การเตรียมแอลคิลไอโอไดด์และแอลคิลเฟนิลซีลีไนด์จากแอลคิลไดเฟนิลฟอสฟีไนต์

นายพูนลาภ เงินมณีรัตน์

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PREPARATION OF ALKYL IODIDES AND ALKYL PHENYL SELENIDES FROM ALKYL DIPHENYLPHOSPHINITES

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A Thesis Submitted in Partial Fulfillment of the Requirements
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Thesis Title	PREPARATION OF ALKYL IODIDES AND ALKYL PHENYL SELENIDES FROM ALKYL DIPHENYL PHOSPHINITES
By	Mr. Poonlarp Ngernmaneerat
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พูนลาภ เงินมณีรัตน์ : การเตรียมแอลคิลไอโอไดด์และแอลคิลเฟนิลซีลีไนด์จากแอลคิลไดเฟนิลฟอสฟีไนท์. (PREPARATION OF ALKYL IODIDES AND ALKYL PHENYL SELENIDES FROM ALKYL DIPHENYL PHOSPHINITES) อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ดร.วรินทร ชวศิริ, 65 หน้า.

ได้พัฒนาวิธีการเตรียมแอลคิลไอโอไดด์และแอลคิลเฟนิลซีลีไนด์จากแอลคิลไดเฟนิลฟอสฟีไนท์ที่มีประสิทธิภาพภายใต้ภาวะการทดลองที่ไม่รุนแรง ในกรณีของการเตรียมแอลคิลเฟนิลซีลีไนด์เลือกใช้อะดาเมนทิลไดเฟนิลฟอสฟีไนท์เป็นสารต้นแบบ ระบบรีเอเจนต์ผสมระหว่างไดเฟนิลไดซีลีไนด์และอินเดียม ที่อุณหภูมิรีฟลักซ์ ให้ปริมาณผลิตภัณฑ์แอลคิลเฟนิลซีลีไนด์ในปริมาณสูง แม้แต่ในกรณีของการเตรียมแอลคิลเฟนิลซีลีไนด์ตติยภูมิ ปฏิกิริยาโดยใช้สารตั้งต้นที่สามารถหมุนระนาบแสงได้แสดงให้เห็นว่ากลไกปฏิกิริยาเกิดผ่านปฏิกิริยาแทนที่แบบ S_N2 สำหรับการเตรียมแอลคิลไอโอไดด์จากแอลคิลไดเฟนิลฟอสฟีไนท์ เลือกใช้โอเลอิลไดเฟนิลฟอสฟีไนท์เป็นสารต้นแบบ การใช้ไอโอดีนเป็นไอโอดิเนทิงเอเจนต์ ทำให้ปฏิกิริยาเกิดสมบูรณ์ภายในเวลาสั้น และได้ปริมาณผลิตภัณฑ์สูงแม้แต่ในกรณีของการเตรียมแอลคิลไอโอไดด์ตติยภูมิ นอกจากนี้ได้พัฒนาปฏิกิริยาขั้นตอนเดียวของการเตรียมแอลคิลไอโอไดด์จากแอลคิลไดเฟนิลฟอสฟีไนท์เบื้องต้น พบว่าระบบไอโอดีน-คลอโรไดเฟนิลฟอสฟีนและไพรีดีน โดยใช้ไดคลอโรมีเทนทำปฏิกิริยาที่อุณหภูมิห้องเป็นระบบที่เหมาะสมในการทำปฏิกิริยา โดยสามารถเตรียมสารผลิตภัณฑ์ต้นแบบสองชนิดคือ เฮกซิลไอโอไดด์ และออกทิลไอโอไดด์ ได้ในปริมาณสูง

สาขาวิชา...ปิโตรเคมีและวิทยาศาสตร์พอลิเมอร์...ลายมือชื่อนิสิต.....

ปีการศึกษา.....2550.....ลายมือชื่ออาจารย์ที่ปรึกษาวิทยานิพนธ์หลัก.....

4972424223: MAJOR PETROCHEMISTRY AND POLYMER SCIENCE
KEY WORD: ALKYL DIPHENYLPHOSPHINITES / ALKYL PHENYL SELENIDES / ALKYL IODIDES

POONLARP NGERNMANEERAT: PREPARATION OF ALKYL IODIDES AND ALKYL PHENYL SELENIDES FROM ALKYL DIPHENYL PHOSPHINITES. THESIS PRINCIPAL ADVISOR: ASST.PROF. WARINTHORN CHAVASIRI, Ph.D., 65 pp.

The mild and efficient approaches for preparing alkyl phenyl selenides and alkyl iodides from alkyl diphenylphosphinites were developed. In the case of the synthesis of alkyl phenyl selenides, 1-adamantyl diphenylphosphinite was utilized as a model substrate. The combination of PhSeSePh and indium at reflux afforded alkyl phenyl selenides in high yield. Appealingly, tertiary selenides also worked well under this optimal condition. The reaction of an optically active substrate distinctly revealed that this mechanism took place *via* S_N2 displacement. Considering to iodination of alkyl diphenylphosphinites, *cis*-oleyl diphenylphosphinite was selected as a chemical model. The use of only I_2 as an iodinating agent could complete the reaction in short period of time and acquired high yields of the desired products even in the case of tertiary alkyl iodides. Furthermore, *in situ* iodination of alcohols through alkyl diphenylphosphinites was also preliminarily investigated to develop and simplify this protocol. The $I_2/ClPPh_2$ system in the presence of pyridine in CH_2Cl_2 at RT was affirmed as the optimal reaction condition. The model iodides, 1-hexyl iodide and 1-octyl iodide, were provided in high yields.

Field of Study:..Petrochemistry and Polymer Science..Student's Signature:.....P. Ngt.....
Academic Year:.....2007..... Principal Advisor's Signature:.....W. Chavasiri.....

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LIST OF ABBREVIATIONS

α	alpha
δ	chemical shift
J	coupling constant (NMR)
°C	degree of Celsius
DMAP	4-(dimethylamino)pyridine
d	doublet (NMR)
dd	doublet of doublet (NMR)
equiv	equivalent (s)
GC	Gas chromatography
g	gram (s)
h	hour (s)
Hz	hertz
HMPA	hexamethylphosphoramide
MB	mass balance
m/z	mass per charge ratio
mmol	millimole (s)
mL	milliliter (s)
min	minute (s)
m	multiplet (NMR)
NMR	nuclear magnetic resonance
% yield	percentage yield
quant.	quantitative yield
q	quartet (NMR)
R_f	retardation factor in chromatography
RT	room temperature
s	singlet (NMR)
TMEDA	tetramethylethylenediamine
t	triplet (NMR)
TLC	thin layer chromatography

CHAPTER I

INTRODUCTION

Nowadays, functional group interconversion from large quantity chemicals such as alcohols to their intermediates is indispensable in organic and industrial synthesis. Intermediates play an important role as the media for the preparation of diverse products in downstream industry especially in the case of complicated or tedious procedures required for the direct transformation of substrates. Alkyl phenyl selenides and alkyl iodides are among those examples of appealing intermediates which have abundant utilities. Due to their weak σ bond formation, they have thus gained considerable interest as attractive intermediates serving not only in organic chemistry but also in medical profession, pharmacology and industry.

1.1 Introduction of alkyl phenyl selenides

Selenium was initially discovered by Berzelius in 1817 as a by-product from the treatment of sulfur ore [1]. It is in the same column as the elements oxygen, sulfur, and tellurium of the periodic table (group 16). Only sulfur, selenium and tellurium were occasionally called "chalcogen" because of having *d*-orbital and some similar chemical properties. A wide range of oxidation state (-2 to +6) of selenium brought a variety of organoselenium compounds formation.

Organoselenium chemistry has just become a part of mainstream organic chemistry since the early 1970s, although the element of selenium and the selenium functional groups have been known for a long time. The apparent turning point came when Sharpless and Reich disclosed effective methods for olefin syntheses *via* selenoxide elimination [2-3]. Nowadays, over 1,000 publications developing and utilizing of new organoselenium methodologies appear in print [4-7]. There are a plethora of reasons why these compounds have attracted widespread interest.

First, organoselenium anions are potent nucleophiles that exhibit a strong preference for reaction with soft acid. On the contrary, they can also serve as extremely reactive as soft electrophiles when organoselenium species contain reasonable leaving groups such as -Cl, -Br and $-O_2CCF_3$. Thus, in general, both nucleophilic and electrophilic reagents are available for the introduction of selenium under very mild conditions [8]. Second, in the case of functional group interconversion, many reactions involving the cleavage of C-Se, O-Se and N-Se bonds are rapid because of weak σ bond formation of selenium. In this regard, alkyl selenoxides are faster about 1,000 times than sulfoxides in *syn*-elimination reactions [9].

As mentioned above, organoselenium species can be efficiently introduced, manipulated and removed in a variety of routes under mild conditions. The enormous utilities of organoselenium compounds in organic synthesis are presented in Fig 1.1.

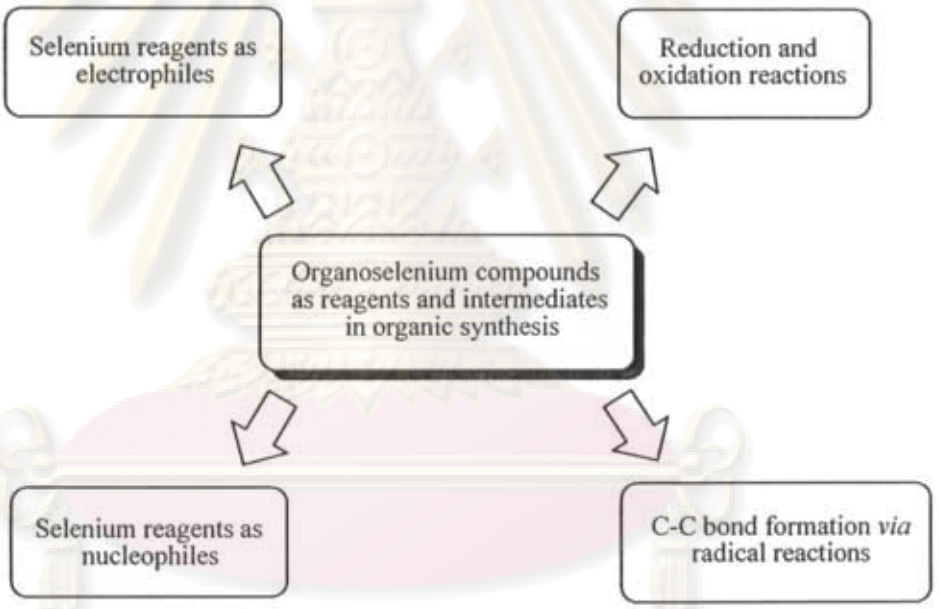


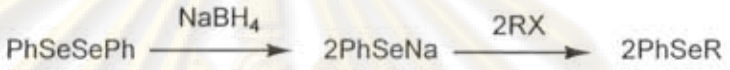
Figure 1.1 The utilities of alkyl phenyl selenides in organic synthesis.

These selenides have also played an important role in biochemical processes, serving as therapeutic compounds ranging from antiviral and anticancer agents to naturally occurring food supplements [10-11]. Furthermore, they are utilized for the manufacture and production of rubber as vulcanizing agents, textiles and photographic emulsions. In addition, because of their anti-bacterial activity and covalently attachment without loss of catalytic activity, some selenides are particularly applied as surface coating agents to inhibit bacteria cell growth used in

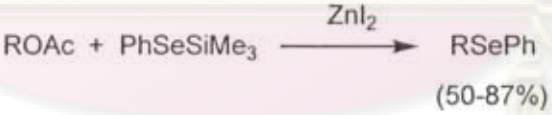
many industries for example: medical devices, textiles, paints and sealants and marine anti-foulings. Material to which selenides has been successfully attached include cellulose sponges, silicone hydrogel lenses, polymethylmethacrylate, epoxy, as well as biological molecules such as peptides and antibody.

1.2 Literature reviews of alkyl phenyl selenides synthesis

The classical method for unsymmetrical diorganyl selenide was a Williamson-type approach. PhSeSePh was reduced with $NaBH_4$ to give a sodium salt of alkyl selenol. This salt then reacted with alkyl halides to afford the unsymmetrical diorganyl selenides [12].



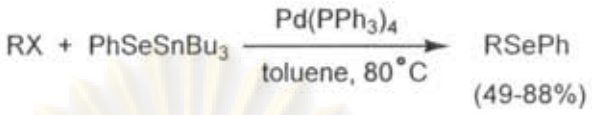
In 1979, Miyoshi and coworkers reported the synthesis of alkyl phenyl selenides by the reaction of $PhSeSiMe_3$, which could be prepared from PhSeSePh and Me_3SiCl in the presence of Na, with alkyl acetates as well as with lactones in the presence of ZnI_2, as a Lewis acid catalyst. In the case of alkyl acetates, *t*-BuOAc displayed higher reactivity than *n*-BuOAc and *sec*-BuOAc. The cleavage in S_N2-like manner for R = *n*-Bu and *sec*-Bu, and that in S_N1-like manner for R = *t*-Bu were suggested. The substitutions of benzyl and allyl acetates were obtained in high yields. Lactones were also found to be converted into selenides in high yields [13].



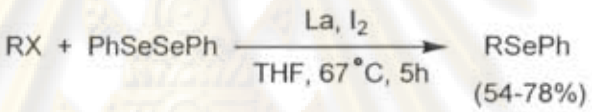
(70-100%)

In 1999, Nishiyama and coworkers introduced that alkyl or aryl halides reacted with tributylstannyl selenide in the presence of a catalytic amount of $Pd(PPh_3)_4$ giving the corresponding selenides in moderate to high yields. $Pd(PPh_3)_4$ could also catalyze aromatic iodides bearing hydroxy and amino groups, which had a

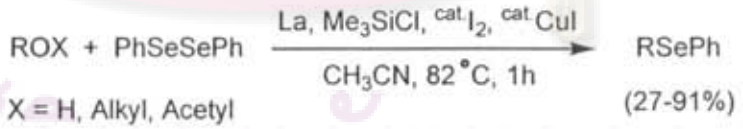
strong coordination ability to Pd metal, affording the corresponding diaryl selenides in moderate yields [14].



Later, in 2002, Nishino *et al.* developed a one-pot and neutral synthetic method for unsymmetrical selenides from the reaction between organic halides and PhSeSePh in the presence of catalytic amount of I_2. Primary alkyl iodides and bromides were formed in moderate to high yields while primary alkyl chlorides and secondary alkyl iodides needed hexamethylphosphoramide (HMPA) or tetramethylethylenediamine (TMEDA) to improve the yields. On the other hand, *tert*-butyl iodide did not proceed at all even under harsh reaction conditions [15].

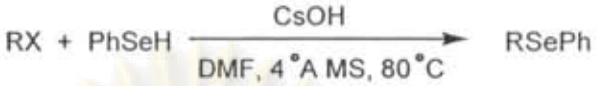


In 2003, Nishino and coworkers investigated a one-pot synthesis of alkyl phenyl selenides *via* the S_H2 reaction of PhSeSePh with alkyl radical generated by the treatment of oxygen-containing compounds: alcohols, ethers and esters with La/Me_3SiCl/$^{cat.}I_2$/$^{cat.}$CuI. Tertiary alkyl phenyl selenides were synthesized in moderate to good yields. Furthermore *tert*-alkyl phenyl sulfide using PhSSPh was also achieved by this method [16].

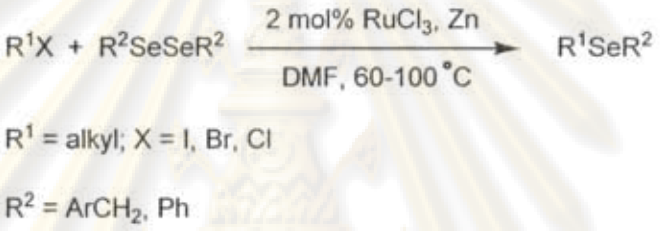


In 2004, Cohen *et al.* explored the preparation of unsymmetrical selenides using a one-pot and mild approach of the cesium-promoted alkylation. Various organic halides reacted with PhSeH in the presence of CsOH and 4°A molecular sieves. Unsymmetrical primary and secondary alkyl phenyl selenides were exclusively formed in high yields, whereas tertiary alkyl phenyl selenide were not observed at all. Moreover, an amino acid derivative successfully generated a

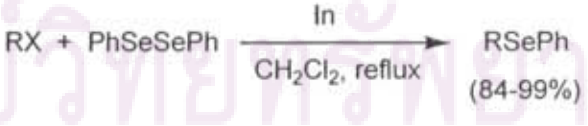
selenopeptide, and the synthesis of unsymmetrical diorganyl selenides on solid support was also investigated [17].

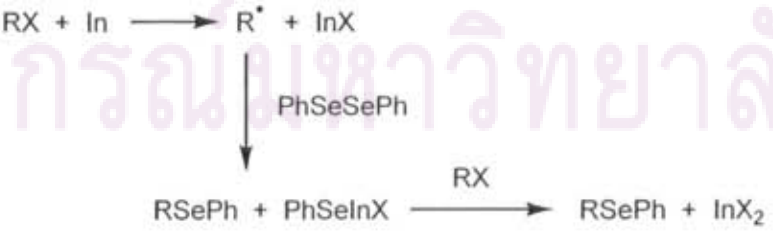


In 2005, a one-pot route to unsymmetrical diorganyl selenides was reported by $RuCl_3$ catalyzed reactions of dibenzyl or diphenyl diselenides with alkyl halides in the presence of Zn. Under these conditions, organic iodides, bromides and activated chlorides afforded the corresponding selenides in moderate to high yields, whereas unreactive organic chlorides required NaBr as the additive [18].

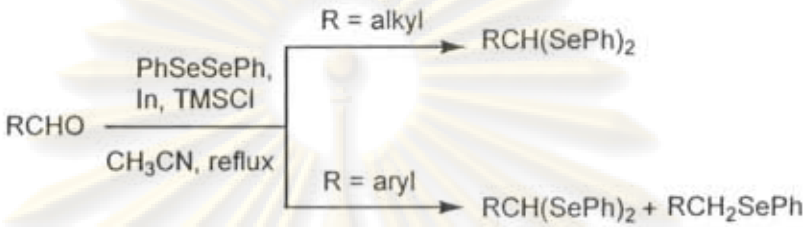


In the same year, Munbunjong and coworkers reported In-mediated mild and one-pot synthesis of alkyl phenyl selenides from alkyl halides and PhSeSePh in CH_2Cl_2. The reaction showed high selectivity for *tert*-alkyl, benzylic and allylic halides over primary and secondary alkyl halides. In addition, alkyl phenyl sulfides and tellurides were also provided by the reaction of tertiary butyl chloride with PhSSPh and PhTeTePh, respectively. The reaction pathway through the S_H2 reaction of alkyl radical which was generated by the reduction of alkyl halides with In was proposed [19].





In 2006, Ranu and Mandal introduced one-pot routes to selenoacetals and alkyl phenyl selenides *via* an In-TMSCl promoted reaction of PhSeSePh and aldehydes. Aliphatic aldehydes produced the corresponding selenoacetals, whereas aromatic aldehydes furnished exclusively or predominantly the corresponding aryl phenyl selenides [20].



Besides the reactions quoted above, there were still many reactions capable of manipulating unsymmetrical diorganylselenides [21-22]. Nevertheless, most of works performed in this field were highly problematic because of the improper handling of selenide reagents used, strongly basic or acidic reaction conditions, and low yields of tertiary alkyl phenyl selenides. The development of new and efficient synthetic methods using stable selenium reagents under mild conditions has been still called for.

1.3 Introduction of alkyl iodides

Organic halides are organic compounds in which one or more hydrogen atoms are substituted by a halogen atom, -Cl, -Br or -I. A variety of reactions involving the cleavage of C-Cl, C-Br and C-I bonds are rapid because of weak σ bond formation. Among halides, chloride, bromide and iodide, organic iodides are the most chemically reactive, although they are less stable than the corresponding chlorides or bromides. Alkyl iodides are in addition the most expensive compounds compared with other alkyl halides. In some cases, alkyl iodides show unique reactivity [23]. Therefore, they served as important reagents and intermediates for a wide range of organic synthesis such as carbon-carbon coupling reactions, substitutions, eliminations and rearrangements. Iodo compounds play important roles not only in organic chemistry but also in medical profession, pharmacology and industry. Iodides appear to function as antioxidant, neutralizing free radical and are needed in trace amounts for the production of thyroid hormones such as thyroxine. Although chlorides are industrially

employed because of their low costs, iodides have been attracted considerable interest due to their greater reactivity. In industrial process for the production of diphenyl sulfone compounds, the developer for leuco dyes to be used in thermal recording papers, alkyl iodides such as isopropyl iodide are used as reagents instead of alkyl chlorides and bromides. Additionally, they are employed as initiators and catalysts in polymerization processes [24].

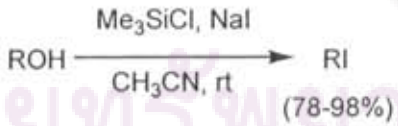
There are many procedures for the preparation of alkyl iodides [25-29]. Among the substrates, alcohols are considered to be the most common ones as they are commercially available and there are large quantities compared with others. The synthetic routes for the transformation of alcohols into iodides might be classified by iodide sources into three categories [30]:

1) using HI
2) using iodide salts
3) using phosphorus-based iodinating agents

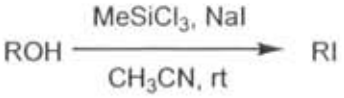
The development of iodination routes has recently called for mild and neutral reaction conditions; hence, only the methods using iodide salts and phosphorus-based iodinating agents are herein mentioned.

1.3.1 Iodination of alcohols using iodide salts

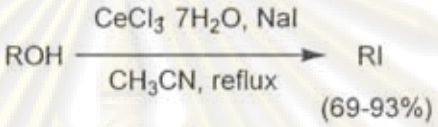
The system using Me_3SiCl and NaI was documented for the cleavage of esters, lactones and carbamates as well as the dealkylation of ethers and the conversion of alcohols into iodides. In the case of iodination of alcohols, primary, secondary and tertiary as well as allylic and benzylic iodides were prepared in high yields [31].



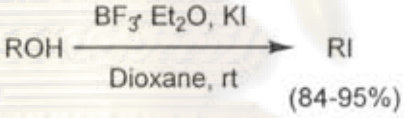
Later, Olah and coworkers developed another similar system for various synthetic methods and reactions using $MeSiCl_3$ instead of Me_3SiCl. In this regard, iodination of tertiary and benzylic alcohols were almost instantly converted to the corresponding iodides when treated the reactions at RT. On the other hand, primary alcohols were found to react extremely slowly such as 72 h in the case of 1-undecanol [32].



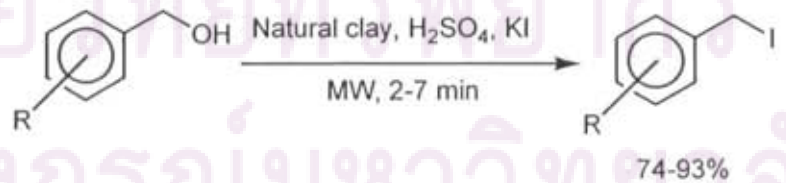
In 2000, Deo and coworkers proposed the new system using NaI as an iodide source and $CeCl_3 \cdot 7H_2O$ as a Lewis acid. The conversion of primary and substituted benzylic alcohols into the corresponding iodides required drastic conditions and long reaction times, 13-48 h. Moreover, the reaction of tertiary alcohols suffered from the problem of the competing elimination [33].



In 2001, Bandger and coworkers reported the synthesis of alkyl iodides with $KI/BF_3 \cdot Et_2O$ system. The reactions were found to be highly selective to only allylic and benzylic alcohols, whereas saturated aliphatic alcohols did not yield iodides even after prolonged stirring in dioxane [34].

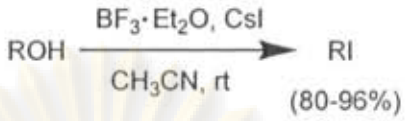


In 2002, the heterogeneous reaction using KI/H_2SO_4 supported on natural kaolinitic clay was developed by Bandger and other coworkers. Under microwave irradiation, the transformation of benzylic alcohols into benzylic iodides were achieved in high yields and short reaction times, whereas using an oil bath as an alternative conventional heating mode at 100°C gave trace amount of iodides [35].

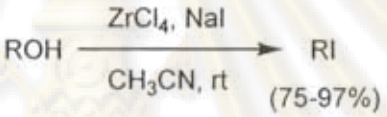


In 2003, Hayat and coworkers studied the preparation of alkyl iodides using $CsI/BF_3 \cdot Et_2O$ system. Benzylic alcohols with electron-donation groups such as -OH, $-OCH_3$, -Cl and electron-withdrawing group such as *p*-nitrobenzyl alcohol proceeded smoothly. Allyic and secondary alcohols were also performed well by this technique;

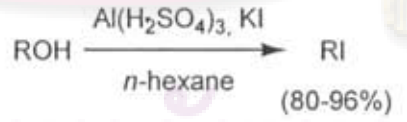
however, saturated aliphatic alcohols did not yield iodides even after prolonged time [36].



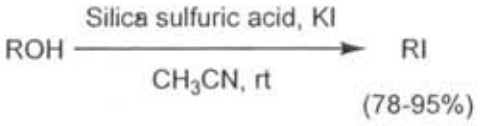
Later, in 2004, Firouzabadi and coworkers prepared alkyl iodides from alcohols and NaI in the presence of $ZrCl_4$. Primary, secondary and even tertiary iodides were achieved in high yields. The reaction worked well for iodination of benzylic alcohols; nevertheless, the rate of the reaction was slower when the substituted group was electron-withdrawing group such as $-NO_2$. In the case of allyl alcohol with a terminal double bond suffered from the allylic rearrangement [37].



In 2006, iodination of benzylic and aliphatic alcohols by $Al(HSO_4)_3$/KI was examined by Tajik and coworkers. Benzylic alcohols with electron-donating or electron-withdrawing groups on the rings were successfully iodinated even if the rate of reaction was slower in the case of the ring containing an electron-withdrawing group. This method could also be employed for the conversion of aliphatic alcohols to the corresponding iodides in good yields even in the case of tertiary alcohols such as 1-adamantanol [38].

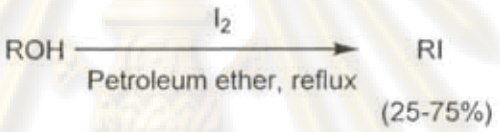


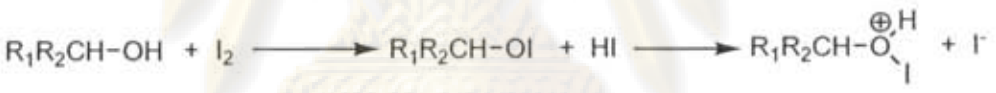
In the same year, Hajipour *et al.* reported the conversion of alcohols into iodides under heterogeneous condition using KI and silica sulfuric acid (SiO_2-H_2SO_4) which could be provided from chlorosulfonic acid and HCl (g). Allylic alcohol was smoothly converted to the corresponding iodide in high yield. In the case of benzylic alcohols, the reaction was slightly accelerated by an electron-donating group such as $-OCH_3$, while the substitution of the electron-withdrawing group such as $-NO_2$ on the aromatic ring retarded the transformation [39].

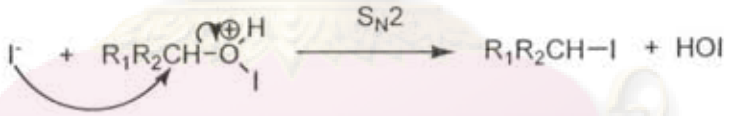


1.3.2 Iodination of alcohols using phosphorus-based iodinating agents

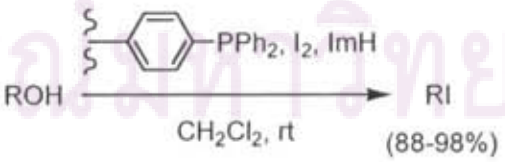
One of the popular methods for iodination of alcohols to the corresponding iodides was the one using iodine as an iodinating agent. Secondary, tertiary and benzylic iodides were successfully afforded in moderate to good yields. Tertiary alcohols underwent facile iodination on the reactions with iodine obtaining *tert*-iodides in moderate yields. The reactions proceeded with completed conversion of configuration; therefore, the possible pathway under S_N2 displacement by iodide ion as a nucleophile was suggested [40].



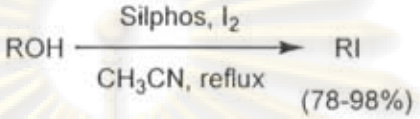




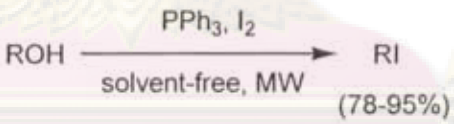
In 2002, Anikumar and coworkers investigated the iodination of alcohols on polymer supported PPh_3. The reaction worked well with *ortho*-, *meta*-, *para*- and multisubstituted benzylic systems containing electron-donating and electron-withdrawing substituents in excellent yields. This method could also be applicable for the reactions of allylic and primary alcohols [41].



Later in 2005, Iranpoor and coworkers introduced a new heterogeneous reagent, silicaphosphine $[PCl)_{3-n}(SiO_2)_n]$ which could be prepared from the reaction of silica gel and PCl_3, for the transformation of alcohols into iodides. By this method, primary, secondary and tertiary alcohols were converted into their iodides in excellent yields. The alcohols substituted with electron-withdrawing groups such as -Cl or $-NO_2$ required longer time to complete the reaction. [42].



In 2006, Hajipour *et al.* reported the procedure for the conversion of benzylic, allylic and aliphatic alcohols to the corresponding iodides using PPh_3/I_2 under solvent-free conditions using microwave irradiation. The reaction was highly selective for the conversion of alkyl aryl, allyl, alkyl and cyclic alcohols. On the contrary, the transformation of phenol into the corresponding iodide was not achieved even after prolonged time. The chemoselectivity evaluation of this method was investigated by competing the iodination of benzylic alcohols with phenol and saturated alcohols. The remarkable selectivity of these reactions allowed only benzylic hydroxy groups to be iodinated without affecting other OH groups [43].



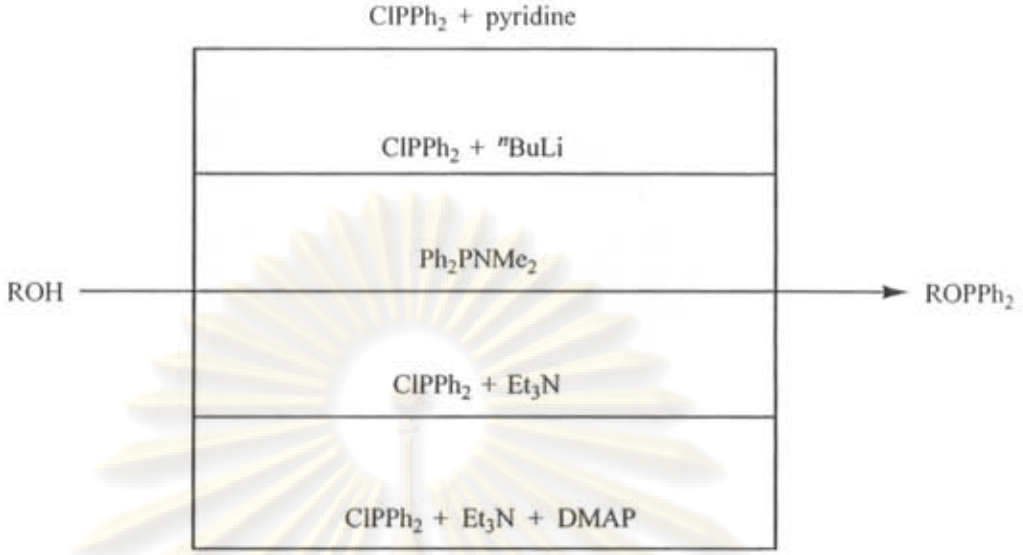
According to the aforementioned results, many efficient methods for iodination of alcohols have been disclosed. Nevertheless, some reactions still suffered from drawbacks such as low yields, long reaction time, drastic and tedious work-up procedures. Therefore, the new methodologies which could solve these problems are still called for.

1.4 Introduction of alkyl diphenylphosphinites

Oxidation-reduction condensation is known as one of very convenient and useful synthetic reactions for the preparation of C-O bond such as esters and ethers [44-45]. The fundamental concept of oxidation-reduction condensation is to perform dehydration condensation by eliminating H_2O as 2[H] and [O] by a combined use of a

weak oxidant and a reductant [45]. The most characteristic feature of this reaction is that it proceeds under mild and neutral conditions without any assistance of acidic or basic promoters. Previously, the reducing agents such as tri-*n*-butylphosphine [44-45] were ongoing employed in these reactions. Subsequently, Mitsunobu developed this concept into the efficient alkylation methods by using a combination of PPh_3 and diethyl azodicarboxylate (DEAD) and achieved condensation reaction between alcohols and various nucleophiles, which is a method widely known as Mitsunobu reaction [45]. After the efforts on these condensation reactions, a challenging problem still remained when bulky secondary or tertiary alcohols were used as alkylating agents. It was then considered that the formation of an important key reaction intermediate, alkoxyphosphonium salts, was strongly interfered by steric hindrance of the alcohols.

The attempt to search for new and suitable combinations of weak reductant and oxidant for the oxidation-reduction condensation has been a matter of continued interest for chemists since the analogous reactions have been reported uninterruptedly. Alkyl diphenylphosphinites were then speculated to form an important intermediate phosphonium salt. Introduction of the alkoxy moiety to a trivalent phosphorus compound before the condensation step is effective for smooth generation of the corresponding pentavalent intermediate, alkoxyphosphonium salt. Moreover, reducing ability of these phosphinites should be higher than that of PPh_3 in order to form the alkoxyphosphinium salt when weak oxidants such as 1,4-benzoquinones were used [46]. With regard to the oxidation-reduction condensation, the utilities of alkyl diphenylphosphinites were reported in the preparation of C-O bond formation such as ethers and ethers [47-50], C-N bond formation such as nitriles [51-52] and C-S bond formation such as alkyl aryl sulfides [53-54]. The preparing methods of alkyl diphenylphosphinites are illustrated in Scheme 1.1.



Scheme 1.1 The conversion of alcohols to alkyl diphenylphosphinites.

Up till now, it was notwithstanding that there was no report optimizing a methodology for the development of intermediates such as alkyl iodides and alkyl phenyl selenides *via* these phosphinites.

1.5 The objectives of this research

The objectives of this research are to explore and develop the optimized conditions for the preparation of alkyl phenyl selenides and alkyl iodides from alkyl diphenylphosphinites which can be performed from alcohols and chlorodiphenyl-phosphine.

CHAPTER II

EXPERIMENTAL

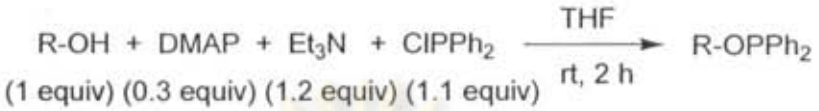
2.1 General procedures

The reactants and products were identified by several spectroscopic techniques. 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). Spectrometers: 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 spectrometric analysis was recorded on Agilent Technologies G1530N instrument (6890N Network GC system-5973 mass selective detector, EI, 70 eV).

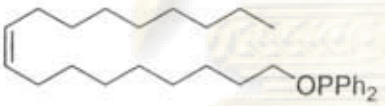
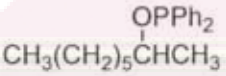
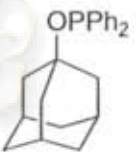
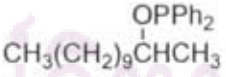
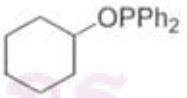
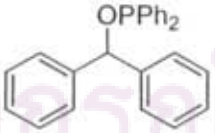
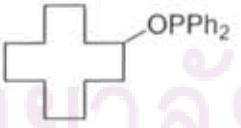
2.2 Chemical reagents

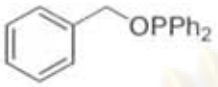
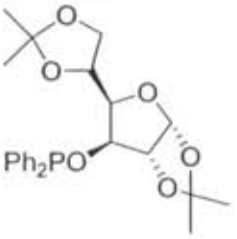
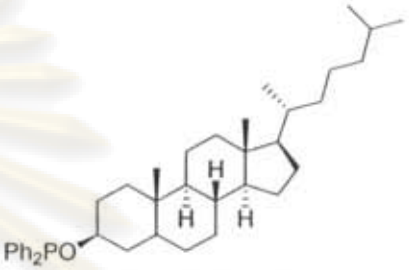
All solvents used in this research were purified, except for reagent grades, and dried prior to use by standard methodology. The substrates and reagents for synthesizing the precursors and products employed in this work were purchased from Fluka and Aldrich chemical companies and were used without further purification. All reactions in non-aqueous solutions were carried out under N_2 or Ar.

2.3 General procedure for the synthesis of alkyl diphenylphosphinites



A solution of alcohol (5 mmol), $ClPPh_2$ (5.5 mmol, 1.0 mL), DMAP (1.5 mmol, 182.5 mg) and Et_3N (6 mmol, 0.8 mL) in dried THF (10 mL) was stirred at RT for 2 h under Ar. The white slurry was concentrated by a rotary evaporator. After the dilution of the residue with hexane/EtOAc (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 phosphinite, which was stored at <10 °C under dry Ar.

	$ROPPh_2$		**$ROPPh_2$**
P1	$CH_3(CH_2)_{15}OPPh_2$	**P8**	
P2		**P9**	$^tBuOPPh_2$
P3		**P10**	
P4		**P11**	
P5		**P12**	

	ROPPh$_2$		ROPPh$_2$
P6		P13	
P7		P14	

1-Hexadecanyl diphenylphosphinite **(P1)**. White solid (90%), R_f 0.62 (hexane: EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 6.82 Hz, CH_3), 1.28-1.38 (26H, m, 13×CH_2), 1.70 (2H, m, CH_2), 3.87 (2H, dd, J = 16.00, 6.80 Hz, CH_2), 7.34-7.39 (6H, m, Ph) and 7.49-7.53 (4H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.2, 22.8, 25.7, 25.9, 29.4, 29.5, 29.6 (2C), 29.7 (2C), 29.8 (2C), 31.5, 31.6, 32.0, 70.3, 128.3 (2C), 128.4 (2C), 129.2 (2C), 130.3 (2C), 130.5 (2C), 142.3 and 142.5.

(Z)-Oleyl diphenylphosphinite **(P2)**. Colorless oil (80%), R_f 0.67 (hexane: EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 6.84 Hz, CH_3), 1.29 (22H, s, 11×CH_2), 1.70 (2H, m, CH_2), 2.02 (4H, m, $\underline{CH_2}CH{=}CH\underline{CH_2}$), 3.86 (2H, dd, J = 16.00, 6.40 Hz, CH_2), 5.37 (2H, m, $C\underline{H}{=}C\underline{H}$), 7.33-7.39 (6H, m, Ph) and 7.49-7.53 (4H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.3, 22.9, 26.1, 27.4, 27.5, 29.5, 29.5, 29.6, 29.7, 29.8, 30.0 (2C), 31.6, 31.7, 32.1, 70.4, 128.4(2C), 128.5 (2C), 129.4 (2C), 130.4 (2C), 130.6 (2C), 131.8, 131.9, 142.4 and 142.6.

2-Octyl diphenylphosphinite **(P3)**. Colorless oil (79%), R_f 0.15 (hexane: EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, J = 6.92 Hz, $C\underline{H_3}CH_2$), 1.22-1.24 (10H, m, 5×CH_2), 1.27 (3H, d, J = 6.20 Hz, $CHC\underline{H_3}$), 4.04 (1H, m, $C\underline{H}OPPh_2$), 7.31-7.37 (6H, m, Ph) and 7.47-7.51 (4H, m, Ph); MS *m/z* (relative intensity): 314 (M^+, 0.7), 202 (100), 183 (26.6), 155 (26.3), 124 (16.3), 112 (5.8), 96 (3.1), 83 (4.6), 77 (27.1), 70 (8.7) and 55 (17.6).

2-Dodecyl diphenylphosphinite **(P4)**. 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, $C\underline{H_3}CH_2$), 1.17-

1.30 (19H, m, 8×CH_2 and $CHC\underline{H}_3$, 1.41-1.61 (2H, m, $C\underline{H}_2CH$), 3.95 (1H, s, $C\underline{H}OPPh_2$), 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, 61.1, 128.1 (2C), 128.2 (2C), 128.9, 129.0, 130.0, 130.2, 130.3, 130.5, 130.8 and 132.6; MS *m/z* (relative intensity): 370 (M^+, 0.6), 202 (100), 183 (13.6), 155 (17.8), 125 (8.1), 77 (4.1) and 55 (2.4).

Diphenylmethyl diphenylphosphinite **(P5)**. Colorless oil (30%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 6.15 (1H, s, CH) and 7.30-7.44 (20H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 64.2, 127.8 (10C), 128.1 (4C), 128.5 (8C) and 141.1 (2C); MS *m/z* (relative intensity): 366 ($[M-2]^+$, 0.01), 202 (3.9), 182 (1.6), 167 (100), 152 (32.8), 139 (7.5), 128 (2.7), 115 (5.9), 105 (2.0), 83 (10.1), 77 (4.6), 63 (4.9) and 51 (4.0).

Benzyl diphenylphosphinite **(P6)**. Colorless oil (80%), R_f 0.63 (hexane: EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.80 (2H, d, J = 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/z* (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).

Allyl diphenylphosphinite **(P7)**. Colorless oil (quant.), R_f 0.67 (hexane: EtOAc, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.38 (2H, dd, J = 9.92, 5.27 Hz, $C\underline{H}_2OPPh_2$), 5.35 (2H, dd, J = 17.53, 10.44 Hz, $HC{=}C\underline{H}_2$), 5.97 (1H, m, $\underline{H}C{=}CH_2$), 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/z* (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).

trans-Cinnamyl diphenylphosphinite **(P8)**. Yellow solid (quant.), R_f 0.57 (hexane: EtOAc, 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 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): 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/z* (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).

tert-Butyl diphenylphosphinite **(P9)**. White solid (92%), 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/z* (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).

1-Adamantyl diphenylphosphinite **(P10)**. White solid (96%), R_f 0.50 (hexane: EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.64 (6H, s, 3×CH_2), 1.99 (6H, s, 3×CH_2), 2.17 (3H, s, 3×CH), 7.30-7.35 (6H, m, Ph), 7.48-7.53 (4H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 31.1 (3C), 36.2 (3C), 44.1 (3C), 75.8, 128.1 (2C), 128.2 (2C), 128.7 (2C), 130.0 (2C), 130.2 (2C), 143.8, 144.0; MS *m/z* (relative intensity): 336 (M^+, 57.7), 201 (33.7), 183 (27.5), 155 (8.4), 135 (100), 107 (20.2), 93 (28.9), 79 (27.4), 67 (9.0), 51 (5.2).

Cyclohexyl diphenylphosphinite **(P11)**. 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, CH), 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/z* (relative intensity): 284 (M^+, 3.8), 202 (100), 183 (21.2), 155 (32.2), 125 (10.9), 107 (10.9), 77 (8.7) and 55 (4.7).

Cyclododecyl diphenylphosphinite **(P12)**. Colorless oil (79%), R_f 0.15 (hexane: EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.12-0.15 (18H, m, 9×CH_2), 1.60-1.64 (2H, m, CH_2), 1.75-1.81 (2H, m, CH_2), 4.09 (1H, q, J = 5.79; CH), 7.31-7.36 (6H, m, Ph), 7.48-7.51 (4H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 20.5 (2C), 22.7 (2C), 22.9 (2C), 23.6, 24.0 (2C), 30.5, 30.8, 78.9, 127.7 (2C), 127.8 (2C), 128.5 (2C), 129.6 (2C), 129.8 (2C), 142.7, 142.8.

Diacetone-D-glucosyl diphenylphosphinite **(P13)**. Colorless oil (61%), R_f 0.20 (hexane: EtOAc, 9:1); MS *m/z* (relative intensity): 445 ($[M+1]^+$, 5.6), 301 (30.5), 219 (100), 201 (41.5), 169 (4.7), 152 (1.9), 141 (7.8), 127 (4.1), 113 (2.5), 101 (6.6), 77 (11.2), 68 (1.5), 59 (4.9).

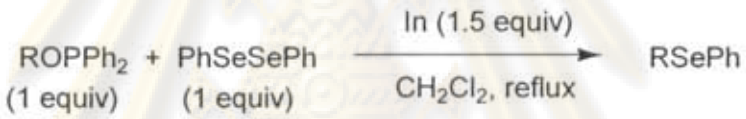
(+)-Dihydrocholesteryl diphenylphosphinite **(P14)**. White solid (60%), R_f 0.62 (hexane: EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.63-1.97 (46H, m, CH, CH_2, CH_3), 4.32 (1H, m, CH), 7.43-7.52 (6H, m, Ph), 7.79-7.84 (4H, m, Ph).

2.4 Study on the optimized conditions for synthesis of alkyl phenyl selenides from alkyl diphenylphosphinites

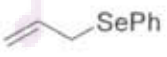
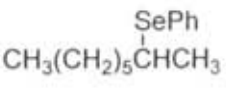
The reactions using various ratios of *tert*-butyl diphenylphosphinite, PhSeSePh and In in CH_2Cl_2 were carried out at reflux temperature under Ar. After the reaction was completed, the mixture was quenched with 1 M HCl, and then extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and purified by silica gel column eluting with hexane giving *tert*-butyl phenyl selenide.

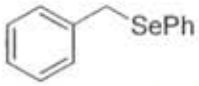
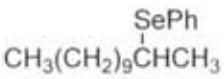
The synthesis of 1-adamantyl phenyl selenide was performed in the same manner as described above to confirm the obtained optimal condition.

2.5 General procedure for synthesis of alkyl phenyl selenides from alkyl diphenyl phosphinites



A mixture of alkyl diphenylphosphinite (0.5 mmol), PhSeSePh (156.1 mg, 0.5 mmol) and In (86.1 mg, 0.75 mmol) in CH_2Cl_2 was heated at reflux temperature for 2 h under Ar. The reaction mixture was quenched with 1 M HCl, and then extracted with Et_2O. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and purified by silica gel column eluting with hexane giving the corresponding alkyl phenyl selenide.

	RSePh		RSePh
Se1	^{t}BuSePh	**Se5**	
Se2		**Se6**	
Se3	$CH_3(CH_2)_{15}SePh$	**Se7**	

	RSePh		RSePh
Se4		Se8	

tert-Butyl phenyl selenide **(Se1)**. 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/z* (relative intensity): 214 (M^+, 29.6), 158 (100), 156 (50.9), 117 (5.0), 78 (24), 57 (45.5) and 51 (8.0).

1-Adamantyl phenyl selenide **(Se2)**. Yellow oil (81%), R_f 0.52 (hexane:EtOAc, 24:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.66 (6H, t, J = 15.69, 3×CH_2), 1.98-2.00 (9H, m, 3×CH and 3×CH_2), 7.28-7.32 (2H, t, J = 7.20, Ph), 7.35-7.39 (1H, t, J = 7.28, Ph) and 7.61-7.63 (2H, d, J = 6.76; Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 30.7 (3C), 36.2 (3C), 44.6 (3C), 47.0, 126.3, 128.3, 128.4 (2C) and 138.3 (2C); MS *m/z* (relative intensity): 292 (M^+, 9.9), 157 (8.8), 135 (100), 107 (11.3), 93 (20.9), 79 (21.2), 67 (6.5) and 55 (3.7).

1-Hexadecanyl phenyl selenide **(Se3)**. White solid (89%), R_f 0.58 (hexane: EtOAc, 24:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J = 6.78, CH_3), 1.26-1.42 (26H, m, 13×CH_2), 1.71 (2H, m, CH_2), 2.92 (2H, t, J = 7.40, CH_2), 7.23-7.28 (3H, m, Ph) and 7.48-7.50 (2H, d, J = 7.03, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.2, 22.8, 28.0, 29.2, 29.4, 29.6 (2C), 29.7 (2C), 29.8 (2C), 29.9 (2C), 30.2, 32.0 (2C), 126.6, 129.0 (2C), 130.8 and 132.4 (2C); MS *m/z* (relative intensity): 382 (M^+, 31.8), 183 (2.8), 171 (4.9), 158 (11.0), 117 (4.1), 105 (2.2), 91 (18.5), 83 (15.1), 71 (40.2) and 57 (100).

Benzyl phenyl selenide **(Se4)**. Yellow solid (84%), R_f 0.42 (hexane:EtOAc, 24:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.12 (2H, s, CH_2), 7.20-7.27 (8H, m, Ph) and 7.45-7.47 (2H, m, Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 32.3, 126.9, 127.3, 128.5 (2C), 128.9 (2C), 129.0 (2C), 130.4, 133.6 (2C) and 138.7; MS *m/z* (relative intensity): 248 ($[M+1]^+$, 25.2), 165 (3.2), 157 (10.6), 117 (1.8), 91 (100), 77 (8.3), 65 (16.6) and 51 (5.7).

Allyl phenyl selenide **(Se5)**. Yellow solid (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, CH_2SePh), 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/z* (relative intensity): 198 ($[M+1]^+$, 100), 197 (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).

trans-Cinnamyl phenyl selenide **(Se6)**. Yellow solid (69%), R_f 0.35 (hexane: CH_2Cl_2, 96:4); ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.68 (2H, d, J = 7.37 Hz, C$\underline{H}_2$SePh), 6.25 (1H, d, J = 15.78 Hz, HC=C$\underline{H}$Ph), 6.34 (1H, d, J = 15.80 Hz, $\underline{H}$C=CHPh), 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/z* (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).

2-Octyl phenyl selenide **(Se7)**. Yellow oil (98%), R_f 0.50 (hexane: EtOAc, 24:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J = 6.94, CH_3), 1.27 (10H, s, 5×CH_2), 1.14 (3H, d, J = 6.78, CHC$\underline{H}_3$), 3.30 (1H, m, CH), 7.26-7.29 (3H, m, Ph) and 7.54-7.56 (2H, dd, J = 3.18; Ph); ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 22.6, 27.8, 29.1, 29.8, 31.8, 37.6, 39.9, 127.3, 128.9 (2C), 129.6 and 134.9 (2C); MS *m/z* (relative intensity): 270 ($[M+1]^+$, 37.8), 158 (100), 117 (2.6), 105 (4.3), 91 (2.6), 77 (15.4), 71 (19.2) and 57 (22.8).

2-Dodecyl phenyl selenide **(Se8)**. 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).

2.6 General procedure for synthesis of alkyl iodides from alcohols

2.6.1 General procedure for synthesis of triiodoacetic acid [55]

A solution of malonic acid (19 mmol, 1.98 g) in 3 mL of water was added to a boiling solution of iodic acid (23 mmol, 2.98 g) in 8 mL of water. The resulting solution was cautiously heated and then cooled immediately by plunging the mixture into an ice bath after vigorous CO_2 was occured. Several small pieces of ice were added to the solution to relieve the reaction. After the reaction had subsided, the yellow mixture was allowed to stand at RT. In about 1.5 h, the solution became bright

yellow-orange color and the golden yellow crystals then setted out. The crystals were filtered after another one hour.

2.6.2 General procedure for iodination of 2-phenylethanol

2-Phenylethanol (0.25 mmol, 30.5 mg), PPh_3 (0.27 mmol, 72.1 mg) and imidazole (0.62 mmol, 42.5 mg) in dried CH_2Cl_2 were stirred with I_2 (0.25 mmol, 63.5 mg) at reflux temperature for 1 h under N_2. The mixture was washed with saturated $Na_2S_2O_3$. The organic layer was extracted with Et_2O, dried over anhydrous Na_2SO_4, and purified by silica gel column eluting with hexane to give the corresponding alkyl iodides.

2.7 Study on the optimized conditions for iodination of alkyl diphenylphosphines

2.7.1 Effect of the amount of I_2, temperature and reaction time

The reaction of oleyl diphenylphosphinite (0.25 mmol, 113 mg) with various amounts of I_2: 0.5, 1.0, 1.5 and 2.0 equiv in CH_2Cl_2 (2 mL) was stirred under Ar at room and reflux temperatures at the reaction time ranging from 15 to 60 min. The crudes were concentrated and analyzed by ^{1}H-NMR based on a standard toluene 10 μL.

2.7.2 Effect of solvents

The reaction of oleyl diphenylphosphinite (0.25 mmol, 113 mg) with I_2 (0.37 mmol, 95.2 mg) was carried out using five different solvents: benzene, toluene, THF, CH_3CN and CH_2Cl_2 at reflux temperature for 30 min under Ar. After evaporation, the corresponding products were analyzed by ^{1}H-NMR based on a standard toluene 10 μL.

2.8 General procedure for iodination of alkyl diphenylphosphinites

$$\underset{\text{(1 equiv)}}{ROPPh_2} + \underset{\text{(1.5 equiv)}}{I_2} \xrightarrow[\text{reflux, 30 min}]{CH_2Cl_2} RI$$

The reaction of alkyl diphenylphosphinite (0.5 mmol) and I_2 (0.75 mmol, 190.4 mg) in CH_2Cl_2 (3 mL) was stirred at reflux under Ar. After 30 min, the mixture was washed with saturated $Na_2S_2O_3$. The organic layer was extracted with Et_2O, dried

over anhydrous $MgSO_4$, and purified by silica gel column eluting with hexane to give the corresponding alkyl iodides.

	RI		RI
I1	$CH_3(CH_2)_6I$	I3	
I2	$CH_3(CH_2)_{15}I$	I4	

1-Hexyl iodide **(I1)**. Colorless oil (81%), R_f 0.66 (hexane: EtOAc, 24:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.82 (3H, t, J = 6.65, CH_3), 1.26-1.40 (8H, m, 4×CH_2), 1.83 (2H, p, J = 7.28, CH_2) and 3.19 (2H, t, J = 7.03, CH_2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 7.4, 14.1, 22.6, 28.3, 30.5, 31.0 and 33.6.

1-Hexadecanyl iodide **(I2)**. Colorless oil (74%); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 6.02, CH_3), 1.27-1.39 (26H, m, 13×CH_2), 1.83 (2H, m, CH_2) and 3.20 (2H, t, J = 7.03, CH_2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 7.4, 14.1, 22.7, 28.6, 29.4 (2C), 29.5, 29.6 (2C), 29.7 (4C), 30.5, 32.0 and 33.6.

(Z)-Oleyl iodide **(I3)**. Colorless oil (79%), R_f 0.74 (hexane: EtOAc, 24:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 6.78, CH_3), 1.29 (22H, s, 11×CH_2), 1.83 (2H, m, CH_2), 2.02 (4H, m, $\underline{CH_2}CH{=}CH\underline{CH_2}$), 3.20 (2H, t, J = 7.15, CH_2) and 5.36 (2H, m, $C\underline{H}{=}C\underline{H}$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 7.5, 14.4, 22.9, 27.4, 27.5, 28.7, 29.4. 29.6 (2C), 29.8, 29.9 (2C), 30.0, 30.7, 32.1, 33.8, 130.0 and 130.2.

1-Adamantyl iodide **(I4)**. White solid (88%), R_f 0.52 (hexane:EtOAc, 24:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81 (6H, t, J = 14.34, 3×CH_2), 1.96 (3H, s, CH) and 2.64 (6H, s, 3×CH_2); ^{13}C-NMR ($CDCl_3$) δ (ppm): 33.1 (3C), 35.6 (3C), 51.2 and 52.5 (3C).

2.9 General procedure for the one-pot iodination of alcohols through alkyl diphenylphosphinites

A solution of alcohol (0.25 mmol), $ClPPh_2$ (0.27 mmol, 51 μL), DMAP (0.075 mmol, 9.2 mg) and Et_3N (0.3 mmol, 42 μL) in CH_2Cl_2 (2 mL) was stirred at RT for 2 h under N_2, then added I_2 (0.625 mmol, 0.16 g) into the mixture and stirred at reflux

temperature for 30 min. After evaporation, the corresponding products were analyzed by ^{1}H-NMR based on a standard toluene 10 μL.

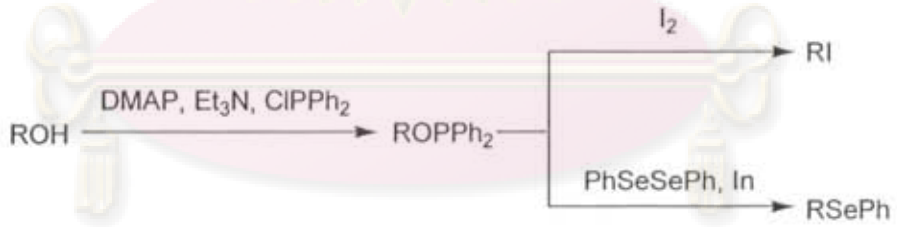
2.10 General procedure for the *in situ* iodination of alcohols through alkyl diphenylphosphinites

A solution of alcohol (0.25 mmol) and $ClPPh_2$ (0.27 mmol, 51 μL in the presence of pyridine (0.075 mmol, 6 μL) in CH_2Cl_2 (2 mL) was stirred with I_2 (0.625 mmol, 0.16 g) at RT for 2.5 h under N_2. After evaporation, the corresponding products were analyzed by ^{1}H-NMR based on a standard toluene 10 μL.

CHAPTER III

RESULTS AND DISCUSSION

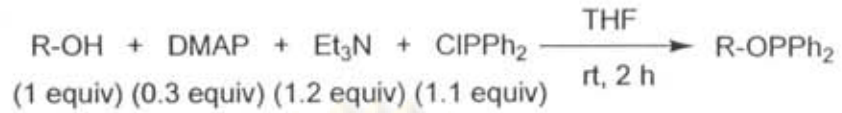
The main purposes of this research are to synthesize two intermediates: alkyl iodides and alkyl phenyl selenides from alkyl diphenylphosphinites which are easily prepared in excellent yields from the corresponding alcohol, chlorodiphenylphosphine ($ClPPh_2$) and triethylamine (Et_3N) in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) [54]. Many literatures, especially from Mukaiyama's research group, reported that alkyl diphenylphosphinites were the key intermediates for the oxidation-reduction condensation to prepare several organic compounds such as isocyanates, diorganyl sulfides, esters and ethers, *etc.* [44-54]. Up till now, it was notwithstanding that there was no report optimizing a methodology for the development of alkyl iodides and alkyl phenyl selenides *via* these phosphinites. The general equation can be simplified as shown below.



3.1 Synthesis and characterization of alkyl diphenylphosphinites

In the republic of Korea, alkyl diphenylphosphinites could be successfully prepared in moderate to excellent yields according to Mukaiyama's method. The reaction of alcohols (1.0 equiv), Et_3N (1.2 equiv) and $ClPPh_2$ (1.1 equiv) in the presence of a catalytic amount of DMAP (0.3 equiv) was carried out at RT for 2 h and purified by filtration through a pad of alumina and celite using hexane/EtOAc (9/1) as an eluent [54]. The results are tabulated in Table 3.1.

Table 3.1 Synthesis of alkyl diphenylphosphinites from various alcohols



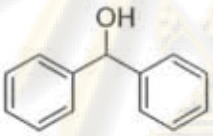
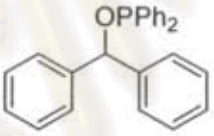
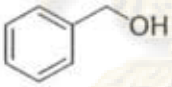
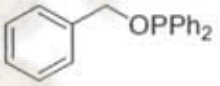
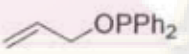
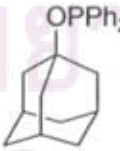
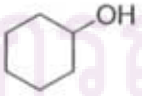
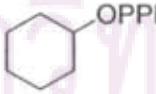
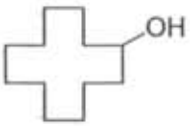
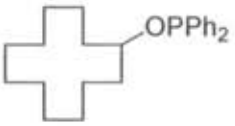
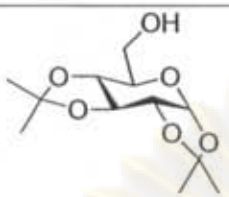
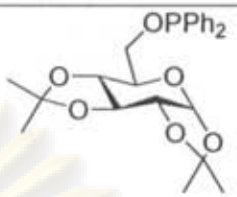
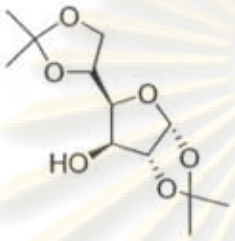
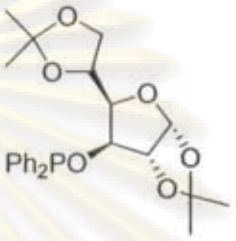
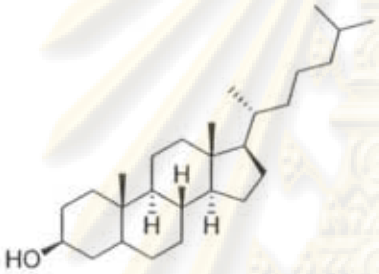
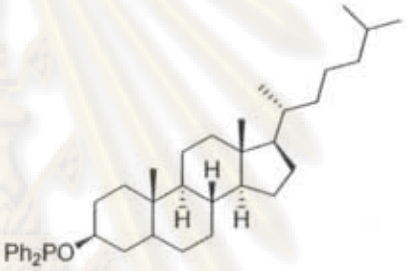
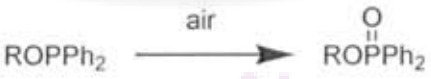
Entry	ROH	$ROPPh_2$	Yield (%)
1	$CH_3(CH_2)_6OH$	$CH_3(CH_2)_6OPPh_2$	66[a]
2	$CH_3(CH_2)_{15}OH$	$CH_3(CH_2)_{15}OPPh_2$	90
3	*cis* $CH_3(CH_2)_7CH{=}CH(CH_2)_8OH$	*cis* $CH_3(CH_2)_7CH{=}CH(CH_2)_8OPPh_2$	80
4	$CH_3(CH_2)_5CH(OH)CH_3$	$CH_3(CH_2)_5CH(OPPh_2)CH_3$	79
5	$CH_3(CH_2)_9CH(OH)CH_3$	$CH_3(CH_2)_9CH(OPPh_2)CH_3$	89
6			30
7			80
8			quant
9			93
10	^tBuOH	$^tBuOPPh_2$	92
11			96
12			90
13			93

Table 3.1 (cont)

Entry	ROH	$ROPPh_2$	Yield (%)
14			47[a]
15			61
16			60

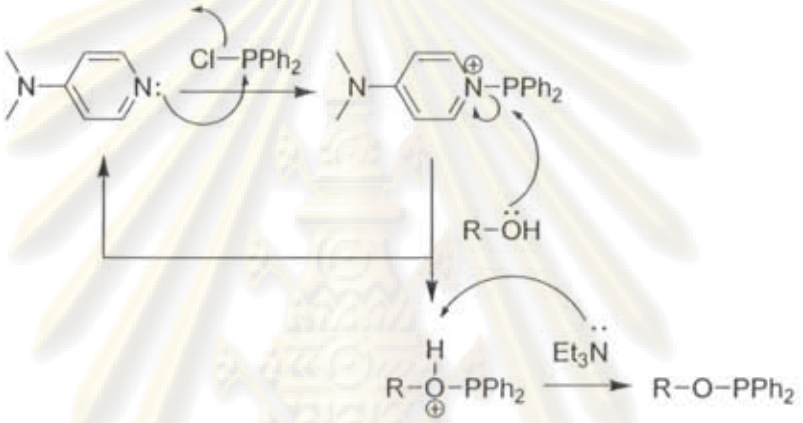
[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

Primary and secondary alcohols could be completely converted to the corresponding alkyl diphenylphosphinites in high yield except for diphenylmethyl diphenylphosphinite (entries 1-6). This problem was believed to occur from the rapid decomposition of alkyl diphenylphosphinites to alkyl diphenylphosphine oxides pending in the purification step.



Benzyl diphenylphosphinite was furnished in 80% yield, whereas the same reaction tried in Thailand gave only 63% yield (entry 7). The reaction suffered from the rapid decomposition as quoted above. It might be considered that the climate and moisture in Thailand caused the drawback of this reaction. Allylic and substituted allylic compounds, allyl and cinnamyl diphenylphosphinites, were both obtained in excellent yields (entries 8-9). In a similar fashion, tertiary alkyl diphenylphosphinites were achieved in high yield (entries 10 and 11). For an investigation of cyclic compounds,

both cyclohexanol and cyclododecanol could be transformed to the corresponding phosphinites in excellent yields (entries 12 and 13). In addition, bulky phosphinites such as diacetone-D-glucosyl, diacetone-D-galactosyl and (+)-dihydrocholesteryl diphenylphosphinites were obtained in moderate yields (entries 14-16). Steric hindrance might cause the lower yields of these bulky phosphinites comparing with the others. The common mechanism started with the activation of $ClPPh_2$ with DMAP and then it was substituted by alcohols. After a base abstracted an acidic proton from this intermediate, the corresponding phosphinites were obtained with retention of configuration as shown in Scheme 3.1.



Scheme 3.1 A possible mechanism for the transformation of alcohols into alkyl diphenylphosphinites

All desired alkyl diphenylphosphinites were characterized their identities by ^{1}H-NMR technique. The example of ^{1}H-NMR spectrum of *cis*-oleyl diphenyl-phosphinite is presented in Fig 3.1. The spectrum pattern showed that a triplet signal of methylene protons connecting to -$OPPh_2$ at δ_H 3.86 was shifted compared with common methylene protons of *cis*-oleyl alcohol at δ_H 3.63. The *cis*-olefinic signal was detected at δ_H 5.36 (J = 6.4 Hz) and ten aromatic protons were visualized at δ_H around 7.33-7.53.

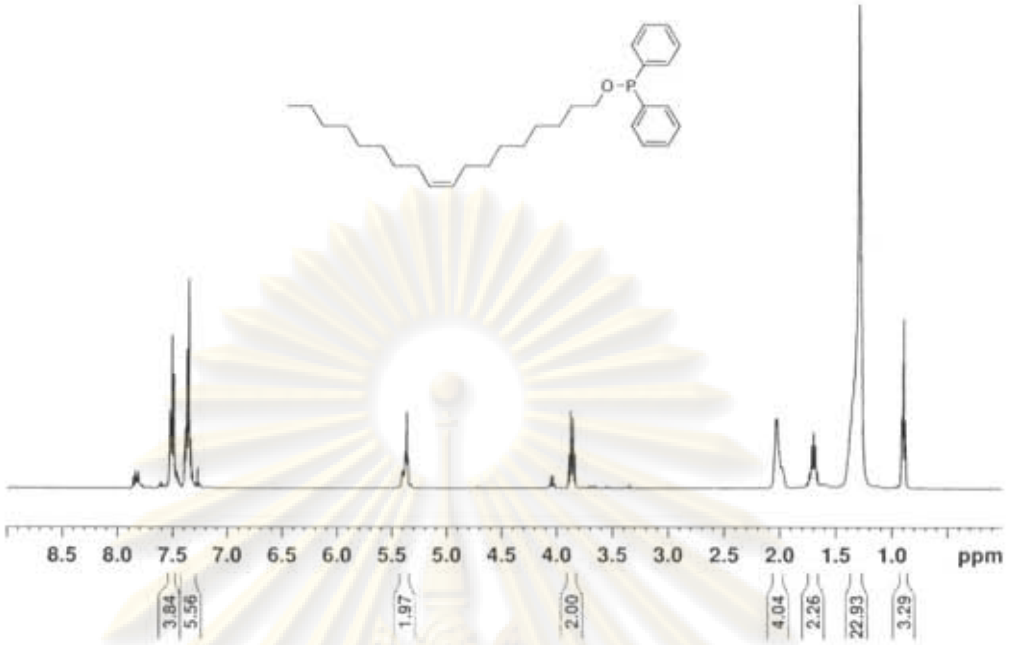


Figure 3.1 ^{1}H-NMR spectrum of *cis*-oleyl diphenylphosphinite

3.2 Synthesis of alkyl phenyl selenides from alkyl diphenylphosphinites

The methods performed under mild and neutral conditions without any assistance of acids or bases to prepare selenide compounds have been speculated as a challenging topic in selenide syntheses. Recently, alkyl phenyl selenides could be achieved in high yield from the reaction between alkyl halides and PhSeSePh in the presence of In [19]. Interestingly, this technique has many advantages such as simple experimental procedure, neutral and mild reaction conditions and high yield of the desired selenides even in the case of tertiary alkyl phenyl selenides.

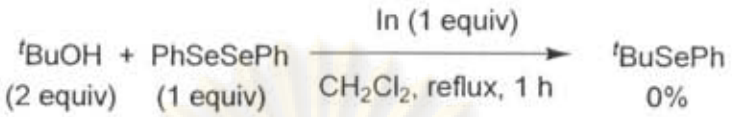
$$\underset{(2\ \text{equiv})}{RX} + \underset{(1\ \text{equiv})}{PhSeSePh} \xrightarrow[CH_2Cl_2,\ \text{reflux}]{In\ (1\ \text{equiv})} RSePh$$

With regards to an attempt to extend the scope of the method above, the preparation of alkyl phenyl selenides using a new type of precursor, alkyl diphenylphosphinites, was focused on.

3.2.1 Study on the optimized conditions for selenide syntheses

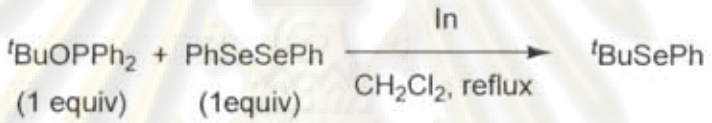
The attempt to employ a new type of precursor as alcohols was initially tried by using the same conditions as mentioned above. However, the treatment between

tert-butyl alcohol and PhSeSePh in the presence of In in CH_2Cl_2 at reflux for 1 h was not achieved.



Subsequently, alkyl diphenylphosphinites were synthesized and employed as the substrates instead of alcohols. The conversion of *tert*-butyl diphenylphosphinite with PhSeSePh in the presence of In was first investigated. The ratios of substrate and reagents were varied as the results in Table 3.2.

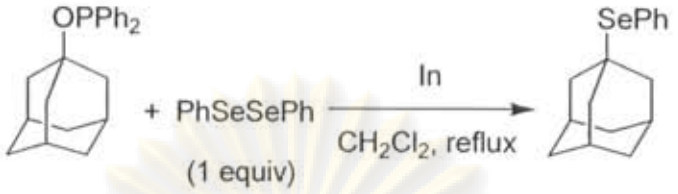
Table 3.2 Synthesis of *tert*-butyl phenyl selenides from *tert*-butyl diphenylphosphinites



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

In the absence of In, the conversion of *tert*-butyl diphenylphosphinite to *tert*-butyl phenyl selenide was inactive (entry 1). On the other hand, the similar reaction in the presence of 1.0 equiv of In afforded the desired product in 56% yield (entry 2). The best reaction seemed to be in entry 3 when 3.0 equiv of In was employed. In addition, using the same technique with 1-adamantyl diphenylphosphinite as a substrate to verify the optimized condition was carried out. The outcomes are presented in Table 3.3.

Table 3.3 Synthesis of 1-adamantyl phenyl selenides from 1-adamantyl diphenylphosphinites



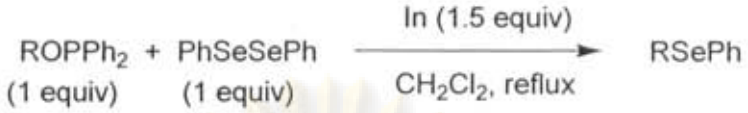
Entry	$ROPPh_2$ (equiv)	In (equiv)	Temp (°C)	Time (h)	Yield (%)
1	2	3	rt	24	47
2	2	3	reflux	2	45
3	1	1.5	rt	24	53
4	1	1.5	reflux	2	83
5	1	0	reflux	2	0

At RT (20 °C), when the reaction proceeded for 24 h, 1-adamantyl phenyl selenide 47% yield was obtained, whereas the identical yield could be attained in shorter reaction time at reflux (entries 1 and 2). Half of starting material still remained and In was also detected in excess; therefore, the amount of 1-adamantyl diphenylphosphinite and In were reduced to 1:1.5, respectively, furnishing the desired product in 53% at RT for 24 h and in 83% at reflux for 2 h (entries 3 and 4). In the absence of In, the reaction did not proceed revealing the essence of In for the reaction (entry 5). The reaction between alkyl diphenylphosphinite (1 equiv) and PhSeSePh (1 equiv) in the presence of In (1.5 equiv) in CH_2Cl_2 at reflux was applied as the optimized conditions in screening the limitation of substrates.

3.2.2 The screening of substrates

In order to explore the scope and limitations of this methodology, the treatment of various alkyl diphenylphosphinites (1 equiv) with PhSeSePh (1 equiv) in the presence of In (1.5 equiv) in CH_2Cl_2 at reflux afforded a wide range of alkyl phenyl selenides as summarized in Table 3.4.

Table 3.4 Synthesis of various alkyl phenyl selenides from the corresponding alkyl diphenylphosphinites



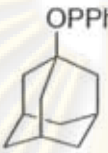
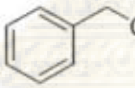
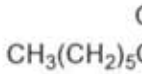
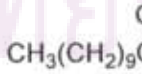
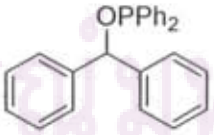
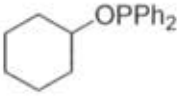
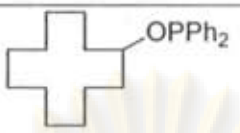
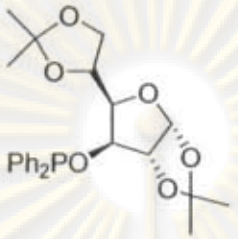
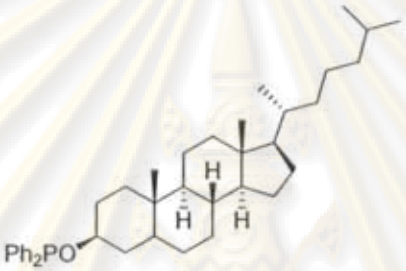
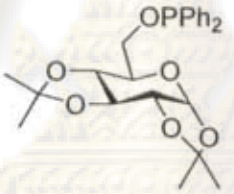
Entry	$ROPPh_2$	Time (h)	Yield (%)
1	$^tBuOPPh_2$	2	71
2		2	83
3	$CH_3(CH_2)_6OPPh_2$	2	96[a]
4	$CH_3(CH_2)_{15}OPPh_2$	2	89 (0)[b]
5	*cis* $CH_3(CH_2)_7CH{=}CH(CH_2)_8OPPh_2$	2	80[a]
6		3	89
7		2	78
8		2	69
9		4	98
10		3	86
11		4	0
12		2	28[c]

Table 3.4 (cont)

Entry	$ROPPh_2$	Time (h)	Yield (%)
13		24	0 (23)[d]
14		24	0
15		18	0
16		8	33[a]

[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

[b]The reaction was tried in the absence of In for 4 h

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

[d]Reaction was tried in the presence of 0.5 equiv of I_2 for 4 h

Under this particular condition, primary and tertiary alkyl phenyl selenides could be attained in high yield (entries 1-5). Similarly, the preparation of benzyl and allyl phenyl selenides were also achieved (entries 6-8). Allyl diphenylphosphinite was more reactive than a substituted allyl diphenylphosphinite (entries 7 and 8). It might be assumed that the substituted allylic compound gave a mixture of two monoselenides because the substituted allylic radical could react at either carbon of C=C of the generated intermediates. Acyclic secondary alkyl diphenylphosphinites underwent a clean reaction to provide the corresponding alkyl phenyl selenides in high yield; however, the longer reaction time was needed comparing with using primary and tertiary phosphinites (entries 9 and 10). On the other hand, diphenylmethyl diphenylphosphinite was inactive even if the reaction time was

extended to 4 h (entry 11). In the case of cyclic secondary alkyl diphenylphosphinites, the reaction did not smoothly proceed (entries 12-15), while cyclohexyl phenyl selenide was obtained in 28% (GC) based on starting material (entry 12). The others including cyclododecyl, diacetone-D-galactosyl and (+)-dihydrocholesteryl diphenylphosphinites did not proceed at all (entries 13-15). There were many reports mentioned that the reactions using metal could be catalyzed by the addition of I_2 [5, 16]. Therefore, the conversion of cyclododecyl diphenylphosphinite was tried in the presence of 0.5 equiv of I_2. Interestingly, the corresponding selenide could be obtained even in low yield (entry 13 in the parenthesis). It might be speculated that adding I_2 under this reaction condition enhanced the rate of reaction. Moreover, diacetone-D-glucosyldiphenyl-phosphinite was performed for 8 h to yield the desired product in 33% yield (entry 16).

To compare this protocol with other previous methods, this method provided tertiary alkyl phenyl selenides in high yield, whereas most of prior reports did not present the manipulation of tertiary compounds [12-18]. Additionally, this optimized condition required shorter reaction time to complete the reactions comparing with many procedures such as the InI-promoted methods using PhSeSePh [5, 7, and 15].

All alkyl phenyl selenides were characterized by ^{1}H- and ^{13}C-NMR spectroscopies. ^{1}H- and ^{13}C-NMR spectra of 1-adamantyl phenyl selenide were illustrated as example (Figs 3.2 and 3.3). The ^{1}H-NMR spectrum (Fig 3.2) showed two peaks of six methylene and three methine groups at δ_H 1.66 and 2.00. The signals of five aromatic protons were detected at δ_H around 7.28-7.63. The ^{13}C-NMR spectrum of 1-adamantyl phenyl selenide (Fig 3.3) revealed the carbon connecting to selenium at δ_C 47.0. The carbon signals of two methylene and one methine groups were observed at δ_C 30.7, 36.2 and 44.6. Four remaining signals could be assigned for six aromatic carbons.

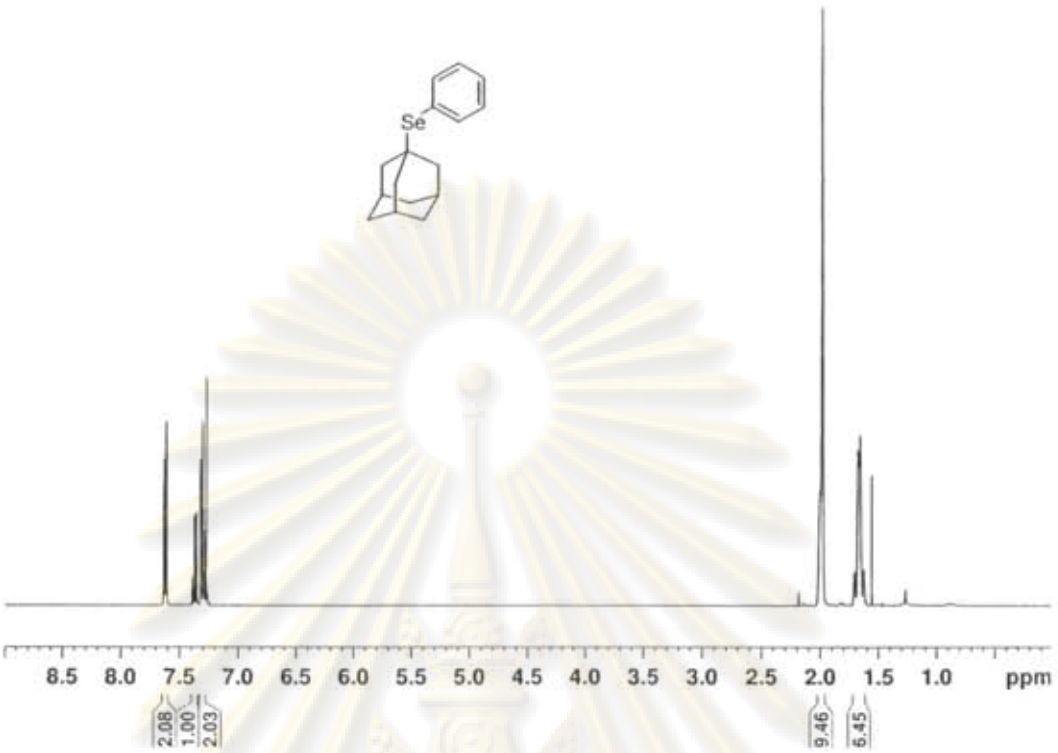


Figure 3.2 ^{1}H-NMR spectrum of 1-adamantyl phenyl selenide.

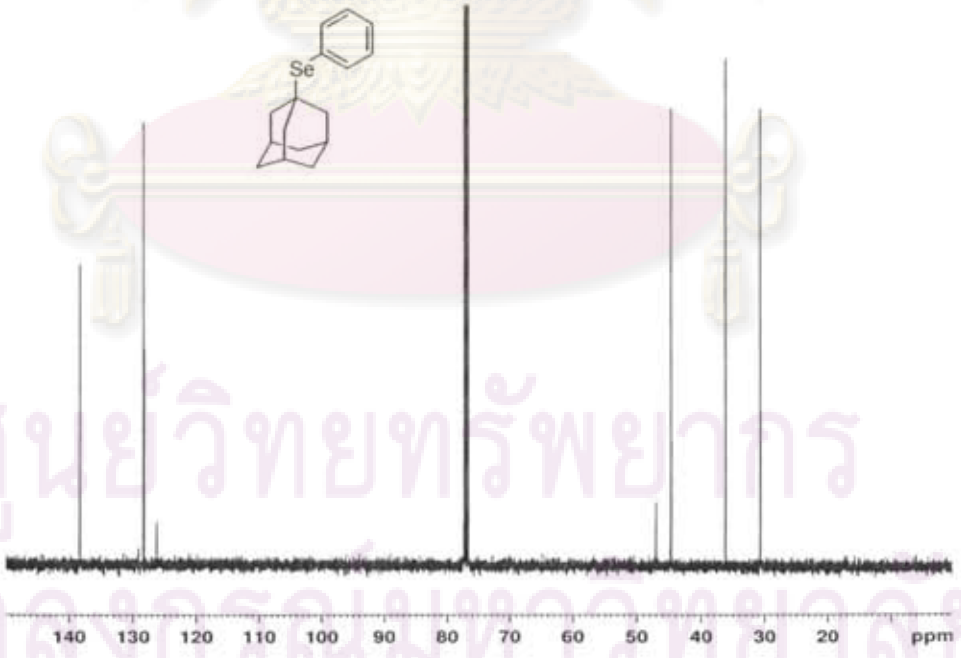
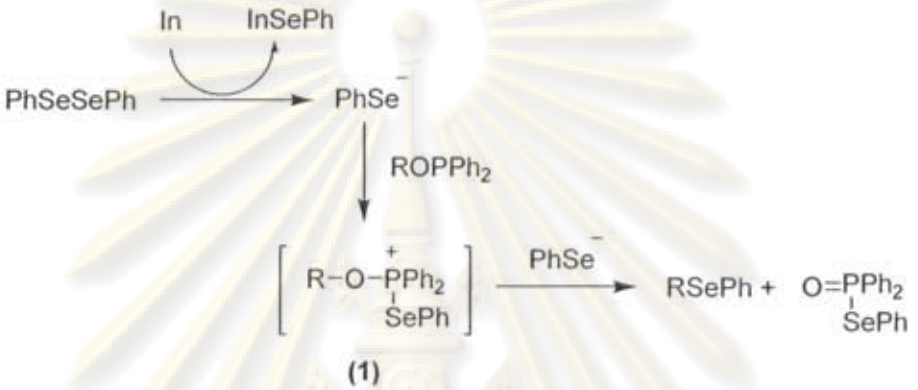


Figure 3.3 ^{13}C-NMR spectrum of 1-adamantyl phenyl selenide.

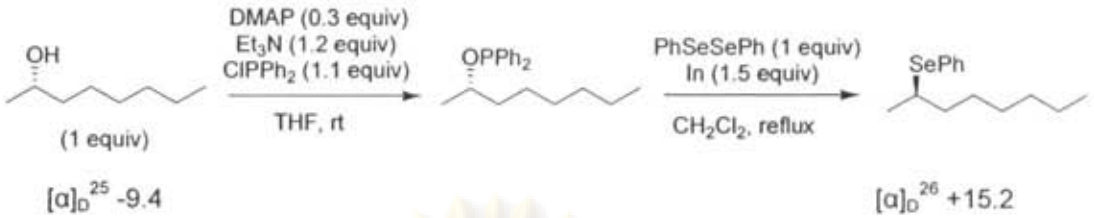
3.2.3 Possible mechanism

A plausible mechanism for the formation of alkyl phenyl selenides is proposed as shown in Scheme 3.2. The first step involved the generation of **1** form alkyl diphenylphosphinite and phenyl selenide anion and then the substitution of the intermediate with another phenyl selenide anion formed alkyl phenyl selenide and $PhSeP(O)Ph_2$ which could be detected by GC-MS.



Scheme 3.2 A plausible reaction mechanism for the conversion of alkyl diphenylphosphinites to alkyl phenyl selenides.

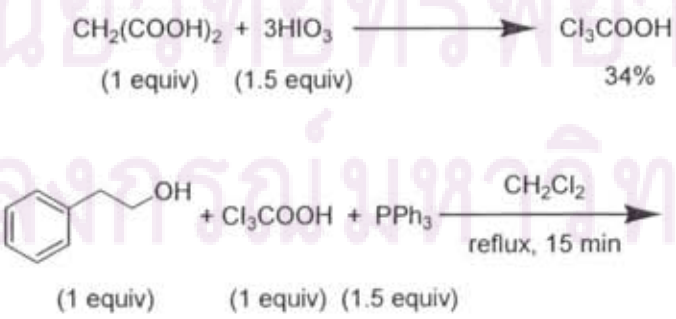
For better understanding about the reaction pathway, a series of experiments was performed. Firstly, the reaction of PhSeSePh and In afforded pale yellow solution, whereas the reaction of 1-adamantyl diphenylphosphinite with only PhSeSePh or with only In did not proceed at all. These results clearly revealed that the reaction should commence with the interaction of PhSeSePh and In. Certain reports have been addressed that selenides could be synthesized through a radical pathway initiated by In [19-20]. To prove whether this reaction condition underwent a free radical process, the reaction of 1-hexadecanyl diphenylphosphinite was performed under the standard condition in the presence of galvinoxyl free redical [56]. The corresponding selenide was still attained in 87% with the yield being not different from the same reaction in the absence of this scavenger. Finally, the reaction of an optically active substrate, *R*(-)-2-octanol ($[\alpha]_D^{25}$ -9.4 (*c* 1.0, CH_2Cl_2)) could be successfully transformed into a chiral *S*(+)-2-octyl phenyl selenide ($[\alpha]_D^{26}$ +15.2 (*c* 1.0, CH_2Cl_2)) with complete conversion. It was thus clearly that under this particular optimized condition, the reaction proceeded *via* S_N2 mechanism.



In the case of tertiary alkyl phenyl selenides, the mechanistic pathway possibly underwent S_N1 as the strong P=O bond was readily formed in diphenylphosphine oxide; therefore, the reaction might be driven forward to generate tertiary carbocation. Upon reacting with phenyl selenide anion, the selenide product was formed.

3.3 Synthesis of alkyl iodides from alcohols

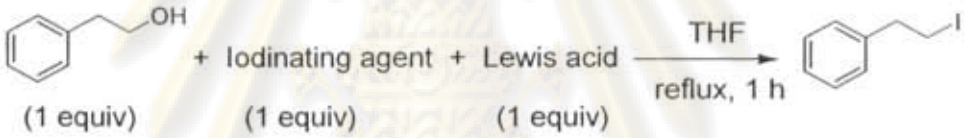
As aforementioned, many reports on the transformation of alcohols into alkyl iodides have been documented. Those reports mainly involved the use of two kinds of iodinating sources: iodide salts and iodine [31-43]. To search for a novel and mild approach for the preparation of alkyl iodides, the iodination of alcohols using new protocols was concentrated on. Regarding to previous methods for the preparation of alkyl halides from alcohols, the reactions using the combination of halogenating agents such as $Cl_3CCOCCl_3$, $Br_3CCOCBr_3$ and Br_3CCO_2Et coupled with PPh_3 could provide chlorides and bromides, respectively in higher yield and required shorter reaction time comparing with common halogenating agents such as CBr_4 [57-58]. These multi-halides reagents were, hence, extended the idea for iodination. Triiodoacetic acid which could be prepared from the reaction between malonic acid and iodic acid [55], was initially selected as a new iodinating agent. Unfortunately, the treatment of 2-phenylethanol, PPh_3 and triiodoacetic acid in CH_2Cl_2 at reflux was not fruitful.



According to the unsuccessful results above, the endeavor to transform triiodoacetic acid to ethyl triiodoacetate, which was expected as another new iodinating agent, was then performed. Esterification of triiodoacetic acid with EtOH in the presence of a catalytic amount of conc H_2SO_4 was tried at reflux for 6 h; nevertheless, the reaction did not proceed at all. It was noteworthy that ethyl triiodoacetate could be instantly decomposed to I_2 even if it was kept and refrigerated in the dark at temperature around 4°C. Air-sensitive might also cause of these inactive reactions.

As the results above, the turning point to search for a new iodination approach using common iodide sources was subsequently focused on. In this study, 2-phenylethanol was still selected as a substrate to treat with a variety of iodinating agents under reflux for 1 h. The results are summarized in Table 3.5.

Table 3.5 Iodination of 2-phenylethanol with various iodinating agents



Entry	Reagent		%yield[a]
	Iodinating agent	Lewis acid	
1	KI	$CrCl_3.6H_2O$	0
2	LiI	$CrCl_3.6H_2O$	0 (2)[b]
3	LiI	$Cr(NO_3)_3.9H_2O$	0
4	LiI	-	0[c] (0)[d]
5	I_2	$CrCl_3.6H_2O$	0
6	I_2	$CrBr_3.6H_2O$	0[c]
7	I_2	$Cr(NO_3)_3.9H_2O$	0
8	I_2	-	81[e] (38)[f]

[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

[b]Benzyl alcohol was used instead of 2-phenylethanol

[c]2.5 Equiv of imidazole was added

[d]2.5 Equiv of imidazole and 1.1 equiv of PPh_3 were added

[e]2.5 Equiv of imidazole was added

[f]2.5 Equiv of imidazole and 1.1 equiv of PPh_3 were added and CH_2Cl_2 was used as solvent

The reactions were not proceeded at all when the following iodinating agents: KI/$CrCl_3 \cdot 6H_2O$, LiI/$CrCl_3 \cdot 6H_2O$, LiI/$Cr(NO_3)_3 \cdot 9H_2O$, I_2/$CrCl_3 \cdot 6H_2O$, I_2/$CrBr_3 \cdot 6H_2O$ and I_2/$Cr(NO_3)_3 \cdot 9H_2O$ were employed (entries 1-7). According to previous methods for the iodination of alcohols using PPh_3/I_2 under solvent-free using microwave irradiation [43], this condition was imitated to improve the yield of product. The reaction could be proceeded in refluxing CH_2Cl_2 to give the corresponding iodide in 81% and in 38% yields in the presence and absence of imidazole, respectively (entry 8). The general mechanism of this system started with the activation of alcohols with PPh_3 and then these intermediates were iodinated by iodine to generate the desired iodides. From these results, the PPh_3/I_2 system was attractive as the key idea for the development of iodide syntheses.

In this regard, iodination of direct activated alcohols, alkyl diphenylphosphinites, which could be converted from the reaction of alcohols with $ClPPh_2$ was focused on next.

3.4 Iodination of alkyl diphenylphosphinites

As the results above, the conversion of direct alcohol with several iodinating agent systems was not smoothly proceeded. Therefore, a method for the preparation of alkyl iodides *via* alkyl diphenylphosphinites instead of alcohols was investigated.

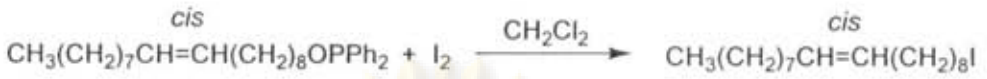
3.4.1 Study on the optimized conditions for iodination of alkyl diphenylphosphinites

To search for an optimized condition for the iodination of alkyl diphenylphosphinites, effects of the amounts of I_2, temperature, reaction time and type of solvents were investigated. *cis*-Oleyl diphenylphosphinite was selected as a model substrate for these examinations. The treatment of this phosphinite (1 equiv) with various amounts of I_2 under several reaction temperatures, reaction time and type of solvents were performed. In this optimizing study, the obtained product was characterized by ^{1}H-NMR based on a standard toluene 10 μL.

3.4.1.1 Effects of the amounts of I_2, temperature and reaction time

The reactions of *cis*-oleyl diphenylphosphinite (1 equiv) with various amounts of I_2, temperature and reaction time were tried to quest for the optimized condition. The results are described in Table 3.6.

Table 3.6 Effects of the amounts of I_2, temperature and reaction time in the synthesis of *cis*-oleyl iodide (1 equiv)



Entry	I_2 (equiv)	Temp.	Time (min)	Yield (%)[a]
1	0.5	rt	60	57
2	1.0	rt	60	73
3	1.5	rt	60	quant.
4	2.0	rt	60	89
5	1.5	rt	30	82
6	1.5	reflux	30	quant. (0)[b]
7	1.5	reflux	15	61

[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 μL

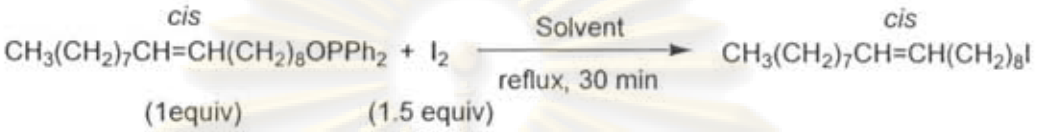
[b]1.5 Equiv of NaI was used instead of I_2

Iodination of *cis*-oleyl diphenylphosphinite was performed at RT using the amounts of iodine ranging from 0.5 to 2.0 equiv (entries 1-4). The reaction was completed within 1 h when 1.5 equiv of I_2 was employed (entry 3). When the reaction time was lessened to 30 min, *cis*-oleyl iodide was merely obtained in 82% yield, whereas the same reaction at reflux yielded the desired product in almost quantitative yield (entries 5 and 6). Only 61% yield was observed when the reaction time was decreased to 15 min at reflux (entry 7). Furthermore, the reaction using NaI as an iodinating agent was tried without success (entry 6 in the parenthesis). It might be considered that the reaction mixture did not be homogeneous in this solvent. From the above results, the optimal equivalent ratio of *cis*-oleyl diphenylphosphinite and I_2 for the synthesis of *cis*-oleyl iodide was 1:1.5, respectively. This optimal ratio at reflux for 30 min was applied to examine the optimized conditions with various substrates.

3.4.1.2 Effect of solvents

Solvent was another important factor for iodination of alkyl diphenylphosphinites. In this study, five diverse solvents were examined using *cis*-oleyl diphenylphosphinites as a model substrate. The results are shown in Table 3.7.

Table 3.7 Solvent effects on the reaction of *cis*-oleyl diphenylphosphinites with I_2



Entry	Solvent	Yield (%)[a]
1	Benzene	78
2	Toluene	48
3	THF	51
4	CH_3CN	59
5	CH_2Cl_2	quant.

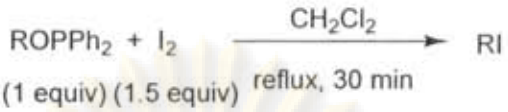
[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

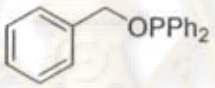
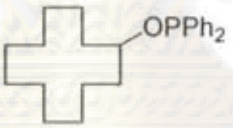
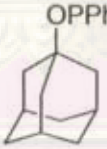
The treatment of *cis*-oleyl diphenylphosphinite (1 equiv) with I_2 (1.5 equiv) was performed in various solvents at reflux for 30 min. Common solvents which were cheap and commercially available such as benzene, toluene, THF and CH_3CN provided the desired product in low to moderate yields (entries 1-4). When CH_2Cl_2 was used, *cis*-oleyl iodide was obtained in excellent yield (entry 5). Therefore, the reaction of alkyl diphenylphosphinite (1 equiv) and I_2 (1.5 equiv) in CH_2Cl_2 at reflux for 30 min was applied to be the optimized condition for screening substrates.

3.4.2 The screening substrates

Under this optimized condition, various alkyl diphenylphosphinites (1 equiv) were treated with I_2 (1.5 equiv) in CH_2Cl_2 at reflux for 30 min to investigate the limitation and generality of this developed method. The results are summarized in Table 3.8.

Table 3.8 Synthesis of alkyl iodides from various alkyl diphenylphosphinites under the optimal condition



Entry	$ROPPh_2$	Yield (%)[a]
1	$CH_3(CH_2)_6OPPh_2$	quant (81)
2	$CH_3(CH_2)_{15}OPPh_2$	86 (74)
3	*cis* $CH_3(CH_2)_7CH{=}CH(CH_2)_8OPPh_2$	quant. (79)
4		83
5	$CH_3(CH_2)_5CH(OPPh_2)CH_3$	45
6		61
7		94 (88)

[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL
The yields in the parenthesis were isolated yields.

Primary alkyl iodides: *n*-heptyl iodide, 1-hexadecyl iodide and *cis*-oleyl iodide underwent a clean reaction providing the corresponding alkyl iodides in excellent yield (entries 1-3). Similarly, the preparation of benzyl iodide was also achieved using benzyl diphenylphosphinites in 83% yield (entry 4). On the contrary, 2-octyl iodide was obtained only in moderate yield as the reaction was not completed within this optimized time (entry 5). Steric hindrance of substrate might cause of this incomplete reaction. In the case of cyclic secondary iodide, the reaction did not smoothly proceed (entry 6). It suffered from the elimination of alkyl iodide to its corresponding alkene.

Appealingly, tertiary alkyl iodide could be furnished in high yield under this technique (entry 7).

To compare with other previous literatures, this protocol has some significantly advantages such as high yield of tertiary alkyl iodides and short reaction time, whereas most of prior documents mentioned only the preparation of primary and secondary alkyl iodides because those reaction pathways were proposed as S_N2 displacement. Moreover, this optimized condition required shorter reaction time to complete the reactions comparing with many procedures such as the iodination of alcohols using $MeSiCl_3$/NaI system and using $Ce_3Cl{\cdot}7H_2O$/NaI required the reaction time over 10 h [32, 33].

The corresponding iodides was fully characterized their identities by NMR technique. The examples of ^{1}H- and ^{13}C-NMR spectra of *n*-heptyl iodide are illustrated in Figs 3.2 and 3.3, respectively. The ^{1}H-NMR spectrum displayed the triplet signal of methylene protons adjacent to iodine at δ_H 3.19. The ^{13}C-NMR of this compound revealed the shifted signal at δ_C 33.4 assigned to the carbon connecting to iodine. Six remaining signals were six carbons on an aliphatic chain.

Figure 3.4 ^{1}H-NMR spectrum of *n*-heptyl iodide.

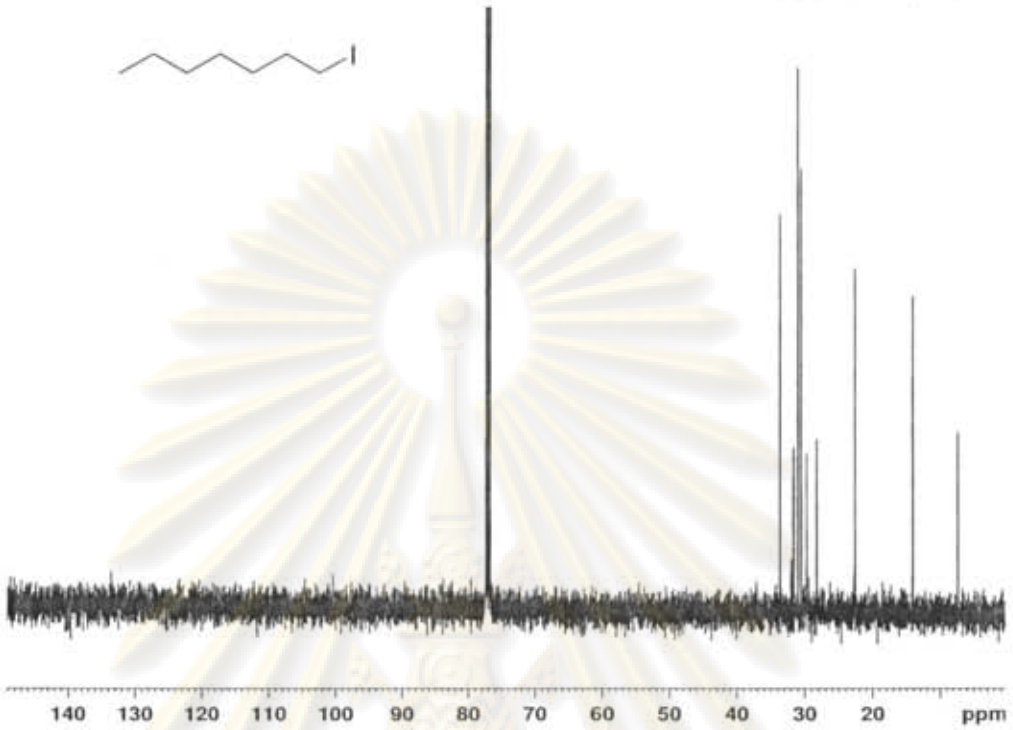
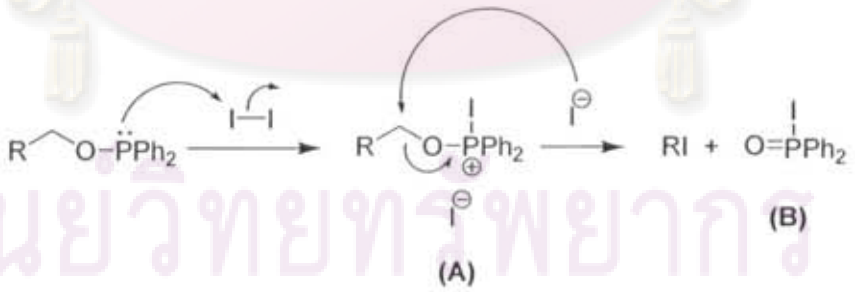


Figure 3.5 ^{13}C-NMR spectrum of *n*-heptyl iodide.

3.4.3 Possible mechanism

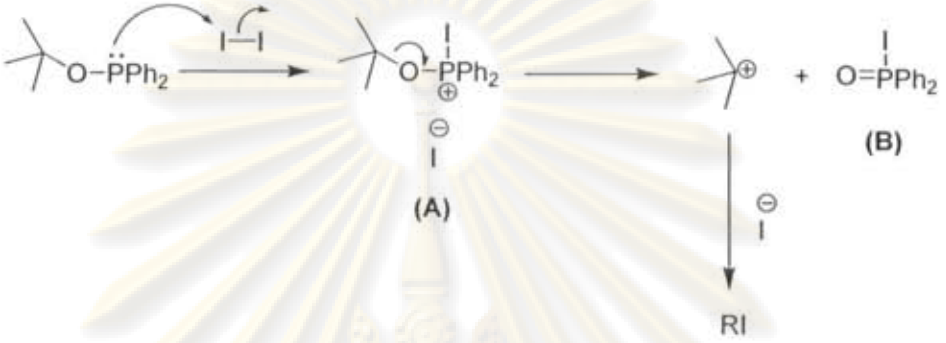
The reaction pathway for the formation of alkyl iodides was proposed as illustrated in Scheme 3.3. In the first step, alkyl diphenlyphosphinite initially reacted with I_2 to generate intermediate **A**. Then the S_N2 reaction of the intermediate with iodide anion formed alkyl iodide and by-product **B**.



Scheme 3.3 Possible mechanism pathway for iodination of alkyl diphenyl-phosphinites.

In this study, tertiary iodide could be easily attained under the optimized condition. The possible mechanism might proceed under the similar manner as the selenide syntheses. The first step involved the generation of **A** which could be

converted to alkyl tertiary carbocation and followed by the S_N1 displacement of this carbocation with iodide anion to form alkyl iodide. The mechanism pathway possibly underwent S_N1 displacement as the strong P=O bond was readily formed **B**; therefore, the reaction might be driven forward to generate tertiary carbocation which was stable intermediate as shown in Scheme 3.4.

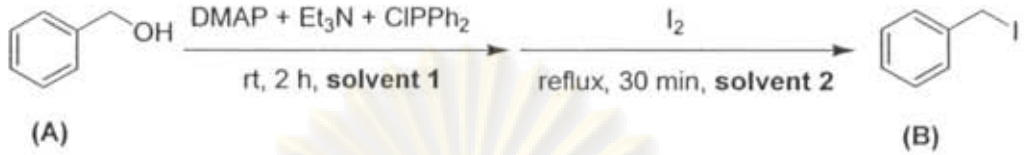


Scheme 3.4 Possible mechanism pathway for iodination of tertiary alkyl diphenylphosphinites.

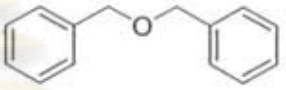
3.5 One-pot iodination of alcohols through alkyl diphenylphosphinites

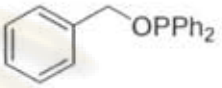
To develop and simplify the two-step protocol, one-pot iodination of alcohols through alkyl diphenylphosphinites was concentrated on. Benzyl alcohol was selected as a model substrate to search for an optimized condition. The treatment of benzyl alcohol with the same reagents above was performed to generate benzyl diphenylphosphinite and then I_2 was added into the mixture without any purification step to furnish the corresponding iodide. THF and CH_2Cl_2 which were the optimal solvents in the previous technique in the 1st and 2nd steps, respectively, were primarily employed to examine on the solvent effect. The consequences are demonstrated in Table 3.9.

Table 3.9 Solvent effect on the one-pot iodination of benzyl alcohol through benzyl diphenylphosphinite



(A) (B)

(C) = 

(D) = 

Entry	Solvent 1	Solvent 2	% Yield[a]				MB
			A	B	C	D	
1	THF	THF	10	36	51	5	102
2	CH_2Cl_2	CH_2Cl_2	trace	61	30	5	96
3	THF[b]	CH_2Cl_2	17	48	26	4	95
4	THF	CH_2Cl_2	22	22	56	4	104

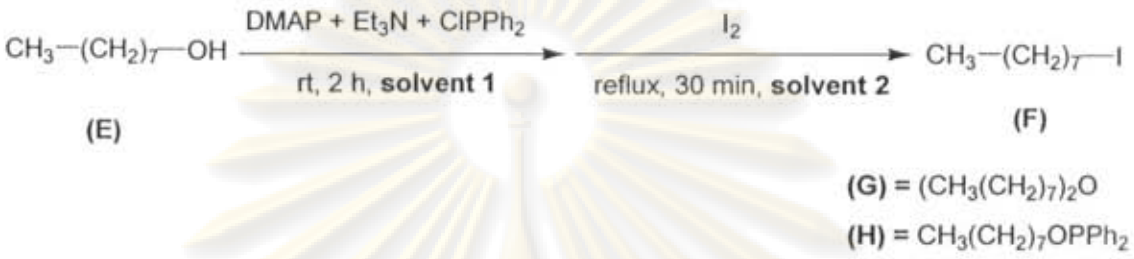
[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

[b]Evaporated the solvent out before added I_2

In this study, the results were discussed in three aspects: the desired iodide, the corresponding by-product and the unreacted substrate. Benzyl iodide **(B)** in THF could be only afforded in 36% yield, whereas approximately double yield was obtained in CH_2Cl_2 (entries 1 and 2). Astonishingly, dibenzyl ether **(C)** was also detected as a by-product in both solvents even lower amount was observed when CH_2Cl_2 was used. These outcomes exposed that the iodide and its by-product were preferably formed in CH_2Cl_2 and THF, respectively. The examination on the effect of these two solvents on the reaction in details was performed. The reaction using THF in the 1st step and CH_2Cl_2 in the 2nd step gave higher iodide and lower ether comparing with that employing a mixed solvent of THF-CH_2Cl_2 (entries 3 and 4). With regard to the recovered substrate, benzyl alcohol **(A)** was still remained in all experiments. Benzylic effect of this substrate might cause of the ether synthesis; therefore, 1-octanol was selected as another substrate to repeat the trials. The

reactions of 1-octanol with the same manner as benzyl alcohol was tried to scrutinize the solvent effect as shown in Table 3.10.

Table 3.10 Solvent effect on the one-pot iodination of 1-octanol through 1-octyl diphenylphosphinite



Entry	Solvent 1	Solvent 2	% Yield[a]				MB
			E	F	G	H	
1	THF	THF	10	44	30	13	97
2	CH_2Cl_2	CH_2Cl_2	22	56	16	10	104
3	THF[b]	CH_2Cl_2	20	44	20	20	104

[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

[b]Evaporated the solvent out before added I_2

The obtained results displayed the identical tendency as previous experiments. The side reaction was more preferable formed in THF than in CH_2Cl_2 (entries 1 and 2). Both results confirmed the hypothesis above that THF caused higher side reaction than CH_2Cl_2. The reaction using two types of solvents did not provide better yield of the desired product than prior trials (entry 3). From aforementioned results, CH_2Cl_2 was selected as the optimal solvent.

The example of the crude ^{1}H-NMR containing 1-octanol **(E)**, 1-octyl iodide **(F)**, dioctyl ether **(G)** and 1-octyl diphenylphosphinite **(H)** is shown in Fig 3.6. Herein, the signals of protons adjacent to electron-withdrawing functional groups: -OH, -I, -OR and $-OPPh_2$ were discussed. The proton signal of the desired iodide **(F)** was displayed at δ_H 3.19 [42], whereas the signal of unreacted alcohol **(E)** and its intermediate **(H)** were presented at δ_H 3.64 and 4.03, respectively. The triplet signal of the corresponding by-product **(G)** was shifted to δ_H 3.54.

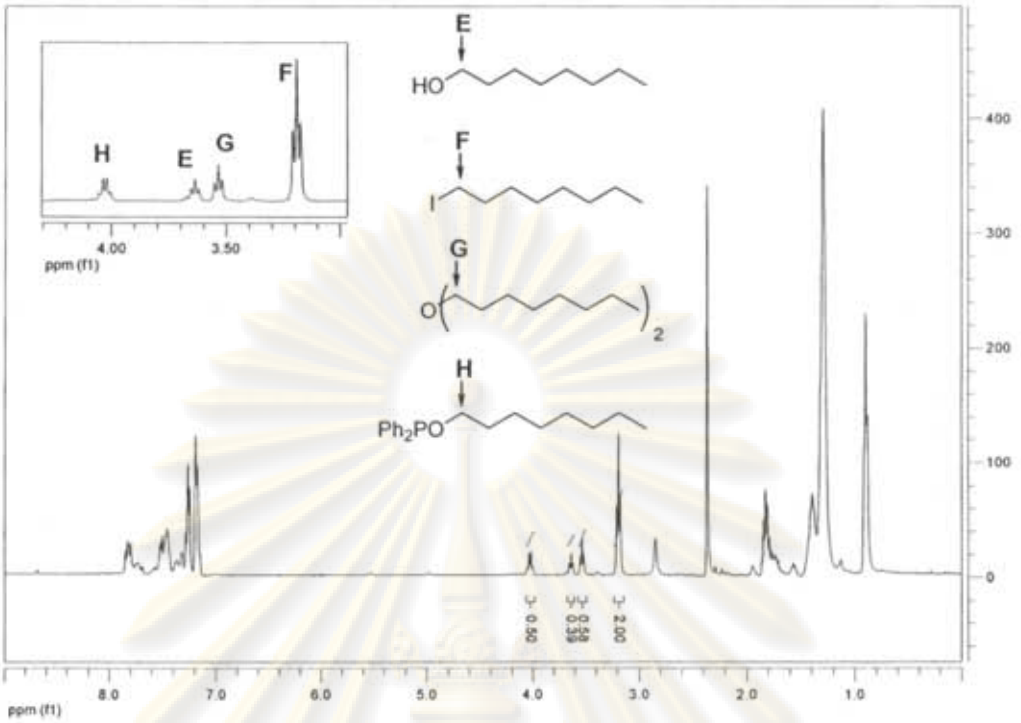
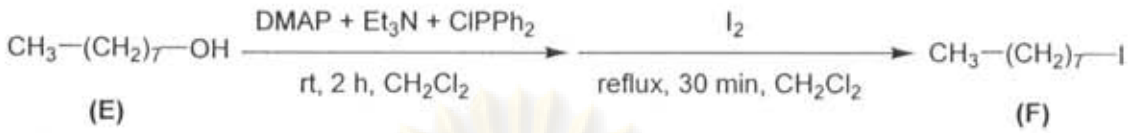


Figure 3.6 The ^{1}H-NMR spectrum of crude containing 1-octanol **(E)**, 1-octyl iodide **(F)**, dioctyl ether **(G)** and 1-octyl diphenylphosphinite **(H)** (Table 3.10 entry 1).

Due to the detection of the unreacted substrate and its intermediate, benzyl alcohol **(E)** and benzyl diphenylphosphinite **(F)**, the amounts of reagents were then varied to complete the reaction. The reactions of 1-octanol (1 equiv) with various amounts of DMAP, Et_3N, $ClPPh_2$ and I_2 were performed in CH_2Cl_2 and the results are summarized in Table 3.11.

Table 3.11 Effects of the amounts of reagents in the synthesis of 1-octyl iodide



(E) **(F)**

(G) = $(CH_3(CH_2)_7)_2O$

(H) = $CH_3(CH_2)_7OPPh_2$

Entry	Reagent (equiv)				% Yield[a]				MB
	DMAP	Et_3N	$ClPPh_2$	I_2	E	F	G	H	
1	0.3	1.2	1.1	1.5	24	56	16	8	104
2	0.3	1.2	2.0	1.5	-	56	24	15	95
3	0.3	1.2	2.0	2.0	-	60	25	10	95
4	0.3	1.2	2.0	2.5	-	67	28	-	95
5	-	-	2.0	2.5	76	12	-	12	100

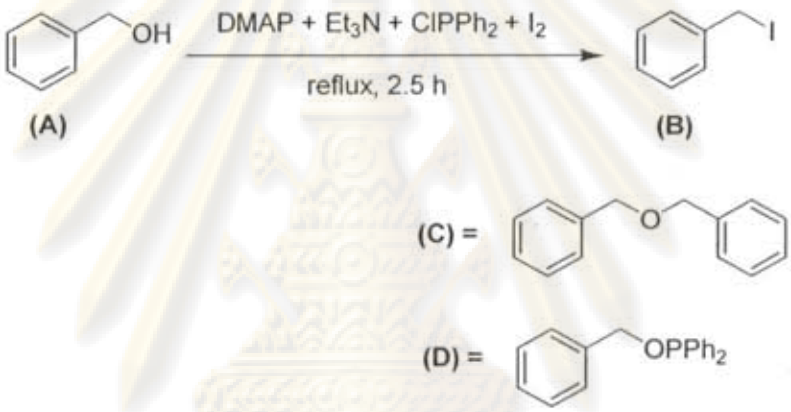
[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

With respect to the classical reaction, the unreacted 1-octanol **(E)** and its phosphinite **(H)** still remained in 24% and 8% yields, respectively (entry 1). The corresponding phosphinite was completely synthesized when 2.0 equiv of $ClPPh_2$ was used (entry 2). The latter was the variation of the amounts of I_2 to consume the phosphinite to be 1-octyl iodide **(F)** (entries 3 and 4). When 2.5 equiv of I_2 was employed, the phosphinite was used up (entry 4). In spite of the fact that both unreacted 1-octanol and its phosphinite were devoured, iodide was barely increased, whereas its by-product was still slightly increased. To search for the factors of ether formation, the reaction in the absence of DMAP and Et_3N was tried (entry 5). The substrate still left over in a large quantity, whereas its by-product was not found. From this result, it might be supposed that DMAP and Et_3N were crucial for the conversion of alcohols to its phosphinite; however, they both also caused of the side reaction of this procedure. The one-pot technique seemed to be convoluted for iodide syntheses under this condition; hence, the *in situ* iodination of alcohols through alkyl diphenyl-phosphinites was investigated afterwards to compare with this one.

3.6 The *in situ* iodination of alcohols through alkyl diphenylphosphinites

To compare the consequences with the one-pot technique, *in situ* iodination of alcohols through alkyl diphenylphosphinites was subsequently investigated. Benzyl alcohol was first selected as a model substrate to explore the solvent effect on this reaction. The treatments of benzyl alcohol (1 equiv), DMAP (0.3 equiv), Et_3N (1.2 equiv) and $ClPPh_2$ (1.1 equiv) in the presence of I_2 (1.5 equiv) in THF and CH_2Cl_2 were performed at reflux for 2 h obtaining benzyl iodide as displayed in Table 3.12.

Table 3.12 Solvent effect on the *in situ* iodination of benzyl alcohol through benzyl diphenylphosphinite



Entry	Solvent	% Yield[a]				MB
		A	B	C	D	
1	THF	trace	44	48	12	104
2	CH_2Cl_2	11	56	22	7	96

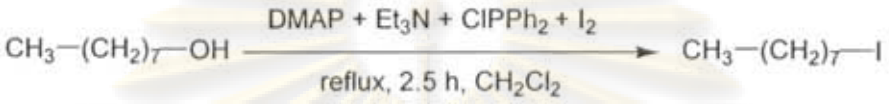
[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

Benzyl iodide **(B)** was furnished in 44 and 56% yields in THF and CH_2Cl_2, respectively (entries 1 and 2). The corresponding ether **(C)** was produced as equal as the desired product in THF, whereas it was half produced in CH_2Cl_2. From these results, CH_2Cl_2 was chosen as the optimal solvent similar to the one-pot technique. Benzyl alcohol **(A)** and benzyl diphenylphosphinite **(D)** still left over in the mixture revealing the incomplete reactions; therefore, the amount of reagents was subsequently examined.

As criticized above that benzylic effect might cause of this side reaction, 1-octanol was employed as another substrate to search for an optimized condition. The

reactions of 1-octanol (1 equiv) and $ClPPh_2$ (1.1 equiv) with various amounts of reagent in CH_2Cl_2 were carried out at reflux for 2.5 h. The outcomes are shown in Table 3.13.

Table 3.13 Effect of the amounts of reagents on the *in situ* iodination of 1-octanol through 1-octyl diphenylphosphinite



(E) (F)

(G) = $(CH_3(CH_2)_7)_2O$

(H) = $CH_3(CH_2)_7OPPh_2$

Entry	Reagent (equiv)			% Yield[a]				MB
	DMAP	Et3N	I_2	E	F	G	H	
1	0.3	1.2	1.5	-	60(38)	18(42)	24(16)	102(96)
2	0.3	1.2	2.0	-	62	24	12	99
3	0.3	1.2	2.5	-	70	29	-	99
4	0.3	-	2.5	-	72	14	9	95
5	-	1.2	2.5	-	69	12	15	96
6	-	-	2.5	-	75	9	15	99

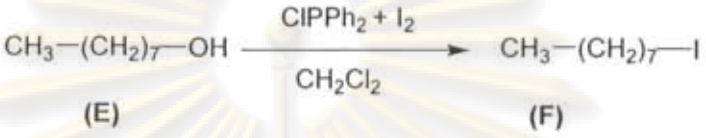
[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

The result in the parenthesis was proceeded in THF.

The classical reactions in THF and CH_2Cl_2 were initially tried to confirm the solvent effect of this *in situ* method. The outcome displayed the same inclination as prior one that the reaction in CH_2Cl_2 afforded higher yield of the desired iodide **(F)** (entry 1). As 1-octyl diphenylphosphinite **(H)** found above, the amounts of I_2 ranging from 1.5 to 2.0 equiv were then varied to complete the reaction (entries 2 and 3). 1-Octyl diphenylphosphinite was fully consumed when 2.5 equiv of I_2 was employed (entry 3). The reactions in the absence of either Et_3N or DMAP raised 1-octyl iodide and lessened its by-product (entries 4 and 5). These results revealed that Et_3N and DMAP caused of this side reaction. The corresponding ether still remained even if both Et_3N and DMAP were in absence (entry 6). It might be explained that there should be other factors besides these bases which caused of the etherification;

therefore, the effects of time and temperature were then explored. The treatments of 1-octanol (1 equiv), $ClPPh_2$ (1.1 equiv) and I_2 (2.5 equiv) with various reaction time and temperature were performed in CH_2Cl_2. The results are tabulated in Table 3.14.

Table 3.14 Effects of time and temperature on the *in situ* iodination of 1-octanol through 1-octyl diphenylphosphinite



(E) (F)

(G) = $(CH_3(CH_2)_7)_2O$

(H) = $CH_3(CH_2)_7OPPh_2$

Entry	Time (h)	Temp. (°C)	% Yield[a]				MB
			E	F	G	H	
1	2.5	reflux	-	75	9	15	99
2	3.0	rt	-	56	-	45	101
3	3.5	rt	-	68	-	34	102
4	4.5	rt	-	84	-	16	100
5	5.0	rt	-	96	-	-	96
6[b]	5.0	rt	-	96	-	-	96

[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

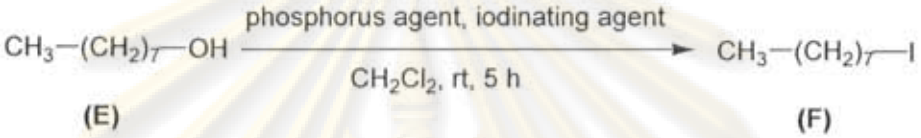
[b]*n*-Hexanol was used as a substrate instead of 1-octanol

Dioctyl ether **(G)** was still found under refluxing condition, whereas the reaction at RT yielded the desired product **(F)** without any corresponding ether (entries 1 and 2). Even though the by-product was not produced, the reaction was not completed (entry 2). As the rest 1-octyl diphenylphosphine **(H)** detected above, the reaction time ranging from 3.0 to 5.0 h was subsequently tried to complete the reactions (entries 2-5). The desired iodide was completely acquired when the reaction time was extended to 5.0 h (entry 5). Moreover, *n*-hexanol was employed as another substrate to confirm the result above. The corresponding iodide was obtained in 96% yield (entry 6). From these outcomes, it was distinctly concluded that there were three factors which caused of the side reaction: the presence of Et_3N, DMAP and high temperature. The adoptable condition for the *in situ* iodination of alcohols through

alkyl diphenylphosphinites was treating alcohols with $ClPPh_2$ (1.1 equiv) and I_2 (2.5 equiv) in CH_2Cl_2 at RT for 5 h.

To collate the reactivity of this reagent system with the others, the treatment of 1-octanol with several reagent systems underwent the optimal condition producing the corresponding iodide as summarized in Table 3.15.

Table 3.15 Effect of reagent systems on the *in situ* iodination of 1-octanol through 1-octyl diphenylphosphinite



Entry	Reagent (equiv)		% Yield[a]		MB
	Phosphorus agent	Iodinating agent	E	F	
1	$ClPPh_2$	I_2	-	96	96
2	$ClPPh_2$	LiI	32	68	100
3	PPh_3	I_2	72	29	101

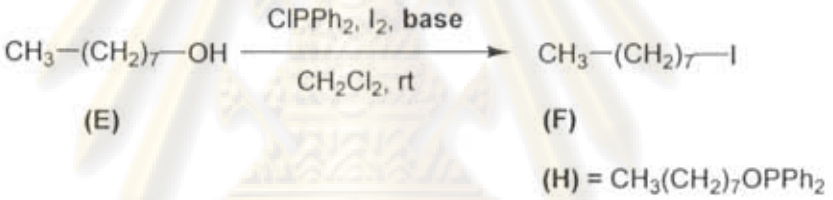
[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL

Employing $ClPPh_2$ as a phosphorus agent, the reaction using I_2 successfully furnished 1-octyl iodide **(B)** in excellent yield, whereas the reaction was not completed when LiI was used (entries 1 and 2). It might be assumed that LiI was not thoroughly homogeneous in the mixture; hence, its capability to be an iodinating agent was diminished. With respect to the comparison of phosphorus agents between $ClPPh_2$ and PPh_3, the system using $ClPPh_2$ gave higher yield of the desired product than using PPh_3 (entries 1 and 3). Since lone pair electron of phosphorus could delocalize into three aromatic rings of PPh_3 and its cone angle was larger than $ClPPh_2$, PPh_3 was more stable and thus less reactive than $ClPPh_2$. In summary, the reactivity of iodinating agents and phosphorus agents for the transformation of 1-octanol to the corresponding iodide under this condition could be placed as follows: I_2 > LiI and $ClPPh_2$ > PPh_3, respectively. Moreover, these outcomes revealed that iodination of alcohols using both I_2 and iodide salt as iodide sources could be proceeded under this

condition even the desired product was obtained in low yield in the case of the reaction using iodide salt.

Although this *in situ* technique was more simplified than two-step technique above, its optimized condition required longer reaction time to complete the reactions. To shorten the reaction time, the utilization of weak bases which were expected to be both catalysts and proton abstractors to enhance the rate of reactions was reconsidered. 1-Octanol was still selected as a model substrate in this study. The treatments of this alcohol (1 equiv) in the presence of several types of base (0.3 equiv) under the optimal condition were executed affording 1-octyl iodide as tabulated in Table 3.16.

Table 3.16 Effect of type of bases on the *in situ* iodination of 1-octanol through 1-octyl diphenylphosphinite



Entry	Base	pK_a	Time (h)	% Yield[a]		MB
				F	H	
1	-	-	5.0	96	-	96
2	quinoline	4.95	2.5	84	14	98
3	pyridine	5.25	2.5	quant.	-	100
4	4-picoline	6.02	2.5	80	16	96
5	imidazole	6.95	2.5	72	26	98
6	DMAP	9.70	2.5	98	-	98
7	pyridine	5.25	2.0	85 (92)	10 (8)	96 (100)
8	DMAP	9.70	2.0	72	28	100

[a]Analyzed by ^{1}H-NMR based on a standard toluene 10 µL
The result in the parenthesis was proceeded in the presence of 0.6 equiv of pyridine

Among these bases, the reactions in the presence of pyridine and DMAP thoroughly furnished 1-octyl iodide in half of reaction time comparing with the previous optimal condition which required 5.0 h to complete the reaction (entries 1, 3

and 6). It might be presumed that terse structure of pyridine and two basic side of DMAP induced in the completed reactions over the others. When the reaction time was abated to 2.0 h, both of these bases could not complete the reaction (entries 7 and 8). In addition, the yield of the desired product using the double amount of pyridine was not significantly increased (entry 7 in the parenthesis). With respect to factors of cost and generality of base, pyridine was more appropriate than DMAP. From above information, the *in situ* mild and simplified iodination of alcohols with I_2/$ClPPh_2$ system in the presence of pyridine was developed. This protocol was preliminary approach for the further development of iodide syntheses.

The crude ^{1}H-NMR of 1-octyl iodide (Fig 3.7) displayed its entire identity pattern referring to the previous literature [42]. The triplet signal of two protons adjacent to iodide was shifted to δ_H 3.19. The rest three groups of proton signals were manifested at δ_H ranging from 0.6 to 1.8.

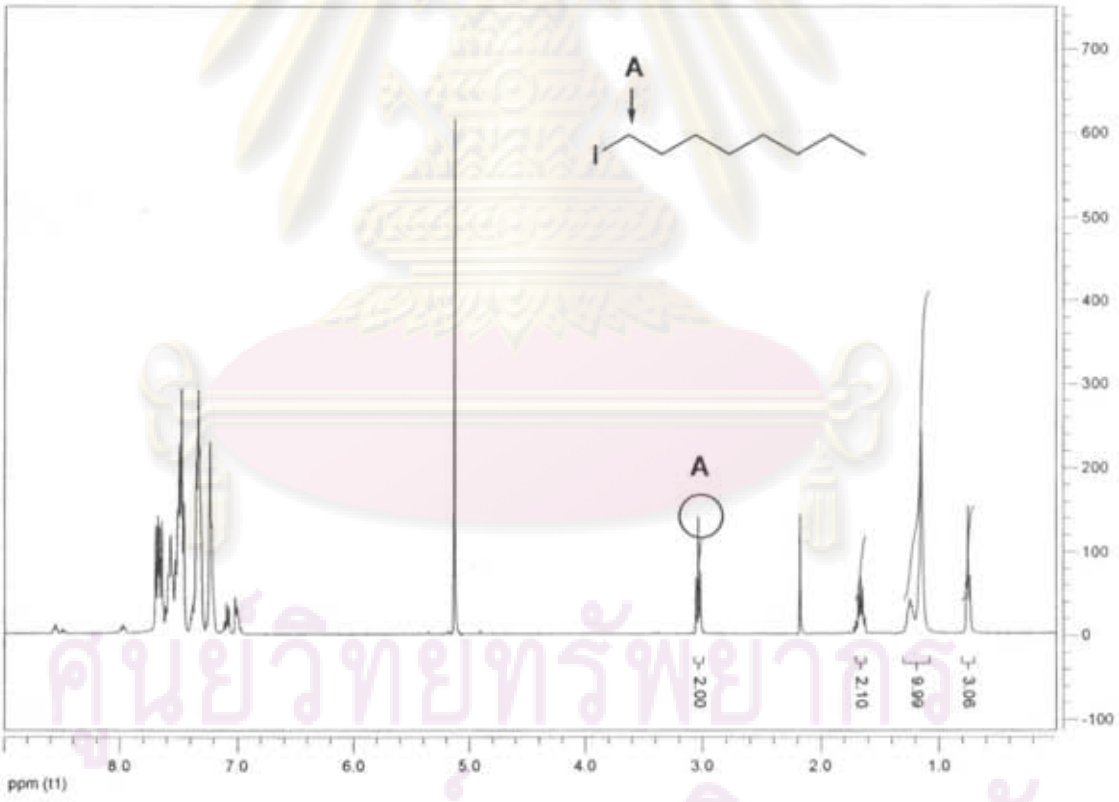
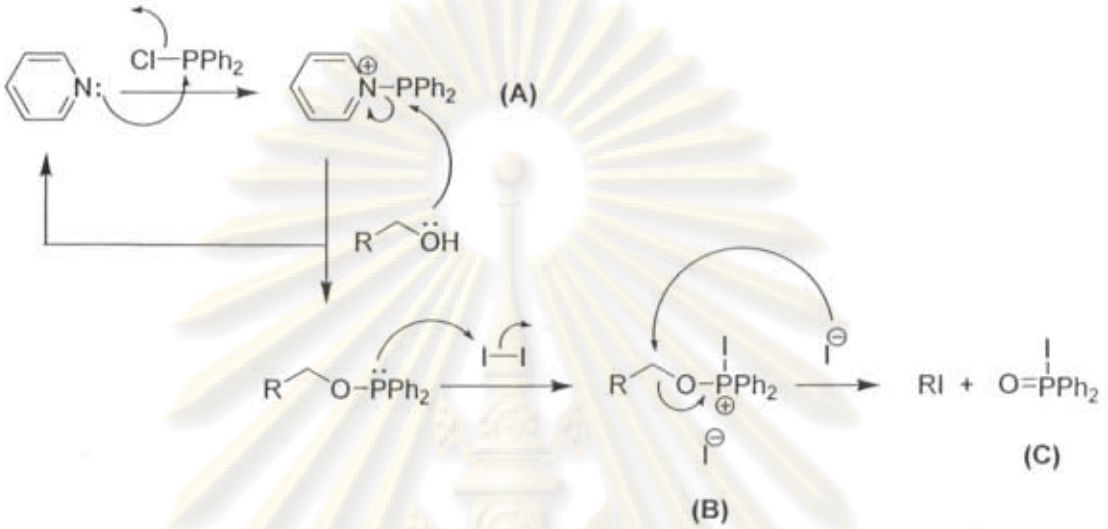


Figure 3.7 The crude ^{1}H-NMR spectrum of 1-octyl iodide (Table 3.16 entry 3).

The possible pathway for the *in situ* iodination of alcohols might proceed under the similar manner as the two-step technique. In the first step, $ClPPh_2$ was initially activated by pyridine and then alcohol substituted the activated $ClPPh_2$ **(A)** to

produce alkyl diphenylphosphinite. This phosphinite further reacted with I_2 to generate intermediate **B** and then the S_N2 reaction of the intermediate with iodide anion formed alkyl iodide and by-product **C**.



Scheme 3.5 Possible mechanism pathway for *in situ* iodination of alcohols through alkyl diphenylphosphinites.

CHAPTER IV

CONCLUSION

The objectives of this research are to search for optimized conditions for the transformation of alkyl diphenylphosphinites to their analogous iodides and selenides. These developed methods could be performed under mild conditions, short reaction time and high yields of the desired products even in the case of tertiary alkyl iodides and alkyl phenyl selenides.

During the course of this research for the preparation of alkyl phenyl selenides from alkyl diphenylphosphinites which could be prepared in high yields from the reaction among the corresponding alcohols (1 equiv), DMAP (0.3 equiv), Et_3N (1.1 equiv) and $ClPPh_2$ (1.2 equiv) in THF at RT, the optimized condition was disclosed that alkyl diphenylphosphinite 1 equiv and PhSeSePh 1 equiv in the presence of 1.5 equiv of In was approved under refluxing CH_2Cl_2 for approximately 2 h or followed by TLC. From variation of alkyl diphenylphosphinites, this method was suitable for primary and tertiary alkyl diphenylphosphinites. Acyclic secondary alkyl phenyl selenides were also afforded in high yields at longer reaction time. The treatment of *R*(-)-2-octanol under this optimal condition revealed that the possible mechanism of this technique was proceeded *via* a nucleophilic substitution reaction.

The outcome of the optimized condition for the iodination of alkyl diphenylphosphinites was that alkyl diphenylphosphinite (1 equiv) as a substrate and iodine (1.5 equiv) as an iodinating agent were recommended to carry out under refluxing CH_2Cl_2 for 30 min. Primary and tertiary alkyl diphenylphosphinites were exclusively transformed to the corresponding iodides in high yields. The mechanism of the iodination of alkyl diphenylphosphinites was proposed in the similar manner as the preparation of selenides. Additionally, *in situ* mild and simplified iodination of alcohols through alkyl diphenylphosphinites using 1-octanol as a selected model substrate was preliminarily investigated. The $I_2/ClPPh_2$ system in the presence of 0.3

equiv of pyridine in CH_2Cl_2 for 2.5 h was affirmed as the optimal reaction condition at RT. Moreover, the outcomes exposed the efficient methodology which could extensively manipulate in both of iodide sources, I_2 and iodide salt, even the desired product preferably formed when I_2 was employed as an iodinating agent under this condition.

Propose for the future work

This research distinctly revealed the successful methodology development for the preparation of alkyl iodides and alkyl phenyl selenides *via* alkyl diphenyl-phosphinites. The outcome opened many possibilities to deal with future exploration. In the future, the applications of these newly methods for the preparation of some commercial compounds such as methyl-*tert*-butyl ether (MTBE), dimethyl ether (DME), isobutene and cyclohexene which can be utilized in both organic and industrial syntheses will be ongoing planed to synthesize.

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