CHAPTER II

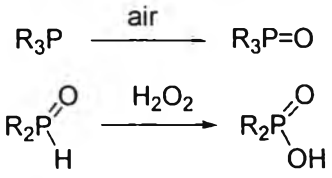
OLEFINATION *via* β-HYDROXYDIPHENYLPHOSPHINE OXIDES APPROACH

2.1 Introduction and literature reviews

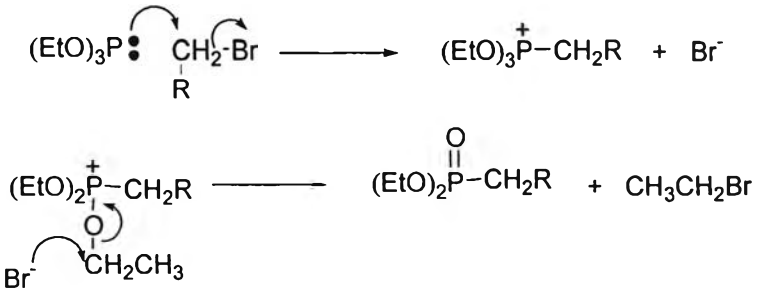
- **System Containing Phosphorus Reagents** [63-64]

Compared with most of synthetic methods, reagents contained phosphorus, sulfur, or boron had been introduced recently, within the last 25 years. There is still very active research toward further development.

Phosphorus-containing reagents owed their usefulness to three characteristics of phosphorus chemistry. The characteristics of phosphorus chemistry compared with that of nitrogen were that three-valent phosphorus in readily oxidized to the five valent state and that P-O bonds were more stable than N-O bonds. Since the relatively strong bonds formed by phosphorus to oxygen and to sulfur; the availability of 3*d* orbitals for bonding, in each of these respected phosphorus differed from nitrogen. Thus, oxidation at phosphorus occurred under mild conditions, such as



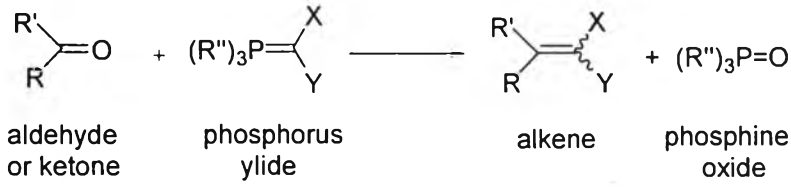
For instance, in the Arbuzov reaction of triethyl phosphite with an alkyl bromide was strong affinity of phosphorus to oxygen.



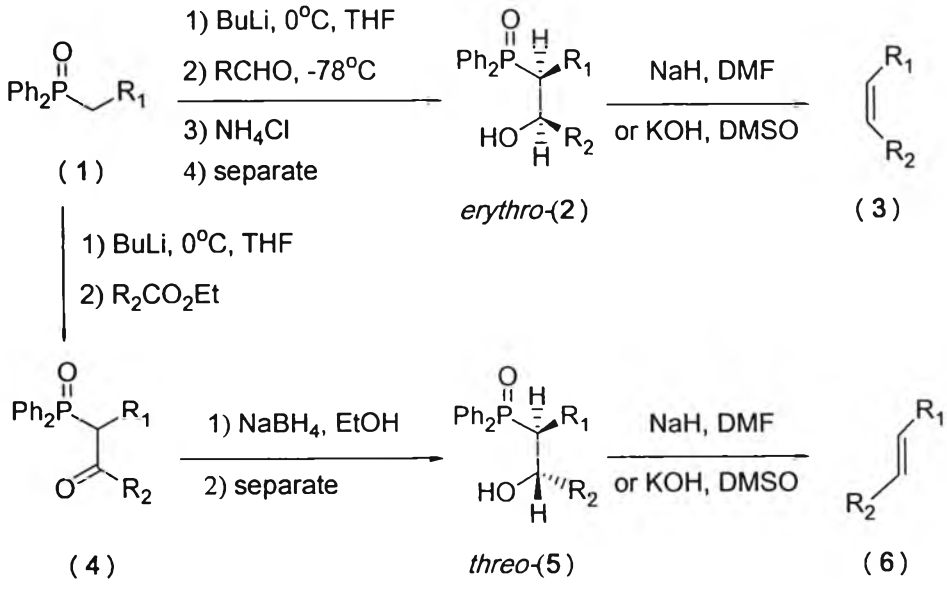
In the analytical, or retrosynthetic phase of the planning, it was useful to adopt the habit of mentally disconnecting the target molecule and seeking synthons which could be related to precursor molecules. To take a simple example, supposed in a target molecule the fragment C=C, which contained biologically active natural products being highly valued synthetic methods, was present. One of the major synthons in the olefin production was disconnected, it was apparent that a carbonyl group had to be transformed into a carbon-carbon double bond. The most common reaction of this carbonyl compounds involved the Wittig and related reactions which will be mentioned in the next topic.

- **The Wittig and Horner-Wittig reaction** [33,46]

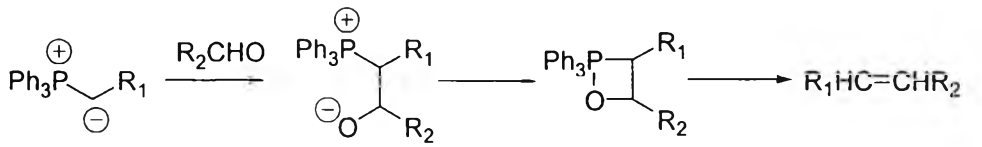
Wittig Reaction



Horner-Wittig Reaction



The Wittig reaction involved the reaction of a phosphonium ylide with an aldehyde or ketone. The highly reactive ylide could then participate as nucleophile and attack at an electrophilic carbonyl centre of either an aldehyde or ketone to generate a betaine. It could cyclize to afford an oxaphosphetane which was very unstable and undergo rapid *syn*-elimination to afford the corresponding alkene and phosphine oxide ($P(O)PPh_3$) as by-product. Although the Wittig olefin synthesis was stereoselective in good yield of predominantly one isomer, *E*- or *Z*-alkene, it lacked full stereochemical control. Moreover, mixtures of alkenes were produced and were difficult to separate from each other and from triphenylphosphine oxide.

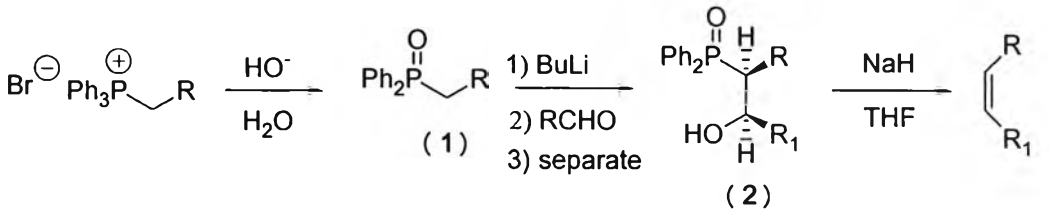


(12) **(13)** **(14)** **(15)**

The stereoselectivity of the Wittig reaction was determined at the formation of betain (**13**) since the formation and decomposition of the oxaphosphetane (**14**) were stereospecific. In fact, the formation of betain was often reversible, although, in rule, the reaction should be stopped at this stage giving a single diastereomer of betain to obtain a single geometrical isomer: (*Z*)-(**15**) from *erythro*-(**13**) and (*E*)-(**15**) from *threo*-(**13**). That was why, the Horner-Wittig reaction having the diphenylphosphinoyl (Ph_2PO) group as a stabilized-anion group in the phosphine oxides (**1**) was developed.

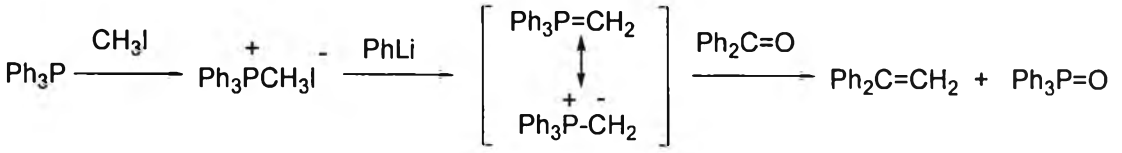
When the ylide in Wittig reaction was replaced with a phosphine oxide carbanion, the reaction was referred to as the Horner-Wittig reaction. The lithio derivatives of alkyldiphenylphosphine oxides reacted with aldehyde or ketone led to predominantly *erythro* hydroxyphosphine oxides which were purified by column chromatography and then eliminated to afford pure *Z*-alkene in high yield.

The advantages of the Horner-Wittig reaction using the diphenylphosphinoyl (Ph_2PO) group in phosphine oxides (**1**) were as: (a) 80-90% stereoselective syntheses in good yield of either *erythro* and *threo* intermediates from essentially the same starting materials; (b) simple purification of either stable crystalline intermediate; (c) nearly 100% stereospecific elimination of $Ph_2PO_2^-$; (d) crossing from *Z*–selective to *E*–selective pathways by a redox sequence.

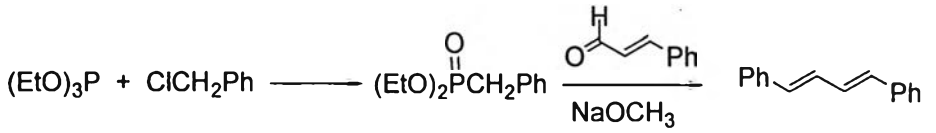


- **Literature Reviews**

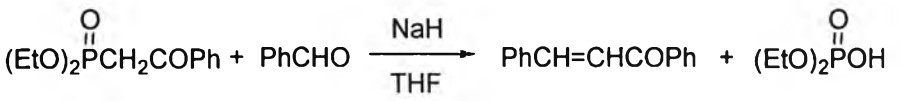
In 1953 Wittig and Geissler found that the reaction of methyltriphenyl-phosphonium iodide with phenyllithium to generate an alkylidene-triphenylphosphine or an ylide that treated with benzophenone gave 1,1-diphenylethylene [42].



In 1959, Horner applied the use of phosphonates instead of triphenylphosphoranes or Wittig reagents and reacted with aldehyde or ketone. It was found that the yield of adducts was higher than the previous report and the separation problem could be solved. For instance, the reaction of phosphonate with α,β-unsaturated aldehyde generated diene product [65-66].

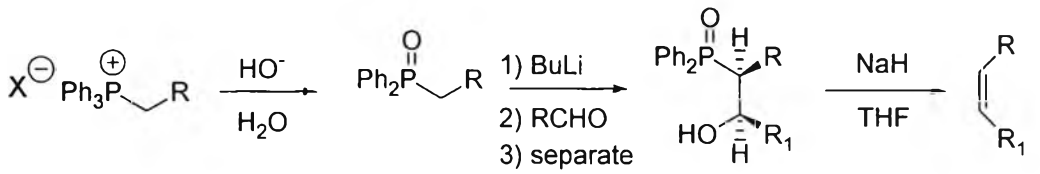


In 1961, Wadsworth and Emmons synthesized alkene using an electron-withdrawing stabilized-phosphonate carbanion reacted with aldehyde or ketone. This reagent was generally cheaper and more reactive than triarylphosphorane or Wittig reagent, as so-called Horner-Wadsworth-Emmons Reaction [49].

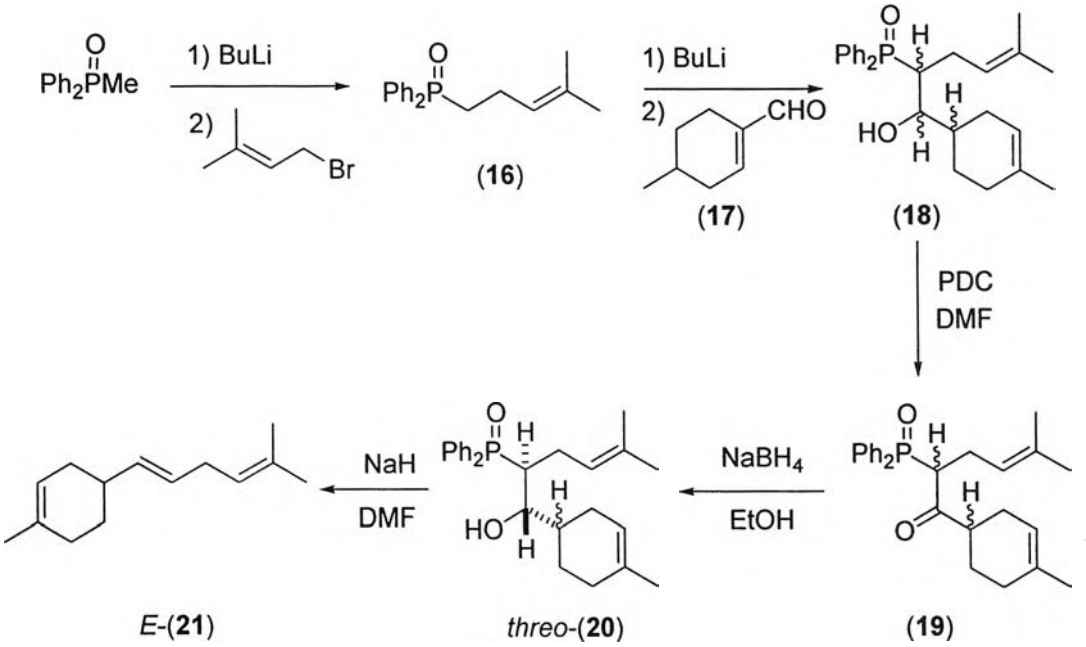


In 1983, Warren and Buss synthesized *cis*-olefin from the Horner-Wittig reaction using diphenylphosphinoyl group (Ph_2PO) as anion-stabilized group and butyl lithium as base in high yield of *erythro* intermediates. Stereospecific elimination with NaH was subsequently performed to yield pure *Z*-alkene. The optimization of

stereochemistry for preparation of *erythro* Horner-Wittig intermediates was also studied [45].

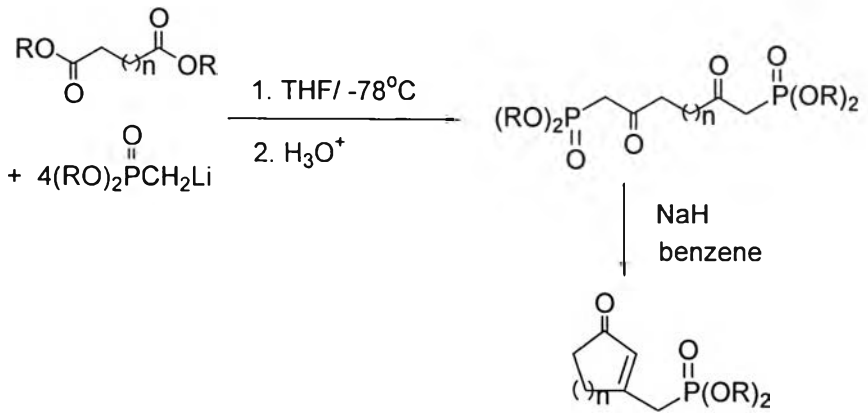


In 1985, Warren and Buss also prepared some *Z*- or *E*-alkenes using lithium derivative of phosphineoxides $Ph_2P(O)CH_2R$ treated with aldehyde to produce high yields of *erythro* intermediates with good stereoselectivity. Moreover, the reduction of *α*–diphenylphosphinoyl ketones gave *threo* intermediates with good selectivity. Purification by flash column chromatography and/or crystallization followed by elimination of Ph_2PO_2 gave pure *Z*- or *E*-alkenes. An example for the preparation of *E*-triene was illustrated by the oxidative approach to ketone (**19**). Allylphosphine oxide (**16**) was reacted with butyl lithium and then added to the Diels-Alder adduct (**12**) to give a mixture of diastereomers of three chiral adduct (**18**). The oxidation with PDC gave the ketone which was reduced to another mixture of diastereoisomers in *threo*-alcohol (**20**). After purification by chromatography gave pure *E*-triene (**21**) in 75% yield [46].

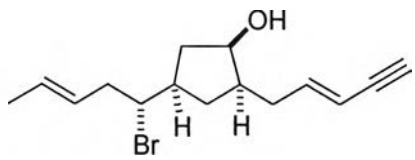


In 1994, Mikolajczyk and Mikina applied the intramolecular Horner-Wittig reaction of *bis*-*β*-ketophosphonate to prepare cyclized adduct as 3-phosphorylmethyl

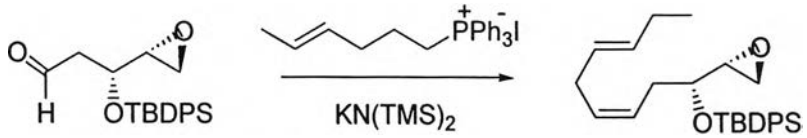
cycloalkenones. The reaction of dicarboxylic acid diesters with lithiomethyl-phosphonates gave *bis*-β-ketophosphonate $[(RO)_2P(O)CH_2C(O)]_2(CH_2)_n$ (n = 2, 3, 4) [48].



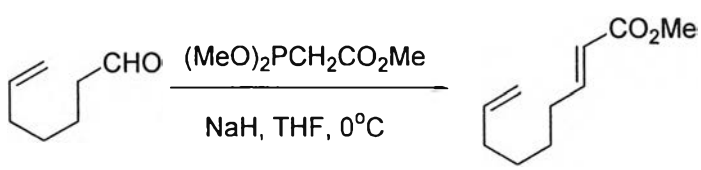
In 1997, Martin prepared *trans*-(+)-deacetylkumausyne, a marine natural product in a series of nonterpenoid C15-metabolites named lauroxanes. One of key steps for synthesizing this compound was that an aldehyde reacted with the corresponding Wittig reaction yielding the diene with excellent stereocontrol [43].



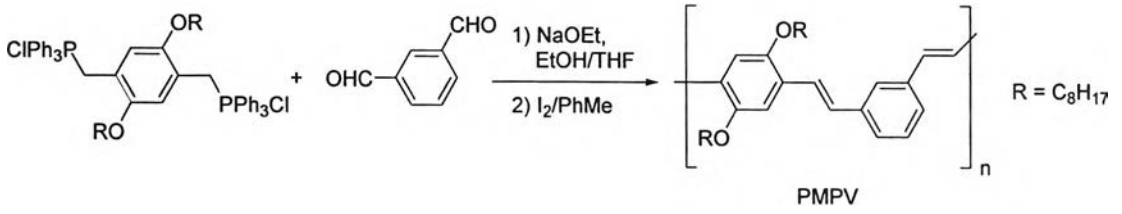
trans-Deacetylkumausyne



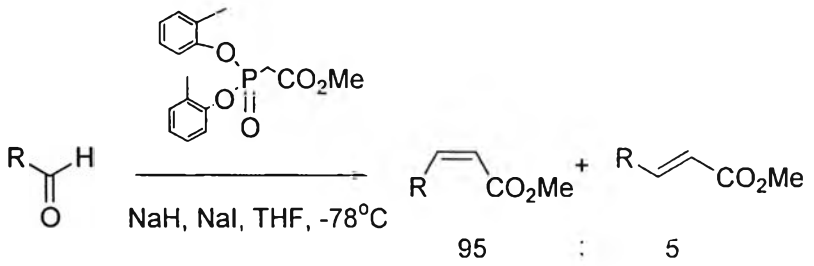
In 1998, Denmark and Middleton prepared azapropellanes *via* many step procedures. One step in this synthetic route involved the conversion of 6-heptanal to nonadienoates which achieved by the Horner-Emmons olefination with trimethyl phosphonoacetate in 80% yield [67].



An example of Wittig reaction to prepare nanotube/poly{(*m*-phenylenevinylene)-*co*-[(2,5-dioctoxy-*p*-phenylene)]} (PmPV)-based composities polymer using as carbon single-walled nanotubes (SWNTs), applied in numerous technologies as ultrahigh strength materials, and in molecular computer, in 2002. The multistep Wittig condensation of bis(triphenylphosphonium) salt and isophaldehyde was used as shown in equation [68].



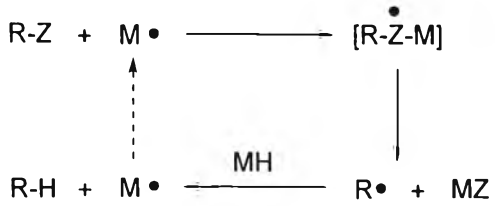
In 2003, Pihko and Salo investigated and improved conditions for *Z* selective Horner-Wadsworth-Emmons olefination with Ando's bis(*o*-methylphenyl) phosphonates affording in high *Z* selectivity. It was found that the addition of NaH and NaI furnished *Z* olefins in up to >99:1 selectivity and good yield [50].



- **Radical Chemistry**

- Radical reactions

Radical reactions have become extremely usefulness for selective organic transformation and the number of applications of these reactions in organic synthesis has increased enormously. A free-radical reaction was a chemical process in which molecules having unpaired electrons were involved as radical intermediates in organic chemistry. The radical reaction, homolytic bond cleavaged into two parts yielded free radical species which had unpaired electrons. Generally, in radical chemistry, the functional group *Z* in starting material was removed by reducing agent MH *via* intermediate to generate alkyl radical such as in radical deoxygenation.

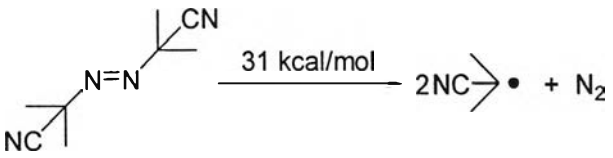


Radical reactions have several advantages over conventional ionic reactions. They could be highly chemoselective and able to proceed under neutral conditions. They had also fewer tendencies to give rearranged products than ionic reactions. Moreover, they were compatible with sensitive polyfunctional compounds. For instance, in natural products, C=O, OH and NH groups in their molecules did not need to be protected in free-radical reactions due to their neutral condition and free of salvation. Therefore, radical reactions were less affected by steric hindrance than ionic reactions, which cations or anions were bulky by solvation and influenced by the polarity of the surrounding functional groups. Radical reaction also had a low tendency to unwanted eliminations and neighboring group participations.

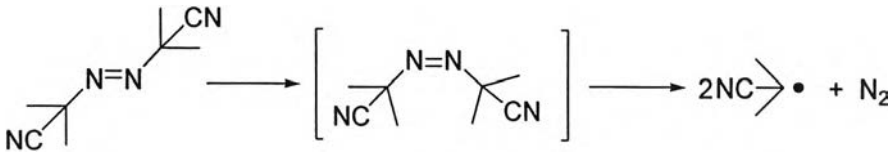
The radical reaction involved three steps in radical chain processes as initiation, propagation and termination steps. First, initiation step was the step in which the reactive intermediates were generated from initiators, as sources of free radicals. They should be stable at room temperature but decomposed to produce radicals under mild condition. Secondly, the propagation step was characterized and repeated and the chain reaction was lastly terminated by radical combination or disproportionation.

The methods of radical generation were classified based on energy supplied into 4 types as follows:

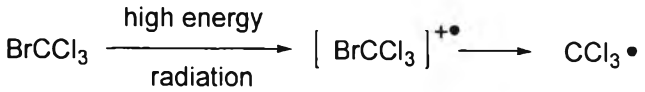
1) by thermolysis: cleavage a covalent bond by high temperature.



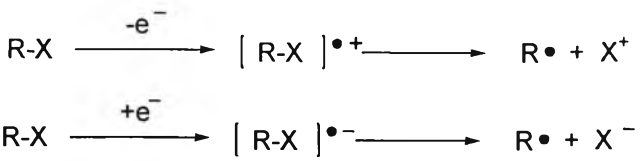
2) by photolysis: homolytic cleavage by photo light energy.



3) by radiation: using high-energy radiation *e.g.* X-ray.



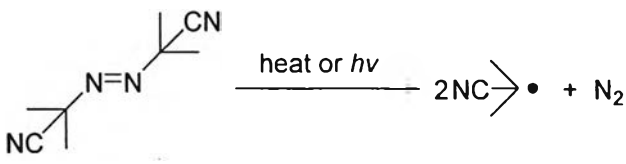
4) by redox system: generate radical by oxidation or reduction reaction and intermolecular electron transfer.



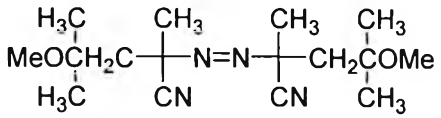
- **Radical initiators in organic synthesis**

The source of initiators depended very much on the reaction temperature and the character of initiating radicals. Several reactions were used as radical sources such as:

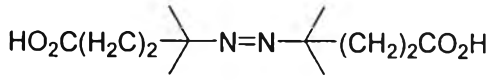
Azo compounds were a widely used as radical initiators in organic synthesis. AIBN (2,2′-azobisisobutyronitrile) was one of the most commonly used initiators due to its high decomposition ability and stability and had a half-life of 10 h in toluene at 65°C, 2 h at 80°C, and 0.1 h at 100°C. Azo compounds were decomposed by heat or light to the corresponding alkyl radical and nitrogen. There were a variety of azo compounds such as V-70 and V-501.



AIBN



2,2'-Azobis(4-methoxy-2,4-dimethylvaleronitrile)
(V-70)



4,4'-Azobis(4-cyanopentanoic acid)
(V-501)

Peroxides were common radical initiators. They produced alkoxy radicals and acyloxy radicals, produced generally electrophilic, by cleavage of the weak peroxide or oxygen-oxygen bond. The decomposition of peroxides could be accomplished by heat at low temperature or photolysis. There were widely use of thermolysis peroxides *e.g.* benzoyl peroxide, acetal peroxide, *t*-butyl peroxybenzoate and di-*tert*-butyl peroxide. The half-lives of the peroxides are given in Table 2.1.

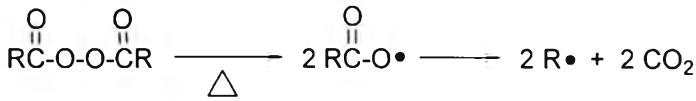
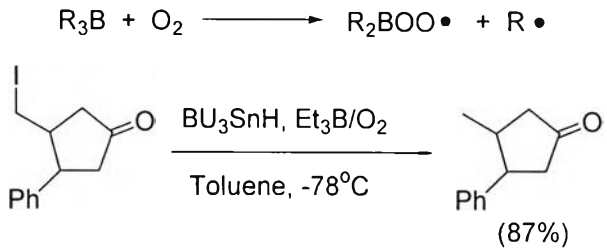


Table 2.1 Commonly used peroxides radical initiators [69]

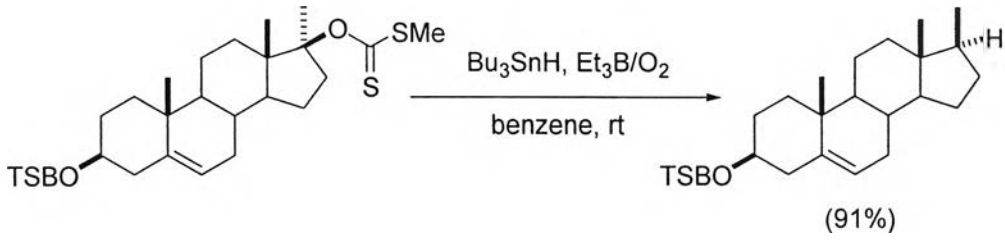
Initiators	Radicals produced	Half-life (h)	Temperature (°C)
Benzoyl peroxide	PhCOO• and Ph•	7	70
$(PhCOO)_2$		2	90
		0.5	100
Acetal peroxide	MeCOO• and Me•	8	70
		1	85
t-Butyl peroxybenzoate	*t*-BuO•, Me•, PhCOO•	20	100
[PhC(O)OO*t*-Bu]	and Ph•	1	125
Di- *t*-Butyl peroxide	*t*-BuO• and Me•	218	100
$(t\text{-BuO})_2$		6.4	300

Trialkylborane could also generate alkyl radicals in the presence of oxygen. In the case of triethylborane (Et_3B) as a radical initiator was generated free ethyl radical upon treatment with oxygen at low temperatures. The use of triethylborane was superior to AIBN and BPO due to reactions at low temperature allowing to control the stereoselectivity. The first application reaction of Et_3B with oxygen was published by Utimoto and Oshima. The Et_3B was an efficient initiator for the generation of tin radicals from tin hydrides. A wide range of alkyl iodides and bromides were readily

reduced by the treatment with tributyltin hydride in the presence of a catalytic amount of Et_3B (10 mol %) at -78°C.

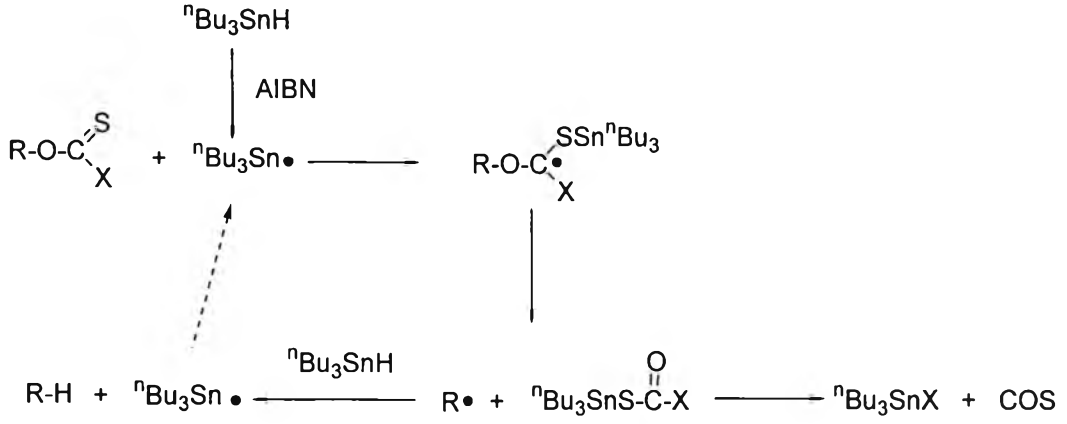


Radical initiation with Et_3B/O_2 at room temperature was also applied to the deoxygenation of secondary and tertiary alcohols *via* the corresponding thiocarbonates, which alternated to the classical thermal initiation of the Barton-McCombie deoxygenation.

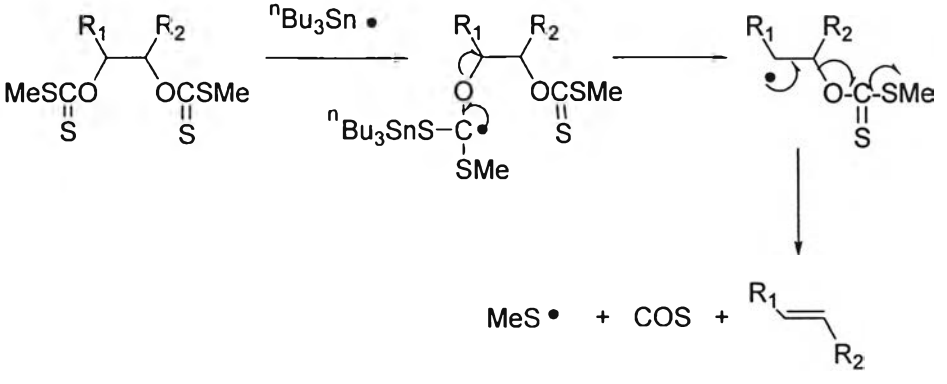


- Tributyltin hydride and diphenylsilane

In 1971, Barton *et al.* invented a new method for radical deoxygenation (Barton-McCombie Reaction) and reported that thiobenzoate *O*-esters which had potential conjugation with the resulting olefins were photolyzed to give the conjugated olefins. A tributyltin radical, generated by AIBN, attacked the thiocarbonyl group of thiono ester derivative of alcohols to give a radical intermediate that gave an alkyl radical and tin-containing byproduct (then gave fragment ^nBuSnX and COS). The alkyl radical reduced tributyltin hydride to generate deoxy product (RH). The formation of a strong Sn-S bond, the step of transition state from thiocarbonyl to carbonyl, was a driving force for this radical deoxygenation of alcohol [70-71].



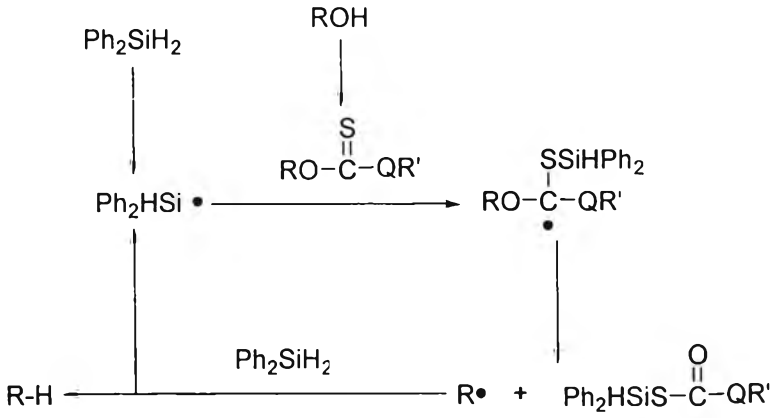
By the way, a number of methods for olefin synthesis have been reported such as synthesized from vicinal diols. In fact, β-substituents to a carbon centered radical resulted in undesired β-elimination reactions, however, this elimination reaction could be utilized to make olefins. The β-substituent to a carbon centered radical for the radical fragmentation could be a halogen, sulfide, selenide, nitro group, sulfone, xanthate, but not an acetate or mesylate. Therefore, *bis*-xanthates were prepared by the reaction of diols with NaH-CS_2-MeI and then were treated with tributyltin hydride in the presence of AIBN to generate the desired olefins in refluxing toluene. The tributyltin hydride attacked the thiocarbonyl sulfur to generate carbon centered radicals which then fragmented to give olefins and methylthio radical and COS.



Tin hydride was employed in radical condition since tributyltin hydride played an almost exclusive role as a hydrogen atom source or reducing agent and chain carriers in the early years of radical chemistry [72]. For the tin-hydrogen bond was sufficiently weak and the tributyltin radical was a useful carrier of the radical chain. However, it was expensive and not easy to remove traces of toxic tin compounds from the reaction mixtures and this problem complicated the work-up. Therefore, the

search for alternative hydrogen atom transfer agents that would also produce efficient chain-carrying radicals had started relatively early. It was found that diphenylsilane could replace efficiently tributyl tin hydride, such as in the deoxygenation of primary and secondary alcohols [73-75]. It was also used in a high-yielding transformation of dixanthates, formed from *vic*-diol, into their corresponding olefins [76-77].

Later in 1993, Barton *et al.* [78] used diphenylsilane as hydrogen source, in deoxygenation and dehalogenation, and as good alternatives to organotin hydrides in radical chemistry. Because of the silicon-hydrogen bond was relatively weak in some silanes and the silicon-heteroatom bonds that were formed in the radical chain process were relatively strong. Moreover, organosilanes were much less toxic and expensive, and the work-up was much easier than that of the tin hydride. In addition, diphenylsilane was found to be a good hydrogen atom source and the diphenylsilyl radical generated was a chain carrier in radical deoxygenation of alcohols and dehalogenation of various organic halides. In most cases the use of diphenylsilane allowed high yielding transformation of xanthates, thionocarbonates, iodides and bromides to the corresponding hydrocarbons. Primary amines could be deaminated in radical reaction with diphenylsilane *via* the corresponding isonitriles. The relatively short radical chains, however, required initiation of the radical reaction.



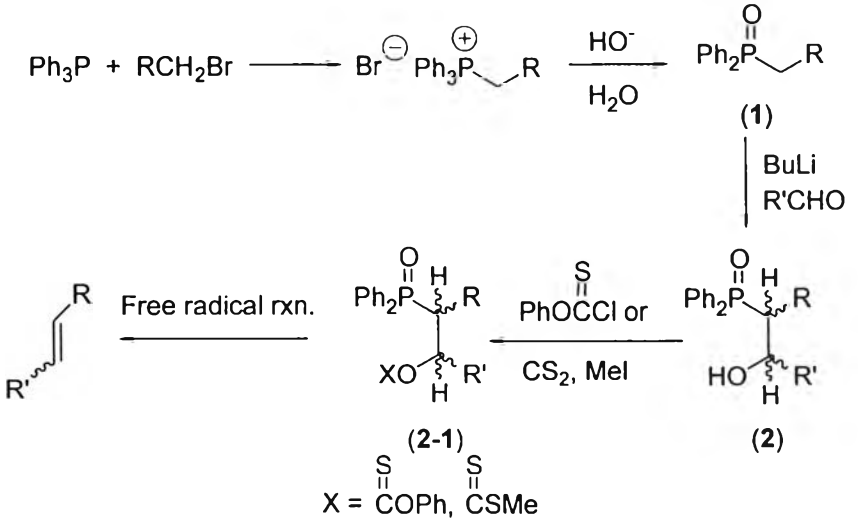
- **The objectives of this research**

As mentioned above, the phosphine oxides were attractive reagents, and high stereoselectivity could be achieved; however, the intermediate *β*–hydroxy phosphine oxides had to be isolated and purified prior to their stereospecific decomposition to alkenes. One-step or one-pot Horner-Wittig procedures that could essentially give pure (*Z*)- and (*E*)-alkenes would be a useful improvement. In addition, radical

reactions displayed many advantages in organic synthesis such as the reaction being performed under neutral condition. For this reason, the aim of this research was to develop the new methodology of Horner-Wittig reaction using a radical reaction for preparing stereospecific alkenes, without purification step of the mixture of *erythro* and *threo* diastereomers.

2.2 Results and discussion

According to the Horner-Wittig reaction procedure, before the last step of alkene synthesis, the mixture of *erythro* and *threo* *β*–hydroxyphosphine oxides needed the separation and purification by column chromatography to give pure isomer, followed by elimination of $Ph_2P(O)OH$ to generate olefin products. To make a single geometrical isomer of *β*–hydroxyphosphine oxides, sometimes it was difficult in the separation of their diastereomers. Moreover, the elimination step was stereospecific; *erythro* hydroxyphosphine oxide giving *Z*-alkene while *threo* hydroxyphosphine oxide yielding *E*-alkene, preferred *syn* elimination *via* a four-membered cyclic transition state. In addition, the reaction required the use of a strong base such as NaH. Therefore, for setting out to find new condition that could prepare the *erythro* and *threo* *β*–hydroxyphosphine oxides without separation of their diastereomers, and then transformed to alkene adduct *via* *O'*-phenyl thiocarbonate or xanthate derivatives using radical reaction under neutral conditions. The plan of this essential part of research in this chapter was proposed in Scheme 2.1.

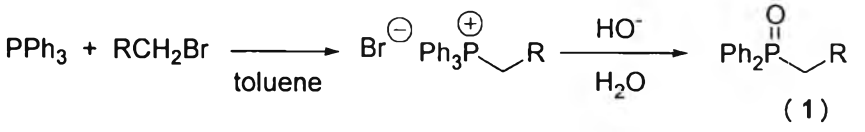


Scheme 2.1 The plan for synthesis of alkene *via* *O'*-phenyl thiocarbonates or xanthate derivatives

2.2.1 Synthesis of alkyldiphenylphosphine oxides

The subject matter to overcome this introduction for alkene synthesis required the synthesis of alkyldiphenylphosphine oxides. They could be prepared by the reaction of PPh_3 with alkyl halides to afford phosphonium salts and then hydrolysis of alkyldiphenylphosphine oxides with aq base, 30% w/w aq NaOH. The results of the preparation of selected diphenylphosphine oxides are shown in Table 2.2.

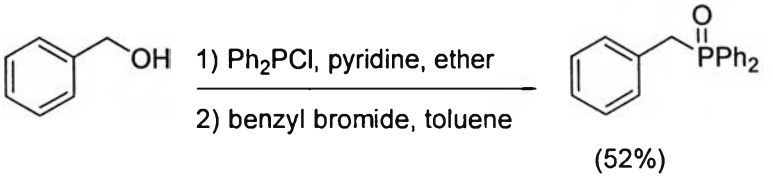
Table 2.2 Synthesis of selected alkyldiphenylphosphine oxides



Entry	RBr	$Ph_2P(=O)R$ (1)	% Isolated yield
1	$CH_3(CH_2)_2CH_2Br$	$CH_3(CH_2)_2CH_2P(=O)Ph_2$ (**1a**)	69
2	$CH_3(CH_2)_4CH_2Br$	$CH_3(CH_2)_4CH_2P(=O)Ph_2$ (**1b**)	80
3	$CH_3(CH_2)_{10}CH_2Br$	$CH_3(CH_2)_{10}CH_2P(=O)Ph_2$ (**1c**)	82
4	$PhCH_2Br$	$PhCH_2P(=O)Ph_2$ (**1d**)	trace

As the results presented in Table 2.2, four alkyl halides were varied to react with PPh_3 to obtain the desired alkyldiphenylphosphine oxides in high yield: butyldiphenylphosphine oxide (**1a**, 69%); hexyldiphenylphosphine oxide (**1b**, 80%) and dodecyldiphenylphosphine oxide (**1c**, 82%). Benzyldiphenylphosphine oxide (**1d**) could however not be prepared under the reaction conditions (entry 4).

Therefore, the reaction condition was altered to use benzyl alcohol instead of benzyl bromide as a substrate. The treatment of benzyl alcohol with Ph_2PCl in the presence of pyridine and then added a drop of benzyl bromide or a small crystal of iodine affording benzyldiphenylphosphine oxide (**1d**) in 52% yield [46].



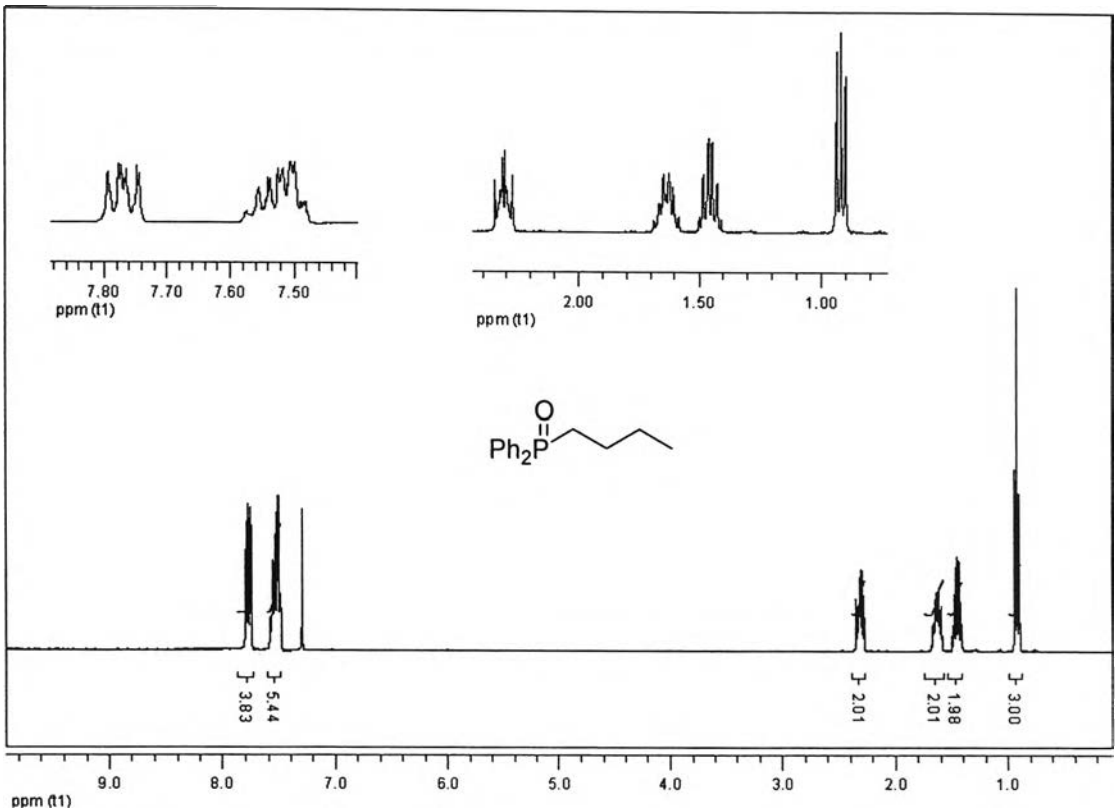


Figure 2.1 The ^{1}H-NMR spectrum of butyldiphenylphosphine oxide (**1a**)

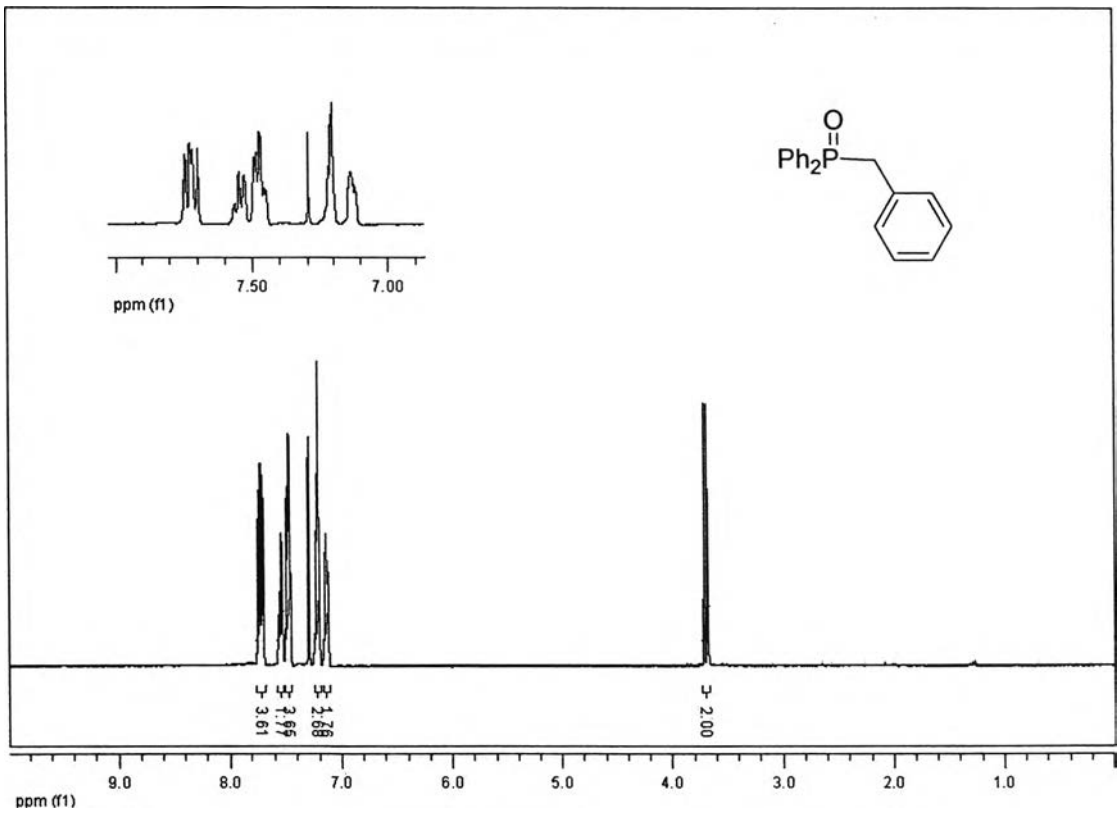


Figure 2.2 The ^{1}H-NMR spectrum of benzyldiphenylphosphine oxide (**1d**)

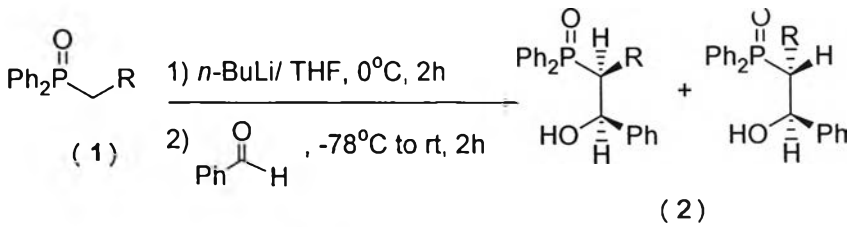
All of synthesized alkyldiphenylphosphine oxides were soluted in $CDCl_3$ and well-characterized their structures by ^{1}H-NMR and IR spectroscopy. The ^{1}H-NMR spectra of two alkyldiphenylphosphine oxides (**1a** and **1d**) as examples are presented in Figures 2.1 and 2.2.

The ^{1}H-NMR spectrum of **1a** (Figure 2.1) revealed two groups of signals commonly assigned as alkyl and aromatic protons. Interestingly, two protons integration of methylene ($\underline{CH_2}PO$) as a doublet of triplet at δ_H 2.32 showed a coupling constant with phosphorus, J = 11.41 Hz. Similarly, two protons at benzylic protons in phosphine oxide **1d** (Figure 2.2) was also coupled with phosphorus atom and showed coupling constant as 13.71 Hz. The aromatic protons on benzene ring of $\underline{Ph}CH_2$ displayed low field signals around δ_H 7.10-7.20. The remaining aromatic protons ($\underline{Ph}_2PO$) having around δ_H 7.40-7.80 exhibited higher complicated signals than $\underline{Ph}CH_2$ protons.

2.2.2 Synthesis of β-hydroxydiphenylphosphine oxides

The resulting oxides in Table 2.2 were next reacted with *n*-BuLi to generate the lithio derivatives of their alkyldiphenylphosphine oxides. The lithio derivatives was then allowed to react with aldehyde to give the mixture of the corresponding β–hydroxyphosphine oxides (**2**).

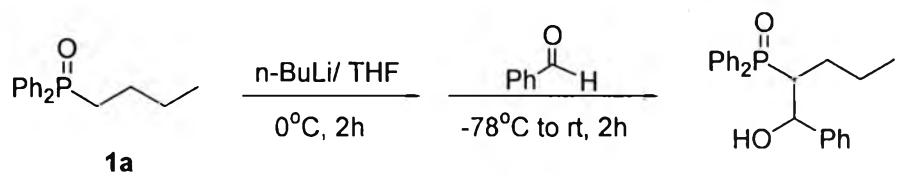
Table 2.3 The synthesis of β-hydroxydiphenylphosphine oxides



Entry	$Ph_2P(O)R$ (**1**)	% Isolated yield (**2**)
1	$CH_3(CH_2)_2CH_2PPh_2$ (**1a**)	78 (**2a**)
2	$CH_3(CH_2)_4CH_2PPh_2$ (**1b**)	92 (**2b**)
3	$CH_3(CH_2)_{10}CH_2PPh_2$ (**1c**)	93 (**2c**)
4	$PhCH_2PPh_2$ (**1d**)	18 (**2d**)

The mixture of *erythro* and *threo* hydroxyphosphine oxides was obtained in high yield such as 2-diphenylphosphinoyl-1-phenylpentan-1-ol (**2a**) attaining in quantitative yield from its butyldiphenylphosphine oxide (entry 1). Oxide (**2a**) was separated by column chromatography to easily screen and find out the optimal condition. After separation, it gave 61% yield of *erythro*-(**2a**) and 17% yield of *threo*-(**2a**). Both hexyl and dodecyl diphenylphosphine oxides were exclusively transformed into predominant *erythro* hydroxyphosphine oxides (**2**), a mixture of 2-diphenylphosphinoyl-1-phenylheptan-1-ol (**2b**, 92%) and 2-diphenyl- phosphinoyl-1-phenyltridecan-1-ol (**2c**, 93%) without separation needed (entries 2-3). However, benzyldiphenylphosphine oxide was obtained only in 18% yield of 2-diphenylphosphinoyl-1,2-diphenylethan-1-ol (**2d**, entry 4). The mixture of adducts, in entry 4, was attained in low yield because of low solubility of benzyldiphenyl-phosphine oxide in THF.

The mixture of *erythro* and *threo* hydroxyphosphine oxides (**2**) were derived in high yield. 2-Diphenylphosphinoyl-1-phenylpentan-1-ol occurred in 78% yield and revealed the ratio of *erythro* and *threo* hydroxyphosphine oxides **2a** in 78:22 which could be characterized by ^{1}H-NMR as shown in Figures 2.3 and 2.4.



1a (1 equiv) (1 equiv) (1 equiv) **2a** (78%) (*erythro*:*threo* = 78:22)

The *erythro* and *threo* hydroxyphosphine oxides (**2a**) were the target molecules from starting material butyldiphenylphosphine oxides condensed with aldehyde. The desired products were determined and identified by ^{1}H-NMR data. The ^{1}H-NMR spectrum of *erythro*-**2a** (Figure 2.3) displayed four signals of two groups of methylene protons near each other in the period of δ_H 0.50-1.90. The methine proton connecting with phosphorus atom exhibited a signal at δ_H 2.47 and another methine proton closed to a hydroxyl group as doublet at δ_H 5.29.

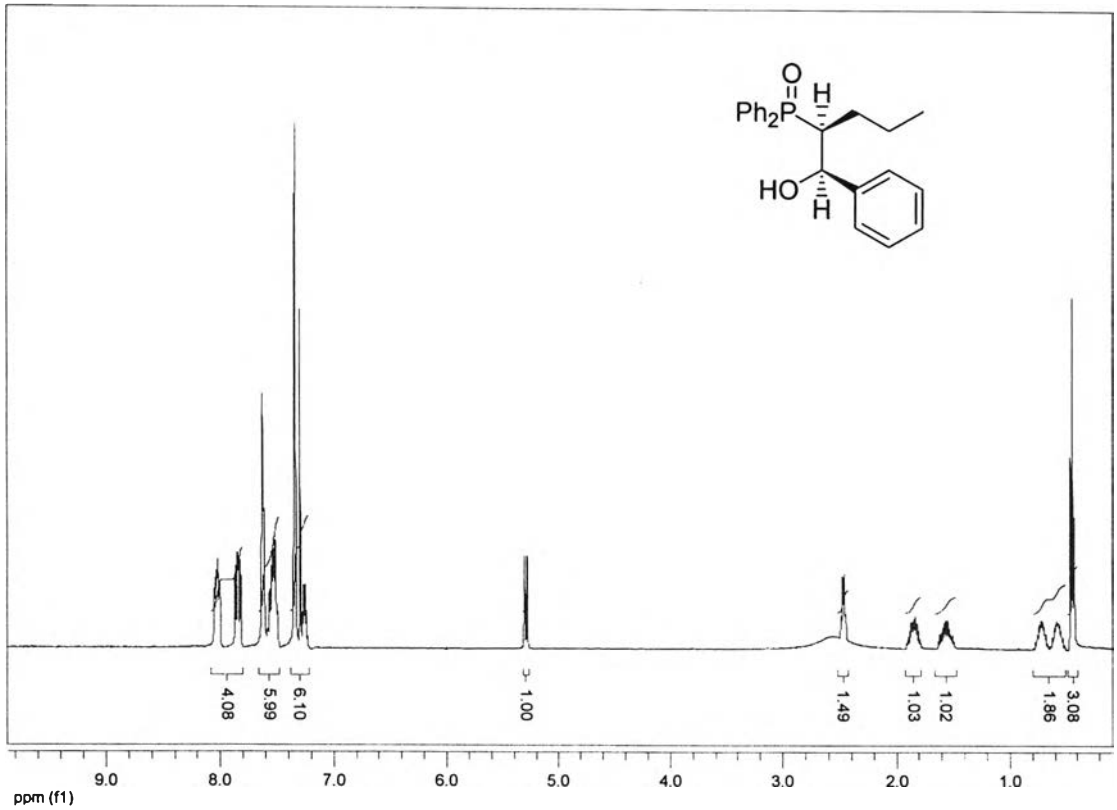


Figure 2.3 The ^{1}H-NMR spectrum of *erythro*-2-diphenylphosphinoyl-1-phenyl-pentan-1-ol (*erythro*-**2a**)

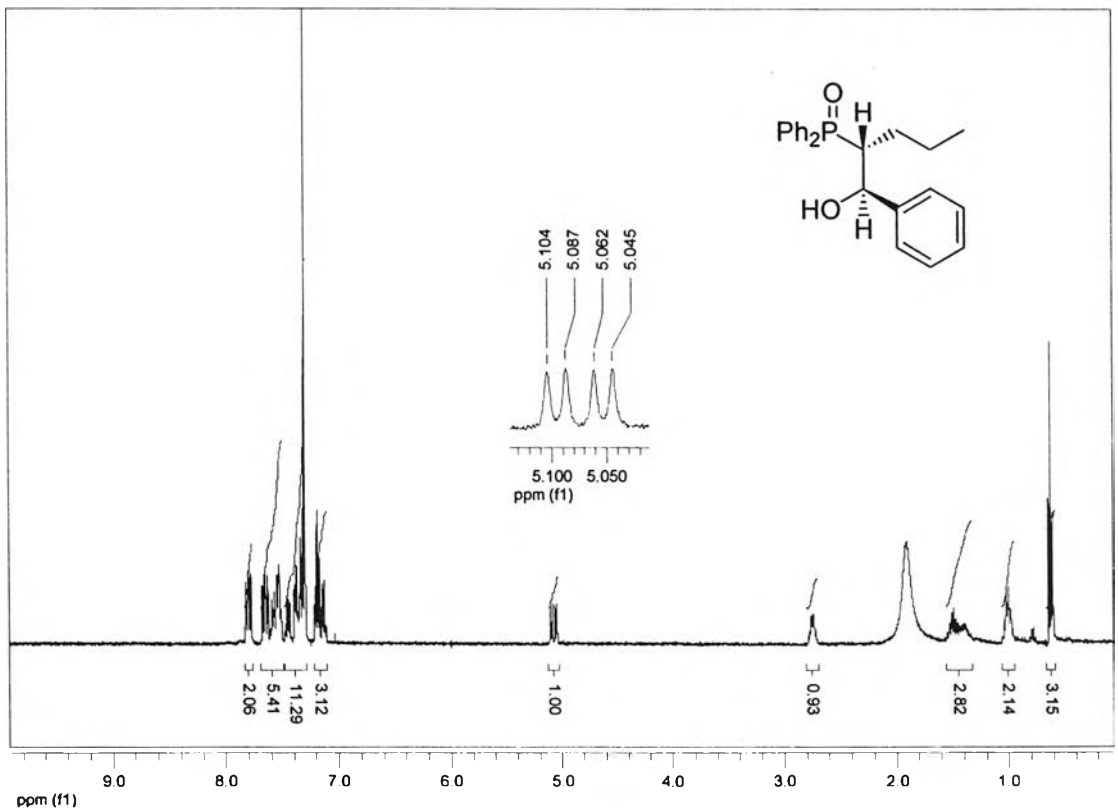
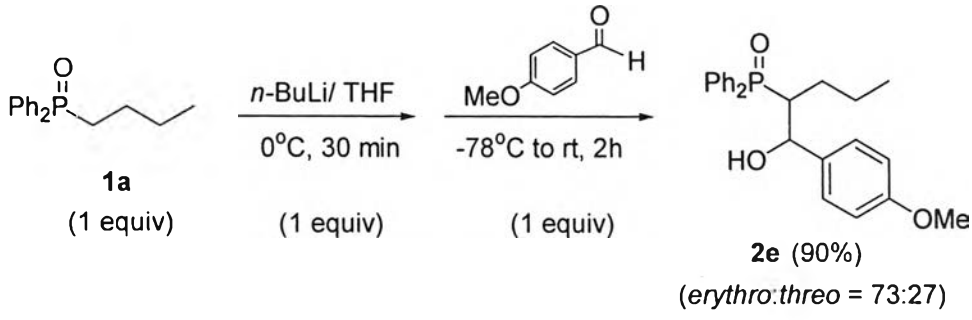


Figure 2.4 The ^{1}H-NMR spectrum of *threo*-2-diphenylphosphinoyl-1-phenylpentan-1-ol (*threo*-**2a**)

The spectrum of *threo*-**2a** (Figure 2.4) also exhibited similar pattern to that of *erythro* spectrum. However, the chemical shift at 2.75 which was ascribed for methine proton next to phosphorus was observed at higher chemical shift than *erythro* proton. While the methine proton closed to a hydroxyl group of *erythro*-**2a** showed doublet at 5.29 ppm (J_{HP} = 9.56 Hz), *threo* methine proton revealed as doublet of doublet at 5.08 (J_{HP} = 17.00 Hz and J_{HH} = 6.80 Hz).

In addition, butyldiphenylphosphine oxide (**1a**) could similarly transform to the corresponding *β*–hydroxyphosphine oxides by reacting with base such as *n*-BuLi to generate the lithio derivatives of its butyldiphenylphosphine oxides. The lithio derivatives then reacted with 4-methoxybenzaldehyde to afford the mixture of the corresponding *β*–hydroxyphosphine oxides, named as 2-diphenylphosphinoyl-1-(4-methoxyphenyl)-pentan-1-ol (**2e**) in 90% yield (*erythro*: *threo* = 73:27).



1a (1 equiv) (1 equiv) (1 equiv)

2e (90%)
(*erythro*:*threo* = 73:27)

The ^{1}H-NMR spectrum of isolated *β*–hydroxyphosphine oxide (**2e**, Figure 2.5) revealed the same proton pattern as that of *erythro* hydroxyphosphine oxide (**2a**). To illustrate this, a methine doublet of CHOH at δ_H 5.20 (J_{HP} = 9.20 Hz) and methine quartet of CHP at δ_H 2.35 (J = 5.74 Hz). Unlike the aromatic protons of *erythro*-**2a**, *p*-methoxy benzene ring of **2e** clearly displayed two doublet signals at δ_H 6.82 and 7.21 which lower than aromatic protons of Ph_2PO group.

The reaction of lithio derivatives of alkyldiphenylphosphine oxides with aldehyde led to the predominantly *erythro* hydroxyphosphine oxides without further purification by column chromatography, as the results *vide supra*. The *β*-hydroxy-diphenylphosphine oxides, especially both **2a** and **2e**, could be continually prepared as the xanthate derivatives and then eliminated to afford pure *Z*- or *E*-alkene.

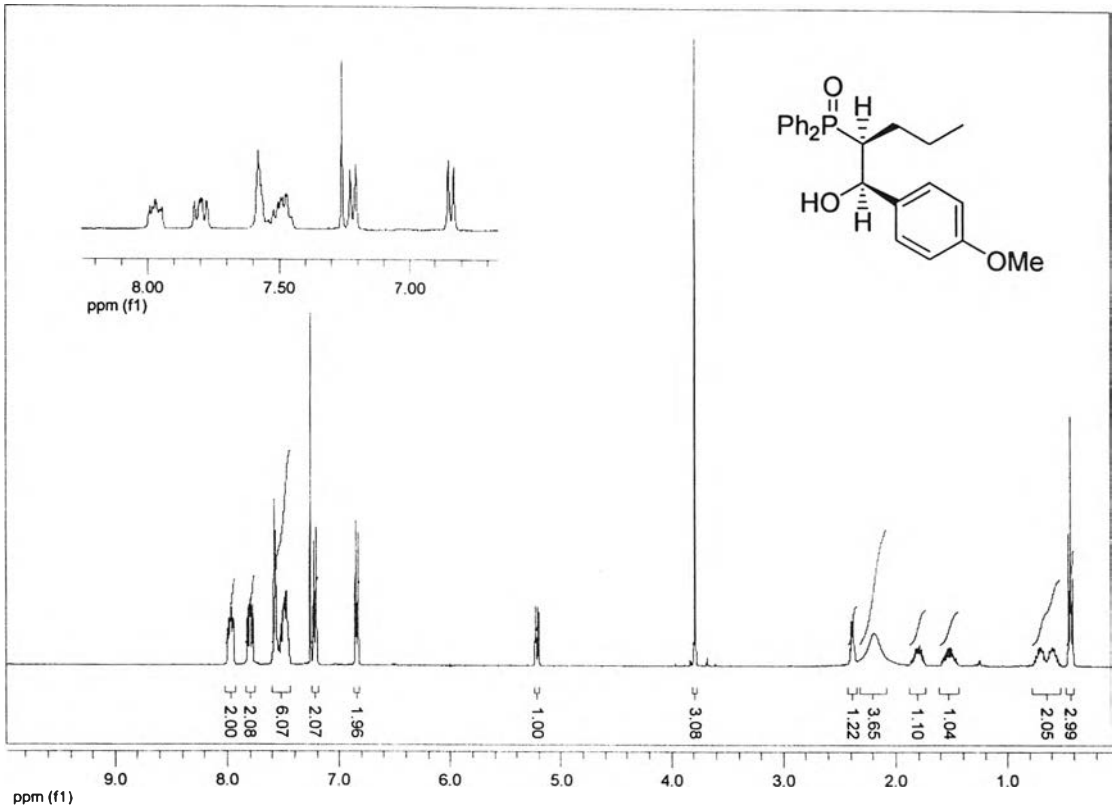
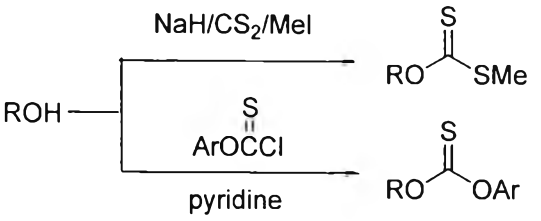


Figure 2.5 The ^{1}H-NMR spectrum of 2-diphenylphosphinoyl-1-(4-methoxyphenyl)-pentan-1-ol (**2e**)

2.2.3 Synthesis of xanthate derivatives

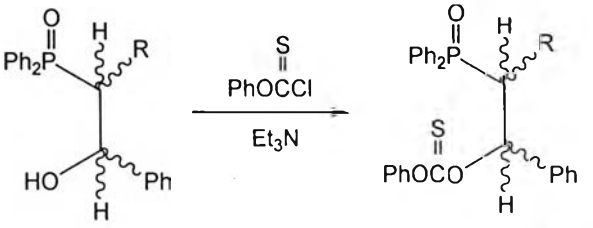
Xanthate derivatives or dithiocarbonates were introduced into synthetic radical chemistry in the early 1970s and were well-known by Barton-McCombie reaction which involved the radical deoxygenation of various alcohols. These reactions utilized the radicophilic nature of thiocarbonates and xanthates. It was found that the formation of alkyl radicals was occurred *via* xanthates as mentioned in the introduction part.

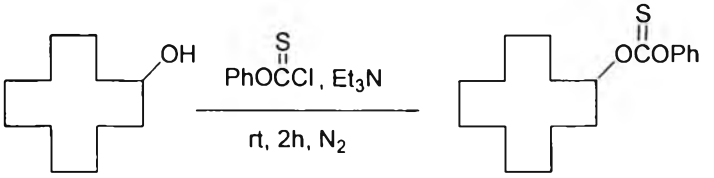
The popular derivatives of alcohols for the radical deoxygenation were dithiocarbonates and aryl thiocarbonates due to the ease of the preparation, mild conditions, and high yields in deoxygenation. Dithiocarbonates could be made by treatment of the alcohol with base (NaH or *n*-BuLi) followed by the addition of carbon disulfide and methyl iodide. Aryl thionocarbonates could be prepared by the reaction of alcohols and aryl chlorothionoformates in the presence of pyridine or 4-dimethylaminopyridine (DMAP) at room temperature.



The Barton-McCombie process possessed good chemoselectivity. However, alcohol which had neighboring substituents such as sulfides, sulfones, thiocarbonates, and dithiocarbonates at the *β*-position produced olefins by the radical *β*–elimination. Therefore, the preparation of alkenes in this research was conducted *via* *O'*-phenyl thiocarbonate or xanthate derivatives and then proceeded using radical reaction under neutral conditions.

Prior to the preparation of xanthate derivatives of *β*–hydroxyphosphine oxides, the reaction of *β*–hydroxyphosphine oxides (**2**) with phenyl chlorothionoformate in the presence of triethylamine was first tried to synthesize *O*-alkyl *O'*-phenylthiocarbonate (**2-2a**). Unfortunately, the reaction was not successful; all starting material (**2**) remained. This was probably because the basicity of base was not enough. However, cyclododecanol could be converted to *O*-cyclododecyl *O'*-phenyl thiocarbonate (**2-2b**) in 67% yield without any problem as previously reported [78].



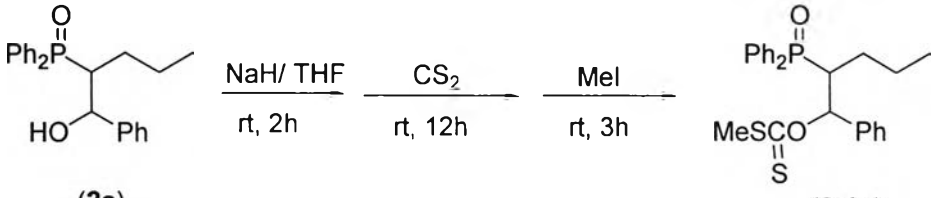


(**2-2b**, 67%)

Accordingly, xanthate derivatives or dithiocarbonates played a crucial role in this applied synthetic method. Moreover, the *S*-methyl dithiocarbonate or xanthates of **2a** could be easily generated by using alcohol derivatives treating with NaH, CS_2, and lastly MeI. That was the reason why, the conversion of *β*–hydroxylphosphine oxide

(**2a**) to xanthate derivative (**2-1a**) was newly generated and used as starting material in the radical olefination. However, it was found that the application of xanthates with *β*–hydroxylphosphine oxides has not been reported in any reviews. The study on the optimal conditions in order to fulfill an aspiration of forming alkyl radicals *via* xanthates and then elimination to generate the corresponding olefins is appeared in Table 2.4.

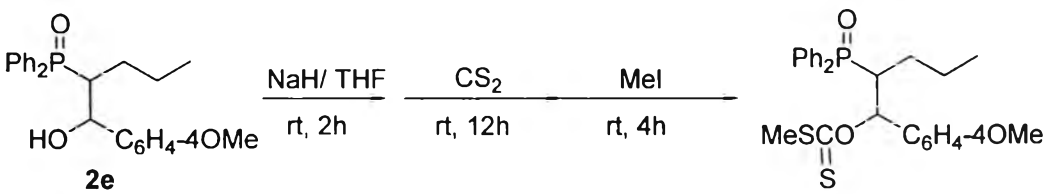
Table 2.4 The optimized condition for the synthesis of xanthate derivatives of *β*–hydroxylphosphine oxides



(**2a**) (**2-1a**)

Entry	Ratio of reagents (equiv)			Time (h)	Yield
	NaH	CS_2	MeI	(in the last step)	(%)
1	1.5	3	3	3	5
2	1.5	5	5	3	18
3	3	5	5	3	62
4	3	5	5	4	73

The best result was achieved in entry 4. The reaction of an equivalent of *β*–hydroxylphosphine oxides (**2a**) with NaH (3 equiv), CS_2 (5 equiv), and MeI (5 equiv) afforded *O*-[2-diphenylphosphinoyl-1-(4-methoxyphenyl)-pentan-1-yl]-*S*-methyl dithiocarbonate (**2-1a**) in 62% and 73% yield, at 3 and 4 h, respectively. Under these optimal conditions for 4 h, *β*–hydroxylphosphine oxides (**2e**), prepared from *p*-methoxybenzaldehyde could be converted into xanthate derivative of *β*–hydroxylphosphine oxide (**2-1e**) in highly satisfactory yield (87%).



2e (1 equiv) (3 equiv) (5 equiv) (5 equiv) (**2-1e**, 87%)

Xanthate derivatives of *β*–hydroxylphosphine oxides (**2-1a** and **2-1e**) were also confirmed their identity by ^{1}H-NMR spectroscopic technique. Their spectra are presented in Figures 2.6 and 2.7. The significant assignment for xanthate **2-1a** was slightly different from its *β*–hydroxylphosphine oxide **2a** (Figure 2.6). The distinctly different peak was methine proton connecting to oxygen of hydroxyl group as doublet at δ_H 5.20, while the methine proton jointed with *S*-methyldithiocabonate revealed a doublet of doublet at δ_H 6.75. Unlike the spectrum of **2a**, the second one displayed a increased singlet peak of methyl group (SCH_3) at δ_H 2.48. In the case of xanthate **2-1e** (Figure 2.7), the ^{1}H-NMR looked like its starting material **2e** whereas the unique methyl peak (SCH_3) as a singlet peak at δ_H 2.30 increased and the methine proton (CHP) shifted up to δ_H 2.85. The methine proton connecting with phosphorus atom exhibited a multiplet signal at δ_H 2.85 ppm (J_{HP} = 10.74 Hz and J_{HH} = 5.21 Hz), while another methine proton closed to xanthate group showed nearly the same position at δ_H 5.12.

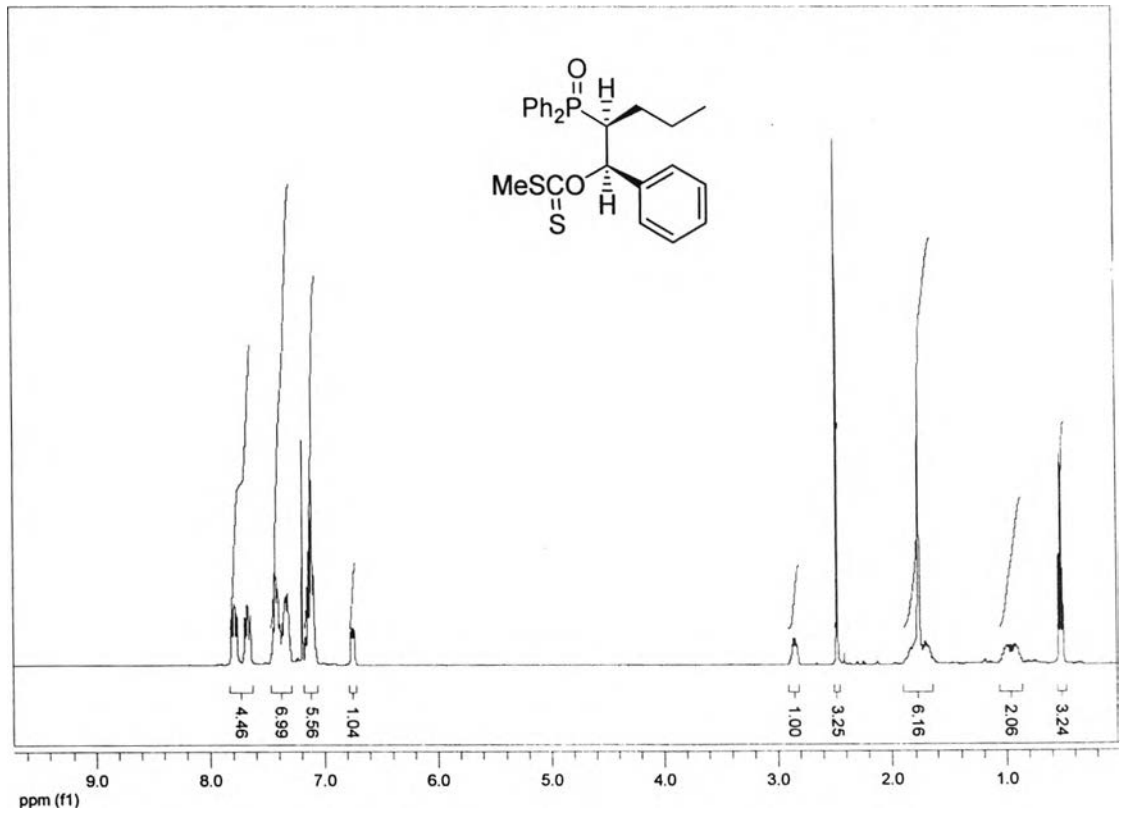


Figure 2.6 ^{1}H-NMR of xanthate derivative of 2-diphenylphosphinoyl-1-phenylpentan-1-ol (**2-1a**)

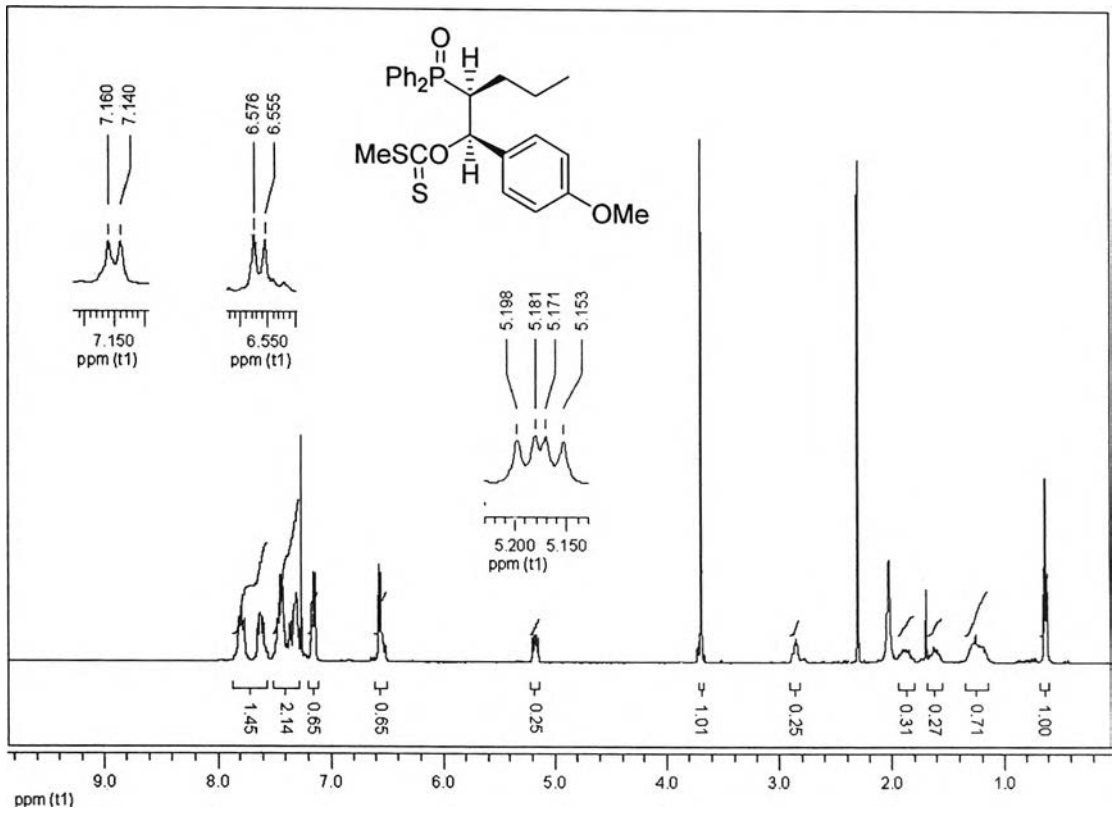
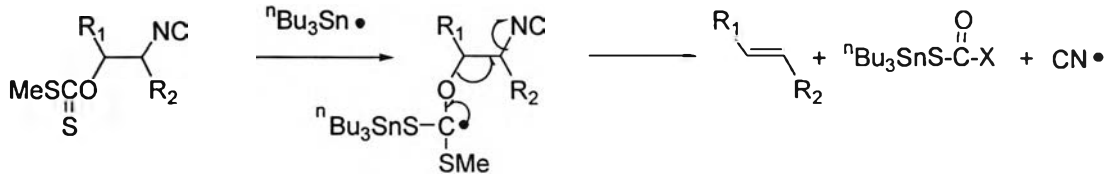


Figure 2.7 ^{1}H-NMR of xanthate derivative of 2-diphenylphosphinoyl-1-(4-methoxy-phenyl)-pentan-1-ol (**2-1e**)

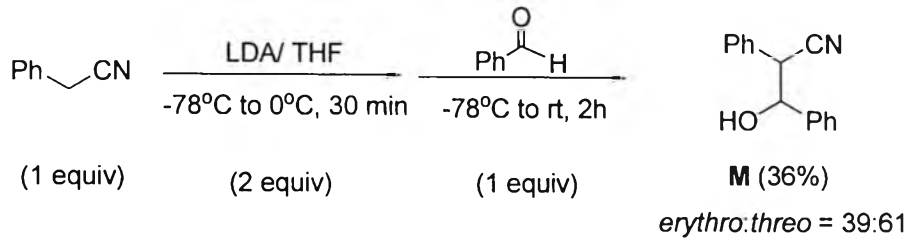
Synthesis of xanthate derivatives of *β*–hydroxylnitriles

From the previous reports, it was found that a vicinal isocyanodithiocarbonate could undergo *β*-elimination and deamination to give olefins. This was analogous to the formation of olefins from *bis*-dithiocarbonates. The lack of *β*-elimination in the reaction of 1,2-diisocyanides implied that the initial attack of the tributyltin radical was on the isonitriles group in the reaction of *vic*-isocyanodithiocarbonates.

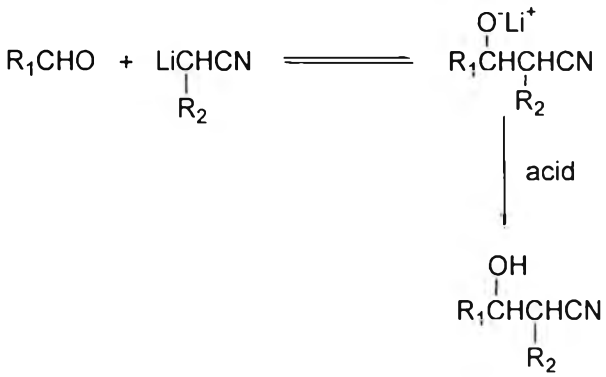


According to the literature reviews, it was found that there was no report concerning the radical elimination of *vic*-cyanodithiocarbonates. For this reason, the idea for newly preparation of olefins from *β*-elimination of *vic*-cyanodithiocarbonates was attempted in this research. Thus, *β*-hydroxynitriles were first prepared by the

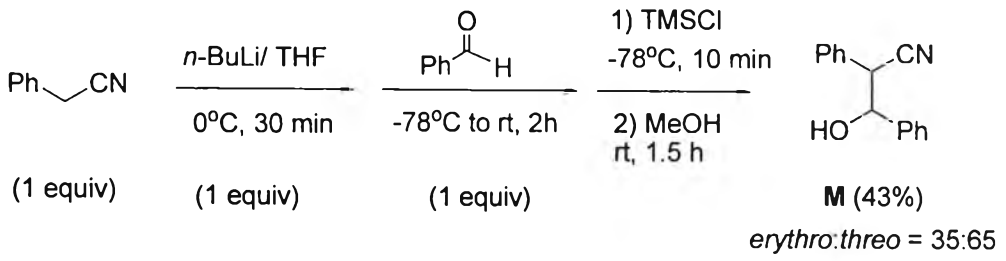
condensation of carbonyl compounds with alkali acetonitriles, prepared by α–deprotonation of suitable nitriles with LDA or *n*-BuLi. Starting with benzyl cyanide reacted with freshly prepared LDA at -78 °C, and then added benzaldehyde to generate β–hydroxylnitriles (**M**) in 36% yield (*erythro*: *threo* = 39:61).



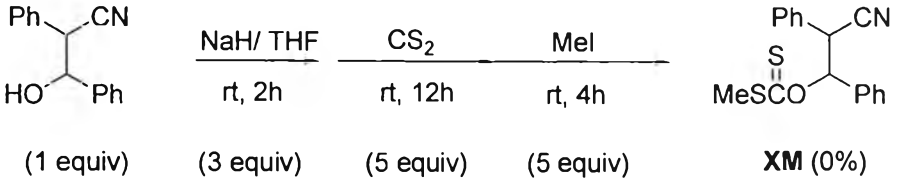
The first reaction using LDA as base did not give a satisfactory yield of product (**M**) since the reactions were reversible and the structures of both the carbonyl compounds and the α–alkali nitriles having significant influences over the position of the equilibrium. Generally, in the cases of hindered carbonyl compounds or hindered α–alkali nitriles, the yield were low.



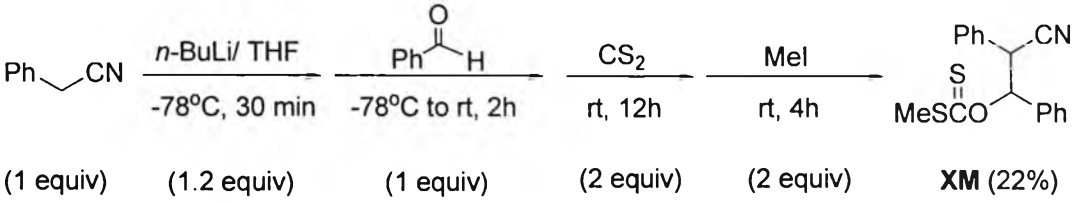
Therefore, the treatment of benzyl cyanide with *n*- BuLi in stead of LDA, as method B was conducted [79-80]. After addition of benzaldehyde, then TMSCl and MeOH were added into the reaction generated the mixture of β–hydroxylnitriles (**M**) in 43% yield (*erythro*: *threo* = 35:65). It was well known that chlorotrimethylsilane acted as a scavenger of alkoxide ions to form trimethylsilyl (TMS) ethers. The addition of chlorotrimethylsilane to the reaction mixture of lithioacetonitriles and aldehydes would trap the alkoxide intermediate and prevent reversal of the addition reaction, followed by mild hydrolysis of the TMS ether with MeOH, obtained higher yield of the desired products.



S-Methyl dithiocarbonate or xanthate derivatives of *β*–hydroxylnitriles (**M**) was prepared by using the same optimal conditions for *β*–hydroxylphosphine oxides (**2**), treated with NaH (3 equiv), CS_2 (5 equiv), and MeI (5 equiv). This was nevertheless not suitable conditions for affording xanthate derivatives **XM** (0% yield).

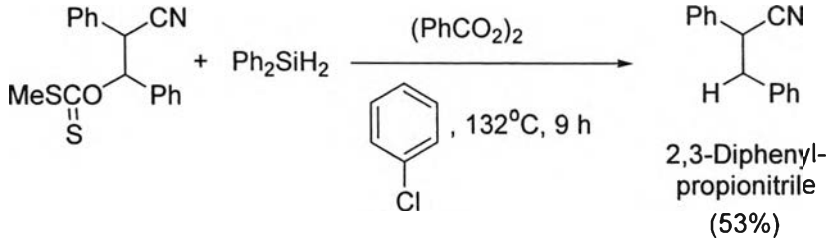


For this first unsuccess, the preparation of xanthate derivatives **XM** was subsequently repeated using the above two-step conditions in one-pot process. Therefore, benzyl cyanide was first reacted with *n*-BuLi and benzaldehyde to generate *β*–hydroxylnitriles. After 2 h, CS_2 was then added into further stirred-overnight reaction and MeI was added and stirred for 4 h to obtain xanthate derivatives (**XM**) in 22% yield.



The preparation of olefins *via* xanthate derivatives would be presented and discussed in radical olefination topic. However, radical olefinations *via O-[2-cyano-1,2-diphenylethan-1-yl]-S-methyl dithiocarbonates* (**XM**) treated with Ph_2SiH_2 using Et_3B or benzoyl peroxide as initiators in non-polar solvents, benzene (at 80°C) or chlorobenzene (at 132°C), did not form the corresponding olefins. The proposed olefin product, as *trans*-stilbene having *m/e* 223 (M^+) in MS spectrum, could not occur under these conditions. From the spectroscopic data, the major product might be

deoxygenation product as 2,3-diphenyl-propionitrile in 53% yield, *m/e* 207 (M^+). That was a reason why, in the last step for olefination from xanthate **XM** was not including in the last topic and did not further study to improve the yield of its olefin. Moreover, another significant reason that we did not try to find out the optimal conditions since the preparation of xanthate **XM** was quite difficult and its yield was not satisfactory to develope its condition.

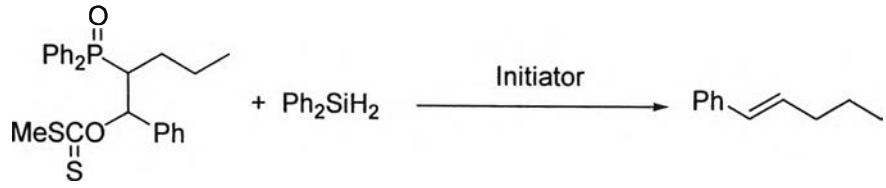


2.2.4 Radical olefination

Synthesis of alkenes from xanthate derivatives (2-1a and 2-1e)

To find out the optimized conditions to synthesize olefin in good yield with high stereoselectivity, the variation of reagent: initiators (AIBN, benzoyl peroxide, *etc.*) and chain carriers such as diphenylsilane (Ph_2SiH_2) was carried out. All dithiocarbonates used as starting materials were soluted in various solvents in this study (Tables 2.5 and 2.6).

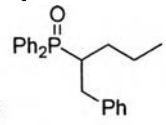
Table 2.5 Radical olefination of xanthate derivatives (**2-1a**)

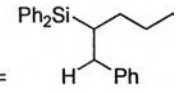


2-1a (0.2 mmol)

Entry	Ph_2SiH_2 (equiv)	Initiator (equiv)	Conditions			Olefin (%)[a]	Remarks[b]
			Solvent	Temp. (°C)	Time (h)		
1	3.3	AIBN (3)	toluene	reflux	17	-	**2-1a** (28%), A(30%)
2	2.2	Benzoyl peroxide (1)	mesitylene	reflux	4	-	**2-1a** (50%), A(20%)
3	5	Lauroyl peroxide (1)	chloro-benzene	reflux	8	2	**2-1a** (34%), A(10%), by-pdts. from lauroyl peroxide
4	0	Lauroyl peroxide (1)	chloro-benzene	reflux	24	-	**2-1a** (34%), by-pdts. from lauroyl peroxide
5	1	Lauroyl peroxide (1.5)	chloro-benzene	reflux	24	trace	**2-1a** (40%), A, by-pdts. from lauroyl peroxide
6	1[c]	Lauroyl peroxide (1)	chloro-benzene	reflux	24	trace	**2-1a** (remaining but uncollecting)
7	2	*t*-butyl peroxide (1)	benzene	reflux	72	trace	**2-1a**, A, B (GC-MS data)
8	2	Et_3B (10), O_2	benzene	80	25	trace	**2-1a** (remaining but uncollecting), $Ph_2SiHP(O)Ph_2$, MeSC(O)SEt
9	1[d]	Et_3B (5), O_2	benzene	80	16	3.5	**2-1a** (remaining but uncollecting), $Ph_2SiHP(O)Ph_2$, MeSC(O)SEt
10	1	Et_3B (5), O_2	benzene	80	22	8	**2-1a** + A (86%), MeSC(O)SEt
11	0	Et_3B (5), O_2	benzene	80	24	2.9	**2-1a** (remaining but uncollecting), $Ph_2P(O)OC(S)SM$, MeSC(O)SEt

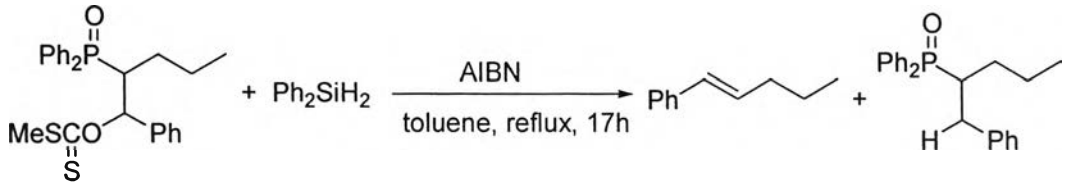
[a]determined by ^{1}H-NMR (100MHz) analysis comparing with 4-nitrobenzaldehyde
[c]slow addition of Ph_2SiH_2/peroxide/chlorobenzene through syringe pump

[d]used $PhSiH_3$ [b] **A** = 

B = 

When AIBN, benzoyl peroxide, or Et_3B was used as radical initiators in refluxing non-polar solvents. It was found that its low boiling point made it easy to work-up the reaction mixture. Using Ph_2SiH_2 after the completion of the radical reaction, it was much easier to isolate the product. In addition less toxic substrate of Ph_2SiH_2 than tributyltin hydride was realized. The strength of silicon-hydrogen bond of Ph_2SiH_2 was weak enough to break homolytically which had bond dissociation energy (BDE) about 85 kcal mol^{-1} compared with BDE of tributyltin hydride 74 kcal mol^{-1} [73]. Although the bond dissociation energy of the silicon-hydrogen bond (Si-H) in Ph_2SiH_2 was relatively stronger than the bond dissociation energy of the tin-hydrogen bond (Sn-H) in tributyltin hydride and the reaction of Ph_2SiH_2 with *tert*-butoxy radical (rate constant, $k = 1.3 \times 10^7\ M^{-1}s^{-1}$) was slower than that of tributyltin hydride ($k = 2.2 \times 10^8\ M^{-1}s^{-1}$), Ph_2SiH_2 was also worked as well as tributyltin hydride in radical reaction.

For the plan to generate the radical elimination adducts using the similar conditions of deoxygenation with AIBN and Ph_2SiH_2. Various reaction conditions of *S*-methyl dithiocarbonate (**2-1a**) with Ph_2SiH_2 in the presence of many kinds of initiators in non-polar solvents were studied. First, the reaction of the dithiocarbonate **2-1a** with Ph_2SiH_2 in refluxing toluene, at 110°C, in the presence of AIBN as initiator gave none of the alkene product (Table 2.5, entry 1). The major product which was found in these conditions was 2-diphenylphosphinoyl-1-phenylpentane as the product from radical deoxygenation.

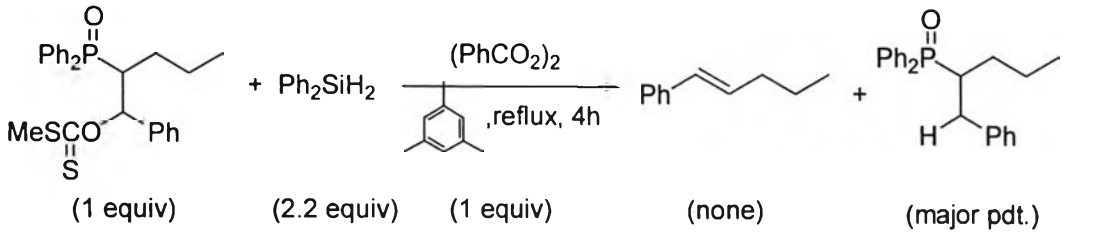


(1 equiv) (3.3 equiv) (3 equiv) (none) (major pdt.)

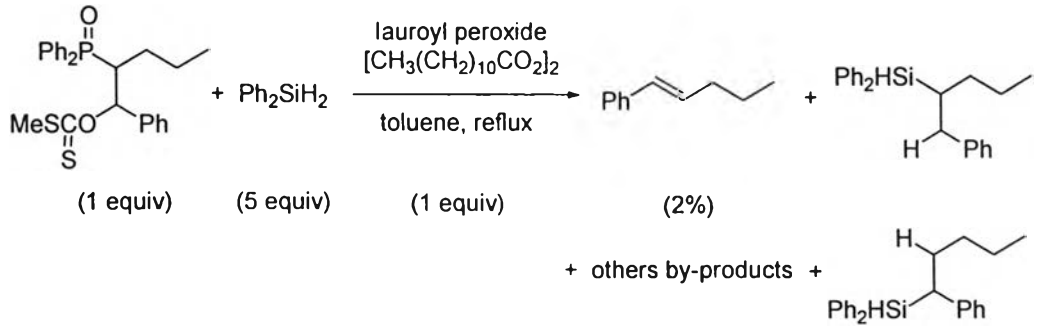
"radical deoxygenation"

Second, the reaction of the *S*-methyl dithiocarbonate (**2-1a**) with Ph_2SiH_2 was changed to use benzoyl peroxide in stead of AIBN as initiator and increased temperature to 162°C by soluted in mesitylene. The result was still the same as the first one which gave none of the alkene product. The major product was also radical deoxygenation product (entry 2). Although the reaction temperature was much increased, it was not much for cleavage of carbon-phosphorus bond. In parallel with

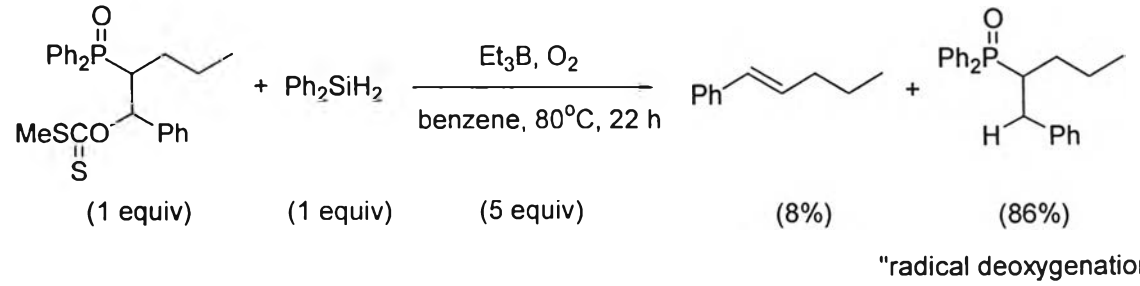
benzoyl peroxide, using *tert*-butyl peroxide in benzene at 80°C could generate only trace amount of alkene and (1-benzyl-butyl)-diphenylsilane (**B**) was also detected from GC-MS data (entry 7).



Third, lauroyl peroxide was applied to use as a new initiator for the reaction of dithiocarbonate **2-1a** with Ph_2SiH_2 (entries 3-6). Like the results of the above conditions, the best result using lauroyl peroxide gave olefin only 2% yield in spite of variation of various ratios of lauroyl peroxide.

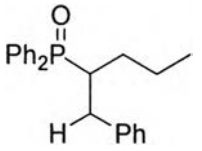


The last one for optimal condition of this radical olefination was used Et_3B as one of trial initiators (entries 8-11). It was found that the best result of Table 2.5 was entry 10, which used 1 equiv of Ph_2SiH_2, 5 equiv of Et_3B and oxygen in benzene at 80°C, gave the olefin 8% yield.



As the results, the elimination products (olefins) were not occurred while the major products from this radical reaction condition were deoxygenation products. The

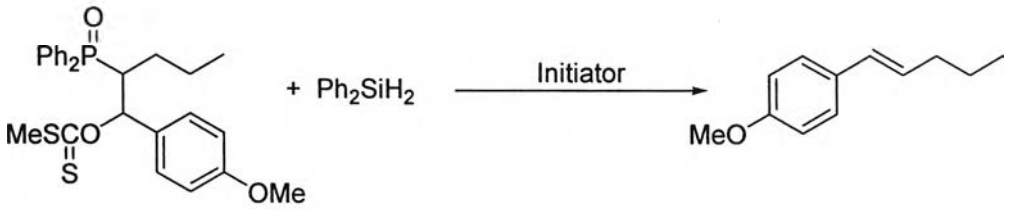
strength of C-P bond (DBE = 513.4 kJ mol^{-1}) was much higher than C-O bond (DBE = 355-380 kJ mol^{-1}) [81]. It was implied that the strength of C-P bond was too much and then resulted in the difficulty of homolytic cleavage of C-P bond in its molecule. Therefore, these radical conditions could be efficiency to develop for preparation new deoxygenation products, such as 2-diphenylphosphinoyl-1-phenylpentane, having embodied phosphorus molecules.



"radical deoxygenation product"

As the results in Table 2.5, it was found that Et_3B was more efficient radical initiator in this reaction than AIBN and other peroxides. Therefore, the next reaction of *S*-methyl dithiocarbonate **2-1e** with Ph_2SiH_2 in the presence of Et_3B was performed.

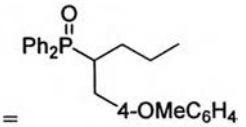
Table 2.6 Radical olefination of xanthate derivatives (**2-1e**)



2-1e (0.2 mmol)

Entry	Ph_2SiH_2 (equiv)	Initiator (equiv)	Conditions			Olefin (%)[a]	Remarks[b]
			Solvent	Temp. (°C)	Time (h)		
1	1	Et_3B (5), O_2	benzene	80	24	16	**2-1e** (56%), A (7%)
2	1	Et_3B (2)[c], O_2	toluene	100	72	11	**2-1e** (34%), A (12%)

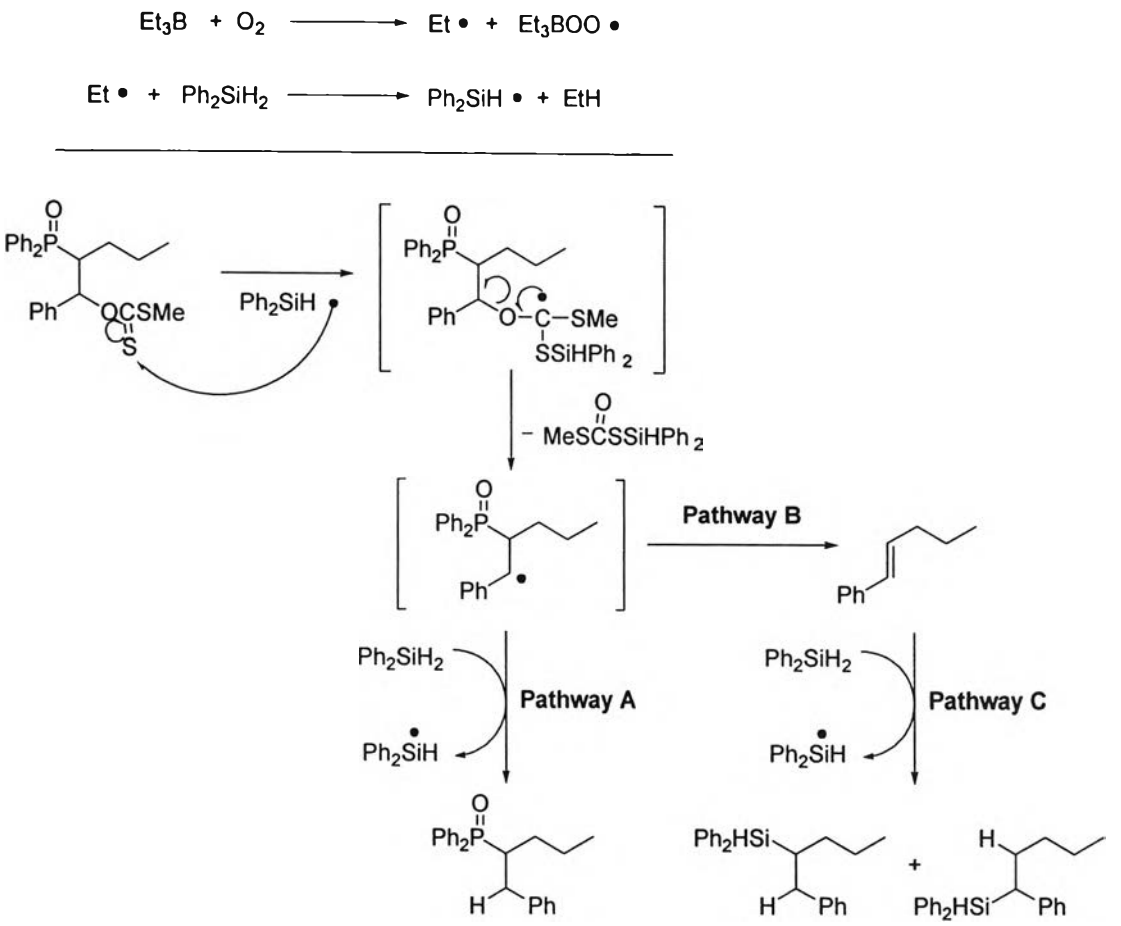
[a]determined by ^{1}H-NMR (100MHz) analysis comparing with 4-nitrobenzaldehyde

[b] **A** = 

[c]adding 2 eq./ 3 h. (total 12 times)

Under these reaction conditions using an equivalent of Ph_2SiH_2 in the presence of Et_3B (2 or 5 equiv) in benzene or toluene could generate olefin product only 11 and 16% yields from *S*-methyl dithiocarbonate **2-1e** (Table 2.6, entries 1-2). Most of starting material was also remained in the reaction mixture and a small amount of deoxygenation product (**A**) was occurred. From all results, the best condition for this radical olefination could be prepared the maximum of olefin only 15% yield. It was implied that these reaction conditions were not sufficient for the homolytic cleavage of C-P bond and then resulted in the absence of olefin products. Furthermore, these developed conditions were more suitable for radical deoxygenation than radical olefination.

The pathway for the radical elimination of xanthates of *β*–hydroxylphosphine oxides and *vic*-phosphinoyldithiocarbonates to olefin was presented in Scheme 2.2. The silicon radical attacked the thiocarbonyl sulfur instead of sulfide sulfur in the *S*-methyl xanthates. The reaction pathway could be occurred *via* pathways A, B or C. Pathway A was radical deoxygenation process. Pathway B was radical elimination process through *β*-scission. And pathway C was radical addition process. Interestingly, from the results, pathway C was minor reaction pathway because the reactivity of olefin product was low. Consequently, major reaction pathway should be pathway A while *β*-scission of Pathway B was not easy to occur since the C-P bond strength was too strong and resulted in unsuccessful homolytic cleavage.



Scheme 2.2 Mechanistic pathway for the occurrence of olefin and deoxygenation product

2.3 Conclusion

The modified one-pot Horner-Wittig reaction *via* the *S*-methyl dithiocarbonate or xanthates of *β*–hydroxylphosphine oxides was first investigated. The xanthates of *β*–hydroxyphosphine oxides could be easily generated by using alcohol derivatives treating with NaH, CS_2, and lastly MeI, and then eliminated to generate olefin. As the results, diphenylsilane turned out to be useful hydrogen sources in radical chemistry, however, this silane could not be efficiently used for the transformation of xanthates of *β*–hydroxyphosphine oxides and *vic*-cyanodithiocarbonates to olefin due to the strength of C-P bond. Although from the results in this research to prepare alkene *via* this introducing reaction process was not successfully, these xanthates that embodied phosphorus reagents with inherent asymmetry should offer a fertile area for future research both of deoxygenation and other related fields.

2.4 Experiment

2.4.1 Instruments and equipments

Melting points (m.p.) was measured on a Fisher-Johns melting point apparatus or Electrothermal digital melting point apparatus model IA9100 and are uncorrected. The optical rotations were measured at the ambient temperature with a Jasco P-1010 Polarimeter.

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). Gas chromatography analysis was carried out on Shimadzu gas chromatograph GC-14A instrument equipped with flame ionization detector (FID) using nitrogen as a carrier gas, the column used for chromatography was a capillary column type HP-5 (30m x 250mm) from Hewlett Packard company.

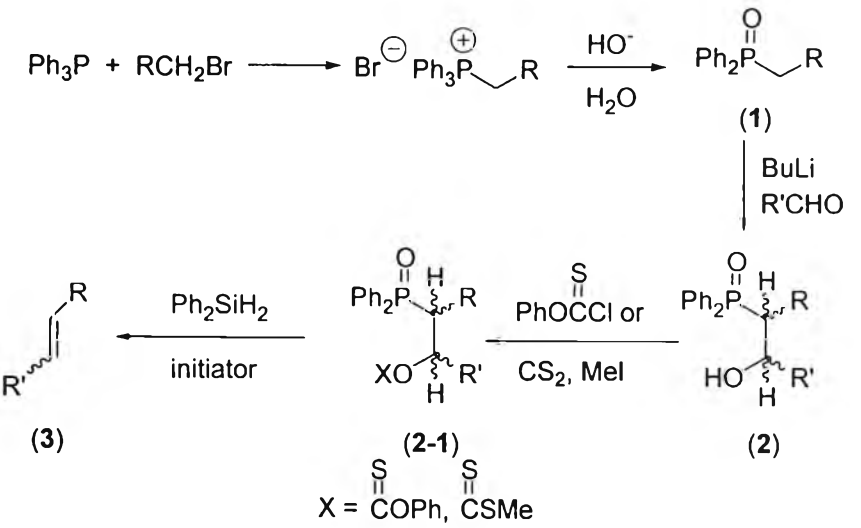
Spectrometers: Fouirer transform-infrared spectra (FT-IR) were performed on Nicolet Impact 410 FT-IR spectrometer. Solid samples were incorporated to potassium bromide (KBr) to form pellet. As a liquid sample, a drop of the liquid was squeezed between flat plates of sodium chloride cells. The ^{1}H and ^{13}C-NMR spectra were obtained in deuterated chloroform ($CDCl_3$) or dimethylsulfoxide (DMSO-d_6), with Fourier transform nuclear magnetic resonance spectrometer of Varian model Mercury+400 spectrometer which was operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei.

2.4.2 Chemicals

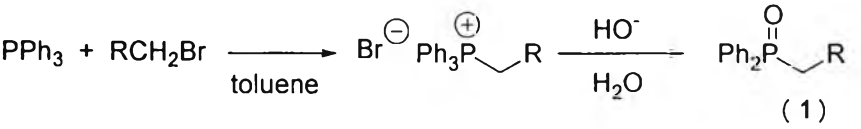
All solvents used in this research were purified, excepted for those which were reagent grades, and dried prior to use by standard methodology. The substrates and reagents employed for synthesizing the precursors and products used in this work were purchased from Fluka, Aldrich Chemical Company or otherwise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

2.4.3 General procedure

Synthesis of alkene *via O'*-phenyl thiocarbonate or xanthate derivatives



Preparation of alkyldiphenylphosphine oxide *via* phosphonium salts

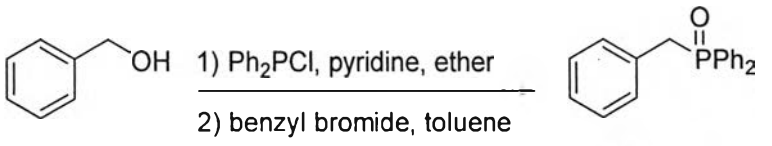


PPh_3 (2.6 g, 0.01 mol) was heated under reflux with an excess of alkyl halide (0.04 mol). The precipitated phosphonium salt was filtered off, washed well with ether, and then heated with 30% w/w aq NaOH (*cc*. 4 mL/g) until all the benzene had distilled out. The mixture was cooled and extracted with CH_2Cl_2, and the extract were dried ($MgSO_4$) and evaporated to dryness. In this way the following alkyldiphenylphosphine oxides (**1**) were prepared.

Butyldiphenylphosphine oxide (**1a**; R = $(CH_2)_2CH_3$). 1-Bromobutane (5.48 g, 40 mmol) and PPh_3 (2.62 g, 10 mmol) gave the phosphonium salt as white needles 5.35 g (69%), m.p. 91-93°C (lit. [46], m.p. 93-94°C) (hexane/EtOAc), R_f 0.35 (EtOAc); IR (KBr): 3054, 2957, 2930, 2867, 1443, 1342, 1174, 1116, 972, 750 and 691 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.92 (3H, t, J = 7.32 Hz, CH_3), 1.45 (2H, s, J = 7.39 Hz, $C\underline{H}_2CH_3$), 1.64 (2H, p, J = 8.44 Hz, $C\underline{H}_2CH_2CH_3$), 2.32 (2H, dt, J = 11.41, 5.12 Hz, $C\underline{H}_2PO$), 7.47-7.58 (6H, m, $\underline{Ph}_2PO$) and 7.74-7.80 (4H, m, $\underline{Ph}_2PO$).

Hexyldiphenylphosphine oxide (**1b**; R = $(CH_2)_4CH_3$). 1-Bromohexane (6.60 g, 40 mmol) and PPh_3 (2.62 g, 10 mmol) gave the phosphonium salt as white needles 2.29 g (80%), m.p. 48-50°C (hexane/EtOAc), R_f 0.38 (EtOAc); IR (KBr): 3054, 2926, 2860, 1634, 1583, 1443, 1400, 1307, 1190, 1116, 999, 789 and 743 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.86 (3H, t, J = 6.82 Hz, CH_3), 1.26-1.28 (4H, m, $CH_2CH_2CH_3$), 1.38-1.45 (2H, m, $CH_2CH_2CH_2CH_3$), 1.59-1.69 (2H, s, J = 8.10 Hz, CH_2CH_2PO), 2.37-2.35 (2H, td, J = 11.30, 5.24 Hz, CH_2PO), 7.48-7.57 (6H, m, Ph_2PO) and 7.73-7.78 (4H, m, Ph_2PO).

Dodecyldiphenylphosphine oxide (**1c**; R = $(CH_2)_{10}CH_3$). 1-Bromododecane (6.10 g, 25 mmol) and PPh_3 (2.62 g, 10 mmol) gave the phosphonium salt as white solid 6.07 g (82%), m.p. 59-61°C (hexane/EtOAc), R_f 0.47 (EtOAc); IR (KBr): 3054, 2922, 2844, 1595, 1470, 1435, 1183, 1120, 1073, 789, 719 and 656 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J = 6.83 Hz, CH_3), 1.24-1.36 (16H, m, $(CH_2)_8CH_3$), 1.38-1.45 (2H, m, $CH_2CH_2CH_2PO$), 1.59-1.69 (2H, m, CH_2CH_2PO), 2.31 (2H, td, J = 11.28, 5.25 Hz, CH_2PO), 7.49-7.55 (6H, m, Ph_2PO) and 7.74-7.79 (4H, m, Ph_2PO).

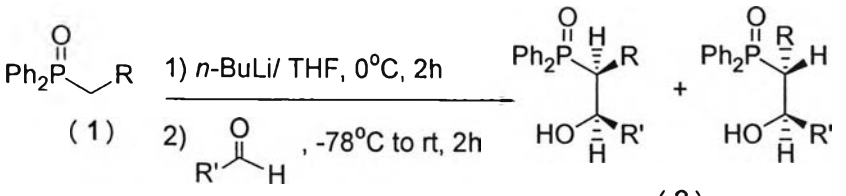


(1d)

Benzyldiphenylphosphine oxide (**1d**). Chlorodiphenylphosphine (5.49 g, 24.9 mmol) in dry ether (30 mL) was added dropwise to benzyl alcohol (2.70 g, 24.9 mmol), dry pyridine (2.0 mL) and dry ether (45 mL) at -78°C. The mixture was stirred at -78°C for 1.5 h and then for 45 min at 25°C before the pyridinium hydrochloride was filtered off and the filtrate was evaporated to dryness. The residual colourless oil was dissolved in dry toluene (75 mL) containing a small crystal of iodine or a drop of benzyl bromide and heated under reflux for 24 h. The mixture was, cooled, filtered, and the product washed with a little dry toluene followed by plenty of dry ether after recrystallized to give the phosphine oxide as white needles 3.79 g (52%), m.p. 190-192°C (lit. [46], m.p. 192-193 °C) (EtOAc/EtOH), R_f 0.50 (EtOAc); IR (KBr): 3054, 2934, 2848, 1645, 1595, 1498, 1431, 1241, 1178, 1116, 1066, 855, 770 and 692 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 3.70 (2H, d, J = 13.71 Hz, CH_2PO), 7.05-7.08 (3H, m,

$CH_2\underline{Ph}$), 7.09-7.22 (2H, m, $CH_2\underline{Ph}$), 7.42-7.50 (4H, m, $\underline{Ph}_2PO$), 7.53-7.58 (2H, m, $\underline{Ph}_2PO$) and 7.68-7.75 (4H, m, $\underline{Ph}_2PO$).

Synthesis of *β*-Hydroxydiphenylphosphine Oxide



n-BuLi (2.3 mL, 1.6 M in hexane) was added from a syringe to a stirred solution of the phosphine oxide (**1**, 3.42 mmol) in dry THF (30 mL) at 0°C. After 30 min the red reaction solution was cooled to -78°C (acetone-solid CO_2) and neat aldehyde (3.42 mmol) was added dropwise at such a rate that the solution temperature was maintained at -78°C. The pale yellow solution was allowed to warm to room temperature over 2 h and then water was added. The THF was removed under reduced pressure and brine added to the aqueous residue before extraction with dichloromethane (3x). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness to give following *β*-hydroxydiphenylphosphine oxides were prepared.

2-Diphenylphosphinoyl-1-phenylpentan-1-ol (**2a**; R = $(CH_2)_2CH_3$ and R′ = Ph). Butyldiphenylphosphine oxide (**1a**; R = $(CH_2)_2CH_3$) (2.58 g, 10 mmol), *n*-butyl lithium (6.25 mL, 1.6 M in hexane), and benzaldehyde (1.06 g, 10 mmol) in THF (60 mL) gave an oil which contained two diastereoisomers that were separated by flash column chromatography (elution with 20-50% EtOAc in hexane). The first diastereomer to be eluted from the column was the (1*RS*, 2*SR*)-adduct, *erythro*-(**2a**) as white needles 2.22 g (61%), m.p. 140-142°C (lit. [46], m.p. 140-141°C) (hexane/EtOAc), R_f 0.33 (hexane:EtOAc, 1:1); $[\alpha]_D^{26}$ = +0.25°; IR (KBr): 3260, 3054, 2953, 2864, 1972, 1595, 1459, 1439, 1334, 1163, 1116, 1034, 898 and 704 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.44 (3H, t, J = 7.18 Hz, CH_3), 0.51-0.65 (1H, m, $C\underline{H}_2Me$), 0.66-0.78 (1H, m, $C\underline{H}_2Me$), 1.48-1.36 (1H, m, $C\underline{H}_2CH_2Me$), 1.74-1.91 (1H, m, $C\underline{H}_2CH_2Me$), 2.44-2.50 (1H, m, C<u>H</u>P), 2.61 (1H, br. s, OH), 5.29 (1H, d, J_{HP} = 9.56 Hz, C<u>H</u>OH), 7.22-7.38 (5H, m, <u>Ph</u>C) and 7.45-8.06 (10H, m, $\underline{Ph}_2PO$); ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.9 (1C, CH_3), 23.1 (1C, $\underline{C}H_2Me$), 44.2 (1C, $\underline{C}H_2CH$), 44.8 (1C,

CHPO), 70.8 (1C, CHOH), 125.4 (2C, PhC), 127.1 (1C, PhC), 128.2 (2C, PhC), 128.7 (1C, Ph_2PO), 128.8 (1C, Ph_2PO), 129.1 (1C, Ph_2PO), 129.2 (1C, Ph_2PO), 130.7 (1C, Ph_2PO), 130.8 (1C, Ph_2PO), 130.9 (1C, Ph_2PO), 131.0 (1C, Ph_2PO), 132.1 (1C, Ph_2PO), 132.2 (1C, Ph_2PO), 132.3 (1C, PhC), 142.2 (1C, Ph_2PO) and 142.3 (1C, Ph_2PO). The second diastereomer to be eluted from the column was the (1*RS*, 2*RS*)-adduct, *threo*-(**2a**) as white needles 0.62 g (17%), m.p. 124-126°C (lit. [46], m.p. 126-128°C) (hexane/EtOAc), R_f 0.25 (hexane:EtOAc, 1:1); IR (KBr): 3180, 3055, 2954, 2860, 1595, 1459, 1440, 1334, 1150, 1116, 1036, 890 and 720 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.63 (3H, t, J = 7.29 Hz, CH_3), 0.96-1.08 (2H, m, CH_2Me), 1.33-1.58 (2H, m, CH_2CH_2Me), 2.70-2.80 (1H, m, CHP), 5.08 (1H, dd, J_{HP} = 17.00 Hz, J_{HH} = 6.80 Hz, CHOH), 7.10-7.23 (3H, m, PhC) and 7.25-7.84 (12H, m, PhC and Ph_2PO); ^{13}C-NMR (DMSO-d_6) δ (ppm): 13.9 (1C, CH_3), 28.8 (1C, CH_2Me), 44.0 (1C, CH_2CH), 44.7 (1C, CHPO), 74.6 (1C, CHOH), 126.6 (2C, PhC), 127.6 (1C, PhC), 128.1 (2C, PhC), 128.4 (1C, Ph_2PO), 128.5 (1C, Ph_2PO), 128.6 (1C, Ph_2PO), 128.7 (1C, Ph_2PO), 130.5 (1C, Ph_2PO), 130.6 (1C, Ph_2PO), 131.4 (1C, Ph_2PO), 131.5 (1C, Ph_2PO), 131.9 (1C, Ph_2PO), 132.0 (1C, Ph_2PO), 133.2 (1C, PhC), 142.3 (1C, Ph_2PO) and 142.4 (1C, Ph_2PO).

2-Diphenylphosphinoyl-1-phenylheptan-1-ol (**2b**; R = $(CH_2)_4CH_3$ and R′ = Ph). Hexyldiphenylphosphine oxide (**1b**; R = $(CH_2)_4CH_3$) (2.00 g, 6.99 mmol), *n*-butyl lithium (4.70 mL, 1.6 M in hexane), and benzaldehyde (0.74 g, 6.99 mmol) in THF (60 mL) gave an oil which contained two diastereoisomers that were not separated from each other, as pale yellow oil 2.54 g (92%), R_f 0.60 and 0.50 (EtOAc); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.59 (3H, t, J = 6.90 Hz, CH_3), 0.71-1.00 (6H, m, $(CH_2)_3Me$), 1.56-1.60 (1H, m, CH_2CH), 1.80-1.91 (1H, m, CH_2CH), 2.01 (1H, br. s, OH), 2.42-2.46 (1H, m, CHP), 5.28 (1H, d, J_{HP} = 9.48 Hz, CHOH), 7.15-7.40 (5H, m, PhC) and 7.47-8.03 (10H, m, Ph_2PO).

2-diphenylphosphinoyl-1-phenyltridecan-1-ol (**2c**; R = $(CH_2)_{10}CH_3$ and R′ = Ph). Dodecyldiphenylphosphine oxide (**1c**; R = $(CH_2)_{10}CH_3$) (2.86 g, 7.74 mmol), *n*-butyl lithium (5.2 mL, 1.6 M in hexane), and benzaldehyde (0.82 g, 7.74 mmol) in THF (60 mL) gave an oil which contained two diastereoisomers that were not separated from each other, as pale yellow oil 3.46 g (93%), R_f 0.57 and 0.50 (hexane:EtOAc, 7:3); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.81 (3H, t, J = 6.80 Hz, CH_3),

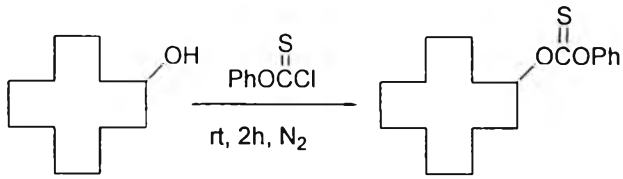
0.88-1.17 (16H, m, ($C\underline{H}_2$)$_8$Me), 1.37-1.44 (2H, m, $C\underline{H}_2CH_2CH$), 1.52-1.64 (1H, m, $C\underline{H}_2CH$), 1.80-1.89 (1H, m, $C\underline{H}_2CH$), 2.05 (1H, br. s, OH), 2.38-2.46 (1H, m, C<u>H</u>P), 5.28 (1H, d, J_{HP} = 9.37 Hz, C<u>H</u>OH), 7.11-7.40 (5H, m, <u>Ph</u>C) and 7.51-8.04 (10H, m, <u>Ph</u>$_2$PO).

2-diphenylphosphinoyl-1,2-diphenylethan-1-ol (**2d**; R = Ph and R′ = Ph). Benzyldiphenylphosphine oxide (**1d**; R = Ph) (1.0 g, 3.87 mmol), *n*-butyl lithium (2.3 mL, 1.6 M in hexane), and benzaldehyde (0.41 g, 3.87 mmol) in THF (30 mL) gave an oil which contained two diastereoisomers that were not separated from each other, as white solid 0.28 g (18%), R_f 0.23 (hexane:EtOAc, 7:3); ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.13 (1H, dd, J_{HP} = 14.31 Hz, J_{HH} = 7.19 Hz, C<u>H</u>P), 5.14 (1H, br. s, OH), 5.51 (1H, d, J_{HP} = 7.53 Hz, C<u>H</u>OH), 6.86-7.18 (10H, m, 2<u>Ph</u>C) and 7.45-8.04 (10H, m, <u>Ph</u>$_2$PO).

2-diphenylphosphinoyl-1-(4-methoxyphenyl)-pentan-1-ol (**2e**; R = $(CH_2)_2CH_3$ and R′ = *p*-OMePh). Butyldiphenylphosphine oxide (**1a**; R = $(CH_2)_2CH_3$) (1.03 g, 4.0 mmol), *n*-butyl lithium (2.51 mL, 4.02 mmol, 1.6 M in hexane), and 4-methoxybenzaldehyde (0.49 mL, 4.0 mmol) in THF (15 mL) gave an oil which contained two diastereoisomers that were separated by flash column chromatography (elution with 30-50% EtOAc in hexane). The first diastereomer to be eluted from the column was *erythro*-(**2a**) as white solid 1.12 g (65%), m.p. 126-128°C (hexane/EtOAc), R_f 0.50 (hexane:EtOAc, 3:7); $[\alpha]_D^{26}$ = +0.26°; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.43 (3H, t, J = 8.67 Hz, CH_3), 0.54-0.78 (2H, m, $C\underline{H}_2$Me), 1.45-1.58 (1H, m, $C\underline{H}_2CH_2$Me), 1.75-1.84 (1H, m, $C\underline{H}_2CH_2$Me), 2.35 (1H, q, J = 5.74 Hz, C<u>H</u>P), 3.06 (1H, br. s, OH), 3.78 (3H, s, $SC\underline{H}_3$), 5.20 (1H, d, J_{HP} = 9.20 Hz, C<u>H</u>OH), 6.82 (2H, d, J = 8.71 Hz, *p*-OM<u>ePh</u>), 7.21 (2H, d, J = 8.09 Hz, *p*-OM<u>ePh</u>), 7.45-7.61 (6H, m, <u>Ph</u>$_2$PO), 7.77-7.82 (2H, m, <u>Ph</u>$_2$PO) and 7.94-8.00 (2H, m, <u>Ph</u>$_2$PO); ^{13}C-NMR (DMSO-d_6) δ (ppm): 13.9, 23.1, 44.2, 44.8, 55.2, 70.4, 113.5 (2C), 126.5 (2C), 128.6, 128.7, 129.0, 129.1, 130.6, 130.7, 130.8, 130.9, 131.5, 132.0, 132.4, 134.2, 134.3 and 158.6. The second diastereomer to be eluted from the column was *threo*-(**2e**) whereas its contaminated with its *erythro*-(**2a**) as as white solid 0.39 g (25%), R_f 0.30 and 0.50 (hexane:EtOAc, 3:7); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.37 (3H, t, J = 8.70 Hz, *erythro*-CH_3), 0.55 (3H, t, J = 7.60 Hz, *threo*-CH_3), 0.69-0.92 (2H, m, $C\underline{H}_2$Me), 1.19-1.74 (2H, m, $C\underline{H}_2CH_2$Me), 2.29 (1H, q, J = 6.43 Hz, *erythro*-C<u>H</u>P), 2.45-2.65 (1H, m, *threo*-C<u>H</u>P), 3.61 (3H, s, *threo*-$SC\underline{H}_3$), 3.67 (3H, s, *erythro*-$SC\underline{H}_3$), 4.42 (1H, br. s,

OH), 4.89 (1H, dd, J_{HP} = 16.8 Hz, J_{HH} = 6.84 Hz, *threo*-CHOH), 5.10 (1H, d, J_{HP} = 9.30 Hz, *erythro*-CHOH), 6.64 (2H, d, J = 7.50 Hz, *threo-p*-OMePh), 6.84 (2H, d, J = 8.00 Hz, *erythro-p*-OMePh), 7.12 (2H, d, J = 7.79 Hz, *erythro-p*-OMePh), 7.45-7.61 (8H, m, *threo-p*-OMePh and Ph_2PO) and 7.69-8.06 (4H, m, Ph_2PO).

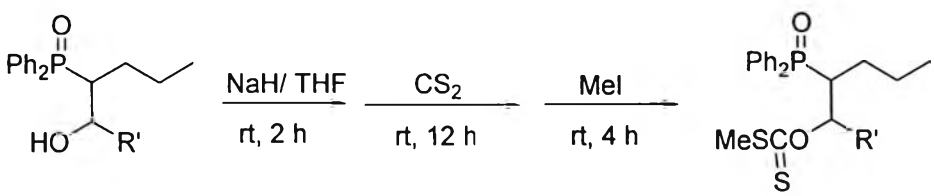
Synthesis of *O'*-phenyl thiocarbonate derivatives



(2-2b)

O-cyclododecyl O'-phenyl thiocarbonate (**2-2b**). To a solution of cyclododecanol (0.46 g, 2.5 mmol) and dry pyridine (0.7 mL) in dry CH_2Cl_2 (15 mL) was added phenyl chlorothionoformate (0.5 mL, 2.75 mmol) under nitrogen. Then the solution was stirred for 2 h at room temperature. The organic layer was washed with 1M HCl, saturated $NaHC0_3$ and brine and dried over anhydrous $MgS0_4$. After filtration and concentration in vacuum the residue was crystallized from EtOH to give 0.53 g (67%) of the thionocarbonate: mp 60-61 °C (lit. [78], m.p. 60-62 °C) (EtOH), R_f 0.5 (hexane:EtOAc, 95:5); IR (KBr): 2950,2830,1485,1260 and 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25-1.60 (18H, m, CH_2), 1.64-2.00 (4H, m, CH_2), 5.45-5.58 (1H, m, CHO), 7.04-7.18 (2H, m, Ph), 7.20-7.30 (1H, m, Ph) and 7.35-7.50 (2H, m, Ph).

Synthesis of *S*-methyl dithiocarbonate or xanthate derivatives [82]



(2a or **2e)** **(2-1a** or **2-1e)**

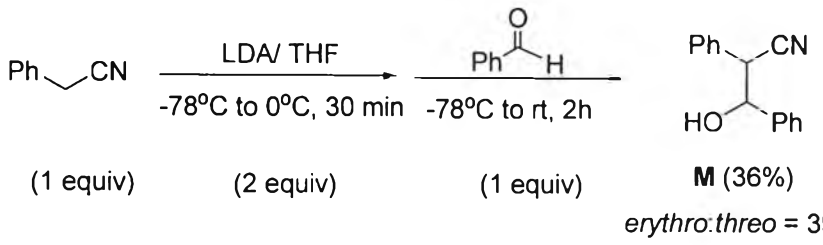
To a solution of *β*-hydroxydiphenylphosphine oxide (**2a**, 1.5 mmol) in THF (10 mL) was added *n*-butyllithium (2.51 mL, 4.02 mmol, 1.6 M solution in THF) at 0°C under nitrogen. The solution was stirred for 30 min at 0°C before the addition of

carbon disulfide (mL, mmol). The mixture was then stirred at room temperature for 4 h followed by the addition of methyl iodide (mL, mmol). The final solution was stirred at room temperature for 1 h. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine successively. After the solution was dried over anhydrous $MgSO_4$ and solvent was evaporated, the residue crude product was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (9:1) to give the xanthate products in high yield.

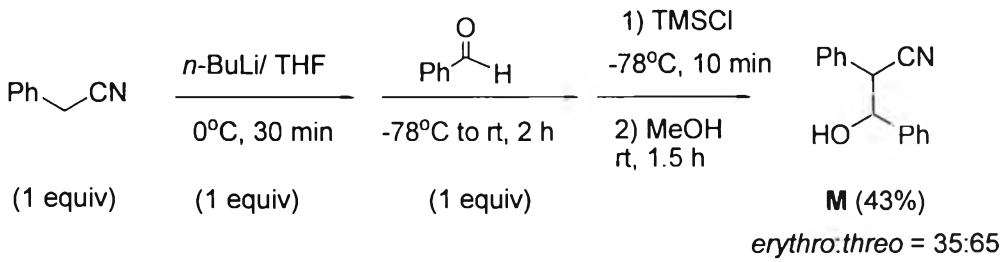
O-[2-Diphenylphosphinoyl-1-phenylheptan-1-yl]-S-methyl dithiocarbonate (**2-1a,** R′ = Ph). White solid (73%), m.p. 183-185°C (hexane/EtOAc), R_f 0.52 (CH_2Cl_2:MeOH, 95:5); $[\alpha]_D^{26}$ = -0.53°; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.52 (3H, t, J = 7.19 Hz, CH_3), 0.91-1.00 (2H, m, CH_2CH_3), 1.65-1.85 (2H, m, $CH_2CH_2CH_3$), 2.48 (1H, s, SCH_3), 2.85 (1H, dd, J_{HP} = 10.74 Hz, J_{HH} = 5.21 Hz, CHP), 6.75 (1H, dd, J_{HP} = 8.21 Hz, J_{HH} = 4.04 Hz, CHOC(S)SMe), 7.10-7.15 (5H, m, PhC), 7.32-7.45 (6H, m, Ph_2PO), 7.65-7.70 (2H, m, Ph_2PO) and 7.76-7.81 (2H, m, Ph_2PO); ^{13}C-NMR (DMSO-d_6) δ (ppm): 14.1, 18.9, 22.3, 26.9, 45.4, 81.9, 126.3 (2C), 127.9, 128.3 (2C), 128.5, 128.6, 128.6, 128.7, 130.9, 130.9, 131.0, 131.0, 131.1, 131.4, 131.7, 137.9 and 213.2.

O-[2-Diphenylphosphinoyl-1-(4-methoxyphenyl)-pentan-1-yl]-S-methyl dithiocarbonate (**2-1e**; R′ = *p*-OMePh). Pale yellow solid (87%), m.p. 169-171°C (hexane/EtOAc), R_f 0.42 (CH_2Cl_2:MeOH, 95:5); $[\alpha]_D^{26}$ = +0.27°; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.62 (3H, t, J = 7.14 Hz, CH_3), 1.16-1.29 (2H, m, CH_2CH_3), 1.59-1.89 (2H, m, $CH_2CH_2CH_3$), 2.30 (1H, s, SCH_3), 2.85 (2H, m, CHP), 3.70 (1H, s, OCH_3), 5.18 (1H, dd, J_{HP} = 10.96 Hz, J_{HH} = 7.04 Hz, CHOC(S)SMe), 6.56 (2H, J = 8.29 Hz, *p*-OMePh), 7.15 (2H, J = 8.32 Hz, *p*-OMePh), 7.35-7.47 (6H, m, Ph_2PO), 7.60-7.65 (2H, m, Ph_2PO) and 7.76-7.81 (2H, m, Ph_2PO); ^{13}C-NMR (DMSO-d_6) δ (ppm): 13.1, 14.1, 21.7, 29.7, 44.7, 49.2, 55.1, 113.4 (2C), 128.1, 128.2, 128.4, 128.5, 129.6 (2C), 130.2, 130.6, 130.7, 130.8, 130.9, 131.0, 131.5, 132.7, 158.6 and 187.8.

Synthesis of xanthate derivatives of *β*-hydroxylnitriles



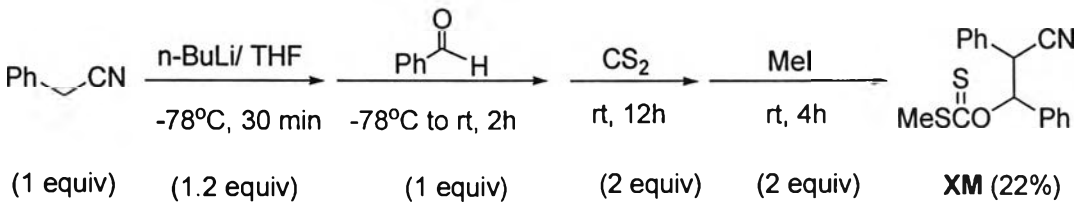
Method A: [83] To a stirred solution of diisopropylamine (1.43 mL, 10 mmol) in anhydrous THF (4 mL) at 0°C under nitrogen was slowly added dropwise *n*-butyllithium in hexanes (6.0 mL, 10 mmol, 1.6 M in hexane). After stirred for 40 min, at -78°C, a solution of benzyl cyanide (0.58 mL, 5 mmol) in THF (2.5 mL) was slowly added *via* dropping funnel and further stirred for 30 min at 0°C. After that at -78°C, benzaldehyde (0.51 mL, 5 mmol) was added *via* syringe. After stirred at room temperature for 2 h, most of the THF was removed *in vacuo*, and the residue was taken up with CH_2Cl_2, washed with 1 M HCl, saturated $NaHCO_3$ and NaCl; and dried with anhydrous $MgSO_4$. Concentration to dryness afforded yellow oil which further purified by column chromatography (elution with 20% EtOAc in hexane). To obtain the first mixtures of *erythro* and *threo* diastereomers (**M**) was as brown oil 0.33 g (30%) and the second diastereomer to be eluted from the column was *threo*-(**M**) as a yellow solid 0.06 g (6%).



Method B: [79] To a stirred solution of *n*-butyllithium in hexanes (3.15 mL, 5.0 mmol, 1.6 M in hexane) at -78°C under nitrogen was added 7 mL of anhydrous THF followed immediately by the addition of benzyl cyanide (0.58 mL, 5 mmol). A white suspension formed. After being stirred for 30 min at -78°C, a solution of benzaldehyde (0.51 mL, 5 mmol) in THF (5 mL) was added. The resulting yellow-brown mixture was stirred at -78 °C for 30 min, and then chlorotrimethylsilane (0.94 mL, 7.4 mmol) was added *via* syringe at -78°C. Ten min later, methanol (1 mL) was

added. The reaction mixture was warm to room temperature for 1.5 h, most of the THF was removed *in vacuo*, and the residue was taken up with EtOAc, washed with water, and dried with $MgSO_4$. Concentration to dryness afforded yellow oil which further purified by column chromatography (elution with 20% EtOAc in hexane). To obtain a mixture of *erythro* and *threo* diastereomers (**M**) was as brown oil 0.48 g (43%), R_f 0.30 and 0.37 (hexane:EtOAc, 7:3); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.21 (1H, br. s, OH), 3.99 (1H, d, J = 5.80 Hz, CHCN), 4.09 (1H, d, J = 6.60 Hz, CHCN), 4.90 (1H, d, J = 5.83 Hz, CHOH), 4.93 (1H, d, J = 6.62 Hz, CHOH) and 7.13-7.30 (10H, m, 2Ph).

3-Hydroxy-2,3-diphenylpropionitrile (**M**). *threo*-(**M**) as a yellow solid, m.p. 99-101°C (lit. [79], m.p. 101-102°C) (hexane/EtOAc), R_f 0.30 (hexane:EtOAc, 7:3); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.07 (1H, br. s, OH), 4.07 (1H, d, J = 6.69 Hz, CHCN), 4.92 (1H, d, J = 6.65 Hz, CHOH) and 7.09-7.28 (10H, m, 2Ph); MS *m/e* (relative intensity): 223 (M^+, 10), 205 (100), 117 (80), 107 (100) and 79 (45).

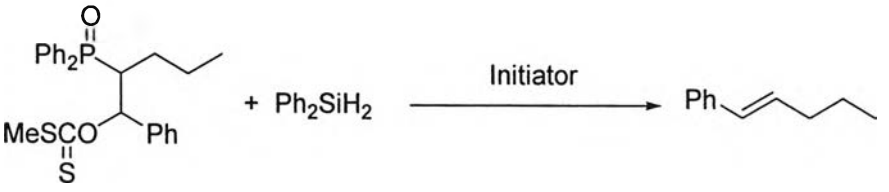


To a stirred solution of *n*-butyllithium in hexanes (4.69 mL, 6.2 mmol, 1.6 M in hexane) at -78°C under nitrogen was added 7 mL of anhydrous THF followed immediately by the addition of benzyl cyanide (0.58 mL, 5 mmol). A white suspension formed. After being stirred for 30 min at -78°C, a solution of benzaldehyde (0.51 mL, 5 mmol) in THF (5 mL) was added. The resulting yellow-brown mixture was stirred at -78 °C for 30 min, and then chlorotrimethylsilane (0.94 mL, 7.4 mmol) was added *via* syringe at -78°C. Ten min later, methanol (1 mL) was added. The reaction mixture was warm to room temperature for 1.5 h. Then, a mixture solution of *β*–hydroxylnitriles in THF was added carbon disulfide (0.60 mL, 10 mmol). The mixture was then stirred at room temperature for 12 h followed by the addition of methyl iodide (0.62 mL, 10 mmol). The final solution was stirred at room temperature for 4 h. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, and brine successively. After the solution was dried over anhydrous $MgSO_4$ and solvent was evaporated, the residue crude product was purified by column

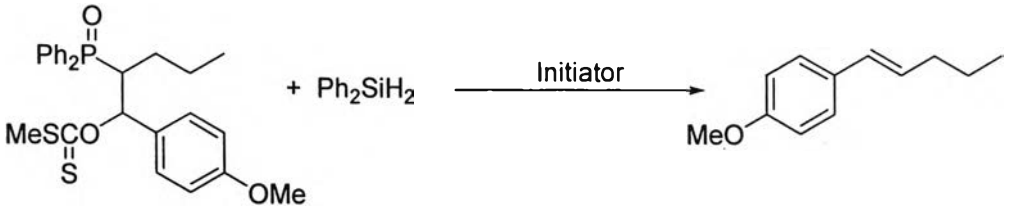
chromatography on silica gel eluting with hexane/ethyl acetate (9:1) to give the xanthate products, *O-[2-cyano-1,2-diphenylethan-1-yl]-S-methyl dithiocarbonate* (**XM**) as brown syrup 0.34 g (22%), R_f 0.65 (hexane:EtOAc, 9:1); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.70 (3H, s, CH_3S), 4.80 (1H, d, J = 4.96 Hz, CHCN), 5.29 (1H, d, J = 4.65 Hz, CHOC=S) and 7.03-7.20 (10H, m, 2Ph); MS *m/e* (relative intensity): 205 ([M-HSC(O)SMe]$^+$, 100), 190 (43), 176 (19), 151 (6.9), 89 (11), 77 (6.2) and 51 (4.5).

Radical olefination

Synthesis of alkene from xanthate derivatives



2-1a (0.2 mmol)



2-1e (0.2 mmol)

Method A: To a solution of the starting xanthate (0.2 mmol) in dry toluene (3 mL), diphenylsilane (40 μL, 0.22 mmol) was added under argon. Then the solution was brought to the boil and treated with 250 μL portions of a solution of AIBN in toluene at 30 minute intervals (32.8 mg AIBN was dissolved in 1.0 mL dry toluene). The reaction was monitored by TLC. When the reaction was complete the solvent was evaporated in vacuum and work-up by extraction with CH_2Cl_2/H_2O. The product was isolated by column chromatography on silica gel (eluent: hexane).

Method B: To a solution of the starting xanthate (0.2 mmol) in dry mesitylene (3 mL), diphenylsilane (40 μL, 0.22 mmol) was added under argon. Then the solution was brought to the boil and treated with 250 μL portions of a solution of benzoyl peroxide in mesitylene at 30 minute intervals (48.5 mg benzoyl peroxide was dissolved in 1.0 mL dry mesitylene). The reaction was monitored by TLC. When the reaction was complete the solvent was evaporated in vacuum and work-up by

extraction with CH_2Cl_2/H_2O. The product was isolated by column chromatography on silica gel (eluent: hexane).

Method C: To a solution of the starting xanthate (0.2 mmol) in dry chlorobenzene (3 mL), diphenylsilane (180 μL, 1.0 mmol) was added under argon. Then the solution was brought to the boil and treated with 250 μL portions of a solution of lauroyl peroxide in chlorobenzene at 2 hour intervals (79.7 mg lauroyl peroxide was dissolved in 1.0 mL dry chlorobenzene). The reaction was monitored by TLC. When the reaction was complete the solvent was evaporated in vacuum and work-up by extraction with CH_2Cl_2/H_2O. The product was isolated by column chromatography on silica gel (eluent: hexane).

Method D: To a solution of the starting xanthate (0.2 mmol) in dry benzene (3 mL), diphenylsilane (80 μL, 0.4 mmol) was added under argon. Then the solution was brought to the boil and treated with 250 μL portions of a solution of di-*tert*-butyl peroxide in benzene at 6 hour intervals (146.2 mg di-*tert*-butyl peroxide was dissolved in 2.0 mL dry benzene). The reaction was monitored by TLC. When the reaction was complete the solvent was evaporated in vacuum and work-up by extraction with CH_2Cl_2/H_2O. The product was isolated by column chromatography on silica gel (eluent: hexane).

Method E: To a solution of the starting xanthate (0.2 mmol) in dry benzene (5 mL) under argon was added diphenylsilane (40 μL, 0.2 mmol) and triethylborane (1.0 mL, 1.0 mmol, 1 M solution in hexane). Dry air was entered by a needle on top of septum and then the reaction was refluxed. The reaction was monitored by TLC. After completed reaction and evaporation of the solvent, the residue was work-up by extraction with CH_2Cl_2/H_2O and separated by column chromatography on silica gel (eluent: hexane).