works of Sharpless and Meldal demonstrated that use of Cu(I) could enable this cycloaddition proceed under milder conditions with a regioselectivity for 1,4-adduct formation (Scheme 3A) thus enabling the use of this extremely convenient reaction for a variety of applications like functional group transformation, ligation of biomolecules and fluorophores, linker to connect to solid support in solid phase synthesis, etc.[16] This energetically favourable Huisgen cycloaddition, results in a exclusive 1,4-disubstituted-1,2,3-triazole formation

between the alkyne and the azide , mechanism of which is described in Scheme 3B. The Cu(I) along with base activate the alkyne terminal carbon forming a copper acetylide (**I**). This specie undergoes further complexation with an azide producing **II** which subsequently allows the formation of triazole **III** in a regioselective fashion.



Scheme 3: Copper(I) catalysed azide alkyne Huisgen cycloaddition (**A**), its mechanism **(B)**, and its application in chemically stapling biomolecules **(C)**, linker for solid phase synthesis (**D**).

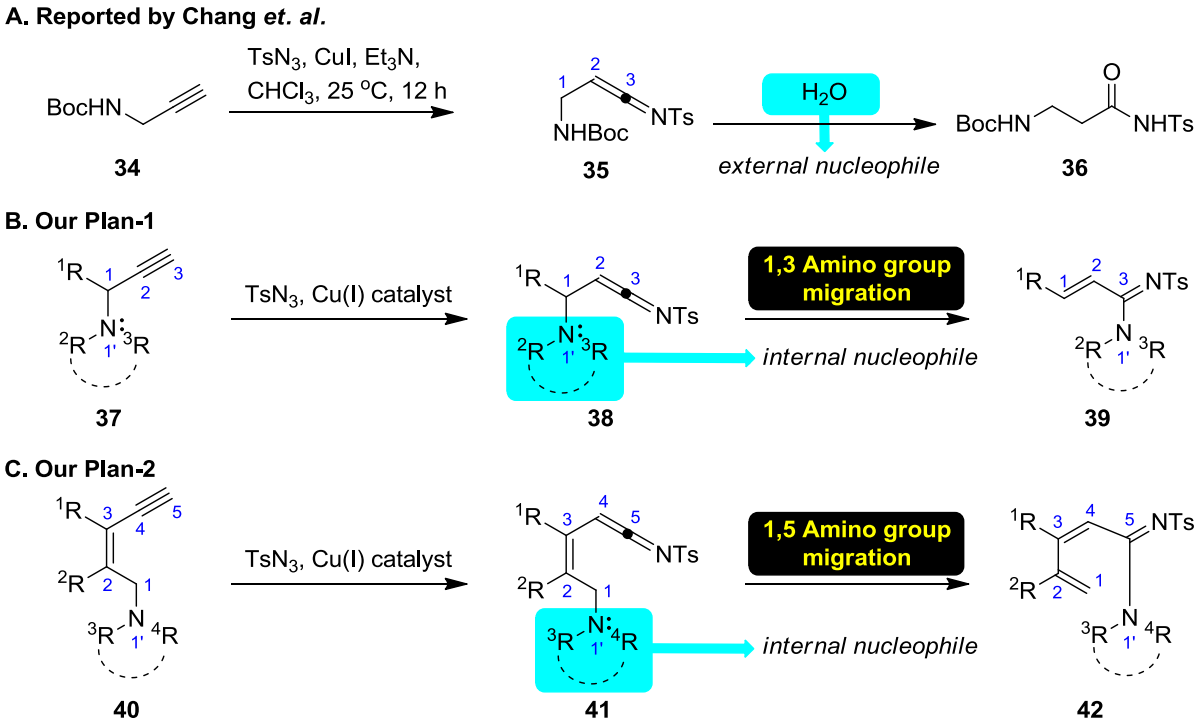
While exploring various synthetic applications of 1,2,3-triazoles, Chang et. al discovered that azides bearing an electron withdrawing group such as sulfonyl, phosphoryl, carbonyl, etc. promotes the collapse of triazole **III,** releasing a molecule of nitrogen to produce a reactive ketenimine **29**.[17] The ketenimine thus formed is highly electrophilic and can react with a variety of nucleophiles like amines, alcohols and water to yield amidines (**31**), imidates (**32**) and amides (**33**) respectively (**Scheme 4**).[18]



Scheme 4: (**A**) Formation of ketenimine intermediate from alkyne and azide under Cu(I) catalytic conditions. (**B**) Reactions of the ketenimine intermediate with various nucleophiles.

Objectives

In 2005, Chang and co-workers reported nucleophilic addition of water to ketenimine which is formed during the reaction between alkyne and sulfonylazide.[19] The article describes generation of β-amino sulphonamide **36** from Boc protected propargylamine **34** and tosylazide via the generation of a ketenimine intermediate (**Scheme 5A**). In this reaction, water acts as an external nucleophile similar to previously reported reactions with alcohols, amines, *etc.* Although, an internal amino group (-NHBoc group) is present in the molecule, its participation is not favoured due to electron withdrawing -Boc group. We envisaged the potential of the tethered amino group to undergo migration if it is made sufficiently nucleophilic because, Wentrup *et. al*. have already reported a ketenimine-ketene rearrangement mediated by a flanking amino group under flash vacuum thermolysis conditions.[20] However, Cu(I)-catalytic formation of ketenimine is advantageous to investigate the amino group migration under milder reaction conditions. With propargylamine **37**, corresponding ketenimine **38** would undergo a 1,3-amino group migration to form acrylamidine **39** (**Scheme 5B**).



Scheme 5: (**A**) Scheme developed by Chang and co-workers (**B**) 1,3-amino group migration (**C**) 1,5- amino group migration.

The same concept can also be translated to 1,5-amino group migration to form more conjugated acrylamidine **42** if a C=C group is introduced between the C≡C and aminomethylene groups (**Scheme 5C**).

Therefore, the aim of the thesis is to develop and explore scopes of such strategies. The work is divided into flowing two sections:

Section 1: [1,3] Amino Group Migration Route to Acrylamidines.

Section 2: [1,5] Amino Group Migration Route to Acrylamidines.

Materials and Methods

A. General Methods:

All reactions were conducted under the nitrogen atmosphere. All the chemicals were purchased from commercial sources and used as received unless stated otherwise. Solvents: petroleum ether, ethyl acetate (EtOAc), dichloromethane (DCM), and methanol (MeOH) were distilled prior to thin layer and column chromatography. Column chromatography was performed on Merck silica gel (100–200 mesh). TLC was carried out with E. Merck silica gel 60-F-254 plates.

B. Physical Measurements:

The ^{1}H and ^{13}C spectra were recorded on 400 MHz Jeol ECS-400 (or 100 MHz for ^{13}C) spectrometers using either residual solvent signals as an internal reference or from internal tetramethylsilane on the δ scale ($CDCl_3$ δH, 7.24 ppm, δC 77.0 ppm). The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. The following abbreviations are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet) dd (doublet of doublet), dt (doublet of triplet), q (quartet), and sex (sextet). High-resolution mass spectra were obtained from MicroMass ESI-TOF MS spectrometer. Absorption spectra were recorded on a Thermo Scientific, Evolution 300 UV-VIS spectrophotometer. Steady State fluorescence experiments were carried out in a micro fluorescence cuvette (Hellma, path length 1.0 cm) on aHoriba JobinYvon, FluoroMax-4 instrument. (FT-IR) spectra were obtained using Bruker: α ALPHA spectrophotometer (neat) and reported in cm^{-1}. Melting points were measured using a VEEGO Melting point apparatus. All melting points were measured in open glass capillary and values are uncorrected. Crystal structures were recorded on a Bruker single crystal X-Ray diffractometer.

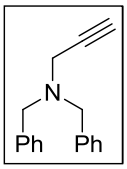
C. Experimental Procedures:

Section 1. [1,3] Amino Group Migration Route to Acrylamidines

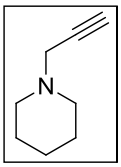
Preparation of propargylamine derivatives:

General Procedure A (Scheme 6A): To the round bottomed flask under N_2 atmosphere was added propargylbromide (1.0 equiv) in acetonitrile. To this solution were added amine (1.0 equiv), anhydrous K_2CO_3 (2.0 equiv) at 0 ^{o}C and the

resultant reaction mixture was stirred at room temperature for 18 h. After completion of reaction, acetonitrile was evaporated. The obtained residue was washed with water, extracted with EtOAc (2 × 5 mL) and the combined organic layers was dried over anhydrous Na_2SO_4. The solvent was evaporated and resultant crude product was purified by column chromatography.

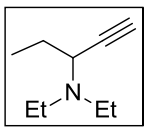


Synthesis of *N,N*-dibenzylprop-2-yn-1-amine (43) [$C_{17}H_{17}N$]:[26] The compound **43** was prepared by following the *General Procedure A* and obtained as a colourless solid after column chromatographic purification. *Eluent*: 3% EtOAc in Petroleum ether (R_f = 0.7). Obtained data was matched with the reported literature data.



Synthesis of 1-(prop-2-yn-1-yl)-piperidine (37i) [$C_8H_{13}N$]:[27] The compound **37i** was prepared by following the *General Procedure A* and obtained as a pale yellow liquid after column chromatographic purification. The poor yield of compound is because of volatile nature of compound. *Eluent*: 2% dichloromethane in MeOH (R_f = 0.4). Obtained data was matched with the reported literature data.

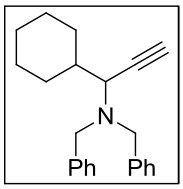
General Procedure B (Scheme 6B): To a two-neck round bottomed flask fitted with reflux condenser and placed under the N_2 atmosphere was added the aldehyde (1 equiv) followed by addition of acetonitrile. To the solution were added amine (1.2 equiv), calcium carbide (1.5 equiv) and CuI catalyst (0.1 equiv). The reaction mixture was stirred at 80 ^oC for 18 h. After the completion of the reaction, the mixture was passed through celite pad and washed with Et_2O (2 × 10 mL). The combined filtrate was concentrated under reduced pressure to obtain a liquid which was purified by column chromatography to obtain the propargylamine.



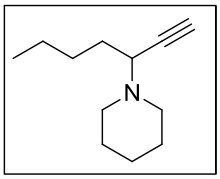
Synthesis of *N,N*-diethyl-1-pent-1-yn-3-amine (37b) [$C_9H_{17}N$]: The compound **37b** was prepared by following the *General Procedure B* affording **37b** as a colourless liquid. The compound **37b** was volatile, so purification was avoided. The obtained data was recorded for crude compound. IR (neat): ν/cm^{-1} 3296, 3049, 2969, 2931, 2872, 2820, 1509, 1459, 1383, 1288, 1258, 1191, 1163, 1117, 1046; ^1H NMR (400 MHz, $CDCl_3$): δ 3.35 (td, *J* = 6.48, 2.16 Hz, 1H), 2.64 (sex, *J* = 7.40 Hz, 2H), 2.38 (sex, *J* = 7.00 Hz, 2H), 2.15 (d, *J* = 2.20 Hz, 1H), 1.64 (m, 2H), 1.03 (t, *J* = 7.20 Hz, 6H), 0.97 (t, *J* = 7.40 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 82.8, 72.0, 54.8, 44.8, 27.2, 13.8, 11.3; HRMS (ESI): Calc. for $C_9H_{18}N$ $[M+H]^+$: 140.1439; Found: 140.1436.

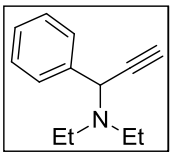
Synthesis of *N,N*-dibenzyl-1-cyclohexylprop-2-yn-1-amine (37e) [$C_{23}H_{27}N$]:[28] The compound **37e** was prepared by following the *General Procedure B* affording **37e** as a colourless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). Obtained data was matched with the reported literature data.



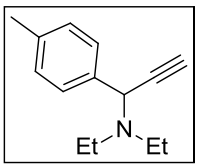
Synthesis of 1-(hept-1-yn-3-yl)-piperidine (37j) [$C_{12}H_{21}N$]: The compound **37j** was prepared by following the *General Procedure B* affording **37j** as a pale yellow liquid after column chromatographic purification. *Eluent*: 2% EtOAc in Petroleum ether (R_f = 0.85). IR (neat): ν/cm^{-1} 3304, 2930, 2859, 2805, 2752, 2686, 2362, 1648, 1561, 1456, 1376, 1330, 1301, 1263, 1158, 1096, 1061, 1034; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.21 (td, *J* = 6.44, 1.92 Hz, 1H), 2.55 – 2.49 (m, 2H), 2.32 (m, 2H), 2.18 (d, *J* = 2.12 Hz, 1H), 1.58 – 1.25 (m, 13H), 0.85 (t, *J* = 14.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 82.2, 73.0, 58.0, 50.3, 33.2, 29.0, 26.2, 24.6, 22.5, 14.1; HRMS (ESI): Calc. for $C_{12}H_{22}N$ $[M+H]^+$: 180.1752; Found: 180.1755.



Synthesis of *N,N*-diethyl-1-phenylprop-2-yn-1-amine (37n) [$C_{13}H_{17}N$]:[22] The compound **37n** was prepared by following the *General Procedure B* affording **37n** as a colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). Obtained data was matched with the reported literature data.

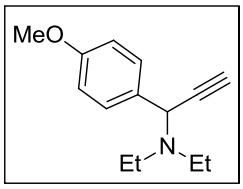


Synthesis of *N,N*-diethyl-1-(*p*-tolyl)-prop-2-yn-1-amine (37o) [$C_{14}H_{19}N$]: The compound **37o** was prepared by following the *General Procedure B* affording **37o** as a colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). IR (neat): ν/cm^{-1} 3300, 2968, 2927, 2823, 2361, 1646, 1510, 1459, 1381, 1291, 1264, 1190, 1168, 1115, 1050; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.00 Hz, 2H), 7.14 (d, *J* = 8.00 Hz, 2H), 4.79 (d, *J* = 1.36 Hz, 1H), 2.59 (m, 2H), 2.46 (m, 3H), 2.33 (s, 3H), 1.03 (t, *J* = 7.14 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

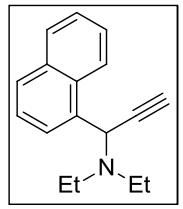


137.0, 136.3, 128.8, 128.2, 80.3, 74.8, 56.1, 44.4, 21.2, 13.6; HRMS (ESI): Calc. for $C_{14}H_{20}N$ $[M+H]^+$: 202.1596; Found: 202.1603.

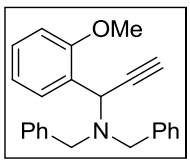
Synthesis of *N,N*-diethyl-1-(4-methoxyphenyl)-prop-2-yn-1-amine (37p) [$C_{14}H_{19}NO$]: The compound **37p** was prepared by following the *General Procedure B* affording **37p** as a colorless liquid after column chromatographic purification. *Eluent*: 3% EtOAc in Petroleum ether (R_f = 0.7). IR (neat): ν/cm^{-1} 3295, 2968, 2933, 2829, 2362, 1610, 1584, 1508, 1461, 1381, 1299, 1244, 1171, 1114, 1038; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 8.68, 0.56 Hz, 2H), 6.86 (dd, *J* = 6.60, 2.16 Hz, 2H), 4.77 (d, *J* = 2.20 Hz, 1H), 3.79 (s, 3H), 2.58 (m, 2H), 2.44 (m, 3H), 1.03 (t, *J* = 7.20 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 131.4, 129.4, 113.4, 80.4, 74.8, 55.8, 55.3, 44.3, 13.6; HRMS (ESI): Calc. for $C_{14}H_{20}NO$ $[M+H]^+$: 218.1545; Found: 218.1540.



Synthesis of *N,N*-diethyl-1-(naphthalen-1-yl)-prop-2-yn-1-amine (37q) [$C_{17}H_{19}N$]: The compound **37q** was prepared by following the *General Procedure B* affording compound **37q** as a colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.9). IR (neat): ν/cm^{-1} 3295, 3049, 2969, 2931, 2872, 2820, 1509, 1459, 1383, 1288, 1256, 1191, 1163, 1117, 1046; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.00 Hz, 1H), 7.95 (d, *J* = 7.08 Hz, 1H), 7.84 (dd, *J* = 7.60, 1.88 Hz, 1H), 7.79 (d, *J* = 8.20 Hz, 1H), 7.51 (m, 3H), 5.52 (d, *J* = 2.16 Hz, 1H), 2.73 (m, 2H), 2.55 (d, *J* = 2.28 Hz, 1H), 2.53 (m, 2H), 1.03 (td, *J* = 7.24, 2.28 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 134.0, 131.8, 128.7, 128.5, 127.2, 125.8, 125.6, 124.9, 80.2, 75.7, 55.2, 44.7, 13.5; HRMS (ESI): Calc. for $C_{17}H_{20}N$ $[M+H]^+$: 238.1596; Found: 238.1598.

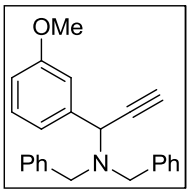


Synthesis of *N,N*-dibenzyl-1-(2-methoxyphenyl)-prop-2-yn-1-amine (37s) [$C_{24}H_{23}NO$]: The compound **37s** was prepared by following the *General Procedure B* affording **37s** as a colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.82). M.p.: 104-105 ^{o}C; IR (neat): ν/cm^{-1} 3291, 3060, 3028, 2935, 2832, 1596, 1491, 1457, 1367, 1283, 1249, 1109, 1029; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.48 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 4H), 7.25 (t, *J* = 7.32 Hz,



4H), 7.18 (q, *J* = 7.00 Hz, 3H), 6.88 (t, *J* = 7.44 Hz, 1H), 6.81 (d, *J* = 8.16 Hz, 1H), 5.00 (s, 1H), 3.75 (d, *J* = 13.6 Hz, 2H), 3.66 (s, 3H), 3.44 (d, *J* = 13.6 Hz, 2H), 2.51 (d, *J* = 2.16 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 139.8, 130.4, 129.1, 127.9, 126.8, 126.5, 119.7, 110.8, 79.9, 74.9, 55.0, 54.6, 50.7; HRMS (ESI): Calc. for $C_{24}H_{24}NO$ $[M+H]^+$: 342.1858; Found: 342.1866.

Synthesis of *N,N*-dibenzyl-1-(3-methoxyphenyl)-prop-2-yn-1-amine (37t) [$C_{24}H_{23}NO$]: The compound **37t** was prepared by following the *General Procedure B* to obtain **37t** as yellow liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.82). IR (neat): ν/cm^{-1} 3290, 3061, 3028, 2937, 2834, 1598, 1488, 1454, 1310, 1276, 1251, 1110, 1048; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.40 Hz, 4H), 7.30 (t, *J* = 7.60 Hz, 4H), 7.24 (s, 2H), 7.22 (m, 3H), 6.78 (m, 1H), 4.67 (s, 1H), 3.78 (s, 3H), 3.73 (d, *J* = 13.6, 2H), 3.43 (d, *J* = 13.52 Hz, 2H), 2.61(d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 140.3, 139.4, 129.1, 128.9, 128.4, 127.1, 120.6, 114.1, 112.8, 78.8, 76.1, 55.4, 55.4, 55.3, 54.5; HRMS (ESI): Calc. for $C_{24}H_{24}NO$ $[M+H]^+$: 342.1858; Found: 342.1867.

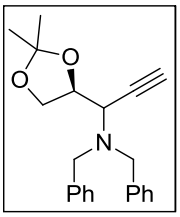


General Procedure C (Scheme 6C):

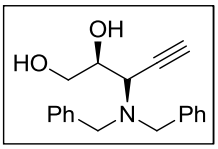
Step I. Preparation of trimethylsilanyl propargyamines: To a solution of aldehyde (1.0 equiv) in dry toluene were added amine (1.0 equiv), 4 Å molecular sieves (500 mg), CuBr (0.05 equiv), and alkyne (1.0 equiv). The reaction mixture was stirred at room temperature for 48 h. After completion, the reaction mixture was filtered through celite bed and washed with Et_2O (2 × 10 mL). The combined filtrate was concentrated under reduced pressure to obtain a liquid which was further purified by column chromatography over silica gel to furnish the corresponding propargylamine.

Step II. Desilylation of trimethylsilanyl propargyamines: To a stirred solution of TMS protected propargylamine in THF at 0 ^{o}C, TBAF solution (1 equiv) was added drop wise. The resultant solution was stirred at room temperature for 2 h. Upon completion, the solvent was evaporated and the residue was dissolved in EtOAc. The organic phase was washed with water (2 x 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product which was purified by column chromatography.

Synthesis of *N,N*-dibenzyl-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-prop-2-yn-1-amine (37g) [$C_{22}H_{25}NO_2$]:[23] The compound **37g** was prepared by following the *General Procedure C*. Compound **37g** was obtained (1.80 g, yield = 70%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.9). Obtained data was matched with the reported literature data.



Synthesis of (*2S*)-3-(dibenzylamino)pent-4-yne-1,2-diol (37h) [$C_{19}H_{21}NO_2$]: To a round bottom flask, compound **37g** (1g) was dissolved in methanol (10 mL).The resultant solution was acidified using 1 mL of 2N HCl and was stirred for 3 hrs. Upon completion of the reaction as observed from TLC, the reaction mixture was reduced in vacuo and washed with water (10 mL) and extracted using ethyl acetate (3 x 10mL). The organic layer was dried over Na_2SO_4 and evaporated. The resulting residue was purified using flash chromatography (10% ethyl acetate in Petroleum ether) to afford compound **37h** as a colorless liquid (830 mg, yield = 95%). IR (neat): ν/cm^{-1} 3441, 3291, 3061, 3029, 2925, 2844, 1543, 1493, 1370, 1288, 1250, 1209, 1071; ^{1}H NMR (400 MHz, DMSO): δ 7.35 – 7.16 (m, 10H), 4.43 (s, 2H), 3.82 (d, *J* = 13.80 Hz, 2H), 3.58 (br. s, 1H), 3.53 (m, 1H), 3.38 (m, 4H), 2.45 (d, *J* = 1.56 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.2, 128.8, 128.7, 127.7, 76.0, 70.1, 62.9, 55.2, 53.4; HRMS(ESI): Calc. for $C_{19}H_{22}NO_2$ $[M+H]^+$: 296.1650; Found: 296.1654.



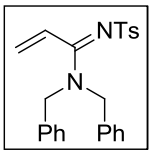
Preparation of acrylamidines via 1,3-amino group migration:

General Procedure D:

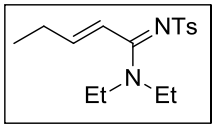
Synthesis of acrylamidines via 1,3-amino group migration (Scheme 5B): To a round bottomed flask placed in water bath at room temperature was added propargylamine (1.0 equiv) in $CHCl_3$. To the stirring solution were added sequentially triethylamine (1.2 equiv) and azide (1.1 equiv) at 0 ^{o}C followed by CuCl (0.1 equiv) when the evolution of N_2 gas was observed. The reaction mixture was stirred for either three minutes (for propargylamine with acyclic amino group) or 30 minutes (for propargylamine with cyclic amino group) under open atmospheric condition. After the completion, a saturated solution of NH_4Cl was added to the reaction mixture and stirred for additional 30 minutes. The crude product was extracted with $CHCl_3$ (three times) and combined organic layer was washed with brine, dried over anhydrous

Na_2SO_4 and concentrated under reduced pressure to give pale green residue which was purified by column chromatography over silica gel to obtain the desired acrylamidine.

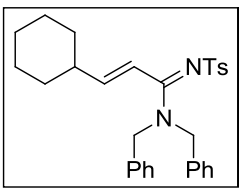
Synthesis of *N*,*N*-dibenzyl-*N*'-tosylacrylimidamide (44) [$C_{24}H_{24}N_2O_2S$]: The compound **44** was prepared by following the *General Procedure D* to obtain **44** as a colourless solid. *Eluent*: Dichloromethane (R_f = 0.15). M.P. = > 108 ^oC (decomposed); IR (neat): ν/cm^{-1} 3029, 2923, 1629, 1596, 1516, 1444, 1431, 1359, 1281, 1144, 1086, 1023: ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.20 Hz, 2H), 7.28 (br. s, 6H), 7.20 (d, *J* = 8.40 Hz, 2H), 7.12 (br. s, 4H), 6.72 (dd, *J* = 18.00, 12.00 Hz, 1H), 5.72 (t, *J* = 17.40, 11.80 Hz, 2H), 4.63 (br. s, 2H), 4.56 (br. s, 2H), 2.37 (s, 3H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.4, 142.0, 141.0, 135.6, 135.2, 129.1, 128.9, 128.6, 128.5, 128.2, 128.0, 127.0, 126.6, 125.0, 51.9, 49.9, 21.6; HRMS (ESI): Calc. for $C_{24}H_{24}N_2O_2S$ $[M+H]^+$: 405.1637; Found: 405.1632.



Synthesis of (2*E*)-*N*,*N*-diethyl-*N'*-tosylpent-2-enimidamide (39b) [$C_{16}H_{24}N_2O_2S$]: The compound **39b** was prepared by following the *General Procedure D*. *Eluent*: Dichloromethane (R_f = 0.2). M.P. = > 72 ^oC (decomposed); IR (neat): ν/cm^{-1} 2974, 2878, 2328, 1771, 1656, 1604, 1530, 1461, 1358, 1281, 1217, 1145, 1087, 1045, 1014, 979; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.24 Hz, 2H), 7.20 (d, *J* = 8.00 Hz, 2H), 6.15 (dt, *J* = 16.48, 1.56 Hz, 1H), 5.96 (dt, *J* = 16.48, 6.12 Hz, 1H), 3.45 (br. s, 2H), 3.37 (br. s, 2H), 2.36 (s, 3H), 2.17 (qd, *J* = 7.48, 1.60 Hz, 2H), 1.13 (m, 6H), 1.03 (t, *J* = 7.40, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.7, 142.6, 141.8, 141.5, 128.9, 126.5, 119.9, 44.4, 42.6, 25.9, 21.5, 13.8, 12.2; HRMS (ESI): Calc. for $C_{16}H_{24}N_2O_2S$ $[M+H]^+$: 309.1637; Found: 309.1653.

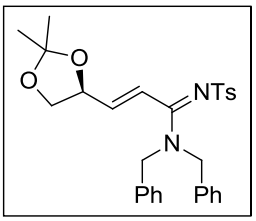


Synthesis of (2*E*)-*N*,-*N*-dibenzyl-3-cyclohexyl-*N*'-tosylacrylimidamide (39e) [$C_{30}H_{34}N_2O_2S$]: The compound **39e** was prepared by following the *General Procedure D* as a courless semi solid. *Eluent*: Dichloromethane (R_f = 0.3). IR (neat): ν/cm^{-1} 3017, 2925, 2852, 2361, 1649, 1596, 1513, 1445, 1359, 1280, 1142, 1086, 970 ; ^1H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.20 Hz, 2H), 7.28 (br. s, 6H), 7.23 (d, *J* = 8.40 Hz, 2H), 7.12 (br. s, 4H), 6.27 (d, *J* = 16.50 Hz, 1H), 6.13 (dd, *J* = 16.56, 6.44

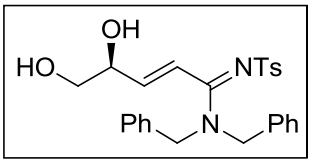


Hz, 1H), 4.63 (br. s, 2H), 4.56 (br. s, 2H), 2.37 (s, 3H), 2.08 (m, 1H), 1.71 (m, 5H), 1.31 - 1.03 (m, 6H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.2, 147.9, 141.8, 141.4, 135.8, 135.6, 129.0, 128.0, 127.0, 126.5, 118.3, 52.0, 50.0, 41.0, 31.5, 29.8, 25.7, 21.5 ; HRMS (ESI): Calc. for $C_{30}H_{34}N_2O_2S$ $[M+H]^+$: 487.2419; Found: 487.2434.

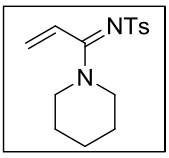
Synthesis of (2*E*)-*N*,*N*-dibenzyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*'-tosylacrylimidamide (39g) [$C_{29}H_{32}N_2O_4S$]: The compound **39g** was prepared by following the *General Procedure D* and obtained as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.2). M.P. = > 100 ^oC (decomposed); IR (neat): ν/cm^{-1} 3029, 2986, 2930, 2362, 1657, 1518, 1450, 1430, 1367, 1282, 1214, 1146, 1088, 1059; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.28 Hz, 2H), 7.27 (br.s, 6H), 7.20 (d, *J* = 8.04 Hz, 2H), 7.11 (br.s, 4H), 6.62 (dd, *J* = 16.44, 1.24 Hz, 1H), 6.20 (dd, *J* = 16.4, 5.72 Hz, 1H), 4.74 (br. d, *J* = 14.20 Hz, 1H), 4.60 (m, 4H), 4.15 (dd, *J* = 8.48, 6.64 Hz, 1H), 3.71 (dd, *J* = 8.32, 7.28 Hz, 1H), 2.36 (s, 3H), 1.35 (d, *J* = 1.64 Hz, 6H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.8, 142.0, 141.1, 139.0, 135.6, 135.1, 129.1, 128.9, 128.5, 128.2, 128.0, 127.0, 126.5, 121.8, 110.1, 75.5, 68.6, 52.0, 50.0, 26.4, 25.9, 21.5 ; HRMS (ESI): Calc. for $C_{29}H_{32}N_2O_4S$ $[M+H]^+$: 505.2161; Found: 505.2162.



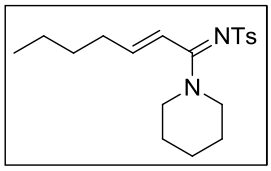
Synthesis of (*S*,2*E*)-*N*,*N*-dibenzyl-4,5-dihydroxy-*N*'-tosylpent-2-enimidamide (39h) [$C_{26}H_{28}N_2O_4S$]: The compound **39h** was prepared by following the *General Procedure D* to obtain **39h** as a colorless semi-solid after column chromatographic purification. *Eluent*: 3% MeOH/Dichloromethane (R_f = 0.2 in EtOAc/Petroleum ether). IR (neat): ν/cm^{-1} 3030, 2924, 1602, 1522, 1352, 1280, 1144, 1088; ^{1}H NMR (400 MHz, DMSO): δ 7.47 (d, *J* = 8.24 Hz, 2H), 7.34 – 7.24 (m, 6H), 7.22 (d, *J* = 7.28 Hz, 2H), 7.13 (d, *J* = 7.15 Hz, 4H), 6.43 (dd, *J* = 16.40, 1.80 Hz, 1H), 6.05 (dd, *J* = 16.40, 3.88 Hz, 1H), 5.11 (d, *J* = 5.16 Hz, 1H), 4.60 (m, 5H), 3.99 (t, *J* = 5.64 Hz, 1H), 3.20 (td, *J* = 5.90, 2.72 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 143.0, 141.9, 141.6, 136.3, 129.4, 129.2, 128.9, 128.1, 127.8, 127.5, 126.5, 119.8, 79.6, 71.6, 65.4, 52.8, 50.6, 21.4; HRMS (ESI): Calc. for $C_{26}H_{29}N_2O_4S$ $[M+H]^+$: 526.1800; Found: 526.1807.



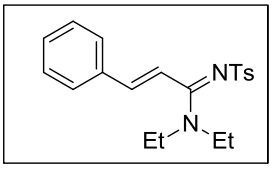
Synthesis of 4-methyl-*N*-(1-(piperidin-1-yl) allylidene) benzenesulfonamide (39i) [$C_{15}H_{20}N_2O_2S$]: The compound **39i** was prepared by following the *General Procedure D* to obtain **39i** as a colorless solid after column chromatographic purification. *Eluent*: 2% MeOH/Dichloromethane (R_f = 0.25). M.P. = > 75 ^oC (decomposed); IR (neat): ν/cm^{-1} 2937, 2860, 2362, 1707, 1601, 1526, 1449, 1399, 1362, 1274, 1144, 1086, 1015, 969 ; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.28 Hz, 2H), 7.21 (d, *J* = 8.00 Hz, 2H), 6.60 (dd, *J* = 18.16, 12.00 Hz, 1H), 5.65 (dd, *J* = 11.92, 0.80 Hz, 1H), 5.43 (dd, *J* = 17.68, 0.84 Hz, 1H), 3.67 (br. s, 2H), 3.51 (br. s, 2H), 2.36 (s, 3H), 1.66 (m, 2H), 1.62 (br. s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.6, 141.8, 141.3, 129.0, 128.9, 126.6, 124.0, 49.2, 45.8, 26.5, 25.4, 24.2, 21.5; HRMS (ESI): Calc. for $C_{15}H_{20}N_2O_2S$ $[M+H]^+$: 293.1324; Found: 293.1332.



Synthesis of 4-methyl-*N*-((*E*)-1-(piperidin-1-yl)-hept-2-en-1-ylidene)-benzenesulfonamide (39j) [$C_{19}H_{28}N_2O_2S$]: The compound **39j** was prepared by following the *General Procedure D* to obtain **39j** as a colorless viscous liquid after column chromatographic purification. *Eluent*: 1% MeOH/dichloromethane (R_f = 0.2). IR (neat): ν/cm^{-1} 2929, 2860, 2361, 1651, 1601, 1516, 1442, 1366, 1273, 1142, 1085, 1020, 979; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.20 Hz, 2H), 7.20 (d, *J* = 8.24 Hz, 2H), 6.20 (d, *J* = 16.44 Hz, 1H), 5.87 (dt, *J* = 16.44, 6.72 Hz,1H), 3.64 (br. s, 2H), 3.51 (br. s, 2H), 2.36 (s, 3H), 2.12 (q, *J* = 6.72 Hz, 2H), 1.64 (m, 7H), 1.38 – 1.27 (m, 5H), 0.89 (t, *J* = 7.12 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.1, 142.0, 141.6, 129.0, 126.6, 120.7, 32.5, 30.2, 24.3, 22.4, 21.5, 13.9; HRMS (ESI): Calc. for $C_{19}H_{28}N_2O_2S$ $[M+H]^+$: 349.1950; Found: 349.1949.

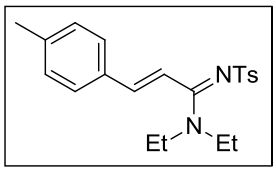


Synthesis of *N,N*-diethyl-*N′*-tosylcinnamimidamide (39n) [$C_{20}H_{24}N_2O_2S$]: The compound **39n** was prepared by following the *General Procedure D* to obtain **39n** as a colourless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.3). M.P. = > 130 $^{o\ C}$(decomposed); IR (neat): ν/cm^{-1} 2977, 2361, 1693, 1642, 1531, 1467, 1438, 1360, 1276, 1216, 1143, 1085; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.24 Hz, 2H), 7.36 (m, 5H), 7.10 (d, *J* = 8.36 Hz, 2H), 6.81 (d, *J* = 16.90 Hz, 1H), 6.56 (d, *J* = 16.88 Hz, 1H), 3.52 (br. s, 2H), 3.45 (br. s, 2H), 2.32 (s, 3H), 1.17 (t, *J* = 6.20 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.5,



141.6, 141.4, 137.4, 134.8, 129.4, 129.0, 128.8, 127.3, 126.7, 119.2, 44.7, 42.8, 21.5, 14.0, 12.2; HRMS (ESI): Calc. for $C_{20}H_{24}N_2O_2S$ $[M+H]^+$: 357.1636; Found: 357.1630.

Synthesis of (2*E*)-*N,N*-diethyl-3-(*p*-tolyl)-*N'*-tosylacrylimidamide (39o) [$C_{21}H_{26}N_2O_2S$]: The compound **39o** was prepared by following the *General Procedure D* to obtain **39o** as a colourless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.3). M.P. = > 130 ^oC (decomposed); IR (neat): ν/cm^{-1} 2977, 2932, 2361, 1640, 1605, 1527, 1460, 1360, 1278, 1215, 1144, 1086, 1041; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.28 Hz, 2H), 7.26 (d, *J* = 8.20 Hz, 2H), 7.16 (d, *J* = 7.96 Hz, 2H), 7.10 (d, *J* = 8.56 Hz, 2H), 6.76 (d, *J* = 16.88 Hz, 1H), 6.53 (d, *J* = 16.88 Hz, 1H), 3.48 (br. s, 4H), 2.35 (s, 3H), 2.32 (s, 3H), 1.18 (t, *J* = 6.32 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.7, 141.5, 141.4, 139.7, 137.6, 132.0, 129.5, 129.0, 127.3, 126.7, 118.1, 44.7, 42.8, 21.5, 21.4, 14.0, 12.3; HRMS (ESI): Calc. for $C_{21}H_{26}N_2O_2S$ $[M+H]^+$: 371.1793; Found: 371.1800.

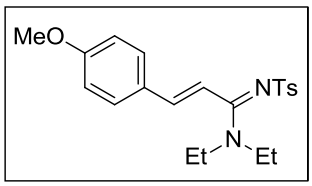


Variable temperature ^1H-NMR spectra for 39o:

^1H-NMR (400 MHz, $CDCl_3$) at 323 K: δ 7.74 (d, *J* = 8.20 Hz, 2H), 7.32 (d, *J* = 8.04 Hz, 2H), 7.20 (d, *J* = 8.00 Hz, 2H), 7.15 (d, *J* = 8.12 Hz, 2H), 6.80 (d, *J* = 16.88 Hz, 1H), 6.64 (d, *J* = 16.88 Hz, 1H), 3.55 (q, *J* = 6.86 Hz, 4H), 2.39 (s, 3H), 2.36 (s, 3H), 1.23 (t, *J* = 7.10 Hz, 6H).

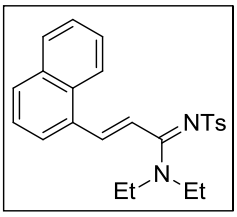
^1H-NMR (400 MHz, $CDCl_3$) at 273 K: δ 7.70 (d, *J* = 8.12 Hz, 2H), 7.29 (d, *J* = 7.90 Hz, 2H), 7.20 (d, *J* = 7.96 Hz, 2H), 7.13 (d, *J* = 8.08 Hz, 2H), 6.79 (d, *J* = 16.88 Hz, 1H), 6.50 (d, *J* = 16.88 Hz, 1H), 3.59 (q, *J* = 6.88 Hz, 2H), 3.46 (q, *J* = 6.88 Hz, 2H), 2.39 (s, 3H), 2.35 (s, 3H), 1.24 (t, *J* = 6.84 Hz, 3H), 1.19 (t, *J* = 6.84 Hz, 3H).

Synthesis of (2*E*)-*N,N*-diethyl-3-(4-methoxyphenyl)-*N'*-tosylacrylimidamide (39p) [$C_{21}H_{26}N_2O_3S$]: The compound **39p** was prepared by following the *General Procedure D* to obtain **39p** as a colourless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.3). M.P. = > 133 ^oC (decomposed); IR (neat): ν/cm^{-1} 2976, 2936, 2839, 2361, 1637, 1604, 1518, 1458, 1359, 1250, 1216, 1174, 1142, 1084, 1029; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J*

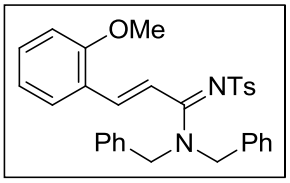


= 8.20 Hz, 2H), 7.31 (d, *J* = 8.68 Hz, 2H), 7.09 (d, *J* = 8.00 Hz, 2H), 6.87 (d, *J* = 8.72 Hz, 2H), 6.66 (d, *J* = 16.84 Hz, 1H), 6.55 (d, *J* = 16.84 Hz, 1H), 3.81 (s, 3H), 3.47 (br. s, 4H), 2.31 (s, 3H), 1.17 (t, *J* = 7.00 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.8, 160.7, 141.5, 142.4, 137.5, 128.9, 128.8, 127.5, 126.7, 116.7, 114.3, 55.5, 44.7, 42.9, 31.0, 21.5, 14.0, 12.3; HRMS (ESI): Calc. for $C_{21}H_{26}N_2O_3S$ $[M+H]^+$: 387.1742; Found: 387.1744.

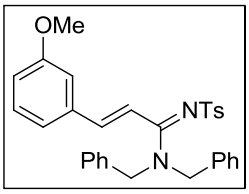
Synthesis of (2*E*)-*N,N*-diethyl-3-(naphthalen-1-yl)-*N'*-tosylacrylimidamide (39q) [$C_{24}H_{26}N_2O_2S$]: The compound **39q** was prepared by following the *General Procedure D* to obtain **39q** as a colourless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.35). M.P. = > 137 ^oC (decomposed); IR (neat): ν/cm^{-1} 2978, 2936, 2361, 1707, 1638, 1527, 1438, 1357, 1274, 1215, 1141, 1083, 1041; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (m, 1H), 7.86 (m, 2H), 7.74 (d, *J* = 8.16 Hz, 3H), 7.52 – 7.45 (m, 4H), 7.08 (d, *J* = 8.08 Hz, 2H), 6.90 (d, *J* = 16.64 Hz, 1H), 3.55 (br. s, 4H), 2.26 (s, 3H), 1.24 (t, *J* = 7.16 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.2, 141.7, 135.2, 133.6, 132.7, 131.2, 129.7, 128.7, 126.7, 126.5, 126.1, 125.7, 124.8, 123.6, 122.1, 44.7, 43.0, 21.5, 14.1, 12.3; HRMS (ESI): Calc. for $C_{24}H_{26}N_2O_2S$ $[M+H]^+$: 407.1793; Found: 407.1799.



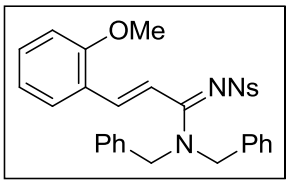
Synthesis of (2*E*)-*N,N*-dibenzyl-3-(2-methoxyphenyl)-*N'*-tosylacrylimidamide (39s) [$C_{31}H_{30}N_2O_3S$]: The compound **39s** was prepared by following the *General Procedure D* to obtain **39s** as a colourless semi-solid after column chromatographic purification. *Eluent*: 25% EtOAc/Petroleum ether (R_f = 0.2). IR (neat): ν/cm^{-1} 3028, 2934, 2839, 1632, 1597, 1514, 1460, 1359, 1284, 1249, 1144, 1087, 1024; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.40 (d, *J* = 7.64 Hz, 1H), 7.28 (br. s, 6H), 7.24 (s, 1H), 7.16 (br. s, 4H), 7.11 (s, 1H), 7.09 (d, *J* = 4.8 Hz, 2H), 7.02 (d, *J* = 17.12 Hz, 1H), 6.90 (t, *J* = 7.5Hz, 1H), 6.80 (d, *J* = 8.32, 1H), 4.65 (br. s, 4H), 3.67 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 157.8, 141.7, 141.1, 135.7, 134.6, 130.8, 129.0, 128.9, 125.5, 127.9, 127.2, 126.7, 123.7, 120.8, 119.2, 111.0, 55.4, 52.3, 50.2, 21.5; HRMS (ESI): Calc. for $C_{31}H_{31}N_2O_3S$ $[M+H]^+$: 511.2055; Found: 511.2059.



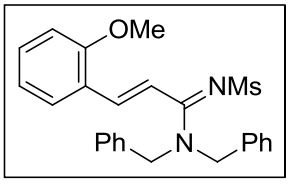
Synthesis of (*2E*)-*N,N*-dibenzyl-3-(3-methoxyphenyl)-*N'*-tosylacrylimidamide (39t) [$C_{31}H_{30}N_2O_3S$]: The compound **39t** was prepared by following the *General Procedure D* to obtain **39t** as a viscous yellow liquid after column chromatographic purification. *Eluent*: 25% EtOAc/Petroleum ether (R_f = 0.2). IR (neat): ν/cm^{-1} 3028, 2927, 1638, 1588, 1514, 1458, 1429, 1359, 1277, 1144, 1087, 1042; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.20 Hz, 2H), 7.29 (br. s, 7H), 7.20 (d, *J* = 7.88 Hz, 1H), 7.15 (br. s, 4H), 7.12 (d, *J* = 8.16 Hz, 2H), 6.90 (d, *J* = 8.48 Hz, 1H), 6.84 (s, 1H), 6.81 (br. s, 1H), 6.73 (d, *J* = 16.8 Hz, 1H), 4.70 (br. s, 2H), 4.58 (br. s, 2H), 3.76 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 159.9, 141.9, 141.0, 138.8, 136.0, 129.8, 129.1, 128.1, 127.0, 126.7, 120.1, 118.9, 115.6, 112.5, 55.4, 52.3, 50.3, 21.5; HRMS(ESI): Calc. for $C_{31}H_{31}N_2O_3S$ $[M+H]^+$: 511.2055; Found: 511.2059.



Synthesis of (*2E*)-*N,N*-dibenzyl-3-(2-methoxyphenyl)-*N'*-tosylacrylimidamide (39y) [$C_{30}H_{27}N_3O_5S$]: The compound **39y** was prepared by following the *General Procedure D* to obtain **39y** as a pale yellow solid after column chromatographic purification. *Eluent*: 20% EtOAc/Petroleum ether (R_f = 0.3). IR (neat): ν/cm^{-1} 3843, 3744, 2929, 1632, 1519, 1462, 1350, 1293, 1148, 1089, 1024; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8 Hz, 2H), 7.95 (d, *J* = 8 Hz, 1H), 7.4 (br. s, 10H), 7.19 (br. s, 4), 6.98 (t, *J* = 8 Hz, 1H), 6.87 (d, *J* = 8 Hz, 1H), 4.74 (d, J= 12 Hz, 4H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 157.7, 149.4, 149.0, 135.4, 134.8, 131.2, 129.1, 128.8, 128.2, 127.7 127.0, 123.6, 122.9, 120.8, 118.5, 110.9, 55.3, 52.8, 50.5, 29.6; HRMS (ESI): Calc. for $C_{30}H_{28}N_3O_5S$ $[M+H]^+$: 542.1744; Found: 542.1749.



Synthesis of (2*E*)-*N*,*N*-dibenzyl-3-(2-methoxyphenyl)-*N*'-(methylsulfonyl)-acrylimidamide (39z) [$C_{25}H_{26}N_2O_3S$]: The compound **39z** was prepared by following the *General Procedure D* to obtain **39z** as a colourless semi-solid after column chromatographic purification. *Eluent*: 20% EtOAc/Petroleum ether (R_f = 0.2). IR (neat): ν/cm^{-1} 3027, 2931, 1632, 1597, 1519, 1461, 1360, 1281, 1250, 1162, 1124, 1024, 873; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8 Hz, 1H), 7.45 (m, 12H), 7.14 (d, J= 16 Hz, 6H), 6.96 (t, *J* = 8 Hz, 1H), 6.85 (d, *J* = 8 Hz, 1H), 4.73 (br. s, 4H), 3.73 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0,



157.6, 135.5, 134.9, 130.6, 128.7, 128.3, 127.7, 126.9, 123.4, 120.6, 118.6, 110.8, 55.2, 51.9, 49.8, 43.0; HRMS (ESI): Calc. for $C_{25}H_{27}N_2O_3S$ $[M+H]^+$: 435.1737; Found: 435.1735.

Section 2: [1,5] Amino Group Migration Route to Acrylamidines

General Procedure E (Scheme 8):

Step I. Preparation of β-bromoenals: To a solution of DMF (3 equiv) in chloroform, PBr_3 (3 equiv) was added dropwise at 0 ^oC. The mixture was stirred for 60 min, and then acetophenone (1 equiv) was added. The solution was stirred for 48 h at room temperature, and the content was poured into water (150 mL), neutralized with solid $NaHCO_3$ and extracted with dichloromethane (3 × 150 mL). The extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford β-bromoenal as a yellow oil.

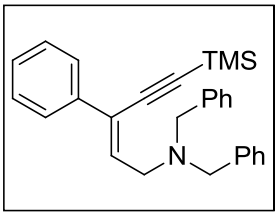
Step II. Preparation of substituted 5-trimethylsilanyl-2-en-4-yn-1-als: To a solution of β-bromoenal (1 equiv) in dry THF, TMS-acetylene (1.2 equiv), triethylamine (1.5 equiv) were added followed by degassing the system by N_2. After cooling the mixture to 0 ^oC, $(Ph_3P)_2PdCl_2$ (0.04 equiv) and CuI (0.02 equiv) were added. The reaction mixture was then warmed to room temperature and was monitored by TLC. Upon completion the reaction mixture was filtered through celite bed and the solvent was evaporated. The residue was dissolved in EtOAc and washed with water (2 x 20 mL) and brine (20 mL). The separated organic layer was dried over Na_2SO_4 and evaporated to give a brown residue which was used for subsequent step without further purification.

Step III. Preparation of substituted 5-trimethylsilanyl-2-en-4-yn-1-ols: To a solution of TMS protected eneyne-aldehyde (1 equiv) in methanol, $NaBH_4$ (0.25 equiv) was added in one portion at 0 ^oC and stirred for 15 min. Upon completion as observed by TLC, the reaction mixture is quenched using saturated NH_4Cl solution (5 mL) and filtered through celite. The filtrate was evaporated, dissolved in EtOAc and washed with water (3 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford alcohol as a yellow oil.

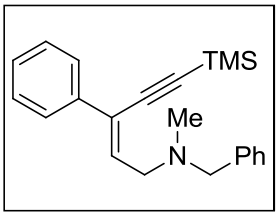
Step IV. Preparation of substituted 5-trimethylsilanyl-2-en-4-yn-1-bromide: At -15 ^{o}C, a solution of PBr_3 (0.38 equiv) in Et_2O was added drop wise to a stirred solution of alcohol (1 equiv) and pyridine (0.03 equiv) in Et_2O. Stirring was continued at room temperature for 2 h. Upon completion, the mixture was poured into ice water (50 mL). The organic phase was separated and washed with 2% aq. $NaHCO_3$ solution (2 x 50 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to obtain orange oil which was used for subsequent reaction without further purification.

Step V. Preparation of substituted 5-trimethylsilanyl-2-en-4-yn-1-amines: Amines **39a-39c** were prepared by following the ***General Procedure A, Scheme 6A***.

Step VI. Desiylation of substituted 5-trimethylsilanyl-2-en-4-yn-1-amines: Amines **40a-40c** were prepared by following desilylation procedure described the ***General Procedure C, Scheme 6C***.



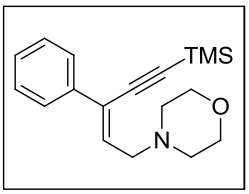
(*Z*)-*N*,*N*-dibenzyl-3-phenyl-5-(trimethylsilyl)-pent-2-en-4-yn-1-amine (40a) [$C_{25}H_{24}N$]: Compound **40a** was prepared according to *General Procedure E* producing **40a** as a yellow liquid. *Eluent*: 10% EtOAc/Petroleum ether (R_f = 0.3). IR (neat): ν/cm^{-1} 3060, 3028, 2958, 2797, 2146, 1600, 1494, 1449, 1364, 1249, 1122, 1072, 1029, 844, 752; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8 Hz, 2 H), 7.42 (m, 5H), 7.35 (m, 10H), 7.26 (m, 3H), 6.62 (t, *J* = 8 Hz, 1H), 3.66 (s, 4H), 3.55 (d, *J* = 8 Hz, 2H), 3.33 (s, 1H), 0.26 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 139.4, 137.4, 136.8, 128.8, 128.3, 128.2, 127.7, 126.8, 126.0, 125.2, 101.7, 101.5, 58.4, 54.1, 0.01; HRMS (ESI): Calc. for $C_{25}H_{24}N$ $[M+H]^+$: 338.1903, Found: 338.1909.



Synthesis of (*Z*)-*N*-benzyl-*N*-methyl-3-phenyl-5-(trimethylsilyl)-pent-2-en-4-yn-1-amine (40b) [$C_{22}H_{26}NSi$]: Compound **40b** was prepared according to *General Procedure E* producing **40b** as a yellow liquid. *Eluent*: 10% EtOAc/Petroleum ether (R_f = 0.2). IR (neat): ν/cm^{-1} 3060, 3029, 2957, 2839, 2787, 2147, 1494, 1451, 1362, 1250, 845, 758; ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.63 (d, *J* = 8 Hz, 2H), 7.37 (m, 8H), 6.61 (t, *J* = 8 Hz, 1H), 3.60 (s, 2H), 3.52 (d, *J* = 4 Hz, 2H), 2.29 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 138.7, 135.9, 129.1, 128.3, 128.2, 127.8, 127.0, 126.0, 125.5, 101.7, 101.6, 62.0, 57.5, 42.4, -0.01; HRMS (ESI): Calc. for $C_{22}H_{27}NSi$ $[M]^+$: 333.1913, Found: 333.1680.

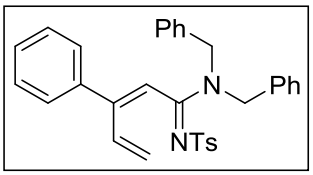
Synthesis of (*Z*)-4-(3-phenyl-5-(trimethylsilyl)-pent-2-en-4-yn-1-yl)-morpholine (40c) [$C_{18}H_{25}NOSi$]: Compound **40c** was prepared according to *General Procedure E* producing **40c** as a yellow liquid. *Eluent*: 20% EtOAc/Petroleum ether (R_f = 0.2). IR (neat): ν/cm^{-1} 2959, 2856, 2809, 2148, 1450, 1353, 1326, 1251, 1118, 1072, 1002, 907, 848; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 12 Hz, 2H), 7.37 (m, 3H), 6.54 (t, *J* = 8Hz, 1H), 3.76 (t, *J* = 4 Hz, 4H),3.48 (d, *J* = 4 Hz, 2H), 2.58 (t, *J* = 4 Hz, 4H), 0.27 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 136.9, 133.8, 128.3, 128.0, 126.5, 126.0, 101.9, 101.4, 66.8, 58.8, 53.6, -0.06; HRMS (ESI): Calc. for $C_{18}H_{26}NOSi$ $[M+H]^+$: 300.1778, Found: 300.1789.



Preparation of acrylamidines via 1,3-amino group migration:

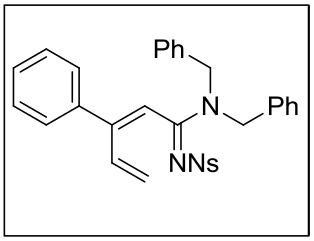
General Procedure F (Scheme 5C): To a round bottomed flask placed in water bath at room temperature was added propargylamine (1.0 equiv) in $CHCl_3$. To the stirring solution were added sequentially triethylamine (1.2 equiv) and azide (1.1 equiv) at 0 ^oC followed by CuCl (0.1 equiv) when the evolution of N_2 gas was observed. The reaction mixture was stirred for 6 h under open atmospheric condition and the progress of reaction was monitored by TLC. After the completion, a saturated solution of NH_4Cl was added to the reaction mixture and stirred for additional 30 minutes. The crude product was extracted with $CHCl_3$ (three times) and combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give pale green residue which was purified by column chromatography to provide the desired acrylamidine.

Synthesis of (*2E*)-*N*,*N*-dibenzyl-3-phenyl-*N′*-tosylpenta-2,4-dienimidamide (42a) [$C_{32}H_{30}N_2O_2S$]: Compound **42a** was prepared according to *General Procedure F* affording **42a** as a orange semisolid. *Eluent*: 20% EtOAc/Petroleum ether (R_f = 0.25). IR (neat): ν/cm^{-1} 3030, 2925, 1514, 1445, 1289, 1147, 1087, 867; ^{1}H NMR (400 MHz, $CDCl_3$):

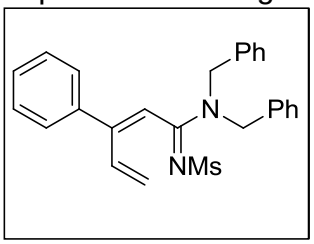


δ 7.74 (d, *J* = 8 Hz, 2H), 7.35 (m, 12H), 7.14 (m, 4H), 6.30 (s, 1H), 6.21 (dd, *J* = 12, 16 Hz, 1H), 5.18 (d, *J* = 12 Hz, 1H), 5.14 (d, *J* = 16 Hz, 1H), 4.54 (br. s, 4H), 2.35 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.6, 144.6, 141.8, 140.5, 137.7, 135.6, 135.0, 131.9, 129.0, 128.9, 128.8, 128.7, 128.3, 127.2, 126.67, 122.3, 120.3, 77.2, 51.7, 49.8, 21.4; HRMS (ESI): Calc. for $C_{32}H_{31}N_2O_2S$ $[M+H]^+$: 507.2101; Found: 507.2139.

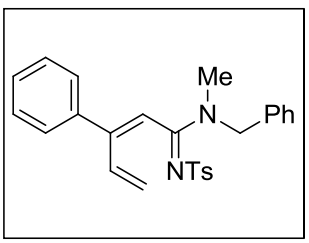
Synthesis of (*1Z,2E*)-*N,N*-dibenzyl-*N'*-((4-nitrophenyl)-sulfonyl)-3-phenylpenta-2,4-dienimidamide (42b) [$C_{31}H_{27}N_3O_4S$]: Compound **42b** was prepared according to *General Procedure F* affording **42b** as a orange semisolid. *Eluent*: 20% EtOAc/Petroleum ether (R_f = 0.25). IR (neat): ν/cm^{-1} 3743, 3030, 1519, 1452, 1348, 1295, 1149, 1087, 860; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8 Hz, 2H), 7.99 (d, *J* = 8 Hz, 2H), 7.42 (m, 12H), 7.16 (m, 3H), 6.35 (s, 1H), 6.26 (dd, *J* = 12, 20 Hz, 1H), 5.26 (d, *J* = 8 Hz, 1H), 5.22 (d, *J* = 16 Hz, 1H), 4.64 (br. s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.9, 148.9, 145.0, 137.2, 135.1, 134.4, 131.6, 130.0, 129.3, 129.1, 128.7, 128.6, 128.3, 128.0, 127.8, 127.2, 126.0, 125.6, 123.5, 123.1, 119.9, 52.5, 50.4; HRMS (ESI): Calc. for $C_{31}H_{28}N_3O_4S$ $[M+H]^+$: 538.1795; Found: 538.1813.



Synthesis of (*2E*)-*N,N*-dibenzyl-*N'*-(methylsulfonyl)-3-phenylpenta-2,4-dienimidamide (42c) [$C_{26}H_{26}N_2O_2S$]: Compound **42c** was prepared according to *General Procedure F* affording **42c** as a brown semi-solid. *Eluent*: 50% EtOAc/Petroleum ether (R_f = 0.15). IR (neat): ν/cm^{-1} 3028, 2929, 1519, 1445, 1287, 1127, 965, 869; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 13H), 7.11 (d, *J* = 8 Hz, 2H), 6.44 (dd, *J* = 8, 12 Hz, 1H), 6.06 (s, 1H), 4.99 (d, *J* = 12 Hz, 1H), 4.88 (d, *J* = 20 Hz, 1H), 3.91 (br. s, 4H), 1.95 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ; HRMS (ESI): Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1788; Found: 431.1793;

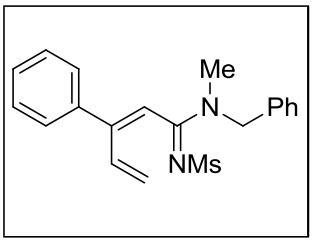


Synthesis of (*2E*)-*N*-benzyl-*N*-methyl-3-phenyl-*N'*-tosylpenta-2,4-dienimidamide (42d) [$C_{26}H_{26}N_2O_2S$]: Compound **42d** was prepared according to *General Procedure F* affording **42d** as a brown liquid. *Eluent*: 30% EtOAc/Petroleum ether (R_f = 0.2). IR (neat): ν/cm^{-1} 3743, 3250, 3059, 2926, 1707, 1595, 1530, 1448, 1335, 1278, 1147, 1086, 866, 814, 754; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8 Hz, 2H), 7.31 (m, 10H), 7.10 (d, *J* = 8 Hz, 2H), 6.23 (s, 1H), 6.20 (dd, *J*

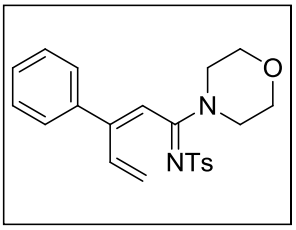


= 12, 16 Hz, 1H), 5.19 (dt, *J* = 12, 20 Hz, 2H), 4.79 (s, 1H), 4.56 (s, 1H), 2.36 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.4, 143.3, 140.5, 139.1, 135.3, 131.9, 129.6, 128.3, 126.3, 122.3, 120.5, 55.1, 53.1, 36.8, 36.04, 29.6, 21.3; HRMS (ESI): Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1788; Found:431.1837.

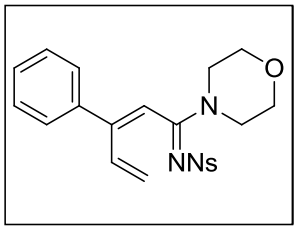
Synthesis of (*2E*)-*N*-benzyl-*N*-methyl-*N'*-(methylsulfonyl)-3-phenylpenta-2,4-dienimidamide (42e) [$C_{20}H_{22}N_2O_2S$]: Compound **42e** was prepared according to *General Procedure F* affording **42e** as a orange liquid. *Eluent*: 50% EtOAc/Petroleum ether (R_f = 0.5). IR (neat): ν/cm^{-1} 3027, 2926, 1533, 1486, 1447, 1407, 1281, 1130, 964, 869; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (m, 10H), 6.65 (dq, *J* = 12, 16 Hz, 1H), 6.34 (s, 1H), 5.53 (m, 1H), 5.41 (dd, *J* = 4, 20 Hz, 1H), 4.84 (s, 1H), 4.68 (s, 1H), 3.09 (d, *J* = 16 Hz, 3H), 3.02 (d, *J* = 4 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.1, 144.7, 137.9, 135.4, 135.1, 132.8, 132.4, 129.0, 128.8, 128.6, 128.3, 122.9, 120.6, 120.5, 55.0, 52.8, 42.7, 36.5, 35.6; HRMS (ESI): Calc. for $C_{20}H_{23}N_2O_2S$ $[M+H]^+$: 355.1475; Found: 355.1582.



Synthesis of 4-methyl-*N*-((*E*)-1-morpholino-3-phenylpenta-2,4-dien-1-ylidene)-benzenesulfonamide (42f) [$C_{22}H_{24}N_2O_3S$]: Compound **42f** was prepared according to *General Procedure F* affording **42f** as a yellow liquid. *Eluent*: 30% EtOAc/Petroleum ether (R_f = 0.15). IR (neat): ν/cm^{-1} 3743, 2965, 2922, 2858, 1602, 1519, 1442, 1275, 1145, 1114, 1087, 866, 820, 756; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8 Hz, 2H), 7.40 (m, 5H), 7.17 (d, J = 4 Hz, 2H), 6.24 (s, 1H), 6.22 (dd, *J* = 12, 20 Hz, 1H), 5.30 (d, *J* = 12 Hz, 1H), 5.21 (d, *J* = 16 Hz, 1H), 3.92 (s, 2H), 3.76 (s, 2H), 3.68 (s, 2H), 3.57 (s, 2H), 2.37 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.1, 145.0, 141.9, 140.2, 137.5, 131.9, 128.9, 128.5, 128.3, 126.7, 122.6, 119.5, 77.2, 66.5, 66.1, 47.6, 44.6, 29.6, 21.3; HRMS (ESI): Calc. for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$: 397.1580, Found: 397.1640.

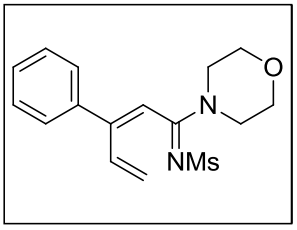


Synthesis of (*Z*)-*N*-((*E*)-1-morpholino-3-phenylpenta-2,4-dien-1-ylidene)-4-nitrobenzenesulfonamide (42g) [$C_{21}H_{21}N_3O_5S$]: Compound **42g** was prepared according to *General Procedure F* affording **42g** as a brown semisolid. *Eluent*: 25% EtOAc/Petroleum ether (R_f = 0.2). IR (neat): ν/cm^{-1} 2923, 2859, 1521, 1438,



1349, 1293, 1222, 1147, 1088, 865, 825; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 12 Hz, 2H), 8.19 (d, *J* = 12 Hz, 2H), 7.42 (m, 3H), 7.34 (m, 2H), 5.97 (s, 1H), 5.92 (dd, *J* = 12, 20 Hz, 2H), 4.83 (d, *J* = 12 Hz, 1H), 4.72 (d, *J* = 20 Hz, 1H), 3.06 (br. s, 2H), 2.88 (br. s, 2H), 2.79 (br. s, 2H), 2.68 (br. s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 185.3, 167.4, 166.9, 162.7, 152.2, 145.4, 142.1, 141.4, 141.0, 135.6, 135.3, 129.9, 77.4, 64.0, 63.5, 40.9, 37.1, 18.0; HRMS (ESI): Calc. for $C_{21}H_{22}N_3O_5S$ $[M+H]^+$: 428.1275; Found:428.1329.

Synthesis of *N*-((*E*)-1-morpholino-3-phenylpenta-2,4-dien-1-ylidene)-methanesulfonamide (42h) [$C_{16}H_{20}N_2O_3S$]: Compound **42h** was prepared according to *General Procedure F* affording **42h** as a pale brown viscous liquid. *Eluent*: 50% EtOAc/Petroleum ether (R_f = 0.15). IR (neat): ν/cm^{-1} 3743, 2858, 1524, 1443, 1360, 1279, 1126, 1067, 964, 866, 824; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (m, 5H), 6.38 (dd, *J* = 12, 20 Hz, 1H), 5.99 (s, 1H), 5.09 (d, *J* = 12 Hz, 1H), 5.05 (d, *J* = 20 Hz, 1H), 3.01 (br. s, 2H), 2.89 (br. s, 2H), 2.81 (br. s, 2H), 2.70 (br. s, 2H), 1.89 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 184.3, 162.4, 152.9, 146.4, 141.6, 141.5, 141.3, 135.1, 130.5, 77.4, 64.1, 63.5, 40.3, 36.4, 34.2; HRMS (ESI): Calc. for $C_{16}H_{21}N_2O_3S$ $[M+H]^+$: 321.1267; Found: 321.1393.



Results and Discussions

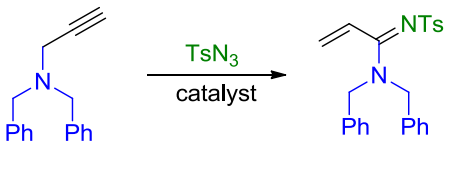
Section 1: 1,3-Amino Group Migration Route to Acrylamidines

A. Optimization of reaction conditions

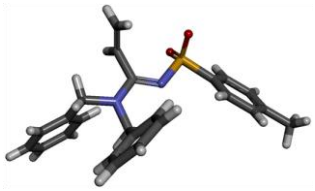
The first attempt to establish the 1,3-amino group migration strategy began from *N*,*N*-dibenzylpropargylamine **43** which was prepared following reported protocol.[21] We envisaged that the intramolecular migration if feasible, should not be affected by solvents which are potentially nucleophilic. Furthermore, an intramolecular source of nucleophile also ensures fewer side reactions, higher reaction rates and improved yields. When **43** was treated with one equivalent of tosylazide in H_2O under open air conditions in the presence of CuI catalyst (10 mol %) and Et_3N at room temperature, the reaction proceeded up to 3 h, generating the acrylamidine **44** in 95% yield (**Table 1**, entry 1). Any by-product corresponding to water addition to the ketenimine intermediate were not observed. This data, confirmed our prediction of intramolecular 1,3-migration as the more favourable route. The structure of acrylamidine **44** was also confirmed by ^{1}H-NMR spectroscopy and single crystal X-ray crystallography. When the solvent was replaced with $CHCl_3$, the reaction was faster but, marginal decrease in the yield (84%) of **44** was observed (entry 2). Therefore, further optimization of the reaction conditions were carried out. Introduction of CuBr as catalyst (10 mol %) facilitated the reaction to proceed within 3 minutes and improving the yield to 95% (entry 3). A further alteration of catalyst to CuCl (10 mol %) resulted in 96% yield of **44** (entry 4).

In the next stage, the significance of catalyst and base in the rearrangement reaction was verified. The reaction did not afford any product in the absence of the catalyst (entry 5) and moderate yield (60%) was obtained when carried out in the absence of a base. In order to demonstrate the effectiveness of the rearrangement, the rearrangement was carried out in the presence of various potentially competing nucleophiles *e.g.* EtOH (2 equivalents, entry 8), S-methyl-L-cysteine (2 equivalents, entry 9) and N-acetyl-L-cysteine (2 equivalents, entry 10), but **44** was the only product isolated. These results unambiguously confirmed that intramolecular amine migration is uncompromised even after the addition of an external nucleophile.

Table 1. Optimization of reaction conditions for formation of acrylamidine **44**.[a]



43 **44**



crystal structure of **44**

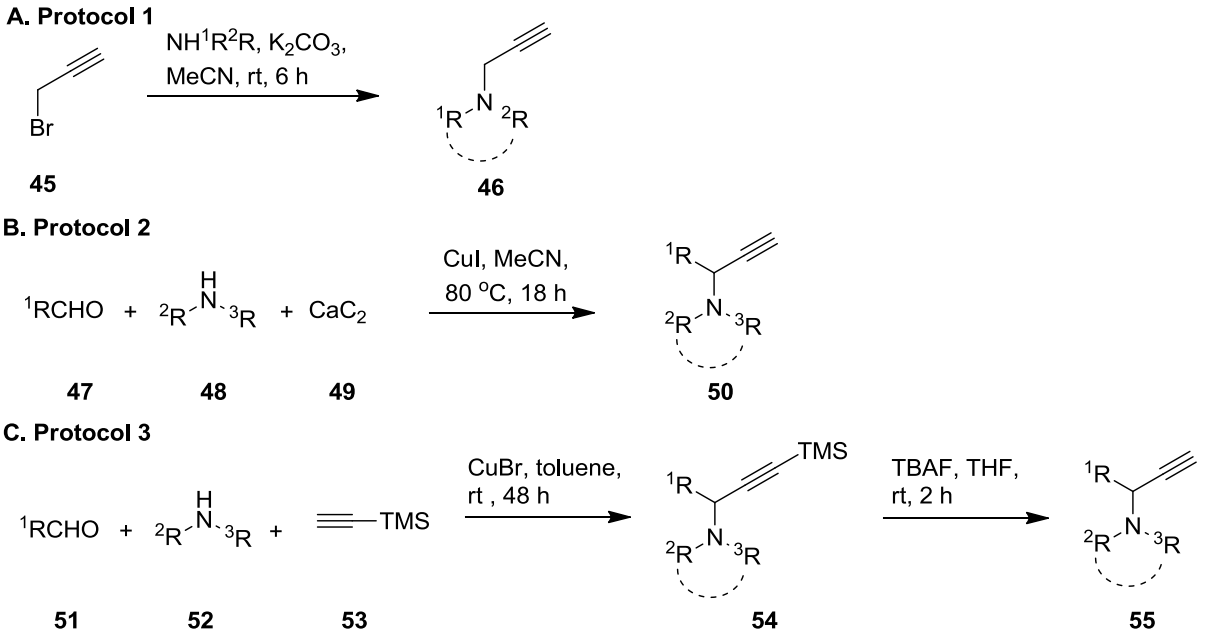
Entry	Catalyst	Solvent	Base	Comp. Nu[b]	Yield (%)[c]	Time (min)
1	CuI	H_2O	Et_3N	-	95	180
2	CuI	$CHCl_3$	Et_3N	-	84	30
3	CuBr	$CHCl_3$	Et_3N	-	95	3
4	CuCl	$CHCl_3$	Et_3N	-	96	3
5	-	$CHCl_3$	Et_3N	-	0	30
6	-	$CHCl_3$	-	-	0	30
7	CuCl	$CHCl_3$	-	-	60	30
8	CuCl	$CHCl_3$	Et_3N	EtOH	91	3
9	CuCl	$CHCl_3$	Et_3N	SMC[d]	91	3
10	CuCl	$CHCl_3$	Et_3N	NAC[e]	90	3

[a] With 0.1 eq. of catalyst, 1.2 eq. of base and 3 mL of solvent; [b] competing nucleophile; [c] Isolated yields;[d] S-methyl cysteine; [e] N-acyl cysteine; carried out by SVJ; carried out by senior group member DC.

B. Scope of the Methodology

With the optimized reaction conditions in hand, we analysed the effect of substrate variation on the amino group migration. Due to non-availability of the precursors through commercial sources, three different methodologies were adopted to synthesize propargylamine derivatives. Propargylamines with no substitution at C_1-position (*i.e.* ^{1}R = H) were prepared by nucleophilic substitution of propargylbromide by a secondary amine giving the desired propargylamines in moderate yields (**Scheme 6A**).[21] In order to generate propargylamines with substitution at C_1-position, two independent procedures were employed: (a) one step protocol of three-component aldehyde-amine-calcium carbide reaction (**Scheme 6B**)[22] or (b) two-step Cu(I) catalytic strategy based on aldehyde-amine-alkyne three-component

reaction followed by deprotection of trimethylsilyl (TMS) group (**Scheme 6C**).[23] All schemes generated the propargylamine derivatives in excellent yields.



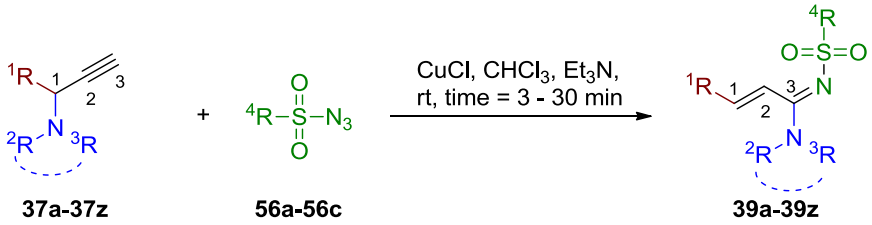
Scheme 6. Synthesis of propargylamine via (**A**) nucleophilic substitution, (**B**) three-component aldehyde-amine-calcium carbide reaction, (**C**) a two step Cu(I) catalysed aldehyde-amine-alkyne multicomponent reaction followed by deprotection.

To establish the scope of the methodology, the optimised reaction conditions were applied to a variety of substrates **37a-37z**. The results are depicted in Table 2.

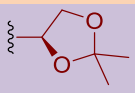
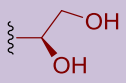
Variations in alkyl substituent ^{1}R: To study the effects of substituents at C_1 position, various propargylamines **37a-37f** containing alkyl substituents (^{1}R = alkyl) and acyclic amine substituents were reacted with tosylazide to give corresponding acrylamidines **39a-39f** (**Table 2**, entries 1-9). No noticeable difference was observed by varying the C_1 substituent from acyclic ethyl group (entry 2, yield 95%) to cyclic cyclohexyl group (entry 5, yield 91%). Further, keeping the amine fixed (-N^{2}R^{3}R = -NBn_2 or -NEt_2), studies were also carried out varying the alkyl group ethyl, butyl, cyclohexyl but no considerable alteration in yield were observed.

To observe any effect of neighbouring nucleophilic groups on the rearrangement, the ^{1}R group was modified to either acetal protected (*S*)-2,2-dimethyl-1,3-dioxolane (entry 7) or (*S*)-ethyl-1,2-diol (entry 8). Upon reacting with tosylazide, the acetal protected substrate **37g** afforded 95% yield of **39g** whereas free di-hydroxy substrate

Table 2. Scope of 1,3-amino group migration route in the synthesis of acrylamidines.



37a-37z + **56a-56c** → **39a-39z**

Entry	37	-^{1}R	–N(^{2}R)(^{3}R)	-^{4}R	39	Yield (%)[4]
1	**37a**[2]	–Et	–NBn$_2$	–C$_6$H$_4$-*p*-Me	**39a**	96
2	**37b**[2]	–Et	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39b**	95
3	**37c**[2]	–Bu	–NBn$_2$	–C$_6$H$_4$-*p*-Me	**39c**	91
4	**37d**[2]	–Bu	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39d**	96
5	**37e**[2]	–Cy	–NBn$_2$	–C$_6$H$_4$-*p*-Me	**39e**	91
6	**37f**[2]	–Cy	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39f**	96
7	**37g**[2]		–NBn$_2$	–C$_6$H$_4$-*p*-Me	**39g**	95
8	**37h**[2]		–NBn$_2$	–C$_6$H$_4$-*p*-Me	**39h**	60
9	**37i**[1]	–H	–N-piperidine	–C$_6$H$_4$-*p*-Me	**39i**	48
10	**37j**[1]	–Bu	–N-piperidine	–C$_6$H$_4$-*p*-Me	**39j**	51
11	**37k**[1]	–Bu	–N-pyrollidine	–C$_6$H$_4$-*p*-Me	**39k**	58
12	**37l**[1]	–Cy	–N-piperidine	–C$_6$H$_4$-*p*-Me	**39l**	63
13	**37m**[1]	–Cy	–N-pyrollidine	–C$_6$H$_4$-*p*-Me	**39m**	70
14	**37n**[3]	-Ph	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39n**	96
15	**37o**[3]	-C$_6$H$_4$-*p*-Me	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39o**	93
16	**37p**[3]	-C$_6$H$_4$-*p*-OMe	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39p**	95
17	**37q**[3]	-α–naphthyl	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39q**	96
18	**37r**[3]	–1-pyrenyl	–NEt$_2$	–C$_6$H$_4$-*p*-Me	**39r**	98
19	**37s**[3]	-C$_6$H$_4$-*o*-OMe	–NBn$_2$	–C$_6$H$_4$-*p*-Me	**39s**	89
20	**37t**[3]	-C$_6$H$_4$-*m*-OMe	–NBn$_2$	–C$_6$H$_4$-*p*-Me	**39t**	96

21	**37u**[3]	⦚-C_6H_4-*o*-NO_2	⦚–NBn_2	⦚–C_6H_4-*p*-Me	**39u**	80
22	**37v**[3]	⦚-C_6H_4-*m*-NO_2	⦚–NBn_2	⦚–C_6H_4-*p*-Me	**39v**	75
23	**37w**[3]	⦚-C_6H_4-*p*-CN	⦚–NBn_2	⦚–C_6H_4-*p*-Me	**39w**	71
24	**37x**[3]	⦚-C_6H_4-*m*-Br	⦚–NBn_2	⦚–C_6H_4-*p*-Me	**39x**	96
25	**37s**	⦚-C_6H_4-*o*-OMe	⦚–NBn_2	⦚–C_6H_4-*p*-NO_2	**39y**	92
26	**37s**	⦚-C_6H_4-*o*-OMe	⦚–NBn_2	⦚–Me	**39z**	91

[1] Prepared following protocol 1 of **scheme 6**; [2] prepared following protocol 2 of **scheme 6**; [3] prepared following protocol 3 of **scheme 6**; ■ carried out by SVJ; ■ carried out by senior group member DC; [4] Isolated yields.

37h provided reduced yields of **39h** (60%). We believe that the presence of two nucleophilic hydroxyl groups is responsible for the formation of by-products via the nucleophilic attack of hydroxyl on ketenimine. However, no such product was isolated in our hands.

Next we explored the effect of introducing an aryl substituent at C_1 position. For substrate **37n** with phenyl substituent at C_1 provided the respective acrylamidine **39n** in 96% yield (entry 14). Increasing the conjugation further to α-naphthyl **37q** gave the product **39q** in 96% yield (entry 17). A similar study with an even more conjugated aromatic pyrene is demonstrated in entry 18. This made us conclude that increasing the conjugation at C_1 position led to increase of overall conjugation of the final product, thereby favouring the product formation.

For aryl groups consisting of electron donating –OMe substituent at *ortho*-, *meta*- and *para*- positions, reactions proceeded smoothly with excellent yields of **37t** (89%), **37s** (96%), and **37p** (95%), respectively (entries 20, 19 and 16 respectively). This data was complemented by the work of my colleague, who studied the effect of strong electron withdrawing substituents *e.g. ortho*-NO_2, *meta*-NO_2 and *para-CN* (entries 24-26). However, weak electron withdrawing *meta*-Br substituent did not affect the yield at all.

Variations in amine substituents ^{2}R and ^{3}R: To observe the effect of various types of amines *i.e.* acyclic versus cyclic, we employed various propargylamines with cyclic amino group (entries 10-13). The inflexibility of cyclic amines towards spiro intermediate formation was reflected in the yields of acryl amidines containing cyclic

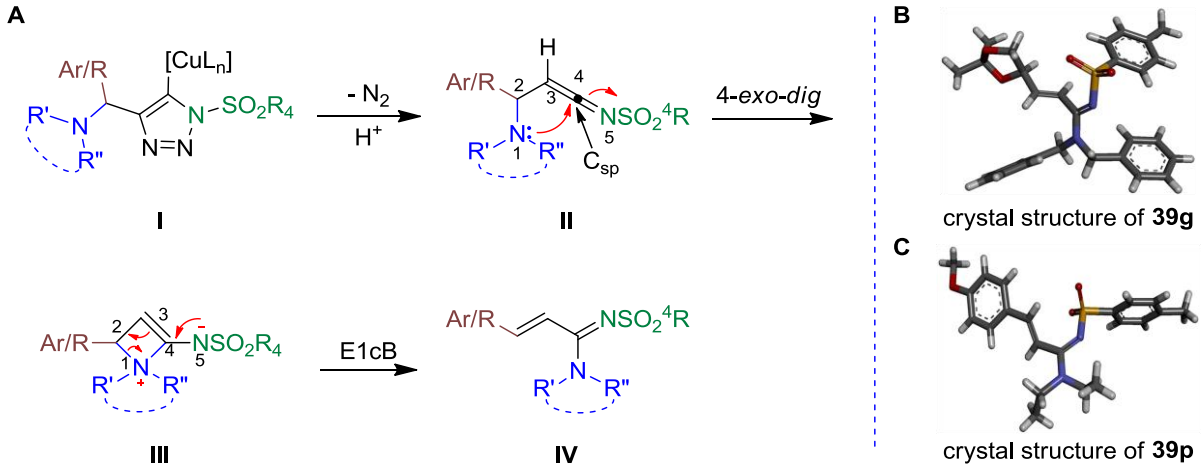
amino substituent. Compared to their acyclic counterparts (entries 4 and 6) these propargylamines **37j**-**37m** provided only moderate yields. Employing a larger ring containing piperidine substituted propargylamine **37i** and **37j** brought significantly low yields (entry 9 and 10 with 48% and 51% respectively) in product formation. The variation of alkyl group to cyclohexyl brought only a nominal improvement (entry 12). On the other hand, studies on propargylamines with pyrollidine substituent **37k** and **37m** exhibited improved yields (entries 11 and 13) owing to its smaller ring size.

Variations in azide substituent ^{4}R: In order to completely analyse the scope of the methodology we decided to study the variations in the sulfonyl group substituents. For this, the propargylamine with *o*-methoxy benzene substituent at C_1 position, **37s** was reacted with an array of sulfonylazides. It is discussed earlier that the tosylazide with electron donating toluene group gave 89% yield for the formation of **39s** (entry 19). Change of azide substrate to either *p*-nitrophenylsulfonylazide (entry 25) or mesylazide (entry 26) did not affect the yields (92% for **39y** and 91% for **39z**).

C. Mechanism of 1,3-amino group migration

The following mechanism has been postulated for the formation of acrylamidine from *N*,*N*-di-substituted propargylamine which is depicted in **Scheme 7**. *N*-Sulfonyl triazolyl copper intermediate **I**, formed upon reaction of propargylamine with tosylazide, releases one molecule of N_2 and undergoes protonation to generate ketenimine **II**.[24a,b] The rearrangement of **II** to **IV** occurs in a stepwise manner. As a first step a 4-*exo*-*dig* cyclization of **II** occurs to generate the intermediate **III** through the attack of the nucleophilic pendent nitrogen (N_1) on the highly electrophilic C_4-center. Additionally, the formation of **III** is assisted by the delocalization of the negative charge on N_5-center by sulfonyl group. The next step involves a E1cB type ring opening of the heterocycle to produce **IV**. Overall, the process can be considered as a formal [1,3]-sigmatropic rearrangement because, it involves intermediate steps. The rate determining step in the above sequence is the entropically unfavourable formation of the strained 4-membered ring **III** from an acyclic system **II**. This claim was supported by the fact that longer reaction times of cyclic amino group containing propargylamines **37i-37m** and lower yields corresponding products **39i-39m** compared to acyclic counterparts. The spiro-transition state formation in these transition states lowers the reaction rates.

Furthermore, the preferential *E*-stereochemistry around the newly formed C=C bond as predicted by the mechanism, was confirmed by NMR and single crystal X-ray diffraction studies of **39g** (**Scheme 7B**) and **39o** (**Scheme 7C**).



Scheme 7. (A) Proposed mechanism for amidine formation through intramolecular amine migration. Crystal structures of compounds (**B**) **39g** and (**C**) **39p**.

D. NMR Experiments for resolving rotamer interconversion

NMR spectral data of acrylamidines often provided unresolved and broad signals for the α-protons and α-carbons (and occasionally β-protons and β-carbons, too) of the amine nitrogen (*e.g.* **Figure 5**). Therefore, variable temperature experiments were carried out for **39o**. From variable temperature ^{1}H-NMR studies, it is evident that at 293 K, signals signals for a and a' protons merged and appeared as broad signal (**Figure 5A**). The observation was similar for protons b and b'. Upon lowering the temperature to 273 K, separate resolved signals a, a' and b, b' were observed indicating freezing of rotation along the C-N bond. When the temperature was raised to 323 K, protons a and a' provided identical signal as quartet and protons b and b' together exhibited a triplet. This data confirms fast rotation (faster than the NMR time scale) along the C-N bond. Variable temperature ^{13}C-NMR studies for **39o** also confirmed the rotamer interconversion (**Figure 5B**).

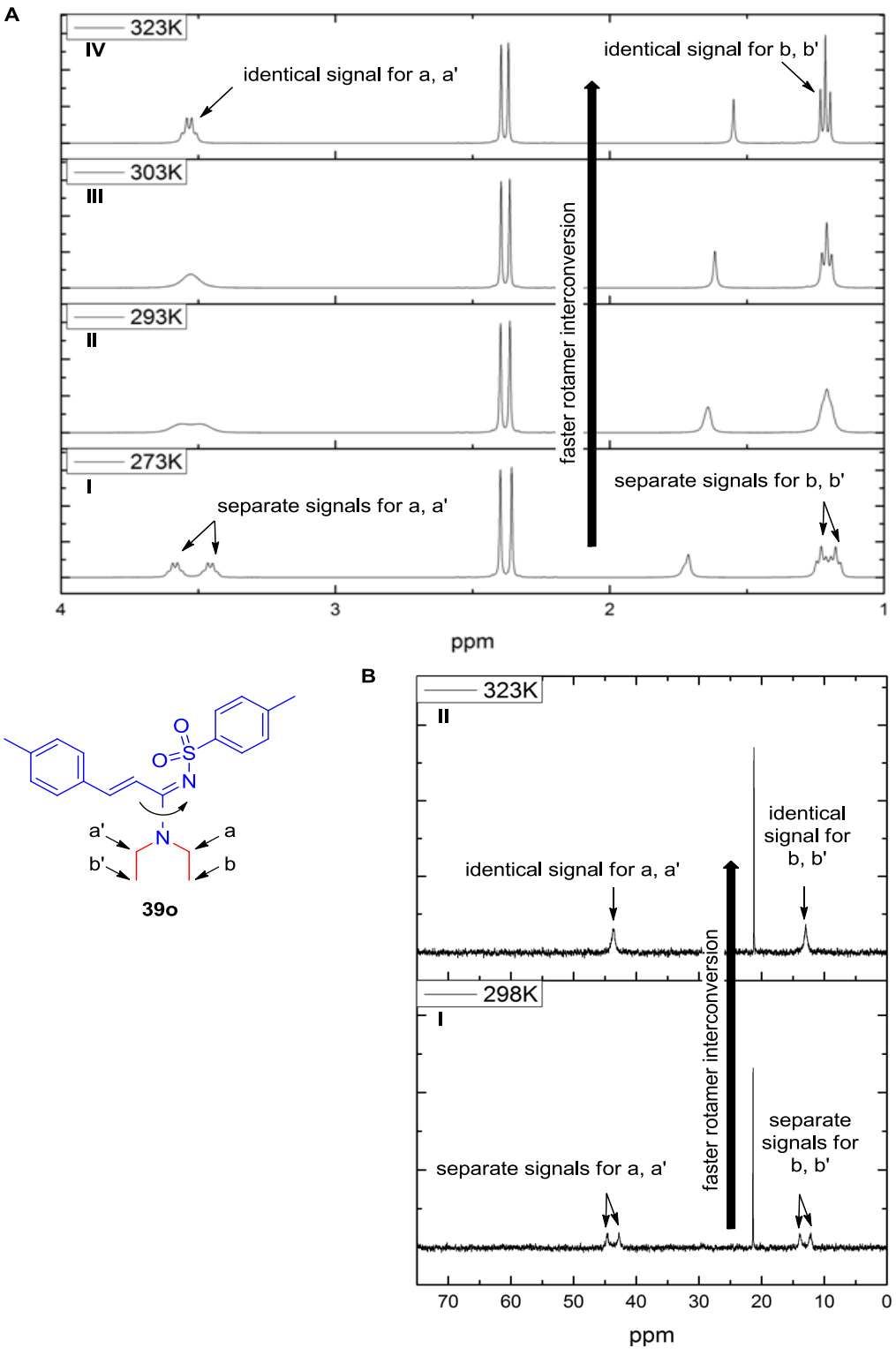


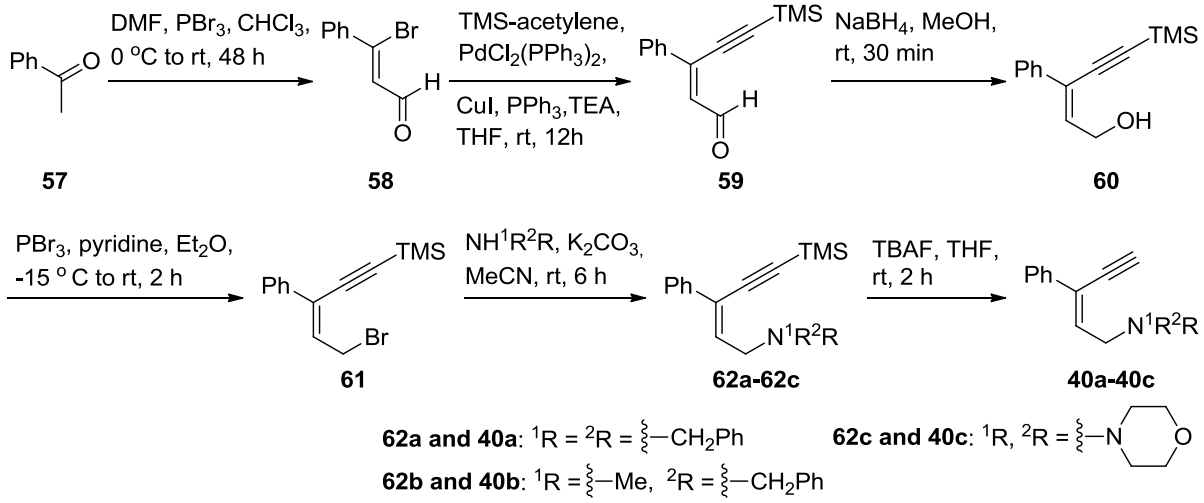
Figure 5: Variable temperature ^{1}H-NMR (**A**) and ^{13}C-NMR **(B)** spectral studies for **39o**.

Section 2: 1,5- Amino Group Migration Route to Acrylamidines

With the fascinating 1,3-amino group migration (a formal [1,3]-sigmatrotic rearrangement) already established, we saw the potential of a homologous migrations that obeys the Woodward-Hoffman rules on orbital symmetry. We examined the possibility of a 1,5-amino group migration on the in situ generated ketenimine (**Scheme 5**). A substrate for such migration can be designed as **40** (**Scheme 5**). Reaction of **40** with a sulfonylazide would form ketenimine **41** which subsequently undergo 1,5-amino group migration to form conjugated amidine **42**. Such structures are expected to be even more versatile molecules for a variety of transformations including inverse electron demand Diels Alder and other pericyclic reactions in addition to conjugate addition and metathesis.

A. Synthesis of precursors

The central feature of substrate that allows it to undergo a 1,5-amine migration is the *cis* stereochemistry of alkyne and the amino group, around the alkene moiety. For this purpose, the ene-yne bromide **61** was prepared according to the methodology reported by Liu *et. al*. (**Scheme 8**).[25] Subsequently, various amino groups were introduced under K_2CO_3 conditions for form **62a-62c**. The TMS protecting group was removed by treating with TBAF obtain ene-yne **40a-40c**.

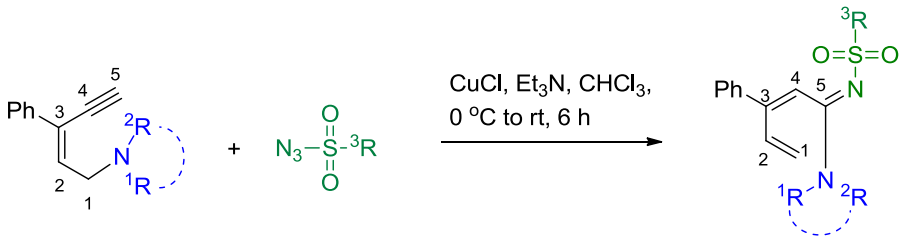


Scheme 8: Synthesis of ene-yne **40a-40c**.

B. 1,5-Amino group migration methodology and its scope

Optimization of the reaction conditions led to a protocol (*i.e.* 10 mol% CuCl catalyst, $CHCl_3$ solvent, Et_3N base, and room temperature) which is similar to 1,3-amino group migration. Reactions of ene-yne substrates **40a-40c** with an array of sulfonylazides **56a-56c** are presented in **Table 3**. Reaction of ene-yne with *N*,*N*-di-benzylamino group **40a** with **56a** provided acrylamidine **42a** in 70% yield (entry 1). Altering the azide to electron withdrawing group containing *p*-nitrobenzenesulfonylazide, while keeping the alkyne same gave lower yields (45%) for the product **42b** (entry 2). Usage of non-aromatic methanesulfonylazide gave 56% yield for the amidine **42c** (entry 3). In similar fashion when the ene-yne **40b** (with two different substitution on amino group *i.e.* $-N^1R^2R$ = -NMeBn) was treated with tosylazide **56a**, acrylamidine **42d** was formed in 22% yield (entry 4). Improvement of yield (35%) was noted when mesylazide **56c** was introduced (entry

Table 3. Scope of 1,5-amino group migration route in the synthesis of acrylamidines.



40a-40c **56a-56c** **42a-42h**

Entry	40	^2R $-N$ ^1R	$-^4R$	42	Yield (%)[1]
1	**40a**	$-NBn_2$	$-C_6H_4$-*p*-Me	**42a**	70
2	**40a**	$-NBn_2$	$-C_6H_4$-*p*-NO_2	**42b**	45
3	**40a**	$-NBn_2$	$-$Me	**42c**	56
4	**40b**	$-$NMeBn	$-C_6H_4$-*p*-Me	**42d**	22
5	**40b**	$-$NMeBn	$-$Me	**42e**	35
6	**40c**	$-$*N*-morpholine	$-C_6H_4$-*p*-Me	**42f**	45
7	**40c**	$-$*N*-morpholine	$-C_6H_4$-*p*-NO_2	**42g**	56
26	**40c**	$-$*N*-morpholine	$-$Me	**42h**	63

Carried out by SVJ; [1] Isolated yields.

5). Finally, to explore the effect of cyclic amino substituent, ene-yne **40c** was employed (*i.e.* with amine with *N*-morpholine group). Reaction of **40c** with tosylazide **56a** gave 45% yield (entry 6). Reaction of **40c** with *p*-nitrobenzenesulfonylazide **56b** afforded moderate yield of 56% (entry 7). Further improvement of yield (63%) was observed during the reaction of **40c** with mesylazide (entry 8). We believe these substrate scope should be repeated to further improve yields of these reactions and to achieve trend of yields which can be rationalized properly.

Conclusions

We have demonstrated 1,3- and 1,5-amino group migration reactions of ketenimines that are formed during the reaction of alkynes with sulfonylazides under Cu(I) catalysed conditions. Starting from *N*,*N*-disubstituted propargylamines, the ketenimine intermediate allowed the 1,3-migration of flanking amino group to form acrylamidines in excellent yields. A mechanism was proposed via two step process involving a 4-*exo*-*dig* cyclization followed by E1cB type ring opening. Variable temperature NMR experiments were helpful in resolving rotamer interconversion. Subsequently, the methodology was extended to study 1,5-migration, a translation of the observed 1,3-migration. Although the migration proceeded with moderate yields, further optimisation followed by demonstrating its synthetic utility is under exploration.

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Appendix

Spectral data:

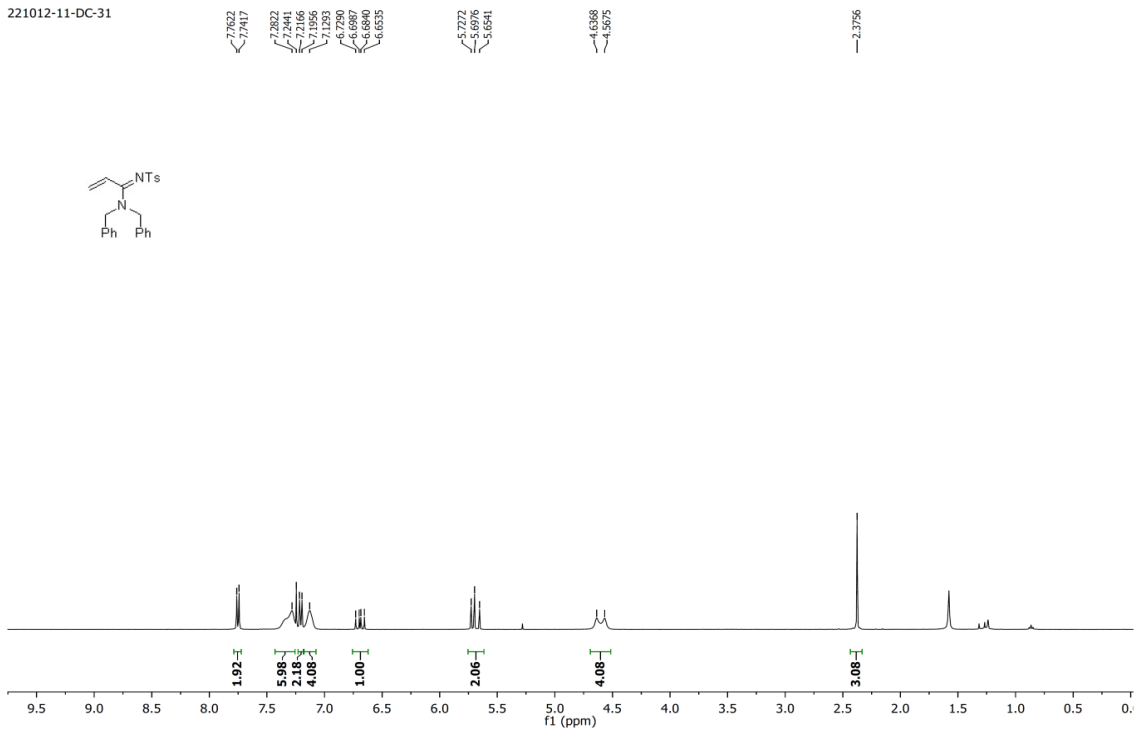

Figure 6: ^{1}H NMR spectra of **44** in $CDCl_3$.

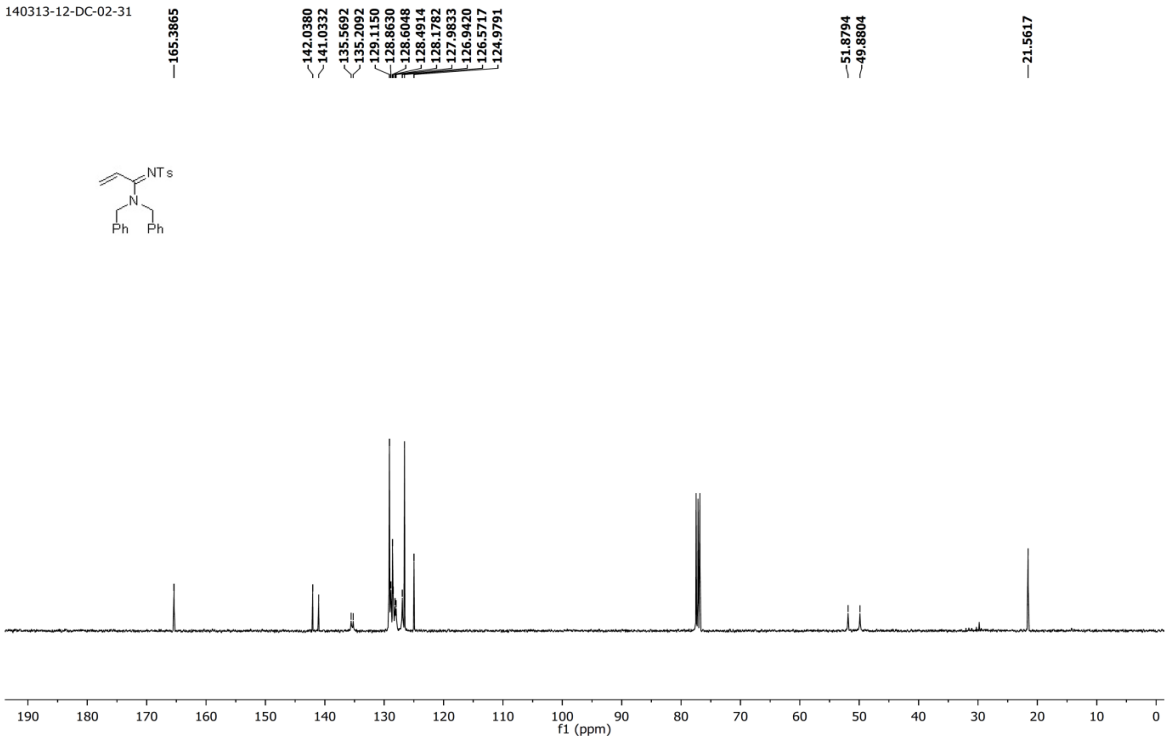

Figure: 7 ^{13}C NMR spectra of **44** in $CDCl_3$.

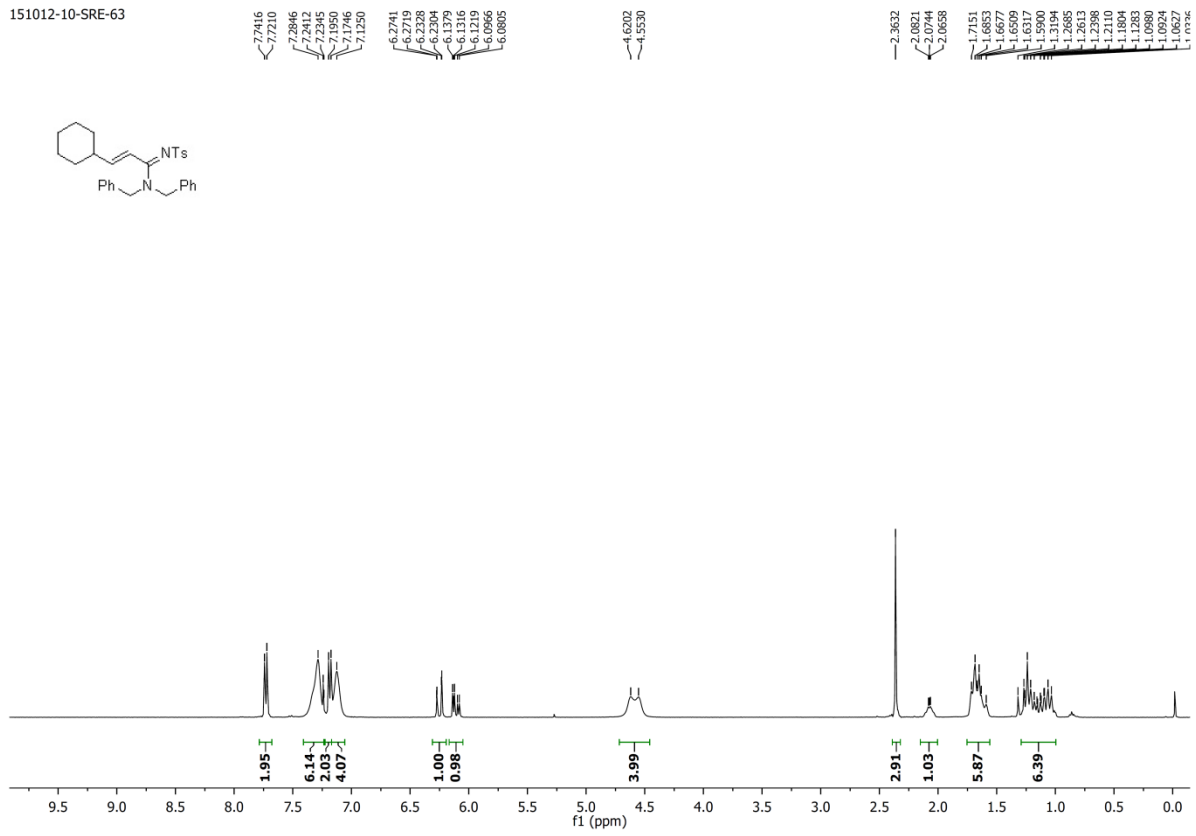

Figure: 8 ^{1}H NMR spectra of **39e** in $CDCl_3$.

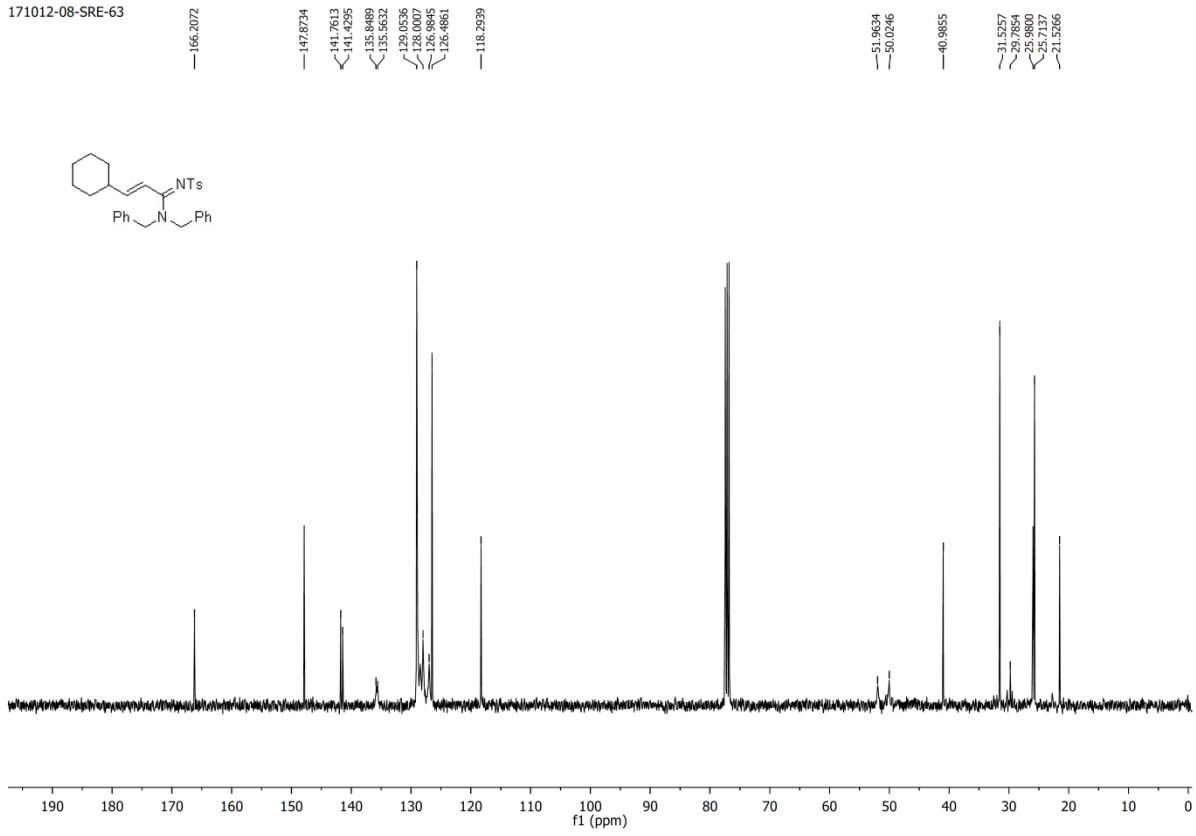

Figure: 9 ^{13}C NMR spectra of **39e** in $CDCl_3$.

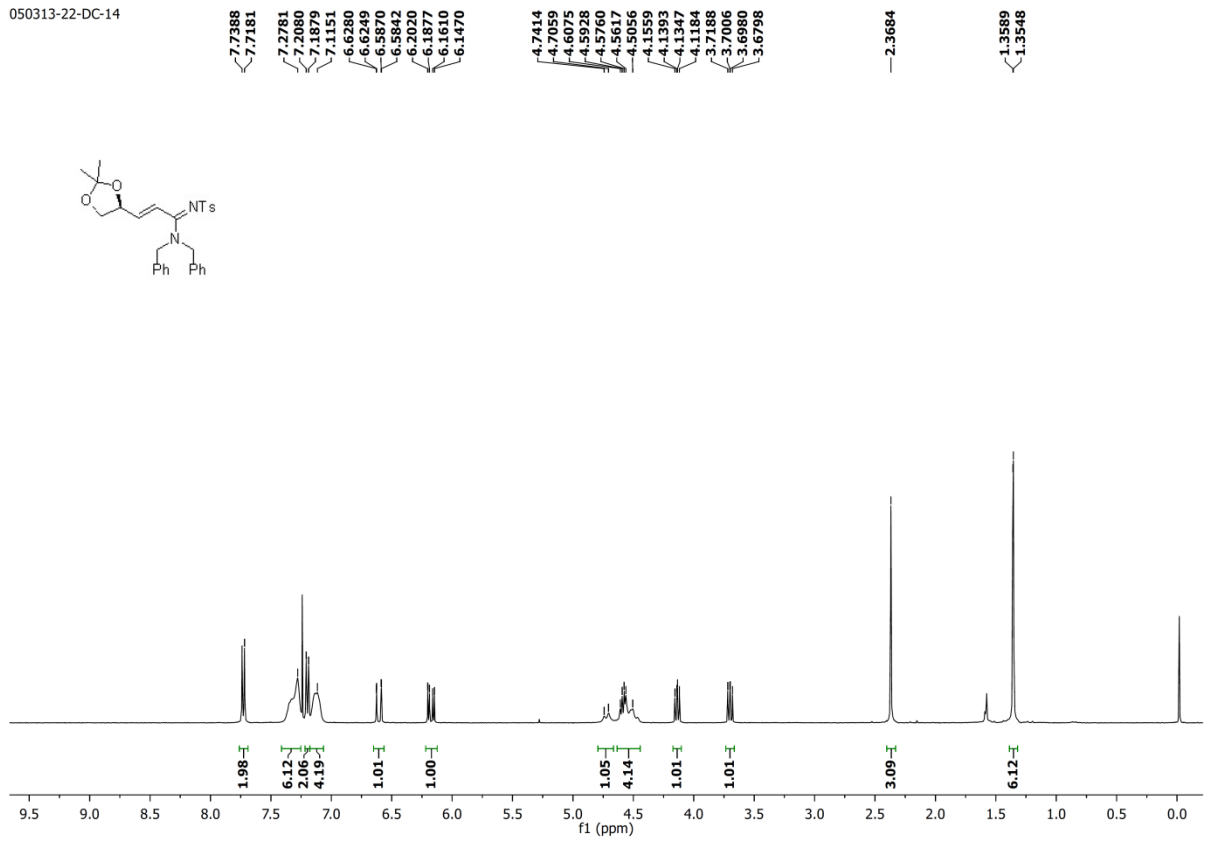

Figure: 10 ^{1}H NMR spectra of **39g** in $CDCl_3$.

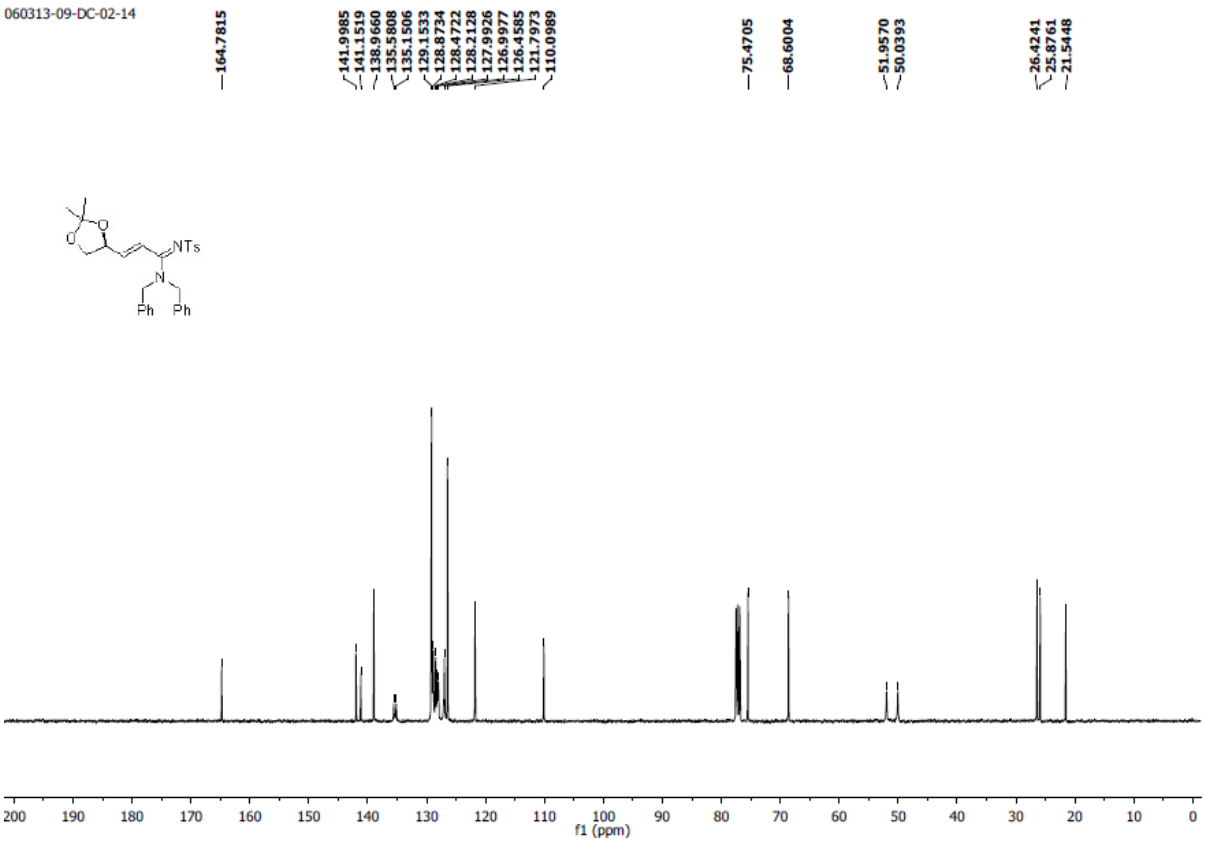

Figure: 11 ^{13}C NMR spectra of **39g** in $CDCl_3$.

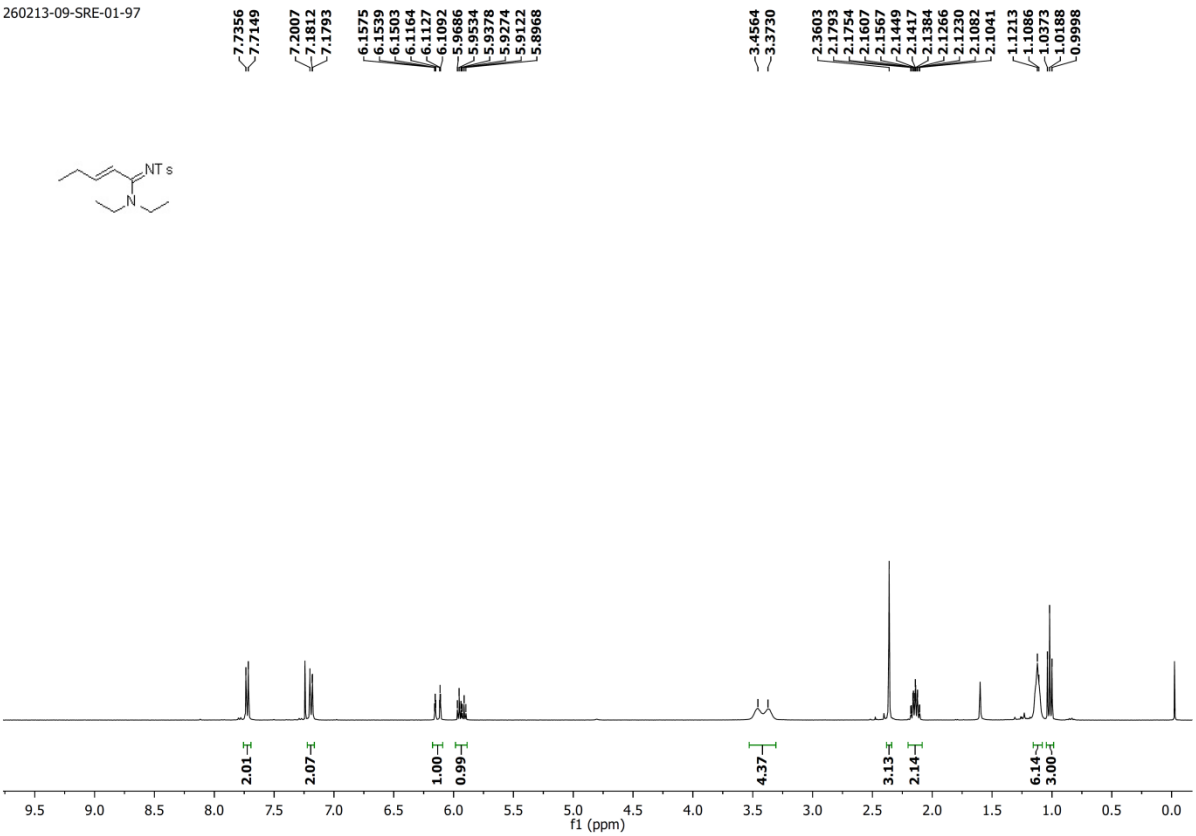

Figure: 12 ^{1}H NMR spectra of **39b** in $CDCl_3$.

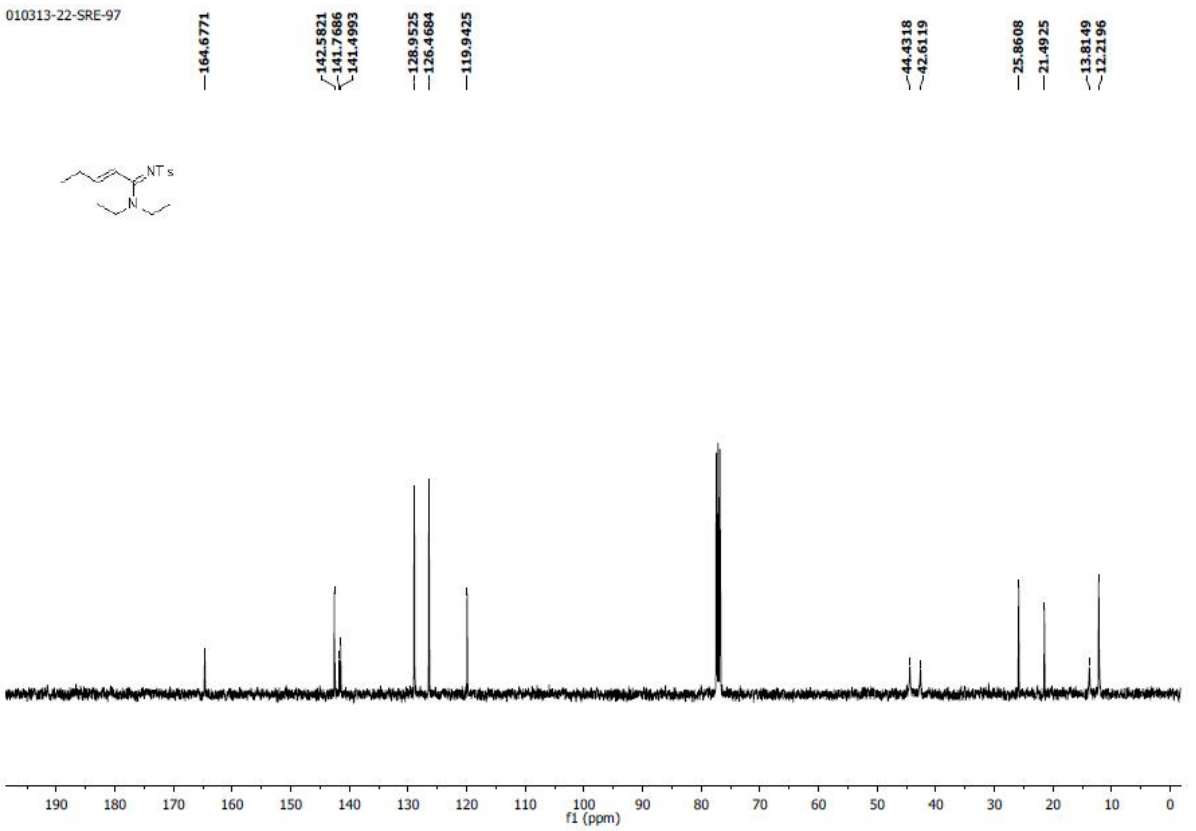

Figure: 13 ^{13}C NMR spectra of **39b** in $CDCl_3$.

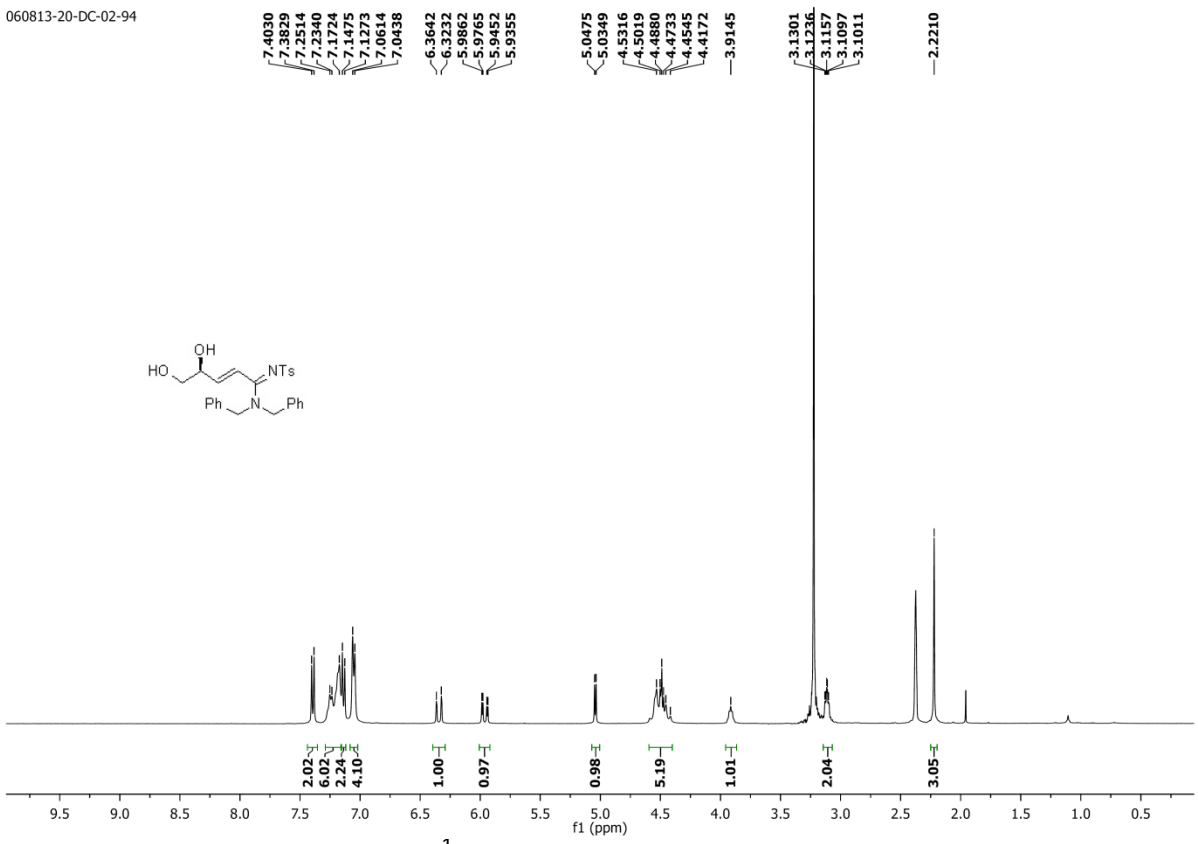

Figure: 14 ^{1}H NMR spectra of **39h** in DMSO.

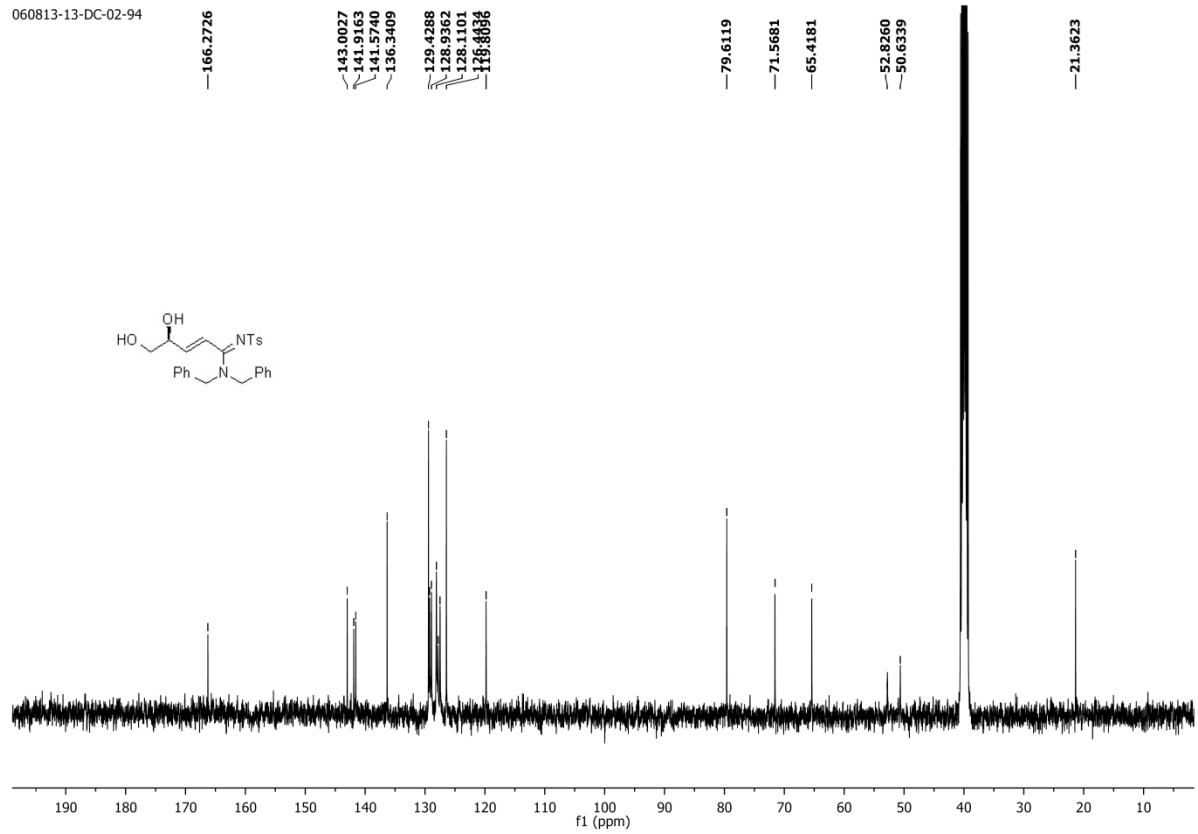

Figure: 15 ^{13}C NMR spectra of **39h** in DMSO.

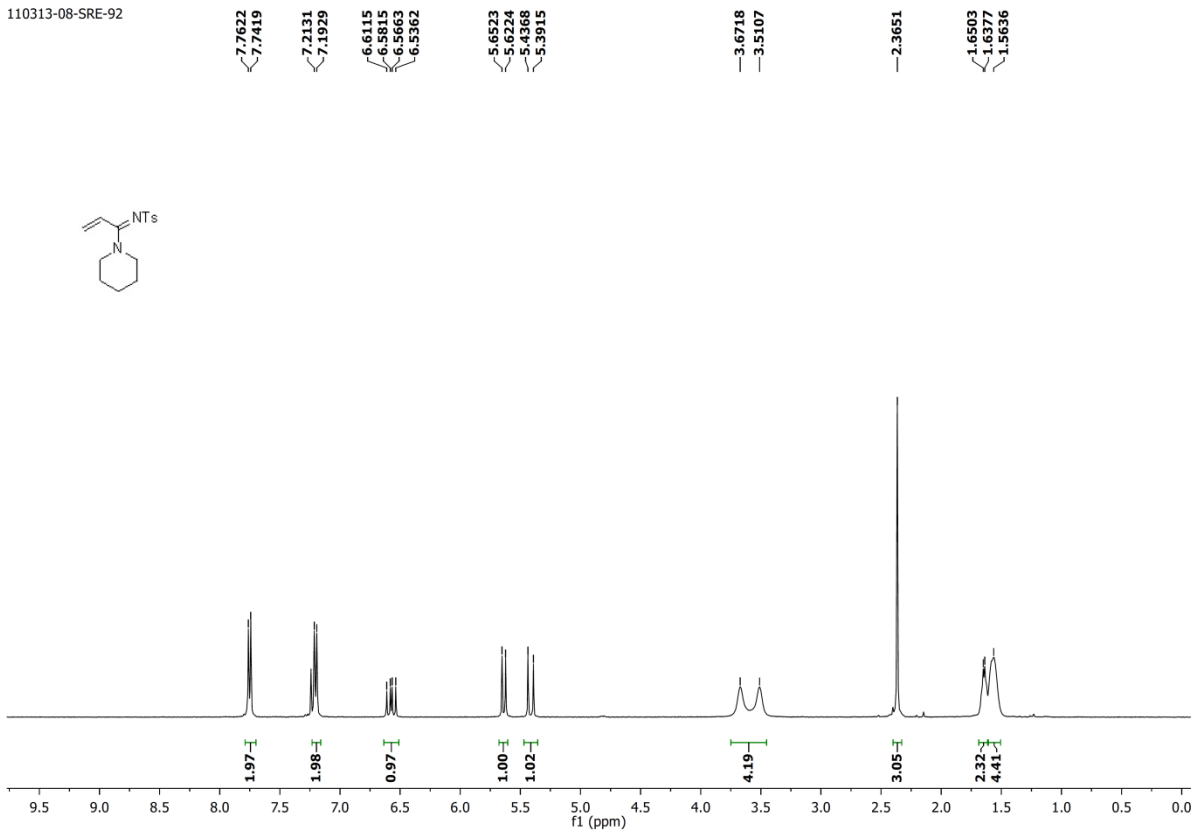

Figure: 16 ^{1}H NMR spectra of **39i** in $CDCl_3$.

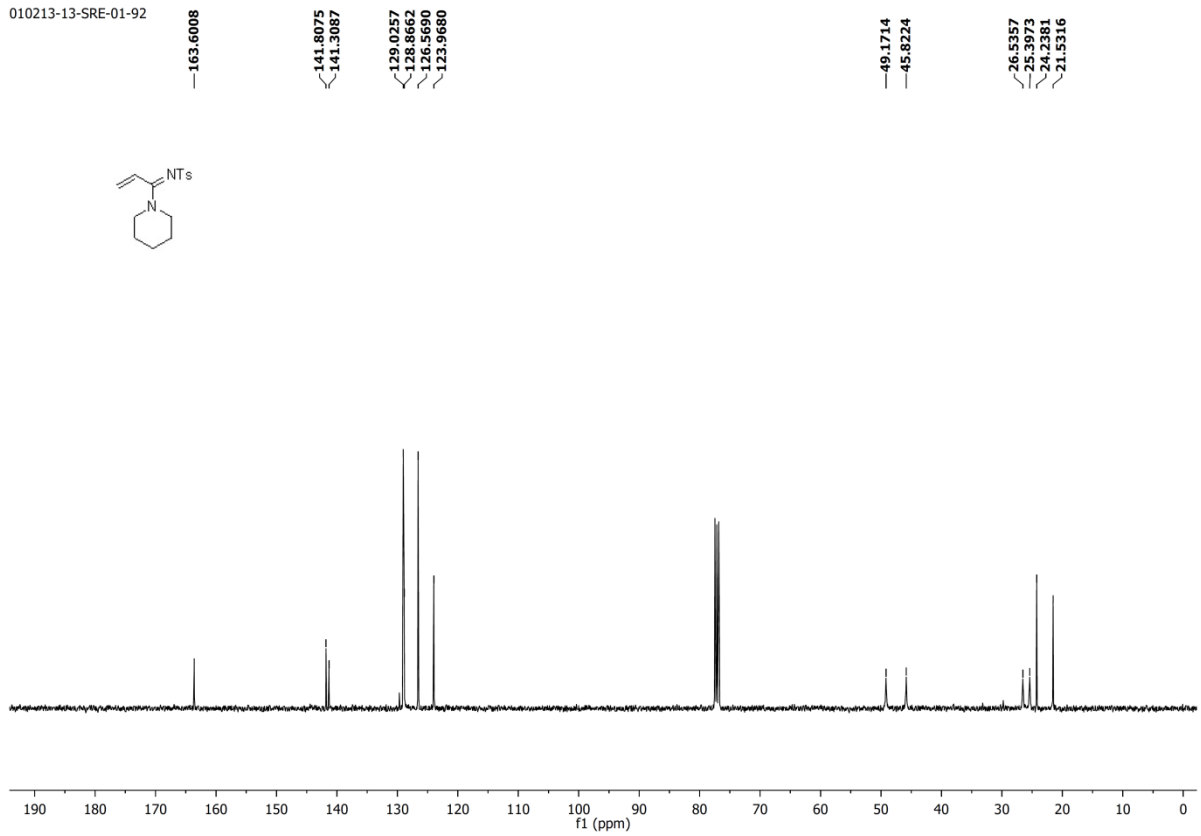

Figure: 17 ^{13}C NMR spectra of **39i** in $CDCl_3$.

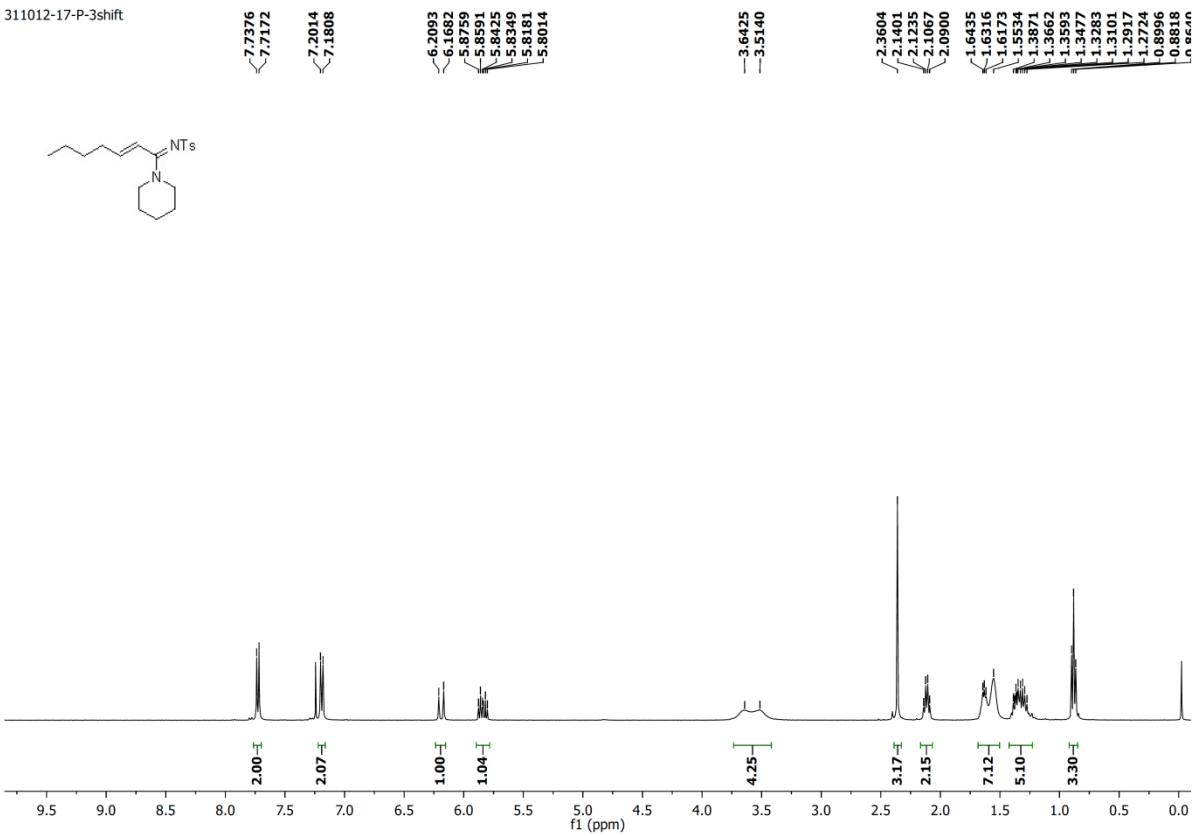

Figure: 18 ^{1}H NMR spectra of **39j** in $CDCl_3$.

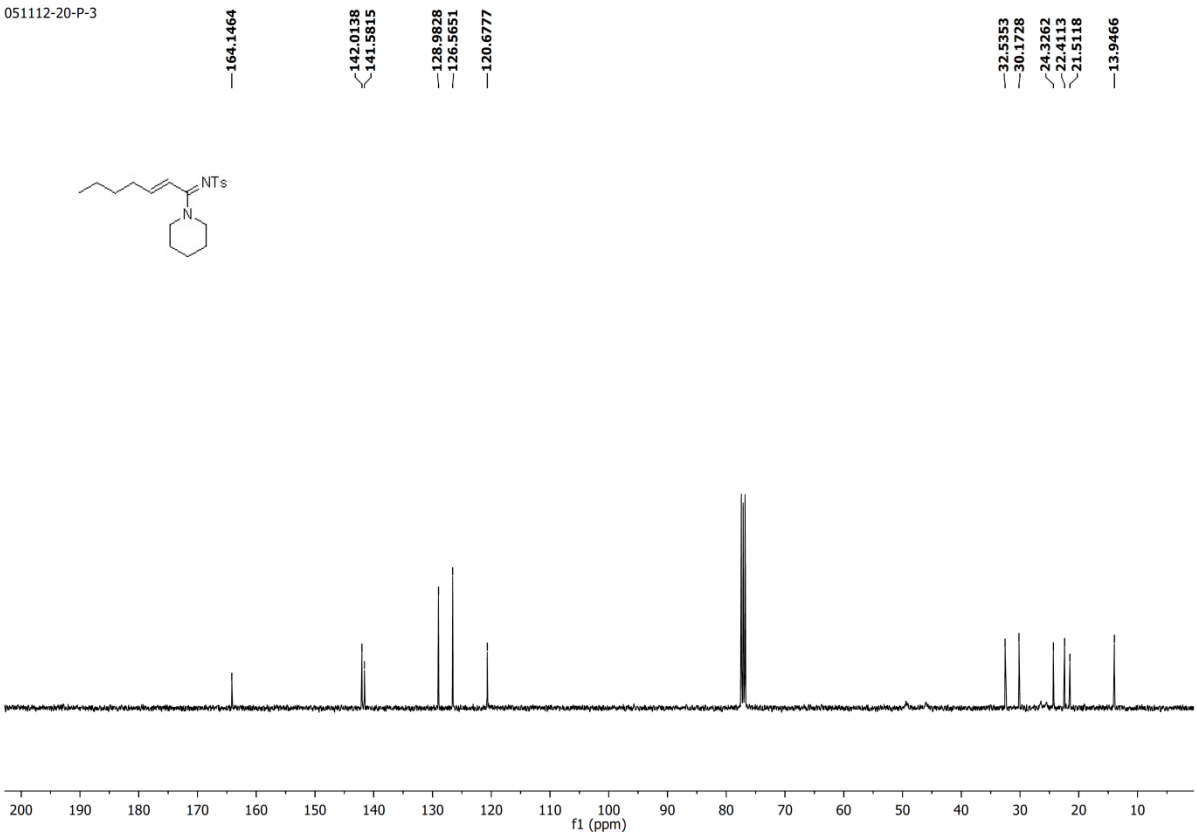

Figure: 19 ^{13}C NMR spectra of **39j** in $CDCl_3$.

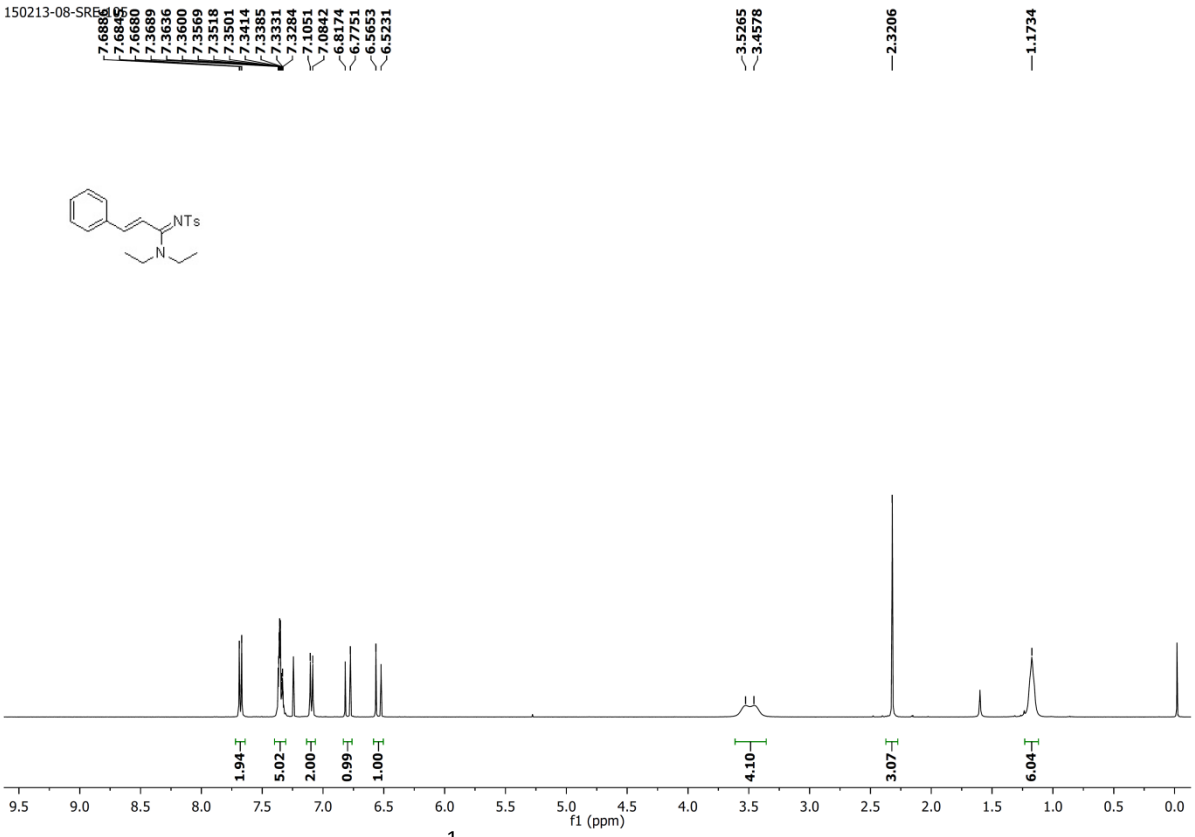

Figure: 20 ^{1}H NMR spectra of **39n** in $CDCl_3$.

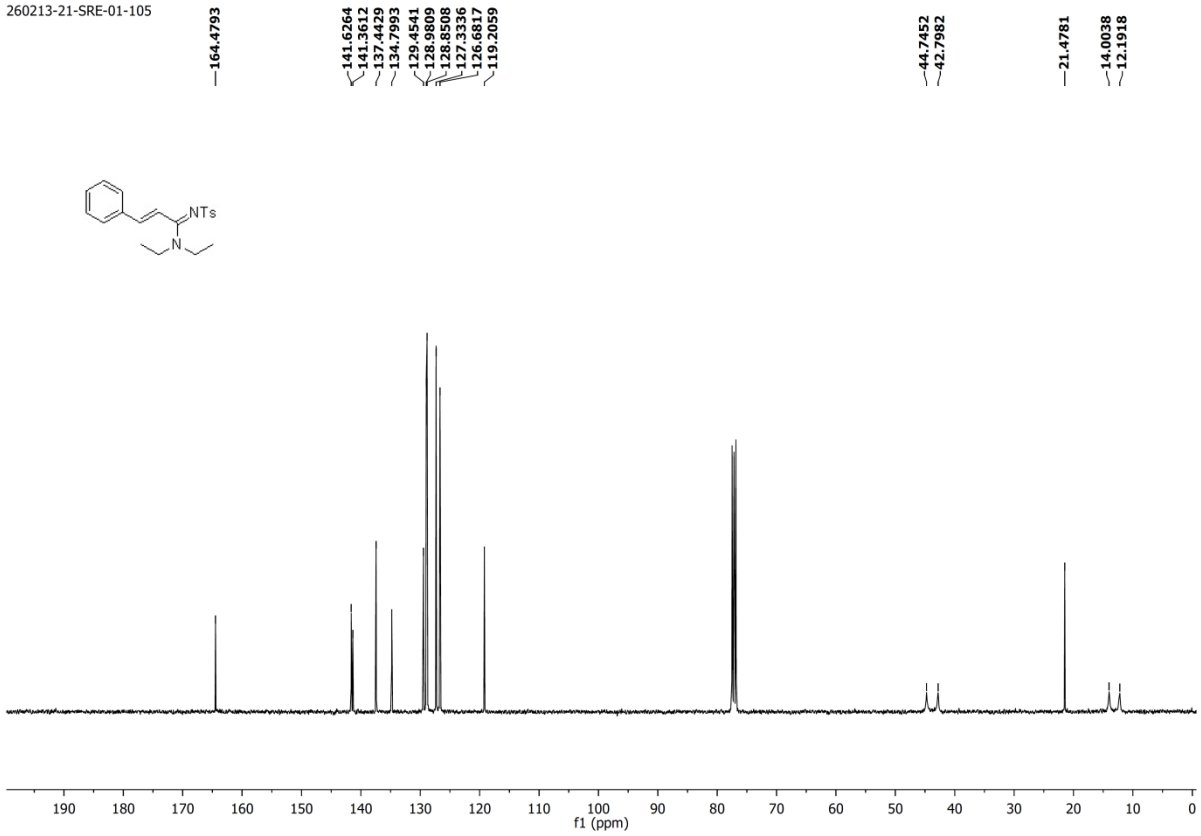

Figure: 21 ^{13}C NMR spectra of **39n** in $CDCl_3$.

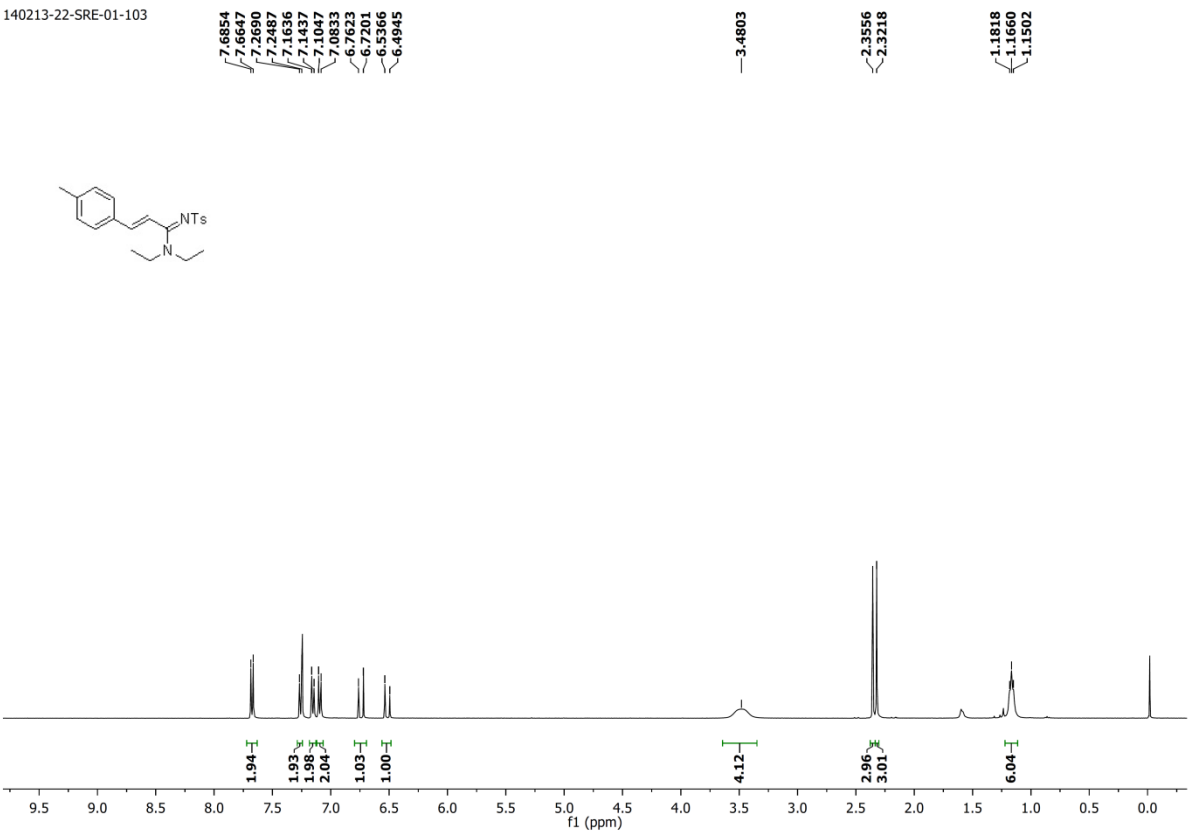

Figure: 22 ^{1}H NMR spectra of **39o** in $CDCl_3$.

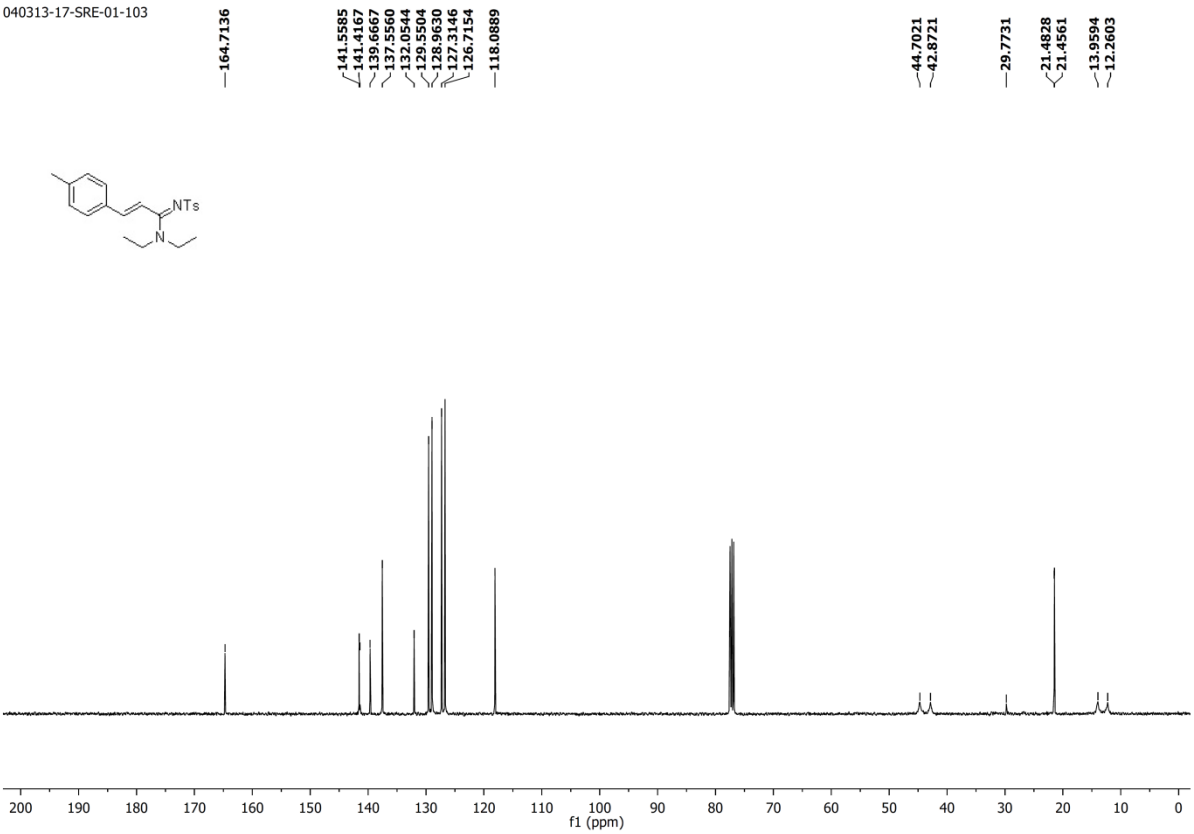

Figure: 23 ^{13}C NMR spectra of **39o** in $CDCl_3$.

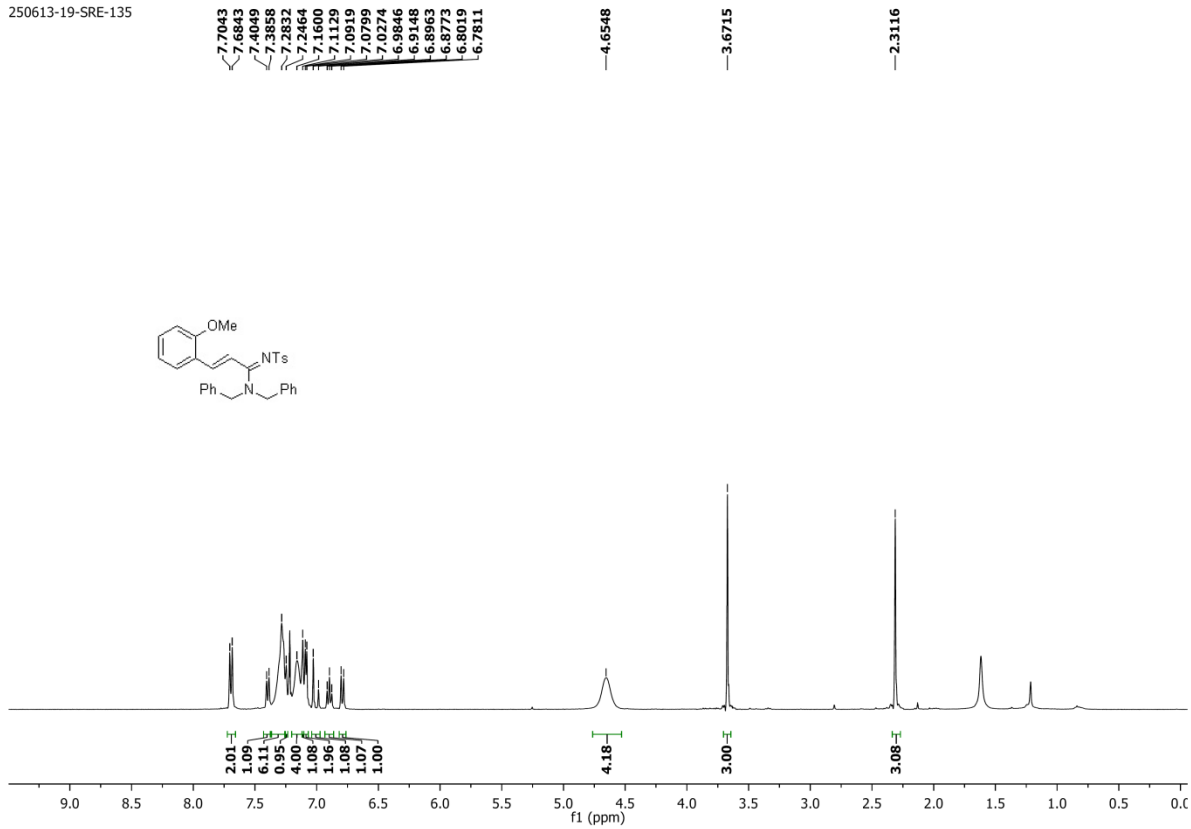

Figure: S92 ^{1}H NMR spectra of **39s** in $CDCl_3$.

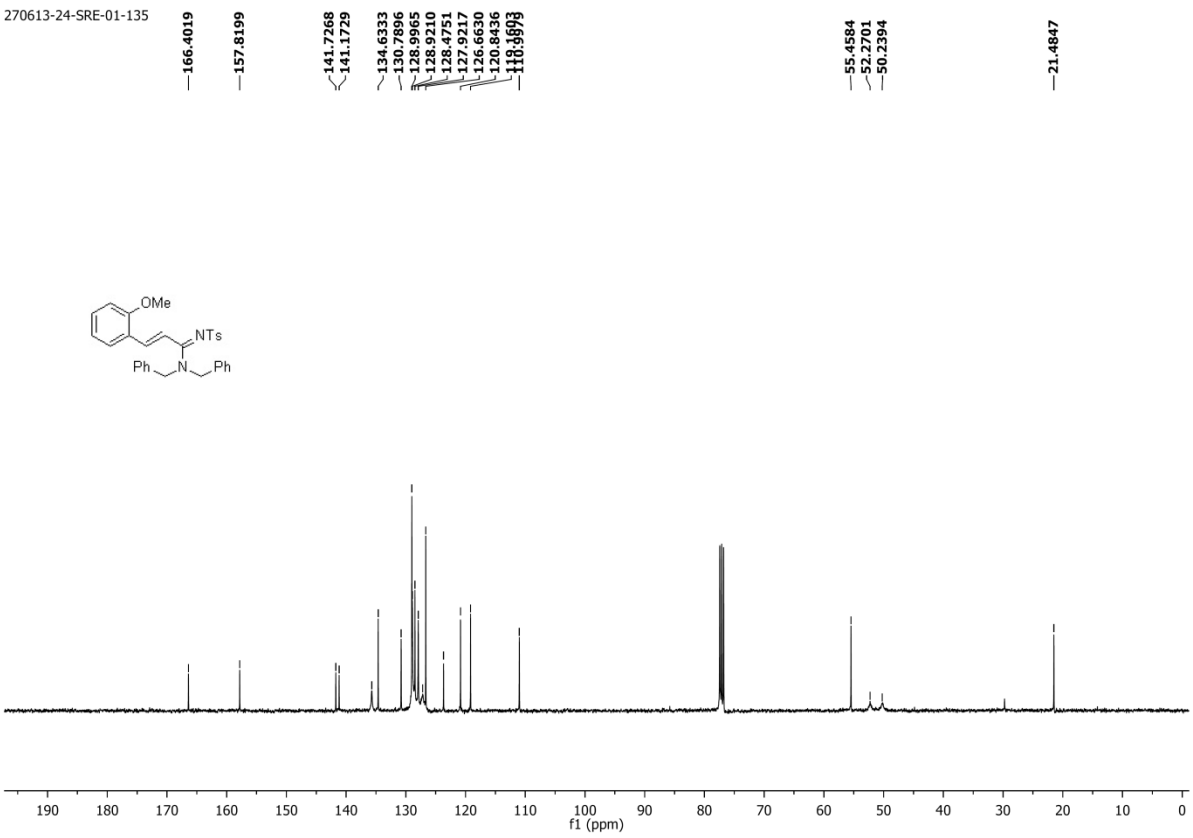

Figure: 24 ^{13}C NMR spectra of **39s** in $CDCl_3$.

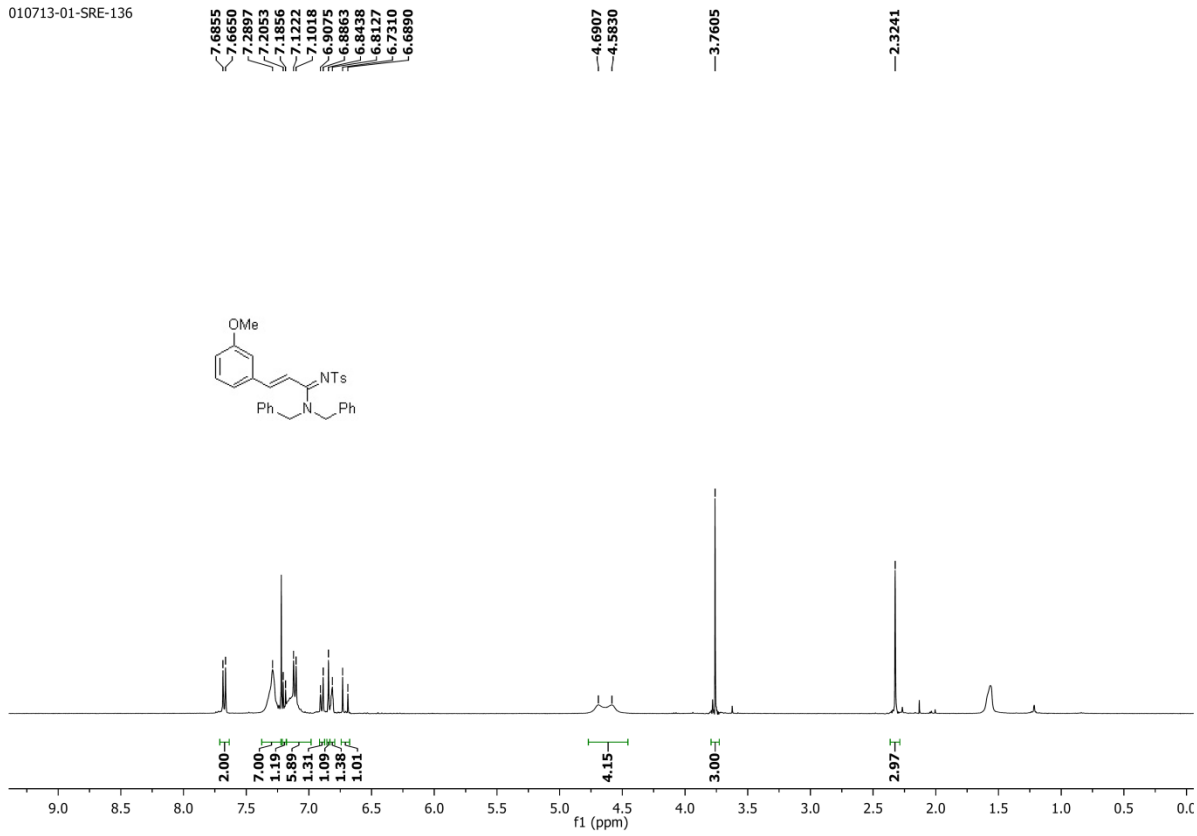

Figure: 25 ^{1}H NMR spectra of **39t** in $CDCl_3$.

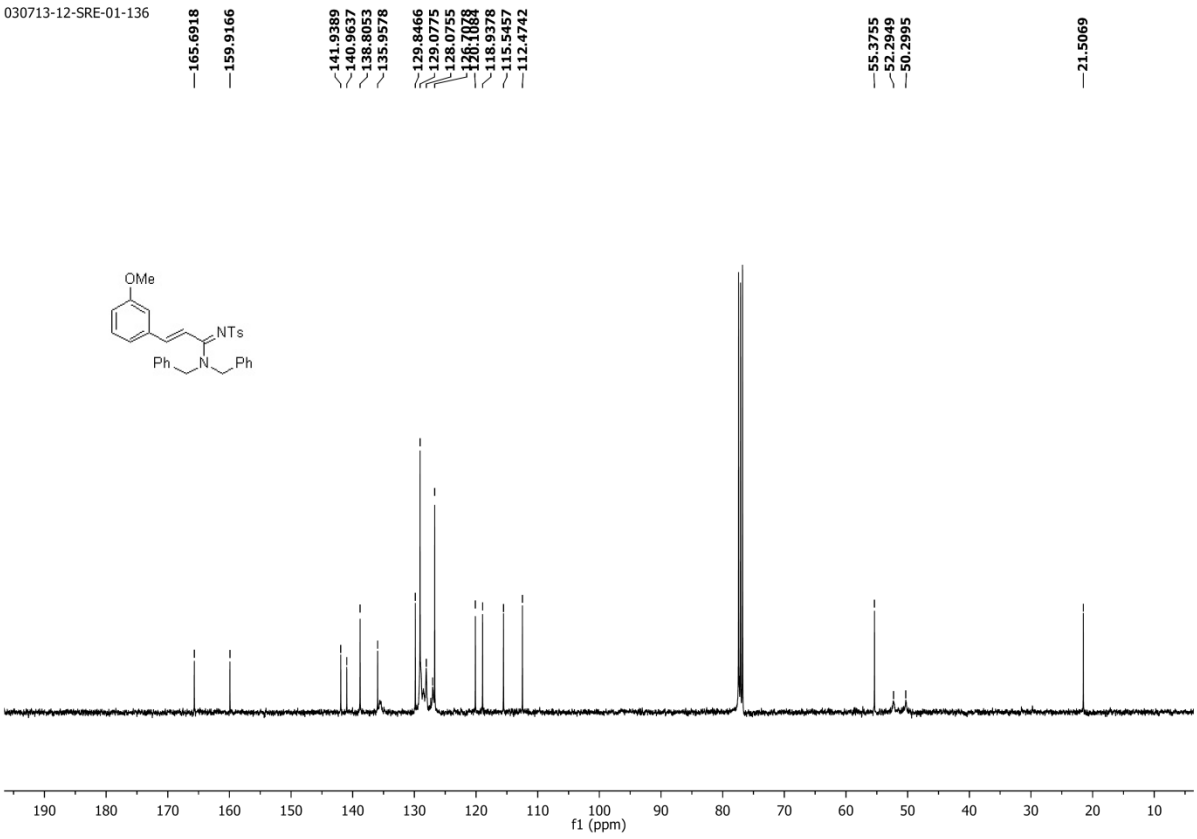

Figure: 26 ^{13}C NMR spectra of **39t** in $CDCl_3$.

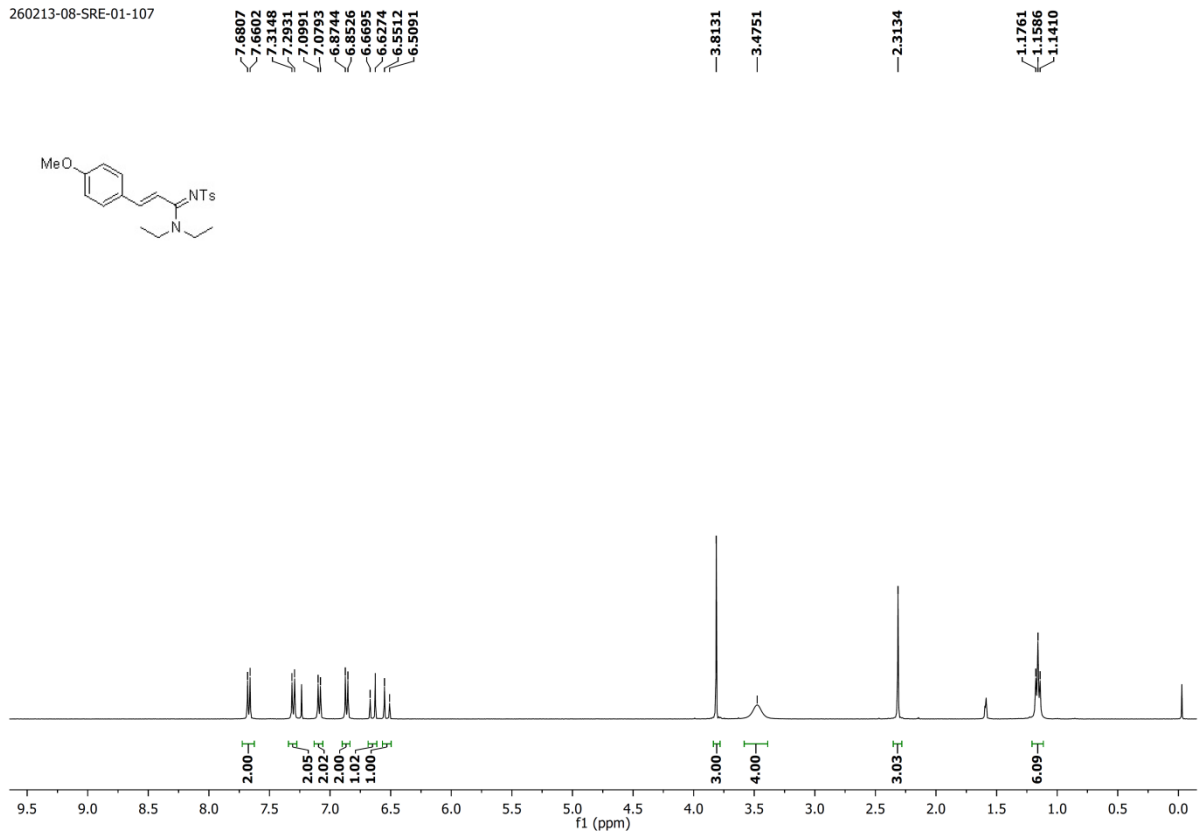

Figure: 27 ^{1}H NMR spectra of **39p** in $CDCl_3$.

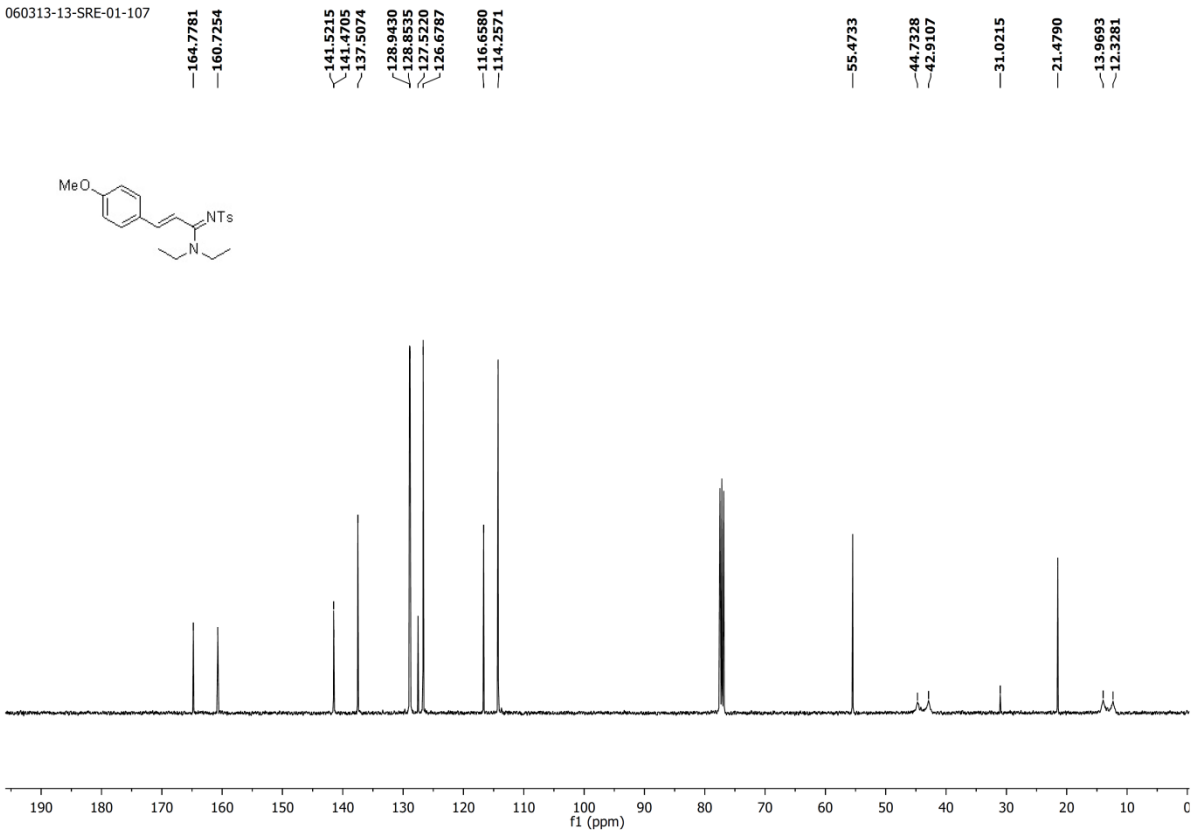

Figure: 28 ^{13}C NMR spectra of **39p** in $CDCl_3$.

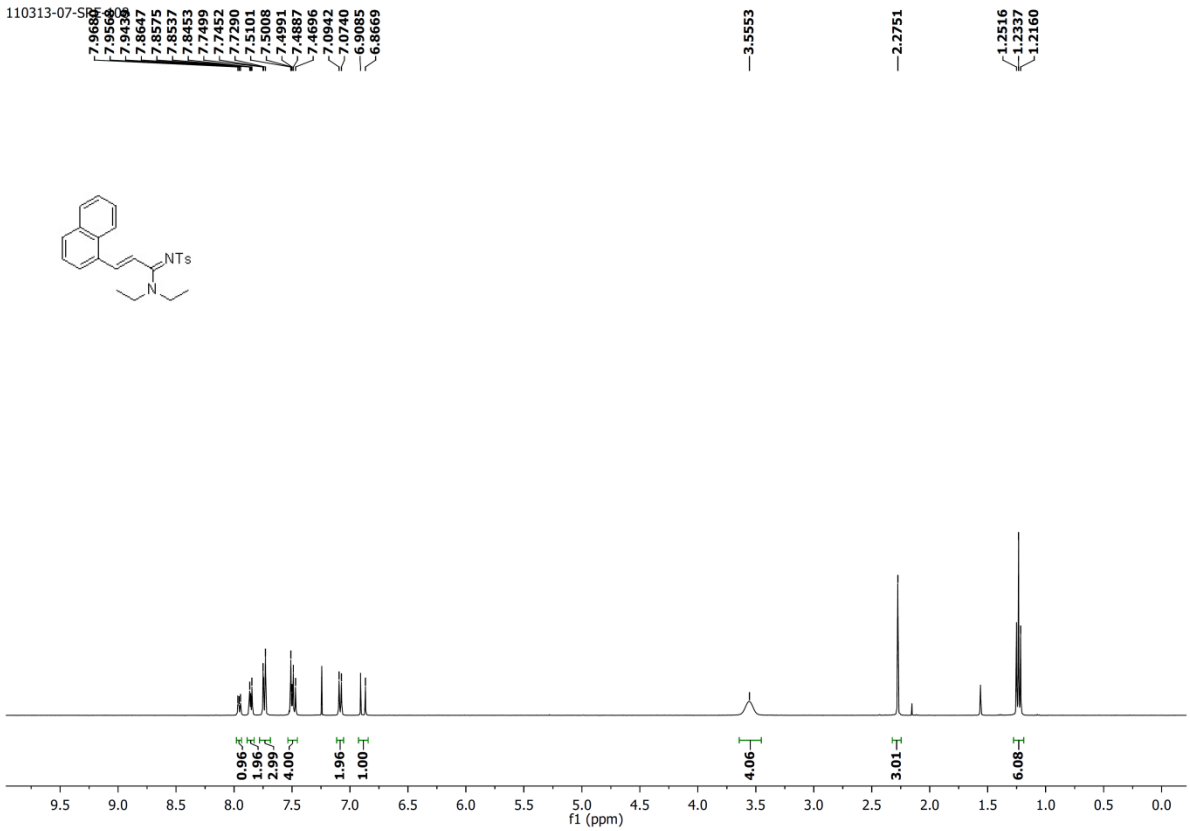

Figure: 29 ^{1}H NMR spectra of **39q** in $CDCl_3$.

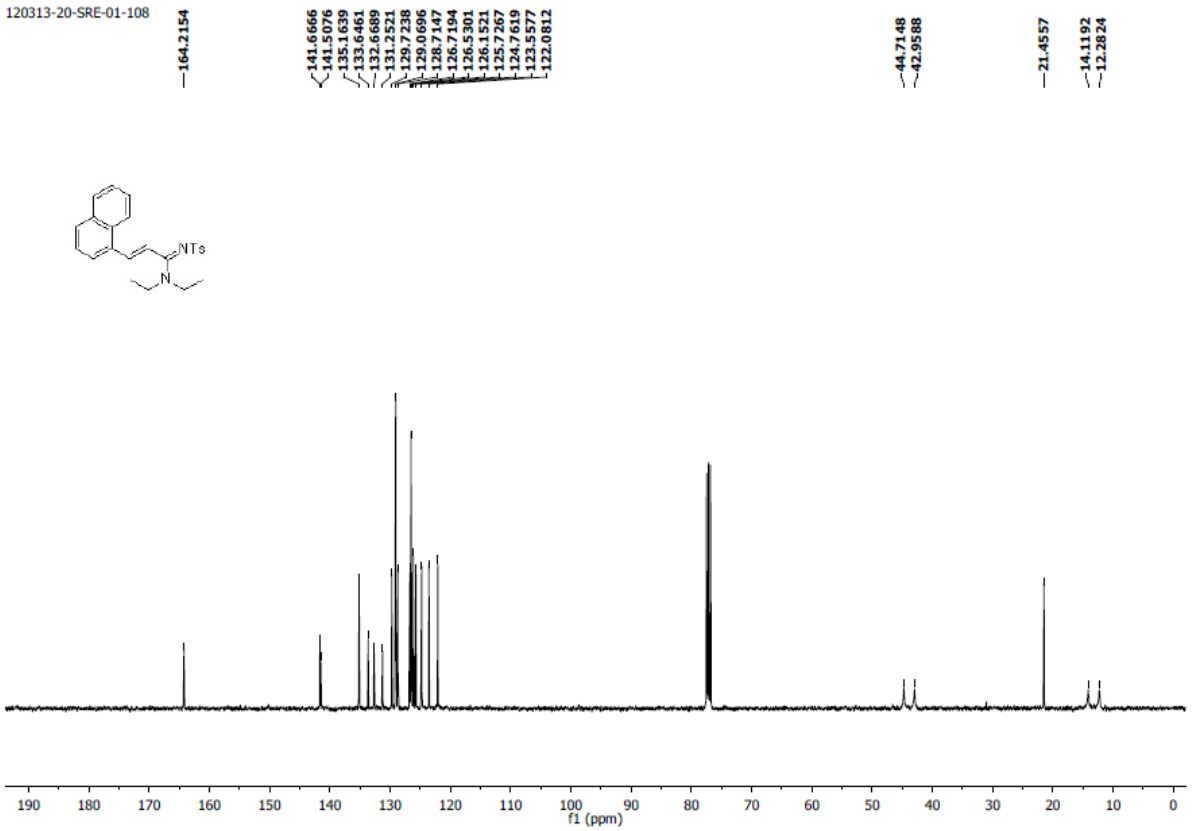

Figure: 30 ^{13}C NMR spectra of **39q** in $CDCl_3$.

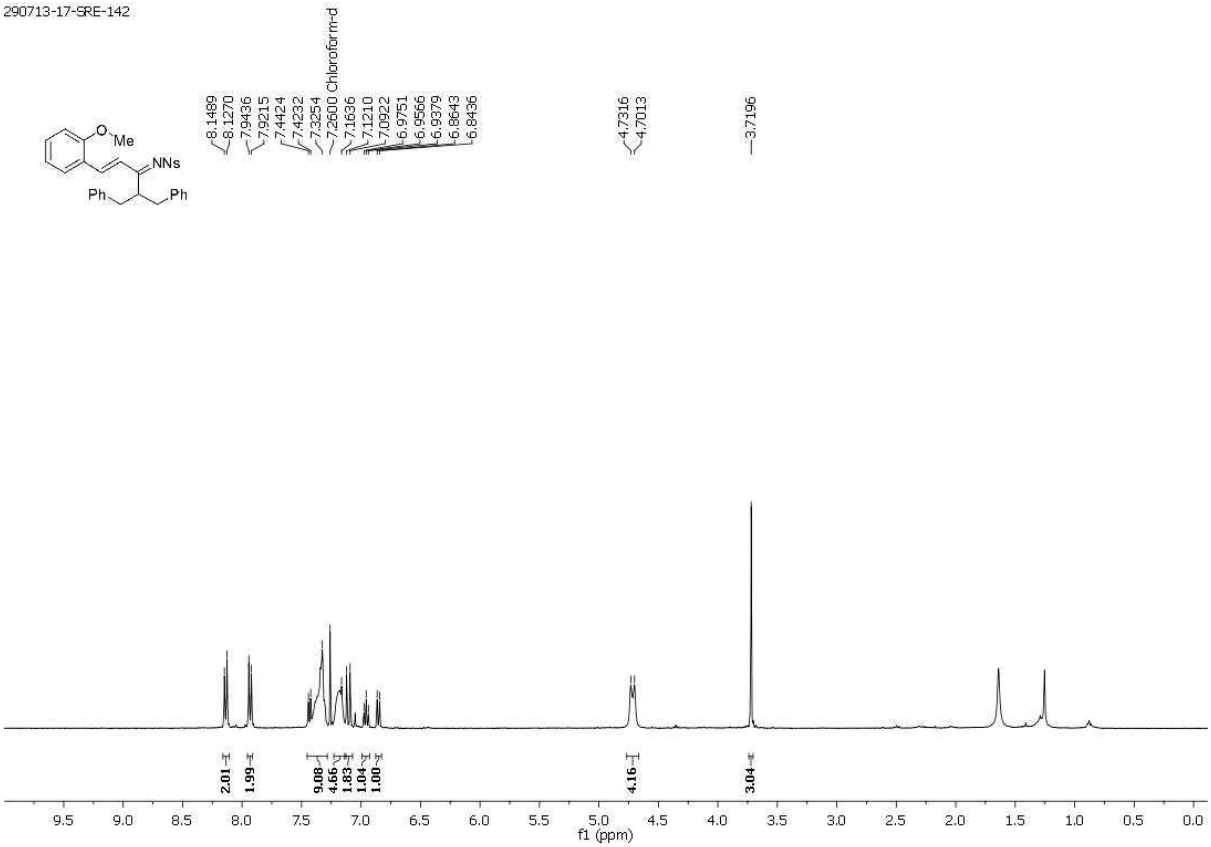

Figure: 31 ^{1}H NMR spectra of **39y** in $CDCl_3$.

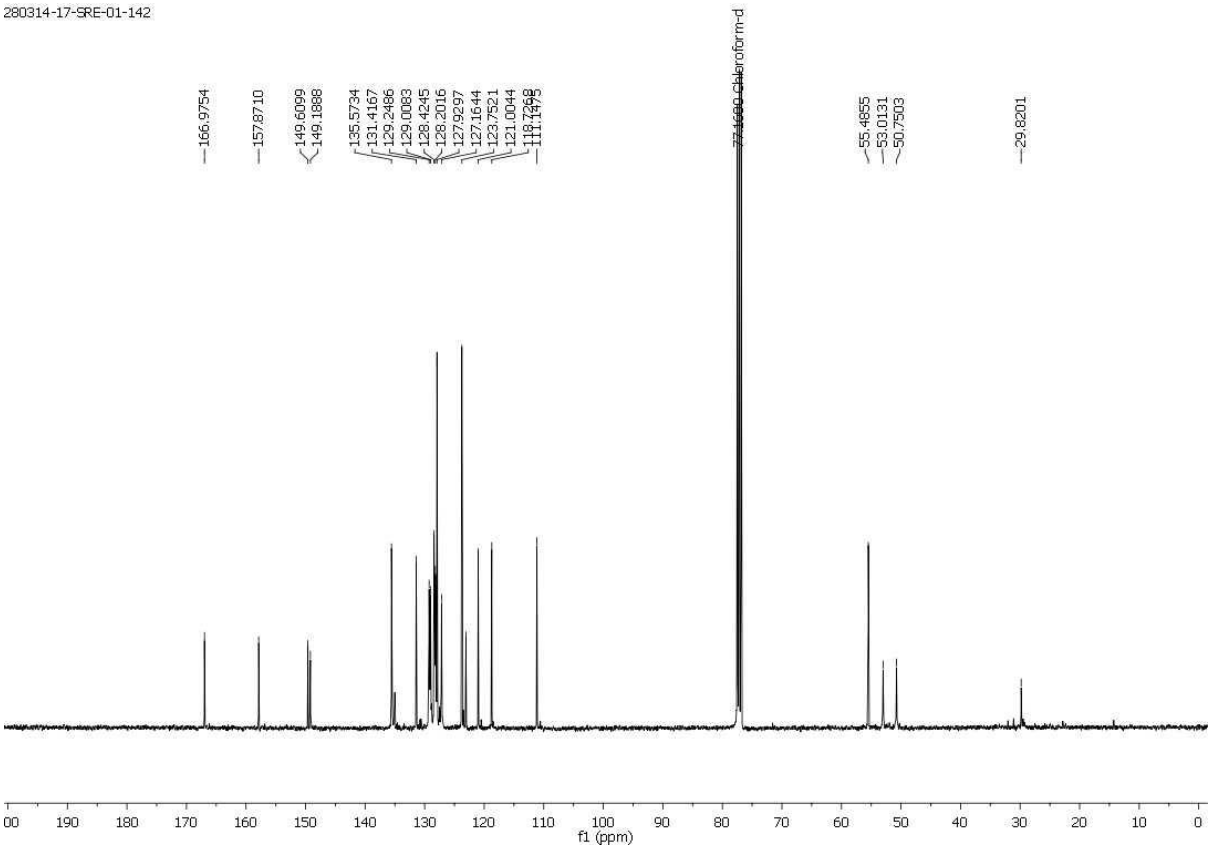

Figure: 32 ^{13}C NMR spectra of **39y** in $CDCl_3$.

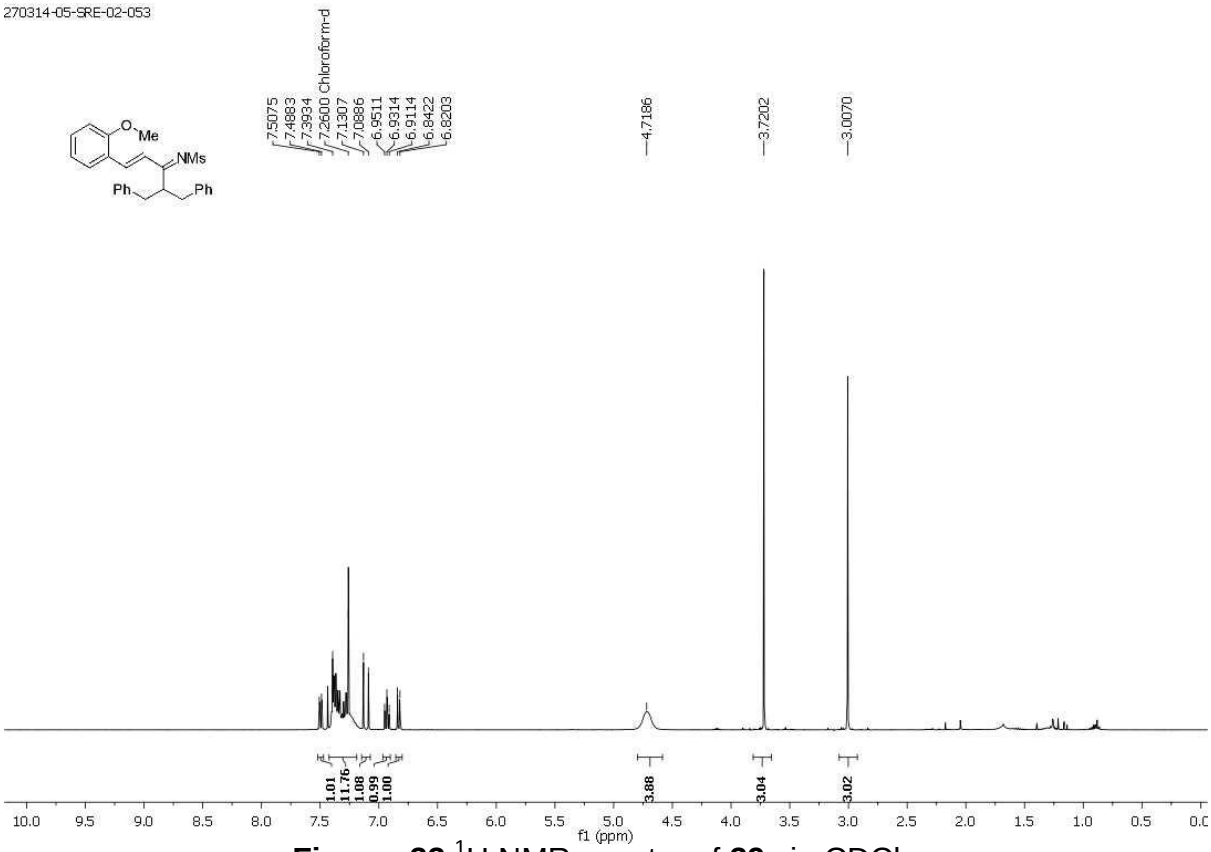

Figure: 33 ^{1}H NMR spectra of **39z** in $CDCl_3$.

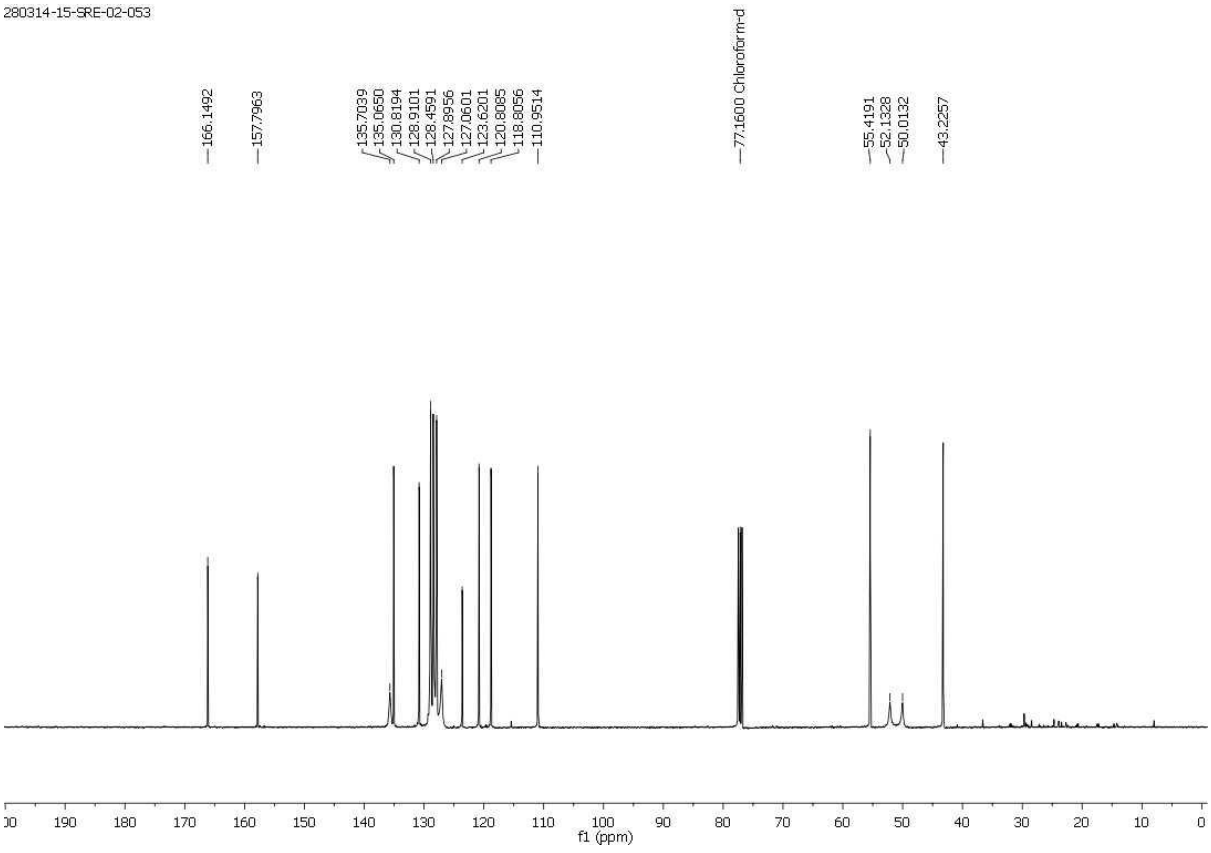

Figure: 34 ^{13}C NMR spectra of **39z** in $CDCl_3$.

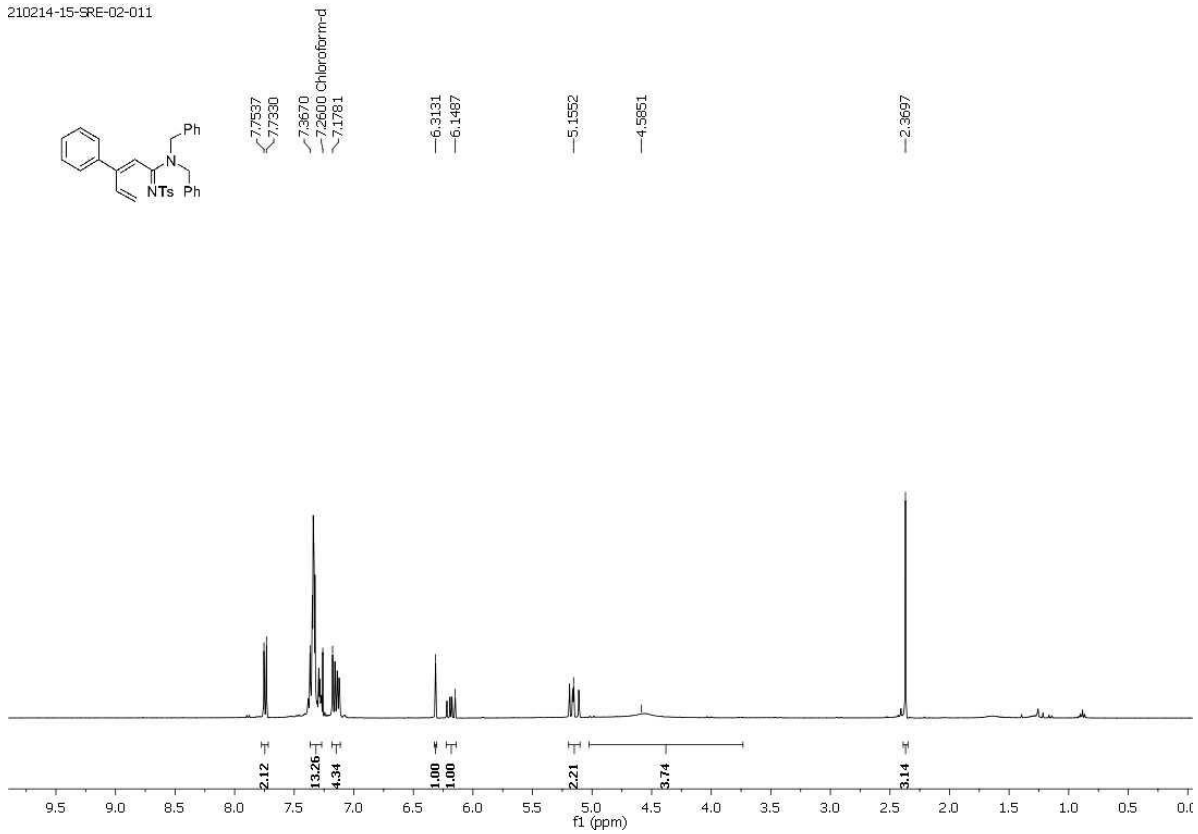

Figure: 35 ^{1}H NMR spectra of **42a** in $CDCl_3$

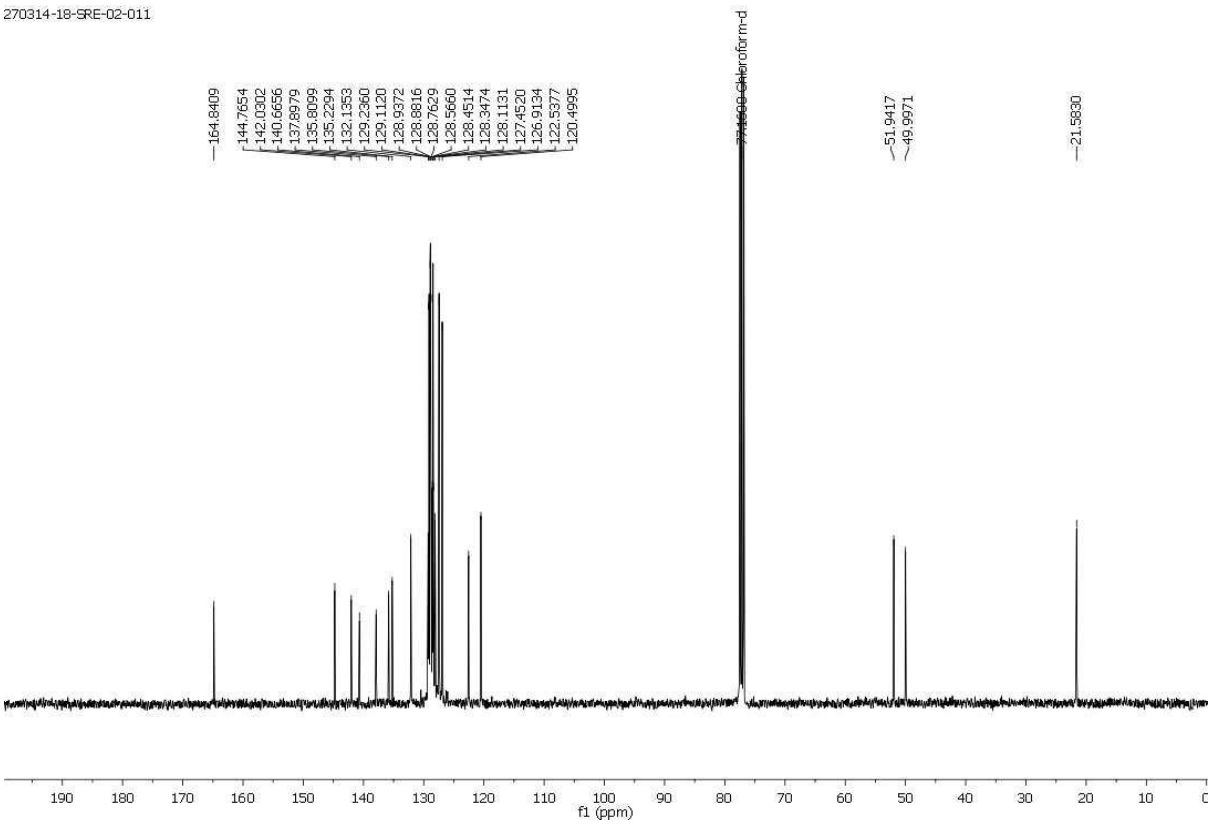

Figure: 36 ^{13}C NMR spectra of **42a** in $CDCl_3$.

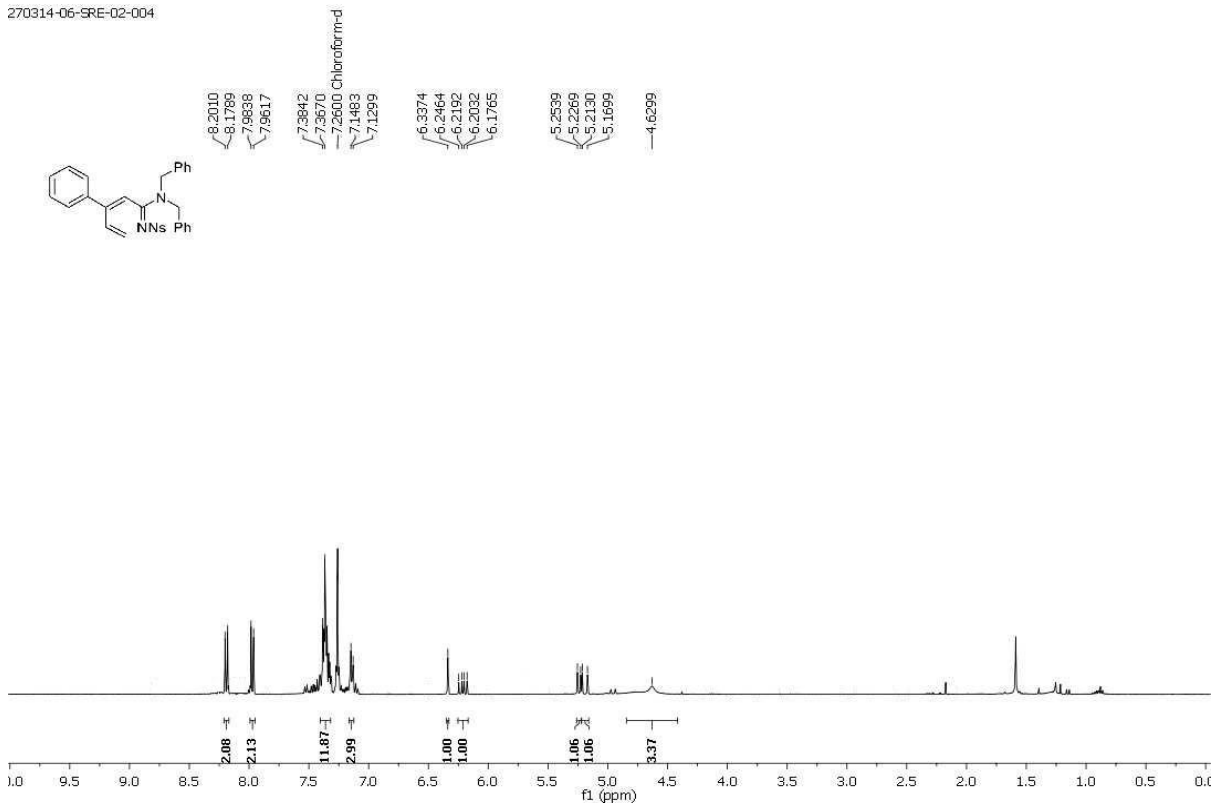

Figure: 37 ^{1}H NMR spectra of **42b** in $CDCl_3$

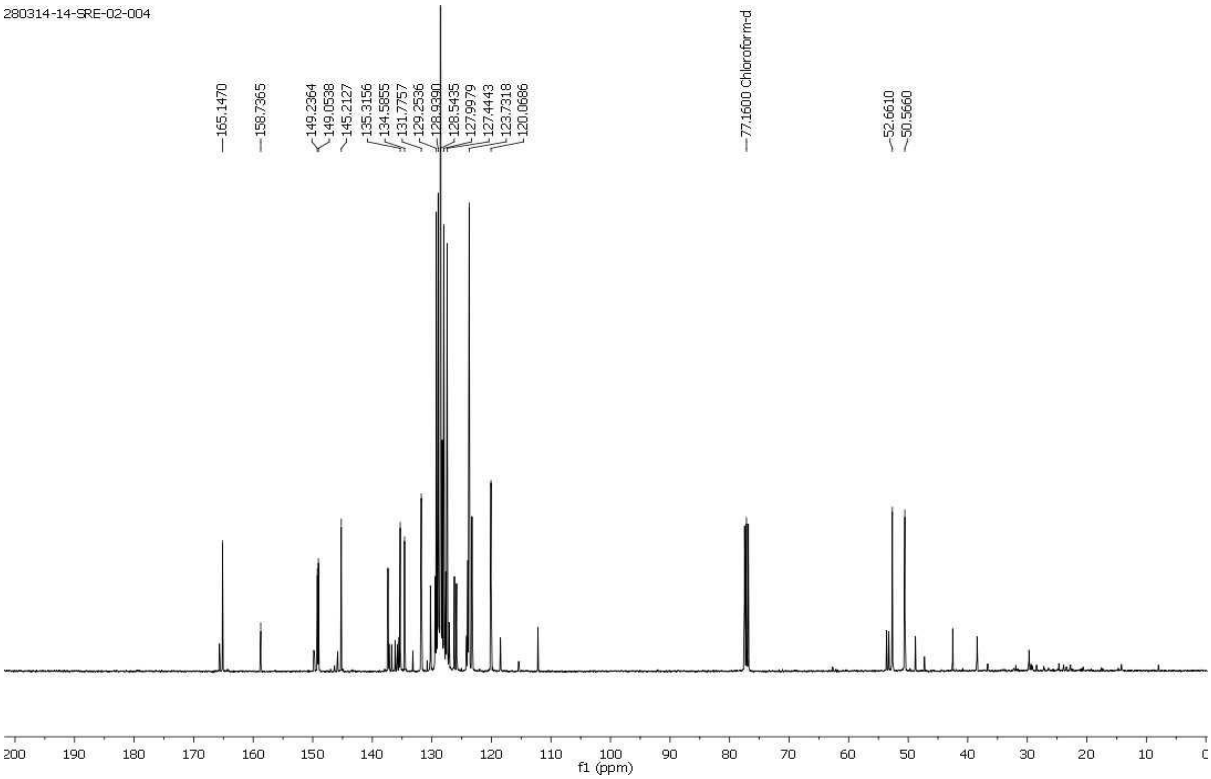

Figure: 38 ^{13}C NMR spectra of **42b** in $CDCl_3$.

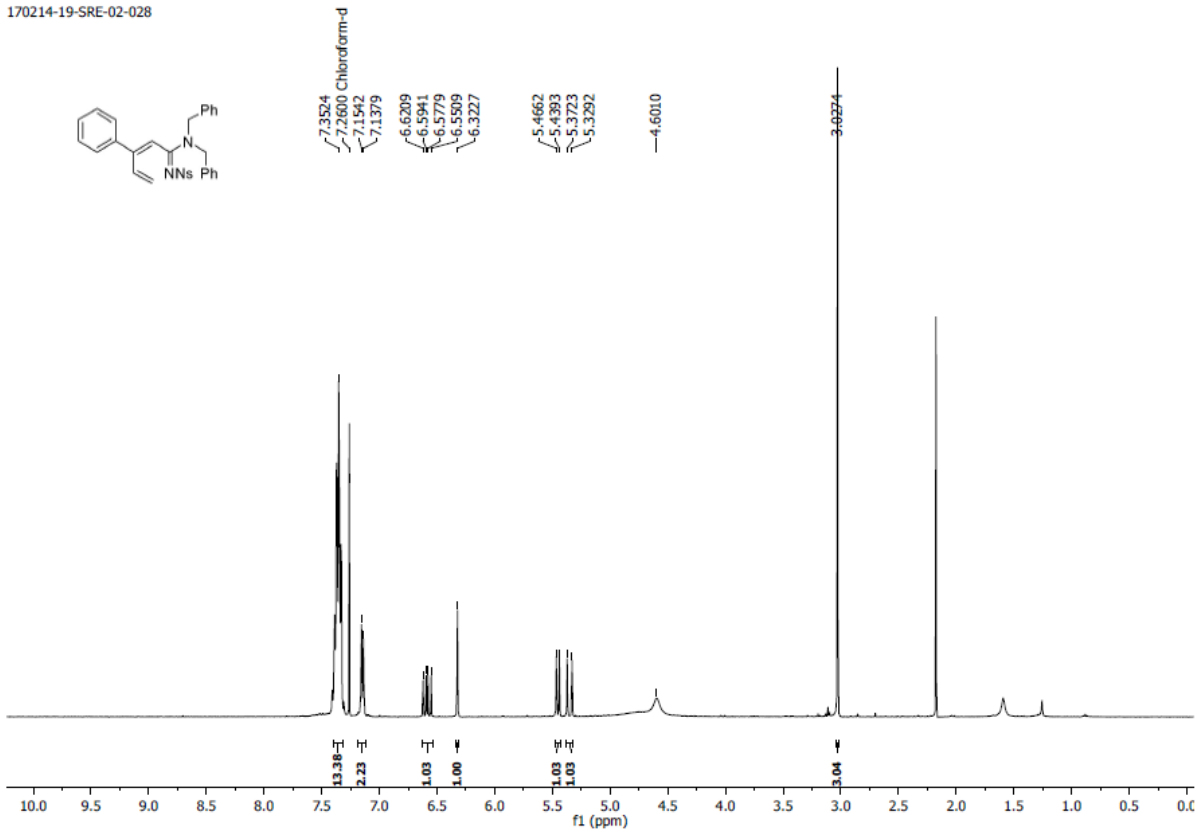

Figure: 39 ^{1}H NMR spectra of **42c** in $CDCl_3$

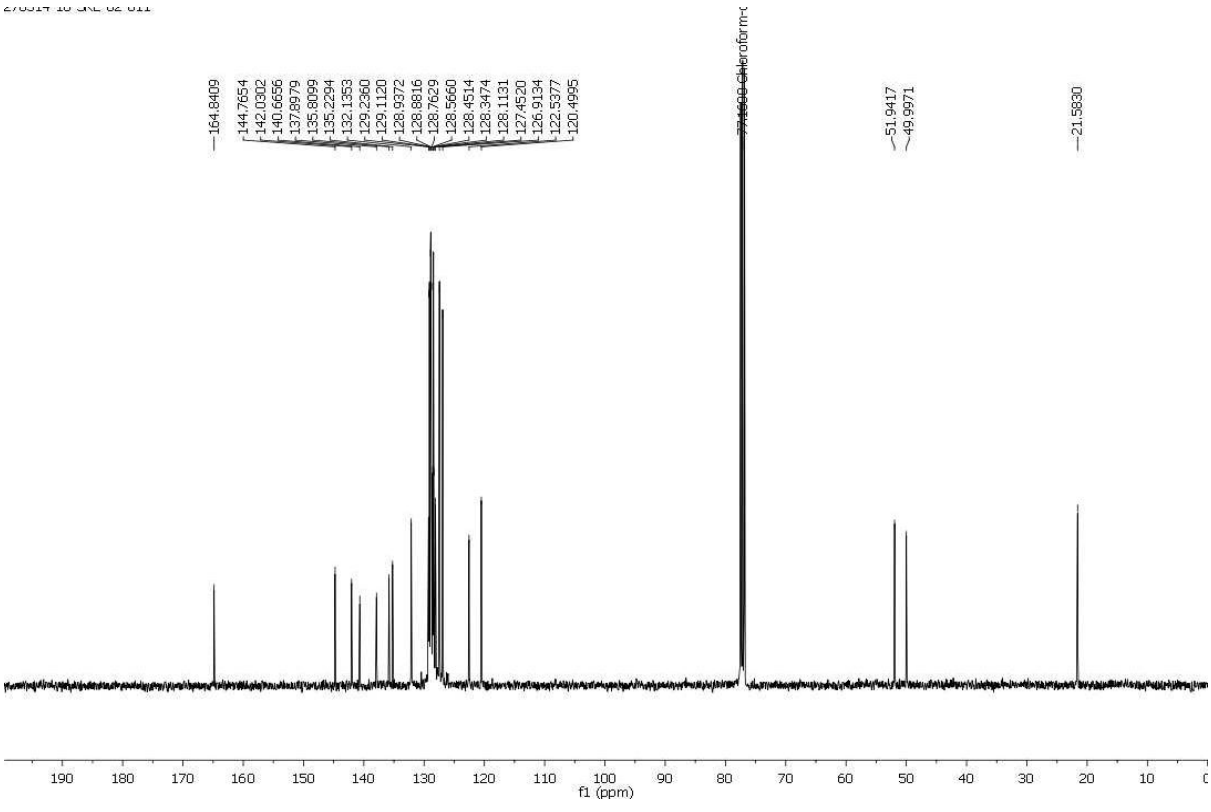

Figure: 40 ^{13}C NMR spectra of **42c** in $CDCl_3$.

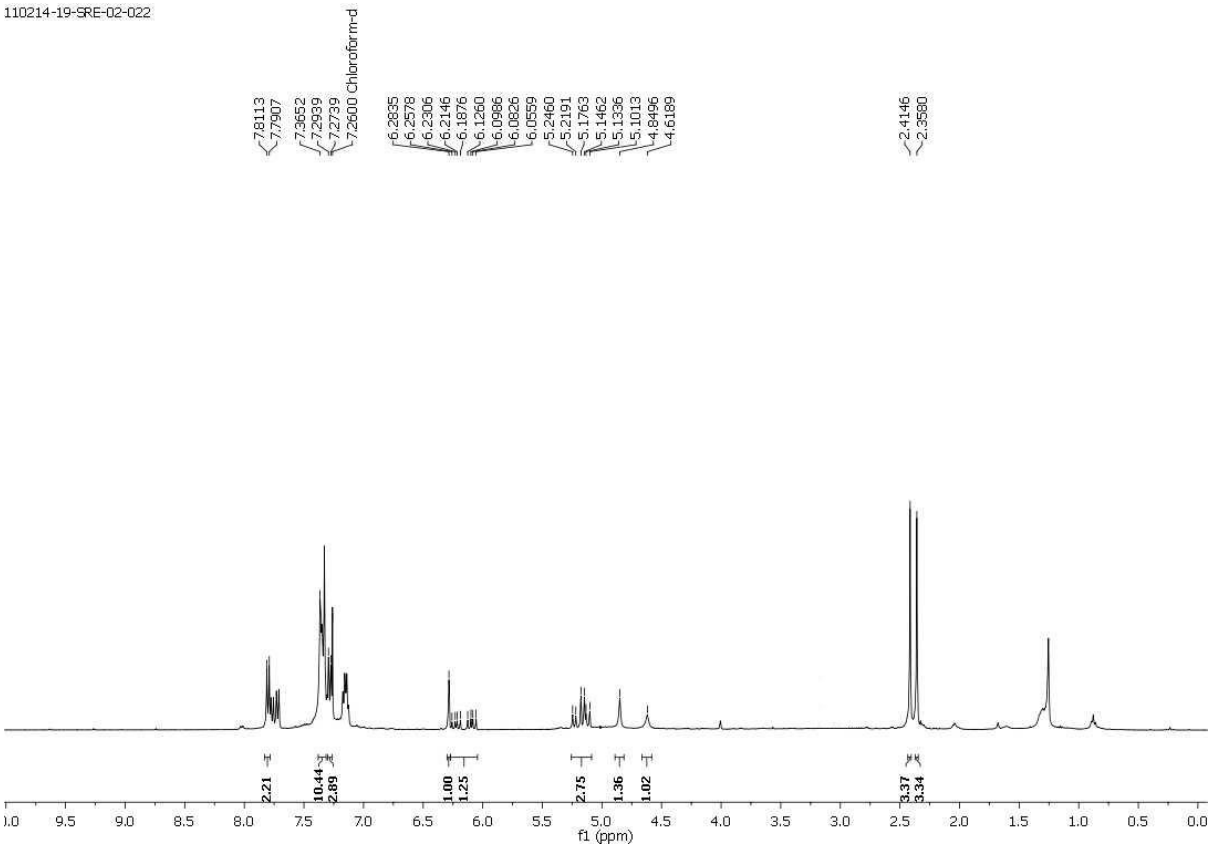

Figure: 41 ^{1}H NMR spectra of **42d** in $CDCl_3$

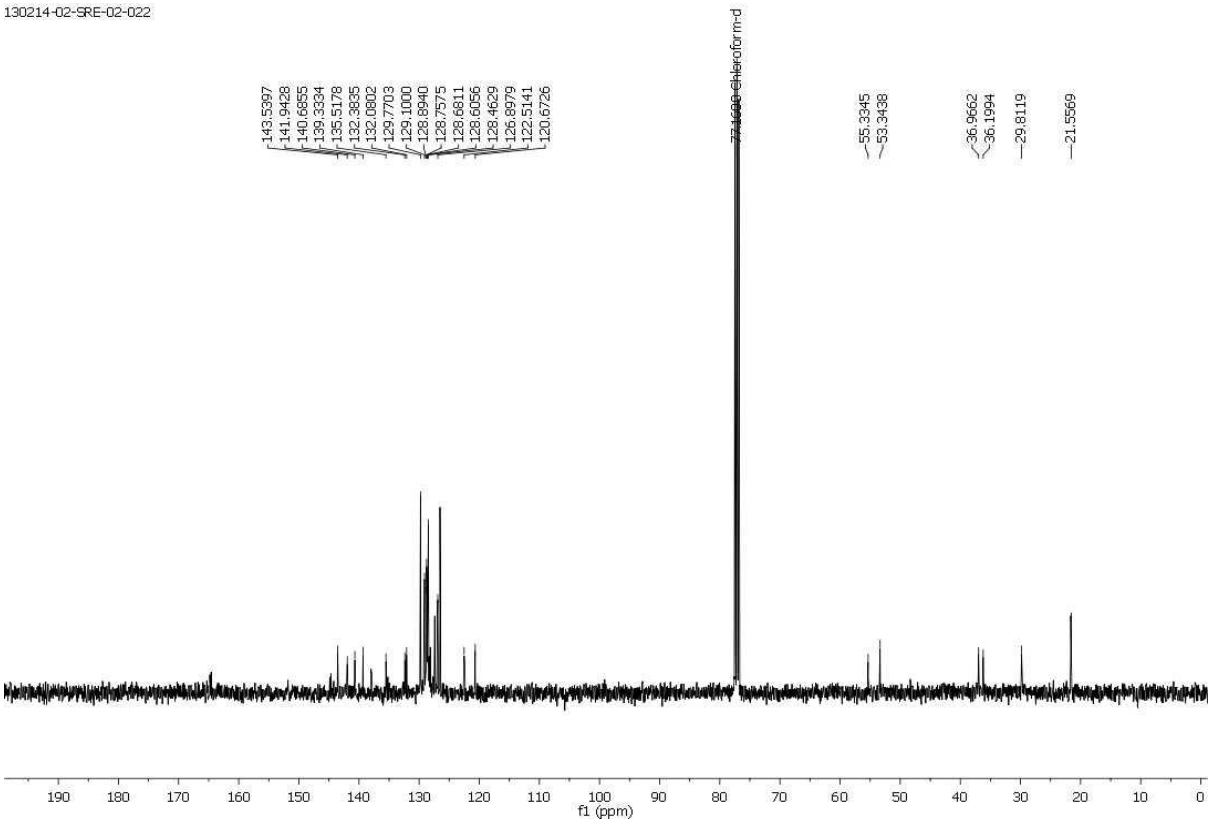

Figure: 42 ^{13}C NMR spectra of **42d** in $CDCl_3$.

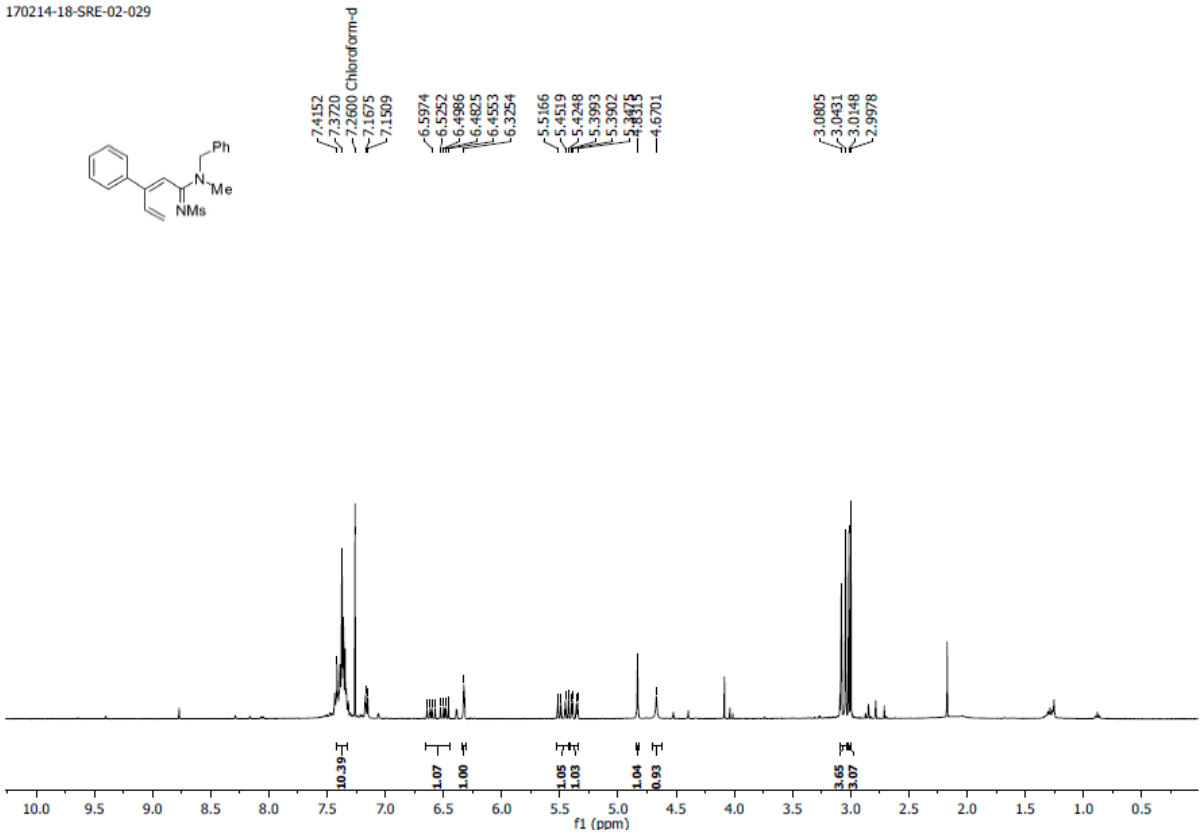

Figure: 43 ^{1}H NMR spectra of **42e** in $CDCl_3$

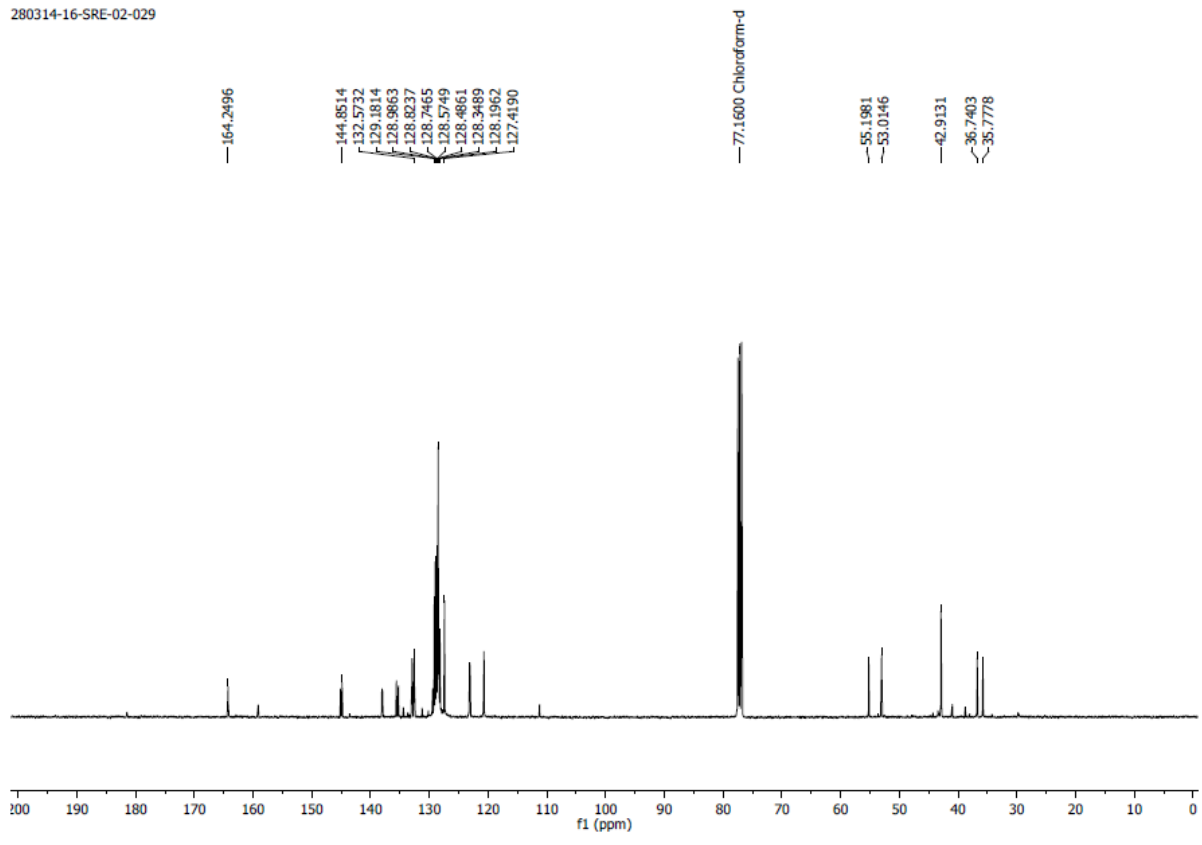

Figure: 44 ^{13}C NMR spectra of **4e** in $CDCl_3$.

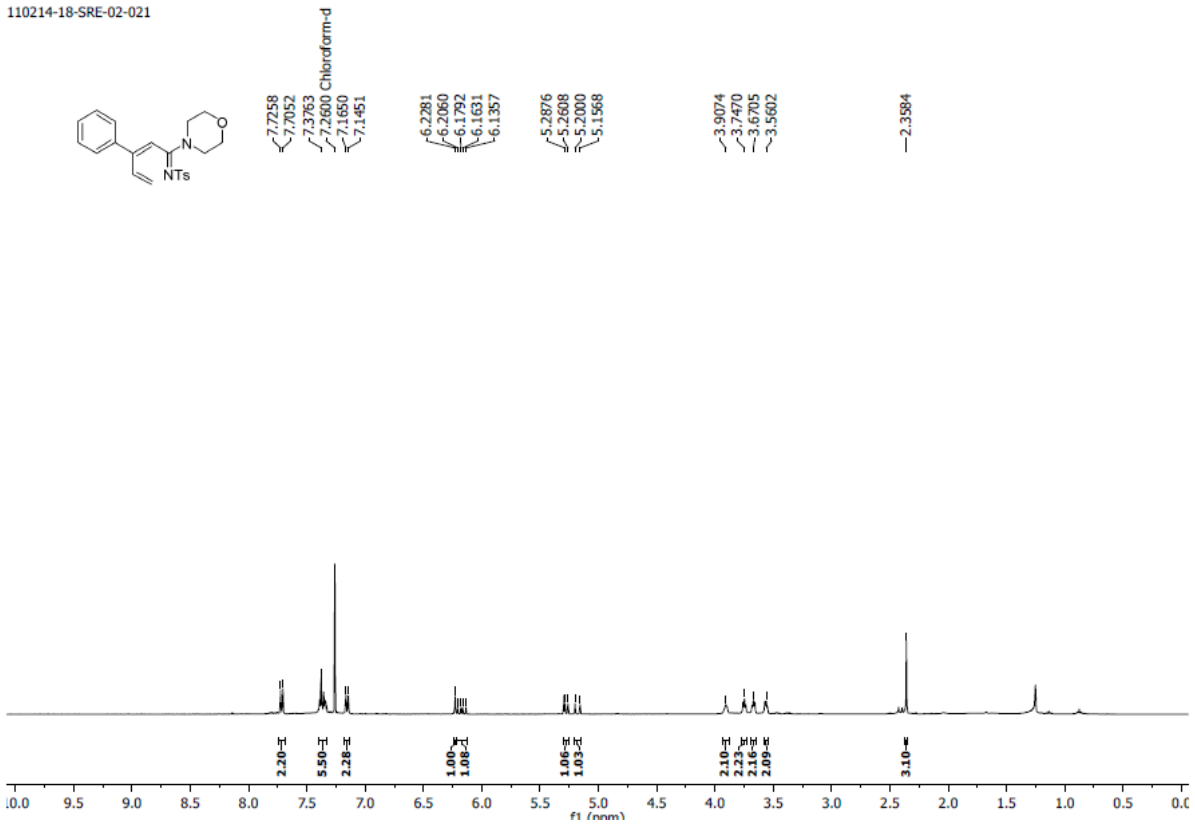

Figure: 45 ^{1}H NMR spectra of **42f** in $CDCl_3$

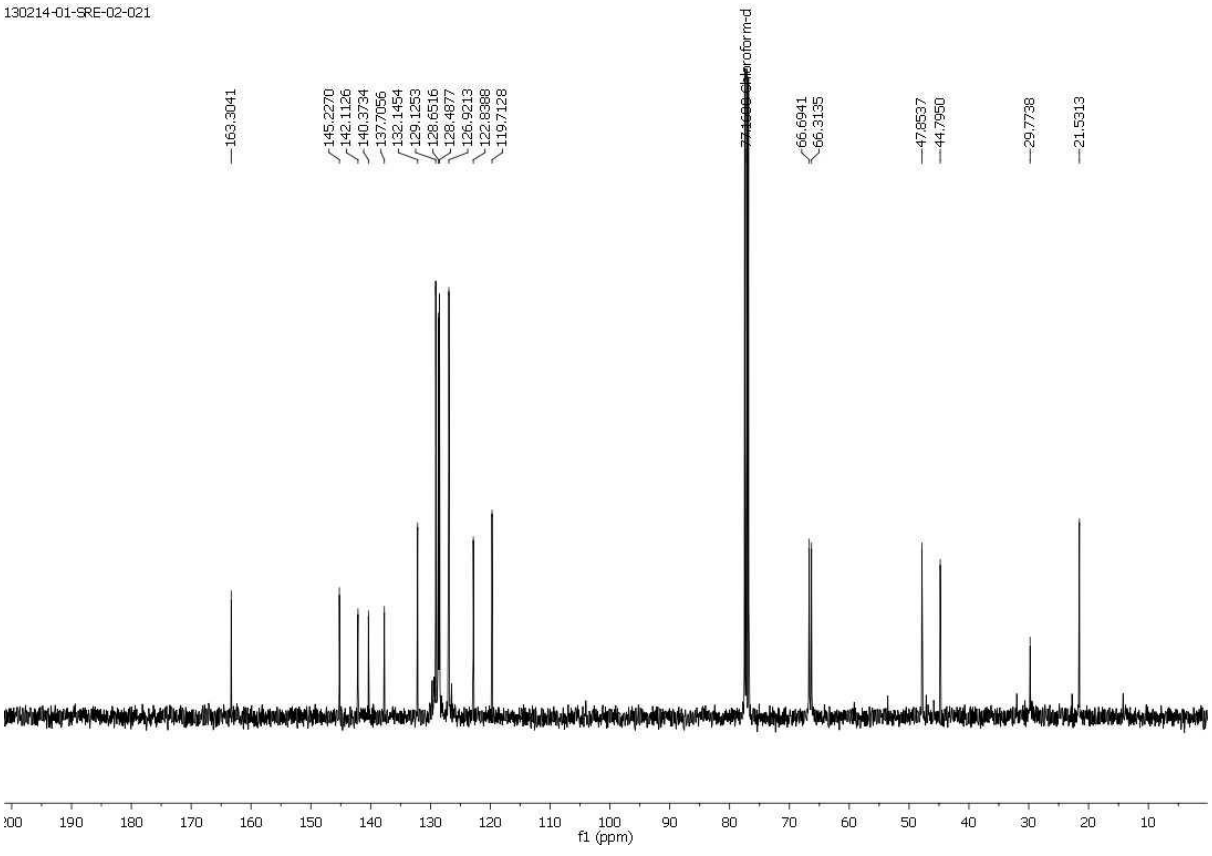

Figure: 46 ^{13}C NMR spectra of **4b´** in $CDCl_3$.

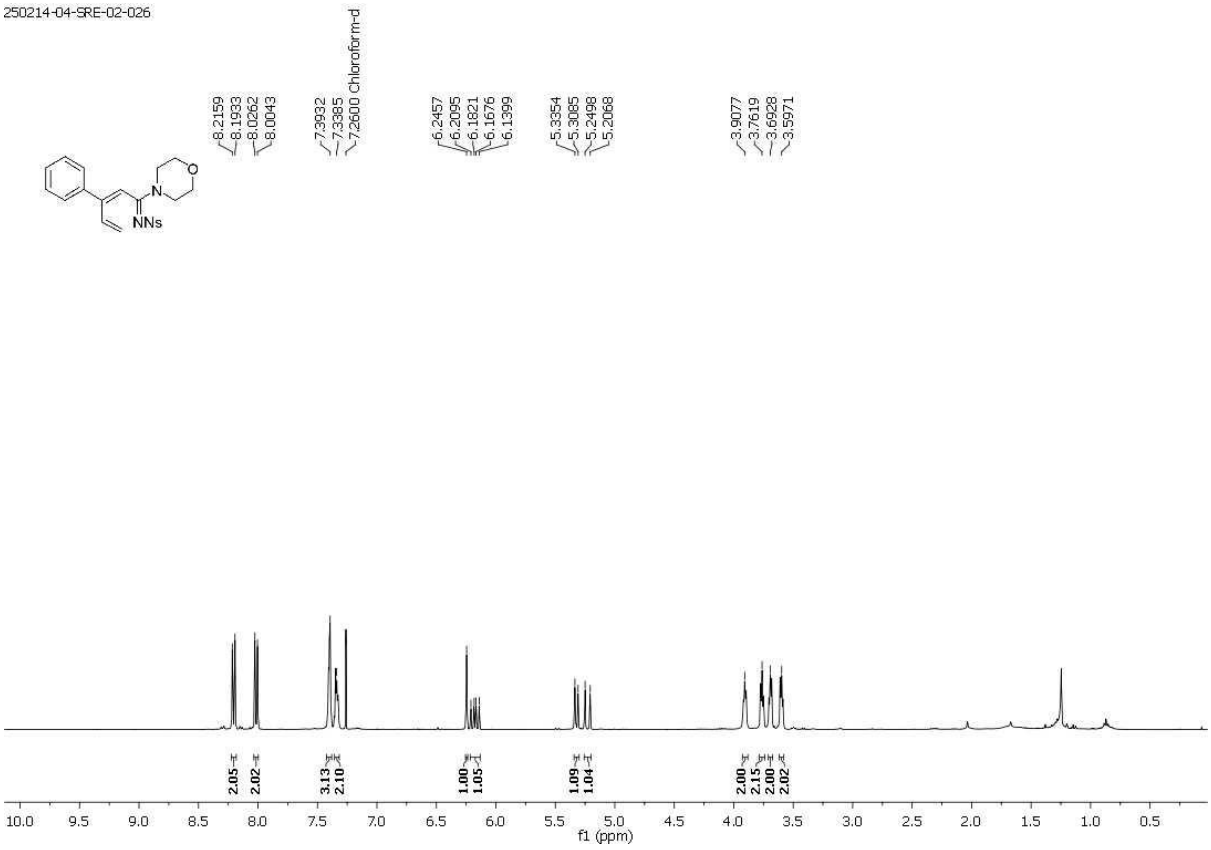

Figure: 47 ^{1}H NMR spectra of **42g** in $CDCl_3$

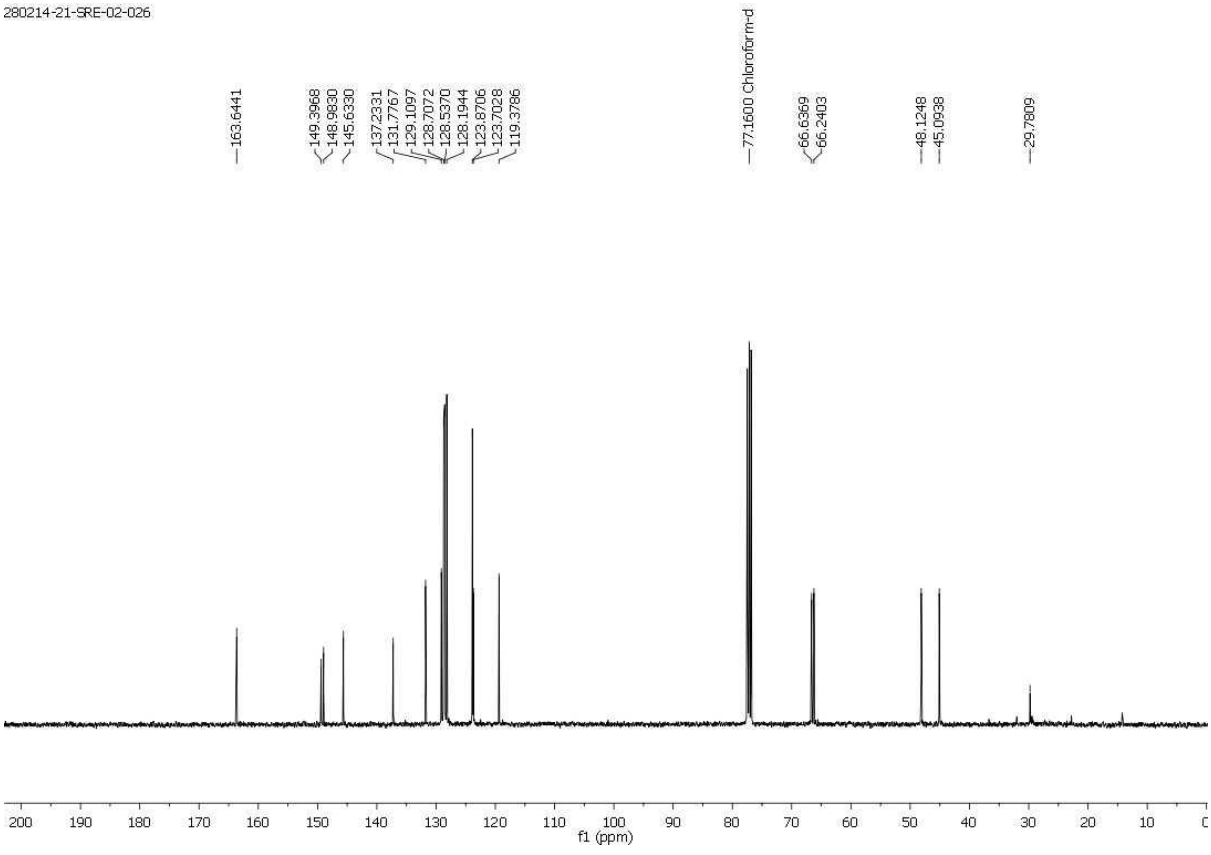

Figure: 48 ^{13}C NMR spectra of **42g** in $CDCl_3$.

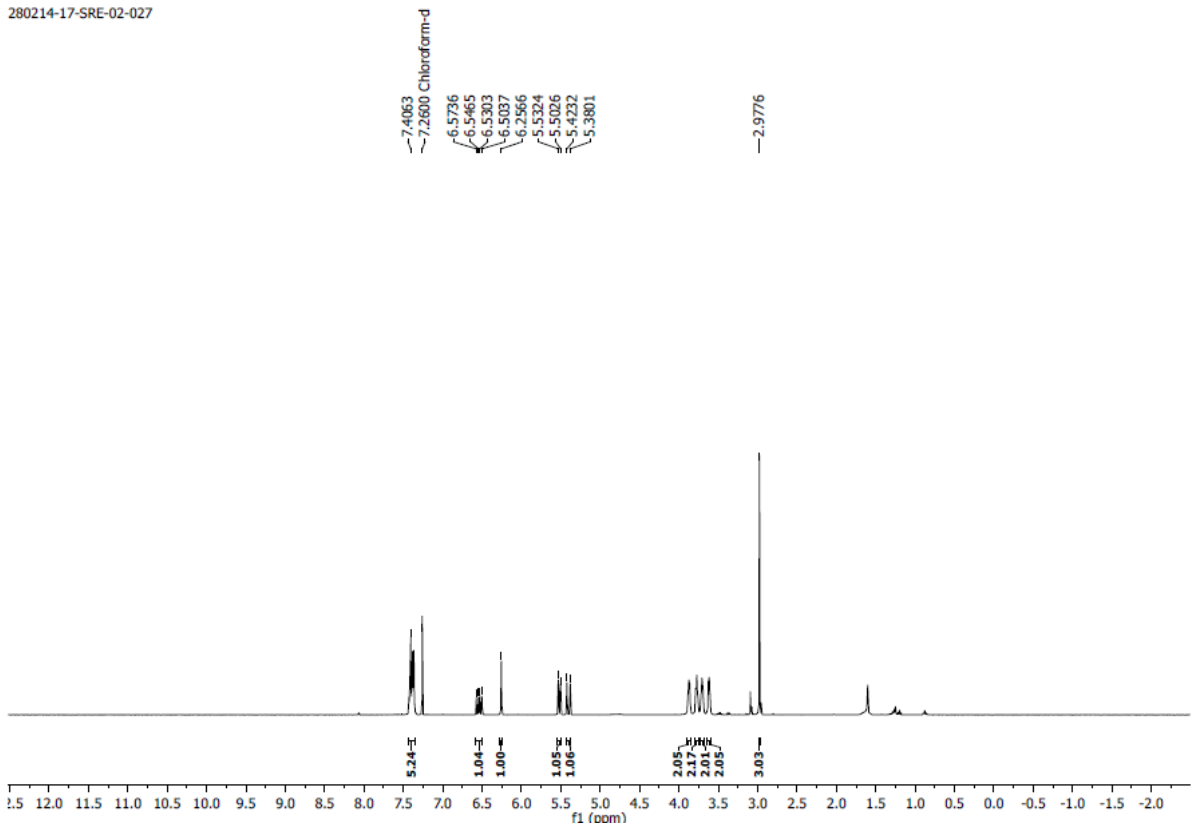

Figure: 49 ^{1}H NMR spectra of **42h** in $CDCl_3$

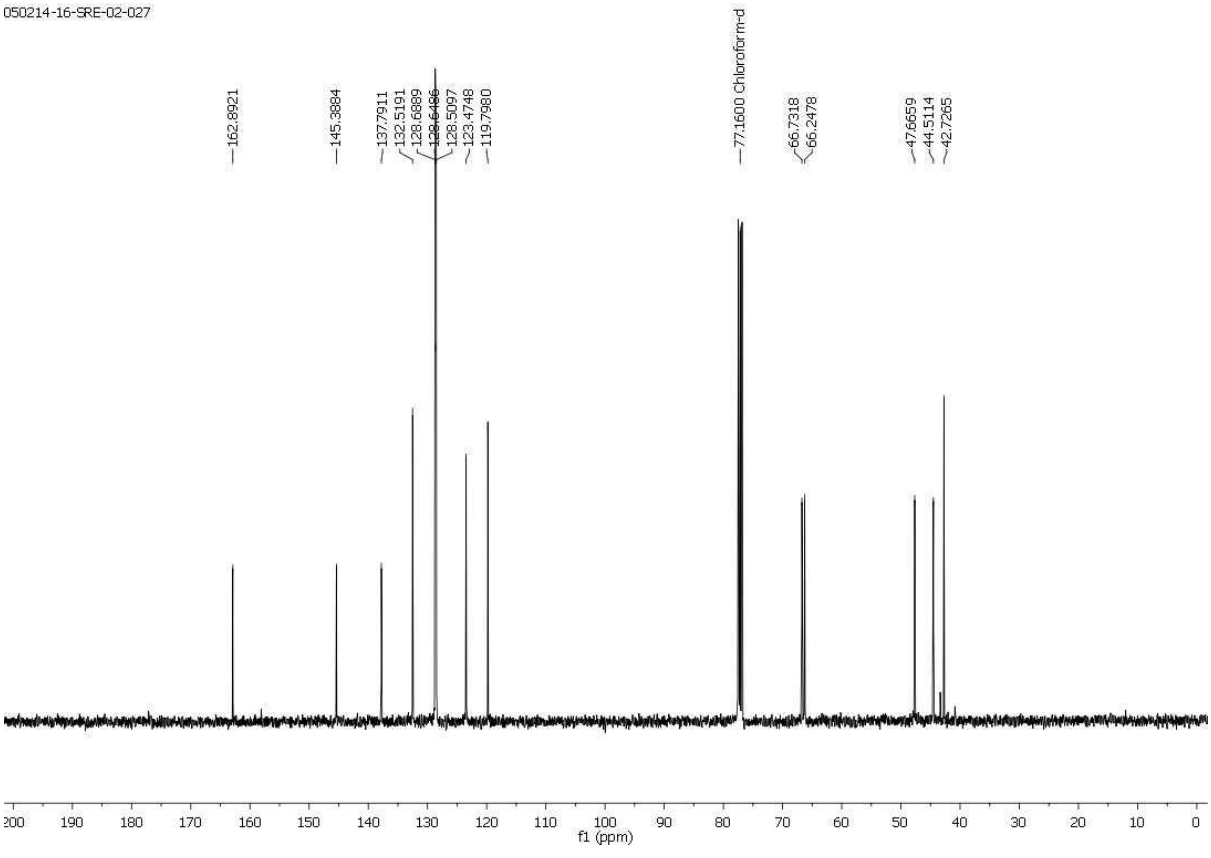

Figure: 50 ^{13}C NMR spectra of **42h** in $CDCl_3$.