CHAPTER I

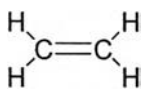
INTRODUCTION

Organic chemistry started as the chemistry of life, that was the chemistry of carbon compounds along with other elements found in living thing and elsewhere. Life processes were supported by the chemical reactions of complex organic compounds such as enzymes, hormones, proteins, carbohydrates, lipids, and nucleic acids. Chemists, in attempts to improve on nature, created millions of organic compounds both of existence and nonappearance in nature originally, and the researches have been continued. The goals of organic synthesis were of two types: the development of new synthetic methods, such as a route for making olefin referred to in this research, and the synthesis of target molecules. The majority of this research was concerned with the former goal, the development of new synthetic methods. Nevertheless, the synthesis of naturally occurring compounds remained a vigorously pursued field for two reasons. First, natural products gave some materials only in such small quality or with such difficulty that synthesis could provide cheaper and more abundant material. This was especial important if the compound had valuable pharmaceutical properties. In addition, the total synthesis would usually give precursors of the natural compounds from which related structures could be synthesized. This could be of value in the pharmaceutical field since the structural variants might be associated with different or more powerful biological properties. The second was natural product synthesis being the most fruitful source of new synthetic methods; a particular step in the order might lead to the development of a new and general method for its success.

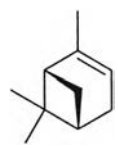
1.1 Olefins and their advantages as bioactive compounds

The compounds discussed earlier in this chapter concerning alkenes. Alkenes, or olefins as synonym, are hydrocarbons being carbon-carbon double bond functional group. They form a homologous series with formula C_nH_{2n}, unsaturated hydrocarbons, and are relatively low oxidation level hydrocarbons [1]. They occur abundantly in nature, however, a more interesting of these compounds raise when

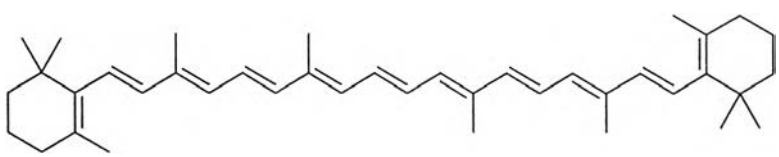
many have important biological roles. For example, ethylene (**I**) is a plant hormone that induces ripening in fruit, and α–pinene (**II**) is the major component of turpentine and a starting material converted to verbenone which component in food additive [2]. β-Carotene (**III**) as a compound that contains 11 double bonds is the orange pigment in carrots. It serves as a valuable dietary source of vitamin A and is though to offer some protection against certain types of cancer [3].



Ethylene (**I**)



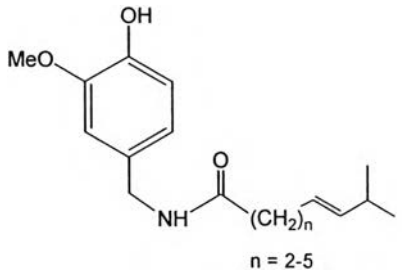
α–Pinene (**II**)



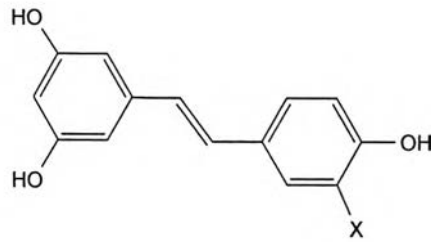
β-Carotene (**III**)

In addition, some bioactive compounds had carbon-carbon double bond in their molecules. For instance, capsaicin (**IV**, n = 4), which was an example of the benzylamine type of alkaloids, was a major component of pungent constituent of *capsicum* species [4,5]. Its formulation as *N*-(4′-hydroxy-3′-methoxybenzyl)-8-methylnon-6-enamide was first due to Nelson [6,7]. Subsequently, it was confirmed through a synthesis having the *trans* configuration of olefinic bond. Because of its biological importance such as neurogenic inflammation inhibitors [8], and a sensor neuron specificity [9], its synthetic studies were continually employing and was including in capsaicinoids [10,11], Moreover, another example of unsaturated compounds was stilbenoids which possessed vastly biological activities; thus resulted in continually synthesizing of these compounds [12,13]. Stilbenoids were found in a number of plant species [14-21], especially in genus *Artocarpus* and family Moraceae [22]. Stilbenoids were of interest in many cases from a pharmacological point of view [23-25], such as resveratrol (**V**, X = H) and piceatannol (**V**, X = OH) acting as platelet antiaggregating activity [26], antioxidant [27,28], herpes simplex virus inhibition (HSV) and anticarcinogenic effects [14,29,30]. Other applications of other stilbenoids were the uses as polymer, from a monomer commonly named *p*-vinyl-*trans*-stilbene

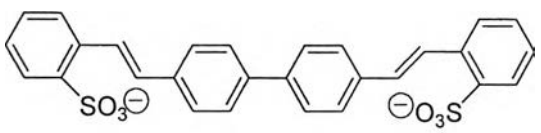
(PVTS) (**VI**) [31], and fluorescent whitening agent (FWAs) in detergents, *e.g.* distyryl biphenyl (DSBP) (**VII**) [32], or tyrosinase inhibitors as whitening agents in cosmetic products, *e.g.* artogomezianol (**VIII**) and andalasin A (**IX**) [22].



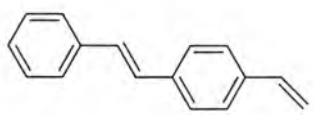
Capsaicin (**IV**)



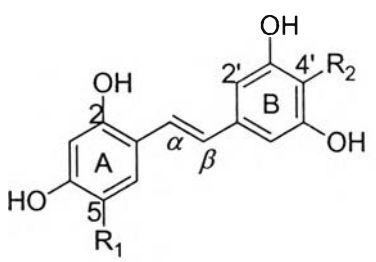
Stilbenoids (**V**)



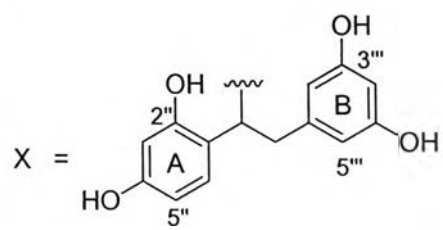
DSBP (**VII**)



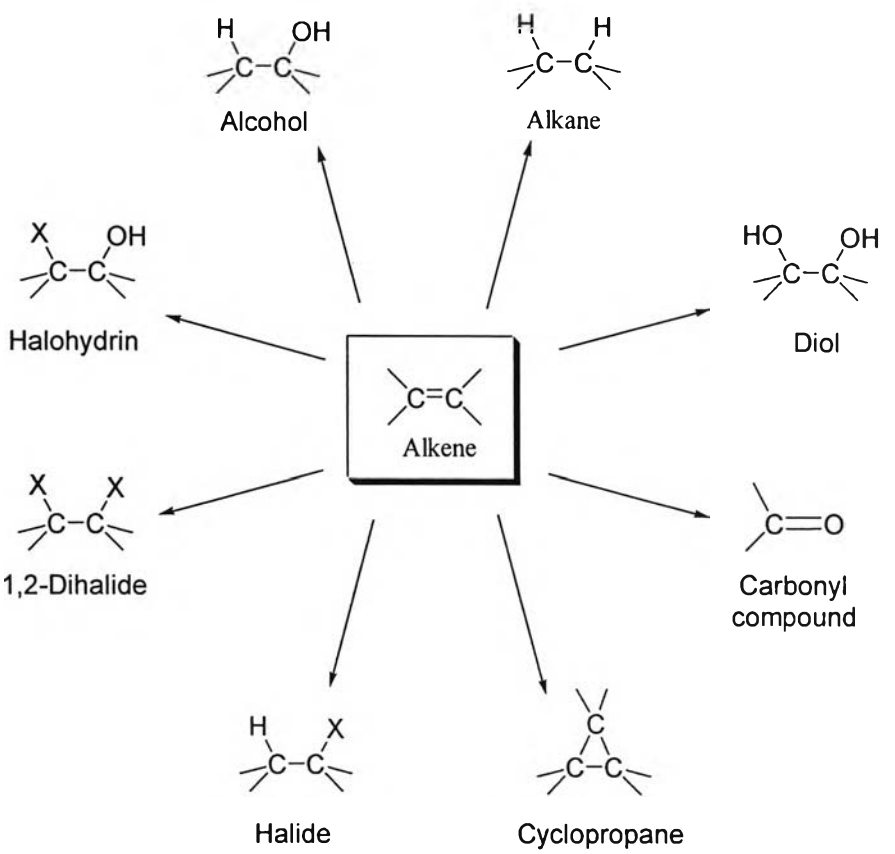
PVTS (**VI**)



	R_1	R_2
artogomezianol (**VIII**)	X	H
andalasin A (**IX**)	H	X



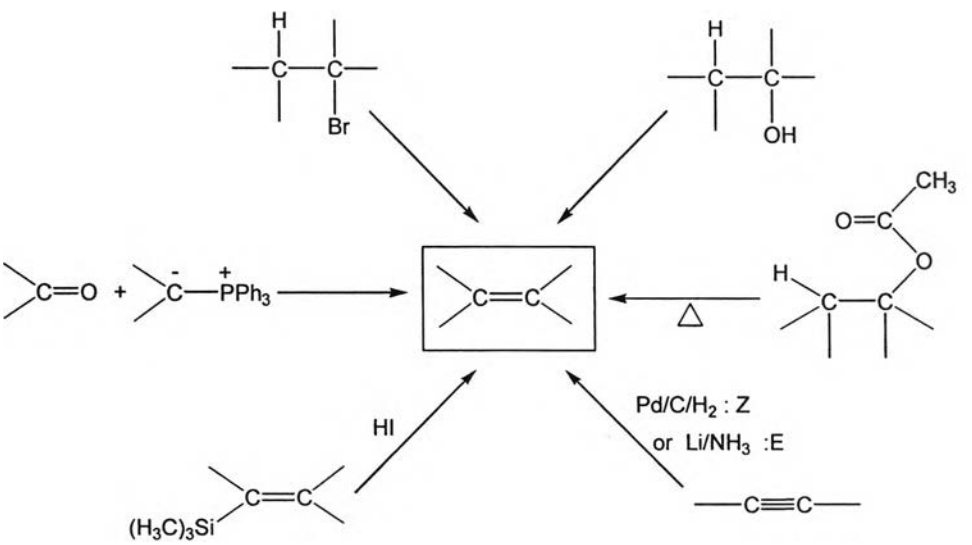
The next topic in this chapter presented how to prepare the alkenes and reviewed a variety of methods used to form alkenes. Before getting to the main subject of this chapter, the reactions of alkenes in organic synthesis as shown in Scheme 1.1, the addition of electrophiles to alkenes was a useful and general reaction, making possible the synthesis of many different kinds of compounds.



Scheme 1.1 The reactions of alkenes in organic synthesis

1.2 Olefinations

As mentioned above, in this chapter, the review and introducing of the development of some synthetic methods, focused on the formation of olefin, were referred to as shown in Scheme 1.2.



Scheme 1.2 Methodologies for the formation of alkenes

- **Formation of carbon-carbon double bonds**

The construction of a C=C bond was probably the most important operation in organic synthesis, especially if it could be accomplished with chemo-, regio-, and stereoselectivity. The complexity of most of today's synthesis target demanded that selectivity, general, and high-yield means of introducing new C=C bonds were available.

The reactions of carbon-carbon double bond formations were categorized into 13 subtitles as followed in the book named "Some Modern Methods of Organic Synthesis" [33]:

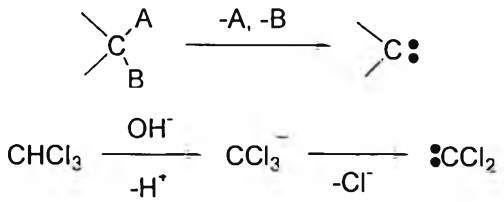
1) β-Elimination reactions
2) Pyrolytic *syn*-elimination
3) Sulfoxide–sulphenate rearrangement
4) The Witttig and related reactions
5) Alkene from sulfone
6) Decarboxylation of β-lactones
7) Stereoselective synthesis of tri-, and tetra-substituted alkenes
8) Fragmentation reaction
9) Oxidative decarboxylation of carboxylic acids
10) Alkenes from arylsulphonylhydrazones
11) Stereospecific synthesis from 1,2-diols
12) Claisen rearrangement of allyl vinyl ethers
13) Reductive dimerisation of carbonyl compounds

As mentioned above, a variety of fundamentally different approaches to synthesize alkenes have been developed. The remained section in this chapter would mention only some topics of alkene synthesis concerning with this research.

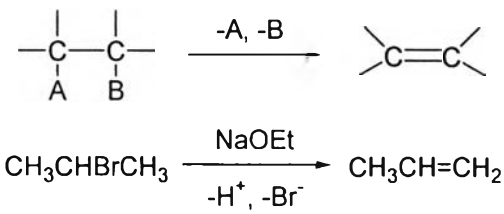
- **Elimination reaction**

Elimination reactions were classified under two general headings:

(a) α-Eliminations: two groups were eliminated from the same atom and carbenes, unstable species, were formed which underwent further reactions. This elimination type did not involve the reactions of carbon-carbon double bond formations.

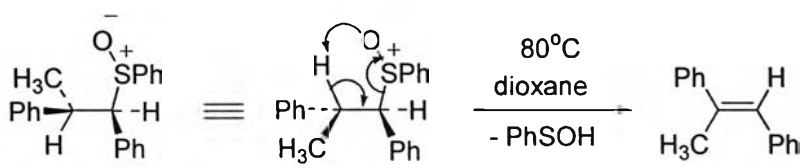


(b) β-Eliminations: group on adjacent atoms were eliminated with the formation of an unsaturated bond. The most common way to prepare alkenes was to carry out the elimination of a small molecule between vicinal carbon atoms.

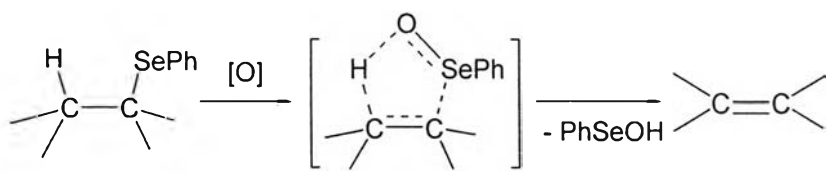


There were many methods for carrying out 1,2-elimination (X = halogen, OH, OCOR, $ROSO_2CH_3$, $ROSO_2Ar$, $\overset{+}{N}R_3$, $\overset{+}{S}R_2$) to give olefins. Several were particularly useful and widely used. Of course, dehydration or the base-catalyzed transformation of alkyl halides or alkyl sulfonates to alkenes was easily synthesized from the corresponding alcohol or alkyl halide. The choice of base was important to give predominantly elimination; generally using a sterically bulky base. Including the acid-catalyzed dehydration (X = OH), alcohol underwent elimination eliminated easily in acidic media. They proceeded by E1, E2, or less frequently, E1cB mechanism.

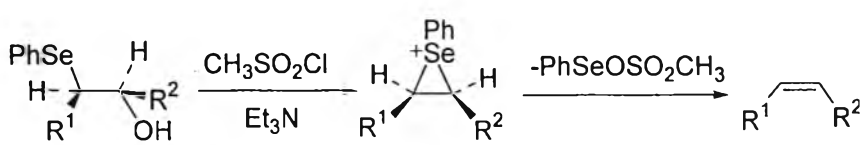
Other important elimination reactions were thermal *cis*-elimination and cleavage of sulfoxides, selenoxides and sulfones. In the case of sulfoxides with β-hydrogen atom readily underwent *syn*-elimination on pyrolysis to form alkene and took place by way of a concerted cyclic pathway. They were highly stereoselective, the *erythro* sulfoxide leading predominantly to *trans*-methylstilbene while the *threo* isomer gave mainly *cis*-methylstilbene. Pyrolysis of sulfoxides was a feature of a useful new method for introducing unsaturation at the α–position of aldehydes, ketones and esters.



Even better results, under milder conditions than sulfoxides, were obtained by using selenoxides. Alkyl phenyl selenoxides with β–hydrogen atom underwent mild condition at room temperature or below. The selenoxides were readily obtained from the corresponding selenides by oxidation with H_2O_2 or other oxidizing agents. They occurred by concerted, cyclic, *syn*-elimination process, to give the alkenes directly. Selenoxide eliminations were frequently use to install the double bond of α,β-unsaturated carbonyl compounds, without isolation of selenoxides [34]. Better yields of alkenes were sometimes obtained by elimination from *o*-nitrophenyl selenoxides than from the phenylselenoxides themselves [35].



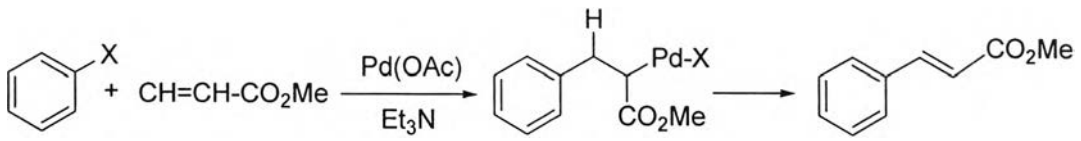
Selenoxide elimination also formed a step in a good method for converting epoxides into allylic alcohols and for introducing unsaturation at the α–position of carbonyl compounds. Alkenes were also obtained by elimination of PhSeOH from β-hydroxy selenides, best by the action of methanesulphonyl chloride and triethylamine, although acidic conditions could be used. The reaction was highly stereospecific and proceeded by *anti* (*trans*) elimination, probably by way of the episelenonium ion. High yields were obtained when the reaction used for the preparation of di-, tri- and tetrasubstituted alkenes.



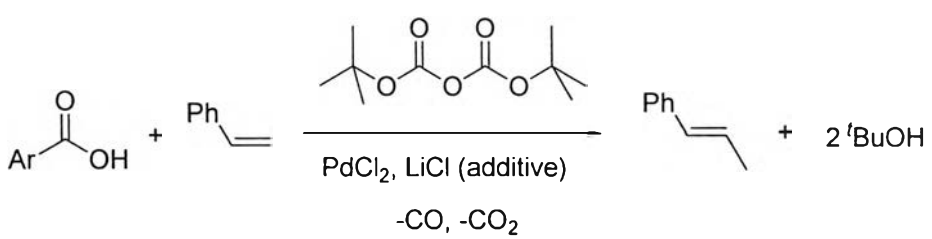
- **Heck reaction** [36-39]

One of well known protocols for carbon-carbon double bond formation was the Heck reaction, an intermolecular coupling reaction, being catalytic in Pd, the example of C=C insertion most useful to synthesis. The transformation was similar in scope to Pd-catalyzed carbonylation, only instead of CO insertion, introduction of a C=C group into Pd-C bond occurs. The below equation showed the reaction involving

the oxidation addition of R-X, where R = aryl, vinyl, benzyl, or allyl (substrate lacking β–hydrogens substituted at an sp^3 hybridized carbon), followed by alkene complexation and 1,2-insertion of an alkene. The last step was β–elimination.



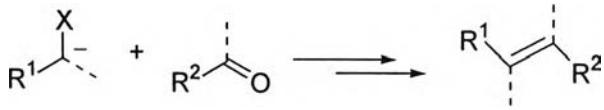
The rate of reaction and regioselectivity was sensitive to steric hindrance about the C=C bond of the vinyl partner. For example, aryl halides reacting with alkenes, the rate of reaction as a function of alkene substituent varied according to the following: CH_2=CH_2 > CH_2=CH-OAc > CH_2=CH-Me > CH_2=CH-Ph > CH_2=C(Me)Ph [40]. Other example of the Heck olefination of aromatic carboxylic acids was first reported. The reaction of carboxylic acid and di-*tert*-butyl dicarbonate were converted to mixed anhydride as reactive intermediate, which reacted with olefin in the presence of palladium catalyst to obtain stilbene derivatives [41].



- **Wittig and other related reactions**

One of the most efficient and general synthetic methods for the preparation of alkenes involved the direct olefination of carbonyl compounds. Some common reactions were selected and presented in Table 1.1.

Table 1.1 Selected methodologies for the olefination of carbonyl compounds



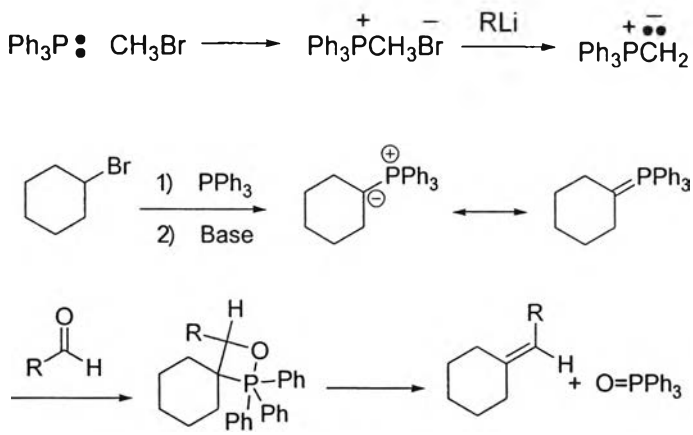
X	Reaction	X	Reaction
R_3P^+	Wittig	R_3Si	Peterson
$R_2P(=O)$	Horner-Wittig	$ArS(=O)(=NMe)$	Johnson
$(RO)_2P(=O)$	Horner-Wadsworth	$ArS(=O)_2$	classical Julia
	-Emmons (HWE)	$HetS(=O)_2$	modified Julia

Wittig Reaction [42-44]

The Wittig reaction, first published by Wittig and Geissler in 1950s, was the most common way of constructing alkene moieties in organic compounds *via* a one step process (nucleophilic addition and then elimination). The conventional Wittig reaction entailed the reaction of a phosphonium ylide with an aldehyde or ketone. It was a simple reaction to carry out and required either the aldehyde or ketone starting material. This olefination method had enjoyed widespread prominence and recognition because of its simplicity, convenience, and efficiency.

Phosphorous atoms could serve to increase the acidity of protons adjacent to them on a carbon skeleton. Positively charged phosphorous atoms increased this effect. Phosphonium salts could be made readily by treatment of an alkyl halide with a phosphine (normally triphenylphosphine, PPh_3) and the salts thus formed could be easily deprotonated by moderately strong base (aq NaOH) to generate a species called an ylide. The ylide formally carried both a positive and negative charge although it could also be represented as neutral double bond phosphorane systems. The ylid was prepared *via* a two-step process: an SN_2 reaction between PPh_3 and an alkyl halide

followed by treatment with a strong base such as an organolithium reagent. The highly reactive ylide could then participate in nucleophilic and attack at an electrophilic carbonyl centre of either an aldehyde or ketone. This generated a doubly charged species called a betaine; this could cyclize to afford an oxaphosphetane ring. Oxaphosphetanes were very unstable and undergo rapid *syn*-elimination to afford the corresponding alkene and phosphine oxide ($POPPh_3$). Although, the oxygen-phosphorous double bond was extremely strong, the formation of this bond drove this reaction.

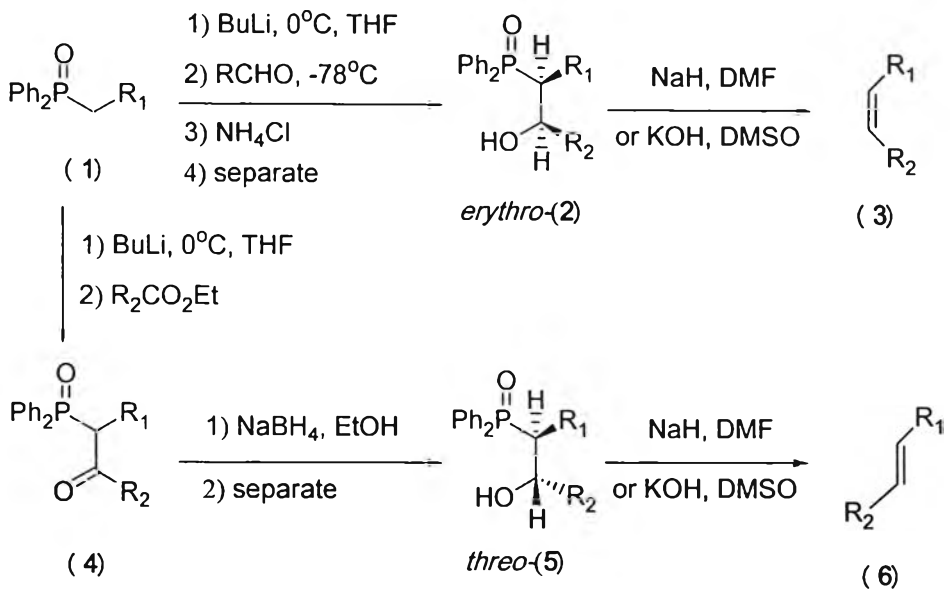


High selectivity for (*Z*)- or (*E*)-alkenes was available, depending on their circumstances, *e.g.* the type of ylide, type of carbonyl compound, or reaction conditions. Phosphorus ylides had classified according to their general reactivity. Stabilized ylides had strongly conjugating substituents (CO_2Me, CN, SO_2Ph) on the ylidic carbon and favor to produce (*E*)-alkene. In the case of semistabilized ylides gave no great preference one way or the other whereas nonstabilized ylides lacked such functionalities and favored (*Z*)-alkene.

Horner-Wittig Reaction [45-48]

When the ylide in Wittig reaction was replaced with a phosphine oxide carbanion, the reaction was referred to as the Horner-Wittig reaction. The reaction of phosphoryl–stabilized carbanion with aldehydes and ketones produced olefin. The oxide (**1**) was obtained by the treatment of PPh_3 with alkyl halide to give the phosphonium salt and hydrolysis of its salt. The oxide was reacted with base as butyl lithium to generate the lithio derivatives and then reacted with aldehyde or ketone to give *β*–hydroxyphosphine oxides (**2**) which were separated to pure isomer and then smoothly eliminated of water-soluble $Ph_2P(O)ONa$ on the treatment with NaH to form

the corresponding alkene. The separation of the *erythro* and *threo* hydroxyphosphine oxides before elimination led to a route to pure *Z*- or *E*-alkene. The elimination step was stereospecific, *erythro* hydroxyphosphine oxide giving *Z*-alkene and *threo* hydroxyphosphine oxide giving *E*-alkene, preferred *syn* elimination *via* four-membered cyclic transition state.

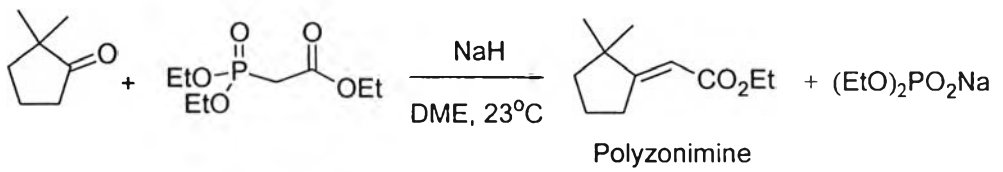


Normally, the lithio derivatives of alkyldiphenylphosphine oxides reacted with aldehyde or ketone led to predominantly *erythro* hydroxyphosphine oxides which were purified by column chromatography and then eliminated to afford pure *Z*-alkene in high yield. On the other hand, the reduction of the ketone formed by the lithio diphenylphosphine oxide acylated with ester or lactone and then eliminated from the *threo*-alcohol produces *E*-alkene.

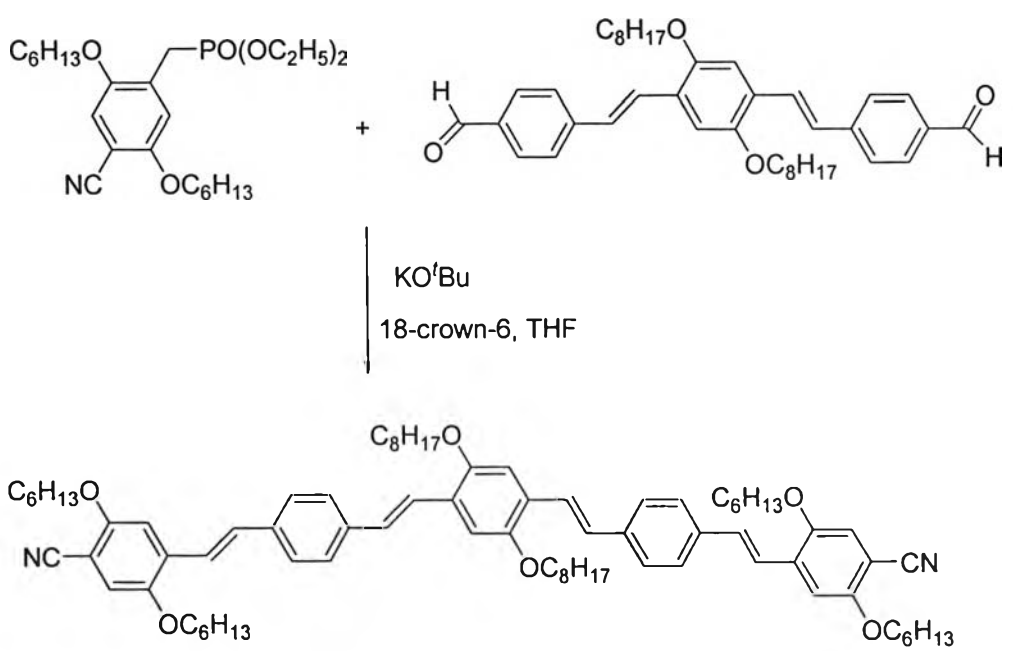
Horner-Wadsworth-Emmons Reaction (HWE) [49-52]

Phosphonate esters could also be deprotonated in a similar fashion with NaH or alkoxide anions to afford enolate type anions that could react efficiently with aldehydes or ketones to generate *E*-alkenes. Alkene-formation *via* phosphonates was referred to as Wadsworth-Horner-Emmons reaction. When the ylide in Wittig reaction was replaced with a phosphonate carbanion, the reaction was referred to as the Horner-Wadsworth-Emmons. The example shown below was the synthesis of polyzonimine that is a natural insect repellent secreted by millipedes. It had several practical advantages over Wittig reaction involving the by-product dialkylphosphate

salt was water soluble and easily removed by aq extraction. In contrast to phosphonium ylides, phosphonate-stabilized carbanions were readily alkylated and more nucleophilic (more basic) than the corresponding phosphonium ylides. Carbanion-stabilizing group at the phosphonate-substituted carbon was necessary for elimination to occur; nonstabilized-phosphonates afforded stable *β*–hydroxyphosphonates.

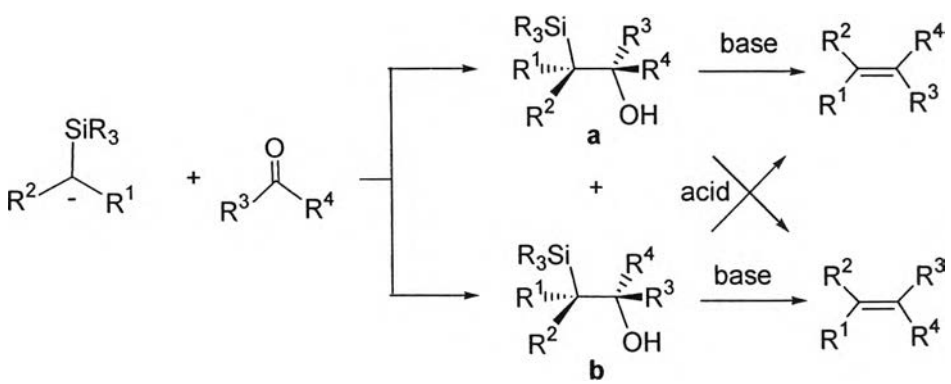


An example of this modified reaction was applied to the synthesis oligo(phenylene-vinylene)s terminated with nitiriles and aryloxadiazolyl groups as stilbenoid oligomers (OPVs) and a polymer (PPVs), used as highly fluorescent organic conductors made them valuable in light emitting diodes (LEDs). The reaction of substituted benzyl phosphonates and aromatic dialdehydes in the presence of KO*t*Bu and 18-crown-6 in THF was a simple and efficient route [53].

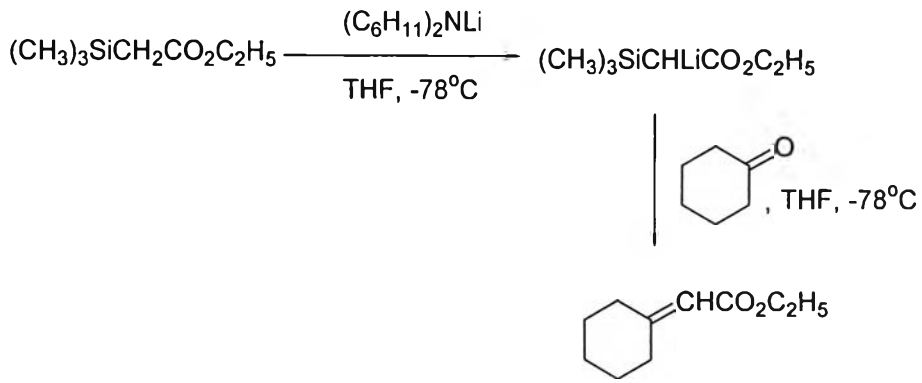


Peterson Olefination [54-59]

Peterson reaction was a silicon version of the Wittig reaction involving an elimination of trimethylsilanol (R_3SiOH) from a β-hydroxyalkyltrimethylsilane. It was the reaction of an α–silylcarbanion with an aldehyde or ketone to afford the β-hydroxysilyl intermeidiates (**a** and **b**), and then treated with acid or base to afford the desired olefins stereoselectively. It was a practical advantage over the Wittig reaction that the by-product of the reaction, hexamethyldisiloxane, was volatile and much easily to remove from the reaction product than triphenylphosphine oxide. Both the *Z*- and *E*-forms of an alkene could be separately obtained from a single stereomer of the β-hydroxysilane, as a mixture of *threo* and *erythro* forms, depending on whether the elimination was effected under basic or acidic conditions. Under basic condition *syn*-elimination was took place, by way of a cyclic four-membered transition state like that in the Wittig reaction, while under acidic condition the elimination was *anti*. For instance, treatment of the *erythro* β-hydroxysilane with acid would favor the formation of the *E*-isomer, whereas the *Z*-isomer would be formed under basic condition. Therefore, the Peterson olefination was considered to be an attractive to Wittig reaction.

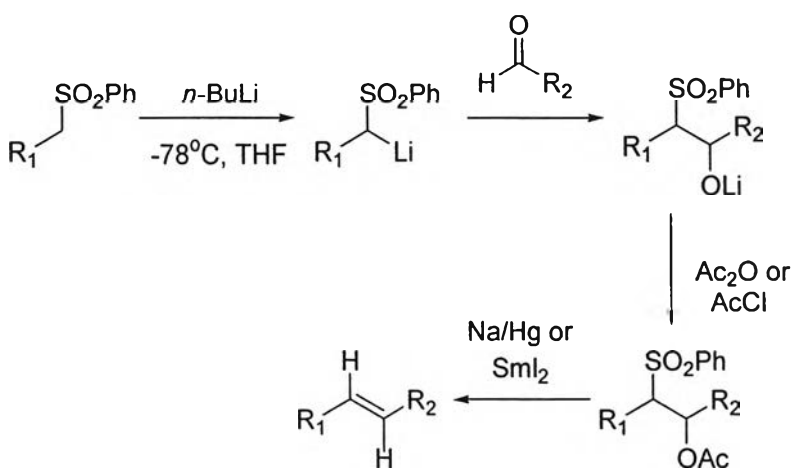


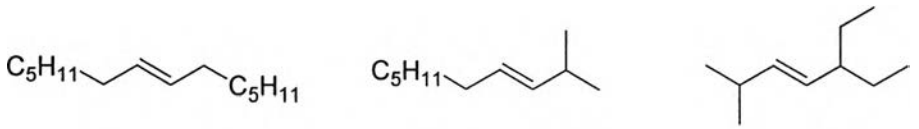
Herein, an example of this reaction used for preparation of α,β–unsaturated esters, and the phosphonate modification of the Wittig reaction, silicon reagent, was more reactive than phosphonate anions. Even easily enolisable ketones, which often give poor yields in the Wittig reaction, reacted readily with the silicon reagents.



Julia Olefination [60-62]

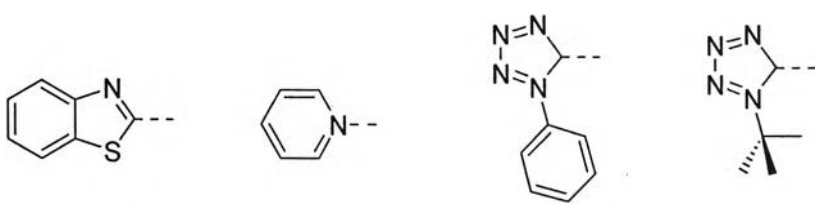
The classical Julia olefination (commonly known as the Julia-Lythgoe olefination) was discovered nearly thirty years ago by Julia and Paris. The method was later significantly developed by Lythgoe and Kocienski. The Julia olefination procedure based on the reductive elimination of *β*–hydroxysulfone derivatives with amalgam was shown to give essentially *trans* olefins. The reaction, consisting four steps, was first metallated a phenylsulfone with base as *n*-BuLi, the metallate secondly added to an aldehayde, then acrylation of the resulting *β*-acryloxysulfone and the last reductive elimination of *β*–acryloxysulfones as an alkene forming step with a single electron donor to afford alkene products. It was generally highly stereoselective and favored formation of *trans* alkene. The geometry of the alkene product was independent of the relative configuration of the intermediate *β*–acryloxysulfone and *trans* selectivity rose with increased chain branching about the newly formed double bond as shown below the equation.





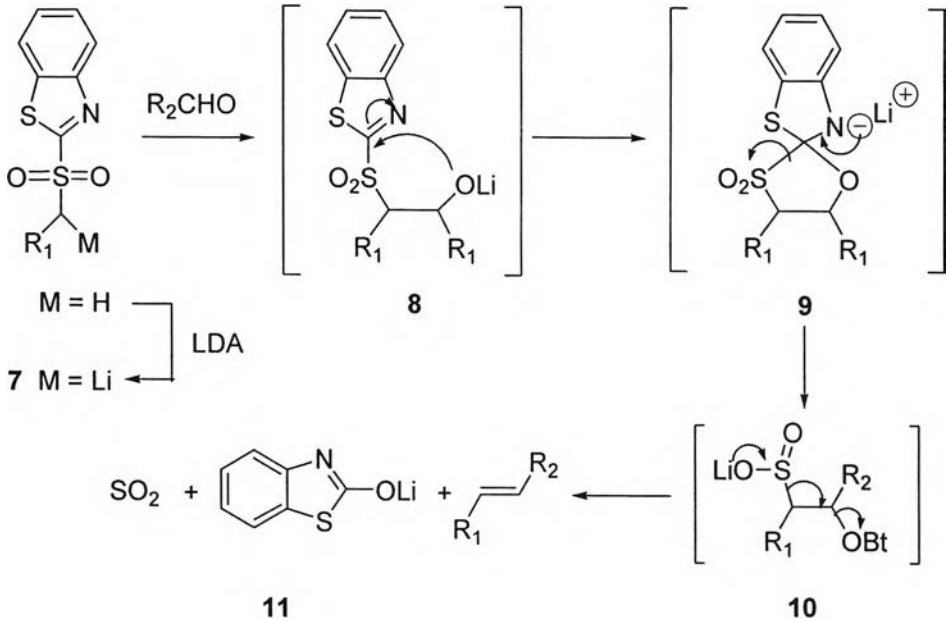
E:*Z* = 80:20 *E*:*Z* = 90:10 *E*:*Z* = >99:1

One advantage of this method over the Wittig reaction was the facile preparation of the *β*-hydroxysulfones formed by the condensation of an aryl sulfone and an aldehyde or a ketone. However, the reductive step was more difficult to realize and poor yields were often reported when applied to complex natural syntheses. Therefore, the so-called as one-pot and modified Julia olefination was a new variant of the classical Julia olefination. The phenylsulfones, used in classical Julia olefination, was replaced with heteroarylsulfones. For heterocyclic sulfones for alkene synthesis, four heterocyclic activators of this reaction were benzothiazol-2-yl (BT), pyridine-2-yl (PYR), 1-phenyl-1*H*-tetrazol-5-yl (PT) and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT).



BT PYR PT TBT

The modified Julia olefination was directly alkene synthesis *via* the reactions of matallated heteroarylsulfones with carbonyl compounds and applied in the synthesis of some biologically active natural product molecules. The reaction pathway was first occurred by the addition of metallated BT-sulfone (**7**) to an aldehyde proceeded in analogous fashion to the first step of classical Julia olefination; however, the resulting *β*-alkoxysulfone (**8**) was unstable and experiences a facile Smile rearrangement. The rearrangement occurred *via* a putative spirocyclic intermediate (**9**) and resulted in transferring of the heterocycle from sulfur to oxygen to yield sulfinate salt (**10**). Spontaneous elimination of sulfur dioxide and lithium benzothiazolone (**11**) from **10** yielded the alkene products directly.



1.3 The objectives of this research

The aims of this research were to develop a new methodology for carbon-carbon double bond formations which could be summarized as follows:

1. To study the effect of carbon-carbon double bond formations *via* the combination of Horner-Wittig reaction and radical olefination.
2. To develop a new strategy using indium metal and to study the optimal conditions for the preparation of unsymmetrical diorganyl selenides
3. To explore the olefination *via* unsymmetrical diorganyl selenides as intermediates which prepared from both organic halides and organodiphenyl-phosphinites.