Rearrangement Strategies Towards the Synthesis of δ-Unsaturated γ-Amino Acids and Functionalized Amidines

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By

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This Thesis is Dedicated to…

My Beloved Brother

Lakhan

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CERTIFICATE

Certified that the work incorporated in the thesis entitled *"**Rearrangement Strategies Towards the Synthesis of δ-Unsaturated γ-Amino Acids and Functionalized Amidines**"* submitted by **Mr. Dinesh P. Chauhan** was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

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DECLARATION

I declare that, this written submission represents my ideas in my own words and where others' ideas have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea / data / fact/ source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

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List of Symbols and Abbreviations

ee	Enantiomeric excess
Boc	*tert*-Butoxycarbonyl
HPLC	High Performance Liquid Chromatography
MALDI	Matrix Assisted Laser Desorption Ionization
DIBAL-H	Diisobutylaluminium hydride
RCM	Ring-closing metathesis
THF	Tetrahydrofuran
PPh_3	Triphenylphosphine
Et_2O	Diethyl ether
Na_2SO_4	Sodium sulphate
SAR	Structural activity relationship
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
Bn	Benzyl
PMB	*p*-methoxy benzyl
PCB	*p*-cyano benzyl
CuAAC	Copper catalyzed azide alkyne cycloaddition
TBDPS-Cl	*tert*-butyldiphenylsilyl chloride
TBAF	Tetrabutylammonium fluoride
AcOH	Acetic acid
GABA	γ-Aminobutyric acid
Cbz	Carboxybenzyl
Et_3N	Triethylamine
Ac_2O	Acetic anhydride
MsCl	Methanesulfonyl chloride
NsCl	*p*-nitro phenylsulfonyl chloride
TsN_3	tosyl azide
MsN_3	Mesyl azide
NsN_3	Nosyl azide
TFA	Trifluoroacetic acid
LAH	Lithium aluminium hydride
PTSA	p-toluenesulfonic acid

n-BuLi	n-Butyllithium
K_2CO_3	Potassium carbonate
NaOH	Sodium hydroxide
Ph	phenyl
Me	methyl
t-BuOH *tert*	Butyl alcohol
HCl	Hydrochloric acid
^{1}H NMR	Proton nuclear magnetic resonance spectroscopy
^{13}C NMR	Carbon-13 nuclear magnetic resonance spectroscopy
HR-MS	High resolution mass spectrometry
IR	Infrared spectroscopy
XRD	X-ray diffraction
ORTEP	Oak ridge thermal ellipsoid plot
TLC	Thin-layer chromatography
TMS	Tetramethylsilane
Brine	Saturated aqueous sodium chloride
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
H	Hour
Min	Minute
A	Absorbance
Mg	Milligram(s)
Mmol	Millimole(s)
µM	Micromolar
µL	Microlitre
mL	Millilitre
mol	Mole(s)
M.p.	Melting point
α	Alpha
β	Beta
γ	Gamma
δ	Delta
br	Broad singlet
m	Multiplet
s	Singlet

d	Doublet
dd	Doublet of doublet
t	Triplet
^{o}C	Degree Celsius
rt	Room temperature
δ	Chemical shift
calcd.	Calculated
cm^{-1}	Reciprocal centimetres
Hz	Hertz
MHz	Mega Hertz
J	Coupling constant
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
CH_2Cl_2	Methylene chloride
CCl_4	Carbon tetrachloride
DMF	*N*,*N* –Dimethylformamide
DMSO	Dimethyl sulfoxide
D_2O	Deuterated water
Na_2SO_4	Sodium sulphate
EtOAc	Ethyl acetate
CH_3CN	Acetonitrile

Synopsis

The thesis entitled ***"Rearrangement Strategies Towards the Synthesis of δ-Unsaturated γ-Amino Acids and Functionalized Amidines"*** includes four chapters.

The research area of my doctoral study was targeted on the development of new synthetic methodologies for the synthesis of unnatural amino acids and structurally diverse amidine derivatives using rearrangement reactions. In organic chemistry, rearrangements represent a fundamental method for the installation of molecular complexity in organic molecules and have been extensively used for the synthesis of natural product and medicinal agents. Considering the importance of these reactions, several asymmetric methods have been developed using these rearrangements. We have successfully utilized the chirality transfer approach of [3,3]-sigmatropic Overman rearrangement for enantioselective synthesis of γ-amino acids. We have also developed the rearrangements where we have achieved the [1,3] and [1,5]-migration of amino groups for the synthesis of amidine derivatives.

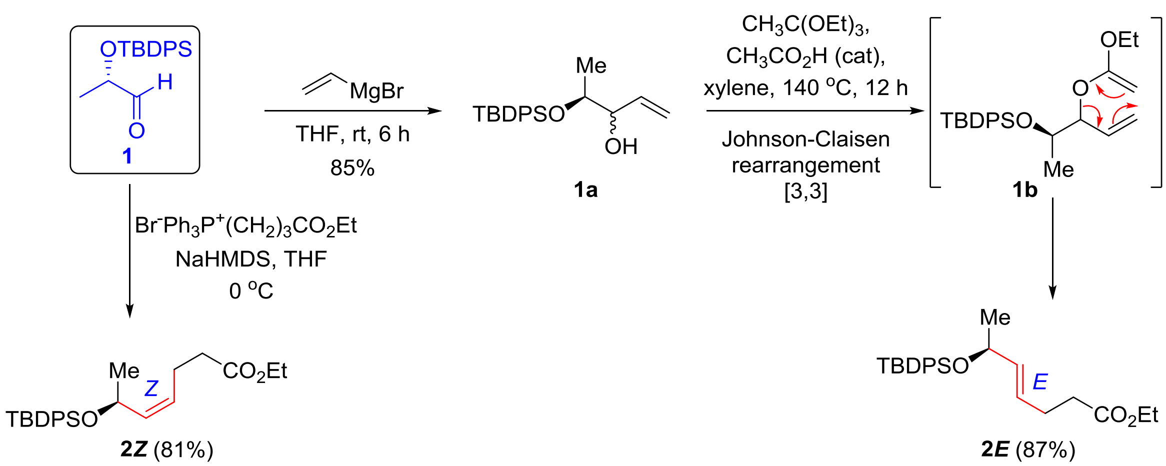
Chapter 1: Introduction to Rearrangements

This chapter represents the brief overview about the rearrangements in organic chemistry. In the beginning we defined the rearrangement in terms of its mechanistic way which occurs through several phenomenons like delocalization of the generated radical, cation or anion species over the atoms of the molecules with the mostly probable localization on the thermodynamically favored site to give a resultant intermediate which will resemble with the final product. Later, we have discussed about the five types of molecular rearrangements: 1) electron deficient skeletal rearrangement, 2) electron rich skeletal rearrangement, 3) radical rearrangement, 4) rearrangement on aromatic ring, 5) sigmatropic rearrangement. We have briefly explained the each type of reaction with their sub-type and some named rearrangements with mechanism and their reported examples. There are several rearrangements occurring through cyclization, these cyclizations are defined by some rules proposed by Baldwin, we have given a short look at these rules. These rearrangements are the basis of my entire work explained in further chapters.

Chapter 2: Enantiodivergent Synthesis of δ-Unsaturated γ-Amino Acids via Overman Rearrangement.

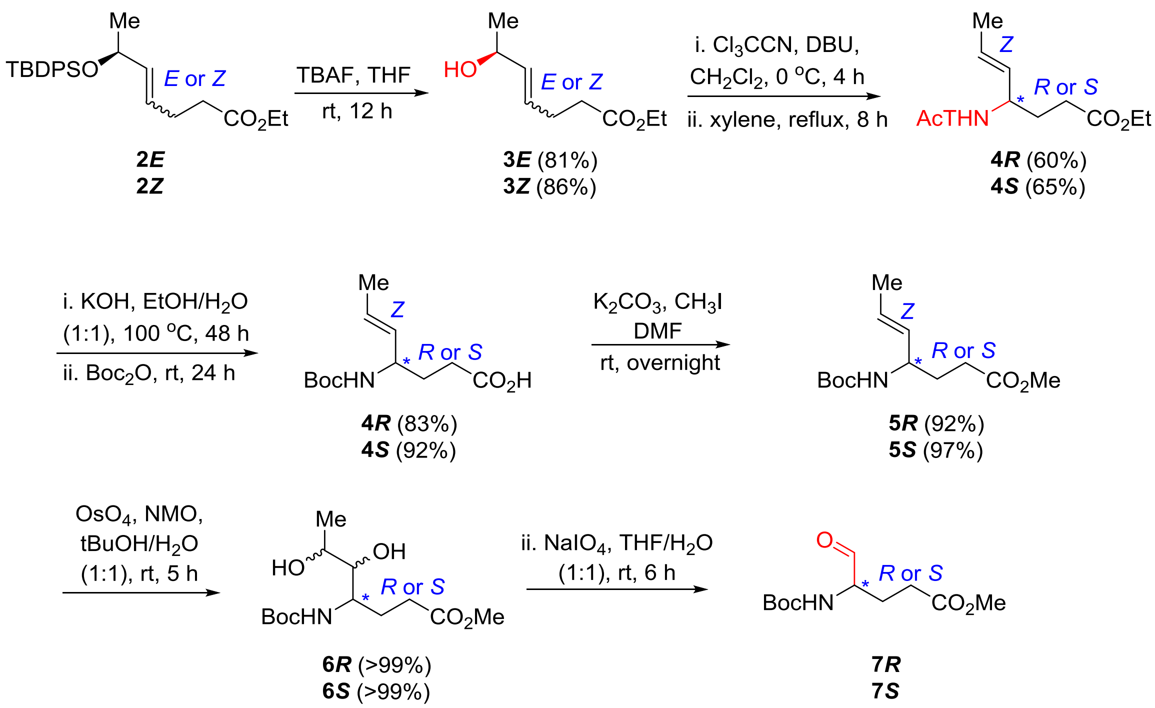
Unnatural amino acids play crucial role in the design and synthesis of pharmacologically important molecules. In this regard, the access of enantiomerically pure amino acid derivatives offers a challenge in stereocontrolled synthesis. γ-amino acids have attracted the attention as a biologically important compound in the CNS of mammals. For example, γ-amino butyric acid (GABA) is the major inhibitory neurotransmitter in mammals. Other derivatives of γ-amino acids are biologically potent and are available in the market as drug. In past few years, the stereoselective synthesis and their practical applications have been reported.

In this chapter, we have demonstrated the enantioselective synthesis of γ-amino acids by two different routes using the single starting material. Our methodology was based on the chirality transfer approach of Overman rearrangement where *E*-allyl trichloro acetamidate was rearranged into allyl amine with retention of configuration and *Z*-allyl trichloro acetamidate was converted into allyl amine with inversion of configuration so in this way, the stereocentres are forming at N-centre. The next aim was to incorporate the carboxyl group at γ-position to N-centre. Therefore we targeted to synthesize the *E* and *Z*-allyl alcohols from the single starting material in such a way that the carboxylic group could be incorporated in the beginning. Our synthesis started from the protected lactaldehyde **1** on which we have carried out a Wittig reaction to obtain *Z*-allyl alcohol **2*Z*** with 81% yield and the *E*-allyl alcohol **2*E*** was synthesized by treating **1** with vinyl magnesium bromide followed by Johnson Claisen rearrangement with 87% yield.



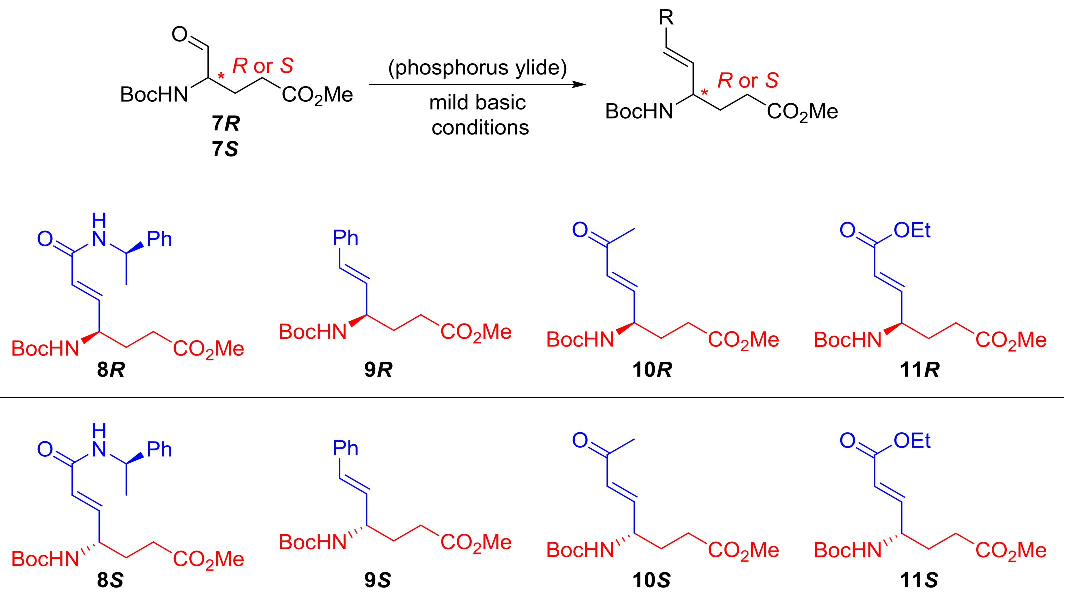
Scheme 1: Synthesis of *Z* and *E*-allylic alcohols.

Later, the silyl protection of **2*Z*** and **2*E*** was removed using TBAF and the hydroxyl groups were protected with trichloro acetonitrile independently to obtain trichloro acetamidate which were subjected further for Overman rearrangement without any purification to obtain trichloro acetamides **4*R*** and **4*S*** as a pair of enantiomers with 60 and 65% yields respectively. The trichloroacetamide groups were deprotected and protected with Boc group to mentain the orthogonality in molecule, the free carboxyl groups were esterified with methyl to obtain the pair of enantiomers **5*R*** and **5*S***. The double bond was converted to diol with OsO_4 and subsequently cleaved to achieve the enantiomeric pair of aldehydes **7*R*** and **7*S*** (Scheme 2).



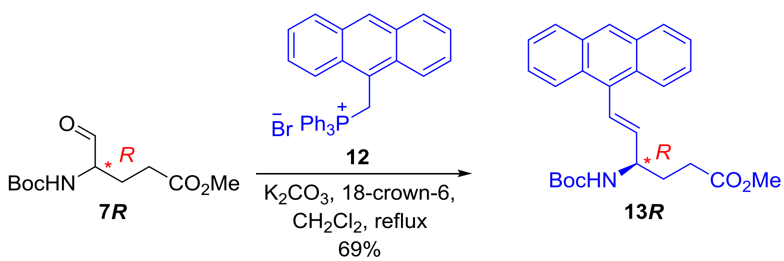
Scheme 2: Chirality transfer approach for the synthesis of γ-amino acids enantiomers with aldehyde as side chain.

Later, the library of δ-unsaturated γ-amino acids were generated by treating these pair of aldehydes with four different stable Wittig ylides independently to achieve *E*-δ,ε-unsaturated γ-amino acids. The HPLC data was carried out for δ-unsaturated γ-amino acids **8*R*** and **8*S***, it was found that compound **8*R*** showed 94% of distereomeric excess and compound **8*S*** was showing > 99% distereomeric excess. It was concluded that no recimization was occurring while Overman rearrangement and Wittig rearrangement.



Scheme 3: Wittig reactions on enantiomeric aldehydes **14-*R*** and **14-*S*** using different ylides.

The aldehyde **7*R*** was treated with fluorescent Wittig Ylide **12** to obtain the fluorescent amino acid considering the importance of fluorescent amino acids which are useful in the studies of intracellular processes.



Scheme 4: Synthesis of fluorescent amino acid.

The obtained fluorescent amino acid was incubated into live cells to check its cell permeability and cell imaging was carried out.

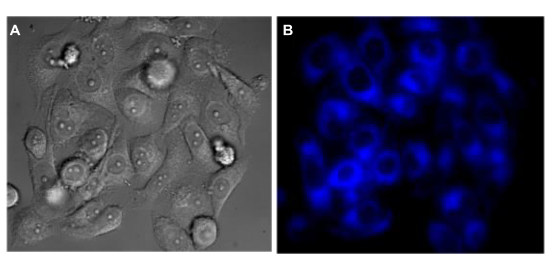
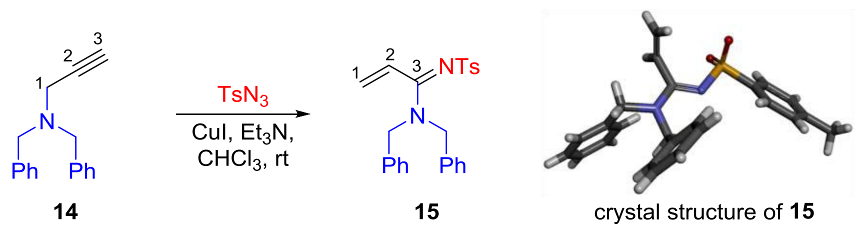


Figure 1: DIC (A) and fluorescence (B) images of HeLa cells.

Chapter 3: Synthesis of Acrylamidines by 1,3-Amino Group Migration via Ketenimine Intermediates Derived from Propargyl Amines.

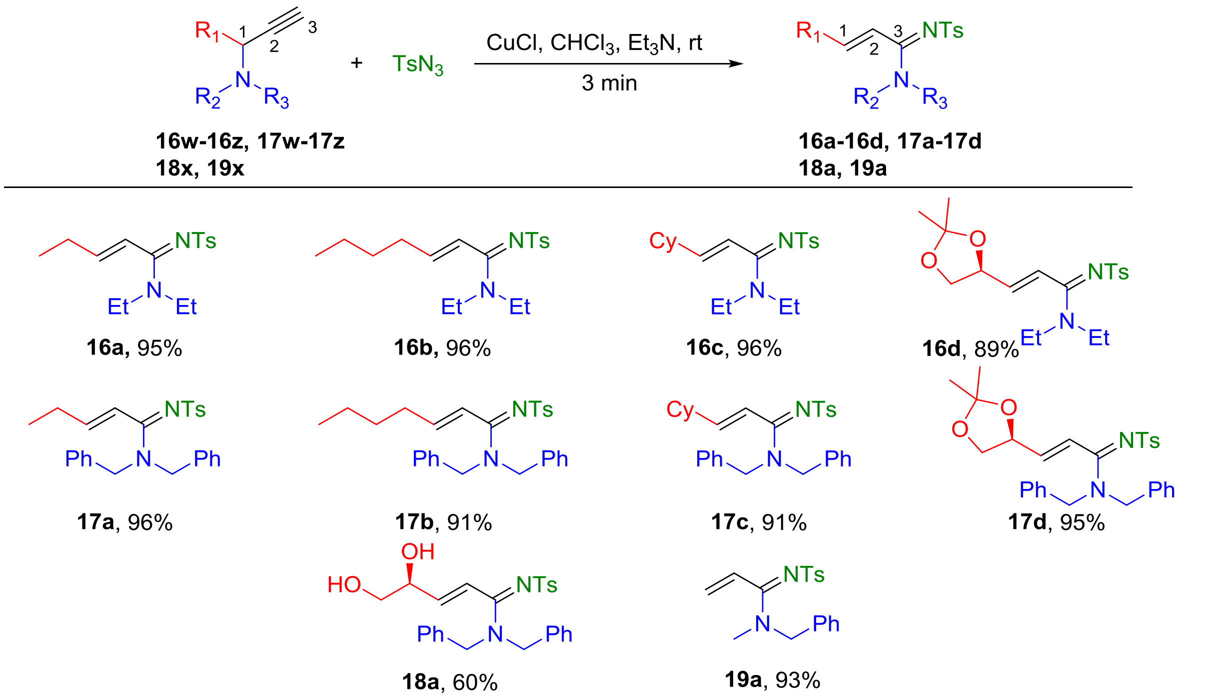
Amidine derivatives have wide ranges of applications in organic chemistry. They serve as strong organic bases e.g. DBU and DBN are used in dehydro halogenations reactions. Amidine entity is found in variety of drugs, agrochemicals and natural products as a structural unit. Several methods have been reported for their synthesis. We have achieved the synthesis of acrylamidines by a novel rearrangement of propargyl amines via ketenimne intermediate.

Ketenimines are known to undergo addition reactions by external nucleophiles but we envisioned to capture the ketenimine by internal nucleophile therefore we carried the copper catalyzed reaction on propargylamine **14** and obtained the acrylamidine **15** by 1,3-amino group migration with 96% yield under optimized condition.



Scheme 5: Cu(I) catalyzed formation of acrylamidines **15** from propargylamine **14** and its crystal structure.

To check the viability of this reaction, we varied the amino groups and varied the substitution at C_2. At first we prepared the substrates **16v**, **16x**, **16y,** and **16z** by taking diethylamino group and varied the substituent as ethyl, n-butyl, cyclohexyl and dioxolane groups at C_2 and carried out the Cu-catalyzed reaction to afford the acrylamidines **16a, 16b, 16c,** and **16d** with 95, 96, 96, and 89% yields respectively. Substrates **17v-17z** gave acrylamidines **17a-17d** with 96, 91, 91, and 95% yield respectively. The substrate **18x** having two free hydroxyl groups also gave product **18a** with 60% yield and the substrate **19x** having unsymmetrical amino group gave the product **19a** with 93% yield (Scheme 6).



Scheme 6: Scope of the [1,3]-amino migartion strategy with aliphatic substituent at C_1-position.

Next, we explored the effect of cyclic amino groups such as pyrrolidine, piperidine and morpholine in the formation of acrylamidines. In this case, the reactions were found to be slower and the yields were dropped down. The substrates **20, 21,** and **22** containing pipyridine and C_2-substituent as n-butyl, cyclohexyl, and hydrogen gave products **20a, 21a,** and **22b** with 51, 63, and 48% of yields respectively. In case of pyrrolidine, the substrates **23,** and **24** gave **23a,** and **24a** with 58, 70% yields respectively. Unexpectedly, in case of morpholine substrates **25, 26,** and **27** afforded **25a, 26a,** and **27a** with 95, 93, and 83% yields respectively.

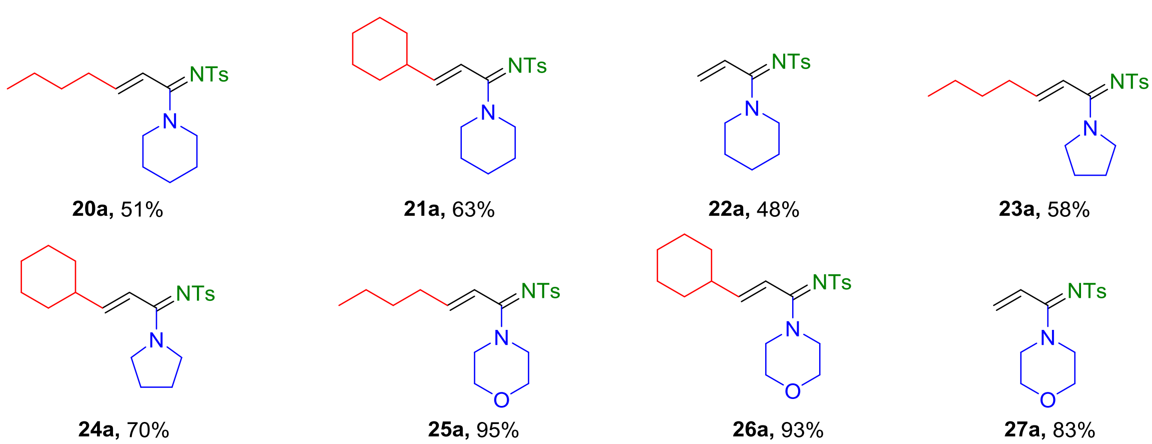


Figure 2: Scope of the aza-[1,3]-amino group migration strategy with cyclic amino groups.

Further, we have varied the C_2 substituents by aromatic groups from electron rich to electron deficient systems. The electron rich substrates **28, 29, 30,** and **31** gave the resultant products **28a, 29a, 30a,** and **31a** with 93, 89, 96, and 95% yields respectively. Similarly, the electron withdrawing substituent on substrates **32, 33, 34,** and **35** afforded the acrylamidines **32a, 33a, 34a,** and **35a** with 80, 75, 71, and 96% of yields respectively. Finally, the substrates with phenyl, naphthaline and Pyrene substituents **36-38** gave products **36a-38a** with 96, 96, and 98% of yields respectively (Figure 3).

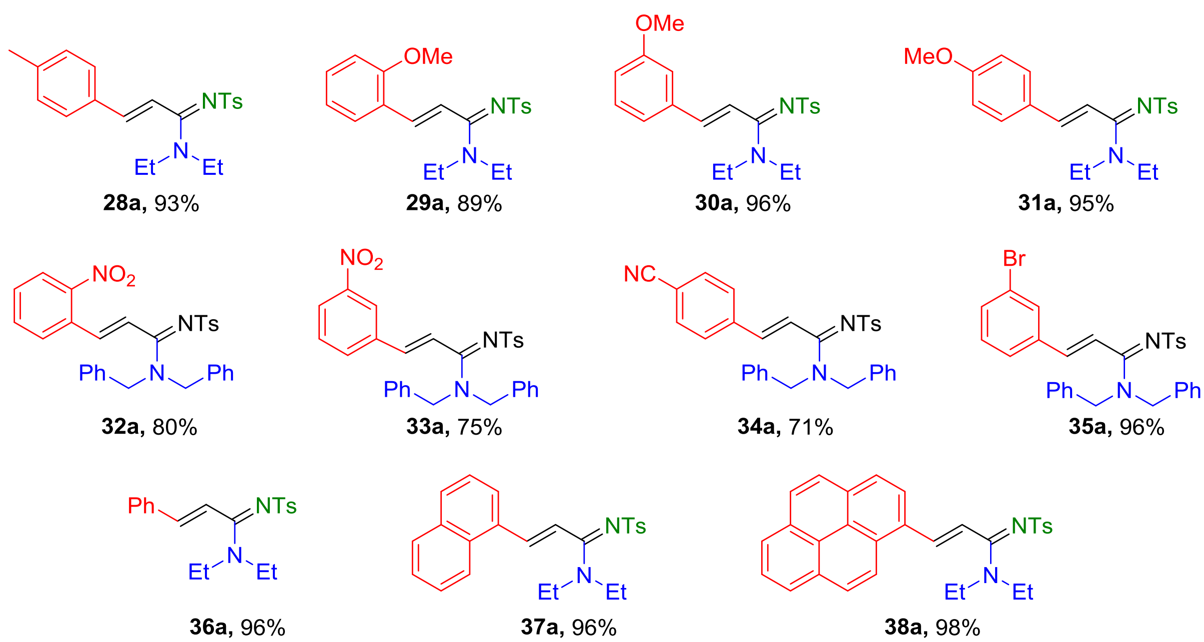
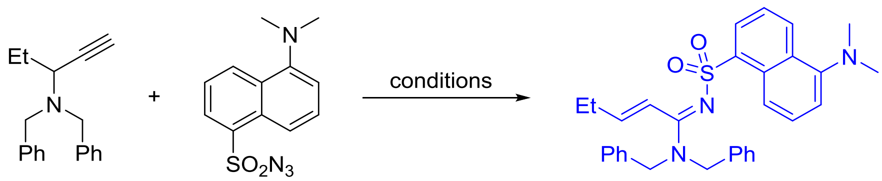


Figure 3: Scope of the 1,3-amino group migration strategy with aromatic substituent at C_1-position.

To explore the application of this methodology, we have developed a fluorescent probe in which we have treated the non-fluorescent dansyl azide **39** with propargyl amine **17w** and carried out the Cu-catalyzed reaction, the obtained product **40** was fluorescent. The same reaction we have carried out under physiological conditions, it worked well therefore this concept can be applied to tag any bio-molecule by incorporating the propargyl amine in it.

Table 1: Synthesis of fluorescent compound using Cu-catalyzed reaction.



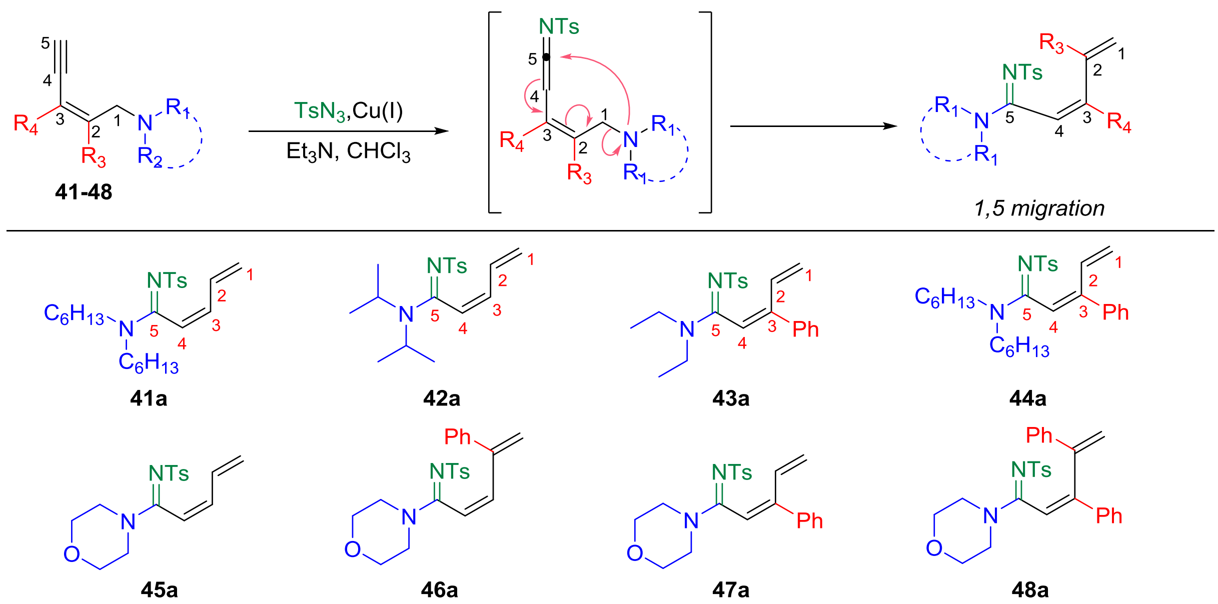
17w **39** **40**

Entry	Cat.	Solvent	Base	Time (min)	yield
1	CuCl	$CHCl_3$	Et_3N	15	95
2	$[Cu(CH_3CN)_4]PF_6$	HEPES	-	30	60

Chapter 4: Synthesis of Conjugated Unsaturated Acrylamidines, Cyclic Amidines, and Dihydro Pyridines by Cascade Rearrangements of Enyne-Amine Derived Ketenimines.

Encouraged by the success of 1,3-amino group migration methodology, we decided to achieve carry out the 1,5-migration of amino group using the same strategy. We have designed four kinds of enyne-amine substrates where we varied the amino groups. As per our planning we have achieved the 1,5-amino migration of amino groups but along with it, we got some unexpected products obtained through the cascade rearrangement. These unexpected rearrangements were studied by varying the substrates and amino groups. We tried to explain these results using theoretical calculations.

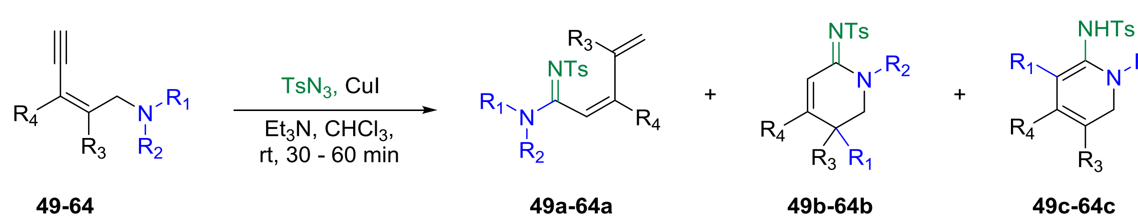
In the beginning we carried out the Cu-catalyzed reactions with substrates using aliphatic amino groups and cyclic amino group (morpholino) to afford the 1,5-amino group migrated product i.e. conjugated unsaturated acrylamidine. The substrates **41-44** gave the 1,5- amino group migrated products **41a-44a** with 62, 57, 67, and 62% yields respectively. The substrates with cyclic amino group **45-48** afforded amidines **45a-48a** with 67, 76, 70, and 65% yields respectively (Scheme 6).



Scheme 6: Cu-catalyzed 1,5-amino group migration to form conjugated unsaturated acrylamidines.

Further, when we changed the N-substituent to benzyl or substituted benzyl groups in substrates and carried out the Cu-catalyzed reaction, we found the mixture of three products. The distribution of products was changing by changing the substrate and by changing the amino groups. It was found that the formation of products was depending upon types of substrate and migratory aptitude of N-substituents. The observed variation in product distribution with respect to substrate is listed in below table 2.

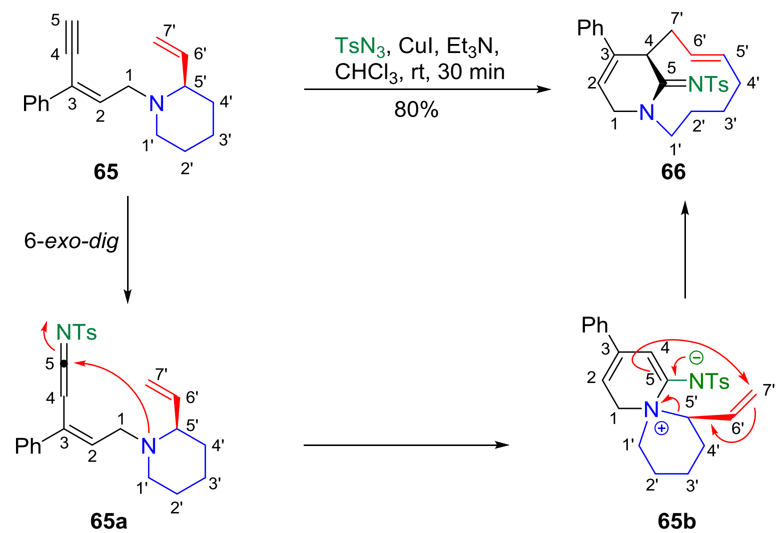
Table 2: Copper catalyzed reactions of various enyne-amine with TsN_3.



entry	**49-64**	substrates R$_1$	R$_2$	R$_3$	R$_4$	**49a-64a** (yield)	**49b-64b** (yield)	**49c-64c** (yield)
1	**49**	Bn	Bn	H	H	**49a** (23%)	**49b** (51%)	**49c** (16%)
2	**50**	Bn	Bn	Ph	H	**50a** (0%)	**50b** (50%)	**50c** (40%)

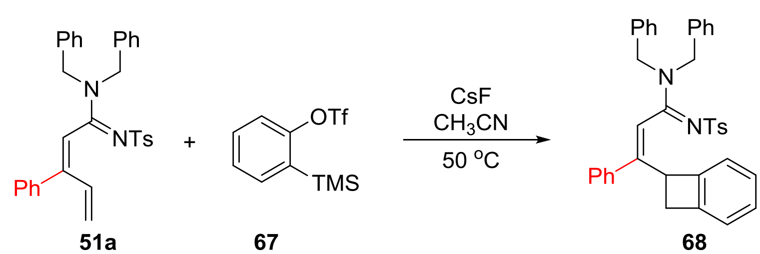
3	**51**	Bn	Bn	H	Ph	**51a** (84%)	**51b** (5%)	**51c** (0%)
4	**52**	Bn	Bn	Ph	Ph	**52a** (48%)	**52b** (30%)	**52c** (0%)
5	**53**	4-C*N*$C_6H_4CH_2$	4-C*N*$C_6H_4CH_2$	H	H	**53a** (13%)	**53b** (37%)	**53c** (23%)
6	**54**	4-C*N*$C_6H_4CH_2$	4-C*N*$C_6H_4CH_2$	Ph	H	**54a** (0%)	**54b** (51%)	**54c** (32%)
7	**55**	4-C*N*$C_6H_4CH_2$	4-C*N*$C_6H_4CH_2$	H	Ph	**55a** (77%)	**55b** (0%)	**55c** (0%)
8	**56**	4-C*N*$C_6H_4CH_2$	4-C*N*$C_6H_4CH_2$	Ph	Ph	**56a** (73%)	**56b** (18%)	**56c** (0%)
9	**57**	4-*MeO*$C_6H_4CH_2$	4-*MeO*$C_6H_4CH_2$	H	H	**57a** (0%)	**57b** (63%)	**57c** (12%)
10	**58**	4-*MeO*$C_6H_4CH_2$	4-*MeO*$C_6H_4CH_2$	Ph	H	**58a** (0%)	**58b** (60%)	**58c** (11%)
11	**59**	4-*MeO*$C_6H_4CH_2$	4-*MeO*$C_6H_4CH_2$	H	Ph	**59a** (8%)	**59b** (70%)	**59c** (6%)
12	**60**	4-*MeO*$C_6H_4CH_2$	4-*MeO*$C_6H_4CH_2$	Ph	Ph	**60a** (0%)	**60b** (68%)	**60c** (0%)
13	**61**	Bn	4-C*N*$C_6H_4CH_2$	H	H	**61a** (14%)	**61b** (39%)	**61c** (23%)
14	**62**	Bn	4-C*N*$C_6H_4CH_2$	Ph	H	**62a** (0%)	**62b** (50%)	**62c** (25%)
15	**63**	Bn	4-C*N*$C_6H_4CH_2$	H	Ph	**63a** (86%)	**63b** (0%)	**63c** (0%)
16	**64**	Bn	4-C*N*$C_6H_4CH_2$	Ph	Ph	**64a** (46%)	**64b** (29%)	**64c** (0%)

Later, we carried out the reactions by varying the sulfonyl azides to mesyl azide and nosyl azide, we found no effect on yields and distribution of products. Further, to explore the application of this methodology, we synthesized the new kind of bridged bicyclic amidine **66** from enyne-amine **65.**



Scheme 7: Synthesis of bridged bicyclic amidine by Cu-catalyzed reaction.

We also have shown the novel 2+2 cycloaddition reaction of benzyne with unsaturated conjugated acrylamidine, the cycloaddition occurred at terminal double bond. When the amidine **51a** was heated with benzyne precursor **67** and CsF in acetonitrile, we obtained the resultant product **68** with 80% yield.



Scheme 8: 2+2 cycloaddition of amidine with benzyne.

List of Publications

1. A 1,3-amino group migration route to form acrylamidines, Chauhan, D. P.; Varma, S. J.; Vijeta, A.; Banerjee, P. Talukdar, P. *Chem. Commun.* **2014**, *50*, 323.

2 δ-Unsaturated γ-amino acids: enantiodivergent synthesis and cell imaging studies, Kand, D.; Chauhan, D. P.; Lahiri, M.; Talukdar, P. *Chem. Commun.* **2013***, 49,* 3591.

3 Intramolecular Cascade Rearrangements of Enyne-Amine Derived Ketenimines: Access to Conjugated Acyclic and Cyclic Amidines, Chauhan, D. P.; Varma, S. J.; Gudem, M.; Singh, K; Hazra, A; Talukdar, P. *Manuscript Under Revision*

4 BODIPY based ‘click on’ fluorogenic dyes: application in live cell imaging Chauhan, D. P.; Saha, T.; Lahiri, M.; Talukdar, P. *Tetrahedron Lett.* **2014**, *55,* 244.

Chapter 1

Introduction to Rearrangements

1.1 Introduction

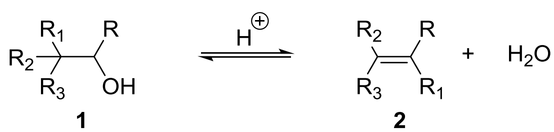
Organic reactions usually end up with products that are in line with the regularly accepted mechanisms. Therefore the products are often called normal products. In many cases, reactions do not give entirely and solely the expected products, but may lead to other ones that twig from mechanistically different pathways. These unexpected products are referred as abnormal products or rearranged products. Sometimes the rearranged product is not only the abnormal but also the major one. This is the result of plausible rearrangement occurring during the mechanistic course to fulfill the principle of the minimum energy state of the whole system, that is, of the transition state. A rearrangement reaction is a broad class of organic reactions where the carbon skeleton of a molecule is altered to give a structural isomer of the original molecule. Often a substituent moves from one atom to another atom in the same molecule. Either a certain energetic relief or a certain ease of the system must manifest to yield the rearrangement product as the stable outcome. This can be provided through several phenomena: *a*) a delocalization of the generated radical, cation or anion species over the atoms of the molecules with the mostly probable localization on the thermodynamically favored site, a phenomenon called resonance; this final stage of the intermediate, that is, the activated complex, would resemble the resulted product in accord with the Hammond postulate, *b*) a shift or a migration of one atom or a group of atoms (radical) from one site to another via a breaking-forming bond rule. Overall, all these mechanistic phenomena are likely to occur intramolecularly. In several cases, the rearrangement affords the products via isomerization, united with some stereochemical changes. An energetic requirement is also observed in order for a rearrangement to take place; that is, the rearrangement usually involves a heat evolution to be able to yield a more stable compound. There are five types of molecular rearrangements: 1) electron deficient skeletal rearrangement, 2) electron rich skeletal rearrangement, 3) radical rearrangement, 4) rearrangements on aromatic ring, 5) sigmatropic rearrangement. This exceptionally versatile class of bond reorganization processes has extensive applications in biological processes and organic synthesis. These classes of reactions often can explain the formation of complex natural products in biological systems. They are also useful for the preparation of synthetically challenging products from readily accessible precursors.

1.2 Electron deficient skeletal rearrangement:

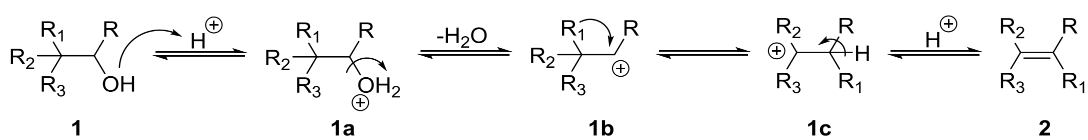
It involves the [1,2] migration of alkyl or aryl group from one carbon to adjacent carbon atom, having six electrons in the valence shell. The molecular system may be either a cation or neutral molecule.

1.2.1 Wagner-Meerwein rearrangement

It is one of the simplest systems where an alkyl group migrates, with its bonding pair, to an electron-deficient carbon atom (scheme 1.1).[1]

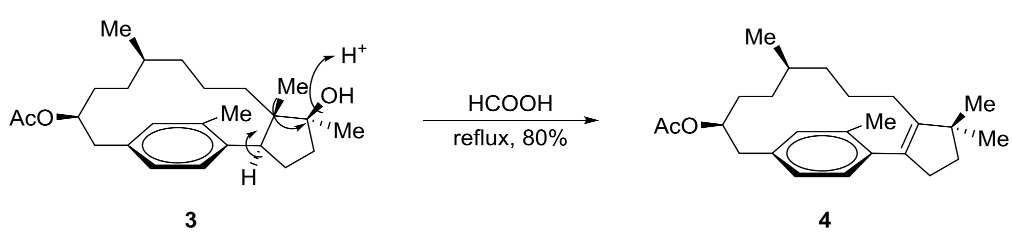


Mechanism



Scheme 1.1: 1,2 alkyl shift in Wagner-Meerwein reaction.

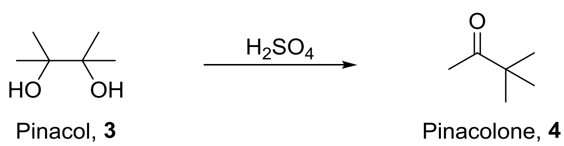
The driving force for the rearrangement resides in the greater stability of a tertiary carbocation compared to that of primary carbocation. Wagner-Meerwein rearrangement has been utilized in the synthesis of several natural products and steroids (scheme 1.2).[2] For example, in the synthesis of natural ansa-steroids one of the key step was the methyl migration in intermediate **3** occurred in acidic condition by elimination of water molecule.



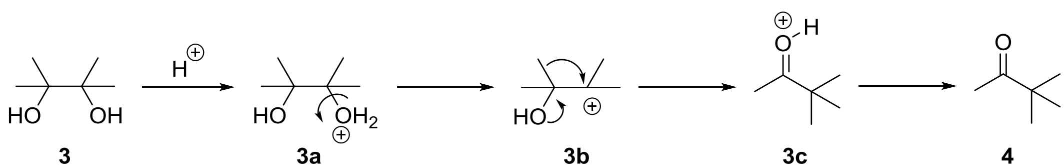
Scheme 1.2: Utilization of Wagner-Meerwein rearrangement in the synthesis of ansa-steroid.

1.2.2 Pinacol-Pinacolone rearrangement

Treatment of 1,2-diols (pinacol) with acid lead to rearrangement to give ketone. Although this rearrangement fundamentally is similar to the above-described Wagner-Meerwein rearrangement, but differs in that the rearranged ion, the conjugate acid of ketone, is relatively more stable than the rearranged carbocation formed in Wagner-Meerwein rearrangement (scheme 1.3). Thus, the driving force for pinacol is greater compared to Wagner-Meerwein rearrangement. However, the characteristics of the Wagner-Meerwein is applicable to the pinacol rearrangement.[3]

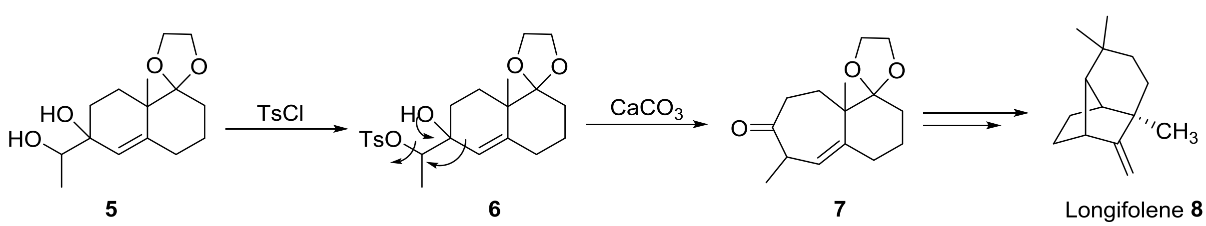


Mechanism:



Scheme 1.3: 1,2 alkyl shift in Pinacol-Pinacolone rearrangement.

The synthesis of natural product Longifolene **8** was achieved through a convenient ring expansion reaction of key intermediate **6** by semi-pinacolone reaction where the secondary hydroxyl group was made a better leaving group by tosylation (scheme 1.4).[4]



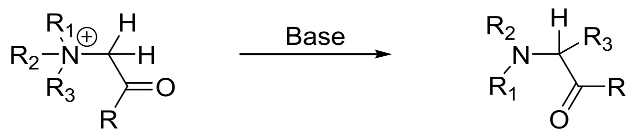
Scheme 1.4: Synthesis of Longifolene by Semi-pinacolone rearrangement.

1.3 Electron rich skeletal rearrangement

This group of reaction has been less explored, and exhibited limited synthetic importance compared to the rearrangements to electron deficient carbons.

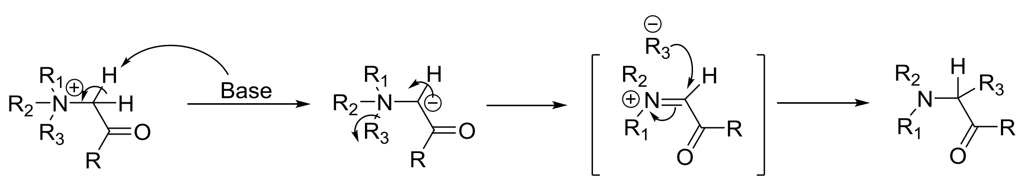
1.3.1 Stevens rearrangement

In case of quaternary ammonium salts containing β-ketone or ester or aryl group, an α-hydrogen is removed by base to give an ylide and then the rearrangement occurs (scheme 1.5). [5]



9 10

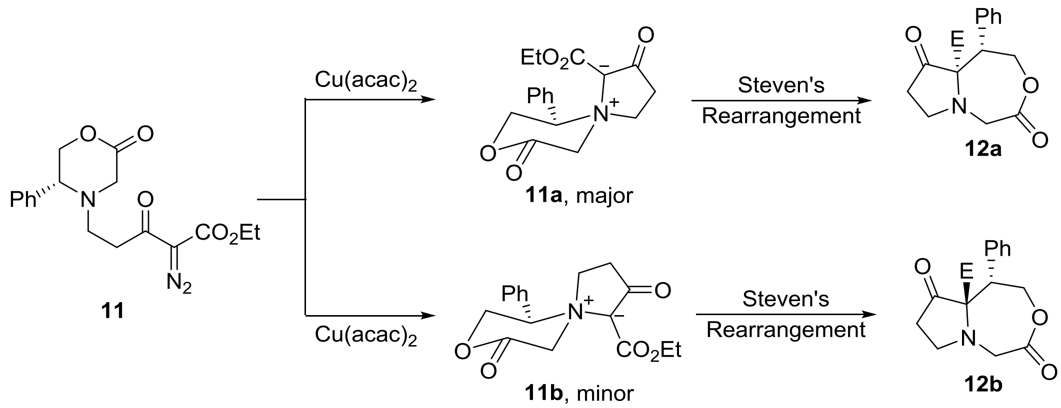
Mechanism:



9 9a 9b 10

Scheme 1.5: 1,2 Alky/aryl shift in Stevens rearrangement.

The potential to access many different alkaloid natural product ring systems is one of the most appealing aspects of the Stevens rearrangement of ammonium ylides. An efficient way to access a variety of amine natural product ring systems is through the formation of a spirocyclic ylide and subsequent ring expansion/Stevens rearrangement. A recent application of this type of chemistry is seen in the work of Saba and co-workers during their synthesis of 5,7-fused bicyclic amine ring systems **12a** and **12b**, which are potential precursors to more elaborate polycyclic alkaloid systems (scheme 1.6).[6]

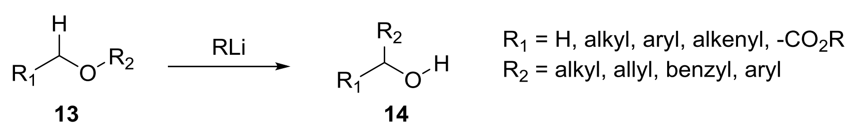


Scheme 1.6: Synthesis of alkaloids using Stevens rearrangement.

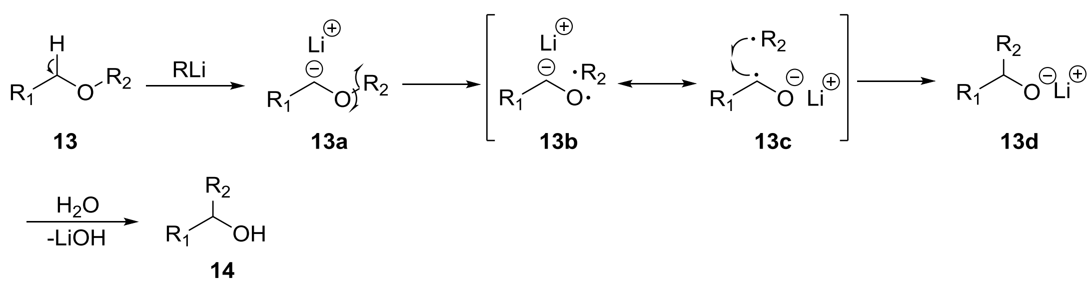
1.4 Radical rearrangement

1.4.1 Wittig rearrangement

Ethers undergo [1,2]-sigmatropic rearrangement in the presence of strong base such as amide ion or phenyllithium to give more stable oxyanion. The mechanism is analogous to that of Stevens rearrangement. The mechanism has been fully elucidated, and a discussion can be found in a recent publication by Nakai (scheme 1.7).[7]

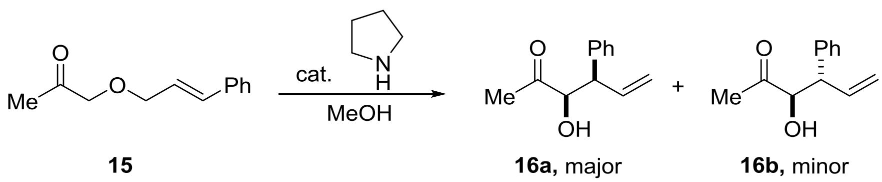


Mechanism:



Scheme 1.7: 1,2 shift in Wittig rearrangement.

A new organocatalytic [2,3] Wittig rearrangement by secondary amine catalysis which operates under ambient and operationally simple conditions and also precludes the use of strong bases often required in conventional [2,3] Wittig rearrangements. Furthermore, this organocatalytic transformation provides an important platform for the development of a catalytic enantioselective [2,3] rearrangement (scheme 1.8).[8]



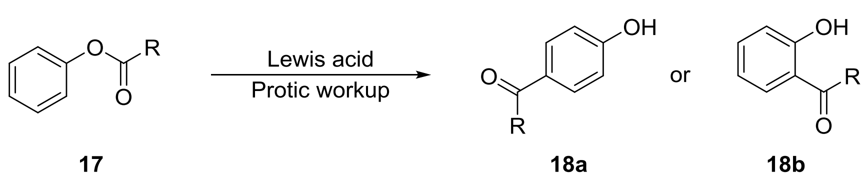
Scheme 1.8: Enantioselective organocatalytic [2,3] Wittig rearrangement.

1.5 Rearrangements on an aromatic ring

A number of rearrangements occur in aromatic compounds. For example, a) Fries rearrangement, b) Claisen rearrangement and, c) Rearrangements on aniline derivatives.

1.5.1 Fries rearrangement

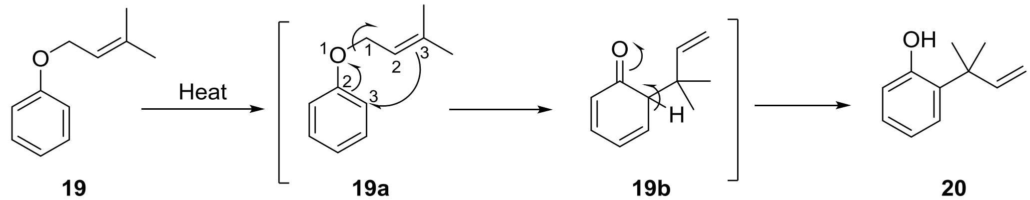
Aryl esters with Lewis acid undergo rearrangement to give phenols having keto substituent at *ortho* and *para* positions. The complex between the ester and Lewis acid gives an acylium ion which reacts at the *ortho* and *para* positions as in Friedel-Crafts acylation (scheme 1.9).[9]



Scheme 1.9: Lewis acid catalyzed Fries rearrangement.

1.5.2 Claisen rearrangement

Aryl allyl ethers undergo [3,3]-sigmatropic rearrangement on being heating to allylphenols (scheme 1.10).[10]



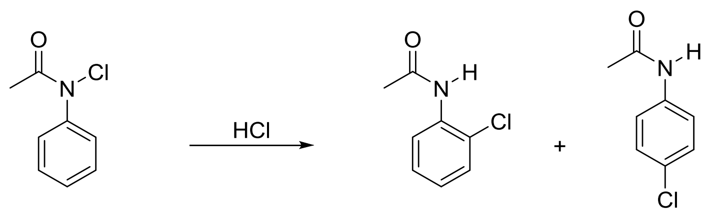
19 **19a** **19b** **20**

Scheme 1.10: [3,3]**-** sigmatropic rearrangement of allyl aryl ethers.

1.5.3 Rearrangements on aniline derivatives

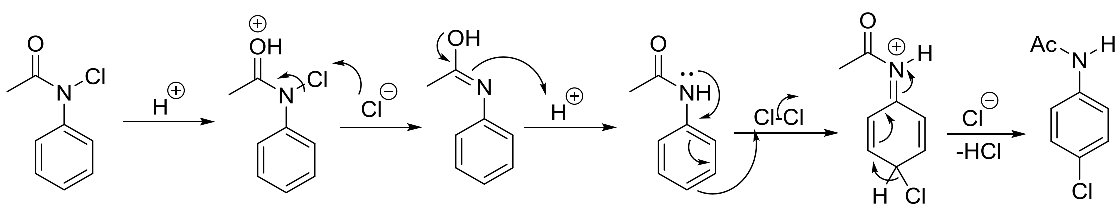
Aniline derivatives readily precede rearrangement on treatment with acid. First, the formation of conjugate acid of the amine takes place which then eliminates the electrophilic species that reacts at the activated *ortho* or *para* position of the aromatic ring.[11]

Treatment of *N*-chloroacetanilide with hydrochloric acid undergoes Orton rearrangement affords a mixture of *ortho* and *para*-chloroacetanilides in the same proportions as in the direct chlorination of acetanilide (scheme 1.11).[12]



21 **22a** **22b**

Mechanism:

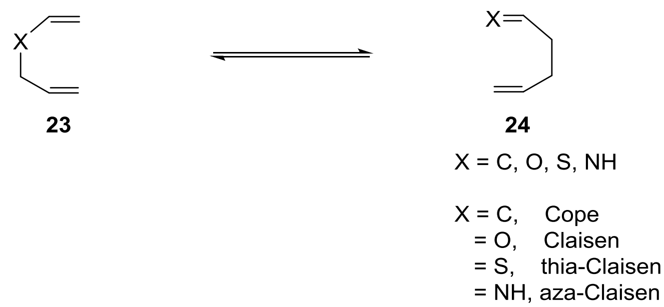


21 **21a** **21b** **21c** **21d** **22b**

Scheme 1.11: Orton rearrangement of N-chloroacetanilide.

1.6 Sigmatropic rearrangements

Sigmatropic rearrangement is a bond reorganization in which a hydrogen atom or an alkyl is shifted intramolecularly to a π bond and the shift is usually brought about thermally or photochemically. On the basis of the Woodward-Hoffmann theory,[13] a sigmatropic shift is always designated as [*n*, *m*] where *n* and *m* stand for the initial and the final positions of attachment of the moving bond ends. For instance, a [1,2] sigmatropic shift (scheme 1.12) means that one end of the bond remains attached to its initial site while the other end migrates to the adjacent bond.

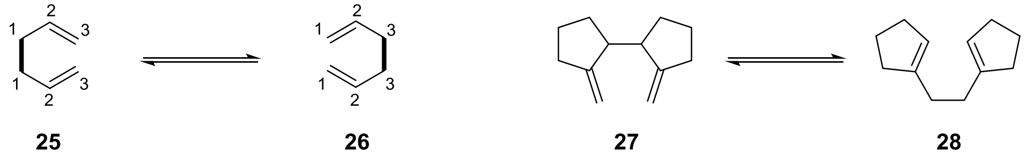


Scheme 1.12: General [3,3]-sigamtropic rearrangement.

Though many sigmatropic shifts are well known and well studied such as the allylic system, the [3,3] rearrangement is probably the most interesting as far as the synthesis is concerned.

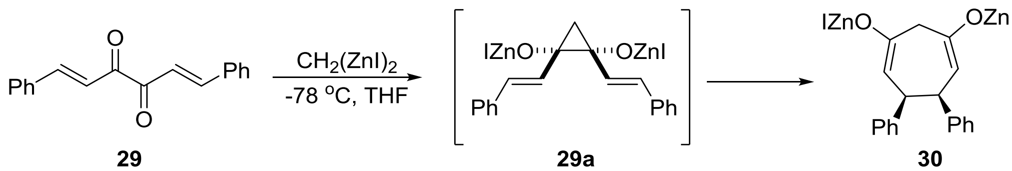
1.6.1 Cope rearrangement

Cope rearrangement (scheme 1.13)[14] is usually a reversible reaction, thus, the final equilibrium position depends strongly on the stability difference between the starting material and the product. Thermodynamic studies of the sigmatropic shift of this kind are in accord with a concerted mechanism.[15]



Scheme 1.13: [3,3]-sigmatropic Cope rearrangement.

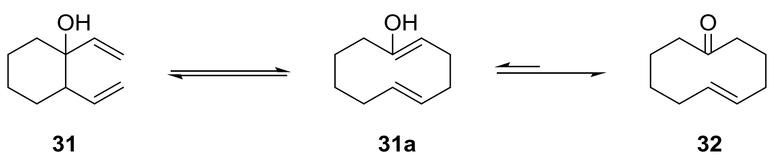
The Cope rearrangement of cis-divinyl cyclopropane has been recognized as an efficient route to obtain a cycloheptane skeleton. Bis(iodozincio)methane converted the diketone into the cis-divinylcyclopropane-1,2-diol stereoselectively; this diol transformed into the corresponding cycloheptane derivative stereospecifically via Cope rearrangement (scheme 1.14).[16]



Scheme 1.14: Stereoselective syntheses of cycloheptane derivative by Cope rearrangement.

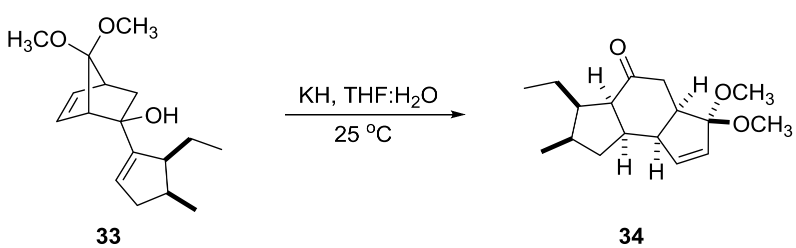
1.6.2 Oxy-Cope rearrangement

The Oxy-Cope rearrangement involves compounds with a hydroxyl group affixed to C-3 so that the rearranged product is an enol which tautomerizes to the keto form (scheme 1.15).[17]



Scheme 1.15: [3,3]-sigamtropic oxy-Cope rearrangement.

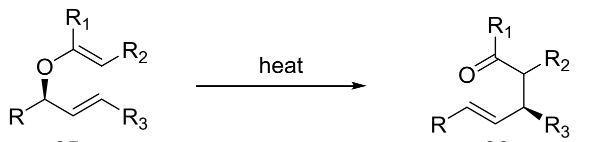
A concise synthesis of the carbo-tricyclic alkaloid was achieved by oxy-Cope rearrangement (scheme 1.16).[18]



Scheme 1.16: Construction of carbo-tricyclic skeleton using oxy-Cope rearrangement.

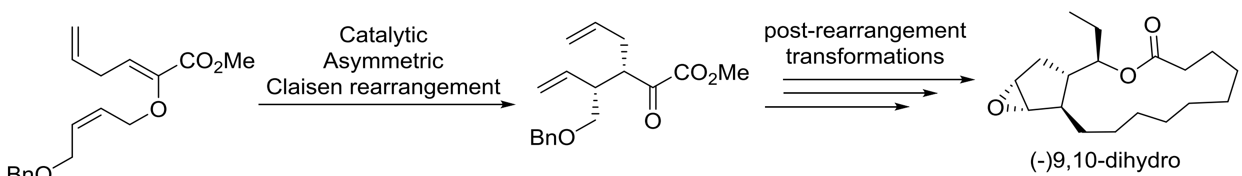
1.6.3 Claisen rearrangement

A closely related Cope rearrangement is that of Claisen, a very early reported rearrangement (1912).[10a] The starting material containing an oxygen atom in place of the C-3 may undergo a [3,3] sigmatropic shift. The aliphatic Claisen Rearrangement is a [3,3]-sigmatropic rearrangement in which an allyl vinyl ether is converted thermally to an unsaturated carbonyl compound (scheme 1.17).[19]



Scheme 1.17: [3,3]-sigmatropic Claisen rearrangement.

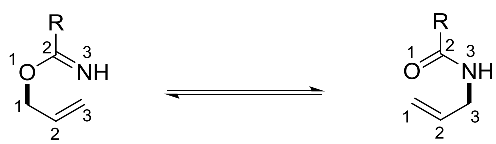
The enantioselective synthesis of (−)-9,10- dihydroecklonialactone B is reported. The catalytic asymmetric Claisen rearrangement of Gosteli-type allyl vinyl ether was utilized to afford an acyclic α-keto ester building block endowed with functionality amenable to the preparation of the carbocyclic target molecule by suitable post-rearrangement transformations (scheme 1.18).[20]



Scheme 1.18: Synthesis of (−)-9,10- dihydroecklonialactone B via asymmetric Claisen rearrangement.

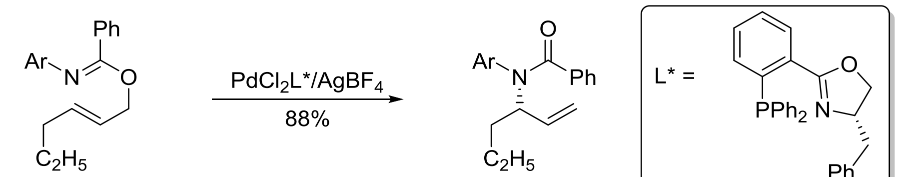
1.6.4 Aza-Claisen rearrangement

In this rearrangement, one allyl carbon atom is displaced by a nitrogen atom and the carbon-nitrogen bond is the bond to break (scheme 1.19).[21]



Scheme 1.19: [3,3]-sigmatropic aza-Claisen rearrangement.

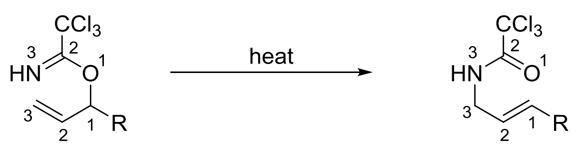
The asymmetric aza-Claisen rearrangement of (*E*)-3-alkyl-2-propenyl*N*-[4-trifluoromethyl)phenyl]benzimidates was catalyzed by a homochiral cationic palladium(II) complex (scheme 1.20).[22]



42 Ar = 4-$CF_3C_6H_4$ **43**

Scheme 1.20: [3,3]-sigmatropic asymmetric aza-Claisen rearrangement.

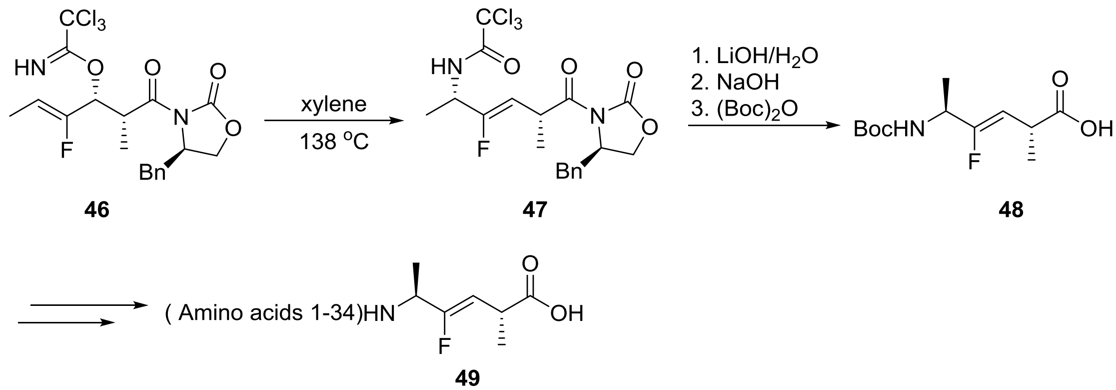
The sigmatropic rearrangement of allylic imidates offers a valuable entry into the preparation of protected allylic amines, conversion of an imidate to the amide is essentially irreversible. This reaction has wide application for the synthesis of variety types of nitrogen-containing compounds. Since the discovery of the thermal allylic imidate rearrangement in 1937, a number of systems have been investigated for the practical preparation of allylic amines by this route. However, it was the discovery and development of the rearrangement of allylic trichloroacetimidates that overwhelmingly demonstrated the widespread utility of this synthetic method called as Overman rearrangement (scheme 1.21).[23]



44 **45**

Scheme 1.21: [3,3]-sigmatropic Overman rearrangement.

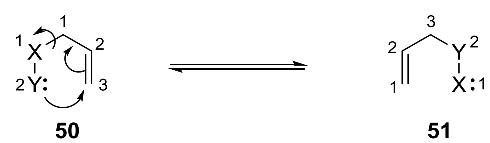
The scope of this rearrangement is such that primary, secondary, and tertiary allylic amides are readily accessible, thus providing entry into a wide variety of nitrogen-containing products including amino sugars, nucleotides, amino acids, peptides, and various nitrogen heterocycles. In addition, the Overman rearrangement has found extensive application in the total synthesis of natural products.[24] This rearrangement has been central to the synthesis of several peptide analogs. For example, a range of dipeptide olefin isosteres has been synthesized in a study of parathyroid hormone receptor activation by analogs of the *N*-terminal fragment of the natural hormone (scheme 1.22).[25]



Scheme 1.22: Synthesis of dipeptide olefin isoster using Overman rearrangement.

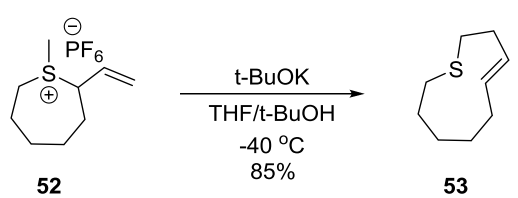
1.6.5 [2,3]-sigmatropic rearrangement

[2,3]-sigmatropic reaction is a thermal isomerization that proceeds through a six-electron, five-membered cyclic transition state reactions which encompasses a vast number of synthetically useful variants in terms of both the atom pair involved (X, Y) and the electronic state (Y: anions, non-bonding electron pairs, ylides, etc.) (scheme 1.23).[26]



Scheme 1.23: [2,3]-sigmatropic rearrangement.

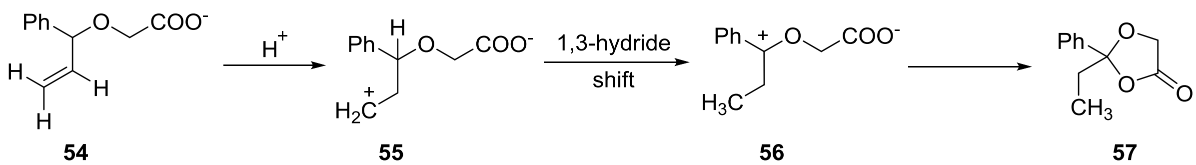
For example, synthesis of eight- to ten-membered thiacycloalk-4-enes were achieved through ring expansion by [2,3] Sigmatropic shifts of unstabilized sulfonium ylides (scheme 1.24).[27]



Scheme 1.24: Ring expansion by [2,3]-sigamtropic rearrangement.

1.6.6 [1,3]-hydride shift

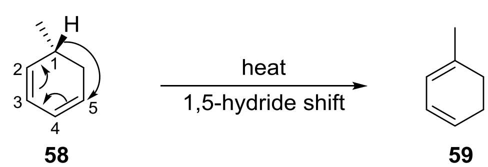
The [1,3]-hydride shifts seem to play only a minor role in organic chemistry. According Woodward–Hoffmann rules [1,3]-hydride shift would proceed in an antarafacial shift. Although such a shift is symmetry allowed, the Mobius topology required in the transition state prohibits such a shift because it is geometrically impossible. This theory accounts for the fact that enols do not isomerize without an acid or base. [1,3]-hydride shifts are observed in bicyclic systems, e.g., norbornyl[28] cations, where they can compete with Wagner-Meerwein rearrangements. The same can be said about the reported [1,3]-hydride shifts observed in adamantane.[29] The following report is regarding [1,3]-hydride shift under hydrolytic condition (scheme 1.25).[30]



Scheme 1.25: [1,3]-hydride shift under hydrolytic condition.

1.6.7 [1,5]-hydride shift

A [1,5]-hydride shift involves the shift of 1–H down 5 atoms of a π system. Hydrogen has been shown to shift in both cyclic and open-chain systems at temperatures at or above 200 ˚C. These reactions are predicted to proceed suprafacially via a Huckel-topology transition state (scheme 1.26).[31]



Scheme 1.26: [1,5]-hydride shift in cyclic system.

1.7 Research outlook

Even though great numbers of rearrangements are reported in the literature for the synthesis of complex molecules or biologically important molecules, we have developed the methodologies for the synthesis of δ-unsaturated γ-amino acids using [3,3]-sigmatropic Overman rearrangement, and functionalized amidine molecules were synthesized by 1,3 and 1,5 migration of amino group.

In chapter 2, we have successfully utilized the characteristic chirality transfer approach of Overman rearrangement where *E*-allyl trichloro acetamidate was converted into allylamine with retention of configuration and *Z*-allyl trichloro acetamidate was converted into allylamine with inversion of configuration. Both *E* and *Z* substrates were prepared in such a way that after rearrangement δ-unsaturated γ-amino acids skeleton was achieved. Further, the enantiomeric pair of δ-unsaturated γ-amino acids were carried forward for library construction by using diversity oriented synthesis (DOS) approach. Using the same approach fluorescent γ-amino acid was also achieved and its cell permeability was checked by live cell imaging. In chapter 3, we have demonstrated the synthesis of acrylamidines from propargylamines via ketenimine intermediate which underwent 4-*exo-dig* cyclization by internal amino group, the ring opened up by E1cb mechanism by migration of amino group from carbon 1 to carbon 3. In this way, we have achieved a novel 1,3-amino group migration through a specific cyclization which subsequently opened to give a migrated product. In chapter 4, we have developed a methodology where we have synthesized a conjugated unsaturated acrylamidines, cyclic amidines, and di-hydro pyridines from enyne-amines via 6-*exo-dig* cyclization on ketenimine intermediate by an internal amino group, the cyclization and subsequent opening of ring provided the 1,5-amino migrated conjugated unsatutared acrylamidines in the similar fashion as described for 1,3-amino migartion, generally 1,2 and 1,3 shifts are easy to achieve as compare to 1,5 shifts but we have achieved the 1,5 shift rearrangement exclusively by our methodology. Cyclization followed by other cascade reactions provided us the two kinds of cyclic products; cyclic amidines and dihydro pyridines. These modes of cylizations, 4-*exo-dig* and 6-*exo-dig* were named according to Baldwin's rule. A series of guidelines that describe the propensity of various systems to participate in ring forming reactions was put forth by J. E. Baldwin in the 1970's.[32] This set of guidelines, which describe the relative ease of ring formations, has become known as Baldwinís rules of ring closure and has proved a useful tool in evaluating the feasibility of ring forming reactions. Baldwin described his rules in terms of three features of the reaction: (1) the ring size being formed (indicated through a numerical prefix), (2) the hybridized state of the carbon atom undergoing the ring closing reaction (sp = digonal, sp^2 = trigonal, and sp^3 = tetrahedral), and (3) the nature of the breaking bond (*exo*- the breaking bond it is external to the newly formed ring, and *endo* - the breaking bond is within newly formed ring).[33] Examples of these formalizations are shown for the 6-membered ring closing reactions in Figure 1.1.

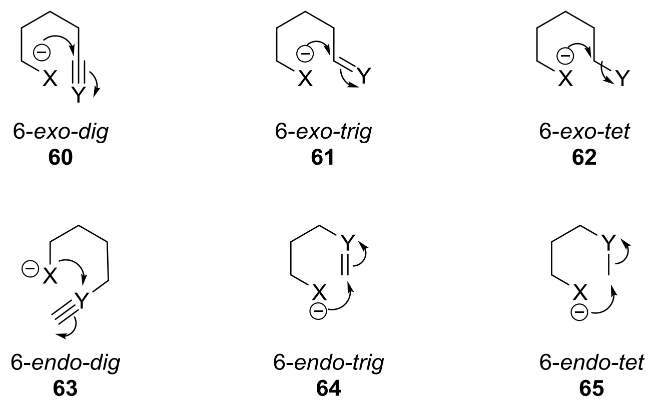


Figure 1.1: Modes of 6-membered ring closure according to Baldwin's rule.

The presence of cyclic structures in the basic framework of many complex and biologically interesting molecules has made their formation a fundamental process in organic synthesis. Therefore, ring-forming processes have garnered the attention of synthetic chemists for many years.

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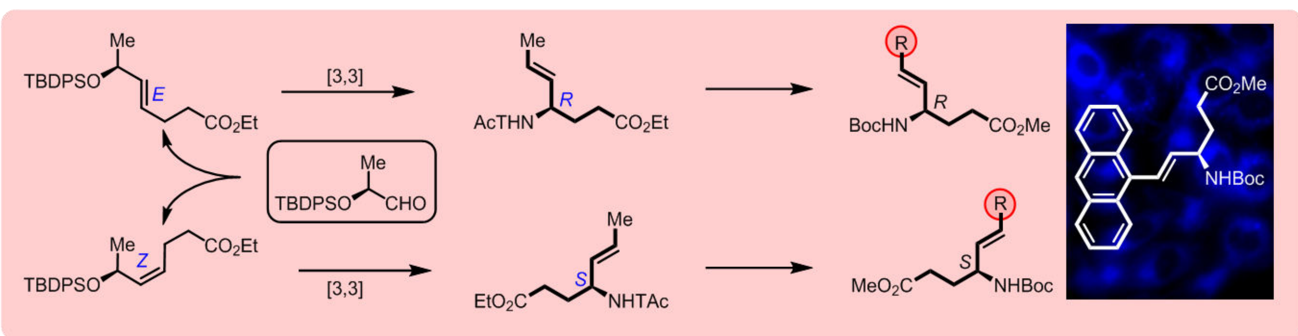
Chapter 2

Enantiodivergent Synthesis of δ-Unsaturated γ-Amino Acids via Overman Rearrangement



2.1 Introduction:

Peptides are important modulators in the human body gifted by the nature. All biological and physiological processes are governed by peptides and proteins. However, when we look into their therapeutic properties, these types of molecules often have not been preferential. Because of their fast degradation, poor bioavailability, lower absorption, lack of selectivity towards the target receptors made them less potential. Higher manufacturing costs of some bioactive peptides are not affordable for health industries. Under these circumstances, the development of unnatural amino acids as indispensable tools provided enormous support to the peptide science. The incorporation of proper unnatural amino acids into a peptide or protein significantly improves the cell permeability, half-life, bio-distribution, etc. of peptides and proteins. In addition, their potency and selectivity towards receptor/acceptor could also be enhanced. Site-specific modifications of peptides and proteins using unnatural amino acids under physiological conditions also have been made easier with the advances of biotechnology. Therefore, our research described in this chapter contributes to the efforts in the development of novel unnatural amino acids. In particular, we have focused on a novel method for the synthesis of δ-unsaturated γ-amino acids by using a [3,3]-sigmatropic Overman rearrangement.

γ-Amino acids have gained significant interest as biologically active compounds in the central nervous system (CNS) of mammals.[1] For example, GABA (γ-amino butyric acid) is a major inhibitory neurotransmitter which exerts its physiological action through the interaction with three receptors as $GABA_A$, $GABA_B$, and $GABA_C$. The receptors $GABA_A$ and $GABA_C$ are similar to ligand-gated ion channels, permeable to anions and convey the fast synaptic transmission. $GABA_B$ is a G-protein coupled receptor which helps in modulating the synaptic transmission through intracellular effector systems.[2] The deficiency of GABA leads to several important neurological disorders such as Huntington's and Parkinson's disease, epilepsy, and other psychiatric disorders, e.g. anxiety and pain. [3] The lower lipophilicity of GABA and its poor ability to cross the blood-brain barrier (BBB) makes it inefficient for administration orally or intravenously. [4] Therefore the synthesis of more lipophilic GABA derivatives capable of crossing the blood-brain barrier (BBB) became the target for a great number of studies. For example, 4-amino-3-(*p*-chlorophenyl)butyric acid (Baclofen) **2** is one of the important drug for the treatment of paroxysmal pain of trigeminal neuralgia[5] as well as spinal spasticity without affecting sedation[6]. It is commercially available in its racemic form with names Lioresal® and Baclon®.

Next, (*S*)-3-Aminomethyl-5-methylhexanoic acid (Pregabalin) **3** is a potent anticonvulsant drug, but its (*S*)-enantiomer is only the biologically active component. 4-Amino-5-hexenoic acid (γ-vinyl GABA or Vigabatrin) **4** is an important anticonvulsant drug which is also available in the market in the racemic form as Sabril®. However, only the (*S*)-enantiomer is pharmacologically active[7] (Figure 2.1). Due to their potential biological activities, considerable efforts towards the asymmetric and stereodivergent routes for the synthesis of γ-amino acid derivatives have been expended.

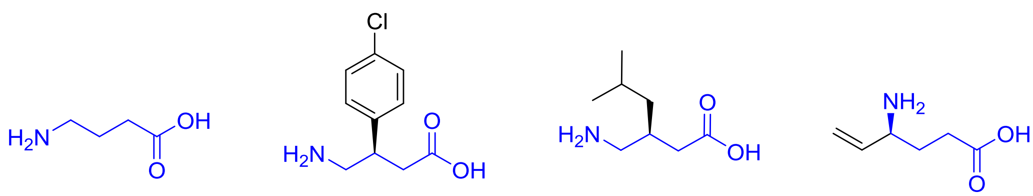
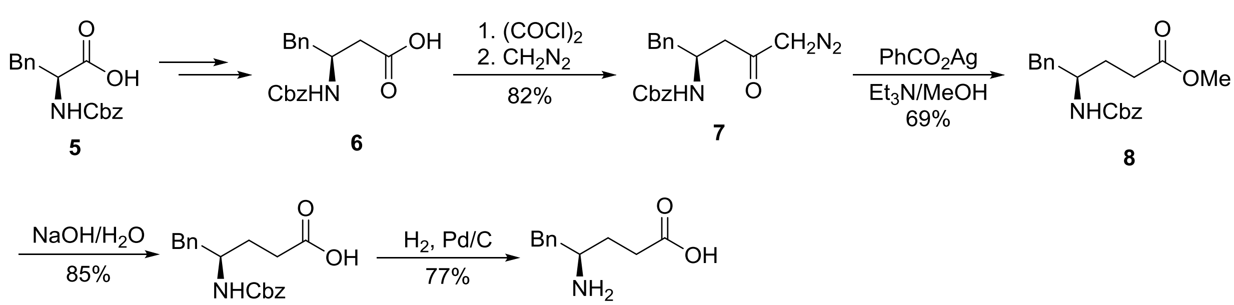


Figure 2.1: Structures of GABA derivatives.

2.2 Stereoselective synthesis of γ-amino acids

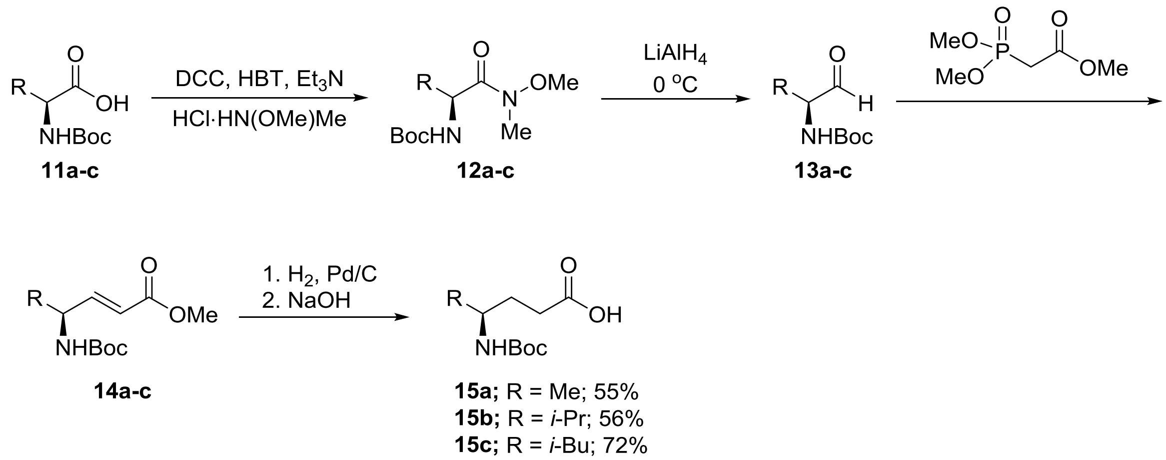
2.2.1 Homologation of α-amino acids

A double Arndt–Eistert homologation strategy of α-amino acids were used to achieve γ-amino acids. For example, the first Arndt–Eistert homologation of (*S*)-*N*-Cbz-α-amino acid **5** yielded (*S*)-*N*-Cbz-β-amino acid **6** which upon second homologation with oxalyl chloride followed by treatment with diazomethane gave the corresponding β-diazoketone **7** in 82% yield. A Wolff rearrangement of β-diazoketone **7** using silver benzoate and Et_3N in methanol afforded the γ-amino acid methyl ester **8** in 69% yield. The methyl ester group of **8** upon basic hydrolysis gave the corresponding carboxylic acid **9**, further Cbz group deprotection of **9** by catalytic hydrogenation led to (*S*)-γ-amino acid **10** in 77% yield (Scheme 2.1).[8]



Scheme 2.1: Synthesis of (S)-γ-amino acid **10** by a double Arndt–Eistert homologation of α-amino acid.

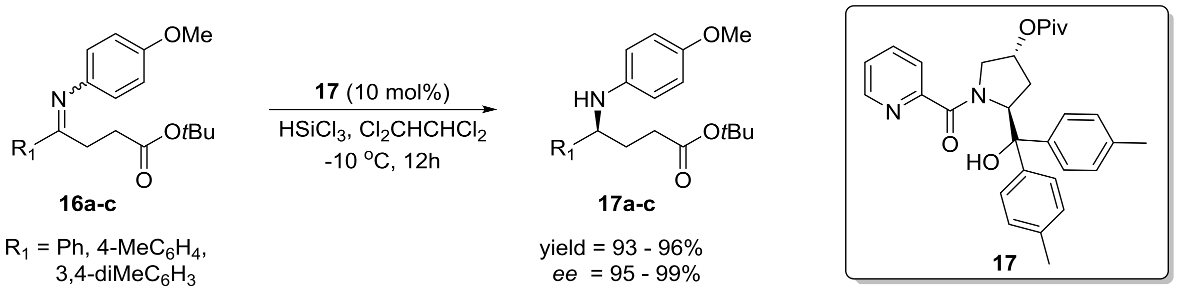
Synthesis of Weinreb amides **12a-c** from Boc-protected α-amino acids **11a-c** were reduced to aldehydes **13a-c** which were carried for Horner–Wadsworth–Emmons reaction yielded the α,β-unsaturated *N*-Boc-γ-amino acid methyl esters **14a-c** as *E*/*Z* mixture (3:1 to 7:1). Reduction of double bond with catalytic hydrogenation of **14a-c** followed by hydrolysis afforded the *N*-Boc-γ-amino acids **15a-c** (Scheme 2.2).[9]



Scheme 2.2: Synthesis of N-Boc-γ-amino acids **15a-c** using Horner–Wadsworth–Emmons reaction.

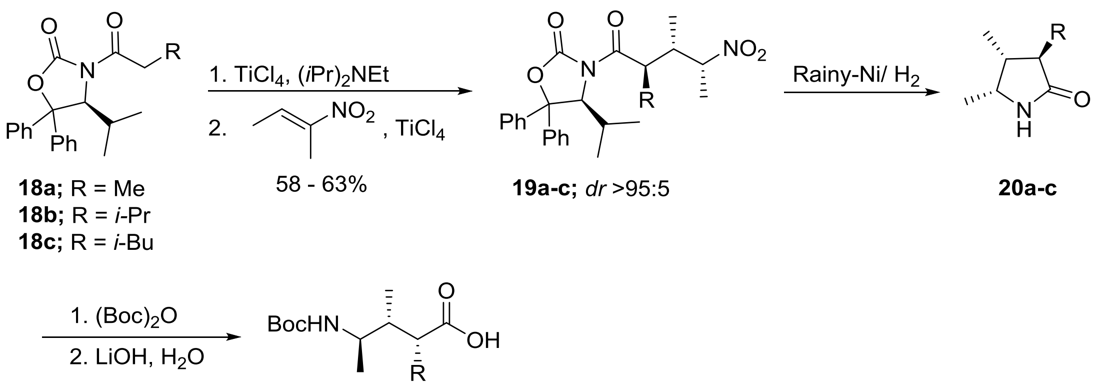
2.2.2 Asymmetric synthesis of γ-amino acids

Asymmetric synthesis has become a key strategy in the modern organic chemistry. Challenging efforts have been taken for the formation of stereoisomerically pure organic compounds. Using the existed stereocenter in starting material, the direction of path of upcoming chiral reagent is controlled at the reactive centre. The asymmetric synthesis of γ-amino acids is becoming fundamental challenge and momentous efforts have been made in this field. The synthesis of enantiopure γ-amino acids in the presence of chiral auxiliaries, chiral reagents or chiral catalysts is reported. The synthesis of highly enantiopure γ-amino esters **17a-c** by enantioselective hydrosilylation of γ-imino esters **16a-c** with trichlorosilane catalyzed by a proline derived chiral Lewis base **17** proceeded smoothly to provide various optically active γ-amino esters **17a-c** in good yields up to 96% with excellent enantiomeric excess (*ee*) up to 99% (Scheme 2.3).[10]



Scheme 2.3: Enantioselective hydrosilylation of γ-imino esters **20a-c** promoted by **17**.

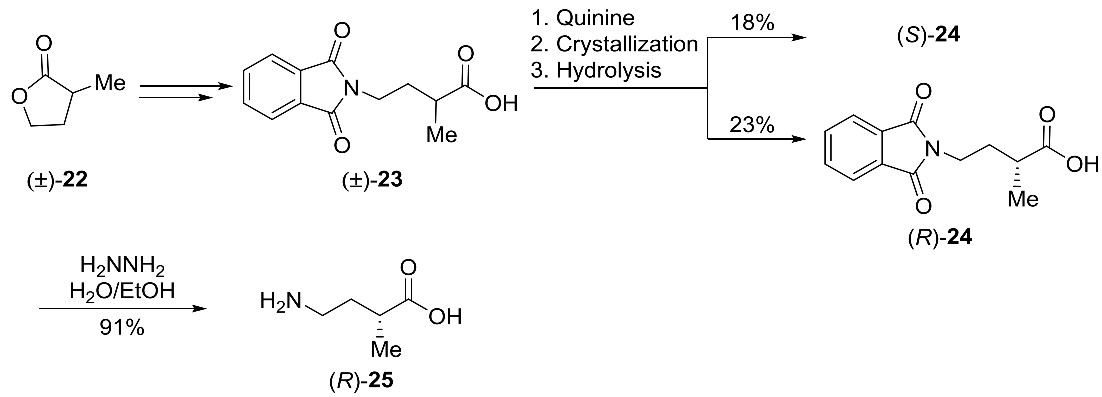
In this case, the Michael addition of titanium enolates derived from **18a-c** with nitro olefins gave nitro derivatives **19a-c** with excellent diastereoselectivity. The catalytic hydrogenation of **19a-c** in presence of Rainy-Ni directly affords the γ-lactums **20a-c**. The Boc protection of γ-lactums **20a-c** followed by the basic hydrolysis gave the enantiopure *N*-Boc protected α,β,γ-substituted γ-amino acids **21a-c** (Scheme 2.4).[11]



Scheme 2.4: Enantioselective synthesis of γ-amino acids by using chiral oxazolidinones as chiral auxiliaries.

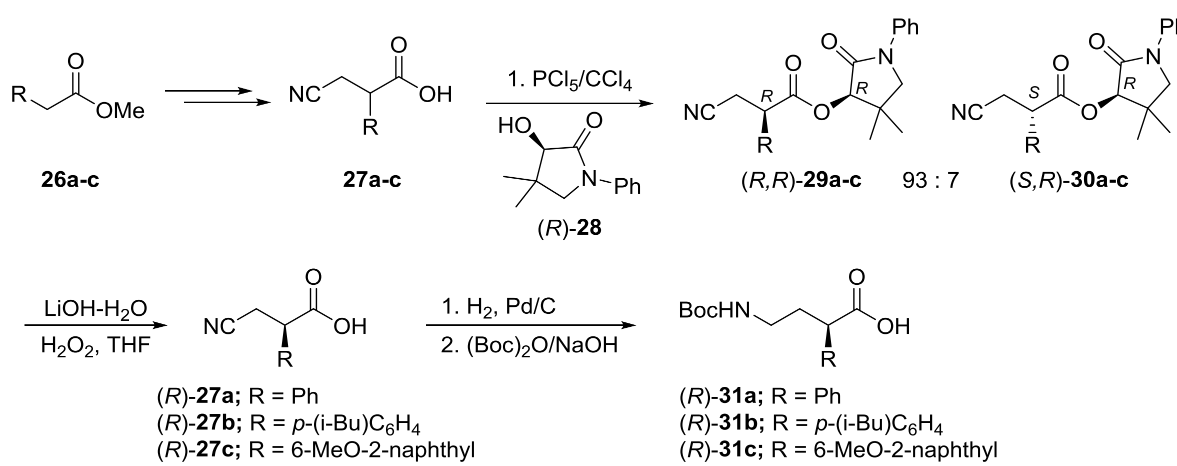
2.2.3 Resolution method

The first synthesis of (*R*)-4-Amino-2-methylbutanoic acid [(*R*)-2MeGABA] **25**, an important GABA antagonist was reported 50 years ago by resolution procedure. 2-methylbutyrolactone (±)-**22** was converted into (±)-**23,** the treatment of (±)-**23** with quinine gave the mixture of diastereoisomeric salts which was crystallized and hydrolyzed to afford enantiomerically pure (*R*)-**24** and (*S*)-**24** in 23% and 18% yield respectively. Finally, hydrazinolysis of (*R*)-**24** afforded the enantiomerically pure (*R*)-2MeGABA **25** in 91% yield (Scheme 2.5).[12]



Scheme 2.5: Synthesis of α-methyl γ-aminobutyric acid by resolution procedure.

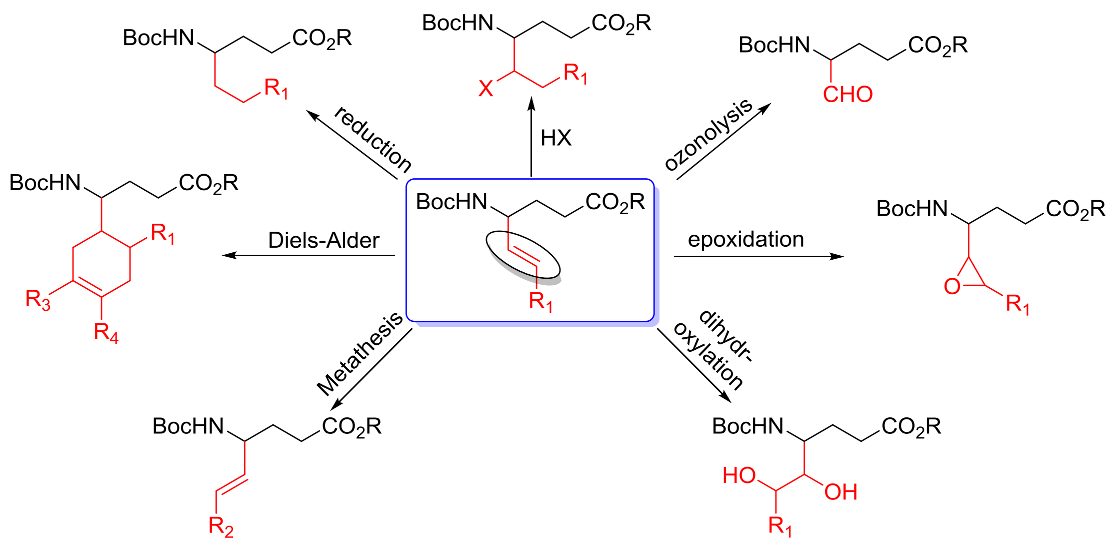
The synthesis of (±)-3-cyano-2-arylpropionic acids **27a–c** was achieved from readily available methyl arylacetates **26a–c**, the deracemization of (±)-3-cyano-2-arylpropionic acids **27a–c** was carried by using (*R*)- or (*S*)-*N*-phenylpantolactam **28** as the resolution agent. Hence, (±)-3-cyano-2-arylpropionic acids **27a–c** were treated with PCl_5 followed by condensation with (*R*)-*N*-phenylpantolactam **28** gave diastereoisomeric mixture of *N*-phenylpantolactam esters (α*R*,3'*R*)-**29a–c** and (α*S*,3'*R*)-**30a–c** in a 93:7 diastereoisomeric ratio. The pure diastereomer (α*R*,*R*)-pantolactam esters **29a–c** were hydrolyzed under basic medium to give enantiomerically pure carboxylic acids **27a-c**. The cyano group of acids **27a-c** was reduced by catalytic hydrogenation and subsequently treated with Boc-anhydride to produce (*R*)-*N*-Boc-α-aryl-γ-amino acids **31a–c** in > 99% *ee*. The (*S*)-*N*-Boc-α-aryl-γ-amino acids can also be synthesized following similar reaction sequences using the (*S*)-*N*-phenylpantolactam (Scheme 2.6).[13]



Scheme 2.6: Synthesis of (*R*)-*N*-Boc-α-aryl-γ-amino acids **31a–c** by resolution procedure.

2.3 Significance of double bonds in unsaturated amino acids:

In past decades, the nonproteinogenic amino acids having unsaturated double bonds in the side chain has gained the importance either for conformational restriction or chemical transformation to aldehydes, alcohols, halides, epoxides, amines, carboxylic acids, etc (Scheme 2.7).[14]



Scheme 2.7: Versatile reactivity of double bond in δ-unsaturated γ-amino acids.

These kinds of amino acids also show antimicrobial[15] antibiotic,[16] antiepileptic,[17] and other diverse activities. One of the most important applications of unsaturated double bond in side chain is for chemical stapling. Recently, Verdine and co-workers have demonstrated that the C=C bonds can be used in chemical stapling which reinforces α-helix formation (Figure 2.2). [14]

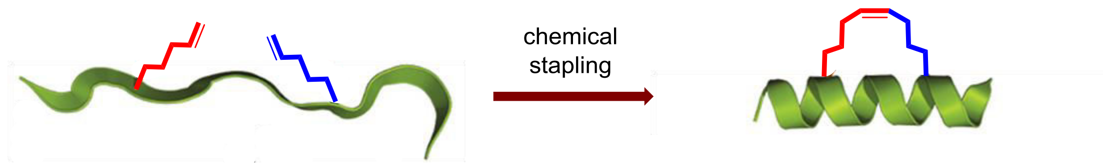
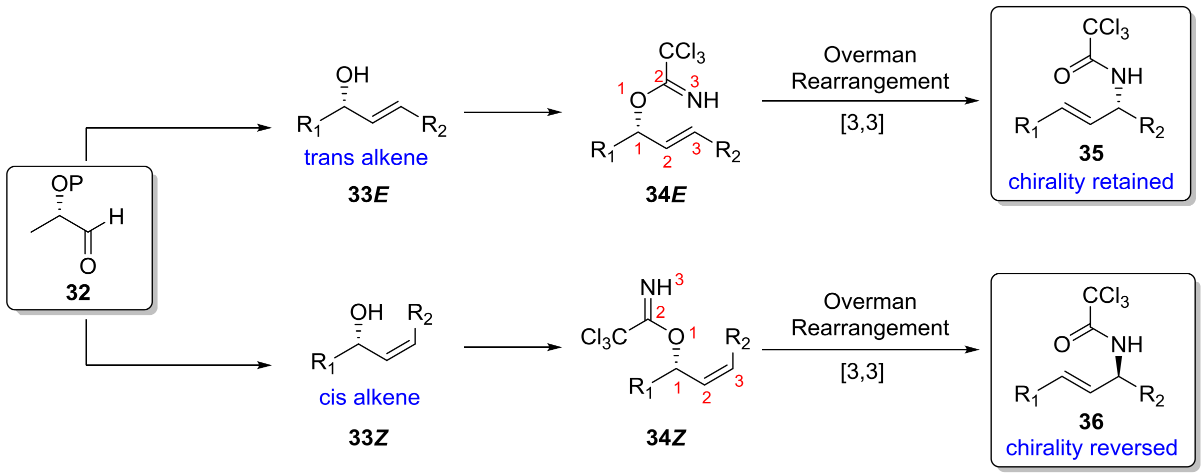


Figure 2.2 Chemical stapling methods for stabilizing the α-helix motif.

2.4 Present work and synthetic planning

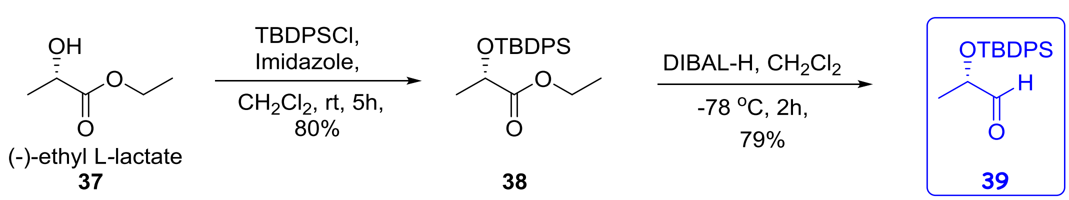
Reported methodologies for the preparation of enantiomeric pairs of nonproteinogenic amino acids are generally employ respective L- and D-amino acid precursors.[18] Enantioselective catalytic method[19] and use of chiral auxillaries[20] have also implied on single achiral precursor to get high *ee*. According to our strategy, synthesis of both enantiomers of δ-unsaturated γ-amino acids is possible from single non-amino acid precursor **32** without using any expensive chiral catalyst or chiral auxiliary. We were inspired by the work of Tanner *et al.*[21] who demonstrated that the suprafacial nature of the rearrangement and chair-like topography can be exploited in the preparation of either enantiomers of an *E*-allylic amine (**35** and its enantiomer **36**) starting from the appropriate enantiomer of the starting from appropriate allylic alcohol **33*E*** and **33*Z*** which is known as self immolative asymmetric approach (scheme 2.8).



Scheme 2.8: Chirality transfer approach for generation of *E*-allylic amine enantiomers.

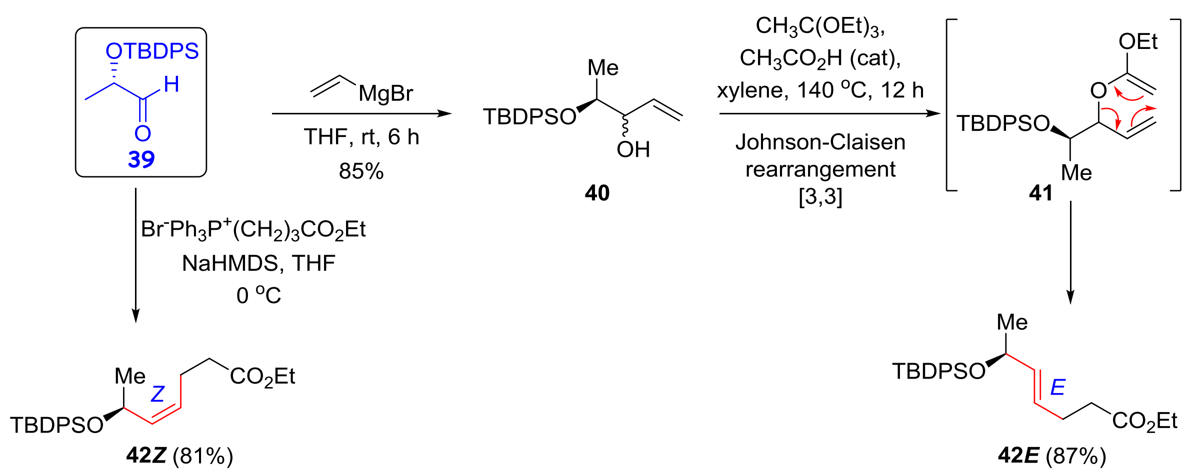
This strategy was envisaged to provide both the enantiomers of allylic amines from a single substrate. A molecular library generation was also planned to establish the versatility of the strategy by the further synthetic modification of the R_1 group. Our next goal was to incorporate the source of carboxylic group at R_2 on the scaffold for constructing the γ-amino acid skeleton.

In order to pursue our goals, we selected TBDPS protected (*S*)-lactaldehyde **39** as a chiral precursor which was prepared from (-) ethyl L-lactate **37** by protecting with TBDPSCl to achieve protected ester **38** followed by reduction with DIBAL-H to obtain aldehyde **39** (Scheme 2.9).[22]



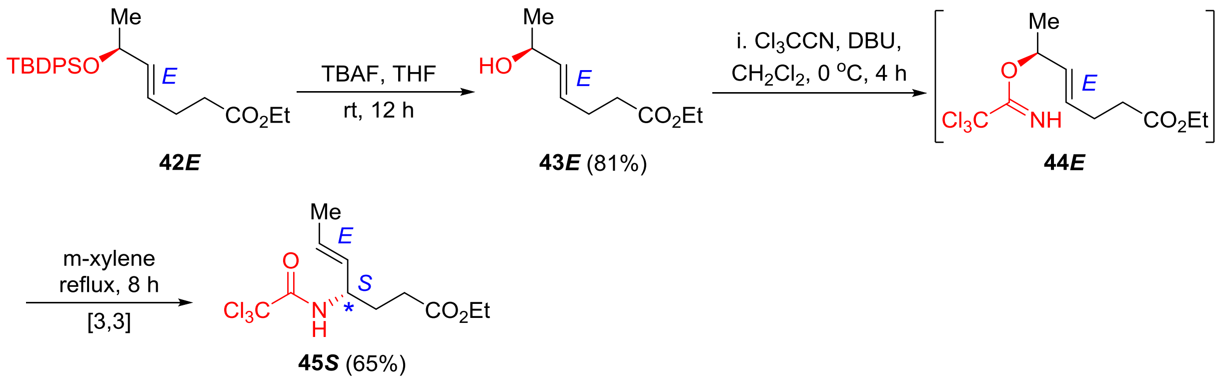
Scheme 2.9: Synthesis of protected lactaldehyde.

In the next stage, we planned to install either *E* or *Z*-allyl alcohol scaffold on the aldehyde **39** for further [3,3]-sigmatropic strategy. At the same time, we also planned to install the protected carboxyl group so the γ-amino acid backbone could be generated after the [3,3]-sigmatropic reaction. The Grignard reaction of **39** with vinylmagnesium bromide resulted in the formation of **40** as a diastereomeric mixture in 85% of yield (scheme 2.10). The diastereomeric mixture was carried forward for the next Johnson-Claisen rearrangement by treating with $CH_3C(OEt)_3$ in presence of catalytic propionic acid to get the adduct **41** which upon [3,3]-sigmatropic rearrangement gave *E*-allyl alcohol ***42E*** as a single stereoisomer in 87% yield. On the other hand, Wittig reaction on **39** following the reported protocol by Perlmutter and co-workers[23] gives the *Z*-allyl alcohol ***42Z*** with *Z*/*E* ratio 94:6. Purification by column chromatography provided the single stereoisomer ***42Z*** with 81% yield (Scheme 2.10).



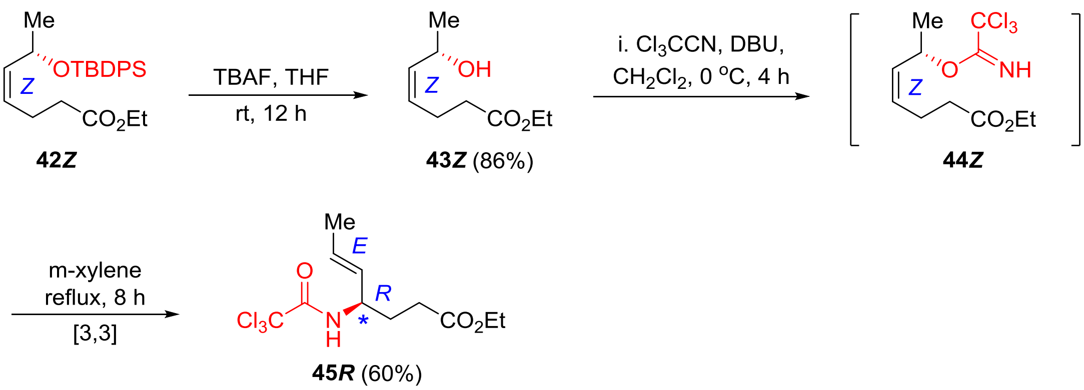
Scheme 2.10: Synthesis of *E*- and *Z*-allylic alcohols.

In the next stage, deprotection of the TBDPS group of ***42E*** using TBAF resulted into (*E*)-allyl alcohol ***43E*** with 81% yield. The conversion of alcohol ***43E*** into corresponding trichloroacetamide was carried out by reacting with Cl_3CCN in presence of 0.6 equivalent of DBU as a base. The crude product ***44E*** was used further without any purification after washing with 2N HCl solution. The obtained trichloroacetamide ***44E*** then refluxed in xylene to carry out Overman rearrangement to obtain allylic trichloroacetamide ***45S*** with 65% yield over two steps. The Overman rearrangement provides the source of amine group at the γ-position (Scheme 2.11).



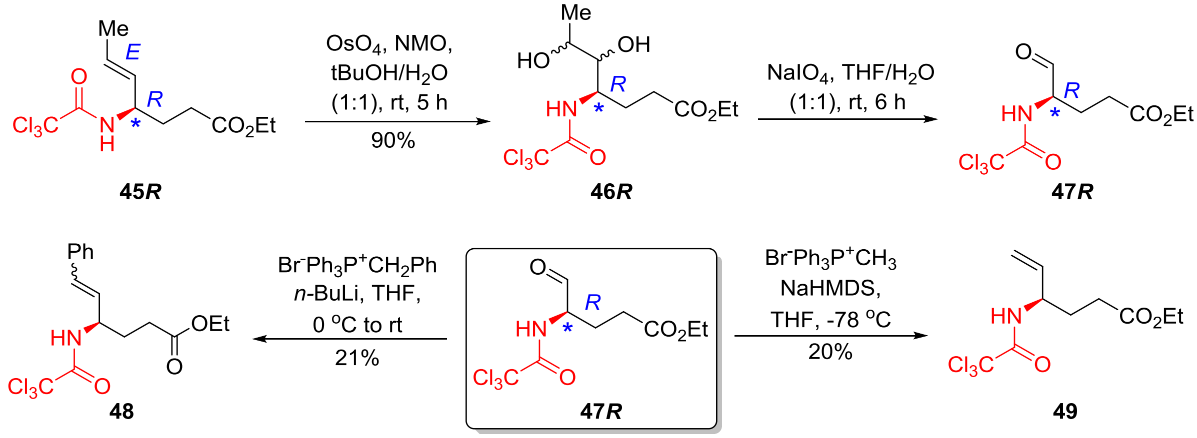
Scheme 2.11: Synthesis of trichloro acetamide **45*S*** by Overman rearrangement.

Similarly, the TBDPS deprotection of **42*Z*** was carried out to obtain (*Z*)-allyl alcohol **43*Z*** with 86% yield. The subsequent protection of **43*Z*** with Cl_3CCN in presence of 0.6 equivalent of DBU gave **44*Z*** which was washed with 2N HCL solution and then refluxed in xylene to carry out Overman rearrangement to obtain allylic trichloro acetamide **45*R*** with 60% yield over two steps (Scheme 2.12).



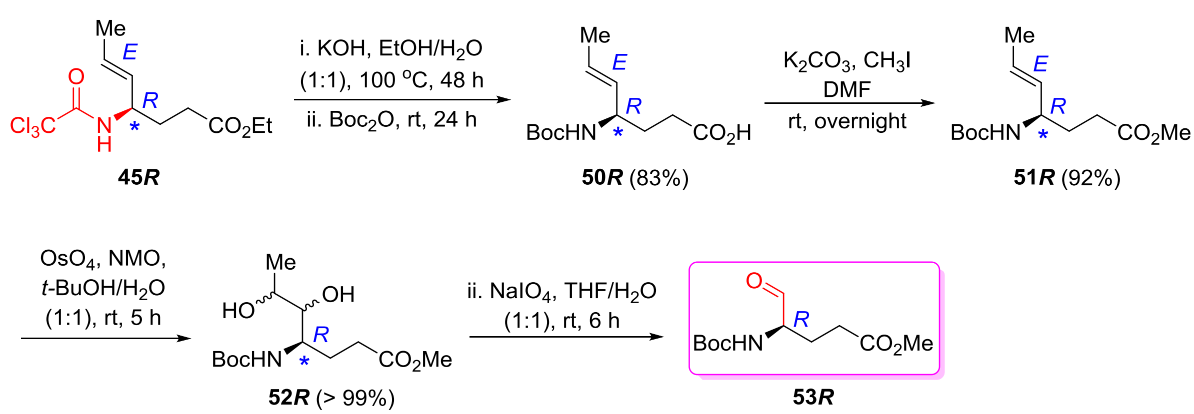
Scheme 2.12: Synthesis of trichloro acetamide **4R*S*** by Overman rearrangement.

Subsequently, the dihydroxylation of **45*R*** was carried out using OsO_4 and NMO in *t*BuOH and water mixture to afford dihydroxylated compound **46*R*** which was cleaved using $NaIO_4$ to get aldehyde **47*R*.** We planned for the construction of library of compounds using aldehyde **46*R*** as a key intermediate for the different Wittig reactions. But when we carried out the Wittig reactions using several conditions we found out that the yields were poor. The Wittig reaction of **46*R*** with methyl Wittig ylide gave **49** with 20% yield and the Wittig reaction of **46*R*** with benzyl Wittig ylide gave **48** with 21% yield (Scheme 2.13). The trichloro acetamide group on nitrogen might be playing role in getting lower yields. Therefore, we decided to replace the trichloroacetamide group with Boc to bring the orthogonality in molecule.



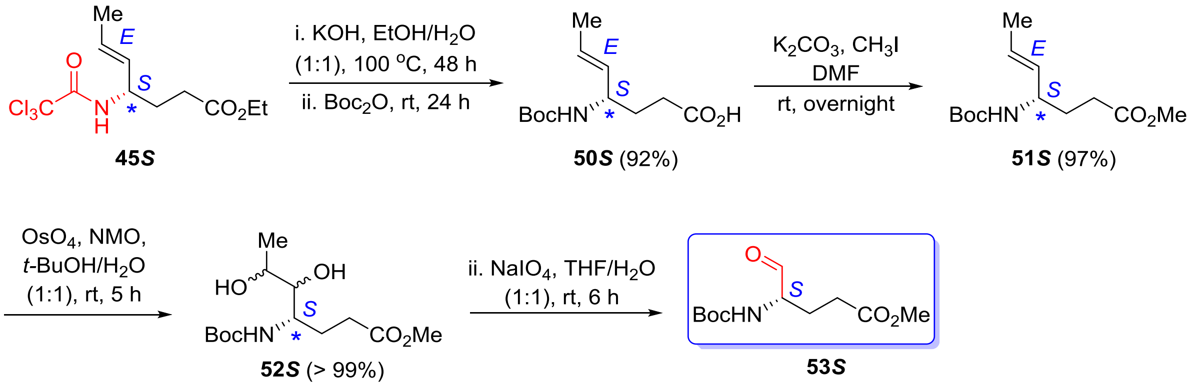
Scheme 2.13: Synthesis and Wittig reactions of aldehyde **47R**.

But the selective deprotection of trichloro acetamide group of either **45*R*** or **45*S*** could not be achieved. Basic hydrolysis of **45*R*** with KOH in ethanol:water mixture resulted in the deprotection of trichloro acetamide along with the hydrolysis of the ester group. Further one pot protection of amino group with Boc-anhydride gave **50*R*** with 83% yield. The consequent esterification of acid **50*R*** with methyl iodide gave methyl esters **51*R*** with 92% yield. The dihydroxylation of **51*R*** afforded **52*R*** with more than 99% yield and subjected for diol cleavage using $NaIO_4$ to achieve the enantiomerically pure aldehyde **53*R*** which was carried forward without any purification (Scheme 2.14).



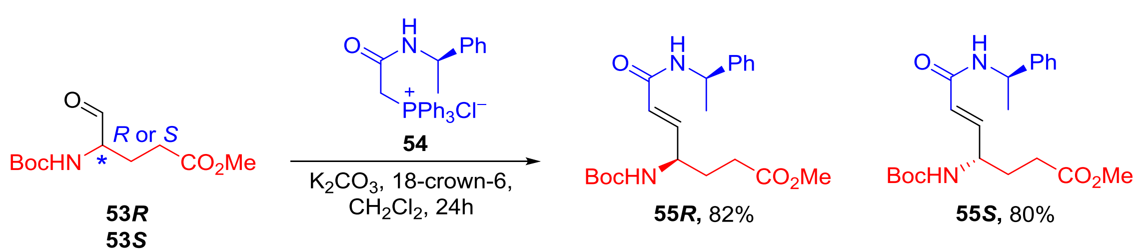
Scheme 2.14: Synthesis of aldehydes **53*R***.

Similarly, the basic hydrolysis of **45*S*** with KOH in ethanol:water mixture followed by in situ Boc protection provided **50*S*** with 92% yield. The consequent esterification with methyl iodide gave methyl esters **51*S*** with 97% yield. The dihydroxylation of **51*S*** afforded **52*S*** with more than 99% yield and subjected for diol cleavage using $NaIO_4$ to achieve aldehyde **53*S*** which was carried forward without any purification (Scheme 2.15).



Scheme 2.15: Synthesis of aldehyde **53*S***.

Further, the library of δ-unsaturated γ-amino acids was generated from the enantiomeric pair of aldehydes **53*R*** and **53*S*** by using diversity-oriented synthesis. The Wittig reaction of **53*R*** and **53*S*** with chiral ylide **54** in presence of K_2CO_3 and catalytic 18-crown-6 in CH_2Cl_2 under reflux condition provided the corresponding olefin **55*R*** and **55*S*** with complete *E*-selectivity and 82, 80% of yield respectively (Scheme 2.16). HPLC analysis of the compound **55*R*** provided the diastereomeric ratio (*dr*) of 97:3 indicating the diastereomeric excess (*de*) of 94%. Similarly, after injecting the enantiomer **55*S***, no isomeric product, epimeric at C_γ-position was found, indicating > 99% of diastereomeric excess (*de*) (Figure 2.7). The HPLC data of **55*R*** and **55*S*** confirmed that no significant racemization occurred during either the Overman rearrangement or Wittig reaction.

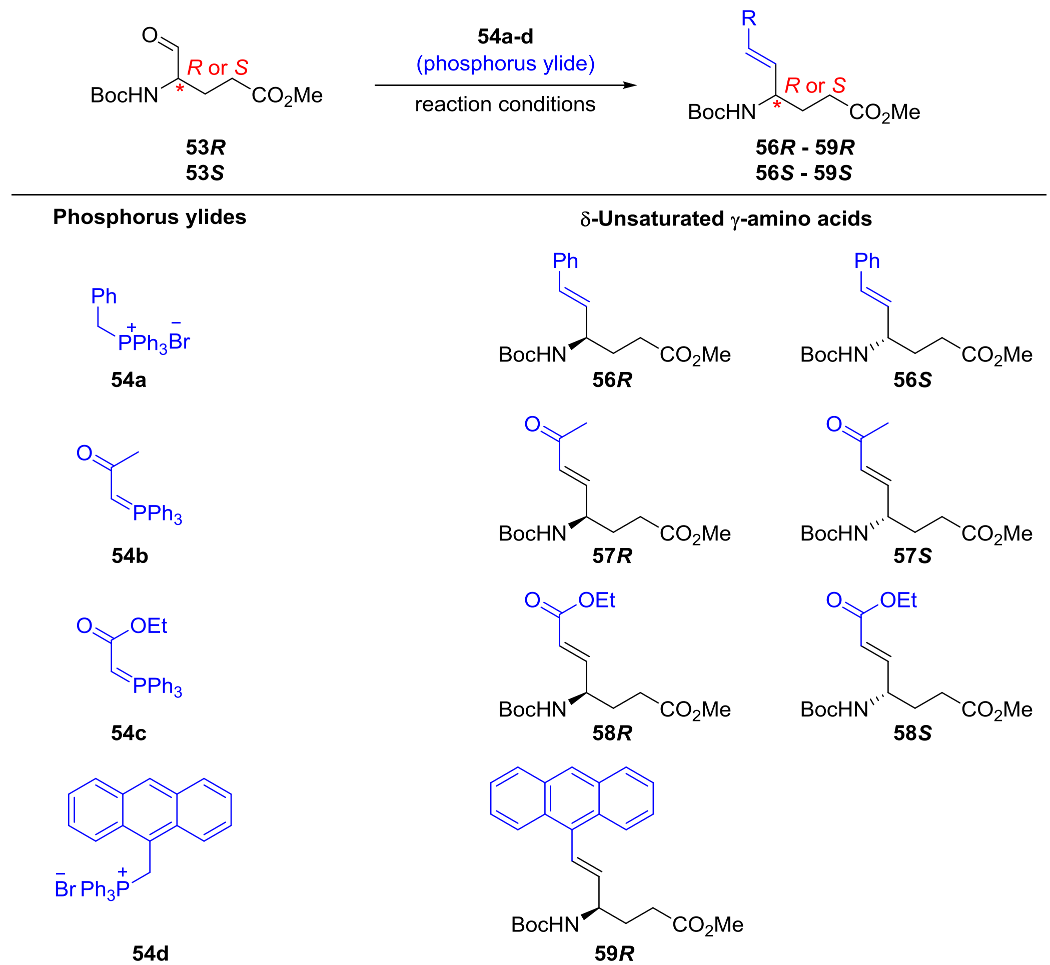


Scheme 2.16: Wittig reaction on enantiomeric pair of aldehydes **53*R*** and **53*S*** with chiral Wittig salt **54**.

Later, these both enantiomeric aldehydes **53*R*** and **53*S*** were subjected to Wittig reactions using different Wittig ylides. The treatment of ylide **54a** with **53*R*** and **53*S*** independently under mild basic condition in presence of K_2CO_3 and catalytic 18-crown-6 on reflux in dichloromethane gave the enantiomeric pair of δ-unsaturated γ-amino acids **56*R*** and **56*S*** with 78, 82% of yields respectively (Table 2.1, entry 1). The ylide **54b** on refluxing in THF with aldehydes **53*R*** and **53*S*** independently afforded **57*R*** and **57*S*** with 83 and 84% yield respectively (Table 2.1, entry 2). Similarly, the ylide **54c** was refluxed with aldehydes **53*R*** and **53*S*** independently to obtain **58*R*** and **58*S*** with 87 and 82% yield respectively (Table 2.1, entry 3).

More recently, attention has focused on the development of unnatural amino acids that possess solvate-chromic fluorophores as the side chain group. The fluorescent amino acids, many of which are of similar size to tryptophan, have been incorporated into biologically active peptides and proteins and used for studying biological structure and function and for visualizing intracellular processes. These kinds of proteins or peptides derived from fluorescent amino acids can be used as a powerful tool for investigating receptor-ligand binding, and enzyme activity in vitro as well as in vivo. Considering the importance of fluorescent amino acids we envisaged to synthesize fluorescent γ-amino acid. We treated the aldehyde **53*R*** with anthracene derived fluorescent Wittig salt **54d** under mild basic condition using K_2CO_3, and catalytic 18-crown-6 and refluxed in dichloromethane for 3 hours to obtain fluorescent γ-amino acid **59*R*** with 69% of yield (Table 2.1, entry 4).

Table 2.1: Reaction conditions for Wittig olefinations with various ylides.



Entry	Substrate	Ylide	Condition	Time (h)	Product	Yield[a] (%)
1	***53R*, 53*S***	**54a**	K_2CO_3, 18-crown-6, CH_2Cl_2, reflux	6	***56R*, 56*S***	78, 82
2	***53R*, 53*S***	**54b**	THF, reflux	24	***57R*, 57*S***	83, 84
3	***53R*, 53*S***	**54c**	THF, rt	4	***58R*, 58*S***	87, 82
4	**53*R***	**54d**	K_2CO_3, 18-crown-6, CH_2Cl_2, reflux	3	**59*R***	69

[a] Yields were calculated with respect to either **53*R*** or **53*S*** over two steps.

Cell permeability of amino acid **59*R*** was demonstrated by the fluorescence microscopic imaging using HeLa cells. When cells were incubated with **59*R*** (100 mM in 1 : 200 DMSO–DMEM v/v, pH = 7.4) at 37 ^{o}C for 30 min, strong fluorescence was observed (Figure 2.3).

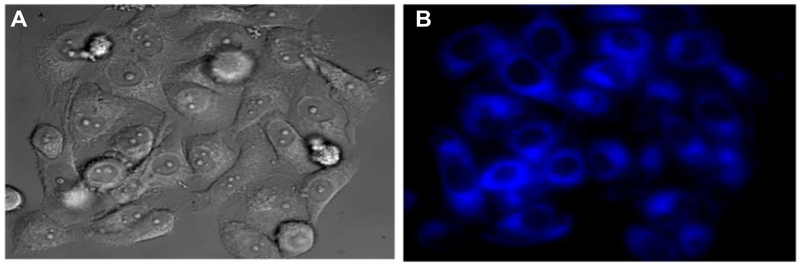


Figure 2.3: Transmission (A) and fluorescence (B) images of HeLa cells.

2.5 Conclusion:

In summary, we have developed an enantiodivergent strategy for the synthesis of both enantiomers of δ-unsaturated γ-amino acids with excellent *ee*. The methodology involves two kinds [3,3]-sigmatropic rearrangement, Johnson-Claisen rearrangement for the preparation of *E*-allylic alcohol and Overman rearrangement for the generation of opposite stereocentres starting from *E*- and *Z*-allylic alcohols. A library of (*E*)-δ-unsaturated γ-amino acid derivatives and their enantiomers were obtained via the Wittig reaction of intermediate pairs of chiral aldehydes. The methodology also highlights the formation of a fluorescent δ-unsaturated γ-amino acid. Cell permeability of the amino acid was demonstrated. Saturated γ^4-amino acids were synthesized by catalytic hydrogenation of corresponding δ-unsaturated γ-amino acids with the excellent yields.

2.6 Experimental Section

General Methods.

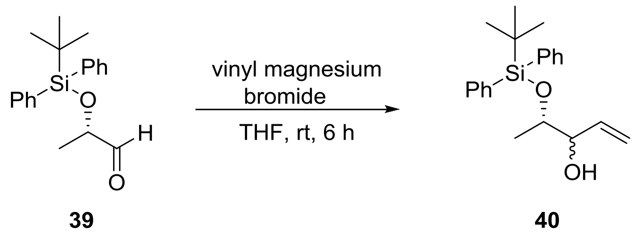
All the chemicals were purchased from commercial sources and used as received unless stated otherwise. Solvents: petroleum ether and ethyl acetate (EtOAc) were distilled prior to thin layer and column chromatography. THF and *m*-xylene were pre-dried over Na wire. Then each of the solvents was refluxed over Na (1% w/v) and benzophenone (0.2% w/v) under an inert atmosphere until the blue color of the benzophenone ketyl radical anion persists. Methylene chloride (DCM) was pre-dried over calcium hydride and then distilled. *N*, *N*-Dimethylformamide (DMF) was pre-dried over calcium hydride and then distilled under vacuum. Column chromatography was performed on silica gel (100–200 mesh). TLC was carried out with silica gel 60-F_{254} plates. All air and water sensitive reactions were performed under nitrogen atmosphere. Crystal structures were recorded on a single crystal X-Ray diffractometer. HPLC for determining diastereomeric excess was performed on a High-Performance Liquid Chromatography (HPLC) instrument using a reverse phase column.

Physical Measurements

The ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz (or 100 MHz for ^{13}C) spectrometers using either residual solvent signals as an internal reference or from internal tetramethylsilane on the δ scale ($CDCl_3$ δ_H 7.24 ppm, δ_C 77.0 ppm, CD_3OD δ_H 3.31 ppm, δ_C 49.0 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). High-resolution mass spectra were obtained from ESI-TOF MS spectrometer. (FT-IR) spectra were obtained using FT-IR spectrophotometer as KBr disc and reported in cm^{-1}. All melting points were measured in open glass capillary and values are uncorrected. The fluorescence images were taken on a confocal fluorescence microscope.

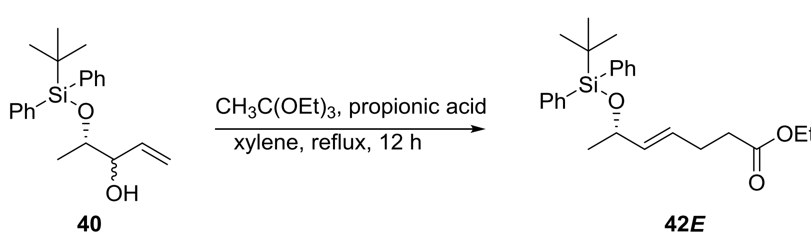
2.6.1 Experimental Procedures:

Synthesis of (4*S*)-4-((tert-butyldiphenylsilyl) oxy) pent-1-en-3-ol [$C_{21}H_{28}O_2Si$] (40):



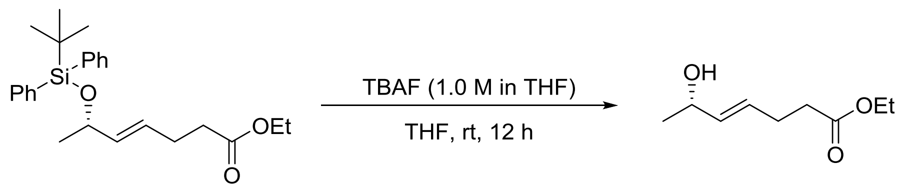
A 250 mL round bottom flask containing a solution of aldehyde **39** (8.0 g, 25.6 mmol) in THF (80 mL) was cooled to 0 °C in an ice bath. To this solution was added dropwise the vinyl magnesium bromide (31.0 mL, 1.0 M in THF, 30.7 mmol) at 0 ^oC. After stirring for 6 h at room temperature, the reaction mixture was evaporated under reduced pressure. The residue was partitioned between EtOAc and H_2O. The organic layer was dried over Na_2SO_4 and concentrated to afford a residual oil, which was chromatographed on silica gel with petroleum ether / EtOAc (20:1) to afford the diastereomeric mixture of allylic alcohol **40** (7.4 g, 85%) as colorless oil. IR (Neat): ν_{max}/cm^{-1} 3744, 2933, 2891, 2859, 1466, 1426, 1383, 1103; ^1H NMR (400 MHz, $CDCl_3$): Major isomer: 7.64 – 7.70 (m, 4H), 7.36 – 7.45 (m, 6H), 5.70 – 5.83 (m, 1H), 5.12 – 5.22 (m, 1H), 4.05 – 4.06 (m, 1H), 3.86 – 3.93 (m, 1H), 3.77 (q, *J* = 6.4 Hz, 1H), 2.34 (d, *J* = 3.7 Hz, 1H), 1.07 (s, 9H), 0.98 (s, 3H); minor isomer: 7.64 – 7.70 (m, 4H), 7.36 – 7.45 (m, 6H), 5.70 – 5.83 (m, 1H), 5.28 – 5.34 (m, 1H), 5.12 – 5.22 (m, 2H), 2.57 (d, *J* = 4.6 Hz, 1H), 1.05 (s, 9H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):137.53, 136.4, 136.0, 135.9, 134.0, 133.4, 130.0, 129.9, 127.9, 127.7, 127.6, 116.9, 116.6, 73.0, 72.5, 27.1, 19.6, 19.5, 19.4, 17.1; HRMS (ESI): Calc. for $C_{21}H_{28}NaO_2Si$ $[M+Na]^+$: 363.1756; Found: 363.1758.

Synthesis of (*S*, *E*)-ethyl 6-((tert-butyldiphenylsilyl)oxy)hept-4-enoate [$C_{25}H_{34}O_3Si$] (42*E*):



To a 50 mL round bottom flask containing a solution of allylic alcohol **40** (900 mg, 2.64 mmol) in *m*-xylene (15 mL) were added triethyl orthopropionate (4.9 mL, 26.4 mmol) and propionic acid (25 µL, 0.3 mmol) at room temperature. After stirring at 140 ^oC for 12 h, the reaction mixture was evaporated under reduced pressure. The crude product was chromatographed on silica gel with petroleum ether/ethyl acetate (96:4) to give ester **42*E*** (1.3 g, 87%) as colorless oil. IR (Neat): ν_{max}/cm^{-1}: 3398, 1732, 1728; ^{1}H NMR (400 MHz, $CDCl_3$): 7.63 – 7.68 (m, 4H), 7.32 – 7.43 (m, 6H), 5.46 (ddd, *J* = 1.1, 6.0, 15.3 Hz, 1H), 5.32 – 5.38 (m, 1H), 4.23 (quintet, *J* = 6.2, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.16 – 2.31 (m, 4H), 2.13 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.2, 136.0, 135.9, 135.5, 134.7, 134.4, 129.6, 129.5, 127.5, 127.4, 127.3, 70.2, 60.4, 34.0, 27.4, 27.1, 24.5, 19.3, 17.7; $[\alpha]^{24}_D$ = - 8.2 (*c* = 1.0, $CHCl_3$); HRMS (ESI): Calc. for $C_{25}H_{34}NaO_3Si$ $[M+Na]^+$: 433.2175; Found: 433.2129.

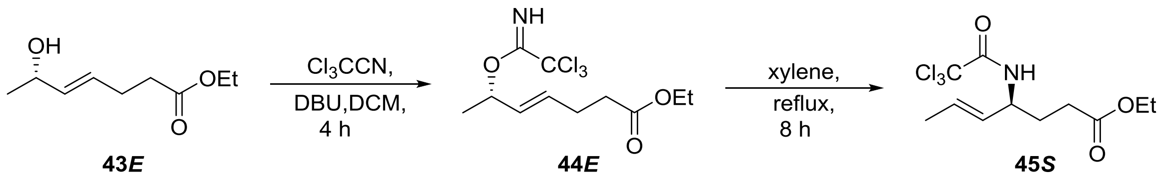
Synthesis of (*S*, *E*)-ethyl 6-hydroxyhept-4-enoate [$C_9H_{16}O_3$] (43*E*):[24]



42*E* **43*E***

To a 500 mL round bottom flask containing THF (200 mL) were added ester **42*E*** (22.0 g, 53.6 mmol) and Tetrabutylammonium fluoride ($Bu_4N^+F^-$) (64.0 mL, 1.0 M in THF, 64 mmol). The solution was stirred at room temperature for 12 h and evaporated under reduced pressure. The thick oil was poured into H_2O. The product was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford a residual oil, which was chromatographed on silica gel with petroleum ether / EtOAc (from 10:1 to 2:1) to afford allylic alcohol **43*E*** (7.5 g, 81 %). IR (Neat): ν_{max}/cm^{-1} 3441, 2976, 1726, 1449, 1372, 1342, 1249, 1166, 1140, 1099, 1059; ^{1}H NMR (400 MHz, $CDCl_3$): 5.63 – 5.49 (m, 2H), 4.22 (quintet, *J* = 6.1 Hz, 1H), 4.12 – 4.06 (m, 2H), 2.37 – 2.30 (m, 4H), 1.88 (br s, 1H), 1.25 – 1.19 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.1, 135.5, 128.4, 68.6, 60.4, 33.9, 27.4, 23.4, 14.3; $[\alpha]^{24}_D$ = + 3.92 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_9H_{16}NNaO_3$ $[M+Na]^+$: 195.0917; Found: 195.0973.

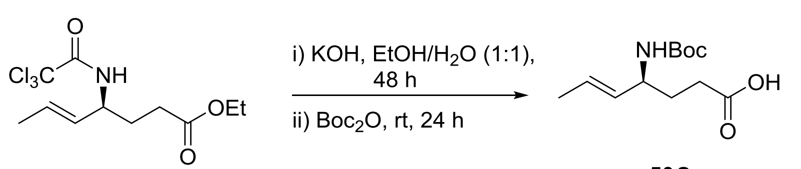
Synthesis of (*R*, *E*)-ethyl 4-(2, 2, 2-trichloroacetamido)hept-5-enoate [$C_{11}H_{16}Cl_3NO_3$] (45*S*):



43*E* **44*E*** **45*S***

A 50 mL round bottom flask containing a solution of allylic alcohol **43*E*** (500 mg, 2.9 mmol) in DCM (10 mL) was cooled to 0°C in an ice bath. To the solution were added DBU (260 µL, 1.74 mmol) and Cl_3CN (349 µL, 3.48 mmol) over period of 15 min. After stirring at 0°C for 1 h, the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5% Aqueous HCl solution (2 mL). The organic layer was evaporated under reduced pressure to give crude trichloroacetimidate intermediate **44*E***, which was used for the next step without any purification. The crude imidate was dissolved in dry *m*-xylene (20 mL). The mixture was heated at reflux temperature for 8 h. After cooling to rt, the mixture was evaporated in vacuo. The residue was chromatographed on silica gel with petroleum ether/EtOAc (9:1) to give trichloroacetamide **45*S*** (555 mg, 65% over 2 steps) as yellow oil. IR (Neat): ν_{max}/cm^{-1} 3333, 2980, 1697, 1514, 1446, 1375, 1338, 1173, 1099, 1068, 1028; ^{1}H NMR (400 MHz, $CDCl_3$): 6.96 (d, *J* = 3.1 Hz, 1H), 5.74 – 5.65 (m, 1H), 5.39 – 5.34 (m, 1H), 4.34 (quintet, *J* = 5.8 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.46 – 2.30 (m, 2H), 1.94 (q, *J* = 7.1 Hz, 2H), 1.74 – 1.68 (m, 3H), 1.27 – 1.21 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 161.2, 128.6 (2C), 92.7, 60.8, 53.2, 30.6, 29.1, 17.8, 14.1; $[\alpha]^{24}_D$ = + 6.4 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{11}H_{16}Cl_3NNaO_3$ $[M+Na]^+$: 338.0093; Found: 338.0120.

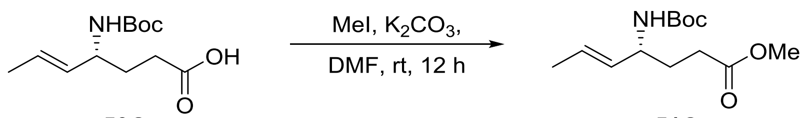
Synthesis of (*R*, *E*)-4-((tert-butoxycarbonyl)amino)hept-5-enoic acid [$C_{12}H_{21}NO_4$] (50*S*):



45*S* **50*S***

To a 100 mL round bottom flask containing a solution of trichloroacetamide **45*S*** (2.0 g, 17.0 mmol) in ethanol: H_2O (1:1) (40 mL) was added KOH (2.0 g, 17.0 mmol) and heated at 100°C for 48 h. Then reaction mixture was allowed to cool at room temperature. Then BOC anhydride (2.0 g, 17.0 mmol) was added to the reaction mixture and stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was evaporated under reduced pressure to remove ethanol and acidified with 6 N HCl. The aqueous solution was extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to afford an acid **50*S*** (1.3 g, 83%) as off white solid. M.p. = 88 – 89 °C; IR (Neat): ν_{max}/cm^{-1} 3362, 2983, 1711, 1682, 1515, 1445, 1411, 1392, 1369, 1307, 1289, 1238, 1168, 1049; ^1H NMR (400 MHz, $CDCl_3$): 5.57 – 5.63 (m, 1H), 5.28 – 5.34 (m, 1H), 4.50 (br s, 1H), 4.05 (br s, 1H), 2.37 (t, *J* = 7.4 Hz, 2H), 1.74 – 1.85 (m, 2H), 1.65 – 1.67 (m, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 178.6, 155.6, 130.9, 126.9, 79.6, 51.9, 30.8, 30.4, 28.4 (3C), 17.7; $[\alpha]^{24}_D$ = + 10.4 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{12}H_{21}NNaO_4$ $[M+Na]^+$: 266.1368; Found: 266.1363.

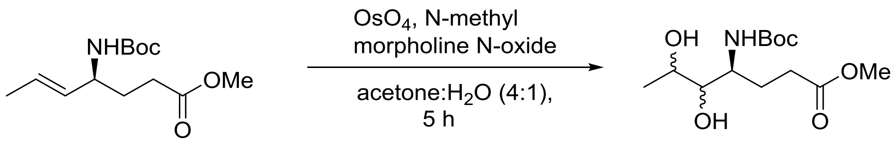
Synthesis of (*R*, *E*)-methyl 4-((tert-butoxycarbonyl) amino) hept-5-enoate [$C_{13}H_{23}NO_4$] (51*S*):



50*S* **51*S***

To a 25 mL round bottom flask containing a solution of the acid **50*S*** (600 mg, 2.47 mmol) in DMF (5 mL) were added K_2CO_3 (340 mg, 2.47 mmol) and MeI (0.62 mL, 9.88 mmol). The resulting solution was stirred at room temperature for 12 h and poured into H_2O. The product was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford a residual oil, which was chromatographed on silica gel with petroleum ether / EtOAc (from 10:1 to 2:1) to afford ester **51*S*** (580 mg, 92 %) as yellow oil. IR (KBr): ν_{max}/cm^{-1} 3366, 2986, 1706, 1678, 1519, 1449, 1390, 1281, 1161; ^1H NMR (400 MHz, $CDCl_3$): 5.64 – 5.55 (m, 1H), 5.32 (dd, *J* = 7.5, 3.2 Hz, 1H), 4.49 (br s, 1H), 4.03 (br s, 1H), 3.68 – 3.65 (m, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.83 – 1.78 (m, 2H), 1.67 (d, *J* = 6.5 Hz, 3H), 1.44 – 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 174.0, 155.4, 131.1, 126.7, 79.3, 52.0, 1.7, 30.7, 30.5, 28.4 (3C), 17.7; $[\alpha]^{24}_D$ = + 3.0 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{13}H_{23}NNaO_4$ $[M+Na]^+$: 280.1525; Found: 280.1533.

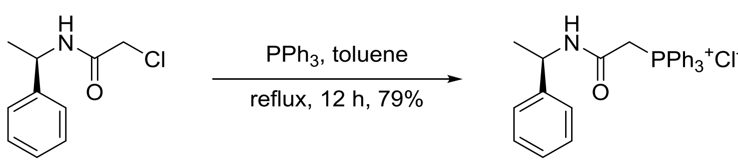
Synthesis of (4*R*)-methyl4-((tert-butoxycarbonyl)amino)-5,6-dihydroxyheptanoate [$C_{13}H_{25}NO_6$] (52*R*):



51*S* **52*S***

A 50 mL round bottom flask containing a solution of olefin **51*S*** (100 mg, 0.31 mmol) in acetone:H_2O (4:1) (5 mL) was cooled to 0°C in an ice bath. To the solution were added NMO (50% aq. solution, 128 μL, 0.47 mmol), OsO_4 (1 mg) were added and the reaction mixture was stirred at room temperature for 5 h. Reaction mixture was evaporated to remove acetone and then diluted with H_2O (4.0 mL). The product was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a residual oil, which was chromatographed on silica gel with petroleum ether / EtOAc (from 3:7) to afford diol **52*S*** (112 mg, > 99 %). IR (Neat): ν_{max}/cm^{-1} 3362, 2978, 1714, 1682, 1520, 1454, 1418, 1392, 1366, 1247, 1164, 1050,1019; ^{1}H NMR (400 MHz, $CDCl_3$): 4.79 – 4.89 (m, 2H), 3.84 – 4.01 (m, 2H), 3.68 – 3.69 (m, 6H), 3.41 – 3.50 (m, 2H), 3.03 (t, *J* = 4.6 Hz, 1H), 2.35 – 2.49 (m, 5H), 2.19 – 2.78 (m, 1H), 1.85 – 1.92 (m, 2H), 1.65 – 1.73 (m, 7H), 1.42 – 1.43 (m, 19H), 1.22 – 1.25 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$):174.5, 157.3, 156.3, 85.1, 80.4, 79.6, 69.7, 66.2, 52.9, 51.9, 51.0, 31.0, 30.7, 28.4, 26.1, 19.2, 19.0; HRMS (ESI): Calc. for $C_{13}H_{25}NNaO_6$ $[M+Na]^+$: 314.1580; Found: 314.1581.

Synthesis of (*R*)-2-(chlorotriphenylphosphoranyl)-N-(1-phenylethyl) acetamide [$C_{28}H_{27}ClNOP$] (54):

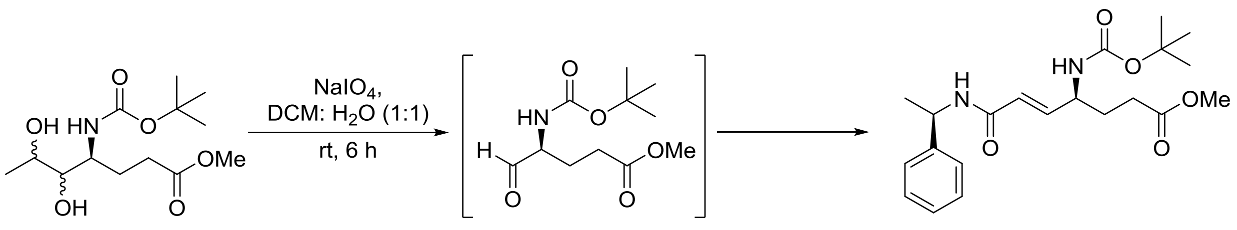


54' **54**

To a 50 mL round bottom flask containing a solution of (*R*)-2-chloro-*N*-(1-phenylethyl) acetamide **54′** (1.0 g, 5.08 mmol) in Toluene (20 mL) was added PPh_3 (1.6 g, 6.09 mmol). The reaction mixture was refluxed for 12 h. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel ($CHCl_3$ /MeOH 9:1) to afford the corresponding Wittig salt **54** (1.7 g, 79 %) as white solid M.p. = 213 – 214 ^{o}C; IR (Neat): ν_{max}/cm^{-1} 3183, 2993, 2819, 2755, 1660, 1563, 1538, 1485, 1438, 1327, 1104; ^{1}H NMR (400 MHz, CD_3OD): 7.63 – 7.84 (m, 15H), 7.15 – 7.31 (m, 5H), 4.85 (s, 3H), 4.80 (q, *J* = 6.8

Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): 162.1, 142.9, 134.9, 133.8, 133.7, 130.0, 129.9, 128.3, 127.0, 125.9, 119.1, 118.2, 49.7, 47.0, 20.9; HRMS (ESI): Calc. for $C_{28}H_{27}NOPPh_3^+$ [M- Cl]$^+$: 424.1825; Found: 424.1831.

Synthesis of (*S*, *E*)-methyl 4-((tert-butoxycarbonyl)amino)-7-oxo-7-(((*R*)-1-phenylethyl)amino)hept-5-enoate [$C_{21}H_{30}N_2O_5$] (55*S*):

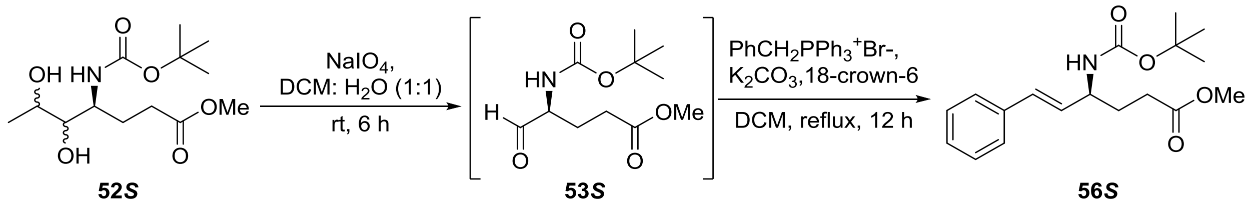


52*S* **53*S*** **55*S***

A 50 mL round bottom flask containing a solution of diol **52*S*** (350 mg, 1.20 mmol) in DCM: H_2O (4:1) (30 mL) was cooled to 0°C in an ice bath. To the reaction mixture $NaIO_4$ (390 mg, 1.80 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in DCM (8 mL) was added wittig salt **54** (610 mg, 1.44 mmol) and the reaction mixture was refluxed for 6 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 9:1) to afford the corresponding unsaturated compound **55*S*** (380 mg, 82 %) as white solid. M.p. = 160 – 161 ^oC; IR (Neat): ν_{max}/cm^{-1} 3344, 2982, 1734, 1679, 1633, 1523, 1448, 1368, 1302, 1255, 1166, 1047, 1016; ^{1}H NMR (400 MHz, $CDCl_3$): 7.33 (s, 5H), 6.68 (dd, *J* = 15.0, 7.0, Hz, 1H), 5.89 (dd, *J* =15.0, 1.1 Hz, 1H), 5.80 (br s, 1H), 5.19 (quintet, *J* = 7.2 Hz, 1H), 4.64 (br s, 1H), 4.27 (br s, 1H), 3.66 (s, 3H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.81 – 1.95 (m, 2H), 1.53 (d, *J* = 6.9 Hz, 3H),1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.6, 164.3, 155.3, 143.3, 143.0, 128.8, 127.5, 126.4, 124.1, 79.9, 51.9, 51.2, 48.9, 30.5, 29.6, 28.5 (3C), 21.7; HRMS (ESI): Calc. for $C_{21}H_{30}N_2NaO_5$ [M+Na]$^+$: 413.2052; Found: 413.2056; HPLC: CHIRALPAK IC column (2-Propanol: *n*-Hexane = 10:90, flow rate 1.0 mL/min, λ = 250 nm). Retention time (min): 26.79 (major), *de* 100%. (Figure 2.7).

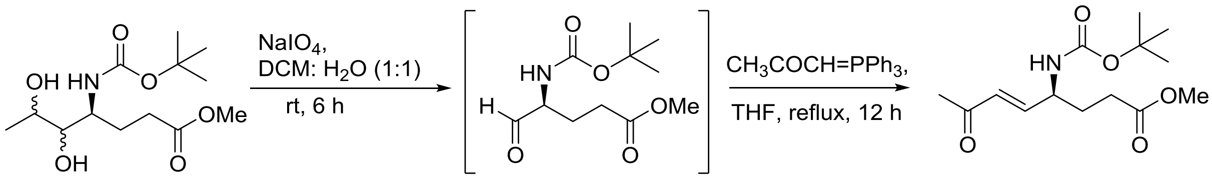
Synthesis of (*S*)-methyl 4-((tert-butoxycarbonyl) amino)-6-phenylhex-5-enoate [$C_{18}H_{25}NO_4$] (56*S*):



A 25 mL round bottom flask containing a solution of diol **52*S*** (200 mg, 0.69 mmol) in DCM: H_2O (8 mL) was cooled to 0°C in an ice bath. To the reaction mixture $NaIO_4$ (220 mg, 1.03 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde **53*S*** which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in DCM (10 mL) were added phosphonium salt of $[PhCH_2PPh_3]^+Br^-$ **54a** (300 mg, 0.69 mmol), potassium carbonate (100 mg, 0.76 mmol) and 18-crown-6 (33 mg, 0.12 mmol) and the reaction mixture was refluxed for 12 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 9:1) to afford the corresponding unsaturated compound **56*S*** (170 mg, 82%) as white solid. M.p. = 86 – 87 °C; IR (Neat): ν_{max}/cm^{-1} 3334, 2973, 1679, 1522, 1420, 1351, 1149; ^1H NMR (400 MHz, $CDCl_3$): 7.21 – 7.35 (m, 5H), 6.52 (d, *J* = 15.8 Hz, 1H), 6.07 (dd, *J* = 15.9, 6.2 Hz, 1H), 4.61 (br s, 1H), 4.29 (br s, 1H), 3.65 (s, 3H), 2.42 (t, *J* = 14.9 Hz, 2H), 1.91 – 1.98 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.9, 155.4, 136.6, 130.7, 129.6, 128.8, 127.8, 126.5, 79.6, 51.8, 30.8, 30.5, 28.5 (3C); $[\alpha]^{24}_D$ = + 16.2 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{21}H_{16}NNaO$ $[M+Na]^+$: 342.1681; Found: 342.1681.

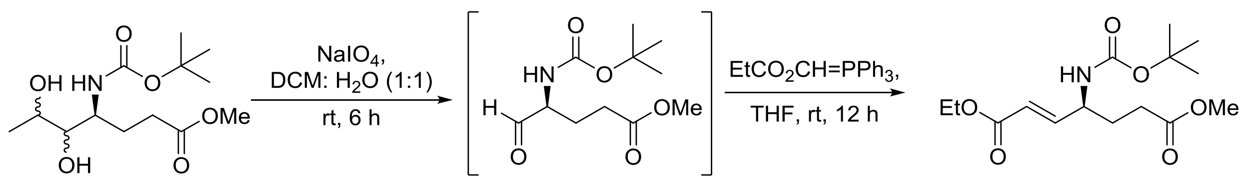
Synthesis of (*S*, *E*)-methyl 4-((tert-butoxycarbonyl) amino)-7-oxooct-5-enoate [$C_{14}H_{23}NO_5$] (57*S*):



A 25 mL round bottom flask containing a solution of diol **52*S*** (150 mg, 0.51 mmol) in DCM: H_2O (6 mL) was cooled to 0°C in an ice bath. To the reaction mixture $NaIO_4$ (170 mg, 0.76 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde **53*S*** in THF (8 mL) was added methylcarbonylmethylenephosphorane ($CH_3COCHPPh_3$) **54b** (160 mg, 0.51 mmol) and the reaction mixture was refluxed for 12 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 8:2) to afford the corresponding unsaturated compound **57*S*** (130 mg, 84 %) as pink colored oil. IR (Neat): ν_{max}/cm^{-1} 3744, 2977, 1680, 1515, 1444, 1363, 1247, 1161, 1051, 1022; ^1H NMR (400 MHz, $CDCl_3$): 6.66 (d, *J* = 15.7 Hz, 1H), 6.17 (d, *J* = 15.7 Hz, 1H), 4.66 (br s, 1H), 4.33 (br s, 1H), 3.67 (s, 3H), 2.42 – 2.39 (m, 2H), 2.25 (s, 3H), 1.97 (br s, 1H), 1.82 (br s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 198.3, 173.5, 155.2, 146.5, 130.0, 80.1, 52.0, 51.2, 30.5, 29.4, 28.4 (3C), 27.5; $[\alpha]^{24}_D$ = + 12.32 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{21}H_{16}NNaO$ $[M+Na]^+$: 308.1474; Found: 308.1475.

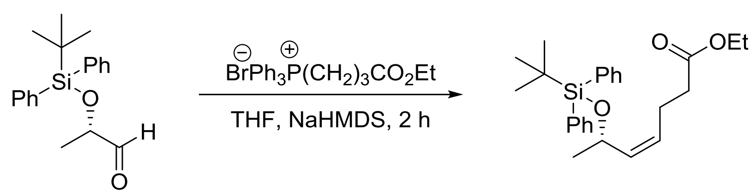
Synthesis of (*S*, *E*)-1-ethyl7-methyl4-((tert-butoxycarbonyl)amino)hept-2-enedioate [$C_{15}H_{25}NO_6$] (58*S*):



A 25 mL round bottom flask containing a solution of diol **52*S*** (200 mg, 0.69 mmol) in DCM: H_2O (8 mL) was cooled to 0°C in an ice bath. To the reaction mixture $NaIO_4$ (220 mg, 1.03 mmol) was added and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in DCM (8 mL) was added ethoxycarbonylmethylenephosphorane ($EtO_2CCHPPh_3$) **54c** (280 mg, 0.82 mmol) and the reaction mixture was refluxed for 12 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 9:1) to afford the corresponding unsaturated compound **58*S*** (140 mg, 87%). IR (Neat): ν_{max}/cm^{-1} 2978, 1706, 1658, 1515, 1446, 1367, 1247, 1160, 1092, 1037; ^1H NMR (400 MHz, $CDCl_3$): 6.82 (dd, *J* = 12.5, 4.2 Hz, 1H), 5.94 (dd, *J* = 12.5, 1.1 Hz, 1H), 4.60 (br s, 1H), 4.33 (br s, 1H), 4.18 (q, *J* = 5.7 Hz, 2H), 3.68 (s, 3H), 2.40 (t, *J* = 5.9 Hz, 2H), 1.98 – 1.95 (m, 1H), 1.84 – 1.79 (m, 1H), 1.44 (s, 9H), 1.28 (t, *J* = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 166.2, 155.2, 147.5, 121.4, 80.0, 60.6, 51.9, 51.1, 30.5, 29.5, 28.4 (3C), 14.3; $[\alpha]^{24}_D$ = + 7.8 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{15}H_{25}NNaO_6$ $[M+Na]^+$: 338.1580; Found: 338.1578.

Synthesis of (*S*, *Z*)-ethyl 6-((tert-butyldiphenylsilyl) oxy) hept-4-enoate [$C_{25}H_{34}O_3Si$] (42*Z*):

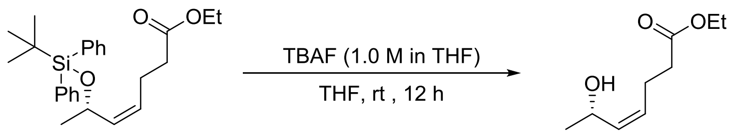


39 **42*Z***

A 250 mL round bottom flask containing the solution of phosphonium salt of $[EtCO_2(CH_2)_3PPh_3]^+Br^-$ (24.2 g, 52.8 mmol) in THF (80 mL) was cooled to 0°C in an ice bath. To the solution was added $NaN(TMS)_2$ (52.8 mL, 1.0 M in THF, 52.8 mmol) dropwise at 0°C. After 0.5 h stirring at ice-bath temperature, the mixture was cooled to -78°C and a solution of aldehyde **39** (11.0 g, 35.2 mmol) in THF (25 mL) was added slowly. After the addition, the mixture was stirred at -78 °C for 2 h and then allowed to warm to ambient temperature, stirred for 2 h and poured into saturated NH_4Cl. The product was extracted with EtOAc (2 x 500 mL).

The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a residual oil, which was subjected to chromatography on silica gel with petroleum ether / EtOAc (20:1) to afford olefin **42*Z*** (23.4 g, 81%) as colorless oil. Obtained data was matched with the literature data.

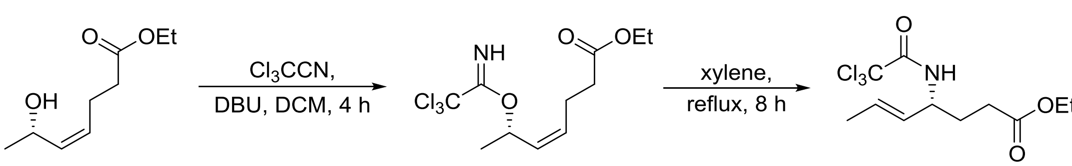
Synthesis of (*S*, *Z*)-ethyl 6-hydroxyhept-4-enoate [$C_9H_{16}O_3$] (43*Z*):



42*Z* **43*Z***

To a 500 mL round bottom flask containing THF (200 mL) were added olefin **42*Z*** (22.0 g, 53.6 mmol) and Tetrabutylammonium fluoride ($Bu_4N^+F^-$) (64 mL, 1.0 M in THF, 64 mmol). The solution was stirred at room temperature for 12 h and evaporated under reduced pressure. The thick oil was poured into H_2O. The product was extracted with EtOAc (2 x 500 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a residual oil, which was chromatographed on silica gel with petroleum ether / EtOAc (from 10:1 to 2:1) to afford allyl alcohol **43*Z*** (7.9 g, 86%) as colorless oil. Obtained data was matched with the literature data.

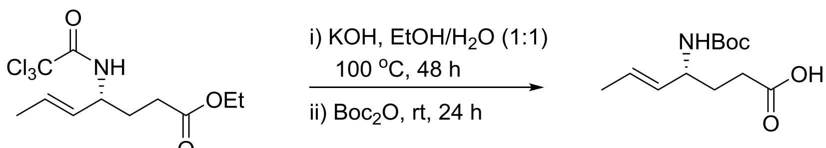
Synthesis of (*R*, *E*)-ethyl 4-(2, 2, 2-trichloroacetamido)hept-5-enoate [$C_{11}H_{16}Cl_3NO_3$] (45*R*):



43*Z* **44*Z*** **45*R***

A 50 mL round bottom flask containing a solution of allyl alcohol **43*Z*** (500 mg, 2.9 mmol) in DCM (10 mL) was cooled to 0°C in an ice bath. To the reaction mixture were added DBU (260 µL, 1.74 mmol) and Cl_3CN (349 µL, 3.48 mmol) over period of 15 min. After stirring at 0°C for 1 h, the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 5% Aqueous HCl solution (2 mL). The organic layer was evaporated under reduced pressure to give crude trichloroacetimidate **44*Z***, which was used for the next step without any purification. The crude imidate was dissolved in dry *m*-xylene (20 mL). The mixture was heated at reflux temperature for 8 h. After cooling to rt, the mixture was evaporated in vacuo. The residue was chromatographed on silica gel with petroleum ether/EtOAc (9:1) to give trichloroacetamide **45*R*** (597 mg, 65% over 2 steps) as yellow oil. IR (Neat): ν_{max}/cm^{-1} 3333, 2980, 1697, 1514, 1447, 1375, 1338, 1247, 1173, 1099, 1066, 1028; ^{1}H NMR (400 MHz, $CDCl_3$): 6.95 (d, *J* =2.2 Hz, 1H), 5.72 – 5.65 (m, 1H), 5.39 – 5.32 (m, 1H), 4.34 (quintet, *J* = 7.1 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.44 – 2.30 (m, 2H), 1.96 – 1.91 (m, 2H), 1.70 (d, *J* = 6.5 Hz, 3H), 1.23 (t, *J* = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 161.2, 128.6 (2C), 92.7, 60.8, 53.2, 30.6, 29.1, 17.7, 14.1; $[\alpha]^{24}_D$ = - 6.0 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{11}H_{16}Cl_3NNaO_3$ $[M+Na]^+$: 338.0093; Found: 338.0120.

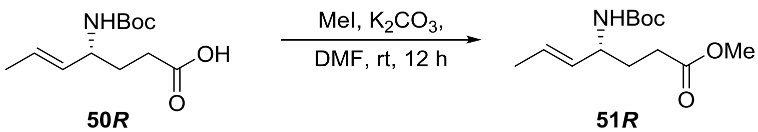
Synthesis of (*R*, *E*)-4-((tert-butoxycarbonyl) amino)hept-5-enoic acid [$C_{12}H_{21}NO_4$] (50*R*):



45*R* **50*R***

To a 50 mL round bottom flask containing a solution of trichloroacetamide **45*R*** (300 mg, 0.95 mmol) in ethanol: H_2O (1:1) (10 mL) was added KOH (636 mg, 11.37 mmol) and heated at 100 °C for 48 h. The reaction mixture was allowed to cool at room temperature. Then Boc anhydride (248 mg, 1.14 mmol) was added to the reaction mixture and stirred at room temperature for 24 h. After completion of the reaction, the reaction mixture was evaporated under reduced pressure to remove ethanol and acidified with 6 N HCl. The aqueous solution was extracted with ethyl acetate. The combined extract was washed with brine, dried over Na_2SO_4, and concentrated to afford acid **50*R*** (212 mg, 92 %) as off white solid. M.p. = 89 – 90 °C; IR (KBr): ν_{max}/cm^{-1} 3366, 2978, 1713, 1672, 1511, 1444, 1392, 1286, 1168; ^{1}H NMR (400 MHz, DMSO-d_6): 11.96 (s, 1 H), 5.37 – 5.43 (m, 1H), 5.23 – 5.27 (m, 1H), 3.9 (br s, 1H), 2.09 – 2.12 (m, 2H), 1.52 – 1.56 (m, 5H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 178.5, 155.5, 130.9, 126.9, 79.6, 52.0, 30.8, 30.4, 28.4, 17.7; $[\alpha]^{24}_D$ = - 10.1 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{12}H_{21}NNaO_4$ $[M+Na]^+$: 266.1368; Found: 266.1364.

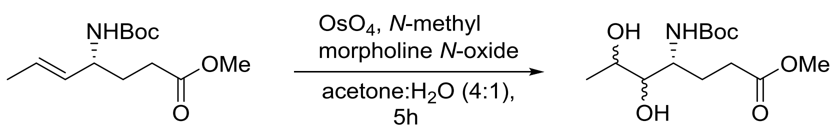
Synthesis of (*R*, *E*)-methyl 4-((tert-butoxycarbonyl) amino) hept-5-enoate [$C_{13}H_{23}NO_4$] (51*R*):



50*R* **51*R***

To a 50 mL round bottom flask containing a solution of the acid **50*R*** (600 mg, 2.47 mmol) in DMF (5 mL) were added K_2CO_3 (340 mg, 2.47 mmol) and MeI (0.62 mL, 9.88 mmol). The solution was stirred at room temperature for 12 h and poured into H_2O. The product was extracted with EtOAc (2 x 15 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a residual oil, which was chromatographed on silica gel with petroleum ether / EtOAc (from 10:1 to 2:1) to afford ester **51*R*** (610 mg, 97 %) as colorless oil. IR (Neat): ν_{max}/cm^{-1} 3360, 2974, 1694, 1513, 1445, 1365, 1243, 1163, 1048, 1021; ^1H NMR (400 MHz, $CDCl_3$): 5.64 – 5.55 (m, 1H), 5.32 (ddd, *J* = 15.3, 6.4, 1.5 Hz, 1H), 4.48 (br s, 1H), 4.03 (br s, 1H), 3.66 (s, 1H), 2.34 (t, *J* = 7.6 Hz, 2H), 1.84 – 1.76 (m, 2H), 1.67 – 1.65 (m, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.9, 155.4, 131.1, 126.7, 79.4, 52.1, 51.7, 30.8, 30.5, 28.4 (3C), 17.8; $[\alpha]^{24}_D$ = - 2.8 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{13}H_{23}NNaO_4$ $[M+Na]^+$: 280.1525; Found: 280.1525.

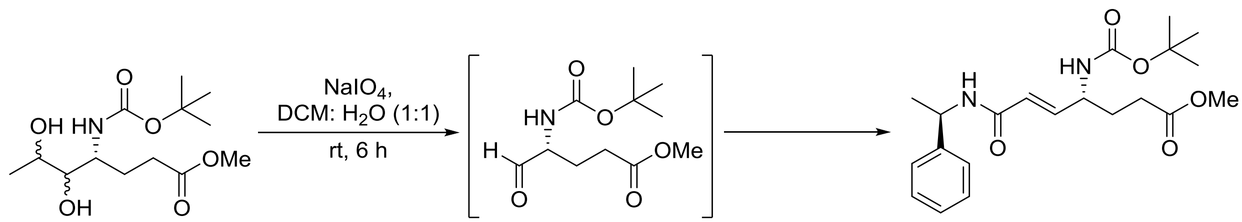
Synthesis of (4*S*)-methyl 4-((tert-butoxycarbonyl) amino)-5, 6-dihydroxyheptanoate [$C_{13}H_{25}NO_6$] (52*R*):



51*R* **52*R***

A 50 mL round bottom flask containing a solution of olefin **51*R*** (100 mg, 0.31 mmol) in acetone: H2O (4:1) (5 mL) was cooled to 0°C in an ice bath. To the solution were added NMO (50% aq. Solution, 128 µL, 0.47 mmol), OsO_4 (1 mg) and the reaction mixture was stirred at room temperature for 5 h. Reaction mixture was evaporated to remove acetone and then diluted with H_2O. The product was extracted with EtOAc (2 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a residual oil, which was chromatographed on silica gel with petroleum ether / EtOAc (from 3:7) to afford diastereomeric mixture of diol **52*R*** (110 mg, 95 %). IR (KBr): ν_{max}/cm^{-1} 3360, 2981, 1713, 1683, 1514, 1446, 1390, 1366, 1287, 1167, 1050; ^{1}H NMR (400 MHz, $CDCl_3$): 5.34 – 5.35 (m, 2H), 4.75 – 4.85 (m, 2H), 4.61 (d, *J* = 8.2 Hz, 1H), 3.90 – 3.97 (m, 6H), 3.82 – 3.84 (m, 4H), 3.66 – 3.69 (m, 12H), 3.47 (s, 6H), 3.23 – 3.25 (m, 2H), 3.00 – 3.02 (m, 1H), 2.56 – 2.74 (m, 7H), 2.37 – 2.46 (m, 10H), 2.13 – 2.20 (m, 2H), 1.81 – 1.88 (m, 8H), 1.40 – 1.44 (m, 48H), 1.20 – 1.33 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): 176.8, 174.5, 157.3, 156.3, 85.1, 80.4, 79.6, 68.7, 66.3, 52.8, 51.9, 50.9, 30.9, 30.7, 28.4, 25.9, 25.5, 19.9, 19.0, 18.9; HRMS (ESI): Calc. for $C_{13}H_{25}NNaO_6$ $[M+Na]^+$: 314.1580; Found: 314.1580.

Synthesis of (*R*, *E*)-methyl 4-((tert-butoxycarbonyl)amino)-7-oxo-7-(((*R*)-1-phenylethyl)amino)hept-5-enoate [$C_{21}H_{30}N_2O_5$] (55*R*):

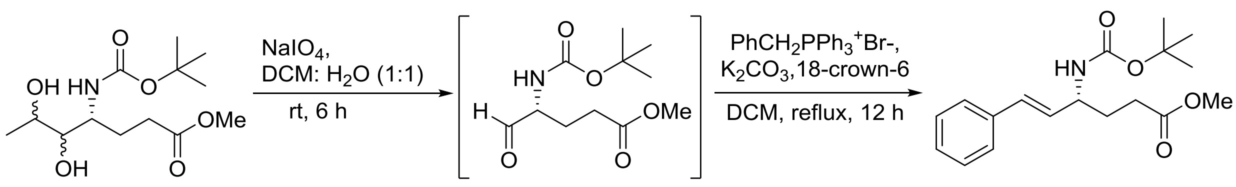


52*R* **53*R*** **55*R***

A 50 mL round bottom flask containing a solution of diol **52*R*** (300 mg, 1.03 mmol) in DCM: H_2O (4:1) (15 mL) was cooled to 0°C in an ice bath. To the solution was added $NaIO_4$ (340 mg, 1.59 mmol) and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in DCM (8 mL) was added wittig salt **54** (520 mg, 1.24 mmol) and the reaction mixture was refluxed for 6 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 9:1) to afford the corresponding unsaturated compound **55*R*** (320 mg, 80 %) as off white solid. M.p. = 154 – 156 ^{o}C; IR (Neat): ν_{max}/cm^{-1} 3342, 3322, 2981, 1731, 1679, 1520, 1441, 1367, 1296; ^{1}H NMR (400 MHz, $CDCl_3$): 7.30 (s, 5H), 6.68 (dd, *J* = 15.1, 5.9 Hz, 1H), 5.87 (d, *J* = 15.1 Hz, 1H), 5.76 (br s, 1H), 5.17 (quintet, *J* = 7.4 Hz, 1H), 4.59 (br s, 1H), 4.27 (br s, 1H), 3.65 (s, 3H), 2.37 (t, *J* = 7.2 Hz, 2H), 1.85 – 1.96 (m, 2H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.6, 164.3, 155.3, 143.4, 143.0, 128.8, 127.5, 126.3, 123.9, 79.9, 51.9, 51.2, 48.9, 30.5, 29.7, 28.4 (3C), 21.7; HRMS (ESI): Calc. for $C_{21}H_{30}N_2NaO_5$ $[M+Na]^+$: 413.2052; Found: 413.2044; HPLC: CHIRALPAK IC column (2-Propanol:*n*-Hexane = 10:90, flow rate 1.0 mL/min, λ = 250 nm). Retention time (min): 26.81(minor) and 29.05 (major), *de* = 94% (Figure 2.6).

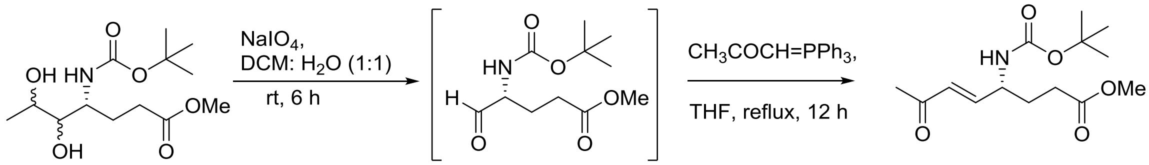
Synthesis of (*R*)-methyl 4-((tert-butoxycarbonyl) amino)-6-phenylhex-5-enoate [$C_{18}H_{25}NO_4$] (56*R*):



A 25 mL round bottom flask containing a solution of diol **52*R*** (300 mg, 1.03 mmol) in DCM: H_2O (4:1) (10 mL) was cooled to 0°C in an ice bath. To the solution was added $NaIO_4$ (340 mg, 1.59 mmol) and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in DCM (10 mL) was added phosphonium salt of $[PhCH_2PPh_3]^+Br^-$ **54a** (450 mg, 1.03 mmol), potassium carbonate (160 mg, 1.13 mmol) and 18-crown-6 (49 mg, 0.18 mmol) and the reaction mixture was refluxed for 12 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 9:1) to afford the corresponding unsaturated compound **56*R*** (270 mg, 78 %) as white solid. M.p. = 86 – 87°C; IR (Neat): ν_{max}/cm^{-1} 3332, 2971, 1684, 1513, 1417, 1358, 1251, 1155; ^1H NMR (400 MHz, $CDCl_3$): 7.21 – 7.36 (m, 5H), 6.53 (d, *J* = 15.8 Hz, 1H), 6.07 (dd, *J* = 15.9, 6.4 Hz, 1H), 4.60 (br s, 1H), 4.29 (br s, 1H), 3.66 (s, 3H), 2.42 (t, *J* = 14.9 Hz, 2H), 1.88 – 1.99 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.9, 155.4, 136.6, 130.7, 129.6, 128.6, 127.8, 126.5, 79.6, 51.8, 30.8, 30.1, 28.5; $[\alpha]^{24}_D$ = - 18.2 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{18}H_{26}NNaO_4$ $[M+Na]^+$: 342.1681; Found: 342.1682.

Synthesis of (*R*, *E*)-methyl 4-((tert-butoxycarbonyl) amino)-7-oxooct-5-enoate [$C_{14}H_{23}NO_5$] (57*R*):

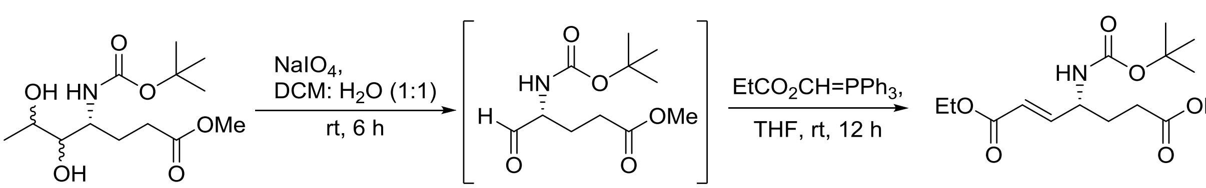


52*R* 53*R* 57*R*

A 25 mL round bottom flask containing a solution of diol **52*R*** (400 mg, 1.37 mmol) in DCM: H_2O (6 mL) was cooled to 0°C in an ice bath. To the solution was added $NaIO_4$ (440 mg, 2.06 mmol) and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in THF (10 mL) was added methylcarbonylmethylenephosphorane ($CH_3COCHPPh_3$) **54b** (430 mg, 1.37 mmol) and the reaction mixture was refluxed for 3 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 8:2) to afford the corresponding unsaturated compound **57*R*** (330 mg, 83%) as colorless oil. IR (Neat): ν_{max}/cm^{-1} 3744, 2977, 1680, 1515, 1444, 1363, 1247, 1161, 1051, 1022; ^1H NMR (400 MHz, $CDCl_3$): 6.69 (dd, *J* = 16.0, 5.0 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 4.67 (br s, 1H), 4.35 (br s, 1H), 3.69 (s, 3H), 2.43 (t, *J* = 7.3 Hz 2H), 2.27 (s, 3H), 1.97 – 2.02 (m, 1H), 1.81-1.86 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 198.3, 173.5, 155.3, 146.5, 129.9, 80.0, 51.9, 51.2, 30.5, 29.3, 28.4 (3C), 27.5; $[\alpha]^{24}_D$ = - 12.40 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{21}H_{16}NNaO$ $[M+Na]^+$: 308.1474; Found: 308.1471.

Synthesis of (*R*, *E*)-1-ethyl7-methyl4-((tert-butoxycarbonyl)amino)hept-2-enedioate [$C_{15}H_{25}NO_6$] (58*R*):

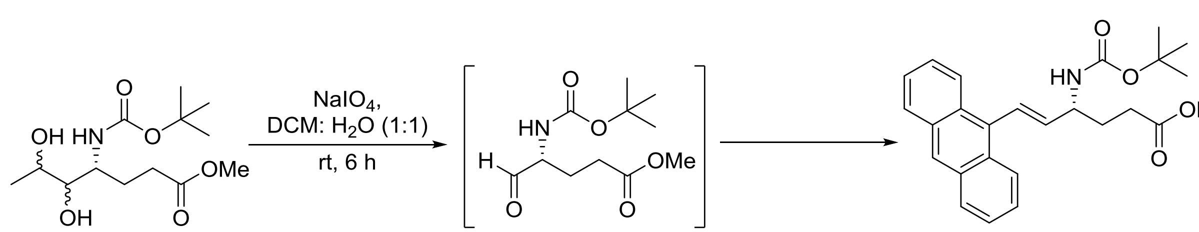


52*R* 53*R* 58*R*

A 25 mL round bottom flask containing a solution of diol **52*R*** (300 mg, 1.03 mmol) in DCM: H_2O (4:1) (10 mL) was cooled to 0°C in an ice bath. To the solution was added $NaIO_4$ (340 mg, 1.59 mmol) and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in DCM (8 mL) was added ethoxycarbonylmethylenephosphorane ($EtO_2CCHPPh_3$) **54c** (430 mg, 1.24 mmol) and the reaction mixture was refluxed for 12 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 9:1) to afford the corresponding unsaturated compound **58*R*** (270 mg, 82 %) as colorless oil. IR (Neat): ν_{max}/cm^{-1} 2978, 1706, 1658, 1515, 1446, 1367, 1247, 1160, 1092, 1037; ^1H NMR (400 MHz, $CDCl_3$): 6.82 (dd, *J* = 12.5, 4.2 Hz, 1H), 5.93 (d, *J* = 12.5 Hz, 1H), 4.61 (br s, 1H), 4.33 (br s, 1H), 4.19 (q, *J* = 5.7 Hz, 2H), 3.67 (s, 3H), 2.40 (t, *J* = 5.9 Hz, 2H), 1.98 – 1.94 (m, 1H), 1.83 – 1.80 (m, 1H), 1.43 (s, 9H), 1.28 (t, *J* = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.5, 166.2, 155.2, 147.5, 121.4, 80.0, 60.6, 51.9, 51.1, 30.5, 29.5, 28.4 (3C), 14.3; $[\alpha]^{24}_D$ = - 7.2 (*c* = 0.50, $CHCl_3$); HRMS (ESI): Calc. for $C_{15}H_{25}NNaO_6$ $[M+Na]^+$: 338.1580; Found: 338.1580.

Synthesis of (*R*, *E*)-methyl 6-(anthracen-9-yl)-4-((tert-butoxycarbonyl)amino)hex-5-enoate [$C_{26}H_{29}NO_4$] (59*R*):



52*R* 53*R* 59*R*

A 50 mL round bottom flask containing a solution of diol **53*R*** (350 mg, 1.20 mmol) in DCM: H_2O (4:1) (30 mL) was cooled to 0°C in an ice bath. To the solution was added $NaIO_4$ (390 mg, 1.80 mmol) and the reaction mixture was stirred at room temperature for 6 h. The resulting solution was partitioned between DCM and H_2O. The organic layer was separated, dried over

Na_2SO_4 and concentrated to afford an aldehyde which was used for next reaction without any purification.

To a 25 mL round bottom flask containing a solution of crude aldehyde in DCM (8 mL) was added wittig salt **54d** (790 mg, 1.44 mmol) and the reaction mixture was refluxed for 6 h in nitrogen atmosphere. The resulting solution was allowed to cool to room temperature, concentrated in vacuo and chromatographed on silica gel (petroleum ether /ethyl acetate 9:1) to afford the corresponding unsaturated compound **59*R*** (350 mg, 69 %) as yellow solid. M.p. = 114 – 115 ^{o}C; IR (Neat): ν_{max}/cm^{-1} 3344, 2982, 1734, 1679, 1633, 1523, 1448, 1368, 1302, 1255, 1166, 1047, 1016; ^{1}H NMR (400 MHz, $CDCl_3$): 8.36 (s, 1H), 8.15 – 1.30 (m, 2H), 7.90 – 8.04 (m, 2H), 7.37 – 7.52 (m, 4H), 7.28 (d, *J* = 16.2 Hz, 1H), 5.87 (dd, *J* = 16.2, 6.4 Hz, 1H), 4.79 (s, 1H), 4.53 (s, 1H), 3.71(s, 3H), 2.58 (t, *J* = 7.4 Hz, 2H), 1.97 – 2.23 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 173.9, 155.5, 138.2, 131.4, 129.5, 128.7, 127.0, 126.4, 126.0, 125.5, 125.2, 79.8, 53.0, 52.0, 31.0, 30.3, 28.5 (3C); HRMS (ESI): Calc. for $C_{26}H_{29}NNaO_4$ $[M+Na]^+$: 442.1994; Found: 442.1987.

2.7 Photophysical Properties of 59*R*

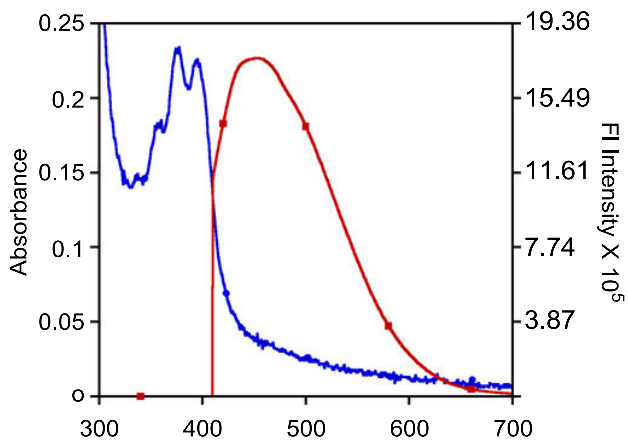


Figure 2.4: Normalized UV-vis absorption and fluorescent emission spectra **59*R***.

2.8 Crystal structures.

Crystal structure of compound 56*S* (CCDC 922311): $C_{21}H_{30}N_2O_5$; Compound **56*S*** was crystallized from slow evaporation of methanol/water at room temperature. A colorless needle shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/n*; *a* = 19.851(4) *b* = 20.966(5) *c* = 5.1137(11) Å, α = 90^{o} β = 90^{o} γ = 90^{o};

V = 2128.3(8) Å^3; T = 296 (2) K; Z = 4; ρ_{calc} = 1.219 Mgm^{-3}; $2\theta_{max}$ = 54.76°; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0361 (for 4159 reflection $I>2\sigma(I)$), wR = 0.0820 which was refined against $|F2|$ and S = 0.935 for 258 parameters and 4839 unique reflections. The structure was obtained by direct methods using SHELXS-97.[25] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the fil cycle of refinement as riding over atoms to which they are bonded. μ = 0.087 mm^{-1}.

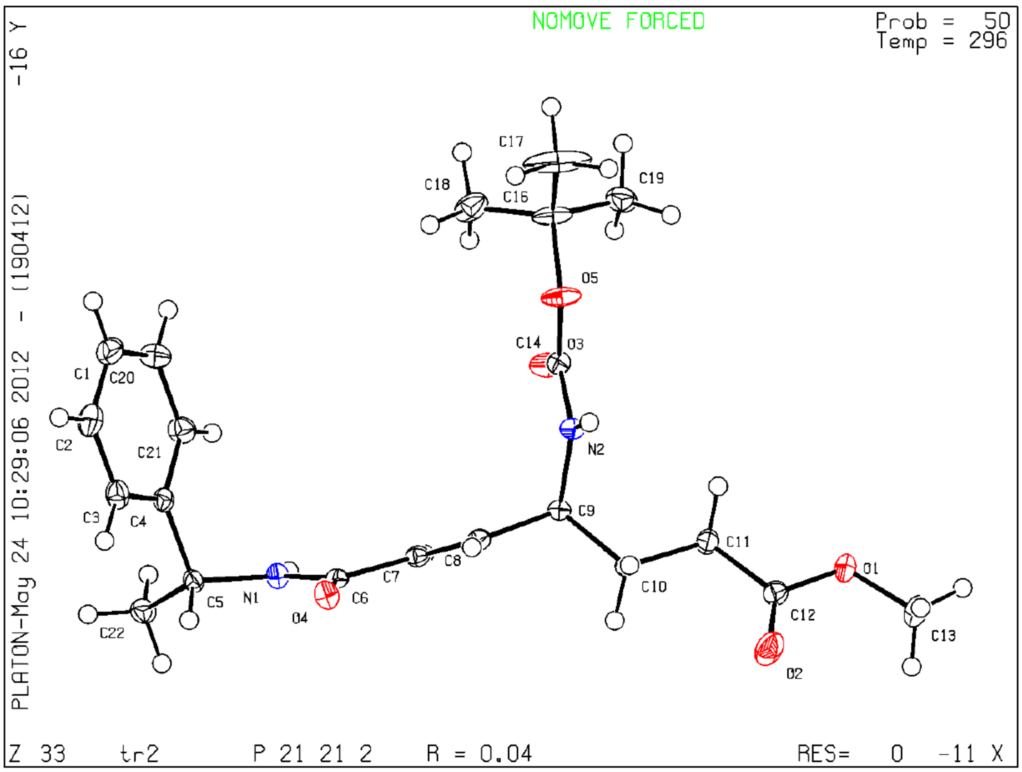


Figure 2.5: ORTEP diagram of **56*S***.

Crystal structure of compound 56*R* (CCDC 922310): $C_{21}H_{30}N_2O_5$; Compound **56*R*** was crystallized from slow evaporation of methanol/water at room temperature. A colorless needle shaped crystal with approximate dimensions 0.224 x 0.148 x 0.022 mm gave an Monoclinic with space group $P21$; a = 5.155(3) b = 36.609(18) c = 11.688(6) Å, α = 90° β = 102.638(9)° γ = 90°; V = 2152(2) Å^3; T = 200 K; Z = 4; ρ_{calc} = 1.205 Mgm^{-3}; $2\theta_{max}$ = 52.86°; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0632 (for 4811 reflection $I>2\sigma(I)$), wR = 0.1503 which was refined against $|F2|$ and S = 0.999 for 516 parameters and

8384 unique reflections. The structure was obtained by direct methods using SHELXS-97.[25] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. $\mu = 0.086\ mm^{-1}$.

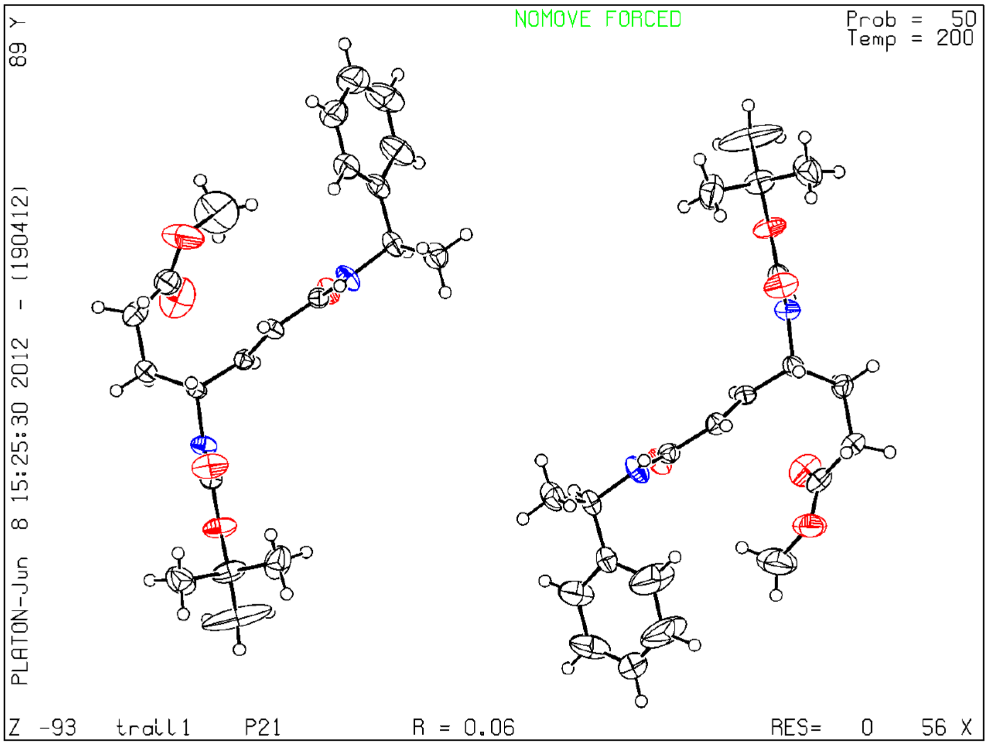


Figure 2.6: ORTEP diagram of **56*R***.

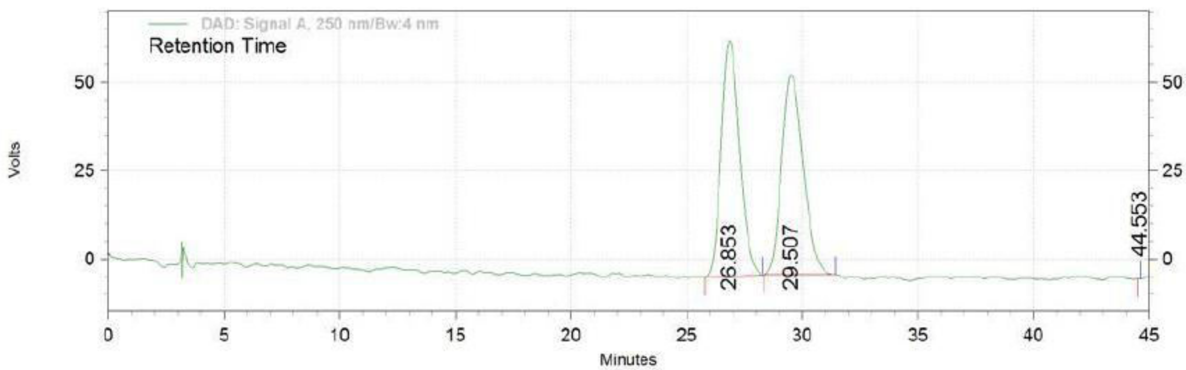
2.9 HPLC Data:

Chiral HPLC of mixture of 55*R* and 55*S*:

Page 1

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\Kavita\DK chiral 14.dat
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\PT\DK\Chiral_10%IPA hexane.met
Acquired: 5/28/2012 10:57:39 PM
Printed: 5/29/2012 9:40:35 AM



DAD: Signal A,
250 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
26.853	7698448	50.19	140041	54.10
29.507	7640147	49.81	118694	45.86
44.553	358	0.00	100	0.04
Totals	15338953	100.00	258835	100.00

Figure 2.7: Chiral HPLC of diastereomeric mixture of ***55R*** and ***55S***.

Column: CHIRALPAK IC (0.46 cm × 25 cm)

Flow: 1.0 mL/min

Method: Isocratic

10 % Isopropanol

90 % *n*-hexane

Wavelength: 250 nm.

Racemic sample: *tR* [**55*S***] = 26.85 min, *tR* [**55*R***] = 29.51 min.

Chiral HPLC of mixture of 55*R*:

Area % Report

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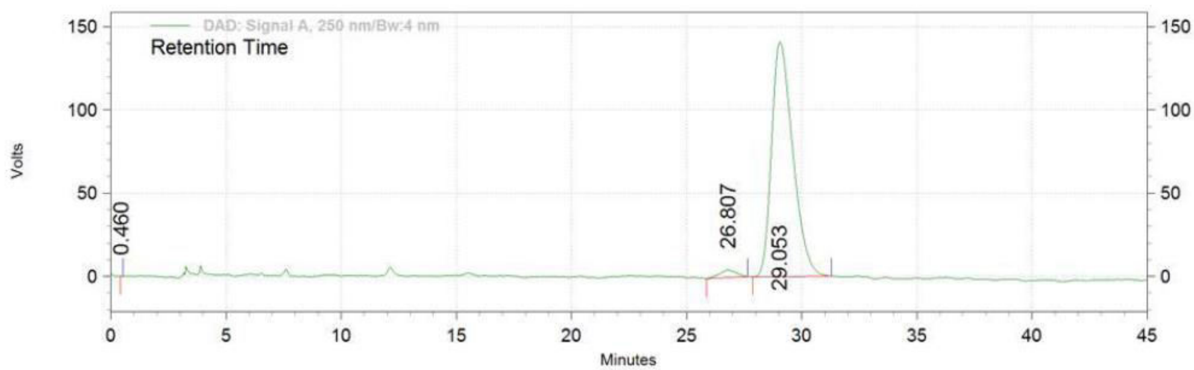
Printed: 5/29/2012 10:18:25 AM



DAD: Signal A,
250 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
0.460	110	0.00	42	0.01
26.807	477599	2.46	9614	3.15
29.053	18964853	97.54	295577	96.84
Totals	19442562	100.00	305233	100.00

Figure 2.8: Chiral HPLC of ***55R***.

Column: CHIRALPAK IC (0.46 cm × 25 cm)

Flow: 1.0 mL/min

Method: Isocratic

10 % Isopropanol

90 % *n*-hexane

Wavelength: 250 nm.

tR [**55*S***] = 26.81 min, *tR* [**55*R***] = 29.05 min.

Chiral HPLC of compounds 55*S*:

Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\Kavita\DK 04-58R5.dat
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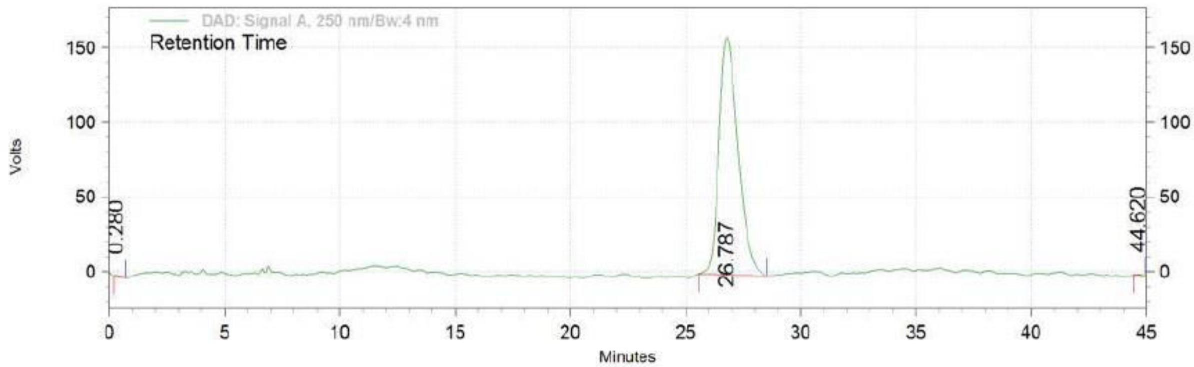

DAD: Signal A,
250 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
0.280	23025	0.12	833	0.25
26.787	19051483	99.77	333101	99.34
44.620	21272	0.11	1386	0.41
Totals	19095780	100.00	335320	100.00

Figure 2.9: Chiral HPLC of **55*S***.

Column: CHIRALPAK IC (0.46 cm × 25 cm)

Flow: 1.0 mL/min

Method: Isocratic

10 % Isopropanol

90 % *n*-hexane

Wavelength: 250 nm.

tR [**56*S***] = 26.79 min.

2.10 NMR Data

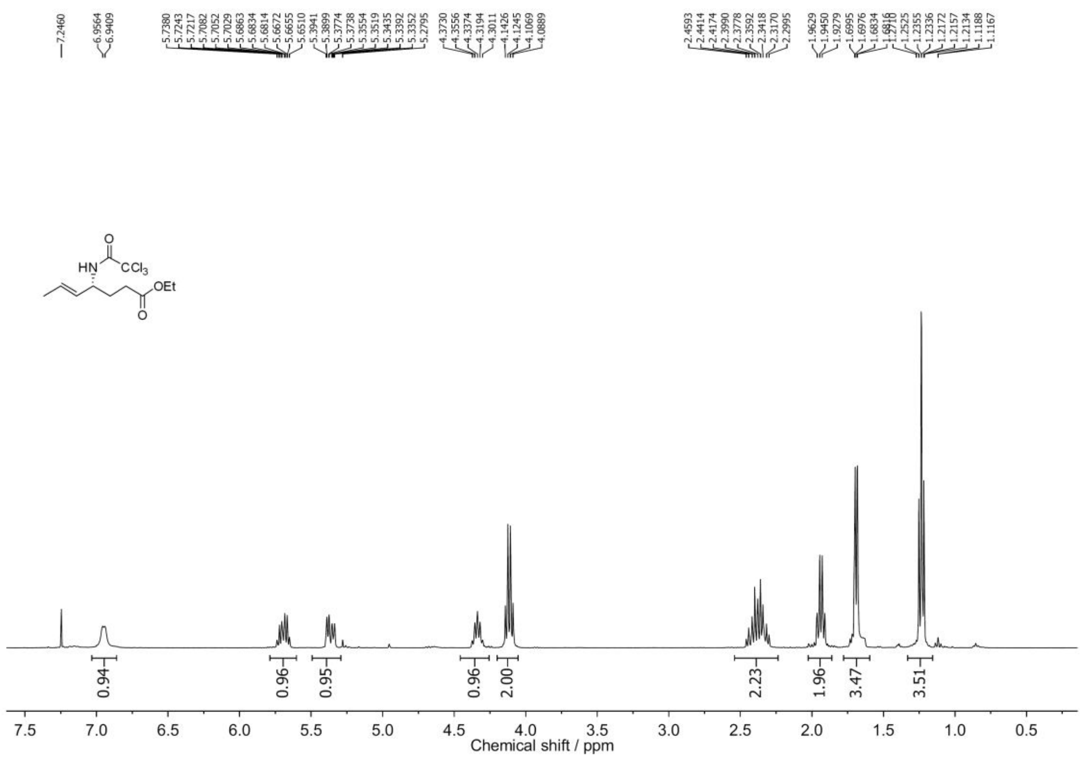

Figure 2.10: ^{1}H NMR spectra of **45*R*** in $CDCl_3$.

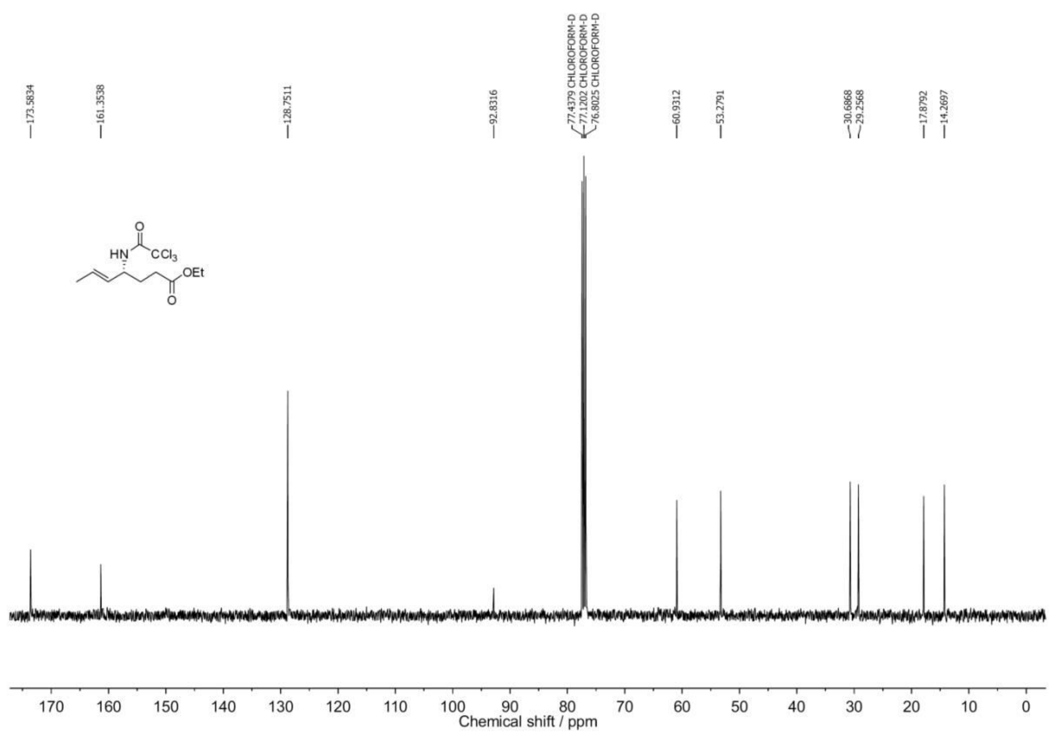

Figure 2.11: ^{13}C NMR spectra of **45*R*** in $CDCl_3$.

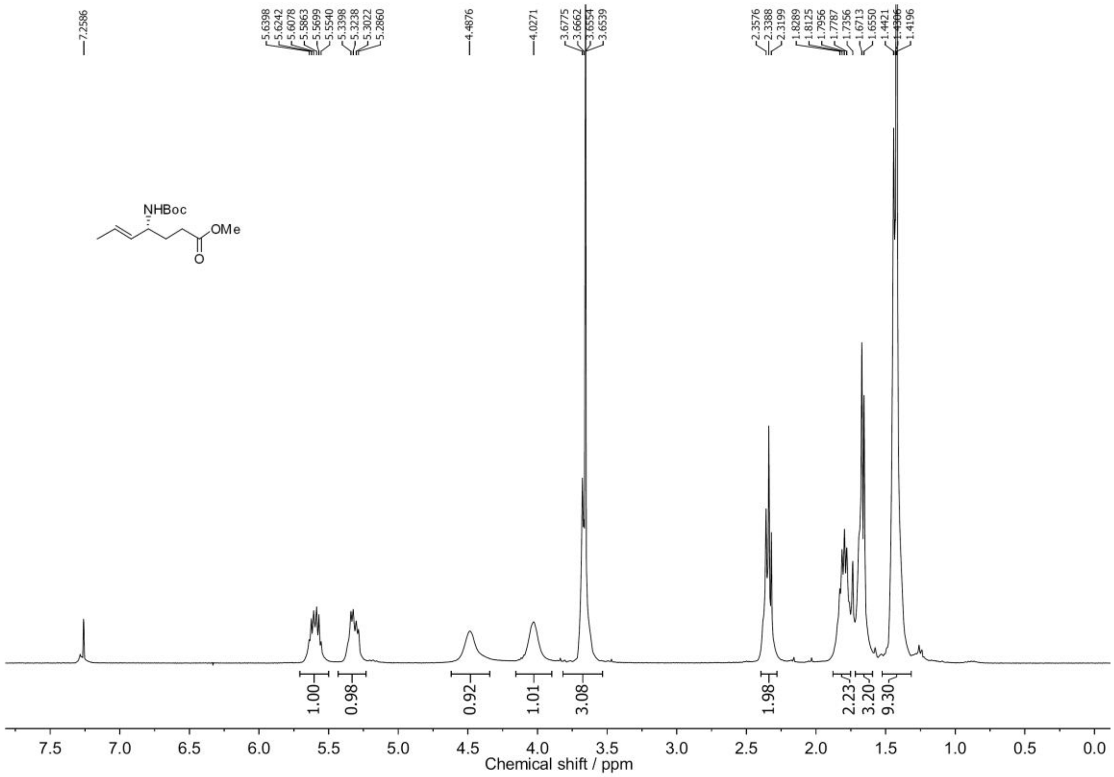

Figure 2.12: ^{1}H NMR spectra of **51*R*** in $CDCl_3$.

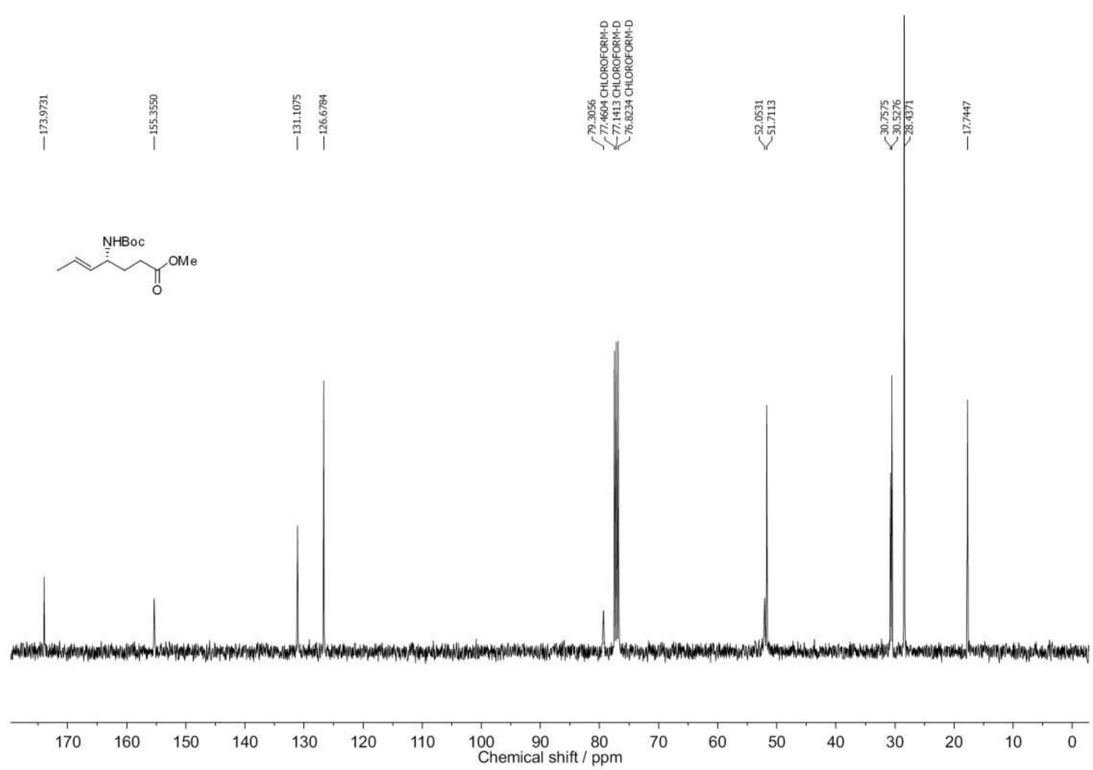

Figure 2.13 ^{13}C NMR spectra of **51*R*** in $CDCl_3$.

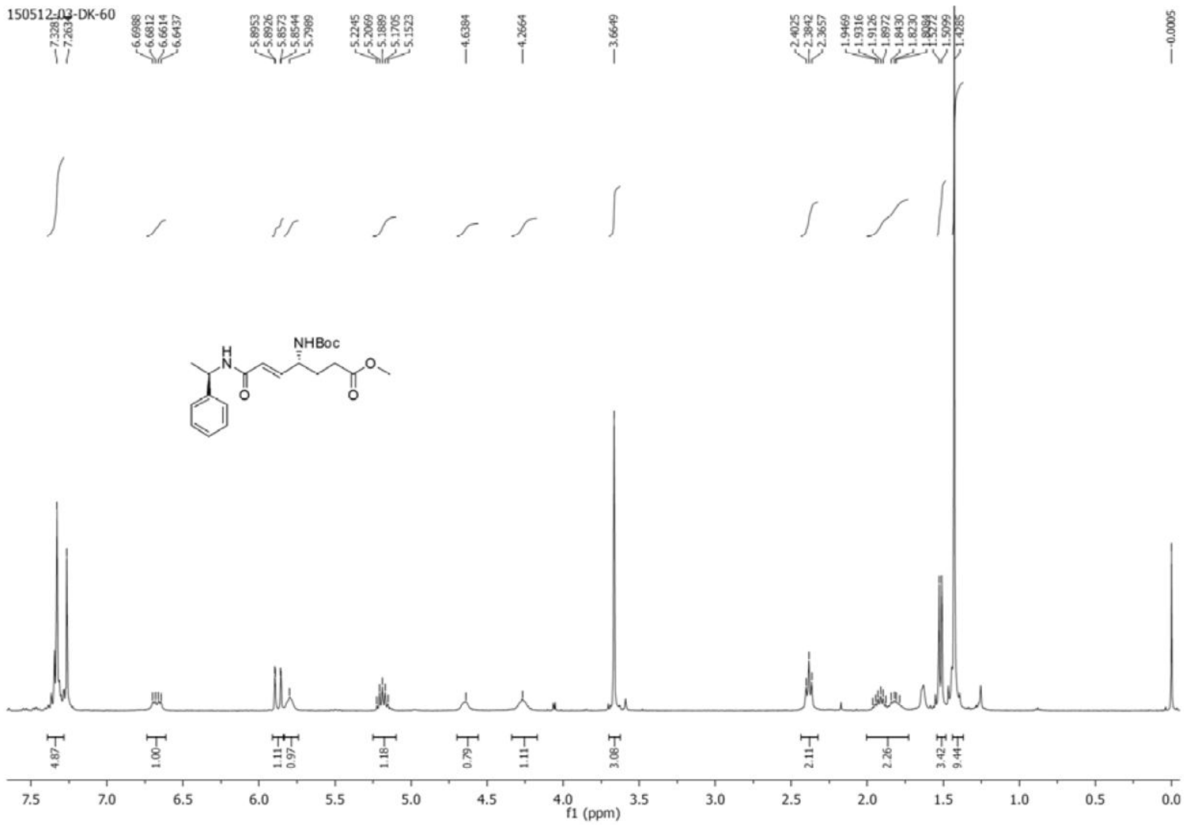

Figure 2.14: ^{1}H NMR spectra of **55*R*** in $CDCl_3$.

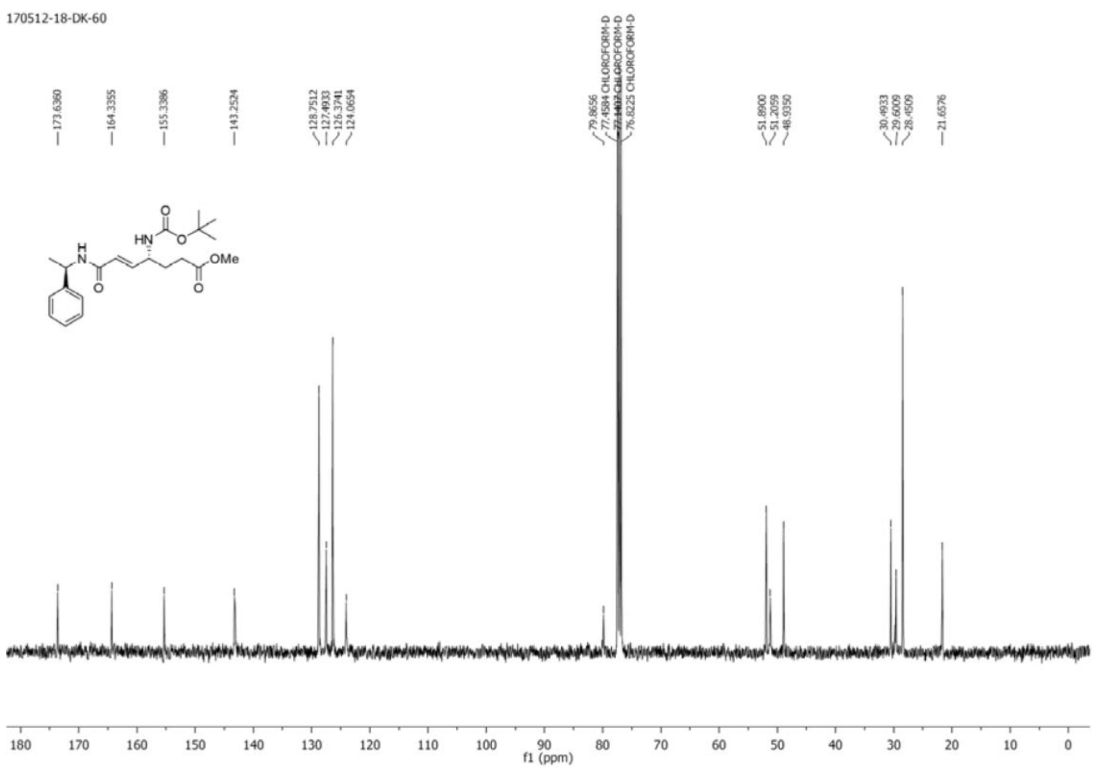

Figure 2.15; ^{13}C NMR spectra of **55*R*** in $CDCl_3$.

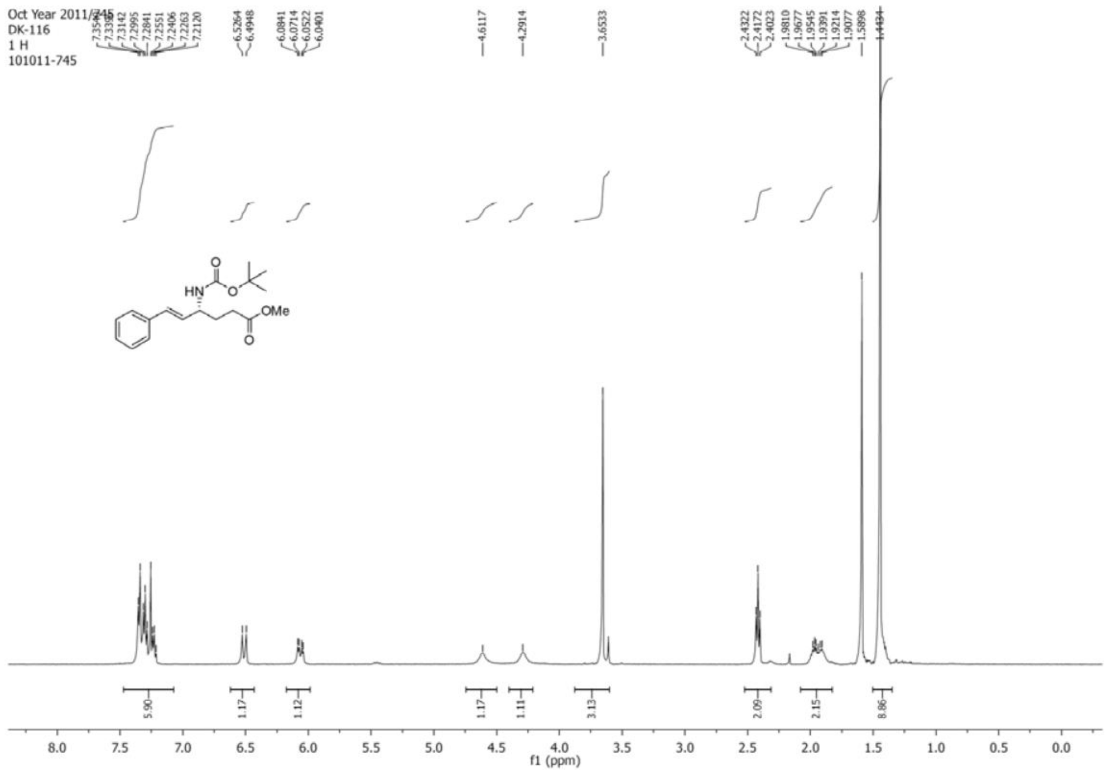

Figure 2.16 ^{1}H NMR spectra of **56*R*** in $CDCl_3$.

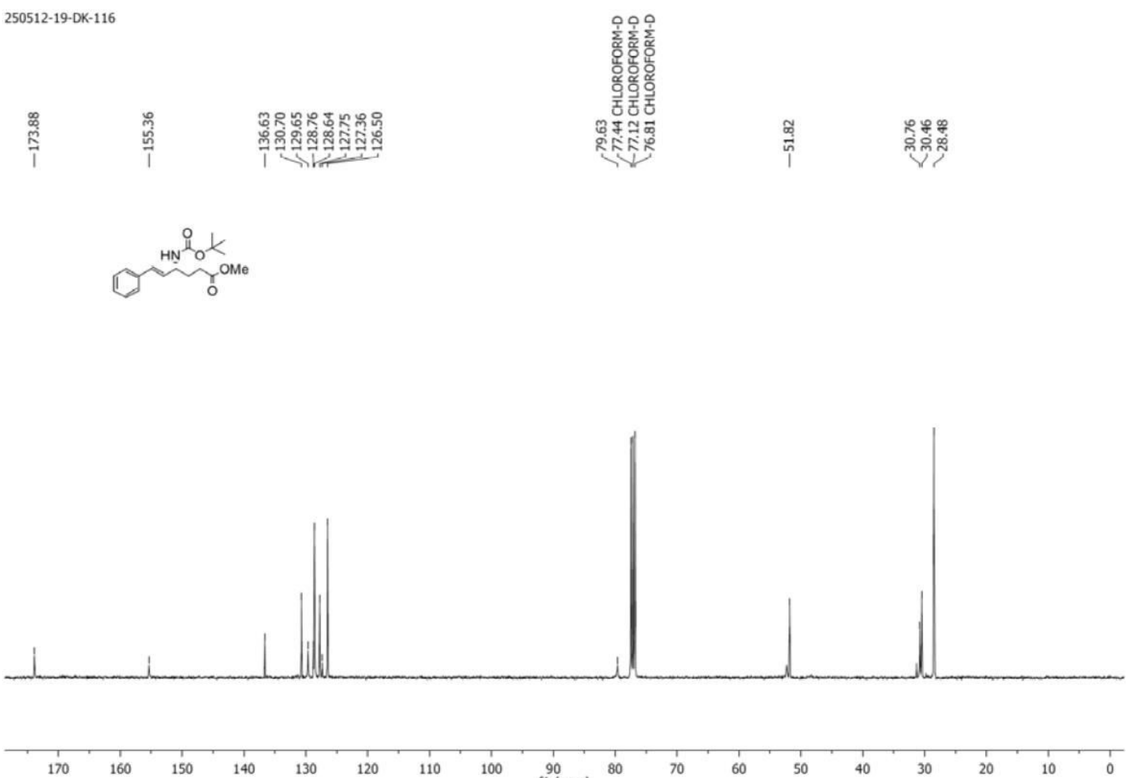

Figure 2.17: ^{13}C NMR spectra of **56*R*** in $CDCl_3$.

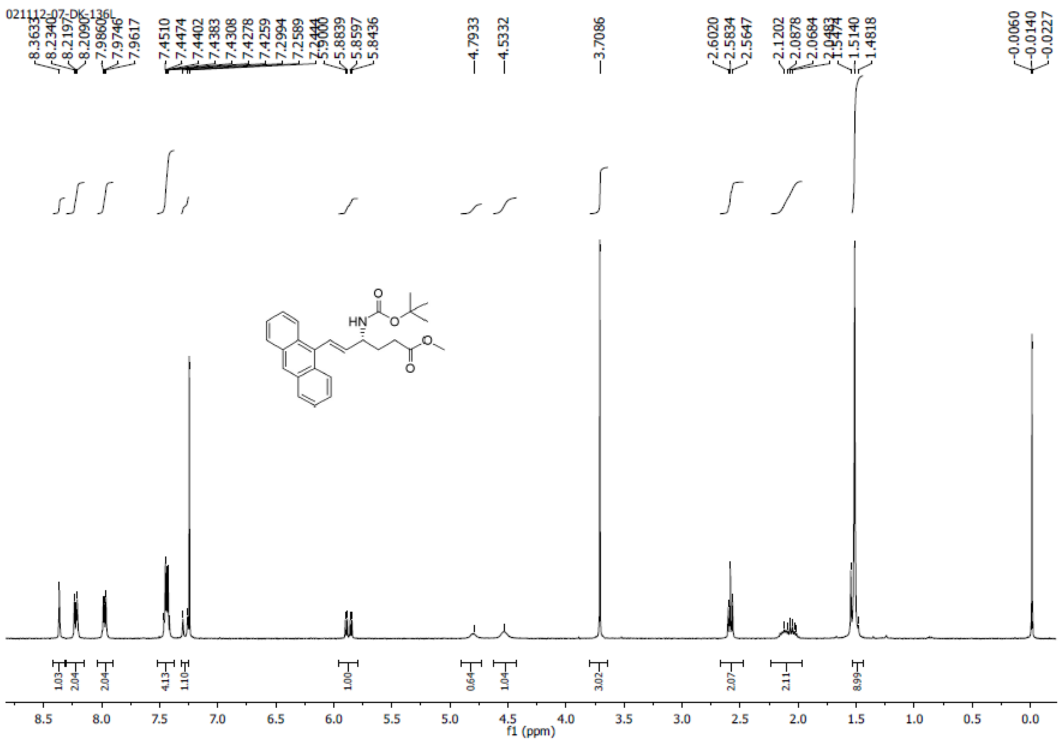

Figure 2.18: ^{1}H NMR spectra of **59*R*** in $CDCl_3$.

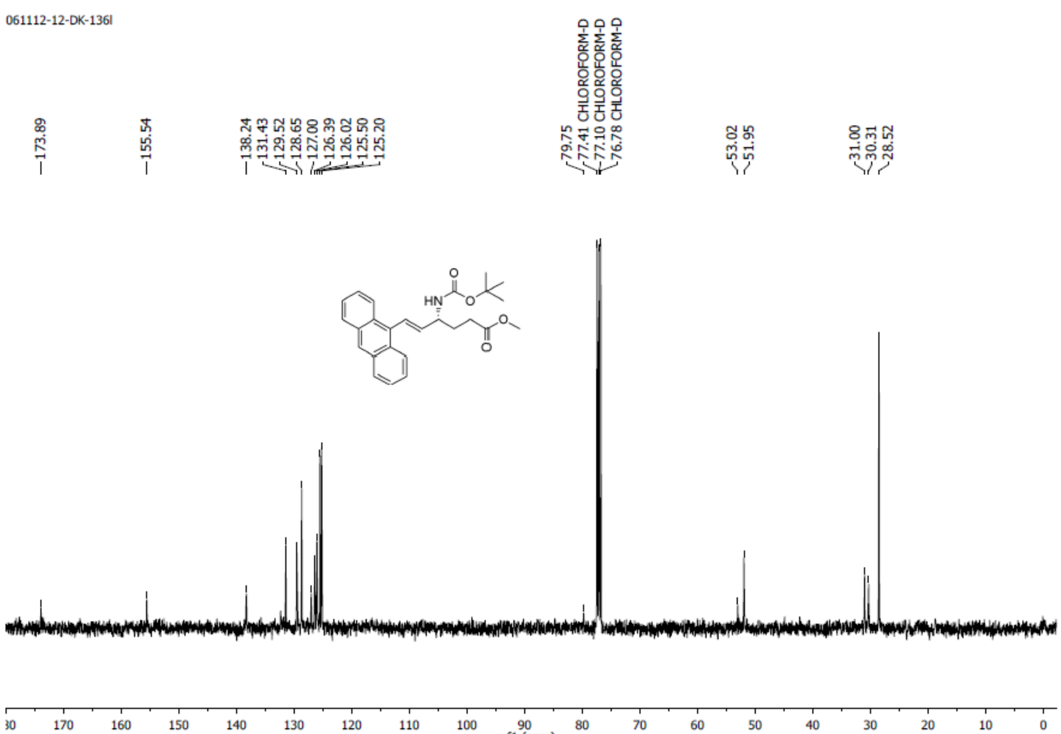

Figure 2.19: ^{13}C NMR spectra of **59*R*** in $CDCl_3$.

2.11 Refferences

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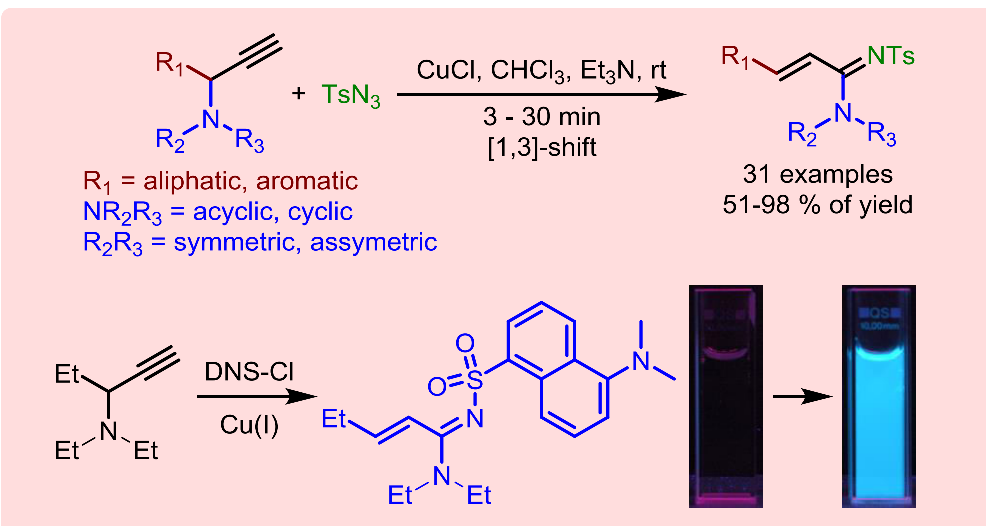
Chapter 3

Synthesis of Acrylamidines by 1,3-Amino Group Migration via Ketenimine Intermediates Derived from Propargyl Amines



3.1 Introduction:

Amidines are important structural motifs found in diverse natural and unnatural compounds. Amidines are *N*-isosters of amides **III**, and bis-nitrogen analogue of carboxylic acids and esters **IV**.[1] In comparison to their amide isoster **III**, an essential motif of peptides and proteins,[2] amidines have an extra trivalent nitrogen atom in place of the carbonyl oxygen atom (Figure 3.1). This endows the amidine moiety with more potential for structural and functional diversification.

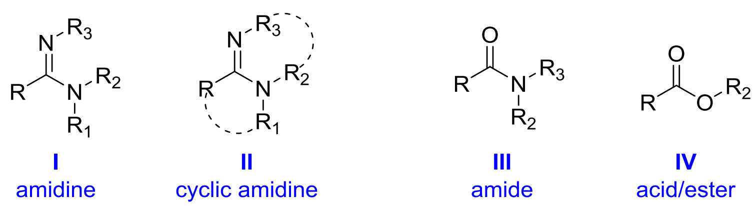


Figure 3.1: General structures of amidine, cyclic amidine, amide and acid/ester.

In chemistry, amidines are frequently used as organic bases because of their wide ranges of pK_a values (Figure 3.2A).[3] The basicity of amidines attributes to the stability of the conjugated acids via delocalization of charge over two nitrogen atoms. These bases are widely used in numerous organic reactions, and found to be more advantageous compared to the other organic bases. For example, the bicyclic amidines 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) are frequently used as bases for dehydrohalogenation reactions under milder conditions (Figure 3.2A).[4] Structural relevance of amidines also lies in their dual nature as hydrogen bond donor as well as hydrogen bond acceptor. In protonated form, they act as hydrogen bond donors and in neutral form they function as hydrogen bond acceptors. For example, the replacement of amide group by amidine in the Vancomycin aglycon residue-4 enables effective binding to both unaltered peptidoglycan D-Ala-D-Ala, and altered ligand D-Ala- D-Lac (Figure 3.2B).[5]

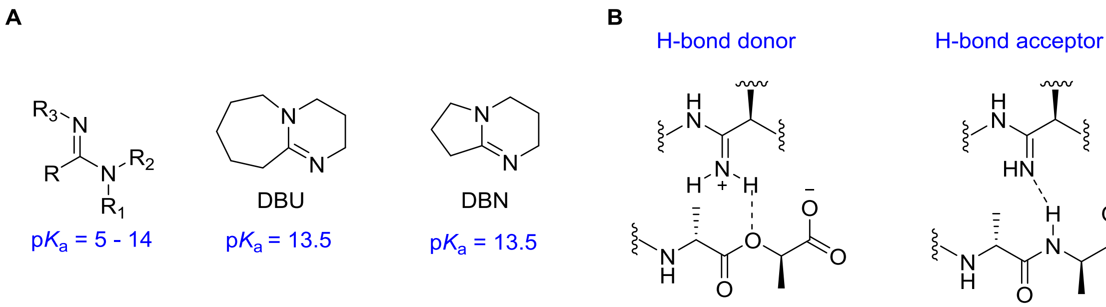


Figure 3.2: Structure and pK_a range of some commonly used amidines (**A**) and their role as hydrogen bond donor and hydrogen bond acceptor (**B**).

A variety of drugs, agrochemicals, and natural products contain amidine entity as one of the key structural unit.[6] According to the list of prescribed top selling drugs, as published in 2010, the amide moiety appears in 200 drugs. For example, Dasatinib **1** and Gefitinib **3** are anti-cancer drugs whereas Quetiapine **2** is an anti-psychotic drug, and pentamidine **4** is an anti-microbial agent, and all these molecules contain the amidine moiety in their structures (Figure 3.3).[7]

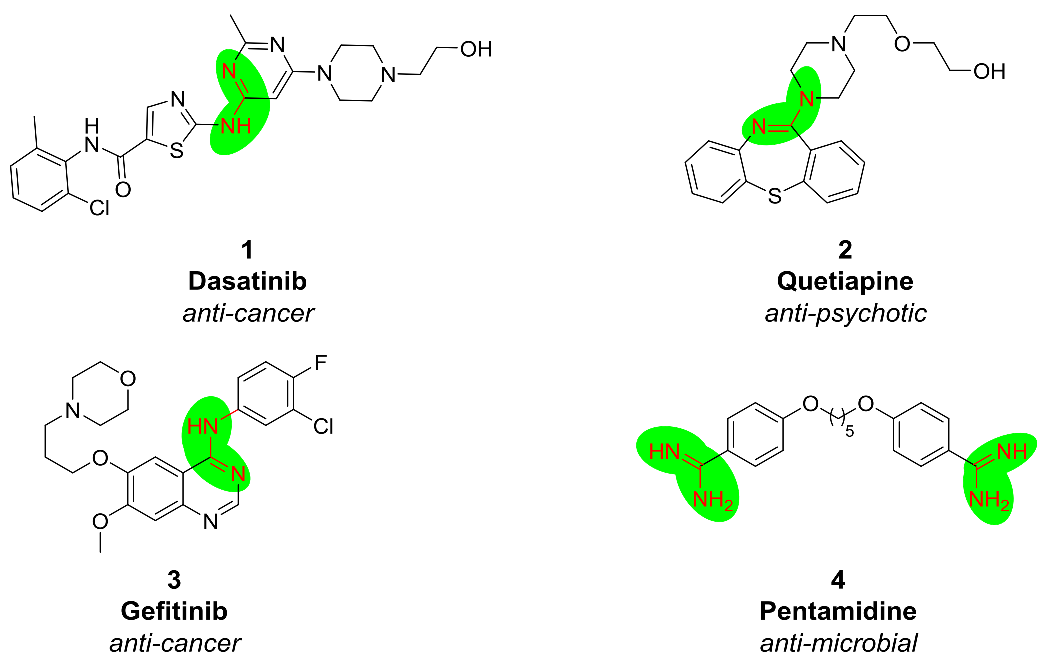
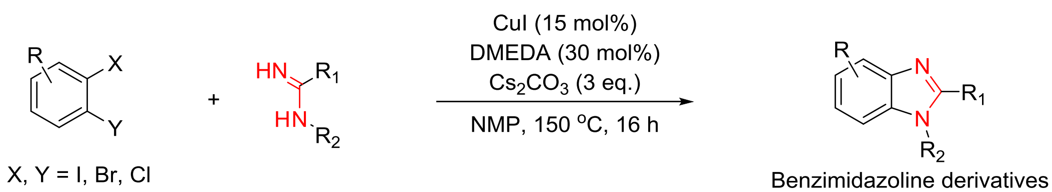


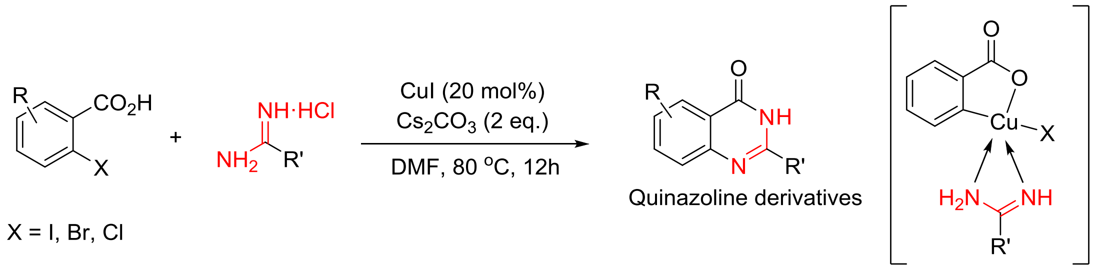
Figure 3.3: Selected examples of amidine containing drugs.

Amidines are also important synthetic precursors used in the synthesis of biologically important heteroaromatics such as benzimidazoles,[8] and quinazolines.[9] Benzimidazoles are highly important class of compounds in the pharmaceutical industry.[10] The benzimidazole core structure can be found in many commercial drugs such as Prilosec, Nexium, Protonix, Atacand, Famvir, and Vermox, as well as in numerous experimental drug candidates which are under clinical trials in in a wide range of therapeutic areas.[11] Therefore, it is not surprising that the synthesis of benzimidazoles has always been of great interest to organic chemists.[12] For example, Deng et al in 2009 reported the synthesis of benzimidazole by inter and intramolecular amination using amidines and dihaloarenes as coupling partners ; CuI/*N*,*N′*-dimethylethylenediamine (DMEDA) proved to be a reasonably efficient catalyst system for the amination of aryl halides with amidines (Scheme.3.1).[13]



Scheme 3.1: Synthesis of 1*H*-benzimidazoles via Cu-catalyzed tandem amination with amidines.

Quinazolinone is a key core structure that occurs in many natural products.[14] Which have useful biological and medicinal activities *e.g.* these can be used as hypnotic, sedative, analgesic, anticonvulsant, antitussive, antibacterial, antidiabetic, anti-inflammatory, and antitumor agents.[9, 15] Additionally, some therapeutic agents containing quinoline core are either in the market or in clinical trials for the treatment of cancer.[16] Among diverse reported strategies, an efficient synthesis of quinazolin-4(3*H*)-one derivatives appeared in 2009 using Cu-catalyst. The reaction of 2-bromo- and 2-iodobenzoic acid derivatives with amidines gave the quinazoline derivatives. The reactions were performed at 80 ^{o}C with CuI as catalyst without the addition of a ligand. A mechanistic rationale for reaction was also given pointing to the formation of a Cu–carboxylate prior to the carbon-halogen bond activation step via oxidative addition (Scheme 3.2).[17]



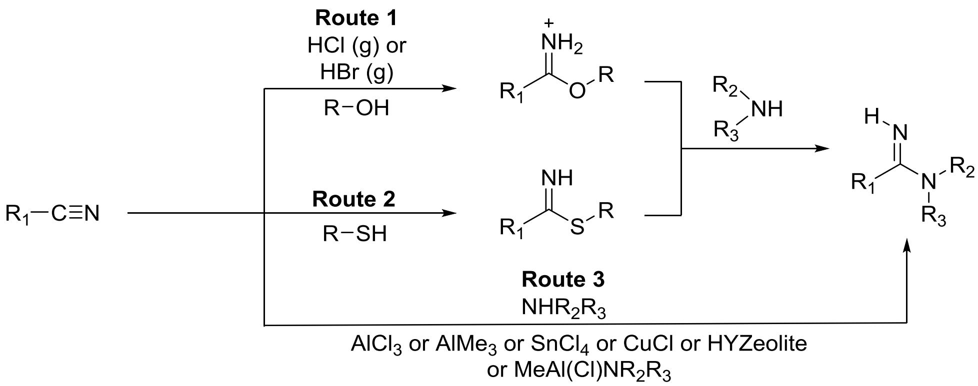
Scheme 3.2: Quinazolin-4(3*H*)-one synthesis *via* tandem reaction of 2-halobenzoic acids with amidines.

3.2 Synthesis of amidines:

Wide functional and synthetic applications rendered amidine as a crucial target in organic synthesis. The most common methods for the amidine synthesis start from nitriles, amides, and thioamides. All these methods involve the formation of an iminium/imine synthon followed by the attack of a nitrogen nucleophile.

3.2.1 Synthesis of amidines from nitriles

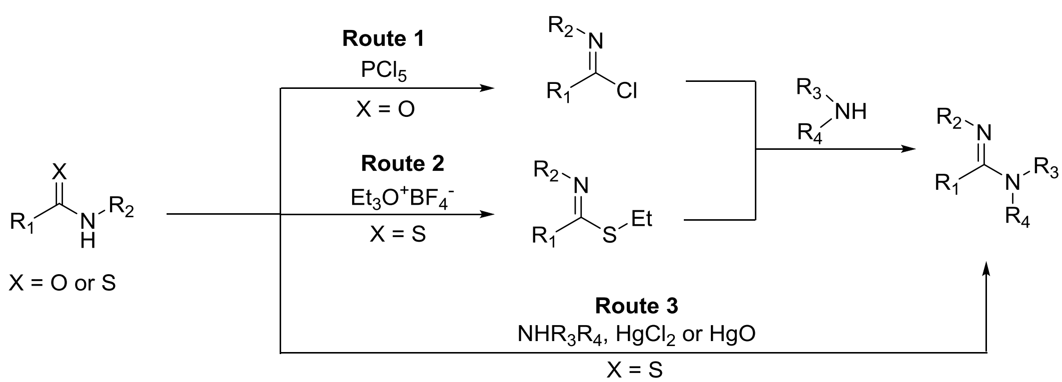
The most common way of making primary and secondary amidines is the Pinner reaction.[18] According to the reaction, nitrile on treatment with an alcohol in the presence of gaseous hydrogen halide (halide = chloride or bromide) in anhydrous condition formed the amidic ester salt which on further treatment with amine gave the corresponding amidine (Scheme 3.3, route 1). Further modification of the Pinner reaction involves the formation of isolable thioamidic ester intermediate which upon reaction with amine gave amidine (Scheme 3.3, route 2).[19] Preparation of *N*-substituted or *N,N*-disubstituted amidines have been extensively achieved by a method in which the nitrile was heated with a primary or secondary amine in the presence of aluminium chloride (Scheme 3.3, Route 3).[20] Other Lewis acids[21] such as methylchloroaluminium amide[22] were also used to activate the nitrile but also metal salt[23] and zeolite[24] were also employed (Scheme 3.3, Route 3). When the nitrile is flanked with electron withdrawing groups, it reacts directly with amines to give the corresponding amidine without any activation.



Scheme 3.3: Synthesis of primary and secondary amidine from nitrile.

3.2.2 Synthesis of amidines from amides and thioamides

Tertiary amidines or *N,N′*-secondary amidines can be prepared from amides or thioamides (Scheme 3.4). The monosubstituted amide upon treatment with phosphorous pentachloride forms imidoyl chloride[25] which on further reaction with an amine gives amidine (Scheme 3.4, route 1).[26] Activation of thioamide via alkylation with triethyloxonium tetrafluoroborate gave thioimidic esters which reacted more readily with amine to give amidine (Scheme 3.4, route 2).[27] Thioamide on condensation with amine directly forms amidine without any activation (Scheme 3.4, route 3).[28] Addition of sulfur scavengers such as $HgCl_2$ or HgO further improves the rate of reaction.[29]

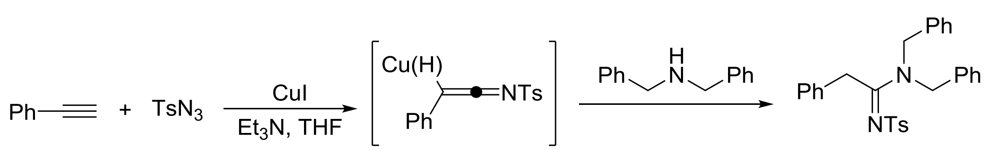


Scheme 3.4: Synthesis of secondary and tertiary amidine from amide and thioamide.

The traditional synthesis of amidines as mentioned above involves either strong acidic, or alkaline or strongly reducing reaction conditions and also requires high temperatures. As a result these methods are less suitable for the synthesis of highly functionalized amidines. Only few strategies have adopted a one-pot approach albeit with limited scope and generality.[30] Recently, new one-pot strategies for amidine synthesis have evolved based on transition metal catalysis (copper, palladium, etc) *via* the formation of ketenimines.[31]

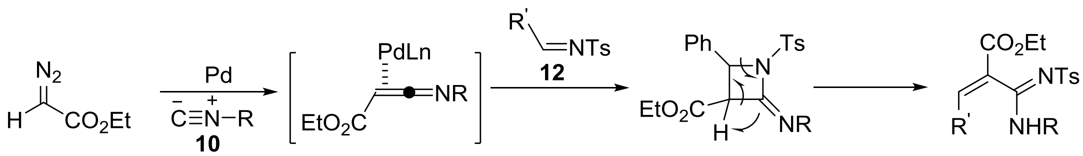
3.2.3 Synthesis of amidines from ketenimines

For example, Chang and co-workers reported the synthesis of amidines by copper catalyzed multi-component reactions of *N*-sulfonyl azides, alkynes and amines in which *N*-sulfonyl ketenimine was generated from terminal alkyne and sulfonyl azide on which amine attacks to give corresponding amidine. Phenylacetylene **5** upon treatment with tosyl azide **6** in presence of CuI and triethylamine as a base in THF produced ketenimine intermediate **7** which upon reaction with dibenzyl amine gave amidine **8** (Scheme 3.5)[32]



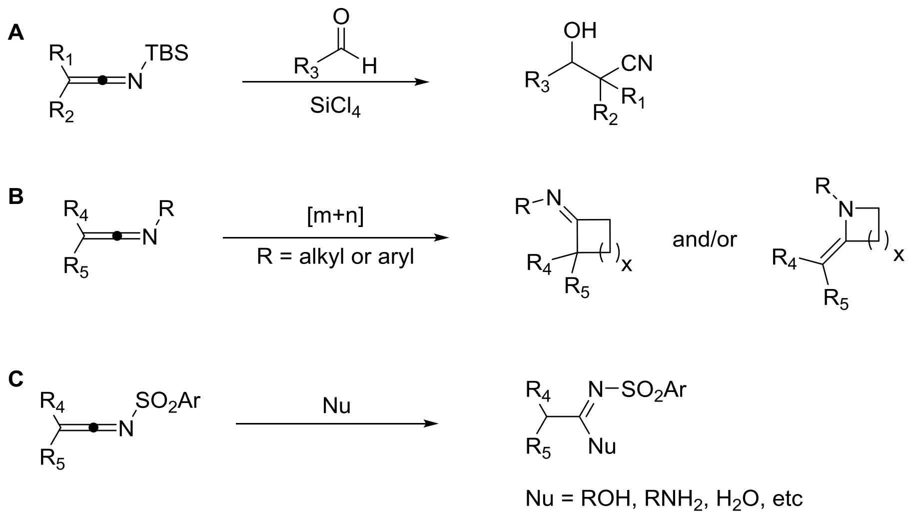
Scheme 3.5: Copper catalyzed multi-component reaction for the formation of amidine.

Recently, Qian and co-workers reported the palladium catalyzed one-pot synthesis of acrylamidine using ethyl diazoacetate, isocyanide, and imine.[33] The coupling of diazoacetate **9** and isocyanide **10** in presence of palladium catalyst afforded the ketenimine intermediate **11** which upon subsequent [2+2] cycloaddition reaction with imine **12** produced 2-iminoazetidine **13** intermediate.[34] Spontaneous ring opening of **13** gave acrylamidine **14** (Scheme 3.6). Facile formation of ketenimine and its reactivity have established this moiety as crucial synthetic intermediate in organic synthesis. Acrylamidines[33, 35] are important skeleton for atropisomerism studies,[36] they are also a synthetic precursor of amidines. Considering the wide synthetic applicability of amidine,[37] the α,β-unsaturation can be viewed as a handle for various chemical transformations *e.g.* epoxidation, dihydroxylation, C═C cleavage, Michael addition, etc.



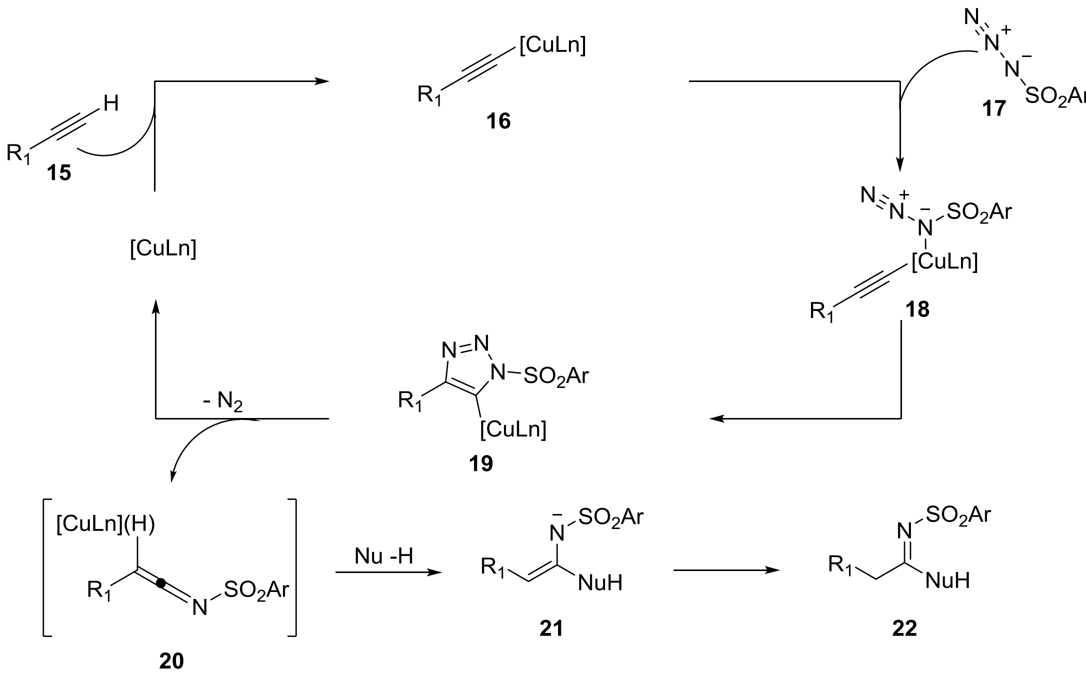
Scheme 3.6: Palladium catalyzed multi-component reaction for the formation of acrylamidines.

The above two reports of amidine synthesis based on ketenimine chemistry inspired us to explore alternative reactions of the intermediate for the synthesis of acrylamidines. In last two decades, several approaches have been developed for the generation of ketenimines, and further exploration of several new chemical reactions. Ketenimines are used both as electrophiles and nucleophiles, and five different classes of reactions on ketenimines are reported which cover nucleophilic additions, radical additions, cycloaddition reactions, electrocyclic ring closure reactions, and σ rearrangements, many articles have been reviewed on this part of chemisrty.[31b, 38] These reactions have been used for the construction of various complex compounds including biologically relevent heterocycles. On comparison with their oxygen congeners ketenes,[39] the ketenimines have an additional substitution site N1 which decides their diverse and tunable reactivity.[38b, 40] It is interesting that the type of N substitution plays a key role in the reactivity of ketenimine. While the silyl ketenimine **A** is well-known for its strong C_3-nucleophilicity,[41] ketenimine **B** carrying *N*-alkyl/aryl groups are often observed in concerted cyclization processes,[42] the reactivity of the *N*-sulfonyl ketenimine **C** is highly electrophilic in nature and mainly characterized by initial nucleophilic attack on C_2 of the ketenimines (Scheme 3.7).[32, 43]



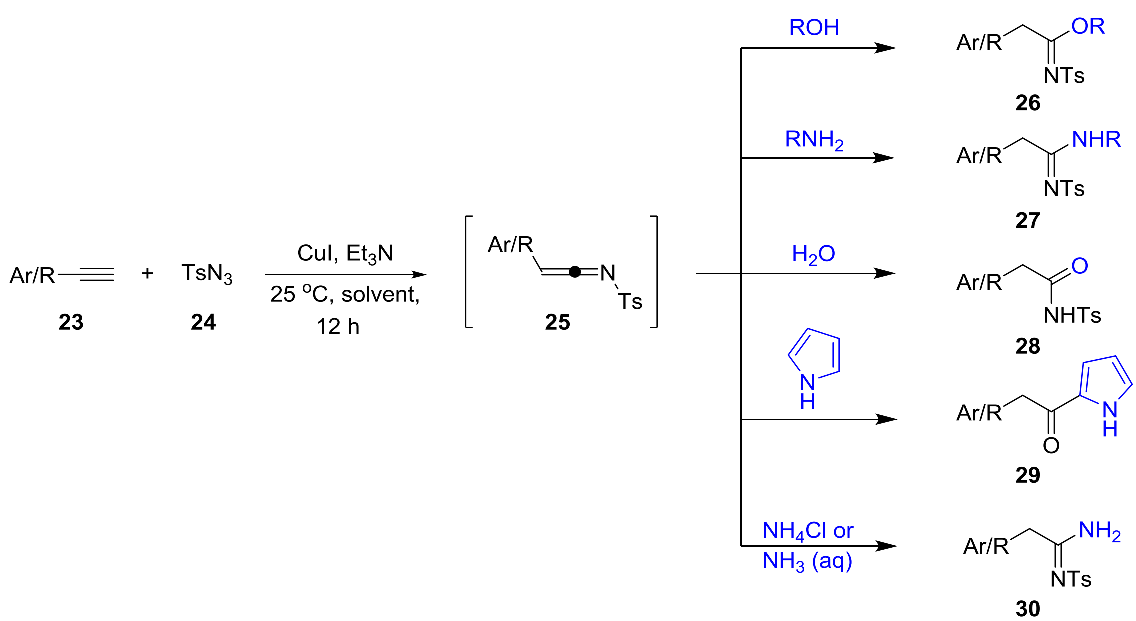
Scheme 3.7: Reaction diversity of ketenimines.

Sulfonyl, phosphoryl, and certain acyl azides are an excellent source of one nitrogen source in copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC) as they release N_2 molecule from the azido species to give a highly reactive ketenimine intermediate and these intermediates are known to undergo nucleophilic addition with several nucleophiles readily.[31b, 38c, 44] The plausible mechanistic pathway for ketenimine generation and subsequent nucleophilic addition is presented in Scheme 3.8. In the initial step, it is proposed that the alkyne **15** and the sulfonyl azide **17** undergo a cycloaddition reaction similarly as in the copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction which involves aryl/alkyl azide and the terminal alkyne.[45] The cycle proceeds through the reaction of copper acetylide **16** with sulfonyl azide **17**. The coordination of sulfonyl azide with the copper that bears acetylide forms the intermediate **18** which cyclizes to give triazole ring **19**. Later, this triazole undergo ring opening by removal of dinitrogen molecule to give ketenimine intermediate **20.** The subsequent addition of nucleophiles gives the corresponding product **22**.



Scheme 3.8: Proposed mechanistic pathways for the copper-catalyzed multi component reactions.

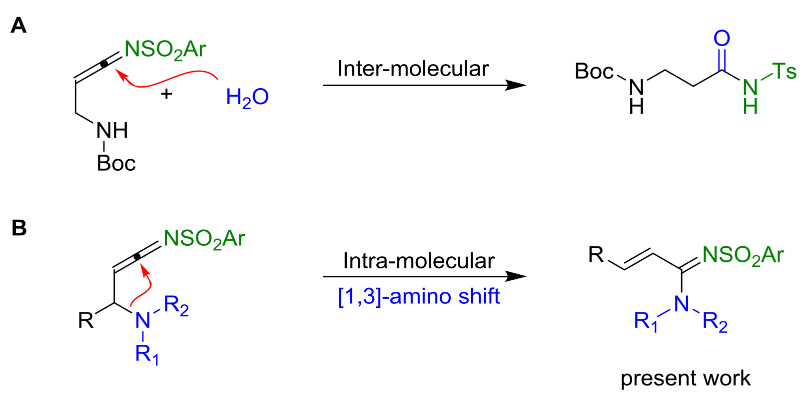
There are several reports in the literature where ketenimines undergo nucleophilic addition reactions[38c] with alcohols[32, 46] amines,[32] water,[43h] pyrroles,[43f] indoles,[43f] ammonium salts,[47] etc. to give corresponding imidates, amidines, amides, ketones, and amidines respectively (Scheme 3.9).



Scheme 3.9: Reaction of ketenimine with possible nucleophiles.

As the chemistry of ketenimine is extensively explored so far by developing the methodologies using external nucleophiles, we planned to construct a system where there will be some internal nucleophile tethered in a molecule which will be able to capture the in situ generated ketenimine. Therefore, while going through literature, we came across to the report of 2005 by Chang and co-workers, the nucleophilic addition of water to ketenimine bearing a tethered –NHBoc group to form the corresponding β-amino sulfonamide (Scheme 3.10).[43h]

We envisioned that the amino group can undergo 1,3-shift if it is made sufficiently nucleophilic by removing Boc group because Wentrup et al. have reported a ketenimine–ketene rearrangement mediated by a flanking amino group under flash vacuum thermolysis conditions.[48] However, Cu(I)-catalytic formation of ketenimine is advantageous to investigate the 1,3-shift under milder reaction conditions. Therefore we synthesized propargyl amine where the amine group is at third position with respect to the central carbon atom of ketenimine, we envisaged that it will attack on ketenimine to form unstable four member cyclic intermediate which will open by migrating amino group from C_1 to C_3 to give migrated product acrylamidine (Scheme 3.10).

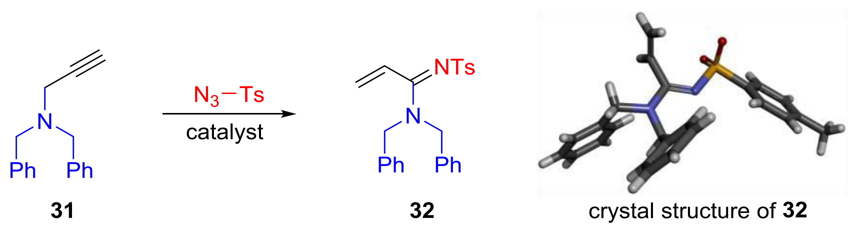


Scheme 3.10: Addition reaction of ketenemine with external nucleophile (A) and internal nucleophile (B).

3.3 Results and Discussion:

In the initial studies, we have planned to construct the simplest propargylamine substrate to carry out the copper catalyzed reaction and checked it's feasibility over the various copper (I) salts in chloroform as a solvent. We have synthesized *N,N′*-dibenzyl propargyl amine **15** as a simple substrate and the reaction was optimized by varying the copper (I) salts. When *N,N′*-dibenzyl propargylamine **31** was treated with 1.1 equivalent of tosyl azide and 1.2 equivalent of Et_3N in $CHCl_3$ in presence of CuI (10 mol%) as a catalyst at room temperature, the reaction was completed in 30 minutes to give acrylamidine **32** with 84% of yield (Table 3.1, entry1). The structure of **32** was confirmed by NMR and single crystal X-ray diffraction studies (Table 3.1). Switching from CuI to CuBr (10 mol%) brought some dramatic results out, the reaction became very fast and the reaction time dropped to 3 minutes, giving **32** which was observed by the vigorous bubbling of N_2 gas and warming of the round bottom flask improving the yield to 95% (Table 3.1, entry 2). A further alteration of catalyst to CuCl (10 mol%) resulted into 96% of yield, completing reaction in 3 minutes (Table 3.1, entry 3). In the absence of CuCl, formation of **32** was not observed confirming the importance of catalyst (Table 3.1, entries 4 and 6). The catalytic reaction when carried out in the absence of Et_3N proceeded for 30 minutes and furnished **32** with only 60% yield (Table 3.1, entry 5).

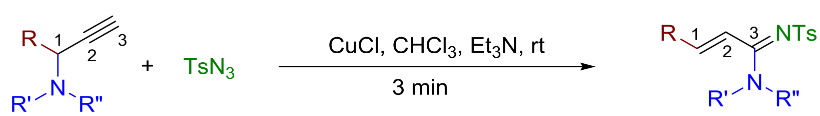
Table 3.1 Cu(I) catalyzed formation of acrylamidines **32** from propargylamine **31** and its crystal structure.



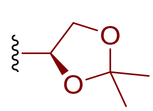
Entry	Catalyst	Solvent	Base	Time (min)	Yield
1	CuI	$CHCl_3$	Et_3N	30	84%
2	CuBr	$CHCl_3$	Et_3N	3	95%
3	CuCl	$CHCl_3$	Et_3N	3	96%
4	—	$CHCl_3$	—	30	0%
5	CuCl	$CHCl_3$	—	30	60%
6	—	$CHCl_3$	Et_3N	30	0%

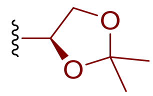
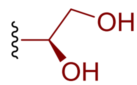
To establish the scope of methodology, the optimized reaction conditions were then applied to a wide range of propargylamines **33a-33j** having alkyl substitution (R = alkyl) at the C_1-position and acyclic amino groups (–NR´R´´) to deliver corresponding acrylamidines **34a-34j** (Table 3.2, entries 1-10). The effect of different R groups on the sulfonylamidine was studied by keeping fixed $–NR_2R_3 = –NBn_2$ and no significant difference was observed upon variation of the R group through ethyl (entry 1, yield = 96%), butyl (entry 2, yield = 91%), cyclohexyl (entry 3, yield = 91%) and (*S*)-2,2-dimethyl-1,3-dioxolane (entry 4, yield = 95%). A subsequent modification of the amino group ($–NR´R´´ = –NEt_2$) also did not offer any influence on the time and yields of the reactions. Excellent yields of 95%, 96%, 96% and 89% for R = Et (entry 5), Bu (entry 6), cyclohexyl (entry 7) and (*S*)-2,2-dimethyl-1,3-dioxolane (entry 8), respectively were observed in these cases. A subsequent introduction of unsymmetrical amino group (–NR´R´´ = –NMeBn) did not influence the yield of the acrylamidine **34i** was isolated in 93% yield (entry 9). When the effect of neighboring nucleophilic groups were evaluated by introducing a diol containing R-group, the desired [1,3]-sigmatropic rearranged product **34j** was obtained in moderate yield (60%). However, no byproduct that corresponds to attack of alcohol nucleophile on ketenimine intermediate was isolated.

Table 3.2. Scope of the aza-[1,3]-sigmatropic strategy with aliphatic substituent at C_1-position.



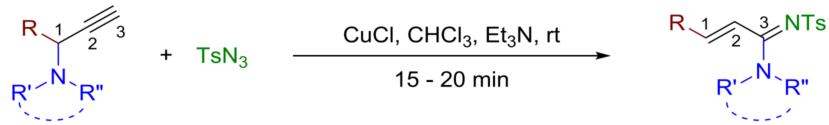
33a-33j **34a-34j**

Entry	**33**	–R	–NR'R"	**34**	Yield
1	**33a**	–Et	-NBn2	**34a**	96%
2	**33b**	–Bu	-NBn2	**34b**	91%
3	**33c**	-Cy	–NBn2	**34c**	91%
4	**33d**		–NBn2	**34d**	95%

5	**33e**	⌇–Et	⌇-NEt_2	**34e**	95%
6	**33f**	⌇-Bu	⌇-NEt_2	**34f**	96%
7	**33g**	⌇-Cy	⌇-NEt_2	**34g**	96%
8	**33h**		⌇-NEt_2	**34h**	89%
9	**33i**	⌇–H	⌇-NMeBn	**34i**	93%
10	**33j**		⌇-NBn_2	**34j**	60%

On the basis of these findings, we next explored the effect of cyclic amino groups such as pyrrolidine, piperidine and morpholine in the formation of acrylamidines. Surprisingly, it was found that reactions of propargylamines **33k-33r** with tosyl azide occurred with much slower rate (reaction time = 15 – 20 min) under the current conditions using CuCl (Table 2.3, entries 1-8). When pyrrolidine containing propargylamines, **33k** (entry 1) and **33l** (entry 2) were used, moderate yields of **34k** (58%) and **34l** (70%), respectively were observed. For piperidine ring containing propargylamines **33m** (entry 3), **33n** (entry 4) and **33o** (entry 5) isolated yields were significantly low, *i.e.* 48%, 51% and 63%, respectively. Propargylamines **33p** (entry 6), **33q** (entry 7) and **33r** (entry 8) having morpholine ring when subjected to the Cu-catalyzed reaction with tosyl azide, significant improvement in yields, *i.e.* 83% for **34p**, 85% for **34q** and 83% for **34r** were observed.

Table 3.3. Scope of the aza-[1,3]-sigmatropic strategy with aliphatic substituent at C_1-position having cyclic amines.

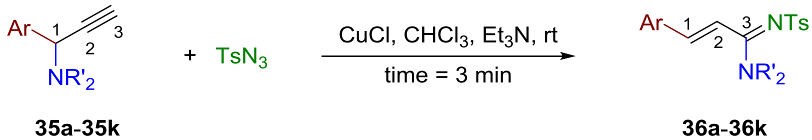


33k-33r **34k-34r**

Entry	33	-R	-NR'R"	34	Yield
1	**33k**	-Bu	-*N*-pyrrolidine	**34k**	58%
2	**33l**	-Cy	-*N*-pyrrolidine	**34l**	70%
3	**33m**	-H	-*N*-piperidine	**34m**	48%
4	**33n**	-Bu	-*N*-piperidine	**34n**	51%
5	**33o**	-Cy	-*N*-piperidine	**34o**	63%
6	**33p**	-H	-*N*-morpholine	**34p**	83%
7	**33q**	-Bu	-*N*-morpholine	**34q**	85%
8	**33r**	-Cy	-*N*-morpholine	**34r**	83%

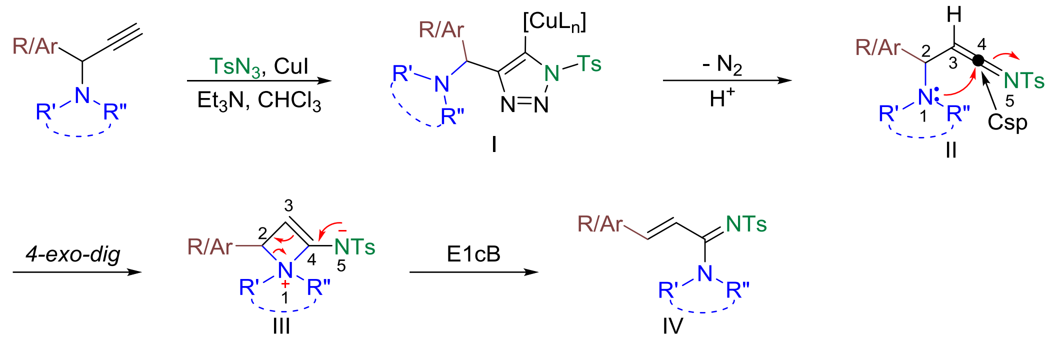
To expand the scope of the reaction, we evaluated the effect of aromatic groups at the C_1-position by introducing propargylamines **35a-35k** (Table 3.4, entries 1-12). In these cases all reactions were completed within 3 minutes. For the substrates **35a** (Ar = Ph) and **35b** (Ar = C_6H_4-*p*-Me), sigmatropic shift reaction provided 96% and 93% yields of **36a** and **36b**, respectively. For aryl groups containing electron donating –OMe subatituent at *ortho*-, *meta*- and *para*- positions (Table 3.4, entries 3-5), reactions proceeded smoothly with excellent yields of **36c** (89%), **36d** (96%), and **36e** (95%), respectively. On the other hand, introduction of strong electron withdrawing substituents *ortho*-NO_2 (entry 7), *meta*-NO_2 (entry 8) and *para*-CN (entry 9) resulted in slight lowering of yields (80% for **36f**, 75% for **36g** and 71% for **36h**). With weak electron withdrawing *meta*-Br (entry 10) substituent on the other hand, there was no compromise in the yield of **36i** (96%). When extended aromatic groups (Ar = α-naphthyl and 1-pyrenyl) were introduced reactions provided excellent yields of **36j** (96%) and **36k** (98%), respectively.

Table 3.4. Scope of the 1,3-amino group migration strategy with aromatic substituent at C_1-position.



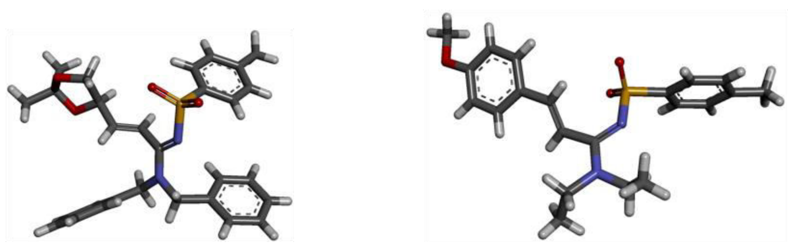
Entry	35	⌇–Ar	⌇–NR'$_2$	36	Yield
1	**35a**	⌇-Ph	⌇-NEt_2	**36a**	96
2	**35b**	⌇–(C_6H_4-*p*-Me)	⌇-NEt_2	**36b**	93
3	**35c**	⌇–(C_6H_4-*o*-OMe)	⌇-NBn_2	**36c**	89
4	**35d**	⌇–(C_6H_4-*m*-OMe)	⌇-NBn_2	**36d**	96
5	**35e**	⌇–(C_6H_4-*p*-OMe)	⌇-NEt_2	**36e**	95
7	**35f**	⌇–(C_6H_4-*o*-NO_2)	⌇-NBn_2	**36f**	80
8	**35g**	⌇–(C_6H_4-*m*-NO_2)	⌇-NBn_2	**36g**	75
9	**35h**	⌇–(C_6H_4-*p*-CN)	⌇-NBn_2	**36h**	71
10	**35i**	⌇–(C_6H_4-*m*-Br)	⌇-NBn_2	**36i**	96
11	**35j**	⌇–(α-Naphthyl)	⌇-NEt_2	**36j**	96
12	**35k**	⌇–(1-pyrenyl)	⌇-NEt_2	**36k**	98

A plausible mechanism for the formation of acrylamidine from *N,N*-disubstituted propargylamine is depicted in Scheme 3.11. *N*-Sulfonyl triazolyl copper intermediate I, formed upon reaction of propargylamine with tosyl azide, releases one molecule of N_2 and undergoes protonation to generate ketenimine II. Subsequent transformation of II to IV occurs in two steps. At first a 4-*exo-dig* cyclization of II generates the intermediate III. The tethered nitrogen (N_1) due to its available lone pair facilitates the attack on the highly electrophilic C_4-center. The formation of III is also favored due to delocalization of the negative charge on the N_5-center by a sulfonyl group. A subsequent E1cB elimination type ring opening process results in the formation of IV. Generation of III from II is considered as the rate determining step due to formation of a strained 4-membered ring from an acyclic system. This prediction was supported by longer reaction times of cyclic amino group containing propargylamines **33k–33r** and poorer yields of the corresponding products **34k–34r**. In these cases, formation of spiro-transition states contributes to the slower reaction rates.



Scheme 3.11: Plausible mechanism for the formation of acrylamidines.

The preferential *E*-stereochemistry around the C=C bond as predicted by the mechanism is also confirmed by single crystal X-ray diffraction studies of **34d** and **36e** (Figure 3.4).



34d **36e**

Figure 3.4: X-ray crystal structures of **34d** and **36e**.

Further, the conversion of propargylamine to acrylamidine was demonstrated by fluorimetric method. In this experement, an aliquot, either from the solution of pyrene substituted propargylamine **35k** in CH_3Cl or from the reaction mixture of **35k** with TsN_3 in presence of CuCl and Et_3N in $CHCl_3$ (after 3 minute) was placed in HEPES buffer (20 µM in 10 mM HEPES, pH = 7.4) and fluorescence spectrum was recorded. The propargylamine **35k** (20 µM in 10 mM HEPES, pH = 7.4) displayed a strong fluorescence with λ_{em} = 485 nm when excited at λ_{ex} = 353 nm (Figure 3.5A). On the other hand, the reaction mixture of **35k** with TsN_3 exhibited a strong fluorescence with λ_{em} = 537 nm when excited at λ_{ex} = 375 nm. The observed 52 nm red shift was corroborated to formation of more conjugated acrylamidine **36k**. When placed under the hand-held UV-lamp (λ_{ex} = 375 nm), **35k** displayed strong cyan fluorescence while the reaction mixture of **35k** with TsN_3 exhibited a strong green fluorescence (Figure 3.5B). This color changing characteristic allows the [1,3]-sigmatropic shift process to be monitored by naked eye.

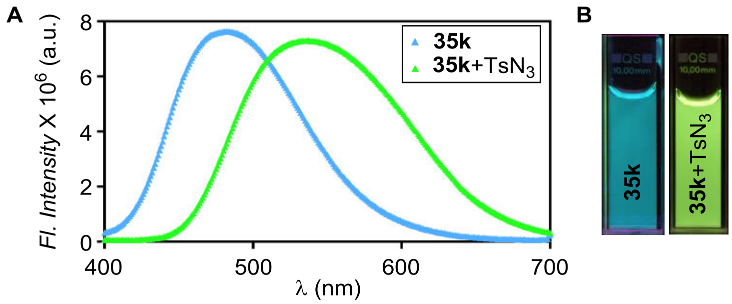
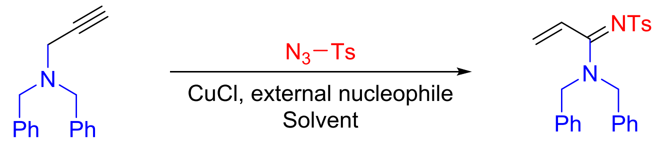


Figure 3.5: Fluorescence spectra of **35k** (20 µM) and [16k+TsN_3] (20 µM) recorded in 10 mM HEPES, pH = 7.4 (**A**); photographs of cuvettes containing either16k or [16k+TsN_3] in 10 mM HEPES, pH = 7.4 taken under the hand-held UV- lamp (**B**).

Further, we have carried out this reaction in presence of external nucleophiles to check the competitive effect of internal nucleophile over external nucleophile (Table 3.5). When the reaction was carried out in presence of 3 equivalents of water, the reaction yielded only the desired product **32** with the yield 94% and no side product was observed (Table 3.5, entry 1). Similarly, the reaction was also carried out in presence of other nucleophiles like EtOH, *S*-methyl cysteine and *N*-acetyl cysteine which yielded the desired product with 91, 91, and 90% of yields respectively without giving any side product. Later, we carried this reaction in water as solvent, we observed **32** with 70% of yield. We did not observe the attack of water on ketenimine to give corresponding amide. This promising nature of reaction towards the formation of acrylamidine **32** indicates that intramolecular reactions are more favorable than intermolecular reactions. The elegancy of reaction inspired us to utilize this reaction in some biological aspect.

Table 3.5 Feasibility of reaction in presence of external nucleophiles.



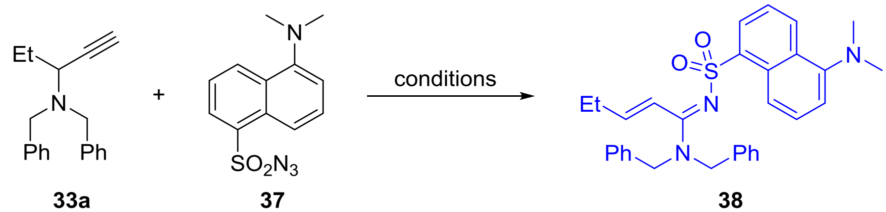
31 32

Entry	Catalyst	Solvent	Base	Competitive Nucleophile	Equivalents	Yield
1	CuCl	$CHCl_3$	Et_3N	H_2O	3	94%
2	CuCl	$CHCl_3$	Et_3N	EtOH	3	91%
3	CuCl	$CHCl_3$	Et_3N	SMC[a]	3	91%
4	CuCl	$CHCl_3$	Et_3N	NAC[b]	3	90%
5	CuCl	H_2O	Et_3N	H_2O	—	70%

[a] *S*-methyl cysteine, [b] *N*-acetyl cysteine

The selectivity feature of the intramolecular amine migration over the attack of H_2O as external nucleophile prompted us to explore a fluorogenic process under the physiological conditions. Non-fluorescent dansylazide **37** and propargylamine **33a** when reacted in $CHCl_3$ solvent and in the presence of CuCl as catalyst for 15 minutes, strongly fluorescent acrylamidine **38** was formed with 95% isolated yield (Table 3.6, entry 1). The increase in reaction time in this case can be attributed to the 5-(dimethylamino)naphthalene group which contribute in decreasing the electron withdrawing effect of the sulfonyl group. When the reaction of **37** with **33a** was carried out in HEPES buffer (10 mM, pH = 7.4) and in the presence of water soluble complex $[Cu(CH_3CN)_4]PF_6$ (10 mol%),[21] complete conversion of **37** to **38** was observed within 30 minutes with 60% yield (Table 3.6, entry 2). Under the reaction conditions, bulk water molecules did not participate as competitive nucleophile to produce any β-amino sulfonamide which was observed by Chang and co-workers while dealing with Boc-protected propargylamine.[43h]

Table 3.6. Fluorogenic reaction of **33a** and dansylazide **37**.



Entry	Cat.	Solvent	Base	Time (min)	yield
1	CuCl	$CHCl_3$	Et_3N	15	95
2	$[Cu(CH_3CN)_4]PF_6$	HEPES	-	30	60

Studies on photophysical properties of **37** (50 µM in 10 mM HEPES, pH = 7.4) and **38** (50 µM in 10 mM HEPES, pH = 7.4) displayed similar UV-absorption bands centred at λ_{max} = 337 nm (Figure 3.6A). When excited at λ_{ex} = 337 nm, the azide **37** displayed negligible fluorescence (Figure 3.6B). On the other hand, the acrylamidine **38** exhibited strong fluorescence emission centered at λ_{em} = 470 nm. When fluorescence intensities of **37** and **38** at λ = 470 nm were compared, an *OFF- ON* ratio of 251-fold was observed confirming the fluorogenic process. The *OFF-ON* feature enabled a naked eye detection of the process under the hand-held UV-lamp (λ_{ex} = 375 nm) via the strong blue fluorescence of **38** in comparison to **37** (Figure 3.6C).

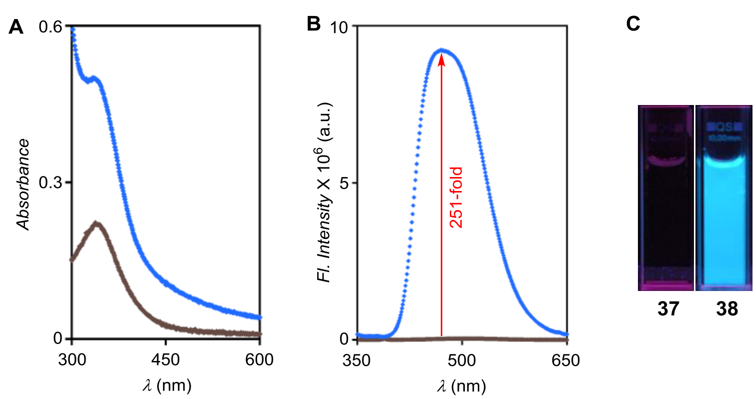
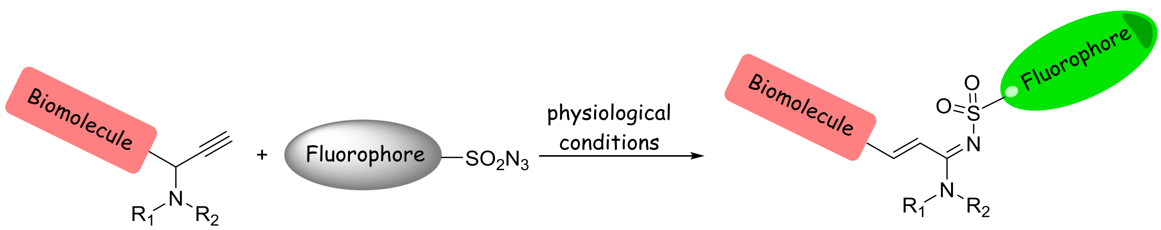


Figure 3.6. UV-visible spectra of **37** (50 µM) and **38** (50 µM) recorded in 10 mM HEPES, pH = 7.4 (**A**); fluorescence spectra of **37** and **38** (**B**); photographs of cuvettes taken under the hand-held UV-lamp (**C**).

Observing the above results and viability of reaction towards the external nucleophiles, it can be used for the tagging of biologically important molecules to study their intracellular processes and location. The propargyl amine moiety can be incorporated in any biomolecule and the resultant biomolecule can be incubated into the cell along with dansyl azide and water soluble copper catalyst to carry out the reaction to obtain the fluorescent acrylamidine product even in the presence of bio-relevant nucleophiles. The resultant fluorescent product containing biomolecule can be studied further (Scheme 3.12).



Scheme 3.12: Tagging of biomolecules using *OFF-ON* phenomenon.

3.4 Conclusion:

In conclusion, we have demonstrated a new reaction of ketenimine bearing a tethered amino group facilitating its 1,3-migration. The methodology portrays rapid reactions of *N,N*-disubstituted propargylamines with tosyl azide under CuCl catalytic, open air conditions to synthesize acrylamidines. For propargylamines with an alkyl/aryl substituent at the C_1-position, products were isolated in moderate to excellent yields. However, for *N,N*-cyclic substituted propargylamines, reactions were slower and isolated yields were also affected. The 1,3-migration of amine was predicted via a 4-*exo-dig* cyclization followed by an E1cB elimination type ring opening step. The ketenimine intermediate which is formed upon spontaneous decomposition of initial triazole product participates selectively in the rearrangement even in the presence of competing nucleophiles *e.g.* H_2O, EtOH, *S*-methyl cysteine and *N*-acetyl cysteine. The *E*-stereochemistry around the C=C of acrylamidines were confirmed by ^{1}H-NMR and crystallographic data. With a pyrene chromophore at the C_1-position, the formation of a more conjugated product was demonstrated by 22 nm red shift of lmax and change in fluorescence from cyan to green. Viability of the reaction in the presence of ranges of competing nucleophiles triggered the development of a new fluorogenic reaction starting from dansylazide under the physiological conditions. Viability of the reaction in the presence of various bio-relevant nucleophiles and a 251-fold fluorescent *OFF-ON* characteristic offers the future potential of the strategy in the development of fluorescent probes and tagging of the biomolecules.

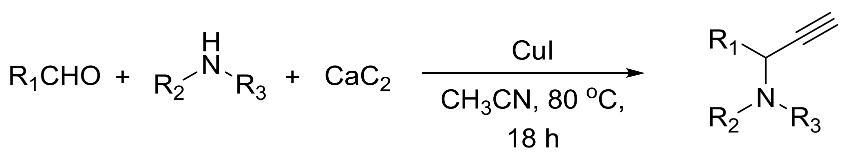
3.5 Experimental Section

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.

3.5.1 Experimental Procedures:

Preparation of propargylamine derivatives:

One step protocol of three-component aldehyde-amine-calcium carbide reaction:[49]



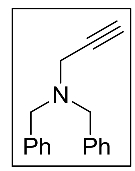
Scheme 3.13: Synthesis of propargylamine via one step protocol of three-component aldehyde-amine-calcium carbide reaction.

General Procedure A: To a two-neck round bottomed flask fitted with reflux condenser and placed under the N_2 atmosphere was added the aldehyde (1.0 mmol) followed by addition of acetonitrile (2 mL). To the solution were added amine (1.2 mmol), calcium carbide (1.5 mmol) and CuI catalyst (0.1 mmol). The reaction mixture was stirred at 80^o C for 18 h. After the completion of the reaction, the mixture was passed through celite pad and washed with Et_2O (2 ×

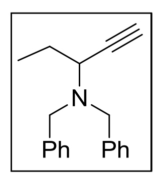
10 mL). The combined filtrate was concentrated under reduced pressure to obtain liquid which was purified by column chromatography over silica gel to obtain the required propargylamine.

General Procedure B: To the round bottomed flask under N_2 atmosphere was added propargyl bromide (1.0 mmol) in acetonitrile (2 mL). To this solution were added amine (1.0 mmol), anhydrous K_2CO_3 (2.0 mmol) at 0^o C and the resultant reaction mixture was stirred at rt for 18 h. After completion of reaction, acetonitrile was evaporated and obtained residue was washed with water and extracted with EtOAc (2 × 5 mL) and dried over anhydrous Na_2SO_4. The organic solvent was evaporated and resultant crude product was purified by column chromatography.

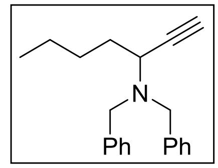
Synthesis of *N,N*-dibenzylprop–2-yn-1-amine (31) [$C_{17}H_{17}N$]:[50] The compound **31** was prepared by following the *General Procedure B*. Starting from propargyl bromide (1.0 g, 8.40mmol), dibenzylamine (1.6 mL, 8.40mmol) and K_2CO_3 (2.30 g, 16.8 mmol) compound **31** was obtained (1.3 g, yield = 66%) as colorless solid. after column chromatographic purification. *Eluent*: 3% EtOAc in Petroleum ether (R_f = 0.70). Obtained data was matched with the reported literature data.



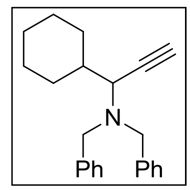
Synthesis of *N,N*-dibenzylpent–1-yn-3-amine (33a) [$C_{19}H_{21}N$]: The compound **33a** was prepared by following the *General Procedure A*. Starting from propionaldehyde (1.0 g, 17.21 mmol), dibenzylamine (3.92 mL, 20.65 mmol) and CaC_2 (1.65 g, 25.81 mmol) in the presence of CuI (326 mg, 1.72 mmol) compound **33a** was obtained (3.45 g, yield = 76%) as colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). IR (neat): ν_{max}/cm^{-1} 3299, 2966, 2933, 1577, 1494, 1452, 1365, 1148, 1129, 1072, 1027; ^{1}H NMR (400 MHz, DCl_3): δ 7.41 (d, *J* = 7.56 Hz, 4H), 7.31 (t, *J* = 7.44 Hz, 4H), 7.24 (t, *J* = 7.24 Hz, 2H), 3.84 (d, *J* = 13.84 Hz, 2H), 3.42 (d, *J* = 13.84 Hz, 2H), 3.33 (td, *J* = 7.68 Hz, 1H), 2.32 (d, *J* = 2.16 Hz, 1H), 1.80 – 1.62 (m, 2H), 0.97 (t, *J* = 7.36 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$):δ 139.8, 128.8, 128.3, 127.0, 82.1, 72.6, 54.8, 53.3, 26.9, 11.2; HRMS (ESI): Calc. for $C_{19}H_{22}N$ $[M+H]^+$: 264.1752; Found: 264.1753.



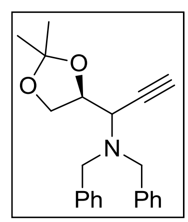
Synthesis of *N, N*-dibenzylhept–1-yn-3-amine (33b) [$C_{21}H_{25}N$]: The compound **3c** was prepared by following the *General Procedure A*. Starting from n-valeraldehyde (1.0 g, 11.62 mmol), dibenzylamine (2.7 mL, 13.95 mmol) and CaC_2 (1.1 g, 17.43 mmol) in the presence of CuI (220 mg, 1.16 mmol) compound **33b** was obtained (2.5 g, yield = 75%) as 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.



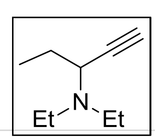
Synthesis of *N,N*-dibenzyl–1-cyclohexylprop-2-yn-1-amine (33c) [$C_{23}H_{27}N$]:[51] The compound **33c** was prepared by following the *General Procedure A*. Starting from cyclohexaladehyde (1.0 g, 8.92 mmol), dibenzylamine (2.05 mL, 10.71 mmol) and CaC_2 (856 mg, 13.38 mmol) in the presence of CuI (169 mg, 0.89 mmol) compound **33c** was obtained (1.8 g, yield = 65%) as colorless 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 *N,N*-dibenzyl–1-((S)–2,2–dimethyl–1,3–dioxolan–4–yl)–prop–2–yn-1–amine (33d) [$C_{22}H_{25}NO_2$]: The compound **33d** was prepared by following the *General Procedure A*. Starting from D-glyceraldehyde (1.0 g, 7.68 mmol), dibenzylamine (1.76 mL, 9.21 mmol) and CaC_2 (737 mg, 11.52 mmol) in the presence of CuI (146 mg, 0.76 mmol) compound **33d** was obtained (1.80 g, yield = 70%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.90). Obtained data was matched with the reported literature data.

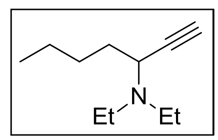


Synthesis of *N,N*-diethyl-1–pent–1-yn-3-amine (33e) [$C_9H_{17}N$]: The compound **33e** was prepared by following the *General Procedure A*. Starting from

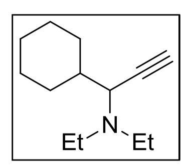


propionaldehyde (1.0 g, 17.21 mmol), diethylamine (1.04 mL, 20.65 mmol) and CaC_2 (1.60 g, 25.81 mmol) in the presence of CuI (326 mg, 1.72 mmol) compound **33e** was obtained (720 mg, yield = 30%) as colorless liquid. The compound **33e** was volatile, it was getting evaporated along with solvent while evaporating on rata evaporator causing poor yield so purification was avoided. The obtained data is recorded for crude compound. IR (neat): ν_{max}/cm^{-1} 3296, 3049, 2969, 2931, 2872, 2820, 1509, 1459, 1383, 1288, 1258, 1191, 1163, 1117, 1046; ^{1}H 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 (400 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*-diethylhept-1-yn-3-amine (33f) [$C_{11}H_{21}N$]: The compound **3f** was prepared by following the *General Procedure A*. Starting from n-valeraldehyde (1.0 g, 11.62 mmol), diethylamine (1.44 mL, 13.94 mmol) and CaC_2 (1.11 g, 17.43 mmol) in the presence of CuI (220 mg, 1.16 mmol) compound **33f** was obtained (970 mg, yield = 50%) as colourless liquid after column chromatographic purification. *Eluent*: 3% EtOAc in Petroleum ether (R_f = 0.65).IR (neat): ν_{max}/cm^{-1} 3306, 2958, 2927, 2864, 1685, 1610, 1562, 1459, 1378, 1278, 1193,1075; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46 (td, *J* = 8.40, 2.16 Hz, 1H), 2.67 (sex, *J* = 7.40 Hz, 2H), 2.39 (sex, *J* = 7.40 Hz, 2H), 2.15 (d, *J* = 2.12 Hz, 1H), 1.63 (m, 2H), 1.45 – 1.26 (m, 4H), 1.05 (t, *J* = 7.24 Hz, 6H), 0.90 (t, *J* =7.12 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$):δ 83.0, 72.0, 53.0, 44.8, 33.8, 29.0, 22.5, 14.1, 13.8; HRMS (ESI): Calc. for $C_{11}H_{22}N$ $[M+H]^+$: 168.1752; Found: 168.1759.

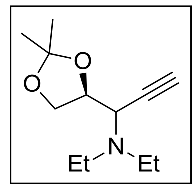


Synthesis of 1-cyclohexyl-*N, N*-diethylprop-2-yn-1-amine (33g) [$C_{13}H_{23}N$]: The compound **33g** was prepared by following the *General Procedure A*. Starting from cyclohexaladehyde (1.0 g, 8.92 mmol), diethylamine (1.10 mL, 10.71 mmol) and CaC_2 (856 mg, 13.38 mmol) in the presence of CuI (169 mg, 0.89 mmol) compound **33g** was obtained (1.03 g, yield = 60%) as colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). IR (neat):

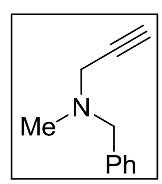


ν_{max}/cm^{-1} 3305, 2967, 2923, 2850, 2361, 1449, 1380, 1294, 1254, 1195; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (dd, *J* = 10.08, 2.20 Hz, 1H), 2.60 (sex, *J* = 7.44 Hz, 2H), 2.33 (sex, *J* = 6.90 Hz, 2H), 2.16 (d, *J* = 2.24 Hz, 1H), 2.04 (d, *J* = 12.80 Hz, 2H), 1.75 (m, 2H), 1.49 (m, 1H), 1.25 (m, 4H), 1.01 (t, *J* = 7.24 Hz, 6H), 0.95 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 82.1, 72.4, 58.6, 44.7, 40.0, 31.2, 30.55, 26.8, 26.2, 26.0, 13.8; HRMS (ESI): Calc. for $C_{13}H_{24}N$ $[M+H]^+$: 194.1909; Found: 194.1900.

Synthesis of 1–((S)–2,2–dimethyl–1,3–dioxolan–4–yl)–*N*, *N*-diethylprop–2–yn-1–amine (33h) [$C_{12}H_{21}NO_2$]: The compound **33h** was prepared by following the *General Procedure A*. Starting from D-glyceraldehyde (1.0 g, 7.68 mmol), diethylamine (961 mL, 9.21 mmol) and CaC_2 (737 mg, 11.52 mmol) in the presence of CuI (146 mg, 0.76 mmol) compound **33h** was obtained (1.05 g, yield = 65%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.90). M.P. >56^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 3300, 2975, 2934, 2877, 2821, 2362, 1513, 1460, 1376, 1293, 1250, 1211,1157, 1119, 1064; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.23 (q, *J* = 6.96 Hz, 1H), 4.10 (t, *J* = 7.40 Hz, 1H), 3.89 (t, *J* = 7.60 Hz, 1H), 3.63 (d, *J* = 7.84 Hz, 1H), 2.72 (sex, *J* = 6.44 Hz, 2H), 2.50 (sex, *J* = 6.73 Hz, 2H), 2.22 (s, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 1.09 (t, *J* = 7.16 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 110.0, 79.0, 76.0, 74.2, 67.7, 56.5, 45.3, 26.8, 25.7, 13.3; HRMS (ESI): Calc. for $C_{12}H_{22}NO_2$ $[M+H]^+$: 212.1651; Found: 212.1656.

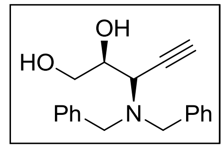


Synthesis of *N*-benzyl-*N*-methylprop-2-yn-1-amine (33i) [$C_{11}H_{13}N$]: The compound **33i** was prepared by following the *General Procedure B*. Starting from propargyl bromide (1.0 g, 8.40mmol), dibenzylamine (1.60 mL, 8.40mmol) and K_2CO_3 (2.30 g, 16.8 mmol) compound **33i** was obtained (500 mg, yield = 50%) as colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.70). IR (neat): ν_{max}/cm^{-1} 3294, 3029, 2940, 2837, 2793, 1494, 1451, 1365, 1328, 1192, 1075, 1027; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.34-7.29 (m, 5H), 3.56 (s, 2H), 3.3 (d, J=2.36 Hz, 2H), 2.33 (s,3H), 2.26 (t, J=2.36, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ138.4, 129.2, 128.4,

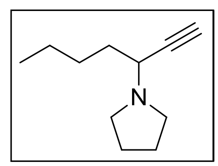


127.3 78.5, 73.3, 59.9, 44.8, 41.7; HRMS(ESI): Calc. for $C_{11}H_{14}N$ $[M+H]^+$: 160.1126; Found: 160.1127.

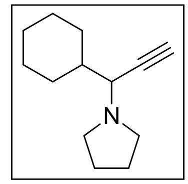
Synthesis of (2*S*)-3-(dibenzylamino)pent-4-yne-1,2-diol (33j) [$C_{19}H_{21}NO_2$]: To a round bottom flask, compound **33j** (1g) was dissolved in methanol (10mL).The resultant solution was acidified using 1 mL of 2N HCl and was stirred for 3 hrs. Upon completion of the reaction as observed from TLC, the reaction mixture was reduced in vacuo and washed with water (10 mL) and extracted using ethyl acetate (3x10mL). 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 **33j** as a colorless liquid (830 mg, yield = 95%). IR (neat): ν_{max}/cm^{-1} 3441, 3291, 3061, 3029, 2925, 2844, 1543, 1493, 1370, 1288, 1250, 1209, 1071; ^1H 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 (400 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.



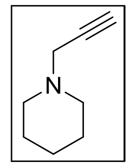
Synthesis of 1–(hept–1–yn–3–yl) pyrrolidine (33k) [$C_{11}H_{19}N$]: The compound **33k** was prepared by following the *General Procedure A*. Starting from n-valeraldehyde (1.0 g, 11.62 mmol), piperidine (1.14 mL, 13.94mmol) and CaC_2 (1.11 g, 17.43 mmol) in the presence of CuI (220 mg, 1.16mmol) compound **33k** was obtained (1.20 g, yield = 63%) as pale yellow liquid after column chromatographic purification. *Eluent*: 4% EtOAc in Petroleum ether (R_f = 0.60). IR (neat): ν_{max}/cm^{-1} 3304, 2956, 2932, 2868, 2813, 2361, 1731, 1691, 1646, 1459, 1349, 317, 1290, 1245, 1139, 1100, 1029; ^1H NMR (400 MHz, $CDCl_3$): δ 3.47 (m, 1H), 2.67 (m, 2H), 2.60 (m, 2H), 2.20 (d, *J* = 2.24 Hz, 1H), 1.77 (m, 4H), 1.62 (m, 2H), 1.35 (m, 4H), 0.88 (t, *J* =7.24 Hz, 3H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ 82.4, 72.7, 54.3, 49.4, 34.7, 28.8, 23.4, 22.5, 14.1; HRMS (ESI): Calc. for $C_{11}H_{20}N$ $[M+H]^+$: 166.1596; Found: 166.1605.



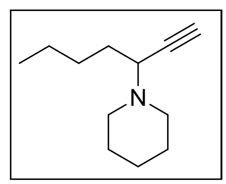
Synthesis of 1–(1–cyclohexylprop-2-yn–1–yl) pyrrolidine (33l) [$C_{13}H_{21}N$]: The compound **33l** was prepared by following the *General Procedure A*. Starting from cyclohexaladehyde (1.0 g, 8.92 mmol), pyrrolidine (1.02 mL, 10.70 mmol) and CaC_2 (857 mg, 13.38 mmol) in the presence of CuI (170 mg, 0.89 mmol) compound **33l** was obtained (860 mg, yield = 50%) as pale yellow solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.90). Obtained data was matched with the reported literature data.



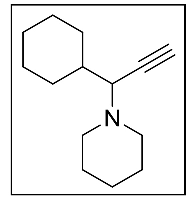
Synthesis of 1–(prop–2–yn–1–yl) piperidine (33m) [$C_8H_{13}N$]: The compound **33m** was prepared by following the *General Procedure B*. Starting from propargyl bromide (1.0 g, 8.40 mmol), piperidine (830 µL, 8.40mmol) and K_2CO_3 (2.30 g, 16.80mmol), compound **33m** was obtained (520 mg, yield = 50%) as 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 = 0.40). Obtained data was matched with the reported literature data.



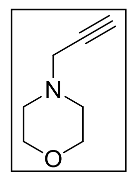
Synthesis of 1–(hept–1–yn–3–yl) piperidine (33n) [$C_{12}H_{21}N$]: The compound **33n** was prepared by following the *General Procedure A*. Starting from n - valeraldehyde (1.0 g, 11.62 mmol), piperidine (1.90 mL, 13.95 mmol) and CaC_2 (1.11 g, 17.43 mmol) in the presence of CuI (220 mg, 1.16 mmol) compound **33n** was obtained (1.32 g, yield = 66%) as pale yellow liquid after column chromatographic purification. *Eluent*: 2% EtOAc in Petroleum ether (R_f = 0.85). IR (neat): ν_{max}/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 (400 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.



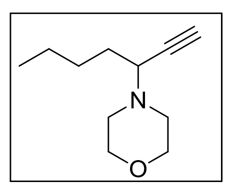
Synthesis of 1–(1–cyclohexylprop-2-yn–1–yl) piperidine (33o) [$C_{14}H_{23}N$]: The compound **33o** was prepared by following the *General Procedure A*. Starting from cyclohexaladehyde (1.0 g, 8.92 mmol), piperidine (1.14 mL, 10.71 mmol) and CaC_2 (856 mg, 13.38 mmol) in the presence of CuI (169 mg, 0.89 mmol) compound **33o** was obtained (1.28 g, yield = 70%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). M.P. >118^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 3303, 2924, 2851, 2804, 2750, 2680, 2361, 1693, 1646, 1514, 1446, 1383, 1311, 1267, 1231, 1157, 1104, 1036; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (m, 1H), 2.51 (m, 2H), 2.29 (m, 2H), 2.24 (d, *J* = 2.16 Hz, 1H), 2.03-1.94 (m, 2H), 1.74-1.48 (m, 9H), 1.42 (q, *J* = 5.76 Hz, 2H), 1.27-1.10 (m, 3H), 0.98-0.79 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 81.5, 73.3, 64.5, 63.7, 50.5, 39.4, 31.4, 31.2, 30.3, 26.8, 26.2, 26.1, 24.7; HRMS (ESI): Calc. for $C_{14}H_{24}N$ $[M+H]^+$: 206.1909; Found: 206.1919.



Synthesis of 4–(prop–2–yn–1–yl) morpholine (33p) [$C_7H_{11}NO$]: The compound **33p** was prepared by following the *General Procedure 2*. Starting from propargyl bromide (1.0 g, 8.40 mmol), morpholine (724 µL, 8.40 mmol) and K_2CO_3 (2.30 g, 16.80 mmol), compound **33p** was obtained (1.0 g, yield = 70%) as colorless solid after column chromatographic purification. *Eluent*: 1% dichloromethane in MeOH (R_f = 0.60). Obtained data was matched with the reported literature data.

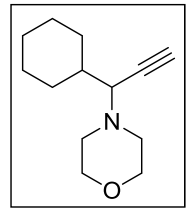


Synthesis of 4–(hept–1–yn–3–yl) morpholine (33q) [$C_{11}H_{19}NO$]: The compound **33q** was prepared by following the *General Procedure 1*. Starting from n-valeraldehyde (1.0 g, 11.62 mmol), morpholine (1.17 mL, 13.95 mmol) and CaC_2 (1.1 g, 17.43 mmol) in the presence of CuI (220 mg, 1.16 mmol) compound **33q** was obtained (1.4 g, yield = 70%) as colorless liquid after column chromatographic purification. *Eluent*: 2% EtOAc in Petroleum ether (R_f = 0.8). IR (neat): ν_{max}/cm^{-1} 3301, 2955, 2929, 2859, 1728, 1656, 1456, 1378, 1328, 1286, 1256, 1177, 1114, 1071, 1034, 1001; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 – 3.65 (m, 4H), 3.27 (td, *J* = 7.60, 2.04 Hz, 1H), 2.66 (m, 2H), 2.48 (m, 2H), 2.28 (d, *J* = 2.04 Hz, 1H), 1.64 (q, *J* = 7.56 Hz, 2H), 1.49 –



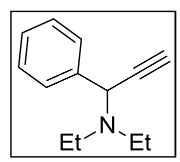
1.27 (m, 5H), 0.89 (t, *J* = 7.16 Hz, 3H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ 81.3, 73.7, 67.1, 57.5, 49.5, 32.5, 28.7, 22.5, 14.1; HRMS (ESI): Calc. for $C_{11}H_{20}NO$ $[M+H]^+$: 182.1545; Found: 182.1546.

Synthesis of 4–(1–cyclohexylprop-2-yn–1–yl) morpholine (33r) [$C_{13}H_{21}NO$]:



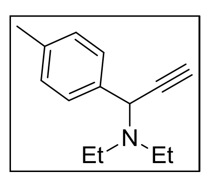
The compound **33r** was prepared by following the *General Procedure 1*. Starting from cyclohexaladehyde (1.0 g, 8.92 mmol), morpholine (914 µL, 10.71 mmol) and CaC_2 (856 mg, 13.38 mmol) in the presence of CuI (169 mg, 0.89 mmol) compound **33r** was obtained (1.38 g, yield = 75%) as colourless liquid after column chromatographic purification. *Eluent*: 2% EtOAc in Petroleum ether (R_f = 0.80). IR (KBr): ν_{max}/cm^{-1} 3299, 2922, 2850, 2753,2362, 1647, 1514, 1449, 1384, 1322, 1287, 1257, 1213, 1114, 1077, 1006; ^1H NMR (400 MHz, $CDCl_3$): δ 3.74 - 3.64 (m, 4H), 2.91 (dd, *J* = 9.96, 2.16 Hz, 1H), 2.61 – 2.56 (m, 2H), 2.42 – 2.37 (m, 2H), 2.28 (d, *J* = 2.24 Hz, 1H), 2.03 (m, 2H), 1.75 – 1.64 (m, 3H), 1.54 – 1.44 (m, 1H), 1.27 – 1.11 (m, 3H), 1.00 – 0.83 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 80.5, 74.1, 67.2, 63.3, 49.7, 38.9, 30.8, 30.2, 26.7, 26.1, 26.0 ; HRMS (ESI): Calc. for $C_{13}H_{21}NO$ $[M+H]^+$: 208.1701; Found: 208.1709.

Synthesis of *N, N*-diethyl-1–phenylprop-2-yn–1 amine (35a) [$C_{13}H_{17}N$]: The compound **35a** was prepared by following the *General Procedure A*. Starting from benzaldehyde (1.0 g, 9.42 mmol), diethylamine (1.18 mL, 11.30 mmol) and CaC_2 (798 mg, 14.13 mmol) in the presence of CuI (215 mg, 1.13 mmol) compound **35a** was obtained (1.14 g, yield = 65%) as 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.



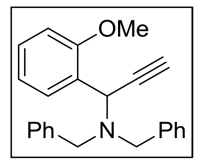
Synthesis of *N, N*-diethyl-1–(*p*-tolyl) prop-2-yn–1 amine (35b) [$C_{14}H_{19}N$]:

The compound **35b** was prepared by following the *General Procedure A*. Starting from 4-methyl benzaldehyde (1.0 g, 8.32 mmol), diethylamine (1.04

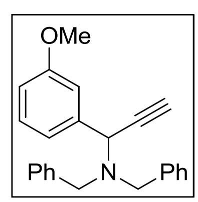


mL, 9.98 mmol) and CaC_2 (798 mg, 12.48 mmol) in the presence of CuI (138 mg, 0.73 mmol) compound **35b** was obtained (1.09 g, yield = 65%) as colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). IR (neat): ν_{max}/cm^{-1} 3300, 2968, 2927, 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 (400 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*-dibenzyl-1-(2-methoxyphenyl)prop-2-yn-1-amine (35c) [$C_{24}H_{23}NO$]: The compound **35c** was prepared by following the *General Procedure A*. Starting from 2-methoxybenzaldehyde (1.0 g, 7.34 mmol), dibenzylamine (1.70 mL, 8.81 mmol) and CaC_2 (705 mg, 11.01 mmol) in the presence of CuI (139 mg, 0.73 mmol) compound **35c** was obtained (1.70 g, yield = 70%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.82). M.P. >105 ^{o} C (decomposed); IR (neat): ν_{max}/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, 4H), 7.18 (q, *J* = 7.00 Hz, 3H), 6.88 (t, *J* = 7.44 Hz, 1H), 6.81 (d, *J* = 8.16, 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 (400 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.

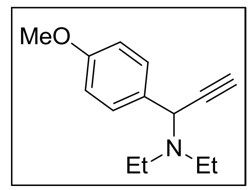


Synthesis of *N,N*-dibenzyl-1-(3-methoxyphenyl)prop-2-yn-1-amine (35d) [$C_{24}H_{23}NO$]: The compound **35d** was prepared by following the *General Procedure A*. Starting from 2-methoxybenzaldehyde (1.0 g, 7.34 mmol), dibenzylamine (1.70 mL, 8.81 mmol) and CaC_2 (705 mg, 11.01 mmol) in the presence of CuI (139 mg, 0.73 mmol) compound **35d** was obtained (1.60 g, yield = 65%) as yellow liquid after column chromatographic purification. *Eluent*: 1% EtOAc in

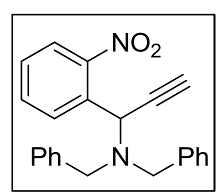


Petroleum ether (R_f = 0.82). IR (neat): ν_{max}/cm^{-1} 3290, 3061, 3028, 2937, 2834, 1598, 1488, 1454, 1310, 1276, 1251, 1110, 1048; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.40 (d, *J* = 7.40 Hz, 4H), 7.30 (t, *J* = 7.60 Hz, 4H), 7.24 (s, 2H), 7.22 (m, 3H), 6.78 (m, 1H), 4.67 (s, 1H), 3.78 (s, 3H), 3.73 (d, *J* = 13.6, 2H), 3.43 (d, *J* = 13.52 Hz, 2H), 2.61(d, *J* = 2.2 Hz, 1H); ^{13}C NMR (400 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.

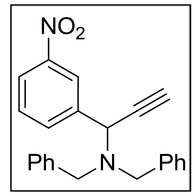
Synthesis of *N, N*-diethyl-1–(4-methoxyphenyl) prop-2-yn–1 amine (35e) [$C_{14}H_{19}NO$]: The compound **35e** was prepared by following the *General Procedure A*. Starting from 4-methoxy benzaldehyde (1.0 g, 7.34 mmol), diethylamine (802 µL, 8.81 mmol) and CaC_2 (704 mg, 11.01 mmol) in the presence of CuI (138 mg, 0.73 mmol) compound **35e** was obtained (798 mg, yield = 50%) as colorless liquid after column chromatographic purification. *Eluent*: 3% EtOAc in Petroleum ether (R_f = 0.70). IR (neat): ν_{max}/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 (400 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.



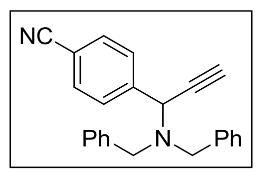
Synthesis of *N,N*-dibenzyl-1-(2-nitrophenyl)prop-2-yn-1-amine (35f) [$C_{23}H_{20}N_2O_2$]: The compound **35f** was prepared by following the *General Procedure A*. Starting from 2-nitrobenzaldehyde (1.0 g, 6.61 mmol), dibenzylamine (1.52 mL, 7.94 mmol) and CaC_2 (635 mg, 9.91 mmol) in the presence of CuI (125 mg, 0.66 mmol) compound **35f** was obtained (1.06 g, yield = 45%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). M.P. >85 ^{o} C (decomposed); IR (neat): ν_{max}/cm^{-1} 3289, 3030, 2837, 1604, 1528, 1493, 1450, 1361, 1308, 1103, 1072; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.76 Hz, 1H), 7.57 (d, *J* = 7.92 Hz, 1H), 7.40 (t, *J*= 7.60 Hz, 1H), 7.30 (t, *J* = 7.70 Hz, 1H), 7.25 – 7.16 (m,



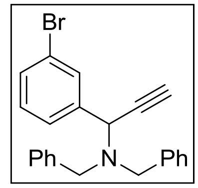
10H), 5.44 (s,1H), 3.50 (d, J = 13.12 Hz, 2H), 3.37 (d, J = 13.12 Hz, 2H), 2.76 (d, J = 1.20 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$):δ 149.8, 137.9, 132.0, 131.2, 130.7, 129.4, 128.8, 128.1, 121.2, 124.3, 78.4, 55.5, 53.3; HRMS (ESI): Calc. for $C_{23}H_{21}N_2O_2$ $[M+H]^+$: 357.1603; Found: 357.1602.



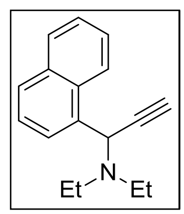
Synthesis of *N,N*-dibenzyl-1-(3-nitrophenyl)prop-2-yn-1-amine (35g) [$C_{23}H_{20}N_2O_2$]: The compound **35g** was prepared by following the *General Procedure A*. Starting from 3-nitrobenzaldehyde (1.0 g, 6.61 mmol), dibenzylamine (1.52 mL, 7.94 mmol) and CaC_2 (856 mg, 13.38 mmol) in the presence of CuI (125 mg, 0.66 mmol) compound **35g** was obtained (1.17 g, yield = 50%) as yellow semi- solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.85). IR (neat): ν_{max}/cm^{-1} 3292, 3062, 3029, 2925, 2837, 1529, 1493, 1452, 1350, 1253, 1109, 1073; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (s, 1H), 8.10 (dd, J = 8.20, 2.20 Hz, 1H), 7.96 (dd, J = 8.00, 0.70 Hz, 1H), 7.50 (t, J = 8.00 Hz, 1H), 7.37 – 7.28 (m, 9H), 7.25 (m, 2H), 4.73 (d, J = 1.60 Hz, 1H), 3.70 (d, J = 13.44 Hz, 2H), 3.45 (d, J = 13.44 Hz, 2H), 2.73 (d, J = 2.32 Hz, 1H);. ^{13}C NMR (400 MHz, $CDCl_3$): δ 148.3, 141.3, 138.7, 134.3, 129.1, 128.9, 128.6, 127.5, 123.2, 122.8, 77.6; HRMS (ESI): Calc. for $C_{23}H_{21}N_2O_2$ $[M+H]^+$: 357.1603; Found: 357.1602



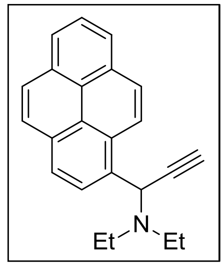
Synthesis of 4-(1-(dibenzylamino)prop-2-ynyl)benzonitrile (35h) [$C_{24}H_{20}N_2$]: The compound **35h** was prepared by following the *General Procedure A*. Starting from 4-cyanobenzaldehyde (1.0 g, 7.62 mmol), dibenzylamine (1.52 mL, 9.14 mmol) and CaC_2 (732 mg, 11.43 mmol) in the presence of CuI (144 mg, 0.76 mmol) compound **35h** was obtained (2.05 g, yield = 80%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.82). M.P. >115 ^{o} C (decomposed); IR (neat): ν_{max}/cm^{-1} 3291, 3061, 3029, 2887, 2836, 2228, 1605, 1496, 1451, 1405, 1368, 1108, 1072; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.20 Hz, 2H), 7.58 (d, J = 8.20 Hz, 2H), 7.32 – 7.25 (m, 8H), 7.21 (m, 2H), 4.66 (s, 1H), 3.64 (d, J = 13.44 Hz, 2H), 3.41 (d, J = 13.44 Hz, 2H), 2.67 (d, J = 1.90 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 144.4, 138.8, 132.1, 129.0, 128.9, 128.5, 127.5, 118.9, 111.6, 55.4, 54.7; HRMS (ESI): Calc. for $C_{24}H_{21}N_2$ $[M+H]^+$: 337.1704; Found: 337.1711.



Synthesis of *N,N*-dibenzyl-1-(3-bromophenyl)prop-2-yn-1-amine (35i) [$C_{23}H_{20}BrN$]: The compound **35i** was prepared by following the *General Procedure A*. Starting from 3-bromobenzaldehyde (1.0 g, 5.40 mmol), dibenzylamine (1.24 mL, 6.48 mmol) and CaC_2 (520 mg, 8.10 mmol) in the presence of CuI (102 mg, 0.54 mmol) compound **35i** was obtained (1.05 g, yield = 50%) as colorless solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.84). M.P. >105 ^{o} C (decomposed); IR (neat): ν_{max}/cm^{-1} 3294, 3061, 3029, 2927, 2889, 2836, 1594, 1568, 1494, 1460, 1418, 1368, 1295, 1251, 1185, 1110, 1071, 1027; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.77 (s, 1H), 7.58 (d, *J* = 7.36 Hz, 5H), 7.30 (t, *J* = 7.50 Hz, 4H), 7.20 (m, 4H), 4.63 (s, 1H), 3.68 (d, *J* =13.44 Hz, 2H), 3.40 (d, *J* = 13.44 Hz, 2H), 2.64 (d, *J* = 2.24 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 141.1, 139.1, 131.2, 130.7, 129.7, 128.9, 128.4, 127.2, 126.9, 122.3, 78.0, 55.0, 54.5; HRMS (ESI): Calc. for $C_{23}H_{21}BrN$ $[M+H]^+$: 390.0857; Found: 390.0855.



Synthesis of *N,N*-diethyl-1-(naphthalen-1-yl) prop-2-yn-1-amine (35j) [$C_{17}H_{19}N$]: The compound **35j** was prepared by following the *General Procedure A*. Starting from α-naphthaldehyde (1.0 g, 6.40 mmol), diethylamine (802 μL, 7.68 mmol) and CaC_2 (614 mg, 9.60 mmol) in the presence of CuI (121 mg, 0.64 mmol) compound **35j** was obtained (850 mg, yield = 56%) as colorless liquid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.90). IR (neat): ν_{max}/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 (400 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.



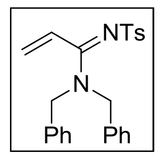
Synthesis of *N*, *N*-diethyl-1-(pyren-1-yl) prop-2-yn-1-amine (35k) [$C_{23}H_{21}N$]: The compound **35k** was prepared by following the *General Procedure 1*. Starting from pyrene aldehyde (1.0 g, 4.34 mmol), diethylamine (544 µL, 5.21 mmol) and CaC_2 (416 mg, 6.51 mmol) in the presence of CuI (81 mg, 0.43 mmol) compound **35k** was obtained (608 mg, yield = 45%) as yellow solid after column chromatographic purification. *Eluent*: 1% EtOAc in Petroleum ether (R_f = 0.90). M.P. >84^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 3294, 3042, 2929, 2820, 2361, 1917, 1593, 1459, 1381, 1322, 1290, 1266, 1240, 1187, 1161, 1117, 1050 ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 9.32 Hz, 1H), 8.49 (d, *J* = 7.92 Hz, 1H), 8.18 – 8.09 (m, 4H), 8.04 (s, 2H), 8.00 (t, *J* = 7.60 Hz, 1H), 5.81 (d, *J* = 2.24 Hz, 1H), 2.76 – 2.68 (sex, *J* = 7.32 Hz, 2H), 2.65 (d, *J* = 2.28 Hz, 1H), 2.62 – 2.53 (sex, *J* = 6.96 Hz, 2H), 1.06 (t, *J* = 7.12 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 131.9, 131.3, 131.2, 130.9, 129.4, 127.5, 127.4, 127.3, 127.1, 125.9, 125.3, 125.2, 124.8, 124.2, 124.1, 80.5, 76.0, 55.4, 44.8, 13.5 ; HRMS (ESI): Calc. for $C_{23}H_{22}N$ $[M+H]^+$: 312.1752; Found: 312.1752.

Synthesis of acrylamidine 32 in $CHCl_3$ under CuI catalytic conditions (Table 3.1, entry 1):

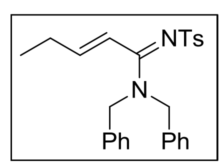
To a round bottomed flask placed in a water bath at room temperature was added propargylamine **31** (300 mg, 1.27mmol) in $CHCl_3$ (3.0 mL). To the stirring solution were added sequentially triethylamine (207 µL, 1.52 mmol) and tosylazide (273 mg, 1.39mmol) followed by CuI (28 mg, 0.15mmol) when the evolution of N_2 gas was observed. The reaction mixture was stirred for thirty minutes under open atmospheric condition. After the completion, a saturated solution of NH_4Cl (10 mL) was added to the reaction mixture and stirred for additional 30 minutes. The crude product was extracted with $CHCl_3$ (2 × 10 mL), combined organic layer was washed with brine (5 mL) and concentrated under reduced pressure to give pale green residue which was purified by column chromatography over silica gel to provide the desired acrylamidine **32** (433 mg, yield 84%).

Synthesis of acrylamidines in $CHCl_3$ under CuCl catalytic conditions:

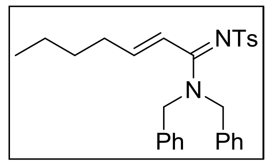
General Procedure C: To a round bottomed flask placed in water bath at room temperature was added propargylamine (1.0 mmol) in $CHCl_3$. To the stirring solution were added sequentially triethylamine (1.2 mmol) and tosylazide (1.1 mmol) followed by CuCl (0.1 mmol) when the evolution of N_2 gas was observed. The reaction mixture was stirred for either three minutes (for propargylamine with acyclic amino group) or 15-20 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 and concentrated under reduced pressure to give pale green residue which was purified by column chromatography over silica gel to provide the desired acrylamidine.



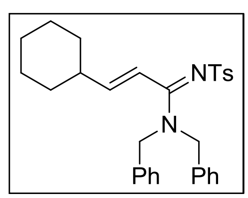
Synthesis of *N*, *N*-dibenzyl–*N′*-tosylacrylimidamide 32 [$C_{24}H_{24}N_2O_2S$]: The compound **32** was prepared by following the *General Procedure C*. Starting from propargylamine **31** (300 mg, 1.27 mmol) in $CHCl_3$ (3.0 mL), triethylamine (209 µL, 1.52 mmol), and tosylazide (273 mg, 1.39 mmol) in presence of CuCl (12 mg, 0.12 mmol) to obtain **2** (495 mg, yield = 96%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.15). M.P. >108^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 3029, 2923, 1629, 1596, 1516, 1444, 1431, 1359, 1281, 1144, 1086, 1023: ^{1}H 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 $C_{24}H_{25}N_2O_2S$ $[M+H]^+$: 405.1637; Found: 405.1632.



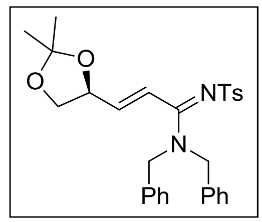
Synthesis of (2*E*)–*N*, *N*-dibenzyl-*N′*-tosylpent-2-enimidamide (34a) [$C_{26}H_{28}N_2O_2S$]: The compound **34a** was prepared by following the *General Procedure C*. Starting from propargylamine **33a** (300 mg, 1.15 mmol) in $CHCl_3$ (3.0 mL), triethylamine (188 µL, 1.36 mmol), and tosylazide (250 mg, 1.26 mmol) in presence of CuCl (11 mg, 0.11 mmol) to obtain **34a** (477 mg, yield = 96%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.25). M.P. >94^o C (decomposed); IR (neat): ν_{max}/cm^{-1}; 2967, 2927, 2362, 1653, 1596, 1516, 1452, 1430, 1359, 1284, 1145, 1089, 1024; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.24 Hz, 2H), 7.29 (br.s, 6H), 7.20 (d, *J* = 8.36, 2H), 7.12 (br.s, 4H), 6.29 (d, *J* = 16.48 Hz,1H), 6.20 (dt, *J* = 16.44, 5.84 Hz, 1H), 4.62 (br.s, 2H), 4.56 (br.s, 2H), 2.36 (s, 3H), 2.18 (qd, *J* = 6.08, 1.2 Hz, 2H), 0.98 (t, *J* = 7.40, 3H) ; ^{13}C NMR (400 MHz, $CDCl_3$):δ 166.0, 144.3, 141.8, 141.4, 135.8, 129.1, 128.0, 127.0, 126.5, 119.6, 52.0, 50.0, 26.0, 21.5, 21.1; HRMS(ESI): Calc. for $C_{26}H_{29}N_2O_2S$ $[M+H]^+$: 433.1950; Found: 433.1958.



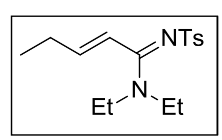
Synthesis of (2*E*)-*N*,*N*-dibenzyl–*N′*-tosylhept–2-enimidamide (34b) [$C_{28}H_{32}N_2O_2S$]: The compound **34b** was prepared by following the *General Procedure C*. Starting from propargylamine **33b** (300 mg, 1.02 mmol) in $CHCl_3$ (3.0 mL), triethylamine (170 µL, 1.23 mmol), and tosylazide (221 mg, 1.12 mmol) in presence of CuCl (10 mg, 0.10mmol) to obtain **34b** (431 mg, yield = 91%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.15).M.P. > 88^{o}C (decomposed); IR (neat): ν_{max}/cm^{-1} 3030, 2955, 2926, 2864, 2363, 1740, 1651, 1597, 1515, 1455, 1430, 1360, 1283, 1145, 1089, 1026; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.28 Hz, 2H), 7.28 (br. s, 6H), 7.20 (d, *J* = 7.96 Hz, 2H), 7.12 (br. s, 4H), 6.31 (d, *J* = 16.44 Hz, 1H), 6.17 (dt, *J* = 16.44, 6.56 Hz, 1H), 4.61 (br. s, 2H), 4.56 (br. s,2H), 2.36 (s, 3H), 2.15(q, *J* = 6.80 Hz, 2H), 1.37 – 1.19 (m, 4H), 0.84(t, *J* = 7.28 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.8, 143.3, 141.8, 141.4, 135.7, 129.1, 128.5, 128.0, 126.9, 126.5, 120.3, 77.5, 77.1, 76.8, 51.9, 50.1, 32.8,30.1, 22.3, 21.5, 13.9; HRMS(ESI): Calc. for $C_{28}H_{33}N_2O_2S$ $[M+H]^+$: 461.2263; Found: 461.2265.



Synthesis of (2*E*)-*N*, *N*-dibenzyl–3–cyclohexyl-*N′*-tosylacrylimidamide (34c) [$C_{30}H_{34}N_2O_2S$]: The compound **34c** was prepared by following the *General Procedure C*. Starting from propargylamine **33c** (300 mg, 0.94 mmol) in $CHCl_3$ (3.0 mL), triethylamine (156 µL, 1.13 mmol), and tosylazide (204 mg, 1.03 mmol) in presence of CuCl (18 mg, 0.09mmol) to obtain **34c** (418 mg, yield = 91%) as a colorless semi-solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.30).IR (neat): ν_{max}/cm^{-1} 3017, 2925, 2852, 2361, 1649, 1596, 1513, 1445, 1359, 1280, 1142, 1086, 970; ^{1}H 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 $C_{30}H_{35}N_2O_2S$ $[M+H]^+$: 487.2419; Found: 487.2434.



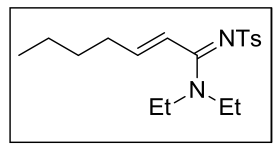
Synthesis of (2*E*)-*N*, *N*-dibenzyl–3–((S)–2,2–dimethyl–1, 3 dioxolan-4-yl)-*N′*-tosylacrylimidamide (34d) [$C_{29}H_{32}N_2O_4S$]: The compound **34d** was prepared by following the *General Procedure C*. Starting from propargylamine **33d** (300 mg, 0.89 mmol) in $CHCl_3$ (3.0 mL), triethylamine (148 µL, 1.07 mmol), and tosylazide (193 mg, 0.97 mmol) in presence of CuCl (8 mg, 0.08 mmol) to obtain **34d** (426 mg, yield = 95%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.20). M.P. >100^o C (decomposed); IR (neat): ν_{max}/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.



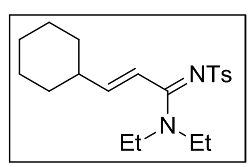
Synthesis of (2*E*)–*N*, *N*-diethyl-*N′*-tosylpent-2-enimidamide (34e) [$C_{16}H_{24}N_2O_2S$]: The compound **34e** was prepared by following the *General Procedure C*. Starting from propargylamine **33e** (300 mg, 2.15 mmol) in

$CHCl_3$ (3.0 mL), triethylamine (356 µL, 2.58 mmol), and tosylazide (466 mg, 2.36 mmol) in presence of CuCl (21 mg, 0.21 mmol) to obtain **34e** (631 mg, yield = 95%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.20). M.P. >72^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2974, 2878, 2328, 1771, 1656, 1604, 1530, 1461, 1358, 1281, 1217, 1145, 1087, 1045, 1014, 979; ^{1}H 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 $C_{16}H_{25}N_2O_2S$ $[M+H]^+$: 309.1637; Found: 309.1653.

Synthesis of (2*E*)-*N*, *N*-diethyl-*N′*-tosylhept–2-enimidamide (34f) [$C_{18}H_{28}N_2O_2S$]: The compound **34f** was prepared by following the *General Procedure C*. Starting from propargylamine **33f** (300 mg, 1.79 mmol) in $CHCl_3$ (3.0 mL), triethylamine (295 µL, 1.97 mmol), and tosylazide (388 mg, 1.97 mmol) in presence of CuCl (17 mg, 0.17 mmol) to obtain **34f** (580 mg, yield = 96%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.20). M.P. = 66^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2961, 2929, 2868, 2362, 1654, 1599, 1526, 1460, 1439, 1359, 1279, 1217, 1144, 1086, 1043; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.20 Hz, 2H), 7.20 (d, *J* = 7.92 Hz, 2H), 6.17 (d, *J* = 16.44 Hz, 1H), 5.95 – 5.88 (dt, *J* = 16.44, 6.60 Hz,1H), 3.45 (br. s, 2H), 3.37 (br. s, 2H), 2.36 (s, 3H), 2.15 (q, *J* = 6.60 Hz, 2H), 1.40 – 1.26 (m, 4H), 1.12 (t, *J* = 6.96 Hz, 6H), 0.90 (t, *J* = 7.20 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.5, 141.8, 141.6, 141.5, 129.0, 126.4, 120.7, 44.4, 42.7, 32.6, 30.2, 29.8, 22.4, 21.5, 13.9, 12.1; HRMS (ESI): Calc. for $C_{18}H_{29}N_2O_2S$ $[M+H]^+$: 337.1950; Found: 337.1956.

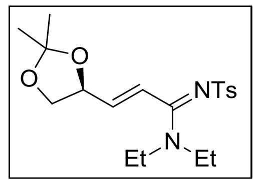


Synthesis of (2*E*)–3-cyclohexyl–*N*,*N*-diethyl-*N′*-tosylacrylimidamide (34g) [$C_{20}H_{30}N_2O_2S$]: The compound **34g** was prepared by following the *General Procedure C*. Starting from propargylamine **33g** (300 mg, 1.55 mmol) in $CHCl_3$ (3.0 mL), triethylamine (255 µL, 1.86 mmol), and

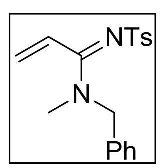


tosylazide (336 mg, 1.70 mmol) in presence of CuCl (15 mg, 0.15 mmol) to obtain **34g** (540 mg, yield = 96%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.25).M.P. > 93° C (decomposed); IR (neat): ν_{max}/cm^{-1} ; 2976, 2925, 2852, 2362, 1710, 1652, 1599, 1523, 1439, 1359, 1277, 1216, 1142, 1084, 1042, 978; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.20 Hz, 2H), 7.20 (d, *J* = 8.00 Hz, 2H), 6.17(d, *J* = 16.56 Hz, 1H), 5.90(dd, *J* = 16.56, 6.48 Hz,1H), 3.45(br. s, 2H), 3.37 (br. s, 2H), 2.36(s, 3H), 2.07(m, 1H), 1.76 – 1.69(m, 5H), 1.28 – 1.07(m, 12H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.9, 146.1, 141.8, 141.5, 129.0, 126.4, 118.7, 44.5, 42.7, 40.8, 31.7, 26.0, 21.5, 13.8, 12.1; HRMS (ESI): Calc. for $C_{20}H_{31}N_2O_2S$ $[M+H]^+$: 363.2106; Found: 363.2119.

Synthesis of (2*E*)–3–((S)–2, 2–dimethyl–1, 3 dioxolan-4-yl)-*N*, *N* - diethyl–*N*'-tosylacrylimidamide (34h) [$C_{19}H_{28}N_2O_4S$]: The compound **34h** was prepared by following the *General Procedure C*. Starting from propargylamine **33h** (300 mg, 1.41mmol) in $CHCl_3$ (3.0 mL), triethylamine (234 µL, 1.70 mmol), and tosylazide (305 mg, 1.55mmol) in presence of CuCl (14 mg, 0.14mmol) to obtain **34h** (480 mg, yield = 89%) as a colorless solid after column chromatographic purification. *Eluent*: 1% MeOH/dichloromethane (R_f = 0.20). M.P. >97° C (decomposed); IR (neat): ν_{max}/cm^{-1} 2983, 2931, 2362, 1709, 1659, 1603, 1529, 1458, 1368, 1277, 1215, 1144, 1084; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.20 Hz, 2H), 7.20 (d, *J* = 7.84 Hz, 2H), 6.49(dd, *J* = 16.44, 1.24 Hz, 1H), 6.01(dd, *J* = 16.44, 6.00 Hz,1H), 4.62(q, *J* = 6.44 Hz,1H), 4.17(dd, *J* = 8.56, 6.48 Hz,1H), 3.73(dd, *J* = 8.56, 7.28 Hz,1H), 2.36(s, 3H), 1.42(s, 3H), 1.39(s, 3H), 1.14(t, *J* = 7.20 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.3, 141.7, 141.6, 137.6, 129.0, 126.3, 122.3, 110.0, 75.6, 68.7, 44.4, 42.7, 26.5, 25.9, 21.5, 13.8, 12.0; HRMS(ESI): Calc. for $C_{19}H_{28}N_2O_4S$ $[M+H]^+$: 381.1848; Found: 381.4848.

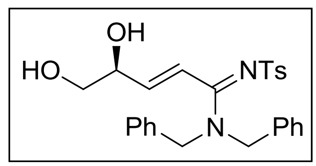


Synthesis of (*E*)-*N*-benzyl-*N*-methyl-*N'*-tosylacrylimidamide (34i) [$C_{18}H_{20}N_2O_2S$]: The compound **34i** was prepared by following the *General Procedure C*. Starting from propargylamine **33i** (300 mg, 1.88 mmol) in $CHCl_3$ (3.0 mL), triethylamine (310 µL, 2.26 mmol), and tosylazide (407 mg, 2.07 mmol)

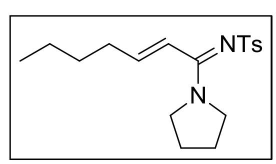


in presence of CuCl (17.82 mg, 0.18 mmol) to obtain **34i** (574 mg, yield = 88%) as a waxy liquid after column chromatographic purification. *Eluent*: 25% EtOAc/Petroleum ether (R_f = 0.30). IR (neat): ν_{max}/cm^{-1} 3029, 1531, 1485, 1449, 1403, 1275, 1140, 1087, 1024; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.80(d, J=7.48 Hz, 1H), 7.73(d, J=7.52 Hz, 1H), 7.33(d, J=6.84, 1H), 7.27(br.s, 2H), 7.22(br.s, 3H), 7.10(d, J=6.84 Hz, 1H), 6.68(dd, J=18.08 Hz, 12.12 Hz, 1H), 5.74(dd, J=16 Hz, 12 Hz, 1H), 5.59(dd, J=17.92, 12.28 Hz, 1H), 4.69(s, 1H), 4.62(s, 1H), 2.97(s, 3H), 2.36(s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 142.0, 141.0, 135.3, 129.1, 128.8, 128.5, 128.3, 128.1, 128.0, 126.7, 126.5, 124.8, 55.3, 53.3, 37.6, 36.3, 21.5; HRMS(ESI): Calc. for $C_{18}H_{21}N_2O_2S$ $[M+H]^+$: 329.1323; Found: 329.1324.

Synthesis of (*S,2E*)-*N,N*-dibenzyl-4,5-dihydroxy-*N'*-tosylpent-2-enimidamide (34j) [$C_{26}H_{28}N_2O_4S$]: The compound **34j** was prepared by following the *General Procedure C*. Starting from propargylamine **33j** (300 mg, 1.01 mmol) in $CHCl_3$ (3.0 mL), triethylamine (165 µL, 1.21 mmol) , and tosylazide (240 mg, 1.2 mmol) in presence of CuCl (19 mg, 0.10 mmol) to obtain **34j** (285 mg, yield = 60%) as a colorless semi-solid after column chromatographic purification. *Eluent*: 3% MeOH/Dichloromethane (R_f = 0.20 in EtOAc/Petroleum ether). IR (neat): ν_{max}/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 (400 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.

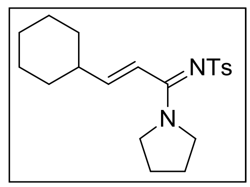


Synthesis of 4–methyl–*N*–((*E*)-1-(pyrrolidin–1-yl) hept–2-en–1–ylidene) benzenesulfonamide (34k) [$C_{18}H_{26}N_2O_2S$]: The compound **34k** was prepared by following the *General Procedure C*. Starting from propargylamine **33k** (300 mg, 1.81 mmol) in $CHCl_3$ (3.0 mL),

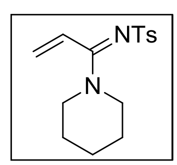


triethylamine (300 µL, 2.17 mmol), and tosylazide (392 mg, 1.99 mmol) in presence of CuCl (18 mg, 0.18 mmol) to obtain **34k** (352 mg, yield = 58%) as a colorless solid after column chromatographic purification. *Eluent*: MeOH/Dichloromethane (R_f = 0.20). M.P. > 67° C (decomposed); IR (neat): ν_{max}/cm^{-1} 2958, 2926, 2873, 2362, 2654, 1600, 1519, 1457, 1337, 1275, 1141, 1089, 1023, 976; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.24 Hz, 2H), 7.19 (d, *J* = 8.00 Hz, 2H), 6.63 (d, *J* = 16.44 Hz, 1H), 6.09 (dt, *J* = 16.44, 6.80 Hz, 1H), 3.53 (t, *J* = 7.04 Hz, 2H), 3.44 (t, *J* = 6.60 Hz, 2H), 2.35 (s, 3H), 2.15 – 2.09 (qd, *J* = 6.50, 1.28 Hz, 2H), 1.89 (q, *J* = 3.12 Hz, 4H), 1.40 – 1.23 (m, 4H), 0.89 (t, *J* = 7.08 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$):δ 162.7, 143.1, 141.6, 129.0, 126.6, 121.7, 50.1, 48.6, 32.7, 30.2, 25.9, 24.4 22.3, 21.5, 14.0; HRMS (ESI): Calc. for $C_{18}H_{26}N_2O_2S$ $[M+H]^+$: 335.1793; Found: 335.1830.

Synthesis of *N*–((*E*)–3-cyclohexyl–1–(pyrrolidin–1–yl) allylidene)–4-methylbenzenesulfonamide (34l) [$C_{20}H_{28}N_2O_2S$]: The compound **34l** was prepared by following the *General Procedure C*. Starting from propargylamine **33l** (300 mg, 1.56 mmol) in $CHCl_3$ (3.0 mL), triethylamine (260 µL, 1.88 mmol), and tosylazide (338 mg, 1.71 mmol) in presence of CuCl (15 mg, 0.15 mmol) to obtain **34l** (395 mg, yield = 70%) as a colorless solid after column chromatographic purification. *Eluent*: MeOH/Dichloromethane (R_f = 0.20). M.P. >127° C (decomposed); IR (neat): ν_{max}/cm^{-1} 2924, 2852, 2361, 1651, 1600, 1518, 1453, 1337, 1275, 1192, 1141, 1089, 1022; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.20 Hz, 2H), 7.20 (d, *J* = 8.40 Hz, 2H), 6.29 (d, *J* = 16.56 Hz, 1H), 6.60 (dd, *J* = 16.60, 6.64 Hz,1H), 3.53 (t, *J* = 6.80 Hz, 2H), 3.44 (t, *J* = 6.44 Hz, 2H), 2.35 (s, 3H), 2.06 (m, 1H), 1.89 (m, 4H), 1.71 (br. s,2H), 1.69 (br. s, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 163.1, 147.7, 141.6, 141.5, 129.0, 126.6, 119.6, 50.2, 48.6, 40.9, 31.7, 29.8, 26.0, 25.9, 25.7, 24.4, 21.5; HRMS (ESI): Calc. for $C_{20}H_{28}N_2O_2S$ $[M+H]^+$: 361.1950; Found: 361.1955.

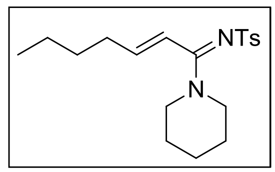


Synthesis of 4-methyl-*N*-(1-(piperidin-1-yl) allylidene) benzenesulfonamide (34m) [$C_{15}H_{20}N_2O_2S$]: The compound **34m** was prepared by following the *General Procedure C*. Starting from propargylamine **33m** (300 mg, 2.43 mmol) in $CHCl_3$

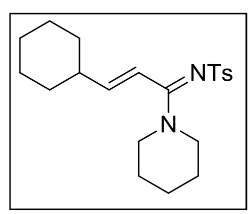


(3.0 mL), triethylamine (402 µL, 2.92 mmol), and tosylazide (526 mg, 2.67 mmol) in presence of CuCl (28 mg, 0.29 mmol) to obtain **34m** (341 mg, yield = 48%) as a colorless solid after column chromatographic purification. *Eluent*: 2% MeOH/Dichloromethane (R_f = 0.25). M.P. >75^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2937, 2860, 2362, 1707, 1601, 1526, 1449, 1399, 1362, 1274, 1144, 1086, 1015, 969; ^{1}H 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 (34n) [$C_{19}H_{28}N_2O_2S$]: The compound **34n** was prepared by following the *General Procedure C*. Starting from propargylamine **33n** (300 mg, 1.67 mmol) in $CHCl_3$ (3.0 mL), triethylamine (276 µL, 2.00 mmol), and tosylazide (362 mg, 1.83 mmol) in presence of CuCl (16 mg, 0.16 mmol) to obtain **34n** (297 mg, yield = 51%) as a colorless viscous liquid after column chromatographic purification. *Eluent*: 1% MeOH/dichloromethane (R_f = 0.20).IR (neat): ν_{max}/cm^{-1} 2929, 2860, 2361, 1651, 1601, 1516, 1442, 1366, 1273, 1142, 1085, 1020, 979; ^{1}H 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), 1.64m, 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 $C_{19}H_{29}N_2O_2S$ $[M+H]^+$: 349.1950; Found: 349.1949.

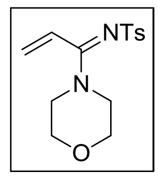


Synthesis of *N*–((*E*)–3-cyclohexyl–1–(piperidin-1-yl) allylidene)–4-methylbenzenesulfonamide (34o) [$C_{21}H_{30}N_2O_2S$]: The compound **34o** was prepared by following the *General Procedure C*. Starting from propargylamine **33o** (300 mg, 1.46 mmol) in $CHCl_3$ (3.0 mL),

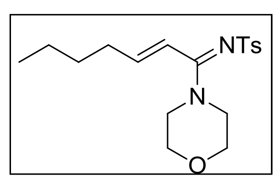


triethylamine (240 μL, 1.75 mmol), and tosylazide (316 mg, 1.60 mmol) in presence of CuCl (17 mg, 0.17 mmol) to obtain **34o** (344 mg, yield = 63%) as a colorless solid after column chromatographic purification. *Eluent*: 1% MeOH/Dichloromethane (R_f = 0.20). M.P. >130^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2925, 2853, 2362, 1649, 1598, 1519, 1446, 1365, 1276, 1145, 1088, 1022, 976; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.24 Hz, 2H), 7.20 (d, *J* = 8.12 Hz, 2H), 6.18 (dd, *J* = 16.70, 1.20 Hz, 1H), 5.83 (dd, *J* = 16.60, 6.48 Hz, 1H), 3.64 (br. s, 2H), 3.50 (br.s, 2H), 2.35 (s, 3H), 2.06 (m, 1H), 1.73 (m, 4H), 1.64 (m, 3H), 1.54 (br.s, 5H), 1.30 – 1.01 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.4, 146.5, 141.5, 141.4, 128.8, 126.4, 118.4, 49.2, 45.8, 40.6, 31.5, 26.3, 25.9, 25.6, 24.2, 21.4; HRMS (ESI): Calc. for $C_{21}H_{30}N_2O_2S$ $[M+H]^+$: 375.2106; Found: 375.2112.

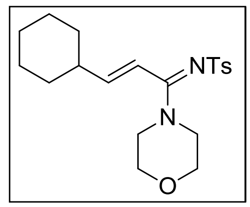
Synthesis of 4–methyl–*N*–(1–morpholinoallylidene) benzenesulfonamide (34p) [$C_{14}H_{18}N_2O_3S$]: The compound **34p** was prepared by following the *General Procedure B*. Starting from propargylamine **33p** (300 mg, 2.39 mmol) in $CHCl_3$ (3.0 mL), triethyl amine (396 μL, 2.87 mmol), and tosyl azide (517 mg, 2.63 mmol) in presence of CuCl (23 mg, 0.16 mmol) to obtain **34p** (585 mg, yield = 83%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.30). M.P. = >120^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2968, 2920, 2858, 2364, 1598, 1521, 1479, 1444, 1114, 1088, 1026; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.28 Hz, 2H), 7.22 (d, *J* = 7.76 Hz, 2H), 6.64 (dd, *J* = 18.20, 12.16 Hz, 1H), 5.74 (d, *J* = 11.9 Hz, 1H), 5.50 (d, *J* = 17.80 Hz, 1H), 3.65 (br. s, 8H), 2.36 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.0, 142.2, 140.7, 129.1, 128.2, 126.6, 125.1, 66.4, 48.2, 44.9, 29.7, 21.5; HRMS (ESI): Calc. for $C_{14}H_{19}N_2O_3S$ $[M+H]^+$: 295.1117; Found: 295.1122.



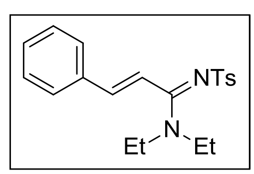
Synthesis of 4–methyl–*N*–((*E*)-1-morpholinohept–2–en–1-yl) hept–2-en–1–ylidene) benzenesulfonamide (34q) [$C_{18}H_{26}N_2O_3S$]: The compound **34q** was prepared by following the *General Procedure B*. Starting from propargylamine **33q** (300 mg, 1.65 mmol) in $CHCl_3$ (3.0 mL), triethyl amine (272 μL, 1.98 mmol), and tosyl azide (357 mg, 1.81 mmol) in presence of



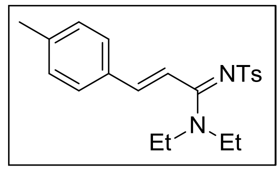
CuCl (16 mg, 0.16 mmol) to obtain **34q** (495 mg, yield = 85%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.30). M.P. = >86^o C (decomposed); IR (neat): ν_{max}/cm^{-1}; 3013, 2960, 2924, 2857, 2362, 1710, 1650, 1601, 1516, 1442, 1360, 1275, 1220, 1143, 1115, 1089; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.20 Hz, 2H), 7.21 (d, *J* = 8.00 Hz, 2H), 6.26 (dt, *J* = 16.48, 1.44 Hz, 1H), 5.96 (dt, *J* = 16.44, 6.72 Hz, 1H), 3.64 (br. s, 6H), 2.37 (s, 3H), 2.18 (qd, *J* = 6.64, 1.52 Hz, 2H), 1.41 – 1.23 (m, 6H), 0.91 (t, *J* = 7.24 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.5, 143.4, 142.0, 141.0, 129.1, 126.6, 120.0, 66.5, 32.6, 30.1, 29.8, 22.4 21.5, 14.00; HRMS (ESI): Calc. for $C_{18}H_{27}N_2O_3S$ $[M+H]^+$: 351.1748; Found: 351.1758.



Synthesis of *N*–((*E*)–3-cyclohexyl–1–morpholinoallylidene)–4-methylbenzenesulfonamide (34r) [$C_{20}H_{28}N_2O_3S$]: The compound **34r** was prepared by following the *General Procedure B*. Starting from propargylamine **33r** (300 mg, 1.44 mmol) in $CHCl_3$ (3.0 mL), triethyl amine (238 µL, 1.73 mmol), and tosyl azide (312 mg, 1.58 mmol) in presence of CuCl (14 mg, 0.14 mmol) to obtain **34r** (450 mg, yield = 83%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.20). M.P. = >139^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2924, 2853, 2362, 1648, 1603, 1517, 1445, 1392, 1359, 1276, 1190, 1145, 1115, 1089, 973; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 8.24 Hz, 2H), 7.20 (d, *J* = 8.08 Hz, 2H), 6.22 (dd, *J* = 16.70, 1.33 Hz, 1H), 5.90 (dd, *J* = 16.64, 6.52 Hz, 1H), 3.65 (br. s, 8H), 2.36 (s, 3H), 2.11 (m, 1H), 1.75 – 1.63 (m, 5H), 1.31 – 1.04 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.9, 148.1, 141.9, 141.1, 129.1, 126.5, 117.9, 66.5, 40.9, 31.6, 26.0, 25.7, 21.5; HRMS (ESI): Calc. for $C_{20}H_{29}N_2O_3S$ $[M+H]^+$: 377.1899; Found: 377.1907.

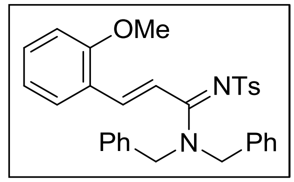


Synthesis of *N*, *N*-diethyl–*N′*-tosylcinnamimidamide (36a) [$C_{20}H_{24}N_2O_2S$]: The compound **36a** was prepared by following the *General Procedure C*. Starting from propargylamine **35a** (300 mg, 1.60 mmol) in $CHCl_3$ (3.0 mL), triethylamine (264 µL, 1.92 mmol), and tosylazide (346 mg, 1.76 mmol) in presence of CuCl (16 mg, 0.16 mmol) to obtain **36a** (548 mg, yield = 96%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.30). M.P. >130^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2977, 2361, 1693, 1642, 1531, 1467, 1438, 1360, 1276, 1216, 1143, 1085; ^{1}H 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.

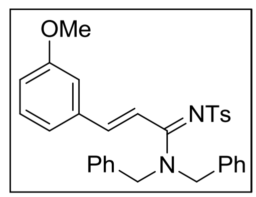


Synthesis of (2*E*)–*N*, *N*-diethyl–3–(*p*-tolyl)-*N′*-tosylacrylimidamide (36b) [$C_{21}H_{26}N_2O_2S$]: The compound **36b** was prepared by following the *General Procedure C*. Starting from propargylamine **35b** (300 mg, 1.49 mmol) in $CHCl_3$ (3.0 mL), triethylamine (246 μL, 1.78 mmol), and tosylazide (323 mg, 1.63 mmol) in presence of CuCl (14 mg, 0.14 mmol) to obtain **36b** (513 mg, yield = 93%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.30). M.P. >130^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2977, 2932, 2361, 1640, 1605, 1527, 1460, 1360, 1278, 1215, 1144, 1086, 1041; ^{1}H NMR (400 MHz, $CDCl_3$): at 298 K (rt): 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); 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); 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); ^{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.

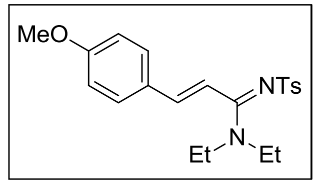
Synthesis of (*2E*)-*N,N*-dibenzyl-3-(2-methoxyphenyl)-*N′*-tosylacrylimidamide (36c) [$C_{31}H_{30}N_2O_3S$]: The compound **36c** was prepared by following the *General Procedure C*. Starting from propargylamine **35c** (300 mg, 0.88 mmol) in $CHCl_3$ (3.0 mL), triethylamine (144 μL, 1.05 mmol) , and tosylazide (190 mg, 0.97 mmol) in presence of CuCl (7.92 mg, 0.08 mmol) to obtain **36c** (400 mg, yield = 89%) as a colorless semi-solid after column chromatographic purification. *Eluent*: 25% EtOAc/Petroleum ether (R_f = 0.20). IR (neat): ν_{max}/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 (400 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.



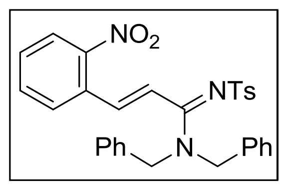
Synthesis of (*2E*)-*N,N*-dibenzyl-3-(3-methoxyphenyl)-*N′*-tosylacrylimidamide (36d) [$C_{31}H_{30}N_2O_3S$]: The compound **36d** was prepared by following the *General Procedure C*. Starting from propargylamine **35d** (300 mg, 0.88 mmol) in $CHCl_3$ (3.0 mL), triethylamine (144 μL, 1.05 mmol) , and tosylazide (190 mg, 0.97 mmol) in presence of CuCl (7.92 mg, 0.08 mmol) to obtain **36d** (430 mg, yield = 96%) as a viscous yellow liquid after column chromatographic purification. *Eluent*: 25% EtOAc/Petroleum ether (R_f = 0.20). IR (neat): ν_{max}/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 (400 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.



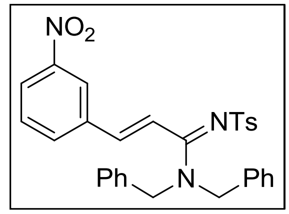
Synthesis of (2*E*)–*N*, *N*-diethyl–3–(4-methoxyphenyl)-*N′*-tosylacrylimidamide (36e) [$C_{21}H_{26}N_2O_3S$]: The compound **36e** was prepared by following the *General Procedure C*. Starting from propargylamine **35e** (300 mg, 1.38 mmol) in $CHCl_3$ (3.0 mL), triethylamine (227 µL, 1.65 mmol) , and tosylazide (300 mg, 1.51 mmol) in presence of CuCl (13 mg, 0.13 mmol) to obtain **36e** (506 mg, yield = 95%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.30). M.P. >133^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2976, 2936, 2839, 2361, 1637, 1604, 1518, 1458, 1359, 1250, 1216, 1174, 1142, 1084, 1029; ^{1}H 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.



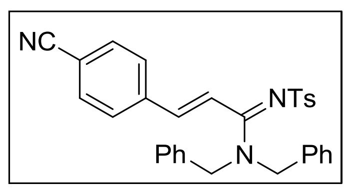
Synthesis of (2*E*)-*N,N*-dibenzyl-3-(2-nitrophenyl)-*N′*-tosylacrylimidamide (36f) [$C_{30}H_{27}N_3O_4S$]: The compound **36f** was prepared by following the *General Procedure C*. Starting from propargylamine **35f** (300 mg, 0.84 mmol) in $CHCl_3$ (3.0 mL), triethylamine (138 µL, 1.01 mmol) , and tosylazide (181 mg, 0.92 mmol) in presence of CuCl (7.92 mg, 0.08 mmol) to obtain **36f** (353 mg, yield = 80%) as a pale yellow solid after column chromatographic purification. *Eluent*: EtOAc/Petroleum ether (R_f = 0.23). M.P. >154^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 3033, 1603, 1570, 1521, 1455, 1346, 1281, 1144, 1088, 1024; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J=8.24 Hz, 1H), 7.9 (d, J=7.56, 1H), 7.71 (d, J=6.36 Hz, 2H), 7.69 (t, J=6 Hz, 1H), 7.50 (t, J=7.24 Hz, 1H), 7.28 (br.s, 6H), 7.17 (m, 7H), 6.95 (d, J=16.6 Hz, 1H), 4.79 (br.s, 2H), 4.70 (br.s, 2H), 2.35 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.4, 147.3, 142.2, 140.7, 135.5, 135.2, 134.5, 133.5, 131.8, 130.5, 129.7, 129.2, 128.9, 128.4, 128.2, 128.0, 127.2, 126.4, 124.7, 124.0, 52.2, 21.5; HRMS (ESI): Calc. for $C_{30}H_{28}N_3O_4S$ [M+H]$^+$: 526.1800; Found: 526.1799.



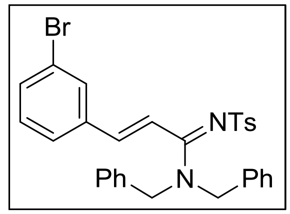
Synthesis of (*2E*)-*N,N*-dibenzyl-3-(3-nitrophenyl)-*N′*-tosylacrylimidamide (36g) [$C_{30}H_{27}N_3O_4S$]: The compound **36g** was prepared by following the *General Procedure C*. Starting from propargylamine **35g** (300 mg, 0.84 mmol) in $CHCl_3$ (3.0 mL), triethylamine (138 µL, 1.01 mmol) , and tosylazide (181 mg, 0.92 mmol) in presence of CuCl (7.92 mg, 0.08 mmol) to obtain **36g** (330 mg, yield 75%) as a pale yellow solid after column chromatographic purification. *Eluent*: EtOAc/Petroleum ether (R_f = 0.23). M.P. >113^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 3030, 2924, 1602, 1522, 1352, 1280, 1144, 1088; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (m, 2H), 7.76 (d, *J* = 8.20 Hz, 1H), 7.70 (d, *J* = 8.20 Hz, 2H), 7.53 (m, 1H), 7.13 (br.s, 6H), 7.20 (d, *J* = 8.20 Hz, 1H), 7.17 (d, *J* = 8.10 Hz, 1H), 7.13 (br.s, 4H), 7.00 (d, *J* = 16.90 Hz, 1H), 6.85 (d, *J* = 16.70 Hz, 1H), 4.72 (br.s, 2H), 4.58 (br.s, 2H), 2.36 (s,3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.5, 148.5, 142.2, 140.8, 139.3, 136.3, 135.9, 133.0, 132.6, 129.9, 129.2, 128.5, 128.3, 128.1, 126.9, 126.5, 123.9, 123.3, 123.0, 122.0, 121.4, 52.3, 50.4, 21.5; HRMS (ESI): Calc. for $C_{30}H_{28}N_3O_4S$ $[M+H]^+$: 526.1800; Found: 526.1807.



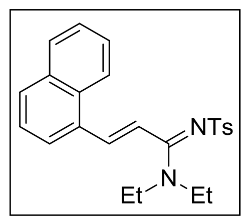
Synthesis of (*2E*)-*N,N*-dibenzyl-3-(4-cyanophenyl)-*N′*-tosylacrylimidamide (36h) [$C_{31}H_{27}N_3O_2S$]: The compound **36h** was prepared by following the *General Procedure C*. Starting from propargylamine **35h** (300 mg, 0.89 mmol) in $CHCl_3$ (3.0 mL), triethylamine (146 µL, 1.07 mmol) , and tosylazide (193 mg, 0.98 mmol) in presence of CuCl (7.92 mg, 0.08 mmol) to obtain **36h** (320 mg, yield = 71%) as a colorless solid after column chromatographic purification. *Eluent*: EtOAc/Petroleum ether (R_f = 0.25). M.P. >75^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 3032, 2225, 1638, 1602, 1520, 1461, 1360, 1282, 1145, 1088; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.24 Hz, 2H), 7.60 (d, *J* = 8.24 Hz, 2H), 7.41 (d, *J* = 8.32 Hz, 2H), 7.30 (br.s, 6H), 7.15 (d, *J* = 8.32 Hz, 2H), 7.11 (br.s, 4H), 7.01 (d, *J* = 16.88 Hz, 1H), 6.81 (d, *J* = 16.88 Hz, 1H), 4.70 (br.s, 2H), 4.56 (br.s, 2H), 2.34 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.5, 142.2, 140.7, 139.0, 136.4, 132.6, 129.2, 128.6, 127.9, 127.4, 126.9, 126.5, 122.6, 118.5, 112.7, 52.3, 50.5, 21.5; HRMS (ESI): Calc. for $C_{31}H_{28}N_3O_2S$ $[M+H]^+$: 506.1902; Found: 506.1909.



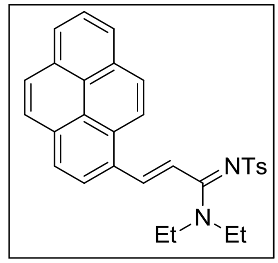
Synthesis of (2*E*)-*N,N*-dibenzyl-3-(3-bromophenyl)-*N′*-tosylacrylimidamide (36i) [$C_{30}H_{27}BrN_2O_2S$]: The compound **36i** was prepared by following the *General Procedure C*. Starting from propargylamine **35i** (300 mg, 0.77 mmol) in $CHCl_3$ (3.0 mL), triethylamine (126 µL, 0.92 mmol) , and tosylazide (167 mg, 0.85 mmol) in presence of CuCl (6.93 mg, 0.07 mmol) to obtain **36i** (412 mg, yield 96%) as a viscous yellow liquid after column chromatographic purification. *Eluent*: 25% EtOAc/Petroleum ether (R_f = 0.20). IR (neat): ν_{max}/cm^{-1} 3030, 2922, 1640, 1593, 1518, 1429, 1359, 1285, 1204, 1145, 1088; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.10 Hz, 2H), 7.42 (d, *J* = 9.00 Hz, 2H), 7.30 (br.s, 6H), 7.25 – 7.12 (m, 10H), 6.86 (d, *J* = 16.80 Hz, 1H), 6.67 (d, *J* = 16.80 Hz, 1H), 4.70 (br.s, 2H), 4.56 (br.s, 2H), 2.34 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.1, 142.0, 140.8, 137.0, 136.6, 135.4, 132.4, 130.3, 130.2, 129.1, 128.1, 126.9, 126.6, 126.0, 122.9, 120.2, 52.3, 50.3, 21.5; HRMS (ESI): Calc. for $C_{30}H_{28}BrN_2O_2S$ $[M+H]^+$: 559.1055; Found: 559.1066.



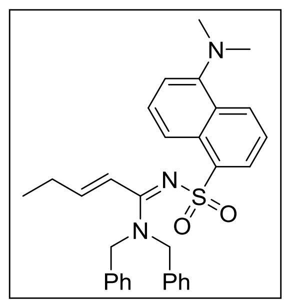
Synthesis of (2*E*)–*N*, *N*-diethyl–3–(naphthalen-1-yl)-*N′*-tosylacrylimidamide (36j) [$C_{24}H_{26}N_2O_2S$]: The compound **36j** was prepared by following the *General Procedure C*. Starting from propargylamine **35j** (300 mg, 1.26 mmol) in $CHCl_3$ (3.0 mL), triethylamine (208 µL, 1.51 mmol), and tosylazide (273 mg, 1.38 mmol) in presence of CuCl (12 mg, 0.12 mmol) to obtain **36j** (494 mg, yield 96%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.35). M.P. >137 ^{o}C (decomposed); IR (neat): ν_{max}/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*-diethyl–3–(pyren-1-yl)-*N′*-tosylacrylimidamide (36k) [$C_{30}H_{28}N_2O_2S$]: The compound **36k** was prepared by following the *General Procedure B*. Starting from propargylamine **35k** (300 mg, 0.96 mmol) in $CHCl_3$ (3.0 mL), triethyl amine (160 µL, 1.15 mmol), and tosyl azide (208 mg, 1.05 mmol) in presence of CuCl (9 mg, 0.09 mmol) to obtain **36k** (451 mg, yield 98%) as a colorless solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.35). M.P. = >194^o C (decomposed); IR (neat): ν_{max}/cm^{-1} 2977, 2932, 2361, 1707, 1628, 1597, 1526, 1460, 1359, 1275, 1216, 1184, 1142, 1084, 1043; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.12 Hz, 1H), 8.20 (m, 4H), 8.10 (m, 4H), 7.78 (d, 3H), 7.07 (m, 3H), 3.59 (br.s, 4H), 2.24 (s, 3H), 1.28 (t, *J* = 7.08 Hz, 6H) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.5, 141.7, 141.5, 135.3, 132.1, 131.4, 130.8, 129.1, 129.1, 128.4, 128.2, 127.5, 126.6, 126.3, 125.8, 125.6, 125.3, 124.9, 124.7, 124.1, 122.7, 121.7, 44.8, 43.0, 29.8, 21.4, 14.2, 12.5; HRMS (ESI): Calc. for $C_{30}H_{29}N_2O_2S$ $[M+H]^+$: 481.1950; Found: 481.1950.



Synthesis of (1*Z*, 2*E*)–*N*, *N*-dibenzyl–*N′*–((5-(dimethylamino) naphthalen-1-yl) sulfonyl) pent-2-enimidamide (38) [$C_{31}H_{33}N_3O_2S$]: The compound **38** was prepared by following the *General Procedure B*. Starting from propargylamine **33a** (300 mg, 1.13 mmol) in $CHCl_3$ (3.0 mL), triethyl amine (138 mg, 1.36 mmol), and tosyl azide (245 mg, 1.24 mmol) in presence of CuCl (11 mg, 0.11 mmol) to obtain **38** (553 mg, yield 95%) as a colorless semi-solid after column chromatographic purification. *Eluent*: Dichloromethane (R_f = 0.35). IR (KBr): ν_{max}/cm^{-1} 3015, 2937, 2871, 2833, 2785, 1653, 1579, 1510, 1454, 1357, 1290, 1227, 1159, 1127, 1091, 1064; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (t, *J* = 8.18 Hz, 2H), 8.21 (d, *J* = 7.20 Hz, 1H), 7.48 (t, *J* = 7.90 Hz, 1H), 7.41 (t, *J* = 8.12 Hz, 1H), 7.36 (br.s, 6H), 7.12 (d, *J* = 7.48 Hz, 1H), 7.02 (br.s, 4H), 6.07 (d, *J* = 16.52 Hz, 1H), 5.97 (dt, *J* = 16.52, 5.80 Hz, 1H), 4.68 (br.s, 2H), 4.45 (br.s, 2H), 2.86 (s, 6H), 2.05 (q, *J* = 7.32 Hz, 2H), 0.90 (t, *J* = 7.40 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 166.2, 151.4, 144.0, 139.5, 135.5, 130.0, 129.8, 129.0, 128.7, 127.9, 127.5, 127.4, 126.8, 123.1, 121.2, 119.0, 114.8, 51.7, 49.8, 45.5, 25.8, 11.9; HRMS (ESI): Calc. for $C_{31}H_{33}N_3O_2S$ $[M+H]^+$: 512.2372; Found: 512.2397.



3.6 Crystal Structure Parameters.

CCDC 932113 (**32**), CCDC 932111 (**34d**), CCDC 932112 **(34p)** and CCDC 933156 (**36e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal structure of compound 32 (CCDC 932113): $C_{24}H_{24}N_2O_2S$; Compound **32** was crystallized from DCM/Hexane at room temperature. A colorless rectangular shaped crystal with approximate dimensions 0.24 x 0.17 x 0.03 mm gave an Monoclinic with space group *C2/c*; a = 20.925(3) b = 11.0264(14)c = 18.650(2) Å, α = 90^o β = 92.884(5)^o γ = 90^o; V = 4297.6(10) Å^3; T = 173 K; Z = 8; ρ_{calc}= 1.250Mgm^{-3}; $2\theta_{max}$= 57.06^o; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0506 (for 4242 reflection $I>2\sigma(I)$), wR= 0.1503 which was refined against $|F2|$ and S = 1.026 for 264 parameters and 5425 unique reflections. The structure was obtained by direct methods using SHELXS-97.[S9] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.173 mm^{-1}.

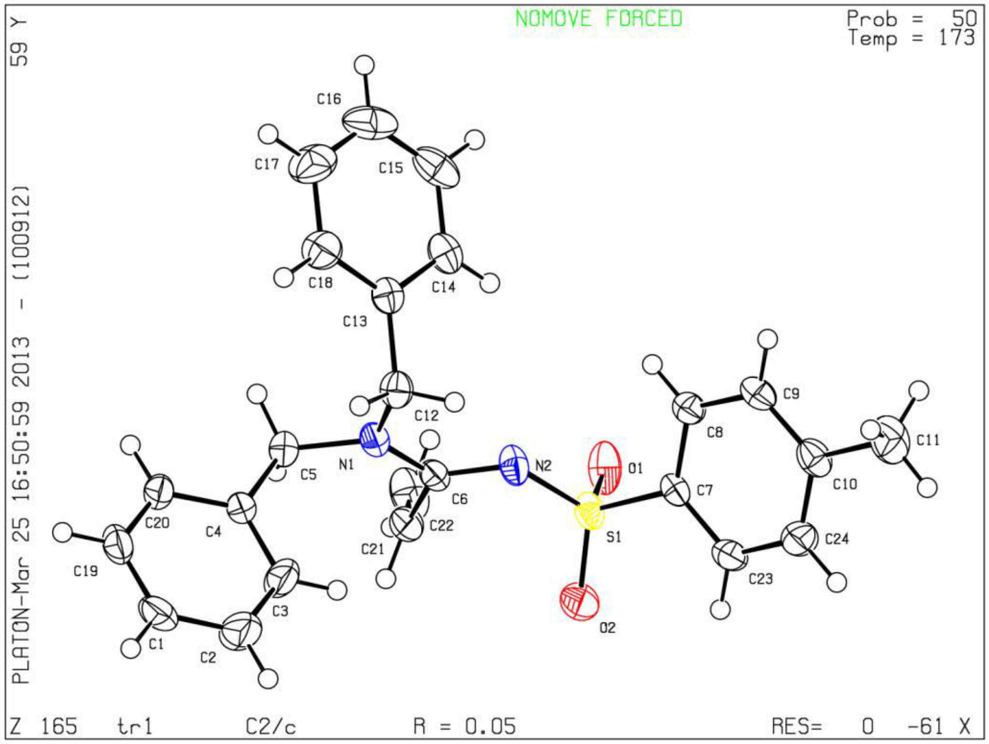


Figure: 3.7: ORTEP diagram of acrylamidine 2.

Crystal structure of compound 34d (CCDC 932111): $C_{29}H_{32}N_2O_4S$; Compound **34d** was crystallized from DCM/Hexane at room temperature. A colorless rectangular shaped crystal with approximate dimensions 0.32 x 0.18 x 0.06 mm gave an Monoclinic with space group *P 21*; a = 9.7934(18) b = 11.215(2)c = 12.187(2) Å, $\alpha = 90^o$ $\beta = 96.377(4)^o$ $\gamma = 90^o$; V = 1330.2(4) Å^3; T = 100 K; Z = 2; ρ_{calc}= 1.260 Mgm^{-3}; $2\theta_{max}$= 56.66^o; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0496 (for 4223 reflection $I>2\sigma(I)$), wR= 0.1323 which was refined against $|F2|$ and S = 1.052 for 329 parameters and 3466 unique reflections. The structure was obtained by direct methods using SHELXS-97.[S9] All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.159 mm^{-1}.

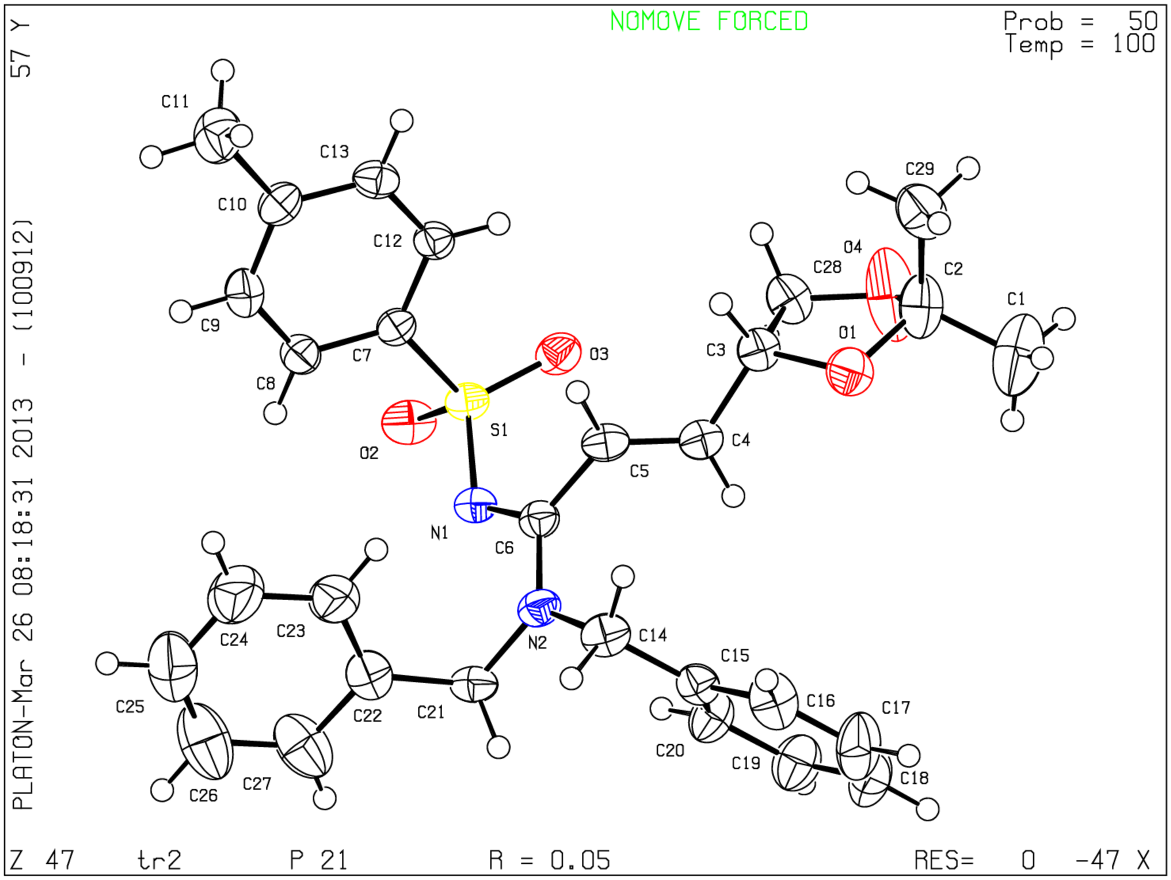


Figure 3.8: ORTEP diagram of acrylamidine **34d**.

Crystal structure of compound 34p (CCDC 932112): $C_{14}H_{18}N_2O_3S$; Compound **34p** was crystallized from DCM/Hexane at room temperature. A colorless rectangular shaped crystal with approximate dimensions 0.32 x 0.18 x 0.06 mm gave an Monoclinic with space group *P 21/n*; a = 8.2660(12) b = 25.831(4) c = 13.5551(19) Å, α = 90° β = 97.899(4)° γ = 90°; V = 2866.8(7) Å^3; T = 173 K; Z = 8; ρ_{calc} = 1.364 Mgm^{-3}; $2\theta_{max}$ = 57.04°; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0395 (for 5766 reflection $I > 2\sigma(I)$), wR = 0.1035 which was refined against $|F2|$ and S = 1.019 for 364 parameters and 7267 unique reflections. The structure was obtained by direct methods using SHELXS-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.235 mm^{-1}.

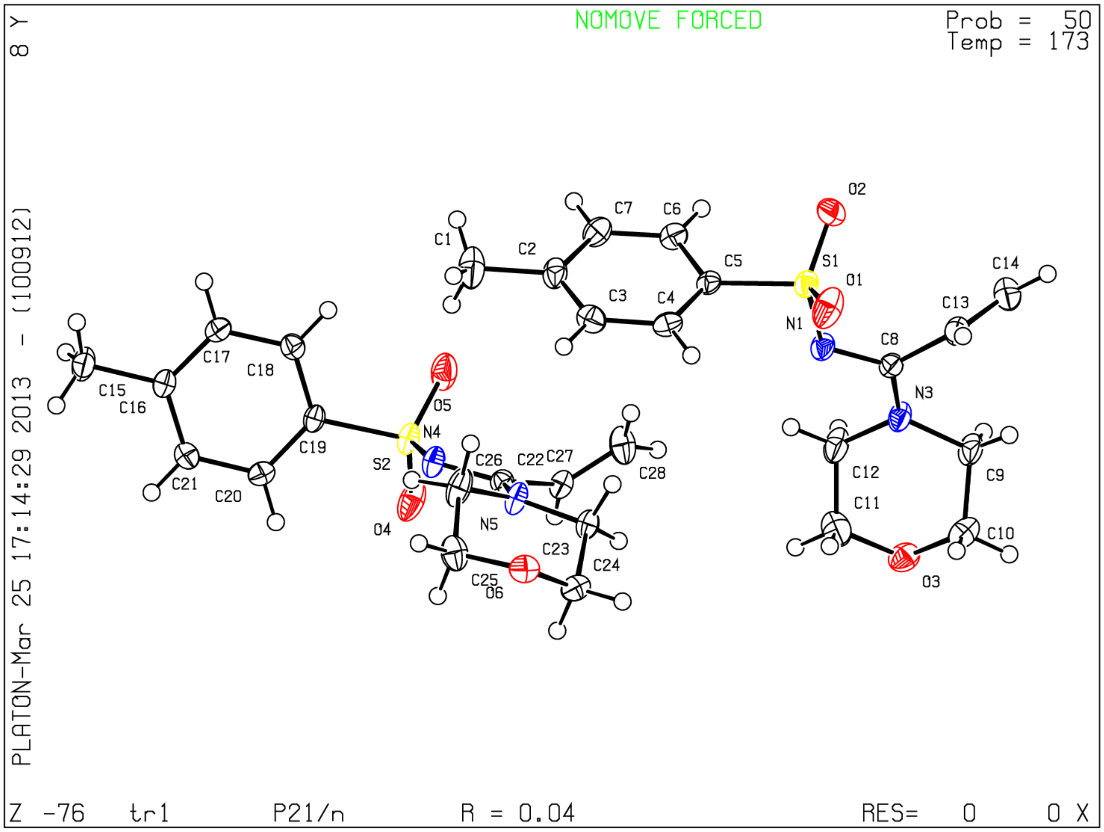


Figure 3.9: ORTEP diagram of α,β-unsaturated sulfonylamidine **34p**.

Crystal structure of compound 36e (CCDC933156): $C_{21}H_{26}N_2O_3S$; Compound **36e** was crystallized from DCM/Hexane at room temperature. A colorless rectangular shaped crystal with approximate dimensions 0.263 x 0.206 x 0.048 mm gave an Triclinic with space group *P-1*; a = 9.0234(13) b = 9.3284(13)c = 12.4285(18) Å, α = 76.805(2)^o β = 86.796(2)^o γ = 74.132(2)^o; V = 979.7(2) Å^3; T = 173 K; Z = 2; ρ_{calc}= 1.310Mgm^{-3}; $2\theta_{max}$= 56.86^o; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0346 (for 4400 reflection $I>2\sigma(I)$), wR= 0.1406 which was refined against |*F2*| and S = 1.188 for 248 parameters and 4916 unique reflections. The structure was obtained by direct methods using SHELXS-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the final cycle of refinement as riding over the atoms to which they are bonded. μ = 0.189 mm^{-1}.

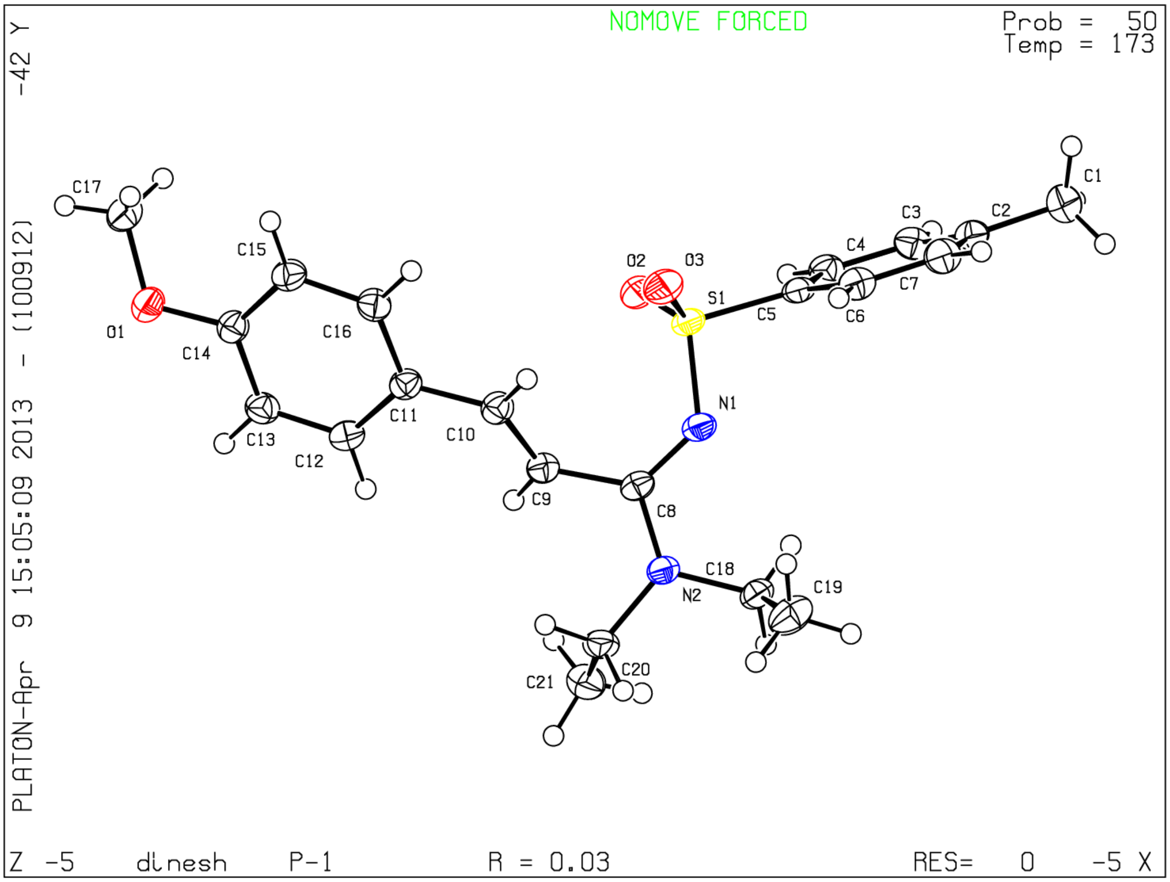


Figure 3.10. ORTEP diagram of acrylamidine **36e**.

3.7 Photophysical Properties:

Procedures:

Medium of Photophysical studies: Deionized water was used throughout all experiments. All photophysical experiments were carried out in HEPES buffer (10 mM, pH 7.4).

Preparation of the primary stock solution of 35k (Solution A): Compound **35k** (300 mg) was dissolved in 3.0 mL $CHCl_3$ to provide the stock solution of concentration = 320 mM.

Preparation of first diluted solution of 35k (Solution B): 10 µL of solution A (concentration = 320 mM) was added to 3190 µL HEPES buffer (10 mM, pH 7.4) to obtain the resulting concentration = 1000 µM.

Preparation of solution for Photophysical measurement of 35k (Solution C): 40 µL of solution B (concentration = 1000 µM) was added to 1960 µL HEPES buffer (10 mM, pH 7.4) to obtain the resulting concentration = 20 µM.

Preparation of the primary stock solution of 35k with TsN_3 (Solution D): Compound **35k** (300 mg) was dissolved in 3.0 mL $CHCl_3$ followed by addition of TsN_3 (208 mg), Et_3N (160 µL), CuCl (9 mg) and the resulting solution was stirred for 3 minutes at room temperature for provide stock solution D.

Preparation of first diluted solution of 35k with TsN_3 (Solution E): 10 µL of solution D (concentration = 320 mM) was added to 3190 µL HEPES buffer (10 mM, pH 7.4) to obtain the resulting concentration = 1000 µM.

Preparation of solution for Photophysical measurement of 35k with TsN_3 (Solution F): 40 µL of solution E (concentration = 1000 µM) was added to 1960 µL HEPES buffer (10 mM, pH 7.4) to obtain the resulting concentration = 20 µM.

UV-visible studies: UV-visible studies for either **35k** (20 µM) or for the mixture **35k+TsN_3** was carried out in HEPES buffer (10 mM, pH = 7.4).

Fluorescence studies: Fluorescence spectrum for either **35k** (20 µM) or for the mixture **35k+TsN_3** was carried out in HEPES buffer (10 mM, pH = 7.4).

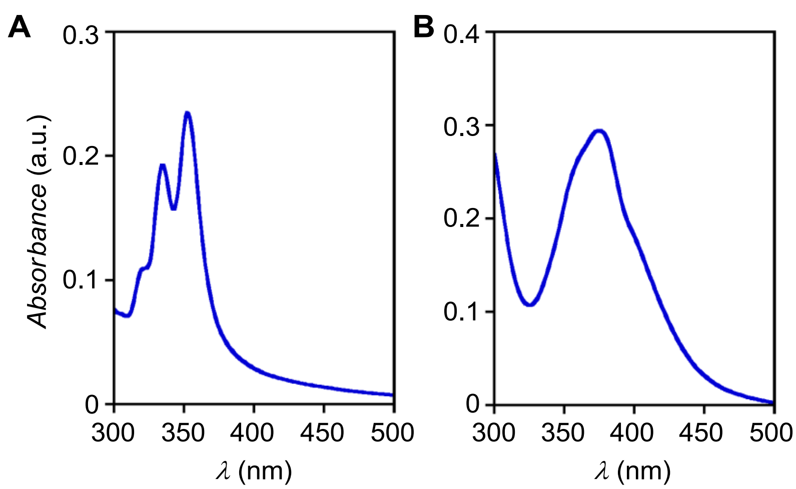


Figure 3.11: UV-visible spectra of **35k** (20 µM) and **35k+TsN_3** (20 µM) recorded in HEPES buffer (concentration = 10 mM, pH = 7.4).

3.8 NMR data

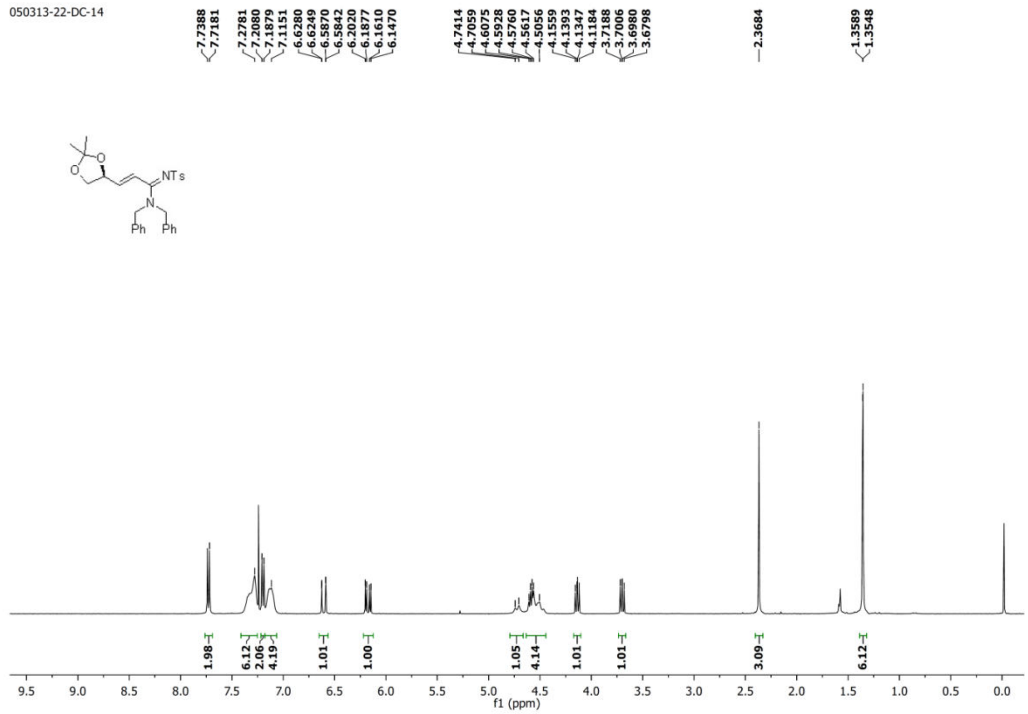


Figure 3.12: [1]H NMR spectra of **34d** in $CDCl_3$.

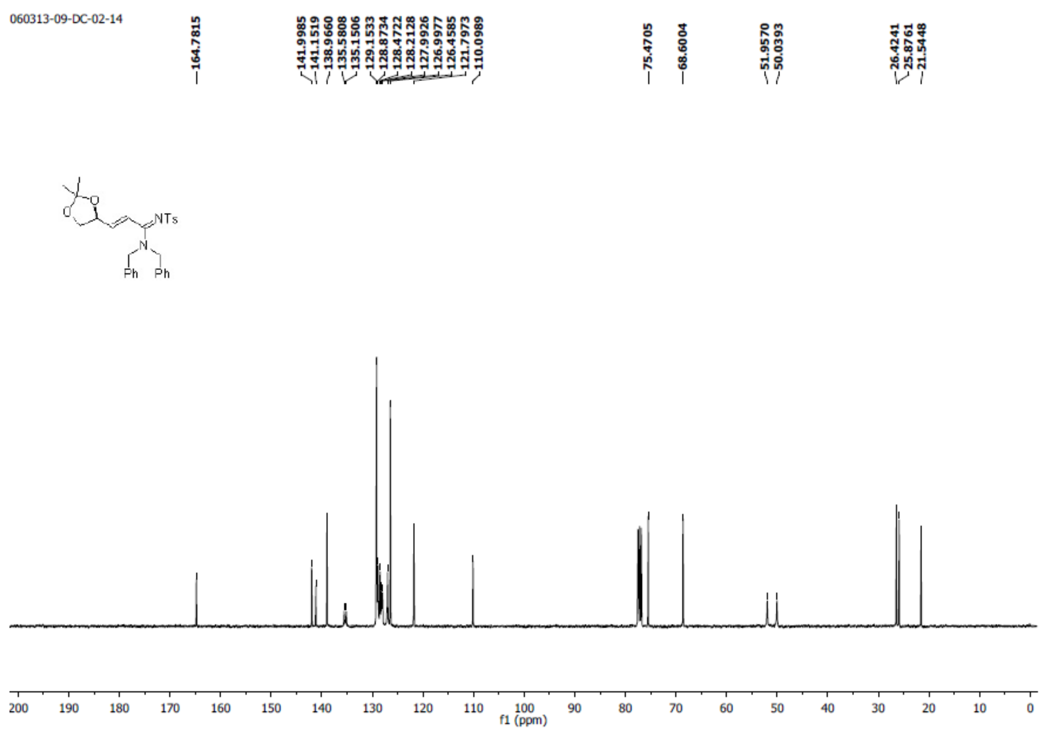


Figure 3.13:[13]C NMR spectra of **34d** in $CDCl_3$.

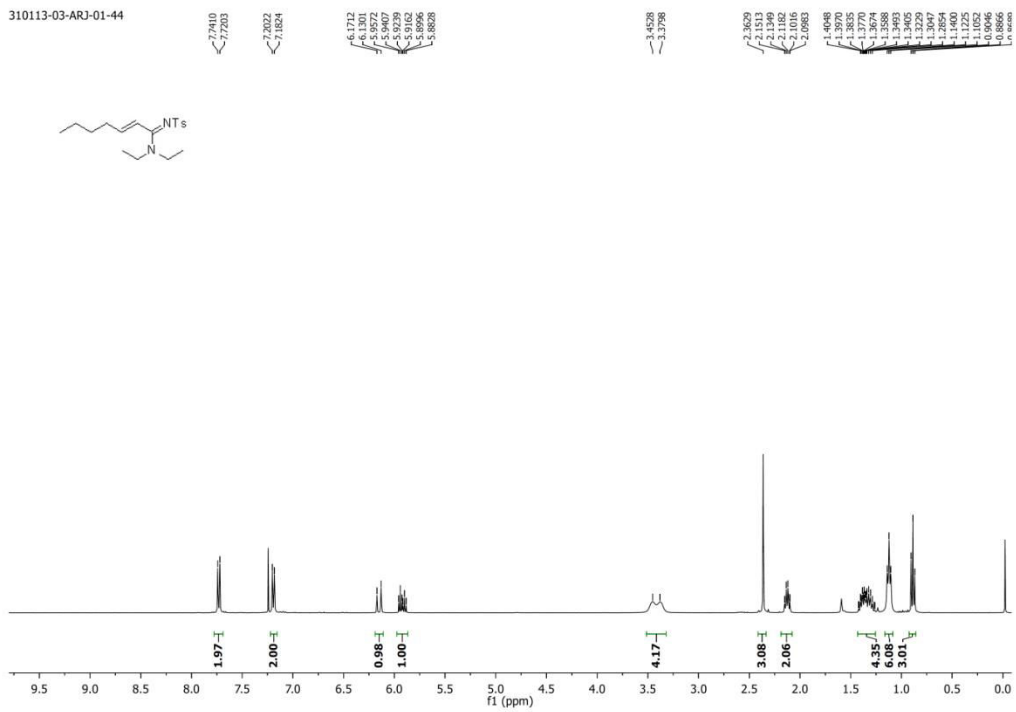


Figure 3.14: ^{1}H NMR spectra of **34f** in $CDCl_3$.

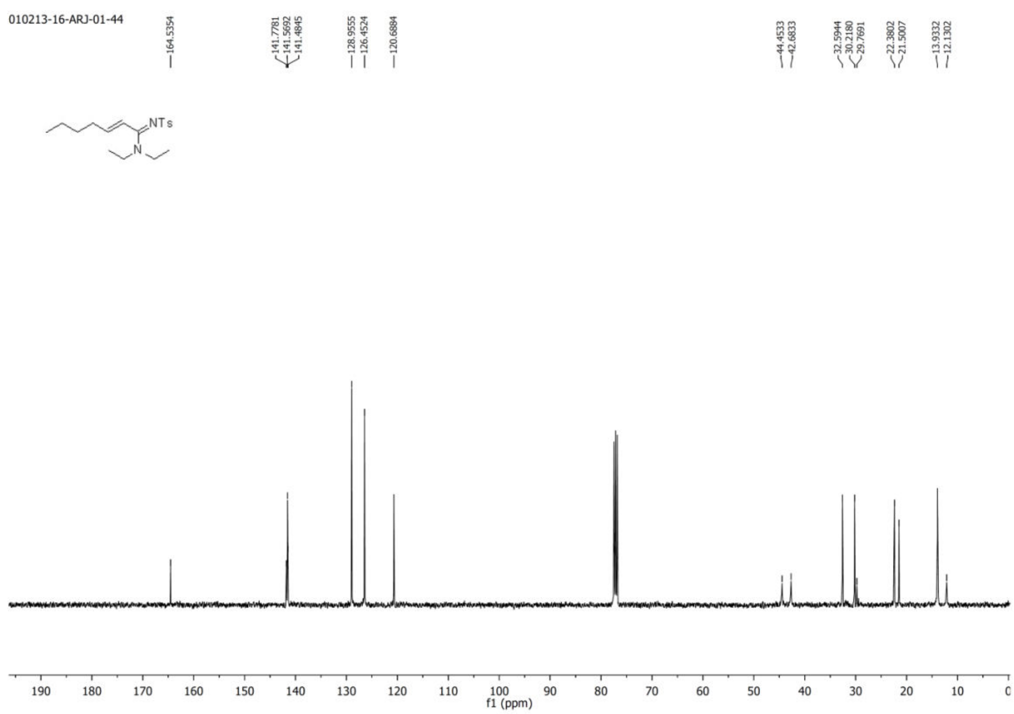


Figure 3.15: ^{13}C NMR spectra of **34f** in $CDCl_3$.

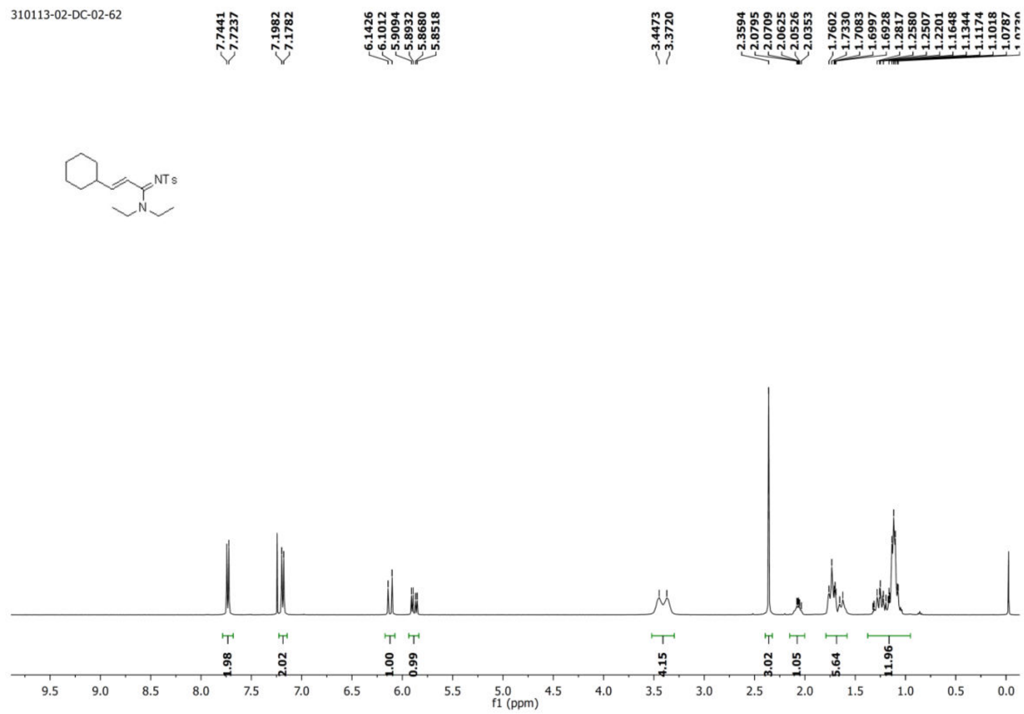


Figure 3.16: ^{1}H NMR spectra of **34g** in $CDCl_3$.

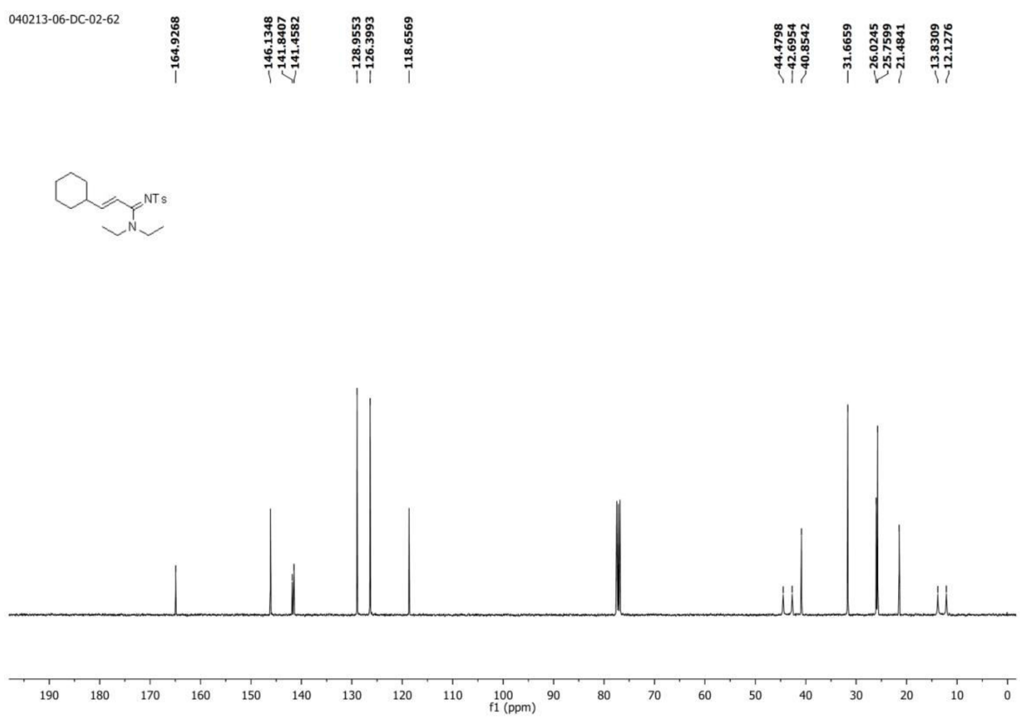


Figure 3.17: ^{13}C NMR spectra of **34g** in $CDCl_3$.

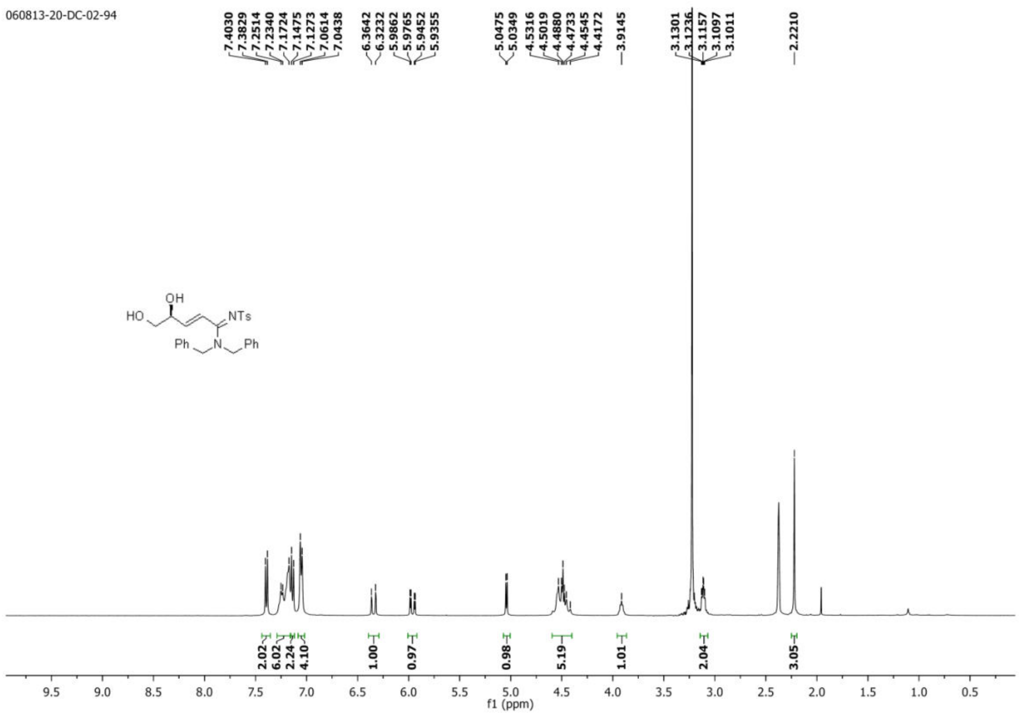


Figure 3.18: ^{1}H NMR spectra of **34j** in DMSO.

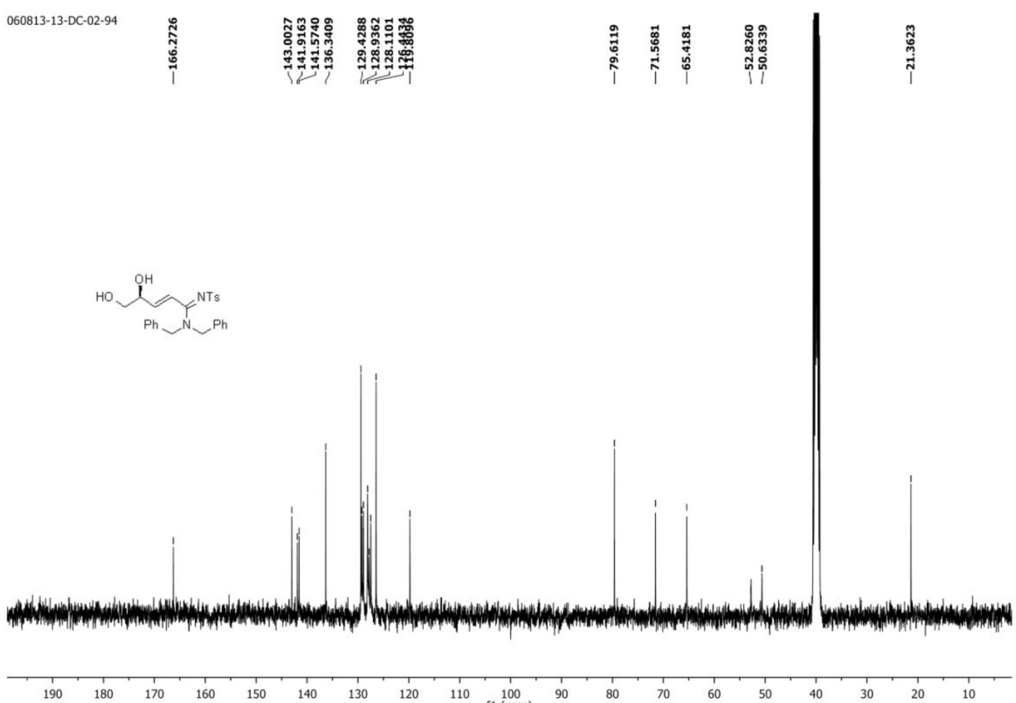


Figure 3.19: ^{13}C NMR spectra of **34j** in DMSO.

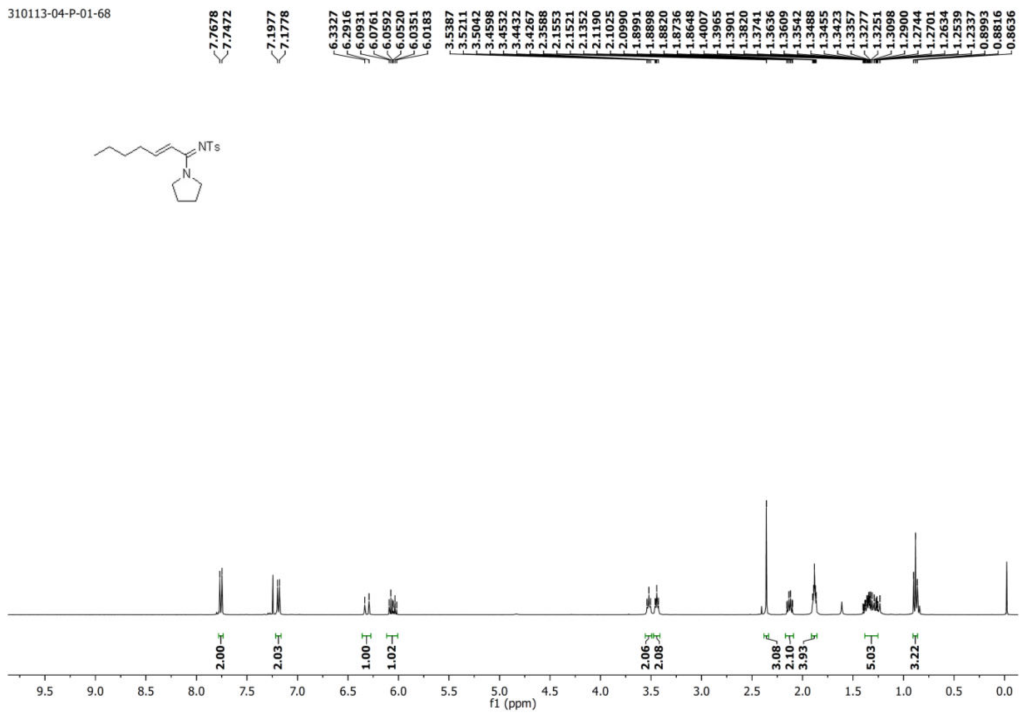


Figure 3.20: ^{1}H NMR spectra of **34k** in $CDCl_3$.

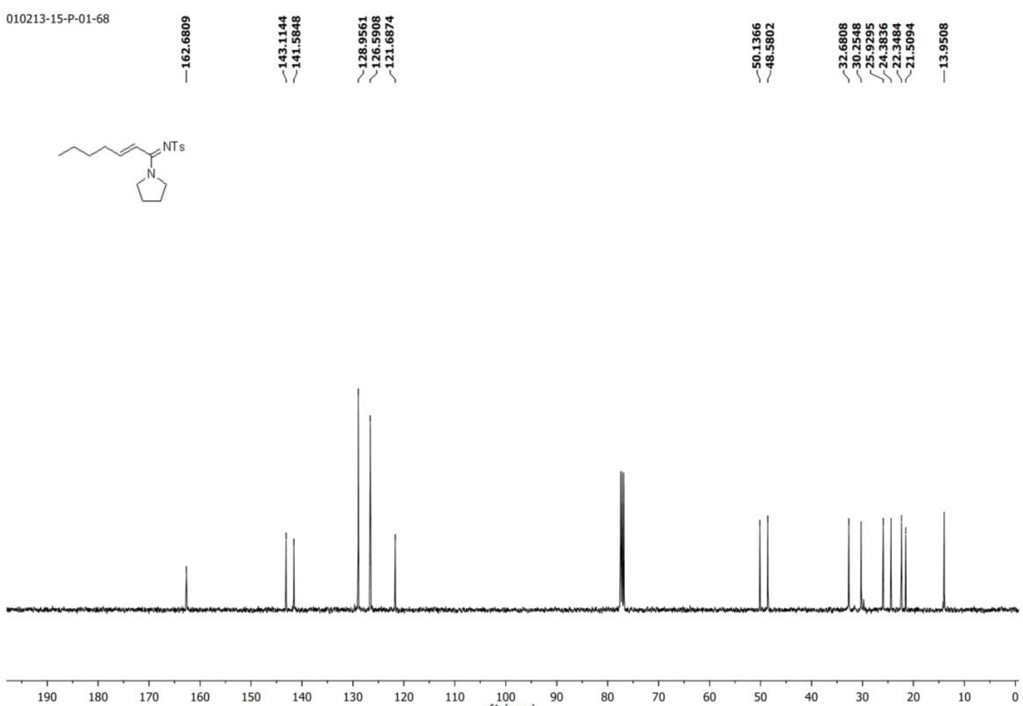


Figure 3.21: ^{13}C NMR spectra of **34k** in $CDCl_3$.

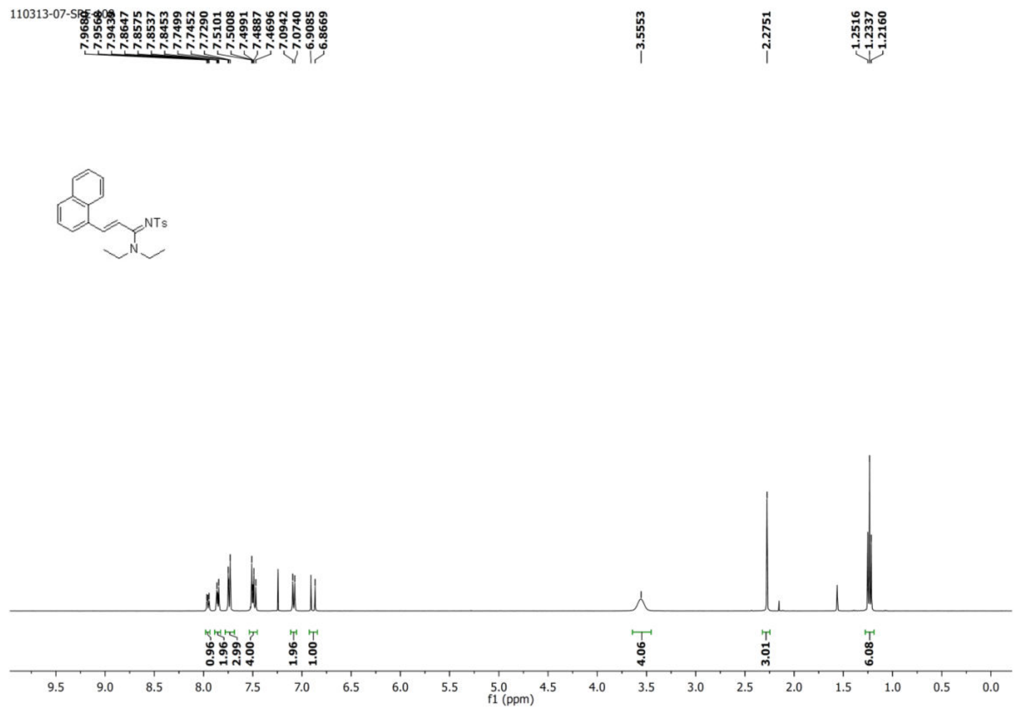


Figure 3.22 ^{1}H NMR spectra of **36j** in $CDCl_3$.

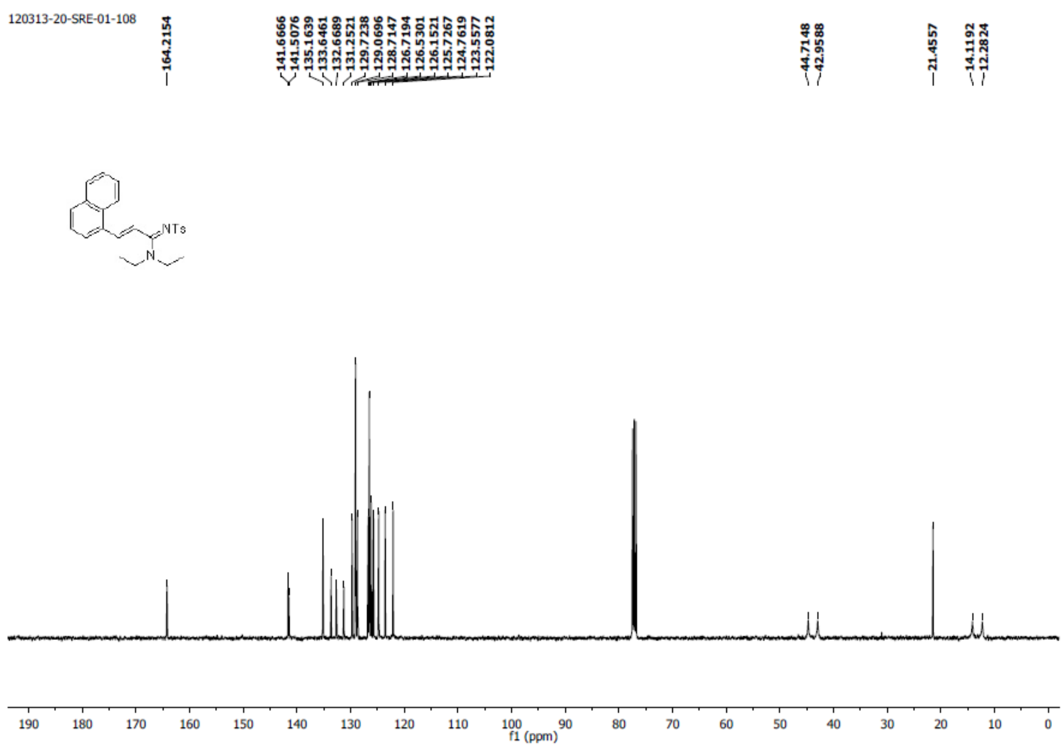


Figure 3.23: ^{13}C NMR spectra of **36j** in $CDCl_3$.

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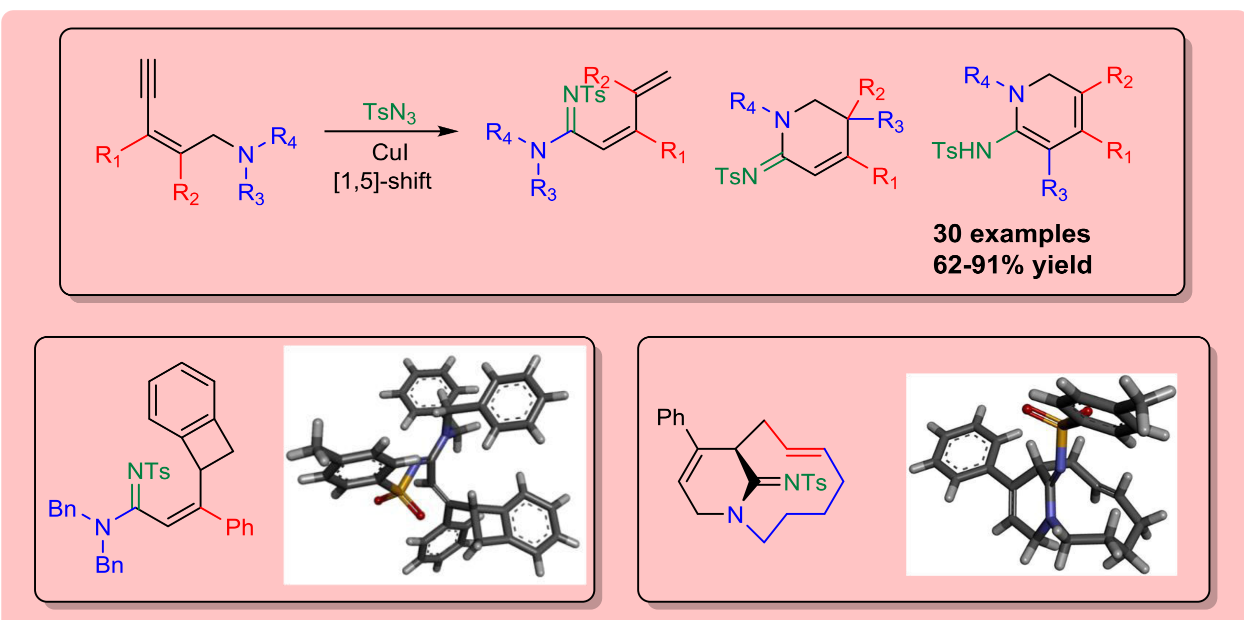
Chapter 4

Synthesis of Conjugated Unsaturated Acrylamidines, Cyclic Amidines, and Dihydro Pyridines by Cascade Rearrangements of Enyne-Amine Derived Ketenimines



4.1 Introduction:

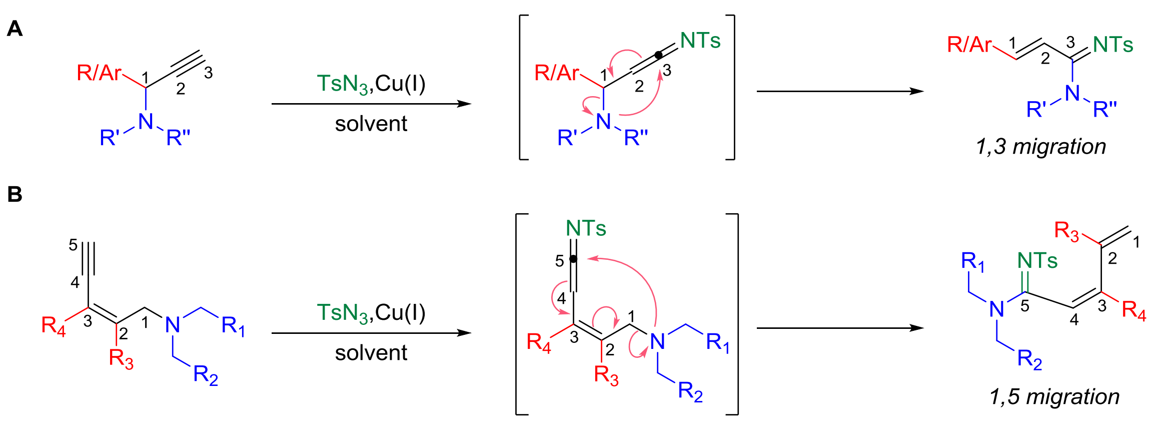
Cascade reactions represent a fascinating branch of organic chemistry which has been the subject of overwhelming research in recent years.[1] The reactions proceeding through more than a single step in a simultaneous fashion have been described as ‘cascade’ reactions. The cascade reactions are classified in to two classes, domino reactions and tandem reactions. The reactions in which the transformation occurs via two (or more) reactions one after another in an inseparable fashion are called as domino reactions. In this case both individual reactions belong tightly together and rather difficult to perform in independent fashion. Therefore the intermediate between both steps is likely to be unstable and difficult to isolate and characterize. In contrast, the tandem reactions are known to be two step reactions that proceed in a consecutive manner where each step can be performed separately. Thus, it can be predicted that the intermediate species is rather stable compound. The unarguable benefits of these reactions are well recognized, and have been recounted on several occasions, and include atom economy,[2] as well as economies of time, labor, resource management, and waste generation, and allow the synthesis of complex molecules from simple starting materials.[2b] Generally, the synthesis of an organic compound is carried out by traditional procedures in which the stepwise formation of individual bonds occurs towards the construction of the target molecule. However, it would be much more efficient if several bond formations happen in a single sequence without isolation of intermediates. It is obvious that this kind of reaction would be more cost-effective by requiring fewer reagents, solvents and adsorbents and less energy and labour together with a reduction of waste.[3]

Cascade or domino reactions show remarkable advantages as they proceed via a highly reactive (unstable) intermediate[4] which gives the final product in good yields because the decomposition of intermediate is highly avoided as it transforms in to the product at the same instant when it forms. These unstable intermediates play a vital role in cascade reactions which constitute species like carbanions, carbocations, carbenes or radicals, allenes, ketenimines, metal mediated electrofiles etc. Ketenimines are one of the intermediates extensively involved in cascade reactions and have attracted much attention in recent years for the easy formation, the relative reactivity, the tolerance of procedure, and the diversity of products. Ketenimines are widely used for the construction of various heterocyclic compounds which are important in pharmaceuticals and pesticides for their biological activities and in optoelectronics for their unique photo-physical characters.

An impressive number of chemo-catalyzed cascade reactions especially those involving cyclizations have been achieved by using transition metal catalysts like palladium, rhodium, ruthenium, copper, etc.[3] Other types of typical cascade reactions have been extensively reviewed and classified according to their type of mechanism.[4] All of these reaction sequences were initiated by an organic or inorganic catalyst, or by thermal reactions. In this chapter, we have discussed the copper (I) catalyzed cascade reactions of ketenimines where we have studied the cyclization and amino group migration reactions of enyne-amine derived ketenimines.

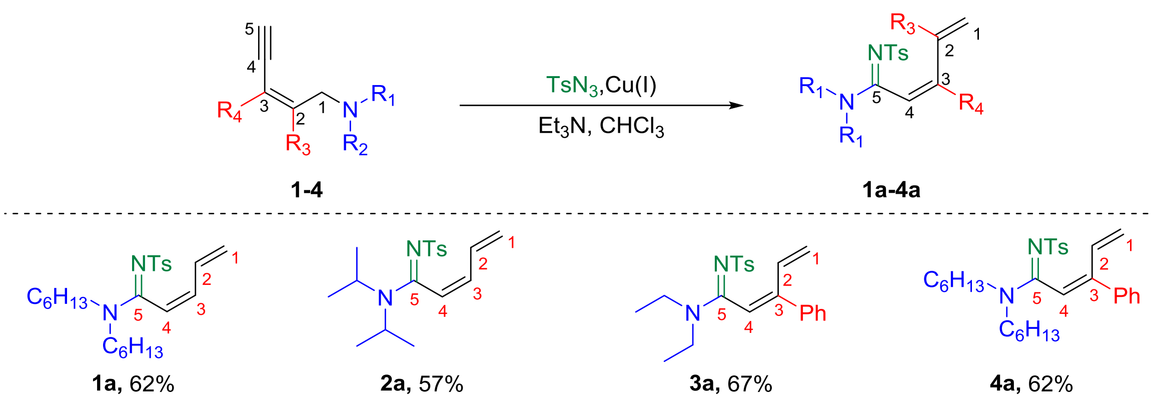
4.2 Results and discussion

Our success in the methodology of 1,3-amino group migration[5] as described in previous chapter has encouraged us to investigate a new chemistry of 1,5-amino group migration from conjugated enyne amine substrate and sulfonylazide to construct highly functionalized amidine (Scheme 4.1).



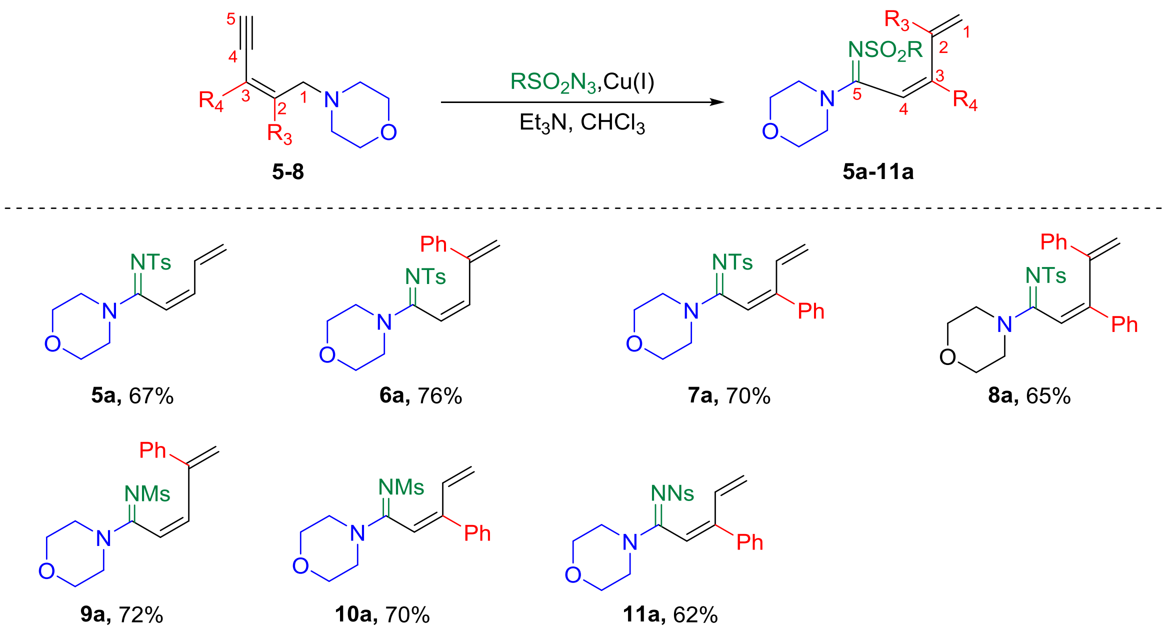
Scheme 4.1: 1,3 amino group migration (A), 1,5 amino group migration (B).

We have designed the substrates where we inserted a double bond in conjugation with the terminal alkyne to achieve 1,5 migration. Later, we have varied the substrates by substituting the double bond with phenyl group at either of the position or at both the positions. These substrates were prepared according to two general sequences described in (Scheme 4.9, 4.11, 4.13, 4.15). Our investigation was initiated by carrying out the copper catalyzed reaction on **1** under optimized condition with tosyl azide in presence of 10 mol% of CuI and triethylamine in chloroform as a solvent, we got the expected 1,5 amino group migrated product **1a** with 62% yield where the dihexyl amino group was migrated from C_1 to C_5 to give a conjugated unsaturated acrylamidine. Similar substrate **2** was prepared by varying the amino group from diexylamino to diisopropyl amino group which was treated with tosyl azide under similar conditions and gave the unsaturated conjugated product **2a** with 57% yield. Further the substrate **3** with phenyl substitution on double bond at C_3 with diethylamino group was treated with tosyl azide under similar conditions gave the amidine **3a** with 67% yield. The replacement of diethyl amino group by dihexylamino group in **4** yielded the product **4a** with 62% yield (Scheme 4.2). The substrates having phenyl substitution at C_2 and di phenyl substitution at C_2 and C_3 with aliphatic amines could not be prepared.



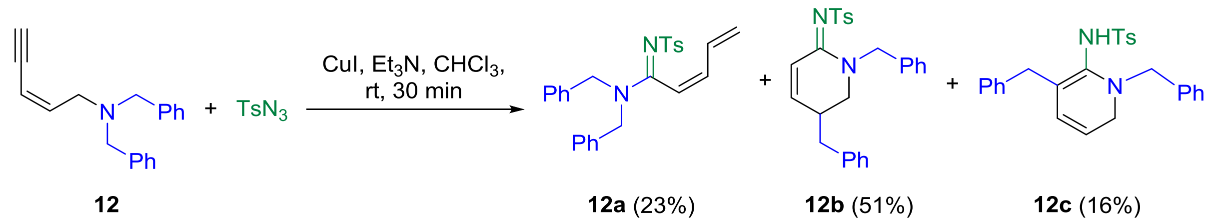
Scheme 4.2: Copper Catalyzed 1,5-amino migration reaction.

In the next stage, we changed the amino moiety with *N*-morpholinyl group. Here, we have carried out the copper catalyzed reaction with four sets of substrates. Irrespective of modification of the alkene moiety with phenyl group, each enyne amine provided the 1,5-amino group migration product as single isomer *i.e.* **5a** (yield = 67%), **6a** (yield = 76%), **7a** (yield = 70%) and **8a** (yield = 65%) were obtained from **5** (R_3 = H and R_4 = H), **6** (R_3 = H and R_4 = Ph), **7** (R_3 = Ph and R_4 = H) and **8** (R_3 = Ph and R_4 = Ph), respectively (entries 1-4, Table 4.2). Further, we treated the substrates **6** and **7** with mesyl azide but no effect on yield was observed, **9a** and **10a** were obtained in 72 and 70% yields respectively, we further varied the azide and treated the substrate **7** with nosyl azide to obtained product **11a** with 62% yield (Scheme 4.3). In this way the sulfonyl azides were tolerated in this methodology.



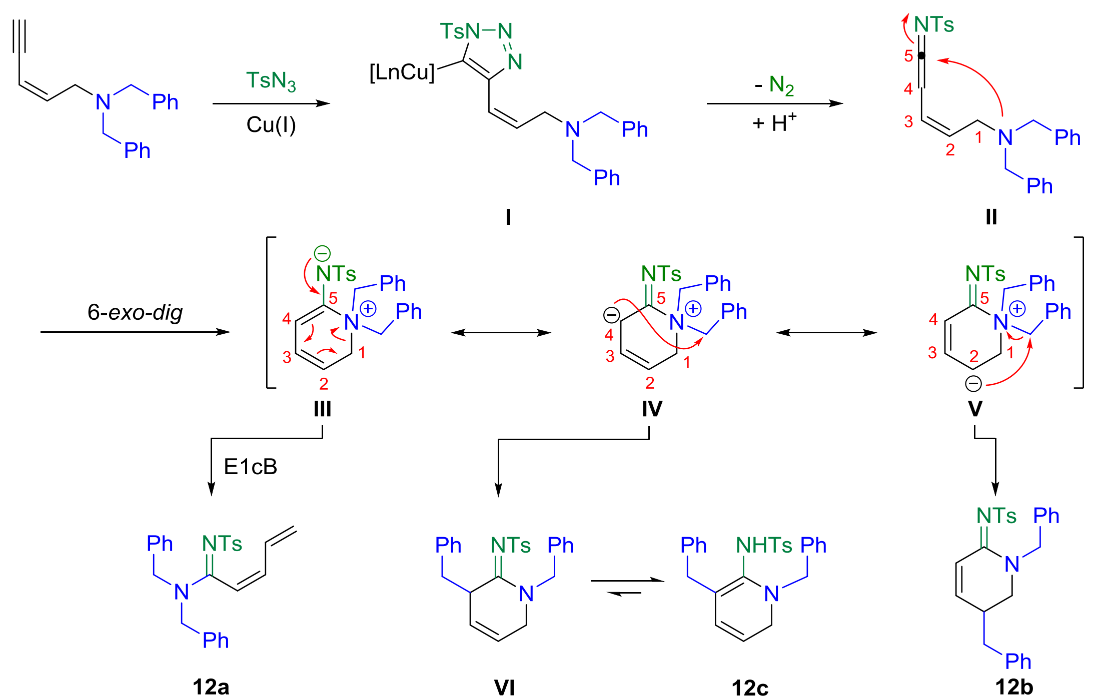
Scheme 4.3: Copper catalyzed 1,5-migration reactions of enyne-amines.

Later, when we carried out the reaction of conjugated enyne amine substrate **12**, linked to two benzyl groups at the N-center with tosyl azide (1.1 equiv) in presence of catalytic CuI (10 mol%) and Et_3N (1.5 equiv) in $CHCl_3$ provided the expected 1,5-amino group migration product **12a** (23%) along with two unexpected rearranged products **12b** (51%) and **12c** (16%) (Scheme 4.4). The possibility of such rearrangement cascade is not unexpected particularly when the conjugated enyne amine is linked to a facile migrating group at the N-atom according to the report by Xu and co-workers.[6] They have shown the migration of allyl group of nitrogen atom in tertiary amino enyne to give α-allyl cyclic amidine. In their case, the cascade occurs by ketenime generation at the terminal alkyne with sulfonyl azide followed by the cyclization and migration of allyl group. Therefore, we envisaged that when the tertiary amino group of the conjugated enyne amine is linked to a facile migrating group, the 6-*exo-dig* cyclic intermediate may also favor the shift of the facile migrating group to give cyclic products.



Scheme 4.4: Copper catalyzed reaction of enyne-amine **12**.

The plausible mechanism of the process is depicted in Scheme 4.5. Reaction of **12** with tosylazide under Cu(I) catalytic conditions provides the triazole intermediate **I** which upon releasing N_2 molecule gives ketenimine **II**.[7] Capture of the ketenimine by internal amino group leads to a 6-*exo-dig* cyclization[8] to form the next intermediate **III** which can also exists as its canonical forms **IV** and **V**. C_1–N bond cleavage of the cyclic intermediate **III** via E1cB process leads to the formation of 1,5-amino group migration product **12a**. The electrophilic migration of a benzyl group of the intermediate **V** to its C_2-center gives the cyclic amidine **12b**. In intermediate **IV,** electrophilic migration of a benzyl group to the C_4-center facilitates the formation of sulfonylamidine adduct **VI** which upon further tautomerization gives the sulfonamide **12c** (Scheme 4.5).



Scheme 4.5: Proposed mechanism for the formation of **12a**, **12b** and **12c**.

Encouraged by these findings, we decided to extend the methodology to conjugated enyne amines in order to obtain more insight of the product distribution. We envisaged that the conjugated enyne, and the migratory aptitude of the substituent at the N-center are responsible for the complex behavior of the reaction. Therefore, the library of substrates were prepared by varying the amino groups on four sets of enyne-amines by varying the electron donating or withdrawing effects of nitrogen substituents (Figure 4.1).

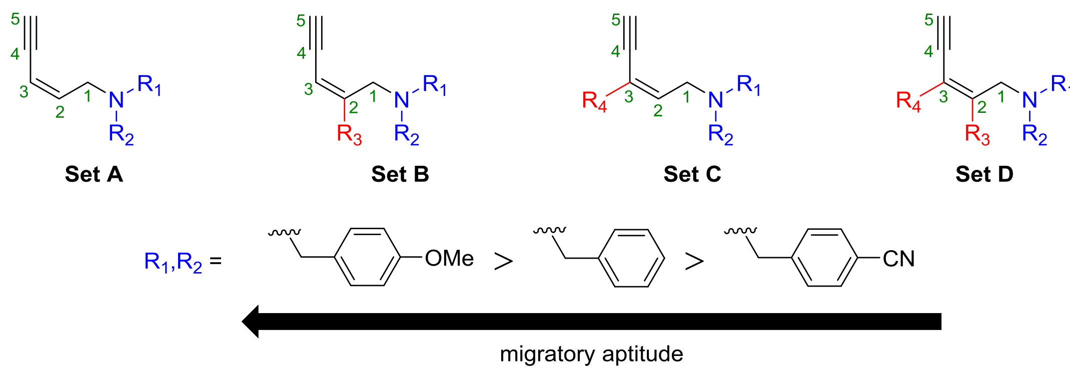
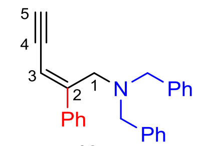
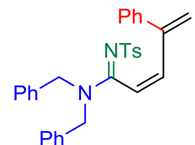
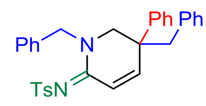
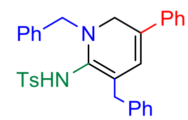
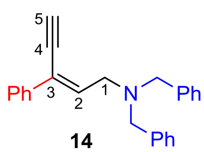
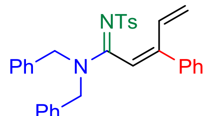
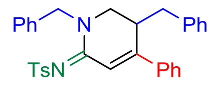
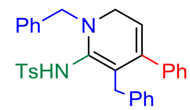
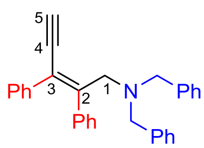
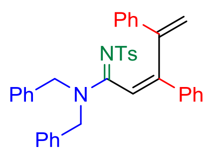
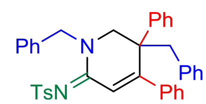
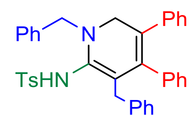
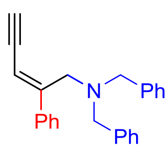
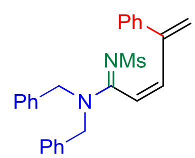
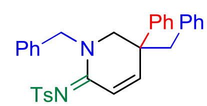
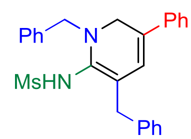
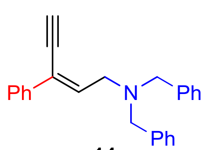
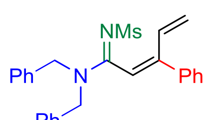
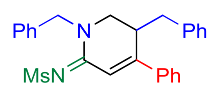
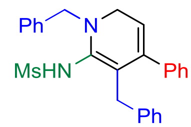
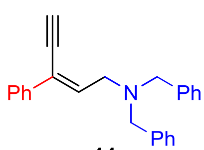
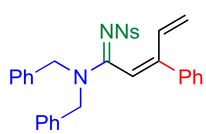
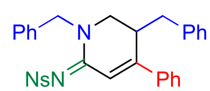
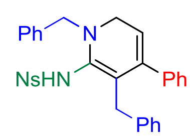


Figure 4.1: Substrate variation by varying alkene substitution and amine substituents.

Conjugated enyne amine substrate **13,** with a phenyl group C_2-center (*i.e.* R_3 = Ph and R_4 = H), when treated with tosyl azide under the optimized Cu(I) catalytic conditions provided cyclic amidine **13b** (50%) and dihydropyridine **13c** (40%) as rearranged products (Table 4.1, entry 1). Corresponding acyclic amidine **13a** (*i.e.* 1,5-amino group migration product) could not be traced from the reaction mixture. On the contrary, substrate **14** (*i.e.* R_3 = H and R_4 = Ph) under similar reaction conditions provided the 1,5-amino group migration product **14a** (84%) as the major isomer (Table 4.1, entry 2). In this case, the cyclic amidine **14b** was isolated as the minor product (yield = 5%) and formation of **14c** could not be detected. Next we introduced phenyl groups at both C_2 and C_3 positions to get substrate **15** (*i.e.* R_3 = Ph and R_4 = Ph), and its reaction with tosyl azide gave two products **15a**, and **15b.** In this case, we got acyclic amidine product **15a** as a major product with 48% yield, and **15b** with 30% of yield, other cyclic product dihydro pyridine **15c** was not observed (Table 4.1, entry 3). In this way, the different types of substrates gave the different types of distribution of products. Further, we checked the effect of sulfonyl azide on reaction, the substrates **13** and **14** were treated with mesyl azide and the distribution of products was observed to be similar as in case of tosyl azide. **13** gave two cyclic products **16b** and **16c** with 52 and 34% yield respectively (Table 4.1, entry 4). **14** gave **17a** with 73% yield (Table 4.1, entry 5). Substrate **14** was further treated with nosyl azide and **18a** with 76% yield (Table 4.1, entry 6).

Table 4.1: Copper catalyzed reactions of various enyne-amines by varying sulfonyl azides.

Entry	Substrates	Azide	1,5 shift product	Cyclic amidine	Dihydro pyridine
1	 **13**	TsN_3	 **13a**, 0%	 **13b**, 50%	 **13c**, 40%
2	 **14**	TsN_3	 **14a**, 84%	 **14b**, 5%	 **14c**, 0%
3	 **15**	TsN_3	 **15a**, 48%	 **15b** 30%	 **15c**, 0%
4	 **13**	MsN_3	 **16a**, 0%	 **16b**, 52%	 **16c**, 34%
5	 **14**	MsN_3	 **17a**, 73%	 **17b**, 0%	 **17c**, 0%
6	 **14**	NsN_3	 **18a**, 76%	 **18b**, 0%	 **18c**, 0%

It was intriguing to find that only the unsubstituted enyne amine **12** gave all three rearranged products. On the other hand, position of the phenyl group on mono-phenyl substituted (at either C_2 or C_3 position) enyne amine plays an important factor for driving the process to either 1,5-amino group migration or benzyl group migration. The phenyl group on C_2 in **13** stabilizes the corresponding negative charge in intermediates **13x, 13y,** and **13z** on carbon atom C_2 and C_4 because of extended conjugation and this negative charge makes the C_2 and C_4 as nucleophiles which further attack on benzyl group present on quarternary nitrogen atom to give the benzyl migrated cyclic products. In case of **14**, the phenyl group at C_3 does not contribute for the stabilization of negative charge in the intermediates **14x, 14y,** and **14z** (figure 4.2) therefore the negative charge prefers to delocalise forward and breaks the C_1-N bond to give acyclic product **14a** as a major product.

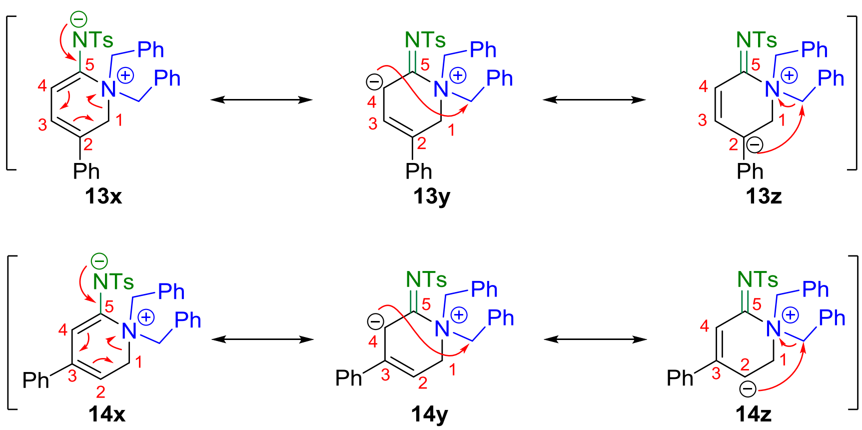


Figure 4.2: Stabilization of negative charge in intermediates of **13,** and **14.**

We further elaborated these results with the help of theoretical quantum calculations to rationalize the positional dependency of the phenyl group (either substituted at C_2 or C_3) on the products distribution of the reaction.

4.2.1 Theoretical Calculation

All the Stationary points (reactant and product minima and first order saddle points) on the potential energy surface were obtained with density functional theory (DFT) using traditional hybrid Becke, three-parameter, Lee-Yang-Par exchange correlation functions (B3LYP) and standard 6-31G basis set have been used throughout to perform all geometry optimizations without imposing any symmetry (using C1 symmetry). All the stationary points have been characterized with the frequency analysis i.e. minima has all real frequencies and the first order saddle point has single imaginary frequency. For the verification of the first order saddle point being the transition state between the reactant and the corresponding product, intrinsic reaction coordinates have been calculated. Møller-Plesset second order perturbation (MP2) method has been used to estimate the systematic error of the DFT/B3LYP reaction barriers by calculating single point energies with MP2 at the DFT/B3LYP optimized geometries. All calculations were performed with the GAMESS program package.

We have considered five sets of enyne amine reactions here, $R_1 = R_2$ = Bn and $R_3 = R_4$ = H (**9**), $R_1 = R_2$ = Bn and R_3 = Ph, R_4 = H (**10**), $R_1 = R_2$ = Bn and R_3 = H, R_4 = Ph (**11**), $R_1 = R_2$ = Bn and $R_3 = R_4$ = Ph (**12**) and $R_1 = R_2$ = PMB and $R_3 = R_4$ = H (**17**). The stationary points on the ground state potential energy surface for a simpler set of reaction where $R_1 = R_2$ = Me and R_3 = R_4 = H (Set-I′) have been shown in Figure .

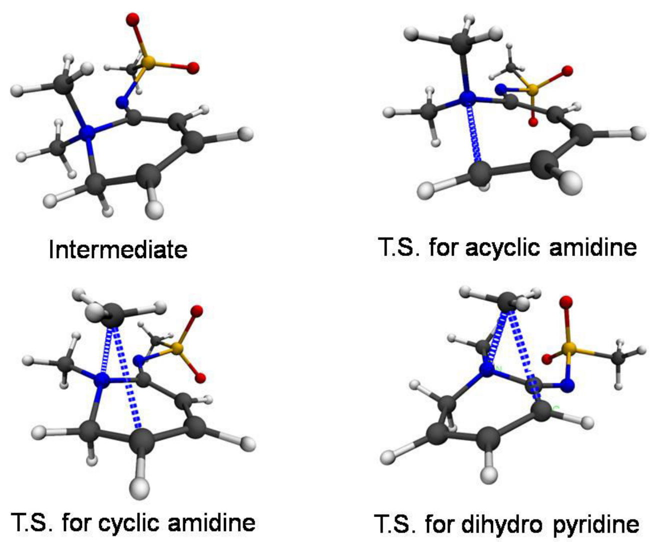


Figure 4.3: Stationary points on the PES of ketenimine reaction for set-I′.

The transition state that corresponds to one of the cyclic products was not possible to obtain with currently used quantum chemical methods. Thus, ab initio calculations have been used to explain the formation of cyclic versus acyclic products for the mentioned five sets of reactions. DFT methods are known to underestimate the reaction barriers. To get this barrier underestimation error, we calculated reaction barriers for set-I′ using MP2 and compared these barriers with DFT calculated barriers. Table 4.2 shows the comparison between MP2 and DFT barriers for set-I′.

Table 4.2: Comparison of MP_2 and DFT barriers for set-I′ reaction.

Product	DFT	MP2
Acyclic	14.275 kcal/mol	21.278 kcal/mol
Cyclic_b	39.390 kcal/mol	44.122 kcal/mol

From the above table 4.2, one can see that the difference between MP2 and DFT reaction barrier for the formation of acyclic product is 7 kcal/mol and for the formation of cyclic product **b** is around 4 kcal/mol. This indicates us that the DFT underestimates the reaction barrier for acyclic by around 3 kcal/mol as compared to the cyclic product. Because of computational reasons, the MP2 calculation is intractable when $R_1 = R_2 =$ Bn (or $R_1 = R_2 =$ paramethoxy benzyl). In these cases we notice that there seems to be systematic underestimation of the barrier of the acyclic product **a** by 7.0 kcal/mol as compared to the cyclic product **b**. The barrier heights after addition of this correction are shown in Table 4.3 and are consistent with all the observations.

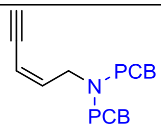
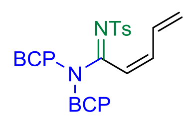
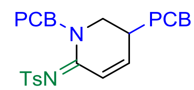
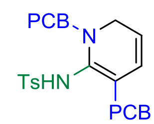
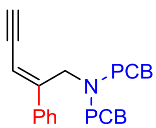
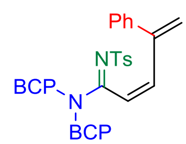
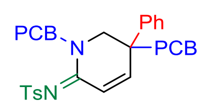
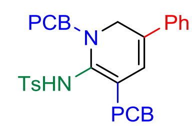
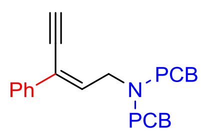
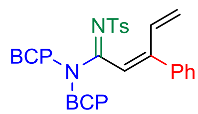
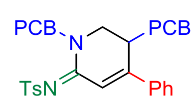
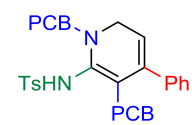
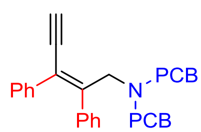
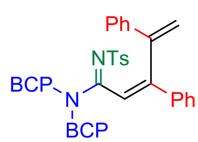
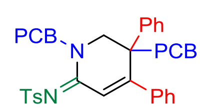
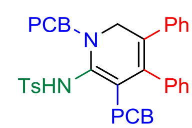
Table 4.3: Calculated reaction barriers for five sets of reactions in kcal/mol.

Entry	Substrates	**a**	[1]**a**(7kcal/mol added)	**b**
1	substrate **12**	16.4	23.4	22.7
2	substrate **13**	16.5	23.5	19.6
3	substrate **14**	11.6	18.6	21.3
4	substrate **15**	9.2	16.2	16.3
5	substrate **17**	16.9	23.9	21.3

Having established the effect of substituents at C_2 or C_3 positions, we next evaluated the effect of amino group substituents on the course of reaction. At first, both benzyl groups were changed to electron deficient 4-cyano benzyl groups and phenyl positions were varied around the alkene moiety. In these cases, the observed trends were similar to those observed for **12-15**.

Enyne-amine **19** (*i.e.* R_3 = H and R_4 = H) upon reaction with tosyl azide gave **19a, 19b** and **19c** with 13%, 37% and 23% yields, respectively (entry 1, table 4.4). Enyne amine **20** (*i.e.* R_3 = Ph and R_4 = H) only cyclic rearranged products **20b** and **20c** with 51% and 32% yields, respectively (entry 2, table 4.6). For enyne amine **21** (*i.e.* R_3 = H and R_4 = Ph), formation of only 1,5-amino group migration product **21a** (yield = 77%) was observed (entry 3, table 4.4). Di-phenyl substituted enyne amine **22** (*i.e.* R_3 = Ph and R_4 = Ph) gave two products **22a**, and **22b** with yields 73, and 18%, respectively (entry 4, table 4.4).

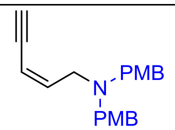
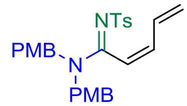
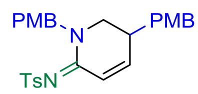
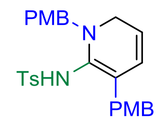
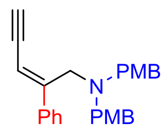
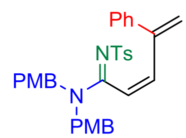
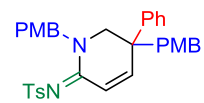
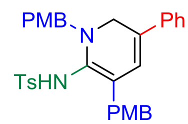
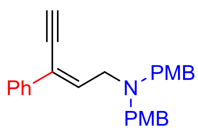
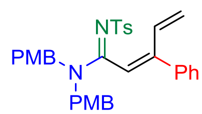
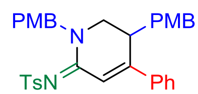
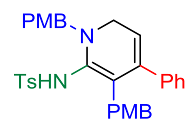
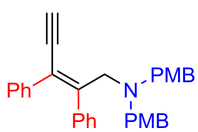
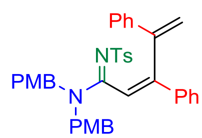
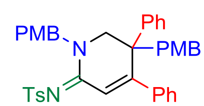
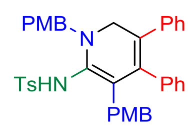
Table 4.4: Copper catalyzed reactions of various enyne-amines.

Entry	Substrate	1,5 shift product	Cyclic amidine	Dihydro pyridine
1	 **19**	 **19a,** 13%	 **19b**, 37%	 **19c,** 23%
2	 **20**	 **20a,** 0%	 **20b**, 51%	 **20c**, 32%
3	 **21**	 **21a,** 77%	 **21b**, 0%	 **21c**, 0%
4	 **22**	 **22a,** 73%	 **22b**, 18%	 **22c**, 0%

PCB = 4-cyano benzyl

When amino group substituents were changed to electron rich 4-methoxy benzyl groups, an interesting bias of product distribution towards rearranged cyclic products were observed. Enyne amine **23** (*i.e.* R_3 = H and R_4 = H) upon reaction with tosyl azide gave **23b** (yield = 63%), **23c** (yield = 12%) and formation of corresponding acyclic product **23a** was not observed (entry 1, table 4.5). The observation was similar for **24** (*i.e.* R_3 = Ph and R_4 = H) which provided **24b** and **24c** with 60% and 11% yields, respectively (entry 2, table 4.5). Enyne amine **25** (*i.e.* R_3 = H and R_4 = Ph) provided **25b** as the major product (yield = 70%), compounds **25a** (yield = 8%) and **25c** (yield = 6%) were obtained as minor isomers (entry 3, table 4.5). Di-phenyl substituted enyne amine **26** (*i.e.* R_3 = Ph and R_4 = Ph) gave rearranged cyclic product **26b** with yield 68% (entry 4, table 4.5). The higher migratory aptitude of PMB group led selectively to cyclic product as the electron rich PMB group prefers only to migrate.

Table 4.5: Copper catalyzed reactions of various enyne-amines.

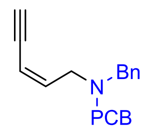
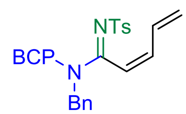
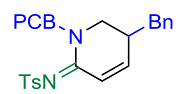
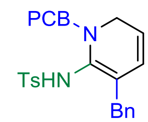
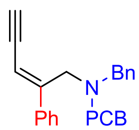
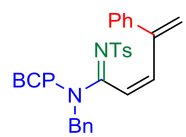
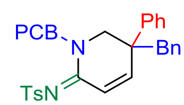
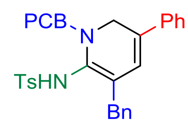
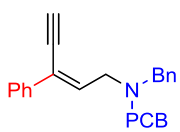
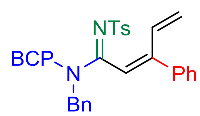
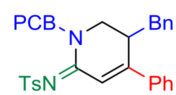
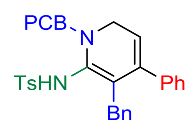
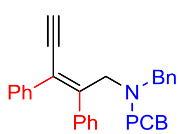
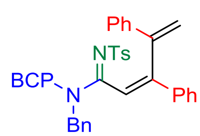
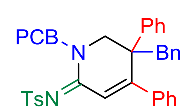
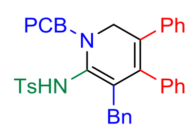
Entry	Substrate	1,5 shift product	Cyclic amidine	Dihydro pyridine
1	 **23**	 **23a**, 0%	 **23b**, 62%	 **23c**, 12%
2	 **24**	 **24a**, 0%	 **24b**, 56%	 **24c**, 11%
3	 **25**	 **25a**, 6%	 **25b**, 70%	 **25c**, 8%
4	 **26**	 **26a**, 0%	 **26b**, 68%	 **26c**, 0%

PMB = 4-methoxy benzyl

We next compared migratory aptitudes of two groups connected at the amino position by introducing a benzyl and 4-cyano benzyl group. Enyne amine **27** (R_1 = Bn, R_2 = 4-*CN*$C_6H_4CH_2$, R_3 = H and R_4 = H) when reacted with tosyl azide, formation of **27a** (yield = 14%), **27b** (yield = 39%) and **27c** (yield = 23%) (entry 1, table 4.6). Structural analysis of **27b** and **27c** clearly indicated the migration of benzyl group to either C_2 or C_4 position. Therefore, the observation correlates to the better migratory aptitude of benzyl over 4-cyano benzyl group. Similarly, **28** (R_1 = Bn, R_2 = 4-*CN*$C_6H_4CH_2$, R_3 = Ph and R_4 = H) provided cyclic products **28b** (yield = 50%) and **28c** (yield = 25%) via selective migration of benzyl over 4-cyano benzyl group (entry 2, table 4.6). Substrate **29** (R_1 = Bn, R_2 = 4-*CN*$C_6H_4CH_2$, R_3 = H and R_4 = Ph) gave only **29a** (yield =

86%), the 1,5-amino group migration product (entry 3, table 4.6). Reaction of enyne amine **30** (R_1 = Bn, R_2 = 4-*CN*$C_6H_4CH_2$, R_3 = Ph and R_4 = Ph) with tosyl azide also confirmed preferred migration of benzyl group compared to 4-cyano benzyl group, as indicated by rearranged cyclic products **30b** (yield = 29%) and the acyclic isomer **30a** (yield = 46%) was isolated as the major product (entry 4, table 4.6).

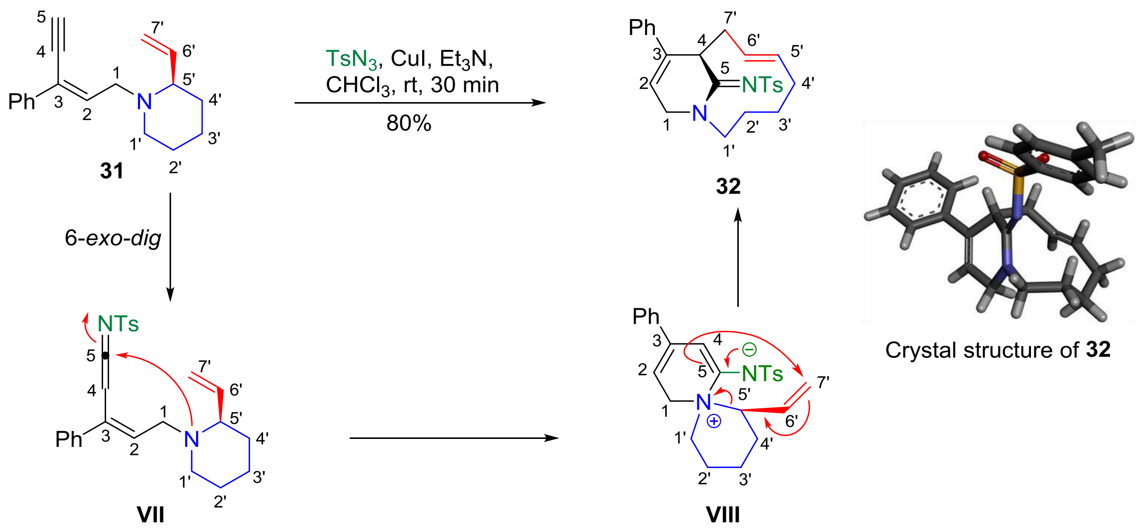
Table 4.6: Copper catalyzed reactions of various enyne-amines.

Entry	Substrate	1,5 shift product	Cyclic amidine	Dihydro pyridine
1	 **27**	 **27a,** 14%	 **27b,** 39%	 **27c,** 23%
2	 **28**	 **28a,** 0%	 **28b,** 49%	 **28c,** 25%
3	 **29**	 **29a,** 86%	 **29b,** 0%	 **29c,** 0%
4	 **30**	 **30a,** 46%	 **30b,** 29%	 **30c,** 0%

PCB = 4-cyano benzyl

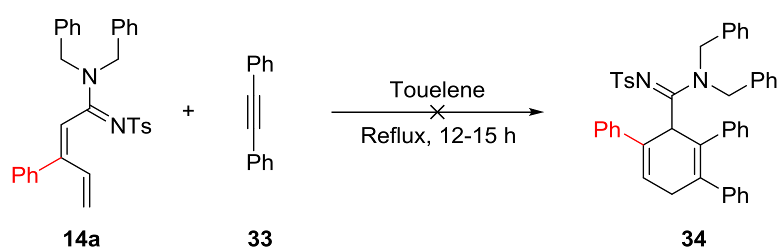
The above results proved that aryl groups have migrating ability with respect to their electron density and resulted in the various distribution of products.

In order to verify the efficiency of this protocol, we further achieved a stereoselective and efficient synthesis of a bridged bicyclic alkenyl amidine using cyclic *N*-allyl-aminoenyne as a substrate. It was envisioned that cyclic enyne-amine **31** would react with sulfonyl azide to form ketenimine intermediate **VII** utilizing base and a catalytic amount of CuI, subsequent cyclization led to zwitterion **VIII**, and finally the attack of C_4 at terminal alkenyl carbon $C_{7'}$ resulted in the ring expansion to acquire bicyclic amidine **32** (Scheme 4.6).



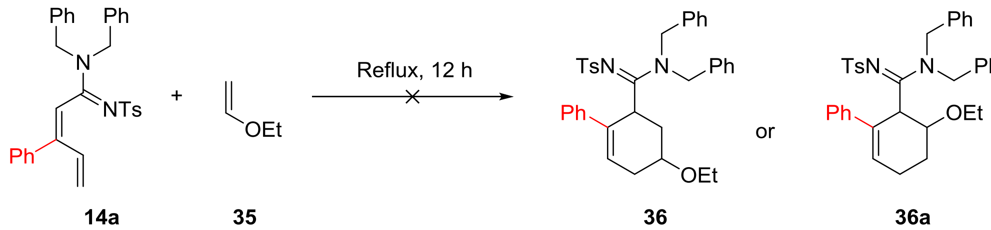
Scheme 4.6: Synthesis of bridged bicyclic amidine via ring expansion.

Finally, considering the diene system obtained in all conjugated unsaturated acrylamidines, we planned to carry out Diels-Alder reactions on them to achieve cyclic amidines. First, we have heated **14a** with diphenyl acetylene at various temperatures in toluene and later the reaction mixture was refluxed for 12-15 hours but we have not observed any conversion (Scheme 4.7).



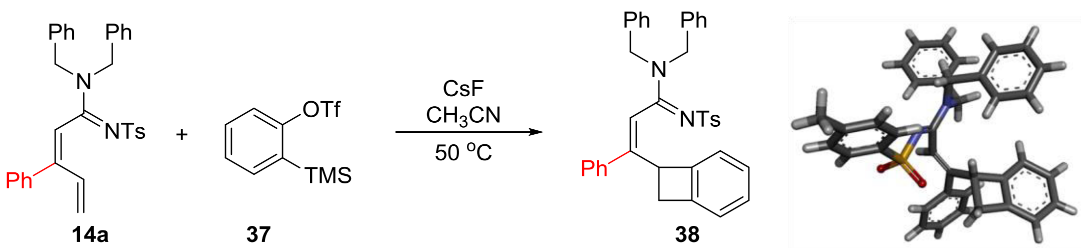
Scheme 4.7: Diels-Alder reaction with diphenyl acetylene.

Later, we refluxed the same substrate **14a** with ethyl vinyl ether for overnight but there was no conversion observed (Scheme 4.8).



Scheme 4.8: Diels-Alder reaction with ethyl vinyl ether.

After observing the inertness of **14a** towards the two different alkynes, we decided to treat **14a** with some reactive species to obtain Diels-Alder reaction. Arynes are well known for their reactivity, they are highly reactive even at low temperature. Because of their extreme reactivity, arynes must be generated in situ.[9] There are several methods reported in the literature for their generation. Aryl triflates have been exclusively used to generate arynes more efficiently than any other routes.[9c] For example, fluoride ion displacement of the trimethylsilyl group provides a convenient route to benzyne under mild conditions. Therefore we chose 2-(trimethylsilyl)phenyl trifluoromethanesulfonate and treated with **14a** in presence of CsF in acetonitrile at 50 ^{o}C for 8 hours, when we isolated the obtained product it was found that instead of Diels-Alder product it was [2+2]-cyclized product **38** obtained with 80% yield which was confirmed by NMR and crystal structure (Scheme 4.9).



Scheme 4.9: [2+2] cyclo-addition of amidine **14a** with benzyne **37**.

Benzyne [2+2]-cycloaddition is well-known, 1,7 there are very few examples involving enamines, and enamides. Here we have discovered the novel [2+2]-cycloaddition of benzyne with a double bond flanked with acrylamidine for the first time. This chemistry can be explored further with different arynes and conjugated unsaturated acrylamidines. While conceptually simple, this attempt is appropriate and noteworthy because amidines represent an increasingly more accessible substrate and a useful functional group in modern organic synthesis.

4.3 Conclusion

Hence, we have developed the methodology where we have successively achieved the 1,5 migartion of amino group of enyne-amines to obtain conjugated unsaturated amidines in case of aliphatic amino groups and cyclic amino group. The reaction of enyne-amines having benzyl or substituted benzyl groups at N-centre gave a rearrangement cascade in which three kinds of products were observed. We have explored these new kinds of cascade rearrangements of ketenimine by carrying out the copper-catalyzed reaction on each set of substrate by varying the N-substituents with respect to their electron donating or withdrawing nature. We have observed that in each case, the product distribution was different. The change in distribution of products with respect to substrate was explained by the intermediate stability. Further, theoretical quantum calculations were carried out to support the practically observed results. While varying the amino groups, we have not observed any change in the distribution of products when the dibenzylamine was replaced with di(*p*-cyano)benzylamine. The trend of product distribution was also found to be similar when unsymmetrical amino group, 4-((benzylamino)methyl)benzonitrile was used. In unsymmetrical amine case, cyclization occurred with the migration of benzyl group as its migratory aptitude was greater than *p*-cyanobenzyl group. When amino group was changed to electron rich *p*-methoxybenzyl (PMB) group, we have observed only the cyclic products as the migratory aptitude of PMB group is so high that it migrates preferentially to give cyclic product. Synthesis of structurally unprecedented amidine with bridged bicycle framework was achieved from cyclic *N*-allyl amino-enyne. To explore the synthetic applications of this methodology we have carried out a novel [2+2]-cycloaddtion reaction of acyclic amidine with benzyne.

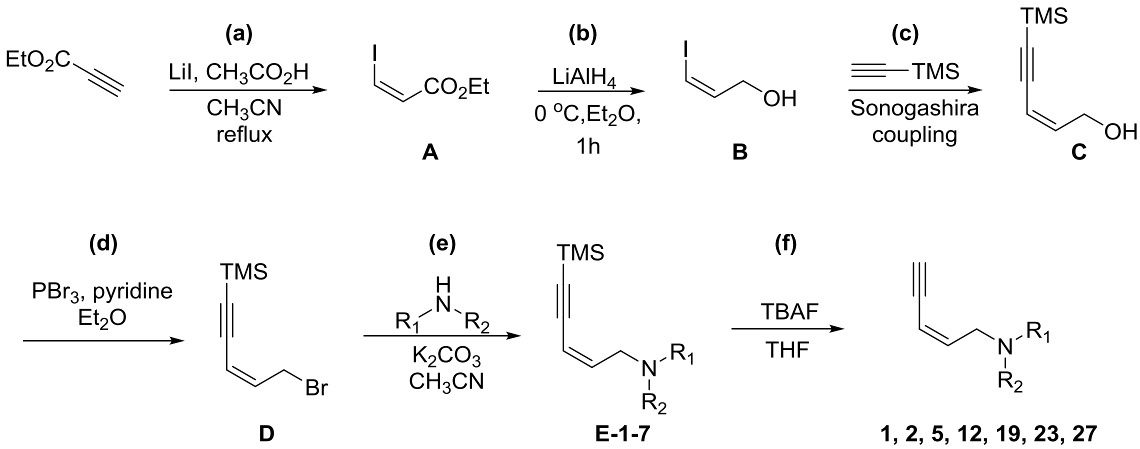
4.4 Experimental section

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.

Experimental Procedures:

General procedure for the synthesis of *(Z)-N,N*-disubstituted pent-2-en-4-yn-1-amine 1, 2, 5, 12, 19, 23, 27.



Scheme 4.10: Synthesis of *(Z)-N,N*-disubstitutedpent-2-en-4-yn-1-amine.

(a) Synthesis of (*Z*)-methyl-3-iodoacrylate A[10]

In a 100 mL flask ethyl propiolate (2.0 g, 20.38 mmol) was dissolved in 20 mL CH_3CN. Then lithium iodide (3.0 g, 22.43 mmol) was added followed by acetic acid (1.35 mL, 22.43 mmol). The resulting solution was heated to reflux under vigorous stirring. After 10 minutes white precipitate was formed, the stirring was continuous for overnight. After cooling, the reaction mixture was neutralized by pouring 50 mL 0.3 M K_2CO_3 solution. The resultant solution was extracted for four times with 120 mL of diethyl ether. The combined layers were washed with brine solution and dried over Na_2SO_4. Removal of the solvents under reduced pressure yielded the crude enoate, which was directly used without any further purification.

(b) Synthesis of (*Z*)-3-Iodoprop-2-en-1-ol B[10]

A 250 mL flask was charged with $LiAlH_4$ (0.77 g, 20.38 mmol) in diethyl ether 60 mL. The resultant reaction mixture was cooled 0 ^{o}C and (*Z*)-3-iodopropenoate (4.6 g, 20.38 mmol) dissolved in diethyl ether 20 mL was added dropwise.The reaction was stirred for 30 minutes at 0 ^{o}C and allowed to warm at room temperature. The reaction was quenched at 0 ^{o}C by adding ethyl acetate 5 mL and saturated solution of Na_2SO_4 5 mL and resultant mixture was stirred vigorously for 30 minutes and filtered through celite pad. The obtained filtrate was washed with brine, extracted in ether and dried over Na_2SO_4. The solvent was evaporated and obtained compound was used for further reaction without purification.

(c) Synthesis of (*Z*)-5-(trimethylsilyl)pent-2-en-4-yn-1-ol C[11]

The solution of 1.2 equivalents of TMS acetylene and 1 equivalents of (*Z*)-3-iodoprop-2-en-1-ol **B** in degassed triethyl amine was further degassed for 10 minutes. To the resultant solution 2 mol% $PdCl_2(PPh_3)_2$ was added and stirred at room temperature for 15 minutes before 4 mol% CuI was added. The mixture was stirred for overnight. The reaction mixture was diluted with dichloromethane and filtered through celite pad. The solvent was evaporated and purified through column chromatography. The obtained yield was 79%.

(d) Synthesis of (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane D[12]

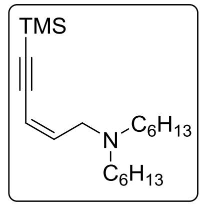
(*Z*)-5-(trimethylsilyl)pent-2-en-4-yn-1-ol **C** was dissolved in diethyl ether and cooled to -15 ^oC. To this PBr_3 (0.4 equivalent) was added drop wisely followed by the addition of pyridine (0.03 equivalent). The resultant mixture was allowed to warm at room temperature and stirred for 2 hours. The reaction was quenched with ice cubes, extracted in ether and dried over Na_2SO_4. The obtained product was purified with column chromatography with 92% of yield.

IR (neat): ν_{max}/cm^{-1} 2959, 2151, 1712, 1437, 1248, 1198, 1056, 972, 841; ^1H NMR (400 MHz, $CDCl_3$) δ 6.13 (dt, *J* = 11.0, 6.3 Hz, 2H), 5.62 (dt, *J* = 11.0, 1.5 Hz, 2H), 4.44 (d, *J* = 6.2 Hz, 4H), 0.21 (s, 19H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.99, 110.42, 62.94, 29.77, -0.05; HRMS (ESI): Calc. for $C_8H_{14}BrSi$ $[M+H]^+$: 217.0048; Found: 217.0050.

(e) Synthesis of (*Z*)-*N,N*-substituted-5-(trimethylsilyl)pent-2-en-4-yn-1-amine E

To the solution of (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane **D** in acetonitrile was added the amine (2 equivalent) drop wisely followed by K_2CO_3 (2 equivalent) at 0 ^oC. The resultant mixture was stirred for overnight. The solvent was evaporated and directly loaded on column for purification.

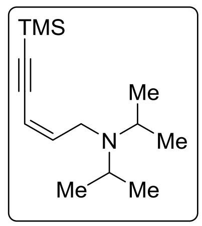
***(Z)-N*-hexyl-*N*-(5-(trimethylsilyl)pent-2-en-4-yn-1-yl)hexan-1-amine E-1**



The compound **E-1** was prepared by using the above procedure **(e).** (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane (200 mg, 0.92 mmol) in acetonitrile was cooled to 0 ^{o}C and dihexyl amine (316 µL, 1.84 mmol) was added followed by K_2CO_3 (255 mg, 1.84 mmol) to give **E-1** with 86% yield.

IR (neat): ν_{max}/cm^{-1} 2954, 2927, 2859, 2149, 1625, 1461, 1375, 1250, 1152, 1082, 986; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.08 (dt, *J* = 11.0 Hz, 7.0 Hz, 1H), 5.63 (dt, *J* = 11.0 Hz, 1.4 Hz, 1H), 3.4 (dd, *J* = 7.0 Hz, 1.4 Hz, 2H), 2.44 (m, 4H), 1.47 (m, 4H), 1.29 (m, 12H), 0.91 (t, *J* = 3.2 Hz, 6H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.3, 111.1, 101.6, 99.6, 54.2, 52.8, 31.8, 27.2, 27.0, 22.6, 14.0, 0.07; HRMS (ESI): Calc. for $C_{20}H_{39}NSi$ $[M+H]^+$: 322.2930; Found: 322.2933.

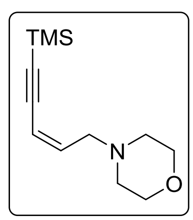
***(Z)-N,N*-diisopropyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine E-2**



The compound **E-2** was prepared by using the above procedure **(e).** (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane (200 mg, 0.92 mmol) in acetonitrile was cooled to 0 ^{o}C and di isopropyl amine (190 mg, 1.84 mmol) was added followed by K_2CO_3 (255 mg, 1.84 mmol) to give **E-2** with 79% yield.

IR (neat): ν_{max}/cm^{-1} 2962, 2147, 1461, 1385, 1368, 1327, 1250, 1204, 1173, 1079, 1038; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.02 (m, 1H), 5.5 (dt, *J* = 11.0 Hz, 1.7 Hz, 1H), 3.38 (dd, *J* = 7.0 Hz, 1.7 Hz, 2H), 3.05 (sept, *J* = 6.5 Hz, 2H), 1.06 (s, 6H), 1.04 (s, 6H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 108.9, 102.0, 99.3, 49.0, 44.8, 20.8, 0.03; HRMS (ESI): Calc. for $C_{14}H_{27}NSi$ $[M+H]^+$: 238.1991; Found: 238.1990.

***(Z)*-4-(5-(trimethylsilyl)pent-2-en-4-yn-1-yl)morpholine E-3**



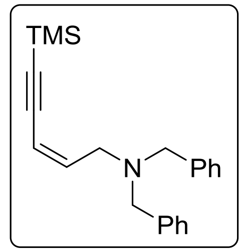
The compound **E-3** was prepared by using the above procedure **(e).** (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane (200 mg, 0.92 mmol) in acetonitrile was cooled to 0 ^{o}C and morpholine (160 µL, 1.84 mmol) was added followed by K_2CO_3 (255 mg, 1.84 mmol) to give **E-3** with 92% yield.

IR (neat): ν_{max}/cm^{-1} 2959, 2856, 2811, 2148, 1707, 1516, 1453, 1369, 1328, 1292, 1249, 1249, 1213, 1118, 1074, 1002; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (dt, *J* = 11.0 Hz, 7.0 Hz, 1H), 5.70 (dt, *J* = 11 Hz, 0.14 Hz, 1H), 3.74 (t, *J* = 4.6 Hz, 4H), 4.29 (dd, *J* = 7.0 Hz, 1.4 Hz, 2H), 2.51 (t, *J*

= 4.5 Hz, 4H), 0.21 (s, 9H) ; [13]C NMR (100 MHz, $CDCl_3$): δ 140.0, 112.6, 101.1, 100.4, 66.9, 57.7, 53.6, 0.1; HRMS (ESI): Calc. for $C_{12}H_{21}NOSi$ $[M+H]^+$: 224.1471; Found: 224.1474.

***(Z)-N,N*-dibenzyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine E-4**

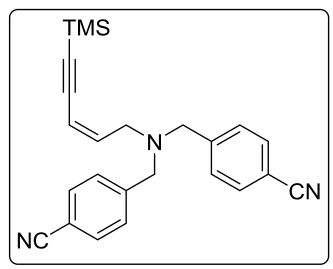
The compound **E-4** was prepared by using the above procedure **(e).** (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane (200 mg, 0.92 mmol) in acetonitrile was cooled to 0 °C and dibenzyl amine (355 µL, 1.84 mmol) was added followed by K_2CO_3 (255 mg, 1.84 mmol) to give **E-4** with 82% yield.



IR (neat): ν_{max}/cm^{-1} 3028, 2958, 2798, 2147, 1742, 1599, 1493, 1448, 1363, 1326, 1248, 1119, 1071, 992; [1]H NMR (400 MHz, $CDCl_3$): δ 7.37-7.21 (m, 10H), 6.1 (dt, *J* = 11 Hz, 6.7 Hz, 1H), 5.64 (d, *J* = 11 Hz, 1H), 3.61 (s, 4H), 3.36 (d, *J* = 6.8 Hz, 2H), 0.17 (s, 9H); [13]C NMR (100 MHz, $CDCl_3$):δ 142.0, 138.9, 128.9, 128.2, 126.9, 111.6, 101.4, 100.1, 58.0, 52.6, 0.03; HRMS (ESI): Calc. for $C_{22}H_{27}NSi$ $[M+H]^+$: 334.1991; Found: 334.1993.

***(Z)*-4,4'-(((5-(trimethylsilyl)pent-2-en-4-yn-1-yl)azanediyl)bismethylene)) dibenzonitrile E-5**

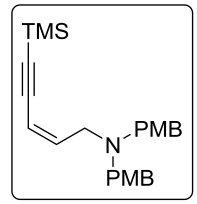
The compound **E-5** was prepared by using the above procedure **(e).** (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane (200 mg, 0.92 mmol) in acetonitrile was cooled to 0 °C and 4,4'-(azanediylbis(methylene))dibenzonitrile (455 mg, 1.84 mmol) was added followed by K_2CO_3 (255 mg, 1.84 mmol) to give **E-5** with 83% yield.



IR (neat): ν_{max}/cm^{-1} 3029, 2958, 2817, 2228, 2147, 1740, 1693, 1647, 1608, 1499, 1450, 1406, 1367, 1249, 1123, 1076, 1023; [1]H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 4H), 7.45 (d, *J* = 8.2 Hz, 4H), 6.01 (dt, *J* = 11.0, 6.9 Hz, 1H), 5.65 (d, *J* = 11.0 Hz, 1H), 3.63 (s, 4H), 3.30 (dd, *J* = 6.9, 1.1 Hz, 2H), 0.15 (s, 9H); [13]C NMR (100 MHz, $CDCl_3$): δ 144.66, 140.11, 132.21, 129.23, 118.79, 112.88, 111.10, 100.91, 100.83, 57.94, 52.81, -0.11; HRMS (ESI): Calc. for $C_{23}H_{26}N_2Si$ $[M+H]^+$: 359.1944; Found: 359.1945.

***(Z)*-*N,N*-bis(4-methoxybenzyl)-5-(trimethylsilyl)pent-2-en-4-yn-1-amine E-6**

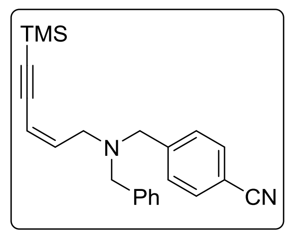
The compound **E-6** was prepared by using the above procedure **(e).** (*Z*)-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane (200 mg, 0.92 mmol) in acetonitrile was cooled to 0 °C and bis(4-methoxybenzyl)amine (475 mg, 1.84 mmol) was added followed by K_2CO_3 (255 mg, 1.84 mmol) to give **E-6** with 95% yield.



IR (neat): ν_{max}/cm^{-1} 3000, 2955, 2830, 2146, 1611, 1583, 1509, 1459, 1366, 1297, 1242, 1173, 1105, 1036; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.3 Hz, 4H), 6.88 (d, *J* = 8.3 Hz, 4H) 6.11 (dt, *J* = 11 Hz, 6.6 Hz, 1H), 5.64 (d, *J* = 11 Hz, 1H), 3.8 (s, 6H), 3.5 (s, 4H), 3.34 (d, *J* = 6.7 Hz, 2H), 0.2 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 158.6, 142.7, 131.4, 130.0, 113.6, 111.2, 101.5, 57.3, 55.2, 52.4, 0.05; HRMS (ESI): Calc. for $C_{24}H_{31}NO_2Si$ $[M+H]^+$: 394.2202; Found: 394.2202.

***(Z)*-4-((benzyl(5-(trimethylsilyl)pent-2-en-4-yn-1-yl)amino)methyl)benzonitrile E-7**

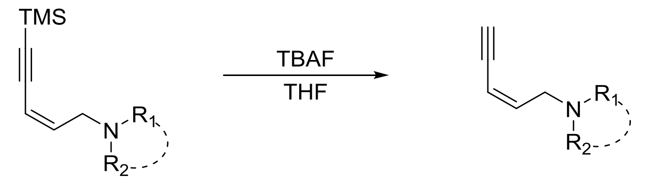
The compound **E-7** was prepared by using the above procedure **(e).** *(Z)*-(5-bromopent-3-en-1-yn-1-yl)trimethylsilane (200 mg, 0.92 mmol) in acetonitrile was cooled to 0 °C and 4-((benzylamino)methyl)benzonitrile (410 mg, 1.84 mmol) was added followed by K_2CO_3 (255 mg, 1.84 mmol) to give **E-7** with 91% yield.



IR (neat): ν_{max}/cm^{-1} 3029, 2958, 2817, 2228, 2147, 1740, 1693, 1647, 1608, 1499, 1450, 1406, 1367, 1249, 1123, 1076, 1023; ^{1}H NMR (400 MHz, $CDCl_3$^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.34 (q, *J* = 7.6 Hz, 4H), 7.28 – 7.24 (m, 1H), 6.09 (dt, *J* = 11.1, 6.8 Hz, 1H), 5.66 (d, *J* = 11.0 Hz, 1H), 3.63 (d, *J* = 8.6 Hz, 4H), 3.35 (d, *J* = 6.8 Hz, 2H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 141.4, 138.8, 132.2, 129.4, 128.9, 128.4, 127.3, 119.1, 112.2, 110.7, 101.2, 100.5, 58.5, 57.7, 52.9, 0.01; HRMS (ESI): Calc. for $C_{23}H_{26}N_2Si$ $[M+H]^+$: 359.1944; Found: 359.1943.

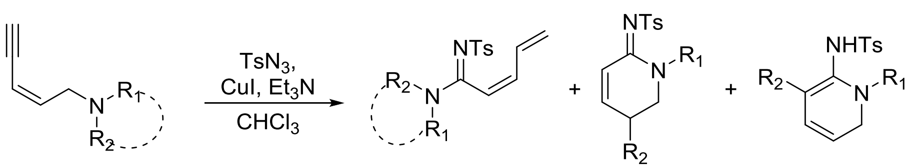
(f) Desilylation

To the ice cooled solution of (*Z*)-*N,N*-disubstituted-5-(trimethylsilyl)pent-2-en-4-yn-1-amine (1 equivalent) was added TBAF (0.5 equivalent) and allowed to stir for two hours. The reaction was quenched by sat.NH_4Cl and extracted by ethyl acetate. The solvent was evaporated and obtained product was used further without any purification.

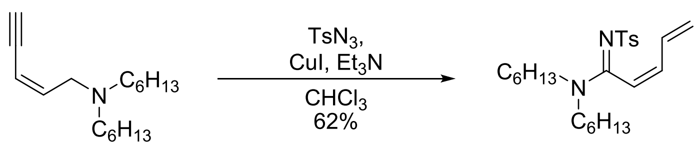


Scheme 4.11: Silyl deprotection of enyne-amines **E-1-7**.

General procedure A: Cu(I)-catalyzed formation of conjugated amidines and cyclic amidines.

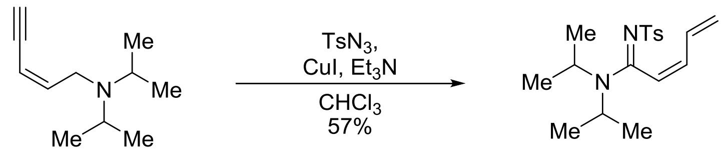


To the solution of amino eneyn (1 equiv) in chloroform was added tosyl azide (1.2 equiv), Et_3N (1.5 equiv) followed by CuI (10 mol%) and stirred for 30 – 60 minutes at room temperature. The reaction was quenched by sat. NH_4Cl and compound was extracted in chloroform. Solvent was evaporated and obtained crude product was purified by column chromatography (Hexane : EtOAc) to afford desired compound and yields were calculated over two steps.



Compound **1a** (62%) was formed by following the general procedure **A.**

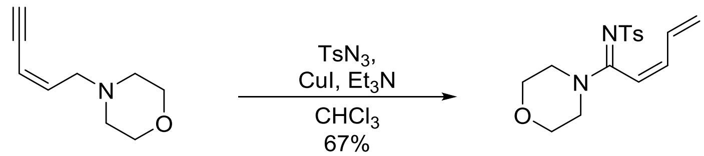
1a: colorless semi-solid, : IR (neat): ν_{max}/cm^{-1} 3744, 3678, 3648, 3619, 2954, 2927, 2861, 2318, 1739, 1707, 1693, 1645, 1606, 1529, 1463, 1372, 1282, 1145, 1088; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 6.28 (t, J = 11.2 Hz, 1H), 6.17 (d, J = 11.5 Hz, 1H), 6.0 (dt, J = 16.8 Hz, 10.2 Hz, 1H), 5.32 (d, J = 16.7 Hz, 1H), 5.18 (d, J = 10.0 Hz, 1H), 3.49 (br.s, 2H), 3.26 (t, J = 7.6 Hz, 2H), 2.38 (s, 3H), 1.46 (m, 2H), 1.25 (m, 14H), 0.88 (td, J = 7.12 Hz, 2.45 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 142.5, 141.0, 134.0, 131.7, 128.8, 126.6, 122.2, 121.6, 50.0, 48.1, 31.4, 31.3, 28.4, 26.9, 26.7, 26.3, 22.5, 22.4, 21.4, 13.9, 13.8; HRMS (ESI): Calc. for $C_{24}H_{38}N_2O_2S$ $[M+H]^+$: 419.2732; Found: 419.2732.



2 **2a**

Compound **2a** (57%) was formed by following the general procedure **A.**

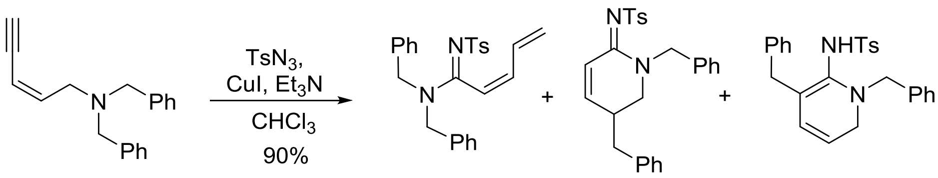
2a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3740, 3672, 3642, 3615, 2950, 2922, 2860, 2314, 1733, 1705, 1691, 1641, 1602, 1524, 1461, 1370, 1280, 1141, 1082; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.26 – 6.01 (m, 3H), 5.25 (d, *J* = 16.4 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 4.23 (sept, *J* = 6.7 Hz, 1H), 3.64 (sept, *J* = 6.7 Hz, 1H), 2.34 (s, 3H), 1.46 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 162.1, 141.4, 141.1, 133.4, 131.8, 128.8, 126.5, 122.8, 121.6, 52.0, 47.9, 21.4, 20.4, 19.9; HRMS (ESI): Calc. for $C_{18}H_{26}N_2O_2S$ $[M+H]^+$: 335.1793; Found: 335.1793.



5 **5a**

Compound **5a** (67%) was formed by following the general procedure **A.**

5a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3743, 3678, 3648, 3619, 2967, 2921, 2861, 2319, 1740, 1693, 1643, 1595, 1519, 1476, 1444, 1346, 1273, 1190, 1141, 1114, 1087; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.30 (t, *J* = 11.4 Hz, 1H), 6.16 (d, *J* = 11.5 Hz, 1H), 5.96 (dt, *J* = 16.7 Hz, 10.7 Hz, 1H), 5.32 (d, *J* = 16.9 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 3.81 (t, *J* = 4.5 Hz, 2H), 3.68 (t, *J* = 5.0 Hz, 2H), 3.59 (t, *J* = 5.0 Hz, 2H), 3.46 (t, *J* = 5.0 Hz, 2H), 2.33(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 142.1, 140.2, 135.4, 131.3, 129.1, 126.9, 123.6, 120.3, 66.7, 66.3, 47.9, 44.7, 21.5; HRMS (ESI): Calc. for $C_{16}H_{20}N_2O_3S$ $[M+H]^+$: 321.1273; Found: 321.1281.



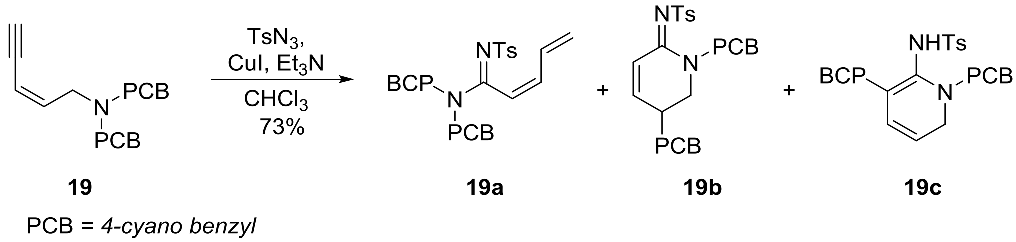
12 **12a** **12b** **12c**

Compounds **12a** (23%), **12b** (51%) and **12c** (16%) were formed by following the general procedure **A.**

12a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3744, 3027, 2925, 2864, 1739, 1692, 1639, 1533, 1484, 1383, 1342, 1273, 1139, 1083, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.40-7.31 (m, 6H), 7.24 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 6.5 Hz, 2H), 6.33 (m, 2H), 6.08 (m, 1H), 5.35 (dt, *J* = 16.7 Hz, 0.7 Hz, 1H), 5.22 (d, *J* = 10 Hz, 1H), 4.72 (br.s, 2H), 4.5 (s, 2H), 2.4 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 141.8, 137.1, 135.2, 130.2, 129.1, 128.7, 128.1, 128.1, 126.5, 126.2, 121.9, 53.2, 48.2, 21.5; HRMS (ESI): Calc. for $C_{26}H_{26}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1785.

12b: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) : IR (neat): ν_{max}/cm^{-1} 3742, 3029, 2924, 2863, 1740, 1691, 1638, 1531, 1481, 1382, 1340, 1270, 1137, 1081, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.33 (m, 3H), 7.24 – 7.20 (m, 9H), 6.84 (dd, *J* = 7.7 Hz, 2.3 Hz, 2H), 6.58 (dd, *J* = 9.8 Hz, 4.16 Hz, 1H), 4.92 (d, *J* = 14.4 Hz, 1H), 4.51 (d, *J* = 14.4 Hz, 1H), 4.92 (d, *J* = 14.4 Hz, 1H), 4.51 (d, *J* = 14.4 Hz, 1H), 3.37 (dd, *J* = 12.8 Hz, 5.6 Hz, 1H), 3.17 (dd, *J* = 12.7 Hz, 5.8 Hz, 1H), 2.67 (m, 2H), 2.41 (m, 1H), 2.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 157.9, 144.0, 142.1, 141.2, 137.7, 135.9, 129.2, 128.9, 128.9, 128.7, 128.6, 128.1, 126.8, 126.4, 119.9, 52.8, 48.9, 37.3, 35.7, 21.6; HRMS (ESI): Calc. for $C_{26}H_{26}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1790.

12c: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) : IR (neat): ν_{max}/cm^{-1} 3743, 3030, 2925, 2859, 1708, 1647, 1597, 1552, 1516, 1495, 1450, 1341, 1270, 1141, 1084, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.80 (d, *J* = 8.24 Hz, 2H), 7.28 – 7.21 (m, 10H), 7.09 (dd, *J* = 7.16 Hz, 1.6 Hz, 2H), 5.74 (m, 2H), 4.91 (d, *J* = 14.54 Hz, 1H), 4.74 (m, 1H), 4.26 (d, *J* = 14.6 Hz, 1H), 3.50 (m, 1H), 3.35 (dd, *J* = 13 Hz, 7.7 Hz, 1H), 3.06 (d, *J* = 17.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.3, 141.7, 141.6, 137.0, 135.2, 130.1, 129.1, 128.7, 128.0, 128.0, 127.8, 126.6, 126.4, 126.1, 121.7, 53.1, 48.1, 40.4, 40.2, 21.4; HRMS (ESI): Calc. for $C_{26}H_{26}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1792.

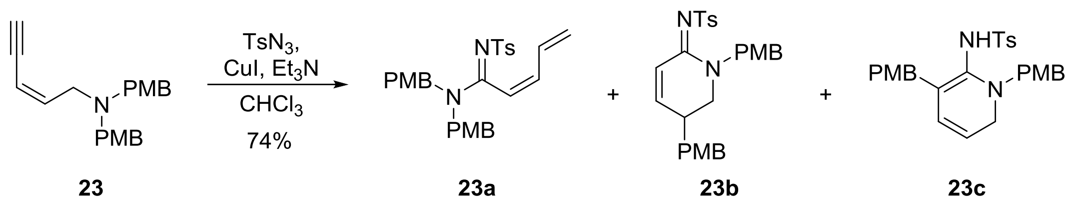


Compounds **19a** (13%), **19b** (37%) and **19c** (23%) were formed by following the general procedure **A.**

19a: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 4H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 4H), 6.43 (t, *J* = 11.4 Hz, 1H), 6.24 (d, *J* = 11.6 Hz, 1H), 6.05 (dt, *J* = 16.8, 10.6 Hz, 1H), 5.42 (d, *J* = 16.7 Hz, 1H), 5.31 (d, *J* = 10.1 Hz, 1H), 4.77 – 4.66 (m, 2H), 4.61 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 142.6, 140.8, 140.1, 139.7, 136.1, 133.0, 132.6, 130.9, 129.1, 129.0, 127.8, 126.7, 124.4, 119.9, 52.2, 50.3, 29.7, 21.5; HRMS (ESI): Calc. for $C_{28}H_{25}N_4O_2S$ $[M+H]^+$: 481.1698; Found: 481.1702.

19b: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.59 (dd, *J* = 8.4, 3.4 Hz, 4H), 7.29 (dd, *J* = 13.3, 8.4 Hz, 6H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.56 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.77 (d, *J* = 15.0 Hz, 1H), 4.64 (d, *J* = 15.0 Hz, 1H), 3.44 (dd, *J* = 12.9, 5.5 Hz, 1H), 3.18 (dd, *J* = 12.8, 6.6 Hz, 1H), 2.86 – 2.75 (m, 2H), 2.63 (td, *J* = 10.6, 3.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.70, 143.30, 142.87, 141.22, 140.65, 138.71, 132.67, 132.63, 129.67, 129.34, 128.90, 128.67, 126.34, 120.38, 118.74, 111.20, 55.88, 52.91, 50.07, 37.67, 35.18, 21.59; HRMS (ESI): Calc. for $C_{28}H_{25}N_4O_2S$ $[M+H]^+$: 481.1698; Found: 481.1699.

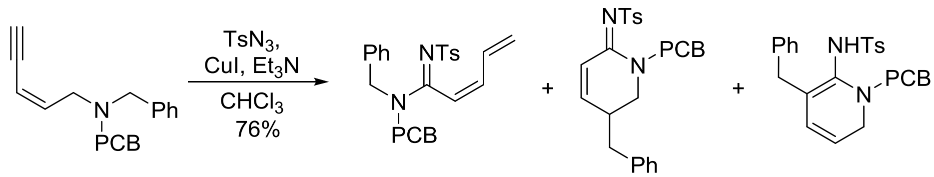
19c: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.83 (dd, *J* = 10.0, 4.1 Hz, 1H), 5.77 (dd, *J* = 8.6, 4.0 Hz, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 4.77 (s, 1H), 4.18 (d, *J* = 15.1 Hz, 1H), 3.64 (d, *J* = 15.7 Hz, 1H), 3.38 (m, 3H), 2.98 (s, 3H), 2.90 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 142.7, 142.4, 140.8, 140.5, 132.5, 131.9, 130.7, 129.2, 128.2, 126.1, 126.0, 121.9, 118.8, 118.3, 111.7, 110.8, 53.1, 49.0, 40.5, 39.9, 21.5; HRMS (ESI): Calc. for $C_{28}H_{24}N_4O_2S$ $[M+H]^+$: 481.1698; Found: 481.1697.



Compounds **23a** (0%), **23b** (62%) and **23c** (12%) were formed by following the general procedure **A.**

23b: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3743, 3007, 2927, 2839, 1638, 1610, 1533, 1510, 1479, 1382, 1350, 1274, 1244, 1173, 1139, 1083, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.20 (dd, *J* = 10.0 Hz, 4.2 Hz, 1H), 7.1 (d, *J* = 8.7 Hz, 2H), 6.8 (d, *J* = 8.6 Hz, 2H), 6.75 (s, 4H), 6.51 (dd, *J* = 10.0 Hz, 4.2 Hz, 1H), 4.83 (d, *J* = 14.2 Hz, 1H), 4.41 (d, *J* = 14.3 Hz, 1H), 3.8 (s, 3H), 3.77 (s, 3H), 3.32 (dd, *J* = 13.0 Hz, 5.7 Hz, 1H), 3.12 (dd, *J* = 12.7 Hz, 5.84 Hz, 1H), 2.58 (m, 2H), 2.4 (s, 3H), 2.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 158.4, 157.8, 144.0, 142.0, 141.3, 130.0, 129.9, 129.6, 129.2, 128.0, 126.4, 119.9, 114.2, 114.1, 55.4, 55.3, 52.1, 48.7, 36.5, 35.8, 21.5; HRMS (ESI): Calc. for $C_{28}H_{30}N_2O_4S$ $[M+H]^+$: 491.2005; Found: 491.2006.

23c: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3011, 2928, 2838, 1673, 1607, 1551, 1509, 1338, 1243, 1173, 1138, 1243, 1173, 1138, 1082, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 5.78 – 5.67 (m, 2H), 4.76 (d, *J* = 14.3 Hz, 1H), 4.69 (s, 1H), 4.25 (d, *J* = 14.3 Hz, 1H), 3.86 – 3.81 (m, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.48 (m, 1H), 3.35 (dd, *J* = 13.3, 7.5 Hz, 1H), 3.15 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.00 (d, *J* = 17.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 159.2, 158.5, 141.8, 141.7, 131.1, 129.7, 129.1, 129.0, 127.2, 126.4, 126.1, 121.8, 114.0, 113.3, 55.2, 52.5, 47.9, 40.5, 39.3, 21.4; HRMS (ESI): Calc. for $C_{28}H_{30}N_2O_4S$ $[M+H]^+$: 491.2005; Found: 491.2004.



27 **27a** **27b** **27c**

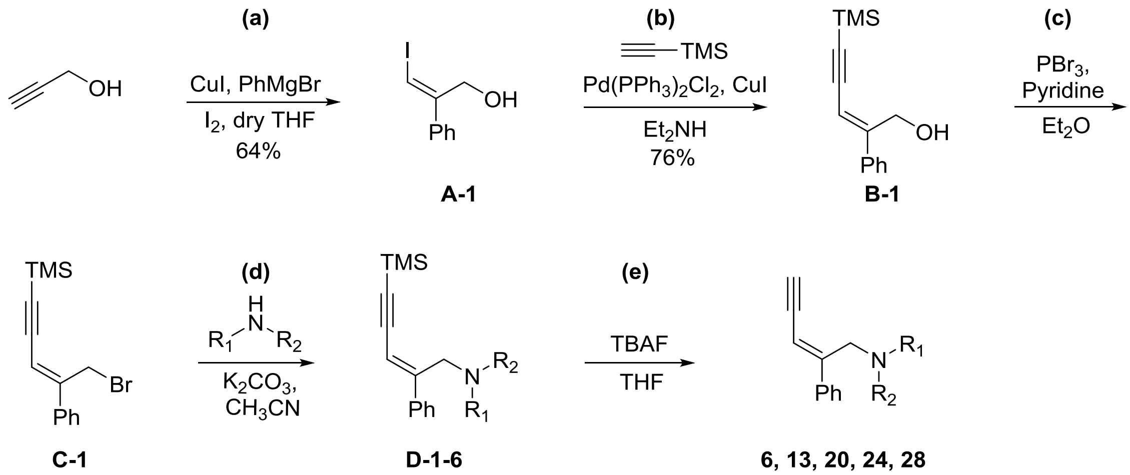
PCB = *4-cyano benzyl*

Compounds **27a** (14%), **27b** (39%) and **27c** (23%) were formed by following the general procedure **A.**

27a: colorless semi-solid, **27a** could not be isolated as pure compound therefore the ^{1}H NMR was recorded as a mixture with **27b.** ^{1}H NMR (400 MHz, $CDCl_3$) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.36 (ddd, *J* = 14.0, 7.8, 4.3 Hz, 4H), 7.27 – 7.18 (m, 9H), 7.11 (d, *J* = 8.4 Hz, 3H), 6.49 – 6.34 (m, 1H), 6.26 (dd, *J* = 23.8, 11.8 Hz, 1H), 6.07 (dq, *J* = 16.7, 10.6 Hz, 1H), 5.86 – 5.73 (m, 2H), 5.47 – 5.33 (m, 1H), 5.26 (t, *J* = 10.9 Hz, 1H), 4.90 (d, *J* = 15.2 Hz, 1H), 4.77 (dd, *J* = 6.1, 3.8 Hz, 2H), 4.56 (s, 1H), 4.18 (d, *J* = 15.2 Hz, 1H), 3.53 – 3.38 (m, 2H), 3.22 (dd, *J* = 13.1, 3.3 Hz, 1H), 3.08 (d, *J* = 17.4 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 2H); HRMS (ESI): Calc. for $C_{27}H_{25}N_3O_2S$ $[M+H]^+$: 456.1746; Found: 456.1753.

27b: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.21 (m, 9H), 6.95 (dd, *J* = 7.7, 1.6 Hz, 2H), 6.62 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.76 (d, *J* = 15.0 Hz, 1H), 4.64 (d, *J* = 15.0 Hz, 1H), 3.38 (dd, *J* = 12.8, 5.8 Hz, 1H), 3.19 (dd, *J* = 12.8, 7.1 Hz, 1H), 2.83 – 2.70 (m, 2H), 2.59 – 2.49 (m, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 157.94, 144.50, 142.29, 141.34, 140.74, 137.25, 132.49, 129.19, 128.83, 128.81, 128.73, 126.97, 126.27, 119.67, 118.46, 111.78, 52.84, 50.00, 37.44, 35.61, 21.49; HRMS (ESI): Calc. for $C_{27}H_{25}N_3O_2S$ $[M+H]^+$: 456.1746; Found: 456.1753.

27c: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.30 – 7.17 (m, 6H), 7.05 (d, *J* = 6.4 Hz, 2H), 5.79 – 5.73 (m, 1H), 5.73 – 5.65 (m, 1H), 4.72 (s, 1H), 4.63 (d, *J* = 14.4 Hz, 1H), 4.45 (d, *J* = 14.4 Hz, 1H), 3.63 – 3.51 (m, 1H), 3.39 (dd, *J* = 13.0, 8.0 Hz, 1H), 3.32 (dd, *J* = 12.9, 3.5 Hz, 1H), 3.19 (d, *J* = 19.6 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 142.8, 142.0, 141.3, 134.8, 131.8, 130.7, 129.2, 128.8, 128.3, 128.1, 126.1, 125.8, 122.2, 118.9, 110.6, 53.3, 48.3, 40.3, 40.1, 21.3; HRMS (ESI): Calc. for $C_{27}H_{25}N_3O_2S$ $[M+H]^+$: 456.1746; Found: 456.1753.



Scheme 4.12: Synthesis of *(Z)-N,N*-disubstituted-2-phenylpent-2-en-4-yn-1-amine.

(a) Synthesis of *(Z)*-3-iodo-2-phenylprop-2-en-1-ol A-1[13]

To a solution of propargyl alcohol (1.0 g, 17.8 mmol) and CuI (338 mg, 1.7 mmol) in dry THF (20 mL) was added 3.0 M PhMgBr (15 mL, 44.5 mmol) at -10 ^{0}C. Upon complete addition of Grignard reagent, the reaction mixture was allowed to come at room temperature and stirred for overnight. The resultant mixture was then cooled to -78 ^{o}C and then added a solution of I_2 (9.0 g, 35.6 mmol) in THF (20 mL), the reaction mixture was allowed to cool at room temperature and stirred for 1 hour then cooling at 0 ^{o}C, the reaction mixture was quenched by saturated NH_4Cl. The reaction mixture was brought to room temperature and extracted with EtOAc, washed with brine dried over Na_2SO_4 and concentrated under reduced pressure. The obtained compound was purified by column chromatography to give **A-1** with 64% of yield.

(b) Synthesis of *(Z)*-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol B-1

To a solution of *(Z)*-3-iodo-2-phenylprop-2-en-1-ol **A-1** in Et_2NH (0.5 M) was added $(Ph_3P)_2PdCl_2$ (2 mol %)and CuI (4 mol %) at 0 ºC. The system was degassed by N_2 and the resulting was added trimethyl silyl acetylene (1.3 equiv). Then it was warmed up to room temperature. The reaction was monitored by TLC. When the reaction completed, the reaction mixture was concentrated, and the residue was purified through silica gel flash column.

(c) Synthesis of *(Z)*-(5-bromo-4-phenylpent-3-en-1-yn-1-yl)trimethylsilane C-1

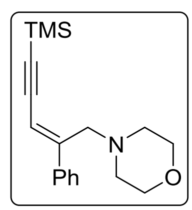
To a solution of *(Z)*-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol **B-1** (1 equiv.) in Et_2O was added pyridine (0.06 equiv.) and PBr_3 (0.45 equiv.) at 0°C. The reaction was warmed to room temperature with additional stirring for 1 h. After completion of reaction, the mixture was quenched by ice cubes and extracted in EtOAc. Solvent was removed and obtained product was used for next reaction without purification.

IR (neat): ν/cm^{-1} 3060, 2959, 2852, 2148, 1644, 1597, 1492, 1447, 1339, 1250, 1197, 1077, 990; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.44 – 7.37 (m, 3H), 6.07 (s, 1H), 4.65 (s, 2H), 0.30 (s, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 137.3, 128.9, 128.7, 125.8, 110.8, 104.9, 101.6, 29.7, -0.13; HRMS (ESI): Calc. for $C_8H_{14}BrSi$ $[M+H]^+$: 217.0048, Found: 217.0048.

Synthesis of *(Z)-N,N*-disubstituted-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine

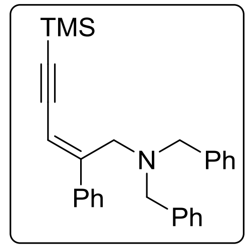
To the solution of substituted *(Z)*-(5-bromo-4-phenylpent-3-en-1-yn-1-yl)trimethylsilane **C-1** in acetonitrile was added the amine (1.2 equiv) at 0 ^{o}C drop wisely followed by the addition of K_2CO_3 (1.5 equiv) and allowed to warm at room temperature and stirred for 4 h. The reaction mixture was washed with water and extracted with EtOAc and purified by column chromatography.

***(Z)*-4-(2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)morpholine D-1**



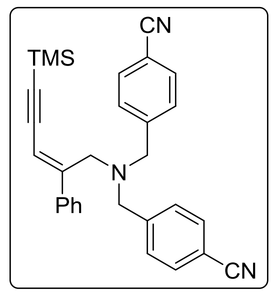
The compound **D-1** was prepared by following the above procedure (d). *(Z)*-(5-bromo-4-phenylpent-3-en-1-yn-1-yl)trimethylsilane **C-1** (200 mg, 0.68 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added morpholine (115 μL, 1.36 mmol) followed by the addition of K_2CO_3 (190 mg, 1.36 mmol) to give **D-1** as a yellow liquid with 90% of yield. IR (neat): ν/cm^{-1} 2955, 2853, 2809, 2144, 1705, 1512, 1450, 1364, 1325, 1290, 1245, 1242, 1211, 1115, 1071, 1000; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (m, 2H), 7.34 – 7.28 (m, 3H), 6.03 (s, 1H), 3.63 (t, *J* = 5.6 Hz, 6H), 2.5 (t, *J* = 4.5 Hz, 4H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.0, 139.8, 128.4, 126.3, 110.7, 103.1, 101.6, 67.1, 59.0, 53.5, 0.05; HRMS (ESI): Calc. for $C_{18}H_{25}NOSi$ $[M+H]^+$: 300.1784, Found: 300.1777.

(Z)-N,N-dibenzyl-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine D-2



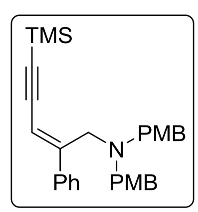
The compound **D-2** was prepared by following the above procedure (d). *(Z)*-(5-bromo-4-phenylpent-3-en-1-yn-1-yl)trimethylsilane **C-1** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added dibenzylamine (260 µL, 1.36 mmol) followed by the addition of K_2CO_3 (190 mg, 1.36 mmol) to give **D-2** as a yellow liquid with 92% of yield. IR (neat): ν/cm^{-1} 3028, 2958, 2798, 2147, 1742, 1599, 1493, 1448, 1363, 1326, 1248, 1119, 1071, 992; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.18 (m, 11H), 7.11 (d, *J* = 7.2 Hz, 4H), 5.92 (s, 1H), 3.71 (s, 2H), 3.48 (s, 4H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 139.5, 139.4, 129.3, 128.1, 128.0, 126.9, 110.1, 103.1, 101.2, 58.2, 54.4, 0.14; HRMS (ESI): Calc. for $C_{28}H_{31}NSi$ $[M+H]^+$: 410.2304, Found: 410.2305.

(Z)-4,4'-(((2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)azanediyl)bis (methylene))dibenzonitrile D-3



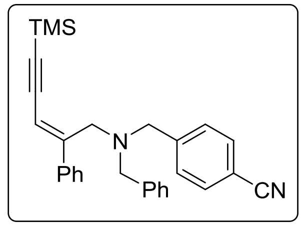
The compound **D-3** was prepared by following the above procedure (d). *(Z)*-(5-bromo-4-phenylpent-3-en-1-yn-1-yl)trimethylsilane **C-1** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added dibenzylamine (338 mg, 1.36 mmol) followed by the addition of K_2CO_3 (190 mg, 1.36 mmol) to give **D-3** as a yellow liquid with 93% of yield. IR (neat): ν/cm^{-1} 3021, 2959, 2826, 2228, 2137, 1706, 1500, 1448, 1411, 1367, 1248, 1099, 1017; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.3 Hz, 4H), 7.37 (t, *J* = 7.1 Hz,1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 4H), 7.14 (d, *J* = 7.0 Hz, 2H), 5.94 (s, 1H), 3.75 (s, 2H), 3.58 (s, 4H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 144.6, 139.1, 132.0, 129.6, 128.5, 128.2, 126.6, 118.8, 111.2, 111.1, 102.5, 101.9, 58.0, 54.7, 0.0; HRMS (ESI): Calc. for $C_{30}H_{29}N_3Si$ $[M+H]^+$: 460.2209, Found: 460.2204.

(Z)-N,N-bis(4-methoxybenzyl)-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine D-4



The compound **D-4** was prepared by following the above procedure (d). *(Z)*-(5-bromo-4-phenylpent-3-en-1-yn-1-yl)trimethylsilane **C-1** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added dibenzylamine (350 mg, 1.36 mmol) followed by the addition of K_2CO_3 (190 mg, 1.36 mmol) to give **D-4** as a yellow liquid with 90% of yield. IR (neat): ν/cm^{-1} 3001, 2955, 2831, 2135, 1694, 1609, 1509, 1451, 1365, 1299, 1242, 1174, 1099, 1034; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.23 (m, 6H), 7.06 (d, *J* = 8.6 Hz, 4H), 6.82 (d, *J* = 8.6 Hz, 4H), 5.96 (s, 1H), 3.81 (s, 6H), 3.72 (s, 2H), 3.44 (s, 4H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 148.0, 135.0, 127.2, 126.0, 123.7, 123.6, 122.6, 109.0, 105.5, 100.0, 98.8, 96.7, 52.9, 50.9, 49.7, - 4.2, - 4.3; HRMS (ESI): Calc. for $C_{30}H_{35}NO_2Si$ $[M+H]^+$: 470.2515, Found: 470.2514.

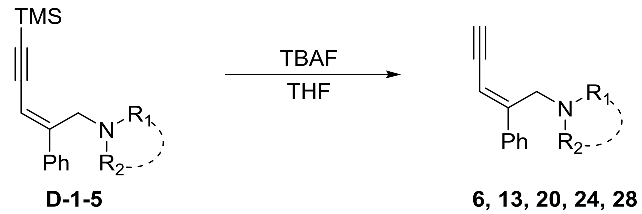
***(Z)*-4-((benzyl(2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)amino)methyl) benzonitrile D-5**



The compound **D-5** was prepared by following the above procedure (d). *(Z)*-(5-bromo-4-phenylpent-3-en-1-yn-1-yl)trimethylsilane **C-1** (200 mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added 4-((benzylamino)methyl)benzonitrile (302 mg, 1.36 mmol) followed by the addition of K_2CO_3 (190 mg, 1.36 mmol) to give **D-5** as a yellow liquid with 84% of yield. IR (neat): ν/cm^{-1} 3021, 2959, 2826, 2228, 2137, 1706, 1500, 1448, 1411, 1367, 1248, 1099, 1017; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.26 (m, 7H), 7.19 (m, 3H), 7.16 (d, *J* = 6.3 Hz, 2H), 5.95 (s, 1H), 3.76 (s, 2H), 3.57 (s, 2H), 3.53 (s, 2H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 141.2, 134.8, 134.3, 127.5, 125.2, 124.9, 124.0, 123.9, 123.8, 122.9, 122.4, 114.8, 106.2, 98.5, 97.2, 54.3, 53.3, 50.2, -4.3, -4.2.; HRMS (ESI): Calc. for $C_{29}H_{30}N_2Si$ $[M+H]^+$: 435.2257, Found: 435.2259.

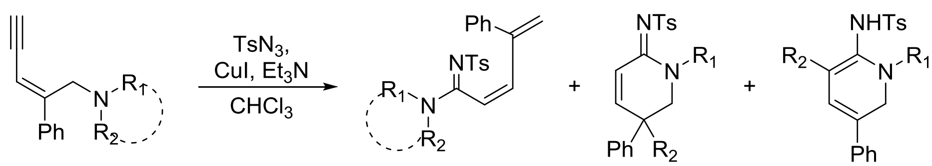
(d) Desilylation

To the solution of (*Z*)-*N,N*-disubstituted-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine in THF was added TBAF (0.5 equiv) at 0 °C. Then reaction mixture allowed to warm at room temperature and reaction was monitored by TLC. When reaction was completed, the reaction mixture was quenched by sat. NH_4Cl. The compound was extracted with ethyl acetate and used further for next reaction without any purification.

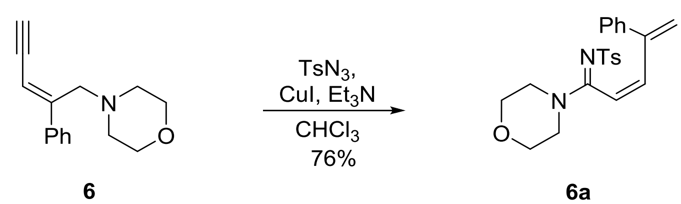


Scheme 4.13: Silyl deprotection enyne-amines **D-1-5**.

General procedure A: Cu(I)-catalyzed formation of conjugated amidines and cyclic amidines.

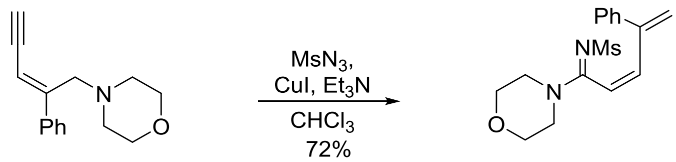


To the solution of amino enyne (1 equiv) in chloroform was added tosyl azide (1.2 equiv), Et_3N (1.5 equiv) followed by CuI (10 mol%) and stirred for one hour at room temperature. The reaction was quenched by sat. NH_4Cl and compound was extracted in chloroform. Solvent was evaporated and obtained crude product was purified by column chromatography (Hexane : EtOAc) to afford desired compound.



Compound **6a** (76%) was formed on by following the general procedure **A.**

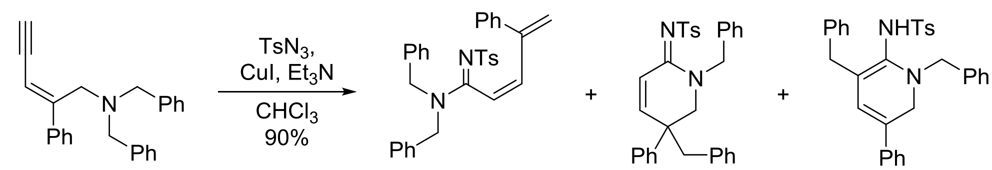
6a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2967, 2920, 2860, 1721, 1597, 1521, 1443, 1344, 1344, 1275, 1225, 1150, 1113, 1088, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.34 (dd, *J* = 6.6, 3.3 Hz, 3H), 7.32 – 7.22 (m, 7H), 6.71 (dd, *J* = 12.4, 0.8 Hz, 1H), 6.48 (d, *J* = 12.5 Hz, 1H), 5.52 (s, 1H), 5.44 (s, 1H), 3.46 (dd, *J* = 11.3, 6.4 Hz, 4H), 3.34 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 143.8, 142.2, 140.6, 138.2, 136.4, 129.2, 128.5, 128.4, 126.7, 126.7, 120.7, 120.4, 66.3, 65.7, 47.6, 44.1, 29.8, 21.6; HRMS (ESI): Calc. for $C_{22}H_{24}N_2O_3S$ $[M+H]^+$: 397.1586; Found: 397.1584.



6 9a

Compound **6a** (76%) was formed on by following the general procedure **A.**

9a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2970, 2925, 2864, 1724, 1593, 1522, 1443, 1345, 1342, 1272, 1224, 1153, 1115, 1092, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.75 (dd, *J* = 12.4, 0.8 Hz, 1H), 6.45 (d, *J* = 12.5 Hz, 1H), 5.54 (s, 1H), 5.46 (s, 1H), 3.48 (dd, *J* = 11.3, 6.4 Hz, 4H), 3.35 (s, 2H), 2.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 148.8, 140.6, 136.4, 129.2, 128.5, 128.4, 126.7, 120.7, 66.3, 65.7, 47.6, 44.1; HRMS (ESI): Calc. for $C_{16}H_{21}N_2O_3S$ $[M+H]^+$: 321.1273; Found: 321.1275.



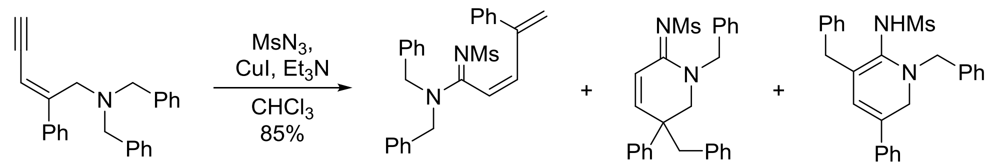
13 13a 13b 13c

Compounds **13a** (0%), **13b** (50%), and **13c** (40%) were formed by following the general procedure **A.**

13b: colorless semi-solid, IR (neat): ν/cm^{-1} 3008, 2931, 2838, 1621, 1577, 1534, 1514, 1467, 1441, 1381, 1275, 1246, 1174, 1140, 1113, 1084, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 10.2 Hz, 1H), 7.28 – 7.08 (m, 11H), 7.04 (d, *J* = 6.9 Hz, 2H), 6.98 (dd, *J* = 8.1, 1.5 Hz, 2H), 6.79 (d, *J* = 10.2 Hz, 1H), 6.65 (d, *J* = 6.8 Hz, 2H), 4.81 (d, *J* = 14.6 Hz, 1H), 4.54 (d, *J* = 14.6 Hz, 1H), 3.58 (s, 2H), 3.04 (d, *J* = 13.5 Hz, 1H), 2.92 (d, *J* = 13.5 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 146.6, 142.0, 141.2, 140.8, 135.3, 135.2, 130.4, 129.2, 128.7, 128.4, 128.1, 127.8, 127.4, 127.0, 126.5, 126.4, 120.1, 56.2, 52.9, 44.7, 44.0, 21.6; HRMS (ESI): Calc. for $C_{32}H_{30}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2115.

13c: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 3H), 7.29 – 7.17 (m, 11H), 7.13 (m, 4H), 6.05 (dd, *J* = 5.6, 2.7 Hz, 1H), 4.94 (d, *J* = 14.5 Hz, 2H), 4.33 (d, *J* = 14.6 Hz, 1H), 3.77 (dd, *J* = 17.1, 1.7 Hz, 1H), 3.56 (dd, *J* = 13.1, 7.2 Hz, 1H), 3.29 (dd, *J* = 13.1, 3.5 Hz, 1H), 3.20 (dt, *J* = 17.1, 2.9 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$): δ 165.0, 141.8, 141.6, 136.9, 135.0, 133.4, 130.2, 129.1, 128.7, 128.7, 128.2, 128.1, 128.0, 127.8, 126.7, 126.2, 124.9, 122.3, 53.3, 49.9, 40.8, 40.4, 21.4; HRMS (ESI): Calc. for $C_{32}H_{30}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2115.

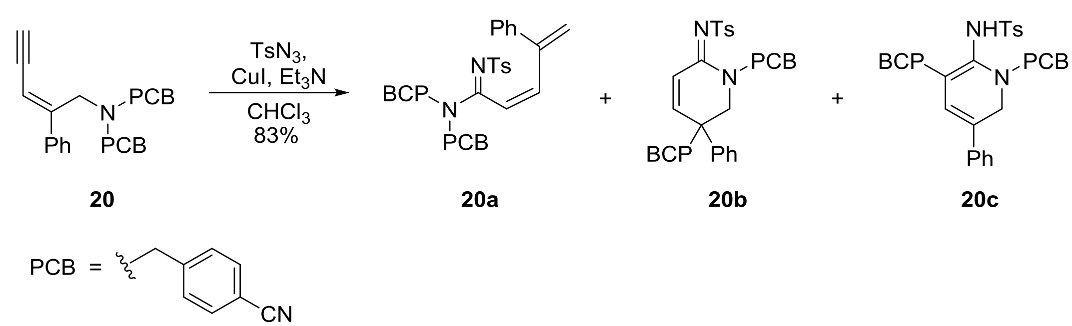


13 **16a** **16b** **16c**

Compounds **16a** (0%), **16b** (52%), and **16c** (34%) were formed by following the general procedure **A.**

16b: colorless semi-solid, IR (neat): ν/cm^{-1} 3031, 2930, 2833, 1628, 1571, 1536, 1515, 1462, 1444, 1378, 1277, 1242, 1171, 1141, 1115, 1094, 1031; ^1H NMR (400 MHz, CHLOROFORM-D) δ 7.26 (d, J = 10.3 Hz, 1H), 7.24 – 7.19 (m, 5H), 7.15 – 7.06 (m, 5H), 7.06 – 7.00 (m, 2H), 6.81 (d, J = 10.1 Hz, 1H), 6.67 (dd, J = 7.9, 1.4 Hz, 2H), 4.76 (d, J = 14.7 Hz, 1H), 4.49 (d, J = 14.7 Hz, 1H), 3.55 (s, 2H), 3.03 (d, J = 13.5 Hz, 1H), 3.00 (s, 3H), 2.95 (d, J = 13.5 Hz, 1H); ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 164.51, 145.22, 137.99, 135.84, 135.20, 132.81, 129.20, 128.97, 128.77, 128.47, 128.43, 128.33, 128.17, 127.51, 123.10, 120.31, 51.69, 49.62, 43.07; HRMS (ESI): Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1798.

16c: colorless semi-solid, ^1H NMR (400 MHz, CHLOROFORM-D) δ 7.29 (m, 8H), 7.22 – 7.13 (m, 7H), 7.09 (dd, J = 7.6, 1.7 Hz, 2H), 6.00 (dd, J = 5.6, 2.7 Hz, 1H), 4.92 (d, J = 14.7 Hz, 1H), 4.86 – 4.71 (m, 1H), 4.32 (d, J = 14.7 Hz, 1H), 3.72 (d, J = 17.0 Hz, 1H), 3.50 (dd, J = 13.1, 7.2 Hz, 1H), 3.19 (tt, J = 14.3, 8.5 Hz, 2H), 3.07 (s, 3H); 163.51, 143.22, 138.99, 134.84, 132.20, 132.81, 129.20, 128.37, 128.77, 128.47, 128.43, 128.33, 128.17, 127.51, 122.10, 120.31, 51.69, 49.62, 43.07; HRMS (ESI): Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1798.

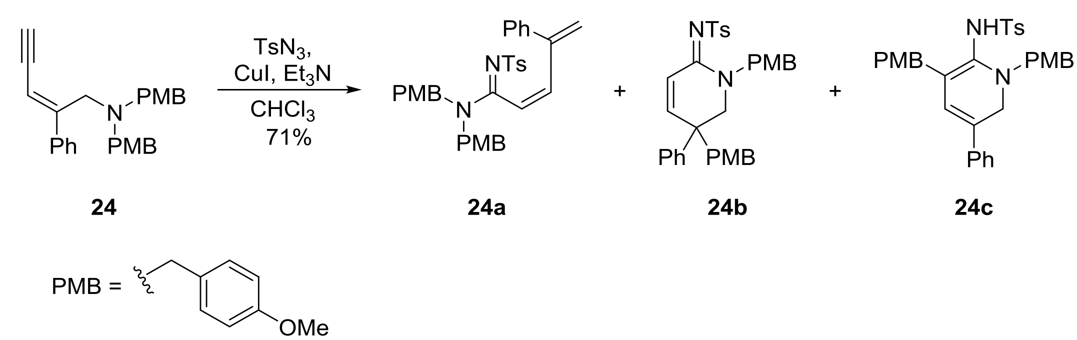


20 **20a** **20b** **20c**

Compounds **20a** (0%), **20b** (51%), and **20c** (32%) were formed by following the general procedure **A.**

20b: colorless semi-solid, IR (neat): ν/cm^{-1} 3019, 2926, 2228, 1703, 1605, 1555, 1498, 1446, 1415, 1343, 1270, 1215, 1173, 1140, 1083, 1019; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.67 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 10.2 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.15 (m, 6H), 6.92 (t, *J* = 7.4 Hz, 4H), 6.76 (d, *J* = 8.2 Hz, 2H), 6.69 (d, *J* = 10.3 Hz, 1H), 5.02 (d, *J* = 15.1 Hz, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.64 (d, *J* = 12.9 Hz, 1H), 3.56 (d, *J* = 12.9 Hz, 1H), 3.13 (d, *J* = 13.4 Hz, 1H), 2.96 (d, *J* = 13.4 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 145.3, 142.4, 140.5, 140.5, 139.8, 132.3, 131.9, 130.9, 129.2, 128.9, 128.5, 127.9, 126.4, 126.3, 120.7, 118.4, 111.5, 111.2, 57.5, 52.7, 44.53, 44.1, 21.5; HRMS (ESI): Calc. for $C_{34}H_{28}N_4O_2S$ $[M+H]^+$: 557.2011; Found: 557.2012.

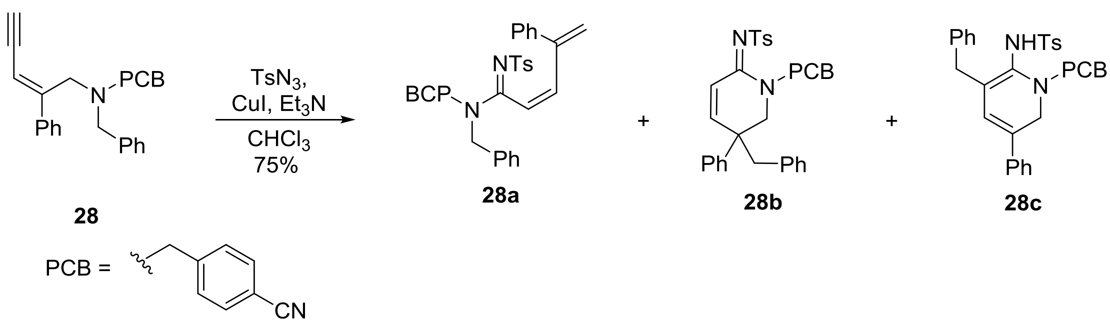
20c: colorless semi-solid, IR (neat): ν/cm^{-1} 3032, 2928, 2234, 1710, 1611, 1550, 1493, 1441, 1418, 1349, 1278, 1219, 1175, 1147, 1088, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.31 (m, 3H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.17 – 7.10 (m, 4H), 6.02 (dd, *J* = 5.5, 2.6 Hz, 1H), 4.96 (d, *J* = 15.2 Hz, 2H), 4.24 (d, *J* = 15.1 Hz, 1H), 3.89 (dd, *J* = 17.1, 1.7 Hz, 1H), 3.55 (dt, *J* = 17.1, 2.8 Hz, 1H), 3.44 (qd, *J* = 13.0, 5.7 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 164.31, 142.84, 142.55, 140.76, 140.42, 136.10, 133.27, 132.62, 132.00, 130.86, 129.30, 129.09, 128.87, 128.33, 126.11, 124.81, 121.66, 118.85, 118.41, 111.92, 111.03, 53.29, 50.71, 40.74, 40.40, 21.58; HRMS (ESI): Calc. for $C_{34}H_{28}N_4O_2S$ $[M+H]^+$: 557.2011; Found: 557.2012.



Compounds **24a** (0%), **24b** (60%), and **24c** (11%) were formed by following the general procedure **A.**

24b: colorless semi-solid, IR (neat): ν/cm^{-1} 3011, 2924, 2840, 1638, 1609, 1535, 1510, 1477, 1379, 1351, 1276, 1244, 1173, 1138, 1113, 1082, 1030 ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 10.2 Hz, 1H), 7.28 – 7.17 (m, 5H), 6.97 (m, 4H), 6.75 (d, *J* = 10.2 Hz, 1H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.55 (d, *J* = 8.7 Hz, 2H), 4.75 (d, *J* = 14.4 Hz, 1H), 4.48 (d, *J* = 14.4 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.54 (s, 2H), 2.97 (d, *J* = 13.6 Hz, 1H), 2.85 (d, *J* = 13.7 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.24, 158.50, 157.68, 146.70, 141.98, 141.25, 140.97, 131.36, 129.85, 129.21, 128.63, 127.28, 127.23, 126.58, 126.42, 120.06, 114.06, 113.48, 55.85, 55.34, 55.22, 52.23, 44.02, 43.84, 21.57; HRMS (ESI): Calc. for $C_{34}H_{34}N_2O_4S$ $[M+H]^+$: 567.2317; Found: 567.2314.

24c: colorless semi-solid, IR (neat): ν/cm^{-1} 3007, 2926, 2840, 1693, 1609, 1555, 1507, 1449, 1341, 1246, 1173, 1139, 1111, 1084, 1032; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.31 (dt, *J* = 7.9, 5.1 Hz, 7H), 7.13 (dd, *J* = 12.5, 8.0 Hz, 4H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 6.03 (dd, *J* = 5.4, 2.3 Hz, 1H), 4.88 (s, 1H), 4.79 (d, *J* = 14.3 Hz, 1H), 4.35 (d, *J* = 14.3 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.75 (s, 1H), 3.52 (dd, *J* = 13.3, 7.0 Hz, 1H), 3.20 (dd, *J* = 10.6, 7.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.8, 159.3, 158.6, 141.7, 137.0, 133.2, 131.2, 129.7, 129.1, 128.9, 128.7, 128.1, 127.1, 126.2, 124.9, 122.4, 114.1, 113.4, 55.2, 55.2, 52.7, 49.7, 41.0, 39.5, 21.4; HRMS (ESI): Calc. for $C_{34}H_{34}N_2O_4S$ $[M+H]^+$: 567.2319; Found: 567.2314.



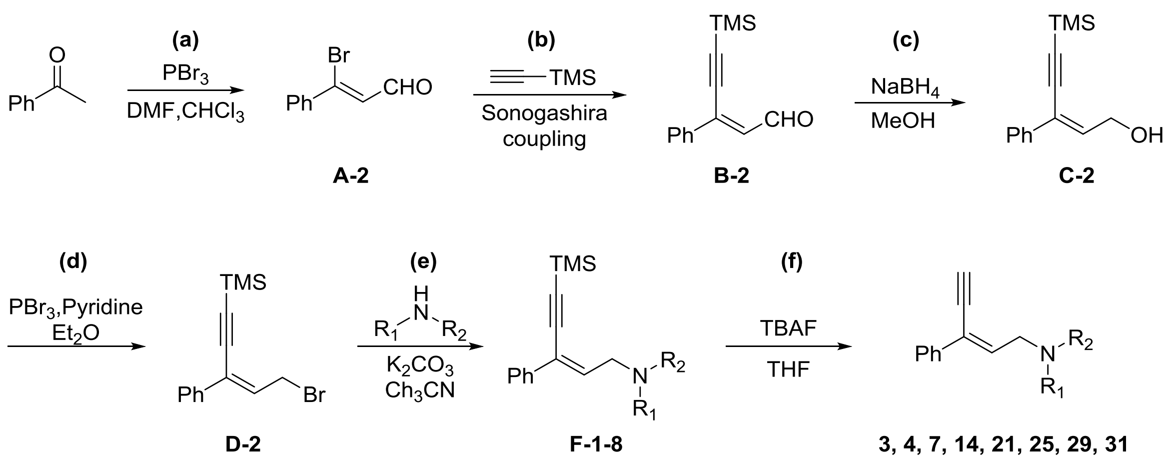
Compounds **28a** (0%), **28b** (50%), and **28c** (25%) were formed by following the general procedure **A.**

28b: colorless semi-solid, IR (neat): ν/cm^{-1} 3017, 2928, 2230, 1701, 1600, 1550, 1496, 1440, 1412, 1341, 1272, 1211, 1172, 1142, 1081, 1020; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 10.2 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.15 (m, 8H), 6.94 (d, *J* =

7.6 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 10.2 Hz, 1H), 6.74 (d, *J* = 6.5 Hz, 2H) 5.1 (d, *J* = 15.1 Hz, 1H), 4.21 (d, *J* = 15.1 Hz, 1H), 3.73 (d, *J* = 15.1 Hz, 1H), 3.73 (d, *J* = 12.8 Hz, 1H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.14 (d, *J* = 13.5 Hz, 1H), 2.96 (d, *J* = 13.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 146.7, 142.2, 140.7, 140.7, 135.0, 132.2, 130.3, 129.1, 128.7, 128.4, 128.2, 127.5, 127.1, 126.6, 126.3, 120.2, 118.5, 111.3, 57.4, 52.7, 44.8, 44.2, 29.7, 21.5.; HRMS (ESI): Calc. for $C_{33}H_{29}N_3O_2S$ $[M+H]^+$: 532.2058; Found: 532.2057.

28c: colorless semi-solid, IR (neat): ν/cm^{-1}3008, 2931, 2838, 1621, 1577, 1534, 1514, 1467, 1441, 1381, 1275, 1246, 1174, 1140, 1113, 1084, 1032 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.36 (m, 3H), 7.22 (m, 7H), 7.16 (d, *J* = 7.6 Hz, 4H), 6.09 (dd, *J* = 5.6 Hz, 2.6 Hz, 1H), 4.97 (d, *J* = 15.1 Hz, 2H), 4.26 (d, *J* = 15.2 Hz, 1H), 3.75 (dd, *J* = 16.8 Hz, 1.6 Hz, 1H), 3.60 (dd, *J* = 13.1 Hz, 7.0 Hz, 1H), 3.27 – 3.20 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 165.1, 142.2, 141.2, 140.7, 136.8, 136.7, 133.2, 132.5, 130.3, 129.2, 128.9, 128.5, 128.4, 128.1, 127.0, 126.1, 124.9, 122.4, 118.5, 111.7, 53.2, 50.7, 40.7, 40.5, 21.6 HRMS (ESI): Calc. for $C_{33}H_{29}N_3O_2S$ $[M+H]^+$: 532.2059; Found: 532.2057.

General procedure for the synthesis of *(E)-N,N*-disubstituted-3-phenylpent-2-en-4-yn-1-amines.



Scheme 4.14. Synthesis of *(E)-N,N*-disubstituted-3-phenylpent-2-en-4-yn-1-amines.

(a) Synthesis of (*Z*)-3-bromo-3-phenylacrylaldehyde A-2 (This step was followed by a known procedure: Lian, J.-J.; Odedra, A.; Wu, C.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 4186–4187.)

To a solution of DMF (167.9 mmol, 12.9 mL) in chloroform (80 mL), PBr_3 (152.8 mmol, 15.4 mL) was added dropwise at 0 ^oC. The mixture was stirred for 60 min, and then a solution of acetophenone (50.9 mmol) was added. The solution was stirred for 48 h at room temperature, and the content was poured to water (300 mL), neutralized with solid $NaHCO_3$ and extracted with dichloromethane (3×150 mL). The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by passing through short silica gel column to afford (*Z*)-3-bromo-3-phenylacrylaldehyde as yellow oil.

(b) Synthesis of (*Z*)-3-phenyl-5-(trimethylsilyl)pent-2-en-4-ynal B-2

The solution of (*Z*)-3-bromo-3-phenylacrylaldehyde in THF and triethyl amine (1.5 equiv) was degassed by N_2 for 10 minutes and trimethyl silyl acetylene (1.3 equiv) was added followed by PPh_3 (2 mol%) and degassed further for 5 minutes and $Pd(PPh_3)_2Cl_2$ (4 mol%) was added. CuI (4 mol%) was added after 10 minutes of degassing further at 0 ^oC and resulting reaction mixture was stirred for 24 h. After completion, reaction mixture was filtered through celite pad and washed with sat $NaHCO_3$ and extracted in ethyl acetate. The obtained crude product was carried forward for reduction without any purification.

(c) Synthesis of (*Z*)-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol C-2

The crude product **B-2** was dissolved in MeOH and cooled to 0 ^oC and then was added $NaBH_4$ (1 equiv) and stirred for 30 minutes. Reaction was quenched with sat.NH_4Cl and compound was extracted with EtOAc and purified by column chromatography. The two step yield was 79%.

(d) Synthesis of (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane D-2

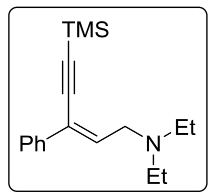
(*Z*)-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol **C-2** was dissolved in diethyl ether and cooled to -15 ^oC and PBr_3 (0.4 equiv) was added drop wisely followed by the addition of pyridine (0.03equiv) and allowed to warm at room temperature and stirred for 4 h. The reaction was quenched by ice cubes and extracted by ether. The obtained product was purified by column chromatography with 90% of yield.

IR (neat): ν/cm^{-1} 3060, 2960, 2897, 2136, 1689, 1596, 1494, 1445, 1249, 1206, 1098, 989; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 4H), 7.33 – 7.20 (m, 10H), 6.54 (t, *J* = 6.8 Hz, 1H), 3.64 (s, 4H), 3.52 (d, *J* = 6.7 Hz, 2H), 0.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 131.6, 128.7, 128.5, 127.6, 126.4, 104.7, 99.9, 30.4, -0.1; HRMS (ESI): Calc. for $C_8H_{14}BrSi$ $[M+H]^+$: 217.0048, Found: 217.0051.

(e) Synthesis of (*Z*)-*N,N*-disubstituted-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine F-1-8

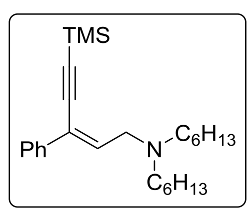
To the solution of substituted (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane in acetonitrile was added the amine (1.2 equiv) at 0 °C drop wisely followed by the addition of K_2CO_3 (1.5 equiv) and allowed to warm at room temperature and stirred for 4 h. The reaction mixture was washed with water and extracted with EtOAc and purified by column chromatography.

***(Z)-N,N*-diethyl-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine F-1**



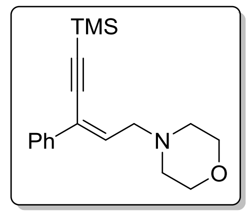
The compound **F-1** was prepared by following the above procedure **(e)**. (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane **D-2** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added diethylamine (145 μL, 1.36 mmol) followed by K_2CO_3 (190 mg, 1.36 mmol) to give **F-1** as a yellow liquid with 61% of yield. IR (neat): ν/cm^{-1} 3060, 2955, 2928, 2860, 2150, 1678, 1550, 1498, 1458, 1370, 1250, 1158, 1081; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.0 Hz, 2H), 7.25 (t, *J* = 7.1 Hz, 1H), 6.54 (t, *J* = 7.1 Hz, 1H), 3.58 (d, *J* = 7.0 Hz, 2H), 2.61 (q, *J* = 7.0 Hz, 4H), 1.09 (t, *J* = 7.0 Hz, 6H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 135.8, 128.4, 127.9, 126.1, 125.6, 101.8, 101.6, 53.1, 47.2, 29.8, 11.8, 0.1; HRMS (ESI): Calc. for $C_{18}H_{27}NSi$ $[M+H]^+$: 286.1991, Found: 286.1993.

***(Z)-N*-hexyl-*N*-(3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)hexan-1-amine F-2**



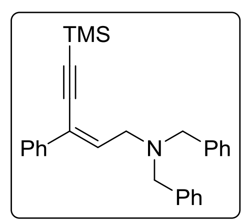
The compound **F-2** was prepared by following the above procedure **(e)**. (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane **D-2** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added dihexylamine (252 mg, 1.36 mmol) followed by K_2CO_3 (190 mg, 1.36 mmol) to give **F-2** as a yellow liquid with 70% of yield. IR (neat): ν/cm^{-1} 2954, 2926, 2858, 2148, 1676, 1549, 1495, 1457, 1368, 1249, 1155, 1079; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.1 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 1H), 6.58 (t, *J* = 6.9 Hz, 1H), 3.58 (d, *J* = 6.9 Hz, 2H), 2.53 (d, *J* = 7.5 Hz, 2H), 2.50 (d, *J* = 7.5 Hz, 2H), 1.52 (m, 4H), 1.31 (br.s, 14H), 0.90 (t, *J* = 6.9 Hz, 6H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 136.7, 128.3, 127.7, 126.0, 125.0, 101.9, 101.2, 54.4, 54.3, 31.8, 27.3, 27.2, 22.7, 14.0, 0.01; HRMS (ESI): Calc. for $C_{26}H_{43}NSi$ $[M+H]^+$: 398.3243, Found: 398.3236.

***(Z)*-4-(3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)morpholine F-3**



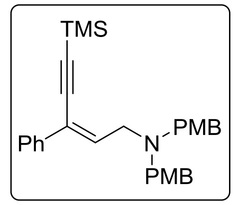
The compound **F-3** was prepared by following the above procedure (**e**). (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane **D-2** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added morpholine (115 μL, 1.36 mmol) followed by K_2CO_3 (190 mg, 1.36 mmol) to give **F-3** as a yellow liquid with 85% of yield. IR (neat): ν/cm^{-1} 2960, 2858, 2815, 2150, 1710, 1518, 1455, 1370, 1330, 1295, 1250, 1247, 1211, 1115, 1078, 1001; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, *J* = 7.2 Hz, 2H), 7.35 – 7.25 (m, 3H), 6.5 (t, *J* = 7.0 Hz, 1H), 3.73 (t, *J* = 4.6 Hz, 4H), 3.46 (d, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 4.3 Hz, 4H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1, 134.0, 128.5, 128.1, 126.7, 126.1, 102.1, 101.6, 67.0, 59.0, 53.8, 0.07; HRMS (ESI): Calc. for $C_{18}H_{25}NOSi$ $[M+H]^+$: 300.1784, Found: 300.1780.

***(Z)-N,N*-dibenzyl-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine F-4**



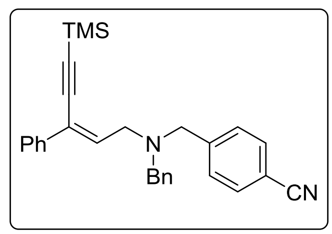
The compound **F-4** was prepared by following the above procedure (**e**). (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane **D-2** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added dibenzylamine (260 μL, 1.36 mmol) followed by K_2CO_3 (190 mg, 1.36 mmol) to give **F-4** as a yellow liquid with 92% of yield. IR (neat): ν/cm^{-1} 3028, 2958, 2798, 2147, 1742, 1599, 1493, 1448, 1363, 1326, 1248, 1119, 1071, 992; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 6.8 Hz, 6H), 7.42 – 7.33 (m, 10H), 6.62 (t, *J* = 8.3 Hz, 3H), 4.44 (d, *J* = 8.3 Hz, 6H), 0.31 (s, 27H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 137.5, 136.9, 129.0, 128.4, 128.3, 127.8, 127.0, 126.1, 125.4, 101.9, 101.7, 58.5, 54.2, 0.1; HRMS (ESI): Calc. for $C_{28}H_{31}NSi$ $[M+H]^+$: 410.2304, Found: 410.2305.

***(Z)-N,N*-bis(4-methoxybenzyl)-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine F-5**



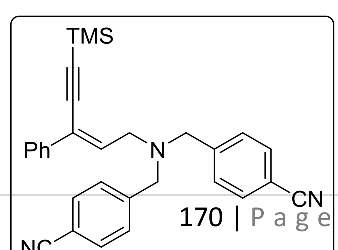
The compound **F-5** was prepared by following the above procedure (**e**). (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane **D-2** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added bis(4-methoxybenzyl)amine (350 mg, 1.36 mmol) followed by K_2CO_3 (190 mg, 1.36 mmol) to give **F-5** as a yellow liquid with 95% of yield. IR (neat): ν/cm^{-1} 3000, 2955, 2830, 2147, 1610, 1509, 1451, 1363, 1298, 1244, 1174, 1101, 1036; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.6 Hz, 2H), 7.30 (m, 8H), 6.89 (d, *J* = 8.4 Hz, 4H), 6.56 (t, *J* = 6.6 Hz, 1H), 3.82 (s, 6H), 3.6 (s, 4H), 3.54 (d, *J* = 6.7 Hz, 2H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 137.5, 137.2, 131.5, 130.0, 128.3, 127.7, 126.0, 125.0, 113.6, 101.9, 101.5, 57.7, 55.2, 53.9, 0.03; HRMS (ESI): Calc. for $C_{30}H_{35}NO_2Si$ $[M+H]^+$: 470.2515, Found: 470.2513.

***(Z)*-4-((benzyl(3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)amino)methyl) benzonitrile F-6**



The compound **F-6** was prepared by following the above procedure (**e**). *(Z)*-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane **D-2** (200mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added 4-((benzylamino)methyl)benzonitrile (302 mg, 1.36 mmol) followed by K_2CO_3 (190 mg, 1.36 mmol) to give **F-6** as a yellow liquid with 86% of yield. IR (neat): ν/cm^{-1} 3026, 2959, 2826, 2228, 2147, 1675, 1607, 1499, 1447, 1410, 1365, 1249, 1104, 994; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 7.0 Hz, 2H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.41-7.26 m, 9H), 6.52 (t, *J* = 6.9 Hz, 1H), 3.71 (s, 2H), 3.69 (s, 2H), 3.55 (d, *J* = 6.9 Hz, 2H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 138.8, 137.2, 135.6, 132.1, 129.3, 128.8, 128.4, 128.0, 127.2, 126.0, 119.0, 110.7, 102.0, 101.6, 58.9, 58.0, 54.4, 0.00; HRMS (ESI): Calc. for $C_{29}H_{31}N_2Si$ $[M+H]^+$: 435.2256, Found: 435.2256.

***(Z)*-4,4'-(((3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)azanediyl)bis (methylene))dibenzonitrile F-7**

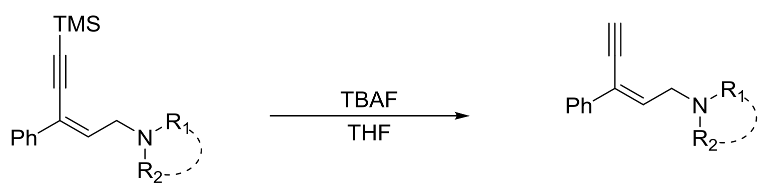


The compound **F-7** was prepared by following the above procedure (**e**). (*Z*)-(5-bromo-3-phenylpent-3-en-1-yn-1-yl)trimethylsilane **D-2**

(200mg, 0.68 mmol) in acetonitrile was cooled to 0 °C and to the reaction mixture was added 4,4'-(azanediylbis(methylene))dibenzonitrile (335 mg, 1.36 mmol) followed by K_2CO_3 (190 mg, 1.36 mmol) to give **F-7** as a yellow liquid with 79% of yield. IR (neat): ν/cm^{-1} 3026, 2959, 2826, 2228, 2147, 1675, 1607, 1499, 1447, 1410, 1365, 1249, 1104, 994; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.4 Hz, 4H), 7.53 – 7.50 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 4H), 7.36 – 7.26 (m, 3H), 6.43 (t, *J* = 7.0 Hz, 1H), 3.69 (s, 4H), 3.49 (d, *J* = 7.0 Hz, 2H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 137.1, 134.5, 132.3, 129.3, 128.5, 128.3, 126.7, 126.1, 118.91, 111.1, 102.4, 101.4, 58.4, 54.5, 0.06; HRMS (ESI): Calc. for $C_{30}H_{29}N_3Si$ $[M+H]^+$: 460.2209, Found: 460.2204.

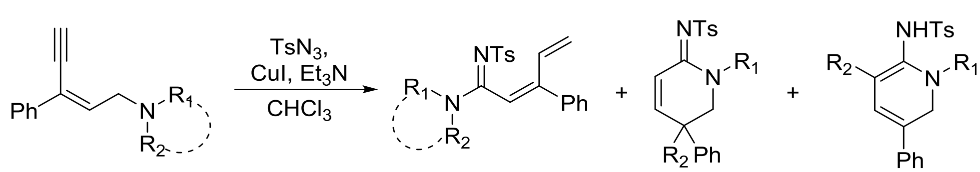
Desilylation

To the solution of (*Z*)-*N,N*-disubstituted-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine in THF was added TBAF (0.5 equiv) at 0 °C. Then reaction mixture allowed to warm at room temperature and reaction was monitored by TLC. When reaction was completed, the reaction mixture was quenched by sat. NH_4Cl. The compound was extracted with ethyl acetate and used further for next reaction without any purification.

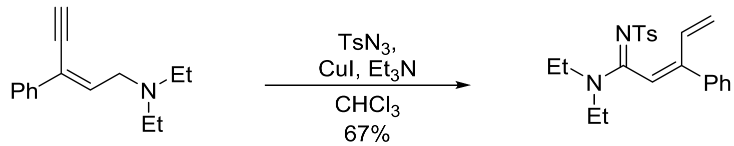


Scheme 4.15: Silyl deprotection of enyne-amines **F-1-8**.

General procedure A: Cu(I)-catalyzed formation of conjugated amidines and cyclic amidines



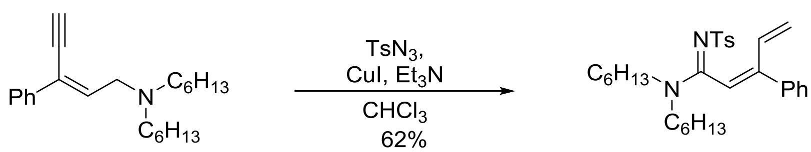
To the solution of amino enyne (1 equiv) in chloroform was added tosyl azide (1.2 equiv), Et_3N (1.5 equiv) followed by CuI (10 mol%) and stirred for one hour at room temperature. The reaction was quenched by sat. NH_4Cl and compound was extracted in chloroform. Solvent was evaporated and obtained crude product was purified by column chromatography (Hexane : EtOAc) to afford desired compound.



3 **3a**

Compound **3a** (67%) was formed by following the general procedure **A.**

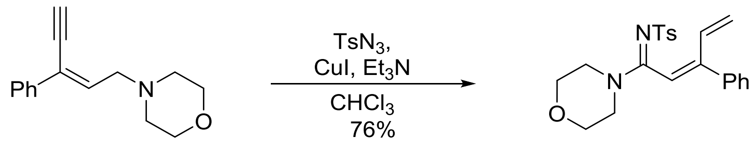
3a: colorless semi-solid : IR (neat): ν_{max}/cm^{-1} 3740, 3675, 3641, 3611, 2955, 2927, 2868, 2315, 1735, 1705, 1694, 1645, 1605, 1522, 1461, 1375, 1287, 1145, 1088; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.40 (m, 5H), 7.17 (d, *J* = 8.1 Hz, 2H), 6.21 (s, 1H), 6.14 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.14 (dd, *J* = 21.5, 14.0 Hz, 2H), 3.67 (d, *J* = 6.3 Hz, 2H), 3.44 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 4H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.35, 143.50, 141.60, 140.96, 137.99, 132.10, 128.99, 128.94, 128.67, 128.33, 126.74, 121.58, 121.15, 44.51, 42.63, 21.41, 13.81, 12.17; HRMS (ESI): Calc. for $C_{22}H_{28}N_2O_2S$ $[M+H]^+$: 383.1793; Found: 383.1794.



4 **4a**

Compound **4** (62%) was formed by following the general procedure **A.**

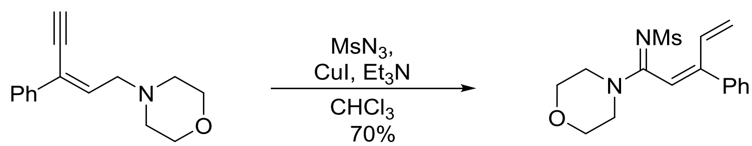
4a: colorless semi-solid : IR (neat): ν_{max}/cm^{-1} 3742, 3677, 3645, 3614, 2951, 2924, 2865, 2313, 1734, 1703, 1691, 1642, 1603, 1524, 1462, 1372, 1284, 1141, 1085; ^{1}H NMR (400 MHz, CDCl3) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.35 (m, 5H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.13 (dd, *J* = 15.9, 9.5 Hz, 2H), 5.13 (dd, *J* = 25.1, 14.2 Hz, 2H), 3.52 (s, 2H), 3.30 (s, 2H), 2.33 (s, 3H), 1.62 (m, 3H), 1.57 – 1.45 (m, 3H), 1.26 (t, *J* = 8.2 Hz, 13H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.42, 143.44, 141.52, 141.11, 138.11, 132.32, 128.88, 128.66, 128.32, 128.25, 126.65, 121.61, 121.40, 50.12, 48.22, 31.49, 31.34, 28.49, 26.85, 26.74, 26.40, 22.54, 22.46, 21.40, 14.01, 13.93; HRMS (ESI): Calc. for $C_{30}H_{42}N_2O_2S$ $[M+H]^+$: 495.3045; Found: 495.3042.



7 **7a**

Compound **7a** (76%) was formed by following the general procedure **A.**

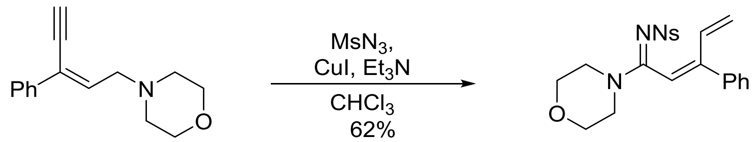
7a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2967, 2920, 2860, 1721, 1597, 1521, 1443, 1344, 1344, 1275, 1225, 1150, 1113, 1088, 1029; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.44 – 7.35 (m, 5H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.25 (s, 1H), 6.20 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.30 (dt, *J* = 10.8, 1.2 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 3.96 – 3.89 (m, 2H), 3.80 – 3.75 (m, 2H), 3.72 – 3.67 (m, 2H), 3.62 – 3.56 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 145.2, 142.1, 140.4, 137.7, 132.1, 129.1, 128.7, 128.6, 128.5, 126.9, 122.8, 119.7, 66.7, 66.3, 47.8, 44.8, 29.8, 21.5; HRMS (ESI): Calc. for $C_{22}H_{24}N_2O_3S$ $[M+H]^+$: 397.1586; Found: 397.1584.



7 **10a**

Compound **10a** (70%) was formed by following the general procedure **A.**

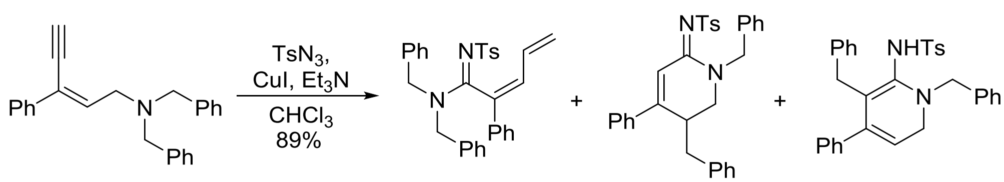
10a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2967, 2920, 2860, 1721, 1597, 1521, 1443, 1344, 1344, 1275, 1225, 1150, 1113, 1088, 1029; ^1H NMR (400 MHz, CHLOROFORM-D) δ 7.44 – 7.32 (m, 5H), 6.52 (dd, *J* = 17.2, 10.8 Hz, 1H), 6.24 (s, 1H), 5.54 – 5.46 (m, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 3.91 – 3.72 (m, 4H), 3.73 – 3.55 (m, 4H), 2.96 (s, 3H); ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 162.91, 145.41, 137.81, 132.54, 128.71, 128.67, 128.53, 123.49, 119.81, 66.75, 66.26, 47.68, 44.53, 42.74; HRMS (ESI): Calc. for $C_{16}H_{21}N_2O_3S$ $[M+H]^+$: 321.1273; Found: 321.1275.



7 11a

Compound **11a** (70%) was formed by following the general procedure **A.**

11a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2961, 2918, 2855, 1720, 1597, 1512, 1432, 1340, 1338, 1271, 1221, 1144, 1123, 1078, 1023; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 8.19 (dd, *J* = 8.9, 1.0 Hz, 2H), 8.06 – 7.97 (m, 2H), 7.43 – 7.34 (m, 3H), 7.36 – 7.27 (m, 2H), 6.23 (s, 1H), 6.21 – 6.10 (m, 1H), 5.31 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.21 (d, *J* = 17.2 Hz, 1H), 3.97 – 3.82 (m, 2H), 3.80 – 3.72 (m, 2H), 3.72 – 3.64 (m, 2H), 3.64 – 3.53 (m, 2H); ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 163.64, 149.39, 148.98, 145.63, 137.23, 131.77, 129.10, 128.70, 128.53, 128.19, 123.86, 123.70, 119.37, 66.63, 66.23, 48.12, 45.08; HRMS (ESI): Calc. for $C_{21}H_{22}N_3O_5S$ $[M+H]^+$: 321.1273; Found: 428.1280.

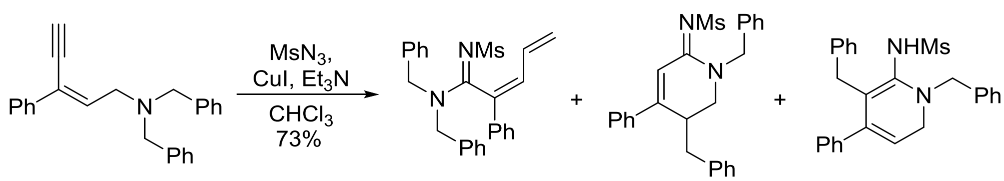


14 14a 14b 14c

Compound **14a** (84%), **14b** (5%), and **14c** (0%) were formed by following the general procedure **A.**

14a: colorless semi-solid, IR (neat): ν/cm^{-1} 3740, 3025, 2922, 2862, 1733, 1690, 1635, 1530, 1480, 1381, 1341, 1271, 1135, 1081, 1022; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.39-7.28 (m, 13H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.16 (dd, *J* = 8.1 Hz, 1.7 Hz, 2H), 6.33 (s, 1H), 6.22 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 5.21 (dt, *J* = 10.8 Hz, 1.2 Hz, 1H), 5.13 (dd, *J* = 17.2 Hz, 0.84 Hz, 1H), 4.59 (br.s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 144.8, 142.0, 140.7, 137.9, 135.8, 135.2, 132.1, 129.2, 129.1, 128.9, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 127.4, 126.9, 122.5, 120.5, 51.9, 50.0, 21.5; HRMS (ESI): Calc. for $C_{32}H_{30}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2106.

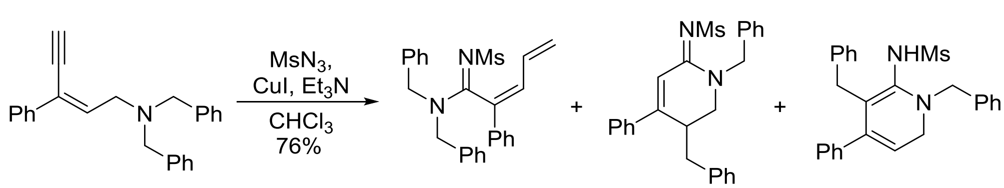
14b: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 3740, 3025, 2921, 2861, 1743, 1693, 1635, 1535, 1485, 1384, 1342, 1273, 1135, 1085, 1021; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.60 (m, 3H), 7.43 (m, 3H), 7.32 (m, 3H), 7.26 (m, 5H), 7.11 (m, 3H), 6.53 (dd, *J* = 7.2 Hz, 3.7 Hz, 2H), 5.09 (d, *J* = 14.3 Hz, 1H), 4.39 (d, *J* = 14.3 Hz, 1H), 3.47 (dd, *J* = 13.2 Hz, 5.0 Hz, 1H), 3.23 (d, *J* = 13.2 Hz, 1H), 3.02 (m, 1H), 2.59 (dd, *J* = 14.0 Hz, 3.16 Hz, 1H), 2.39 (s, 3H), 2.31 (dd, *J* = 14.0 Hz, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 153.7, 142.0, 141.5, 138.3, 136.1, 135.9, 130.5, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.2, 127.0, 126.7, 126.4, 114.7, 52.6, 47.2, 38.0, 36.1, 21.5 HRMS (ESI): Calc. for $C_{32}H_{30}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2110.



14 17a 17b 17c

Compound **17a** (73%), **17b** (0%), and **17c** (0%) were formed by following the general procedure **A.**

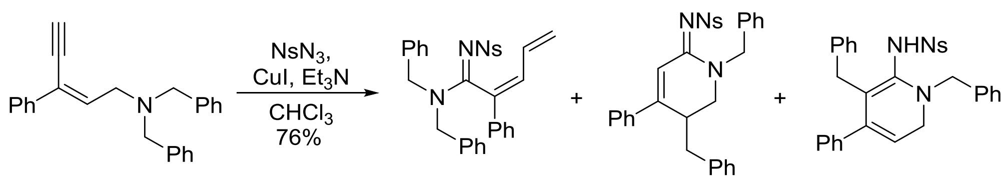
17a: colorless semi-solid, IR (neat): ν/cm^{-1} 3740, 3025, 2922, 2862, 1733, 1690, 1635, 1530, 1480, 1381, 1341, 1271, 1135, 1081, 1022; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 7.41 – 7.29 (m, 26H), 7.17 – 7.09 (m, 4H), 6.57 (dd, *J* = 17.2, 10.8 Hz, 2H), 6.31 (s, 2H), 5.44 (dd, *J* = 11.8, 1.1 Hz, 2H), 5.34 (d, *J* = 17.2 Hz, 2H), 4.58 (s, 7H), 3.01 (s, 6H); ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 164.51, 145.22, 137.99, 135.84, 135.20, 132.81, 129.20, 128.97, 128.77, 128.47, 128.43, 128.33, 128.17, 127.51, 123.10, 120.31, 51.69, 49.62, 43.07; Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1790.



14 18a 18b 18c

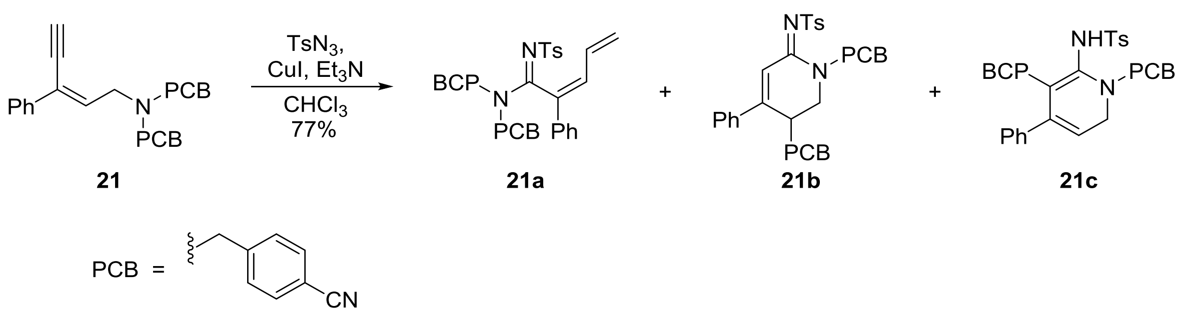
Compound **17a** (73%), **17b** (0%), and **17c** (0%) were formed by following the general procedure **A.**

17a: colorless semi-solid, IR (neat): ν/cm^{-1} 3740, 3025, 2922, 2862, 1733, 1690, 1635, 1530, 1480, 1381, 1341, 1271, 1135, 1081, 1022; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 7.41 – 7.29 (m, 26H), 7.17 – 7.09 (m, 4H), 6.57 (dd, *J* = 17.2, 10.8 Hz, 2H), 6.31 (s, 2H), 5.44 (dd, *J* = 11.8, 1.1 Hz, 2H), 5.34 (d, *J* = 17.2 Hz, 2H), 4.58 (s, 7H), 3.01 (s, 6H); ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 164.51, 145.22, 137.99, 135.84, 135.20, 132.81, 129.20, 128.97, 128.77, 128.47, 128.43, 128.33, 128.17, 127.51, 123.10, 120.31, 51.69, 49.62, 43.07; Calc. for $C_{26}H_{27}N_2O_2S$ $[M+H]^+$: 431.1793; Found: 431.1790.



14 18a 18b 18c

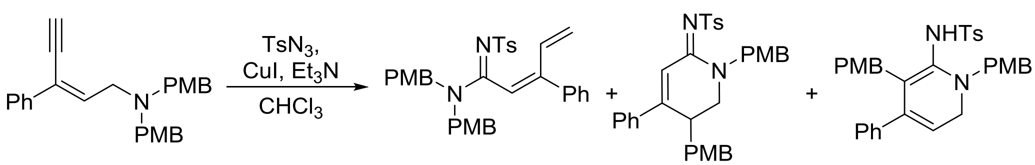
18a: colorless semi-solid, IR (neat): $ν_{max}$/cm^{-1} 3740, 3025, 2921, 2861, 1743, 1693, 1635, 1535, 1485, 1384, 1342, 1273, 1135, 1085, 1021; ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 8.18 (d, *J* = 8.8 Hz, 6H), 7.96 (d, *J* = 8.8 Hz, 6H), 7.39 – 7.32 (m, 30H), 7.27 – 7.23 (m, 11H), 7.13 (dd, *J* = 7.7, 1.5 Hz, 9H), 6.32 (s, 3H), 6.20 (dd, *J* = 17.2, 10.8 Hz, 3H), 5.27 – 5.13 (m, 6H), 4.62 (s, 10H); ^{13}C NMR (101 MHz, CHLOROFORM-D) δ 165.24, 145.30, 135.41, 134.68, 131.87, 129.34, 129.03, 128.90, 128.63, 128.33, 128.09, 127.53, 123.82, 120.16, 52.75, 50.65; HRMS (ESI): Calc. for $C_{31}H_{28}N_3O_4S$ $[M+H]^+$: 538.1801; Found: 538.1808.



21 21a 21b 21c

Compound **21a** (77%), **21b** (0%), and **21c** (0%) were formed by following the general procedure **A.**

21a: colorless semi-solid, IR (neat): ν/cm^{-1} 3022, 2924, 2226, 1703, 1605, 1555, 1498, 1444, 1414, 1343, 1275, 1210, 1170, 1145, 1085, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.1 Hz, 4H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.36 (m, 4H), 7.35 (s, 1H), 7.31 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.27 (s, 1H), 6.20 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 4.68 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.86, 145.69, 142.59, 140.78, 140.31, 139.84, 137.36, 133.01, 132.56, 131.82, 129.16, 128.85, 128.51, 128.45, 127.83, 126.75, 123.41, 119.20, 118.31, 118.07, 112.54, 112.08, 52.41, 50.57, 21.50; HRMS (ESI): Calc. for $C_{34}H_{28}N_4O_2S$ $[M+H]^+$: 557.2011; Found: 557.2018.

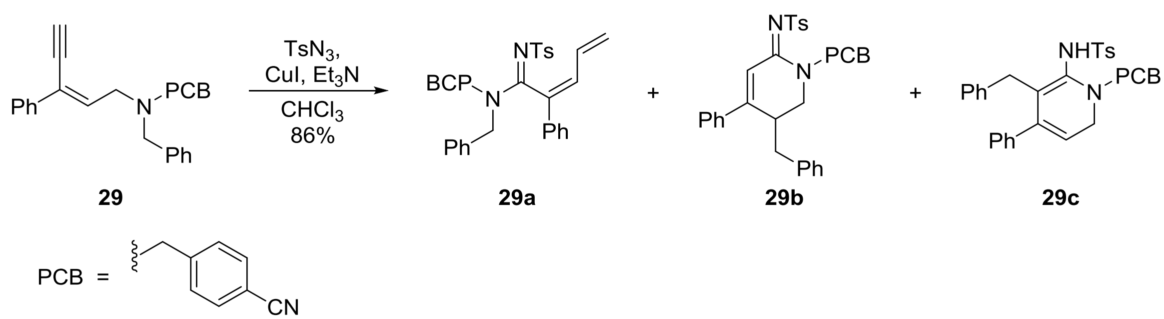


25 **25a** **25b** **25c**

Compound **25a** (8%), **25b** (70%), and **25c** (6%) were formed by following the general procedure **A.**

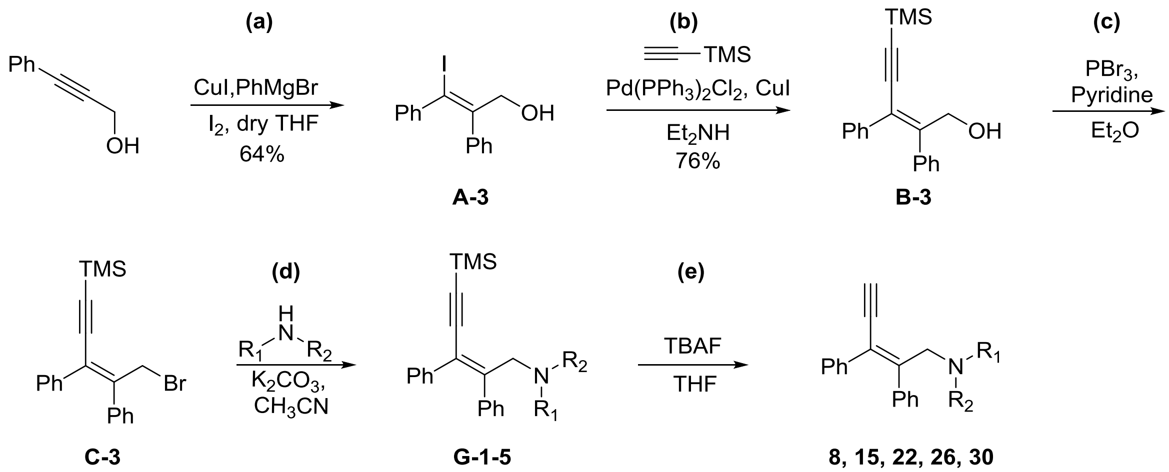
25a and 25c: colorless semi-solid, the mixture of **25a** and **25c** could not be separated hence the mixture was charecterized, IR (neat): ν/cm^{-1} 3014, 2925, 2844, 1633, 1601, 1534, 1515, 1474, 1375, 1352, 1274, 1242, 1171, 1133, 1118, 1088, 1034; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 8H), 7.78 (d, *J* = 8.3 Hz, 11H), 7.52 – 7.45 (m, 9H), 7.44 – 7.34 (m, 39H), 7.32 – 7.28 (m, 11H), 7.21 (dd, *J* = 14.9, 8.3 Hz, 23H), 7.06 (dd, *J* = 8.6, 5.6 Hz, 19H), 6.97 (d, *J* = 8.6 Hz, 8H), 6.89 (dd, *J* = 11.3, 8.7 Hz, 23H), 6.78 (d, *J* = 8.7 Hz, 8H), 6.64 (d, *J* = 8.6 Hz, 8H), 6.33 (s, 5H), 6.19 (dd, *J* = 17.2, 10.8 Hz, 5H), 5.93 (d, *J* = 3.6 Hz, 4H), 5.40 (s, 4H), 5.20 (d, *J* = 10.8 Hz, 6H), 5.15 (d, *J* = 17.3 Hz, 6H), 4.85 (d, *J* = 14.2 Hz, 5H), 4.49 (s, 13H), 4.13 (d, *J* = 14.3 Hz, 4H), 3.85 (s, 16H), 3.83 (s, 17H), 3.80 (s, 12H), 3.77 (s, 12H), 3.75 – 3.66 (m, 6H), 3.48 (ddd, *J* = 17.9, 5.4, 1.3 Hz, 5H), 2.87 (dd, *J* = 13.7, 3.6 Hz, 4H), 2.56 (d, *J* = 18.0 Hz, 4H), 2.44 (s, 12H), 2.39 (s, 17H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.95, 164.31, 159.51, 159.32, 159.27, 158.63, 144.51, 141.84, 141.79, 140.73, 137.89, 137.16, 136.11, 132.12, 131.30, 130.24, 129.95, 129.17, 128.99, 128.89, 128.83, 128.65, 128.59, 128.41, 128.33, 128.26, 127.78, 127.06, 127.00, 126.79, 126.20, 125.88, 122.30, 120.60, 118.50, 114.46, 114.06, 113.94, 113.09, 55.37, 55.32, 55.26, 55.18, 52.34, 51.05, 48.89, 48.04, 42.22, 37.51, 29.70, 21.47, 21.45; HRMS (ESI): Calc. for $C_{34}H_{34}N_2O_4S$ $[M+H]^+$: 567.2318; Found: 567.2325.

25b: colorless semi-solid, IR (neat): ν/cm^{-1} 3008, 2931, 2838, 1621, 1577, 1534, 1514, 1467, 1441, 1381, 1275, 1246, 1174, 1140, 1113, 1084, 1032 ; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.58 (m, 2H), 7.55 (s, 1H), 7.42 (t, *J* = 3.5 Hz, 3H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 8.6 Hz, 2H), 6.50 (d, *J* = 8.6 Hz, 2H), 5.02 (d, *J* = 14.2 Hz, 1H), 4.33 (d, *J* = 14.2 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.42 (dd, *J* = 13.2 Hz, 5.0 Hz, 1H), 3.24 (d, *J* = 13.0 Hz, 1H), 2.95 (m, 1H), 2.53 (dd, *J* = 14.0 Hz, 3.0 Hz, 1H), 2.39 (s, 3H), 2.24 (dd, *J* = 14.0 Hz, 11.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 158.4, 158.3, 153.7, 142.0, 141.6, 135.9, 130.5, 130.3, 129.9, 129.3, 129.1, 128.2, 127.0, 126.4, 114.7, 114.2, 114.0, 55.4, 55.3, 51.9, 46.9, 38.1, 35.2, 21.6.; HRMS (ESI): Calc. for $C_{34}H_{34}N_2O_4S$ $[M+H]^+$: 567.2318; Found: 567.2325.



Compound **29a** (86%), **29b** (0%), and **29c** (0%) were formed by following the general procedure **A.**

29a: colorless semi-solid, IR (neat): ν/cm^{-1} 3021, 2922, 2224, 1701, 1602, 1552, 1495, 1442, 1412, 1341, 1274, 1211, 1171, 1143, 1080, 1015; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.1 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 6.3 Hz, 8H), 7.33 – 7.10 (m, 6H), 6.37 – 6.13 (m, 2H), 5.22 (dt, *J* = 23.8, 8.6 Hz, 2H), 4.63 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 164.7, 145.2, 142.3, 142.2, 141.4, 140.9, 140.3, 140.2, 137.7, 137.6, 135.2, 134.6, 132.8, 132.4, 132.1, 131.9, 129.2, 129.2, 129.1, 129.1, 128.9, 128.8, 128.6, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 127.8, 127.5, 126.8, 126.7, 122.96, 122.8, 119.9, 119.8, 118.5, 118.2, 112.2, 111.7, 52.9, 51.6, 50.6, 50.1, 21.4; HRMS (ESI): Calc. for $C_{33}H_{30}N_3O_2S$ $[M+H]^+$: 532.2059; Found: 532.2063.



Scheme 4.16: Synthesis of *(E)-N,N,*disubstituted-2-methyl-3-phenylpent-2-en-4-yn-1-amine.

(a) Synthesis of *(Z)*-3-iodo-2-methyl-3-phenylprop-2-en-1-ol A-3

To a solution of propargyl alcohol (1.0 g, 17.8 mmol) and CuI (338 mg, 1.7 mmol) in dry THF (20 mL) was added 3.0 M PhMgBr (15 mL, 44.5 mmol) at -10 ^{0}C. Upon complete addition of Grignard reagent, the reaction mixture was allowed to come at room temperature and stirred for overnight. The resultant mixture was then cooled to -78 ^{o}C and then added a solution of I_2 (9.0 g, 35.6 mmol) in THF (20 mL), the reaction mixture was allowed to cool at room temperature and stirred for 1 hour then cooling at 0 ^{o}C, the reaction mixture was quenched by saturated NH_4Cl. The reaction mixture was brought to room temperature and extracted with EtOAc, washed with brine dried over Na_2SO_4 and concentrated under reduced pressure. The obtained compound was purified by column chromatography to give **A-3** with 64% of yield.

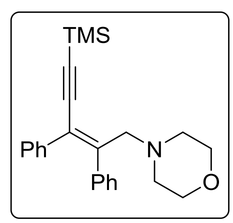
(b) Synthesis of *(Z)*-2,3-diphenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol B-3 To a solution of *(Z)*-3-iodo-2-phenylprop-2-en-1-ol **B-3** in Et_2NH (0.5 M) was added $(Ph_3P)_2PdCl_2$ (2 mol %)and CuI (4 mol %) at 0 ºC. The system was degassed by N_2 and the resulting was added trimethyl silyl acetylene (1.3 equiv). Then it was warmed up to room temperature. The reaction was monitored by TLC. When the reaction completed, the reaction mixture was concentrated, and the residue was purified through silica gel flash column.

(c) Synthesis of *(Z)*-(5-bromo-3,4-diphenylpent-3-en-1-yn-1-yl)trimethylsilane C-3 To a solution of *(Z)*-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol **C-3** (1 equiv.) in Et_2O was added pyridine (0.06 equiv.) and PBr_3 (0.45 equiv.) at 0°C. The reaction was warmed to room temperature with additional stirring for 1 h. After completion of reaction, the mixture was quenched by ice cubes and extracted in EtOAc. Solvent was removed and obtained product was purified by column chromatography.

IR (neat): ν_{max}/cm^{-1} 2960, 2138, 1756, 1682, 1598, 1490, 1442, 1249, 1210, 1148, 1069, 1000; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 3H), 7.18 – 7.12 (m, 7H), 4.76 (s, 2H), 0.31 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.47, 138.29, 137.26, 129.92, 129.72, 129.12, 128.25, 127.75, 125.62, 103.83, 103.60, 36.88, -0.14; HRMS (ESI): Calc. for $C_{20}H_{22}BrSi$ $[M+H]^+$: 369.0674; Found: 369.0678.

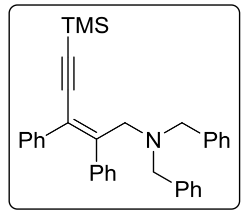
(d) Synthesis of *(Z)-N,N*-disubstituted-2,3-diphenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine To the solution of substituted *(Z)*-(5-bromo-3,4-diphenylpent-3-en-1-yn-1-yl)trimethylsilane **C-3** in acetonitrile was added the amine (1.2 equiv) at 0 ^{o}C drop wisely followed by the addition of K_2CO_3 (1.5 equiv) and allowed to warm at room temperature and stirred for 4h. The reaction mixture was washed with water and extracted with EtOAc and purified by column chromatography.

***(Z)*-4-(2,3-diphenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)morpholine G-1**



The compound **G-1** was prepared by following the above procedure **(d)**. *(Z)*-(5-bromo-3,4-diphenylpent-3-en-1-yn-1-yl)trimethylsilane **C-3** (200mg, 0.41 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added morpholine (72 mg, 0.82 mmol) followed by K_2CO_3 (113 mg, 0.82 mmol) to give **G-1** as a yellow liquid with 86% of yield. IR (neat): ν/cm^{-1} 2960, 2858, 2815, 2150, 1710, 1518, 1455, 1370, 1330, 1295, 1250, 1247, 1211, 1115, 1078, 1001; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.07 (m, 10H), 3.79 (s, 2H), 3.73 – 3.61 (m, 4H), 2.67 – 2.54 (m, 4H), 0.27 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.65, 140.39, 138.30, 129.86, 129.20, 127.79, 127.66, 127.04, 126.97, 124.79, 105.42, 100.41, 67.10, 63.67, 53.59, 0.02; HRMS (ESI): Calc. for $C_{24}H_{30}NOSi$ $[M+H]^+$: 376.2097, Found: 376.2095.

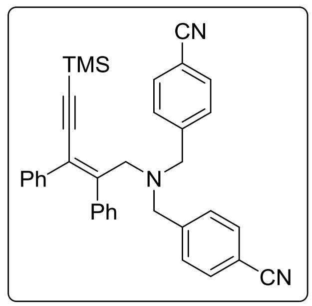
***(Z)-N,N*-dibenzyl-3-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine G-2**



The compound **G-2** was prepared by following the above procedure **(d)**. *(Z)*-(5-bromo-3,4-diphenylpent-3-en-1-yn-1-yl)trimethylsilane **C-3** (200mg, 0.41 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added dibenzylamine (160 µL, 0.82 mmol) followed by K_2CO_3 (113 mg, 0.82 mmol) to give **G-2** as a yellow liquid with 92% of yield.

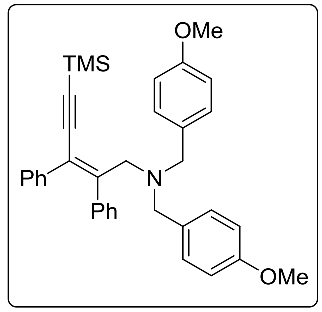
IR (neat): ν/cm^{-1} 3333, 3060, 2927,1748, 1600, 1491, 1445, 1350, 1263, 1190, 1077, 1000, 949; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 7H), 7.17 – 7.06 (m, 11H), 6.86 (d, *J* = 6.9 Hz, 2H), 3.89 (s, 2H), 3.60 (s, 4H), 0.30 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.5, 139.7, 139.3, 138.4, 129.9, 129.7, 128.9, 127.9, 127.6, 127.5, 126.9, 126.8, 126.7, 126.0, 123.6, 106.9, 105.6, 102.7, 100.0, 98.2, 59.0, 58.1, 0.1; HRMS (ESI): Calc. for $C_{34}H_{35}NSi$ $[M+H]^+$: 486.2617, Found: 486.2618.

***(Z)*-4,4'-(((2,3-diphenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)azanediyl)bis (methylene))dibenzonitrile G-3**



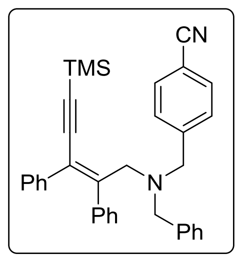
The compound **G-3** was prepared by following the above procedure (**d**). *(Z)*-(5-bromo-3,4-diphenylpent-3-en-1-yn-1-yl)trimethylsilane **C-3** (200mg, 0.41 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added 4,4'-(azanediylbis(methylene))dibenzonitrile (202 mg, 0.82 mmol) followed by K_2CO_3 (113 mg, 0.82 mmol) to give **G-3** as a yellow liquid with 89% of yield. IR (neat): ν/cm^{-1} 3028, 2962, 2830, 2238, 2145, 1681, 1617, 1512, 1452, 1418, 1369, 1243, 1114, 1001; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 13H), 7.25 (d, *J* = 7.4 Hz, 3H), 7.18 (t, *J* = 7.4 Hz, 7H), 7.13 (d, *J* = 8.3 Hz, 13H), 7.11 (s, 15H), 6.81 (d, *J* = 7.0 Hz, 6H), 3.88 (s, 6H), 3.64 (s, 13H), 0.30 (s, 28H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.82, 144.89, 139.10, 137.81, 132.00, 129.78, 129.37, 129.31, 127.88, 127.73, 127.36, 127.19, 124.59, 118.87, 110.89, 105.12, 100.68, 59.32, 57.93, 0.05; HRMS (ESI): Calc. for $C_{36}H_{34}N_3Si$ $[M+H]^+$: 536.2522, Found: 536.2527.

(Z)-N,N-bis(4-methoxybenzyl)-2,3-diphenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine G-4



The compound **G-4** was prepared by following the above procedure **(d)**. *(Z)*-(5-bromo-3,4-diphenylpent-3-en-1-yn-1-yl)trimethylsilane **C-3** (200mg, 0.41 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added bis(4-methoxybenzyl)amine (210 mg, 0.82 mmol) followed by K_2CO_3 (113 mg, 0.82 mmol) to give **G-4** as a yellow liquid with 90% of yield. IR (neat): ν/cm^{-1} 3003, 2958, 2835, 2138, 1698, 1612, 1512, 1455, 1368, 1301, 1245, 1176, 1103, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.07 (m, 8H), 6.97 (d, *J* = 8.3 Hz, 4H), 6.86 (d, *J* = 7.8 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 4H), 3.87 (s, 2H), 3.80 (s, 6H), 3.50 (s, 4H), 0.29 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.43, 148.80, 139.35, 138.50, 131.78, 129.98, 129.92, 129.72, 127.60, 127.46, 126.82, 126.79, 123.32, 113.33, 105.68, 99.91, 58.74, 57.22, 55.24, 0.08; HRMS (ESI): Calc. for $C_{36}H_{40}NO_2Si$ $[M+H]^+$: 546.2828, Found: 546.2832.

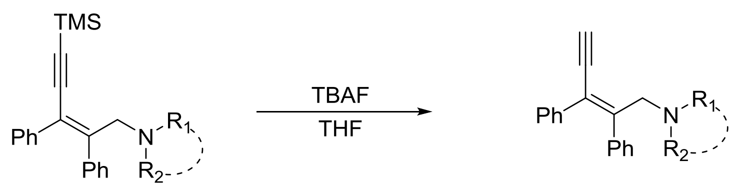
(Z)-4-((benzyl(2,3-diphenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-yl)amino)methyl) benzonitrile G-5



The compound **G-5** was prepared by following the above procedure **(d)**. *(Z)*-(5-bromo-3,4-diphenylpent-3-en-1-yn-1-yl)trimethylsilane **C-3** (200mg, 0.41 mmol) in acetonitrile was cooled to 0 ^{o}C and to the reaction mixture was added 4-((benzylamino)methyl)benzonitrile (182 mg, 0.82 mmol) followed by K_2CO_3 (113 mg, 0.82 mmol) to give **G-5** as a yellow liquid with 90% of yield. IR (neat): ν/cm^{-1} 3021, 2960, 2821, 2225, 2149, 1678, 1610, 1500, 1450, 1412, 1368, 1250, 1105, 1000; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.21 (m, 4H), 7.16 (t, *J* = 7.3 Hz, 2H), 7.10 (dt, *J* = 5.2, 3.6 Hz, 9H), 6.84 (d, *J* = 7.0 Hz, 2H), 3.89 (s, 2H), 3.62 (s, 4H), 0.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 145.8, 139.3, 139.1, 138.2, 131.9, 129.9, 129.6, 129.4, 129.0, 128.2, 127.8, 127.7, 127.2, 127.1, 127.1, 124.1, 119.2, 110.5, 105.4, 100.4, 59.3, 58.5, 57.7, 0.1; HRMS (ESI): Calc. for $C_{35}H_{35}N_2Si$ $[M+H]^+$: 511.2570, Found: 511.2579.

(e) Desilylation

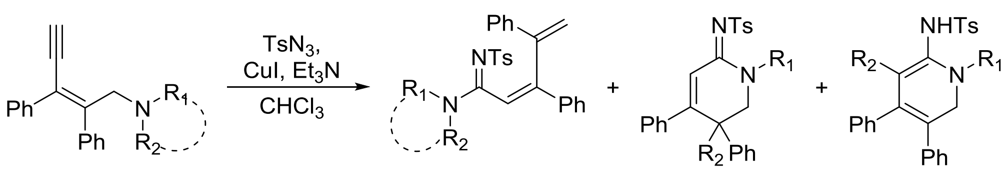
To the solution of (*Z*)-*N,N*-disubstituted-2-phenyl-5-(trimethylsilyl)pent-2-en-4-yn-1-amine in THF was added TBAF (0.5 equiv) at 0 ^{o}C. Then reaction mixture allowed to warm at room temperature and reaction was monitored by TLC. When reaction was completed, the reaction mixture was quenched by sat. NH_4Cl. The compound was extracted with ethyl acetate and used further for next reaction without any purification.



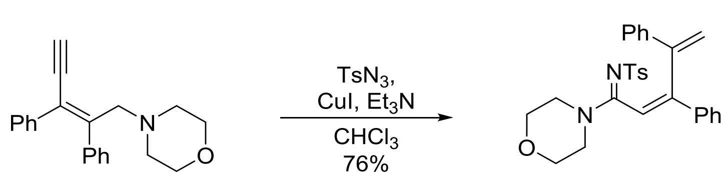
G-1-5 **8, 15, 22, 26, 30**

Scheme 4.17: Silyl deprotection of enyne-amines **G-1-5**.

General procedure A: Cu(I)-catalyzed formation of conjugated amidines and cyclic amidines



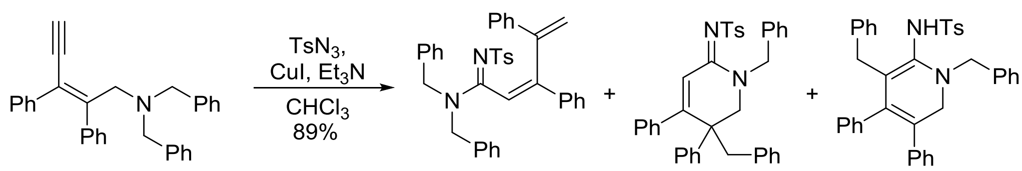
To the solution of amino enyne (1 equiv) in chloroform was added tosyl azide (1.2 equiv), Et_3N (1.5 equiv) followed by CuI (10 mol%) and stirred for one hour at room temperature. The reaction was quenched by sat. NH_4Cl and compound was extracted in chloroform. Solvent was evaporated and obtained crude product was purified by column chromatography (Hexane : EtOAc) to afford desired compound.



8 **8a**

Compound **8a** (65%) was formed by following the general procedure **A.**

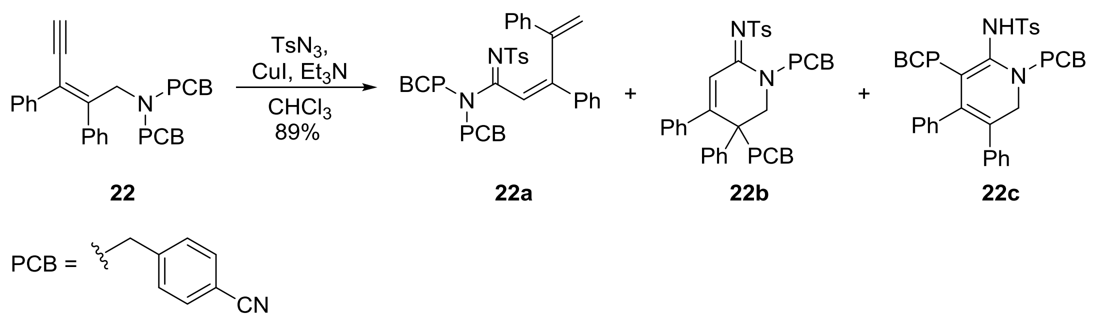
8a: colorless semi-solid, IR (neat): ν_{max}/cm^{-1} 2967, 2920, 2860, 1721, 1597, 1521, 1443, 1344, 1344, 1275, 1225, 1150, 1113, 1088, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.39 (m, 2H), 7.34 (m, 3H), 7.26 (dd, *J* = 6.7, 3.3 Hz, 2H), 7.23 – 7.19 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 6.79 (s, 1H), 5.86 (d, *J* = 0.6 Hz, 1H), 5.34 (s, 1H), 3.58 (s, 4H), 3.40 (s, 2H), 3.25 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.49, 148.81, 143.98, 142.01, 140.37, 139.06, 137.34, 129.04, 128.76, 128.65, 128.54, 128.18, 128.06, 127.96, 127.41, 126.88, 126.56, 119.30, 119.03, 66.11, 65.68, 48.12, 44.53, 21.49; HRMS (ESI): Calc. for $C_{28}H_{29}N_2O_3S$ $[M+H]^+$: 473.1899; Found: 473.1894.



Compound **15a** (24%), **15b** (45%), and **15c** (0%) were formed by following the general procedure **A.**

15a: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.40 – 7.34 (m, 6H), 7.31 (m, 6H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.01 (m, 10H), 6.90 (s, 1H), 5.69 (d, *J* = 0.6 Hz, 1H), 5.37 (d, *J* = 0.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 148.2, 142.7, 141.9, 140.6, 138.7, 137.1, 135.5, 135.2, 129.1, 129.5, 129.3, 128., 128.6, 128.4, 128.7, 128.1, 127.8, 127.7, 127.2, 127.1, 126.7, 126.6, 119.5, 119.2, 52.2, 49.6, 21.4; HRMS (ESI): Calc. for $C_{38}H_{35}N_2O_2S$ $[M+H]^+$: 583.2419; Found: 583.2430.

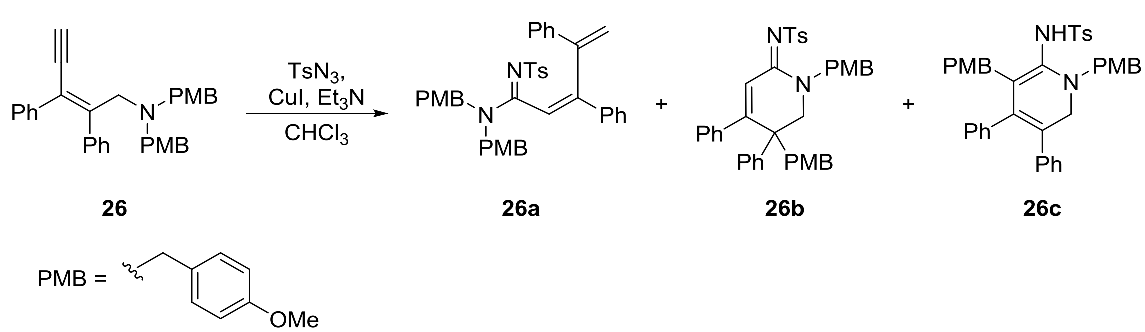
15b: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 4H), 7.63 (s, 2H), 7.42 – 7.31 (m, 7H), 7.28 – 7.13 (m, 23H), 7.13 – 7.02 (m, 8H), 6.76 (d, *J* = 7.5 Hz, 4H), 6.61 (d, *J* = 7.4 Hz, 4H), 4.92 (d, *J* = 14.7 Hz, 2H), 4.06 (d, *J* = 14.7 Hz, 2H), 3.91 (d, *J* = 13.0 Hz, 2H), 3.46 (d, *J* = 14.3 Hz, 2H), 3.39 (d, *J* = 13.0 Hz, 2H), 3.26 (d, *J* = 14.3 Hz, 2H), 2.41 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.52, 156.04, 141.74, 141.46, 141.31, 137.96, 135.91, 134.88, 130.55, 129.29, 129.01, 128.73, 128.49, 128.46, 128.37, 128.02, 128.01, 127.45, 127.33, 127.14, 126.90, 126.37, 121.50, 57.74, 52.28, 47.61, 42.00, 21.46;HRMS (ESI): Calc. for $C_{38}H_{35}N_2O_2S$ $[M+H]^+$: 583.2419; Found: 583.2420.



Compound **22a** (73%), **22b** (18%), and **22c** (0%) were formed by following the general procedure **A.**

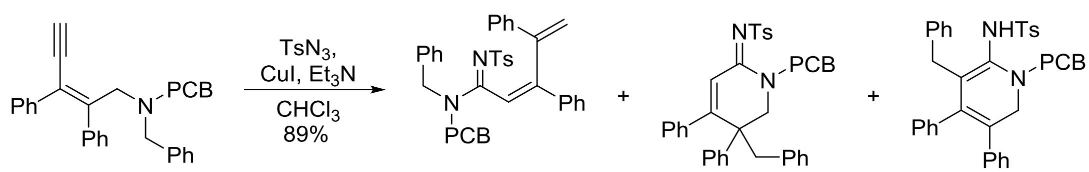
22a: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.34 (m, 6H), 7.23 – 7.13 (m, 10H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.86 (s, 1H), 5.79 (d, *J* = 0.5 Hz, 1H), 5.40 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 149.1, 143.1, 142.6, 140.5, 140.3, 139.8, 138.3, 136.6, 132.9, 132.2, 129.3, 129.2, 129.2, 128.8, 128.6, 128.2, 128.1, 127.7, 127.5, 127.1, 126.7, 126.5, 119.1, 118.5, 118.1, 112.4, 111.8, 52.7, 50.2, 21.5; HRMS (ESI): Calc. for $C_{40}H_{33}N_4O_2S$ $[M+H]^+$: 633.2324; Found: 633.2317.

22b: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 5.8 Hz, 6H), 7.62 (s, 3H), 7.38 – 7.29 (m, 17H), 7.23 (d, *J* = 8.2 Hz, 8H), 7.22 – 7.16 (m, 19H), 7.14 (d, *J* = 7.9 Hz, 6H), 6.69 (dd, *J* = 8.1, 5.8 Hz, 12H), 5.13 (d, *J* = 15.1 Hz, 3H), 3.95 (d, *J* = 12.7 Hz, 3H), 3.81 (d, *J* = 15.1 Hz, 3H), 3.51 (d, *J* = 14.3 Hz, 3H), 3.37 (d, *J* = 12.8 Hz, 3H), 3.30 (d, *J* = 14.4 Hz, 3H), 2.40 (s, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.30, 141.37, 140.92, 140.71, 140.43, 137.43, 132.12, 131.72, 131.22, 129.88, 129.14, 129.03, 128.86, 128.26, 128.13, 127.99, 127.01, 126.30, 121.59, 118.53, 118.43, 111.12, 111.00, 58.58, 52.07, 47.83, 42.07, 21.49; HRMS (ESI): Calc. for $C_{40}H_{33}N_4O_2S$ $[M+H]^+$: 633.2324; Found: 633.2321.



Compound **26a** (0%), **26b** (68%), and **26c** (0%) were formed by following the general procedure **A.**

26b: colorless semi-solid, IR (neat): ν/cm^{-1} 3015, 2927, 2843, 1642, 1612, 1539, 1515, 1472, 1382, 1354, 1278, 1248, 1175, 1143, 1111, 1084, 1035; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.60 (s, 1H), 7.42 – 7.30 (m, 4H), 7.27 – 7.10 (m, 10H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.61 (dd, *J* = 15.6, 8.7 Hz, 4H), 6.49 (d, *J* = 8.7 Hz, 2H), 4.86 (d, *J* = 14.5 Hz, 1H), 4.00 (d, *J* = 14.5 Hz, 1H), 3.87 (d, *J* = 13.0 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.39 (d, *J* = 13.5 Hz, 1H), 3.34 (d, *J* = 13.5 Hz, 1H), 3.18 (d, *J* = 14.4 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.85, 158.43, 157.32, 155.99, 141.68, 141.54, 138.02, 131.57, 129.43, 129.00, 128.63, 128.45, 128.35, 127.14, 126.36, 121.58, 113.85, 113.40, 55.24, 55.20, 47.66, 41.15, 29.70, 27.43, 21.45; HRMS (ESI): Calc. for $C_{40}H_{39}N_2O_4S$ $[M+H]^+$: 643.2631; Found: 643.2638.



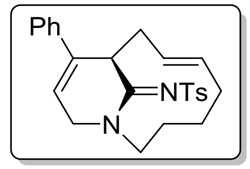
30 30a 30b 30c

Compound **30a** (46%), **30b** (29%), and **30c** (0%) were formed by following the general procedure **A.**

30a: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.34 (m, 6H), 7.23 – 7.13 (m, 10H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.86 (s, 1H), 5.79 (d, *J* = 0.5 Hz, 1H), 5.40 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 149.1, 143.1, 142.6, 140.5, 140.3, 139.8, 138.3, 136.6, 132.9, 132.2, 129.3, 129.2, 129.2, 128.8, 128.6, 128.2, 128.1, 127.7, 127.5, 127.1, 126.7, 126.5, 119.1, 118.5, 118.1, 112.4, 111.8, 52.7, 50.2, 21.5; HRMS (ESI): Calc. for $C_{39}H_{34}N_3O_2S$ $[M+H]^+$: 608.2372; Found: 608.2375.

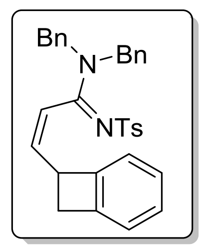
30b: colorless semi-solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.66 (s, 1H), 7.36 (dd, *J* = 12.8, 8.1 Hz, 5H), 7.26 – 7.15 (m, 10H), 7.10 (t, *J* = 7.5 Hz, 2H), 6.80 (d, *J* = 7.3 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 4.85 (d, *J* = 14.6 Hz, 1H), 4.08 (d, *J* = 14.7 Hz, 1H), 3.81 (d, *J* = 12.9 Hz, 1H), 3.48 (dd, *J* = 28.6, 13.6 Hz, 2H), 3.33 (d, *J* = 14.3 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.58, 156.55, 142.10, 141.54, 140.90, 140.68, 137.80, 135.70, 132.06, 130.57, 129.57, 129.06, 128.85, 128.65, 128.34, 128.21, 128.12, 127.68, 127.19, 127.05, 126.31, 121.30, 118.63, 110.96, 58.66, 52.11, 47.78, 41.95, 21.47; HRMS (ESI): Calc. for $C_{39}H_{34}N_3O_2S$ $[M+H]^+$: 608.2372; Found: 608.2375.

Synthesis of 4-methyl-*N*-((1S,6*E*,9*R*,13*Z*)-10-phenyl-1-azabicyclo[7.3.1]trideca-6,10-dien-13-ylidene)benzenesulfonamide 32.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 2H), 7.38 (m, 8H), 6.05 (d, *J* = 2.8 Hz, 1H), 5.69 – 5.35 (m, 2H), 5.17 (d, *J* = 5.1 Hz, 1H), 4.76 (s, 1H), 4.24 (d, *J* = 18.8 Hz, 1H), 3.71 (d, *J* = 18.7 Hz, 1H), 3.17 – 3.01 (m, 1H), 2.82 (d, *J* = 13.6 Hz, 1H), 2.43 (s, 3H), 2.32 (dd, *J* = 12.5, 4.5 Hz, 2H), 1.88 (s, 2H), 1.79 – 1.60 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 141.2, 141.1, 139.4, 134.8, 133.7, 129.7, 128.6, 128.5, 128.2, 128.1, 127.9, 126.4, 126.3, 125.6, 125.5, 115.1, 50.8, 45.7, 38.0, 33.7, 27.6, 26.7, 26.3, 21.3; HRMS (ESI): Calc. for $C_{25}H_{29}N_2O_2S$ $[M+H]^+$: 421.1950; Found: 421.1955.

Synthesis of (1Z,2Z)-*N*,*N*-dibenzyl-3-(bicyclo[4.2.0]octa-1(6),2,4-trien-7-yl)-*N*'-tosylacrylimidamide 38.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 8H), 7.37 – 7.29 (m, 14H), 7.25 – 7.15 (m, 56H), 7.14 – 7.08 (m, 14H), 6.91 (d, *J* = 6.9 Hz, 8H), 6.36 (s, 4H), 5.00 (s, 9H), 4.56 (s, 7H), 3.12 (dd, *J* = 14.4, 5.5 Hz, 4H), 2.84 (s, 4H), 2.36 (s, 13H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.00, 142.05, 140.99, 139.16, 135.61, 135.06, 129.25, 129.20, 128.86, 128.71, 128.33, 128.11, 128.00, 127.58, 127.44, 126.60, 122.94, 120.52, 49.79, 45.66, 21.56. HRMS (ESI): Calc. for $C_{32}H_{31}N_2O_2S$ $[M+H]^+$: 507.2106; Found: 507.2109.

4.5 Crystal structures.

Crystal structure of compound 14a: $C_{26}H_{26}N_2O_2S$; Compound **14a** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/n*; a = 19.851(4) b = 20.966(5) c = 5.1137(11) Å, α = 90° β = 90° γ = 90°; V = 2128.3(8) Å^3;

T = 296 (2) K; *Z* = 4; ρ_{calc} = 1.219 Mgm^{-3}; $2\theta_{max}$ = 54.76^o; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0361 (for 4159 reflection *I*>2σ(*I*)), *wR* = 0.0820 which was refined against ǀ*F2*ǀ and S = 0.935 for 258 parameters and 4839 unique reflections. The structure was obtained by direct methods using SHELXS-97.[14] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the fil cycle of refinement as riding over atoms to which they are bonded. μ = 0.087 mm^{-1}.

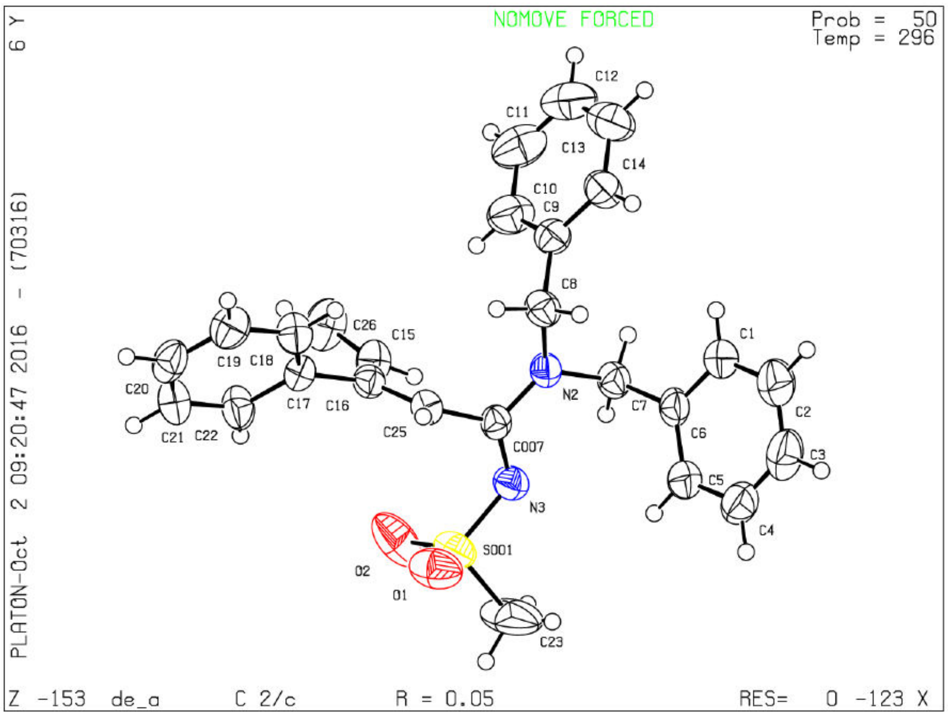


Figure 4.4: ORTEP diagram of **14a**.

Crystal structure of compound 13b: $C_{32}H_{30}N_2O_2S$; Compound **13b** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/n*; *a* = 19.851(4) *b* = 20.966(5) *c* = 5.1137(11) Å, α = 90^o β = 90^o γ = 90^o; *V* = 2128.3(8) Å^3; *T* = 296 (2) K; *Z* = 4; ρ_{calc} = 1.219 Mgm^{-3}; $2\theta_{max}$ = 54.76^o; *MoKαλ* = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0361 (for 4159 reflection *I*>2σ(*I*)), *wR* = 0.0820 which was refined against ǀ*F2*ǀ and S = 0.935 for 258 parameters and 4839 unique reflections. The structure was obtained by direct methods using SHELXS-97.[14] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the fil cycle of refinement as riding over atoms to which they are bonded. $\mu = 0.087$ mm^{-1}.

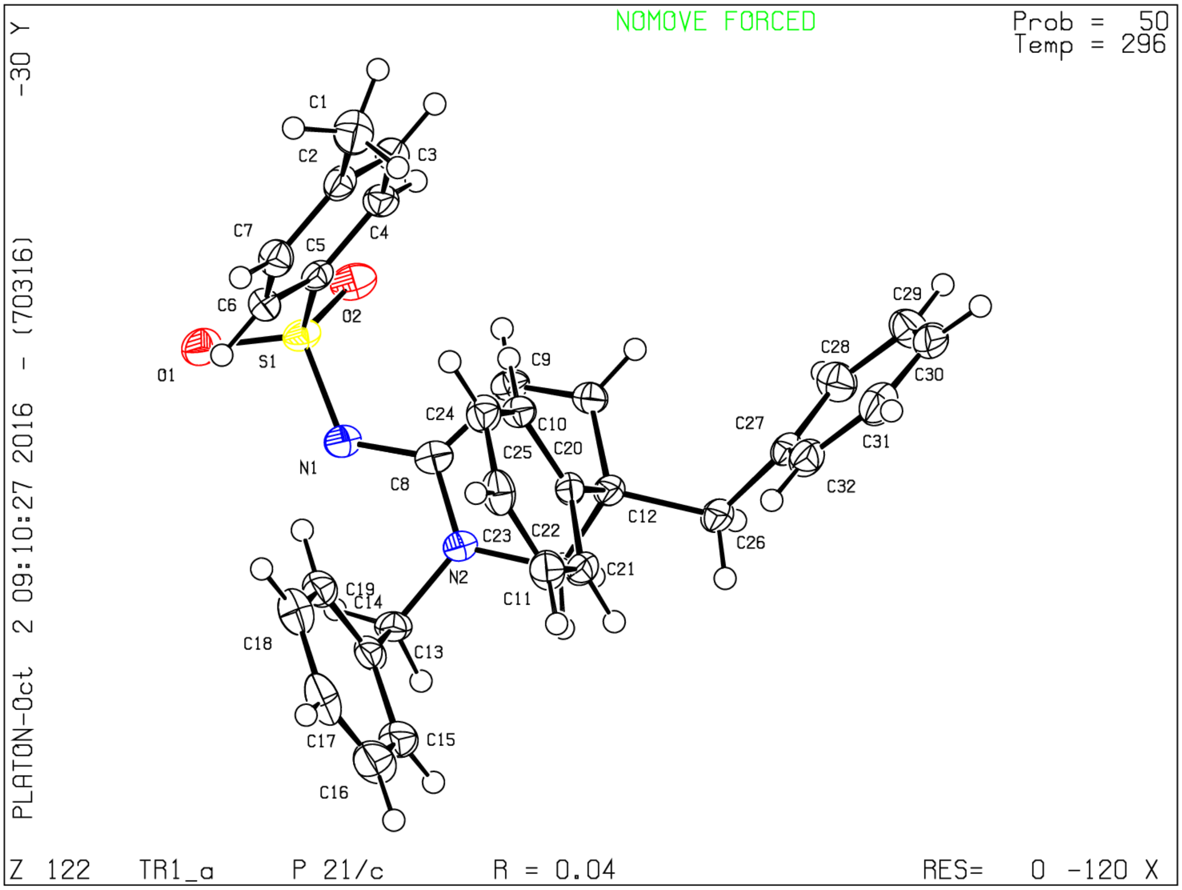


Figure 4.5: ORTEP diagram of **13b**.

Crystal structure of compound 32: $C_{25}H_{28}N_2O_2S$; Compound **32** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/n*; a = 19.851(4) b = 20.966(5) c = 5.1137(11) Å, $\alpha = 90^o$ $\beta = 90^o$ $\gamma = 90^o$; V = 2128.3(8) Å^3; T = 296 (2) K; Z = 4; ρ_{calc} = 1.219 Mgm^{-3}; $2\theta_{max}$ = 54.76^o; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0361 (for 4159 reflection $I>2\sigma(I)$), wR = 0.0820 which was refined against $|F2|$ and S = 0.935 for 258 parameters and 4839 unique reflections. The structure was obtained by direct methods using SHELXS-97.[14] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the fil cycle of refinement as riding over atoms to which they are bonded. μ = 0.174 mm^{-1}.

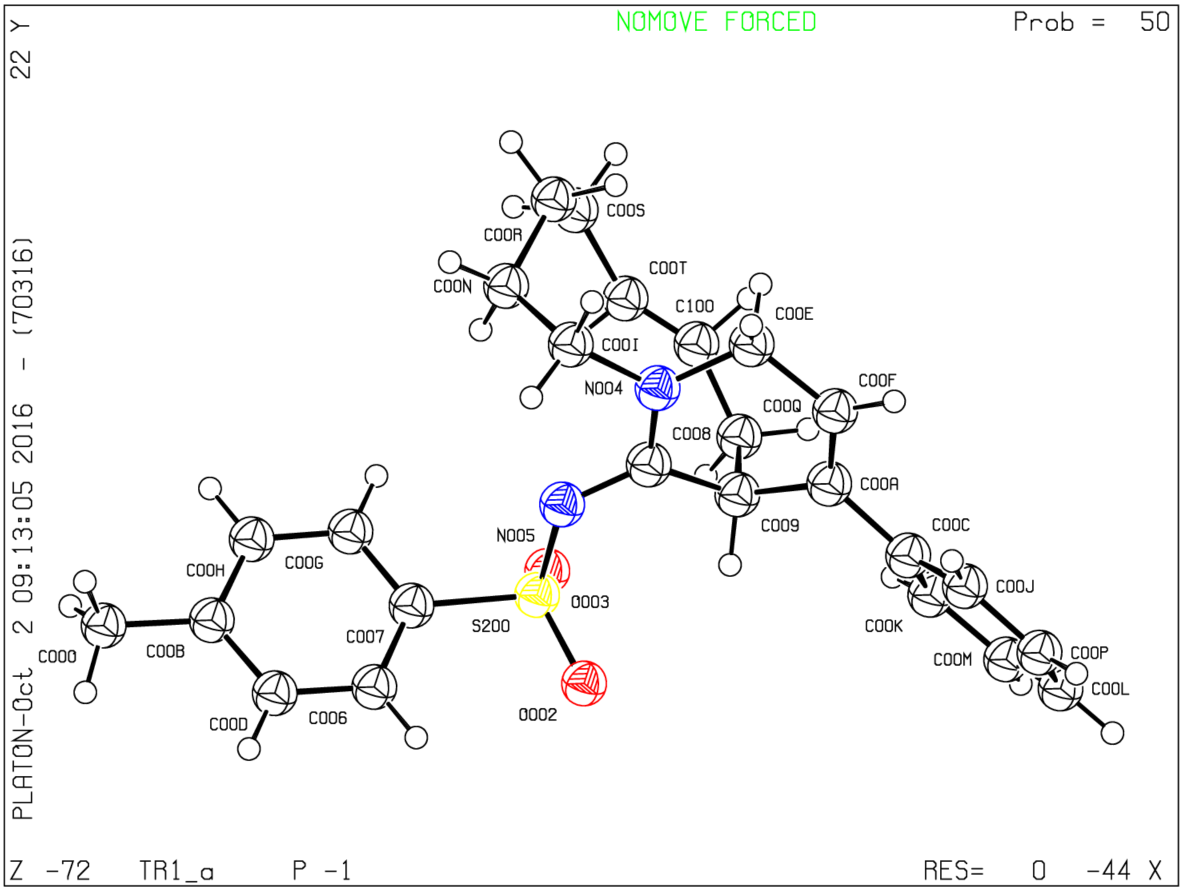


Figure 4.6: ORTEP diagram of **32**.

Crystal structure of compound 38: $C_{38}H_{34}N_2O_2S$; Compound **38** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/n*; *a* = 19.851(4) *b* = 20.966(5) *c* = 5.1137(11) Å, α = 90° β = 90° γ = 90°; *V* = 2128.3(8) $Å^3$; *T* = 296 (2) K; *Z* = 4; ρ_{calc} = 1.219 Mgm^{-3}; $2\theta_{max}$ = 54.76°; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. *R* = 0.0361 (for 4159 reflection $I>2\sigma(I)$), *wR* = 0.0820 which was refined against ǀ*F2*ǀ and S = 0.935 for 258 parameters and 4839 unique reflections. The structure was obtained by direct methods using SHELXS-97.[14] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the fil cycle of refinement as riding over atoms to which they are bonded. $\mu = 0.139\ mm^{-1}$.

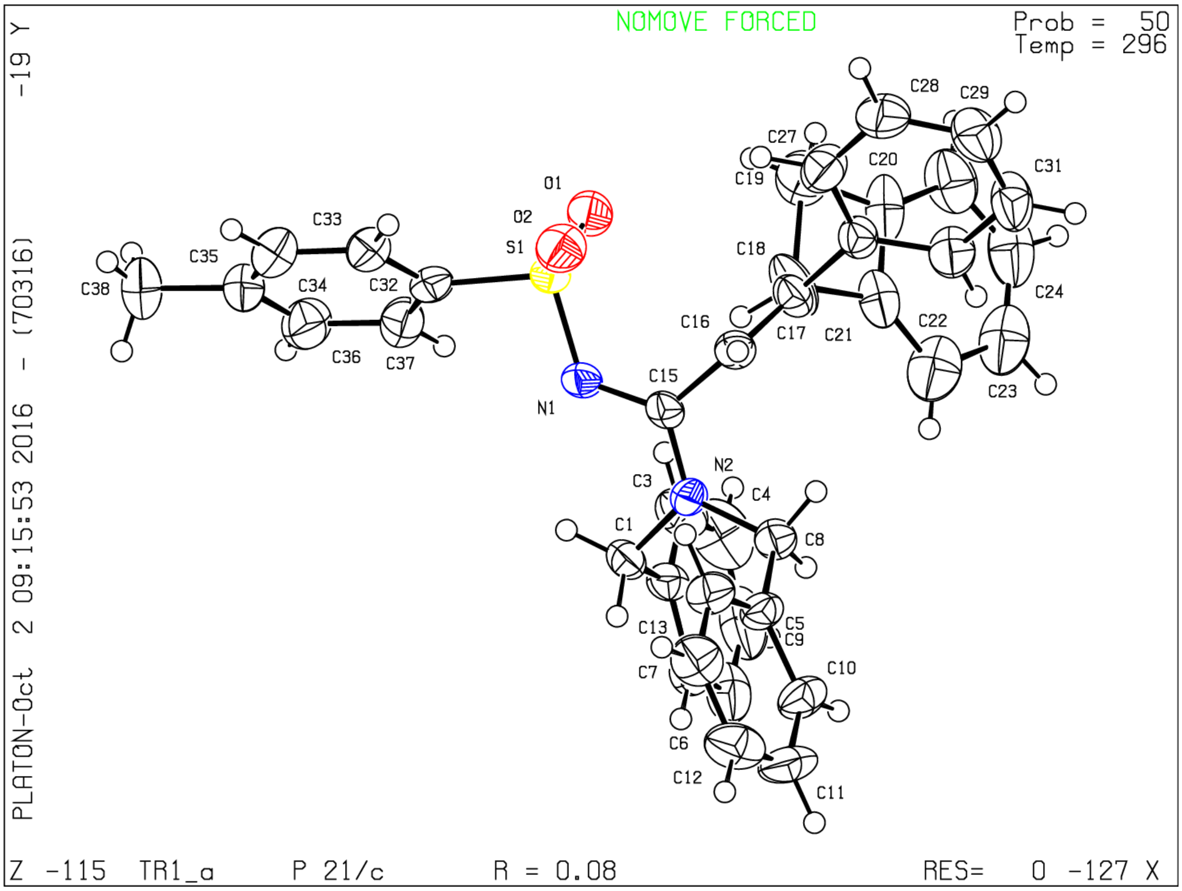


Figure 4.7: ORTEP diagram of **38**.

Crystal structure of compound 27b: $C_{38}H_{34}N_2O_2S$; Compound **27b** was crystallized from slow evaporation of CH_2Cl_2/hexane at room temperature. A colorless cubic shaped crystal with approximate dimensions 0.185 x 0.161 x 0.058 mm gave an Orthorhombic with space group *P21/n*; a = 19.851(4) b = 20.966(5) c = 5.1137(11) Å, $\alpha = 90^o$ $\beta = 90^o$ $\gamma = 90^o$; V = 2128.3(8) Å^3; T = 296 (2) K; Z = 4; ρ_{calc} = 1.219 Mgm^{-3}; $2\theta_{max} = 54.76^o$; $MoK\alpha\lambda$ = 0.71073 Å. Fine-focus sealed tube source with graphite monochromator. R = 0.0361 (for 4159 reflection $I>2\sigma(I)$), wR = 0.0820 which was refined against $|F2|$ and S = 0.935 for 258 parameters and 4839 unique reflections. The structure was obtained by direct methods using SHELXS-97.[14] All non-hydrogen atoms were refined isotropically. The hydrogen atoms were fixed geometrically in the idealized position and refined in the fil cycle of refinement as riding over atoms to which they are bonded. $\mu = 1.334\ mm^{-1}$.

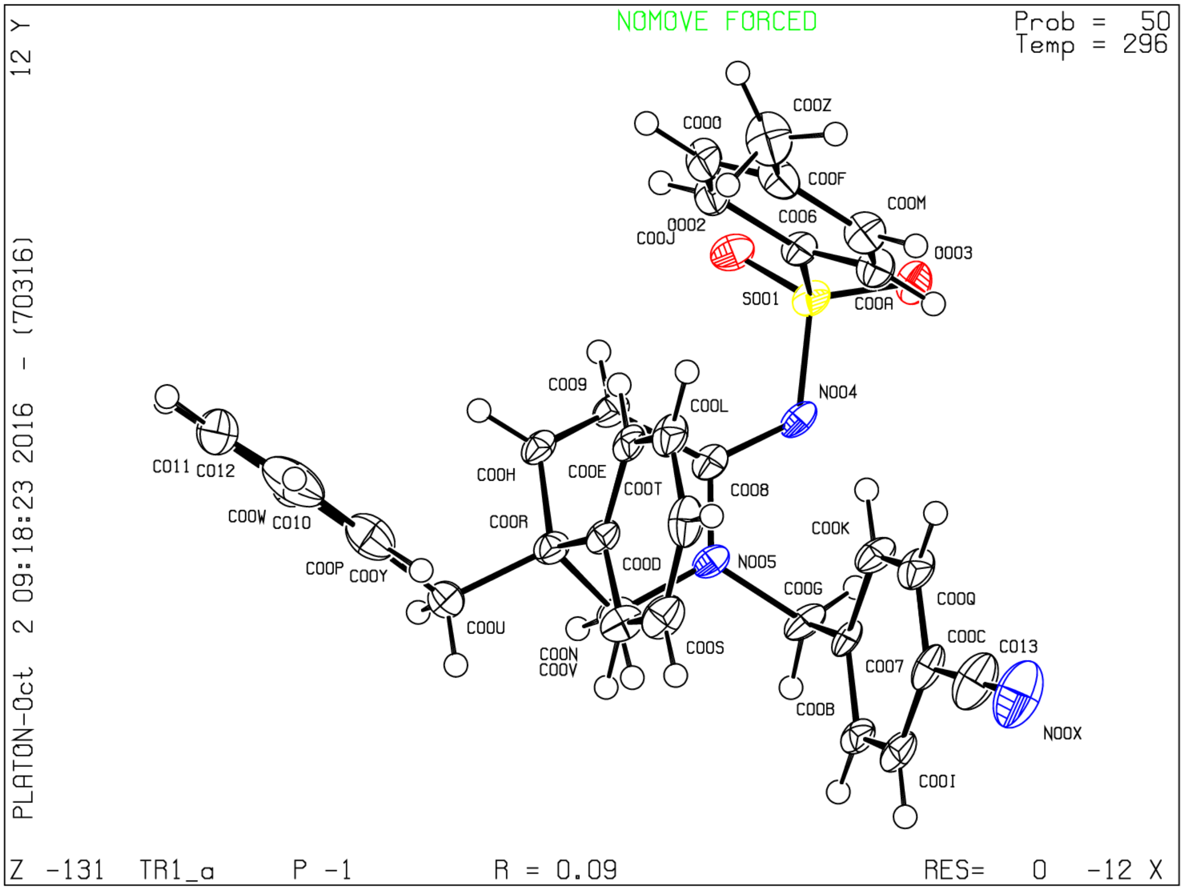


Figure 4.8: ORTEP diagram of **27b**.

4.6 NMR Data:

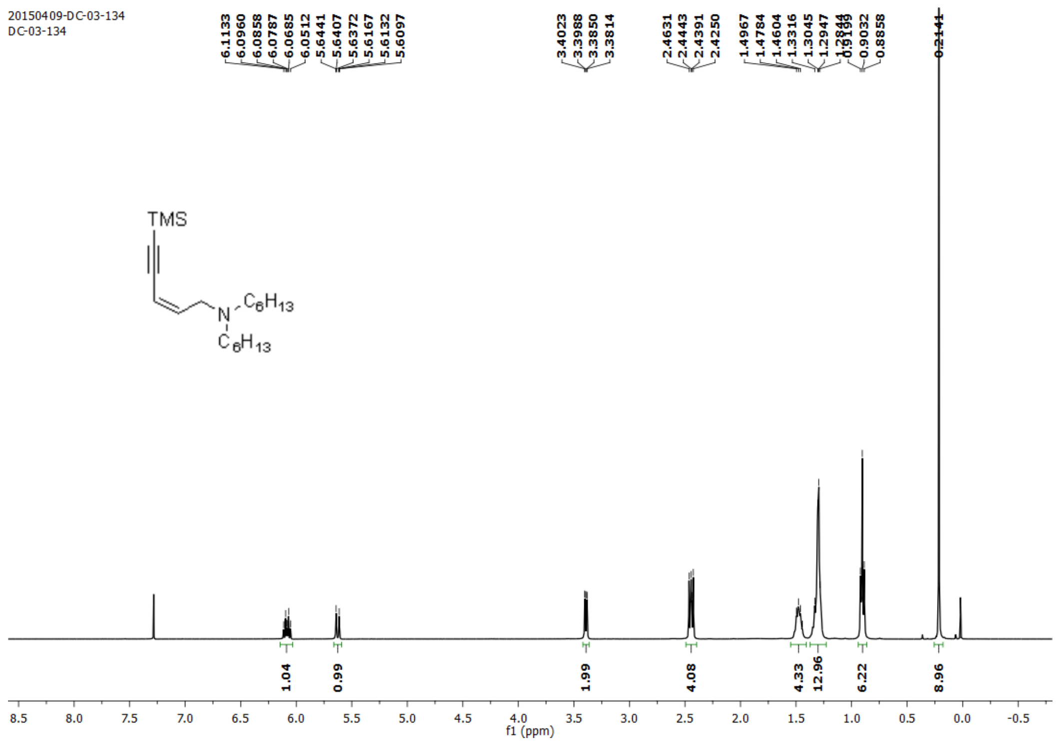


Figure 4.9: ^{1}H NMR spectra of **1** in $CDCl_3$.

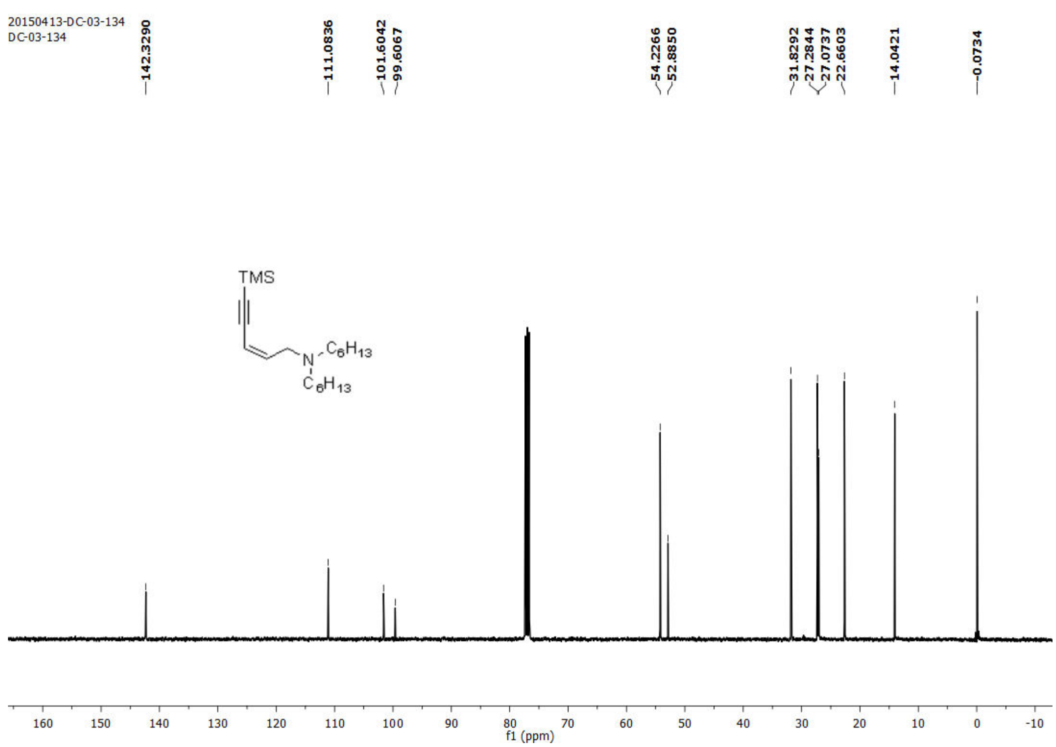


Figure 4.10: ^{13}C NMR spectra of **1** in $CDCl_3$.

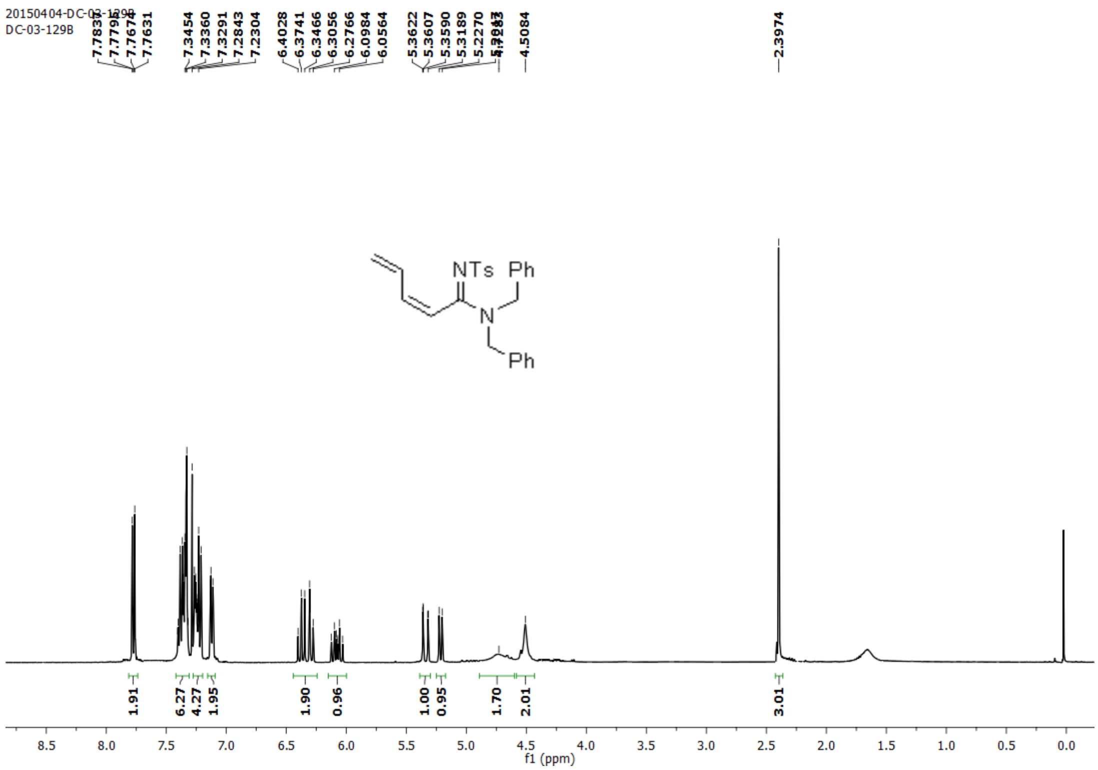


Figure 4.11: ^{1}H NMR spectra of **12a** in $CDCl_3$.

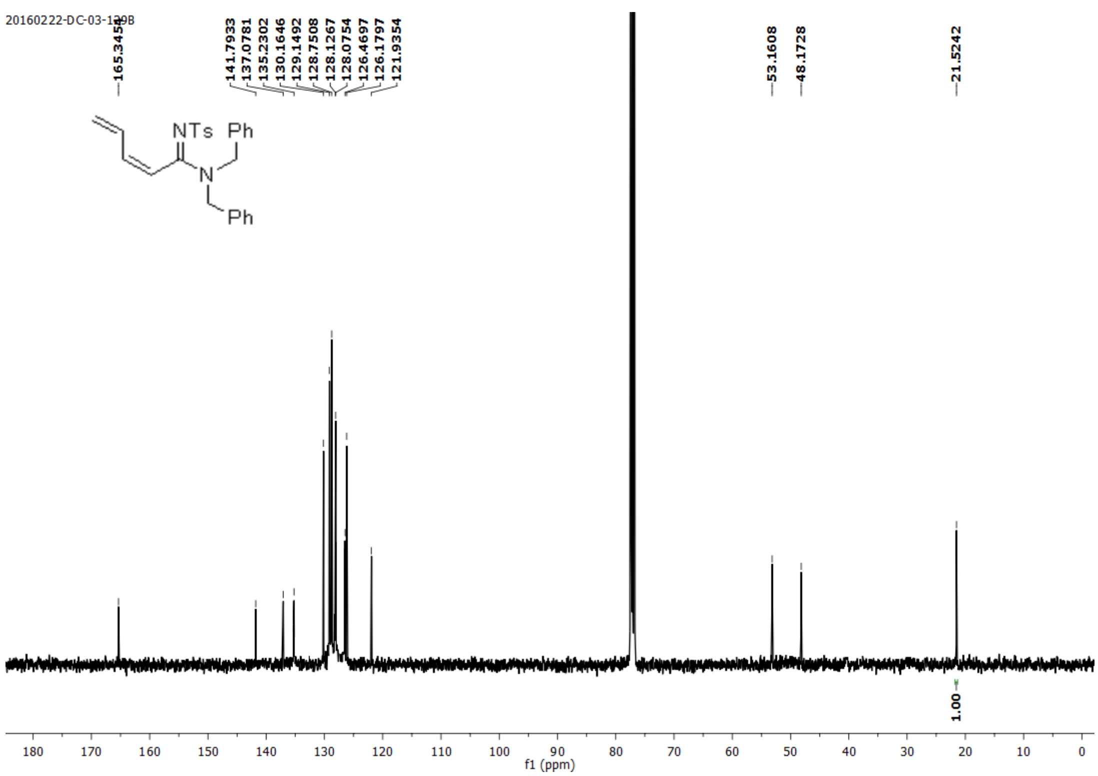


Figure 4.12: ^{13}C NMR spectra of **12a** in $CDCl_3$.

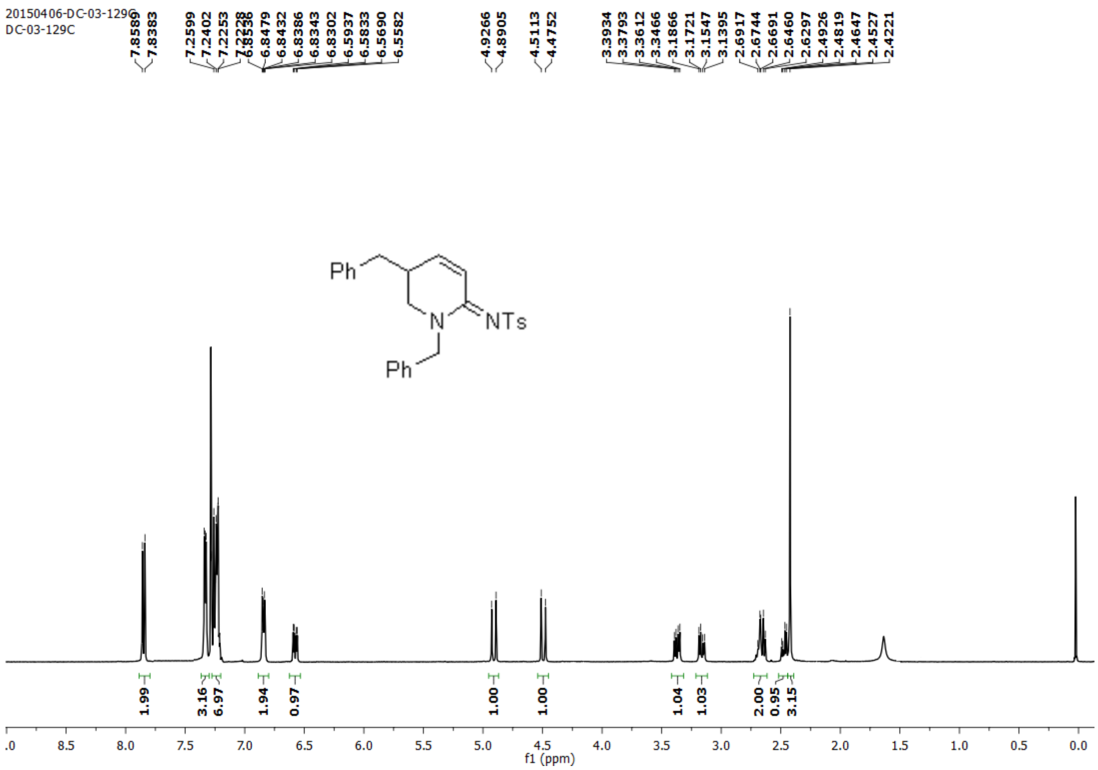


Figure 4.13: ^{1}H NMR spectra of **12b** in $CDCl_3$.

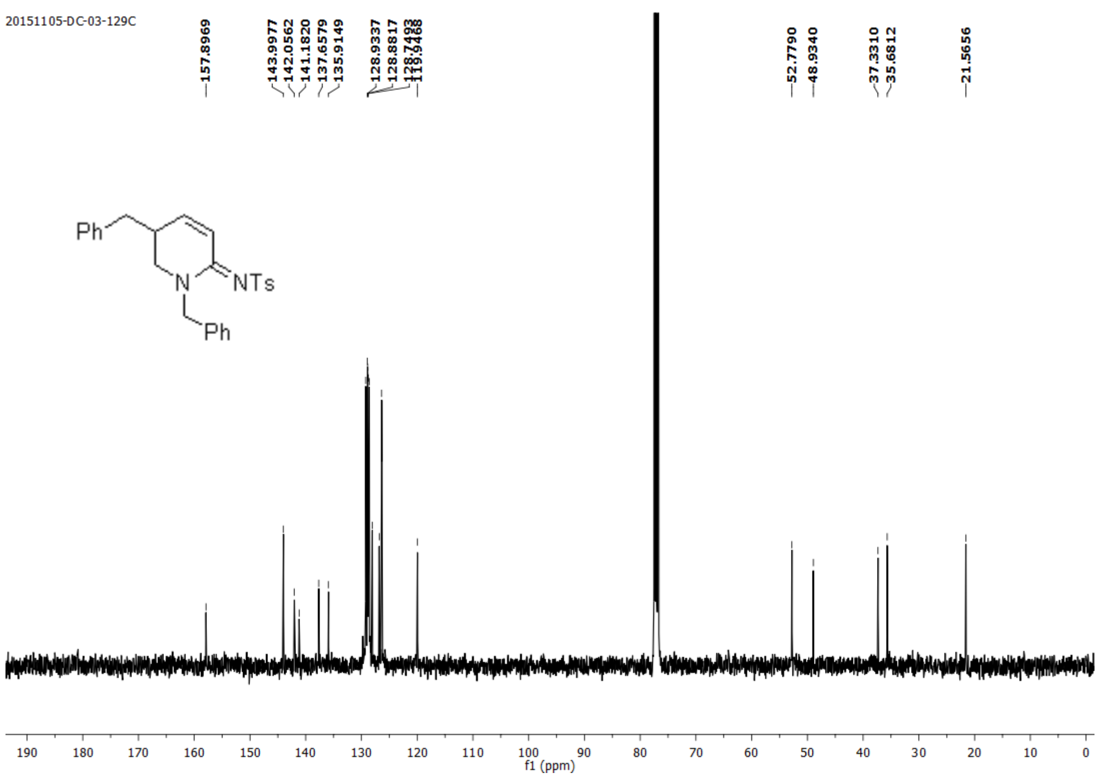


Figure 4.14: ^{13}C NMR spectra of **12b** in $CDCl_3$.

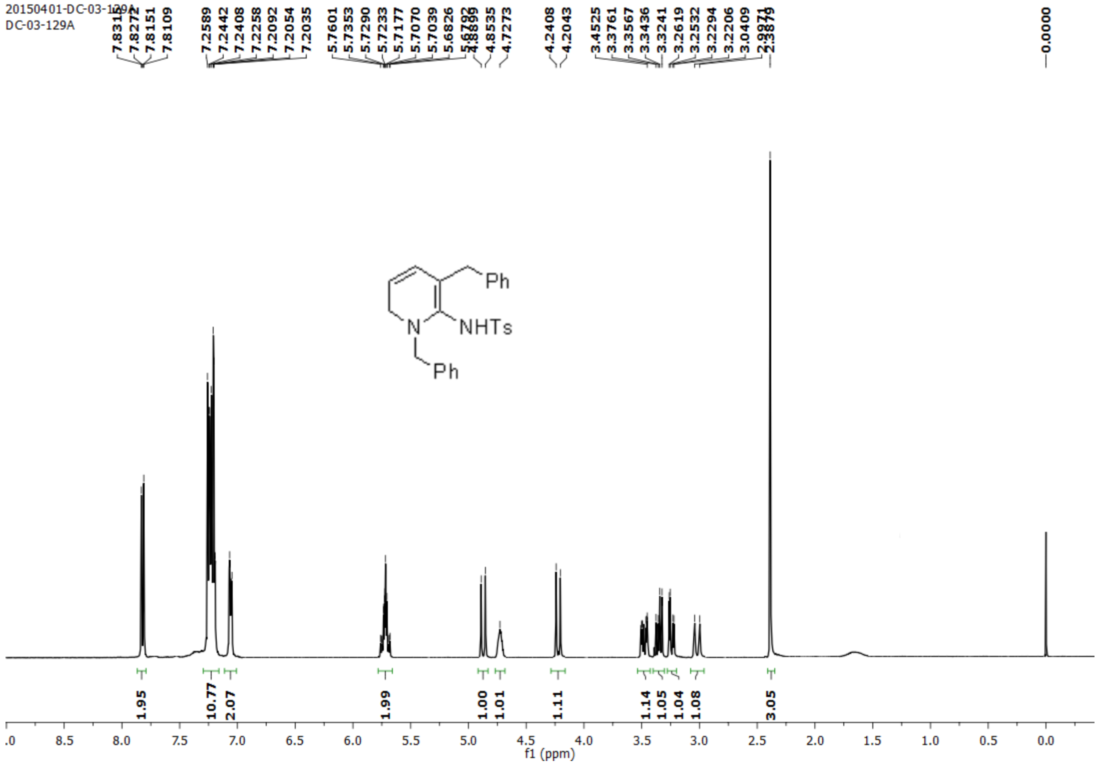


Figure 4.15: ^{1}H NMR spectra of **12c** in $CDCl_3$.

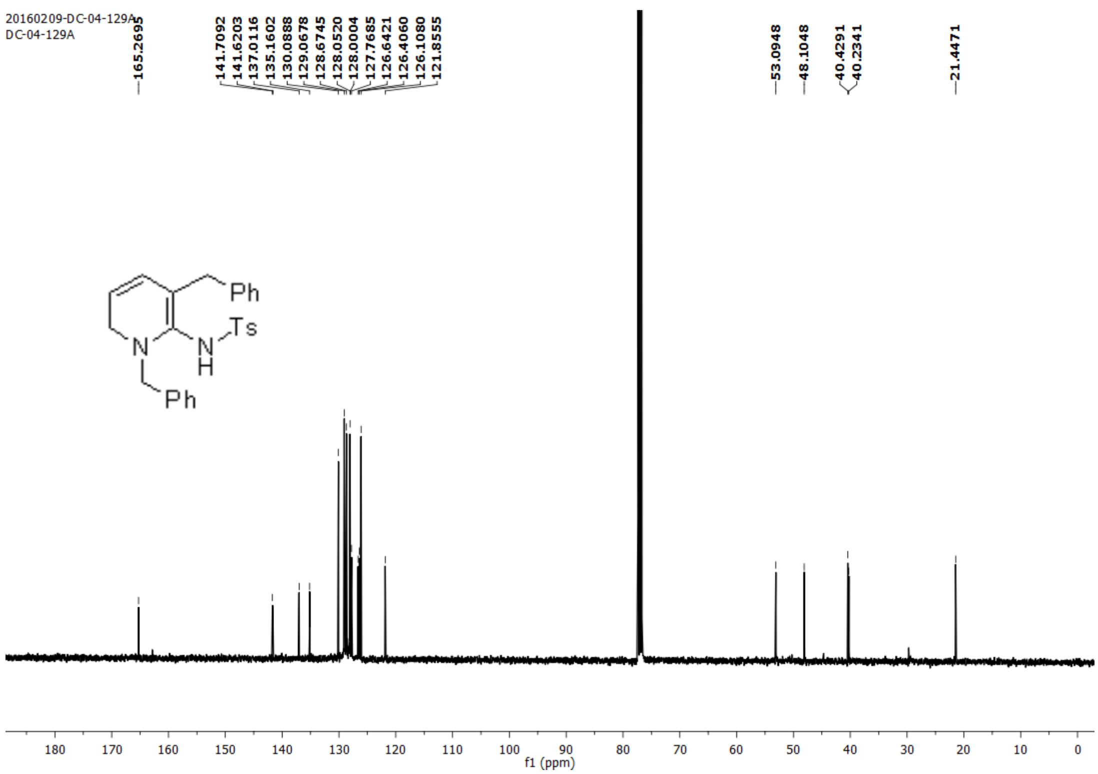


Figure 4.16: ^{13}C NMR spectra of **12c** in $CDCl_3$.

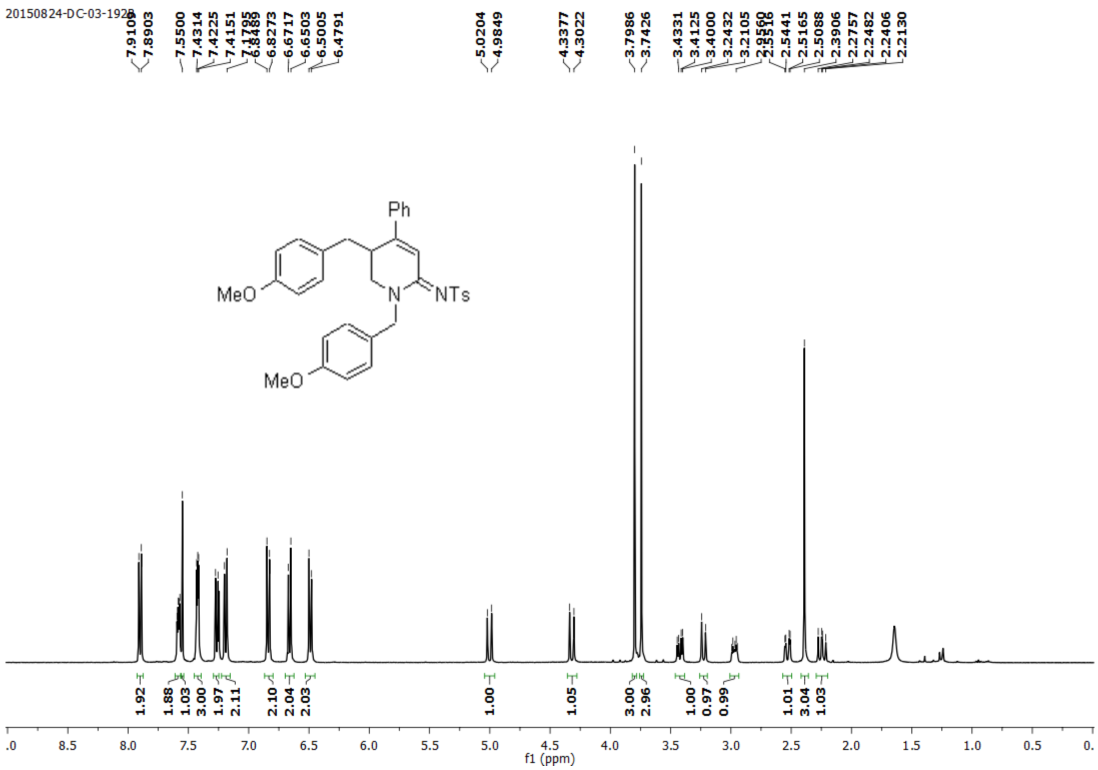


Figure 4.17: ^{1}H NMR spectra of **25b** in $CDCl_3$.

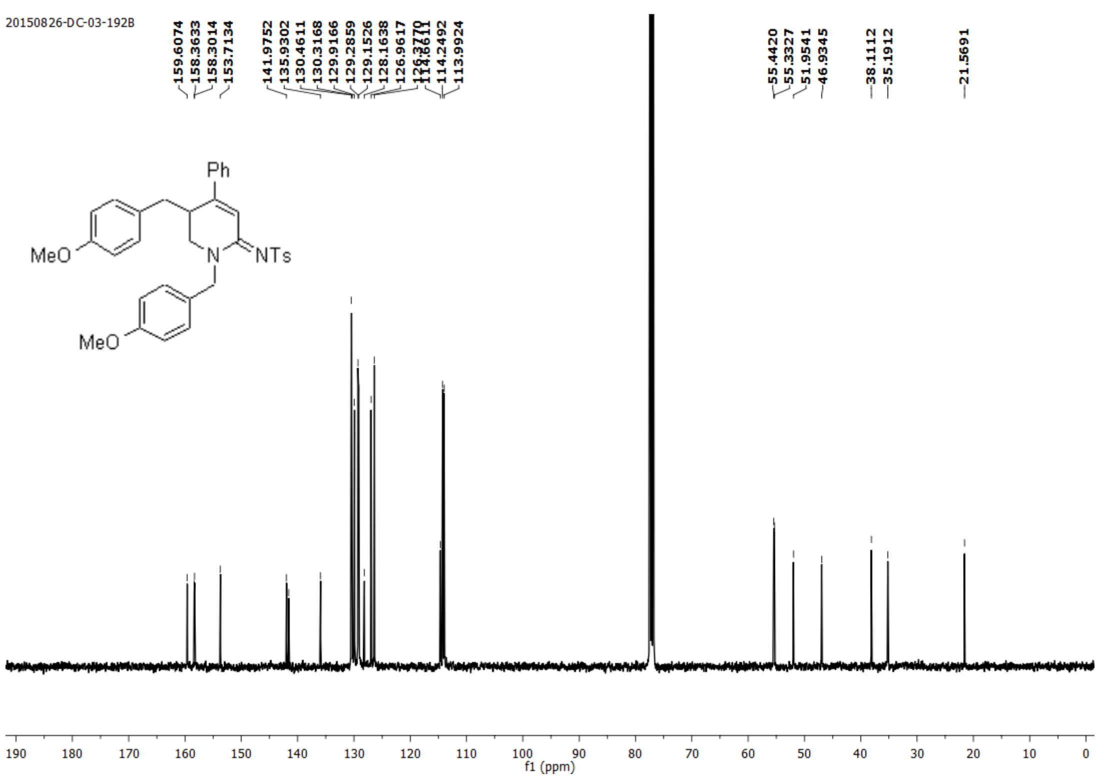


Figure 4.18: ^{13}C NMR spectra of **25b** in $CDCl_3$.

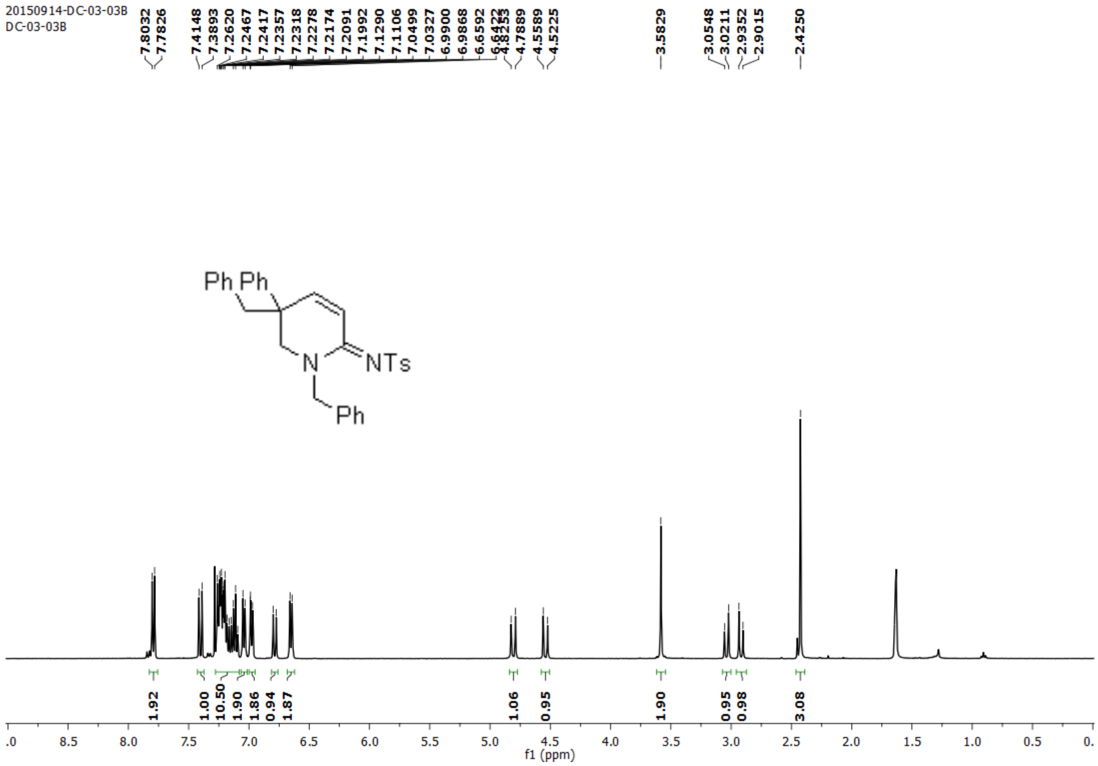


Figure 4.19: ^{1}H NMR spectra of **13b** in $CDCl_3$.

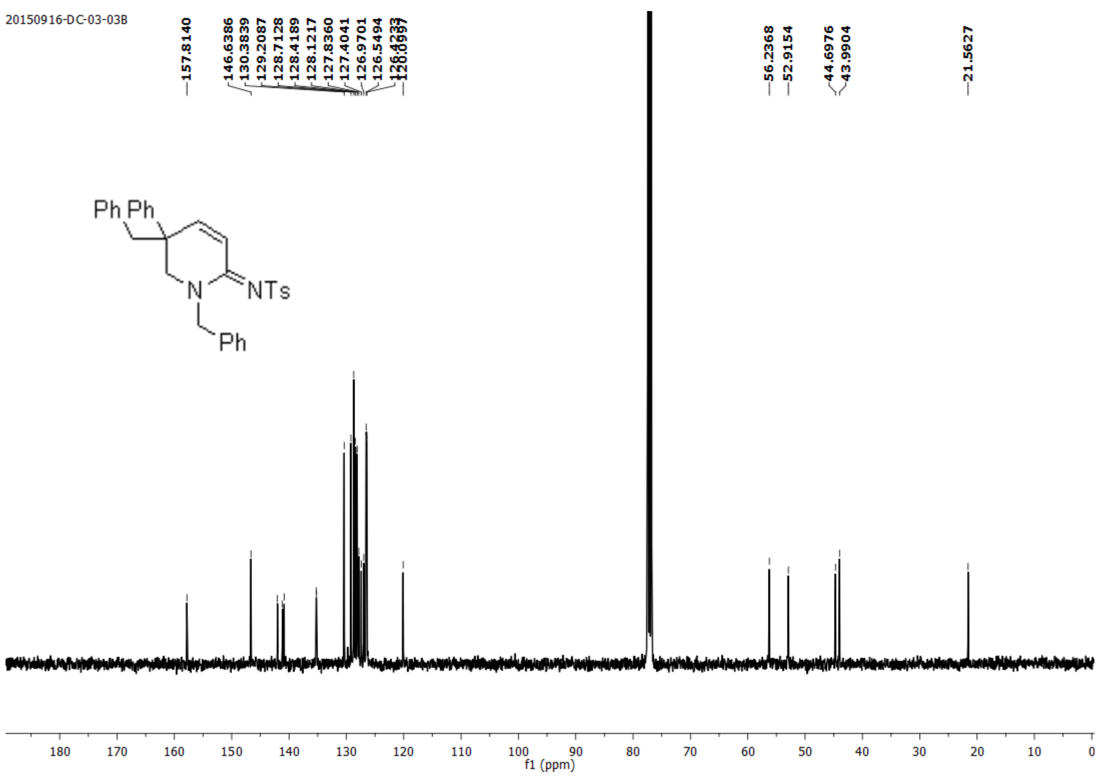


Figure 4.20: ^{13}C NMR spectra of **13b** in $CDCl_3$.

4.7 References

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