CHAPTER III

RESULTS AND DISCUSSION

3.1 Catalytic asymmetric synthesis of α-aminophosphonates

3.1.1 Analytical methods for the determination of enantiomeric purity of α-aminophosphonates

3.1.1.1 Chromatographic method

Due to the highly polar nature of aminophosphonates, GC-based separation is not quite practical. However, rapid progress in developing sensitive and accurate HPLC methods of analysis of enantiomeric α-aminophosphonates has been made in the past years. Most of the reported works employ enantiomeric chromatographic analysis techniques on chiral HPLC columns such as Daicel ChiralPak AD®, Chiralcel OD®, or Chiralpak AS® to determine the optical purity of α-aminophosphonates.[37,42,50] Efficient chiral HPLC systems offer good separations for two components having $\alpha \geq 1.05$. The principle of enantiomer separation by chiral chromatography involves short-term diastereomeric interactions of the two enantiomers with a chiral stationary phase. The diastereoisomeric complexes formed will have non-identical stabilities and hence elute at different times.

3.1.1.2 NMR spectroscopy

Although enantiomers cannot be distinguished in an achiral medium because the resonances of enantiotopic nuclei are isochronous (equivalent), diastereoisomers may be distinguished because the resonances are anisochronous (non-equivalent). The determination of the enantiomeric purity using NMR, therefore, requires the use of a chiral auxiliary that converts the mixture of enantiomers into a diastereoisomeric mixture. As long as there is a large enough chemical shift nonequivalence to give baseline resolution of the appropriate signals, the integration gives a direct measure of diastereomeric composition which can be related directly to the enantiomeric composition of the original mixture.

In general, there are three types of chiral auxiliary that are widely used. Chiral lanthanide shift reagents and chiral solvating agents form diastereoisomeric complexes *in situ* with substrate enantiomers and may be used directly. Chiral derivatizing agents (CDAs) require the separate formation of discrete diastereoisomers prior to NMR analysis and care has to be taken to ensure that neither kinetic resolution of the substrate to be analyzed nor racemization of the derivatizing agent occurs during derivatization. A control experiments using racemic substrates must always be performed in order to validate the derivatizing procedure.

Chiral derivatizing agents (CDAs)

A CDA forms discrete diastereoisomers for which the observed chemical shift nonequivalence ($\Delta\delta$), is typically several times greater than for related complexes with a CSA. Smith[15] used (*S*)-Mosher's amides to derivatize α-aminophosphonates to form diastereoisomeric amides. A comparison of the ^{1}H or ^{19}F NMR spectrum of the derivatized crude product with that of a derivatized authentic racemate would yield information on the preference of the enantiomer being formed.

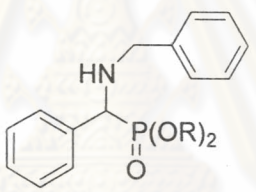
Chiral solvating agents (CSAs)

Chiral solvating agents form diastereoisomeric solvation complexes with enantiomeric solute *via* rapidly reversible equilibria in competition with the bulk solvent. One of the advantages of this method is quick and simple to perform with no problem associated with kinetic resolution or sample recemization provided that the complexes formed remain in the solution. Furthermore, in contrast to the method using CDA, the enantiomeric purity of the CSA is not critical. If it is less than 100% then only the degree of the chemical shift nonequivalence is reduced. However, the relative signal integrations remain unchanged. The main drawback of the method is that $\Delta\delta$ values tend to be small, but with high modern field NMR instrumentation widely available nowadays, this is no longer critical. In addition, another disadvantage is that only a limited range of cosolvents may be used. Nonpolar solvents ($CDCl_3$, CCl_4, and C_6D_6) tend to maximize the observed anisochrony between the diastereoisomeric complexes while more polar solvents preferentially solvate the solute and the $\Delta\delta$ falls to zero. An example of successful enantiopurity

determination of α-hydroxyphosphonates by ^{31}P NMR spectroscopy where quinine was employed as a chiral solvating agent was demonstrated by Kee.[51]

Chiral lanthanide shift reagents (CLSRs)

Addition of a lanthanide shift reagent to an organic compound may result in shifts of resonance to higher (or lower) frequencies, the size of which is determined primarily by the distance of the given type of proton from the donor group. The six-coordinate lanthanide complex forms a weak addition complex with a large variety of organic compounds that is in fast exchange with the unbound organic substrate on the NMR time scale. The magnitude of the chemical shift non-equivalence depends on the strength of the complexation. The association the complexes formed are especially moisture sensitive. One drawback of this technique is the severe line broadening which occurs as a result of paramagnetic properties of lanthanide shift reagents.



II-1 : R = Et
II-2 : R = Me

In order to find a suitable method for determination of %*ee*, two analytical techniques were compared in this study. A normal phase chiral HPLC as well as NMR methods by using chiral solvating agents (CSAs) and lanthanide shift reagents were used.

3.1.2 The results of analytical methods

Initial experiments involved a search for suitable model substrates for the study. The imine substrates themselves can be formed by the conventional aldehyde-amine condensation. What needs to be taken into consideration include the ease to manipulate the reaction as well as to analyze dialkyl phosphonates, the product resulting from the reaction of the so-formed imine substrate and dialkyl phosphite. In general, dimethyl phosphite and diethyl phosphite are common commercially available phosphonylating agents. Unfortunately, such phosphorus reagents could not be obtained due to export regulations by the US government. Therefore, they need to

be synthesized. It turned out that diethyl phosphite can be synthesized with higher purity than that of dimethyl phosphite. In addition, solubility problem in non-polar solvent such as toluene was encountered when dimethyl phosphite was used. Therefore, racemic diethyl phosphonates **II-1** was chosen as model α-aminophosphonates to be tested with various analytical methods. There are precedent reports on liquid chromatographic enantiomeric separation of these compounds on chiral columns for comparison.

3.1.2.1 Chiral HPLC analysis

As reported by Sasai and coworkers,[42] commercially available chiral HPLC columns efficiently used in the determination of enantiomeric composition of α-aminophosphonates include Daicel ChiralPak AD® and Chiralpak AS® columns. In the present work, analysis of racemic mixtures of α-aminophosphonate **II-1** on a readily available Chiralcel OD® and ChiralPak AD® HPLC columns was carried out. A pure sample of product to be analyzed was prechromatographed on silica gel column prior to injection to either of the chiral columns to avoid ambiguity of peak assignment. After exhaustive attempts to separate the racemic mixture on the Chiralcel OD® HPLC column (mobile phase: hexanes/2-propanol at various ratio), it was found that no separation was obtained. While the chiralcel OD® column failed to give any peak separation, the ChiralPak AD® column gave satisfactory separations of the racemic α-aminophosphonates **II-1** (hexanes/2-propanol) provided that the sample loadings were small. A representative chromatogram obtained from the best conditions for separation of the racemic α-aminophosphonate **II-1** is shown in Figure 1 (Appendix). It clearly shows that the enantiomeric pair was separated and eluted as two peaks of equal peak area. However, due to a time-consuming prechromatography requirement as well as the limited timeslot for the HPLC machine, this method seems a little less practical. Therefore, we had turned our focus from chromatographic resolving technique towards classical NMR techniques.

3.1.2.2 ^{1}H NMR spectroscopic analysis

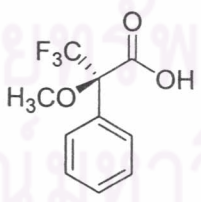
In theory, determination of enantioselectivity of the reaction by ^{1}H-NMR spectroscopy can be achieved by monitoring the integral ratios of the proton at the α position to the phosphonyl group. This is successful under a circumstance where

adequate asymmetric environment is experienced by the enantiomeric α protons of the 2 isomers.

For α-aminophosphonic acid derivatives, the α-proton NMR signal appears as a doublet due to the phosphorus-proton coupling ($^2J_{PH}$ = 19.7 Hz). In a regular ^{1}H-NMR spectrum of **II-1**, this doublet appears in the same region as the methylene proton multiplets of the ethoxy groups (3.60-4.00 ppm) as illustrated in Figure 4 (Appendix). However, in some cases the doublet will shift further downfield upon an addition of an acidic chiral solvating agent as the environment is altered by protonation of the amino group. This results in a clear doublet peak with no interference by the ethoxy protons. Whether or not this doublet of enantiomeric protons would split into 2 sets of doublet depends on the type of chiral solvating agent and/or chiral Lanthanide shift reagent employed which will be discussed next (*vide infra*).

3.1.2.3 Analysis employing chiral solving agents

Chiral solvating agents offer a more practical and economical way to the determination of enantiomeric compositions of a mixture. In order to screen for a good CSA, the sample aminophosphonate **II-1** was chosen as the representative model compound. At the beginning, one of the most widely used chiral solvating agent for the determination of enantiomeric composition of alcohols and amines by the NMR method, α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA or Mosher's acid, **65**), was tested as a CSA.



(*R*)-65

At the beginning *R*-(-)-Mosher's acid (**65**) was employed for analysis of racemic α-aminophosphonate **II-1**. After 2 eq of **65** were added to a $CDCl_3$ solution of **II-1**, the peak of the enantiomeric proton, H-C_α-P, were separated into two signals of doublet peaks of equal intensity at 4.18, 4.23, 4.28, and 4.32 ppm. It was not possible at this stage to assign which doublet belongs to which diastereomeric complex. Although MTPA could give good peak separation, the analysis method may

be too costly due to the price of MTPA (**65**). Baseline-to-baseline separation is not absolutely required at the initial stage. The more important thing is the speed and convenience of the screening method. Once a selectivity is observed, a more reliable means can later be used to determine percent enantiomeric excess of the reaction. We have, therefore, attempted to investigate other CSAs for alternatives.

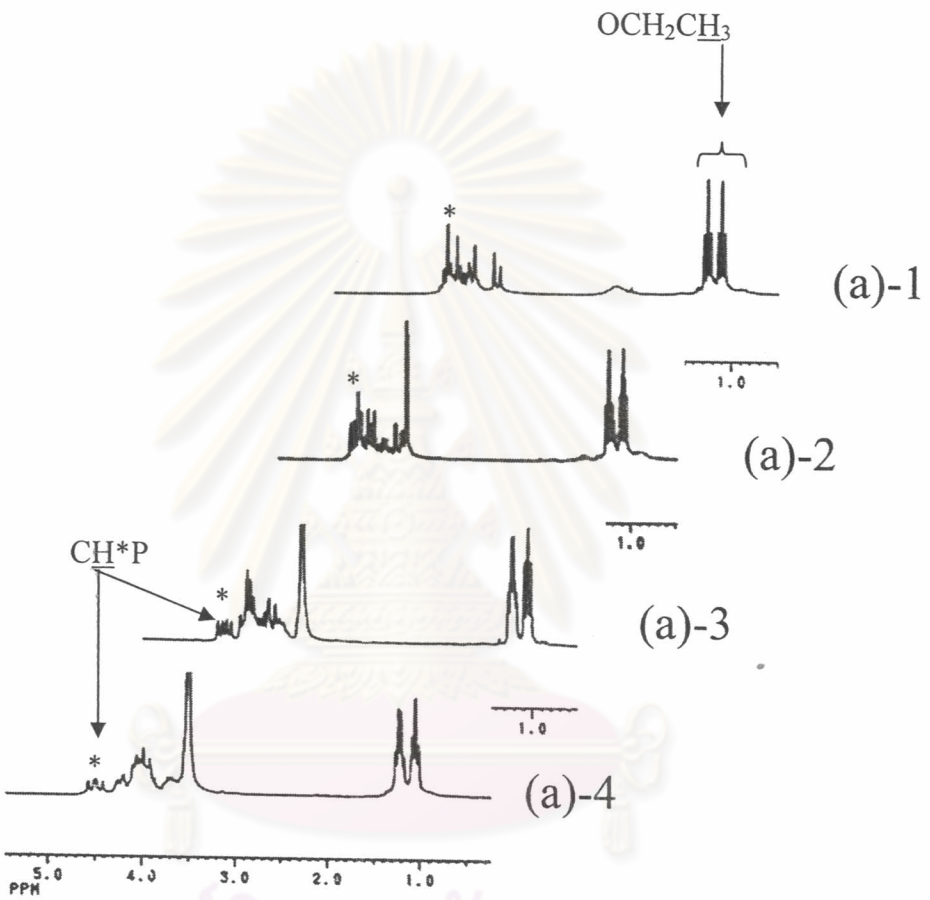
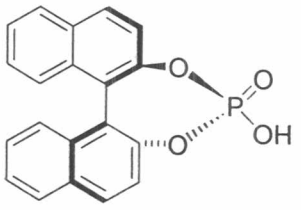
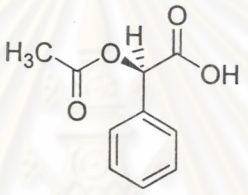


Figure 3.1 The ^{1}H NMR spectra of α-aminophosphonate **II-1** in the presence of **65** as CSA: (a)-1 Before adding **65**; (a)-2 After adding 1 eq of **65**; (a)-3 After adding 2 eq of **65**; (a)-4 After adding 3 eq of **65**



(*R*)-66

Next, the separation of an enantiomeric pair of **II-1** was examined using *R*-(-)-1,1'-binaphthalene-2,2'-diylhydrogen phosphate (BNP, **(R)-66**). Although upto 2 eq of **66** was added in a $CDCl_3$ solution of **II-1**, no sign of splitting of the H_α signal was detectable. Due to the low solubility of **66** in $CDCl_3$, a higher amount of **66** could not be added. Therefore, **66** was not a good CSA to distinguish **II-1** enantiomeric protons.



(*R*)-67

R-(-)-α-acetoxyphenylacetic acid (APA, **(*R*)-67**) was next employed as an alternative CSA in the NMR analysis of racemic α-aminophosphonate **II-1**. It was found that addition of 2 eq of **67** to a solution of **II-1** in $CDCl_3$ resulted in a marked downfield shift of a doublet signal of enantiomeric proton. Although this doublet shifted downfield further from the multiplet peak of the ethoxy proton, no sign of splitting of the signal at 4.20 and 4.14 ppm was observed. When another 1 eq of **67** was added, the peak characteristics remained unchanged.

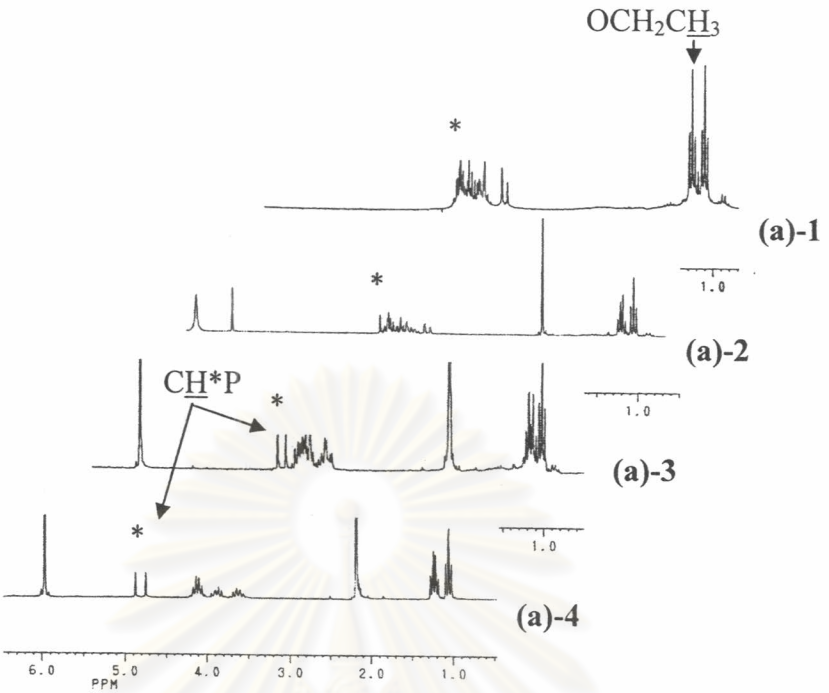
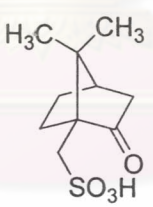
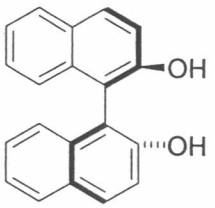


Figure 3.2 The ^{1}H NMR spectra of α-aminophosphonate **II-1** in the presence of **67** as CSAs: (a)-1 Before adding **67**; (a)-2 After adding 1 eq of **67**; (a)-3 After adding 2 eq of **67**; (a)-4 After adding 3 eq of **67**

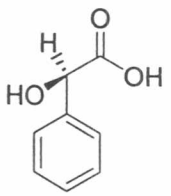


(*S*)-68

Another CSA, (*1S*)-(+)-camphor-10-sulfonic acid (**(R)-68**), was tested for analysis of racemic α-aminophosphonate **II-1**. Addition of 1 eq of **68** to a solution of **II-1** did not show any separation. It was found that an increased amount of **68** may provide a better separation. However, its low solubility in $CDCl_3$ had prevented further addition to the sample.



(*R*)-69



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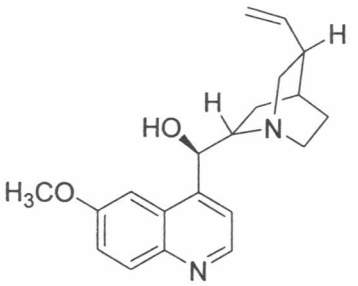
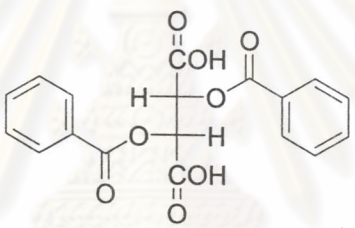


71

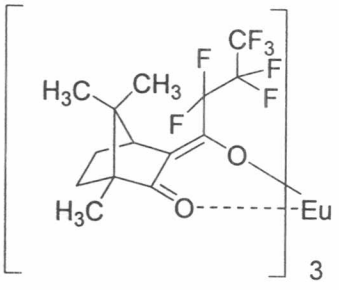
In addition, (*R*)-(+)-1,1'-bi(2-naphthol) (**(*R*)-69**), D-(-)-mandelic acid (**70**), and quinine (**71**) were tested for use in an enantiomeric determination of **II-1**. Due to the low solubility of **69** and **70** only about 1 eq could be added to the mixture. Disappointingly, separation of enantiomeric α-proton signals was not observed in both cases. Even though a solubility problem was not encountered in an attempt to utilize **71** as a CSA, addition of **71** to the NMR sample resulted in no hint of separation of the signal of interest.



72

(-)-*O,O'*-dibenzoyl tartaric acid (**72**) was also investigated as a potential CSA. When 1 eq of **72** was added, two sets of doublet peak appeared at 4.10 and 4.19 ppm but not a satisfactory baseline separation. As its solubility in $CDCl_3$ is low, it was anticipated that an increased amount of **72** would not result in a better separation.

The chiral lanthanide shift reagent, Europium (III) tris [3-(heptafluoropropyl hydroxymethylene)-d-camphorate], $Eu(hfc)_3$ (**73**) was employed as alternative to CSAs. When **73** was added to a $CDCl_3$ solution of **II-1**, separation of H_α-C-P peak was not achieved before broadening of the peaks was observed. All of ^1H NMR spectroscopic analysis results were summarized in Table 3.1.



73

Table 3.1 Summary of the ^{1}H NMR spectroscopic analysis of α-aminophosphonate **II-1** using various chiral solvating agents at 200 MHz in $CDCl_3$

CSA	amount added (eq)	Δδ (ppm)[b]
65	2	0.096
66	2[a]	0
67	2	0
68	2[a]	0
69	2[a]	0
70	2[a]	0
71	2	0
72	2[a]	splitting but not baseline-baseline separation
73	2	0

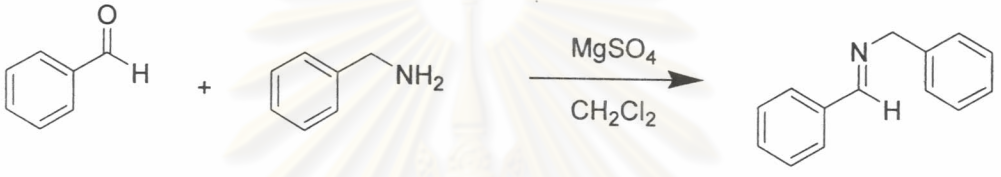
[a] low solubility. [b] Δδ of H_α of **II-1**.

All results described above indicated that among all methods tested, enantiomeric analysis of α-aminophosphonate **II-1** by means of ^{1}H NMR spectroscopy employing Mosher's acid (**65**) as a chiral solvating agent is the suitable method available at hands. Although **65** is relatively expensive, it was the only choice. Therefore, the ^{1}H NMR spectroscopy was chosen as the method for the determination of enantiomeric compositions described herein.

3.1.3 The results of asymmetric synthesis of α-aminophosphonate

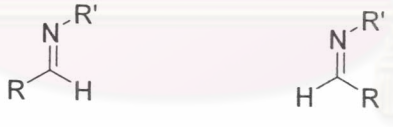
3.1.3.1 Synthesis of imines

Imines are nitrogen analogues of ketones and aldehydes, with a carbon-nitrogen double bond in place of the carbonyl group. They are usually synthesized from a condensation of aldehydes and amines. A dehydrating agent, such as anhydrous magnesium sulfate or molecular sieves is generally added to ensure the forward equilibrium. Imine **I-1** could be easily synthesized by stirring benzaldehyde and benzylamine in the presence of $MgSO_4$ in dichloromethane at room temperature overnight. The imines are unstable and difficult to purify by distillation or by column chromatography. Therefore, it was used instantly after preparation.



I-1

In principle, imines can exist in two geometric isomers, namely *E*- and *Z*-isomers, (Figure 3.3). Regarding the preferred isomer, the *Z*- form should be sterically less favorable than the *E*-form because of the repulsion of the R and R′ groups locating on the same side of the C=N bond. On the other hand, the more stable E form possesses R and R′ opposite to each other, hence the more stable isomer.



E-form *Z*-form

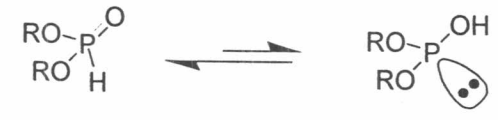
Figure 3.3 The possible geometric isomers of imines

3.1.3.2 Asymmetric synthesis of α-aminophosphonate:

Method A: A chiral Lewis acid approach

Qian[26] reported the reaction of imines with diethyl phosphite to afford α-aminophosphonates in good yields (62-93%), by using $Yb(OTf)_3$ or $Sc(OTf)_3$ as a catalyst. As mentioned earlier that the keto form is the unreactive form of this phosphorus species, it is encouraging to see from Qian's results that diethyl phosphite can still be used as a reagent for such a preparation. Apparently, the keto (inactive) form has been converted to the active enol form in an adequate amount to drive the reaction forward. In general, dialkyl phosphites are more stable than its three-

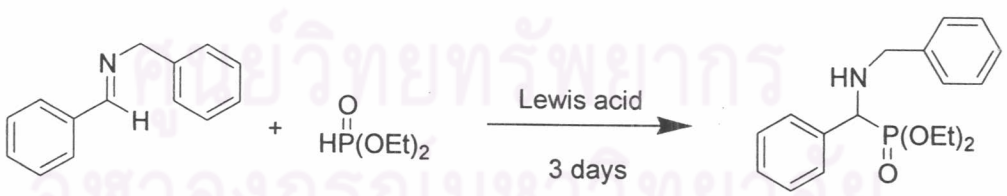
coordinate enol counterpart (or trialkyl phosphites) which are air-sensitive. Therefore, it is easier to handle. Encouraged by these findings, we first investigated the preparation of α-aminophosphonate **II-1** from imine **I-1** and diethyl phosphite in the presence of 1 eq of a Lewis acid in CH_2Cl_2.



Phosphonate tautomer **34** ⇌ Phosphite tautomer **35**

In order to search for suitable Lewis acids for the system, various metal salts namely $SnCl_4$, $TiCl_4$, $Ti(O^iPr)_4$, and $Al(O^iPr)_3$ were used in the reaction. At the beginning a full equivalent of the metal salt was used in dichloromethane at room temperature for 3 d. The results are summarized in Table 3.2. As shown, the reaction in the presence of $Al(O^iPr)_3$ gave a higher amount of product than that with $Ti(O^iPr)_4$ (Table 3.2, entries 4 and 3). It was originally expected that the result would be in the opposite direction since the Ti(IV) complex of chiral ligands of interest tends to give better selectivity for a related Strecker reaction of the same imine than the corresponding Al(III) complexes.[52-53] Therefore, $Ti(O^iPr)_4$ was chosen as a catalyst in the reaction.

Table 3.2 Hydrophosphonylation of imine **I-1** by diethyl phosphite with various Lewis acid catalysts.



I-1 **II-1**

entry	Lewis acid	mol%	solvent	yield (%)[a]
1	$SnCl_4$	100	CH_2Cl_2	-[b]
2	$TiCl_4$	100	CH_2Cl_2	5
3	$Ti(O^iPr)_4$	100	CH_2Cl_2	18
4	$Al(O^iPr)_3$	100	CH_2Cl_2	40

[a] Isolated yield. [b] No reaction.

Next, solvent effect on the reaction was examined. The reaction of imine **I-1** and diethyl phosphite in the presence of 100%mol $Ti(O^iPr)_4$ was carried out in various solvents at room temperature for 3 d. The results suggested that dichloromethane and tetrahydrofuran were the best solvents among those tested, such as toluene (13%), and THF:toluene (1:7) (5%). THF was selected as the solvent for the reaction during condition optimization because the reaction can be performed at higher temperatures due to its higher boiling point (67 °C).

Table 3.3 Hydrophosphonylation of diethyl phosphite and imine **I-1** in different solvents

entry	Solvent	yield (%)[a]
1	CH_2Cl_2	18
2	THF	16
3	CH_3CN	-[b]
4	Toluene	13
5	THF/Toluene	5

[a] Isolated yield. [b] No reaction.

In order to search for preliminary suitable conditions, reactions probing for the influence of various factors, *i.e.*, reaction time, temperature, and amount of diethyl phosphite, on the course of the reaction were carried out. Selected results are listed in Table 3.4. First, the reaction time was taken into consideration. The reactions of imine **I-1** with 1.2 eq of diethyl phosphite were performed at room temperature for 3 and 6 days (entries 1 and 2) to determine the effect of reaction time. The yields were, however, comparable. A similar trend can be seen when the reactions were carried out at 65°C for 3 and 5 days (entries 5 and 6). These representative results suggest that there is no significant difference in the length of time the reaction was carried out.

Table 3.4 Hydrophosphonylation of diethyl phosphite and imine **I-1** under various conditions

entry	DEP (eq)	time	temp	yield (%)[a]
1	1.2	3d	rt	36
2	1.2	6d	rt	23
3	3.5	3d	rt	43
4	5.0	3d	rt	42
5	1.2	3d	65°C	44
6	1.2	5d	65°C	43
7	3.5	3d	65°C	71
8	5.0	3d	65°C	54

DEP : diethyl phosphite. [a] Isolated yield.

Next, the effect of temperature on the outcome of the reaction was studied. Entries 1 and 5 represent reactions of imine **I-1** with 1.2 eq of diethyl phosphite at room temperature and 65°C (refluxing THF), respectively. As shown in Table 3.4, at room temperature the reaction proceeded with marginal yields. An increase in reaction temperature resulted in a slightly improved yield. The same trend is observed when 3.5 eq of diethyl phosphite was used in the reactions at room temperature and 65°C (3 and 7), although the yields were significantly improved.

In theory, only one equivalent of dialkyl phosphite should be adequate for the reaction. However, as illustrated by Shibasaki[43] that a hydrophosphonylation using heterobimetallic catalyst systems afford much higher yields (without affecting the percent enantiomeric excesses) when a significantly higher amount of diethyl phosphite (5 eq) was used. Therefore, an influence of the amount of diethyl phosphite on yields was studied. The reactions were performed at room temperature with increased amounts of diethyl phosphite from 1.2 eq to 3.5 and 5 eq (entries 1, 3, and 4) to give product **65** in 36, 44, and 43%, respectively. It can be seen that an increase from 1.2 to 3.5 eq gave higher yields, whereas increasing the amount to 5 eq did not improve the yields. Likewise, at 65°C, an increase in product yields from 43 to 71% was achieved when the amount of diethyl phosphite was increased from 1.2 eq to 3.5 eq, while when 5 eq was used **II-1** was obtained in even lower yield of 54%. Apparently, higher amounts of phosphonylating agent could not significantly drive the equilibrium further in the forward direction in this case.

A report by Qian[26] showed that a one-pot reaction of benzaldehyde, benzylamine, and diethyl phosphite in CH_2Cl_2 at ambient temperature for 15-30 h gave only a trace amount of the desired product. This strongly suggests that no background reaction is involved, *i.e.*, a catalyst is needed for the reaction.

A series of experiments have been carried out to search for an adequate amount of metal ion catalyst for the reaction. It was found that only 10 mol% of $Ti(O^iPr)_4$ can still catalyze the reaction. Therefore, the optimum condition of the reaction under study requires the use of 10 mol% $Ti(O^iPr)_4$, 3.5 eq of diethyl phosphite under reflux at 65°C in THF for 3 days. Under this developed condition α-aminophosphonate **II-1** can be prepared in 71% yield. This condition was used for the rest of the reactions of imine **I-1** and diethyl phosphite.

The optimized conditions were the utilized to search for the most efficient catalyst. The reactions were carried out in the presence of 10 mol% of Ti(IV)-chiral ligand complexes formed *in situ* from the reaction of $Ti(O^iPr)_4$ and chiral ligands such as (*R*)-(+)-1,1'-bi(2-naphthol) (BINOL, **69**), Schiff base **74**, amino alcohol **75**, amino acid derived amino alcohol **76**, peptide Schiff bases **77** and **78**, and (-)-diisopropyl tartrate (DIPT, **79**). Ligands **74** to **77** were obtained from Ms.Woraluk Mansawat, whereas, ligand **78** was from Ms. Siriporn Jiwpanich.

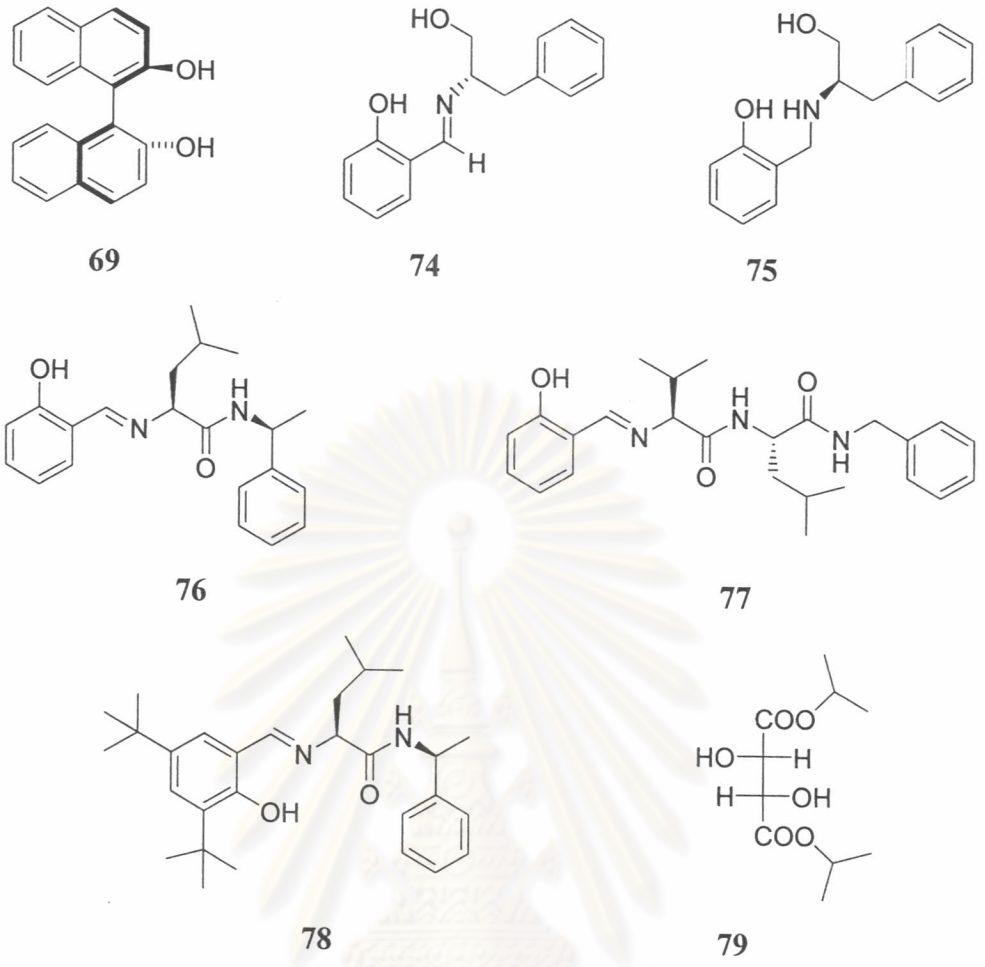


Figure 3.4 Various interesting chiral ligands

In reports by Mansawat and coworkers, complexes formed from $Ti(O^iPr)_4$ and chiral amino alcohols[53] or peptide Schiff bases[52] have shown to be efficient catalysts in asymmetric Strecker reaction. Therefore, it is envisaged that they might also be efficient catalysts for hydrophosphonylation. Alternative ligands include commercially available BINOL (**69**) and (-)-diisopropyl tartrate (DIPT, **79**) which have reportedly been used as catalysts in hydrophosphonylation of cyclic imines to give corresponding cyclic aminophophonates in fair yields (57-62%) and in moderate enantioselectivity (29-44%*ee*).[44]

The reactions of diethyl phosphite and imine **I-1** generated *in situ* were carried out in THF at 65°C for 3 days. Representative results are shown in Table 3.5.

Table 3.5 Asymmetric synthesis of **II-1** via titanium-complex-catalyzed hydrophosphonylation of **I-1**

entry	Chiral ligand	yield (%)[a]	*ee* (%)[b]
1	**69**	43	0
2	**74**	68	0
3	**75**	75	0
4	**76**	69	0
5	**77**	62	0
6	**78**	86	0
7	**79**	71	0

[a] Isolated yield. [b] The enantiomeric excess of the α-aminophosphonate (**II-1**) was determined by ^{1}H NMR analysis of the pure product employing *R*-MTPA as a CSA.

The data revealed that in the presence of Ti(IV)-chiral ligand complexes the reaction proceeded with good to excellent yields. When imine **I-1** was treated with chiral titanium-BINOL complex (10 mol%), an efficient catalyst in enantioselective Strecker syntheses,[44] the desired product **II-1** was obtained in only 43%. Furthermore, no enantiomeric excess was observed. When [Ti(O^{i}Pr)$_2$(L-DIPT)] was used as a catalyst, the desired product **II-1** was afforded in a much improved 71% yield (entry 7) and also no selectivity was detected. It is rather disappointing that both ligands and all other ligands though gave products in high yields, did not induced any detectable enantioselectivity.

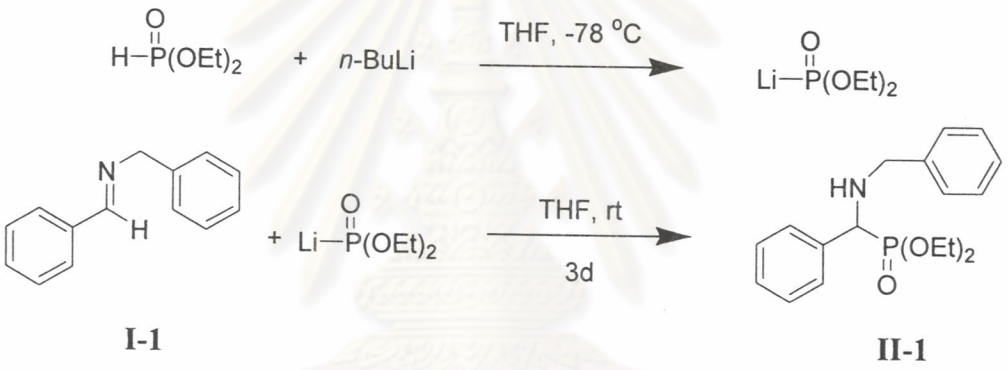
3.1.3.3 Catalytic asymmetric synthesis of α-aminophosphonate: Method B: A chiral Lithium phosphonate approach

This method is based on the fact that (RO)$_2$P(O)H exists in two tautomeric forms, namely, H-phosphonate **34** and phosphite **35**. The anionic form of the phosphite tautomer **35** would be the most nucleophilic and would make the main contribution to the formation of the carbon-phosphorus bond under the basic conditions of the hydrophosphonylation.

Therefore, it is anticipated that appropriate bases should act as an activator to drive the equilibrium forward and convert the phosphonate tautomer to its thermodynamically less stable anionic form of phosphite tautomer. As shown by

Smith's report lithium salt of diethyl phosphite ($LiPO_3Et_2$) indeed gave much higher product yields.

With this idea in mind, attempts to utilize a more reactive species of phosphonylating agent were carried out following Smith's procedure. The lithium salt of diethyl phosphite ($LiPO_3Et_2$) was generated *in situ* by using diethyl phosphite and *n*-butyllithium. Tetrahydrofuran emerged as the solvent of choice offering minimal inhomogeneity. The reaction was carried out in THF at the 1.2 eq of diethyl phosphite and *n*-BuLi (10 mol%). Disappointingly, a very poor yield (3%) was obtained. The efficiency of the reaction was somewhat improved by increasing the amount of diethyl phosphite to 2 eq and the reaction time to 3 days. Under this condition the product was obtained in 36% yield. (Table 3.6, entries 5)



I-1 **II-1**

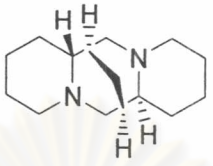
Table 3.6 Asymmetric addition of $LiPO_3Et_2$ to imine **I-1**

entry	eq of DEP	time	temp	yield (%)[a]
1	1.2	1d	rt	3
2	2	1d	rt	30
3	3.5	1d	rt	20
4	5	1d	rt	10
5	2	3d	rt	36

DEP : diethyl phosphite. [a] Isolated yield.

Although the yield is low, it was worth checking enantioselectivity of the reaction in which chiral ligand is employed. The reactions were carried out in the presence of 10 mol% of a complex formed *in situ* from (-)-sparteine ligand (**80**) and the Li phosphonate at room temperature. The use of chiral (-)-sparteine ligands as catalyst in THF solvent, afforded 30% product yield but no enantioselectivity was

observed in the product. There have been reports on successful asymmetric addition of organolithium reagents to imines using (-)-sparteine as a chiral ligand. Denmark,[21] and Lete[24] reported that (-)-sparteine induced the enantioselective addition of organolithium reagents (methyllithium, *n*-butyllithium, and phenyllithium) to *N*-aryl imines with good enantioselectivity (30-82% *ee*, 3-34% *ee*).



(-)-sparteine

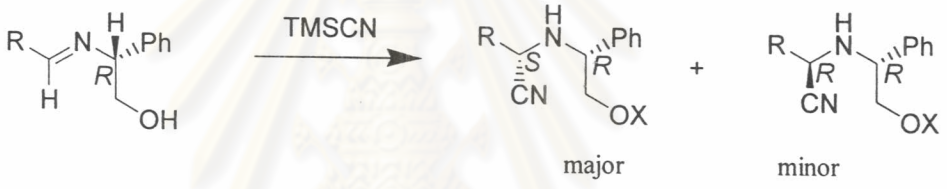
80

All results obtained thus far suggested that the catalyst group of chiral Schiff base, amino alcohols, and peptide Schiff base series were not capable of inducing enantioselectivity of asymmetric hydrophosphonylation under the conditions employed.

3.2 Asymmetric synthesis of α-aminophosphonates from chiral aldimines derived from aldehydes and (*S*)-phenylglycinol

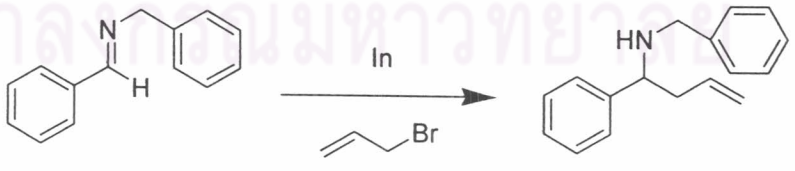
As shown earlier that all attempts to carry out catalytic asymmetric hydrophosphonylation of imines with dialkyl phosphite afforded the products in moderate yield, however, with undetectable level of enantioselectivity in the product. Therefore, we had shifted our interest back to trying the second generation asymmetric induction.

It is evidenced that by using chiral aldimines derived from chiral amines, asymmetric addition is possible. Chakraborty and coworkers[54] illustrated that both enantiomers of α-phenylglycinol can serve as excellent chiral auxiliaries for diastereoselective Strecker synthesis of optically pure L- as well as nonproteogenic D-amino acids.



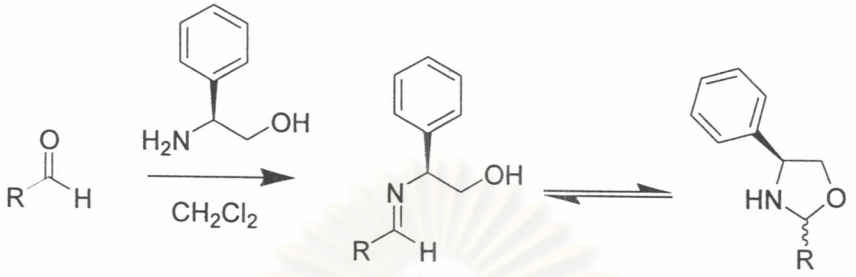
X = H in CH_3OH
X = TMS in $CHCl_3$

Very recently, Vilaivan[55-56] had also disclosed that asymmetric allylation employing (*R*)-phenylglycinol as a chiral auxiliary with a variety of aldimine derived from both substituted aromatic and aliphatic aldehydes gave the products in fair to good yields and in excellent diastereoselectivity. In most cases the diastereoselectivity is approaching 100% as analyzed by ^1H and ^{13}C NMR spectroscopy.



Based on the aforementioned reports, it seemed very likely that aldimines bearing a chiral auxiliary similar to Vilaivan's report would undergo asymmetric hydrophosphonylation. Therefore, imine **III**, derived from (*S*)-phenylglycinol, bearing ^{i}Pr and phenyl group as representative models for aliphatic and aromatic aldimines, respectively, were synthesized. The chiral imine **III** were obtained by

stirring (*S*)-phenylglycinol with the corresponding aldehyde in the presence of anhydrous magnesium sulfate in CH_2Cl_2 at room temperature overnight. The desired products **III-1** and **III-2** were obtained in 70 and 65% yield, respectively. The structures of the products were established by ^1H NMR spectroscopy.



IIIa
III-1 : R = Ph
III-2 : R = ^{i}Pr

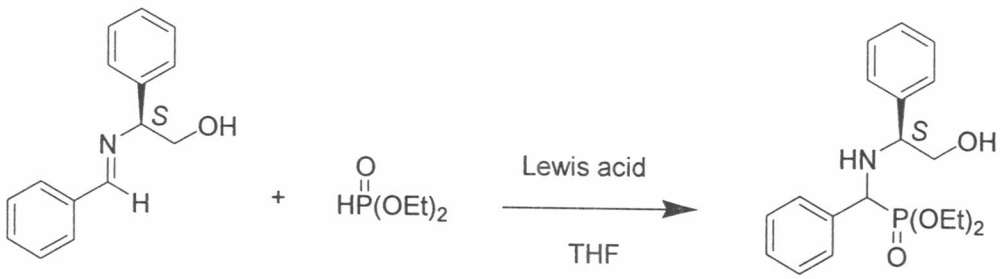
IIIb

Scheme 3.1 Preparation of aldimines from (*S*)-phenylglycinol and aromatic aldehydes, tautomeric oxazolidine **IIIb** also shown.

Similar to Vilaivan's results, ^1H NMR analysis showed that imines derived from aromatic aldehydes existed in equilibrium with the tautomeric oxazolidine diastereomers **IIIb** as indicated by the presence of oxazolidine C-H signals as 4.26 ppm. The content of the oxazolidine increases with more electrophilic aldehydes. For imines of aliphatic aldehydes, the oxazolidine is the major tautomer and no CH=N signal was observed.

3.2.1 Addition of phosphite reagent to chiral aldimines derived from benzaldehyde and (*S*)-phenylglycinol

Aldimine **III-1** prepared from (*S*)-phenylglycinol and benzaldehyde was tested as a representative aromatic aldimine for asymmetric hydrophosphonylation with diethyl phosphite. The reaction was carried out in the presence of LiCl as a Lewis acid in THF at reflux for 1d to afford the crude product mixture which was further purified by chromatography.



III-1 **IV-1**

It is interesting to observe that the desired product **IV-1** was obtained as a mixture of diastereomers in moderate yield (50%) and good diastereoselectivity (major:minor = 88:12). The structure of product **IV-1** was comfirmed by ^{1}H and ^{13}C NMR (Figure 3.5). Diastereomeric ratio of the products could not be directly determined from the ^{1}H NMR spectrum due to overlapping of signals. Instead, the diastereoselectivity of the reaction was determined from the ^{13}C NMR spectrum by comparison of relative peak intensity of the two diastereomers formed, assuming similar relaxation rates of the ^{13}C nuclei of interest. The ^{13}C NMR spectrum showed a doublet signal of CHP peak at 56.95 and 59.94 ppm along with a singlet peak of CHPh at 66.33 ppm which belong to the major diastereomer. In order to assign the absolute configuration to the isomers, reference compounds or data must be available for comparison. Although the compounds are known, literature data on specific rotations of the compounds has not been reported. Besides, preparation of each authentic diastereomer has not been attempted here. Therefore, at this stage we are not able to make absolute configuration assignment as to which doublet set belongs to which isomer. However, the absolute configuration of the products was proposed based on likely-formed transition states, and will be presented later (section 3.2.3). At a rough estimate, the observed diastereomeric ratio of the major to the minor isomers in the product is 88:12 (entry 10, Table 3.8).

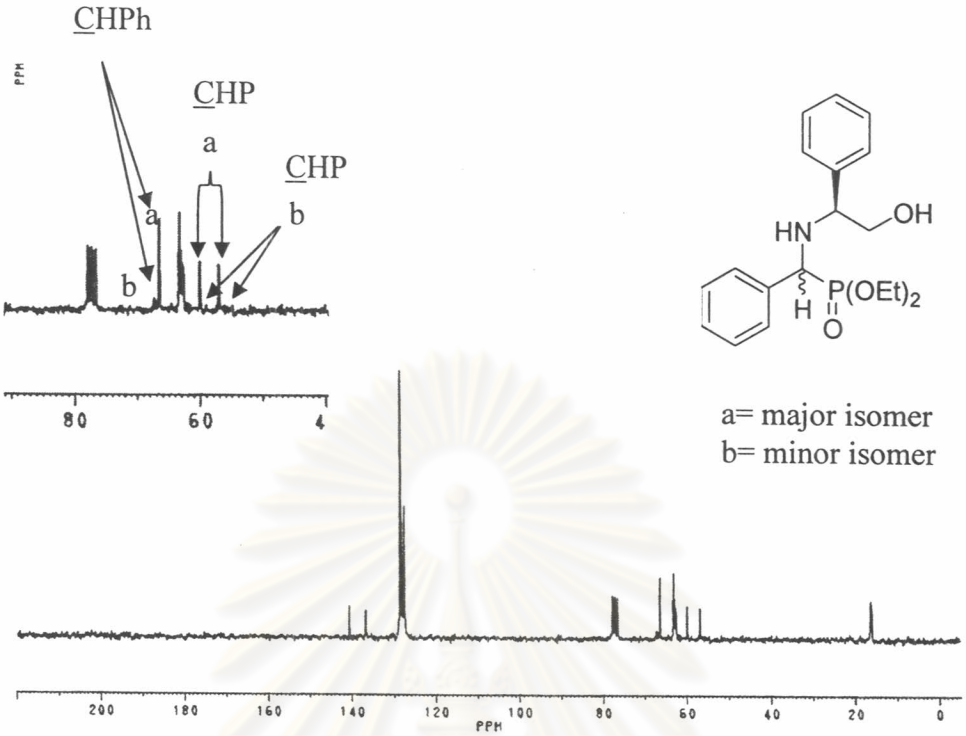
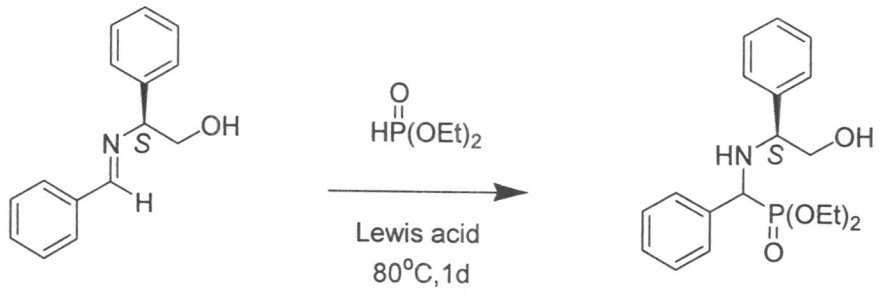


Figure 3.5 ^{13}C NMR spectrum of **IV-1** obtained from LiCl-catalyzed hydrophosphonylation of **III-1**

In order to search for the best solvent system as part of condition optimization, different solvents were utilized in the reaction. The results are summarized in Table 3.7. Polar solvents seemed to give slightly higher yields except when methanol was used. The reaction in methanol proceeded with poor yield and low diastereoselectivity (60:40 dr). The reaction can also occur with a slightly lower yield in less polar solvents such as toluene. The best yield of 50% and high diastereoselectivity (88:12 dr) was obtained when the reaction was performed in THF.

Table 3.7 Hydrophosphonylation of **III-1** in the presence of LiCl in various solvents



III-1 **IV-1**

entry	Lewis acid	solvent	%yield[a]	**IV-1** (major:minor)[b]
1	LiCl	THF	50	88:12
2	LiCl	MeOH	38	60:40
3	LiCl	CH_3CN	43	85:15
4	LiCl	Toluene	34	76:24

[a] Isolated yield. [b] Estimated from relative ^{13}C peak intensity.

Following these preliminary satisfactory results with the imine **III-1** the scope of the reaction was explored employing various types of Lewis acids as illustrated in Table 3.8. As mentioned earlier, the ratios of diastereomeric products were determined from ^{13}C NMR data. All estimates are also included in the table.

Table 3.8 Hydrophosphonylation of **III-1** in the presence of various Lewis acids in THF

entry	Lewis acid	**IV-1** (%yield)[a]	**IV-1** (major:minor)[d]
1	$Ti(O^iPr)_4$	30	69:31
2	$Al(O^iPr)_3$	16	-[c]
3	$Yb(OTf)_3$	-[b]	-
4	$Sc(OTf)_3$	35	-[c]
5	$InCl_3$	36	-[c]
6	$SnCl_4$	-[b]	-
7	$ZnCl_2$	46	60:40
8	$MgCl_2$	40	71:29
9	$ZrCl_4$	-[b]	-
10	LiCl	50	88:12
11	LiOH	-[b]	-
12	LiBr	28	83:17
13	LiOTf	48	71:29
14	no Lewis acid	30	83:17

[a] Isolated yield. [b] No reaction. [c] No ^{13}C NMR spectrum available.
[d] Estimated from relative ^{13}C peak intensity.

It can be seen that, LiCl is the best metal ion for the reaction. In addition, other lithium Lewis acids such as LiBr and LiOTf could also promote the reaction to give the products as a mixture of two diastereomers, albeit in somewhat lower yields and selectivity. On the other hand, the reaction in the presence of LiOH did not give detectable amounts of products. Representative ^1H and ^{13}C NMR spectra of the product mixture are shown. As depicted in Figure 3.6, the ^{13}C NMR spectrum of product **IV-1** from a reaction using $MgCl_2$ as a Lewis acid exhibited two sets of ^{13}C signals of $\underline{C}_\alpha P$ due to the two diastereomers at 55.91/59.01 and 57.04/60.06 ppm. Attempts to find a clear explanation on the role of counter ion to the fate of the reaction have not been made at this time.

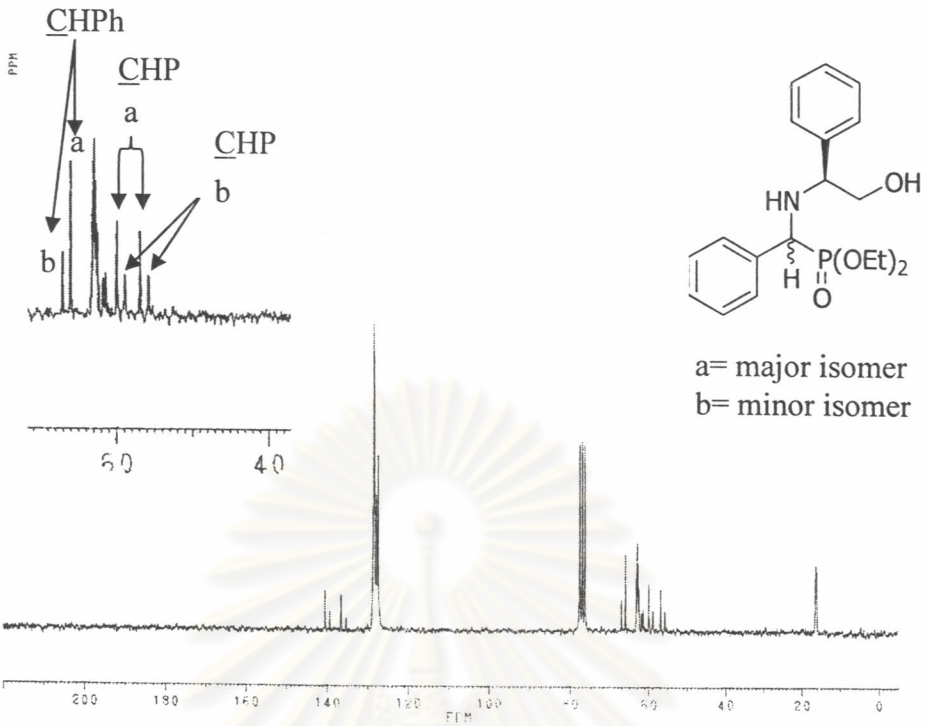


Figure 3.6 ^{13}C NMR spectrumof **IV-1** obtained from $MgCl_2$-catalyzed hydrophosphonylation of **III-1**

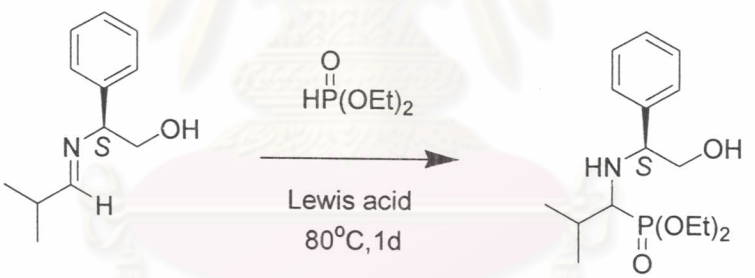
With regards to the type of Lewis acid employed, it was also found that the reaction did not proceed in the presence of $Yb(OTf)_3$, $SnCl_4$, and $ZrCl_4$ while $Ti(O^iPr)_4$, $MgCl_2$, and $ZnCl_2$ provided fair yields of products and appreciable diastereoselectivity (69:31, 71:29, and 60:49 dr, respectively). It seems reasonable to propose that a chelation between the Lewis acid and the substrate (*vide infra*) would be responsible for the observed diastereoselectivity. If this is the case, the results reflect that there is a stronger chelation between Li, Mg, Ti, or Zn and the substrate than between Yb, Sn, or Zr and the substrate. This is in good agreement with the principle of hard and soft acids and bases (HSAB). Therefore, it is sensible to expect no selectivity in the reaction where no Lewis acid is present. Surprisingly, it was found that in the absence of a Lewis acid (entry 14), the reaction proceeded to give the product **IV-1** in 30% yield and a considerably high diastereoselectivity (83:17 dr), a level comparable to when LiBr was used as Lewis acid. A proposed rationale to account for the observed selectivity will be discussed in more details later (section 3.2.3).

3.2.2 Addition of phosphite reagent to chiral aldimines derived from isobutyraldehyde and (*S*)-phenylglycinol

The following experiments were carried out to survey the reactivity of aldimines derived from aliphatic aldehydes. As mentioned earlier, aldimines derived from aliphatic aldehydes and phenylglycinol usually favor the oxazolidine form. This tends to suggest that the reaction might occur to a lesser extent than those of aromatic counterparts unless an appreciable amount of oxazolidine converts back to its imine form as hydrophosphonylation proceeds.

The reactions of imine **III-2** derived from butyraldehyde with diethyl phosphite in the presence of lithium salts as Lewis acids, previously shown to be the most effective metal ion in the case of aromatic aldimine **III-1**, were carried out under the similar conditions applied earlier. The summarized data are shown in Table 3.9.

Table 3.9 Hydrophosphonylation of aldimine derived from (*S*)-phenylglycinol and isobutyraldehyde with diethylphosphite in the presence of various Lewis acids



III-2 **IV-2**

entry	Lewis acid	**IV-2** (%yield) [a]	**IV-2** (major:minor) [b]
1	LiCl	45	79:21
2	LiBr	23	71:29
3	LiOTf	58	65:35
4	no Lewis acid	33	85:15

[a] Isolated yield. [b] Estimated from relative ^{13}C peak intensity.

In general, yields of reactions of aliphatic aldimine **III-2** are slightly lower than those obtained from the reactions of aromatic aldimines except when LiOTf was used. It was found that LiOTf (entry 3) gave the product **IV-2** in highest yield (58%) albeit with poor diastereoselectivity (65:35 dr). LiCl gave a relatively high yield (45%) among Li Lewis acids tested and yet again provided the best selectivity of the product **IV-1** (79:21 dr). Similar to the reaction outcome of the aromatic counterpart, hydrophosphonylation proceeded with considerable yield (33%) along with highest diastereoselectivity (85:15 dr) in the absence of any Lewis acid. ^{13}C NMR revealed two doublet signals of CHP in two diastereomers at 55.69/58.62 and 57.18/60.01 ppm in ratio 1:4 in the presence of LiCl.

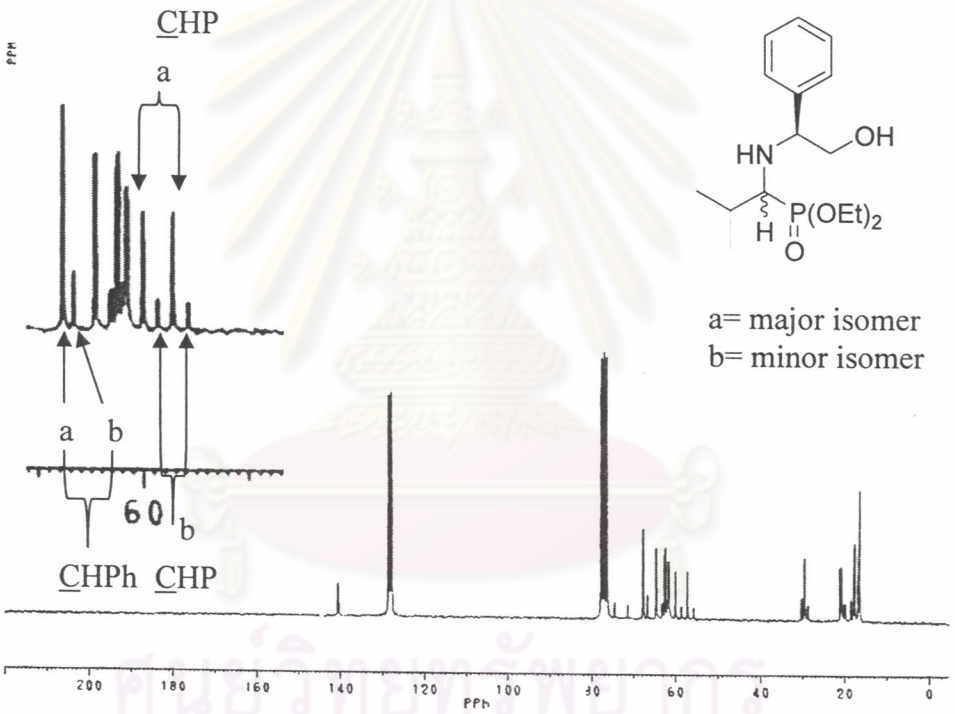
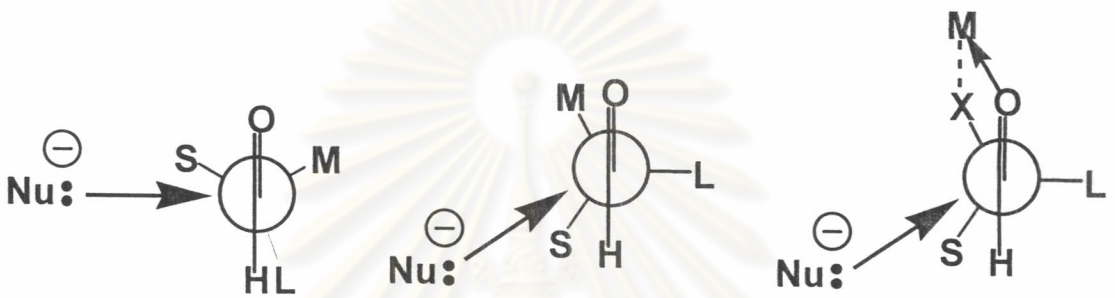


Figure 3.7 ^{13}C NMR spectrum of **IV-2** obtained from LiCl-catalyzed hydrophosphonylation of **III-2**

3.2.3 Prediction of stereochemical outcome of the reaction

Even though the absolute stereochemistry of the products can not be drawn at present, a prediction can be made based on a modification of transition state models available for nucleophilic addition to the carbonyl. In general, Cram's or Felkin-Anh's models and other modified versions (Figure 3.8) are probably the most widely acceptable models explaining diastereoselectivity observed in nucleophilic addition to carbonyls. In all cases, the stereochemistry of the auxiliary attached to the C=O is the factor determining the stereochemical outcome of the reaction.



Cram model Felkin-Anh model Cram's Chelation control

Figure 3.8 Cram's or Felkin-Anh's models and other modified versions

In imines, however, the nitrogen substituent constitutes a new factor which can also influence the stereoselectivity of the reaction. Chiral auxiliary can be designed to attach to either the imine carbon or the nitrogen atom. In the systems explored in this study the substituent on nitrogen, not the substituent on the imine carbon, is the one bearing an auxiliary group.

From the results obtained, hydrophosphonylation of both aromatic and aliphatic optically active aldimines **III-1** and **III-2**, in the presence of Lewis acids especially the lithium salts, gave products in fair to good yields and in relatively high diastereoselectivity. To explain the results obtained, a transition state model proposed by Qian[26] depicted in Figure 3.9 may be used. In the transition state, the metal is chelated by the imine nitrogen and the oxygen atom forming a stable five-membered ring. This is likely a conformation of the substrate which works towards enhancement of diastereoselectivity. Based on this model, the nucleophilic phosphite would, to a higher extent, attack the imine carbon from the less hindered *Si*-face giving rise to the (1*S*,1′*S*) diastereomer as the major product. The (1*R*,1′*S*) diastereomer resulting from the *Re*-face addition would be formed in a smaller amount.

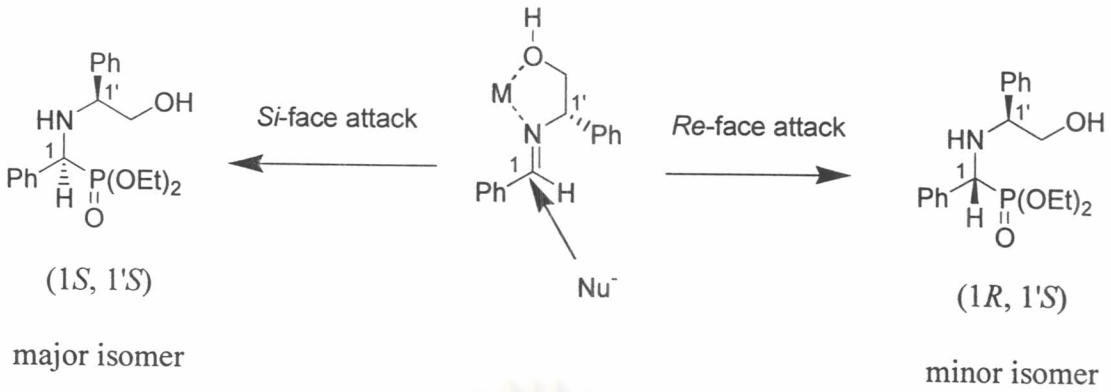


Figure 3.9 A transition state model of Qian

It is noteworthy to recall that in the cases where no Lewis acid were employed, the reaction still proceeded with relatively high diastereoselectivity (Tables 3.8 entry 14, and Table 3.9 entry 4). This raises an ambiguity as to what the exact role of the metal is. Apparently, it is not necessary to use any metal for chelation purposes. This may be explained with an alternative aza analogue of the Anh-Eisenstein hypothesis.[54] Let us consider a Newman projection of a conformer of the substrate. The conformer which can account for the observed stereoselectivity is shown.

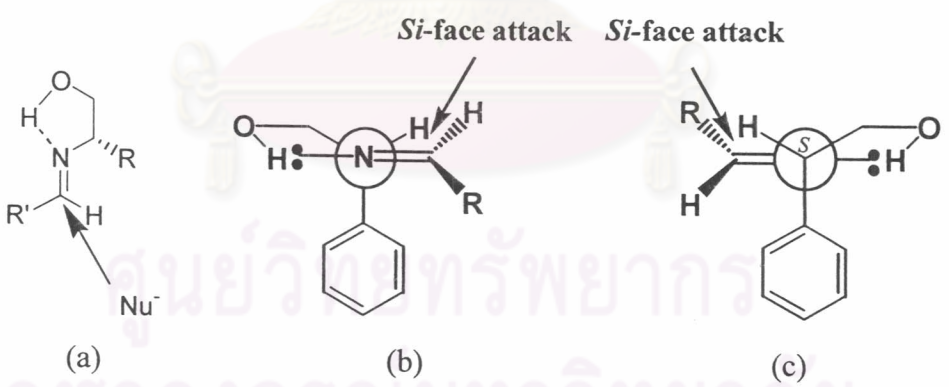


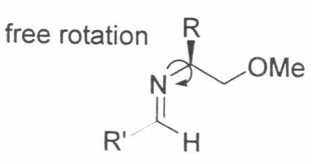
Figure 3.10 A nucleophilic attack to H-bonded aldimine (a) A Nucleophilic trajectory (Bürgi-Dunitz angle). (b) Newman projection of **III**. (c) Newman projection of **III** viewing from the opposite direction.

According to this model, in the absence of a Lewis acid, the phenyl group of the phenyl glycinol moeity which is the most sterically demanding would occupy a position perpendicular to the imine π-plane enabling maximum overlap with orbital lowering its energy and consequently, minimizing the free energy of activation for

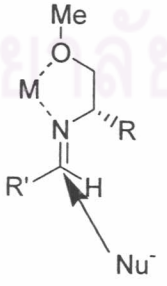
reaction. The nucleophile would then approach more or less antiperiplanar to the phenyl. It appears to us that an alternative nucleophilic trajectory which is an attack from the same face as above but with a Bürgi-Dunitz angle is more likely. Attack from either angle to this *Si* face of the imine would result in the product with the same major stereochemistry. The preference of the *Si* face attack is due not only to steric reasons, *i.e.*, the hydroxymethyl group being away from the imine moiety and the incoming nucleophile, but also to the extra stabilization through intramolecular 5-membered H-bonding. This could explain the observed diastereoselectivity even without added Lewis acids. According to this model, the (1*S*,1′*S*) product is predicted to be the major diastereomer. The prediction falls in good agreement with the previous model discussed earlier. Therefore, it is predicted that the (1*S*,1′*S*) diastereomer would be the major product, while the (1*R*,1′*S*) would be formed in lesser amounts.

The applicability of the proposed models as well as the effect of Lewis acid in the selectivity of the reaction on our systems may be investigated in the future. It is conceivable that if the substrate (*S*)-phenylglycinol is replaced by (*S*)-1-methoxy-2-phenylethylamine, an analogue which is incapable of forming a hydrogen bond with nitrogen nonbonding electrons, this might reveal more evidence to furnish the explanation.

If hydrogen bonding is really crucial, this substrate would undergo hydrophosphonylation with a very small degree of diastereoselectivity, if at all, when no Lewis acid was added. Furthermore, if diastereoselectivity is observed when a metal salt is present, it is strongly indicative that an N-metal-O chelation takes place. Future work also includes exploration of substrate generality of the reaction.

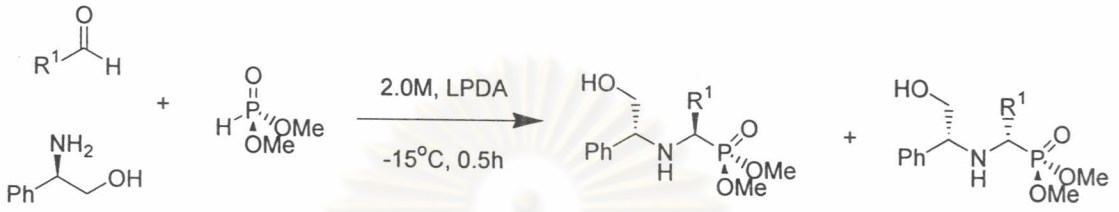


no Lewis acid added
no chelation
lower selectivity, if at all



chelation possible in the
presence of a Lewis acid
higher selectivity

Recently, similar work was reported by Heydari *et al.*[57] on lithium perchlorate catalyzed hydrophosphonylation of imines in high yield (90-95% yield) and good diastereomeric ratio (88:12-91:9 dr). (*R*)-Phenylglycinol was used as a chiral auxiliary attached to nitrogen. The diastereoselectivity observed in the product was also rationalized based on the Anh-Eisenstein hypothesis.



(*R*, *R*)
major isomer

(*R*, *S*)
minor isomer

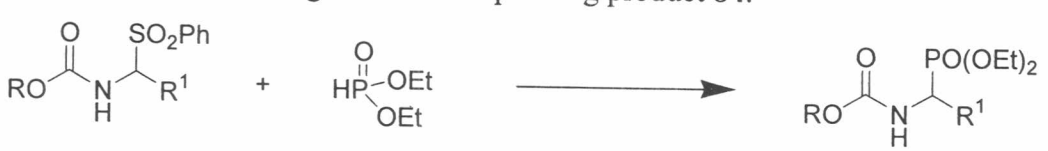
3.3 Synthesis of *N*-protected diethyl 1-aminoalkyl phosphonates from α-amido sulfones

Nucleophilic addition of substrates containing C=N bonds is not a trivial task, since imines are usually less electrophilic than the corresponding carbonyl derivatives. Enolization is a serious side reaction when aldimines obtained from aliphatic aldehydes are forced to react with strongly basic nucleophiles. This drawback can partially be avoided using less basic nucleophilic reagents and/or more powerful electrophilic systems.

N-Sulfonylimines satisfy these requirements because of the electron-withdrawing property of the sulfonyl group. However, only sulfonylimines obtained from aromatic and α,β-unsaturated aldehydes are known to be stable derivatives.[58] Aliphatic aldehydes can be transformed into *N*-sulfonylimines only at low temperature and must be used immediately in order to avoid decomposition. A similar behavior is displayed by *N*-acylimines **82**. However, they can be generated more easily as highly reactive intermediates starting from *N*-acyl-α-substituted amines **81** by a base-induced elimination.

81 **82**

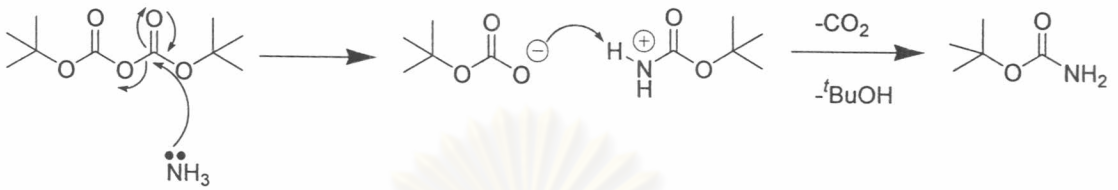
N-acyl amine **81** are thus stable precursors of *N*-acylimines **82**, and their availability depends on the nature of the leaving group X. Among various derivatives of type **81**, *N*-acyl-α-alkoxy amines (**81**, X = OR_2) are undoubtedly the most popular ones. However, they are usually generated by electrochemical oxidation of the corresponding amides or carbamates. Amido sulfones (**83**, X = SO_2Ph) are mostly stable solids that can be prepared by reaction of an amide or a carbamate with an appropriate aldehyde and sodium benzenesulfinate in the presence of formic acid.[59] Amido sulfones **83** thus offer themselves as excellent acylimine precursors for hydrophosphonylation to give the corresponding product **84**.



83 **84**

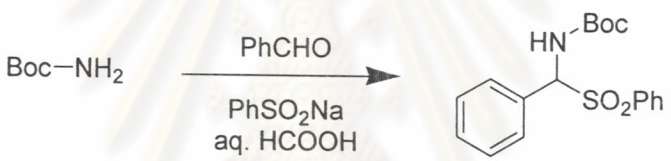
3.3.1 Synthesis of α-amido sulfones

The Boc (*tert*-butoxycarbonyl) group was selected as a nitrogen protecting group and the precursor was prepared following well-documented procedures. Di-*tert*-butyl dicarbonate was reacted with concentrated aqueous ammonia solution to give *tert*-butyl carbamate (Boc-NH_2, **V**) in quantitative yield as shown.



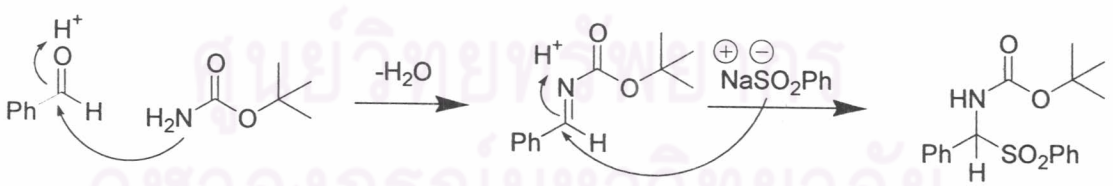
V

Subsequently, condensation of *tert*-butyl carbamate (**V**) with benzaldehyde and sodium benzenesulfinate in the presence of formic acid according to the method of Pearson[59] gave crystalline α-amido sulfones **VI-1** in good yields. Table 3.10 summarizes product yields from the preparation of various sulfones.



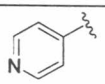
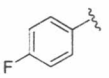
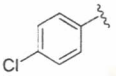
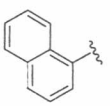
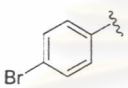
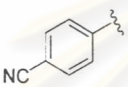
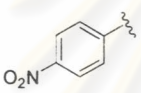
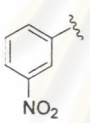
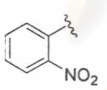
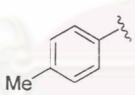
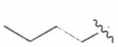
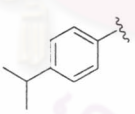
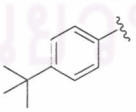
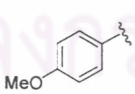
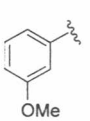
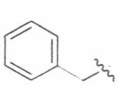
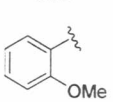
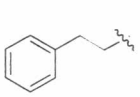
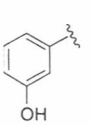
V **VI-1**

Both aromatic and aliphatic amido sulfones can be prepared and isolated by this methods, although the yields are somewhat variable. Mechanistically, the reaction probably proceeds in a manner illustrated below.



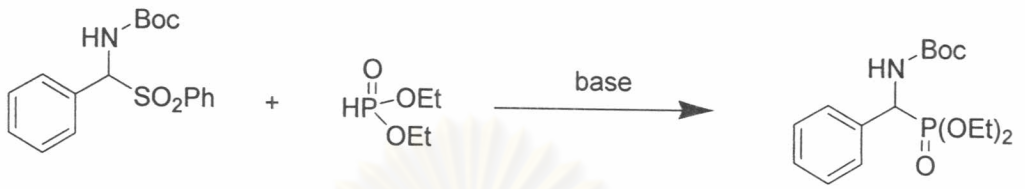
One problem encountered which can account for low yields in some cases, especially aliphatic groups was the failure of some compounds to crystallize and high solubility of the product in the reaction medium or washing solvents.

Table 3.10 Product yields on the preparation of amido sulfones **VI**

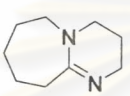
entry	product (VI)	R	yield (%)	entry	product (VI)	R	yield (%)
1	**VI-1**		73	16	**VI-16**		14
2	**VI-2**		51	17	**VI-17**		59
3	**VI-3**		26	18	**VI-18**		10
4	**VI-4**		20	19	**VI-19**		70
5	**VI-5**		54	20	**VI-20**		19
6	**VI-6**		76	21	**VI-21**		10
7	**VI-7**		84	22	**VI-22**		19
8	**VI-8**		82	23	**VI-23**		80
9	**VI-9**		68	24	**VI-24**		40
10	**VI-10**		60	25	**VI-25**		49
11	**VI-11**		57	26	**VI-26**		25
12	**VI-12**		47	27	**VI-27**	n-C_9H_{17}	15
13	**VI-13**		56	28	**VI-28**		65
14	**VI-14**		13	29	**VI-29**		43
15	**VI-15**		40	30	**VI-30**		72

3.3.2 The hydrophosphonylation

The possibility of using various bases as an activator for elimination processes was examined (Table 3.11). The amido sulfone **VI-1** derived from benzaldehyde was first subjected to a reaction with diethyl phosphite in the presence of various bases such as *n*-BuLi, NEt_3, and DBU in order to screen for a suitable base for the reaction.

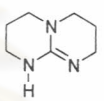


VI- 1 base = *n*-BuLi, NEt_3, DBU, TBD (**85**) **VIII-1**



1,8-diazabicyclo[5.4.0]undec-7-ene

DBU



1,5,7-triazabicyclo[4.4.0]dec-5-ene

TBD, **85**

n-BuLi was tested as activator in the presence of 2 eq of diethyl phosphite in dry THF at room temperature for 1 d. The reaction proceeded to give the desired product in only a marginal yield (52%). Triethylamine was next tested under the same condition. Disappointingly, the desired product **VIII-1** was obtained in only a trace amount. Although the reaction was heated to reflux, the yield of **VIII-1** remained unchanged. The reaction was successful by using 2 equiv of TBD (**85**) as a base to afford **VIII-1** in 62% (Table 3.11, entry 3). In addition, another base, DBU, was also successfully utilized in the reaction (entry 4) and the product was obtained in even a higher yield (79%). Recently, there have been reports involving the use of non-ionic nitrogen base such as tetramethylguanidine (TMG), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and its derivatives to catalyze hydrophosphonylation to a variety of carbonyl compounds and imines under mild conditions.[60-61]

DBU appears to be the best choice of base among those tested. Therefore, more experiments were carried out, by varying the amount of the DBU as well as the phosphite, solvents, and the reaction time, to optimize the reaction conditions. First, the amount of diethyl phosphite was reduced from 2 to 1.1 eq since theoretically only 1 eq (or a slight excess) would be needed for the reaction. Indeed, this is sufficient to give the product in an as comparably high yield (80%, entry 5) as when 2 eq were employed as seen in entry 4 (79%).

Table 3.11 Hydrophosphonylation of amido sulfone (**VI-1**) with diethyl phosphite

entry	Base (eq)	DEP(eq)	solvent	time	yield (%)[a]
1	*n*-BuLi (2)	2	THF	1 d	52
2	NEt_3 (2)	2	THF	1 d	5
3	**85** (2)	1.1	THF	1 h	62
4	DBU (2)	2	THF	1 d	79
5	DBU (2)	1.1	THF	1 d	80
6	DBU (2)	1.1	MeOH	1 d	-[b]
7	DBU (2)	1.1	^{i}PrOH	1 d	43
8	DBU (2)	1.1	Toluene	1 d	73
9	DBU (2)	1.1	CH_2Cl_2	1 d	69
10	DBU (2)	1.1	MeCN	1 d	83
11	DBU (2)	1.1	THF	1 h	83
12	DBU (1)	1.1	THF	1 h	36

DEP : diethyl phosphite. [a] Isolated yield. [b] No reaction.

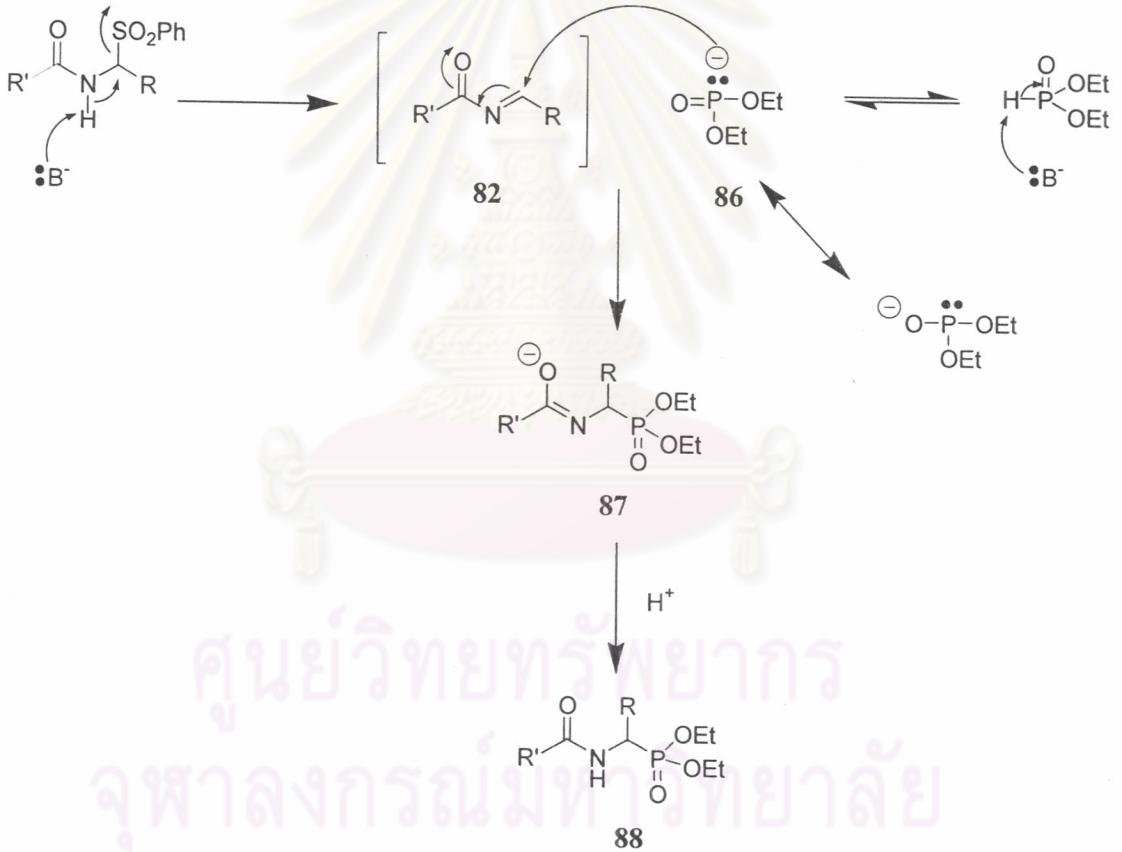
The choice of solvents was then varied to screen for the best medium. The reactions were performed using 2 eq of DBU, 1.1 eq of diethyl phosphite, at room temperature for 1 day and using various solvents namely, methanol, 2-propanol, toluene, dichloromethane, and acetonitrile. The results in entries 6-10 present product yields obtained from reactions in those solvents, respectively. As shown, the reaction performed in acetonitrile gave even a higher yield (83%, entry 10) than that obtained in THF (80%, entry 5), hence the highest among all. When toluene and dichloromethane were used as solvents, the product was also obtained in relatively good yields (73 and 69%, respectively). The reaction carried out in 2-propanol gave the product in a substantially reduced yield (43%). On the contrary, when methanol was used, no desired product was observed. One possible explanation as to why methanol does not promote the reaction includes the reaction of the nucleophilic methanol with the substrate. Moreover, transesterification of the phosphite ester is also possible.

In order to optimize the reaction time, hydrophosphonylation was performed under the best conditions obtained thus far, but the time was reduced to 1 h (entry 11). Surprisingly, this is sufficient for the reaction to proceed to completion. The observed

yields as shown in entries 5 (reaction time: 1d) and 11 (reaction time: 1h) are comparable.

Next, the amount of base was reduced from 2 to 1 eq and the reactions were carried out under the conditions optimized so far (1.1 eq of diethyl phosphite, THF, 1 h). The observed yield has dropped from 80% (2 eq of DBU) to 36% (1 eq). Therefore, the more desirable amount of base is 2 eq.

In summary, the optimal conditions for hydrophosphonylation of α-amido sulfones **VI-1** derived from benzaldehyde is to use 1.1 eq of diethyl phosphite and 2 eq of DBU in THF for 1 h (Table 3.11, entry 12). The method will be referred to as Method A. The mechanism of the reaction may be viewed as a two-step process as depicted in Scheme 3.2.



Scheme 3.2 Mechanism for base-catalyzed hydrophosphonylation of amido sulfone

In the first step, when a base is added to the amido sulfones **VI-1**, the reaction proceeds *via* deprotonation of the carbamate **VI-1** by the first equivalent of the base. This facilitates the elimination of the sulfinate resulting in the *N*-Boc-imine **82**. The second equivalent of base would then deprotonate the diethyl phosphite to form the more nucleophilic anion **86**. The so-formed *N*-Boc-imine intermediate would then

undergo a nucleophilic attack by the anion **86** giving rise to the intermediate **87**. Subsequent protonation yields the desired *N*-Boc α-aminophosphonate **88**.

The failure of triethylamine to promote the reaction suggests that it is too weak of a base either to promote the elimination of benzenesulfinate or to deprotanate the diethyl phosphite, or both.

Some organic bases have so far been shown to be excellent activators for the reaction. It seemed interesting to try more readily available and inexpensive inorganic bases such as potassium carbonate and sodium hydroxide. Therefore, the reaction was investigated in the presence of these bases and the results are presented in Table 3.12.

Table 3.12 Hydrophosphonylation of phenyl amido sulfone (**VI-1**) in inorganic bases

entry	Base (eq)	DEP (eq)	solvent	time	yield (%)[a]
1	NaOH[b] (10)	1.1	CH_2Cl_2	1 h	64
2	NaOH[c] (10)	1.1	CH_2Cl_2	1 h	83
3	K_2CO_3 (2)	1.1	MeCN	1 h	74
4	K_2CO_3 (2)	1.1	MeCN	1 d	80
5	K_2CO_3[c] (10)	1.1	CH_2Cl_2	1 d	-[d]

DEP : diethyl phosphite. [a] Isolated yield. [b] in the presence of 10%mol Bu_4NHSO_4 as a phase transfer catalyst. [c] in the presence of 10%mol $BnEt_3NCl$ as a phase transfer catalyst. [d] No reaction.

When NaOH was utilized, it was found that a reaction can proceed in CH_2Cl_2 and in order to facilitate the reaction, a phase-transfer catalyst (PTC) was needed. Moreover, additional conditions of the reaction under study also require the use of excess (10 eq) of NaOH. The phase transfer catalyst employed in the reactions were benzyltriethylammonium chloride and tetrabutylammonium sulfate. As shown in the table, reactions carried out using 1.1 eq of diethyl phosphite at room temperature for 1 h in the presence of NaOH and PTC proceeded in good to high yields. It appears that $BnEt_3NCl$ performs better than Bu_4NHSO_4 in this case. When the use of an alternative base, K_2CO_3, was investigated, it was found that the reaction could be performed heterogeneously in acetonitrile solvent. The reaction readily occurred at room temperature in high yields. Also, the reaction time can be decreased from 1d to 1h while the product yields remained relatively high. Unexpectedly, when the phase

transfer catalyst ($BnEt_3NCl$) was used in the reaction in the presence of K_2CO_3 as a base (entry 5), no the reaction occurred.

These studies showed that hydrophosphonylation can be carried out under mild conditions with various choices of bases. The preferred choices are DBU or the less expensive K_2CO_3.

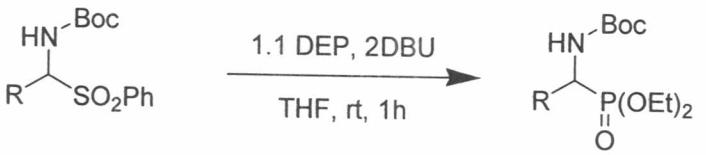
3.3.3 The substrate generality

Following the successful results with the aromatic amido sulfone **(VI)**, the scope of the reaction was explored employing a number of structurally different substituted aromatic amido sulfones under the same reaction conditions. In all cases, the products were purified by column chromatography after work up. All compounds were fully characterized by ^1H, ^{13}C, and ^{31}P NMR spectroscopy.

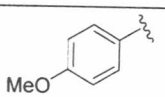
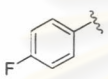
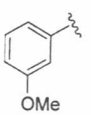
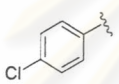
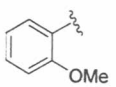
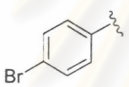
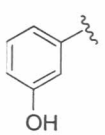
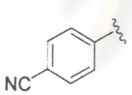
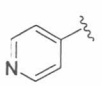
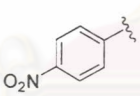
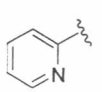
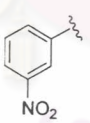
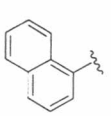
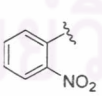
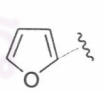
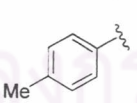
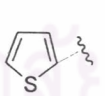
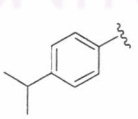
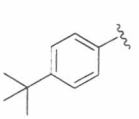
3.3.3.1 Variation of type and position of substituents on the aromatic amido sulfones

As illustrated so far, hydrophosphonylation of aromatic amido sulfones by diethyl phosphite in the presence of DBU proceeded smoothly to give the expected product in good to high yields. We were encouraged to explore further the scope of the reaction. This section will focus mainly on the generality of substituents on the aromatic substrates. Amido sulfones **VI** bearing various substituents on different positions were synthesized, the data of which were shown earlier in Table 3.12. They were then subjected to the reaction with diethyl phosphite (1.1 eq) in the presence of DBU under the optimum conditions obtained previously (Method A). Product yields of these aromatic substrates are shown in Table 3.13 (entries 1-20).

Table 3.13 Hydrophosphonylation of various amido sulfones (**VI**) bearing different substituents on the aromatic ring by diethyl phosphite in the presence of DBU (2 eq)



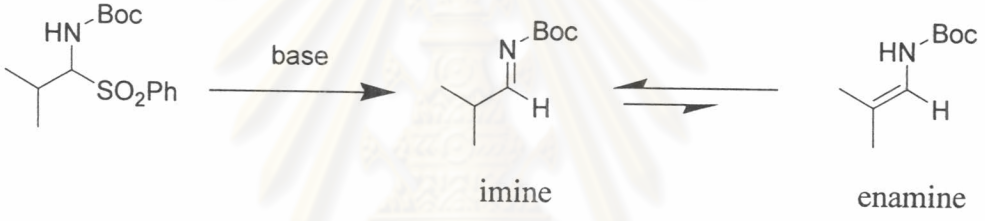
VI **VIII**

entry	Product (**VIII**)	R	yield (%)[a]	entry	Product (**VIII**)	R	yield (%)[a]
1	**VIII-1**		83	12	**VIII-12**		78
2	**VIII-2**		80	13	**VIII-13**		93
3	**VIII-3**		75	14	**VIII-14**		74
4	**VIII-4**		77	15	**VIII-15**		77
5	**VIII-5**		80	16	**VIII-16**		79
6	**VIII-6**		57	17	**VIII-17**		86
7	**VIII-7**		57	18	**VIII-18**		87
8	**VIII-8**		70	19	**VIII-19**		82
9	**VIII-9**		88	20	**VIII-20**		59
10	**VIII-10**		84	21	**VIII-23**		14
11	**VIII-11**		94	22	**VIII-26**		57
				23	**VIII-27**	*n*-C_9H_{17}	10

DEP: diethyl phosphite. [a] Isolated yield.

As shown, in general the reaction of these aromatic compounds proceed very smoothly to give good to very high yields in most cases.

The success in hydrophosphonylation of aromatic amido sulfone **VI** prompted us to further investigate similar reactions with their aliphatic counterparts. Similar reactions were carried out with aliphatic substrate models **VI-23**, **VI-26**, and **VI-27** bearing an isopropyl, *tert*-butyl, and *n*-nonyl group, respectively (entries 21-23, Table 3.13). It was observed that the reaction sluggishly proceeded to give the desired products (**VIII-23**, **VIII-26**, and **VIII-27**) in much lower yields compared to the aromatic substrates. It is noticeable that poor yields of product was obtained when R = ^{i}Pr and *n*-C_9H_{17} while a reasonable yield was obtained when R = ^{t}Bu. The much lower yields observed with reactions of enolizable aliphatic substrates such as those with R = ^{i}Pr and *n*-C_9H_{17} can be explained by isomerization of the imine to its less reactive enamine form.

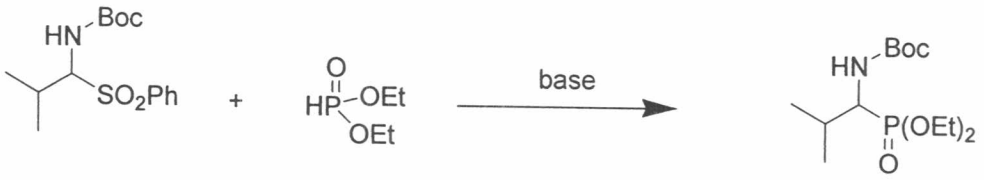


When R = ^{t}Bu, the yield is higher, although not quite as high as those obtained in the aromatic cases. The steric congestion experienced in the pivalaldehyde-derived sulfone would hinder an addition of diethyl phosphite, therefore, a lower yield than the aromatic amido sulfone was obtained.

As a result, the application of DBU-mediated hydrophosphonylation of *N*-Boc imines are limited to aromatic and aliphatic substrates without α-hydrogen. The reaction conditions more suitable for substrate derived from aliphatic aldehydes were yet to be optimized.

It was envisaged that the generality and/or the limitation of the reaction could be better investigated with the more difficult enolizable aliphatic amido sulfones.

3.3.3.2 Addition of diethyl phosphite to aliphatic amido sulfones



VI-23 **VIII-23**

Several attempts to improve the product yields of aliphatic phosphonates under basic condition were performed using various bases. The isopropyl amido sulfone (**VI-23**) was chosen as a model substrate to screen for suitable reaction conditions. Table 3.14 presents the results obtained. Entry 1 is included for comparison purposes. As shown in entries 1-6, among all bases investigated (DBU, K_2CO_3, NaH, NEt_3, and **85**), K_2CO_3 was found to give the most impressive results whereby the desired product was isolated in 66% in MeCN as a solvent at room temperature (entry 6).

Table 3.14 Hydrophosphonylation of diethyl phosphite and isopropyl amido sulfone (**VI-23**) in different bases

entry	Base (eq)	solvent	time	temp	yield (%)[a]
1	DBU (2)	THF	1 d	rt	14
2	**85** (2)	THF	1 d	rt	-[b]
3	NaH (2.2)	THF	1 d	rt	11
4	NEt_3 (2)	THF	1 d	rt	-[b]
5	NEt_3 (2)	THF	1 d	80°C	-[b]
6	K_2CO_3 (2)	MeCN	1 d	rt	66
7	K_2CO_3 (2)	MeCN	1 d	80°C	35
8	K_2CO_3 (2)	MeCN	5 h	50°C	57
9	K_2CO_3 (2)	MeCN	2 d	rt	80
10	K_2CO_3 (5)	MeCN	2 d	rt	70
11	K_2CO_3 (10)	MeCN	2 d	rt	48

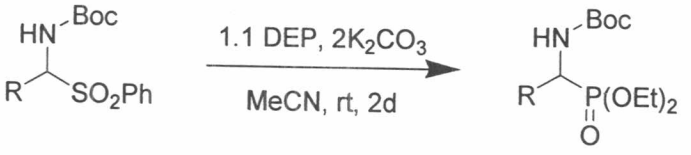
[a] Isolated yield. [b] No reaction.

From the results presented in the table 3.14, it is evidenced that K_2CO_3 can promote the reaction efficiently (entries 6-11). Increasing the reaction temperature to 80°C for 1 day (entry 7) resulted in a lower yield (35%), while a reaction performed for 5 h at 50°C gave 57% of the products (entry 8). Longer reaction time led to increased product yields. Therefore, a reaction carried out for 2 days gave a higher yield (80%, entry 9) compared to a reaction run for 1 day (66%, entry 6).

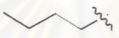
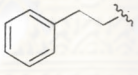
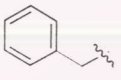
Furthermore, it was conceivable that a higher concentration of nucleophile could assist in driving the reaction forward. Therefore, reactions were carried out where the amount of K_2CO_3 was increased up to 5 or 10 eq. However, as shown in entries 10 and 11, the higher the amount of DEP, the more product yields dropped (70 and 48%, respectively). Therefore, the best condition (2 eq K_2CO_3 , MeCN, rt, 2 d) was selected for use with other aliphatic amido sulfones. The method will be referred to as Method B.

Reactions of various substrates derived from different aliphatic aldehydes were investigated using Method B as illustrated in Table 3.15.

Table 3.15 Comparison of yields of aliphatic substrates between Methods B and A.



VI **VIII**

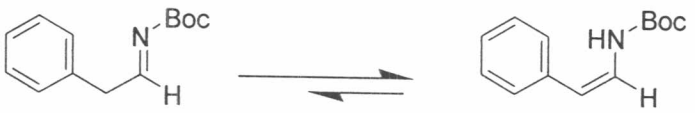
entry	Product (**VIII**)	R	yield (%)[a]	
			Method B	Method A
1	**VIII-21**		54	N/A
2	**VIII-22**		65	N/A
3	**VIII-23**		80	14
4	**VIII-24**		59	N/A
5	**VIII-25**		68	N/A
6	**VIII-26**		78	57
7	**VIII-27**	nC$_9$H$_{17}$	62	10
8	**VIII-29**		50	N/A
9	**VIII-30**		87	N/A
10	**VIII-28**		-[b]	N/A

DEP : diethyl phosphite. [a] Isolated yield. [b] No reaction.

The results indicate that Method B is more suitable for hydrophosphonylation of aliphatic substrates than Method A. It is emphasized by the increased yield from 57% to 78% in the case of non-enolizable ^{t}butyl substrate (entry 6). The effect is more pronounced for enolizable ^{i}Pr and n-C$_4$H$_9$ amido sulfones where product yields increased dramatically from 14% and 10% to 80% and 62%, respectively (entries 3 and 7).

In addition, the results also revealed that good to high yields of aliphatic phosphonates can be obtained when using amido sulfones bearing branched chain alkyl substituents as substrates, while straight chain counterparts provided fair yields of product. It is noteworthy to point out that no reaction took place with a substrate bearing a phenylmethyl group (Table 3.15, entry 10). This may be rationalized by the

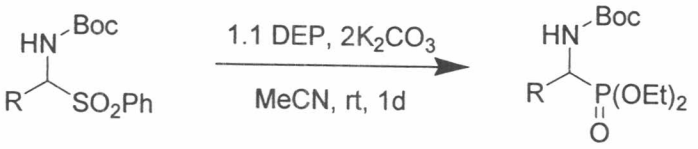
fact that the enamine form is highly more favored than the imine form. This is due to a strong resonance stabilization experienced by the enamine tautomer (thermodynamic factor) as well as the high acidity of the α-hydrogen (kinetic factor).



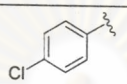
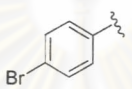
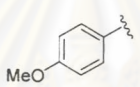
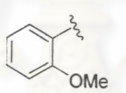
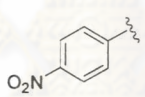
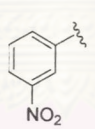
This novel and facile hydrophosphonylation condition for aliphatic substrate employing K_2CO_3 as a base had also been applied successfully to the aromatic counterparts. Preliminary tests on a selected aromatic amido sulfone revealed that a reaction carried out by a modified Method B, i.e. the reaction time reduced to 1 d, can still afford comparable yields. Therefore, conditions under modified Method B was utilized for reactions of other aromatic amido sulfones as well. The data are summarized in Table 3.15 with results from Method A included for comparison purposes.

We were very pleased to see that in most cases, amido sulfones derived from aromatic aldehydes undergo hydrophosphonylation very efficiently under both Method A, with DBU as a base, and modified Method B using the K_2CO_3/MeCN system.

Table 3.16 Hydrophosphonylation of aromatic substrates using a modified Method B.



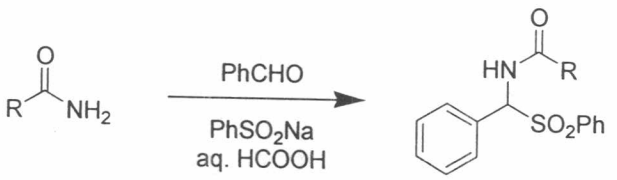
VI **VIII**

entry	Product (**VIII**)	R	yield (%)[a]	
			Modified Method B	Method A
1	**VIII-3**		72	75
2	**VIII-4**		80	77
3	**VIII-12**		79	78
4	**VIII-14**		71	74
5	**VIII-6**		40	57
6	**VIII-7**		63	57
7	**VIII-20**		67	59

DEP : diethyl phosphite. [a] Isolated yield.

3.3.3.3 Variation of type of *N*-protected 1-amido sulfones

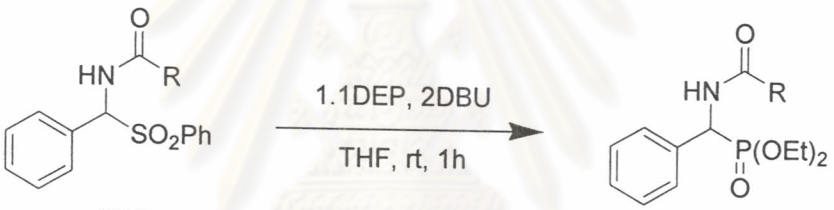
For synthetic application purposes, it is sensible to check the validity of the reaction on compounds with other substituents on nitrogen which can later be removed. To further explore the scope of the hydrophosphonylation of amido sulfones, the reactions were preformed using other substrates with various *N*-protecting groups such as formyl, acetyl, ethoxycarbonyl, and benzyloxy carbonyl. The substrates were synthesized in the same way as the *N*-Boc derivatives.



VII
VII-1 R = H (10% yield)
VII-2 R = CH_3 (15% yield)
VII-3 R = OEt (62% yield)
VII-4 R = OCH_2Ph (27% yield)

The aromatic amido sulfones **VII-1** to **VII-4** were subjected to the hydrophosphonylation reaction. The conditions employed were the optimized conditions suitable for aromatic substrates (Method A). In all cases, satisfactorily yields were observed as shown in Table 3.17.

Table 3.17 Hydrophosphonylation of various of types of *N*-protected amido sulfones **(VII-1-4)**



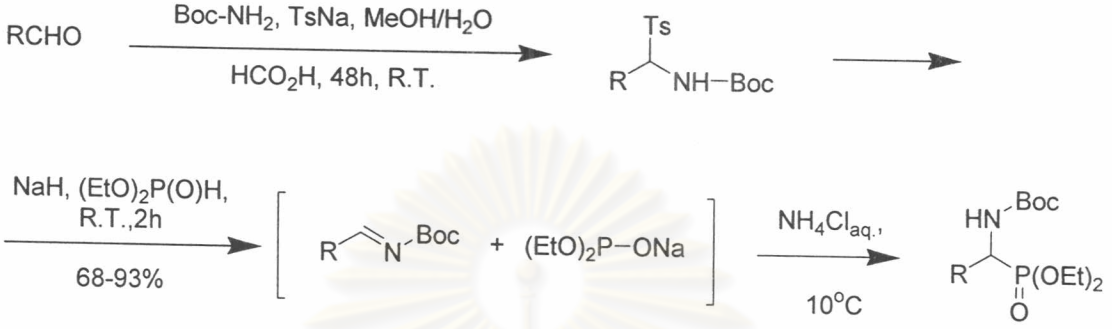
VII **IX**

entry	Substrate (VII)	Product (IX)	R	yield (%)[a]
1	**VII-1**	**IX-1**	H	60
2	**VII-2**	**IX-2**	CH_3	50
3	**VII-3**	**IX-3**	OEt	79
4	**VII-4**	**IX-4**	OCH_2Ph	74

DEP : diethyl phosphite. [a] Isolated yield.

The methods developed in our research indeed present themselves as versatile and economical approach to the synthesis of α-aminophosphonic acid precursors which can further be elaborated to other functionalities for potential use in the future.

During the course of our study, a parallel work utilizing α-amidoalkyl-*p*-tolyl sulfones to prepare *N*-Boc-1-aminoalkylphosphonates was reported by Zwierzak[62] as part of their studies to search for alternative substrates for the synthesis of phosphonamidate peptides.



R = H, Me, Et, Pr, ^{i}Pr, Bu, ^{i}Bu, Ph, *p*-OMePh

The reactions were performed upon α-amidoalkyl-*p*-tolyl sulfones derived from aromatic and aliphatic aldehydes. However, the generality of the substrates is of more limited scope. The yields of the reactions are comparable to our systems. However, the choice of base employed in our system is far more superior since DBU and K_2CO_3 can be handled with much more ease than NaH. Moreover, the synthetic methods developed in our work has been proven to be applicable to a wide range of both aromatic and aliphatic, even enolizable, α-amido sulfones. In addition, the reaction can be expanded to cover reactions of different *N*-protected compounds.

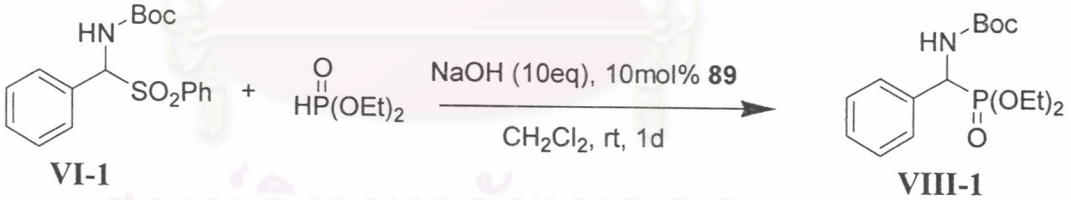
Kabachnik and coworkers[63] have previously reported the utilization of K_2CO_3 as a bases for the synthesis of α-aminophosphonates from simple imines (benzene, 20°C, 8 h) in the presence of tetrabutylammonium iodide (TBAI) which acted as a PTC. The product yields ranged from 64-80%.

3.3.4 Attempts on asymmetric synthesis of *N*-protected diethyl 1-aminoalkyl phosphonates from α-amido sulfones.

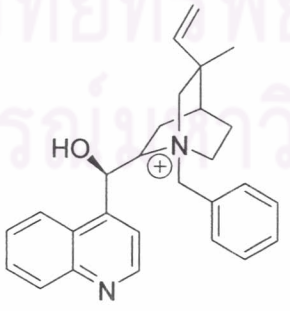
It is anticipated that asymmetric induction in hydrophosphonylation of the amido sulfones of choice may be achieved. The second generation (auxiliary-controlled) method, the third generation (reagent-controlled) method, and the fourth generation (catalyst-controlled) method offer themselves as possible procedures. Therefore, this section will cover attempts to perform all of auxiliary-controlled, reagent-controlled, and catalyst-controlled methodologies towards the synthesis of the asymmetric product.

3.3.4.1.Catalyst-controlled (fourth generation) method

Since the reaction of amido sulfone **VI** with diethyl phosphite can take place in the presence of NaOH/PTC, it is sensible to attempt an asymmetric reaction using chiral PTC. The chiral phase transfer catalyst **89** was used as a catalyst for hydrophosphonylation of the amido sulfone **VI-1** in the presence of NaOH as a base in CH_2Cl_2 at room temperature for 1 h. The desired product **VIII-1** was obtained in only poor yield (28%). Due to the poor yield obtained, the method was not investigated further.



VI-1 **VIII-1**

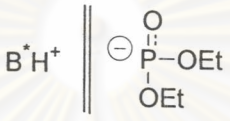


N-benzylcinchonidinium chloride **89**

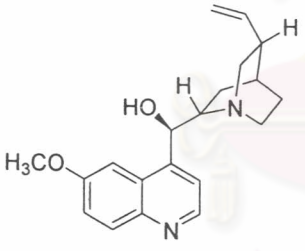
3.3.4.2 Reagent-controlled (third generation) method

According to the proposed mechanism of the base-catalyzed addition of the active phosphorus species to the imine formed *in situ* from the elimination of the sulfinate, depicted in scheme 3.2 (section 3.3.2), one might expect that the phosphorus species is present in the ion pair form having the protonated base as the counterion. This species will then attack the imine carbon giving rise to the product.

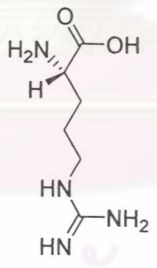
It is anticipated that if an optically active base is employed in the reaction, the anion of the so-formed ion pair (as depicted) would act as a chiral nucleophile and attack the imine. Asymmetric induction may then be achieved.



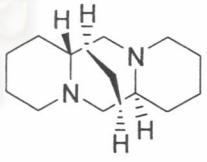
Based on this principle, selected chiral bases were put to the test. Naturally occuring optically active bases which are easily accessible such as quinine (**71**), arginine (**90**), and sparteine (**80**) were employed as a substitute for DBU in different solvents (modified Method A) in the reaction of the amido sulfone **VI-1** derived from benzaldehyde. The data are presented in Table 3.18.



71

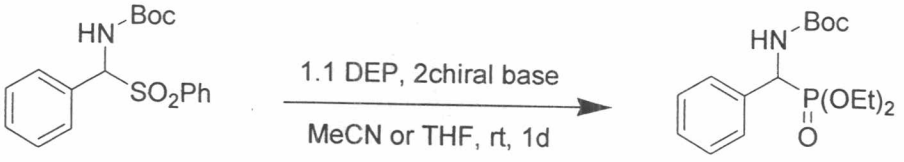


90



80

Table 3.18 Attempts on asymmetric phosphonylation in the presence of chiral bases.



VI-1 **VIII-1**

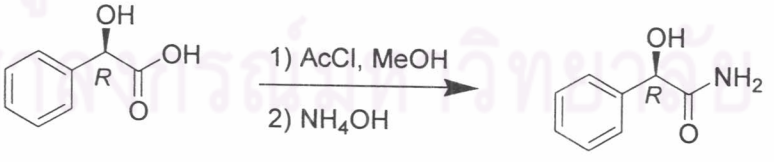
entry	Base(eq)	DEP(eq)	solvent	time	yield (%)
1	Quinine (2)	1.1	MeCN	1 d	-[a]
2	Arginine (2)	1.1	MeCN	1 d	-[a]
3	Sparteine (2)	1.1	THF	1 d	-[a]

DEP : diethyl phosphite. [a] No reaction.

It was rather unfortunate that after several attempts the reaction failed to give the desired product. One factor responsible for the unsuccessful reaction, at least in the case of arginine, was the insolubility of the bases in most organic solvents. This still leaves room for future development of such a method.

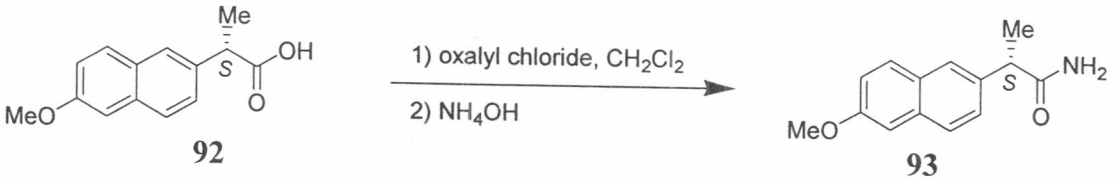
3.3.4.3 Auxiliary-controlled (second generation) method

Attempts to apply this reaction to asymmetric synthesis by means of chiral auxiliary such as D-(-)-madelamide (**91**) and (*S*)-(+)-Naproxen amide (**92**)have been made. In the preliminary experiments, the conversion of D-(-)-mandelamide from D-(-)-mandelic acid (**70**) according to the literature procedure of Meyers[64] was carrried out.



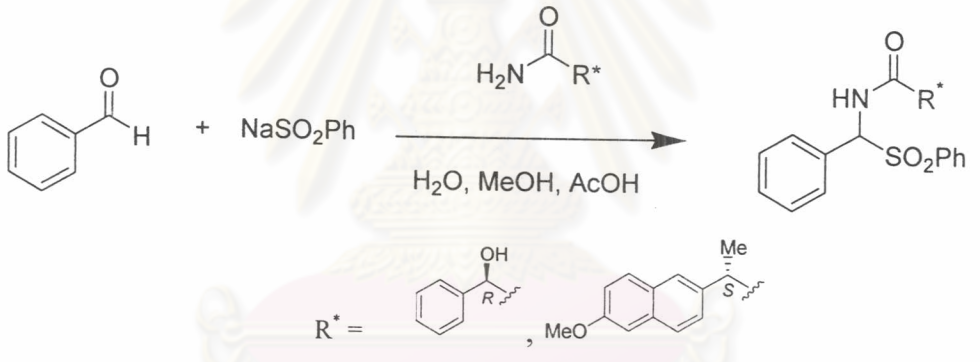
70 **91**

In addition, (*S*)-(+)-Naproxen amide was prepared from the reaction of (*S*)-(+)-Naproxen®, [2-(6-methoxynaphthalen-2-yl)propionic acid], (**92**) with oxalyl chloride in dichloromethane at room temperature and subsequetly quenched with ammonium hydroxide.



92 **93**

The preparation of chiral amido sulfones derived from benzaldehyde, sodium benzenesulfinate, and chiral carbamate **91** or **93** in formic acid at room temperature was performed under standard conditions. Unfortunately, the Naproxen amide has low solubility in methanol/water solvent system. Changing the solvent to 2-propanol/water solvent system could not solve the problem. Increasing the temperature of the mixture did not improve the solubility. The alternative chiral auxiliary, mandelamide, dissolved more readily in this solvent system (methanol/water), however, the desired product was obtained only in a trace amount. Substantial amount of the unreacted starting material (benzaldehyde) was recovered.



Unsuccesful preliminary experiments leaves room for improvement of the preparation of chiral amido sulfones provided that the problem of solubility of can be solved. In addition, reaction of substrates prepared from other readily available chiral carbamates could be explored.

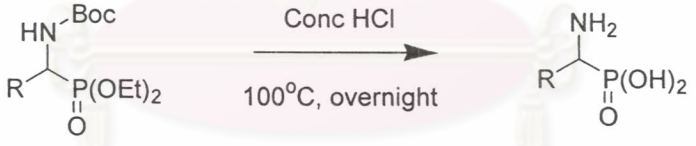
3.4 Hydrolysis of α-aminophosphonates

α-Aminophosphonates offer themselves as excellent phosphonic acid precursors. α-Aminophosphonates enabled the hydrolytic removal of the phosphonate ester groups by acid hydrolysis or catalytic hydrogenation

94 **95**

From the literature review, Shibasaki *et al.*[42] employed a two step sequence. First, α-aminophosphonate (**94**) is treated with H_2 5 mol% $Pd(OH)_2$ in MeOH. The product is then treated with concentrated HCl at reflux temperature, to remove the ester group giving the free amine.

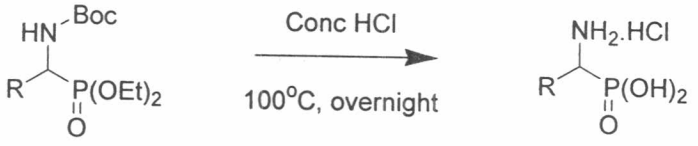
Smith *et al.*[15] reported hydrolysis of diethyl phosphonates to phosphonic acids by hydrolysis in hot concentrated HCl for 14-16 h, furnishing the known α-amino phosphonic acids.



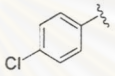
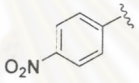
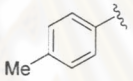
VIII **X**

This is the method of choice for this work. Hydrolysis with hot concentrated HCl simultaneously removed both the phosphonate ester and Boc groups giving α-aminophosphonic acids (**X**) as hydrochloride salt. Aliphatic and aromatic substrates electron withdrawing and electron donating substituents gave the expected products in high yields as illustrated in Table 3.19. All products were characterized by ^{1}H NMR as evidenced by the absence of Boc and ethyl peaks at 1.40 and 1.09-1.28 ppm together with characteristic doublet $C_\alpha P$ signals ($^1J_{HP}$ = 16.3 Hz) around 4.25 ppm.

Table 3.19 Hydrolysis of diethyl phosphonates to α-aminophosphonic acids (**X**) using concentrated HCl



VIII **X**

Entry	Product **X**	R	%yield
1	**X-1**		92
2	**X-2**		90
3	**X-3**		99
4	**X-4**		87
5	**X-5**		82
6	**X-6**		95