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CENTRO DE CIÊNCIAS FÍSICAS E MATEMÁTICAS
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Jamal Rafique Khan

Synthesis of Heterocycles Containing Chalcogens by C-H Functionalization: A Green Approach

Florianópolis
2014

Jamal Rafique Khan

Synthesis of Heterocycles Containing Chalcogens by C-H Functionalization: A Green Approach

Tese apresentada ao Programa de Pós-Graduação em Química de Universidade Federal de Santa Catarina, como requisito parcil para obtenção grau de Doutor Química.
Área de concentração: Química Orgânica.

Orientador: Prof. Dr. Antonio Luiz Braga

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Jamal Rafique Khan

Synthesis of Heterocycles Containing Chalcogens by C-H Functionalization: A Green Approach

Dissertation submitted to the Post-graduation Program of the Federal University of Santa Catarina in partial fulfillment of the requirements for degree of the Doctor of Philosophy in Chemistry
Area: Organic Chemistry

Supervisor: Prof. Dr. Antonio Luiz Braga

Florianópolis
2014

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JAMAL RAFIQUE KHAN

Synthesis of Heterocycles Containing Chalcogens by C-H Functionalization: A Green Approach

This thesis has been evaluated by the Post-graduation program of the **Department of Chemistry** at **Federal University of Santa Catarina** and approved for obtaining the degree of **Doctor of Philosophy in Chemistry**

Florianópolis-SC, 08 December 2014

Prof. Dr. Hugo Alejandro Gallardo Olmedo
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Federal University of Santa Catarina-UFSC

Examination Committee:

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Research Supervisor (UFSC)

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Member of the defense committee

Prof. Dr. Gustavo Amadeu Micke (UFSC)
Member of the defense committee

Prof. Dr. Fábio Zazyki Galetto (UFSC)
Member of the defense committee

Prof. Dr. Márcio Weber Paixão (UFSCAR)
Member of the defense committee

Prof. Dr. Gustavo Pozza Silveira (UFRGS)
Member of the defense committee

Dedicated to my parents (Muhammad Rafique Khan and Begum Asia Rafique), my sister (Naila Rafique Khan), wife (Sumbal Saba) and brother (Saqib Rafique Khan).

"Those who educate children well are more to be honored than they who produce them; for these only gave them life, those the art of living well."
— Aristotle

To my dear mentor, Professor Dr. Antonio Luiz Braga

I have no words to express my sincere thanks and gratitude to you. A special thanks for granted me the opportunity to be a part of your research group, for full support in difficult times and always helped me as a friend.

I'll always be grateful for your sincere academic teachings, research training and suggestions for improving my personality

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"In the name of God, most gracious, most compassionate. All respects for the Holy Prophet Muhammad (PBUH) for enlightening our souls with the essence of faith in Allah (SWT)."

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It is beyond the words to express my gratitude to LabSelen family (past and present members). André, Bolachian (Juliano), Breno, Bruna, Cabelo (Marcelo), Cirilo (Alisson), Dada (Daiane), Daniel, Flavio, Felipe, Galetto, Gian (Giancarlo), Greice, Igor, Jesus, João, Jovenzinho (Eduardo), Julia, Lais, Leandro, Lu (Luana), Lucas, Marcus, Manu (Manuela), Natasha, Rômulo, Sumbal, Tiago and friends from the other labs for full support and keeping a very friendly and caring environment which make working enjoyable. All the moments spent together during lab cleaning, travelling for conferences, waiting in queue of the university restaurant, social gatherings and barbecue parties. I wish best of luck to all in academic and scientific endeavors and hope the friendship established since 2011 will last in years to come.

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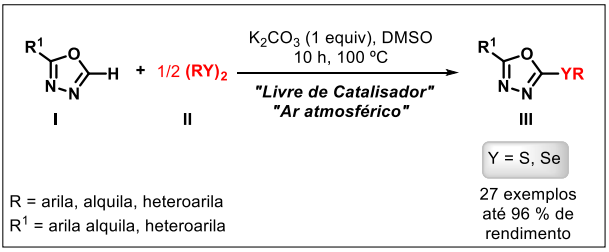
Jamal Rafique Khan,
Florianopolis-Brazil.
08 December 2014

RESUMO

No presente trabalho desenvolveram-se novas metodologias eficientes, econômicas e ambientalmente adequadas para a síntese de oxadiazóis e benzotiazóis contendo uma porção organocalcogênio

Primeiramente, desenvolvemos a síntese de oxadiazóis selenados e tiolados através da funcionalização de ligação C_{sp2}-H promovida por K_2CO_3, em um meio reacional livre de metais de transição.

Em uma primeira etapa foram preparados oxadiazóis selenados com potencial para aplicações biológicas. Sob condições suaves, a reação ocorreu de maneira eficiente na presença de um equivalente do correspondente oxadiazol **I**, um equivalente de base (K_2CO_3), 0,5 equivalentes do correspondente dicalcogeneto de organoíla **II**, na presença de ar atmosférico. Através dessa metodologia, uma série de oxadiazóis calcogenados **III** na posição 5 do heterociclo foram obtidos em rendimentos que variaram de bons a excelentes (Esquema 1).



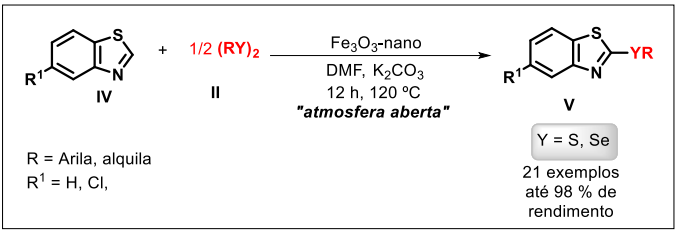
Esquema 1

Adicionalmente, explorou-se a reatividade dos oxadiazóis selenados 3 em reações de troca calcogênio-lítio. Os intermediários oxadiazóis litiado assim obtidos foram capturados, in situ, com diferentes eletrófilos.

É importante salientar, também que essa reação ocorreu de forma eficiente quando se aumentou sua escala para 10 mmol.

Em uma segunda etapa desenvolvemos um novo método para a incorporação de calcogênios em benzotiazóis via reação de calcogenação direta da ligação C-H. Realizou-se a síntese de 2-organocalcogeno-1,3-benzotiazóis **V** através da calcogenação direta entre 1,3-benzotiazóis **IV** e dicalcogenetos de organoíla **II** catalizada por Fe_3O_4 nanopartículado. Esta metodologia permitiu a obtenção dos respectivos produtos calcogenolados **V**, em rendimentos que variaram de moderados a excelentes. Realizou-se, também, com sucesso, a reciclagem do

catalisador em 4 ciclos sem um decréscimo acentuado no rendimento (Esquema 2).



Esquema 2

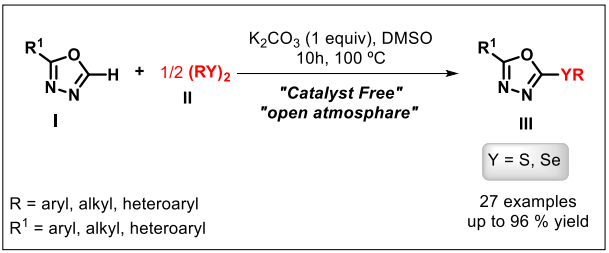
Palavras-chave: química verde; funcionalização de ligação C-H; oxadiazol; benzotiazol; selenetos; sulfetos; disselenetos, dissulfetos.

ABSTRACT

In the present work, we developed efficient, economical and greener procedures for to the synthesis of chalcogenated oxadiazoles and benzothiazoles.

In the first part, we developed a K_2CO_3-promoted procedure for the synthesis of selenated and thiolated oxadiazoles 3 through C_{sp2}-H bond functionalization, under transition metal-free conditions.

We prepared for the first time selenated oxadiazoles, compounds with potential for biological applications. Under mild conditions, the reaction worked well in the presence of 1equiv. of oxadiazole **I**, a half equiv. of diorganyl dichalcogenides **II**, 1 equiv. of base (K_2CO_3), without the exclusion of air and moisture, affording a wide range of chalcogenated oxadiazoles **III** at the C5 position in good to excellent yields. The various substituents with different electronic effects and steric effects tolerated the optimized reaction conditions (Scheme 1).



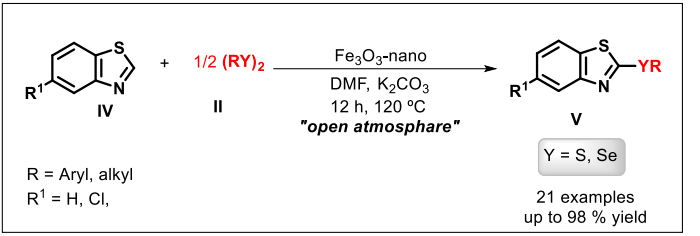
Scheme 1

Furthermore, selenated oxadiazole was explored for selenium−lithium exchange reaction and lithium-intermediate was trapped by different electrophiles.

We were also successful in scaling up the reaction in up to 10 mmol.

Subsequently, we developed a new method of incorporation of organoyl chalcogenides in benzothiazoles via direct chalcogenation of C-H bond.

In this work, we report the synthesis of 2-organochalcogeno-1,3-benzothiazoles **V** via direct chalcogenation reactions between 1,3-benzothiazoles **IV** and diorganyl dichalcogenides **II** catalyzed by Fe_3O_4 nano particle. This methodology allowed us to obtain 2-chalcogen-1,3-benzothiazoles in moderate to excellent yields, as well as recycling successful the catalyst in up to 4 cycles without any major decrease in the yield (Scheme 2).



Scheme 2

Keywords: green chemistry; carbon-hydrogen bond functionalization; cross-coupling; benzothiazoles; oxadiazoles; benzothiazoles; selenides

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SYMBOLS & ABBREVIATIONS

^{1}H NMR	Hydrogen – Nuclear Magnetic Resonance
^{13}C NMR	Carbon 13 – Nuclear Magnetic Resonance
^{77}Se NMR	Selenium 77 – Nuclear Magnetic Resonance
Ar	Aryl
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
Bu	Butyl
CC	Column Chromatography
CDC	Cross dehydrogenative coupling
$CDCl_3$	Deuterated chloroform
CuO nano	Copper (II) oxide nanoparticles
DMC	Dimethyl carbonate
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
ee.	Enantiomeric excess
ESI	Electrospray ionization
equiv.	Equivalent
δ	Chemical shift
GCMS	Gas chromatography mass spectrometry
HRMS	High resolution mass spectrometry
IR	Infrared spectroscopy
J	Coupling constant
KO*t*Bu	Potassium *tert*-butoxide
Me	Methyl
MeI	Methyl iodide
MeOH	Methanol
min	Minute
MW.	Microwave
NH_2NH_2	Hydrazine
ppm	Part per million
Ph	Phenyl
PhH	Benzene
R	Organic Group
rt	Room temperature
t	Time
T	Temperature
TBAF	Tetrabutylammonium bromide
TBHP	*tert*-Butyl hydroperoxide

TEOF	Triethyl orthoformate
THF	Tetrahyrofuran
TLC	Thin layer Chromatography
TM	Transition metal
TMS	tetramethylsilane
Y	Chalcogen
Zn	Zinc

TABLE OF CONTENT

Chapter 1
Introduction

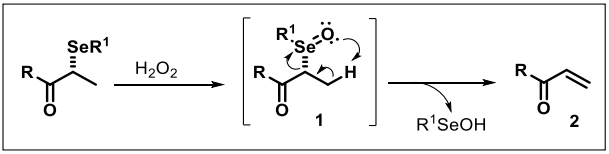
INTRODUCTION

This PhD Thesis Project involves the development of heterocycles containing selenium and sulfur through C-H functionalization using more sustainable transformation. In the following headings there will be a short introductions related to the topics involved with our goal. In this sequence, we will present our specific objectives**,** methodology, preliminary results, discussions, and conclusions.

1.1. Organoselenium chemistry

Since last few decades organoselenium compounds have become an attractive building block because selenium-containing compounds are important auxiliary function in many synthetic sequences.[1] Synthetic versatility and applicability of organoselenium compounds in organic chemistry is well described in a great number of scientific articles,[2] reviews[3] and books.[4]

From the synthetic point of view, organic selenium compounds have received special attention after Walter and coworkers describe the reaction of β-elimination of selenoxides **1** to the formation of alkenes **2** under milder reaction conditions (Scheme 1).[5] Since then, several studies have been published in the literature using the chemistry of selenium in organic synthesis.[6]



Scheme 1. Selenoxide elimination reaction

Organoselenium compounds are attractive synthetic targets because of their selective reactions,[1a-c,7,8] their use as ionic liquids,[9] as efficient chiral ligand in symmetric catalysis,[10] as catalysts,[11] synthetic intermediates in total synthesis[12] and their fluorescent properties.[13] Another important advancement in this context is the formation of C-Se bonds, which has contributed to the synthesis of a wide range of biologically active molecules[14] and functional materials.[15]

A large number of organoselenium compounds have been found to function as antioxidant, antitumor, antimicrobial, antidepressant apoptosis inducers, chemopreventors in several organs and many of these

compounds are competitive inhibitors for target proteins etc. Some of biologically relevant organoselenium compounds **3-14**[4a,14] are shown in Figure 1.

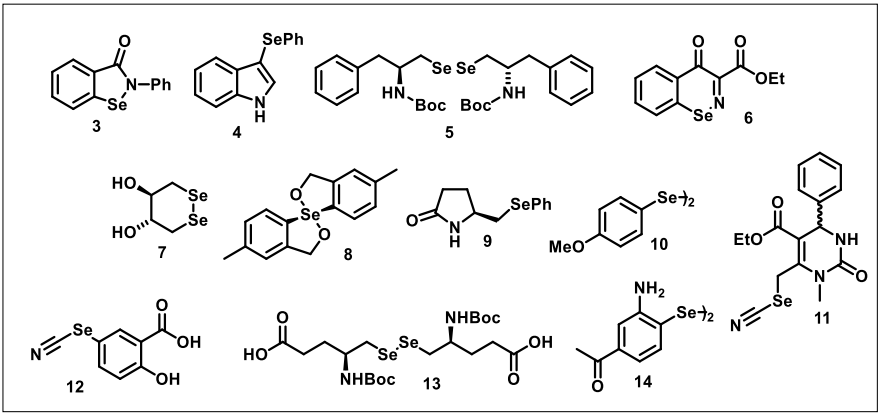


Figure 1. Biologically active organoselenides and diselenides

1.2. Heterocyclic compounds

Heterocyclic compounds are highly important class of compounds, because of their abundance in numerous natural products such as vitamins,[16] alkaloids[17] as well as pharmaceuticals of biological activity and electroactive materials.[18,19] Some of relevant heterocyclic compounds **15-23**[16-19] are shown in Figure 2.

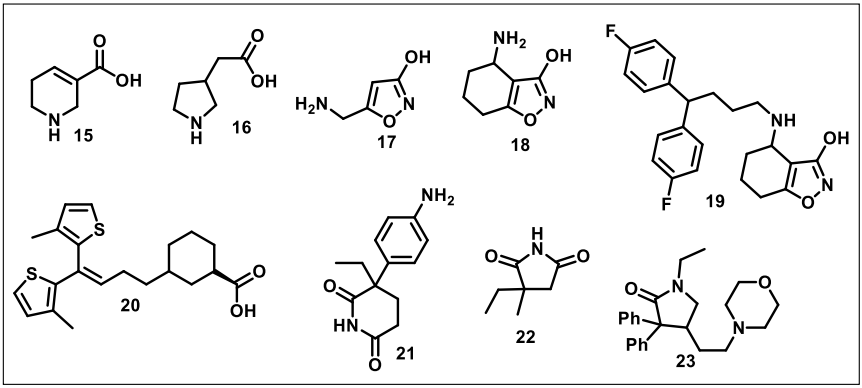


Figure 2. Heterocyclic pharmaceuticals

Normally compounds containing heterocyclic ring systems are of great importance both medicinally and industrially. Therefore, much effort has been devoted not only to construct basic skeletons of heterocyclic molecules but also to introduce new functional groups onto those compounds mainly through carbon–carbon or carbon–heteroatom bond formation.[20]

1.2.1. Oxadiazoles

Five-membered ring heterocycles **24-27** (Figure 3) containing two carbon atoms, two nitrogen atoms, and one oxygen atom, known as oxadiazoles, are of considerable interest in different areas of medicinal, pesticide chemistry and also polymer and material science.[21,22] These nucleuses attracted a wide attention for the chemist due to its versatility. The level of interest of oxadiazole chemistry is increasing sharply, e.g. from 2004-12 the number of patent applications containing oxadiazole rings has increased considerably (100%), to a total of 686 (Figure 3).[22]

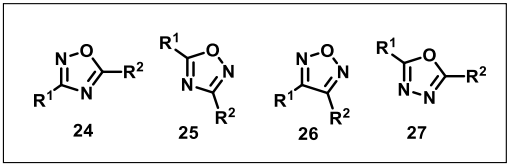


Figure 3. Structurally different oxadiazoles

1.2.2. 1,3,4-oxadiazoles

1,3-4-oxadiazoles is an important heteroaromatic compound among other oxadiazoles. Functionalization of the 1,3-4-oxadiazoles scaffold is a significant synthetic task, since oxadiazoles are well established as "privileged scaffolds" and are widely used for pharmaceutical, biological and material applications.[23] They show a very broad spectrum of biological activity, being used, for instance, as inhibitors of various enzymes and as antimicrobial, analgesic, antiviral and antitumor agents.[24,26] Interestingly, few of the active compounds have a sulfur linkage at C-5.[25a] 1,3,4-oxadiazoles motifs are also of interest in material science and have been widely used to create novel materials.[27,28]

Within drug discovery and development, a number of compounds containing an 1,3,4-oxadiazole moiety are in the late stage clinical trials and some of them are commercial market drugs, e.g. zibotentan **28a** as an

anticancer agent,[28] tiodazosin **28b** as alpha-1_blocker and antihypertensive agents,[29] and furaminzole **28c** as nitorfuran antibacterial drug (Figure 4).[30] So far, one oxadiazole containing compound, raltegravir **28d** an antiretroviral drug for the treatment of HIV infection, has been launched onto the marketplace.[31]

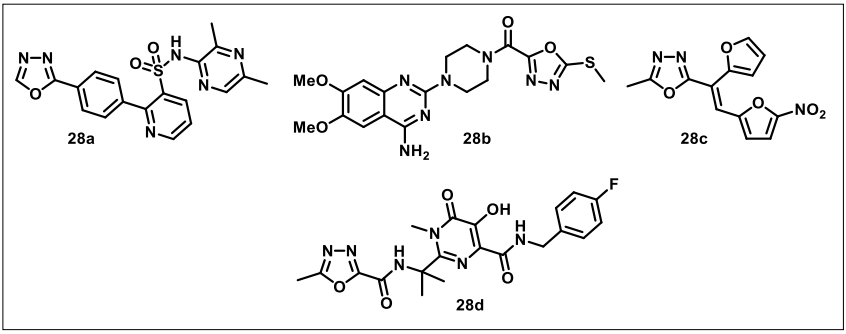


Figure 4. Pharmaceuticals with 1,3,4-oxadiazole moiety

1.2.3. Thiazoles

Five-membered heteroaromatic **29-31** (Figure 4) containing three carbon atoms, one nitrogen atoms, and one sulfu atom, known as thiazoles, are of considerable interest in different areas of medicinal, biological chemistry and also polymer and material science.[32,33] These nucleuses represent some important natural proucts.[33] Due to versatility of these nucleases, there is always a greater focus on these compounds by different researchers.[34]

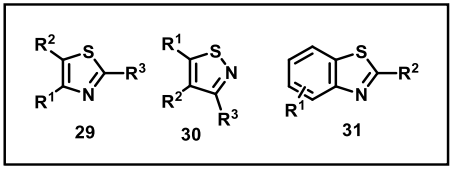


Figure 5 Structurally different thiazoles

1.2.4. 1,3-Benzothiazole

A fused benzene ring on thiazoles i.e.1,3-Benzothiazole is an important heteroaromatic compound among other thiazoles. Functionalization of the **31** scaffold is a significant synthetic task, since

thiazoles are well established as "privileged scaffolds" and are widely used for pharmaceutical, biological and material applications.[35] They show a very broad spectrum of biological activity, being used, for instance, as inhibitors of various enzymes and as antimicrobial, analgesic, antiviral and antitumor agents.[36.37] Interestingly, few of the active compounds have a sulfur linkage at C-5.[38] 1,3,4-oxadiazoles motifs are also of interest in material science and have been widely used to create novel materials.[39]

Within drug discovery and development, a number of compounds containing an 1,3-benzothiazole moiety are in the late stage clinical trials and some of them are commercial market drugs, e.g. Zopolrestat **32a**,[40] a medication used to treat diabetes, SKLB-163 **32b**,[41] a potent anticancer drug is in Clinical Trial, compound **32c**, an inhibitor of cathepsin (an enzyme that may assist in tumor invasion and proliferation).[42] Also many of benzothiazole containing compounds are having important use in other areas e.g. 2-(methylthiocynato)-1,3-benzothiazole (TCMTB) **32d**,[43] used extensively in agrochemical industry (Figure 6).

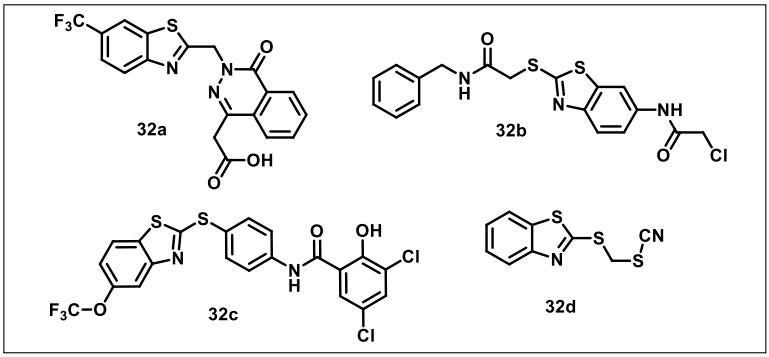


Figure 6. Pharmaceuticals and important compounds with1,3-Benzothiazole moiety

1.3. Green Chemistry and it's Principles

Green Chemistry is a set of ideas aimed for the development and implementation of chemical processes and methodologies in order to reduce or eliminate the use or generation of hazardous substances to the environment. Thus, reactions that avoid the use of any toxic solvents, catalyst or reagents are the important from environmental point of view and are very appropriate, since it reduces the generation of waste as well

as problems related to handling volatile, toxic and flammable substances.[44]

Keeping in view different aspects of Green Chemistry Paul Anastas and John Warner developed 12-principles for green chemistry, the following list outlines an early conception of what would make a greener chemical, process, or product.[45]

- **Prevention:** It is better to prevent waste than to treat or clean up waste after it has been created.
- **Atom Economy**: Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
- **Less Hazardous Chemical Syntheses**: Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
- **Designing Safer Chemicals:** Chemical products should be designed to affect their desired function while minimizing their toxicity.
- **Safer Solvents and Auxiliaries**: The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
- **Design for Energy Efficiency:** Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
- **Use of Renewable Feedstock's:** A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
- **Reduce Derivatives:** Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
- **Catalysis:** Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
- **Design for Degradation:** Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
- **Real-time analysis for Pollution Prevention:** Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

- **Inherently Safer Chemistry for Accident Prevention:** Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires

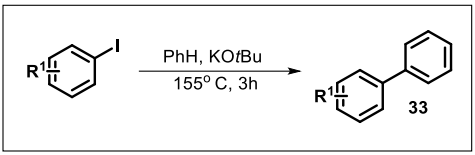
1.3.1. Reactions Following Green Principles

From the synthetic point of view, reactions following green principles e.g. without solvents or catalysts, have been constantly employed, especially in methodologies involving reactions of the type one-pot. These methods have been well accepted in the scientific community, because such methodologies fit the basic principles of green chemistry.[46]

In this context, several researchers have developed new methods of synthesis in the absence of solvents or metal catalysts, making them simpler, saving energy, and preventing waste, hazards related to flammability, volatility and toxicity of these substances. Such reactions are also described, mostly as fast, selective and high level of conversion of reactants to products.[47] Furthermore, some of these processes increase the atom economy by avoiding some of derivatization processes, and reduce waste generation.[48,49]

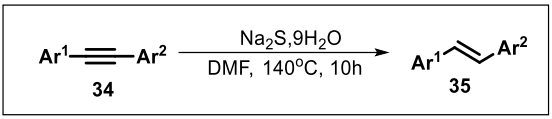
A neat reaction is a great alternative in synthesis because it eliminates the use of solid support and also the organic solvents, being an interesting strategy for minimizing waste, reducing the factor E.[50] This concept (factor E), used mainly in industry, was introduced by Sheldon and is defined as the amount of waste generated for each kilogram of product formed. Thus, considering the above, the present study emphasized the expression "reactions without catalyst" and "reactions without solvent".

One of the most important observations in organic chemistry in recent years has been the discovery that certain reactions previously thought the preserve of transition metal catalysis (for example C–H activation,[51] biaryl couplings,[52,53] certain Heck[54] and Sonogashira[55] processes) can be effected without the requirement for a transition metal. Recently Gray and Wilden demonstrated that transition metals or ligands are not essential components in the synthesis of biaryl (Scheme 2). Biaryl coupling **33** (often labelled ‘C–H activation’) of aromatic systems can be achieved by potassium *tert*-butoxide alone in the absence of transition metal and any amine or bipyridine catalyst.[56]



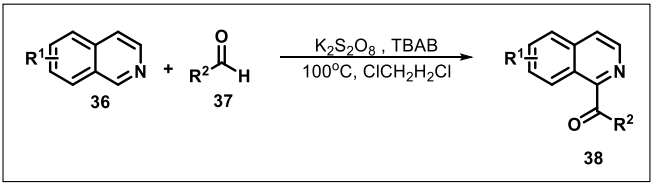
Scheme 2: Metal free synthesis of biaryl

The selective semi-hydrogenation of alkynes to alkenes with a defined *Z*- or *E*-configuration is an important transformation in organic chemistry.[57] Among the various efficient methods to access *Z*-alkenes, Lindlar's catalyst ($Pd/CaCO_3$) and its variants are the most popular choices.[58] Lu and coworkers recently showed a highly stereoselective and efficient TM-free semihydrogenation of internal alkynes **34** to *E*-alkenes **35** using cheap and green water as hydrogen donor (Scheme 3).[59]



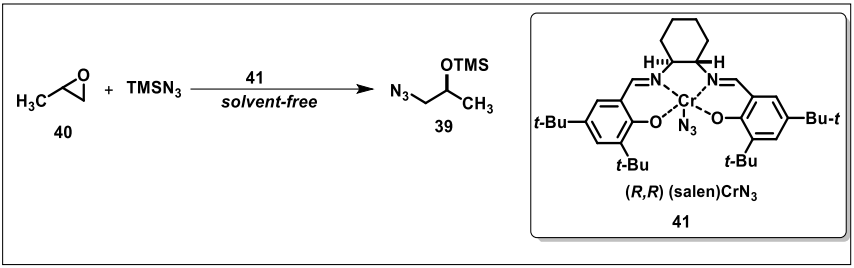
Scheme 3: Synthesis of *E*-alkenes

Acyl derivatives of heterocyclic compounds are present in a variety of drugs that are important in pharmacological studies.[60] Acylation of electron deficient heteroarenes is a challenging task,[61] whereas acylation of electron-rich arenes is facile.[62] In this regard Prabhu and coworkers developed a TM-free acylation of isoquinoline, quinoline, and quinoxaline derivatives **36** employing a cross dehydrogenative coupling (CDC) reaction with aldehydes **37** using substoichiometric amount of TBAB (tetrabutylammonium bromide, 30 mol %) and $K_2S_2O_8$ as an oxidant, resulting in the acylated derivatives **38** (Scheme 4). [63]



Scheme 4. Acylation of isoquinolines

There are also many important examples regarding synthesis of different molecules under solvent free conditions. In 1995, Jacobsen and coworkers showed the synthesis of enantiomerically enriched azidoalcohols **39** from racemic epoxide **40** by using chiral catalyst (*R*,*R*)(salen)CrN_3 **41** (Scheme 5) under solvent-free conditions affording the product **39** in quantitative yield and 97% of enantiomeric excess.[64]



Scheme 5: Synthesis of enantiomerically enriched Azidoalcohol

1.3.2. Microwave irradiations and organic chemistry

Similarly, in organic synthesis, several studies under microwave irradiation have been conducted to establish the best reaction conditions in order to obtain the desired products in high yields, generating the least possible waste, and shorter reaction times. Thus, reaction carried out under microwaves irradiation in solvent free condition, have proven to be efficient reactive systems.

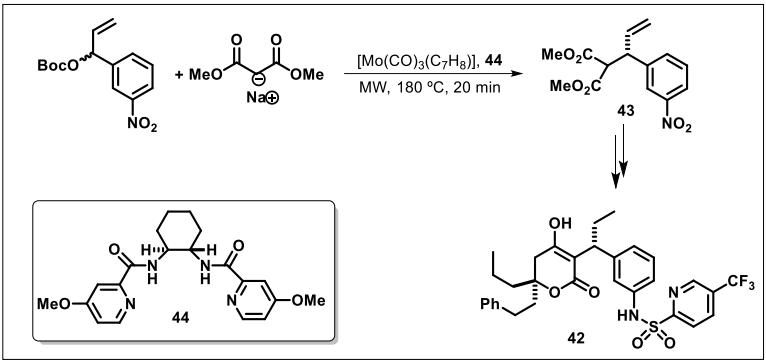
The use of this energy source to accelerate organic reactions is gaining more prominence by the academic community. This method is highly versatile since, compared to reactions in conventional heating; it reduces the reaction times and could also decrease the formation of by-products, making the reactions cleaner.[65]

In this context, several studies have been published showing the use of microwave radiation instead of conventional heating, which follows the Green Chemistry Principles[66] e.g. reactions which require a lower reaction time and decreasing the formation of byproducts,[67]

In the field of organic synthesis, several microwave-accelerated transformations are described, for example, Heck reactions,[68] Suzuki[69] and Stille,[70] provided that its corresponding product in high yields. Furthermore, reactions of formation of carbon-heteroatom bond[71] and

asymmetric allylic alkylation reactions[72] have also been reported due to the use of the microwave.

MW-assisted heating is also used in the synthesis of the precursor drug molecule. In 2002, Trost and colleagues used this technique in one step for the synthesis of anti-HIV drug Tipranavir **42** (Scheme 6).[73]



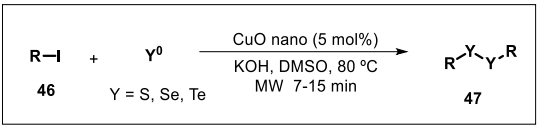
Scheme 6. Asymmetric allylic alkylation step in the synthesis of Tipranavir **42**

The asymmetric allylic alkylation reaction in the formation of the intermediate **43** occurred in 20 minutes, using chiral ligand **44** together with a molybdenum complex under microwave irradiation afforded **43** with 94% yield and 94% enantiomeric excess.

Various selenium derivative compounds have also been synthesized using microwave, such as the vinyl selenides **45**, as described by Perin and coworkers.[74] These organoselenium compounds were prepared by the addition of sodium selenolates (generated by the cleavage of diorganyl diselenide using $Al_2O_3/NaBH_4$) and acetylene ester **44.** The product **45** was obtained in good yields in only 1.5 minute of reaction (Scheme 7).

Scheme 7. Synthesis of vinyl selenides employing microwave energy

Reactions promoted by MW-irradiations are also becoming a major focus of interest in our research group.[75] Recently, our group synthesized diorganyl diselenide **47** using this principle, starting with aryl halides **46** and elemental selenium, catalyzed by copper nanoparticles (Scheme 8). The product **47** was obtained in up to 97 % yields and in short reaction times.

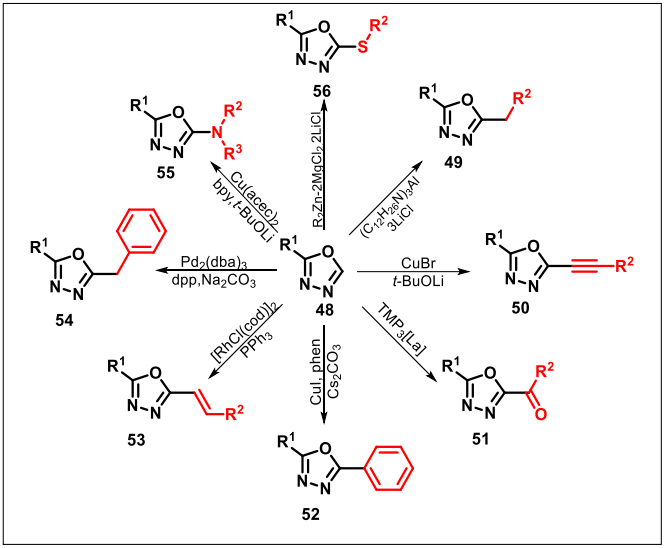


Scheme 8. Synthesis of diselenides catalyzed by CuO nanoparticles under MW

1.4. C-H Functionalization of 1,3,4-oxadiazoles

Along with the importance in biological and material sciences, the chemistry of 1,3-4-oxadiazoles is always fascinated the synthetic organic community due to generation of carbines and its reaction with electrophilic functionalities. Therefore, remarkable progress has been made by various groups on the chemistry of 1,3,4-oxadiazoles. The methodologies reported for the substitution at C-5 position of 2-substituted 1,3,4-oxadiazole **48** usually involve the direct reaction of the oxadiazole core with various electrophiles, catalyzed by metals.[76-83] To date, the literature reports many methods for the C-H functionalization of 1,3,4-oxadiazoles **48** with the formation of C-alkyl **49**,[76] C-alkynyl **50**,[77] C-carbonyl **51**,[78] C-aryl **52**,[79] C-allyl **53**,[80] C-benzyl **54**,[81] C-amine **55**,[82] C-sulfide **56**,[83] etc, some of them are following (Scheme 9):

However, the disadvantages associated with most of previous methodologies, owing to the use of complicated catalysts, expensive or excess of reagents, harsh reaction conditions, hazardous materials, oxygen-free techniques or elaborated multi-stepped processes, have limited their synthetic scope.

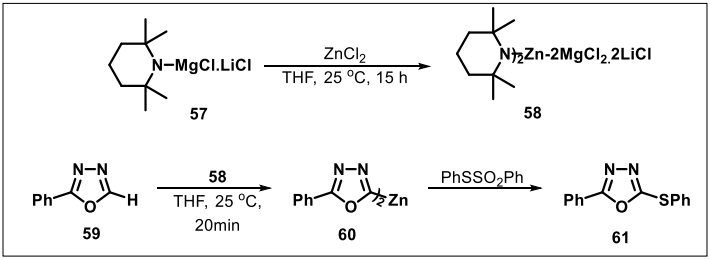


Scheme 9. Various methods of C-H functionalization of1,3,4-oxadiazoles

1.4.1. Chalcogenation of 1,3,4-oxadiazoles

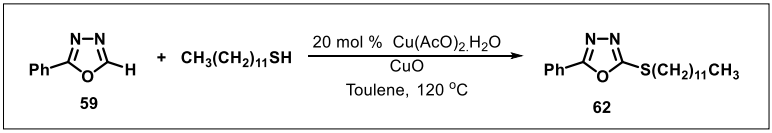
Selenation of 1,3,4-oxadiazoles through C_{sp2}-H bond functionalization is not explored so far. but there are few reports regarding thiolation through C-H bond functionalization. In the following we will discuss about different method for thiolaion of 1,3,4-oxadiazole.

In the same way, there are few work related to the thiolation of oxadiazole. In this regard the first report was cited by Wunderlich and Knochel in 2007.[82,84] They report the synthesis of only 2-phenyl-5(thiophenyl)-1,3,4-oxadiazoles **61** and found that the treatment of (tmp)MgCl·LiCl **57**[85] with $ZnCl_2$ (0.5 equiv, 25°C, 15 h) provides $(tmp)_2Zn·2MgCl_2·2$ LiCl **58** (Scheme 9). The reaction of 2-phenyl-1,3,4-oxadiazole **59** with **58** (0.55 equiv.) provided the zincated heterocycles **60** after 20 min at 25°C. After, quenching with $PhSSO_2Ph$ in the presence of catalytic amounts of CuCN·2LiCl (5 mol%)[86] the 2-phenyl-5(thiophenyl)-1,3,4-oxadiazoles **61** were isolated in 75% yield (Scheme 10).



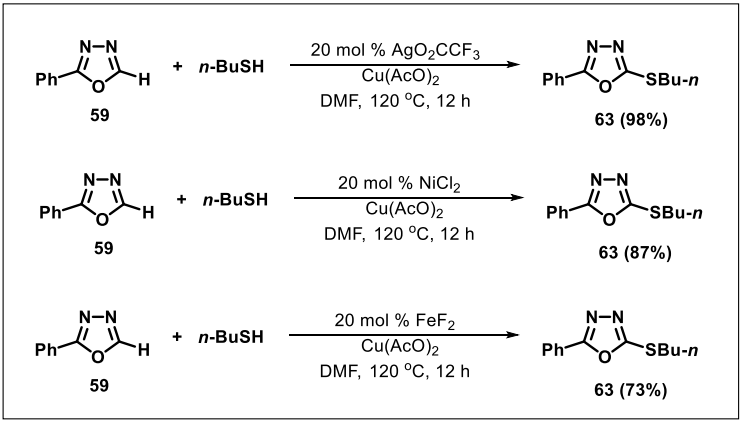
Scheme 10. Synthesis of 2-phenyl-5(thiophenyl)-1,3,4-oxadiazoles

Liu and coworkers described Cu(II)-catalyzed direct thiolation of 2-phenyl-1,3,4-oxadiazole **59** with dodecylthiol via intermolecular C–S bond formation/C–H functionalization under oxidative conditions and the desired product **62** was obtained with 50% yield (Scheme 11).[87]



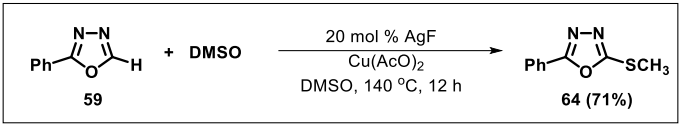
Scheme 11. Thiolation of 2-phenyl-1,3,4-oxadiazole with dodecylthiol

In 2012, Gao and coworkers described a lewis acid (Ag^{I}, Ni^{II}, or Fe^{II}) catalyzed, Cu^{II}-mediated thiolation reaction between **59** and butylthiol. The thiolated products **63** were obtained in good to excellent yield, depending upon the catalyst (Scheme 12).[88]



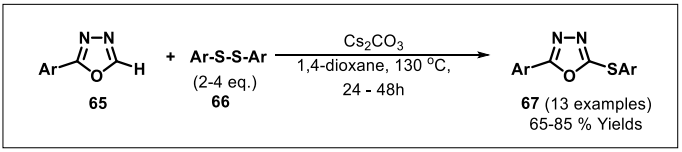
Scheme 12. Thiolation of 2-phenyl-1,3,4-oxadiazole with butylthiol

In the same work they mentioned that DMSO can serve as an effective methylthiolating reagent for the synthesis of **64** (Scheme 13).



Scheme 13. Methylthiolation of 2-phenyl-1,3,4-oxadiazole with DMSO

As far as we know, the only direct thiolatiion reaction of 1,3,4-oxadiazole was done by Bolm's group. In this study they used a transition metal free condition for the direct thiolation of 1,3,4-oxadiazole **65** through C-H bonds using 2-4 equiv. of diaryl disulfdes **66** under inert atmosphere. The reaction was carried out in dry 1,4-dioxane for a period of 24-48 hours using Cs_2CO_3 as base (Scheme 14). The thiolated product was obtained from good to moderate yield. [89]



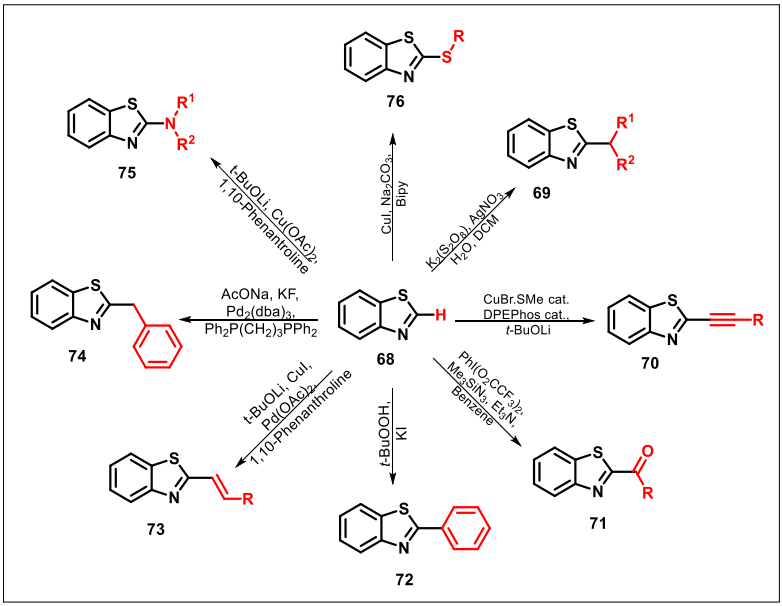
Scheme 14. Direct thiolation of 2-subsited-1,3,4-oxadiazole with diaryldisulfides

Since this procedure was involved a high excess of disulfides, an inert atmosphere, an expensive base as well as a long reaction time, we envisioned to develop a greener and sustainable methodology. Besides, we could extend this transformation in the preparation of the similar seleneted compounds that are unknown.

1.5. C-H Functionalization of 1,3-benzothiazoles

Along with the importance in biological and material sciences, the chemistry of 1,3-benzothiazole is always fascinated the synthetic organic community due to generation of carbines and its reaction with electrophilic functionalities. Therefore, remarkable progress has been made by various groups on the chemistry of 1,3-benzothiazole. The methodologies reported for the substitution at C-2 position of 1,3-

benzothiazole **68** usually involve the direct reaction of the thiazole core with various electrophiles, catalyzed by metals.[90-97]



Scheme 15. Various methods of C-H functionalization of1,3-benzothiazoles

To date, the literature reports many methods for the C-H functionalization of 1,3-benzothiazole **68** with the formation of C-alkyl **69**,[90] C-alkynyl **70**,[91] C-carbonyl **71**,[92] C-aryl **72,**[93] C-allyl **73**,[94] C-benzyl **74**,[95] C-amine **75**,[96] C-sulfide **76**,[97] etc, some of them are shown in Scheme 15.

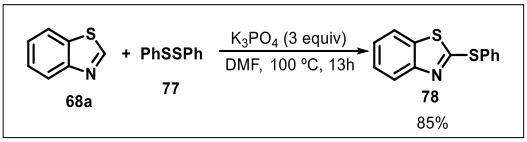
However, the disadvantages associated with most of previous methodologies, owing to the use of complicated catalysts, expensive or excess of reagents, harsh reaction conditions, hazardous materials, oxygen-free techniques or elaborated multi-stepped processes, have limited their synthetic scope.

1.5.1. Chalcogenation of 1,3-benzothiazoles

So far, there is only one report available for selenation of 1,3-benzothiazoles but there are few reports regarding thiolation through C-

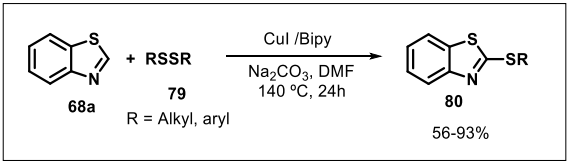
H bond functionalization. In the following we will discuss about recent methods for chalcogenation of 1,3-benzothiazoles.

In 2009, Daugulis and coworkers reported the thiolation of benzothiazole **68a** using diphenyl disulfide **77** as an organic sulfur source in DMF using 3 equiv. of K_3PO_4 as base.[98] By this procedure, 2-phenylthio-benzothiazole **78** was obtained in 85% yield (Scheme 16).



Scheme 16. Thiolation of benzothiazole in the presence of of K_3PO_4

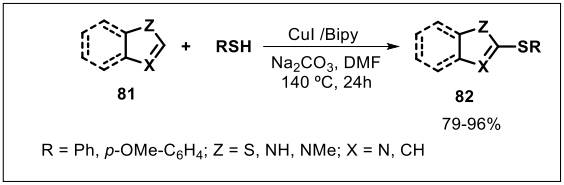
Liu and coworkers reported the synthesis of a series of 2-organothiol-benzothiazoles **80** through direct benzothiazole thiolation of **68a** with dialkyl and diaryl disulfides **79**. This transformation was mediated by stoichiometric amounts of CuI, 2,2'-bipyridine (1 equiv.) and Na_2CO_3 (2.5 equiv.) in DMF at 140 °C.



Scheme 17. Thiolation of benzothiazole in the presence of CuI and ligand

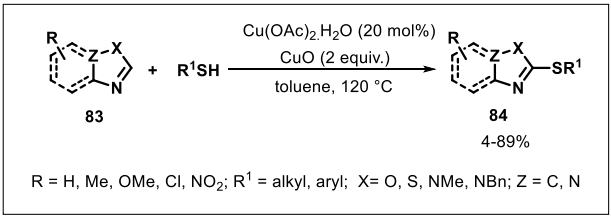
By this methodology, alkyl thiols and aryl substituents with electron donating effect showed better yields compared to aryl thiols containing electron withdrawing substituents. The products were obtained in yields ranging from 56 to 93% (Scheme 17).[99]

The authors expanded this methodology of thiolation to other substrates **81** heteroaryl, such as thiazoles, indoles and 1-methylimidazole to give the respective product **82** in 79-96% yield (Scheme 18).



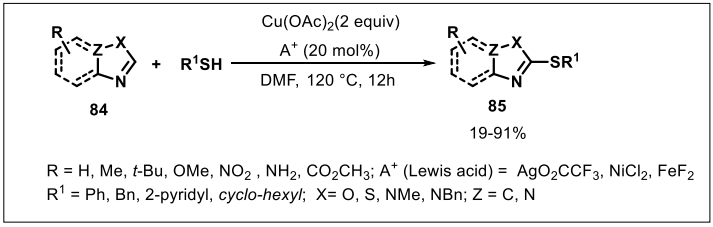
Scheme 18. Thiolation of heterocylces in the presence CuI and ligand

In 2011, Liu and coworkers described the formation of C-S bond of **83** with thiols. Various azoles through direct thiolation using $Cu(OAc)_2.H_2O$ (20 mol%) as catalyst and CuO (2 equiv.) as an additive in toluene.[100] After 8 hours of reaction at 129 ºC, benz imidazole, benzoxazoles, thiazoles, benzothiazoles, 1-phenyl-imidazole, 5-phenyloxazol and 2-phenyl-1,3,4 diazoxazol were thiolated efficiently generating the corresponding products **84** in 4 to 89% yields. The method allowed the use of alkyl and aryl thiols. However, aryl thiols were less effective, producing the products in lower yields (Scheme 19).



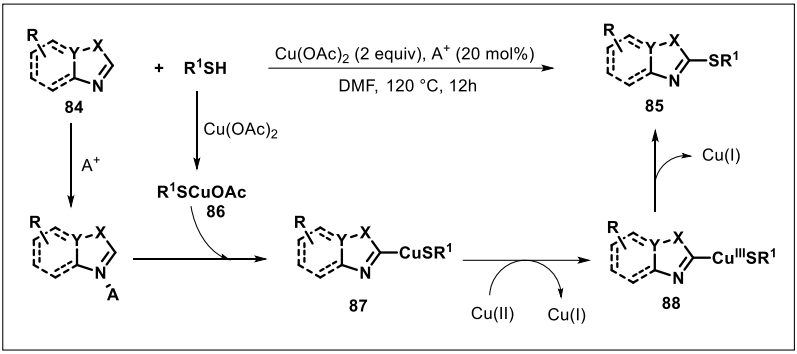
Scheme 19. Thiolation of heterocycles in the presence CuI and ligand

The thiolation of heteroarenes **84** with thiols mediated by $Cu(OAc)_2$ in the presence of catalytic amounts of a suitable Lewis acid [Ag (I), Ni (II) or Fe (II)] in DMF at 120 °C, was described by Gao and coworkers.[101] The method developed enabled the direct formation of various heteroarenes C-S connection, affording thiolated product **85** in moderate to good yields (Scheme 20).



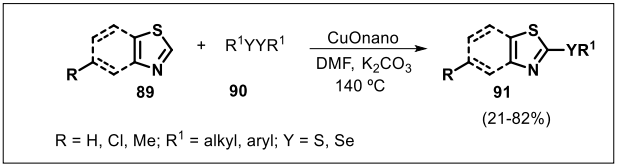
Scheme 20. Thiolation of heterocycles catalyzed by Lewis acid

According to the experimental results, the authors suggest a proposed mechanism, which can be divided into the following steps: first the reaction occurs between thiol and $Cu(OAc)_2$ species generating RSCuOAc **87**. Subsequently, the heteroarene coordinated to Lewis acid undergoes thiolation step through a joint mechanism deprotonation-metallation, leading to formation of the organometallic intermediate **87**. In next step change in the oxidation state of copper from Cu(II) to Cu(I) and formation of Cu (III) species **88**, take place. This justifies the need of excess $Cu(OAc)_2$. Finally, the reductive elimination occurs leading to the formation of the product **85** and removal of Cu (I) (Scheme 21).



Scheme 21. Proposed Mechanism of thiolation in the presence of Lewis acid

Recently, Zeni and coworkers developed a new method for thiolation and selenaion of 1,3-benzothiazoles and thiazoles **89** in the presence of K_2CO_3, catalyzed by CuO nano under inert atmosphere. In this study, the authors used 1 equiv. of diorganyl dichalcogenides **90** and 2 equiv. of base at 130 °C for 24-48 hours (Scheme 22).[102]



Scheme 22. CuO catalyzed thiolation of 1,3-benzothiazoles and thiazoles

The respective chalcogenated product **91** were obtained from 21 to 82%. It is worth noting that depending on the substrate employed, some changes in reaction condition were necessary.

Since this procedure was involved an excess of dichalcogenide and base, an inert atmosphere, problem with recyclability of the catalyst as well as a long reaction time, we envisioned to develop a greener and sustainable methodology.

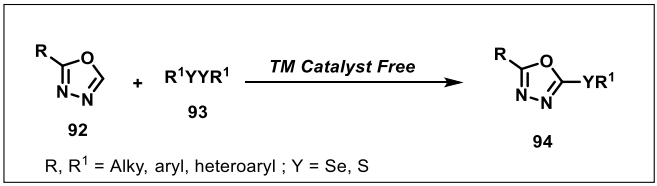
Chapter 2
Motivations and Objectives

MOTIVATIONS AND OBJECTIVES

Considering the significance of organoselenium compounds as well as the oxadiazoles and benzothiazoles, we proposed to develop a new methodology involving the reaction of 1,3,4-oxadiazoles and benzothiazoles with diselenides through direct C-H bond functionalization. These studies can also be extendable to disulfides involving a new greener approach that provide the desired products with high efficiency. For instance, we were successful in decreasing the amount of dichalcogenides considering it is stoichiometry as well as by using cheaper and more accessible base under open atmosphere.

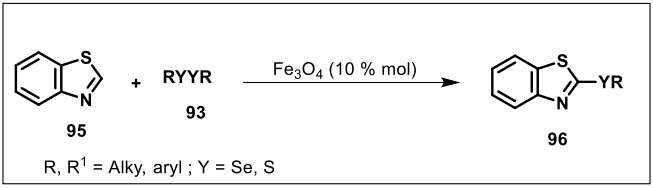
Besides, the development of chalcogenation of heteroaromatics and other organic moieties through direct C-H bond is an important research area.[103] Thus, as part of our wider research program aimed for designing and developing eco-friendly processes,[104] in this work of PhD we planned to study, for the first time, a straightforward, and environmentally benign protocol for the direct selenation of C-H of 1,3,4-oxadiazole (Scheme 23), which could be applicable to analogous disulfides.

In fact, this protocol was being developed in open atmosphere using one equiv. of 2-subsitituted-1,3,4-oxadiazole **92** and a half equiv. of dichalcogenide **93** to afford the desired chalcogenated oxadiazoles **94**.



Scheme 23. Synthesis of 2-subsituted-5-organochalcogeno-1,3,4-oxadiazoles

We also planned to extend our studies of chalcogenation of C-H bond of heteroarenes to benzothiazole. Therefore, in second part of this work of PhD we planned to develop, a straightforward, efficient and ecofriendly protocol for the direct C-H bond selenation of 1,3-benzothiazole (Scheme 24), which could be applicable to analogous disulfides. In fact, this protocol was being developed in open atmosphere using one equiv. of benzothiazole **95** and stoichiometric amount of dichalcogenide 93 catalyzed by 10% mol of Fe_3O_4, to afford the desired chalcogenated benzothiazole **94**.



Scheme 24. Synthesis of 2-organochalcogeno-1,3-benzothiazoles

2.1. Specific Objectives

Based on our planning we decided to achieve following objectives in this PhD work:

Chalcogenation of Oxadiazoles

- Development of an ideal reaction conditions for the synthesis of 5-organoselenated 1,3,4-oxadiazole from diorganyl diselenide and 2-subsituted 1,3,4-oxadiazole under conventional heating.
- Search for the appropriate base, solvent and other reaction parameters to be used in this reaction system.
- Synthesis of a series of organoselanyl oxadiazoles under the best reaction conditions.
- Study some aspects of this transformation to support proposed mechanism
- Explore the reactivity of organoselanyl oxadiazoles by its transmetalation followed by capturing of the oxadiazoles anion generated with electrophiles.
- Expand the methodology for the synthesis of thiolated oxadiazoles.
- Characterization of all the synthesized compounds by ^{1}H, ^{13}C NMR, ^{77}Se, IR, melting point and HRMS, when necessary.
- Present the results in important congresses and meetings.
- Publish the results in the form of patents and scientific articles in well-recognized journals among the scientific community.

Chalcogenation of Benzothiazoles.

- Development of an ideal reaction conditions for the synthesis of 2-organoselenated 1,3-benzothiazole from diorganyl diselenide and 1,3-benzothiazole under conventional heating.
- Search for the appropriate base, catalyst, solvent and other reaction parameters to be used in this reaction system.
- Synthesis of a series of organoselanyl benzothiazoles under the best reaction conditions.
- Study of recyclability of catalyst
- Expand the methodology for the synthesis of thiolated benzothiazoles.
- Characterization of all the synthesized compounds by ^{1}H, ^{13}C NMR, ^{77}Se, IR, melting point and HRMS, when necessary.
- Present the results in important congresses and meetings.

- Publish the results in the form of patents and scientific articles in well-recognized journals among the scientific community.

Chapter 3
Results and Discussions

RESULTS AND DISCUSSIONS

Considering the importance of organochalcogen compounds and 1,3,4-oxadiazoles and benzothiazoles themselves, the direct chalcogenation of 1,3,4-oxadiazoles and benzothiazoles through C-H bond functionalization, were investigated in the present work of PhD Thesis. The chalcogenated heterocycles **94** and **96** (Figure 7) were prepared by coupling of different diorganyl dichalcogenides with 1,3,4-oxadiazoles and benzothiazoles nuclei.

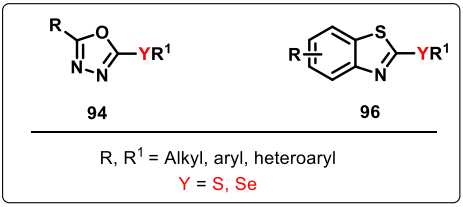
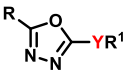


Figure 7. Chalcogenated 1,3,4-oxadiazoles and benzothiazoles

In the following, we will present and discuss the results obtained during the course of this work. First we will discuss various results obtained from the chalcogenation of 2-substituted-1,3,4-oxadiazoles at C-5 under catalyst free conditions. In second part, we will discuss the different results achieved during chalcogenation of benzothiazoles using iron (II, III) oxide (Fe_3O_4) nanoparticles.



R, R^1 = Alkyl, aryl, heteroaryl

Y = S, Se

Chapter 3: Part A
Results and Discussions

3.1. Synthesis of 2-substituted-5-organochalcogeno-1,3,4-oxadiazoles in the absence of metal catalyst

In recent years, our research group has shown a great interest in the chemistry of heterocyclic compounds and organocalcogenides, particularly in the area of developing new methods for the synthesis and/or functionalization of heterocycles with organochalcogens. Moreover, functionalization of 1,3,4-oxadiazoles *via* direct C-H bond with different organic moieties has emerged an important and simple method for the synthesis of wide range of substituted oxadiazoles.

The goal of the current work is mainly focused on the development of sustainable methodologies for the synthesis of 1,3,4-oxadiazoles containing organoselenium **97** and organosulfur **98** moieties (Figure 8), which could have potential applications in biological and/or in material sciences.

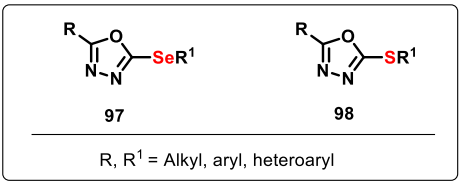


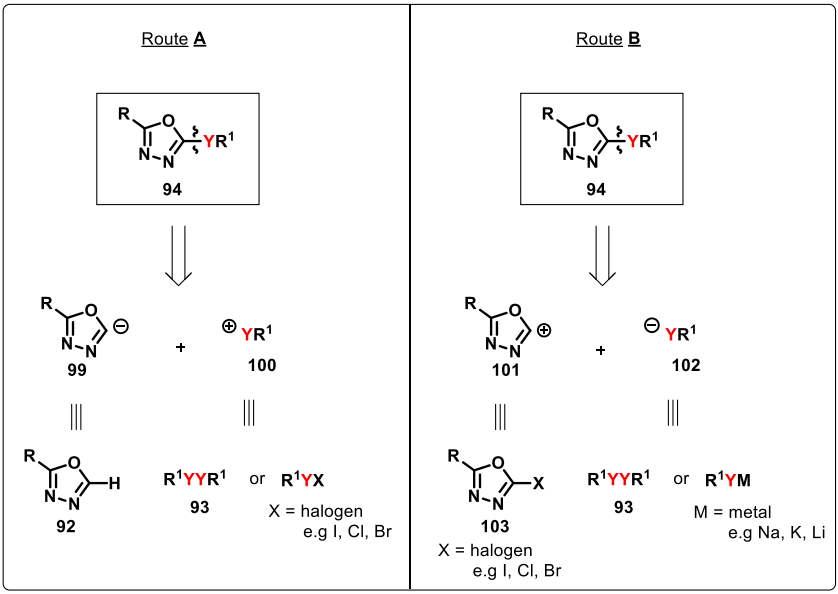
Figure 8. Selenated and thiolated 1,3,4-oxadiazoles

To the best of our knowledge there is no report regarding selenation of 1,3,4-oxadizoles. However, there are few reports for direct Thiolation of 1,3,4-oxadizoles via C_{sp2}-H bond, but they have their own peculiar disadvantages. Based on this, and according to our interest in developing new methodologies for the synthesis of compounds containing sulfur and selenium, it was decided to design a straightforward, mild, and environmentally benign protocol for the direct selenation of 1,3,4-oxadiazole, which is also applicable to disulfides, with a large structural diversity.

3.1.1. Retrosynthetic Analysis of Chalcogenated-1,3,4-Oxadiazole

Before commencement of this project first retrosynthetic analysis of the desired compound **94** was proposed aiming a direct and appropriate synthetic route (Scheme 25). As can be observed from the retrosynthetic analysis of chalcogenated oxadiazole **94**, two different rout can be

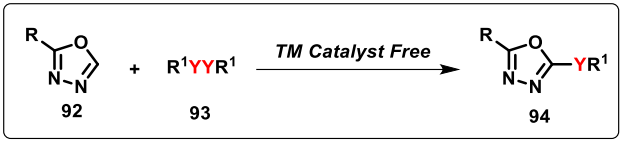
devised. In route **A** it can be seen that the oxadiazoles **92** are the synthetic equivalent to carbanion **99** "synthon", while organochalcogen specie could be introduce into the molecule by using an organochalcogen cation **100**, which are synthetic equivalent to diorganyl dichalcogenide **93** or organochalcogeno halides.



Scheme 25. Retrosynthetic analysis of chalcogenated-1,3,4-oxadiazole **94**

Similarly, in route **B** it can be seen that the halogenated oxadiazoles **103** are the synthetic equivalent to carbocation **101** "synthon", while organochalcogen specie could be introduce into the molecule by using an organochalcogen anion **102**, which are synthetic equivalent to diorganyl dichalcogenide **93** or nucleophilic organochalcogen species having metal cation. Comparing the two methods, most practical and simple route will be through first one.

In our planning, the fundamental strategy was the development of a new methodology *via* in one pot and one-step procedure (Scheme 26). The reactions were carried out with 1,3,4-oxadiazole, in the presence of base, to generate carbanion *in situ*, followed by coupling with different diorganyl dichalcogenide (aryl, heteroaryl or alkyl), in the absence of metal catalyst under open atmosphere .



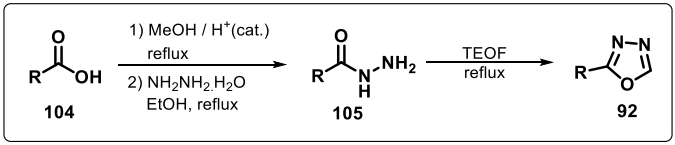
Scheme 25. Retrosynthetic analysis of chalcogenated-1,3,4-oxadiazole **94**

3.1.2. Synthesis of Starting Materials

As most of the starting materials were not commercially available, we synthesized a number of oxadiazoles **92** and diorganyl diselenides **93**.

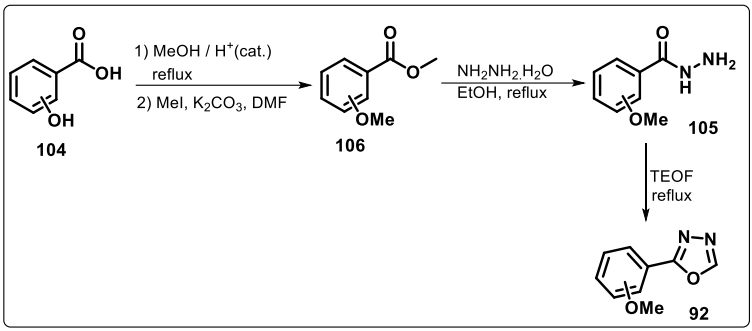
3.1.2.1. Synthesis of 2-Substituted-1,3,4-Oxadiazoles

Substituted-1,3,4-oxadiazoles were prepared from carboxylic acids **104** following standard synthetic procedure (Scheme 27).[105] Carboxylic acids **104** were esterified using methanol in the presence of catalytic amount of acid under reflux condition, which on reaction with hydrazine hydrate under reflux afforded hydrazide **105**. Hydrazide **105** was subsequently cyclized using triethyl orthoformate (TEOF), resulted corresponding substituted-1,3,4-oxadiazoles **92,** with 40-55 % overall yield .



Scheme 27. Synthetic route for accessing substituted 1,3,4-oxadiazole **92**

In case of carboxylic acids containing hydroxyl group, the esterified product was first methylated using methyl iodide, affording ester with methoxy group **106**, which was subsequently converted to hydrazide **105** and finally cyclized to oxadiazole **92** with 45-50 % overall yield (Scheme 28).[106]



Scheme 28. Synthetic route for accessing substituted 1,3,4-oxadiazole **92**

Based on synthetic procedure shown in Scheme 3 and 4, a number of 2-substituted-1,3,4-oxadiazoles **92** were prepared with a large structural diversity (Fig. 9).

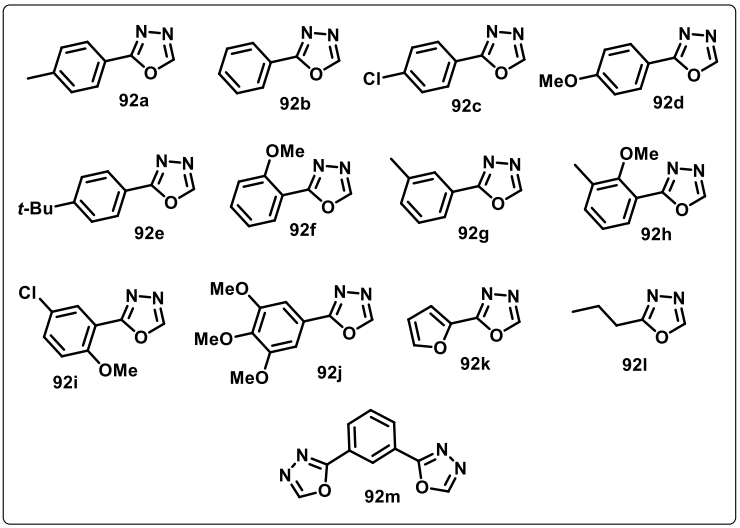
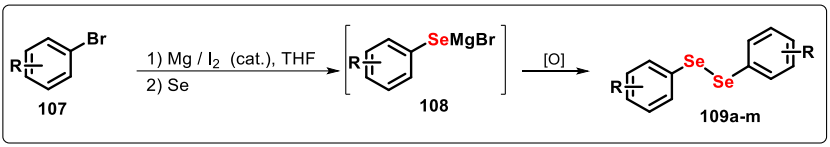


Figure 9. Synthesized library of 2-substituted-1,3,4-oxadiazoles **92**

3.1.2.2. Synthesis of Diorganyl Diselenides

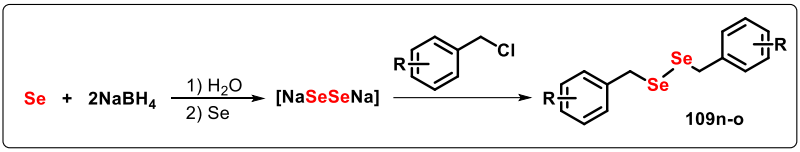
Diorganyl diselenides were through Grignard reagent starting from aryl and alkyl bromides **107**.[107] In first step Grignard reagent was regenerated *in situ* under inert atmosphere from the reaction of corresponding bromide **107**, which on subsequent reaction with elemental

selenium form intermediate **108**. Oxidation of **108** resulted respected diselenide **109**, with 40-65 % overall yield (Scheme 29).



Scheme 29. Synthetic route for accessing diorganyl diselenides **109a-m**

Dibenzyl diselenide **109n** and di-(4-Methylbenzyl) diselenide **109o** were prepared from the reaction of disodium diselenide (Na_2Se_2) and respective chloride. While Na_2Se_2 was generated in situ from the reaction of elemental selenium and sodium borohydride in water (Scheme 30).[108]



Scheme 30. Synthetic route for accessing dibenzyl diselenide **109n-o**

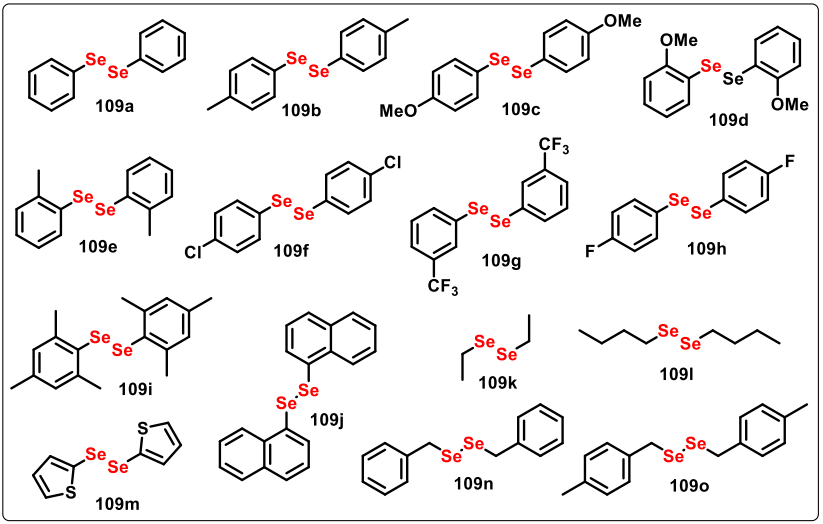


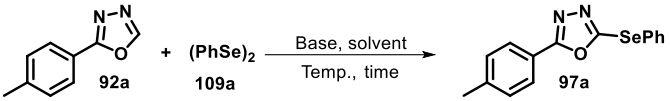
Figure 10. Synthesized library of diorganyl diselenides **109**

Based on synthetic procedure shown in Scheme 29 and 30, a number of diorganyl diselenides **109** were prepared with a large structural diversity (Figure 10).

3.1.3. Optimization of Reaction Conditions

To identify the best reaction conditions, we commenced our study by using 2-(4-tolyl)-1,3,4-oxadiazole **92a** and diphenyl diselenide **109a** as standard substrates and a diverse range of bases, temperature, solvents, reaction time and reaction stoichiometry, was screened. The results are summarized in Table 1-2. Considering the presence and type of base in a specific solvent is important for the removal of functionalized/C_{sp2}-H proton.[102] As well as keeping in mind the previously cited conditions in literature for Thiolation of heteroarenes through C-H bond functionalization using metal catalysts under inert atmosphere, our initial efforts were addressed to verify the importance of catalyst under inert atmosphere (Table 1, entry 1-3). The preliminary experiment was performed by using **92a** and **109a** in a 1 : 0.52 ratio, in the presence of K_2CO_3 (1 equiv.) as base and 20 mol % CuO-nanopowder as catalyst for 18 h at 100 °C under argon atmosphere in DMSO as solvent (Table 1, entries 1), affording the selenated oxadiazole **97a** in 56% yield. Notably, when the reaction was carried out in the absence of catalyst by keeping other conditions constant, there was not any change in the yield and product **97a** was obtained in 58 % yield (Table 1, entry 2). However, we observed some improvement in the isolated yield of **97a** when the reaction was performed in the open atmosphere, affording **97a** with 63 % yield (Entry 3). These results suggest that the use of catalyst-free and open atmosphere conditions were appropriate for the selenation of **97a**.

Table 1 Optimization of the reaction conditions for **97a**[a]



Entry	Temp. (°C)	Time (h)	Yield[b] (%)
1 [c,d]	100	18	56
2 [d]	100	18	58

3	100	18	63
4	100	12	81
5	**100**	**10**	**86**
6	100	8	82
7	100	4	55
8	150	10	30
9	120	10	59
10	80	10	71
11	RT	10	9

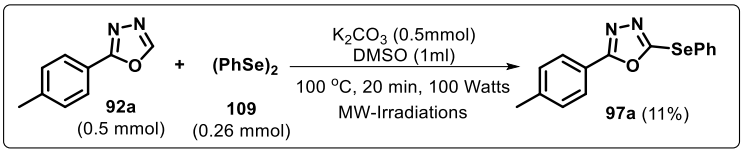
[a] Reaction conditions: **92a** (0.5 mmol), **109a** (0.26 mmol), K_2CO_3 (0.5 mmol), DMSO (1 ml) at a specific time under air. [b] Isolated yield based on **92a**. [c] CuO-nano (20 mol%). [d] Under argon atmosphere.

In the next step the reaction time and temperature were screened for this transformation (Table 1, entries 4-11). First we evaluated different duration of time In order to confirm ideal time for this transformation, in this regard a-set of experiments were carried out (Entries 4-7). Decreasing the reaction time interval from 18 h to 12 h, resulted the product **97a** with 81 % yield (Entry 4). With this improvement in the yield at 12 h, we further decrease the time and an experiment was carried out for 10 h, which resulted not only in further improvement in the yield but also greater purity of **97a**, with 86 % isolated yield (Entry 5). During reaction, the progress was monitored time to time by thin layer chromatography (TLC) and we observed that in 10 h all of the oxadiazole **92a** was totally consumed. When the reaction time was further decreased, the desired product was obtained with less yield (Entry 6 and 7 *vs* 5). It was noticed through TLC that oxadiazole **92a** was not fully consumed during these reactions.

Furthermore, we noticed that temperature had a very strong influential on the reaction. Drastic result was obtained when temperature was increased to 150 or 120 ^{o}C, which sharply decrease **97a** to 36 and 59

%, respectively (Entries 7, 8). During these experiments, decomposition of the oxadiazole was been observed (through TLC), which might be the reason of low yield. Decreasing the temperature below 100 °C, also afforded the oxadiazole **97a** in low yields as compare to 100 °C (Entry 9 and 10 *vs* 5). TLC analysis showed the presence of unreacted oxadiazole **109a**, which signify the necessity of the higher temperature. In order to confirm the importance of temperature, a reaction was performed at room temperature and as predicted, **97a** was purified in very poor yield (Table 1, entry 9), while unreacted starting materials were completely recovered through column chromatography (CC).

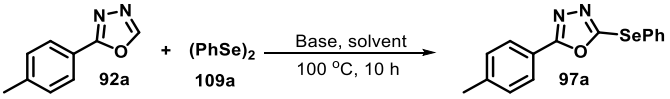
We also tried Microwave-irradiation technique as an alternate source of energy. As microwave assisted synthesis is considered to be quick and can be performed in shorter time, we performed an experiment under microwave irradiation at 100 watt (power), 100 °C for 20 minutes while keeping other parameters of the reaction constant, but **97a** was obtained in very low yield (Scheme 31).



Scheme 31. Proposed route for accessing chalcogenated 1,3,4-oxadiazole **97a**

With previous observations by different groups, that in few cases use of excess of dichalcogenides increases the yield of desired product during the cross coupling reaction of dichalcogenides.[89,102]

Table 2 Optimization of base and solvent for **97a**[a]



Entry	Base	Solvent	Yield[b] (%)
1	K_2CO_3	**DMSO**	**86**
2 [c]	K_2CO_3	DMSO	85

3	K_2CO_3	DMSO-dry	84
4	K_2CO_3	DMF	67
5	K_2CO_3	H2O	-
6	K_2CO_3	THF	-
7	K_2CO_3	EtOH	-
8	K_2CO_3	Toluene	11
9	K_2CO_3	Acetonitrile	12
10	K_2CO_3	1,4-dioxane	-
11	K_2CO_3	DMC	-
12	K_2CO_3	NMP	-
13	K_2CO_3	Et_3N	-
14	K_2CO_3	Pyridine	-
15	--	DMSO	-
16	Na_2CO_3	DMSO	59
17	Cs_2CO_3	DMSO	32
18	*t*-BuOK	DMSO	-
19	Et3N	DMSO	-
20	K_3PO_4	DMSO	21
21	KOH	DMSO	13
22	$NaHCO_3$	DMSO	39

23 [d]	K_2CO_3	DMSO	82
24 [e]	K_2CO_3	DMSO	61
25 [f]	K_2CO_3	DMSO	41

[a] Reaction conditions: 2-(4-tolyl)-1,3,4-oxadiazole **7a** (0.5 mmol), diphenyl diselenide **8a** (0.26 mmol), base (0.5 mmol), solvent (1 ml) at a specific time under air. [b] Isolated yield based on **1a**. [c] **2a** (0.5 mmol). [d] K_2CO_3 (2 equiv.). [e] K_2CO_3 (0.5 equiv.). [f] K_2CO_3 (30 mol%).

It is noteworthy, that increasing stoichiometric amount of **109a** to 0.5mmol (1 equiv.) didn't show any influence on the isolated yield of 4a (Table 2, entry 2 *vs* 1), while the unreacted diselenide was recovered easily through CC. This was very important finding because during the course of reaction we did not observer any formation of PhSePh, which is a common by-product, and during optimization. In our case, during optimization 0.26mmol of diselenide **109a** was enough for complete consumption of oxadiazole **92a**.

It is well known that solvents play a crucial role in cross-coupling reactions; hence, in order to evaluate the influence of solvents in this coupling reaction, we tested different solvents (Table 2, entry 3-14). Screening of different solvents revealed that DMSO was the best solvent for selenation of oxadiazole **92a** (Entry 1 *vs* 3-14). Dry DMSO did not alter the yield of product and when freshly distilled DMF was used the **97a** was obtained in 84 % yield (Entry 3). DMF was less effective, resulting **97a** in 67 % yield (Entry 4). No product was observed when water, THF, EtOH, 1,4-dioxane, dimethyl carbonate (DMC), NMP, triethyl amine and pyridine were used (Entries 5-7, 10-14). These solvents seem to be stagnant to this reaction, while **97a** was been isolated with 11% and 12% yields when the experiments were performed in toluene or acetonitrile, respectively (Table 2, entries 8 and 9).

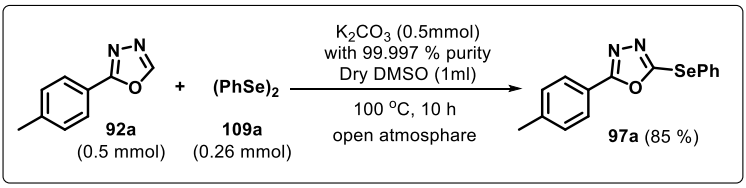
Subsequently, the influence of base on the selenation of oxadiazole **92a** was then evaluated, and the results are reported in Table 2, entries 15–25. Initially, we performed an experiment without the involvement of base (K_2CO_3), entry 15. In this experiment after 10h, desired product was not formed, which shows the importance of presence of base for this coupling reaction. Further studies showed that when this reaction was performed in the presence of organic bases e.g. *t*-BuOK and triethyl amine, the formation of product **97a** was not observed (Entries 18,19),

while the use of other carbonates e.g. Na_2CO_3 and Cs_2CO_3 (Entries 16, 17) and $NaHCO_3$ (Entry 22) were less effective. KOH and K_3PO_4 were also not good bases, affording **97a** in poor yield (Entries 20, 21).

Lastly, we evaluated the stoichiometry of K_2CO_3. Increasing the stoichiometric amount of K_2CO_3 to 2 equiv. showed some inverse effect and slight decrease in yield of **97a** was observed (Table 2, entry 23). Similarly, when less amount of base was used e.g. 0.5 equiv. and 30 mol %, the yield of **97a** was constantly decreasing (Entries 24, 25). During these experiments, TLC analysis revealed that starting materials were not fully consumed.

3.1.4. Trace Metal Contamination

In recent few years many reports are been published regarding the involvement of trace metal contamination in regents, solvent, and even unclean glassware. Many reactions which were previously considered to perform under catalyst free conditions, were actually having involvement of trace metal contamination.[109] In order to eliminate any possible catalytic effect due trace metal impurities in K_2CO_3, DMSO or glassware, a control experiment was carried out by using K_2CO_3 with a purity of 99.997% from sigma, DMSO was distilled freshly and new glassware and magnetic bar were used (Scheme 32). Notably, **97a** was obtained in 85 % yield which excludes any possibility of catalytic effect due trace metal contamination.



Scheme 32. Control Reaction, to eliminate trace metal contamination

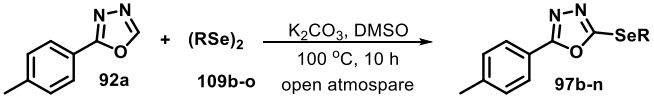
3.1.5. The Reaction Scope

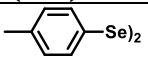
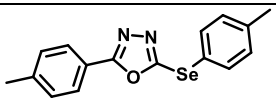
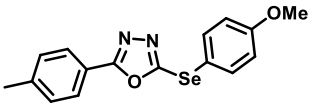
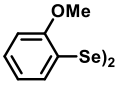
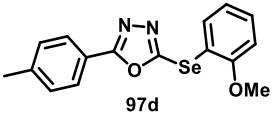
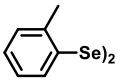
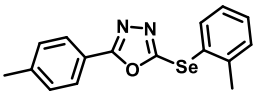
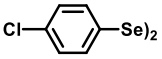
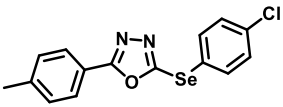
Based on the results of optimization, as shown in Table 1-2, we concluded the best reaction conditions for the selenation of oxadiazole **92a**, were the use of oxadiazole **92** (0.5 mmol), diorganyl diselenide **109** (0.26 mmol), K_2CO_3 (1.0 equiv.) with stirring in DMSO (1 mL) at 100 °C for 10 h under an open atmosphere without the need of any catalyst. The reaction was repeated several times under same condition in order to

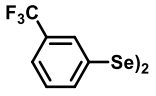
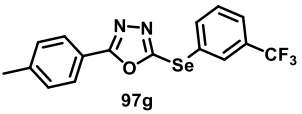
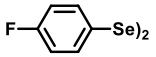
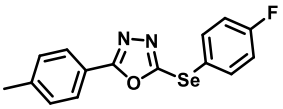
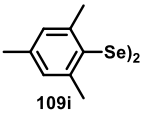
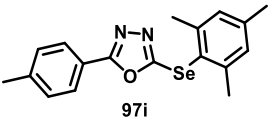
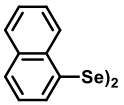
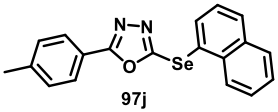
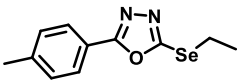
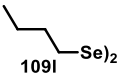
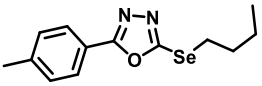
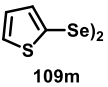
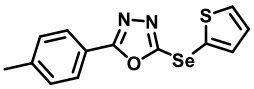
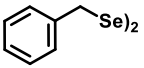
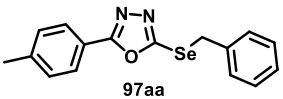
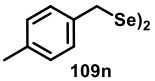
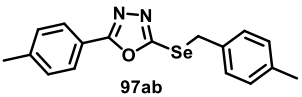
confirm the reproducibility. After confirming the reproducibility of the reaction, we explored the efficiency and generality of our methodology to various oxadiazole **92** diselenides **109** (with different functional groups) under optimized condition. The results are summarized in Table 3-4.

First, influence of several diorganyl diselenides **109** was checked in order to verify the efficiency of optimized protocol. A variety of diorganyl diselenides **109** with different electronic effects, were reacted with 2-(4-tolyl)-1,3,4-oxdiazole **92a** in order to synthesize various 2-(4-tolyl)-5-organoseleno-1,3,4-oxdiazoles **97b-n** and **97aa-ab** (Table 3, entries 1–14). The reaction works well with a range of diorganyl diselenides **109** containing both electron-donating (–Me and –OMe) and electron-withdrawing groups (CF_3, F and Cl) as well as bulky and aliphatic groups, showing up the sensitivity and tolerance to electronic effects and steric effects to several different substituents.

Table 3 Selenation of 2-(4-tolyl)-1,3,4-oxadiazole **92a** [a]



Entry	$(RSe)_2$ 109	Product 97	Yield[b] (%)
1	 109b	 97b	88
2	 109c	 97c	96
3	 109d	 97d	88
4	 109e	 97e	84
5	 109f	 97f	82

6	 109g	 97g	70
7	 109h	 97h	65
8	 109i	 97i	92
9	 109j	 97j	63
10	 109k	 97k	81
11	 109l	 97l	80
12	 109m	 97m	79
13	 109n	 97aa	39*
14	 109n	 97ab	45*

[a] Reaction conditions: 2-(4-tolyl)-1,3,4-oxadiazole **92a** (0.5 mmol), diorganyl diselenide **109** (0.26 mmol), K_2CO_3 (0.5 mmol), DMSO (1 ml) at a 100 °C for 10 h, under air. [b] Isolated yield based on **97a**.

Generally speaking, it was noticed that electron-donating groups afforded the selenated product **97** in good results, for example, when -Me and -OMe, are present on the aromatic ring of the diselenide **109** (Table

3, entry 1-4). By comparing methyl and methoxy group it can be noticed that the yield of **97** improve when electron-donating group was getting stronger effect at *para*-position, such as *p*-MeO substituted diselenide **109c** afforded the desired product in 96 % yield while **p**-Me substituted diselenide **109b** afforded the **97b** in 88 % (Table 3, entry 2 *vs*. 1). We found that the electron-withdrawing groups had showed some adverse effect and decrease in the yield of the corresponding product was noticed (Entries 5-7). For instance, when diselenide containing electron-withdrawing groups attached at the *para*-position on phenyl ring, such as *p*-chloro **109f** and *p*-fluoro **109h**, the corresponding products were obtained in low yields with 82 % and 60 %, respectively (Entries 5, 7). A similar behavior was also noticed for *meta*-substituted CF_3 **109g**, an electron-withdrawing (Entry 6).

It is well known that steric hindrance of *ortho*-substituted aryl substrates could gave lower yields as compare to *para*-substituted, herein, under optimized conditions a weaker influence on the yields of selenated product **97** were observed i.e. hindered substituent *o*-Me and *o*-MeO substituted diorganyl diselenide (Table3, entry 3 and 4 *vs*. 2 and 1, respectively). Interesting, not only complete tolerance but improved result was observed from sterically hindered dimesityl diselenide **109i**, giving the desired product **97i** in 91% (Table 3, Entry 8). Bulky and hindered substrate, i.e. bis(2-naphthyl)diselenide **109j**, afforded the desired product **97j** with 60 % yield.

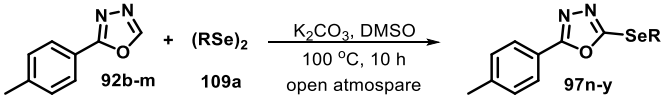
Next, we tried different dialkyl diselenide for this coupling reaction because aliphatic selenides are important synthetic intermediates and can be use selenium−lithium exchange reaction and trapping Lithium Intermediate with different electrophiles. It is well recognized that diaryl diselenides are more reactive than aliphatic ones and are much more easily cleaved. Also alkyl group directly bonded to selenium atom could undergo *β*-selenoxide elimination, during the purification or work-up process, giving the desired product without the selenium group incorporated in the structure. Therefore, aliphatic diselenide afford desire products in low yield.

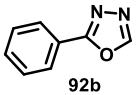
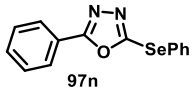
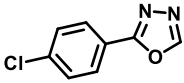
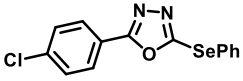
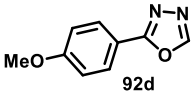
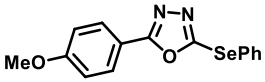
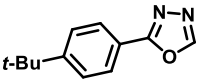
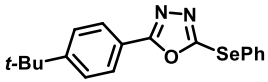
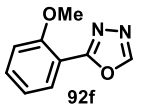
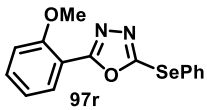
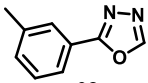
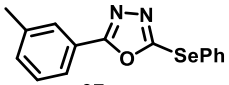
Gratifyingly, by applying our methodology to aliphatic diselenides **109k** and **109l**, with ethyl and *n*-butyl group directly bonded to the selenium atom. These reaction produced the corresponding coupling products **97k** and **97l** in 79% and 78% yields, respectively (Table 3, entries 10 and 11), showing the significance of this methodology. We further extended our protocol on benzylic diselenides **109n-o**, resulting the selenated oxadiazoles **97aa** and **97ab** with 39 % and 45 % isolated yield, respectively (Entries 13,14). The only problem we faced in the

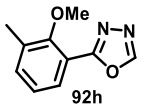
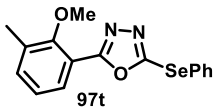
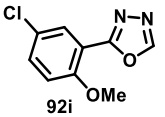
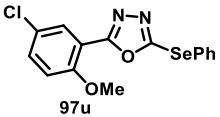
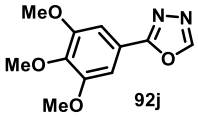
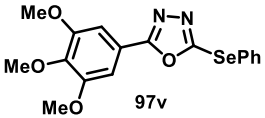
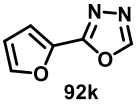
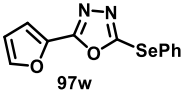
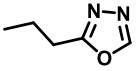
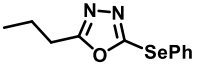
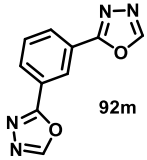
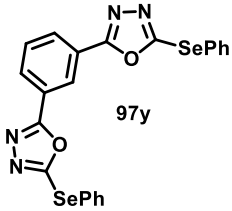
synthesis of **97aa** and **97ab**, was stability because these products were not stable enough for characterization. To appraise the versatility of the methodology, heteroaromatic diselenide **109m** was also tested and the desired product **97m** was obtained in good yield (Table 3, entry 12).

Continuing to investigate the reaction scope, we extended our approach to other 2-substituted-1,3,4-oxadiazoles **92b-m** and to our gratification, good to excellent results were obtained from the combination of a range of structurally diverse oxadiazoles, including aliphatic and heteroaromatic substituents on oxadiazole, with diphenyl diselenide. These results indicated that substituted groups at C-2 on 1,3,4-oxadiazole **92** perfectly tolerated the optimized reaction condition. The results are summarized in Table 4

Table 4 Selenation of 2-(substituted)-1,3,4-oxadiazoles **92** with **109a** [a]



Entry	$(RSe)_2$ 109	Product 97	Yield[b] (%)
1	 92b	 97n	84
2	 92c	 97o	79
3	 92d	 97p	95
4	 92e	 97q	96
5	 92f	 97r	83
6	 92g	 97s	85

7	 92h	 97t	88
8	 92i	 97u	89
9	 92j	 97v	92
10	 92k	 97w	82
11	 92l	 97x	84
12	 92m	 97y	61

[a] Reaction conditions: 2-(substituted)-1,3,4-oxadiazoles **92** (0.5 mmol), diphenyl diselenide **109a** (0.26 mmol), K_2CO_3 (0.5 mmol), DMSO (1 ml) at a 100 °C for 10 h, under air. [b] Isolated yield based on **97**. [c] **92m** (0.25 mmol)

Generally, there was no prominent electronic effect of the substituents on isolated yield. Unsubstituted phenyl ring gave the corresponding product in good yield with 84 % yield (Table 4, entry 1). There was slight decrease in the yield was observed when electron withdrawing group at *para*-position (i.e. *p*-Cl phenyl-1,3,4-oxadiazole **92c**) was used, resulting the corresponding product in good yield with 79 % yield (Entry 2). In contrary, electron-donating group (e.g. OMe, *t*-Bu, Me) at various position on phenyl ring gave desired product with good results (Entries 3-6). Normally, electron donating groups at *para*-position

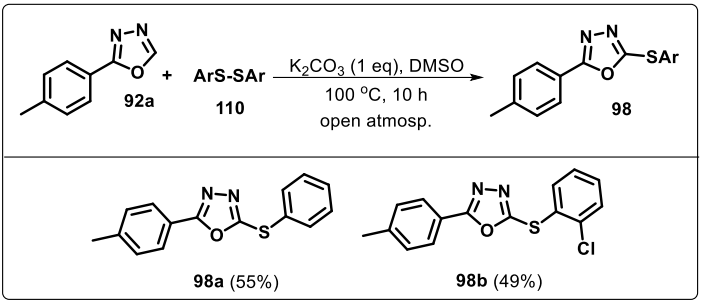
i.e. OMe **92d** and *t*-butyl **92e** seems to be ideal and afforded the final product with excellent yields (Entries 3, 4).

Phenyl ring on oxadiazole with multiple substitutes **92h** and **92i** with, a combination of similar and opposite electronic effects, gave the final product with 89 % and 84 % yields (Entries 7, 8). Similarly, 3,4,5-trimthoxy phenyl substituted oxadiazole **92j** resulted corresponding oxadiazole **97w** in 92 % yield (Entry 9). These experiments confirm that the electronic properties of substituents and their position in the phenyl ring exerted a very limited influence on the reactivity and coupled product was obtained with up to 79-96 % yields.

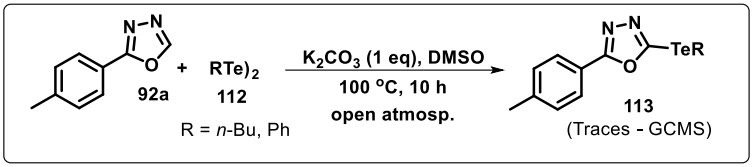
Furthermore, the optimal reaction conditions were extended to structurally diverse 1,3,4-oxadiazoles with aliphatic and heteroaromatic substitutes, in order to ascertain the scope of the methodology. Interestingly, 2'-furyl **92k** and *n*-propyl **92l** reacted smoothly rendering the selenated oxadiazole **97w** and **97x** with 82 % and 84 yields (Entries 10-11). Finally, to explore further the versatility of this methodology on different oxadiazole, an experiment was carried out by utilizing 0.25 mmol of 1,3-di(1,3,4-oxadiazol-2-yl)benzene **92m**. To our delight, the desired product, **97y** was obtained in 61 % (Table 4, entry 12). This kind of symmetric nucleus can be an excellent candidate for material sciences and could be use in preparation of new series of liquid crystals.

With the successful results in the synthesis of selenated oxadiazoles **97a-y** by intermolecular C-Se bond formations, applying diorganyl diselenides **109a-o** as selenium source, prompted us to extend this methodology under optimal reaction conditions to diaryl disulfides **110** as an access to organylthio-oxadiazoles **98**, in order to ascertain the scope of the methodology Interestingly, the reaction of different disulfides **110** with 2-C(4-tolyl)-1,3,4-oxadizoles **92a** proceeded smoothly to afford the corresponding thiolated oxadiazoles **98a** and **98b** in 55 % and 49 % yield (Scheme 33). The stronger S–S bond of diaryl disulfides as compare to respective diaryl diselenides may explain the decreases in the yield values.

The good results from the reaction of oxadiazole selenation (Table 3 and 4) and Thiolation (Scheme 8) encouraged us to further expand the scope of the reaction to diorganyl ditelluride (Scheme 34). However, trace amount of desired product **113** was formed under the optimal reaction conditions (used for the preparation of selenated and thiolated oxadiazoles), even when the reaction was allowed for shorter and longer reaction times. This behavior was expected, since organotellurides are less stable as compared to other corresponding organochalcogen compounds.[110]



Scheme 33. Thiolation of 2-(4-tolyl)-1,3,4-oxadiazole **92a** with diaryl disulfides **110**



Scheme 34. Telluration of 2-(4-tolyl)-1,3,4-oxadiazole **92a** with diorganyl ditelluride **112**

3.1.6. Reaction on Large Scale

One of major drawback of few methods of synthesis in organic chemistry is that generally synthetic reaction works well on small scale but on larger scale the reaction don't affords the desired product in expected yields. This is an important factor, which restrict the applicability many methods in industry. Therefore, in order to demonstrate the synthetic utility of this new protocol, a series of reactions was carried out on different scales by increasing incrementally the scale up to 10 mmol. For this purpose 2-(4-tolyl)-1,3,4-oxadiazole **92a** and diphenyl diselenide **109a** were selected as the test starting materials (Figure 11). There was no drastic effect by increasing scale of the reaction from 0.5 mmol (on bases on **92a**) to 2.5 mmol and selenated oxadiazole **97a** was isolated with 84 % yield, similarly the yield remain constant at 5 mmol scale. On further increasing the scale of reaction to 10 mmol, there was no major effect and desired product **97a** was obtained with 82% yield

Based on the experiments on different scale, as shown in Fig 5, we can say that this method could be used as a practical method to synthesize biologically relevant lead compounds.

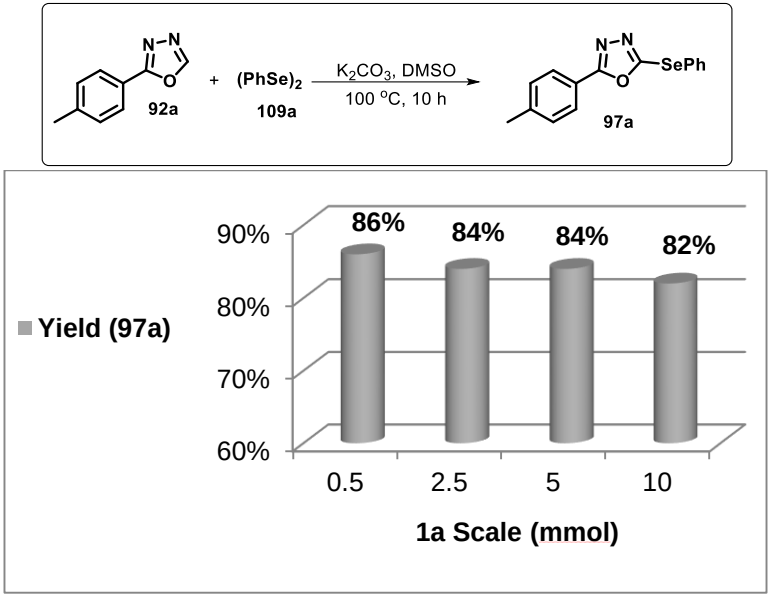
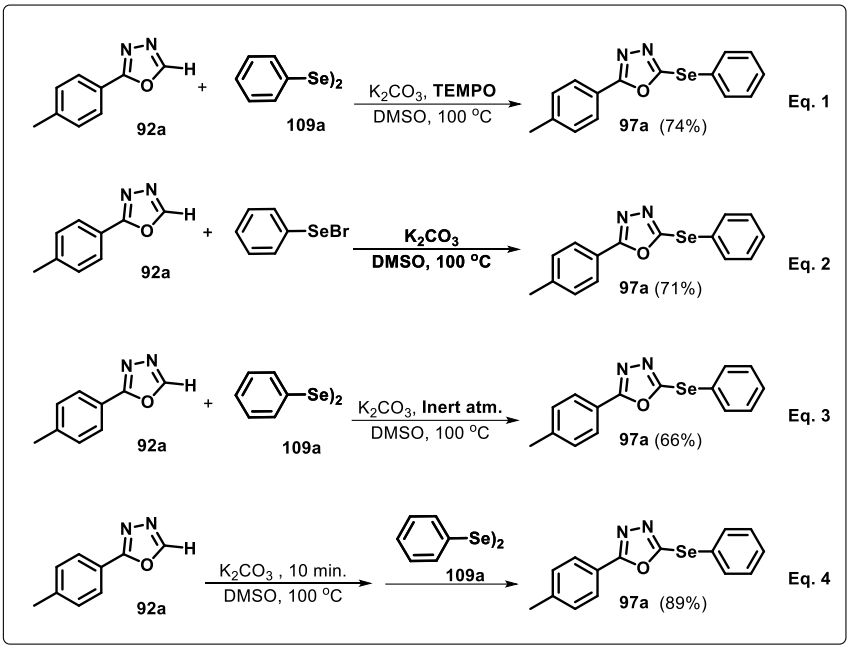


Figure 11. Results for the reaction at different scales

3.1.7. Investigation of the mechanism and Proposed Mechanism

Considering that little is known about the reaction of diorganyl diselenides under metal free condition for C_{sp2}-H bond functionalization, it was proposed to run some experiments and taking help from literature in order to develop a proposed mechanism for this transformation (Scheme 35).

Firstly, we evaluated the hypothesis of any possible radical mechanism for this coupling reaction using 2-(4-tolyl)-1,3,4-oxadiazole **92a** and diphenyl diselenide **109a** in the presence of radical inhibitor (TEMPO) under standard conditions. Use of TEMPO did not hamper the reaction and the **97a** was obtained in 74% yield (Scheme 10, Eq. 1). This result indicates that a free radical mechanism, which could involve the PhSe radical species, is unlikely.



Scheme 35. Investigation of the mechanism for chalcogenation of **92**

In the secondly step, we used oxadiazole **92a** and electrophilic selenium specie i.e. PhSeBr (1 equiv.) under optimized reaction conditions. However, selenated product **97a** was isolated with 71 % yield (Scheme 35, Eq. 2), signifying the involvement of selenium as an electrophilic entity. In the third test, we performed a test reaction under inert atmosphere keeping other parameters of the optimized condition without any alteration (Scheme 35, Eq. 3). However, we observe the decrease in the yield of **97a** and was purified wit 66 % yield. This analysis indicates the importance of oxidation due to the atmospheric oxygen, which probably regenerates of diphenyl diselenide **109a**. Lastly, in order the appoint a proper sequence of reaction, we first added K_2CO_3 (base) in the solution of oxadiazole **92a** in DMSO and left the reaction for stirring for 10 minutes under the standard condition, followed by the addition of diphenyl diselenide **109a.** Interesting there was slight improvement in isolated yield of **97a** i.e. 89% (Scheme 35, Eq. 4). These experiments suggest that deprotonation of the oxadiazole core is an important step during the reaction.

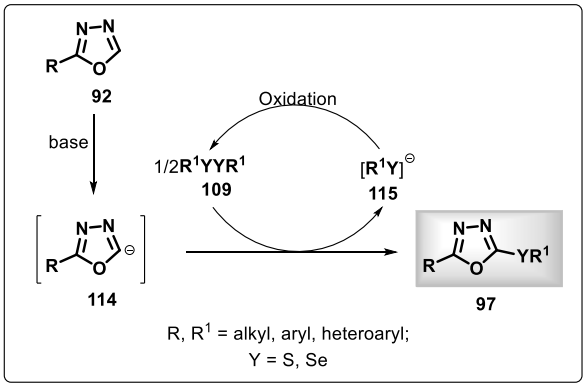
Based on the experiments described above and in the literature data, the following ionic mechanism was proposed for this coupling reaction (Scheme 36).

Step 1: Deprotonation of oxadiazole core **7** at C5 position took place in the presence of base, generating nucleophilic oxadiazole specie **114** with carbanion at C5 position.

Step 2: Nucleophilic attack of intermediate **114** on diorganyl dichalcogenide **109** took place, resulting in chalcogenation of oxadiazole at C5 and forming anionic specie of organochalcogenide **115**.

Step 3: In the final step, anionic chalcogenide intermediate **115** undergoes oxidation in the presence of environmental oxygen and regenerating dichalcogenide **109**, which enter in new cycle.

Interestingly, due to the regeneration of dichalcogenide **109**, only half equiv. dichalcogenide was required for complete consumption of oxadiazole **92**. Another important thing that due to low temperature and short reaction time, we didn't observe the thermal decomposition of selenolate species which occur due to carbon-selenium bond homolysis with the formation of PhSePh.[111] On these grounds we could justify the use of less amount of diorganyl dichalcogenides **109**.

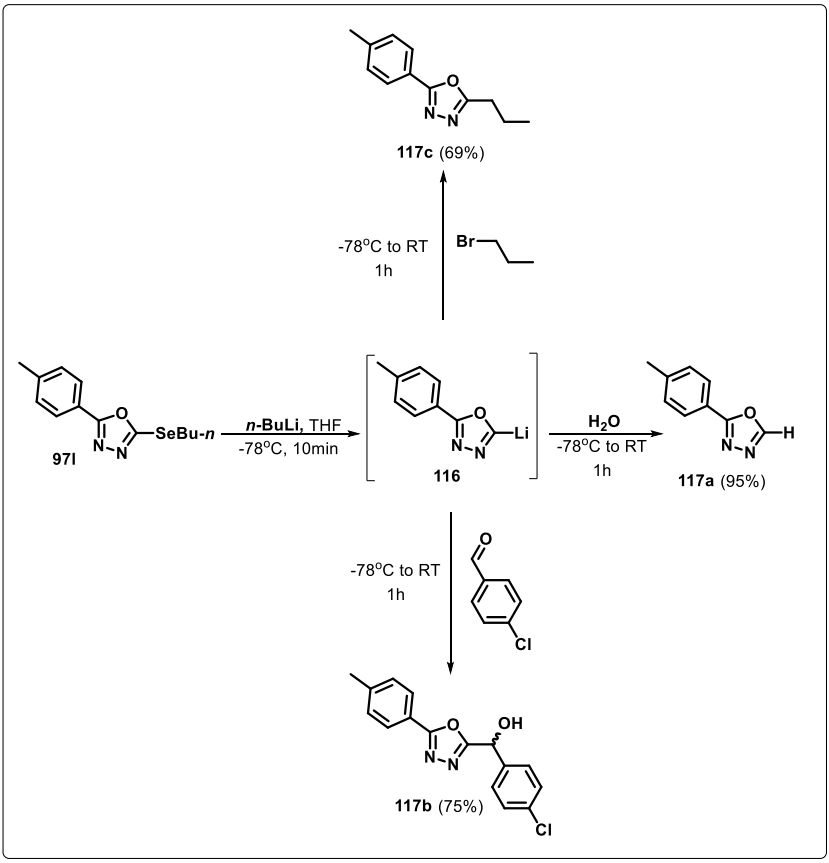


Scheme 36. Proposed mechanism for the chalcogenation of oxadiazole **92**

3.1.8. Selenium−Lithium Exchange Reaction & Trapping of Lithium-Intermediate

The chalcogen−lithium exchange consists of a useful synthetic tool since the corresponding organolithium species[112] are able to react with a number of different electrophiles providing grossly functionalized

organic molecules.[113] Furthermore, as RSe group is a good precursor for the selenium−lithium exchange reaction, we have carried out this reaction employing the selenated oxadiazole **97l** with *n*-butyllithium.



Scheme 37. Transmetallation of **97l** with different electrophiles.

In the first experiment, the generation of the organolithium intermediate **116** from selenide **97l** was attempted by the addition of *n*-BuLi (1.1 equiv.) to a solution of 2-tolyl-5-(*n*-butylselenyl)-1,3,4-oxadiazoe **97l** (0.25mmol) in THF (3 mL) at −78 °C. The resulting solution was stirred for 15 min at this temperature and quenched in water. Under these conditions, the corresponding 5-hydrogenated product **117a** was isolated in 95 % yield (Scheme 37). After this result, we extended this method by trapping the corresponding lithium intermediate **116** with

aldehyde and *n*-propyl bromide as electrophilic sources, affording the desired product with **117b** and **117c** with 75 % and 69 % yield (Scheme 37).

Through this method, the synthesized 2-(4-tolyl)-5-(*n*-butyl)selenyl-1,3,4-oxadizoles **97l** proved to be convenient precursors for the preparation of oxadiazole derivatives bearing different functional groups, furnishing the target compounds in good to excellent yields (Scheme 37). The C-Se bond on oxadiazole was converted to C-H and C-C bond through one pot protocol.

3.1.9. Characterization

The proposed structures of all synthesized 2-substututed-5-organochalcogeno-1,3,4-oxadiazoles **97-98** were confirmed by nuclear magnetic resonance (NMR) spectroscopy and high resolution mass spectrometry (HRMS) and by other relevant techniques. In the following we will discuss the assignment of different signals from Hydrogen, Carbon-13 and Selenium-77 NMR spectra of 2-(4-tolyl)-5-(phenylselanyl)-1,3,4-oxadiazole **97a**, as a representative compound. The spectra were obtained in $CDCl_3$.

In the ^1H NMR spectrum (Figure 12), there is a singlet at 2.38 ppm with integral value of 3, referring to the hydrogen of methyl group attached directly to the aromatic ring on oxadiazole.

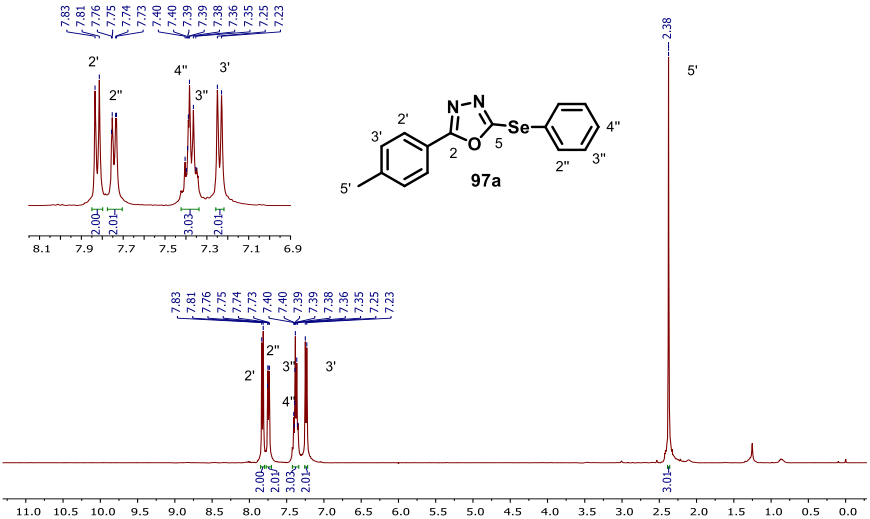


Figure 12. ^1H NMR (400 MHz, $CDCl_3$) spectrum of **97a**

At 7.24 ppm, a doublet with integral value of 2 and with coupling constant J = 8.2 Hz, which can be attributed to two aromatic hydrogen bounded C-3' of the oxadiazole. Next a multiple at 7.42 – 7.34 ppm can be observer with integral value 3, referring to the aromatic hydrogens on C-3" and C-4" of phenyl ring attached with selenium. On extreme left hand side, there is a doublet at 7.82 ppm with integration value 2 and coupling constant J = 8.2 Hz, referring the 2 hydrogen at C-2' position on phenyl ring attached with oxadiazole.

In the ^{13}C NMR spectrum (Fig. 13), all carbons for 3a can be seem clearly; a total 11 signals are expected. A signal at 21.66 pm chemical shift (δ) is for C-5' for -Me group, while rest of signals are for aromatic carbon. There are two peaks for quaternary carbon at 120.69 ppm and 124.36 ppm representing C-1,' and C-1', respectively. A signal at 126.l5 ppm is for two carbons at C-3', another peak for methylene carbon at 129.56 ppm for C-4", three peaks for 3 set of six chemically equivalent carbons at 129.71 ppm, 129.82 ppm and 134.94 ppm for C-2', C-2" and C-3", respectively. On extreme left, three most deshielded quaternary carbons at 142.41 ppm, 155.74 ppm and 167.33 ppm, representing C-4', C-5 and C-2, respectively.

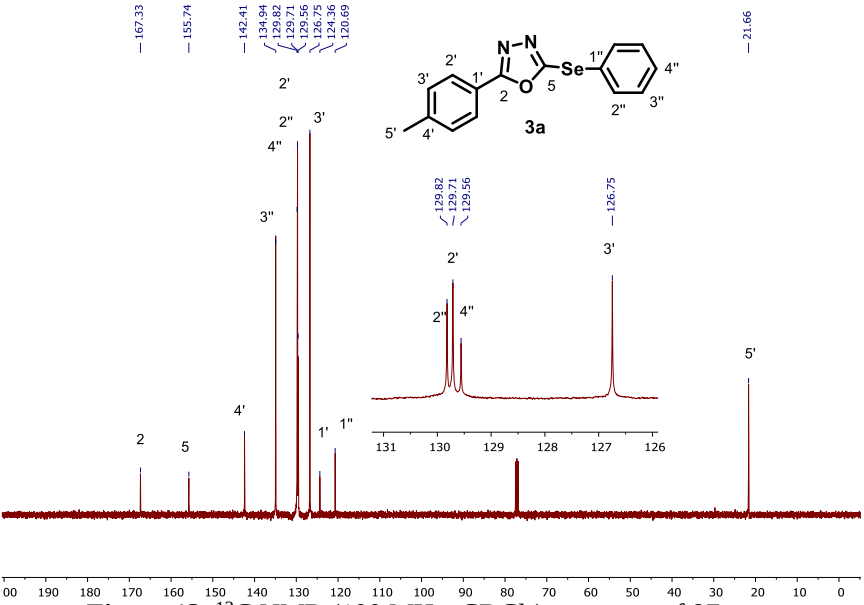


Figure 13. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **97a**

For this particular case we also performed ^{77}Se-NMR and the experiment was carried out in presence of $PhSe)_2$ as an external standard (Fig. 14). Chemical shift from selenium of $PhSe)_2$ can be seen at 463.33 ppm and while selenium from selenated product **97a** can be observe at 365.34 ppm.

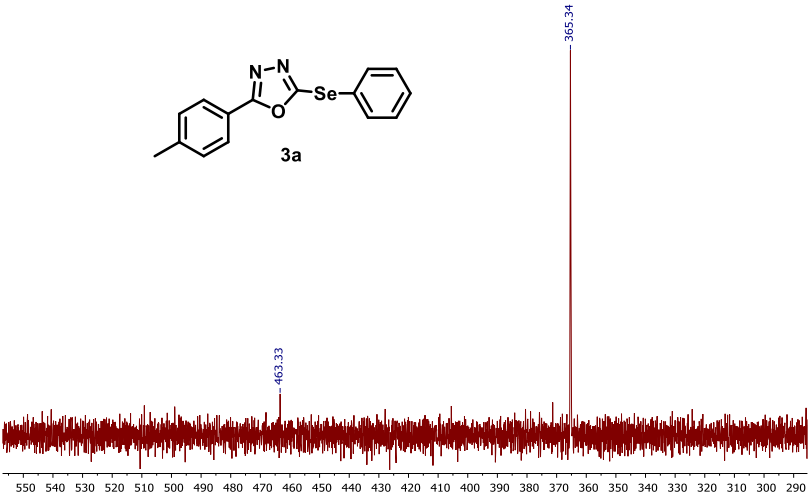


Figure 14. ^{77}Se NMR (38.14 MHz, $CDCl_3$) spectrum of **97a**

All compounds are new and are not reported before in literature, we performed high-resolution mass spectrometry (HRMS) using electrospray ionization (ESI) or atmospheric pressure photoionization (APPI) technique for ionization. Compound **3a** was been analyzed by APPI-HRMS technique (Fig. 15). The molecular ion of the compound **3a** was obtained by adding a proton to the molecular weight i.e. $[M+H]^+$, and experimental value for $C_{15}H_{13}N_2OSe$ $[M + H]^+$ found was to be 317.0187, and the calculated theoretical value for $[M+H]^+$ was 317.0188. In addition, the isotopic abundance of simulated and experimental spectrum matches with each other.

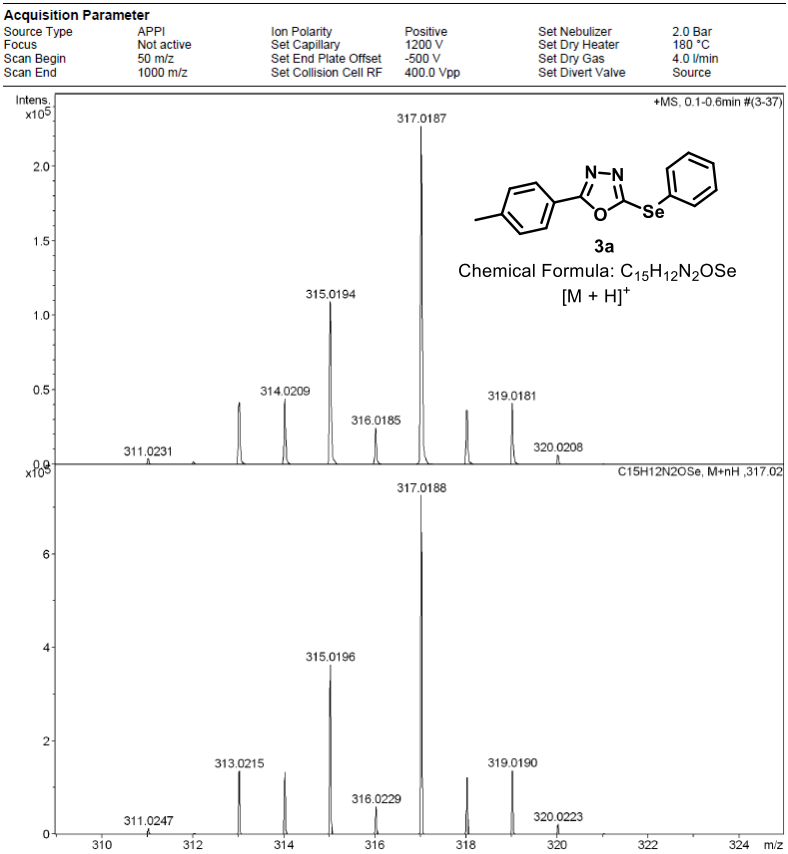
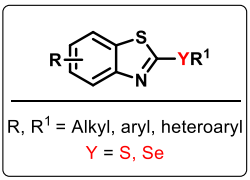


Figure 15. Spectrum of high resolution mass of the compound **97a**, using APPI



Chapter 3: Part B
Results and Discussions

3.2. Synthesis of 2-organochalcogeno-1,3-benzothiazole catalyzed by Fe_3O_4-nanoparticles

After successful studies on chalcogenation of oxadiazoles we extended our studies on 1,3-benzothiazole as another class of heterocyclic compounds. Previously we discussed about the importance organocalcogenides and heterocyclic compounds as well as synthesis and/or functionalization of heterocycles in section 2.1. Functionalization of 1,3-benzothiazole *via* direct C-H bond with different organic moieties has also emerged an important and simple method for the synthesis of wide range of substituted benzothiazoles.

The goal of the current work is mainly focused on the development of sustainable methodologies for the synthesis of 1,3-benzothiazole containing organoselenium **118** and organosulfur **119** moieties (Fig. 16), which could have potential applications in biological and/or in material sciences.

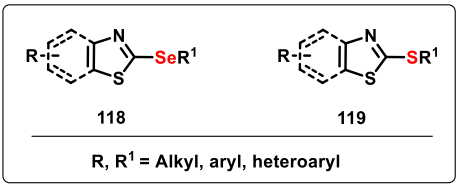


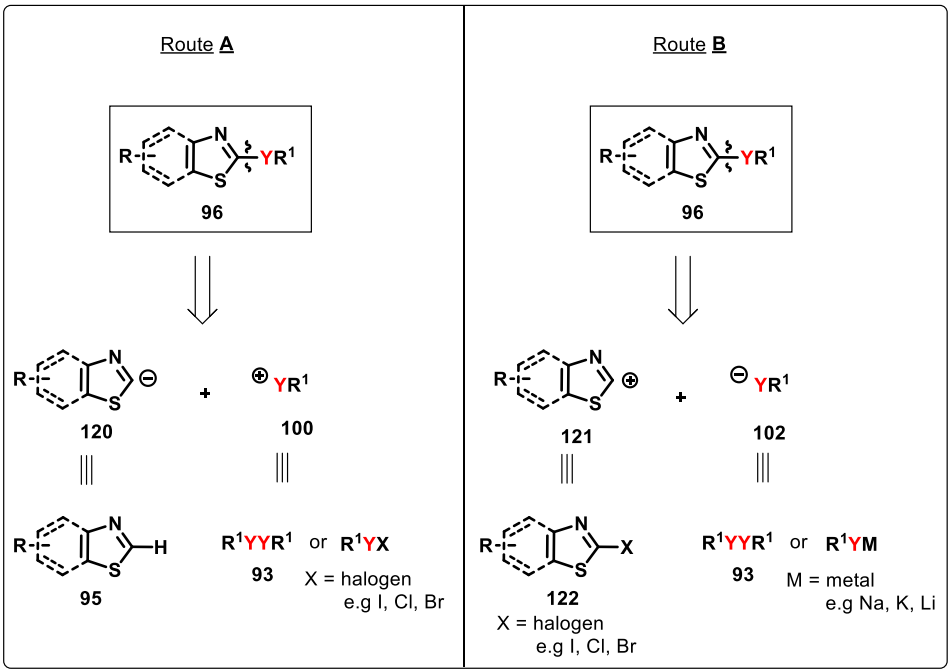
Figure 16. Selenated and thiolated 1,3-benzothiazole

So far there is only one report regarding selenation of 1,3-benzothiazole,[89] while there are few methods for direct thiolation via C_{sp2}-H bond, but they have their own peculiar disadvantages. Based on this, and according to our interest in developing new methodologies for the synthesis of compounds containing sulfur and selenium, it was decided to design a straightforward, mild, and environmentally benign protocol for the direct chalcogenation of 1,3-benzothiazole, with a large structural diversity.

3.2.1. Retrosynthetic Analysis of Chalcogenated-1,3-benzothiazole

Before commencement of this project first retrosynthetic analysis of the desired compound **96** was proposed aiming a direct and appropriate synthetic route (Scheme 38). As can be observed from the retrosynthetic analysis of chalcogenated-1,3-benzothiazole **96**, two different rout can be devised. In route **A** it can be seen that the benzothiazole **95** are the synthetic equivalent to carbanion **120** "synthon", while organochalcogen

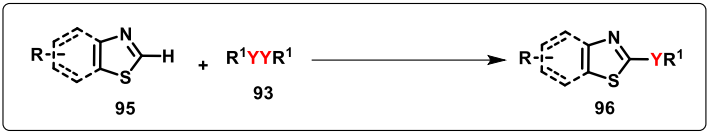
specie could be introduce into the molecule by using an organochalcogen cation **100**, which are synthetic equivalent to diorganyl dichalcogenide **93** or organochalcogeno halides.



Scheme 38. Retrosynthetic analysis of chalcogenated-1,3-benzothiazole

Similarly, in route **B** it can be seen that the halogenated benzothiazole **122** are the synthetic equivalent to carbocation **121** "synthon", while organochalcogen specie could be introduce into the molecule by using an organochalcogen anion **102**, which are synthetic equivalent to diorganyl dichalcogenide **93** or nucleophilic organochalcogen species having metal cation. Comparing the two methods most feasible and simple route will be through first one.

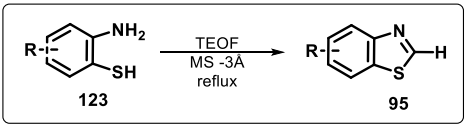
In our planning, the fundamental strategy was the development of a new methodology *via* in one pot and one step procedure (Scheme 39). The reactions were carried out with 1,3-benzothiazole **95**, in the presence of base, to generate carbanion *in situ*, followed by coupling with different diorganyl dichalcogenide **93**(aryl, heteroaryl or alkyl), under open atmosphere to afford chalcogenated benzothiazole **96**.



Scheme 39. Proposed route for accessing chalcogenated-1,3-benzothiazole.

3.2.2. Synthesis of Starting Materials

As previously described in section 3.1.2.2, a library of diorganyl diselenides (Fig. 3) was prepared through Scheme 3-4. 1,3-Benzothiazole was obtained from commercial source and where needed subsituted-1,3-benzothiazole was prepared from substituted 2-aminothiophenol **123** (Scheme 40), according to the literature**.** Compound **123** was cyclized using triethyl orthoformate (TEOF) in the presence of molecular sieves 3 Å, resulted corresponding subsituted-1,3-benzothiazole **95**.



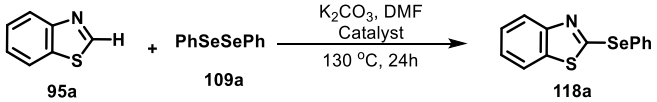
Scheme 40. Synthetic route for accessing substituted 1,3-benzothiazole **95**

3.2.3. Optimization of Reaction Conditions

To identify the best reaction conditions, we begin our study by using 1,3-benzothiazle **95a** and diphenyl diselenide **109a** as standard substrates and a diverse range of catalysts, bases, temperature, solvents, reaction time and reaction stoichiometry, was screened. The results are summarized in Table 5-7. We carried out initial reaction by utilizing 0.5 mmol **95a**, 0.26 mmol **109a** and 1 mmol K_2CO_3 (as base) in DMF (1ml) under open atmosphere at 130 ^oC (Table 5, entry 1), to functionalized/C_{sp2}-H proton from benzothiazoles **95a**, resulting no reaction (Table 5, entries 1). As previous methods involve inert atmosphere, we repeated same reaction under inter atmosphere affording (Entry 2) but we didn't observe any progress in the reaction. Surprisingly, introduction of Ce_2O_4 (20% mol) in the reaction mixture afforded selenated product **118a** with 88 % isolated yield (Entry 3). Encouraged from this result we tired available metal catalyst for this coupling reaction

(Entries 4-12). Considering Cerium to be rare metal we begin exploring transition metal catalyst.

Table 5 Optimization of catalyst for the synthesis of **118a**[a]



Entry	Catalyst	Yield[b] (%)
1	-	NR
2 [c]	-	NR
3	Ce_2O_4 nano	88
4	**Fe_3O_4 nano**	**Quantitative**
5	Fe Powder	61
6	$CuZnFe_2O_4$ nano	89
7	CuO. Fe_2O_3 nano	85
8	CuO nano	57
9	CuI	51
10	$Cu(OAc)_2$	49
11	ZnO nano	58
12	Zn Powder	52
13 [c]	Fe_3O_4 nano	45

[a] Reaction conditions: **95a** (0.5 mmol), **109a** (0.5 mmol), K_2CO_3 (1 mmol), Catalsyt (20% mol) DMF (1 ml) at 130 °C, 24h under air. [b] Isolated yield based on **95a**. [c] Under argon atmosphere.

In first set of trial we used iron based catalyst (Entries 4-7), as iron is considered to be greener and environmentally friendly. Interestingly, using Fe_3O_4 nano afforded the desired product quantitatively (Entry 4). When we used iron power as catalyst, there was sharp decrease in the yield of **118a** i.e. 61 % (Entry 5), showing the superiority of the nano particle due to larger surface area which increase the efficiency of the catalyst. In the next step iron based composite nanoparticles were been used as catalyst e.g. $CuZnFe_2O_4$ nano (Entry 6) and CuO. Fe_2O_3 nano (Entry 7), resulted the desired product in 89 % and 85 yield, respectively.

As, in literature CuO nano was effective catalyst under inert atmosphere. Interestingly, when we performed a test reaction in the presence of CuO nano under open atmosphere, the selenated product was achieved in moderate yield (Entry 8). Similarly, CuI and $Cu(OAc)_2$ were also non effective and resulted **118a** with 51 % and 49 % isolated yield, respectively (Entries 9, 10).

In the next phase of catalyst, we tried ZnO nano particle and elemental Zn as catalyst (Entries 11, 12). Experimental results showed that they were also not very effective and resulted the selenated product **118a** in moderate yield with 58 % and 52%. As we observed previously (during chalcogenation of oxadiazole) that open atmosphere plays a crucial role in the reaction and causing total consumption of starting materials. On this basis, we carried out an experiment using the Fe_3O_4 nano and performed the reaction under positive pressure of argon (Entry 13). As predicated, there was sharp decrease in the yield of **118a** (Entry 13 *vs* 4). This was an important finding, which could help in proposing the possible mechanistic route for this coupling reaction.

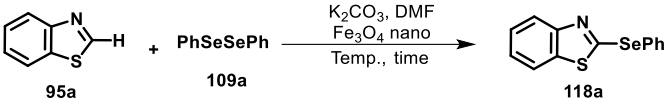
With best catalyst in hand, next we studied the stoichiometry of the catalyst (Table. 6). Decreasing the catalyst load from 20 % mol to 10 % mol, didn't show any negative influence on the reaction, but decreasing further the catalyst loading to 5 % mol resulted decrease in the yield of **118a** (Table 6, entries 1-3).

In the next step, the reaction time and temperature were screened for this transformation (Entries 4-10). First, we evaluated different duration of time In order to confirm ideal time for this transformation, in this regard a-set of experiments were carried out (Entries 4-7). Decreasing the reaction time interval from 24h to 12 h, resulted did not showed any inverse effect on the reaction yield (Entry 4 *vs* 2). During the whole duration of the reaction, the progress was monitored time to time by thin layer chromatography (TLC) and it was observed that in 12 h all of the benzothiazoles **95a** was totally consumed. Further decrease in the reaction time showed a negative effect i.e. affording 24a in low yield

(Entries 5, 6). It was noticed through TLC that benzothiazoles **95a** was not fully consumed during these reactions.

Furthermore, we noticed that temperature had a very strong influential on the reaction. Drastic result was obtained when temperature was increased to 150 °C, which decrease **118a** to 91 % (Entry 7). There was no effect on yield when the temperature was lowered to 120 °C (Entry 8). Further decreasing the temperature below 120 °C, afforded the selenated benzothiazole **118a** in lower yields as compare to 120 °C (Entry 9 *vs* 8). TLC analysis showed the presence of unreacted benzothiazoles **95a**, which signify the necessity of the higher temperature. Lastly, when a reaction was performed at room temperature, **118a** was purified in very poor yield (Entry 10), while unreacted starting materials were completely recovered through column chromatography (CC).

Table 6. Optimization of catalyst loading, time & temperature for **118a**[a]



Entry	Fe_2O_3 (% mol)	Temp. (°C)	Time (h)	Yield[b] (%)
1	20	130	24	Quantitative
2	10	130	24	Quantitative
3	5	130	24	75
4	10	130	12	Quantitative
5	10	130	8	79
6	10	130	4	41
7	10	150	12	91
8	10	120	12	Quantitative
9	10	100	12	66

10	10	RT	12	9
11 [c]	10	120	12	Quantitative
12 [d]	**10**	**120**	**12**	**Quantitative**
13 [e]	10	120	12	96

[a] Reaction conditions: **95a** (0.5 mmol), **109a** (0.5 mmol), K_2CO_3 (1 mmol), Fe_2O_3, DMF (1 ml) at a specific time under air. [b] Isolated yield based on **95a**. [c] **109a** (0.375 mmol). [d] **109a** (0.27 mmol). [e] **109a** (0.25 mmol)

In the next step we confirmed the stoichiometry of diselenide **109a** (Entries 11-13) and by decreasing the amount for **109a** from 0.5 mmol to 0.375 and to 0.275 mmol didn't showed any effect on the isolated yield **118a** (Entries 11, 12). Further decrease in stoichiometry of **109a** (Entry 13) shows slight decrease in the yield. It is important to point out that while the unreacted diselenide was recovered easily through CC (Entry 13). This was very important finding because during the course of reaction we didn't observer any formation of PhSePh which is a common by-product, observed in previous works.[89]

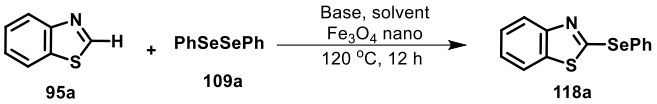
It is well known that solvents play a crucial role in cross-coupling reactions; hence, in order to evaluate the influence of solvents in this coupling reaction, we tested different solvents (Table 7, Entries 1-13). Screening of different solvents revealed that DMF was the best solvent for selenation of benzothiazole affording **118a** quantitatively (Entry 1 *vs* 2-13).

Dry DMF didn't alter the yield of product a lot and when freshly distilled DMF was used the **118a** was obtained in 92 % yield (Entry 2). DMSO was less effective, resulting **118a** in 69 % yield (Entry 3). No product was observed when water, THF, EtOH, 1,4-dioxane, dimethyl carbonate (DMC), NMP, trietyl amine and pyridine were used (Entries 4-13). These solvents seem to be stagnant to this reaction.

Subsequently, the influence of base on the selenation of benzothiazole **95a** was then evaluated, and the results are summarized in Table 7, entries 14–24. Initially, we performed an experiment without the involvement of base (K_2CO_3), entry 14. In this experiment after 12 h, desired product **118a** was not formed, which shows the importance of presence of base for this coupling reaction. Further studies showed that

when this reaction was performed in the presence of organic bases e.g. *t*-BuOK and triethyl amine, the formation of product **118a** was also not been observed (entries 18 and19), while the use of other carbonates e.g. Na_2CO_3 and Cs_2CO_3 (Entries 15, 16) and $NaHCO_3$ (Entry 17) were less effective. KOH and K_3PO_4 were also not good bases, affording **118a** in poor yield (Entries 20, 21).

Table 7. Optimization of base and solvent for **118a**[a]



Entry	Base	Solvent	Yield[b] (%)
1	**K_2CO_3**	**DMF**	**Quantitative**
2	K_2CO_3	DMF-dry	92
3	K_2CO_3	DMSO	69
4	K_2CO_3	H_2O	-
5	K_2CO_3	THF	-
6	K_2CO_3	EtOH	-
7	K_2CO_3	Toluene	-
8	K_2CO_3	Acetonitrile	-
9	K_2CO_3	1,4-dioxane	-
10	K_2CO_3	DMC	-
11	K_2CO_3	NMP	-
12	K_2CO_3	Et_3N	-
13	K_2CO_3	Pyridine	-

14	--	DMF	-
15	Cs_2CO_3	DMF	27
16	Na_2CO_3	DMF	36
17	$NaHCO_3$	DMF	30
18	*t*-BuOK	DMF	-
19	Et_3N	DMF	-
20	K_3PO_4	DMF	12
21	KOH	DMF	17
22 [c]	K_2CO_3	DMF	Quantitative
23 [d]	K_2CO_3	DMF	92
24 [e]	K_2CO_3	DMF	41

[a] Reaction conditions: **95a** (0.5 mmol), **109a** (0.27 mmol), base (0.5 mmol), Fe_3O_4 (10% mol), Solvent (1 ml) at 120 ºC, 24h under air. [b] Isolated yield based on **95a**. [c] K_2CO_3 (1.5 equiv.). [e] K_2CO_3 (1 equiv.). [f] K_2CO_3 (30 mol%).

Lastly, we evaluated the stoichiometry of K_2CO_3. Increasing the stoichiometric amount of K_2CO_3 to 1.5 equiv. kept maintain the isolated yield of **118a** constant (Table 7, Entry 22). When less amount of base was used e.g. 1 equiv. and 30 mol %, the yield of **118a** was constantly decreasing (Entries 23, 24).

3.2.4. The Reaction Scope

Based on the results of optimization, as shown in Table 5-7, we concluded the best reaction conditions for the selenation of benzothiazole **118a**, were the use of benzothiazole **95a** (0.5 mmol), diorganyl diselenide **109** (0.27 mmol), K_2CO_3 (1.5 equiv.), Fe_3O_4 (10 % mol) with stirring in DMF (1 mL) at 120 ºC for 12 h under an open atmosphere. The reaction

was repeated several times under same condition in order to confirm the reproducibility. After confirming the reproducibility of the reaction, we explored the efficiency and generality of our methodology to various benzothiazole **95**, dichalcogenides **109** and **110** (with different functional groups) under optimized condition. The results are summarized in Table 8-9 and in Scheme 16

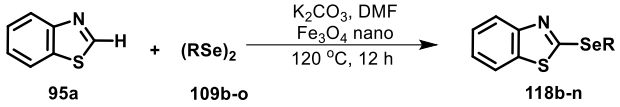
First, influence of several diorganyl diselenides **8** was checked in order to verify the efficiency of optimized protocol. A variety of diorganyl diselenides **109** with different electronic effects, were reacted with 1,3-benzothiazole **95a** in order to synthesize various 2-(organoselanyl)benzo[*d*]thiazole **118b-o** (Table 8, entries 1–14). The reaction works well with a range of diorganyl diselenides **109** containing both electron-donating (–Me and –OMe) and electron-withdrawing groups (CF_3, F and Cl) as well as bulky and aliphatic groups, showing up the sensitivity and tolerance to electronic effects and steric effects to several different substituents.

Generally speaking, it was noticed that electron-donating groups afforded the selenated product **118** in good results, for example, when -Me and -OMe, are present on the aromatic ring of the diselenide **109** (Table 8, entry 1-4). By comparing methyl and methoxy group it can be noticed that the yield of **118** improve when electron-donating group was getting stronger effect at *para*-position, such as *p*-MeO substituted diselenide **109c** afforded the desired product **118c** in 96 % yield while *p*-Me substituted diselenide **109b** afforded the **118b** in 90 % (Table 8, entry 2 vs. 1). We found that the electron-withdrawing groups had showed some adverse effect and decrease in the yield of the corresponding product was noticed (Entries 5-7). For instance, when diselenide containing electron-withdrawing groups attached at the *para*-position on phenyl ring, such as *p*-chloro **109f** and *p*-fluoro **109h**, the corresponding products were obtained in low yields with 85 % and 68 %, respectively (Entries 5, 7). A similar behavior was also noticed for *meta*-substituted CF_3 **109g**, an electron-withdrawing (Entry 6).

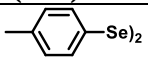
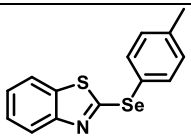
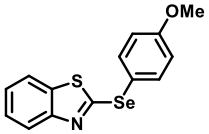
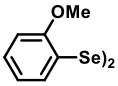
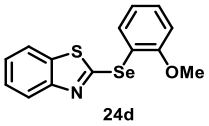
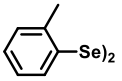
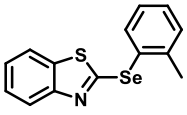
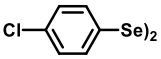
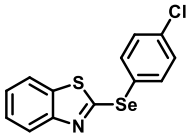
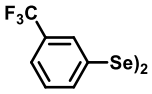
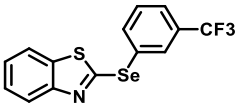
It is well known that steric hindrance of *ortho*-substituted aryl substrates could gave lower yields as compare to *para*-substituted, herein, under optimized conditions a weaker influence on the yields of selenated product **118** were observed i.e. hindered substituent *o*-Me and *o*-MeO substituted diorganyl diselenide (Table 8, entry 3 and 4 *vs*. 2 and 1, respectively). Interesting, not only complete tolerance but improved result was observed from sterically hindered dimesityl-diselenide **109i**, giving the desired product **118i** quantitatively (Table 8, entry 8). Bulky and

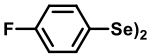
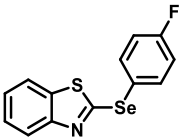
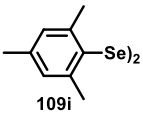
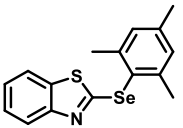
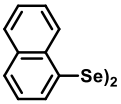
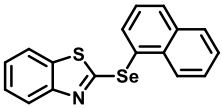
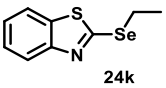
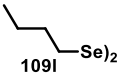
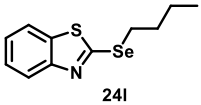
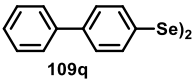
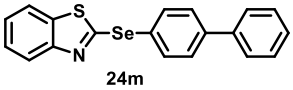
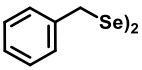
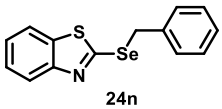
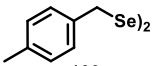
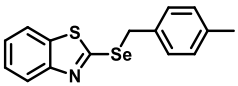
hindered substrate, i.e. bis(2-naphthyl)diselenide **109j**, afforded the desired product **118j** with 72 % yield.

Table 8. Selenation of 1,3-benzothiazole **95a** [a]



95a 109b-o 118b-n

Entry	$(RSe)_2$ 109	Product 118	Yield[b] (%)
1	 109b	 24b	90
2	 109c	 24c	96
3	 109d	 24d	89
4	 109e	 24e	92
5	 109f	 24f	85
6	 109g	 24g	68

7	 109h	 24h	79
8	 109i	 24i	Quantitative
9	 109j	 24j	72
10	 109k	 24k	80
11	 109l	 24l	78
12	 109q	 24m	83
13	 109n	 24n	32*
14	 109n	 24o	36*

[a] Reaction conditions: 2-(4-tolyl)-1,3,4-oxadiazole **92a** (0.5 mmol), diorganyl diselenide **109** (0.26 mmol), K_2CO_3 (0.5 mmol), DMSO (1 ml) at a 100 °C for 10 h, under air. [b] Isolated yield based on **95a**.

Next, we tried different dialkyl diselenide **109k-l** for this coupling reaction because aliphatic selenides are important synthetic intermediates and can be use selenium−lithium exchange reaction and trapping Lithium Intermediate with different electrophiles. It is well recognized that diaryl

diselenides are more reactive than aliphatic ones and are much more easily cleaved. In addition, alkyl group directly bonded to selenium atom could undergo *β*-selenoxide elimination, during the purification or work-up process, giving the desired product without the selenium group incorporated in the structure. Therefore, aliphatic diselenide afford desire products in low yield.

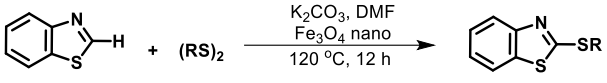
Gratifyingly, by applying our methodology to aliphatic diselenides **109k** and **109l**, with ethyl and *n*-butyl group directly bonded to the selenium atom. These reaction produced the corresponding coupling products **118k** and **118l** in 80% and 78% yields, respectively (Table 8, entries 10 and 11), showing the significance of this methodology. We further extended our protocol on benzylic diselenides **109n-o**, resulting the selenated benzothiazole **118n** and **118o** with 32 % and 36 % isolated yield, respectively (Entries 13,14). The only problem we faced in the synthesis of **118n** and **118o**, was stability because these products were not stable enough for characterization. To appraise the versatility of the methodology, bis(biphenyl) diselenide **109q** was also tested and the desired product **118m** was obtained in good yield (Table 8, entry 12).

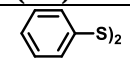
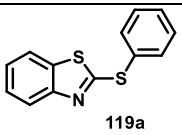
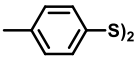
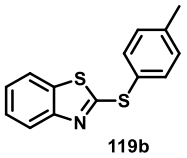
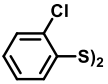
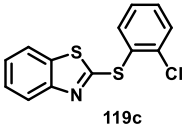
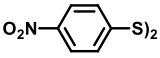
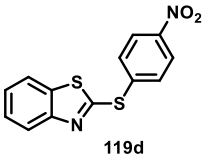
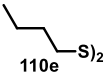
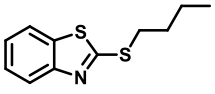
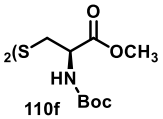
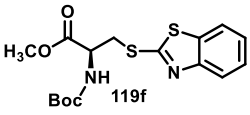
Continuing to investigate the reaction scope, we extended our approach to diorganyl disulfides **110** and to our gratification, good to excellent results were obtained from the combination of a range of structurally diverse disulfides **110**, including aliphatic and aromatic substituents on disulfides **110** moiety, with 1,3-benzothiazole **95a**. The results are summarized in Table 9. Generally, the stronger S–S bond of diorganyl disulfides **110** as compare to respective diorganyl diselenides **109** could explain the decreases in the yield values of thiolated product **119**.

By examining the yields of the reactions between the benzothiazole **95a** and disulfide **110**, one realizes there was a little influence of electronic effects on this cross coupling reaction, since the methodology was tolerated by diaryl disulfides with neutral substituents, electronic donating and withdrawing substituents resulting the desired thiolated product **119a-d** in satisfactory yields (Table 9, entries 1-4). Electron donating group e.g. *p*-Me showed some improvement in yield of final product **119b**, while electron withdrawing groups e.g. *o*-Cl and *p*-nitro resulted the corresponding products **119c** and **119d** with 61 and 54 % isolated yield, respectively (Entries 3, 4). By using dialkyl disulfides such as n-butyl disulfide, good yields of the corresponding product **119e** were obtained (Table 9, Entry 5).

It must be emphasized that the method was inefficient when the *N*-Boc-cysteine methyl ester **110f** was used as the substrate, we did not thiolated benzothiazole **119f** (Table 9, entry 6).

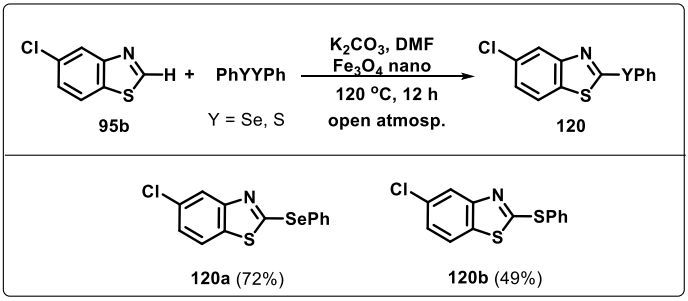
Table 9. Thiolaion of 1,3-benzothiazole **27a** [a]



Entry	$(RS)_2$ 110	Product 119	Yield[b] (%)
1	 110a	 119a	68
2	 110b	 119b	77
3	 110c	 119c	61
4	 110d	 119d	54
5	 110e	 119e	74
6	 110f	 119f	NR-

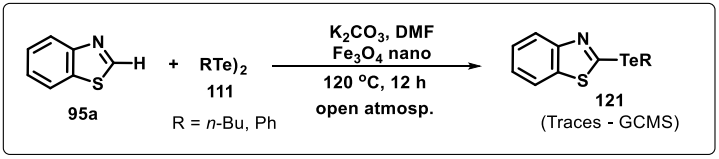
[a] Reaction conditions: **95a** (0.5 mmol), **110** (0.27 mmol), K_2CO_3 (0.75 mmol), Fe_3O_4 (10% mol), DMF (1 ml) at 120 °C, 12h under air. [b] Isolated yield based on **95a**.

With the successful results from the chalcogenation of 1,3-benzothiazole **95a** by intermolecular C-Se an C-S bond formations, applying diorganyl diselenides **109a-o** and diorganyl disulfides **110a-f** as selenium and sulfur source, respectively, prompted us to extend this methodology under optimal reaction conditions to of 5-chloro-1,3-benzothiazole **95b**. Interestingly, the reaction of diphenyl diselenide **109a** and diphenyl disulfide **110a** with **95b** proceeded smoothly to afford the corresponding chalcogenated product **120a** and **120b** in 72 % and 49 % yield (Scheme 41).



Scheme 41. Chalcogenation of 5-chloro-1,3-benzothiazole **95b**

The good results from the reaction of thiolation and selenation of benzothiazole **95a** from Table 8 and 9 and from chalcogenation of 5-chloro-1,3-benzothiazole **95b** (Scheme 41) encouraged us to further expand the scope of the reaction to diorganyl ditelluride (Scheme 42). However, trace amount of desired product **121** was formed under the optimal reaction conditions (used for the preparation of selenated and thiolated benzothiazole), even when the reaction was allowed for shorter and longer reaction times. This behavior was expected, since organotellurides are less stable as compared to other corresponding organochalcogen compounds.[110]



Scheme 42. Telluration of 1,3-benzothiazole with diorganyll ditelluride **18**

3.2.5. Recyclability of the catalyst (Fe_3O_4 nano)

In order to demonstrate the versatility of the protocol, we evaluate the recyclability of the Fe_3O_4 nanoparticles (Fig. 11). One of major drawback of few methods of synthesis in organic chemistry carried out in the presence of catalyst is that generally, catalyst could not be reused and each time fresh load of catalyst is need. From environmental point of view it is also not desirable as well as this is an important factor which restrict the applicability many methods in industry. Therefore, in order to demonstrate the synthetic utility of this new protocol, a series of reactions was carried out by recycling the iron catalyst after each reaction simply b using an external magnet, washing with ether and drying under vacuum.

For this purpose benzothiazole **95a** and diphenyl diselenide **109a** were selected as the test starting materials (Fig. 11). There was no drastic effect during each cycle and selenated product **118a** was isolated without any decline in yield.

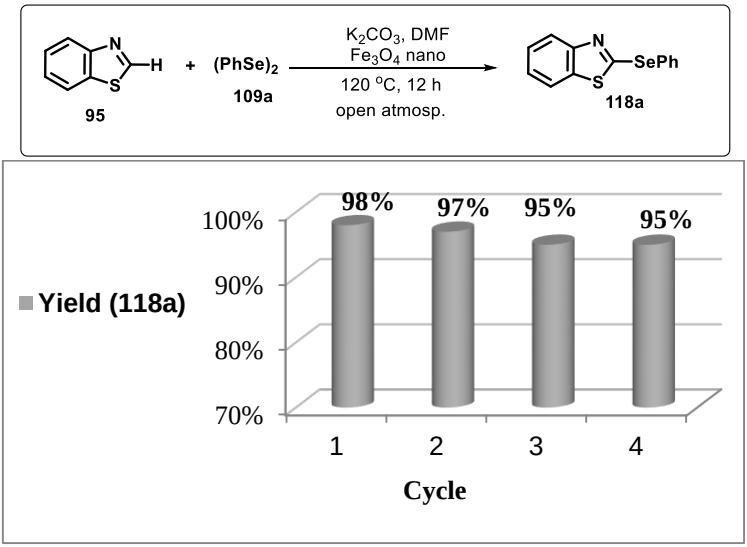


Figure 17. Recyclability of the catalyst

Based on the experiments on recyclability of catalyst, as shown in Figure 17, we can say that this method could be used as a practical method to synthesize lead compounds with biological relevance and applications in material sciences.

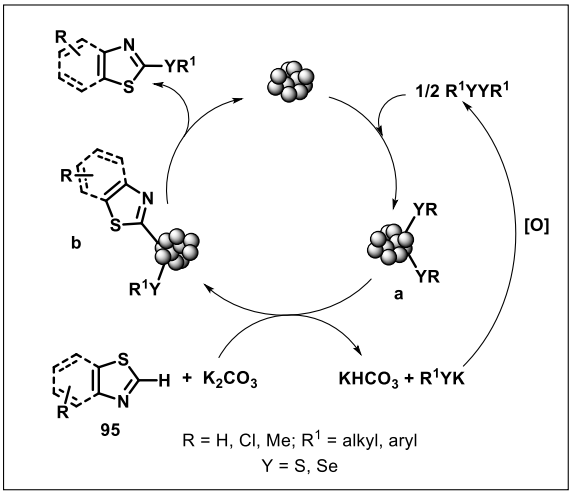
3.2.6. Proposed Mechanism

Based on our group previous experience[114] and chalcogenation of oxadiazole (Scheme 36), the following mechanism has been proposed for this cross coupling reaction (Scheme 43).

Step 1: Oxidative Insertion of iron catalyst between chalcogen atoms of dichalcogenide, leading to the intermediate "**a**". Likely to be the rate determining step of the reaction, requiring the temperature to be 120 °C.

Step 2: Deprotonation of benzothiazole by the base took place, followed by transmetalation step resulting benzothiazole intermediate "**b**" and elimination of potassium salt of organocalcogenide. In the mean, potassium salt oxidize back to diorganyl dichalcogenide.

Step 3: In the last step, reductive elimination resulting in the formation of chalcogenated product and the regeneration of the catalyst occurs.



Scheme 43. Proposed mechanism for the reaction for the chalcogenation of benzothiazole

Interestingly, due to the regeneration of dichalcogenide, only half equiv. dichalcogenide was required for complete consumption of **95**. Another important thing, during the course of reaction we did not observe the thermal decomposition of selenolate species which occur due to carbon-selenium bond homolysis with the formation of PhSePh.[89] On

these grounds we could justify the use of less amount of diorganyl dichalcogenides.

3.2.7. Characterization

The proposed structures of all synthesized 2-(organoselanyl)benzo[*d*]thiazoles **118** and **120a** were confirmed by nuclear magnetic resonance (NMR) spectroscopy and by other relevant techniques. In the following we will discuss the assignment of different signals from Hydrogen and Carbon-13 NMR spectra of 2-(mesitylselanyl)benzo[*d*]thiazole **118i**, as a representative compound. The spectra were obtained in $CDCl_3$.

In the ^1H NMR spectrum (Figure 18), all signals corresponds to hydrogens of **24i.** There is a singlet at 2.35 ppm with integral value of 3, referring to the hydrogen of C-6' methyl group attached directly to the aromatic ring attached with selenium. At 2.53 ppm there is a singlet with integral value of 6, referring to the hydrogen of two methyl group i.e. C-5', attached directly to the aromatic ring attached with selenium. At 7.24 ppm, another singlet with 2 integral value, representing C-3' protons. Next to it, there are two multiples i.e. 7.30 - 7.43 ppm and 7.27 - 7.14 ppm, with integral value one for each, are the hydrogen at C-5 and C-6 of benzothiazole nucleus. On extreme left hand side there are two doublet at 7.60 ppm and at 7.88 with integration value 1 for each and coupling constant J = 7.9 Hz and 8.7 Hz, referring the hydrogen at C-4 and C-7 position on fused aromatic ring.

In the ^{13}C NMR spectrum (Fig. 19), all carbons for **118i** can be seem clearly, a total 13 signals are expected. There are two most shielded signal i.e. at 21.31 pm and 24.39 ppm chemical shift (δ) are for C-5' and C-6' -Me group on phenyl ring attached with selenium, while rest of signals are for aromatic carbon. There are 4 peaks for tertiary carbons of fused benzene ring at 120.95 ppm, 121.60 ppm, 123.95 ppm and 125.95 ppm representing C-5, C-6, C4 and C-7, respectively. A signal for quaternary carbon at 125.70 ppm is for C-4' and big signal for two carbon of C-3' at 136.40 ppm. Rest of signal are for quaternary carbons i.e. 141.12 ppm for C-9, 144.26 ppm for C-2', 155.19 ppm for C-8 and 164.42 ppm for C-2.

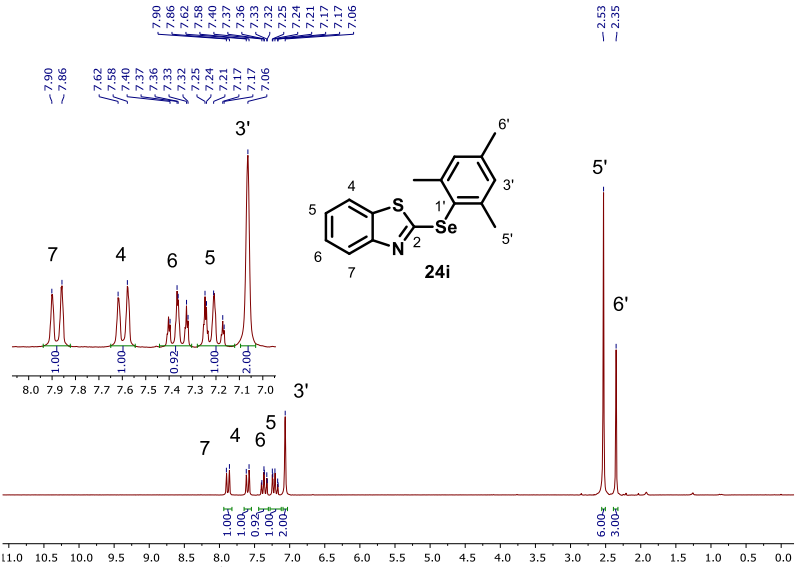


Figure 18. ^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118i**

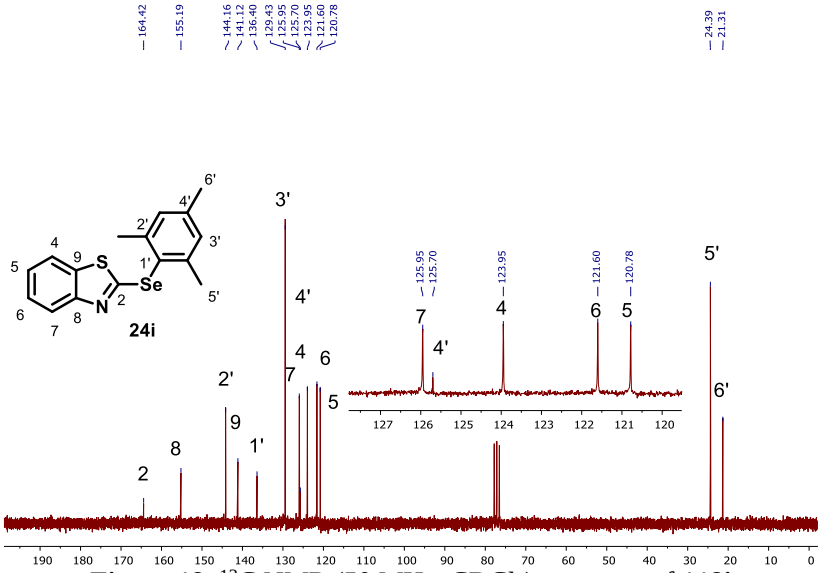


Figure 19. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118i**

Chapter 4
Final Remarks, Conclusions and Perspectives

FINAL REMARKS, CONCLUSIONS AND PERSPECTIVES

Considering the proposed objectives for this PhD study and analyzing the obtained results, it is possible to draw some observations relevant to the research we carried out.

In the first part of the work, we developed a new an efficient, economical and greener K2CO_3-promoted procedure for the synthesis of selenated and thiolated oxadiazoles through $C_{sp2\text{-}H}$ bond functionalization, under transition metal-free conditions in the absence of metal catalyst. We prepared for the first time selenated oxadiazoles, compounds with potential for biological applications. Under mild conditions, the reaction worked well in the presence of K_2CO_3, with a half equiv. of diorganyl dichalcogenides, without the exclusion of air and moisture, affording a wide range of chalcogenated oxadiazoles (most similar methodologies use large excess of disulfides) at the C5 position in good to excellent yields. The various substituents with different electronic effects and steric effects tolerated the optimized reaction conditions.

The chemistry described herein represents a feasible eco-friendly synthetic approach for the preparation of chalcogenated oxadiazoles through the C-S/Se bond. This novel method provides a complementary, environmentally benign, and easy-operation approach to accessing 5-chalcogenayloxadiazole derivatives.

With successful results from the chalcogenation of oxadiazoles, we extended our studies to benzothiazole. In this part of the work we developed a new efficient and greener methodology for the synthesis of 2-(organochalcogen)benzothiazole derivatives by a direct C-H bond functionalization on thiazoles catalyzed by Fe_3O_4 nanoparticle. The use of stoichiometric amount of diorganyl diselenides having an electron-donating or electron-withdrawing substituent as well as neutral substituents, in the aromatic ring bonded to the chalcogen atom required one equiv. of base. The protocol was further extended to diorganyl disulfides. In general, a variety of differently substituted 2-(organochalcogen)benzothiazole were synthesized in moderate to excellent yields. After successful reactions, we performed test to check recyclability of the catalyst, which was used for further three catalytic cycles.

This novel feature in association with the ability of organochalcogen compounds to participate in transition metal-catalyzed cross-coupling reactions and their growing importance as therapeutic agents, mark the 2-(organochalcogen)benzothiazole as promising reagents for applications in organic synthesis and drug discovery.

Currently, we are working on chalcogenation of oxadiazoles and benzothiazoles under microwave irradiations. Another aspect of this PhD work is that we are motivated to extend these studies to some of other important classes of heteroaromatic compounds e.g. compounds a-p in Figure 20, under conventional heating as well as under microwave irradiations. Keeping this perspective in mind, we will further explore functionalization C-H bond by chalcogenation and C-X bond (X = C, N, S, P etc) formation, by using the methods described in this Phd work as well as through well-established methods by our research group.[115] It is important to mention that some of initial studies are in progress.

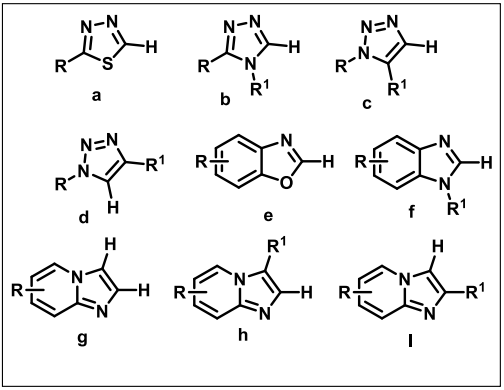


Figure 20. $C_{sp2\text{-}H}$ bond functionalization of different heteroaromatic compounds

Chapter 5
Experimental Section

EXPERIMENTAL SECTION

5.1. MATERIALS & METHODS

5.1.1. Reagents and Solvents

The purified and dried solvents used in reactions were obtained according to procedures described in the literature. All solvents and reagents were purchased from commercial sources (Aldrich, Merck, Fluka, Synth, Brenttag) and in most cases were used without further purification. Potassium carbonate (99.997 %) for controlled reactions, was purchased from Sigma-Aldrich.

Dry DMF and DMSO were prepared by drying overnight over pre-activated 4 °A molecular sieves, followed by decantation of the drying agent and vacuum distillation (~20 mmHg is a sufficient vacuum to lower the boiling point over DMF and DMSO to a reasonable value). Dry DMF and DMSO were stored over pre-activated 4°A molecular sieves.

To dry THF, commercially available THF was distilled from sodium benzophenone ketyl by adding sodium wire and benzophenone to a volume of THF (pre-dried over calcium hydride or 4 °A molecular sieves), heat at reflux under inter atmosphere for several hours until the solvent turns deep blue in color. This indicates the solvent was dry, and can be distill off freshly for the reaction.

Purification of reaction products were performed through column chromatography (CC), the material used was a glass column and flash silica gel (230-400 mesh) or gravity silica gel (70-230 mesh). For high performance flash chromatography, Super Flash SF25-40g Sepra Si 50 column coupled to a BSR (bottomless Solvent Reservoir) pump system was used. An elution solvent (hexane), or mixture of suitable solvents (hexane and ethyl acetate) were used.

Thin layer chromatography (TLC) was performed using commercially available TLC plates (Merck Silica Gel GF254, 0.25 mm thickness). For visualization different methods were used, TLC plates were placed under ultraviolet light, stained with iodine vapor and/or sprayed with acidified solution of vanillin, followed by heating at 110 °C. The progress of all reactions were monitored by TLC for disappearance of starting materials. Solvents used in the synthesis, extraction, purification, CC and TLC are of analytical grade.

Reactions under inert atmosphere are conducted in flame-dried or oven dried glassware equipped with tightly fitted rubber septa and under a positive atmosphere of dry argon. Reagents and solvents are handled

using standard syringe techniques. Temperatures above room temperature are maintained by use of a mineral oil bath with an electrically heated coil connected to a Variac speed controller.

5.1.2. Microwave

The reactions in microwave were performed in special sealed tube (10ml) for microwave in a microwave reactor with focused field CEM Discover (CEM Corporation) connected with auto-sampler Explorer 24 (CEM Corporation), with pressure and temperature monitoring infrared controller and equipped with CEM's Synergy™ software for monitoring the reaction progress.

5.1.3. Solvent Evaporation

For removal of the organic solvent following rotary-evaporator and glass vacuum line were used:

- Büchi Rotavapor R 215 Digital Rotary Evaporators
- IKA Rotary Evaporators, RV 10 Digital, D (Diagonal) Condenser
- Glass vacuum line equipped with a high vacuum pump, vacuum pump model RD 4-4.3 m^3 / h.

5.2. Characterization

Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Carbon Nuclear Magnetic Resonance (^{13}C-NMR), Gas chromatography coupled to mass spectrometry (GC-MS) and melting point when solid, characterized the synthesized compounds previously reported in literature. While for new synthesized compounds along with previously mentioned techniques other techniques such as high-resolution mass spectrometry (HRMS) and infrared spectroscopy (IR), are used. Where needed Selenium Nuclear Magnetic Resonance (^{77}Se-NMR) are applied.

5.2.1. Nuclear Magnetic Resonance Spectroscopy

The NMR technique provide information regarding the characterization of the synthesized compounds. ^{1}H NMR spectra are obtained at 200 MHz on a Bruker AC-200 NMR spectrometer or at 400 MHz on a Varian AS-400 NMR spectrometer. Spectra are recorded in deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO

*d*6) solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of deuterated solvent or tetramethylsilane (TMS) as internal reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (*J*) in Hertz and integrated intensity. ^{13}C NMR are obtained either at 50 MHz on a Bruker AC-200 NMR spectrometer or at 100 MHz on a Varian AS-400 NMR spectrometer. Spectra are recorded in $CDCl_3$ or DMSO *d*6 solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or DMSO *d*6. ^{77}Se NMR at 38.14 MHz on a Bruker AC-200 NMR spectrometer. Spectra are recorded in CDCl3 solutions. Chemical shifts are reported in ppm, referenced to diphenyl diselenide as the external reference (463.15 ppm). Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet) and m (multiplet).

5.2.2. Low Resolution Mass Spectrometry

The mass spectra were obtained with low resolution from a Shimadzu GCMS-QP5050A apparatus equipped with a DB-5 capillary column (30 m) and ionization voltage of 70 eV.

5.2.3. High Resolution Mass Spectrometry

High resolution mass spectra were obtained from micrOTOF Q-II (Bruker Daltonics), at Centro de Biologia Molecular Estrutural (CEBIME), equipped with automatic syringe (KD Scientific) for injection of samples. The mass spectrometer with electro-spray ionization equipped with time of fight analyzer (ESI-QTOF MS) was operated in positive ion mode, where the samples were injected at a constant flow rate of 3 μL/min, using as solvent a mixture of acetonitrile and Liquid chromatography–mass spectrometry (LCMS) grade methanol. Data were processed on a Bruker Data Analysis software version 4.0.

5.2.4. Infrared

The infrared analysis (IR) were recorded on a Bruker Optics Alpha bench top FT-IR spectrometer instrument using KBr pellets for sample preparation. Data were reported in frequency of absorption (cm^{-1}).

5.2.5. Melting Point

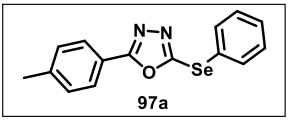
The melting points were determined in a Microquimica MQRPF-301 digital model equipment with heating plate. Data were reported in degree Celsius.

5.3. EXPERIMENTAL PROCEDURES FOR CHALCOGENATED OXADIAOZOLE

5.3.1. General procedure for synthesis of 2-organyl 5-organochalcogeno-1,3,4-oxadiazoles

Unless otherwise stated, all reactions were carried out in open atmosphere. In a Schlenk tube with a magnetic stirring bar, containing DMSO (1 mL), the appropriate oxadiazoles **92** (0.5 mmol), diorganyl dichalcogenide **109**or **110**(0.26 mmol), was added K_2CO_3 (0.5 mmol). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for specific time. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5 ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase.

5.3.1.1. 2-(4-methylphenyl)-5-(phenylselanyl)-1,3,4-oxadiazole (97a).

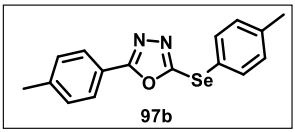


97a

In a Schlenk tube with a magnetic stirring bar, containing DMSO (1 mL), the 2-(4-methylphenyl)-1,3,4-oxadiazole **92a** (0.5 mmol, 80 mg), diphenyl diselenide **109a** (0.26 mmol, 81 mg), was added K_2CO_3 (0.5 mmol, 68 mg). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for 10h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 86 %;

Yellow solid; mp: 84 – 85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.82 (d, J = 8.2 Hz, 2H), 7.78 – 7.70 (m, 2H), 7.42 – 7.34 (m, 3H), 7.24 (d, J = 8.2 Hz, 2H), 2.38 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.3, 155.7, 142.4, 134.9, 129.8, 129.7, 129.6, 126.7, 124.4, 120.7, 21.7.; ^{77}Se NMR (38.14 MHz, $CDCl_3$) δ = 365.34.; IR (KBr): 3050, 2881, 2761, 1614, 1482, 1356, 1256, 1142, 1085, 1025, 964, 835, 734, 642 cm^{-1}; ESI-HRMS m/z: calcd. for $C_{15}H_{13}N_2OSe$ $[M + H]^+$ 317.0188, found: 317.0193.

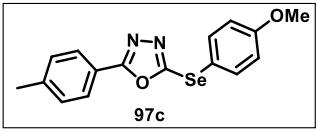
5.3.1.2. 2-(4-methylphenyl)-5-((4-methylphenyl)selanyl)-1,3,4-oxadiazole (97b)



97b

The experimental procedure similar to 5.3.1.1 was followed but using di(4-methylphenyl) diselenide **109b** instead of diphenyl diselenide **109a**. Yield: 88%; Yellow solid; mp: 82 – 84 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.76 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.20 – 7.09 (m, 4H), 2.32 (s, 3H), 2.29 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.4, 156.2, 142.4, 140.1, 135.4, 130.7, 129.8, 126.9, 120.9, 120.7, 21.8, 21.4.; IR (KBr): 3056, 2922, 2853, 1652, 1558, 1478, 1362, 1209, 136, 1066, 1022, 950, 836, 805, 730, 668 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H$ $C_{16}H_{15}N_2OSe$ $[M + H]^+$ 331.0348, found: 331.0352.

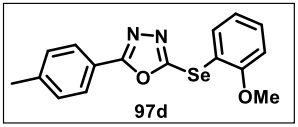
5.3.1.3. 2-(4-methylphenyl)-5-((4-methoxyphenyl)selanyl)-1,3,4-oxadiazole (97c).



97c

The experimental procedure similar to 5.3.1.1 was followed but using di(4-methoxyphenyl) diselenide **109c** instead of diphenyl diselenide **109a**. Yield: 96%; Yellow solid; mp: 74 – 75 °C. 1H NMR (200 MHz, $CDCl_3$) δ = 7.74 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.1 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 3.74 (s, 3H), 2.31 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.2, 161.0, 156.5, 142.3, 137.6, 137.4, 129.7, 126.7, 120.8, 115.8, 115.5, 114.0, 55.4, 21.6.; IR (KBr): 3098, 3065, 2994, 2925, 2842, 1658 1610, 1575, 1478, 1297, 1268, 1184, 1156, 1036, 954, 830, 740, 662 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{16}H_{15}N_2O_2Se$ $[M + H]$+ 347.0294, found: 347.0291.

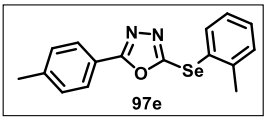
5.3.1.4. 2-(4-methylphenyl)-5-((2-methoxyphenyl)selanyl)-1,3,4-oxadiazole (97d).



97d

The experimental procedure similar to 5.3.1.1 was followed but using di(2-methoxyphenyl) diselenide **109d** instead of diphenyl diselenide **109a**. Yield: 88%; Yellow solid; mp: 69 – 71 °C. 1H NMR (200 MHz, $CDCl_3$) δ = 7.88 (d, J = 8.3 Hz, 2H), 7.57 (dd, J = 8.0, 1.6 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.28 (d, J = 8.4 Hz, 2H), 6.98 – 6.90 (m, 2H), 3.87 (s, 3H), 2.41 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.5, 157.6, 155.2, 142.5, 133.7, 130.4, 129.8, 126.9, 122.1, 120.9, 115.2, 111.3, 56.2, 21.7.; IR (KBr): 3104, 3038, 2990, 2861, 1610, 1594, 1484, 1439, 1344, 1258, 1193, 1127, 1063, 964, 835, 840, 803, 766, 738, 662, 605 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{16}H_{15}N_2O_2Se$ $[M + H]^+$ 347.0294, found: 347.0297.

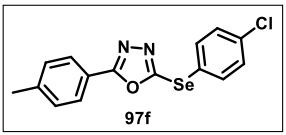
5.3.1.5. 2-(4-methylphenyl 5-((2-methylphenyl)selanyl)-1,3,4-oxadiazole (97e).



97e

The experimental procedure similar to 5.3.1.1 was followed but using di(2-methylphenyl) diselenide **109e** instead of diphenyl diselenide **109a** .Yield: 88%; Yellow solid; mp: 58 – 59 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.83 (d, J = 8.0 Hz, 2H), 7.39 – 7.16 (m, 5H), 2.55 (s, 3H), 2.39 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.3, 155.7, 142.4, 141.8, 136.5, 130.9, 130.3, 129.8, 127.2, 126.8, 125.5, 120.8, 23.0, 21.7.; IR (KBr): 3062, 3032, 2955, 2924, 2868, 1698, 1652, 1558, 1457, 1435, 1337, 1260, 1156, 1064, 950, 848, 821, 728, 688 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{16}H_{15}N_2OSe$ $[M + H]^+$ 331.0345, found: 331.0346.

5.3.1.6. 2-(4-methylphenyl)-5-((4-chlorophenyl)selanyl)-1,3,4-oxadiazole (97f).

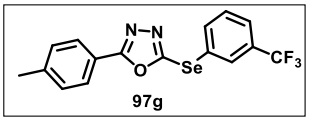


97f

The experimental procedure similar to 5.3.1.1 was followed but using di(4-chlorophenyl) diselenide **109f** instead of diphenyl diselenide **109a.** Yield: 82%; Yellow solid; mp: 82 – 83 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.77 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 2.33 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.6, 155.4, 142.6, 136.4, 136.3, 130.1, 129.8, 126.9, 122.4, 120.7, 21.7.; IR (KBr): 3076, 3045, 2914, 2850, 1629, 1566, 1482, 1344, 1303, 1292, 1272, 1189, 1163, 1115, 1101, 1078, 1015, 993, 964, 838, 738, 677,

630 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H_{12}ClN_2OSe$ $[M + H]^+$ 350.9796, found: 350.9790.

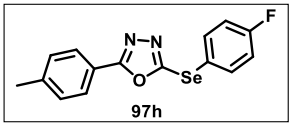
5.3.1.7. 2-(4-methylphenyl)-5-((3-(trifluoromethyl)phenyl)selanyl) - 1,3,4-oxadiazole (97g).



97g

The experimental procedure similar to 5.3.1.1 was followed but using di(3-(trifluoromethyl)phenyl) diselenide **109g** instead of diphenyl diselenide**109**. Yield: 70%; Yellow solid; mp: 60 – 61 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.97 (s, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.78 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 7.9 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 8.1 Hz, 2H), 2.34 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.7, 154.8, 142.2, 138.2, 132.26 (d, J_{C-F} = 32.9 Hz), 131.59 (q, J_{C-F} = 3.8 Hz),130.3, 129.9, 126.9, 126.53 (q, J_{C-F} = 3.7 Hz),125.5, 123.49 (q, J_{C-F} = 272.9 Hz), 120.68, 21.7.; IR (KBr): 3100, 3052, 2992, 2915, 2881, 1629, 1564, 1478, 1431, 1322, 1223, 1152, 1110, 803, 713, 679, 662. cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{16}H_{12}F_3N_2OSe$ $[M + H]^+$ 385.0062, found: 385.0066.

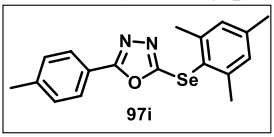
5.3.1.8. 2-(4-methylphenyl)-5-((4-fluorophenyl)selanyl)-1,3,4-oxadiazole (97h).



97h

The experimental procedure similar to 5.3.1.1 was followed but using di(4-fluorophenyl) diselenide **109h** instead of diphenyl diselenide **109a.** Yield: 65%; Yellow solid; mp: 85 – 87 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.83 (d, J = 8.2 Hz, 2H), 7.80 – 7.72 (m, 2H), 7.26 (d, J = 8.2 Hz, 2H), 7.14 – 7.04 (m, 2H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.4, 163.76 (d, J_{C-F} = 250.7 Hz), 155.76, 142.52, 137.66 (d, J_{C-F} = 8.4 Hz), 129.79, 126.79, 120.72, 118.84, 117.20 (d, J_{C-F} = 22.0 Hz), 21.69.; IR (KBr): 3106, 3165, 2979, 2885, 1692, 1629, 1594, 1492, 1460, 1441, 1322, 1299, 1254, 1152, 1170, 1080, 962, 832, 742, 603 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H_{12}FN_2OSe$ $[M + H]^+$ 335.0092, found: 335.0098.

5.3.1.9. 2-(4-methylphenyl)-5-(mesitylselanyl)-1,3,4-oxadiazole (97i).

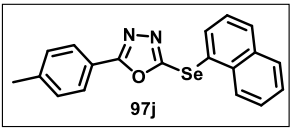


97i

The experimental procedure similar to 5.3.1.1 was followed but using dimesityl diselenide **109i** instead of diphenyl diselenide **109a**. Yield: 62%; Yellow solid; mp: 62 – 64 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.2

Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.01 (s, 2H), 2.56 (s, 6H), 2.39 (s, 3H), 2.30 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.0, 156.2, 143.6, 142.2, 140.6, 129.7, 129.3, 126.7, 122.8, 121.0, 24.5, 21.7, 21.1.; IR (KBr): 3083, 3000, 2952, 2923, 2846, 2831, 1601, 1564, 1513, 1480, 1441, 1333, 1291, 1176, 1127, 1083, 991, 864, 832, 740, 675, 630 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{18}H_{19}N_2OSe$ $[M + H]^+$ 359.0658, found: 359.0656.

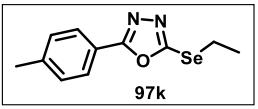
5.3.1.10. 2-(4-methylphenyl)-5-(naphthalen-1-ylselanyl)-1,3,4-oxadiazole (97j).



97j

The experimental procedure similar to 5.3.1.1 was followed but using dinaphthalen-1,1'-diselenide **109j** instead of diphenyl diselenide **109a**. Yield: 63%; Yellow solid; mp: 122 – 124 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.42 (d, *J* = 7.8 Hz, 1H), 8.09 (dd, *J* = 7.2, 1.0 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.86 (dd, *J* = 7.1, 2.0 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.63 – 7.52 (m, 2H), 7.49 – 7.40 (m, 1H), 7.17 (d, J = 8.2 Hz, 2H), 2.34 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.3, 155.6, 142.3, 136.3, 134.4, 131.4, 129.7, 129.6, 128.8, 127.7, 127.6, 126.8, 126.7, 126.7, 126.0, 125.9, 123.4, 120.7, 21.6.; IR (KBr): 3089, 3052, 3023, 2954, 2918, 1629, 1594 1548, 1513, 1480, 1348, 1266, 1174, 1083, 1038, 964, 834, 807, 781, 662 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{19}H_{15}N_2OSe$ $[M + H]^+$ 367.0345, found: 367.0346.

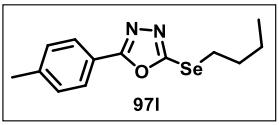
5.3.1.11. 2-(4-methylphenyl)-5-(ethylselanyl)-1,3,4-oxadiazole (97k).



97k

The experimental procedure similar to 5.3.1.1 was followed but using diethyl diselenide **109k** instead of diphenyl diselenide **109a.** Yield: 80%; Yellow solid; mp: 41 – 42 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.33 (q, *J* = 7.4 Hz, 2H), 2.41 (s, 3H), 1.65 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.0, 156.2, 142.2, 129.7, 126.7, 121.0, 32.2, 22.2, 21.6, 16.0.; IR (KBr): 3055, 3046, 2977, 2959, 2916,2870, 2863, 1684, 1615, 1558, 1464, 1331, 1238, 1184, 1062, 954, 834, 795, 672, 668, 613 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{11}H_{13}N_2OSe$ $[M + H]^+$ 269.0188, found: 269.0197.

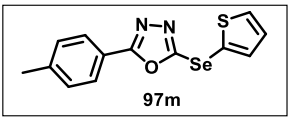
5.3.1.12. 2-(4-methylphenyl)-5-(butylselanyl)-1,3,4-oxadiazole (97l).



97l

The experimental procedure similar to 5.3.1.1 was followed but using dibutyl diselenide **109l** instead of diphenyl diselenide **109a**. Yield: 81%; Yellow solid; mp: 58 – 60 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.05 – 7.79 (m, 2H), 7.35 – 7.22 (m, 2H),), 3.33 (t, J = 7.5 Hz, 2H), 2.40 (s, 3H), 1.99 – 1.80 (m, 2H), 1.58 – 1.39 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.8, 156.2, 142.0, 129.6, 126.5, 120.8, 32.2, 28.0, 22.7, 21.5, 13.4.; IR (KBr): 3049, 3002, 2972, 2948, 2883, 2861,1658, 1629, 1572, 1513, 1480, 1321, 1225, 1176, 1085, 991, 834, 818, 736, 701, 660 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{13}H_{17}N_2OSe$ $[M + H]^+$ 297.0501, found: 297.0501.

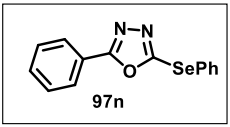
5.3.1.13. 2-(4-chlorophenyl)-5-(thiophen-2-ylselanyl)-1,3,4-oxadiazole (97m).



97m

The experimental procedure similar to 5.3.1.1 was followed but using dithiophen-2,2'-diselenide **109m** instead of diphenyl diselenide **109a**. Yield: 79%; Yellow solid; mp: 68 – 69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.81 (d, J = 8.3 Hz, 2H), 7.57 – 7.46 (m, 1H), 7.30 – 7.21 (m, 3H), 7.13 – 6.98 (m, 1H), 2.37 (s, 3H).; ^{13}C (100 MHz, $CDCl_3$) δ = 167.2, 155.5, 142.2, 138.6, 133.7, 131.9, 129.7, 128.4, 126.7, 120.6, 21.68.; IR (KBr): 3055, 2998, 2921, 2846, 1612, 1566, 1460, 1403, 1304, 1299, 1176, 1091, 1025, 972, 928, 836, 813, 722, 709 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{13}H_{11}SN_2OSe$ $[M + H]$+ 322.9751, found: 322.9755.

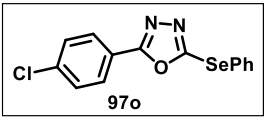
5.3.1.14. 2-phenyl-5-(phenylselanyl)-1,3,4-oxadiazole (97n).



97n

The experimental procedure similar to 5.3.1.1 was followed but using 2-phenyl-1,3,4-oxadiazole **92b** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 84%; Yellow solid; mp: 51 – 52 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.96 – 7.91 (m, 2H), 7.81 – 7.70 (m, 2H), 7.49 – 7.37 (m, 6H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 167.2, 156.2, 135.0, 131.8, 129.8, 129.6, 129.0, 126.8, 124.2, 123.4.; IR (KBr): 3094, 3055, 2977, 2920, 1546, 1484, 1463, 1335, 1280, 1158, 1111, 1061, 1022, 982, 782, 741, 688 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{14}H_{11}N_2OSe$ $[M + H]^+$ 303.0031, found: 303.0028.

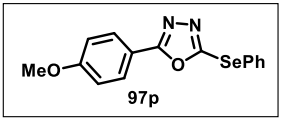
5.3.1.15. 2-(4-chlorophenyl)-5-(phenylselanyl)-1,3,4-oxadiazole (97o).



97o

The experimental procedure similar to 5.3.1.1 was followed but using 2-(4-chlorophenyl)-1,3,4-oxadiazole **92c** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 79%; Yellow solid; mp: 85 – 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$)δ = 7.82 (d, *J* = 8.2 Hz, 2H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.40 – 7.31 (m, 5H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.3, 162.5, 156.5, 138.0, 135.1, 129.8, 129.7, 129.4, 128.0, 121.9.; IR (KBr): 3064, 3044, 2917, 1655, 1613, 1553, 1482, 1464, 1384, 1293, 1189, 1084, 1067, 953, 817, 725, 669, 623 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{14}H_{10}ClN_2OSe$ $[M + H]^+$ 336.9639, found: 336.9638.

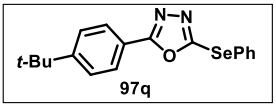
5.3.1.16. 2-(4-methoxyphenyl)-5-(phenylselanyl)-1,3,4-oxadiazole (97p).



97p

The experimental procedure similar to 5.3.1.1 was followed but using 2-(4-methoxyphenyl)-1,3,4-oxadiazole **92d** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 95%; Yellow solid; mp: 93 – 95 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.01 – 7.63 (m, 4H), 7.43 – 7.36 (m, 2H), 7.03 – 6.87 (m, 2H), 3.85 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.3, 162.5, 155.3, 134.9, 129.9, 129.6, 128.7, 124.6, 116.1, 114.5, 55.5.; IR (KBr): 3059, 3034, 2985, 2952, 1652, 1609, 1553, 1541, 1498, 1464, 1337, 1306, 1255, 1178, 1150, 1062, 1017, 958, 835, 738, 687 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H_{13}N_2O_2Se$ $[M + H]^+$ 333.0137, found: 317.0133.

5.3.1.17. 2-(4-(tert-butyl)phenyl)-5-(phenylselanyl)-1,3,4-oxadiazole (97q).

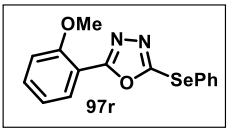


97q

The experimental procedure similar to 5.3.1.1 was followed but using 2-(4-(tert-butyl)phenyl)-1,3,4-oxadiazole **92e** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 96%; Yellow solid; mp: 59 – 60 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.88 (dt, *J* = 8.7, 1.3 Hz, 2H), 7.82 – 7.66 (m, 2H), 7.51 – 7.35 (m, 5H), 1.33 (s, 9H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.3, 155.8, 155.5, 135.0, 129.9, 129.6, 126.7, 126.1, 124.4, 120.7, 35.1, 31.1.; IR (KBr): 3089, 3008, 2949, 2923, 2916, 2903, 2860, 1614, 1581, 1565, 1546, 1495, 1463, 1378, 1333, 1265, 1150, 1122, 1107, 1061, 1012, 984, 951, 847,

838, 739, 704, 685 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{18}H_{19}N_2OSe$ $[M + H]^+$ 359.0658, found: 359.0659.

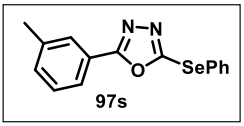
5.3.1.18. 2-(2-methoxyphenyl)-5-(phenylselanyl)-1,3,4-oxadiazole (97r).



97r

The experimental procedure similar to 5.3.1.1 was followed but using 2-(2-methoxyphenyl)-1,3,4-oxadiazole **92f** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 83%; Yellow solid; mp: 63 – 64 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.90 – 7.64 (m, 3H), 7.51 – 7.32 (m, 4H), 7.07 – 6.92 (m, 2H), 3.86 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 165.9, 157.7, 155.8, 135.0, 133.2, 130.2, 129.7, 129.4, 124.5, 120.7, 112.6, 111.9, 55.9.; IR (KBr): 3057, 3020, 2971, 2936, 2836, 1652, 1558, 1495, 1455, 1435, 1413, 1354, 1240, 1178, 1125, 1006, 1004, 915, 842, 770, 738, 689, 666 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H_{13}N_2O_2Se$ $[M + H]^+$ 333.0137, found: 317.0135.

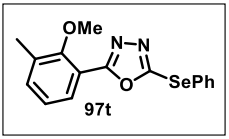
5.3.1.19. 2-(3-methylphenyl)-5-(phenylselanyl)-1,3,4-oxadiazole (97s).



97s

The experimental procedure similar to 5.3.1.1 was followed but using 2-(3-methylphenyl)-1,3,4-oxadiazole **92g** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 85%; Yellow viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.84 – 7.65 (m, 4H), 7.44 – 7.28 (m, 5H), 2.38 (s, 3H).; ^{13}C NMR (50 MHz, CDCl3) δ = 167.3, 156.0, 138.9, 134.9, 132.6, 129.8, 129.5, 128.9, 127.3, 124.3, 123.9, 123.3, 21.3.; IR (KBr): 3020, 2911, 2861, 1610, 1411, 1331, 1278, 1155, 1091, 1020, 968, 832, 735, 642 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H_{13}N_2OSe$ $[M + H]^+$ 317.0185, found: 317.0185.

5.3.1.20. 2-(2-methoxy-3-methylphenyl)-5-(phenylselanyl)-1,3,4-oxadiazole (97t).

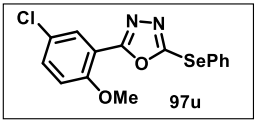


97t

The experimental procedure similar to 5.3.1.1 was followed but using 2-(2-methoxy-3-methylphenyl)-1,3,4-oxadiazole **92h** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole**92a**. Yield: 88%; Yellow solid; mp: 59 – 60 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.83 – 7.62 (m, 3H), 7.41 – 7.26 (m, 4H), 7.08 (t, J = 7.7 Hz, 1H), 3.61 (s, 3H), 2.32 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 165.7, 156.8, 156.3, 135.3, 134.9, 132.9, 129.8,

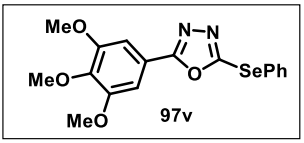
129.6, 127.7, 124.2, 124.1, 117.4, 60.9, 15.9.; IR (KBr): 3042, 3021, 2975, 2937, 2861, 2853, 1612, 1604, 1547, 1512, 1488, 1454, 1328, 1310, 1257, 1173, 1155, 1052, 1007, 957, 829, 738, 686 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{16}H_{15}N_2O_2Se$ $[M + H]^+$ 347.0294, found: 347.0291.

5.3.1.21. 2-(5-chloro-2-methoxyphenyl)-5-phenylselanyl-1,3,4-oxadiazole (97u).



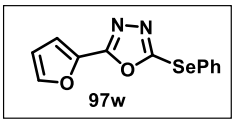
The experimental procedure similar to 5.3.1.1 was followed but using 2-(5-chloro-2-methoxyphenyl)-1,3,4-oxadiazole **92i** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 89%; Yellow solid; mp: 56 – 58 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.83 – 7.66 (m, 3H), 7.45 – 7.35 (m, 4H), 6.93 (d, J = 8.9 Hz, 1H), 3.83 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.2, 164.7, 156.2, 135.0, 134.9, 132.6, 129.6, 129.5, 125.5, 124.1, 113.8, 113.3, 56.2.; IR (KBr): 3060, 3040, 2960, 2928, 2861, 2847, 1652, 1617, 1576, 1558, 1539, 1507, 1497, 1486, 1470, 1456, 1439, 1337, 1272, 1180, 1027, 989, 874, 823, 740, 668 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H_{12}ClN_2O_2Se$ $[M + H]^+$ 366.9745, found: 366.9744.

5.3.1.22. 2-(3,4,5-trimethoxyphenyl)-5-phenylselanyl-1,3,4-oxadiazole (97v).



The experimental procedure similar to 5.3.1.1 was followed but using 2-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole **92j** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 92%; Yellow solid; mp: 122 – 125 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.88 – 7.67 (m, 2H), 7.46 – 7.34 (m, 3H), 7.19 (s, 2H), 3.90 (s, 9H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.1, 155.9, 153.6, 141.1, 134.9, 129.8, 129.6, 124.4, 118.5, 104.1, 61.0, 56.3.; IR (KBr): 3057, 3020, 2971, 2936, 2864, 2830, 1652, 1594, 1558, 1541, 1497, 1456, 1435, 1411, 1354, 1240, 1125, 1005, 862, 842, 742, 666 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{17}H_{17}N_2O_4Se$ $[M + H]^+$ 393.0327, found: 393.0321.

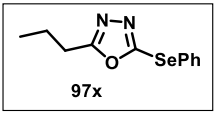
5.3.1.23. 2-(furan-2-yl)-5-phenylselanyl-1,3,4-oxadiazole (97w).



The experimental procedure similar to 5.3.1.1 was followed but using 2-(furan-2-yl)-1,3,4-oxadiazole **92k** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 82%; Yellow solid; mp: 60 – 61 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ =

7.83 – 7.69 (m, 2H), 7.61 (bd, *J* = 1.8 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.09 (d, *J* = 3.5 Hz, 1H), 6.56 (dd, *J* = 3.5, 1.8 Hz, 1H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 160.0, 155.7, 145.8, 139.1, 135.1, 129.9, 129.7, 124.0, 114.4, 112.2.; IR (KBr): 3133, 3061, 2985, 2928, 1698, 1932, 1560, 1513, 1460, 1448, 1348, 1132, 1081, 949, 900, 826, 748, 689, 675 cm-1.; ESI-HRMS m/z: calcd. for $C_{12}H_9N_2OSe$ $[M + H]^+$ 292.9824, found: 292.9834.

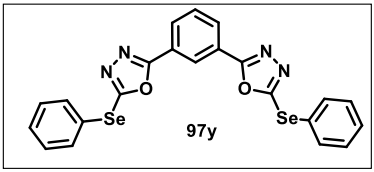
5.3.1.24. 2-(n-propyl)-5-phenylselanyl-1,3,4-oxadiazole (97x).



97x

The experimental procedure similar to 5.3.1.1 was followed but using 2-(n-propyl)-1,3,4-oxadiazole **92l** instead of 2-(4-methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 84%; Yellow viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.82 – 7.61 (m, 2H), 7.46 – 7.30 (m, 3H), 2.78 (t, *J* = 7.4 Hz, 2H), 1.82 – 1.69 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 169.5, 155.8, 134.8, 129.7, 129.4, 124.2, 27.1, 19.8, 13.4.; IR (KBr): 3053, 2977, 2959, 2916, 2863, 1661, 1615, 1558, 1505, 1464, 1158, 1062, 1017, 954, 834, 726, 668, 636 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{11}H_{13}N_2OSe$ $[M + H]^+$ 269.0188, found: 269.0195.

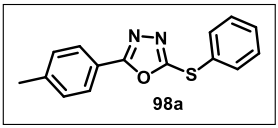
5.3.1.25. (1,3-bis(5-phenylselanyl)-1,3,4-oxadiazol-2-yl)benzene (97y).



97y

The experimental procedure similar to 5.3.1.1 was followed but using 1,3-di(1,3,4-oxadiazol-2-yl)benzene **92m** instead of 2-(4 methylphenyl)-1,3,4-oxadiazole **92a**. Yield: 61%; yellow solid; mp: 122 - 124 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.53 (t, *J* = 1.7 Hz, 1H), 8.12 (dd, *J* = 7.9 Hz, 1.7 Hz, 2H), 7.82 – 7.75 (m, 4H), 7.64 – 7.56 (m, 1H), 7.46 – 7.38 (m, 6H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.2, 157.1, 135.3, 130.0, 129.9, 129.8, 125.0, 124.7, 124.0.; IR (KBr): 3074, 3045, 2979, 2937, 1648, 1567, 1492, 1465, 1327, 1282, 1159, 1163, 1051, 1028, 981, 788, 734, 668 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{22}H_{15}N_4O_2Se_2$ $[M + H]^+$ 526.9522, found: 596.9519.

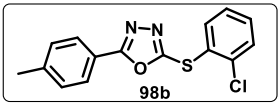
5.3.1.26. 2-(4-Methylphenyl)-5-(phenylthio)-1,3,4-oxadiazole (98a).



98a

In a Schlenk tube with a magnetic stirring bar, containing DMSO (1 mL), the 2-(4-methylphenyl)-1,3,4-oxadiazole **92a** (0.5 mmol, 80 mg), diphenyl disulfide **110** (0.26 mmol, 57 mg), was added K_2CO_3 (0.5 mmol, 68 mg). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for 10h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5).Yield: 55%; white solid; mp: 68 – 69 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.69 (d, *J* = 8.1 Hz, 2H), 7.59 – 7.44 (m, 2H), 7.39 – 7.15 (m, 3H), 7.11 (d, *J* = 8.1 Hz, 2H), 2.24 (s, 3H).; ^{13}C NMR (50 MHz, CDCl3) δ = 166.4, 162.2, 142.3, 133.3, 129.6, 127.1, 126.5, 120.5, 21.5.; IR (KBr): 3075, 3021, 2938, 1612, 1558, 1478, 1460, 1304, 1285, 1254, 1176, 1117, 1065, 1163, 1067, 1022, 955, 835, 803, 752, 733, 697 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{15}H_{13}N_2OS$ $[M + H]^+$ 269.0743, found: 269.0738.

5.3.1.27. 2-(4-Methylphenyl)-5-(2-chlorophenylthio)-1,3,4-oxadiazole (98b).



98b

The experimental procedure similar to 5.3.1.26 was followed but using di(4-methylphenyl) diselenide **110b** instead of di(2-chlorophenyl) disulfide **110a**. Yield: 49%; white solid; mp: 87 - 89 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.78 (d, *J* = 8.2 Hz, 2H), 7.61 – 7.55 (m, 1H), 7.43 (dd, *J* = 7.7 Hz, 1.7 Hz, 1H), 7.33 – 7.22 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 2.32 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.8, 161.1, 142.6, 136.9, 134.7, 130.9, 130.6, 129.8, 127.9, 127.3, 126.9, 120.7, 21.7.; IR (KBr): 3098, 3016, 1652, 1594, 1548, 1492, 1462, 1268, 1142, 1021, 962, 832, 728, 707, 669 cm^{-1}; ESI-HRMS m/z: calcd. for $C_{15}H_{12}ClN_2OS$ $[M + H]^+$ 303.0353, found: 303.0357.

5.3.2. Control Experiments for the Study of Mechanism

5.3.2.1. Radical Trapping Through 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO)

In a Schlenk tube with a magnetic stirring bar, containing DMSO, the oxadiazole **92a** (0.5 mmol), diphenyl diselenide **109a** (0.26 mmol), was added K_2CO_3 (0.5 mmol) and TEMPO (0.5 mmol). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for 10 h After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 74%.

5.3.2.2. Reaction Between Oxadiazole 92a and Phenylselenium Bromide

In a Schlenk tube with a magnetic stirring bar, containing DMSO, the oxadiazole **92a** (0.5 mmol), phenylselenium bromide (0.5 mmol), was added K_2CO_3 (0.5 mmol). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for 10 h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 71%.

5.3.2.3. Reaction between oxadiazole 92a and diselenide 109a under inert atmosphere

In a Schlenk tube with a magnetic stirring bar was purged with argon, containing DMSO, the oxadiazole **92a** (0.5 mmol), diphenyl diselenide **109a** (0.26 mmol), was added K_2CO_3 (0.5 mmol). Positive pressure of argon kept constant throughout reaction time. The reaction

was placed in a pre-heated oil bath at 100 ºC for 10 h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 76%.

5.3.2.4. Control Addition for diphenyl diselenide 109a

In a Schlenk tube with a magnetic stirring bar, containing DMSO, the oxadiazole **92a** (0.5 mmol), was added K_2CO_3 (0.5 mmol). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere. After 10 minutes diphenyl diselenide **109a** (0.26 mmol) was added to the tube and reaction was further stirred for 10 h. After this, the mixture was diluted with ethyl acetate (30 mL) and washed with a saturated solution of NaCl (20 mL). After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 89%.

5.3.3. Scaling-up the Reaction

5.3.3.1. Reaction at oxadiazole 92a at 2.5 mmol scale

In a Schlenk tube with a magnetic stirring bar, containing DMSO (5 ml), the oxadiazole **92a** (2.5 mmol, 400 mg), diphenyl diselenide **109a** (1.28 mmol, 399 mg), was added K_2CO_3 (2.5 mmol, 345 mg). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for 10.5 h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 20 ml of saturated

solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (3 x 15 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 84%.

5.3.3.2. Reaction at oxadiazole 92a at 5 mmol scale

In a Schlenk tube with a magnetic stirring bar, containing DMSO (10 ml), the oxadiazole **92a** (5 mmol, 800 mg), diphenyl diselenide **109a** (2.55 mmol, 795 mg), was added K_2CO_3 (5 mmol, 690 mg). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for 11.5 h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 30 ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (3 x 20 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 84%.

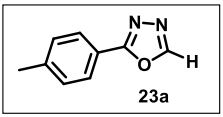
5.3.3.3. Reaction at oxadiazole 92a at 10 mmol scale

In a Schlenk tube with a magnetic stirring bar, containing DMSO (20 ml), the oxadiazole **92a** (10 mmol, 1600 mg), diphenyl diselenide **109a** (5.05 mmol, 1575 mg), was added K_2CO_3 (10 mmol, 1380 mg). The reaction was placed in a pre-heated oil bath at 100 ºC under open atmosphere for 10 h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 60 ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (3 x 60 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 82%.

5.3.4. General Procedure for the Selenium−Lithium Exchange Reaction and Trapping Lithium Intermediate with Different Electrophiles

To a two-necked round-bottomed flask with a magnetic stirring bar, under argon, containing a solution of **97l** (0.25 mmol) in THF (4 mL) at −78 °C was added dropwise *n*-BuLi (0.275 mmol, of a 2.5 M solution in hexane). The reaction mixture was stirred for 15 min and then was gradually added a solution of the appropriate electrophilic specie (0.275 mmol) in THF (2 mL), at −78 °C. The reaction mixture was allowed to stir at 25 °C for 1 h. After this time, the mixture was diluted in ethyl acetate (20 mL) and washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5).

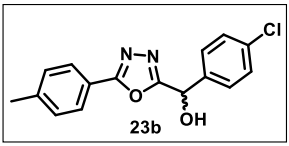
5.3.4.1. 2-(4-methylphenyl)-1,3,4-oxadiazole (117a).



23a

To a two-necked round-bottomed flask with a magnetic stirring bar, under argon, containing a solution of **97l** (0.25 mmol) in THF (4 mL) at −78 °C was added drop wise *n*-BuLi (0.275 mmol, of a 2.5 M solution in hexane). The reaction mixture was stirred for 15 min and then was gradually added a solution of the water (0.275 mmol) in THF (2 mL), at −78 °C. The reaction mixture was allowed to stir at 25 °C for 1 h. After this time, the mixture was diluted in ethyl acetate (20 mL) and washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 95%; white solid; mp: 89 - 92 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.49 (s, H), 7.95 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 2.41 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 165.0, 152.5, 142.7, 129.9, 127.1, 120.8, 21.7; IR (KBr): 3090, 3012, 1659, 1589, 1545, 1491, 1460, 1261, 1147, 1020, 963, 837, 729, 701, 667 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_9H_9ClN_2O$ $[M + H]^+$ 161.0709, found: 161.0708.

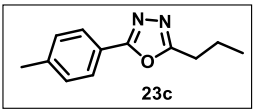
5.4.3.4.2. 2-(4-methylphenyl)-(4-chlorophenyl)-1,3,4-oxadiazol-5-yl)methanol (117b).



23b

To a two-necked round-bottomed flask with a magnetic stirring bar, under argon, containing a solution of **97l** (0.25 mmol) in THF (4 mL) at −78 °C was added dropwise *n*-BuLi (0.275 mmol, of a 2.5 M solution in hexane). The reaction mixture was stirred for 15 min and then was gradually added a solution of the 4-chlorobenzaldehyde (0.275 mmol) in THF (2 mL), at −78 °C. The reaction mixture was allowed to stir at 25 °C for 1 h. After this time, the mixture was diluted in ethyl acetate (20 mL) and washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 75%; white solid; mp: 94 - 87 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.80 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6,12 (s, 1H), 5.08 (s, 1H), 2.38 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.5, 165.7, 142.8, 136.5, 134.8, 129.8, 129.1, 128.1, 127.0, 120.5, 67.5, 21,7; IR (KBr): 3258, 3016, 1652, 1594, 1548, 1492, 1462, 1268, 1142, 1021, 962, 832, 728, 707, 669 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{16}H_{15}ClN_2O_2$ [M + H]$^+$ 301.0690, found: 301.0700.

5.4.3.4.3. 2-(4-methylphenyl)-5-propyl-1,3,4-oxadiazole (117c).



23c

To a two-necked round-bottomed flask with a magnetic stirring bar, under argon, containing a solution of **97l** (0.25 mmol) in THF (4 mL) at −78 °C was added dropwise *n*-BuLi (0.275 mmol, of a 2.5 M solution in hexane). The reaction mixture was stirred for 15 min and then was gradually added a solution of the n-propyl bromide (0.275 mmol) in THF (2 mL), at −78 °C. The reaction mixture was allowed to stir at 25 °C for 1 h. After this time, the mixture was diluted in ethyl acetate (20 mL) and washed with a saturated aqueous solution of NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 69%; Yellow liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.91 (d, J =

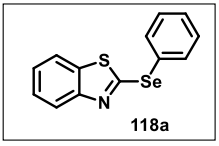
8.2 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 2.89 (t, *J* = 7.4, 2H) 2.41 (s, 3H), 1.88 (h, *J* = 7.4, 2H), 1.06 (t, *J* = 7.4, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 166.6, 161.1, 164.8, 142.0, 129.7, 126.7, 121.2, 27.3, 21.6, 20.1 13.6.; IR (KBr): 3085, 3009, 1648, 1587, 1540, 1485, 1469, 1274, 1138, 1029, 962, 837, 721, 709 cm^{-1}.; ESI-HRMS m/z: calcd. for $C_{12}H_{15}N_2O$ $[M + H]^+$ 203.79 found: 203.1180.

5.4. EXPERIMENTAL PROCEDURES FOR CHALCOGENATED BENZOTHIAZOLE

5.4.1. Experimental procedures for chalcogenated benzothiazole

Unless otherwise stated, all reactions were carried out in open atmosphere. In a Schlenk tube with a magnetic stirring bar, containing DMF (1 mL), the appropriate benzothiazole **95** (0.5 mmol), diorganyl dichalcogenide **109** or **110** (0.27 mmol), was added K_2CO_3 (0.75 mmol). The reaction was placed in a pre-heated oil bath at 120 ºC under open atmosphere for 12 h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase.

5.4.1.1. 2-(phenylselanyl)benzo[*d*]thiazole (118a).

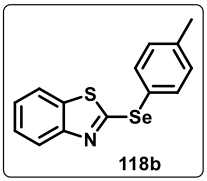


118a

In a Schlenk tube with a magnetic stirring bar, containing DMF (1 mL), the 1,3-benzothiazole **95a** (0.5 mmol, 67.5 mg), diphenyl diselenide **109a** (0.27 mmol, 84.9 mg), was added K_2CO_3 (0.75 mmol, 102.7 mg). The reaction was placed in a pre-heated oil bath at 120 ºC under open atmosphere for 12h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude

product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5).
Yield: 98%; Yellow solid; mp: 34 – 36 °C (lit. 35 – 36 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.95 – 7.78 (m, 3H), 7.74 – 7.58 (m, 1H), 7.52 – 7.34 (m, 4H), 7.33 – 7.13 (m, 1H).; ^{13}C NMR (5 MHz, $CDCl_3$) δ = 162.8, 154.5, 136.6, 130.1, 129.9, 126.5, 126.5, 124.4, 121.9, 120.8.

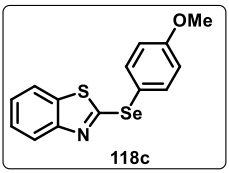
5.4.1.2. 2-(4-tolylselanyl)benzo[*d*]thiazole (118b).



118b

The experimental procedure similar to 5.4.1.1 was followed but using di(4-methylphenyl) diselenide **109b** instead of diphenyl diselenide **109a**. Yield: 90%; Yellow solid; mp: 52 – 53 °C (lit. 51 – 53 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.88 (d, J = 8.2 Hz, 1H), 7.76 – 7.51 (m, 3H), 7.44 – 7.27 (m, 2H), 7.18 (d, J = 7.8 Hz, 4H), 2.37 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 163.7, 154.6, 140.5, 136.7, 136.5, 130.7, 125.9, 124.1, 122.8, 121.8, 120.7, 21.4.

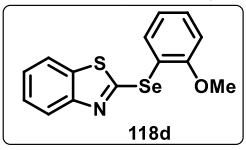
5.4.1.3. 2-(4-anisoylselanyl)benzo[*d*]thiazole (118c).



118c

The experimental procedure similar to 5.4.1.1 was followed but using di(4-methoxyphenyl) diselenide **109c** instead of diphenyl diselenide **109a**. Yield: 96%; Yellow solid; mp: 72 – 74 °C (lit. 75 – 77 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.90 (d, J = 8.0 Hz, 1H), 7.80 – 7.55 (m, 3H), 7.47 – 7.15 (m, 3H), 6.96 (d, J = 7.4 Hz, 2H), 3.86 (s, 1H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 161.5, 154.9, 138.8, 136.6, 126.1, 124.2, 121.9, 120.9, 116.8, 115.7, 55.5.; ESI-HRMS m/z: calcd. for $C_{14}H_{11}NOSSe$ $[M + H]^+$ 321.9799, found: 321.9796.

5.4.1.4. 2-(2-anisoylselanyl)benzo[*d*]thiazole (118d).

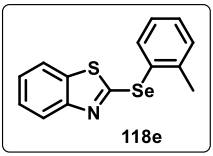


118d

The experimental procedure similar to 5.4.1.1 was followed but using di(2-methylphenyl) diselenide **109d** instead of diphenyl diselenide **109a**. Yield: 89%; Yellow solid; mp: 44 – 46 °C (lit. 47 – 49 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.76 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.20 – 7.09 (m, 4H), 2.32 (s, 3H), 2.29 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 161.8, 159.2, 154.7, 137.4, 137.0, 131.9, 126.0, 124.5, 122.2, 121.9, 120.9, 116.4,

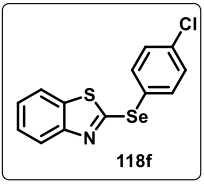
111.6, 56.2. ESI-HRMS m/z: calcd. for $C_{14}H_{11}NOSSe$ $[M + H]^+$ 321.9799, found: 321.9797.

5.4.1.5. 2-(2-tolylselanyl)benzo[*d*]thiazole (118e).



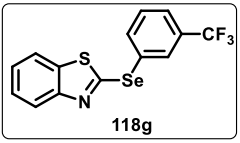
The experimental procedure similar to 5.4.1.1 was followed but using di(2-methylphenyl) diselenide **109e** instead of diphenyl diselenide **109a**. Yield: 92 %; Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ δ 7.97 – 7.73 (m, 2 H), 7.65 (d, J = 7.8 Hz, 1H), 7.53 – 7.31 (m, 3H), 7.32 – 7.16 (m, 2H), 2.54 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 163.1, 154.9, 143.1, 138.4, 136.7, 131.0, 131.0, 127.7, 127.4, 126.1, 124.3, 121.9, 120.9, 23.3.

5.4.1.6. 2-(4-chlorophenylselanyl)benzo[*d*]thiazole (118f).



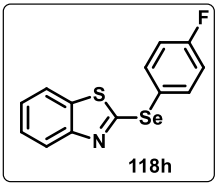
The experimental procedure similar to 5.4.1.1 was followed but using di(4-chlorophenyl) diselenide **109f** instead of diphenyl diselenide **109a**. Yield: 85%; Yellow solid; mp: 53 – 55 °C (lit. 54 – 56 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.92 (d, J = 8.1 Hz, 1H), 7.77 – 7.65 (m, 3H), 7.46 – 7.35 (m, 3H), 7.33 – 7.23 (m, 1H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 161.6, 154.6, 137.8, 136.8, 136.7, 130.3, 126.3, 124.8, 124.7, 122.2, 121.0.

5.4.1.7. 2-(3-(trifluoromethyl)phenylselanyl)benzo[*d*]thiazole (118g).



The experimental procedure similar to 5.4.1.1 was followed but using di(3-(trifluoromethyl)phenyl) diselenide **109g** instead of diphenyl diselenide **109a**. Yield: 68%; Yellow solid; mp: 64 – 67 °C (lit. 65 – 66 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = δ 8.11 (s, 1H), 8.05 – 7.89 (m, 2H), 7.79 – 7.69 (m, 2H), 7.61 – 7.50 (m, 1H), 7.50 – 7.39 (m, 1H), 7.38 – 7.28 (m, 1H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 160.0, 154.4, 139.4 (q, $J_{C\text{-}F}$ = 1 Hz), 136.8, 132.8 (q, $J_{C\text{-}F}$ = 3.5 Hz),132.3 (q, $J_{C\text{-}F}$ = 32.5 Hz), 130.3, 127.8, 126.7 (q, $J_{C\text{-}F}$ = 3.5 Hz), 126.4, 124.9, 123.5 (q, $J_{C\text{-}F}$ = 271.5 Hz), 122.4, 121.0..

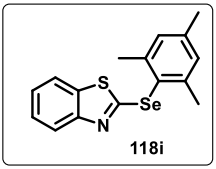
5.4.1.8. 2-(4-fluorophenylselanyl)benzo[*d*]thiazole (118h).



118h

The experimental procedure similar to 5.4.1.1 was followed but using di(4-fluorophenyl) diselenide **109h** instead of diphenyl diselenide**109a**. Yield: 79%; Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.90 (d, J = 8.0 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.67 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 8.1 Hz, 2H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 164.1 (d, $J_{C\text{-}F}$ = 249.5 Hz), 162.6, 154.6, 139.0 (d, $J_{C\text{-}F}$ = 8.5 Hz), 136.5, 126.2, 124.5, 122.0, 121.3 (d, $J_{C\text{-}F}$ = 4 Hz), 120.9, 117. 6 (d, $J_{C\text{-}F}$ = 21.5 Hz).

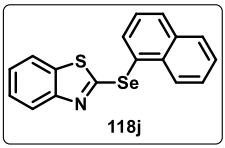
5.4.1.9. 2-(mesitylsenalyl)benzo[d]thiazole (118i).



118i

The experimental procedure similar to 5.4.1.1 was followed but using dimesityl diselenide **109i** instead of diphenyl diselenide **109a**. Yield: 98%; Yellow solid; mp: 97 – 99 °C (lit. 96 – 98 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.88 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.44 – 7.29 (m, 1H), 7.28 – 7.13 (m, 1H), 7.06 (s, 2H), 2.53 (s, 6H), 2.35 (s, 3H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 164.4, 155.2, 144.2, 141.1, 136.4, 129.4, 126.0, 125.7, 123.9, 121.6, 120.8, 24.4, 21.3.

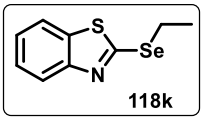
5.4.1.10. 2-(napthylselanyl)benzo[*d*]thiazole (118j).



118j

The experimental procedure similar to 5.4.1.1 was followed but using dinaphthalen-1,1'-diselenide **109j** instead of diphenyl diselenide **109a**. Yield: 72 %; Yellow solid; mp: 66 – 68 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.45 (dd, J = 6.0, 3.7 Hz, 1H), 8.13 (dd, J = 7.1, 1.1 Hz, 1H), 7.99 (d, J = 8.2 Hz, 1H), 7.92 – 7.84 (m, 2H), 7.58 – 7.28 (m, 6H), 7.22 – 7.12 (m, 1H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 163.1, 154.6, 137.7, 136.6, 134.8, 134.4, 131.9, 128.8, 128.0, 127.9, 126.9, 126.1, 126.0, 125.8, 124.2, 121.9, 120.8. ESI-HRMS m/z: calcd. for $C_{17}H_{11}NSSe$ $[M + H]^+$ 341.9850, found: 341.9856.

5.4.1.11. 2-(ethylselanyl)benzo[*d*]thiazole (118k).

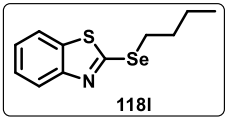


118k

The experimental procedure similar to 5.4.1.1 was followed but using diethyl diselenide **109b** instead of diphenyl diselenide **109a**. Yield: 80 %; Yellow oil ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.93 (d, J = 8.1 Hz, 1H), 7.80 (d, J = 7.1 Hz, 1H), 7.51 – 7.22 (m, 3H), 3.36 (q, J = 7.5 Hz,

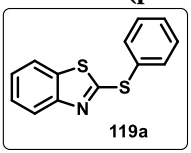
2H), 1.63 (t, J = 7.5 Hz, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 159.1, 154.2, 136.6, 126.1, 124.4, 121.8, 121.0, 22.9, 15.8.

5.4.1.12. 2-(butylselanyl)benzo[*d*]thiazole (118l).



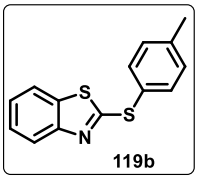
The experimental procedure similar to 5.4.1.1 was followed but using dibutyl diselenide **109b** instead of diphenyl diselenide **109a**. Yield: 78%; Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.91 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.44 – 7.18 (m, 3H), 3.33 (t, J = 7.3 Hz, 2H), 1.85 (p, J = 7.3 Hz, 2H), 1.46 (dq, J = 14.2, 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 159.3, 154.1, 136.4, 125.9, 124.2, 121.7, 120.9, 32.3, 28.8, 23.0, 13.6.

5.4.1.13. 2-(phenylthio)benzo[*d*]thiazole (119a).



In a Schlenk tube with a magnetic stirring bar, containing DMF (1 mL), the 1,3-benzothiazole **95a** (0.5 mmol, 67.5 mg), diphenyl disulfide **110a** (0.26 mmol, 57 mg), was added K_2CO_3 (0.75 mmol, 102.7 mg). The reaction was placed in a pre-heated oil bath at 120 ºC under open atmosphere for 12h. After completion of the reaction, the tube was removed from oil bath and left outside to gain room temperature and then the reaction mixture was quenched by addition of 5ml of saturated solution of NaCl (brine). Subsequently, the mixture was extracted with ethyl acetate (2 x 10 mL). The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed on rotary-evaporator under vacuum, affording crude product. The crude was purified by column chromatography using flash silica as stationary phase and eluted with a mixture of hexane / ethyl acetate as mobile phase (95:5). Yield: 68 %; Yellow solid; mp: 32 – 34 °C (lit. 30 – 31 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.88 (d, J = 8.1 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.64 (d, J = 7.8 Hz, 1H), 7.52 – 7.36 (m, 4H), 7.32 – 7.19 (m, 1H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 169.8, 154.0, 135.6, 135.5, 130.6, 130.2, 130.0, 126.3, 124.4, 122.1, 120.9.

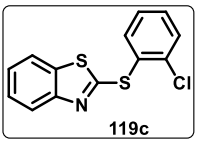
5.4.1.4. 2-(4-tolylthio)benzo[*d*]thiazole (119b).



The experimental procedure similar to 5.4.1.13 was followed but using di(4-methylphenyl) disulfide **110b** instead of diphenyl disulifde **110a**. Yield: 77 %; Yellow solid; mp: 52 – 53 °C (lit. 51 – 53 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.76 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.20 – 7.09 (m, 4H), 2.32 (s,

3H), 2.29 (s, 3H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.4, 156.2, 142.4, 140.1, 135.4, 130.7, 129.8, 126.9, 120.9, 120.7, 21.8, 21.4.

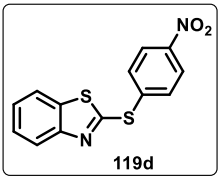
5.4.1.15. 2-(2-chlorophenylthio)benzo[*d*]thiazole (119c).



119c

The experimental procedure similar to 5.4.1.13 was followed but using di(2-chlorophenyl) disulfide**110c**instead of diphenyl disulfide **110a.** Yield: 61%; Yellow solid; mp: 35 – 37 °C (lit. 35 – 37 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 7.9 Hz, 6H), 7.48 – 7.16 (m, 8H).; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 170.9, 154.1, 141.3, 135.7, 135.5, 130.9, 126.3, 126.2, 124.3, 121.9, 120.8.

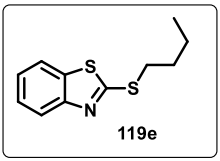
5.4.1.16. 2-(4-nitrophenylthio)benzo[*d*]thiazole (119d).



119d

The experimental procedure similar to 5.4.1.13 was followed but using di(4-nirophenyl) disulfide **110d** instead of diphenyl disulfide **110a.** Yield: 54 %; Yellow solid; mp: 121 – 123 °C (lit. 123 – 125 °C)[102]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.24 – 8.17 (m, 3H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.36 – 7.32 (m, 1H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 144.2, 142.8, 134.7, 131.8, 131.3, 128.5, 128.4, 126.6, 124.8, 124.6, 124.4.

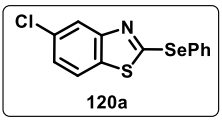
5.4.1.17. 2-(butylthio)benzo[*d*]thiazole (119e).



119e

The experimental procedure similar to 5.4.1.13 was followed but using dibutyl disulfide **110e** instead of diphenyl disulfide **110a**. Yield: 74 %; Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.29 – 7.22 (m, 1H), 3.35 (t, J = 7.3 Hz, 2H), 1.80 (p, J = 7.4 Hz, 2H), 1.57 – 1.44 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 167.4, 156.2, 142.4, 140.1, 135.4, 130.7, 129.8, 126.9, 120.9, 120.7, 21.8, 21.4.

5.4.1.18. 6-chloro-2-(phenylselanyl)benzo[*d*]thiazole (120a).

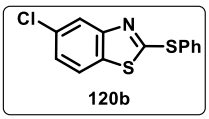


120a

The experimental procedure similar to 5.4.1.1 was followed but using 5-chloro-1,3-benzothiazole **95b** instead of 1,3-benzothiazole **95a**. Yield: 72 %; Yellow solid; mp: 84 – 86 °C (lit. 84 – 86 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.29 – 7.22 (m, 1H),

3.35 (t, *J* = 7.3 Hz, 2H), 1.80 (p, J = *7*.4 Hz, 2H), 1.57 – 1.44 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.4, 153.6, 135.4, 126.1, 124.2, 121.7, 121.0, 33.5, 31.5, 22.1, 13.7.

5.4.1.19. 6-chloro-2-(phenylthio)benzo[*d*]thiazole (120b).



120b

The experimental procedure similar to 5.4.1.13 was followed but using 5-chloro-1,3-benzothiazole **95b** instead of 1,3-benzothiazole **95a**. Yield: 49 %; Yellow solid; mp: 38– 40 °C (lit. 35 – 37 °C)[102]. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.80 – 7.70 (m, 3H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.36 (dd, *J* = 8.7, 2.0 Hz, 1H)..; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 170.7, 152.6, 136.8, 135.6, 130.9, 130.4, 130.2, 129.6, 127.0, 122.7, 120.6.

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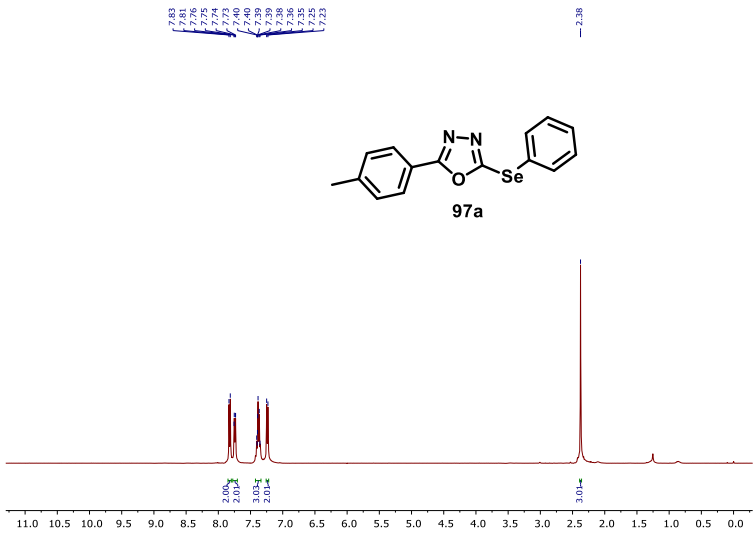
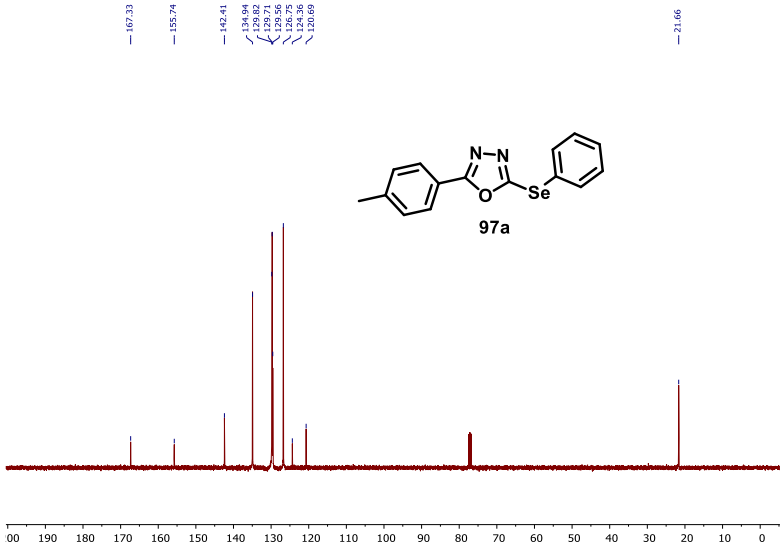
Spectroscopic Section



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **97a**



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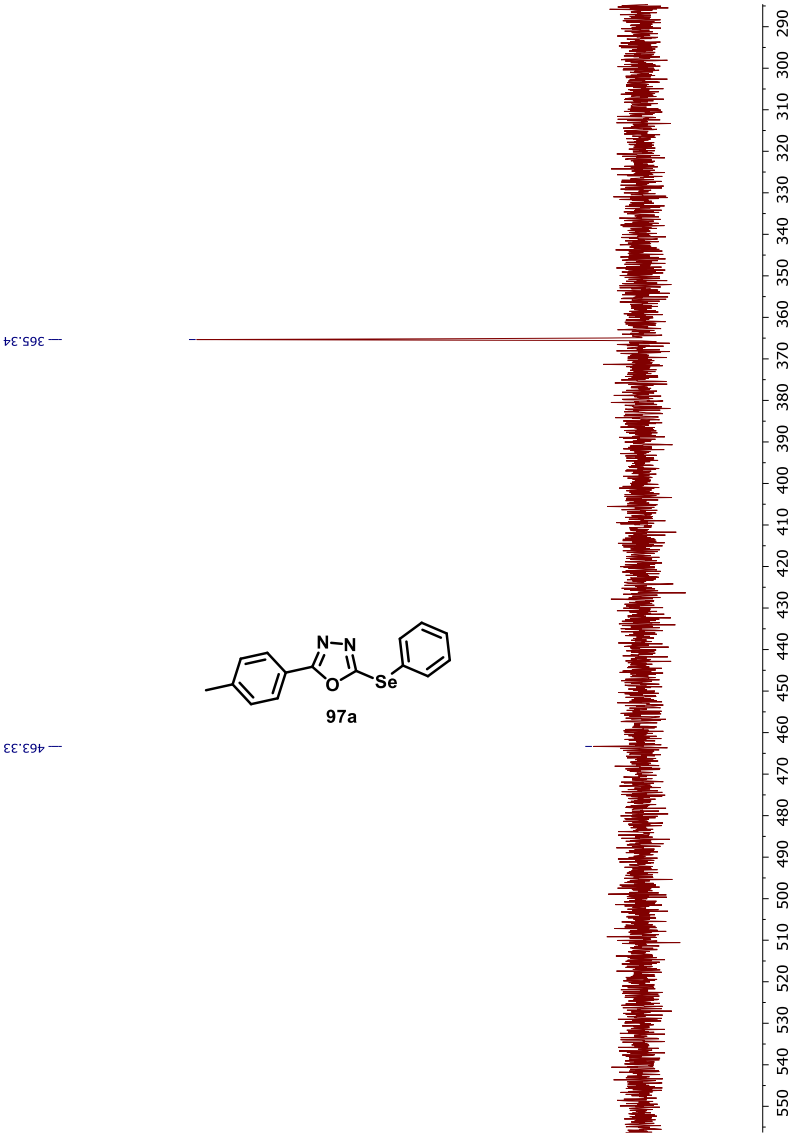

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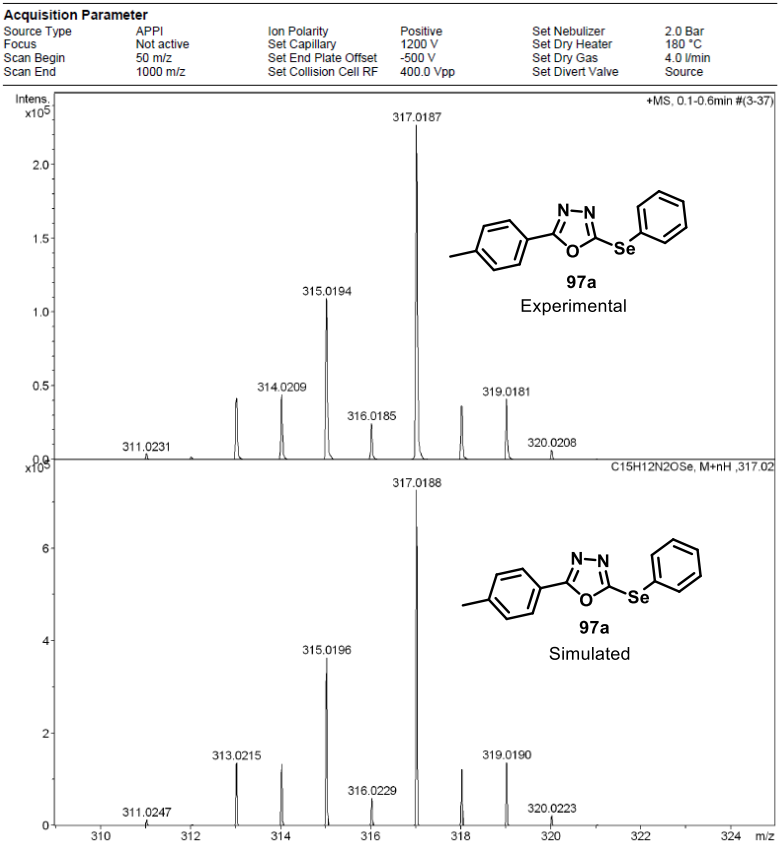
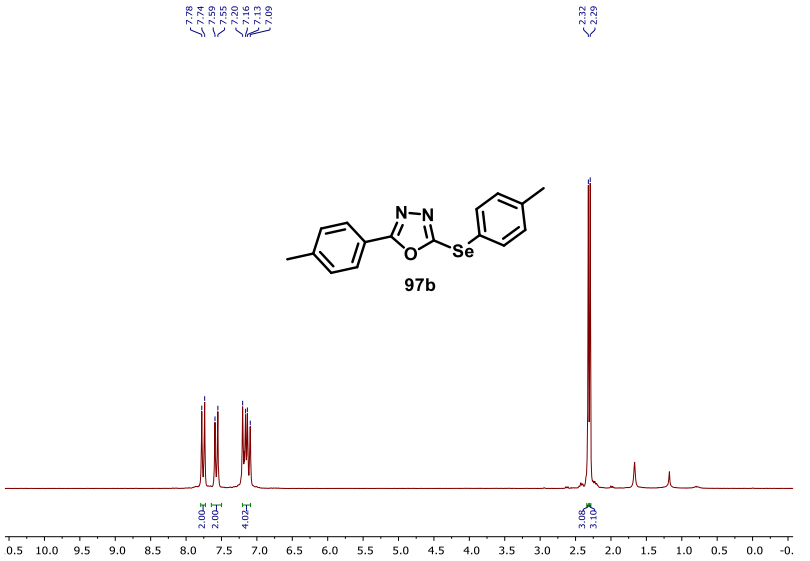
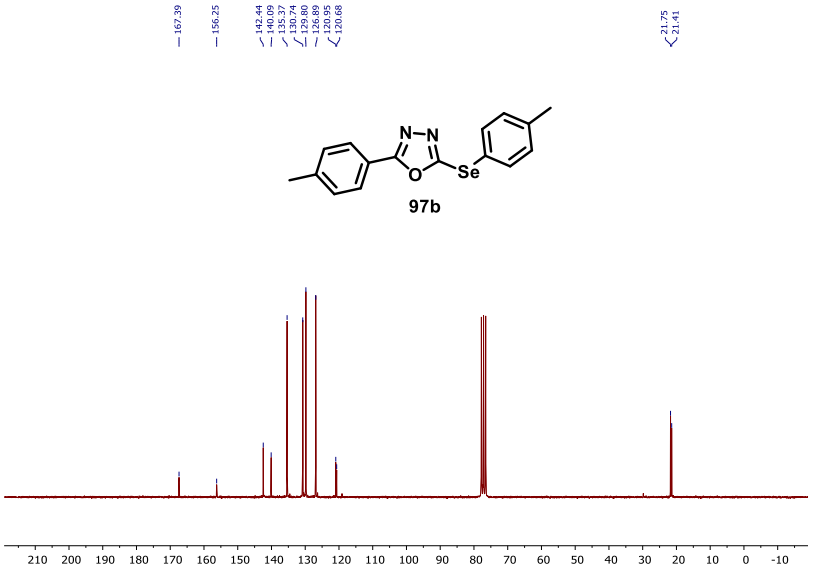


High-resolution mass spectrum of compound **97a**



^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97b**



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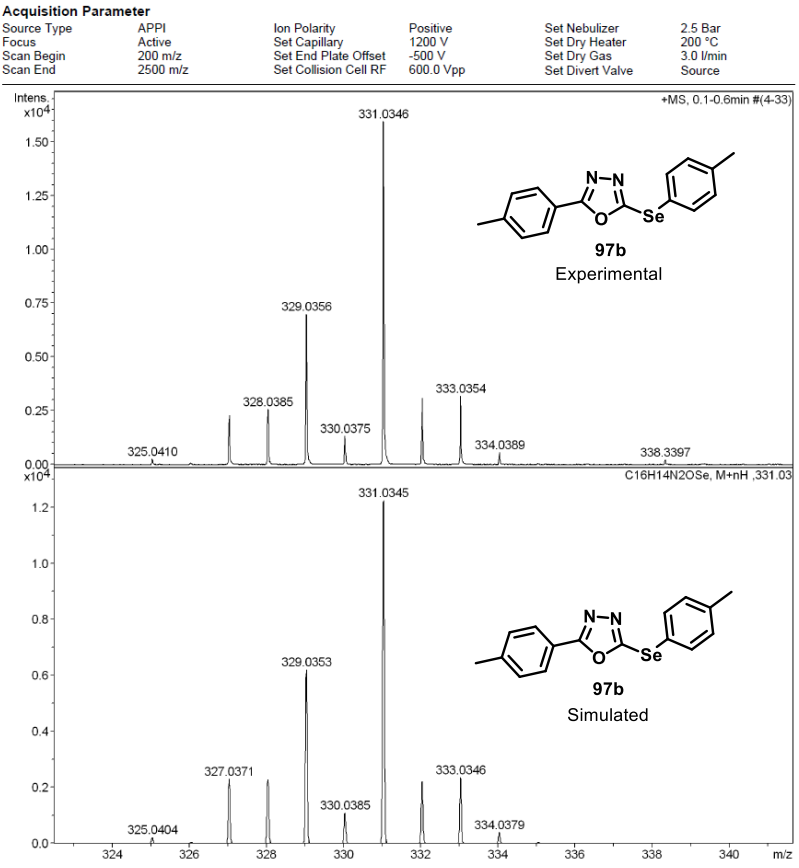
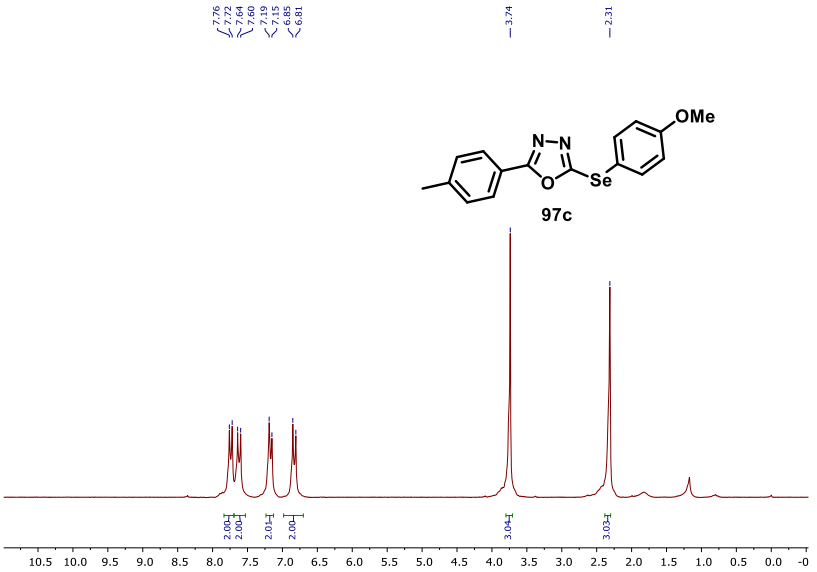


High-resolution mass spectrum of compound **97b**



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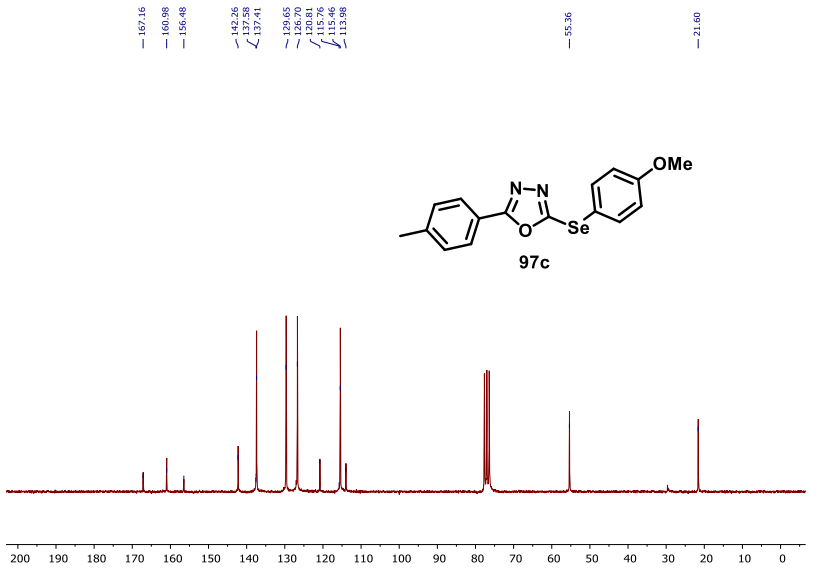
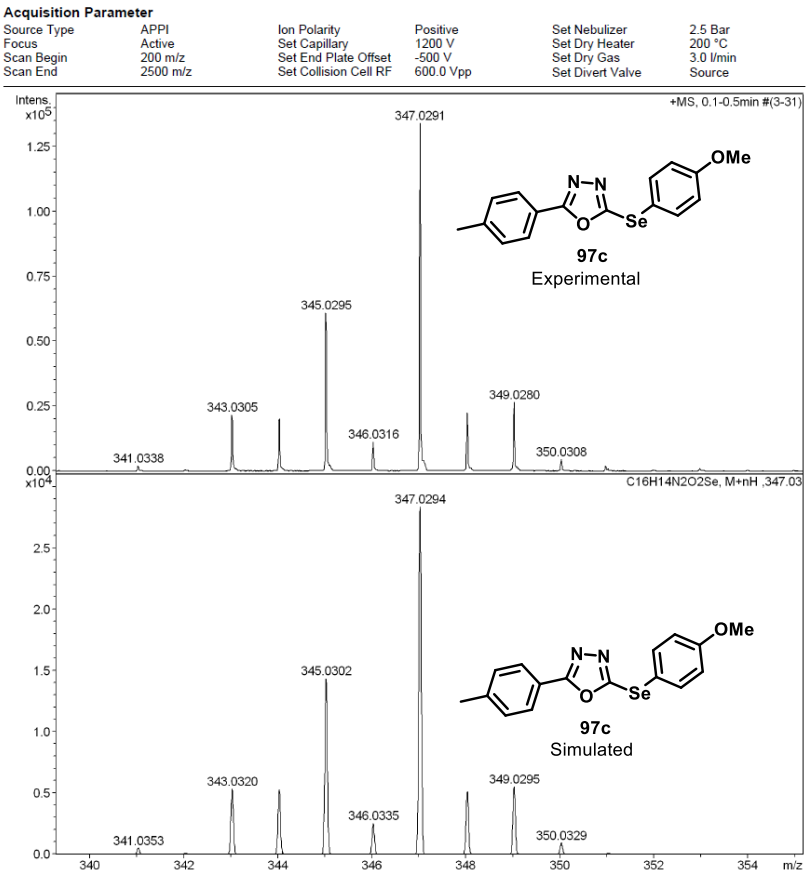
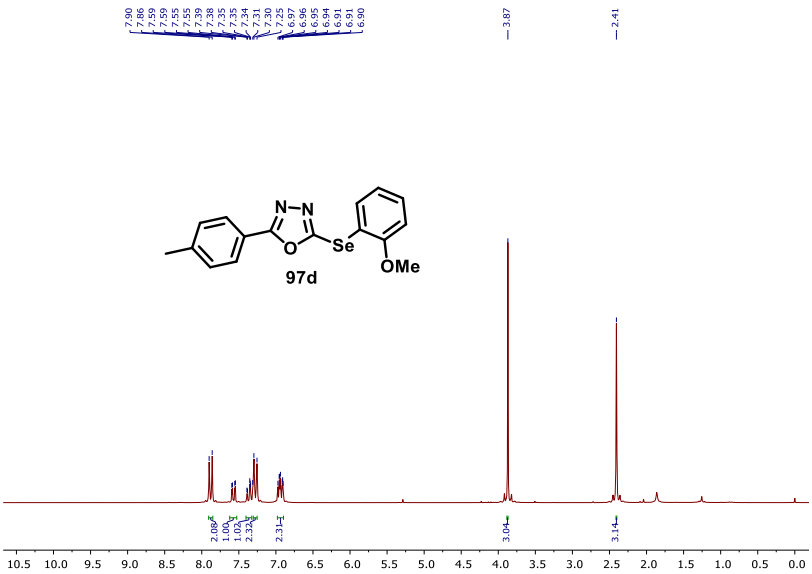


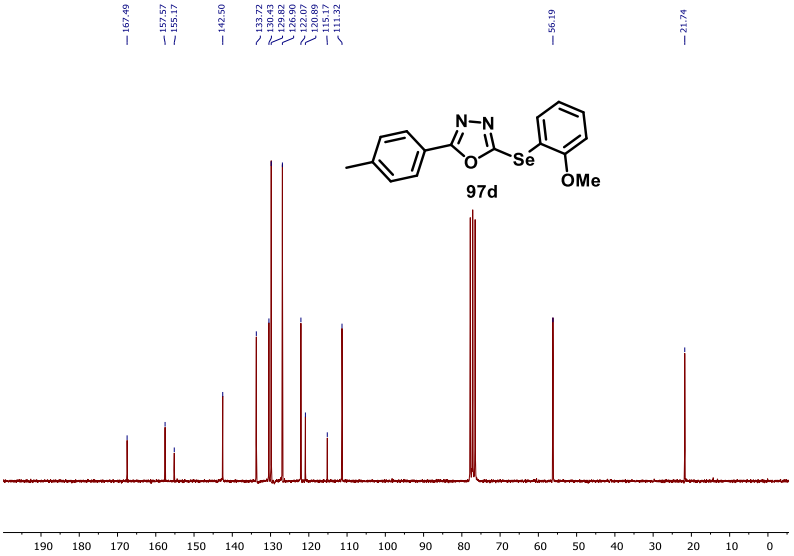
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97c**



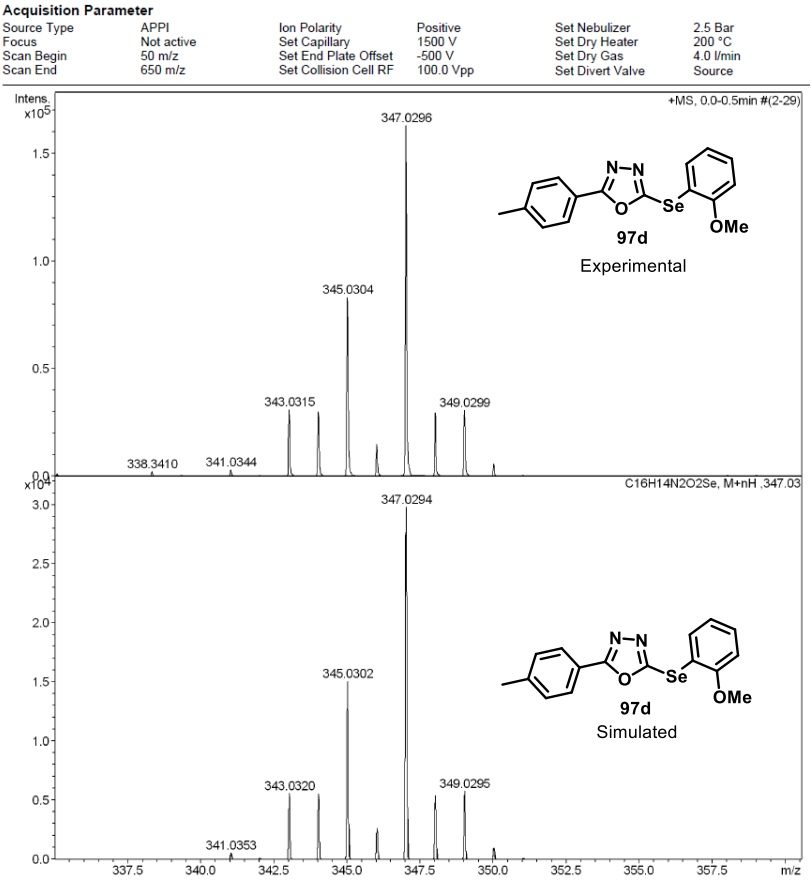
High-resolution mass spectrum of compound **97c**



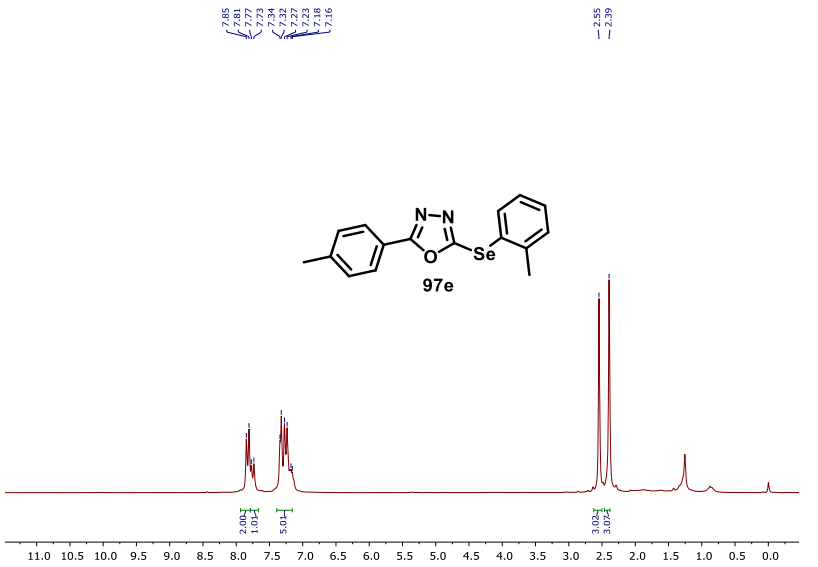
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97d**



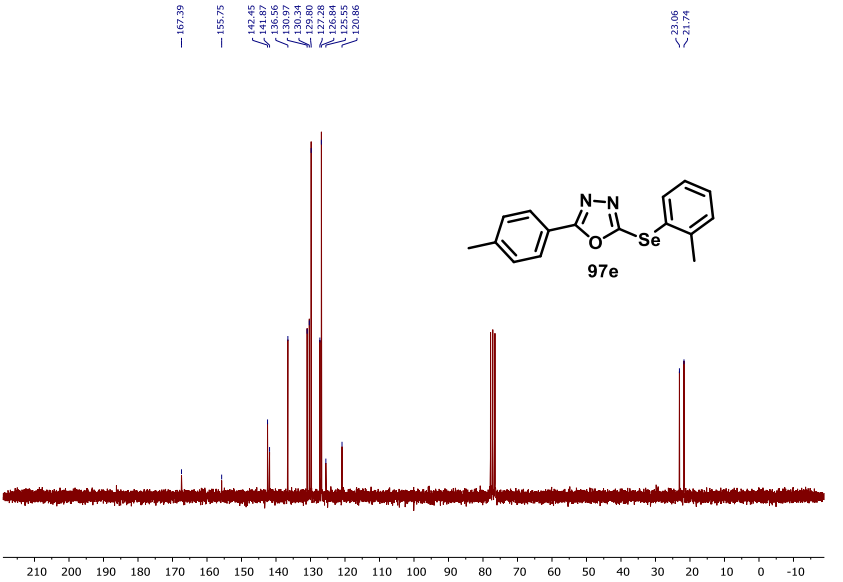
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97d**



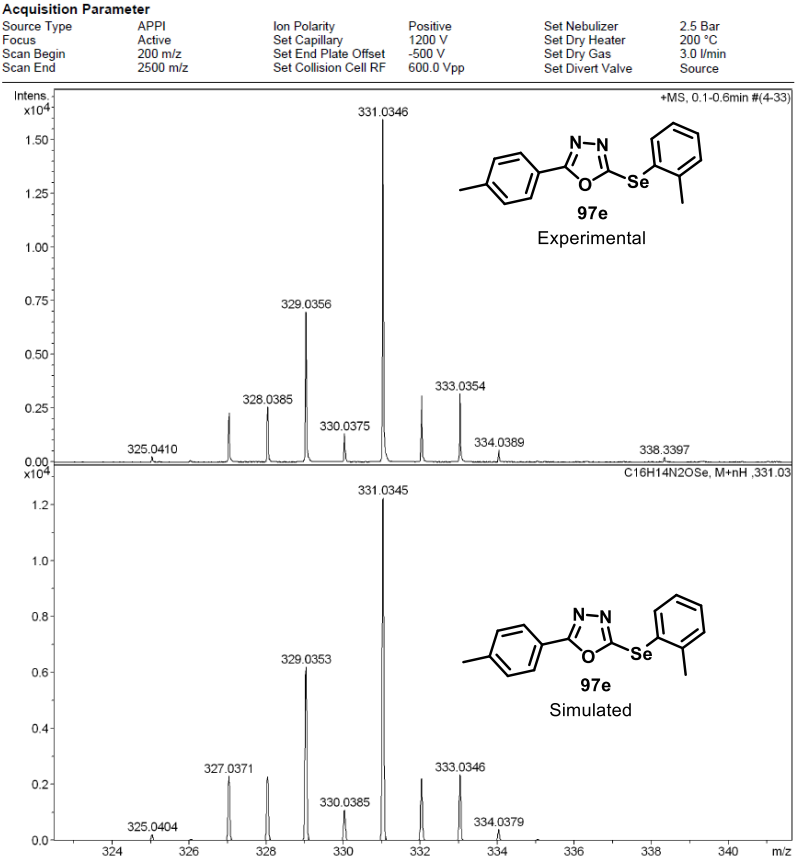
High-resolution mass spectrum of compound **97d**



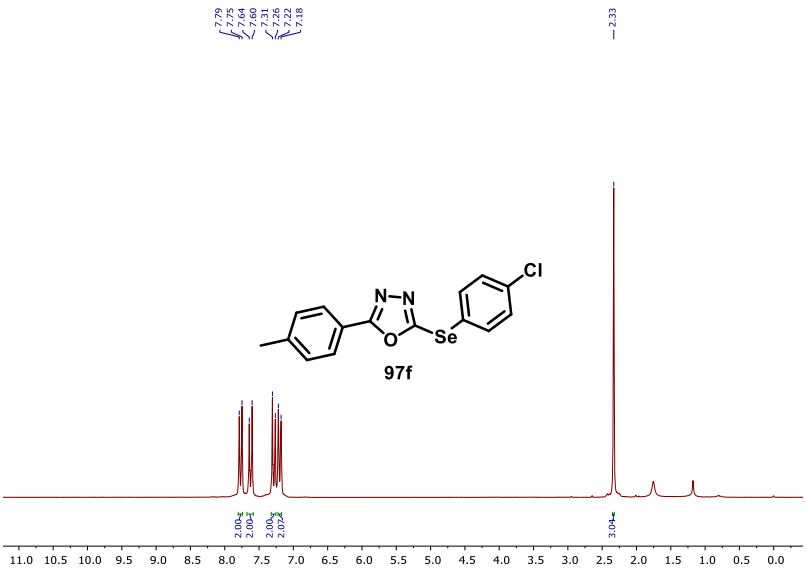
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97e**



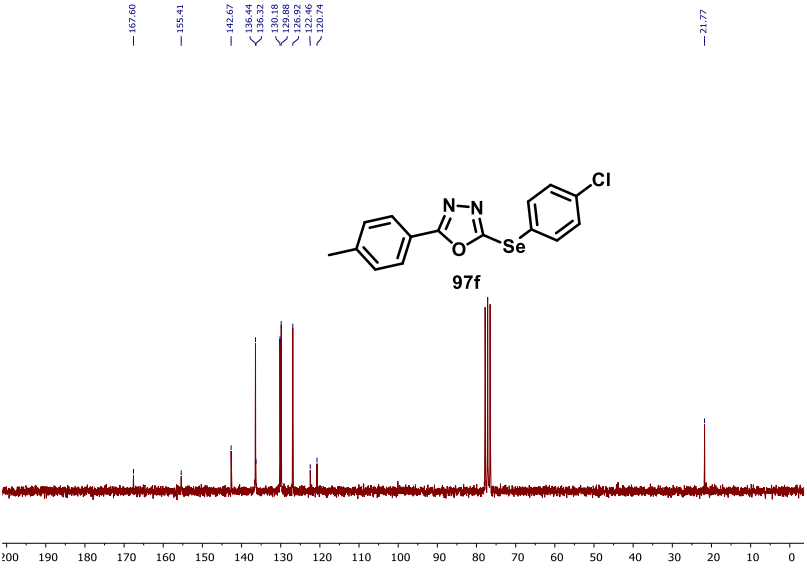
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97e**



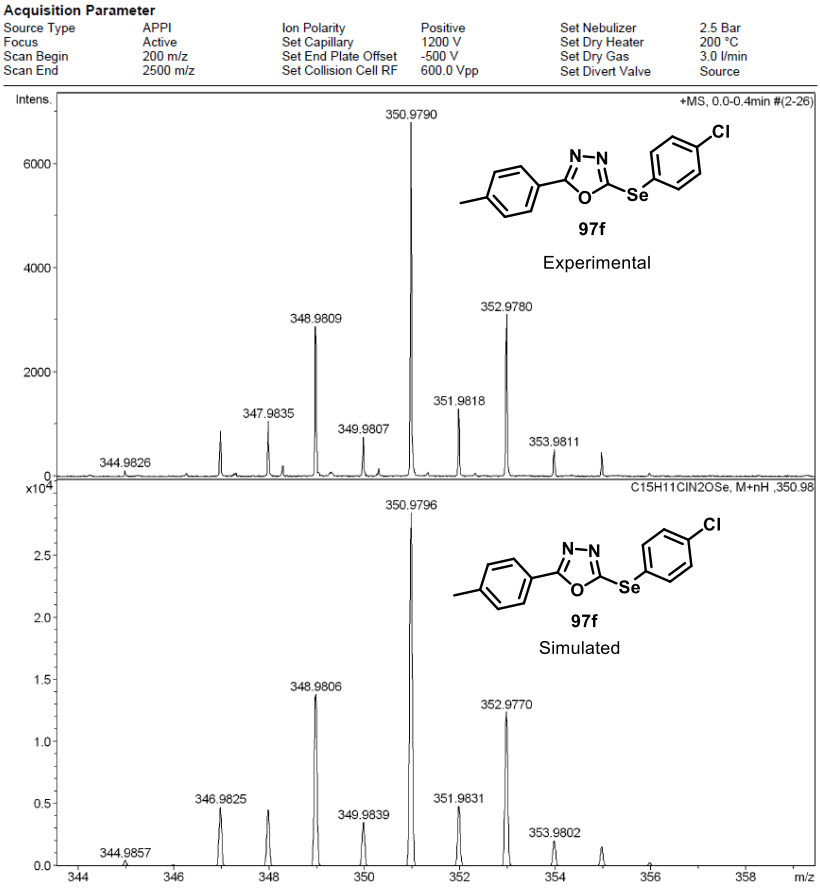
High-resolution mass spectrum of compound **97e**



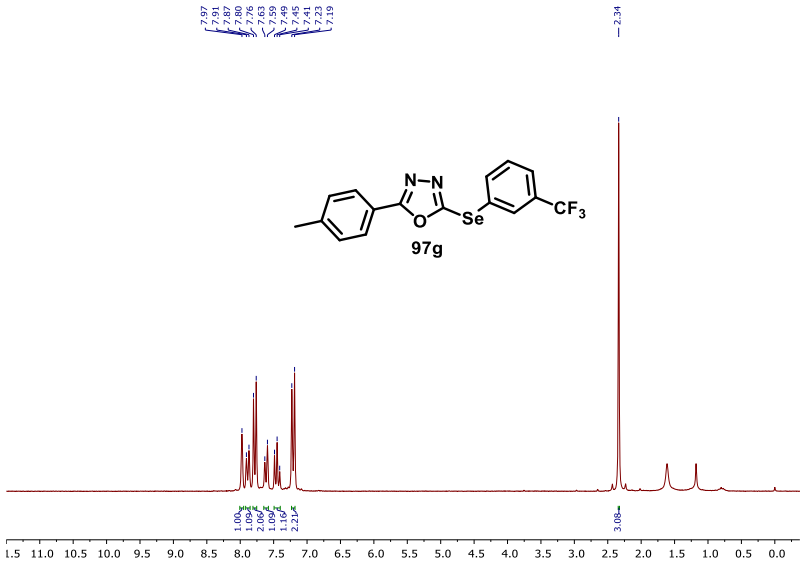
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **3f**



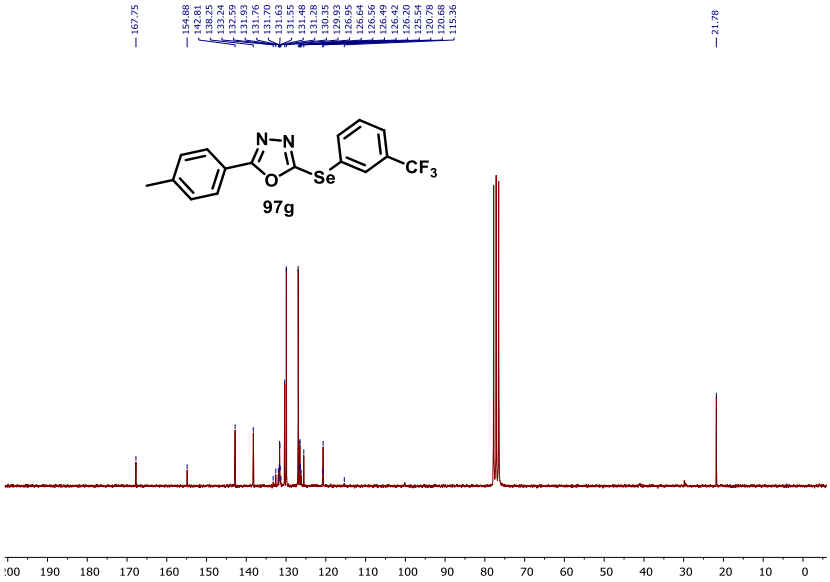
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97f**



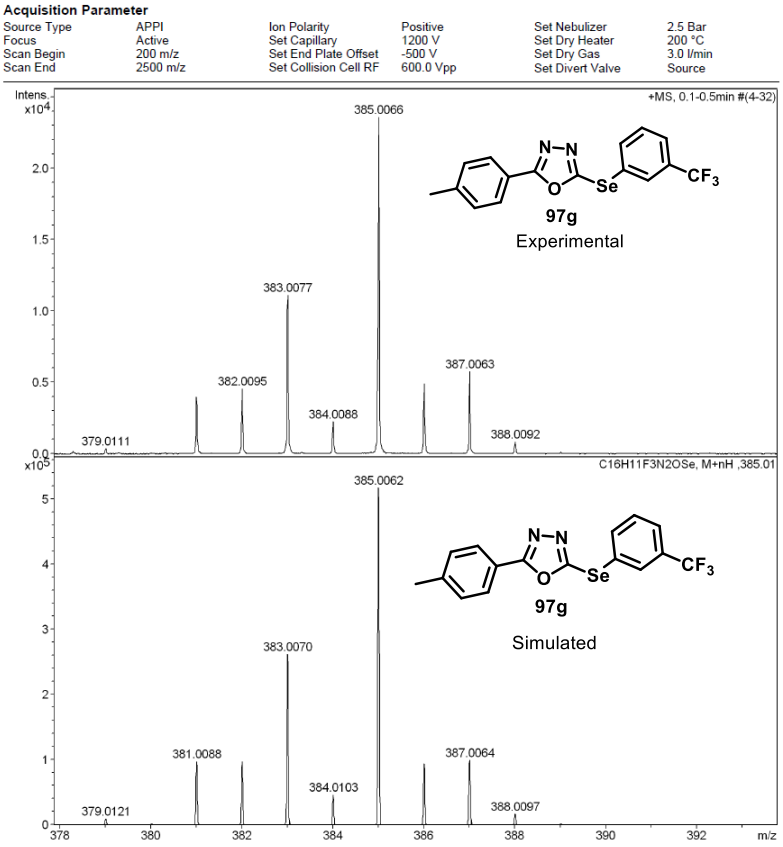
High-resolution mass spectrum of compound **97f**



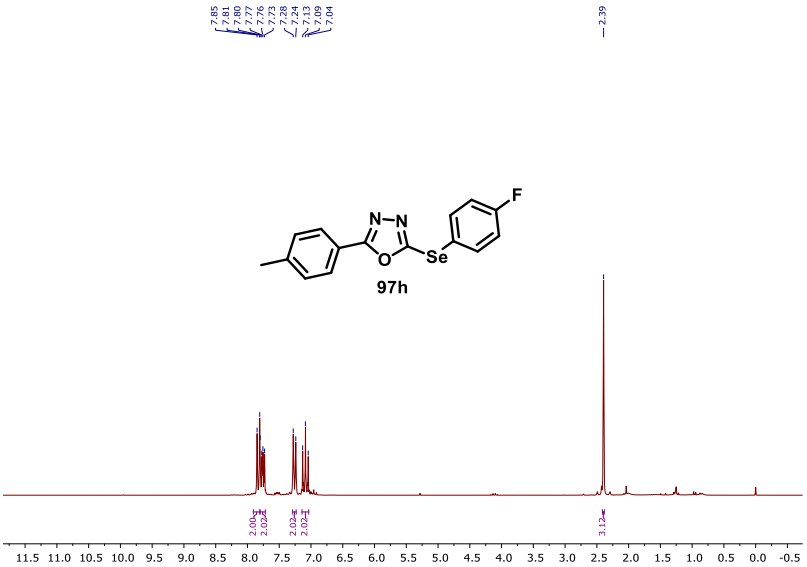
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97g**



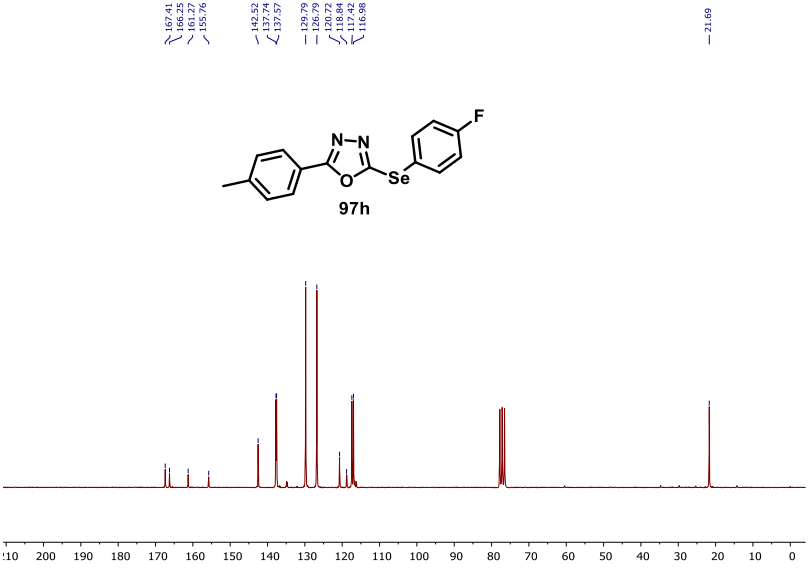
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97g**



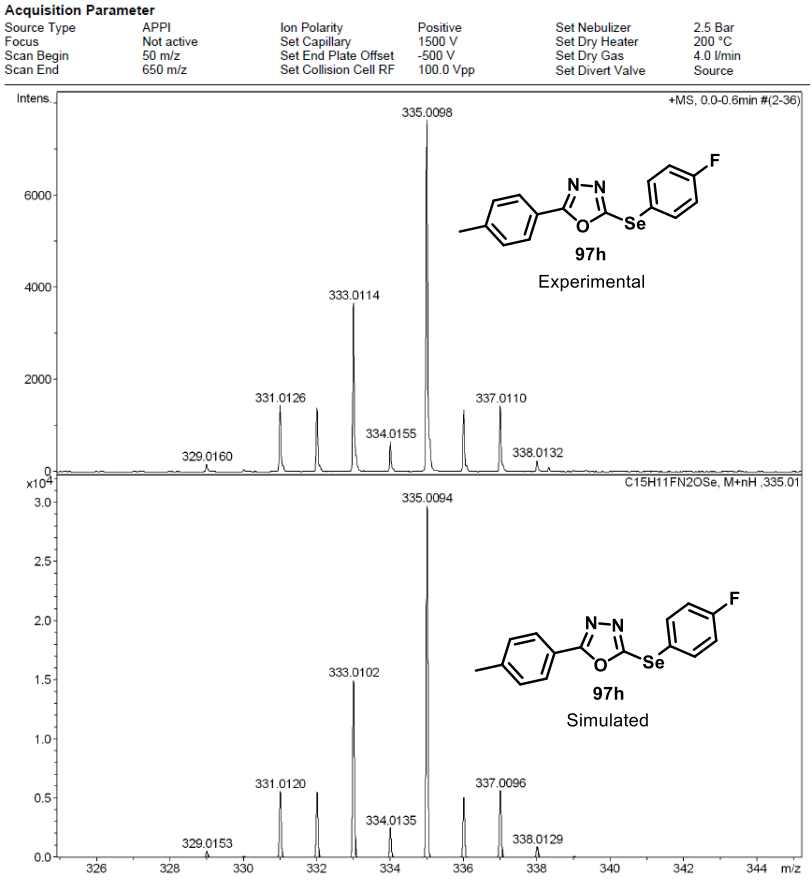
High-resolution mass spectrum of compound **97g**



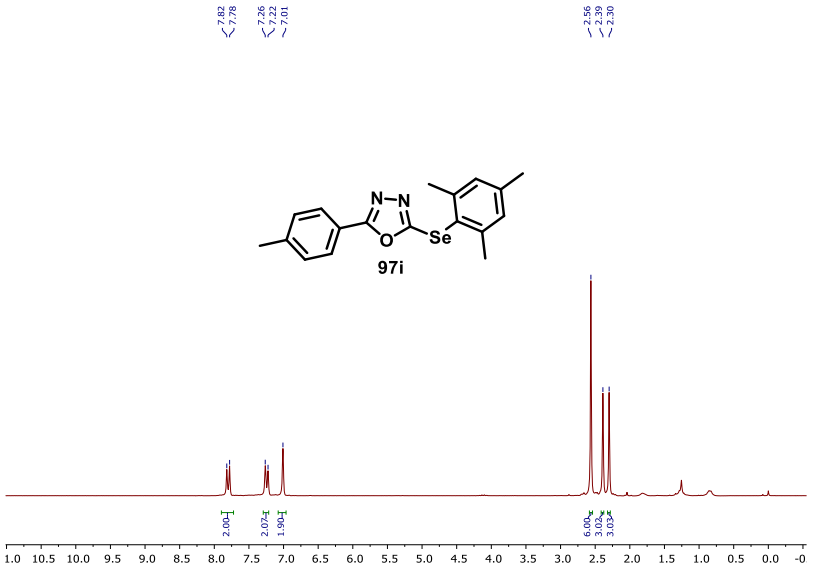
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97h**



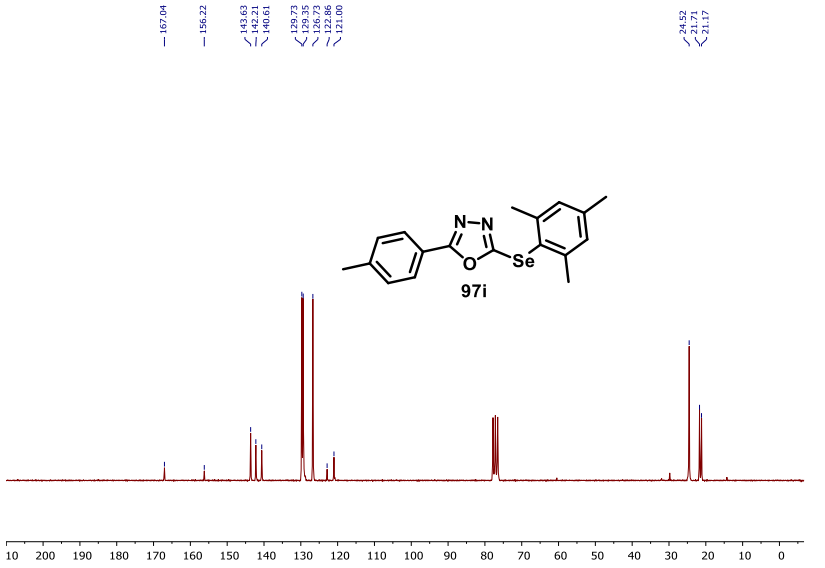
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97h**



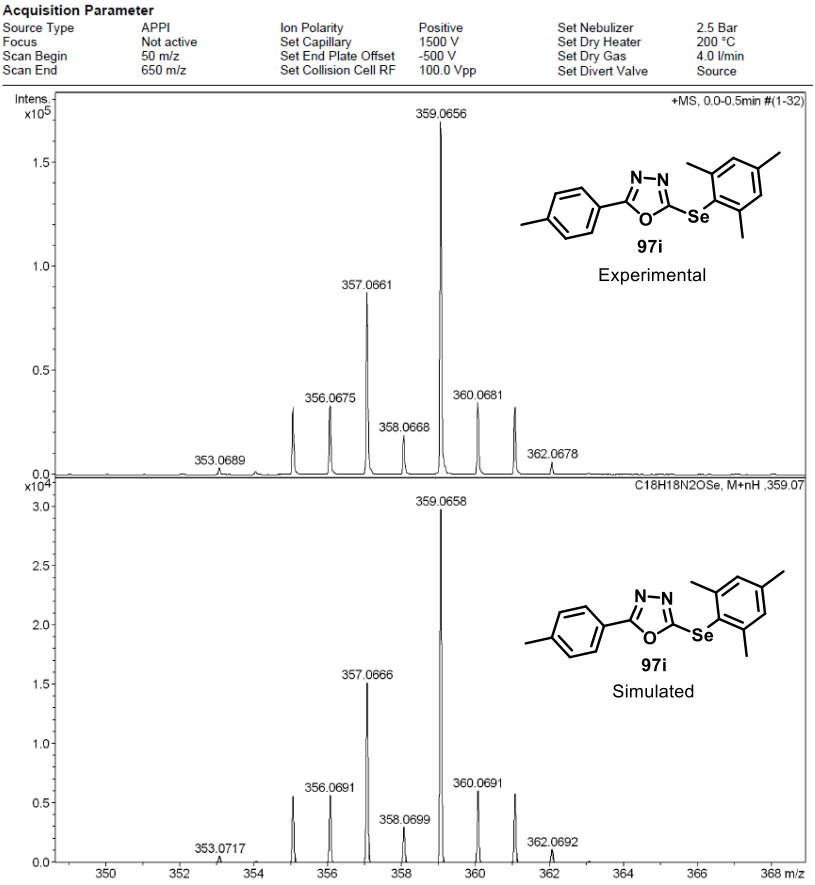
High-resolution mass spectrum of compound **97h**



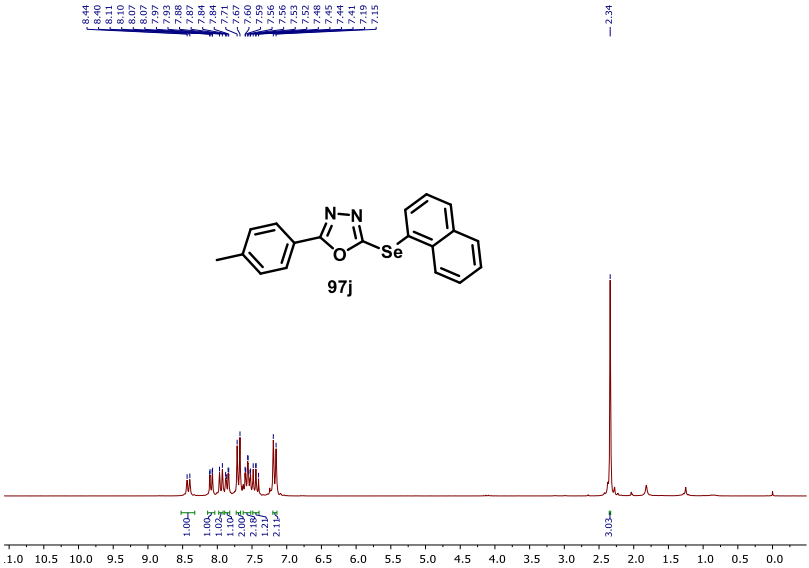
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97i**



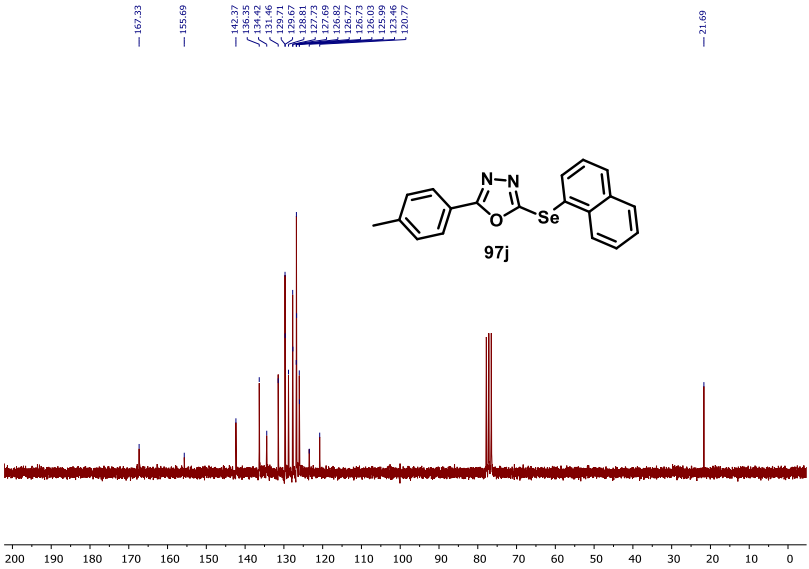
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97i**



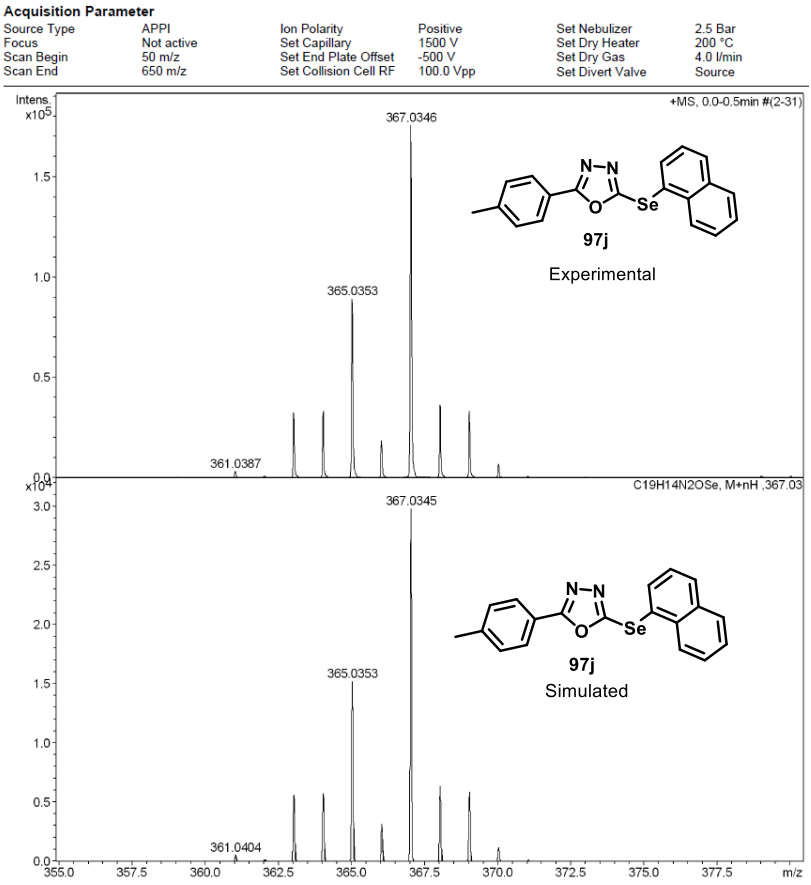
High-resolution mass spectrum of compound **97i**



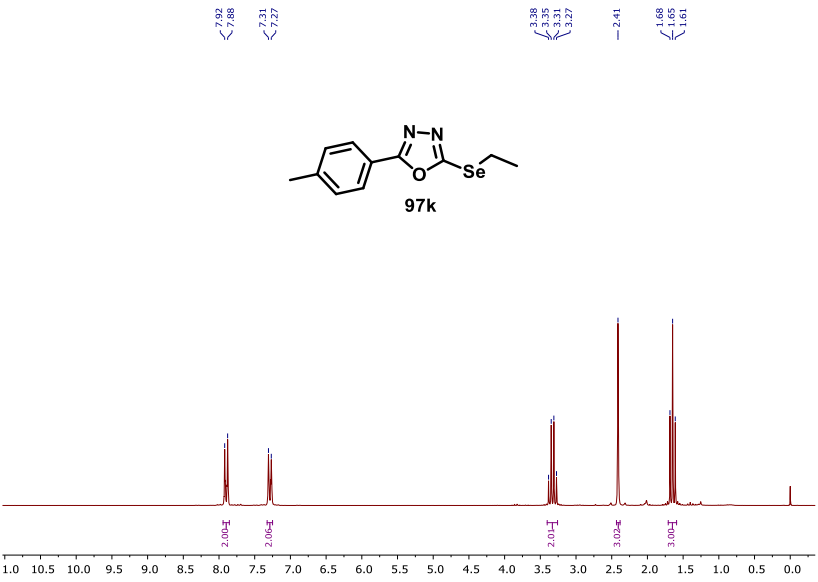
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97j**



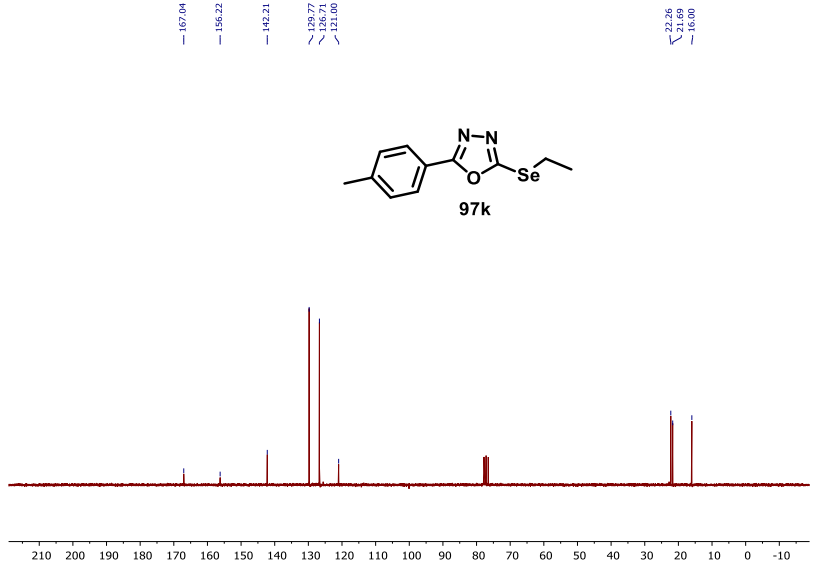
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97j**



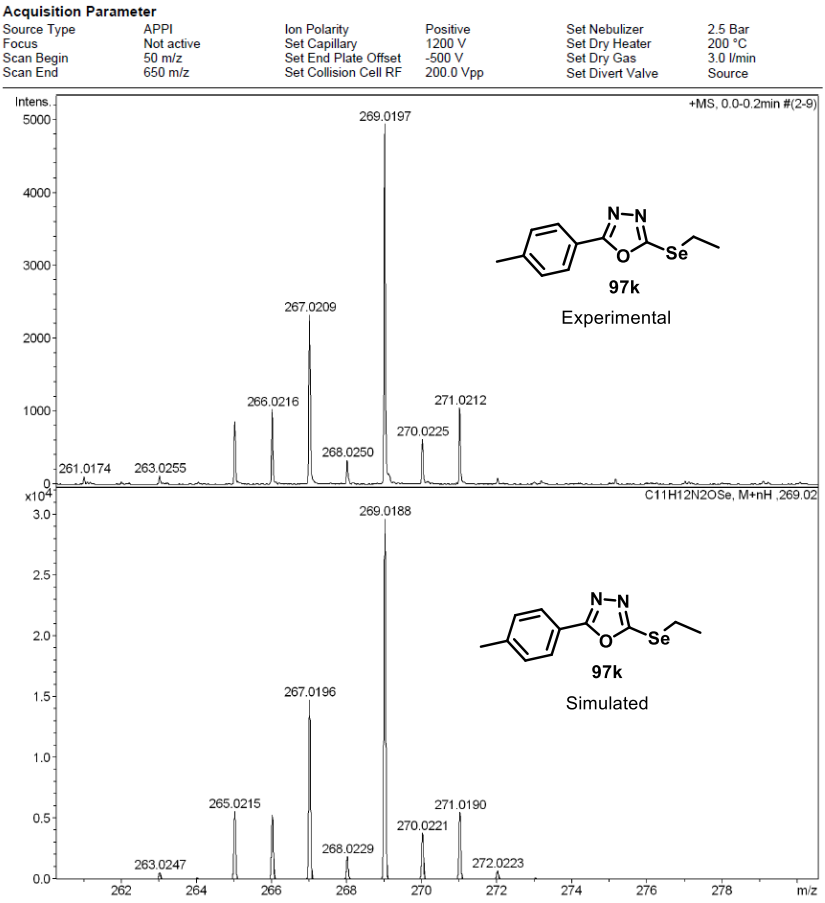
High-resolution mass spectrum of compound **97j**



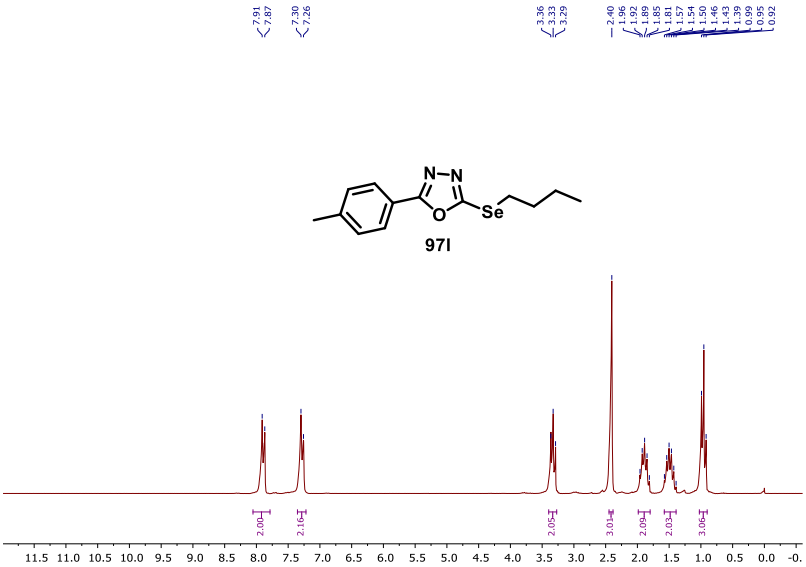
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97k**



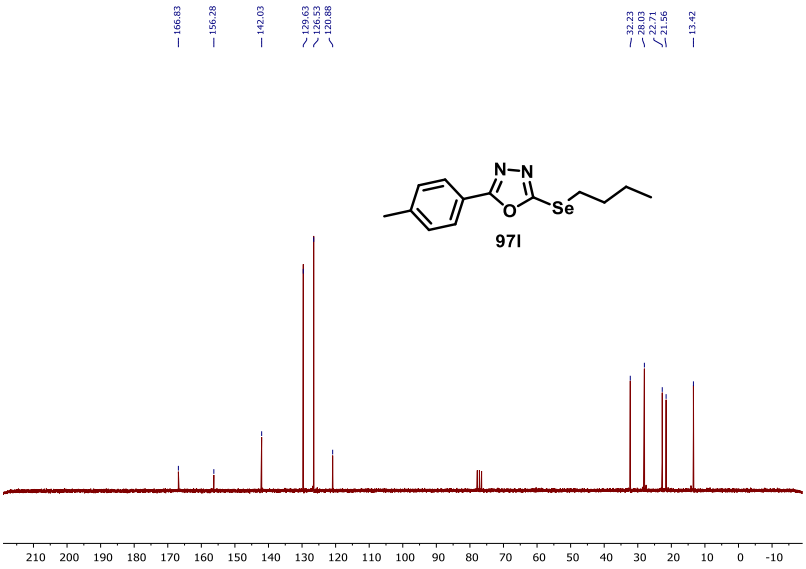
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97k**



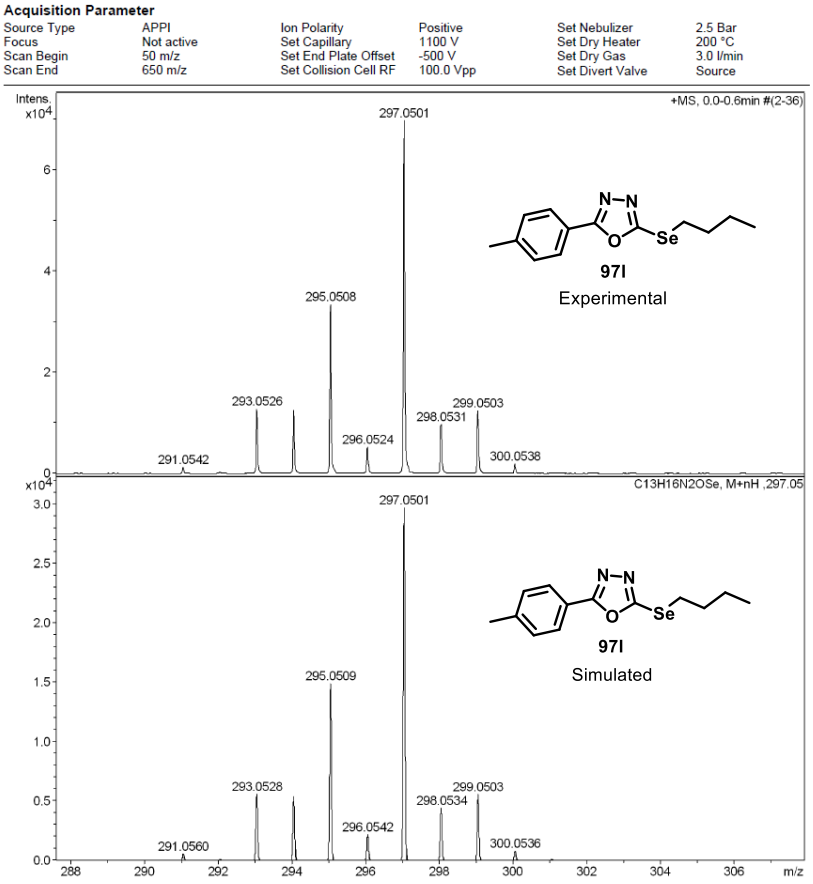
High-resolution mass spectrum of compound **97k**



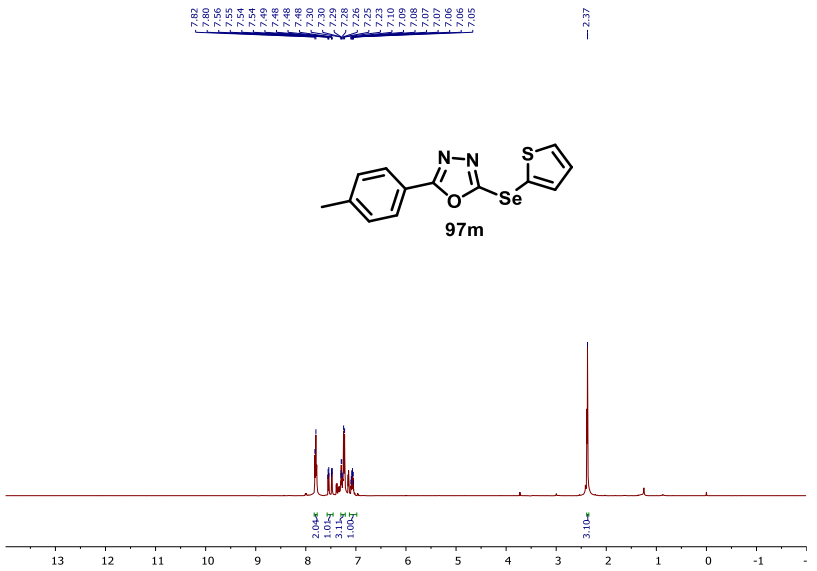
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97l**



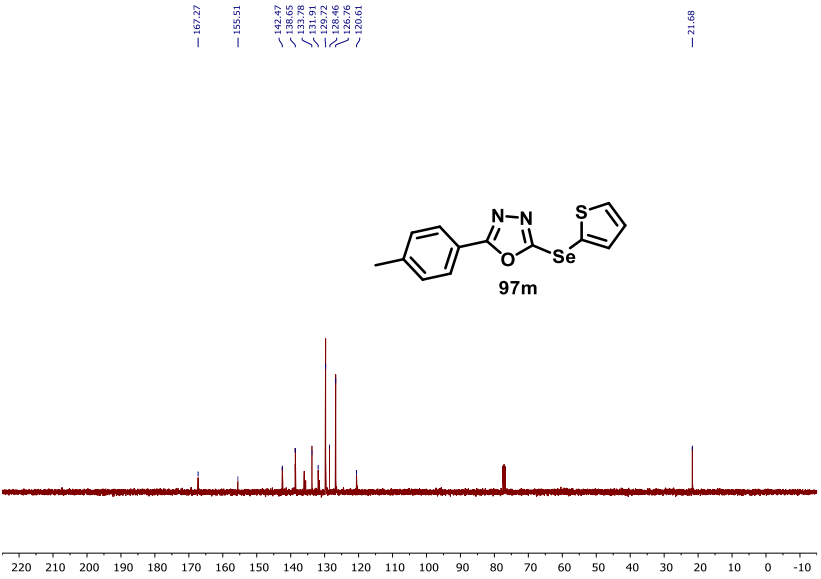
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97l**



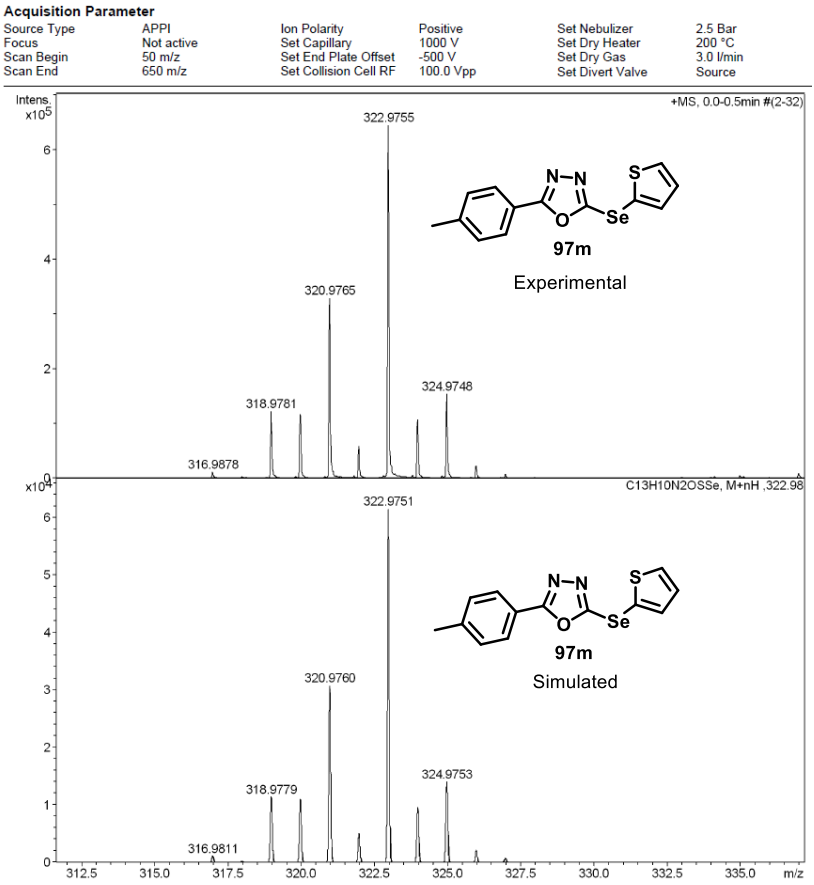
High-resolution mass spectrum of compound **97l**



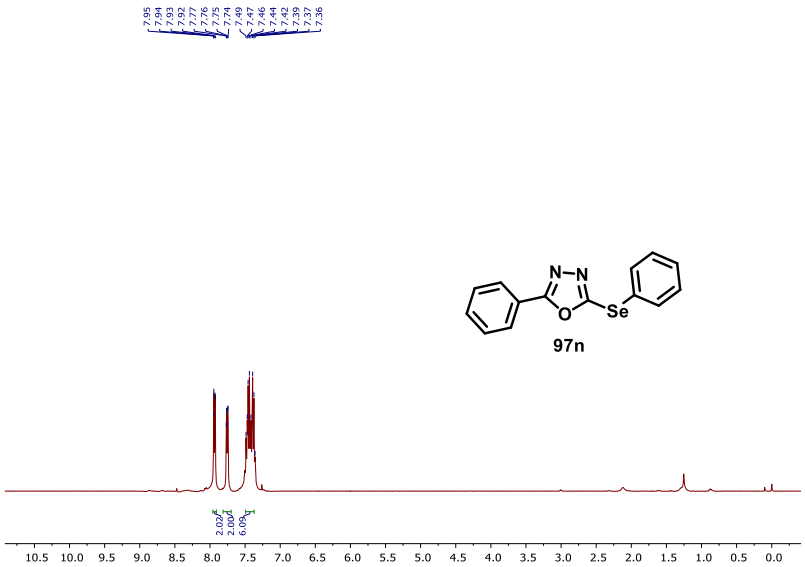
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **97m**



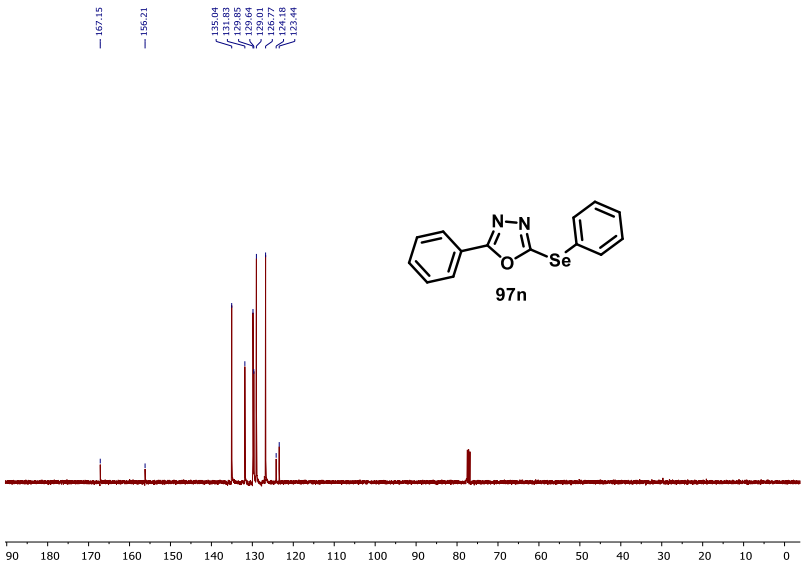
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **97m**



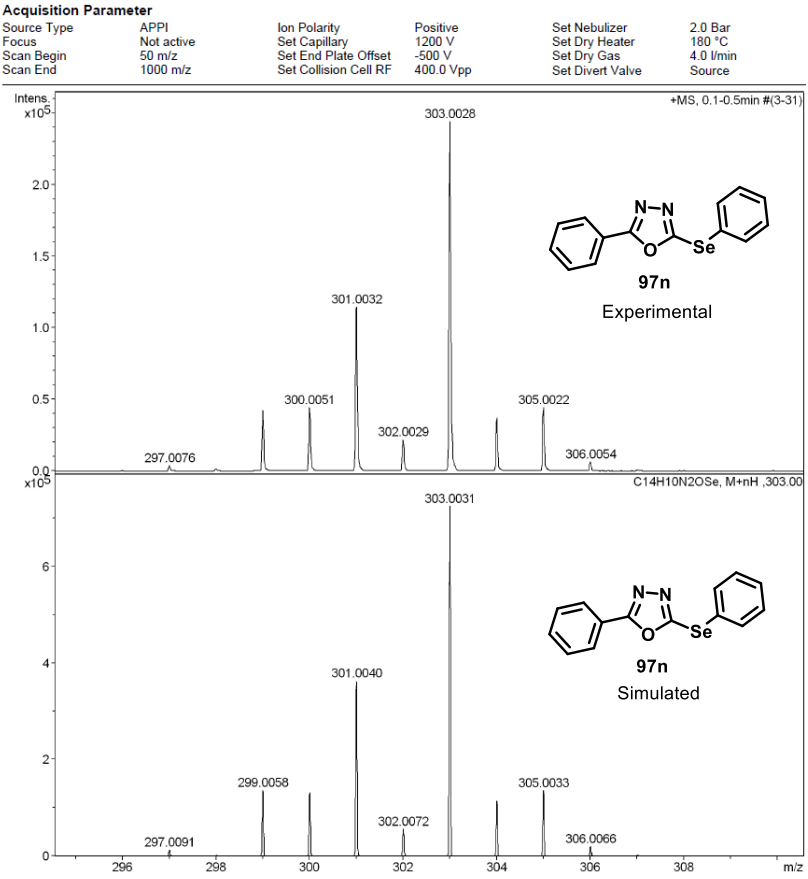
High-resolution mass spectrum of compound **97m**



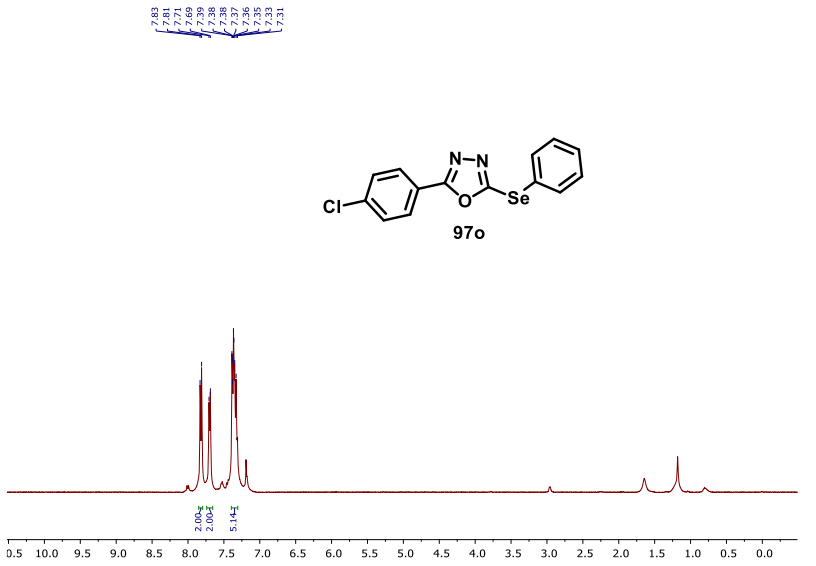
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **97n**



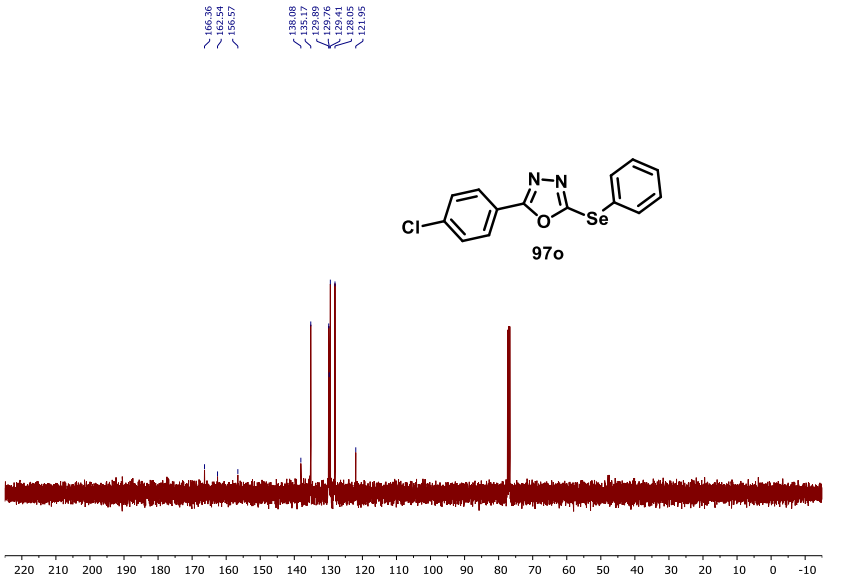
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **97n**



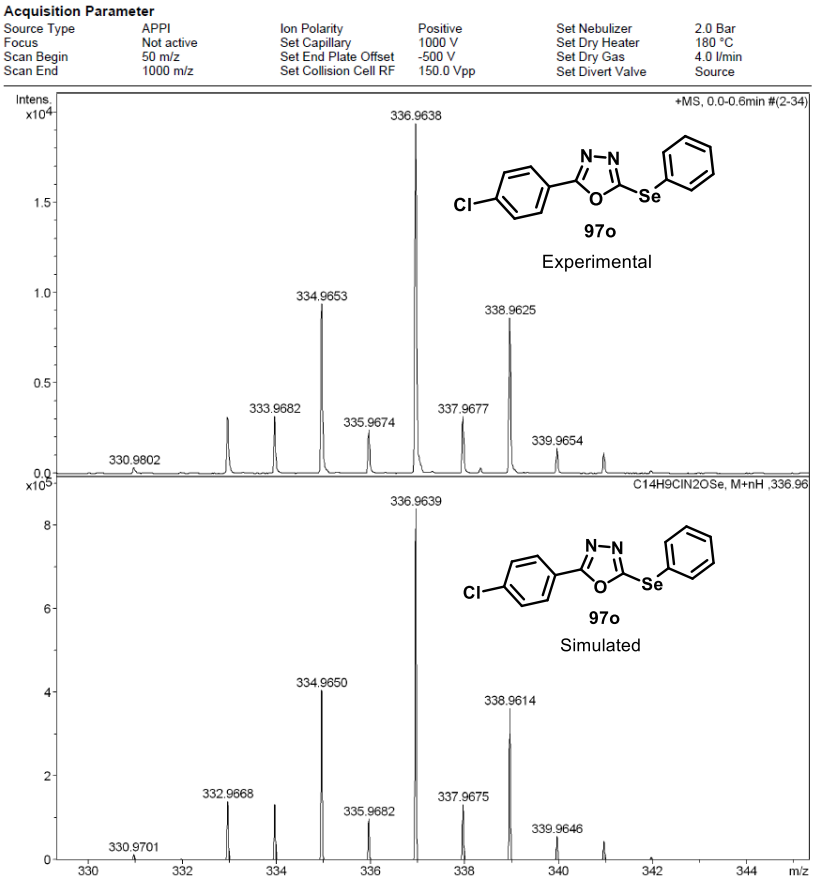
High-resolution mass spectrum of compound **97n**



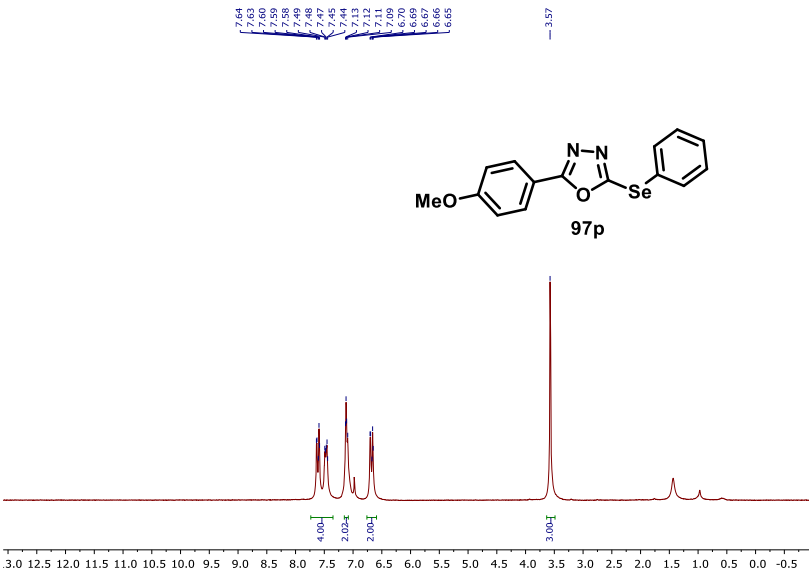
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **97o**



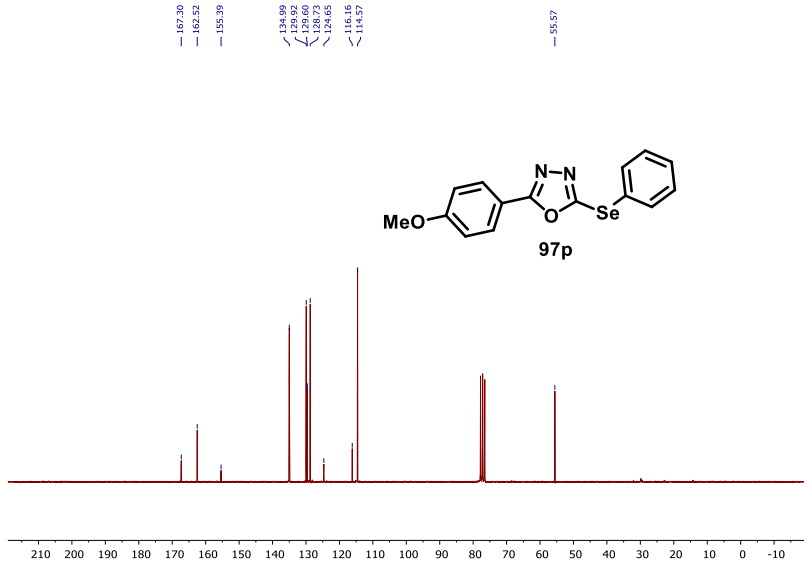
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **97o**



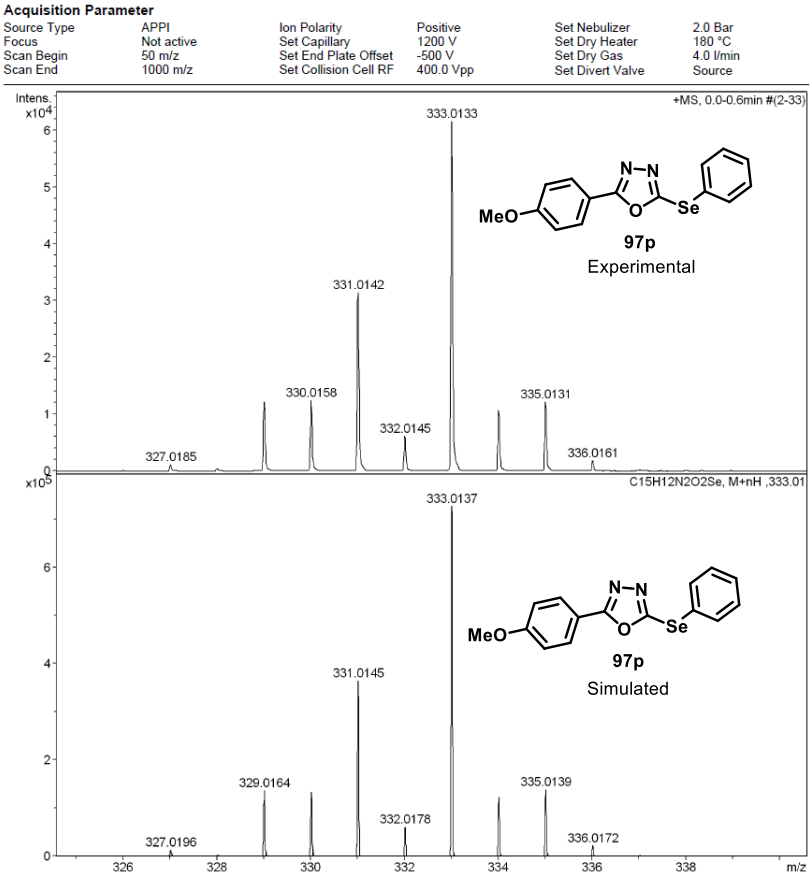
High-resolution mass spectrum of compound **97o**



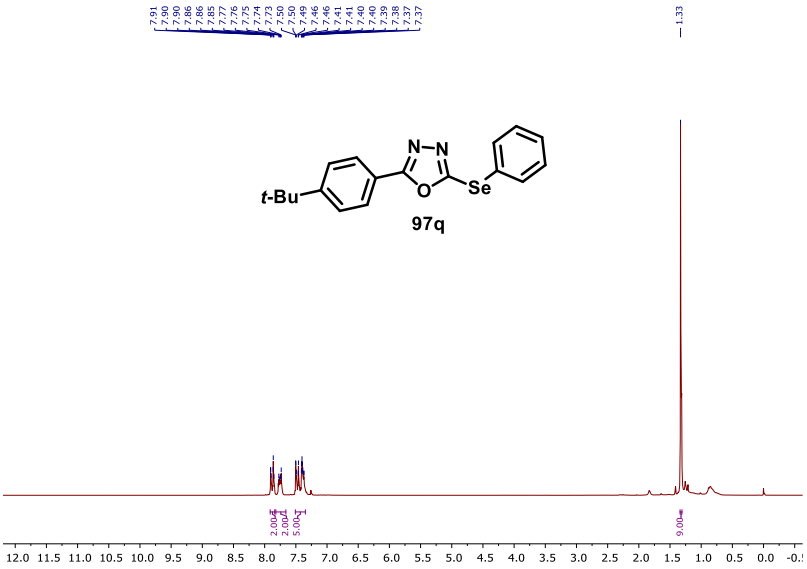
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97p**



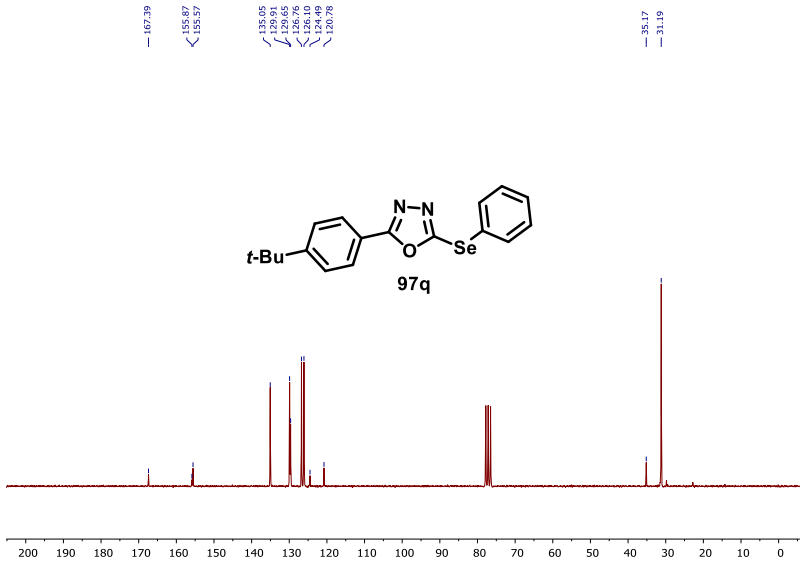
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97p**



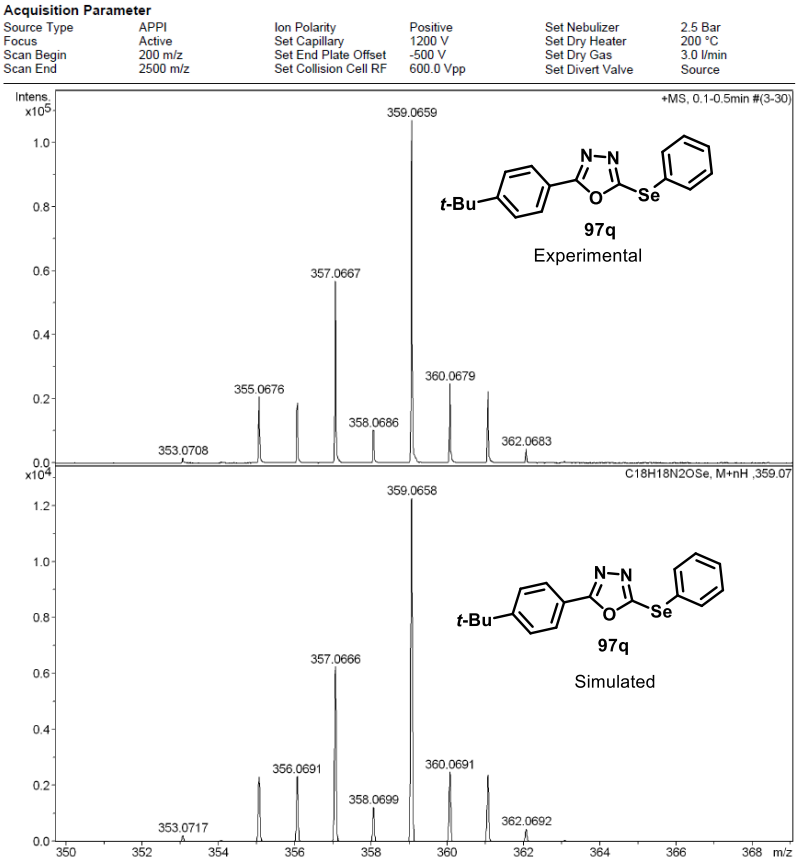
High-resolution mass spectrum of compound **97p**



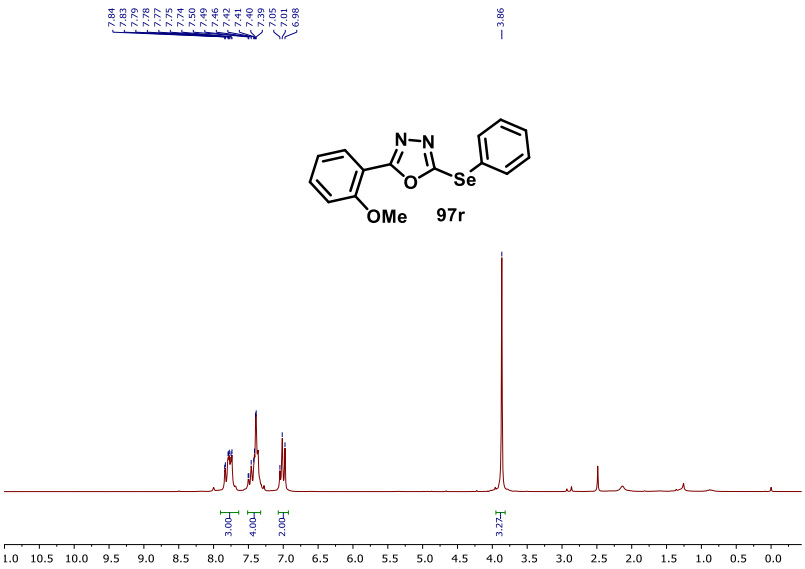
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97q**



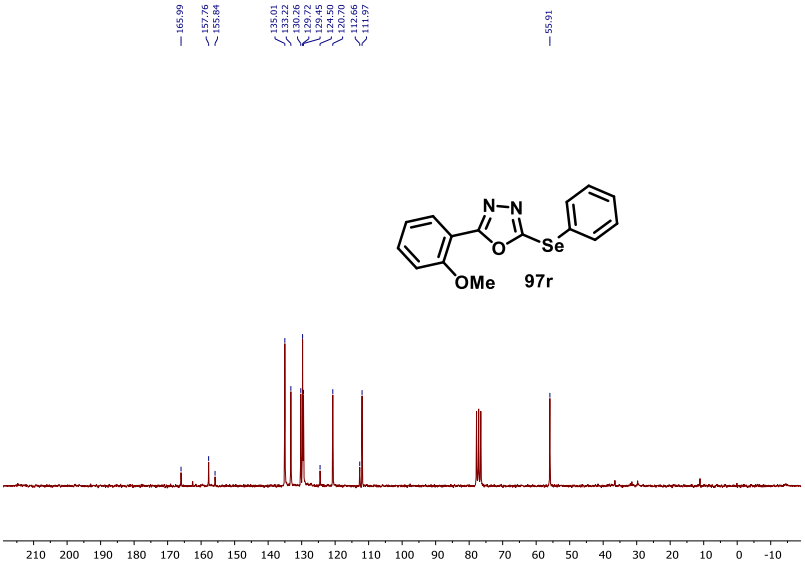
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97q**



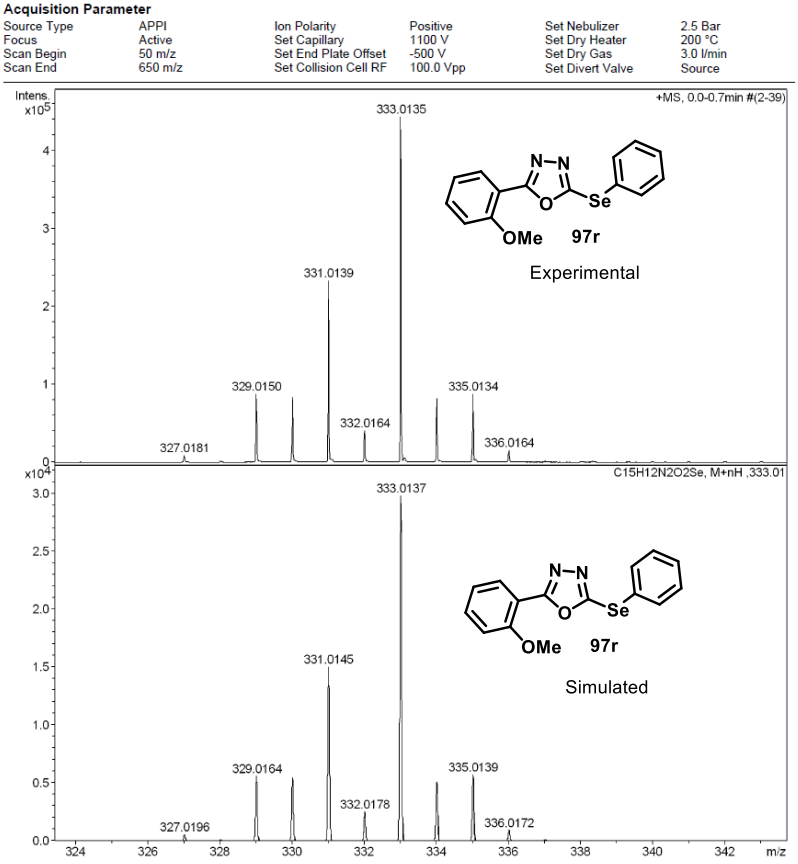
High-resolution mass spectrum of compound **97q**



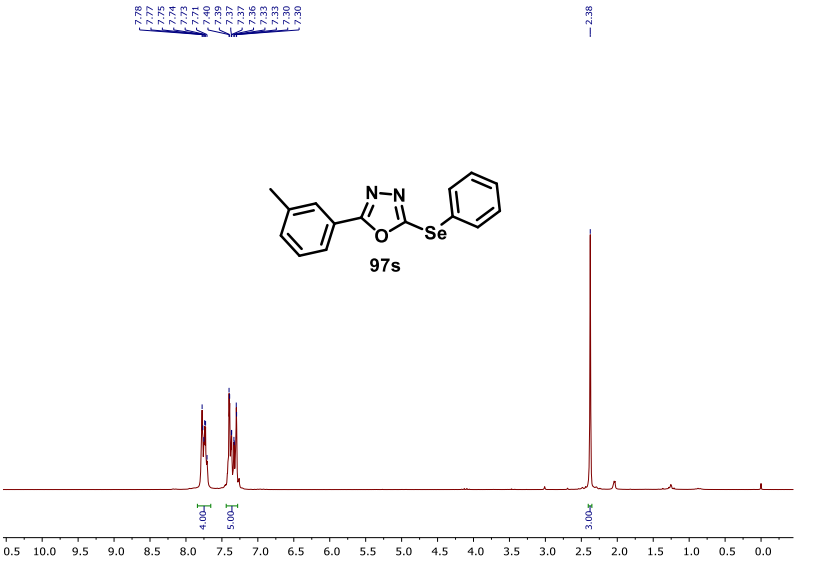
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97r**



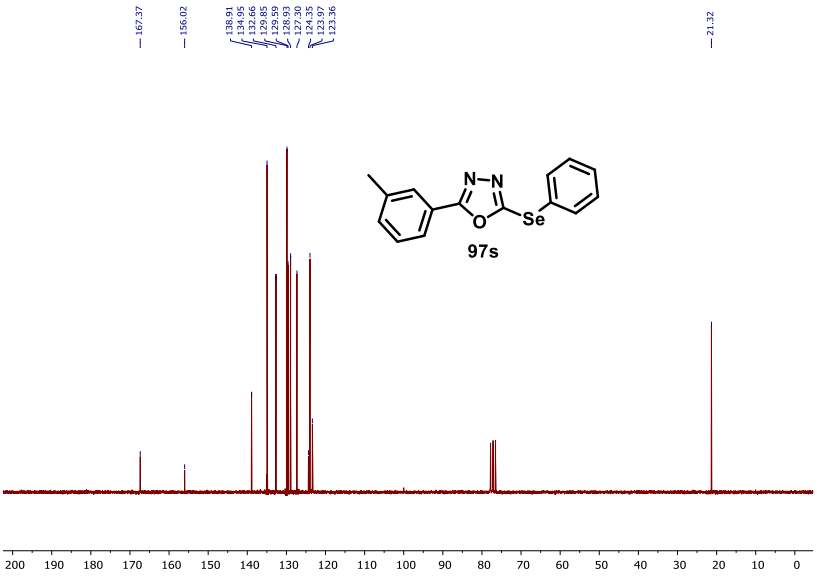
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97r**



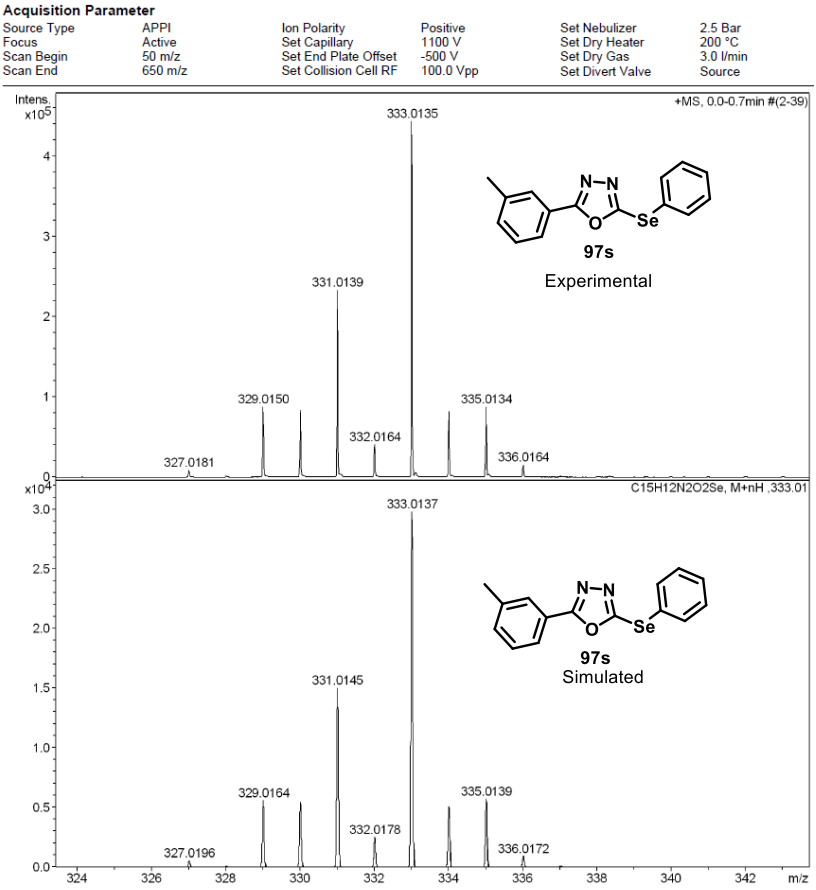
High-resolution mass spectrum of compound **97r**



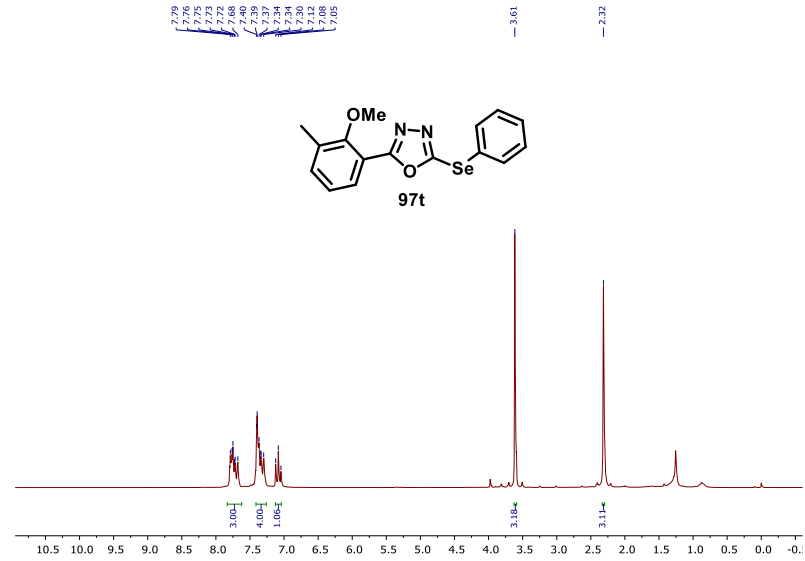
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97s**



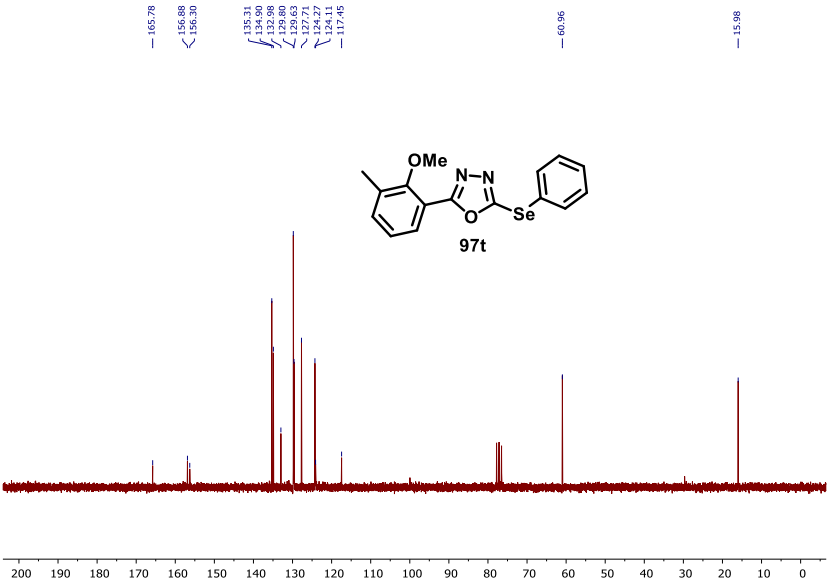
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97s**



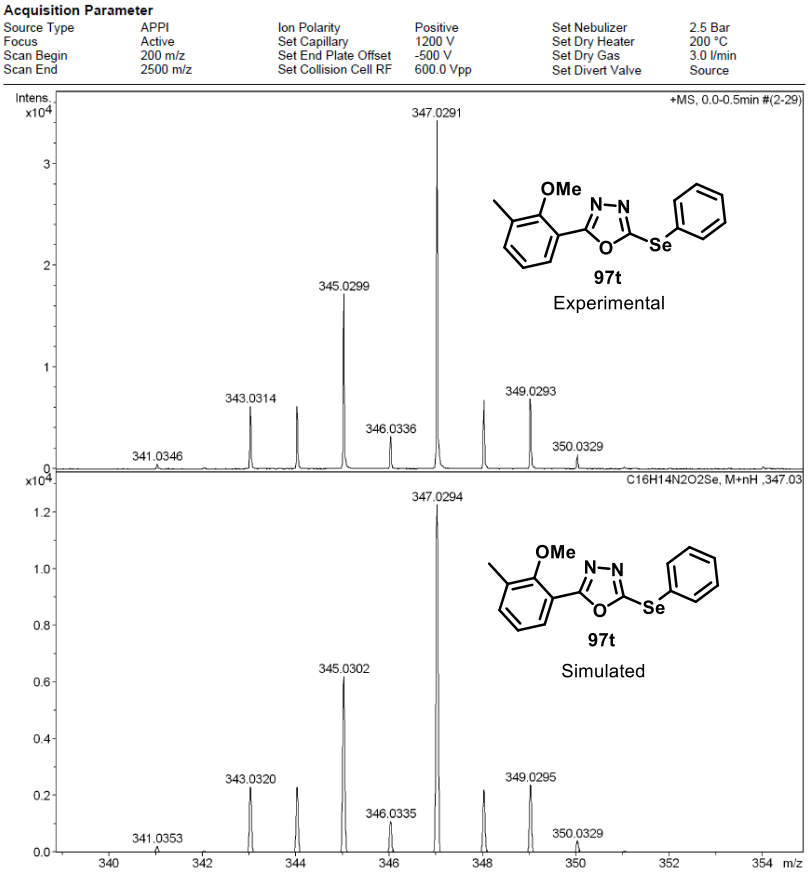
High-resolution mass spectrum of compound **97s**



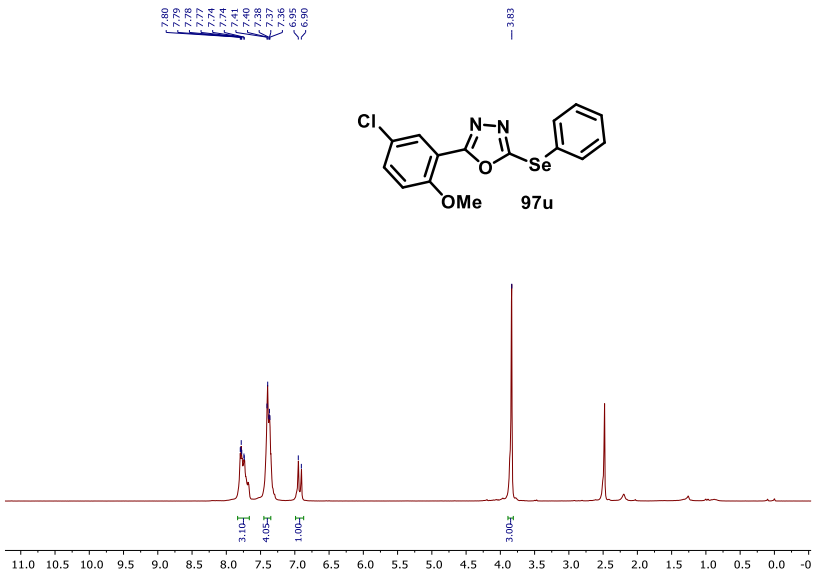
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97t**



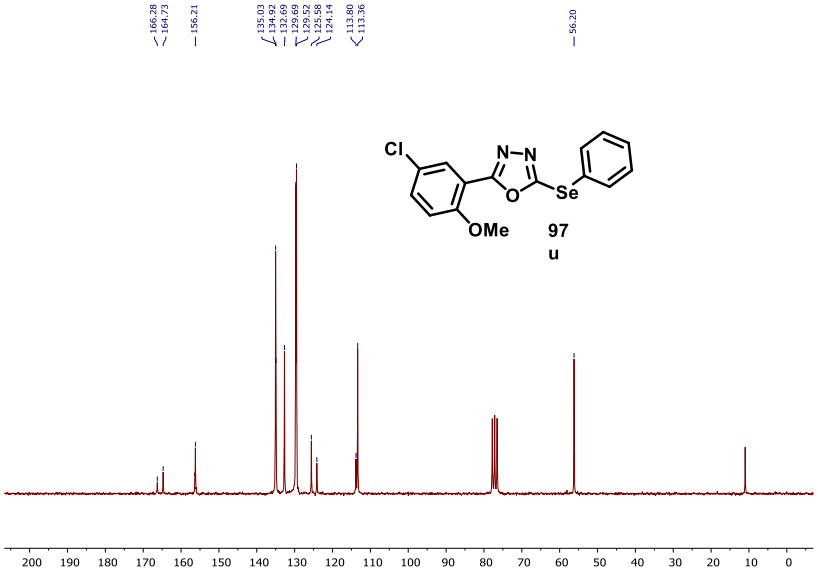
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97t**



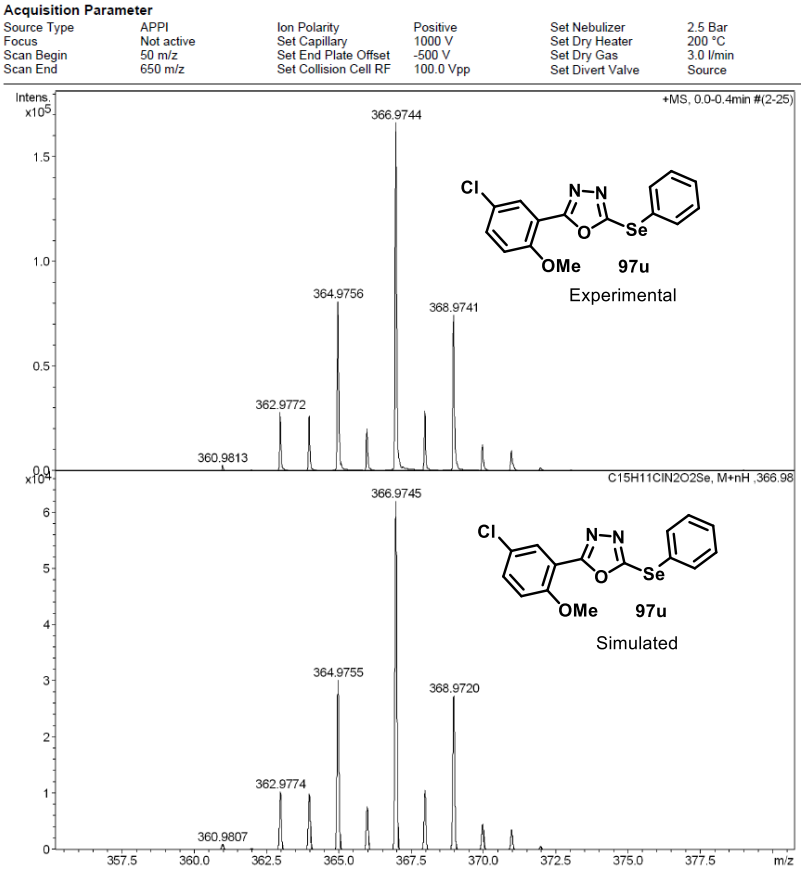
High-resolution mass spectrum of compound **97t**



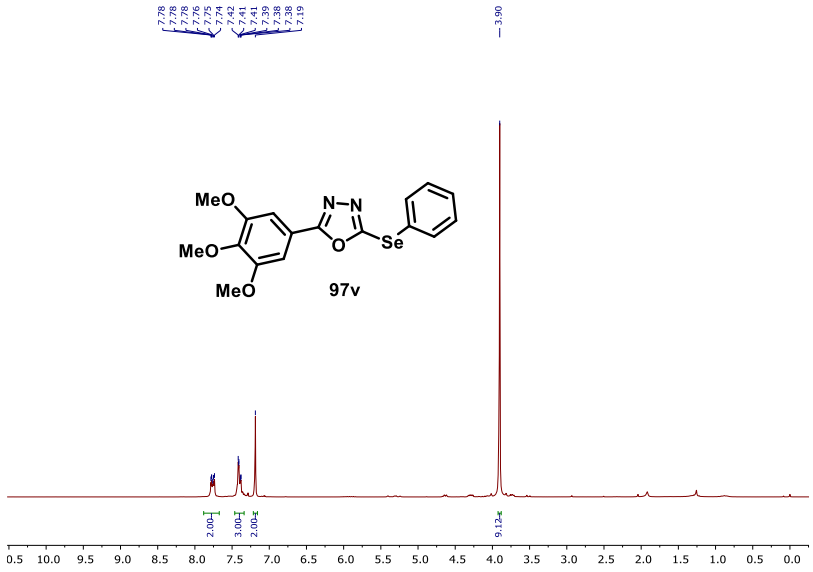
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97u**



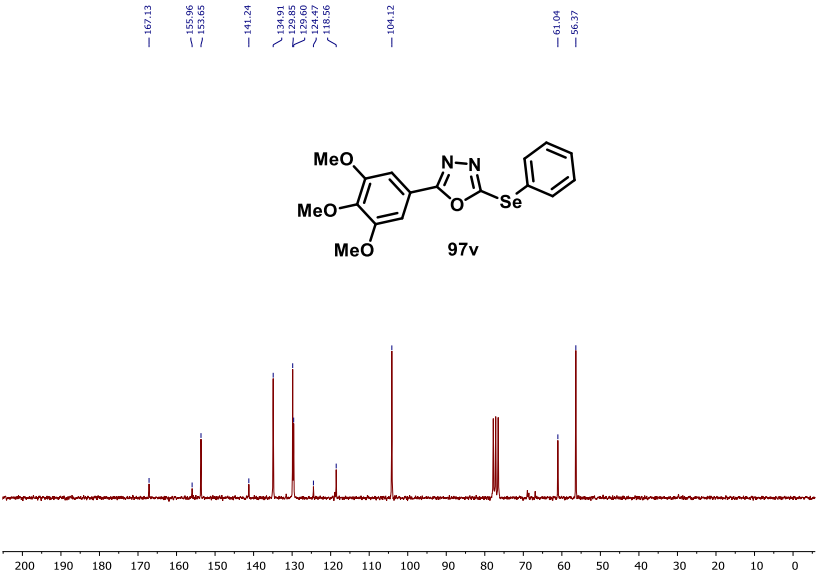
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97u**



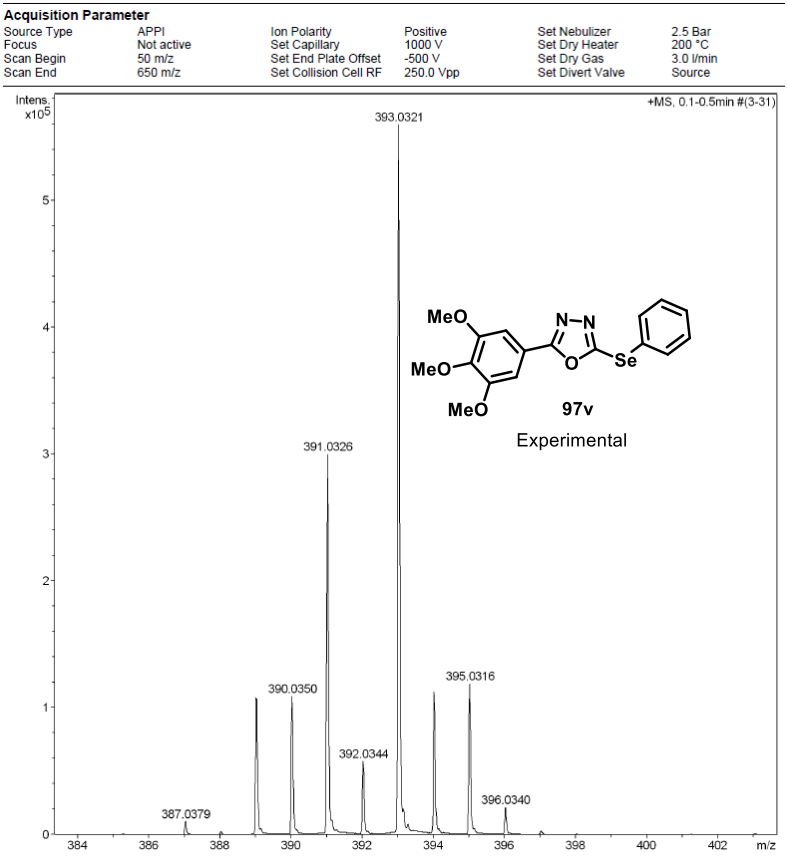
High-resolution mass spectrum of compound **97u**



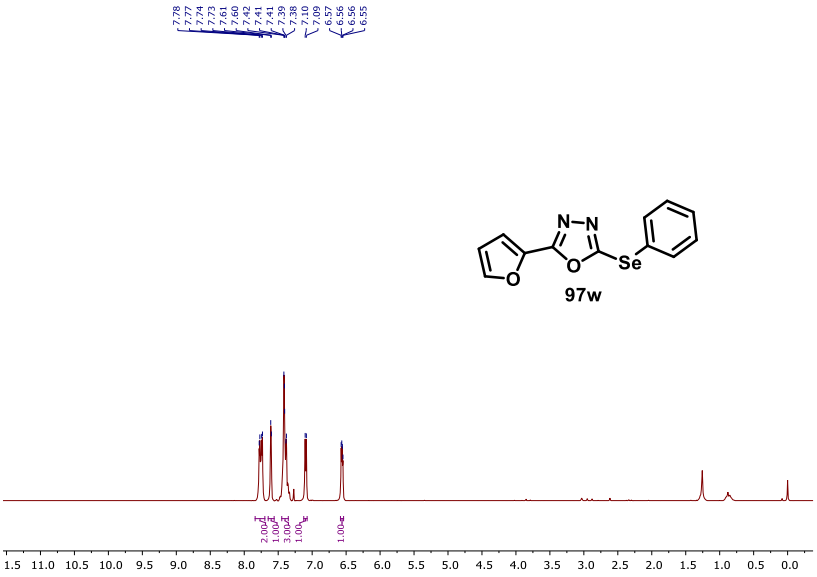
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97v**



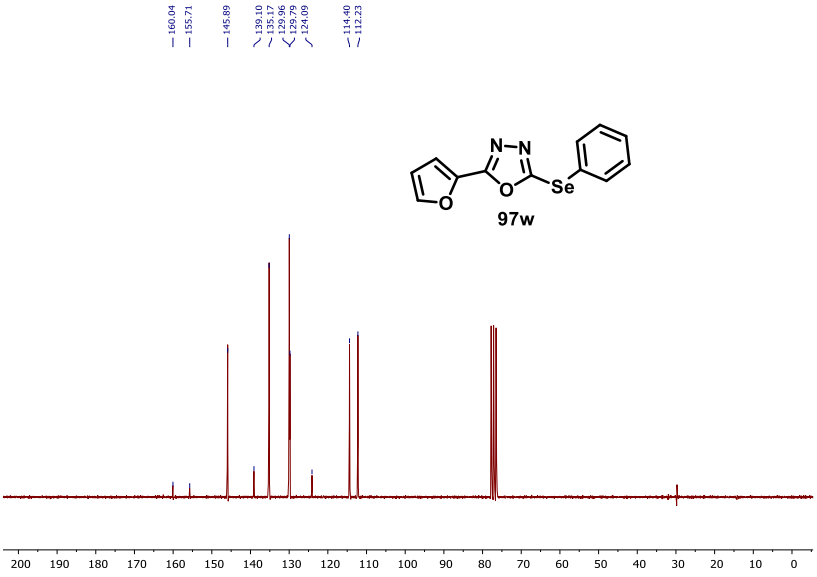
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97v**



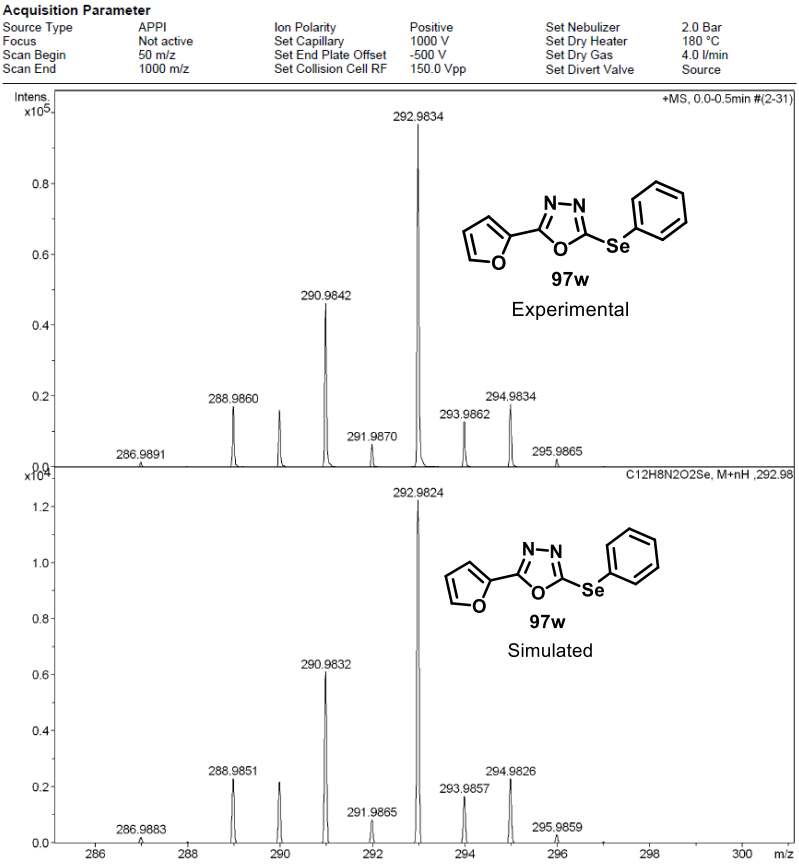
High-resolution mass spectrum of compound **97v**



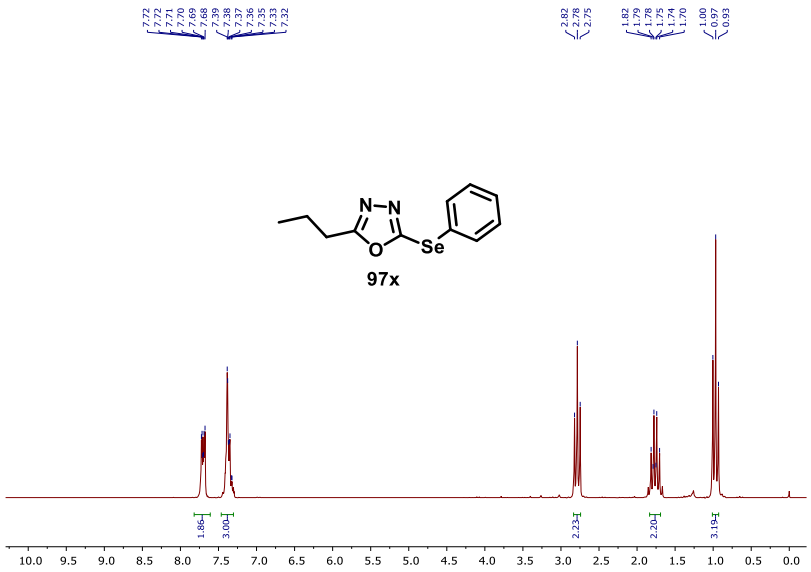
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97w**



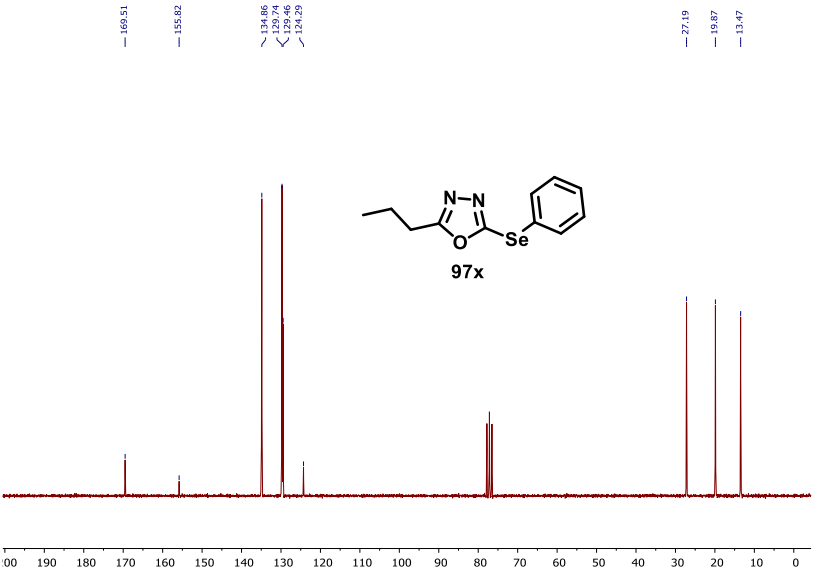
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97w**



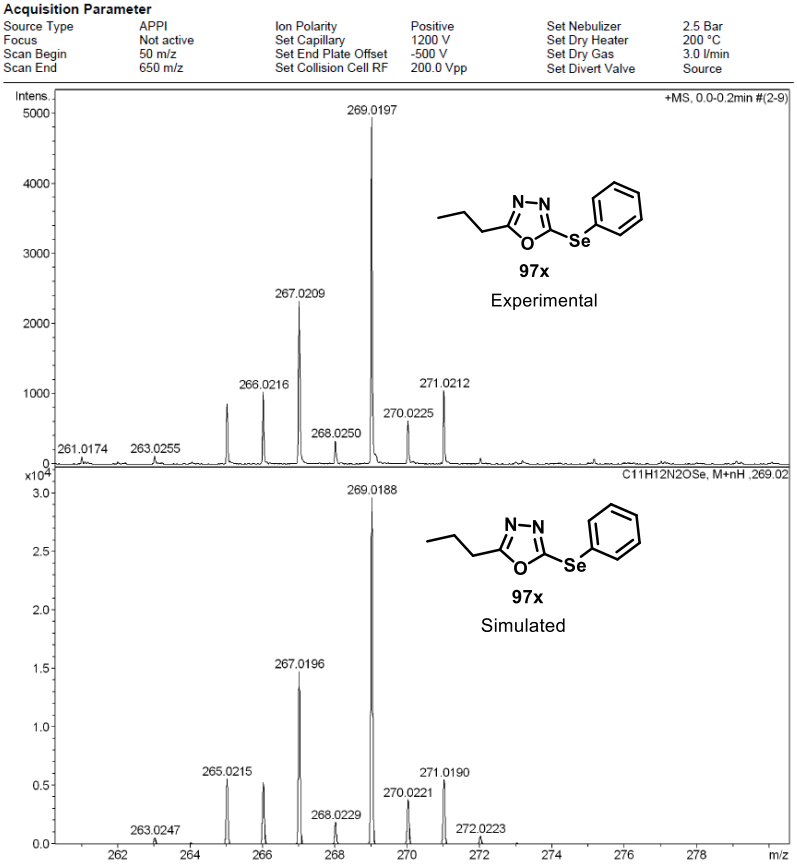
High-resolution mass spectrum of compound **97w**



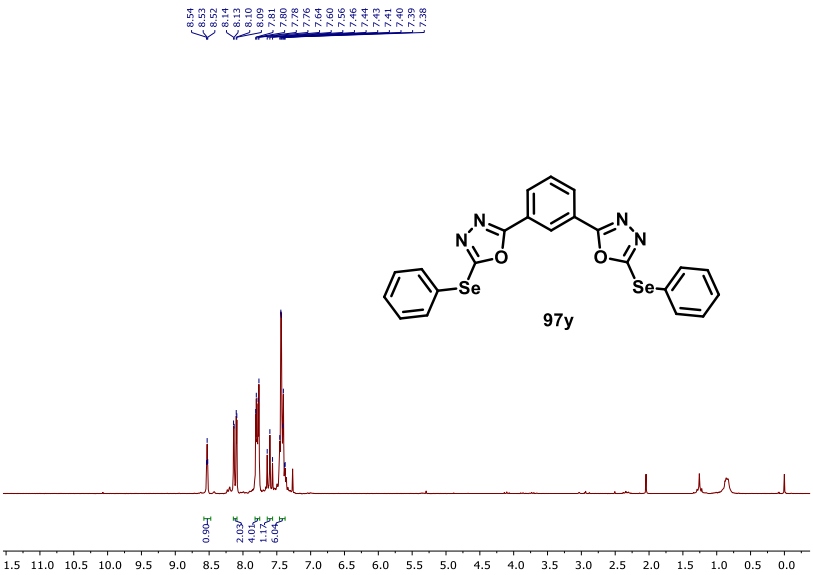
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97x**



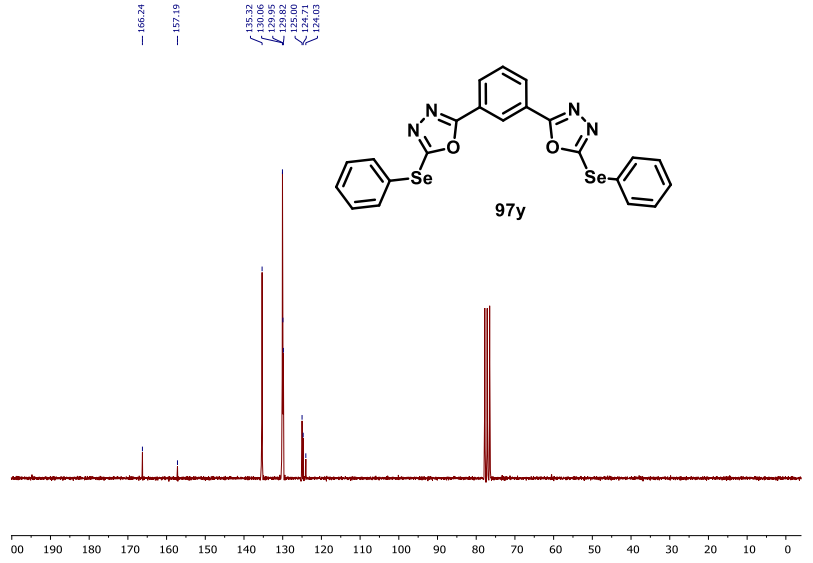
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97x**



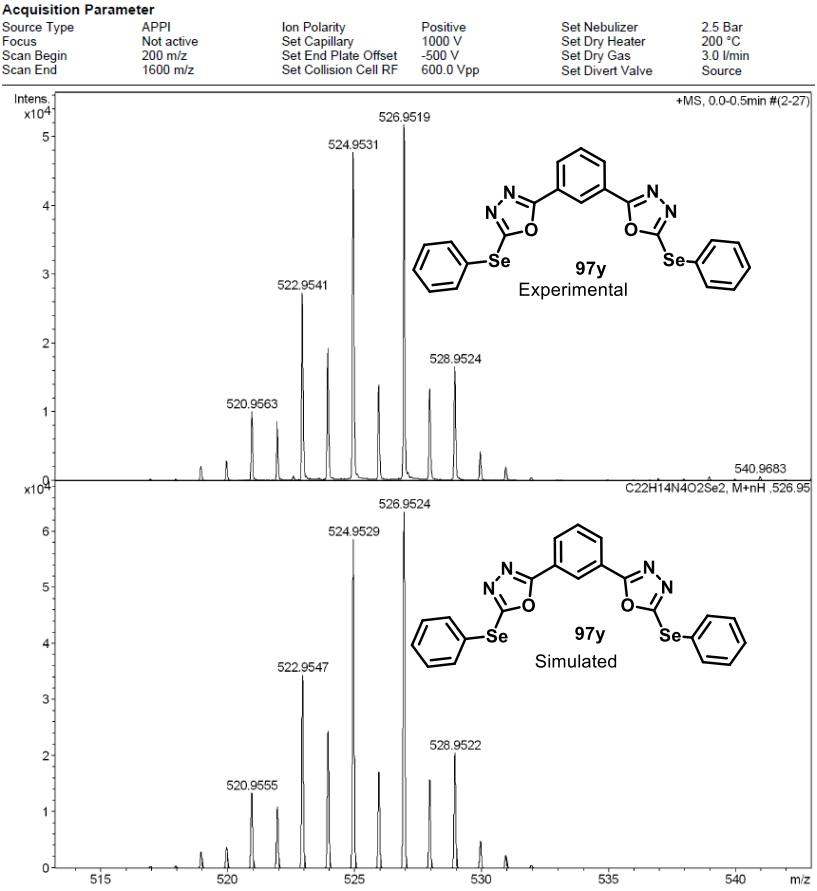
High-resolution mass spectrum of compound **97x**



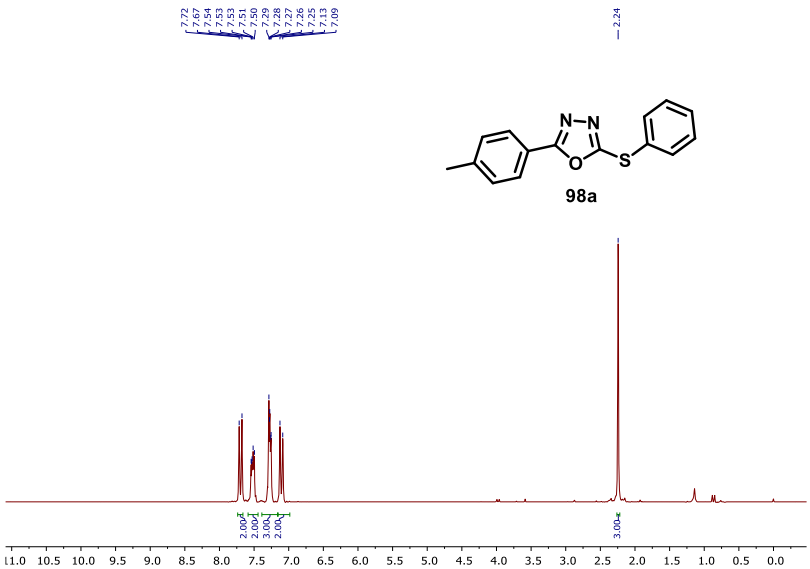
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **97y**



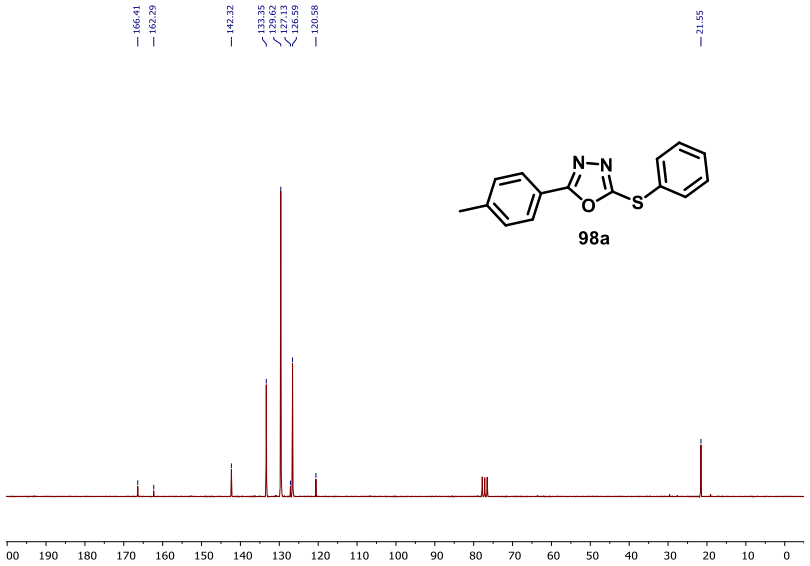
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **97y**



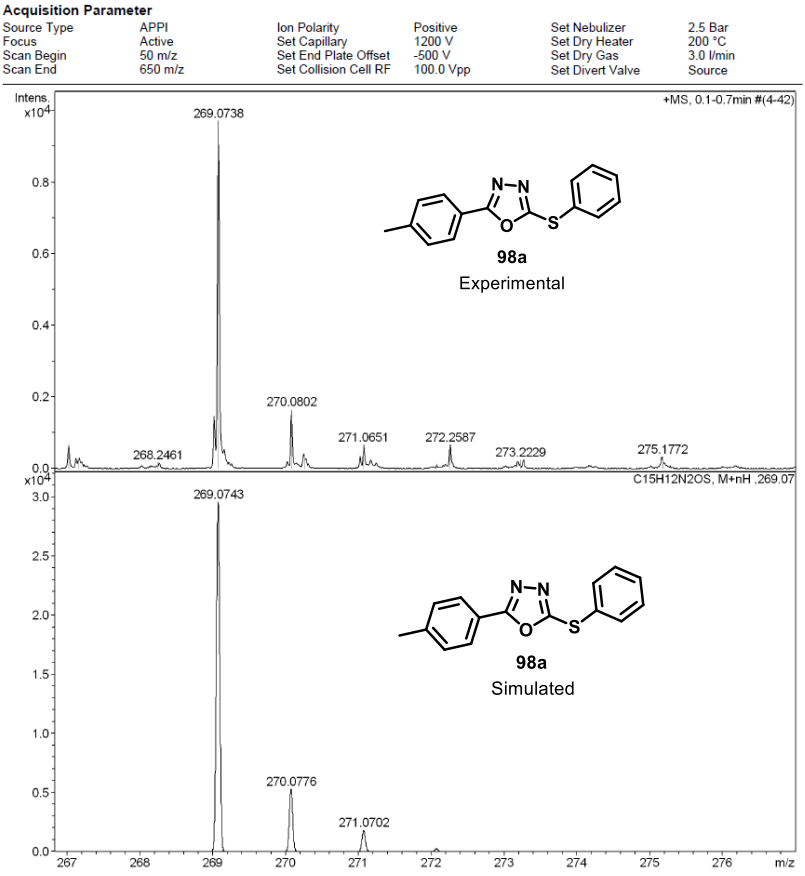
High-resolution mass spectrum of compound **97y**



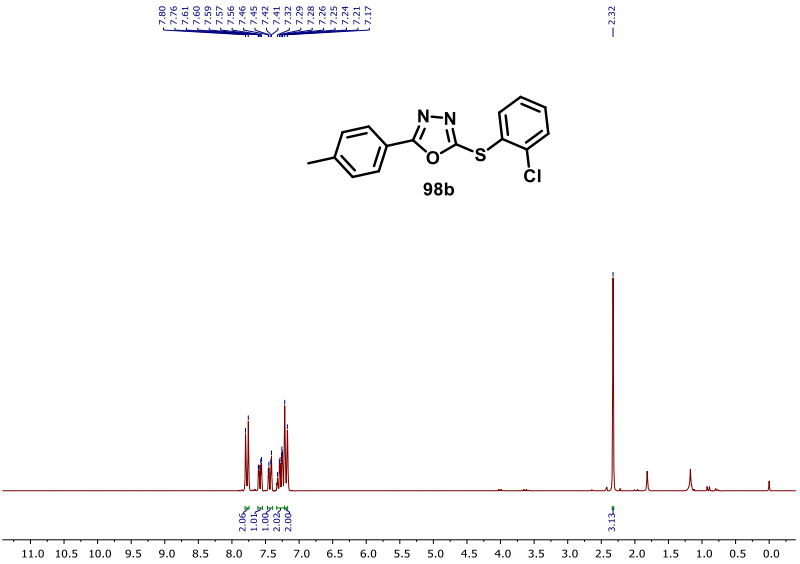
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **98a**



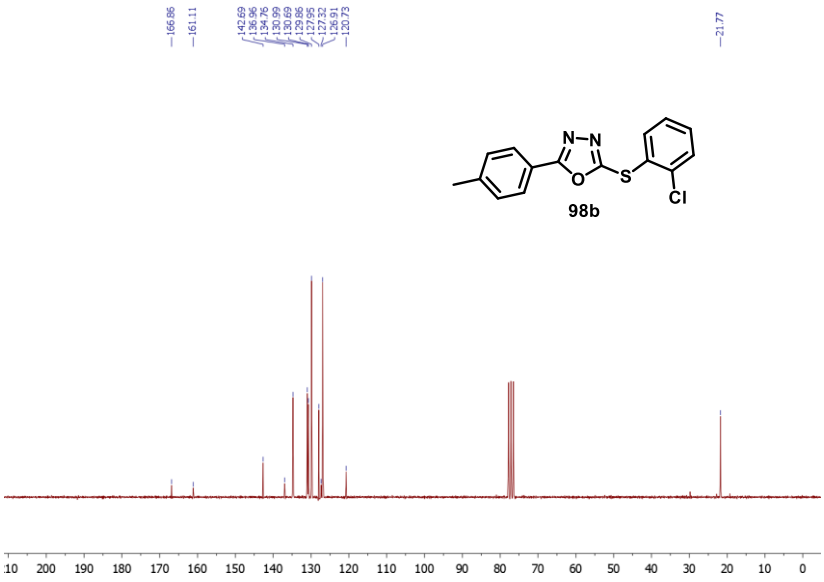
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **98a**



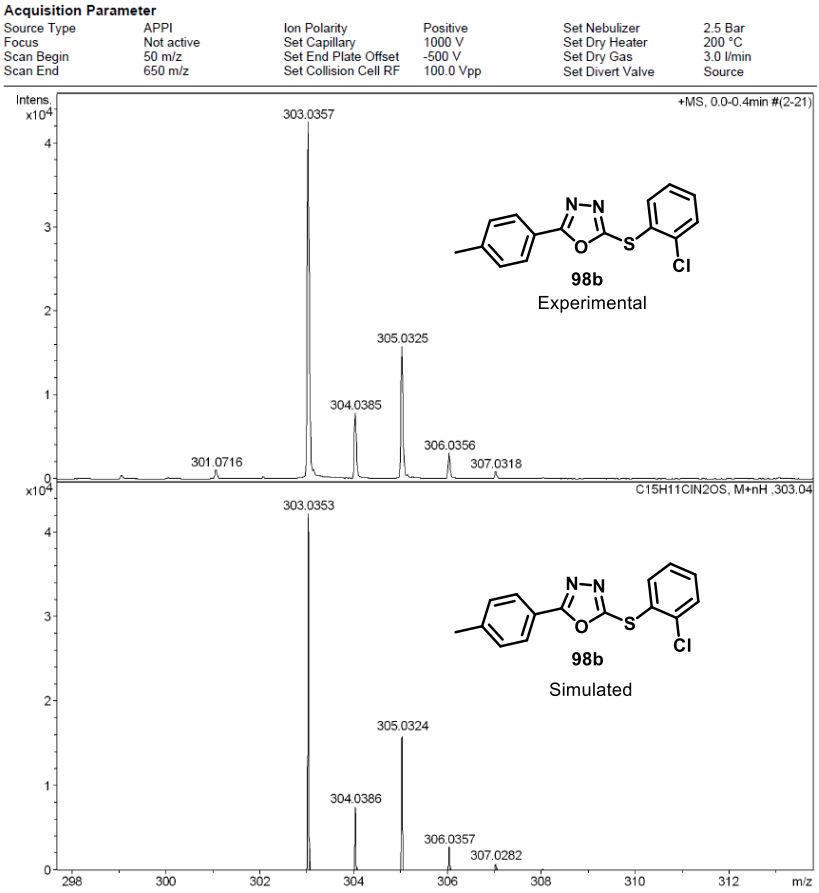
High-resolution mass spectrum of compound **98a**



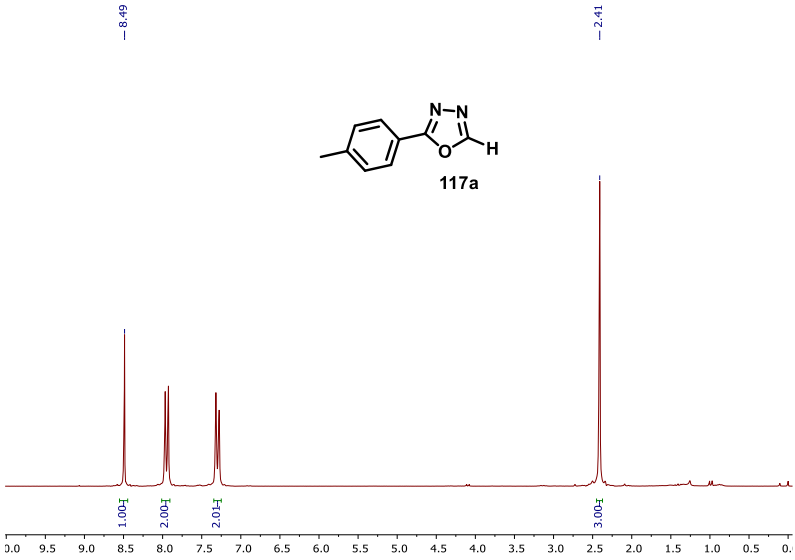
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **98b**



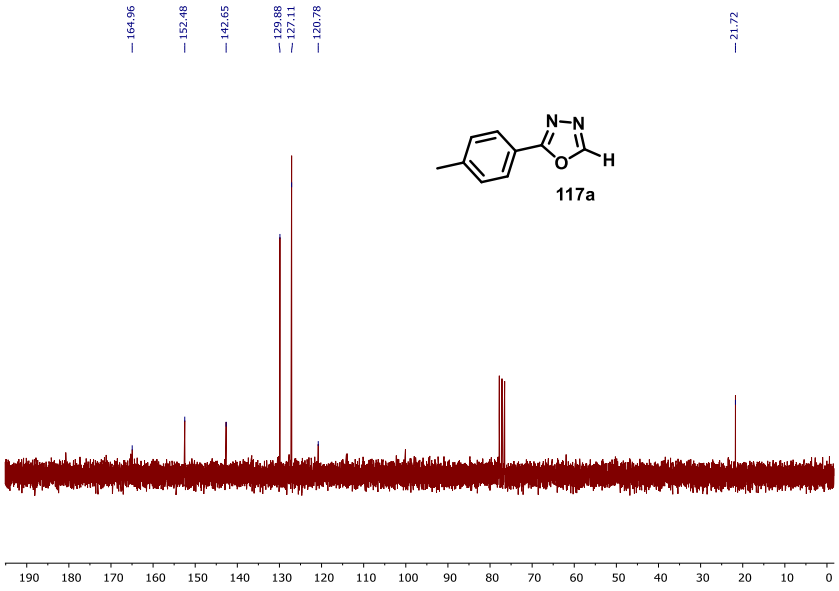
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **98b**



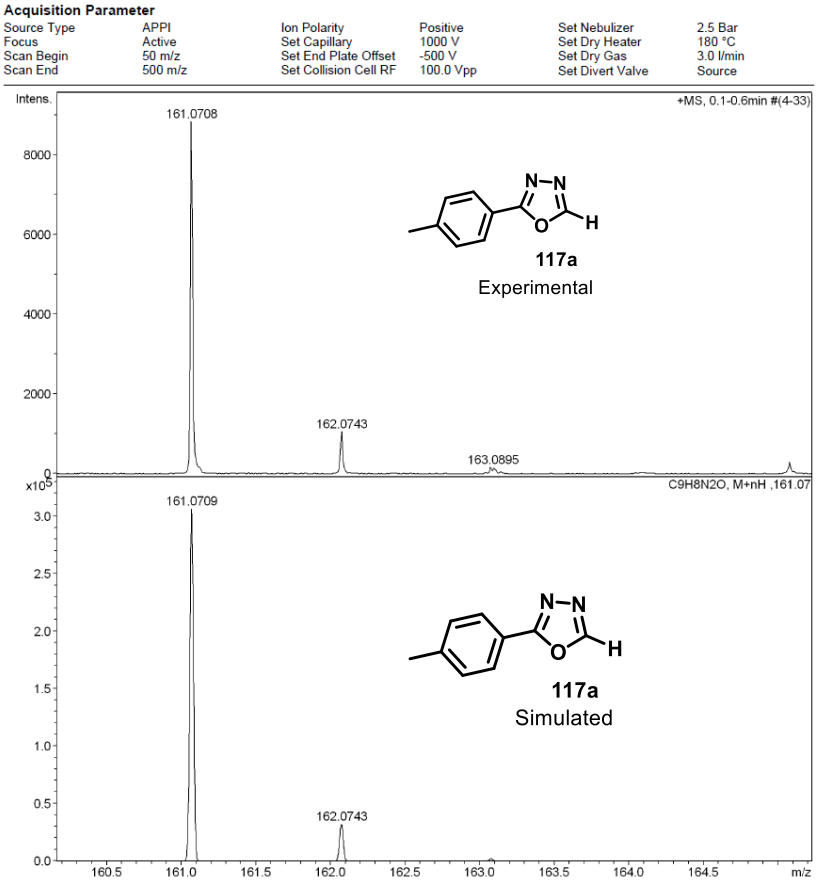
High-resolution mass spectrum of compound **98b**



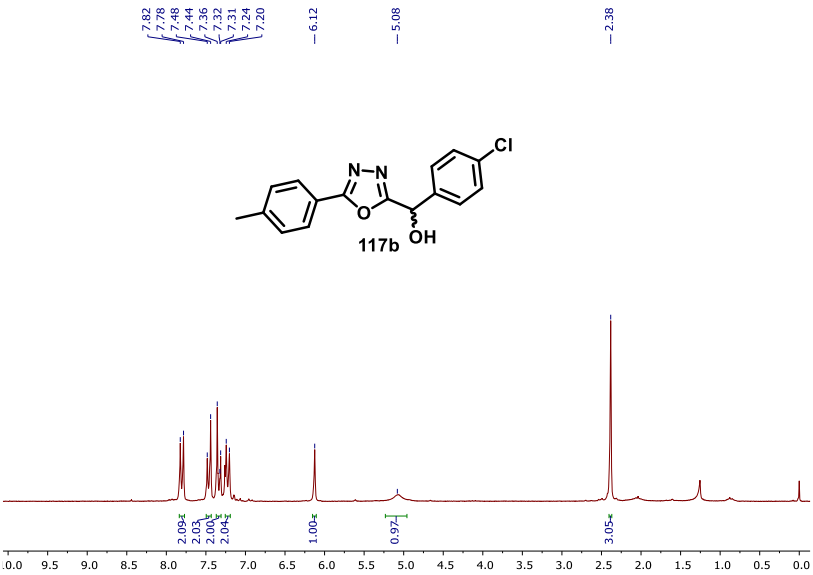
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **117a**



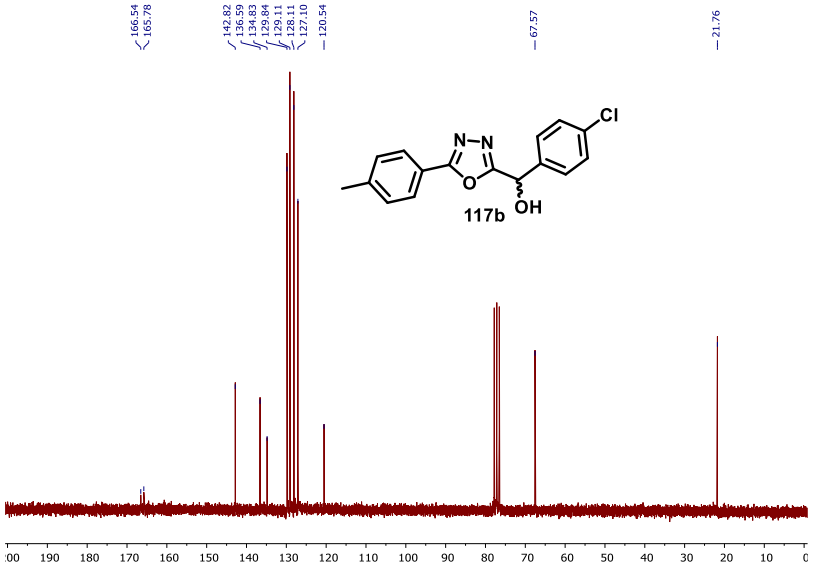
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **117a**



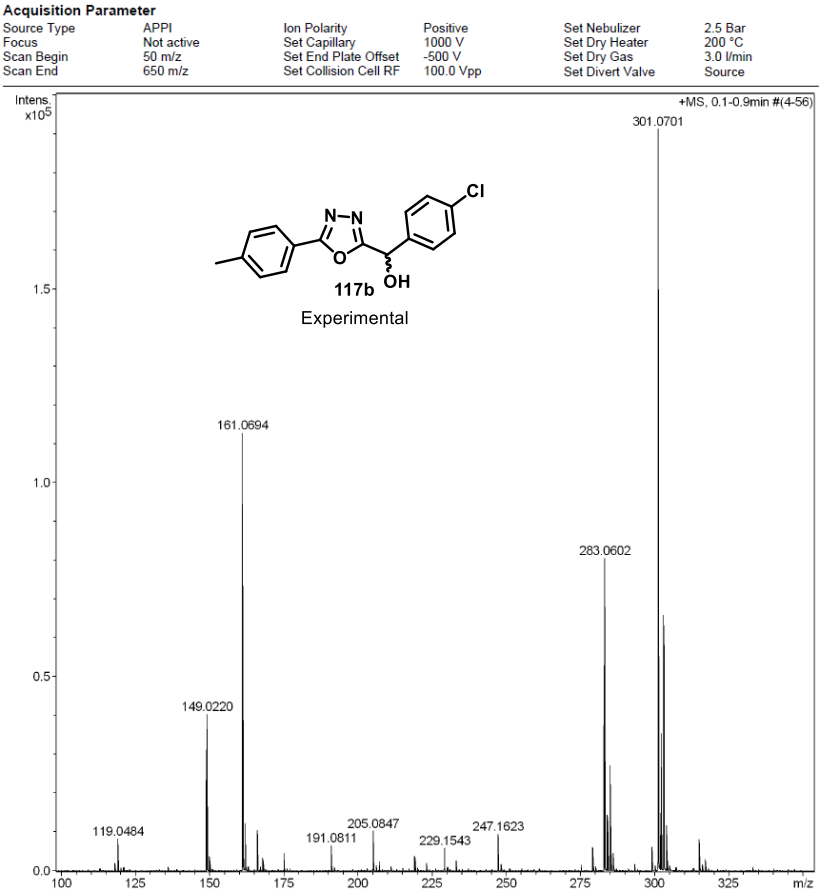
High-resolution mass spectrum of compound **117a**



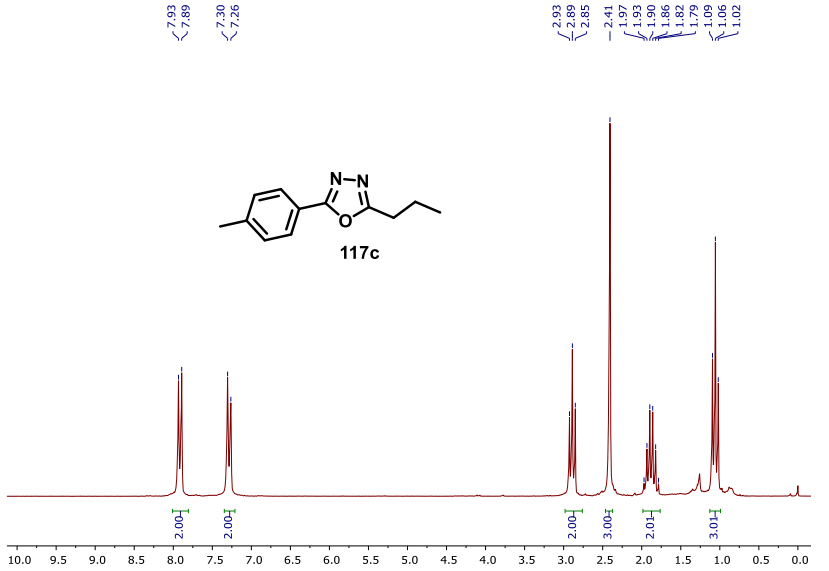
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **117b**



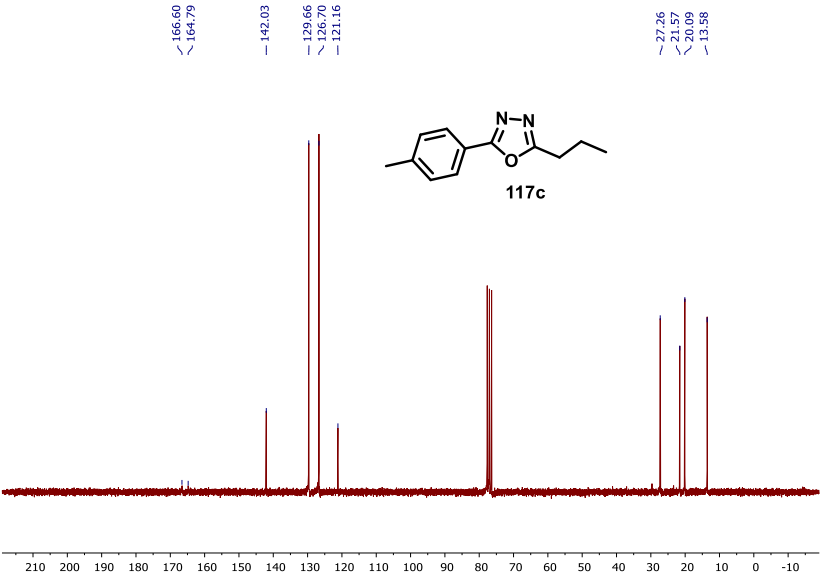
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **117b**



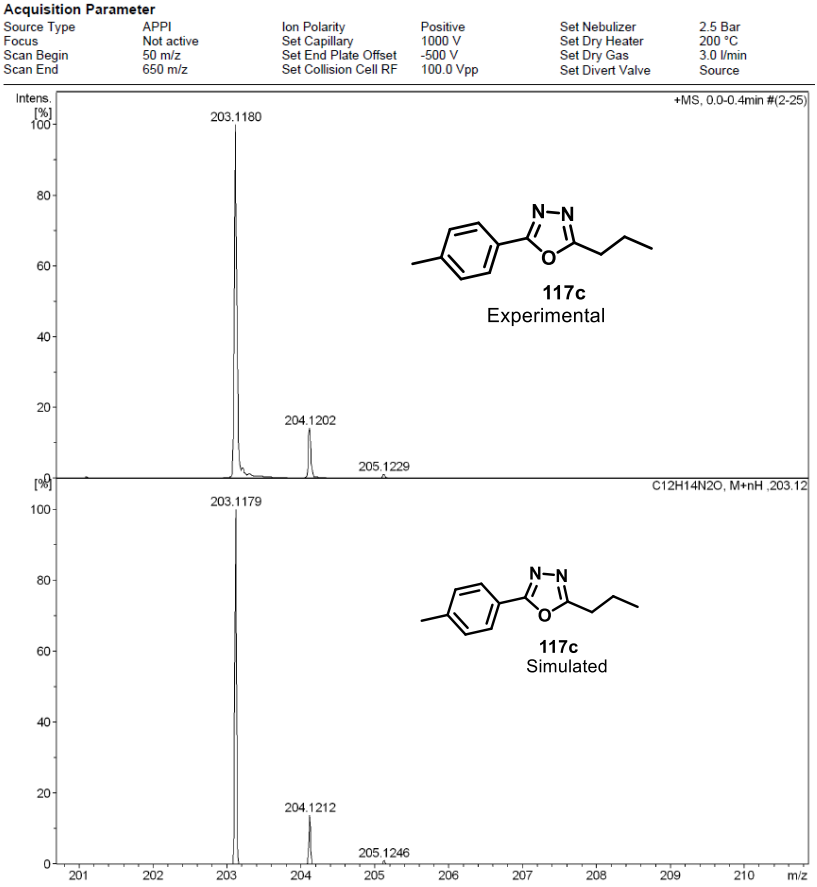
High-resolution mass spectrum of compound **117b**



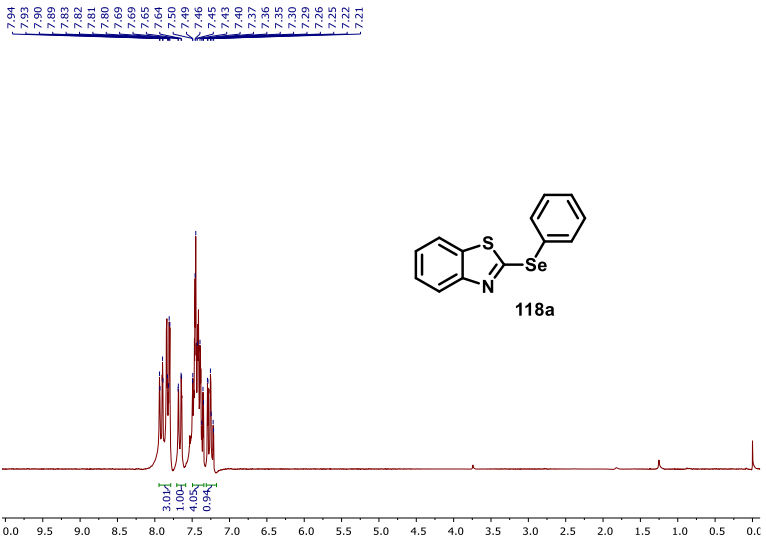
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **117c**



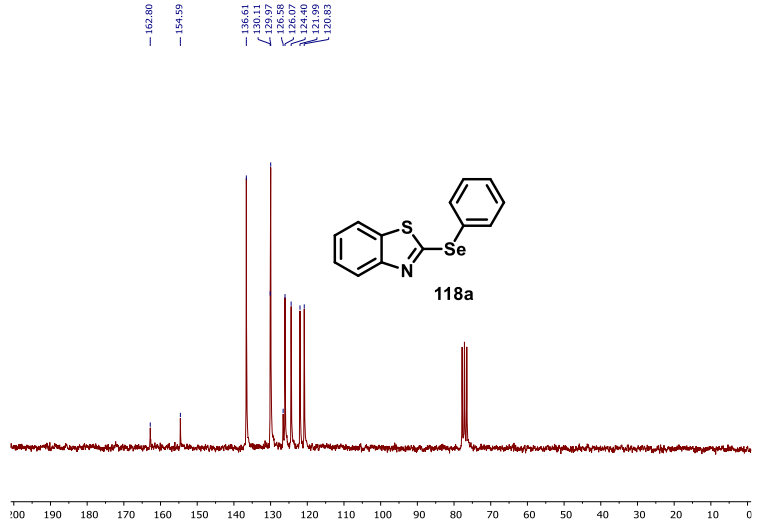
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **117c**



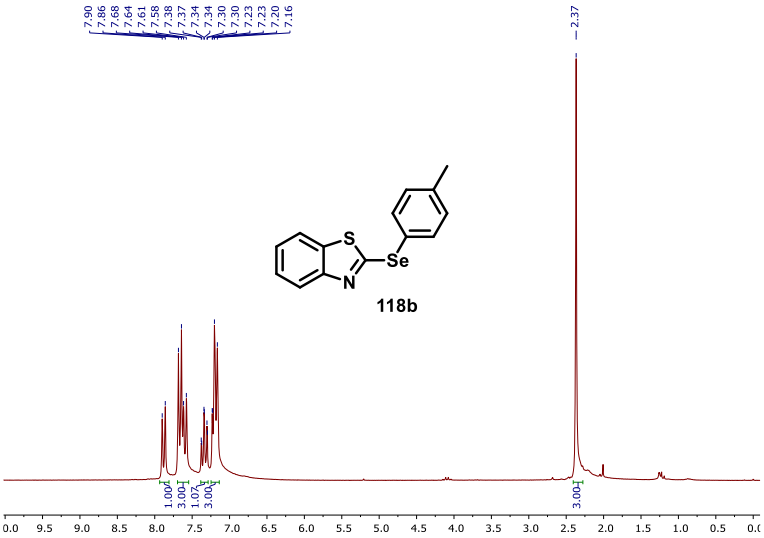
High-resolution mass spectrum of compound **117c**



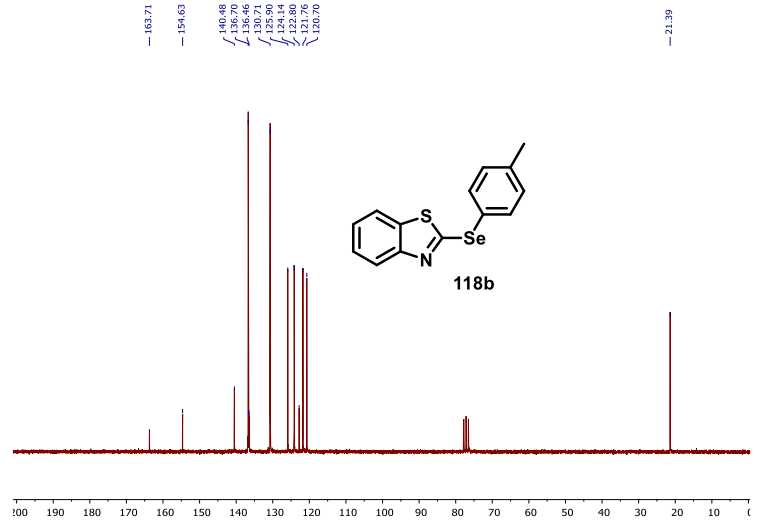
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118a**



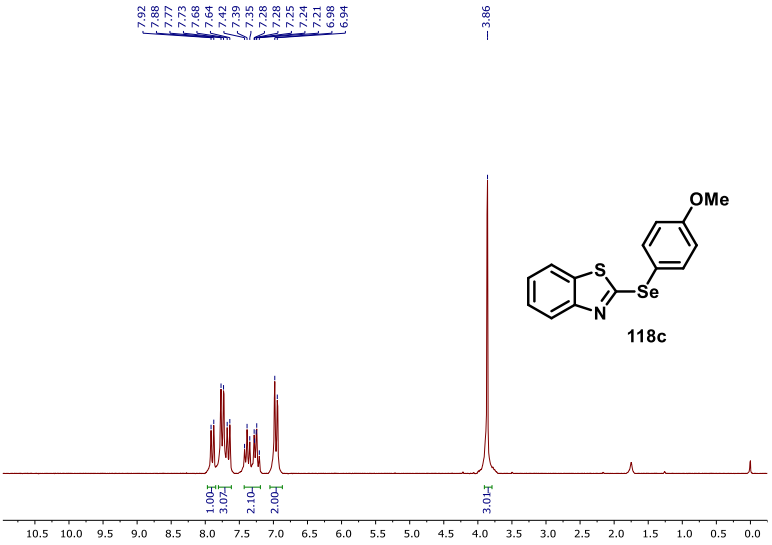
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118a**



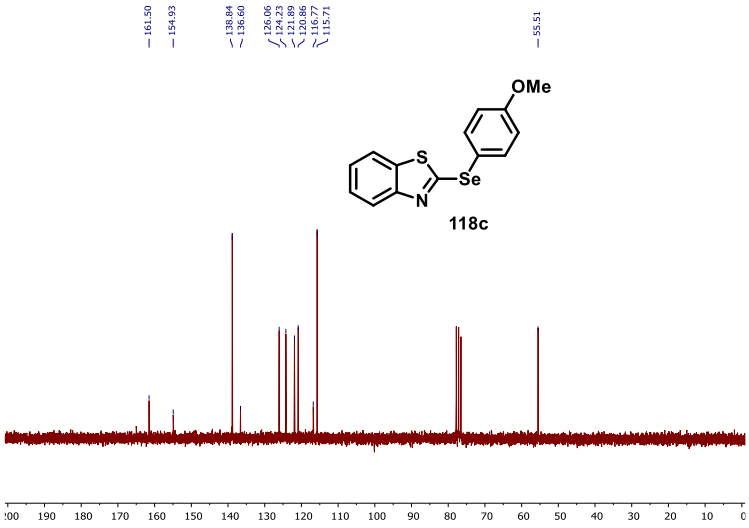
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118b**



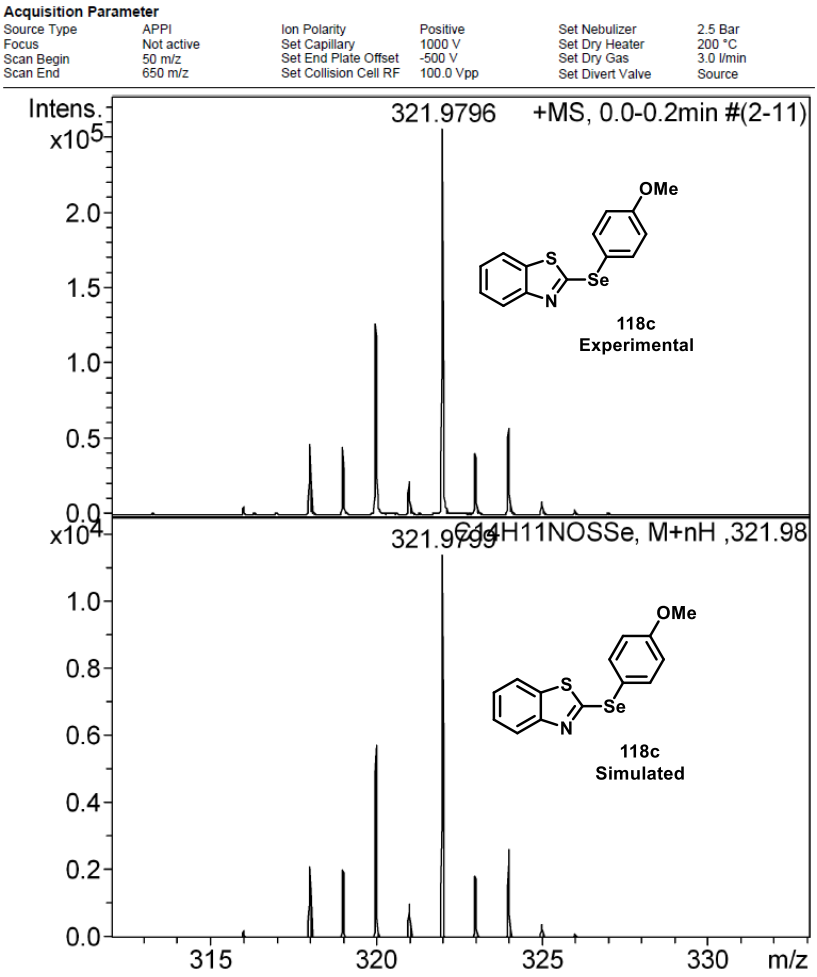
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118b**



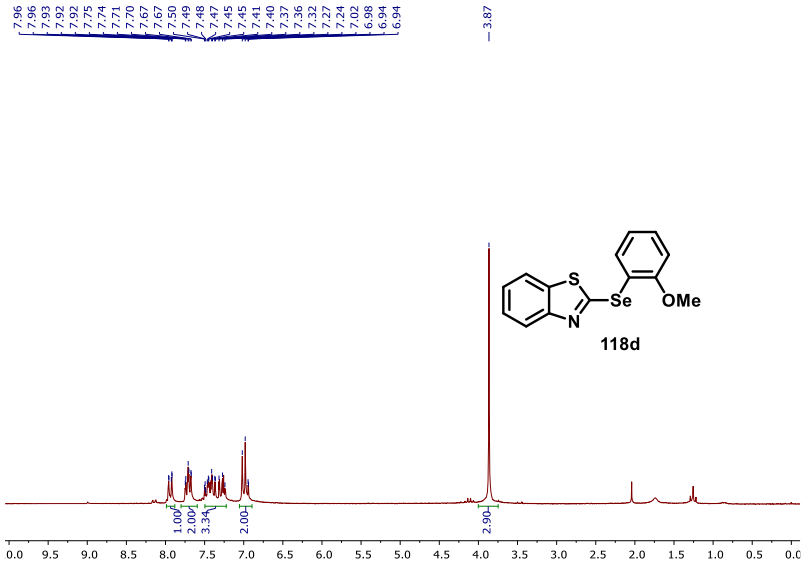
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118c**



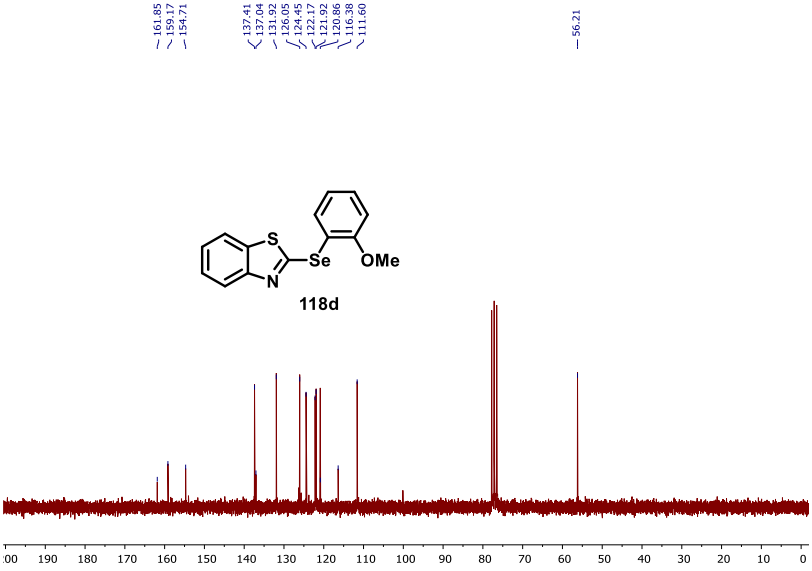
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118c**



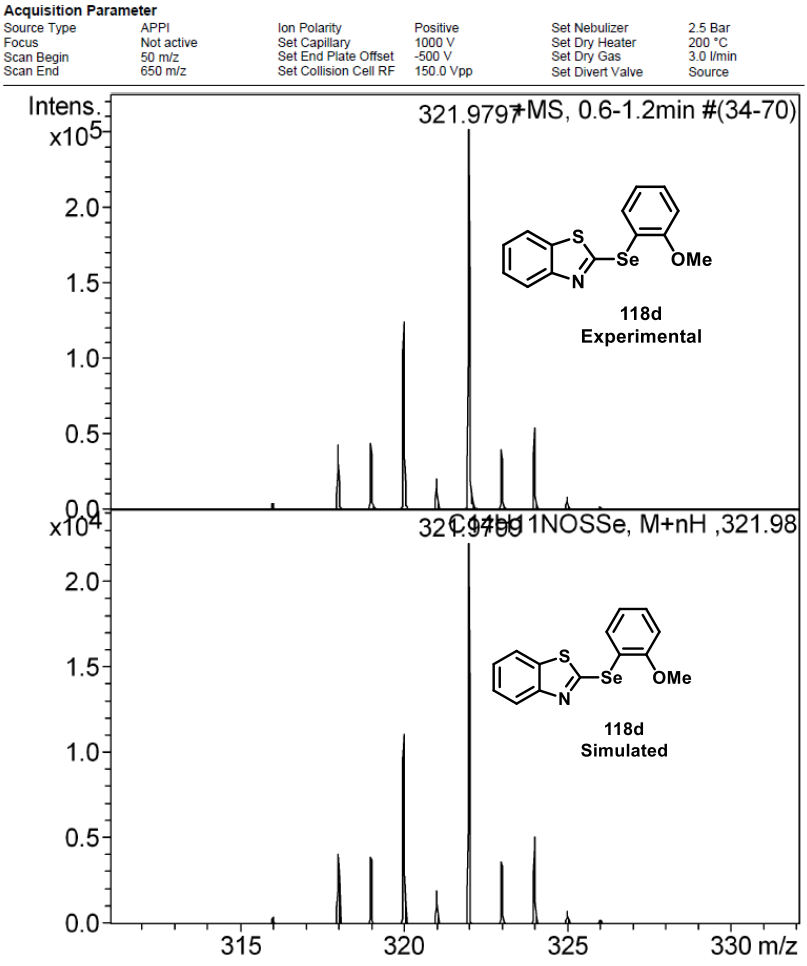
High-resolution mass spectrum of compound **118c**



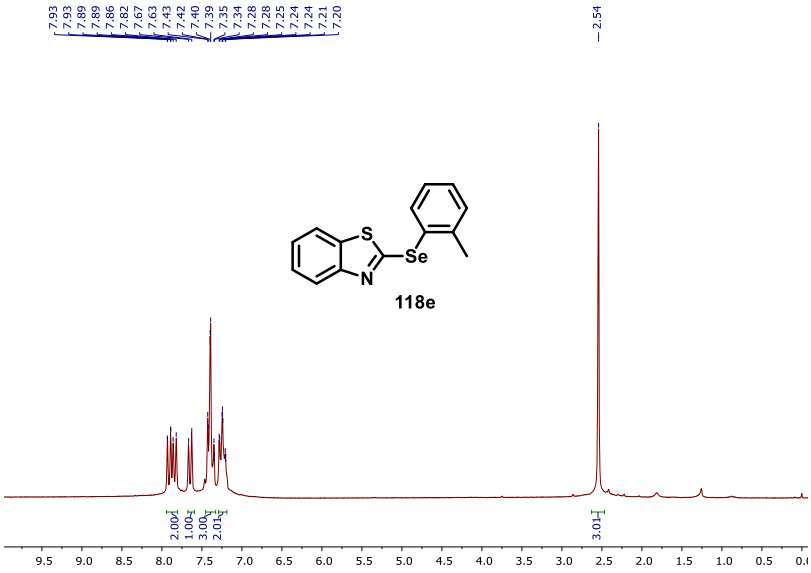
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118d**



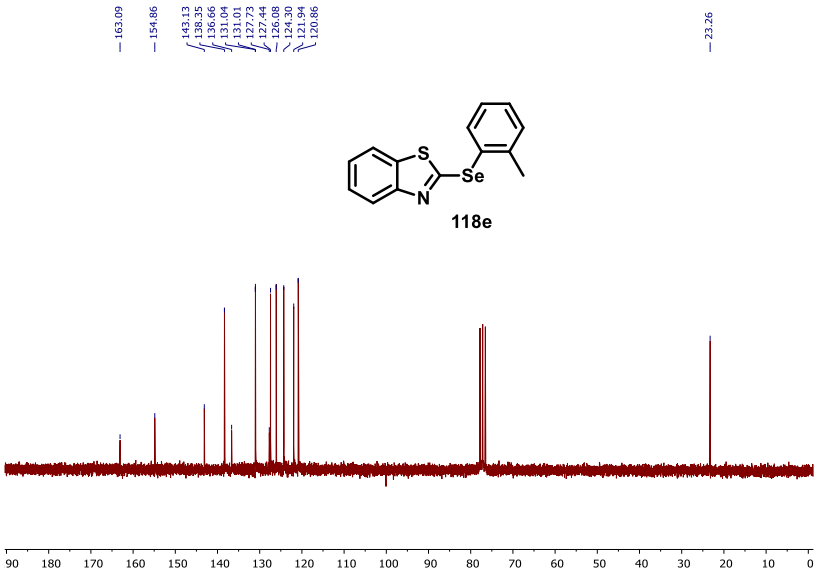
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118d**



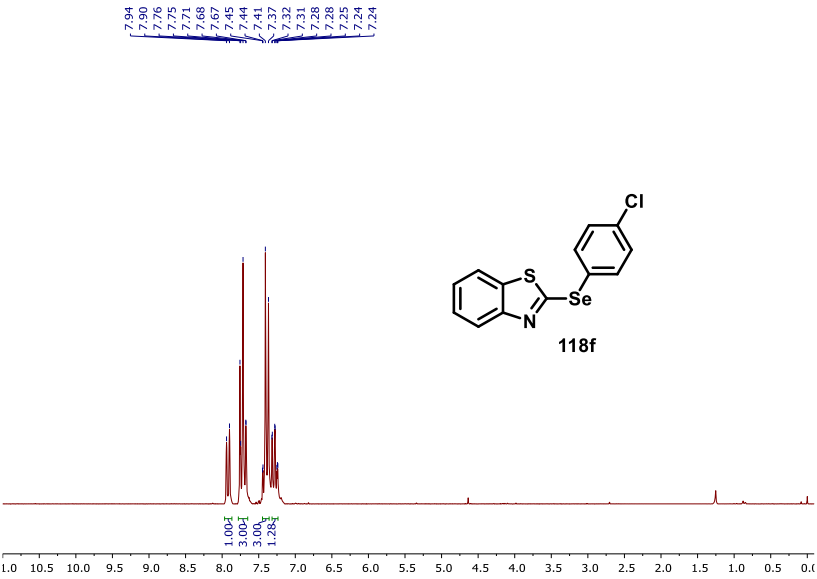
High-resolution mass spectrum of compound **118d**



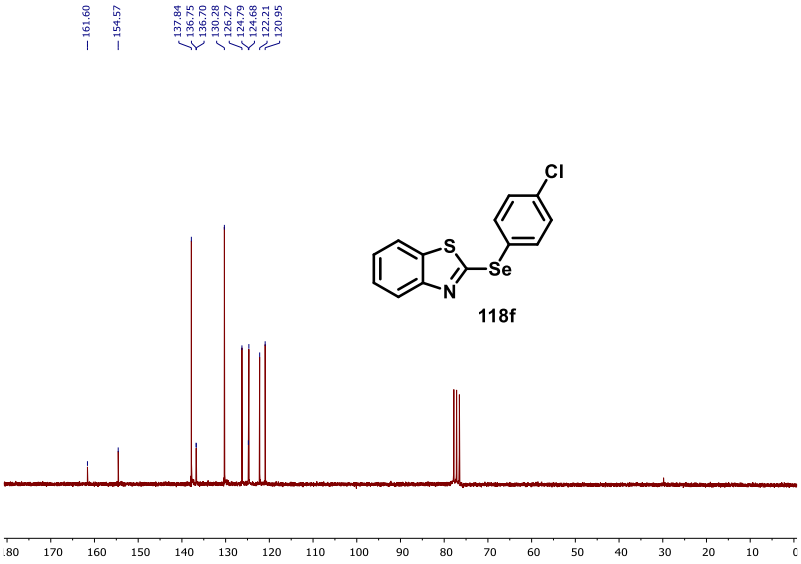
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118e**



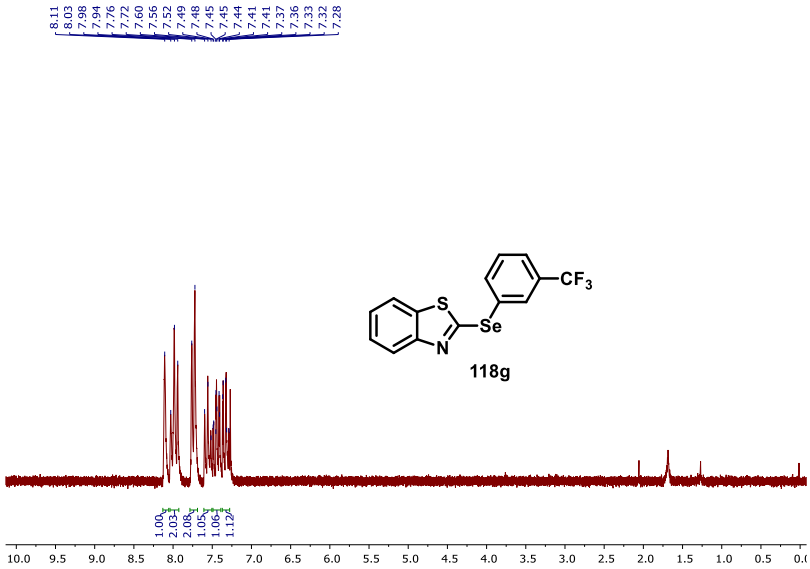
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118e**



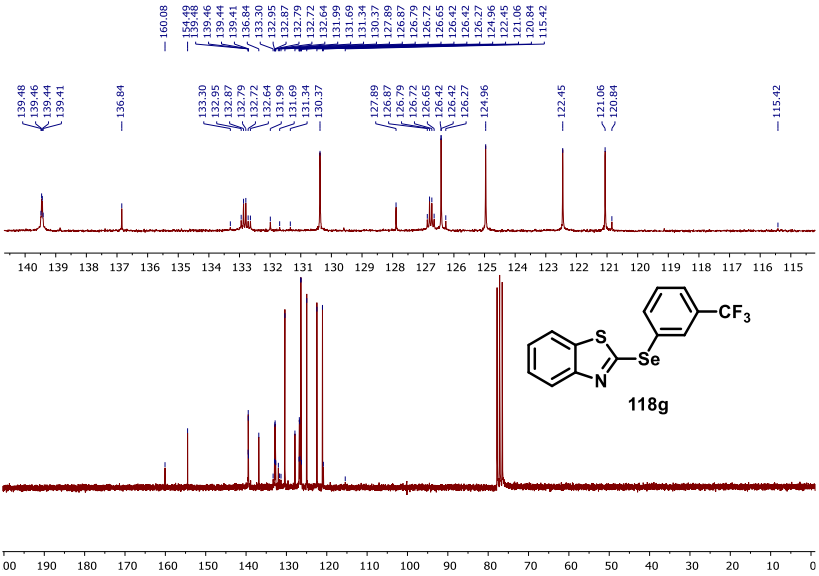
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118f**



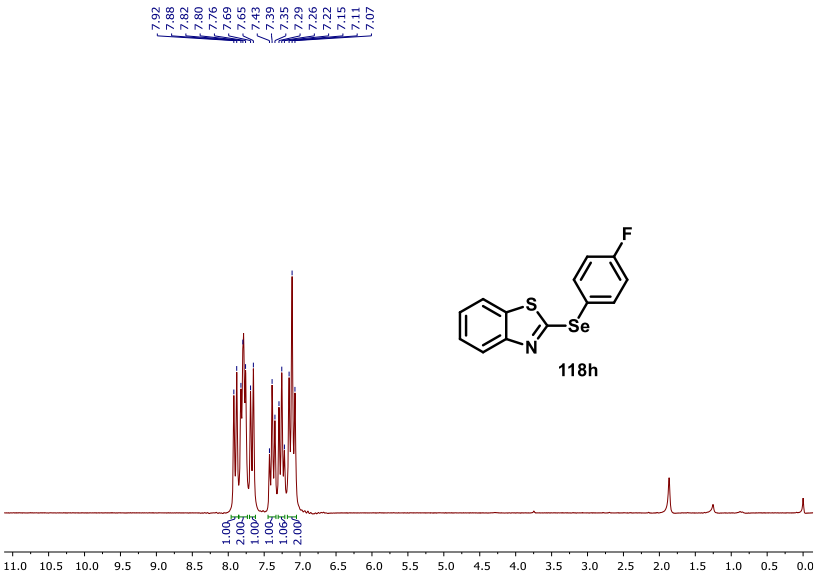
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118f**



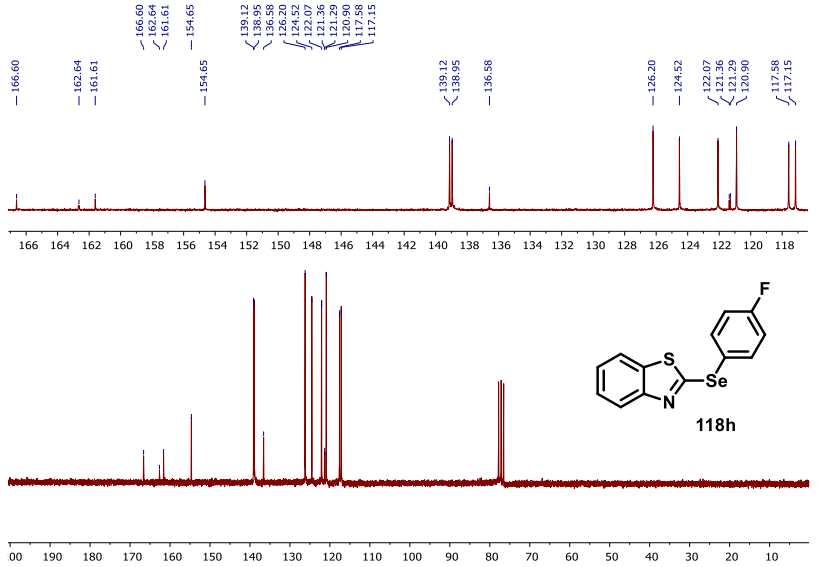
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118g**



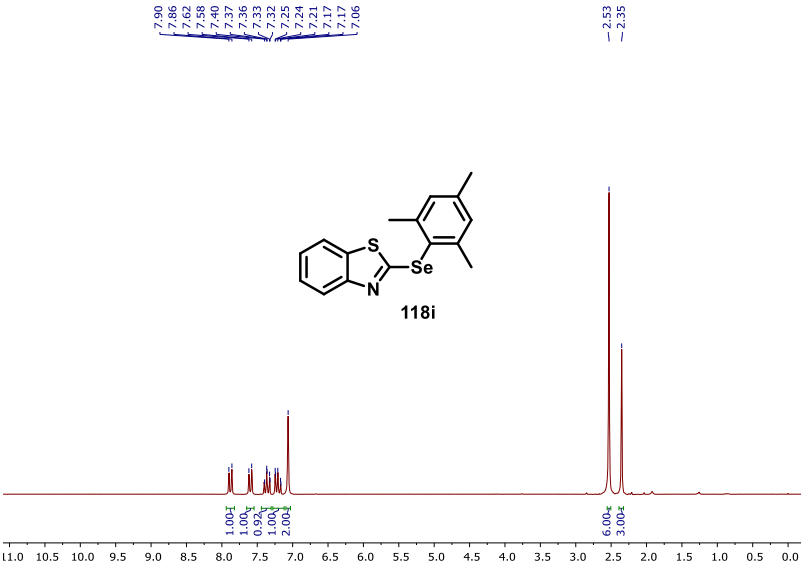
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118f**



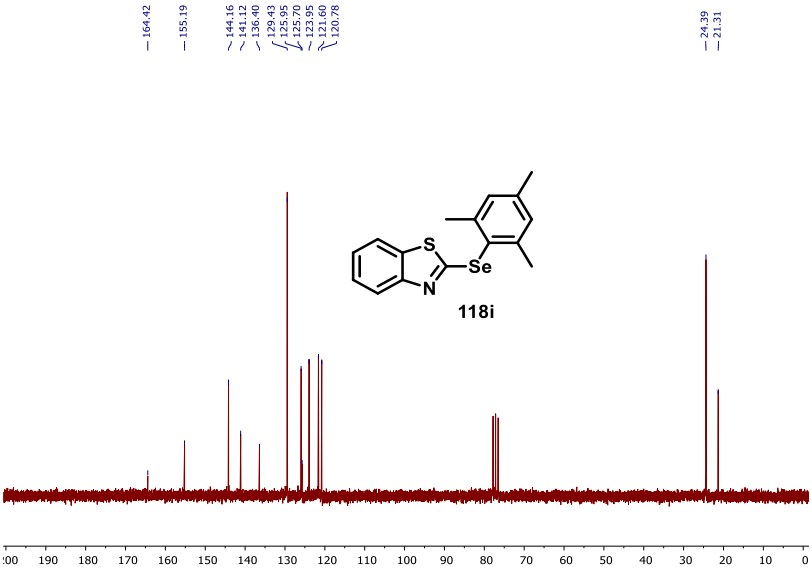
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118h**



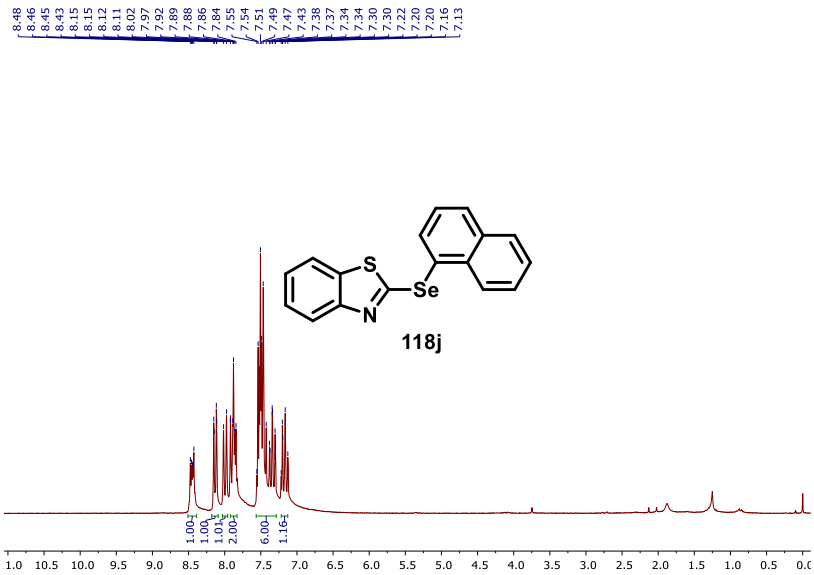
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118h**



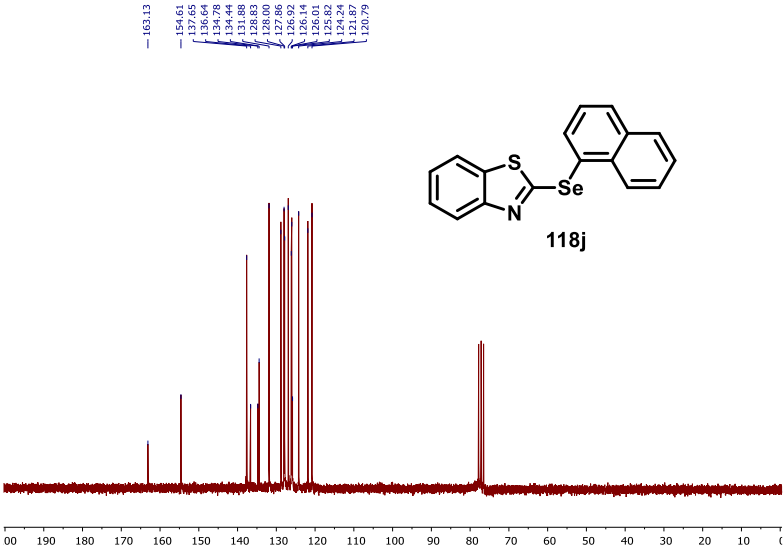
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118i**



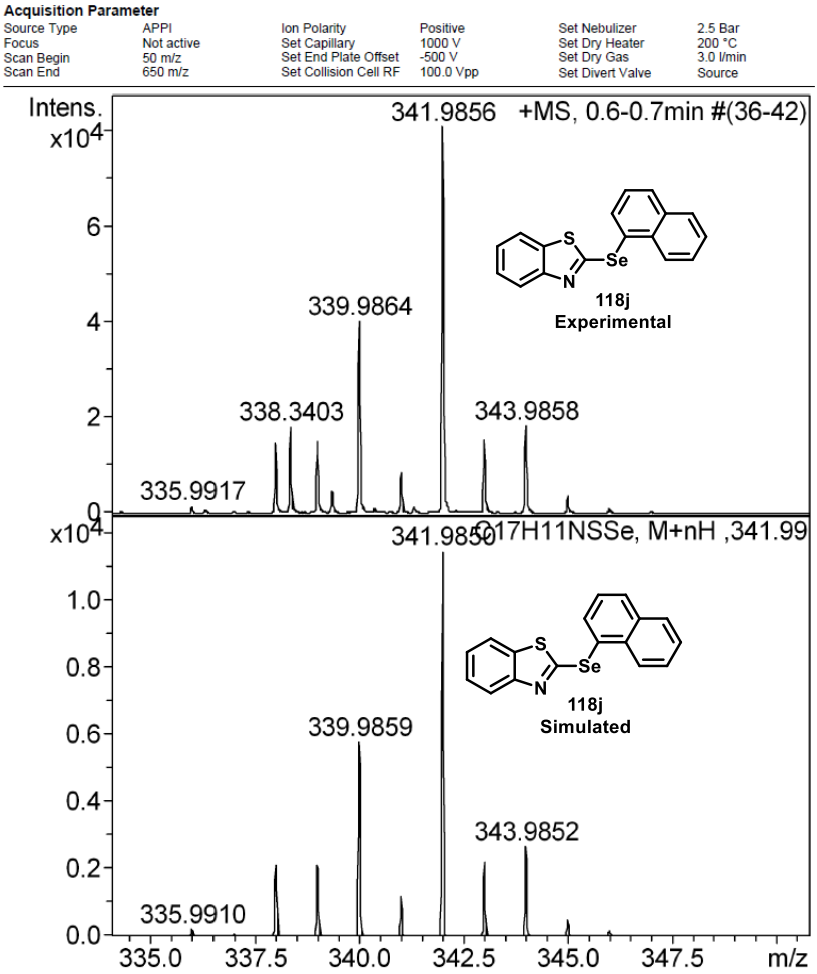
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118i**



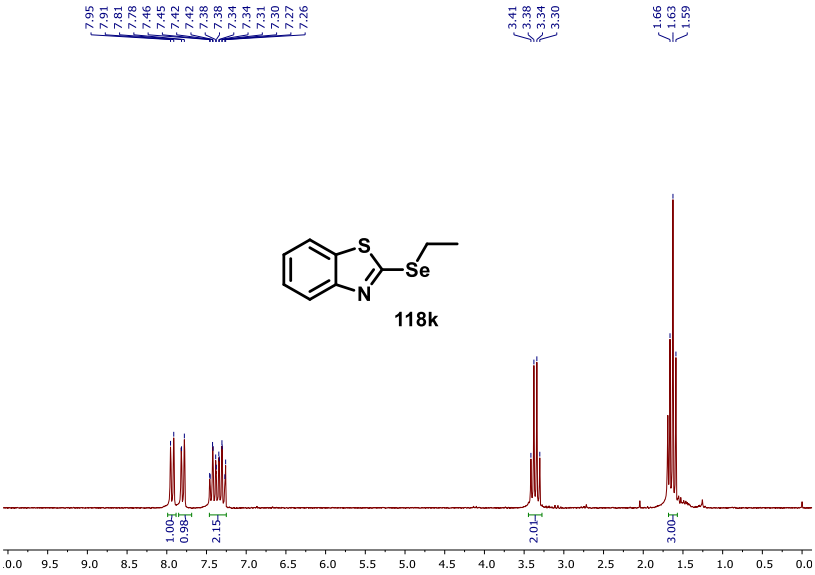
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118j**



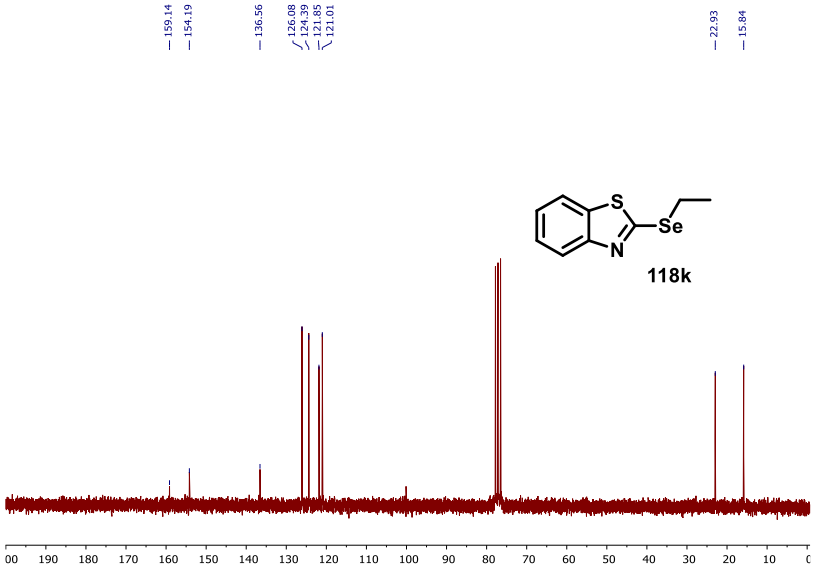
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118j**



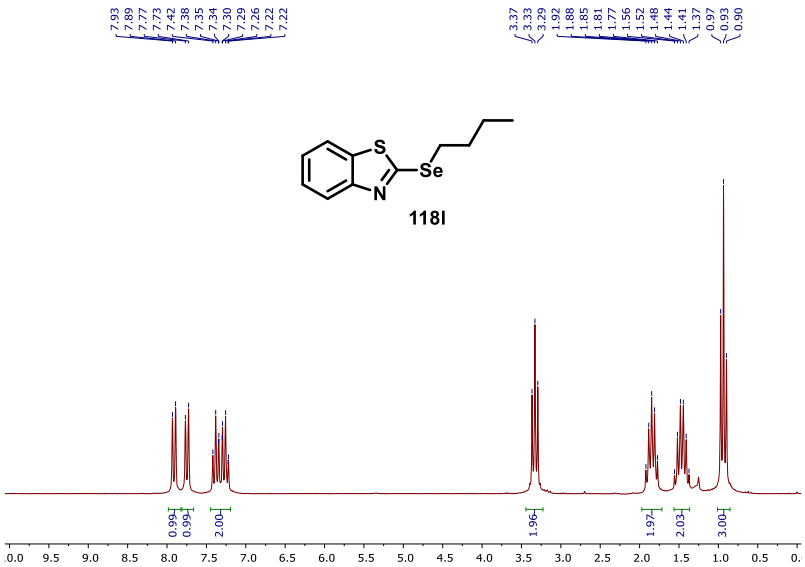
High-resolution mass spectrum of compound **118j**



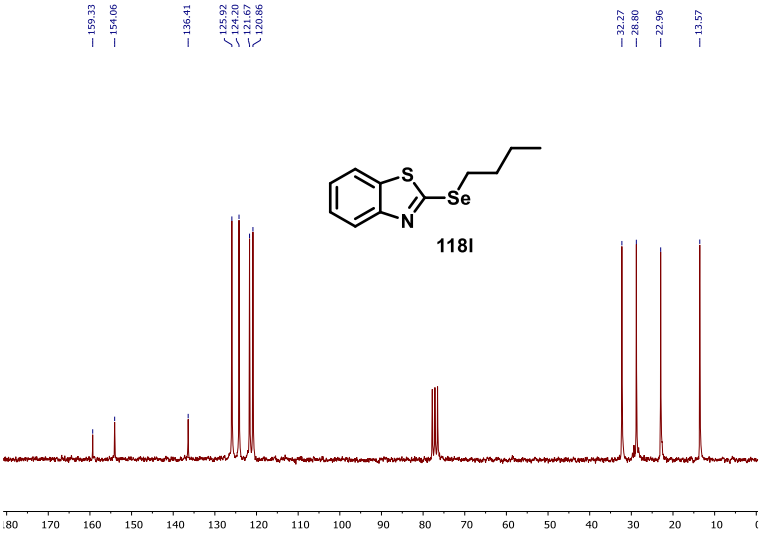
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118k**



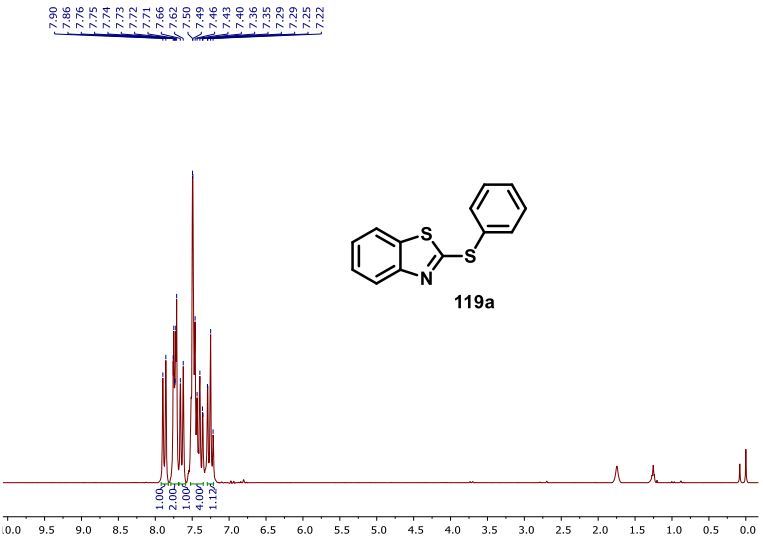
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118k**



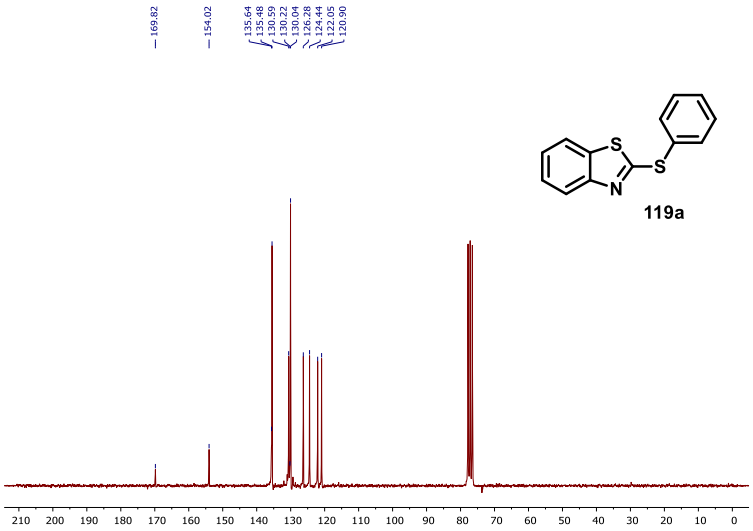
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **118l**



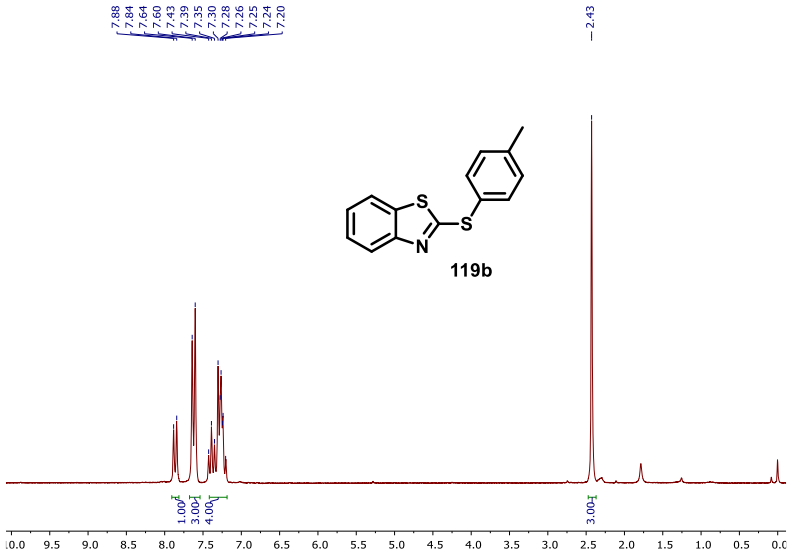
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **118l**



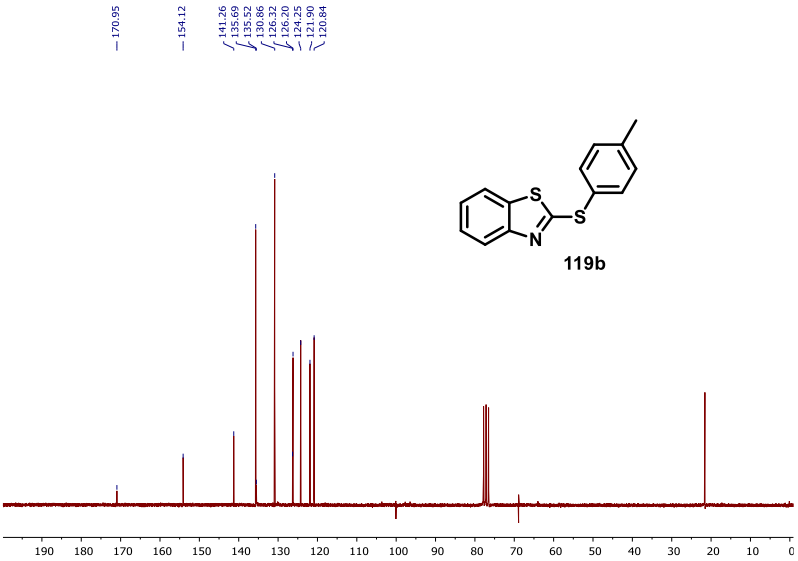
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **119a**



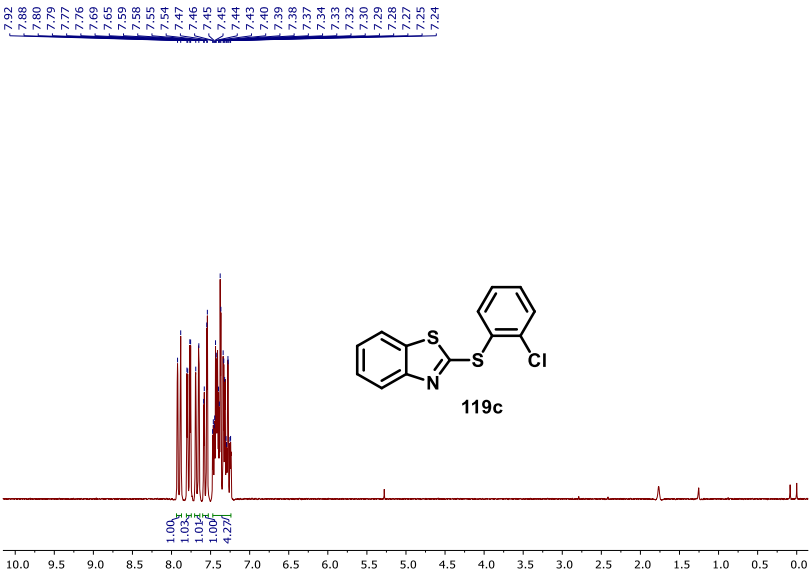
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **119a**



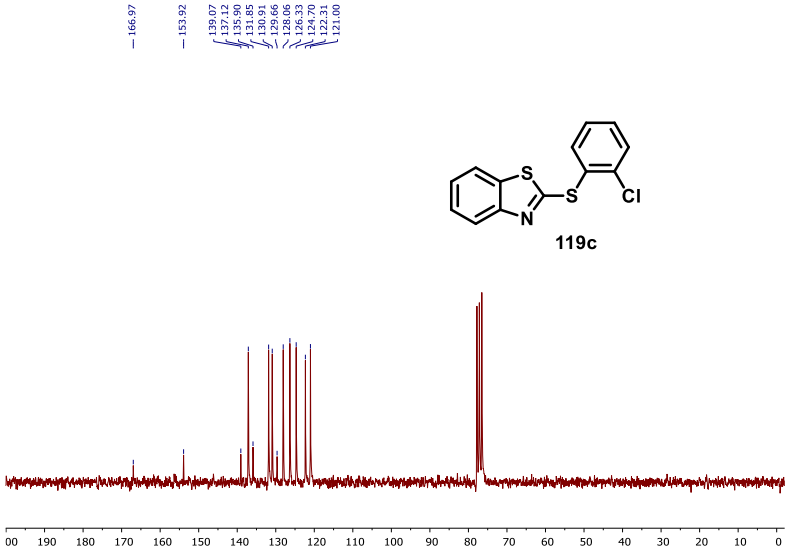
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **119b**



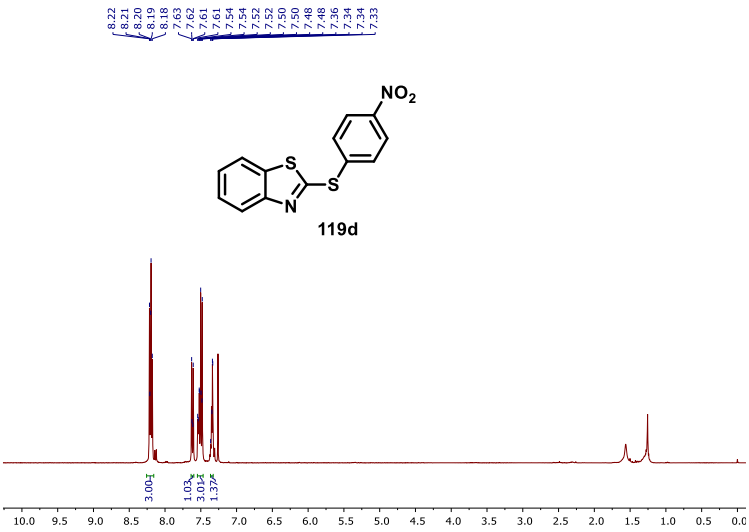
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **119b**



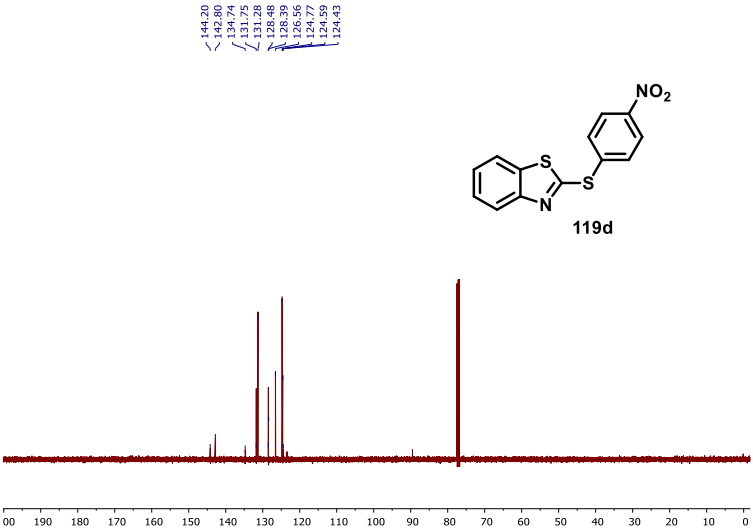
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **119c**



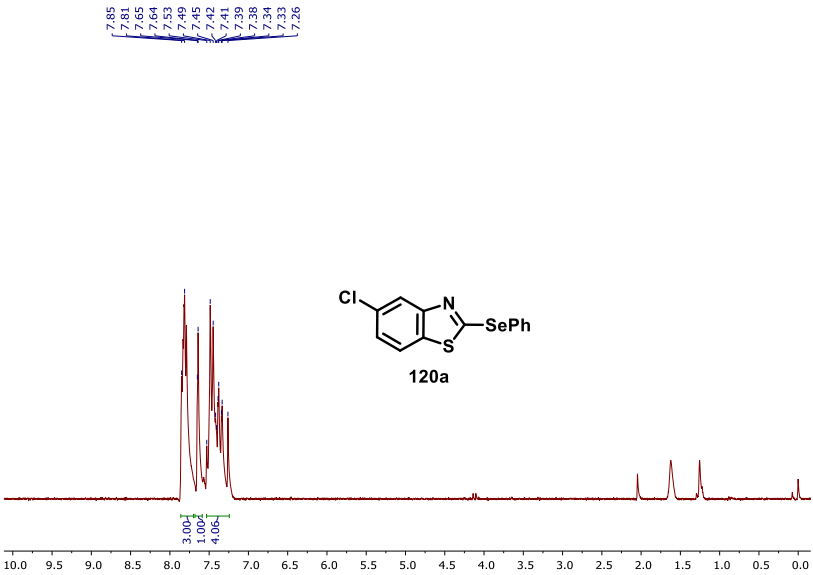
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **119c**



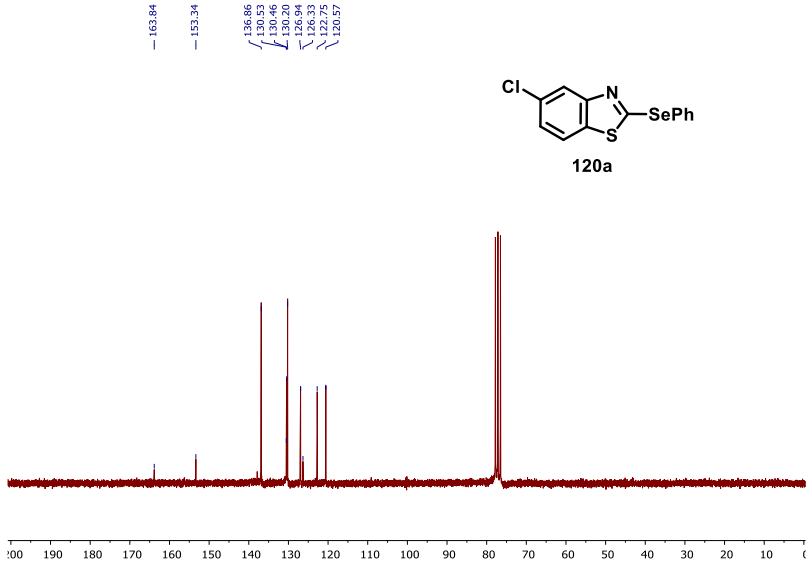
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **119d**



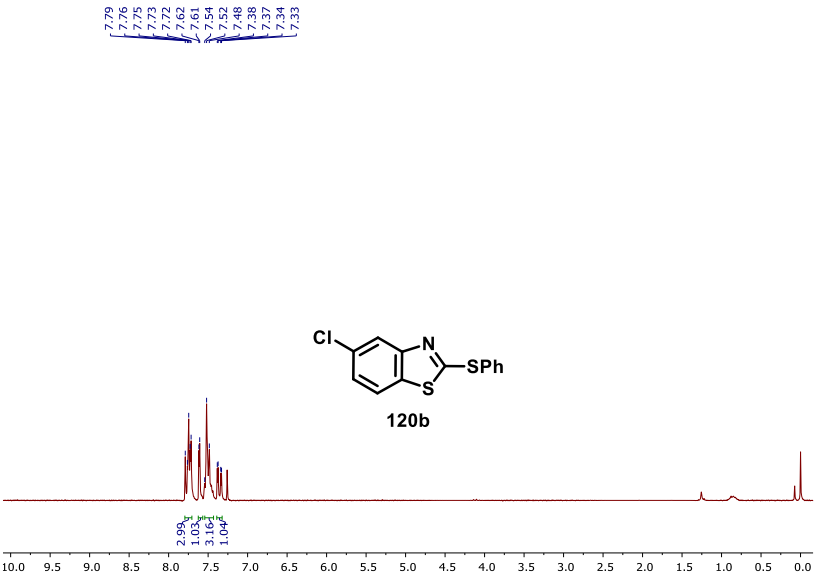
^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **119d**



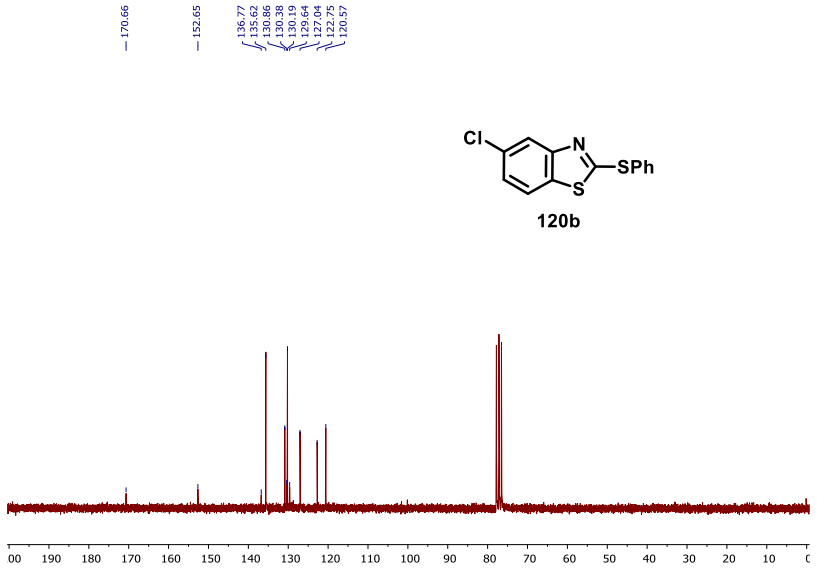
^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **120a**



^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **120a**



^{1}H NMR (200 MHz, $CDCl_3$) spectrum of **120b**



^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **120b**

Annexes

1. Published Article

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K_2CO_3-mediated, direct C–H bond selenation and thiolation of 1,3,4-oxadiazoles in the absence of metal catalyst: an eco-friendly approach†

Jamal Rafique,[a] Sumbal Saba,[a] Alisson R. Rosário,[a] Gilson Zeni[b] and Antonio L. Braga*[a]

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An eco-friendly, straightforward and high-yielding methodology for the synthesis of chalcogenyl oxadiazoles *via* the K_2CO_3-promoted direct C–H bond chalcogenation of 2-substituted-1,3,4-oxadiazoles is described herein. The reaction was performed in the absence of metal catalyst and inert atmosphere using only half an equiv. of dichalcogenide and a low-cost base.

Metal-free reactions can be applied in the functionalization of C–H bonds to access C–C and C–heteroatom bonds and this has become a rapidly developing area.[1] In this regard, one of the most important discoveries made in organic synthesis in recent years is that certain reactions which were thought to involve transition metal (TM) catalysis can, in fact, proceed without the requirement for a TM.[2] Reactions carried out under metal-free conditions are particularly attractive in the synthesis of pharmaceuticals.[3] Therefore, from the economic and environmental viewpoints, it would be advantageous and desirable to develop TM-free systems in the area of organic synthesis.

The synthetic versatility of organochalcogenides has been explored extensively in research articles,[4] reviews[5] and books.[6] This group includes the organoselenium compounds, which can be employed in certain reactions[7] as catalysts,[8] ionic liquids,[9] and synthetic intermediates in total synthesis.[5f,10] Another important advancement in this context is the formation of C–Se bonds, which has contributed to the synthesis of a wide range of biologically active molecules[11] and functional materials.[12] A large number of organoselenides have been found to function as antioxidants, antinociceptive agents, antidepressant apoptosis inducers and chemopreventors in several organs, *etc.*[5d–e,11]

Functionalization of the 1,3-4-oxadiazoles scaffold is an important synthetic task, since oxadiazoles are well established as "privileged scaffolds" and are widely used for pharmaceutical, biological and material applications.[13] They show a very broad spectrum of biological activity, being used, for instance, as inhibitors of various enzymes and as antimicrobial, analgesic, antiviral and antitumor agents.[14] Interestingly, few of the active compounds have a sulphur linkage at C-5.[14b] 1,3,4-Oxadiazole motifs are also of interest in material science and have been widely used to create novel materials.[15]

Many methods for the C–H functionalization of 1,3,4-oxadiazoles have been reported in the literature with the formation of C-alkyl,[16a] C-allyl,[16b] C-alkynyl,[16c] C-aryl,[16d] C-benzyl,[16e] C–N,[16f] C–S,[16g–h] *etc.* However, the disadvantages associated with many of these methodologies, owing to the use of TM catalysts, expensive reagents, harsh reaction conditions, hazardous materials, oxygen-free techniques or elaborate multi-stepped processes, have limited their synthetic scope.

Considering the significance of these compounds, the challenging task of developing new green routes for the syntheses of chalcogenides which provide high efficiency, through direct substitution with heteroaromatics and other organic moieties, is an important research area.[17] As part of our wider research program aimed at designing and developing eco-friendly processes,[18] herein we report for the first time a straightforward, mild, and environmentally benign protocol for the direct selenation of 1,3,4-oxadiazole, which is also applicable to disulphides. The functionalization of C_{sp^2}–H bonds proceeded smoothly with half equiv. of different dichalcogenides and a low-cost base in the absence of a metal catalyst and in an inert atmosphere.

To identify the best reaction conditions, 2-(4-methylphenayl)-1,3,4-oxadiazole (**1a**) and diphenyl diselenide (**2a**) were initially used as standard substrates under different conditions, Table 1. Considering the need for a metal catalyst and base under inert atmosphere for C_{sp^2}–H bond funtionalization,[17b] a preliminary experiment was performed using 1 equiv. of K_2CO_3 and 20 mol% of CuO-nanopowder under an inert atmosphere in

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† Electronic supplementary information (ESI) available: Details on the experimental procedure and characterization, as well as the spectral data for all synthesized compound. See DOI: 10.1039/c4ra10490k

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2 Published Article

ASIAN JOURNAL OF ORGANIC CHEMISTRY

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Solvent-Free Fmoc Protection of Amines Under Microwave Irradiation

Marcelo Godoi, Giancarlo V. Botteselle, Jamal Rafique, Manuela S. T. Rocha, Jesus M. Pena, and Antonio L. Braga*[a]

The development of selective and mild methods for the protection of amines is important for organic synthesis and has proved to be particularly useful for reactions that involve multistep transformations.[1] In this context, carbamates have become one of the most attractive protecting group for amines.[2] Consequently, several kinds of protecting groups have been successfully used in this regard.[3] Among them, the 9-fluorenylmethoxycarbonyl (Fmoc) group has become one of the most versatile protecting groups[4] because of its important features of lability in basic media and stability in acidic media.[5] The Fmoc group has been notably used for orthogonal protection of organic molecules[6] as well as in transprotection[7] and in cascade elimination reactions.[8] Furthermore, Fmoc-protected amino compounds have been used as a synthetic intermediates in nucleophilic additions of enamines to acyl iminium ions.[9]

As a result of their importance, several methods for the preparation of Fmoc-protected amines have been developed to date. Some of these methods have used commercially available reagents, such as Fmoc chloride[10] and 9-fluorenemethanol.[11] Also, Fmoc-protected amines have been prepared from different compounds,[12] including polymers,[13] dimethoxytriazinyloxy moiety,[14] triazoles[15] and through photochemical acylation.[16]

Nevertheless, all of these procedures have their own particular drawbacks, such as the use of expensive catalysts, long reaction time, and/or the use of toxic (e.g. carcinogenic) solvents. Furthermore, some methods require compounds that are not readily available and the Fmoc-derived reagents must be synthesized beforehand.

More recently, Gawande and Branco have used water as a solvent for the Fmoc protection of amines.[17] Despite the good features, there is still the issue of the wastewater, which requires appropriate treatment and, with some exceptions, this is associated with a high cost.[18] Therefore, a mild and environmentally benign method for obtaining high yields in the Fmoc protection of amines remains highly desirable.

In this regard, microwave irradiation has been shown to provide higher yields under milder reaction conditions in shorter reaction times for several reactions compared with conventional methods.[19] From a sustainable point of view, studies that involve microwave irradiation associated with neat conditions have arisen as a promising choice for the development of sustainable chemical protocols.[20] In this context, we recently reported a method for the protection of selenolate anions by using this type of attractive combination.[21]

Thus, in connection with our continuing interest in solvent-free transformations in short reaction times, herein we describe the Fmoc protection of amines in the absence of solvent under microwave irradiation (Scheme 1).

Scheme 1. Solvent-free Fmoc protection of amines.

To optimize our method, we initiated our studies by evaluating the reaction between aniline (**1a**) and FmocCl (**2**) in the absence of solvent, under microwave irradiation (Table 1).

At first, the reaction was carried out for one minute, and furnished the desired product in only 63% yield (Table 1, entry 1). To improve the yield we performed the reaction under argon (Table 1, entry 2). However, the inert atmosphere had no influence on the reaction; therefore, further experiments were conducted open to the atmosphere.

On the other hand, on increasing the time to three minutes the yield improved significantly (Table 1, entry 3). It is noteworthy that when the reaction was carried out for five minutes the desired product was obtained in 96% yield (Table 1, entry 4).

After establishing the best reaction time, we evaluated the effect of temperature on the reaction by raising the temperature from 80 to 110 °C, and the yield did not change significantly (Table 1, entry 5). However, when the reaction was performed at 50 °C the desired product was

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Abstract

The design and synthesis of organoselenium compound as bioactive structures have achieved a new dimension since the 1970s, when many reports described the identification of various selenoproteins, which are involved in a wide variety of biological processes, including antioxidant defense, thyroid hormone production and immune response. In this chapter, strategies and methods for the preparation of synthetic antioxidants containing selenium are reviewed. The unique redox properties of selenium confer catalytic activity to organoselenium compounds and influence their biological properties as well as the methods selected for their preparation. Several approaches can be applied in order to obtain organoselenium compounds, such as reaction of elemental selenium or diselenides with different types of carbanions or reaction of organic electrophiles with selenolate anions generated by different methods, as discussed herein.

Keywords:
Selenium; diselenide; selenide; ebselen; Gpx; antioxidants; lipid peroxidation; peroxynitrite

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Abstract

In the 19705 many reports described the identification of various selenoproteins, which are involved in a wide variety of biological processes, including antioxidant defense, thyroid hormone production and immune response. This brought a new dimension to the design and synthesis of organoselenium compounds as bioactive structures. In this chapter, strategies and methods for the preparation of anti-infective, chemopreventive as well as anticancer compounds are reviewed. The unique redox properties of selenium confer catalytic activity to organoselenium compounds and influence their biological propert ies as well as the methods selected for their preparation. Several approaches can be applied In order to obtain organoselenium compounds, such as reaction of elemental selenium or diselenides with different types of carbon nucleophiles or reaction of organic electrophiles with selenolate anions generated by different methods, as discussed herein.

Keywords:
selenium; diselenide; antibacterial; antifungal; antiviral; chemopreventive agents; anticancer agents

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Abstract

Organoselenium compounds are known as antioxidants, antithyroid, antinociceptive, antidepressant, thioredoxin reductase (TrxR) mimetic agents with a variety of protective behaviors (e.g. cardioprotective, neuroprotective and hepatoprotective). In addition. they can be used as virueides, bactericides, fungicides, cytokine inducers and immunomodulators. The chemical and biological activity of organose leniumcompounds is discussed herein.

The strategies and methods for the preparation of biologically relevant small molecules containing selenium are reviewed in this chapter. The unique redox properties of selenium confer catalytic activity to organoselenium compounds and influence their biological properties as well as the methods selected for their preparation. The approaches available to obtain organoselenium compounds, including reaction of elemental selenium or diselenides with different types of carbanions or reaction of organic electrophiles with selenolate anions generated by different methods, are disclosed in this chapter.

Keywords:
selenium; diselenide; selenidc; antithyroid; antinociceptive; antidepressant; thioredoxin reductase

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DOU_Nomeia_Reitora.pdf *[OUTROS-3.pdf]*	Documentos de qualquer outra natureza em formato eletrônico PDF	1

2 Deposited Patent

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DIRPA	Tipo de Documento: Formulário	DIRPA	Página: 1/3
Título do Documento: Depósito de Pedido de Patente		Código: FQ001	Versão: 2
		Procedimento: DIRPA-PQ006	

Ao Instituto Nacional da Propriedade Industrial:
O requerente solicita a concessão de um privilégio na natureza e nas condições abaixo indicadas:

1. Depositante (71):

1.1 Nome: UNIVERSIDADE FEDERAL DE SANTA CATARINA
1.2 Qualificação: Autarquia Federal
1.3 CNPJ/CPF: 83.899.526/0001-82
1.4 Endereço Completo: Campus Universitário, s/n, Trindade, Florianópolis/SC
1.5 CEP: 88040-900
1.6 Telefone: (48) 37219628 1.7 Fax:
1.8 E-mail: dit@contato.ufsc.br

☐ continua em folha anexa

2. Natureza: ☒ Invenção ☐ Modelo de Utilidade ☐ Certificado de Adição

3. Título da Invenção ou Modelo de Utilidade (54):

PROCESSO DE SÍNTESE DE DISSELENETOS DE ÁCIDO SALICÍLICO, E, SELENOCIANATO DE DERIVADO DE ÁCIDO SALICÍLICO

☐ continua em folha anexa

4. Pedido de Divisão: do pedido Nº **Data de Depósito:**

5. Prioridade: ☐ Interna (66) ☐ Unionista (30)

O depositante reivindica a(s) seguinte(s):

País ou Organização do depósito	Número do depósito (se disponível)	Data de depósito

☐ continua em folha anexa

3 Deposited Patent

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Título do Documento: Depósito de Pedido de Patente		Código: FQ001	Versão: 2
		Procedimento: DIRPA-PQ006	

Ao Instituto Nacional da Propriedade Industrial:
O requerente solicita a concessão de um privilégio na natureza e nas condições abaixo indicadas:

1. **Depositante (71):**

1.1 Nome: UNIVERSIDADE FEDERAL DE SANTA CATARINA

1.2 Qualificação: Autarquia Federal

1.3 CNPJ/CPF: 83.899.526/0001-82

1.4 Endereço Completo: Campus Universitário, s/n, Trindade, Florianópolis/SC

1.5 CEP: 88040-900

1.6 Telefone: (48) 3721-9628 1.7 Fax:

1.8 E-mail: dit@contato.ufsc.br

☐ continua em folha anexa

2. **Natureza:** ☒ Invenção ☐ Modelo de Utilidade ☐ Certificado de Adição

3. **Título da Invenção ou Modelo de Utilidade (54):**

DISSELENETO DERIVADO DE COLESTEROL, PROCESSO DE OBTENÇÃO E USO DE UM DISSELENETO

☐ continua em folha anexa

4. **Pedido de Divisão: do pedido Nº** **Data de Depósito:**

5. **Prioridade:** ☐ Interna (66) ☐ Unionista (30)

O depositante reivindica a(s) seguinte(s):

País ou Organização do depósito	Número do depósito (se disponível)	Data de depósito

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4 Deposited Patent

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DIRPA	Tipo de Documento: Formulário	DIRPA	Página: 1/3
Título do Documento: Depósito de Pedido de Patente		Código: FQ001	Versão: 2
		Procedimento: DIRPA-PQ006	

Ao Instituto Nacional da Propriedade Industrial:
O requerente solicita a concessão de um privilégio na natureza e nas condições abaixo indicadas:

1. Depositante (71):

1.1 Nome: UNIVERSIDADE FEDERAL DE SANTA CATARINA
1.2 Qualificação: Autarquia Federal
1.3 CNPJ/CPF: 83899526000182
1.4 Endereço Completo: Campus Universitário, S/N, Trindade
1.5 CEP: 88040-900
1.6 Telefone: 48 3721-9628 1.7 Fax:
1.8 E-mail: dit@reitoria.ufsc.br

☐ continua em folha anexa

2. Natureza: ☒ Invenção ☐ Modelo de Utilidade ☐ Certificado de Adição

3. Título da Invenção ou Modelo de Utilidade (54):

DISSELENETO DERIVADO DA 2-PICOLILAMINA E PROCESSO PARA SUA OBTENÇÃO

☐ continua em folha anexa

4. Pedido de Divisão: do pedido Nº **Data de Depósito:**

5. Prioridade: ☐ Interna (66) ☐ Unionista (30)

O depositante reivindica a(s) seguinte(s):

País ou Organização do depósito	Número do depósito (se disponível)	Data de depósito

☐ continua em folha anexa

Universidade Federal de Santa Catarina
Pró-Reitoria de Pós-Graduação

HISTÓRICO ESCOLAR

Nome: **Jamal Rafique Khan** Matrícula: 201101847
Data de nascimento: 3 de Maio de 1984 Identificação: 4100042
Naturalidade: não informada Nacionalidade: paquistanesa
Filiação: Muhammad Rafique Khan
Begum Asia Rafique
Programa de Pós-Graduação em Química
Portaria nº 1077/MEC/2012 de 31/08/2012 DOU de 13/09/2012
Pólo: Universidade Federal de Santa Catarina
Nível: Doutorado
Área de Concentração: Química Orgânica
Linha de Pesquisa: Não definida
Orientador: Antonio Luiz Braga
Data de Início no Curso: 01/03/2011 Regimento: 2010
Situação: Curso concluído com Defesa de Trabalho de Conclusão
Modalidade: Presencial

Pendência: não entregou versão final da Tese na Biblioteca Universitária

DISCIPLINAS

Periodo Letivo: 2011/1

Disciplina		Conc.	Freq.	- Créd. - T	TP	P	Val.	Professor
QMC510018	Metodologia da Pesquisa 1	A	FS	4				Dr. ALMIR SPINELLI

Periodo Letivo: 2011/2

Disciplina		Conc.	Freq.	- Créd. - T	TP	P	Val.	Professor
QMC510007	CATÁLISE HOMOGÊNEA	B	FS	4				Dr. FARUK JOSE NOME AGUILERA
QMC510019	Metodologia da Pesquisa 2	A	FS	4				Dr. ALMIR SPINELLI

Periodo Letivo: 2012/1

Disciplina		Conc.	Freq.	- Créd. - T	TP	P	Val.	Professor
QMC3208000	Análise Orgânica	B	FS	4				Dr. MIGUEL SORIANO BALPARDA CARO
QMC3410000	Seminário	S	FS					

Periodo Letivo: 2012/2

Disciplina		Conc.	Freq.	- Créd. - T	TP	P	Val.	Professor
QMC3209000	Síntese Orgânica	B	FS	4				Dr. ANTONIO LUIZ BRAGA

Periodo Letivo: 2013/1

Disciplina		Conc.	Freq.	- Créd. - T	TP	P	Val.	Professor
EST510006	Estágio de Docência 2 Semestre: 20131 Disciplina: QMC5230 Química Orgânica Experimental I 04216B Fase: 04 Créditos: 4 Curso: ENGENHARIA QUÍMICA Prof(a): ANTONIO LUIZ BRAGA	A	FS	4				Antonio Luiz Braga

Periodo Letivo: 2014/2

Disciplina		Conc.	Freq.	- Créd. - T	TP	P	Val.	Professor
EST510005	Estágio de Docência 1 Semestre: 20142 Disciplina: QMC5230 Química Orgânica Experimental I 04216B Fase: 04 Créditos: 4 Curso: ENGENHARIA QUÍMICA Prof(a): ANTONIO LUIZ BRAGA	A	FS	4				Antonio Luiz Braga
QMC510035	QMC3120 Tópicos Especiais em Química: Element Analysis for Speciaton, Bioanalysis and Metallomics	A	FS	1				Dr. BERNHARD WELZ Dr. JÖRG FELDMANN

Índice de aproveitamento: 3,59		**Créditos completados em disciplinas:**	**29**
Carga horária: 975 horas/aula		**Créditos externos à UFSC em Disciplinas:**	**24**
Créditos exigidos em Disciplinas:	**48**		
Créditos exigidos em Tese:	**12**		
Total de créditos exigidos:	**60**	**Créditos completados em Tese:**	**12**
		Total de créditos completados:	**65**

Escala de Equivalência dos Conceitos:	Conceito	Descrição	Valor
	A	EXCELENTE, com direito a créditos	4
	B	BOM, com direito a créditos	3
	C	REGULAR, com direito a créditos	2
	E	INSUFICIENTE, sem direito a créditos	0
	I	INCOMPLETO, sem direito a créditos	0
	T	TRANSFERIDO, sem direito a conceito e com direito a créditos	0

É considerado aprovado se obtém Frequência Suficiente (FS) e conceito igual ou superior a C.

Legenda
Conc. Conceito
Freq. Frequência
Créd. Créditos, onde:
T = Teórico (1 = 15 Horas Aula)
TP = Teórico-Prático (1 = 30 Horas Aula)
P = Prático (1 = 45 Horas Aula)
Val. Validação

BOLSAS

Descrição	Data de Início	Data de Término
CNPq	01/03/2011	08/12/2014

EVENTOS

Descrição	Data da Avaliação	Avaliação	Data de Início	Data de Término	Crédito/Carga Horária
Seminários	28/06/2012	Aprovado	05/03/2012	28/06/2012	
Seminários oferecidos pelo Programa de Pós-Graduação em Química da UFSC.					
Seminários	02/12/2011	Aprovado	08/08/2011	02/12/2011	
Seminários oferecidos pelo Programa de Pós-Graduação em Química da UFSC.					
Qualificação do Projeto de Tese	15/10/2014	Aprovado	01/03/2011	15/10/2014	
Exame de Qualificação defendino no Programa de Pós-Graduação em Química da UFSC. Portaria Nº 056/PPGQ/2014.					
Tese	08/12/2014	Aprovado	01/03/2011	08/12/2014	12 créditos - 180 horas/aula
Tese defendida no Programa de Pós-Graduação em Química da UFSC. Portaria Nº 070/PPGQ/2014.					
Proficiência em Língua - Inglês	20/07/2010	Aprovado			
Exame de Proficiência de Língua Estrangeira (Inglês), realizado na University of Malakand e validado para o Programa de Pós-Graduação em Qu´mica da UFSC.					
Proficiência em Língua - Português	08/10/2012	Aprovado			
Exame de Proficiência de Língua Estrangeira (Português), elaborado e aplicado no Programa de Pós-Graduação em Qu´mica da UFSC.					

INFORMAÇÕES DA TESE

Título:Synthesis of Heterocycles Containing Chalcogens By C-H Functionalization: A Green Approach.
Orientador: Antonio Luiz Braga

Resumo: KHAN, Jamal Rafique. Síntese de heterociclos contendo calcogênios através da funcionalização C-H: uma abordagem verde. Florianópolis, 2014. 217 p. Tese de Doutorado em Química - Programa de Pós-Graduação em Química, Universidade Federal de Santa Catarina.

Orientador: Antonio Luiz Braga
Defesa: 08/12/2014

No presente trabalho desenvolveram-se novas metodologias eficientes, econômicas e ambientalmente adequadas para a síntese de oxadiazóis e benzotiazóis contendo uma porção organocalcogênio. Primeiramente, desenvolvemos a síntese de oxadiazóis selenados e tiolados através da funcionalização de ligação Csp2-H promovida por K2CO3,em um meio reacional livre de metais de transição. Em uma primeira etapa, foram preparados oxadiazóis selenados com potencial para aplicações biológicas. Sob condições suaves, a reação ocorreu de maneira eficiente na presença de um equivalente do correspondente oxadiazol, um equivalente de base (K2CO3,), 0,5 equivalentes do correspondente dicalcogeneto de organoíla, na presença de ar atmosférico. Através dessa metodologia, uma série de oxadiazóis calcogenados na posição 5 do heterociclo foram obtidos em rendimentos que variaram de bons a excelentes. Adicionalmente, explorou-se a reatividade dos oxadiazóis selenados em reações de troca calcogênio-lítio. Os intermediários oxadiazóis litiado assim obtidos foram capturado, in situ, com diferentes eletrófilos. É importante salientar, também que essa reação ocorreu de forma eficiente quando se aumentou sua escala para 10 mmol. Em uma segunda etapa, desenvolveu-se um novo método para a incorporação de calcogênios em benzotiazóis via reação de calcogenação direta da ligação C-H. Realizou-se a síntese de 2-organocalcogeno-1,3-benzotiazóis através da calcogenação direta entre 1,3-benzotiazóis e dicalcogenetos de organoíla catalizada por Fe3O4nanopartículado. Esta metodologia permitiu a obtenção dos respectivos produtos calcogenolados, em rendimentos que variaram de moderados a excelentes. Realizou-se, também, com sucesso, a reciclagem do catalisador em 4 ciclos sem um decréscimo acentuado no rendimento.

Palavras-chave: química verde; funcionalização de ligação C-H; disselenetos.

Situação atual da Tese: Curso concluído com defesa da tese
Data da defesa: 08/12/2014 Portaria: Nº 070/PPGQ/2014
Carga Horária: 180 horas/aula Creditos: 12 Conceito: aprovado

BANCA EXAMINADORA

Membro	Função
MARIA DA GRACA NASCIMENTO, Drª.	Membro Titular
GUSTAVO AMADEU MICKE, Dr.	Membro Titular
ANTONIO LUIZ BRAGA, Dr.	Orientador
FÁBIO ZAZYKI GALETTO, Dr.	Membro Titular
MÁRCIO WEBER PAIXÃO, Dr.	Membro Titular - Relator(a)
GUSTAVO POZZA SILVEIRA, Dr.	Membro Titular - Externo

OBSERVAÇÕES

Validados 24 créditos referente disciplinas cursadas no Mestrado em química da University of Malakand, e University of Peshawar, para integralização dos 48 créditos exgidos no Curso de Doutorado em Química da UFSC, área de Química Orgânica.
Aprovado na reunião do colegiado realizada em 24/08/2011, conforme segue abaixo:

Disciplina	Créditos	Carga Horária
MSC01 Physical Chemistry	04	60 - Equivalente a disciplina QMC 3426 Físico-Química do PPGQ/UFSC. (Fora da área)
MSC02 Organic Chemistry	04	60 - Equivalente a disciplina QMC 3207 Química Orgânica Avançada do PPGQ/UFSC. (Dentro da área)
MSC03 In-Organic Chemistry	04	60 - Equivalente a Disciplina QMC 3111 Química Inorgânica Avançada do PPGQ/UFSC. (Fora da área)
MSC04 Analytical Chemistry	04	60 - Equivalente a Disciplina QMC 3306 Química Analítica Avançada do PPGQ/UFSC. (Fora da área)
MSCF1 Environmental Chemistry	04	60 - Equivalente a Disciplina QMC 3443 TEQA: Química Ambiental do PPGQ/UFSC. (Fora da área)
MSCF3 Oxidation/Reduction	04	60 - Equivalente a Disciplina QMC 4209 Química Orgânica Avançada II do PPGQ/UFSC. (Dentro da área)

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