CHAPTER II

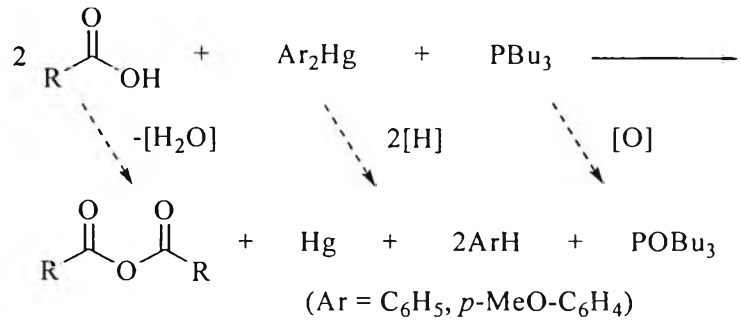
QUINONED-MEDIATED CARBON-SULFUR AND CARBON-CARBON BOND FORMATION BY OXIDATION-REDUCTION CONDENSATION

2.1 Introduction

Ever since strong bases such as alkyllithium compounds became relatively easily accessible, numerous useful syntheses have been developed in which the chemistry of organosulfur derivatives, dianions, alkylcopper compounds or related species plays an integral role. In the case of acids, the discovery of super acids has made it possible to generate synthetically useful carbocations and Lewis acids have provided organic chemists with a means of performing numerous reactions involving strong bases and strong acids rather than with those performed in the presence of weak oxidizing agents and weak reducing agents (oxidation-reduction condensation). Organic compound containing trivalent phosphorus such as trialkylphosphine can readily take up an oxygen atom and are therefore frequently used as reducing agents [3].

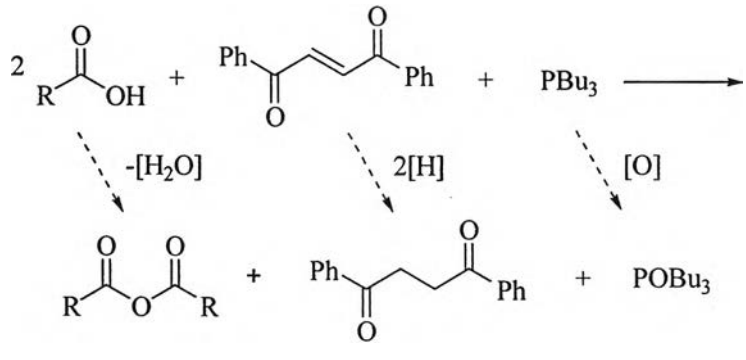
Oxidation-reduction condensation is known as one of very convenient and useful synthetic reactions for the preparation of C-O bond formation such as esters and ethers [4]. The fundamental concept of oxidation-reduction condensation is to perform dehydration condensation by eliminating H_2O as 2[H] and [O] by a combination of a weak reductant and an oxidant. The most characteristic feature of this reaction is that it proceeds under mild and neutral conditions without any assistance of acidic or basic promoters.

The first example of this type of condensation in acylation was reported by Mukaiyama and co-workers in 1963. The corresponding acid anhydride was afforded in high yield along with mercury and tri-*n*-butylphosphine oxide on treating two equivalents of carboxylic acid with the combination of diphenyl- or *bis*-(*p*-methoxyphenyl)mercury (Ar_2Hg) (hydrogen acceptor) and tri-*n*-butylphosphine (PBu_3) (oxygen acceptor) [4].

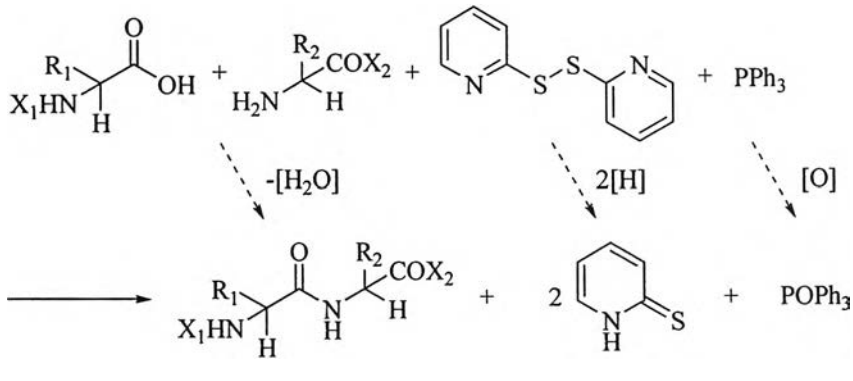


2.2 Literature Reviews

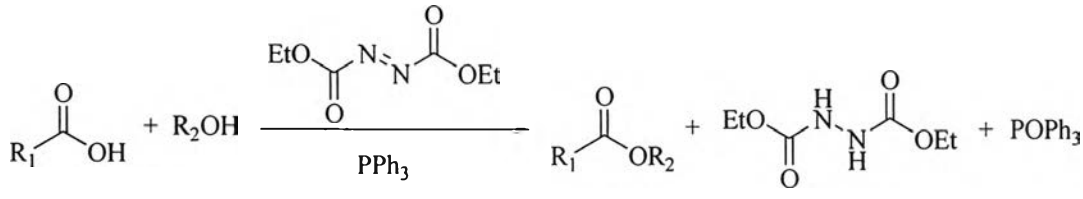
Since these dehydration reactions essentially proceed *via* an oxidation and a reduction process, it is important that suitable oxidants and reductants (phosphorus(III) compounds) be chosen. It has been reported that similar dehydration condensation reactions of acids also took place successfully when PBu_3 and a conjugated dicarbonyl compound such as *trans*-1,2-dibenzoylethylene were used as the acceptors [5].



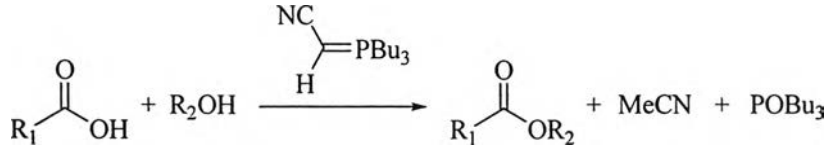
Furthermore, it has been also shown that treatment of Bz-L-Leu-OH (Bz = benzoyl) with H-Gly-OEt in the presence of triphenylphosphine (PPh_3, reductant) and di-(2-pyridyl)disulfide (oxidant) led to the formation of Bz-L-Leu-Gly-OEt in high yield [6].

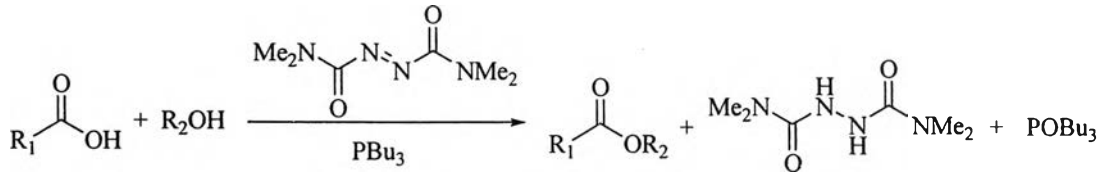


In 1967, Mitsunobu developed this concept as an efficient alkylation method for preparation of esters by using a combination of diethyl azodicarboxylate (DEAD) and PPh_3 (Mitsunobu reaction) [7]. After that, Shi and co-workers used this reaction for the stereospecific synthesis of chiral tertiary alkyl aryl ethers in about 50% yield with complete inversion of configuration [8].

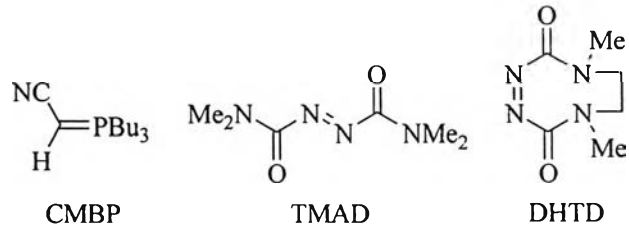


Tsunoda and co-workers reported an alkylation reaction using alcohols and cyanomethylenetributylphosphorane (CMBP) or *N,N,N′,N′*-tetramethylazo dicarboxamide (TMAD) [9].

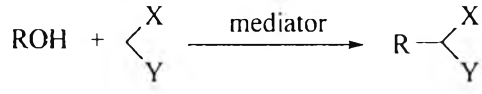




Furthermore, Tsunoda and coworkers applied these reagents for carbon-carbon formation. The efficiency of three azodicarboxylic acid derivatives such as CMBP, TMAD and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD) and a stabilized phosphorane was compared utilizing the reactions of three nucleophiles and several alcohols. The corresponding products were obtained in moderate to high yields [10].

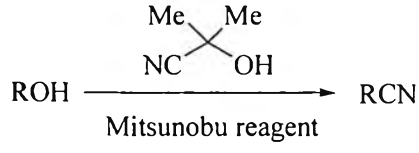


CMBP TMAD DHTD

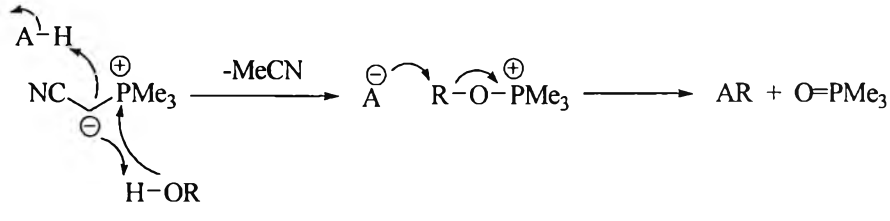


X, Y = CN, CO_2Et, SMe, SO_2Tol, *etc*

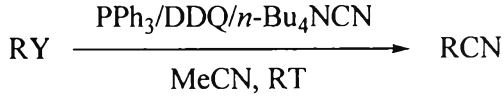
Some new Mitsunobu reagents, especially TMAD-tributylphosphine and CMMP, mediated the direct transformation of primary and secondary alcohols into the corresponding nitriles in the presence of acetone cyanohydrin. This type of cyanation process can convert 3β-cholestanol to 3α-cyanocholestane in high yield [11].



Later, CMMP mediates Mitsunobu-type reactions, which are a versatile method for the alkylation of various nucleophiles (HA) with alcohols (ROH) to give RA. CMMP is quite effective for the reaction of carbon nucleophiles whose pK_a value are higher than 13 [12].



In 2003, Iranpoor and co-workers reported a conversion of alcohols, thiols and trimethylsilyl ethers to alkyl cyanides. Triphenylphosphine and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded as adduct, which in the presence of *n*-Bu_4NCN converted alcohols, thiols and trimethylsilyl ethers into their corresponding alkyl cyanides in good to excellent yields at room temperature. This method was highly selective for conversion of primary alcohols in the presence of secondary and tertiary ones, thiols and silyl ethers [13].



Y = OH, SH, $OSiMe_3$

However, a challenging problem still remained; for example, the corresponding esters or ethers were obtained in low yield when bulky secondary or tertiary alcohols were used as alkylating reagents. It was then considered that the formation of an important key reaction intermediate (alkoxyphosphonium salts) was strongly interfered by steric hindrance of the alcohols.

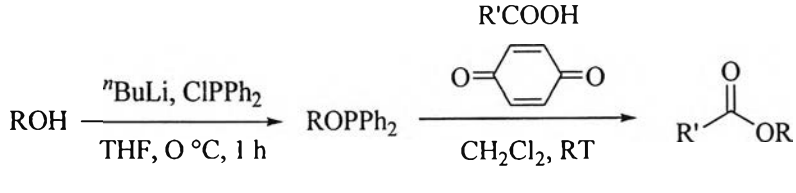
The search for new and suitable combinations of weak reductant and oxidant for the oxidation-reduction condensation has been a matter of continued interest for chemists since the analogous reactions have been reported continually. For example, Mukaiyama has long expected that quinones could be used as effective oxidants in this type of condensation. It was then cautiously considered that for the interaction of alkyl diphenylphosphinite ($ROPPh_2$) with weak oxidants, quinone would provide the alkoxyphosphonium salt more smoothly than PPh_3. This was because the former is a stronger reductant. In addition, the alkyl diphenylphosphinite formed by introduction an alkoxy group into a trivalent phosphorus compound worked more effectively in the formation of the alkoxyphosphonium salt.

The followings are the literature reviews disclosing the preparation of carbon-oxygen (esters or ethers), carbon-nitrogen (amines), carbon-sulfur (sulfides) and carbon-carbon (nitriles) bond formations using the combination of 1,4-benzoquinone derivatives and alkyl diphenylphosphinites.

2.2.1 Carbon-Oxygen Bond Formation

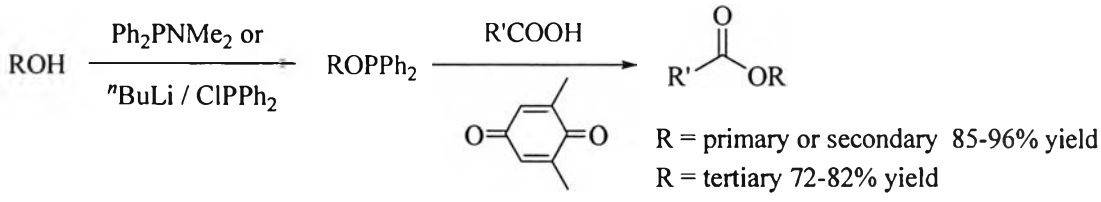
2.2.1.1 Preparation of Esters Using Alkyl Diphenylphosphinites and Carboxylic Acids

An oxidation-reduction condensation using a combination of 1,4-benzoquinone (BQ) and alkyl diphenylphosphinites was reported for the preparation of esters. The desired alkyl carboxylates were obtained in moderate to high yields by combined use of primary, bulky secondary or tertiary alkyl diphenylphosphinites and a carboxylic acid under mild and neutral conditions [14]. The corresponding esters with inverted configuration were also achieved in high optical purity and chemical yields in the case of chiral secondary or tertiary alkyl diphenylphosphinite.

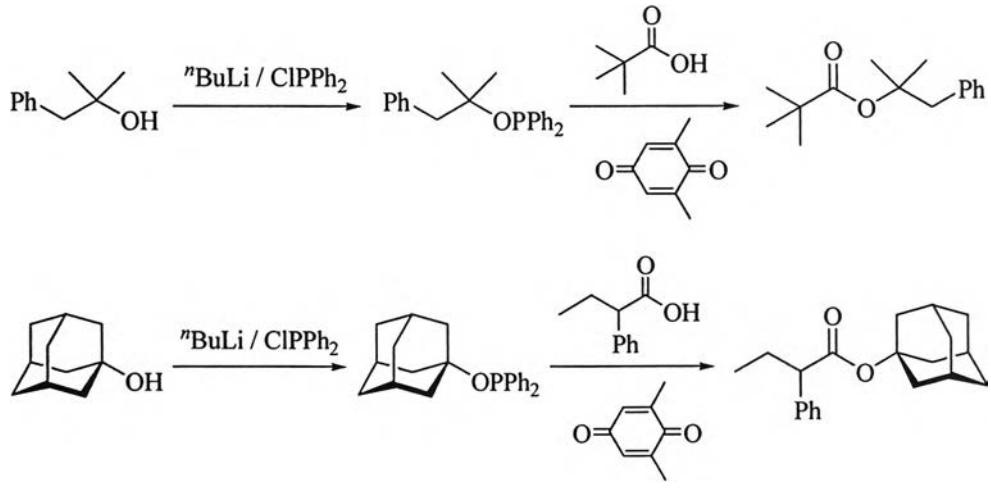


2.2.1.2 Preparation of Esters Using Chiral Alkyl Diphenylphosphinites

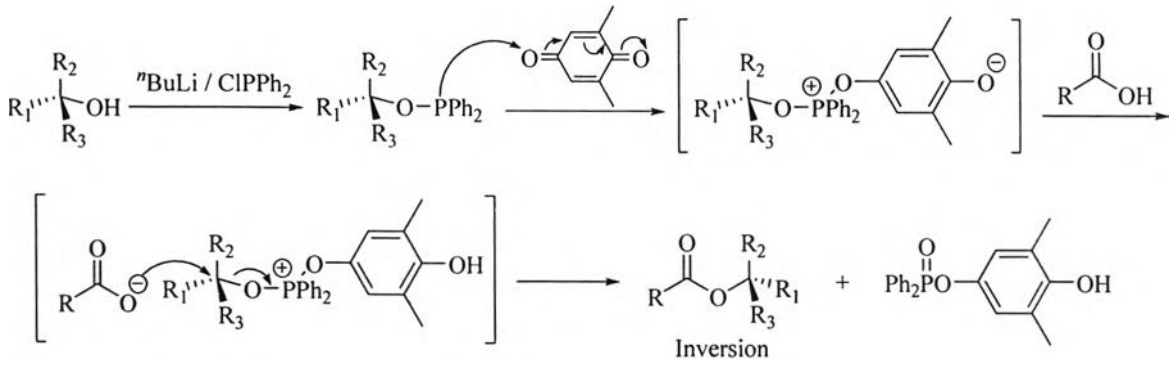
An oxidation-reduction condensation using the combination of 2,6-dimethyl-1,4-benzoquinone (DMBQ) and chiral alkyl diphenylphosphinites, formed *in situ* from alcohols and chlorodiphenylphosphine or (*N,N*-dimethylamino)diphenyl-phosphine, affords alkyl carboxylates in high yields from the corresponding alcohols and carboxylic acids by a one-pot procedure under neutral and mild conditions [15].



The esterification of various secondary alcohols proceeded in a similar manner successfully in high yield with complete inversion of configuration at the C-OH atom. Furthermore, the reactions of various carboxylic acids with chiral tertiary alkyl diphenylphosphinites formed *in situ* were addressed to proceed smoothly; for example, 2,2-dimethylpropionic acid and 2-methyl-1-phenylpropan-2-ol or 2-phenylbutyric acid and 1-adamantanol furnished the corresponding tertiary alkyl carboxylates in 85% and 96% yield, respectively [15].

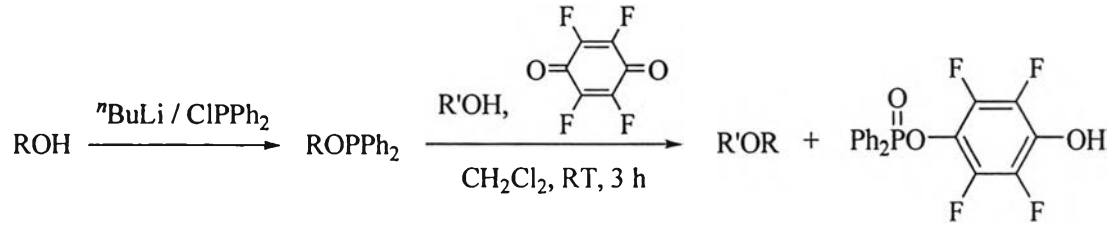


The stereochemistry of the above ester-forming reaction was examined and indeed this oxidation-reduction method worked effectively in converting tertiary alcohols into their corresponding esters with almost complete inversion of configuration [16].

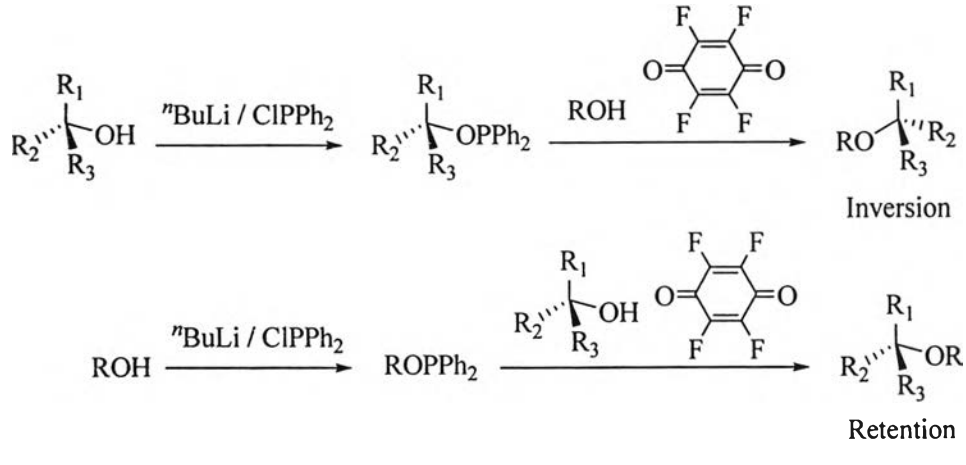


2.2.1.3 Preparation of Symmetrical or Unsymmetrical Ethers

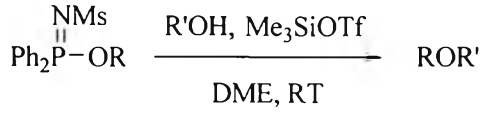
For the first time, the *O*-alkylation of alcohol with the combination of DMBQ and alkyl diphenylphosphinites was studied; nevertheless the desired ether was not obtained. A more powerful oxidant such as tetrafluoro-1,4-benzoquinone (fluoranil) instead of DMBQ was used. The corresponding symmetrical or unsymmetrical ethers could be prepared successfully in moderate to high yields at room temperature when benzyl alcohols having either electron-donating or electron-withdrawing groups and primary, secondary or tertiary alcohols were used.



Furthermore, the etherification of chiral alcohols with either retention or inversion of configuration was established, *i.e.*, treatment of chiral alkyl diphenylphosphinite with a chiral alcohol afforded the ether with inversion of configuration while the reaction of achiral alkyl diphenylphosphinite and a chiral alcohol afforded the ether with retention of configuration [15].

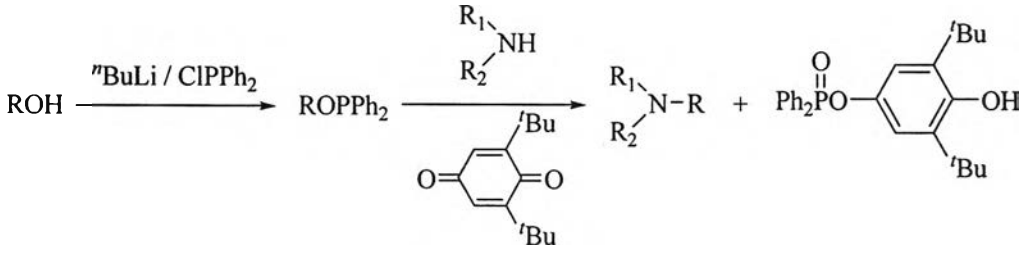


Later, Mukaiyama applied an oxidation-reduction condensation concept for *O*-alkylation of alcohols by using alkyl *P*,*P*-diphenyl-*N*-(methanesulfonyl) phosphinimidates as a useful reagent in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf). The phosphorus reagent could be easily prepared from alkyl diphenylphosphinites and methanesulfonyl azide [17].



2.2.2 Carbon-Nitrogen Bond Formation

Mukaiyama and co-workers reported a new method for preparation of C-N bond formation by oxidation–reduction condensation. Various *N*-alkylamides were obtained in high yields under mild conditions by treating alkyl diphenylphosphinite with phthalimide, carboxamide or sulfonamides in the presence of 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ) [18].

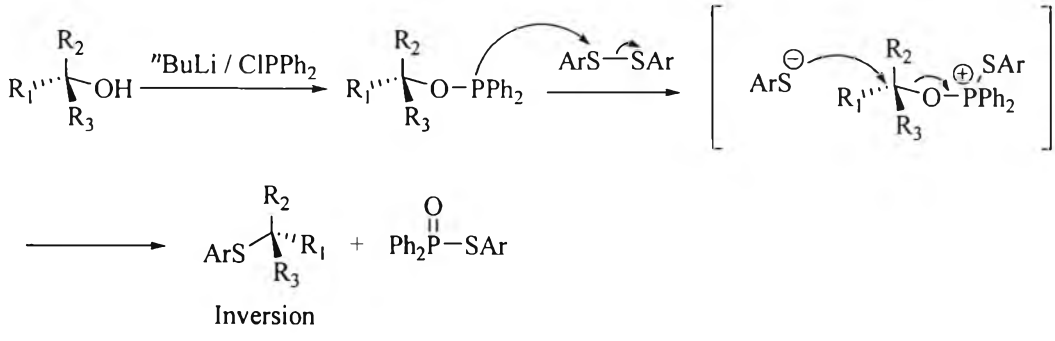


2.2.3 Carbon-Sulfur Bond Formation

2.2.3.1 Common Reagents

In the past, the preparation of alkyl aryl sulfides is one of important synthetic problems in organic and medicinal chemistry [19]. Especially, the bimolecular nucleophilic substitution (S_N2) reaction that uses chiral alkylating agents is a simple and particularly-effective tool for the stereospecific preparation of chiral molecules in synthetic organic chemistry [8]. Usually, the methods for the conversion of alcohols into the corresponding sulfides by oxidation-reduction condensation using phosphorus reagent systems such as PPh_3/DEAD/RSH or PBu_3/RSSR are usefully considered [20-21]. However, it has generally been known that sterically-hindered tertiary alcohols do not give the corresponding sulfides by the above condensation reactions because the starting alcohols are recovered or the undesired olefins are produced exclusively by the elimination reactions [21-22].

Mukaiyama reported the synthesis of stereo-inverted *tert*-alkyl aryl sulfides from chiral tertiary alkyl diphenylphosphinite and was carried out successfully *via* a new-type of oxidation-reduction condensation. Moreover, various primary, secondary and tertiary alkyl diphenylphosphinites were also converted into the alkyl aryl sulfides in moderate to high yields [23].

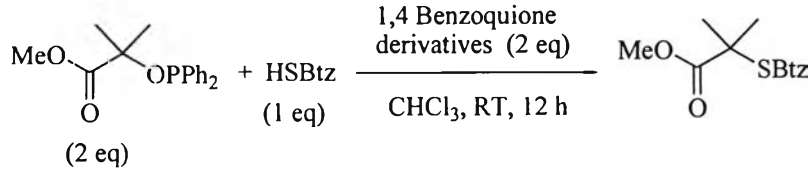


2.2.3.2 The Combination of Alkyl Diphenylphosphinite and 1,4-Benzoquinone Derivatives

The study of stereo-controlled formation of carbon-sulfur bond formation by oxidation-reduction condensation using alkyl diphenylphosphinites and 1,4-benzoquinoene derivatives such as DBBQ and DMBQ under mild and neutral conditions was further disclosed by Mukaiyama and co-workers in recently publication [24-25]. The results from this literature were addressed below.

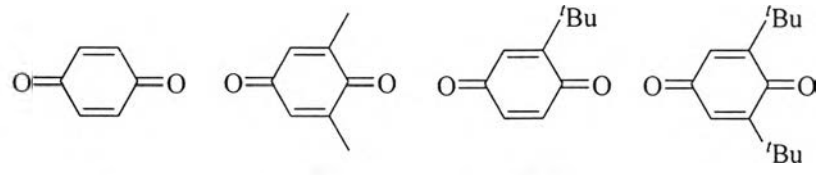
- Effect of 1,4-Benzoquinone Derivatives

The reactivities of various 1,4-benzoquinone derivatives were examined in the condensation of methyl 2-[(diphenylphosphino)oxy]-2-methylpropionate (one of most suitable substrates for S_N2 substitution because the reaction center of this compound is activated by the α-carboxylic ester group [8]) with 2-sulfanyl-1,3-benzothiazole (HSBtz, one of the most reactive sulfur-nucleophiles [23]) as a model.



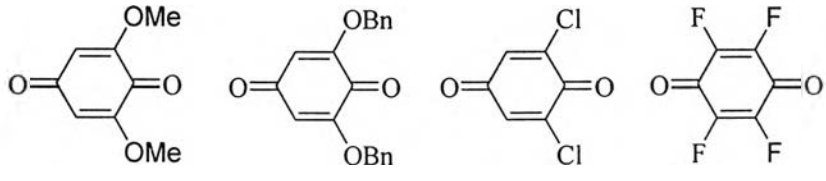
The reactivities of various 1,4-benzoquinone derivatives in the condensation of the alkyl diphenylphosphinite with HSBtz depended on the substituents at 2- and 6-position of 1,4-benzoquinone. It was considered that the effectively decreased the

undesired competitive E_2 elimination caused by the phenolic anion generated from 1,4-benzoquinone. This result could be clearly indicated that the introduction of bulky substituents at 2- and 6-positions of 1,4-benzoquinone is essential for this reaction.



%Yield of the desired sulfide	34%	51%	84%	quant

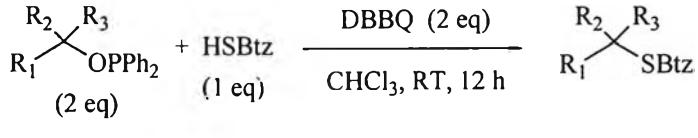
Other substituents at 2- and 6-position of 1,4-benzoquinone such as dimethoxy or dibenzyloxy were also disclosed as effective oxidants and the desired sulfide was obtained in 91% yield in both cases. In contrast, the use of electron deficient such as dichloro gave the desired sulfide in quite low yield. Moreover, the product was not obtained when powerful oxidizing agent as fluoranil was used.



%Yield of the desired sulfide	91%	91%	6%	0

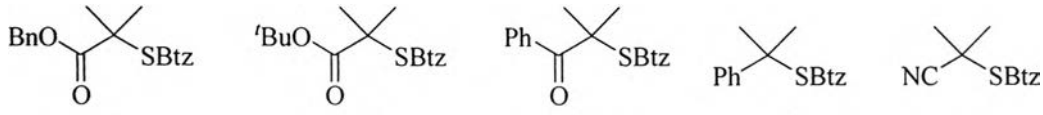
- Effect of Tertiary Alkyl Diphenylphosphinites

The investigation on *S*-alkylation of various tertiary alkyl diphenylphosphinites with HSBtz by oxidation-reduction condensation was also reported. The generality of this condensation methodology was summarized below.



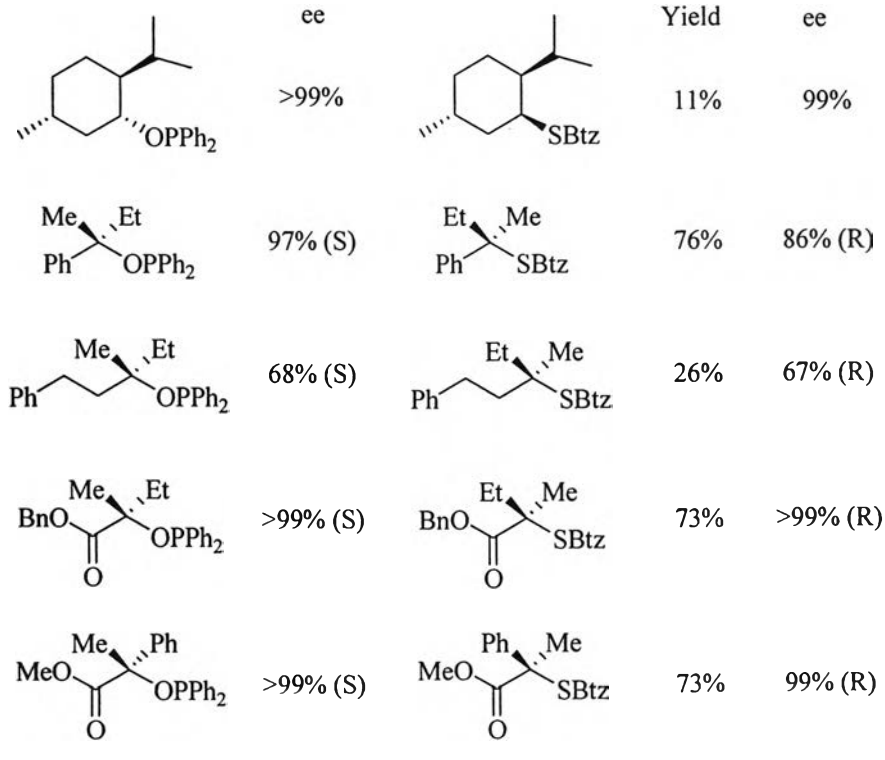
Almost, tertiary alkyl diphenylphosphinites having a α-ester, ketone or phenyl group at the quaternary centers were smoothly converted to the corresponding sulfides in moderate to high yields. Moreover, %yield of desired sulfides could be increased by using DBBQ. In the case of benzylic phosphinites, the condensation of benzylic effect did not affect to give the corresponding sulfide in the presence of DBBQ. On the other

hand, phosphinite derived from the corresponding cyanohydrin was found to be quite stable under the above conditions, presumably because the reducing ability of the phosphinite was weakened by the strongly electron-withdrawing property of the α-cyano group.



- Effect of Chiral Tertiary Alkyl Diphenylphosphinites

Taking the above results into consideration, the possibility of stereo-inversion of chiral tertiary alcohols was further investigated as depicted. Thus, different types of chiral tertiary alcohols were prepared, transformed into the corresponding alkyl diphenylphosphinites and subjected to the subsequent *S*-alkylation using HSBtz and DBBQ.



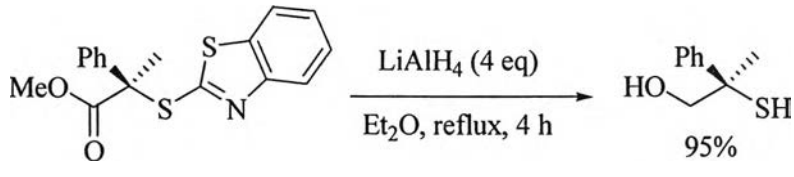
Almost, chiral tertiary alkyl diphenylphosphinites containing alkyl, phenyl or *α*-ester group at the quaternary centers could provide the desired chiral sulfides in moderate to high yields. Whereas, menthyl diphenylphosphinite derived from

(-)-menthol was not converted to the *S*-alkylated product, probably because the isopropyl group located in the neighboring position interfered with the attack of the thiolate anion.

Interestingly, enantiomerically enriched chiral sulfides could be afforded with either complete or nearly complete inversion of configuration at the quaternary centers. However, benzylic phosphinites provided the desired sulfide with not complete inversion of configuration from 97% (S) to 86% (R) probably because the reaction proceeded *via* two competitive pathways of S_N1 and S_N2 reaction.

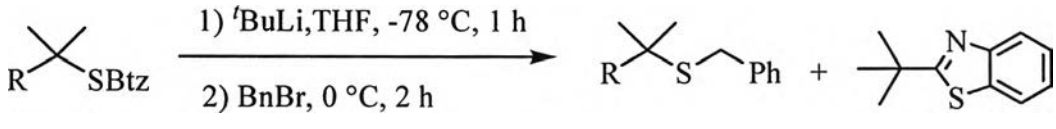
- Deprotection of Benzothiazol-2-yl Group

The cleavage of benzothiazol-2-yl group (Btz) of the above sulfide was documented to be successfully removed by using lithium aluminium hydride ($LiAlH_4$) in reflux temperature of diethyl ether for 4 h. The corresponding thiol was obtained in high yield. The example of this reaction is shown below.



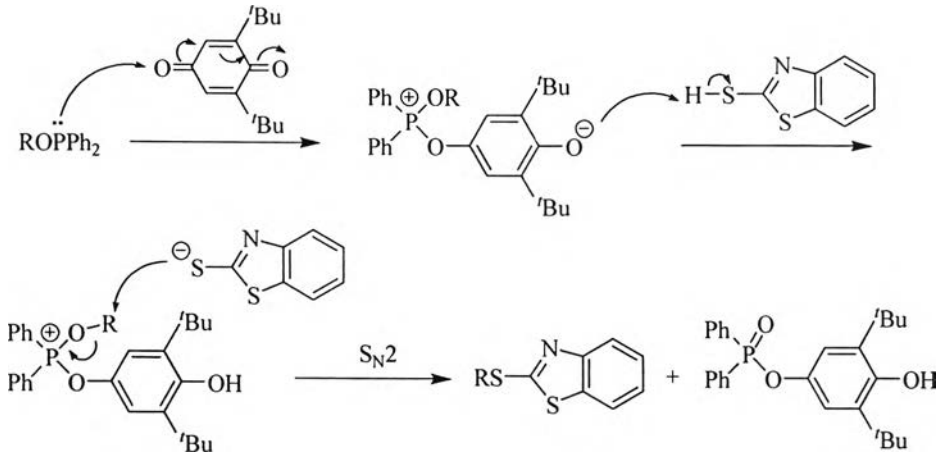
- Synthesis of Alkyl *tert*-Alkyl Sulfides from Btz Sulfides

The protocol was then applied to the tertiary Btz sulfides. The treatment of the Btz sulfides with ^{t}BuLi in anh THF generated the corresponding lithium thiolate *in situ* along with the formation of by product as 2-*tert*-butyl-1,3-benzothiazole. The subsequent trapping of the thiolate with benzyl bromide afforded the *tert*-alkyl benzyl sulfides in high yields.



- Proposed Mechanism

The proposed mechanism of oxidation-reduction condensation for carbon-sulfur bond formation from the combination of alkyl diphenylphosphinite and DBBQ using HSBtz as the sulfur nucleophile is shown below.

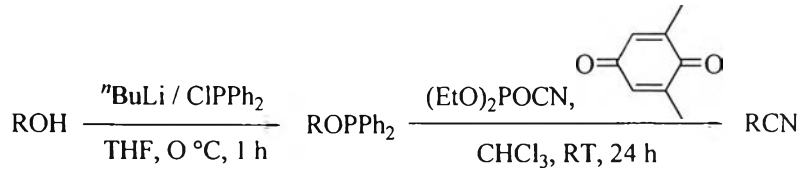


The first step, alkyl diphenylphosphinite initially reacted with regioselectively less hindered oxo group of DBBQ to form a phenoxide anion surrounded by two tertiary butyl groups. After that, this adduct could react with an acidic nucleophile of HSBtz to produce the phosphonium salt intermediate. The last step, alkylation of SBtz anion to a carbon atom adjacent to oxygen atom of the alkoxy group of intermediate afforded the corresponding sulfide along with diphenylphosphiric acid 4-hydroxy-3,5-di-*tert*-butyl-4-hydroxyphenyl ester.

2.2.4 Carbon-Carbon Bond Formation

The preparation of nitriles from alcohols was known to accomplish by two-step procedure which involves prior conversion of alcohols into their halides or sulfonates. After that, following substitution with sodium cyanide has generally been employed. However, some reaction conditions such as high temperature and the use of strong bases often caused undesirable elimination reaction. Therefore, procedures such as one-pot cyanation of alcohols by using Mitsunobu reaction were devised to let the transformation under mild and neutral conditions [26]. Recently, a conversion of alcohols into nitriles using PPh_3/DDQ/^{n}Bu_4NCN system has been reported [13]. There are however some limitations in applying this system to other cyanations since it was too strong to use DDQ as an oxidant and too difficult to use extremely hygroscopic ^{n}Bu_4NCN.

Mukaiyama reported afterwards a cyanation of alkyl diphenylphosphinites, *in situ* prepared from ^{n}BuLi and various primary alcohols, with DMBQ and diethyl cyanophosphonate. The corresponding nitriles were obtained in high yield.



2.3 Scope of This Work

Based on the above successful results of oxidation-reduction condensation between alkyl diphenylphosphinites and various nucleophiles such as carboxylic acids, phenol or amines, the *S*- and *C*-alkylation reactions using sulfur- and carbon-nucleophiles, respectively, the objective of the research described in this chapter is to continuously develop a new combination of alkyl diphenylphosphinites as reductant and suitable oxidants for carbon-sulfur and carbon-carbon bond formations. Furthermore, the use of alkyl diphenylphosphinite as phosphorus donor was studied to apply for the *O*- and *C*-glycosylations under developed condensation.

2.4 Experimental

2.4.1 Instruments and Equipment

All melting points were determined on a Yanagimoto micro melting point apparatus (Yanaco MP-S3) and remain uncorrected. Infrared (IR) spectra were recorded on a HORIBA FT-300 or a SensIR Technologies Travel*IR*^{TM} spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM EX270L (270 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C-NMR spectra were recorded on a JEOL EX270L (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ = 77.0 ppm). Carbon–^{31}P coupling constants are reported when possible. Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. All reactions were carried out under an argon atmosphere in dried glassware, unless otherwise noted.

2.4.2 Chemicals

The reagents used for synthesis were purchased from Tokyo Chemical Industry (TCI). Dehydrated solvents (THF, $CHCl_3$), $LiAlH_4$ and ^{t}BuLi in pentane

were purchased from Kanto Chemical Co., Inc. Activated alumina (ca.300 mesh) was purchased from Wako Pure Chemical Industries, Ltd.

2.4.3 General Procedure

2.4.3.1 Preparation of Alkyl Diphenylphosphinites

To a solution of alcohol 1 eq (10.0 mmol), DMAP 0.3 eq (3.0 mmol), and Et_3N 1.2 eq (12.0 mmol) in 20 mL of anh THF was added $ClPPh_2$ 1.1 eq (11.0 mmol) at room temperature. After having been stirred for 2 h, the white slurry was concentrated in *vacuo*. The residue was diluted with a mixed solution of hexane/EtOAc (v/v = 8/1; *ca.* 100 mL), filtered through a pad of alumina-celite on a buchner funnel (ϕ 40 mm disc diagram; the thickness of the alumina layer was *ca.* 10 mm) and the filtered cake was then washed with additional hexane/EtOAc (v/v = 8/1; *ca.* 100 mL). After concentration, the corresponding phosphinite was obtained as an analytically pure form and was stored under dry argon in a refrigerator (< 10 °C). For ^1H and ^{13}C-NMR spectra of the alkyl diphenylphosphinites, $CDCl_3$ stabilized with a silver foil (containing 0.03 vol.% TMS; purchased from Merck) was used as the solvent.

Benzyl diphenylphosphinite [15]: colorless oil; ^1H-NMR ($CDCl_3$) δ 7.47-7.54 (m, 4H), 7.27-7.37 (m, 11H) and 4.89 (d, J = 9.2 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 141.7, 141.4, 130.5, 130.2, 129.2, 128.3 (d, J = 6.7 Hz), 127.6, 127.4 and 71.6 (d, J = 20.1 Hz).

^{t}Butyl diphenylphosphinite [25]: colorless oil; ^1H-NMR ($CDCl_3$) δ 7.46-7.51 (m, 4H), 7.31-7.28 (m, 6H) and 1.40 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 143.6 (d, J = 15.6 Hz), 129.9 (d, J = 21.8 Hz), 128.5, 128.1 (d, J = 6.7 Hz), 76.7 (d, J = 12.3 Hz) and 30.2 (d, J = 8.4 Hz).

3-Phenylpropyl diphenylphosphinite [25]: colorless oil; ^1H-NMR ($CDCl_3$) δ 7.43-7.56 (m, 4H), 7.37-7.04 (m, 11H), 3.77-3.94 (m, 2H), 2.60-2.78 (m, 2H) and 1.88-2.06 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 142.0 (d, J = 18 Hz), 141.4, 130.3, 130.0 (x2), 129.1, 128.3, 128.2, 128.2, 128.1, 125.6, 69.2 (d, J = 9 Hz), 33.1 (d, J = 8 Hz) and 32.1.

1-Methyl-3-phenylpropyl diphenylphosphinite [25]: colorless oil; ^1H-NMR ($CDCl_3$) δ 7.44-7.58 (m, 4H), 7.02-7.41 (m, 11H), 4.00-4.16 (m, 1H), 2.52-2.78 (m, 2H), 1.75-2.10 (m, 2H) and 1.31 (d, J = 6.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 143.0 (d,

J = 17 Hz), 142.6 (d, J = 16 Hz), 141.9, 130.6, 130.3, 130.1, 129.8, 129.1, 128.8, 128.3, 128.2, 128.1, 128.1, 128.0, 125.6, 76.9 (d, J = 11 Hz), 40.1 (d, J = 6 Hz), 31.9 and 22.4 (d, J = 6 Hz).

Methyl 2-[(diphenylphosphino)oxy]-2-methylpropionate [25]: white solid; mp 61-63 °C; ^{1}H-NMR ($CDCl_3$) δ 7.45-7.57 (m, 4H), 7.25-7.40 (m, 6H), 3.66 (s, 3H) and 1.60 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 174.7 (d, J = 1 Hz), 142.5 (d, J = 15 Hz), 130.0 (d, J = 22 Hz), 128.8, 128.0 (d, J = 7 Hz), 79.1 (d, J = 15 Hz), 52.1 and 27.0 (d, J = 9 Hz).

Benzyl 2-[(diphenylphosphino)oxy]-2-methylpropionate [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.42-7.57 (m, 4H), 7.19-7.40 (m, 11H), 5.11 (s, 2H) and 1.62 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 174.0, 142.4 (d, J = 15 Hz), 135.4, 130.3, 129.9, 128.8, 128.1, 128.0, 128.0, 79.2 (d, J = 15 Hz), 66.9 and 27.0 (d, J = 10 Hz).

^{t}Butyl 2-[(diphenylphosphino)oxy]-2-methylpropionate [25]: white solid; mp 56-58 °C; ^{1}H-NMR ($CDCl_3$) δ 7.46-7.60 (m, 4H), 7.24-7.40 (m, 6H), 1.56 (s, 6H) and 1.35 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 173.3 (d, J = 1 Hz), 143.0 (d, J = 16 Hz), 130.0 (d, J = 23 Hz), 128.7, 128.0 (d, J = 7 Hz), 81.5, 79.6 (d, J = 15 Hz), 27.9 and 27.0 (d, J = 9 Hz).

2-Methyl-2-[(diphenylphosphino)oxy]propiophenone [25]: white solid; mp 71-72 °C; ^{1}H-NMR ($CDCl_3$) δ 7.90-7.98 (m, 2H), 7.10-7.45 (m, 13H) and 1.72 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 202.2, 141.7 (d, J = 15 Hz), 132.1, 130.7, 130.3, 130.2, 129.1, 128.1, 128.0, 127.6, 84.8 (d, J = 13 Hz) and 27.4 (d, J = 10 Hz).

2-[(Diphenylphosphino)oxy]-2-methylpropionitrile [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.32-7.53 (m, 10H) and 1.73 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 140.5 (d, J = 15 Hz), 130.5 (d, J = 22 Hz), 129.6, 128.3 (d, J = 7 Hz), 121.0 (d, J = 2 Hz), 71.6 (d, J = 20 Hz) and 29.0 (d, J = 8 Hz).

1-Methyl-1-phenylethyl diphenylphosphinite [25]: white solid; mp 87-88 °C; ^{1}H-NMR ($CDCl_3$) δ 7.41-7.56 (m, 6H), 7.18-7.37 (m, 9H) and 1.73 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 147.3 (d, J = 3 Hz), 143.2 (d, J = 16 Hz), 130.1 (d, J = 22 Hz), 128.7, 128.1, 128.0, 126.8, 125.3, 79.5 (d, J = 14 Hz) and 30.4 (d, J = 10 Hz).

1-Methylcyclopentyl diphenylphosphinite [25]: white solid; mp 42-43 °C; ^{1}H-NMR ($CDCl_3$) δ 7.14-7.53 (m, 10H), 1.97-2.19 (m, 2H) and 1.34-1.80 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ 143.6 (d, J = 16 Hz), 129.9 (d, J = 22 Hz), 128.6, 128.0 (d, J = 7 Hz), 87.8 (d, J = 12 Hz), 40.3 (d, J = 8 Hz), 26.6 (d, J = 11 Hz) and 23.9.

1,1-Dimethyl-3-phenylpropyl diphenylphosphinite [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.45-7.62 (m, 4H), 7.00-7.33 (m, 11H), 2.60-2.70 (m, 2H), 1.92-2.02 (m, 2H) and 1.40 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 143.6 (d, J = 16 Hz), 142.3, 130.1, 129.7, 128.6, 128.2, 128.1, 128.0, 125.5, 78.4 (d, J = 12 Hz), 45.1 (d, J = 6 Hz), 30.7 and 28.1 (d, J = 10 Hz).

1-Adamantyl diphenylphosphinite [25]: white solid; mp 66-68 °C; ^{1}H-NMR ($CDCl_3$) δ 7.42-7.55 (m, 4H), 7.21-7.38 (m, 6H), 2.09-2.21 (m, 3H), 1.91-2.04 (m, 6H) and 1.54-1.69 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 143.7 (d, J = 17 Hz), 129.9 (d, J = 22 Hz), 128.5, 128.0 (d, J = 7 Hz), 75.7 (d, J = 11 Hz), 44.2 (d, J = 8 Hz), 36.2 and 31.1.

(1R, 2S, 5R)-2-Isopropyl-5-methylcyclohexyl diphenylphosphinite [15]: colorless oil; $[\alpha]_D^{21}$ -57.5 (*c* 1.05, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.41-7.54 (m, 4H), 7.24-7.39 (m, 6H), 3.62-3.79 (m, 1H), 2.02-2.19 (m, 2H), 1.55-1.65 (m, 2H), 1.29-1.48 (m, 2H), 0.75-1.18 (m, 9H) and 0.63 (d, J = 6.9 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 143.5, 143.3, 142.6, 142.3, 131.0, 130.6, 130.0, 129.7, 129.1, 128.6, 128.1, 128.0 (x2), 127.9, 81.3 (d, J = 18 Hz), 49.2 (d, J = 6 Hz), 43.5 (d, J = 5 Hz), 34.4, 31.8, 25.4, 22.9, 22.2, 21.1 and 15.6.

1,4-Di-(diphenylphosphinite)butane [27]: white solid; ^{1}H-NMR ($CDCl_3$) δ 7.25-7.47 (m, 20H), 3.85 (dd, J = 8.1, 2.7 Hz, 4H) and 1.78 (m, 4H).

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl diphenylphosphinite [28]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 6.98-7.59 (m, 30H), 4.79-4.97 (m, 4H), 4.43-4.71 (m, 5H) and 3.51-3.71 (m, 6H).

2,3,4,6-Tetra-*O*-benzoyl-D-glucopyranosyl diphenylphosphinite [29]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 6.93-8.14 (m, 30H), 6.25 (t, J = 9.72 Hz, 1H), 5.68-5.93 (m, 3H), 5.42 (dd, J = 10.0, 3.8 Hz, 1H) and 4.17-4.27 (m, 2H).

2.4.3.2 Oxidation-Reduction Condensation of Alkyl Diphenylphosphinites with HSBtz

To a suspension of the alkyl diphenylphosphinite 2 eq (1.0 mmol) and HSBtz 1 eq (0.5 mmol) in 0.5 mL of $CHCl_3$ was added camphor quinone (CPQ) 2 eq (1.0 mmol) at room temperature. HSBtz gradually dissolved as the reaction proceeded. After 12-24 h, the formation of corresponding sulfide together with 3,5-di-*tert*-butyl-4-hydroxyphenyl diphenylphosphinate was confirmed by TLC monitoring and the

crude product was directly purified by preparative TLC on silica gel (hexane/EtOAc = 90/10 or 95/5) to afford the desired sulfide.

Methyl-2-[(1,3-benzothiazol-2-yl)sulfanyl]-2-methylpropionate [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.22-7.50 (m, 2H), 3.74 (s, 3H) and 1.74 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 173.5, 161.0, 153.0, 136.1, 125.9, 124.8, 122.3, 120.8, 53.8, 52.8 and 26.3.

Benzyl-2-[(1,3-benzothiazol-2-yl)sulfanyl]-2-methylpropionate [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.18-7.44 (m, 7H), 5.17 (s, 2H) and 1.78 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 172.9, 161.8, 153.1, 136.1, 135.4, 128.2, 127.9, 127.8, 125.9, 124.8, 122.4, 120.8, 67.4, 54.0 and 26.4.

2-[(1-Methyl-3-phenylpropyl)sulfanyl]-1,3-benzothiazole [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.86 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.7 Hz, 1H), 7.18-7.42 (m, 7H), 3.92-4.03 (m, 1H), 2.78-2.84 (m, 2H) 1.93-2.19 (m, 2H), 1.55 (s, 3H) and 1.53 (s, 3H).

^{t}Butyl-2-[(1,3-benzothiazol-2-yl)sulfanyl]-2-methylpropionate [25]: white solid, mp 40-42 °C; ^{1}H-NMR ($CDCl_3$) δ 7.90 (d, J = 7.9 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.22-7.48 (m, 2H), 1.73 (s, 6H) and 1.42 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ 171.9, 162.4, 153.1, 136.1, 125.8, 124.6, 122.1, 120.8, 81.6, 54.7, 27.7 and 26.5.

2-[(1,3-Benzothiazol-2-yl)sulfanyl]-2-methylpropiophenone [25]: white solid, mp 41-42 °C; ^{1}H-NMR ($CDCl_3$) δ 8.10 (d, J = 7.7 Hz, 2H), 7.88 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.21-7.52 (m, 5H) and 1.85 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 200.3, 161.1, 152.9, 136.5, 136.1, 131.6, 128.9, 127.7, 125.9, 124.8, 122.3, 120.8, 58.0 and 27.3.

2-[(1-Methyl-1-phenylethyl)sulfanyl]-1,3-benzothiazole [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.94 (d, J = 8.1 Hz, 1H)), 7.57-7.72 (m, 3H), 7.11-7.47 (m, 5H) and 1.96 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 163.3, 152.8, 144.7, 136.4, 128.2, 127.2, 126.7, 125.8, 124.7, 122.5, 120.7, 54.8 and 30.3.

2-[(1-Methylcyclopentyl)sulfanyl]-1,3-benzothiazole [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.24-7.51 (m, 2H), 2.08-2.26 (m, 2H) and 1.63-1.98 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 164.4, 153.4, 135.9, 125.8, 124.5, 122.2, 120.7, 60.0, 40.9, 28.8 and 24.3.

2-[(1,1-Dimethyl-3-phenylpropyl)sulfanyl]-1,3-benzothiazole [25]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 7.7 Hz, 1H), 7.00-

7.48 (m, 7H), 2.77-2.91 (m, 2H) 2.08-2.22 (m, 2H) and 1.61 (s, 6H); ^{13}C-NMR ($CDCl_3$) δ 162.9, 153.6, 141.9, 136.2, 128.3 (x 2), 125.9, 125.7, 124.8, 122.5, 120.8, 54.2, 44.4, 31.6 and 29.0.

2-[(1-Adamantyl)sulfanyl]-1,3-benzothiazole [25]: white solid; mp 73-74 °C; ^{1}H-NMR ($CDCl_3$) δ 8.01 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.32-7.50 (m, 2H), 2.05-2.20 (m, 9H) and 1.66-1.75 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 161.6, 153.5, 136.8, 125.9, 124.8, 122.7, 120.7, 53.0, 43.5, 36.1 and 30.3.

(1S, 2S, 5R)-2-(2-Isopropyl-5-methylcyclohexylsulfanyl)-1,3-benzothiazole [23]: colorless oil; $[\alpha]_D^{20}$ +101.8 (*c* 0.85, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.84 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.20-7.42 (m, 2H), 4.55 (br, 1H), 2.18-2.29 (m, 1H), 1.57-1.96 (m, 4H), 1.35-1.48 (m, 1H), 1.20-1.33 (m, 1H) and 0.84-1.23 (m, 11H); ^{13}C-NMR ($CDCl_3$) δ 167.3, 153.2, 134.9, 125.7, 123.8, 121.2, 120.7, 50.5, 48.5, 41.3, 35.1, 30.6, 27.7, 27.0, 22.1, 21.1 and 20.8.

3-(Benzothiazol-2-ylsulfanyl)butan-2-one: to a solution of the methyl 2-[(diphenylphosphino)oxy]-2-methylpropionate 2 eq (1.0 mmol) in anh $CHCl_3$ (0.5 mL) were added HSBtz 1 eq (0.5 mmol) and diacetyl as oxidant 2 eq (1.0 mmol) at room temperature. After being stirred for 12 h, the crude product was purified by preparative TLC on silica gel (hexane/EtOAc = 95/5) to afford the title compound as a colorless oil (52.9 mg, 45%). ^{1}H-NMR ($CDCl_3$) δ 7.72-7.88 (m, 2H), 7.24-7.48 (m, 2H), 4.77 (q, J = 7.3 Hz, 1H), 2.39 (s, 3H) and 1.60 (d, J = 7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 204.9, 164.2, 152.7, 135.4, 126.0, 124.5, 121.6, 121.0, 51.1, 27.4 and 16.5.

2.4.3.3 Deprotection of Benzothiazol-2-yl Group

At -78 °C, to a solution of (1S, 2S, 5R)-2-(2-isopropyl-5-methylcyclohexylsulfanyl)-1,3-benzothiazole 1 eq (0.52 mmol) in anh THF (2.6 mL) was added ^{t}BuLi (1.48 M in pentane; 0.349 mL). After 1 h at -78 °C, benzyl bromide 1.2 eq (0.62 mmol) was added, and the mixture was warmed up to 0 °C and stirred for an additional 1 h. The reaction was worked up with pyrolidine (0.05 mL). The mixture was diluted with ethyl acetate, washed with water and brine, and then dried over anh Na_2SO_4. After concentration, the crude product was purified by preparative TLC on silica gel (hexane/EtOAc = 98/2)

Benzyl-(1S, 2S, 5R)-2-isopropyl-5-methylcyclohexyl sulfide [25]: colorless oil; $[\alpha]_D^{14}$ +169.5 (*c* 1.13, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.15-7.45 (m, 5H), 3.55-3.75

(m, 2H), 3.00 (br, 1H), 1.45-2.05 (m, 5H) and 0.60-1.28 (m, 13H); ^{13}C-NMR ($CDCl_3$) δ 138.8, 128.8, 128.2, 126.7, 48.8, 45.5, 40.1, 35.7, 35.4, 29.9, 26.5, 26.3, 22.3, 21.2 and 20.4.

2.4.3.4 Oxidation-Reduction Condensation of Alkyl Diphenylphosphinites with Active Methylene Compound

To a suspension of the alkyl diphenylphosphinite 1 eq (1.0 mmol) and active methylene compound 1.5 eq (1.5 mmol) in 0.5 mL of $CHCl_3$ was added DBBQ 1.1 eq (1.1 mmol) at room temperature. After 1-12 h, the crude product was directly purified by preparative TLC on silica gel (hexane/EtOAc = 90/10 or 95/5) to afford the carbon-carbon bond formation product.

5-Phenyl-2-(phenylsulfonyl)pentanenitrile [30]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.92-8.00 (m, 2H), 7.56-7.78 (m, 3H), 7.08-7.33 (m, 5H), 3.90 (dd, J = 10.2, 4.5 Hz, 1H), 2.66 (t, J = 7.3 Hz, 2H), 2.10-2.28 (m, 1H) and 1.69-2.04 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 140.1, 135.3, 135.1, 129.4, 129.4, 128.4, 128.1, 126.2, 113.8, 57.3, 34.9, 28.2 and 26.2.

3-Phenyl-2-(phenylsulfonyl)propanenitrile [30]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.04-8.07 (m, 2H), 7.62-7.78 (3H, m), 7.25-7.34 (m, 5H), 4.10 (dd, J = 10.8, 5.4 Hz, 1H), 3.58 (dd, J = 13.5, 2.5 Hz, 1H) and 3.08 (t, J = 13.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 134.9, 134.8, 132.9, 129.2, 129.1, 128.6, 128.5, 127.6, 113.2, 58.8 and 32.1.

3-Phenyl-2-(phenylsulfonyl)butanenitrile [31]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.81-7.94 (m, 3H), 7.44-7.56 (m, 5H), 7.15-7.30 (m, 2H), 4.06 (q, J = 8.1 Hz, 1H), 2.75 (t, J = 8.1 Hz, 1H) and 2.08 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 138.4, 136.5, 135.0, 129.8, 129.6, 129.1, 129.0, 127.6, 85.5 and 31.7.

(3R)-3-Phenyl-2-(phenylsulfonyl)butanenitrile [31]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.81-7.92 (m, 3H), 7.40-7.53 (m, 5H), 7.13-7.31 (m, 2H), 4.05 (q, J = 8.2 Hz, 1H), 2.78 (t, J = 8.2 Hz, 1H) and 2.03 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 138.5, 136.7, 135.2, 129.9, 129.7, 129.0, 128.9, 127.7, 85.4 and 31.6.

Ethyl-(3R)-3-cyano-2-methyl-3-(phenylsulfonyl)propanoate: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.01-8.05 (m, 2H), 7.63-7.82 (m, 3H), 4.60 (d, J = 5.4 Hz, 1H), 4.22 (q, J = 8.1 Hz, 2H), 3.34-3.39 (m, 1H), 1.53 (d, J = 5.4 Hz, 3H) and 1.31 (t, J =

8.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 171.4, 135.5, 129.8, 129.5, 112.4, 62.4, 59.0, 37.1, 15.2 and 14.0.

(3S)-3-Methyl-5-phenyl-2-(phenylsulfonyl)pentanenitrile [32]: Pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 7.52-8.01 (m, 5H), 7.09-7.36 (m, 5H), 3.77-3.90 (m, 1H), 2.43-2.85 (m, 3H), 1.61-1.87 (m, 2H), 1.31 (d, J = 6.7 Hz, 2H) and 1.22 (d, J = 6.9 Hz, 2H).

2-Cyclopentyl-2-(phenylsulfonyl)acetonitrile [30]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.00-8.04 (m, 2H), 7.61-7.80 (m, 3H), 4.05 (d, J = 5.4 Hz, 1H), 2.63-2.71 (m, 1H), 1.96-2.08 (m, 2H) and 1.45-1.77 (m, 6H).

Dibenzyl-2-benzylmalonate [33]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.13-7.32 (m, 15H), 5.09 (s, 4H), 3.77 (t, J = 8.1 Hz, 1H) and 3.25 (d J = 8.1 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 168.0, 137.0, 134.7, 128.3, 128.0, 128.0, 127.8, 127.6, 126.2, 66.6, 53.3, and 34.1.

Benzyl-*bis*(phenylsulfonyl)methane [34]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.84-7.87 (m, 4H), 7.48-7.68 (m, 6H), 6.99-7.18 (m, 5H), 4.76 (t, J = 5.4 Hz, 1H) and 3.53 (d, J = 5.4 Hz, 2H).

3-Phenylpropyl-*bis*(phenylsulfonyl)methane [35]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.82-7.92 (m, 4H), 7.62-7.71 (m, 6H), 7.00-7.24 (m, 5H), 4.40-4.49 (m, 1H), 2.37-2.55 (m, 4H) and 1.45-1.62 (m, 2H).

Methyl-2-cyano-5-phenylpentanoate: colorless oil: ^{1}H-NMR ($CDCl_3$) δ 7.18-7.32 (m, 5H), 3.79 (s, 3H), 3.50 (t, J = 5.4 Hz, 1H), 2.67 (t, J = 5.4 Hz, 2H), and1.41-1.98 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 166.0, 140.2, 128.0, 127.8, 125.7, 115.8, 52.9, 36.7, 34.4, 28.7 and 27.8.

2-(3-Phenylpropyl)malononitrile [36]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.15-7.35 (m, 5H), 3.67 (t, J = 5.4 Hz, 1H), 2.73 (t, J = 5.4 Hz, 2H) and 1.96-2.08 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 140.3, 129.2, 128.8, 127.0, 112.9, 34.9, 30.6, 28.4 and 23.0.

Dibenzyl-2-(3-phenylpropyl)malonate [31]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.07-7.32 (m, 15H), 5.12 (s, 4H), 3.45 (t, J = 8.1 Hz, 1H), 2.09 (t, J = 8.1 Hz, 2H), 1.93-2.02 (m, 2H) and 1.58-1.64 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 169.0, 141.5, 135.3, 128.5, 128.3, 128.1, 125.8, 66.9, 51.7, 35.3, 28.9 and 28.3.

2-Benzyl-5-phenyl-2-(phenylsulfonyl)pentanenitrile: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.52-8.00 (m, 5H), 7.20-7.35 (m, 10H), 2.40-2.66 (m, 2H), 2.10-2.25 (m, 1H) and 1.65-2.01 (m, 3H).

Methyl-2-benzyl-2-cyano-5-phenylpentanoate: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.16-7.29 (m, 10H), 3.63 (s, 3H), 3.16 (d, J = 13.5 Hz, 1H), 3.01 (d, J = 13.5 Hz, 1H), 2.64 (t, J = 8.1 Hz, 2H) and 1.54-2.06 (m, 4H).

Dibenzyl-2-benzyl-2-(3-phenylpropyl)malonate: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 6.82-7.30 (m, 20H), 5.12 (s, 4H), 3.22 (s, 2H), 2.52 (t, J = 8.1 Hz, 1H), 1.81-1.87 (m, 2H) and 1.50-1.58 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 170.8, 141.6, 135.8, 135.3, 129.8, 128.5, 128.4, 128.4, 128.3, 128.2, 126.8, 125.9, 66.9, 58.7, 37.9, 35.7, 31.2 and 26.0.

3-Methyl-5-phenyl-2-(phenylsulfonyl)pentanenitrile [28]: Pale yellow oil; ^{1}H-NMR ($CDCl_3$) δ 7.83-8.03 (m, 2H), 7.52-7.80 (m, 3H), 7.09-7.36 (m, 5H), 3.79-3.91 (m, 1H), 2.46-2.88 (m, 3H), 1.62-1.88 (m, 2H), 1.32 (d, J = 6.6 Hz, 2H) and 1.24 (d, J = 6.8 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 140.4, 140.1, 136.6, 136.5, 134.7, 129.8, 128.7, 128.6, 128.2, 128.1, 127.9, 125.9, 125.8, 112.7, 112.4, 62.8, 61.9, 37.0, 33.9, 32.5, 31.3, 18.2 and 16.3.

3-Methyl-2-(4-nitrophenylsulfonyl)-5-phenylpentanenitrile: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.40-8.45 (m, 2H), 8.10-8.15 (m, 2H), 7.17-7.34 (m, 5H), 3.86 (d, J = 2.7 Hz, 1H), 2.55-2.84 (m, 3H), 1.78-1. 87 (m, 2H) and 1.36 (d, J = 5.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 151.9, 142.7, 142.6, 140.9, 140.6, 131.2, 131.2, 129.2, 129.0, 128.9, 128.8, 126.9, 126.8, 125.2, 112.9, 112.6, 63.7, 62.7, 37.5, 34.7, 33.3, 33.0, 32.0, 31.8, 18.9 and 17.2.

3-Methyl-5-phenyl-2-(pyridin-2-ylsulfonyl)pentanenitrile: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.01-8.87 (m, 4H), 7.20-7.26 (m, 5H), 3.98 (br 1H), 2.45-2.80 (m, 3H), 1.74-1.85 (m, 2H) and 1.30 (d, J = 5.6 Hz, 3H).

1-Acetyl-3-benzylindolin-2-one [37]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.12-8.15 (d, J = 8.1 Hz, 1H), 7.22-7.24 (m, 4H), 7.08-7.11 (m, 3H), 6.86-6.88 (m, 1H), 3.90 (dd, J = 8.1, 5.4 Hz, 1H), 3.46 (dd, J = 13.5, 5.4 Hz, 1H), 3.05 (dd, J = 13.5, 8.1 Hz, 1H) and 2.62 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 178.1, 171.2, 140.9, 137.2, 129.8, 128.9, 128.8, 127.8, 127.4, 125.2, 124.5, 116.8, 48.0, 37.9 and 27.1.

1-Acetyl-3-(3-phenylpropyl)indolin-2-one: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.15-8.10 (m, 1H), 7.10-7.34 (m, 8H), 4.13 (t, J = 5.4 Hz, 1H), 2.82 (m, 2H), 2.66 (s, 3H) and 2.62 (m, 4H).

1-Acetyl-3-(4-phenylbutan-2-yl)indolin-2-one: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.20-8.25 (m, 1H), 7.15-7.34 (m, 8H), 3.65 (d, J = 2.7 Hz, 1H), 2.72-2.78

(m, 2H), 2.67 (s, 3H), 2.28-2.48 (m, 2H) and 0.92 (dd, J = 10.8, 5.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ 178.2, 177.6, 170.9, 141.8, 141.6, 140.9, 140.8, 128.5, 128.4, 128.3, 128.2, 128.1, 127.4, 126.4, 126.0, 125.9, 125.0, 124.9, 123.9, 123.4, 116.4, 116.4, 50.8, 50.4, 36.4, 36.2, 35.6, 34.9, 33.8, 33.7, 26.8, 16.1 and 15.5.

1-(Phenylsulfonyl)cyclopentanecarbonitrile [32]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.76-7.94 (m, 5H), 2.23-2.48 (m, 4H) and 1.46-1.56 (m, 4H).

2.4.3.5 *O*-Glycosylation using MeI

The typical experimental procedure is as follows: to a stirred suspension of MS 5A (300 mg), β-glycosyl diphenylphosphinite 1.2 eq (0.25 mmol) and nucleophile 1 eq (0.21 mmol) in CH_2Cl_2 was added MeI 10 eq (2.10 mmol) at room temperature. After stirring for 1-2 days, the reaction mixture was diluted with EtOAc, filtered through celite and washed with saturated $NaHCO_3$. After having been dried over anh $MgSO_4$, filtered and evaporated, the resulting residue was purified by PTLC (silica gel) to afford the corresponding glycoside. The ratios were determined by HPLC analysis (hexane/EtOAc = 4/1).

2.4.3.6 *O*-Glycosylation using TfOH

A stirred suspension of MS 5A (300 mg), β-glycosyl diphenylphosphinite or β-glycosyl diphenylphosphinimidate 1.2 eq (0.12 mmol), and nucleophile 1 eq (0.10 mmol) in selected solvents (2.5 mL) was successively added TfOH (3.0 mg in toluene, 0.2 mL, 0.02 mol) at 0 °C. After completion of the glycosylation reaction by monitoring with TLC, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (2 mL). Then, the mixture was diluted with EtOAc and 1 M HCl, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and brine, and was dried over anh $MgSO_4$. After filtration and evaporation, the resulting residue was purified by PTLC (silica gel) and afforded the corresponding glycoside.

Methyl-2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-D-glucopyranosyl)-α-D-glucopyranoside [38]: white solid; mp 98–99 °C; $[\alpha]_D^{24}$ +53.0 (*c* 0.57, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.20-7.36 (m, 33H), 7.10-7.14 (m, 2H), 4.98 (d, J = 3.7 Hz, 1H), 4.96 (d, J = 11.0 Hz, 1H), 4.94 (d, J = 10.7 Hz, 1H), 4.91 (d, J = 11.6 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 4.81 (d, J = 10.7 Hz, 1H), 4.77 (d, J = 11.0 Hz, 1H), 4.71 (d, J = 11.9 Hz, 1H), 4.62-4.69 (m, 3H), 4.53-4.58 (m, 2H), 4.55 (d, J = 3.4 Hz,

1H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 3.98 (dd, *J* = 9.5, 9.2 Hz, 1H), 3.96 (dd, *J* = 9.5, 9.2 Hz, 1H), 3.82 (dd, *J* = 11.3, 4.3 Hz, 1H), 3.76-3.79 (m, 2H), 3.71 (d, *J* = 11.3 Hz, 1H), 3.59-3.68 (m, 3H), 3.52-3.56 (m, 2H), 3.44 (dd, *J* = 9.5, 3.4 Hz, 1H) and 3.35 (s, 3H).

Methyl-2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-D-glucopyranosyl)-β-D-glucopyranoside [38]: white solid; $[\alpha]_D^{24}$ +19.0 (*c* 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 7.23-7.40 (m, 29H), 7.14–7.20 (m, 6H), 4.97 (d, *J* = 11.0 Hz 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 4.77-4.81 (m, 2H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.61 (d, *J* = 3.7 Hz, 1H), 4.57-4.61 (m, 2H), 4.52-4.56 (m, 2H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 8.2 Hz, 1H), 4.16-4.20 (m, 1H), 3.99 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.81-3.85 (m, 1H), 3.64-3.74 (m, 3H), 3.63 (dd, *J* = 9.2, 8.9 Hz, 1H), 3.57 (dd, *J* = 9.8, 9.2 Hz, 1H), 3.52 (dd, *J* = 9.5, 3.7 Hz, 1H), 3.51 (dd, *J* = 9.8, 9.5 Hz, 1H), 3.49 (dd, *J* = 8.9, 8.2 Hz, 1H), 3.32 (s, 3H) and 3.42-3.46 (m, 1H).

4-Benzyloxyphenyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.12-7.43 (m, 25H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 5.36 (d, *J* = 5.4 Hz, 1H), 4.42-5.07 (m, 10H), 4.18 (t, *J* = 8.1 Hz, 1H), 3.32 (d, *J* = 10.8 Hz, 1H), 3.66-3.79 (m, 3H) and 3.58 (dd, *J* = 10.8, 2.7 Hz, 1H).

4-Methoxyphenyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside; colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.13-7.40 (m, 20H), 7.02 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 5.36 (d, *J* = 5.4 Hz, 1H), 4.38-5.07 (m, 8H), 4.19 (t, *J* = 9.5 Hz, 1H) and 3.66-3.94 (m, 8H).

2-Phenyl-6-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-4H-chromen-4-one: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 7.88-7.98 (m, 3H), 7.18-7.56 (m, 25), 6.85 (s, 1H), 5.63 (d, *J* = 3.1, 1H), 5.18, (d, *J* = 6.2, 1H), 4.43-5.11 (m, 8H), 4.26 (t, *J* = 9.0, 1H), 3.74-3.91 (m, 5H) and 3.61 (d, *J* = 10.6, 1H); ^{13}C-NMR ($CDCl_3$) δ 178.5, 164.0, 163.3, 154.4, 153.8, 151.9, 151.8, 138.7, 138.5, 138.1, 138.0, 138.0, 137.9, 131.8, 131.7, 131.6, 129.1, 128.6, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 126.3, 124.7, 124.6, 124.3, 119.5, 110.5, 110.4, 106.9, 101.5, 95.9, 84.6, 81.9, 79.6, 77.3, 75.8, 75.2, 75.1, 75.0, 73.5, 73.4, 71.4, 68.5 and 68.1.

2.4.3.7 *C*-Glycosylation using Grignard Reagent

At 0 °C, a stirred of pyrrole 3 eq (0.3 mmol) in THF (1.0 mL) was successively added PhMgCl 3 eq (0.3 mol in THF, 0.15 mL) and glycosyl donor 1 eq (0.1 mmol) and the mixture was warmed up to room temperature. After completion of the glycosylation reaction by monitoring with TLC, the reaction mixture was quenched by addition of NH_4Cl and the aq layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, and dried over and $MgSO_4$. After filtration and evaporation, the resulting residue was purified by preparative TLC on silica gel (hexane/EtOAc = 3/1) to afford the corresponding glycoside.

2-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)pyrrole [39]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.94 (br, 1H), 7.07-7.32 (m, 20H), 6.71 (m, 1H), 6.33 (m, 1H), 6.14 (m, 1H), 5.32 (J = 5.4, 1H), 4.42-4.98 (m, 8H), 3.95 (m, 2H) and 3.42-4.01 (m, 4H).

2-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)pyrrole [39]: colorless oil; ^{1}H-NMR ($CDCl_3$) δ 8.54 (br, 1H), 7.06-7.35 (m, 20H), 6.76 (m, 1H), 6.27 (m, 1H), 6.18 (m, 1H), 4.31-4.98 (m, 8H), 3.92 (d, J = 10.2 Hz, 1H) and 3.46-3.81 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ 138.5, 128.6, 128.3, 128.3, 128.2, 128.2, 127.9, 127.7, 127.6, 127.5, 127.5, 117.1, 108.4, 107.6, 86.4, 82.9, 78.9, 77.9, 75.6, 75.1, 74.6, 73.5 and 69.0.

2.5 Results & Discussion

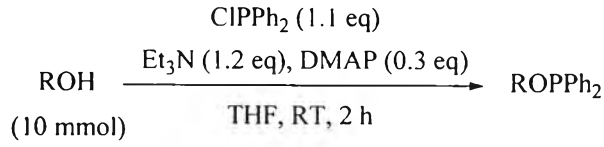
2.5.1 Preparation of Alkyl Diphenylphosphinites

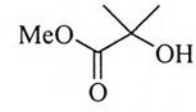
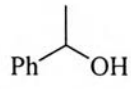
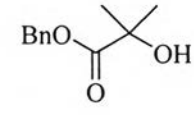
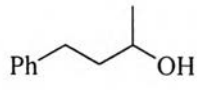
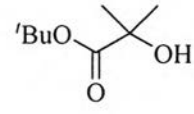
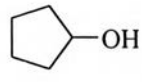
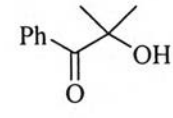
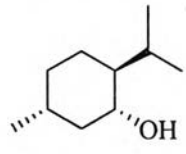
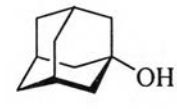
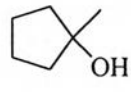
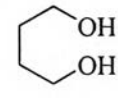
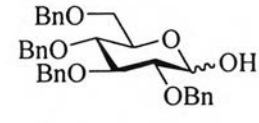
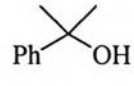
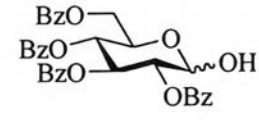
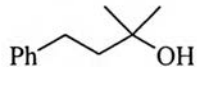
Alkyl diphenylphosphinites as starting material for oxidation-reduction condensation step could be easily prepared from the corresponding alcohols by simply adding $ClPPh_2$ in the presence of Et_3N and catalytic amount of DMAP. The reactions could be proceeded within 2 h at room temperature and pure alkyl diphenylphosphinites were obtained just by filtration through a pad of alumina using an eluent of hexane/EtOAc (9/1). Additionally, under the necessary conditions resisting to air-oxidation of alkyl diphenylphosphinites that might decompose to alkyl diphenylphosphine oxide, Ar or N_2 atmosphere were used.

$$ROPPh_2 \xrightarrow{\text{air}} RO\overset{O}{\overset{\|}{P}}Ph_2$$

The preparation results of alkyl diphenylphosphinites from primary, secondary and tertiary alcohols are tabulated in Table 2.1.

Table 2.1 Synthesis of alkyl diphenylphosphinites from selected alcohols



Entry	ROH	% Yield	Entry	ROH	% Yield
1		quant	10		94
2		95	11		94
3		99	12		99
4		93	13		94
5		quant	14		98
6		98	15		97
7		97	16		95
8		90	17		47
9		96			

Primary and secondary alcohols could be completely converted to the corresponding alkyl diphenylphosphinites in moderate to high yields (entries 1-3). The same result was obtained when cyclic alcohols were tried (entries 4-6). Moreover, tertiary alcohols containing alkyl, phenyl, benzylic, ester or ketone group at the quaternary centers could be transformed to the tertiary alkyl diphenylphosphinites in high to excellent yields (entries 7-14). This method was thus considered as an effective approach since various substituents of alcohol were not intact.

In addition, this preparation could be applied for diol or glucose derivatives to furnish the corresponding alkyl diphenylphosphinites in excellent yields (entries 15-16) except for the use of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose (entry 17). This problem was believed to occur from the purification step. After filtration certain amount of phosphinite was still remained on pad of alumina because this corresponding phosphinite could be slightly dissolved in eluent of hexane/EtOAc (9/1).

From the above result, it was found that alkyl diphenylphosphinites could be prepared from all alcohols by adding $ClPPh_2$ in the presence of Et_3N and catalytic amount of DMAP. It should be noted that conditions are obviously milder than those of the previously reported procedure by using a strong base as ^{n}BuLi [15]. Especially, %yield of the desired alkyl diphenylphosphinite did indeed not depend on steric hindrance or other functional groups present in the parent alcohol.

The example of ^{1}H-NMR spectrum of alkyl diphenylphosphinite, 3-phenylpropyl diphenylphosphinite was presented in Fig 2.1. Fifteen aromatic protons could be detected at δ_H 7.04-7.43. Three multiplet signals at δ_H 3.77-3.94, δ_H 2.60-2.78 and δ_H 1.88-2.06 was ascribed for six protons of three methylene groups connecting with $-OPPh_2$, phenyl group and $-CH_2OPPh_2$, respectively.

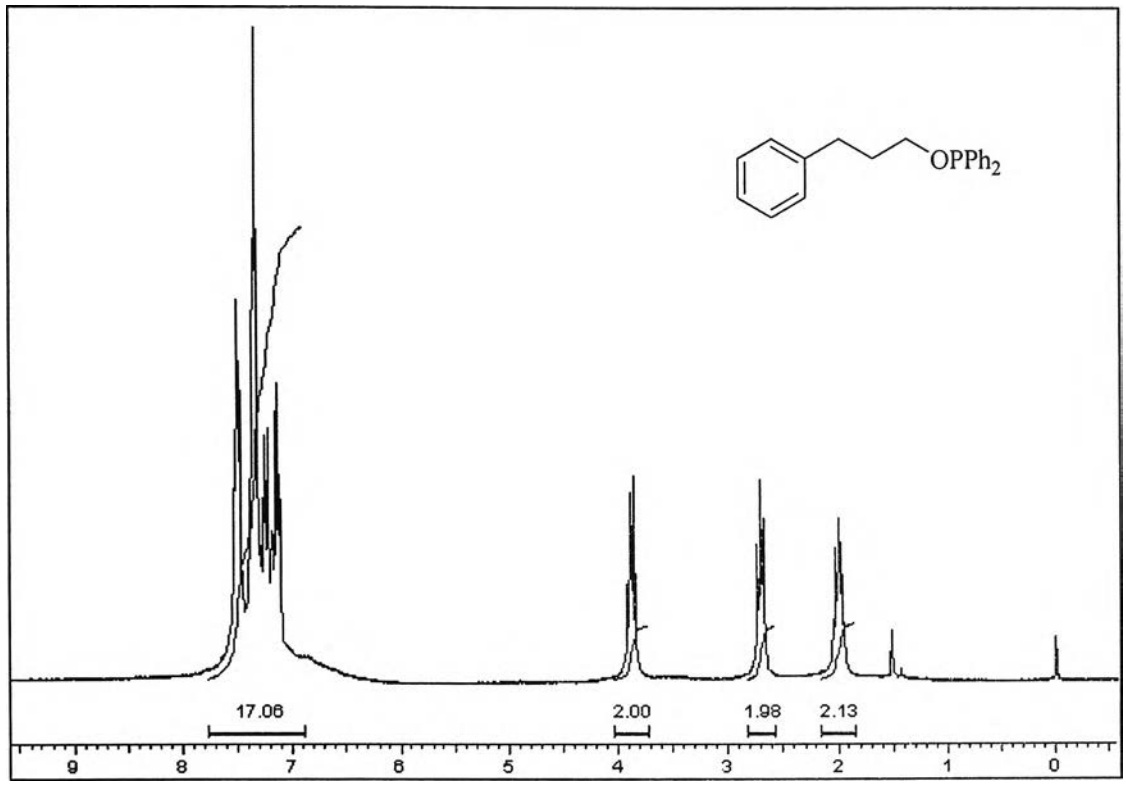


Figure 2.1 ^{1}H-NMR spectrum of 3-phenylpropyl diphenylphosphinite

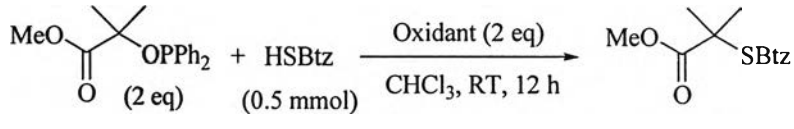
2.5.2 Carbon-Sulfur Bond Formation

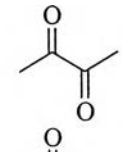
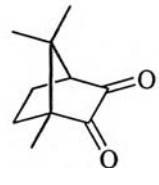
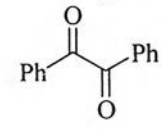
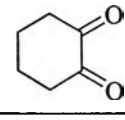
Nucleophilic substitution at quaternary carbon centers *via* S_N2-type displacement has been regarded as one of the most challenging topics in current organic synthesis. Although, the oxidation-reduction condensation of alkyl diphenylphosphinites and HSBtz with DBBQ from above literature review could be achieved *via* inversion of configuration by S_N2 displacement, the cost of DBBQ were rather expensive (5g/63.90 US dollar, Aldrich catalogue 2003/2004). It should indeed mention at this point that this chapter would devote for the exploration of a new and efficient oxidant to utilize in a practical and convenient method for carbon-sulfur bond formation, 1,2-dicarbonyl compounds were chosen to test for their efficiency as the oxidant in this reaction with alkyl diphenylphosphinites and HSBtz.

2.5.2.1 Effect of 1,2-Dicarbonyl Derivatives

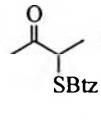
A screening of oxidants in the class of 1,2-dicarbonyl compounds was examined for the condensation of tertiary alkyl diphenylphosphinites derived from methyl 2-hydroxyisobutyrate with HSBtz. Significant differences in the reactivities of the desired sulfide were mainly caused from 1,2-dicarbonyl compounds. To observe this assumption, the variation of four 1,2-dicarbonyl compounds was explored and the results are described in Table 2.2.

Table 2.2 Effect of 1,2-dicarbonyl compounds



Entry	Oxidant	% Isolated Yield	Entry	Oxidant	% Isolated Yield
1	DBBQ	quant[a]	4		0[b]
2		96	5		0
3		0			

a) The results were cited from *Chem. Lett.*, **2005**, *34*, 638-639

b)  was obtained in 45% yield

The ^{1}H-NMR spectrum of methyl 2-[(1,3-benzothiazol-2-yl)sulfanyl]-2-methylpropionate (Fig 2.2) as the desired product in this screening displayed four aromatic protons at δ_H 7.22-7.92. The two signals at δ_H 3.74 and 1.74 could be assigned to nine protons of three methyl groups.

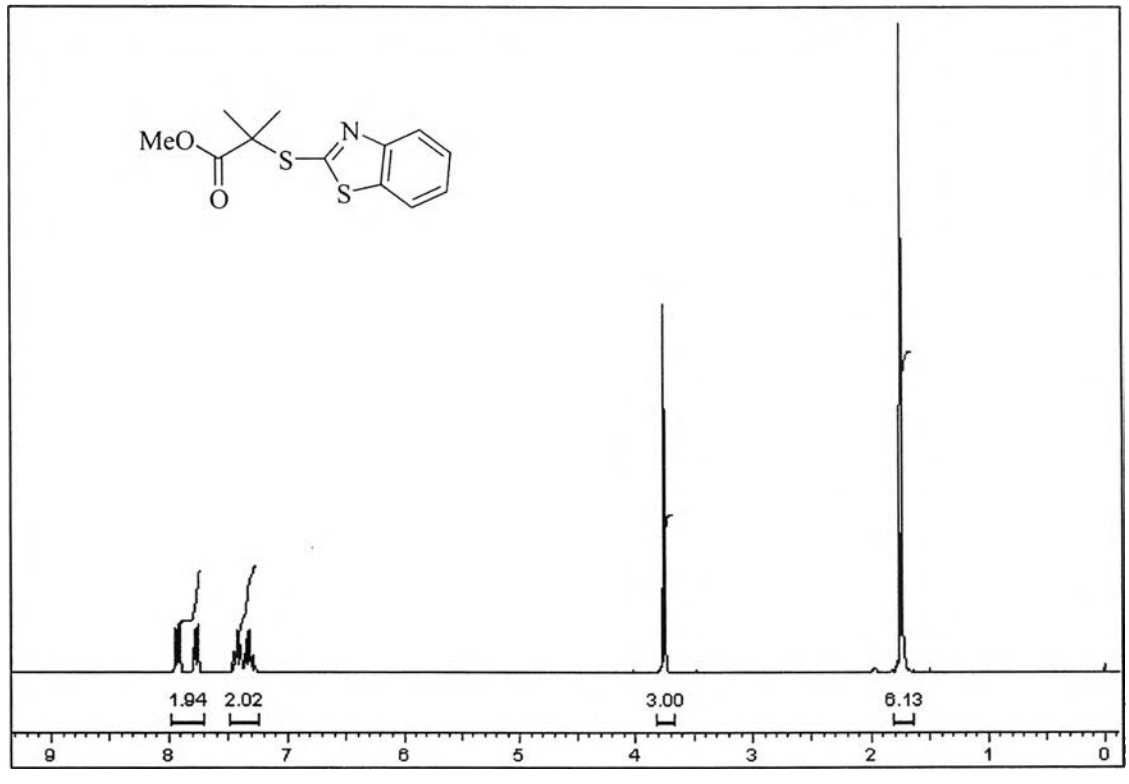


Figure 2.2 ^{1}H-NMR spectrum of 2-[(1,3-benzothiazol-2-yl)sulfanyl]-2-methylpropionate

In order to search for an alternative of DBBQ, camphorquinone (CPQ,) was the best oxidant to promote the reaction and afforded the desired sulfide in 96% yield (entry 2). CPQ displayed a nearly efficient oxidant and cheaper cost (5g/40.60 US dollar, Aldrich catalogue 2003/2004) compared with DBBQ. On the other hand, the use of cyclohexan-1,2-dione, diacetyl and benzil could not accomplish the desired sulfide (entries 3-5).

Three unreactive oxidants were further examined to look for other generated product(s) besides the desired sulfide. Using diacetyl as a model, it was found that the *S*-alkylation of methyl 2-[(diphenylphosphino)oxy]-2-methylpropionate, diacetyl and HSBtz afforded 3-(benzothiazol-2-ylsulfanyl)butan-2-one as the undesired product in 45% yield (entry 4). The ^{1}H-NMR spectrum of this sulfide (Fig 2.3) exhibited signals around δ_H 7.24-7.88 belonged to four aromatic protons of Btz group and the quartet

signal at δ_H 4.77 (J = 7.3 Hz). Two methyl groups were visualized at δ_H 2.39 and δ_H 1.60 (J = 7.3 Hz).

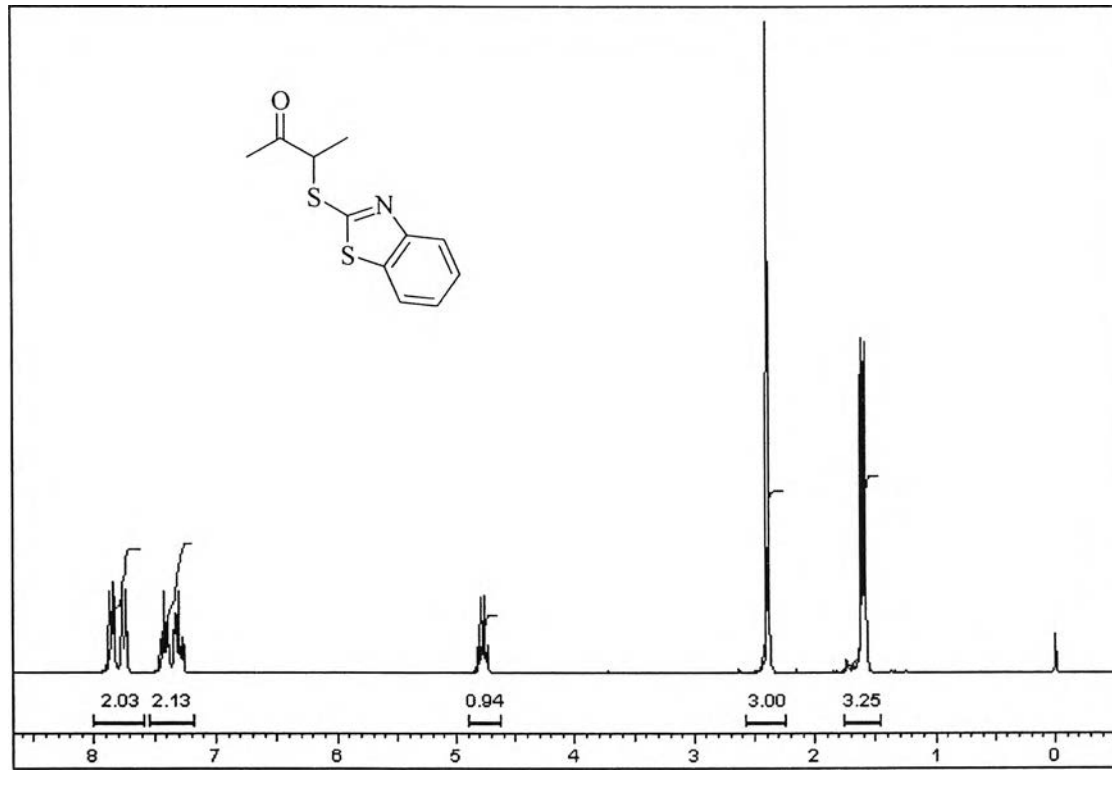
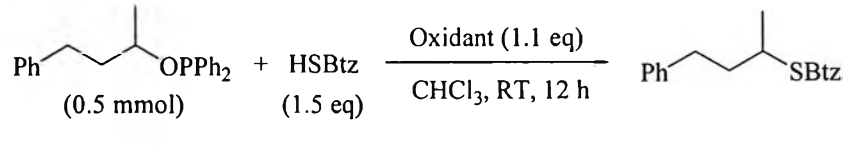
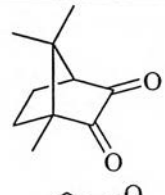
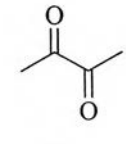
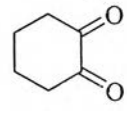
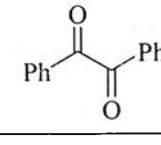


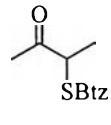
Figure 2.3 ^{1}H-NMR spectrum of 3-(benzothiazol-2-ylsulfanyl)butan-2-one

CPQ was further examined to confirm its efficiency with 1-methyl-3-phenylpropyl diphenylphosphinite with HSBtz. The results of *S*-alkylation with four 1,2-dicarbonyl compounds are tabulated in Table 2.3.

Table 2.3 Effect of 1,2-dicarbonyl compounds



Entry	Oxidant	% Isolated Yield	Entry	Oxidant	% Isolated Yield
1		80	3		0[a]
2		0	4		0

a)  was obtained in 37% yield

The ^{1}H-NMR spectrum of the attained sulfide, 2-[(1-methyl-3-phenylpropyl)sulfanyl]-1,3-benzothiazole (Fig 2.4) exhibited nine aromatic protons at δ_H 7.18-7.88 and the multiplet at δ_H 3.95-4.02 of methine group. Two multiplet signals at δ_H 2.78-2.84 and δ_H 1.96-2.14 were ascribed for four protons of two methylene groups connecting with phenyl group and -CH_2Ph, respectively. The methyl group was visualized at δ_H 1.54 (J = 5.4 Hz).

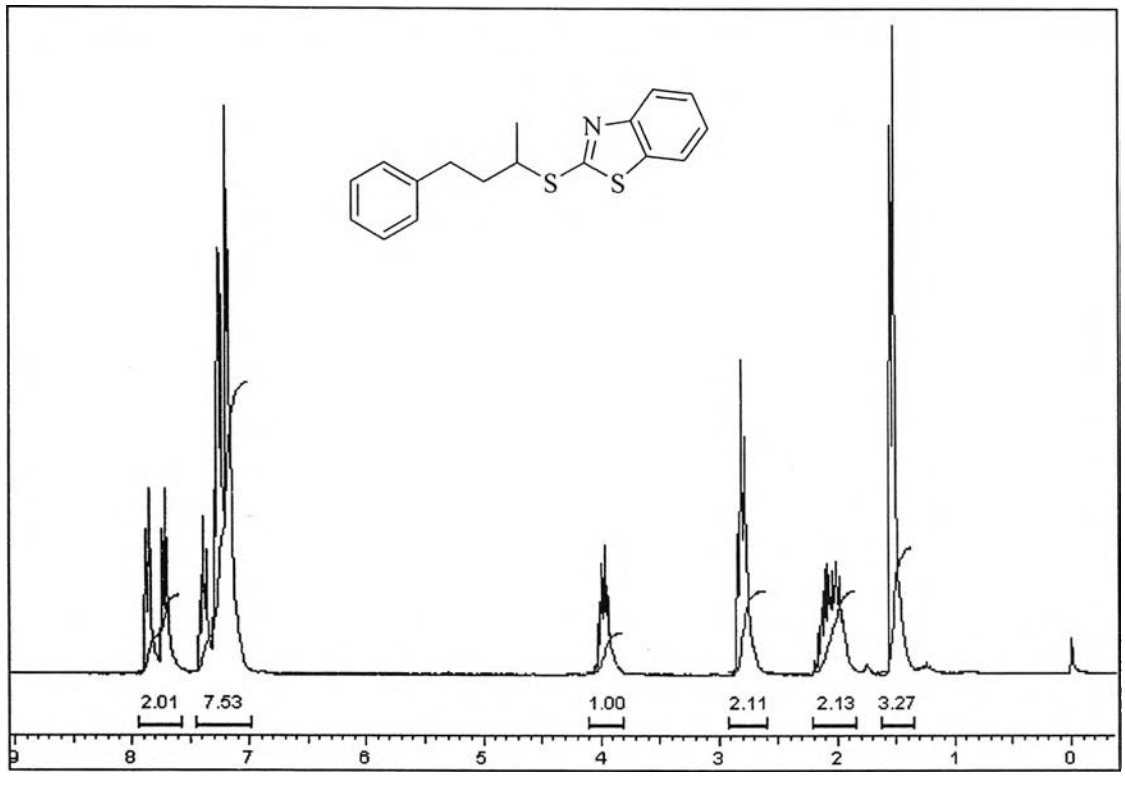
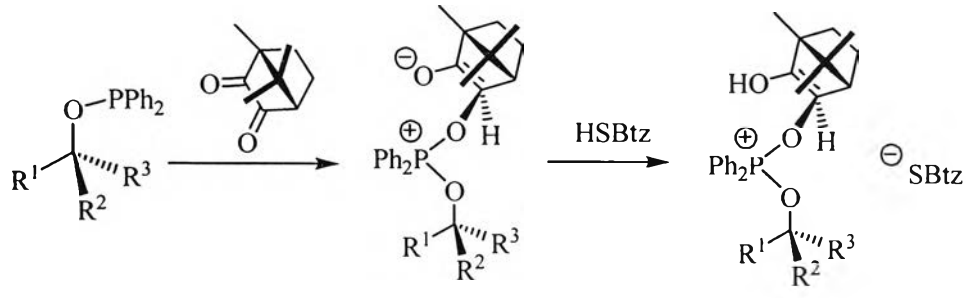


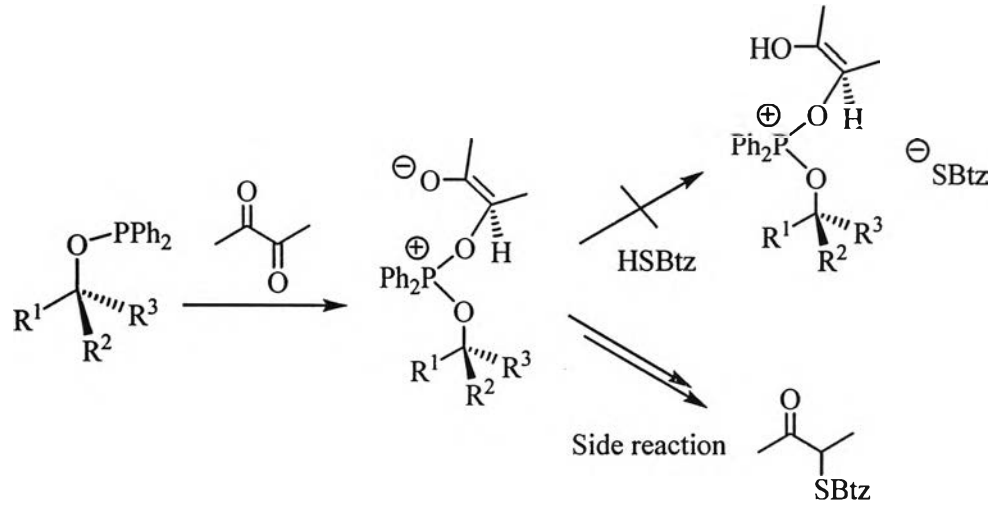
Figure 2.4 ^{1}H-NMR spectrum of 2-[(1-methyl-3-phenylpropyl)sulfanyl]-1,3-benzothiazole

It was clearly found that the corresponding sulfide was attained in high yield in the presence of CPQ (entry 1) whereas in the presence of cyclohexan-1,2-dione, diacetyl and benzil there was no desired sulfide detectable (entries 3-4). However, in the case of using diacetyl the undesired sulfide in 37% yield was obtained (entry 3).

From the above screening results, it was postulated that alkyl diphenylphosphinite initially reacted with oxo group of CPQ to form a stable anion adduct as a base to deprotonate with acidic proton of HSBtz in next step. A rigid structure could be stabilized this anion to display a suitable characteristic of base for deprotonation. Moreover, the steric hindrance at CPQ side of this adduct was difficultly attacked by nucleophile as shown below.



A flexible anion adduct derived from alkyl diphenylphosphinite and diacetyl could not be displayed as a good base for deprotonation of nucleophile. On the other hand, a side reaction was smoothly proceeded to furnish the undesired sulfide.

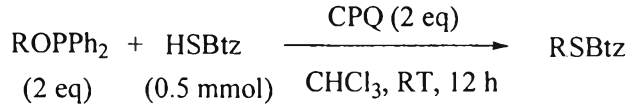


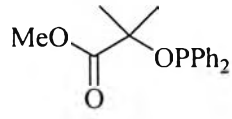
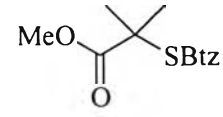
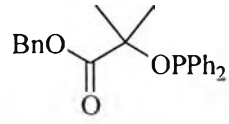
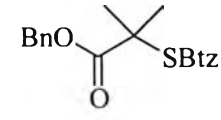
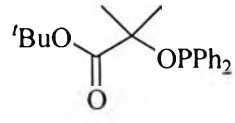
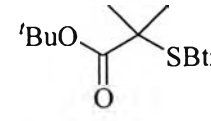
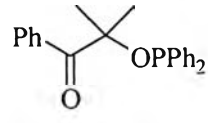
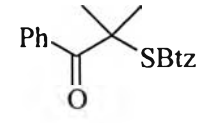
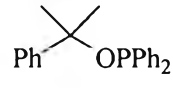
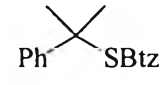
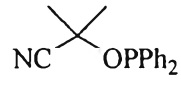
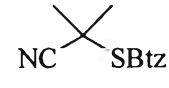
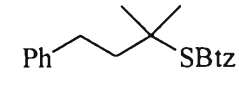
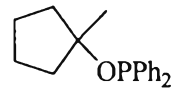
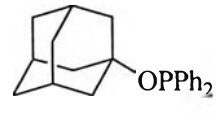
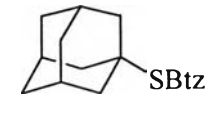
Based on the results obtained, CPQ was conceivably considered as the most proper oxidant for further investigation because it has not been addressed, commercially available reagent and cheaper than DBBQ.

2.5.2.2 Effect of Tertiary Alkyl Diphenylphosphinites

These disclosed reaction conditions were extended to investigate the condensation of various tertiary alkyl diphenylphosphinites containing various substituents into their analogous sulfides. The generality of this condensation is summarized in Table 2.4.

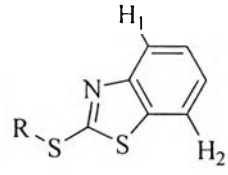
Table 2.4 Carbon-sulfur bond formation of tertiary alkyl diphenylphosphinites

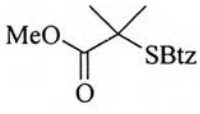
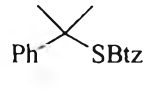
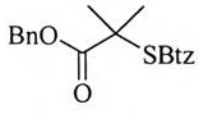
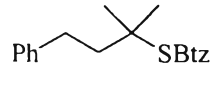
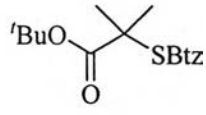
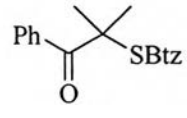
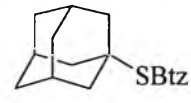


Entry	$ROPPh_2$	RBtz	% Isolated Yield
1			96
2			87
3			63
4			93
5			76
6			0
7			31
8			35
9			73

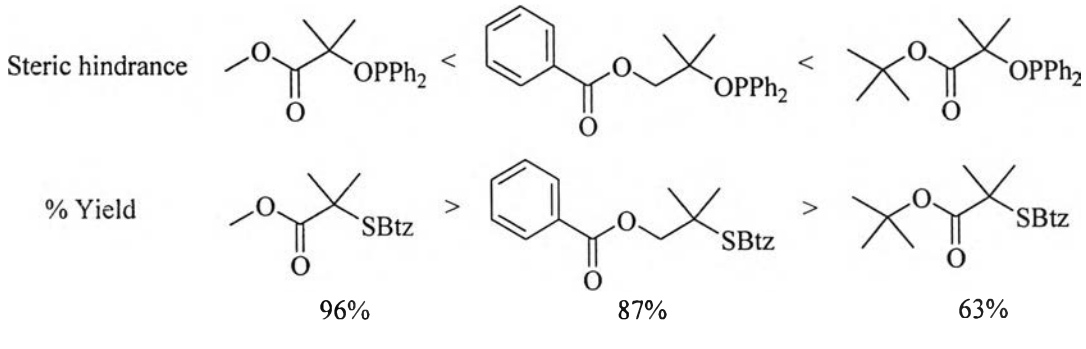
The characteristic ^{1}H-NMR spectral pattern of *S*-alkylated product displayed two aromatic protons of Btz group around δ_H 7.84-8.10 and 7.76-7.88 as summarized in Table 2.5.

Table 2.5 The characteristic ^{1}H-NMR spectral pattern of *S*-alkylated product



Sulfide	δ_H		Sulfide	δ_H	
	H_1	H_2		H_1	H_2
	7.92, d J = 8.2 Hz	7.76, d J = 7.7 Hz		7.94, d J = 8.1 Hz	7.57-7.72, m
	7.84, d J = 8.1 Hz	7.73, d J = 7.9 Hz		7.97, d J = 8.1 Hz	7.77, d J = 7.7 Hz
	7.90, d J = 7.7 Hz	7.76, d J = 7.9 Hz		7.94, d J = 8.2 Hz	7.76, d J = 7.9 Hz
	8.10, d J = 7.9 Hz	7.88, d J = 8.1 Hz		8.01, d J = 7.9 Hz	7.80, d J = 7.8 Hz

The *S*-alkylation mediated by CPQ with HSBtz and tertiary alkyl diphenylphosphinites having α-ester group at quaternary carbon was smoothly converted to the corresponding sulfides in moderate to excellent yields (entries 1-3). However, the proceeding reaction was depended on steric hindrance of substituent group. The substrate having more bulky substituent at ester group (-$CO_2{}^t$Bu) was difficultly proceeded to give a yield of the corresponding sulfide. Steric hindrance of ester groups was believed to markedly affect on the proceeding reaction.

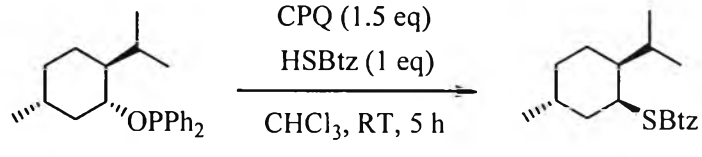


S-alkylation employing alkyl diphenylphosphinites containing ketone or phenyl groups in the presence of CPQ could be smoothly proceeded to afford the desired sulfide in moderate to high yields (entries 4-5). In contrast, non-reactive aliphatic alkyl diphenylphosphinites yielded the corresponding sulfide in poor yields (entries 7-8) except for the case of alkyl diphenylphosphinite derived from 1-adamentanol (entry 9). The poor result was also attained with the alkyl diphenylphosphinite derived from the corresponding cyanohydrin under developed conditions (entry 6). Presumably, the reducing ability of this alkyl diphenylphosphinite was weakened by the strongly electron-withdrawing property of the α-cyano group.

2.5.2.3 Stereochemistry Study

Stereochemistry study of this developed condensation was performed by using an optically active substrate, (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl diphenylphosphinite derived from (-)-menthol.

A stirred solution of the (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl diphenylphosphinite 2 eq and HSBtz 1 eq in $CHCl_3$ 0.5 mL was added camphor quinone (CPQ) 2 eq at room temperature. After 5 h, the crude product was directly purified by PTLC on silica gel (hexane/EtOAc = 95/5) to afford (1*S*, 2*S*, 5*R*)-2-(2-isopropyl-5-methylcyclohexyl-sulfanyl)-1,3-benzothiazole in 77%.



(0.5 mmol) 77%

$[\alpha]_D^{21}$ -57.5 $[\alpha]_D^{20}$ +101.8

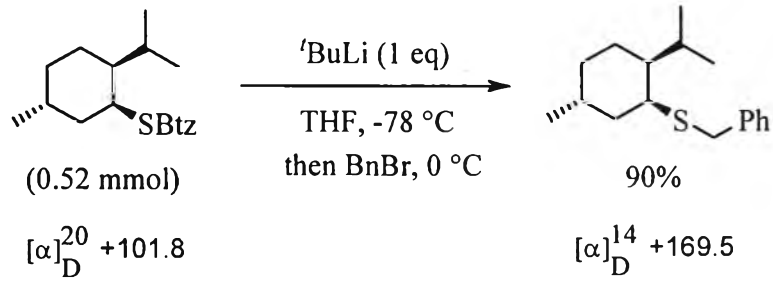
The ^{1}H-NMR spectrum of (1S, 2S, 5R)-2-(2-isopropyl-5-methylcyclohexyl-sulfanyl)-1.3-benzothiazole displayed four aromatic protons of Btz group at δ_H 7.84 (J = 7.6 Hz), 7.72 (J = 7.9 Hz) and δ_H 7.20-7.42. The broad singlet at δ_H 4.55 was assigned to one proton of CH-S. The multiplet signal at δ_H 0.84-2.29 could be assigned to eighteen protons of the alkyl groups.

A chiral (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl diphenylphosphinite ($[\alpha]_D^{21}$ -57.5 (*c* = 1.05, $CHCl_3$)) could be successfully transformed into the enantiomerically enriched (1S, 2S, 5R)-2-(2-isopropyl-5-methylcyclohexylsulfanyl)-1.3-benzothiazole ($[\alpha]_D^{20}$ +101.8 (*c* = 0.85, $CHCl_3$)) with perfectly complete inversion of configuration. In addition, the stereochemistry of the *S*-alkylated product was confirmed by HPLC using commercially available chiral column (DAICEL CHIRALCEL OD-H column).

From above results, it could clearly be indicated that the carbon-sulfur bond formation under this developed condition proceeded *via* S_N2 mechanism.

2.5.2.4 Deprotection of Benzothiazol-2-yl Group

A cleavage of benzothiazol-2-yl group (Btz) of (1S, 2S, 5R)-2-(2-isopropyl-5-methylcyclohexylsulfanyl)-1.3-benzothiazole was successfully removed by treatment with ^{t}BuLi to generate lithium thiolate. Subsequent trapping of the thiolate anion with BnBr furnished benzyl (1S, 2S, 5R)-2-isopropyl-5-methylcyclohexyl sulfide in 90% yield without epimerization of stereogenic-centers (confirmed by HPLC analysis).

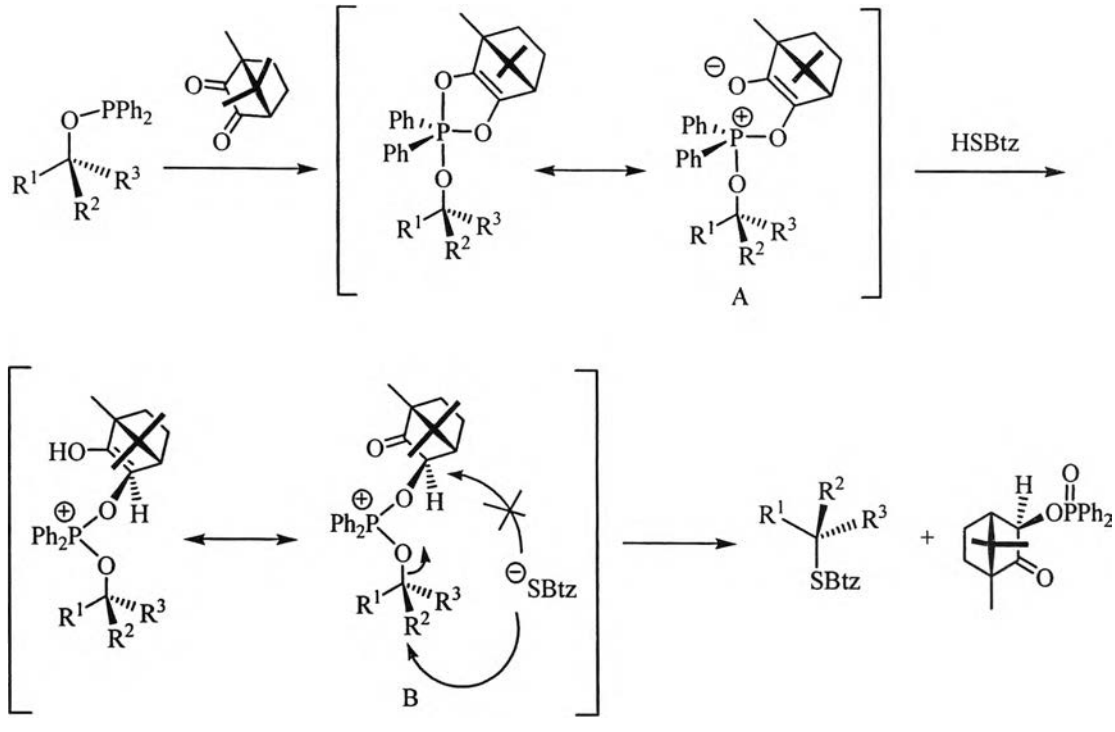


The ^{1}H-NMR spectrum of benzyl (1S, 2S, 5R)-2-isopropyl-5-methylcyclohexyl sulfide exhibited five aromatic protons at δ_H 7.15-7.45 and the multiplet at δ_H 3.55-3.77 of two protons of the benzylic group. The broad singlet at δ_H 3.00 was belonged to one proton of CH-S proton. The multiplet at δ_H 2.05-1.45 and 1.28-0.60 of eighteen protons of the alkyl groups were clearly observed.

From above results, this *S*-alkylation could be disclosed that the stereospecific synthesis of an inverted chiral tertiary thiol from a chiral tertiary alcohol *via* S_N2 displacement.

2.5.2.5 Proposed Mechanism

A proposed mechanism for carbon-sulfur bond formation from the use of the combination of alkyldiphenylphosphinite and CPQ with HSBtz is depicted below.



The first step, alkyl diphenylphosphinite initially reacted with oxo group of CPQ to form the cyclic phosphorane (**A**). Subsequently, the phosphorane deprotonated the active proton of HSBtz to produce intermediate **B**. Then, *S*-alkylation of SBtz anion to a carbon atom adjacent to oxygen atom of the alkoxy group of intermediate afforded the desired sulfide and phosphinate derivative *via* S_N2-type substitution. However, the substitution of SBtz anion at CPQ residue was not proceeded to produce undesired product because that side had more steric hindrance than the other.

According to the aforementioned results, a new protocol for carbon-sulfur bond formation was successfully achieved by utilizing tertiary alkyl diphenylphosphinites, HSBtz and CPQ as the new and efficient oxidant to promote this condensation under mild and neutral conditions. The corresponding sulfides from chiral alcohols were smoothly proceeded with inversion of configuration by S_N2 displacement. Subsequent removal of benzothiazol-2-yl group of sulfide could provide a new and convenient route to the synthesis of chiral thiols from chiral alcohols.

2.5.3 Carbon-Carbon Bond Formation

The development of new carbon-carbon bond forming reactions, one of the most fundamental chemical transformations, has been a major topic in synthetic organic chemistry, resulting now in a wide variety of such reaction. However, the conversion through the direct replacement of hydroxyl groups by carbon nucleophiles had only a few precedents, despite the obvious advantage that the reaction required no prerequisite activation of the alcohol. Mitsunobu reaction is a unique reaction of that type and could be applied to the alkylation of active methylene compounds [40]. However, there was still a serious limitation, *i.e.* the reaction towards the *C*-alkylation in satisfactory yield was not proceeded when weakly acidic nucleophile (p*K*a > 9) was employed [41].

The development for carbon-carbon bond formation by oxidation-reduction condensation using alkyl diphenylphosphinites and 1,4-benzoquinoene derivatives would thoroughly examine to solve that problem.

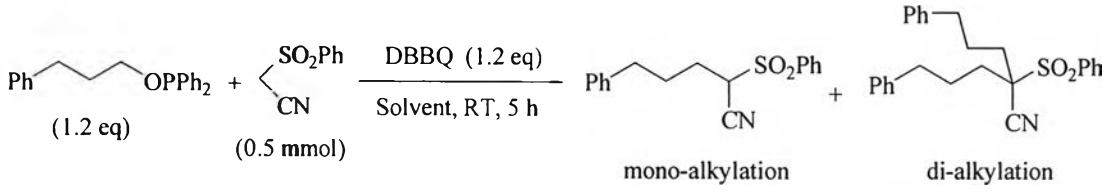
Optimum conditions for carbon-carbon bond formation from alkyl diphenylphosphinite utilizing 1,4-benzoquinone derivatives such as DBBQ, DMBQ and BQ were examined. Variable parameters studied included solvents, types of oxidants and active methylene compounds.

(Phenylsulfonyl)acetonitrile ($CNCH_2SO_2Ph$, pK_a value of 12.0 in DMSO [10]) was allowed to react with 3-phenylpropyl diphenylphosphinite (1.2 eq) in the presence of DBBQ (1.2 eq) as a chemical model to give both mono- and di-alkylated products. However, the mono-alkylated product was only focused as the desired product under this optimization condition.

2.5.3.1 Effect of Solvent

According to previous studies, $CHCl_3$ was the first medium used, that was because it could dissolve both substrate and reagent used. Other common solvents were chosen to examine whether they could replace with $CHCl_3$ in this condensation. The results are presented in Table 2.6.

Table 2.6 Effect of solvent



Entry	Solvent	%Isolated Yield		Entry	Solvent	%Isolated Yield	
		Mono-	Di-			Mono-	Di-
1	$CHCl_3$	73	<11	8	THF	74	<9
2	CH_2Cl_2	70	<13	9	^{t}BuOMe	70	<10
3	$ClCH_2CH_2Cl$	61	15	10	Pyridene	65	<5
4	Benzene	49	<22	11	DMF	35	<6
5	Toluene	61	<16	12	1,4-Dioxane	69	<14
6	CF_3Ph	55	<23	13	MeCN	61	<19
7	Et_2O	65	<18				

Only two products could be detected from this studied reaction. After separation and purification by PTLC, the identifies of these two products were performed by ^{1}H-NMR.

The ^{1}H-NMR spectrum of mono-alkylated product 5-phenyl-2-(phenylsulfonyl)pentanenitrile (Fig 2.5) displayed ten aromatic protons at δ_H 7.08-8.00. The double doublet signal at δ_H 3.90 (J = 10.2, 4.5 Hz) was ascribed for methine proton connecting with -CN. Three multiplet signals at δ_H 2.64-2.69 and δ_H 1.74-2.22 could be assigned for six protons of three methylene groups. The ^{1}H-NMR spectrum of di-alkylated product, 5-phenyl-2-(3-phenylpropyl)-2-(phenylsulfonyl)pentanenitrile (Fig 2.6) displayed fifteen aromatic protons around δ_H 7.09-7.88. The multiplet signal at δ_H 2.57-2.63 was assigned for four protons of two methylene groups connecting with phenyl group. The multiplet signal at δ_H 1.77-2.00 was ascribed for eight protons of four methylene groups.

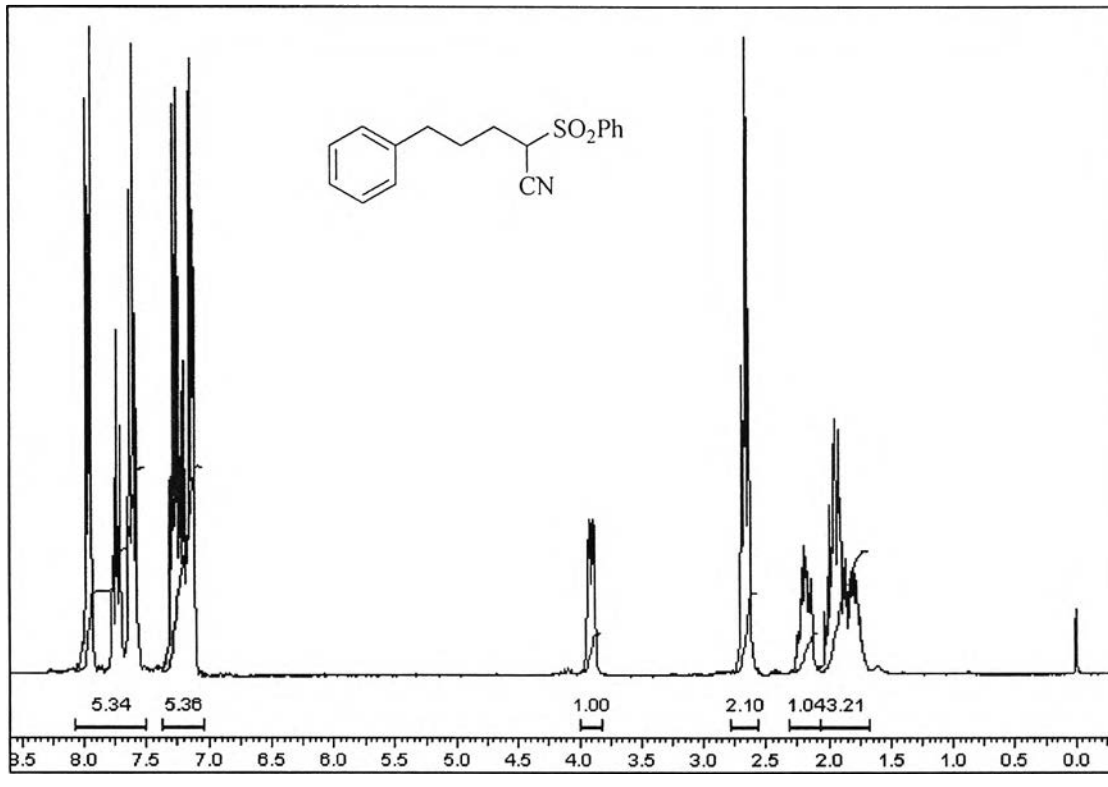


Figure 2.5 ^{1}H-NMR spectrum of mono-alkylated product

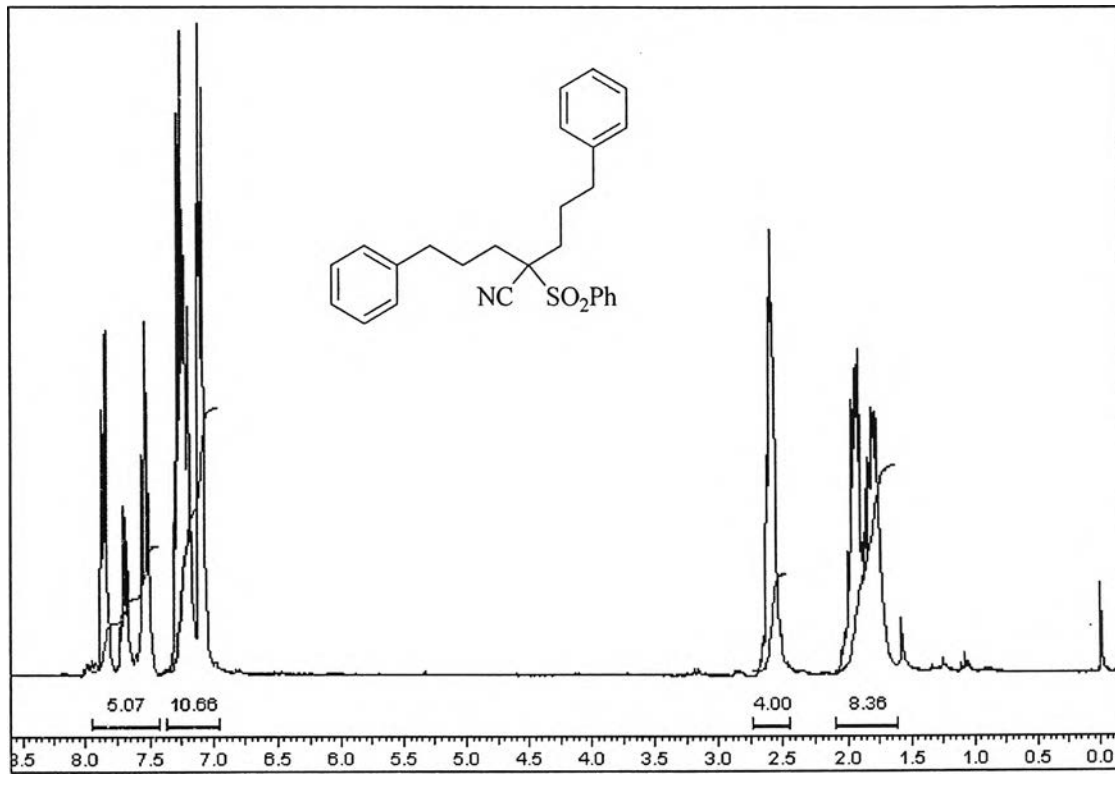
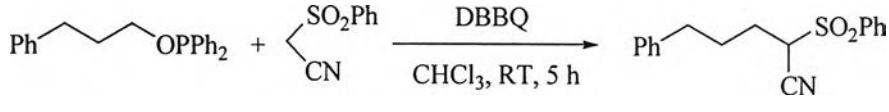


Figure 2.6 ^{1}H-NMR spectrum of di-alkylated product

It was noticed that when $CHCl_3$ was used as solvent, the high yield of mono-alkylated product was observed (entry 1). Similarly, performing with CH_2Cl_2, THF, ^tBuOMe and 1,4-dioxane as a solvent instead of $CHCl_3$ the reaction was still smoothly provided the mono-alkylated product in high yields (entries 2, 8-9 and 12). On the other hand, %yield of desired mono-alkylated product was lessen around 49-65% when $ClCH_2CH_2Cl$, benzene, toluene, CF_3Ph, Et_2O, pyridine and MeCN were used (entries 3, 4-7, 10 and 13). Polar aprotic solvent as DMF also produced the mono-alkylated product in low yield (entry 11).

2.5.3.2 Effect of Mole Ratio

According to the literature reviews, the amount of substrate and reagent played an important factor towards carbon-carbon bond formation. Thus, the screening for proper amount of alkyl diphenylphosphinite, DBBQ and (phenylsulfonyl) acetonitrile was further studied.

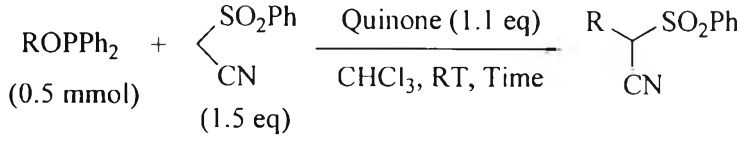


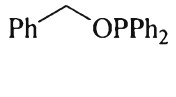
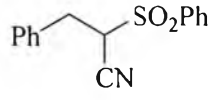
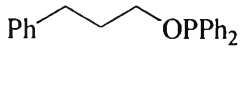
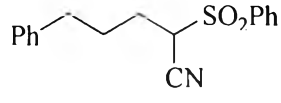
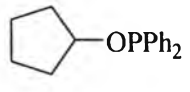
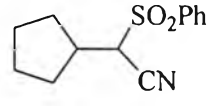
After 12 h, the substrate reacted with DBBQ 1.1 eq and (phenylsulfonyl)acetonitrile 1.5 eq (based on alkyl diphenylphosphinites) furnished the desired product in 84% yield. On the other hand, the desired product was decreasingly detected in 44% yield when alkyl diphenylphosphinites and DBBQ 1.5 eq each (based on active methylene compound) were used. Based on the results derived from two conditions studied, the use of alkyl diphenylphosphinites 1 eq, DBBQ 1.1 eq and (phenylsulfonyl)acetonitrile 1.5 eq was a suitable ratio to be utilized for further examination.

2.5.3.3 Effect of 1,4-Benzoquinone Derivatives

DBBQ could be displayed the efficient oxidant according to the literature reviews. In this experiment, DBBQ was also further examined to confirm its capability for carbon-carbon bond formation with (phenylsulfonyl)acetonitrile and to compare its efficiency with DMBQ and BQ. The results are demonstrated in Table 2.7.

Table 2.7 Effect of 1,4-benzoquinone derivatives



Entry	$ROPPh_2$	Mono-alkylated product	Quinone	Time (h)	% Isolated Yield
1			DBBQ	5	77
2			DMBQ	1	69
3			BQ	1	<10
4			DBBQ		84
5			DMBQ	12	43
6			BQ		trace
7			DBBQ		69
8			DMBQ	3	trace
9			BQ		0

The ^{1}H-NMR spectrum of 3-phenyl-2-(phenylsulfonyl)propanenitrile (Fig 2.7) displayed ten aromatic protons around δ_H 7.34-8.04. The double doublet signal at δ_H 4.10 (J = 10.8, 5.4 Hz) was ascribed for methine proton connecting with -CN. The double doublet and triplet signals at δ_H 3.58 (J = 2.7, 13.5 Hz) and δ_H 3.08 (J = 2.7, 13.5 Hz) could be assigned for two protons of benzyl group.

The ^{1}H-NMR spectrum of 2-cyclopentyl-2-(phenylsulfonyl)acetonitrile (Fig 2.8) displayed five aromatic protons around δ_H 7.61-8.04. The doublet signal at δ_H 4.05 (J = 5.4 Hz) was ascribed for methine proton connecting with -CN. Three multiplet signals around δ_H 2.63-2.71, 2.63-2.71 and 1.45-1.77 could be assigned for nine protons of cyclopentyl group.

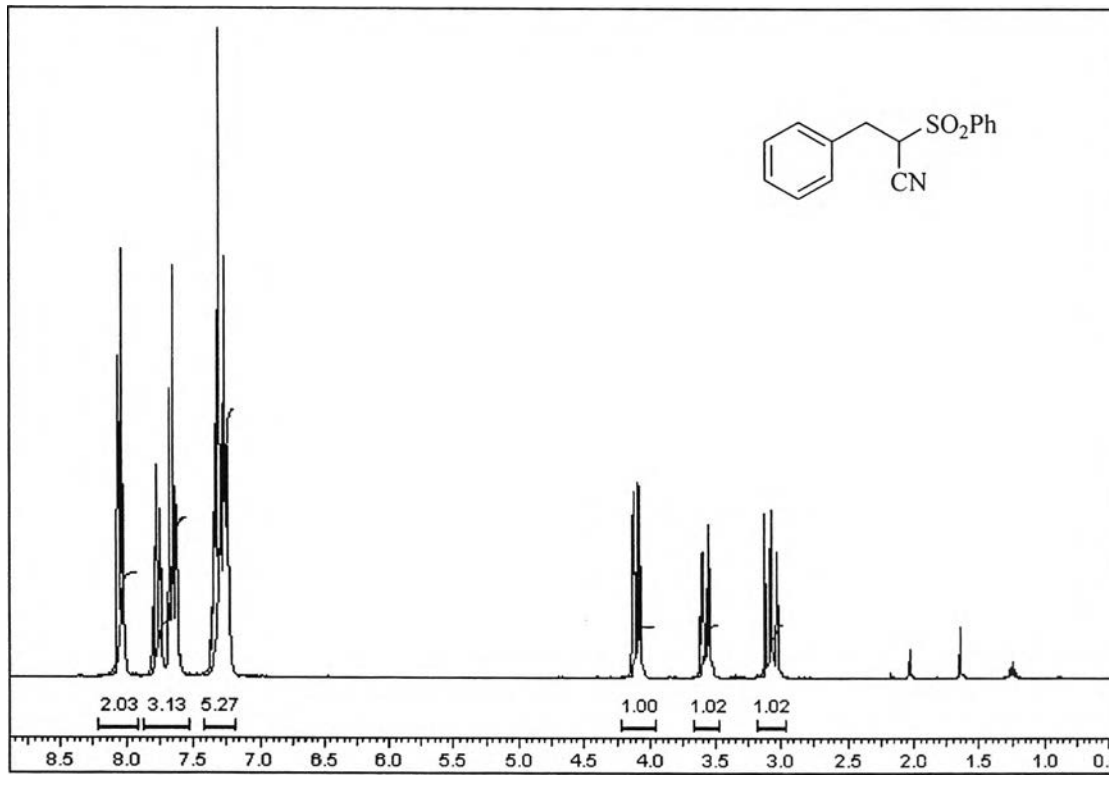


Figure 2.7 ^{1}H-NMR spectrum of 3-phenyl-2-(phenylsulfonyl)propanenitrile

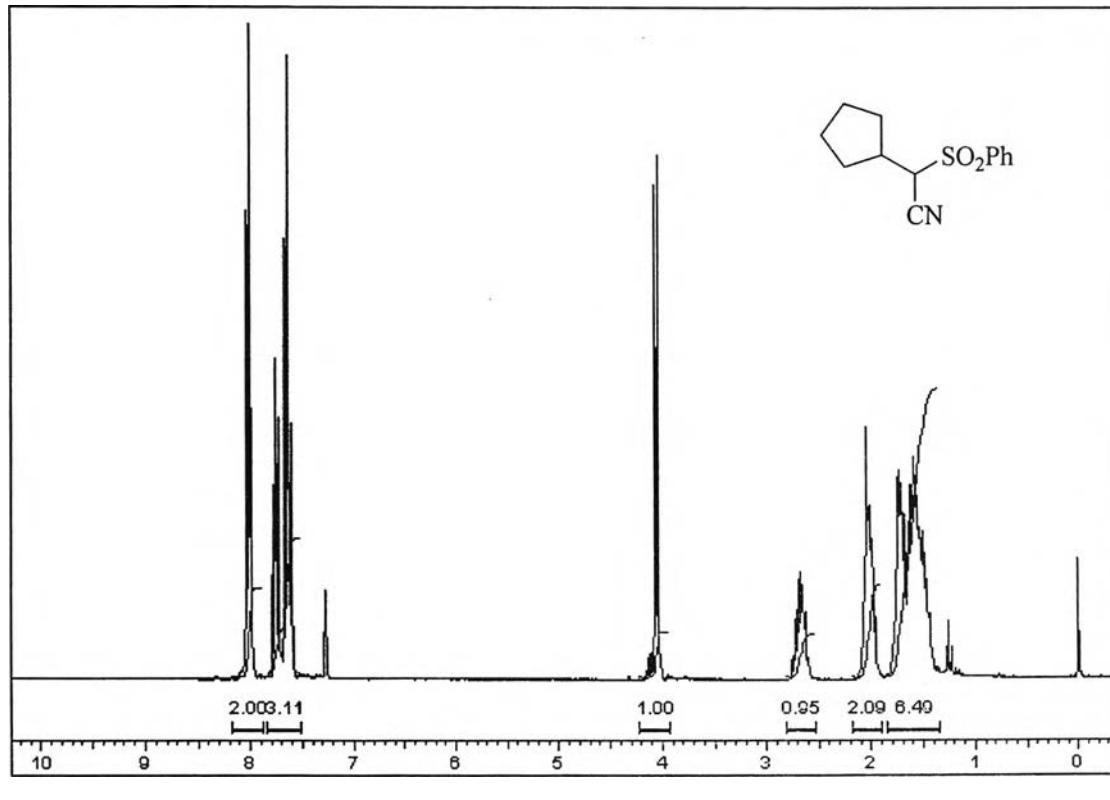


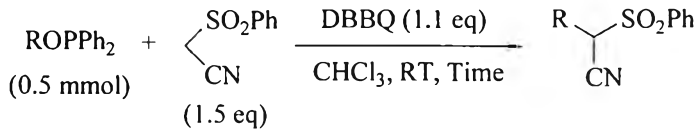
Figure 2.8 ^{1}H-NMR spectrum of 2-cyclopentyl-2-(phenylsulfonyl)acetonitrile

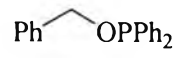
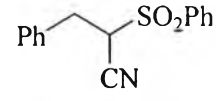
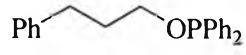
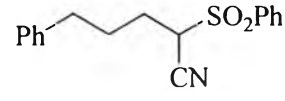
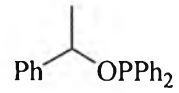
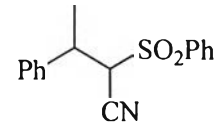
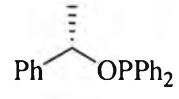
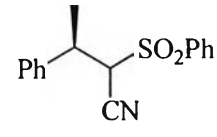
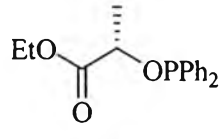
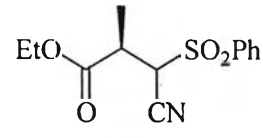
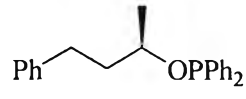
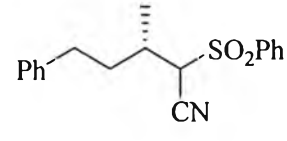
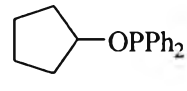
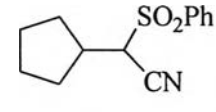
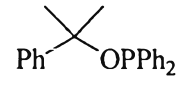
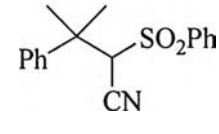
The DBBQ-mediated condensation of primary alkyl diphenylphosphinites with (phenylsulfonyl)acetonitrile could be proceeded smoothly at room temperature to form the corresponding mono-alkylated products in high yields (entries 1 and 4). On the other hand, the yield of the desired products was strongly decreased when the condensation was tried with DMBQ and BQ (entries 2-3 and 5-6). The reaction of cyclic diphenylphosphinites with DBBQ could be taken place producing the mono-alkylated product in good yields (entry 7), whereas that product was obtained in poor yield or not detected in the presence of DMBQ and BQ, respectively. It was therefore confirmed that DBBQ still displayed as an efficient oxidant for *C*-alkylation more than DMBQ and BQ.

2.5.3.4 *C*-Alkylation of (Phenylsulfonyl)acetonitrile

Carbon-carbon bond formation of various alkyl diphenylphosphinites derived from primary, secondary and tertiary alcohols with (phenylsulfonyl)acetonitrile under developed conditions was further examined. The results are shown in Table 2.8.

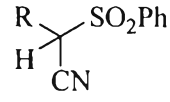
Table 2.8 Effect of various alkyl diphenylphosphinites

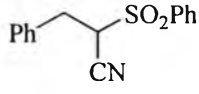
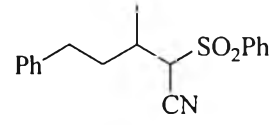
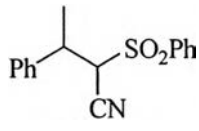
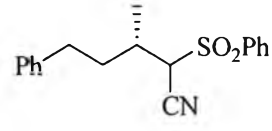
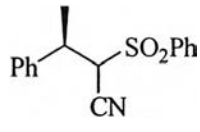
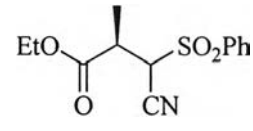
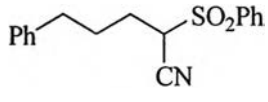
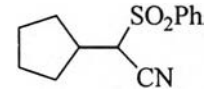


Entry	$ROPPh_2$	Mono-alkylated product	Time (h)	% Isolated Yield
1			5	77
2			12	84
3			5	38
4			5	41
5			5	49
6			5	56
7			3	69
8			22	0

The ^{1}H-NMR spectral pattern of the compounds in this series, generally exhibited signal with 1H integration at δ_H 3.79-4.60 which could be assigned for the methine proton connecting with -CN and -SO_2Ph groups. The ^{1}H-NMR spectral assignment for mono-alkylated products derived from alkyl diphenylphosphinite, (phenylsulfonyl)acetonitrile and DBBQ are tabulated in Table 2.9.

Table 2.9 The characteristic ^{1}H-NMR spectral pattern of *C*-alkylated product



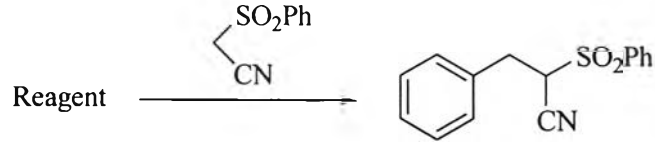
Nitrile	δ_H	Nitrile	δ_H
	4.10 dd, J = 10.8, 5.4 Hz		3.79-3.91 m
	4.06 q, J = 8.1		3.79-3.90 m
	4.05 q, J = 8.2 Hz		4.60 d, J = 5.4 Hz
	3.90 dd, J = 10.2, 4.5 Hz		4.05 d, J = 5.4 Hz

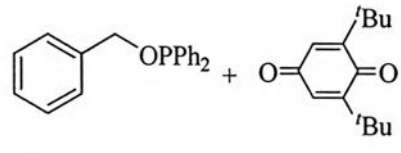
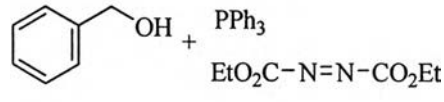
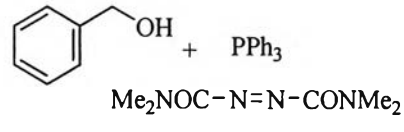
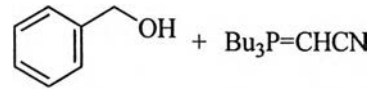
Primary alkyl diphenylphosphinites could be smoothly converted to mono-alkylated products in high yields under developed conditions (entries 1-2). However, the condensation of secondary alkyl diphenylphosphinites containing alkyl, benzylic cyclic and ester group provided the corresponding products in moderate yields (entries 3-4). On the other hand, secondary alkyl diphenylphosphinites containing alkyl, cyclic and ester groups could furnish the corresponding mono-alkylated products in higher yield than above results (entries 5-7). This was probably because S_N1 took place concomitantly influenced by benzylic effect to generate undesired product. Moreover, the corresponding mono-alkylated product was not detected when tertiary alkyl diphenylphosphinite was examined (entry 8) plausibly owing to steric hindrance of alkyl diphenylphosphinite.

From aforementioned results, primary alkyl diphenylphosphinites were found to be more reactive substrate than secondary and tertiary alkyl diphenylphosphinites, respectively for carbon-carbon bond formation under developed conditions.

This developed combination of alkyl diphenylphosphinite and DBBQ disclosed the highest efficient method to afford *C*-alkylation product among those declared in chemical literature [10]. The comparative examples between developed and common reagents are shown in Table 2.10.

Table 2.10 The comparative data on the *C*-alkylation of (phenylsulfonyl)acetonitrile



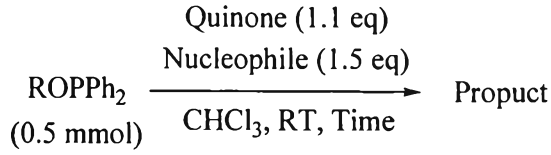
Entry	Reagent	Time (h)	Temp (°C)	% Yield
1		5	RT	77
2		24	RT	32
3		24	RT	59
4		24	RT	75
5			100	77

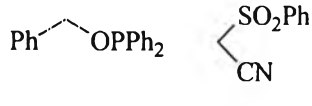
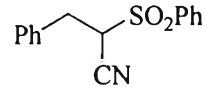
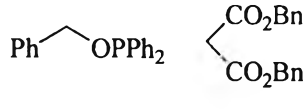
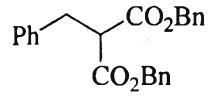
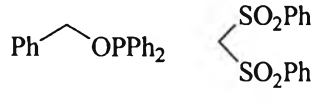
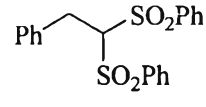
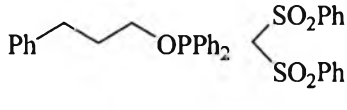
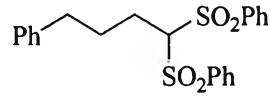
The developed reagent (alkyl diphenylphosphinite/DBBQ) could be smoothly proceeded to give 3-phenyl-2-(phenylsulfonyl)propanenitrile in the same or better yields within short reaction time under mild conditions compared with the reported reagents (entries 1 *vs* 2-5). This result could thus be addressed as a new and efficient method for carbon-carbon bond formation.

2.5.3.5 Effect of Active Methylene Compounds

Various active methylene compounds such as dibenzyl malonate ($CH_2(CO_2Bn)_2$) and *bis*(phenylsulfonyl)methane ($CH_2(SO_2Ph)_2$) were chosen to examine the *C*-alkylation by comparison with (phenylsulfonyl)acetonitrile under the same conditions. The results are shown in Table 2.11.

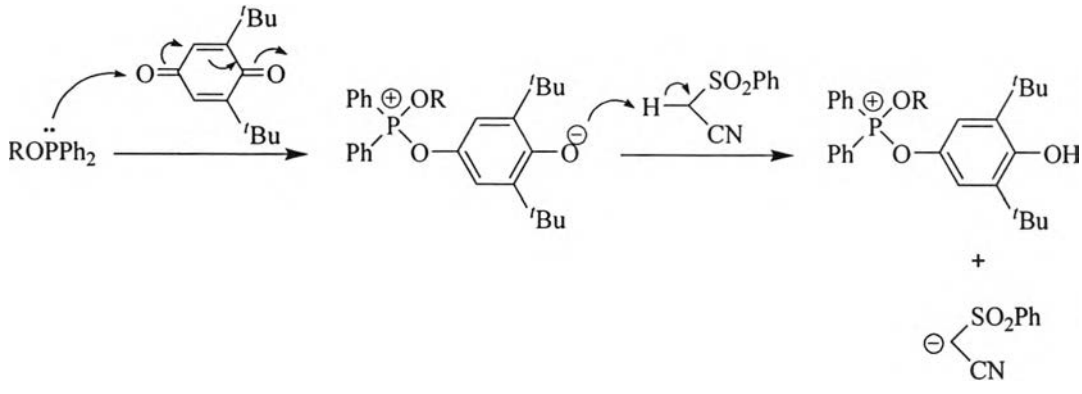
Table 2.11 Effect of various active methylene compounds

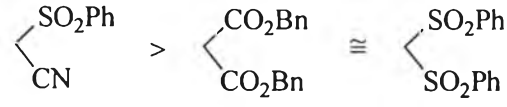


Entry	$ROPPh_2$	Nucleophile	Mono-alkylated product	Quinone	Time (h)	% Isolated Yield
1				DBBQ	5	77
2				DMBQ	1	69
3				BQ	1	<10
4				DBBQ		59
5				DMBQ	2	7
6				BQ		0
7				DBBQ		50
8				DMBQ	2	34
9				BQ		17
10				DBBQ		58
11				DMBQ	3	17
12				BQ		5

It was found that the reactions could well proceeded in the presence of DBBQ affording the corresponding mono-alkylated product in moderate to high yields (entries 1, 4, 7 and 10). On the other hand, the yields of the desired products were significantly lower in the presence of DMBQ and BQ (entries 2-3, 5-6,7-9 and 11-12).

This result clearly revealed that active methylene compounds having strong electron-withdrawing group (more acidic proton) could be easily deprotonated by phenoxide anion adduct derived from alkyl diphenylphosphinite and DBBQ as shown below.



Reactivity 

Thus, the condensation of *C*-alkylation could be accomplishly performed under developed conditions depended on a type of electron-withdrawing substituent on methylene carbon, for example -CN > $-SO_2Ph \cong -CO_2Bn$.

The illustration of ^{1}H-NMR spectrum of mono-alkylated product, dibenzyl-2-benzylmalonate was presented in Fig 2.9. Fifteen aromatic protons could be detected at δ_H 7.13-7.32. The singlet signal at δ_H 5.09 was ascribed for four protons of two methylene group. The triplet signals at δ_H 3.77 (J = 8.1 Hz) could be assigned for a methine proton connecting with ester group. The methylene protons of benzyl group were observed as doublet at δ_H 3.25 (J = 8.1 Hz).

The ^{1}H-NMR spectrum of benzyl-*bis*(phenylsulfonyl)methane (Fig 2.10) displayed the multiplet signal around δ_H 7.18-7.87 as fifteen aromatic protons. The triplet signals at δ_H 4.76 (J = 5.4 Hz) could be ascribed for a methine proton connecting with phenylsulfonyl group. The methylene protons of benzyl group were visualized as doublet at δ_H 3.53 (J = 5.4 Hz).

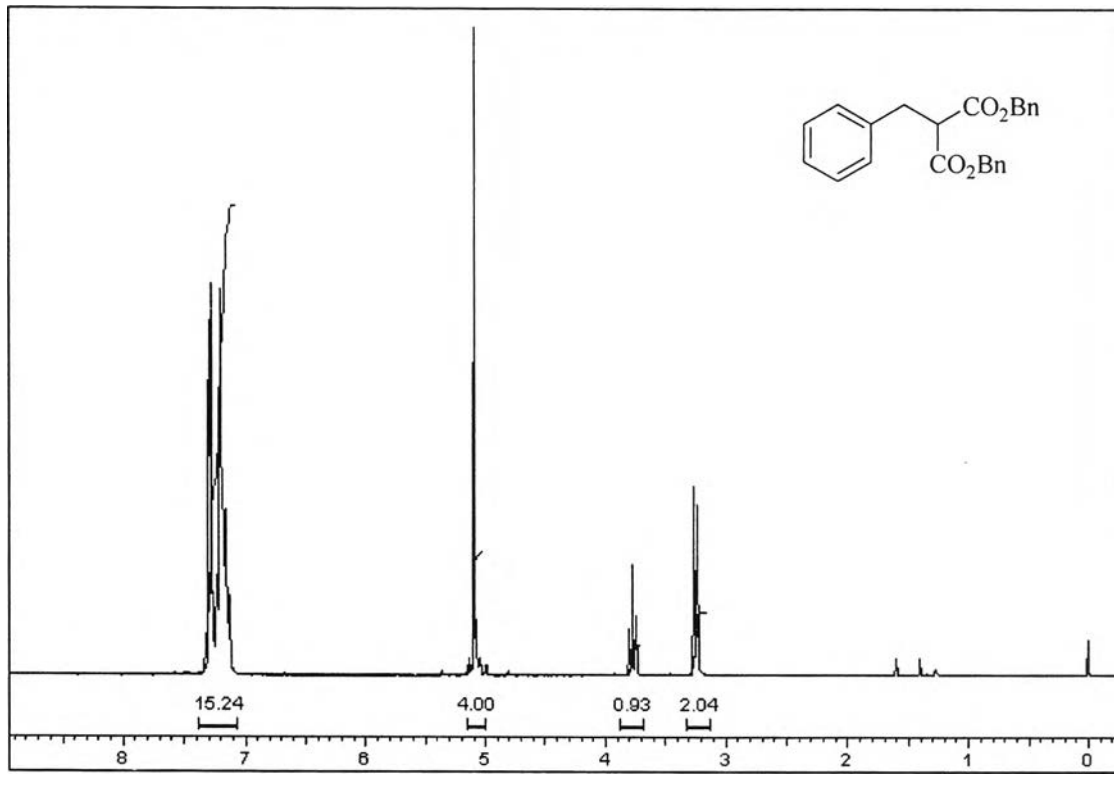


Figure 2.9 ^{1}H-NMR spectrum of dibenzyl-2-benzylmalonate

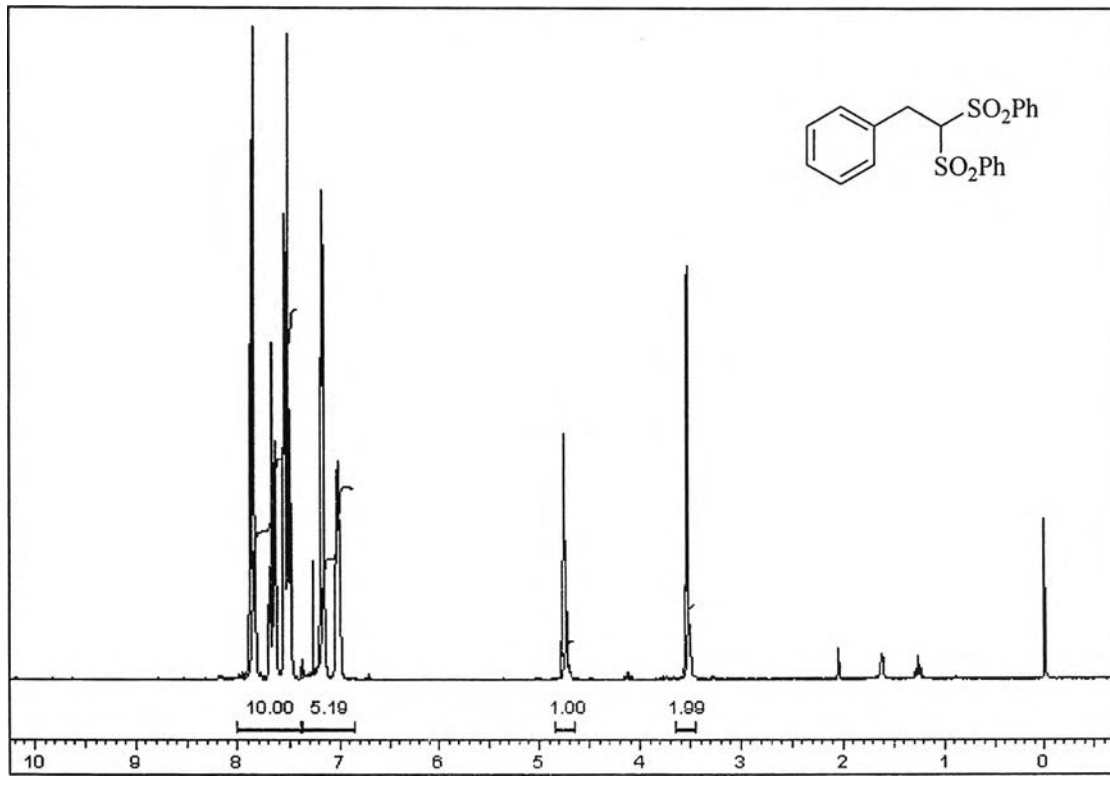
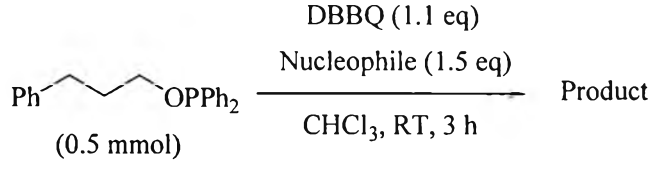
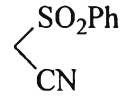
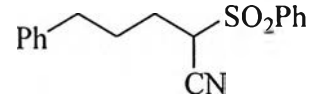
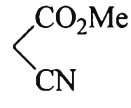
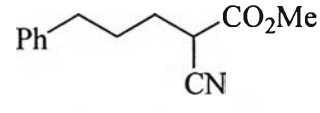
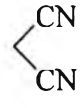
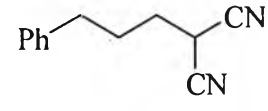
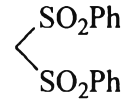
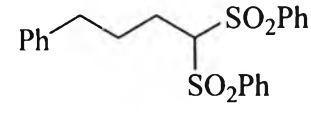
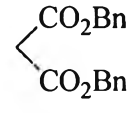
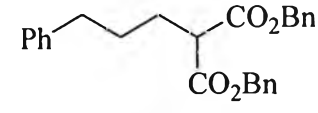
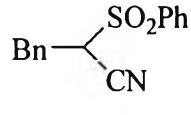
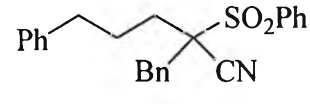
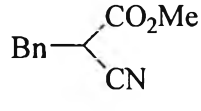
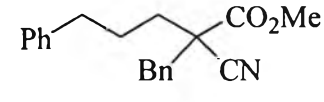
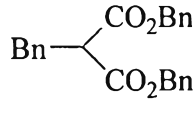
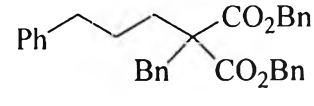


Figure 2.10 ^{1}H-NMR spectrum of benzyl-*bis*(phenylsulfonyl)methane

The effect of substituent on active methylene compounds was also examined to confirm above postulation by using selected eight active methylene compounds. The expansion of *C*-alkylation with eight active methylene compounds under developed conditions is shown in Table 2.12.

Table 2.12 *C*-Alkylation of active methylene compound



Entry	Nucleophile	Mono-alkylated product	% Isolated Yield
1			84
2			62
3			14
4			58
5			62
6			quant
7			74
8			32

(Phenylsulfonyl)acetonitrile as more reactive nucleophile could be converted to the desired product in 84% yield (entry 1). However, the yield of the corresponding mono-alkylated product was decreasingly observed from 84% to 62% yield when sulfonyl group was replaced with ester group (entry 2). Malononitrile (two -CN) as mostly reactive nucleophile from above postulation was next examined. Surprisingly, the corresponding mono-alkylated product was obtained in low yield (entry 3). This was considered that the proceeding condensation was difficultly stopped at mono-alkylated product because mono-alkylated product remained one acidic proton that could be deprotonated to generate the di-alkylated or undesired products. On the other hand, *bis*(phenylsulfonyl)methane (two -SO_2Ph) and dibenzyl malonate (two -CO_2Bn) could be converted to the corresponding mono-alkylated products in good yields (entries 4-5).

From above results, it was postulated that the yield of the desired mono-alkylated products under developed conditions was not achieved in satisfactory yield because the side reaction would be concomitantly occurred to give the di-alkylated product. This postulation was confirmed by the use of protected active methylene compound containing only one acidic proton. Three selected active methylene compounds from entries 1, 2 and 5 were protected with benzyl group at methylene carbon.

The comparison of *C*-alkylation between (phenylsulfonyl)acetonitrile and protected (phenylsulfonyl)acetonitrile (entries 1 *vs* 6) displayed that the yield of the corresponding mono-alkylated product was increased from 84% to quantitative yields (entry 6). Moreover, di-alkylated product was not detected in the case of protected active methylene compound. The same result was obtained when protected methyl cyanoacetate was used as nucleophile under the same conditions (entry 7). However, the protected dibenzyl malonate did not provide the better yield of the corresponding product (entry 8) compared with entry 5. It may be because of steric hindrance of intermediate being disturbed the proceeding of *C*-alkylation.

All above results, it could be clearly found that the yield of the corresponding mono-alkylated product depended on substituent at methylene carbon. If active methylene compound contained strongly electron-withdrawing group, the desired product was obtained in moderate to high yields except for the case of malononitrile.

A selected example of ^{1}H-NMR spectrum of methyl-2-cyano-5-phenylpentanoate was displayed in Fig 2.11. Five aromatic protons could be ascribed around δ_H 7.18-7.32. The singlet signal at δ_H 3.79 was assigned as three protons of methoxy group. The methine proton connecting with -CN group was visualized at δ_H 3.50 (J = 5.4 Hz). The triplet and multiplet signals at δ_H 3.16 (J = 13.5 Hz) and around δ_H 1.41-1.98 could be ascribed for six protons of three methylene groups.

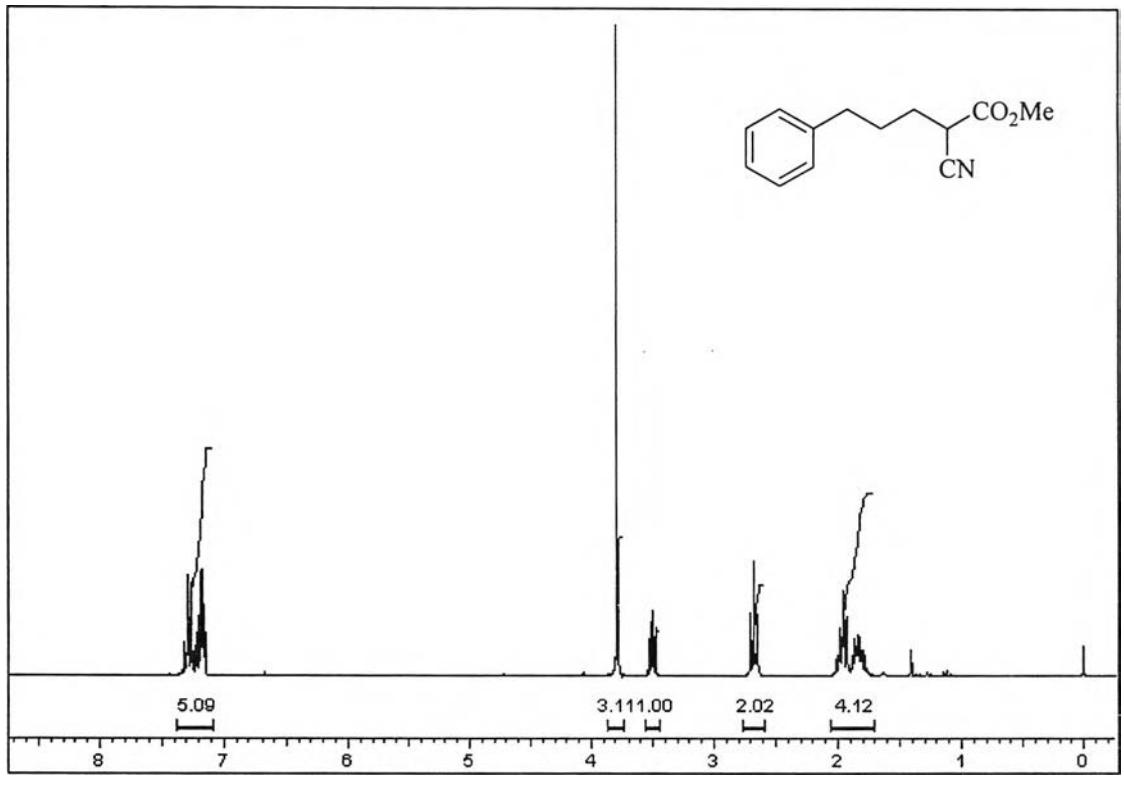


Figure 2.11 ^{1}H-NMR spectrum of methyl-2-cyano-5-phenylpentanoate

The ^{1}H-NMR spectrum of methyl-2-benzyl-2-cyano-5-phenylpentanoate (Fig 2.12) displayed ten aromatic protons around δ_H 7.16-7.29. The singlet signal at δ_H 3.63 was assigned as three protons of methoxy group. The methylene protons of benzyl group were visualized as two doublet signals at δ_H 3.16 (J = 13.5 Hz) and 3.01 (d, J = 13.5 Hz). The triplet and multiplet signals at δ_H 3.16 (J = 8.1 Hz) and around δ_H 1.54-2.06 were assigned for six protons of three methylene groups.

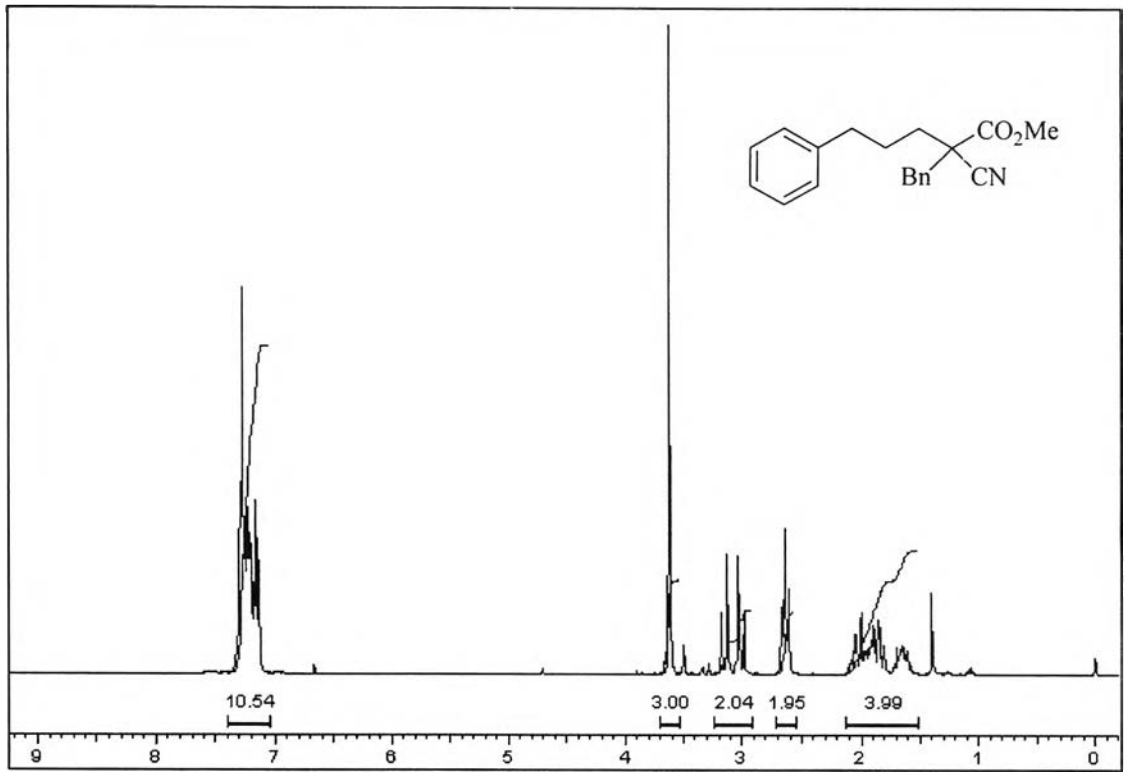
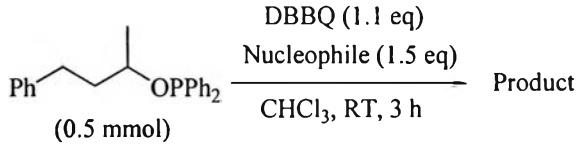
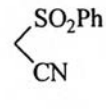
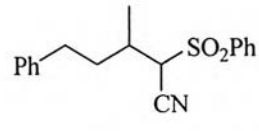
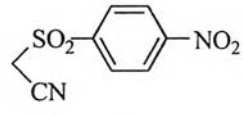
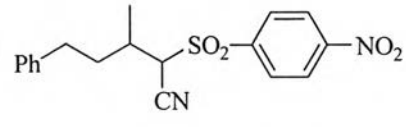
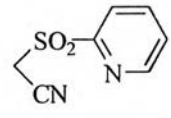
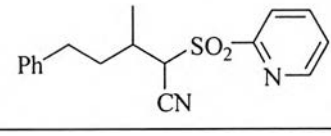


Figure 2.12 ^{1}H-NMR spectrum of methyl-2-benzyl-2-cyano-5-phenylpentanoate

In addition, the effect of substituent at phenyl group of (phenylsulfonyl) acetonitrile with the combination of DBBQ and alkyl diphenylphosphinites under developed conditions was further examined. The results are shown in Table 2.13.

Table 2.13 Effect of substituent at sulfonyl group of (phenylsulfonyl)acetonitrile



Entry	Nucleophile	Mono-alkylated product	% Isolated Yield
1			84
2			31
3			62

The mono-alkylated product from *C*-alkylation of (phenylsulfonyl)acetonitrile containing a nitro substituent at 4-position of a phenyl ring (a more reactive nucleophile than (phenylsulfonyl)acetonitrile) was obtained in low yield (entry 2). This was postulated that two *C*-alkylations were easily occurred to yield di-alkylation as major reaction. Furthermore, the mono-alkylated product was observed in moderate yield when phenyl group on (phenylsulfonyl)acetonitrile was replaced with pyridinyl group. This may be because the nitrogen in pyridine ring could deprotonated the active methylene compound and eventually end up with the undesired alkylated product.

The ^{1}H-NMR spectrum of 3-methyl-2-(4-nitrophenylsulfonyl)-5-phenyl-pentanenitrile (Fig 2.13) exhibited four aromatic protons of 4-nitrophenylsulfonyl group around δ_H 8.15-8.45 and five aromatic protons around δ_H 7.17-7.34. The doublet signal of methine proton connecting with -CN group was detected at δ_H 3.86 (J = 2.7 Hz). Two multiplet signals at δ_H 2.55-2.84 and δ_H 1.78-1.87 were ascribed for five protons of one methine and two methylene groups connecting with phenyl group and -CH_2Ph, respectively. The methyl group was visualized at δ_H 1.36 (J = 5.4 Hz).

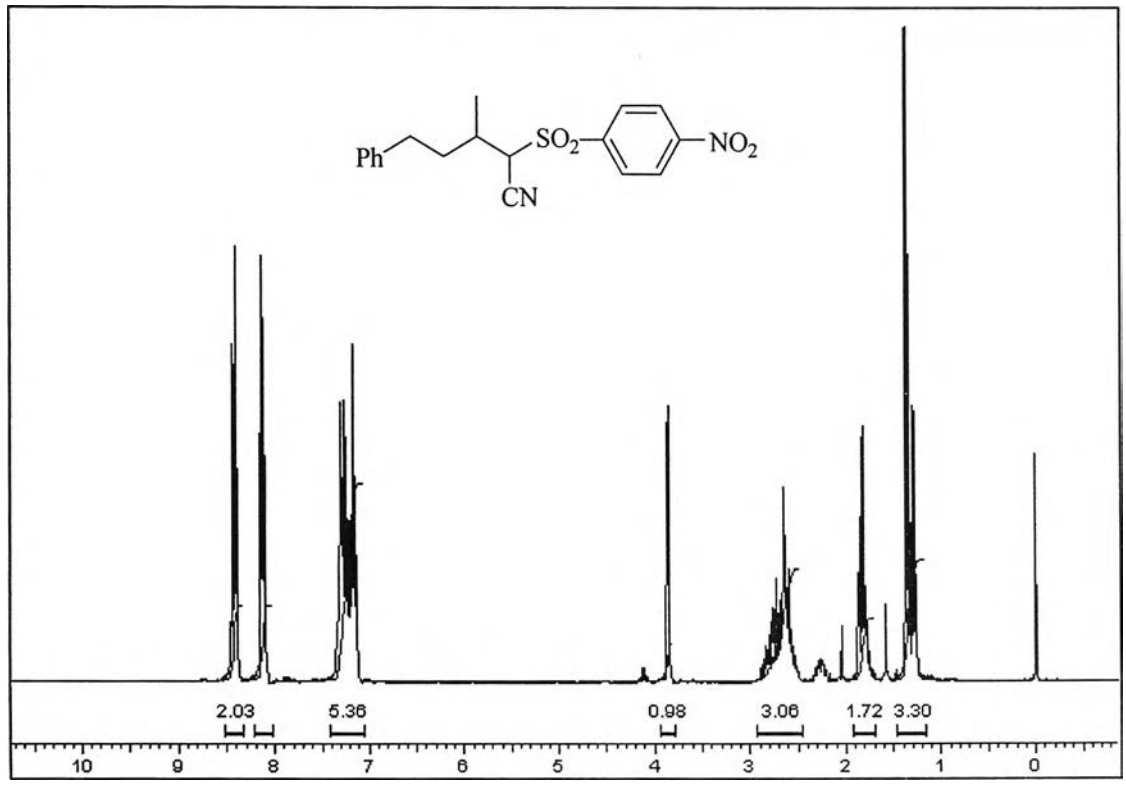
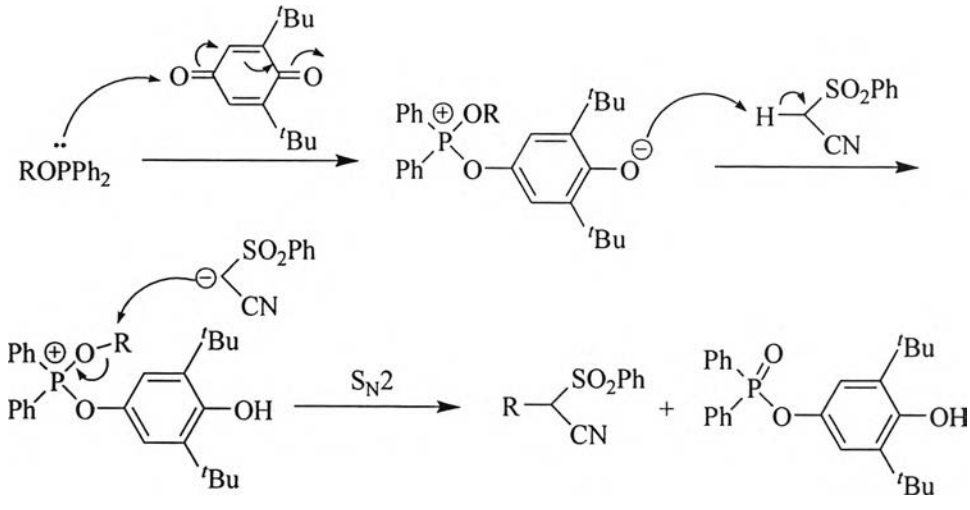


Figure 2.13 ^{1}H-NMR spectrum of 3-methyl-2-(4-nitrophenylsulfonyl)-5-phenylpentanenitrile

2.5.3.6 Proposed Mechanism

A proposed mechanism of carbon-carbon bond formation from the combination of alkyldiphenylphosphinite and DBBQ by oxidation-reduction condensation using (phenylsulfonyl)acetonitrile is shown below.



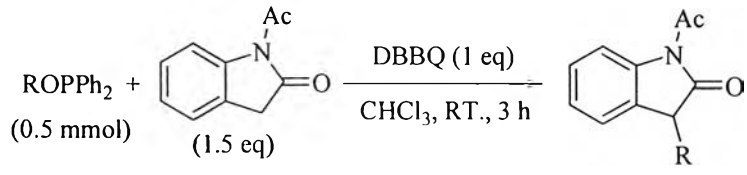
The first step, alkyl diphenylphosphinite could initially be reacted regioselectively with less hindered oxo group of DBBQ to form phenoxide adduct surrounded by two tertiary butyl groups. Subsequently, the acidic proton of (phenylsulfonyl)acetonitrile was deprotonated by adduct to generate the phosphonium salt intermediate. Attack of nucleophile anion to the intermediate was converted to the mono-alkylated product and diphenylphosphiric acid 4-hydroxy-3,5-di-*tert*-butyl-4-hydroxyphenyl ester.

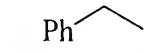
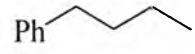
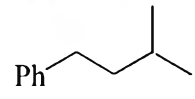
This developed method was disclosed as a new method for carbon-carbon bond formation of alkyl diphenylphosphinites and DBBQ using various active methylene compounds in good yields under mild and neutral conditions.

2.5.3.7 Carbon-Carbon Bond Formation of Oxindole

This developed method for carbon-carbon bond formation by oxidation-reduction condensation was further applied to another nucleophile such as oxindole. Oxindole ring is a prominent structural motif found in numerous natural products and pharmaceutically active compounds [42]. Moreover, many oxindole derivatives were used as starting material for the preparation of bioactive compounds in total synthesis [41]. The screening results of *C*-alkylation by using the combination of alkyl diphenylphosphinites and DBBQ with oxindole are shown in Table 2.14.

Table 2.14 *C*-Alkylation of *N*-acetyloxindole



Entry	R	% Isolated Yield
1		31
2		<39
3		19

The mono-alkylated product of *N*-acetyloxindole was not observed in satisfactory yield with DBBQ (entries 1-3). It was considered that the developed conditions were not suitable to apply for *C*-Alkylation of *N*-acetyloxindole. However, this result could confirm the observation as presented in Table 2.7 that primary alkyl diphenylphosphinites were more reactive than secondary alkyl diphenylphosphinites for carbon-carbon bond formation under developed condition.

A chosen example of the ^{1}H-NMR spectrum of *C*-alkylated product of *N*-acetyloxidiole, 1-acetyl-3-benzylindolin-2-one was displayed in Fig 2.14. Nine aromatic protons could be ascribed at δ_H 8.12-8.15 (doublet, J = 8.1 Hz), 7.22-7.24 (multiplet), 7.08-7.11 (multiplet) and 6.86-6.88 (multiplet). Three double doublet signals at δ_H 3.90 (J = 8.1, 5.4 Hz), 3.46 (J = 13.5, 5.4 Hz) and 3.05 (J = 13.5, 8.1 Hz) were attributed to three protons of methylene and methine groups, respectively. Three protons of methyl group connecting with a carbonyl group were visualized at δ_H 2.62 as a singlet signal.

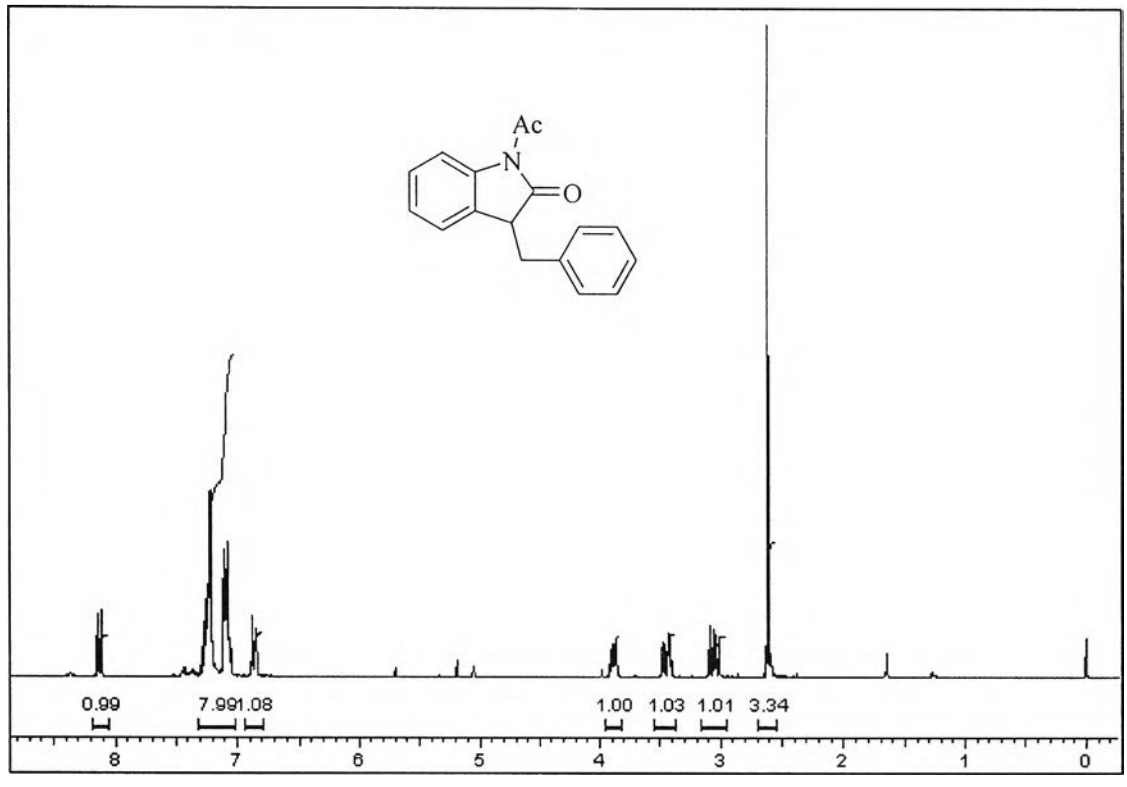
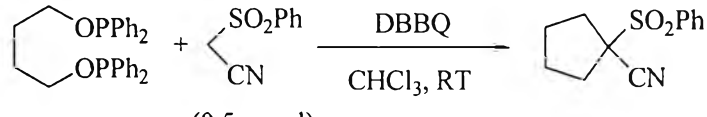


Figure 2.14 ^{1}H-NMR spectrum of 1-acetyl-3-benzylindolin-2-one

2.5.3.8 Cyclization of Active Methylene Compound

In addition, the developed carbon-carbon bond formation was also applied for double *C*-alkylation of (phenylsulfonyl)acetonitrile leading to cyclic compound. The results of cyclization under developed conditions are shown in Table 2.15.

Table 2.15 Construction of cyclic carbon-frameworks



Entry	$ROPPh_2$ (eq)	DBBQ (eq)	$CHCl_3$ (M)	Time (h)	% Yield
1	1.2	1.2	0.5	43	18
2	1.2	1.2	0.05	43	18
3	2.2	2.2	0.5	46	11

%Yield of cyclized product was still obtained in low yield even with long reaction time (entry 1). The same results were obtained when the reactions were conducted under highly concentrated condition or excess of di-phosphinite and DBBQ (entries 2-3). This may be due to the steric congestion in the di-phosphinite precursors thus the reaction was not proceeded to give the desired cyclic compounds in high yield under developed conditions. Suitable conditions for the ring closure may require high or reflux temperatures.

2.5.4 Glycosylation Using Phosphorus Donor

With the stimulant biological background, the glycosylation method, which is a crucial synthetic organic methodology to attach sugar to the other sugar moieties or other molecules (aglycon), is again becoming more and more important. Since the major historical advance of the Koenings-Knorr method presented in 1901, considerable attention has been directed toward the efficiency of the glycosylation method. Therefore, many organic chemists have focused on the high chemical yield and high stereoselectivity of this reaction.

The development of efficient and stereocontrolled glycosylation reactions is becoming of crucial importance owing to the increasingly recognized significance of saccharide components of biomolecules containing the glycosidic linkage in the biological processes. Despite many advances in this area [44], however, there still remains a need for appreciable developments in terms of efficacy, generality and stereocontrol. Considering that the leaving group of glycosyl donors is one of the most critical factors responsible for the selectivity and yield of glycosylation reaction.

Several glycosyl donors possessing a phosphorus atom in the leaving group at the anomeric center have also been investigated [45]. Since phosphorus compounds can be easily modified by several kinds of other atoms, a wide variety of leaving groups with different properties can be designed.

From carbon-sulfur and carbon-carbon bond formations study, it was found that alkoxydiphenylphosphonium salts, generated from alkyl diphenylphosphinite and DBBQ were found to react with several nucleophiles such as HSBtz or active methylene compounds to give the corresponding products in high yields. In order to expand the scope of this condensation, the application of the above concept to glycosylation reaction was considered. Thus, a stereoselective glycosylation of

phosphorus donor as glycosyl diphenylphosphinite with nucleophile under developed conditions was tried to investigate in this research.

2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl diphenylphosphinite as phosphorus donor could easily be prepared from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside by simply adding $ClPPh_2$ in the presence of Et_3N and catalytic amount of DMAP. The reaction completely proceeded within 2 h at room temperature to give a mixture of stereoisomers after filtration through a pad of alumina using an eluent of hexane/EtOAc (9/1). Recrystallization from hexane and EtOAc afforded β-stereoisomer in 45% yield.

The ^{1}H-NMR spectrum of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl diphenylphosphinite (Fig 2.15) appeared thirty aromatic protons at δ_H 6.98-7.59 as the multiplet signal. The β-anomer proton and four methylene protons were visualized around at δ_H 4.97-4.43 as two multiplet signals. Six protons of glucose derivative were observed as multiplet at δ_H 3.51-3.71.

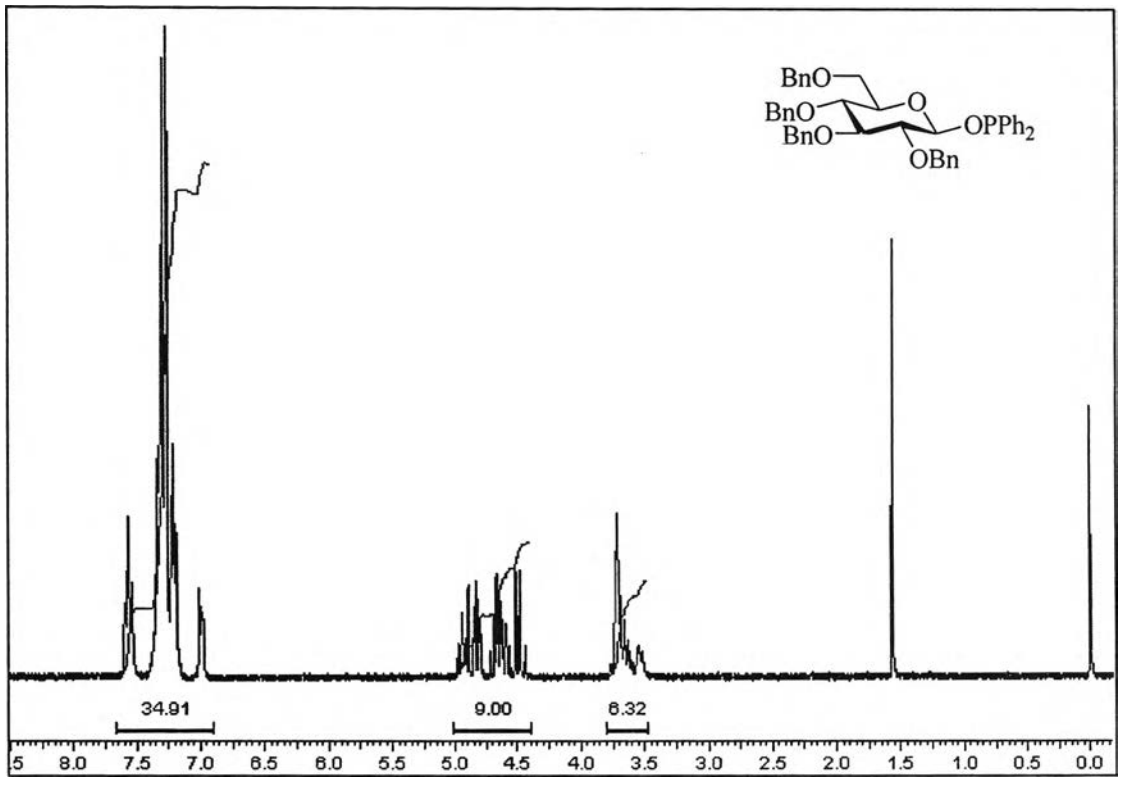
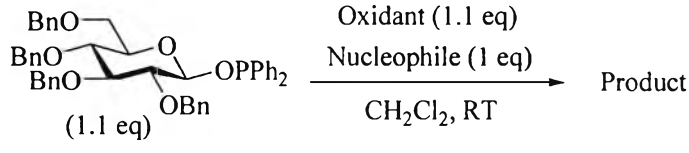


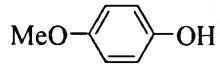
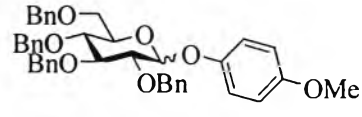
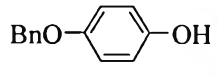
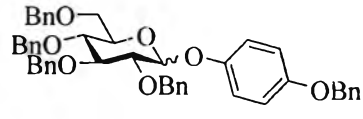
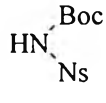
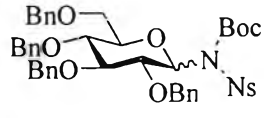
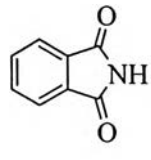
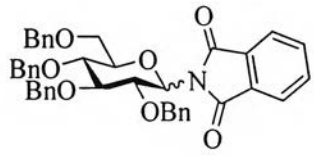
Figure 2.15 ^{1}H-NMR spectrum of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl diphenylphosphinite

2.5.4.1 Glycosylation of β-Glycosyl Diphenylphosphinite by Oxidation-Reduction Condensation

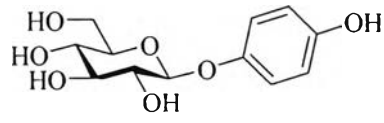
The glycosylation of various nucleophiles such as phenolic compounds and amides with 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl diphenylphosphinite in the presence of DBBQ in CH_2Cl_2 at room temperature was screened. The results are shown in Table 2.16.

Table 2.16 Glycosylation of β-glycosyl diphenylphosphinite with selected nucleophiles



Entry	Nucleophile	Product	Oxidant	Time (h)	% Yield
1			DBBQ	28	50
2			DBBQ	63	41
3			DMBQ		46
4			DBBQ	28	0
5			DBBQ	26	0
6			DMBQ		0
7			BQ		0

Glycosylation of glycosyl diphenylphosphinite and 4-methoxyphenol was proceeded under developed condition to afford the corresponding glycoside in moderate yield (entry 1). The same result for glycosylation with hydroquinone monobenzyl ether (HME) was obtained to produce pentabenzyl arbutin, a precursor for the preparation of arbutin as well-known bioactive compound [46] in the presence of both DBBQ and DMBQ (entries 2-3).



Arbutin

The ^{1}H-NMR spectrum of 4-benzyloxyphenyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside as an α/β mixture while a major product being a α-isomer (Fig 2.16) displayed twenty five aromatic protons as multiplet around δ_H 7.12-7.43 and four aromatic protons of hydroquinone ring as two doublet at δ_H 7.02 and 6.87 (J = 8.1 Hz each). The proton signal of α-anomer proton was observed as doublet singlet at δ_H 5.36 (J = 5.4 Hz). Five methylene protons of benzyl group were detected as multiplet around δ_H 4.42-5.07. The remaining proton signals of glucose were found around δ_H 3.58-4.18.

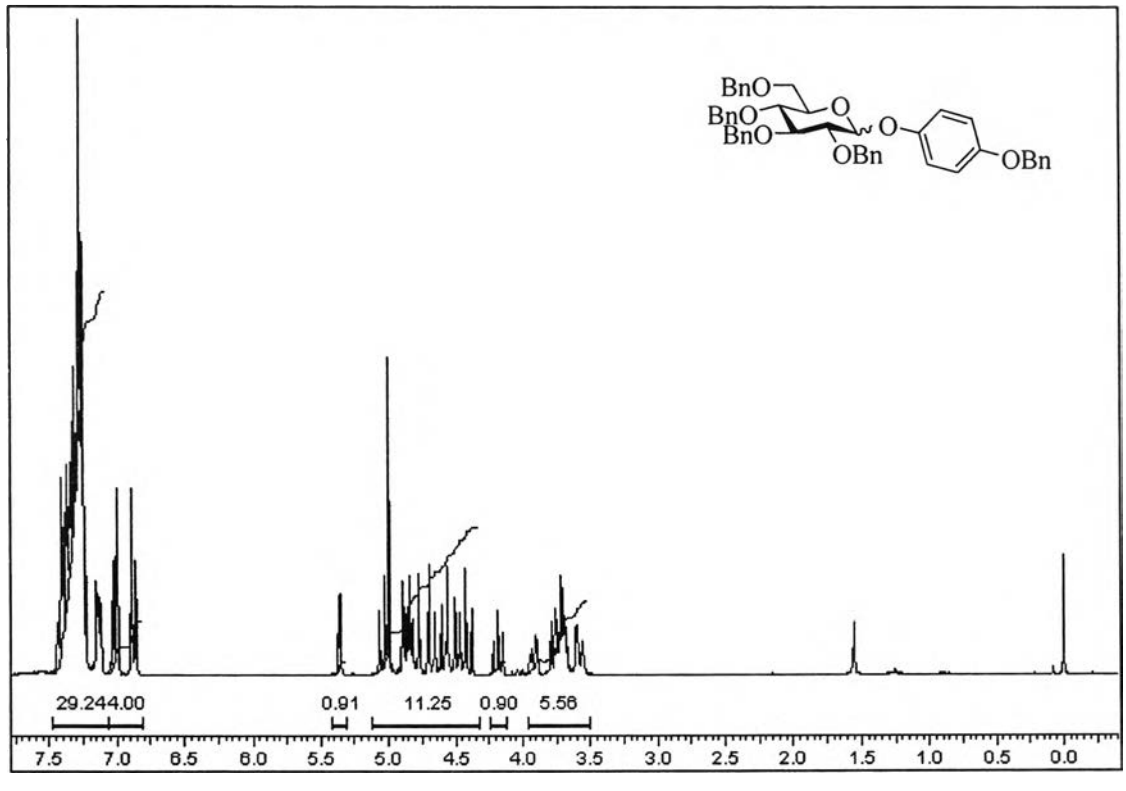


Figure 2.16 ^{1}H-NMR spectrum of 4-benzyloxyphenyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside

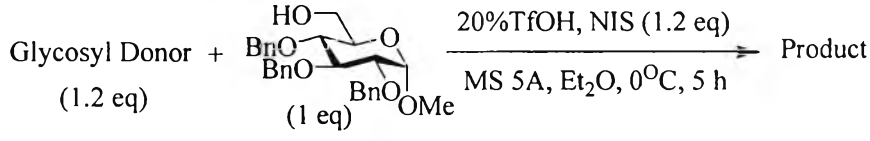
Moreover, glycosylation under this developed condition was not successful to obtain the corresponding glycosides when amides were used as nucleophile (entries 4-7). The oxidation-reduction condensation of β-glycosyl diphenylphosphinite with nucleophiles in the presence of DBBQ could not be applied as a suitable procedure for

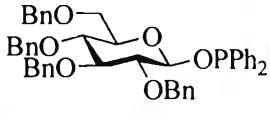
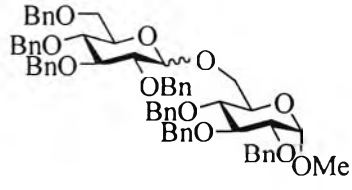
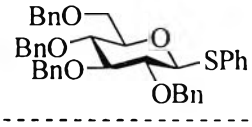
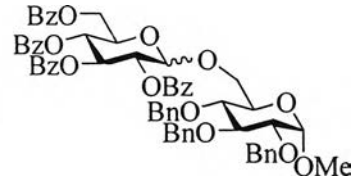
this glycosylation. This may be due to the steric hindrance in the glycosyl diphenylphosphinite thus the S_N2 reaction was difficultly proceeded.

2.5.4.2 Glycosylation of β-Glycosyl Diphenylphosphinite Using TfOH

Glycosylation was further studied by using 20 mol% of trifluoromethane sulfonic acid (TfOH) in Et_2O [36] in order to develop β-glycosyl diphenylphosphinite as an efficiency glycosyl donor for glycosylation. The results of glycosylation are shown in Table 2.17

Table 2.17 Glycosylation of β-glycosyl diphenylphosphinite and glycosyl acceptor



Entry	Donor	Product	% Yield (α/β)
1			56 (62/38)
2			95 (75/25)
3			30

Glycosylation of β-glycosyl diphenylphosphinite with 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside as nucleophile in the presence of TfOH was tried and compared with glycosyl sulfide as common glycosyl donor for this condition study. It was found that the glycosylation of β-glycosyl diphenylphosphinite with nucleophile provided the desired disaccharide in lower yield and selectivity than that using glycosyl sulfide (entries 1 *vs* 2). The poor result was still obtained when glycosyl diphenylphosphinite which was protected hydroxy with benzoyl group (entry 3). From these results, it was postulate that the glycosylation with phosphorus donor could not be carried out under acidic condition. This donor was easily decomposed and generated an undesired product.

It could be concluded that acidic condition was not a compatible condition for glycosylation of glycosyl diphenylphosphinite with nucleophile. However, the suitable reagent and condition for glycosylation of glycosyl diphenylphosphinite was continually studied to improve both yield and stereoselectivity.

The ^{1}H-NMR spectrum of methyl-2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-D-glucopyranosyl-D-glucopyranoside (Fig 2.17) as an α/β mixture (62/38) displayed aromatic proton signal as multiplet around δ_H 7.10-7.40. For the proton signal of α-anomer, it was observed as doublet at δ_H 4.98 (J = 3.7 Hz) while that of β-anomer proton was detected as doublet at δ_H 4.34 (J = 8.2 Hz). Seven methylene protons of benzyl group were ascribed as multiplet around δ_H 4.39-4.98. Another signal detected approximately around δ_H 3.38-4.03 could be designated for glucose protons and singlet signal at δ_H 3.32 and 3.35 as protons of methoxy group.

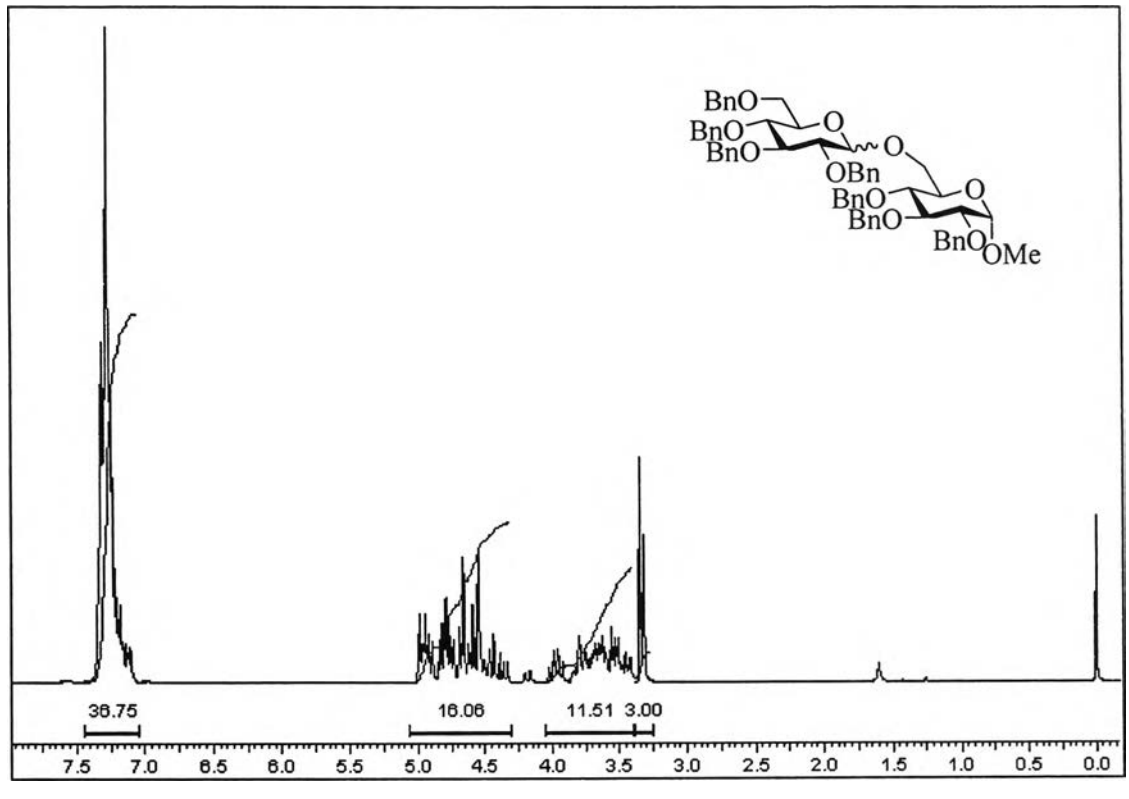


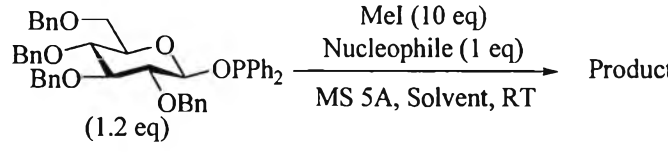
Figure 2.17 ^{1}H-NMR spectrum of methyl-2,3,4-tri-*O*-benzyl-6-*O*-(2′,3′,4′,6′-tetra-*O*-benzyl-D-glucopyranosyl)-D-glucopyranoside

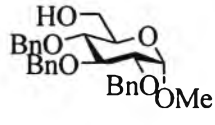
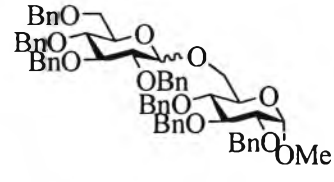
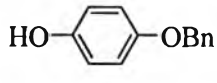
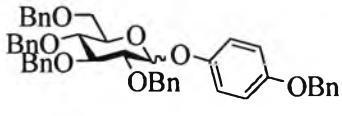
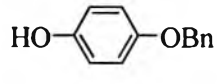
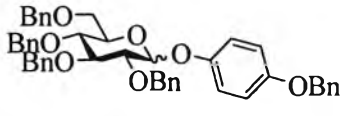
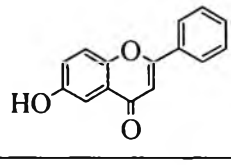
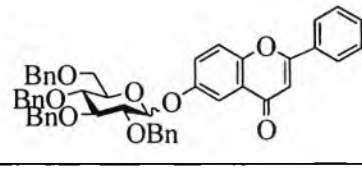
2.5.4.3 Glycosylation of β-Glycosyl Diphenylphosphinite Using MeI

Recently, Mukaiyama and co-workers reported that a mild and highly α-selective glycosylation of several glycosyl acceptors was performed with an *in situ* formed glycosyl donor, benzyl-protected glycosyl methyldiphenylphosphonium iodide, to afford the corresponding α-disaccharides in high yields without any assistance of acid promoters [47].

Thus, that concept was applied to study the efficiency of stereoselective glycosylation using β-glycosyl diphenylphosphinite and nucleophiles. The results are demonstrated in Table 2.18

Table 2.18 Glycosylation of various nucleophiles with β-glycosyl diphenyl-phosphinite

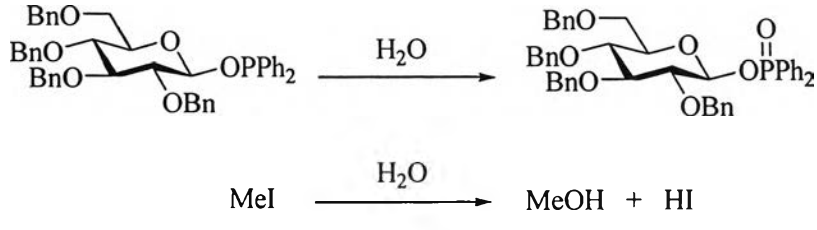


Entry	Nuclophile	Product	Solvent	Time (h)	% Yield (α/β)
1			CH_2Cl_2	25	86 (95/5)
2				22	74 (90/10)
3			CH_2Cl_2	36	76[a] (91/9)
4				36	31[b] (86/14)
5			Toluene		trace
6			Et_2O	48	trace
7			MeCN		51 (58/42)
8			CH_2Cl_2	72	24

a) $POPh_3$ (3 eq) was added to reaction

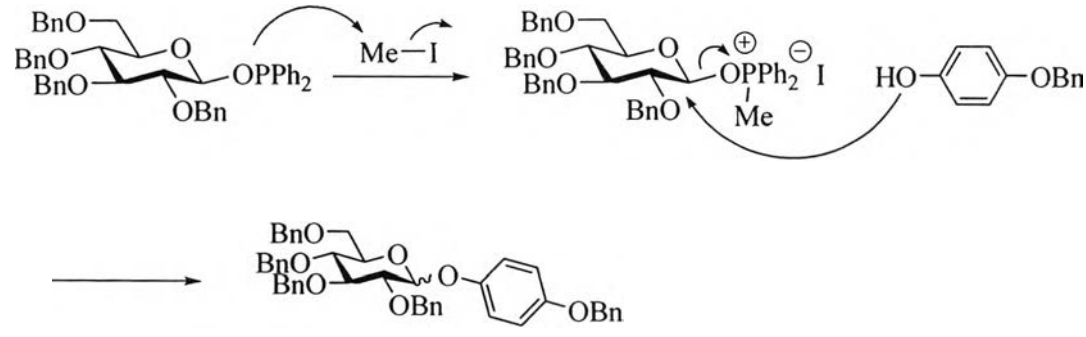
b) $POPh_3$ (3 eq) was added to reaction & without MS 5A

Glycosylation of β-glycosyl diphenylphosphinite with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside was carried out in MeI to obtain α-disaccharide in high yield and stereoselectivity (86%, α/β = 95/5) (entry 1). HME was also tried under same conditions and found that pentabenzyl arbutin could be obtained in 74% yield with enriched α-stereoselectivity (α/β = 90/10) (entry 2). In addition, both $POPh_3$ and molecular sieve 5A (MS 5A) was proved to be useful. Addition of $POPh_3$ as additive under the same reaction condition was not affected to promote this glycosylation of β-glycosyl diphenylphosphinite with HME (entry 3). On the other hand, the yield of pentabenzyl arbutin was strongly reduced from 76% to 31% yield when the reaction was proceeded without MS 5A (entry 4). It was considered that H_2O as by product from glycosylation could be decomposed β-glycosyl diphenylphosphinite or MeI to glycosyl diphenylphosphine oxide and methanol, respectively.



Thus, MS 5A was important determinant for this glycosylation. Moreover, the effect of solvent was also examined in entries 5-7. It was found that the pentabenzyl arbutin was detected in trace and moderate yields when the reactions were carried out in toluene, Et_2O and MeCN. Interestingly, the use of MeCN afforded the mixture product (α/β = 58/42) with no stereoselectivity. CH_2Cl_2 was found to be a suitable solvent of this glycosylation to afford the α-corresponding glycoside in high yield.

The postulated mechanism was proposed that β-glycosyl diphenylphosphinite worked as a nucleophile to attack MeI to form a reactive phosphonium salt intermediate, which in turn formed α-glycosyl linkage by the subsequent reaction with nucleophile.



α-stereoselectivity

From the above results, the glycosylation of β-glycosyl diphenylphosphinite with various nucleophiles could be worked to produce interesting α-glycoside except for the use of 6-hydroxyflavone (entry 8). This nucleophile did not provide the corresponding glycoside in satisfactory yield even with a long reaction time. It was considered that this condition was not suitable for glycosylation with bulky nucleophile.

The ^{1}H-NMR of 2-phenyl-6-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-4H-chromen-4-one as an α/β mixture (Fig 2.18) displayed twenty eight protons as multiplet around δ_H 7.18-7.98. The singlet signal of an olefin proton of flavonoid moiety was assigned at δ_H 6.85. The anomeric proton was observed as doublet at δ_H 5.63 (J = 3.1 Hz). Four methylene protons of benzyl group of glucose derivative were detected as multiplet around δ_H 4.26-5.18. The remaining proton signals of glucose were visualized as multiplet and doublet around δ_H 3.61-3.91. The ^{13}C-NMR spectrum (Fig 2.19) showed the important carbon signal of carbonyl group at δ_C 178.5. The aromatic carbons of benzyl protecting groups and flavonoid were observed around δ_C 101.5-164.0. For anomeric carbon, it was found at δ_C 93.5 while the other carbons of glucose derivative and methylene carbons could be seen around δ_C 68.1-84.6.

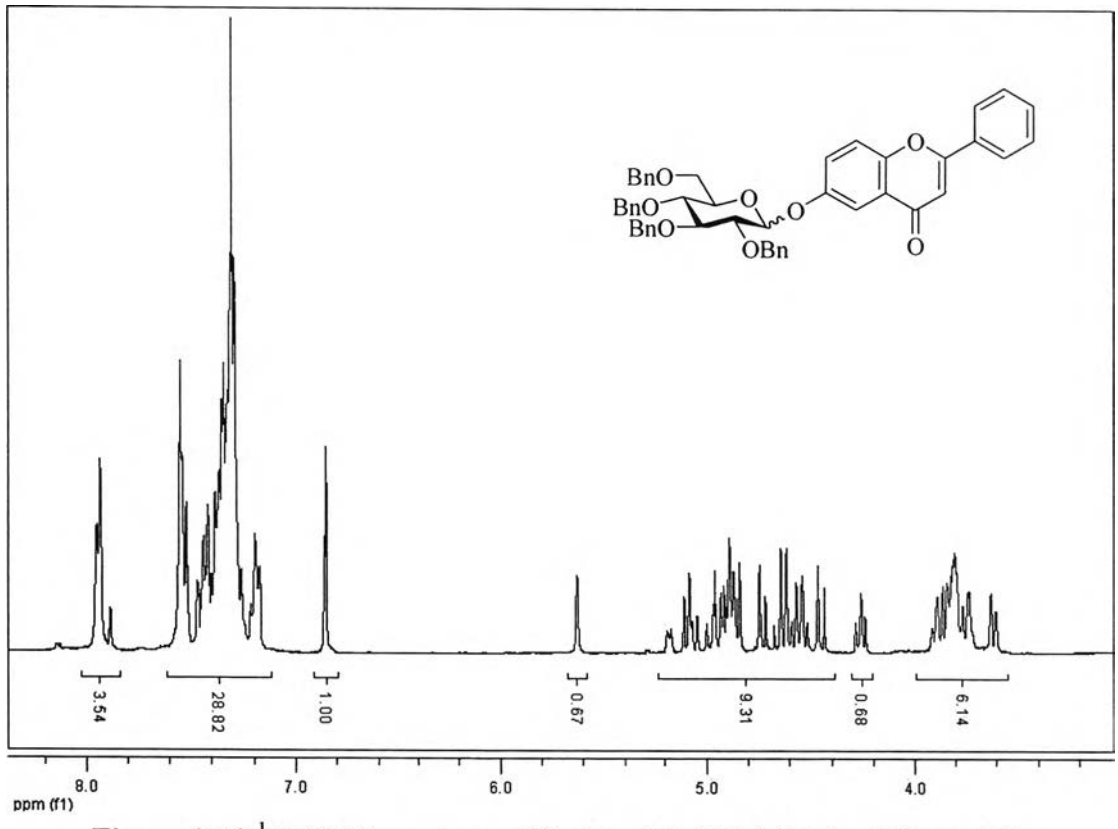


Figure 2.18 ^{1}H-NMR spectrum of 2-phenyl-6-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-4H-chromen-4-one

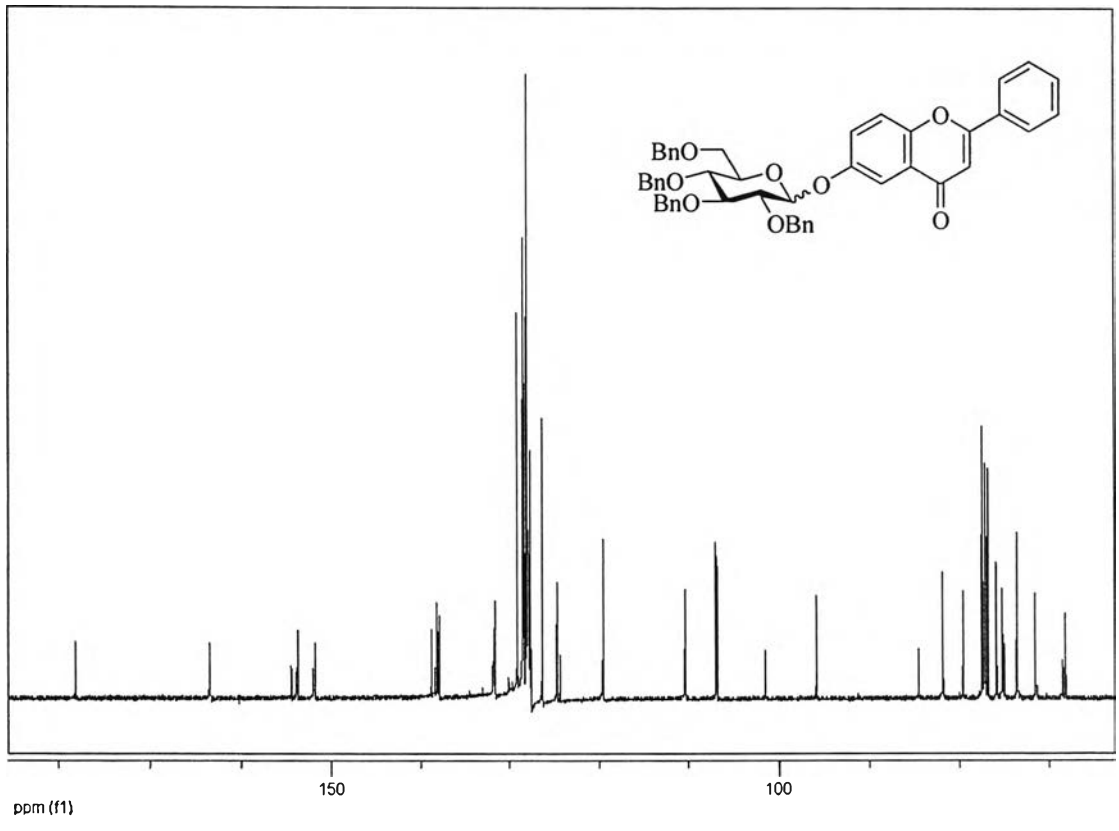
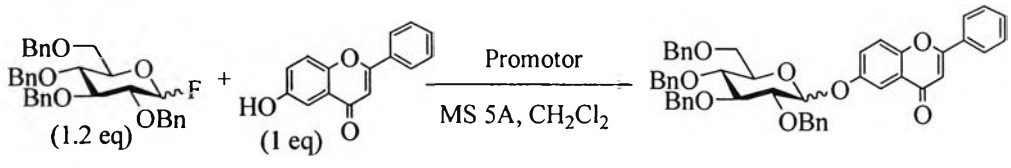


Figure 2.19 ^{13}C-NMR spectrum of 2-phenyl-6-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl)-4H-chromen-4-one

Thus, glycosylation of 6-hydroxyflavone with glycosyl fluoride as the well-known glycosyl donor with a fluorophilic activator [38] was also tried under common reagent and condition from literature as shown in Table 2.19.

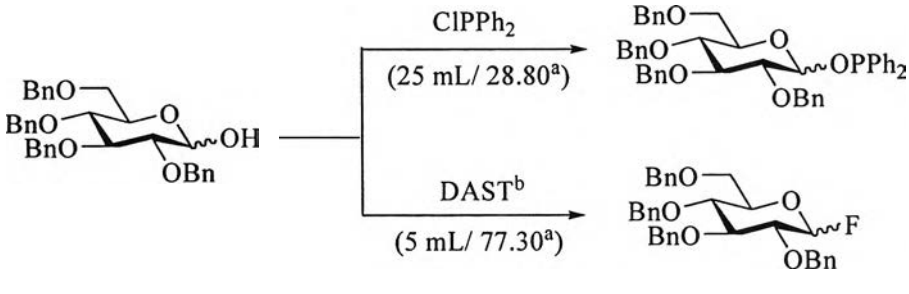
Table 2.19 Glycosylation of glycosyl fluoride with 6-hydroxyflavone



Entry	Promotor	Temp (°C)	Time (h)	% Yield
1	$BF_3.OEt_2$	0	7	80
2	$BF_3.OEt_2$	RT	16	94
3	TMSOTf	0	7	10

The reaction was smoothly converted to the desired glycoside in high yield in the presence of $BF_3.OEt_2$ (entry 1). Moreover, %yield of the higher yield of the desired glycoside was obtained when the reaction conditions such as reaction time and temperature were a bit altered (entry 2).

However, the need of optimized conditions study for glycosylation of β-glycosyl diphenylphosphinite and 6-hydroxyflavone should be seriously considered for the future work. That was because the cost of reagent using for preparation of glycosyl fluoride was rather expensive. The comparison between two reagents for the preparation of two glycosyl donors is shown below.

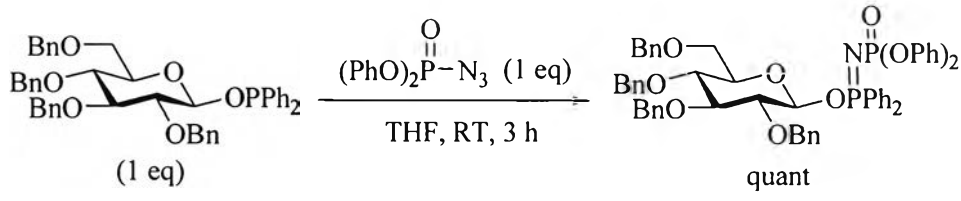


a) US dollar (from Fluka catalogue 2003-2004)

b) DAST = Diethylamino sulfur trifluoride

2.5.4.4 Glycosylation of β-Glycosyl Diphenylphosphinimidate

The efficient method for stereocontrolled construction of glycosidic linkage using glycosyl diphenylphosphinimidate was also examined. β-Glycosyl diphenyl-phosphinimidate could be easily prepared from β-glycosyldiphenylphosphinite and diphenylphosphoryl azide in quantitative yield under mild condition as shown below.



The ^{1}H-NMR spectrum of isolated β-glycosyl diphenylphosphinimidate (Fig 2.20) displayed forty aromatic protons at δ_H 7.80-7.01. The multiplet signal of four methylene groups of the benzyl group was occurred around δ_H 4.84-4.06. A triplet signals at δ_H 5.44 (J = 8.1 Hz) and a multiplet signal around δ_H 3.75-3.34 was ascribed for seven protons of glucose moiety.

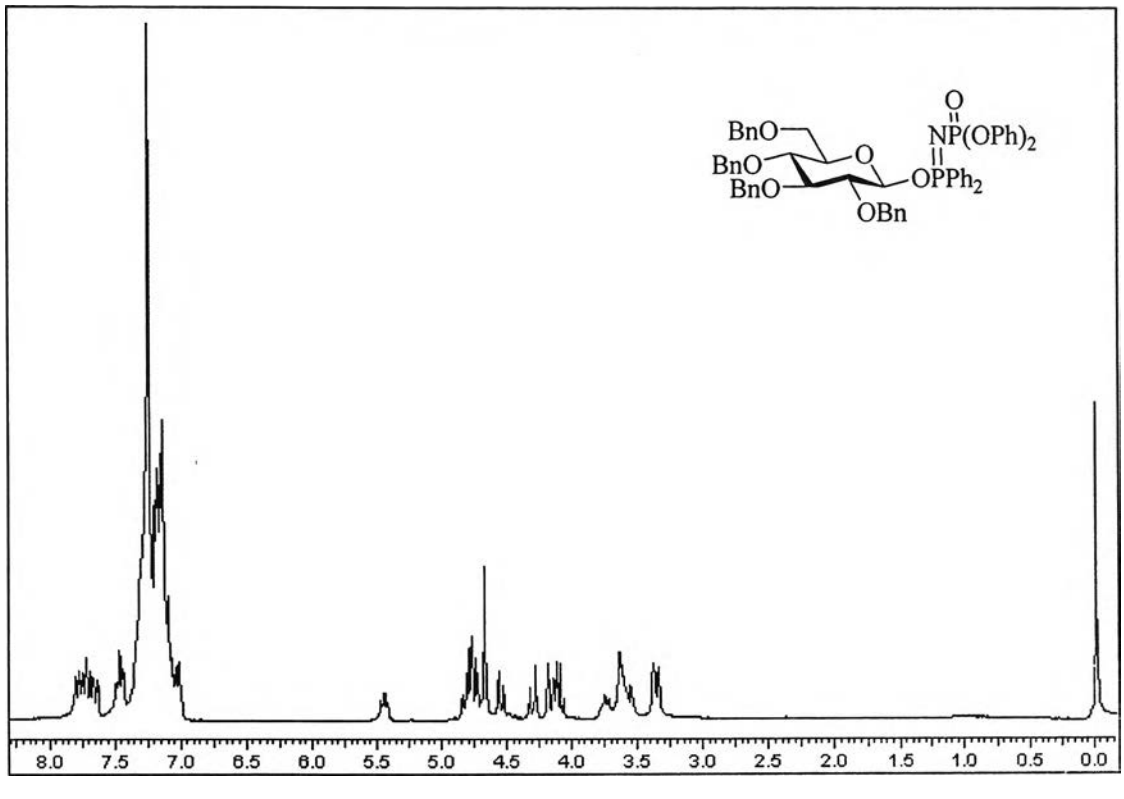
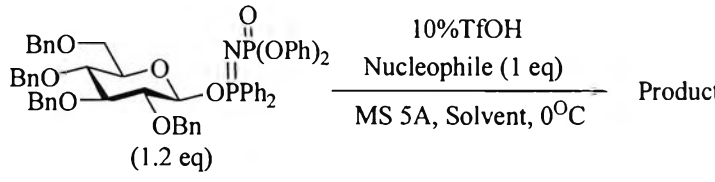
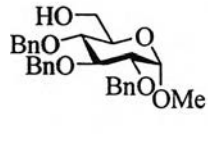
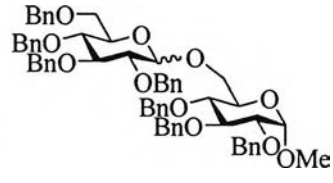
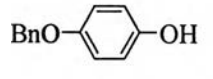
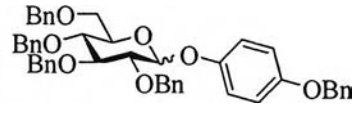


Figure 2.20 ^{1}H-NMR spectrum of β-glycosyl diphenylphosphinimidate

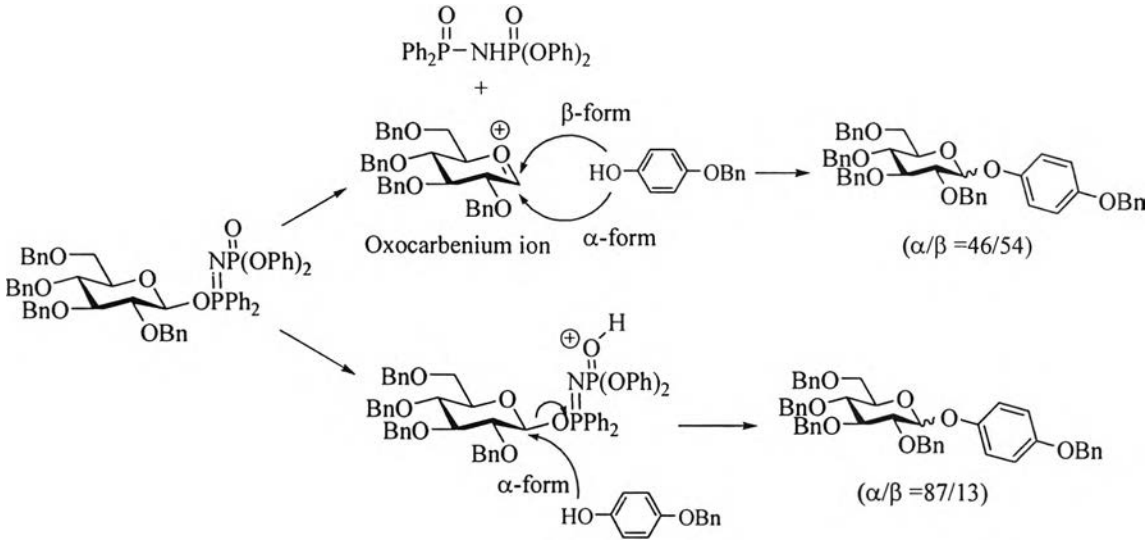
The effect of solvents on glycosylation of β-glycosyl diphenyl-phosphinimidate with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside and HME was first tried because some solvents were quite well known to have influential on the stereoselectivity of glycosylation [38]. Glycosylation was carried out in two solvents by using 10 mol% of TfOH at room temperature as a model reaction. The results of solvent effect are shown in Table 2.20.

Table 2.20 Stereoselectivity of glycosylation



Entry	Nucleophile	Product	Solvent	Time (h)	%Yield (α/β)
1			MeCN	1	90 (34/66)
2			Et_2O		76 (53/47)
3			MeCN	3	60 (46/54)
4			Et_2O		56 (87/13)

Glycosylation of β-glycosyl diphenylphosphinimidate with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside or HME furnished the corresponding glycosides in moderate to high yields (entries 1-4). Surprisingly, the stereochemistry of disaccharide was detected in β-form more than α-form when MeCN was used (entries 1 and 3). On the other hand, to use of Et_2O changed the selectivity of the reaction; α-form was predominantly attained (entries 2 and 4). It was indicated that the solvent displayed markedly effect on stereoselectivities of glycosylation. The proposed mechanism for α-selectivity is shown below.



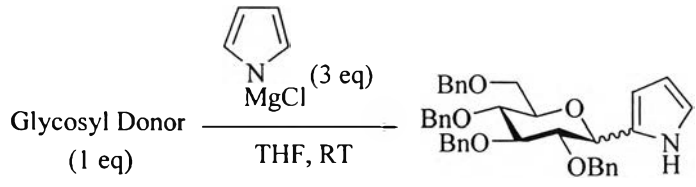
The stereoselectivity of glycosylation of β-glycosyl diphenylphosphinimidate with HME in the presence of TfOH could be controlled. The proceeding reaction was greatly depended on two competitive pathways. The first pathway, with the use of MeCN, was reasonably explained by assuming that a S_N1 type reaction replaced the diphenylphosphinimidate group with nucleophile *via* oxocarbenium ion intermediate, which could be stabilized by aprotic polar solvent. For the other pathway, the reaction proceeded smoothly *via* S_N2 type reaction to afford the predominant α-glycoside in Et_2O as non polar solvent. However, the α-selectivity in Et_2O did not follow by above postulation in the case of the bulky nucleophile such as methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside.

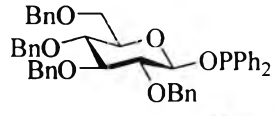
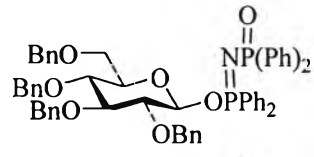
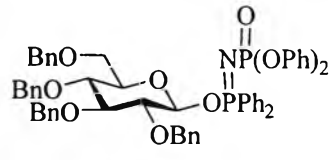
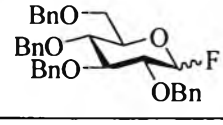
2.5.4.5 *C*-Glycosylation of Various Phosphorus Donors

An efficient chemical *C*-glycosylation with high regio- and stereoselectivity is of particular interest as well as *O*-glycosylations. *C*-glycoconjugates of certain nitrogen heterocycles from as important subclass of nucleosides which display strong and varied biological activities (48); as a consequence, there has recently been considerable in the preparation of carbon-linked nucleoside congeners and analogs including acylonucleosides, for testing and structure-activity studies (49)

Three phosphorus glycosyl donors were chosen to study the efficient of *C*-glycosylation with Grignard reagent derived from pyrrole and phenylmagnesium chloride solution (PhMgCl). The results are tabulated in Table 2.21.

Table 2.21 *C*-Glycosylation of phosphorus donors



Entry	Glycosyl Donor	Time (h)	% Yield (α/β)
1		6	0
2		14	13 (99/1)
3		11	17 (99/1)
4		20	34 (0/100)

The ^{1}H-NMR spectrum of 2-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-pyrrole (Fig 2.21) showed broad signal of an N-H proton at δ_H 8.94. The multiplet signal of twenty aromatic protons was assigned around δ_H 7.07-7.32 and displayed three protons of pyrrole signals at δ_H 6.71, 6.33 and 6.14. The doublet signal of α-anomeric proton could be detect at δ_H 5.32 (J = 5.4 Hz). Four methylene protons of benzyl group were observed around δ_H 4.42-4.98. Six protons of glucose moiety were visualized around δ_H 3.42-4.01.

The ^{1}H-NMR spectrum of 2-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-pyrrole (Fig 2.22) displayed broad signal which was indicative of an N-H proton at δ_H 8.45. Twenty aromatic protons as multiplet around δ_H 7.17-7.41 were observed. Three multiplet signals at δ_H 6.76, 6.27 and 6.18 could be assigned to three protons of pyrrole. Four methylene protons of benzyl group were observed around δ_H 4.31-4.98. The doublet signal of β-anomeric proton and the multiplet signal of remaining proton of glucose were visualized at δ_H 3.92 (J = 10.2 Hz) and around δ_H 3.46-3.81, respectively.

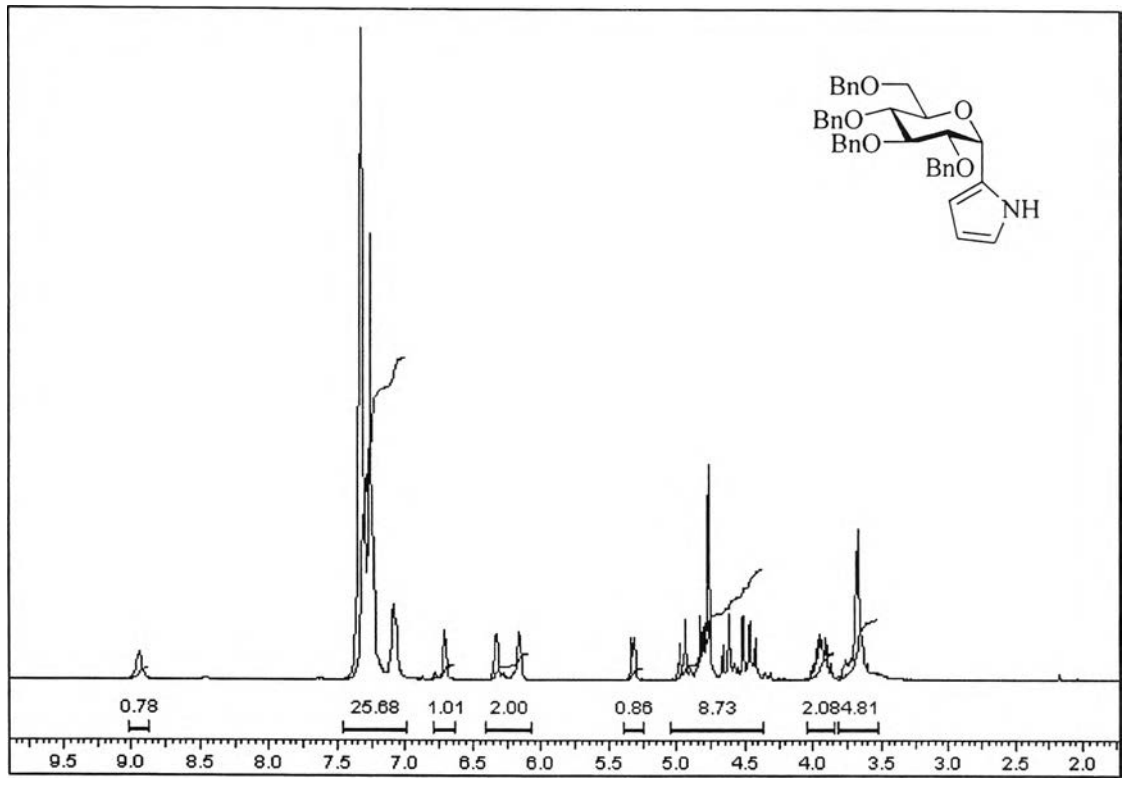


Figure 2.21 ^{1}H-NMR spectrum of 2-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)pyrrole

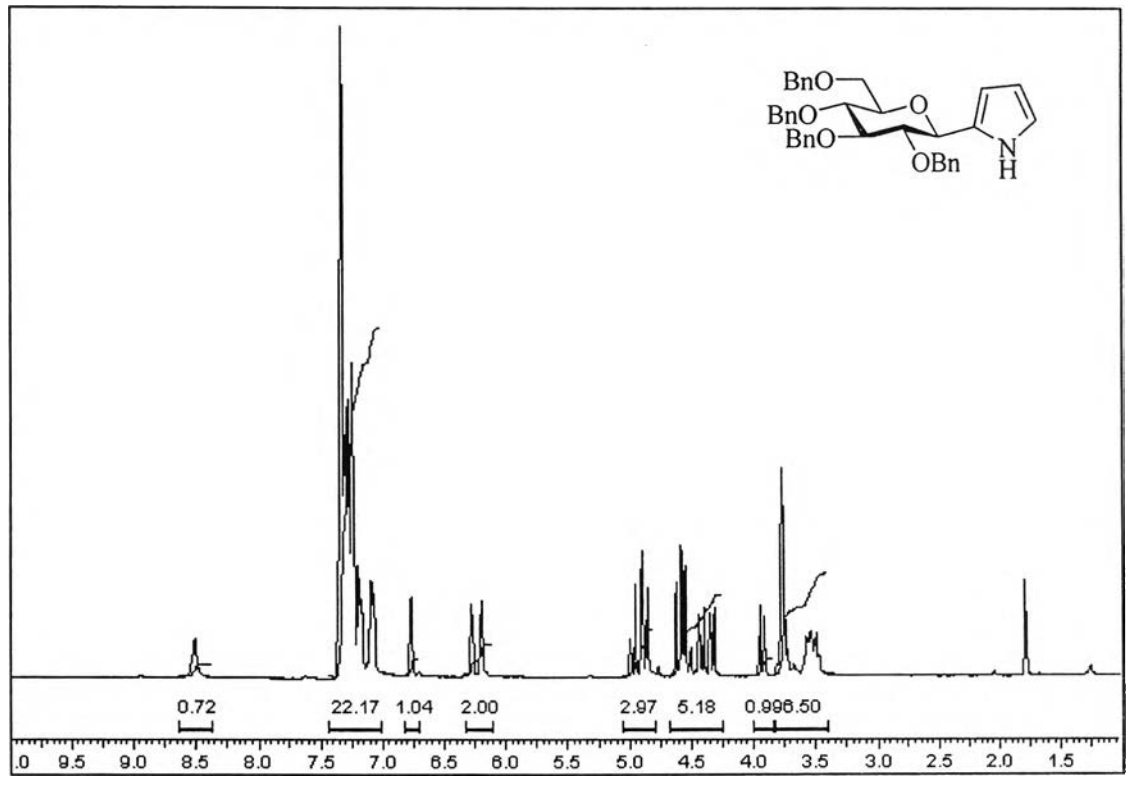


Figure 2.22 ^{1}H-NMR spectrum of 2-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)pyrrole

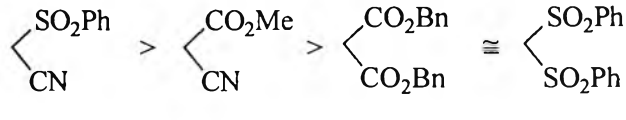
Under this condition, β-glycosyl diphenylphosphinite did not react with PhMgCl (entry 1) whereas employing two β-glycosyl diphenylphosphinimidates could be converted to 2-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)pyrrole in both low yields (entries 2-3). Although, the use of three phosphorus donors for *C*-glycosylation with Grignard reagent exhibited less reactive than glycosyl fluoride (entry 4), the α-selectivity of the desired glycoside was still observed.

2.6 Conclusion

The objective of this present work is to search for a new method to synthesize carbon-sulfur and carbon-carbon bond formation by oxidation-reduction condensation using phosphorus reagent. This developed methodology was indeed disclosed to be an efficient and convenient system under mild conditions, and provided the high yield of desired products. The results are summarized below.

1. Alkyl diphenylphosphinites could be easily prepared from alcohols by adding $ClPPh_2$ in the presence of Et_3N and catalytic amount of DMAP in high to excellent yields.
2. Camphorquinone was disclosed as a new and efficient oxidant for carbon-sulfur bond formation using tertiary alkyl diphenylphosphinites and sulfur nucleophiles under mild and neutral conditions. This developed reaction can be used to synthesize chiral sulfide in high yield with inversion of configuration (S_N2).
3. A new methodology for carbon-carbon bond formation of alkyl diphenylphosphinites and active methylene compounds using DBBQ under mild and neutral conditions was addressed. The proceeding condensation depended on type of alkyl diphenylphosphinites and electron-withdrawing substituent group at active methylene carbon.

Reactivity: Primary > Secondary > Tertiary alkyl diphenylphosphinites



4. Phosphorus donors could be displayed as efficient glycosyl donors. *O*-Glycosylation of β-glycosyl diphenylphosphinite and MeI in CH_2Cl_2 or β-glycosyl diphenylphosphinimidate and TfOH in Et_2O with nucleophiles furnished the corresponding glycoside in high yield with α-stereoselectivity.