วิธีที่มีประสิทธิภาพสำหรับปฏิกิริยาคาลโคจินิลเลชันของสารประกอบอินโดล

The Efficient Method for Chalcogenylation of Indoles

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Burapha University

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วิธีที่มีประสิทธิภาพสำหรับปฏิกิริยาคาลโคจินิลเลชันของสารประกอบอินโดล

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The efficient methods of C-Se and C-S bond formation for synthesizing of chalcogenylindoles were demonstrated. This work consists of two parts of research containing selective synthesis of 3-chalcogenylindoles *via* silver-catalyzed direct chalcogenation of indoles with dichalcogenides (work 1) and controllable synthesis of mono- and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system (work 2).

In work I, the new method was developed for direct regioselective C-H chalcogenylation of indoles promoted by $AgNO_3$ at the C3-position. The reaction was performed by diselenides and disulfides under aerobic mild reaction conditions with economical and eco-friendly process to produce the corresponding 3-chalcogenylindoles in good to high yields and a short reaction time. This method could be scalable up to gram scale synthesis.

In work 2, the development of selective and controllable sulfenylation of indoles with disulfides and thiols was studied using KI as a catalytic system under mild conditions. Mono-sulfenylindoles and bis-sulfenylindoles were obtained in moderate to excellent yields. This method was successfully performed with metal-free conditions moisture tolerant and operationally simple.

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TABLE OF CONTENTS

Page

ABSTRACT ..... D
ACKNOWLEDGEMENTS ..... E
TABLE OF CONTENTS ..... F
LIST OF TABLES ..... H
LIST OF FIGURES I
CHAPTER 1 12
INTRODUCTION 12
1.1 Selective synthesis of 3-chalcogenylindoles *via* silver-catalyzed direct chalcogenation of indoles with dichalcogenides 12
1.2 Controllable synthesis of mono- and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system 16
CHAPTER 2 22
LITERATURE REVIEWS 22
2.1 Selective synthesis of 3-chalcogenylindoles *via* silver-catalyzed direct chalcogenation of indoles with dichalcogenides 22
2.2 Controllable synthesis of mono- and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system 38
CHAPTER 3 45
RESEARCH METHODOLOGY 45
3.1 General Considerations 45
3.2 Experimental Procedures 46
CHAPTER 4 64
RESULTS AND DISCUSSION 64
CHAPTER 5 117
CONCLUSIONS 117

REFERENCES 118
BIOGRAPHY 125

LIST OF TABLES

Page

Table 1 Condition screening for C3-chalcogenation system.....48

Table 2 Optimization of the Reaction Conditions 55

Table 3 Optimization of the reaction conditions.....65

Table 4 Scope of indoles for chalcogenation with diphenyl diselinide and disulfide 66

Table 5 Scope of indoles for chalcogenation with dibenzyl diselinide and dibenzyl disulfide.....67

Table 6 Optimization of the Reaction Conditions 87

Table 7 Mono-sulfenylation of indoles with disulfides. 88

Table 8 Mono-sulfenylation of indoles with thiols. 90

Table 9 Bis-sulfenylation of indoles with disulfides. 91

Table 10 Bis-sulfenylation of indoles with thiols.....92

LIST OF FIGURES

Page

Figure 1 Examples of biologically relevant 3-chalcogenyl indoles. 13

Figure 2 Different strategies for the synthesis of 3-chalcogenyl indoles via direct C–H chalcogenation. 15

Figure 3 Representative examples of bioactive sulfenylindoles. 17

Figure 4 Deferent strategies for the synthesis of sulfenylindoles. 20

Figure 5 Molecular iodine catalyzed 3-sulfenylation of indoles with disulfides. 23

Figure 6 Proposed mechanism for the iodine-catalyzed 3-sulfenylation of indoles. .24

Figure 7 Molecular iodine catalyzed 3-chalcogenylation of indoles under solvent-free conditions. 24

Figure 8 Synthesis of 3-selanylindoles from indole derivatives and diselenides catalyzed by IK/mCPBA. 25

Figure 9 Proposed mechanism for the selenation of indole catalyzed by KI/mCPBA. 25

Figure 10 Synthesis of 3-chalcogenylindoles under TCCA-MgO catalysis system. 26

Figure 11 Sulfenylation and bromosulfenylation of indoles with disulfides. 26

Figure 12 Chalcogen functionalization of N-heteroarenes. 27

Figure 13 Plausible reaction mechanism for chalcogenation of N-heteroarenes. 27

Figure 14 Base promoted 3-sulfenylation of indoles and heteroarenes in ionic liquid. 28

Figure 15 Synthesis of 3-selenylindoles. 29

Figure 16 Proposed mechanism for the synthesis of 3-selenylindoles. 29

Figure 17 t-BuOK promoted C3-chalcogenylation of indoles. 30

Figure 18 Scale-up reaction of 3-chalcogenylindoles synthesis. 30

Figure 19 CuI-catalyzed direct C-H chalcogenylation of aromatic azaheterocycles with dichalcogenides. 31

Figure 20 The possible reaction mechanism. 31

Figure 21 The direct selective C-H thiolation/selenation of electron-rich hetero-arenes with disulfides or diselenides. 32

Figure 22 Synthesis of 3-arylselenyl and 3-arylthioindoles under US irradiation. ...33

Figure 23 C–H selenation of substituted indoles. 34

Figure 24 Gram-scale visible-light-mediated aerobic selenation of N-methyl indole. 34

Figure 25 Rose Bengal catalyzed photo-induced selenylation of indoles, imidazoles and arenes. 35

Figure 26 Scope of indoles. 35

Figure 27 Electrocatalytic C–H selenation of indole derivatives. 37

Figure 28 Gram-scale synthesis of 3-selenylindole. 37

Figure 29 Synthesis of 3-sulfanylindoles under molecular oxygen. 39

Figure 30 Plausible reaction mechanism. 39

Figure 31 Synthesis of 3-sulfenylindoes from indoles and various disulfides. 40

Figure 32 Proposed reaction mechanism. 41

Figure 33 Sulfenation of various indoles with Bunte salts, thiols and disulfides. 42

Figure 34 Proposed reaction mechanism via aerobic oxidative C–S Bond Coupling. 42

Figure 35 Synthesis of 3-chalcogenylindoles. 43

Figure 36 Proposed reaction mechanism. 43

Figure 37 Synthesis of indole derivatives. 47

Figure 38 Chalcogenation of indoles with diphenyl diselenide (2a) and disulfide(3a).....50

Figure 39 Chalcogenation of indoles with dibenzyl diselenide (2b) and disulfide (3b).....51

Figure 40 Gram-scale chalcogenation of indole (1a).....52

Figure 41 Control experiments for mechanistic studies.....53

Figure 42 Mono-sulfenylation of indoles with disulfides.....56

Figure 43 Mono-sulfenylation of indoles with thiols.....57

Figure 44 Bis-sulfenylation of indoles with disulfides.....59

Figure 45 Bis-sulfenylation of indoles with thiols.....60

Figure 46 Gram-scale synthesis (isolated yields).....60

Figure 47 Control Experiments 63

Figure 48 Chalcogenation of indole (1m) with diphenyl diselenide (2a).....67

Figure 49 Gram-scale synthesis (isolated yields).....68

Figure 50 Control experiments for mechanistic studies.....69

Figure 51 Proposed mechanism.....70

Figure 52 Gram-scale synthesis (isolated yields).....93

Figure 53 Control Experiments.....95

Figure 54 Proposed mechanism for the formation of mono- and bis-sulfenylindoles.
.....97

CHAPTER 1
INTRODUCTION

This research consists of two works containing selective synthesis of 3-chalcogenylindoles *via* silver-catalyzed direct chalcogenation of indoles with dichalcogenides and controllable synthesis of mono- and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system.

1. 1 Selective synthesis of 3-chalcogenylindoles *via* silver-catalyzed direct chalcogenation of indoles with dichalcogenides

Indoles are important heterocyclic compounds that found in many bioactive natural products and frequently use in pharmaceutical, biological and materials applications (Rino Ragno, Ettore Novellino, & Marino Artico, 2006), (Bandini & Eichholzer, 2009), (Hamann, 2010), (M. Z. Zhang, Chen, & Yang, 2015) (M. Z. Zhang et al., 2015) and (Owczarczyk et al., 2013). It is also consistently used in the synthesis of various organic compounds by binding with different compounds that have diverse biological activities, which makes indole as important privileged scaffolds in drug design and development. Among indole derivatives, 3-selenyl and 3-sulfenyl indoles are currently receiving increasing attention because theirs biological and medicinal properties such as anti-inflammatory, antitumor, HIV inhibitor, antinociceptive and antiviral activities (Casaril et al., 2017), (Guan et al., 2014), (Wen et al., 2015), (La Regina et al., 2013), (Nuth, Guan, Zhukovskaya, Saw, & Ricciardi, 2013) and (Birmann et al., 2018); (Figure 1).

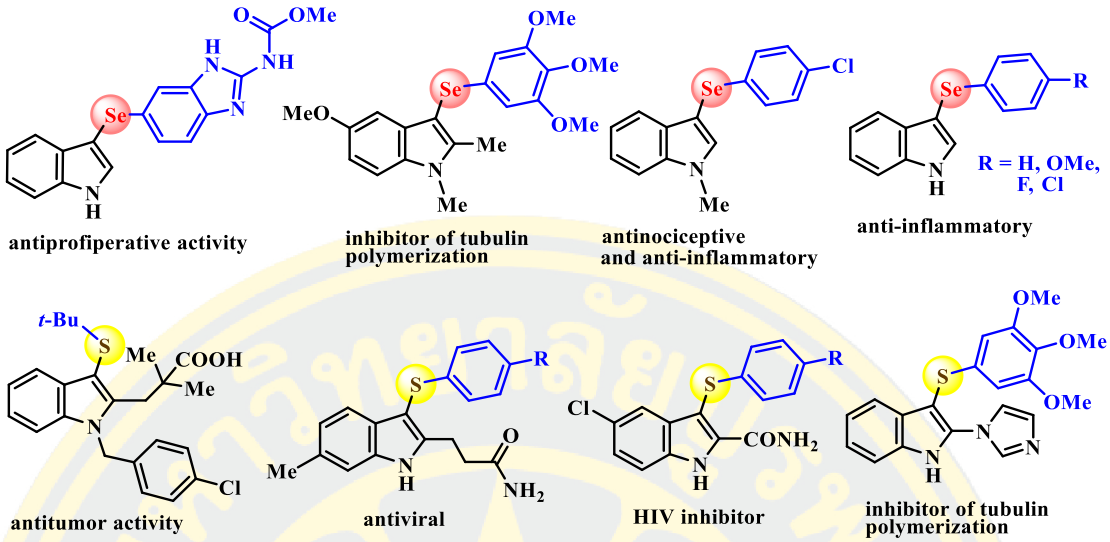


Figure 1 Examples of biologically relevant 3-chalcogenyl indoles.

Consequently, the selective C–Se and C-S bond formation for 3-chalcogenyl indoles synthesis *via* C(sp^2)–H functionalization is becoming an interesting approach. Furthermore, various approaches for C3-chalcogenation through C(sp^2)–H have been established during the past few years. In previous work, diselenides and disulfides are commonly used as the chalcogenylating agents because they are stable, easily accessible and easy to handle during manipulations. Generally, the direct C(sp^2)–H chalcogenation of C3 position in indole core *via* electrophilic chalcogenation by *in situ* generated RYX catalyzed by oxidants (W. Ge & Wei, 2012), (Azeredo, Godoi, Martins, Silveira, & Braga, 2014), (H. Li, Wang, & Yan, 2017), (Silveira, Mendes, Wolf, Martins, & von Mühlen, 2012), (Huang et al., 2012) and (Bettanin et al., 2018) and another was proceeded through the strong base (La Regina et al., 2013), (Gao, Zhu, & Zhang, 2014), (Ferreira, Azeredo, Fiorentin, & Braga, 2015) and (Yu, Zhou, Song, & Liang, 2018) and transition metal-based catalysis process (Z. Li, Hong, & Zhou, 2011) and (Vasquez-Cespedes, Ferry, Candish, & Glorius, 2015); (Figure 2). Recently, the development of synthetic technology, microwave or ultrasound and photocatalysis in the presence of catalysts (Wen et al., 2015),(Wen et al., 2016), (Q.-B. Zhang et al., 2017) and (Saba et al., 2018); (Figure 2) has also been applied to the C(sp^2)–H selenation of indoles. However, these methods frequently require use of toxic reagents, excess additives or strong base or costly catalysts in harsh reaction

conditions with high temperatures or oxygen-free techniques. Additionally, the low atom economy caused by the loss of RY^- 1 equiv. as waste (H. Li et al., 2017), (Gao et al., 2014), (Ferreira et al., 2015) and (Yu et al., 2018). Therefore, this work aimed to develop the efficient method for direct C(sp^2)–H chalcogenylation of indoles at the C3-position using mild conditions, low-cost and atom economy with a wide substrate scope.

However, the direct C(sp^2) –H chalcogenation of indoles with diorganyl chalcogenides using silver catalyst have not been reported. In the part of cross-coupling reaction of aryl boronic acids with diaryl diselenides employing silver as catalyst (Goldani et al., 2016) and silver-mediated oxidative functionalization of alkylsilanes (Wang, Xu, Cong, & Tang, 2018) that are simplify syntheses such as reducing the number of steps and waste generation. Therefore, we became interested in the development of the new method for regioselective chalcogenylation of indole derivatives with dichalcogenides using $AgNO_3$ as catalyst under aerobic and mild reaction conditions.

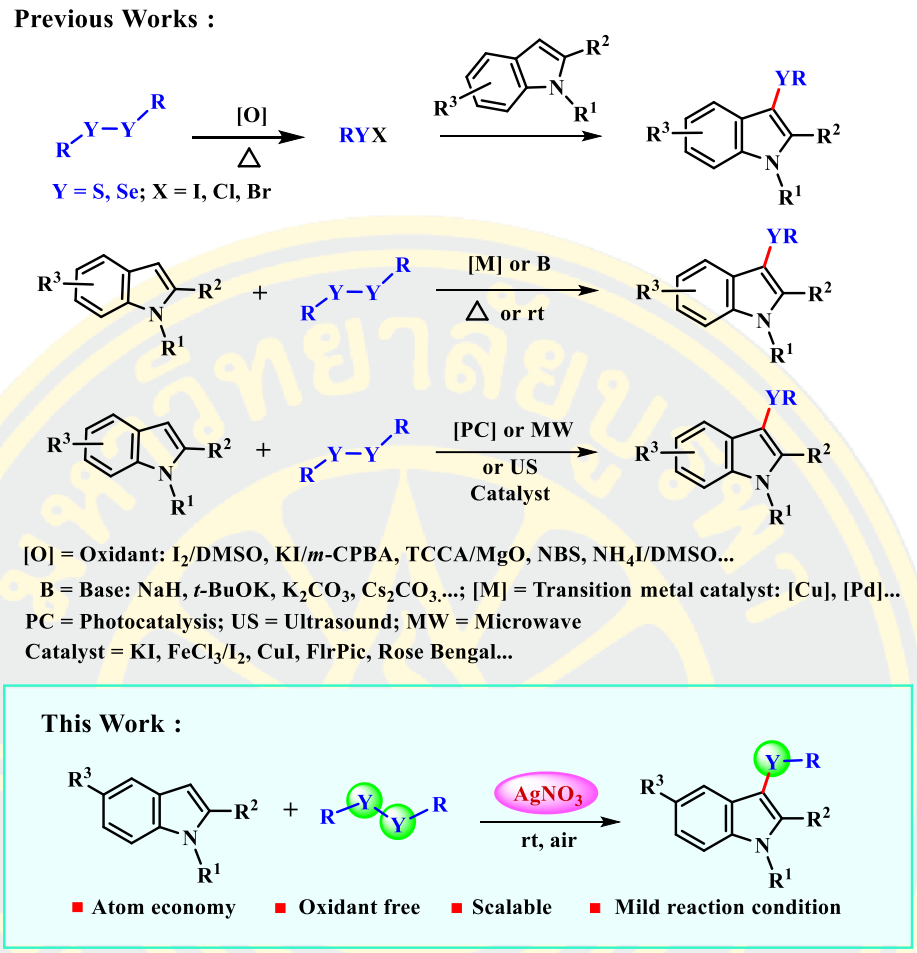


Figure 2 Different strategies for the synthesis of 3-chalcogenyl indoles *via* direct C–H chalcogenation.

1.1.1 Objectives

To develop a new methodology with efficient strategy using $AgNO_3$ for regioselective synthesis of 3-chalcogenyl indoles *via* direct C(sp^2)–H chalcogenylation of indole derivatives under mild reaction conditions, low-cost and atom economy with a wide substrate scope.

1.1.2 Scope of the study

1. Optimization study was focused on the reaction of indole with diphenyl diselenide in the presence of various amount of $AgNO_3$ using different solvents under aerobic conditions at room temperature.

2. *N*-substituted indoles were prepared to employ as substrate for direct C(sp^2)–H chalcogenylation of indole derivatives of diselenides and disulfides under optimized condition.
3. 3-Chalcogenyl indoles were synthesized with various substrate scope and characterized by ^{1}H NMR, ^{13}C NMR, IR and high-resolution mass.
4. The synthetic utility of this approach was performed in gram-scale reaction under the standard conditions
5. Possible mechanism of this protocol will be explored.

1.1.3 Contribution to knowledge

The new approach from this study will lead to the efficient synthesis of 3-chalcogenylindoles, which is scalable, economical and mild reaction condition. The developed method can be applied for the synthesis of different chalcogenyl arenes and chalcogenyl heteroarenes using various diaryl/ diheteroaryl dichalcogenides with a broad substrate scope. Especially, this strategy can also be applied to the pharmaceutical industry in convenient synthetic chemistry.

1. 2 Controllable synthesis of mono- and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system

The efficient method of C-S bond construction has received increasing development for synthesis of sulfenylindoles due to these compounds have a wide range of biological and pharmaceutical applications such as compound I (La Regina et al., 2013), (Figure 3) have been reported to represent potent inhibitor of tubulin polymerization, which was proven as anti-cancer agent. Analogously, compound II (Nuth et al., 2013), compound III (Rino Ragno et al., 2006) and compound IV or MK886 (Cianchi et al., 2006), (Figure 3) have been reported to use for potential therapeutic as antiviral, HIV inhibitor and antitumor activity.

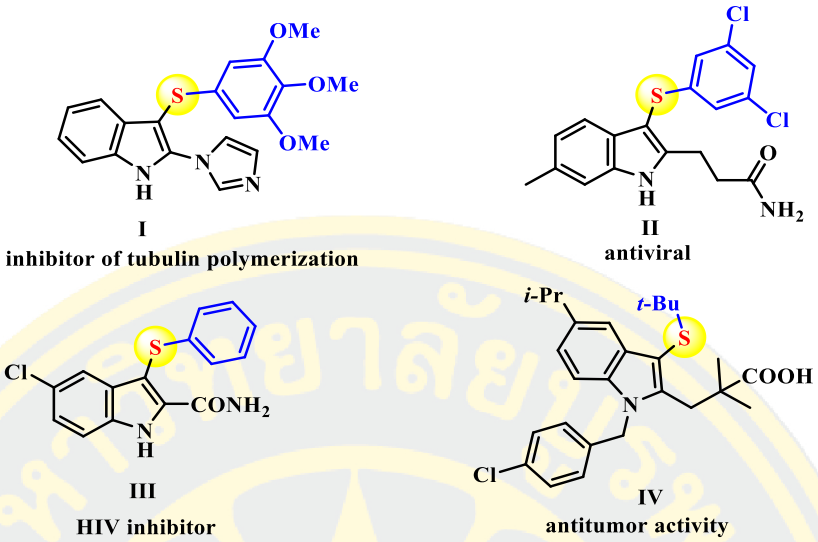


Figure 3 Representative examples of bioactive sulfenylindoles.

The direct C-H sulfenylation of indoles by *in situ* generated RSX in the presence of oxidant is a powerful method that currently obtains high attention. Accordingly, the direct sulfenylation for sulfenylindoles synthesis is still considerably desired efficient, mild condition and sustainable method without transition-metal catalysts and harsh reaction conditions. There are many method that has been uses various sulfenylating reagents such as thiol (Shen et al., 2018), (M. Chen et al., 2019), (Saima, Equbal, Lavekar, & Sinha, 2016), (Guo et al., 2017), (Yi et al., 2016) and (Ohkado, Ishikawa, & Iida, 2018) disulfide (Shen et al., 2018, Vásquez-Céspedes et al., 2015, Yu et al., 2018, Silveira et al., 2012, Bettanin et al., 2018, (Ye, Chen, Mao, Zhang, & Yan, 2017), (Hazarika & Barman, 2019) and Gao et al., 2014) Bunte salts (Shen et al., 2018, (Harrity, Al-Saedy, & Nassoy, 2017; J. Li, Cai, Wang, & Ji, 2016) and (Qi, Zhang, Wan, & Luo, 2016) sulfonylhydrazide (Ravi, Semwal, Kumar, Reddy, & Adimurthy, 2018), (Rahaman, Devi, Sarma, & Barman, 2016) and (Yang & Tian, 2013) sulfenyl halides (Hamel, 2002) and sulfur powder (X. Ge et al., 2019) for sulfenylation of indoles. Among sulfenylating reagents, thiols and disulfides are the most atom-economical sulfenylation agents and ready availability.

Previously, Ravi and co-worker (Ravi et al., 2018) described I_2 (20 mol%) catalyzed decarboxylative sulfenylation of indole carboxylic acids under transition metal-free conditions at 100 °C using benzenesulfonohydrazides as sulfenylating

agent to obtain both mono and bis-sulfenyl indoles in excellent yields. In 2015, Zhang and co-worker (H. Zhang, Bao, Song, Qu, & Wang, 2015) reported the protocol for the selective synthesis of mono and bis-sulfenylindoles *via* direct oxidative sulfenylation of indoles with thiophenols. The selectivity of bis-sulfenylindoles synthesis need to use I_2 (50 mol%) and *tert*-butyl hydroperoxide (TBHP, 2.1 equiv.) as catalyst furnishing the desired product in good to excellent yields. Recently, Changqing et al. (Changqing et al., 2018) reported an I_2 (1 equiv.)/PPh_3 (2 equiv.) as catalytic system for sulfenylation of indoles in water with sodium sulfinates as the sulfur source to afford mono-sulfenylindoles in moderate to excellent yields. In addition, bis-sulfenylindole was also performed under double C-H sulfenylation of indoles at 2- and 3-positions by using excess sodium sulfinates under the optimized reaction conditions. Although these methods have been successfully selective mono- and bis-sulfenylation of indoles, there are remains an unsolved problem from using of sub-equivalent amounts of oxidant.

In recent years, potassium iodide (KI) combined with different oxidants to catalyze the direct sulfenylation of indoles has been a highly efficient and convenient approach for the synthesis of 3-sulfenylindoles compounds. Additionally, KI is a non-toxic, inexpensive, and readily available catalyst procedure, that is applicated in various organic synthesis. For example, in 2004, Uemura group (Yasunari Maeda, 2004) reported the direct synthesis of 3-sulfanylindoles from indoles and thiols using the combination of KI (10 mol%), butylhydroxytoluene (BHT) , (5 mol%) and vanadium oxyacetyl- acetonate [$VO(acac_2$] , (1 mol%) as catalyst under an atmospheric pressure of molecular oxygen. Products were obtained in yields up to 86% (Figure 4a) . Subsequently, Chen et al. (C. Chen, Niu, Shen, & Li, 2018) successfully applied the electrochemical system for the direct sulfenylation of indoles with disulfides through C-S bond formation mediated by KI at a low potential to synthesize the corresponding 3-sulfenylindoles in medium to excellent yields (Figure 4b). Furthermore, Shen et al. (Shen et al., 2018) described the sulfenylations that were performed with KI combined sodium nitrite ($NaNO_2$) as the catalytic system in the presence of acetic acid and molecular oxygen. (Figure 4c). They have successfully developed this catalytic oxidation system for the sulfenylation of indoles with a variety of sulfenylation agents including Bunte salts, thiols and disulfides to generate

target products in yields up to 89%. Recently, Rampon et al. (Luz et al., 2019) developed a protocol for synthesis of 3-chalcogenylindoles from dichalcogenides and indoles derivatives using the Fe(III)/KI system *via* direct electrophilic sulfenylation strategy (Figure 4d).

Although diferent methods containing KI have been successfully applied to construct structurally diverse 3-sulfenylindole or mono-sulfenylindoles, there are no report about KI system that can accomplish double C-H sulfenylation in indoles at C2- and C3-positions to synthesize bis-sylfenylindole. We became interested to employ selenium oxide (SeO_2) as oxidant with KI because SeO_2 have been often applied in various oxidations for many organic syntheses such as allylic hydroxylation (Strommer et al., 2004), (Kang, 2001) and (Choi et al., 2009) 1,2-dihydroxylation (Chang, Lin, & Chen, 2010), (Pranjal Gogoi, 2007) and (Meng-Yang Chang, 2006) and α-oxyfunctionalization (Lauer, 1972) of alkenes. Additionally, SeO_2 can also successful mediated oxidative coupling (Rohman et al., 2012) and (Vollbrecht et al., 2008) oxidative amidation (Shaw, Denning, & Hulme, 2012), dehydrogenation (Saravanan, Purushothaman, Bernadette Amali, & Muthusubramanian, 2009) and (Meenakshi, Ramamoorthy, Muthusubramanian, & Sivasubramanian, 2001) and aromatization (Satya Paul, 2007). In the past few years, Lenardão et al (Vieira et al., 2017) reported the use of CuI/SeO_2 as a catalytic system in DMSO for the synthesis of 3-selanylindoles and 3-selanylimidazopyridines under ultrasound irradiation. However, DMSO is not green solvent and solutions of inorganic salts or organic compounds in DMSO are potentially dangerous to skin membranes (Leake, 1966). Herein, we report a new method for the selective and controllable synthesis of mono- and bis-sulfenylindoles using KI/SeO_2 system *via* the C-H sulfenylation of indoles with disulfides or thiols (Figure 4e.) Especially, this development is mind condition, no adding of metal transition, ligands or additives and without exclusion of air and moisture.

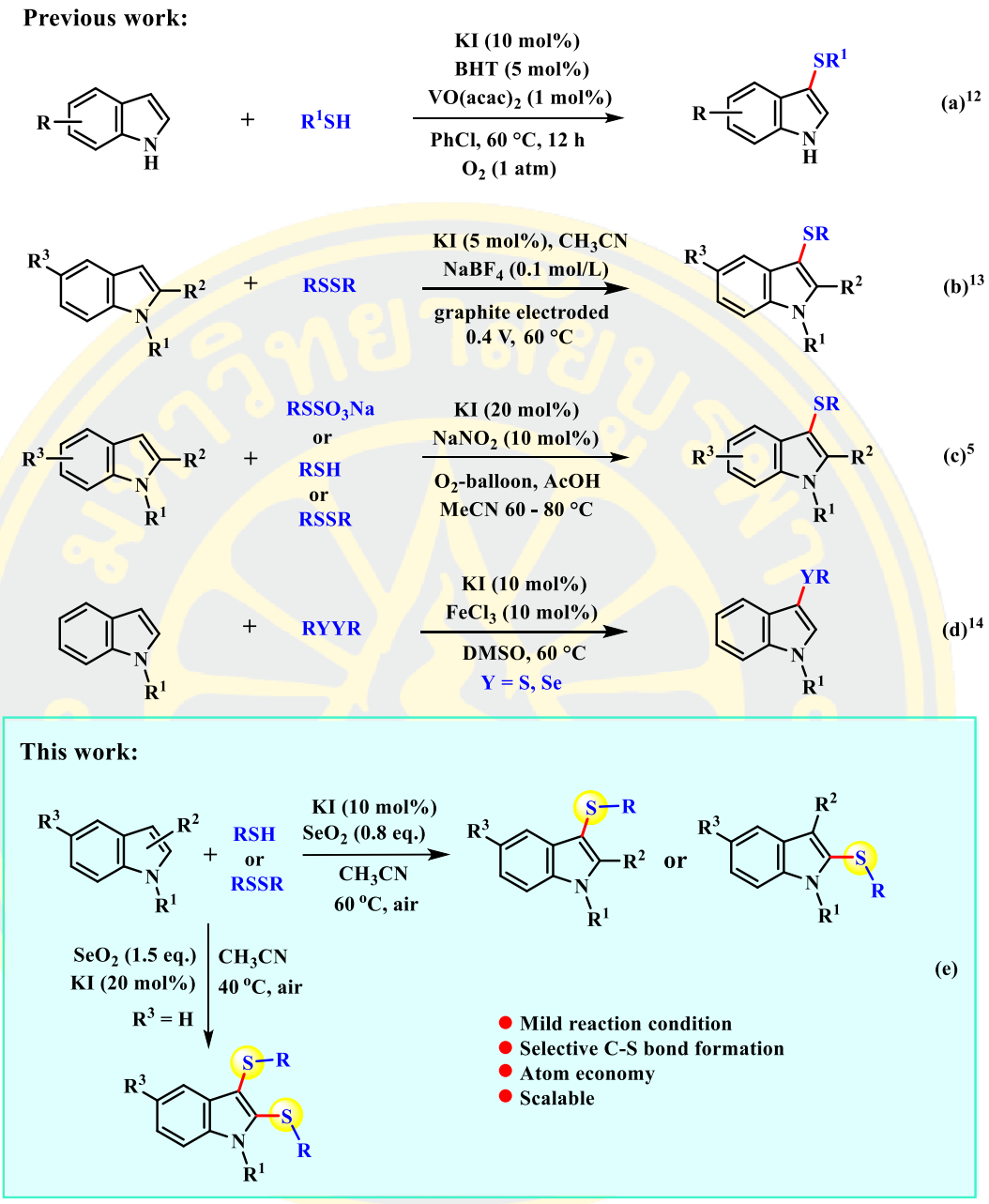


Figure 4 Deferent strategies for the synthesis of sulfenylindoles.

1.2.1 Objectives

To develop a new synthetic method using KI/SeO_2 for selective synthesis of mono- and bis-sulfenylindoles *via* direct C(sp^2)–H chalcogenylation of indole and its derivatives under mild reaction conditions, low-cost and atom economy.

1.2.2 Scope of the study

1. Optimization study was focused on the reaction of indole with diphenyl disulfide in the presence of KI/SeO_2 using different solvents and temperature under aerobic conditions.
2. A series of mono- and bis-sulfenylindoles analogues were synthesized using various indoles and different disulfides and thiols and characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS.
3. A gram scale reaction was performed under the standard conditions
4. The mechanism for selective formation of mono- and bis-sulfenylindole was investigated.

1.2.3 Contribution to knowledge

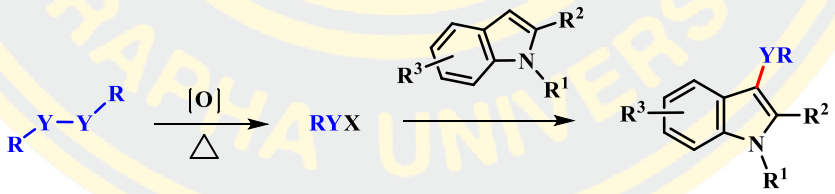
The developed approach from this study will lead to the efficient synthesis of mono- and bis-selenylindoles, which is scalable, economical and mild reaction condition. The developed protocol can be applied for the preparation of different mono- and bis-sulfenyl arenes or heteroarenes using other sulfenylating reagents with a broad substrate scope.

CHAPTER 2
LITERATURE REVIEWS

2.1 Selective synthesis of 3-chalcogenylindoles *via* silver-catalyzed direct chalcogenation of indoles with dichalcogenides

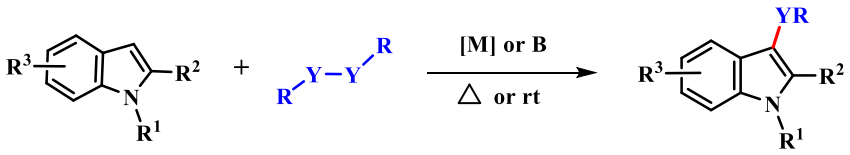
To develop a new and efficient methodology for 3-chalcogenylindoles synthesis, the information and background regarding the appropriate research methodologies are necessary. In this chapter, previous approaches for synthesis of C3-chalcogenyl indoles *via* direct C(sp^2)–H chalcogenation (thiolation/selenation) were discussed. In previous works, diselenides and disulfides were commonly used as the chalcogenylating agents for coupling with indoles or various (hetero)arenes because they are stable, easily accessible, commercially available, and easy to handle during manipulations. Generally, different strategies of the direct C(sp^2)–H chalcogenation, which have been developed for 3-sulfenylindoles and 3-selenylindoles synthesis can be classified as follows:

1. **Electrophilic chalcogenation by in situ generated RYX in the presence of oxidants.**



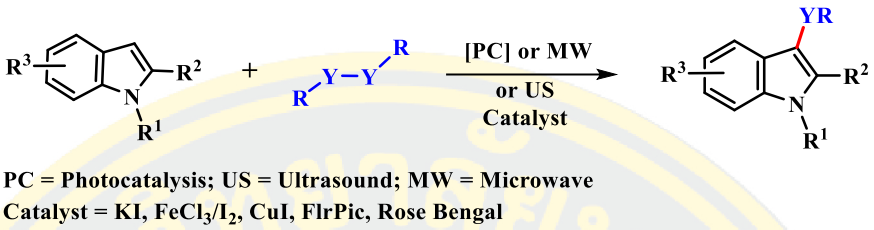
Y = S, Se; R = Ph, Bn; R^1, R^2, R^3 = H, Halide, Me, Aryl, X = I, Cl, Br
O = Oxidant: I_2/DMSO, KI/*m*-CPBA, TCCA/MgO, NBS, NH_4I/DMSO

2. **Direct C(sp^2) –H chalcogenation *via* bases or transition metal-based catalysis process.**



B = Base: NaH, *t*-BuOK, K_2CO_3, Cs_2CO_3,; M = Transition metal: [Cu], [Pd]

3. The C(sp^2)–H chalcogenation of indoles by synthetic technology using microwave, ultrasound and photocatalysis in the presence of different catalysts.



2.1.1 Previous approaches for the preparation of sulfenylindoles

1. Electrophilic chalcogenation by in situ generated RYX in the presence of oxidants.

Generally, the direct C–H chalcogenation of indoles *via* activation of dichalcogenides is carried out by an electrophilic attack of RY^+ from in situ generated RYX using different oxidants. Wenlei Ge and Yunyang Wei (W. Ge & Wei, 2012) reported the sulfenylation of indoles with disulfides using an I_2–DMSO oxidative system and dimethyl carbonate (DMC) as solvent without the need of oxygen and moisture-free reaction conditions. 3-Sulfenylindoles were obtained in good to excellent yields (Figure 5). Under this method, a plausible reaction mechanism was proposed according to Figure 6. Firstly, RSSR reacts with I_2 to form an electrophilic species RSI (**A**), then react with indole to produce intermediate **B**. Deprotonation of **B** gives the desired product and HI, which is oxidized by DMSO to regenerate I_2 for next catalytic cycle with the formation of water and dimethyl sulfane.

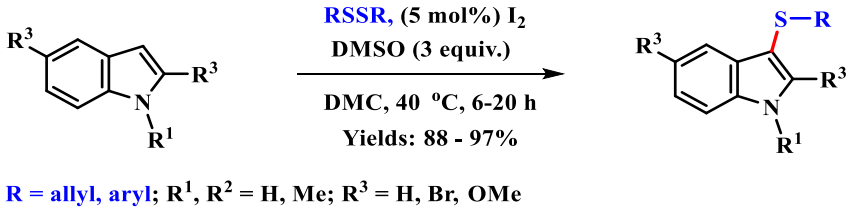


Figure 5 Molecular iodine catalyzed 3-sulfenylation of indoles with disulfides.

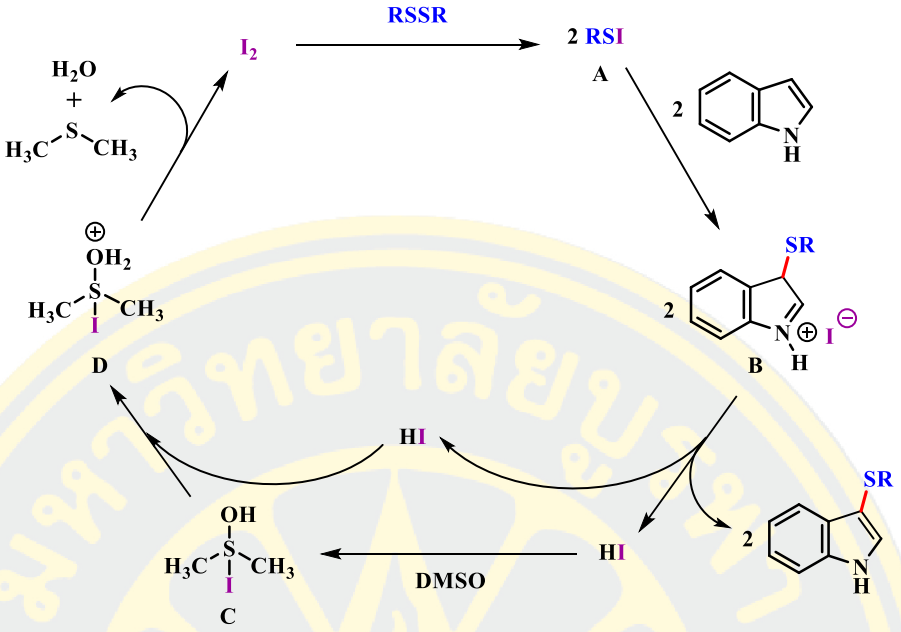
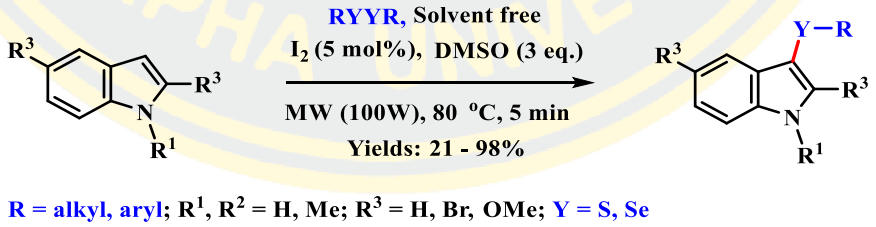


Figure 6 Proposed mechanism for the iodine-catalyzed 3-sulfenylation of indoles.

Juliano B. Azeredo and co-workers (Azeredo et al., 2014) described a solvent- and metal-free method, under microwave irradiation in short reaction time and employing molecular iodine as a catalyst. This method showed the excellent yields of 3-selenyl- and 3-sulfenyl-indoles from a wide range of indoles and diorganyl dichalcogenides (Figure 7).



R = alkyl, aryl; R^1, R^2 = H, Me; R^3 = H, Br, OMe; Y = S, Se

Figure 7 Molecular iodine catalyzed 3-chalcogenylation of indoles under solvent-free conditions.

In the presence of KI combined with oxidant *m*CPBA catalytic system, the preparation of 3-selanylindoles from indoles and diselenides (Figure 8) was developed by Hongjie Li and and co-workers (Li et al., 2017). In this protocol, a plausible mechanism is depicted in Figure 9, in which KI is first oxidized by *m*CPBA into

hypoiodous acid (HOI). Then, hypoiodous acid reacts with diselenide to cleave Se-Se bond producing active electrophilic selenium species (RSeI), followed by selenation of indole at the C3-position to afford 3-selanylindole *via* an electrophilic substitution mechanism.

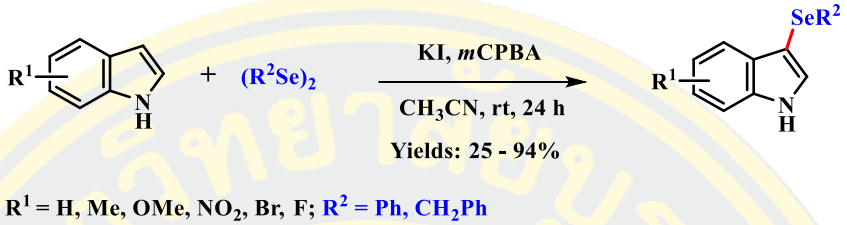


Figure 8 Synthesis of 3-selanylindoles from indole derivatives and diselenides catalyzed by IK/mCPBA.

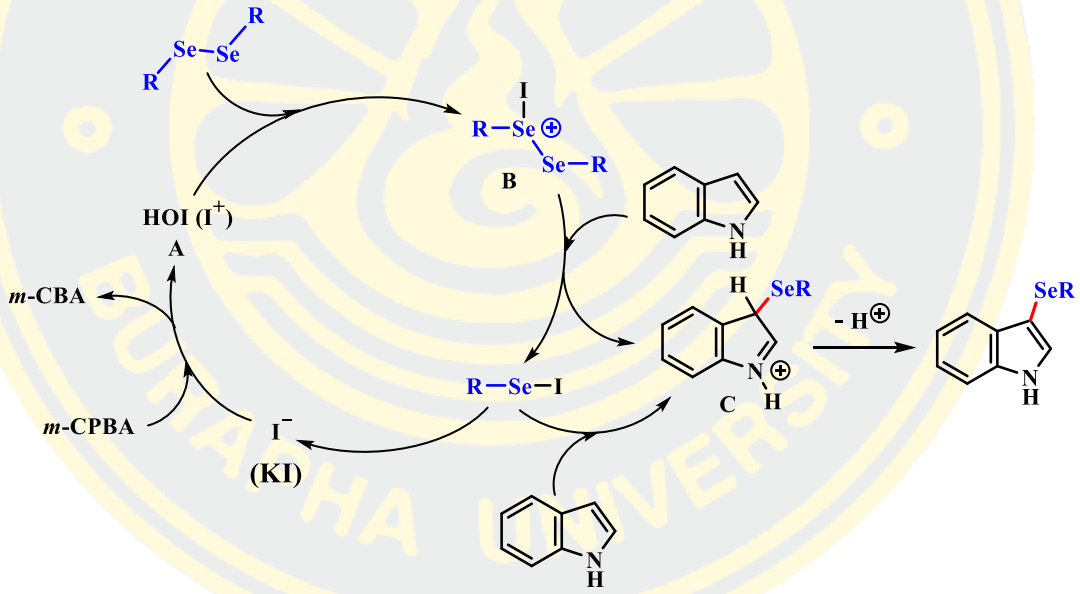


Figure 9 Proposed mechanism for the selenation of indole catalyzed by KI/mCPBA.

The electrophilic substitution reaction of indole derivatives with the diaryl dichalcogenide for the synthesis of 3-chalcogenylindoles under the trichloro-isocyanuric acid (TCCA)-MgO catalysis system (Figure 10) was explored by Claudio C. Silveira and co-workers (Silveira et al., 2012). According to this method, the active electrophilic chalconium species was firstly generated *via* TCCA-MgO catalysis

process into ArYCl, allowing direct C(sp^2)–H chalcogenation at the C3-position of the indole nucleus to form the corresponding 3-arylchalcogenyl indoles.

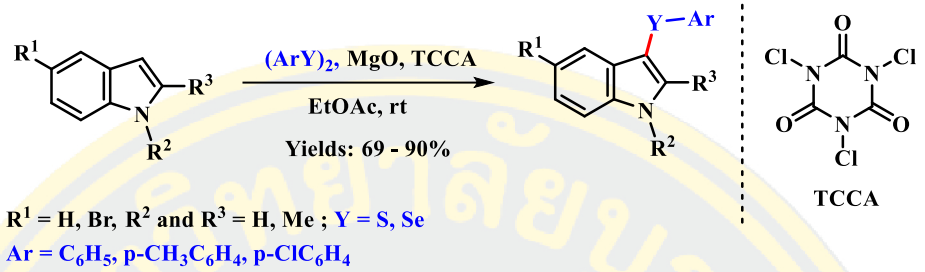


Figure 10 Synthesis of 3-chalcogenylindoles under TCCA-MgO catalysis system.

Additionally, Dayun Huang and co-workers (Huang et al., 2012) have been reported a route to 3-aryl thioindoles by regioselective sulfenylation of indoles with disulfides in the presence of *N*-bromosuccinimide (NBS, 3 equiv.) under metal-free conditions leading to yields in moderate to excellent yields of desired products. Furthermore, controllable synthesis of 2-bromo-3-arylthioindoles derivatives by the one-pot construction of C-S and C-Br bonds *via* bromosulfenylation of indoles with disulfides and *N*-bromosuccinimide (NBS, 5 equiv.) was described (Figure 11).

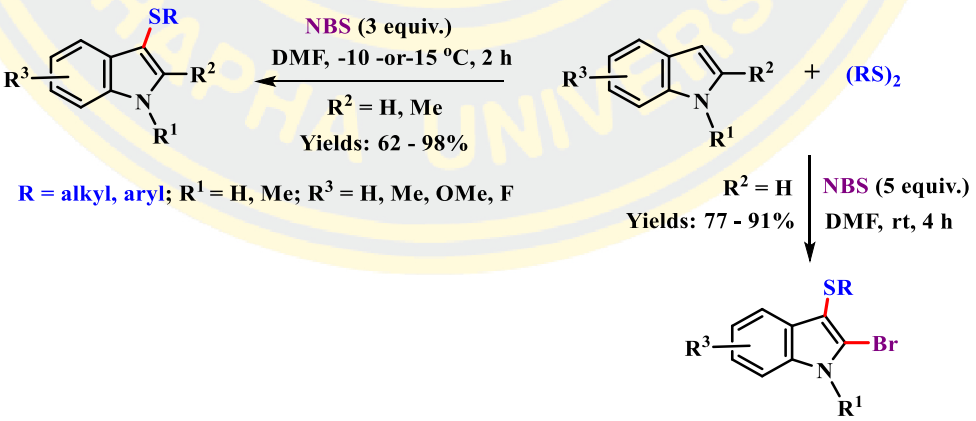


Figure 11 Sulfenylation and bromosulfenylation of indoles with disulfides.

Recently, the NH_4I-catalyzed C-H bond chalcogenation of *N*-heteroaryls in the presence of DMSO/H_2O/acetic acid system as additives (2.5/2.5/1M equiv., respectively), under metal free conditions (Figure 12) was described by Luana

Bettanin and co-workers (Bettanin et al., 2018). Under this approach, a wide variety of sulfenyl or selenyl different 5-membered *N*-heteroaryls, such as indole, imidazothiazole, indazole and imidazopyrimidine derivatives were prepared up to good yields. According to this experiment, the reaction mechanism is proposed in Figure 13. HI is firstly generated from NH_4I in the presence of an acid under heated conditions. Then, HI react with DMSO to afford I_2, which is converted to RSI by react with disulfide **2a**. Subsequently, RSI react with the imidazopyridine ring **1a** at the 3-position to give the desired product **3a** and regeneration of HI for next catalytic cycle.

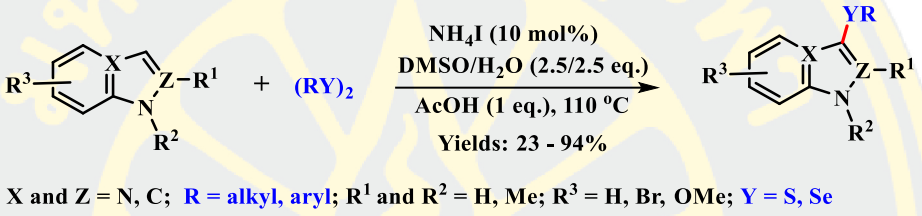


Figure 12 Chalcogen functionalization of *N*-heteroarenes.

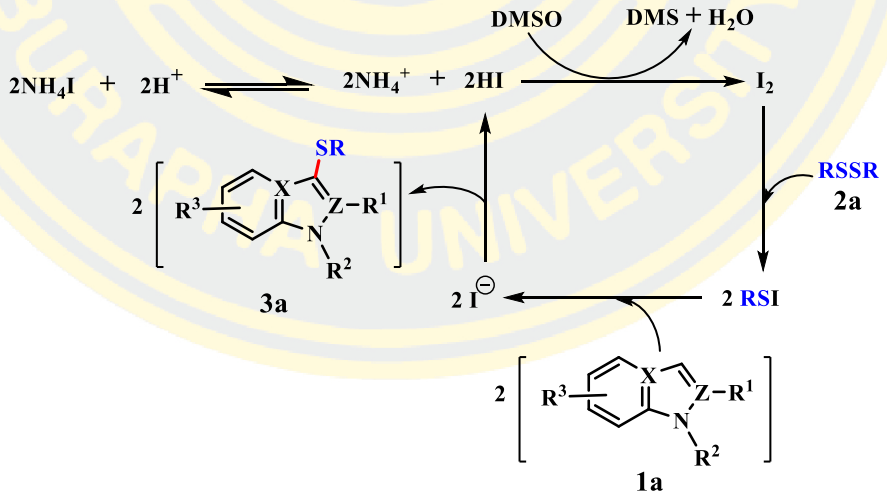


Figure 13 Plausible reaction mechanism for chalcogenation of *N*-heteroarenes.

2. Direct C(sp^2) –H chalcogenation *via* bases or transition metal-based catalysis process

In recent years, a few metal-catalyzed chalcogenation of heterocycles with dichalcogenides have been developed. Zhaochang Gao and co-workers (Gao et al., 2014) have developed a route for the synthesis of 3-sulfenyl indoles and related heteroarenes in good to excellent yields. The reaction was performed *via* base (Cs_2CO_3) promoted direct C–H bond sulfenylation of indoles and related heteroarenes with disulfides in 1-benzyl-3-octyl 2-ethyl-imidazolium tetrafluoroborate-based ionic liquid or [BnEOIm] BF_4 (IL3) (Figure 14). This protocol proposed mechanism involving deprotonation of the heterocycle by base to afford an anion, which was a key reaction step. Then the anion reacted with disulfide by nucleophilic attack, resulting in C–S bond formation.

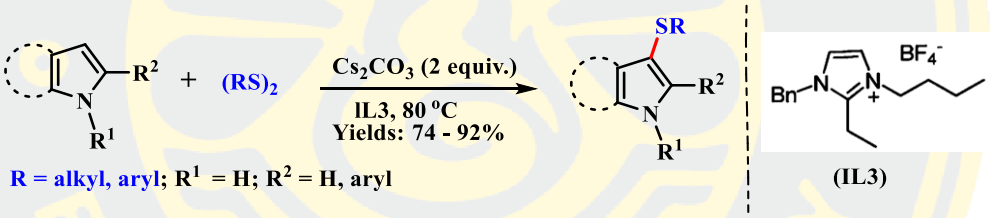


Figure 14 Base promoted 3-sulfenylation of indoles and heteroarenes in ionic liquid.

In 2015, Natasha L. Ferreira and co-workers reported the synthesis of 3-selenylindoles from indoles and diselenides under a greener protocol by using K_2CO_3 as catalyst and ethanol as a solvent in open air (Figure 15), (Ferreira et al., 2015). They obtained a library of 3-selenylindoles with different functionalities in yields up to 99%.

The reaction mechanism was proposed according to Figure 16. Based on these observations, the authors presented the hydrogen atom of indole is firstly removed by K_2CO_3, which generates a negative charge on the indole. Subsequently, the indole anion is oxidized into radical form under atmospheric air that can undergo reacts with diselenide to generate the 3-selenylindole and a selenide radical. The selenide radical would then removed the hydrogen atom from another indole

molecule, which is converted to selenol to complete the catalytic cycle, whereas the selenol is oxidized back to the diselenide.

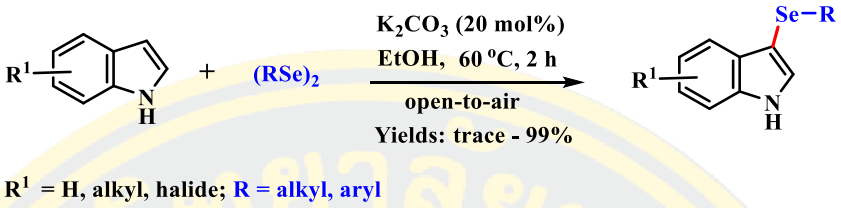


Figure 15 Synthesis of 3-selenylindoles.

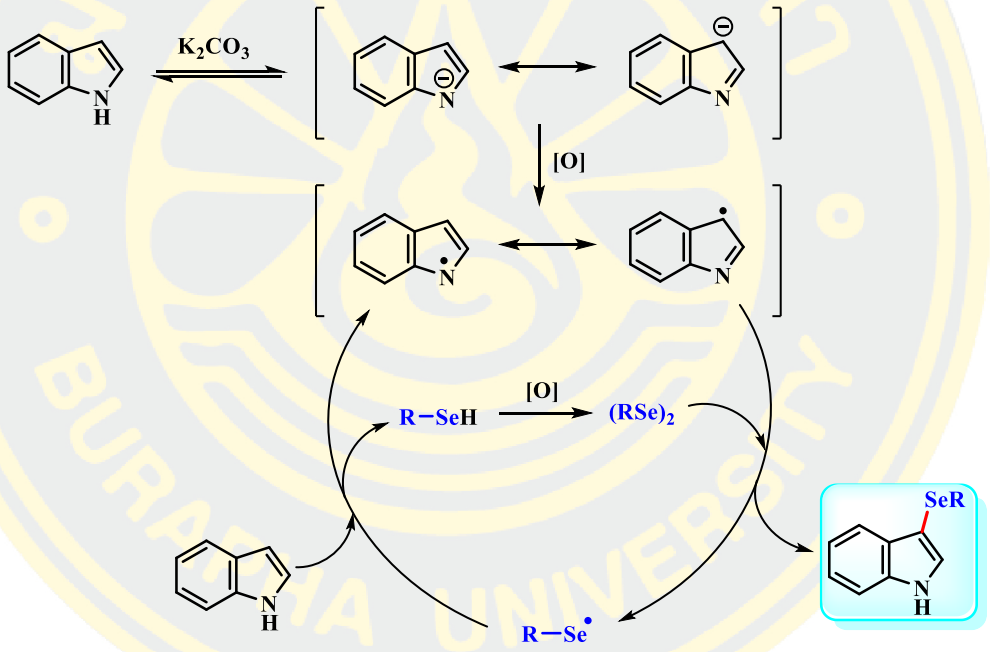


Figure 16 Proposed mechanism for the synthesis of 3-selenylindoles.

Another similar research was reported by Yuanzu Yu and co-workers, who recently developed a general strategy by utilizing *t*-BuOK promoted regioselective C–H chalcogenylation of indole derivatives at the C3-position with dichalcogenides at room temperature (Figure 17), (Yu et al, 2018). Based on the mechanism study, they proposed that 3-chalcogenylindoles were generated by base (*t*-BuOK) promoted nucleophilic attack of the C3-position of indoles to dichalcogenides. Theirs protocol exhibited mild reaction conditions, good compatibility with different functional

groups as well as broad substrate scopes, which produce the target product in good to excellent yields with high regioselectivities. Moreover, the developed protocol is also suitable for the chalcogenylation of *N*-protected indoles, affording the corresponding products with or without protecting groups. It was found that no reactions occurred when methyl and benzyl protected indoles at C1-position were used as substrates for this chalcogenation. Furthermore, this reaction can be readily scaled up to prepare 3-chalcogenylindoles on a gram-scale in high yields (Figure 18).

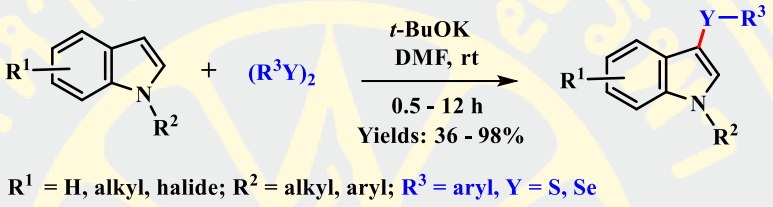


Figure 17 *t*-BuOK promoted C3-chalcogenylation of indoles.

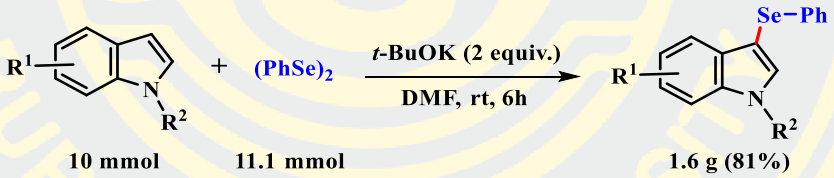


Figure 18 Scale-up reaction of 3-chalcogenylindoles synthesis.

Several strategies for synthesis of 3-chalcogenylindoles have been developed *via* transition metal-catalyzed direct C-H chalcogenylation of heterocycles with dichalcogenides. In 2011, Zhen Li and co-worker employed CuI as catalyst for chalcogenylation of aromatic azaheterocycles with dichalcogenides under air (Figure 19), (Li et al. , 2011). The chalcogenation reactions were carried out at high temperature (110 ºC) in dimethylformamide (DMF) without additive to yield the target products in 40–98% yields. The heteroarenes under investigation included imidazopyridines, imidazopyrimidines, pyrrolo[2,3-b]pyridines and indole substrates. They proposed a plausible mechanism for the copper-catalyzed chalcogenylation of azaheterocycles with dichalcogenides that is illustrated in Figure 20 (Hamel, 2002),

(Andre´ L. Stein & Zeni, 2008) , (Taniguchi, 2006). Initially, CuI reacts with dichalcogenides (2) to generate a RY cation (I) form as observed previously (Andre´ L. Stein et al., 2008) and (Taniguchi et al., 2006). Then the imidazole ring was produced regioselectively electrophilic attack cation **I** to form substituted imidazolenium (**II**), which is deprotonated to give the corresponding products **III** and the CuI is regenerated. In the meanwhile, the in situ generated RYH was oxidized by air reproduces dichalcogenides (**IV**).

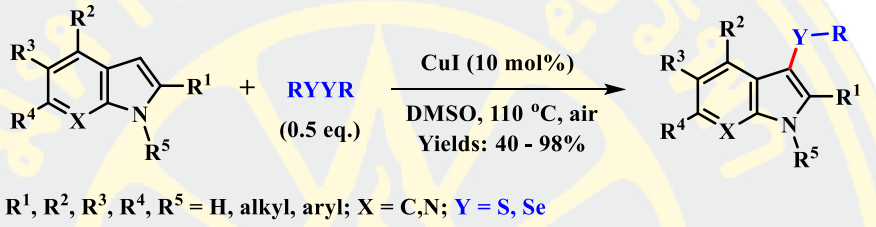


Figure 19 CuI-catalyzed direct C-H chalcogenylation of aromatic azaheterocycles with dichalcogenides.

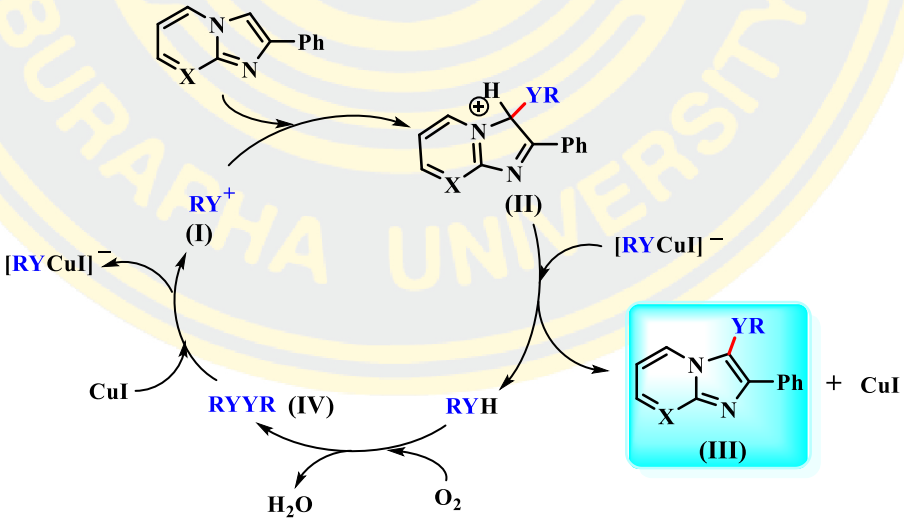


Figure 20 The possible reaction mechanism.

In 2015, Suhelen Vásquez-Céspedes and co-workers reported the first general methodology for the direct selective C-H thiolation/selenation of electron-rich heteroarenes with disulfides or diselenides that was developed by employing

Pd/Al_2O_3, a recoverable and commercially available heterogeneous catalyst, and $CuCl_2$ at high temperature (Figure 21), (Vásquez-Céspedes et al., 2015). The Pd/Al_2O_3 catalysts are easy removed from the reaction mixture and the recycling of transition metal catalysts were also investigated, however a decrease in yield was found for the second (63%) and third (42%) cycles.

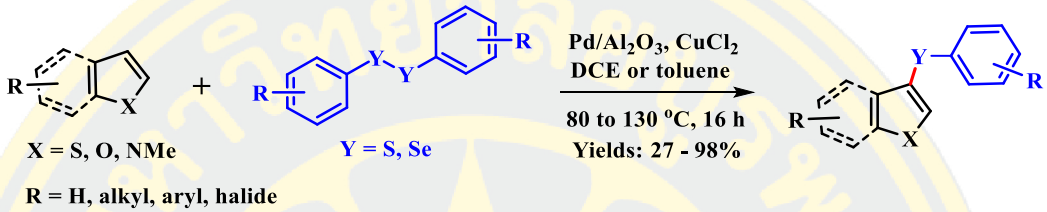


Figure 21 The direct selective C-H thiolation/selenation of electron-rich hetero-arenes with disulfides or diselenides.

3. The C(sp^2) –H chalcogenation of indoles by synthetic technology using microwave, ultrasound and photocatalysis in the presence of different catalysts.

Previously, ultrasound (US) is green energy source that becoming a widely used for organic synthesis laboratory and industrial technique and has been proven to enhance the reaction rates under quite mild conditions. In 2016, Zhiyong Wen and co-worker improved the method for synthesis of 3-arylselenylindoles and 3-arylthioindoles in the presence of $FeCl_3/I_2$ catalysts *via* a convenient ultrasound (US)-assisted to shorten the reaction times and increase the yields (Figure 22), (Wen et al., 2016). Additionally, they have also evaluated antiproliferative activities of the synthesized target compounds by test against human cancer cell lines in vitro and found that most of them exhibited moderate to potent anticancer activities.

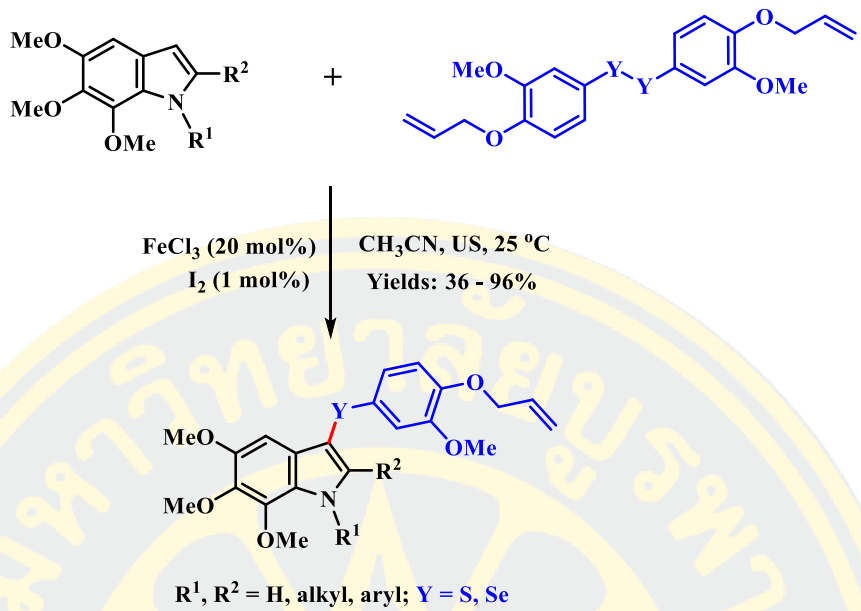


Figure 22 Synthesis of 3-arylselenyl and 3-arylthioindoles under US irradiation.

In recent years, photo-induced protocol has emerged as an attractive and suitable approach for the selenylation of (*N*-hetero) arenes. Qing-Bao Zhang and co-workers developed the first visible-light driven aerobic oxidation for the direct selenation of indole derivatives using FIrPic (bis[2-(4,6-difluorophenyl) pyridinato C2, *N*] (picolinato) iridium(III)) as a photocatalyst, which is an eco-friendly, atom-economical protocol (Figure 23), (Zhang et al., 2017). The selenation is scalable to gram scale (Figure 24) and tolerates a wide scope of substrates to deliver target products in very high yields. Nevertheless, this reaction had limited from substituted indoles when *N*-protected groups is tosyl (**16**) and the substituent at the C2 position is 2-methoxycarbonyl (**20**).

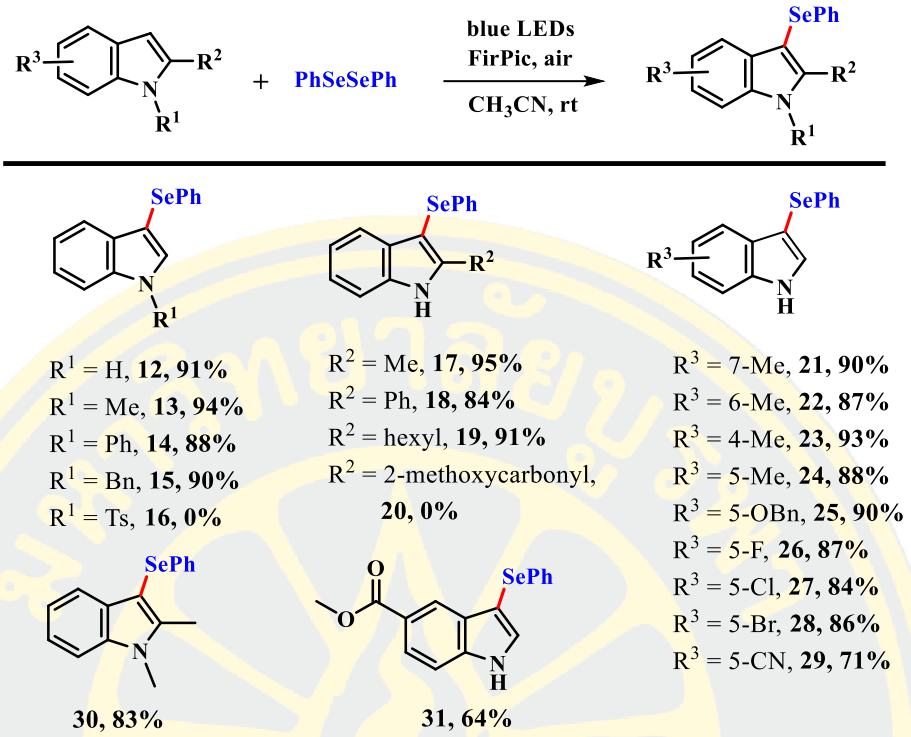


Figure 23 C–H selenation of substituted indoles.

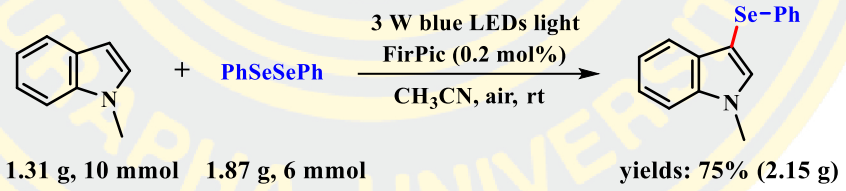


Figure 24 Gram-scale visible-light-mediated aerobic selenation of *N*-methyl indole.

In 2018, Sumbal Saba and co-workers firstly reported the Rose Bengal-catalyzed photo-induced synthesis of selenyl-indoles, -imidazoles and -arenes through C(sp^2)–H bond selenylation using diselenide under mild conditions (Figure 25) (Saba et al., 2018). This protocol resulted in selenylated products up to excellent yields by using a half molar equiv. of diselenides. Additionally, the reaction features are an atom economic, gram-scalable and metal-free approach. However, the reaction failed when *N*-Boc and *N*-Ts were used as substrates for the selenylation of indoles under

the optimized conditions. Furthermore, the reaction was not observed when 3-methyl indole was employed as the substrate (Figure 26).

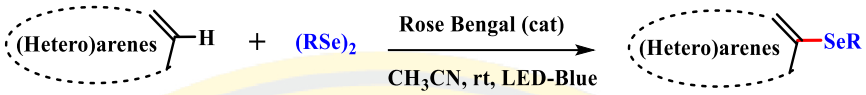


Figure 25 Rose Bengal catalyzed photo-induced selenylation of indoles, imidazoles and arenes.

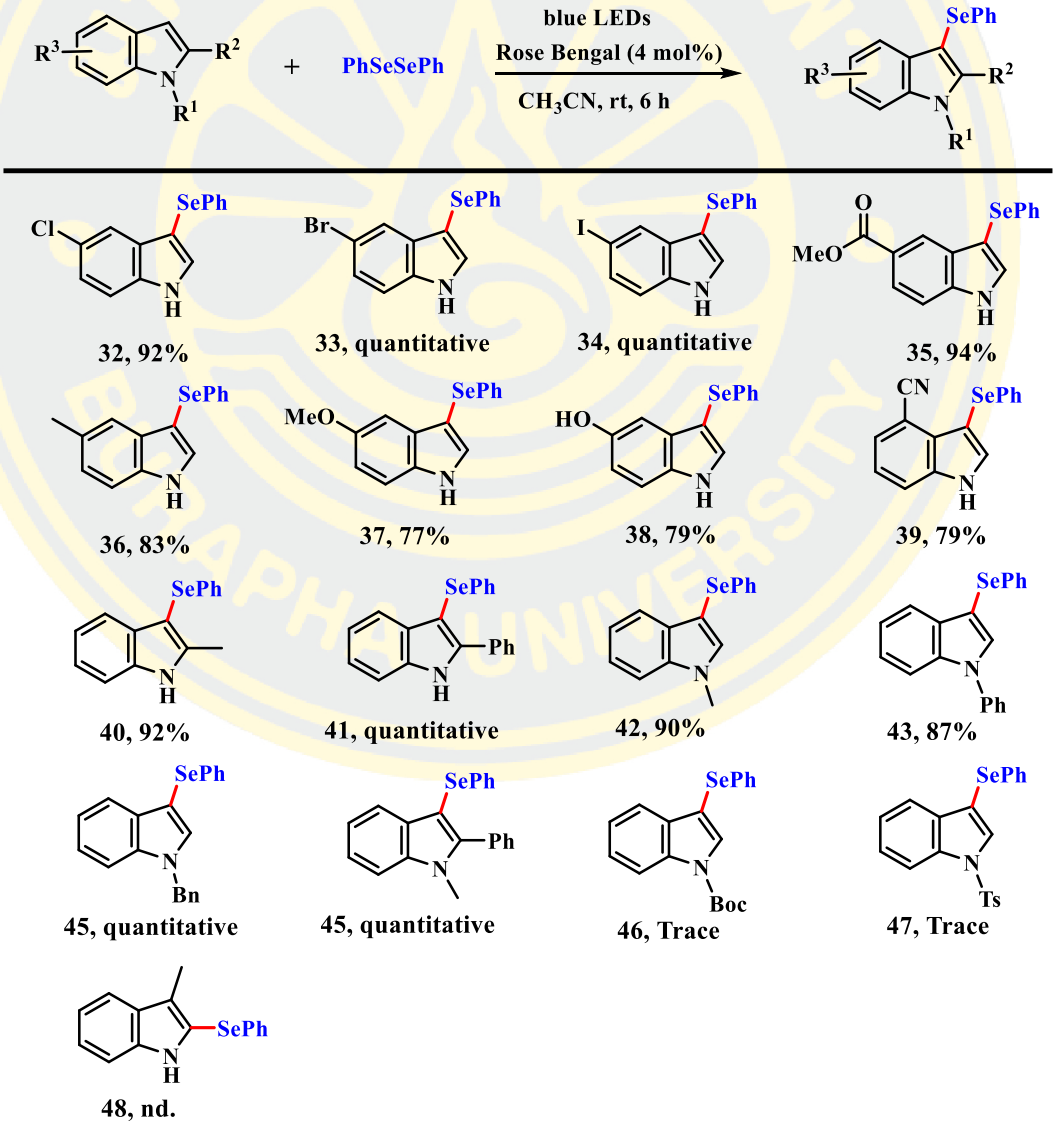


Figure 26 Scope of indoles.

In 2018, Xing Zhang and co-workers reported a transition metal- and oxidant-free method for the synthesis of selenyl indoles with diselenides through iodideion-catalyzed electrochemical C(sp^2)–H selenation (Figure 27) (X. Zhang, Wang, Jiang, & Sun, 2018). The electrocatalytic C–H selenation at the C3 position of various indole derivatives delivered the corresponding 3-selenylindoles in moderate to excellent yields. However, this selenation could not occur when the substrate such as *t*-butyl 1*H*-indole-1-carboxylate and *N*-(*p*-toluenesulfonyl)indole were employed due to the strong electron-withdrawing effect of the ‘‘Boc’’ and ‘‘Ts’’ groups. Moreover, 3-methyl-1*H*-indole could not undergo selenation at the C2 position of the indole ring. This strategy was scalable to gram scale that could be produced the product in excellent yields (Figure 28).

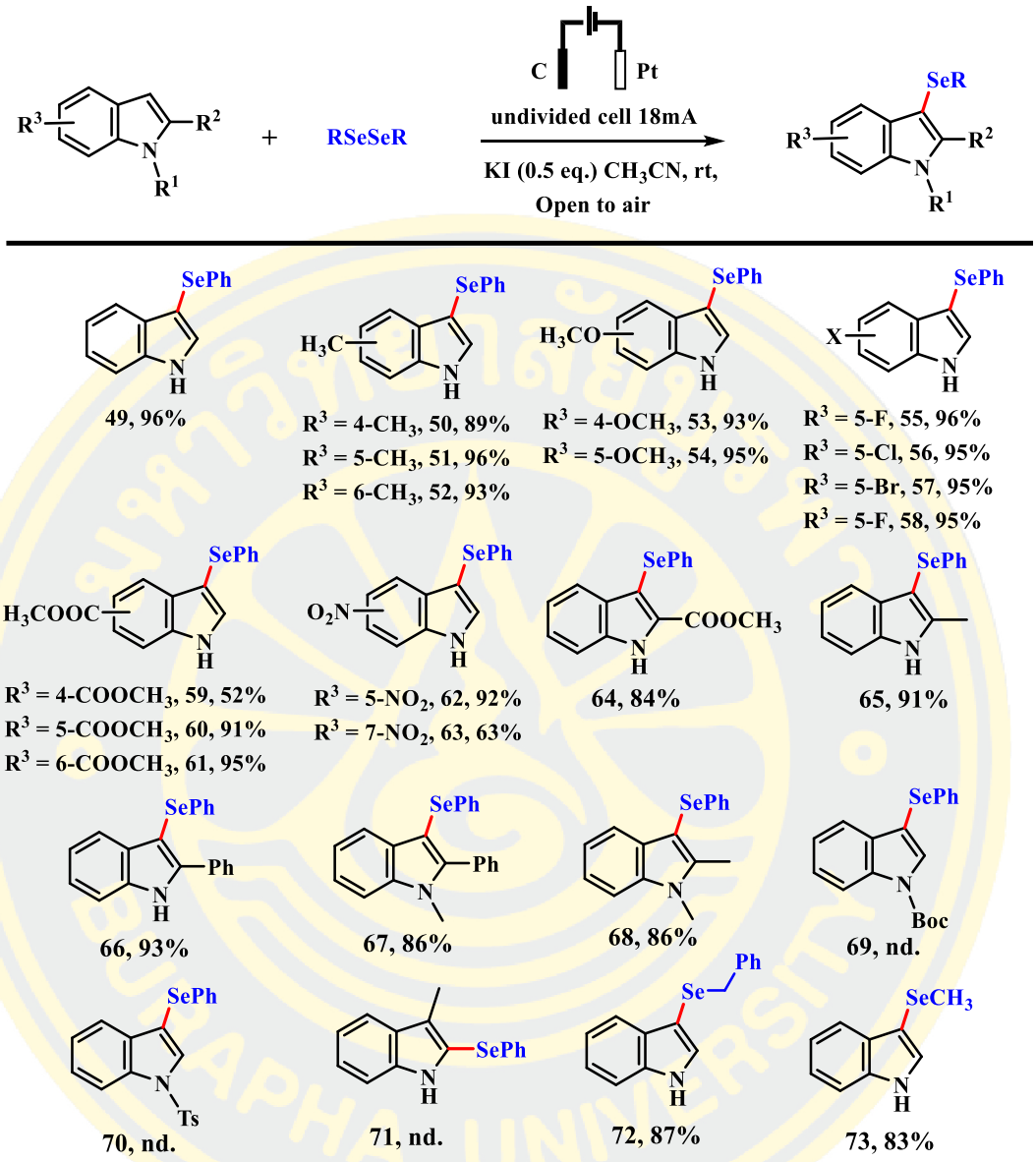


Figure 27 Electrocatalytic C–H selenation of indole derivatives.

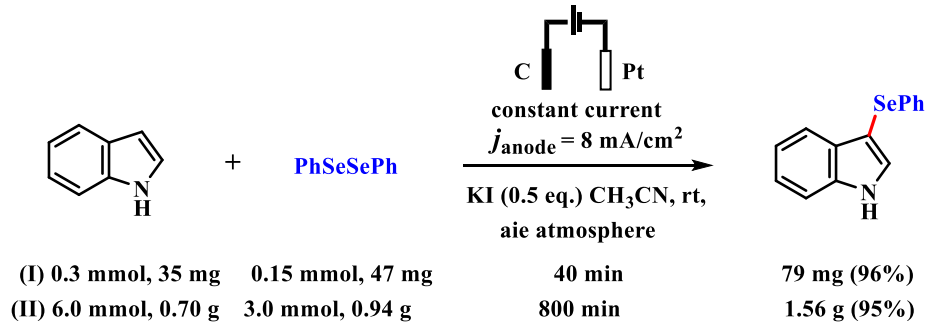


Figure 28 Gram-scale synthesis of 3-selenylindole.

From previous literature reports, the direct C(sp^2)–H chalcogenation of indole ring *via* electrophilic chalcogenation by in situ generated RYX in the presence of oxidants including I_2, KI, TCCA, NBS and NH_4I were studied and frequently used for synthesis of 3-chalcogenylindole (Ge et al., 2012), (Azeredo et al., 2014), (Li et al., 2017), (Silveira et al., 2012), (Huang et al., 2012) and (Bettanin et al., 2018). The strong base such as NaH, K_2CO_3, Cs_2CO_3, *t*-BuOK (La Regina et al., 2013), (Gao et al., 2014), (Ferreira et al., 2015) and (Yu et al, 2018) and transition metal-based catalysis process such as CuI, Pd/Al_2O_3 (Li et al., 2011) (Vasquez-Cespedes et al., 2015) were also employed for synthesis of 3-chalcogenyl indole. Recently, the synthetic technologies using microwave, ultrasound and photocatalysis in the presence of catalysts (Wen et al., 2015), (Wen et al., 2016), (Zhang et al., 2017) and (Saba et al., 2018) has also been applied to the C(sp^2)–H selenation of indoles. However, these methods require utilization of toxic reagents, excess additives or strong base in high temperatures or oxygen-free techniques. Furthermore, the low atom economy caused by the loss of RY anion (1 equiv.) as waste in some methods (Li et al., 2017), (Gao et al., 2014), (Ferreira et al., 2015) and (Yu et al., 2018).

2. 2 Controllable synthesis of mono- and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system

Previously, potassium iodide (KI) was often used to catalyze in various organic synthesis. Because KI is a non-toxic, inexpensive, and readily available catalyst procedure. Therefore, different methods containing KI combined with different oxidants have been successfully applied to mediate the direct sulfenylation of indoles for the synthesis of 3-sulfenylindoles compound. In this part, previous report for synthesis of mono- and bis-selenylindoles employing the combination of KI and various oxidants catalyzed direct C(sp^2)–H sulfenation of indoles with different sulfenylating reagents were discussed.

In 2015, Uemura group (Maeda et al., 2004) reported the direct synthesis of 3-sulfanylindoles from indoles and thiols using the combination of KI (10 mol%), butylhydroxytoluene (BHT, 5 mol%), and vanadium oxyacetylacetonate [$VO(acac)_2$, 1 mol%] catalyst under an atmospheric pressure of molecular oxygen at 60 °C for 12 h. Products were obtained in yields up to good yield (Figure 29). They proposed a plausible mechanism for the system of KI/BHT/$VO(acac)_2$-catalyzed sulfenation of

indoles with thiols that is illustrated in Figure 30. They reported the reaction seems to be electrophilic in the reactivity as well as the substituted indoles orientation, which are similar to those of other known electrophilic substitution reactions of indoles and a radical scavenger (BHT) does not inhibit this reaction. In proposed mechanism, a vanadium (IV) species (A) firstly react with thiol (RSH) and molecular oxygen to generate a vanadium(V) species (B). Subsequently, indoles react with an electrophilic sulfur moiety in species B or to obtain the product 3-sulfanylindoles and a hydroxy vanadium (III) species (C), which undergo dehydrated to from an oxovanadium (III) species (D). Finally, the species D was oxidized to dioxo vanadium (V) species (E) by molecular oxygen, and species B was reproduced to a catalytic cycle *via* the reaction of E with thiols (Figure 30).

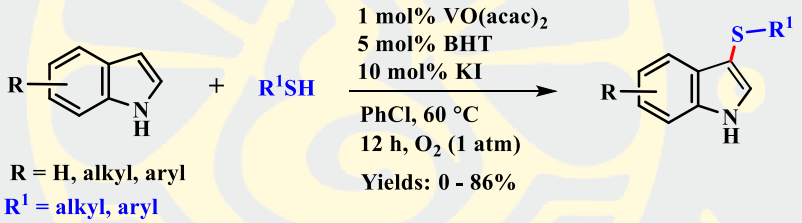


Figure 29 Synthesis of 3-sulfanylindoles under molecular oxygen.

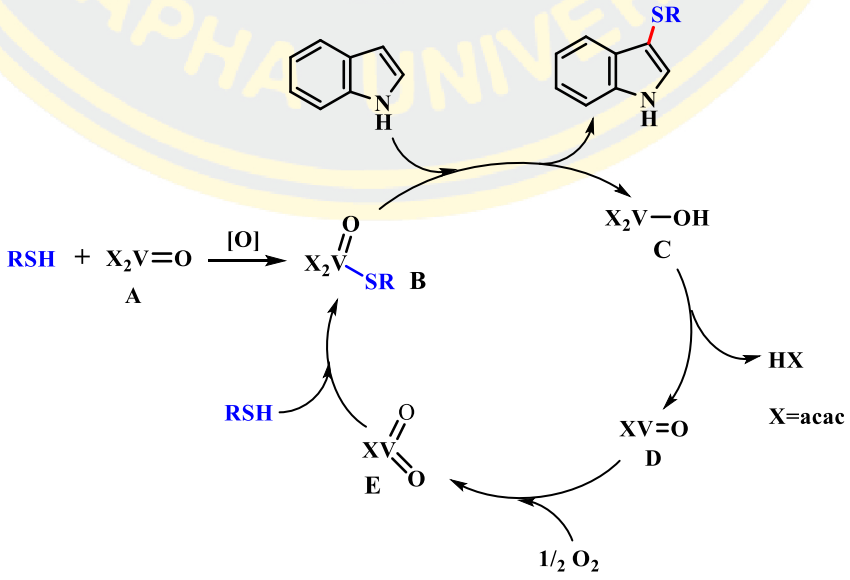


Figure 30 Plausible reaction mechanism.

Li group (Chen et al., 2018) successfully applied the electrochemical system for the direct sulfenylation of indoles with disulfides through direct C-H sulfenylation mediated by KI at a low potential to synthesize 3-sulfenylindoles with medium to excellent yields (Figure 31). They reported a plausible mechanism including two paths for electrochemical sulfenylation of 2-methylindole with diphenyl disulfide that is shown in Figure 31. In path a, iodide ion is initially electrooxidized to the molecular iodine at the anode surface. Then, iodine added to the C-3 position of 2-methylindole to form intermediate 3-iodo-2-methyl-indole **(4)** and iodide ion which can be oxidized to next redox cycle. After that, phenyl sulfide radical, which is generated from diphenyl disulfide reacts with **4** to furnish intermediate **5**. The iodine radical is then removed from intermediate **5** to give the desired product (2-methyl-3-(phenylthio)-indole). Meanwhile, released iodine radical would be turned to molecular iodine and furnished hydrogen ions that are then reduced to H_2 at the cathode. In path b, PhSI that is generated from reaction of diphenyl disulfide and molecular iodine attacks the C-3 position of 2-methylindole to afford intermediate **6**. Finally, **6** is deprotonated to furnishing the target product.

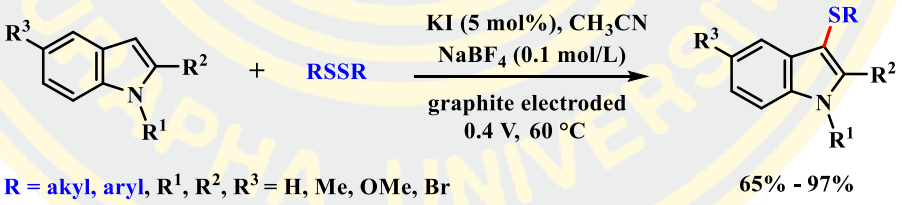


Figure 31 Synthesis of 3-sulfenylindoes from indoles and various disulfides.

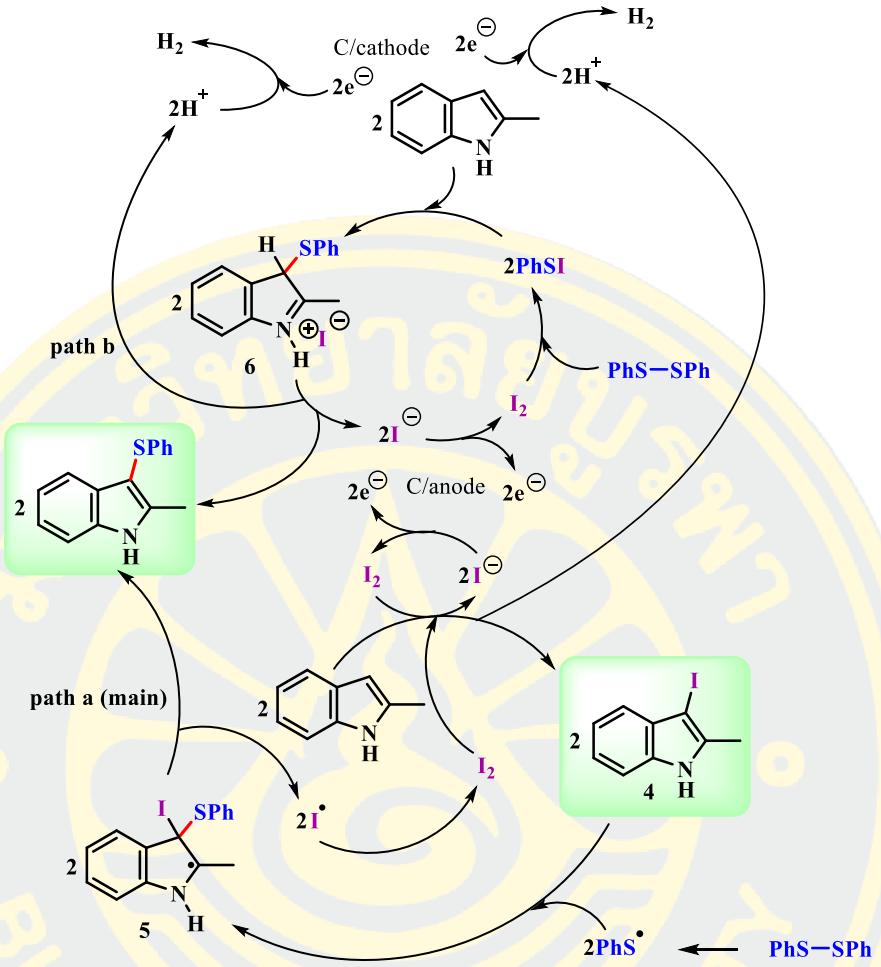


Figure 32 Proposed reaction mechanism.

Shen et al. (Shen et al., 2018) employed KI combined sodium nitrite ($NaNO_2$) as the catalytic system in the presence of acetic acid and molecular oxygen for direct C3 chalcogenylation of indoles. (Figure 33). They have successfully developed the catalytic oxidation system for the sulfenylation of indoles with a variety of sulfenylation agents including Bunte salts, thiols and disulfides to generate target products in yields up to 89% (Figure 33). They proposed a plausible reaction mechanism for the synthesis of 3-sulfenylindoles from indoles and Bunte salts with the KI/$NaNO_2$ catalytic system in the presence of AcOH and molecular oxygen that is illustrated in Figure 34. Under acidic conditions, NO that is released from $NaNO_2$ will be readily oxidized to NO_2 by O_2. Subsequently, NO_2 will be oxidized iodide ion to form iodine. Initially, the Bunte salt is hydrolyzed with water (from the Bunte salt and the undried solvent) to form the corresponding thiol. Then, the corresponding

disulfide is produced by reaction between a second molecule of the Bunte salt and the *in situ* generated thiol. Electrophilic sulfenyl iodides (RSI), which can further produced from reaction of disulfides and iodine react with indole at the C-3 position to generate intermediate A. Finally, A is deprotonated to give the desired product the 3-sulfenyl indole and iodine ion.

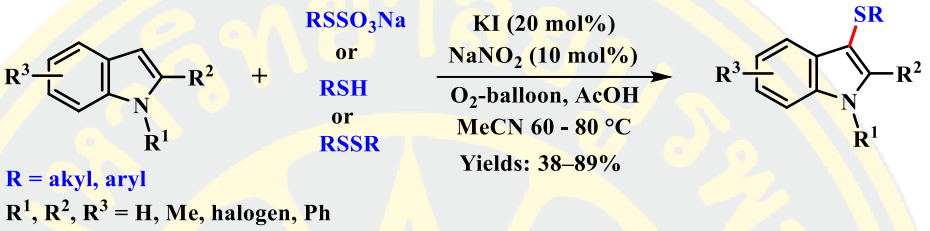


Figure 33 Sulfenation of various indoles with Bunte salts, thiols and disulfides.

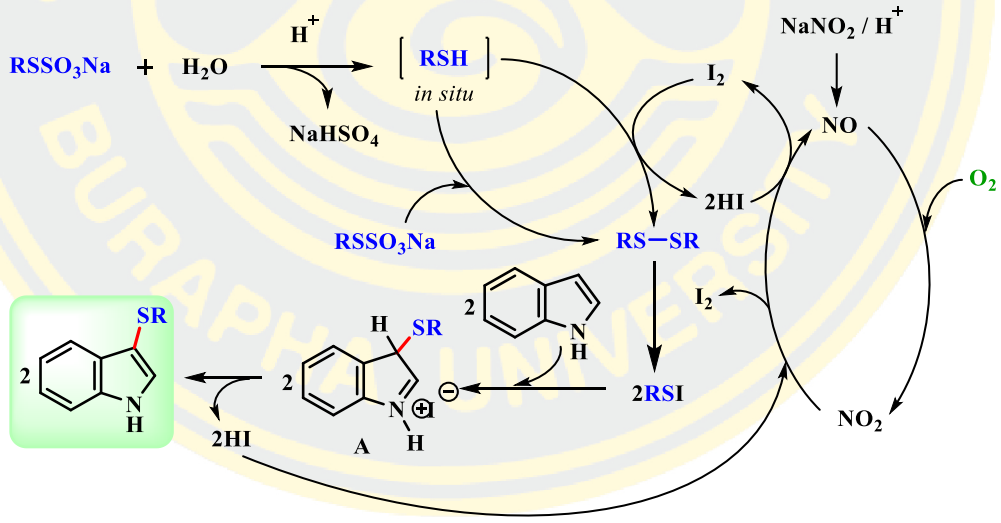


Figure 34 Proposed reaction mechanism via aerobic oxidative C–S Bond Coupling.

Recently, Rampon et al. (Luz et al., 2019) reported an approach for synthesis of 3-chalcogenylindoles *via* direct electrophilic chalcogenation from dichalcogenides and indoles derivatives using the Fe(III)/KI as catalytic system furnishing the target products in yields up to 98% (Figure 35). They reported a plausible mechanism that presented in Figure 36. First, I_2 and Fe(II) in the reaction

medium is formed by the reaction of the $FeCl_3$ and KI. Subsequently, RYI (Y = S, Se) is generated leading to the reaction at C-3 position of the indole derivatives, which catalyzed by Fe(III) in the system to afford the desired 3-chalcogenylindole and hydrogen iodide (HI). Finally, HI could be oxidized with DMSO producing the I_2 to next catalytic cycle.

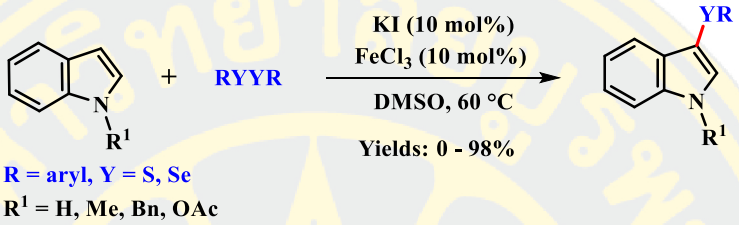


Figure 35 Synthesis of 3-chalcogenylindoles.

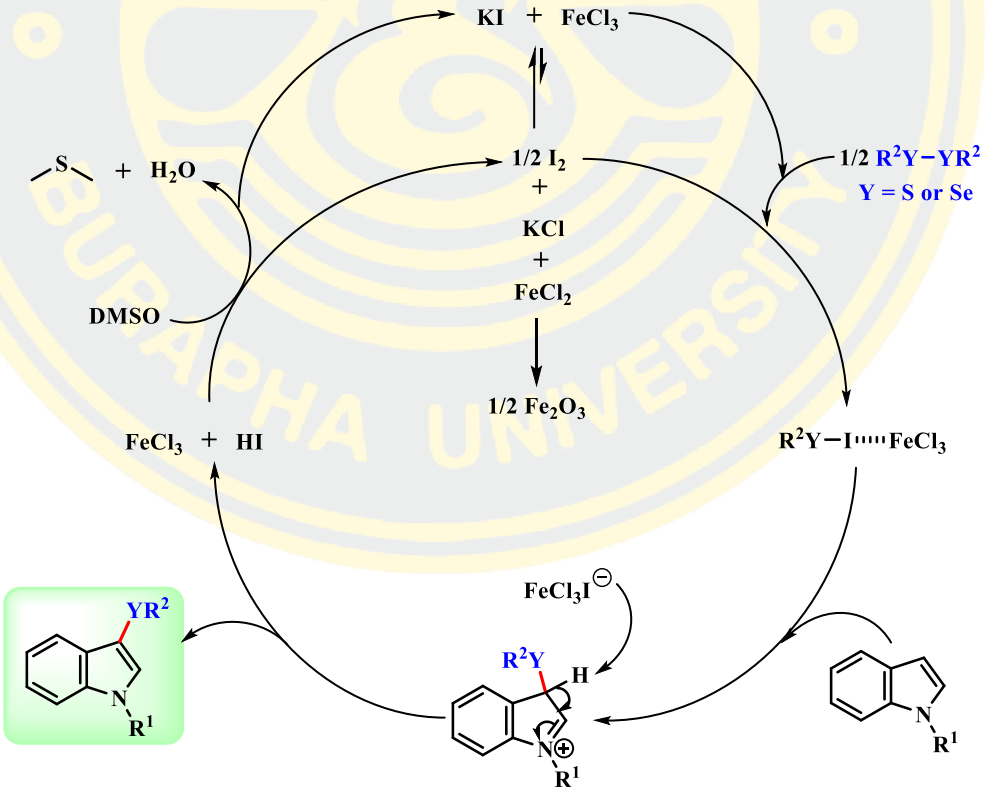


Figure 36 Proposed reaction mechanism.

Although several catalytic systems containing KI have been successfully applied to construct structurally diverse 3-sulfenylindole or mono-sulfenylindoles, there are no report the synthesis of bis-sulfenylindole *via* double C-H sulfenylation at C2- and C3-positions of indoles using KI catalytic system.

From the interesting previous reports, we became interested to develop the new and efficient methods for synthesis chalcogenylindole by C-H sulfenylation at C2- or C3- or both positions of indole by convenient method which reported in following chapters.

CHAPTER 3
RESEARCH METHODOLOGY

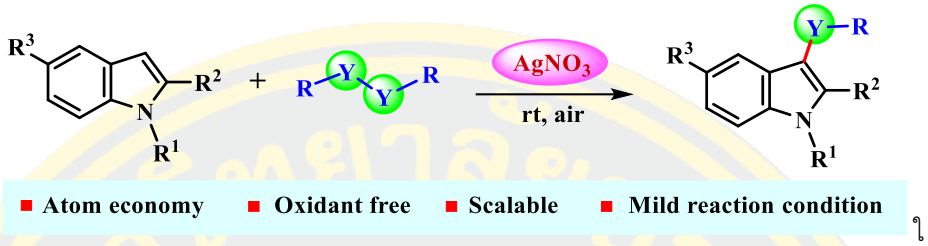
3.1 General Considerations

All reagents and solvents were obtained from commercial sources and used without any further purification. Every glassware was oven dried at 70 - 85 °C for 2 hours and cooled down before used. Reactions were carried out under air atmosphere and monitored by thin layer chromatography (TLC) using silica gel 60F-254 [E. Merck, Darmstadt, Germany], and the products were visualized by UV detection. The products were obtained by purification on open-column chromatography utilizing silica gel 60 PF254 [E. Merck, Darmstadt, Germany].

^{1}H and ^{13}C NMR data were recorded with BRUKER AVANC 400 MHz spectrometers with tetramethylsilane (TMS) as the internal standard. Chemical shifts for protons (^{1}H NMR) are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$ = δ 7.26; DMSO = δ 2.50). Data are reported as follows; chemical shift (multiplicity, integrated intensity or assignment, coupling constants in Hz, assignment). Chemical shifts for carbon (^{13}C NMR) are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.16; DMSO = δ 39.60). High-resolution mass spectra (HRMS) data were obtained using electrosprayionization (ESI). Infrared spectra were determined on a PERKIN ELMER FT-IR-2000S spectrophotometer and are reported in wave number (cm^{-1}). Melting points were measured using a Melting point apparatus (Griffin) and are uncorrected.

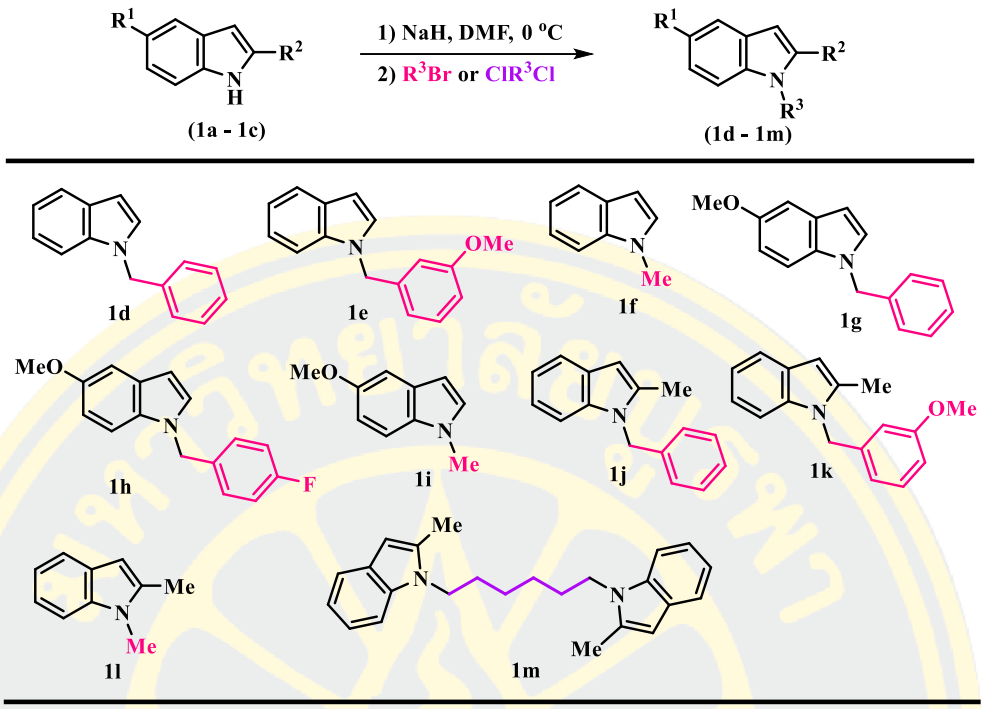
3.2 Experimental Procedures

3. 2.1 Selective synthesis of 3-chalcogenylindoles via silver-catalyzed direct chalcogenation of indoles with dichalcogenides



3.2.1.1 Synthesis of indole derivatives

Indole derivatives (**1d-1m**) were prepared according to Figures 37. Indole, 5-methoxyindole (**1a-1e**, 5.0 mmol) and DMF (15 mL) were added to an oven-dried round bottom flask and stirred under N_2 atmosphere at 0 ^oC for 5 minutes. Then, NaH (60%wt, 10.0 mmol) was added, and the mixture stirred at 0 ^oC for 30 minutes. Next, aryl bromide (R^3Br, 6.0 mmol for prepared **1d-1l**) or 1,6-dichlorohexane (ClR^3Cl, 2.0 mmol for prepared **1m**) was added together with DMF (2 mL) at 0 ^oC, then stirred at room temperature for 1-4 hours. After the reaction was completed, the mixture was cooled to 0 °C and quenched by added saturated NH_4Cl 20 mL, after that extracted with EtOAc (30 mL×3) and washed with water. The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by silica gel column chromatography (SiO_2, 10% EtOAc/n-Hexane as eluent) to afford indole derivatives (**1d-1m**).



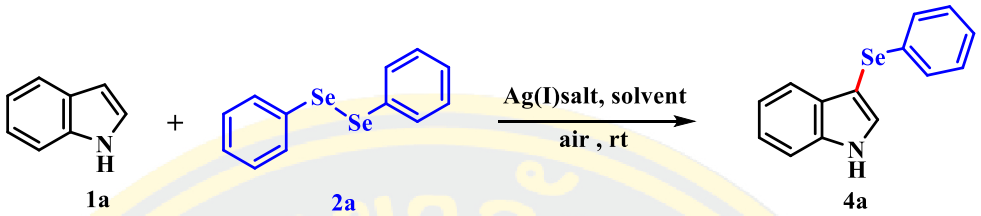
Reaction conditions: **1** (5 mmol), **NaH** (10 mmol), **R^3Br** (6 mmol) or **ClR^3Cl** (2 mmol) **DMF** (15mL) under N_2 atmosphere at **0 °C**.

Figure 37 Synthesis of indole derivatives.

3.2.1.2 Optimization of reaction conditions

The first investigation was optimization conditions for synthesis of 3-chalcogenylindoles focusing on the reaction between 1*H*-indole (**1a**) and diphenyl diselenide (**2a**) according to Table 1. Initially, the reactions were carried out in CH_2Cl_2 (2 ml) at room temperature under air atmosphere by using a various Ag(I)salt (entries 1-4) including AgOAc, Ag_2SO_4, AgOTf and $AgNO_3$ 10 mol% and no addition of catalyst (entry 10) for the sulfenylation between indole (**1a**, 0.4 mmol) and diphenyl diselenide (**2a**, 0.2 mmol). Subsequently, the influence of diphenyl Ag(I)salt amount on the 3-selenylindoles synthesis was evaluated by varying the loading from 5 to 50 mol% (entries 5-9). Finally, different solvents including DMF, THF, CH_3CN, EtOH, EtOAc, toluene and H_2O were also investigated (entries 11-17). After each reaction completed, the mixtured reaction was filtered and evaporated in vacuo, and the crude product was then purified by column chromatography on silica gel using a mixture of 10% ethyl acetate in hexane as the eluent to obtain the target product.

Table 1 Condition screening for C3-chalcogenation system



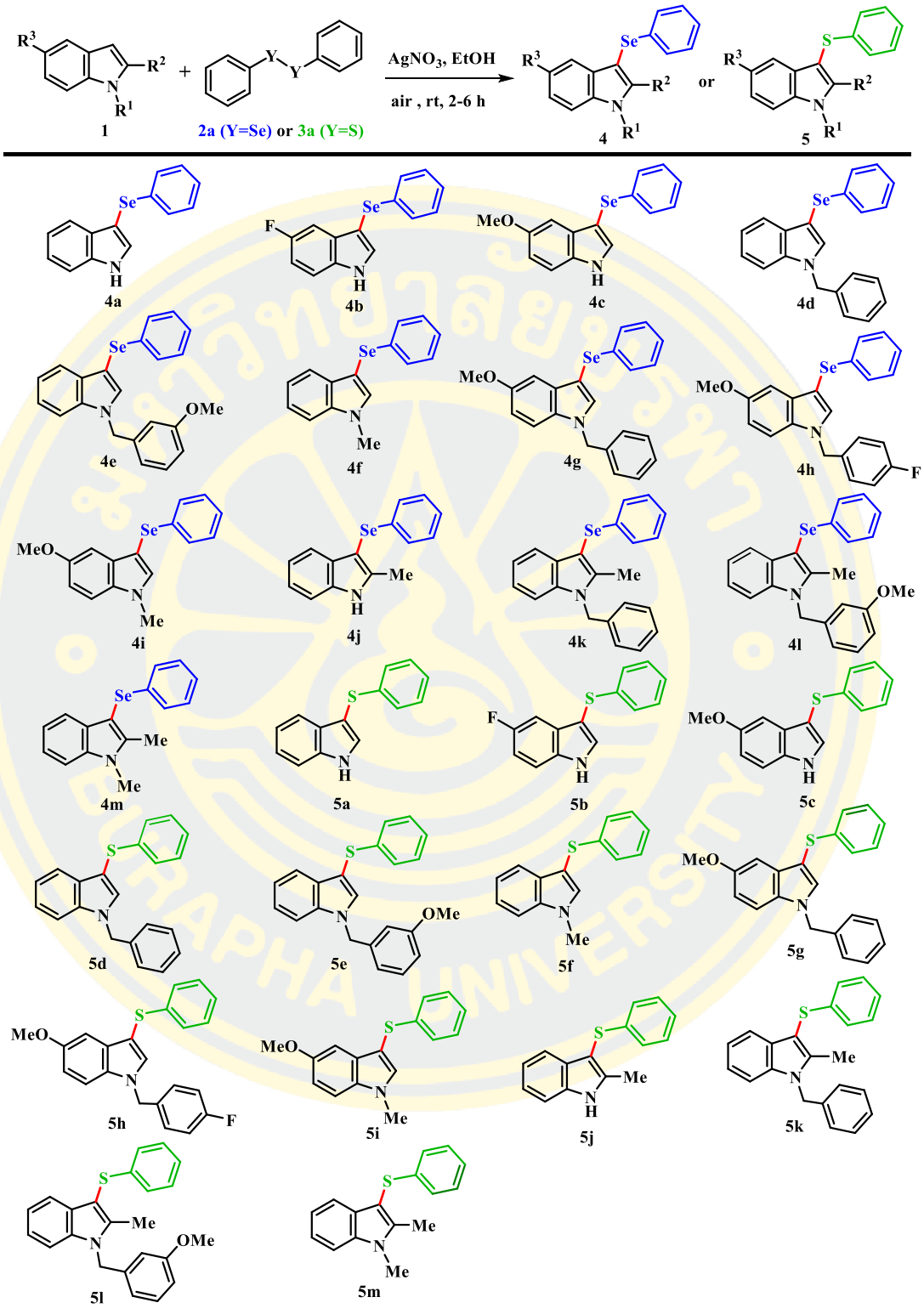
1a **2a** **4a**

entry	silver(I)salt (mol%)	solvent
1	AgOAc (10)	CH_2Cl_2
2	Ag_2SO_4 (10)	CH_2Cl_2
3	AgOTf (10)	CH_2Cl_2
4	$AgNO_3$ (10)	CH_2Cl_2
5	Optimized Ag(I)salt (20)	CH_2Cl_2
6	Optimized Ag(I)salt (30)	CH_2Cl_2
7	Optimized Ag(I)salt (40)	CH_2Cl_2
8	Optimized Ag(I)salt (50)	CH_2Cl_2
9	Optimized Ag(I)salt (5)	CH_2Cl_2
10[a]	-	CH_2Cl_2
11	Optimized Ag(I)salt	DMF
12	Optimized Ag(I)salt	THF
13	Optimized Ag(I)salt	CH_3CN
14	Optimized Ag(I)salt	EtOH
15	Optimized Ag(I)salt	EtOAc
16	Optimized Ag(I)salt	Toluene
17	Optimized Ag(I)salt	H_2O

Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), solvent (2 mL) under air at rt. [a]Reaction was carried out without Ag(I)salt catalyst.

3.2.1.3 Chalcogenation of substituted indoles with dichalcogenides.

3-Chalcogenylindoles were synthesized *via* direct C-H chalcogenylation of indoles as follows in Figure 38-40. A mixture of indole and its derivatives (**1a–1l**, 100 mg, 0.42-0.85 mmol), dichalcogenides (**2** and **3**, 0.5 eq., 0.21-0.42 mmol), $AgNO_3$ (10 mol%) and EtOH (5 mL) were added into a round-bottomed flask. Compound **4n** (Figure 40) was synthesized by addition of indole **1m** (100 mg, 0.29 mmol), diphenyl diselenide **2a** (0.29 mmol), $AgNO_3$ (10 mol%) into a round-bottomed flask. Each mixture reaction was stirred at room temperature by open to air atmosphere until TLC showed the conversion was completed. Then, the completed reaction was filtered and evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using a mixture of 5% - 10% ethyl acetate in hexane as the eluent to afford the target products.



Reaction conditions:**1** (0.8 mmol), **2a** or **3a** (0.4 mmol.), $AgNO_3$ (10 mol%) in EtOH (5 mL) under air at rt.

Figure 38 Chalcogenation of indoles with diphenyl diselenide (**2a**) and disulfide(**3a**).

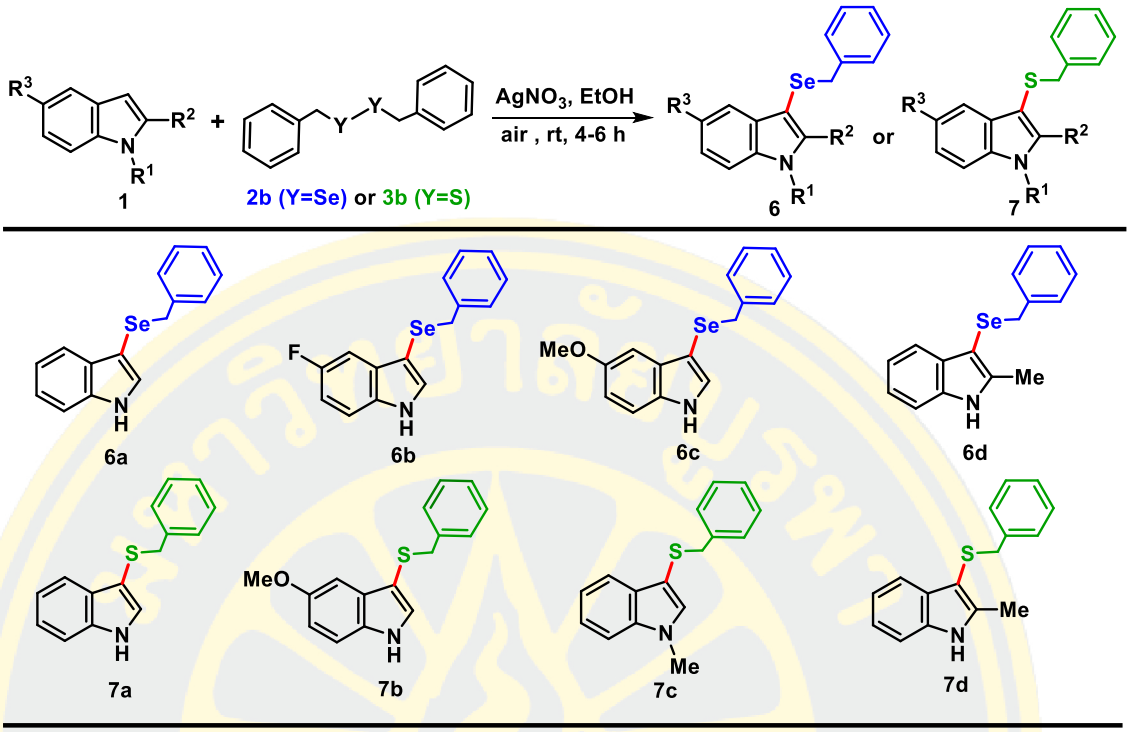


Figure 39 Chalcogenation of indoles with dibenzyl diselenide (**2b**) and disulfide (**3b**).

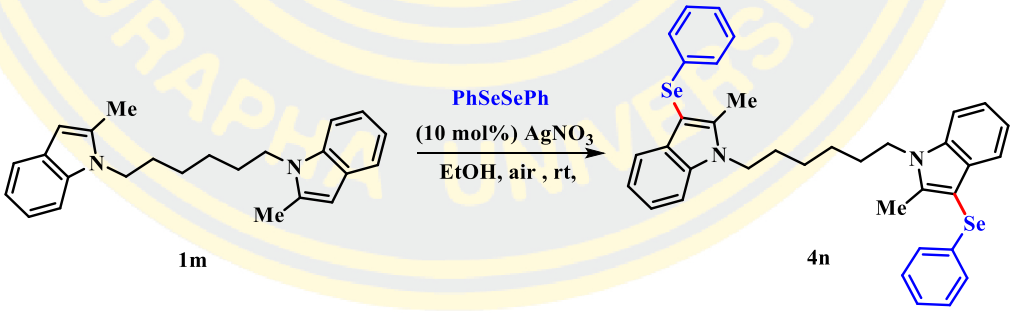


Figure 40 Chalcogenation of indole (**1m)** with diphenyl diselenide (**2a**).

3.2.1.4 Gram-scale chalcogenation

A gram scale reaction was performed under the optimized conditions according to Figure 41. A mixture of indole **1a** (1.00g, 8.54 mmol), dichalcogenide **2a** (4.25 mmol), $AgNO_3$ (10 mol%), and EtOH (20.00 mL) were added in a round-bottomed flask, which was stirred at room temperature under open to air atmosphere

for 6 h. When the reaction was completed, the mixture was filtered and evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using a mixture of 10% ethyl acetate in hexane as the eluent to afford the desired products (**4a** and **5a**).

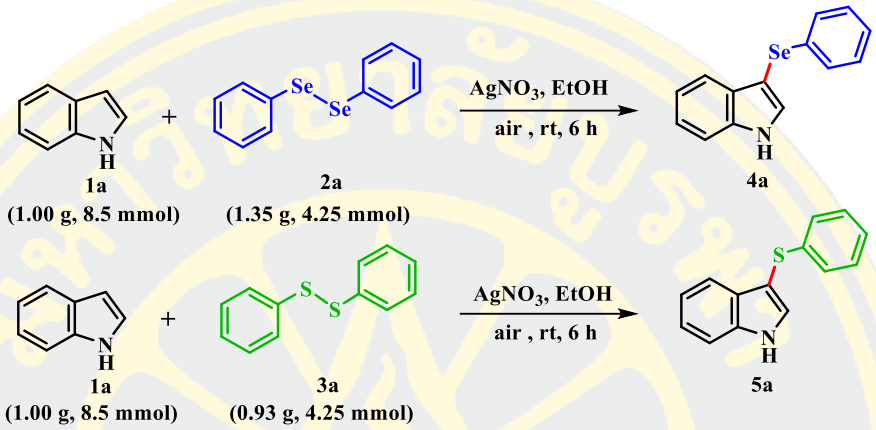


Figure 40 Gram-scale chalcogenation of indole **(1a)**.

3.2.1.5 Control experiments for mechanistic studies

Procedure a (Figure 42)

Indole (**1a**, 0.85 mmol), diphenyl diselenide (**2a**, 0.425 mmol), $AgNO_3$ (10 mol%), and EtOH (5.0 mL) were added to a round bottomed flask. The resulting solution was stirred for 4 h at room temperature under nitrogen atmosphere. Then, the completed reaction was filtered and evaporated in vacuo. The crude product was purified by column chromatography on silica gel using a mixture of 10% ethyl acetate in hexane as the eluent to give the products **4a**.

Procedure b (Figure 42)

Indole (**1a**, 0.85 mmol), diphenyl diselenide (**2a**, 0.425 mmol), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 0.85 mmol), $AgNO_3$ (10 mol%), and EtOH (5.0 mL) were added to a round bottomed flask. The resulting solution was stirred for 4 h at room temperature under air atmosphere. After 4 h, the mixtured reaction was filtered and evaporated in vacuo. The crude product was purified by column chromatography on silica gel using a mixture of 10% ethyl acetate in hexane as the eluent to obtain the products **4a**.

Procedure c (Figure 42)

Indole (**1a**, 0.85 mmol), diphenyl diselenide (**2a**, 0.425 mmol) and EtOH (5.0 mL) were added to a round bottomed flask (without adding $AgNO_3$). The mixtured solution was stirred for 4 h at room temperature under air atmosphere. After 4 h, the mixtured reaction was filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel using a mixture of 10% ethyl acetate in hexane as the eluent to obtain the products **4a**.

^{77}Se NMR spectroscopy analysis

Product **3a** and diphenyl diselenide **2a** were analyzed by ^{77}Se NMR and ^{1}H NMR. Diphenyl diselenide **2a** (0.03 mmol), $AgNO_3$ (0.03 mmol) and $CDCl_3$ was added to NMR tube and mixture for 1 h at room temperature, then also analyzed by ^{77}Se NMR and ^{1}H NMR.

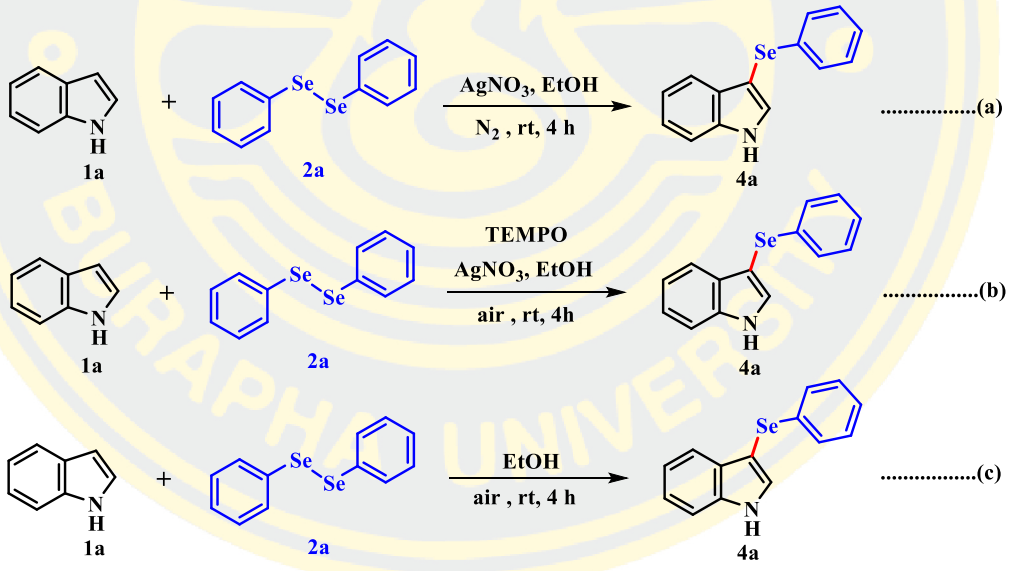
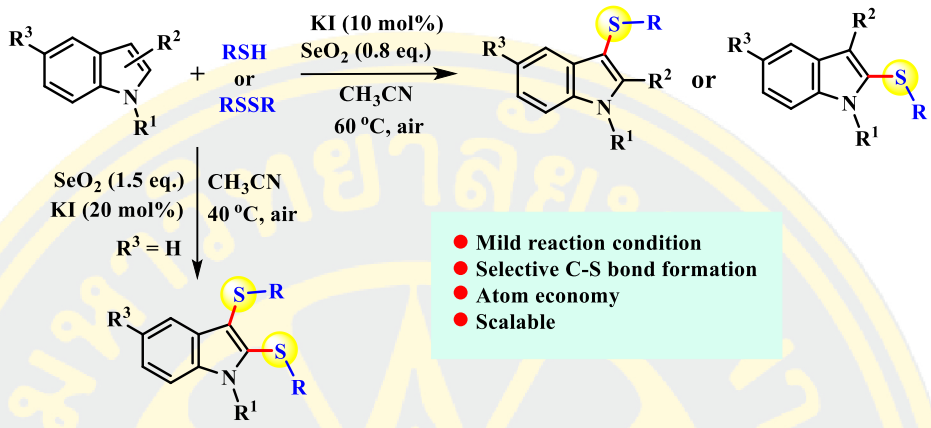


Figure 41 Control experiments for mechanistic studies.

3.2.2 Controllable synthesis of mono- and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system



3.2.2.1 Optimization of reaction conditions

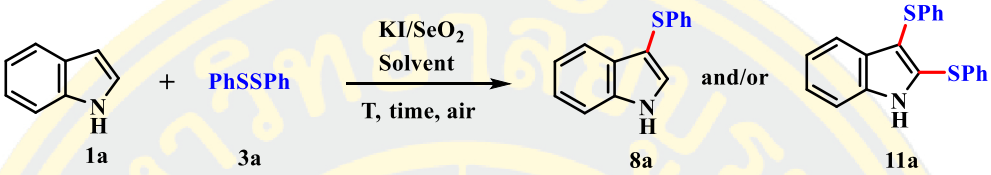
Indole **1a** (0.42 mmol), diohenyl disulfides **3a** (0.21 mmol, entries 1-15 or 1.6 mmol, entries 16-24), SeO_2 (Table 2) and KI (Table 2) were added successively to solvent according to Table 2 (2 mL) in glass tube. The suspension was vigorously stirred at temperature as Table 2 (water bath) under air atmosphere until the reaction completed. Next, the reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ (1 mL) and H_2O (5 mL), then extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica-gel chromatography column using hexane/ethyl acetate as the eluent to obtain the target products.

3.2.2.2 General experimental procedure for mono-sulfenylation of indoles with disulfides and thiols

Mono-sulfenylindoles were synthesized *via* sulfenation of different indoles with various disulfides and thiols according to Figure 43 and 44. A mixture of indole **1** 100 mg (0.48 - 0.85 mmol), disulfides **3** 0.5 equivalent (0.24 - 0.42 mmol) or thiols **10** 1.0 equivalent (0.48 - 0.85 mmol), 80 mol% SeO_2 (0.38 - 0.64 mmol) , 10 mol% KI (0.05 - 0.08 mmol) and MeCN (5 mL) were added to glass tube, which was vigorously stirred at 60 °C (water bath) under air atmosphere for 1.5 – 3 h. When the reaction completed, sat. aq. $Na_2S_2O_3$ (2 mL) and H_2O (10 mL) were added to each reaction, respectively. The reaction mixture was extracted three times with ethyl acetate (20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and

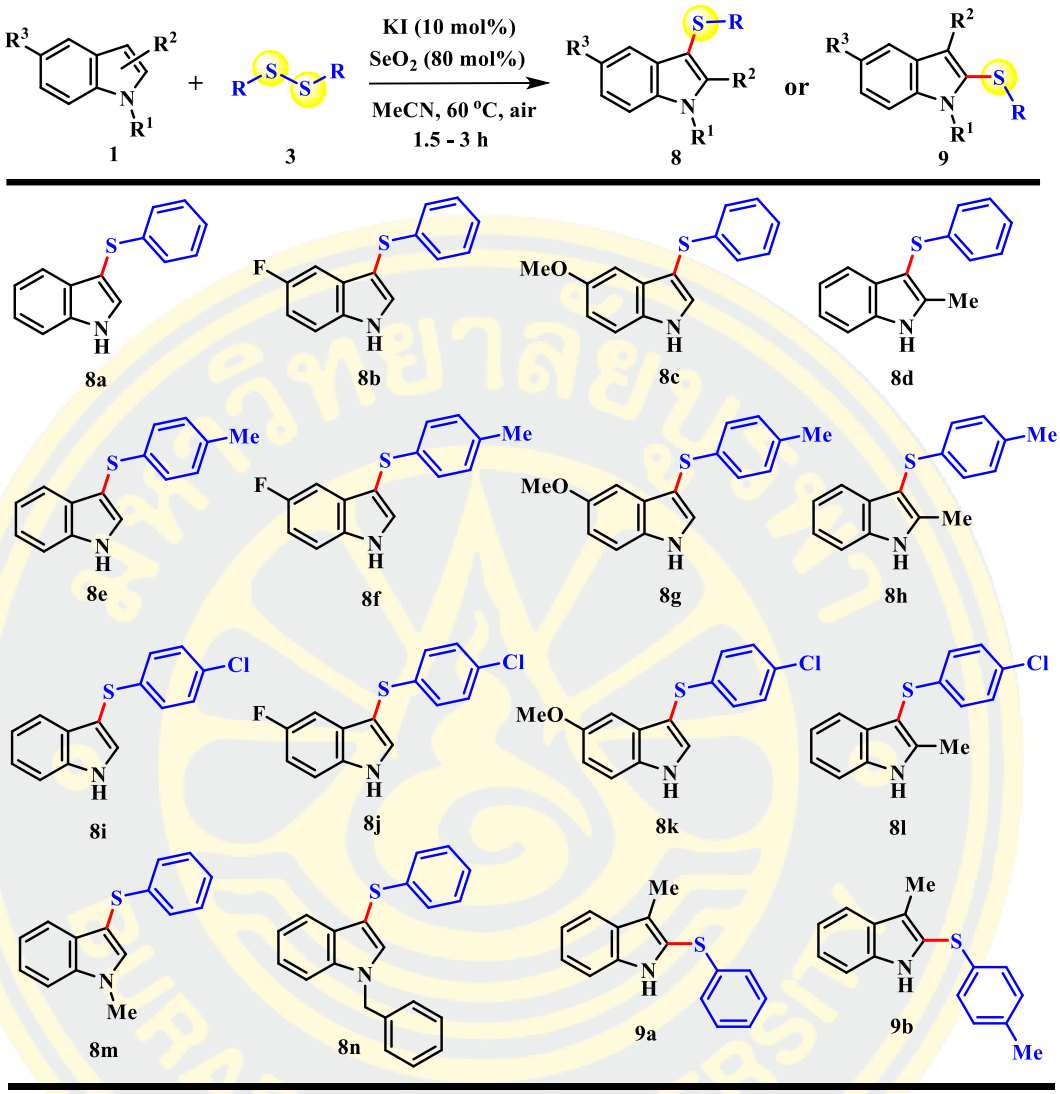
concentrated under reduced pressure. The residue was then purified by silica-gel chromatography column with hexane/ethyl acetate as the eluent to furnish products **8, 9**, **11, 12**, **13** and **14**.

Table 2 Optimization of the Reaction Conditions



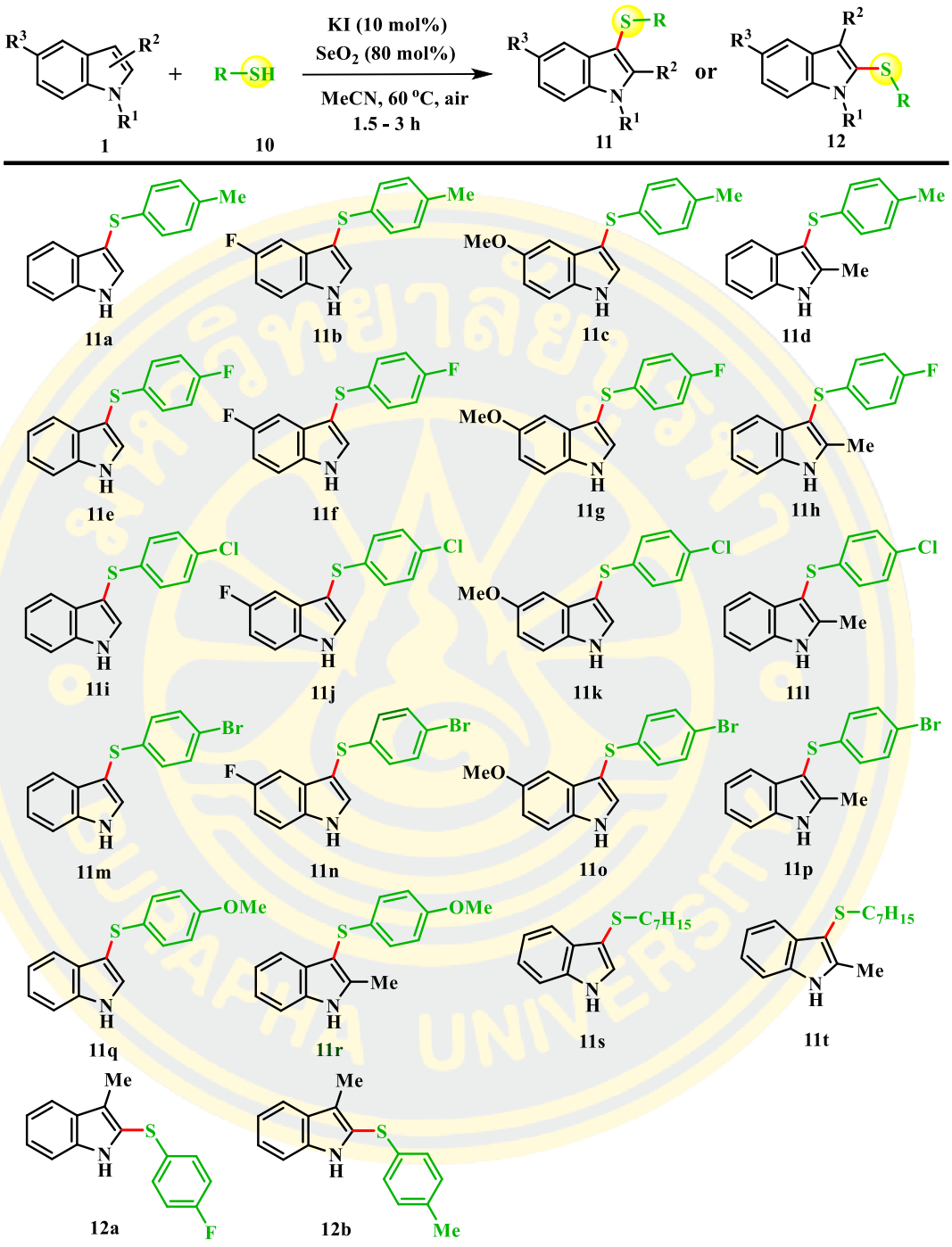
entry	2a (equiv.)	KI (mol%)	SeO_2 (mol%)	solvent	T (°C)
1	0.5	10	60	MeCN	60
2	0.5	10	70	MeCN	60
3	0.5	10	80	MeCN	60
4	0.5	10	90	MeCN	60
5	0.5	10	100	MeCN	60
6	0.5	10	Optimized SeO_2	EtOH	60
7	0.5	10	Optimized SeO_2	H_2O	60
8	0.5	10	Optimized SeO_2	MeCN	60
9	0.5	10	Optimized SeO_2	DMF	60
10	0.5	10	Optimized SeO_2	THF	60
11	0.5	10	Optimized SeO_2	DCE	60
12	0.5	10	Optimized SeO_2	DEM	60
13	0.5	10	Optimized SeO_2	Optimized Solvent	80
14	0.5	10	Optimized SeO_2	Optimized Solvent	40
15	0.5	10	Optimized SeO_2	Optimized Solvent	RT
16	1	10	130	Optimized Solvent	40
17	1	10	150	Optimized Solvent	40
18	1	10	170	Optimized Solvent	40
19	1	20	130	Optimized Solvent	40
20	1	20	150	Optimized Solvent	40
21	1	20	170	Optimized Solvent	40
22	1	30	150	Optimized Solvent	40
23	1	20	150	Optimized Solvent	60
24	1	20	150	Optimized Solvent	RT

Reactions were carried out with **1a** (0.4 mmol), **2a**, KI and SeO_2 in a solvent (2.0 mL) under air atmosphere



Reaction conditions: **1** (0.8 mmol), **3** (0.4 mmol), KI (10 mol%), SeO_2 (80 mol%) MeCN (5 mL), 60 °C, under air, 1.5-3 h.

Figure 42 Mono-sulfenylation of indoles with disulfides.



Reaction conditions: **1** (0.8 mmol), **10** (0.8 mmol), KI (10 mol%), SeO_2 (80 mol%) MeCN (5 mL), 60 °C, under air, 1.5-3 h.

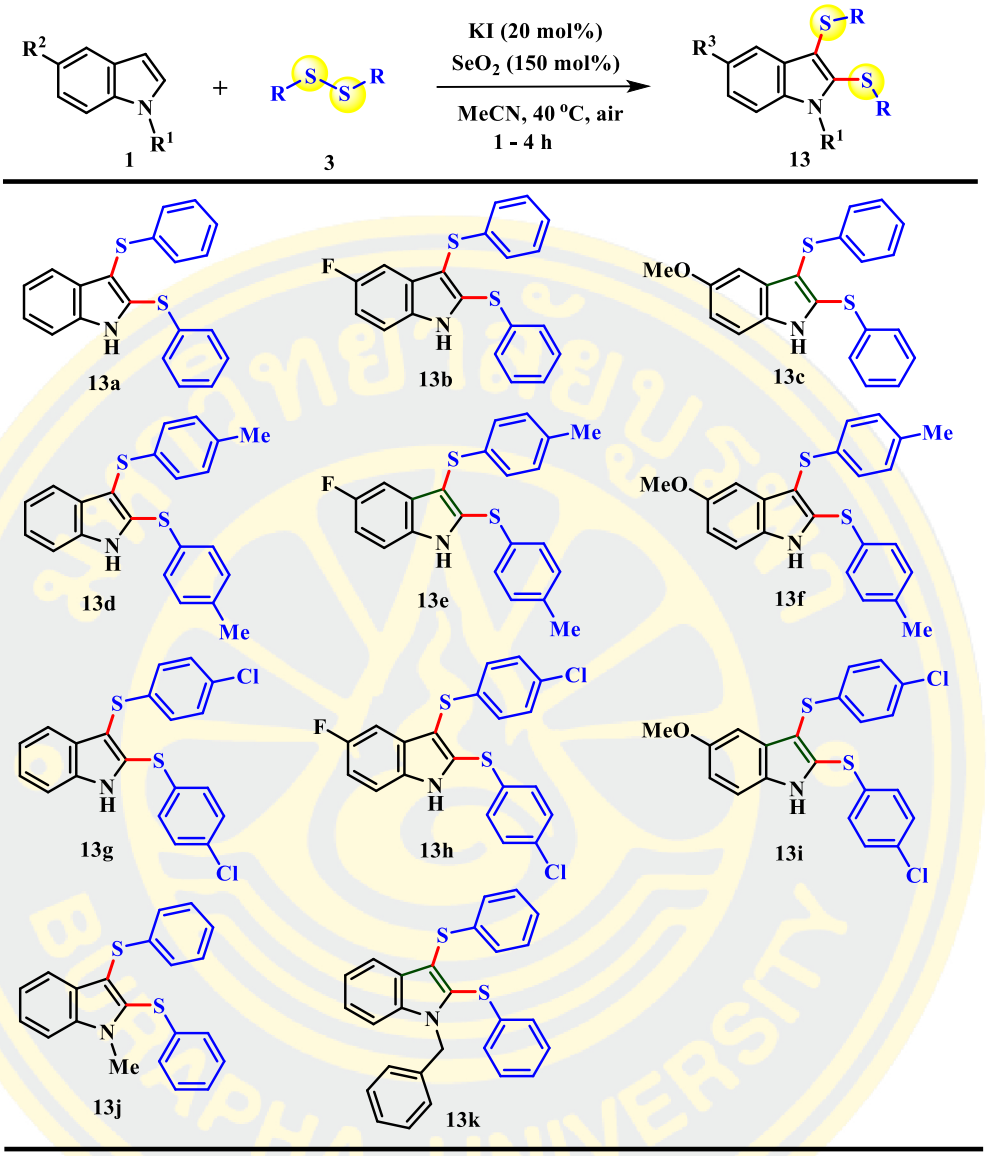
Figure 43 Mono-sulfenylation of indoles with thiols.

3.2.2.3 General experimental procedure for bis-sulfenylation of indoles with disulfides and thiols

Bis-sulfenylindoles were synthesized *via* 2,3-disulfenylation of different indoles with various disulfides and thiols according to Figure 45 and 46. Indole **1** 100 mg (0.48 - 0.85 mmol), disulfides **3** 1.0 equivalent (0.48 - 0.85 mmol) or thiols **10** 2.0 equivalent (0.96 - 1.70 mmol), 150 mol% SeO_2 (0.72 - 1.28 mmol) and 20 mol% KI (0.10 - 0.17 mmol) were added successively to MeCN (5 mL) in glass tube. Each suspension was vigorously stirred at 40 °C (water bath) under air atmosphere until the reaction completed. Next, the reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ (2 mL) and H_2O (10 mL), then extracted with ethyl acetate (3 x 20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica-gel chromatography column using hexane/ethyl acetate as the eluent to obtain products **13** and **14**.

3.2.2.4 Gram-scale synthesis

Mono- and bis-sulfenylindole was performed up to gram-scale synthesis under the optimized conditions according to Figure 47. Under mono-sulfenylindole gram-scale synthesis, a mixture of indole **1** (8.54 mmol), diphenyl disulfides **3a** (4.27 mmol), SeO_2 (80 mol%, 6.83 mmol), KI (10 mol%, 0.85 mmol) and MeCN (50 mL) were added in round bottomed flask, which was vigorously stirred at 60 °C (water bath) under air atmosphere for 2 h. In gram-scale synthesis of bis-sulfenylindole, a mixture of indole **1** (8.54 mmol), diphenyl disulfides **3a** (8.54 mmol), SeO_2 (150 mol%, 12.81 mmol), KI (20 mol%, 1.71 mmol) and MeCN (5 mL) were added in round bottomed flask, which was vigorously stirred at 40 °C (water bath) under air atmosphere for 3 h. When each reaction completed, it washed with sat. aq. $Na_2S_2O_3$ (10 mL), H_2O (50 mL), and extracted with EtOAc (3×50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography column with 5% EtOAc/hexane as the eluent to furnish products **8a** and **13a**.



Reaction conditions: **1** (0.8 mmol), **3** (0.8 mmol), KI (20 mol%), SeO_2 (150 mol%) MeCN (5 mL), 40 °C, under air, 1 - 4 h.

Figure 44 Bis-sulfenylation of indoles with disulfides.

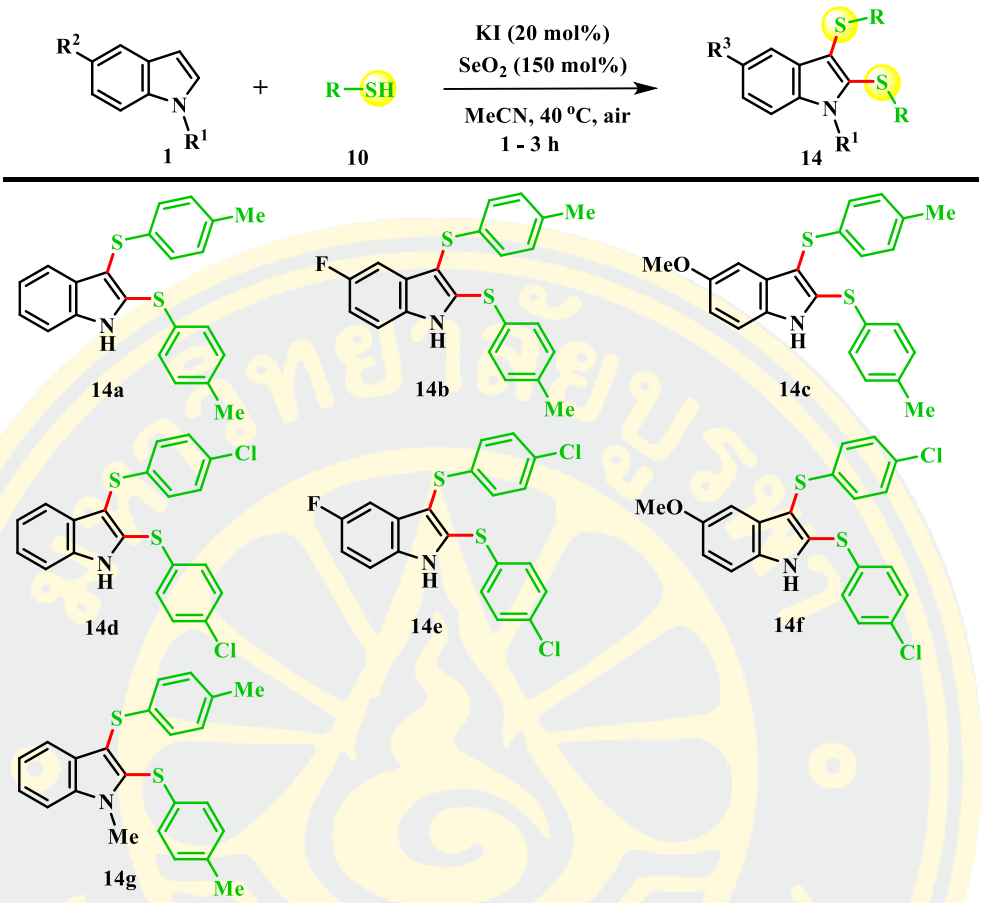


Figure 45 Bis-sulfenylation of indoles with thiols.

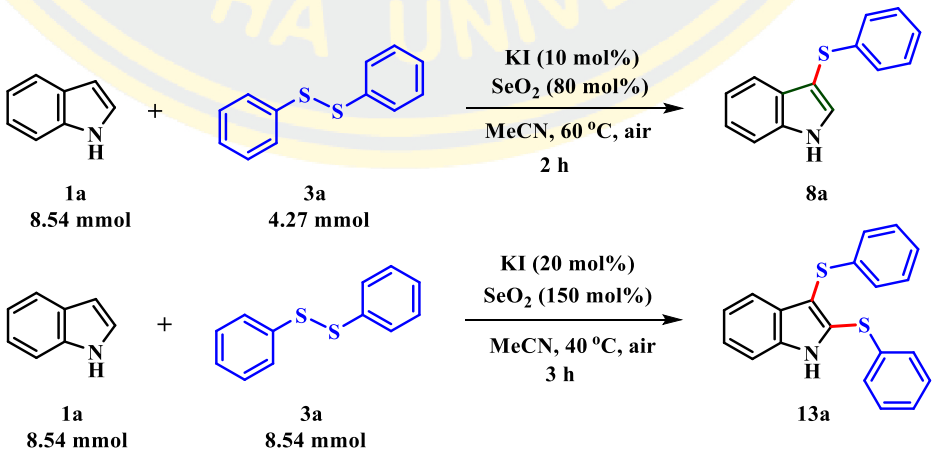


Figure 46 Gram-scale synthesis (isolated yields).

3.2.2.5 Control experiments for mechanistic studies

Procedure a (Figure 48)

A mixture of indole **1a** (0.85 mmol), diphenyl disulfides **3a** (0.425 mmol), KI (10 mol%, 0.085 mmol) and MeCN (5 mL) were added in glass tube, which was vigorously stirred at 60 °C (water bath) under air atmosphere until the reaction completed. Then, it was mixed with sat. aq. $Na_2S_2O_3$ (2 mL) and H_2O (10 mL), respectively, and extracted three times with ethyl acetate (20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was then purified by silica gel chromatography column with hexane/ethyl acetate as the eluent.

Procedure b (Figure 48)

A mixture of indole **1a** (0.85 mmol), SeO_2 (80 mol%, 0.68 mmol) and MeCN (5 mL) were added in glass tube, which was stirred at 60 °C (water bath) under air atmosphere. When the reaction completed, the reaction mixture was concentrated under reduced pressure and then purified by silica gel chromatography column with hexane/ethyl acetate as the eluent.

Procedure c (Figure 48)

A mixture of indole **1a** (0.85 mmol), SeO_2 (80 mol%, 0.68 mmol), KI (10 mol%, 0.08 mmol) and MeCN (5 mL) were added in glass tube, which was stirred at 60 °C (water bath) under air atmosphere until the reaction completed. Then, the reaction was quenched by addition of sat. aq. $Na_2S_2O_3$ (2 mL) and H_2O (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was analyzed by HRMS.

Procedure d (Figure 48)

The crude product from procedure c was mixed with MeCN (5 mL) follow by addition of diphenyl disulfides **3a** (0.425 mmol), SeO_2 (80 mol%, 0.64 mmol) and KI (10 mol%, 0.08 mmol), then vigorously stirred at 60 °C (water bath) by open to air until the reaction completed. Then, the reaction was work up and purified as procedure a.

Procedure e (Figure 48)

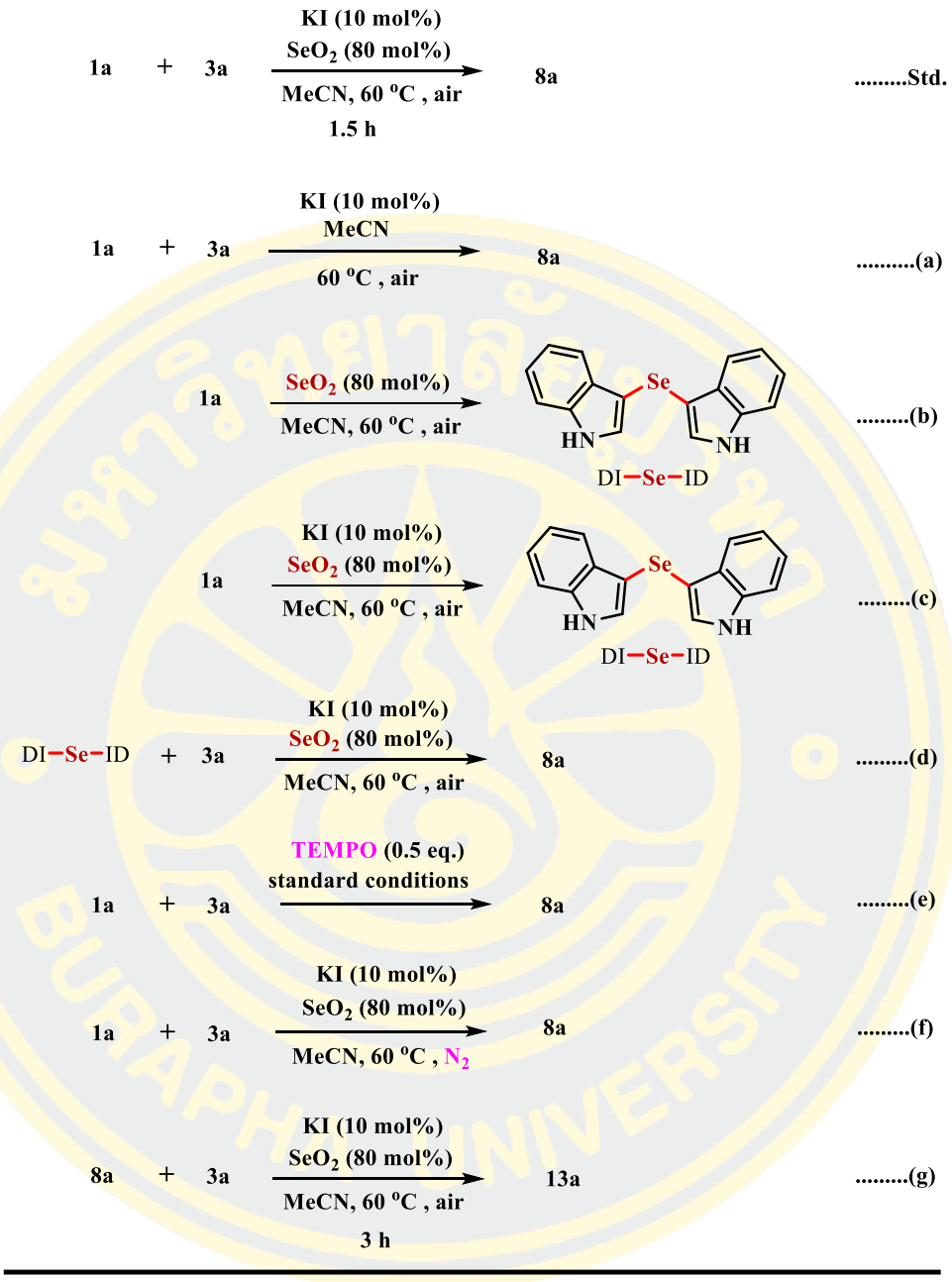
A mixture of indole **1a** (0.85 mmol), disulfides **3a** (0.425 mmol), SeO_2 (80 mol%, 0.68 mmol), KI (10 mol%, 0.08 mmol), 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, 0.425 mmol) and MeCN (5 mL) were added in glass tube, which was vigorously stirred at 60 °C (water bath) under air atmosphere until the reaction completed. Finally, the reaction was work up and purified as procedure a.

Procedure f (Figure 48)

A mixture of indole **1a** (0.85 mmol), disulfides **3a** (0.425 mmol), SeO_2 (80 mol%, 0.68 mmol), KI (10 mol%, 0.08 mmol), and MeCN (5 mL) were added in glass tube, which was vigorously stirred at 60 °C (water bath) under N_2 atmosphere. When the reaction completed, the product obtained by work up and purified as procedure a.

Procedure g (Figure 48)

Procedure (g) A mixture of **8a** (0.44 mmol), diphenyl disulfides **3a** (0.22 mmol), SeO_2 (80 mol%, 0.35 mmol), KI (10 mol%, 0.04 mmol), and MeCN (5 mL) were added in glass tube, which was vigorously stirred at 60 °C (water bath) under air atmosphere. When the reaction completed, the product obtained by work up and purified as procedure (a).



a) %conversion

Figure 47 Control Experiments

CHAPTER 4
RESULTS AND DISCUSSION

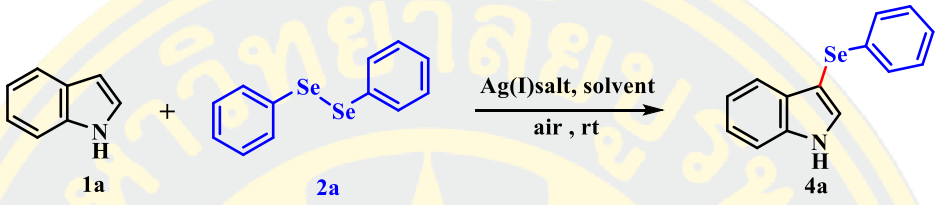
4.1 Selective synthesis of 3-chalcogenylindoles *via* silver-catalyzed direct chalcogenation of indoles with dichalcogenides

Initially, the catalytic activities of different silver catalysts including AgOAc, Ag_2SO_4, AgOTf and $AgNO_3$ were investigated by evaluating the sulfenation between indole (**1a**) and diphenyl diselenide (**2a**) in CH_2Cl_2 at room temperature by open to air atmosphere (Table 3). Among the four silver(I)salt (10 mol%), $AgNO_3$ showed the best result furnishing the desired product **4a** in 82% yield within 4 h (entry 4). Subsequently, the amount of catalyst was examined by varying the loading of $AgNO_3$ from 5 to 50 mol% (entries 5-9), and no addition of catalyst (entry 10). The obtained result found that the loading 10 mol% $AgNO_3$ (entry 4) was the optimal amount. The influence of the solvent in the reaction and diverse solvents with different characteristics, such as DMF, THF, CH_3CN, EtOH, EtOAc, toluene and H_2O (entried 11-17) were also screened in this sulfenation for 4 h. Surprisingly, EtOH (entry 14) is the most efficient for this reaction system with **4a** was obtained in 92% isolated yield, while DMF, CH_3CN, THF, EtOAc provided lower yields and H_2O do not furnish the desired products. Based on these results, we used 10 mol% $AgNO_3$ as catalyst, EtOH as the solvent for the direct C-H chalcogenation of indoles at room temperature under air atmosphere as the conditions for further evaluation (entry 14).

Under the optimized reaction conditions, the substrate scope of indoles (**1**) was examined for direct C-H chalcogenation with diphenyl diselinide (**2a**) and diphenyl disulfide (**3a**, Table 4). The received results indicated that various indole derivatives (**1**) reacted smoothly with **2a** to afford the corresponding 3-selenylindoles (**4**) in 70%-95% yields within 2 h to 6 h (Table 4). The sulfenation of different indole substrates with **3a** required higher reaction time (4 h to 6 h), providing the desired product **5** in 70% - 86% yields. When indoles with *N*-protected groups such as benzyl, 3-methoxybenzyl, 4-fluorobenzyl and methyl were used as substrate, furnishing the corresponding products with good yields (**4d**-**4m**, **5d**-**5m**). Additionally, the substrate scope of indoles (**1**) was then investigated for chalcogention with dibenzyl diselinide

(**2b**) and dibenzyl disulfide (**3b**). These substrates showed high reactivity with both **2b** and **3b** (Table 5) to produce the target product **6** and **7** in 65%-85% yields within 4 h to 6 h.

Table 3 Optimization of the reaction conditions



1a **2a** **4a**

entry	silver(I)salt (mol%)	solvent	time (h)	yields[a] (%)
1	$AgOAc$ (10)	CH_2Cl_2	24	trace
2	Ag_2SO_4 (10)	CH_2Cl_2	24	22
3	AgOTf (10)	CH_2Cl_2	24	trace
4	$AgNO_3$ (10)	CH_2Cl_2	4	82
5	$AgNO_3$ (20)	CH_2Cl_2	2	80
6	$AgNO_3$ (30)	CH_2Cl_2	2	71
7	$AgNO_3$ (40)	CH_2Cl_2	1	62
8	$AgNO_3$ (50)	CH_2Cl_2	1	60
9	$AgNO_3$ (5)	CH_2Cl_2	12	90
10[b]	-	CH_2Cl_2	24	NR
11	$AgNO_3$ (10)	DMF	4	trace
12	$AgNO_3$ (10)	THF	4	20
13	$AgNO_3$ (10)	CH_3CN	4	60
14	**$AgNO_3$ (10)**	**EtOH**	**4**	**92**
15	$AgNO_3$ (10)	EtOAc	4	45
16	$AgNO_3$ (10)	Toluene	4	Trace
17	$AgNO_3$ (10)	H_2O	4	NR

Reaction conditions:**1a** (0.4 mmol), **2a** (0.2 mmol), solvent (2 mL) under air at rt. [a]Isolated yield. [b]Reaction was carried out without $AgNO_3$., NR = no reaction.

Table 4 Scope of indoles for chalcogenation with diphenyl diselinide and disulfide

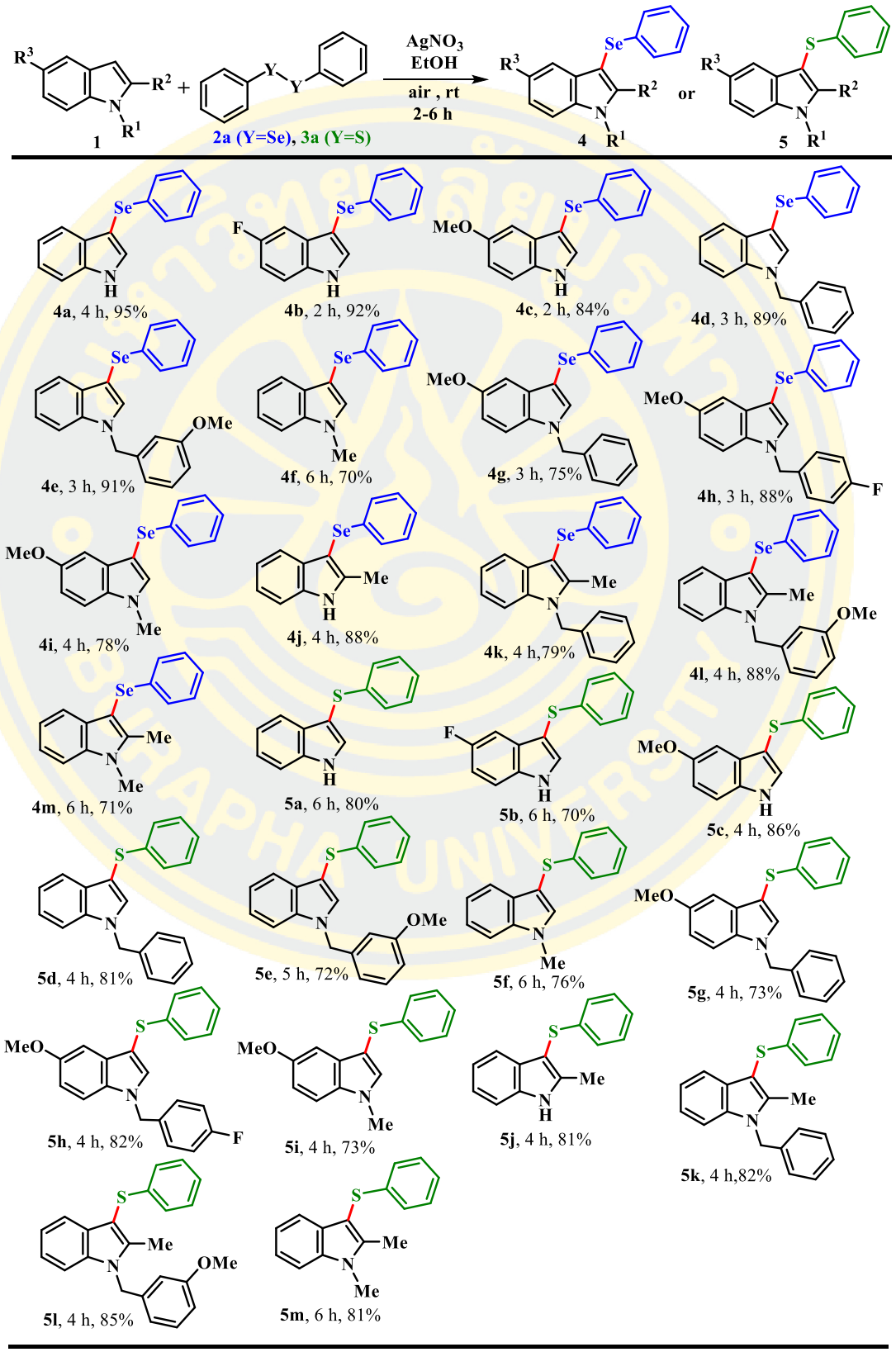


Table 5 Scope of indoles for chalcogenation with dibenzyl diselinide and dibenzyl disulfide

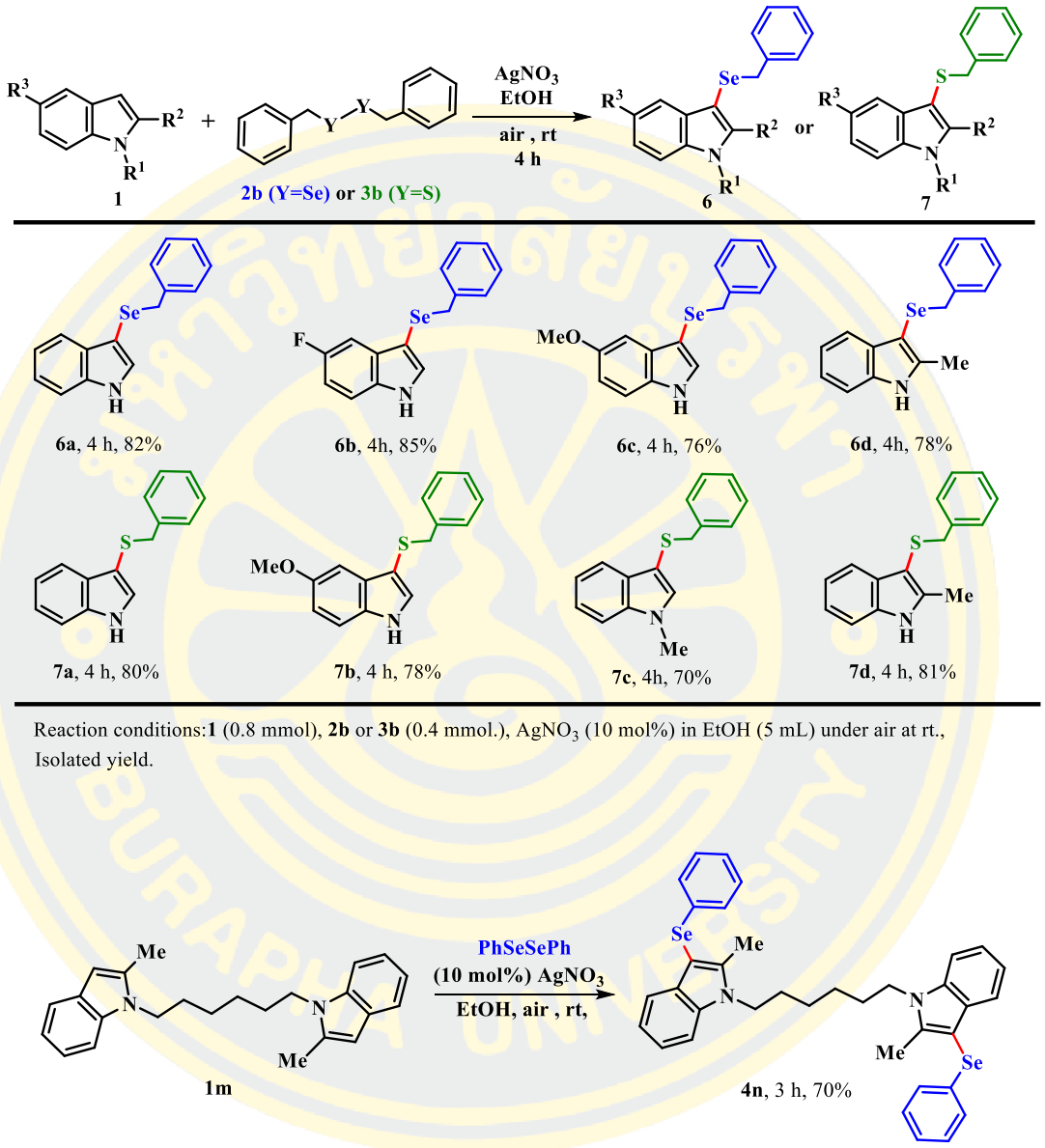


Figure 48 Chalcogenation of indole (**1m)** with diphenyl diselenide (**2a**).

The scalability of the developed approach was also evaluated by performed the chalcogenation of 1*H*-indole (**1a**) on a gram-scale between **1a** (8.5 mmol) and **2a** or **3a** (4.25 mmol) using the standard conditions. After 6 h, the desired product **4a** and **5a** were obtained in 80% and 75% yields respectively, which indicated the high potential of this approach to synthesize 3-chalcogenylindoles on a gram-scale synthesis (Figure 50).

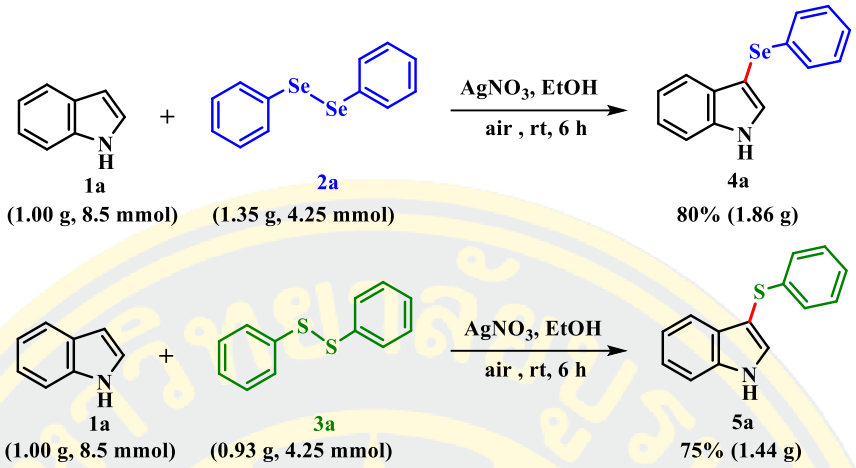


Figure 49 Gram-scale synthesis (isolated yields).

Next, control experiments were carried out to gain insight into the reaction mechanism, as shown in Figure 51. The isolated yield of product **4a** decreased to 38% when the reaction was performed under nitrogen atmosphere (Figure 51a). This demonstrated that atmospheric oxygen in air plays a role as an oxidant might be enhanced the potential in this transformation. In addition, 2,2,6,6-tetramethyl piperidin-1-oxyl (TEMPO), which as a radical scavenger was added into the reaction under the standard conditions furnishing product **4a** in 81% yield. (Figure 51b). This result confirmed that the reaction did not proceed through a radical mechanism. Finally, the product **4a** was not detected when dipenyl diselenide (**2a**) was used to react with the indole (**1a**) under standard conditions without adding $AgNO_3$ (Figure 51c).

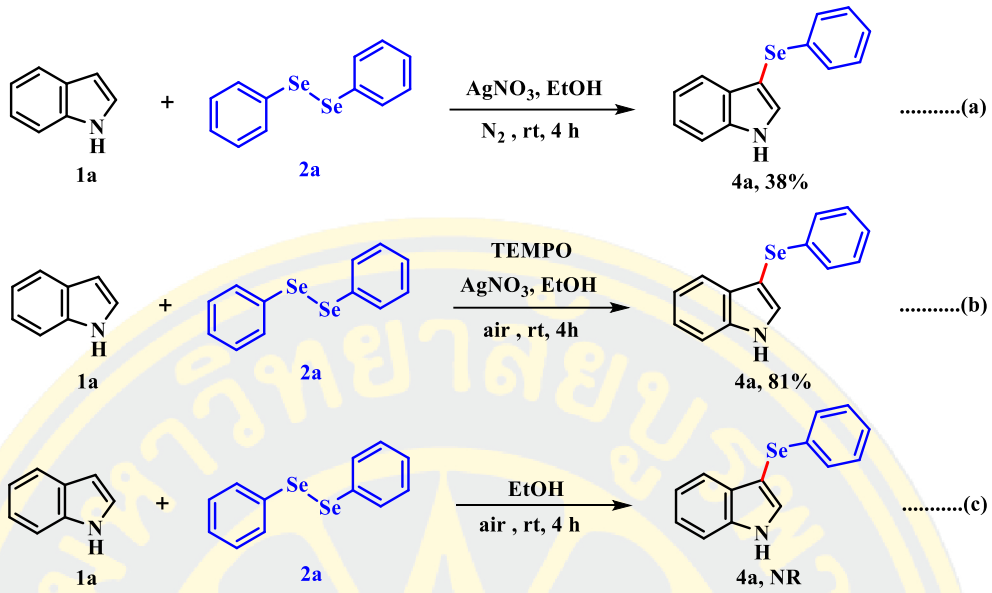


Figure 50 Control experiments for mechanistic studies.

Based on our control experiments and previous reports about silver-catalyzed reactions (Goldani et al., 2016), a plausible mechanism for this Ag(I)-catalyzed C-H selenation of indole **1a** with dipenyl diselenides **2a** to synthesized selanylindole **4a** can be proposed, as depicted in Figure 52. Initially, $AgNO_3$ reacts with the diselenide **2a** to form the Ag(III) intermediate **A** through an oxidative addition. Then, indole **1a** would attack the intermediate **A** leading to the intermediate **C** and selenophenol **B**. Additionally, selenophenol **B** can be oxidized back to the diphenyl diselenide **2a** by atmospheric oxygen in air. Finally, intermediate **C** can undergo a reductive elimination to produce the product **4a** and regenerate the $AgNO_3$ catalyst for next catalytic cycle.

Additionally, ^{77}Se NMR spectroscopy were conducted to prove the formation of the intermediate **A** and product **4a**. Product **4a** was analyzed by ^{77}Se NMR and ^{1}H NMR. Diphenyl diselenide **2a** and the mixture of **2a** (0.03 mmol) and $AgNO_3$ (0.03 mmol) in $CDCl_3$ in a NMR tube for 1 h at room temperature, then analyzed by ^{77}Se NMR and ^{1}H NMR (can see supporting information). It was found that the presence of the signals in the ^{77}Se NMR at 462.85 ppm (**2a**), at 383.75 ppm (**2a** + $AgNO_3$), due to Ph_2Se_2AgIII A (Goldani et al., 2016) and at 209.92 ppm (**4a**), which support proposed mechanism (Figure 52).

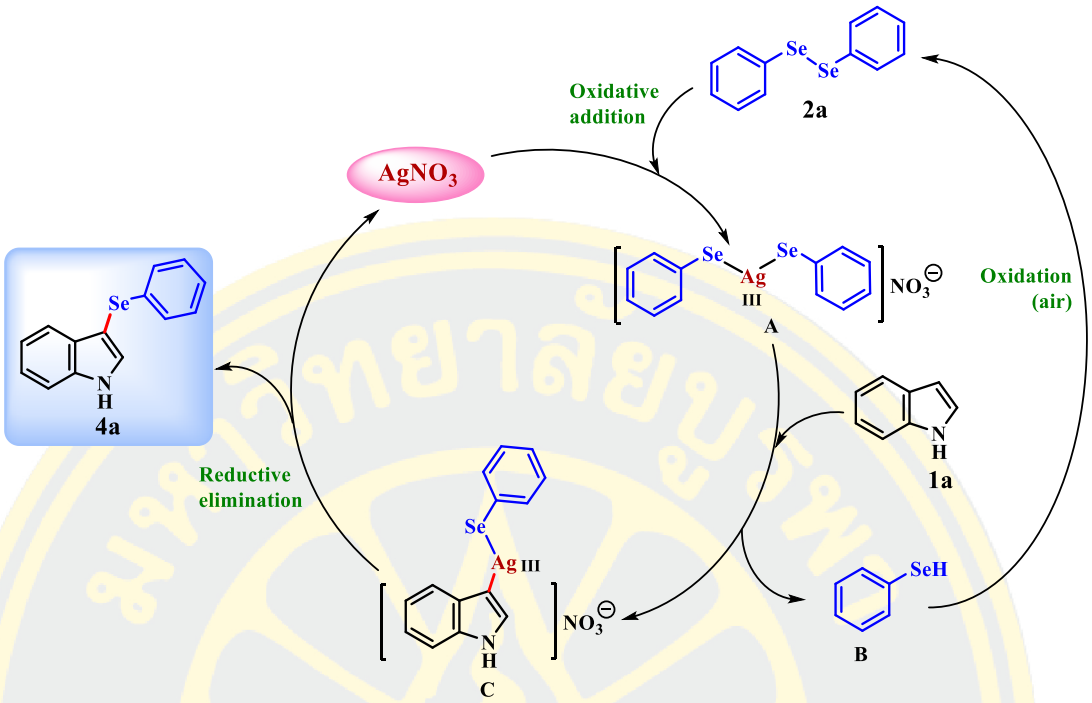
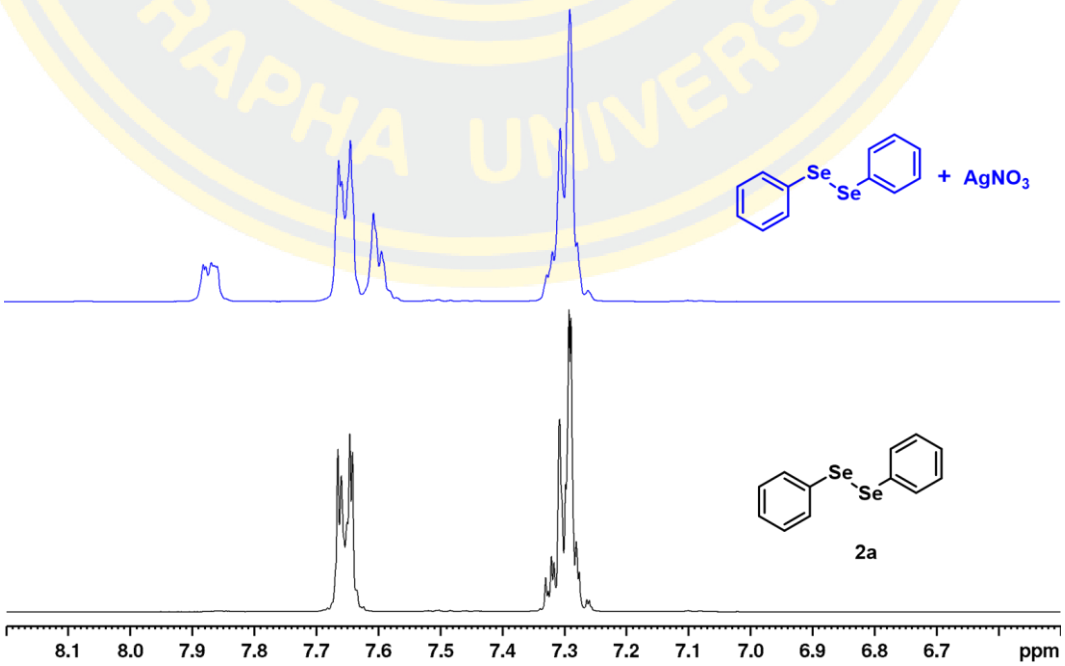
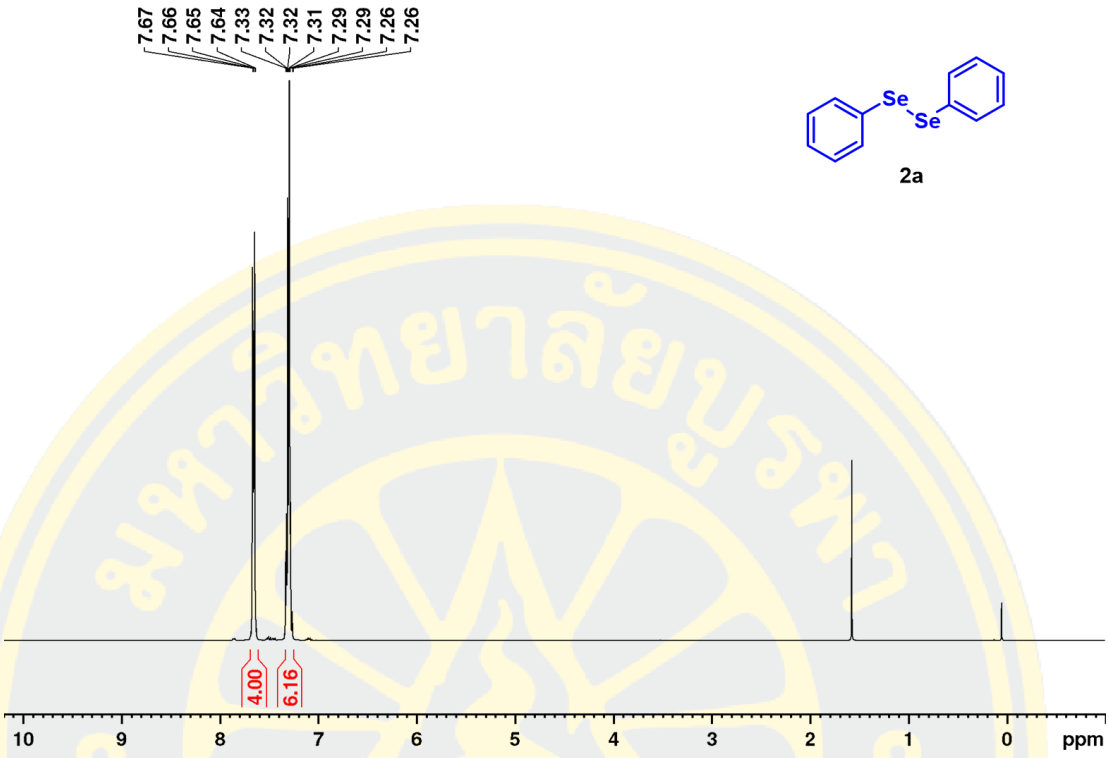


Figure 51 Proposed mechanism.

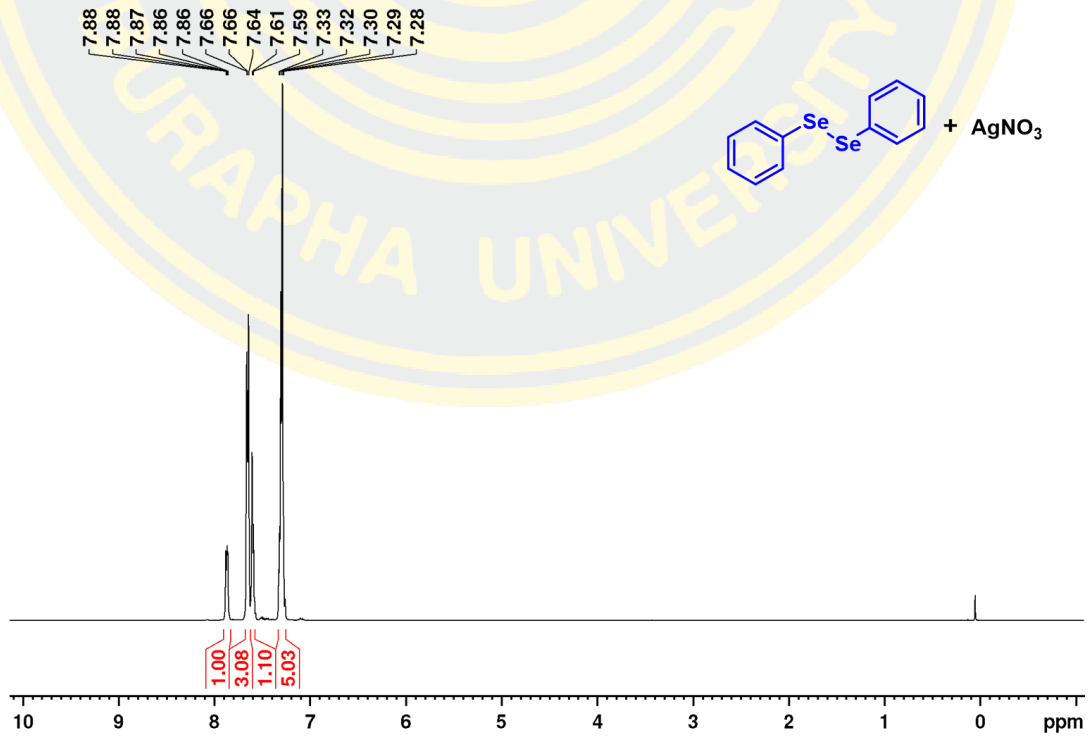
All the spectral data of compounds **2a**, **2a + AgNO3** are in agreement with those from literature (Goldani et al., 2016) as shown in the following NMR spectra.



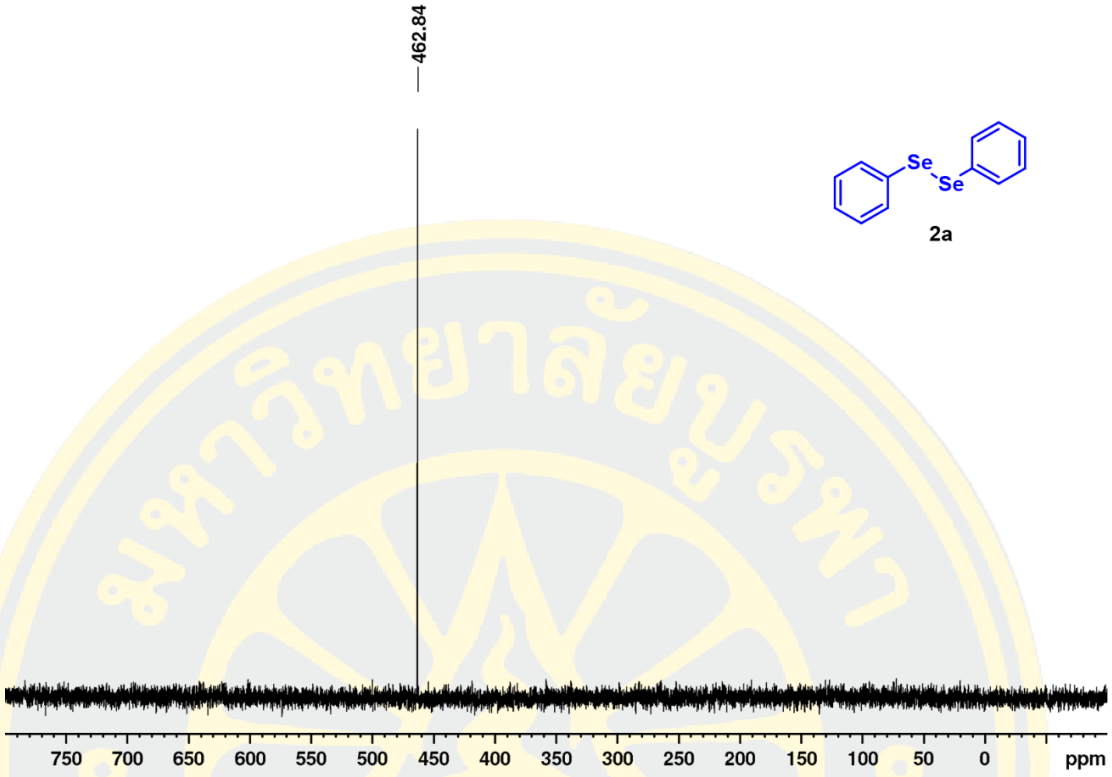
^{1}H NMR (400 MHz) spectrum of **2a** and **2a** + $AgNO_3$



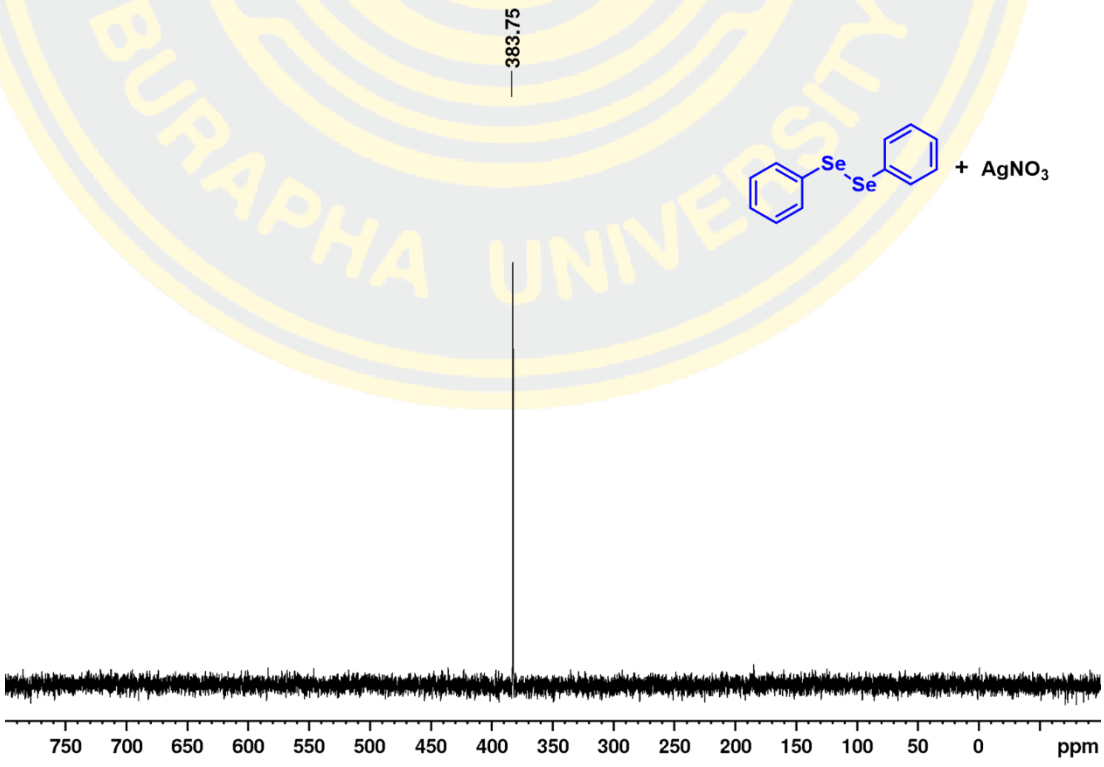
^{1}H NMR (400 MHz) spectrum of **2a** in $CDCl_3$



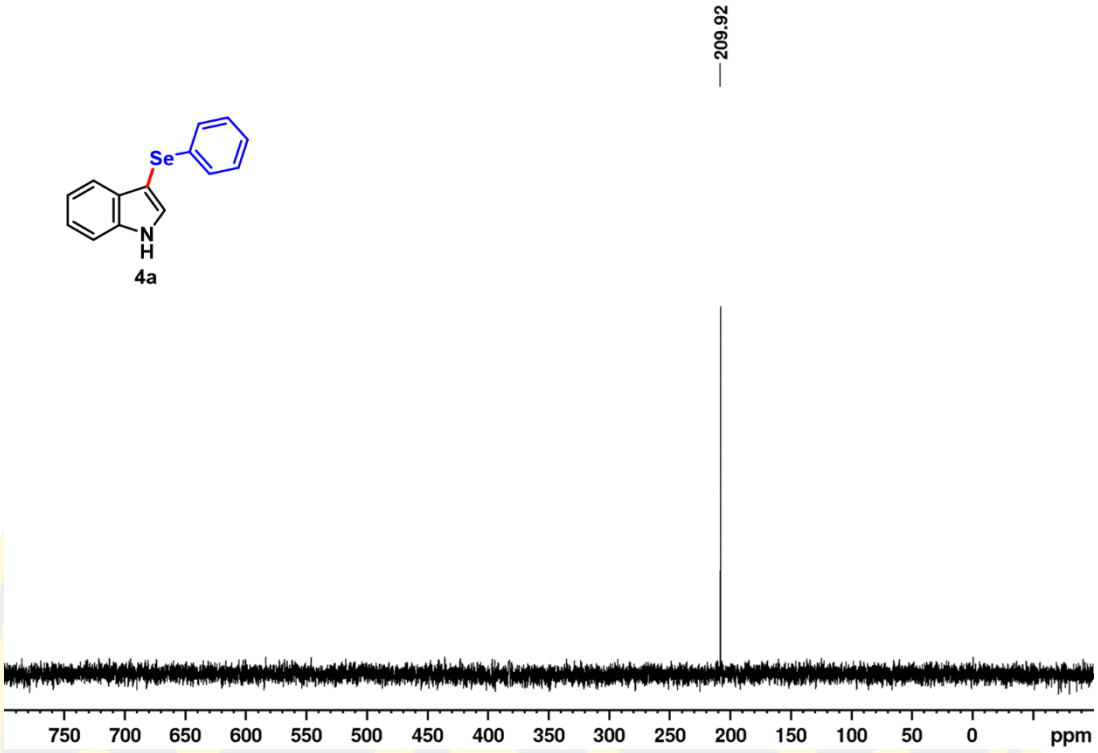
^{1}H NMR (400 MHz) spectrum of **2a** + $AgNO_3$ in $CDCl_3$



^{77}Se NMR (75 MHz) spectrum of **2a** in $CDCl_3$

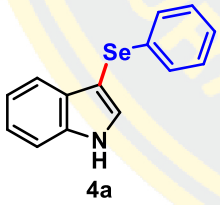


^{77}Se NMR (75 MHz) spectrum of diphenyl diselenide **2a** + $AgNO_3$ in $CDCl_3$

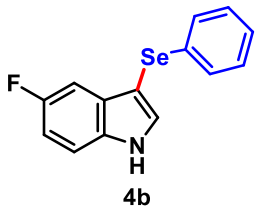


^{77}Se NMR (75 MHz) spectrum of product **4a** in $CDCl_3$

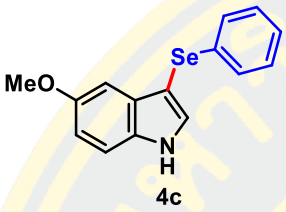
4.1.1 Characterization data of the synthesized compounds



3-(Phenylselanyl)-1*H*-indole (4a)[Azeredo et al., 2014]**;** 95 % yield (0.2202 g) as a white solid; mp 134-137 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.46 (br, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.52-7.46 (m, 2H), 7.32-7.25 (m, 3H), 7.23-7.11 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 136.4, 133.8, 131.2, 130.0, 129.0, 128.8, 128.7, 125.6, 123.0, 120.9, 120.4, 111.4, 98.3.

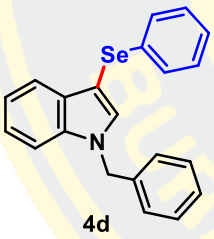


5-Fluoro-3-(phenylselanyl)-1*H*-indole (4b)[H. Li et al., 2017]**;** 92 % yield (0.1970 g) as a pale orange solid; mp 118-120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.45 (br, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.37-7.34 (m, 1H), 7.30-7.21 (m, 3H), 7.17-7.10 (m, 3H), 7.01 (td, *J* = 9.0, 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 159.9, 157.5, 133.4, 132.9, 130.9, 130.8, 129.0, 128.8, 125.8, 112.2, 112.1, 111.7, 111.4, 105.6, 105.3, 98.4.



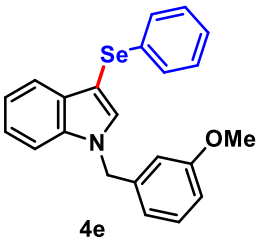
4c

5-Methoxy-3-(phenylselanyl)-1*H*-indole (4c) [Azeredo et al., 2014]**;** 84 % yield (0.1734 g) as a yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.41 (br, 1H), 7.44 (d, *J* = 2.6 Hz, 1H), 7.34-7.28 (m, 3H), 7.21-7.13 (m, 4H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 155.1, 134.0, 132.0, 131.4, 130.8, 129.1, 128.6, 125.6, 113.5, 112.3, 101.6, 97.6, 55.9.



4d

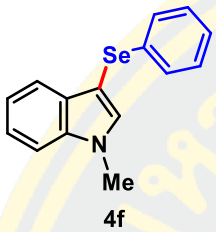
1-Benzyl-3-(phenylselanyl)-1*H*-indole (4d)[25]**;** 89 % yield (0.1555 g) as a pale orange solid; mp 77-79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.41 (s, 1H), 7.35-7.22 (m, 7H), 7.19-7.09 (m, 6H), 5.37 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.1, 136.8, 135.1, 134.1, 131.0, 129.0, 128.7, 128.6, 128.5, 128.0, 127.0, 125.6, 122.7, 120.7, 110.1, 96.9, 50.4.



4e

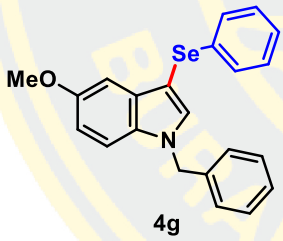
1-(3-Methoxybenzyl)-3-(phenylselanyl)-1*H*-indole (4e); 91 % yield (0.1503 g) as a pale yellow solid; mp 81-83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.70 (d, *J* = 7.9

Hz, 1H), 7.45 (s, 1H), 7.40-7.38 (m, 1H), 7.30-7.28 (m, 4H), 7.23-7.13 (m, 4H), 6.88-6.85 (m, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.73 (s, 1H), 5.36 (s, 2H), 3.78 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 160.1, 138.4, 137.2, 135.1, 134.2, 130.9, 130.1, 129.0, 128.7, 128.6, 128.5, 125.6, 122.7, 120.7, 120.7, 119.3, 113.2, 112.8, 110.1, 96.9, 55.2, 50.4. HRMS (ESI) *m/z* $C_{22}H_{19}NOSe$ $(M+H)^+$ calcd 394.0705, found 394.0664.



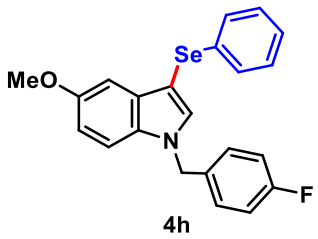
4f

1-Methyl-3-(phenylselanyl)-1*H*-indole (4f) (Azeredo et al., 2014)**;** 70 % yield (0.1526 g) as a white solid; mp 66-68 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.71 (d, J = 7.9 Hz, 1H), 7.44-7.42 (m, 1H), 7.37-7.28 (m, 4H), 7.24-7.22 (m, 1H), 7.20-7.14 (m, 3H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 137.5, 135.7, 134.3, 130.8, 129.0 128.7, 128.6, 125.6, 122.5, 120.5, 109.6, 96.0, 33.1.



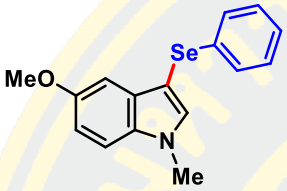
4g

1-Benzyl-5-methoxy-3-(phenylselanyl)-1*H*-indole (4g); 75 % yield (0.0923 g) as a white solid; mp 99-101 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.42 (s, 1H), 7.40-7.25 (m, 6H), 7.22-7.15 (m, 6H), 6.94 (d, J = 8.8 Hz, 1H), 5.35 (s, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 155.2, 136.9, 135.6, 134.3, 132.2, 131.8, 129.1, 129.0, 128.5, 128.0, 127.0, 125.6, 113.2, 111.1, 101.9, 96.2, 55.8, 50.6. HRMS (ESI) *m/z* $C_{22}H_{19}NOSe$ $(M+H)^+$ calcd 394.0705, found 394.0654.



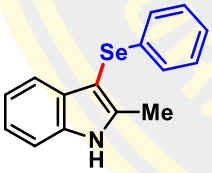
4h

1-(4-Fluorobenzyl)-5-methoxy-3-(phenylselanyl)-1*H*-indole (4h); 88 % yield (0.1416 g) as a orange oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.38 (s, 1H), 7.28-7.22 (m, 3H), 7.20-7.10 (m, 6H), 7.06-7.01 (m, 2H) 6.91 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.32 (s, 2H), 3.82 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 163.6, 161.2, 155.2, 135.3, 134.1, 132.6, 132.0, 131.8, 129.0, 126.6, 128.4, 125.6, 116.0, 115.7, 113.3, 110.9, 101.9, 96.4, 55.8, 49.9. HRMS (ESI) *m/z* $C_{22}H_{18}FNOSe$ $(M+H)^+$ calcd 412.0610, found 412.0610.



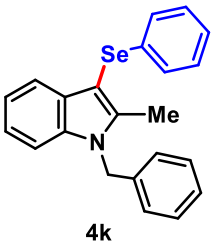
4i

5-Methoxy-1-methyl-3-(phenylselanyl)-1*H*-indole (4i); 78 % yield (0.1529 g) as a pale orange solid; mp 113-115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.32-7.27 (m, 4H), 7.20-7.11 (m, 4H), 6.99 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 155.0, 136.1, 134.4, 132.7, 131.5, 129.0, 128.4, 125.5, 113.0, 110.5, 101.7, 95.2, 55.9, 33.2. HRMS (ESI) *m/z* $C_{16}H_{15}NOSe$ $(M+H)^+$ calcd 318.0392, found 318.0365.



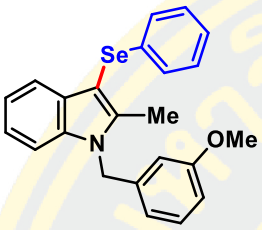
4j

2-Methyl-3-(phenylselanyl)-1*H*-indole (4j) [Azeredo et al., 2014]**;** 88 % yield (0.1919 g) as a white solid; mp 99-100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.23 (br, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.35-7.33 (m, 1H), 7.23-7.08 (m, 7H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 140.9, 135.8, 134.0, 131.3, 129.0, 128.4, 128.4, 128.3, 125.4, 122.1, 120.7, 119.8, 110.5, 96.3, 13.2.



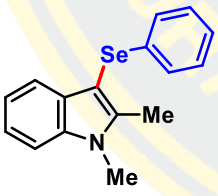
4k

1-Benzyl-2-methyl-3-(phenylselanyl)-1*H*-indole (4k); 79 % yield (0.1343 g) as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.66 (d, J = 7.1 Hz, 1H), 7.34-7.27 (m, 4H), 7.23-7.09 (m, 7H), 7.02-7.04 (m, 2 H), 5.45 (s, 2H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 142.5, 137.2, 134.2, 130.8, 128.9, 128.2, 127.5, 126.0, 125.3, 122.0, 120.6, 120.0, 109.5, 96.3, 47.5, 12.0. HRMS (ESI) *m/z* $C_{22}H_{19}NSe$ $(M+H)^+$ calcd 378.0755, found 378.0719.



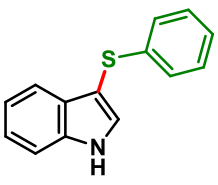
4l

1-(3-Methoxybenzyl)-2-methyl-3-(phenylselanyl)-1*H*-indole (4l); 88 % yield (0.1423 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.70 (d, J = 7.6 Hz, 1H), 7.34-7.32 (m, 1H), 7.28-7.12 (m, 8H), 6.84 (d, J = 8.2 Hz, 1 H), 6.64 (d, J = 7.6 Hz, 1 H), 6.59 (s, 1H), 5.43 (s, 2H), 3.76 (s, 3H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 160.2, 142.5, 139.0, 137.3, 134.3, 130.8, 130.1, 129.0, 128.3, 128.2, 125.4, 122.1, 120.7, 120.0, 118.3, 112.6, 112.0, 109.5, 96.3, 55.2, 47.4, 12.1. HRMS (ESI) *m/z* $C_{23}H_{21}NOSe$ $(M+H)^+$ calcd 408.0861, found 408.0830.



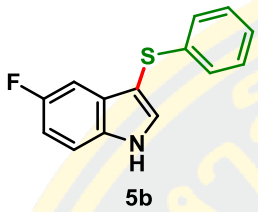
4m

1,2-Dimethyl-3-(phenylselanyl)-1*H*-indole (4m)[25]; 71 % yield (0.1469 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.69 (d, J = 7.8 Hz, 1H), 7.40-7.38 (m, 1H), 7.33-7.30 (m, 1H), 7.28-7.13 (m, 6H), 3.80 (s, 3H), 2.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 142.6, 137.4, 134.4, 130.7, 129.0, 128.3, 125.4, 121.7, 120.4, 119.9, 109.1, 95.2, 30.5, 12.1.



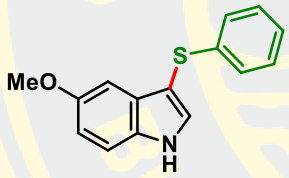
5a

3-(Phenylthio)-1*H*-indole (5a)[12]; 80 % yield (0.1539 g) as a brick red solid; mp 130-132 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.45 (br, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 6.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.32-7.28 (m, 2H), 7.21-7.17 (m, 3H), 7.14-7.12 (m, 2H), 7.10-7.05 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 139.2, 136.5, 129.1, 128.7, 125.9, 124.8, 123.1, 120.9, 119.7, 111.5, 103.0.



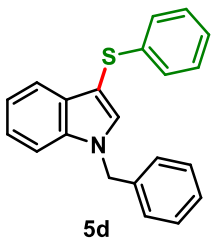
5b

5-Fluoro-3-(phenylthio)-1*H*-indole (5b)[21]; 70 % yield (0.1256 g) as a yellow solid; mp 167-169 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.44 (br, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.40- 7.37 (m, 1H), 7.30- 7.21 (m, 1H), 7.20- 7.16 (m, 2H), 7.17- 7.05 (m, 3H), 7.02 (td, *J* = 9.1, 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 159.7, 157.3, 132.7, 132.1, 128.6, 125.8, 124.8, 112.3, 112.2, 111.6, 111.4, 104.7, 104.4, 103.0.



5c

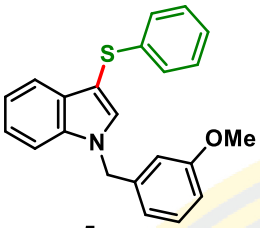
5-Methoxy-3-(phenylthio)-1*H*-indole (5c)[12]; 86 % yield (0.1491 g) as a brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.35 (br, 1H), 7.44 (d, *J* = 2.7 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.19- 7.15 (m, 2H), 7.11- 7.04 (m, 4H), 6.93 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 155.2, 139.3, 131.3, 130.0, 128.7, 125.7, 124.7, 113.6, 112.4, 102.3, 100.8, 55.8.



5d

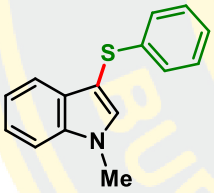
1-Benzyl-3-(phenylthio)-1*H*-indole (5d)[22]; 81 % yield (0.1230 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.66 (d, *J* = 2.7 Hz, 1H), 7.44 (s, 1H), 7.39- 7.32 (m, 4H), 7.29- 7.25 (m, 1H), 7.21-7.18 (m, 5H), 7.15-7.13 (m, 2H), 7.10-7.06 (m, 1H),

5.39 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 139.5, 137.2, 136.6, 134.5, 130.1, 129.0, 128.7, 128.0, 127.0, 125.8, 124.7, 122.8, 120.7, 119.9, 110.3, 101.5. 50.5.



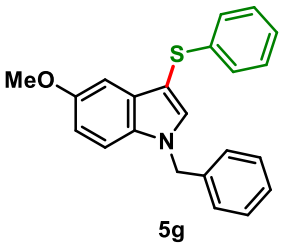
5e

1-(3-Methoxybenzyl)-3-(phenylthio)-1*H*-indole (5e); 72 % yield (0.1040 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.65 (d, J = 7.8 Hz, 1H), 7.44 (s, 1H), 7.39- 7.30 (m, 1H), 7.29- 7.25 (m, 2H), 7.21-7.17 (m, 3H), 7.14-7.12 (m, 2H), 7.10-7.06 (m, 1H), 6.86 (dd, J = 8.2, 2.4 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.72, (s, 1H), 5.36 (s, 2H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 160.1, 139.5, 138.2, 137.2, 134.5, 130.0, 128.7, 125.8, 124.7, 122.8, 120.7, 119.3, 113.2, 112.8, 110.3, 101.5, 55.2, 50.4. HRMS (ESI) *m/z* $C_{22}H_{19}NOS$ $(M+H)^+$ calcd 364.1260, found 364.1239.



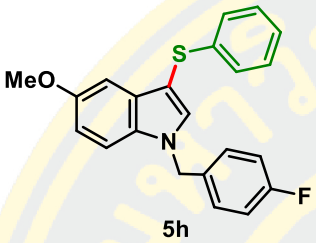
5f

1-Methyl-3-(phenylthio)-1*H*-indole (5f)[12]; 76 % yield (0.1396 g) as a pale yellow solid; mp 86-88 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.61 (d, J = 7.9 Hz, 1H), 7.40-7.39 (m, 1H), 7.34 (s, 1H), 7.32- 7.28 (m, 1H), 7.19- 7.13 (m, 3H), 7.11-7.08 (m, 2H), 7.06-7.02 (m, 1H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 139.7, 137.6, 135.1, 135.0, 129.9, 128.7, 125.8, 125.7, 124.7122.6, 120.5, 119.8, 109.7, 100.6, 33.1.



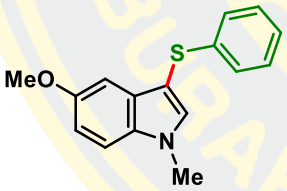
5g

1-Benzyl-5-methoxy-3-(phenylthio)-1*H*-indole (5g); 73 % yield (0.1060 g) as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.40-7.28 (m, 4H), 7.24-7.14 (m, 5H), 7.32- 7.28 (m, 1H), 7.12- 7.07 (m, 4H), 6.89 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.35 (s, 2H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 155.2, 139.7, 136.7, 135.0, 129.0, 128.0, 126.9, 125.6, 124.7, 113.3, 111.2, 101.1, 100.6, 55.8, 50.7. HRMS (ESI) *m/z* $C_{22}H_{19}NOS$ $(M+H)^+$ calcd 364.1260, found 364.1251.



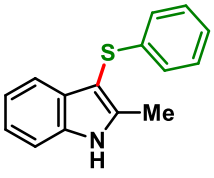
5h

1-(4-Fluorobenzyl)-5-methoxy-3-(phenylthio)-1*H*-indole (5h); 92 % yield (0.1314 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.36 (s, 1H), 7.20-7.08 (m, 7H), 7.06-6.99 (m, 4H), 6.89 (dd, *J* = 8.9, 2.5 Hz, 1H), 5.29 (s, 2H), 3.78 (s, 3H). 13C NMR ($CDCl_3$, 100 MHz, ppm) δ 163.6, 161.2, 155.2, 139.5, 134.7, 132.5, 132.4, 132.0, 131.0, 128.7, 128.6, 125.6, 124.7, 116.0, 115.8, 113.4, 111.1, 101.1, 100.9, 55.8, 50.0. HRMS (ESI) *m/z* $C_{22}H_{18}FNOS$ $(M+H)^+$ calcd 364.1166, found 364.1179.



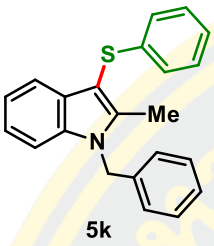
5i

5-Methoxy-1-methyl-3-(phenylthio)-1*H*-indole (5i)[18]; 73 % yield (0.1219 g) as a brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.32-7.31 (m, 1H), 7.29-6.28 (m, 1H), 7.21-7.17 (m, 2H), 7.13-7.05 (m, 4H), 6.97 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 155.1, 139.8, 135.5, 132.7, 130.7, 128.7, 125.6, 125.5, 124.6, 113.1, 110.6, 100.9, 99.7, 99.6, 55.8, 33.3.



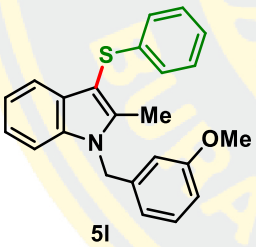
5j

2-Methyl-3-(phenylthio)-1*H*-indole (5j)[12]; 85 % yield (0.1543 g) as a white solid; mp 116-118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.25 (br, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.21-7.10 (m, 4H), 7.05-7.01 (m, 3H), 2.53 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 141.1, 139.3, 135.4, 130.3, 128.7, 125.5, 124.5, 122.2, 120.7, 119.0, 110.6, 99.5, 12.2.



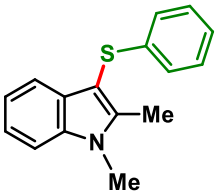
5k

1-Benzyl-2-methyl-3-(phenylthio)-1*H*-indole (5k); 82 % yield (0.1221 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.66-7.64 (m, 1H), 7.35-7.24 (m, 4H), 7.22-7.16 (m, 4H), 7.09-7.06 (m, 5H), 5.44 (s, 2H), 2.50 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 142.8, 139.6, 137.1, 137.1, 129.9, 128.9, 128.7, 127.6, 126.0, 125.4, 124.5, 122.1, 120.7, 119.1, 109.6, 99.1, 47.4, 10.9. HRMS (ESI) *m/z* $C_{22}H_{19}NS$ $(M+H)^+$ calcd 330.1311, found 330.1314.



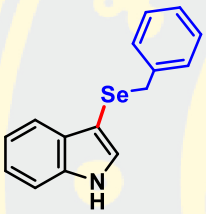
5l

1-(3-Methoxybenzyl)-2-methyl-3-(phenylthio)-1*H*-indole (5l); 85 % yield (0.1216 g) as a pale brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.63-7.60 (m, 1H), 7.31-7.29 (m, 1H), 7.24-7.13 (m, 5H), 7.06-7.02 (m, 3H), 6.79 (dd, J = 8.2, 2.2 Hz, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.55 (s, 1H), 5.38 (s, 2H), 3.73 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 160.1, 142.8, 139.7, 138.8, 137.0, 130.0, 129.9, 128.7, 125.4, 124.5, 122.1, 120.7, 119.1, 118.2, 112.6, 111.9, 109.5, 99.1, 55.2, 47.3, 10.9. HRMS (ESI) *m/z* $C_{23}H_{21}NOS$ $(M+H)^+$ calcd 360.1417, found 360.1414.



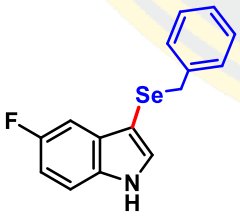
5m

1,2-Dimethyl-3-(phenylthio)-1*H*-indole (5m)[21]; 81 % yield (0.1414 g) as a yellow solid; mp 85-87 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.2 Hz,1H), 7.28-7.24 (m, 1H), 7.06-7.02 (m, 3H), 7.18-7.14 (m, 3H), 7.07-7.03 (m, 3H), 3.80 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 142.9, 139.8, 137.1, 129.8, 128.6, 125.4, 124.4, 121.8, 120.5, 119.0, 109.0, 98.1, 30.4, 10.9.



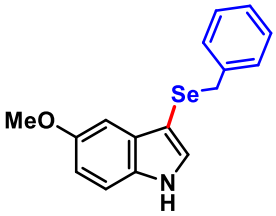
6a

3-(Benzylselanyl)-1*H*-indole (6a) (Azeredo et al., 2014); 82 % yield (0.2004 g) as a yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.24 (br, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.30-7.17 (m, 5H), 7.09-7.06 (m, 3H), 3.91 (s, 2H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 139.8, 136.2, 130.7, 130.2, 128.8, 128.2, 126.5, 122.6, 120.5, 120.2, 111.3, 99.0, 32.2.



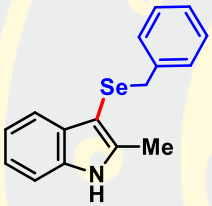
6b

3-(Benzylselanyl)-5-fluoro-1*H*-indole (6b) (H. Li et al., 2017); 85 % yield (0.1913 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.24 (br, 1H), 7.31-7.28 (m, 1H), 7.25-7.23 (m, 1H), 7.20-7.14 (m, 3H), 7.08 (d, *J* = 2.6 Hz, 1H), 7.03-6.95 (m, 3H), 3.85 (s, 2H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 159.7, 157.4, 139.6, 132.6, 132.4, 131.2, 131.1, 128.8, 128.2, 126.5, 112.0, 111.9, 111.2, 110.9, 105.3, 105.1, 99.0, 98.9, 32.2.



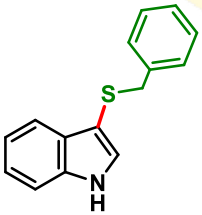
6c

3-(Benzylselanyl)-5-methoxy-1*H*-indole (6c); 76 % yield (0.1633 g) as a brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.18 (br, 1H), 7.27-7.25 (m, 1H), 7.20-7.12 (m, 3H), 7.04-7.02 (m, 4H), 6.88 (dd, J = 8.6, 2.3 Hz, 1H), 7.03-6.95 (m, 3H), 3.85 (s, 5H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 154.9, 140.0, 131.4, 131.1, 131.0, 128.8, 128.2, 126.5, 113.1, 112.0, 101.5, 98.6, 55.8, 32.4. HRMS (ESI) *m/z* $C_{16}H_{15}NOSe$ $(M+H)^+$ calcd 318.0392, found 318.0377.



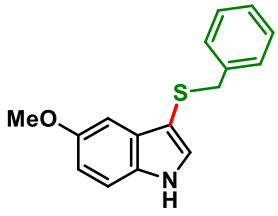
6d

3-(Benzylselanyl)-2-methyl-1*H*-indole (6d); 78 % yield (0.1785 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.98 (br, 1H), 7.68-7.66 (m, 1H), 7.30-7.27 (m, 1H), 7.20-7.15 (m, 5H), 6.97-6.94 (m, 2H), 3.76 (s, 2H), 1.99 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 140.8, 138.9, 134.9, 130.0, 128.6, 127.7, 126.2, 121.5, 120.0, 118.3, 110.1, 101.0, 40.0, 11.1. HRMS (ESI) *m/z* $C_{16}H_{15}NSe$ $(M+H)^+$ calcd 302.0442, found 302.0432.



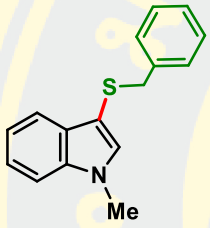
7a

3-(Benzylthio)-1*H*-indole (7a)[12]; 80 % yield (0.1635 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.12 (br, 1H), 7.71-7.69 (m, 1H), 7.35-7.33 (m, 1H), 7.25-7.08 (m, 5H), 7.06-6.98 (m, 2H), 6.97 (s, 1H), 3.86 (s, 2H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 138.9, 136.1, 129.7, 129.1, 128.9, 128.1, 126.6, 122.5, 120.3, 119.1, 111.4, 105.0, 40.9.



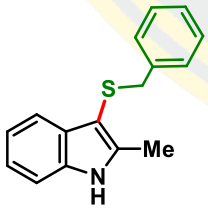
7b

3-(Benzylthio)-5-methoxy-1*H*-indole (7b)[30]; 78 % yield (0.1427 g) as a brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 8.11 (br, 1H), 7.25-7.18 (m, 5H), 7.08-6.99 (m, 3H), 6.87-6.85 (m, 1H), 3.83 (s, 5H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 154.8, 139.3, 131.1, 130.7, 130.1, 129.0, 128.8, 128.5, 128.2, 113.1, 112.2, 104.8, 100.6, 55.8, 41.2.



7c

3-(Benzylthio)-1-methyl-1*H*-indole (7c)[30]; 70 % yield (0.1351 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.74 (d, J = 7.8 Hz, 1H), 7.35-7.21 (m, 6H), 7.17-7.15 (m, 2H), 6.92 (s, 1H), 3.91 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 139.2, 137.13, 134.4, 130.0, 129.1, 128.3, 126.9, 122.3, 120.1, 119.5, 109.7, 103.4, 41.1, 32.9.



7d

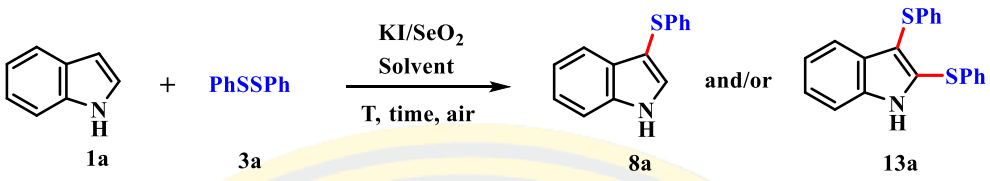
3-(Benzylthio)-2-methyl-1*H*-indole (7d)[18]; 81 % yield (0.1564 g) as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.91 (s, 1H), 7.66-7.64 (m, 1H), 7.27-7.24 (m, 1H), 7.18-7.13 (m, 5H), 6.95-6.93 (m, 2H), 3.74 (s, 2H), 1.96 (s, 3H). ^{13}C NMR (CDCl3, 100 MHz, ppm) δ 141.0, 139.1, 135.1, 130.2, 128.8, 127.9, 126.4, 121.6, 120.2, 118.4, 110.4, 101.1, 40.2, 11.3.

4.2 Controllable synthesis of mono-and bis-sylfenylindoles from indoles and various sulfenylation agents using KI/SeO_2 system

1*H*-Indole (**1a**; 1 equiv.) and diphenyl disulfide **3a** (0.5 equiv.) were firstly employed as a model reaction for synthesizing mono-indole (**3a**) and screening results are summarized in Table 6 (entries 1–15). Preliminary tests were performed under air atmosphere at 60 °C in acetonitrile (MeCN) as the solvent to evaluate and optimize the amounts of catalyst and oxidant using 10 mol% of KI and 60 mol% of SeO_2. The target product **3a** was isolated in 94% yield after heating at 60 °C for 4 h (entry 1). After that, the oxidant loading was optimized to improve the yield of the product by gradually increasing the amount of SeO_2 to 100 mol% (entries 2-5). When the loading of SeO_2 was increased to 80 mol%, the isolated yield of **3a** enhanced to 97% using the reaction time for 1.5 h (entry 3). Next, a series of reaction solvents was investigated at 60 °C for 1 h, found that the reaction did not work when employing ethanol (EtOH), H_2O, dimethylformamide (DMF) and dimethylsulfoxide (DMSO) as solvents (entries 6–7 and 9–10). When dichloroethane (DCE) and dichloromethane (DCM) were used as solvents, the yields of **3a** decreased to 44% and 58%, respectively (entries 11–12). For further inspection, MeCN is the best choice for synthesizing sulfenylindole **8a** (entry 8). Afterward, the effect of temperature was tested, upon increasing the temperature to 80 °C resulted in a considerable decrease in the yield (entry 13). However, decreasing the temperature to 40 °C and room temperature affected decreasing in the yield, and long reaction times were required (entries 14-15). Based on these results, the optimal conditions for the selective synthesis of mono-sulfenylindole **8a** comprises 10 mol% of KI and 80 mol% of SeO_2 in MeCN under air at 60 °C (entry 3) employing **1a** (1 equiv.) and **3a** (0.5 equiv.). Next, the optimum condition was determined for the selective preparation of bis-sulfenylindole. Initially, 1*H*-indole **1a** (1 equiv.) and disulfide **3a** (1 equiv.) were performed under air atmosphere at 40 °C in the presence of different loadings of KI and SeO_2 (entries 16-22). The reaction temperature was then investigated at 60 °C and room temperature (entries 23-24). Ultimately, 20 mol% of KI and 150 mol% of SeO_2 were found to be the best catalytic system to obtain a maximum yield of the desired bis-sulfenylindole **13a** at 40 °C (entry 20).

With the optimized reaction conditions (Table 6, entry 3), the efficiency and general applicability of our methodology were firstly investigated for the mono-sulfenylation of various indoles **1** with different disulfides **3** and the results are summarized in Table 7. In each case, the mono-sulfenylation of indoles with disulfides were completed within 1.5 to 3 hours that could isolate the desired products in yields of 70% - 98% (**8a**-**9c**). When diphenyl disulfide (**3a**) was used as sulfenylation agent, the direct 3-sulfenylation of indoles was completed within a shorter time than using di-*p*-tolyl and 4,4'-dichloro diphenyl disulfides (**3c** and **3d**) as sulfenylation agents. This strategy was successfully extended to *N*-protected indoles including *N*-methylindole (**1e**) and *N*-benzylindole (**1f**), which reacted with diphenyl disulfide (**3a**) to provide the 3-selenyl-indoles **8m** and **8n** in 90% and 93% yields, respectively. Additionally, the developed protocol can also be applied for the synthesis of 2-selenylindoles using 3-methylindole and different disulfides (**3a**, **3c** and **3d**), furnishing the corresponding products with good yields (**9a**–**9b**) within 2.5 to 3 hours.

Table 6 Optimization of the Reaction Conditions

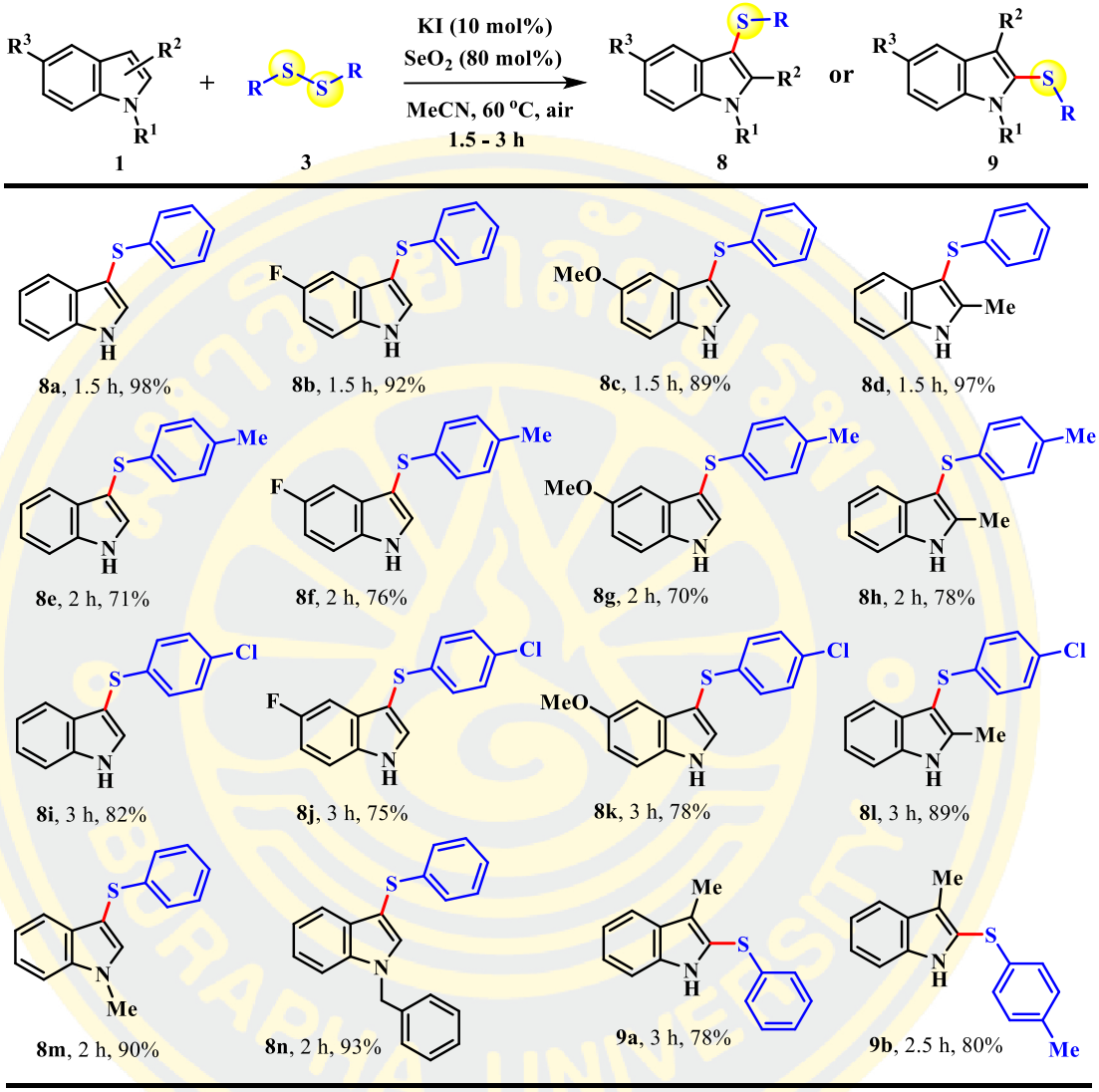


1a 3a 8a 13a

entry	2a (equiv.)	KI (mol%)	SeO_2 (mol%)	solvent	T (°C)	time (h)	yields (3a/4a)[a] (%)
1	0.5	10	60	MeCN	60	4	94/0
2	0.5	10	70	MeCN	60	3	95/0
3	**0.5**	**10**	**80**	**MeCN**	**60**	**1.5**	**97/0**
4	0.5	10	90	MeCN	60	2	86/0
5	0.5	10	100	MeCN	60	2	84/0
6	0.5	10	80	EtOH	60	1	trace/0
7	0.5	10	80	H_2O	60	1	0/0
8	0.5	10	80	MeCN	60	1	89/0
9	0.5	10	80	DMF	60	1	0/0
10	0.5	10	80	THF	60	1	0/0
11	0.5	10	80	DCE	60	1	44/0
12	0.5	10	80	DEM	60	1	58/0
13	0.5	10	80	MeCN	80	1	72/0
14	0.5	10	80	MeCN	40	5	81/0
15	0.5	10	80	MeCN	RT	8	70/0
16	1	10	130	MeCN	40	4	0/68
17	1	10	150	MeCN	40	4	0/76
18	1	10	170	MeCN	40	4	0/80
19	1	20	130	MeCN	40	2	0/73
20	**1**	**20**	**150**	**MeCN**	**40**	**2**	**0/87**
21	1	20	170	MeCN	40	2	0/74
22	1	30	150	MeCN	40	2	0/77
23	1	20	150	MeCN	60	2	0/75
24	1	20	150	MeCN	RT	8	28/65

[a]Isolated yield

Table 7 Mono-sulfenylation of indoles with disulfides.



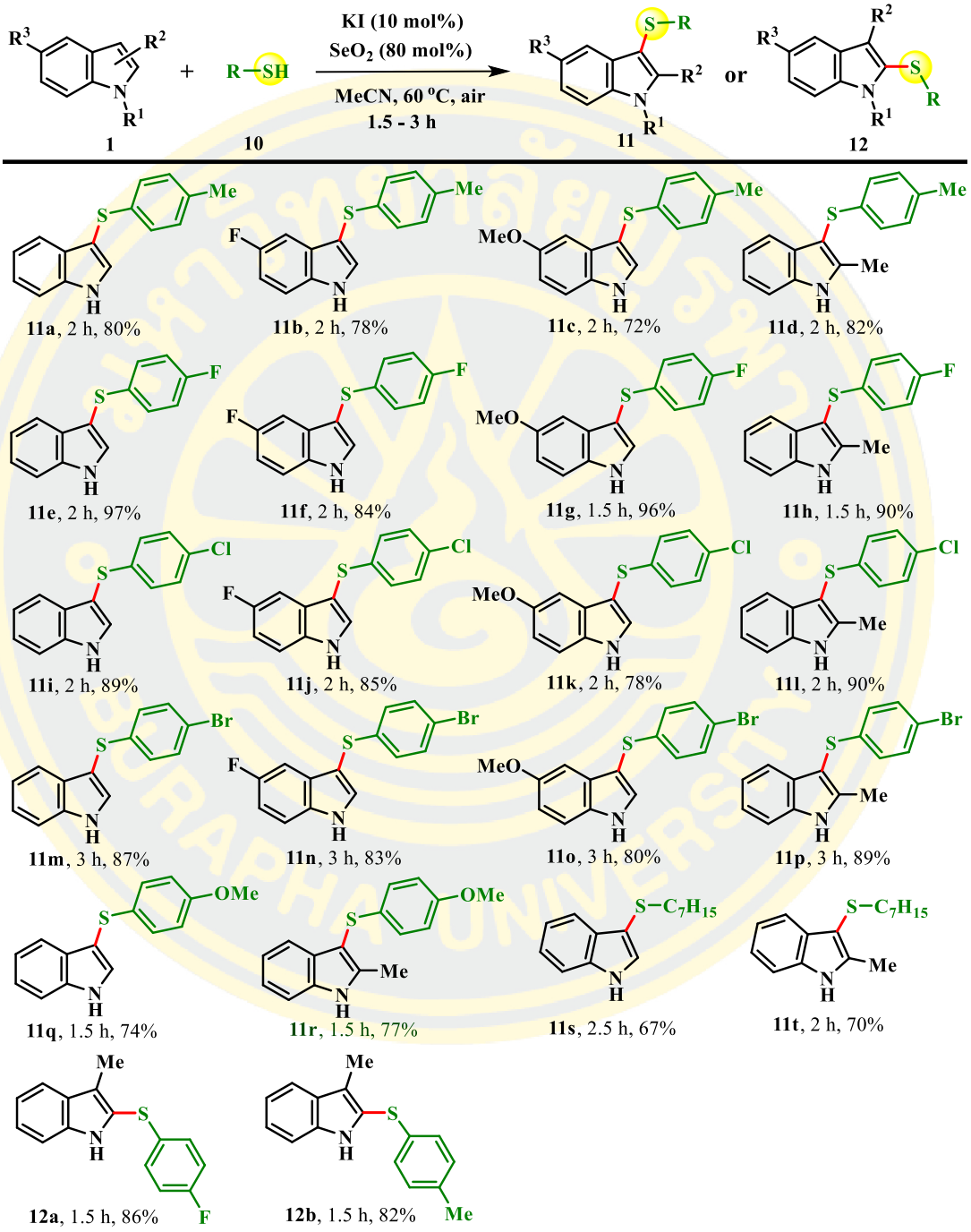
Isolated yields.

Next, thiols were also used as sulfenylation reagents to investigate the ability in the direct mono-sulfenation of indoles under optimized conditions (Table 8). Indole and its derivatives including 5-fluoro-, 5-methoxy-, and 2-methylindoles were efficiently 3-sulfenylated by aryl thiols comprising 4-methyl-, 4-fluoro-, 4-chloro-, 4-bromo- and 4-methoxybenzenethiol to provide the corresponding 3-sulfenylindoles, **11a-11r**, in 72–97% isolated yield within 1.5 to 3 hours. Additionally, alkyl thiol, heptanethiol, was also employed as reagent for sulfenylation of indole and 2-methylindole under standard condition to produce the product **11s** and **11t** in isolated

yields of 67%and 70, respectively. Especially, sulfenylation of 3-methylindole proceeded regioselectively at C-2 position with 4-fluoro- and 4-methylbenzenethiol to generate the sulfenylated products **12a** and **12b** in high yields.

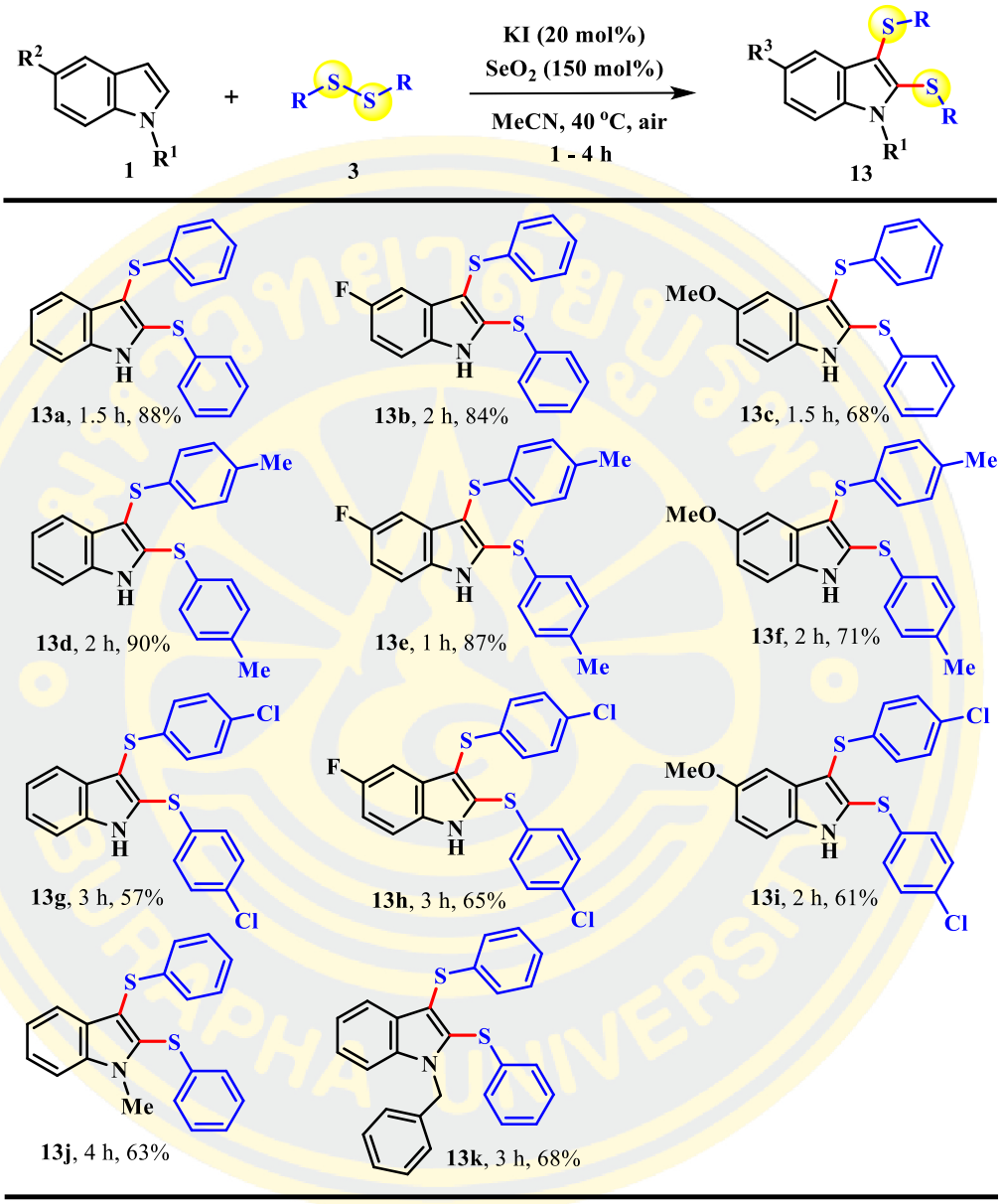
The optimized conditions described in Table 1, entry 20 was next used to synthesize the bis-sulfenylindoles **13** *via* 2,3-disulfenylation of indoles **1** with diaryl disulfides **3** (Table 9). It was found that both diphenyl disulfide and diaryl disulfides bearing an electron-donating group (4-Me) on the benzene ring reacted smoothly with indole to give the corresponding products **(13a** and **13d**) in high yield, while the sulfenylation of indoles with disulfides bearing an electron-withdrawing group (4-Cl) on the benzene ring produced the corresponding products **13g** in moderate yield. Additionally, indoles with electron-withdrawing group gave better results than those with electron-donating group. In the effect of *N*-substituents on the indole ring, the target products (**13j** and **13k**) were obtained in good yield.

Table 8 Mono-sulfenylation of indoles with thiols.



Isolated yields.

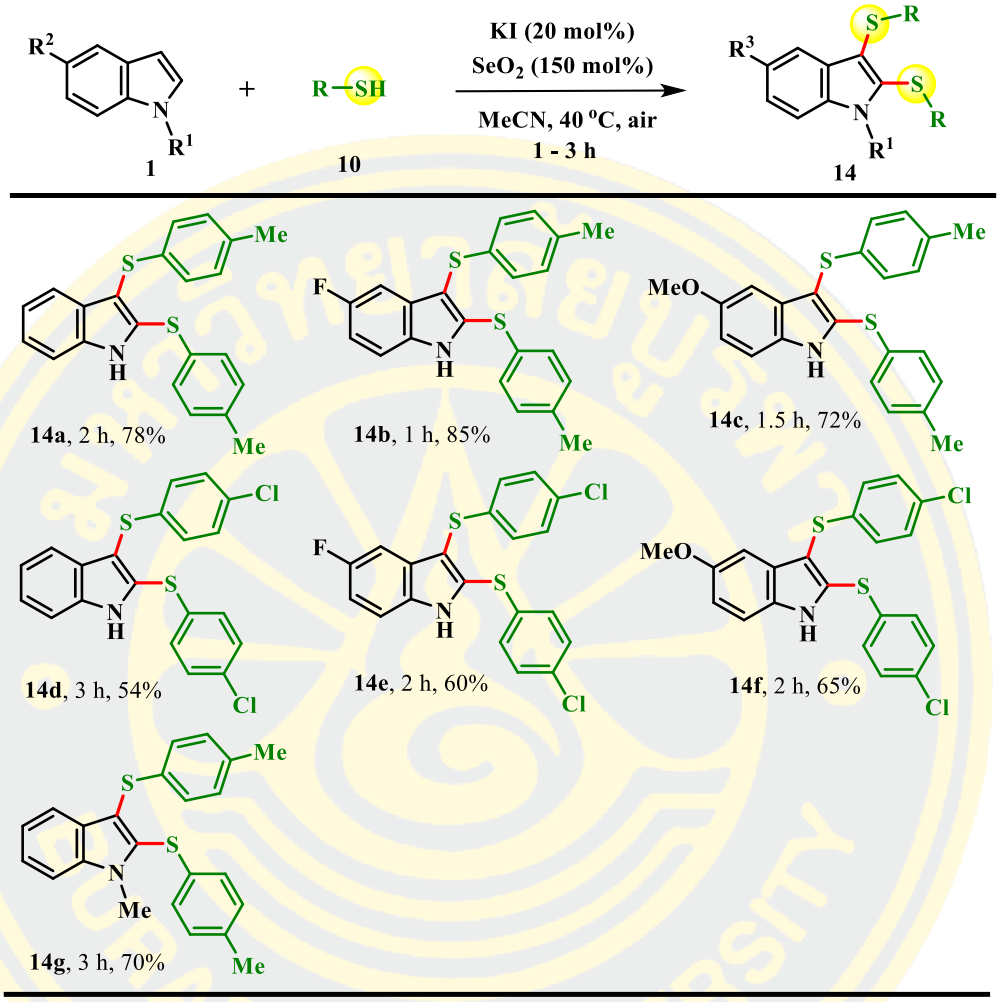
Table 9 Bis-sulfenylation of indoles with disulfides.



Isolated yields.

Thiols **10** were also applicable to this 2,3-disulfenylation method, as demonstrated in the reaction with indoles **1** using the optimized condition (Table 6, entry 3). As shown in Table 10, thiols with electron-rich aromatic rings gave better results than those with electron-deficient aromatic rings. Additionally, protected-*N*-indole worked smoothly to give the corresponding product **14g** in good yield.

Table 10 Bis-sulfenylation of indoles with thiols.



Isolated yields.

To evaluate the synthetic utility of this approach, a gram-scale reaction was performed under the optimized conditions (Figure 53). The desired product 3-sulfenylindole **8a** and 2,3-bis-sulfenylindole **13a** could be afforded in high yields, which confirmed the potential application of this protocol to prepare mono- and bis-sulfenylindoles on a gram-scale synthesis.

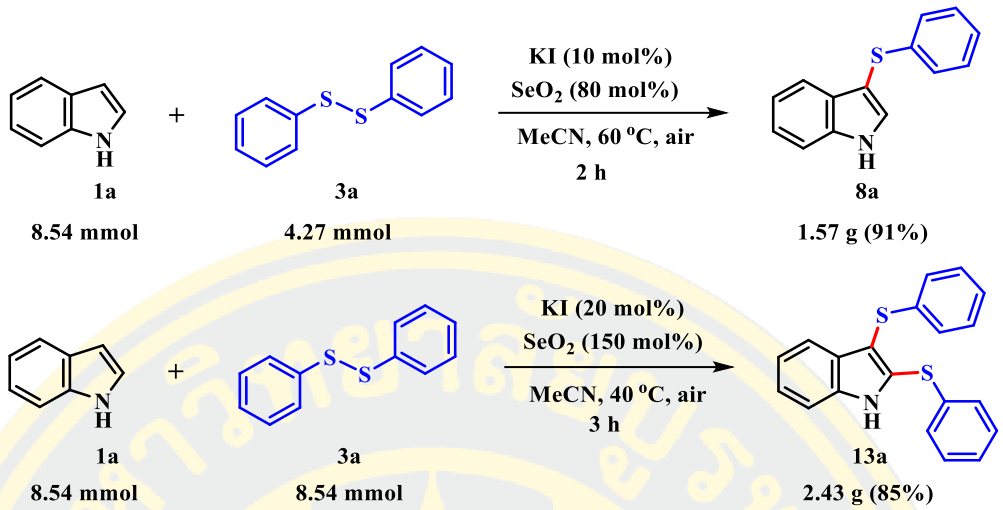


Figure 52 Gram-scale synthesis (isolated yields).

To clarify the reaction mechanism, some control experiments were investigated (Figure 54). Initially, considering the plausible formation of molecular iodine *via* oxidation of iodide anions with SeO_2 to produce phenylsulfenyliodide (PhSI). Notably, the product **8a** was not detected when indole was reacted with diphenyl disulfide (**3a**) using KI as the only catalyst under the optimized condition (Figure 54a), which indicated the crucial role of SeO_2 in this reaction. Recently, Ranadeep T. (Talukdar, 2019) used SeO_2 as selenylating agent for the reaction of indole with SeO_2 to prepare 3,3'-diindolyl selenide (ID-Se-ID). Thus, we hypothesized that ID-Se-ID could be the intermediate in the reaction, which proved by reaction of **1a** with SeO_2 (Wilshir, 1967) to obtain 41% conversion of ID-Se-ID after 24 h (Figure 54b). When KI was added to the reaction of indole **1a** and SeO_2 under standard condition, 100 %conversion of ID-Se-ID was formed after 30 min (Figure 54c). Therefore, we speculated that KI could increase the reactivity by reducing SeO_2 into Se. Next, ID-Se-ID was reacted with diphenyl disulfide **3a** under optimized condition to obtain **8a** in 57% yield after 1 hour (Figure 54d), which indicated that the reactivity of intermediate ID-Se-ID is low than starting from indole **1a**. The reaction did not proceed through a radical mechanism due to adding 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) to the reaction between **1a** and **3a** under the optimized conditions could furnish product **8a** in 90% yield (Figure 54e).

The standard conditions of preparing **8a** were performed under nitrogen atmosphere and a decrease in the yield from 98% (Figure 54Std.) to 41 % was observed (Figure 54f). This result showed that atmospheric oxygen plays a role as a co-oxidant that improves the reaction efficiency. Finally, **13a** was synthesized under standard condition form **8a** using diphenyl disulfide **3a** as sulfenylating reagents leading to the target product in 78% yield after 3 h (Figure 54g). This reaction showed that the sulfenylation reaction occurs at the 2-position of **8a** to give a bis-sulfenylindole (**13a**).

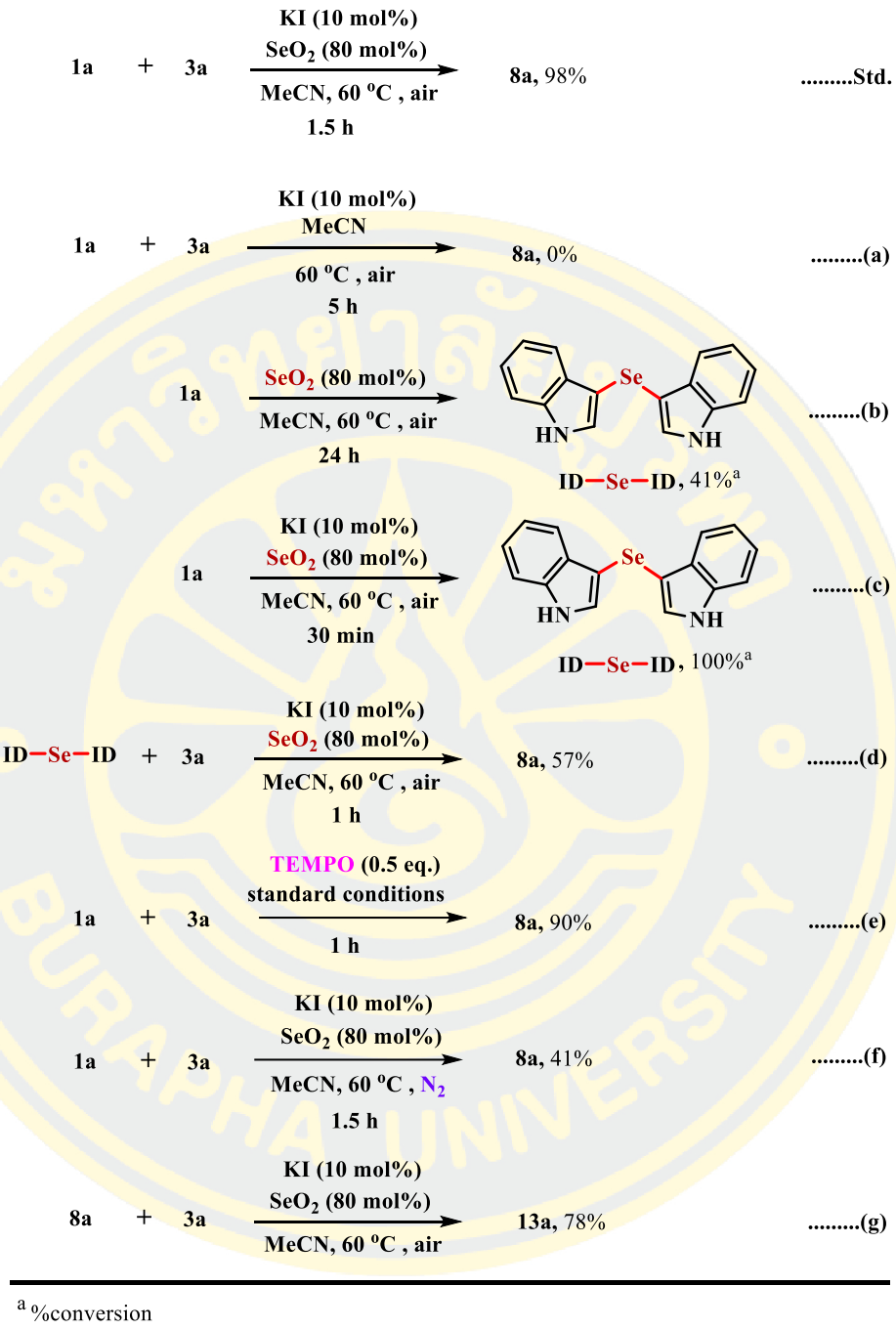


Figure 53 Control Experiments.

Based on these experiments and previous study, a possible mechanism for mono- and bis-sulfenylindoles formation was proposed including three catalytic cycles (Figure 55). In cycle A, the first step involves oxidation of KI by SeO_2 to form I_2 and by-product Se(0). The RSH was oxidized simultaneously by SeO_2 to afford RSSR. Next, RSI was in situ-generated from reaction of RSSR and I_2 follow by

sulfenylation of **1a** to deliver **8a** and HI, which was oxidized back to I_2 by SeO_2 and Se(0) was generated simultaneously. In cycle B, indole reacts with Se(0) to give ID-Se-ID, then further reacts with RSI to give intermediate E leading to a disproportionation process SeO_2 (Wilshir et al., 1967) to produce product **8a** and selenone F that is completed by nucleophilic attack of F with **1a** to deriver D for next cycle. Previous study (Hamel et al., 2002) (Zhang et al., 2015), (Rahaman & Barman, 2017), (Changqing Liu, 2018), the sulfenylation reaction occurs initially at the C3-position of indole, leading to a 3-sulfenylindole. Then, a second sulfide group is introduced at the 2-position to obtain 2,3-disulfenylindole as show in cycle C (Figure 55). Product **13a** might occur by initial attack on the 3-position of **8a** to give intermediate B, followed by migration of the sulfide one group from 3-position to 2-position providing an episulfonium species E and subsequent release of proton to generate 2,3-bis-sulfenylindole **13a**.

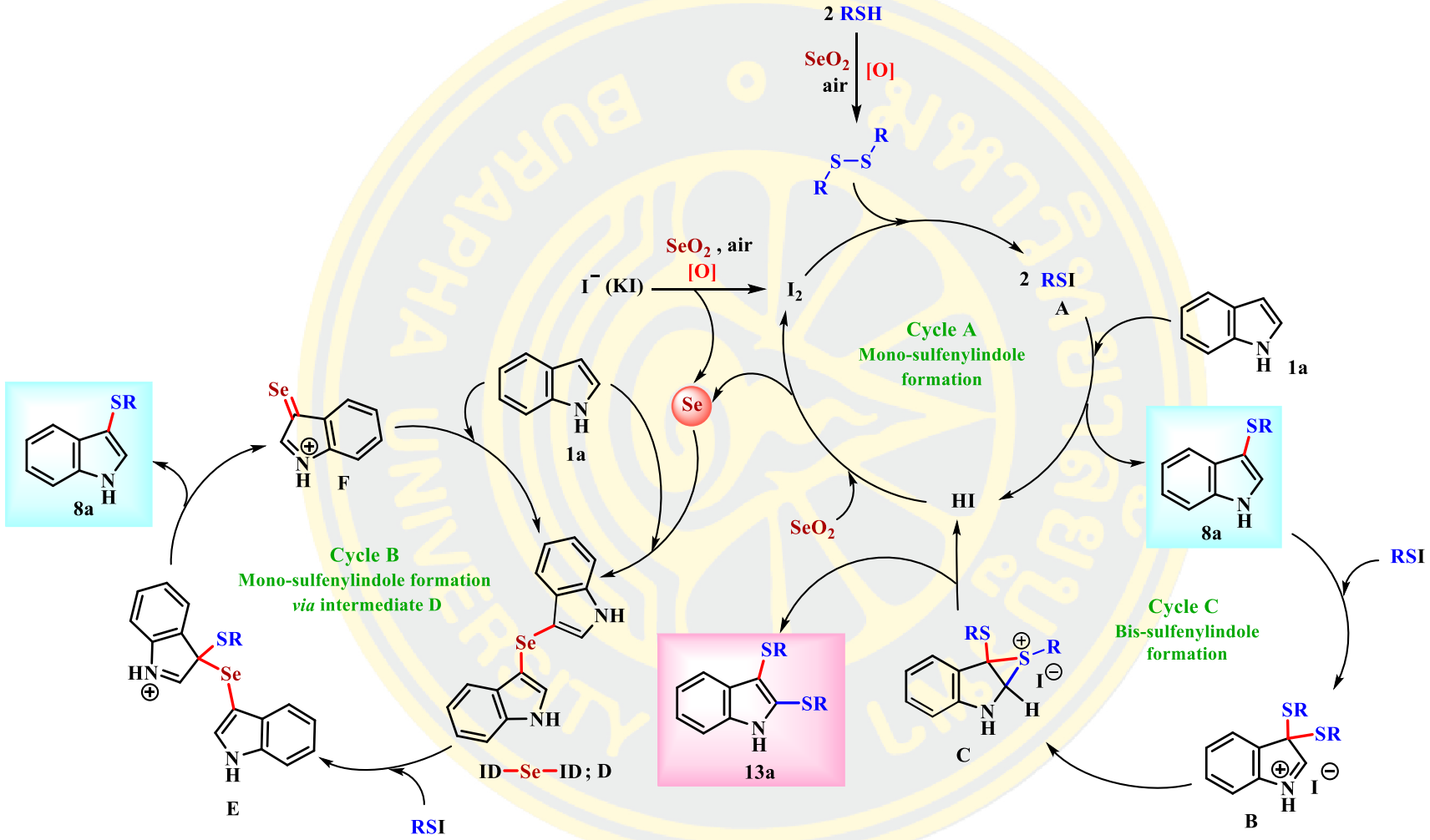
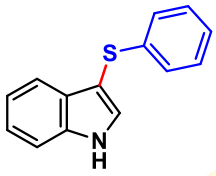


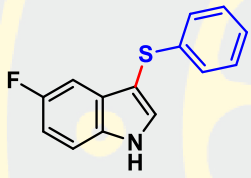
Figure 54 Proposed mechanism for the formation of mono- and bis-sulfenylindoles.

4.2.1 Characterization data of the synthesized compounds



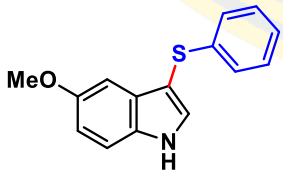
8a

3-(Phenylthio)-1*H*-indole (3a)[7(c)]: Light brown solid; 98 % yield; 0.1885 g; mp 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (br, 1H), 7.62 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.46 – 7.43 (m, 1H), 7.32-7.28 (m, 1H), 7.19-7.15 (m, 3H), 7.12-7.10 (m, 2H), 7.08 -7.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 136.5, 130.7, 129.1, 128.7, 125.9, 124.8, 123.1, 120.9, 119.7, 111.6, 102.9.



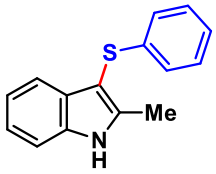
8b

5-Fluoro-3-(phenylthio)-1*H*-indole (3b) [7(c)]: Pale yellow solid; 92 % yield; 0.1656 g; mp 168 - 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.37- 7.34 (m, 1H), 7.27- 7.24 (m, 1H), 7.20- 7.15 (m, 2H), 7.11- 7.05 (m, 3H), 7.01 (td, *J* = 9.1, 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.5, 138.8, 132.9, 132.3, 130.0, 129.9, 128.8, 125.9, 125.0, 112.4, 112.3, 111.8, 111.5, 104.9, 104.6, 103.2, 103.2.



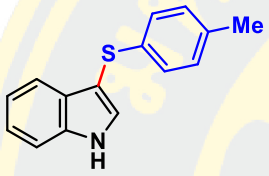
8c

5-Methoxy-3-(phenylthio)-1*H*-indole (3c)[7(c)]: Light brown oil; 89 % yield; 0.1541 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br, 1H), 7.43 (d, *J* = 2.7 Hz, 1H), 7.33 (d, *J* = 8.8 Hz 1H), 7.19- 7.15 (m, 2H), 7.11- 7.04 (m, 4H), 6.93 (dd, *J* = 2.4, 8.8 Hz 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 139.4, 131.4, 131.3, 130.0, 125.7, 124.7, 113.6, 112.4, 102.3, 100.8, 55.8.



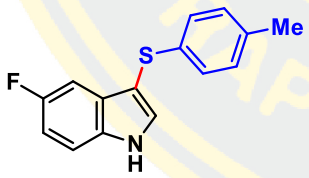
8d

2-Methyl-3-(phenylthio)-1*H*-indole (3d) [7(c)]**:** Light brown solid; 90 % yield; 0.1765 g; mp 116-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz 1H), 7.22- 7.12 (m, 4H), 7.06 - 7.03 (m, 3H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 139.4, 135.5, 130.3, 128.7, 125.5, 124.5, 122.2, 120.7, 119.0, 110.6, 99.4, 12.2.



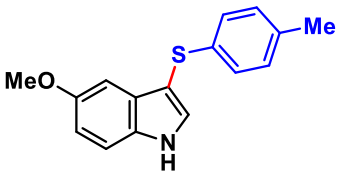
8e

3-(*p*-Tolylthio)-1*H*-indole (3e) [7(c)]**:** Yellow solid; 71 % yield; 0.1420 g; mp 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (br, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.47-7.43 (m 2H), 7.33- 7.28 (m, 1H), 7.23- 7.19 (m, 1H), 7.11- 7.08 (m, 2H), 7.04- 7.02 (m, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 135.5, 134.7, 130.5, 129.6, 129.1, 123.0, 120.9, 119.7, 111.6, 103.4, 20.9.



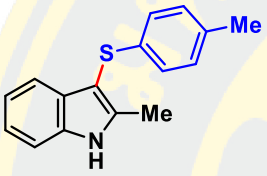
8f

5-Fluoro-3-(p-tolylthio)-1*H*-indole (3f) [27]**:** Pale yellow solid; 76 % yield; 0.1545 g; mp 128-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (br, 1H), 7.51 (d, *J* = 2.7 Hz, 1H), 7.37- 7.34 (m, 1H), 7.31-7.28 (m, 1H), 7.08-7.00 (m, 5H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.4, 135.0, 132.9, 132.1, 130.0, 129.6, 126.4, 112.4, 112.3, 111.7, 111.4, 104.9, 103.8, 20.9.



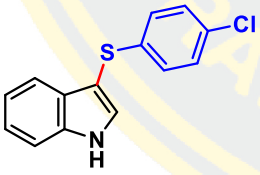
8g

5-Methoxy-3-(p-tolylthio)-1*H*-indole (3g) [27]**:** Yellow oil; 70 % yield; 0.1280 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br, 1H), 7.41 (d, *J* = 2.6 Hz, 1H), 7.31- 7.28 (m, 1H), 7.09-6.99 (m, 5H), 6.93 (dd, *J* = 2.4, 8.8 Hz 1H), 3.80 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 135.7, 134.6, 131.4,.131.2, 130.0, 129.5, 126.1, 113.5, 112.5, 102.8, 100.9, 55.8, 20.9.



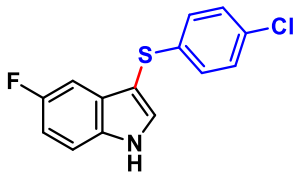
8h

2-Methyl-3-(p-tolylthio)-1*H*-indole (3h) [27]**:** Light browwn solid; 78 % yield; 0.1505 g; mp 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (br, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.24-7.14 (m, 2H), 7.03 (s, 4H), 2.53 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 135.8, 135.5, 134.4, 130.4, 129.6, 125.9, 122.2, 120.7, 119.0, 110.8, 99.8, 20.9, 12.1.



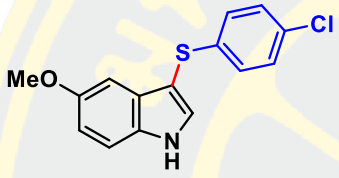
8i

3-((4-Chlorophenyl)thio)-1*H*-indole (3i) [7(c)]**:** White solid; 82 % yield; 0.1819 g; mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.48-7.44 (m, 2H), 7.32-7.28 (m, 1H), 7.21-7.17 (m, 1H), 7.15-7.11 (m, 2H), 7.05-7.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.5, 130.8, 130.6, 128.8, 127.2, 123.2, 121.1, 119.5, 111.7, 102.4.



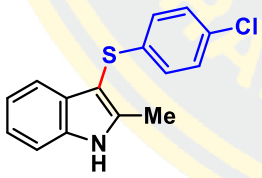
8j

3-((4-Chlorophenyl)thio)-5-fluoro-1*H*-indole (3j) [27]**:** Pale yellow solid; 75 % yield; 0.1541 g; mp 126-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.38-7.35 (m, 1H), 7.22 (dd *J* = 9.1, 2.5 Hz, 1H), 7.15-7.12 (m, 2H), 7.04-6.99 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.5, 137.4, 132.9, 132.4, 130.8, 129.8, 128.9, 127.2, 112.6, 112.5, 112.0, 111.7, 104.7, 104.5, 102. 8, 102.7.



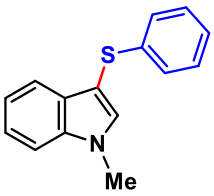
8k

3-((4-Chlorophenyl)thio)-5-methoxy-1*H*-indole (3k) [27]**:** Yellow solid; 78 % yield; 0.1535 g; mp 84-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br, 1H), 7.43 (d, *J* = 2.7 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.14-7.12 (m, 2H), 7.03-7.01 (m, 3H), 6.95 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.81 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 138.0, 131.4, 130.5, 129.7, 128.8, 126.9, 113.7, 112.6, 101.8, 100.7, 55.8.



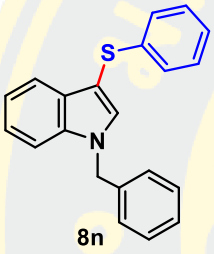
8l

3-((4-Chlorophenyl)thio)-2-methyl-1*H*-indole (3l) [27]**:** Yellow solid; 89 % yield; 0.1857 g; mp 91-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.30-7.15 (m, 4H), 7.04-7.00 (m, 2H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 138.0, 135.5, 130.3, 130.1, 128.8, 126.8, 122.4, 120.9, 118.9, 110.9, 89.9, 12.1.



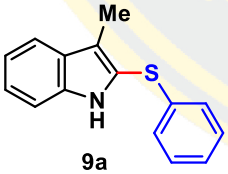
8m

1-Methyl-3-(phenylthio)-1*H*-indole (3m) [27]**:** Pale yellow solid; 90 % yield; 0.1641 g; mp 86-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.34-7.29 (m, 2H), 7.20-7.10 (m, 5H), 7.07-7.03 (m, 1H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.6, 135.1, 135.0, 129.9, 128.7, 125.8, 125.7, 124.7, 122.6, 120.5, 119.8, 109.7, 100.6, 33.1.



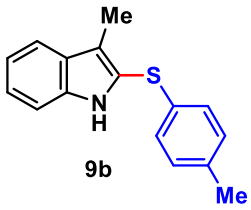
8n

1-Benzyl-3-(phenylthio)-1*H*-indole (3n) [14]**:** Yellow oil; 93 % yield; 0.1413 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.44 (s, 1H), 7.39-7.32 (m, 4H), 7.29-7.25 (m, 1H), 7.21-7.18 (m, 5H), 7.15-7.13 (m, 2H), 7.10-7.07 (m, 1H), 5.39 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 137.2, 136.6, 134.5, 130.1, 129.0, 128.7, 128.0, 127.0, 125.8, 124.7, 122.8, 120.7, 119.9, 110.3, 101.5, 50.5.



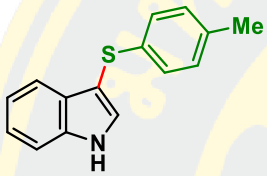
9a

3-Methyl-2-(phenylthio)-1*H*-indole (4a) [14]**:** White solid; 78 % yield; 0.1431 g; mp 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.35-7.33 (m, 2H), 7.31-7.25 (m, 3H), 7.24-7.19 (m, 1H), 7.16-7.14 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 137.0, 129.2, 128.6, 126.6, 125.8, 123.6, 121.5, 120.0, 119.7, 119.5, 111.0, 9.54.



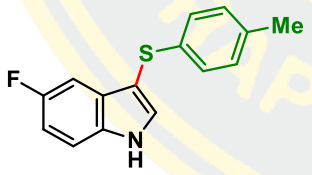
9b

3-Methyl-2-(p-tolylthio)-1*H*-indole (4b) [27]**:** White solid; 80 % yield; 0.1543 g; mp 81-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.37-7.27 (m, 3H), 7.16-7.11 (m, 4H), 2.55 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 135.9, 133.6, 130.1, 128.7, 127.2, 123.5, 122.4, 119.8, 119.6, 119.5, 111.1, 21.1, 9.6.



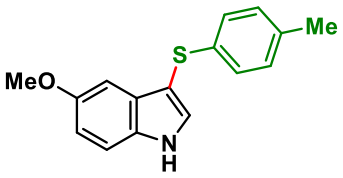
11a

3-(*p*-Tolylthio)-1*H*-indole (6a) [7(c)]**:** Yellow solid; 80 % yield; 0.1635 g; mp 119-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (br, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.49-7.44 (m, 2H), 7.31- 7.27 (m, 1H), 7.21- 7.17 (m, 1H), 7.08- 7.06 (m, 2H), 7.02- 7.00 (m, 2H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 135.5, 134.7, 130.4, 129.5, 129.1, 126.3, 123.0, 120.8, 119.7, 111.5, 103.6, 120.9



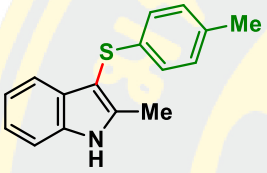
11b

5-Fluoro-3-(p-tolylthio)-1*H*-indole (6b) [27]**:** White solid; 78 % yield; 0.1485 g; mp 127-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (br, 1H), 7.51 (d, *J* = 2.6 Hz, 1H), 7.36-7.32 (m, 1H), 7.27- 7.24 (m, 1H), 7.04-6.97 (m, 5H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.4, 135.9, 134.9, 132.9, 132.0, 130.0, 129.9, 129.6, 126.4, 112.4, 112.3, 111.7, 111.4, 104.9, 104.6, 103.9, 20.9.



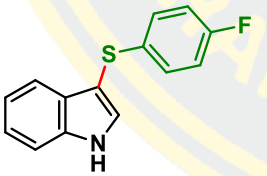
11c

5-Methoxy-3-(p-tolylthio)-1*H*-indole (6c) [27]: Brown oil; 72 % yield; 0.1316 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (br, 1H), 7.41 (d, *J* = 2.6 Hz, 1H), 7.31- 7.29 (m, 1H), 7.09-7.00 (m, 3H), 6.93 (dd, *J* = 8.8, 2.4 Hz 1H), 3.81 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 135.4, 134.3, 131.1, 130.9, 129.7, 129.3, 125.8, 113.2, 112.2, 102.4, 100.6, 55.5, 20.6.



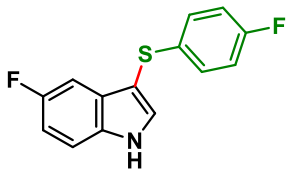
11d

2-Methyl-3-(p-tolylthio)-1*H*-indole (6d) [27]: White solid; 82 % yield; 0.1593 g; mp 97-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.21-7.10 (m, 2H), 6.99-6.94 (m, 4H), 2.48 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 135.7, 135.4, 134.3, 130.4, 129.5, 125.8, 122.1, 120.7, 119.0, 110.6, 99.9, 20.9, 12.2.



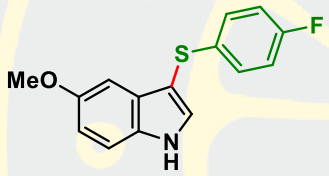
11e

3-((4-Fluorophenyl)thio)-1*H*-indole (6e) [14]: White solid; 97 % yield; 0.2015 g; mp 133-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (br, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.47-7.45 (m, 1H), 7.32-7.28 (m, 1H), 7.22-7.18 (m, 1H), 7.14-7.11 (m, 2H) 6.92-6.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 159.7, 136.5, 134.0, 130.5, 128.9, 128.0, 127.9, 123.2, 121.0, 119.5, 115.9, 115.6, 111.6, 103.4.



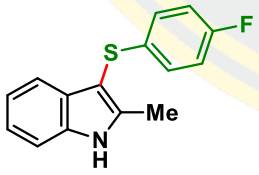
11f

5-Fluoro-3-((4-fluorophenyl)thio)-1*H*-indole (6f): White solid; 84 % yield; 0.1624 g; mp 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.37-7.34 (m, 1H), 7.24 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.10-7.07 (m, 2H), 7.03 (td, *J* = 9.1, 2.5 Hz,1H), 6.91-6.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.9, 157.5, 133.6, 132.9, 132.1, 129.7, 128.1, 128.0, 116.0, 115.7, 112.4, 111.6, 104.7, 104.5, 103.8, 103.8, 103.7, 103.8; HRMS (ESI) *m/z* $C_{14}H_{10}F_2NS$ $(M+H)^+$ calcd 262.0479, found 262.0479.



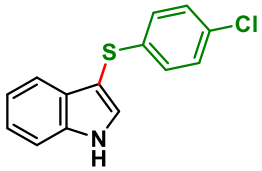
11g

3-((4-Fluorophenyl)thio)-5-methoxy-1*H*-indole (6g)[28]: Yellow oil; 96 % yield; 0.1782 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br, 1H), 7.44 (d, *J* = 2.7 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.10-7.07 (m, 2H), 7.03 (d, *J* = 2.4 Hz,1H), 6.94-6.85 (m, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 159.7, 155.2, 134.2, 134.1, 131.4, 131.2, 129.7, 127.7, 127.6, 115.9, 115.7, 113.6, 112.5, 102.7, 100.8, 55.8.



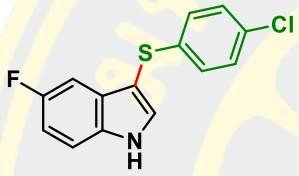
11h

3-((4-Fluorophenyl)thio)-2-methyl-1*H*-indole (6h) [7(f)]**:** Light brown solid; 90 % yield; 0.1765 g; mp 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.20 (td, *J* = 7.2, 1.3 Hz, 1H), 7.16-7.12 (m, 1H), 7.05-6.99 (m, 2H), 6.89-6.83 (m, 2H), 2.53 (s, 3H). ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 159.6, 141.0, 135.4, 134.2, 130.1, 127.4, 122.3, 120.8, 118.9, 115.8, 115.6, 110.7, 99.9, 12.2.



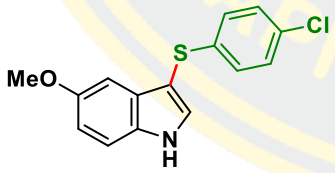
11i

3-((4-Chlorophenyl)thio)-1*H*-indole (6i) [7(c)]**:** White solid; 89 % yield; 0.1974 g; mp 125-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.49-7.44 (m, 2H), 7.30-7.28 (m, 1H), 7.20-7.16 (m, 1H), 7.13-7.10 (m, 2H), 7.04-7.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.5, 130.7, 130.6, 128.8, 127.1, 123.2, 121.1, 119.5, 111.7, 102.5.



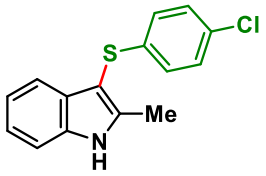
11j

3-((4-Chlorophenyl)thio)-5-fluoro-1*H*-indole (6j) [27]**:** Light brown solid; 85 % yield; 0.1746 g; mp 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (br, 1H), 7.53 (d, *J* = 2.7 Hz, 1H), 7.38-7.35 (m, 1H), 7.22 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.15-7.12 (m, 2H), 7.04-7.00 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.3, 137.4, 132.9, 132.4, 130.8, 129.8, 129.7, 128.9, 127.2, 112.6, 112.5, 112.0, 111.7, 104.7, 104.5, 102.8, 102.7.



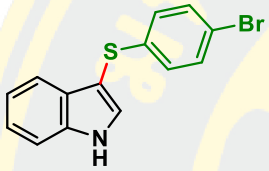
11k

3-((4-Chlorophenyl)thio)-5-methoxy-1*H*-indole (6k) [27]**:** White solid; 78 % yield; 0.1535 g; mp 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (br, 1H), 7.44 (d, *J* = 2.7 Hz, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.14-7.12 (m, 2H), 7.03-7.00 (m, 3H), 6.94 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 138.9, 131.4, 130.5, 129.7, 128.8, 126.9, 113.7, 112.5, 101.8, 100.7, 55.8.



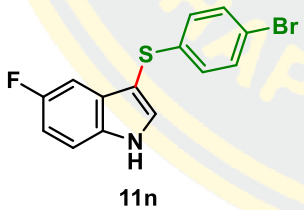
11l

3-((4-Chlorophenyl)thio)-2-methyl-1*H*-indole (6l) [7(f)]**:** Orange solid; 90 % yield; 0.1879 g; mp 89-91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (br, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.21 (td, *J* = 7.2, 1.2 Hz, 1H), 7.16-7.09 (m, 3H), 6.98-6.94 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 138.0, 135.5, 130.3, 130.0, 128.8, 126.8, 122.4, 120.9, 118.8110.8, 99.0, 12.1.



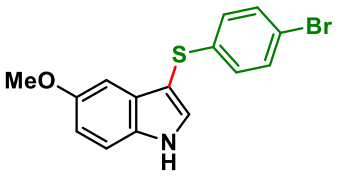
11m

3-((4-Bromophenyl)thio)-1*H*-indole (6m) [5]**:** White solid; 87 % yield; 0.2260 g; mp 149-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50-7.46 (m, 2H), 7.34-7.28(m, 3H), 7.24-7.20 (m, 1H), 7.01-6.98 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 136.5, 131.7, 130.8, 128.8, 127.4, 123.3, 121.1, 119.5, 118.3, 111.7, 102.3.



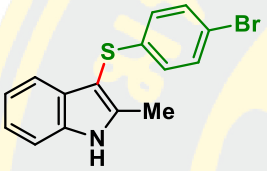
11n

3-((4-Bromophenyl)thio)-5-fluoro-1*H*-indole (6n)[27]**:** White solid; 83 % yield; 0.1978 g; mp 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br, 1H), 7.49 (d, *J* = 2.7 Hz, 1H), 7.35-7.23 (m, 1H), 7.26-7.23 (m, 2H), 7.18 (dd, *J* = 9.1, 2.4 Hz, 1H), 7.01 (td, *J* = 9, 2.5 Hz, 1H), 6.93-6.90 (m, 2H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.5, 138.1, 132.9, 132.4, 131.7, 129.7, 129.7, 127.5118.6, 112.6, 112.5, 112.0, 111.7, 104.7, 104.5, 102.6.



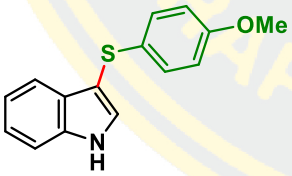
11o

3-((4-Bromophenyl)thio)-5-methoxy-1*H*-indole (6o)[28]: Pale yellow solid; 80 % yield; 0.1816 g; mp 127-129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br, 1H), 7.46 (d, *J* = 2.7 Hz, 1H), 7.35 (d, J = 8.8 Hz, 1H), 7.30-7.29 (m, 2H), 7.04 (d, *J* = 2.5 Hz, 1H), 7.00-6.96 (m, 3H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.7, 131.7, 131.5, 129.7, 127.2, 118.3, 113.7, 112.7, 101.5, 100.7, 55.9.



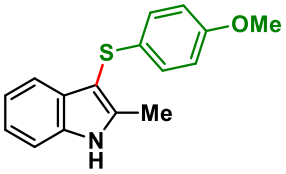
11p

3-((4-Bromophenyl)thio)-2-methyl-1*H*-indole (6p) [7(f)]**:** Pale yellow solid; 89 % yield; 0.2158g; mp 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (br, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30-7.22 (m, 3H), 7.17-7.15 (m, 1H), 6.95-6.91 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 138.7, 135.5, 131.7, 130.0, 127.1, 122.4, 120.9, 118.9, 118.1, 110.8, 98.8,12.2.



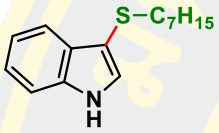
11q

3-((4-Methoxyphenyl)thio)-1*H*-indole (6q) [7(c)]**:** White solid; 74 % yield; 0.1614 g; mp 95-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (br, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.47-7.42 (m, 2H), 7.30-7.28 (m, 1H), 7.21-7.15 (m, 3H), 6.79-6.75 (m, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 136.5, 133.6, 130.1, 129.6, 129.0, 128.6, 123.0, 120.8, 119.6, 115.2, 114.5, 111.6, 104.5, 55.4.



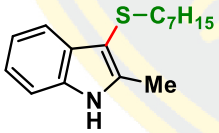
11r

3-((4-Methoxyphenyl)thio)-2-methyl-1*H*-indole (6r) [7(f)]**:** Brown solid; 77 % yield; 0.1579 g; mp 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.25-7.19 (m, 2H), 7.14-7.12 (m, 2H), 6.81-6.79 (m, 2H), 3.77 (s, 3H), 2.52 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 140.8, 135.5, 130.3, 130.0, 128.0, 122.1, 120.7, 119.0114.6110.8100.7, 55.4, 12.1.



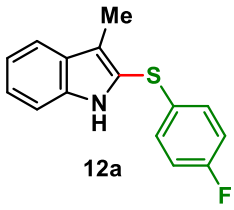
11s

3-(Heptylthio)-1*H*-indole (6s): Yellow oil; 67 % yield; 0.1416 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (br, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.42-7.40 (m, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.29-7.21 (m, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.63-1.54 (m, 2H), 1.43-1.25 (m, 8H), 0.89 (t, *J* = 6.9, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 129.5, 129.2, 122.6, 120.4, 119.4, 111.4, 106.3, 36.5, 31.8, 29.9, 28.9, 28.6, 22.6, 14.1; HRMS (ESI) *m/z* $C_{15}H_{21}NS$ $(M+H)^+$ calcd 248.1473, found 248.1474.



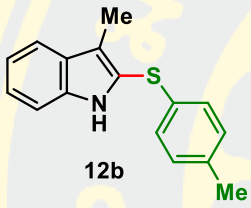
11t

3-(Heptylthio)-2-methyl-1*H*-indole (6t): Yellow oil; 70 % yield; 0.1394 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br, 1H), 7.78-7.76 (m, 1H), 7.30-7.22 (m, 3H), 2.70 (t, *J* = 7.3 Hz, 2H), 2.53 (s, 3H), 1.58-1.53 (m, 2H), 1.45-1.39 (m, 8H), 0.95 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 135.4, 130.8, 121.8, 120.3, 118.8, 110.8, 102.6, 36.4, 31.9, 30.1, 29.1, 28.7, 22.7, 14.2, 12.1; HRMS (ESI) *m/z* $C_{16}H_{23}NS$ $(M+H)^+$ calcd 262.1629, found 262.1625.



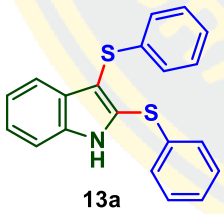
12a

2-((4-Fluorophenyl)thio)-3-methyl-1*H*-indole (7a): Yellow oil; 86 % yield; 0.1697 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.34-7.28 (m, 2H), 2.24-7.20 (m, 1H), 7.13-7.09 (m, 2H), 7.00-6.95 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.2, 136.9, 132.1, 132.0, 128.8, 128.7, 123.6, 121.9, 119.7, 119.5, 116.3, 116.1, 111.0, 9.5; HRMS (ESI) *m/z* $C_{15}H_{12}FNS$ $(M+H)^+$ calcd 258.0747, found 258.0713.



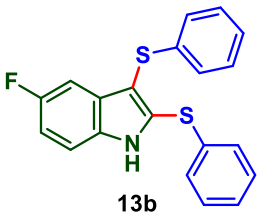
12b

3-Methyl-2-(p-tolylthio)-1*H*-indole (7b) [27]**:** Yellow oil; 82 % yield; 0.1582 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (br, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.20-7.08 (m, 3H), 6.97-6.92 (m, 4H), 2.36 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.2, 133.9, 130.4, 129.0, 127.5, 123.8, 122.6, 120.0, 119.8, 111.4, 21.4, 9.9.



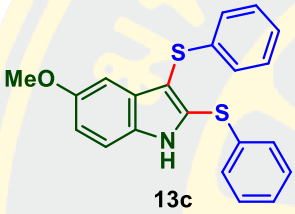
13a

2,3-bis(Phenylthio)-1*H*-indole (8a) [27]**:** Yellow oil; 88 % yield; 0.2506 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.35-7.26 (m, 7H), 7.25-7.18 (m, 5H), 7.15-7.11 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.7, 134.5, 133.6, 130.0, 129.7, 129.5, 128.9, 128.8, 127.3, 126.7, 125.2, 124.0, 121.3, 120.0, 111.4, 111.3, 109.3.



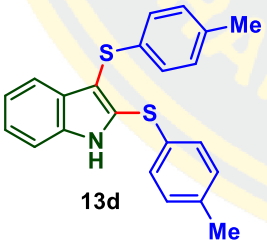
13b

5-Fluoro-2,3-bis(phenylthio)-1*H*-indole (8b) [27]**:** Pale yellow solid; 84 % yield; 0.1927 g; mp 91-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (br, 1H), 7.32-7.19 (m, 9H), 7.16-7.10 (m, 3H), 7.01 (td, *J* = 9.0, 2.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 157.5, 137.7, 136.0, 133.7, 133.3, 130.9, 130.8, 130.3, 129.6, 128.9, 127.7, 126.7, 125.4, 112.4, 112.2, 112.1, 112.0, 108.5, 105.0, 104.7.



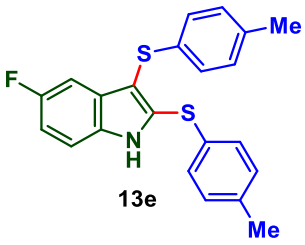
13c

5-Methoxy-2,3-bis(phenylthio)-1*H*-indole (8c) [27]**:** Yellow oil; 68 % yield; 0.1678 g;; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (br, 1H), 7.27-7.23 (m, 6H), 7.21-7.07 (m, 5H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 138.1, 134.5, 133.8, 131.8, 130.8, 129.6, 129.4, 128.8, 127.2, 126.4, 125.0, 115.6, 112.1, 108.6, 100.9, 55.8.

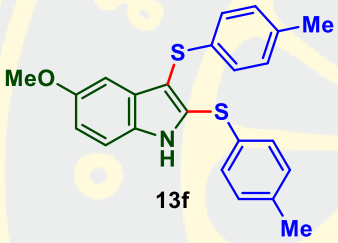


13d

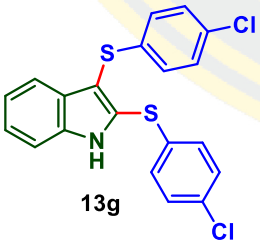
2,3-bis(*p*-Tolylthio)-1*H*-indole (8d) [27]**:** Pale yellow oil; 90 % yield; 0.2777 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (br, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.32-7.24 (m, 4H), 7.19-7.16 (m, 1H), 7.13-7.08 (m, 1H), 7.02-7.00 (m, 2H), 2.36 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.8, 134.9, 134.7, 134.5, 130.8, 130.2, 129.5, 127.0, 123.5, 121.1, 119.7, 108.4, 21.1, 20.9.



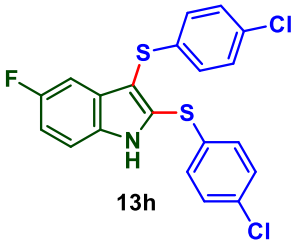
5-Fluoro-2,3-bis(p-tolylthio)-1*H*-indole (8e) [27]**:** Orange oil; 87 % yield; 0.2156 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.31-7.29 (m, 2H), 7.25 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.22-7.18 (m, 1H), 7.15-7.13 (m, 2H), 7.09-7.07 (m, 2H), 7.03-7.01 (m, 2H), 6.97 (td, *J* = 9.0, 2.5 Hz, 1H), 2.37 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.5, 138.3, 137.1, 135.2, 134.1, 133.1, 131.4, 131.1, 131.0, 130.4, 129.6, 129.3, 127.1, 111.9, 111.8, 111.7, 111.6, 107.6, 104.8, 104.5, 21.1, 20.9.



5-Methoxy-2,3-bis(*p*-tolylthio)-1*H*-indole (8f)[27]**:** Yellow oil; 71% yield; 0.1888 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br, 1H), 7.22-7.16 (m, 3H), 7.08-7.02 (m, 5H), 6.98-6.96 (m, 2H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.78 (s, 3H), 2.31 (2, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 137.7, 135.0, 134.8, 134.6, 131.7, 131.0, 130.7, 130.2, 129.5, 126.7, 114.0, 111.8, 107.7, 100.9, 55.8, 21.1, 20.9.

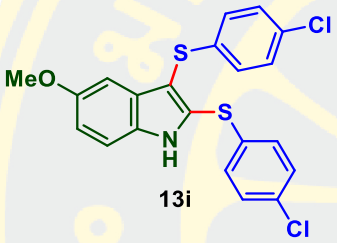


2,3-bis((4-Chlorophenyl)thio)-1*H*-indole (8g) [27]**:** Yellow solid; 57% yield; 0.1958 g; mp 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (br, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.40-7.31 (m, 2H), 7.24-7.20 (m, 3H), 7.18-7.12 (m, 4H), 7.04-7.02 (M, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 136.5, 133.4, 132.9, 131.1, 130.7, 129.8, 129.5, 128.9, 127.9, 124.4, 121.6, 119.9, 111.4, 109.6.



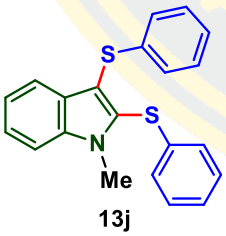
13h

2,3-bis((4-Chlorophenyl)thio)-5-fluoro-1*H*-indole (8h) [27]**:** Light brown oil; 65% yield; 0.1784 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br, 1H), 7.32-7.28 (m, 1H), 7.25-7.19 (m, 5H), 7.15-7.12 (m, 2H), 7.08-6.98 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 157.6, 136.0, 135.1, 133.9, 133.2, 132.2, 131.3, 130.7, 130.7, 130.6, 129.6, 128.9, 127.9, 113.0, 112.7, 112.3, 112.2, 109.0, 104.9, 104.7.



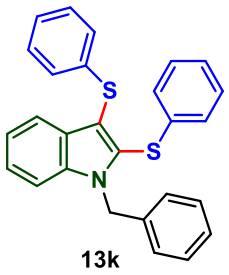
13i

2,3-bis((4-Chlorophenyl)thio)-5-methoxy-1*H*-indole (8i) [27]**:** Yellow solid; 61% yield; 0.1791 g; mp 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 7.20-7.12 (m, 6H), 7.02-6.95 (m, 4H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 136.6, 133.3, 133.1, 131.8, 131.0, 130.6, 129.4, 128.8, 127.6, 115.1, 112.4, 108.9, 100.8, 55.8.



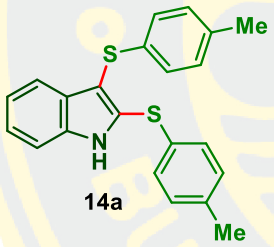
13j

1-Methyl-2,3-bis(phenylthio)-1*H*-indole (8j) [27]**:** Yellow oil; 63 % yield; 0.1668 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 1H), 7.45-7.37 (m, 2H), 7.25-7.14 (M, 8H), 7.10-7.06 (m, 3H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 135.9, 134.3, 129.2, 128.7, 127.4, 126.6, 126.2, 125.0, 124.0, 121.1, 120.4, 111.1, 110.2, 31.1.



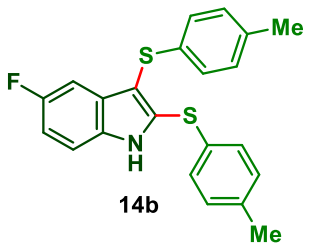
13k

1-Benzyl-2,3-bis(phenylthio)-1*H*-indole (8k) [25]**:** Pale yellow oil; 68 % yield; 0.1388 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.37-7.09 (m, 17H), 7.06-7.04 (m, 2H), 5.58 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.2, 137.0, 135.6, 134.5, 129.5, 129.1, 129.0, 128.8, 128.7, 127.8, 127.5, 126.7, 126.5, 126.4, 125.1, 124.3, 121.3, 120.6, 112.2, 111.2, 48.4; HRMS (ESI) *m/z* $C_{27}H_{21}NS_2$ $(M+H)^+$ calcd 424.1188, found 424.1163.



14a

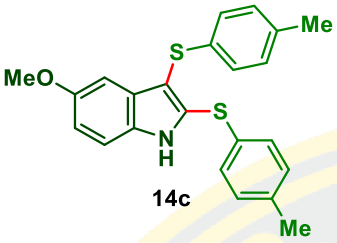
2,3-bis(*p*-Tolylthio)-1*H*-indole (9a) [25]**:** Yellow oil; 78 % yield; 0.2408 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.24-7.18 (m, 4H), 7.14-7.02 (m, 5H), 7.96-7.94 (m, 2H), 2.30 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.9, 135.0, 134.6, 130.6, 130.4, 130.3, 130.2, 129.6, 127.1, 123.6, 121.2, 120.0, 111.3, 108.6, 21.2, 21.0.



14b

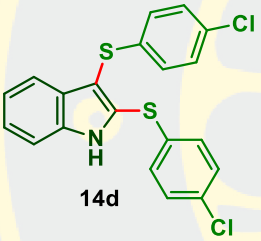
5-Fluoro-2,3-bis(*p*-tolylthio)-1*H*-indole (9b) [27]**:** Yellow oil; 85 % yield; 0.2106 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (br, 1H), 7.21-7.16 (M, 3H), 7.11-7.08 (M, 1H), 7.06-7.04 (m, 2H), 6.94-6.92 (m, 2H), 6.88 (td, *J* = 9.0, 2.5 Hz, 1H), 2.27 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.5, 138.3, 137.1, 135.2, 134.1,

133.1, 131.4, 131.1, 131.0, 130.4, 129.6, 129.4, 127.1, 111.9, 111.8, 111.7, 107.6, 104.8, 104.5, 21.2, 21.0.



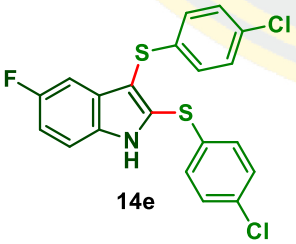
14c

5-Methoxy-2,3-bis(*p*-tolylthio)-1*H*-indole (9c) [27]**:** Yellow oil; 72 % yield; 0.1914 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br, 1H), 7.20-7.15 (m, 3H), 7.07-7.00 (m, 5H), 6.97-6.95 (m, 2H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.77 (s, 3H), 2.30 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 137.7, 135.0, 134.8, 134.6, 131.7, 131.0, 130.7, 130.2, 129.5, 126.7, 114.0, 111.8, 107.7, 100.9, 55.8, 21.1, 20.9.



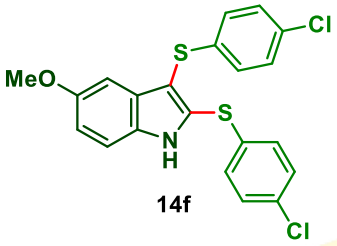
14d

2,3-bis((4-Chlorophenyl)thio)-1*H*-indole (9d) [27]**:** Yellow oil; 54 % yield; 0.1855 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.37-7.29 (m, 2H), 7.23-7.18 (m, 3H), 7.16-7.10 (m, 4H), 7.03-7.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 136.5, 133.4, 133.0, 132.9, 131.1, 130.7, 129.8, 129.5, 128.9, 128.0124.4, 121.7, 119.9, 111.5, 109.6.



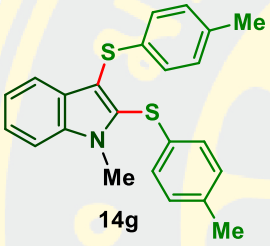
14e

2,3-bis((4-Chlorophenyl)thio)-5-fluoro-1*H*-indole (9e) [27]**:** Yellow oil; 60 % yield; 0.1647 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (br, 1H), 7.29-7.27 (m, 1H), 7.23-7.17 (m, 5H), 7.13-7.10 (m, 2), 7.05-6.96 (m, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 157.6, 136.0, 135.1, 133.9, 133.2, 132.2, 131.3, 130.7, 130.6, 129.6, 128.9, 127.9, 113.0, 112.7, 112.3, 112.2, 109.0, 104.9, 104.7.



14f

2,3-bis((4-Chlorophenyl)thio)-5-methoxy-1*H*-indole (9f) [27]**:** Yellow oil; 65 % yield; 0.1908 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (br, 1H), 7.27 (d, *J* = 8.9 Hz, 1H), 7.19-7.11 (m, 6H), 7.03-6.95 (m, 4H), 3.82 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 136.6, 133.3, 133.1, 133.0, 131.8, 131.0, 130.6, 129.4, 128.8, 127.6, 115.1, 112.4, 108.9, 100.8, 55.8.



14g

1-Methyl-2,3-bis(*p*-tolylthio)-1*H*-indole (9g) [27]**:** Yellow oil; 70 % yield; 0.2003 g; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.46-7.39 (m, 2H), 7.29-7.25 (m,1H), 7.16-7.14 (m, 2H), 7.10-7.03 (m, 6H), 3.86 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.3, 135.1, 134.9, 134.8, 132.3, 130.0, 129.5, 129.3, 128.0, 127.1, 123.9, 121.0, 120.4, 111.5, 110.2, 31.2, 21.1, 21.0.

CHAPTER 5
CONCLUSIONS

In work 1, an efficient and convenient strategy for selective synthesis of 3-chalcogenylindoles such as 3-selenyl and 3-sulfenyl indoles was developed. Silver(I)nitrate was employed as catalyst in the direct C(sp^2)–H chalcogenation of indole and its derivatives at the C3-position with diselenides and disulfides under aerobic and mild reaction conditions in a short reaction time. Especially, this approach is scalable, economical and eco-friendly furnishing the corresponding chalcogeny indoles in good to high yields. Additionally, the developed approach can be further applied for direct chalcogenation of other heterocyclic compounds with various dichalcogenides.

In work 2, KI catalytic system was successfully developed for selective and controllable sulfenylation of indoles to synthesized mono-sulfenylindoles and bis-sulfenylindoles in moderate to excellent yields. This strategy used KI/SeO_2 as catalytic system utilizing both disulfides and thiols as sulfenylation reagents, which is scalable, not moisture sensitive without metal catalyst and operationally simple under mind reaction. Under the catalytic cycle, the reduction of Se(VI) to Se(0) and the formation of I_2 in the reaction enhanced effectively catalyzing the sulfenylation. In addition, this developed protocol can lead to the efficient synthesis of mono-selenylindoles and bis-selenylindoles using other sulfenylating reagents.

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