CHAPTER III

OLEFINATION *via* ALKYL PHENYL SELENIDES APPROACH

3.1 Introduction and literature reviews

- **Biologically important synthetic organoselenium compounds**

Organic synthesis is the science practiced by chemists who concern themselves with the construction of carbon-containing molecules, many of which posses biological significance. Natural constitutes the premier laboratory for the creation of organic compounds. Natural products representing target for laboratory synthesis have provided chemists with tremendous challenges which have been difficult. The last decade has seen an explosion of papers reporting new synthetic methods and descriptions of successful total syntheses of highly complex molecules. Of considerable assistance to synthetic chemist has been the recent development of new reagents and reaction conditions involving organoselenium compounds. There were several approaches to describe the applications of organoselenium chemistry to organic synthesis.

During the last few decades, the chemistry of selenium has been growing; as a result organoselenium compounds have recently attracted considerable interest, and can be attributed to specific properties of organic selenium molecules fitting the requirements of modern organic synthesis [84-86]. Most of them were well adapted to chemo-, regio-, and stereo-selectivities [87]. Furthermore, they could be used in mild and simple experimental conditions which were compatible with the stability of substrates and products in the preparation of unsaturated and functional complex molecules, especially natural products.

In fact, the selenium functional groups had been known for a long time whereas the use of selenium reagents or intermediate was recently. Over the last 30 years, selenium chemistry became particularly useful for synthetic organic chemistry. Inorganic as well as organic selenium compounds allowed transformation which otherwise could not be done or required more harsh conditions to proceed. In addition, over the last 25 years, the reactivity of elemental selenium as well as its inorganic and organic derivatives was explored [88].

In 1818, Berzelius discovered the element selenium and named the Greek goddess of the moon (Selene).

In 1836, Lowig prepared the first synthetic organoselenium (diethyl selenide).

In 1973, selenium biochemistry emerged when two bacterial enzymes were reported to contain selenium and its role in mammals was part of the active site of the antioxidant enzyme glutathione peroxidase (GPx) [86]. At the same time, modern organoselenium chemistry was born and it was also the year that the first important book dealing the synthesis and properties of its compound was published [89].

In 1970s; several useful new reactions resulting in organoselenium research intensified and various novel structures of organoseleniums were discovered and began to more general interest in the discipline. For example, Sharpless and Reich demonstrated an effective olefin-forming method *via* selenoxide elimination [90-92].

In 1980-present; the chemistry of selenium and its utilities in organic synthesis have been growing. The development of stable organoselenium compounds could be used as antioxidants, antitumors and enzyme inhibitors, *etc*. For instance, they were parts of the active site of the antioxidant enzyme glutathione peroxidases (GPx). The GPx were antioxidant selenoenzymes protecting various organisms from oxidative stress by catalyzing the reduction of hydroperoxides at the expense of glutathione (GSH) as substrate. A number of synthetic organoselenium compounds were known to act as antioxidants by reducing H_2O_2 and $ONOO^-$ and also by preventing lipid peroxidase [93].

Since organoselenium had a role in the synthesis of a large number of biological compounds, such as selenocarbohydrates, selenoamino acids and selenopeptides; organoselenium has continued to attract considerable attention [94-95]. Furthermore, it intensely emerged because of a role in biochemical process, serving as important therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements [96-97].

- **Selenium in organic synthesis and reaction of organic selenides**

Selenium, 0.09 ppm of the Earth's crust, was as a by-product from the treatment of sulfur ore [98]. It as same as tellurium belonged to Group 16 of the periodic table, with oxygen and sulfur. Only sulfur, selenium and tellurium were often called "chalcogen" because of having *d*-orbital and sometimes having similar

chemical properties such as "soft" character. Selenium had a wide-range of oxidation state (-2 to +6) brought about forming a variety of organoselenium compounds.

Organoselenium compounds or selenoorganic functional groups could be divided into five categories [89]:

1) Hydrogen selenide (H_2Se) and its metal (MSe, M_2Se)

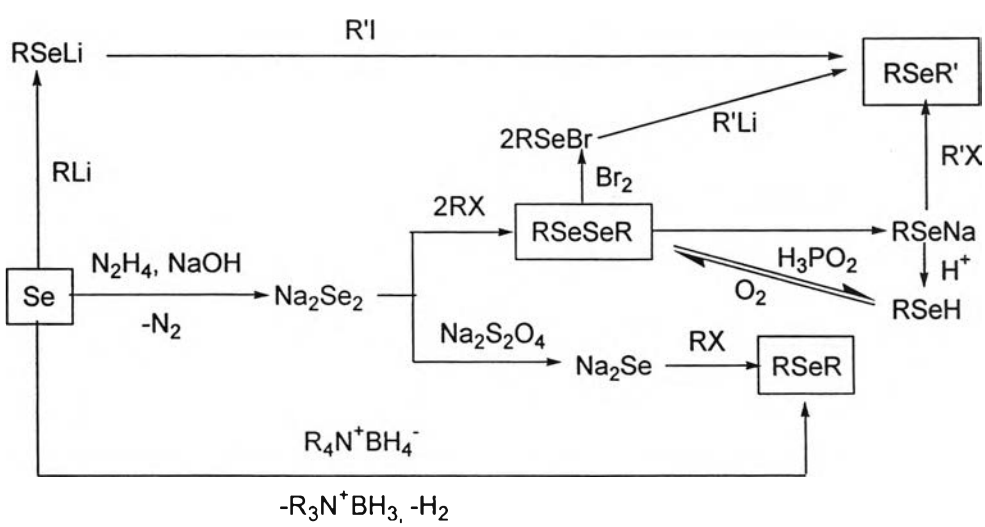
2) Selenols (PhSeH) and their metal salts (PhSeM)

3) Selenides (R_2Se) and diselenides (R_2Se_2)

4) Selenenic acids and their derivatives (PhSeOH)

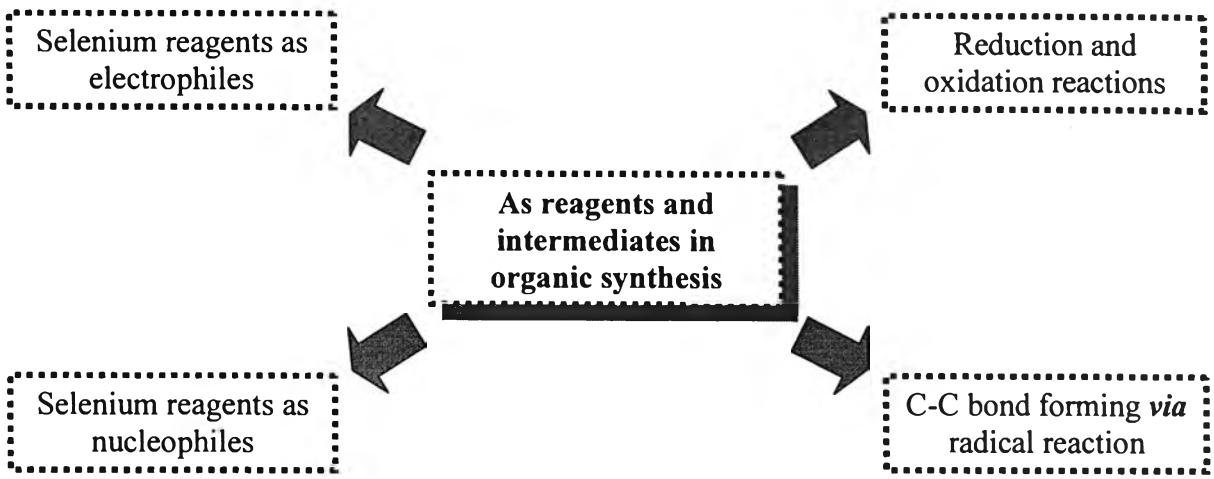
5) Seleninic acids ($RSe(=O)OH$) and their anhydrides ($RSe(=O)OSe(=O)R$)

Selenides were classified as compounds containing the C-Se-C group. Dialkyl selenides were colorless volatile compounds and sensitive to light. Diaryl selenides were more stable than dialkyl selenides and the higher members were crystalline. Organoselenides (R_2Se) and organodiselenides (RSeSeR) could be prepared from various ways (Scheme 3.1). Furthermore, they were employed as starting materials for many conversions, reasonably made them importance in organic synthesis. For instance, a variety of oxo-, hydroxo-, and halo-organoselenium compounds could be prepared from these organoselenides and organodiselenides compounds. For this reason, organoselenide, especially unsymmetrical diorganyl selenides, were interestingly focused on in this research.



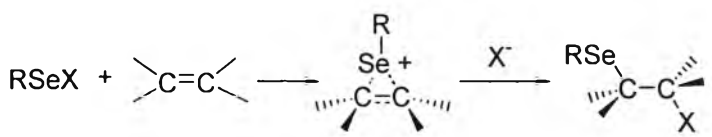
Scheme 3.1 Preparation of organoselenides and organodiselenides [99]

Although organoselenium had a role in the synthesis of a large number of biological compounds, the enormous utilities of organoselenium compounds in organic synthesis was also presented below.

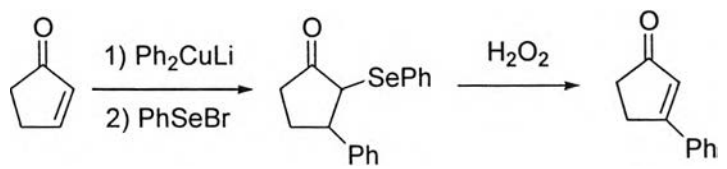


a) Selenium reagents as electrophiles

In the case of electrophilic addition to unsaturated bonds, a series of selenenyl compounds such as selenyl halides acted as excellent electrophilic reagents toward carbon-carbon double bonds. The addition *via* seleniranium ion as intermediate in rate-determining step leaded to the *anti* addition [100-101].

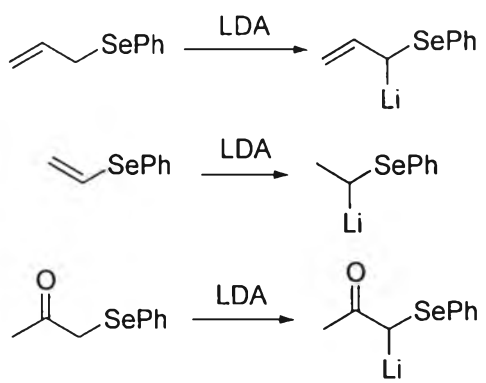


Generally, the treatment of carbonyl compounds with selenenyl halides formed the α–seleno carbonyl compounds then oxidative elimination leading to the synthesis of α,β–unsaturated carbonyl compounds. The selenenylation of copper enolates generated by conjugate addition of lithium diphenylcuprate to cyclopentenone [91].



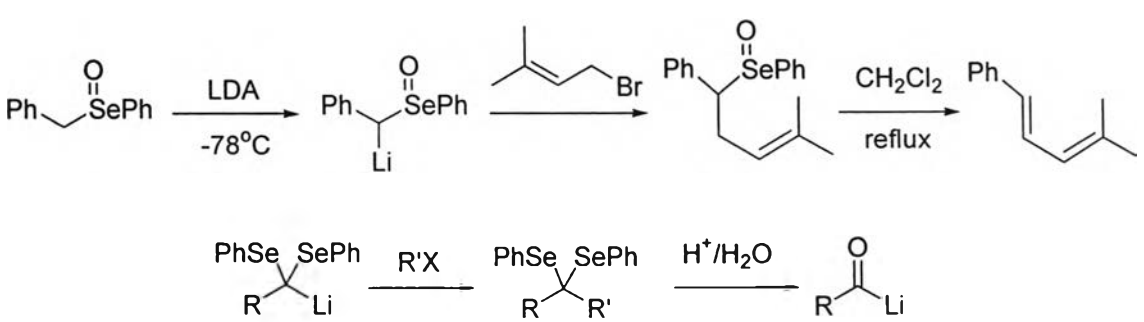
b) Selenium reagents as nucleophiles

The selenium group could be introduced in organic substrate by both nucleophilic and electrophilic reactions. Organoselenium anions were powerful nucleophiles and they were prepared *in situ* because of their sensitivity to air oxidation carbanions, generated from allyl phenyl selenides and BuLi, with allylic or benzylic halides [93]. They were well-known to stabilize anions on α–carbon atoms and a variety of α–seleno-substituted substrates were used as useful building blocks in organic synthesis. Organoselenium compounds could be deprotonated with strong bases such as LDA, BuLi or NaH. Allyl/allyl or benzyl/allyl coupling reactions were affected by allyl carbanions, generated from allyl phenyl selenides and BuLi, with allylic or benzylic halides carbanions, generated from allyl phenyl selenides and BuLi, with allylic or benzylic halides [102].

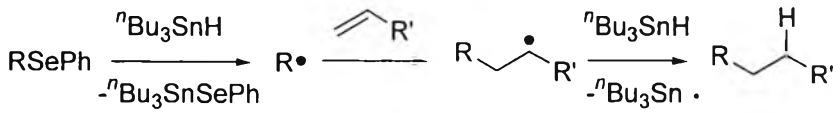


Selenoles (RSeH) were more acidic than thiols (RSH), so it made selenides (RSe^-) more nucleophilic than sulfides (RS^-). Selenyl halides (RSeX) were more electrophilic than the corresponding sulfenyl halides (RSX).

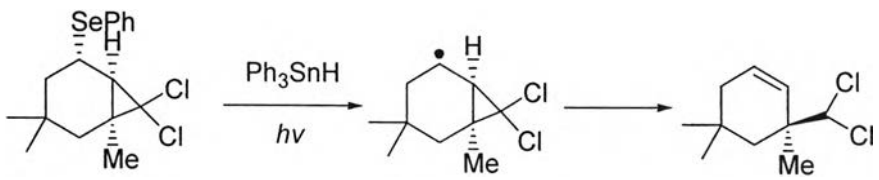
The selenium-stabilized carbanions reacted with a variety of electrophiles to transform them into several functional groups as exemplified [103-106].



c) Selenium reagents in radical reactions as C-C bond forming [107-108]

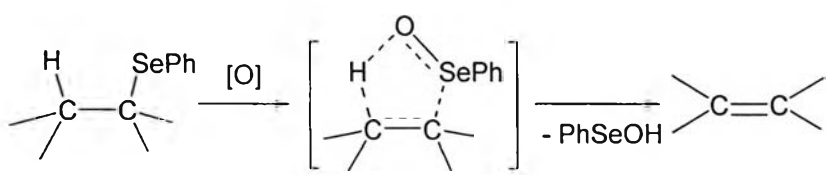


Organoselenium compounds were employed as carbon radical precursors in radical reactions. Since tin-hydrogen bond was sufficiently weak, the tributyltin radical was thus a useful carrier of the radical chain [109]. For instance, as shown below, the selenide generated the cyclopropylcarbinyl radical intermediate on photoirradiation in the presence of Ph_3SnH to obtain the corresponding ring-opened product in 96% yield [110].



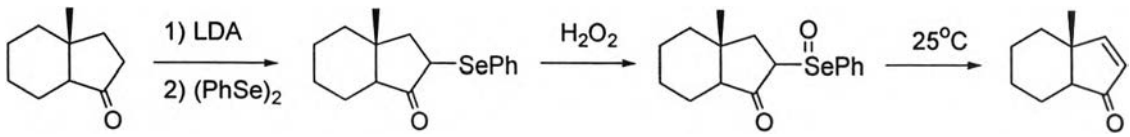
d) Reduction and oxidation reactions [111-119]

Selenoxide *syn*-elimination, one of the most important methods for olefin formation, converted organyl selenides to olefin under mild conditions [120].

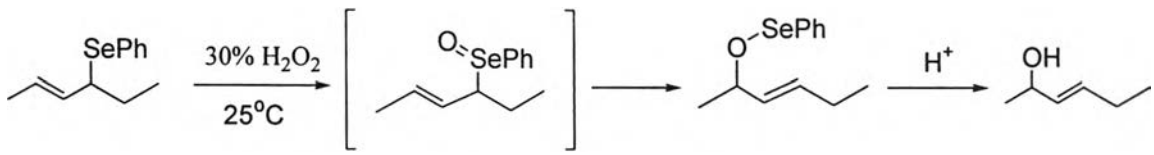


The most importance to refer in this research was focused on the preparation of alkenes. One of the important method for the preparation of alkenes was elimination reactions involving heteroatomic groups. They often provided very useful synthetic routes to generate alkenes such as elimination of phosphine oxide (Wittig reaction) and silyloxide (Peterson olefination). Furthermore, alkenes were formed efficiently by elimination of sulfoxide or selenoxide groups. In the following discussion of these transformations particular emphasis was placed on the synthetic utility of the elimination reaction *via* selenoxide groups. Particularly selenoxide eliminations were frequently used to install the double bond of α,β-unsaturated carbonyl compounds because selenoxide elimination occurred at lower temperature

than the corresponding sulfoxide elimination. They occurred by concerted, cyclic, *syn*-elimination process as shown below [63].



Generally, the elimination proceeded *via* [2,3]sigmatropic rearrangement of selenoxides when a seleninyl group (PhSe(O)˙) was presented at allylic position. In this case it was normally different from other selenides and was much easier than with the corresponding sulfur compounds. The reaction proceeded by following the mechanism shown below providing the corresponding allylic oxidation products. The procedure could be applied to the synthesis of optically active allylic alcohols [109].

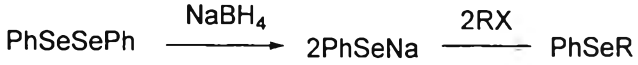


As mentioned above, organoselenium compounds in their chemical behavior bear strong resemblance to organosulfur compounds [126]. The organoselenium compounds were similar to those of the better known and much less expensive organic sulfur compounds. However, synthetically important reactions for selenium intermediates was facilitated and proceeded under simpler and milder conditions such as simple and efficient syntheses of unsaturated functional structures.

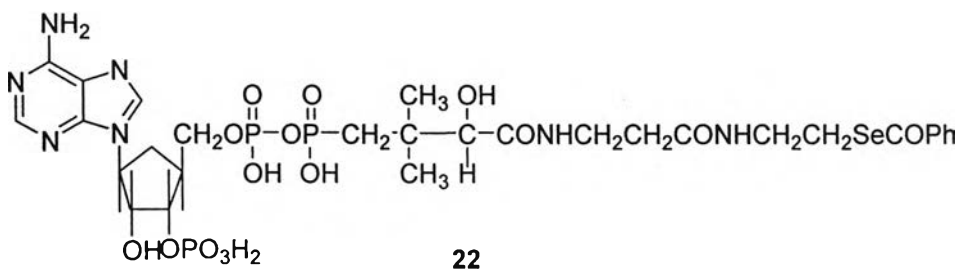
Organoselenium compounds were expensive but it must be remembered that especially selenides, diselenides and seleninic acids, which were the most commonly use and produced, could be recovered, transformed and re-used. Indeed, many preparation methods have been developed in many cases and could be used more generally.

- **Preparation of unsymmetrical diorganyl selenides**

The classical method or general preparative method for unsymmetrical diorganyl selenide was a Williamson-type approach. Diselenide (PhSeSePh) was reduced with sodium borohydride to give the sodium salt of alkyl selenol. This salt reacted with alkyl halides to provide the unsymmetrical diorganyl selenides [127].



For instance, in 1965, Gunther and Mautner reported the synthesis of selenocoenzyme A which replaced the sulfur with selenium in coenzyme A, important in metabolic pathways. Since selenium should not affect appreciably either the size of this complex molecule or its ability to fit receptor sites similar to that of its sulfur analog. It resulted in the synthesis of selenocoenzyme A (**22**) was taken and the key compound for the synthesis of selenocoenzyme A was 4′-phosphoselenopantethine (**23**). By starting the pathway with condensation of benzylselenol (**24**), prepared from dibenzyldiselenide reduced with sodium borohydride, with 2-bromoethylamine or ethylenimine hydrobromide yielded 2-benzylselenoethylamine (**25**) which was an example for preparation of unsymmetrical diorganyl selenide [126].



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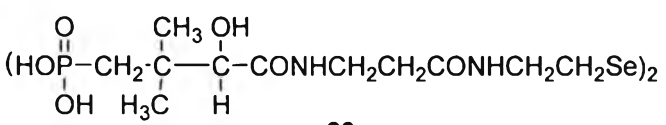

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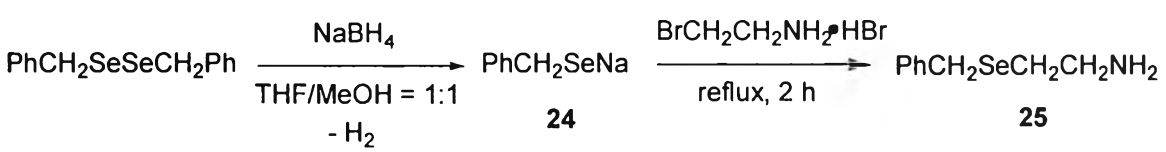
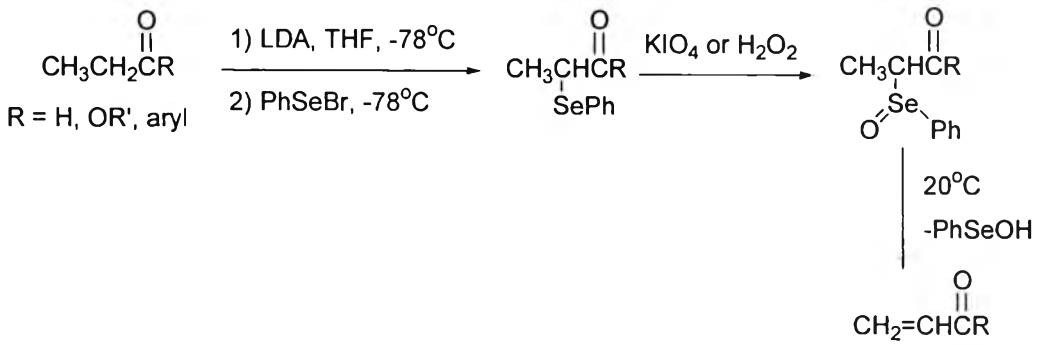
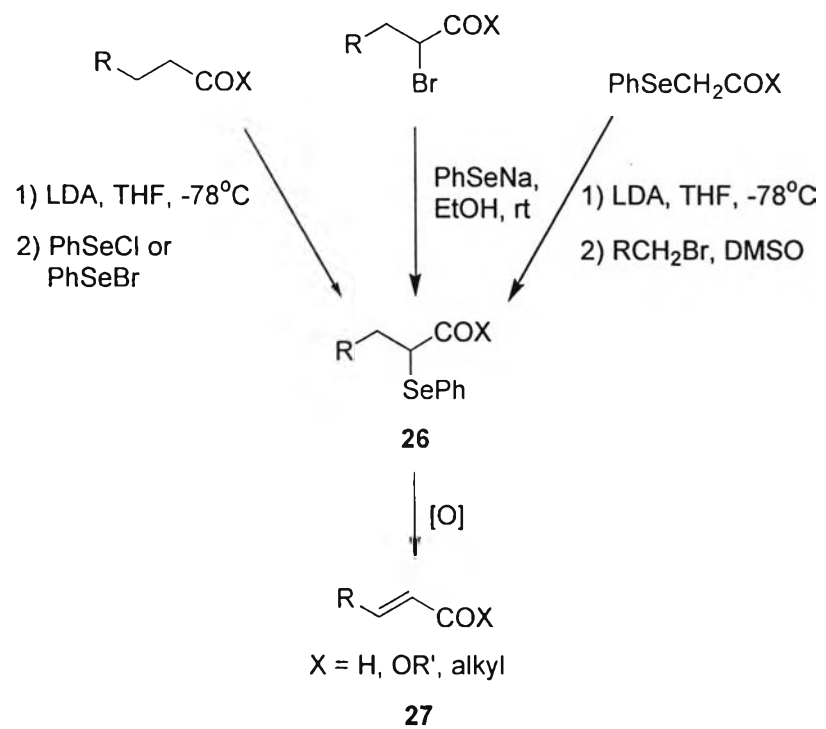


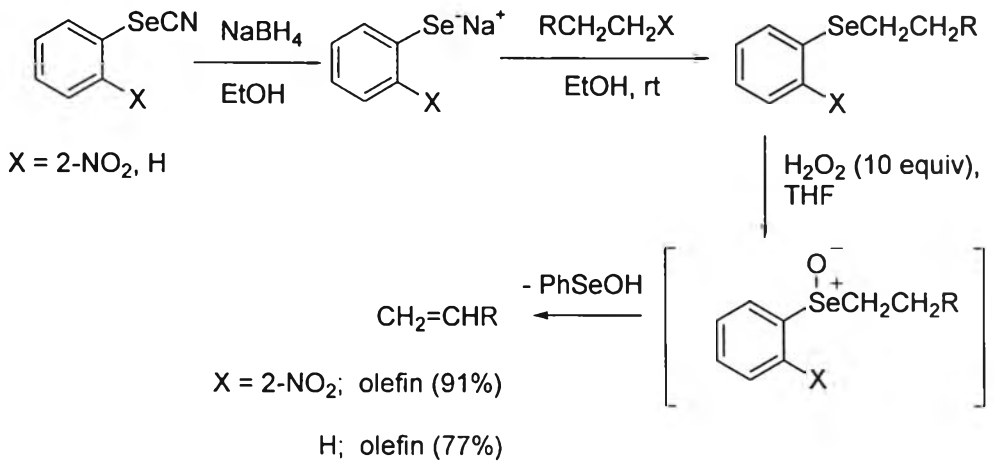
In 1973, Sharpless prepared enones from aldehydes, ketones or esters using mild method formed *β*–ketoselenium oxides *via syn*-elimination of PhSeOH [34].



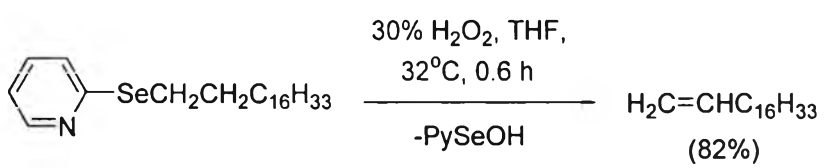
In the process, it involved the oxidation of an α-phenylselenocarbonyl compound (**26**) to the corresponding selenoxide which was eliminated at room temperature to give the desired olefin. X could be hydrogen, alkyl, or alkoxy; thus α,β-unsaturated aldehydes, ketones, and esters could be prepared by this method. The α-phenylselenocarbonyl compounds **(26)** are readily formed in a variety of ways from the previously employed nucleophilic selenium reagent PhSeNa and from the electrophilic selenium reagents PhSeCl and PhSeBr.



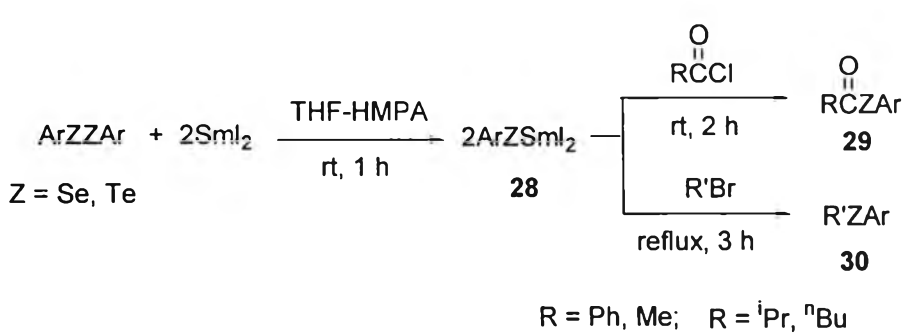
Subsequently, in 1975, Sharpless also studied and prepared the electron-withdrawing substitutents on aromatic ring of aryl alkyl selenoxides. They increased the rate of eliminations and yield of olefins oxidized by excess 30% hydrogen peroxide (10 equiv) [90].



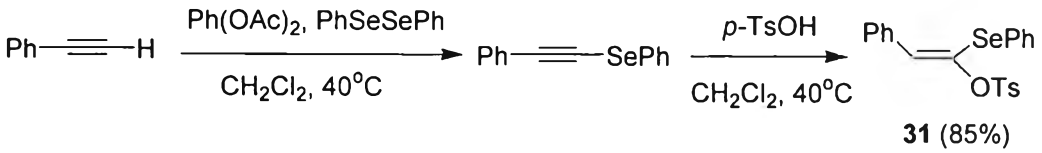
Later, in 1980, Toshimitsu prepared and changed phenyl group of selenides to alkyl pyridyl selenides which were oxidized by aqueous hydrogen peroxide (1.5 equiv) as below here. A pyridylseleno group as an electron withdrawing group showed high ablility in oxidation-elimination reduction, especially being advantage for introduction of double bond into large molecule which had sensitive functional group to oxidation [129].



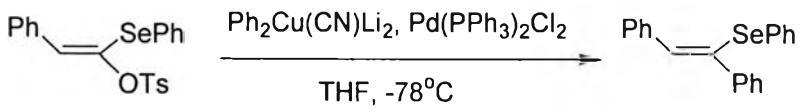
In 1993, Zhang *et al.* examined the reduction of diaryl diselenides and diaryl ditellurides (1 equiv) using samarium iodide (2 equiv), prepared by samarium powder and iodine. It was resulted in the occurrence of samarium arylselenoates and aryltellurolates (**28**) under mild conditions. And then **28** reacted with acyl or alkyl halides (2.5 or 2 equiv, respectively) to generate selenoesters or telluroesters (**29**) and alkyl selenides or tellurides (**30**) in good yields [130].



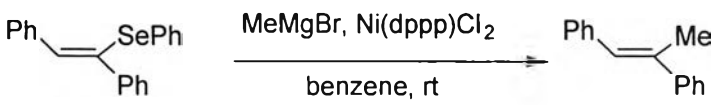
In 1995, Tingoli *et al.* studied the regio- and stereospecific addition of *p*-toluenesulfonic acid to alkynyl phenyl selenides affording (Z)-α-(phenylseleno)vinyl *p*-toluensulfonates (**31**) in good yield. During the reaction between **31** and cyanocuprate occurred the trisubstituted alkene (**32**) with retention of configuration in good yield. At the end, the cross coupling reaction of this vinyl selenide (**32**) with methyl magnesium bromide in the presence of nickel as a catalyst afforded *trans*-stilbene (**33**) with retention of configuration in 60% yield [131].



31 (85%)

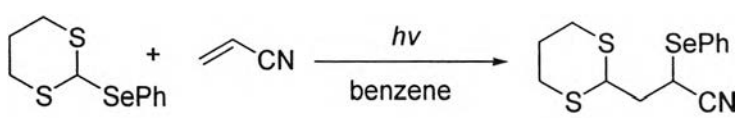


32 (80%)



32 **33** (60%)

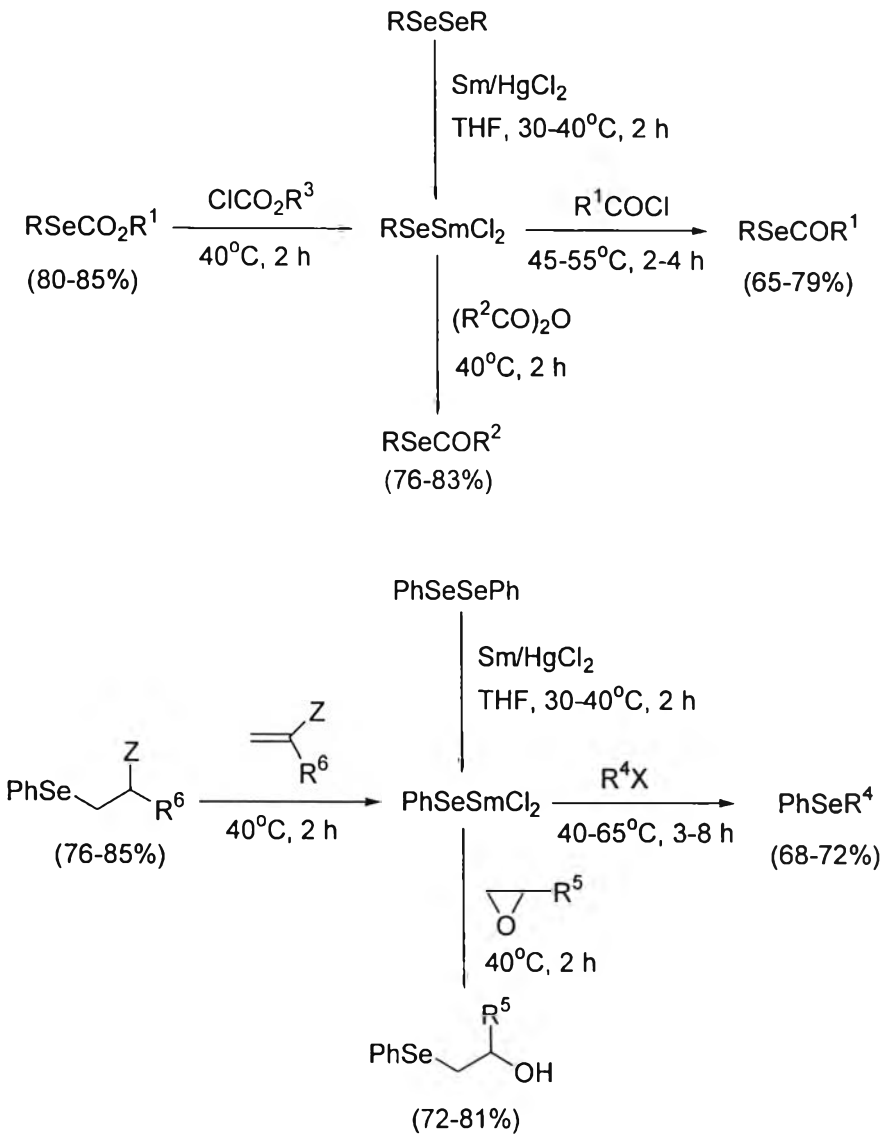
In 1996, Byers *et al.* reported that treatment of 2-phenylseleno-1,3-dithiane, as a carbonyl protecting group, with electron-deficient alkenes by photolysis resulted in the addition products. For example, reaction of dithiane with acrylonitrile generated the addition product which was introduced to a carbonyl group and a phenylseleno group, being a value of subsequent transformation. These reactions were radical atom transfer addition arising from a heteroatom-stabilized radical [132].



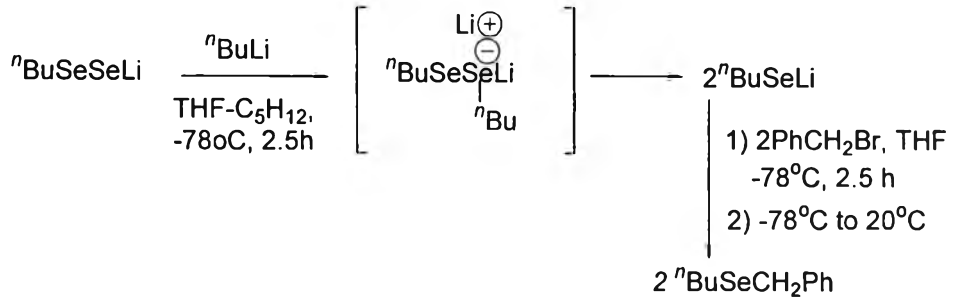
(62%)

In 1999, Wang and Zhang *et al.* investigated the reactions of diphenyl diselenide or dialkyl diselenides with mercury (II) chloride in the presence of samarium metal in THF to generate samarium arylselenolates or alkylselenolates. During the reaction these samarium species could reacted with acid chlorides, acid

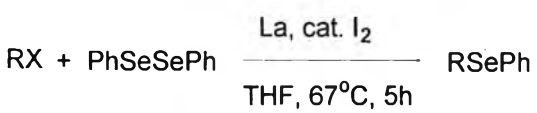
anhydrides, methyl chloroformates, organic halides, epoxides, α,β-unsaturated esters, and α,β-unsaturated nitrile to obtain selenoesters, selenoformates, unsymmetrical selenides, and β-hydroxy alkyl phenyl selenides in good yields [85].



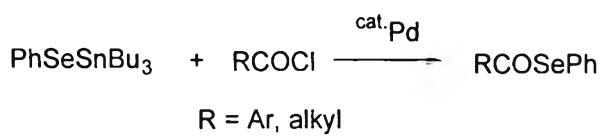
In 2000, Krief *et al.* prepared lithium *n*-butyl diselenoate from butyl lithium, and selenium in THF. It was quite stable under argon even in boiling THF for 1 h. Reacting with *n*-BuLi produced two equivalents of lithium *n*-butyl selenoate. The lithium selenoate was treated with benzyl bromide at very low temperature, -78°C, and stirred for 2.5 h to generate the corresponding selenide in 83% yield which was applied to asymmetric dihydroxylation [88, 133-135].



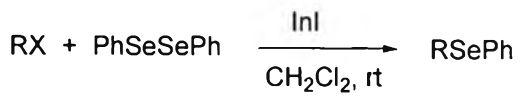
In 2002, Nishino, *et al.* first developed one-pot and neutral synthetic method of unsymmetrical selenides from diphenyl diselenide (1 equiv) which reacted with organic halides (2 equiv) in the presence of an equimolar amount of lanthanum metal and catalytic amount of iodine. Primary alkyl iodides and bromides were formed in moderate to high yields while secondary alkyl iodides were needed hexamethylphosphoramide (HMPA) or tetramethylethylenediamine (TMEDA) to improve their yields. In the case of *tert*-butyl iodide the reaction did not proceed at all under the reaction conditions. The possible pathway including the alkylation pathway of lanthanum phenyl selenolate, prepared by the reduction of diphenyl diselenide with lanthanum metals, with alkyl halides was suggested [136].



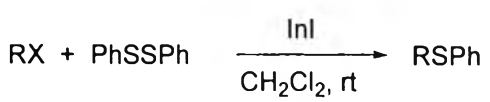
In 2003, Nishiyama *et al.* developed the synthetic method for the preparation of acyl selenides from phenyl tributylstannyl selenides. They reacted with acyl or aroyl chlorides in the presence of a catalytic amount of a palladium complex such as $Pd(PPh_3)_4$. This coupling reaction gave the corresponding selenoester in moderate to high yields. Moreover, the coupling of tributylstannyl selenides with α-halocarbonyl compounds in moderate yields under neutral conditions [92].

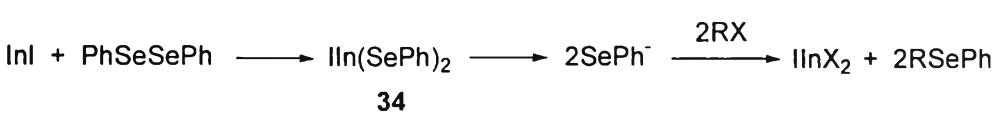


In 2003, Ranu *et al.* reported that various alkyl halides reacted with PhSeSePh in the presence of indium(I) iodide giving moderate to high yields of alkyl phenyl selenides. The method offered one-pot, simple reaction conditions and shorter reaction times [137].

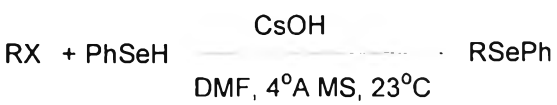


Latter, in 2004, Ranu and coworkers reported on the synthesis of selenides by addition more samples of organic halides. They also reported on the synthesis of alkyl aryl sulfides and alkyl thiobenzoates which occurred in high yields under the same conditions. However, the formation of sulfides required longer reaction times than those of selenides. The reaction pathway through bis(phenylseleno/ thiophenyl)-iodoindium(III) (**34**) which was produced by the reaction of an equimolar quantities of InI and PhSeSePh (use of less than a stoichiometric amount of InI keeped the reaction incomplete) [138].

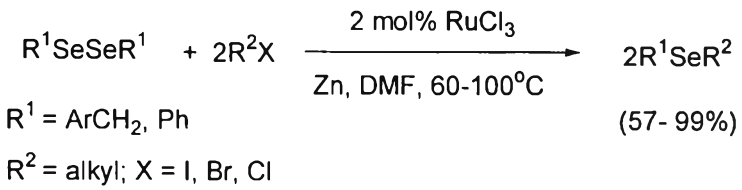




In 2004, Cohen *et al.* also studied for the preparation of unsymmetrical selenides using onet-pot and mild approach of the cesium-promoted alkylation. Benzeneselenol reacted with various organic halides in the presence of cesium hydroxide and 4°A molecular sieve in anhydrous *N*,*N*-dimethylformamide (DMF). Unsymmetrical primary and secondary alkyl phenyl selenides were exclusively formed in high yields whereas tertiary alkyl phenyl selenides did not proceeded at all. Furthermore, an amino acid derivative successfully generated a selenopeptide, and the synthesis of unsymmetrical diorganyl selenides on solid support also employed [94].



In 2005, Zhao *et al.* developed an one-pot synthesis of unsymmetrical diorganyl selenides using ruthenium(III) chloride as catalyst in the presence of zinc. The reaction condition was diselenide 0.5 mmol, organic halides 1.2 mmol, Zn 0.8 mmol, catalyst $RuCl_3 \cdot 3H_2O$, and DMF 3 mL. Under these conditions, the corresponding selenides were generated in moderate to high yields. For unreactive organic chlorides, sodium bromide was needed as an additive [139].



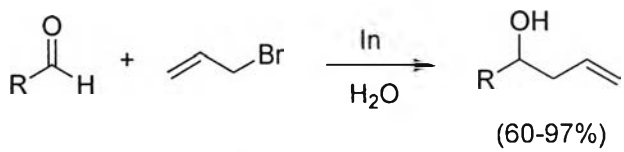
Organoselenides (R_2Se) and organodiselenides (RSeSeR) could be prepared from various ways as seen in Scheme 3.1. Besides the reaction mentioned above, there were still many reactions capable of manipulating unsymmetrical diorganyl selenides [140-147]. However, most of work performed in this area was highly problematic because of the instability of these compounds in air and moisture, as well as their sensitivity to strongly acidic and basic reaction media. Furthermore, many synthetic methods proceeded with many step procedures and sometimes suffered from the improper handling of selenium reagents. Thus, the development of new synthetic methods using stable selenium reagents under mild conditions is invaluable in organic synthesis. For this reason, organoselenides, especially unsymmetrical diorganyl selenides, were interestingly focused on in this research.

- **Indium in organic synthesis**

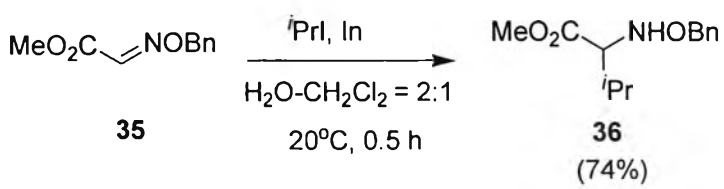
Indium was one of the Group 13 elements in the periodic table, of which boron and aluminum. Indium had first ionization energy 558 kJ mol^{-1} or 5.8 eV as low as that of Na or Li, and much lower than Zn or Sn, or even of Mg. It was easy for ndium to act as an effective single electron transfer (SET) agent.. and it was a soft metal having common oxidation state numbers as 1 or 3.

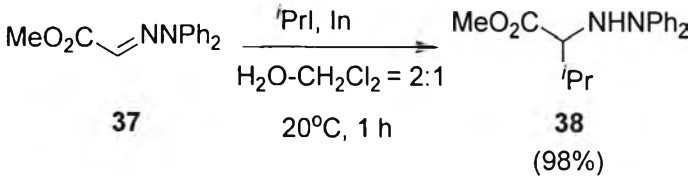
While boron and aluminum were widely used in organic synthesis from the past decades, indium and gallium have just been received little attention until a decade ago. The first organoindium compounds were prepared in 1928 and their application in organic synthesis was published very few [148-149]. However, their extensive use

had to wait until 1988. In that time, allylic indium reagents were readily prepared in organic solvents by reaction of allylic halides and indium powder. The application of allylindium reagents and related organoindium reagents to organic transformation have been widely studied since 1988. Until now their applications in synthetic utility are published more than 100 papers per year. The importance of indium metal and its salts were demonstrated through novel protocols for carbon-carbon bond formations, rearrangements, and a variety of useful reactions over the past decades [150-152]. Since indium-mediated Barbier-type allylation (Barbier-Grignard type reactions) in water was first reported in 1991 [153-154], indium was received increasingly interest for economic and environmental reasons [155].

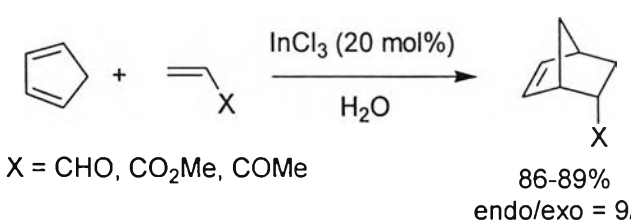


Nowadays, indium metal shows its importance in organic chemistry, especially in the field of green chemistry, since indium metal was comparatively stable in air, and the toxicity observed for many metals was little known for indium [156]. In addition, the use of water as solvent concerning indium-mediated carbon-carbon bond-forming reaction in aqueous media have been of great importance in organic synthesis such as the allylation of unprotecting mannose to afford in three steps the deaminated sialic acid, 3-deoxy-D-*glycero*-D-*galacto*-nonulasonic acid (KDN) [157]. For more examples, in 2002 and 2004, Miyabe and coworkers studied the one-pot intermolecular alkyl radical addition to imine derivatives in aqueous media by using indium as SET radical initiators. The reaction of glyoxylic oxime ether (**35**) with isopropyl iodide in the presence of In gave the corresponding isopropylated product (**36**) in 74% yield. Similarly, glyoxylic hydrazone (**37**) proceeded effectively to afford the carbon-carbon forming product in 98% yield [158-159].

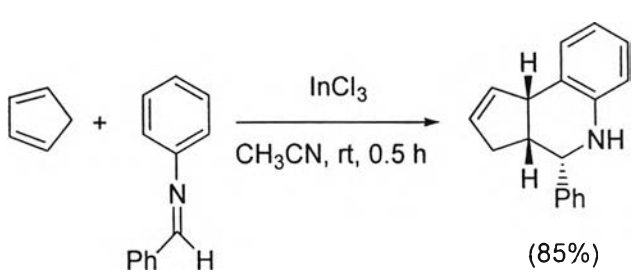




Subsequently, organoindium compounds could be prepared simply by mixing appropriate organic halides with indium. On the account of tolerance of water characterized organoindium reagents in organic synthesis, their reaction could be performed under aqueous conditions without protection of hydroxyl or other protic group on the reactant. This property could be applied in green chemistry field, importantly in environmental friendly. In the case of indium(III) salts such as indium trichloride and indium trifate were used as catalyst in both aqueous and organic solvents. $InCl_3$ and $In(OTf)_3$ were versatile as Lewis acid in organic syntheses [150]. They were also stable in water, and catalyzed a variety of organic reactions *e.g.* Diels-Alder reaction, Michael addition, and other organic transformations. For instance, Loh *et al.* reported that $InCl_3$ catalyzed the Diels-Alder reaction between cyclopentadiene and acrylates in water, and shown that it could be easily recovered from water and reused after the reaction completed [151].



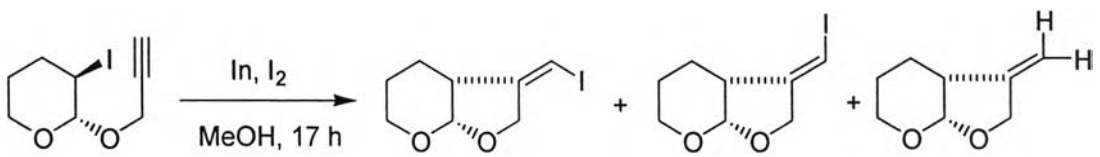
Moreover, the imino Diels-Alder reaction used more than stoichiometric amounts of common Lewis acids while only a catalytic amount of anh $InCl_3$ (20 mol %) in the reaction of Schiff bases with cyclopentadiene afforded cyclopentaquinolines (85% yield).



Utility of indium in organic synthesis, especially in radical chemistry, was increasing. Due to the first ionization energy of indium as 5.8 eV, as low as that of Na or Li, and much lower than Zn or Sn, or even of Mg, it was easy for indium to act as an effective single electron transfer (SET) agent [154,156,158,160].

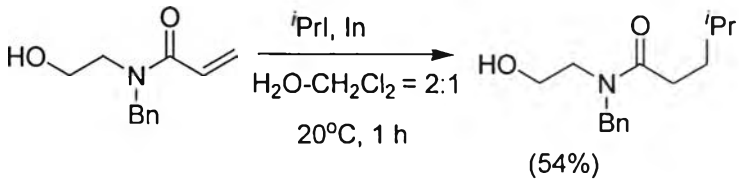
Moreover, in spite of its most important role in radical reactions, tributyltin hydride ($^{t}Bu_3SnH$) [161] has disadvantages including neurotoxicity and difficulty of the complete removal of the tin species from the reaction. This reason made the decrease of its role and application in radical chemistry. For all reasons, the requirement for more convenient and newly useful radical reducing reagents to replace tributyltin hydride was called for. Therefore, many reports on the uses and applications in radical reactions are reviewed as exemplified below:

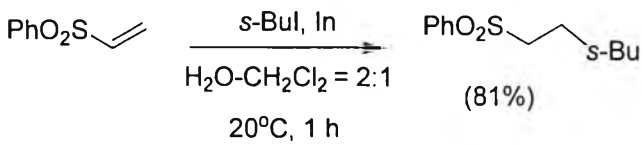
In 2002 and 2004, Yanada *et al.* developed the indium-mediated reaction [162]. For an atom-transfer radical cyclization, 5-exo-cyclization or Kharasch-type reaction, of iodoalkynes using 2 equiv of In and 1.0 equiv of I_2 obtaining heterocyclic iodoalkenes (**39**) in 77% yield was reported. Furthermore, an indium-mediated reductive 5-exo-cyclization of iodoalkynes to heterocyclic alkenes was also developed and gave the alkene (**41**) in 85% yield (2 equiv of In and 1.0 equiv of I_2). This procedure provided a methodology for multibond formation without the use of other radical initiators [156].



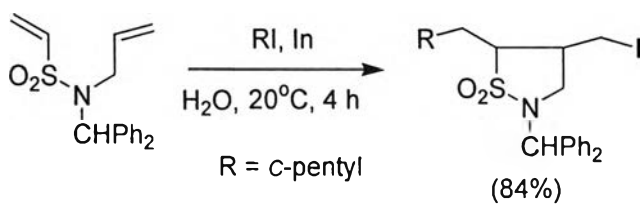
39 **40** **41**

In 2003, Miyabe *et al.* reported the indium-mediated carbon-carbon bond-forming radical addition in aqueous media. The reaction of glyoxylic oxime ether with isopropyl iodide in the presence of indium as radical initiator gave the corresponding isopropylated product in high yield, as mentioned above. Moreover, the indium-mediated alkyl radical addition to other compounds, having electron deficient C=C bond was also investigated. Finally, the radical addition to phenyl vinyl sulfone was studied in the same conditions. As expected, phenyl vinyl sulfone exhibited a good reactivity to give the desired addition products in good yields with no detection of by-products such as a reduced product [162].

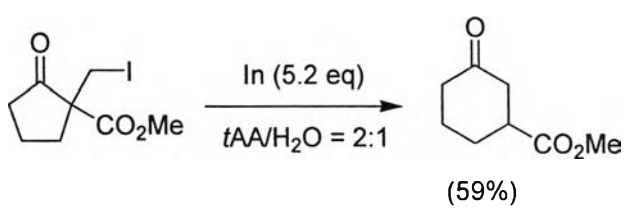


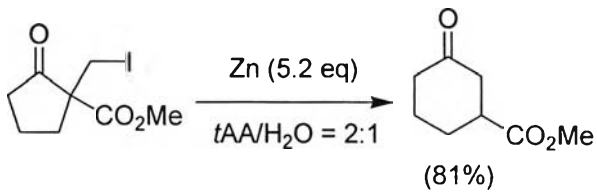


In 2003, Ueda and coworkers studied indium-mediated radical reactions for tandem addition-cyclization as carbon-carbon bond-forming reactions. The reactions proceeded in the absence of toxic tin hydride by using indium metal method in aqueous media. Additionally, this method could be applied to the preparation of various types of highly functionalized cyclic compounds. From the equation, the sulfonamide exhibited good reactivity afforded the good yield of the desired cyclic product [163].



In 2003, Suki and coworkers reported that the ring-expansion reactions of α-halomethyl cyclic β-keto esters and chain-extension reactions of α-halomethyl β-keto esters with zinc or indium powder in refluxing aqueous alcohol were highly effective and environmentally friendly. The reaction pathway was zinc- or indium-mediated radical ring expansion which initiated by the first single electron transfer from metal to α-halomethyl cyclic β-keto esters to form the corresponding methyl radical derivative, followed by *3-exo-trig* cyclization and its radical β-cleavage. The ring-expansion products were effectively formed since there was no good hydrogen donor such as tris-(trimethylsilyl)silane, or tributyltin hydride [164].





*t*AA = *tert*-amyl alcohol

As a conclusion, in view of their importance and utility as reagents and key intermediates for introducing new functional groups in organic synthesis were found in organoselenides. Unsymmetrical phenyl selenides have been used as precursors for carbon–carbon double bonds formations [130,146]. Much efforts were being devoted to accomplish the synthesis of these compounds. Thus, a numerous number of reports on the preparation of organoselenides have been published [89,126,146,147]. However, many preparative methods required the proper handling of unstable reagents, strongly basic or acidic reaction conditions, and two-step procedures [99,126,146]. Therefore, the development of new synthesis methods using one-step procedure under neutral and mild conditions would have significant synthetic values. Moreover, indium metal and its salt have been the subject of a number of investigations over the past decade because of their utility of carbon-carbon bond formation, rearrangements and a variety of useful reaction [165-168]. It has drawn an increasing attention for its unique properties such as low toxicity and high stability in water and air compared with other metals [169-171]. In addition to the important point of this research is that the reaction proceeded under mild and neutral conditions without having any assistance from acids or bases. Because of these reasons, for developing application of indium metal in organic synthesis, herein, the indium-mediated reaction for the preparation of organoselenides was provided under mild and one-pot procedure.

- **The objectives of this research**

The goals of this research could be summarized as follows:

1. To develope an efficient procedure in one-step synthesis of alkyl phenyl selenides using stable reagents under neutral conditions

2. To prepare tertiary alkyl phenyl selenides from tertiary alkyl halides

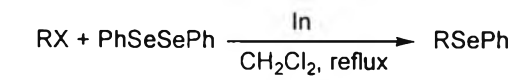
3. To investigate on the use of Indium metal for transformation of alkyl halides into alkyl phenyl selenides

3.2 Results and Discussion

Part I: Optimized conditions for synthesis of alkyl phenyl selenides

3.2.1 Optimized conditions

As mentioned above, olefins could be prepared *via* alkyl phenyl selenides [172-174]. An indium-mediated reaction was selected as a new approach for the preparation of organoselenides under a mild, efficient and convenient one-pot procedure (Scheme 3.2).

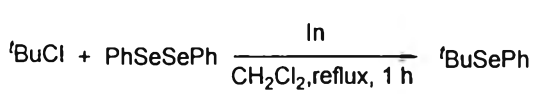


Scheme 3.2 Synthesis of alkyl phenyl selenides in the presence of indium

Some parameters including effects of various alkyl halides of different structural types, solvents, ratios of substrate and reagents and the amount of indium metal were thoroughly investigated. With the synthesis of these selenide compounds, *tert*-butyl chloride (^{t}BuCl) was used as a substrate model of alkyl halide to optimize conditions. The yields of the attained products were analyzed by GC based on alkyl halide (1 mmol). The oven temperature condition of GC was 60°C (initial temperature), 4 min (initial time), 15°C/min (rate), 220°C (final temperature) and 6 min (final time).

The reaction of ^{t}BuCl with diphenyl diselenide (PhSeSePh) in the presence of indium was first investigated to observe the appropriate ratio of substrate and reagents (Table 3.1).

Table 3.1 Effects of ratios of *tert*-butyl chloride and reagents on the synthesis of *tert*-butyl phenyl selenide



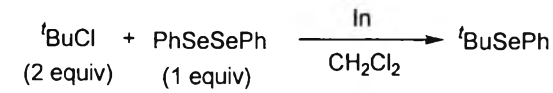
Entry	Equivalent of RCl and reagents (mmol)			Yield (%)[a]
	RCl	PhSeSePh	In	
1	1.0	1.0	1.0	98
2	1.0	0.7	0.7	95
3	1.0	0.5	0.5	95

[a] Analyzed by GC based on ^{t}BuCl (1 mmol).

When PhSeSePh (1.0 mmol) was allowed to react with an equimolar amount of ^{t}BuCl in the presence of indium (1.0 mmol) in CH_2Cl_2 at reflux for 1 h, *tert*-butyl phenyl selenide was obtained in high yield (98% yield based on ^{t}BuCl, entry 1). The yield of the products in entry 2 and 3 was also obtained in high yield (95% yield based on ^{t}BuCl). However, it was found that an amount of PhSeSePh was remained at the end of the reaction as yellow solution (entries 1 and 2). This implied that an excess amount of PhSeSePh (1.0 and 0.7 mmol) should possibly be reduced to 0.5 mmol, in entry 3, because this equivalent of PhSeSePh should be enough for the reaction. Consequently, the optimal equivalent ratio of ^{t}BuCl, PhSeSePh and indium for the synthesis of *tert*-butyl phenyl selenide was 2: 1: 1, respectively (entry 3). This equivalent ratio was applied to examine the optimized conditions and various substrates.

The effect of temperature, reaction time and an amount of indium was then scrutinized and the results are summarized in Table 3.2. When 1.0 equiv of PhSeSePh was reacted with 2.0 equiv of ^{t}BuCl in the presence of indium (1.0 equiv) in CH_2Cl_2 at room temperature for 1 h, *tert*-butyl phenyl selenide was obtained in 86% yield based on ^{t}BuCl (entry 2). Nonetheless, the same reaction carried out in a shorter period of time of 15 min yielded the selenide product in only trace amount (entry 1). The reaction was completed within 3 h at room temperature (entry 3). Similarly, the reaction was accomplished within 1 h in boiling CH_2Cl_2 (entries 5 and 6). From this examination, the reaction time could be reduced when the reaction temperature was lifted up to reflux. It was interesting that the high yields were also observed even the amount of indium was reduced to 0.5 equiv at room and reflux temperature (entries 4 and 8). In the absence of indium metal, the reaction did however not proceed at all (entry 7). This strongly implied that indium was a proper promoter for the reaction. The essential amount of indium that required to promote the reaction was next investigated (entries 9 and10). With 0.25 equiv of In, although the reaction time was increased from 1 to 3 and 6 h, the product was obtained in 55% and 57% yield, respectively (entries 11 and 12). This leads to a conclusion that indium metal used in this reaction was not catalytic.

Table 3.2 Effects of temperature, reaction time and the amount of indium metal on the synthesis of *tert*-butyl phenyl selenide



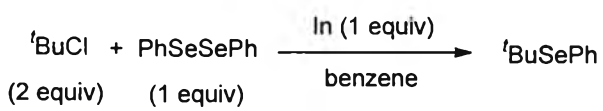
Entry	Temp.	Time (h)	Amount of In (eq)	Yield (%)[a]
1	rt	15 min	In (1.0 eq)	trace
2	rt	1 h	In (1.0 eq)	86
3	rt	3 h	In (1.0 eq)	quant.
4	rt	1 h	In (0.5 eq)	85
5	reflux	30 min	In (1.0 eq)	74
6	reflux	1 h	In (1.0 eq)	95
7	reflux	1 h	In (0 eq)	0
8	reflux	1 h	In (0.5 eq)	91
9	reflux	1 h	In (0.25 eq)	55
10	reflux	1 h	In (0.1 eq)	20
11	reflux	3 h	In (0.25 eq)	55
12	reflux	6 h	In (0.25 eq)	57
13	reflux	1 h	In (1.0 eq), I_2 (0.2 eq)	quant.
14	reflux	30 min	In (1.0 eq), I_2 (0.2 eq)	quant.
15	reflux	15 min	In (1.0 eq), I_2 (0.2 eq)	quant.
16	rt	1 h	In (1.0 eq), I_2 (0.2 eq)	quant.
17	rt	30 min	In (1.0 eq), I_2 (0.2 eq)	quant.
18	rt	15 min	In (1.0 eq), I_2 (0.2 eq)	quant.
19	reflux	1 h	$InCl_3$ (1.0 eq)	3

[a] Analyzed by GC based on the amount of ^{t}BuCl (1 mmol).

There were many reports addressing that the reactions using metal could be promoted by the addition of I_2 or $AlCl_3$ [138,175]. The addition of a catalytic amount of iodine to the reaction caused a tremendously increase in the yield of alkyl phenyl selenides to quantitative yield (entries 13-18). To illustrate this, the addition of a catalytic amount of iodine to the reactions carried out at reflux and room temperature for 1 h, the product was occurred in the excellent yields (entries 13 and 16). Even the reaction time was reduced to 30 and 15 min, quantitative yields were still detected. Finally, under the condition of refluxing for 1 h, with 1 equiv of $InCl_3$, the reaction did not proceed efficiently (entry 19). As a result, the optimized condition for alkyl phenyl selenides was the reaction which was carried out in the presence of 1.0 equiv of indium in CH_2Cl_2 at reflux temperature for 1 h (entry 6).

In addition, the effect of temperature, reaction time and the amount of indium metal in benzene as solvent were also investigated (Table 3.3). When an equivalent of PhSeSePh was allowed to react with two equimolar amounts of ^{t}BuCl in the presence of indium (1.0 equiv) in CH_2Cl_2 at room temperature for 3 h, *tert*-butyl phenyl selenide was obtained in 51% yield based on ^{t}BuCl (entry 1). Comparing with entry 3, the reaction time was reduced when the reaction temperature brought up to reflux and gave the product in moderate yield (entry 3). Adding catalytic amount of iodine (0.2 equiv), the yield was improved both at room and reflux temperature (entries 2, 4 and 5). Moreover, in the presence of 0.2 equiv of iodine, the reaction was completed within half an hour with quantitative yield of the desired product (entry 5).

Table 3.3 Effects of temperature, reaction time and the amount of iodine on the synthesis of *tert*-butyl phenyl selenide in benzene

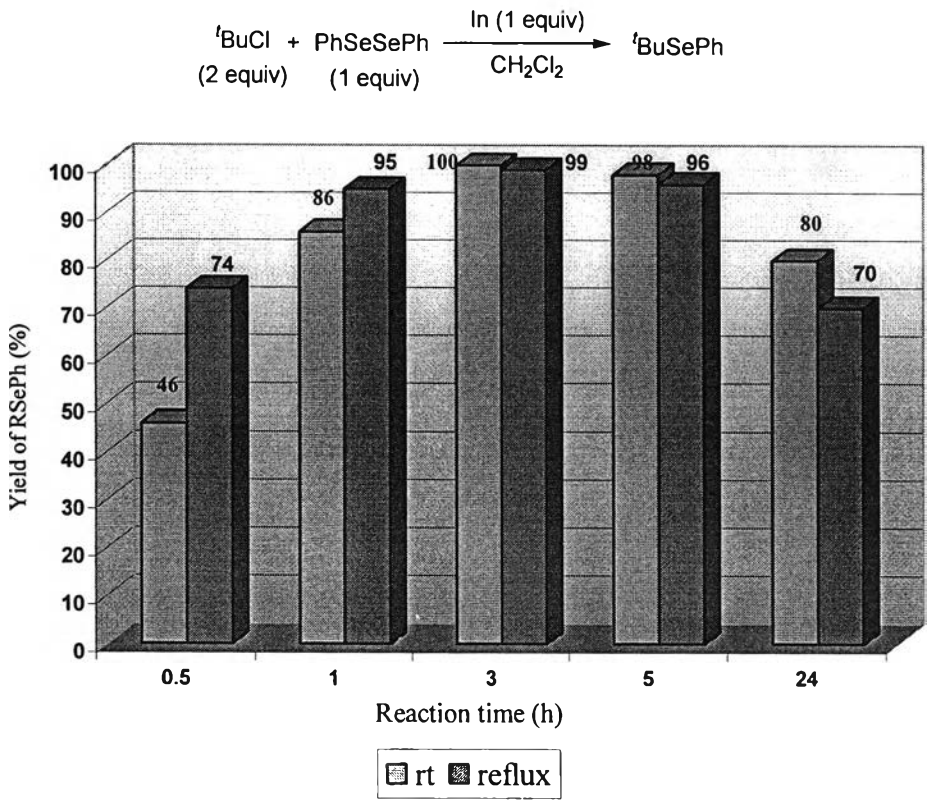


Entry	Temp.	Time (h)	Amount of I_2 (eq)	Yield (%)[a]
1	rt	3	0	51
2	rt	1	0.2	76
3	reflux	1	0	65
4	reflux	1	0.2	quant.
5	reflux	0.5	0.2	quant.

[a] Analyzed by GC based on the amount of ^{t}BuCl (1 mmol).

The temperature effect on the reaction of ^{t}BuCl with PhSeSePh comparing between room and reflux temperature was carried out at various reaction times (Figure 3.1).

Figure 3.1 Temperature effects on the reaction of ^{t}BuCl with PhSeSePh



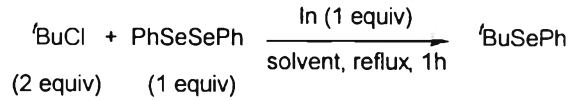
Reaction conditions: RCl (1 mmol), PhSeSePh (0.5 mmol), In (0.5 mmol) and CH_2Cl_2 (3 mL)
GC yield based on ^{t}BuCl (1 mmol)

It was found that the reaction was completely within 3 h at room temperature and 1 h at reflux. On the contrary, when the reaction time increased to 24 h in both reaction temperatures, it caused a decrease in the yield of *tert*-butyl phenyl selenide which might related to the thermal stability of the product.

3.2.2 Effect of solvents

The solvent effects were also examined. The results are summarized in Table 3.4.

Table 3.4 Effects of solvents on the reaction of ^{t}BuCl with PhSeSePh



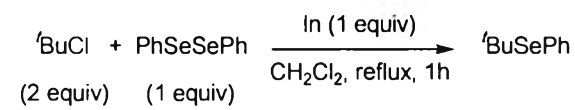
Entry	Solvent	Yield (%)[a]	Yield (%)[b]
1	Benzene	51	65
2	Toluene	38	41
3	THF	0	22
4	$ClCH_2CH_2Cl$	quant.	52
5	CH_3CN	50	66
6	CH_2Cl_2	quant.	95
7	CH_2Cl_2:H_2O (9:1)	42	21

[a] GC yield based on ^{t}BuCl (1 mmol). The reaction was carried out at rt for 3 h.
[b] GC yield based on ^{t}BuCl (1 mmol). The reaction was carried out at reflux for 1 h.

Basical treatment of ^{t}BuCl (2 equiv) with PhSeSePh (1 equiv) in the presence of indium (1 equiv) was performed in various solvents at room temperature for 3 h or reflux for 1 h. Using the optimized conditions common organic solvents such as benzene, toluene, THF, $ClCH_2CH_2Cl$ and CH_3CN provided in low to moderate yields of the desired product (entries 1-5). The reaction performed in CH_2Cl_2 was the most efficient obtaining a 95% yield of *tert*-butyl phenyl selenide (entry 6). However, the poor yield of the product was obtained in aq dichloromethane (CH_2Cl_2:H_2O, 9:1, entry 7).

According to the results in Table 3.4, CH_2Cl_2 was chosen for further study on the effect of solvent concentration (Table 3.5).

Table 3.5 Effect of the amount of CH_2Cl_2 in the reaction of ^{t}BuCl with PhSeSePh



Entry	Volume of CH_2Cl_2 (mL)	Concentration (M)	Yield (%)[a]
1	1	1.0	quant.[b]
2	2	0.5	quant.
3	3	0.33	quant.

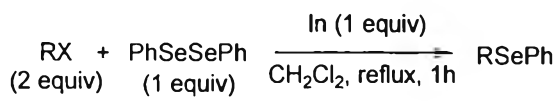
[a] Analyzed by GC based on RX (1 mmol).
[b] White precipitate was observed during the reaction.

The results revealed that in every concentration of 1, 0.5 and 0.33 M the product was achieved in the quantitative yield. Nevertheless, 1 mL of CH_2Cl_2 was too little to run the reaction and became dry. It resulted in aggregation as a white solid (entry 1). Therefore, the volume of solvent for the reaction should be 2 or 3 mL of CH_2Cl_2 (entries 2 and 3) to dissolve alkyl halides (1 mmol).

3.2.3 The screening of substrates

The scope and limitations of the present method employing a variety of sterically different organic halides were investigated. Under the optimal conditions, treatment of ^{t}BuCl (2 equiv) with PhSeSePh (1 equiv) in the presence of indium (1 equiv) in CH_2Cl_2 at reflux for 1 hour gave the corresponding selenides as summarized in Table 3.6.

Table 3.6 Synthesis of alkyl phenylselenides from various types of alkyl halides under optimal conditions



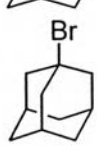
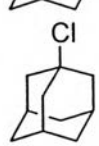
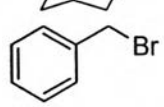
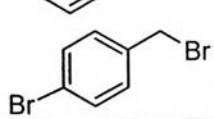
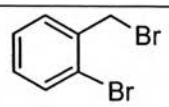
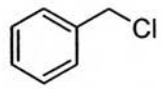
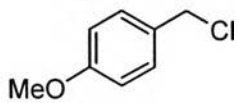
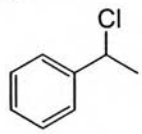
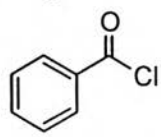
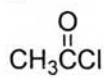
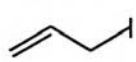
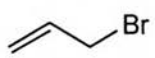
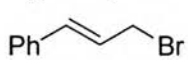
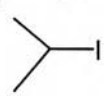
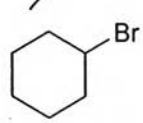
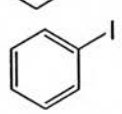
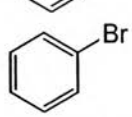
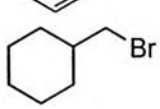
Entry	RX	Yield (%)[a]	Isolated yield (%)
1	^{t}BuI	99	-
2	^{t}BuBr	95	86
3	^{t}BuCl	95	-
4		86	76
5		84	74
6		quant.	88
7		86	70
8		98	85

Table 3.6 (cont.)

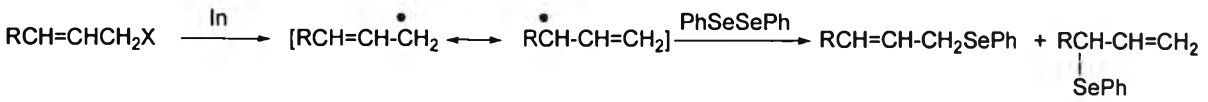
Entry	RX	Yield (%)[a]	Isolated yield (%)
9		quant.	95
10		-	84
11		-	52[b]
12		67	59
13		78	60
14		25	-
15		quant.	89
16		97	73
17		40	32
18		trace	-
19		trace	-
20		trace[c]	-
21		trace	-
22		25	-
23	CH_3CH_2Br	trace	-
24	$CH_3(CH_2)_4CH_2I$	trace	-
25	$CH_3(CH_2)_{10}CH_2I$	trace	-

[a] Analyzed by GC based on RX (1 mmol). [b] The reaction was carried out at reflux for 2 h.
[c] The reaction was carried out at reflux for 24 h.

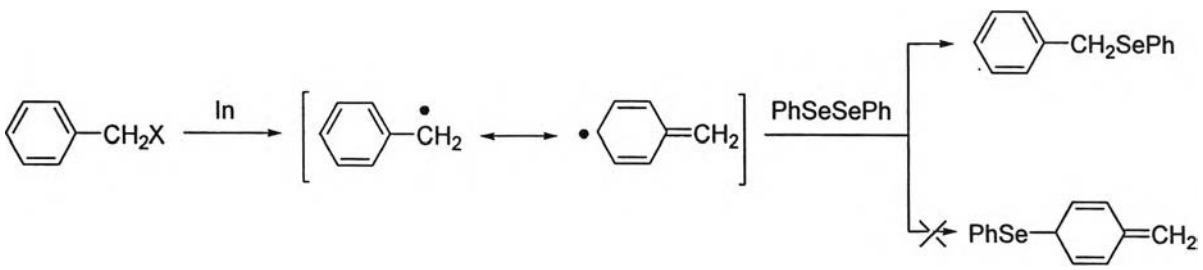
From the obtained results in Table 3.6, tertiary alkyl halides underwent a clean reaction to provide the corresponding alkyl phenyl selenides in high yields (entries 1-6). Both *tert*-butyl and adamantyl phenyl selenides were also formed by the reaction

of *tert*-butyl and adamantyl iodides, bromides and chlorides in more than 80% yields. It is noteworthy that the reaction of *tert*-alkyl halides with metal phenyl selenoates could not be accomplished even under harsh reaction conditions [136]. Although lanthanum metal-assisted reaction of PhSeSePh with ^{t}BuI in the presence of a catalytic amount of iodine did not form *tert*-alkyl phenyl selenide, this indium metal-assisted reaction of PhSeSePh with various tertiary alkyl halides could interestingly be prepared the products in high yields (entries 1-6). It was interesting that the reaction with sterically bridged halide, 1-haloadamantanes, also proceeded without any difficulties (entries 4-6). In addition, benzyl phenyl selenides were also formed from benzyl bromide and chloride in high yields (entries 7 and 10). With substituent groups on benzyl bromides, the positions of bromo groups on *ortho*- and *para*-positions did not decrease the yield of their products. Therefore, entries 8 and 9, *p*- and *o*-bromobenzyl phenyl selenides afforded in excellent yield, 85 and 95% isolated yields, respectively. Thus, the position of electron withdrawing group such as bromo unaffected to the occurrence of the corresponding selenides. However, *p*-methoxybenzyl chloride was converted into *p*-methoxybenzyl phenyl selenide in moderate yield (entry 11). (1-Chloroethyl)benzene generated phenyl(1-phenyl ethyl)selenide in 59% yield (entry 12). Benzoyl chloride giving benzoyl phenyl selenide in moderate yield (entry 13) whereas acetyl chloride afforded acetyl phenyl selenide in low yield (entry 14). These implied that the low yield of acyl phenyl selenides stemmed from the unsuitable reaction conditions or ratios of substrate and reagents. Therefore, the variation of ratios of substrate, benzoyl chloride, and reagents was examined as *vide infra*.

Allyl halides could also be transformed into allyl phenyl selenide (entries 15 and 16). Cinnamyl bromide was converted to cinnamyl phenyl selenide only in 32% isolated yield along with the by-product from rearrangement of radical intermediate (entry 17). Consideration of substitution in allylic and benzylic compounds, unsubstituted allylic (entries 15 and 16) and benzylic halides (entries 7 and 10) selectively reacted and more reactive than substituted allylic halides (entry 17) in radical reaction. It is worth to note that substituted allylic compounds, cinnamyl bromide, of the type RCH=CH-CH_2X gave a mixture of two monoselenide products because the substituted allylic radical could react at each of two carbon atoms in radical intermediates.



On the other hand, in the case of benzylic halides, only one major product was obtained because the possible isomer, being non-aromatic, was of much higher energy-content.



In contrast to tertiary alkyl and benzyl halides, primary and secondary alkyl and aryl halides remained inactive under the reaction conditions (entries 18-25). Due to the alkyl radical as intermediate in the proposed reaction pathway in Scheme 3.3, tertiary alkyl, benzylic and allylic radicals were more stable than secondary and primary alkyl radicals. From Table 3.6, it could be concluded that the consecutive order of reactivity of alkyl halides was *tert*-alkyl, allyl, benzyl > benzoyl >> secondary and primary alkyl halides. Moreover, in this newly developed system, several functional groups such as C=C, C=O and OMe remained unaffected.

All of synthesized alkyl phenyl selenides were well-characterized their structures by ^{1}H- and ^{13}C-NMR spectroscopy. An example of ^{1}H- and ^{13}C-NMR spectra of adamantyl phenyl selenide are presented in Figures 3.2 and 3.3, respectively.

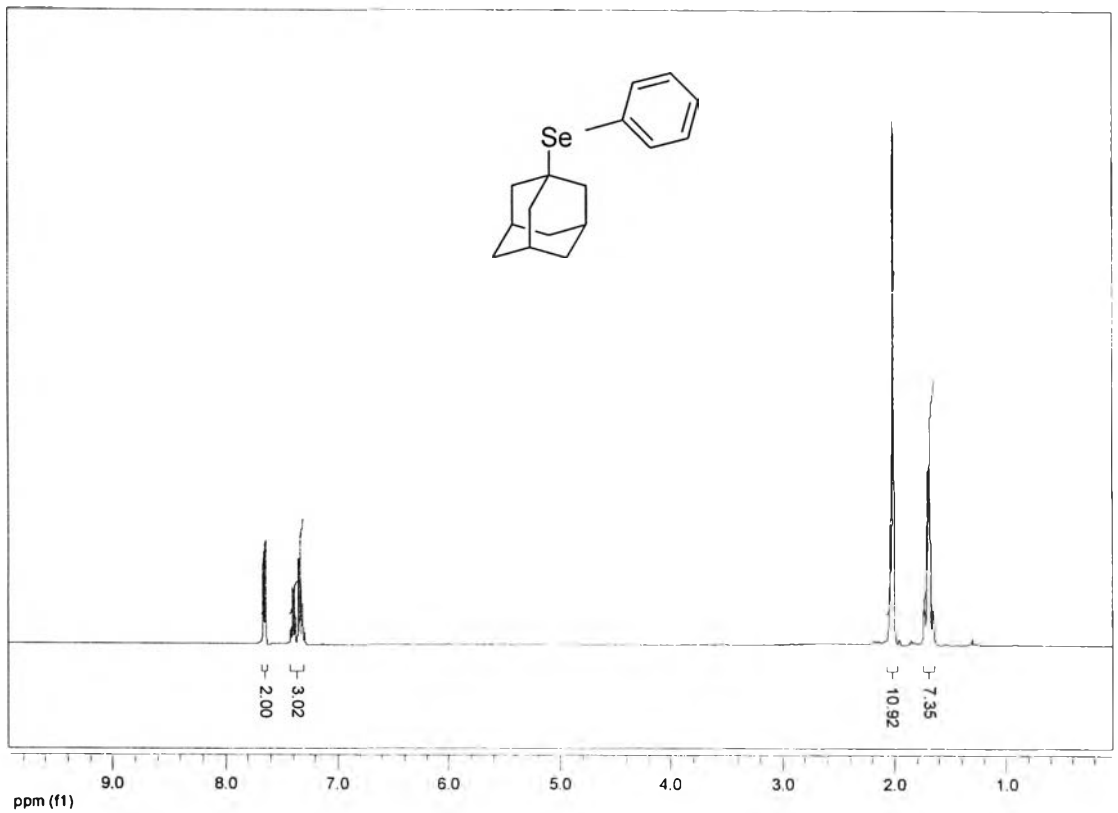


Figure 3.2 The ^{1}H-NMR spectrum of adamantyl phenyl selenide

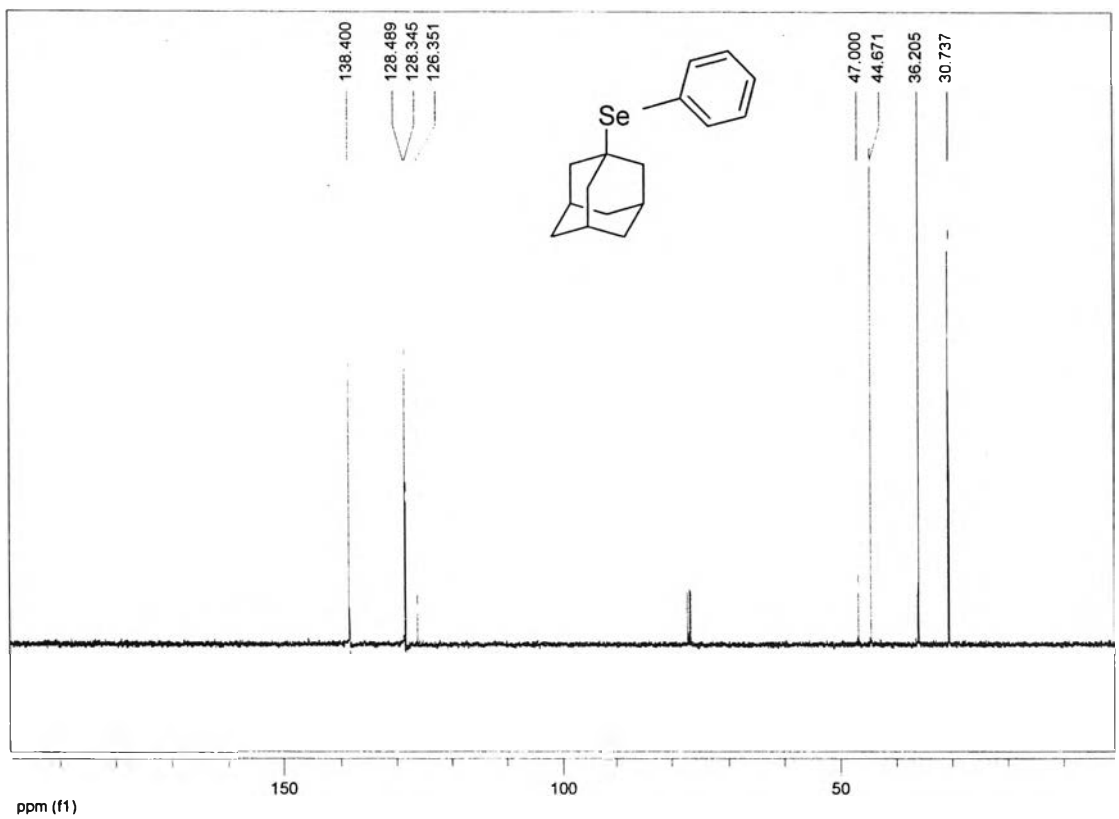


Figure 3.3 The ^{13}C-NMR spectrum of adamantyl phenyl selenide

The ^{1}H-NMR spectrum of adamantyl phenyl selenide (Figure 3.2) revealed two groups of signals commonly assigned as alkyl and aromatic protons. Obviously, the peak at δ_H 2.10 was easily assigned as methylene and methine protons which higher than the same protons of its starting material (at δ_H 2.60). The ^{13}C-NMR spectrum correctly exhibited eight signals which were ten carbons of adamantyl group and six carbons of benzene ring as shown in Figure 3.3.

Another example of ^{1}H- and ^{13}C-NMR spectra of allyl phenyl selenide are presented in Figures 3.4 and 3.5, respectively. The significant peaks in Figures 3.4 were assigned as doublet of methylene group at δ_H 3.53 (J = 7.30 Hz) and two signals of olefin protons. Two protons of external double bond showing as doublet of doublet at δ_H 4.95 was first coupled with its vicinal protons (J = 10.50 Hz) and secondly with its vinylic proton (J = 16.12 Hz). One inner methine proton appeared multiplet peak at δ_H 5.90 coupling with its olefinic and allylic protons. Lastly, the aromatic protons showed multiplet signals in the period of δ_H 7.22-7.55.

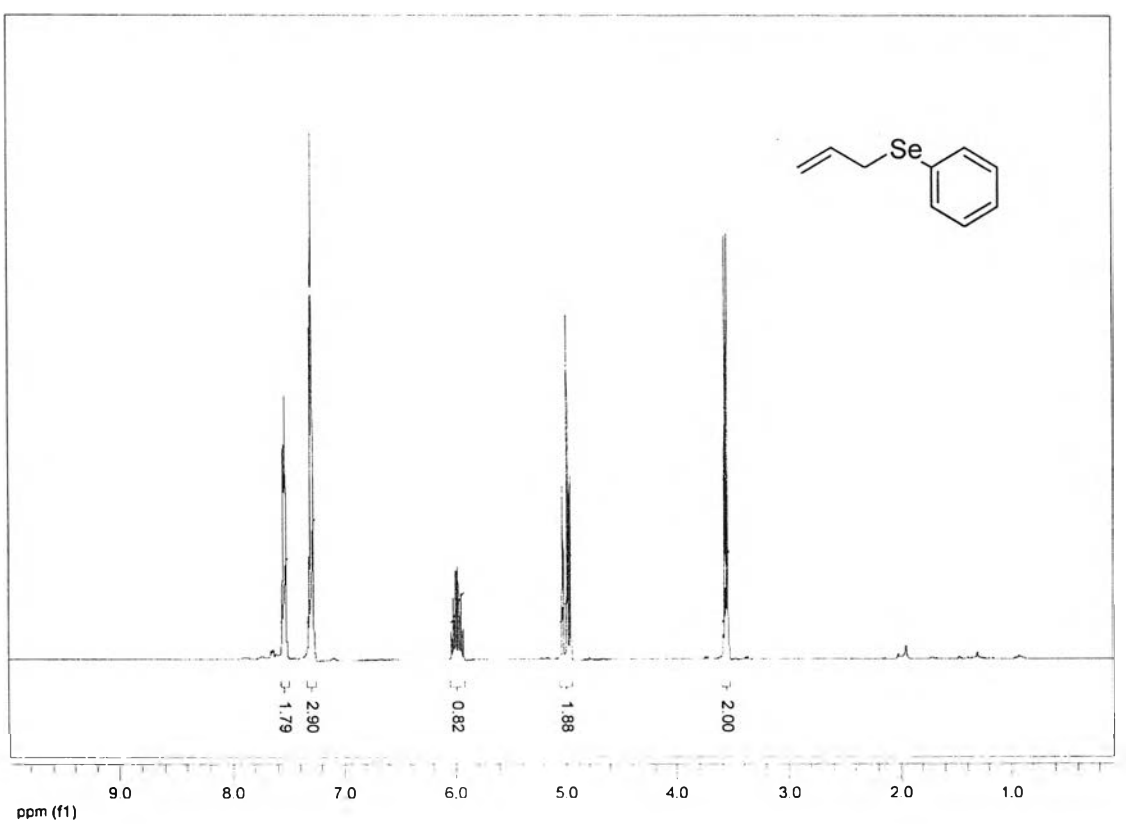


Figure 3.4 The ^{1}H-NMR spectrum of allyl phenyl selenide

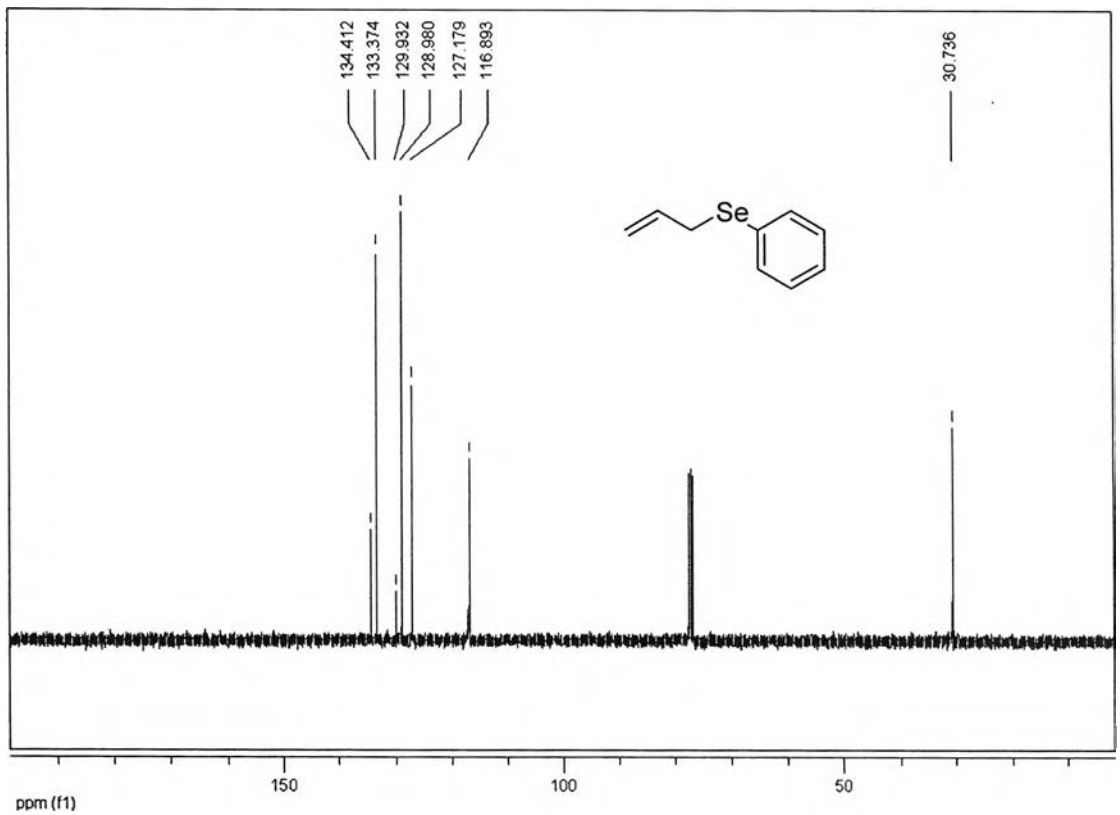
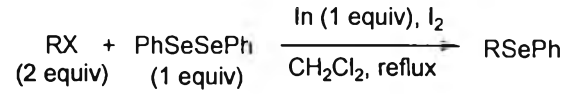


Figure 3.5 The ^{13}C-NMR spectrum of allyl phenyl selenide

The ^{13}C-NMR spectrum of allyl phenyl selenide (Figure 3.5) also revealed identity pattern to that of its structure. The allylic carbon was first showed at δ_C 30.7. The chemical shift at 110.9 was ascribed for methine of external olefinic carbon while internal olefinic carbon was shift to at δ_C 127.2. The four remaining signals were that of six carbons on aromatic ring.

It was interestingly that there were many reports that the reactions using metal were promoted by the addition of iodine [138,175]. Using above optimal conditions were not successful for primary and secondary alkyl halides *vide supra* (entries 18-25 in Table 3.6). On the other hand, the reactions were efficiently accomplished by the addition of a catalytic amount of iodine as the results presented in Table 3.7.

Table 3.7 Synthesis of primary and secondary alkyl phenyl selenides adding catalytic amount of iodine



Entry	RX	Amount of iodine (equiv)	Time (h)	Yield (%)[a]
1	^{i}PrI	0.0	3	trace
		0.2	1	98 (70)
2	Cyclohexyl bromide	0.0	3	trace
		0.2	3	trace
		0.5	4	90 (82)
3	Borneyl iodide	0.2	2.5	96 (81)
4	Cholesteryl chloride	0.5	8	32
5	2-Chloroadamantane	0.5	7	trace
6	(Bromomethyl)cyclohexane	0.0	3	trace
		0.2	3	trace
		0.5	4	40
7	Hexyl bromide	0.0	3	trace
		0.2	3	trace
		0.5	7	85 (74)
8	Hexyl iodide	0.2	4	41
		0.5	4	96 (88)
9	Dodecyl bromide	0.2	7	quant. (85)
10	Dodecyl iodide	0.2	1	47
		0.2	3	quant. (78)
11	Phenyl ethyl chloride	0.0	4	-
		0.5	7	-
12	Octadecyl chloride	0.0	4	-
		0.5	7	-
13	Acetyl chloride	0.2	1	25

[a] Analyzed by GC based on RX (1 mmol). The yields are isolated yields in parenthesis.

Generally, ^{t}BuCl (2 equiv) reacted with PhSeSePh (1 equiv) in the presence of indium (1 equiv) and necessarily added iodine as catalyst (0.2 or 0.5 equiv) in CH_2Cl_2 at reflux to obtain the corresponding selenides. Depend on adding the catalytic amount of iodine, high reactivity could be observed under these conditions (entries 1-10) except for primary and secondary alkyl selenides from primary and secondary alkyl chlorides. From the results in entries 1 and 3, it appeared that secondary alkyl iodides, isopropyl and borneyl iodides, easily formed the corresponding selenides in excellent yields using only 0.2 equiv of iodine for 1 and 2.5 h, respectively. Especially isopropyl phenyl selenides formed in 98% yield within 1 h whereas another procedure cited using lanthanum metal and iodine which was slow reaction with secondary alkyl halides. Using lanthanum metal-assisted reaction, secondary alkyl selenides were generated by elevation of the reaction temperature to 110°C and extension of the reaction time to 13 h [138]. Focusing on secondary alkyl bromides and chlorides, cyclohexyl bromide in the presence of 0.5 equiv of iodine was converted into cyclohexyl phenyl selenide in 90% yield within 4 h (entry 2). However, using 0.5 equiv of iodine with secondary alkyl chlorides, cholesteryl chloride and 2-chloroadamantane furnished the corresponding selenides only 32% isolated yield and trace amount, respectively (entries 4 and 5).

Compared with secondary alkyl iodides, most of primary alkyl iodides and bromides needed more of iodine than 0.5 equiv or multiply the reaction time more than 3 h (entries 6-10). All results showed high reactivity except (bromomethyl)cyclohexane illustrating moderate reactivity in 40% yield of product (entry 6). Basically, alkyl iodide was more reactive than alkyl bromide. For example, both of hexyl and dodecyl iodides were more reactive than hexyl and dodecyl bromides and would converted into the corresponding products in excellent yields. It was easy to notice that the iodides reacted completely within 3 or 4 h (entries 8 and 10) while the bromides required longer time, 7 h (entries 7 and 9). Furthermore, the results exhibited that dodecyl phenyl selenides could be prepared by employing only 0.2 equiv of iodine less than that consumed in hexyl phenyl selenides (0.2 equiv of iodine). The last two primary alkyl chlorides did not give alkyl phenyl selenide even with 0.5 equiv of iodine (entries 11 and 12). In other words, primary alkyl chlorides were not reactive under the reaction condition.

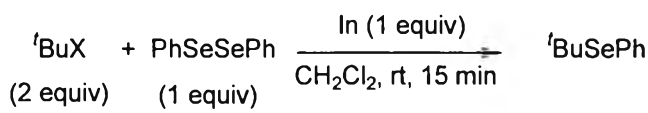
In conclusion adding iodine under the reaction conditions enhanced the rate of reaction; it might be assumed that iodine assisted to produce surface-cleaned indium.

The plausible mechanism was the same as that of tertiary alkyl selenide *via* radical pathway. These applied reactions appending iodine 0.2 equiv (10% mol) or 0.5 equiv (25% mol), the primary and secondary alkyl phenyl selenides could be obtained in high yields with the exception of primary or secondary alkyl chlorides. Therefore, for this novel applied indium method, the reactivity of substrates was arranged in a series as secondary iodides > secondary bromides = primary iodides > primary bromides >> secondary and primary chlorides.

3.2.4 Competitive ability of alkyl halides

A competitive reaction of halides as chloride, bromide and iodide was intentionally screened in order to evaluate their relative reactivity. The competitive results were shown in Table 3.8.

Table 3.8 Competitive reactions of *tert*-butyl halides for evaluated their relative reactivity



Entry	X	Equivalent (eq)	Remained substrates, X (%)	Yield (%)[a]	Mass balance (%)[a]
1	I (15 min)	2	I (5%)	96[b]	101[b]
2	I (30 min)	2	I (0%)	quant.[b]	quant.[b]
3	I	4	I (50%)	50	100
4	Cl I	2 2	Cl (39%) I (6%)	51	96
5	Cl Br	2 2	Cl (43%) Br (12%)	40	95
6	Br I	2 2	Br (39%) I (15%)	48	102
7	Cl Br I	2 2 2	Cl (33%) Br (28%) I (9%)	33[c]	103[c]

[a] Analyzed by GC based on RX (4 eq, 2 mmol)
[b] Analyzed by GC based on RX (2 eq, 1 mmol)
[c] Analyzed by GC based on RX (6 eq, 3 mmol)

As mentioned in entry 1 of Table 3.3, ^{t}BuCl previously underwent by this procedure at ambient temperature, stirred for 15 minutes, giving only trace amount of *tert*-butyl phenylselenide while ^{t}BuI was transformed into the product in 96% and quantitative yield within 15 and 30 minutes, respectively (entries 1 and 2 in Table 3.9). From GC chromatogram using the old GC oven temperature condition, ^{t}BuI peak could be separated from solvent peak while ^{t}BuCl peak included in solvent peak. Changing to newly GC condition to 60°C (initial temperature), 4 min (initial time), 7°C/min (rate), 220°C (final temperature) and 6 min (final time), ^{t}BuCl peak could then be detected.

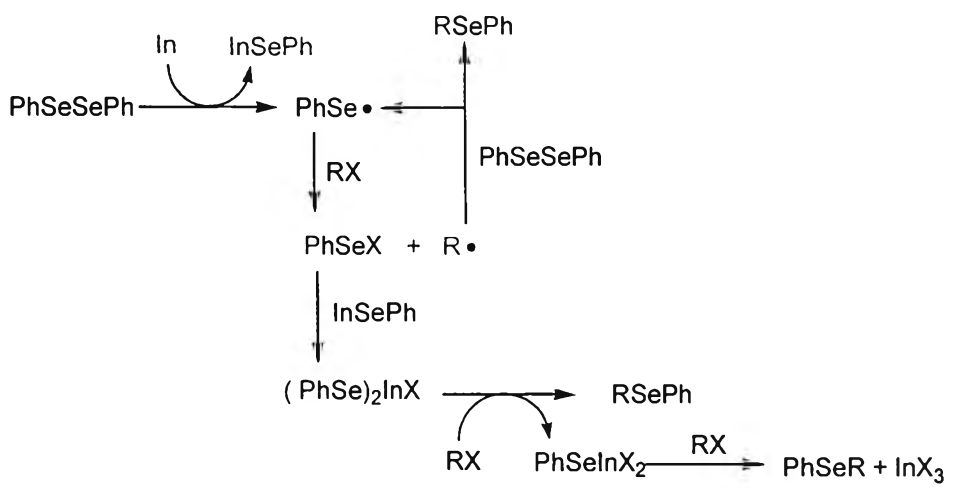
Starting with enhancing the amount of ^{t}BuI to 4 equiv reacting with 1 equiv of PhSeSePh in the presence of indium (1 equiv) at room temperature for 15 min afforded the product in 50% yield based on ^{t}BuI (4 equiv, 2 mmol) with remained ^{t}BuI 50% (entry 3). Because of the excess amount of substrate, it was rationalized that ^{t}BuI was converted into ^{t}BuSePh in quantative yield (1 mmol) and the remained ^{t}BuI in half of starting ^{t}BuI (1 mmol) was detected with acceptable, total mass balance (95-105%). A set of mixture of *tert*-butyl halides was treated with indium metal in CH_2Cl_2 at reflux for 15 min, and analyzed the remaining *tert*-butyl halides. As the results in Table 3.8, the ratio of remaining *tert*-butyl halides as Cl:I, Cl:Br, Br:I, and Cl:Br:I was 6.5:1, 3.6:1, 2.6:1, and 3.7:3.1:1, respectively. Therefore, the relative reactivity of halides could be ordered and followed the sequence: I > Br > Cl. The obtained outcome is consistented with the order of the reactivity of halides under radical reaction conditions. On the basis of these findings, it might be assumed that there was a possibility of not only involving metal selenoates as suggested for the reaction using La or Zn, but also radical intermediates [136,142]. The possible mechanism was proposed *via* radical as *vide infra* in Scheme 3.3.

3.2.5 Plausible mechanism

The reaction of *tert*-alkyl halides with lanthanum phenyl selenoates could not be achieved even under harsh reaction conditions [136]. However, this indium metal-assisted reaction of PhSeSePh with various tertiary alkyl halides prepared the corresponding selenides in high yields (Table 3.6). In addition, the relative reactivity of halides was followed the sequence: I > Br > Cl and the order of halides corresponded to the reactivity under radical reaction conditions. Furthermore, there have been many reports that indium metal was easy to promote SET (single electron

transfer) and resulted in generating alkyl radicals from alkyl halides, and were added to electron-deficient carbon–carbon double bonds [156,159,163,174]. Based on all of these reasons, it might be assumed that there was a possibility of mechanism suggested *via* radical pathway.

The reaction pathway for the formation of alkyl phenyl selenides were proposed and illustrated in Scheme 3.3 [176-177]. Indium metal reduced diphenyl diselenide to generate phenyl selenide radical and then the S_H2 reaction of phenyl selenide radicals with alkyl halide formed alkyl radical and halophenyl selenides which generated $(PhSe)_2InX$ species. The alkyl radical reacted with diphenyl diselenide changed to alkyl phenyl selenide. The PhSeIn species that was generated during the reaction reacted with $(PhSe)_2InX$ species and another alkyl halide to give the another corresponding alkyl phenyl selenides.



Scheme 3.3 Mechanistic pathway for conversion of organic halides

In conclusion, a mild and efficient one-pot method for the synthesis of alkyl phenyl selenides by indium-mediated reaction of diphenyl diselenide with organic halides, which showed the selectivity for *tert*-alkyl, benzylic, and allylic halides over primary and secondary alkyl halides was developed. This novel method had some advantages including a simple experimental procedure, the neutral reaction conditions, high yields of the desired products, and low toxicity.

Moreover, the advantages of this optimized condition could be compared with:

- Conditions: La, THF, 67°C, 5h; in the presence of In using lower temperature and shorter reaction times, higher yields for allyl and benzoyl halides and possible to prepare from various alkyl halides, especially tertiary alkyl halides.

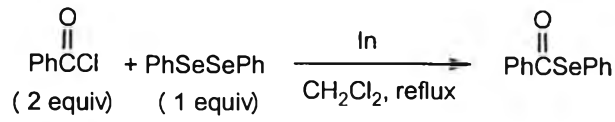
- Conditions: InI, CH_2Cl_2, rt; in the presence of In was specific to prepare tertiary alkyl, allyl and benzyl phenyl selenides over primary and secondary phenyl selenides, which could be synthesized by adding a catalytic amount of iodine. In the case of indium reaction, the amount of indium could be reduced from 1 to 0.5 eq, or less than a stoichiometric amount. In addition, In was less expensive than InI, therefore, it could be save cost to synthesize the selenides.

Part II: Synthesis of alkyl and acyl phenyl chalcogenides

3.2.6 Synthesis of acyl phenyl selenides

The one-step procedure using lanthanum metal and iodine demonstrated low yield of benzoyl phenyl selenide (43% analyzed by GC) and treated with only benzoyl chloride (no other acid chloride has been addressed) [136]. This indium-mediated reaction of PhSeSePh proceeded not only with benzoyl chloride but also with various acid chlorides in the presence of In. Although benzoyl and acetyl chlorides were not completely converted to benzoyl and acetyl phenyl selenides (entries 13-14 in Table 3.6), they were achieved by the elevation of amount of indium from 1 to 1.5 equivalent. Treatment of benzoyl chloride (2 equiv) with PhSeSePh (1 equiv) in CH_2Cl_2 at reflux with varying the amount of indium and reaction time yielded benzoyl phenyl selenide in moderate to excellent yields. The results are presented in Table 3.9.

Table 3.9 Optimal conditions for the preparation of benzoyl phenyl selenide from benzoyl chloride



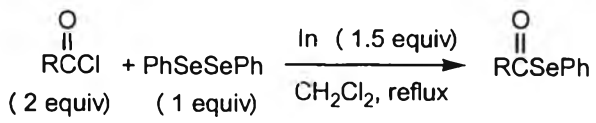
entry	In (equiv)	Time (h)	Yield (%)
1	1	1	60 (78)
2	1	1	50 (60)[a]
3	1	2	62
4	1.5	1	78
5	1.5	2	92
6	2	2	75

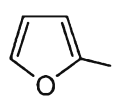
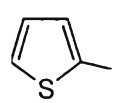
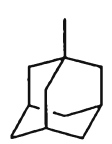
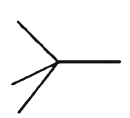
[a]0.2 equiv of I_2 was added. The yields are GC yields based on RX (1 mmol) in parenthesis.

Employing an equivalent of indium for 1 h furnished the selenide in only 60% yield (entry 1). The addition of a catalytic amount of iodine or increment of reaction time to 2 h also achieved the product in moderate yield (entries 2-3). In the presence of indium (1.5 equiv) was resulted in completed preparation of benzoyl phenyl selenide easily observed in large increasing yields from 60% (entry 1) to 78% and 92% isolated yields within 1 and 2 h, respectively (entries 4 and 5). However, too excess amount of indium (2 equiv) brought about small decreasing yield (entry 6). Consequently, the suitable condition for the preparation of benzoyl phenyl selenide from benzoyl chloride (2 equiv) was treating with PhSeSePh (1 equiv) in the presence of indium (2 equiv) in CH_2Cl_2 at reflux. This procedure could be adapted to prepare other acyl phenyl selenides from various acyl chlorides.

A wide range of structural diversed acid chlorides (2 equiv) underwent reaction with diphenyl diselenide (1 equiv) and indium (1.5 equiv) under the optimal conditions to produce the corresponding acyl phenyl selenides in low to very high yields depending on their structures. The results are summarized in Table 3.10.

Table 3.10 Synthesis of acyl phenyl selenides from various acid chlorides



entry	R	Time (h)	Yield (%)[a]
1	Me	2	50
2	Ph	2	92
3	(*p*-OMe)C_6H_4	1.5	80
4	(*p*-Br)C_6H_4	1.5	88
5	(*p*-NO_2)C_6H_4	24[b]	20
6	(*m*-NO_2)C_6H_4	24[b]	10
7	C_6H_{11}	3	62
8		1.5	55
9		1.5	90
10		2	59
11		1.5	65
		4	68
12	$(CH_3)_2CH$	2	92
13	$CH_3(CH_2)_2$	1.5	80
14	$CH_3(CH_2)_7CH{=}CH(CH_2)_7$	3	16

[a] isolated yields based on RX (1 mmol). [b] The reaction was carried out at reflux for 5 h and then at room temperature until 24 h.

In sprite of low yield of acetyl phenyl selenide (25% GC yield, entry 14 in Table 3.6), by this procedure it could be prepared in 50% isolated yield (entry 1). Interestingly, *p*-methoxy and *p*-bromobenzoyl phenyl selenides were obtained in high yields as much as that in the case of benzoyl phenyl selenide (entries 2-4).

Consideration of the effect of substituents, acid chlorides containing methoxy and bromo groups at *para* position of benzene ring reacted faster (1.5 h) and took less time than these having nitro group (24 h). Both *p*- and *m*-nitrobenzoyl phenyl selenides gave very low yields even though they were allowed to react longer time (24 h, entries 5 and 6). Cyclohexylcarbonyl chloride were converted into its analogous selenide in 62% yield (entry 7), while 2-furoyl phenyl selenide was formed in moderate yield, 2-thiophenecarbonyl phenyl selenide was formed in excellent yield (entries 8 and 9). In addition, 1-adamantanecarbonyl chloride also formed its selenide in moderate yield (entry 10). Trimethyl acetyl phenyl selenide or α,α-dimethyl-substituted acetyl chloride afforded the corresponding acyl phenyl selenides in 65% and 68% yield within 1.5 and 4 h, respectively (entry 11). The yield of this product was slightly same as the results of Nishiyama's group using phenyl tributylstannyl selenide ($PhSeSnBu_3$) [178]. In contrast to trimethyl acetyl chloride, buturyl and isobutyryl chlorides were converted to the corresponding acyl selenides in high yields (entries 12 and 13). However, in the case of oleoyl chloride, under these conditions long-chain alkyl group of acyl chloride showed low reactivity (entry 14).

In summary, the reactivity of the substrates for transformation of acyl chlorides (RCOCl) to the corresponding acyl phenyl selenides under these conditions could be placed in a row as R; Ph, *p*-$OMeC_6H_4$, *p*-BrC_6H_4, thiophene, ^{i}Pr, ^{n}Pr > Me, cyclohexyl, furan, adamantane, ^{t}Bu >> *p*-$NO_2C_6H_4$, *m*-$NO_2C_6H_4$, $CH_3(CH_2)_7CH{=}CH(CH_2)_7$, respectively. Furthermore, several functional groups such as OMe, Br, NO_2, C=O and C=C remained unaffected under the reaction conditions. Finally, the reaction mechanism for the formation of acyl phenyl selenides was proposed which was similar to the reaction pathway of alkyl phenyl selenides (Schemes 3.3 and 3.4). Only different point in the mechanism was that acyl radicals were participated in stead of alkyl radical.

All of synthesized acyl phenyl selenides were well-characterized their structures by ^{1}H- and ^{13}C-NMR spectroscopy. Some examples of ^{1}H- and ^{13}C-NMR spectra of acyl phenyl selenides are presented in Figures 3.6-3.10.

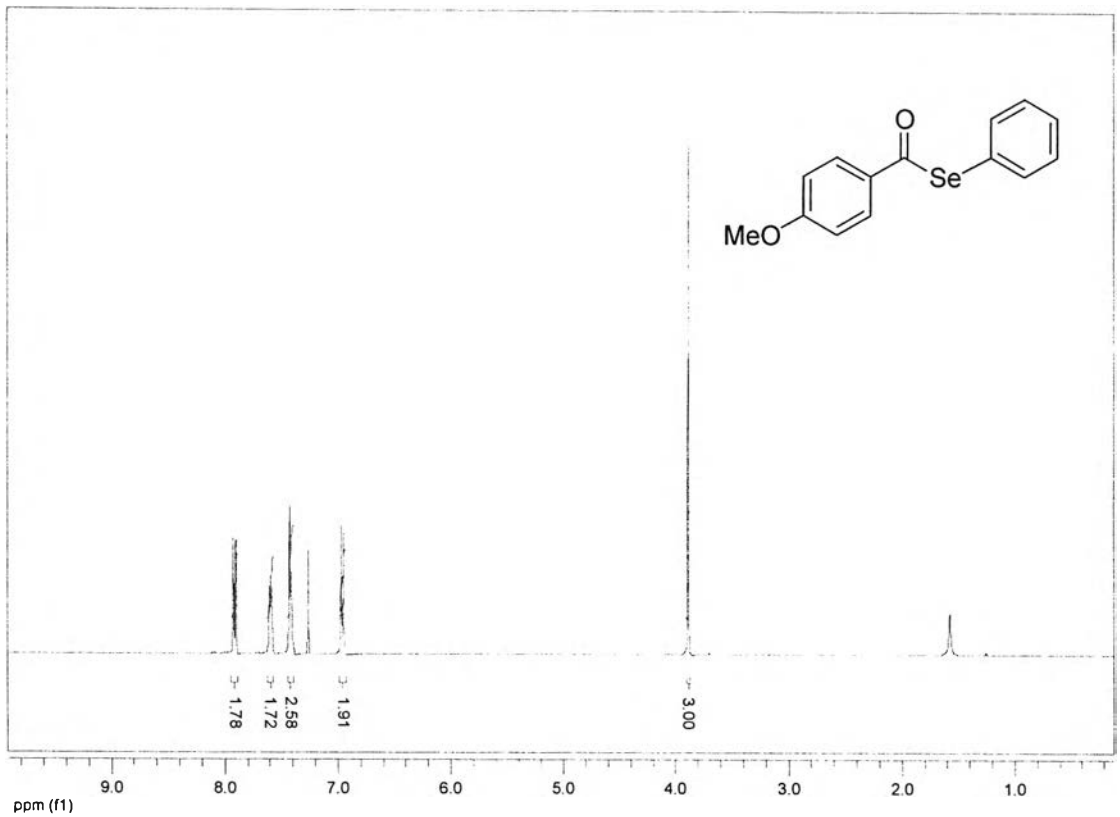


Figure 3.6 The ^{1}H-NMR spectrum of 4-methoxybenzoyl phenyl selenide

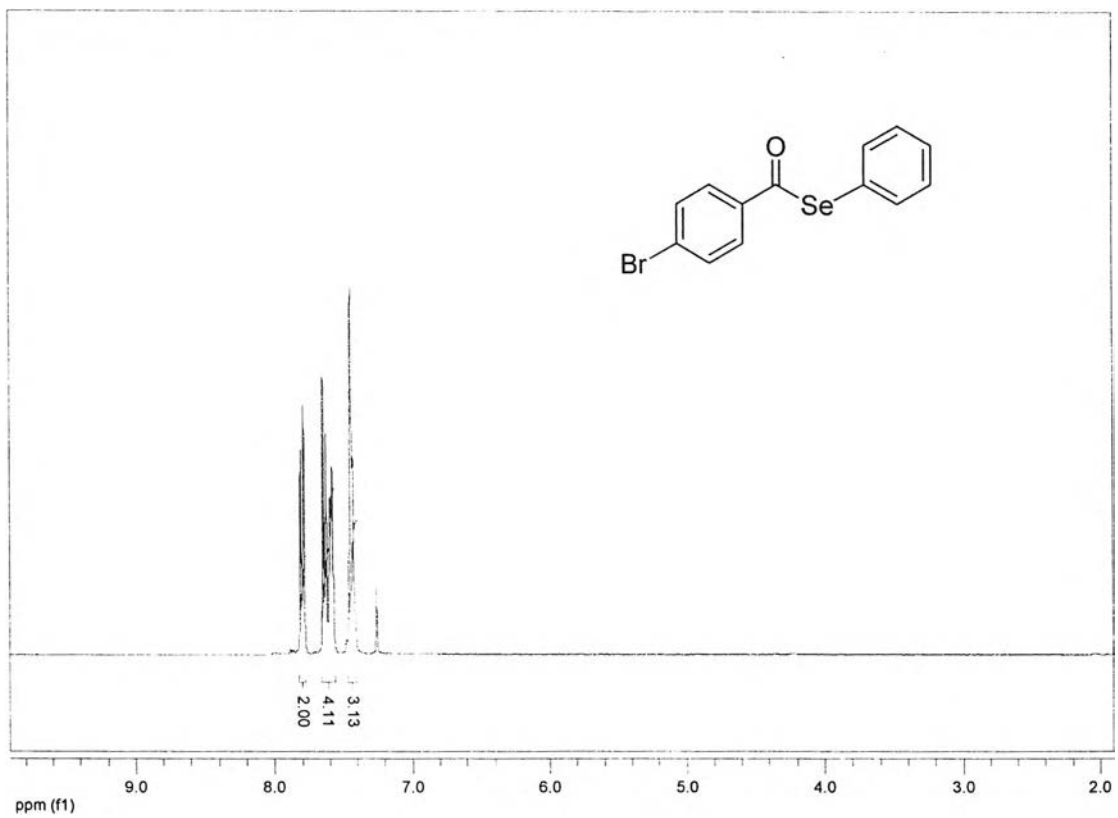


Figure 3.7 The ^{1}H-NMR spectrum of 4-bromobenzoyl phenyl selenide

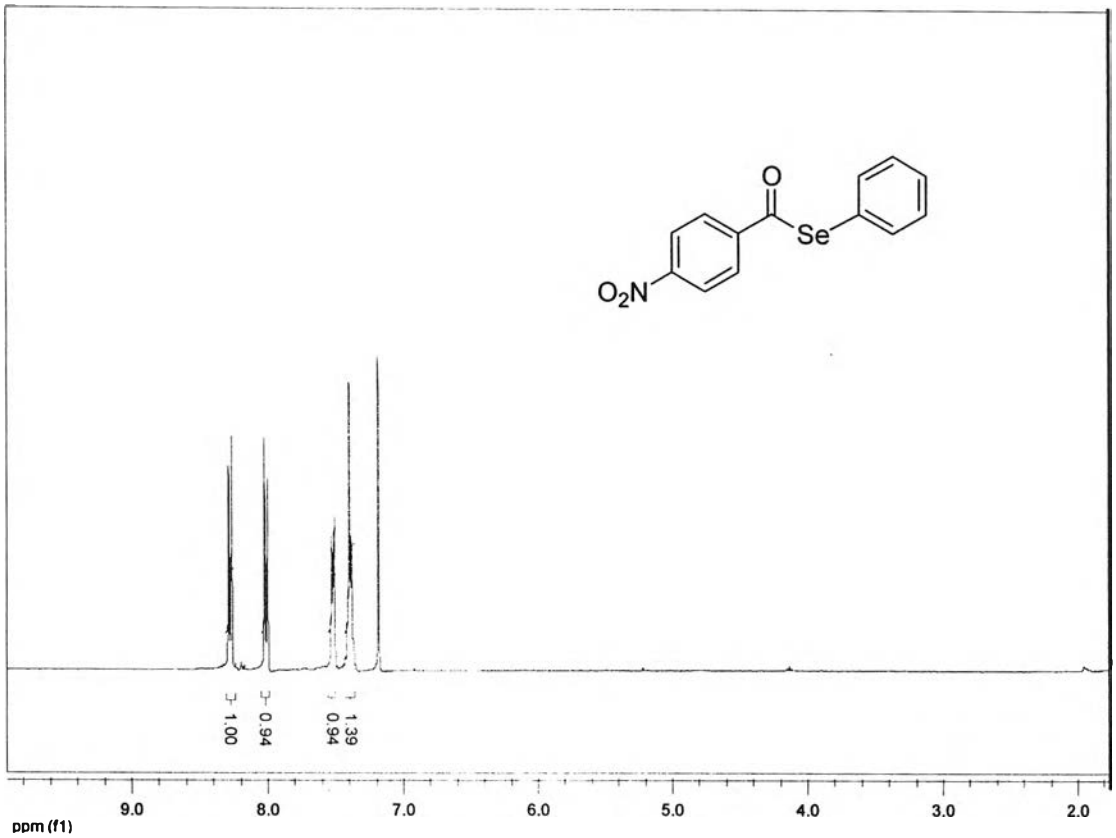


Figure 3.8 The ^{1}H-NMR spectrum of 4-nitrobenzoyl phenyl selenide

The ^{1}H-NMR spectra of isolated *para*-substituted benzoyl phenyl selenides (*p*-Br, *p*-NO_2, *p*-OMe) revealed the corrected proton patterns as that of their structures (Figure 3.6-3.8). To illustrate this, their ^{1}H-NMR patterns looked like each other having two groups of aromatic proton signals: *para*-aromatic and aromatic protons connecting to selenide atom. Two doublet signals of *p*-methoxyphenyl protons showed between phenylselenide protons at δ_H 6.96 and 7.92 (J = 8.96 and 8.80 Hz, respectively). However, *p*-bromophenyl protons showed slightly higher than phenylselenide protons at δ_H 7.63 and 7.81 (J = 8.59 and 8.70 Hz, respectively). In the case of *p*-nitrophenyl protons revealed much higher than phenylselenide protons at δ_H 8.08 and 8.35 (J = 8.79 and 8. 81 Hz, respectively). The distinctly different peak only in *p*-methoxyphenyl selenide was a singlet peak of methoxy at δ_H 3.89.

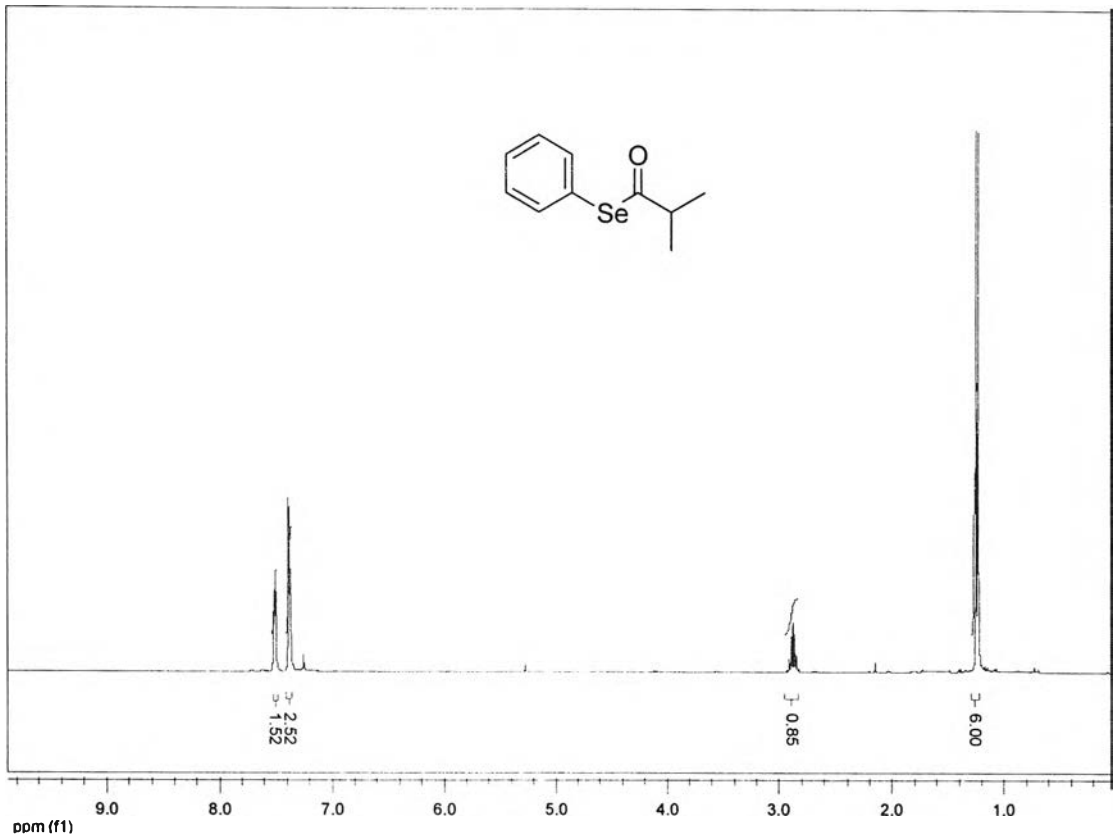


Figure 3.9 The ^{1}H-NMR spectrum of isobutyryl phenyl selenide

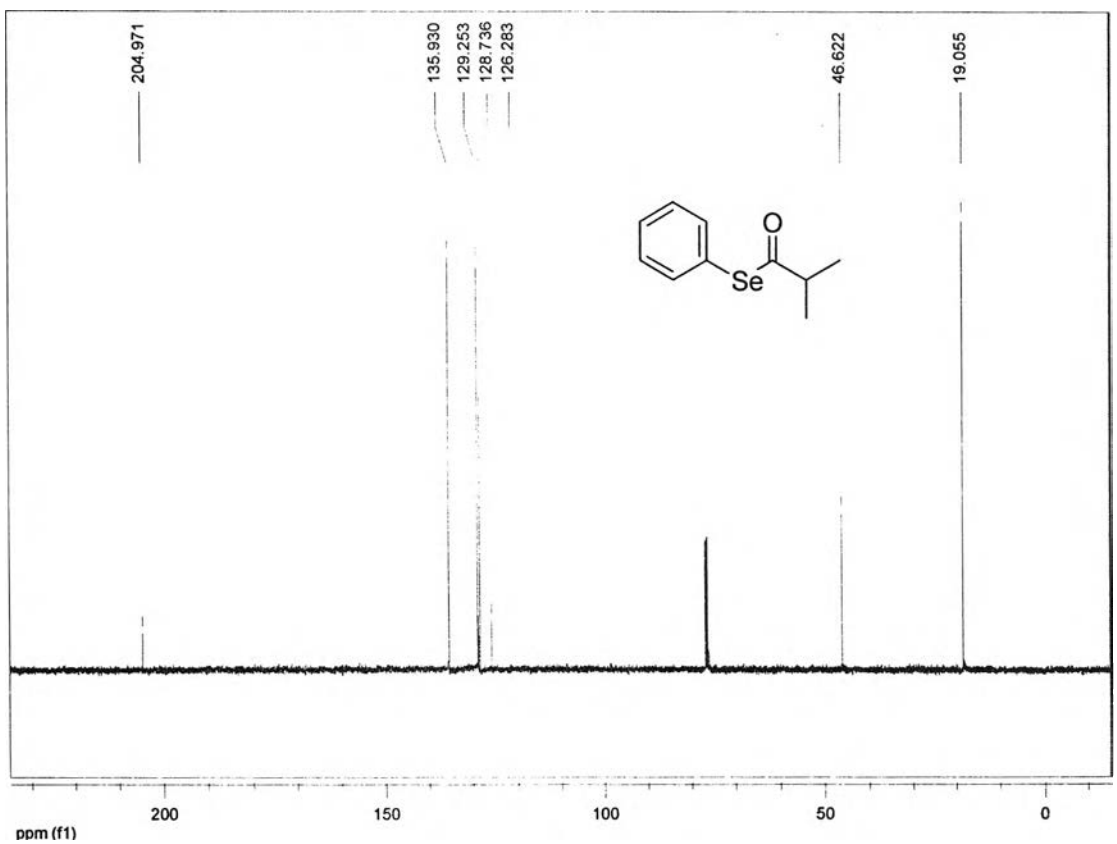


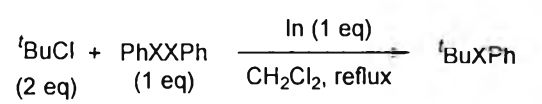
Figure 3.10 The ^{13}C -NMR spectrum of isobutyryl phenyl selenide

One of examples of acyl phenyl selenides was isobutyryl phenyl selenide which also confirmed its identity by ^{1}H- and ^{13}C-NMR spectroscopic technique. The ^{1}H-NMR spectrum of isolated product is presented in Figure 3.9. Two symmetry methyl groups showed as doublet in the same position at δ_H 1.21 (J = 6.79 Hz). The methine proton connecting with selenide atom revealed as septet at δ_H 2.85 (J = 6.75 Hz) and around at δ_H 7.29-7.52 was assigned as aromatic protons. In Figure 3.10, the ^{13}C-NMR spectrum exhibited a simple pattern of two methyl groups (at δ_C 19.1), a methine carbon (at δ_C 46.6) and four aromatic carbons (around at δ_C 126-135). An importantly functional group as carbonyl carbon showed at δ_C 205.0.

3.2.7 Synthesis of alkyl phenyl sulfides and tellurides

With the optimized reaction conditions in hand, that of unsymmetrical diorganyl chalcogenides could be applicable. Reaction of ^{t}BuCl (2 equiv) with diphenyl diselenide (PhSeSePh), diphenyl disulfide (PhSSPh) or diphenyl ditelluride (PhTeTePh) (1 equiv) in the presence of indium (1 equiv) in CH_2Cl_2 at reflux temperature afforded the *tert*-butyl phenyl chalcogenides in high to excellent yields. The results of their chalcogenides are summarized in Table 3.11.

Table 3.11 Synthesis of *tert*-butyl phenyl chalcogenides varying type of reagents under optimal conditions



Reagent (PhXXPh)	Time (h)	Yield (%)[a]
PhSeSePh	1	95 (86)
PhSSPh	1	29
	3	38
	5	80 (72)
	24	55
PhTeTePh	1	quant. (94)

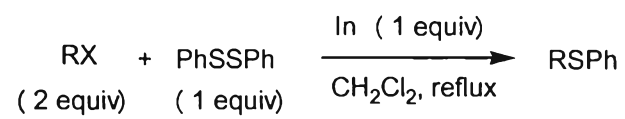
[a] Analzed by GC based on RX (1 mmol).
The yields are isolated yields in parenthesis.

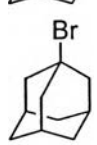
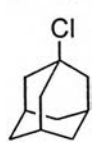
tert-Butyl phenyl selenide and telluride were completely generated in excellent yield within 1 h while *tert*-butyl phenyl sulfide was obtained in low yield.

Extension of reaction time enhanced the yield of sulfide product to 80% yield within 5 h. Keeping in the reaction until 24 h decreased the yield of the sulfide to 55% yield as same as results of selenides in Figure 3.1.

As aforementioned, the preparation of various alkyl phenyl sulfides was then focused on and investigated. Treatment of organyl halides (2 equiv) with PhSSPh (1 equiv) in the presence of indium (1 equiv) in CH_2Cl_2 at reflux temperature gave the corresponding phenyl sulfides in low to high yields. The results are presented in Table 3.12.

Table 3.12 Synthesis of alkyl phenyl sulfides from various alkyl halides



entry	RX	Time (h)	Yield (%)[a]
1	^{t}BuI	1	quant. (89)
2	^{t}BuBr	1	46
		3	96 (85)
3	^{t}BuCl	1	29
		3	(67)[b]
		5	80 (72)
4		3	(80)
5		1 3	48 65 (58)
6		5	trace
7	BnBr	2.5	88 (86)
8	BnCl	3	(80)
9	CH_2=$CHCH_2$I	6	(40)
10	^{i}PrI	8	(10)[b]
11	$CH_3(CH_2)_{11}$I	21	(10)[b]

[a] Analzed by GC based on RX (1 mmol). [b] 0.2 equiv of I_2 was added.
The yields are isolated yields in parenthesis.

Generally, the formation of sulfides took longer time than those of selenides comparing with the same starting material by this reaction procedure. Although ^{t}BuI completely was converted into ^{t}BuSPh within 1 h (entry 1), in the case of ^{t}BuBr and ^{t}BuCl more reaction time over 1 h was needed (entries 2-3). Total amount of ^{t}BuBr was transformed to ^{t}BuSPh in 96% within 3 h whereas ^{t}BuCl was generated the product in 80% yield for 5 h. The reaction with steric halides, 1-iodo and 1-bromoadamantane, also proceeded without any difficulties within 3 h excepted for inactive 1-chloroadamantane (entries 4-6). Circumstance of benzyl halides, entries 7-8, both of benzyl bromide and chloride to benzyl phenyl sulfides in high yield for 2.5 to 3 h consuming reaction time more than its selenides. The transformation of allyl iodide to allyl phenyl sulfide (> 6 h) giving 40% isolated yield was comparatively slower than its selenide (1 h, entry 9). The low yield of primary and secondary alkyl sulfides was parallel to their selenides (entries 10-11).

The arrangement in order of reactivity of alkyl halides for converting to alkyl phenyl sulfides was slightly different from selenides: *tert*-alkyl, benzyl > allyl >> primary and secondary alkyl halides. The fact that some labile functional groups such as C=C were also intact under the reaction condition which was similar to those described in selenide preparation.

As a conclusion, a mild and one-pot synthetic method of organyl phenyl selenides was developed. This simple introducing method could be applied to preparing various organyl phenyl chalcogenides, sulfides and tellurides. Some tertiary alkyl and benzyl phenyl sulfides and tellurides were formed in high yields using the procedure. In addition, the reaction pathway was also suggested *via* radical pathway as same as alkyl phenyl selenide mechanism.

All alkyl phenyl sulfides (entry 1-11) were isolated and then confirmed their identity by ^{1}H- and ^{13}C-NMR spectroscopy. An example as adamantyl phenyl sulfide revealed the ^{1}H- and ^{13}C-NMR patterns as similar as adamantyl phenyl selenide (Figure 3.11-3.12).

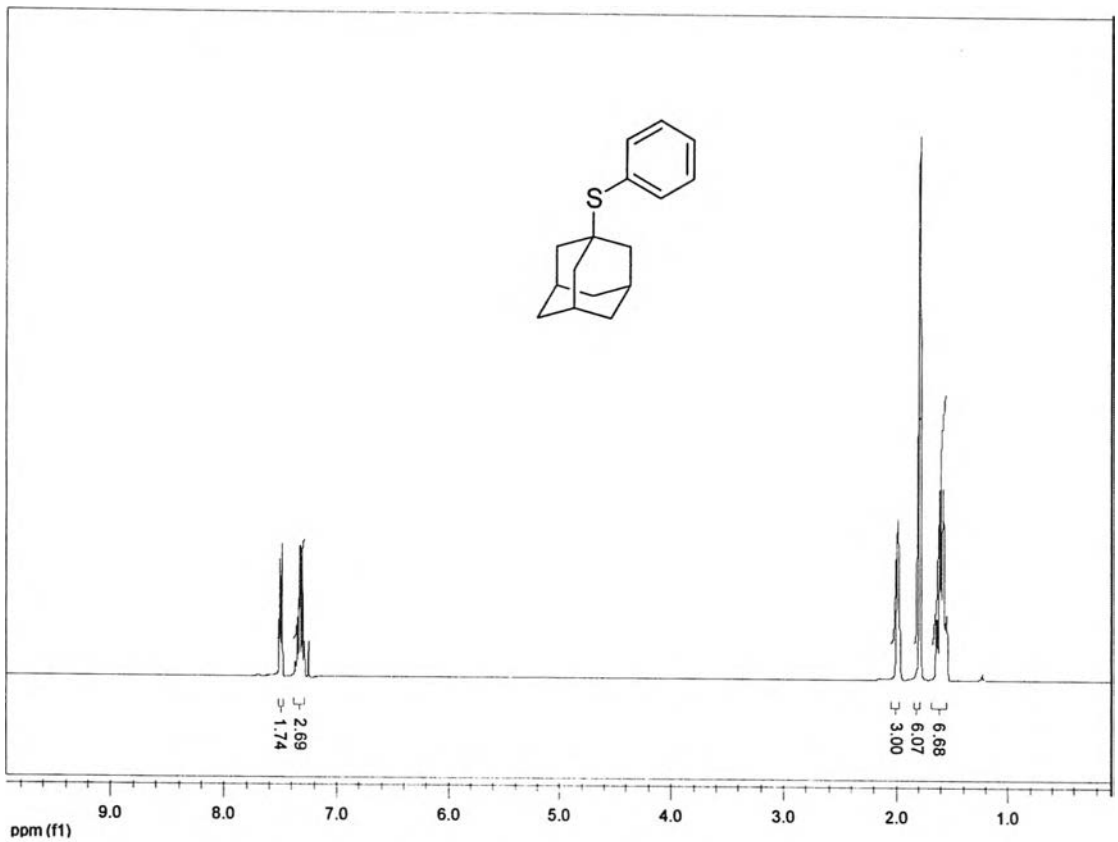


Figure 3.11 The ^{1}H-NMR spectrum of adamantyl phenyl sulfide

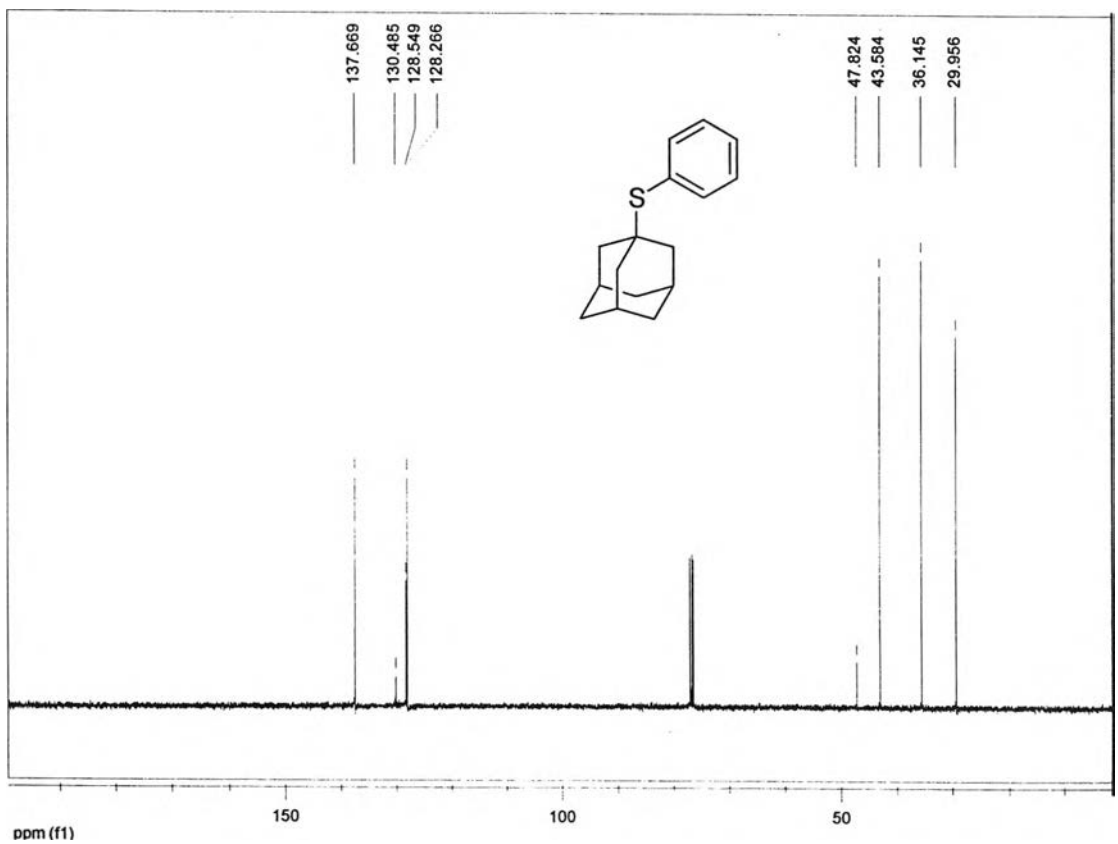


Figure 3.12 The ^{13}C-NMR spectrum of adamantyl phenyl sulfide

Part III: Synthesis of alkyl phenyl selenides from alkyl diphenylphosphinites

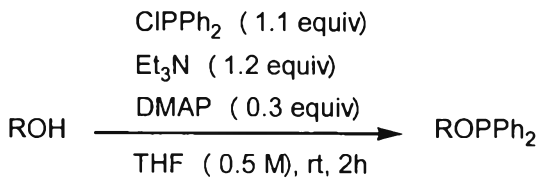
As mentioned above, the important point of this research was that the reaction proceeded under mild and neutral conditions without having any assistance from acids or bases to prepare unsymmetrical diorganyl selenides. On account of synthetic method for alkyl diphenylphosphinites were easily prepared in excellent yield from the corresponding alcohol, chlorodiphenylphosphine ($ClPPh_2$), triethylamine (Et_3N) as base and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) [179]. These last conditions were obviously milder than those of the previously reported procedure of phosphinites using a strong base as *n*-BuLi [180-181]. There have been many reports, especially from Mukaiyama's research group, about these phosphinites as key intermediates for the oxidation-reduction condensation to prepare various organic compounds such as isocyanides, diorganyl sulfides, esters and ethers, *etc.* [179-187] Especially alkyl aryl sulfides were reported and smoothly prepared from less hindered primary and secondary alcohol *via* alkyl diphenylphosphinites in condensation reaction. However, for the occurrence of steric secondary and *tert*-alkyl aryl sulfides were necessary added 2,6-dimethyl-1,4-benzoquinone (DMBQ) in their reaction systems [182].

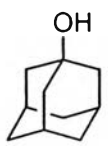
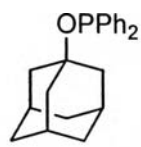
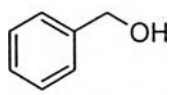
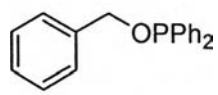
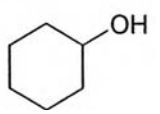
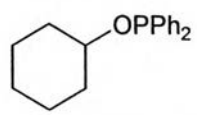
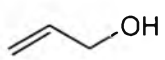
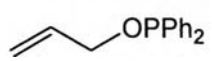
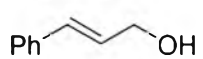
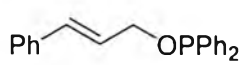
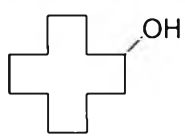
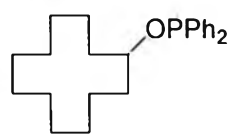
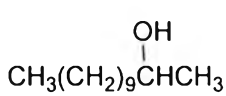
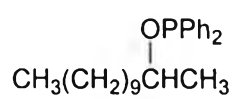
It was notwithstanding that, until now, there was no report optimizing a methodology for the development of unsymmetrical diorganyl selenides *via* these phosphinites. The preparation of these selenides has been regarded as a challenging topic in current organic synthesis, however, only a few successful examples as *tert*-alkyl phenyl selenides, were reported. For this reason, a novel and one-pot method for the preparation of alkyl phenyl selenides *via* alkyl diphenylphosphinites instead of organic halides was established.

3.2.8 Synthesis of alkyl diphenylphosphinites

Selected diphenylphosphinites were easily prepared in excellent yields from the corresponding alcohols (1.0 equiv) and $ClPPh_2$ (1.1 equiv) in the presence of Et_3N (1.2 equiv), and a catalytic amount of DMAP (0.3 equiv) [179]. All the reactions were completed within 2 h at room temperature and purified by filtration through a pad of alumina and celite using an eluent of hexane/ethyl acetate (v/v = 9/1). Eight diversely structural phosphinites were prepared and characterized as shown in Table 3.13.

Table 3.13 Synthesis of alkyl diphenylphosphinites from various alcohols



entry	ROH	$ROPPh_2$	Yield (%)
1	^tBuOH	$^tBuOPPh_2$	92
2			96
3			80
4			90
5			quant.
6			93
7			87
8			89

It was obviously that all phosphinites occurred in high to excellent yields not only from secondary alcohols but also steric tertiary alcohols (Table 3.13). The common mechanism started with base abstracted acidic proton of alcohol and alkoxy anion substituted to chlorodiphenylphosphine, obtained alkyl diphenylphosphinites in retention of configuration.

The ^{1}H-NMR spectrum of allyl diphenylphosphinite is presented in Figure 3.13. The spectrum pattern was similar as allyl phenyl selenide not only aromatic protons but also olefinic protons. However, a methylene signal shift up to δ_H 4.38 and more than common benzylic protons (around at δ_H 3-4).

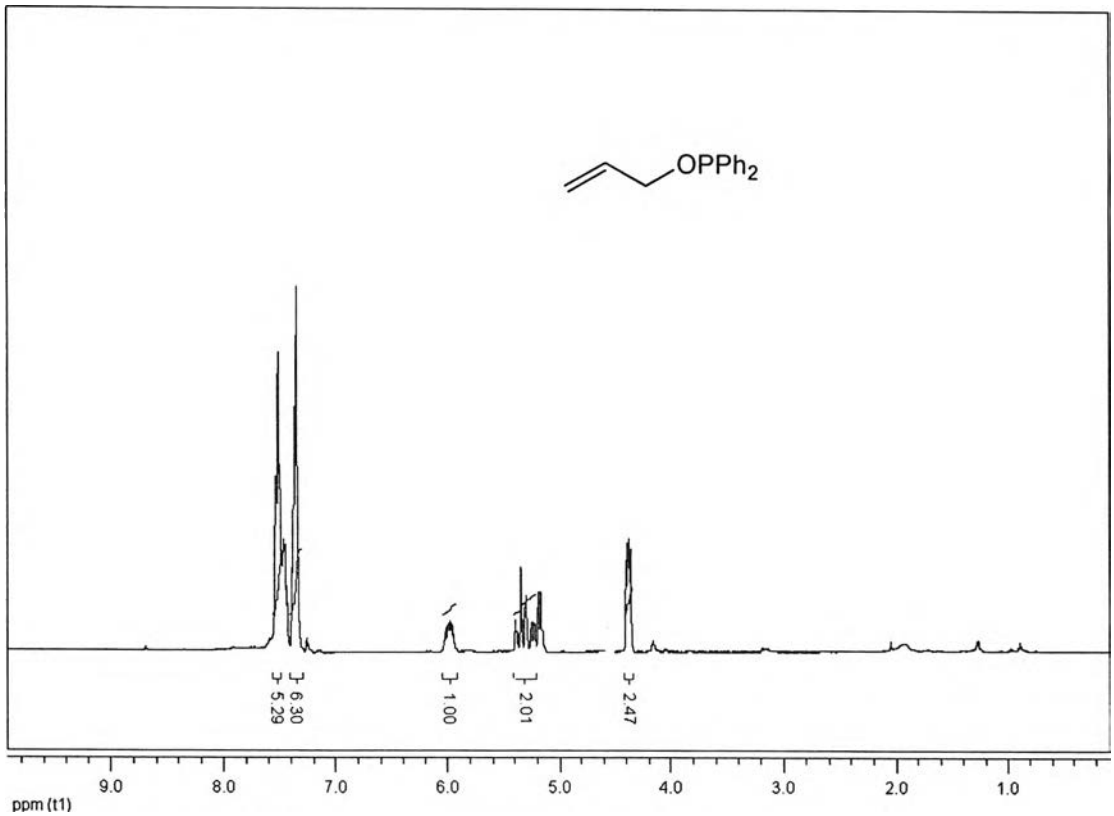


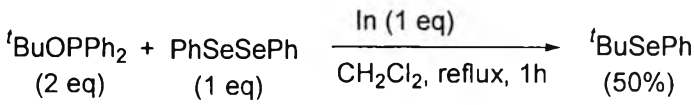
Figure 3.13 The ^{1}H-NMR spectrum of allyl diphenylphosphinite

3.2.9 Optimized conditions

During the course of works directed toward the synthesis of the active principle of selenides. Previously, an attempt to change staring material, alcohol was used instead of alkyl halides in the same condition as mentioned above. The treatment of *tert*-butanol with PhSeSePh in the presence of indium in CH_2Cl_2 at reflux for 1 h did not furnish *tert*-butyl phenyl selenide.

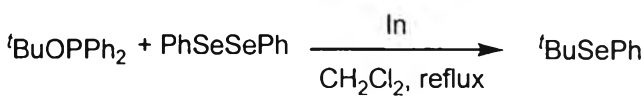
$$\underset{(2\ eq)}{^tBuOH} + \underset{(1\ eq)}{PhSeSePh} \xrightarrow[CH_2Cl_2,\ reflux,\ 1h]{In\ (1\ eq)} \underset{(0\%)}{^tBuSePh}$$

At that time, the reaction using alkyl diphenylphosphinites as substrates in order to replace and apply this new method for preparation of organic selenides was undertaken. The similar condition, as described in Part I, for preparation of organic selenides from alkyl diphenylphosphinites was performed. *tert*-Butyl diphenylphosphinite (2 equiv) was reacted with PhSeSePh (1 equiv) in the presence of indium (1 equiv) in CH_2Cl_2 at reflux for 1 h, resulting in the formation of *tert*-butyl phenyl selenide in 50% yield.



To search for optimized conditions, the reaction of several alkyl diphenylphosphinites and diphenyl diselenide was tried to find the optimized conditions. *tert*-Butyl diphenylphosphinite (^{t}BuOPPh$_2$) was selected as a model substrate and treated with diphenyl diselenide in the presence of indium as the same procedure as using in the preparation of diorganyl selenides from alkyl halides. The reactions were carried out in CH_2Cl_2 at reflux temperature. The ratio of substrate and reagents including the amount of indium were varied as the results in Table 3.14.

Table 3.14 Synthesis of *tert*-butyl phenylselenides from *tert*-butyl diphenylphosphinites



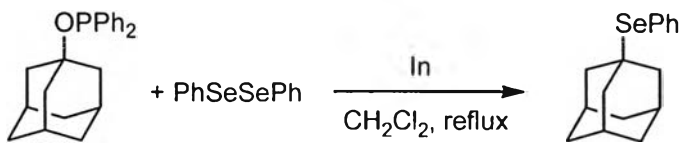
entry	^{t}BuOPPh$_2$ (equiv)	PhSeSePh (equiv)	In (equiv)	Time (h)	Yield (%)
1	2	1	0	2	6
2	2	1	1	1	56
3	1	1	3	1	71

The conversion of alkyl diphenylphosphinites to alkyl phenyl selenides was inactive when indium was absence (entry 1). Using the same ratio of substrate and reagents as 2:1 of ^{t}BuOPPh$_2$ and PhSeSePh yielded ^{t}BuSePh only a half of substrate converted, in 56% isolated yield (entry 2). In the matter of the ratio was 1:1 and added more indium, 3 equiv, obtaining selenide product in 71% (entry 3). It seemed that the best condition for selenide preparation now should be in entry 3 whereas, from the reaction, it also remained much of indium powder mixing with indium metal granule.

The optimized ratio of substrate and reagents using ^{t}BuOPPh$_2$ was performed. All temperature effect and ratio of reagents were withstood comparison with the reaction between adamantyl diphenylphosphinites and diphenyl diselenide. In

addition, the exact amount of indium was repeated to verify as the results shown in Table 3.15.

Table 3.15 Synthesis of adamantyl phenylselenides from adamantyl diphenyl-phosphinites



entry	$ROPPh_2$ (equiv)	PhSeSePh (equiv)	In (equiv)	Temp.	Time (h)	Yield (%)
1	2	1	3	rt	24	47
2	1	1	1.5	rt	24	53
3	2	1	3	reflux	2	45
4	1	1	1.5	reflux	2	83
5	1	1	0	reflux	2	0

As results presented in Table 3.15, both of room and reflux temperature, the ratio of adamantly diphenylphosphinite, PhSeSePh, and indium was 2:1:3, and the reaction was left over though 24 h at room temperature obtaining adamantyl phenyl selenides in low yield (entries 1 and 3). Both PhSeSePh and indium were in excess and remained a half of starting amount. For this reason, the ratio was altered to 1:1:1.5 and the amount of indium was reduced to 1.5 equiv, obtaining selenide product in 53% at room temperature for 24 h (entry 2), and 83% at reflux temperature for 2 h (entry 4). The absence of indium metal, the reaction did not proceed at all. It was implied that indium was also a promoter of the reaction (entry 5).

Depending on this circumstance, the optimal conditions for this effectively new method was the ratio of $^tBuOPPh_2$ and PhSeSePh as 2:1 and 1.5 equiv of indium powder giving *tert*-alkyl phenyl selenides in high yield (entry 4). These conditions would be applied in screening the limitation of substrate in Table 3.16. It was speculated that the reactions were going through the intermediacy of alkyl radical, adamantyl radical, but the reaction pathway might be different from those selenides from alkyl halides as presented in Scheme 3.3 *vide supra*.

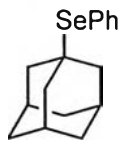
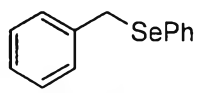
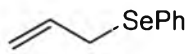
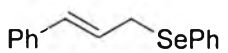
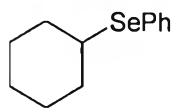
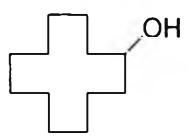
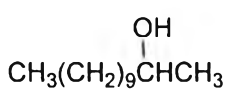
3.2.10 Synthesis of alkyl phenyl selenides from alkyl diphenylphosphinites

The situation was specially relevant to the indium used for reaction of alkyl diphenylphosphinites and diphenyl diselenide. After reaction conditions using indium were optimized, the generality of the reaction was investigated by variation of various alkyl diphenylphosphinites. Several alkyl phenyl selenides were easily prepared from alkyl diphenylphosphinites. The reaction disclosed was not limited to *tert*-alkyl diphenylphosphinites as shown above. Other primary and secondary alkyl diphenylphosphinites also produced the corresponding alkyl phenyl selenides under same optimal conditions. It was likely to be made them by the above optimized conditions.

The scope and limitations of the present method employing a variety of sterically different alkyl diphenylphosphinites were investigated. Under the optimal conditions, treatment of the phosphinites (1 equiv) with PhSeSePh (1 equiv) in the presence of indium (1.5 equiv) in CH_2Cl_2 at reflux for 1 h gave the corresponding selenides as summarized in Table 3.16.

Table 3.16 Synthesis of several alkyl phenyl selenides from corresponding diphenylphosphinites

$$ROPPh_2 \text{ (1 equiv)} + PhSeSePh \text{ (1 equiv)} \xrightarrow[CH_2Cl_2,\ reflux]{In\ (1.5\ equiv)} RSePh$$

entry	RSePh	Time (h)	Yield (%)
1	^{t}BuSePh	2	71
2		2	83
3		3	89
4		2	78
5		2	69
6		2	28[a]
7		24	no rxn.
8		3	86

[a] Analyzed by GC based on starting material 0.5 mmol

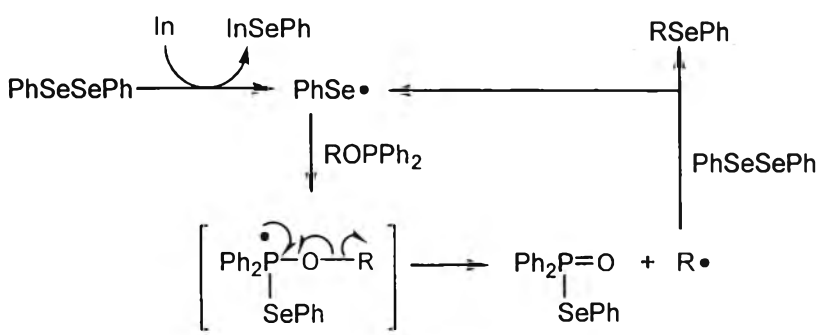
Tertiary alkyl diphenylphosphinites underwent a clean reaction to provide *tert*-alkyl phenyl selenides in high yield (entries 1-2). In a similar fashion as tertiary alkyl phenyl selenides, preparation of benzyl and allyl phenyl selenide was also achieved using benzylic and allylic diphenylphosphinites (entries 3-5). Examination of substitution in allylic and benzylic compounds, allylic and benzylic halides (entries 3-4) were both selectively reacted and more reactive than substituted allylic halides (entry 5) under reaction conditions. It should be noted that substituted allylic compounds, cinnamyl diphenylphosphinites and cinnamyl bromide *vide supra*, of the type $RCH{=}CH\text{-}CH_2X$ gave mixtures of two monoselenide products because the substituted allylic radical could reacted at either carbon of C=C in intermediates generated.

For investigation of secondary alkyl diphenylphosphinites, cyclic structure, both cyclohexyl and cyclododecyl diphenylphosphinites were not smoothly proceeded. While cyclohexyl phenyl selenide was obtained in 28% GC yield based on its starting material (entry 6), cyclododecyl phenyl selenide did not proceed at all (entry 7). However, acyclic secondary alkyl diphenylphosphinites, 2-dodecyl diphenylphosphinite gave the corresponding selenide in 86% isolated yield (entry 8).

3.2.11 Plausible mechanism

It was contemplated that the reactions were going through the reasonable intermediacy of alkyl radical, adamantyl radical, but it might be different in those selenides from alkyl halides in Scheme 3.3.

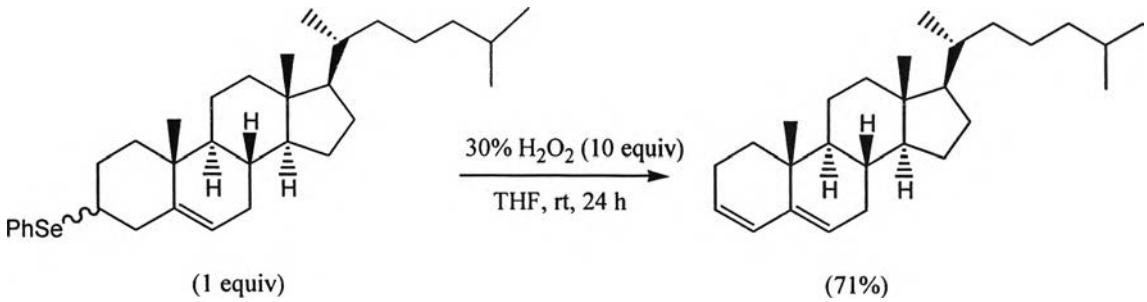
A mechanistic pathway was proposed in Scheme 3.4. Prior to indium metal as an initiator reduced diphenyl diselenide to generate phenyl selenide radical and then the S_H2 reaction of phenyl selenide radicals with alkyl diphenylphosphinite formed intermediate which was converted to alkyl radical and $Ph_2P(O)SePh$ species. The alkyl radical reacted with diphenyl diselenide to give alkyl phenyl selenide.



Scheme 3.4 A mechanistic pathway for conversion of alkyl diphenylphosphinites

Part IV: Olefination

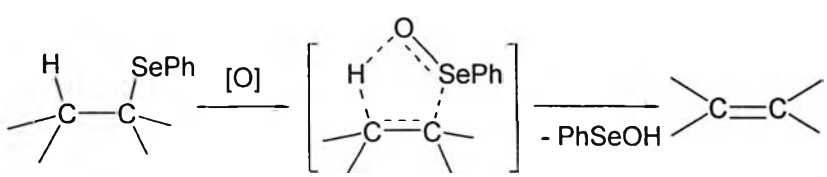
The following discussion was the transformation of organic selenides, especially alkyl phenyl selenides, to their corresponding olefin using mild condition as mentioned above. Particular emphasis was placed on the synthetic utility of the elimination reaction *via* selenoxide groups. Selenoxide eliminations were frequently used to install the double bond of α,β-unsaturated carbonyl compounds. They occurred by concerted, cyclic, *syn*-elimination process [63]. The role of selenoxides in the preparation of carbon-carbon double bonds using aq H_2O_2 was reported here.



$$CH_3(CH_2)_{11}SePh \xrightarrow[THF,\ rt,\ 24\ h]{30\%\ H_2O_2\ (10\ equiv)} CH_3(CH_2)_9CH{=}CH_2$$

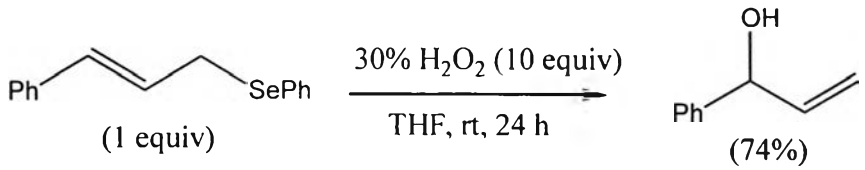
(1 equiv) (70%)

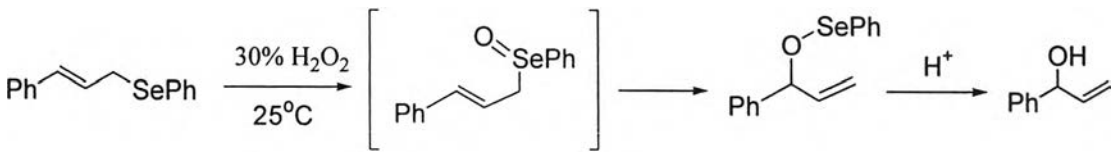
Firstly, cholesteryl phenyl selenide (1 equiv), prepared and reported in entry 4 from Table 3.7, reacted with aq H_2O_2 (10 equiv) in THF as solvent and stirred at room temperature for 24 h gave the corresponding eliminated-product in 71% yield. Secondly, 1-dodecyl phenyl selenide, prepared and reported in entry 10 from Table 3.7, also treated with aq H_2O_2 in THF and stirred at room temperature until 24 h obtaining the corresponding alkene in 70% yield. These transformations particular emphasis was placed on the synthetic utility of the elimination reaction *via* selenoxide groups from unsymmetrical diorganyl selenides as starting materials under mild condition. The selenoxide elimination was frequently used to install the double bond to their starting molecules and eliminated selenenic acid molecules in the same time because selenoxide elimination occurred at lower temperature than the corresponding sulfoxide elimination. Both of them occurred in the same procedure by concerted, cyclic, *syn*-elimination process as equation below.



The reaction of cinnamyl phenyl selenide, prepared and reported in entry 5 from Table 3.16, with aq H_2O_2 in THF as solvent stirred at room temperature for 24 h furnished the corresponding rearrangement product in 74% yield. In fact, the elimination proceeded *via* [2,3]sigmatropic rearrangement of selenides when a seleninyl group ($PhSe(O)^-$) was presented at allylic position. The corresponding

allylic oxidation products as mechanistic equation shown below were observed. The advantage of this procedure could be applied to the synthesis of optically and biologically active allylic alcohol.





3.3 Conclusion

The preparation of unsymmetrical diorganyl selenides has been regarded as a challenging topic in current organic synthesis, especially transformation to olefin, however, only a few successful examples as *tert*-alkyl phenyl selenides, were reported. It was notwithstanding that, until now, there was no report optimizing an indium methodology for the development of unsymmetrical diorganyl selenides *via* organic halides and diphenylphosphinites. For this reason, a novel and one-pot method for the preparation of alkyl phenyl selenides *via* organic halides and diphenylphosphinites using indium metal as a promoter was established.

The novel, one-pot, mild and practical approaches for the synthesis of unsymmetrical diorganyl selenides were developed from two kinds of starting materials which could be summarized as follows:

1. An efficient and simple method for preparation of alkyl and acyl phenyl selenides under neutral conditions: RX (2 equiv), PhSeSePh (1 equiv), In (0.5 equiv); or RCOX (2 equiv), PhSeSePh (1 equiv), In (1.5 equiv) proceeded in CH_2Cl_2 at reflux.

2. The consecutive order of reactivity of alkyl halides was *tert*-alkyl, allyl, benzyl > benzoyl >> secondary and primary alkyl halides. Transformation of primary and secondary alkyl iodides and bromides could be completely occurred by adding catalytic amount of I_2.

3. Reactivity of alkyl halides was: RI > RBr > RCl.

4. This efficient method for transformation of alcohol into alkyl phenyl selenides *via* alkyldiphenylphosphinites using reaction condition: $ROPPh_2$ (1 equiv), PhSeSePh (1 equiv), In (1.5 equiv) proceeded in CH_2Cl_2 at reflux.

5. Both organyl halides and alkyl diphenylphosphinites were exclusively transformed to unsymmetrical diorganyl selenides, primary, secondary and tertiary alkyl and acyl phenyl selenides, in moderate to excellent yields.

6. Several functional groups such as C=C, C=O and OMe remained unaffected in this newly developed system.

7. The useful preparation of unsymmetrical diorganyl selenides was leading to the occurrence of olefin products which applied to the synthesis of some biologically active natural products using H_2O_2 under mild conditions.

3.4 Experiment

3.4.1 Instrument and Equipment

Melting points (m.p.) were measured on Stuart Scientific melting point apparatus model SMP3 or Electrothermal digital melting point apparatus model IA9100 and are uncorrected.

Chromatography: Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck, Kieselgel 60 PF_{254}). Column chromatography was performed on silica gel (Merck, Kieselgel 60G Art 7734, 70-230 mesh; or Art 9385, 230-400 mesh) and aluminium oxide 90 active neutral (70-230 mesh). Gas chromatography analysis was carried out on Shimadzu gas chromatograph GC-14A instrument equipped with flame ionization detector (FID) using nitrogen as a carrier gas, the column used for chromatography was a capillary column type HP-5 (30m x 250mm) from Hewlett Packard company.

Spectrometers: Fouirer transform-infrared spectra (FT-IR) were performed on Nicolet Impact 410 FT-IR spectrometer. Solid samples were incorporated to potassium bromide (KBr) to form pellet. As a liquid sample, a drop of the liquid was squeezed between flat plates of sodium chloride cells. The ^{1}H and ^{13}C-NMR spectra were obtained in deuterated chloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-d_6), with Fourier transform nuclear magnetic resonance spectrometer of Varian model Mercury+400 spectrometer which was operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, or Bruker model AC-100F spectrometer which was operated at 100 MHz for ^{1}H. Gas chromatography-mass spectrometry analysis was carried out on Agilent Technologies G1530N instrument (6890N Network GC system-5973 mass selective detector, EI, 70eV).

3.4.2 Chemicals

All solvents used in this research were purified, excepted for those which were reagent grades, and dried prior to use by standard methodology. The substrates and reagents employed for synthesizing the precursors and products used in this work were purchased from Fluka, Aldrich Chemical Company or otherwise and were used without further purification. All reactions in non-aqueous solutions were carried out under a nitrogen or argon atmosphere.

3.4.3 General procedure for synthesis of alkyl and acyl phenyl selenides

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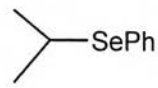
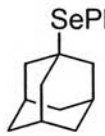
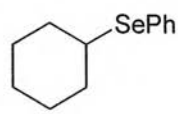
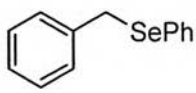
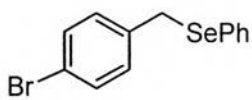
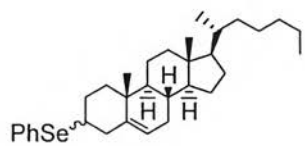
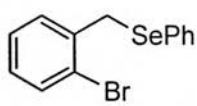
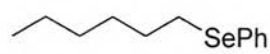
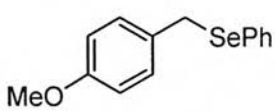
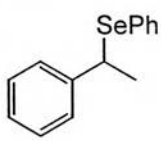
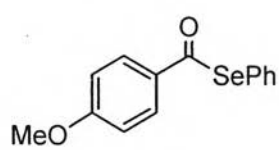
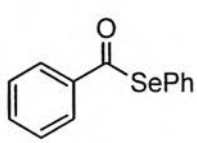
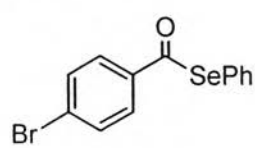
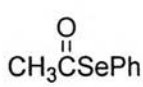
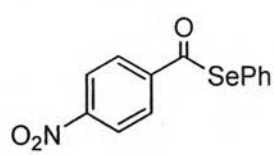
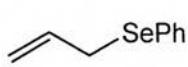
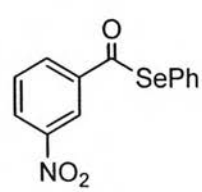
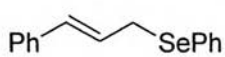
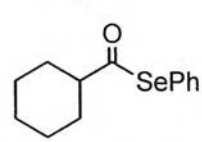
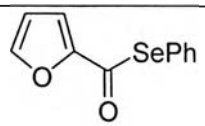
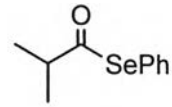
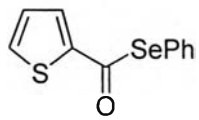
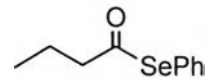
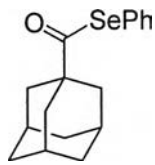
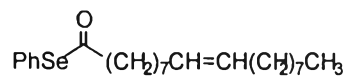
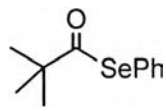
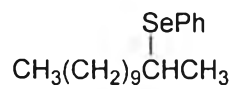
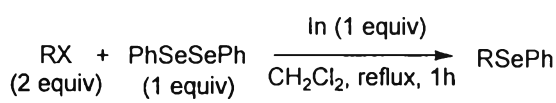
Se1	^{t}BuSePh	**Se12**	
Se2		**Se13**	
Se3		**Se14**	
Se4		**Se15**	
Se5		**Se16**	
Se6		**Se17**	$CH_3(CH_2)_{11}SePh$
Se7		**Se18**	
Se8		**Se19**	
Se9		**Se20**	
Se10		**Se21**	
Se11		**Se22**	

	RSePh		RSePh
Se23		**Se27**	
Se24		**Se28**	
Se25		**Se29**	
Se26		**Se30**	

- **General procedures for synthesis of alkyl phenyl selenides:**



Indium powder (0.5 mmol, 57.4 mg), diphenyl diselenide (0.5 mmol, 156.1 mg), and CH_2Cl_2 (2 mL) were placed in a two-necked flask. Organic halides (1.0 mmol) in CH_2Cl_2 (1 mL) were added to the mixture and the resulting mixture was stirred at reflux for 3 h under nitrogen. The mixture was then quenched with 1 M HCl and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and purified by column chromatography on silica gel eluting with hexane, to give the corresponding alkyl phenyl selenides.

tert-Butyl phenyl selenide (**Se1**). Pale yellow oil (86%), R_f 0.37 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.31 (9H, s, 3×CH_3), 7.19-7.25 (3H, m, Ph) and 7.51-7.53 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 31.1, 127.5 (2C), 128.1, 130.4 and 137.1 (2C); MS *m/e* (relative intensity): 214 (M^+, 29.6), 158 (100), 156 (50.9), 117 (5.0), 78 (24), 57 (45.5), 51 (8.0).

Adamantyl phenyl selenide (**Se2**). Pale yellow oil (88%), R_f 0.37 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.68 (6H, s, 3×CH_2), 1.98 (3H, s, 3×CH), 2.15 (6H, s, 3×CH_2), 7.23-7.33 (3H, m, Ph) and 7.57-7.66 (2H, m, Ph); ^{13}C-

NMR ($CDCl_3$) δ (ppm): 30.7 (3C), 36.2 (3C), 44.7 (3C), 47.0, 126.4, 128.3, 128.5 (2C) and 138.4 (2C); MS *m/e* (relative intensity): 292 (M^+, 8.5), 157 (5.2), 135 (100), 107 (8.1), 93 (14.8), 79 (14.4), 67 (4.5) and 55 (2.2).

Benzyl phenyl selenide (**Se3**). Pale yellow solid (84%), m.p. 32-34°C (lit. [188], m.p. 33-34°C) (hexane/EtOAc), R_f 0.45 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.06 (2H, s, $C\underline{H}_2Ph$), 7.15-7.23 (3H, m, Ph) and 7.33-7.47 (2H,m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 32.3, 126.8, 127.3, 128.4 (2C), 128.8 (2C), 128.9 (2C), 130.8, 133.6 (2C) and 138.7; MS *m/e* (relative intensity): 248 ($[M+1]^+$, 29.2), 165 (2.9), 157 (9.2), 117 (1.5), 91 (100), 77 (5.5), 65 (12.3) and 51 (3.5).

4-Bromobenzyl phenyl selenide (**Se4**). Pale yellow crystal (85%), m.p. 46-48°C (lit. [189], m.p. 61-62°C) (hexane/EtOAc), R_f 0.40 (hexane:EtOAc, 95:5); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.02 (2H, s, $C\underline{H}_2Ph$), 7.03 (2H, d, J = 8.33 Hz), 7.24-7.60 (3H, m, Ph), 7.34 (2H, d, J = 8.37 Hz) and 7.41-7.44 (2H,m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 31.5, 120.6, 127.6, 129.1 (2C), 129.7, 130.5 (2C), 131.5 (2C), 133.9 (2C) and 137.8.

2-Bromobenzyl phenyl selenide (**Se5**). Pale yellow oil (95%), R_f 0.25 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.19 (2H, s, $C\underline{H}_2Ph$), 7.01-7.08 (2H, m, H-4, H-6; *o*-Br$\underline{Ph}$), 7.10-7.15 (2H, t, J = 7.20 Hz, H-5; *o*-Br$\underline{Ph}$), 7.22-7.29 (3H, m, Ph), 7.47-7.49 (2H, m, Ph) and 7.54 (1H, d, J = 7.70 Hz; *o*-Br$\underline{Ph}$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 33.0, 124.4, 127.3, 127.7, 128.5, 129.0 (2C), 130.6, 133.1, 134.5 (2C) and 138.3.

4-Methoxybenzyl phenyl selenide (**Se6**). Pale yellow solid (52%), m.p. 62-64°C (lit. [190], m.p. 66-68°C) (hexane/EtOAc), R_f 0.35 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.69 (3H, s, $OC\underline{H}_3$) 4.00 (2H, s, $C\underline{H}_2Ph$), 6.70 (2H, d, J = 8.59 Hz, *p*-OMe$\underline{Ph}$), 7.05 (2H, d, J = 8.55 Hz, *p*-OMe$\underline{Ph}$), 7.16-7.17 (3H, m, Se$\underline{Ph}$) and 7.36-7.38 (2H, m, Se$\underline{Ph}$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 31.7, 55.3, 113.8 (2C), 127.2, 129.0 (2C), 129.7, 129.9 (2C), 130.5, 133.5 (2C) and 158.5; MS *m/e* (relative intensity): 248 ($[M+1]^+$, 29.2), 165 (2.9), 157 (9.2), 117 (1.5), 91 (100), 77 (5.5), 65 (12.3) and 51 (3.5).

1-Phenylethyl phenyl selenide (**Se7**). Pale yellow crystal (59%), m.p. 58-60°C (hexane/EtOAc), R_f 0.27 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.82 (3H, d, J = 7.04 Hz, CH_3), 7.53 (1H, q, J = 7.04 Hz, CH), 7.27-7.33 (8H, m, Ph) and 7.52 (2H, d, J = 7.70 Hz, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 22.3, 42.2, 127.0, 127.3 (2C), 127.9, 128.4 (2C), 128.9 (2C), 129.9, 135.5 (2C) and 143.7.

Allyl phenyl selenide (**Se10**). Pale yellow oil (89%), R_f 0.53 (hexane:CH_2Cl_2, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.53 (2H, d, J = 7.30 Hz, $C\underline{H}_2$SePh), 4.95 (2H, dd, J = 16.12, 10.50 Hz, HC=C$\underline{H}_2$), 5.90 (1H, m, $\underline{H}$C=CH_2), 7.22-7.42 (3H, m, Ph) and 7.46-7.55 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 30.7, 116.9, 127.2, 129.0 (2C), 130.0, 133.4 (2C) and 134.4; MS *m/e* (relative intensity): 198 ($[M+1]^+$, 100), 157 (M^+, 8.7), 157 (77.1), 117 (86.5), 104 (32.4), 91 (21.4), 77 (36.2), 69 (6.4) and 51 (14.6).

Cinnamyl phenyl selenide (**Se11**). Pale yellow solid (69%), m.p. 48-50°C, R_f 0.35 (lit. [191], m.p. 54-55°C) (hexane:CH_2Cl_2, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.68 (2H, d, J = 7.37 Hz, C$\underline{H}$2SePh), 6.25 (1H, d, J = 15.78 Hz, HC=C$\underline{H}$Ph), 6.34 (1H, d, J = 15.80, 7.89 Hz, HC=C$\underline{H}$CH$_2$), 7.26-7.28 (10H, m, 2×Ph) and 7.51-7.54 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 30.5, 125.8, 126.3 (2C), 127.3, 127.4, 128.5 (2C), 128.9, 132.1, 133.9 (2C) and 136.8; MS *m/e* (relative intensity): 274 ($[M+1]^+$, 5.0), 157 (9.2), 117 (100), 115 (35.5), 91 (12.6), 77 (6.5), 69 (3.2) and 51 (3.0).

Isopropyl phenyl selenide (**Se12**). Pale yellow needles (70%), m.p. 58-60°C (hexane/EtOAc), R_f 0.45 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.42 (6H, d, J = 6.82 Hz, 2×CH_3), 3.46 (1H, s, J = 6.80 Hz, CH), 7.26-7.28 (3H, m, Ph) and 7.54-7.56 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.2 (2C), 33.9, 127.3, 128.9 (2C), 131.5 and 134.8 (2C).

Isobornyl phenyl selenide (**Se14**). Pale yellow oil (81%), R_f 0.32 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.14-1.35 (2H, m, 2×CH_2), 1.76 (2H, d, J = 7.43 Hz, CH_2), 2.07-2.02 (1H, m, CH), 3.30 (1H, dd, J = 2.79, 8.91 Hz, CHSePh), 7.21-7.50 (3H, m, Ph), 7.52-7.54 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 15.7, 20.1, 20.5, 27.4, 38.4, 41.5, 46.3, 47.5, 49.6, 54.1, 126.5, 128.9 (2C), 132.8 (2C), 133.7.

Cholesteryl phenyl selenide (**Se15**). Pale yellow solid (32%), R_f 0.55 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.59 (3H, s, CHC$\underline{H_3}$), 0.79 (3H, d, J = 6.60 Hz, CHC$\underline{H_3}$), 0.83 (3H, d, J = 6.48 Hz, CHC$\underline{H_3}$), 0.90 (3H, s, CH_2C(CH)C$\underline{H_3}$), 1.50 (3H, s, CH=CCC$\underline{H_3}$), 0.78-2.10 (26H, m, CH_2 and CH), 2.26 (1H, d, J = 13.58 Hz, C=CHC$\underline{H_2}$), 2.38 (1H, d, J = 12.97 Hz, C=CHC$\underline{H_2}$), 3.06 (1H, d, J = 12.33 Hz, C=CHC$\underline{H_2}$CHSePh), 5.21 (1H, d, J = 5.02 Hz, C=C$\underline{H}$), 7.46-7.48 (3H, m, $\underline{Ph}$) and 7.52-7.55 (2H, m, $\underline{Ph}$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 11.8, 18.7, 19.3, 20.8, 22.6, 22.8, 23.8, 24.2, 28.0, 28.2, 30.4, 31.7, 31.8, 35.8, 36.1, 36.8, 39.5, 39.7, 40.4, 40.5, 42.3, 43.3, 50.3, 56.1, 56.7, 120.9, 127.3, 128.9 (2C), 131.5, 134.6 (2C) and 142.4.

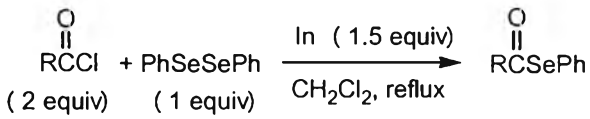
n-Hexyl phenyl selenide (**Se16**). Pale yellow oil (88%), R_f 0.40 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (3H, t, J = 7.68 Hz, CH_3), 1.25-1.28 (4H, m, 2×C$\underline{H_2}$ CH_3), 1.38-1.42 (2H, m, $\underline{CH_2}CH_2CH_2$SePh), 1.70 (2H, t, J = 7.52 Hz, $\underline{CH_2}CH_2$SePh), 2.91 (2H, t, J = 7.50 Hz, $\underline{CH_2}$SePh), 7.21-7.27 (3H, m, Ph) and 7.47-7.49 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.0, 22.5, 27.9, 29.5, 30.1, 31.3, 126.5, 128.9 (2C), 130.7, and 132.3 (2C); MS *m/e* (relative intensity): 240 ($[M+1]^+$, 31.9), 238 (15.8), 156 (50.1), 158 (100), 117 (3.0), 91 (2.6), 83 (19.6), 78 (19.5), 67 (5.6), 55 (46.8), 50 (8.0).

Dodecyl phenyl selenide (**Se17**). Colorless oil (85%), R_f 0.40 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.85 (3H, t, J = 6.05 Hz, CH_3), 1.20 (18H, m, 9×CH_2), 1.57 (2H, p, J = 6.83 Hz, C$\underline{H_2}CH_2$SePh), 2.86 (2H, t, J = 6.94 Hz, C$\underline{H_2}$SePh), 7.15-7.22 (3H, m, Ph) and 7.38-7.48 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.9, 29.1, 29.4, 29.5, 29.6, 29.7 (2C), 29.7 (2C), 29.9, 30.2, 32.0, 126.5, 129.0 (2C), 130.7 and 132.3 (2C); MS *m/e* (relative intensity): 326 ($[M+1]^+$, 100), 325 (M^+, 11.5), 324 (51.1), 185 (2.8), 158 (85.6), 91 (8.5), 77 (9.2) and 57 (25.3).

2-Dodecyl phenyl selenide (**Se30**). Colorless oil (86%), R_f 0.53 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 6.77 Hz, CH_3), 1.25-1.38 (14H, m, 7×CH_2), 1.41 (4H, d, J = 7.89 Hz, C$\underline{H_2}CH_2$CH), 1.56-1.70 (2H, m, C$\underline{H}$SePh), 3.30 (1H, q, J = 6.77 Hz, C$\underline{H}$SePh), 7.26-7.28 (3H, m, Ph) and 7.55-7.57 (2H, m, Ph); ^{13}C-NMR

($CDCl_3$) δ (ppm): 14.2, 22.1, 22.7, 27.8, 29.3, 29.4, 29.5, 29.6 (2C), 31.9, 37.5, 39.8, 127.2, 128.8 (2C), 129.5 and 134.9 (2C).

- **General procedures for synthesis of acyl phenyl selenides:**



Indium powder (0.75 mmol, 86.1 mg), diphenyl diselenide (0.5 mmol, 156.1 mg), and CH_2Cl_2 (2 mL) were placed in a two-necked flask. Acid chlorides (1.0 mmol) in CH_2Cl_2 (1 mL) were added to the mixture and the resulting mixture was stirred at reflux for 1 h under argon or nitrogen. The mixture was then quenched with 1 M HCl and extracted with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$. After evaporation, the residue was then purified by column chromatography on silica gel eluting with hexane to hexane/EtOAc (95:5) to give the corresponding acyl phenyl selenides.

Benzoyl phenyl selenide (**Se8**). Pale yellow crystal (92%); m.p. 38-40°C (lit. [192], m.p. 37-38°C) (hexane/EtOAc), R_f 0.33 (hexane:EtOAc, 95:5). IR (KBr): 3050, 2992, 1758, 1680, 1595, 1579, 1474, 1443, 1307, 1198, 1015, 875 and 774 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42-7.45 (3H, m, SePh), 7.50 (2H, t, J = 7.75 Hz, SePh), 7.61-7.63 (3H, m, PhCO) and 7.95 (2H, d, J = 7.43 Hz, PhCO); ^{13}C-NMR ($CDCl_3$) δ (ppm): 125.8, 127.4 (2C), 128.9 (2C), 129.1, 129.4 (2C), 133.9, 136.4 (2C), 138.5, 193.6; MS *m/e* (relative intensity): 262 ($[M+1]^+$, 2.2), 157 (8), 105 (100), 77 (45) and 51 (8).

Acetyl phenyl selenide (**Se9**). Pale brown oil (50%); R_f 0.38 (hexane:EtOAc, 9:1). IR (neat): 3054, 2949, 1723, 1575, 1474, 1435, 1350, 1104, 1023 and 933 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.47 (3H, s, CH_3CO) and 7.35-7.56 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 34.1, 126.7, 129.4 (2C), 131.5, 135.7 (2C) and 196.8; MS *m/e* (relative intensity): 200 ($[M+1]^+$, 52), 198 (25), 158 (100), 117 (14), 105 (5), 77 (48) and 51 (21).

4-Methoxybenzoyl phenyl selenide (**Se18**). Pale yellow crystal (80%); m.p. 69-71°C (hexane/EtOAc), R_f 0.27 (hexane:EtOAc, 9:1). IR (KBr): 3054, 3019, 2953, 1680, 1599, 1501, 1439, 1252, 1167, 1019 and 875 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.89 (3H, s, OCH_3), 6.96 (2H, d, J = 8.96 Hz, *p*-OMePh), 7.50-7.65 (2H, m, Ph), 7.35-7.49 (3H, m, Ph) and 7.92 (2H, d, J = 8.80 Hz, *p*-OMePh); ^{13}C-NMR ($CDCl_3$) δ (ppm): 55.6, 114.1 (2C), 126.0, 128.9, 129.3 (2C), 129.7 (2C), 131.5, 136.4 (2C) and 164.2; MS *m/e* (relative intensity): 292 ($[M+1]^+$, 0.0079), 157 (4.3), 135 (100), 107 (6.6), 92 (10.6), 77 (16.6) and 64 (4.6).

4-Bromobenzoyl phenyl selenide (**Se19**). Pale yellow solid (88%); m.p. 82-84°C (hexane/EtOAc), R_f 0.34 (hexane:EtOAc, 9:1). IR (KBr): 3046, 1750, 1684, 1575, 1478, 1392, 1198, 1066 and 875 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.40-7.47 (3H, m, Ph), 7.55-7.60 (2H, m, Ph), 7.63 (2H, d, J = 8.59 Hz, *p*-BrPh) and 7.81 (2H, d, J = 8.70 Hz, *p*-BrPh); ^{13}C-NMR ($CDCl_3$) δ (ppm): 125.4, 128.7 (2C), 129.0, 129.3, 129.5 (2C), 132.3 (2C), 136.2 (2C), 137.3 and 192.5; MS *m/e* (relative intensity): 341 ($[M+1]^+$, 1.3), 185 (96.5), 183 (100), 157 (38), 155 (34), 76 (11.7) and 55 (6.4).

4-Nitrobenzoyl phenyl selenide (**Se20**). Pale yellow solid (20%); m.p. 133-135°C (hexane/EtOAc), R_f 0.37 (hexane:EtOAc, 9:1). IR (KBr): 3058, 2930, 1673, 1602, 1525, 1470, 1435, 1342, 1186, 1108 and 894 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.42-7.65 (5H, m, Ph), 8.08 (2H, d, J = 8.79 Hz, *p*-NO_2Ph) and 8.35 (2H, d, J = 8.81 Hz, *p*-NO_2Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 124.2 (2C), 125.0, 128.2 (2C), 129.6, 129.7 (2C), 136.1 (2C), 143.0, 150.6 and 192.6; MS *m/e* (relative intensity): 307 ($[M+1]^+$, 2.8), 157 (7.3), 150 (100), 120 (7.8), 104 (24.3), 76 (16), 64 (1.7) and 50 (6.2).

3-Nitrobenzoyl phenyl selenide (**Se21**). Pale yellow solid (10%); m.p. 109-111°C (hexane/EtOAc), R_f 0.23 (hexane:EtOAc, 9:1). IR (KBr): 3070, 2922, 1680, 1536, 1439, 1346, 1194, 1089, 925 and 844 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.43-7.67 (5H, m, Ph), 7.71 (1H, t, J = 8.01 Hz, H-5), 8.24 (1H, d, J = 7.65 Hz, H-6), 8.48 (1H, d, J = 8.00 Hz, H-4) and 8.77 (1H, s, H-2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 122.2, 124.9, 128.0, 129.6, 129.6 (2C), 130.2, 132.6, 136.2 (2C), 139.9, 148.5 and 191.9; MS

m/e (relative intensity): 307 ($[M+1]^+$, 3), 207 (1), 157 (6.3), 150 (100), 104 (23.3), 92 (3.3), 76 (17.6), 65 (1.3) and 50 (5).

Cyclohexylcarbonyl phenyl selenide (**Se22**). Pale yellow oil (62%); R_f 0.23 (hexane:EtOAc, 9:1). IR (neat): 3062, 2934, 2856, 1719, 1579, 1470, 1443, 1299, 1233, 1143, 953 and 746 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.13 (4H, m, CH_2-4, H_{ax}-2, H_{ax}-6), 1.43 (2H, q, J = 11.72 Hz, H_{eq}-2, H_{eq}-6), 1.73 (2H,d, J = 12.80 Hz, H_{eq}-3, H_{eq}-5), 1.93 (2H, t, J = 12.91 Hz, H_{ax}-3, H_{ax}-5), 2.56 (1H, tt, J = 11.28, 3.40 Hz, CHCO), 7.27-7.29 (3H, m, Ph) and 7.40-7.42 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 25.4 (2C), 25.6, 29.3 (2C), 56.0, 126.4, 128.7, 129.2 (2C), 135.9 (2C) and 203.9; MS *m/e* (relative intensity): 157 ($[M-C_6H_{11}CO]^+$, 21.2), 111 (59.6), 83 (100), 77 (12.2), 67 (2.8), 55 (38.1) and 51 (4.3).

2-Furoyl phenyl selenide (**Se23**). Pale yellow oil (55%); R_f 0.26 (hexane:EtOAc, 95:5). IR (neat): 3136, 3050, 1766, 1657, 1556, 1454, 1377, 1248, 1151, 1023, 945 and 816 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.59 (1H, dd, J = 3.58, 1.59 Hz, H-4), 7.22 (1H, d, J = 3.54 Hz, H-3), 7.38-7.48 (3H, m, Ph), 7.57 (1H, d, J = 3.65 Hz, H-5) and 7.65 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 112.9, 115.4, 124.8, 129.2, 129.4 (2C), 136.4 (2C), 146.8, 151.7 and 180.8; MS *m/e* (relative intensity): 252 ($[M+1]^+$, 13), 157 (8.4), 154 (1.9), 115 (30), 95 (100), 77 (6.8), 67 (2.9) and 51 (3.6).

2-Thiophenecarbonyl phenyl selenide (**Se24**). Pale yellow solid (90%); m.p. 62-64°C (lit. [193], m.p. 63-64°C) (hexane/EtOAc), R_f 0.27 (hexane:EtOAc, 95:5). IR (KBr): 3097, 3054, 1653, 1575, 1411, 1342, 1225, 1190, 1050 and 895 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.14 (1H, dd, J = 8.41, 4.12 Hz, H-4), 7.34-7.40 (3H, m, Ph), 7.51-7.59 (2H, m, Ph), 7.65 (1H, d, J = 5.45 Hz, H-3) and 7.83 (1H, d, J = 3.58 Hz, H-5); ^{13}C-NMR ($CDCl_3$) δ (ppm): 125.5, 128.0, 129.2, 129.4 (2C), 132.1, 133.7, 136.3 (2C), 143.1 and 183.6; MS *m/e* (relative intensity): 268 ($[M+1]^+$, 3.4), 157 (6.5), 155 (3.3), 111 (100), 83 (7.0), 77 (5.8), 65 (1.0), 57 (1.8) and 51 (2.6).

1-Adamantanecarbonyl phenyl selenide (**Se25**). Pale yellow needles (59%); m.p. 51-53°C (hexane/EtOAc), R_f 0.29 (hexane:EtOAc, 9:1). IR (neat): 3070, 2906,

2852, 1715, 1575, 1451, 1342, 1260, 1124, 980 and 902 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.58 (6H, s, CH_2), 1.99 (6H, s, 3×CH_2), 2.09 (3H, s, 3xCH) and 7.32-7.53 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 25.8, 27.8 (2C), 35.1, 37.6 (3C), 37.8 (3C), 129.0, 129.5 (2C), 131.0, 135.2 (2C) and 185.0; MS *m/e* (relative intensity): 320 ($[M+1]^+$, 0.0016), 163 (11.8), 157 (7.2), 135 (100), 107 (5.7), 93 (10.4), 79 (11.1) and 55 (1.7).

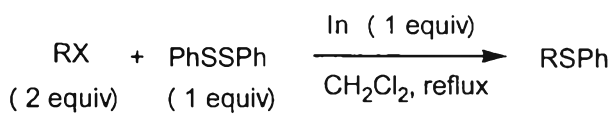
Trimethyl acetyl phenyl selenide (**Se26**). Pale yellow oil (68%); R_f 0.39 (hexane:EtOAc, 96:4). IR (neat): 3066, 2969, 2867, 2358, 1719, 1583, 1474, 1361, 1229, 1023 and 910 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.32 (9H, s, 3×CH_3), 7.38-7.40 (3H, m, Ph) and 7.50-7.52 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 27.1 (3C), 49.9, 126.3, 128.7, 129.2 (2C), 136.4 (2C) and 207.9; MS *m/e* (relative intensity): 242 ($[M+1]^+$, 5.6), 158 (32.6), 156 (17.7), 117 (4.0), 105 (1.1), 85 (44.0), 77 (17.5), 57 (100) and 51 (6.2).

Isobutyryl phenyl selenide (**Se27**). Pale yellow oil (92%); R_f 0.28 (hexane:EtOAc, 96:4). IR (neat): 3054, 2973, 2875, 1786, 1719, 1579, 1478, 1439, 1389, 1178 and 937 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.21 (6H, d, J = 6.79 Hz, 2xCH_3), 2.85 (1H, p, J = 6.75 Hz, C<u>H</u>CH_3), 7.29-7.38 (3H, m, Ph) and 7.46-7.52 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 19.1, 46.6, 126.3, 128.7, 129.3 (2C), 135.9 (2C) and 205.0; MS *m/e* (relative intensity): 228 ($[M+1]^+$, 14.9), 158 (38.5), 117 (6.7), 105 (2.9), 77 (28.9), 71 (100), 65 (4.5) and 51 (10.8).

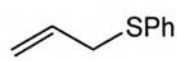
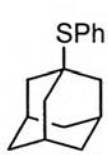
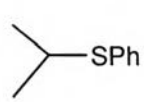
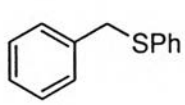
Butyryl phenyl selenide (**Se28**). Yellow oil (80%); R_f 0.31 (hexane:EtOAc, 96:4). IR (neat): 3058, 2965, 2867, 1719, 1579, 1478, 1439, 1256,1198, 960 and 735 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.84 (3H, t, J = 7.27 Hz, CH_3), 1.59 (2H, s, J = 7.36 Hz, C<u>H</u>$_2$$CH_3$), 2.55 (2H, t, J = 7.25 Hz, C<u>H</u>$_2$$CH_2CH_3$), 7.19-7.28 (3H, m, Ph) and 7.32-7.38 (3H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.4, 19.0, 49.4, 126.5, 128.8, 129.3 (2C), 135.8 (2C) and 200.3; MS *m/e* (relative intensity): 228 ($[M+1]^+$, 13.8), 226 (6.7), 157 (30.6), 117 (5.2), 105 (1.8), 91 (1.7), 77 (21.8), 71 (100), 65 (3.6) and 51 (8.5).

Oleoyl phenyl selenide (**Se29**). Yellow oil (16%); R_f 0.35 (hexane:EtOAc, 95:5). IR (neat): 3062, 2926, 2852, 1727, 1579, 1459, 1365, 1011 and 731 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J = 6.24 Hz, CH_3), 1.19 (22H, m, 11×CH_2), 1.63 (2H, t, J = 6.98 Hz, C<u>H</u>C<u>H</u>$_2$), 1.94 (2H, d, J = 5.89 Hz, C<u>H</u>C<u>H</u>$_2$), 2.62 (2H, t, J = 7.37 Hz, C<u>H</u>$_2$CO), 5.27 (2H, m, C<u>H</u>=C<u>H</u>), 7.29-7.32 (3H, m, Ph) and 7.40-7.45 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.7, 25.4, 27.1, 27.2, 28.8, 29.0, 29.1, 29.3 (2C), 29.5, 29.7, 29.8, 31.9, 47.5, 128.8, 129.3 (2C), 129.7, 130.1, 131.5, 135.8 (2C) and 210.0; MS *m/e* (relative intensity): 282 ([M-$CH_3(CH_2)_7CH$=CH]$^+$, 3.3), 265 (100), 207 (85.9), 158 (40.8), 135 (14.1), 121 (14.9), 109 (20.5), 95 (41.6), 78 (60.8), 69 (62.6) and 55 (91.9).

3.4.4 General procedure for synthesis of alkyl phenyl sulfides and tellurides



Indium powder (0.5 mmol, 57.4 mg), diphenyl disulfide or diphenyl ditelluride (0.5 mmol), and CH_2Cl_2 (2 mL) were placed in a two-necked flask. Organic halides (1.0 mmol) in CH_2Cl_2 (1 mL) were added to the mixture and the resulting mixture was stirred at reflux for 1 h under nitrogen. The mixture was then quenched with 1 M HCl and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and purified by column chromatography on silica gel eluting with hexane, to give the corresponding alkyl phenyl sulfides or tellurides.

	RSPh		RSPh
S1	^{t}BuSPh	**S4**	
S2		**S5**	
S3		**S6**	$CH_3(CH_2)_{11}SPh$

tert-Butyl phenyl sulfide (**S1**). Colorless oil (72%), R_f 0.43 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.29 (9H, s), 7.30-7.37 (3H, m, Ph) and 7.50-7.54 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 25.0, 126.3, 128.8 (2C), 129.8 (2C) and 137.4; MS *m/e* (relative intensity): 166 (M^+, 17.9), 110 (100), 77 (2.7), 65 (7.6), 57 (16.0).

Adamantyl phenyl sulfide (**S2**). White crystal (80%), m.p. 75-77°C (lit. [194], m.p. 71-72°C) (hexane:EtOAc), R_f 0.50 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.64 (6H, t, J = 6.16, 2.74 Hz, 3×CH_2), 1.80 (6H, d, J = 2.76 Hz, 3×CH_2), 2.01 (3H, br s, 3×CH), 7.28-7.39 (3H, m, Ph) and 7.57-7.66 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 30.0 (3C), 36.2 (3C), 43.6 (3C), 47.8, 128.3 (2C), 128.6, 130.5 and 137.7 (2C); MS *m/e* (relative intensity): 244 (M^+, 18.8), 135 (100), 107 (8.6), 93 (14.1), 79 (14.1), 67 (3.1) and 55 (1.6).

Benzyl phenyl sulfide (**S3**). Colorless crystal (88%), m.p. 48-50°C, R_f 0.31 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.09 (2H, s, $C\underline{H}_2$Ph), 7.18-7.23 and 7.18-7.25 (10H,m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 39.0, 126.3, 127.2, 128.5, 128.8 (4C), 129.8 (2C), 136.4 and 137.4; MS *m/e* (relative intensity): 201 ($[M+1]^+$, 9.0), 200 (M^+, 60.8), 165 (2.7), 109 (8.3), 91 (100), 77 (1.9), 65 (15.6) and 51 (3.5).

Allyl phenyl sulfide (**S4**). Pale yellow oil (40%), R_f 0.30 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.49 (2H, d, J = 6.57 Hz, $C\underline{H}_2$Ph), 5.10 (2H, dd, J = 16.70, 8.22 Hz, HC=$C\underline{H}_2$), 5.78 (1H, m, $\underline{H}C$=CH_2) and 7.16-7.26 (5H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 37.0, 117.7, 126.2, 128.8 (2C), 129.1, 129.8 (2C) and 133.6; MS *m/e* (relative intensity): 151 ($[M+1]^+$, 2.5), 150 (M^+, 100), 135 (78.3), 123 (5.7), 117 (53.9), 109 (50.2), 105 (9.6), 91 (16.0), 77 (1.9), 69 (12.8), 65 (24.8) and 51 (11.4).

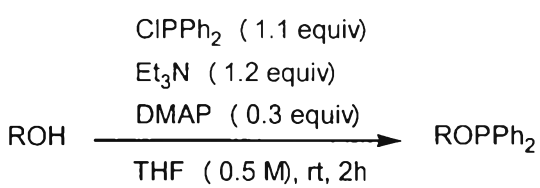
Isopropyl phenyl sulfide (**S5**). Colorless crystal (10%), m.p. 52-54°C (lit. [195], m.p. 56°C) (hexane:EtOAc), R_f 0.24 (hexane); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.22 (6H, d, J = 6.67 Hz, 2×$C\underline{H}_3$), 3.31 (1H, s, J = 6.67 Hz, C$\underline{H}$), 7.15-7.25 (3H, m, Ph), 7.32 (1H, d, J = 7.22 Hz, Ph) and 7.42 (1H, d, J = 7.53 Hz, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 23.1, 127.1, 127.5 (2C), 128.8, 129.1 (2C) and 132.0; MS *m/e* (relative

intensity): 153 ([M+1]$^+$, 5.2), 152 (M$^+$, 49), 137 (4.7), 110 (100), 91 (0.8), 77 (4.9), 66 (9.1), 59 (2.4) and 51 (4.2).

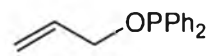
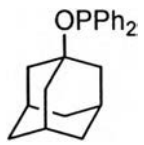
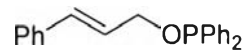
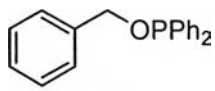
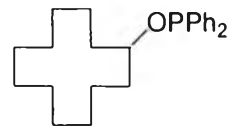
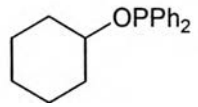
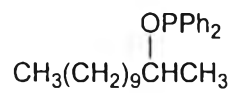
Dodecyl phenyl sulfide (**S6**). Colorless crystal (10%), R_f 0.23 (hexane:EtOAc, 98:2); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.82 (3H, t, J = 6.02 Hz, CH_3), 1.23 (18H, m, 9×CH_2), 1.57 (2H, p, J = 6.84 Hz, CH_2CH_2SPh), 2.88 (2H, t, J = 6.90 Hz, CH_2SPh), 7.11-7,24 (3H, m, Ph) and 7.50 (2H, t, J = 7.03 Hz, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.2, 22.7, 28.9, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.7, 31.9, 33.6, 125.6, 127.1, 127.5, 128.8, 129.1 and 137.1; MS *m/e* (relative intensity): 279 ([M+1]$^+$, 21.3), 278 (M$^+$, 100), 165 (1.7), 123 (20.5), 110 (92.2), 91 (1.3), 77 (2.6), 69 (4.4) and 55 (7.5).

tert-Butyl phenyl telluride (**Te1**). Colorless oil (94%), R_f 0.37 (hexane). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.29 (9H, s, 3×CH_3), 7.30-7.37 (3H, m, Ph) and 7.50-7.54 (2H, m, Ph).

3.4.5 General procedure for the synthesis of alkyl diphenylphosphinites



To a stirred solution of alcohol (10mmol) and DMAP (3 mmol) in dry THF (20 mL) were added Et_3N (12 mmol) followed by $ClPPh_2$ (11 mmol) under Ar atmosphere. After stirring at rt for 2 h, TLC showed complete consumption of the alcohol, and the resulted white slurry was concentrated by a rotary evaporator. After the dilution of the residue with hexane/EtOAc (v/v = 9/1, 100 mL), the mixture was filtered through a pad of alumina (on the top) and Celite (on the bottom). The filtrate was concentrated under reduced pressure to give the desired phosphinites in >90% yields. Since *tert*-alkyl phosphinites were moderately sensitive to air and moisture, they should be stored at <10 °C under dry Ar atmosphere.

	$ROPPh_2$		$ROPPh_2$
P1	$^tBuOPPh_2$	**P5**	
P2		**P6**	
P3		**P7**	
P4		**P8**	

tert-Butyl diphenylphosphinite (**P1**). White crystal (92%), m.p. 33-35°C, R_f 0.69 (hexane:EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.42 (9H, s, 3×CH_3) and 7.29-7.58 (10H, m, 2×Ph); MS *m/e* (relative intensity): 258 (M^+, 0.16), 202 (100), 183 (14.6), 155 (27), 125 (9.0), 115 (1.0), 107 (2.5), 77 (8.2), 57 (26.0), 47 (6.3) and 41 (2.4).

Adamantyl diphenylphosphinite (**P2**). White crystal (90%), m.p. 58-60°C (lit. [183], m.p. 66-68°C), R_f 0.73 (hexane:EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.59 (6H, s, 3×CH_2), 1.95 (6H, s, 3×CH_2), 2.09 (3H, s, 3×CH) and 7.23-7.55 (10H, m, 2×Ph); MS *m/e* (relative intensity): 336 (M^+, 29.2), 335 (23.3), 202 (10.8), 201 (10.3), 183 (10.9), 135 (100), 107 (8.0), 93 (12.0), 79 (1.7), 67 (4.0), 55 (2.0) and 41 (2.0).

Benzyl diphenylphosphinite (**P3**). Colorless oil (80%), R_f 0.63 (hexane:EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.80 (2H, d, J_{HP} = 9.25 Hz, CH_2) and 7.25-7.51 (15H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 127.5, 127.8, 128.3 (2C), 128.4 (2C), 128.6 (2C), 129.4 (2C), 130.4 (2C), 130.7 (2C), 131.7, 131.8, 132.3 and 138.8; MS *m/e* (relative intensity): 292 (M^+, 6.7), 291 (25.7), 201 (100), 183 (5.6), 152 (2.7), 128 (1.3), 91 (8.3), 77 (9.8), 65 (2.6) and 51 (3.2).

Cyclohexyl diphenylphosphinite (**P4**). Colorless oil (90%), R_f 0.50 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.15-2.00 (10H, m, 5×CH_2), 7.22-

7.55 (1H, m, 3×CH_2) and 7.22-7.55 (10H, m, 2×Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.1 (2C), 25.5 (2C), 34.3, 79.4, 128.2 (2C), 128.3 (2C), 128.5, 128.9, 130.1 (2C), 130.3 (2C), 130.8 and 132.6; MS *m/e* (relative intensity): 284 (M^+, 3.8), 202 (100), 183 (21.2), 155 (32.2), 125 (10.9), 107 (10.9), 107 (3.1), 77 (8.7) and 55 (4.7).

Allyl diphenylphosphinite (**P5**). Colorless oil (quant.), R_f 0.67 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.38 (2H, dd, J_{HP} = 9.92 Hz, J_{HH} = 5.27 Hz, CH_2OPPh_2), 5.35 (2H, dd, J = 17.53, 10.44 Hz, HC=CH_2), 5.97 (1H, m, HC=CH_2) 7.35-7.37 (6H, m, 2×Ph) and 7.49-7.53 (4H, m, 2×Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 70.7, 116.7, 128.3 (4C), 129.3 (4C), 130.3, 131.7 (2C) and 135.2 (2C); MS *m/e* (relative intensity): 243 ($[M+1]^+$, 2.4), 242 (M^+, 15.2), 241 ($[M-1]^-$, 14.6), 207 (4.1), 201 (100), 183 (6.2), 171 (2.2), 152 (3.6), 115 (3.0), 107 (1.5), 77 (11.9) and 51 (5.0).

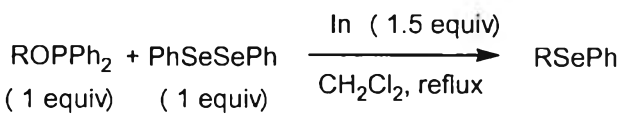
Cinnamyl diphenylphosphinite (**P6**). Pale yellow solid (quant.), m.p. 42-44°C, R_f 0.57 (hexane:EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.68 (2H, d, J = 7.37 Hz, CH2SePh), 6.25 (1H, d, J = 15.78 Hz, HC=CHPh), 6.34 (1H, d, J = 15.80, 7.89 Hz, HC=CHCH_2), 7.26-7.28 (10H, m, 2×Ph) and 7.51-7.54 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 65.5, 70.4, 70.7, 124.1, 126.6 (2C), 128.3 (2C), 128.5 (2C), 129.4 (2C), 130.4 (2C), 130.6 (2C), 131.7, 132.2, 133.8, 136.6 and 141.8; MS *m/e* (relative intensity): 319 ($[M+1]^+$, 14.2), 318 (M^+, 69.8), 317 ($[M-1]^-$, 82.1), 303 (4.2), 201 (100), 193 (13.0), 178 (10.5), 155 (7.5), 125 (5.2), 115 (28.0), 102 (2.4), 91 (10.8), 77 (18.1) and 51 (6.9).

Cyclododecyl diphenylphosphinite (**P7**). White solid (87%), m.p. 65-67°C, R_f 0.86 (hexane:EtOAc, 92:8); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.20-1.50 (18H, m, 9×CH_2), 1.60-1.75 (4H, m, 2×CH_2), 1.77-1.86 (1H, m, CH), 7.45-7.55 (4H, m, Ph) and 7.65-7.78 (6H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.0 (2C), 23.2 (2C), 23.3 (2C), 23.8, 24.2 (2C), 32.4 (2C), 69.0, 128.8, 129.0, 130.7, 130.8, 132.5 and 132.6; MS *m/e* (relative intensity): 166 ($[M-OPPh_2]^-$, 37.7), 138 (4.1), 123 (9.6), 109 (27.8), 96 (58.7), 81 (81.2), 67 (100) and 55 (77).

2-Dodecyl diphenylphosphinite (**P8**). Colorless oil (89%), R_f 0.88 (hexane:EtOAc, 92:8); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.82 (3H, t, J = 6.13 Hz,

$C\underline{H}_3CH_2$), 1.17-1.30 (21H, m, 8×CH_2 and $CHC\underline{H}_3$), 1.41-1.61 (2H, m, $C\underline{H}_2CH$), 3.95 (1H, s, J = 5.87 Hz, $CH_2C\underline{H}$), 7.19-7.37 (6H, m, Ph) and 7.44-7.68 (4H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.2, 22.3, 22.7, 25.6, 29.4, 29.5, 29.6 (2C), 29.6, 31.9, 38.4, 68.1, 128.1 (2C), 128.2 (2C), 128.9, 129.0, 130.0, 130.2, 130.3, 130.5, 130.8, 132.6; MS *m/e* (relative intensity): 370 (M^+, 0.6), 202 (100), 183 (13.6), 155 (17.8), 125 (8.1), 77 (4.1) and 55 (2.4).

General procedure for synthesis of alkyl phenyl selenides from alkyl diphenylphosphinites

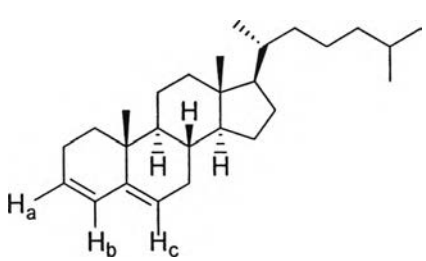


Indium powder (0.75 mmol, 86.1 mg), diphenyl diselenide (0.5 mmol, 156.1 mg), Alkyl diphenylphosphinites (0.5 mmol) and CH_2Cl_2 (3 mL) were placed in a two-necked flask. The resulting mixture was stirred at reflux for 2 h under nitrogen. After completed reaction, the mixture was quenched with 1 M HCl and then extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and purified by column chromatography on silica gel eluting with hexane, to give the corresponding alkyl phenyl selenides.

3.4.6 General procedure for the synthesis of olefination

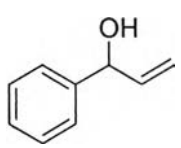
General procedure for olefin synthesis

To a solution of alkyl phenyl selenides (0.5 mmol) in THF (2 mL) was stirred and after cooling in an ice bath, 30% H_2O_2 (250 mL) was added dropwise over a period of 1 h. The ice bath was removed and the solution was stirred for an addition hour. The mixture was diluted with water and extracted with hexane. The hexane layer was washed with aq Na_2CO_3 and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure.



Cholestene. Colorless solid (71%), (lit. [196], m.p. 78-80°C) (hexane), R_f 0.70 (hexane). IR (neat): 3012, 2945, 2864, 1731, 1677, 1466, 1381 and 1027 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.63 (3H, m, CH_3), 0.79 (6H, d, J = 6.54 Hz, 2×CH_3), 0.88 (3H, m, CH_3), 1.19 (3H, m, CH_3), 0.78-2.10 (26H, m, CH_2 and CH), 5.32 (1H, br s, HC=C$\underline{H}_c$), 5.45-5.60 (1H, d, J = 9.48 Hz, CH=C$\underline{H}_b$) and 5.85 (1H, d, J = 9.82 Hz, C$\underline{H}_a$=CH); ^{13}C-NMR ($CDCl_3$) δ (ppm): 12.0, 18.7, 18.8, 21.0, 22.6, 22.8, 23.0, 23.8, 24.2, 28.0, 28.2, 29.7, 31.7, 33.7, 35.2, 35.8, 36.2, 39.5, 39.8, 42.4, 48.4, 56.1, 56.9, 123.2, 125.0, 129.0 and 141.4; MS *m/e* (relative intensity): 369 (M^+, 29.8), 368 (100), 353 (35.6), 326 (4.8), 255 (21.4), 247 (26.8), 213 (21.2), 159 (16.6), 147 (52.8), 120 (17.3), 105 (32.7), 91 (25.9), 81 (29.9), 67 (12.8) and 55 (14.2).

1-Dodecene. Colorless oil (70%), R_f 0.86 (hexane). IR (neat): 3066, 2925, 2848, 1588, 1460 and 1378 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.88 (3H, t, J = 6.78 Hz, CH_3), 1.22-1.30 (14H, m, 7×CH_2), 1.36-1.39 (2H, m, C$\underline{H}_2$CH_2CH=CH_2), 2.05 (2H, q, J = 6.98 Hz, C$\underline{H}_2$CH=CH_2), 4.96 (2H, dd, J = 21.0, 12.35 Hz, HC=C$\underline{H}_2$) and 5.82 (1H, m, $\underline{H}$C=CH_2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.7, 28.9, 29.2, 29.3, 29.5, 29.6 (2C), 32.0, 33.8, 114.1 and 139.3; MS *m/e* (relative intensity): 168 (M^+, 4.8), 140 (5.2), 140 (5.2), 125 (6.9), 111 (20.0), 97 (58.7), 83 (72.6), 69 (84.4), and 55 (100).



3-Phenyl-1-propen-3-ol. Colorless oil (74%), R_f 0.12 (hexane:EtOAc, 92:8). IR (neat): 3144-3603, 3063, 3022, 2925, 1767, 1670, 1445, 1416, 1245, 1182, 1030 and 929 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.15 (2H, dd, J = 17.04, 7.20 Hz, HC=C$\underline{H}_2$), 5.34 (2H, d, J = 17.14, 8.22 Hz, C$\underline{H}$Ph), 5.07 (1H, m, $\underline{H}$C=CH_2) and 7.26-7.41 (5H, m, Ph); MS *m/e* (relative intensity): 134 (M^+, 48.9), 133 (100), 115 (33.2), 105 (63.1), 92 (49.7), 77 (6.2), 63 (6.5), 55 (20.4) and 51 (19.1).