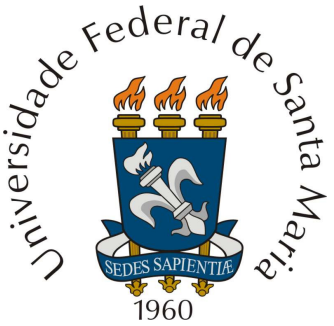

UFSM

PhD THESIS

SYNTHESIS OF CHIRAL β-AMINO ORGANOCHALCOGEN DERIVATIVES OF AZIRIDINES

By

SYED MUHAMMAD SALMAN

PPGQ

Santa Maria, RS, Brasil

2011

SYNTHESIS OF CHIRAL β-AMINO ORGANOCHALCOGEN DERIVATIVES OF AZIRIDINES

By

SYED MUHAMMAD SALMAN

Doctoral thesis submitted to the Graduate Program in Chemistry,
Research Area of Organic Chemistry
at the Universidade Federal de Santa Maria (UFSM, RS),
in partial fulfillment of the requirements for the
Doctor of Philosophy (PhD) in Chemistry

Supervisor: Prof. Dr. Luciano Dornelles
Prof. Dr. Antonio Luiz Braga

The Post Graduate Program in Chemistry

Federal University of Santa Maria

Santa Maria, RS, Brasil

2011

FEDERAL UNIVERSITY OF SANTA MARIA
FACULTY OF NATURAL AND EXACT SCIENCES
GRADUATE PROGRAM IN CHEMISTRY

The undersigned examining committee, approved the thesis entitled

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SYED MUHAMMAD SALMAN

as partial fulfillment of the requirements for the degree of
PhD in Chemistry

EXAMINING COMMITTEE:

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Prof. Dr. Oscar Endrigo Dorneles Rodrigues - UFSM

Prof. Dr. Robert Alan Burrow - UFSM

Prof. Dr. Helmoz Roseniaim Appelt - UNIFRA

DECLARATION

I declare that this dissertation entitled ***"Synthesis of Chiral β-amino organochalcogen derivatives of aziridines"*** *is a original record of my doctoral thesis work at the department of organic chemistry,* ***Federal University of Santa Maria-UFSM, Santa Maria, RS, Brazil*** *and the work has not been the basis for the award of any Degree, Diploma, Association, Fellowship or other similar like of this or any other university.*

Syed Muhammad Salman

To my beloved parents

Acknowledgment

My research work would have not been possible without the nice and general support of the Academy of Science for the Third World(TWAS) and the Brazilian National Council for the Scientific Development (CNPq) i.e. **TWAS-CNPq** for awarding me the doctoral fellowship and I cordially acknowledge their financial

I would like to express my heartious, deepest and most sincere gratitude to my supervisor **Prof. Dr. Antonio Luiz Braga,** Department of Chemistry, Federal University of Santa Catarina-UFSC, Florianopolis, Brazil and **Prof. Dr. Luciano Dornelles,** Department of Chemistry, Federal University of Santa Maria-UFSM, Brazil for their support, friendly behavior, nice company and encouragement, both in fulfillment of this thesis and developing my academic interests. Their constructive comments from the initial conception to the end of this work are highly appreciated.

Special thanks to **Prof. Dr. Oscar Endrigo Dornelles Rodrigues** Department of Chemistry, Federal University of Santa Maria-UFSM, Brazil for their unforgettable and immemorial efforts and contributions to the proof reading of this manuscript as well as their friendly behavior throughout this course of study.

Thanks are due to our lab members and co-workers their support and congenial atmosphere at the laboratory. I also pay thanks to my friends for providing support and friendship that I needed.

I would like to express my deepest sense of gratitude to my mother, brothers, sisters and all family members who remain constant source of special dowas and encouragement throughout my academic career.

Syed Muhammad Salman

ABSTRACT

PhD Thesis

Graduate Program in Chemistry

Universidade Federal de Santa Maria

SYNTHESIS OF CHIRAL β-AMINO ORGANOCHALCOGEN DERIVATIVES OF AZIRIDINES

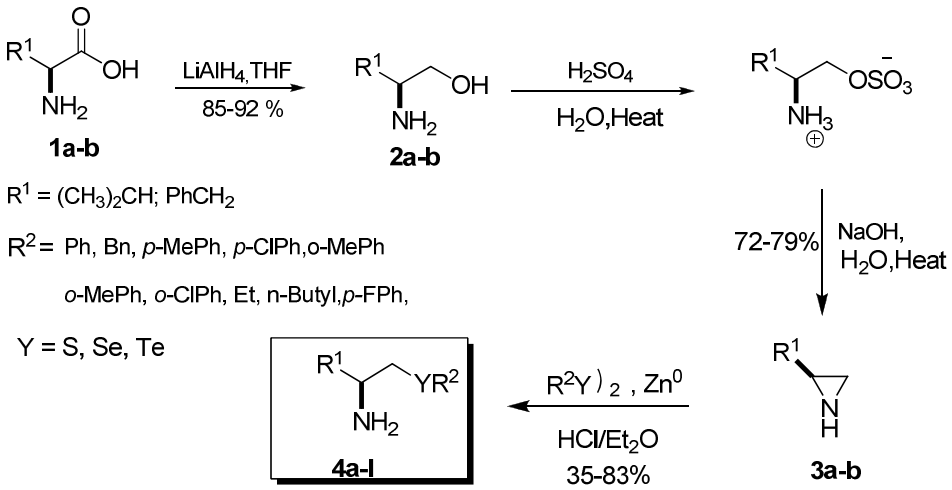
AUTHOR: SYED MUHAMMAD SALMAN

SUPERVISOR: PROF. Dr. LUCIANO DORNELLES

PROF. Dr. ANTONIO LUIZ BRAGA

Date and place of defense: Santa Maria, February 25th, 2011.

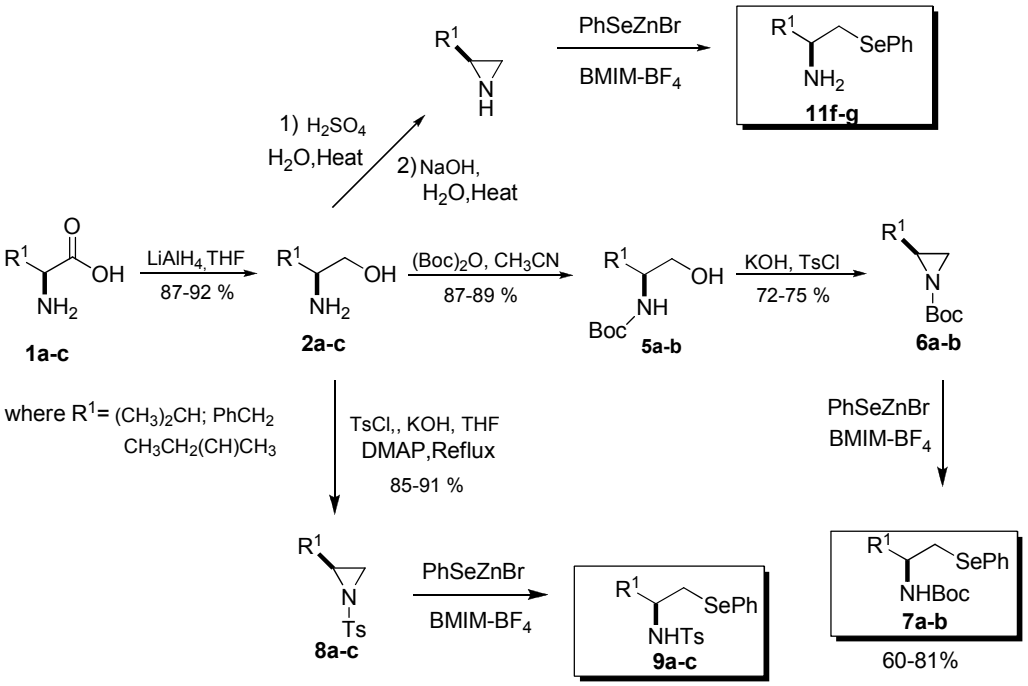
In the present work different methodologies were developed to prepare chiral β- thio, seleno and telluro amines and its derivatives. In the first project we have prepared these compounds in good yields by reaction of unprotected aziridines and diaryl and dialkyl diselenides by employing an acid biphasic system. This easy and straight method allowed a simple preparation of selenium-containing compounds with wide structural diversity.



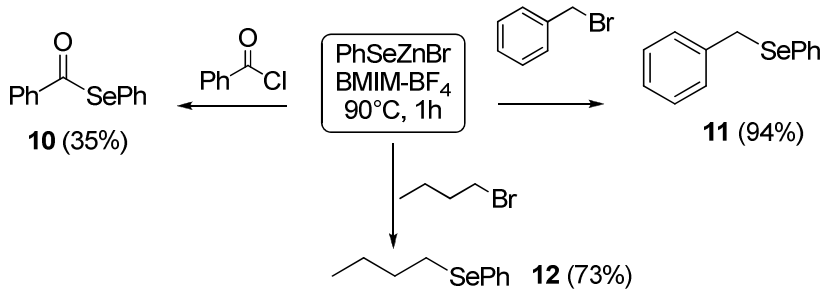
The preparation of these compounds was initially done with the reduction of the respective amino acids (valine and phenylalanine) using lithium aluminum hydride in THF, giving amino alcohols **2**. The chiral aziridines **3** were obtained in two steps in good yields by treatment of free amino alcohols with sulphuric acid followed by potassium hydroxide in water with heating system.

In this methology the selenium was efficiently introduced to the chiral aziridines using zinc selenolate anions, generated by the treatment of commercially available zinc with diaryl diselenides in the presence of HCl solution, via the ring-opening reactions. The selenolates attack the less hindered carbon of aziridines **3**, furnishing the chiral β- thio, seleno and telluro amines **4** by using different dichalcogenides.

Similarly herein was also reported a neutral and smooth protocol to prepare β-seleno amines by using a bench-stable phenyl zinc selenolate specie (PhSeZnBr), to promote the ring opening reaction of protected and unprotected aziridines in ionic liquid. The desired products (**7**, **9** or **11**) were obtained in good to excellent yields, with short reaction time and with the advantage of the ability to recycle the reaction media, which represents an environmentally benign approach.



This protocol was also extended to other electrophiles, and useful compounds such as selenoesters, and diorganyl selenides were synthesized in good to excellent yields.



Keywords: Aziridine ring opening, β-seleno amines, Ionic liquids, Phenyl Selenium Zinc Bromide, Eco friendly protocol.

RESUMO

Tese de Doutorado

Programa de Pós-Graduação em Química

Universidade Federal de Santa Maria

SÍNTESE DE β-AMINO ORGANOCALCOGÊNIOS QUIRAIS DERIVADOS DE AZIRIDINAS

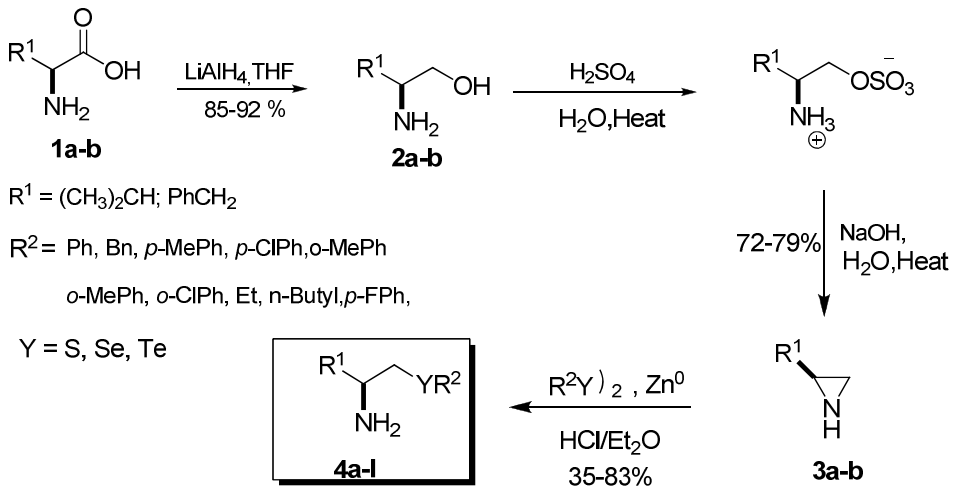
AUTOR: SYED MUHAMMAD SALMAN

ORIENTADOR: PROF. Dr. LUCIANO DORNELLES

PROF. Dr. ANTONIO LUIZ BRAGA

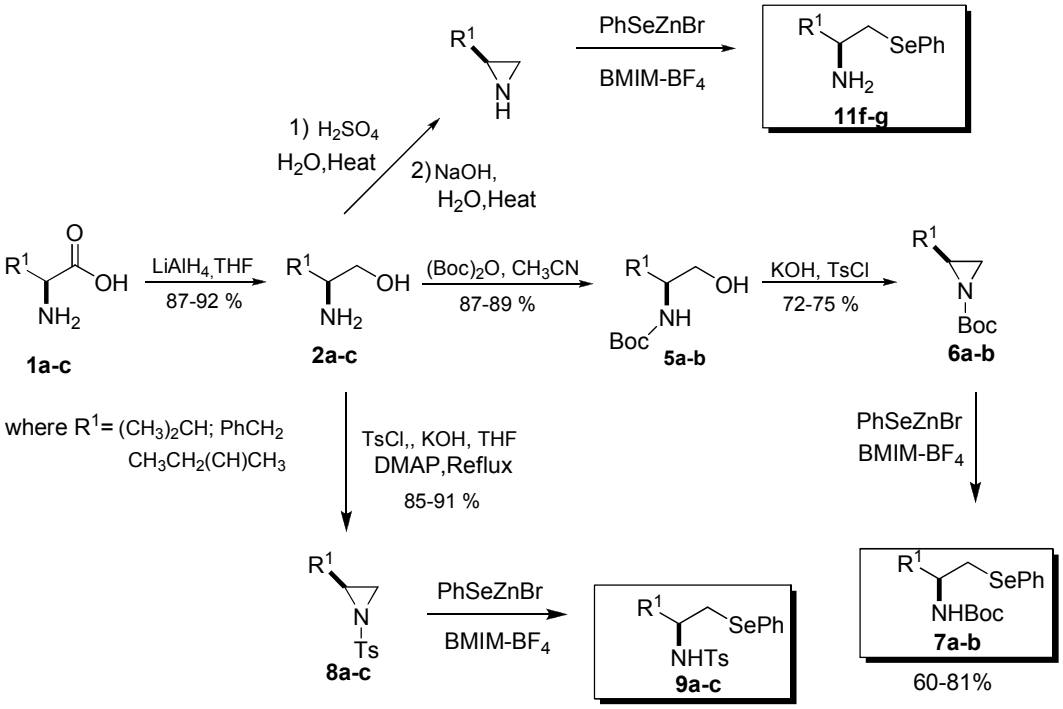
Data e Local da Defesa: Santa Maria, 25 de fevereiro de 2011

No presente trabalho desenvolveu-se novas metodologias para a síntese de β- tio, seleno e teluro-aminas quirais e seus derivados no primeiro método. Esses compostos foram facilmente preparados através de reações de abertura de aziridinas desprotegidas com diaril ou dialquil disselenetos, empregando um sistema bifásico (ácido clorídrico:éter etílico) e zinco como agente redutor. Essa estratégia sintética flexível permitiu a preparação de uma série de compostos de selênio com grande diversidade estrutural.

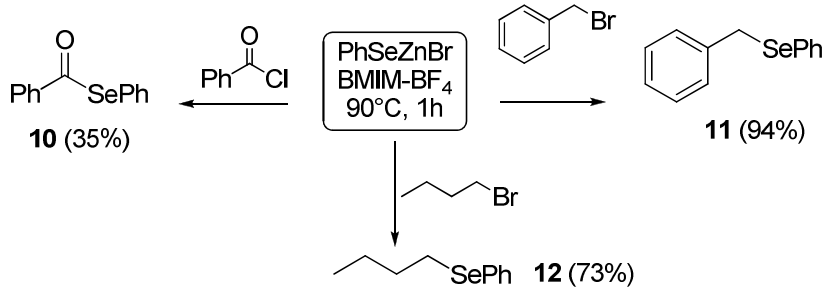


A preparação destes compostos foi realizada inicialmente por meio da redução dos respectivos *L*-aminoácidos (valina e fenilalanina), usando hidreto de lítio de alumínio em THF, levando à formação dos respectivos aminoálcoois **2**. As aziridinas quirais **3** foram obtidas em duas etapas, com bons rendimentos, inicialmente os aminoálcoois foram tratados com ácido sulfúrico seguido de tratamento com hidróxido de potássio em água, sob aquecimento e posterior destilação.

β-selenoaminas protegidas também foram preparadas, utilizando uma metodologia neutra, através da reação de abertura de aziridinas protegidas e desprotegidas por uma espécie de selenolato estável de zinco (PhSeZnBr), em líquido iônico. Os produtos desejados (**7**, **9** ou **11**) foram obtidos em bons rendimentos, em condições reacionais suaves, e em curtos tempos reacionais com a vantagem de reciclar o meio reacional, e reutilizá-lo novamente em um novo ciclo reacional.



Esse último método também foi extendido a outras espécies eletrofílicas, permitindo assim a preparação de selenoésteres e selenetos de diorganoíla em rendimentos satisfatórios.



Palavras-chave: abertura de aziridina, β-seleno aminas, líquidos iônicos, brometo de fenilselênio zinco, protocolo de baixo impacto ambiental.

LIST OF FIGURES

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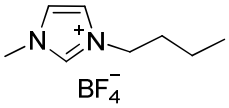
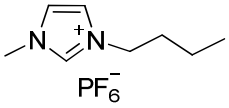
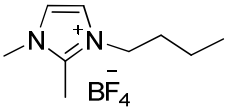
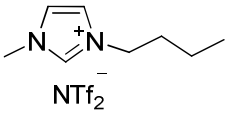
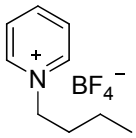
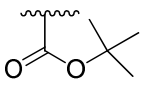
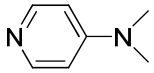
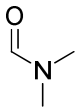
LIST OF SYMBOLS AND ABBREVIATIONS

IL	ionic liquid	
BMIM-BF_4	1-butyl-3-methylimidazolium Tetrafluoroborate	
BMIM-PF_6	1-butyl-3-methylimidazolium hexafluorophosphate	
BMMIM-BF_4	1,2-dimethyl-3-butylimidazoilum Tetrafluoroborate	
BMIM-NTf_2	1-butyl-3-methylimidazolium Bis(trifluoromethane)sulfonamide	
Bpy-BF_4	1-butyl-pyridinuim tetrafluoroborate	
Boc	tert-butyloxycarbonyl	

DMAP	4- N,N-dimethyl aminopiridine	
Tscl	Tosyl chloride	
THF	Tetrahydrofuran	
DMF	dimethylformadide	

CHAPTER 1

Introduction and objectives

Introduction and objectives

Organochalcogen compounds have become an attractive synthetic tool since selenium and sulfur containing groups serve as an important auxiliary function in many synthetic sequences.[1] They are of key interest to synthetic chemists due to the biological importance of oganoselenium compounds. In addition to the synthetic importance, simple organosulfur and organoselenium compounds exhibit many useful biological and medicinal properties. They are generally targeted compounds with antioxidant, antitumor, and antimicrobial activity and many of these compounds are competitive inhibitors for target proteins.[2]

Due to the recognized importance of stereochemistry in the pharmaceutical field, agrochemicals, flavor and fragrance of the preparation and study of enatiomerically pure or enriched are of particular relevance. For example, worldwide sales of enatiomerically pure drugs in 2002 reached the figure of U.S. $ 159 billion and estimates are that the preparation of chiral pharmaceuticals continues to increase in coming years.[3] Thus, the enantioselective synthesis of chiral compounds is an important field of study for synthetic chemicals.

Additionally, various methods for synthesis of chiral compounds of selenium have been developed in recent years and are now regarded as an interesting tool for a variety of organic transformations.[4]

---

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[2] (a) Mugesh, G., H. Singh, *Chem. Soc. Rev.* **2000**, *29*, 347. (b) Mugesh, G., Du Mont, W.W., Sies, H., *Chem. Rev.* **2001**, *101*, 2125. (c) Nogueira,C.W., Zeni,G., Rocha,J. B. T., *Chem. Rev.* **2004**, *104*, 6255. (d) Sarma,B. K., . Mugesh, G.,*Org. Biomol. Chem.* **2008**, *6*, 965. (e) Das, D., Roy,G., and Mugesh, G., *J. Med. Chem.* **2008**, *51,*7313. (f) Bhabak,K. P., Mugesh, G., *Chem. Eur. J.* **2009**, *15*, 9846.

[3](a) Rouhi, A. M. *Chem. Eng. News* **2003**, *81*, 45. (b) Rouhi, A. M. *Chem. Eng. News* **2004**, *82*, 47.

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Furthermore, the chemistry of selenium also plays a significant role in organic chemistry presenting as versatile reagents in organic synthesis and catalysis.[5].

Organic selenium compounds have also attracted considerable attention due to its central role in the synthesis of a large number of biologically active compounds, such as selenocarbohydrates, selenoaminoacids and selenopeptides. Selenium as an integral part of the diet is an essential element in human nutrition, playing significant roles in preventing cancer, immunology, aging, human reproduction and other physiological processes.[6] In fact, organic compounds of selenium has also emerged as an exceptional class of structures that have played key roles in biological processes, acting as a potential therapeutic compounds, ranging from anti-viral and anti-cancer natural food supplements.

Added to this, the biological role of amino acids containing selenium has been intensively studied and the synthesis of selenocysteine derivatives has gained a tremendous interest due to the large number of proteins have been discovered containing this amino acids[8]. In fact, selenocysteine is recognized as the 21st natural amino acid and is found in the peptide chain of several enzymes, among them, glutathione peroxidase, a selenoprotein P, glycine reductase, and thioredoxin reductase. [9]

---

[5] (a) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 835. (b) *Selenium Reagents and Intermediates in Organic Synthesis;* Paulmier, C. Ed.; Pergamon Press: Oxford, 1986. (c) Schmid, G. H.; Garratt, D. G. In *The Chemistry of Double-Bonded Functional Groups;* Patai, S. Ed., Wiley: London,1977; Supp. A, Part 2. (d) Santi, C.; Wirth, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1019. (e) Nishibayashi, Y.; Segawa, K.; Singh, J. D.; Fukuzawa, S. J.; Ohe, K.; Uemura, S. *Organometallics* **1996**, *15*, 370.

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[8] (a) Stadman, T. C. *Annu. Rev. Biochem.* **1996**, *65*, 83. (b) Moroder, R. *J. Peptide Sci.* **2005**, *11,* 187.

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In addition, selenocysteine derivatives can serve as precursors for the synthesis of fatty dihydro amino acids,[10] as these structures that are useful chemo selective electrophiles for the preparation of peptides conjugates .[11]

In this context, the development of new methods for the introduction of groups containing selenium into organic molecules, particularly through the synthesis of stereo-controlled compounds, still comes as a significant challenge. The reduction of Se-Se, especially the cleavage of diphenyl and diaryl diselenides, has aroused great interest for the preparation of non symmetrical diorganyl selenides. The chemical cleavage of Se-Se bonds in the form diaryl diselenide has been carried out with reducing agents such as $NaBH_4$, Na/NH_3, Bu_3SnH, MoS_4^{2-} $LiAlH_4$[12], and indium salts[13]. In this way, Zinc metal and its salts have received considerable attention due to its incredible effectiveness in many synthetic operations.[14, 15],

Moreover, functionalized chiral aziridines represent a system containing a ring of three members and considered to be very valuable in modern organic chemistry, due to its versatility as a recognized manufacturer of synthetic organic compounds and chiral synthesis of many biologically active compounds.[16]

The biological and medicinal properties of selenium and organoselenium compounds are also increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.

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[10] Hashimoto, K.; Sakai, M.; Okuno, T. Shirahama, H. *Chem. Commun*. **1996**, 1139.

[11] Zhu, Y.; van der Donk, W. A. *Org. Lett.* **2001**, *3*, 1189.

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[14] a) Bieber, L. W.; Sá, A. C. P. F.; Menezes, P. H.; Gonçalves, S. M. C. *Tetrahedron Lett.* **2001**, *42*, 4597-4599. b) Andrade, F. M.; Massa, W.; Peppe, C.; Uhl, W. *J. Organomet. Chem.* **2005**, *690*, 1294-1299. c) Movassagh, B.; Shamsipoor, M. *Synlett* **2005**, 121-122. d) Santi, C.; Santoro, S.; Testaferri, L.; Tiecco, M. *Synlett* **2008**, 1471-1474.

[15] Braga, A. L.; Schneider, P. H.; Paixão, M. W.; Deobald, A. M. *Tetrahedron Lett*. **2006**,*47*, 7195-7198

[16] (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ress, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, p 47; (b) Kump, J. E. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, **1991**; 7, p 469.

Based on the general idea of obtaining organic compounds containing selenium from raw materials of low cost and easy way to obtain, amino acids appear as an interesting platform for the chiral preparation of new compounds. Our research group has been working in the area of asymmetric synthesis using amino acids as a source of chirality. Several catalytic systems have been developed and successfully employed in asymmetric reactions.[17, 18, 19, 20.]

Coupled with the success achieved in the development of chiral compounds containing selenium were used as catalysts in enantioselective reactions, such as the addition of diethylzinc to aldehydes[21], conjugate addition of Grignard reagents to enones[22] and allylic substitution catalyzed by palladium[23], it was planned to prepare protected and unprotected β -seleno-chiral amines, by using ionic liquid as a reaction medium as well as in biphasic system.(Figure 1)

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[17] Addition of diethyl zinc to aldehydes. (a) Braga, A. L.; Appelt, H. R.; Schneider, P. H.; Silveira, C. C.; Wessjohann, L. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1733. (b) Braga, A. L.; Appelt, H. R.; Schneider, P. H.; Rodrigues, O. E. D.; Silveira, C. C.; Wessjohann, L. A. *Tetrahedron* **2001**, *57*, 3291. (c) Braga, A. L.; Vargas, F.; Andrade, L. H.; Silveira, C. C. *Tetrahedron Lett.* **2002**, *43*, 2335. (d) Braga, A. L.; Rubim, R. M.; Schrekker, H. S.; Wessjohann, L. A.; de Bolster, M. W. G.; Zeni, G.; Sehnem, J. A. *Tetrahedron: Asymmetry* **2003**, *14*, 3291. (e) Braga, A. L.; Milani, P.; Paixao, M. W.; Zeni, G.; Rodrigues, O. E. D.; Alves, E. F. *Chem. Commun.* **2004**, 2488. (f) Braga, A. L.; Ludtke, D. S.; Paixão, M. W.; Wessjohann, L. A.; Schneider, P. H. *J. Mol. Cat. A: Chemical* **2005**, *229*, 47. (g) Braga, A. L.; Alves, E. F.; Silveira, C. C.; Zeni, G.; Appelt, H. R.; Wessjohann, L. A. *Synthesis* **2005**, 588.

[18] addition of alkynyl zinc to aldehudes. Braga, A. L.; Appelt, H. R.; Silveira, C. C.; Wessjohann, L. A.; Schneider, P. H. *Tetrahedron* **2002**, *58*, 10413.

[19] Addition of boronic acids to aldehydes. Braga, A. L.; Lüdtke, D. S.; Vargas, F.; Paixão, M. W. *Chem. Commun.* **2005**, 2512.

[20] allylic subsitution by palladium: (a) Schneider, P. H.; Schrekker, H. S.; Silveira, C. C.; Wessjohann, L. A.; Braga, A. L. *Eur. J. Org. Chem.* **2004**, 2715. (b) Braga, A. L.; Paixão, M. W.; Milani, P.; Silveira, C. C.; Rodrigues, O. E. D.; Alves, E. F. *Synlett* **2004**, 1297. (c) Braga, A. L.; Sehnem, J. A.; Lüdtke, D. S.; Zeni, G.; Silveira, C. C.; Marchi, M. I. *Synlett* **2005**, 1331.

[21] (a) Braga, A. L.; Rodrigues, O. E. D.; Paixão, M. W.; Appelt, H. R.; Silveira, C. C.; Bottega, D. P. *Synthesis* **2002**, 2338. (b) Braga, A. L.; Paixão, M. W.; Ludtke, D. S.; Silveira, C. C.; Rodrigues, O. E. D. *Org. Lett.* **2003**, *5*, 2635.

[22] Braga, A. L.; Silva, S. J. N.; Lüdtke, D. S.; Drekener, R. L.; Silveira, C. C.; Rocha, J. B. T.; Wessjohann, L. A. *Tetrahedron Lett.* **2002**, *43*, 7329.

[23] (a) Braga, A. L.; Paixão, M. W.; Marin, G. *Synlett* **2005**, 1675. (b) Braga, A. L.; Vargas, F.; Sehnem, J. A.; Braga, R. C. *J. Org. Chem.* **2005**, *70,* 9021. (c) Braga, A. L.; Lüdtke, D. S.; Paixão, M. W.; Alberto, E. E.; Stefani, H. A.; Juliano, L. *Eur. J. Org. Chem.* **2005**, 4260. (d) Braga, A. L.; Lüdtke, D. S.; Sehnem, J. A.; Alberto, E. E. *Tetrahedron* **2005**, *61,* 11664. (e) Braga, A. L.; Lüdtke, D. S.; Alberto, E. E. *J. Braz. Chem. Soc.* **2005**,

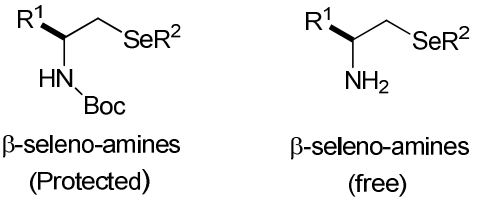
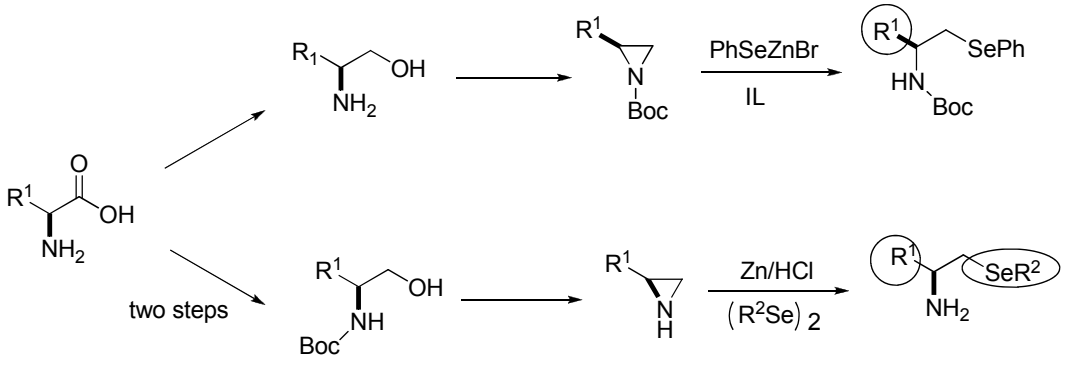


Figure 1. Structures of free and protected chiral β -seleno- amines.

Additionally, the preparation of these compounds should be followed by a flexible synthetic route, to allow a large structural variety, thus demonstrating the achievement of combinatorial small collection of these chiral compounds containing selenium.

It was planned, then the synthesis of compounds that present the selenium atom bound to an sp^3 carbon of an alkyl group, which gives it a fairly unique feature with respect to virtually all the compounds already described. The strategy adopted to lead to the generation of compounds with the profile described above involved the fewest possible steps, raw materials for low cost and high availability. Indeed, as can be seen in scheme 1, initially was the synthesis of free as well as functionalized chiral aziridines as a starting material from raw materials of L-amino acids. Then, the objective was to use a new synthetic and facile strategy for the inclusion of the organoselenium group via regio- and streoselective aziridine ring opening by selenolates anions generated by zinc metal in acidic condition as well bench stable phenyl selenium zinc bromide in ionic liquid.



Scheme 1

For the sake of convenience, this thesis is divided as follows: in Chapter 1, we briefly review the application of aziridines in asymmetric synthesis, emphasizing the reactions of aziridine ring opening in a regio-and streoselective manner. Similarly in Chapter 1, we also comment on the applications of zinc, PhSeZnBr, some ionic liquids and synthesis of some biologically active organoselenium compounds. In Chapter 2, we present and discuss the results obtained during the course of this work, in Chapter 3 will describe the experimental procedures and, in Chapter 4, we present some selected spectra and its interpretations.

Literature Review

1.1 Introduction

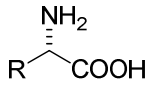
Organochalcogen compounds have become an attractive synthetic tool since selenium and sulfur containing groups serve an important auxiliary function in many synthetic sequences. They are of key interest to synthetic chemists due to the biological importance of organoselenium compounds. In addition to the synthetic importance, simple organosulfur and organoselenium compounds exhibit many useful biological and medicinal properties. They are generally targeted as compounds with antioxidant, antitumor, and antimicrobial activity and many of these compounds are competitive inhibitors for target proteins.[2] Chiral diorganyl selenides are also employed as efficient ligands in asymmetric reactions affording the corresponding products with high selectivity.[24]

The α-amino acids, in turn, show striking differences in their flavors. For example, the L- isomers of amino acids leucine, phenylalanine, tyrosine and tryptophan have bitter taste, while its corresponding D- enantiomers are sweet.[25]

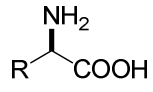
---

[24] For a comprehensive review on the use of chiral organoselenium in asymmetric catalysis see: (a) Wirth, T. *Tetrahedron.* **1999**, *55*, 1. (b) Wirth, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 3740. (c) Braga, A. L.; Lüdtke ,D. S.; Vargas, F.; Braga, R. C. *Synlett.* **2006**, 1453. (d) Braga, A. L.; Lüdtke. D. S.; Vargas, F. *Curr. Org. Chem.* **2006**, *10*, 1921.

[25] (a) Solms, J.; Vuataz, L.; Egli, R. H. *Experientia* **1965,** *21*, 692. (b) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735. (c) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377. (d) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1989**, *54*, 1777. (e) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429. (f) Lucas, M. A. C.; Schiesser, H. *J. Org. Chem.* **1996**, *61*, 5754. (g) Keck, G. E.; Grier, M. C. *Synlett.* **1999**, *10*, 1657. (h) Pattenden, G.; Stoker, D. A.; Winne, J. M. *Tetrahedron.* **2009***, 65,* 5767.



L-Aminoacid



D-Aminoacid

Figure 2. *L* and *D* isomers of amino acid.

Optical isomers may also show differences in toxicity. Take the example thalidomide (Figure 4). In the early '60s, it was used therapeutically as a sedative and hypnotic. Even with an asymmetric center, the drug was administered in the racemic forms. Although the drug seemed relatively harmless, as it was used by pregnant women resulted in a high incidence of stillbirths, neonatal and congenital malformations.[26] The teratogenicity was later identified as being due to only by one enantiomer (S).[27]

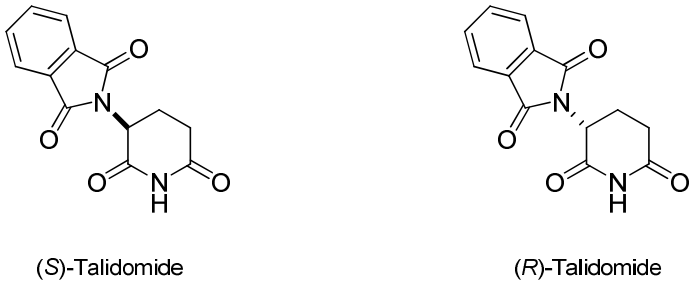


Figure 3. Enantiomers (S) and (R) of Thalidomide.

These are only a few among millions of other examples where biological systems, both in plants and animals or insects, react differently with each enantiomeric form of a given molecule. It is therefore highly desirable, perhaps imperative, to prepare molecules in enantiomerically pure form, to study its physical, chemical and biological weapons.

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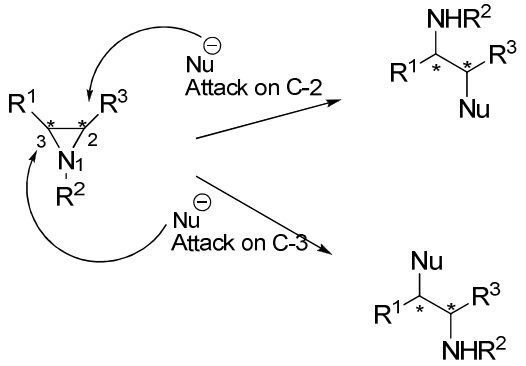
[26] Mellin, G. W.; Katzenstein, M. *New Engl. J. Med.* **1962**, *267*, 1184.
[27] von Blaschke, G.; Kraft, H. P.; Finkentscher, K.; Köhler, F. *Arzneim.-Forsch./Drug Res.* **1979**, *29*, 1640.

1.2 SYNTHETIC APPLICATIONS OF CHIRAL AZIRIDINES:

Chiral aziridines have been widely used in organic synthesis due to their versatility as synthetic intermediates in obtaining biologically important

compounds.[28] Thus, ring opening reactions of aziridines with nucleophiles, presented as a useful tool for obtaining functionalized organic compounds.[29]

The aziridine structure has a high ring strain and can easily be opened with excellent stereo-and regioselective manner in reactions with a variety of nucleophiles.[30] A number of methodologies for the preparation of aziridines is described.[31] These compounds may be classified as non-stabilized and stabilized, depending on the nature of the group attached to the aziridine nitrogen. The forms that contain substituents that stabilize the developing negative charge during the nucleophilic ring opening (e.g. acyl, carbamoyl, and sulfonyl) are said to be stabilized, while the aziridine groups that do not present with these features usually need use of a Lewis acid to promote the opening of the aziridine system and are called non-stabilized. As for the regiochemistry of the opening of aziridines, we have two possibilities: the opening at the carbon 2 (C-2) or at carbon 3 (C-3) (Scheme 2).

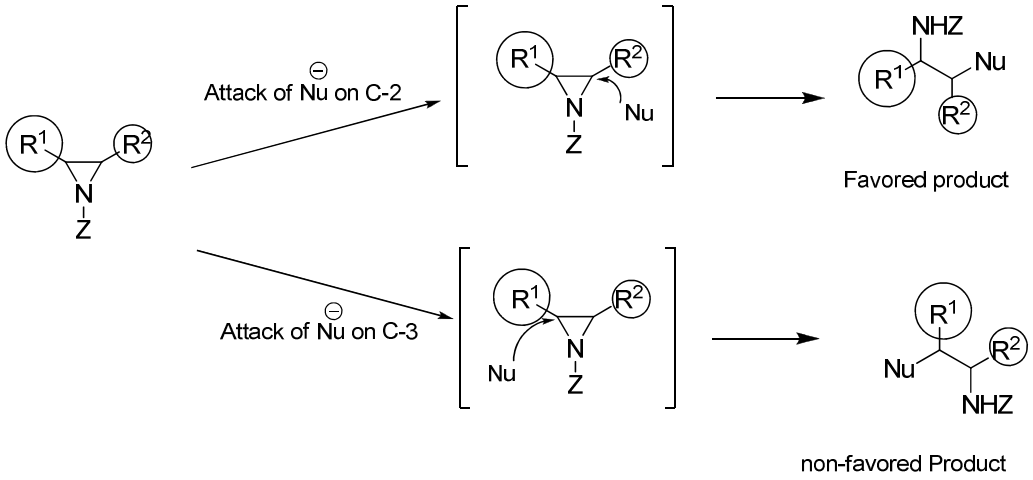


Scheme 2.

[28] (a) Tanner, D. *Pure & Appl. Chem.* **1993**, *65*, 1319. (b) Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599. (c) Mc.Coull, W.; Davis, F. A. *Synthesis* **2000**, *10*, 1347.
[29] Ma, L. G.; Xu, J. X. *Progr. Chem.* **2004**, *16*, 220.
[30] Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
[31] Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693.

The regioselectivity of aziridine ring opening depends on the substituents attached to carbons of the aziridine ring. The addition on carbon of the attacking nucleophile will be in the least sterically hindered, i.e., the carbon

in which there is small steric hinderence between attacking nucleophile and the group attached to aziridine carbon, as represented in (Scheme 3).



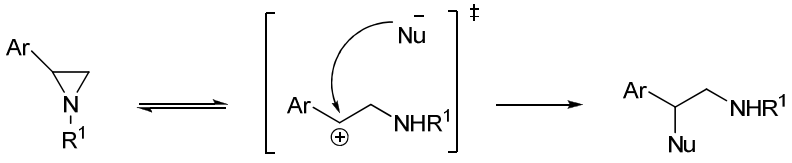
Scheme 3.

This is considered to be a basic trend in ring opening of aziridines in giving the less sterically hindered groups attached to attacking carbon, but in some cases, the opening of the aziridine may occur in the more hindered carbon, ignoring the steric preference. The cases where there is this exception are: aromatic functionalization and where nucleophile work as a chelating agent.[32]

In some examples of reactions with racemic compounds, the presence of a cluster directly connected to aromatic carbon aziridine (phenyl, naphthyl, etc.) causes the substitution occurs by an SN1 path through the formation of a benzyl carbocation highly stabilized at the aziridine carbon, with subsequent nucleophilic addition at that position, regardless of steric hindrance (Scheme 4).[33]

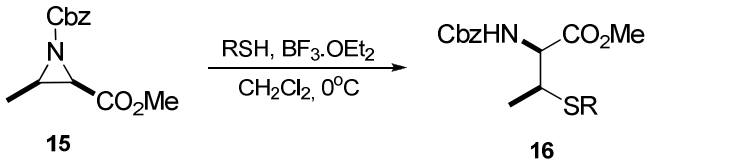
[32] (a) Ghorai, M. K.; Das, K.; Kamur, A.; Ghosh, K. *Tetrahedron Lett.* **2005**, 4103. (b) Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **1998***, 39,* 5739.

[33] Rodrigues, O. E. D. "*Organo-Selenium Compounds in Asymmetric Synthesis: Multicomponent Reactions and Catalysis in Addition of Diethylzinc to Aldehydes"*, PhD Thesis, **2003**, UFSM, Santa Maria.



Scheme 4

Many ring opening reactions of N-functionalized aziridine 2-carboxylate **15** with thiols has been described in the literature.[34] To promote these reactions with this class of aziridine, the use of acidic catalysts or Lewis acids were always needed. An example of opening of 2-carboxylates aziridine with thiols was performed by VanNieuwenhze,[35] $BF_3.OEt_2$ was used to promote the reaction, which led to the formation of derivatives of β-Me-cysteine **16** which were used as intermediates in the synthesis of β -Me-lantionines (Scheme 5).



15 **16**

R = Bn (83 %), PMB (87 %), Trt (40 %)

Scheme 5

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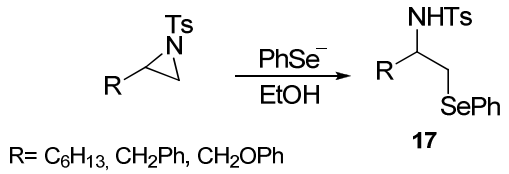
[34] (a) Galonic, D. P.; Ide, N. D.; van der Donk, W. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2005**, *127*, 7359. (b) Galonic, D. P.; van der Donk, W. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2004**, *126,* 12712. (c) Xiong, C.; Wang, W.; Hruby, V. J. *J. Org. Chem.* **2002,** *67,* 3514. (d) Xiong, C.; Wang, W.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002,** *67,* 1399. (e) Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998,** *63,* 5240. (f) Bae, J. H.; Shin, S. H.; Park, C. S.; Lee, W. K. *Tetrahedron* **1999**, *55,* 10041.

[35] Narayan, R. S.; VanNieuwenhze, M. S. *Org. Lett.* **2005,** *7,* 2655.

Reactions of aziridine ring opening with nucleophilic species of selenium present itself as a very useful tool in obtaining a wide variety of compounds with β-seleno-amines, but few examples are described in the literature [36]

In 1998, Engman[37] described the preparation of β-seleno amine **17** via ring opening of N-Tosyl aziridines with phenylselenolate, which was easily

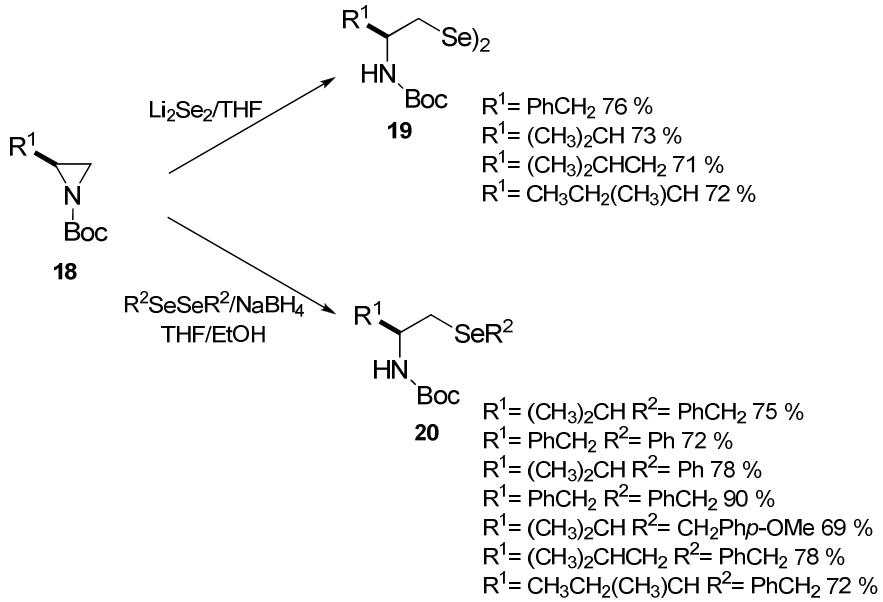
generated by reduction of diphenyl diselenide with sodium borohydride in order to generate free radical precursors for the synthesis of pyrrolidines. Later studies with N-alkyl aziridines reacted with phenylselenolate showed that ring opening occurs only in the presence of TFA, leading to regioselective ring opening to the less sterically hindered carbon (Scheme 6).[38]



Scheme 6

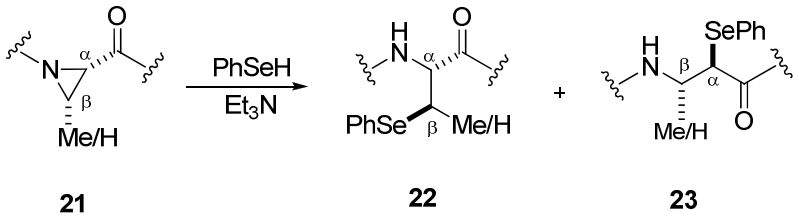
Our research group have also devoted particular attention to develop methods for aziridines ring opening with nucleophilic species of selenium. Recently, it has developed a series of chiral diselenide **19**.[21b] and β-seleno-amines **20**[23a] via the regioselective ring opening of N-Boc-aziridines **18** (Scheme 7).

[36] Barton, D. H. R.; Briten-Kelly, M. R.; Ferreira, D. *J. Chem. Soc. Perkin Trans. 1*, **1978**, 1682.
[37] Gupta,V.; Besev, M.; Engman, L. *Tetrahedron Lett.* **1998**, *39*, 2429.
[38] (a) Besev, M.; Engman, L. *Org Lett.* **2000,** *2,* 1589. (b) Berlin, S.; Ericsson, C.; Engman, L. *J. Org. Chem.* **2003,** *68,* 8386.



Scheme 7

Selenols were also used as nucleophiles in reactions of ring opening in peptides containing aziridine 2-carboxylates for the generation of derivatives phenylselenocystein and peptides containing and α seleno β -amino acid containing peptides (Scheme 8). This reaction proceeds by the addition of selenols to both α or β carbon of the aziridine depending on the peptide bound to the ring.[39]

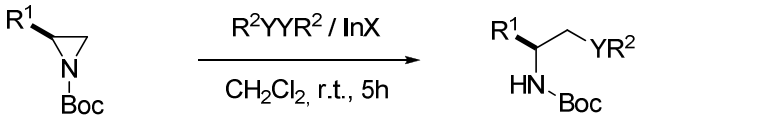


Scheme 8

[39] Ide, N. D.; Galonic, D. P.; van der Donk, W. A.; Gin, D. Y. *Synlett.* **2005**, 2011.

Our group also developed a simpler and new methology for the synthesis of chiral β -seleno-amines and their derivatives by a flexible and modular ring-opening reaction of functionalized aziridines. This easy access allowed a simple preparation of selenium - containing compounds with a wide structural diversity (Scheme 9).

Effectively, the preparation of these compounds was carried out using a new synthetic strategy, where the reactive species of selenium, generated by indium(I) compounds, act as a nucleophile in the ring-opening reactions of functionalized aziridines.[40]



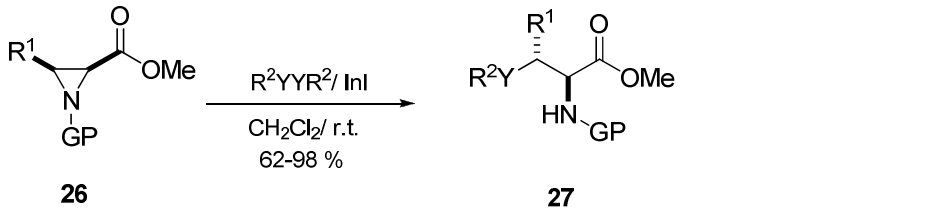
24 **25**

R^1 = $(CH_3)_2CH$; $PhCH_2$
R^2 = Ph, Bn, *p*-MePh, *p*-ClPh, *o*-MePh, *o*-ClPh, Et
Y = Se, S
X = Br, I

Scheme 9

In the same fashion this synthetic strategy furnished the protected selenocysteine and selenothreonine derivatives, as well as, their sulphur and tellurium analogues **27** in good to excellent yields, with mild conditions and short reaction times. This methodology allowed the synthesis of wide range of Chalcogens compounds in a complete regio- and stereo control (Scheme 10).[40]

[40] Braga, A. L.; Schneider, P. H. ; Paixão, M. W; Deobald, A. M; Clovis, P.;Bottega, D. P. *J. Org. Chem.* **2006**, *71,* 4305.



26 **27**

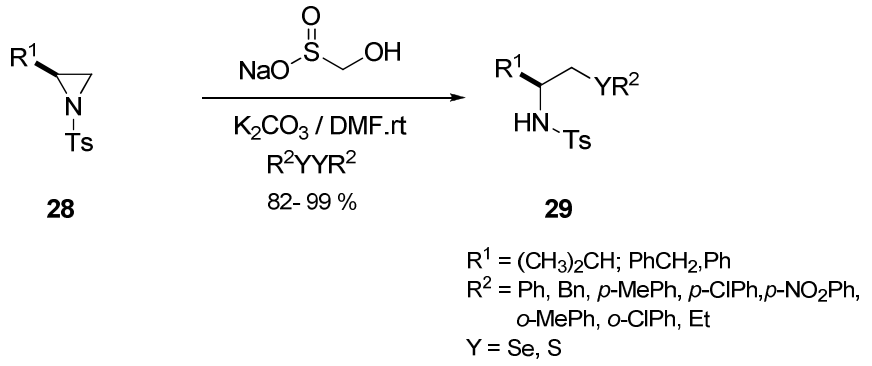
GP= Boc
GP= Cbz
GP= Fmoc

R^1 = H, CH_3
R^2 = Ph, Bn, *p*-MePh, *p*-ClPh, *p*-OMeBn, Et
Y = Se, S, Te

Scheme 10

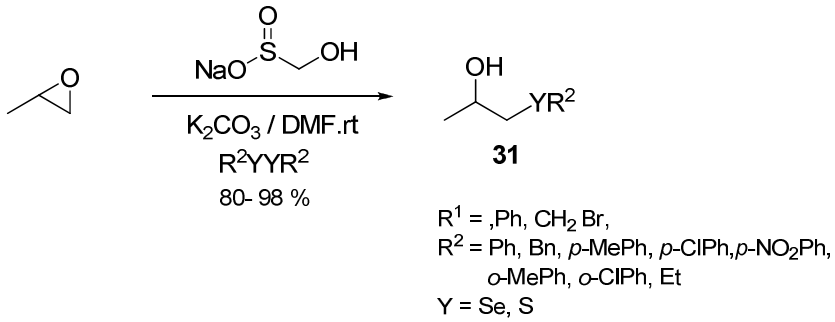
In 2009 Ganesh and co workers developed a new and simple method for the synthesis of β-seleno-amines and β-thio- amines **29**. Diaryl disulfides and diselenides undergo facile cleavage on treatment with rongalite (sodium hydroxymethanesulfinate) to generate the corresponding thiolate and selenolate species in situ, which affect the ring opening of aziridines in a stereo and regioselective manner. A simple, mild, cost-effective protocol has been developed to prepare the required compounds in a one-pot operation (Scheme 11).[41]

[41] Ganesh, V.; Chandrasekaran, S. *Synthesis.* **2009**, 19, 3267.



Scheme 11

In the same fashion the already generated selenolate and thiolate with rongalite was used for the regioselective ring opening of epoxides to obtained the corresponding β-hydroxy sulfides and selenides **31** from good to excellent yields (Scheme 12).

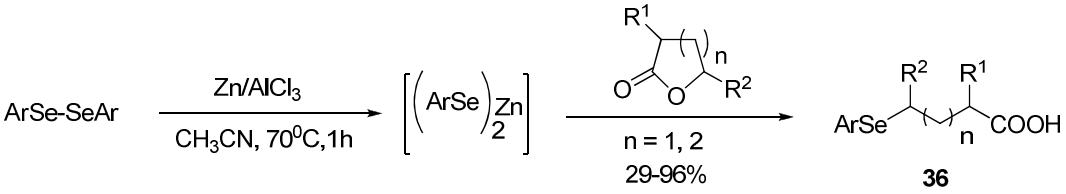


Scheme 12

1.3 Applications of Zn in Chalcogen Chemistry:

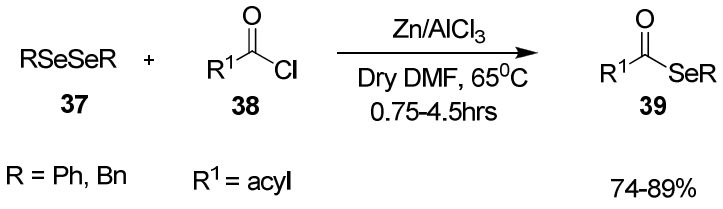
1.3.1 Reaction with $Zn/AlCl_3$

In 2009 Nazari and co-workers investigated the utility of zinc selenolates for effecting nucleophilic cleavage of simple lactones and esters. Zinc selenolate generated via $Zn/AlCl_3$ promoted cleavage of diselenides, was reacted with simple lactones and esters, efficient nucleophilic alkyl-oxygen bond cleavage proceeded (Scheme 13).[42]



Scheme 13

Similarly treatment of diphenyl and dibenzyl diselenides with aliphatic and aromatic acid chlorides in the presence of $Zn/AlCl_3$ system affords seleno esters in good yields (Scheme 14).[43]



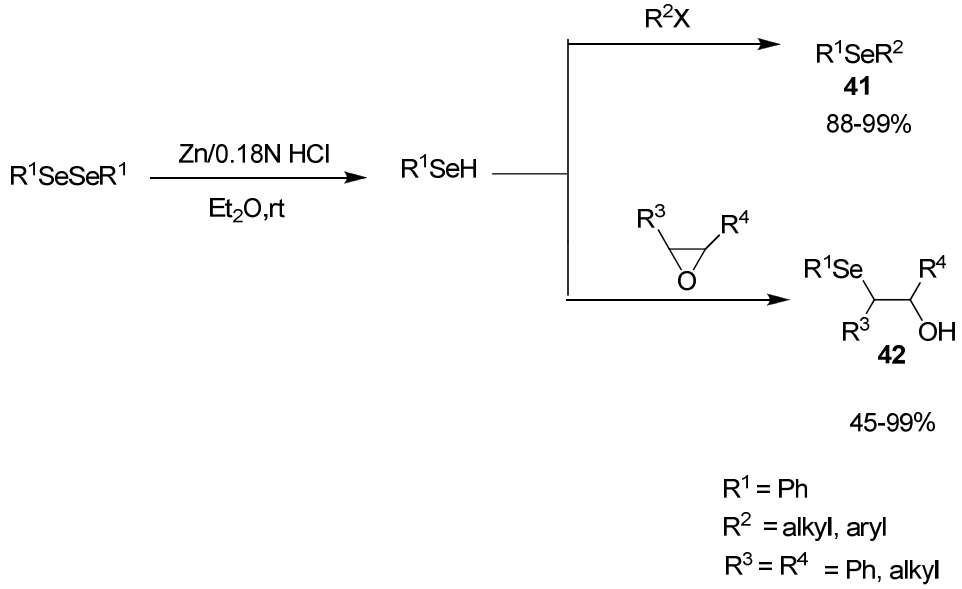
Scheme 14

[42] Nazari, M.; Movassagh, B. *Tetrahedron Lett.* **2009,** 50, 438.

[43] (a) Movassagh, B.; Mirshojaei, F. *Monatshefte für Chemie*. **2003**, *134*, 831. (b) Movassagh, B.; Shamsipoor, M. *Synlett*. **2005**, 121.

1.3.2. Reaction with Zn/HCl

Reductive cleavage of the Se–Se bond mediated by zinc under acidic conditions to afford selenols, which can be either isolated or treated in situ with alkyl halides to produce alkyl selenides or with epoxides to give β-hydroxy selenides (Scheme 15).[44]



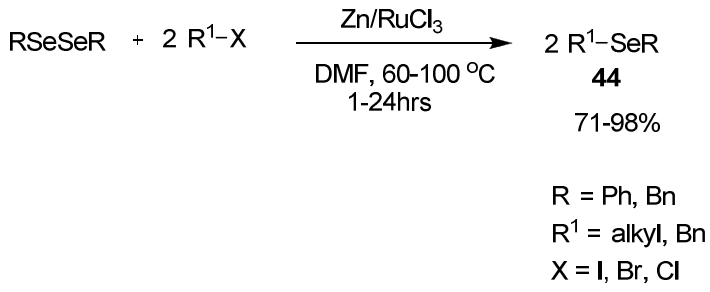
Scheme 15

1.3.3 Reaction with Zn/$RuCl_3$

Ruthenium-(III) chloride catalyzed reactions of dibenzyl or diphenyl diselenides with alkyl halides in the presence of zinc gave the unsymmetrical diorganyl selenides. Organic iodides, bromides, and activated chlorides underwent the reactions efficiently (Scheme 16).[45]

[44] Santi,C.; Santoro, S.; Testaferri, L.; Tiecco, M. *Synlett.* **2008**, 1471.

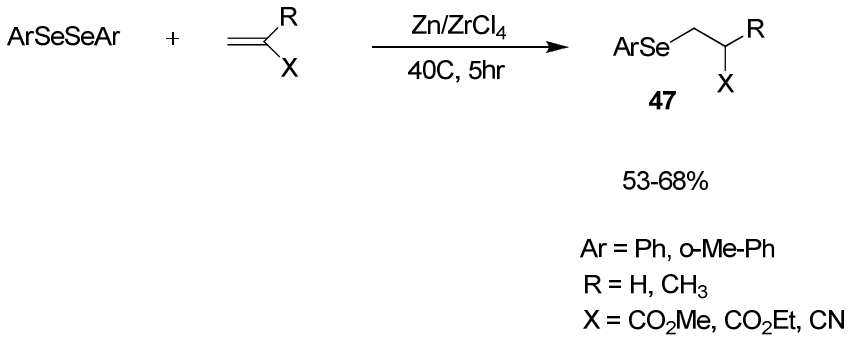
[45] Zhao, X.; Yu, Z.; Yan, S.; Wu, S.; Liu, R.; He, W.; Wang, L. *J. Org. Chem.* **2005,** *70*, 7338.



Scheme 16

1.3.4 Reaction with Zn/$ZrCl_4$

Zn/$ZrCl_4$ was also employed as reducing agent for the cleavage of Se-Se bond and produced selenolate anions. This normally afforded β-selenoesters and β-selenonitriles in very good yields by treating with α-β-unsaturated esters or α-β unsaturated nitriles respectively (Scheme 17).[46]



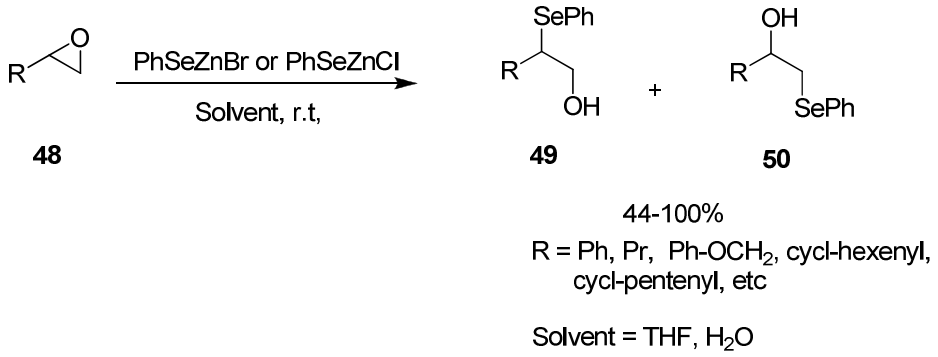
Scheme 17

1.4 Applications of PhSeZnBr

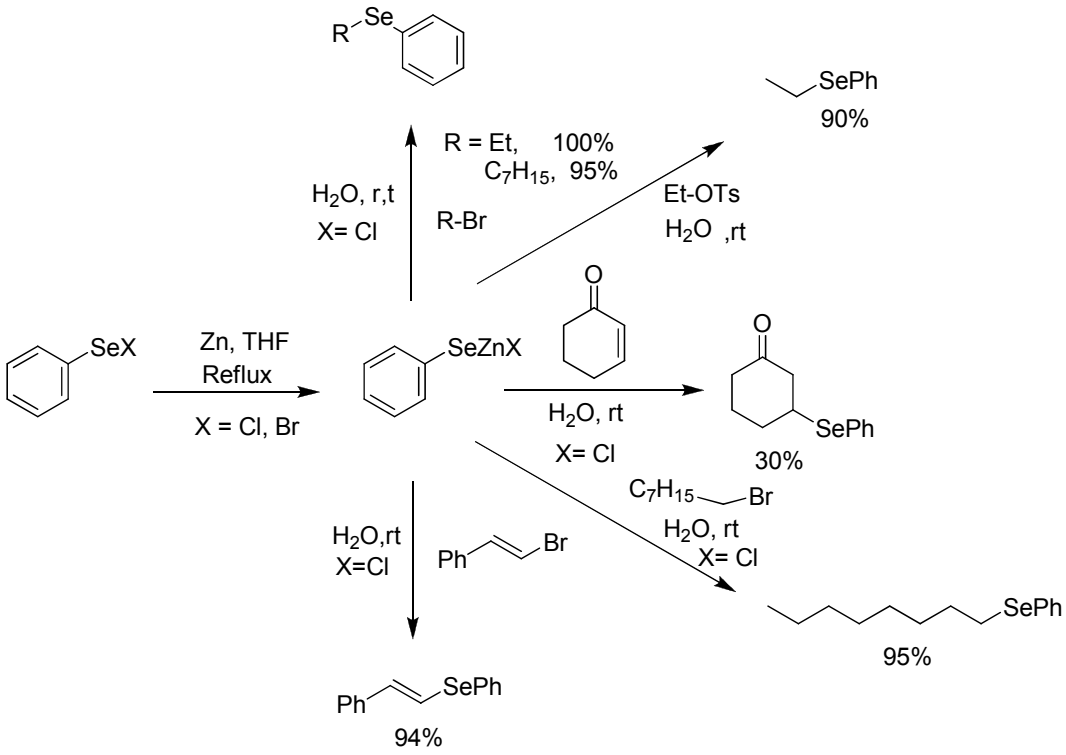
Santi and co-workers reported the synthesis and characterization of the first solid and air stable selenolates, starting from commercially available phenyselenyl halides and elemental zinc dust. These reagents were efficiently employed in the ring opening of epoxides as well as in other nucleophilic

[46] Zhang,S., Tian, F., T. *J. Chem. research (S).* **2001**, 198

substitution and addition reactions showing as unexpected rate acceleration in water suspension at room temperature (Scheme 18, 19).[47]



Scheme 18



Scheme 19

[47] Santi, C.; Santoro, S,; Battistelli, B.; Testaferri, L.; Tiecco, M. *Eur. J. Org. Chem*. **2008**, 5387.

1.5 Ionic liquids

Because the constraints of environment are becoming more and more stringent, organic transformations, catalytic processes and separation technologies require the development of alternative solvents and technologies. The ideal solvent should have a very low volatility, it should be chemically and physically stable, recyclable and reusable and eventually easy to handle. In addition, solvents that allow more selective and rapid transformations will have a significant impact. During these last 20 years,water has emerged as a new useful reaction media.[48] It has been successfully used in many organic reactions. However, its application is still limited due to the low miscibility of organic substrates in water. More, water is a protic coordinating solvent and probably it can react with organometallic compounds.

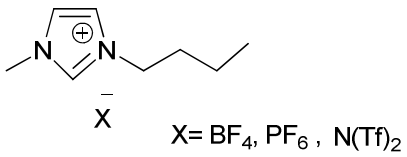


Figure 5 . Room temp ionic liquids.

Now-a-days, ionic liquids were utilized as a effective reaction media for many organic transformations and still it's emerging in trend. The spectrum of their physical and chemical properties is much larger than that of organic solvents. Most commonly used ionic liquids depicted in Figure 5. Initially ionic liquids developed by electrochemists who were looking for ideal electrolytes for batteries, they are now implied in a lot of applications. Some important characteristics of ionic liquids were discussed in the following section.

[48] Cornils, B.; Herrmann, W. A., Cornils, B.; Herrmann, W. A. (Eds.), Aqueous Phase Organometallic Catalysis - Concept and applications, Wiley-VCH, Weinheim, **1998**.

1.5.1 Properties of ionic liquids

Ionic liquids that are liquid at or above 25 ℃ and are referred to as room temperature ionic liquids (RTILs). In general, Ionic liquid consists of a large organic cation together with an organic or inorganic anion. Especially, an imidazolium cation-based ionic liquid has proven to be highly attractive and versatile. Frequently encountered favorable characteristics of imidazolium ionic liquids are, high thermal stability, being liquid over a wide temperature range, very low-vapor pressure, wide electrochemical window, high conductivity and ionic mobility, easy recycling, and being a good solvent for a wide range of organic and inorganic chemical compounds. Besides, ionic liquids are "designable or tunable" because structural modifications in both the cation and anion permit the tuning of its physical properties [49] and this may influence the outcome of reaction yield.

As a result, applications of ionic liquids are numerous which continue to expand such as electrolytes for electrochemical devices and processes, solvents for organic and catalytic reactions, new material production, solvents for separation and extractions processes. They now find additional use in enzyme catalysis or in multiphase bio-process operations.

[49] Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; VCH Wiley: Weinheim, Germany, **2002**.

CHAPTER 2

Results and Discussion

Results and Discussion

In recent years our research group has been primarily working in the area of asymmetric synthesis. Most of the new research methods that are being developed are mainly focused on developing new catalysts and chiral ligands with selenium, amino acid derivatives.[50] In this context, organoselenium compounds have already been used successfully in several classes of asymmetric reactions.[51]

Similarly aliphatic diselenide analogues to these compounds have already been prepared and applied as catalysts in enantioselective addition reactions of diethyl zinc to aldehyde,[52] making the synthesis of β-seleno-amines, an interesting field of study since they present a great potential as ligands and catalysts in asymmetric reactions.

2.1 Preparation of chiral β-seleno amines

According to our interest in the development of chiral compounds containing selenium, and consistent with the objectives outlined, it was proposed a new methodology for the synthesis of free chiral β- seleno amines from unprotected aziridines with the general structure shown in Figure 5, to get better yields, clean and nice reaction conditions and shorter reaction times compared to the other methodology developed by our research group

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[50] Schwab, R. S.; Soares, L. C.; Dornelles, L.; Rodrigues, O. E. D.; Paixão, M. W. ; Godoi, M.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, 3574.

[51] (a) Marin, G. "Preparation and Application of Chiral Seleno-amine Ligands in enantioselective alkylation, "Master's Thesis, **2005**, UFSM, Santa Maria. (b) Ludtke, D. S. "Seleno-oxazoline in Chiral allylic alkylations and Asymmetric Synthesis of Amino Acids and Peptides Containing Unusual Selenium", PhD Thesis, **2005**, UFSM, Santa Maria.

[52] (a) Procter, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 835. (b) Selenium Reagents and Intermediates in Organic Synthesis; Paulmier, C. Ed.; Pergamon Press: Oxford, 1986. (c) Schmid, G. H.; Garratt, D. G. In The Chemistry of Double-Bonded Functional Groups; Patai, S. Ed., Wiley: London,1977; Supp. A, Part 2. (d) Santi, C.; Wirth, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1019. (e) Nishibayashi, Y.; Segawa, K.; Singh, J. D.; Fukuzawa, S. J.; Ohe, K.; Uemura, S. *Organometallics* **1996**, *15*, 370.

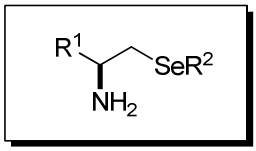


Figure 5. Structure of free chiral β- seleno amine**.**

The main feature of the structure shown in Figure **5** shows the presence of selenium and nitrogen atoms, which gives these two active sites interesting compounds because they have the ability to complex with a range of metals, however, also allows great flexibility in introducing and changing nature of substituents at R^1 and R^2. This special feature gives the system the possibility of introducing a varied range of substituents in the R^2 fragment, derived from the corresponding diselenide.

Therefore it is important and interesting to develop a simple and efficient synthetic route for the synthesis of free chiral β-seleno amine from the reaction of unprotected aziridines and diaryl or dialkyl diselenide. We employed an acid biphasic system and inexpensive and commercially available zinc dust as a reducing agent.

Survey of literature showed that enough methods are known for the efficient synthesis of protected β-seleno amine in organic medium. The use of inexpensive and commercially available zinc dust as a reducing agent in biphasic medium was not yet reported. Hence we are interested to investigate the reactivity of zinc dust with diaryl and dialkyl diselenide and free aziridines to synthesize the unprotected chiral *β*- seleno amine in biphasic system under room temperature.

Thus, through a retro synthetic analysis of β seleno-amino **4** (Figure 6), we can infer that the group could be introduced organoselenium molecule through the reaction regioselective ring opening of unprotected aziridine with nucleophilic species of selenium. The free aziridine **3**, in turn would be prepared by cyclization of *N*-free chiral amino alcohols **2,** obtained by reduction of corresponding *L*-amino acids.

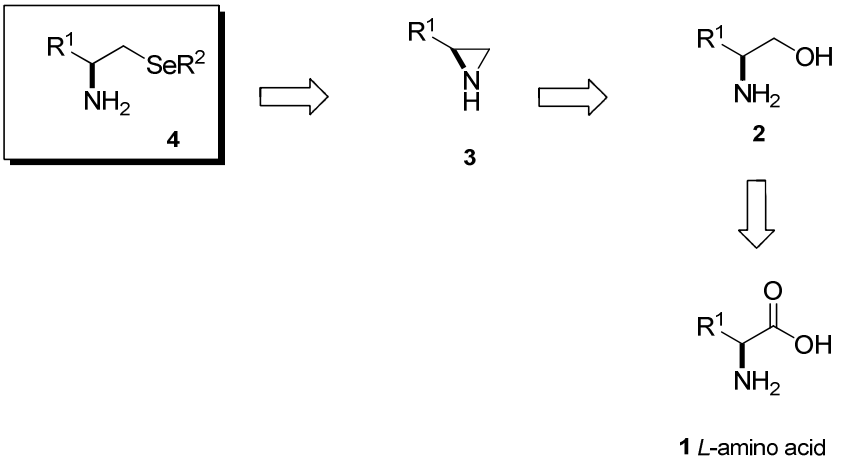
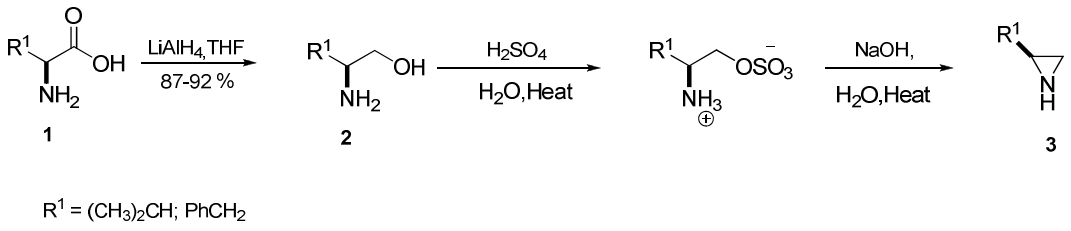


Figure 6. Retro synthetic analysis for Free chiral β-seleno amine.

Based on this analysis, we planned the preparation of free-aziridines **3**, using the following natural amino acids as starting materials: *L*-valine and *L*-phenylalanine and *L*-leucine.

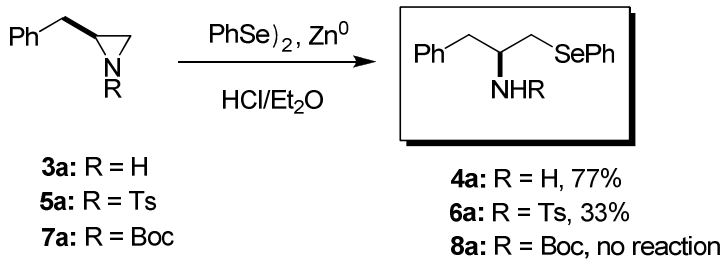


Scheme 20 . Synthesis of free aziridines.

In order to evaluate the performance of aziridine ring opening reaction and resolve the first objective to investigate the possibility to employ the reaction condition for the synthesis of chiral *β*-seleno amine. We firstly used diphenyl diselenide and aziridines derived from *L*-phenylalanine as a standard reagents. Unprotected as well as, Ts and Boc protected aziridine were tested

using Zn as reducing agent in an HCl/diethyl ether biphasic system as illustrated in scheme 21.

A good result was obtained for unprotected aziridine **3a**, affording the desired β-seleno amine **4a** in 77% yield. The reaction was regioselective, giving the product through the attack of selenolate to the less hindered aziridine carbon. The protected aziridine **5a** (Ts) afforded the product in 33% yield and no product was obtained for aziridine **7a** (Boc).



3a: R = H
5a: R = Ts
7a: R = Boc

4a: R = H, 77%
6a: R = Ts, 33%
8a: R = Boc, no reaction

Scheme 21. Ring opening of protected and unprotected aziridines**.**

2.1.1 Screening of reaction conditions:

Encouraged by these results, we tested various reaction conditions in an attempt to improve the efficiency of the ring opening of unprotected aziridines. We choose PhSeSePh as a standard diselenide and to check the best solvent and temperature for this system we select aziridine **3a** as substrate to get the desired *β*-seleno amine by using the following procedure. In a 25 mL round bottom flask, under argon atmosphere was prepared the biphasic solution by the addition of Et_2O (4 mL) and HCl (10%, 4 mL) , to this solution were firstly added the diorganyl diselenide (0.25mmol) and zinc dust (500 mg, 7.7mmol). The mixture was allowed to stir until the yellow solution became colorless (10-30 min), then the unprotected aziridine (0.5mmol) was added and the reaction was stirred at room temperature for 24h and at the end of reaction, all the acid

react with zinc. After completion of the reaction, as indicated by TLC, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted 3 times with CH_2Cl_2 and the combined organic fractions were collected, dried over $MgSO_4$, filtered and the solvent was then removed in vacuum. The crude mixture was purified by column chromatography on silica gel eluting with hexane–ethyl acetate (9:1) and after with ethyl acetate.

The obtained product free chiral β- seleno amine **4a** was characterized by NMR spectrum. The ^{1}H NMR shows the $–NH_2$ protons in broad singlet at δ 1.7. One chiral proton appeared as multiplet between δ 3.03 and 3.30 ppm (H-2), similarly $–CH_2$ attached to selenium appeared as a multiplet between δ 2.73 and 2.92 (H-1). On the other hand the $–CH_2$ attached to aromatic ring appeared between δ 2.54 and 2.69 ppm (H-3). The ten aromatic protons appeared as multiplet in the range of δ 7.61 and 7.03 ppm range. In ^{13} C NMR spectra, aromatic carbons appeared at δ 138.68, 132.62, 130.05, 129.22,129.08, 128.48, 126.90 and 126.41(C4-11). The methylene carbon appeared in δ 36.50 and 43.87 (C-3 and C-1, respectively). The chiral carbon appeared at δ 52.45 ppm(C-2). The ^{1}H and ^{13} C NMR spectral data of the compound **4a** confirmed that the formation of product was successfully accomplished. The spectras are presented in figure 7 and 8.

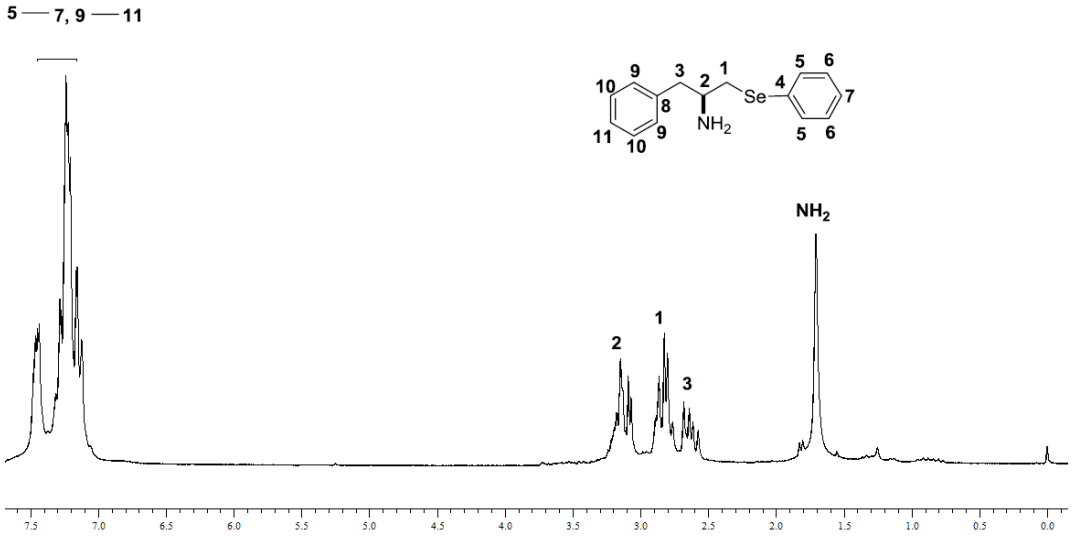


Figure 7. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of **4a**

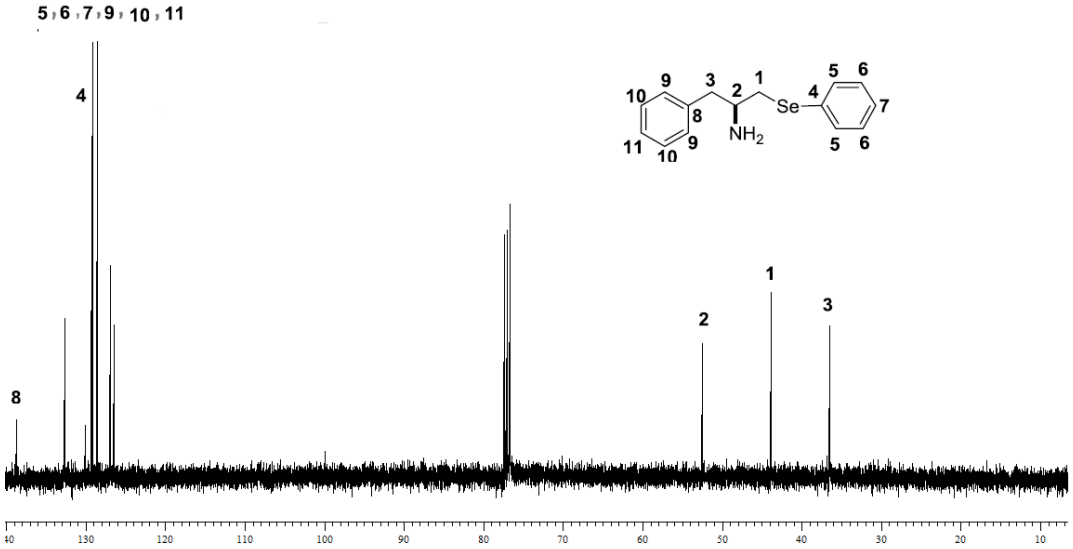


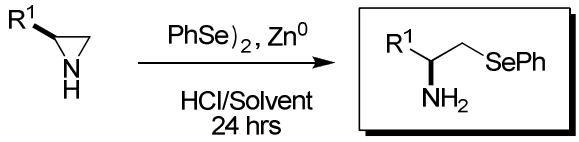
Figure 8. ^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of **4a.**

2.1.2 Optimization of the reaction conditions:

During optimization first of all it was necessary to find the effect of different kinds of organic media. Due to this different organic solvents were employed for this kind of free aziridine ring opening to obtained the free chiral β-

seleno amine.The complete conversion of diselenide into the corresponding selenolate by the addition of zinc under acid conditions was demonstrated by discoloration of the mixture which was followed by the addition of aziridine. It was found that the solvent had a strong influence on the formation of the product, while ethereal solvents such as Et_2O and THF, showed better results (entries 1 and 2). Apolar hexane (entry 3) did not afford the β- seleno amine **4a** in an appreciable yield. The use of CH_2Cl_2 allowed the formation of product **4** in 60% yield (entry 5). A good result was also achieved by using ethyl acetate, giving the product in a yield close to that achieved with Et_2O (entry 4). In an attempt to make the reaction more environmentally friendly, we employed solvents such EtOH and water (entries 6 and 7), but unfortunately the product was obtained only in moderate yield. In addition, the reaction was carried out in Et_2O and AcOEt under reflux in an effort to increase the yield, but quite disappointing results were observed (entries 8 and 9). When the reaction was performed with aziridines derived from *L*-valine and *L*-leucine (entries 10 and 11) using the best conditions, the products were obtained in good yields, but slightly lower than those found for aziridine 1a derived from *L*-phenylalanine.

Table 1: Optimization of ring opening reaction of unprotected aziridine by diphenyl diselenide.



Entry	R^1	Solvent	Temp (ºC)	Yield[a]
1	Bn	Et_2O	rt	77
2	Bn	THF	rt	64

3	Bn	Hexane	rt	26
4	Bn	AcOEt	rt	75
5	Bn	CH_2Cl_2	rt	60
6	Bn	EtOH	rt	52
7	Bn	H_2O	rt	53
8	Bn	Et_2O	Reflux	60
9	Bn	AcOEt	Reflux	43
10	*i*-Pr	Et_2O	rt	58
11	*i*-Bu	Et_2O	rt	70

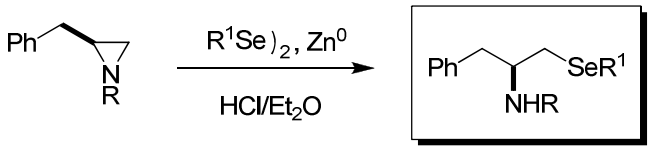
[a] Yields Referred to pure isolated products, characterized by ^{1}H NMR and ^{13}C NMR spectroscopic data.

2.1.3 Synthesis of *β*-seleno amine using Zn/HCl in Et_2O:

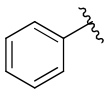
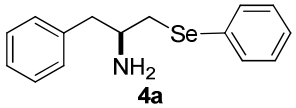
After optimization, we next prepared a series of unprotected chiral β-seleno amine using aryl and alkyl diselenides, Zn/HCl and Et_2O. Based on these results and in order to widen the scope of our protocol, we then tested a broader range of diselenides. The results are listed in Table 2. Notably, electron-withdrawing groups showed better results compared to electron-donating ones. In the reaction using 4-$ClC_6H_4Se)_2$ and 4-$FC_6H_4Se)_2$ the yields were 80% and 83% which show that electron withdrawing but resonance stabilized group substituted diselenides gave good yields due stronger selenolate nucleophilic character (entries 5 and 6) respectively, and were quite higher than the results for 4-$MeC_6H_4Se)_2$ and 4-$MeOC_6H_4Se)_2$ (60% and 58%; entries 3 and 8). Another feature of this system is the strong influence of hindrance effects in the diselenide moiety. When ortho-substituted diselenides were applied, there was a dramatic decrease in yields both for electron-donating and –withdrawing groups (entries 2, 4, and 7 vs 3, 5, and 8). Because ortho group adjacent to selenium observe more steric hinderence and as a result gave low yield. Dibenzyl diselenide and 2-pyridine diselenide were also

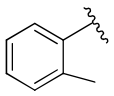
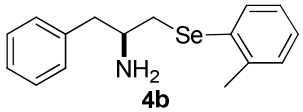
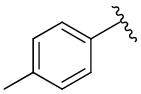
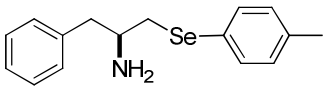
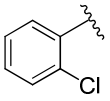
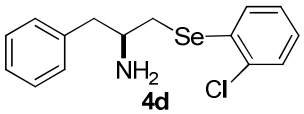
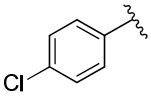
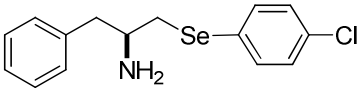
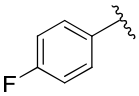
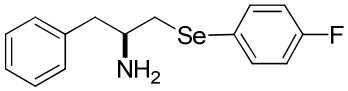
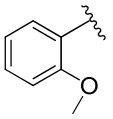
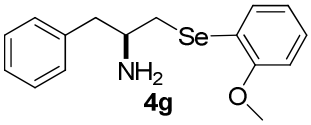
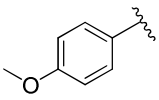
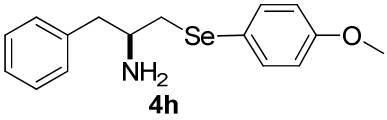
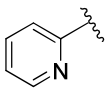
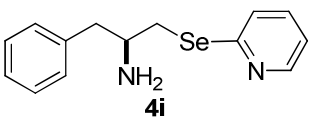
tested (entries 9 and 10). The β-seleno amines 4k and 4l, with aliphatic moieties attached to selenium were also obtained by using dibutyl diselenide and diethyl diselenide (entries 11 and 12). To further improve our method, we promoted the reaction using diphenyl ditellurides. Although the yield was 40% (entry 13) which shows the unstable feature of the tellurium moiety. Our approach is a promising strategy for the preparation of β- telluro amine, which is a current goal in organochalcogen chemistry, due to difficulties in its preparation and handling.

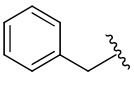
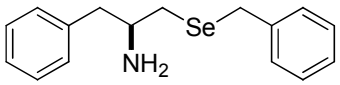
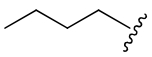
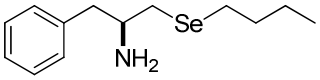
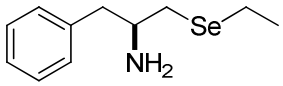
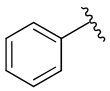
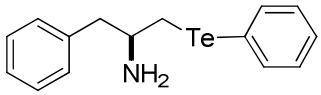
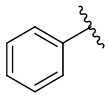
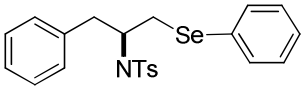
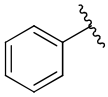
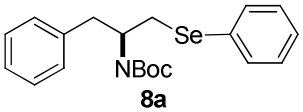
Table 2. Synthesis of chiral β-seleno amine promoted by Zn/HCl.



Where R is H, Boc and Ts

Entry	R^1	Y	Product	[a] Yield(%)
1		Se	 **4a**	77

2		Se	 **4b**	35
3		Se	 **4c**	60
4		Se	 **4d**	55
5		Se	 **4e**	80
6		Se	 **4f**	83
7		Se	 **4g**	51
8		Se	 **4h**	58
9		Se	 **4i**	46

10		Se	 **4j**	35
11		Se	 **4k**	35
12		Se	 **4l**	52
13		Te	 **4m**	40
14		Se	 **6a**	33
15		Se	 **8a**	0

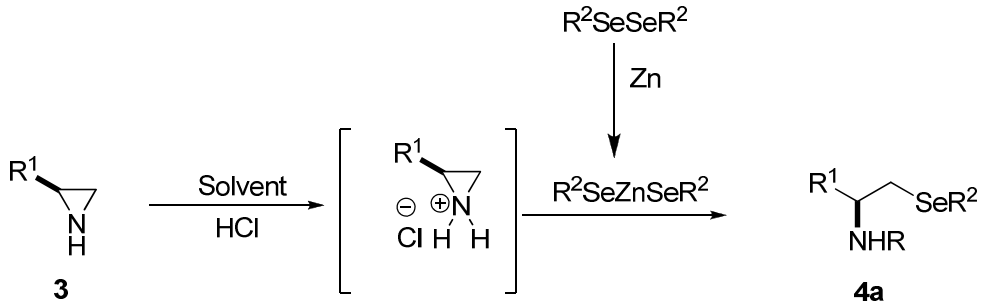
[a] Yields refers to pure isolated products and characterized by ^{1}H NMR and ^{13}C NMR spectroscopic data.

The results shown in Table 2 provide us with the income of β-seleno-amines obtained, with different groups attached to the selenium atom. All β-seleno-amines were obtained in moderate to good yields on reaction with aziridines studied. The presence of electron donor groups such as methyl, or electron withdrawing groups such as chlorine in the aromatic rings of diselenide influenced the reactivity of the reactions, providing the products with varying

yields, mainly by comparing the results of reaction with diselenide 4-FlPh (Reaction 5), 4-ClPh presented the best yield (Reaction 6) than the reaction with 2-MeO-Ph diselenide (Reaction 8), 2-MePh (Reaction 3).

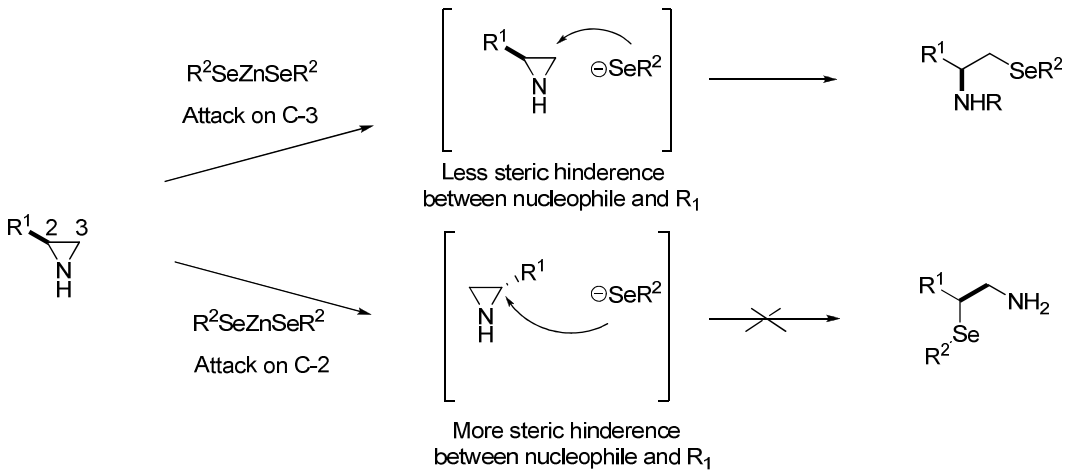
2.1.4 Mechanistic pathway for the synthesis of chiral β-seleno amine:

We believe that the reaction occurs firstly through the 'in situ' formation of water-soluble zinc selenolate. The activation of the unprotected aziridine leads to the protonated intermediate, which undergoes the ring opening by zinc selenolate in the aqueous layer, as depicted in Scheme 22. We conjecture that in the initial step protonation of the aziridines occurred, activating them to undergo the ring-opening reaction by zinc selenolates.



Scheme 22.

An important feature of the present method is its regioselectivity, as the product is given exclusively through the attack of selenolate to the less-hindered aziridine carbon. Several factors may observed in retention of configuration of chiral β-seleno amine .The most important factor in our case is the presence of an aromatic or non aromatic cluster R^1 attached to carbon C-2 aziridine (more hindered) while in the second carbon of aziridine C-3, no bulky substituent's with only hydrogen. This steric differentiation between these carbons directs the attack of the anion selenolate to least hindered carbon C-3 as shown in Scheme 23.



Scheme 23.

2.1.5 Outcome of this new methology:

In summary, we presented in this work a simple and efficient approach for the preparation of chiral *β*-seleno amines. The desired products were prepared in a biphasic system, employing inexpensive and commercially available zinc dust, unprotected aziridines, and alkyl or aryl diselenides, but the methology was not very fruitful for protected (Boc and Ts) aziridines. The most interesting and astonishing feature of our approach is the regio of the ring-opening reactions of unprotected aziridines, leading to the desired products in good yields, which avoids expensive protection-deprotection chemistry. A broad set of chiral *β*-seleno amines were synthesized, as well as a *β*-telluride amine analogue.

To realize and compared the above methology for the synthesis of *β*-seleno amine, it is important and interesting to develop a simple, environmental friendly and efficient synthetic route for the synthesis of chiral *β*-seleno amine**.** Survey of literature showed that there is still no such method reported for the synthesis of this kind of organoselenium compounds using ionic liquid as reaction medium. Due to this we reported here a new methology to prepare *β*-seleno amines in a neutral and smooth protocol. Using a bench-stable phenyl

selenolate specie (PhSeZnBr), recently described by Santi *et al.*[46] to promote the ring opening reaction of protected and unprotected aziridines in BMIM-BF_4. The desired products were obtained in good to excellent yields, in short time and with the advantage of recycle the reaction media, which represents an environmentally benign approach.

The following are the systematic approach carried on to solved the synthetic problem. In this regard, we first synthesized ionic liquids by the methodologies already reported in the literature and further it is used as reaction medium for ring opening of protected and unprotected aziridines with bench-stable phenyl selenium zinc bromide (PhSeZnBr) to synthesize chiral β-seleno amine**.**

2.2. Room temperature ionic liquids.

At the present time, there is still an empirical knowledge of ionic liquid mainly developed on the basis of their solvent effect on organic reactions compared to that of well-know conventional solvents. The challenge would be able to predict their properties in order optimize the choice for a given application.

However, we may consider few important factors such as solvent polarity and type of the reaction has often a strong influence on the outcome of reactions. Concerning about polarity, it's even more complicated in the case of ionic solvents, as many interactions for e.g, characteristic of hydrogen bonding can be involved. In addition, reactions involving charged intermediates such as carbocations or carbanions which could become more long-lived in these media, figure 9.

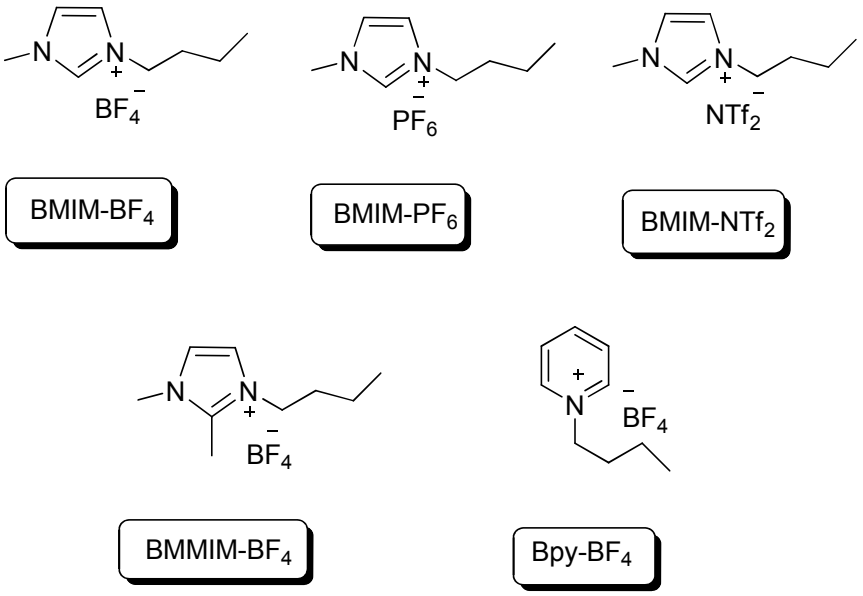


Figure 9. Room temperature ionic liquids

The above shown ionic liquids were synthesized by the available literature procedure and the synthetic procedure is available in the experimental section.

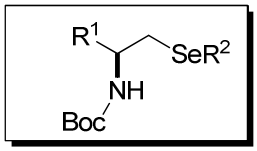


Figure 10. Chiral β-seleno amine

Thus, through a retro synthetic analysis of β - seleno-amine **11** (Figures 10 and 11), we can infer that the group could be introduced organoselenium molecule through the reaction regioselective ring opening of Boc protected aziridine with nucleophilic species of selenium from bench-stable phenyl selenium zinc bromide (PhSeZnBr) .The protected aziridines **10**, in turn, would be prepared by cyclization of *N*-protected chiral amino alcohols, which is obtained by reduction of corresponding *L*-amino acids with lithium aluminum hydride ($LiAlH_4$)

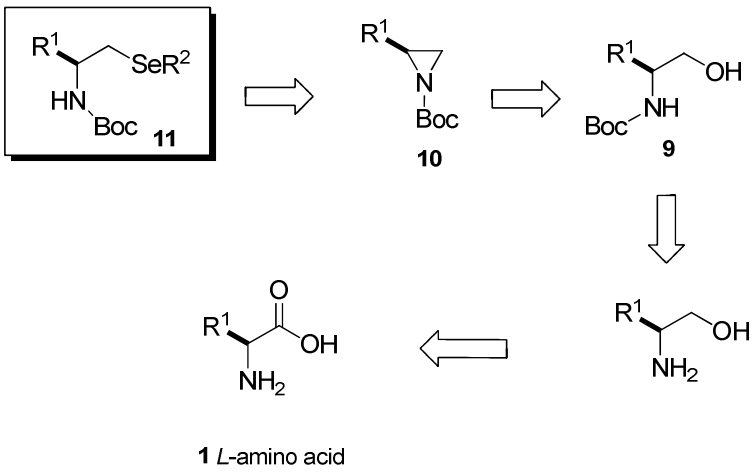
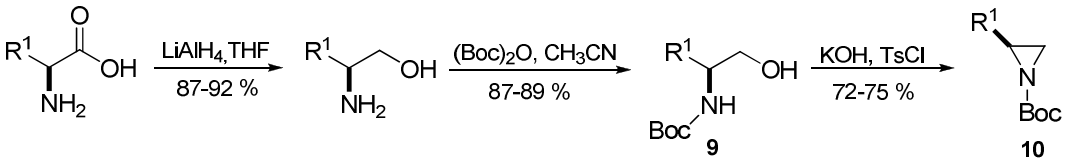


Figure 11. Retro synthetic analysis for chiral β-seleno amine.

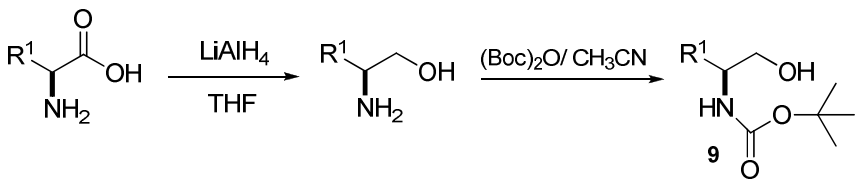
Based on this analysis, we planned the preparation of *N*-Boc-aziridines 10, using the following natural amino acids as starting materials: *L*-valine and *L*-phenylalanine



Scheme 24.

According to Scheme 24, initially was performed the reduction of amino acids to their amino alcohols **2**. For this purpose lithium aluminum hydride was used as the reducing agent, and THF as a solvent. The two desired amino alcohols were obtained in good yields (Table 3). The desired products obtained, there was subsequent protection of the group amine with $(Boc)_2O$. Acetonitrile was used as a solvent due to appropriate solubility of amino alcohols and di-tert-butildicarbonato $(Boc)_2O$ in it, thus leading to the formation of amino-*N*-Boc protected **9**. The yields of these two steps can be seen in Table 3.

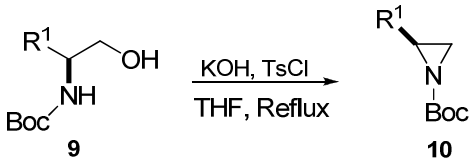
Table 3: Preparation of amino alcohol **2** and **3**



Entry	R^1	Amino alcohol	Yield(%)	N-Boc-Amino alcohol	Yield(%)
1	$PhCH_2$	**2a**	92	**9a**	87
2	$(CH_3)_2CH$	**2b**	87	**9b**	89

In the next stage, we prepared the **10a-b** aziridines from previously protected amino alcohols. This reaction involved the use of tosyl chloride in alkaline (KOH) medium through an intramolecular cyclization under reflux in THF. The aziridines 10a-b were obtained in good yields and purified by column chromatography on silica gel (Table 4).[53]

Table 4. Synthesis of Boc protected aziridines.



Entry	**R^1**	**Aziridine**	**Yield (%)**	**$[\alpha]_D^{20}$ (c=1, CH_2Cl_2)**
1	$PhCH_2$	**10a**	75	+51

2	$(CH_3)_2CH$	**10b**	72	+60

Similarly through a retro synthetic analysis of β seleno-amino-**11** (Figure 12), we can infer that the group could be introduced Organoselenium molecule through the regioselective ring opening of Ts protected aziridine with nucleophilic species of selenium from bench-stable phenyl selenium zinc bromide (PhSeZnBr) .The protected aziridines 10c-e, in turn, would be prepared by cyclization of N-free chiral amino alcohols , which is obtained by reduction of corresponding L-amino acids with lithium aluminum hydride ($LiAlH_4$).

[53] Braga, A. L.; Paixão, M. W.; Ludtke, D. S.; Silveira, C. C.; Rodrigues, O. E. D. *Org. Lett.* **2003**, *5*, 2635.

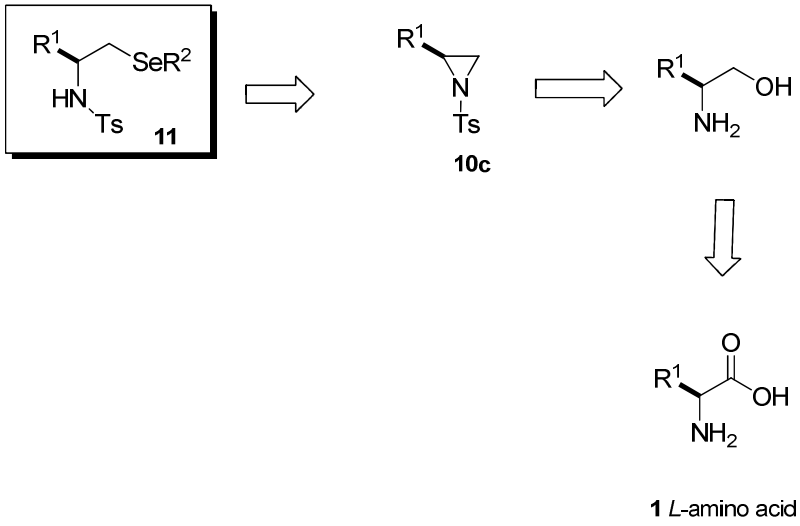
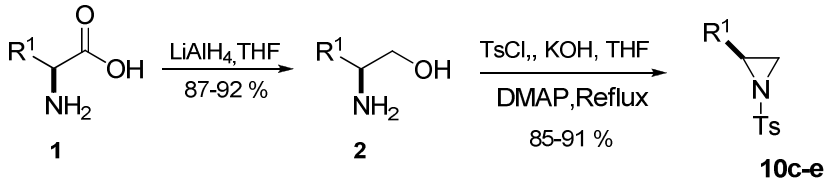


Figure 12. Retro synthetic analysis for chiral β-seleno amine.

Based on the above shown retro synthetic analysis, we decided to prepare functionalized N-Tosyl-aziridines **10** as a precursor in the synthesis of

chiral β-seleno amine using the following natural amino acids as starting materials: *L*-valine, *L*-phenylalanine and *L*-leucine.



Scheme 25.

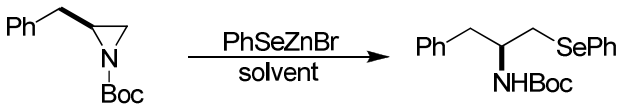
According to Scheme **6**, initially was performed the reduction of amino acids to their corresponding amino alcohols **2**, lithium aluminum hydride was used as the reducing agent, and THF as the solvent. The three required amino alcohols were obtained in good yields (Table 1). The amino alcohols obtained, there was subsequent synthesis the desired tosyl protected aziridine. THF was used as a solvent due to appropriate solubility of amino alcohols in weak basic (Et_3N) medium and in the presence of DMAP through the intramolecular cyclization under reflux, thus leading to the formation of the desired aziridines **10c-e**. The yields of these two steps can be seen in Table 5.

Table 5. %Yields of Boc- protected aziridines.

Entry	R^1	Amino alcohol	Yield (%),	Aziridine	Yield (%)
1	$PhCH_2$	**2a**	87	**10c**	88
2	$(CH_3)_2CH$	**2b**	92	**10d**	82
3	CH_3CH_2 CH CH_3	**2c**	85	**10e**	79

2.3.1 Preparation of functionalized chiral β-seleno amine:

To resolve the first objective is to determine the probability to employ the most simple ionic liquids of BMIM-BF_4, which would function as a reaction medium, for the synthesis of functionalized chiral β-seleno amine. For this purpose we employed bench stable phenyl selenium zinc bromide (PhSeZnBr), which would function as a nucleophilic selenelating agent for the regioselective ring opening of protected and free aziridines as depicted in Scheme 26**.** Although synthesis of functionalized chiral β-seleno amine was successfully accomplished by phenyl selenium zinc bromide in ionic liquid which is most desirable from the environmental point of view, no organic solvents were used.



Scheme 26. Synthesis of chiral β-seleno amine promoted by PhSeZnBr.

2.3.2 Screening of reaction condition using PhSeZnBr:

We tested the reaction of Boc protected aziridine derived from L-phenyl alanine **10a** with bench stable phenyl selenium zinc bromide(PhSeZnBr) using different organic solvents as well as number of ionic liquids as reaction medium for the synthesis of chiral β-seleno amine by using the following procedure. In a schlenk flask, under argon atmosphere, PhSeZnBr (0,5 mmol) and aziridine (0,5 mmol) were stirred in BMIM-BF_4 (1 mL) at 90℃ for 1 h. After this time, the mixture was cooled to room temperature and the β-seleno amines were extracted from BMIM-BF_4 with Et_2O (3x 10 mL) and dried over $MgSO_4$. The solvent was then removed, yielding the crude products **11a**, which were purified by column chromatography. The yields are summarized in Table 6.

The obtained product of chiral β-seleno amine **11a** was characterized by NMR spetrum.The ^{1}H NMR In the ^{1}H NMR spectrum (Figure 13 and 14) of β-seleno-amine **11a** , a full multiplet on the 2H can be observed in the region

7.50 and 7.40, and similarly in between 7.39 to 7.12ppm, can be observe with other full on the multiplet 8H, which shows characteristic of aromatic hydrogen's (H-8). At 4.68, one can observe a broad singlet with shows hydrogen attached to nitrogen atom. In the region between 4.10 and 4.00, a multiplet appears in full on the 1H, referring to the hydrogen H-2 stereocenter.

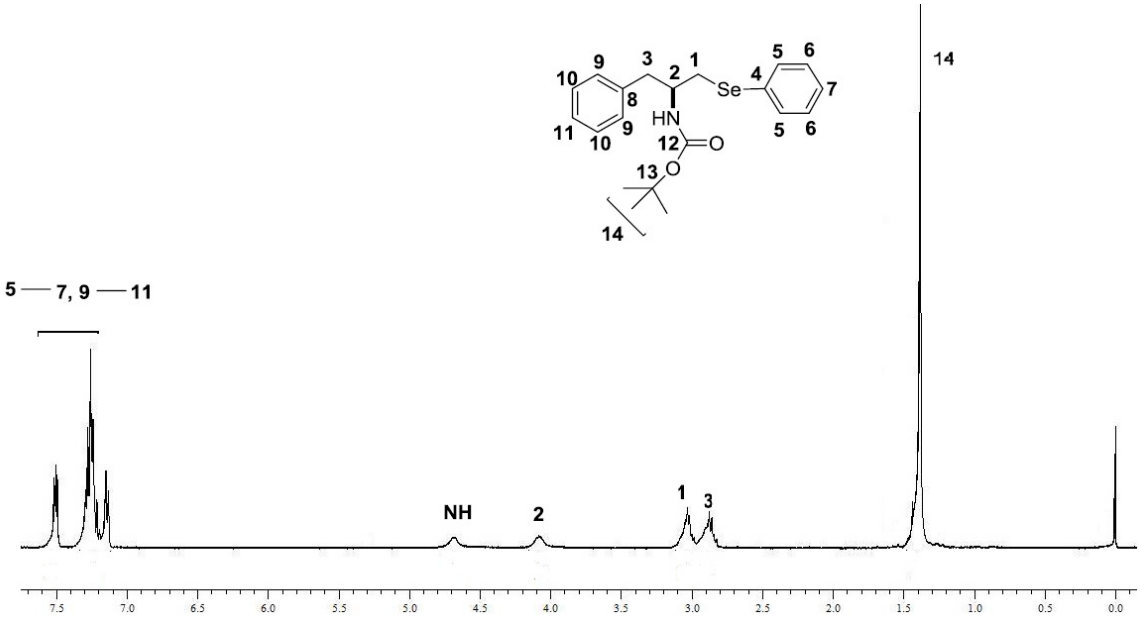


Figure 13. ^{1}H NMR (200 MHz, $CDCl_3$) Spectrum of **11a.**

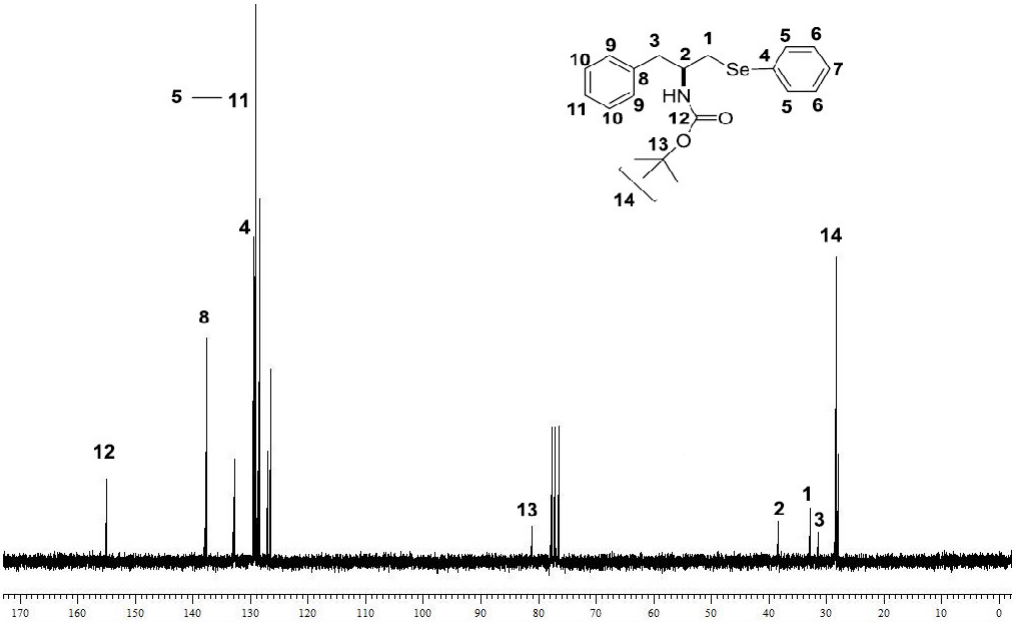
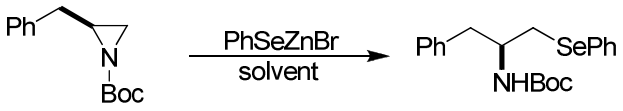


Figure 14. ^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of **11a.**

In relation to the hydrogens H-1 and H-3, first appeared in lower field compared to the second (H-3), which is due to deshielding effect of selenium atom on hydrogens H-1. Similarly, the signal observed in the region between 3.02 and 2.98 ppm which appears as a multiplet which indicate 2H of CH_2 group (H-3). Signs relating to hydrogens H-3 are included in the region between 2.87 and 2.82 also on the integral 2H. In 1.38, we can observe a singlet which shows the 9H, corresponding to the hydrogens of the group of tert-butyl protecting group Boc (H-14). In the ^{13}C NMR spectrum (Figure 14) can be observed at 154.96, a sign shows carbonyl carbon (C-12). The signals related to aromatic carbons are at 137.48, 132.74, 129.29, 129.09, 128.68, 128.40, 126.99 and 126.44 (C 4-11). At 82.90 ppm, one can observe the signal related to the quaternary carbon C-13 of Boc. At 38.21, one can observe the signal related to the chiral carbon C-2. At 32.70, we have a signal corresponding to carbon C-1, which is directly linked to the selenium atom. At 31.50, we can observe a signal corresponding to carbon C-3, linked directly to the aromatic system and 27.07, there is a signal corresponding to methyl carbons of the group of tert-butyl group of Boc C-14.

Table 6.Optimization of reaction conditions for ring opening of aziridine with PhSeZnBr.



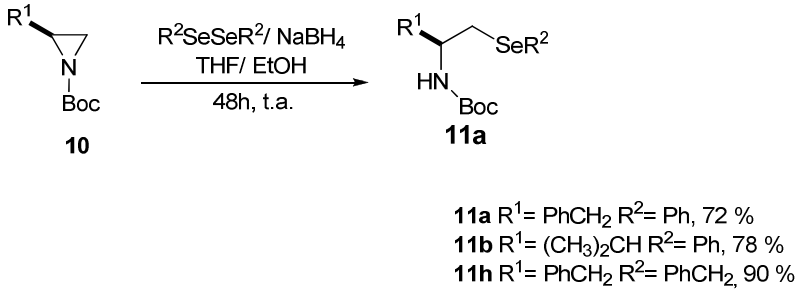
10a **11a**

Entry [a]	Solvent	Time(h)	Temp(°C)	Yield(%)[a]
1	THF	24	rt	65
2	THF	24	reflux	85
3	CH_2Cl_2	24	reflux	70
4	MeCN	24	reflux	67
5	AcOEt	24	reflux	50
6	EtOH	24	reflux	62
7	H_2O	24	reflux	42
8	BMIM-BF_4	24	90	86
9	BMIM-PF_6	24	90	26
10	BMIM-NTf_2	24	90	31
11	BMMIM-BF_4	24	90	50
12	BMIM-BF_4	12	90	84
13	BMIM-BF_4	4	90	82
14	BMIM-BF_4	1	90	81
15[b]	BMIM-BF_4	1	90	68

[a] yields reffered to pure isolated products, characterized by ^{1}H NMR, and ^{13} CNMR spectroscopic data. [b,](PhSeZnCl) was used as a nucleophile instead of (PhSeZnBr).

Aiming to achieve the optimum conditions, Boc protected aziridine **10a** was selected as a model substrate. Our studies started by comparing the feasibility of ionic liquids to promote the reaction efficiently, compared with the well known organic solvents applied for this purpose, Table 6. We selected BMIM-BF_4, BMIM-PF_6 and BMIM-NTf_2 to be evaluated. Using THF under reflux, the product **11a** was obtained with higher yield than when the reaction was carried out at room temperature (entries 1 and 2). When CH_2Cl_2 was used, a decrease in the yield was observed, affording the corresponding product in 70% yield (entry 3). Acetonitrile, ethyl acetate and EtOH were also used and they were less effective than THF: 67%, 50% and 62% respectively (entries 4-6). Water was also used (entry 7), but unfortunately the product was obtained in a lower yield. By using BMIM-BF_4, BMIM-PF_6 and BMIM-NTf_2 at 90 °C for 24h, the product was achieved in 86%, 26 % and 31 % yields respectively (entries 8-10). With these results in hands, BMIM-BF_4 was chosen for the subsequent reactions. When the reaction was conduced at room temperature, a significant decrease in the yield was found (entry 11). The reaction time was also evaluated, and it was noted that, when the time was reduced to 12, 4 and 1h (entries 12, 13 and 14) the yields were at the same level as those in 24h. We also used PhSeZnCl as nucleophile, however the product was obtained in a lower yield when compared with PhSeZnBr, (Entry 15).

The use of nucleophilic selenium species, generated from cleavage of organic diselenide with various reducing agents present themselves as very effective reagent to obtain organoselenium compounds.[54] Recently in our laboratory, was presented a synthetic route for obtaining of β-seleno-chiral amines **11a-c**, via the regioselective opening reaction of *N*-Boc-aziridines 4 with different selenolates, generated with the reducing agent $NaBH_4$, leading to the formation of their products with incomes between 72-90% (Scheme 27).[51]



Scheme 27.

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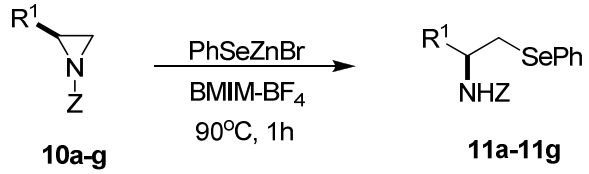
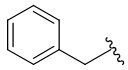
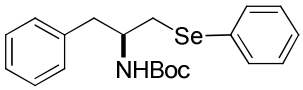
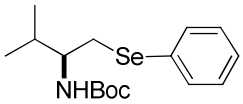
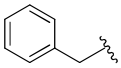
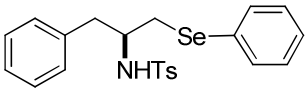
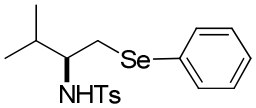
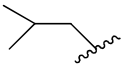
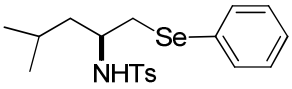
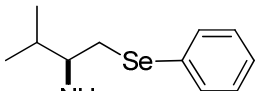
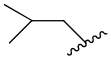
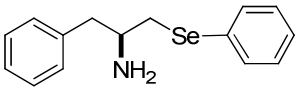
[54] (a) Sakakibara, M.; Katsumata, K.; Watanabe, Y.; Toru, T.;Ueno, Y. *Synthesis* **1992**, 377. (b) Devan, N.; Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2002**, *67,* 9417. (c) Bhasin, K. K.; Singh, N.; Kumar, R.; Deepali, D. G.; Mehta, S. K.; Klapoetke, T. M.; Crawford, M. J. *J. Organomet. Chem.* **2004**, *689*, 3327. (d) Crich, D.; Grant, D. *J. Org. Chem.* **2005**, *70*, 2384

2.3.3 Synthesis of chiral β-seleno amine using PhSeZnBr:

With the optimal conditions in hands, and in order to evaluate the scope and limitations of the reaction procedure, we next prepared a series of chiral β-seleno amine and tried to extend our protocol to broader range of protected and unprotected aziridines with bench stable phenyl selenium zinc bromide in the presence ionic liquid BMIM-BF_4 as reaction medium. The results are summarized in Table 7.

Table 7. Synthesis of chiral β-seleno amine using PhSeZnBr:



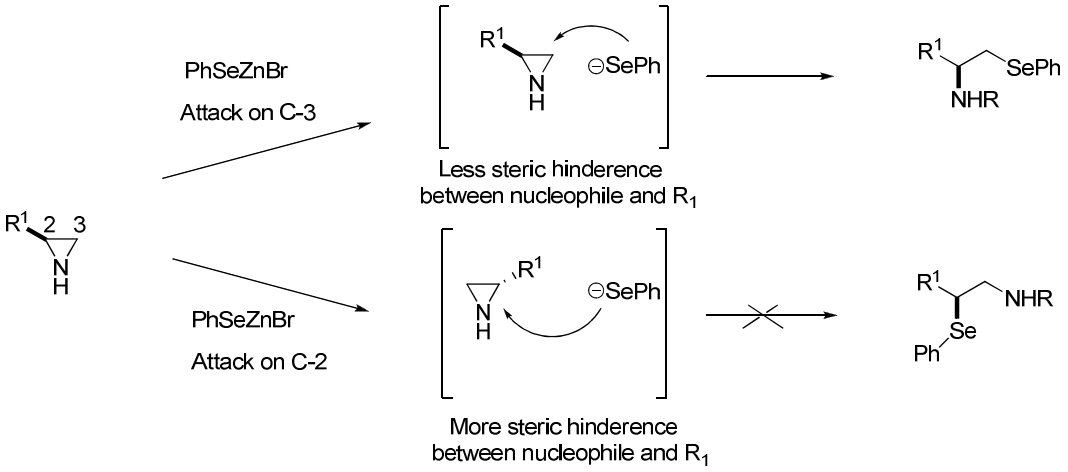
Entry	R^1	Z	Product	[a] Yield (%)
1		Boc	 **11a**	81
2		Boc	 **11b**	60
3		Ts	 **11c**	99
4		Ts	 **11d**	90
5		Ts	 **11e**	85
6		H	 **11f**	70
7		H	 **11g**	52

[a] yields referred to pure isolated products, characterized by ^{1}H NMR, and ^{13} CNMR spectroscopic data.

The N-Boc protected aziridine **10b**, derived from *L*-Valine gave the product in 60% yield (entry 2). For N-Ts protected aziridines **10c-e** better yields

were obtained, the β-seleno amine **11c**, derived from L-Phenylalanine, was achieved in quantitative yield (entry 3). Unprotected aziridines **11f** and **11g** also underwent the reaction, furnishing the desired products in goods yields (entries 6 and 7). These aziridines commonly require severe reaction conditions to underwent ring opening (e.g. use of Lewis acid and reflux for several hours) affording the products in low yield and with poor regioselectivity.

All synthesized protected and free chiral β-seleno amine **11a-g** were characterized by ^{1}H and ^{13}C NMR and the characterization details available in the experimental section.



Scheme 28.

Similarly another most important and interesting feature of the current methodology is its regioselectivity, as the product is given exclusively through the attack of selenolate (PhSeZnBr) to the less-hindered aziridine carbon. aromatic or non aromatic cluster R1 attached to carbon C-2 of aziridine (more hindered) while in the second carbon of aziridine C-3, there is no bulky substituent's with only hydrogen. This steric differentiation between their

carbons directs the attack of the anion selenolate to the less hindered carbon of aziridine ring.

2.3.4 Reuse of ionic liquid/BMIM-BF_4

For further extension of our work and to explore the scope of our method and an effort towards an industrial application, considering economic and environmental aspect, we examined the possibility of reusing of the ionic liquid. Figure 15**.** Accordingly after completion of the reaction, the reaction mixture was extracted with ether (3×20ml), and the combined ether extract was washed with brine, dried with $MgSO_4$ and evaporated to leave the crude product. The residual ionic liquid/ BMIM-BF_4 was diluted in CH_2Cl_2 and filtered through a celite pad to remove the inorganic materials followed by concentrating to remove the organic solvents and being subjected to vacuum for 1hour to eliminate moistures and traces of organic solvents to obtain the solvent and moisture free recovered ionic liquid.

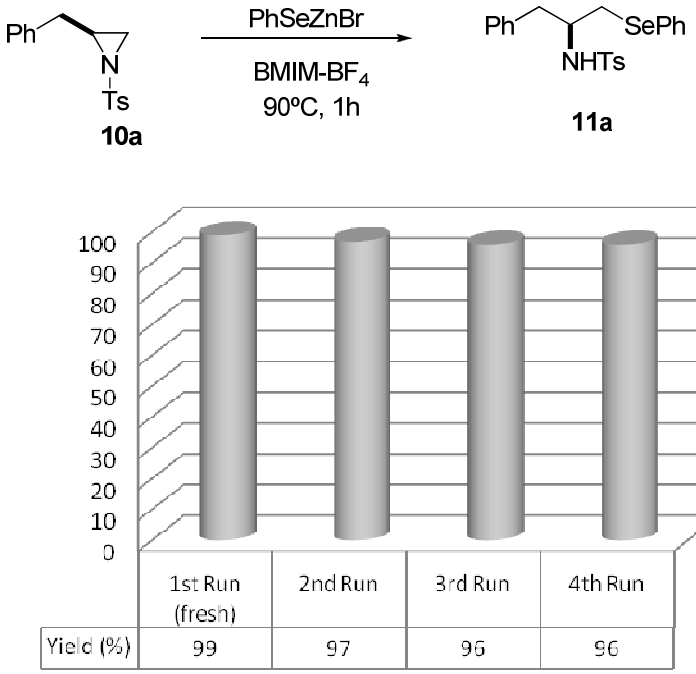
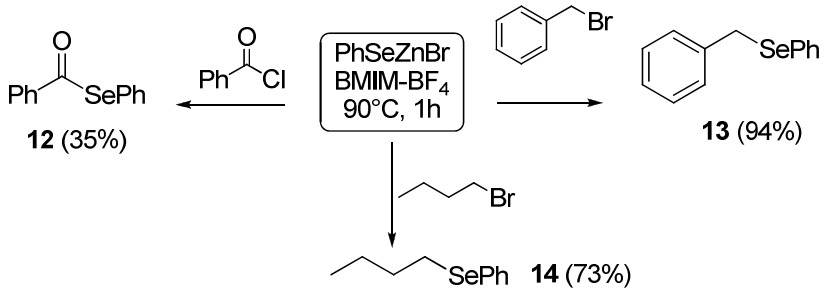


Figure 15. Reuse of ionic liquid/ BMIM-BF_4.

After the recovery process, the same recovered ionic liquid was re used for more successive runs. After additions of one equivalent of PhSeZnBr (0.5 mmol), and aziridine (0.5 mmol) As shown in Figure 15. To our delight, the yield of β-seleno amine obtained was found to similar to that found in the first run. This operation was repeated four times without appreciable loss of efficiency. By comparing its property of recyclability and excellent yields with compared to organic solvents, ionic liquids are considered to be the most interesting reaction medium for our reaction.

Motivated by the excellent results obtained using phenyl selenium zinc bromide for stereo and regioselective ring opening of aziridine in BMIM-BF_4 , which strongly support the function of selenium as a nuclephilic specie in ionic liquid in the shape of PhSeZnBr is possible. We also extended our protocol to other electrophiles, (Scheme 29), and useful compounds such as selenoester **12** and diorganyl selenides **13** and **14** were synthesized in poor to excellent yields



Scheme 29.

The formation of product seleno ester **12** was characterized by NMR spectrum. ^{1}H NMR shows the two aromatic protons as a dublete in δ 7.91 ppm. The three aromatic protons show as multiplet between δ 7.59 and 7.55 ppm. A multiplet between δ 7.46 and 7.39 ppm belongs to the five aromatic protons. In ^{13}C NMR the carbonyl peak appeared at δ 193.18 ppm and the other aromatic carbon peaks appeared at δ 138.5, 136.2, 133.8, 129.3, 128.9, 128.85, 127.2, 125.7 ppm depicted in Figure 16 and 17.

The obtained product benzyl phenyl selenide (**13**) was characterized by NMR spectrum. The ^{1}H NMR shows the $-CH_2$ protons in singlet at δ 4.10 ppm (**H-1**). The eight aromatic protons appeared as a multiplet between δ 7.14 and 7.28 ppm. The other two aromatic protons appeared as a multiplet between δ 7.42 and 7.50 ppm. In ^{13}C NMR spectra, aromatic carbons appeared at δ 138.6, 133.5, 130.4, 128.9, 128.8, 128.4, 127.3 and 126.8 ppm (**C-2-9**). The methylene carbon appeared at δ 32.2 ppm (**C-1**). The ^{1}H and ^{13}C NMR spectral data of the compound **13** confirmed that the formation of product was successfully accomplished. The spectra presented in Figure 18 and 19.

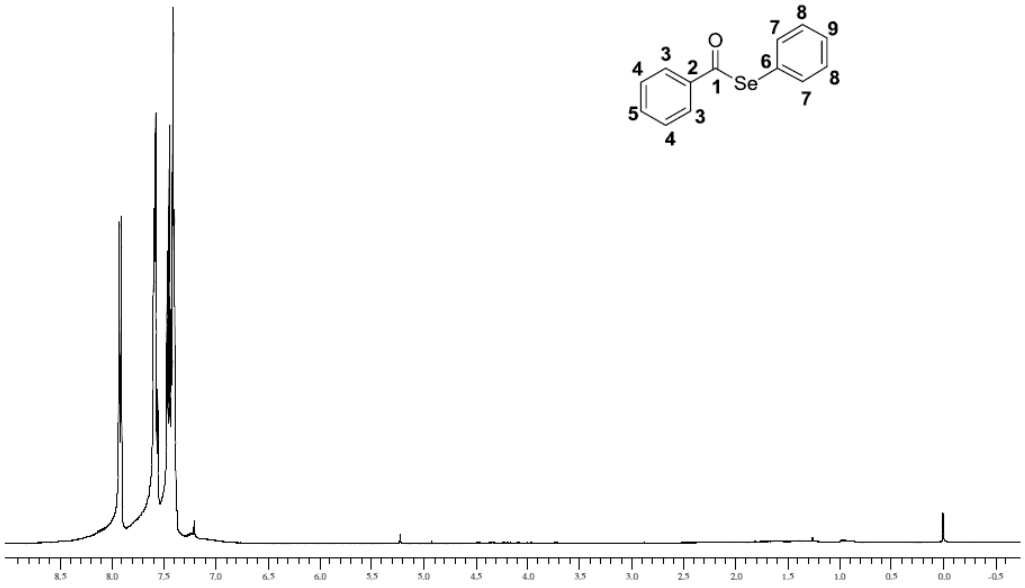


Figure 16 ^{1}H NMR ($CDCl^3$, 400MHz) spectrum of compound **12.**

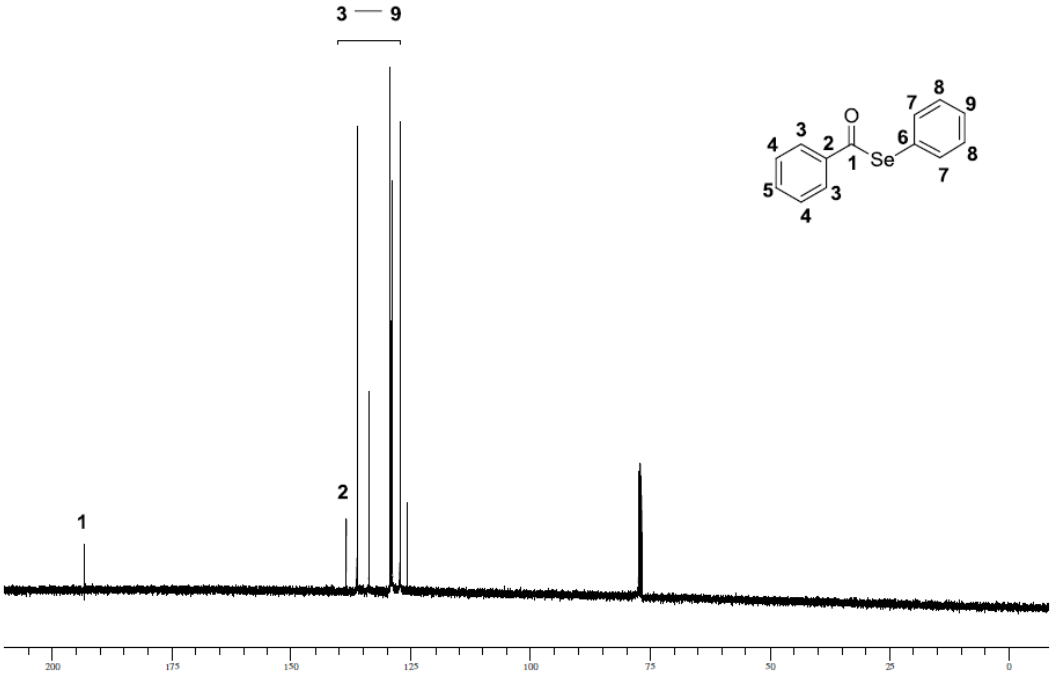


Figure 17. ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of compound **12**.

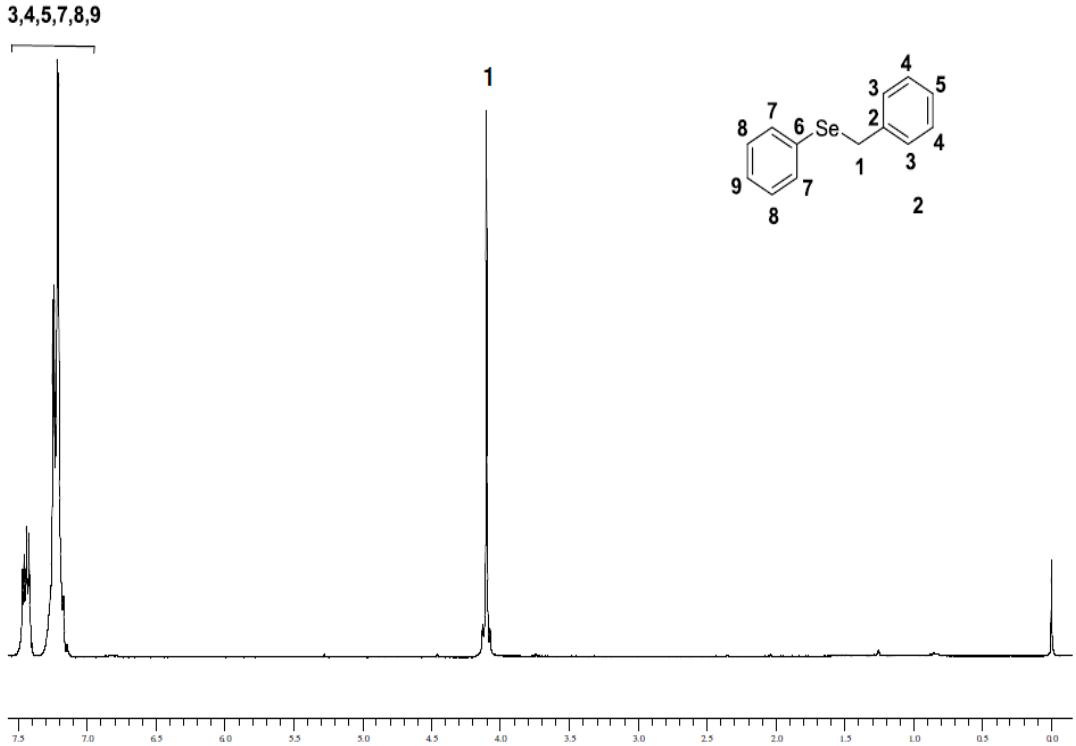


Figure 18. ^{1}H NMR ($CDCl^{3}$, 400MHz) spectrum of compound **13.**

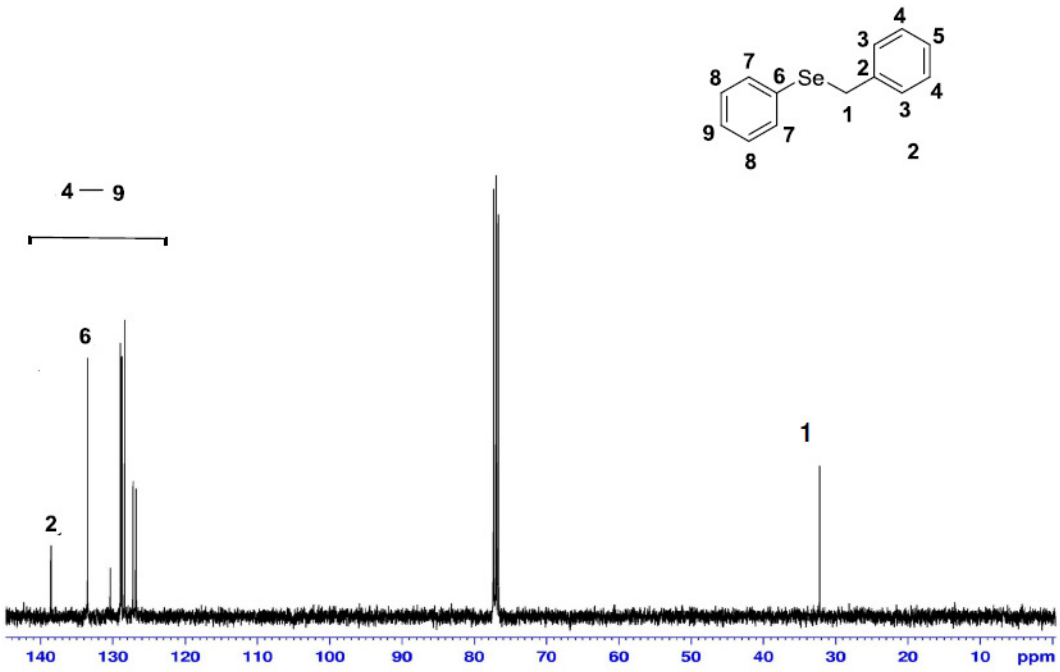


Figure 19. ^{13}C NMR ($CDCl_3$, 100 MHz) Spectrum of compound **13**.

Conclusion

Conclusion.

In conclusion, we have described a practical and concise method for the synthesis of structurally diverse chiral β-seleno amines via the ring opening reaction of protected and unprotected aziridines. In a straightforward and flexible synthetic route, using PhSeZnBr as a nucleophile in BMIM-BF_4, which was susceptible for further reuse without loss of efficiency for at least four runs. Notable features of our approach are the use of bench-stable phenyl selenolate specie in neutral conditions, the recycling of the reaction media and the highly reactivity towards unprotected aziridines, making this an efficient and desirable approach. We believe that the chemistry described herein represents a new route for the synthesis of chiral organoselenium compounds containing nitrogen, among several applications, these compounds are useful chiral ligands in asymmetric catalysis. Some of the noteworthy features of these methodologies are as follow.

(1) Present a simple and efficient approach for the synthesis of chiral β-seleno amines.

(2) The desired product was obtained in a biphasic system, employing inexpensive and commercially available zinc dust, unprotected aziridines with diaryl and dialkyl diselenides.

(3) The most interesting feature of the current methology is its regioselectivity.

(4) A broad set of chiral β-seleno amines were synthesized, as well as a β-telluro amine analogue.

(5) Similarly also developed a concise and practical method for the synthesis of structurally diverse chiral β-seleno amines via ring opening reaction of protected and unprotected aziridines.

(6) In a straightforward and flexible synthetic route, using PhSeZnBr as a nucleophile in BMIM-BF_4, which was susceptible for further reuse without loss of efficiency for at least four runs.

(7) Notable features of our approach are the use of bench-stable phenyl selenolate specie in neutral conditions, the recycling of the reaction media and the highly reactivity towards unprotected aziridines , making this an efficient and desirable approach.

(8) We also extended our protocol to other electrophiles and useful compounds such as selenoesters and diorganyl selenides.

CHAPTER 3

Experimental Section

3.1. General

^{1}H and ^{13}C NMR spectra were recorded at 200 and 400 MHz/ 50 and 100MHz (Department of Chemistry - UFSM) respectively. Chemical shifts (δ) are listed in parts per million (ppm) relative to tetramethylsilane (TMS, used as internal standard for ^{1}H NMR, $CDCl_3$ or DMSO-d6 (for ^{13}C NMR). Column chromatography was performed using Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. All solvents were used as purchased unless otherwise noted. The diselenides and disulfides were used as purchased.

3.2 Experimental section.

3.2.1. Preparation of amino alcohol (2a-b)

In a two neck round-bottom flask under argon atmosphere and fitted with a reflux condenser, was added the appropriate amount of amino acid (50 mmol) in THF (75 mL). After the system was cooled to 0 °C and slowly added $LiAlH_4$ (100 mmol, 3.795 g). The reaction flask was heated to reflux for 20 hours then the solution was cooled to 0 ° C and slowly added NaOH (1N) until formation of a white suspension. The suspension was stirred for additional 30 minutes, filtered on celite, evaporated and purified by distillation, leading to the formation of the corresponding amino alcohols.

3.2.2. Preparation of *N*-Boc amino alcohol (9a-b)

In a single neck round- bottom flask, it was added the appropriate amino alcohol 2 (10 mmol) and acetonitrile (50 mL). Then the system was cooled to 0 ° C and slowly added di-tert-butyl bicarbonate (Boc_2O) (10 mmol, 2.182 g). After the addition, the mixture was stirred for 4 hours at room temperature. Evaporated the solvent and the crude product was purified by column chromatography on silica gel, eluting with a mixture of hexane / ethyl acetate (70:30).

3.2.3. Preparation of *N*-Boc aziridines (10a-b)

In a two neck round-bottom flask, under argon atmosphere and fitted with a reflux condenser, was added appropriate amount of N-Boc amino alcohol 9 (10 mmol) in THF (50 mL), followed by addition of finely powdered KOH (40 mmol, 2.244g) and Tosyl chloride (12 mmol, 2.288 g). The system was heated to reflux for 2 hours, then again added finely powdered KOH (40 mmol, 2.244 g) and the system was heated to reflux for additional 2 hours. Then, the reaction mixture was cooled to room temperature and added NaCl (saturated solution; 30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), organic phases were combined, dried with $MgSO_4$ and the solvent was evaporated. The resulting oil was purified by column chromatography on silica gel using a mixture of hexane / ethyl acetate (95:5) as solvents.

3.2.5. Preparation of β-seleno amines(4a-m)

In a 25 mL round-bottomed flask, under argon atmosphere, was prepared the biphasic solution by the addition of Et_2O (4 mL) and HCl (10%, 4 mL), to this solution were added firstly the diaryl or dialkyl diselenide (0.25 mmol) and zinc dust (500 mg, 7.7 mmol). The mixture was allowed to stir until the yellow solution became colorless (10–30 min), then the unprotected aziridine (0.5 mmol) was added and the reaction was stirred at room temperature for 24 h. After completion of the reaction, as indicated by TLC, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted 3 times with CH_2Cl_2 and the combined organic fractions were collected, dried over $MgSO_4$, filtered and the Solvent was then removed in vacuo. The crude mixture was purified by column chromatography on silica gel eluting hexane / ethyl acetate (95:5) as solvents and after only with ethyl acetate.

3.2.6. Preparation of N-Tosyl aziridines (10c-e)

In a two neck balloon, under argon atmosphere and fitted with a reflux condenser, was added appropriate amount of N-free amino alcohol 2 (30.5

mmol) in THF (120 mL), followed by addition of triethyl amine(4.0 eqv Et_3N, 121.84 mmol, 16.95ml) , DMAP (10mol%, 0.366g) and Tosyl chloride (2.5eqv,190 mmol, 14.46 g). The system was heated to reflux overnight, after that the reaction mixture was cooled down to room temperature, transfer to separatory funnel, washed with saturated solution of ammonium chloride(NH_4Cl 50.0ml), then separate organic phase(containing product) The aqueous phase was also extracted with CH_2Cl_2 (3 x 20 mL), organic phases were combined, dried with $MgSO_4$ and the solvent was evaporated. The resulting crude product was purified by column chromatography on silica gel using a mixture of hexane/ ethyl acetate (90:10) as solvents.

3.2.7. Preparation of PhSeZnBr and PhSeZnCl using PhSeBr (1) and PhSeCl (2).

To a solution of 1 or 2 (10.0 mmol) in THF (20,0 ml), 10.0 mmol of commercial zinc was added. The reaction mixture was refluxed for 30 minutes and then 20 ml of diethyl ether were added. The resulting white solid was filtered, washed 3 times with Et_2O and the solvent was removed under vacuum and a result white solid of PhSeZnBr and PhSeZnCl was obtained.

3.2.8. Preparation of chiral β-seleno amine (11a-g) using PhSeZnBr

In a Schlenk flask, under argon atmosphere, PhSeZnBr (0,5 mmol) and aziridine (0,5 mmol) were stirred in (BMIM)BF_4 (1 mL) at 90℃ for 1 h. After this time, the mixture was cooled to room temperature and the β-seleno amines were extracted from (BMIM)BF_4 with Et_2O (3x 10 mL) and dried over $MgSO_4$. The solvent was then removed, yielding the crude products **11a-g**, which were purified by column chromatography by using a mixture of hexane / ethyl acetate (90:10) as solvents.

3.2.9. Preparation of seleno ester (12) and diorganyl selenides (13 and 14) using PhSeZnBr.

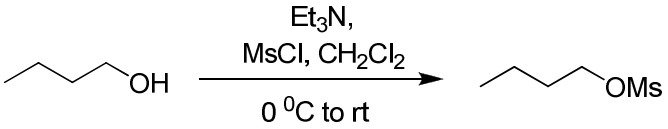
In a schlenk flask, under argon atmosphere, PhSeZnBr (0,5 mmol) and benzoyl chloride,benzyl bromide or butyl bromide (0,5 mmol) were stirred in (BMIM)BF_4 (1 mL) at 90℃ for 1 h. After this time, the mixture was cooled to

room temperature and the product selenoester 12 and diorganyl selenides 13 and 14 were extracted from (BMIM)BF_4 with Et_2O (3x 10 mL) and dried over $MgSO_4$. The solvent was then removed, yielding the crude products which were purified by column chromatography by using a mixture of hexane / ethyl acetate (90:10) as solvents.

3.3. Synthesis of Room temperature ionic liquids

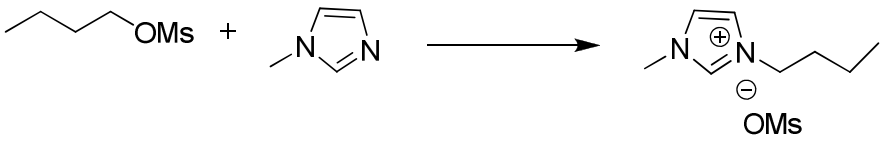
To synthesize the ionic liquids the following systematic procedure were used and discussed in the following sections.

3.3.1. Synthesis of butyl methanesulfonate.



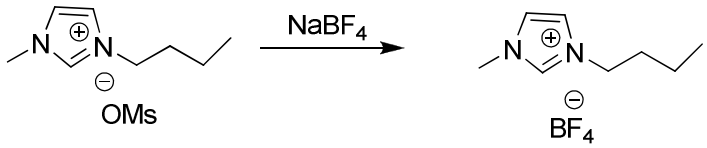
Methanesulfonyl chloride (91.6 g, 0.8 mol) was added (over 45 min), with vigorous stirring, to a solution of n-butanol (59.2 g, 0.8 mol) and triethyl amine (80.8 g, 0.8 mol) in dichloromethane (750 mL). An external water-ice bath was used to control the reaction mixture temperature between 10 –20 0C. After addition, stirring was continued for further 2 h. at room temperature. Water (300 mL) was added, the aqueous layer containing the triethyl ammonium chloride by-product was separated; the organic layer was washed with water (200 mL) and dried with sodium carbonate. Solvent evaporation followed by reduced pressure distillation of the residue afforded the desired butyl methanesulfonate, as a colorless liquid.

3.3.2-Butyl-3-methylimidazolium Methanesulfonate.

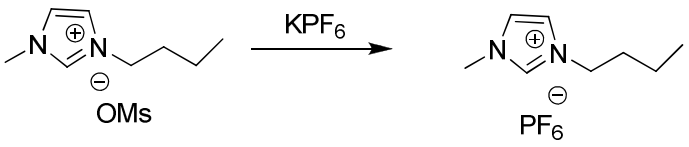


Butyl methanesulfonate (152.1 g, 1.0 mol) was mixed with 1- methyl imidazole (82.07 g, 1.0 mol) and the reaction mixture was kept at room temperature by means of an external water bath. After 24 h, one crystal of 1-butyl-3-methyl imidazolium methanesulfonate was added and the resulting crystalline reaction mass was kept at room temperature for a further 72 h. Recrystallization was performed twice using acetone as solvent (250 mL; from reflux temperature to freezer temperature overnight). After vacuum drying, colorless and very hygroscopic crystals of 1-butyl-3-methylimidazolium methanesulfonate were obtained.

3.3.3. 1-Butyl-3-methylimidazolium Tetrafluoroborate BMIM-BF4.

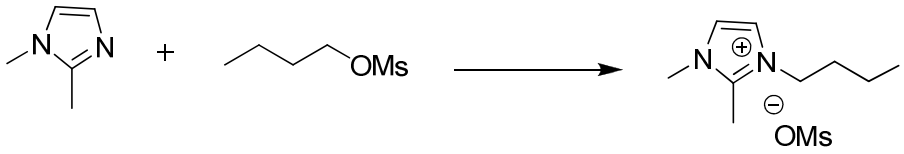


A mixture of 1-butyl-3-methylimidazolium methanesulfonate (41.0 g, 175 mmol), sodium tetrafluoroborate (21.25 g, 193.5 mmol) and distilled water (37 mL) was vigorously stirred for 30 min. The lower aqueous phase was separated and discarded and, to the remaining liquid, sodium tetrafluoroborate (1.5 g, 13.65 mmol) and distilled water (3 mL) were added. Stirring was continued for 15 min and dichloromethane (100 mL) was added. The organic phase was separated, dried with MgSO4 and filtered. Solvent evaporation afforded the desired 1-butyl-3-methylimidazolium tetrafluoroborate as a pale amber liquid



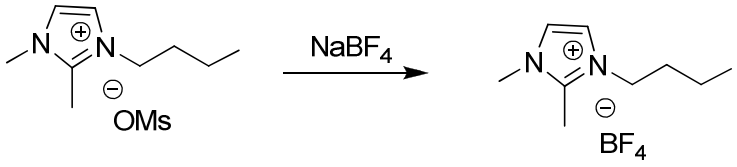
A mixture of 1-butyl-3-methylimidazolium methanesulfonate (36.6 g, 157 mmol), potassium hexafluorophosphate (30.2 g, 164 mmol) and distilled water (83 mL) was vigorously stirred for 30 min. The upper aqueous phase was separated and discarded and, to the remaining liquid, potassium hexafluorophosphate (1.4 g, 7.7 mmol) and distilled water (13 mL) were added. Stirring was continued for 15 min and dichloromethane (83 mL) was added. The organic phase was separated, dried with sodium carbonate and filtered. Solvent evaporation afforded the desired 1-butyl-3-methylimidazolium hexafluorophosphate as a colorless liquid.

3.3.5. 1,2-Dimethyl-3-butylimidazolium Methanesulfonate.



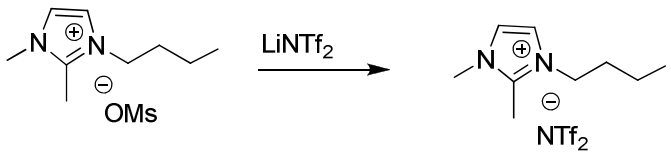
A mixture of 1,2-dimethylimidazole (96.02 g, 1.0 mol) and butyl methanesulfonate (152.05 g, 1.0 mol) was kept at room temperature for 96 h. The resulting crystalline mass was recrystallized twice with acetone (2.0 L), yielding hygroscopic colorless crystals of 1,2-dimethyl-3-butylimidazolium methanesulfonate.

3.3.6. 1,2-Dimethyl-3-butylimidazolium Tetrafluoroborate BMMIM-BF4.



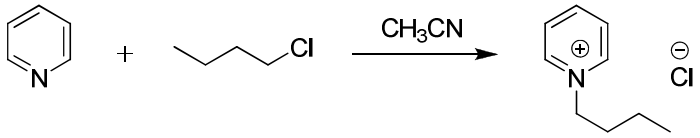
The same procedure discussed in section **4.3.3** was followed to exchange the counter ion.

3.3.7 1-Butyl-3-methylimidazolium bis(trifluoromethane)sulfonimidate BMIM-NTf_2.



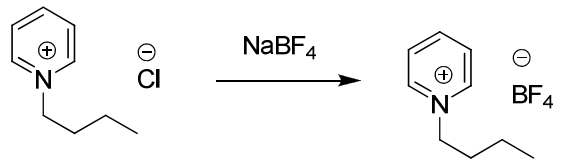
N-Lithium bis (trifluoromethane) sulfonamide salt (25 g, 87 mmol) was dissolved in water (13 mL) and 1-butyl-3-methylimidazolium methanesulfonate (19.3 g, 82.5 mmol) was also dissolved in water (32 mL). Both solutions were mixed, vigorously stirred for 30 min and dichloromethane (100 mL) was added. The organic phase was separated, washed with water (15 mL) and dried with sodium carbonate. Solvent evaporation afforded the desired 1-butyl-3-methylimidazolium bis (trifluoromethane) sulfonimidate as a colorless liquid.

3.3.8 1-Butyl-pyridinium chloride.



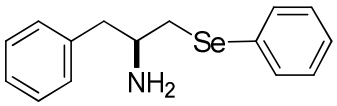
Pyridine (91.6 g, 200 mmol) was added (over 45 min), to a solution of n-chloro butane (59.2 g,200 mmol) in acetonitrile (75 mL). This mixture is allowed to stir 12 hr at 75 0C. After that, acetonitrile was evaporated using roto evaporator followed by washing with ether to remove the unreactive starting materials followed by reduced pressure under vacuum afforded the desired butyl pyridinium chloride, as a turbid crystals .

3.3.9. 1-Butyl-pyridinium Tetrafluoroborate Py-BF4

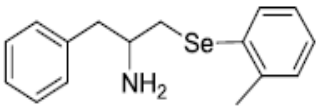


The same procedure discussed in section **4.3.3** was followed to exchange the counter ion.

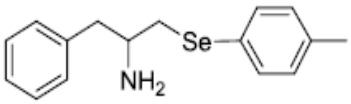
3.4. Spectral details.



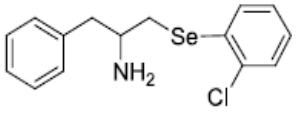
2-Amino,1-phenyl-3-(phenylselanyl)propan, (4a), 62% Yield, ^{1}H NMR (200 MHz, $CDCl_3$), $\delta = 7.51$-7.40(m, 2H), 7.31-7.03(several peaks, 8H), 3.30-3,03(m, 2H), 2.92-2.73(m. 2H), 2.69-2.54(m, 1H), 1.70(brs, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 138.68, 132.62, 130.05, 129.22, 129.08, 128.48, 126.90, 126.41, 52.45, 43.87, 36.50 ppm.



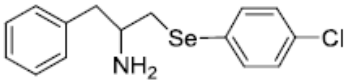
2-amino,1-phenyl-3-(o-tolylselanyl)propan,(4b), 35% Yield**,** ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.37$-7.08 (m, 9H), 3.23-3.16 (m, 1H), 3.11-3.05 (m, 1H), 2.90-2.76 (m, 2H), 2.69-2.62 (m, 1H), 2.40 (s, 3H), 1.58 (brs, 2H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 139.27, 138.59, 131.470, 130.92, 129.99, 129.20, 128.46, 126.70, 126.41, 52.34, 43.92, 35.16, 22.36.



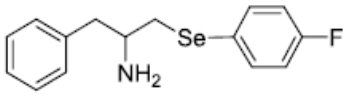
2-amino,1-phenyl-3-(p-tolylselanyl)propan. (4c), 60% Yield**,** ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.40\text{-}7.34$ (d, *J*= 8.18, 2H), 7.28-7.18 (m, 3H), 7.16-7.11 (d, *J*= 7.01,2H), 7.05-7.03 (d, *J*= 7.60, 2H), 3.20-3.13 (m, 1H), 3.09-3.03 (m, 2H), 2.88-2.78 (m, 2H), 2.69-2.62 (m,1H), 3.30 (s, 3H), 2.17 (brs, 2H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 138.55, 136.87, 133.06, 129.87, 128.18, 128.42, 126.37, 125.90, 52.37, 43.44, 36.36, 20.97.



2-amine-1-(2-chlorophenylselanyl)-3-phenylpropan (4d), 55% Yield**,** ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.75\text{-}6.79$ (m, 9H), 3.23-3.16 (m, 1H), 3.11-3.05 (m, 1H), 2.90-2.76 (m, 2H), 2.69-2.62 (m, 1H), 1.40 (brs, 2H), ^{13}CNMR ($CDCl_3$,100 MHz)δ = 138.01, 134.1, 131.3, 129.37, 129.07, 128.95, 128.67, 128.54, 126.46, 51.23, 43.65, 35.50ppm.

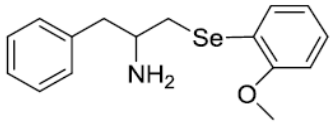


2-amino-1-(4-chlorophenylselanyl)-3-phenylpropan (4e), 80% Yield**,** ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.37\text{-}7.32$(d, *J*= 8.55, 2H), 7.29-7.06(m, 7H), 3.18-3.09(m, 1H), 3.09-3.03(m, 2H), 2.85-2.74(m, 2H), 2.69-2.62(m, 1H), 1.66(brs, 2H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ =138.32, 133.69, 132.89, 129.03, 128.34, 128.15, 126.31, 52.26, 43.67, 36.54.ppm

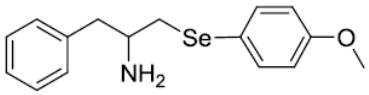


2-amine-1-(4-fluorophenylselanyl)-3-phenylpropan (4f), 85% Yield, ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.65\text{-}6.79$(m, 9H), 3.28-2.96(m , 2H), 2.94-2.73(m, 2H), 2.71-2.56(m , 1H), 1.80(brs, 2H), ^{13}C

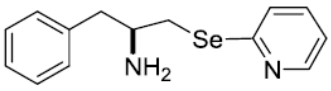
NMR ($CDCl_3$, 100 MHz) δ = 160.90, 138.35, 135.06, 129.06, 128.39, 126.35, 124.16, 52.24, 43.49, 36.98ppm.



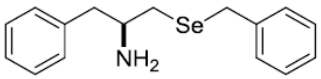
2-amine-1-(2-methoxyphenylselenyl)-3-phenylpropan,(4g), 51% Yield, ^1H NMR (200 MHz, $CDCl_3$) δ = 7.31-7.06(m, 7H), 6.88-6.72(m, 2H), 3.80(s, 3H), 3.68(brs, 2H), 3.21-3.13(m, 1H), 3.12-3.07(m , 1H),2.87-2.64(m, 2H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ =157.71, 138.67, 131.64, 129.13,128.77,128.31,127.91, 127.78, 126.23, 121.24, 55.61, 52.26, 43.86, 33.61.ppm



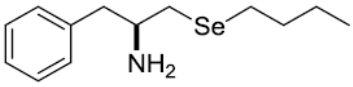
2-amino 1-(4-methoxyphenylselenyl)-3-phenylpropan(4h), 58% Yield, ^1H NMR (400 MHz, $CDCl_3$) δ =7.51-7.43(m, 2H), 7.31-7.11(m, 5H), 6.82-6.76(m, 2H), 3.79(s, 3H), 3.78(brs, 2H), 3.17-3.10(m, 1H), 3.04-2,98(m, 1H), 2.86-2.72(m, 2H), 2.65-2,58(m, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ =159.28, 138.75, 135.47, 135.38, 129.19, 128.44, 126.33, 114.81, 55.23, 52.24, 43.75, 37.70ppm



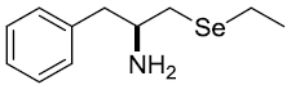
(S) 2-amino-1-phenyl-3-(pyridin-2-ylselanyl)propan(4i),46%, Yield, NMR (400 MHz, $CDCl_3$) δ = 8.62-8.30(m, 1H), 7,78-6.72(m, 8H), 3.50-3.40 (m, 2H), 3.20-3.10 (m. 2H), 2.90-2.80 (m, 1H), 1.3(brs, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 154,27,150.28, 137.89, 136.36, 129.40, 128.58, 126.59, 126.09,52.90, 42.68, 33.13 ppm



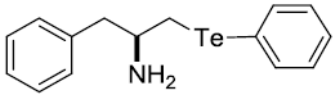
(S) 2-amino-1-(benzylselanyl)-3-phenylpropan(4j), 35%, Yield, NMR (400 MHz, $CDCl_3$) δ =7.67-6.90(m, 10H), 3.74(s, 2H), 3.52(s, 2H), 3.30-3,03(m, 2H), 2.92-2.73(m. 2H), 2.69-2.54(m, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 129.61,129.23, 128.98, 128.80, 128.47, 128.39, 127.05, 126.70, 52.61,42.71, 30.28 ,27.05 ppm.



2-amino-1-(butylselanyl)-3-phenylpropane(4k), 35%, Yield, NMR (400 MHz, $CDCl_3$) δ = 7.37-7.15(m, 5H), 3.21-3.12(m, 1H), 2.99-2.91(m, 1H), 2.88-2.73(m, 2H), 2.64-2.47(m, 3H), 1.89-1.80(d, 2H), 1.45-1.1.32(sextet, 2H), 0.94-.74(quartet, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 138.87, 129.15, 128.41, 126.30, 52.61, 43.97, 39.75, 32.67, 24.35, 22.88, 13.48ppm.

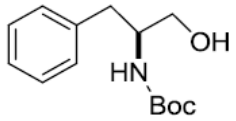


2-amino-1-(ethylselanyl)-3-phenylpropane (4l). 52%, Yield, NMR (400 MHz, $CDCl_3$) δ = 7.33-7.18(m, 5H), 3.23-3.15(m, 1H), 2.89-2.82 ((m, 1H), 2.80-2.74(m, 1H), 2.69-2.50(m, 4H), 2.21(brs, 2H), 1.40-1.34(t, 3H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 138.70, 129.16, 128.44, 126.35, 52.65, 43.71, 31.92, 17.92, 15.77ppm.

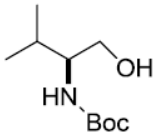


2-amine-1-phenyl-3-(phenyltelluryl) propane,(4m), 40%, Yield, NMR (400 MHz, $CDCl_3$) δ =7.73-7.66(m, 1H), 7.39-7.10(m, 8H), 3,24-3.11(m, 2H), 2.95-2.80(m, 2H), 2.68-2.60(m , 1H), 1.65(brs, 2H). ^{13}C NMR

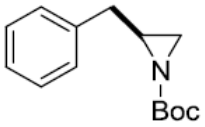
($CDCl_3$, 100 MHz) δ = 138.79, 138.17, 1129.15, 128.45, 127.51, 126.36, 111.79, 53.35, 45.14, 19.69ppm



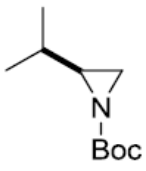
N- Boc phenylalanilol (9a) 92% Yield ; ^1H NMR ($CDCl_4$, 400 MHz), δ(ppm) = 7,32 - 7,20 (m, 5H); 4,79 - 4,77 (m, 1H); 3,81 - 3,78 (m, 1H); 3,65 (dd, *J* = 11,0 e 3,7 Hz, 1H); 3,54 (dd, *J* = 11,0 e 5,2 Hz, 1H); 2,83 (d, *J* = 7,1 Hz, 2H); 2,47 - 2,44 (m, 1H); 1,41 (s, 9H); RMN ^{13}C ($CDCl_3$, 100 MHz) δ (ppm) = 156,13; 137,82; 129,27; 128,52; 126,49; 79,71; 64,29; 53,73; 37,47; 28,32.



N- Boc valinol(9b) 87% **Yield ;** ^1H NMR ($CDCl_4$, 400 MHz), δ(ppm) = 4,99 - 4,96 (m, 1H); 3,63 - 3,60 (m, 2H); 3,39 - 3,36 (m, 1H); 1,86 - 1,82 (m, 1H); 1,44 (s, 9H); 0,94 (d, *J* = 8,5 Hz, 3H); 0,92 (d, *J* = 8,5 Hz, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 156,62; 79,11; 63,39; 60,24; 57,77; 28,23; 19,36; 18,34.

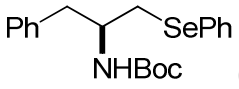


(*S*)-*tert*-butyl 2-benzylaziridine-1-carboxylate (10a) 75% Yield ; ^1H NMR ($CDCl_4$, 400 MHz), δ (ppm) = 7,30 - 7,20 (m, 5H); 2,95 (dd, *J* = 13,9 e 5,6 Hz, 1H); 2,68 - 2,60 (m, 2H); 2,33 - 2,28 (m, 1H); 2,04 - 2,01 (m, 1H); 1,43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 162,27; 137,90; 128,67; 128,32; 126,43; 80,96; 38,31; 38,19; 31,29; 27,78.

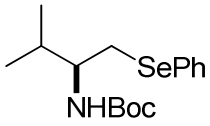


(*S*)-*tert*-butyl 2-isopropylaziridine-1-carboxylate (10b) 75% **Yield ;** ^1H NMR ($CDCl_4$, 400 MHz), δ (ppm) = 2,24 - 2,21 (m, 1H); 2,15 - 2,12

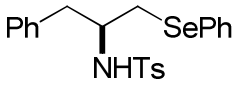
(m, 1H); 1,95 - 1,92 (m, 1H); 1,49 - 1,47 (m, 1H); 1,45 (s, 9H); 1,06 (d, *J* = 6,6 Hz, 3H); 0,96 (d, *J* = 6,6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) = 162,65; 80,48; 44,16; 30,76; 30,40; 27,69; 19,52; 18,92.



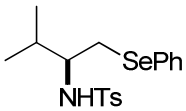
(S)-tert-butyl-1-phenyl-3-(phenyselenyl)propan-2-ylcarbamate (11a) 81% Yield ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.40 (m, 2H), 7.39-7.12 (m, 8H), 4.68 (sl, 1H of NH), 4.10-4.00 (m, 1H), 3.02-2.98 (m, 2H), 2.87-2.82 (m, 2H), 1.38 (s, 9H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 154.96, 137.48, 132.74, 129.29, 129.09, 128.68, 128.40, 126.99, 126.44, 82.90, 38.21, 32.70, 31.50, 27.07.



(S)-tert-butyl-3-methyl-1-(phenylselanyl)butan-2yl carbamate (11b) 60% Yield ; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.55-7.50 (m, 2H), 7.26-7.23 (m, 3H), 4.60-4.55 (m, 1H), 3.69-3.59 (m, 1H), 3.07 (d, *J* = 5.6 Hz, 2H), 1.94-1.77 (m, 1H), 1.42 (s, 9H), 0.91-0.87 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.54, 132.93, 129.05, 126.99, 79.10, 55.64, 32.41, 31.69, 28.33, 19.43, 17.97 ppm.

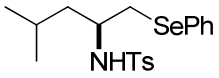


(S)-4-methyl-N-(1-phenyl-3-(phenylselanyl)propan-2-yl)benzenesulfonamide(11c) 99% Yield ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-7.39 (m, 4H), 7.27-7.09 (m, 9H), 6.93-6.91 (m, 2H), 4,69 (d, *J* = 7.2 Hz, 1H), 3.55-3.48 (m, 1H), 3.12 (m, 1H), 2.94 (m, 1H), 2.83 (m, 1H), 2.76 (m, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.13, 136.79, 136.45, 132.92, 129.51, 129.24, 128.61, 127.29, 126.96, 126.72, 54.49, 40.29, 32.87, 21.47 ppm.

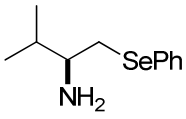


(S)-4-methyl-N-(3-methyl-1-(phenylselanyl)butan-2-yl) benzene sulfonamide(11d) 90% Yield ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62

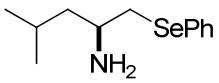
(d, *J* = 8.4 Hz, 2H), 7.37-7.35 (m, 2H), 7.26-7.17 (m, 5H), 4.82 (d, *J* = 6.4 Hz, 1H), 3.23-3.17 (m, 1H), 3.06 (dd, J^1 = 12.8 Hz, J^2 = 4.8 Hz, 1H), 2.74 (dd, J^1 = 12.6 Hz, J^2 = 6.6 Hz, 1H), 2.38 (s, 3H), 2.01-1.93 (m, 1H), 0.81 (d, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.19, 137.65, 133.07, 129.54, 129.15, 127.29, 127.05, 58.57, 31.64, 30.68, 21.49, 19.01, 17.44 ppm.



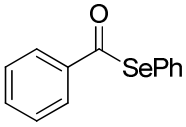
(S)-4-methyl-N-(4-methyl-1-(phenylselanyl)pentan-2-yl)benzenesulfonamide (11e) 85% Yield ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.4 Hz, 2H), 7.42-7.40 (m, 2H), 7.29-7.21 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 2H), 4.86 (d, *J* = 8.4 Hz, 1H), 3.46-3.38 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 2.38 (s, 3H), 1.48-1.36 (m, 2H), 1.29-1.23 (m, 1H), 0.77 (d, *J* = 6.4 Hz, 3H), 0.59 (d, *J* = 6.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.19, 137.65, 133.19, 129.52, 129.08, 127.23, 126.98, 51.54, 43.82, 34.65, 24.30, 22.76, 21.52, 21.43 ppm.



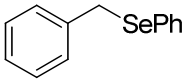
(S)-3-methyl-1-(phenylselanyl)butan-2-amine (11f). 70% Yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53-7.48 (m, 2H), 7.25-7.22 (m, 3H), 3.18-3.11 (m, 1H), 2.83-2.64 (m, 2H), 1.77-1.65 (m, 1H), 1.56 (s, 2H), 0.92 (d, *J* = 2.6 Hz, 3H), 0.89 (d, *J* = 2.6 Hz, 3H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.53, 130.08, 128.95, 126.75, 56.06, 35.04, 33.33, 19.15, 15.62 ppm.



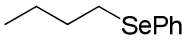
(S)-4-methyl-1-(phenylselanyl)pentan-2-amine (11g). 52% Yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53-7.48 (m, 2H), 7.25-7.22 (m, 3H), 3.12-3.02 (m, 1H), 2.98-2.89 (m, 1H), 2.80-2.71 (m, 1H), 1.75-1.65 (m, 1H), 1.60 (s, 2H), 1.28 (t, *J* = 7.0 Hz, 2H), 0.88-0.82 (m, 6H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.62, 130.06, 128.92, 126.76, 48.51, 46.75, 38.07, 24.94, 23.05, 21.98 ppm.



Se-phenyl selenobenzoate (12) 35% Yield; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.91 (d, *J* = 7.2 Hz, 2H); 7.59-7.55 (m, 3H); 7.46-7.39 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.18, 138.46, 136.23, 133.78, 129.26, 128.95, 128.85, 127.23, 125.74 ppm



benzyl(phenyl)selane (13) 94% Yield ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.42 (m, 2H), 7.28-7.14 (m, 8H), 4.10 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 138.60, 133.53, 130.40, 128.94, 128.82, 128.39, 127.26, 126.82, 32.21 ppm.



butyl(phenyl)selane (14) 73% Yield ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49-7.45 (m, 2H), 7.26-7.18 (m, 3H), 2.90 (t, *J* = 7.6 Hz, 2H), 1.71-1.64 (m, 2H), 1.46-1.37 (m, 2H), 0.90 (t, *J*= 7.2Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 132.42, 130.82, 129.02, 126.62, 32.32, 27.66, 23.02, 13.64 ppm.

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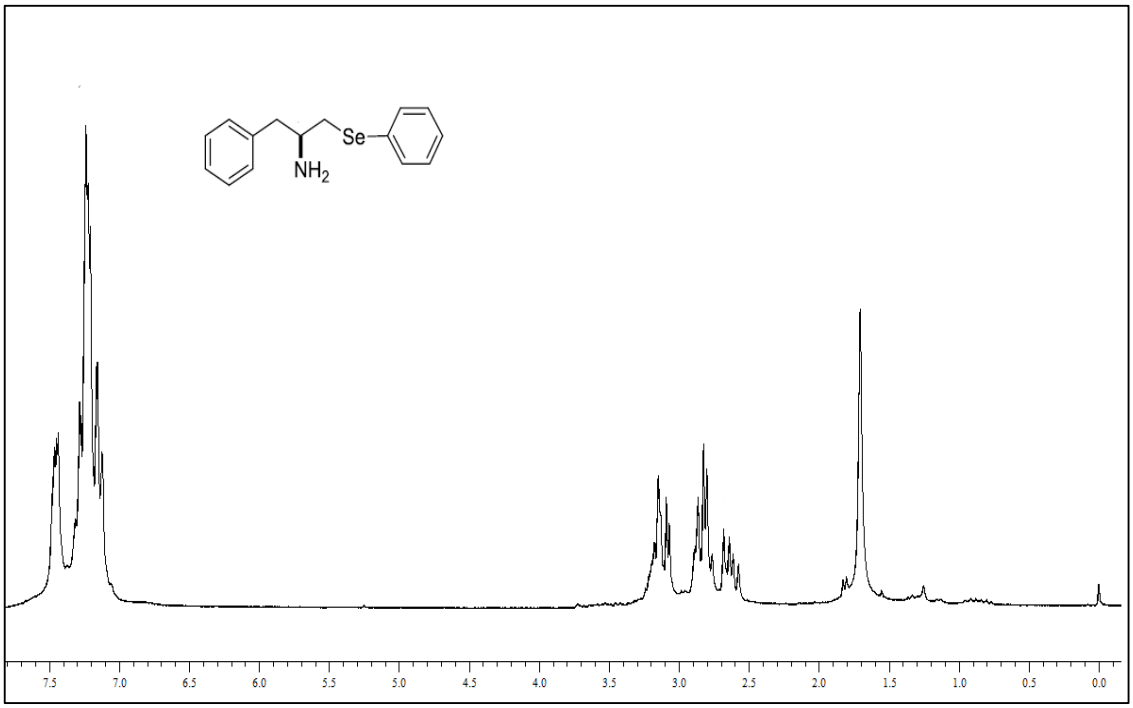
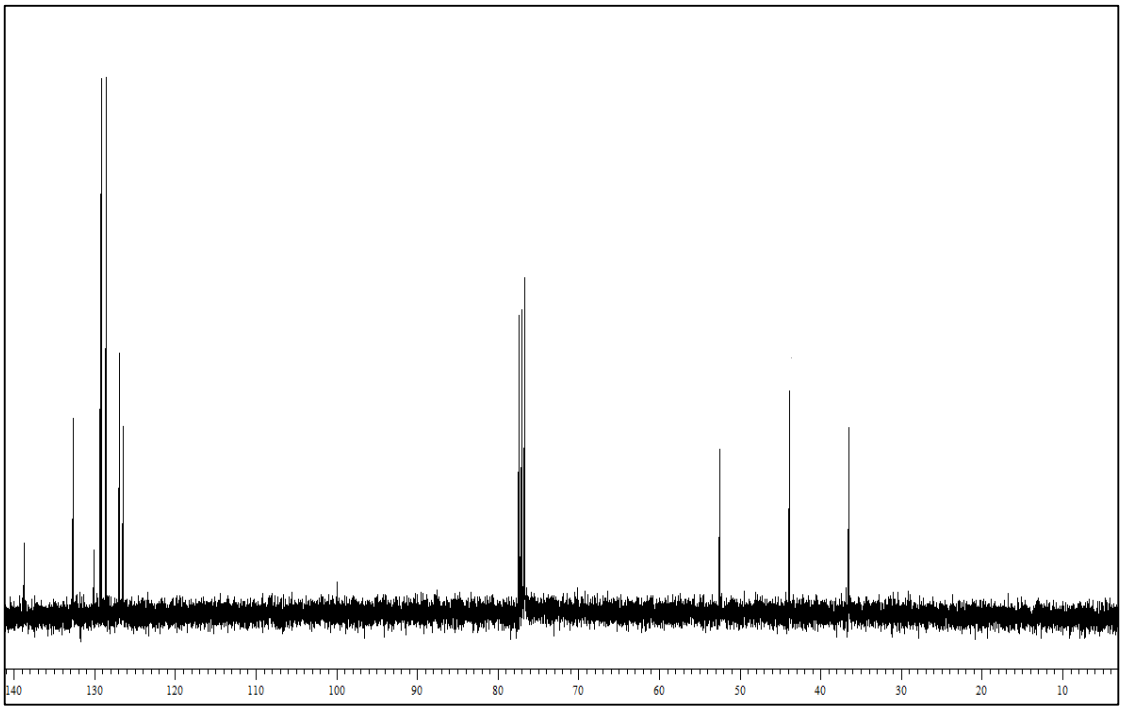
CHAPTER 4

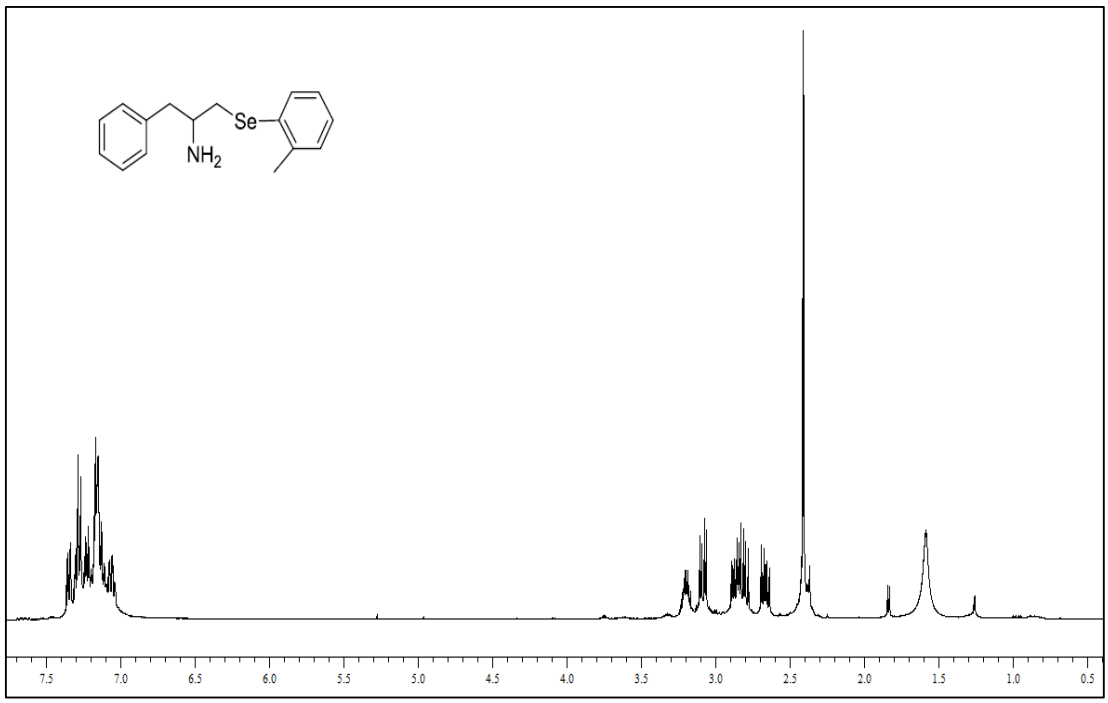
Reproduced Spectras



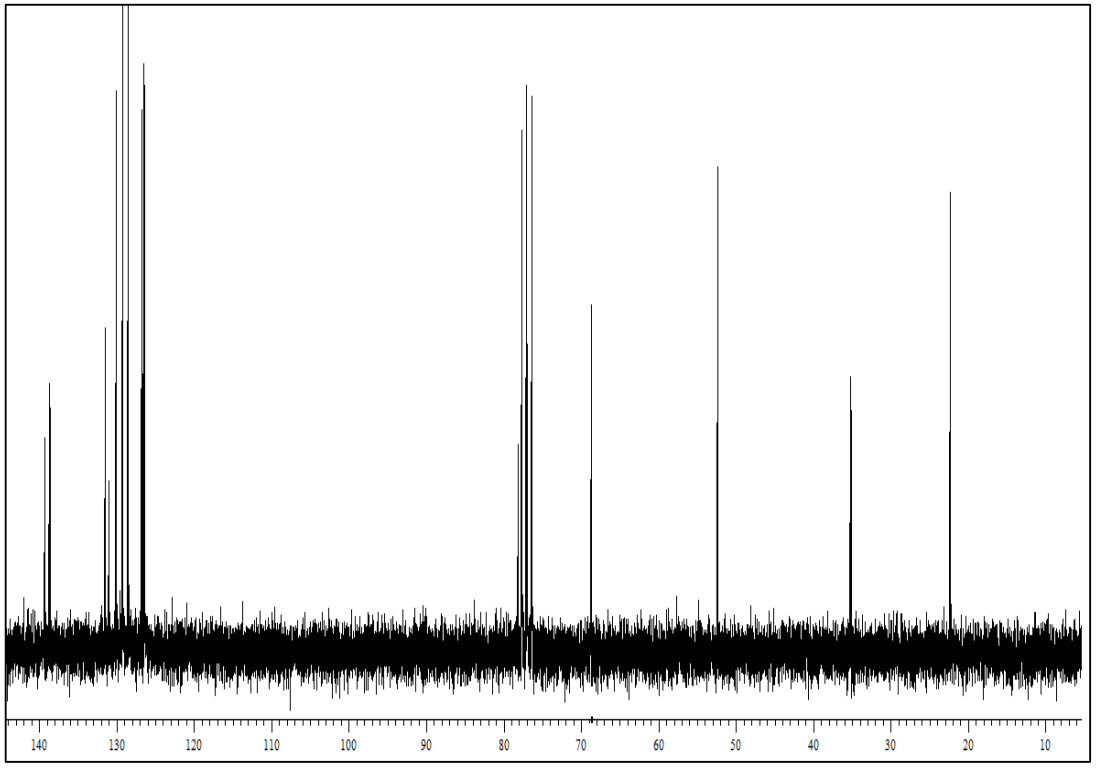
^{1}H NMR (200MHz, $CDCl_3$) spectrum of **4a**



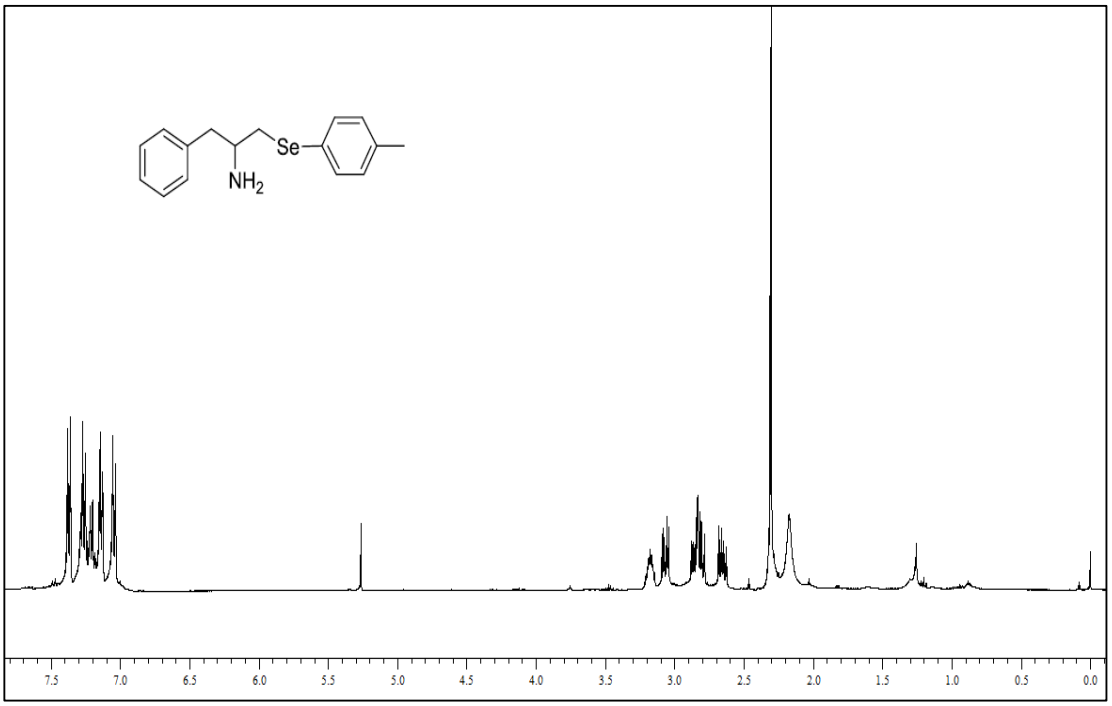
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4a**



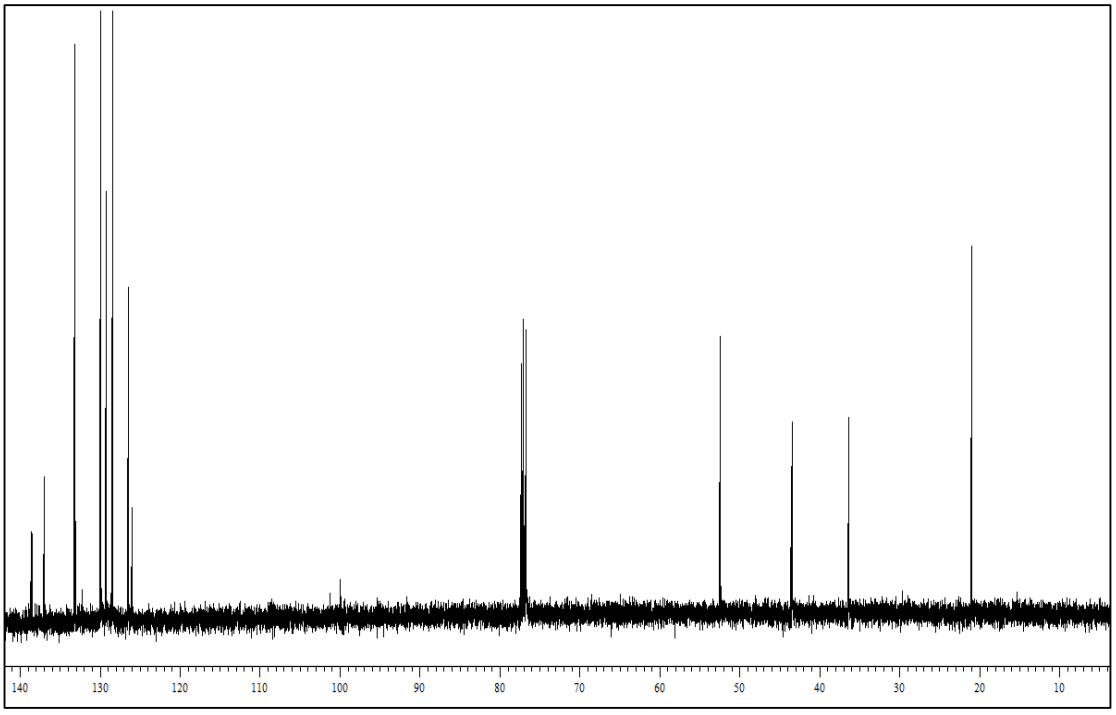
NMR (400MHz, $CDCl_3$) spectrum of **4**



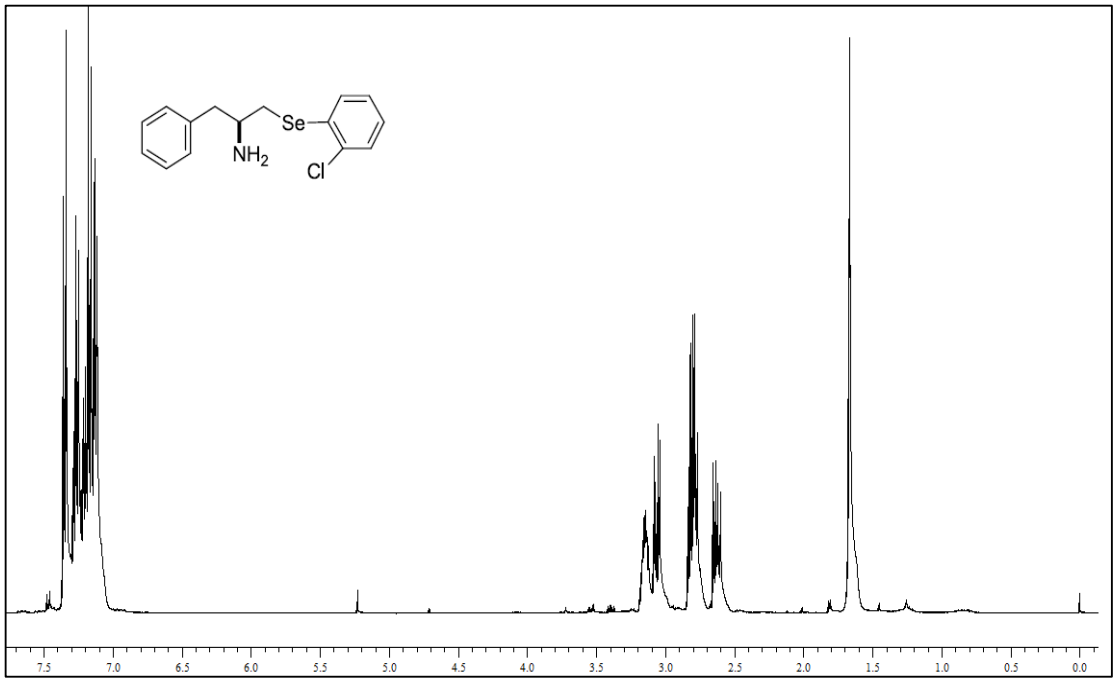
^{13}C NMR (50MHz, $CDCl_3$) spectrum of **4b**



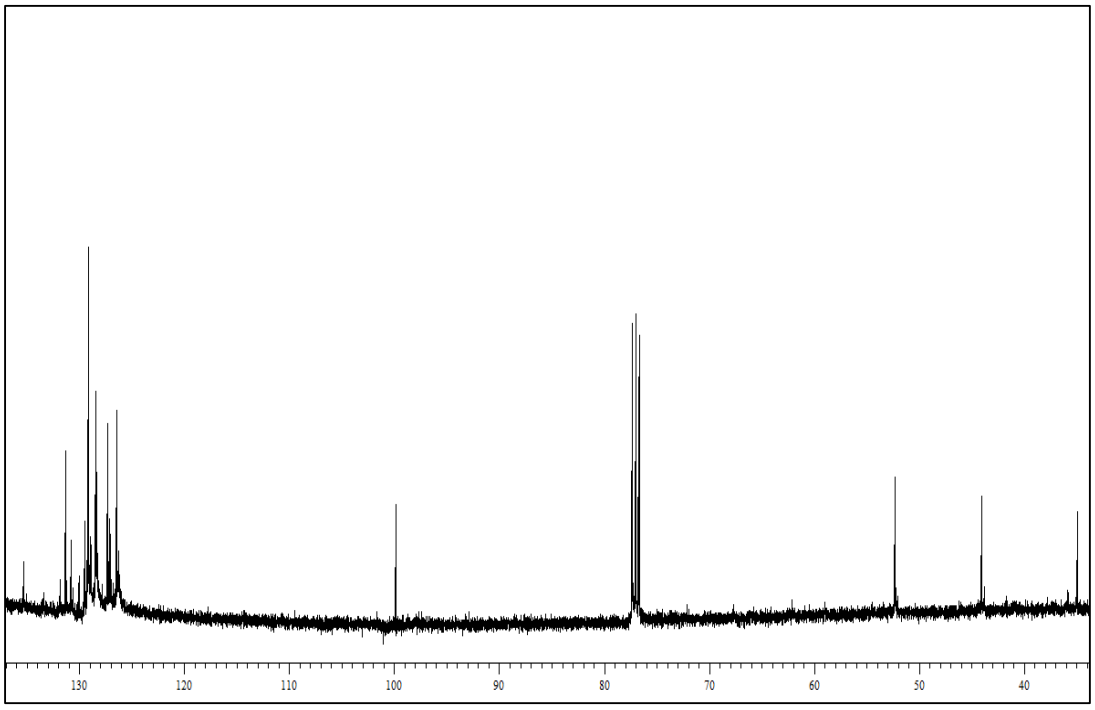
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4c**



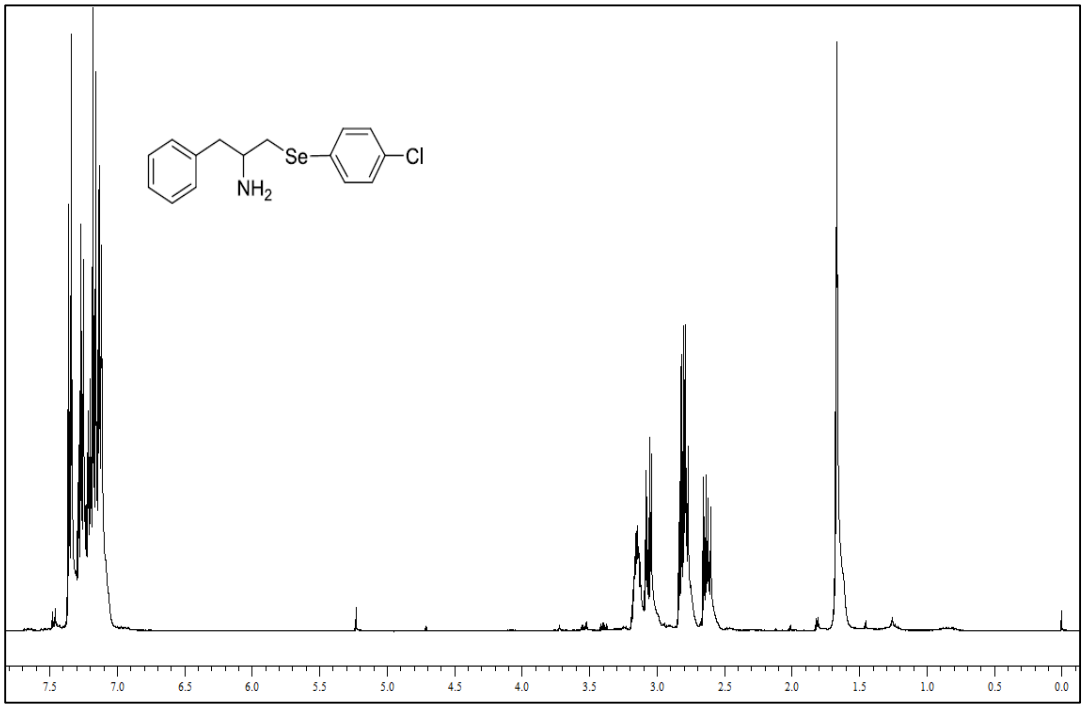
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4c**



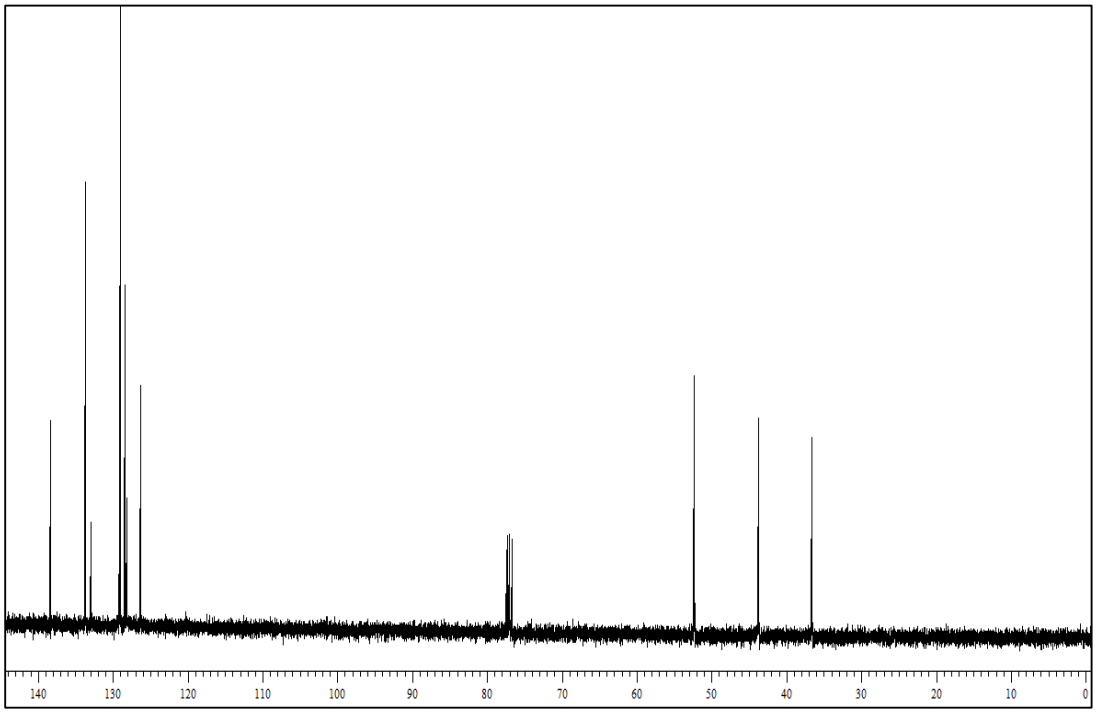
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4d**



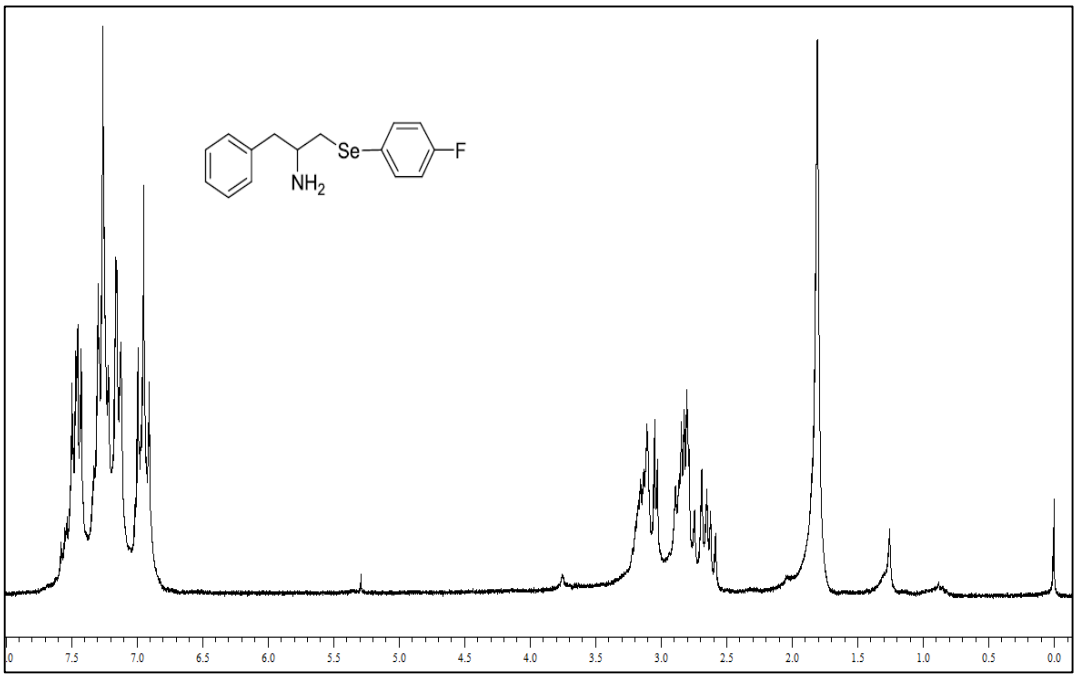
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4d**



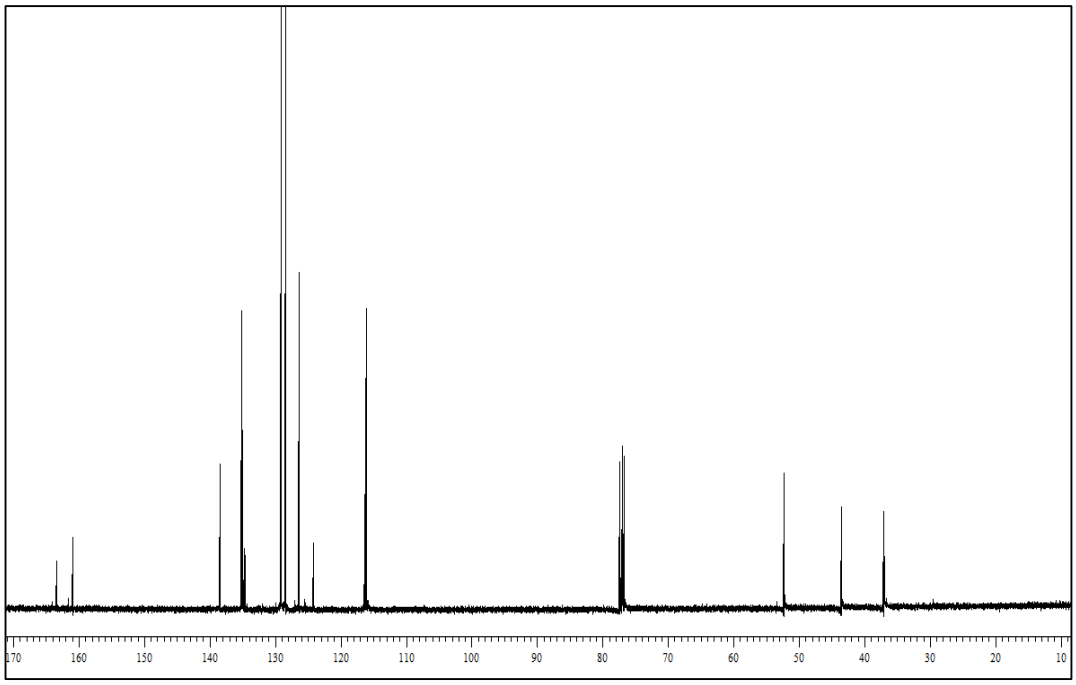
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4e**



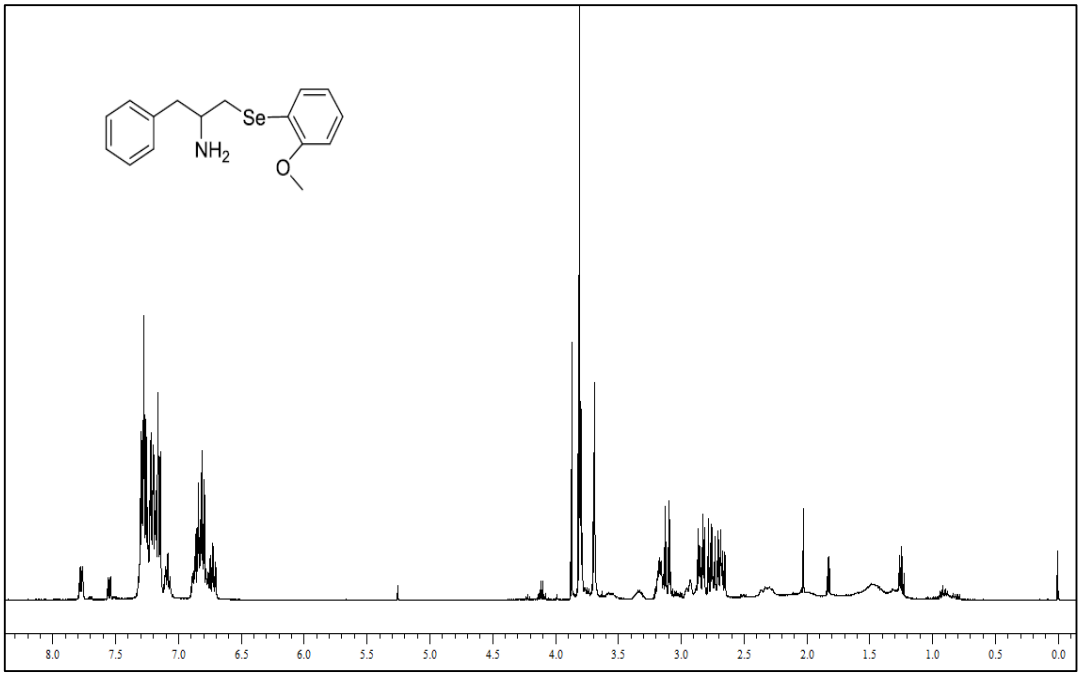
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4e**

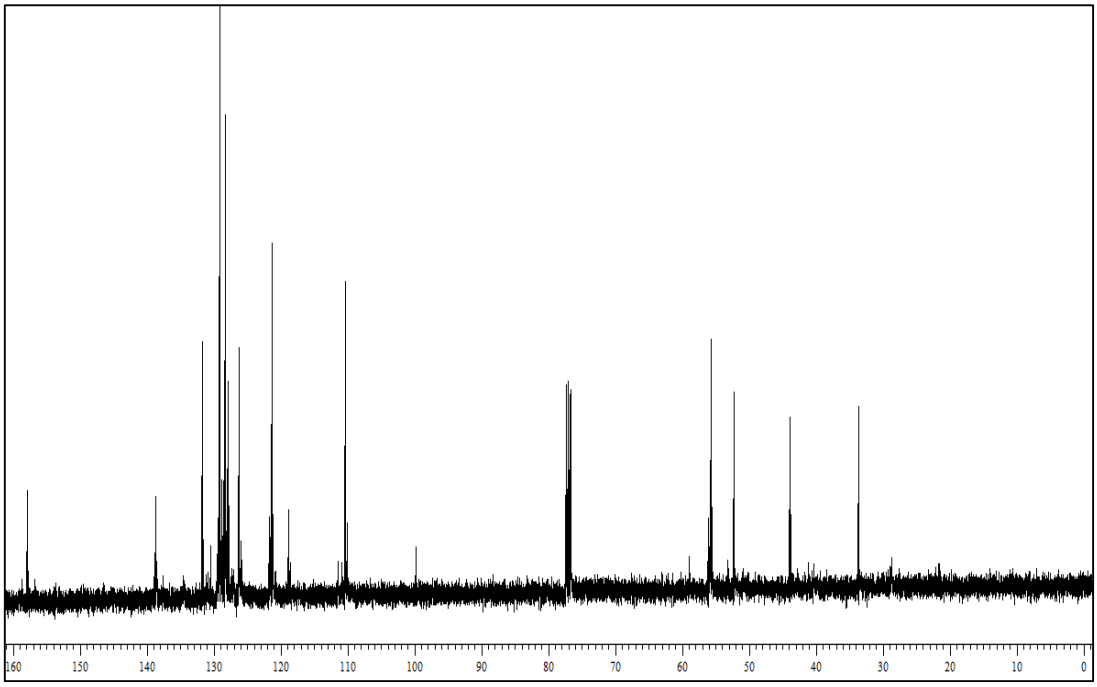


^{1}H NMR (200MHz, $CDCl_3$) spectrum of **4f**

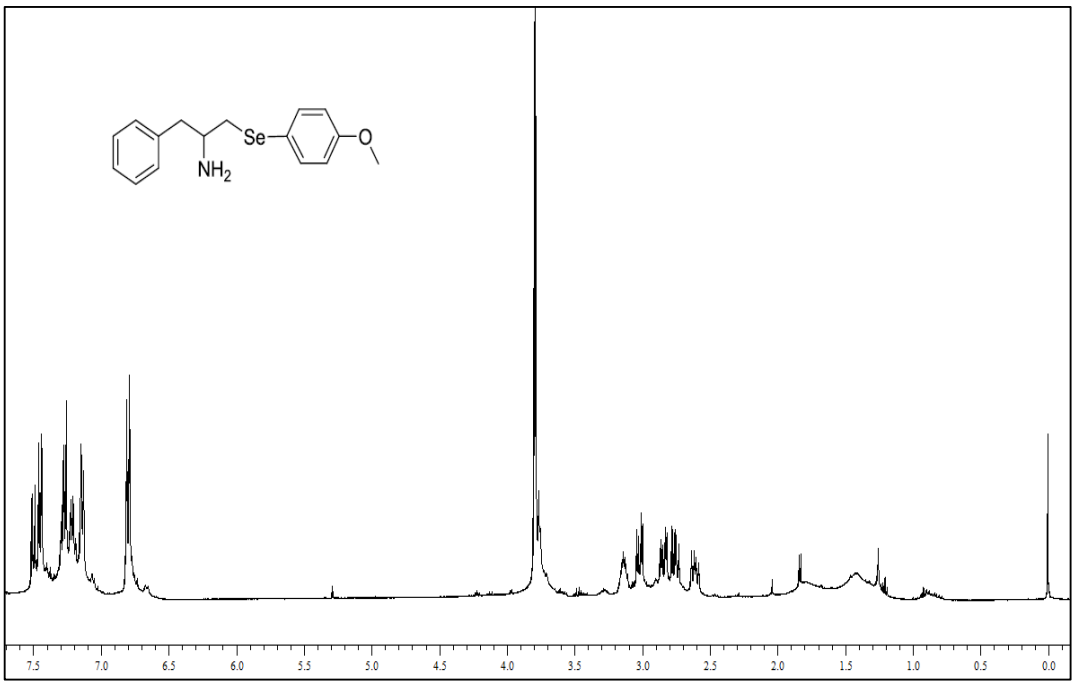


^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4f**

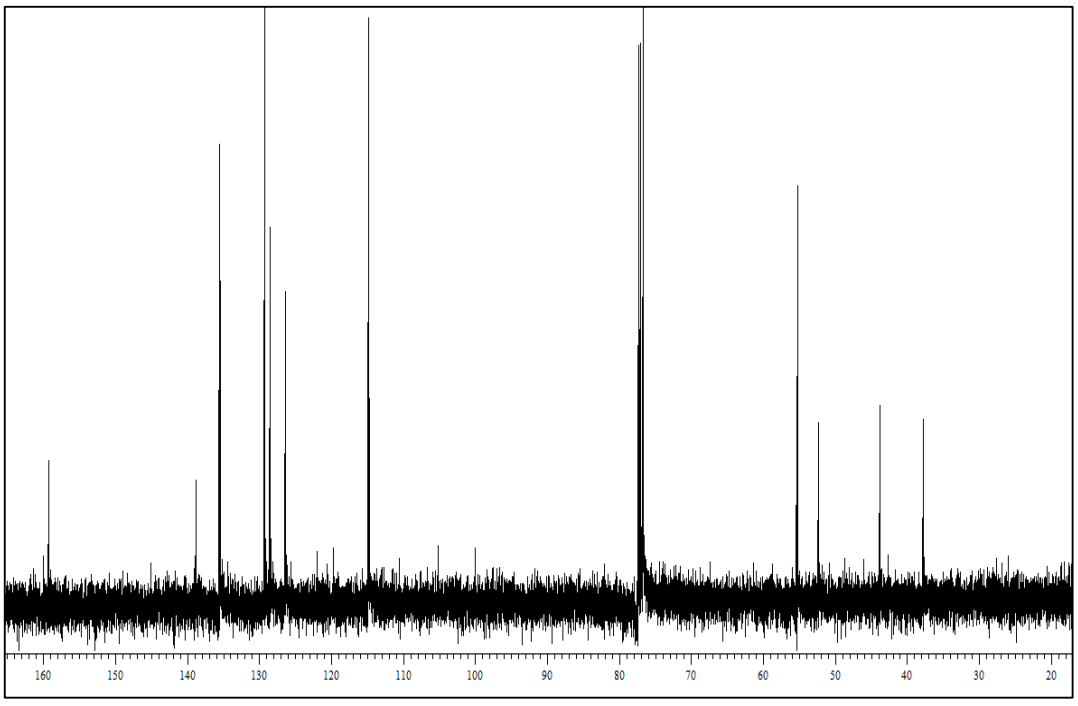




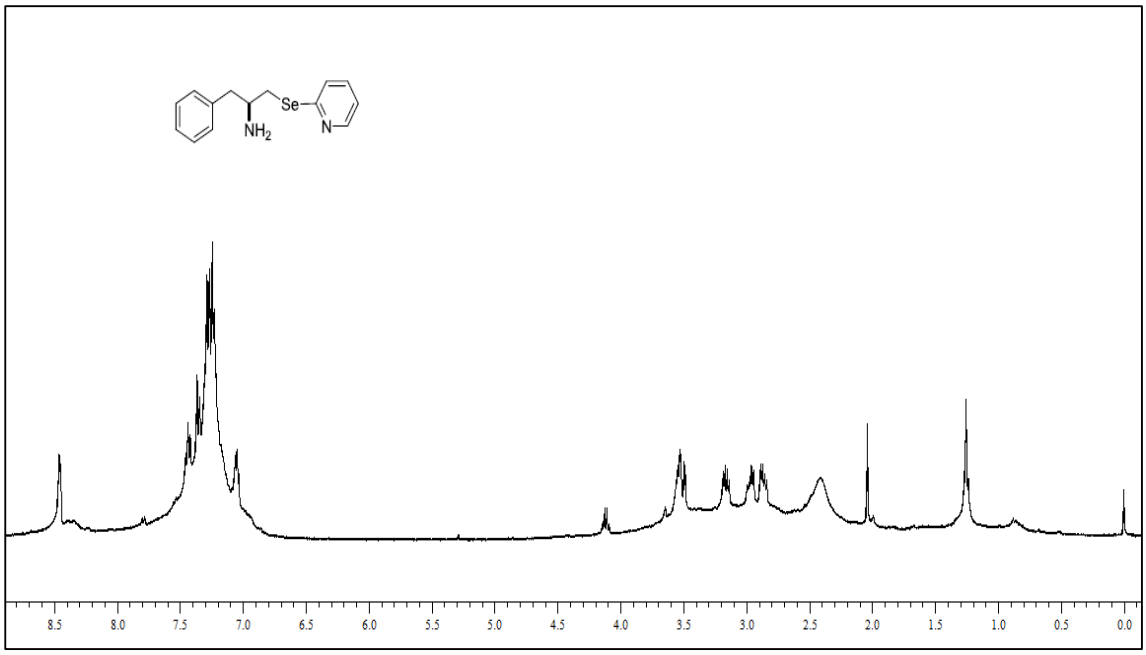
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4g**



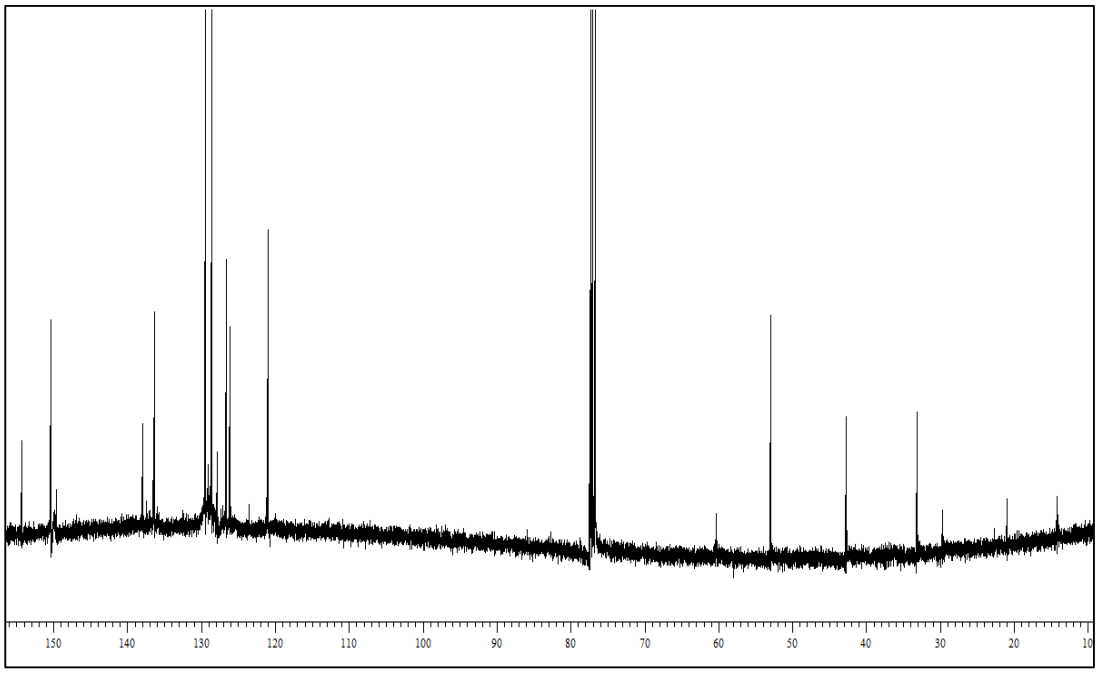
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4h**



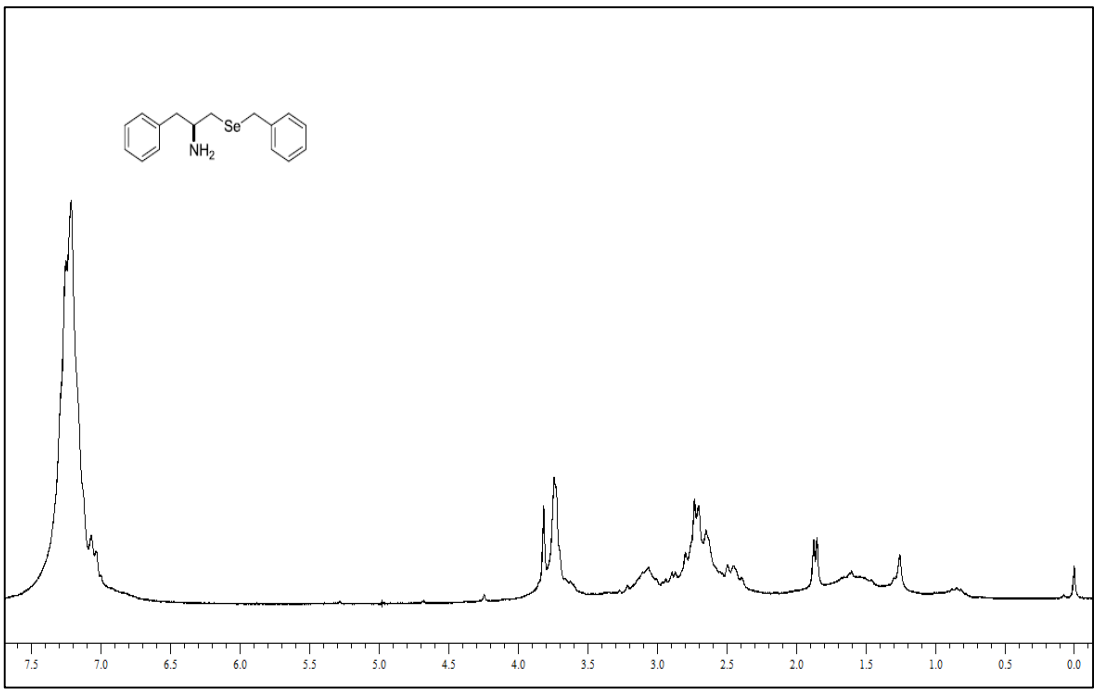
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4h**



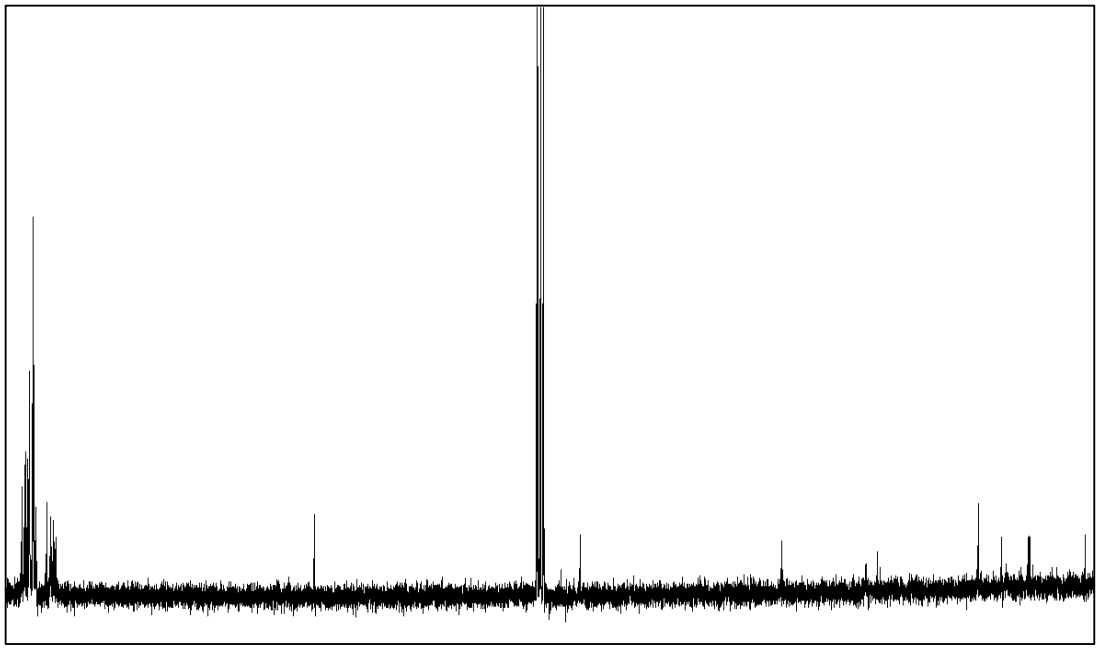
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4i**



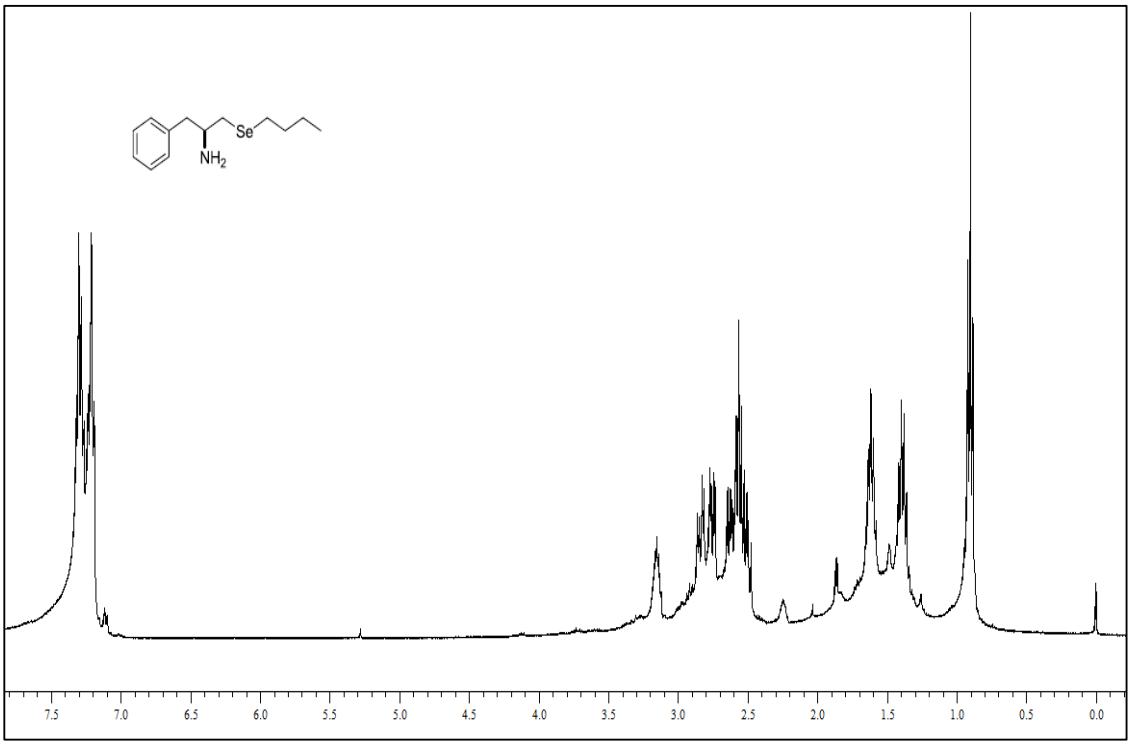
^{13}C NMR(100 MHz, $CDCl_3$) spectrum of **4i**



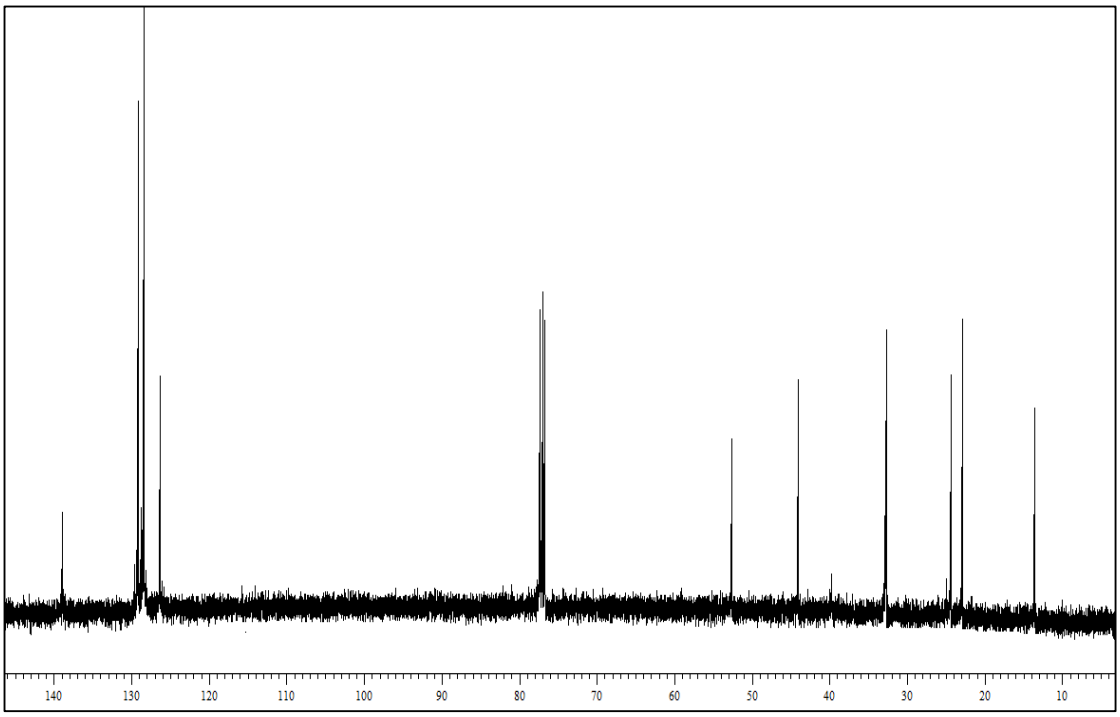
^{1}H NMR (200MHz, $CDCl_3$) spectrum of **4j**



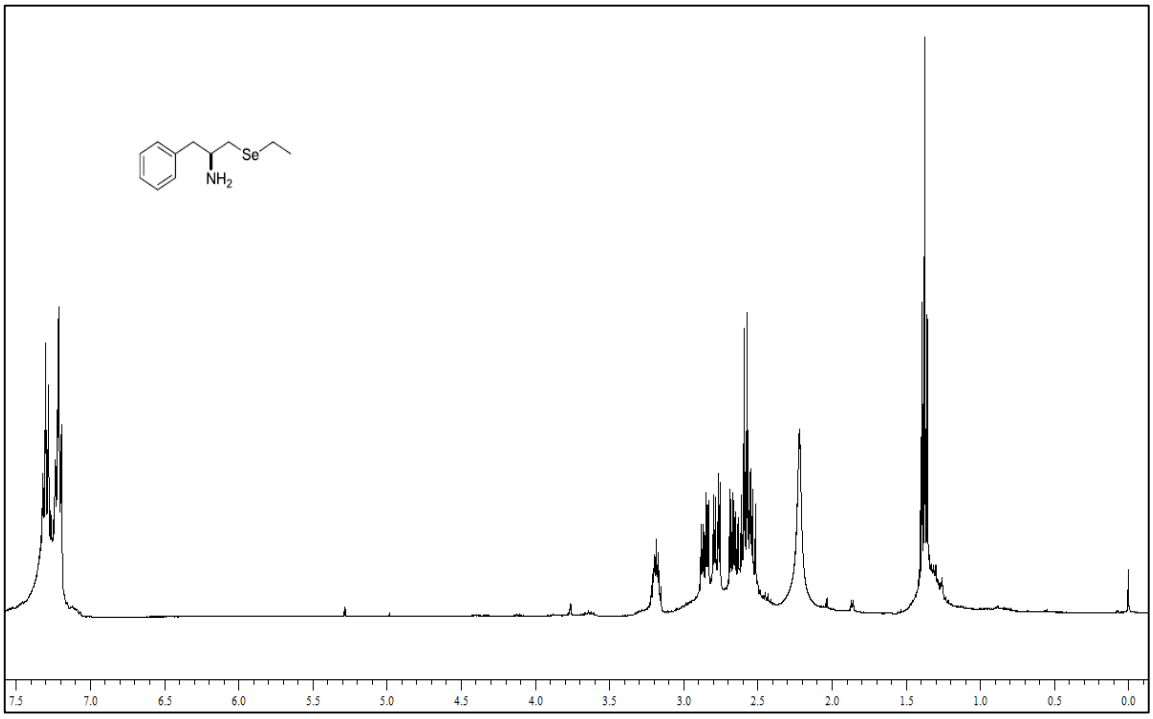
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4j**



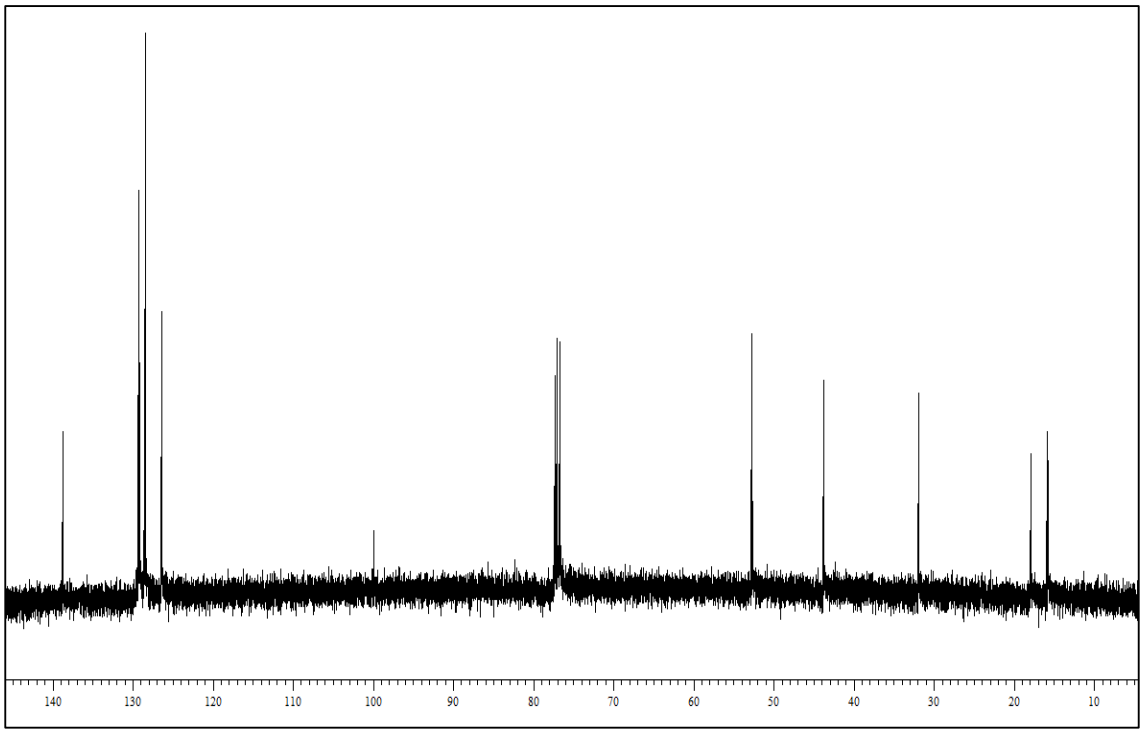
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4k**



^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4k**

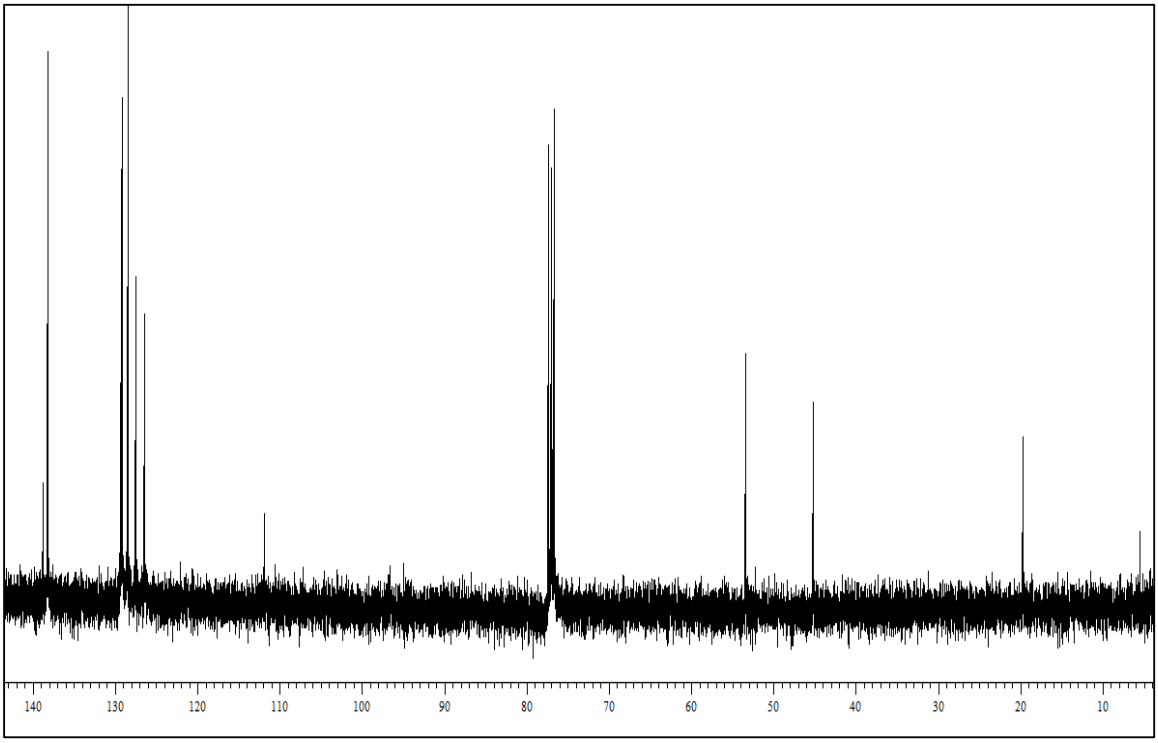


^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4l**

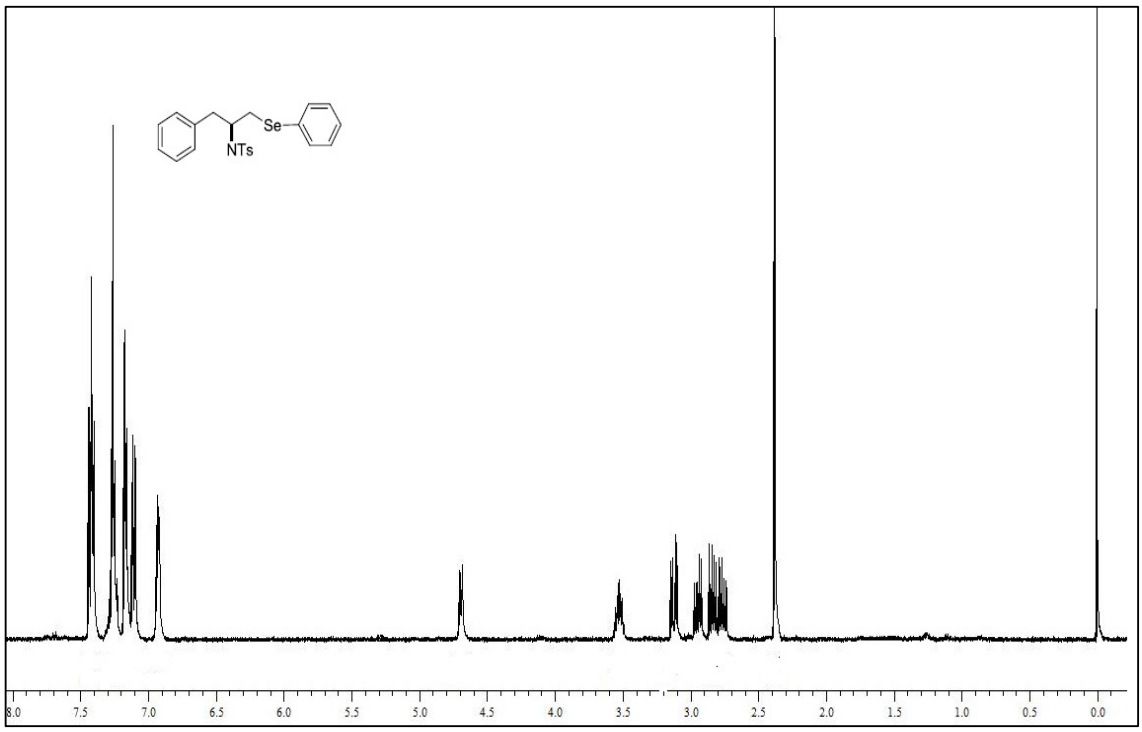


^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4l**

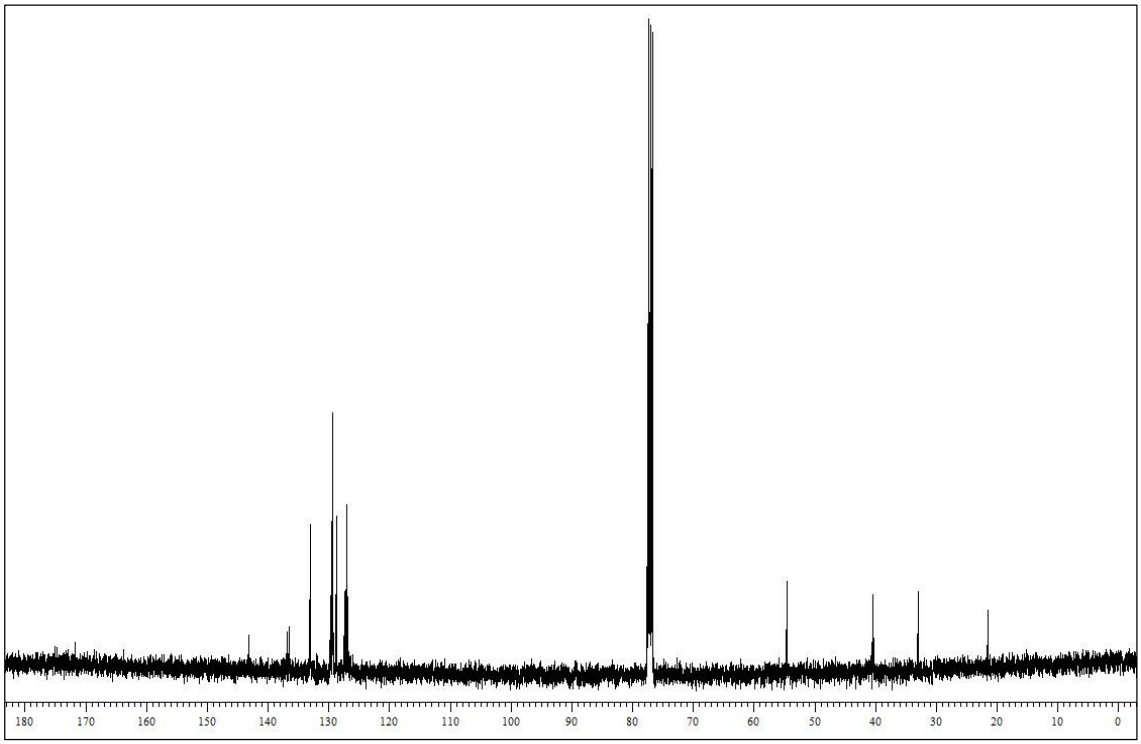
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **4m**



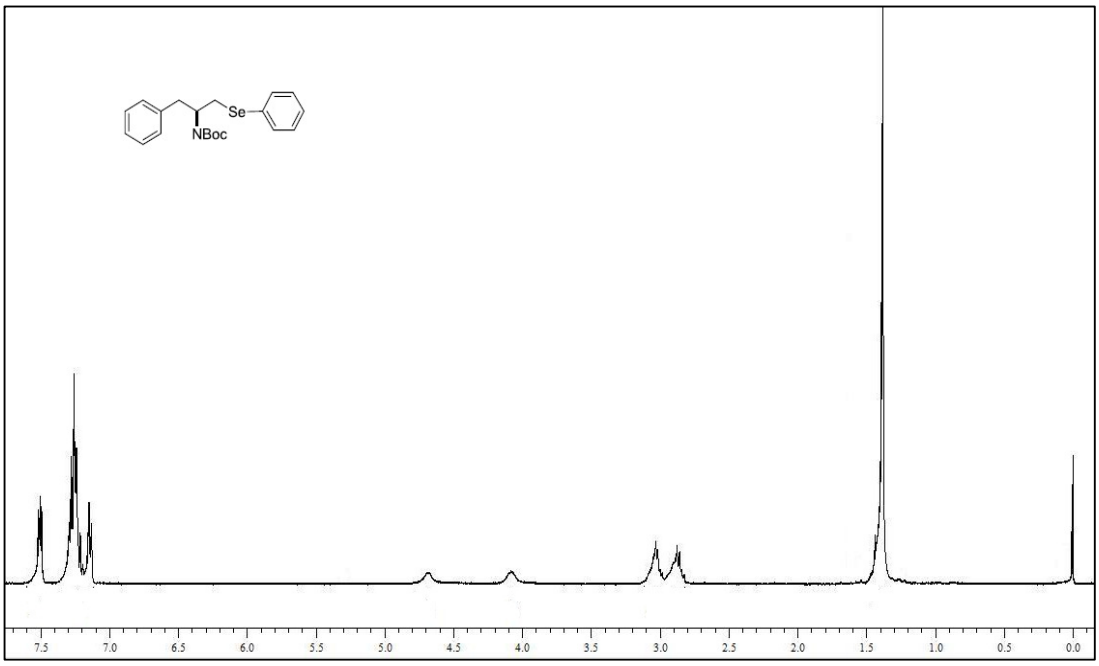
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **4m**



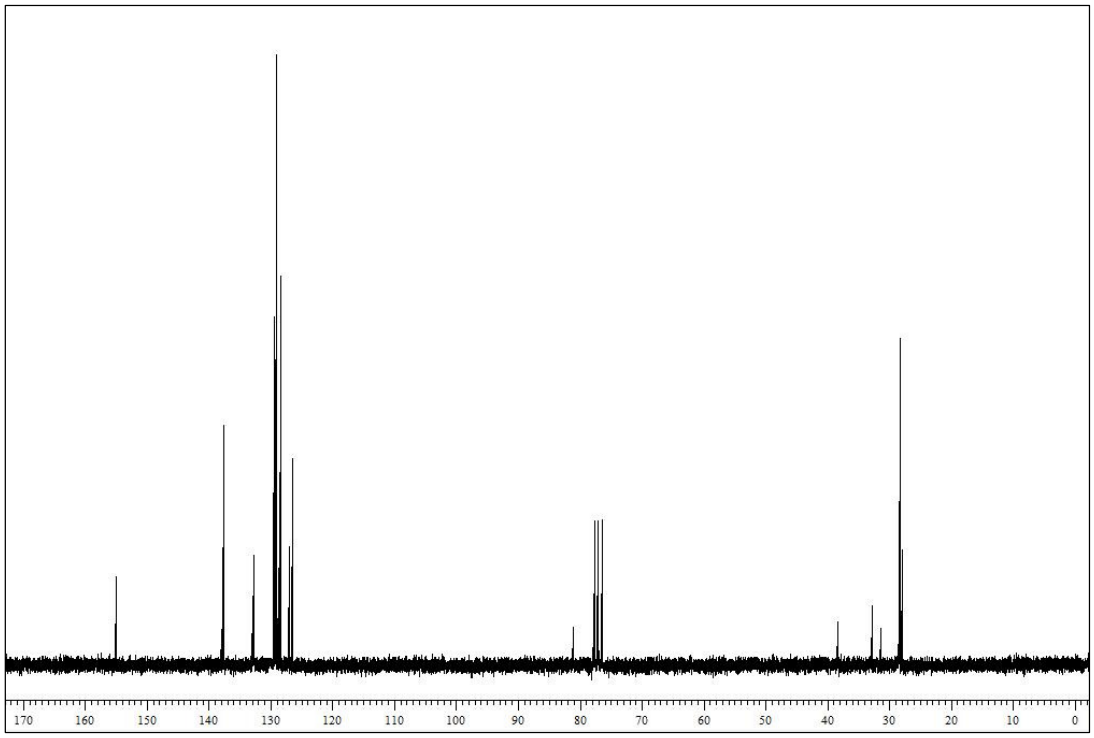
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **6a**



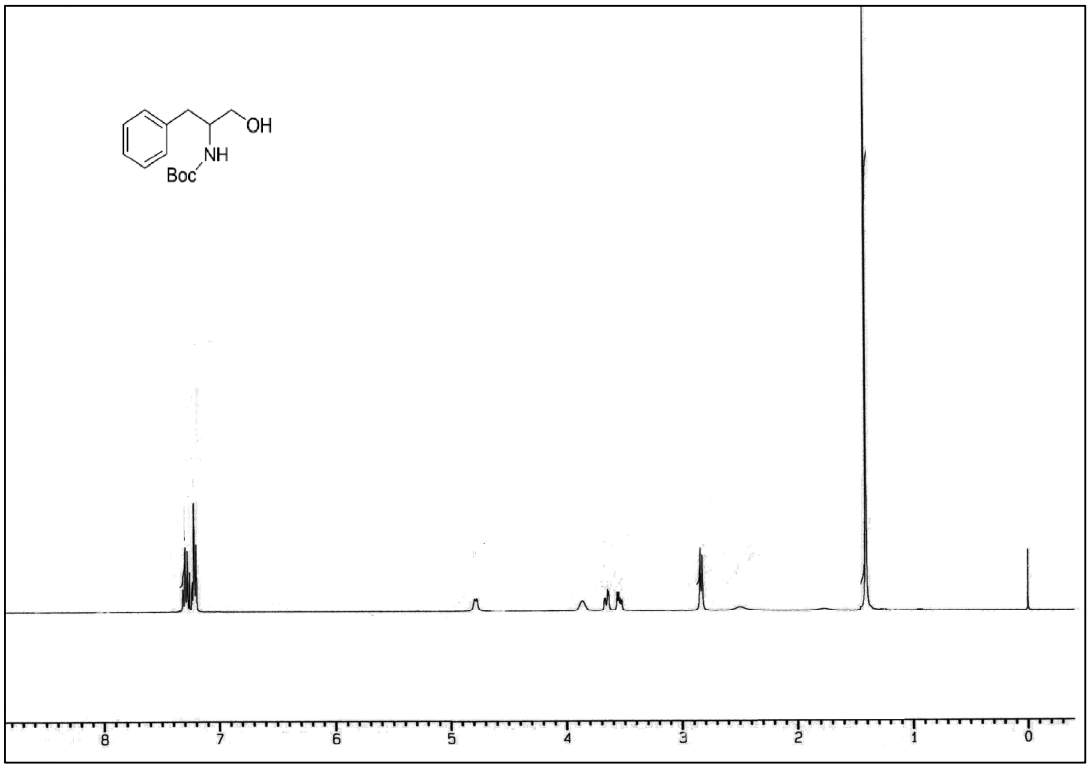
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **6a**



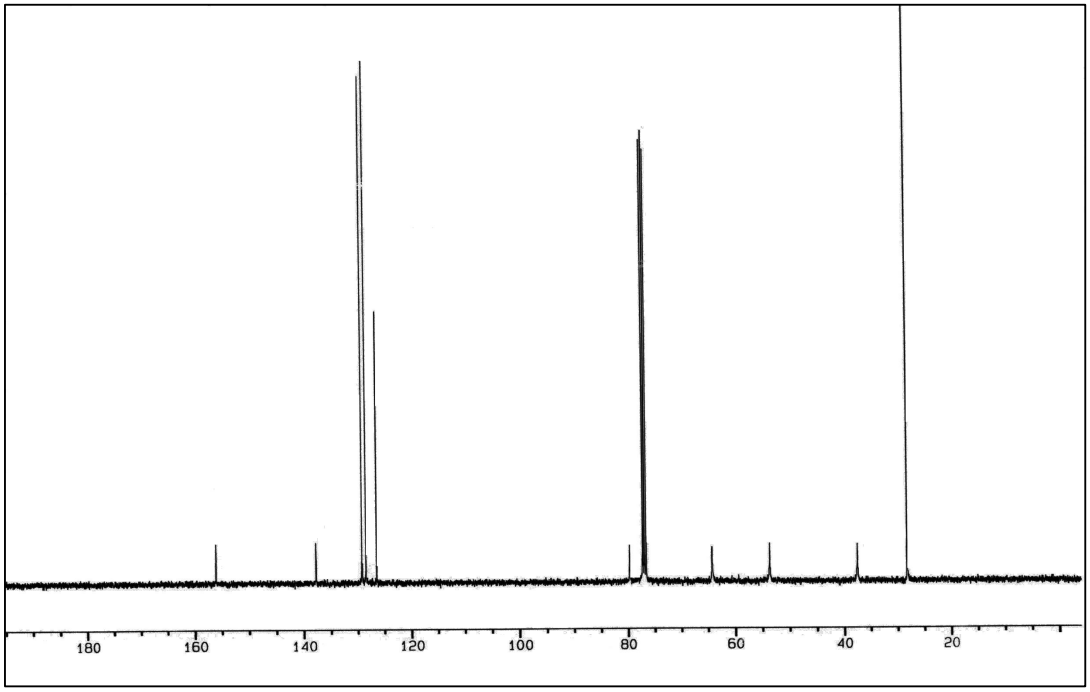
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **8a and 11a**



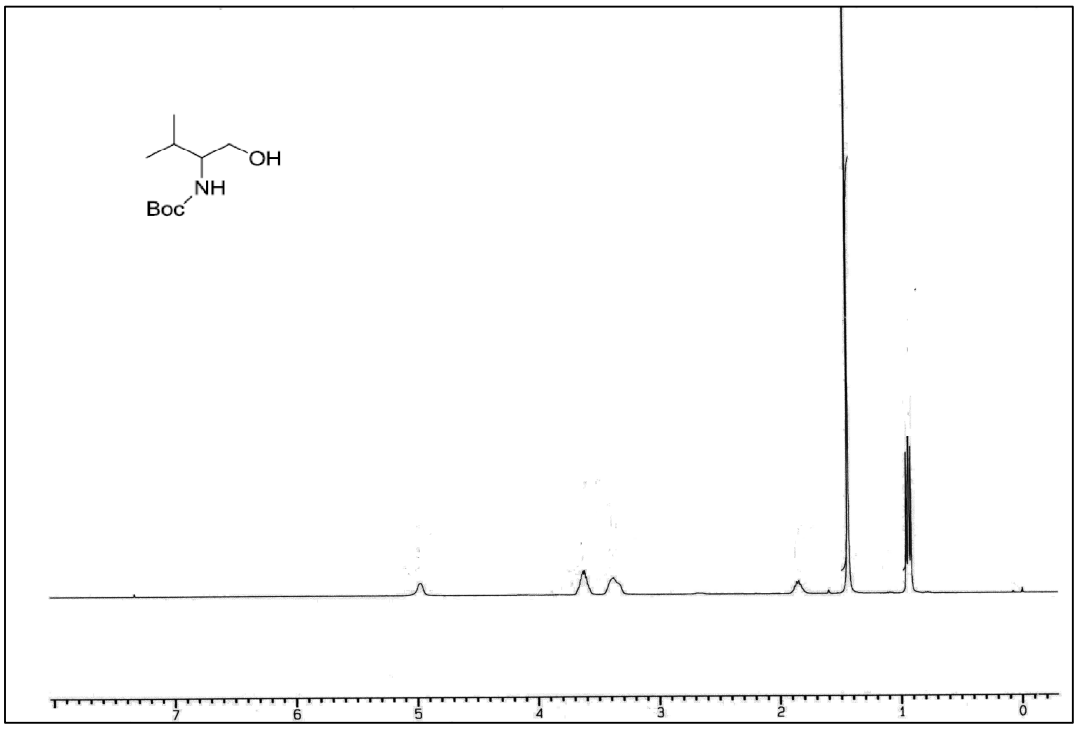
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **8a and 11a**



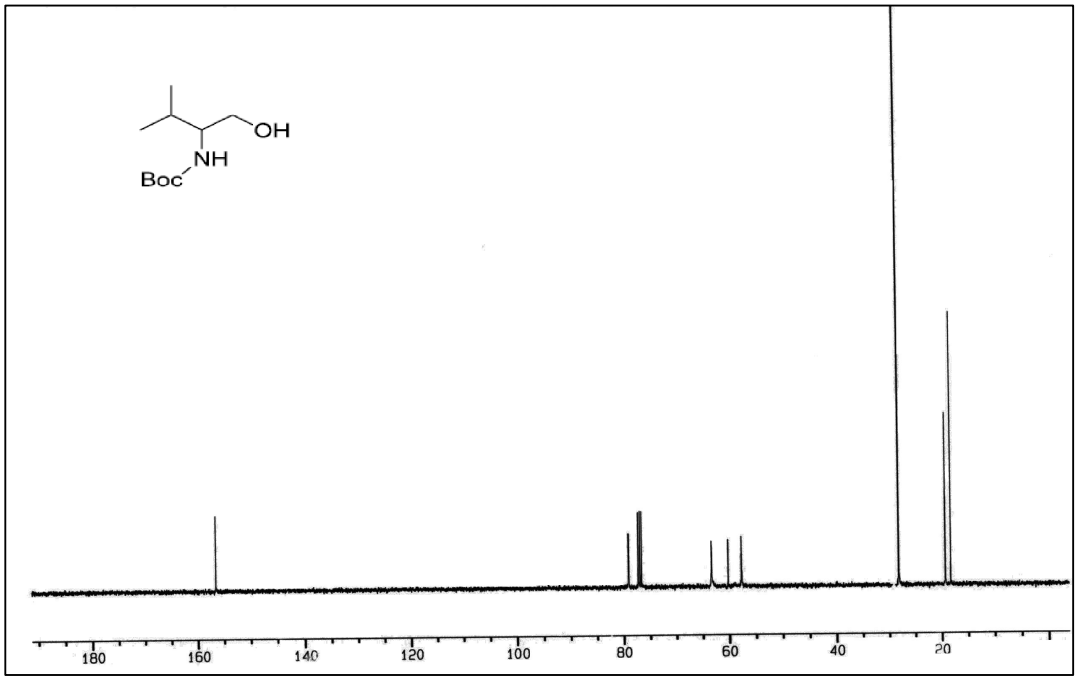
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **9a**



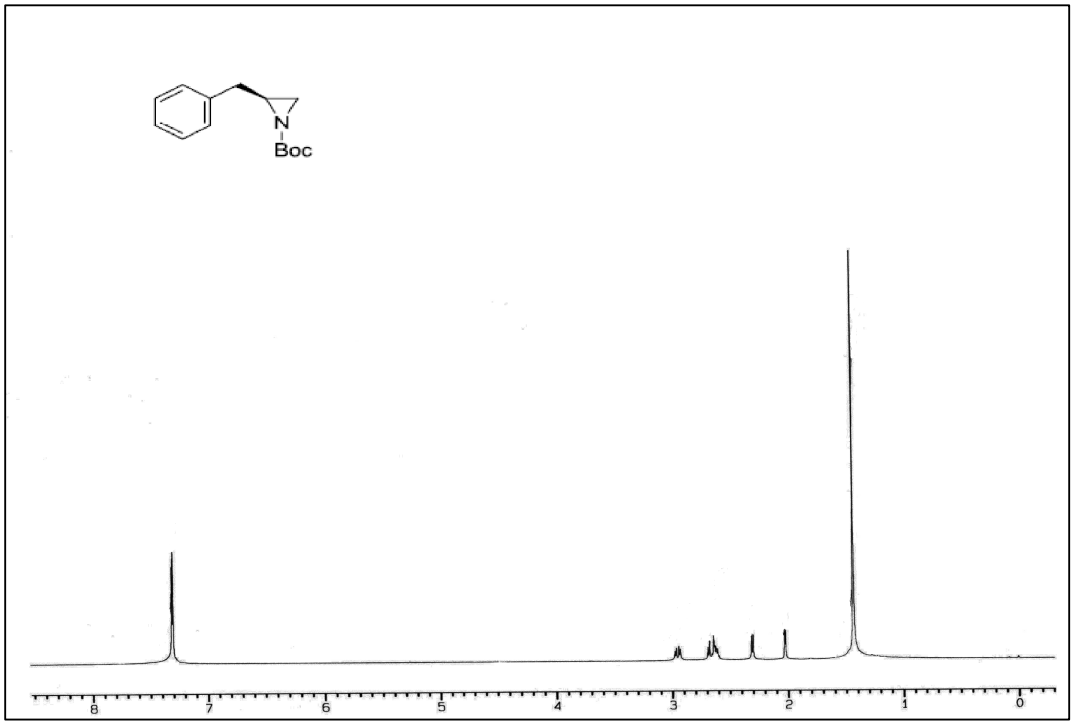
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **9a**



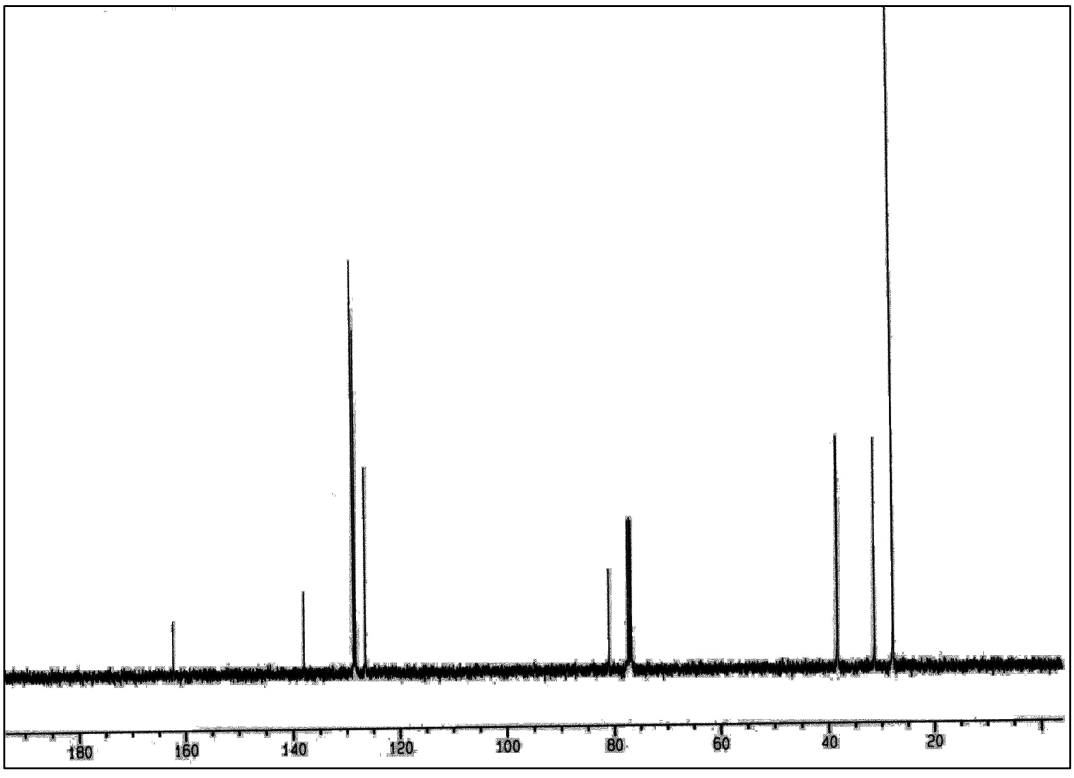
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **9b**



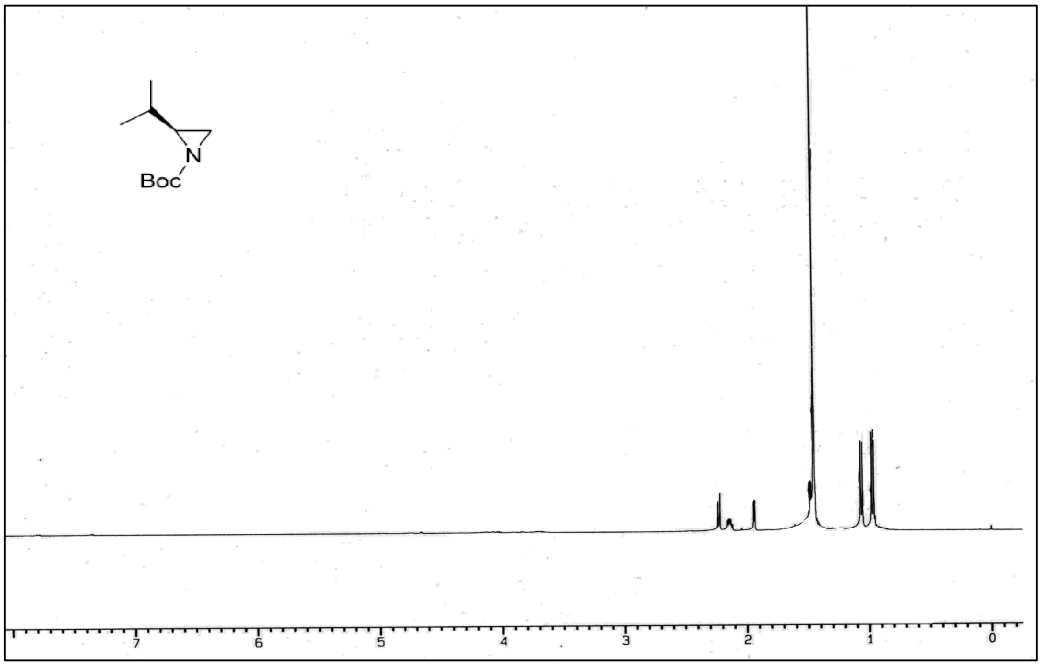
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **9b**



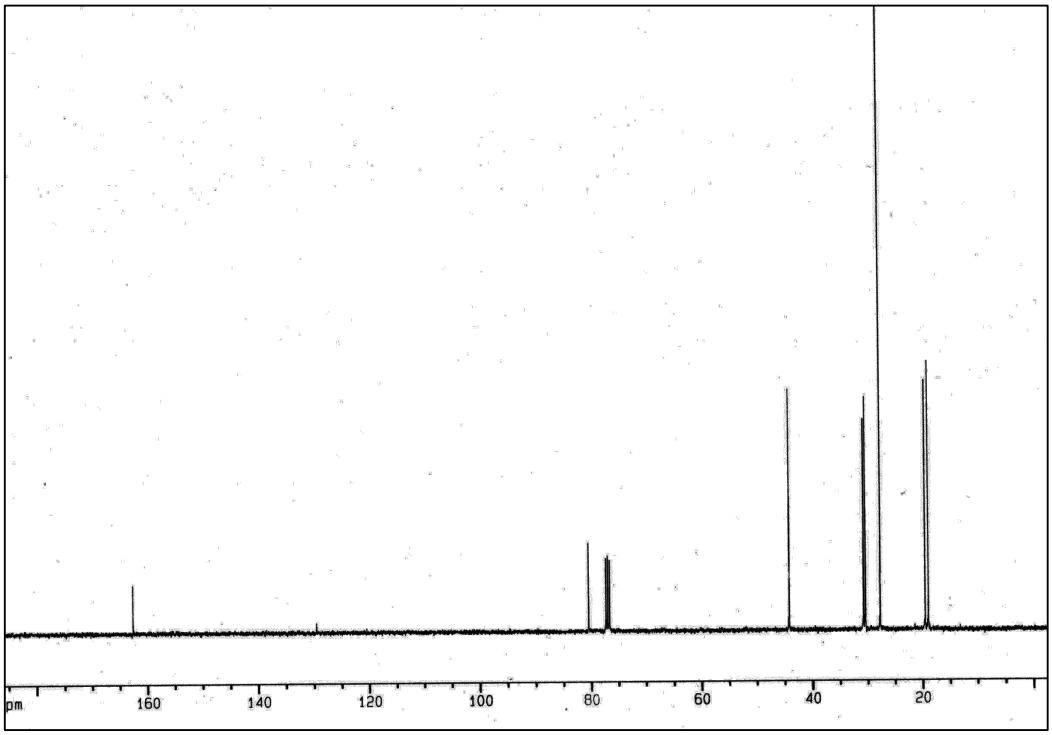
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **10a**



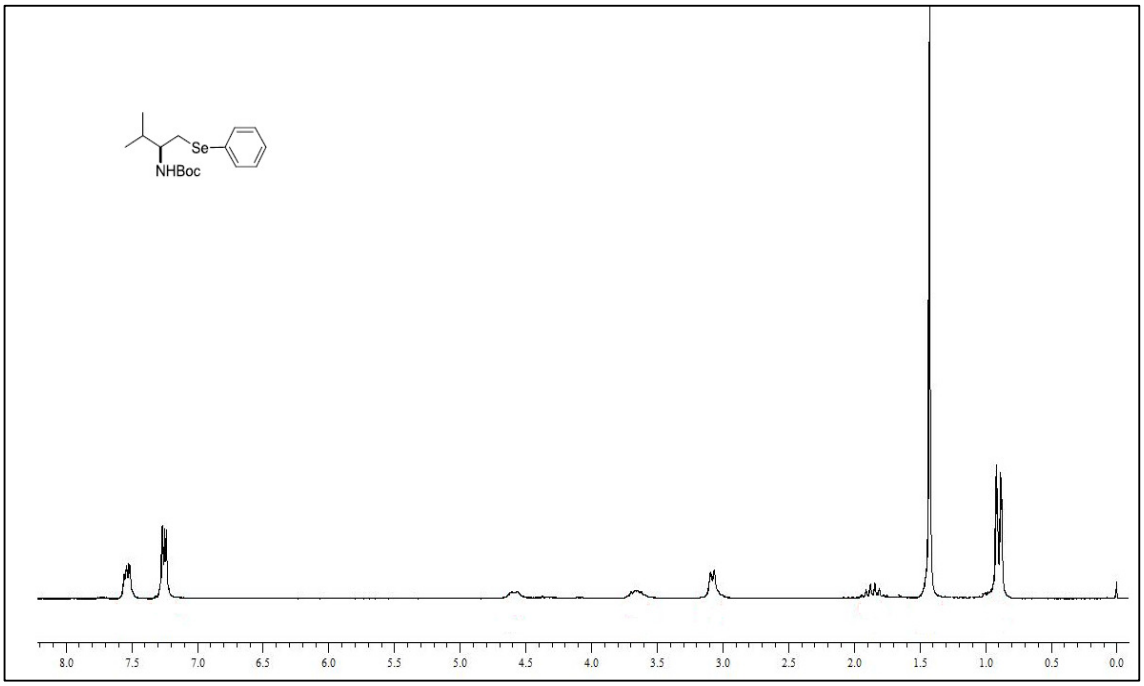
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **10a**



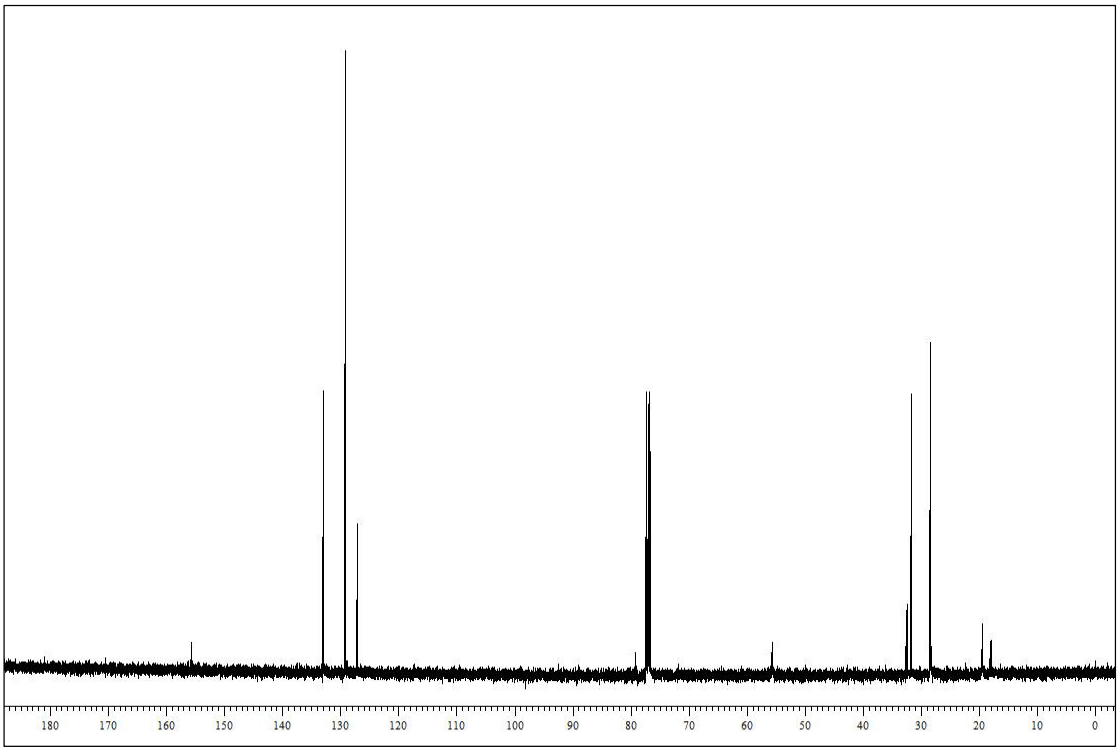
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **10b**

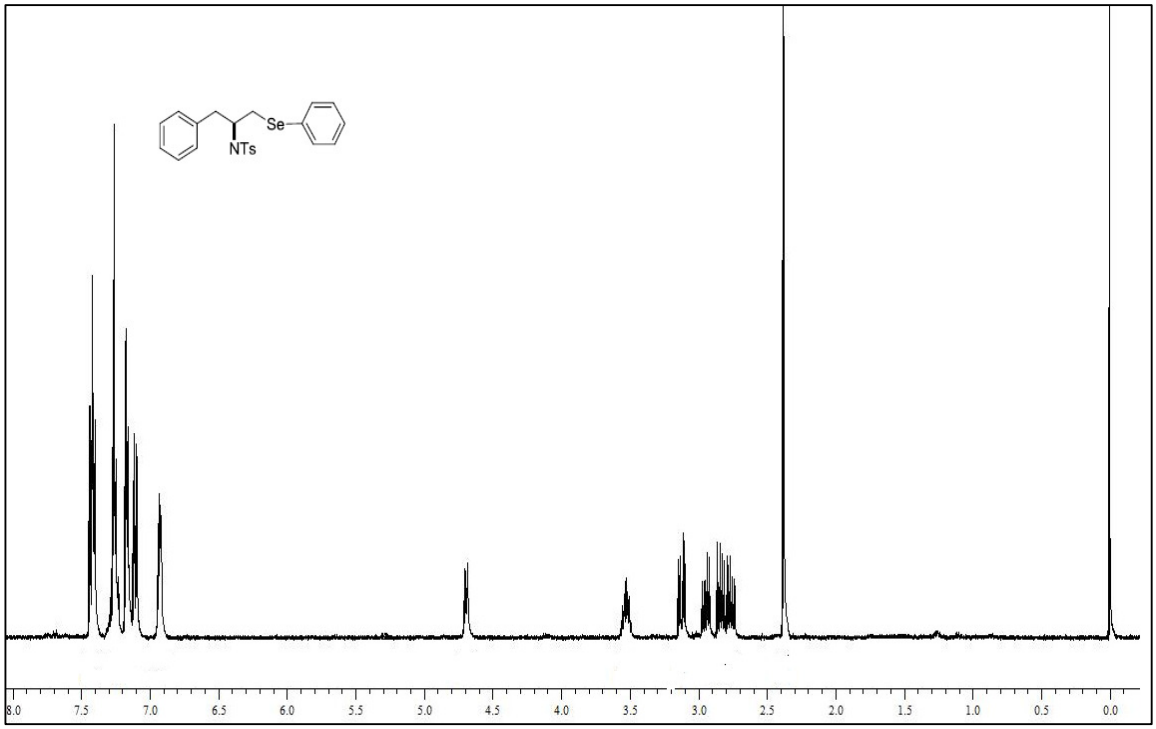


^{13}C NMR (100MHz, $CDCl_3$) spectrum of **10b**

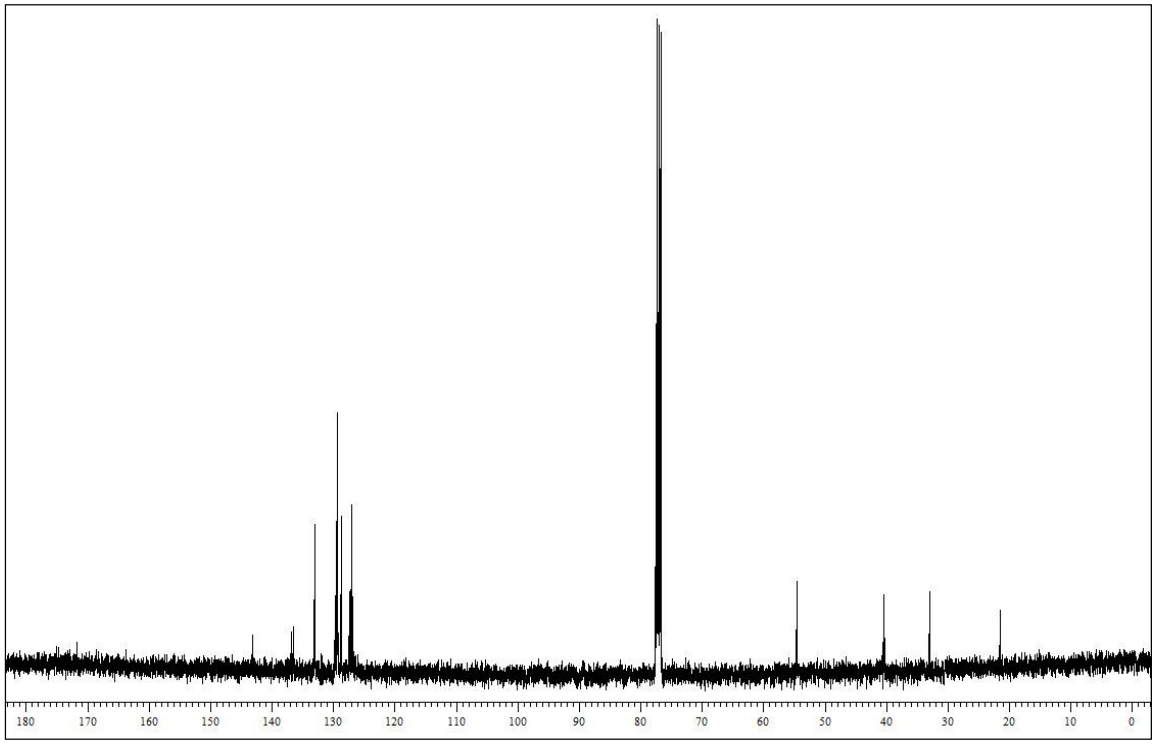


^{1}H NMR (200MHz, $CDCl_3$) spectrum of **11b**

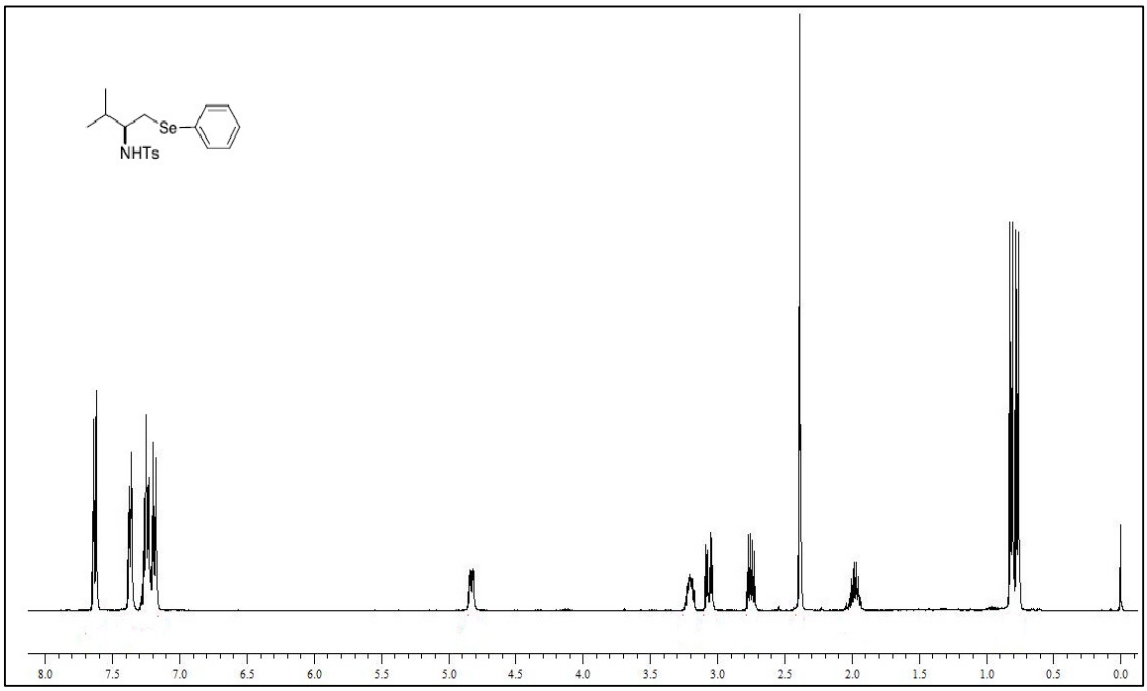




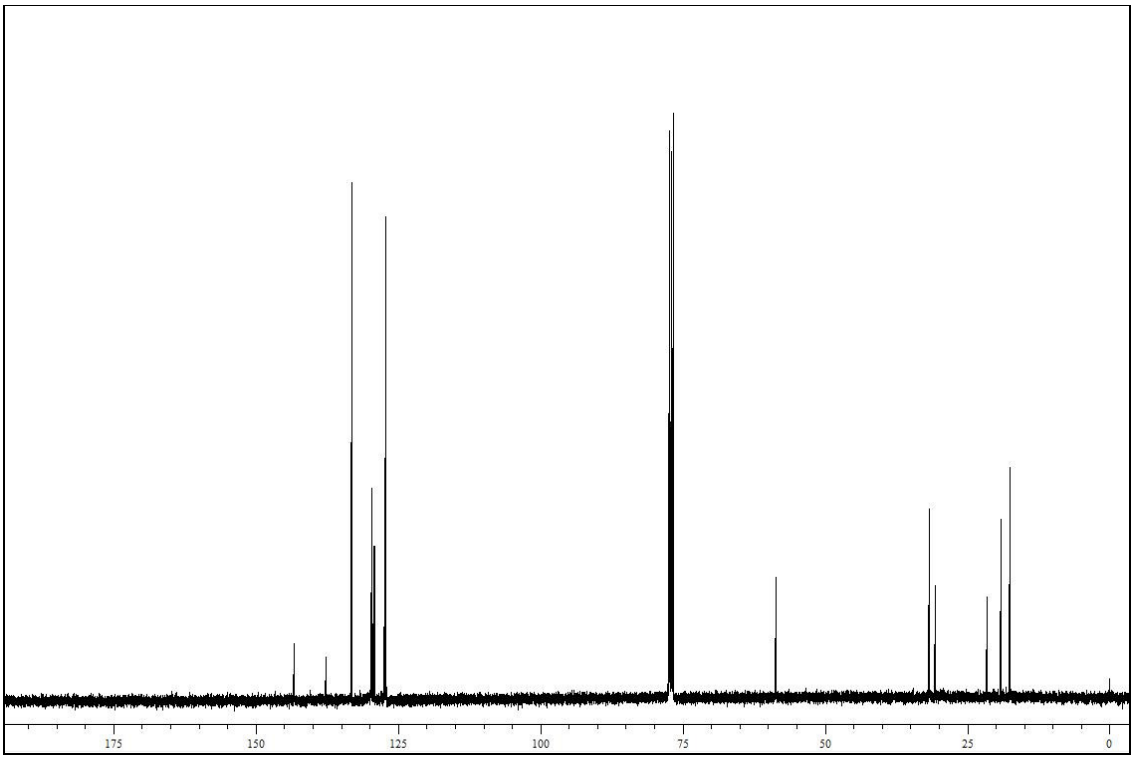
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **11c**



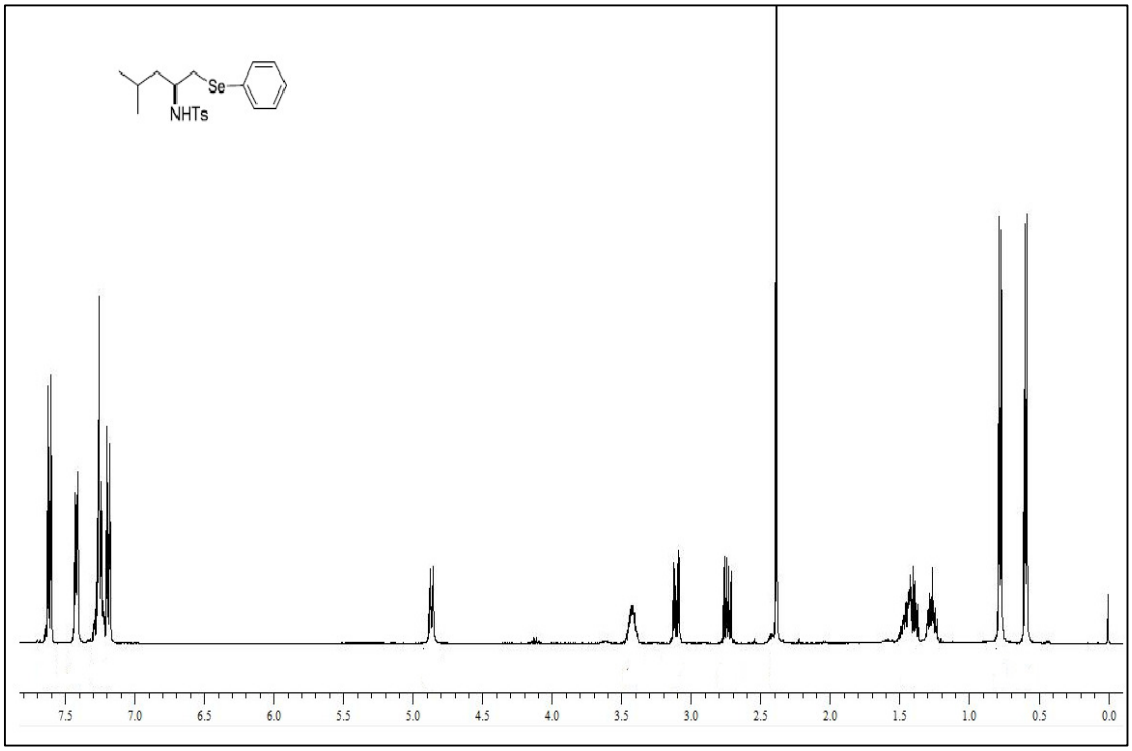
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **11b**



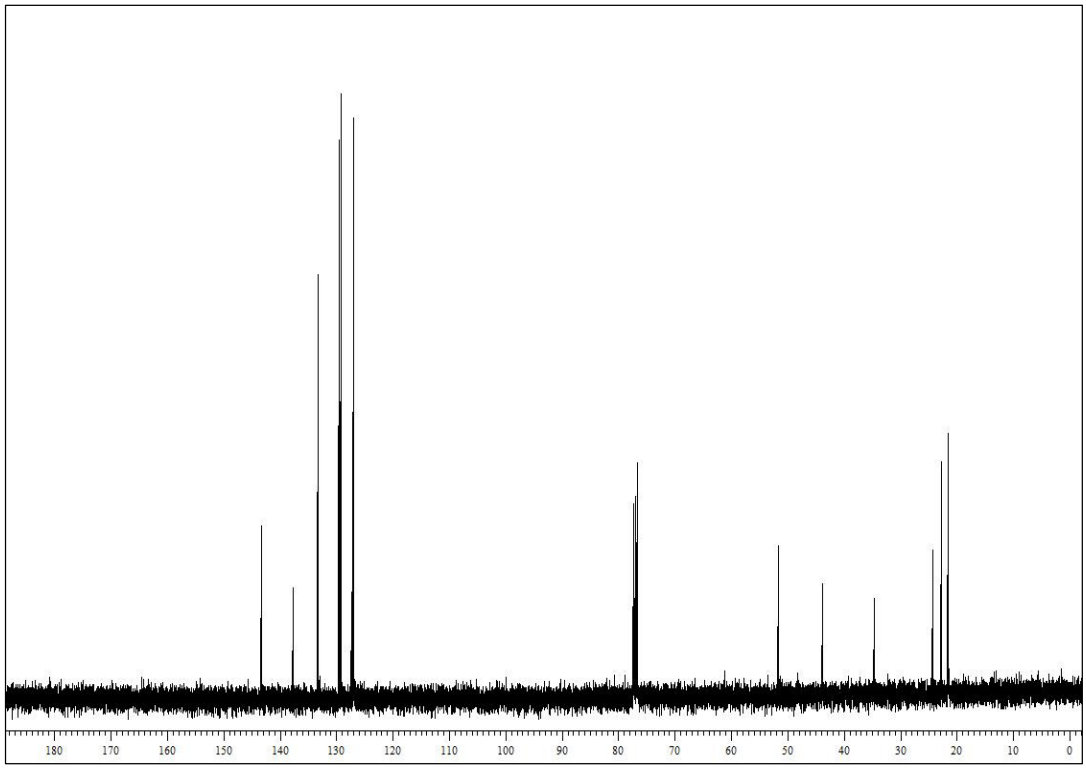
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **11d**



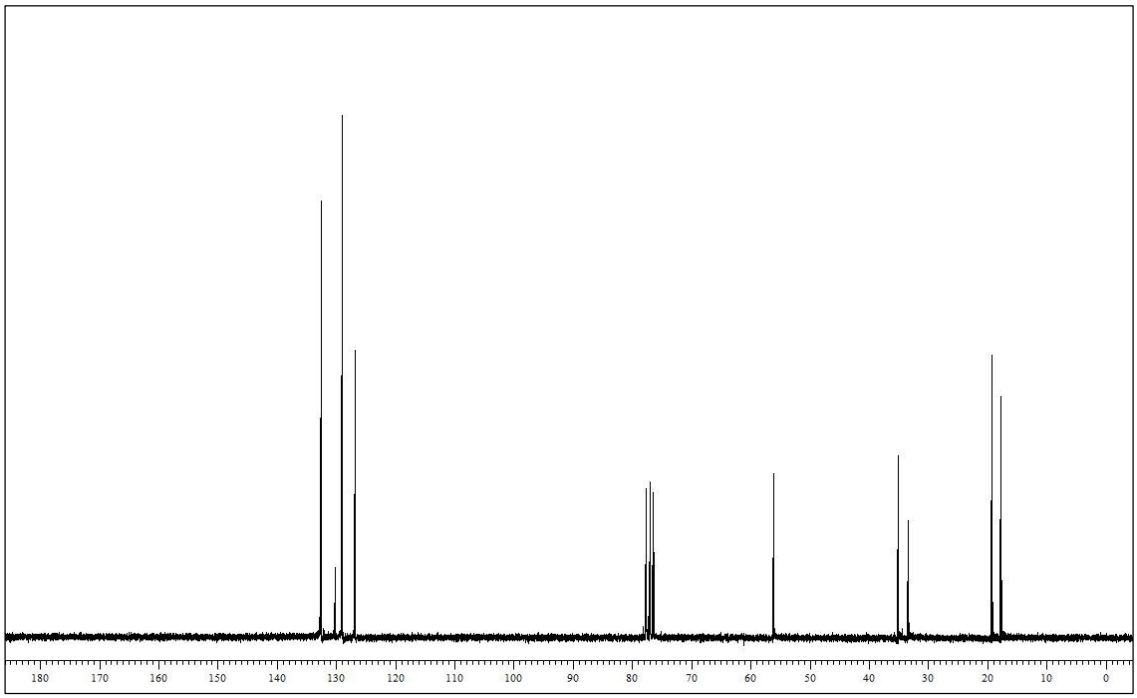
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **11d**



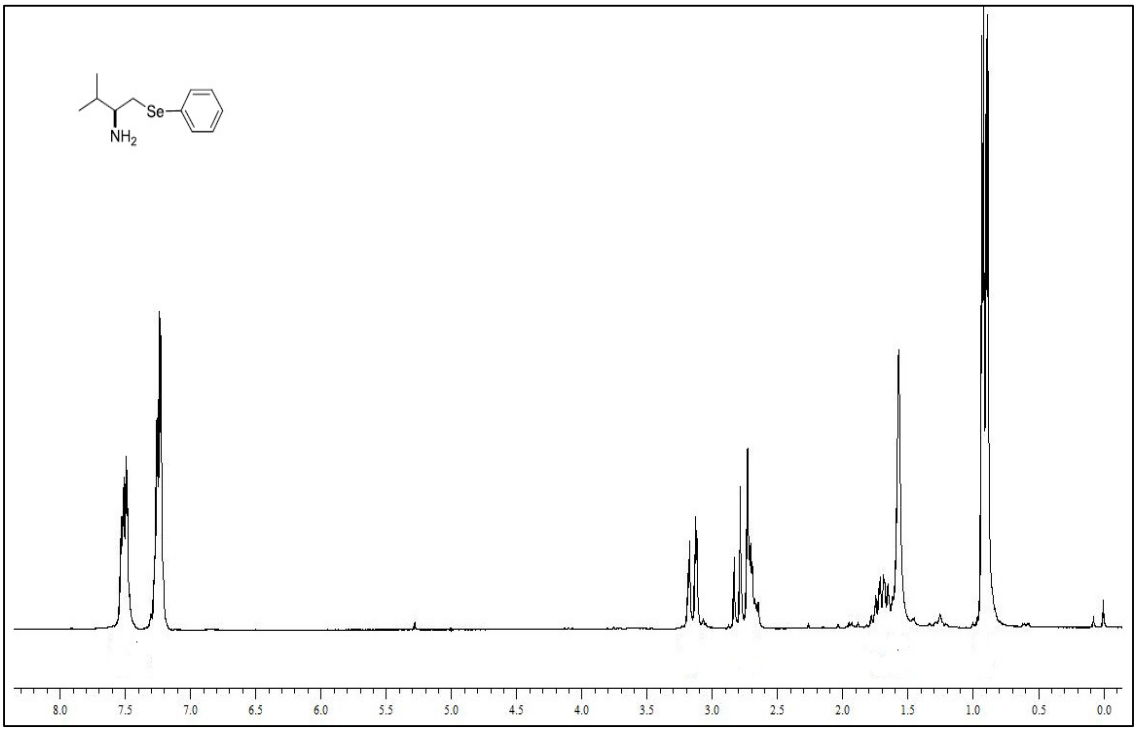
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **11e**



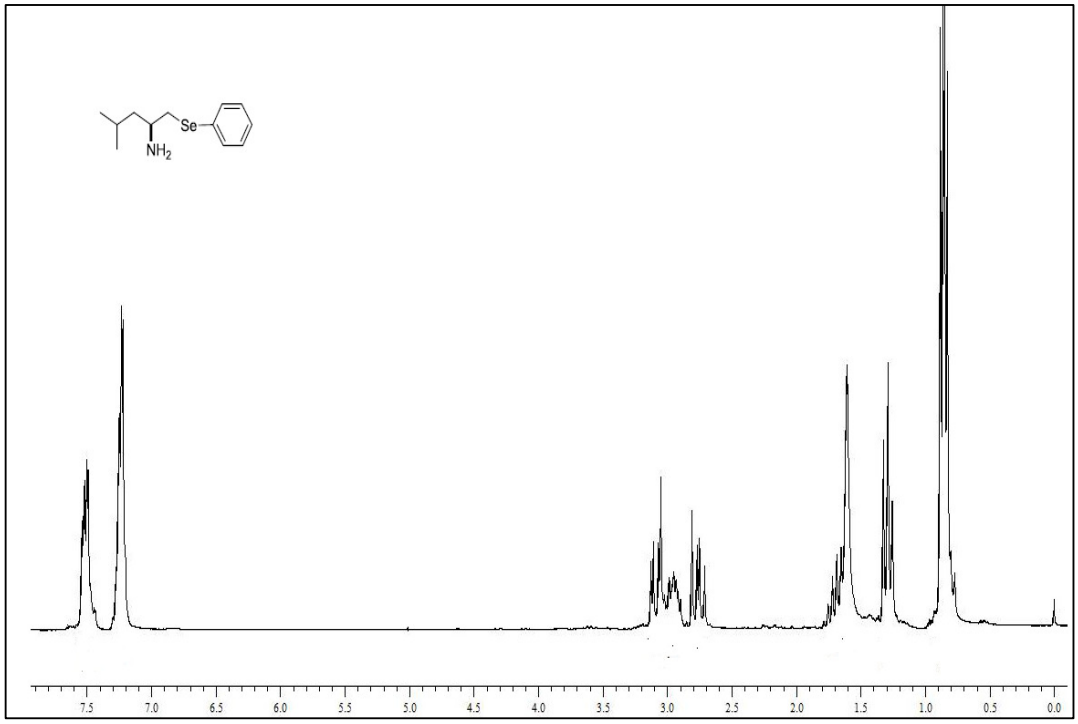
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **11e**



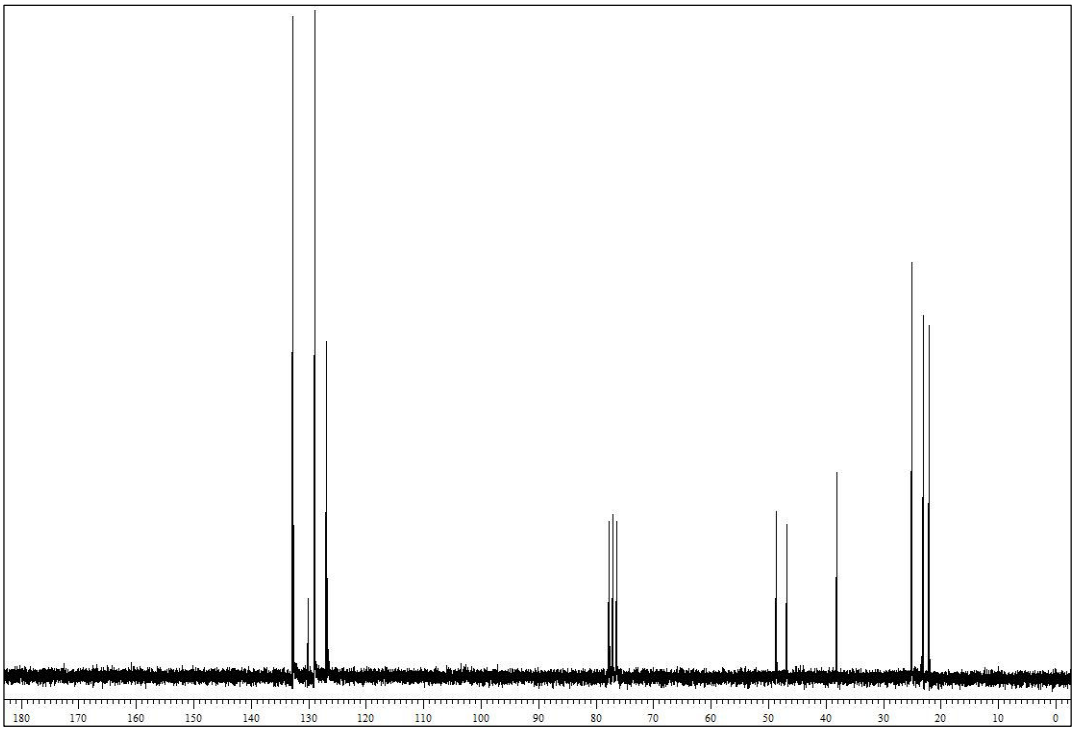
^{1}H NMR (200MHz, $CDCl_3$) spectrum of **11f**

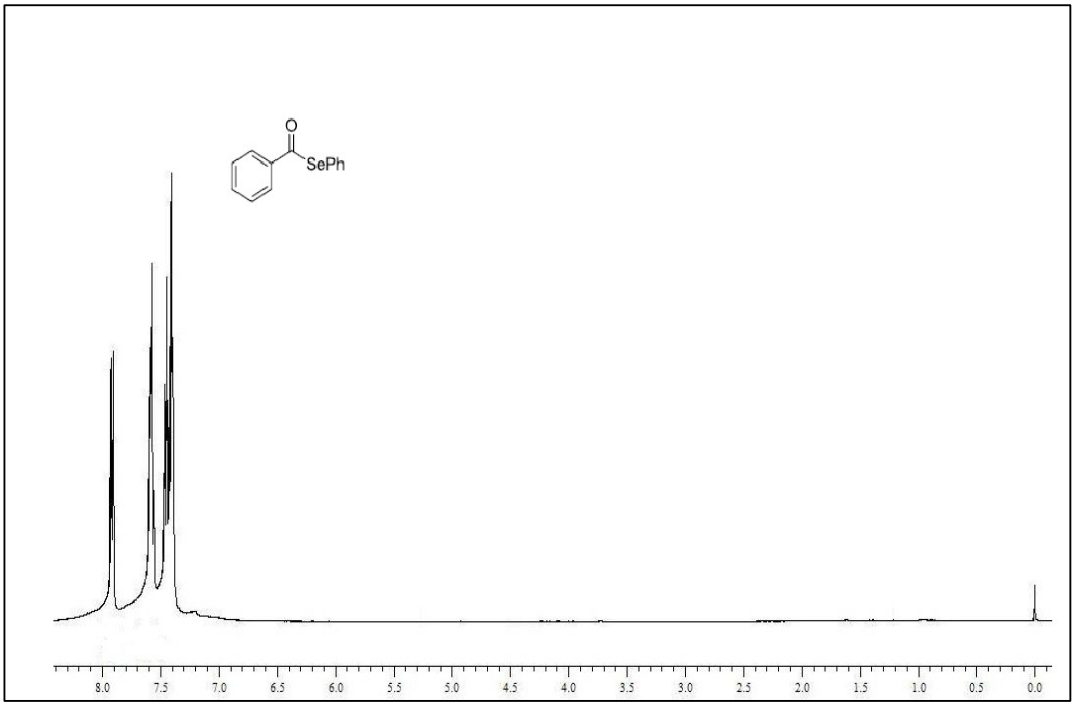


^{13}C NMR (50MHz, $CDCl_3$) spectrum of **11f**

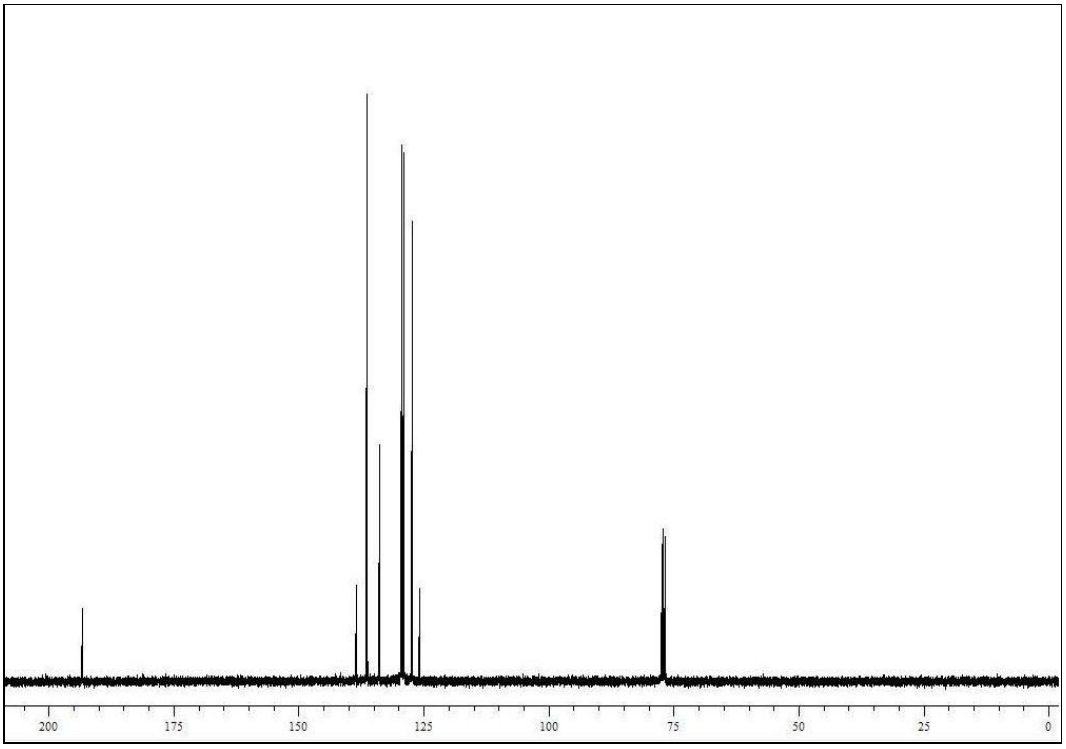


^{1}H NMR (200MHz, $CDCl_3$) spectrum of **11g**

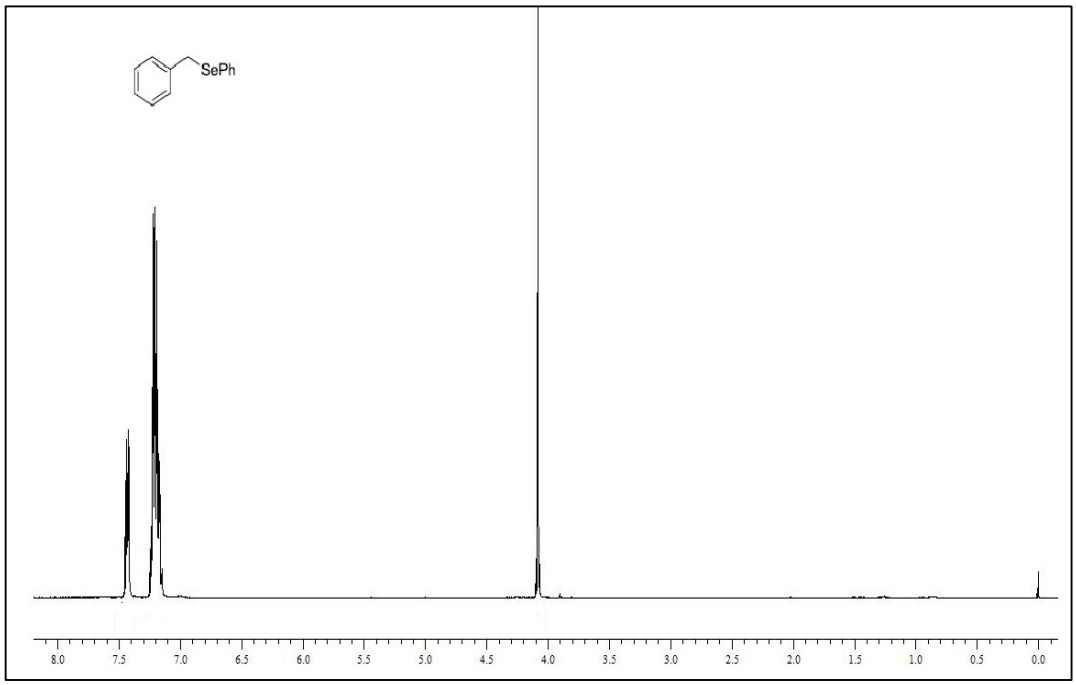




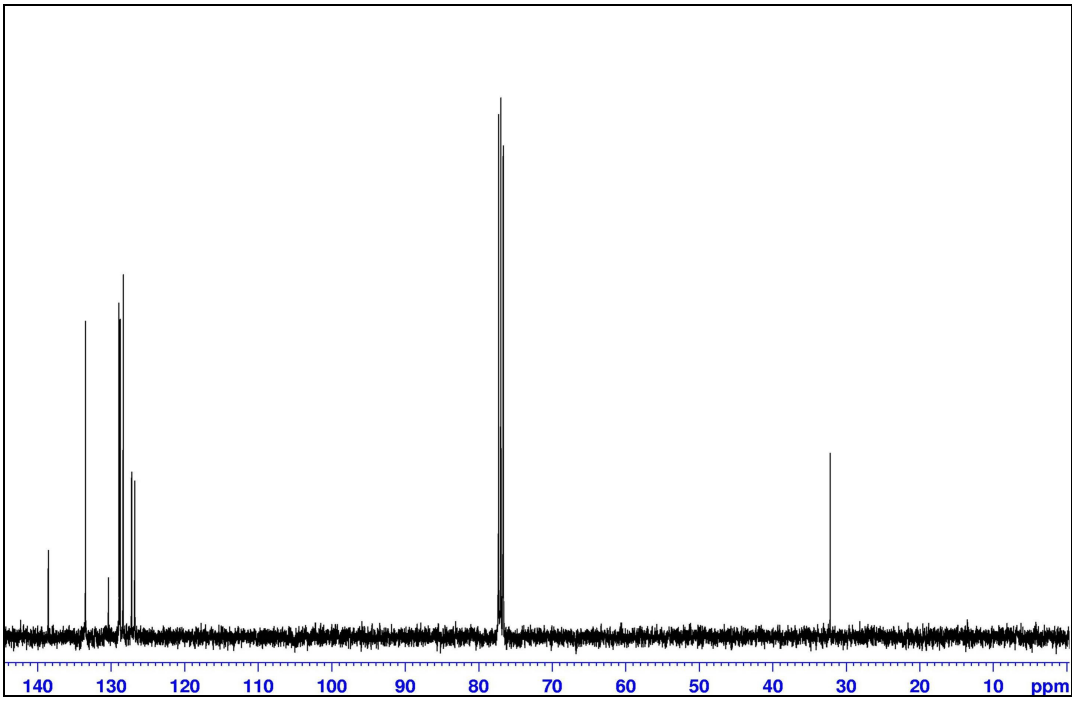
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **12**



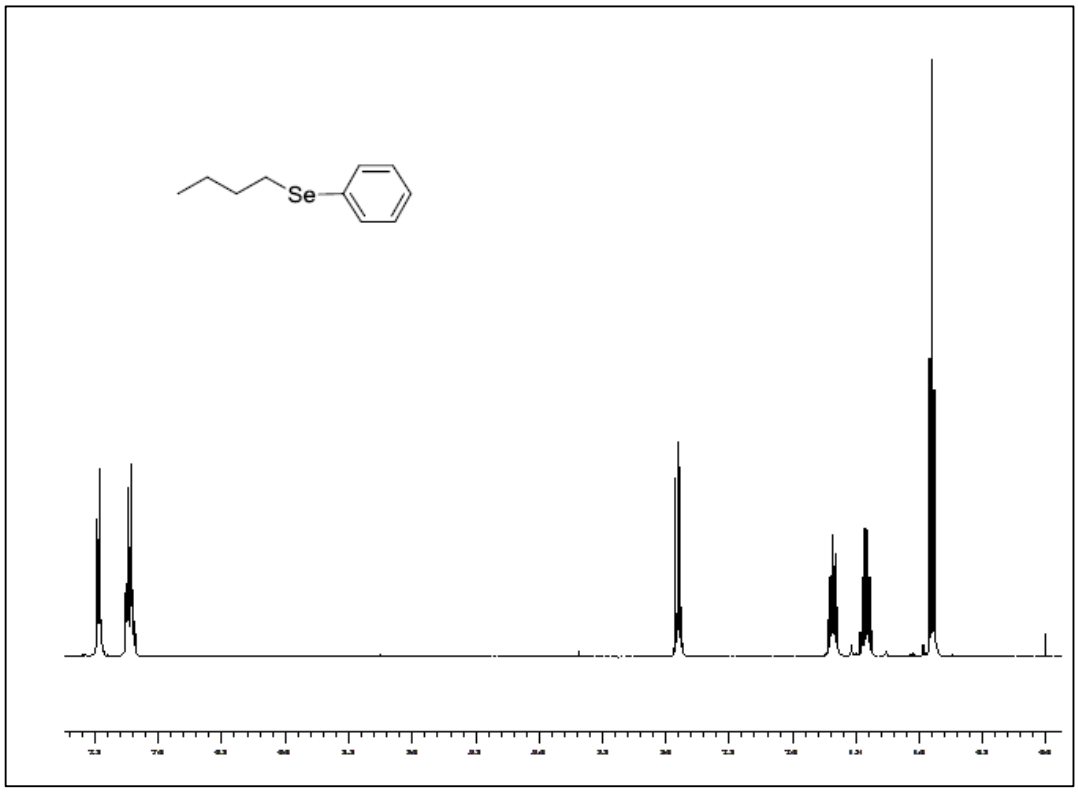
^{13}C NMR (100MHz, $CDCl_3$) spectrum of **12**



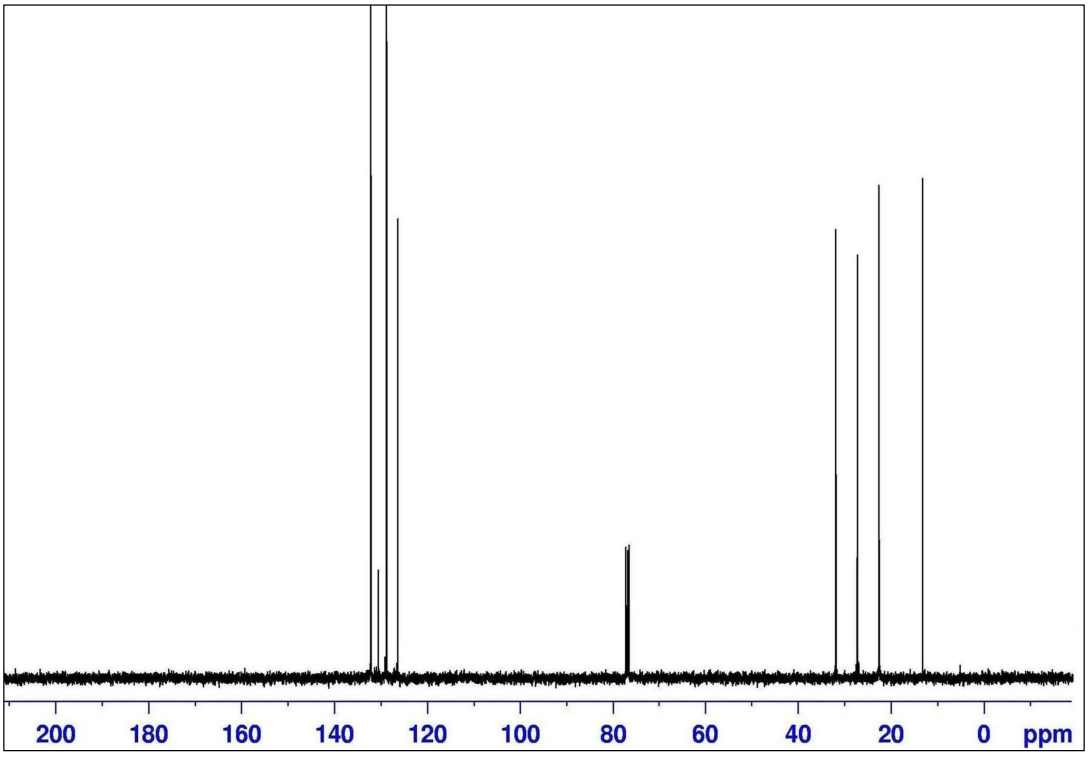
^{1}H NMR (400MHz, $CDCl_3$) spectrum of **13**



^{13}C NMR (100MHz, $CDCl_3$) spectrum of **13**



^{1}H NMR (400MHz, $CDCl_3$) spectrum of **14**



^{13}C NMR (100MHz, $CDCl_3$) spectrum of **14**