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CENTRO DE CIÊNCIAS NATURAIS E EXATAS
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COPPER OXIDE (CuO) NANOPOWDER: A VERSATILE CATALYST TO SYNTHESIZE ORGANOCHALCOGEN COMPOUNDS

Ph.D THESIS

Devender Singh

Santa Maria, RS, Brasil
2011

COPPER OXIDE (CuO) NANOPOWDER: A VERSATILE CATALYST TO SYNTHESIZE ORGANOCHALCOGEN COMPOUNDS

Devender Singh

Doctoral thesis submitted to the Graduate Program in Chemistry,
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in partial fulfillment of the requirements for the
PhD Degree in Chemistry

Supervisor: Prof. Dr. Antônio Luiz Braga

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FEDERAL UNIVERSITY OF SANTA MARIA
FACULTY OF NATURAL AND HARD SCIENCES
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The undersigned examining committee approved the PhD thesis entitled

COPPER OXIDE (CuO) NANOPOWDER: A VERSATILE CATALYST TO SYNTHESIZE ORGANOCHALCOGEN COMPOUNDS

Devender Singh

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

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To my parents,
Avtar Singh and Harjinder Kaur.

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This thesis arose in part out of the years of research carried out since I came to ‘Braga’s group’. During this time, I have worked with a great number of people whose contribution to the research and the making of this thesis in assorted ways deserves special mention. It is a pleasure to convey my gratitude to all of them in my humble acknowledgment.

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ABSTRACT

PhD Thesis
Graduate Program in Chemistry
Universidade Federal de Santa Maria

COPPER OXIDE (CuO) NANOPOWDER: A VERSATILE CATALYST TO SYNTHESIZE ORGANOCHALCOGEN COMPOUNDS

AUTHOR: DEVENDER SINGH
SUPERVISOR: PROF. DR. ANTONIO LUIZ BRAGA
Date and place of defense: Santa Maria, February 24th, 2011.

Herein, we report an eco-friendly synthesis of a series of organochalcogen compounds (selenides**(1)**, selenoesters**(2)**, sulfides**(3)**, diselenides and ditellurides**(4)**) catalyzed by CuO nanopowder in a variety of ionic liquids as recyclable system and in organic solvents in good to excellent yields. This protocol shows high efficiency in catalyzing this transformation, in a greener fashion than previous protocols. Firstly, the coupling reaction of alkyl or aryl bromides with diselenides was carried out using a catalytic amount of CuO nanopowder (0.5 mol %) and BMIM-BF_4 as a recyclable solvent to get aryl or alky selenides **(1)** in good to excellent yields (65-90%). In the same way, acyl chlorides were also subjected with diselenides to get seleno-esters **(2)** in good to excellent yields (57-91%) by using 5.0 mol% of CuO nanopowder and BMIM-PF_6 as solvent in this transformation. Further, aryl Iodides went under cross-coupling reaction with thiols to furnish sulfides **(3)** in good to excellent yields (53-99 %) in recyclable ionic liquid BMIMM-BF_4 (Fig. 1).

Further exploration of this methodology was undertaken in the synthesis of dichalcogen compounds. Aryl, alkyl and hetroaryl diselenides and ditellurides **(4)** were synthesized by applying CuO nanopowder as a catalyst in good to excellent yields (50-96 %). This reaction didn't work in ionic liquids as solvent. As a result, we have developed a CuO nanopowder catalyzed reactions to the synthesis of organochalcogen compounds in good to excellent yields.

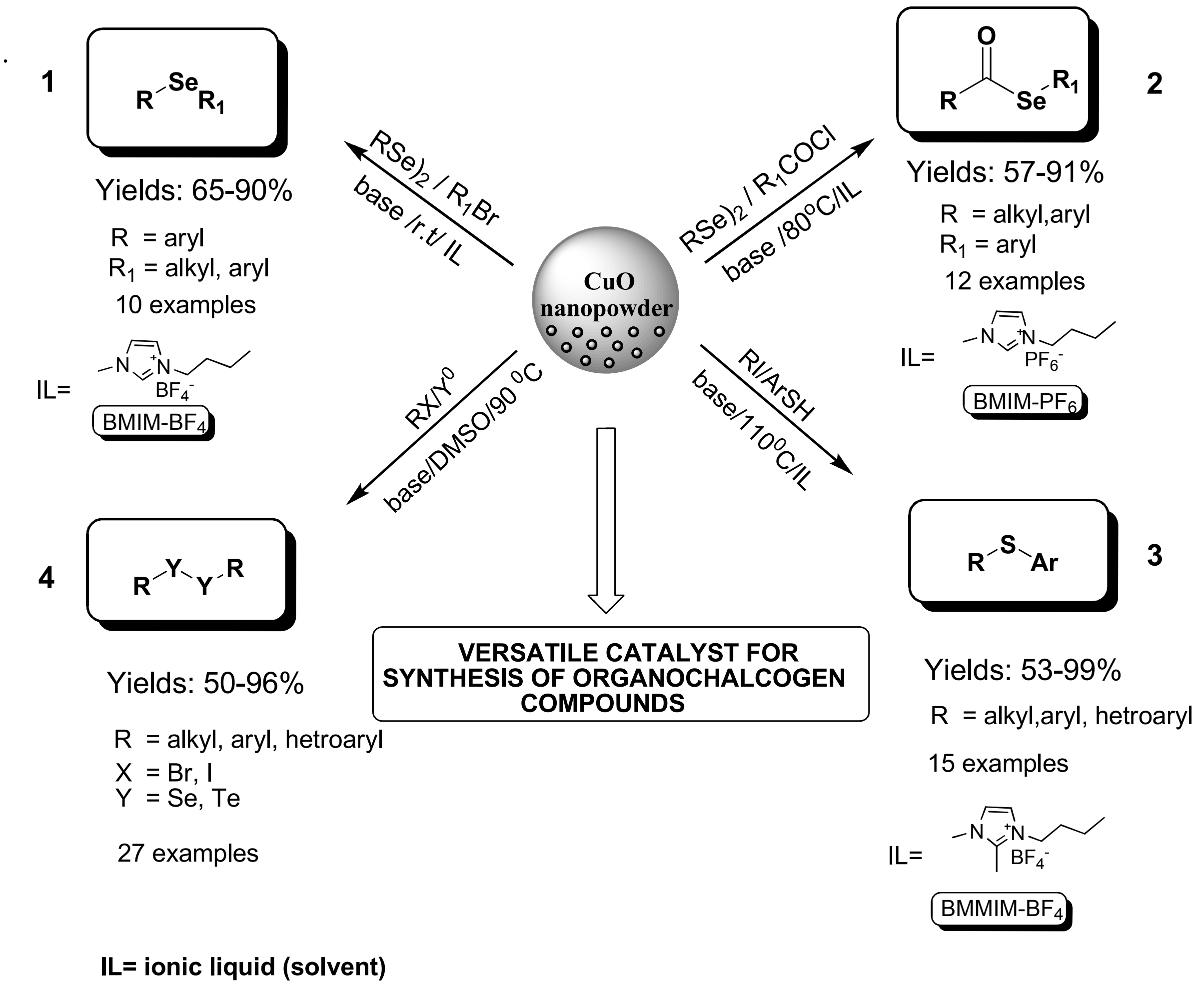

Figure 1. Synthesis of organochalcogen compounds

This coupling reaction underlines the potential of using nanocrystalline CuO as a very user friendly, inexpensive, and efficient catalyst. The catalyst and solvent (ionic liquids) could be easily recovered and reused. The important features of this protocol are: (1) recyclable CuO nanopowder; (2) recyclable solvent; (3) mild reaction conditions; and (4) greener methodology than previous protocols.

Keywords: CuO nanopowder, Organochalcogen Compounds, Ionic Liquids, Eco-friendly protocol

RESUMO

Tese de Doutorado
Programa de Pós-Graduação em Química
Universidade Federal de Santa Maria

ÓXIDO DE COBRE (CuO) NANOPARTICULADO: UM EXCELENTE CATALISADOR PARA A SÍNTESE DE COMPOSTOS ORGANOCALGOGÊNIOS

AUTOR: DEVENDER SINGH
ORIENTADOR: PROF. DR. ANTONIO LUIZ BRAGA
Data e Local da Defesa: Santa Maria, 24 de fevereiro de 2011.

Neste trabalho, apresentamos a síntese de baixo impacto ambiental de uma série de compostos organocalcogênios (selenetos **(1)**, selenoésteres **(2)**, sulfetos **(3),** disselenetos, e diteluretos **(4)**) catalisados por CuO nanoestruturado em uma variedade de líquidos iônicos como solventes recicláveis e em solventes orgânicos em bons e excelentes rendimentos. Esse protocolo mostra alta eficiência na catalitica dessa transformação, de forma mais ecológica do que protocolos anteriores. Primeiramente, foi implementada a reação de acoplamento de aril- e alquil-brometos com disselenetos, empregado-se CuO nanoestruturado (0,5 mol%) e BMIM-BF_4 como solvente reciclável, obtendo-se aril- e alquil-selenetos **(1)** em bons e excelentes rendimentos (65-90%). Da mesma forma, cloretos de acila também foram submetidos à reação com disselenetos para a obtenção de selenoésteres **(2)** em bons e excelentes rendimentos (57-91%), empregando-se 5,0 mol% de CuO nanoestruturado e BMIM-BF_6 como solvente. Além disso, iodetos aromáticos, ao passarem pela reação de acoplamento com tióis em líquido iônico BMIMM-BF_4 (Fig. 1) produziram sulfetos (**3**) em bons e excelentes rendimentos (53-99%).

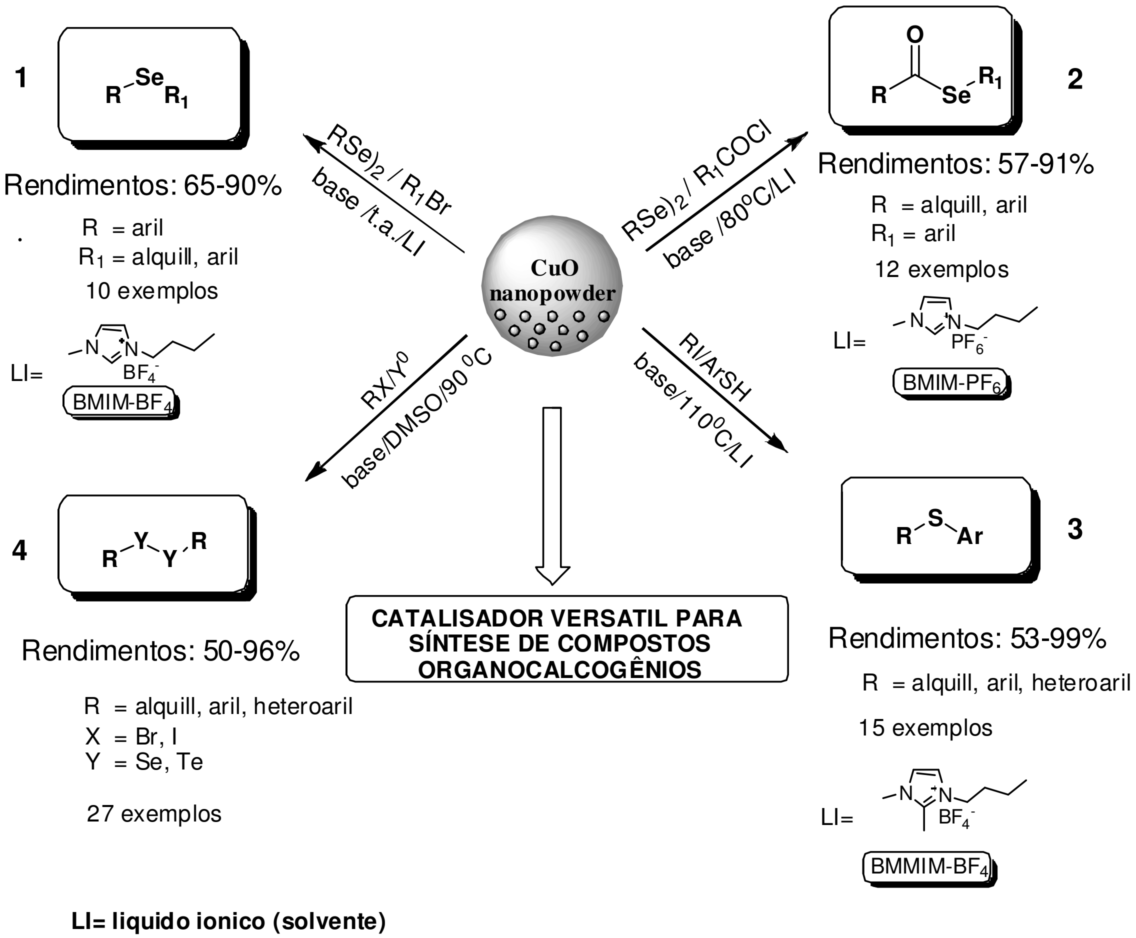

Figura 1. Síntese de compostos organocalgogênios

Uma exploração adicional dessa metodologia foi implementada na síntese de compostos dicalcogênios. Aril, alquil e heteroaril disselenetos e diteluretos **(4)** foram sintetizados com CuO nanoestruturado como catalisador em bons e excelentes rendimentos (50-96%). essa reação não funcionou em líquido iônico como solvente. Em vista dos resultados obtidos, neste estudo desenvolvemos um acoplamento catalisado por CuO nanocristalino para a síntese de compostos organocalcogênios em excelentes rendimentos. Essa reação de acoplamento enfatiza o potencial do CuO nanocristalino como catalisador de fácil manuseio, eficiente e financeiramente viável. O catalisador e o solvente (líquido iônico) puderam ser recuperados facilmente e resusados. Como características importantes desse protocolo destacam-se 1) a possibilidade de recuperação do CuO, 2) a reciclabilidade do solvente, 3) as condições brandas de reação, e 4) a natureza mais ecológica dessa

metodologia em relação a protocolos prévios, uma vez que o impacto ambiental é minimizado.

Palavras-chave: CuO Nanoparticulado, Compostos Organocalcogênios, Líquidos Iônicos, Protocolo de Baixo Impacto Ambiental

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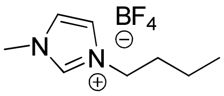
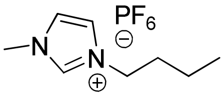
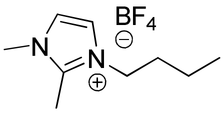
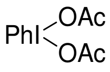
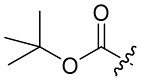
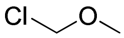
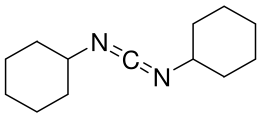
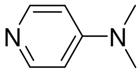
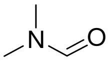
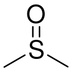
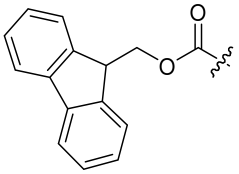
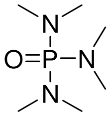
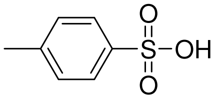
LIST OF ABBREVIATIONS AND SYMBOLS

NP	Nanoparticles	
IL	Ionic liquid	
BMIM-BF_4	1-Butyl-3-methylimidazolium Tetrafluoroborate	
BMIM-PF_6	*1-Butyl-3-methylimidazolium* *hexafluorophospahte*	
BMIMM-BF_4	*1,2-Dimethyl-3-butylimidazolium* *Tetrafluoroborate*	
IBDA	Iodosobenzene diacetate	
Boc	*tert-Butyloxycarbonyl*	
MOMCl	*methoxymethyl chloride*	
DCC	*N,N'-Dicyclohexylcarbodiimide*	

DMAP	*4-Dimethylaminopyridine*	
DMF	*Dimethylformamide*	
DMSO	*Dimethyl sulfoxide*	
Fmoc	*Fluorenylmethyloxycarbonyl*	
HMPA	*Hexamethylphosphoramide*	
p-TsOH	p-Toluenesulfonic acid	

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CHAPTER 1

INTRODUCTION AND OBJECTIVE

Catalysis has played a major role in chemistry, notably in the area of organic synthesis. A wide range of substances have been used as catalysts in catalyzed processes. Very recently, catalysis has been supported by the use of nanoparticles, a high performance catalyst which has increasingly attracted scientific attention. Nanoparticle catalysis directly impacts the environment in a number of ways, mainly by increasing the efficiency of industrial processes due to the reduction in reaction times, the recyclability of nanoparticles and their structural properties. This impact is exponentially intensified by the addition of eco-friendly solvents, such as ionic liquids, to synthetic processes. As a consequence, nanoparticle catalysis in eco-friendly solvents is a major area of research in this era.

Particularly in nanoparticle catalysis, several different metals, including Cu nanoparticles, have been used in previous studies (see Table 1) in combination with green solvents, such as ionic liquids, to synthesize various kinds of compounds. Nevertheless, the association of Cu nanoparticles with ionic liquids for obtaining organochalcogen compounds has been not explored.

In this sense, the present work describes the successful syntheses of a class of organochalcogen compounds, namely selenides, chalcogen-esters, dichalcogenides, and sulfides, using CuO nanoparticles as catalyst and, with the exception of the synthesis of dichalcogenides, in the presence of ionic liquids.

The following sections present a brief characterization of each one of these components of the reaction, initiating with organochalcogen compounds, followed by nanoparticle catalysis, by ionic liquids, and closing with a brief introduction on nanoparticle catalysis in ionic liquids.

1.1 Organochalcogen compounds

The combination of chalcogen elements with organic compounds are known as organochalcogen compounds. In proper words, an **organochalcogen compound** is defined as **a compound containing at least one carbon-chalcogen bond such** as chalcogenides, chalcogen-esters, sulfides, and dichalcogenides etc (Figure 1).

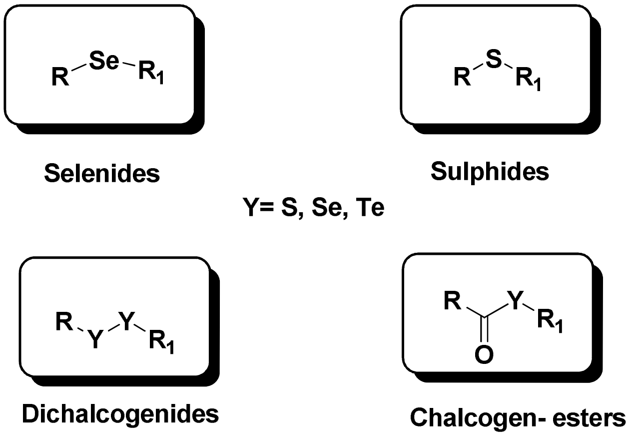

Figure 1. Examples of organochalcogen compounds

Over the past decades, higher organochalcogenides have been established as functional elements in biochemistry and medicine. The biological and medicinal properties of selenium and organochalcogens compounds are also increasingly appreciated, mainly due to their antioxidant and antitumor properties, and their roles as chemoprotectors, apoptosis inducers, or effective chemopreventors of cancer in a variety of organs.[1] More importantly, selenocysteine was established as the 21st proteniogenic amino acid.[2] Until now, at least 25 selenoproteins are known in humans, including glutathione peroxidase (GPx) and thioredoxin reductase (TrxR).[3]

Several organic transformations and these classes of compounds and their derivatives have been found in numerous biological and pharmaceutically active compounds.[4] Nevertheless, an integral part of numerous drugs in therapeutic areas such as diabetes, inflammatory, Alzheimer's, Parkinson's,[5] cancer, [6] and HIV[7] diseases contain the aryl sulfide as functional group.

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[1] C. Ip, J Nutr. 1998, 128, 1845.(b) Mugesh, G.; du Mont, W. W. *Chem. Rev.* **2001**, *101*, 2125. (c) Nogueira, C. W.; Zeni, G.; Rocha, B. T. *Chem. Rev.* **2004**,*104*, 625. (d) Unni, E.; Singh, U.; Ganther, H. E.; Sinha, R. *Biofactors* **2001**, *14*, 169.

[2] Bock, A.; Forchhammer, K.; Leinfelder, W.; Sawers, G.; Veprek, B.; Zinoni, F. *Mol. Microbiol.* **1991**, *5*, 515.

[3] Birringer, M.; Pilawa, S.; Flohe, L. *Nat. Prod. Rep.* **2002**, *19*, 693. (a) Brandt, W.; Wessjohann, L. A. *ChemBioChem* **2005**, *6*, 386; (b) Gromer, S.; Wessjohann, L.; Eubel, A.; Brandt, W. *ChemBioChem* **2006**, *7*, 1649; (c) Bach, R. D.; Dmitrenko, O.; Thorpe, C. *J. Org. Chem.* **2008**, *73*, 12.

[4] (a) Liu, L. P.; Stelmach, J. E.; Natarajan,S. R.; Chen, M. H.; Singh, S. B.; Schwartz, C. D.; Fitzgerald, C. E.; Keefe, S. J.; Zaller, D. M.; Schmatz, D. M.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3979. (b) Kaldor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.

[5] (a) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, F.; Fesik, S. W.; Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202. (b) Nielsen, S. F.; Nielsen, E. O.; Olsen, G. M.; Liljefors, T. D. *J. Med. Chem.* **2000**, *43*, 2217.

Organochalcogen compounds have found such wide utility because of their effects on an extraordinary number of very different reactions, including many carbon-carbon bond formations, under relatively mild reaction conditions. Furthermore, organochalcogen compounds can usually be used in a wide variety of functional groups, thus avoiding protection group chemistry.[8]

Most organochalcogen methodologies proceed stereo- and regioselectively in excellent yields.

Due to all these advantages, our main aim in the present study is to synthesize organochalcogen compounds by an easier, more efficient, and greener way compared to previous protocols.

1.2 Nanoparticle catalysis

Nanocatalysis has gained great attention in the past decade. A simple search through *Scifinder* with the key word “nanocatalysis” clearly indicates an exponential growth in scientific publications in the past 15 years (Figure 2). In 2008 alone, for example, the number of publications was nearly 7000. One of the main branches of nanocatalysis is nanoparticle (NP) catalysis in liquid phase. Higher surface area and low-coordinated sites are mailnly responsible for the increased catalytic activity in Nanoscale heterogeneous catalysts. The sizes of nanoparticles vary between 20 to 100nm. During the application, these clusters restructure and thereby improve the surface mobility. Generally, catalysts in nanoscale allow a more effective process and implement a genuine advance in relation to traditional methodologies. Nanomaterials containing high surface area and reactive morphologies have been studied as

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[6] Martino, G.; Edler, M. C.; Regina, G.; Cosuccia, A.; Barbera, M. C.; Barrow, D. R.; Nicholson, I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947.

[7] Kaldor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.

[8] (a) Nicolaou, K. C.; Petasi, N. A. *Selenium in Natural Products Synthesis*; CIS: Philadelphia, PA, **1984.** (b) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, U.K., **1986**. (c) Patai, S.; Rappoport, Z. *The Chemistry of Organic Selenium and Tellurium Compounds*; Wiley: New York, **1986**, *Vol. 1*. (d) Liotta, D. *Organoselenium Chemistry*; Wiley: New York, **1987**. (e) Krief, A.; Hevesi, L. *Organoselenium Chemistry I*; Springer: Berlin, **1988**. (f) Back,T. G. *Organoselenium Chemistry: A Pratical Approach*; Oxford University Press: Oxford, U.K., **1999.** (g) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22. (h) Liotta, D. *Acc. Chem. Res.* **1984**, *17*, 28. (i) Wirth, T. *Organoselenium Chemistry - Modern Developments in Organic Synthesis*; Topics in Current Chemistry 208, Spring- Verlag: Heidelberg, Germany, **2000**. (j) Mugesh, G.; Singh, H. B. *Acc. Chem. Res.* **2002**, *35*, 226.

effective catalysts for organic synthesis, some of which are listed in Table 1. (reference are listed in table 1).

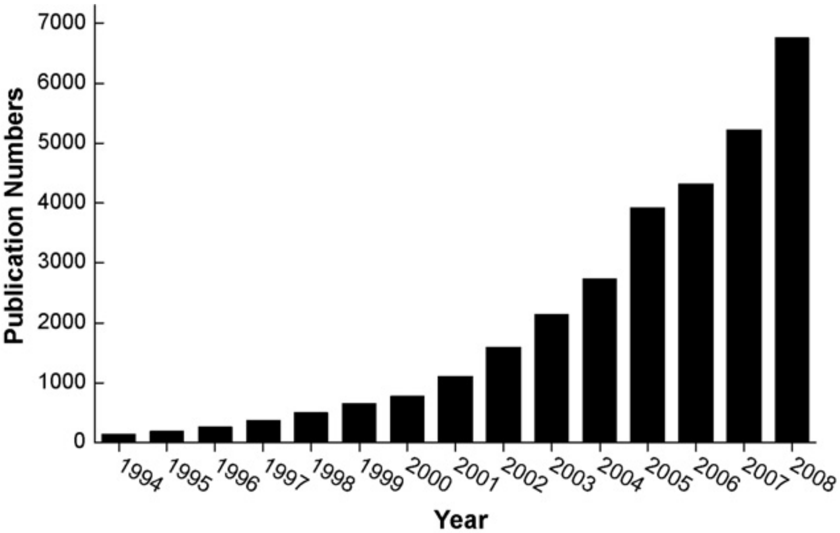

Figure 2. Exponential growth in scientific publications on nanocatalysis

Table 1. Reactions catalyzed by transition - metal nanoparticles

Reactions	References
Hydrogenation	*Applied Homogeneous Catalysis with Organometallic Compounds*, B. Cornils, W. A. Herrmann (Eds.), Wiley - VCH , Weinheim, Vol. *1 and 2* , **1996**
Heck C-C coupling	M. T. Reetz, W. Helbig, *J. Am. Chem. Soc.* **1994,** *116,* 7401; T. Sanji, Y. Ogawa, Y. Nakatsuka, M. Tanaka, H. Sakurai, *Chem. Lett.* **2003**, *32*, 980.
Suzuki C - C coupling	R. Narayanan, M. A. El-Sayed, *J. Am. Chem. Soc.* **2003,** *125,* 8340; Y. Li, E.Boone, M. A. El - Sayed, *Langmuir* **2002,** *18, 4921*.
Sonogashira C - C coupling	S. U. Son, Y. Jang, J. Park, H. B. Na, H. M. Park, H. J. Yun, J. Lee, T. Hyeon, *J. Am. Chem. Soc.* **2004, 126***,* 5026 and references cited therein.
Stille C - C coupling	D. Zhao, Z. Fei, T. Geldbach, R. Scopelliti, P. J. Dyson, *J. Am. Chem. Soc.* **2004**, *126*, 15876.
Negishi C - C coupling	B. H. Lipchitz, P. A. Blomgren, *J. Am. Chem. Soc.* **1999** ,*121*, 5819.
Dehydrohalogenation of aryl halides	V. A. Yakovlev, V. V. Terskikh, V. I.Simagina, V. A. Likholobov, *J. Mol. Catal. A* **2000** ,*153* , 231.
Hydrosilylation	H.Hirai,Y.Nakao,N.J.Toshima, *Macromol.Sci. Chem.* **1978**, *A12*, 1117 and **1979,** *A13, 727.*
[3 + 2] Cycloaddition	M. T. Reetz , R. Breinbauer , P. Wedemann , P. Binger , *Tetrahedron* **1998** , *54* , 1233
Oxidation	M. Haruta, CATTECH, **2002** , *6* , 102
Amination	J. Penzien , C. Haessner , A. Jentys , K. K ö hler , T. E. Muller , J. A. Lercher , *J. Catal.* **2004** , *221* , 302

1.2.1 An ideal nanoparticle catalytic system in solution[9]

There are few excellent reviews on NP catalysis[9], in spite of the various and satisfactory improvements of NP catalysis for industrial demands. Basically, these improvements can be classified into two sets. The first set refers to the efficiency, stability, sustainability, and recyclability **(ESSR)** criteria for the evaluation of a NP catalytic system. The second set is related to the development of methodologies to fulfill the ESSR criteria by designing the three basic elements, namely, the metal core, the stabilizer and the solvent **(MSS)**, of a NP catalytic system (Figure 3).

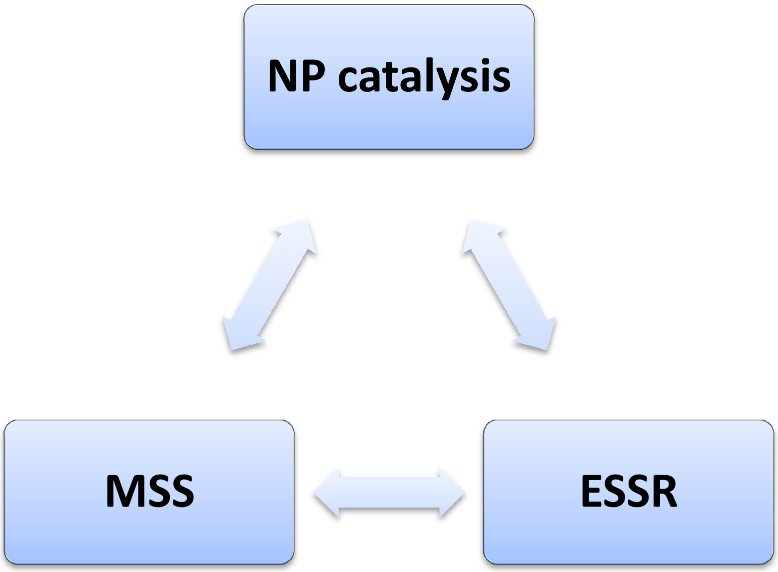

Figure 3. Relationship between ESSR and MSS with NP catalysis

1.2.1.1 The ESSR criteria

The NPs in solution phase are heterogeneous in nature. However, they "appear" incredibly homogenous since the catalyst is well dispersed in solvent so that the reactant reaches the catalytic site by diffusion. Due to this property, a NP catalytic system has similar advantages and limitations to those of the homogenous catalytic system. Homogeneous catalysts, usually transition metal complexes, show structure–reactivity relationship because of a well-defined structure. These catalysts work well

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[9] (a) Roucoux, A.; Schulz, J.; Patin, H. *Chem. Rev.* **2002**, *102*, 3757. (b) Widegren, J. A.; Finke, R. G.; *J. Mol. Catal. A.* **2003**, *191*, 187. (c) Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem. Int. Ed.* **2005**, *44*, 7852.(b) Yan, N.; Xiao, C.; Kou, Y. *Coordination Chemistry Reviews*. **2010**, *254*, 1179.

at low temperature and give very good selectivity.[10] Drawbacks include catalyst decomposition and complex separation of reactants/products from the homogeneous system. NP catalysis faces exactly the same situation.

The recyclability of a NP system is normally a technical issue including the retreatment of the NP and recycling the stabilizer and the solvent. Easy separation, for example, by biphasic approach, and other smart approaches of the stabilizer and the solvent may significantly improve the recyclability of NP catalytic system, and may certainly enhance the possibility of an industrial application. We therefore suggest that efficiency (E), stability (S), sustainability (S) and recyclability (R) are the criteria, **ESSR** criteria, for the evaluation of an NP catalytic system.

- ***Efficiency***

High efficiency, i.e., high selectivity at high conversion rate under mild reaction conditions, is the most prominent benefit that an NP catalyst can provide compared to typical heterogeneous catalysts. A homogenous catalyst can usually be much more active and selective, and in organic synthesis it can be optimized for the system.[11]

Moreover, the E criterion also requires NP catalytic systems, if possible, to be multifunctional to integrate catalytic steps into a one-pot, catalytic cascade process. The most significant merits of such a one-pot process are energy and time saving and waste reducing, in a word, improving reaction efficiency. More attention should be paid to this aspect since it represents the future of green chemistry.[12]

- ***Sustainability***

Sustainability is highly desirable for the long term development of NP catalysis. Sustainability involves many considerations for NP catalysis, there are three factors that are of particular importance. One is the sustainability of the metal incorporated into the NP, since many metals are becoming scarce. Rare metals are,

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[10] Coperet, C.; Basset, J. M. *Adv. Synth. Catal.* **2007**, *349*, 78.
[11] Corma, A.; Garcia, H. *Adv. Synth. Catal.* **2006**, *348*, 1391.
[12] Sheldon, R. A. *Chem. Commun.* **2008**, *29*, 3352.

especially, becoming rarer. It is therefore essential that we start to use metals which are more abundant, including the field of NP catalysis. Two other factors which concern sustainability in NP catalysis are consideration of PBT (persistence, bioaccumulation, and toxicity)[13] for both substrates (as well as products) and solvents.

- ***Stability***

NPs are only kinetically stable and therefore stability is crucial for real processes in which the catalysts are required to be stable for months or years. Mostly stabalizers are added to enhance the stability. What we want to do is to protect the particles against aggregation via weak interactions between the functional group(s) of the stabilizer and the surface sites of the particles. This protection is enhanced via multi-site interaction, i.e. most of the surface atoms of the particle may be involved in the weak interaction. The solvent chosen can have two effects: the first is interactions with the NP surface, which can compete with the stabilizer; the second is solubilizing the stabilizers, the regulation of which can sometimes be helpful.

- ***Recyclability***

It is highly probable that recyclability will be the bottleneck for the industrial application of NP catalysis in solution phase. Good dispersion of NP within a solvent is a double edged sword. It usually results in a catalytic system with high activity under mild reaction conditions. Meanwhile, it makes the separation of the catalyst from the product more complex. An additional concern for the pharmaceutical or polymer industry is metal contamination of the products. To solve this problem, a good strategy for easy and efficient recycling has to be applied. Although it seems to be a general trend to transform a successful homogeneous catalyst into a heterogeneous one[14], other approaches to solve the recycling problem without influencing the activity of the catalyst are still under consideration. For example, a

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[13] Webster, E. C.; Ellsberry, C.; McCarty, L. *Environ. Toxicol. Chem.* **2004**, *23*, 2473.

[14] (a) Corm, A.; Garcia, H. *Chem. Rev.* **2002**, *102*, 3837; (b) Corm, A.; Garcia, H. *Chem. Rev.* **2003**, *103*, 4307.

hydroformylation process is industrialized based on a biphasic aqueous-organic solvent system[15]. Fortunately, the experiences gained from the recycling of homogenous catalysts during the past decades can be easily adapted to NP catalysts for the same purpose. Additionally, some features of certain NP, which a homogenous complex does not share, such as magnetism, can enable more diversified options for the recycling of NP catalysts.

1.2.1.2 Relationship between metal–stabilizer–solvent

An NP based catalytic system involves at least three components, i.e. metal core (M), stabilizer (S), and solvent (S). The metal core is the catalytic material with an activity and selectivity, with the latter with assistance from the stabilizers. The stabilizer protects the metal core against aggregation. However, this protection may negatively affect the activity of the system. The solvent is responsible for the dispersion of both metal core and stabilizer. However, the "solubility" of the metal core is controlled not by the solvent, but by the stabilizer. Thus, the solvent is the carrier transferring the reactant(s) to the metal core and product(s) away from the active site. The solubilities of both the stabilizer and the reactant(s) in the solvent are therefore related to the final activity of the system. This is the cohesive relationship among metal–stabilizer–solvent, the state of- the-art approach to this relationship is fundamental in NP catalysis.

However, a wide range of organic compounds bearing various functionalities have been used as NP stabilizers, suggesting that stabilizers can be used to customize the catalytic system. Indeed, an appropriate stabilizer is the key for a stable and highly active NP catalyst. Additionally, proper solvent design and/or selection could prove advantageous in NP catalysis. The most obvious benefit from the solvent is that it may simplify the separation process. For example, the biphasic approach based on ionic liquids or water, according to the principles of green chemistry, is desired for the separation of a catalyst from products. It has to be kept in mind that metal core, stabilizer, and solvent are not isolated from each other but are acting together to make the system effective. However, to make the story clear,

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[15] Leeuwen, P.W.N.M. *Homogeneous Catalysis-Understanding the Art*, Kluwer, Amsterdam, **2004.**

to elucidate the detailed MSS relationship for satisfying the ESSR criteria, a comprehensive table is given (Table 2).[16]

Table 2. Relationship between the MSS and the ESSR criteria

	Efficiency (**E**)			**Sustainbility** (**S**)	**Stability** (**S**)		**Recyclability** (**R**)
	High activity	*High selectivity*	*Multi-function*		*Long lifetime*	*Poison resistence*	
Metal (**M**)	type selection alloy design size control shape control	type selection alloy design size control shape control	-	use cheap and more abundant metals	mono-disperse	-	magnetic separation
Stabilizer (**S**)	balance between activity and stability	chiral approach for enantioselective reactions	Functionalized stabilizer		strong stabilization ability	effective protection	polarity modulation
Solvent (**S**)	dispersion issue		Functionalized stabilizer	employment of green solvent	stabilization effect	solvation effect	functionalized solvent

1.3 Ionic liquids

Ionic liquids (Figure 4) are viewed as a new and remarkable class of solvents, or as a type of materials that have a long and useful history. In fact, ionic liquids are both, depending on the point of view. It is absolutely clear, though, that whatever "ionic liquids" are, there has been an explosion of interest in them. The increased interest is clearly due to the realization that these materials, formerly used for specialized electrochemical applications, may have greater utility as reaction solvents. ILs has widely been promoted as "green solvents". The reason for calling them green generally includes their nonvolatility, nonflammability, nontoxicity and recyclability. The perceived environmentally friendly nature of ILs is however under scrutiny now since they may not as green as we thought, especially when we consider their toxicity.[17] Recent research results clearly indicate that most ILs in fact exhibit detrimental effects on aquatic ecosystems, microorganisms and animals.[18] Hence, they are not fully environmentally benign.[19] With the introduction of the first IL-based industrial application, ILs have left the academia-only interest, more processes are yet to come.

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[16] Yan, N.; Xiao, C.; Kou, Y. *Coordination Chemistry Reviews*. **2010**, *254,* 1179.

[17] Jastorff, B.; Stormann, R.; Ranke, J.; Molter, K.; Stock, F.; Oberheitmann, B.; Hoffmann, W.; Hoffmann, J.; Nuchter, M.; Ondruschka, B.; Filser, J. *Green Chem.* **2003**, *5*, 136.

[18] Zhao, D.; Liao, Y.; Zhang, Z. *Clean: Soil, Air, Water*, **2007**, *35,* 42.

[19] Ranke, J.; Stolte, S.; Stormann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183.

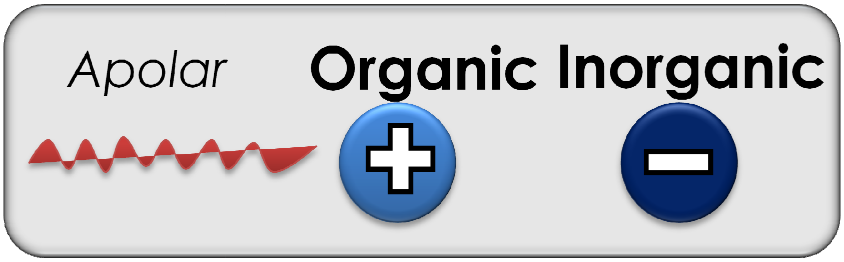

Figure 4. Basic structure of ionic liquids

Ionic liquids are salts which consist of cation and anion (Figure 5). They are liquid at room temperatures or slightly above. Their characteristics include: (1) essentially no vapor pressure, (2) non-flammability, (3) high thermal stability, (4) relatively low viscosity, (5) liquid state over extended temperature ranges, (6) high ionic conductivity. Thus, ILs show excellent abilities to dissolve polar and non-polar organic, inorganic, and polymeric compounds, allowing substantial applications of ILs in various types of catalytic and synthetic reactions,[20] when an ionic liquid is used as a reaction solvent, the solute is solvated by ions only. Thus, the reaction proceeds in a habitat totally different from that when water or ordinary organic solvents are used and therefore, high selectivity is possible.

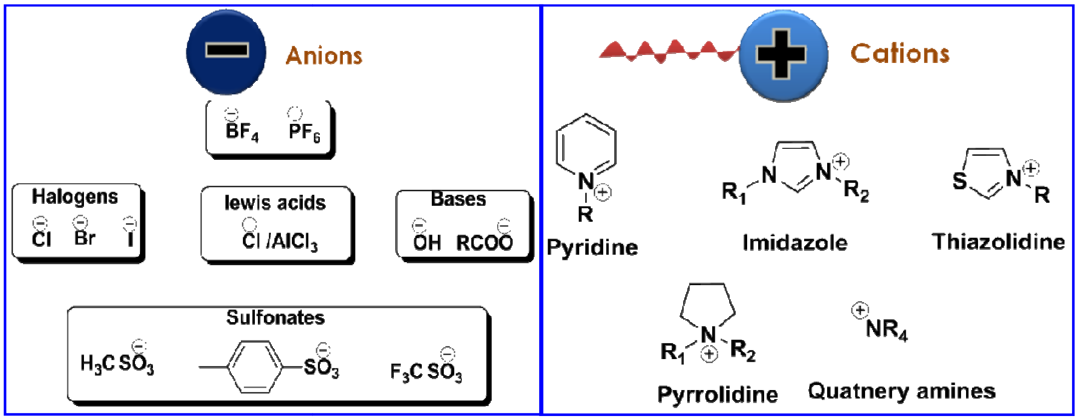

Figure 5. Common cations and anions used to synthesize ionic liquids

To date application in the Friedel-Crafts reaction, Diels-Alder reaction, metal-catalyzed asymmetric synthesis and so forth, have been reported. Furthermore,

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[20] (a) Holbrey, J. D.; Seddon, K. R. *Clean Prod. Process.* **1999**, *1*, 233; (b) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351; (c) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (d) Wasserscheid, P.; Keim, W. *Angew. Chem.* **2000**, *39*, 3772; (e) Sheldon, R. *Chem. Commun.* **2001**,2399; (f) For a comprehensive review about ionic liquids see: (*g*) Dupont, J.; Souza, R. F.; Suarez, P. A. Z. *Chem.Rev.*, **2002**, *102*, 3667; (*h*) Cassol, C. C., Ebeling, G.; Ferrera, B.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 243; (i) Ranke, J.; Stolte, S.; St¨ormann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183; (j) Hapiot, P.; Lagrost, C. *Chem. Rev.* **2008**, *108*, 2238; (k) Gordon, C. M. *Appl. Catal., A*, **2001**, *222*, 101.

some ionic liquids have low solubility in water and low polar organic solvents. By using this property, ionic liquids can be recovered and reused after reaction product is extracted with organic solvents. Recently, methods are being studied which reduce the load on the environment from the viewpoint of green chemistry. Ionic liquids are receiving much attention as a superb solvent from the point of safety, separation/purification procedures, and recyclability.

Currently, many chemically inert ionic liquids are discussed as media within the context of Green Chemistry, although the environmentally friendly image is under investigation. Aspects such as combustibility and toxicity of some ILs gave rise to the necessity to explore the catalytic properties of these solvents, which might give them an advantage compared to classical solvents.

1.4 Nanoparticle catalysis in ionic liquids

There were few studies on NP catalysis in ILs up to the end of 2009. However, we realized that ILs should be of great potential for the development of highly efficient NP catalytic systems. We can conclude, therefore, that ionic liquids offer the opportunity of combining the advantages of both homogeneous and heterogeneous catalysis in one system. That is to say, immobilization of a catalyst (metal/oxide/complex) by supporting it in an ionic liquid rather than on a surface may create highly free, three-dimensional centers as in a homogeneous catalyst, but the catalytic reaction occurs at the interface between the ionic liquid (rather than a solid) and the reactants in either the gas or immiscible liquid phase.

Development of application of three-dimensional heterogeneous catalysis using ionic liquids as supports should present challenges for us over the next decade and beyond.[21] It is indeed a pleasure to note that NP catalysis in ILs has already grown from a little seed into a giant tree. The first example of NP catalysis in ILs comes from Dupont's group, in which Ir NPs were obtained by the reduction of organometallic precursor and stabilized by [BMIM]-PF_6.[22] Following that, extensive studies on NP preparation and application in catalysis were reported, covering a wide

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[21] Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today.* **2002**, *74,* 157.

[22] Dupont, J.; Fonseca, G. S.; Umpierre, A. P.; Fichtner, P. F. P.; Teixeira, S. R. *J. Am.Chem Soc.* **2002**, *124*, 4228.

range of reaction types including hydrogenation, C–C coupling, and occasionally oxidation.[23]

The benefit that ILs can provide first comes from the fact that the tendency of the aggregation of NP is much lower in ionic environment. Therefore, the NP can be stabilized to some extent without any additional stabilizers. Second, the tunable miscibility of ILs enables facial recycling of the solvents as well as the immobilized NP. Furthermore, some reactions catalyzed by NP exhibit unusual but desired selectivity patterns when performed in ILs, These advantages, coupled with the intrinsic "green" nature of ILs, made NP in ILs an appealing field to explore. Among the few excellent reviews on this topic is the recent textbook by Dupont and co-authors.[24]

1.5 Objective

During the last decade the trends in organic synthetic chemistry have bent toward a pollution-free chemistry or, in other words, a "green chemistry". The overall goal of the present work is to develop methodologies to prepare organochalcogen compounds in fast, efficient, and eco-friendly ways, focusing on two of the latest improvements in the field of organic chemistry: reactions in ionic liquids and nanoparticle catalysis.

The synthesis of organochalcogen compounds has been an area of research interest of our lab, due to their various applications in organic chemistry as well as in bio-medicinal chemistry.

The use of ionic liquids as recyclable and less toxic solvents is among several methods that have recently been develop in the field of green chemistry, parallel to reactions in microwave, solvent-free reactions, and reactions in water. Ionic liquids have rapidly gained attention in the field of organic chemistry, being used as alternative reaction media for a broad range of chemical transformations, mainly due to their interesting properties, such as no effective vapor pressure, non-volatility, non-flammability, excellent chemical and thermal stability, and recyclability, which make them attractive media for organic reactions.

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[23] Xue, X. Z.; Lu, T.H.; Liu, C.P.; Xu, W. L.; Su, Y.; Lv, Y. Z.; Xing, W. *Electrochim. Acta*. **2005**, *50*, 3470.

[24] Dupont, J.; Silva, D. O. in: D. Astruc (Ed.), Nanoparticles and Catalysis, *Wiley- VCH, Weinheim,* Germany, **2008**, p. 195.

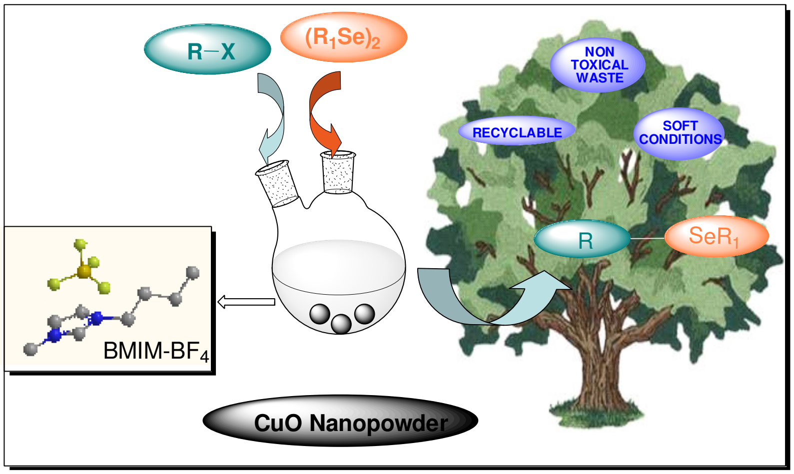
Catalysis has also been an important topic in the field of chemistry, especially metal catalysis. As we know, the 2010 Nobel Prize has also been awarded to chemists who work in the field of metal catalysis in coupling reactions. A recent advance in this field is the use of metal nanoparticles, given that the advantages of nanoparticles are much higher than those of traditional methods.

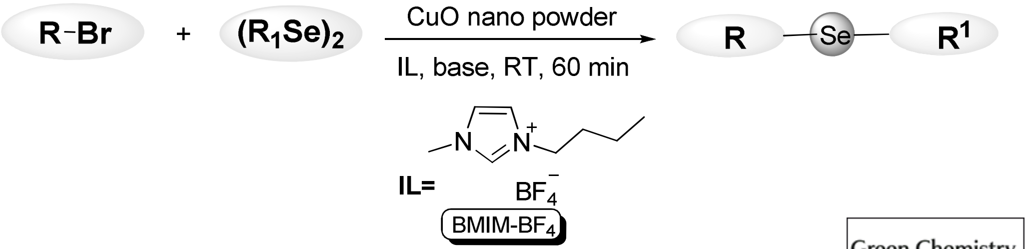
In short, herein we report the synthesis of a series of organochalcogen compounds (selenides, seleno-esters, diselenides, ditellurides, sulfides) in a greener and more efficient way. This was achieved by the development of methods that combine nanoparticle catalysis and ionic liquids as solvent.

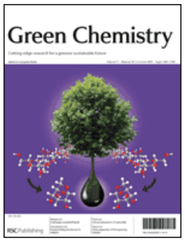
To do so, in Chapter 2 we describe the synthesis of selenides, followed by the synthesis of seleno-esters in Chapter 3. The synthesis of diselenides and ditellurides is reported in Chapter 4, and finally, in Chapter 5, we present the synthesis of sulfides. Chapter 6 provides a general conclusion for the new methods presented, while Chapters 7 and 8 contain experimental data and sprectra, respectively.

CHAPTER 2

ECO-FRIENDLY CROSS-COUPLING OF DIARYL DISELENIDES WITH ARYL AND ALKYL BROMIDES CATALYZED BY CuO NANOPOWDER







Green Chem. **2009**, 11, 1521-1524

2.1 Introduction and previous methods to synthesize organochalcogenides (selenides)

In life sciences, selenium is known as a fundamental element.[25] In addition, organoselenium compounds are involved in a series of biological processes: they have an effective action against free radical species and other important biological proprieties (*e.g.*, antioxidant, antitumor, anti-inflammatory, and anti-infective activity).[26] As the formation of C-Se bonds is an important tool in the synthesis of organochalcogen compounds, various protocols to synthesize or form C-Se bond have been described in the literature.

In general, these compounds are prepared by reductive cleavage of dichalcogenide bonds, employing common reducing agents and expensive metal sources, and high yield selenides were obtained by treatment of diphenyldiselenide with $LiAlH_4$, and methoxymethyl chloride (MOMCl). Another method employs lanthanum metal with a catalytic amount of iodine to prepare the lanthanum complex, which is further reacted with alkyl or aryl halides to give the corresponding selenides (Scheme 1.(1) and (2)).[27]

Ranu and co-workers describe that diphenyl diselenides undergo facile cleavages by indium (I) iodide and the corresponding generated selenolate and thiolate anions condense *in situ* with alkyl or acyl halides present in the reaction mixture, resulting in selenides as final product (Scheme 1. (3)).[28] In a different approach, is was found that, in the presence of cesium hydroxide, molecular sieves, and DMF, benzeneselenol undergoes direct alkylation with various alkyl halides for the synthesis of alkyl phenyl selenides in moderate to excellent yields (Scheme 1. (4)).[29]

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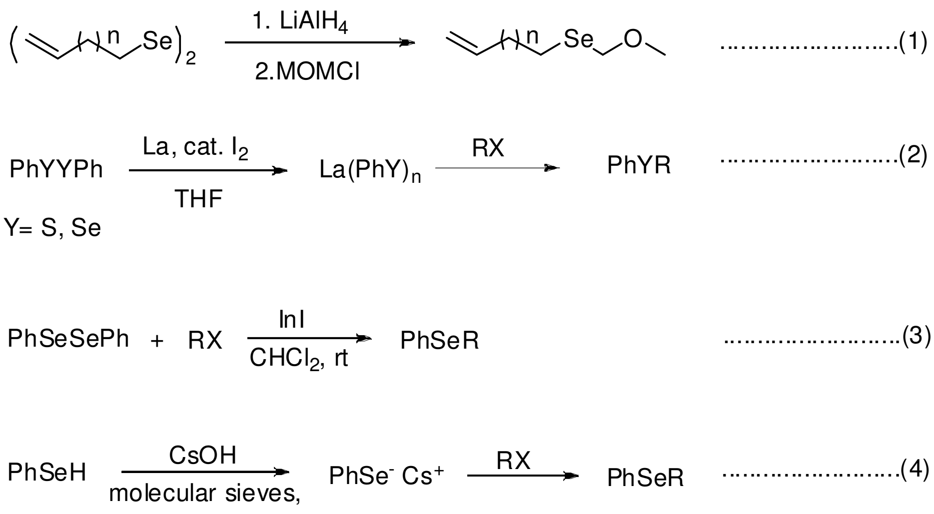
[25] (*a*) Klayman, D. L.; Gunter, H. H. *Organoselenium Compounds: Their Chemistry and Biology*, Wiley-Interscience, New York, **1973**; (*b*) Rotruck, J. T.; Pope, A. L.; Ganther, H. E.; Swanson, A. B.; Hafeman, D. G.; Hoekstra, W. G. *Science*, **1973**, *179*, 588; (*c*) Flohe, L.; Gunzler, E. A.; Schock, H. H. *FEBS Lett.* **1973**, *32*, 132; (*d*) Shamberger, R. J. *Biochemistry of Selenium*, Plenum Press, New York, **1983**; (*e*) Flohe, L.; Andreesen, J. R.; Maiorino, M.; Ursini, F. *IUBMB Life.*, **2000,** *49,* 411; (*f*) Jacob, C.; Giles, G. I.; Giles, N. M.; Sies, H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4742.

[26] (*a*) Mugesh G.; Singh, H. *Chem. Soc. Rev.* **2000**, *29*, 347; (*b*) Mugesh, G.; Du Mont, W. W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125; (*c*) Nogueira, C.W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104,* 6255; (*d*) Sarma, B. K.; Mugesh, G. *Org. Biomol. Chem.* **2008**, *6*, 965.

[27] (a) Yoshimatsu, M.; Sato, T.; Shimizu, H.; Hori, M.; Kataoka, T. *J. Org.Chem.* **1994**, *59*, 1011; (b) Nishino, T.; Okada, M.; Kuroki, T.; Watanabe, T.; Nishiyama, Y.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 8696.

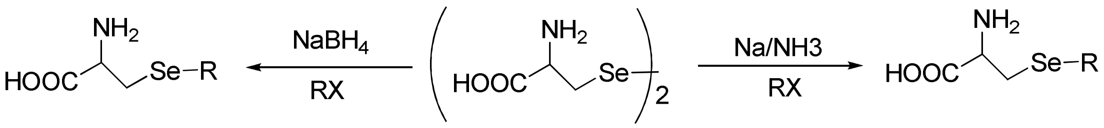
[28] Ranu, B. C.; Mandal, T.; Samanta, S. *Org. Lett.* **2003**, *5,* 1439; (b) Ranu, B. C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793.

[29] Cohen, R. J.; Fox, D. L.; Salvatore, R. N. *J. Org. Chem.* **2004**, *69*, 4265.

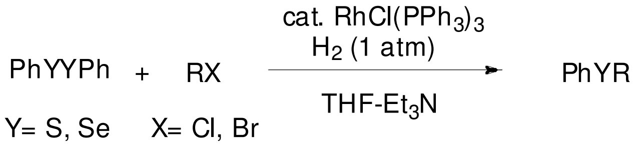


Scheme 1. Previous methods to prepare selenides

A one-pot two-step selenylation reaction to form a C-Se bond was reported by Rossi and co-workers and by Vermeulen and co-workers. In this reaction, R_2Se_2 reacts with Na metal in liquid ammonia or with $NaBH_4$ in ethanol, respectively, to generate selenol, which further reacts with halides to obtain selenides (Scheme 2).[30] Tanaka *et. al.* established that $RhCl(PPh_3)_3$ catalyzes a reductive coupling of disulfides and diselenides with alkyl halides in the presence of triethylamine using hydrogen as a reducing agent. They prepared unsymmetrical sulfides and selenides from disulfides and diselenides (Scheme 3).[31]



Scheme 2. Reduction of diselenides with Na/NH_3 and $NaBH_4$



Scheme 3. Reduction of diselenides by $RhCl(PPh_3)_3$

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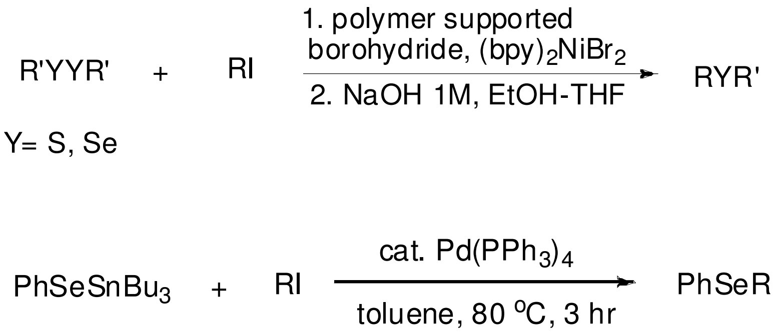
[30] (a) Bonaterra, M.; Martín, S. E.; Rossi, R. A. *Tetrahedron Lett.* **2006**, *47*, 3511; (b) Andreadou, I.; Menge, W. M. P. B.; Commandeur, J. N. M.; Worthington, E. A.; Vermeulen, N. P. E. *J. Med. Chem.* **1996**, *39*, 2040.

[31] Ajiki, K.; Hirano, M.; Tanaka, K. *Org. Lett.* **2005**, *7*, 4193.

Diaz and co-workers reported the synthesis of selenides by polymer supported Ni catalyst to break the dichalogenide bonds, which further react with halides (Scheme 4).[32] Palladium was also used by Sonoda and co-workers to prepare selenides. They used phenyl tributylstannyl selenide ($PhSeSnBu_3$) as starting material to react with halides (Scheme 4).[33]



Scheme 4. Polymer supported synthesis of selenides by nickel and synthesis of selenides by palladium metal

The synthetic protocols discussed above address the synthesis of selenides using diselenides with aryl or alkyl halides. The literature, however, also reports methods for the preparation of selenides by ring-opening of cyclic compounds, such as aziridines, oxazolines, and epoxides. Braga and co-workers describe an aziridine ring-opening reaction with indium iodide. In this transformation, indium made a complex with diphenyl diselenide and this complex is able to activate the aziridine ring further, resulting in the corresponding selenides (Scheme 5).[34] Similarly, the same group also reported a method costisting of the opening of the oxazoline ring with selenolate, regenerated by the $NaBH_4$/EtOH-THF system, and using lewis acid for the activation of the oxazoline ring (Scheme 5).[35] Selenides were also obtained in the the protocol proposed by Procter and co-workers, in which the ring-opening of epoxide was generated with the yeterbium metal (Scheme 5).[36]

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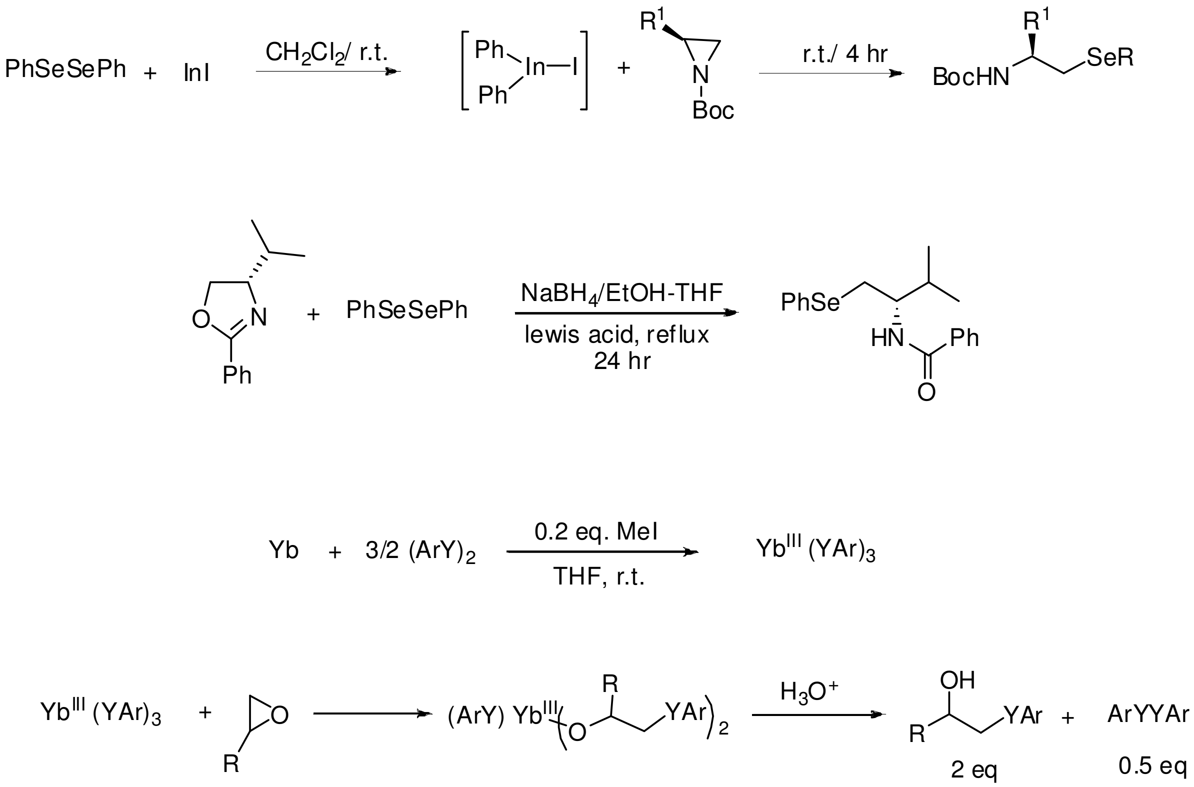
[32] Millois, C.; Diaz, P. *Org. Lett,* **2000,** *2***,** 1705.
[33] Nishiyama, Y.; Tokunaga, K.; Sonoda, N. *Org. Lett.* **1999**, 1, 1725.
[34] Braga, A. L.; Schneider, P. H.; Paixao, M. W.; Deobald, A. M.; Peppe, C.; Bottega D. P. *J. Org. Chem.* **2006**, *71*, 4305.
[35] Braga, A. L.; Vargas, F.; Sehnem, J. A.; Braga, R. C. *J. Org. Chem.* **2005**, *70*, 9021.
[36] Dowsland, J.; McKerlie, F.; Procter, D. J. *Tetrahedron Lett.* **2000**, *41*, 1425.



Scheme 5. Synthesis of selenides by ring opening reactions

A more recent development in the synthesis of alkyl and aryl selenides is the used copper metal in the reactions. Different forms of copper have been used as a catalyst in this kind of transformation, out of which the latest and most important is nanoparticles catalysis. Metal nanoparticles have been employed mostly because of their properties, for example, high surface area, and larger range of applications, such as recyclability and user-friendlyness. Taniguchi reported the synthesis of unsymmetrical organochalcogenides using organoboronic acids with dichalcogenides via cleavage of the S-S, Se-Se, or Te-Te bond by a copper catalyst (CuI),[37] and Engman and co-workers reported the same reaction with halides, using microwave radiation (Scheme 6).[38] In both protocols the reaction time was 6-12 hr with high temperature (Scheme 6). Very recently, Yaming Li and co-workers used CuS as a catalyst in this kind of reaction adding Fe and K_2CO_3 as a base in DMSO for 16 hr. They used different sources of copper, such as Cu, Cu_2S, and CuI, with different additives, as $FeCl_3$, $FeCl_2$, FeS, but the best result was obtained with CuS and Fe

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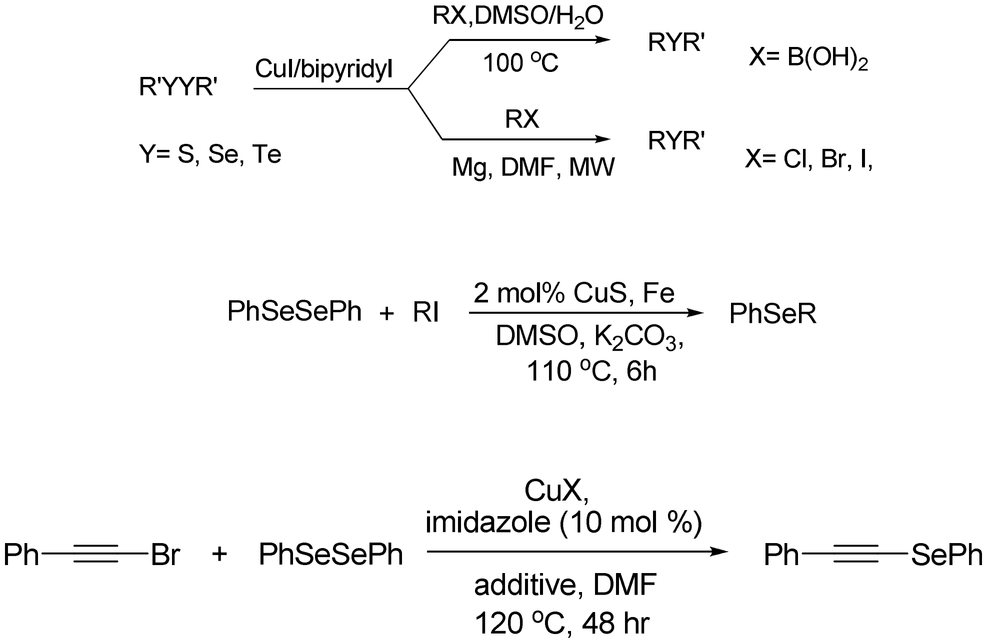
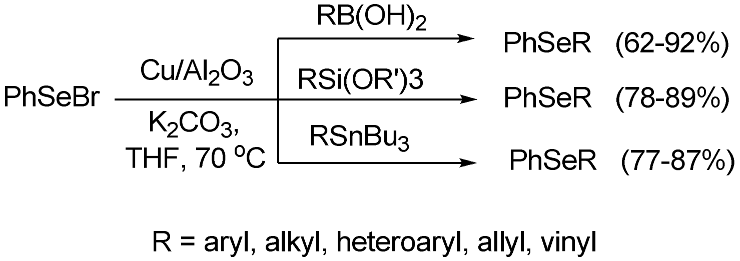
[37] Taniguchi, N. *J. Org. Chem.* **2007**, *72*, 1241.
[38] Kumar, S.; Engman, L. *J. Org. Chem.* **2006**, *71*, 5400.

(Scheme 6).[39] Furthermore, Braga and co-workers reported another method to obtain alkynylselenides from alkynyl bromides and diaryl diselenides employing a copper (I)/imidazole catalytic system. CuI, CuCl, and Cu(OAc) were used for the reaction (Scheme 6).[40]



Scheme 6. Synthesis of selenides by different forms of copper

Ranu and co-workers comment on some of the applications of the copper metal catalyst in the alluminum supported electrophilic substitution by PhSeBr in organoboranes, organosilanes, and organostannanes by an efficient and eco-friendly protocol to obtain unsymmetrical selenides. In this protocol, the catalyst was recovered after the reaction without losing its effectiveness (Scheme 7).[41]



Scheme 7. Synthesis of selenides with organoboranes, organosilanes, and organostannanes

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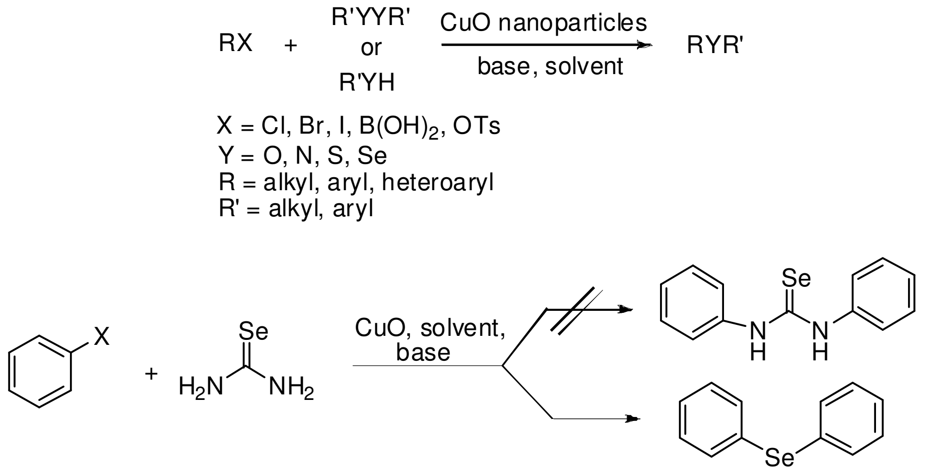
[39] Li, Y.; Wang, H.; Li, X.; Chen, T.; Zhao, D. *Tetrahedron*, **2010**, *66*, 8583.

[40] Sharma, A.; Schwab, R. S.; Braga, A. L.; Barcellos T.; Paixão, M. W. *Tetrahedron Lett.* **2008***, 49, 5172.*

[41] Bhadra, S.; Saha, A.; Ranu, B. C. *J. Org. Chem.* **2010**, *75*, 4864.

In spite of the substantial contributions of the hitherto specified protocols to the synthesis of selenides, the use of a new category of catalyst, namely, nanoparticles, has revelaed that this method can be further optimized, as shown in the latest literature in the field (Scheme 8).[42] [43] [44] [45]According to these authors, nanoparticles are a more effective catalyst in these reactions because of their unique properties, as discussed earlier in Chapter 1. Different types of nanoparticles have been used in these methods, with solvents and different conditions (Table 3). When Cu_2O and CuO were used to synthesize selenides from halides with diselenides or selenourea, the yield was 20-25% in DMSO in the presence of base, at 110-120°C for 24hrs (Table 3, entry 1-4). Nevertheless, when these catalysts were replaced by CuO nanoparticles, the yield was improved up to 98% (Table 3, entry 6) and the time of the reaction was reduced to 12hr, even though it was still necessary to heat up the reaction, given that at room temperature the yield was 20% (Table 3, entry 7). Without the catalyst, the reaction did not work (Table 3, entry 9). Other types of nanoparticles were also used in this kind of transformation, but the best results were obtained with CuO nanoparticles (Table 3, entry 10-13).



Scheme 8. Synthesis of selenides with CuO and CuO nanoparticles

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[42] Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971.

[43] Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R *Org. Lett.* **2009**, *11*, 951.

[44] Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R. *J. Org. Chem.* **2010**, *75*, 8720.

[45] Alves, D.; Santos, C. G.; Paixão, M. W.; Soares, L. C.; Souza, D.; Rodrigues, O. E. D.; Braga, A. L. *Tetrahedron Letters.* **2009,** *50* 6635.

Table 3. Comparison between different forms of copper and copper nanoparticles

Entry	Copper source	Base/solvent	Time(hr)/ °C	Yield (%)/ref
1	Cu_2O	$CsCO_3$/DMSO	24/120	18/47
2	Cu_2O	KOH/DMSO	24/120	20/47
3	CuO	$CsCO_3$/DMSO	24/120	20/46, 47
4	CuO	KOH/DMSO	24/120	25/47
5	CuO	$CsCO_3$/toluene	24/120	Traces/47
6	CuO nano	KOH/DMSO	10-12/80-110	98/47, 48
7	CuO nano	KOH/DMSO	r.t.	20/47
8	CuO nano	KOH/water	24/80	0/47, 48
9	-	KOH/DMSO	24/80	0
10	Fe_2O_3	KOH/DMSO	24/110	69/48
11	Bi_2O_3	KOH/DMSO	24/110	71/48
12	ZnO	KOH/DMSO	24/110	65/48
13	NiO	KOH/DMSO	24/110	72/48

In the current study we propose to improve the synthesis of selenides one step further by combining the use of nanoparticle catalysis with ionic liquids. As presented in Chapter 1, ionic liquids present various interesting properties which alleviate environmental issues, such as no effective vapour pressure, good solubilities for a wide range of compounds, and they allow many combinations of anions and cations. Due to these properties, ionic liquids have frequently been used in the last few years as an alternative reaction media for a broad range of different chemical transformations, except in synthesis of selenides. The first explorations of ionic liquids in this kind of reaction have been reported very recently by our group, using using Zn in ionic liquids to synthesize unsymmetrical selenides.[46] This protocol showed that the reaction progressed much faster in ionic liquid than in traditionally used organic solvents. The origin of its behavior is still an interesting option. Properties of ionic liquids such as strong dipolar and dispersion forces, hydrogen bond acidity (related to the cationic portion), and hydrogen bond basicity (related to the anionic portion) would account for the complex solvent interactions exhibited by ILs.[47]

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[46] Narayanaperumal, S.; Alberto, E. E.; Gul, K.; Rodrigues, O. E. D.; Braga, A. L. *J. Org. Chem.* **2010**, *75*, 3886.

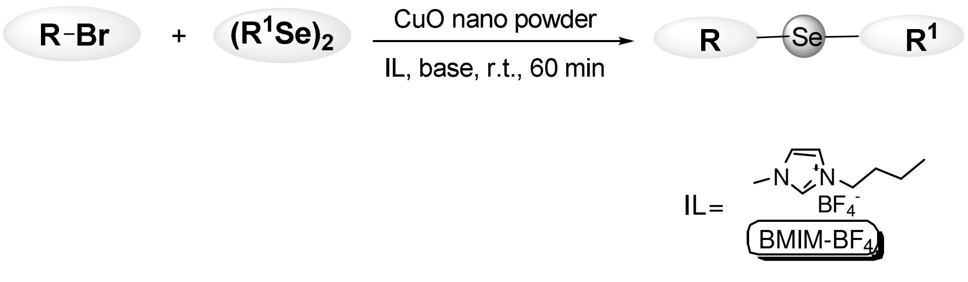
[47] a) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Zanatta, N.; Bonacorso, H. G. Chem. Rev. **2008,** *108*, 2015. (b) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. Tetrahedron Lett. **1999**, *40*, 793. (c) Chakraborti, A. K.; Roy, S. R. J. Am. Chem. Soc. **2009**, *131*, 6902. (d) Baciocchi, E.; Chiappe, C.; Giacco, T. D.; Fasciani, C.; Lanzalunga, O.;

We observed, therefore, that in addition to the increase in the rate of the reactions afforded by the use of nanoparticles, the use of ionic liquids rendered an even faster result, in mild conditions. Moreover, both nanoparticles and ionic liquids share the property of recyclabity, which further extend the effectivess of this protocol when compared to previous methods.

In this sense, in the work reported in this chapter, these two latest improvements in the field of chemistry - (1) nanoparticles catalysis and (2) ionic liquid used as a reaction media – were combined to synthesize selenides, more specifically, to perform chalcogen–carbon coupling. This method is described in the follwing sections.

2.2 Synthesis of selenides

A set of cross-coupling reactions was performed to synthesize selenides with aryl and alkyl bromides with diaryl diselenides using a catalytic amount of commercially available CuO nanopowder as a catalyst and BMIM-BF_4 as a recyclable solvent (Scheme 9). We carried out the reaction employing 4-bromotoluene (1 mmol, 171mg) as representative bromide and (0.5 equiv, 156 mg) of diphenyl diselenide to get the *p*-methyl diphenyl selenide **1b**, to optimize the reaction parameters, and to obtain the best conditions for the reaction.



Scheme 9. General scheme to the synthesis of selenides by cross coupling reaction using CuO nanopowder

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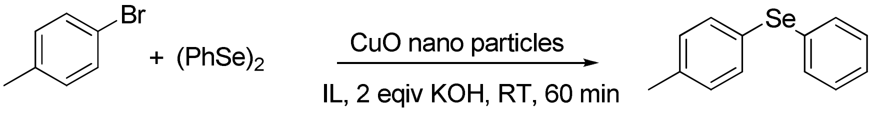
Lapi, A.; Melai, B. Org. Lett. **2009**, *11*, 1413. (e) Anderson, J. L.; Ding, J.; Welton, T.; Armstrong, D. W. J. Am. Chem. Soc. **2002,** *124*, 14247. (f) Tokuda, H.; Tsuzuki, S.; Susan, M. A. B. H.; Hayamizu, K.; Watanabe, M. J. Phys. Chem. B. **2006**, *110*, 19593. (g) Nockemann, P.; Thijs, B.; Hecke, K. V.; Meervelt, L. V.; Binnemans, K. Cryst. Growth Des. **2008**, *8*, 1353.

In a first set of experiments, the influence of different ionic liquids was studied and it was possible to check that in all of them the desired product was obtained, with yields ranging from 74 to 82%. BMIM-BF_4 was a better ionic liquid for this reaction (Table 4, entry 1). In previous reports hydrogen bonds have been evoked as a key interaction in the formation of a given product in reactions performed in ILs.[47b-d] On the basis of our experimental results (Table 4) it is reasonable to visualize that the scale of hydrogen bond acidity of the tested ILs may be an eminent property for the product formation. For example if we consider that this characteristic would facilitate the reaction through the coordination of the acid hydrogen attached to C-2 in the imidazolium ring with the leaving group (bromides) in reaction (Figure 6), the formation of products would be in the same range of yield for BMIM-BF_4, BMIM-PF_6, and BMIM-NTf_2 due to the similarity of their hydrogen bound donor (HBD) parameters.[47e-g] With the exception of BMIM-N(Tf)$_2$, which gives less yield (entry 3), BMIM-BF_4 and BMIM-PF_6 furnished the desired product in good yields, respectively (entries 1 and 2).

Table 4. CuO-nanoparticles catalyzed cross-coupling of 4-bromotoulene with diphenyl diselenide using different ionic liquids



1b

Entry	Ionic liquid	Yield[a](%)
1	BMIM-BF_4	82
2	BMIM-PF_6	74
3	BMIM-NTf_2	78

[a] Yields were determined by GC.

Furthermore, if the extent of hydrogen bond interactions really accounts for an effective formation of products, then the yields should be the same in all ionic liquids. According our assumption BMIM-N(Tf)$_2$ afford less yield because may be the nitrogen anionic part of ionic liquid can cordinate with CuO catalyst and decrease the efficiency of catalyst. All these ionic liquids were prepared in the lab by the standard method.[48]

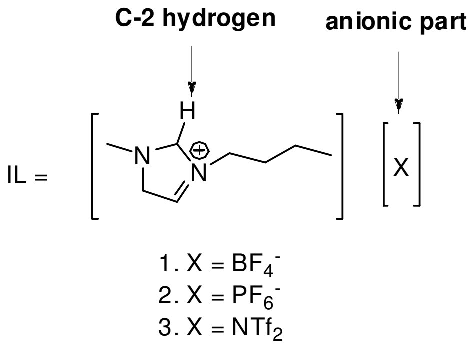


Figure 6. Anionic and cationic parts of ionic liquids used in the reaction

2.3 Optimization of reaction variables (amount of catalyst, time, and base)

After the initial observations reported in the previous section, the amount of catalyst necessary to promote the reaction efficiently was examined (Table 5). We found that variations in the amount of CuO nanopowder had an effective influence in the yields. While 0.1 and 0.25 mol% afforded the desired product in moderate yields (entries 1 and 2), we found that by using 0.5 mol%, the yield was improved to 82% (entry 3). When the amount of CuO nanopowder was increased to 1.0 mol%, the yield of compound **1b** was not significantly altered, affording the desired product in 84% (entry 4).

Table 5. Optimization of CuO nanopowder

Entry	CuO nano (mol %)	Yield[a](%)
1	0.10	45
2	0.25	48
3	0.50	82
4	1.00	84

[a] Yields were determined by GC.

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[48] Cassol, C. C.; Ebeling, G.; Ferrera, B.; Dupont, J. *Adv. Synth. Catal.* **2006**, *348*, 243.

With these results in hand, we selected 0.5 mol% of CuO nanopowder as the best amount of catalyst. We then analyzed the reaction time and the base. The variation in the reaction time from 10 to 120 minutes was studied. As shown in Figure 7, the yield had a linear increase from 10 minutes to a maximum of 60 minutes. After this, longer reaction times did not have an influence on the product's yield.

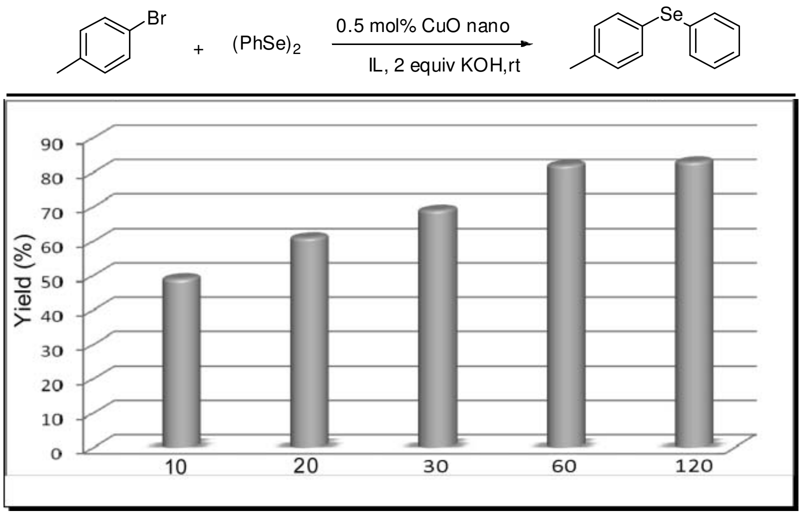


Figure 7. Time optimization in CuO nanocatalysis

In terms of base, the influence of different bases was studied to perform a more efficient cleavage of diselenides affording the nucleophilic selenolate species. Thus, Cs_2CO_3 and KOH provided the diaryl selenides in good yields (Table 6, entries 2 and 3), whereas other bases, such as K_2CO_3 and Na_2CO_3, gave only moderate yields (Table 6, entries 1 and 4). In fact, bases such as K_2CO_3 and Na_2CO_3 are not able to cleave diphenyl diselenide (PhSeSePh) or selenium-selenium bond in normal conditions. Our observation, however, is that, in the presence of ionic liquids, these weak bases can also cleave this bond, but the yield of the reaction was not good. The product was not observed in the absence of base, hence the necessity of that to perform the reaction (entry 5).

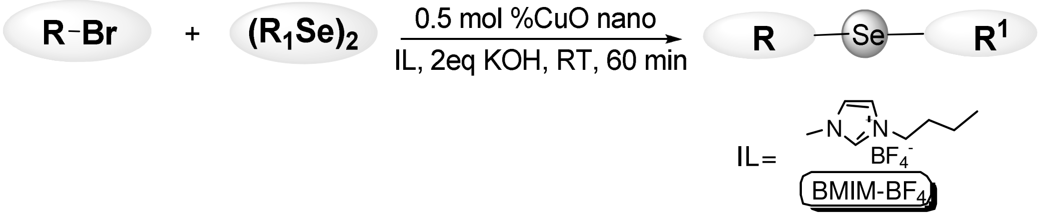
After the optimizations, the reactions were carried out with different alkyl and aryl bromides and substituted diselenides (Table 7). In general, all reactions were very clean and selenides were obtained in excellent yields, as depicted in Table 7. We studied the electronic and steric effects of attached substituents in the aryl bromides and in the diselenide moiety. In terms of electronic effects, the reaction was not very sensitive to this influence, since the coupling of diphenyl diselenide with neutral, electron donating, and electron withdrawing aryl bromides was efficiently achieved (entries 1–5).

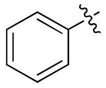
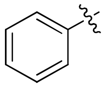
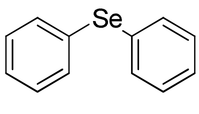
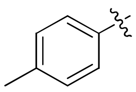
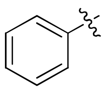
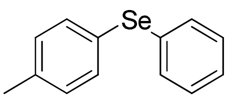
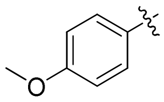
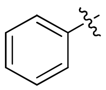
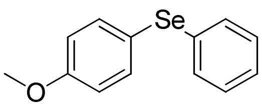
Table 6. Optimization of base

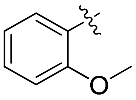
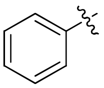
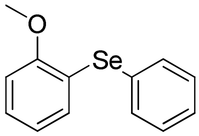
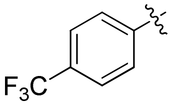
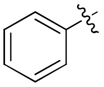
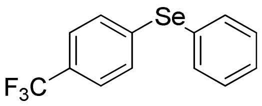
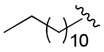
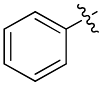
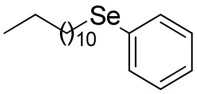
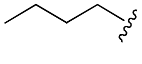
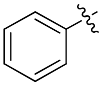
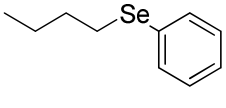
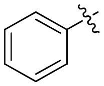
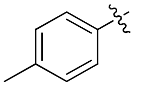
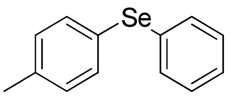
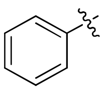
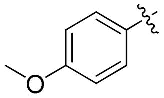
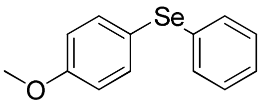
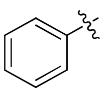
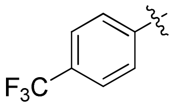
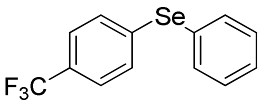
Entry	**Base**	**Yield**[a]**(%)**
1	K_2CO_3	41
2	Cs_2CO_3	78
3	KOH	82
4	Na_2CO_3	46
5	None	0

[a] Yields were determined by GC.

Table 7. CuO-nanopowder catalyzed cross-coupling of organoyl bromides with diphenyl diselenides



Entry	**R**	**R**^{1}	**Product**	**Yield**[a] **(%)**
1			 1a	82
2			 1b	80
3			 1c	80

4			 **1d**	79
5			 **1e**	70
6			 **1f**	75
7			 **1g**	76
8			 **1b**	80
9			 **1c**	76
10			 **1e**	74

[a] Yields were determined by GC.

Comparing the coupling reaction between the aryl bromides (entry 3 and 5), the activated one (**1c**, 4-OMe group) showed a higher yield (entry 3 *vs.* 5). Despite this, the coupling was efficient and allowed the formation of diaryl selenides in good yields. Analyzing Table 7 (entries 3–4 and 8–10), it is possible to observe that, in terms of steric and electronic effects; the reaction was not strongly influenced by these parameters. As described, the reaction was not hampered and the diaryl selenides were obtained in high yields. To extend the scope of our coupling protocol, alkyl bromides were also employed (entries 6 and 7). Although it was possible to prepare alkyl aryl selenides in reasonable yields using this methodology, there were some problems during the purification of the selenides, because the Rf values of selenides and diselenides are almost same. Pure hexane was used to purify most of the compounds, but in some fractions, the mixture of selenides and diselenide was obtained. To solve this problem, yields of the compounds were determined by Gas chromatography.

2.4 Recyclability experiments

The quest for developing economic and environment friendly methods is one of our primary concerns. It prompted us to evaluate the possibility of reusing the ionic liquid employed in our reactions. Therefore, after the work-up, 20ml of ethanol were added and reaction residue was removed from BMIM-BF_4 by filtration using celite. The organic solvent was removed by vacuum and the ionic liquid was dried on high vacuum pump for several hours. It took more time to dry the ionic liquid than normal solvents because of the high density of ionic liquids. Ionic liquid was used again for the next reactions. This operation was repeated for more three times without significant loss of efficiency of ionic liquid as shown in Table 8. A slight change in the color of the ionic liquid was observed after the third run, but the purity of the ionic liquid was checked and confirmed by NMR.

Table 8. Recyclability experiments of ionic liquid

Entry	**Run**	**Yield[a](%)**
1	1	82
2	2	80
3	3	80
4	4	78

[a] Yields were determined by GC.

2.5 Proposed mechanism for CuO nanoparticle catalyzed reactions

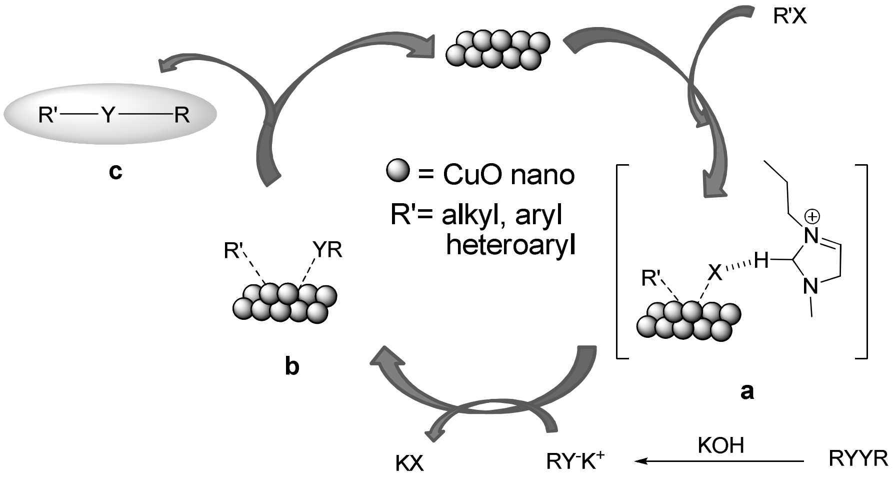


Figure 8. Plausible reaction pathway

The CuO nanoparticles may undergo the reaction with aryl halide to give intermediate ***a*** (Figure 8). The latter ***b*** may then undergo the reaction with selenium nucleophile to give intermediate ***b***, which can complete the catalytic cycle by reductive elimination of the cross-coupled product ***c***. [49] and the mechanisms about these systems shown in the previous reports are not clearly described, so still we working to get some real picture about the mechanistic cycle using nanoparticles. There is some effect of solvent (BMIM-BF_4) also in speed up the reaction. According to the previous reports, the coordination of the acid hydrogen attached to C-2 in the imidazolium ring with the leaving group (bromides) in reaction can facilitate the reaction (Figure 6).

All compounds were characterized by ^1H and ^{13}C NMRs. Experimental details and further information on the characterization of these compounds are given in Chapter 7 and the spectra are presented in Chapter 8.

Figure 9 shows the different magnetic environment of hydrogen (H) and carbon. The chemical shifts in the ^1H NMR spectra of Phenyl (*p*-tolyl) selane **1b** at 7.38-7.32 ppm show a multiplet relative of 4H (H_c, $H_{c'}$, H_a and $H_{a'}$) of the phenyl group. The other 3H (H_d, $H_{d'}$, and H_e) of the phenyl group are confirmed by another multiplet at 7.23-7.16 ppm, and H_b and $H_{b'}$ show a doublet with a coupling constant of

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[49] Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971.

J = 8.5 Hz at 7.04 ppm. The signals of the aliphatic hydrogens of the methyl group appear at 2.33 ppm as a singlet (Figure 10). In the ^{13}C NMR carbon aromatic C1, C1', C2, C2', C3, C3', C4, C4', C5, C5', C6 and C6' appear at shifts ranging from 138-125 ppm with the aliphatic C7 at 21.1 ppm (Figure 11).

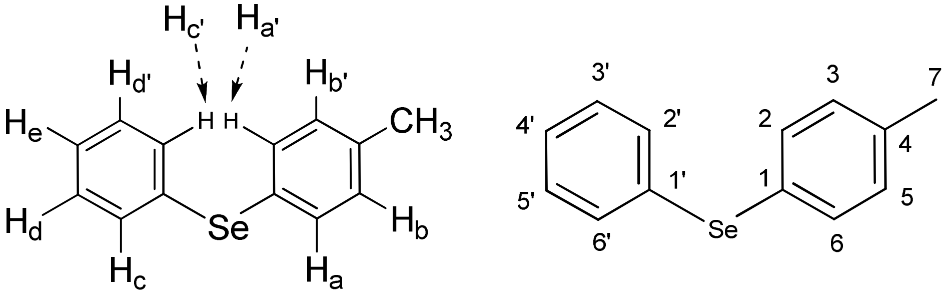


Figure 9. Different magnetic environment of Hydrogen (H) and carbon

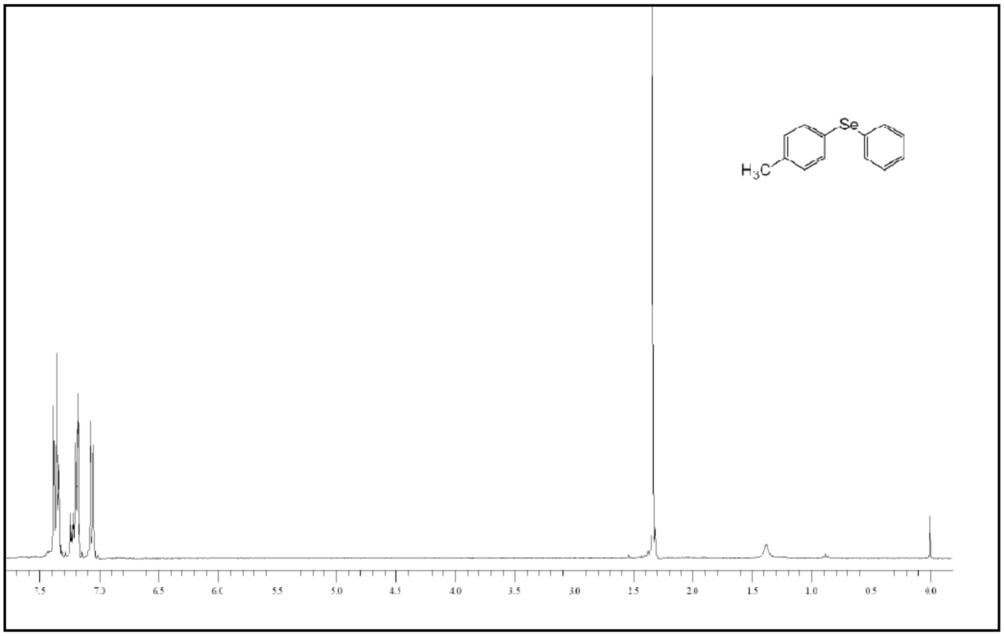


Figure 10.^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **Phenyl (*p*-tolyl) selane (1b)**

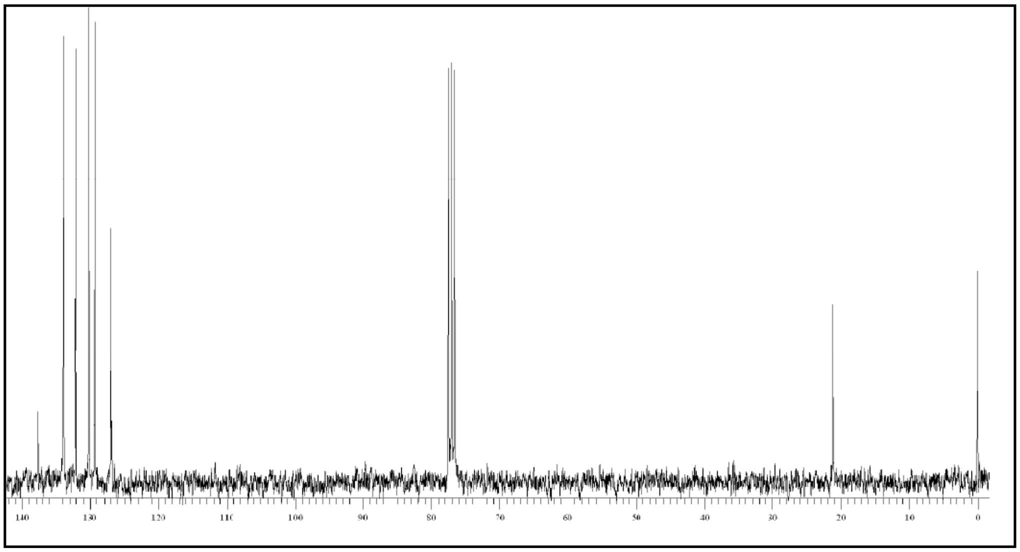


Figure 11. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **Phenyl (*p*-tolyl) selane (1b)**

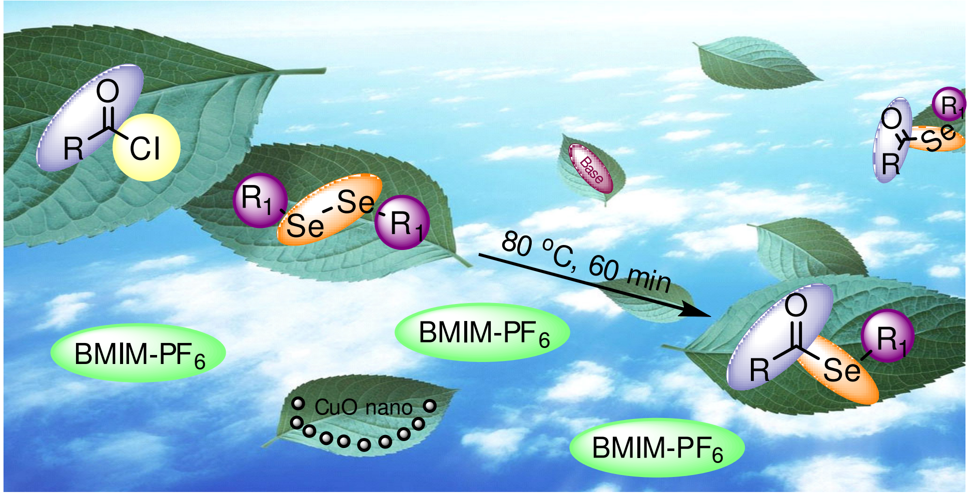
In conclusion, herein, an improved methodology was reported for the synthesis of aryl or alkyl selenides by coupling reaction of alkyl and aryl bromides with diselenides in the presence of CuO nanoparticles in ionic liquid to obtain corresponding selenides in good to excellent yield. There are some previous reports that mention the synthesis of selenides by nanoparticles catalysis.[46], [47] but reaction time is quite high and need to heat up the reaction upto 110 °C. But the combination of CuO nanoparticles with ionic liquid speed up the reaction at room temperarure.

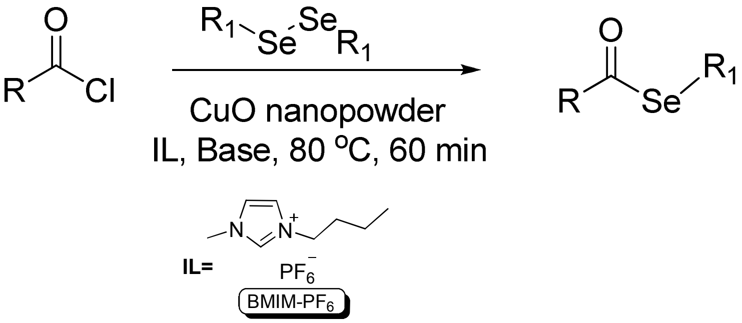
Some important aspects of these methodologies are the high reactivity in the preparation of the different organoselenides compounds, with short reaction times, mild reaction conditions, and excellent yields and, most important recyclability of solvent.

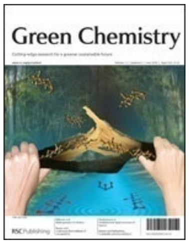
The published article that reports the work discussed in the current chapter can be found in Appendix 1.

CHAPTER 3

EFFICIENT SYNTHESIS OF SELENOESTERS FROM ACYL CHLORIDES MEDIATED BY CuO NANOPOWDER IN IONIC LIQUID







Green Chem. **2010**, 12, 957-960

3.1 Introduction and previous methods to synthesize chalcogen esters (selenoesters)

Selenoesters are important intermediates in several organic transformations. The compounds in this class have been used as precursors of acyl radicals[50] and anions[51] and have attracted attention for the synthesis of new molecular materials, especially superconducting materials and liquid crystals.[52] Applications of selenoesters have been expanded to the synthesis of proteins by chemical ligation of chalcogenol esters,[53] to the synthesis of substrates which undergo facile and efficient radical decarbonylation, as well as to the synthesis of the natural alkaloid (+)-geissoschizine.[54]

A variety of methods for the preparation of thiol- and selenol esters have been developed in previous studies. Among these, more general methods are the alkylation of chalcogen (RYH) and its salts (RYM) – whether of the alkali or alkaline earth metals with acyl halides (Figure 12).[55] Activated Zn has also been used to obtain thio esters from the reaction of acyl halides with thiols in good to excellent yields. The recovery of zinc and its reuse makes the procedure more economic (Figure 12).[56] Using organic bases like triethyl amine or pyridine can also provide thio- or seleno- ester (Figure 12).[57] The reactions of chalcogen silanes with acyl chlorides also reported to obtain thio- or seleno- esters in good yields. Potassium floride has also been used in this reaction because the reaction proceeds through the initial attack of fluoride ion on silicon atom to produce mercaptide ions, which react with acyl chlorides, giving the thio- and seleno- esters (Figure 12).[58];

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[50] (a) Keck, G.; Grier, M. C. *Synlett*, **1999**, 1657; (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429; (c) Chen, C.; Crich, D.; Papadatos, A. *J. Am. Chem. Soc.* **1992**, *114*, 8313.

[51] Hiiro, T.; Morita, Y.; Inoue, T.; Kambe, N.; Ogawa, A.; Ryu, I.; Sonoda, N. *J. Am. Chem. Soc.* **1990**, *112*, 455.

[52] (a) Heppke, G.; Martens, J.; Simon, K. H. *Angew. Chem., Int. Ed. Eng.* **1977**, *16*, 318; (b) Cristiano, R.; Ely, F.; Gallardo, H. *Liq. Cryst.* **2005**, *32*, 15; (c) Cristiano, R.; Westphal, E.; Bechtold, I. H.; Bortoluzzi, A. J.; Gallardo, H. *Tetrahedron.* **2007**, *63*, 2851; (d) Gamota, D. R.; Brazis, P.; Kalyanasundaram, K.; Zhang, J. *Printed Organic and Molecular Electronics*; Kluwer Academic: New York, NY, **2004**; (e) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem. Int. Ed.* **2000**, *39*, 3348; (f) Woon, K. L.; Aldred, M. P.; Vlachos, P.; Mehl, G. H.; Stirner, T.; Kelly, S. M.; ONeill, M. *Chem. Mater.* **2006**, *18*, 2311; (g) Gallardo, H.; Zucco, C.; Da Silva, L. *Mol. Cryst. Liq. Cryst.* **2002**, *373*, 181; (h) Yamada, J.; Akutsu, H.; Nishikawa, H.; Kikuchi, K. *Chem. Rev.* **2004**, *104*, 5057; (i) Cristiano, R.; Vieira, A.; Ely, F. Gallardo, H. *Liq. Cryst.* **2006**, *33*, 381; (j) Tavares, A.; Ritter, O.; Vasconcelos, U.; Arruda, B.; Schrader, A.; Merlo, A.; Schneider, P. H. *Liq Cryst.* **2010**, *37*, 159.

[53] (a) Baca, M.; Muir, T.; Schonolzer, M.; Kent, S. *J. Am. Chem. Soc.* **1995**, *117*, 1881;(b) Inoue, M.; Yamahita, S.; Ishihara, Y.; Hirama, M. *Org. Lett.*, **2006**, *8*, 5805.

[54] Chen, S. F.; Eary, K. X. *Org. Lett.* **1999**, *1*, 79.

[55] Piette, J. L.; Renson, M. *Bull. Soc. Chim. Belg.* **1970**, *79*, 383.

[56] Meshram, H. M.; Reddy, G. S.; Bindu, K. H.; Yadav, J. S. *Synlett* **1998**, 877.

[57] (a) Coutrot, P.; Charbonnier, C.; Grisen, C. *Synthesis* **1991**, 23. (b) Wepplo, P. *Synth. Commun.* **1989**, *19*, 1533.

[58] (a) Ando, W.; Furuhata, T.; Tsumaki, H.; Sekiguchi, A. *Chem. Lett.* **1982**, 885. (b) Derkach, N. Y.; Tishchenko, N. P. *Zh. Organ. Khim.* **1977**, *13*, 100. (c) Sasaki, K.; Ase, Y.; Otsubo, T.; Ogura, F. *Chem. Lett.* **1986**, 977.

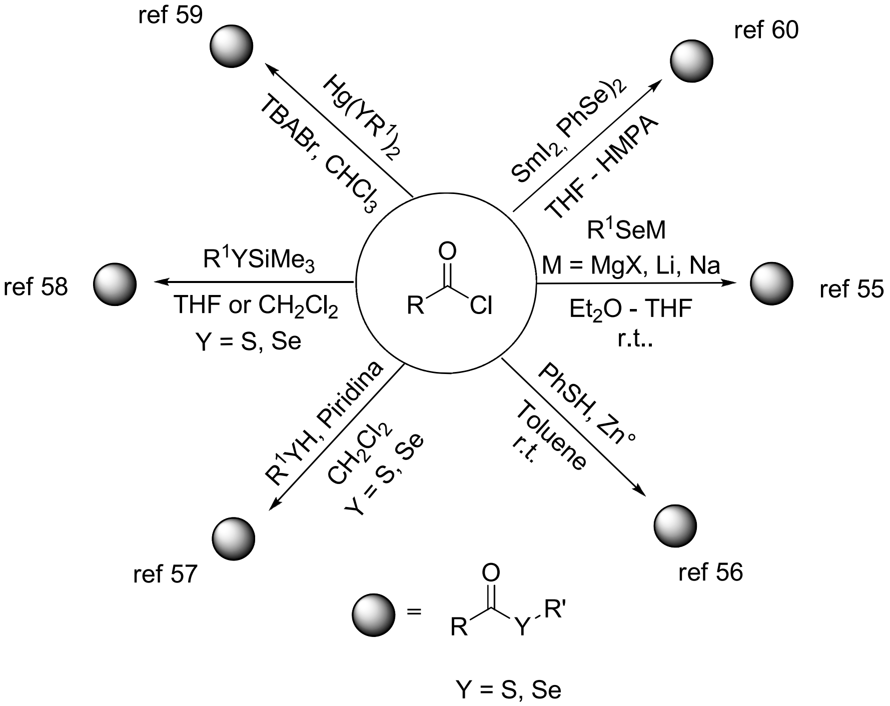

Figure 12. Synthesis of chalcogen esters from acid chlorides

Silveira and co-workers reported the synthesis of thiol, selenol, and tellurol esters by the reaction of bis(organochalcogeno)mercurials with acid chlorides in chloroform or carbon tetrachloride and in the presence of tetrabutylammonium halides as catalysts.[59] Zhang and co-workers reported the preparation of these compounds by using samarium iodide, which react with dichalcoganides to generate chalcognate, which in turn reacts with acyl halide to get the corresponding chalcogen esters in good to excellent yields (Figure 12).[60]

Another important starting material for the synthesis of chalcogen ester is carboxylic acid. Thiol esters can be obtained in good yields with the reaction of carboxylic acid and thiols in the presence of DCC (dicyclohexylcarbodiimide) and of DMAP (4-Dimethylaminopyridine) as a catalyst (Figure 13).[61] Gais reported that carboxylic acid-imidazolides or 1,2,4-triazolides are accessible in almost quantitative yields from carboxylic acids and carbonyl di-imidazole (CDI) or 1,2,4-triazole (CDT), respectively. Carboxylic acid-imidazolides or 1,2,4-triazolides react with aliphatic and

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[59] Silveira, C. C.; Braga, A. L.; Larghi, E. L.; *Organometallics*, **1999**, *18*, 5183.

[60] (a) Zhang, Y. M.; Wang, L. *Synth. Commun*. **1999**, *18*, 3107. (b) Zhang, Y. M.; Liu, Y. K. *Synth. Commun*. **1999**, *22*, 4043.

[61] Grunwell, J. R.; Foerst, D. L. *Synth. Commun*. **1976**, 453.

aromatic thiols or selenols to give the corresponding esters in excellent yields (Figure 13).[62] Another method based on carboxylic acid was reported by Grieco and co-workers, in which carboxylic acid reacts with phenylselenocynate or phenylthiocynate in the presence of tri-*n*- butylphosphine affording the seleno- and thio- esters in good yields (Figure 13).[63]

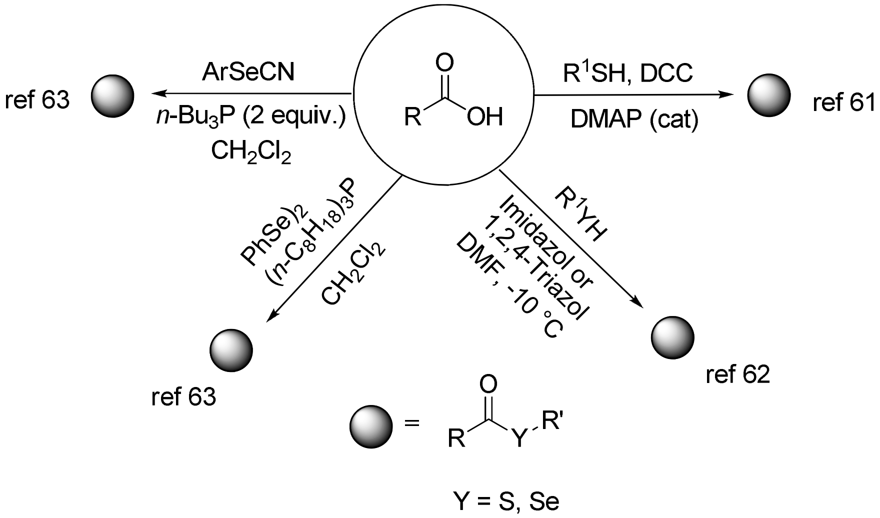

Figure 13. Synthesis of chalcogen esters from carboxylic acid

Apart from these methods, thio- and seleno- ester can be further obtained from starting materials other than acyl chlorides and carboxylic acids. Tingoli and co-workers reported that aldehydes can react with iodosobenzene diacetate (IBDA), with sodium azide, and with diphenyl disulfide or diselenide to afford the corresponding thio- or seleno- esters (Scheme 10).[64] Our group reported the synthesis of this kind of compounds by the addition of *p*-toluenesulfonic acid (*p*-TsOH) or trifluoroacetic acid (TFA) to a dichloromethane suspension of thioacetylenes and silica with its natural water content to obtain thio esters (Scheme 10).[65]

Sonoda and co-workers reported the synthesis of selenoesters catalyzed by the palladium complex and a three-component coupling of phenyl tributylstannyl selenide with aryl iodides and carbon monoxide to afford the corresponding selenol esters in moderate to good yields (Scheme 10).[66]

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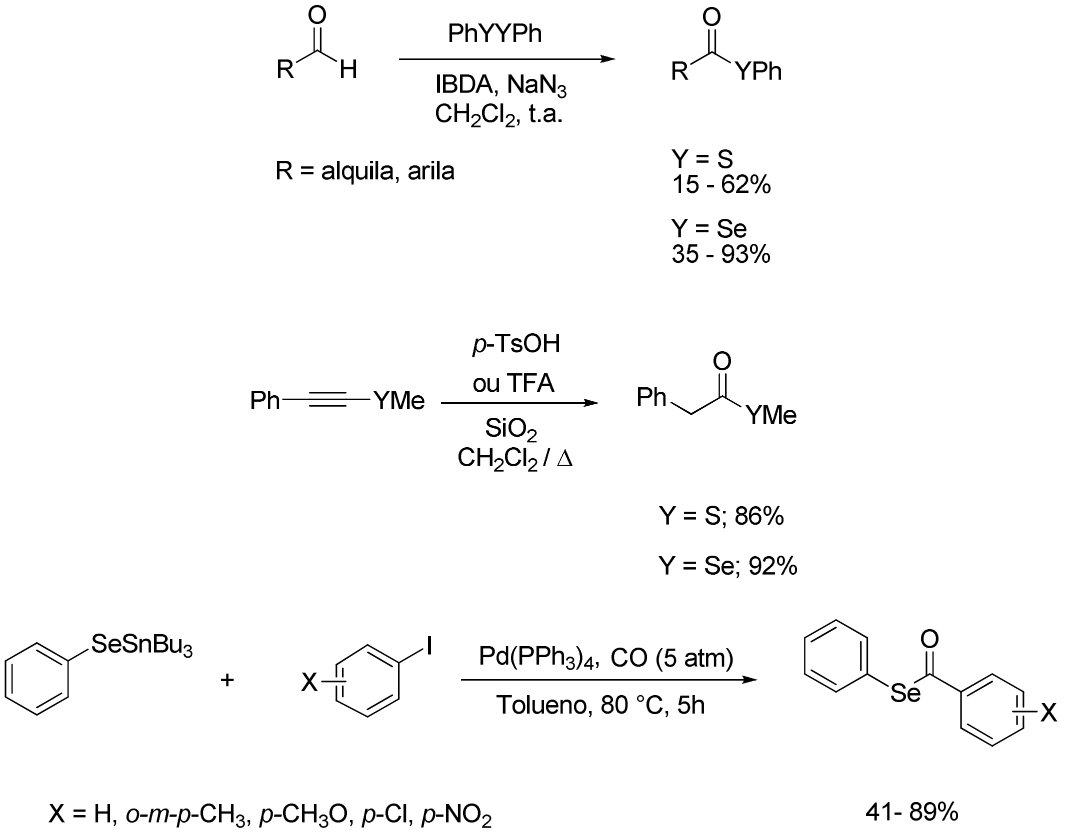
[62] Gais, H. J. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 244.
[63] Grieco, P. A.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1978**, *43*, 1283.
[64] Tingoli, M.; Temperini, A.; Testaferri, L.; Tieco, M. *Synlett* **1995**, 1129.
[65] Braga, A. L.; Ávila, E.; Rodrigues, O. E. D.; Silveira, C. C. *Tetrahedron Lett.* **1998**, *39*, 3395.
[66] Nishiyama, Y.; Tokunaga, K.; Kawamatsu, H.; Sonoda, N. *Tetrahedron Lett.* **2002**, *43*, 1507.



Scheme 10. Synthesis of chalcogen esters in previous methods

Finally, there are a number of metals used in the synthesis of chalcogen esters, but the most frequently used metal is indium, with different sources. Indium metal was used to perform this transformation in one pot, and the reaction worked very well at room temperature in 3 hr.[67] When $InCl_3$ was used, the reaction did not work well even in high temperature and for long time spans. However, when InI was used, the reaction worked very well (Scheme 11).[68] Our group then improved the methodology to synthesise thio- and seleno- esters by using indium metal with ionic liquids.[69] By this method it was possible to get these compounds with excellent yield in 1hr and in 50 °C. According to this method, it is necessary to heat up the reaction.

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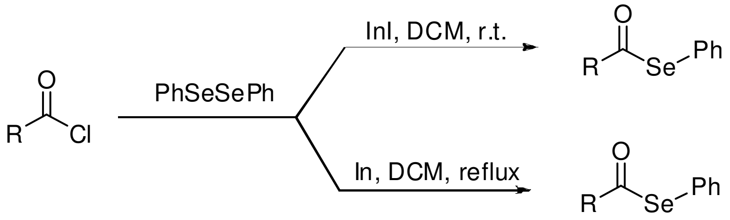
[67] (a) Munbunjong, W.; Lee, E. H.; Ngernmaneerat, P.; Kim, S. J.; Singh, G.; Chavasiri, W.; Jang, D. O. *Tetrahedron.* **2009**, *65*, 2467; (b) Marin, G.; Braga, A. L.; Rosa, A. S.; Galetto, F. Z.; Burrowa, R. A.; Gallardo, H.; Paixao M. W. Tetrahedron. **2009***, 65,* 4614.

[68] Ranu, B. C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793.

[69] Tabarelli, G.; Alberto, E. E.; Deobald, A. M.; Marin, G.; Rodrigues, O. E. D.; Dornelles, L. Braga, A. L. *Tetrahedron Lett.* **2010**, *51*, 5728.

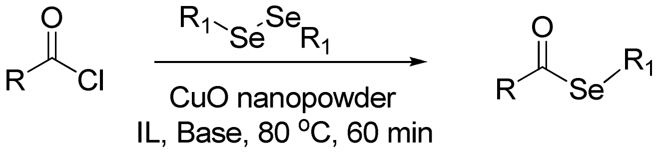


Scheme 11. Synthesis of chalcogen esters in further previous methods

After all these considerations, we planned to combine nanoparticle catalysis and ionic liquid to afford selenoesters and to verify the effect of nanoparticles in this kind of transformation, primarily because there are no reports in the literature about the synthesis of chalcogen esters using nanoparticles as catalyst and ionic liquid, but also because, as reported in Chapter 2, at this point in the research we already knew the positive potential of the combination of nanoparticles catalysis with ionic liquids. The results of this protocol in the synthesis of selenoesters are described in details in the following sections of this chapter.

3.2 Synthesis of selenoesters

Our interest was to develop an efficient methodology to synthesize selenoesters by enviontmentally benign methods. In this regard, we prepared the selenoesters via a cross-coupling reaction of acyl chloride with diselenides, using CuO nanopowder as a recyclable catalyst and BMIM-PF_6 as a solvent (Scheme 12). The improvement in this methodology is that we can recycle the catalyst as well as the solvent after the reaction and reuse them in later reactions.

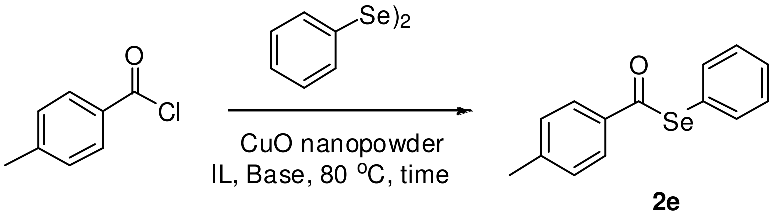


Scheme 12. General synthesis of seleno-esters with CuO nanopowder in ionic liquid

3.3 Optimization of reaction variables

In a similar fashion to the one reported in Chapter 2, here, in order to optimize the protocol and to understand the influence of different variables on the synthesis of selenoesters, several components were studied. To this end, we carried out the reaction employing 4-methylbenzoyl chloride (1.0 mmol, 154 mg) as a representative acyl chloride and (0.5 mmol, 156 mg) of diphenyl diselenide affording the corresponding selenoester **2e** (Table 9).

Table 9. Optimization of the reaction: ionic liquid, base, and time



Entry	Ionic Liquid	Base (2 eq)	Time (min)	Yield[a] (%)
1	BMIM-BF_4	Cs_2CO_3	60	82
2	BMIM-NTf_2	Cs_2CO_3	60	84
3	BMIM-PF_6	Cs_2CO_3	60	90
4	BMIM-PF_6	Cs_2CO_3	60	Traces[b]
5	BMIM-PF_6	KOH	60	88
6	BMIM-PF_6	K_2CO_3	60	72
7	BMIM-PF_6	Na_2CO_3	60	73
8	BMIM-PF_6	Cs_2CO_3	40	76
9	BMIM-PF_6	Cs_2CO_3	30	60
10	BMIM-PF_6	none	60	-
11	BMIM-PF_6	Cs_2CO_3	240	90
12	BMIM-PF_6	Cs_2CO_3	240	30[c]

[a]Yields determined by GC, [b]reaction performed at room temperature, [c]reaction performed without CuO nanopowder.

In a first set of experiments, we studied the influence of different ionic liquids. It was possible to observe that in all examples the desired product was obtained with yields ranging from 82% to 90% (Table 9, entries 1-3). Nevertheless, BMIM-PF_6 was the most efficient ionic liquid for this reaction affording a better yield for selenoester **2e** (Table 9, entry 3). Braga and co-workers explain that there is an adequate effect of counter ion of ionic liquid in the reaction.[69] In this reaction, BMIM-PF_6 works better than BMIM-BF_4 because of the hydrophobic nature of the ionic liquid, and if solvent contains small amount of moisture it can hydrolyse the starting material easily and lower the yield of reaction.

The influence of different bases was studied to perform a more efficient cleavage of the diselenides, affording the nucleophilic selenolate species. Cs_2CO_3 and KOH provided the selenoester **2e** in good yields 90% and 88% respectively

(Table 9, entries 3 and 5), whereas other bases, such as K_2CO_3 and Na_2CO_3, gave only moderate yields, 72%, and 73% respectively (Table 9, entries 6 and 7). The product was not observed in the absence of base (Table 9, entry 10), and the best base for this reaction was Cs_2CO_3 (Table 9, entry 3). When variations in the reaction time from 30 to 60 minutes were studied, we observed that the yield increased from 30 minutes to a maximum of 60 minutes (Table 9, entries 3, 8, and 9). Longer reaction times did not have an influence on the product's yield (Table 9, entry 11).

Finally, to further optimize the protocol, it was necessary to examine the effect of the amount of catalyst in promoting the efficiency of the reaction. Without catalyst, the reaction worked very slowly and the product was obtained in low yield (Table 9, entry 12). We found that varying the amount of CuO nanopowder had an effective influence on the reaction course. When the amount of CuO nanopowder was increased from 1.0 to 2.0 mol%, the yield of compound **2e** was significantly modified from 48% to 82% (Figure 14). By using 5.0 mol% of CuO nanopowder, the yield was further improved to 90%. Nonetheless, raising the amount of CuO nanopowder up to 10 mol% did not change the yield of the desired product, affording the same level of 90%, as shown in Figure 14.

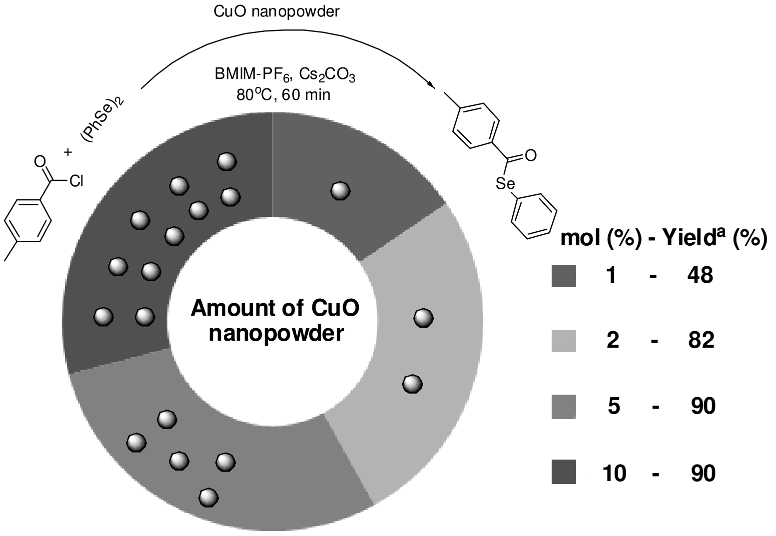
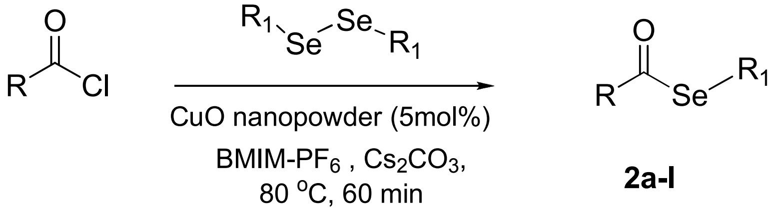


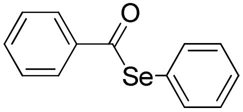
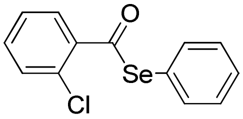
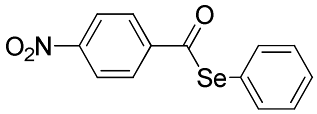
Figure 14. Optimization of CuO nanopowder

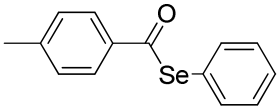
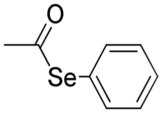
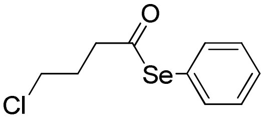
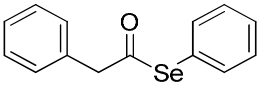
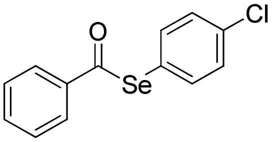
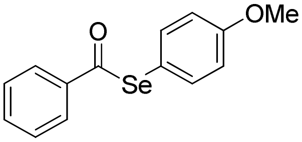
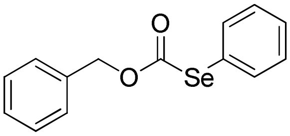
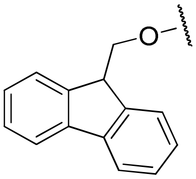
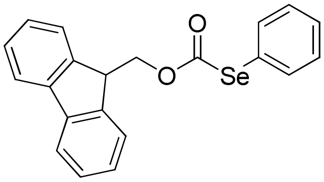
After the optimizations, under standard conditions we performed a series of reactions using different kinds of acyl chlorides with diaryl diselenides to synthesize the selenoesters **2a-l**. All reactions were clean and efficient and the respective compounds were obtained in good to excellent yields, as depicted in Table 10. In terms of electronic effects, it was possible to verify that the reaction is more sensitive to the acid chloride than the diselenide moiety. For instance, a strong electron withdrawing group, such as the nitro attached to acyl chloride (Table 10, entry 3) afforded a moderate yield of 57% of the desired selenolester **2c.** By using a neutral and an electron donating group, the reaction proceeded efficiently and the selenoesters were obtained in excellent yields (Table 10, entries 1 and 5). As expected, when aliphatic acyl chlorides were used to afford alkanoate selenoesters, the corresponding compounds were obtained in good yields (Table 10, entries 6, 7, and 8). In terms of diselenide, this outcome is less effective, but still it was possible to observe that electron withdrawing groups afforded slightly lower yields than the other groups (Table 10, entries 9 and 10). This can be rationalized in terms of the lower nucleophilicity of these selenolate species. As a further extension, we attempted to synthesize a selenocarbonate bearing interesting functionalities and obtained encouraging results. When we used benzyl chloroformate (entry 11) and 9-fluorenylmethyl chloroformate (entry 12), the corresponding selenocarbonates **2k** and **2l** were obtained in yields of 79% and 90%, respectively (Table 10, entries 11 and 12).

Table 10. Synthesis of selenoesters



2a-l

Entry	R	Product	Yield (%)[a]
1	Ph	 **2a**	91
2	*o*-ClPh	 **2b**	83
3	*p*-NO_2Ph	 **2c**	57
4	*p*-BrPh		84

		2d	
5	*p*-MePh	 **2e**	90
6	Me	 **2f**	69
7	ClC_3H_6	 **2g**	61
8	$PhCH_2$	 **2h**	72
9	Ph	 **2i**	80
10	Ph	 **2j**	86
11	$PhCH_2O$	 **2k**	79
12		 **2l**	90

[a] Isolated yields.

3.4 Recyclability experiments

In an attempt to get the efficiency of the catalyst and solvent, the recyclability of the catalyst and of the ionic liquid was studied. The CuO nanopowder was recovered from the reaction mixture and reused for three further runs and no loss of activity was observed, providing the product in very good yields (Table 11, entries 1-4). After the work-up, BMIM-PF$_6$ was separated by filtration and the recovered ionic liquid was used again for the next reactions. This operation was repeated another three times without significant loss of efficiency, as shown in Figure 15. Detailed recyclability procedure is given in Chapter. 7, section. 7.2.12.

Table 11. Recyclabity experiment of CuO nanopowder

Runs	Catalyst recoverability (%)	Product Yield^a (%)
1	96	89
2	92	84
3	85	82
4	80	74

^{a}Yields determined by GC.

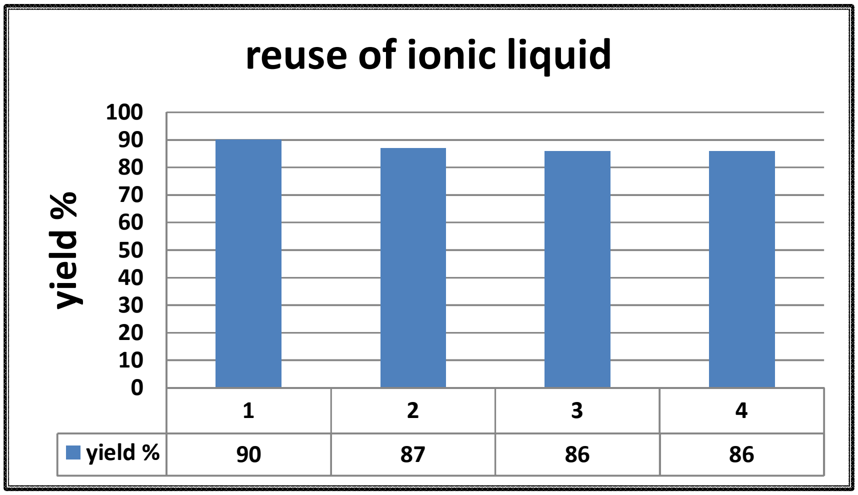


Figure 15. Recyclability of BMIM-PF$_6$

Figure 16 shows the Transmission Electron Microscopy (TEM) analysis of the CuO nanopowder, performed before and after the four reaction runs. The samples showed identical powder morphology and size after reuse of the catalyst in this transformation and these experimental results suggest that the reaction involves a heterogeneous process via a surface CuO nanopowder catalysis.

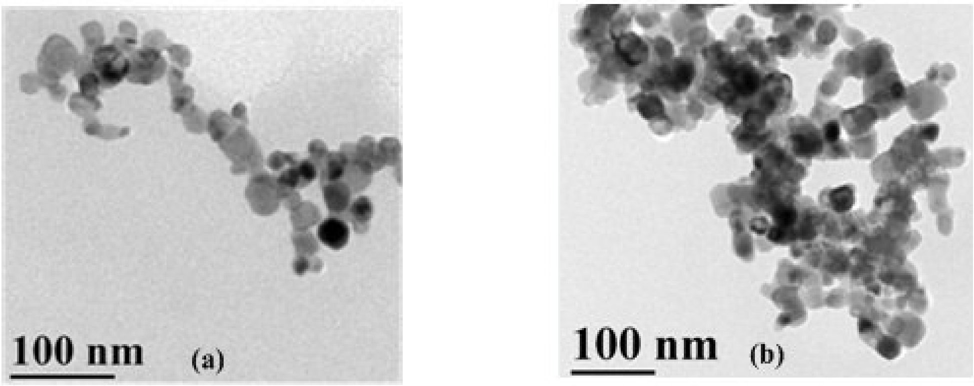


Figure 16. TEM images of CuO nanopowder: (a) fresh CuO nanopowder; (b) CuO nanopowder after four reaction runs

3.5 Proposed mechanism for CuO nanoparticle catalyzed reactions

Figure 17 shows the plausible mechanism of the CuO catalized synthesis of selenoesters. The mechanistic explanation is the same as the one provided in Chapter 2, section 2.5.

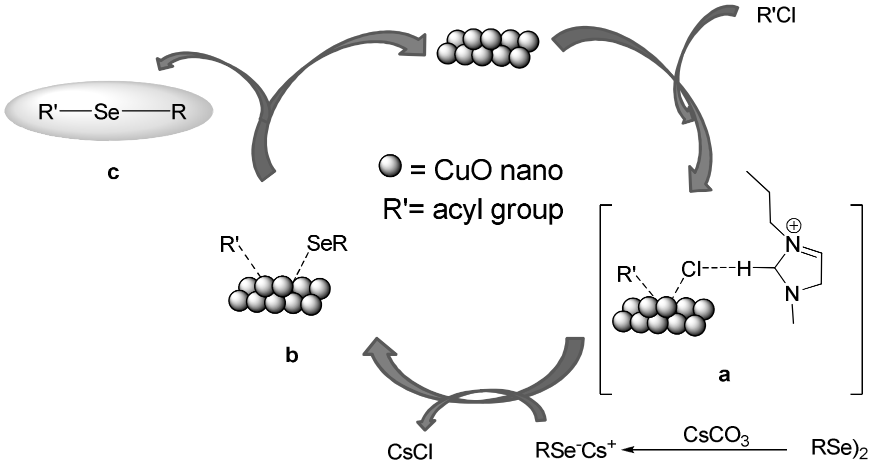


Figure 17. Plausible reaction pathway

All these compounds are characterized by ^{1}H, and ^{13}C NMR. Experimental details and further information on their characterization are given in Chapter 7 and the spectra are presented in Chapter 8.

The NMR spectra of the compound ***Se*-Phenyl *p*-methylselenobenzoate (2e)** shows in ^1H spectrum that in region 7.96-7.80 ppm shows doublet relative of 2H (H_c, $H_{c'}$,) with *j* = 8.1 Hz of phenyl group. Other 5H (H_d, $H_{d'}$, H_e, H_b, and Hb’) of phenyl group are confirmed by another multiplet in region 7.54-7.38, and H_a and $H_{a'}$ show a doublet with *j* = 8.0 Hz 7.18 ppm (Figure 19). The aliphatic hydrogens of methyl group appear at 2.35 ppm (Figure 18).

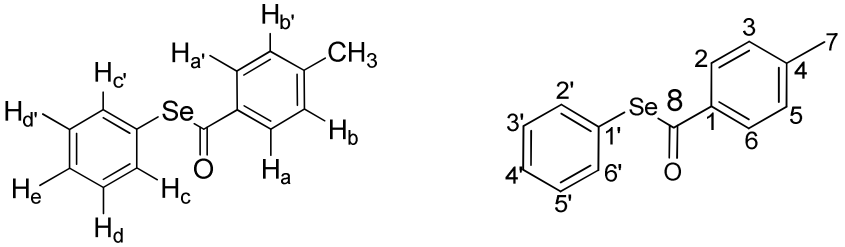


Figure 18. Different magnetic environment of hydrogen (H) and carbon

In ^{13}C NMR carbon C8 (carbonyl carbon) appears at 192.9, C1, C1’, C2, C2’, C3, C3’, C4, C4’, C5, C5’, C6 and C6’ appear in the range of 143-125 ppm (aromatic region) and C7 appear in aliphatic region at 22.9 ppm (Figure 20).

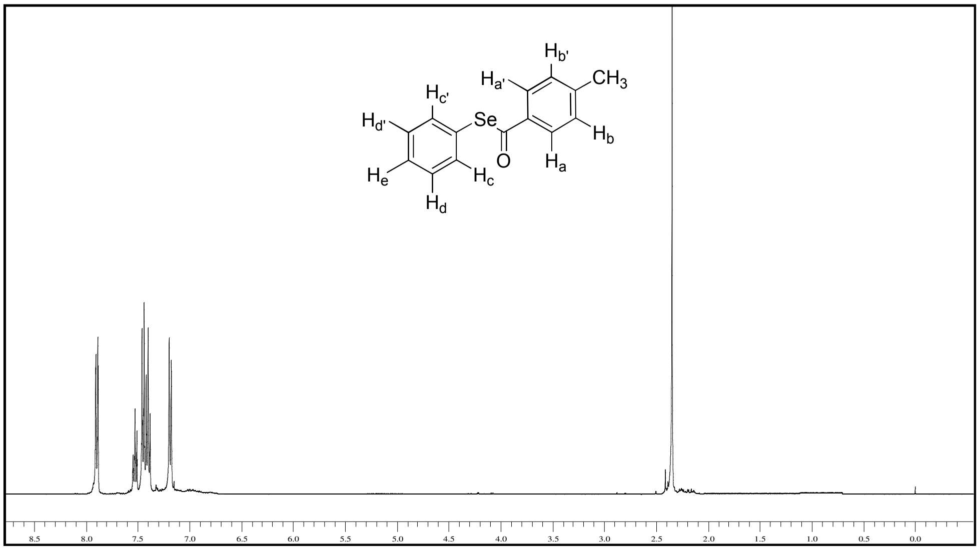


Figure 19.^1H NMR (400 MHz, $CDCl_3$) spectrum of ***Se*-Phenyl *p*-methylselenobenzoate(2e)**

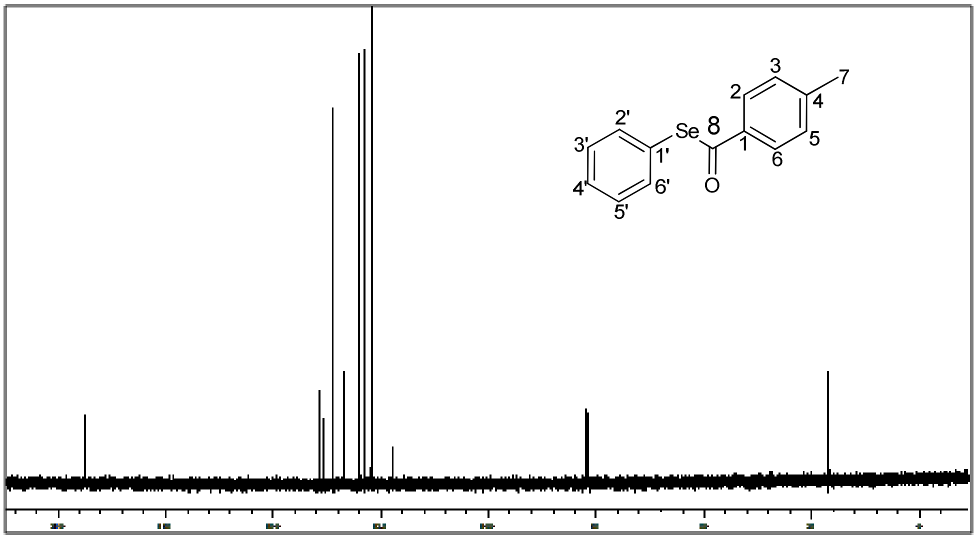


Figure 20. ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of ***Se*-Phenyl *p*-methylselenobenzoate(2e)**

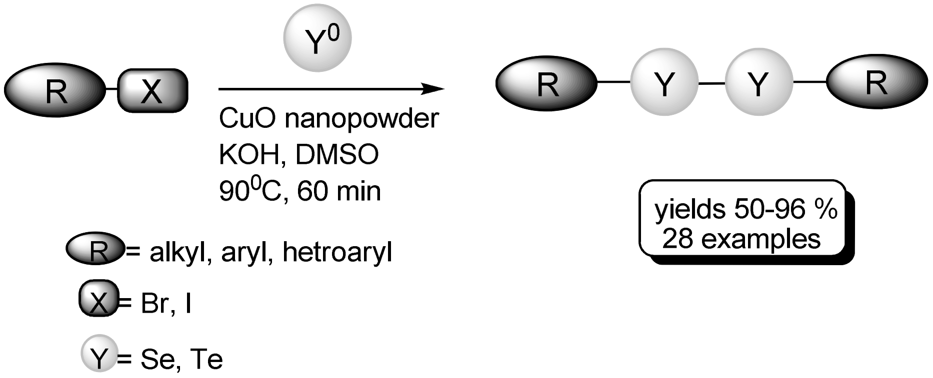
In summary, the present chapter reports an improved methodology for the synthesis selenoesters in the presence of CuO nanoparticles in ionic liquid in good to excellent yield. There are some previous reports that mention the synthesis of selenoesters by different metals and with mild conditions. But, these metals are expansive and lost after reaction. The advantage of this work is the use of cheap and recyclable catalyst and solvent.

Some important aspects of these methodologies are the high reactivity in the preparation of the different selenoesters compounds, with short reaction times, mild reaction conditions, and excellent yields and, most important recyclability of solvent.

The published article that reports the work discussed in the current chapter can be found in Appendix 2.

CHAPTER 4

AN EFFICIENT ONE-POT SYNTHESIS OF SYMMETRICAL DISELENIDES OR DITELLURIDES FROM HALIDES WITH CuO NANOPOWDER/Se^0 OR Te^0/BASE



Org. Lett. **2010**, 12, 3288-3291

4.1 Introduction and previous methods to synthesize dichalcogenides (diselenides and ditellurides)

In this chapter we discuss the synthesis of diselenides and ditellurides. It is known from the past references that dichalocoganide compounds are very important tools in organic chemistry, medicinal chemistry, and bio-chemistry. Related derivatives in which one selenium or tellurium atom is replaced by oxygen or sulfur are also known and play crucial biological roles as antioxidants, antitumor agents, and apoptosis inducers, as well as in the degradation of hydro peroxides and in the chemoprevention of cancer in a variety of organs.[70]

A variety of methods to prepare organic diselenides or ditellurides have been reported. Most of them involve the reaction of metal diselenides or ditellurides with alkyl halides, dimerization with selenocyanates,[71] oxidation of selenols or selenolates, [72, 73] and reactions of aldehydes with sodium hydrogen selenides in the presence of an amine and sodium borohydride.[74]

Synthetic routes to symmetrical dialkyl selenides and diselenides are listed in Scheme 13, showing that Se^{2-} and Se_2^{2-} can be readily prepared by alkali metal-ammonia reduction of Se metal. The reduced species of selenium underwent the reaction with alkyl or aryl halides.[75] In the early 1970's, another method was reported with sodium formaldehyde sulfoxylate or "rongalite" to reduce the selenium metal and to react it with halides, but, in these methods, aqueous solvent systems are required (Scheme 13).[76]

The $NaBH_4$ reduction of Se^0 recently described by Klayman and Griffin is related to our procedure, having many attributes in common. However, water or ethanol were required as solvents, and due to their reactivity only one hydride per

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[70] (a) Stadtman, T. C. *Annu. Rev. Biochem.* **1980**, *49*, 93; (b) Geiger, P. G.; Lin, F.; Girotti, A. W. *Free Radical Biol. Med.* **1993**, *14*, 251; (c) Krief, A.; Janssen, *Chim. Acta* **1993**, *11*, 10; (d) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T *Chem. Rev.* **2004**, *104*, 6255.

[71] (a) Gladysz, J.; Hornby, J.; Garbe, J. E. *J. Org. Chem.* **1978**, *43*, 1204; (b) Syper, L.; Mlochowshi, J. *Tetrahedron* **1988**, *44*, 6119; (c) Li, J. Q.; Bao, W. L.; Lue, P.; Zhou, X. J *Synth. Commun.* **1991**, *21*, 799; (d) Wang, J. X.; Cui, W.; Hu, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2341; (e) Krief, A.; Derock, M. *Tetrahedron Lett.* **2003**, *43*, 3083; (f) Krief, A.; Dumont, W.; Delmotte, C. *Angew. Chem., Int. Ed.* **2000**, *9*, 1669; (g) Salama, P.; Bernard, C. *Tetrahedron Lett.* **1995**, *36*, 5711; (h) Salama, P.; Bernard, C. *Tetrahedron Lett.* **1998**, *39*, 745.

[72] Prabhu, K.; Chandrasekaran, S. *Chem. Commun.* **1997**, 1021.

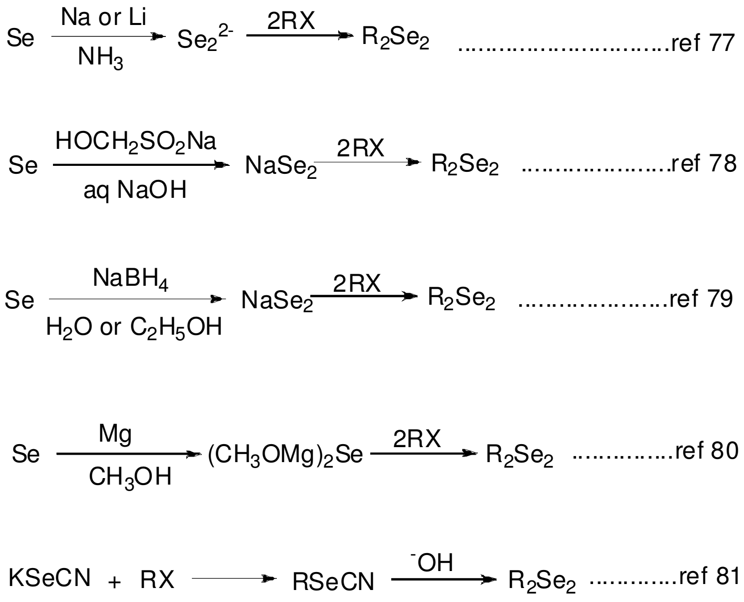
[73] Krief, A.; De Mahieu, A. F.; Dumont, W.; Trabelsi, M. *Synthesis* **1988**, 131.

[74] (a) Krief, A.; Van Wemmel, T.; Redon, M.; Dumont, W.; Delmotte, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2245; (b) Klayman, I. D; Griffin, T. S *J. Am. Chem. Soc.* **1973**, *95*, 197; (c) Lewicki, J. W.; Gu¨nther, W. H. H.; Chu, J. Y. C. *J. Chem. Soc., Chem. Commun.* **1976**, 552; (d) Lewicki, J. W.; Gunther, W. H. H.; Chu, J. Y. C. *J. Org. Chem.* **1978**, *43*, 2672.

[75] (a) Brandsrna, L.; Wijers, H. E. *Red. Trav. Chim. Pays-Bas.* **1963**, *82*, 68; (b) Shlyk, Y. N.; Bogolyubov, G. M.; Petrov, A. A. *Zh. Obshch. Khim.* **1968**, *38*, 1199.

[76] (a) Agenas, L. B. *Acta Chem. Scand.,* **1962,** *16***,** 1809**;** (b) Bergson, G. *Ark. Kemi.* **1962,** *19***,** 195**;** (c) Fredga, A. *Acta Chem. Scand.,* **1963,** *17***,** 51**;** (d) Agenas, L.B. *Ark Kemi,* **1964,** *23***,** 145**;** (e) Rebane, E. *ibid.* **1966,** *25***,** 363**.**

BH_4^- could be utilized. In water, Na_2Se_2 was not prepared directly but via addition of further to NaHSe. In ethanol, Na_2Se_2 formation was accompanied by an equivalent amount of H_2Se. Only benzyl selenides and diselenides were prepared by this procedure (Scheme 13).[77] In 1967, Gunther reported the synthesis of diselenides by the bis(methoxymagnesium) diselenide reagent. This reagent was prepared by treating magnesium with dry methanol in the presence of iodine and this reagent further reacted with halides to get diselenides.[78] Still another method shows the preparation of diselenides by using potassium selenocynate (Scheme 13).[79]



$$Se \xrightarrow[NH_3]{\text{Na or Li}} Se_2^{2-} \xrightarrow{2RX} R_2Se_2 \quad \text{..............................ref 77}$$

$$Se \xrightarrow[\text{aq NaOH}]{HOCH_2SO_2Na} NaSe_2 \xrightarrow{2RX} R_2Se_2 \quad \text{.....................ref 78}$$

$$Se \xrightarrow[H_2O \text{ or } C_2H_5OH]{NaBH_4} NaSe_2 \xrightarrow{2RX} R_2Se_2 \quad \text{.....................ref 79}$$

$$Se \xrightarrow[CH_3OH]{Mg} (CH_3OMg)_2Se \xrightarrow{2RX} R_2Se_2 \quad \text{...............ref 80}$$

$$KSeCN + RX \longrightarrow RSeCN \xrightarrow{^-OH} R_2Se_2 \quad \text{............ref 81}$$

Scheme 13. Various ways to prepare diselenides

Klayman and Griffin reported the selenium with sodium borohydride and introduced selenium in organic molecules. They explain that elemental powdered selenium and sodium borohydride react very readily in water or ethanol to give either sodium hydrogen selenide or sodium diselenide, depending on the ratio of the reactants. The sodium hydrogen selenide and sodium diselenide solutions, thus prepared, can be utilized directly in typical nucleophilic displacement reactions (Scheme 14).[74b]

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[77] Klayman, D. L.; Griffin, T. **S.** *J. Am. Chem. Soc.* **1973,** *95*, 197**.**

[78] Gunther, W. H. H. *J.* Org. *Chem.* **1967,** *32***,** 3929.

[79] Rheinboldt, H. *Method in Org. Chem. (Houben-Weyo, 4th Ed.).* **1955***,* *9*, *1952.*

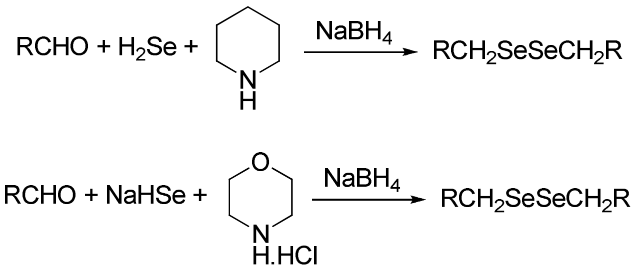
$$4NaBH_4 + 2Se + 7H_2O \longrightarrow 2NaHSe + NaB_4O_7 + 14H_2$$

$$Na_2B_4O_7 + 2NaHSe + 2Se + 5H_2O \longrightarrow 2Na_2Se_2 + 4H_3BO_3$$

$$2NaBH_4 + 3Se + 6C_2H_5OH \longrightarrow Na_2Se_2 + H_2Se + 2B(OCH_3)_3 + 6H_2$$

Scheme 14. Synthesis of Na_2Se_2 from sodium borohydride

Furthermore, another method was used to prepare diselenides starting from aldehydes by Chu and co-workers.[74d] The reaction of H_2Se with aromatic and aliphatic aldehydes in the presence of amines and $NaBH_4$ yielded benzylic and aliphatic diselenides. A variant of this synthesis avoids the handling of toxic H_2Se and involves the reaction of NaHSe with amine hydrochloride and aldehyde, followed by a $NaBH_4$ reduction (Scheme 15).



Scheme 15. Synthesis of diselenide from aldehydes

Nevertheless, the most common method to prepare diselenides, which is widely used worldwide, by our lab inclusive, employs the Grignard reagent. For example, selenolate species were generated by employing the Grignard reagent and further oxidized to diselenides (Scheme 16).[80]

$$PhBr + Mg \longrightarrow PhMgBr \xrightarrow{Se} PhSeMgBr$$

$$PhSeMgBr \xrightarrow{[O]} PhSeSePh$$

Scheme 16. Synthesis of diselenides from Grignard reagent

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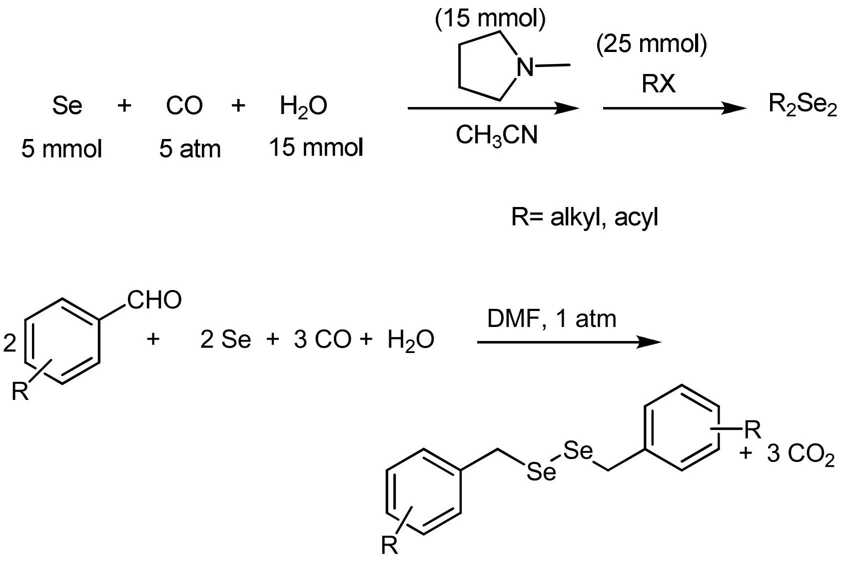
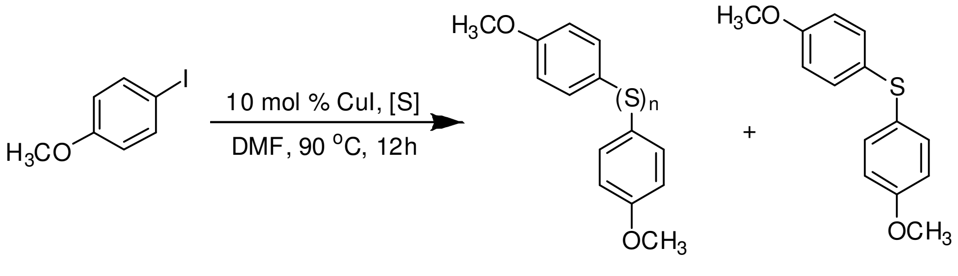
[80] Reich, H. J.; Cohen, M. L.; Clark, P. S. "Reagents for Synthesis of Organoselenium Compounds: Diphenyl Diselenide and Benzeneselenenyl Chloride", Org. Synth. 59: **1979**, *6*, 533.

Sonoda et al. discovered that elemental selenium can be readily reduced by carbon monoxide and water in the presence of base to produce hydrogen selenide, which was successfully applied to the synthesis of aliphatic diselenides from both aliphatic ketones and aldehydes[81] or from alkyl chlorides and acyl chlorides,[82] respectively (Scheme 17).



Scheme 17. Synthesis of diselenides from carbon monoxide

Recently Jiang, Ma and co-workers reported the synthesis of sulfides and disulfide by using sulphur metal and CuI as a catalyst in the presence of DMSO and Base (Scheme 18).[83]



Scheme 18. Synthesis of diselenides with sulphur and CuI

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[81] Huang, Z, Z.; Liu, F. Y.; Du, J. X.; Huang, X. *Org. Prep. Proced. Int.* **1995**, *27*, 492.

[82] Nishiyama, Y.; Hamanaka, S.; Ogawa, A.; Murai, S.; Sonoda, N. *Synth. Commun.* **1986**, *16*, 1059; (b) Miyoshi, N.; Yamana, Y.; Ogawa, A.; Sonoda, N. *J. Org. Chem.* **1991**, *56*, 3776.

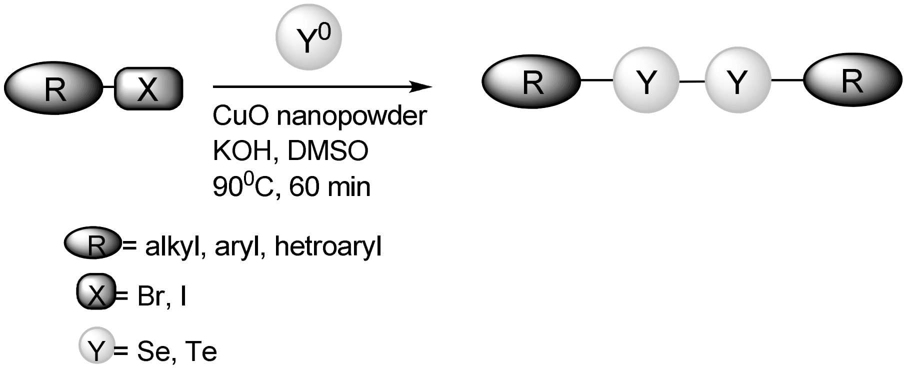
[83] Jiang,Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett.* **2009**, *11*, 5250.

Based on these authors and on our previously reported (Chapters 2 and 3) positive results in the field of the synthesis of organochalcogen compounds by using CuO nanoparticles in ionic liquids, we decided to synthesize diselenides and ditellurides with CuO nanoparticles.

After various efforts, the reaction did not work in ionic liquids. We then learned about another method that describes the reduction of the selenium metal by using the KOH-DMSO system. According to this protocol, the KOH-DMSO system forms a reductive species which is able to reduce selenium and tellurium metals.[84] After all these observations and studies, selenium and tellurium were reduced by the KOH-DMSO system and CuO nanoparticles were used as a catalyst to synthesize symmetrical diselenides and ditellurides from halides.

4.2 Synthesis of diselenides and ditellurides

In the current chapter, we describe a new method to synthesize diselenide and ditelluride derivatives in which a coupling reaction of aryl, alkyl, and heteroaryl iodides with elemental selenium and tellurium takes place in the presence CuO nanopowder and KOH at 90 °C in DMSO (Scheme 19). A wide range of substituted symmetrical diselenides and ditellurides were obtained in good to excellent yields.



Scheme 19. General synthesis for diselenides and ditellurides

4.3 Optimization of different variables

In order to optimize the protocol and to understand the influence of different variables in this reaction, several components were studied. To this end, we carried

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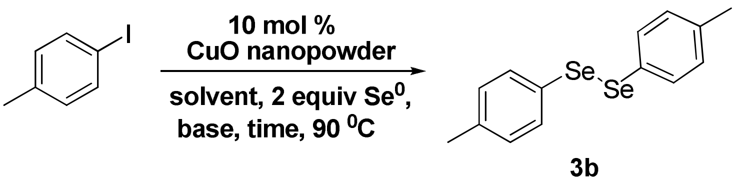
[84] Trofimov, B. A.; Amosova, S. V.; Gusarova, N. K.; Musorin, G. K. *Tetrahedron.* **1982**, *38*, 713.

out the reaction employing 4-iodotoluene (1 mmol, 0.217 g) as a representative halide, 10 mol % of CuO nanopowder, elemental selenium (2.0 equiv), and KOH (2.0 equiv) in DMSO (2.0 ml) for 1 h, affording the corresponding diaryl selenide **3b** in 96% yield (Table 14, entry 1). In a first set of experiments, we studied the influence of different solvents (Table 12, entries 1-7). By analyzing Table 12, it can be observed that the desired product was not obtained in the solvents THF, 1, 4-dioxane, and toluene (entries 4-6). However, the reaction was highly effective in polar aprotic solvents (entries 1-3). These results suggest that the success of the reaction depends on the polarity of the solvent. In this regard, DMSO was the most efficient solvent for this conversion affording the best yield for diselenide **3b** (entry 1).

Table 12. Nano CuO oxide-catalyzed cross-coupling of diphenyl diselenide with 4-methyl 1-Iodobenzene



3b

entry	solvent	base (2 eq)	time (min)	yield[a] (%)
1	DMSO	KOH	60	96
2	DMF	KOH	60	90
3	CH_3CN	KOH	60	91
4	THF	KOH	60	-
5	Toluene	KOH	60	-
6	Dioxane	KOH	60	-
7	CH_2Cl_2	KOH	60	-
8	DMSO	Cs_2CO_3	60	85
9	DMSO	NaOH	60	86
10	DMSO	$NaHCO_3$	60	-
11	DMSO	K_2CO_3	60	36
12	DMSO	KOH	30	64
13	DMSO	KOH	120	81
14	DMSO	KOH	240	45
15	DMSO	KOH	60	traces[b]
16[c]	DMSO	-	60	-

[a] Yields determined by GC. [b] Reaction performed at room temperature.
[c] No coupling reaction occurred without base.

The influence of different bases was the next variable studied. In this context, a number of bases, in DMSO, were used to afford reactive species like Cs_2CO_3, NaOH, $NaHCO_3$, K_2CO_3, and KOH (Table 12, entries 8, 9, 10, and 11 respectively). Notably, KOH allowed the best performance among the screened bases, furnishing the desired product in an excellent yield (Table 12, entry 1). As a result, KOH was selected as the optimum base to perform the subsequent reactions. Another important factor studied was the reaction time. This variable had an effective influence on the reaction course, with yields decreasing from 96 to 64% when the reaction time was reduced from 60 to 30 min (entries 1 and 12). Longer reaction times also had an influence on the product yields. When the reaction time was increased to 120 and 240 min, the product yields decreased to 81% and 45%, respectively (entries 13 and 14). We observed that with longer reaction time selenides was obtained as a side product instead of diselenides. We believe that KOH breaks the diselenides and generates selenolate in the reaction mixture, which further reacts with halides to give selenides.

Finally, in order to optimize the protocol, the impact of the amount of catalyst on the reaction efficiency was investigated. We found that this parameter had an effective influence on the reaction course. For instance, when the amount of CuO nanopowder was increased from 2.0 to 10 mol%, the yield of compound **3b** raised considerably (from 70% to 96%; Table 13, entries 1-3). Raising the amount of CuO nanopowder up to 20 mol% did not show a significant influence, affording the desired product at the same level of 96% (Table 13, entry 4). The product was not observed in the absence of catalyst; hence this component is mandatory in order to perform the reaction (entry 5).

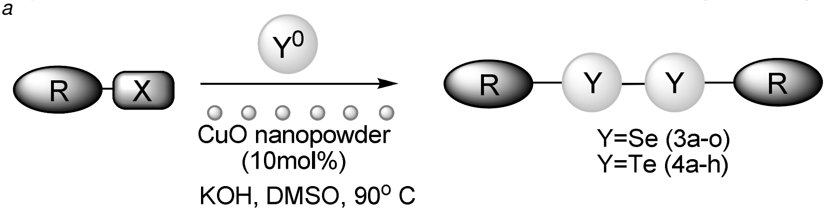
Table 13. Optimization of Nano CuO catalyst[a]

Entry	CuO nano (mol %)	Yield[b](%)
1	2.0	70
2	5.0	89
3	10.0	96
4	20.0	96
5	0.0[c]	-

[a] Reaction condition: 4-iodo toluene (1.0 mmol), CuO nanopowder, Se^0 (2.0 equiv), KOH (2.0 equiv) and DMSO (2.0 ml) were stirred under a nitrogen atmosphere, at 90 °C for 60 min. [b] Yields determined by GC. [c] No coupling reaction occurred without CuO nano.

After the optimized reaction conditions were established, a number of halides were examined to explore the scope and limitations of this methodology. Under standard conditions, a series of reactions using different kinds of aryl, alkyl, and hetroaryl halides was performed to synthesize the symmetrical diselenides 3a-o and ditellurides 4a-h (Table 14).

Table 14. Synthesis of diselenides and ditellurides via a one-pot coupling reduction procedure[a]



entry	R	X	Y	product	yield[c] (%)
1	Ph	I	Se	**3a**	96
		Br	Se	**3a**	52
2	4-MeC$_6$H$_4$	I	Se	**3b**	96
		Br	Se	**3b**	71
3	2-MeC$_6$H$_4$	I	Se	**3c**	90
4	4-ClC$_6$H$_4$	I	Se	**3d**	89[b]
5	2-ClC$_6$H$_4$	I	Se	**3e**	90[b]
6	2-HOC$_6$H$_4$	I	Se	**3f**	72
7	4-BrC$_6$H$_4$	I	Se	**3g**	89[b]
8	4-MeOC$_6$H$_4$	I	Se	**3h**	80
		Br	Se	**3h**	69
9	3-MeOC$_6$H$_4$	I	Se	**3i**	89
10	2-MeOC$_6$H$_4$	I	Se	**3j**	89
11	2,4-MeOC$_6$H$_3$	I	Se	**3k**	50
12	2-H$_2$NC$_6$H$_4$	I	Se	**3l**	87
13	3-Py	I	Se	**3m**	82
14	4-OHCC$_6$H$_4$	Br	Se	**3n**	72
15	C$_7$H$_{15}$	I	Se	**3o**	96
16	Ph	I	Te	**4a**	86
17	Ph	Br	Te	**4a**	56
18	2-MeC$_6$H$_4$	Br	Te	**4b**	88
19	3-Py	I	Te	**4c**	72
20	4-ClC$_6$H$_4$	I	Te	**4d**	90[b]
21	2-HOC$_6$H$_4$	I	Te	**4e**	86
22	2-H$_2$NC$_6$H$_4$	I	Te	**4f**	82
23	4-MeOC$_6$H$_4$	I	Te	**4g**	80
24	C$_7$H$_{15}$	I	Te	**4h**	84

[a] Reaction condition: halide (1.0 mmol), CuO nanoparticles (10.0 mol %), Y^0 (2.0 equiv), KOH (2.0 equiv) and DMSO (2.0 mL) were stirred under a nitrogen atmosphere, at 90 ℃ for 60 min. [b] Reaction complete in 30 min. [c] Yield of the isolated product.

As summarized in Table 14, both electron-rich and electron deficient aryl iodides were effective in this process, giving the corresponding products in good to excellent yields. It is noteworthy that sterically hindered ortho and meta substrates also provided high yields of diselenides (Table 14, entries 3, 5, 6, and 9-12) and ditellurides (Table 14, entries 18, 20, and 22), respectively. One advancement associated with this methodology is that a wide range of functional groups are tolerated in this process, including methyl, methoxy, hydroxyl, aldehyde, amino, bromo, and heteroaryl moieties. Some of them are very sensitive, e.g., aldehyde, and the direct preparation of the related diselenides employing the described methodologies is not efficient for these kinds of substrates. Thus, we conclude that this method provides a general approach to prepare more complex diselenides and ditellurides.

Upon analysis of Table 14, it can be verified that iodide was more reactive than bromides and chlorides, matching our expectations. This result allowed the exploration of the regioselectivity of this reaction, with the preparation of selective bromo and chloro dichalcogenides (Table 14, entries 4, 5, 7, and 20). Additionally, the electron-withdrawing groups attached to the aromatic ring afforded better yields than donating groups (Table 14, entries 4 and 8). This can be explained by the easier insertion of copper into the more electron-deficient aromatic ring. In order to explore the versatility of the current methodology, more complex aromatic halides were employed. As depicted in Table 14, amino (entries 12, 13, 19, and 22), hydroxy (entries 6 and 21), and aldehyde (entry 14) moities were used, and in all cases the corresponding diselenide and ditelluride were obtained in good yields. Alkyl diselenide (entry 15) and ditelluride (entry 24) were obtained from the respective alkyl iodide, yielding 96 and 84%, respectively. Furthermore, diselenides were obtained in high yield, without the use of protection groups or an excess of reagents.

On the basis of previous reports, a plausible mechanism for the CuO nanopowder-catalyzed cross-coupling of halides with selenium and tellurium nucleophiles to obtain diselenides and ditellurides can be proposed, as depicted in section 4.4, Figure 21.

4.4 Proposed mechanism for CuO nanoparticle catalyzed reactions

On the basis of previous reports,[85] a plausible mechanism for the CuO nanopowder catalyzed cross-coupling of halides with selenium and tellurium nucleophiles to obtain diselenides and ditellurides can be proposed, as depicted in Figure 21.

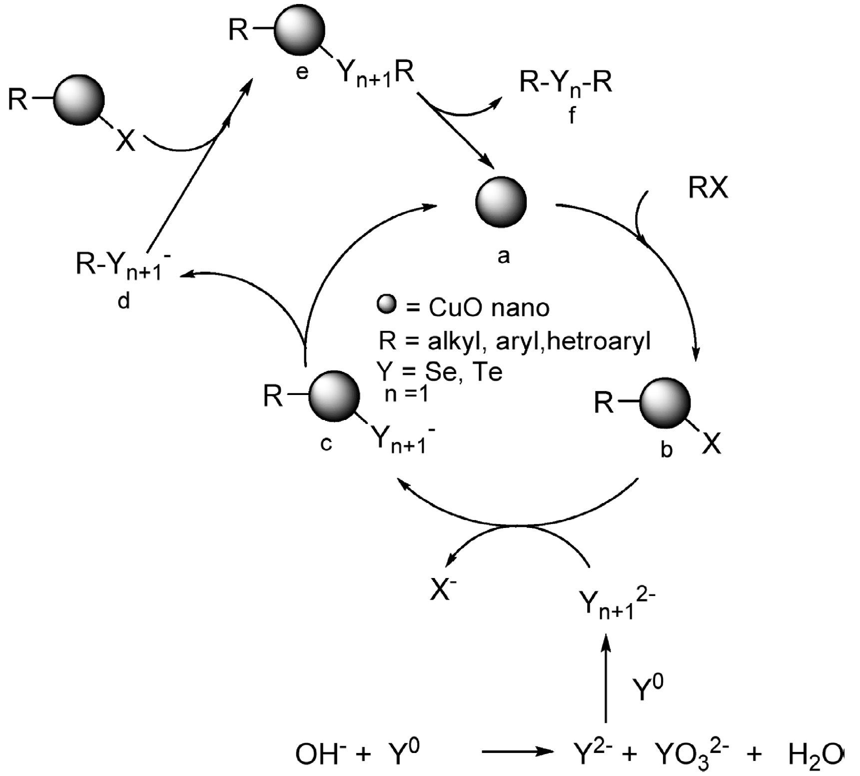


Figure 21. Plausible reaction pathway

Selenium and tellurium may have similar behavior to that established for sulfur in the presence of base, giving the chalcogenolate or dichalcogenolate anion. Using a superbasic DMSO-KOH system, a reductive species is formed,[86] which may selectively allow the preparation of the desired dichalcogenolate anion. We assume that this ion might serve as the active species in the catalytic cycle. The formation of the complexes **a** and **b** followed by the ligand exchange with the dichalogenolate anion might provide complex **c**, which could undergo reductive elimination to give the

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[85] Jiang, Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org.Lett.* **2009**, *11*, 951.

[86] (a) Reddy, V. P.; Kumar, A. V.; Swapna, K.; Rao, K. R *Org. Lett.* **2009**, *11*, 951. (b) Trofimov, B. A.; Amosova, S. V.; Gusarova, N. K.; Musorin, G. K. *Tetrahedron* **1982**, *38*, 713.

initial coupling product **d** and regenerate the CuO nanoparticles. The complex **d** would react with another complex **b** furnishing the complex **e**. Finally, a reductive elimination could afford the desired dichalcogenide **f** and release CuO nanoparticles for use in the catalytic cycle.

All these compounds are characterized by ^{1}H, ^{77}Se, and ^{13}C NMRs, and mass spectroscopy. Experimental details and further information on their characterization are given in Chapter 7 and the spectra are presented in Chapter 8.

The ^{1}H NMR spectrum the compound **2-di*p*-tolyl diselenide** shows doublet at 7.47 ppm for 4H (H_a) (J = 8.0 Hz) and another doublet for 2H (H_b) of the phenyl group at 7.07 ppm (J= 8.4 Hz). The aliphatic hydrogens of the methyl group appear at 2.30 ppm as a singlet (Figure 22). In the ^{13}C NMR four different signals can be identified in the aromatic region of 140-125 ppm. The methylene carbon appears at 22.80 ppm (Figure 23). The Se^{77} NMR shows a single peak of selenium at 409.6 ppm (Figure 24).

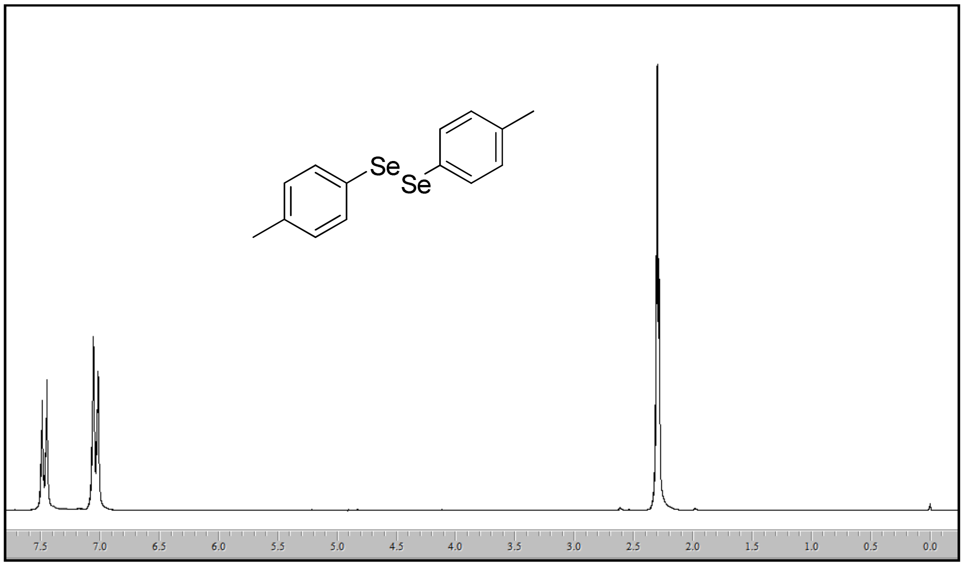


Figure 22. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-di *p*-tolyldiselane(3b)**

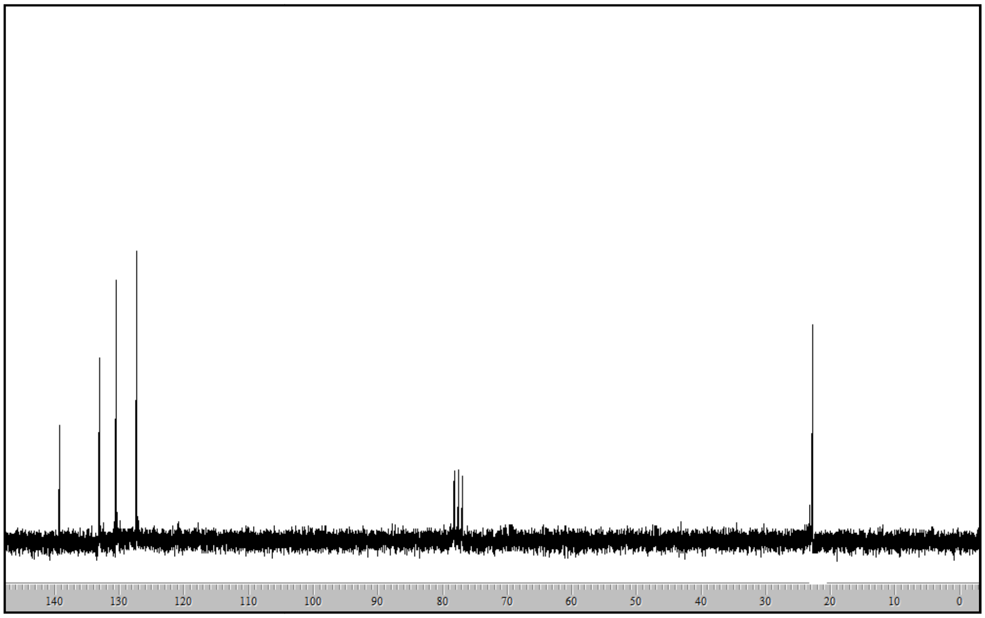


Figure 23. ^{13}C NMR (50 MHz, $CDCl_3$) spectrum of **1,2-di *p*-tolyldiselane (3b)**

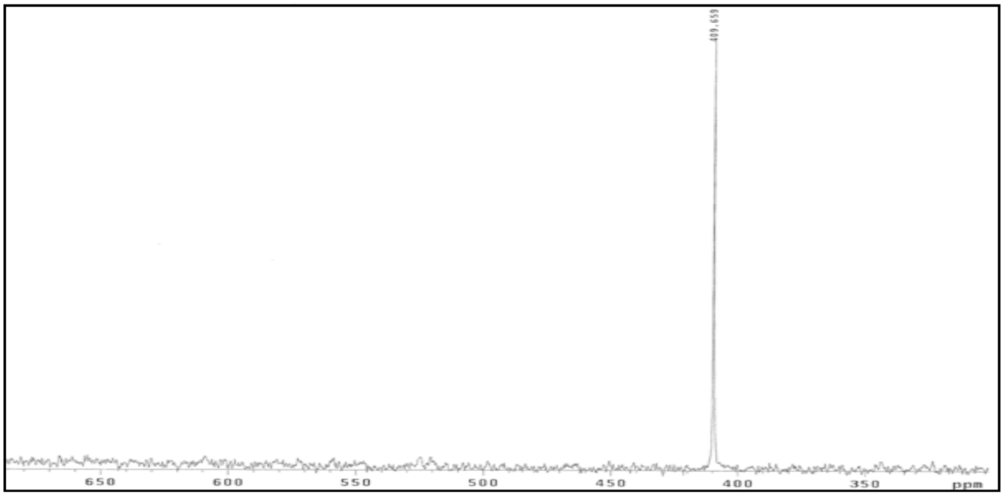


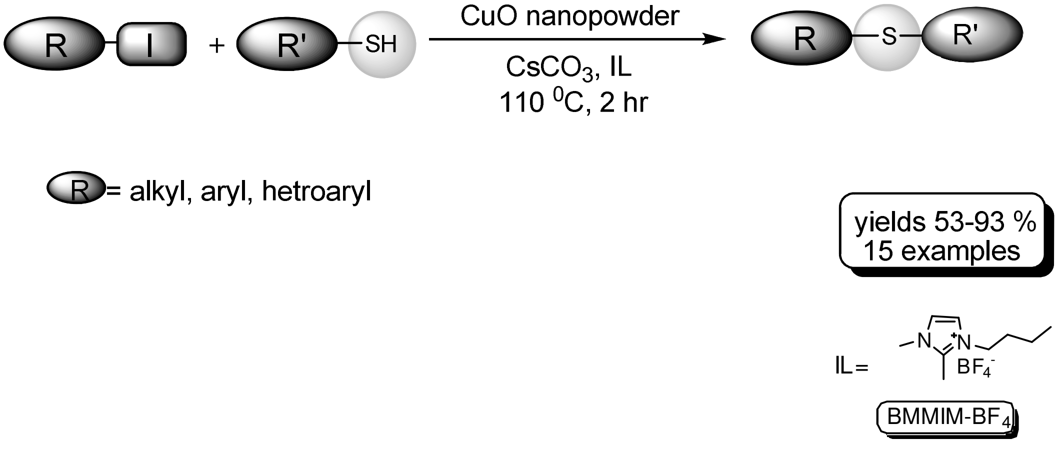
Figure 24. ^{77}Se NMR (78.26 MHz, $CDCl_3$) spectrum of **1,2-di *p*-tolyldiselane (3b)**

In conclusion, in the present chapter a simple, efficient, and straightforward procedure is described for the preparation of diselenides or ditellurides through cross-coupling of selenium and tellurium and aryl iodides using CuO nanopowder. This methodology is highly chemoselective, and allows the preparation of a wide range of substituted symmetrical diselenides and ditellurides containing methoxy, hydroxyl, carboxylate, amino, aldehyde, and bromo groups in good to excellent yields.

The published article that reports the work discussed in the current chapter can be found in Appendix 3.

CHAPTER 5

C-S CROSS-COUPLING OF THIOLS WITH ARYL HALIDES UNDER LIGAND-FREE CONDITIONS USING NANO CuO AS A RECYCLABLE CATALYST IN IONIC LIQUID



5.1 Introduction and previous methods to synthesize sulfides

The formation of C-N, C-O, and C-S by transition-metal-catalyzed cross-coupling reactions of aryl halides with nitrogen, oxygen, and sulfur nucleophiles is a powerful tool in organic synthesis.[87] For the past decade aryl sulfides have been important intermediates in several organic transformations and these classes of compounds and their derivatives have been found in numerous biological and pharmaceutically active compounds.[88] Additionally, an integral part of numerous drugs in therapeutic areas such as diabetes, inflammation, Alzheimer's and Parkinson's disease,[89] cancer, [90] and HIV[91] contain aryl sulfide as the functional group. Among the various cross-coupling reactions, the S-arylation is comparatively less studied.[92] There are some factors which hinder this process: first, S-S oxidative coupling reactions are more favorable, which result in the undesired formation of disulfides, and second, organic sulfur compounds can be effective metal binders, which leads to catalyst modification or deactivation.[93] Various methods to synthesize the organo-sulphur compound with ligand and without ligand are reported in the literature.

Most of the methods to prepare aryl or alky sulfide are the same as the ones discussed in Chapter 2. Sulfides can also be synthesized by the use of a number of metals and different forms of metals as a catalyst with some ligands, as with lanthanum metal with catalytic amount of iodine,[27] with indium iodide,[28] with

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[87] (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131; (b) Metal-Catalyzed Cross-Coupling Reactions (Eds.: Diederich, F.; Meijere, A.), Wiley-VCH, Weinheim, **2004**; (c) J. F. Hartwig, Synlett 2006, 1283.

[88] (a) Liu, L.; Stelmach, J. E.; Natarajan, S. R.; Chen, M.-H.; Singh, S. B.; Schwartz, C. D.; Fitzgerald, C. E.; O'Keefe, S. J.; Zaller, D. M.; Schmatz, D. M.; Doherty, J. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3979. (b) Kaldor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M.A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979.

[89] (a) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, F.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202. (b) Nielsen, S. F.; Nielsen, E. Ø.; Olsen, G. M.; Liljefors, T.; Peters, D. *J. Med. Chem.* **2000**, *43*, 2217.

[90] De Martino, G.; Edler, M. C.; La Regina, G.; Cosuccia, A.; Barbera, M. C.; Barrow, D.; Nicholson, R. I.; Chiosis, G.; Brancale, A.; Hamel, E.; Artico, M.; Silvestri, R. *J. Med. Chem.* **2006**, *49*, 947.

[91] Kadlor, S. W.; Kalish, V. J.; Davies, J. F.; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.***1997**, *40*, 3979.

[92] For some S-arylations of thiols, see: (a) Palomo, C.; Oiarbide, M.; Pez, R. L.; Mez-Bengoa, E. G. *Tetrahedron Lett.* **2000**, *41*, 1283; (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517; (c) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, 4, 2803; (d) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180; (e) Fernandez-Rodriguez, M. A.; Shen, Q.; Hartwig, J. F. *Chem. Eur. J.* **2006**, *12*, 7782; (f) Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199; (g) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Chem. Eur. J.* **2007**, *13*, 5100; (h) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495; (i) Rout, L.; Sen, T.; Punniyamurthy, T. *Angew. Chem.* **2007**, *119*, 5679; *Angew. Chem. Int. Ed.* **2007**, *46*, 5583; (j) Ranu, B. C.; Saha, A.; Jana, R. *Adv. Synth. Catal.* **2007**, *349*, 2690.

[93] For a review dealing with the metal-catalyzed formation of carbon–sulfur bonds, see: Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.

ruthenium complex,[31] nickel complex with borohydride,[32] with yetribium,[36] with copper,[40, 41] and more, as describe in Chapter 2.

In last decade, several methods to synthesize sulfides using various metals with different ligands have been reported (Figure 25). SanMartin and Dominguez reported the synthesis of sulfides, [92g] and explain that reactions were catalysed by a combination of a copper salt and a 1, 2-diamine derivative (acting both as the ligand and as the base), using exclusively water as solvent. Other forms of copper were also used, such as $Cu(OAc)_2$ and $Cu(OTf)_2$. Venkataraman and co-workers reported the reaction of aryl iodides and thiols using 10 mol% CuI and 10 mol% neocuproine, with NaO*t*-Bu as the base, in toluene at 110℃. Using this protocol, they showed that a variety of aryl sulfides can be synthesized in excellent yields from readily available iodides and thiols.[92c]

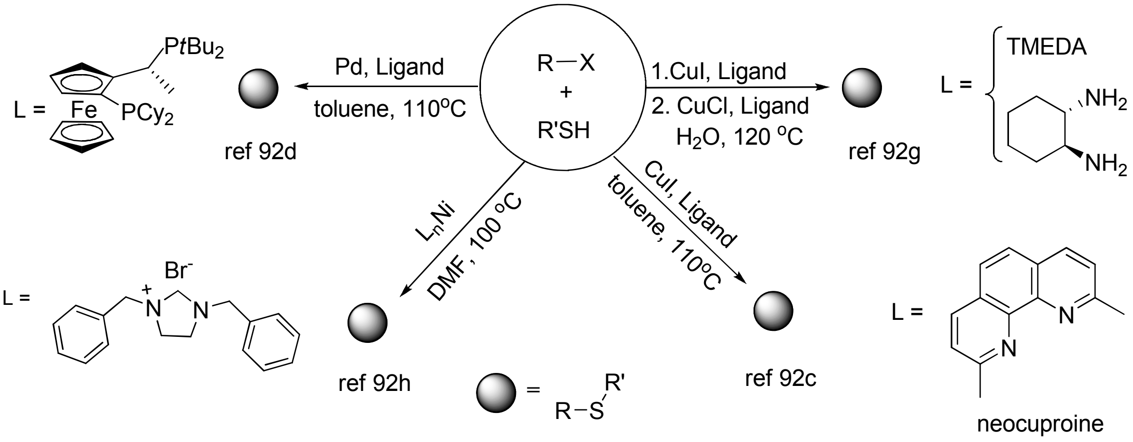


Figure 25. Different methods to prepare sulfides using ligands

In 2007, Ying and co-workers developed the first N-heterocyclic carbene (NHC)-based transition metal catalysts for C-S coupling reactions. They binded nickel with N-heterocyclic carbene (NHC) to form catalysts to perform these reactions and these catalysts showed good to excellent activities toward various aryl halides in C-S coupling reactions.[92h] In another study, Hartwig and co-workers (2006) reported the synthesis of sulfides with $Pd(OAc)_2$ with Josiphos ligand, CyPF-t-Bu in DME or toluene. They explained that palladium thiolates form easily and undergo relatively fast reductive eliminations with aryl groups to get corresponding sulfides.[92d]

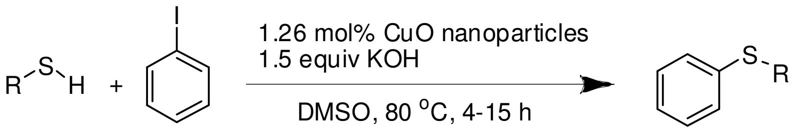
Very recently, different forms of copper metal and its nanoparticles have been used to synthesize alkyl or aryl sulfides. Sreedhar and co-workers report the cross-coupling reactions of various N/O nucleophilic reagents with aryl chlorides by using CuI nanoparticles as a catalyst and this reaction could be successfully carried out under mild conditions in the absence of both the ligands and strong bases. The authors used N/O nucleophic reagents like imidazoles, pyrazoles, Benzimidazole, alkyl amines, and phenols (scheme 20).[94] They also used CuI with the comparison of CuI nanoparticles with different bases and solvents, but the performance of CuI nanoparticles was better. CuI nanoparticles also resulted in a better reaction when compared to CuO nanoparticles.

Moreover, Punniyamurthy and co-workers reported the synthesis of sulfides by using CuO nanoparticles with thiols and aryl iodides. According to their observations, the C-S cross-coupling works better with CuO nanoparticles. And in both cases CuI and CuO can be recovered from the reaction mixture and used again for the further reactions until five runs without losing effectiveness (Scheme 21).[92i]

$$\mathrm{ArCl} + \mathrm{NuH} \xrightarrow[\mathrm{K_2CO_3,\ DMF,\ 110\ ^{o}C,\ 2\text{-}5\ h}]{\mathrm{CuI\ nanoparticles\ 1.25\ mol\%}} \mathrm{ArNu}$$

NuH : Imidazole, Pyrazole, Benzimidazole
Alkyl amines, Phenols

Scheme 20. Cross- coupling reaction of N/O nucleophilic reagent with aryl chloride using CuI nanoparticles



Scheme 21. Synthesis of sulfides using CuO nanoparticles

In another method, Ranu and co-workers reported the coupling reaction of thiols and aryl halides to get aryl- sulphur bond catalyzed by Cu metal nanoparticles without ligands using micro wave irradiation (scheme 22).[92j]

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[94] B. Sreedhar, R. Arundhathi, P. Linga Reddy, and M. Lakshmi Kantam *J. Org. Chem.* **2009**, *74*, 7951.

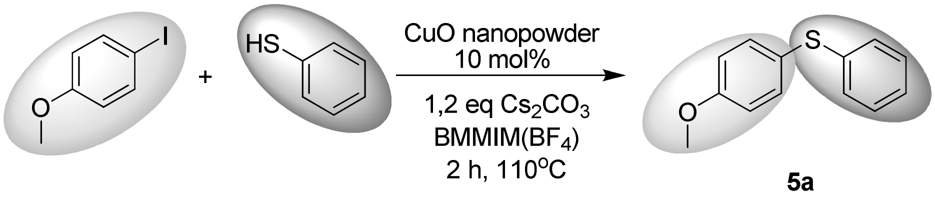
$$\mathrm{ArI} + \mathrm{RSH} \xrightarrow[\substack{K_2CO_3,\ DMF,\\ MW\ (110\ ^oC),\ 5\text{-}7\ min}]{\substack{Cu\ nanoparticles\\ 20\ mol\%}} \mathrm{ArSR}$$

Scheme 22. Synthesis of sulfides using Cu nanoparticles in micro-wave irradiation

In light of the previous reports to synthesize sulfides and based the results of our research presented in chapters 2, 3, and 4, we tryed to develop an efficient and eco-friendly methodology to syhtesiese aryl, and alkyl sulfides using CuO nanoparticles in ionic liquid, as described in the following section.

5.2 Synthesis of sulfides

Herein we report the combination of nanotechnology and ionic liquids to perform C-S cross-coupling with CuO nanopowder as a catalyst in BMMIM-BF_4 in excellent yields. This efficient and ligand-free methodology has the advantages of high atom efficiency, simplified isolation of the product, and easy recovery and recyclability of the catalysts and solvent. In order to optimize the protocol and to understand the influence of different variables on this reaction, several components were studied to increase its efficiency. To this aim, we carried out the reaction employing 4-methoxy iodobenzene and benzenethiol as a model reaction (Scheme 23). In the first set of experiments, we used 10 mol% of CuO nanopowder and 2.0 equiv. of Cs_2CO_3 at 110°C for 2 hours, and four different ionic liquids were evaluated (Table 15). In all of these experiments the desired product was obtained, with yields ranging from 76 to 99%. BMMIM-BF_4 was the best solvent for this reaction (entry 4).



Scheme 23. General synthesis of sulfide from thiols

Table 15. Different ionic liquid used in the reaction

Entry	Ionic liquid	Product Yield[a] (%)
1	BMIM-BF_4	89
2	BMIM-NTf_2	85
3	BMIM-PF_6	76
4	BMMIM-BF_4	99

[a] Yields for isolated pure products.

In order to optimize the protocol, we performed another set of experiments to evaluate the influence of diverse bases and the reaction time (Table 16). In this context, a variety of inorganic bases (entries 1-4, Table 16) and organic bases (entries 5 and 6) were used to afford aryl sulfides. Among several bases that were screened, Cs_2CO_3 showed the best performance, furnishing the desired product in quantitative yield (entry 1). Noteworthy is that in the absence of a base no formation of product was observed (entry 7). As a result, Cs_2CO_3 was selected as the optimum base. It was also verified that decreasing the amount of Cs_2CO_3 up to 1.2 equiv. had no impact in the formation of the product (entries 1 and 8-10).

Table 16. Optimization of base, time, and temperature

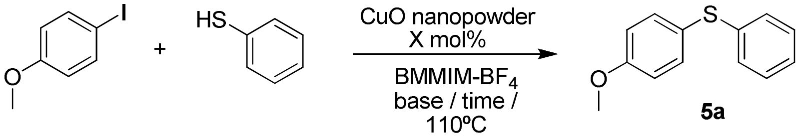
Entry	Base	(equiv.)	Time (h)	Yield[a] (%)
1	Cs_2CO_3	2.0	2	99
2	K_2CO_3	2.0	2	27
3	Na_2CO_3	2.0	2	43
4	KOH	2.0	2	84
5	Et_3N	2.0	2	63
6	Pyridine	2.0	2	42
7	none	-	2	0
8	Cs_2CO_3	1.0	2	86
9	Cs_2CO_3	1.2	2	99
10	Cs_2CO_3	1.5	2	99
11	Cs_2CO_3	1.2	1	81
12	Cs_2CO_3	1.2	0.5	67
13	Cs_2CO_3	1.2	24[b]	25

[a] Yields for isolated pure products. [b] Reaction conduced at r.t.

The time required for the completion of the reaction was then evaluated. Decreasing the reaction time from 2 hours to 1 and 0.5 hours afforded the product in 81 and 67% yield, respectively (entries 11 and 12). An experiment at r.t. was also conduced, but the desired product was obtained in only 25% yield, even after 24 hours (entry 13).

The amount of catalyst required to promote the reaction efficiently was also studied and we found that varying the amount of CuO nanopowder has an influence on the product formation. There was a slight increase in the yield from 60 to 70% when the amount of CuO nanopowder was changed from 1.0 to 2.0 mol% (entry 3 and 4). No significant alteration was verified using 5.0 mol% of CuO nanopowder, affording the respective compound in 76% yield (entry 2). Finally, after increasing the amount of CuO nanopowder up to 10 mol%, the highest yield of the desired product was obtained (99%) (entry 1), as can be observed in Table 17.

Table 17. Optimization of Nano CuO catalyst



5a

Entry	CuO nano (mol %)	Yield[a](%)
1	10.0	99
2	5.0	76
3	2.0	70
4	1.0	60

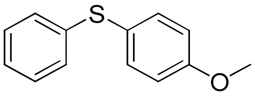
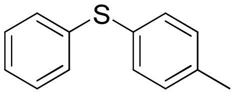
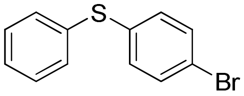
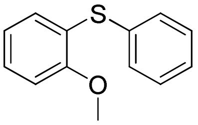
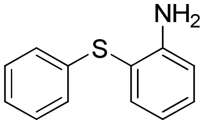
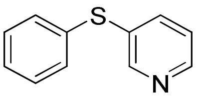
[a] Yields for isolated pure products.

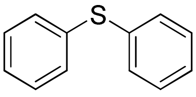
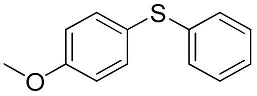
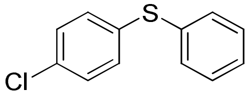
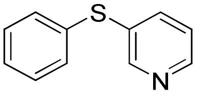
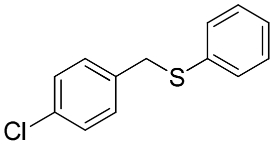
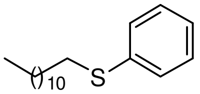
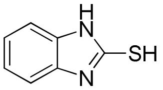
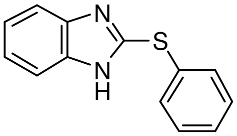
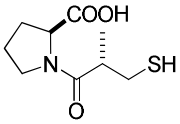
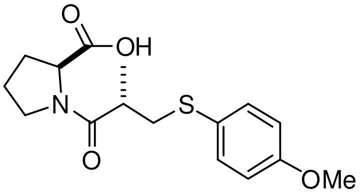
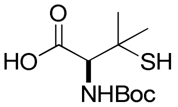
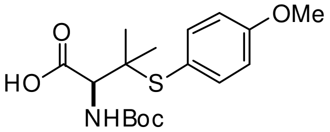
Using the optimized conditions, the present reaction was further expanded to a broader range of aryl thiols and aryl halides in order to evaluate the scope and limitations of the method, as outlined in Table 18. Initially, a set of reactions was performed with benzenethiol and different aryl iodides (entries 1-7). In most examples quantitative yields were achieved, except for 2-iodoaniline and 3-iodopyridine, which produced the desired sulfides in 97 and 96% yields, respectively (entries 5 and 6). The formation of the products seems to be unaffected by steric and electronic effects in the aryl moiety, since in both cases the products were formed with the same level of efficiency (entries 1 vs 4 and 1 vs 3). In another set of experiments, we promoted the coupling using a variety of thiols and similarly the products were formed with high levels of efficiency (entries 8-13). Even alkyl sulfides (entries 11 and 12) successfully underwent C-S coupling.

To check the scope of our methodology, we next subjected the developed protocol to a more complex system. Biologically active sulfides, namely captropil (entry 14) and N-Boc protected L-penicillanime (entry 15), were employed as starting materials for the coupling with 4-methoxy iodobenzene under standard conditions. In both examples the products were obtained in good yields, 70 and 53%, respectively, showing the versatility of the methodology in the presence of more complexes functionalities.

Table 18. Synthesis of sulfides from different thiols

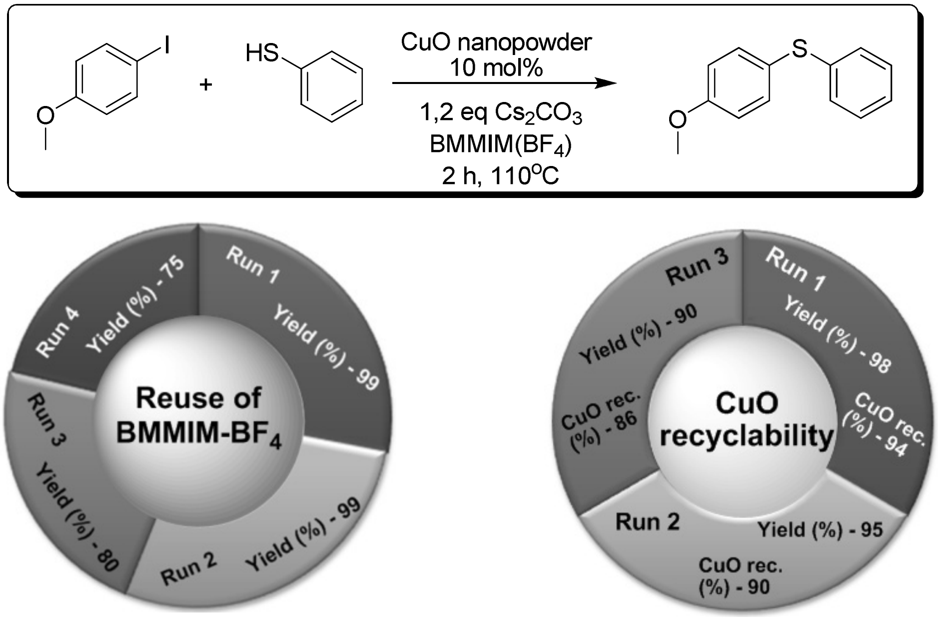
$$\mathrm{RS{-}H} \quad + \quad \mathrm{Ar{-}I} \xrightarrow[\text{1.2 eq } \mathrm{Cs_2CO_3} \text{ / BMMIM(BF}_4\text{)} \\ \text{2 h, } 110^{o}\mathrm{C}]{\text{CuO nanopowder (10 mol\%)}} \mathrm{RS{-}Ar}$$

Entry	R	ArI	Product	Yield (%)
1	Ph	4-OMePh	 **5a**	99
2	Ph	4-MePh	 **5b**	99
3	Ph	4-BrPh	 **5c**	99
4	Ph	2-OMePh	 **5d**	99
5	Ph	$2\text{-}H_2NPh$	 **5e**	97
6	Ph	3-Py	 **5f**	96

7	Ph	Ph	 **5g**	99
8	4-OMePh	Ph	 **5h**	99
9	4-ClPh	Ph	 **5i**	99
10	3-Py	Ph	 **5j**	80
11	4-ClPhCH$_2$	Ph	 **5k**	99
12	C$_{12}$H$_{25}$	Ph	 **5l**	76
13		Ph	 5m	80
14		4-OMePh	 **5n**	70
15		4-OMePh	 **5o**	53

5.3 Recyclability experiments

The development of economic and environmentally friendly methods is one of our prime concerns. This prompted us to further improve the importance of our protocol and perform an evaluation of the recyclability of the ionic liquid and CuO catalyst employed in our reactions. After the work-up, the recovered BMMIM-BF$_4$ was reused for further reactions and found to have comparable efficiency for up to four recycling experiments, as shown in Figure 26.



(a) **(b)**

Figure 26. Recyclability tests: (a) reuse of IL; (b) CuO recyclability

5.4 Proposed mechanism for CuO nanoparticle catalyzed reactions

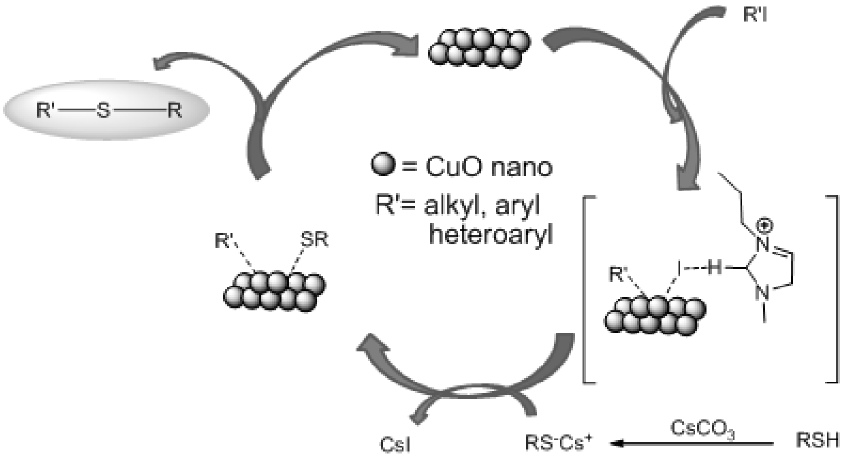


Figure 27. Plausible reaction pathway

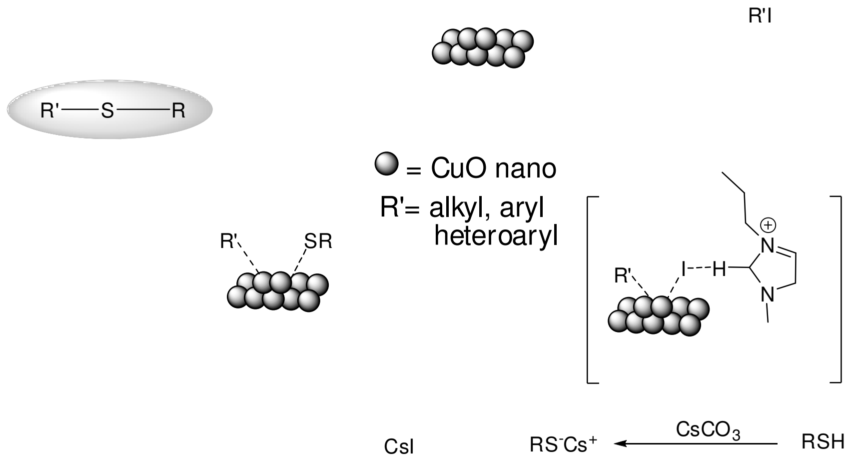


Figure 27 shows the mechanism of the CuO catalized synthesis of sulfides. The mechanistic explanation is the same as the one provided in Chapter 2, section 2.5. All these compounds are characterized by ^{1}H and ^{13}C NMR. Experimental details and further information on the characterization of these compounds are provided in Chapter 7 and the spectra are presented in Chapter 8.

The NMR spectra of the compound **4-methoxyphenyl phenyl sulfide** shows in ^{1}H spectrum that in region 7.41 ppm shows doublet with *j* = 8.82 Hz relative of 2H (H_a and $H_{a'}$) of phenyl group. Other 5H (H_c, $H_{c'}$, H_d, $H_{d'}$, and H_e) of phenyl group are confirmed by another multiplet in region 7.27-7.08, and H_b and $H_{b'}$ show a doublet with *j* = 8.8 Hz 6.88 ppm of 2H. The aliphatic hydrogens of methyl group appear at 3.80 ppm as a singlet (Figure 29). In ^{13}C NMR carbon C1, C1', C2, C2', C3, C3', C4, C4', C5, C5', C6 and C6' (Figure 30) appear in the range of 160-115 ppm (aromatic region) and carbon of CH_3 appear in aliphatic region at 55.6 ppm (Figure 28).

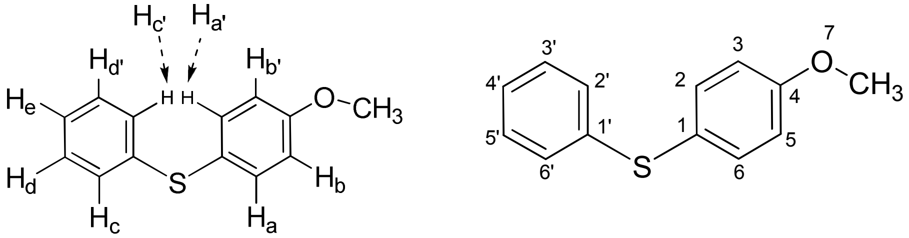


Figure 28. Different magnetic environment of hydrogen (H) and carbon

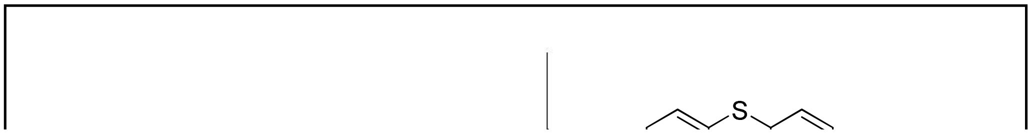


Figure 29. ^{1}H NMR (200 MHz, CDCl3) spectrum of **4-methoxyphenyl phenyl sulfide**

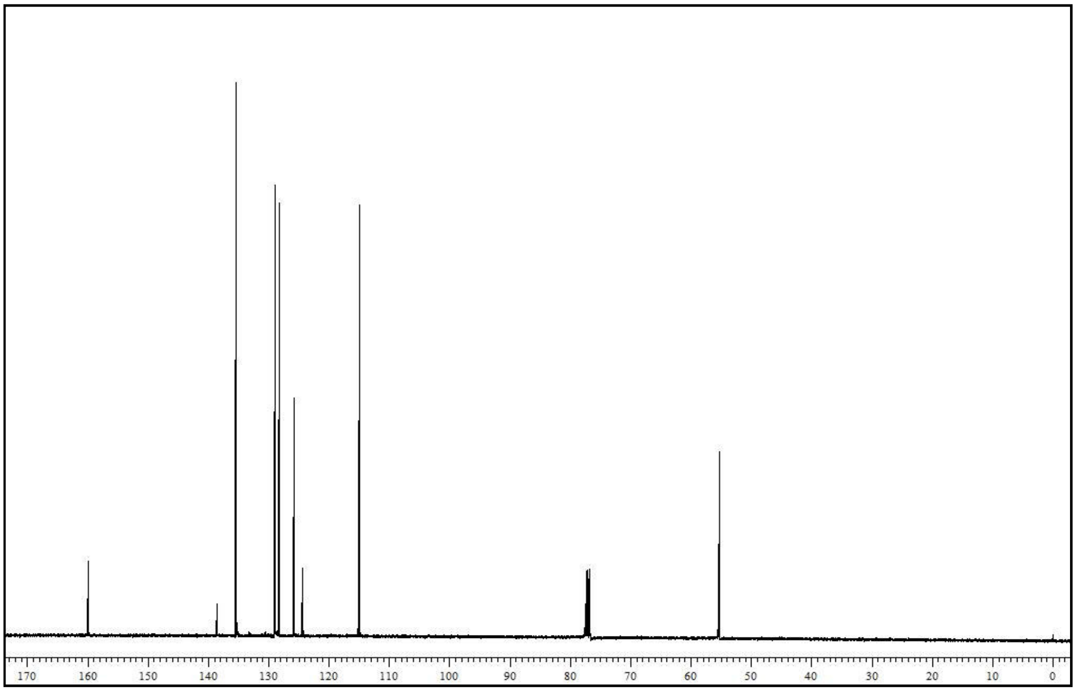


Figure 30. ^{1}H NMR (200 MHz, CDCl3) spectrum of **4-methoxyphenyl phenyl sulfide**

In conclusion, we have developed a clean, inexpensive, and efficient methodology to obtain diaryl or alkyl aryl sulfides from aryl iodides and thiols using CuO nanopowder in ionic liquid as a reusable media. The features of this method include the following: (i) use of easily accessible alkylating agents; (ii) use of very small amount of catalyst; (iii) effectiveness for complex functionalities.

CHAPTER 6

CONCLUSION

In the present work we described efficient methodologies for the preparation of organochalcogen compounds, namely selenides (Chapter 2), seleno-esters (Chapter 3), diselenides and ditellurides (Chapter 4), and sulfides (Chapter 5). Some important aspects of these methodologies are the high reactivity in the preparation of the different organochalcongen compounds by the combination of nanoparticle catalysis with ionic liquids (except Chapter 4), because of the advantageous nature of this association which resulted in short reaction times, mild reaction conditions, excellent yields, and, most importantly, a greener protocol than previous methods.

Table 19 shows a comparison among previous protocols and the new methodologies developed in the current work. As described in Chapter 2, there are numbers of decent methods reported in the literature for the synthesis of alkyl and aryl selenides using different metals and conditions. Recently, CuO nanoparticles have been used to synthesise selenides and DMSO, which is used as a solvent, and the reaction needs 12-14hr to complete at 100°C.[43] However, with the combination of ionic liquids (BMIM-BF_4) and CuO nanoparticles, these compounds are easily obtained at room temperature in 1hr (Table 19, entry 1). Other advantages of this protocol are recyclability of the catalyst as well as of the solvents, although we were not yet aware of the recyclability of the CuO nanoparticles when this particular project was developed.

Similarly different metals were used to synthesize selenoesters as described in Chapter 3. Most recently, indium metal was used by our group to synthesise selenoesters at room temperature in DCM,[67] but this method was bounded by some limitations, like the cost of catalyst, handling, and the recyclability of catalyst. The present protocol is an attempt to overcome all these limitations by using CuO nanoparticles and BMIM-PF_6 (Table 19, entry 2).

Further, there are various methods to prepare sulfides by using different metals and metal nanoparticles, as described in Chapter 5. Let's compare the conditions of CuO nanoparticles and CuBr or Fe in the synthesis of sulfides (Table 19, entry 4). There is not so much difference between the reaction time and the other conditions. Just the benefit to use the nanoparticles is recyclability.[42] Therefore, only the combination of ionic liquids and nanoparticles has proven to be a good method to improve the protocols, because ionic liquids help to speed up the reactions.

Table 19. Comparison between metal salts and nanoparticles for the synthesis of organochalcogen compounds

Entry	Reactions	Solvent / Temperature (°C)	Catalyst	Time(hr)	Yield (%) /ref
1	selenides	DMSO/80	CuO nano	12-14	50-94/43
		BMIM-BF$_4$/ r.t.	**CuO nano**	**1**	**82**
2	seleno-esters	DCM/ rt	InI	1-2	50-72/67
		BMIM-BF$_4$/ 90	**CuO nano**	**1**	**57-91**
3	dichalcogenides	THF/reflux	K or Na or Li	1-12	50-90/95
		DMSO/90	**CuO nano**	**0.5-1**	**50-96**
4	sulfides	DMSO/130	CuO nano	10-24	65-95/42
		Toluene/135	Fe	24	95/96
		DMSO/130	CuBr	16	83/97
		BMIMM-BF$_4$/110	**CuO nano**	**2**	**99**

Finally, the synthesis of dichalcoganides requires the use of very reactive and air sensitive metals (entry 3), which is a limitation of these methods. By using the current methodolgy described in Chapter 4, it was easy to obtain diselenides and ditellurides with a wide range of functional groups being tolerated in this process,

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[95] D. P. Thompson and P. Boudjouk, *J. Org. Chem.* 1988**, 53,** 2109-2112.
[96] A. Correa, M. Carril, and C. Bolm, *Angew. Chem. Int. Ed.* 2008, **47**, 2880 –2883.
[97] Y. Feng, H. Wang, F. Sun, Y. Li*, i. Fu, K. Jin, *Tetrahedron,* 2009, **65**, 9737–9741.

including methyl, methoxy, hydroxyl, aldehyde, amino, bromo, and heteroaryl moieties.

The synthesis of organochalcogen compounds using copper oxide nanoparticles and ionic liquids offers great potential for rapid and easily accessible developments in the area of organic synthesis, due to the efficient, economical, and convenient operations. In conclusion, we have developed a clean, eco-friendly, inexpensive and efficient methodology to obtain organochalcogen compounds using CuO nanopowder in ionic liquid as a recyclable solvent.

CHAPTER 7

METHODS, EXPERIMENTAL PROCEDURES AND SPECTRAL DATA

7.1 Material and methods

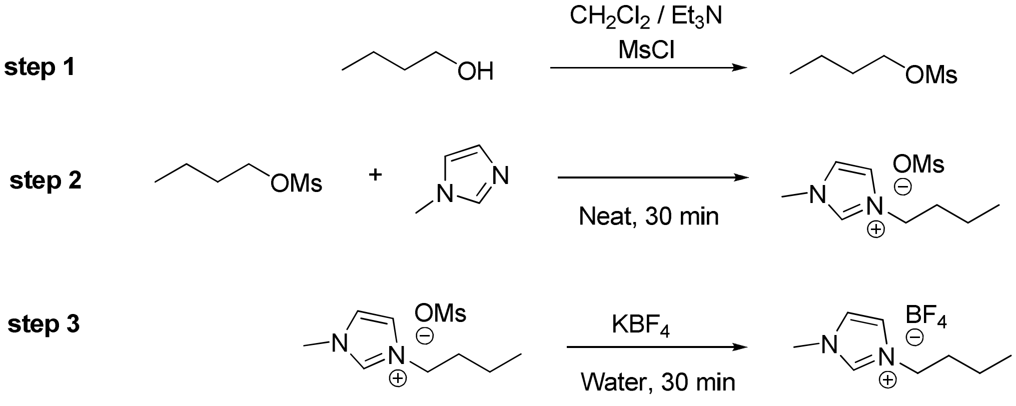
7.1.1 General Information

CuO nano particles (mean particle size, 33 nm, surface area, 29 m^2/g and purity, 99.99%) were purchased from Sigma Aldrich. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz respectively with tetramethylsilane as internal standard. ^{77}Se NMR were recorded at 76.28 MHZ respectively with diphenyl diselenide as a ^{77}Se external reference (463.15 ppm). Column chromatography was performed using Merck Silica Gel (230-400 mesh). Thin layer chromatography (TLC) was performed using Merck Silica Gel GF254, 0.25 mm thickness. For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine vapor, or acidic vanillin. All reagents used were purchased from Sigma Aldrich. ^1H and ^{13}C NMR spectral data of the compounds are identical to those reported. High resolution ESI mass spectra were obtained from a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer, an RF-only hexapole ion guide and an external electrospray ion source.

7.2 Experimental procedures

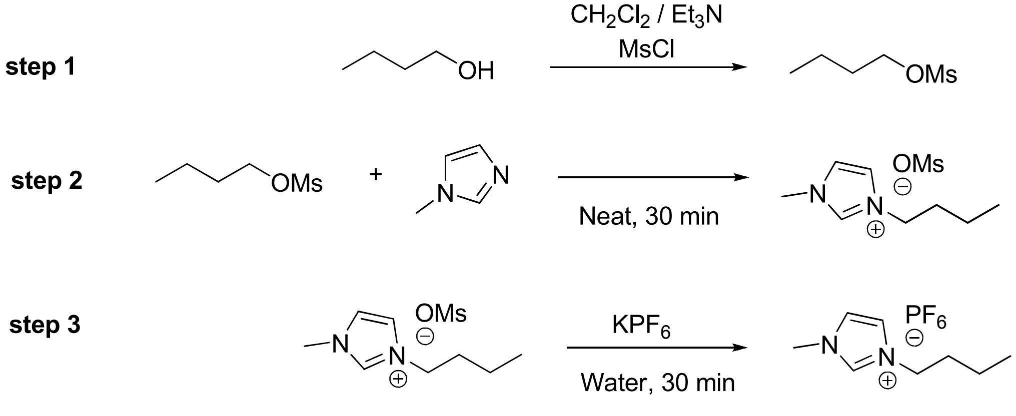
7.2.1 Procedure for the synthesis of various ionic liquids used as a solvent

7.2.1.1 Synthesis of 1-Butyl-3-methylimidazolium Tetrafluoroborate (BMIM-BF$_4$)



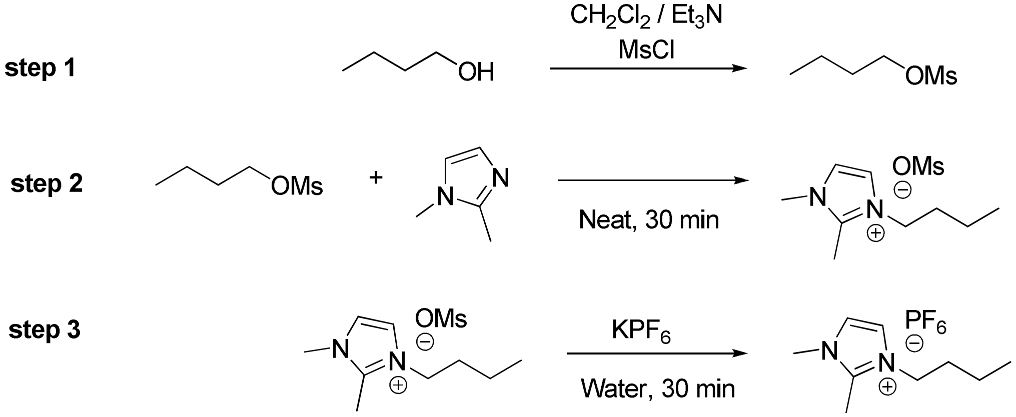
Procedure- same as ref C. C. Cassol, G. Ebeling, B. Ferrera, Jairton Dupont, *Adv. Synth. Catal.* 2006, **348**, 243 – 248.

7.2.1.2 Synthesis of 1-Butyl-3-methylimidazolium hexafluorophospahte (BMIM-PF_6)



Procedure- same as ref C. C. Cassol, G. Ebeling, B. Ferrera, Jairton Dupont, *Adv. Synth. Catal.* 2006, **348**, 243 – 248.

7.2.1.3 Synthesis of 1,2-Dimethyl-3-butylimidazolium Tetrafluoroborate (BMIMM-BF_4)



Procedure- same as ref C. C. Cassol, G. Ebeling, B. Ferrera, Jairton Dupont, *Adv. Synth. Catal.* 2006, **348**, 243 – 248.

7.2.2 General procedure for the synthesis of diorganyl selenides (Chapter 2).1a-1g

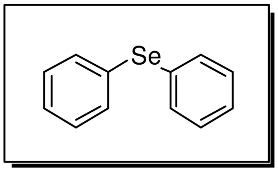
In a Schlenk tube under nitrogen atmosphere and at room temperature CuO nanopowder (0.006 mmol, 0.5 mol %) was added followed by diselenide (0.5 mmol) and KOH (1.0 mmol, 2.0 equiv) were added to a solution of halides (1.0 mmol) in BMIM-BF_4 (1.0 ml). Stirr the reaction mixture at room temperature, the progress of the reaction was monitored by TLC. After, the reaction was complete; the product was extracted by successive washing with diethyl ether (5 x 5 ml) and drying over $MgSO_4$. The solvent and volatiles were completely removed under vacuum to give the crude product. The compounds were purified by column chromatography over silica gel. The purification of these compounds are difficult because the similar Rf value. To avoid this problem, the yields were calculated by Gas choromatography. these compounds were also purified by coloumn choromatography with less yield.

7.2.3 General procedure to reuse BMIM-BF_4

After the work-up of the first run, BMIM-BF_4 is diluted in ethanol and filtered through celite pad to remove the inorganic materials. The filtrate was evaporated by vaccum pump and subjected the resulting ionic liquid to high vaccum to eliminate the moisture and traces of organic solvent. The recovered ionic liquid was reused for the next reaction.

Note: ionic liquid need more time to dry on high vaccum than organic solvents because of its high viscosity.

7.2.4 Preparation of Diphenyl Selenide (1a)



Procedure: Same as 7.2.2.

Yield: 82%

Physical characteristic: yellow oil

IR: (neat) 1580, 1465, 1423 cm^{-1}.

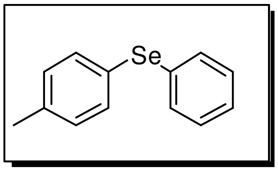
^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.43 – 7.41 (m, 4H), 7.24 – 7.22 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 132.9, 131.3, 129.2, 127.2.

Eluent: hexane

7.2.5 Preparation of Phenyl (p-tolyl) selenides (1b)

Procedure: Same as 7.2.2.



Yield: 80%

Physical characteristic: yellow oil

IR: (neat) 3056, 1574, 1474, 1436 cm^{-1}.

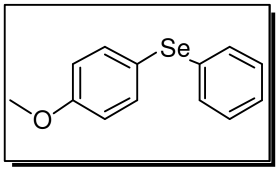
^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.38 – 7.32 (m, 4H), 7.23 – 7.16 (m, 3H), 7.04 (d, 2H, *J* = 8.5 Hz), 2.33 (s, 3H).

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ =137.6, 133.8, 132.0, 130.1, 129.1, 126.8, 21.1

Eluent: hexane

7.2.6 Preparation of (4-methoxyphenyl) (phenyl) selenides (1c)

Procedure: Same as 7.2.2.



Yield: 80%

Physical characteristic: yellow oil

IR: (neat) 3057, 2956, 1577, 1490 cm^{-1};

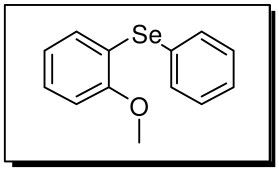
^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ 7.48 (d, *J* = 8.2 Hz, 2H), 7.34–7.33 (m, 2H), 7.22–7.15 (m, 3H), 6.84 (d,*J* = 8.2 Hz, 2H), 3.77 (s, 3H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ 159.7, 136.5, 136.3, 130.9, 129.1, 126.4, 119.9,115.1, 55.2.

Eluent: hexane

7.2.7 Preparation of (2-methoxyphenyl) (phenyl) selenide (1d)

Procedure: Same as 7.2.2.



Yield: 79%

Physical characteristic: yellow oil

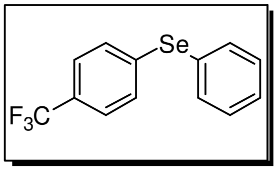
IR: (neat) 3058, 2934, 1575, 1473 cm^{-1}

^{1}HNMR (200 MHz, $CDCl_3$, TMS): δ = 7.44 (d, 2H, *J* = 8.5 Hz), 7.25 – 7.14(m, 5H), 6.82(d, 2H, *J* = 8.5 Hz), 3.79 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 156.6, 135.3, 130.8, 129.4, 128.3, 128.0, 127.7,121.8, 121.6, 110.4, 55.8

Eluent: hexane

7.2.8 Preparation of (4-(trifluoromethyl) Phenyl) (phenyl) selenides (1e)



Procedure: Same as 7.2.2.

Yield: 70%

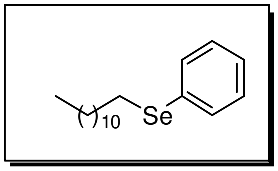
Physical characteristic: yellow viscous oil

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.57 – 7.51(m, 2H), 7.48 – 7.37 (m, 4H), 7.35 – 7.24 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 133.8, 133.7, 132.7, 132.0, 130.1, 129.2, 129.1,128.2, 127.1, 126.8

Eluent: hexane

7.2.9 Preparation of Dodecyl phenyl selenide (1f)



Procedure: Same as 7.2.2.

Yield: 75%

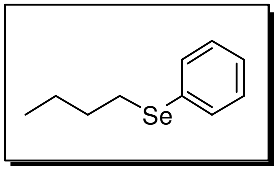
Physical characteristic: yellow oil.

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ= 7.50-7.46 (m, 2H), 7.26-7.22 (m, 3H), 2.90 (t, *J*= 7.2 Hz, 2H), 1.69 (m, 2H), 1.38-1.25 (m, 18H), 0.87 (t, *J*= 6.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ= 132.35, 130.73, 128.92, 126.52, 31.90, 30.14, 29.81, 29.60, 29.56, 29.47, 29.32, 29.06, 28.21, 27.93, 22.67, 14.08

Elutent: hexane

7.2.10 Preparation of n-Butyl phenyl selenides (1g)



Procedure: Same as 7.2.2.

Yield: 76%

Physical characteristic: yellow oil

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ= 7.49-7.45(m, 2H), 7.26-7.18(m, 3H), 2.90 (t, *J*= 7.6 Hz, 2H), 1.71-1.64 (m, 2H), 1.46-1.37 (m, 2H), 0.90 (t, *J*= 7.2Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 132.4, 130.8, 129.0, 126.6, 32.3, 27.7, 23.0, 13.6

Eluent: hexane

7.2.11 General procedure for the synthesis of selenoesters (Chapter 3) 2a-2l

In a Schlenk tube under nitrogen atmosphere, benzoylchloride (1.0 mmol) and CuO nanopowders (0.06 mmol, 5.0 mol %) were added followed by diphenyl diselenide (0.5 mmol) and Cs_2CO_3 (1.0 mmol, 2.0 equiv) (1.0 mmol) in BMIM-PF_6 (1.0 ml) and reaction mixture was stirred at 80°C for 60 min. The progress of the reaction was monitored by TLC. When the reaction was complete, the product was extracted by successive washing with *n*-butanol (5 x 5 mL) and drying over $MgSO_4$. The solvent and volatiles were completely removed under vacuum to give the crude product. The compounds were purified by column chromatography over silica gel.

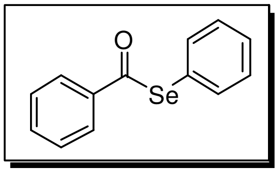
7.2.12 Recyclability experiments

The CuO nanopowders and solvent BMIM-PF_6 can be recycled without loss of activity (Table 11 and Figure 15). After completion of the reaction workup, the reaction mixture was treated with ethanol, and filtered through a Teflon membrane. The CuO nanopowder was recovered from the membrane by washing with water and collected by further centrifugation and drying under vacuum. It was reused for the reactions in the next three runs, and no loss of activity was observed, providing the product in high yields. The ionic liquid was recovered from the ethanol (10 ml) after filtration, evaporation of the solvent and drying the BMIM-PF_6 under vacuum for reuse in subsequent reactions.

7.2.13 Preparation of Se-Phenyl selenobenzoate (2a)

Procedure: Same as 7.2.11.

Yield: 0.237 g, 91%



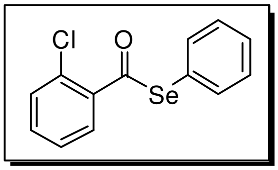
Physical characteristic: yellow solid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.94 - 7.92 (m, 2H), 7.63 - 7.58 (m, 3H) 7.50 - 7.42 (m, 5H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 193.7, 138.9, 138.4, 136.7, 134.2, 129.7, 129.4, 129.3, 127.7, 126.1

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.14 Preparation of Se- Phenyl o-chloro selenobenzoate (2b)



Procedure: Same as 7.2.11.

Yield: 0.244 g, 83%

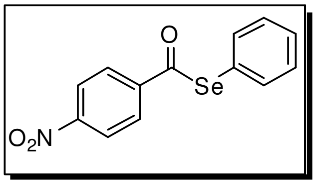
Physical characteristic: yellow oil

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.93 – 7.24 (m, 9H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 191.47, 138.75, 137.84, 133.62, 130.82, 130.35, 129.90, 129.38, 129.18, 128.98, 127.40.

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.15 Preparation of Se- Phenyl p-Nitro selenobenzoate (2c)



Procedure: Same as 7.2.11.

Yield: 0.174 g, 57%

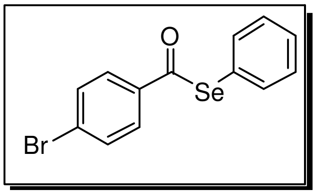
Physical characteristic: yellow solid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 8.35 – 8.33 (m, 2H, Ph); 8.17 – 8.00 (m, 2H, Ph); 7.66 – 7.40 (m, 2H, Ph); 7.30 – 7.23 (m, 3H, Ph);

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 192.50, 150.69, 143.06, 136.11, 131.50, 129.64, 128.16, 124.97, 124.20

Elutent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.16 Preparation of Se-Phenyl p-bromoselenobenzoate (2d)



Procedure: Same as 7.2.11.

Yield: 0.285 g, 84%

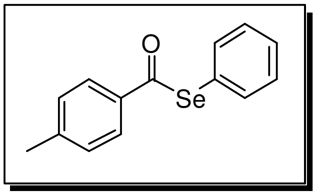
Physical characteristic: yellow solid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.85 (d, *J*= 6.8 Hz, 2H), 7.57 (d, *J*= 6.0 Hz, 2H), 7.44 - 7.41 (m, 5H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 193.4, 140.2, 136.2, 129.4, 129.2, 129.1, 128.5, 125.4, 121.5

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.17 Preparation of Se-Phenyl p-methylselenobenzoate (2e)



Procedure: Same as 7.2.11.

Yield: 0.247 g, 90%

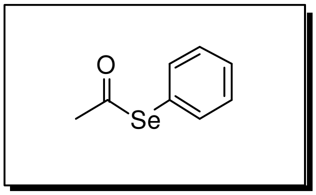
Physical characteristic: yellow liquid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.96 - 7.80 (m, 2H), 7.54 - 7.38 (m, 5H), 7.18 (d, *J*= 8.0 Hz, 2H), 2.35 (s, 3H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 192.7, 142.5, 138.6, 137.7, 133.7, 130.4, 129.8, 128.8, 127.2, 127.2, 126.5, 22.9

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.18 Preparation of Se-Phenyl ethaneselenoate (2f)



Procedure: Same as 7.2.11.

Yield: 0.131 g, 69%

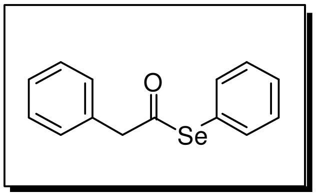
Physical characteristic: Dark yellow liquid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.54 – 7.25 (m, 5H), 2.46 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 196.4, 135.7, 131.4, 129.1, 127.7, 68.8

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.19 Preparation of Se-benzil selenobenzoate (2h)



Procedure: Same as 7.2.11.

Yield: 0.198 g, 72%

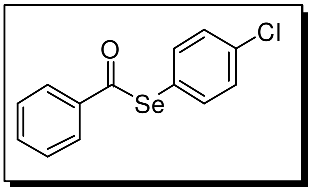
Physical characteristic: yellow liquid

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.87 – 7.84 (m, 2H), 7.49 – 7.32 (m, 3H), 7.24 – 7.17 (m, 5H), 4,30 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 194,50, 138,93, 138,71, 133,60, 128,94, 128,90, 128,72, 127,15, 126,92, 29,12

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.20 Preparation of Se- Phenyl p-cloro selenobenzoate (2i)



Procedure: Same as 7.2.11.

.

Yield: 0.236 g, 80%

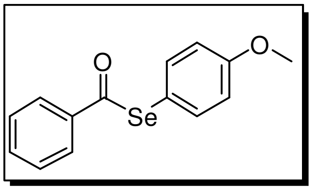
Physical characteristic: yellow liquid

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.91 – 7.89 (m, 5H); 7.61 – 7.59 (m, 2H), 7.50 – 7.37 (m, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 192.45, 138.22, 137.91, 136.45, 133.73, 129.27, 128.67, 12,7.03 123.61

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.21 Preparation of Se-p-methoxy phenyl selenobenzoate (2j)



Procedure: Same as 7.2.11.

Yield: 0.250 g, 86%

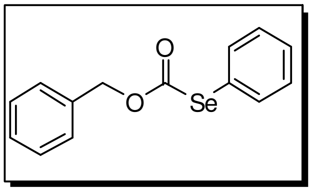
Physical characteristic: pale white solid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.93 – 7.90 (m, 2H), 7.59 – 7.37 (m, 3H), 6.96 – 6.94 (m, 2H), 6.80 – 6.78 (m, 2H), 3.85 (s, 3H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 194.25, 160.45, 137.84, 135.42, 134.57, 133.78, 128.90, 127.30, 114.30, 55.77

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.22 Preparation of O-benzyl Se-phenyl carbonoselenoate (2k)



Procedure: Same as 7.2.11.

Yield: 0.229 g, 79%

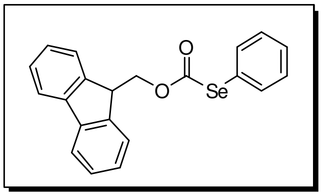
Physical characteristic: yellow liquid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.23 – 7,20 (m, 2H), 7.45 – 7.42 (m, 8H), 4.09 (s, 2H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 166.27, 138.82, 134.45, 130.03, 129.05, 128.71, 128.67, 127.18, 126,54, 70.97

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.23 Preparation of (9H-fluoren-9-yl) methyl Se-phenyl carbonoselenoate (2l)



Procedure: Same as Same as 7.2.11.

Yield: 0.341 g, 90%

Physical characteristic: yellow liquid

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.78 – 7.26 (m, 13H), 4.53 (d, *J* = 7.6 Hz, 2H), 4.12 (t, *J* = 7.2 Hz, 1H)

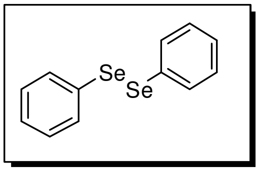
^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 166.50, 134.85, 129.30, 128.10, 127.44, 126.90, 124.92, 119.92, 64.99, 50.23

Eluent: hexane (for eliminate diphenyl diselenide) and 5% EtOAc:hexane (selenoester)

7.2.24 General procedure for the synthesis of diselenides (3a-3o) (Chapter 4)

Se^0 metal (2.0 mmol) and halides (1.0 mmol) were added in dry DMSO (2.0 mL) followed by CuO nanoparticles (10.0 mol %) and KOH (2.0 equiv) under nitrogen atmosphere and stir the reaction mixture at 90°C. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool, which was subjected direct to column chromatographic separation to give pure Diselenides without doing any aqueous workup. The identity and purity of the product was confirmed by ^{1}H, ^{13}C, ^{77}Se NMR spectroscopic analysis and IR spectroscopy.

7.2.25 Preparation of 1, 2-diphenyldiselenide (3a)



Procedure: Same as 7.2.24.

Yield: 0.149 g, 96%.

Physical characteristic: yellow solid.

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.61– 7.57 (m, 2H), 7.25 – 7.21 (m, 3H)

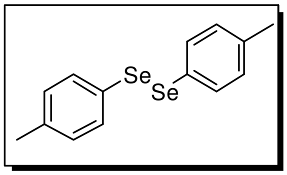
^{77}Se NMR ($CDCl_3$, 76.28 MHz) δ = 463.1

^{13}C NMR (100 MHz, $CDCl_3$, TMS): 132.1, 131.2, 129.4, 127.4

IR (KBr), ν (cm^{-1}): 3040, 1585, 1475, 790

Eluent: hexane

7.2.26 Preparation of 1, 2-di p-tolyldiselenide (3b)



Procedure: Same as 7.2.24.

Yield: 0.163 g, 96%

Physical characteristic: orange solid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.47 (d, *J*= 8.4 Hz, 2H), 7.04 (d, *J*= 8.4 Hz, 2H), 2.30 (s, 3H)

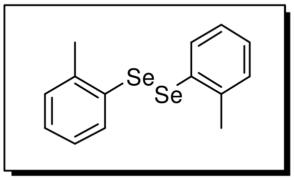
^{77}**Se NMR** ($CDCl_3$, 76.28 MHz) δ = 409.6

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ =139.32, 133.20, 130.51, 127.41, 22.80

IR (KBr), ν (cm^{-1}): 2916, 1627, 1396, 802

Eluent: hexane

7.2.27 Preparation of 1, 2-di o-tolyldiselenide (3c)



Procedure: Same as 7.2.24.

Yield: 0.153 g, 90%

Physical characteristic: yellow solid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.61 (d, *J*= 7.2 Hz, 1H), 7.17 – 6.99 (m, 3H), 2.40 (s, 3H)

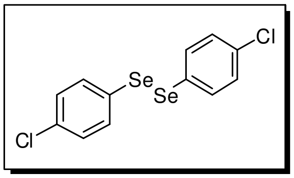
^{77}**Se NMR** ($CDCl_3$, 76.28 MHz): δ = 405.2

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 138.69, 132.57, 130.81, 129.88, 127.91, 126.78, 22.17

IR (KBr), ν (cm^{-1}): 2908, 1581, 1288, 817

Eluent: hexane

7.2.28 Preparation of 1, 2-bis (4-chlorophenyl) diselenide (3d)



Procedure: Same as 7.2.24.

Yield: 0.169 g, 89%

Physical characteristic: Brown solid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.47 (d, *J*= 8.6 Hz, 2H), 7.20 (d, *J*= 8.6 Hz, 2H)

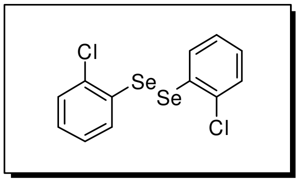
^{77}**Se NMR** ($CDCl_3$, 76.28 MHz): δ = 449.3

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ =134.19, 133.16, 129.53, 129.27

IR (KBr), v (cm^{-1}): 3070, 1465, 1002, 810

Eluent: hexane

7.2.29 Preparation of 1, 2-bis (2-chlorophenyl) diselenide (3e)



Procedure: Same as 7.2.24.

Yield: 0.171 g, 90%

Physical characteristic: orange oil

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.59 – 7.54 (m, 1H), 7.30 – 7.24 (m, 1H), 7.15 – 7.06 (m, 2H)

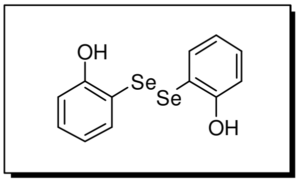
^{77}Se NMR ($CDCl_3$, 76.28 MHz): δ = 476.9

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 134.04, 133.06, 130.52, 129.15, 128.23, 127.78

IR (KBr), v (cm^{-1}): 3070, 1465, 1080, 810

Eluent: hexane

7.2.30 Preparation of 2, 2'-diselenidediyldiphenol (3f)



Procedure: Same as 7.2.24.

Yield: 0.123 g, 72%

Physical characteristic: yellow solid

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.41 – 7.36 (m, 1H), 7.28 – 7.19 (m, 1H), 6.97 – 6.92 (m, 1H), 6.87 – 6.78 (m, 1H), 1.67 (br,1H);

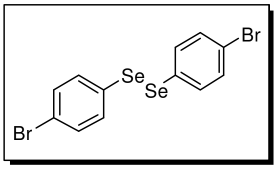
^{77}Se NMR ($CDCl_3$, 76.28 MHz): δ = 329.1

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 155.48, 135.36, 130.79, 121.64, 115.68, 115.30

IR (KBr), v (cm^{-1}): 3425, 1411, 1041, 902

Eluent: hexane

7.2.31 Preparation of 1, 2-bis(4-bromophenyl)diselenide (3g)



Procedure: Same as 7.2.24.

Yield: 0.208 g, 89%

Physical characteristic: yellow solid

^{1}**HNMR** (400 MHz, CDCl$_3$, TMS): δ = 7.44 – 7.35 (m, 4H)

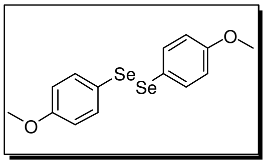
^{77}**Se NMR** (CDCl$_3$, 76.28 MHz): δ = 457.6

^{13}**C NMR** (100 MHz, CDCl$_3$, TMS): δ = 134.49, 133.31, 132.48, 132.23

IR (KBr), ν (cm^{-1}): 3040, 1465, 1010, 810

Eluent: hexane

7.2.32 Preparation of 1,2-bis(4-methoxyphenyl)diselenide (3h)



Procedure: Same as 7.2.24.

Yield: 0.148 g, 80%

Physical characteristic: yellow solid

^{1}**HNMR** (400 MHz, CDCl$_3$, TMS): δ = 7.53 (d, *J*= 8.8 Hz, 2H), 6.83 (d, *J*= 8.8 Hz, 2H), 3.80 (s, 1H)

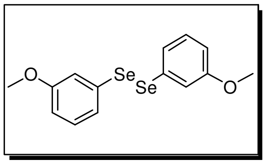
^{77}**Se NMR** (CDCl$_3$, 76.28 MHz): δ = 394.2

^{13}**C NMR** (100 MHz, CDCl$_3$, TMS): δ = 160.03, 138.15, 135.43, 114.70, 55.29

IR (KBr), ν (cm^{-1}): 2908, 1581, 1288, 817

Eluent: hexane

7.2.33 Preparation of 1, 2-bis(3-methoxyphenyl)diselenide (3i)



Procedure: Same as 7.2.24.

Yield: 0.165 g, 89%

Physical characteristic: yellow solid

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.27 – 7.11 (m, 3H), 6.81 – 6.73 (m, 1H), 3.74 (s,3H)

^{77}Se NMR ($CDCl_3$, 76.28 MHz): δ = 333.2

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 159.74, 131.74, 129.81, 123.38, 116.45, 113.71, 55.19

IR (KBr), v (cm^{-1}): 2939, 1573, 1284, 848

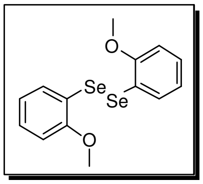
Eluent: hexane

7.2.34 Preparation of 1,2-bis(2-methoxyphenyl)diselenide (3j)

Procedure: Same as 7.2.24.

Yield: 0.165 g, 89%

Physical characteristic: yellow oil



^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.56 – 7.51 (m, 1H), 7.24 – 7.19 (m, 1H), 6.89 – 6.78 (m, 2H), 3.88 (s, 3H)

^{77}Se NMR ($CDCl_3$, 76.28 MHz): δ = 338.6

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 156.70, 130.40, 128.07, 121.79, 110.04, 97.48, 55.84

IR (KBr), v (cm^{-1}): 2931, 1573, 1288, 748

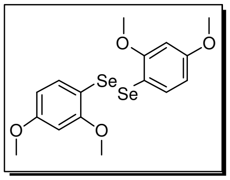
Eluent: hexane

7.2.35 Preparation of 1,2-bis(2,4-dimethoxyphenyl)diselenide (3k)

Procedure: Same as 7.2.24.

Yield: 0.108 g, 50%

Physical characteristic: orange oil



^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.52 – 7.48 (m, 1H), 7.45 – 7.39 (m, 2H), 3.81 (s, 3H), 3.77 (s, 3H)

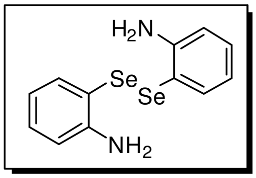
^{77}Se NMR ($CDCl_3$, 76.28 MHz): δ = 413.3

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 161.16, 158.48, 133.71, 110.00, 105.58, 98.50, 55.80, 55.41

IR (KBr), v (cm^{-1}): 2931, 1589, 1211, 833

Eluent: 5 % EtOAc:hexane

7.2.36 Preparation of 2,2'-diselenidediyldianiline (3l)



Procedure: Same as 7.2.24.

Yield: 0.148 g, 87%

Physical characteristic: yellow oil

^{1}**HNMR** (400 MHz, CDCl$_3$, TMS): δ = 7.62 (dd, *J1*= 7.8 Hz, *J2*= 1.4 Hz, 1H), 7.16 – 7.07 (m, 1H), 6.72 (dd, *J* = 7.8 Hz, *J2*= 1.4 Hz, 1H), 6.50 – 6.41 (m, 1H), 4.05 (s, 2H)

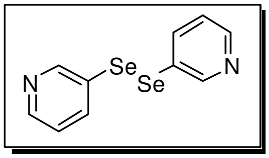
^{77}**Se NMR** (CDCl$_3$, 76.28 MHz): δ = 405.3

^{13}**C NMR** (100 MHz, CDCl$_3$, TMS): δ = 146.62, 138.84, 129.22, 119.86, 114.64, 84.11

IR (KBr), v (cm^{-1}): 3441, 1612, 1311, 848

Eluent: 50 % EtOAc: hexane

7.2.37 Preparation of 1,2-di(pyridin-3-yl)diselenide (3m)



Procedure: Same as 7.2.24.

Yield: 0.128 g, 82%

Physical characteristic: yellow oil

^{1}**HNMR** (400 MHz, CDCl$_3$, TMS): δ = 8.79 – 8.75 (m, 1H), 8.53 – 8.50 (m, 1H), 7.93 – 7.87 (m, 1H), 7.26 – 7.19 (m, 1H)

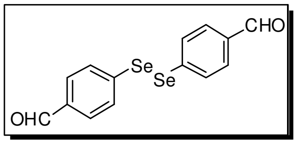
^{77}**Se NMR** (CDCl$_3$, 76.28 MHz): δ = 473.9

^{13}**C NMR** (100 MHz, CDCl$_3$, TMS): δ = 152.37, 149.37, 149.19, 140.08, 124.23

IR (KBr), v (cm^{-1}): 3441, 1558, 1002, 702

Eluent: 20 % EtOAc:hexane

7.2.38 Preparation of 4,4'-diselenidediyldibenzaldehyde (3n)



Procedure: Same as 7.2.24.

Yield: 0.132 g, 72%

Physical characteristic: Red oil

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 9.88 (s, 1H), 7.39 (d, *J*= 8.4 Hz, 2H), 7.14 (d, *J*= 8.4 Hz, 2H)

^{77}**Se NMR** ($CDCl_3$, 76.28 MHz): δ = 481.3

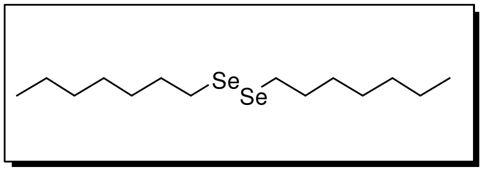
^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 191.19, 136.01, 131.65, 126.79, 123.79

IR (KBr), ν (cm^{-1}): 3422, 1635, 1157, 833

HRMS (ESI-FT-ICR) *m/z*: 369.9011 [M+] +; calcd. for $C_7H_6OSe_2$ fragment. 265.8740

Eluent: hexane

7.2.39 Preparation of 1, 2-diheptyldiselenide (3o)



Procedure: Same as 7.2.24.

Yield: 0.170 g, 96%

Physical characteristic: yellow oil

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 2.90 (t, *J*= 7.2 Hz, 2H), 1.72 (qui, *J* = 7.2 z, 2H), 1.41 – 1.28 (m, 8H), 0.91 – 0.85 (m, 3H)

^{77}**Se NMR** ($CDCl_3$, 76.28 MHz): δ = 509.6

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 31.68, 30.93, 30.16, 29.44, 28.76, 22.56, 14.02

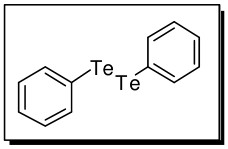
IR (KBr), ν (cm^{-1}): 2924, 1705, 1111, 833

Eluent: hexane

7.2.40 General procedure for the synthesis of ditellurides (4a-4h) (Chapter 4)

Te^0 metal (2.0 mmol) and halides (1.0 mmol) were added in dry DMSO (2.0 mL) then CuO nanoparticles (10.0 mol %) was added followed by KOH (2.0 equiv) under nitrogen atmosphere and stir the reaction mixture at 90 ^{0}C. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool, which was subjected direct to column chromatographic separation to give pure Ditellurides, without doing any aqueous workup. The identity and purity of the product was confirmed by ^{1}H, ^{13}C, NMR spectroscopic analysis and IR spectroscopy.

7.2.41 Preparation of 1,2-diphenylditelluride (4a)



Procedure: Same as 7.2.40.

Yield: 0.175 g, 86%

Physical characteristic: reddish brown solid

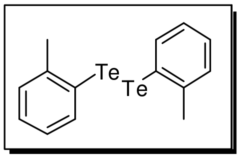
^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.81– 7.76 (m, 2H), 7.24 – 7.12 (m, 3H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 137.59, 129.25, 128.05, 107.90

IR (KBr), v (cm^{-1}): 3016, 1566, 1465, 732

Eluent: hexane

7.2.42 Preparation of 1,2-dio-tolylditelluride (4b)



Procedure: Same as 7.2.40.

Yield: 0.192 g, 88%

Physical characteristic: brown oil

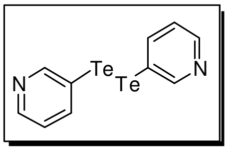
^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.46 (d, *J*= 7.6 Hz, 1H), 7.22 – 7.10 (m, 2H), 6.97 – 6.89 (m, 1H), 2.45 (s, 3H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 142.50, 138.14, 129.35, 128.33, 126.81, 118.45, 26.85

IR (KBr), v (cm^{-1}): 3040, 1897, 1442, 794

Eluent: hexane

7.2.43 Preparation of 1,2-di(pyridin-3-yl)ditellurides (4c)



Procedure: Same as 7.2.40.

Yield: 0.147 g, 72%

Physical characteristic: brown oil

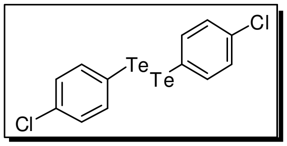
^{1}**HNMR** (400 MHz, CDCl$_3$, TMS): δ = 8.92 – 8.91 (m, 1H), 8.49 – 8.46 (m, 1H), 8.08 – 8.02 (m, 1H), 7.21 – 7.12 (m, 1H)

^{13}**C NMR** (100 MHz, CDCl$_3$, TMS): δ = 152.34, 149.35, 149.18, 140.08, 124.27

IR (KBr), ν (cm^{-1}): 3461, 1530, 1012, 702.

Eluent: hexane

7.2.44 Preparation of 1, 2-bis (4-chlorophenyl) ditellurides (4d)



Procedure: Same as 7.2.40.

Yield: 0.215 g, 90%

Physical characteristic: reddish brown solid

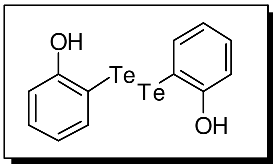
^{1}**HNMR** (400 MHz, CDCl$_3$, TMS): δ = 7.66 (d, *J*= 8.4 Hz, 2H), 7.13 (d, *J*= 8.4 Hz, 2H)

^{13}**C NMR** (100 MHz, CDCl$_3$, TMS): δ = 139.26, 139.11, 129.81, 129.42

IR (KBr), ν(cm^{-1}): 3070, 1465, 1002, 717

Eluent: hexane

7.2.45 Preparation of 2, 2'-ditelluridediyldiphenol (4e)



Procedure: Same as 7.2.40.

Yield: 0.189 g, 86%

Physical characteristic: reddish solid

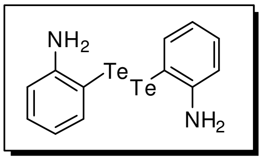
^{1}**HNMR** (400 MHz, CDCl$_3$, TMS): δ = 7.43 – 7.37 (m, 1H), 7.25 – 7.17 (m, 1H), 6.99 – 6.96 (m, 1H), 6.85 – 6.79 (m, 1H), 1.68 (br,1H)

^{13}**C NMR** (100 MHz, CDCl$_3$, TMS): δ = 155.70, 138.08, 128.56, 120.30, 114.49, 83.44

IR (KBr), ν(cm^{-1}): 3430, 1460, 1000, 842

Eluent: 30 % EtOAc:hexane

7.2.46 Preparation of 2, 2'- ditelluridediyldianiline (4f)



Procedure: Same as 7.2.40.

Yield: 0.179 g, 82%

Physical characteristic: Dark red oil

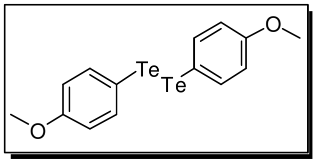
^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.68 – 7.62 (m, 1H), 7.14 – 7.05 (m, 1H), 6.73 – 6.66 (m, 1H), 6.52 – 6.44 (m, 1H), 4.16 (s, 2H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 150.41, 142.92, 131.35, 118.77, 113.42, 94.69

IR (KBr), ν(cm^{-1}): 3440, 1632, 1372, 870

Eluent: 50 % EtOAc:hexane

7.2.47 Preparation of 1, 2-bis(4-methoxyphenyl)ditellurides (4g)



Procedure: Same as 7.2.40.

Yield: 0.187 g, 80%

Physical characteristic: reddish brown solid

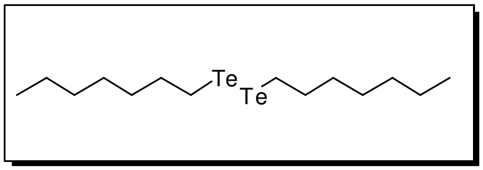
^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 7.66 (d, *J*= 8.8 Hz, 2H), 6.72 (d, *J*= 8.8 Hz, 2H), 3.76 (s, 1H)

^{13}**C NMR** (100 MHz, $CDCl_3$, TMS): δ = 160.08, 138.11, 135.40, 114.72, 55.23

IR (KBr), ν(cm^{-1}): 3052, 1461, 1280, 800

Eluent: hexane

7.2.48 Preparation of 1, 2-diheptylditelluride (4h)



Procedure: Same as 7.2.40.

Yield: 0.190 g, 84%

Physical characteristic: yellow liquid

^{1}**HNMR** (400 MHz, $CDCl_3$, TMS): δ = 2.62 (t, *J*= 7.4 Hz, 2H), 1.75 – 1.68 (m, 2H), 1.35 – 1.28 (m, 8H), 0.91 – 0.85 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 33.62, 32.00, 31.73, 28.64, 28.54, 22.61, 14.07

IR (KBr), ν (cm^{-1}): 2930, 1745, 1100, 810

Eluent: hexane

7.2.49 General procedure for the coupling of aryl iodides with thiols (5a-5o) (Chapter 5)

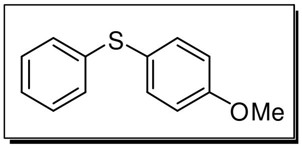
In a Schlenk tube under nitrogen atmosphere CuO nanoparticles (0.055 mmol, 10 mol %) followed by thiol (0.5 mmol) and Cs_2CO_3 (0.6 mmol, 1.2 equiv) were added to a solution of aryl halide (0.55 mmol) in BMMIM-BF_4 (1.0 mL). The mixture was stirred at 110 °C for the appropriate time. The progress of the reaction was monitored by TLC. After, the reaction was complete, the product was extracted by successive washing with diethyl ether (5 x 8 mL) and drying over $MgSO_4$. The solvent was then removed under vacuum to give the crude products, which were purified by column chromatography on silica gel.

7.2.50 Recyclability experiments

The CuO nanopowders and solvent BMMIM-BF_4 can be recycled without loss of activity (Figure 26). After completion of the reaction workup, the reaction mixture was treated with ethanol, and filtered through a Teflon membrane. The CuO nanopowder was recovered from the membrane by washing with water and collected by further centrifugation and drying under vacuum. It was reused for the reactions in the next three runs, and no loss of activity was observed, providing the product in high yields. After the work-up, the BMMIM-BF_4 was recovered, dissolved in 5 mL of acetone and filtered through a celite pad to remove the CuO. The solution was dried over $MgSO_4$ and the volatiles were removed under vacuum. The recovered ionic liquid was reused for the next reaction.

7.2.51 Preparation of 4-methoxyphenyl phenyl sulfide (5a)

Procedure: Same as 7.2.49.



Yield: 0.213 g, 99%

Physical characteristic: colorless oil

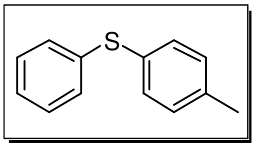
^{1}HNMR (400 MHz, CDCl$_3$, TMS): δ = 7.41 (d, *J* = 8.82 Hz, 2H), 7.27-7.08 (m, 5H), 6.88 (*J* = 8.82 Hz, 2H), 3.80 (s, 3H)

^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ = 159.76, 138.53, 135.27, 128.84, 128.14, 125.68, 124.24, 114.91, 55.26

Eluent: 5 % EtOAc: hexane

7.2.52 Preparation of 4-methylphenyl phenyl sulfide (5b)

Procedure: Same as 7.2.49.



Yield: 0.198 g, 99%

Physical characteristic: colorless oil

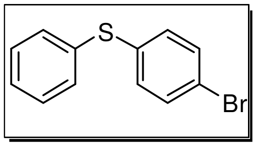
^{1}HNMR (400 MHz, CDCl$_3$, TMS): δ = 7.29-7.13 (m, 7H), 7.11 (d, *J* = 7.82 Hz, 2H), 2,31 (s, 3H)

^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ = 137.51, 137.07, 132.20, 131.24, 130.00, 129.72, 128.97, 126.33, 21.06

Eluent: 5 % EtOAc: hexane

7.2.53 Preparation of 4-bromophenyl phenyl sulfide (5c)

Procedure: Same as 7.2.49.



Yield: 0.262 g, 99%

Physical characteristic: colorless oil

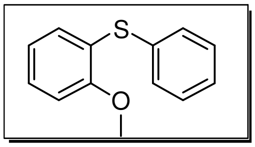
^{1}HNMR (400 MHz, CDCl$_3$, TMS): δ = 7.51-7.11 (m, 9H)

^{13}C NMR (100 MHz, CDCl$_3$, TMS): δ = 136.96, 135.42, 134.76, 132.14, 131.99, 131.46, 129.29, 128.99, 127.47, 127.43, 127.07, 120.78

Eluent: 5 % EtOAc: hexane

7.2.54 Preparation of 2-methoxyphenyl phenyl sulfide (5d)

Procedure: Same as 7.2.49.



Yield: 0.213 g, 99%

Physical characteristic: colorless oil

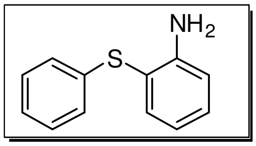
^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.36-7.18 (m, 6H), 7.07 (dd, J^1 = 7.49 Hz, J^2 = 1.76 Hz, 1H), 6.90-6.81 (m, 2H), 3.85 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 157.11, 134.31, 131.42, 131.27, 129.00, 128.21, 126.91, 123.83, 121.08, 110.68, 55.69

Eluent: 5 % EtOAc: hexane

7.2.55 Preparation of 2-Phenylsulfanylaniline (5e)

Procedure: Same as 7.2.49.



Yield: 0.194 g, 97%

Physical characteristic: pale yellow oil

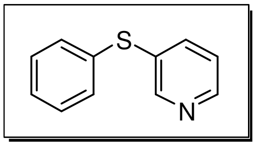
^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.47-7.42 (m, 1H), 7.26-7.04 (m, 6H), 6.78-6.70 (m, 2H), 3.99 (br, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 148.74, 137.41, 136.73, 131.08, 128.93, 126.35, 125.33, 118.67, 115.29, 114.23

Eluent: 10 % EtOAc: hexane

7.2.56 Preparation of 3-(phenylthio) pyridine (5f)

Procedure: Same as 7.2.49.



Yield: 0.179 g, 96%

Physical characteristic: colorless oil

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 8.54 (s, 1H), 8.45-8.43 (m, 1H), 7.61-7.55 (m, 1H), 7.39-7.27 (m, 5H), 7.20-7.16 (m, 1H)

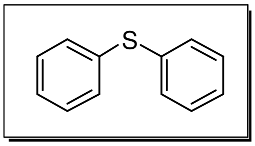
^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 150.80, 147.61, 137.73, 133.74, 131.60, 129.35, 127.71, 123.77

HRMS-ESI: *m/z* calcd for $C_{11}H_9NS$ $[M + H]^+$ 188,0534; found 188.0529

Eluent: 10 % EtOAc: hexane

7.2.57 Preparation of diphenyl sulfide (5g)

Procedure: Same as 7.2.49.



Yield: 0.184 g, 99%

Physical characteristic: colorless oil

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.35-7.14 (m, 10H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 135.71, 130.94, 129.09, 126.93

Eluent: hexane

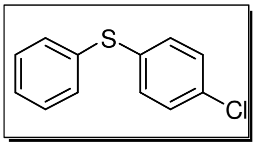
7.2.58 Preparation of 4-methoxyphenyl phenyl sulfide (5h)

Same as 7.2.50.

Yield: 0.213 g, 99%

7.2.59 4-chlorophenyl phenyl sulfide (5i)

Procedure: Same as 7.2.49.



Yield: 0.217 g, 99%

Physical characteristic: colorless oil

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.35-7.23 (m, 9H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 135.06, 134.59, 132.92, 131.94, 131.25, 129.27, 129.24, 127.36.

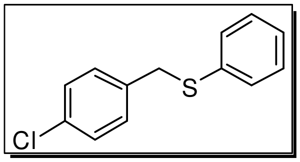
Eluent: 5 % EtOAc: hexane

7.2.60 Preparation of 3-(phenylthio) pyridine (5j)

Same as 7.2.55

Yield: 0.149 g, 80%

7.2.61 Preparation of 4-chlorobenzyl phenyl sulfide (5k)



Procedure: Same as 7.2.49.

Yield: 0.231 g, 99%

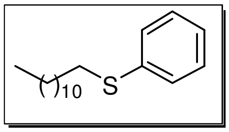
Physical characteristic: white solid

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.31-7.12 (m, 9H), 4.05 (s, 2H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 136.08, 132.87, 130.62, 130.20, 130.06, 128.87, 128.59, 126.63, 38.48

Eluent: 5 % EtOAc: hexane

7.2.62 Preparation of Dodecyl phenyl sulfide (5l)



Procedure: Same as 7.2.49.

Yield: 0.211 g, 76%

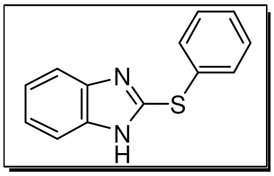
Physical characteristic: white solid

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 7.34-7.14 (m, 5H), 2.90 (t, J = 7.49 Hz, 2H), 1.71-1.55 (m, 2H), 1.25 (s, 18H), 0.88 (t, J = 6.80 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 137.19, 128.73, 125.53, 33.49, 31.89, 29.62, 29.56, 29.48, 29.33, 29.14, 29.09, 28.82, 22.67, 14.10

Eluent: 5 % EtOAc: hexane

7.2.63 Preparation of Benzimidazole phenyl sulfide (5m)



Procedure: Same as 7.2.49.

Yield: 0.180 g, 80%

Physical characteristic: white solid

^{1}HNMR (100 MHz, CD_3OD): δ = 7.52-7.45 (m, 4H), 7.42-7.34 (m, 3H), 7.24-7.18 (m, 2H)

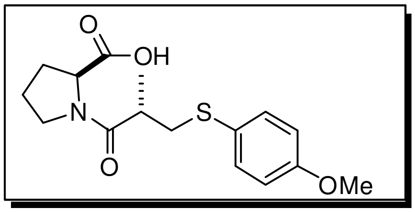
^{13}CNMR (75 MHz, CD_3OD): δ = 149.30, 133.05, 132.39, 130.78, 129.71, 123.93

HRMS-ESI: *m/z* calcd for $C_{13}H_{10}N_2S$ $[M + H]^+$ 227,0643; found 227.0635.

Eluent: 20 % EtOAc: hexane

7.2.64 Preparation of (S)-1-((S)-3-(4-methoxyphenylthio)-2-methylpropanoyl) pyrrolidine-2-carboxylic acid (5n)

Procedure: Same as 7.2.49.



Yield: 0.226 g, 70 %

Physical characteristic: yellow oil

$[\alpha_D]$ = -177.1 ° (*c* = 0.35; CH_2Cl_2)

^{1}HNMR (400 MHz, $CDCl_3$, TMS): δ = 8.37-8.34 (br 1H), 7.35-7.28 (m, 2H), 6.84 (d, *J* = 8.80 Hz, 2H), 4.50-4.46 (m, 1H), 3.79 (s, 3H), 3.52-3.15 (m, 3H), 2.87-2.70 (m, 2H), 2.26-1.89 (m, 4H), 1.21 (d, *J* = 6.60 Hz, 3H)

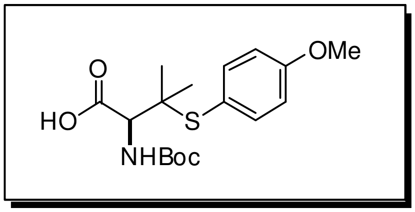
^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 175.60, 173.93, 158.95, 133.08, 125.67, 114.52, 59.24, 55.26, 47.19, 38.83, 38.26, 27.92, 24.55, 16.95

HRMS-ESI: *m/z* calcd for $C_{16}H_{21}NO_4S$ $[M + Na]^+$ 346,1089; found 346.1079.

Eluent: 20 % EtOAc: hexane

7.2.65 Preparation of (S)-2-(tert-butoxycarbonylamino)-3-(4-methoxyphenylthio)-3-methylbutanoic acid (5o)

Procedure: Same as 7.2.49.



Yield: 0.188 g, 53 %

Physical characteristic: yellow oil

$[\alpha_D]$ = +12.4 ° (*c* = 0.31; CH_2Cl_2)

^{1}HNMR (400 MHz, CD_3OD): δ = 9.45-9.43 (br, 1H), 7.47 (d, *J* = 8.80 Hz, 2H), 6.84 (d, *J* = 8.56 Hz, 2H), 5.43-5.40 (m, 1H), 4.14-4.11 (m, 1H), 3.79 (s, 3H), 1.44 (s, 9H), 1.33 (s, 6H)

^{13}C NMR (100 MHz, CD_3OD): δ = 173.76, 162.26, 157.55, 140.24, 122.70, 115.26, 80.78, 62.08, 55.80, 50.56, 28.71, 27.33, 25.35

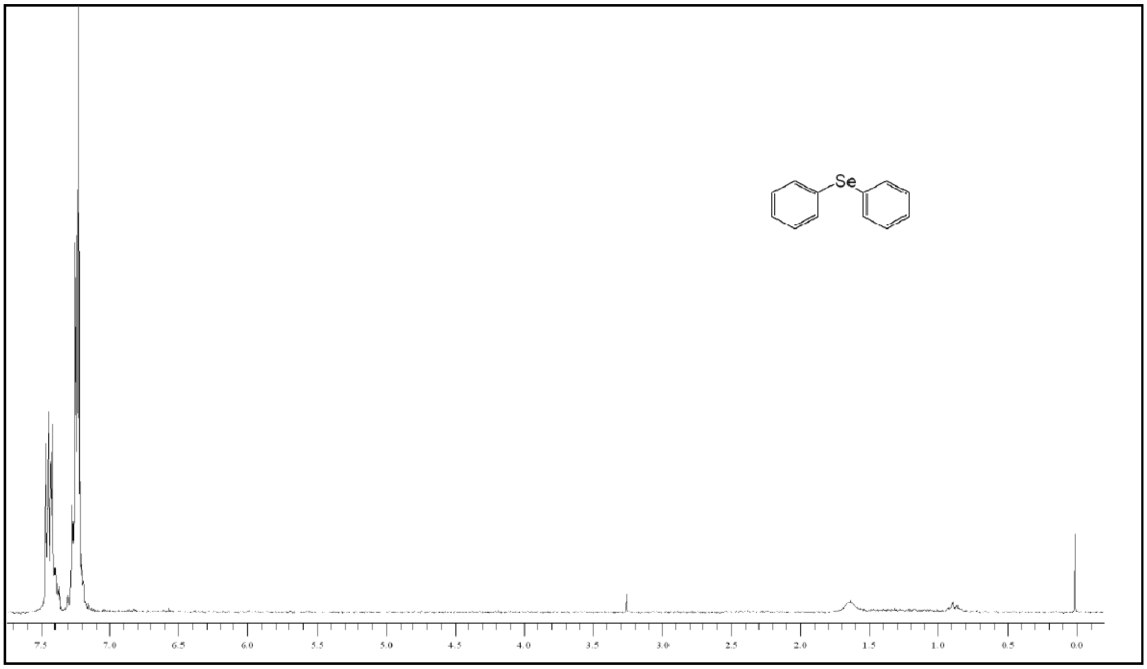
HRMS-ESI: *m/z* calcd for $C_{17}H_{25}NO_5S$ $[M + Na]^+$ 378,1351; found 378.1342.

Eluent: 20 % EtOAc: hexane

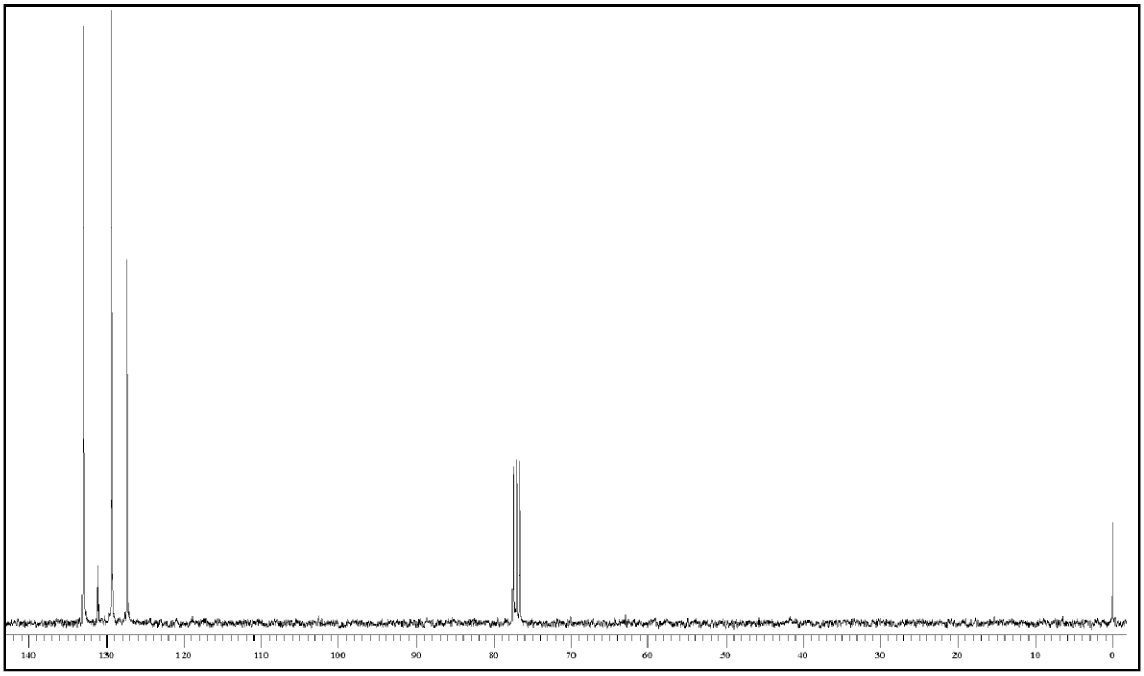
CHAPTER 8

SELECTED SPECTRA: ^{1}H, ^{13}C, ^{77}Se NMR, AND MASS SPECTROSCOPY

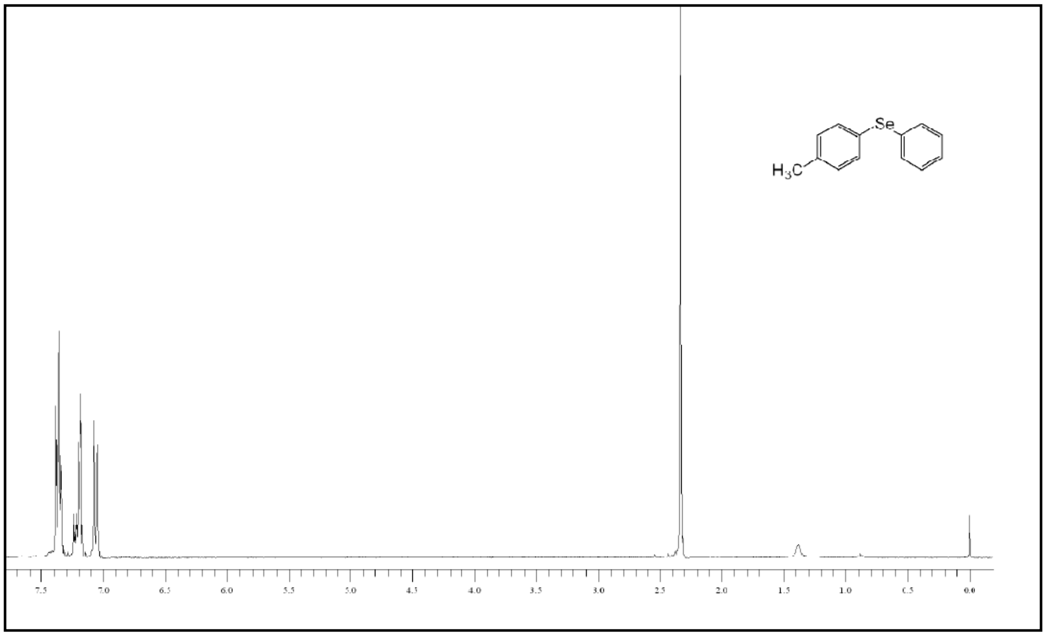
8.1 Selected spectra of selenides



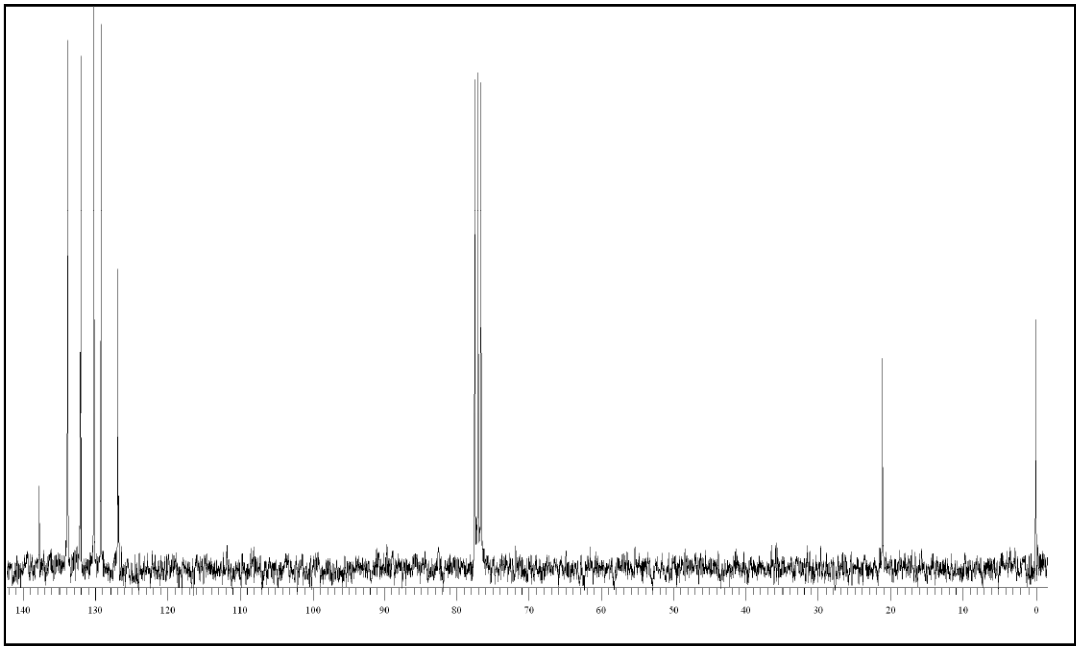
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **DiPhenyl selenide (1a)**



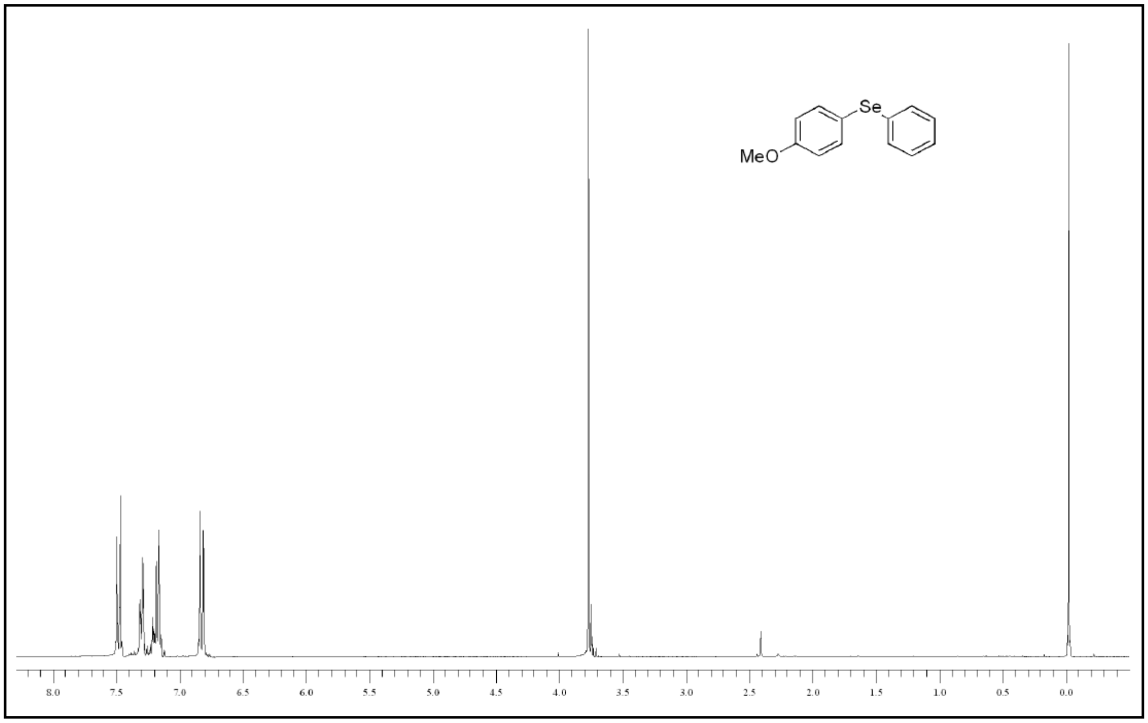
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of **DiPhenyl selenide (1a)**



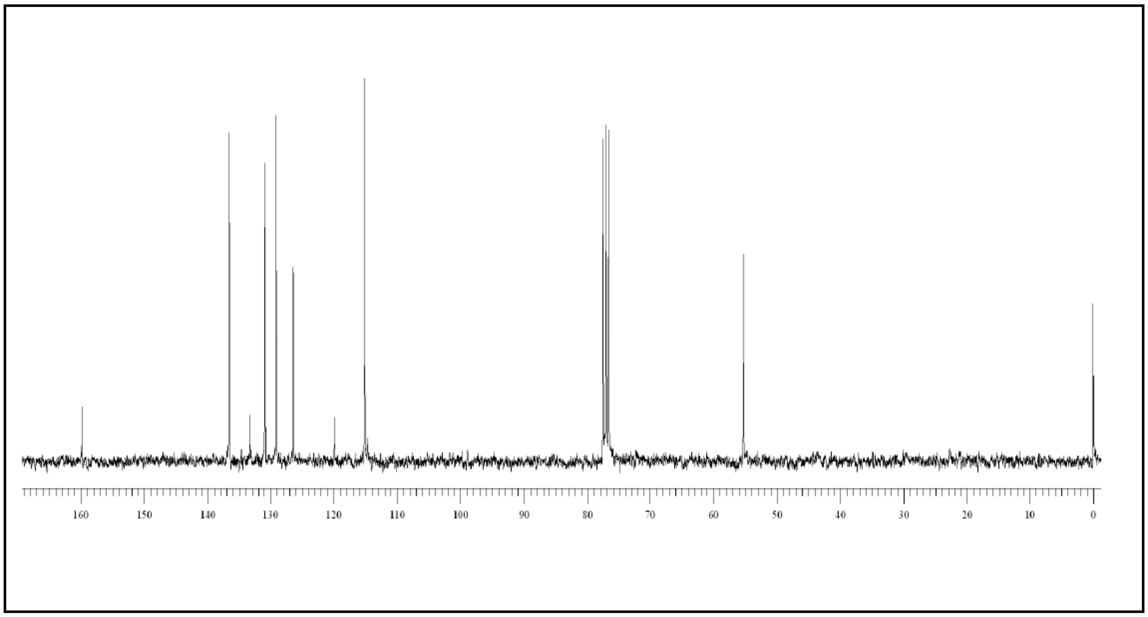
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **Phenyl (*p*-tolyl) selane (1b)**



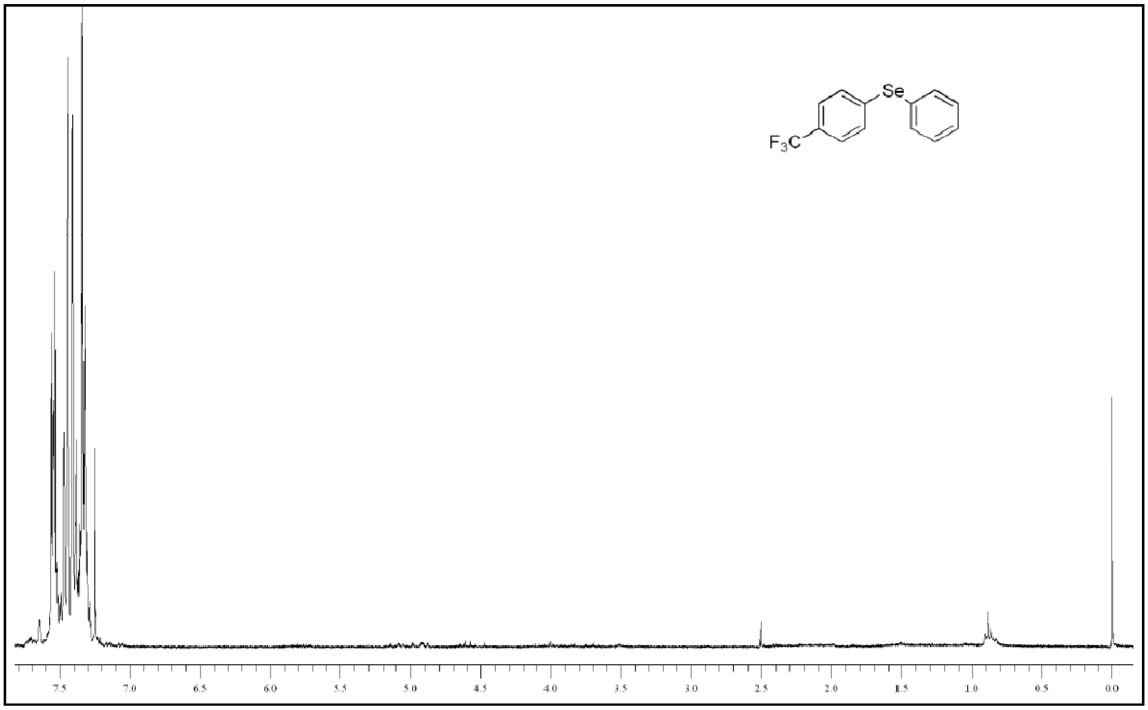
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum. **Phenyl (*p*-tolyl) selane (1b)**



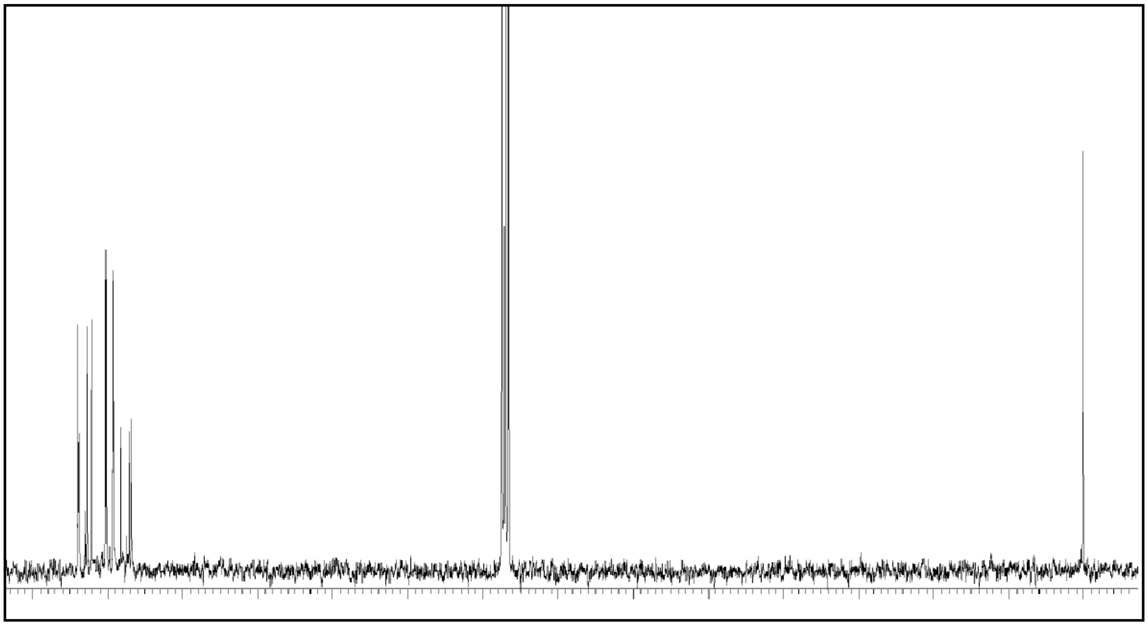
^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **(4-methoxyphenyl)(phenyl) selenide(1c)**



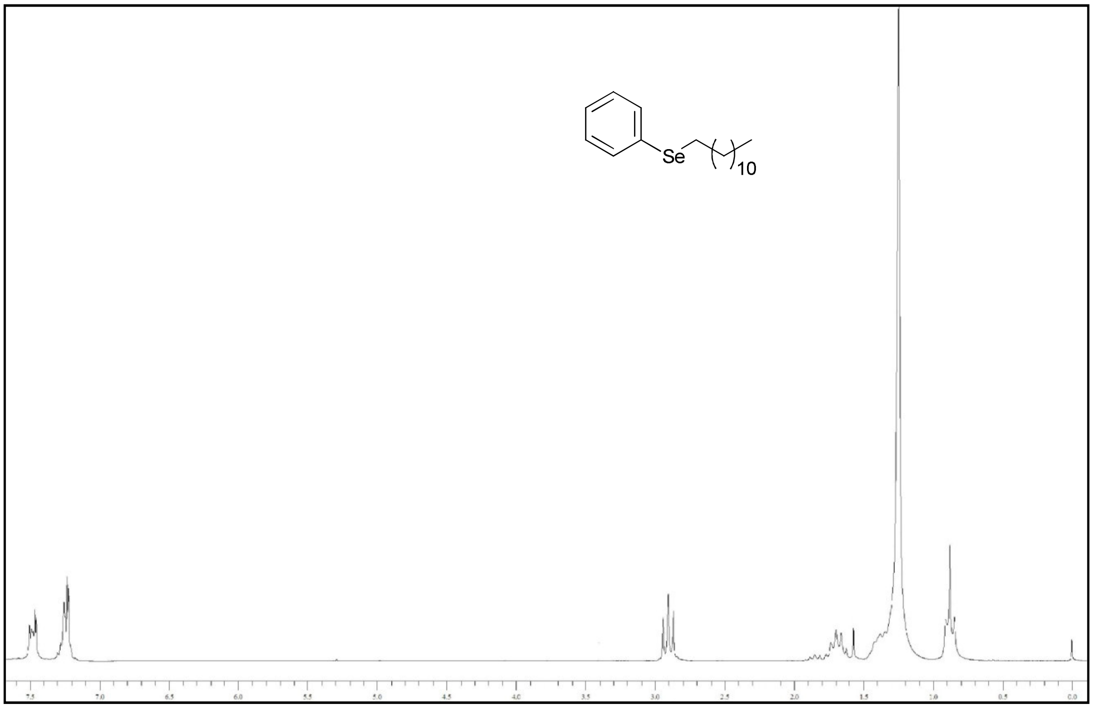
^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of **(4-methoxyphenyl)(phenyl) selenide(1c)**



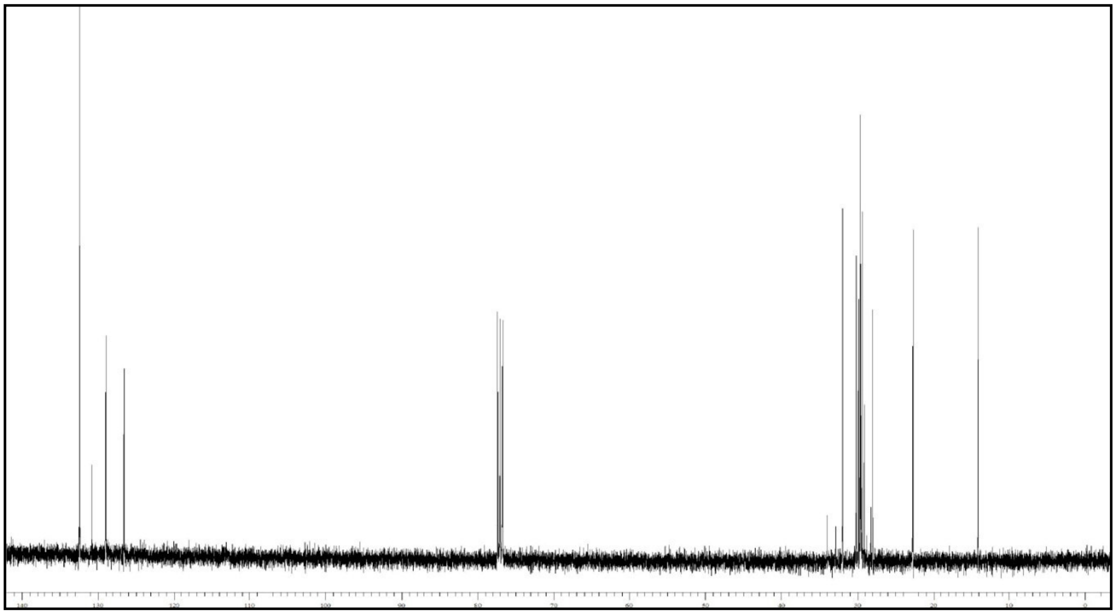
^{1}H NMR (400 MHz, CDCl$_3$) Spectrum of **(4-(trifluoromethyl) Phenyl) (phenyl) selenides (1e).**



^{13}C NMR (100 MHz, CDCl$_3$) Spectrum of **(4-(trifluoromethyl) Phenyl) (phenyl) selenides (1e).**

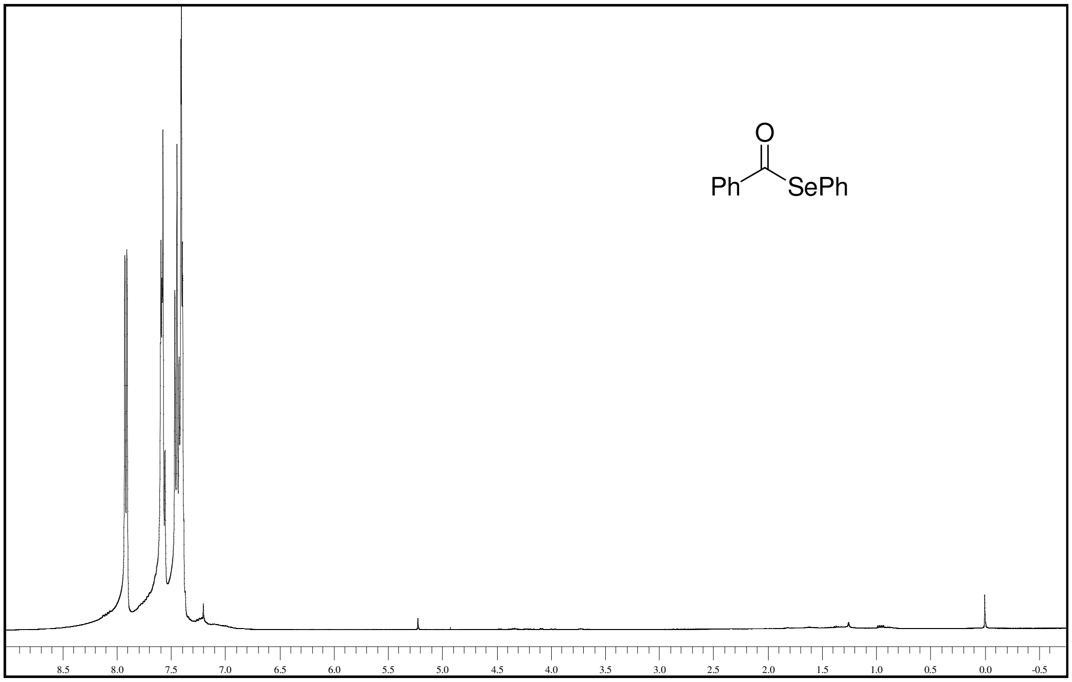


^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of **Dodecyl phenyl selenide (1f).**

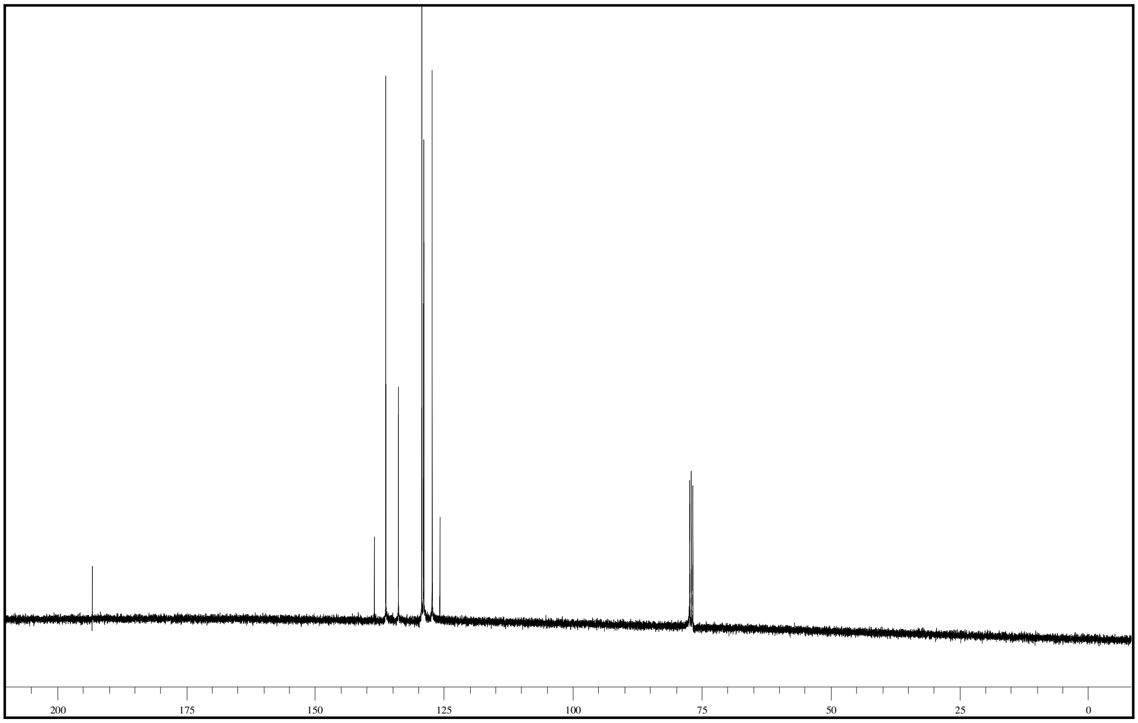


^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of **Dodecyl phenyl selenide (1f).**

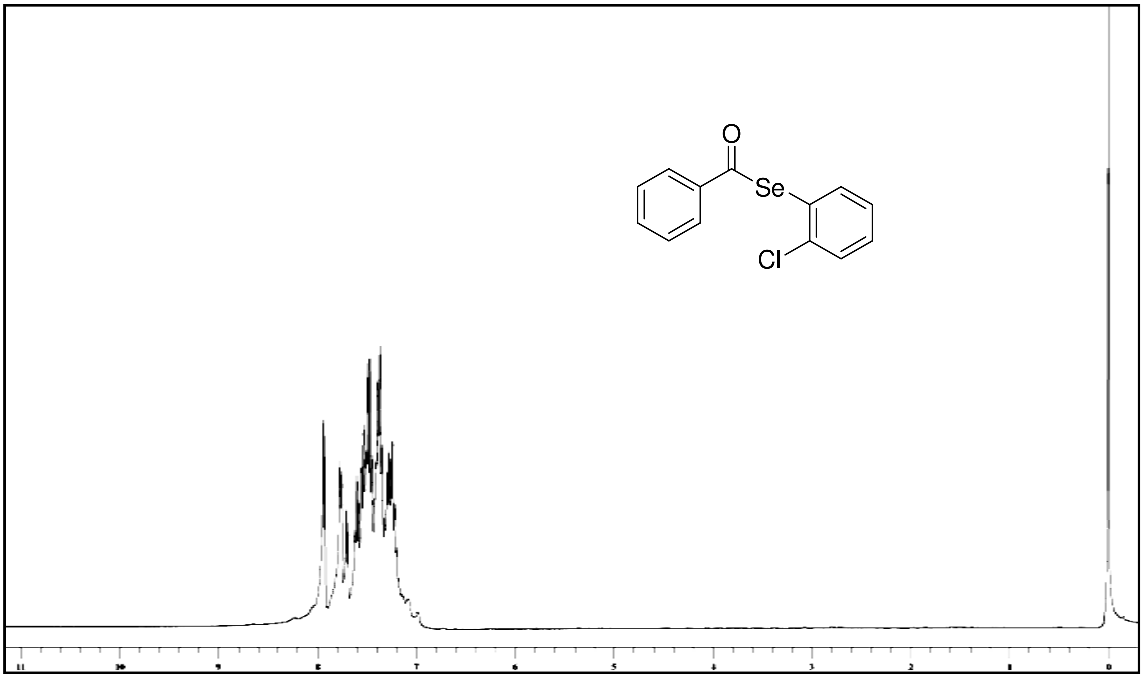
8.2 Selected spectra of seleno-esters



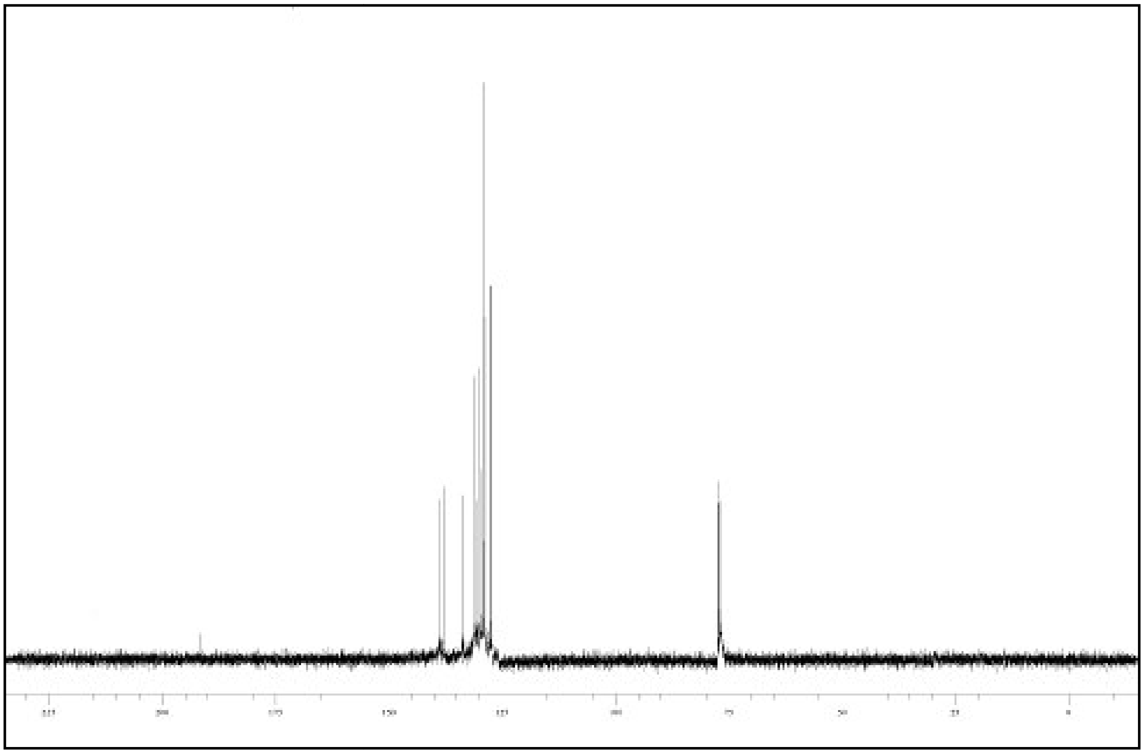
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of ***Se*-phenyl selenobenzoate (2a)**.



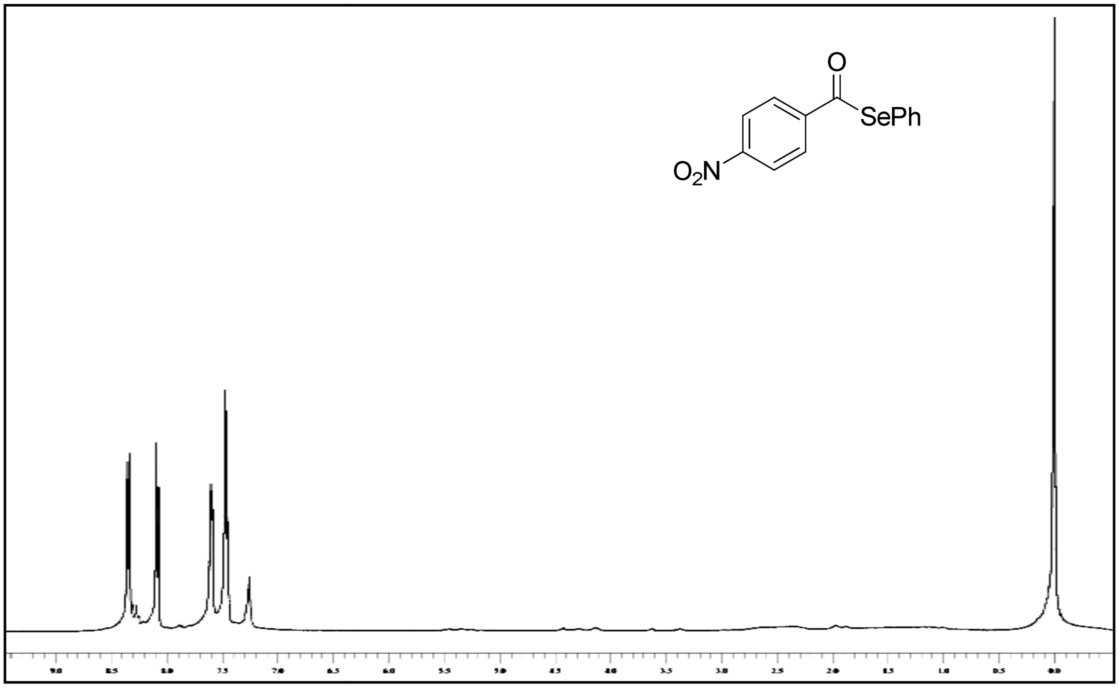
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of ***Se*-phenyl selenobenzoate (2a)**.



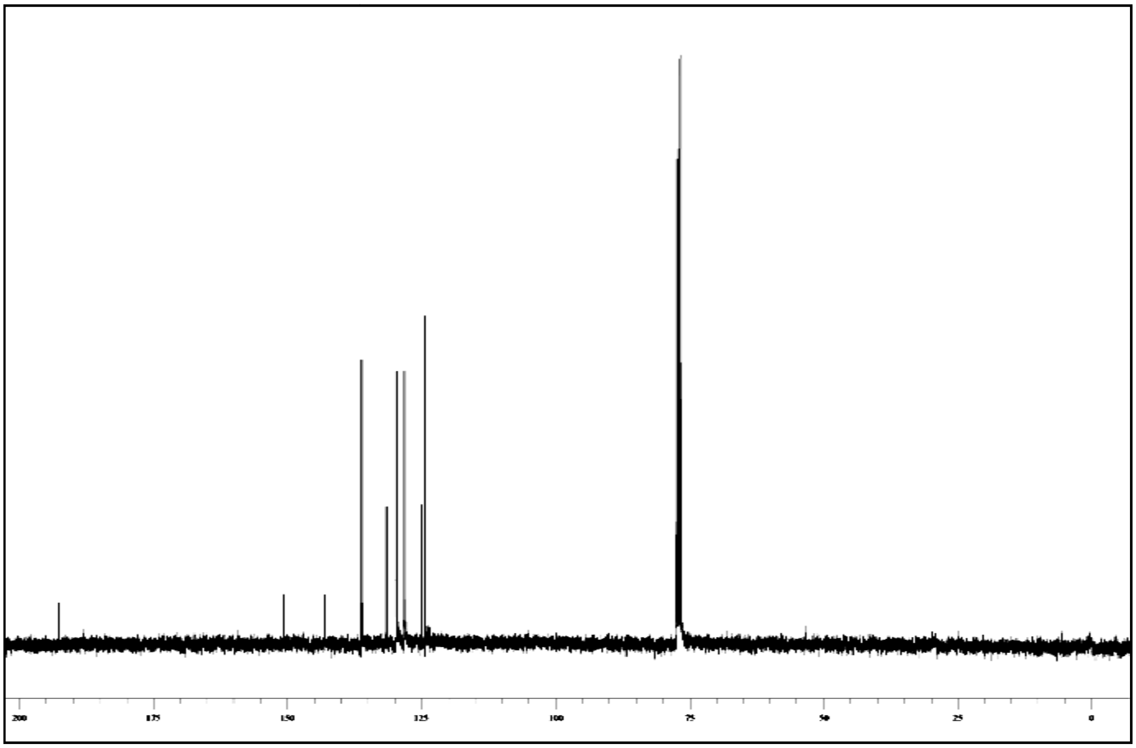
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ***Se-* Phenyl *o*-chloro selenobenzoate (2b)**.



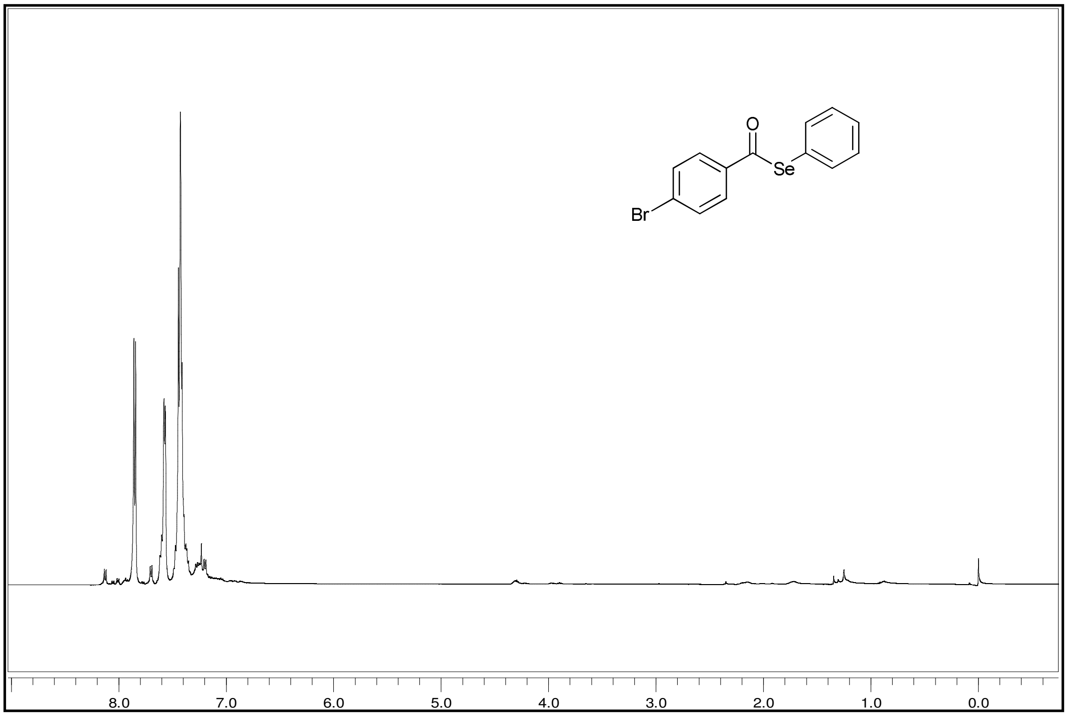
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of ***Se-* Phenyl *o*-chloro selenobenzoate (2b).**



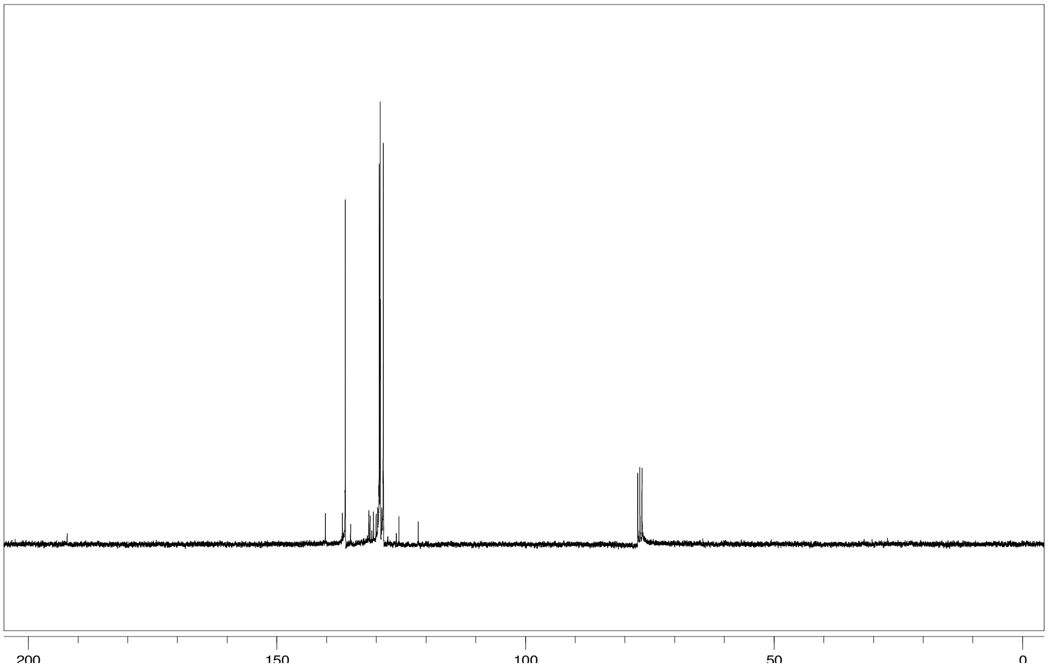
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ***Se-* Phenyl *p*-Nitro selenobenzoate (2c)**.



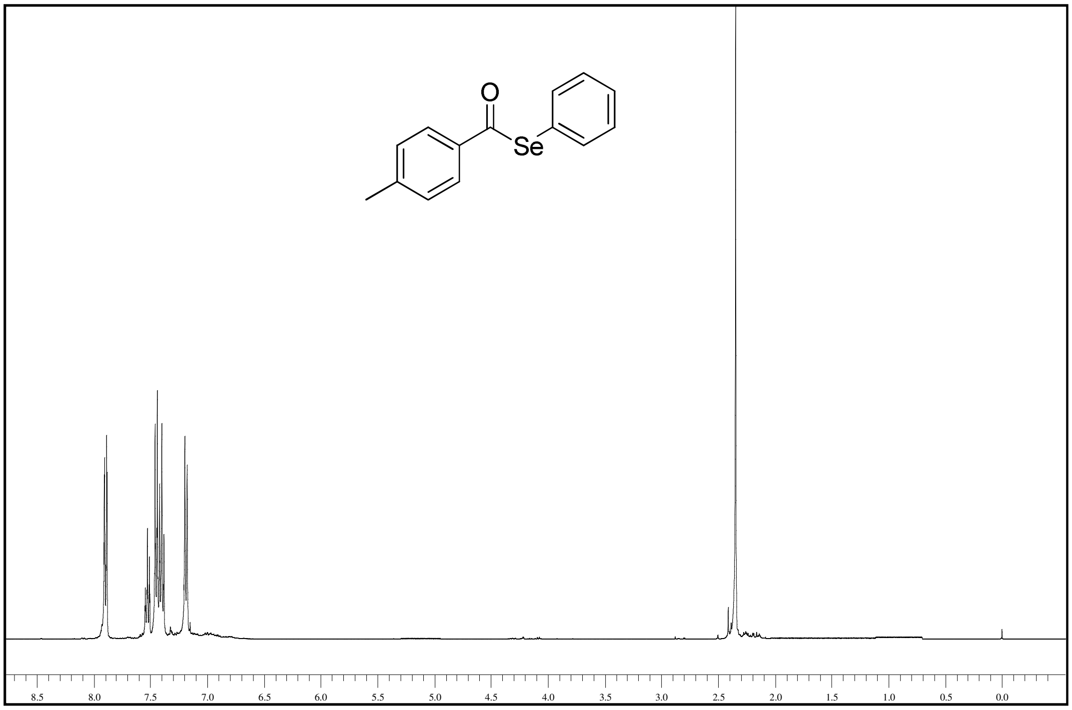
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of ***Se-* Phenyl *p*-Nitro selenobenzoate(2c).**



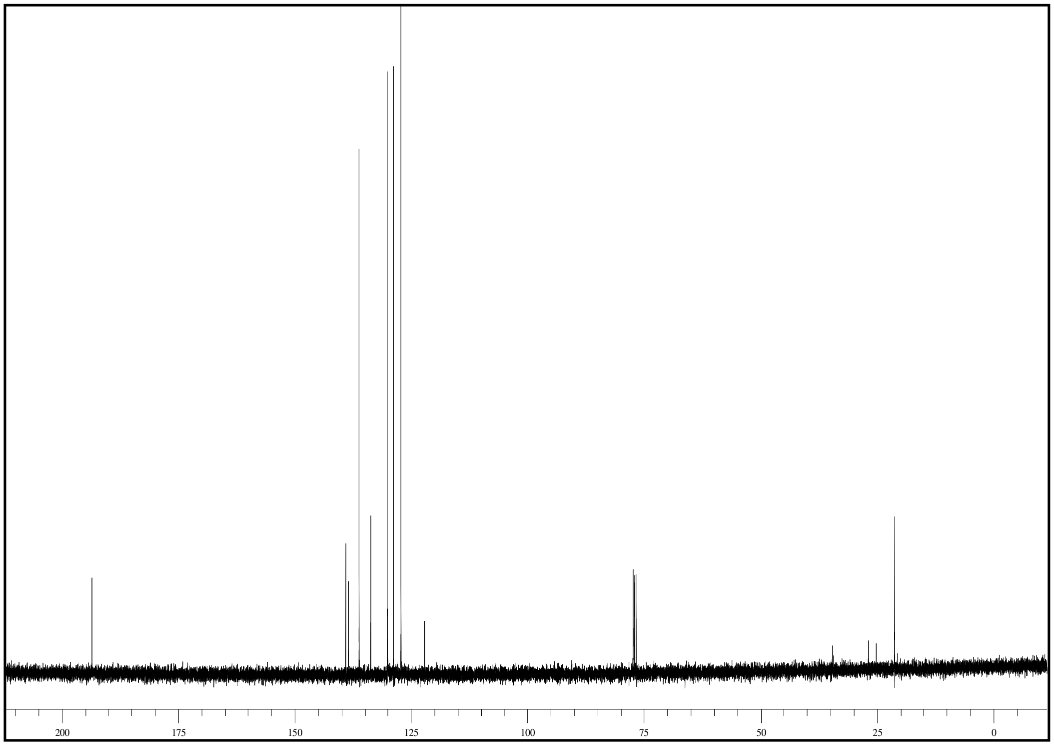
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ***Se*-Phenyl *p*-bromoselenobenzoate (2d)**.



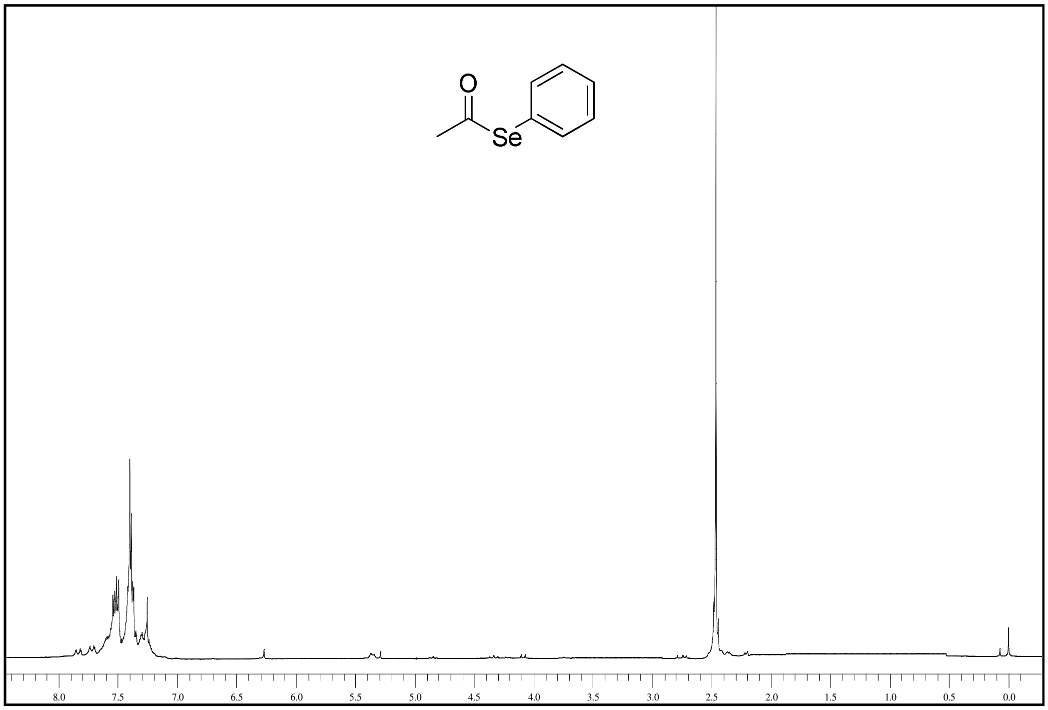
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of ***Se*-Phenyl *p*-bromoselenobenzoate (2d).**



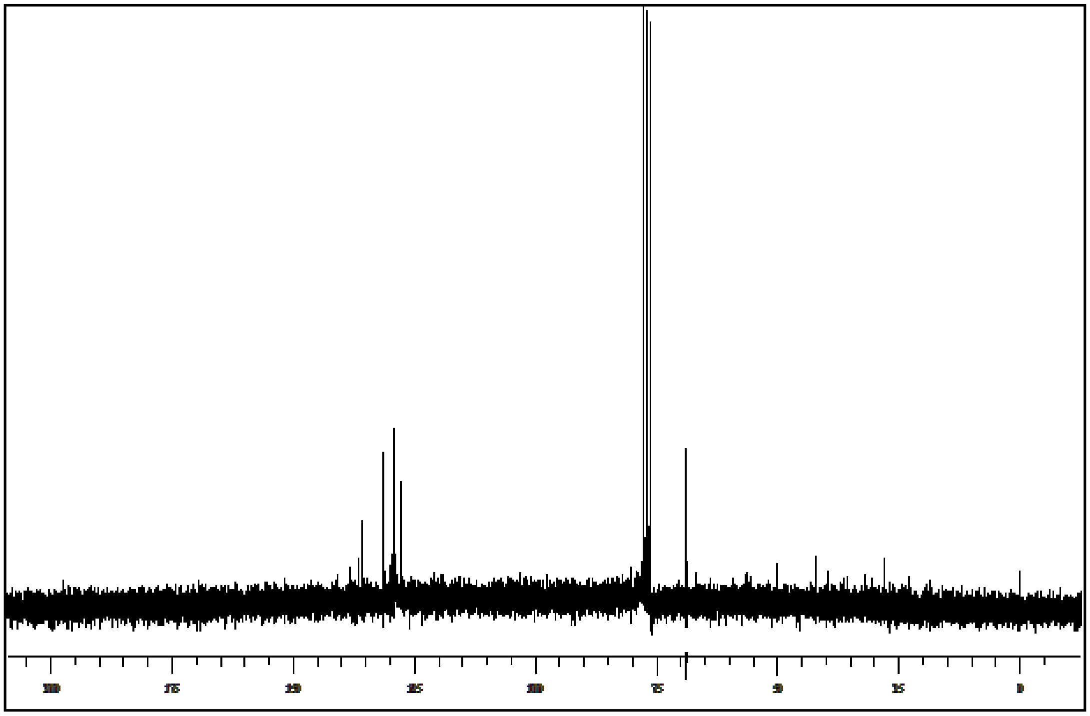
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of ***Se*-Phenyl *p*-methylselenobenzoate(2e).**



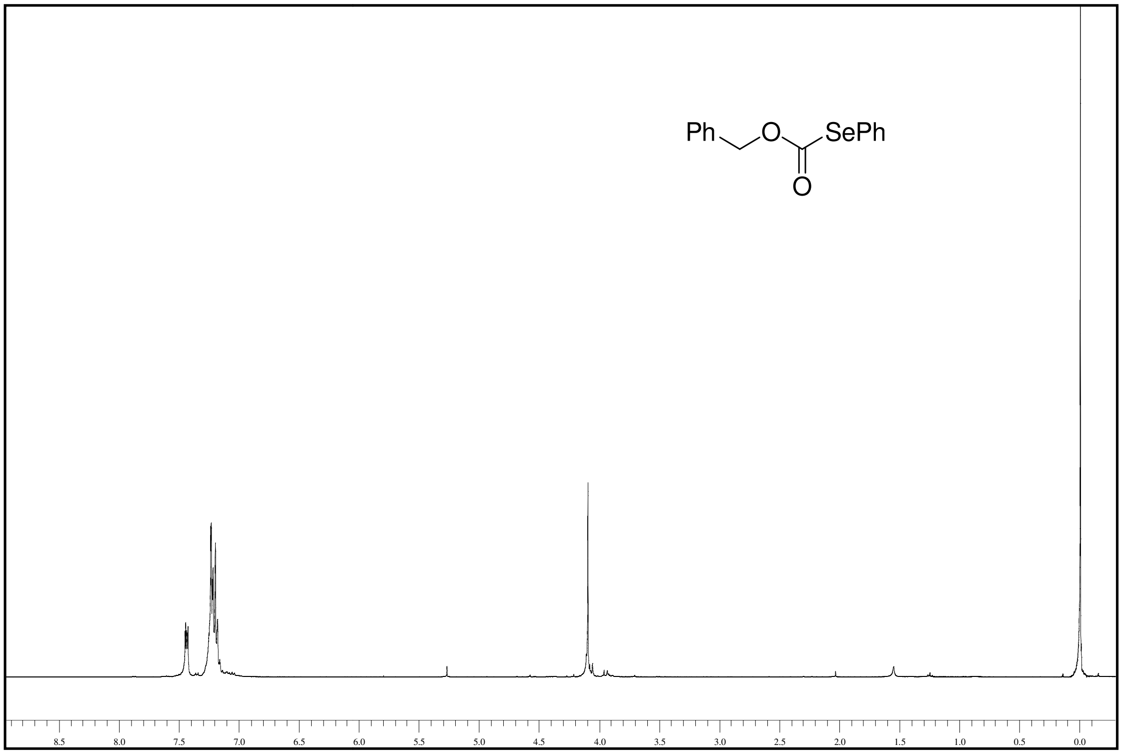
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of ***Se*-Phenyl *p*-methylselenobenzoate(2e).**



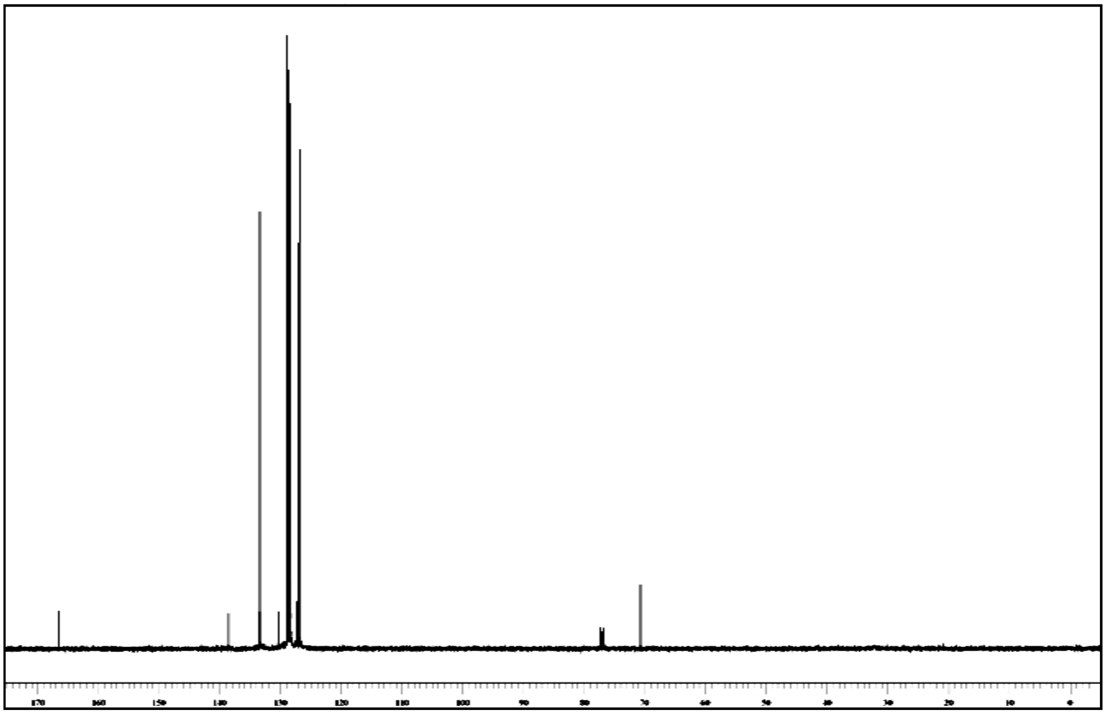
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of ***Se*-Phenyl ethaneselenoate (2f.)**



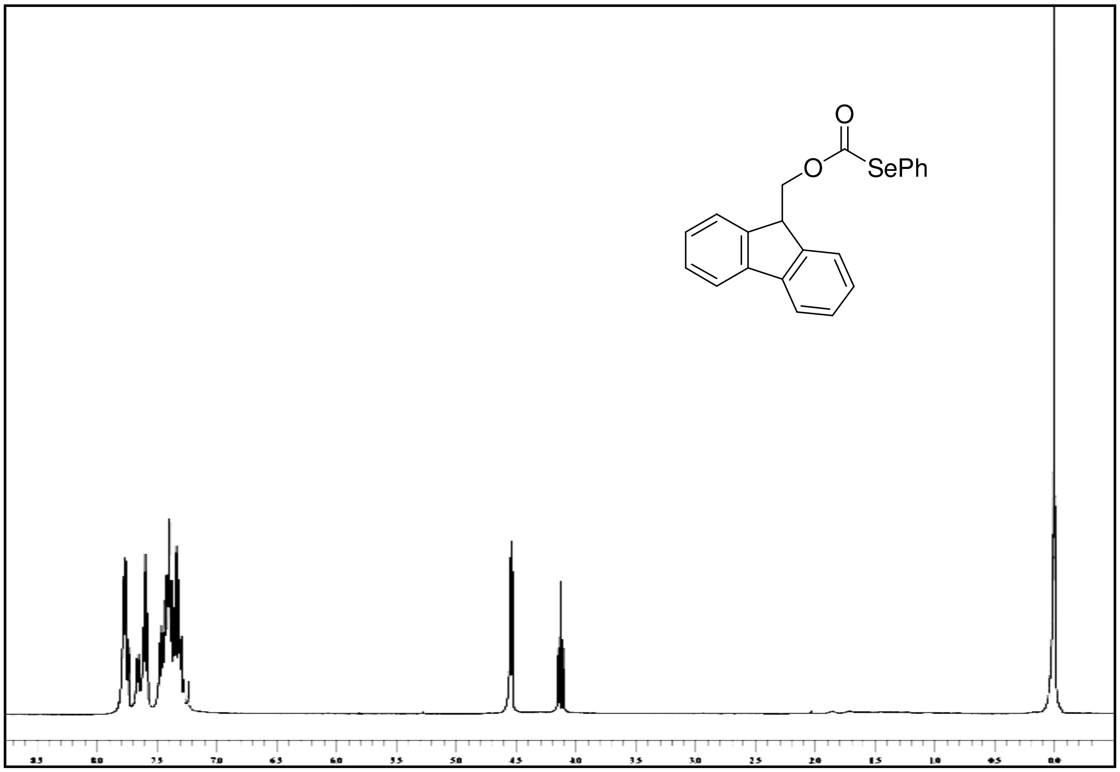
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of ***Se*-Phenyl ethaneselenoate (2f).**



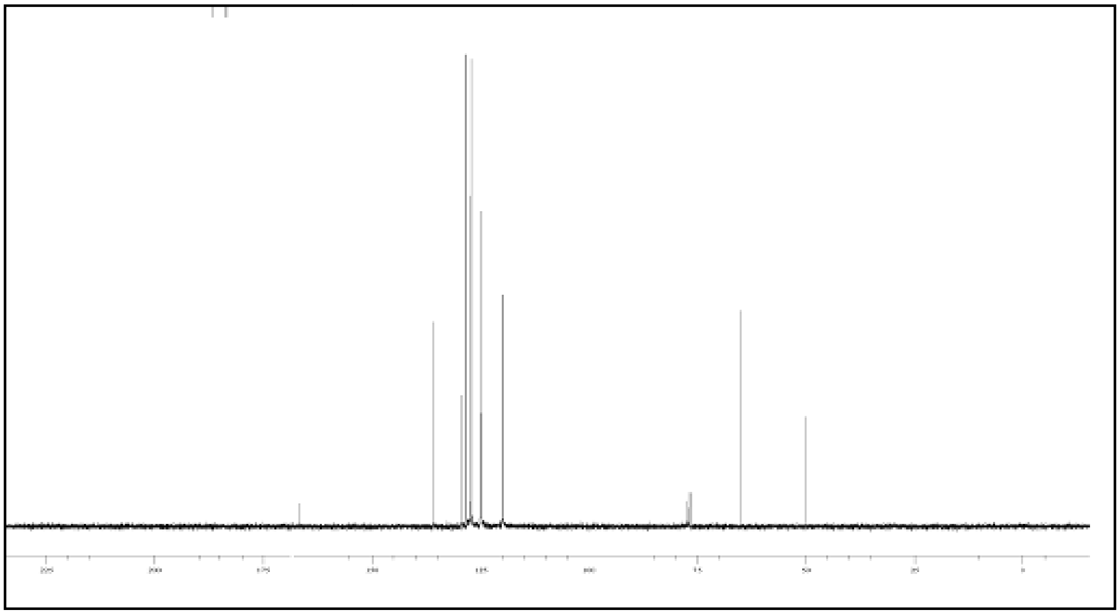
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of ***O*-benzyl *Se*-phenyl carbonoselenoate (2h).**



^{13}C NMR (100 MHz, CDCl$_3$) spectrum of ***O*-benzyl *Se*-phenyl carbonoselenoate (2h).**

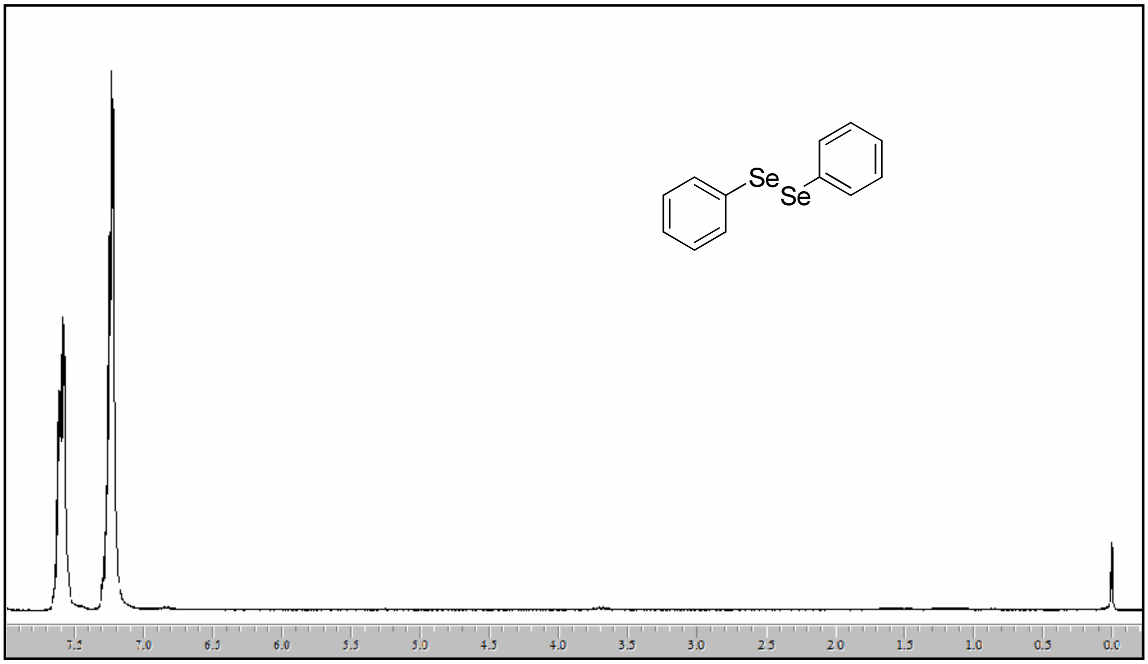


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **(9H-fluoren-9-yl) methyl *Se*-phenyl carbonoselenoate (2l).**

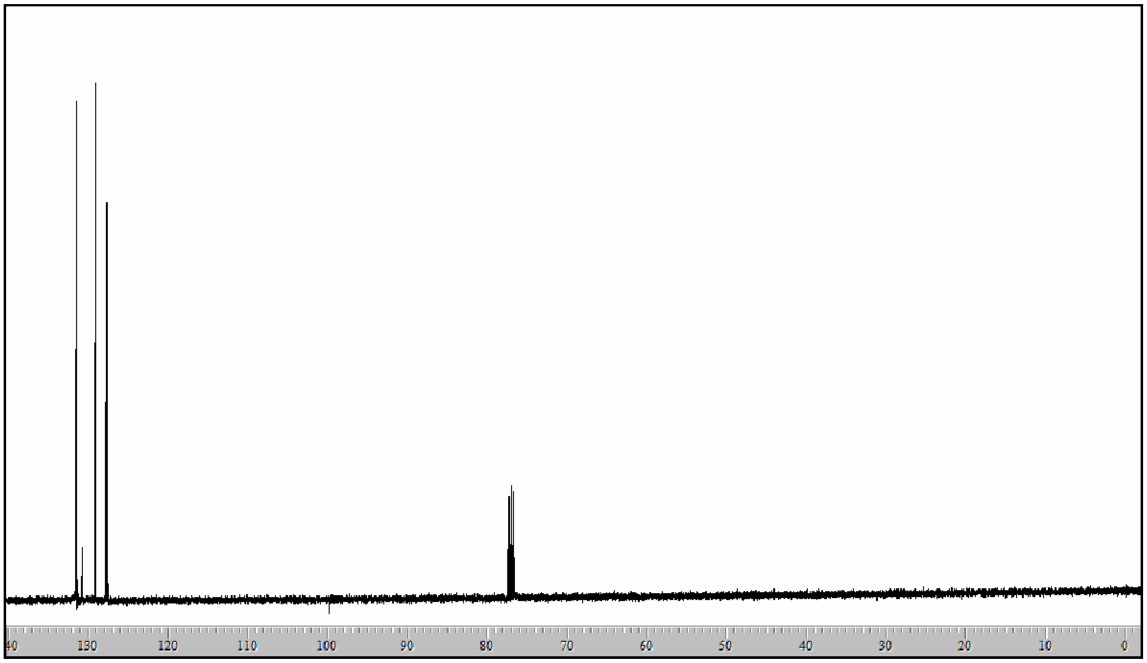


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **(9H-fluoren-9-yl) methyl *Se*-phenyl carbonoselenoate (2l).**

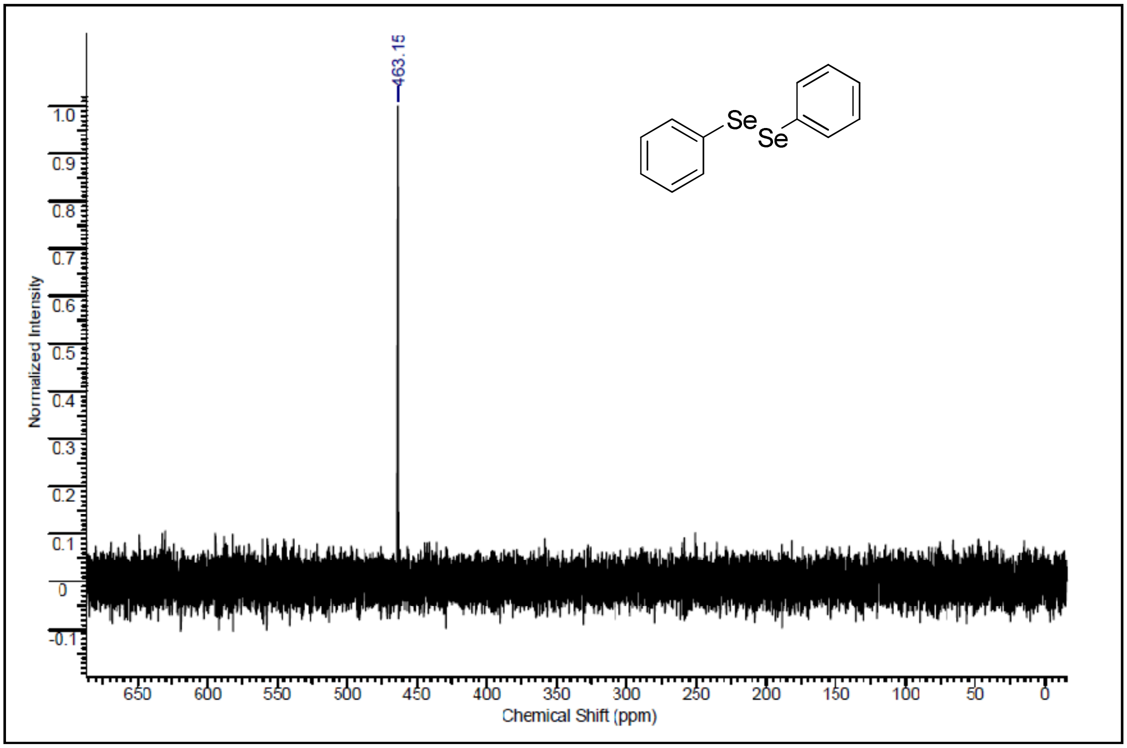
8.3 Selected spectra of diselenides and direllurides



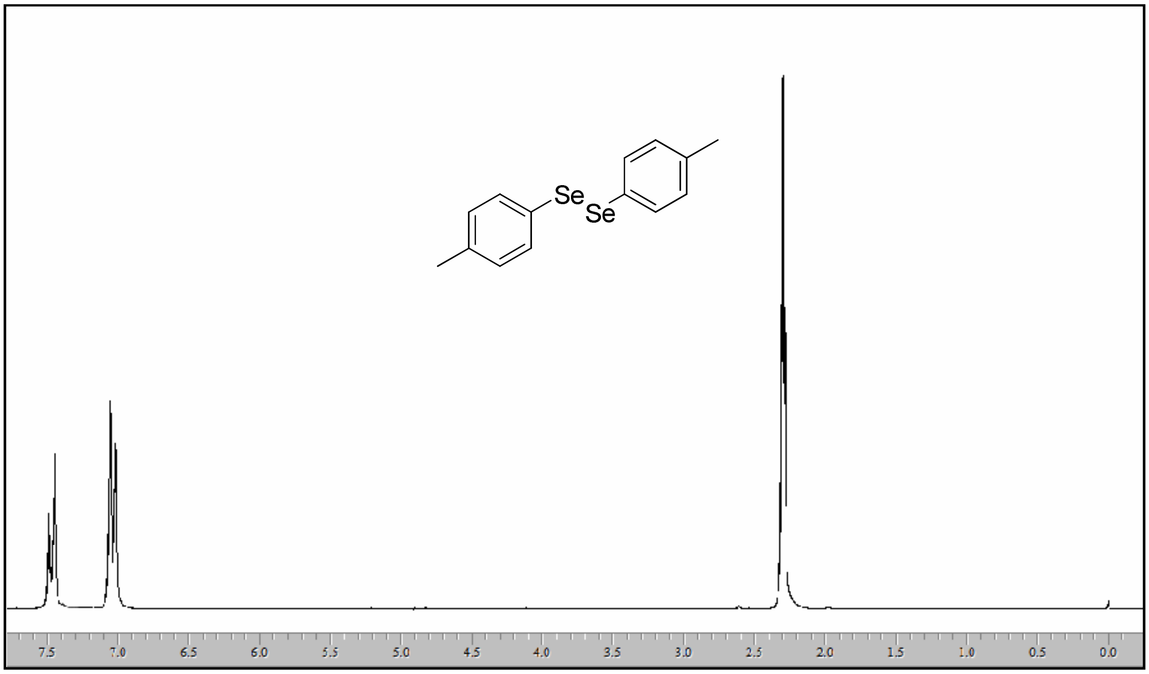
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **1, 2-diphenyldiselenide (3a).**



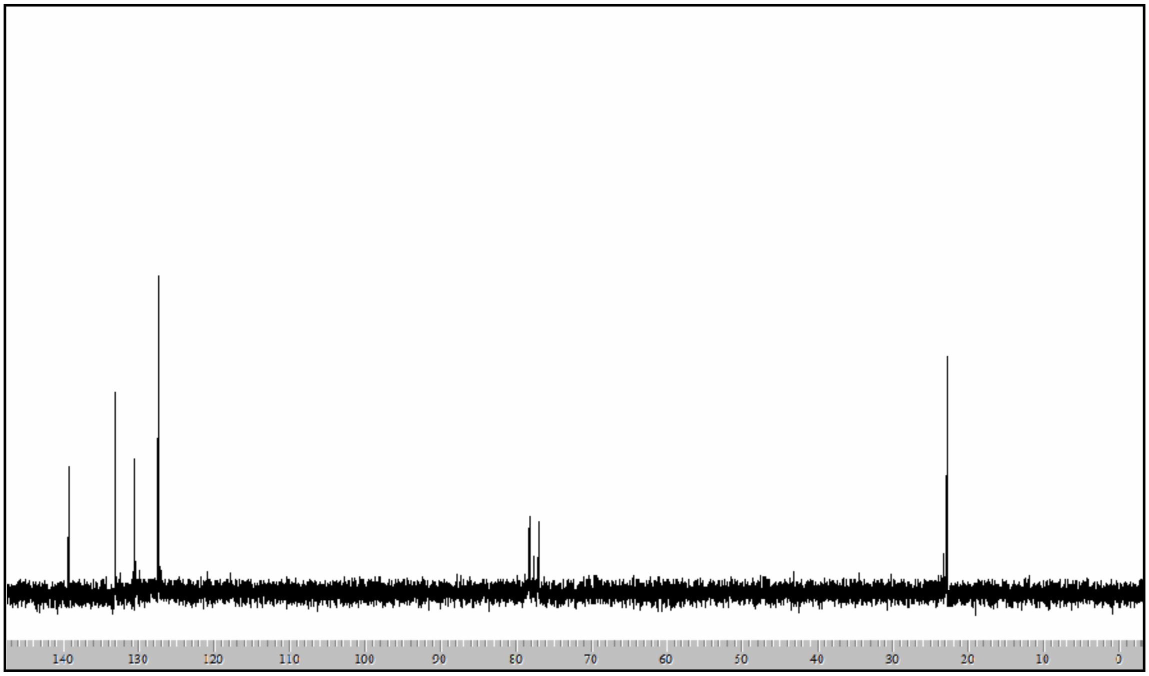
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **1, 2-diphenyldiselenide (3a).**



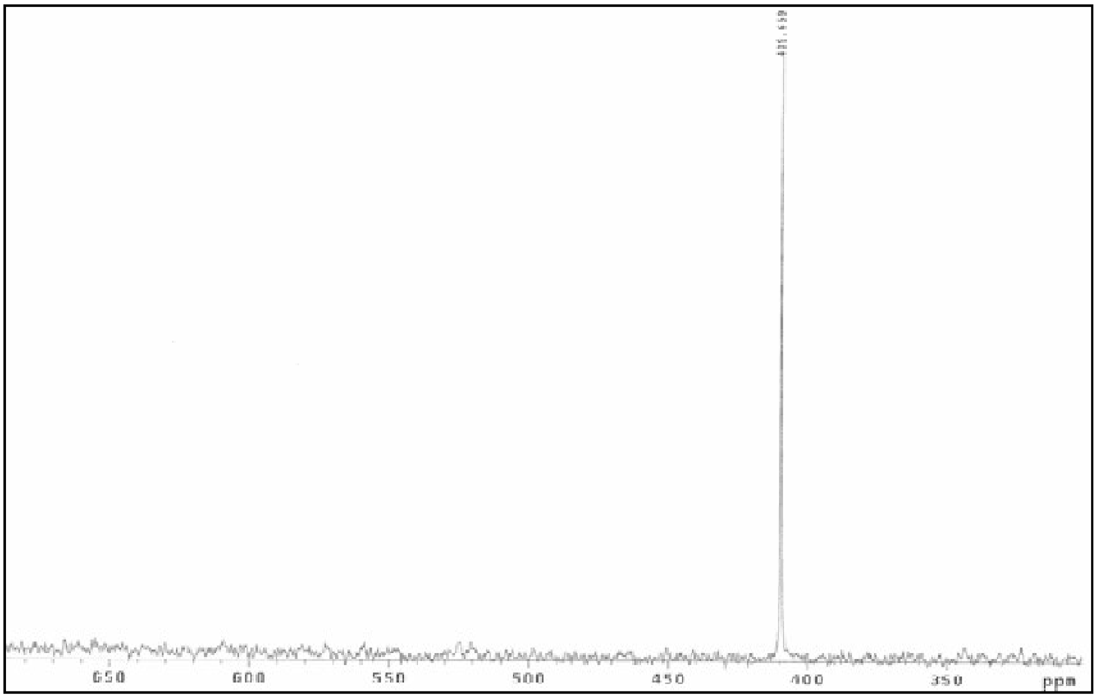
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **1, 2-diphenyldiselenide (3a).**



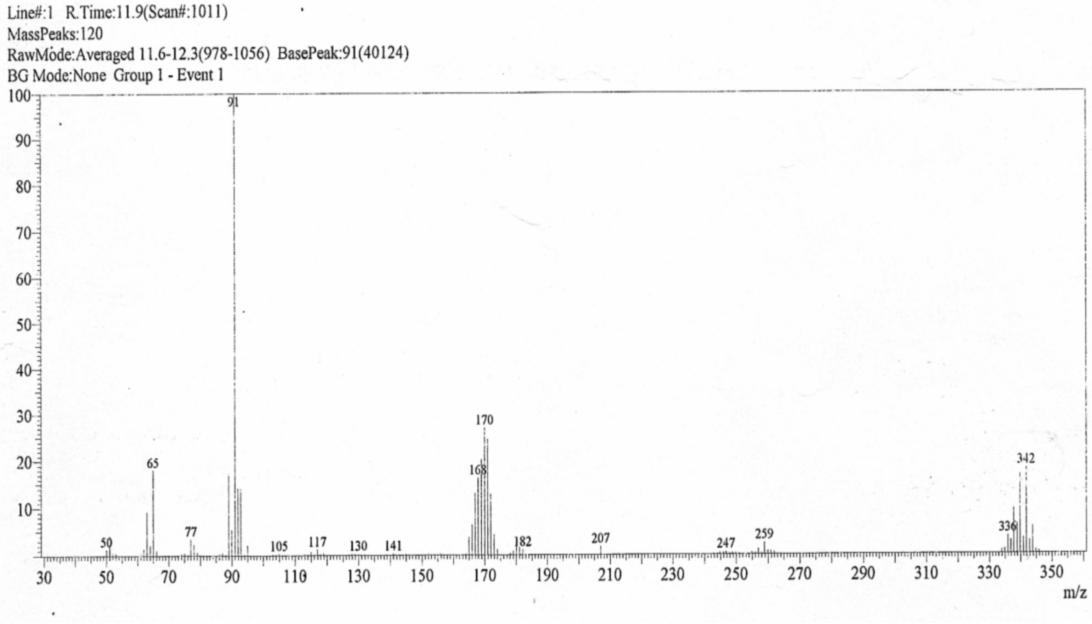
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-dip-tolyldiselenide (3b).**



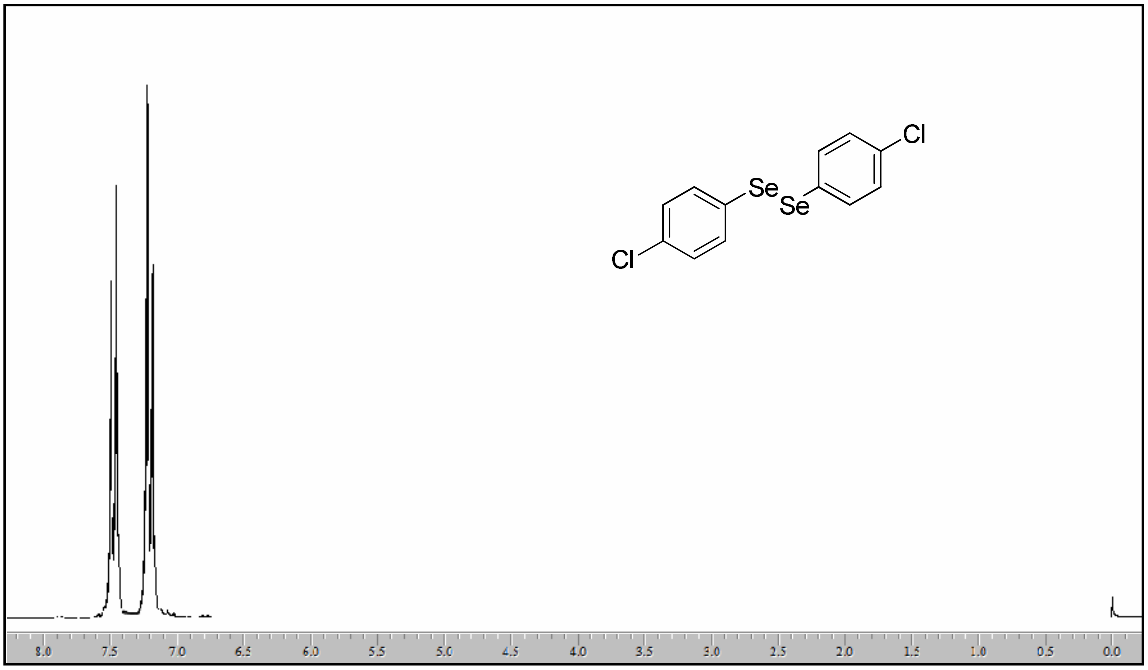
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-dip-tolyldiselenide (3b).**



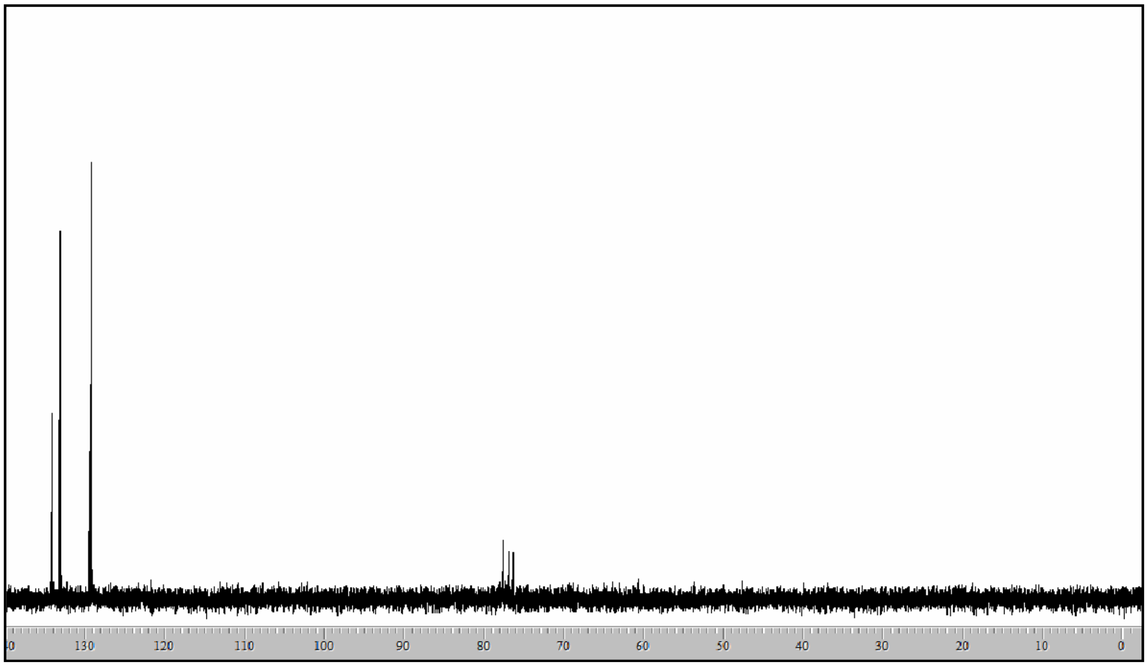
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **1,2-dip-tolyldiselenide (3b).**



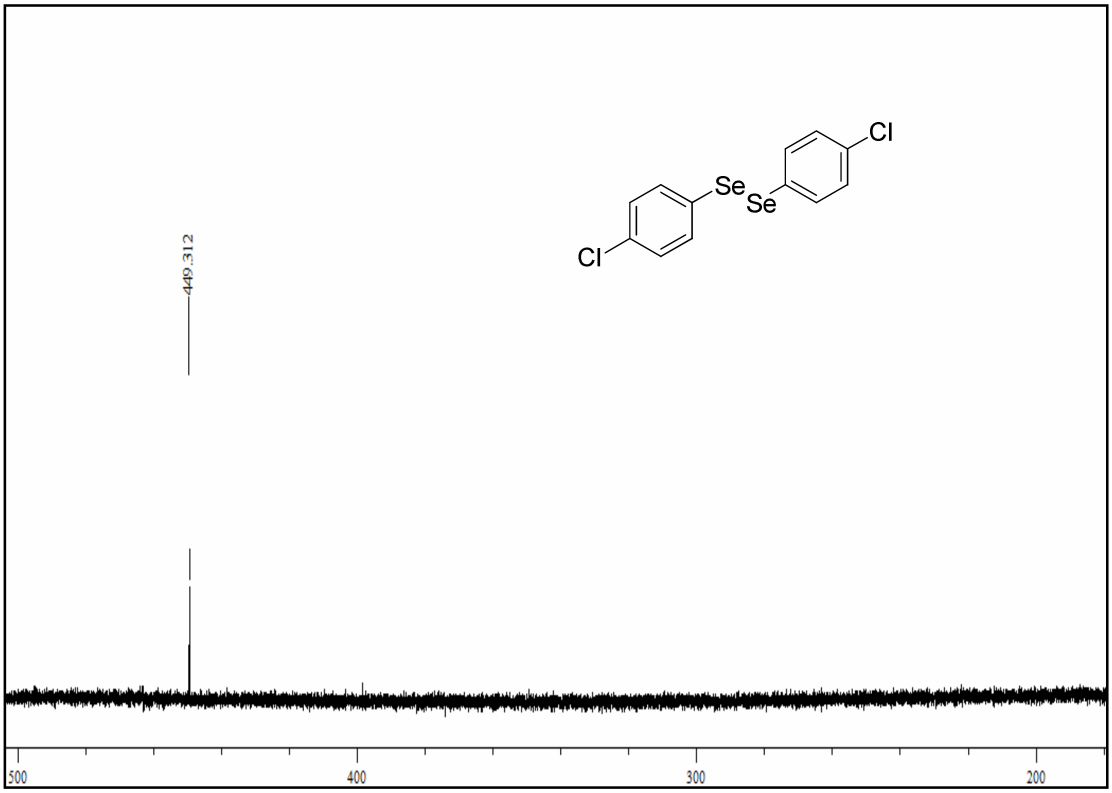
LCMS specta of **1,2-dip-tolyldiselenide (3b).**



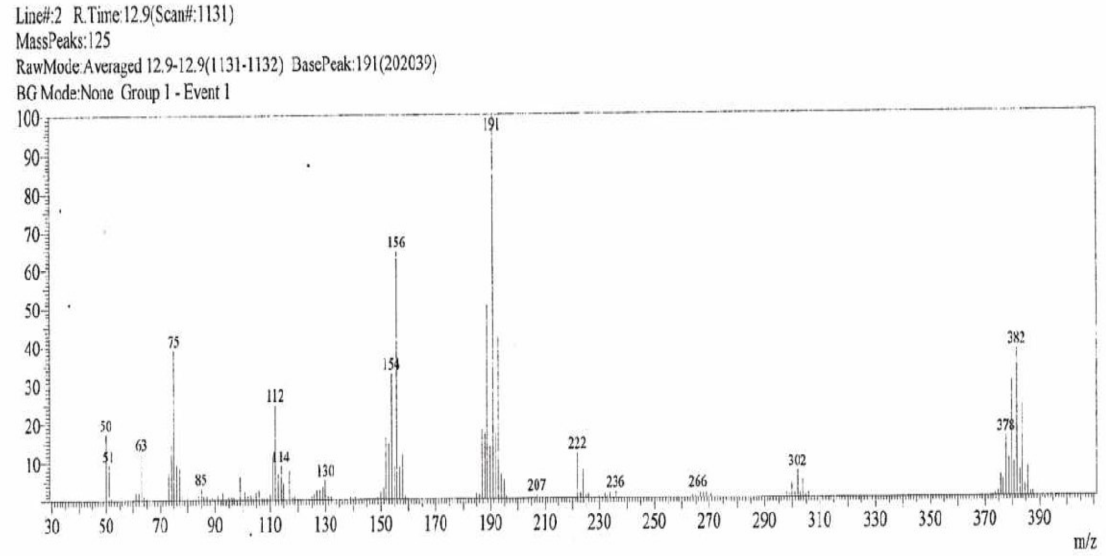
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **1,2-bis(4-chlorophenyl)diselenide (3d).**



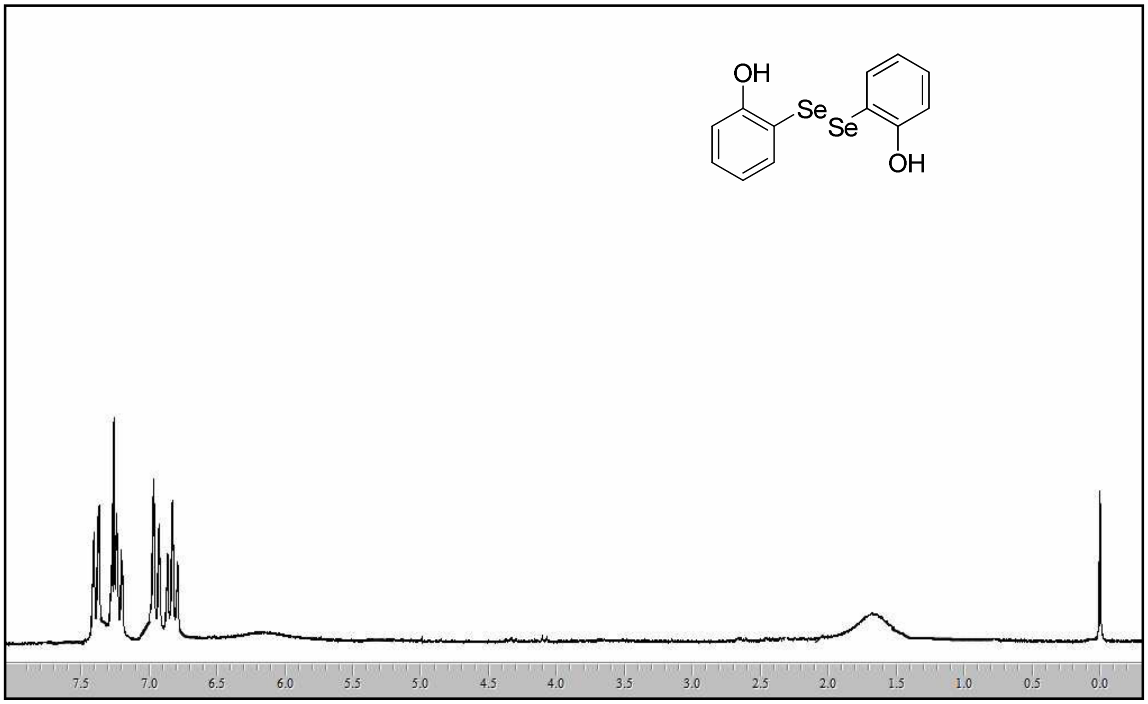
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **1,2-bis(4-chlorophenyl)diselenide (3d).**



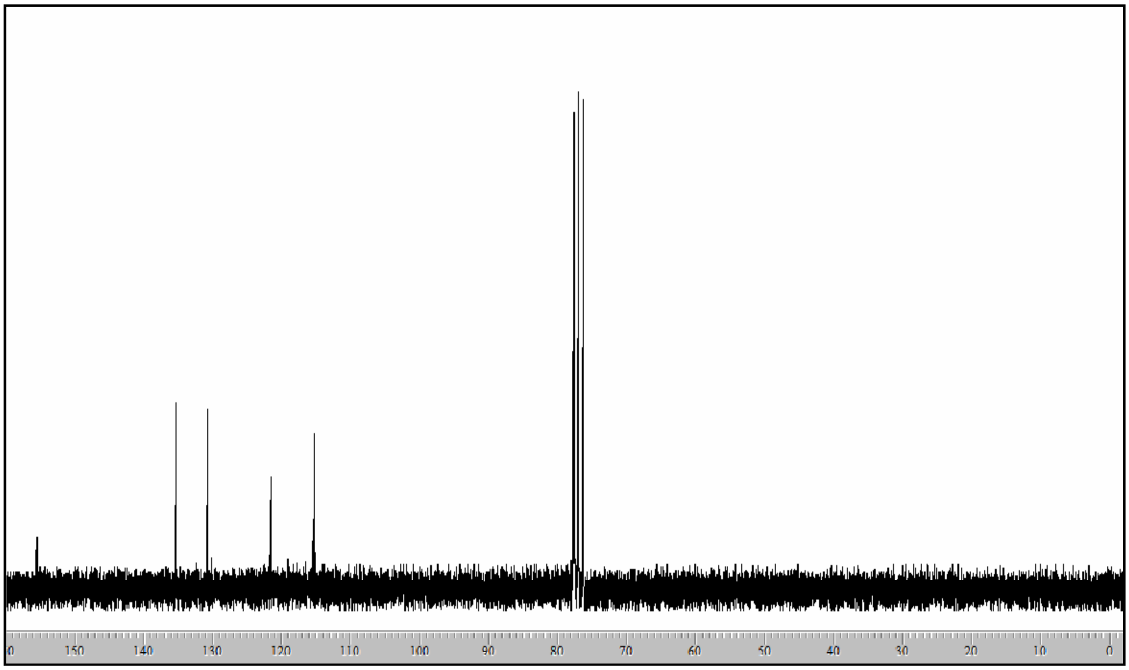
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **1,2-bis(4-chlorophenyl)diselenide (3d).**



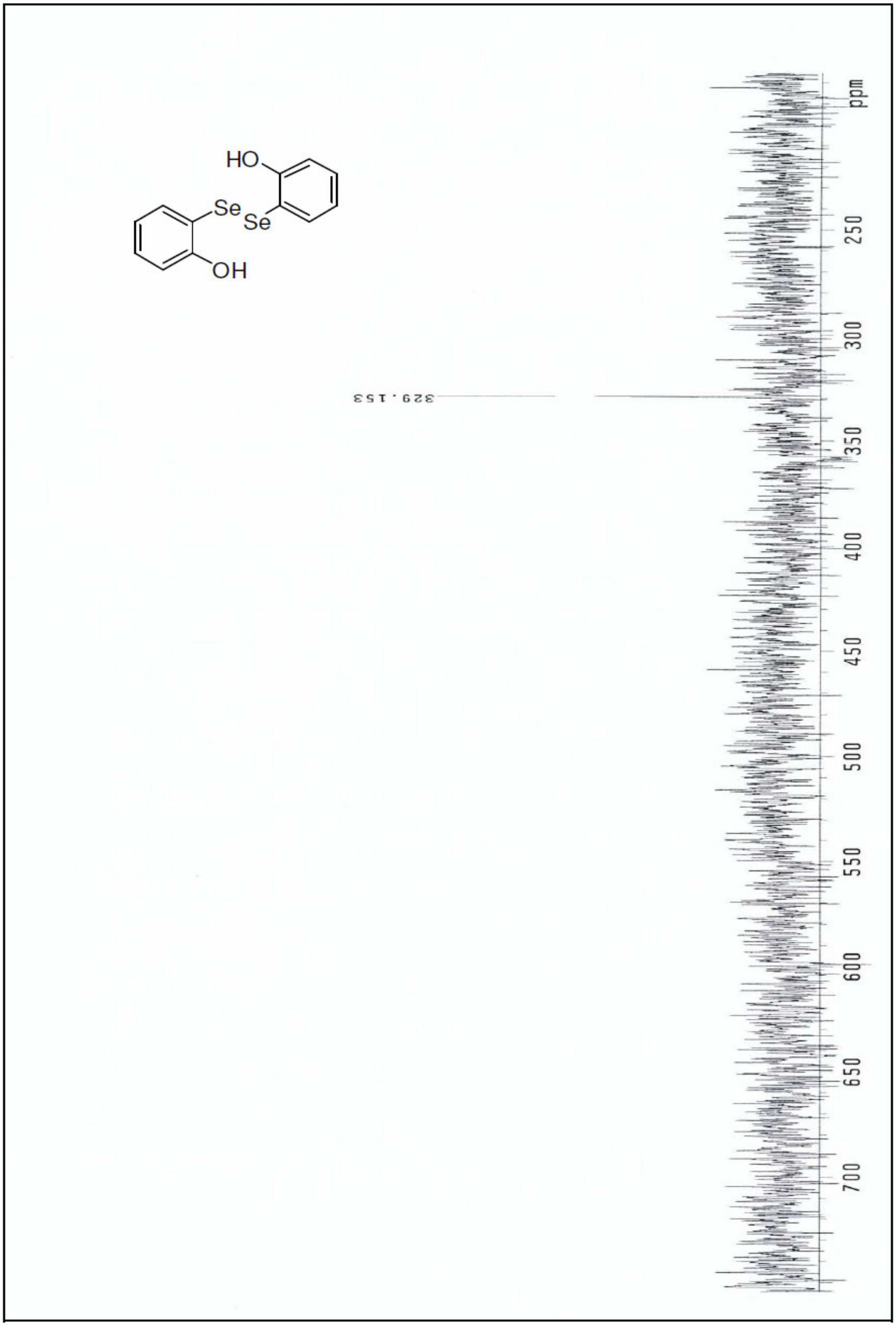
LCMS specta of **1,2-bis(4-chlorophenyl)diselenide (3d).**



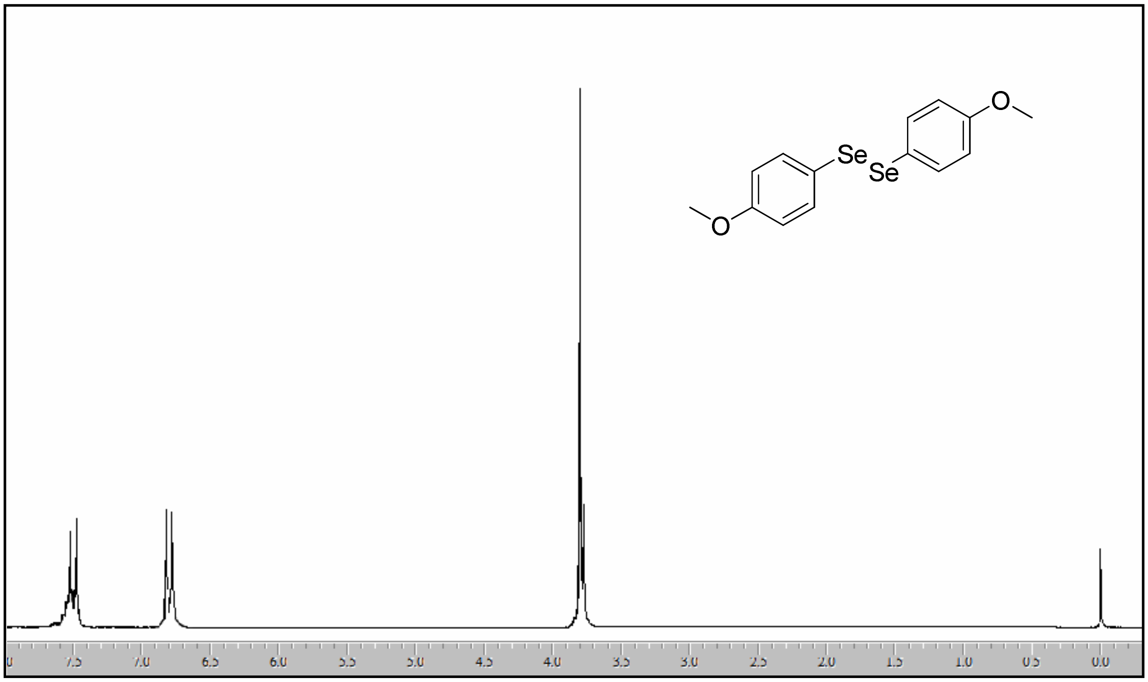
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2,2'-diselenidediyldiphenol (3f).**



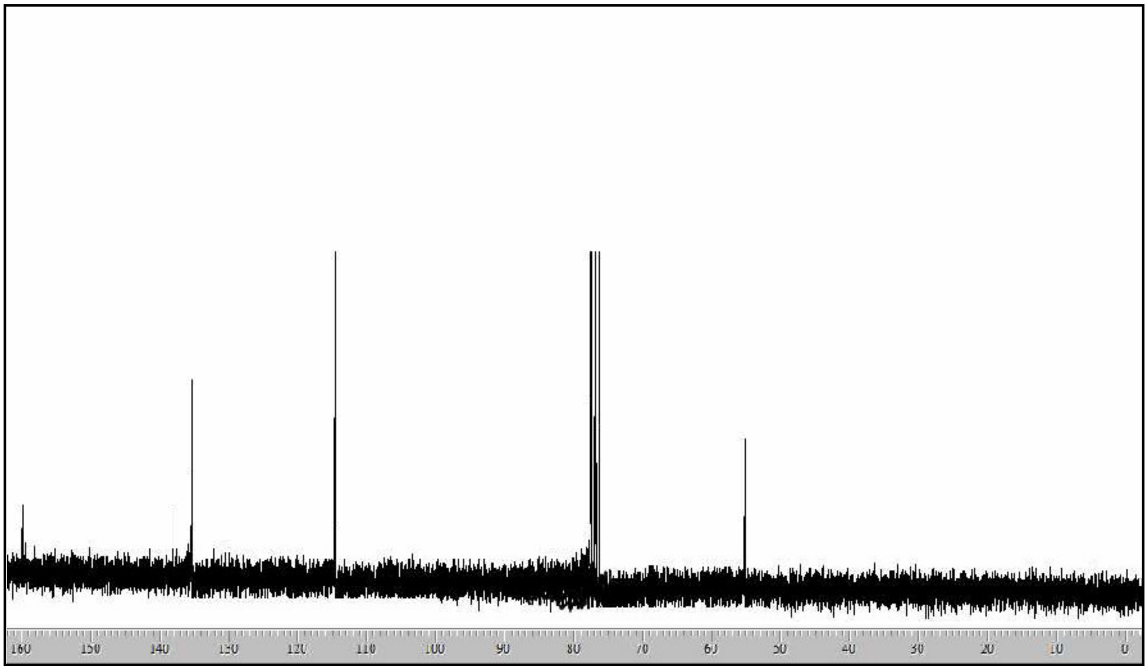
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **2,2'-diselenidediyldiphenol (3f).**



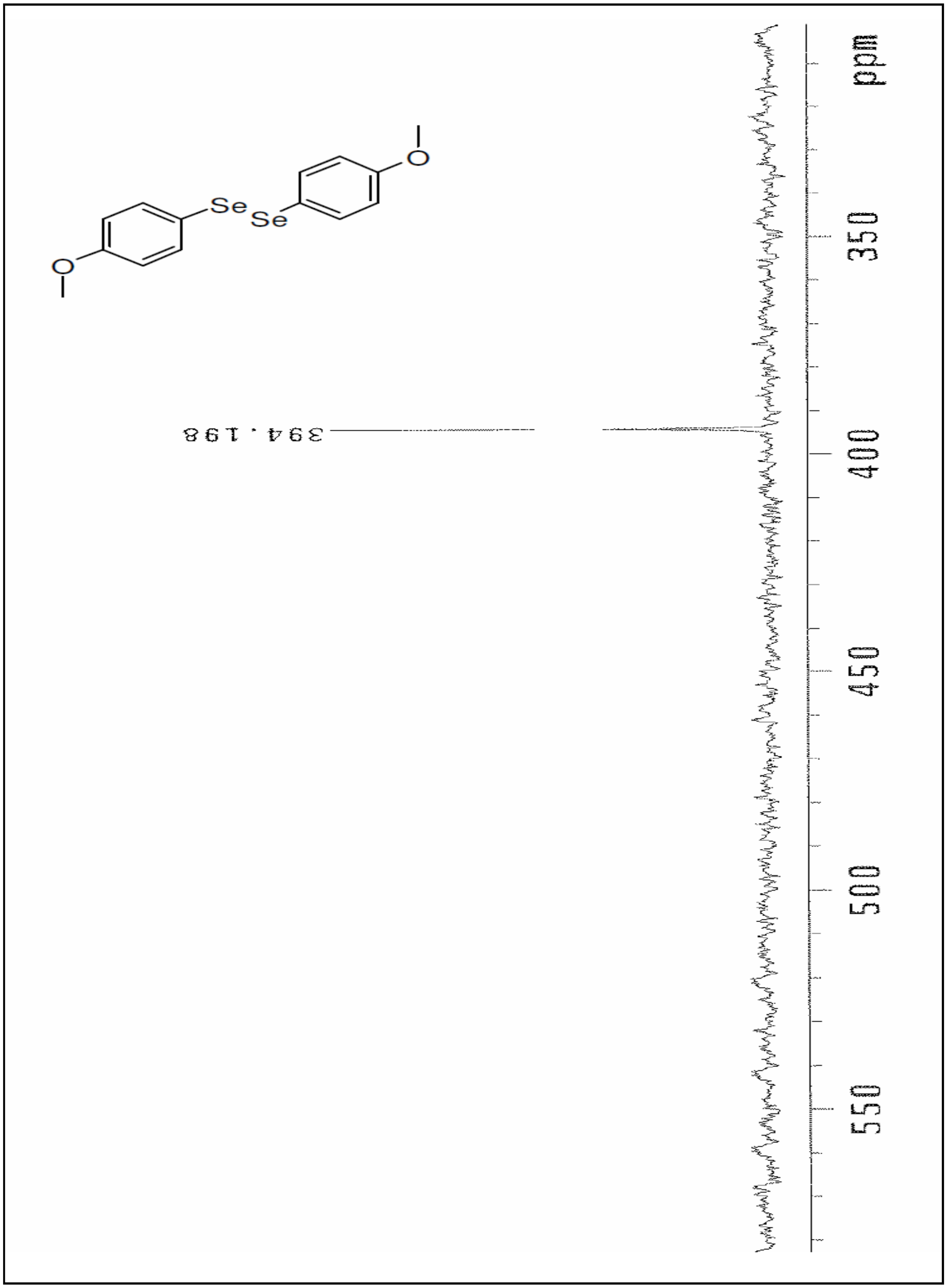
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **2,2'-diselenidediyldiphenol (3f).**



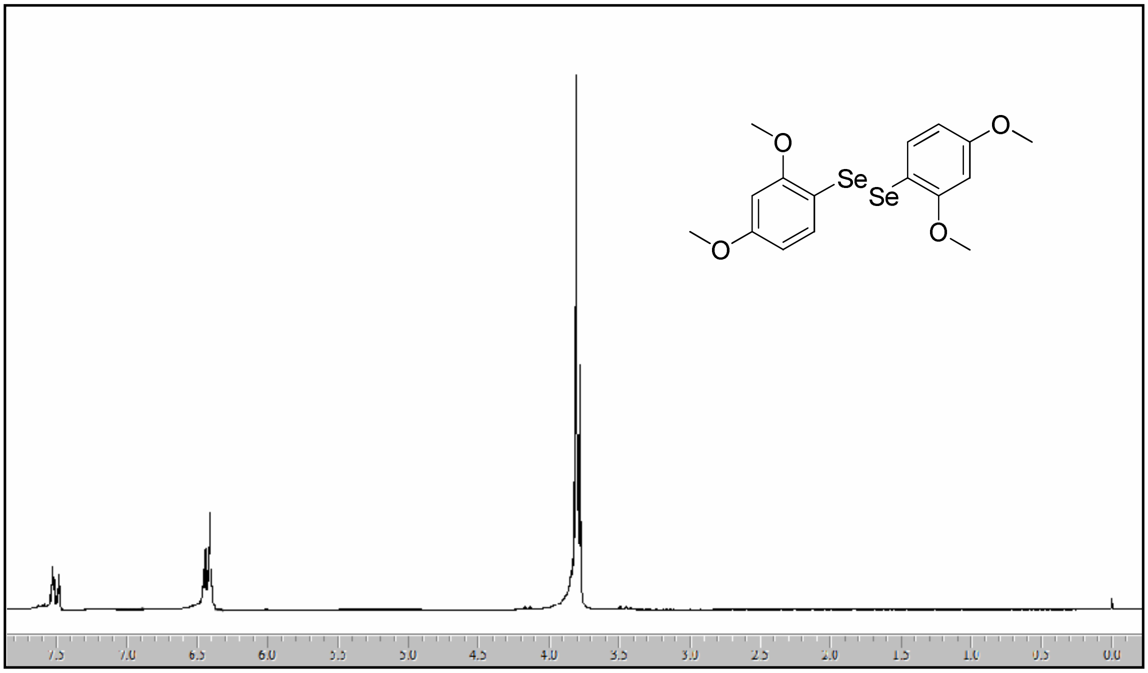
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-bis(4-methoxyphenyl)diselenide (3h).**



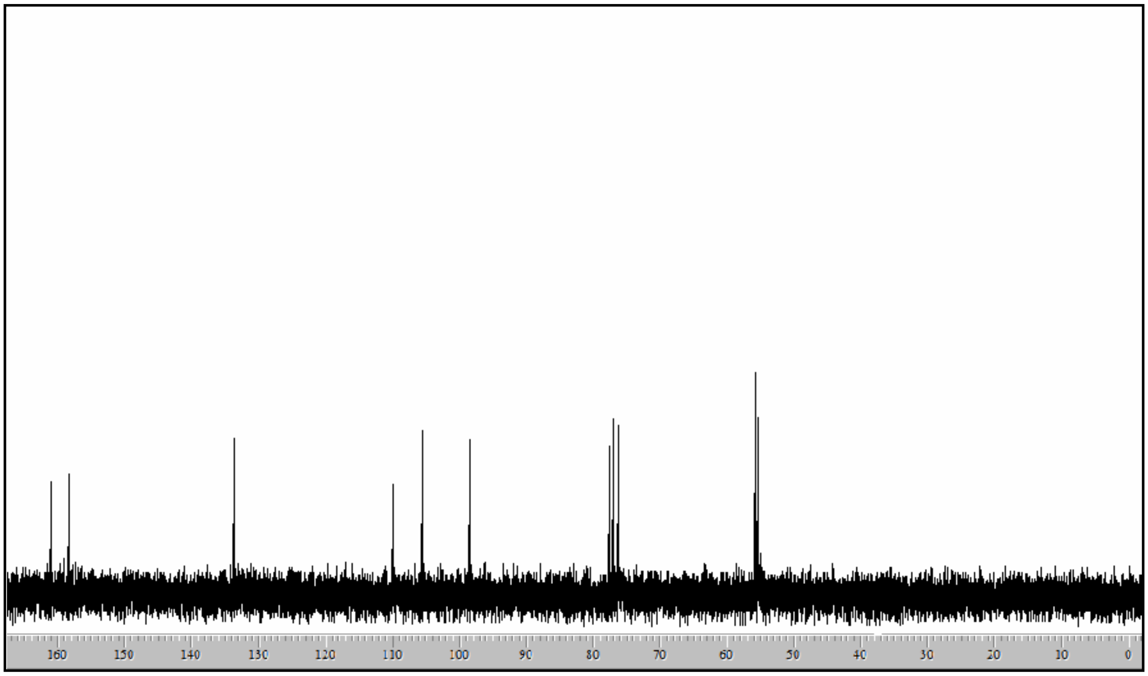
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-bis(4-methoxyphenyl)diselenide (3h).**



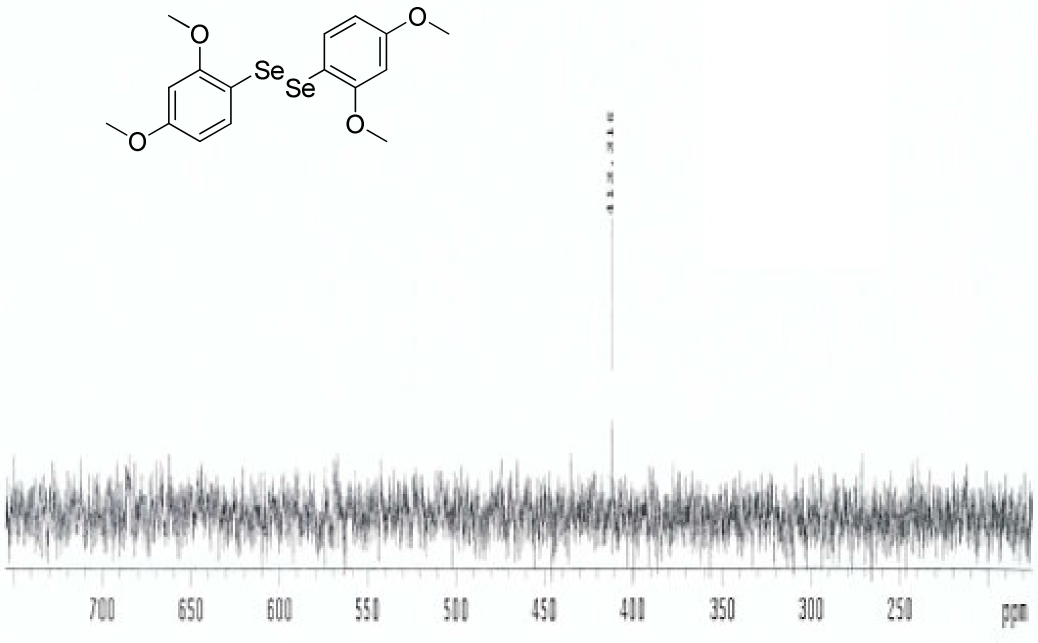
^{77}Se NMR (76.28 MHz, CDCl$_3$) spectrum of **1,2-bis(4-methoxyphenyl)diselenide (3h).**



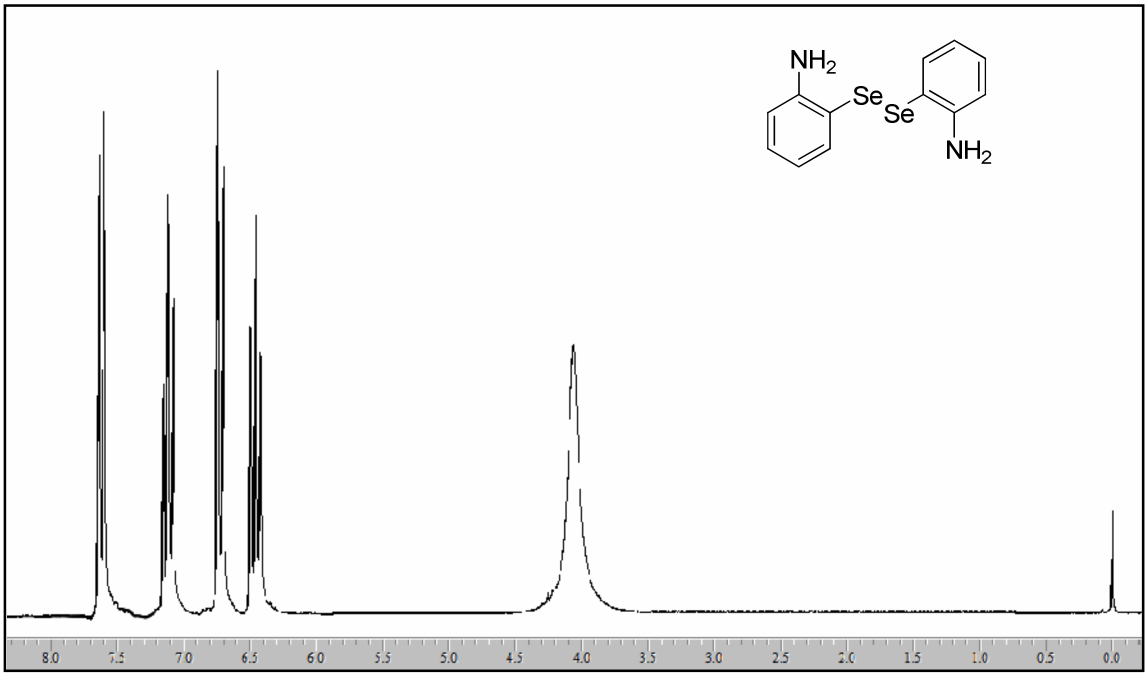
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-bis(2,4-dimethoxyphenyl)diselenide (3k).**



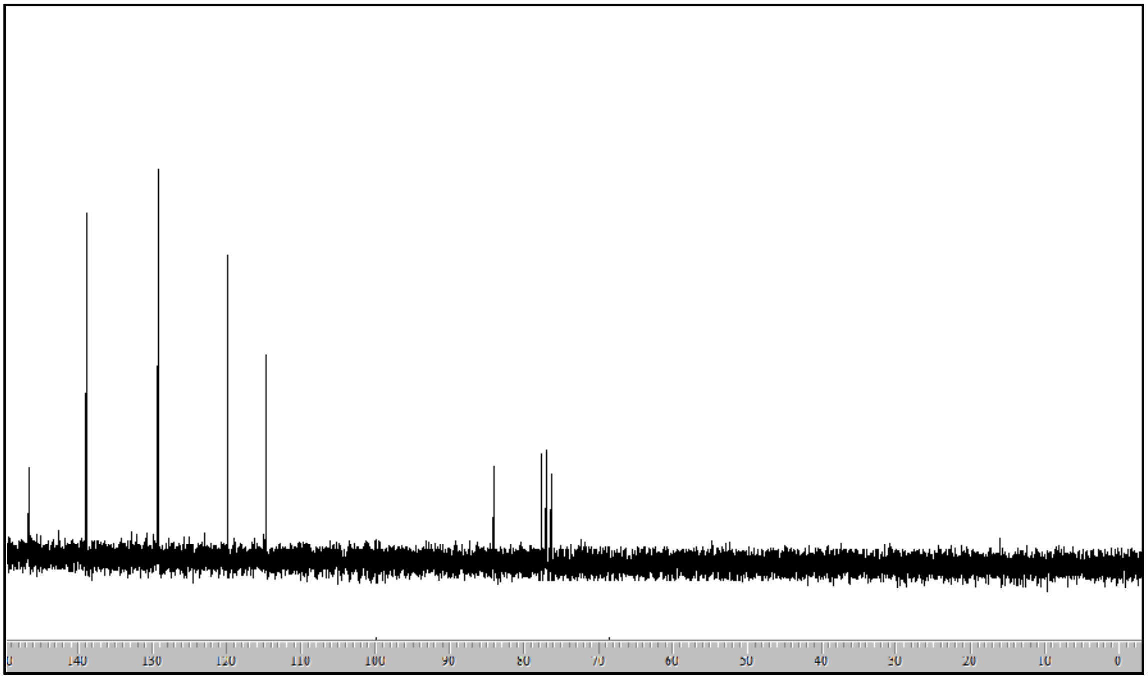
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-bis(2,4-dimethoxyphenyl)diselenide (3k).**



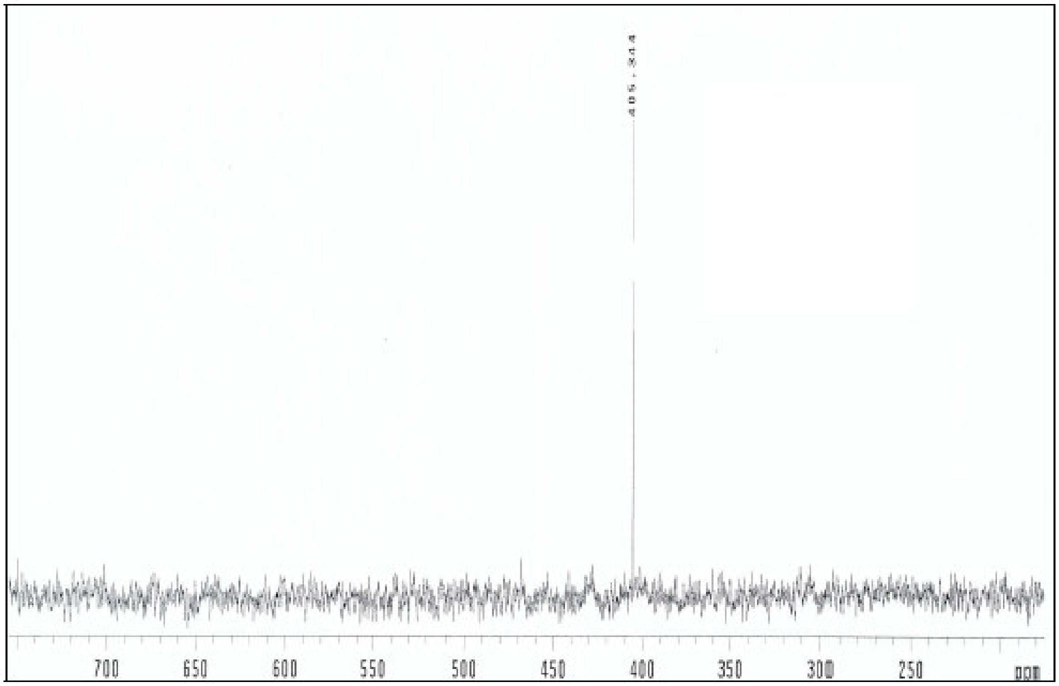
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **1,2-bis(2,4-dimethoxyphenyl)diselenide (3k).**



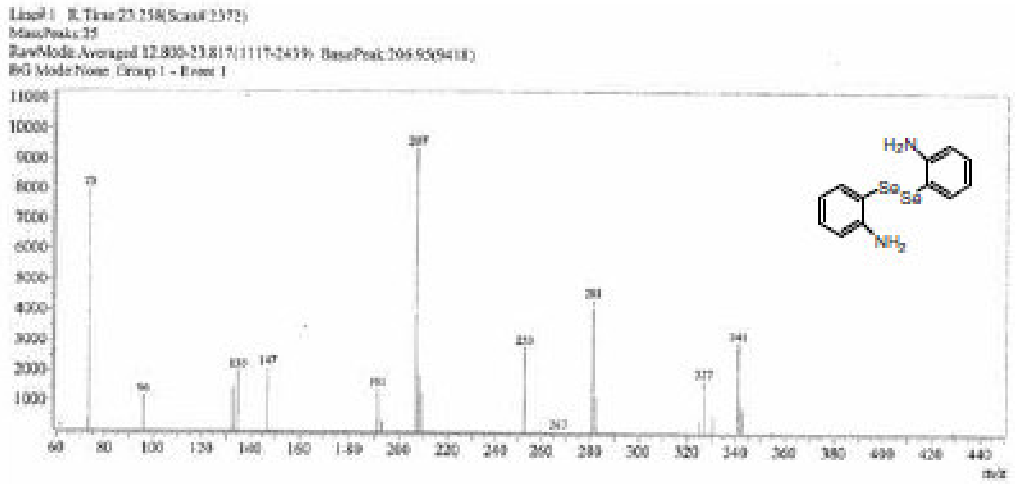
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2,2'-diselenidediyldianiline (3l).**



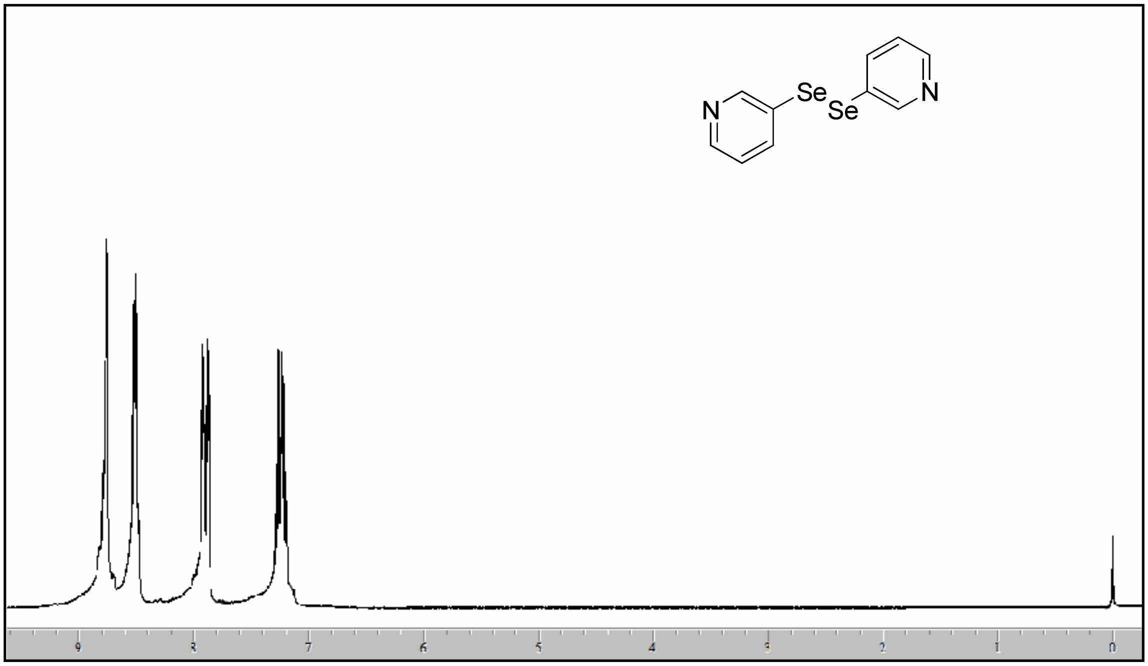
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **2,2'-diselenidediyldianiline (3l).**



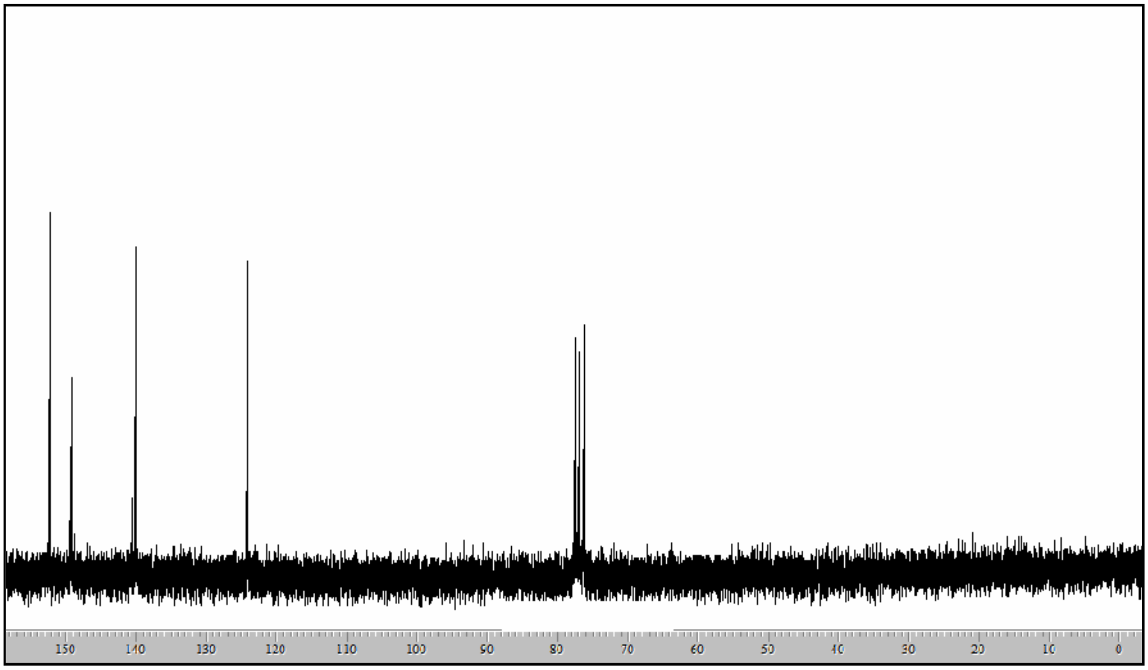
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **2,2'-diselenidediyldianiline (3l).**



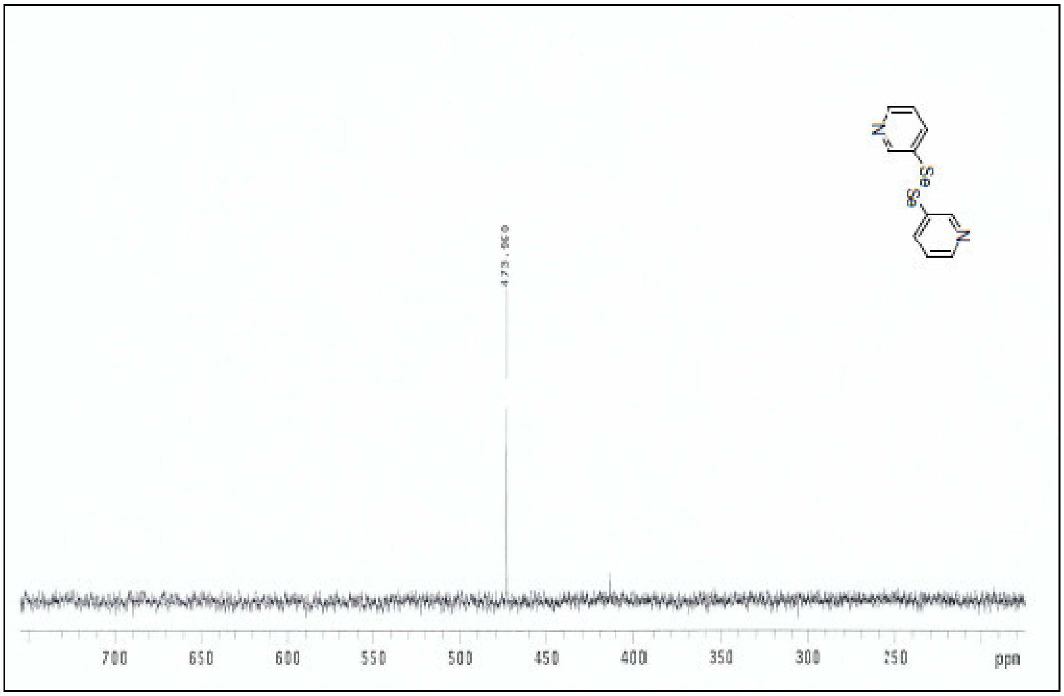
LCMS specta of **2,2'-diselenidediyldianiline (3l).**



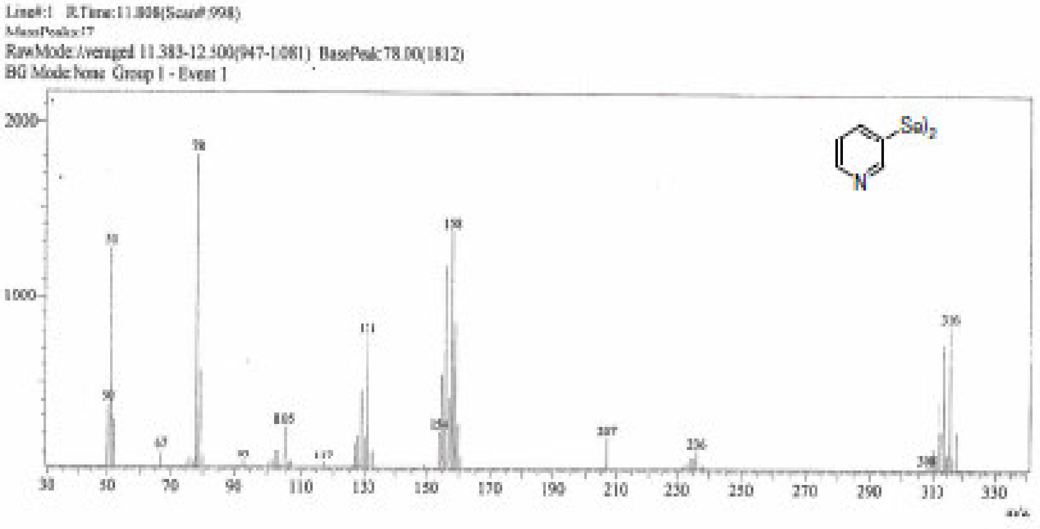
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-di(pyridin-3-yl)diselenide (3m).**



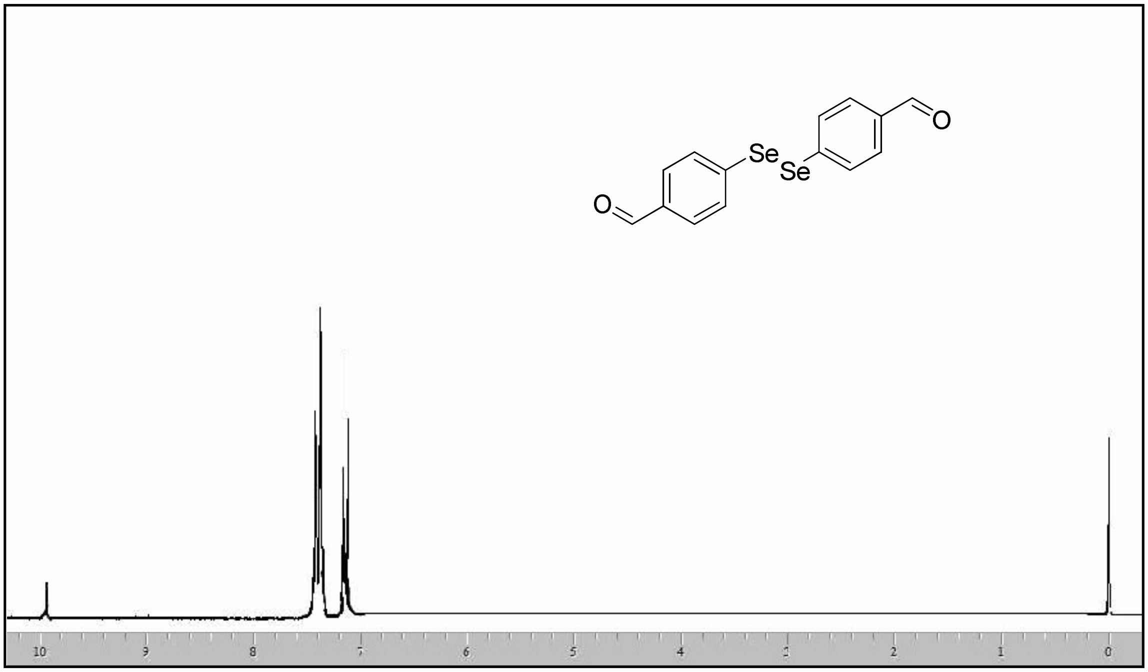
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-di(pyridin-3-yl)diselenide (3m).**



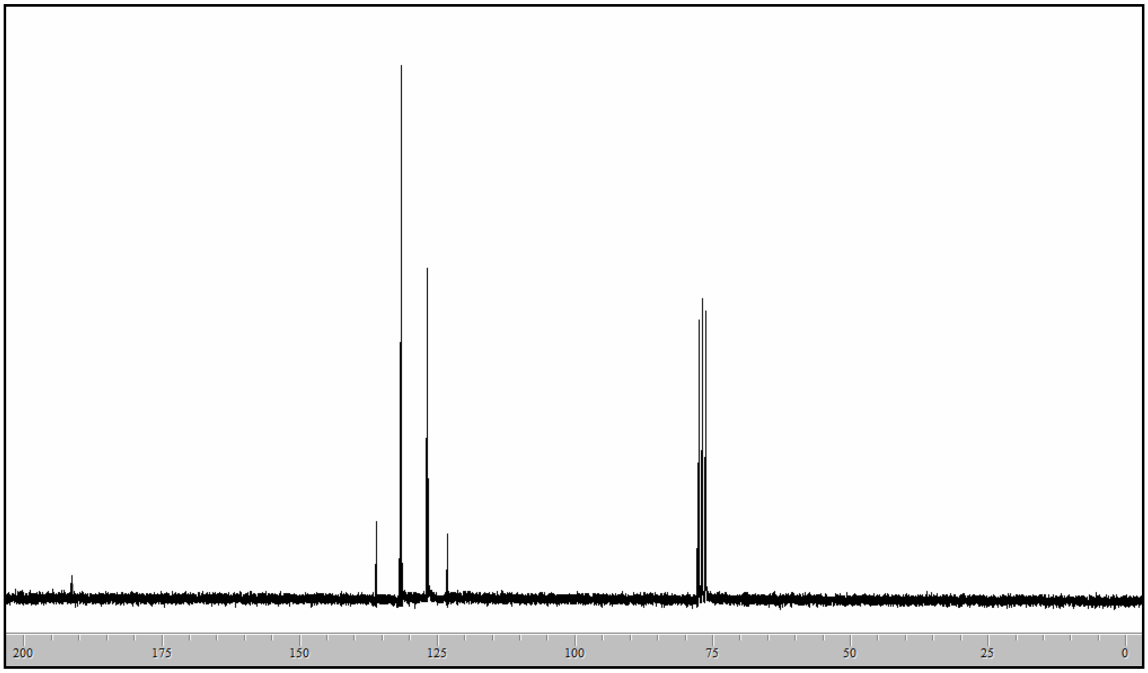
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **1,2-di(pyridin-3-yl)diselenide (3m).**



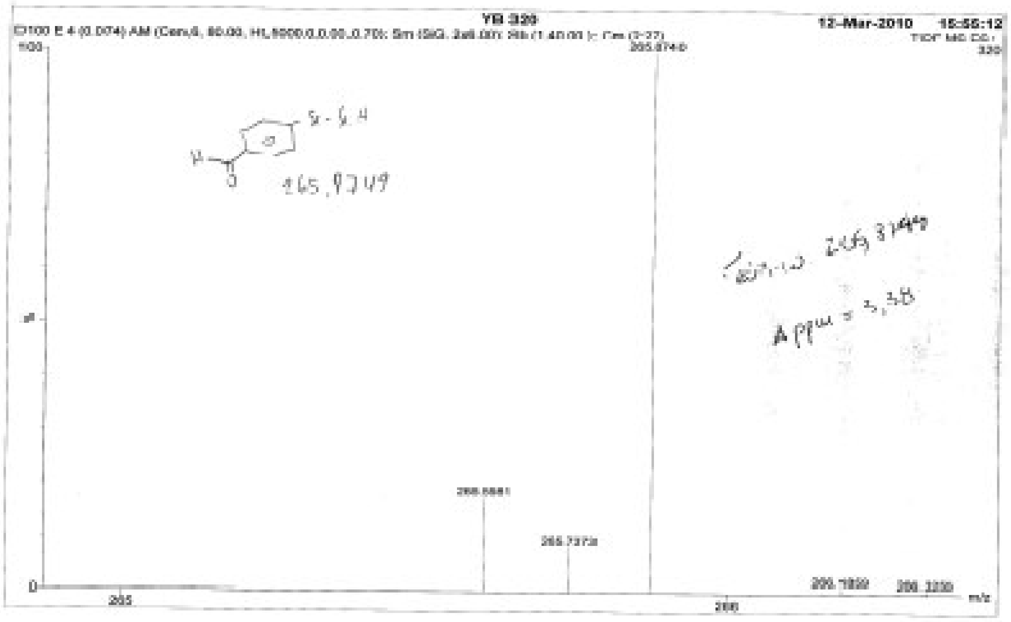
LCMS specta of **1,2-di(pyridin-3-yl)diselenide (3m).**



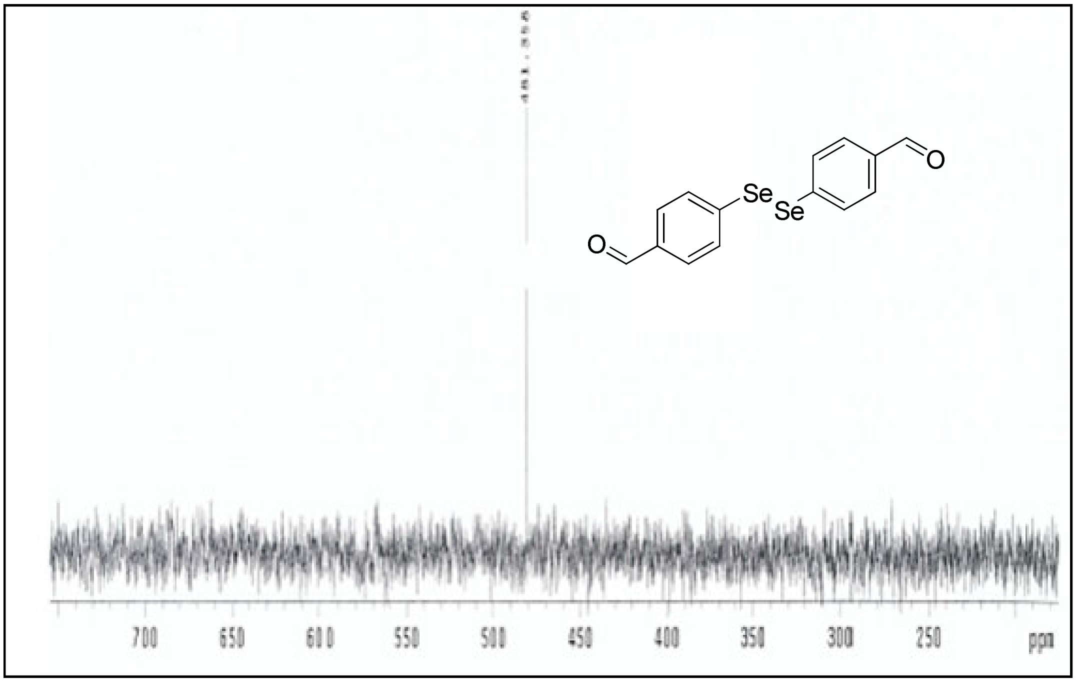
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **4,4'-diselenidediyldibenzaldehyde (3n).**



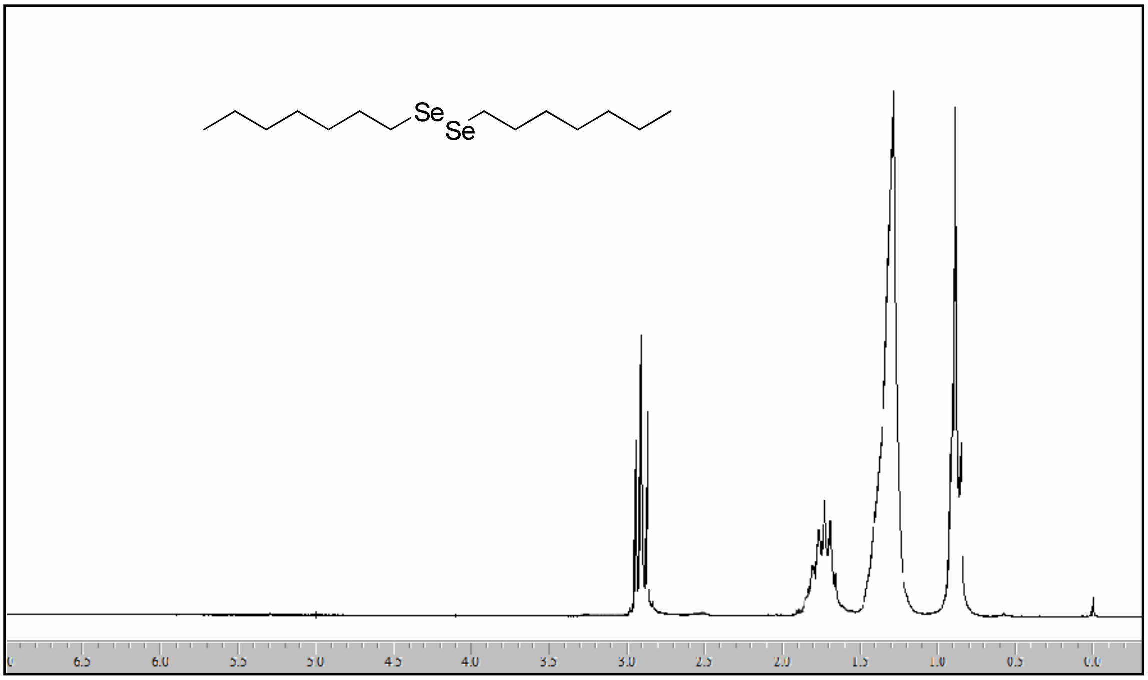
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **4,4'-diselenidediyldibenzaldehyde (3n).**



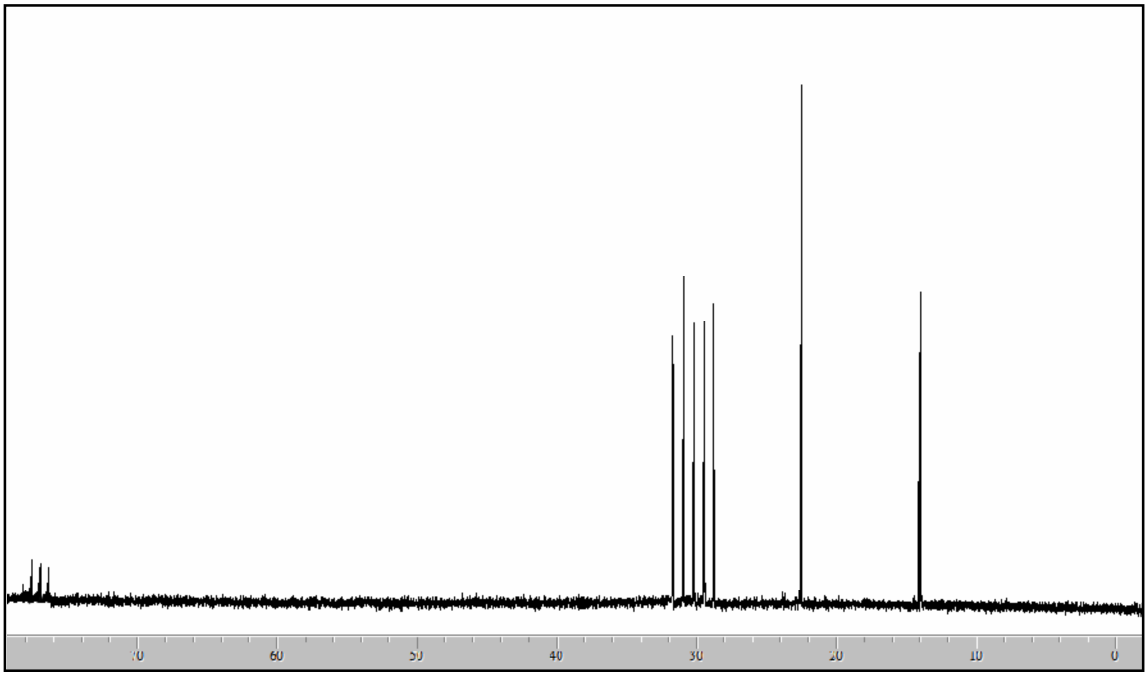
HRMS spectra of of **4,4'-diselenidediyldibenzaldehyde (3n).**



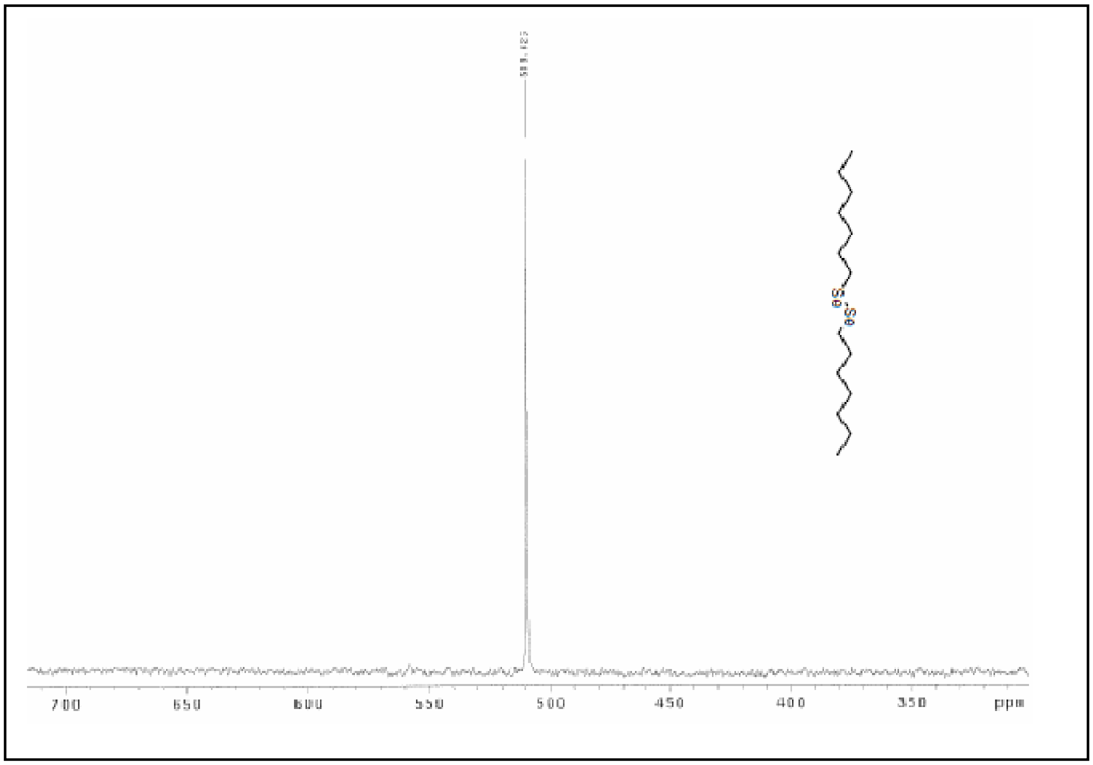
^{77}Se NMR (76.28 MHz, $CDCl_3$) spectrum of **4,4'-diselenidediyldibenzaldehyde (3n).**



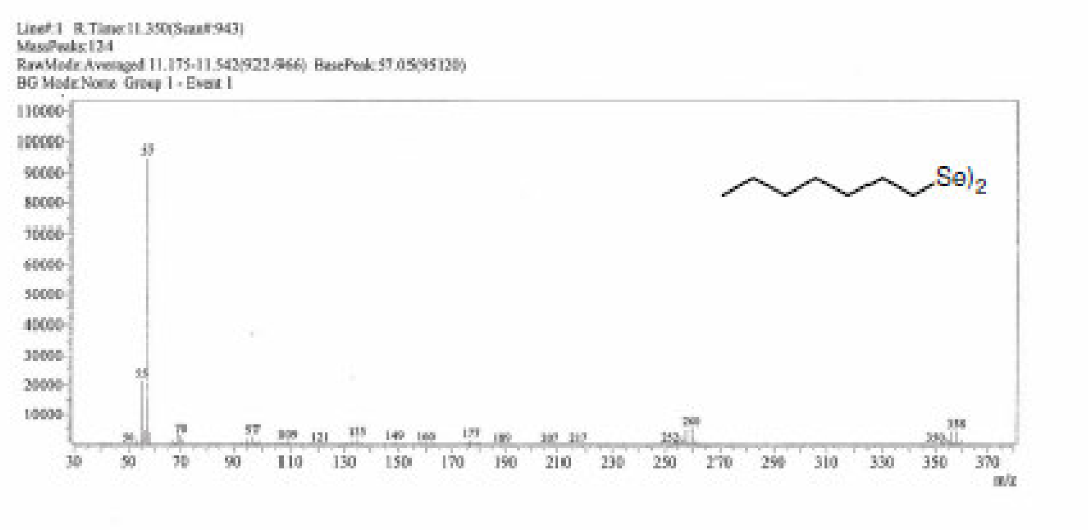
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-diheptyldiselenide(3o).**



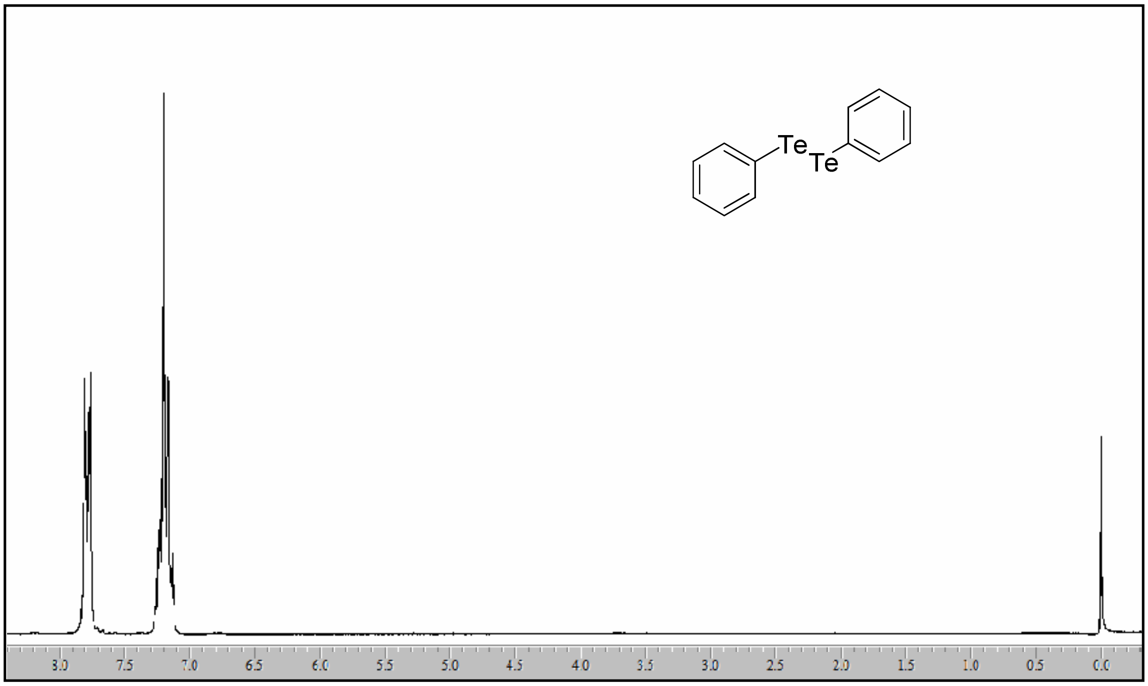
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-diheptyldiselenide(3o).**



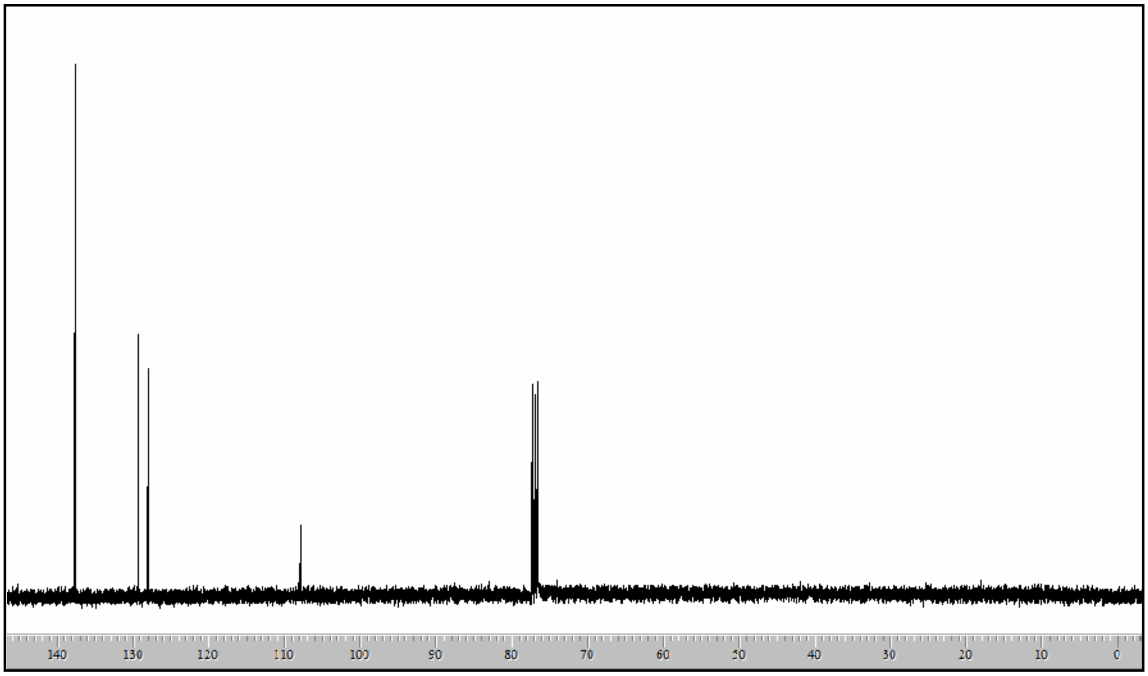
^{77}Se NMR (76.28 MHz, CDCl$_3$) spectrum of **1,2-diheptyldiselenide (3o)**



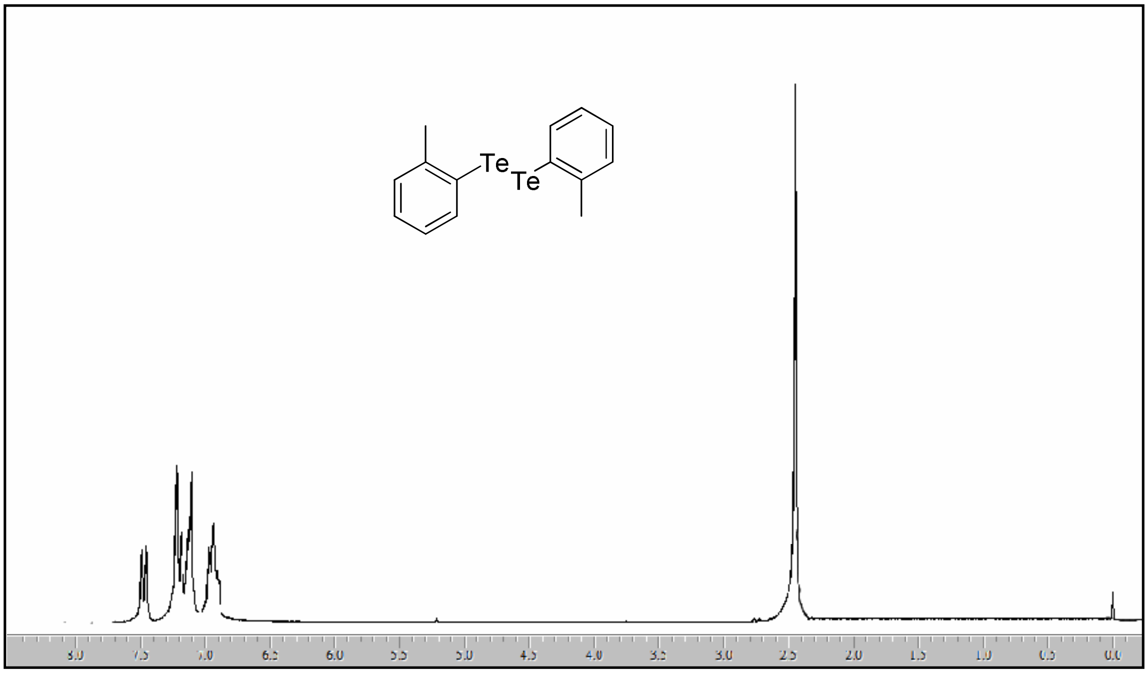
LCMS specta of **1,2-diheptyldiselenide (3o)**



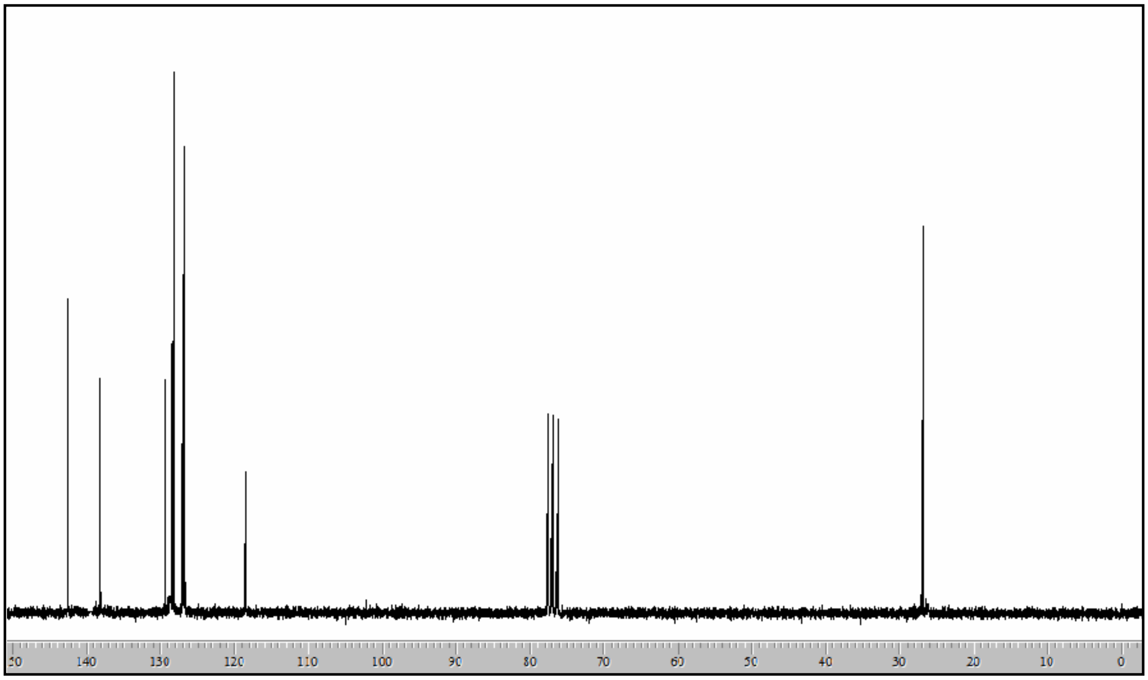
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-diphenylditelluride (4a).**



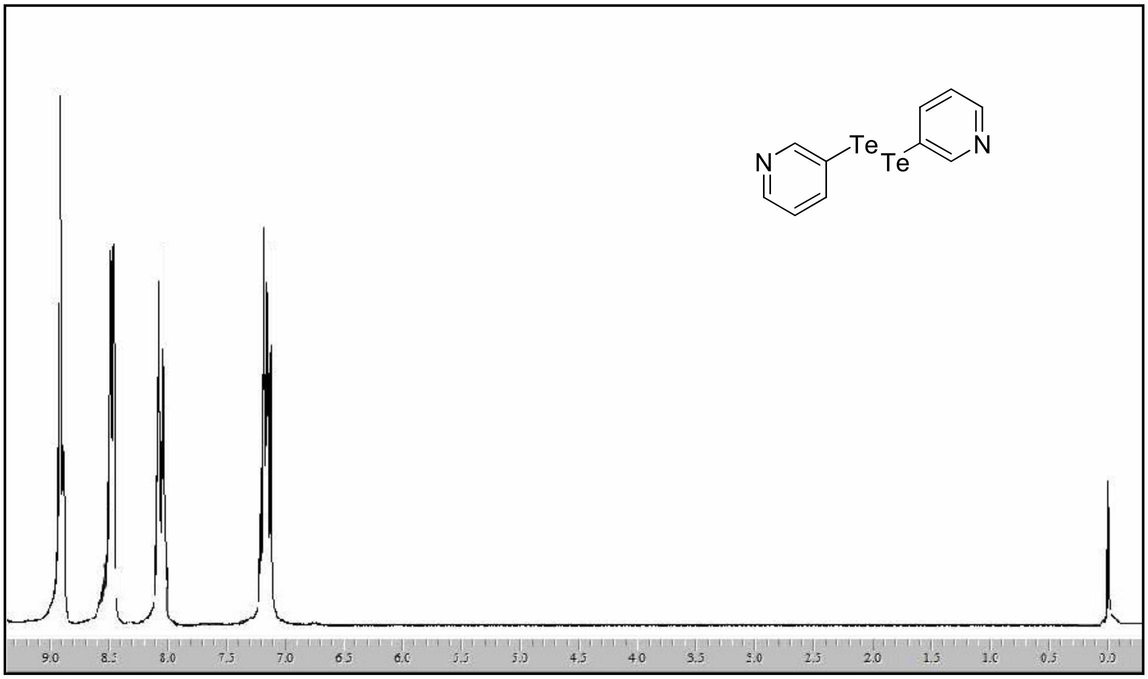
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-diphenylditelluride**



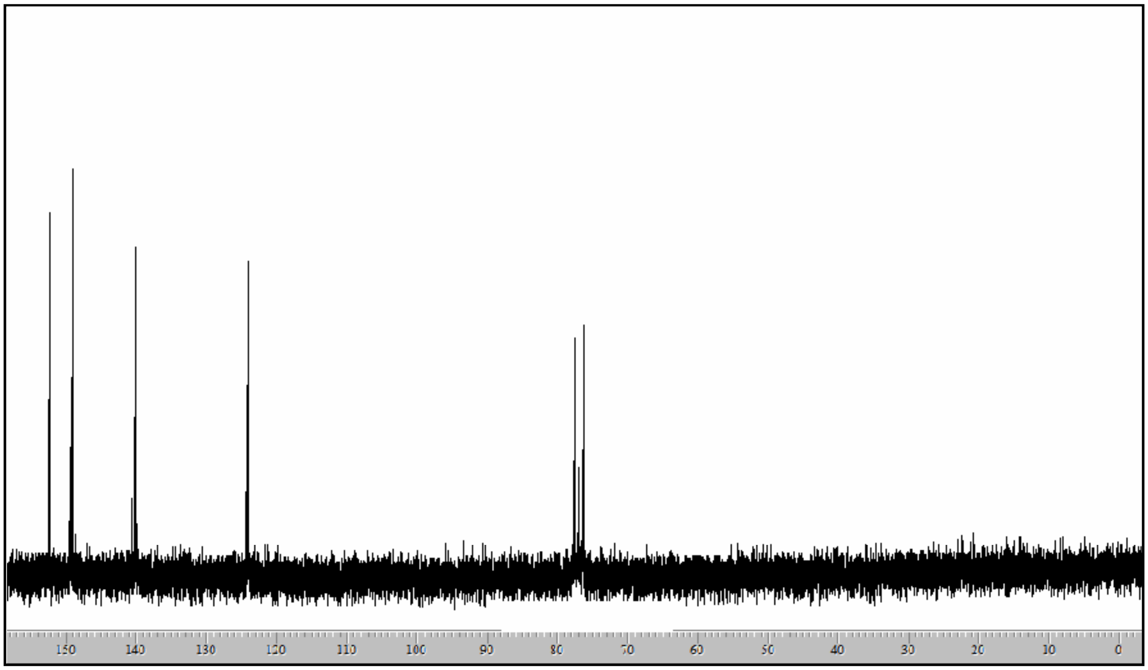
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **1,2-dio-tolylditelluride (4b).**



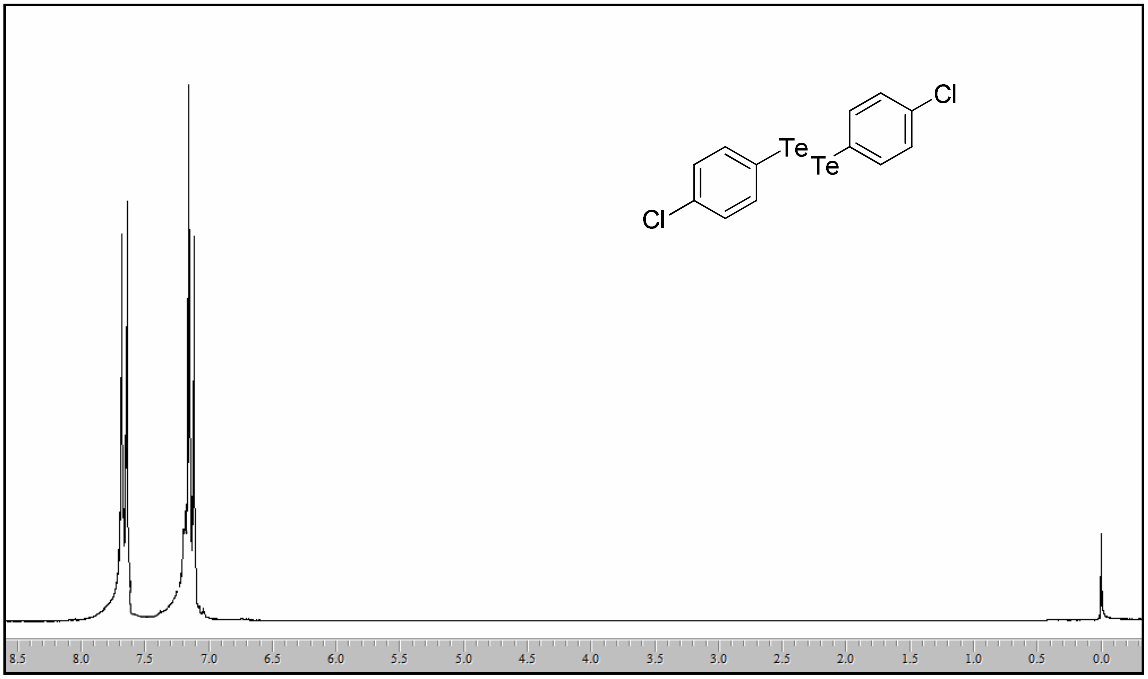
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **1,2-dio-tolylditelluride (4b).**



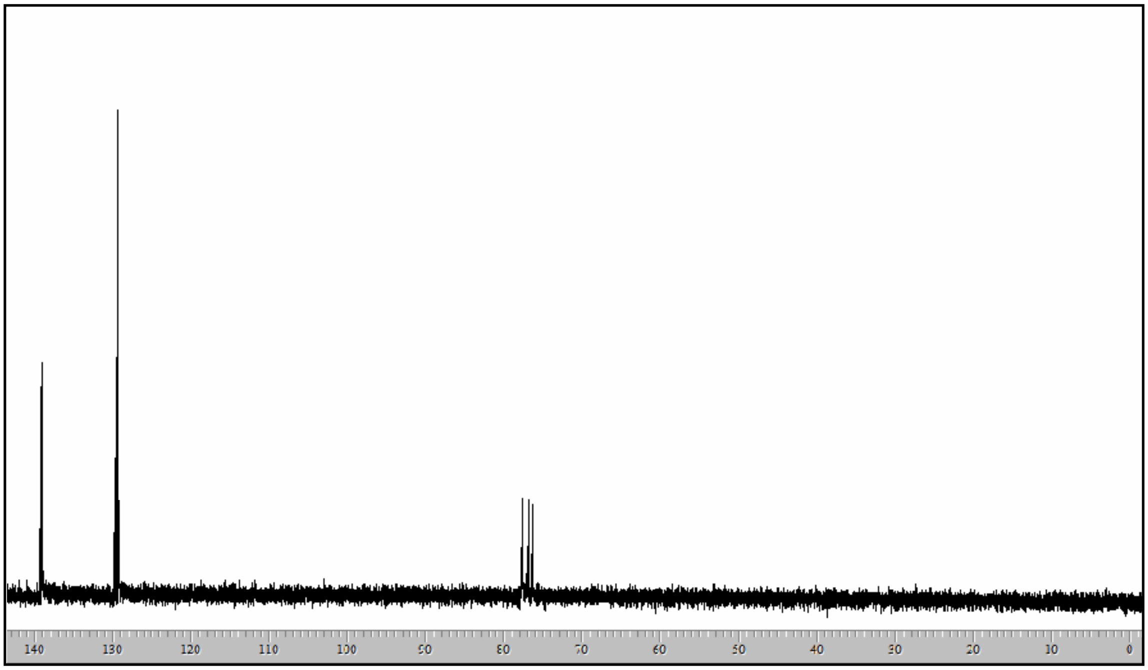
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-di(pyridin-3-yl)ditellurides (4c).**



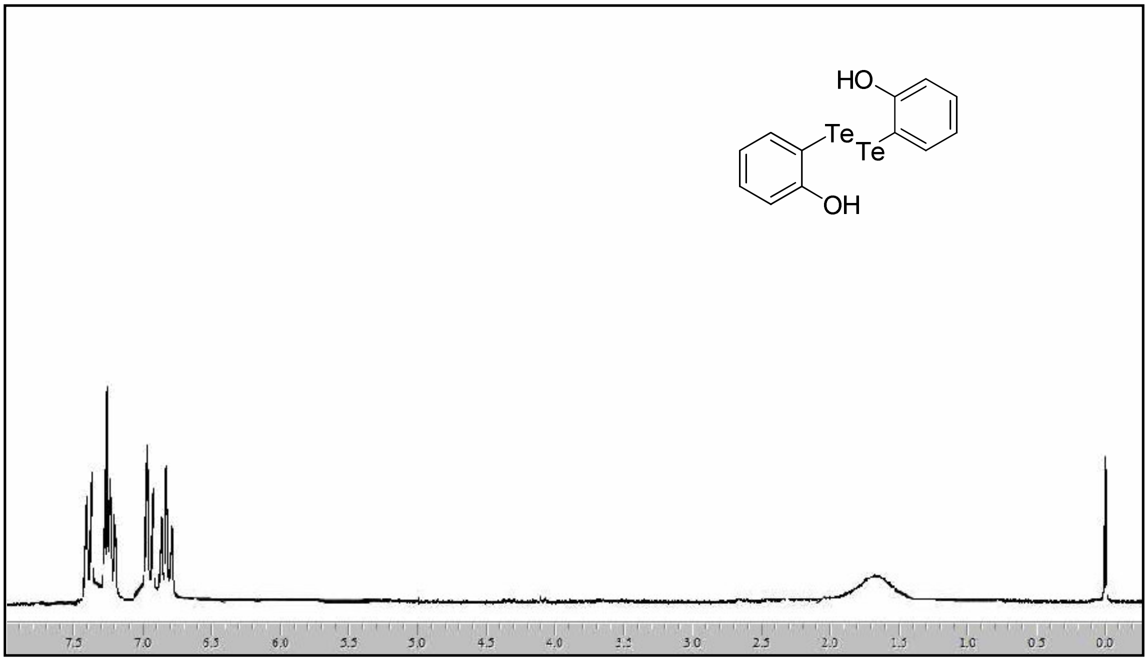
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-di(pyridin-3-yl)ditellurides (4c).**



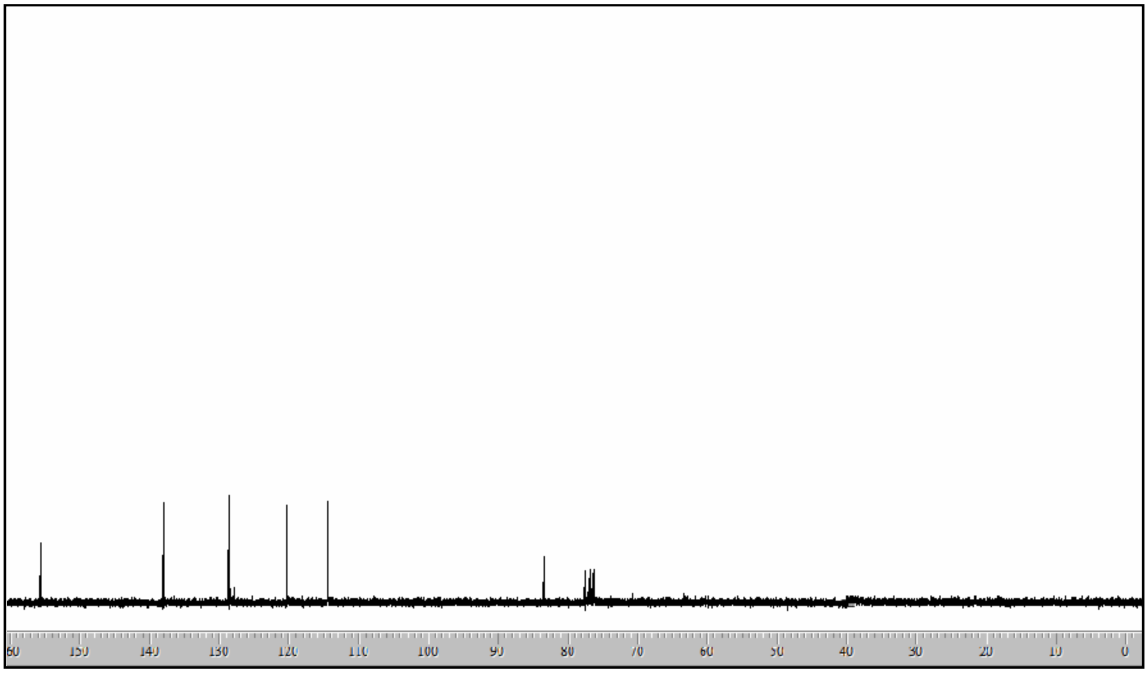
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **1,2-bis(4-chlorophenyl)ditellurides (4d).**



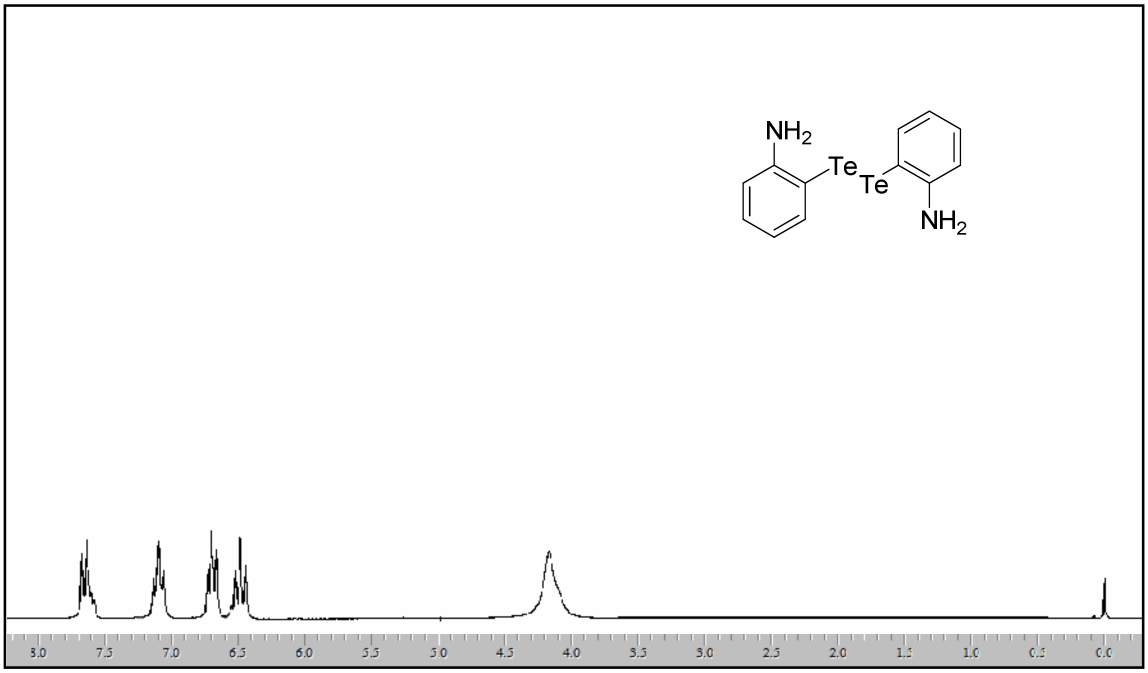
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **1,2-bis(4-chlorophenyl)ditellurides(4d).**



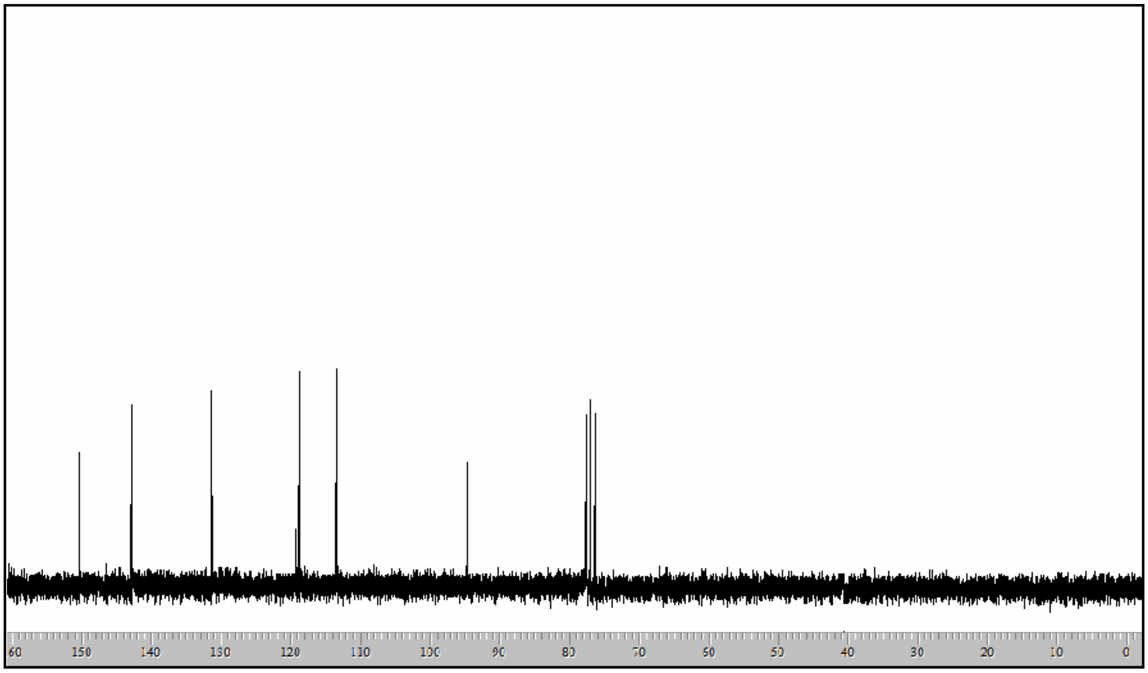
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **2,2'-ditelluridediyldiphenol (4e).**



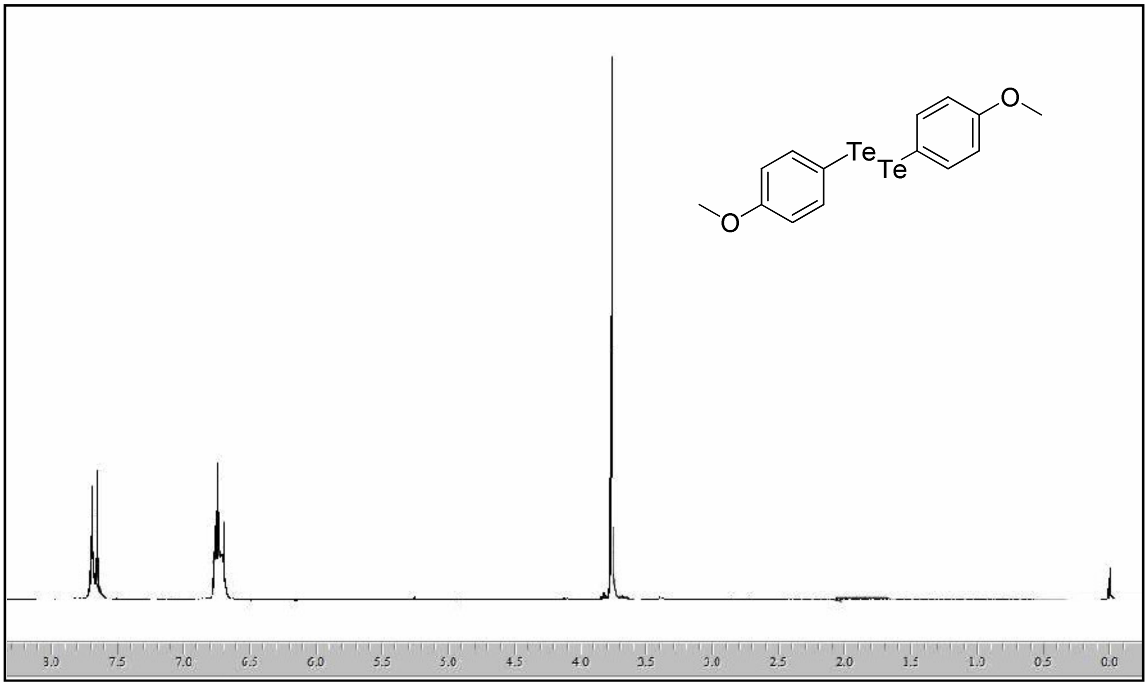
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **2,2'-ditelluridediyldiphenol (4e).**



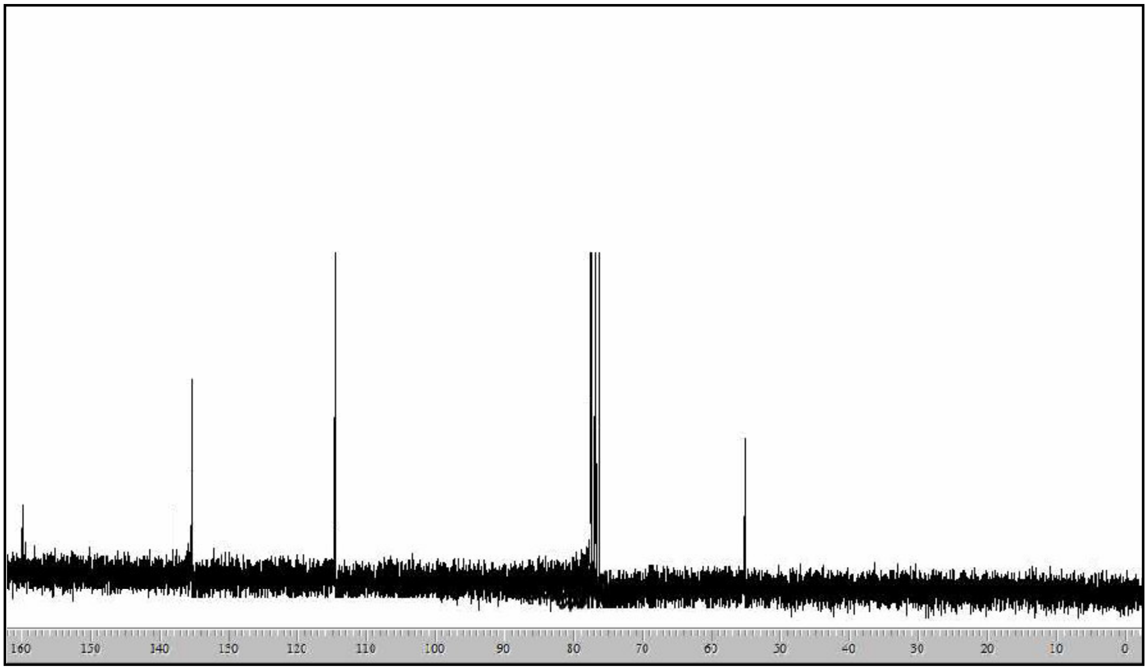
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **2,2'- ditelluridediyldianiline (4f).**



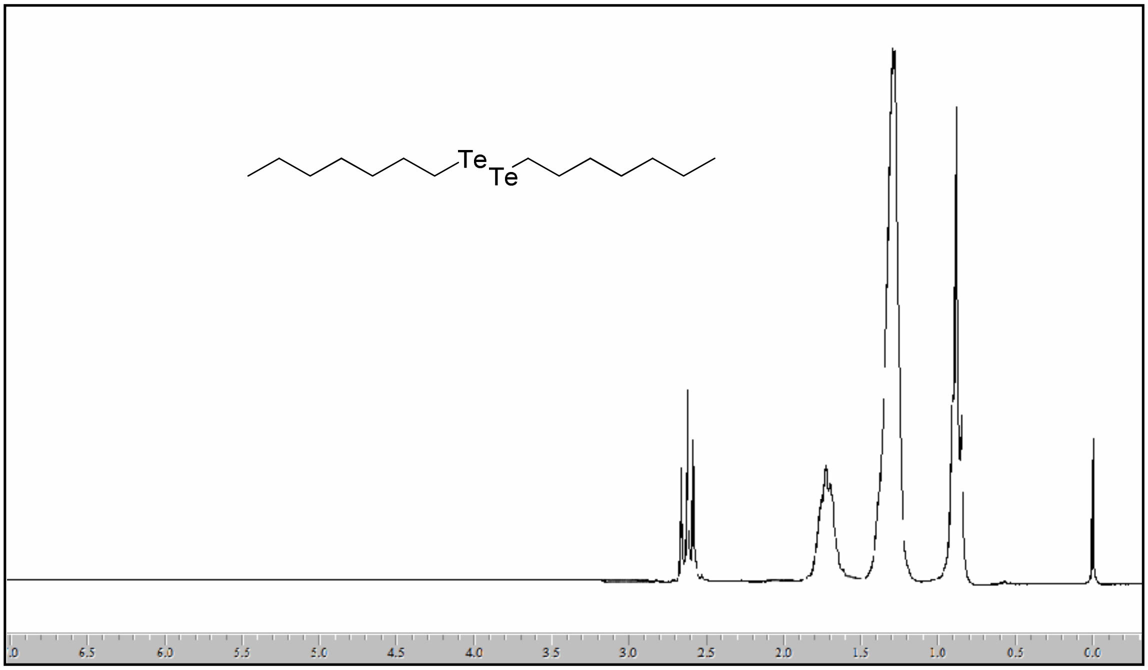
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **2,2'- ditelluridediyldianiline (4f).**



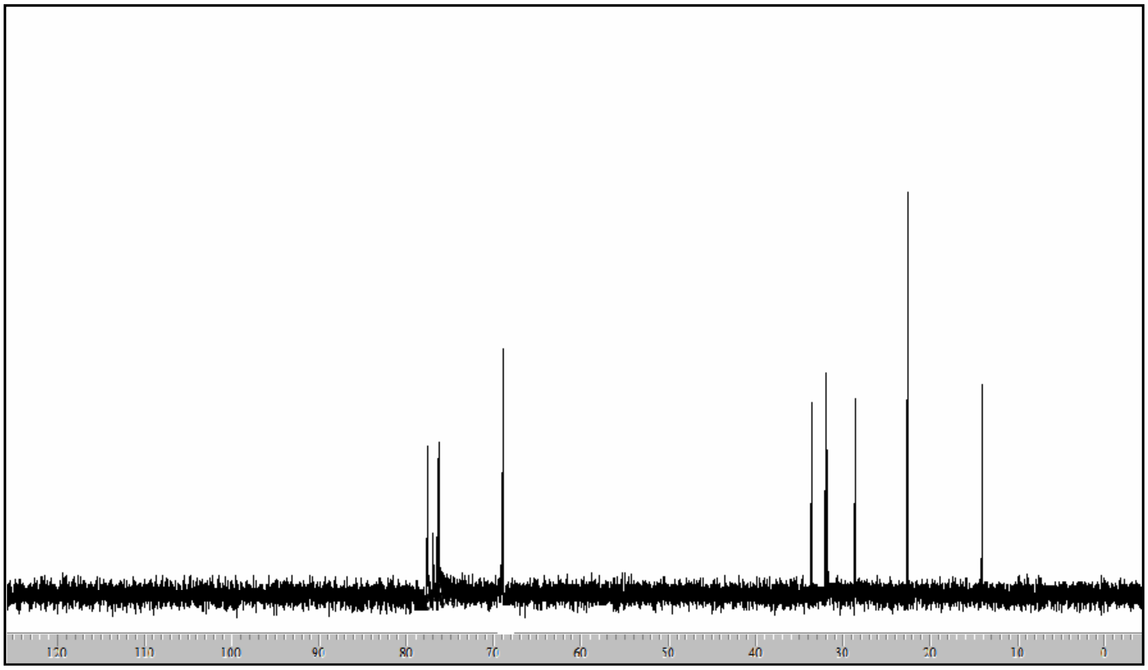
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-bis(4-methoxyphenyl)ditellurides (4g).**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-bis(4-methoxyphenyl)ditellurides (4g).**

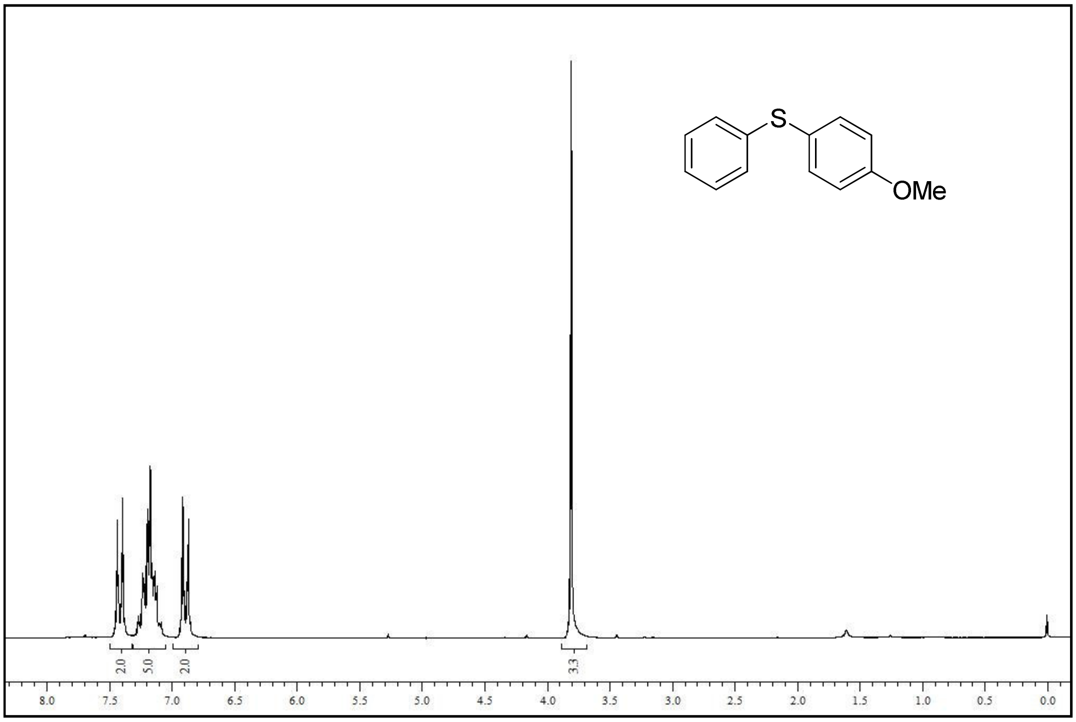


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1,2-diheptylditelluride (4h).**

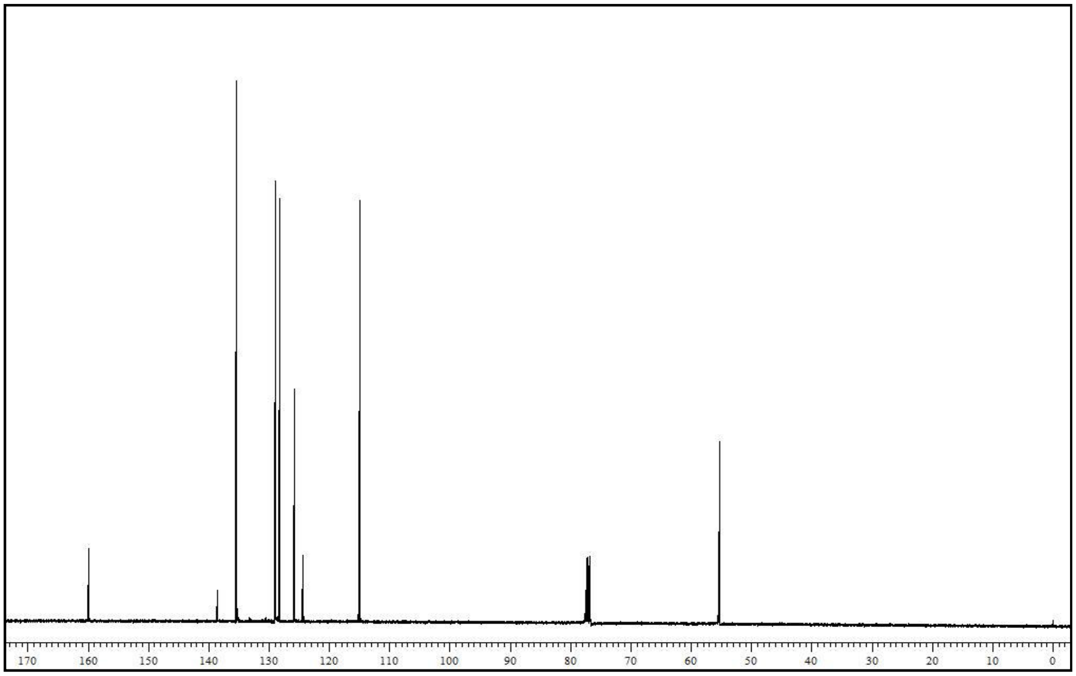


^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1,2-diheptylditelluride (4h).**

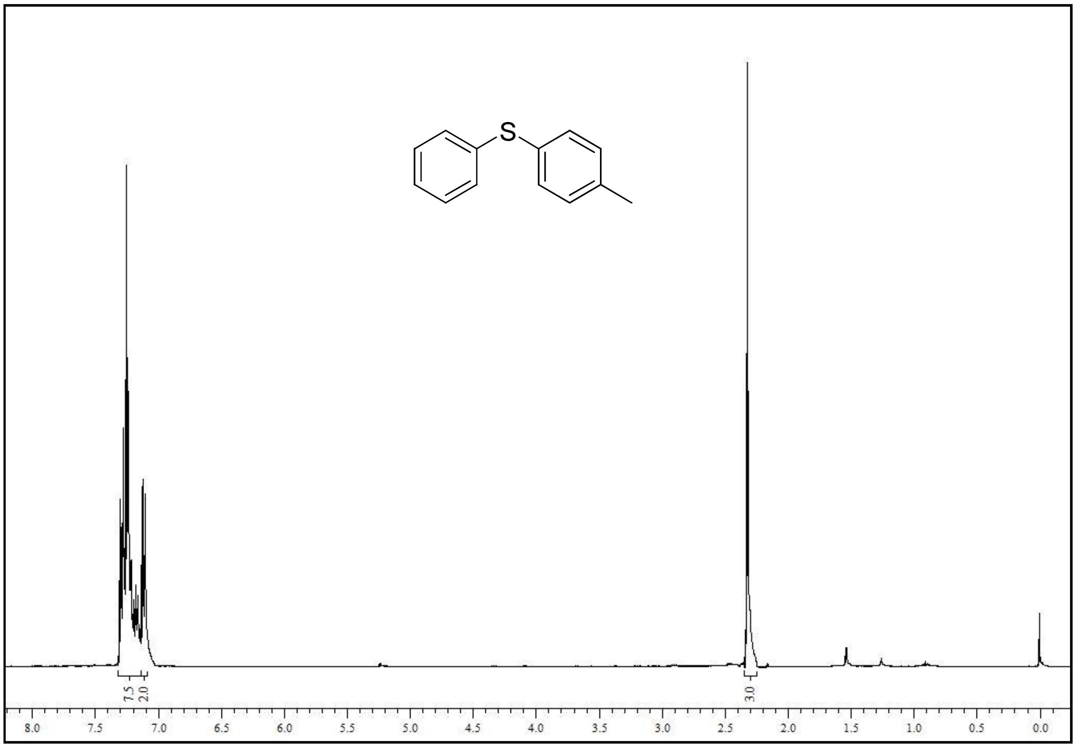
8.4 Selected spectra of sulphides



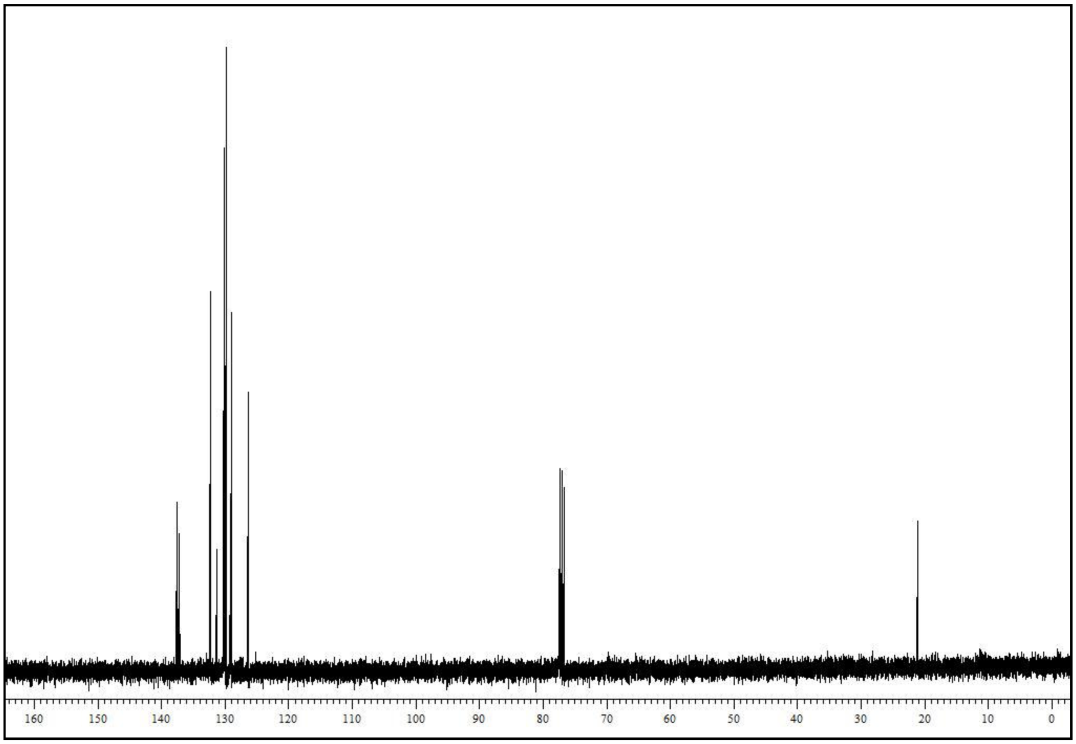
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **4-methoxyphenyl phenyl sulfide (5a).**



^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **4-methoxyphenyl phenyl sulfide (5a).**



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4-methylphenyl phenyl sulfide (5b).**



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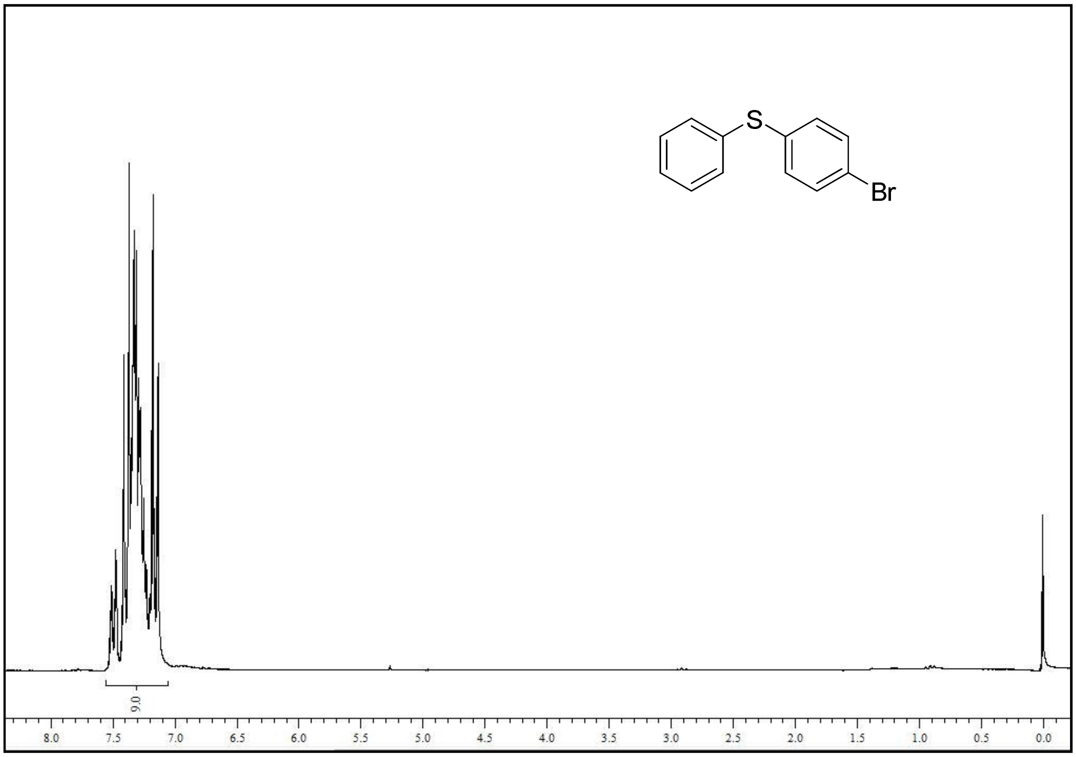
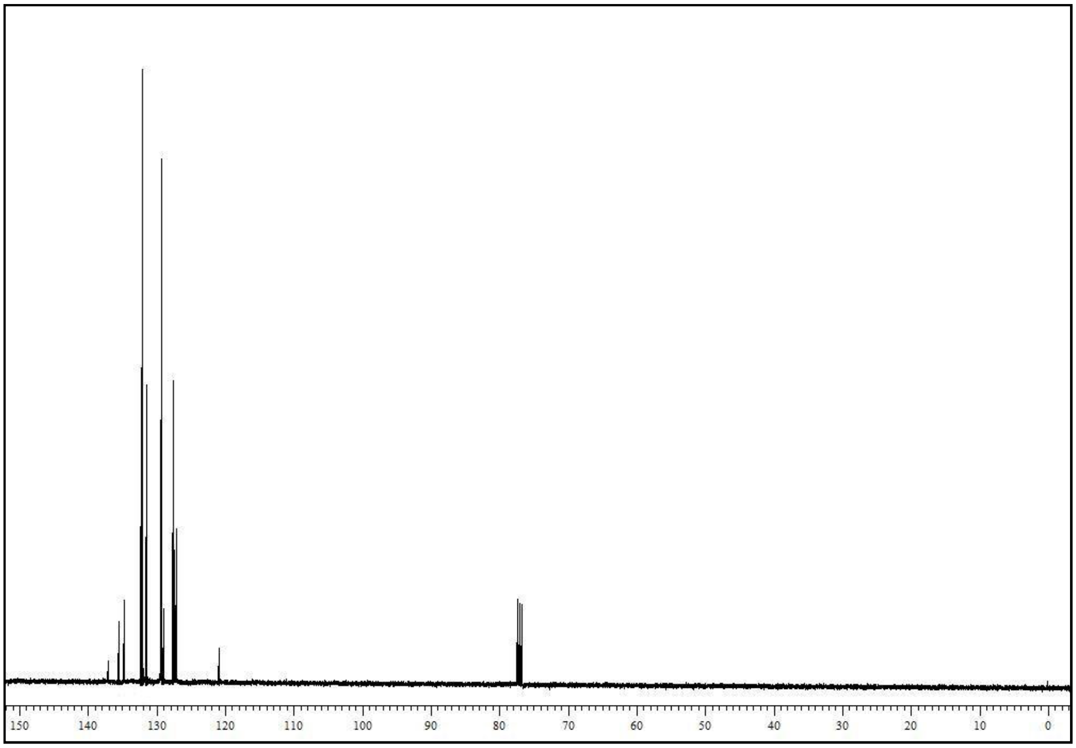
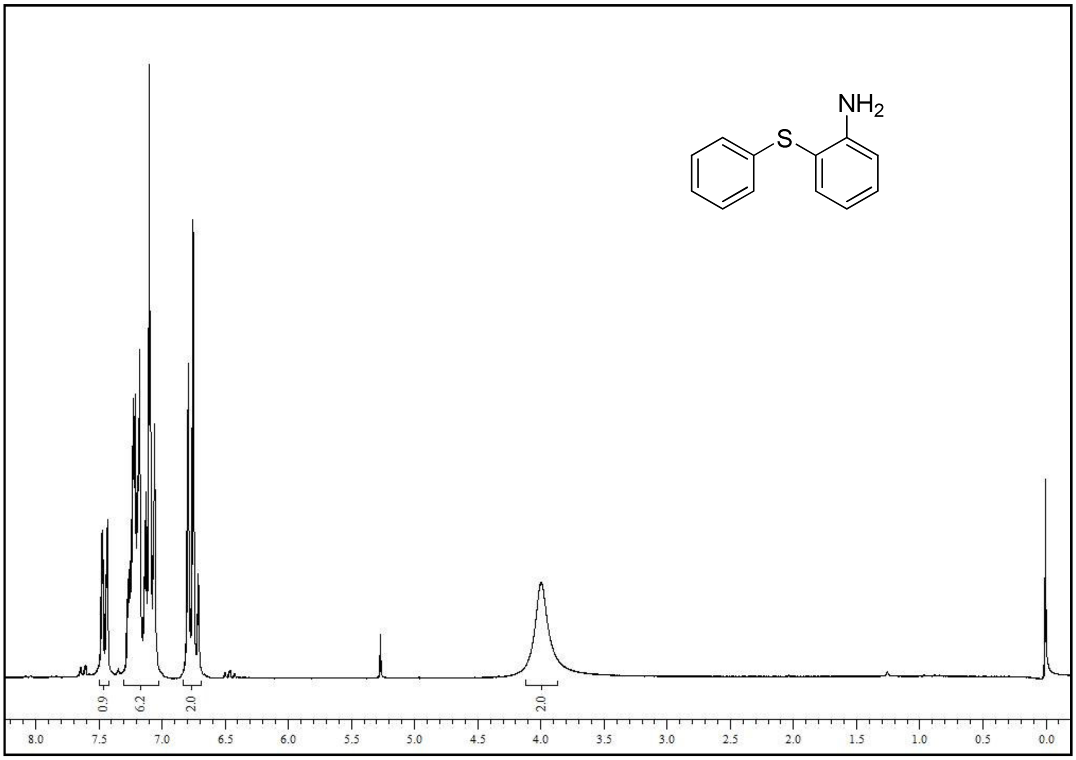


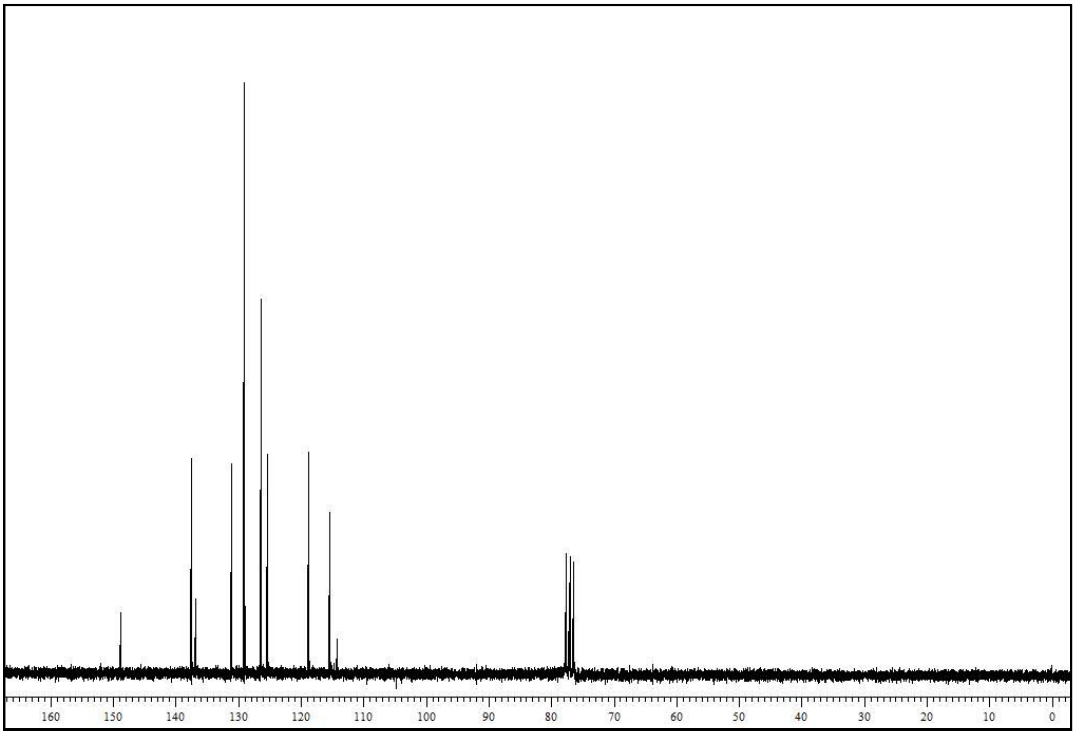
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4-bromophenyl phenyl sulfide (5c).**



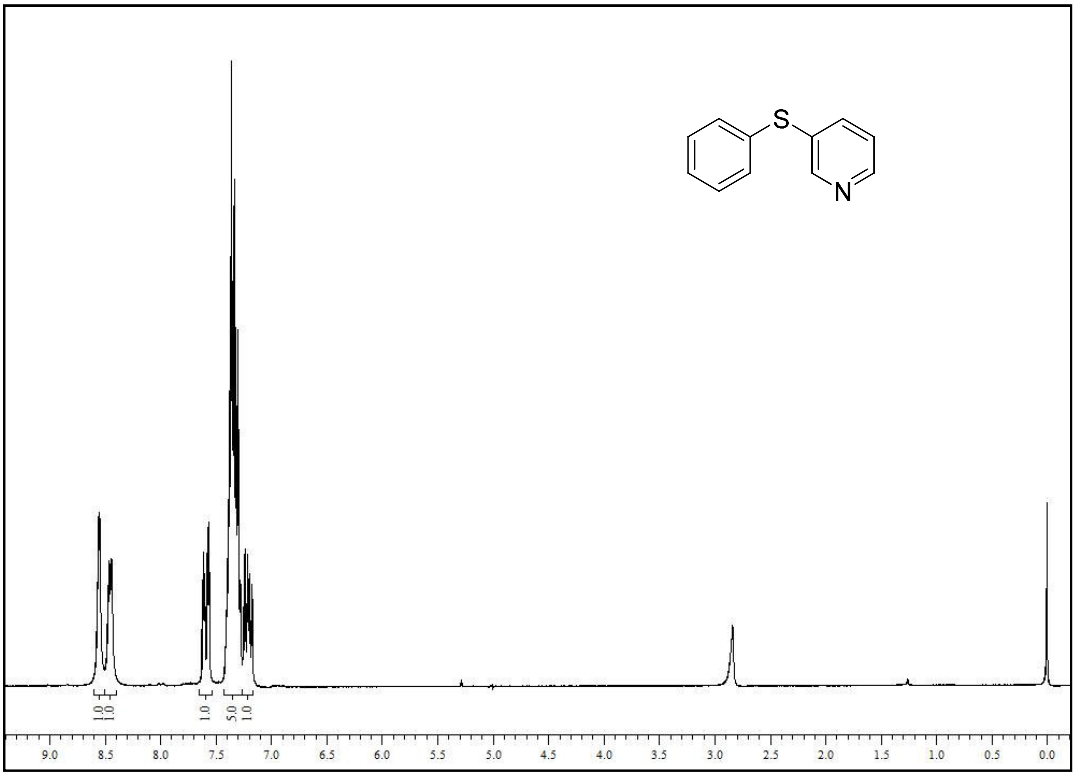
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **4-bromophenyl phenyl sulfide (5c).**



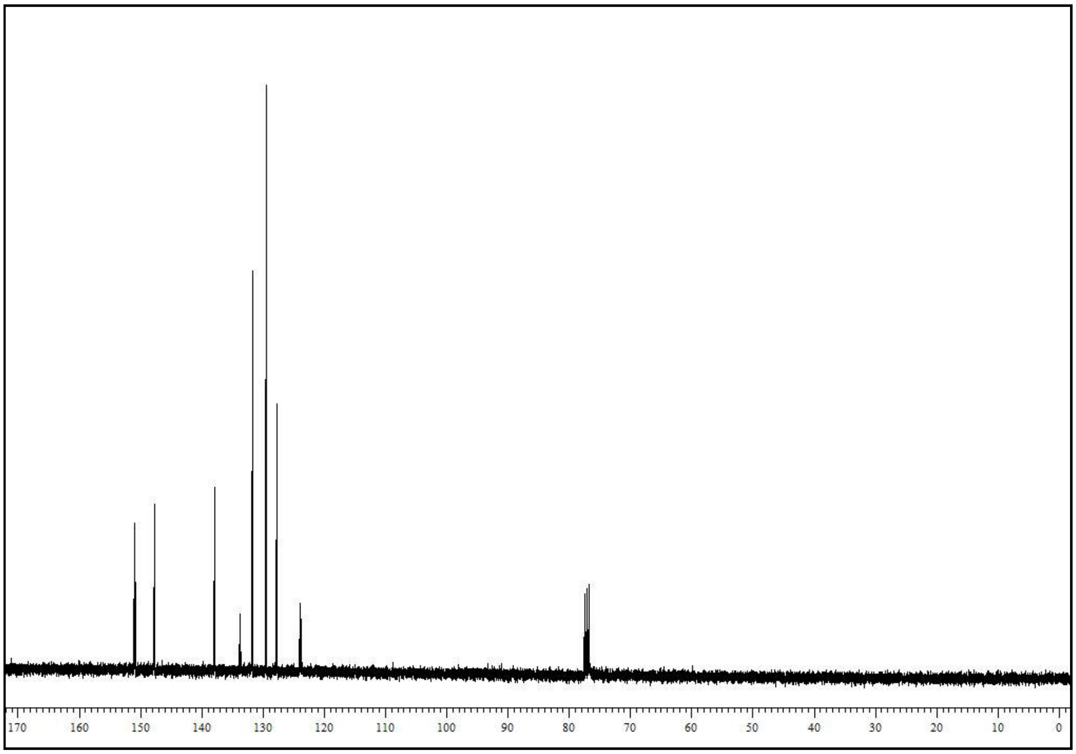
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2-Phenylsulfanylaniline (5e).**



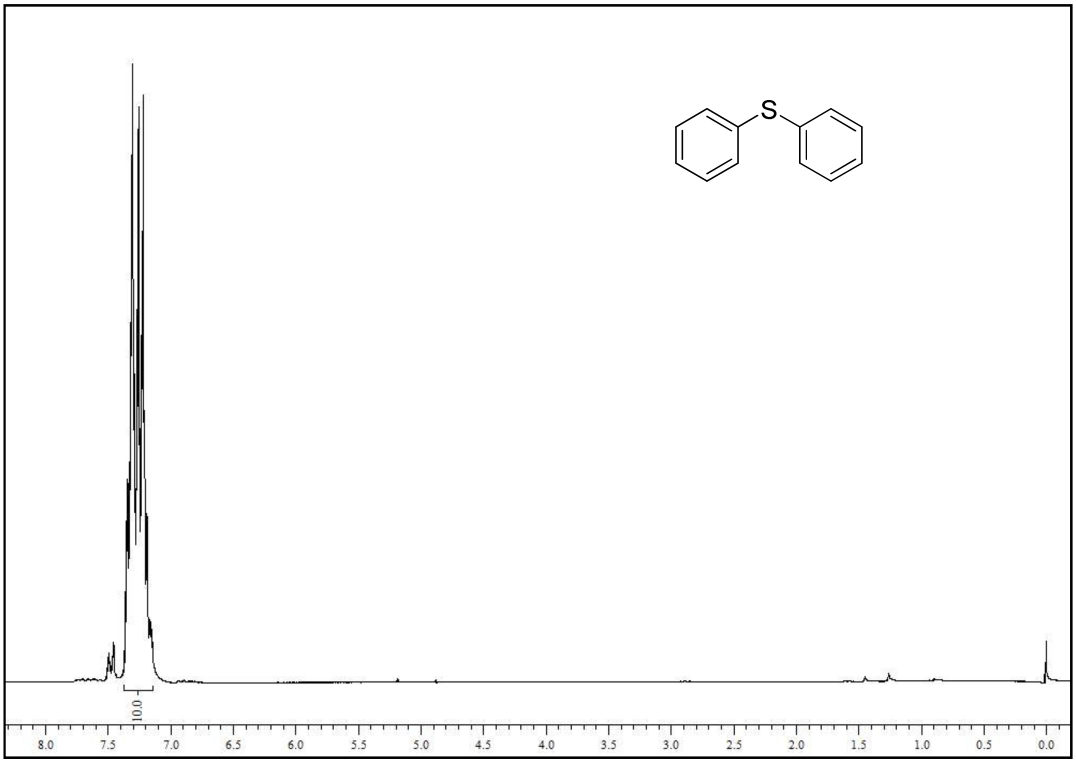
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **2-Phenylsulfanylaniline (5e).**



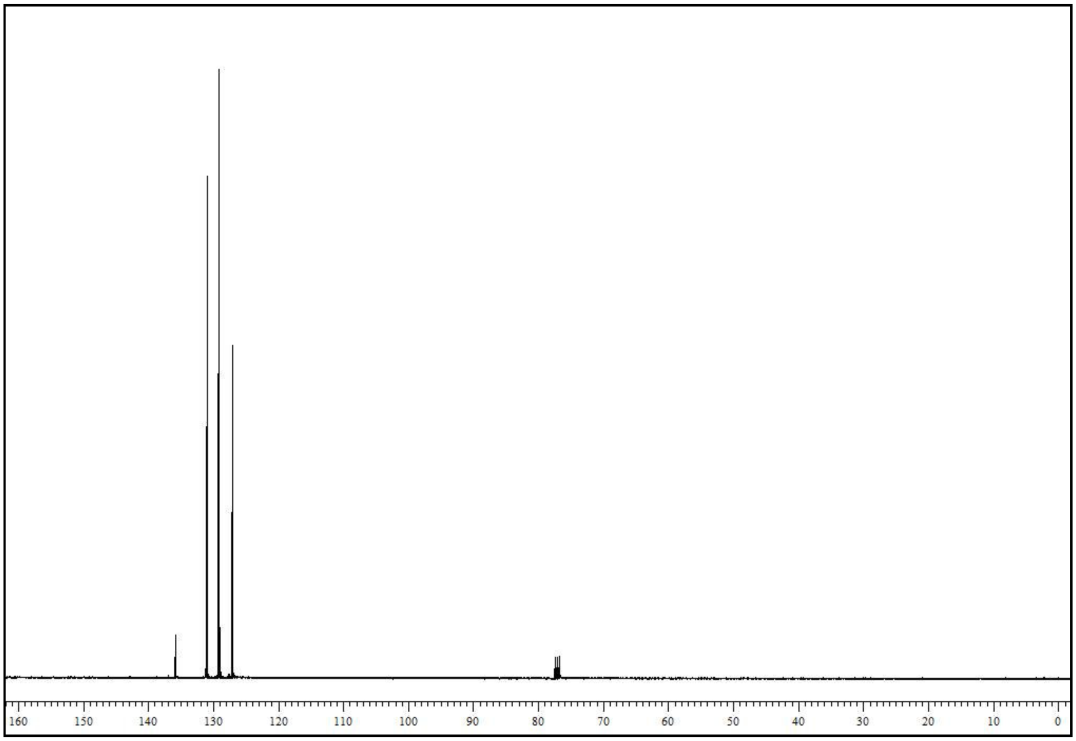
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **3-(phenylthio) pyridine (5f) and (5j).**



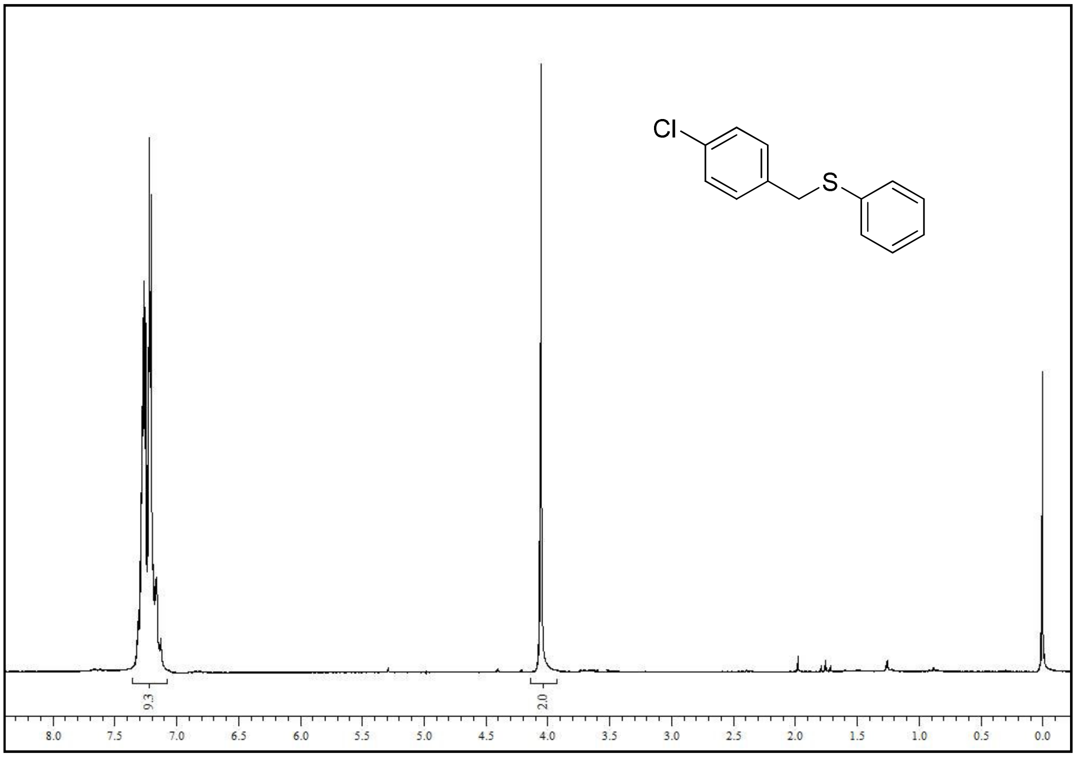
^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **3-(phenylthio) pyridine (5f) and (5j).**



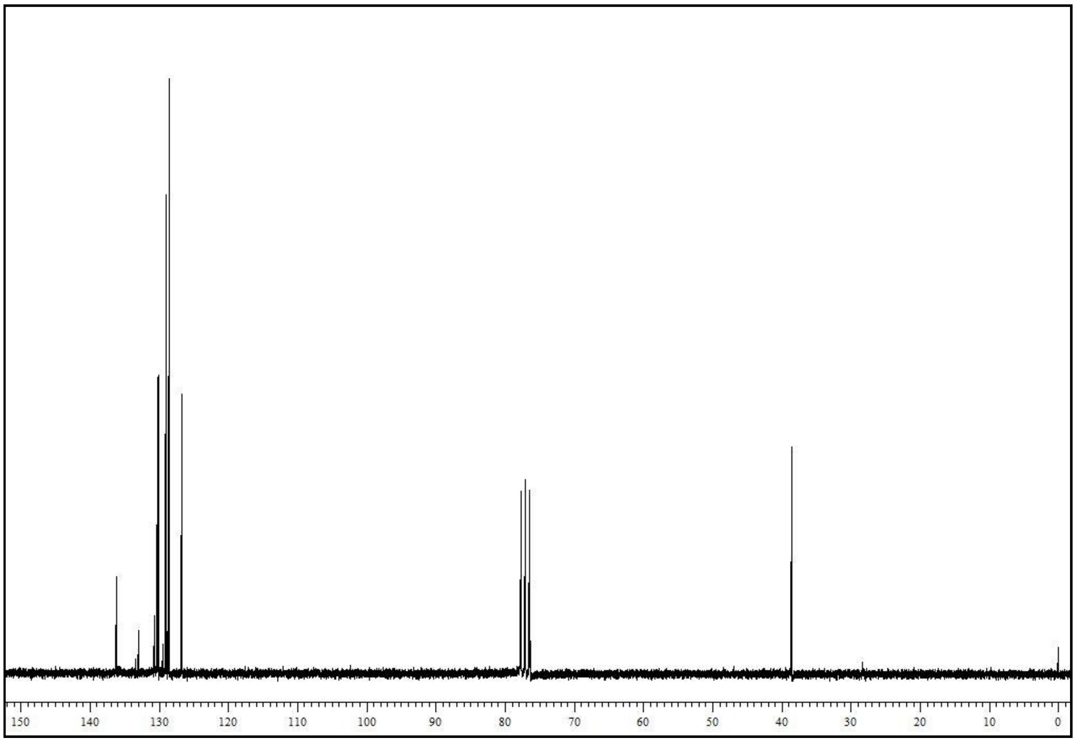
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **diphenyl sulfide (5g).**



^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **diphenyl sulfide (5g).**



^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **4-chlorobenzyl phenyl sulfide (5k).**



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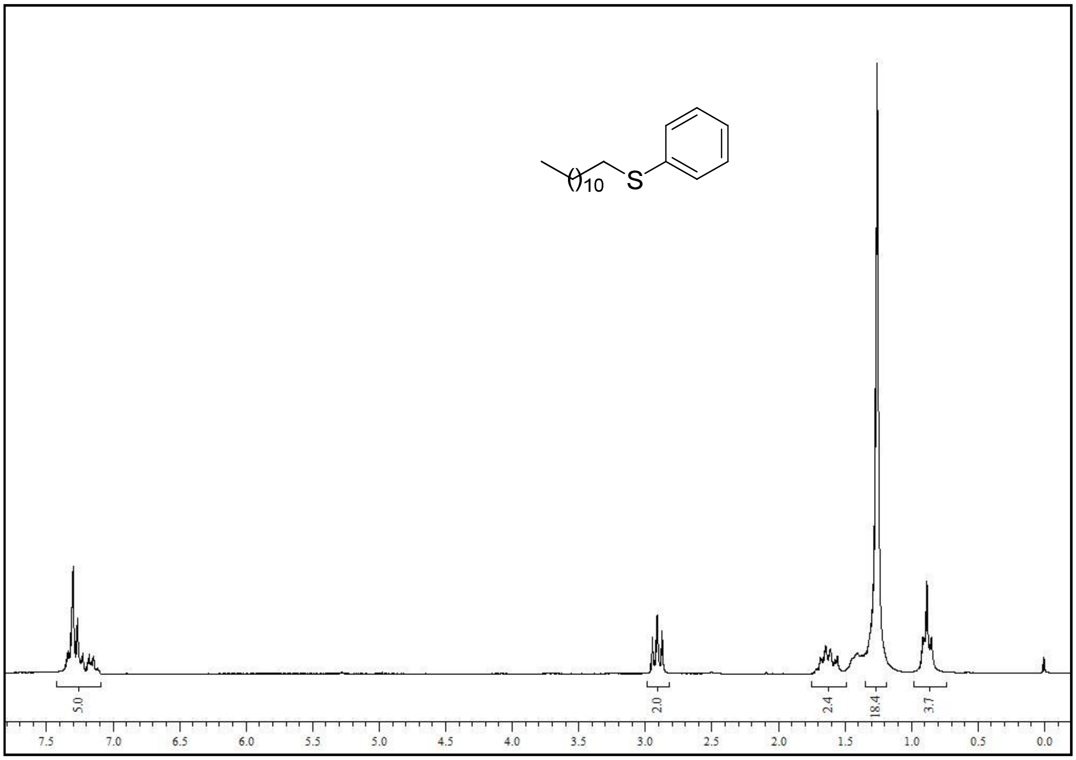
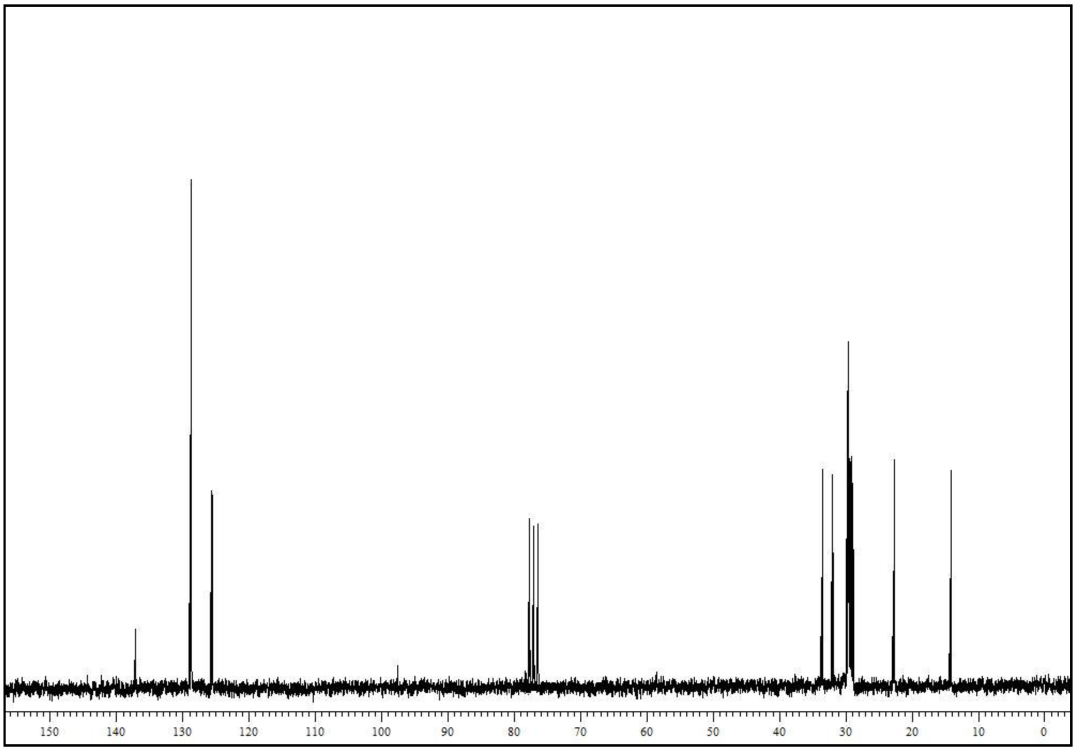
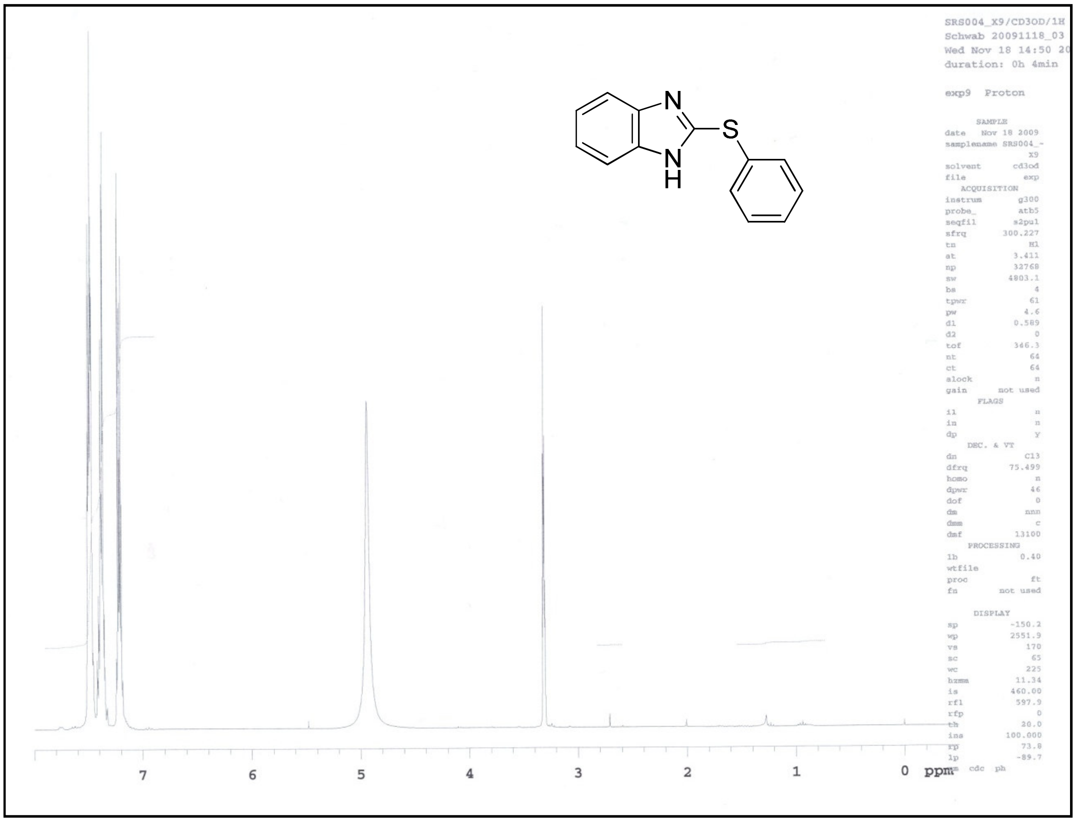


^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **Dodecyl phenyl sulfide (5l).**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **Dodecyl phenyl sulfide (5l).**



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Wed Nov 18 14:50 20
duration: 0h 4min

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pw              4.6
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alock             n
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dp                y
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proc             ft
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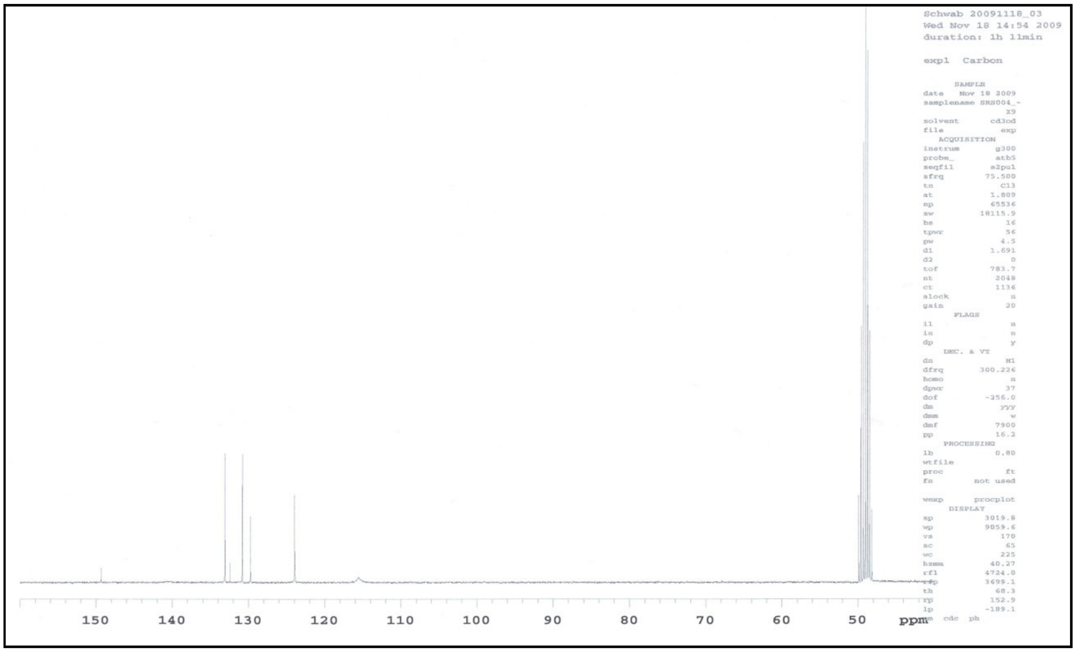
^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **Benzimidazole phenyl sulfide (5m).**



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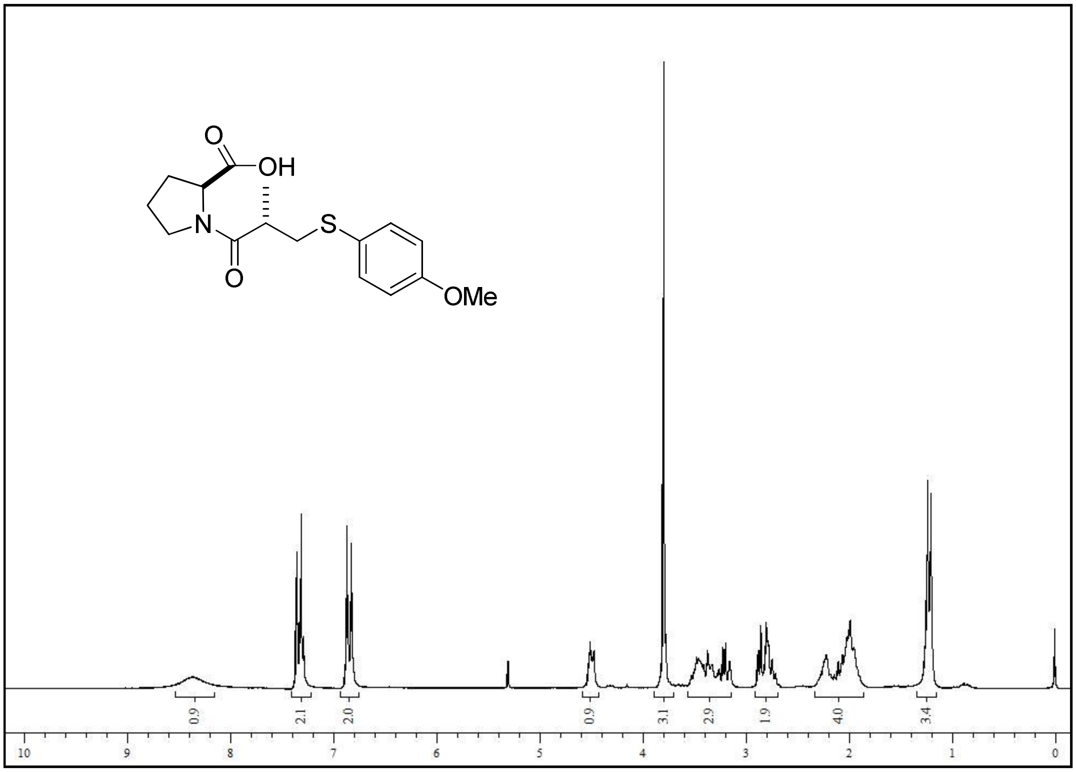
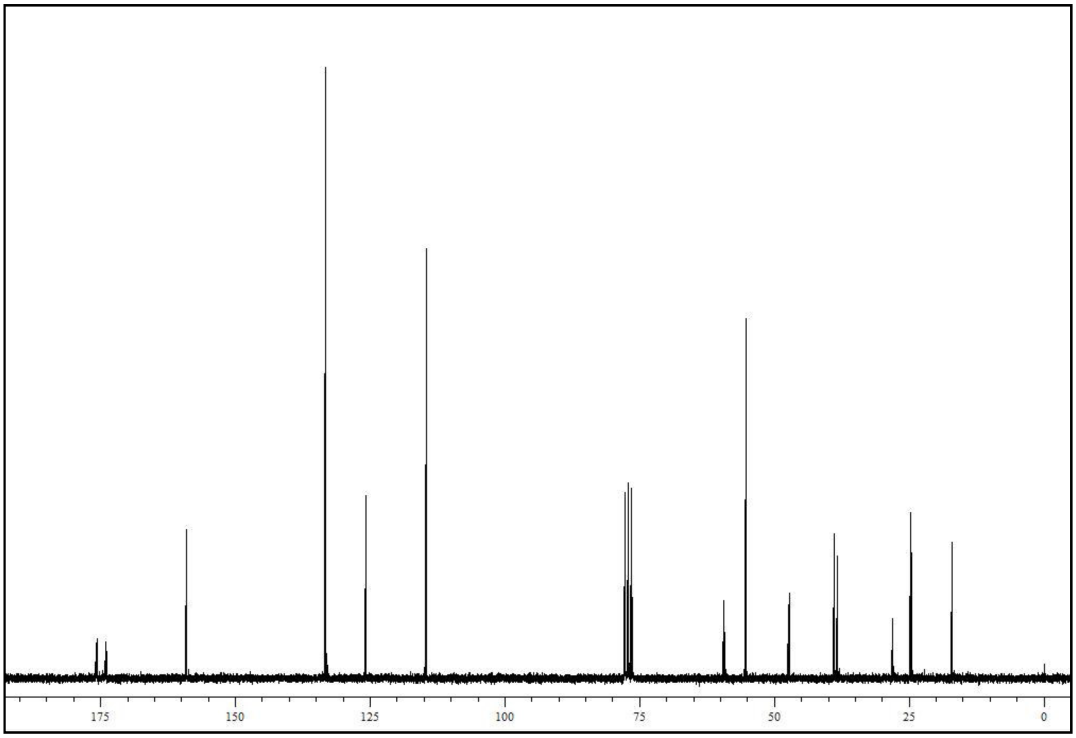
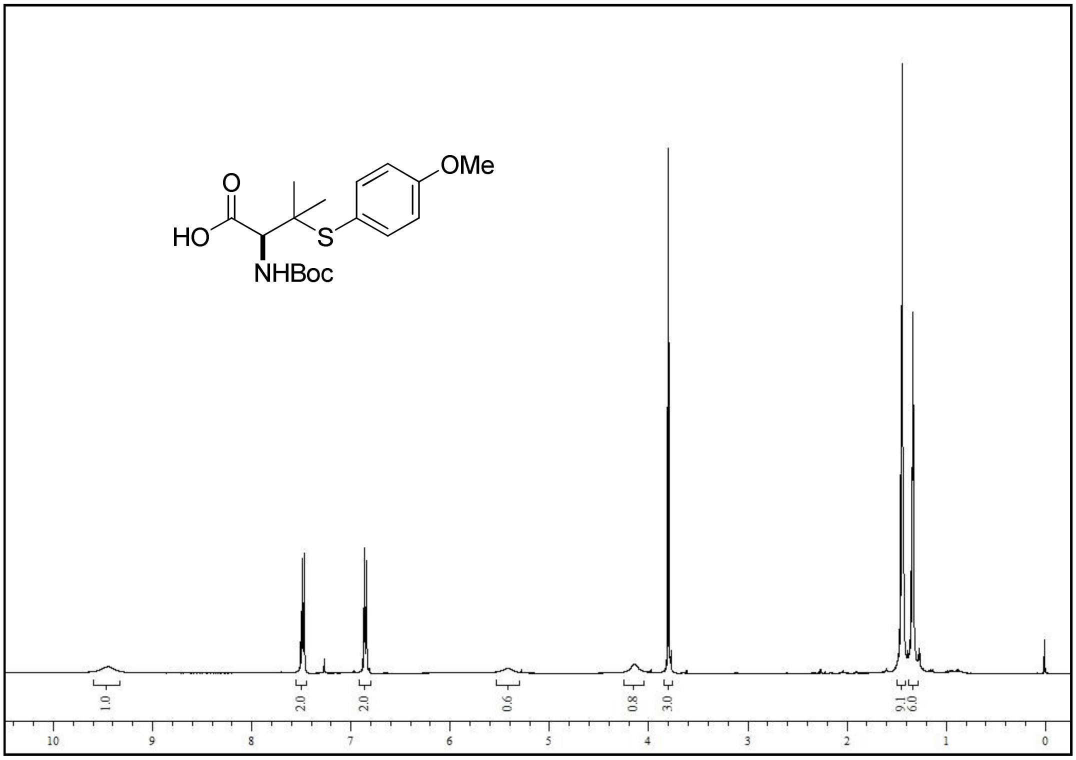
^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **Benzimidazole phenyl sulfide (5m).**



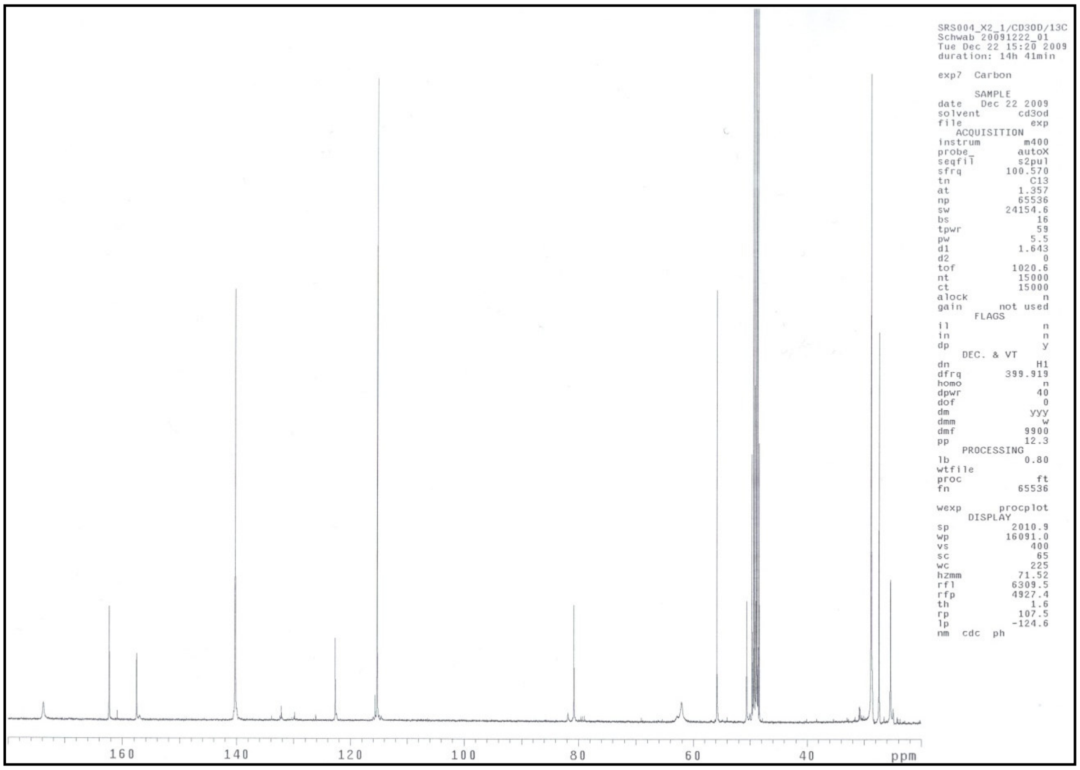
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **(S)-1-((S)-3-(4-methoxyphenylthio)-2-methylpropanoyl) pyrrolidine-2-carboxylic acid (5n).**



^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **(S)-1-((S)-3-(4-methoxyphenylthio)-2-methylpropanoyl) pyrrolidine-2-carboxylic acid (5n).**



^{1}H NMR (400 MHz, CDCl$_3$) spectrum of **(S)-2-(tert-butoxycarbonylamino)-3-(4-methoxyphenylthio)-3-methylbutanoic acid (5o).**



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Tue Dec 22 15:20 2009
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rp            107.5
lp           -124.6
nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$) spectrum of **(S)-2-(tert-butoxycarbonylamino)-3-(4-methoxyphenylthio)-3-methylbutanoic acid (5o).**

APPENDIX 1

Published article for the synthesis of selenides

Eco-friendly cross-coupling of diaryl diselenides with aryl and alkyl bromides catalyzed by CuO nanopowder in ionic liquid

Devender Singh,[a] Eduardo E. Alberto,[a] Oscar Endrigo Dorneles Rodrigues*[a] and Antonio Luiz Braga*[b]

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An eco-friendly cross-coupling reaction of aryl and alkyl bromides with diselenides using a catalytic amount of CuO nanopowder as a catalyst and an ionic liquid as a recyclable solvent is reported. The system shows high efficiency to catalyze this transformation, and in a green fashion due to the recyclable approach and the non-residual design protocol. This procedure has been utilized for the synthesis of a variety of diaryl selenides in good to excellent yields from the readily available aryl and alkyl bromides and diselenides.

Organoselenium compounds have become attractive synthetic targets. These compounds offer chemo-, regio-, and stereoselective reactions, and in life sciences selenium is known as a fundamental element.[1] In addition, organoselenium compounds are involved in a series of biological processes, they have an effective action against free radical species, and other important biological proprieties (*e.g.*, antioxidant, antitumor, anti-inflammatory, and anti-infective activity).[2]

The preparation of aryl selenides involves a transition-metal-catalyzed reaction and a few protocols are reported in the literature.[3–6,9] In earlier methods, for the formation of a C–Se bond, photochemical or harsh reaction conditions such as the use of polar and toxic solvents like HMPA and high reaction temperatures were required.[7] Most of these metal-catalyzed reactions involve specially designed ligands or well-defined catalysts/reagents, which may increase the cost and limit the scope of applications. In this context, it is desirable to find novel catalytic procedures, especially in the absence of ligands, for an efficient route to such highly useful organic products.

On the other hand, nanotechnology has become an attractive new field for catalysis. Nanoscale heterogeneous catalysts offer higher surface area and low-coordinated sites, which are responsible for the higher catalytic activity.[8] Due to this, the investigation of nanoparticles as catalysts in cross-coupling reactions has been of growing interest.

Organic reactions, catalyzed by copper nanostructures, are currently an area of intensive research, with many reports in the literature.[9–14] Recently, a report concerning the synthesis of diaryl selenides using CuO nanoparticles was published.[9] That protocol allowed the preparation of the desired products in good yields, however, long reaction times and high temperatures limit the scope of the reaction to substrates that would withstand with these harsh reaction conditions. Moreover, the use of solvents such as DMSO is undesirable from an environmental point of view.

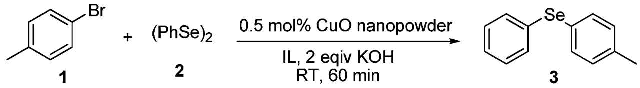
Ionic liquids have been used frequently in the last few years as an alternative reaction media for a broad range of different chemical transformations.[15–21] Ionic liquids have been utilized as solvents in many transition-metal catalyzed C–C bond formation reactions: Heck reactions,[22–29] Stille-coupling,[30] Negishi-coupling,[31] Suzuki-coupling,[32] Kumada-coupling,[33] Ullmann reaction[34] and Tsuji–Trost allylation.[35,36] They present various interesting properties which alleviate some of the environmental issues, such as no effective vapour pressure, good solubilities for a wide range of compounds and they allow many combinations of anions and cations.

Therefore, the combination of nanotechnology and ionic liquids to perform chalcogen–carbon coupling could afford a new green methodology to synthesise this kind of compound. In this context, and in connection with our ongoing interest in synthesis and evaluation of organochalcogen derivatives as ligands in asymmetric transformations[37] we report herein an environmental friendly and efficient cross-coupling reaction of aryl and alkyl bromides with diaryl diselenides using a catalytic amount of commercially available CuO nanopowder as a catalyst and BMIM-BF_4 as a recyclable solvent.

We carried out the reaction employing 4-bromotoluene **1** as representative bromide and 0.5 equiv. of diphenyl diselenide **2** to get the diaryl selenide **3**, Table 1.

In a first set of experiments, we studied the influence of different ionic liquids, Table 1. It was possible to check that in all of them the desired product was obtained, with yields ranging from 74 to 82%. BMIM-BF_4 was a superior ionic liquid for this reaction (Table 1, entry 1).

Table 1 CuO-nanoparticle catalyzed cross-coupling of 4-bromotoulene with diphenyl diselenide using different ionic liquids



Entry[a]	Ionic liquid	Yield (%)[b]
1	BMIM-BF_4	82
2	BMIM-NTf_2	78
3	BMIM-PF_6	74

[a] CuO nanopowder was purchased from Aldrich®, with an average diameter of 30–40 nm, as shown in technical information. [b] GC yields.

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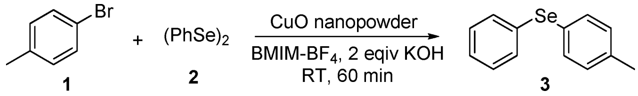
[b] *Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC, 88040-900, Brazil. E-mail: albraga@qmc.ufsc.br; Tel: +55-48 3721 6844*

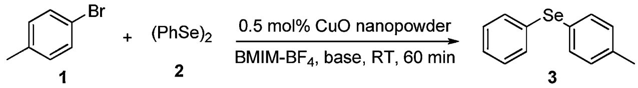
Table 2 CuO-nanopowder catalyzed cross-coupling of 4-bromotoulene **1** with diphenyl diselenide **2**



Entry	CuO nano (mol%)	Yield[a] (%)
1	0.10	45
2	0.25	48
3	0.50	82
4	1.00	84

[a] Yields were determined by GC.

Table 3 CuO-nanopowder catalyzed cross-coupling of **1** with **2**



Entry	Base	Amount (equiv.)	Yield (%)[a]
1	K_2CO_3	2.0	41
2	Cs_2CO_3	2.0	78
3	KOH	2.0	82
4	Na_2CO_3	2.0	46
5	none	—	0

[a] Yields were determined by GC.

To understand the influence of different variables in this reaction, several components were studied to optimize our procedure. Firstly, the amount of catalyst necessary to promote the reaction efficiently was examined, Table 2. We found that the variation of the CuO nanopowder amount had an effective influence. While 0.1 and 0.25 mol% afforded the desired product in moderate yields (entries 1 and 2), by using 0.5 mol%, the yield was improved to 82% (entry 3). When the amount of CuO nanopowder was increased to 1.0 mol%, the yield of compound **3** was not significantly modified, affording the desired product in 84% (entry 4).[38]

With these results in hand, we selected 0.5 mol% of CuO nanopowder as the best amount of catalyst. The additional factors analyzed were the reaction time and the base. The variation in the reaction time from 10 to 120 minutes was studied. As shown in Fig. 1, the yield had a linear increase from 10 minutes to a maximum of 60 minutes. After this, longer reaction times did not have an influence on the product yield.

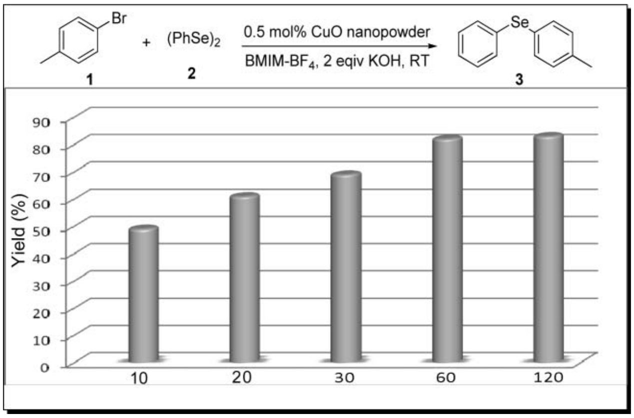
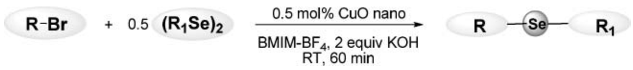
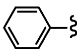
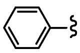
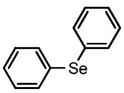
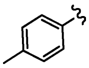
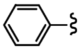
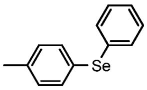
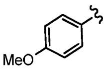
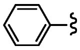
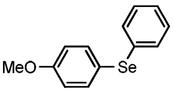
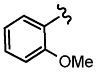
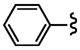
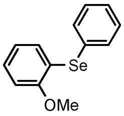
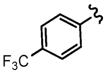
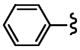
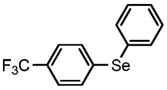
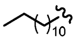
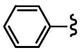
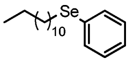
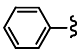
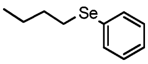
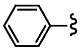
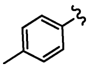
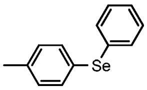
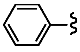
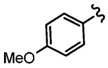
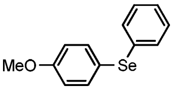
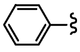
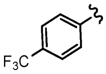
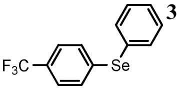


Fig. 1 Time optimization in CuO nanocatalysis.

In terms of base, the influence of different bases was studied to perform a more efficient cleavage of diselenides affording the nucleophilic selenolate species. Thus, Cs_2CO_3 and KOH provided the diaryl selenides **3** in good yields (Table 3, entries 2 and 3), whereas other bases such as K_2CO_3 and Na_2CO_3 gave only moderate yields (Table 3, entries 1 and 4). The product was not observed in the absence of base, hence the necessity of that to perform the reaction (entry 5).

Table 4 CuO nanopowder catalyzed cross-coupling of halides **1a–g** with diaryl diselenides **2a–d**



Entry	R	R_1	Product	Yield (%)[a]
1	 **1a**	 **2a**	 **3a**	82
2	 **1b**	 **2a**	 **3b**	82
3	 **1c**	 **2a**	 **3c**	80
4	 **1d**	 **2a**	 **3d**	79
5	 **1e**	 **2a**	 **3e**	70
6	 **1f**	 **2a**	 **3f**	75
7	 **1g**	 **2a**	 **3g**	76
8	 **1a**	 **2b**	 **3b**	80
9	 **1a**	 **2c**	 **3c**	76
10	 **1a**	 **2d**	 **3e**	74

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

After the optimizations, the reactions were carried with different alkyl and aryl bromides and substituted diselenides, Table 4.[39]

In general, all reactions were very clean and selenides were obtained in excellent yields, as depicted in Table 4. We studied the electronic and steric effects of attached groups in the aryl bromides and in the diselenide moiety. In terms of electronic effects, the reaction was not very sensitive to this influence, since the coupling of diphenyl diselenide with neutral, electron donating and electron withdrawing aryl bromides were efficiently achieved (entries 1–5). Comparing the coupling reaction between the aryl bromide **1c** and **1e**, the activated one (4-OMe group) **1c** showed a higher yield (entry 3 *vs.* 5). Despite this, the coupling was efficient and allowed the formation of diaryl selenides with good yields. Analyzing Table 4 (entries 3–4 and 8–10), it is possible to observe that in terms of steric and electronic effects, the reaction was not strongly influenced by these parameters. As described, the reaction was not hampered and the diaryl selenides were obtained in high yields. To extend the scope of our coupling protocol, alkyl bromides were also employed (entries 6 and 7). Using our methodology it was possible to prepare alkyl aryl selenides in reasonable yields, which are difficult to prepare according to the previous report.[9]

The quest for developing economic and environmental friendly methods is one of our prime concerns. It prompted us to evaluate the possibility of reusing the ionic liquid employed in our reactions. After the work-up, the catalyst CuO nanopowder was removed from BMIM-BF$_4$ by filtration and the recovered ionic liquid was used again for the next coupling reactions.[40] This operation was repeated for more three times without significant lose of efficiency, as shown in Fig. 2.

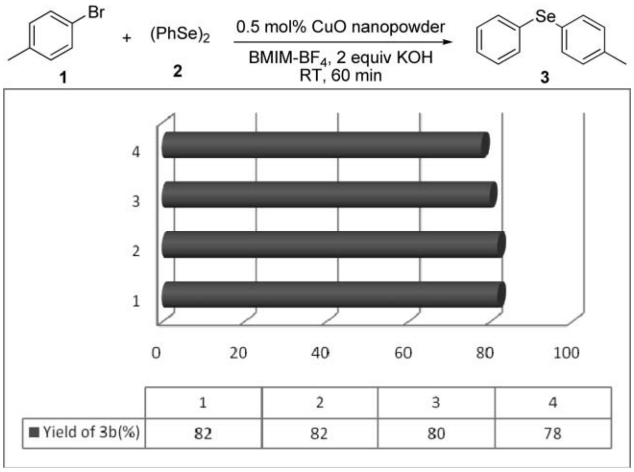


Fig. 2 Reuse of BMIM-BF$_4$.

In conclusion, we have developed a clean, eco-friendly, inexpensive and efficient methodology to obtain diaryl or alkyl aryl selenides from alkyl or aryl halides with diaryl diselenides using CuO nanopowder in ionic liquid as a recyclable solvent. Features of this method include the following: (i) easily accessible alkylating agents were used; (ii) very small amount of catalyst used; (iii) use of recyclable solvent.

Acknowledgements

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38 During the preparation of this manuscript, a similar cross-coupling reaction was published. The methodology employed 2 mol% of catalyst in DMSO, with similar yields as obtained in our protocol (see ref 9).

39 General procedure to the synthesis of selenides **3a–j**: in a Schlenck tube under nitrogen atmosphere and at room temperature CuO nanoparticles (0.006 mmol, 0.5 mol%) followed by diphenyl diselenide **2a** (0.5 mmol) and KOH (1.0 mmol, 2.0 equiv) were added to a solution of bromo toluene **1b** (1.1 mmol) in BMIM-BF$_4$ (1.0 mL). The progress of the reaction was monitored by TLC. After, the reaction was complete, the product was extracted by successive washing with diethyl ether (5 × 5 mL) and drying over MgSO$_4$. The solvent and volatiles were completely removed under vacuum to give the crude product. The compounds were purified by column chromatography over silica gel.

40 After work-up, BMIM-BF$_4$ was treated with DCM and filtered over Celite to remove the CuO residue. The solution was dried over MgSO$_4$ and the volatiles were removed under vacuum. The recovered ionic liquid was reused for the next reaction.

APPENDIX 2

Published article for the synthesis of selenoesters

Efficient synthesis of selenoesters from acyl chlorides mediated by CuO nanopowder in ionic liquid

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Herein, we report an eco-friendly synthesis of selenoesters from acyl chlorides catalyzed by recyclable CuO nanopowder in ionic liquid as a recyclable solvent in good to excellent yields. This protocol shows high efficiency in catalyzing this transformation in a greener fashion than previous protocols due to the non-residual methodological design.

Over the past decades, higher organochalcogenides have been established as functional elements in biochemistry and medicine. In particular, selenium and organoselenium compounds are gaining increasing attention due to their properties as antioxidant and antitumor agents, as apoptosis inducers, and in the effective chemoprevention of cancer in a variety of organs.[1–4]

Selenoesters are important intermediates in several organic transformations. The compounds in this class have been used as precursors of acyl radicals[5] and anions[6] and have attracted attention for the synthesis of new molecular materials, especially superconducting materials and liquid crystals.[7] Applications of selenoesters have been expanded to the synthesis of proteins by chemical ligation of chalcogenol esters,[8] to the synthesis of substrates which undergo facile and efficient radical decarbonylation, as well as to the synthesis of the natural alkaloid (+)-geissoschizine.[9]

There are a number of methods reported in the literature to synthesize selenoesters using different metals, including palladium complexes (such as $Pd(PPh_3)_4$),[10] samarium di-iodide,[11] indium,[12] indium(I) iodide,[13] $Hg(SePh)_2$,[14] $PhSeSnBu_3/Pd$,[15] and Rh/H_2[16] systems. However, these procedures have limitations such as the air reactivity of metals, harsh conditions, and the difficulty involved in handling selenium compounds, besides the use of toxic and carcinogenic solvents.

From a sustainable chemistry point of view, there is a need for new methods that are truly efficient, high yielding, responsive to mild reaction conditions, and byproduct-free. In this regard, ionic liquids have frequently been used in the last few years as alternative reaction media for a broad range of chemical transformations. They present various interesting properties which could alleviate environmental problems, such as no effective vapor pressure, nonvolatility, nonflammability, excellent chemical and thermal stability, and recyclability, which make them attractive media for organic reactions.[17] Additionally, organic reactions catalyzed by metallic nanostructures are currently an area of intensive research, with many reports in the literature.[18] Generally, catalysts in nanoscale afford a more effective process and allow a genuine advance in relation to traditional methodologies. Nanomaterials containing high surface area and reactive morphologies have been studied as effective catalysts for organic synthesis.[19] In this new intensive area, CuO has emerged as a useful catalyst in several transformations.[20]

Considering our ongoing research into organochalcogen chemistry,[21] herein we wish to disclose a new and more eco-friendly approach to the synthesis of selenoesters employing recyclable ionic liquids and CuO nanopowders, as depicted in Scheme 1.

Scheme 1 General synthesis of selenoesters.

In order to optimize the protocol and to understand the influence of different variables on this reaction, several components were studied. To this end, we carried out the reaction employing 4-methylbenzoyl chloride **1e** as a representative acyl chloride and 0.5 equiv. of diphenyl diselenide affording the corresponding selenoester **2e** (Table 1). In a first set of experiments, we studied the influence of different ionic liquids. It was possible to observe that in all examples the desired product was obtained with yields ranging from 82% to 90%. Nevertheless, BMIM-PF_6 was the most efficient ionic liquid for this reaction affording a better yield for selenoester **2e** (Table 1, entry 3).

The influence of different bases was studied to perform a more efficient cleavage of the diselenides, affording the nucleophilic selenolate species. Cs_2CO_3 and KOH provided the selenoester **2e** in good yields (Table 1, entries 3 and 5), whereas other bases, such as K_2CO_3 and Na_2CO_3, gave only moderate yields (Table 1, entries 6 and 7). The product was not observed in the absence of base (Table 1, entry 10), and the best base for this reaction was Cs_2CO_3 (Table 1, entry 3). The variation in the reaction time from 30 to 60 min was studied. The yield increased from 30 min to a maximum of 60 min (Table 1, entries 3, 8 and 9). Longer

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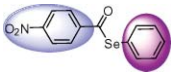
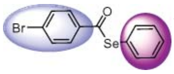
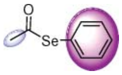
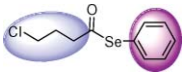
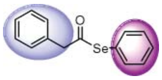
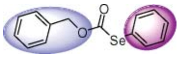
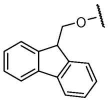
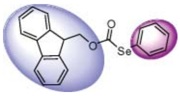
Table 1 Optimization of the reaction: ionic liquid and base

Entry	Ionic Liquid	Base (2 eq.)	Time/min	Yield[a] (%)
1	BMIM-BF_4	Cs_2CO_3	60	82
2	BMIM-NTf	Cs_2CO_3	60	84
3	BMIM-PF_6	Cs_2CO_3	60	90
4	BMIM-PF_6	Cs_2CO_3	60	Traces[b]
5	BMIM-PF_6	KOH	60	88
6	BMIM-PF_6	K_2CO_3	60	72
7	BMIM-PF_6	Na_2CO_3	60	73
8	BMIM-PF_6	Cs_2CO_3	40	76
9	BMIM-PF_6	Cs_2CO_3	30	60
10	BMIM-PF_6	none	60	—
11	BMIM-PF_6	Cs_2CO_3	240	90
12	BMIM-PF_6	Cs_2CO_3	240	30[c]

[a] Yields determined by GC. [b] Reaction performed at room temperature. [c] Reaction performed without CuO nanopowder.

Table 2 Synthesis of several selenoesters

Entry	*R*	Product	Yield (%)[a,b]
1	Ph, **1a**	 **2a**	91
2	*o*-ClPh, **1b**	 **2b**	83
3	*p*-NO_2Ph, **1c**	 **2c**	57
4	*p*-BrPh, **1d**	 **2d**	84
5	*p*-MePh, **1e**	 **2e**	90
6	Me, **1f**	 **2f**	69
7	ClC_3H_6, **1g**	 **2g**	61
8	CH_2Ph, **1h**	 **2h**	72
9	Ph, **1a**	 **2i**	80
10	Ph, **1a**	 **2j**	86
11	$PhCH_2O$, **1i**	 **2k**	79
12	 **1j**	 **2l**	90

[a] Yields determined by GC. [b] All compounds are reported in our previous work, ref. 12.

reaction times did not have an influence on the product yield (Table 1, entry 11).

Finally, to further optimize the protocol, it was necessary to examine the effect of the amount of catalyst in promoting the reaction efficiency. Without catalyst, the reaction worked very slowly and the product was obtained in low yield (Table 1, entry 12). We found that varying the amount of CuO nanopowder had an effective influence on the reaction course. When the amount of CuO nanopowder was increased from 1.0 to 2.0 mol%, the yield of compound **2e** was significantly modified from 48% to 82%. By using 5.0 mol% of CuO nanopowder, the yield was further improved to 90%. Nonetheless, raising the amount of CuO nanopowder up to 10 mol% did not change the yield of the desired product, affording the same level of 90%, as shown Fig. 1.

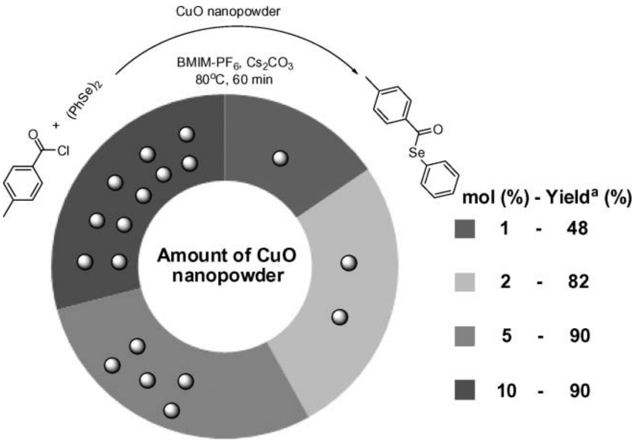


Fig. 1 Optimization of CuO nanopowder. [a]Yields determined by GC.

After the optimizations, under standard conditions we performed a series of reactions using different kinds of acyl chlorides with diaryl diselenides to synthesize the selenoesters **2a–l**. All reactions were clean and efficient and the respective compounds were obtained in good to excellent yields, as depicted in Table 2.[22] In terms of electronic effects, it was possible to verify that the reaction is more sensitive to the acid chloride than the diselenide moiety. For instance, a strong electron withdrawing group, such as the nitro attached to acyl chloride (Table 2, entry 3) affords a moderate yield of 57% of the desired selenolester **2c**. By using **1a** (neutral) and **1e** (electron donating group), the reaction proceeds efficiently and the selenoesters are obtained in excellent yields (Table 2, entries 1 and 5). Aliphatic acyl chlorides were used to afford alkanoate selenoesters. As expected, the corresponding compounds were obtained in good yields (Table 2, entries 6, 7, and 8). In terms of diselenide, this outcome is less effective, but still it was possible to observe that electron withdrawing groups afforded slightly lower yields than the other groups (Table 2, entries 9 and 10). This can be rationalized in terms of the lower nucleophilicity of these selenolate species. As a further extension, we attempted to synthesize a

Table 3 Synthesis of selenoesters catalyzed by CuO nanopowder

Runs	Catalyst recoverability(%)	Product Yield[a] (%)
1	96	89
2	92	84
3	85	82
4	80	74

[a] Yields determined by GC.

selenocarbonate bearing interesting functionalities and obtained encouraging results. When we used benzyl chloroformate (**1i**) and 9-fluorenylmethyl chloroformate (**1j**), the corresponding selenocarbonates **2k** and **2l** were obtained in yields of 79% and 90%, respectively (Table 2, entries 11 and 12).

In addition, to obtain non-residual version of the protocol, the recyclability of the catalyst and ionic liquid was studied. The CuO nanopowder was recovered from the reaction mixture. It was reused for three further runs and no loss of activity was observed, providing the product in very good yields (Table 3, entries 1–4).

In Fig. 2, the TEM analysis of the CuO nanopowder was performed before and after four reaction runs. The samples showed identical powder morphology and size after reuse of the catalyst in this transformation and, as previously reported,[23] these experimental results suggest that the reaction involves a heterogeneous process *via* surface CuO nanopowder catalysis.

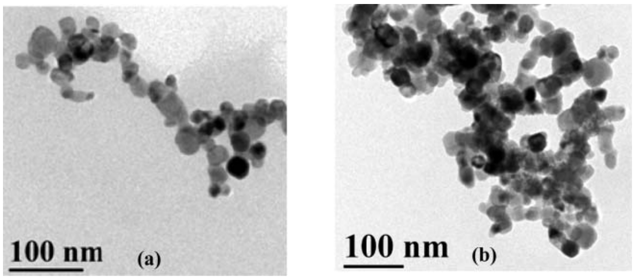


Fig. 2 TEM images of CuO nanopowder. (a) Fresh CuO nanopowder, (b) CuO nanopowder after four reaction runs. CuO nanopowder was purchased from Sigma Aldrich (mean particle size, 33 nm, surface area, 29 m^2 g^{-1} and purity, 99.99%).

Considering the ionic liquid, after the work-up, BMIM-PF$_6$ was separated by filtration and the recovered ionic liquid was used again for the next reactions.[24] This operation was repeated another three times without significant loss of efficiency, as shown in Fig. 3.

A possible mechanism for the CuO nano particle catalyzed C–Se cross-coupling of acyl chlorides and diphenyl diselenide is illustrated in Scheme 2.

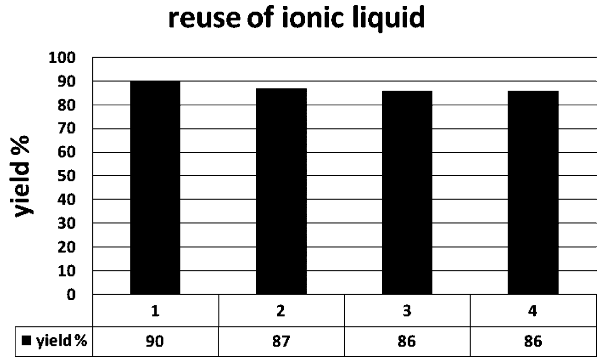
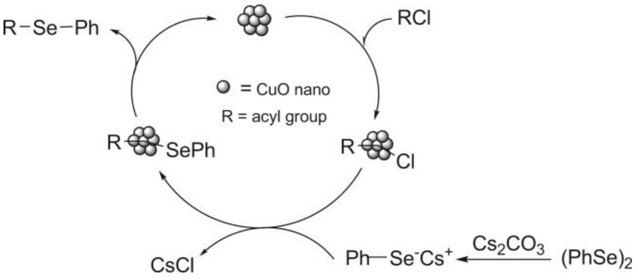


Fig. 3 Recyclability of BMIM-PF$_6$.



Scheme 2 Plausible reaction pathway.

In conclusion, we have developed a nanocrystalline CuO catalyzed coupling of acyl chlorides with diphenyl diselenide to form selenoesters in excellent yields. This new coupling reaction underlines the potential of using nanocrystalline CuO as a very user friendly, inexpensive, and efficient catalyst for this coupling reaction. The catalyst and solvent (BMIM-PF$_6$) can be easily recovered and reused. We are in the process of expanding the substrate scope of the reaction. The important features of this protocol are: (1) recyclable CuO nanopowder; (2) recyclable solvent; (3) mild reaction conditions.

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22 General procedure to the synthesis of selenoesters **2a–k**: In a Schlenk tube under nitrogen atmosphere, 4-methylbenzoylchloride **1e** (1.0 mmol) and CuO nanopowders (0.06 mmol, 5.0 mol%) followed by diphenyl diselenide (0.5 mmol) and Cs_2CO_3 (1.0 mmol, 2.0 equiv.) (1.0 mmol) in BMIM-PF_6 (1.0 mL) were stirred at 80 °C for 60 min. The progress of the reaction was monitored by TLC. When, the reaction was complete, the product was extracted by successive washing with n-butanol (5 × 5 mL) and drying over $MgSO_4$. The solvent and volatiles were completely removed under vacuum to give the crude product. The compounds were purified by column chromatography over silica gel.

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24 Recyclability experiments: The CuO nanopowders and solvent BMIM-PF_6 can be recycled without loss of activity (Table 3 and Fig. 2). After completion of the reaction workup, the reaction mixture was treated with ethanol, and filtered through a Teflon membrane. The CuO nanopowder was recovered from the membrane by washing with water and collected by further centrifugation and drying under vacuum. It was reused for the reactions in the next three runs, and no loss of activity was observed, providing the product in high yields. The ionic liquid was recovered from the ethanol (10 ml) after filtration, evaporation of the solvent and drying the BMIM-PF_6 (1 ml) under vacuum for reuse in subsequent reactions.

APPENDIX 3

Published article for the synthesis of diselenides and ditellurides

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An Efficient One-Pot Synthesis of Symmetrical Diselenides or Ditellurides from Halides with CuO Nanopowder/Se^0 or Te^0/Base

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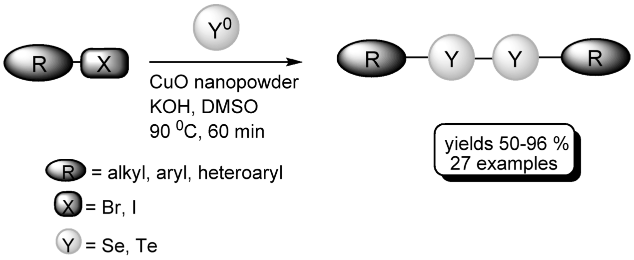
ABSTRACT



A CuO nanopowder-catalyzed coupling reaction of aryl, alkyl, and heteroaryl iodides with elemental selenium and tellurium takes place in the presence of KOH at 90 °C in DMSO. A wide range of substituted symmetrical diselenides and ditellurides were afforded with good to excellent yields.

During the last few decades, organochalcogen (Se or Te) compounds[1] have emerged as important reagents and intermediates in organic synthesis.[2] Organodichalcogenides, the selenium or tellurium counterpart of organic peroxides, play an important role in organochalcogen chemistry since they are stable, easily handled, and reactive enough to produce electrophilic, nucleophilic, and radicophilic species.[3] Related derivatives in which one selenium or tellurium atom is replaced by oxygen or sulfur are also known and play crucial biological roles as antioxidants, antitumor agents, and apoptosis inducers, as well as in the degradation of hydroperoxides and in the chemoprevention of cancer in a variety of organs.[4] There are a

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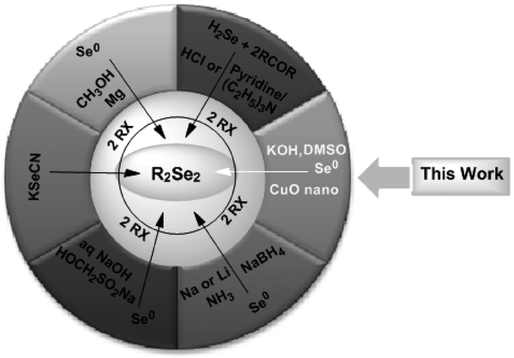
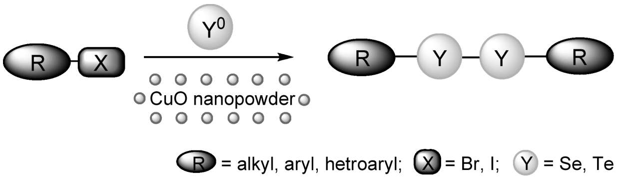


Figure 1. Various ways to prepare diselenides.

variety of methods reported to prepare organic diselenides or ditellurides (Figure 1). Most of them involve the reaction of metal diselenides or ditellurides with alkyl halides, dimerization with selenocyanates,[5−7] oxidation of selenols[8] or selenolates,[9] and reactions of aldehydes with sodium hydrogen selenide in the presence of an amine and sodium borohydride.[10,11] Sonoda et al. discovered that elemental selenium can be readily reduced by carbon monoxide and water in the presence of base to produce hydrogen selenide, which was successfully applied to the synthesis of aliphatic diselenides from both aliphatic ketones and aldehydes[12] or from alkyl chlorides and acyl chlorides,[13] respectively.

Despite the variety of methodologies, there are some drawbacks to these known methods of diselenide synthesis, such as the use of strong reducing agents, highly toxic gas, harsh reaction conditions, low yields, or complex manipulations. From a sustainable chemistry point of view, there is a need for new methods that are truly efficient, high yielding, responsive to mild reaction conditions, byproduct-free, and efficient in the presence of multifunctional groups. Organic reactions catalyzed by metallic nanostructures are currently an area of intensive research, with many reports in the literature.[14] Generally, catalysts in nanoscale afford a more effective process and allow a genuine advance in relation to traditional methodologies. The high surface area and reactive morphologies of nanomaterials allow them to be effective catalysts for organic synthesis.[15]

Scheme 1. General Scheme of Synthesis of Diselenides



In this new intensive area, CuO has emerged as a useful catalyst in several transformations.[16] As previously reported, CuO nanopowder shows an effective influence in the chalcogenide functionalizations, allowing the synthesis of organic selenides in high yields.[17] As part of our ongoing research into organochalcogen chemistry,[18] herein we disclose a new and efficient methodology to prepare symmetrical aryl and alkyl diselenides and ditellurides using CuO nanopowders as a catalyst, with good to excellent yields, as depicted in Scheme 1.

To the best of our knowledge, this is the first report of the use of a CuO nanoparticle-catalyzed reaction to prepare symmetrical organodichalcoganides.

In order to optimize the protocol and to understand the influence of different variables in this reaction, several components were studied. To this end, we carried out the reaction under standard conditions employing 4-iodotoluene

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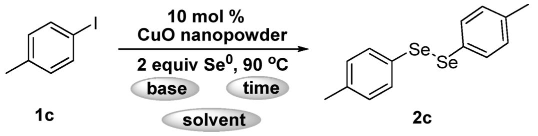
Table 1. Nano CuO Oxide-Catalyzed Cross-Coupling of Diphenyl Diselenide with 4-Methyl-1-iodobenzene



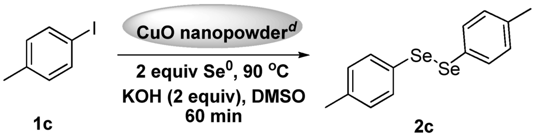
entry	solvent	base (2 equiv)	time (min)	yield[a] (%)
1	DMSO	KOH	60	96
2	DMF	KOH	60	90
3	CH_3CN	KOH	60	91
4	THF	KOH	60	
5	toluene	KOH	60	
6	dioxane	KOH	60	
7	CH_2Cl_2	KOH	60	
8	DMSO	Cs_2CO_3	60	85
9	DMSO	NaOH	60	86
10	DMSO	$NaHCO_3$	60	
11	DMSO	K_2CO_3	60	36
12	DMSO	KOH	30	64
13	DMSO	KOH	120	81
14	DMSO	KOH	240	45
15	DMSO	KOH	60	traces[b]
16[c]	DMSO		60	

[a] Yields determined by GC. [b] Reaction performed at room temperature. [c] No coupling reaction occurred without base.

as a representative halide, 10 mol % of CuO nanopowder, elemental selenium (2.0 equiv), and KOH (2.0 equiv) in DMSO (2.0 mL) for 1 h, affording the corresponding diaryl selenide **2c** in 96% yield (Table 1, entry 1). In a first set of experiments, we studied the influence of different solvents (Table 1, entries 1−7). By analyzing Table 1, it can be observed that the desired product was not obtained in the solvents THF, 1,4-dioxane, and toluene (entries 4−6). However, the reaction was highly effective with polar aprotic solvents (entries 1−3). These results suggest that the success of the reaction depends on the polarity of the solvent. In this regard, DMSO was the most efficient solvent for this reaction affording the best yield for diselenide **2c** (entry 2).

The influence of different bases was the next variable studied. In this context, a number of bases, in DMSO, were used to afford M_2E_n reactive species. In this context, Cs_2CO_3, NaOH, and $NaHCO_3$ were compared to KOH (Table 1, entries 8, 9, and 10, respectively). Notably, KOH allowed the best performance among the screened bases, furnishing the desired product in excellent yield (Table 1, entry 1). As a result, KOH was selected as the optimum base to perform the subsequent reactions. Another important factor studied was the reaction time. This variable has an effective influence on the reaction course, with yields decreasing from 96 to 64% when the reaction time was reduced from 60 to 30 min (entries 1 and 12). Longer reaction times also have an influence on the product yields. When the reaction time was increased to 120 and 240 min, the product yields decreased to 81% and 45%, respectively (entries 13 and 14).

Table 2. Optimization of Nano CuO Catalyst[a]



entry	nano CuO (mol %)	yield[b] (%)
1	2.0	70
2	5.0	89
3	10.0	96
4	20.0	96
5	0.0[c]	

[a] Reaction conditions: 4-iodotoluene (1.0 mmol), CuO nanoparticles, Se^0 (2.0 equiv), KOH (2.0 equiv), and DMSO (2.0 mL) were stirred under a nitrogen atmosphere at 90 °C for 60 min. [b] Yields determined by GC. [c] No coupling reaction occurred without nano CuO. [d] CuO nanopowder was purchased from Sigma-Aldrich, with an average of 30−40 nm as shown in technical support.

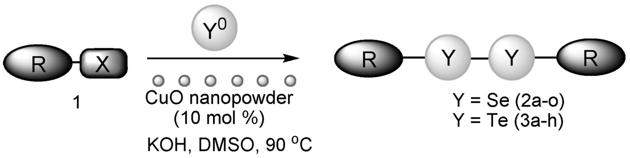
Finally, in order to optimize the protocol, the impact of the catalyst amount on the reaction efficiency was investigated. We found that this parameter had an effective influence on the reaction course. For instance, when the amount of CuO nanopowder was increased from 2.0 to 10 mol %, the yield of compound **2c** raised considerably (from 70% to 96%; Table 2, entries 1−3). Raising the amount of CuO nanopowder up to 20 mol % did not show a significant influence, affording the desired product at the same level of 96% (Table 2, entry 4). The product was not observed in the absence of catalyst; hence this component is required in order to perform the reaction (entry 5).

After the optimized reaction conditions were established, a number of halides were examined to explore the scope and limitations of this methodology. Under standard conditions, a series of reactions using different kinds of aryl, alkyl, and hetroaryl halides was performed to synthesize the symmetrical diselenides **2a−o** and ditellurides **3a−h** (Table 3).

As summarized in Table 3, both electron-rich and electron-deficient aryl iodides were effective in this process, giving the corresponding products in good to excellent yields. It is noteworthy that sterically hindered ortho and meta substrates also provided high yields of diselenides (Table 3, entries 3, 5, 6, and 9−12) and ditellurides (Table 3, entries 18, 20, and 22), respectively. One advancement associated with this methodology is that a wide range of functional groups are tolerated in this process, including methyl, methoxy, hydroxyl, aldehyde, amino, bromo, and heteroaryl moieties. Some of them are very sensitive, e.g., aldehyde, and the direct preparation of the related diselenides employing the described methodologies is not efficient for these kinds of substrates. Thus, we conclude that this method provides a general approach to preparing more complex diselenides and ditellurides.

Upon analysis of Table 3, it can be verified that, as expected, iodide was more reactive than bromides and chlorides. This result allowed the exploration of the regioselectivity of this reaction, with the preparation of selective bromo-and chlorodichalcogenides (Table 3, entries 4, 5, 7, and 19). Additionally, the electron-withdrawing groups attached to the aromatic ring afforded better yields than

Table 3. Synthesis of Diselenides via a One-Pot Coupling−Reduction Procedure[a]



entry	R	X	Y	product	yield[c] (%)
1	Ph	I (**1a**)	Se	**2a**	96
		Br (**1b**)	Se		52
2	4-MeC$_6$H$_5$	I (**1c**)	Se	**2b**	96
		Br (**1d**)	Se		71
3	2-MeC$_6$H$_5$	I (**1e**)	Se	**2c**	90
4	4-ClC$_6$H$_5$	I (**1f**)	Se	**2d**	89[b]
5	2-ClC$_6$H$_5$	I (**1g**)	Se	**2e**	90[b]
6	2-HOC$_6$H$_5$	I (**1h**)	Se	**2f**	72
7	4-BrC$_6$H$_5$	I (**1i**)	Se	**2g**	89[b]
8	4-MeOC$_6$H$_5$	I (**1j**)	Se	**2h**	80
		Br (**1k**)	Se		69
9	3-MeOC$_6$H$_5$	I (**1l**)	Se	**2i**	89
10	2-MeOC$_6$H$_5$	I (**1m**)	Se	**2j**	89
11	2,4-MeOC$_6$H$_4$	I (**1n**)	Se	**2k**	50
12	2-NH$_2$C$_6$H$_5$	I (**1o**)	Se	**2l**	87
13	3-Py	I (**1p**)	Se	**2m**	82
14	4-OHCC$_6$H$_5$	Br (**1q**)	Se	**2n**	72
15	C$_7$H$_{15}$	I (**1r**)	Se	**2o**	96
16	Ph	I (**1a**)	Te	**3a**	86
17	Ph	Br (**1b**)	Te		56
18	2-MeC$_6$H$_5$	I (**1e**)	Te	**3b**	88
19	4-ClC$_6$H$_5$	I (**1f**)	Te	**3c**	90[b]
20	2-HOC$_6$H$_5$	I (**1h**)	Te	**3d**	86
21	4-MeOC$_6$H$_5$	I (**1j**)	Te	**3e**	80
22	2-NH$_2$C$_6$H$_5$	I (**1o**)	Te	**3f**	82
23	3-Py	I (**1p**)	Te	**3g**	72
24	C$_7$H$_{15}$	I (**1r**)	Te	**3h**	84

[a] Reaction conditions: halide (1.0 mmol), CuO nanoparticles (10.0 mol %), Y^0 (2.0 equiv), KOH (2.0 equiv), and DMSO (2.0 mL) were stirred under a nitrogen atmosphere at 90 °C for 60 min. [b] Reaction complete in 30 min. [c] Yield of the isolated product.

donating groups (Table 3, entries 4 and 8). This can be explained by the easier insertion of copper into the more electron-deficient aromatic ring. In order to explore the versatility of the current methodology, more complex aromatic halides were employed. As depicted in Table 3, amino (entries 12, 13, 22, and 23), hydroxy (entries 6 and 20), and aldehyde (entry 14) groups were used, and in all cases the corresponding diselenide and ditelluride were obtained in good yields. Alkyl diselenide (entry 15) and ditelluride (entry 24) were obtained from the respective alkyl iodide, yielding 96 and 84%, respectively. Furthermore, diselenides were obtained in high yield, without the use of protection groups or an excess of reagents.

On the basis of previous reports,[19] a plausible mechanism for the CuO nanopowder-catalyzed cross-coupling of halides with selenium and tellurium nucleophiles to obtain diselenides and ditellurides can be proposed, as depicted in Figure 2.

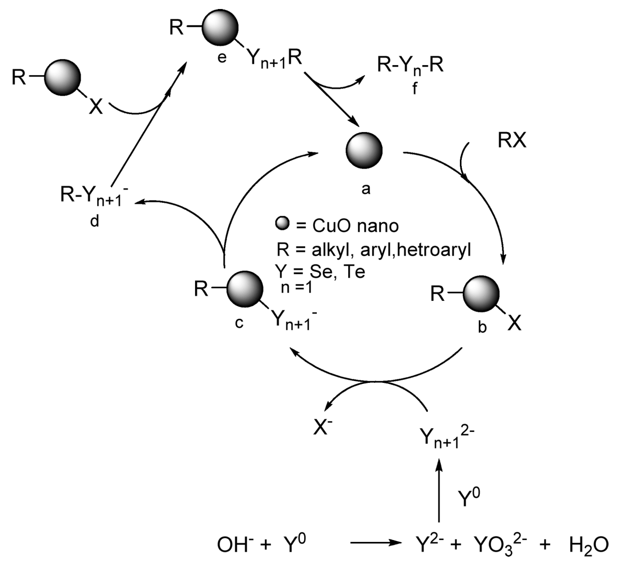


Figure 2. Plausible mechanism for organo dichalcogenide synthesis.

Selenium and tellurium may have behavior similar to that established for sulfur[19] in the presence of base, giving the chalcogenolate or dichalcogenolate anion. Using a superbasic DMSO−KOH system, a reductive dimsyl species is formed[20] which may selectively allow the preparation of the desired dichalcogenolate anion. We assume that this ion might serve as the active species in the catalytic cycle. The formation of the complexes **a** and **b** followed by the ligand exchange with the dichalogenolate anion might provide complex **c**, which could undergo reductive elimination to give the initial coupling product **d** and regenerate the CuO nanoparticles. The complex **d** would react with another complex **b** furnishing the complex **e**. Finally, a reductive elimination could afford the desired dichalcogenide **f** and release CuO nanoparticles for use in the catalytic cycle.

In conclusion, a simple, efficient, and straightforward procedure is described for the preparation of diselenides or ditellurides through cross-coupling of selenium and tellurium and aryl iodides using CuO nanopowder. This methodology is highly chemoselective, uses neutral conditions, and allows the preparation of a wide range of substituted symmetrical diselenides and ditellurides containing methoxy, hydroxyl, carboxylate, amino, aldehyde, and bromo groups in good to excellent yields.

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Supporting Information Available: Detailed experimental procedures and copies of analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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