CHAPTER III

RESULTS AND DISCUSSION

3.1 Analytical methods for the determination of enantiomeric purity of α-hydroxyphosphonates.

3.1.1 NMR spectroscopy.

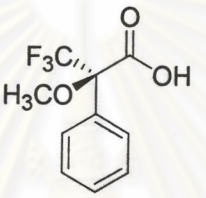
Enantiomers cannot be distinguished in an achiral medium by their NMR spectra because their resonances are chemical shift equivalent (isochronous). In contrast, diastereomers may be distinguished because certain resonances are chemical shift non-equivalent (anisochronous). Determination of enantiomeric purity using NMR requires the intervention of a chiral auxiliary to convert an enantiomeric mixture into a mixture of diastereomers. Provided that the magnitude of the observed chemical shift non-equivalence is sufficient to give baseline resolution, integration of the appropriate signals gives a measure of the diastereomeric composition. This can be directly related to the enantiomeric composition of the original mixture.

There are three types of chiral auxiliary widely used. Chiral derivatizing agents (CDAs) form diastereomers while chiral solvating agents (CSAs) and chiral lanthanide shifts reagents (CLSRs) form diastereomeric complexes *in situ* with substrate enantiomers. An effective chiral auxiliary should induce significant NMR chemical shift anisochronicity in as large a range of substrates as possible. Further, if the sense of non-equivalence is consistent in a series of compounds, then once a standard of known stereochemistry has been studied the absolute configuration of the major and minor enantiomers present in chemically similar unknown mixtures can be deduced from the NMR spectra.

3.1.1.1 Chiral derivatizing agents (CDAs). An enantiomeric mixture can be converted to a pair of diastereomers prior to NMR analysis by the reaction with a chiral derivatizing agent. A CDA forms discrete diastereomers free from the effect of chemical exchange, unlike chiral solvating agents and chiral lanthanide shift reagents which form diastereomeric complexes *via* reversible equilibria. The

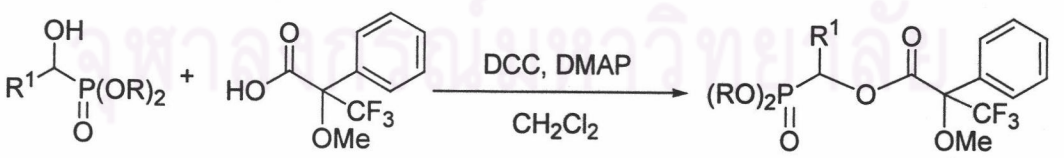
magnitude of the chemical shift non-equivalence, $\Delta\delta$, is typically five times larger than that observed in the presence of a chiral solvating agents (CSA).

The method using optically active α-methoxy-α-(trifluoromethyl)phenylacetic acid (**51**, MTPA; Mosher's acid) as a chiral derivatizing agent has been employed most widely. This procedure, however, is not applicable when the ^{1}H NMR signals of the respective diastereomers are not sufficiently separated, or when the crucial signals overlap with other resonances. In such cases, the presence of CF_3 group allows the use of ^{19}F NMR which is much less congested and therefore baseline separation is more likely.



Mosher's acid (**51**)

In 1994, Hammerschmidt and Li reported on the use of ^{1}H NMR spectroscopy of MTPA esters of α-hydroxyphosphonates to assign their absolute configurations.[51] As mentioned earlier ^{1}H NMR spectroscopy of MTPA esters might not be an accurate method to determine the enantiomeric purity if relevant signals were overlapping with others. The phosphorus atom in the phosphonate part is certainly an auxiliary to determine the absolute configuration and enantiomeric purity with ^{31}P NMR since the chemical shift dispersion is usually large and spectra are simple when broad-band proton decoupling is used.



(*R*)- or (*S*)-MTPA

51

Mosher's ester

52

(**a**: R = Me; **b**: R = Et)

Figure 3.1 Preparation of diastereomeric Mosher's esters.

Alternatively, Spilling and co-workers determined the absolute configuration of α-hydroxyphosphonates by NMR spectroscopy of the *O*-methyl mandelate ester derivatives (**54**).[52] The *O*-methyl mandelate ester diastereomers were cleanly separated by chromatography on silica gel and were distinguishable by their ^{1}H NMR and ^{31}P NMR.

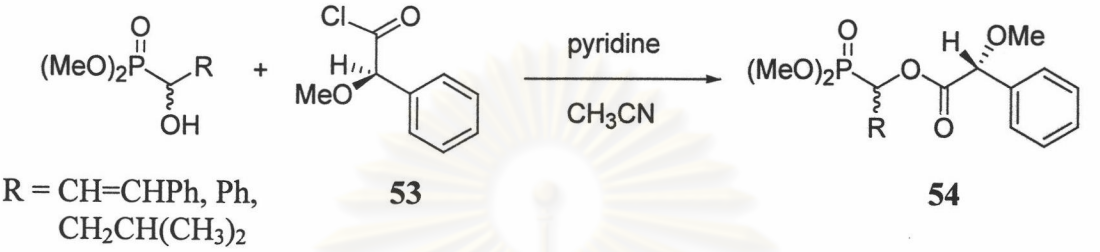


Figure 3.2 Preparation of the *O*-methyl mandelate esters.

Recently, Gajda and Blazewska showed that the enantiomerically pure acid chloride of (*S*)-Naproxen® **55a** and (*S*)-Ibuprofen® **55b** were convenient chiral derivatizing agents for determination of the enantiomeric purity of diethyl 1-hydroxy and 2-hydroxyalkylphosphonates as well as their aminoalkylphosphonates analogues by ^{31}P NMR spectroscopy.[53]

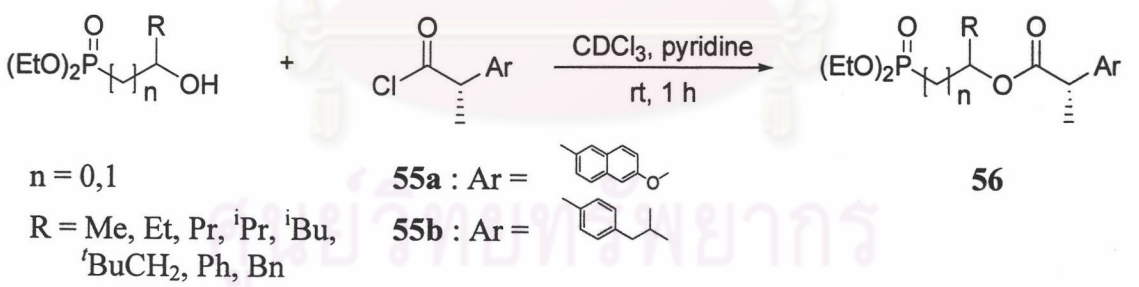


Figure 3.3 Preparation of the Naproxen® and Ibuprofen® derivatives of the diethyl hydroxyphosphonates.

3.1.1.2 Chiral solvating agents (CSAs). When a chiral solute dissolves in a chiral solvating agent a stereochemical interaction must be involved. Chiral solvating agents form diastereomeric solvation complexes with the substrate enantiomers *via* rapidly reversible equilibria in competition with the bulk solvent. The advantage of the CSA technique is that it is quick and simple, requiring no separate derivatizing reaction prior to NMR assay. There is no problem with accidental

enrichment or racemization of the sample due to differential reaction rates, provided that the sample remains in solution in the presence of CSA. The enantiomeric purity of CSA is not crucial. If a CSA of less than 100% *ee* is used, the magnitude of the chemical shift non-equivalence is reduced but the relative signal intensities are not affected. In general, the magnitude of the chemical shift non-equivalence is smaller than when using CDAs, but with the advent of high modern field NMR spectrometers widely available nowadays, this advantage is no longer crucial. In addition, the limitation of this method is that only a limited range of cosolvents may be used. Nonpolar solvents ($CDCl_3$, CCl_4, and C_6D_6) tend to minimize the observed anisochrony between the diastereoisomeric complexes while more polar solvents preferentially solvate the solute and the $\Delta\delta$ falls to zero. Lejczak and co-workers reported an example of successful enantiopurity determination of α-hydroxyphosphonates by ^{31}P NMR spectroscopy where quinine was employed as a chiral solvating agent.[54]

3.1.1.3 Chiral lanthanide shift reagents (CLSRs). Most of these chiral shift reagents are organic complexes of the paramagnetic rare-earth metals from the lanthanide series. Addition of lanthanide shift reagent to an organic compound may result in the shifts (upfield or downfield), which depends primarily on which metal is being used. The size of the shifts is determined by the distance of the given type of proton from the donor group. The six coordinate lanthanide complexes form weak addition complexes with a large variety of organic compound that is in fast exchange with unbond organic substrate on the NMR time scale. The association complexes formed are especially moisture sensitive. One disadvantage of this technique is the severe line broadening which occurs as a result of paramagnetic properties of lanthanide shift reagents.

3.1.2 Chromatographic methods.

3.1.2.1 Gas chromatography. An attractive method for the analysis of mixtures of enantiomers is chiral gas chromatography (GC). This sensitive method is unaffected by trace impurities, and quick and simple to carry out. The premise upon which the method is based is that molecular association may lead to sufficient chiral recognition that enantiomer resolution results. The method uses a chiral

stationary phase, which contains an auxiliary resolving agent of high enantiomeric purity. The enantiomers to be analyzed undergo rapid and reversible diastereomeric interactions with stationary phase and hence may be eluted at different rates. The limitations of this method are that samples should be sufficiently volatile and thermally stable, and should be quantitatively resolved on chiral GC phase.

3.1.2.2 High performance liquid chromatography. The principle of enantiomeric separation by chromatographic method 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. The separability factor, $\Delta\delta$, for two components in HPLC chromatogram depends upon the band shape and is related directly to the efficiency of column, *i.e.* flow rate, particle size, sample size, and quality of packing. Efficient HPLC systems produce good separations for two components having $\alpha \geq 1.05$. In HPLC technique, pre-column derivatization (in the absence of racemization) with a chiral derivatizing agent may be required to give chromatographically separable diastereomers. An alternative is to use an achiral support and to elute with a chiral eluant. Most of reported works employed enantiomeric chromatographic analysis techniques on chiral HPLC columns such as Daicel ChiralPak AD®, or ChiralPak AS® to determine the optical purity of α-hydroxyphosphonates.[38,52]

3.2 The results of analytical methods for the determination of enantiomeric purity of α-hydroxyphosphonates.

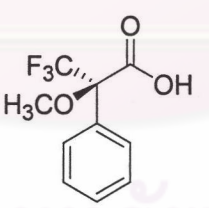
In order to find a suitable method for determination of enantiomeric excess of α-hydroxyphosphonates, two analytical techniques were compared in this study, namely, NMR methods using CDAs and CSAs as well as chiral GC. Although chiral HPLC is widely accepted as a very reliable method for enantiomeric separation, the technique requires expensive columns, solvents, and other accessories. We, therefore, intended to focus first on rapid, convenient, yet reliable methods available at hands.

Initial experiments involved a search for a suitable analytical technique to separate enantiomers of model substrates for the study. Herein the separation techniques for determination of enantioselectivity of α-hydroxyphosphonates were studied. Results from NMR spectroscopy and chiral GC analyses will be reported.

3.2.1 NMR spectroscopic analysis.

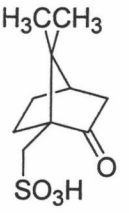
In theory, determination of enantioselectivity of reaction by ^{1}H NMR spectroscopy can be achieved by monitoring the integral ratios of the proton at the α position to the phosphonyl group. For α-hydroxyphosphonic acid derivatives, the methine proton resonance in $CDCl_3$ appears as a doublet due to the phosphorus-proton coupling ($^2J_{PH}$ = 9-12 Hz, δ_H ~ 5 ppm), with no interference by the alkyl proton of the alkoxy groups. This doublet of enantiomeric protons should split in to 2 sets of doublet under chiral environment. Whether or not it will split and its magnitude depends on the type of chiral solvating agents or chiral derivatizing agents employed which will be discussed next.

3.2.1.1 Analysis employing chiral solvating agents. Chiral solvating agents offer a more direct, rapid, clean, and simple method for determination of enantiomeric compositions of a mixture. In order to screen for an effective chiral solvating agent, the example of diethyl 1-hydroxyphenylmethylphosphonate (**50b**) was chosen as the representative model compound. At the beginning, one of the most widely used chiral solvating agents for determination of enantiomeric composition of alcohols and amines by NMR method, α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA or Mosher's acid, **51**), was tested as a potential CSA.



(*R*)-Mosher's acid ((*R*)-**51**)

To a $CDCl_3$ solution of **50b** was added ca. 0.5 equivalent of Mosher's acid. A ^{1}H NMR spectrum was recorded. No separation at the enantiomeric proton peak was observed. Additional amounts of the chiral solvating agent were added at a 0.5 equiv increments. However, even after 3 equivalents of **51** were added to, no separation of the peak of enantiomeric proton was observed. Therefore, the use of another CSA was investigated as an alternative. An attempt to separate enantiomeric isomers of **50b** was carried out by using (1*S*)-(+)-camphor-10-sulfonic acid (**57**). Unfortunately, an addition of up to 2 equivalents of **57** to the NMR solution of **50b** did not result in any peak separation in the ^{1}H NMR spectra.



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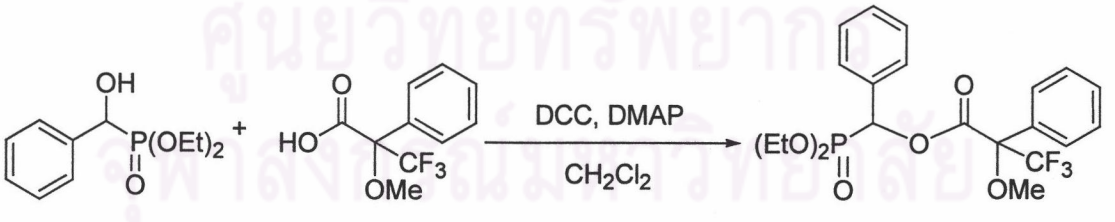
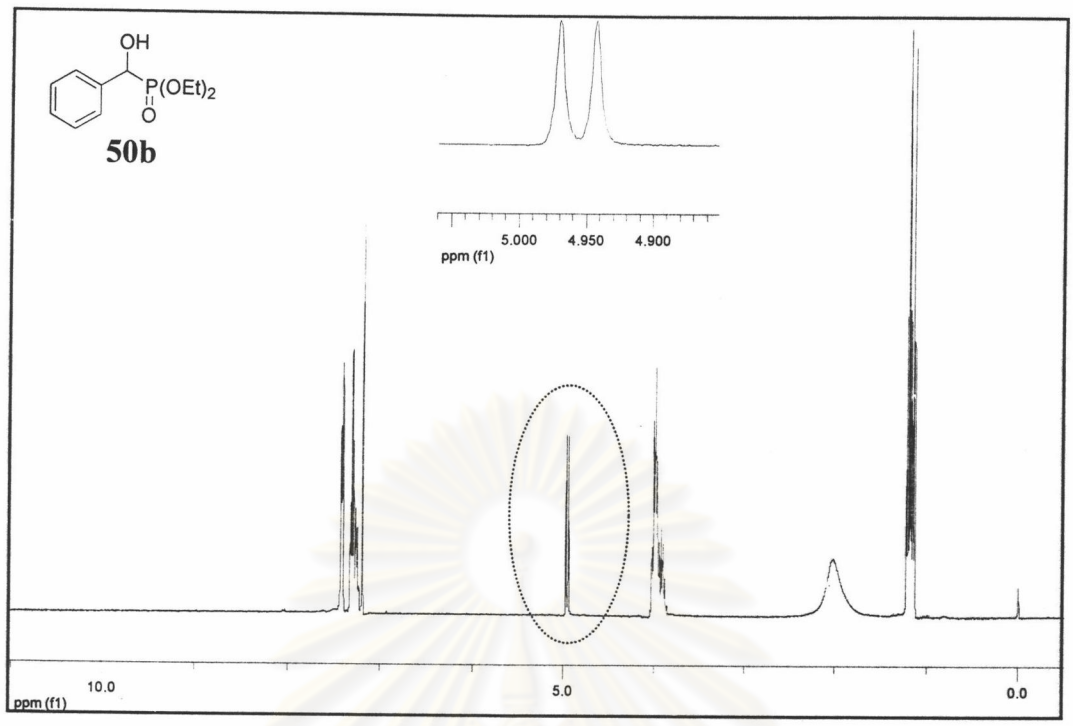
It was speculated that the failure to observe signal resolution in the ^{1}H NMR spectra even after the chiral solvating agents were added may be due to a low magnitude of the chemical shift non-equivalence. A possible alternative explanation include a slow chemical exchange rate between the compound of interest and the CSA. In this case, a preformed diastereomers may be required.

3.2.1.2 Analysis employing chiral derivatizing agents. As mentioned previously, a chiral derivatizing agent form discrete diastereomers free from the effect of chemical exchange hence typically giving larger magnitude of the chemical shift non-equivalence, $\Delta\delta$, than that observed in the presence of a chiral solvating agents. Also, the method using optically active Mosher's acid as CDA has been employed most widely. Therefore, Mosher's ester of α-hydroxyphosphonate **50b** was prepared from the reaction of (*R*)-, or (*S*)-**51** and α-hydroxyphosphonates **50b** by using *N*,*N*-dicyclohexylcarbodiimide and 4,4-dimethylaminopyridine as coupling reagents. The esters obtained were purified by passing through a short plug of silica gel.

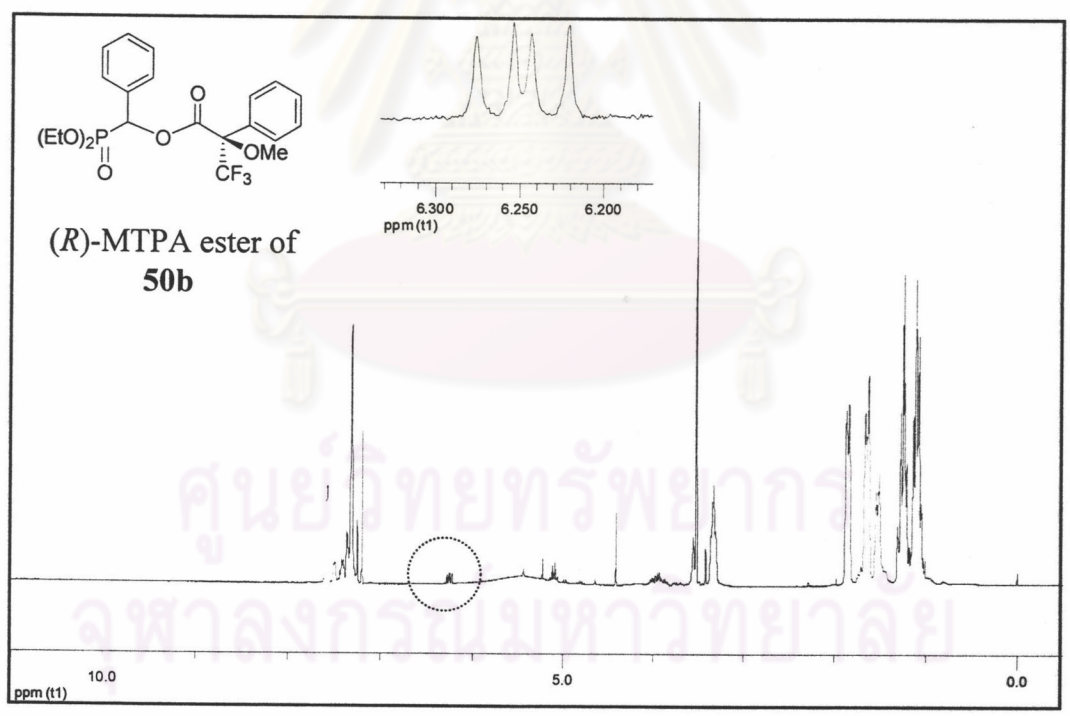


50b **51** **52b**

Figure 3.4 (a) shows a ^{1}H NMR spectrum of racemic phosphonate **50b** prior to derivatization with Mosher's acid. The inset illustrates the doublet peak of the α proton. A ^{1}H NMR spectrum of the isolated MTPA esters of **50b** is shown in Figure 3.4 (b).



(a)



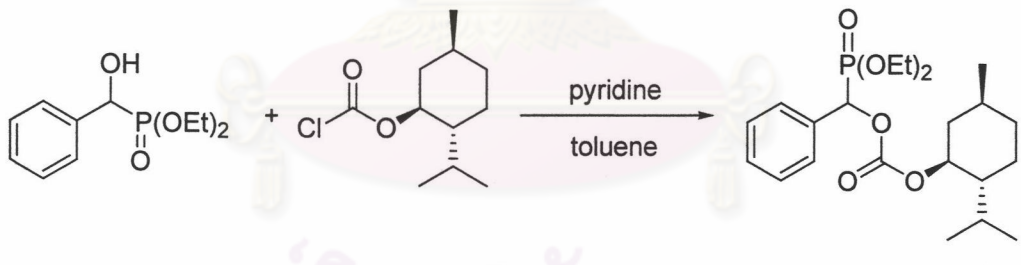
(b)

Figure 3.4 The ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of: (a) α-hydroxyphosphonate **50b** before derivatizing with Mosher's acid; (b) (*R*)-MTPA ester of **50b**.

It can be seen that the α protons of the previously two enantiomers can now be distinguished as they now have diastereomeric relationship. This results in an appearance of two sets of doublet peaks with different chemical shifts. Although the two sets are not completely resolved, reliable determination of peak integral should still be possible.

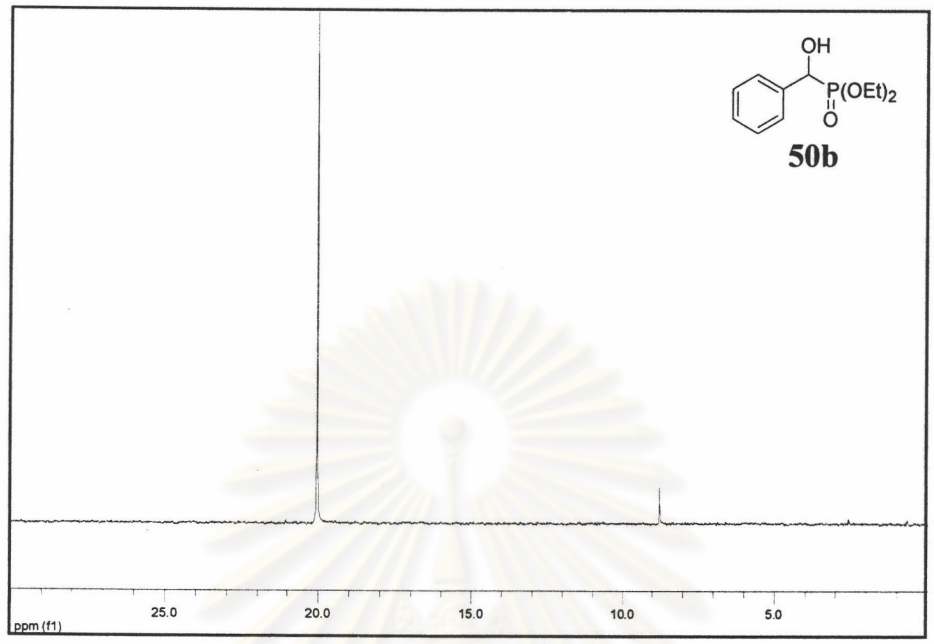
The determination of the enantiomeric composition phosphonate **50b** was also performed employing ^{31}P NMR spectroscopy using the same set of samples. Figure 3.5 (a) shows a ^{31}P NMR spectrum of the racemic phosphonate **50b** prior to derivatization with Mosher's acid. Only one peak corresponding to **50b** was observed. The spectrum of Mosher's esters (Figure 3.5 (b)) appears as 2 peaks of equal intensity corresponding to the two diastereoisomers of the esters.

Alternatively, (1*R*)-(-)-menthylchloroformate (**58**) was also explored for its use as a chiral derivatizing agent. α-Hydroxyphosphonate **50b** was treated with **58** under base catalysis condition. The corresponding formate esters **59** were obtained in 48 % yield. The ^{1}H NMR spectrum of diastereomers **59** obtained did not show adequate peak separation. The ^{31}P NMR spectrum of the compound was not determined due to the lack of instrument access at the time.

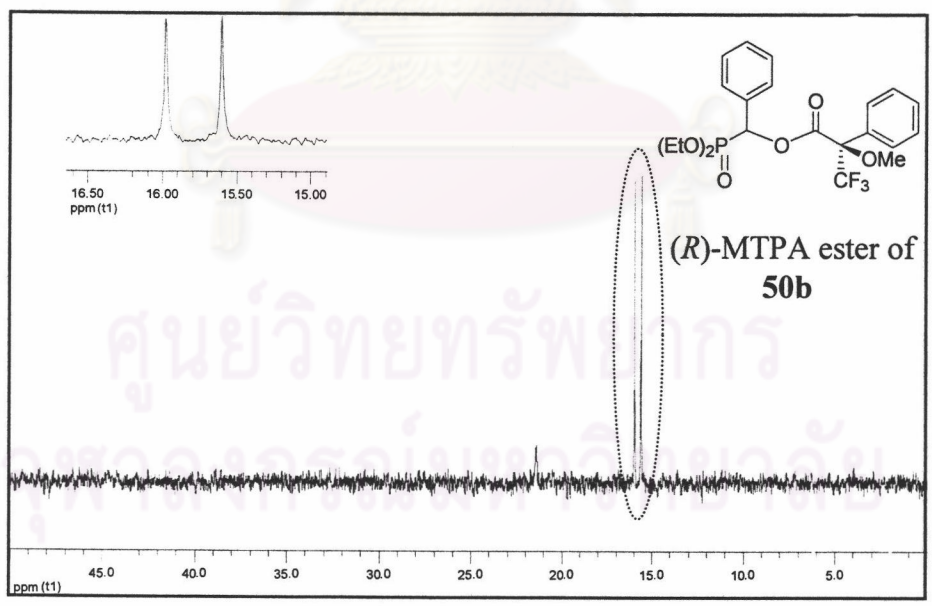


58 **59**

As illustrated above, enantiomeric compositions of the hydrophosphonylaing product can be determined indirectly by means of ^{1}H NMR spectroscopy on the Mosher's esters converted from the α-hydroxyphosphonates. However, this technique requires an equimolar amount of the chiral derivatizing agent at high optical purity, the cost of which is relatively high. Besides, a full step of reaction including work up and purification of the esters, which would obviously lengthen the entire process, prior to NMR analysis is also required. Therefore, this method, although can be used in principle, is of lower priority if a more direct and facile method is available.



(a)



(b)

Figure 3.5 The ^{31}P NMR spectra ($CDCl_3$, 202.35 MHz) of: (a) α-hydroxyphosphonate **50b** before derivatizing with Mosher's acid; (b) (*R*)-MTPA ester of **50b**.

3.2.4 Chiral GC analysis

While determination of enantiomeric purity by means of NMR spectroscopy was explored, an alternative method employing chiral gas chromatographic analysis was also investigated in parallel. It is precedent that determination of 1-phenylethanol and its derivatives by chiral gas chromatography on chiral column containing modified β-cyclodextrins was successful.[55] The chiral stationary phase used was heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (BSiMe). It was then envisaged that enantiomeric pair of α-hydroxyphosphonates **50**, possessing structurally similar chiral moiety to 1-phenylethanol, might separate on such a chiral column. Therefore, separation of racemic mixture of α-hydroxyphosphonates on chiral gas chromatography columns which were 25.5% BSiMe in OV-1701 and 10% BSiMe in PS255 were carried out. As anticipated, separation of the enantiomeric pair of most of the α-hydroxyphosphonates **50** were achieved in good to excellent baseline separation under both isothermal and temperature program conditions. Figure 3.6 (a) shows a representative chromatogram of a well resolved peaks corresponding to the two enantiomers of a racemic mixture of α-hydroxyphosphonate **50aa**. Figure 3.6 (b) shows a product mixture of **50aa** obtained from a catalytic asymmetric reaction with one of the best enantiomeric excesses. Assignment of absolute configuration of the major enantiomer has not been done at this time.

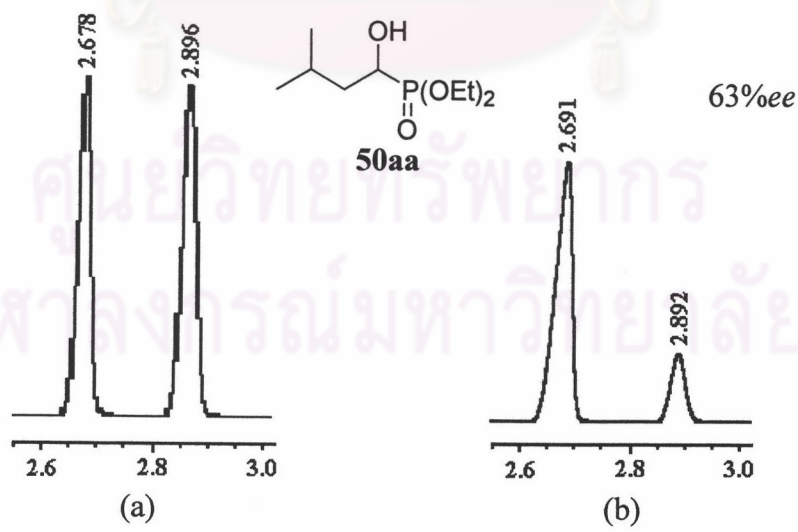


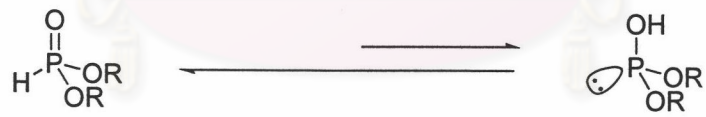
Figure 3.6 GC chromatograms on a 15.092 m long, 0.25mm i.d., capillary, coated with 0.25μm film of 10% BSiMe in PS255. Temperature program: 140°C (12.5 min) 15°C/min 240°C of: (a) racemic mixture of **50aa**; (b) product mixture of **50aa** obtained from a catalytic asymmetric reaction.

Good to excellent baseline separations were observed for almost all of the racemic α-hydroxyphosphonate **50** tested. Apparently, chiral gas chromatography on the specified stationary phase under the conditions explored offers itself as a reliable and speedy method of choice with high accuracy. Therefore, all of the determination for enantiomeric compositions were performed using this technique by Miss Jirawit Yanchinda under the supervision of Dr. Aroonsiri Shitangkoon.

3.3 The synthesis of α-hydroxyphosphonates.

3.3.1 Synthesis of racemic α-hydroxyphosphonates.

Racemic α-hydroxyphosphonates have been synthesized through both base-catalyzed hydrophosphonylation of aldehydes with dialkyl phosphite (Pudovik reaction) and acid-catalyzed reaction (Abramov reaction) where trialkyl phosphites were used as nucleophiles. As mentioned earlier, it is commonly accepted that dialkyl phosphites exist in two tautomeric forms, the enol form (phosphite, **5**) and the keto form (phosphonate, **4**). In general, the phosphonate form is the unreactive form, and it is the predominating form under neutral conditions. However, it is assumed that the anionic form of the phosphite tautomer would be more nucleophilic and would make the main contribution to formation of carbon-phosphorus bond under the basic conditions of the Pudovik reaction.



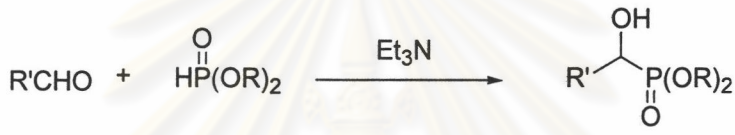
phosphonate tautomer (keto form) **4** ⟷ phosphite tautomer (enol form) **5**

Authentic samples of racemic α-hydroxyphosphonates were needed as reference compounds for verification and comparison purposes where enantiomeric analyses are concerned. In our approach, dialkyl phosphite was used as a phosphonylating agent because it is more easily handled than trialkyl phosphite. In general, dialkyl phosphite is commercially available. Unfortunately, such phosphorus compounds could not be obtained in Thailand due to the strict exporting regulations by the US government and the EU. Therefore, they need to be synthesized by the

reaction of phosphorus trichloride and alcohol in the presence of triethylamine. In general, dialkyl phosphite was added to an aldehyde in the presence of triethylamine under a solvent free condition following the method of Pudovik.[56] For most of the compounds prepared by this method, the reaction was quite slow and low chemical yields of the desired products were obtained. The data are summarized in Table 3.1.

Firstly, **50b** was synthesized from benzaldehyde and diethyl phosphite by using triethylamine at 80 °C, the product was obtained in 78% (entry 1). To synthesize other α-hydroxyphosphonates, various substrates including aliphatic and aromatic aldehydes were examined.

Table 3.1 Synthesis of racemic α-hydroxyphosphonates using triethylamine.



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entry	Product	R	R′	solvent	temp. (°C)	time	yield (%)
1	**50b**	Et	C_6H_5	-	80	8 d	78
2	**50c**	Et	4-$MeOC_6H_4$	-	75	4 d	7
3	**50m**	Et	4-$Me_2NC_6H_4$	-	75	1 d	-
4	**50e**	Et	4-$NO_2C_6H_4$	toluene	75	3 d	29
5	**50g**	Et	4-ClC_6H_4	-	75	4 d	-
6	**50i**	Et	C_6H_5CH=CH	-	75	1 d	9
7	**50a**	Me	C_6H_5	-	75	7 h	4
8	**50a**	Me	C_6H_5	-	75	7 d	14
9	**50k**	Me	4-MeC_6H_4	-	80	2 d	-
10	**50d**	Me	4-$NO_2C_6H_4$	CH_2Cl_2	rt	1 d	26
11	**50d**	Me	4-$NO_2C_6H_4$	-	90	30 min	38
12	**50f**	Me	4-ClC_6H_4	-	80	1 d	20
13	**50h**	Me	C_6H_5CH=CH	-	75	1	17

The progress of the reaction was determined by TLC, the reaction was allowed to stir until the consumption of all substrate was observed. As shown in Table 3.1, the aldehydes with electron donating substituents on aromatic ring, such as methoxy group (entry 2), gave a low yield of the product (7%). Changing the substrate to a

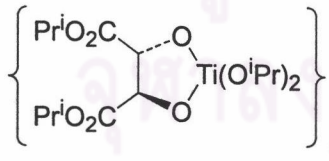
more electrophilic one, containing electron withdrawing substituent such as a nitro group, only marginally improved the yield (29%, entry 4) but the reaction time is significantly shortened.

After several attempts, dimethyl phosphite, a more reactive nucleophile than diethyl phosphite was examined. Several other α-hydroxyphosphonates were synthesized, still in rather low yields. Attempts to use alumina as a catalyst for the reaction following a report by Foucaud and Texier-Biullet,[22] in the synthesis of α-hydroxyphosphonates were carried out. However, low yields were still obtained, for instance 18 % for **50a** and 16% for **50b**.

It was hoped that the use of the more reactive tautomer, trialkyl phosphite, would improve the chemical yields. Attempts to synthesize the desired product with trimethyl phosphite previously prepared in this laboratory was examined. Due tc the sensitivity to oxygen and moisture of trialkyl phosphite, the reaction was carried out under an inert atmosphere. Disappointingly, the chemical yields obtained from the reaction of benzaldehydes and trimethyl phosphite was still low (23%). Anyway, the products obtained thus far were adequate for use as racemic standard for GC analysis.

3.3.2 Asymmetric synthesis of α-hydroxyphosphonates.

3.3.2.1 Pudovik reactions promoted by titanium complexes. As reported by Shibuya and co-workers,[50] the utility of chiral transition metal catalyst such as titanium complex derived from L-tartrate (**60**) and binaphthol-modified lanthanoid alkoxide (**61**) in the asymmetric Pudovik afforded products in good yields and enantioselectivities.



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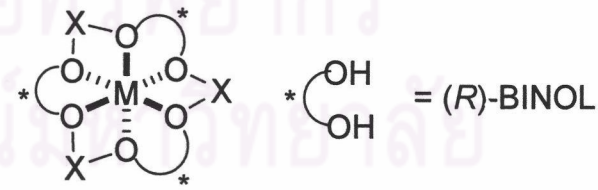

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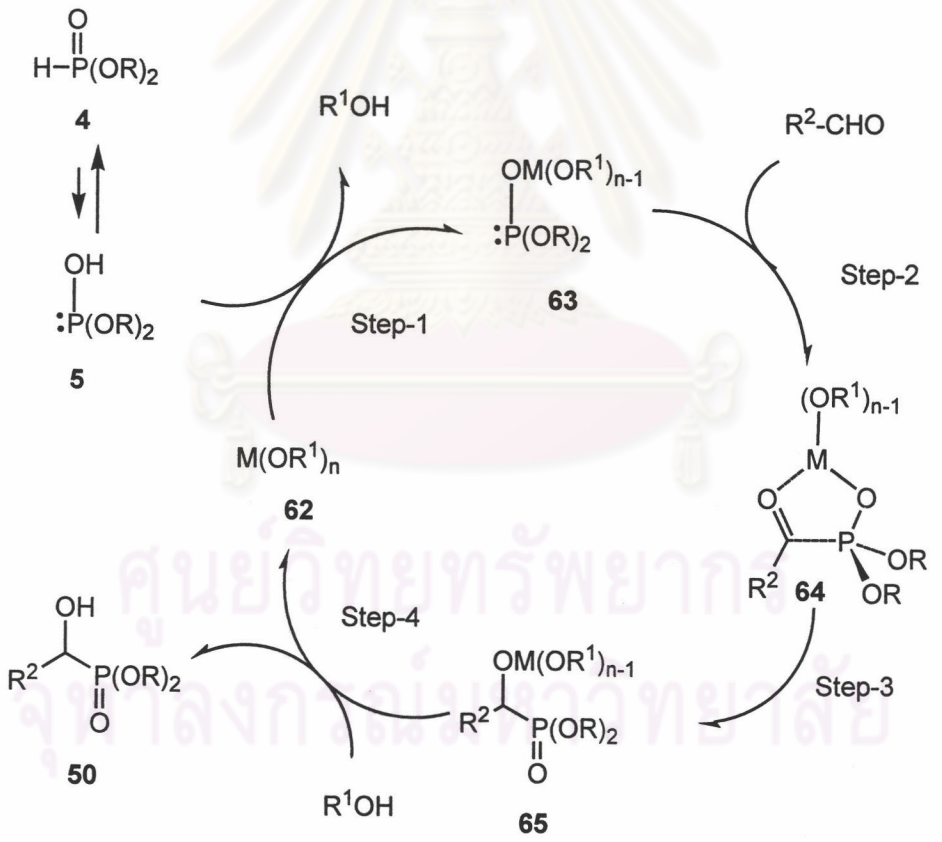
As mentioned earlier, phosphonates exist in two tautomeric forms, the phosphonates **4** and phosphite **5**, with the latter being the predominating species under neutral condition (Figure 3.7).[50] It was, however, assumed that the phosphite tautomer **5**, bearing non bonding electrons, would be more nucleophilic and would

play an important role in the formation of the carbon-phosphorus bond under basic conditions of the Pudovik reaction.[50] In addition, it is well known that transition metal catalysts such as titanium alkoxides and lanthanoid alkoxides can act as weak bases.[57] Shibuya and co-workers, therefore, proposed that these catalysts can also perform as the activator to dialkyl phosphite towards the Pudovik reaction through a ligand-exchange mechanism as shown in Figure 3.7.[50] The resulting organometallic phosphorus species **63** would add to aldehyde to form α-hydroxyphosphonate **50**. In this reaction, the high coordination ability of titanium and lanthanoid atoms would lead to the formation of a more intimate contact between the aldehyde and the organometallic phosphorus species **63** *via* transition state such as **64**. Therefore, introduction of chiral ligand on the catalyst would provide an enantioselective of α-hydroxyphosphonates.



M = Ti or lanthanoid metals

n = 4 or 3

Figure 3.7 Schematic representation for the catalytic Podovik reaction catalyzed by metal alkoxides.

In accordance with the strategy outlined in Figure 3.7 for enantioselective hydrophosphonylation of aldehydes with dialkyl phosphites, the possibility of using titanium isopropoxide, $Ti(O^iPr)_4$, as a catalyst of the Pudovik reaction was examined. In theory, only one equivalent of dialkyl phosphite should be sufficient for the reaction. However, the result reported by Shibuya[50] showed that 2.2 equivalents of diethyl phosphite were needed in order to obtain the desired compound in high yields (80-90%). In addition, a reaction condition used by Shibasaki required a much higher amount of diethyl phosphite (5.0 equivalents in most cases) to imines, the less reactive nitrogen analogs of aldehydes, in order to facilitate the reaction to proceed in good yields (albeit long reaction periods). It then seemed sensible to perform a preliminary study in order to search for suitable conditions which do not require a stoichiometric amount of the catalyst as well as a lower amount of the phosphonylating agent. Therefore, reactions probing for the influence of various factors, *i.e.* amount of dialkyl phosphite, amount of catalyst and metal used as catalyst were carried out. At an extreme condition, a reaction of benzaldehyde and 5.0 equivalents of dimethyl phosphite in the presence of 100 mol% of $Ti(O^iPr)_4$ (1 equiv) in THF was examined. The product was obtained in 67 %.

Table **3.2** Hydrophosphonylation of dimethyl phosphite (DMHP) and benzaldehyde in THF under various amount of DMHP and $Ti(O^iPr)_4$.[a]

Entry	DMHP (equiv)	mol % of $Ti(O^iPr)_4$	yield (%)[b]
1	2.2	20	31
2	2.2	50	49
3	3.1	20	29
4	5.0	20	42
5	5.0	100	67

[a] Reaction time: 2 days. [b] Isolated yield.

Next, the reactions were performed at room temperature at various amounts of dimethyl phosphite from 2.2 equivalents to 3.1 and 5.0 equivalents (entries 1, 3, and 4, Table 3.2) giving product **50a** in 31, 29, and 42%, respectively. It can be seen that although an increased amount of dimethyl phosphite was added, chemical yields did not increase significantly (compare entries 1, and 4). As a result, it can be implied that higher amount of phosphorus nucleophile could not significantly drive the equilibrium

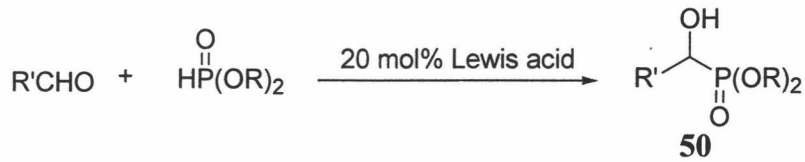
further in the forward direction in this case. In addition, the effect of amount of catalyst was also studied. The amount of catalyst was increased from 20 mol% to 50 mol%. The yield has improved. However, a lower amount was a preferred condition considering that catalytic condition is our ultimate goal. Therefore, the preliminary condition of the hydrophosphonylation under the study required the use of 20 mol% of $Ti(O^iPr)_4$, 2.2 equivalents of dialkyl phosphite at room temperature in THF. This developed condition was used for the rest of the reactions of aldehydes and diethyl phosphite.

Following the optimized condition, racemic α-hydroxyphosphonate **50b** was obtained in 96% yield from the treatment of benzaldehyde with diethyl phosphite in the presence of 20 mol% of $Ti(O^iPr)_4$ in tetrahydrofuran at room temperature. In addition, various metal salts namely, $Ti(O^iPr)_4$, $TiCl_4$, $SnCl_2$, $Al(O^iPr)_3$, $Sc(OTf)_3$, $Yb(OTf)_3$, and $InCl_3$ were also tested as activators in the reactions in various solvents. Table 3.3 summarizes the data obtained.

As shown, in the reaction of benzaldehyde and diethyl phosphite in various metal salts, no product was detected, except when $Ti(O^iPr)_4$ was used which yielded the product in 96% (entry 1). To improve reactivity of reaction, 4-nitrobenzadehyde which is more electrophilic than benzaldehyde was used. Dimethyl phosphite which is more reactive than diethyl phosphite was employed as nucleophile (entries 11-22). It may be pointed out that no product was detected in all cases where metal ions in the lanthanide series were used. Another observation includes the results from reactions where $Al(O^iPr)_3$ was utilized. No product was observed when benzaldehyde was used in the presence of $Al(O^iPr)_3$ (entries 5-7 and 12), whereas, moderate yields of **50d** were obtained when the more electrophilic substrate, 4-nitrobenzaldehyde, was employed (entries 13-15). So far the Lewis acid appropriate for catalyzing the reaction under the chosen condition were $Ti(O^iPr)_4$ and $Al(O^iPr)_3$.

The results also revealed some effects of solvents. It appeared that THF, being a donating solvent, could facilitate the reaction quite cleanly yielding the product in 96%. Relatively non polar solvent with no donating ability such as toluene gave low product yields. THF seemed to be the best choice of solvent and would be used throughout the rest of the experiments.

Table 3.3 Hydrophosphonylation of benzaldehyde with diethyl phosphite by various Lewis acid catalysts at room temperature.[a]



50

entry	product	R	R′	Lewis acid	solvent	time[b]	yield (%)[c]
1	**50b**	Et	C_6H_5	$Ti(O^iPr)_4$	THF	14 h	96
2	**50b**	Et	C_6H_5	$Ti(O^iPr)_4$	toluene	14 h	29
3	**50b**	Et	C_6H_5	$Ti(O^iPr)_4$	CH_2Cl_2	14 h	70
4	**50b**	Et	C_6H_5	$Ti(O^iPr)_4$	Et_2O	14 h	65
5	**50b**	Et	C_6H_5	$Al(O^iPr)_3$	CH_2Cl_2	3 d	-
6	**50b**	Et	C_6H_5	$Al(O^iPr)_3$	toluene	3 d	-
7	**50b**	Et	C_6H_5	$Al(O^iPr)_3$	THF	3 d	-
8	**50b**	Et	C_6H_5	$Yb(CF_3SO_3)_3$	THF	4 d	-
9	**50b**	Et	C_6H_5	$Sc(CF_3SO_3)_3$	THF	4 d	-
10	**50b**	Et	C_6H_5	$InCl_3$	THF	4 d	-
11	**50a**	Me	C_6H_5	$Ti(O^iPr)_4$	THF	2 d	31
12	**50a**	Me	C_6H_5	$Al(O^iPr)_3$	THF	4 d	-
13	**50d**	Me	$4\text{-}NO_2C_6H_4$	$Al(O^iPr)_3$	THF	2 d	68
14[d]	**50d**	Me	$4\text{-}NO_2C_6H_4$	$Al(O^iPr)_3$	toluene[d]	2 d	44
15	**50d**	Me	$4\text{-}NO_2C_6H_4$	$Al(O^iPr)_3$	toluene	2 d	62
16	**50d**	Me	$4\text{-}NO_2C_6H_4$	$Sc(CF_3SO_3)_3$	THF	2 d	-
17	**50d**	Me	$4\text{-}NO_2C_6H_4$	$Yb(CF_3SO_3)_3$	THF	2 d	-
18	**50d**	Me	$4\text{-}NO_2C_6H_4$	$SnCl_4$	THF	2 d	-
19	**50d**	Me	$4\text{-}NO_2C_6H_4$	$TiCl_4$	THF	4 d	-
20	**50d**	Me	$4\text{-}NO_2C_6H_4$	$InCl_3$	THF	3 d	-
21	**50f**	Me	$4\text{-}ClC_6H_4$	$Al(O^iPr)_3$	THF	3 d	-
22	**50h**	Me	$C_6H_5CH{=}CH$	$Al(O^iPr)_3$	THF	3 d	18

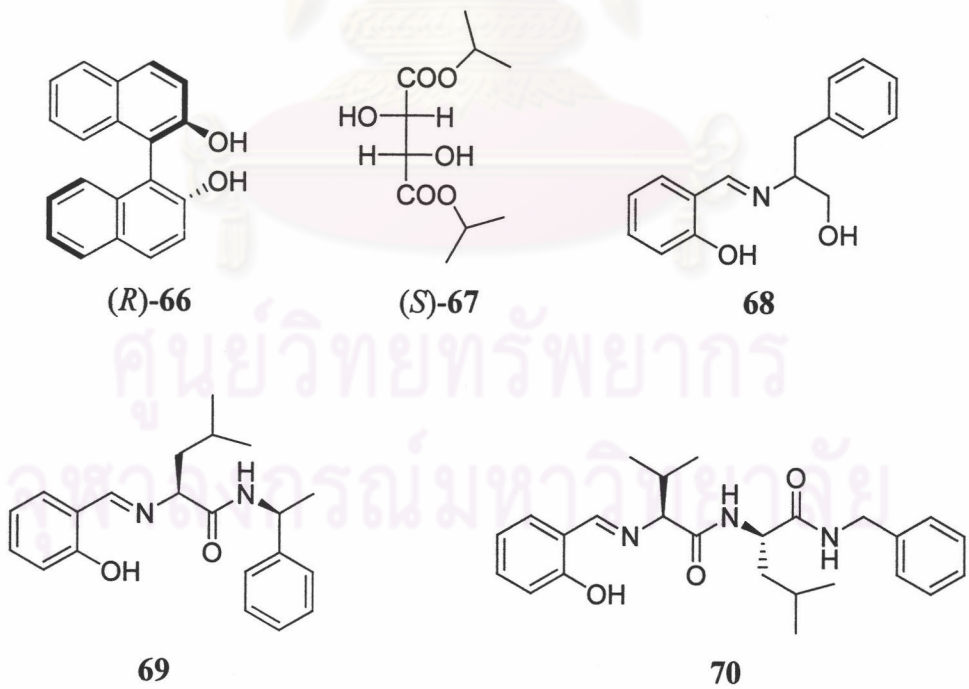
[a] Reaction performed by using 2.2 equivalents of dialkyl phosphite . [b] The reaction was carried out to the total consumption of the substrate. [c] Isolated yields. [d] toluene was used without drying.

Next, preliminary experiments on catalytic asymmetric synthesis of α-hydroxyphosphonates **50** were carried out in the presence of organometallic

complexes of $Ti(O^iPr)_4$ or $Al(O^iPr)_3$ Lewis acids with chiral ligands. Optically active ligands of interest are shown in Figure 3.8. In reports by Mansawat and co-workers, complexes formed from $Ti(O^iPr)_4$ and chiral amino alcohols[46] or peptide Schiff base[48] have shown to be efficient catalysts in asymmetric Strecker reaction. Therefore, it is envisaged that these ligands might also be efficient catalysts for asymmetric hydrophosphonylation.

Alternatively, ligands which are commercially available such as BINOL (**66**) and DIPT (**67**) which have been used as catalysts in hydrophosphonylation of aldehydes to give corresponding α-hydroxyphosphonate in good yield (38-76%) and in moderate enantioselectivity (21-52% *ee*) were also explored.[50]

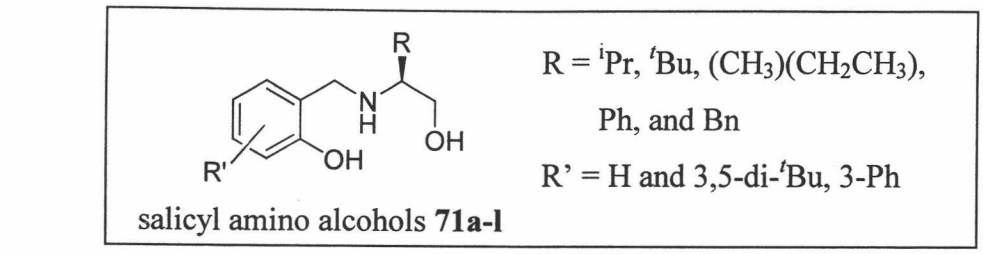
The optimized condition was utilized to search for the most efficient catalyst. The reactions were carried out in the presence of 20 mol% of Ti(IV)-chiral ligands such as (*R*)-(+)-1,1′-bi(2-naphthol) (BINOL, **66**), (-)-diisopropyl tartrate (DIPT, **67**), Schiff bases **68**, amino acid derived amino alcohol **69**, peptide Schiff base **70** and amino alcohol **71a** (**71**, R = Bn). Ligands **68,** and **71** were obtained from Ms. Woraluk Mansawat, whereas, ligands **69** and **70** was from Ms. Siriporn Jiwpanich.[47]



(*R*)-**66** (*S*)-**67** **68**

69 **70**

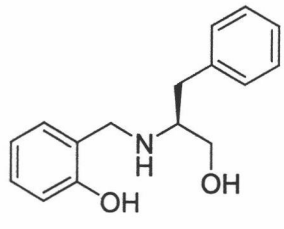
Figure 3.8 Various interesting chiral ligands.



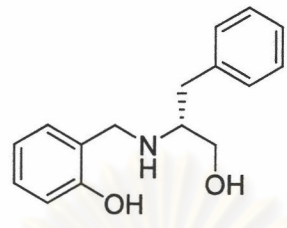
R = ^{i}Pr, ^{t}Bu, $(CH_3)(CH_2CH_3)$, Ph, and Bn

R' = H and 3,5-di-^{t}Bu, 3-Ph

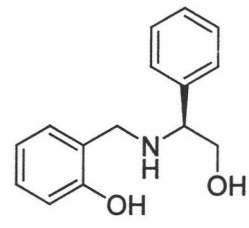
salicyl amino alcohols **71a-l**



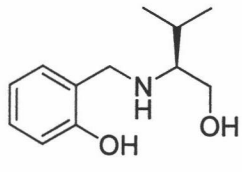
(*S*)-**71a**



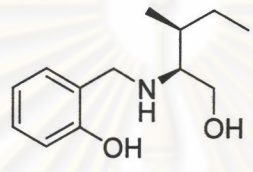
(*R*)-**71a**



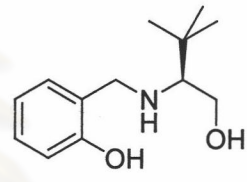
(*S*)-**71b**



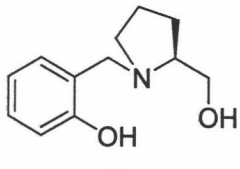
(*S*)-**71c**



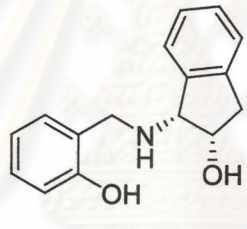
(*S*)-**71d**



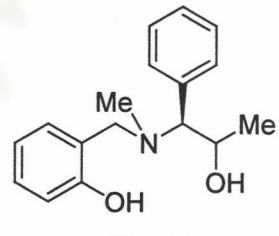
(*S*)-**71e**



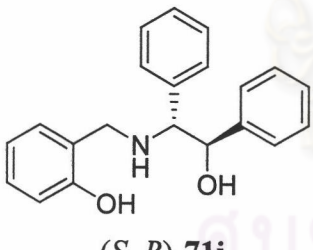
(*S*)-**71f**



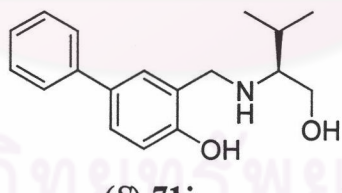
(*S*)-**71g**



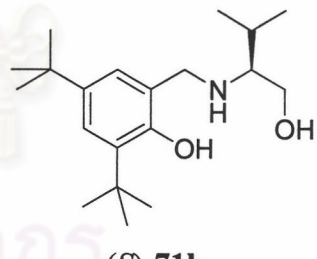
(*S*)-**71h**



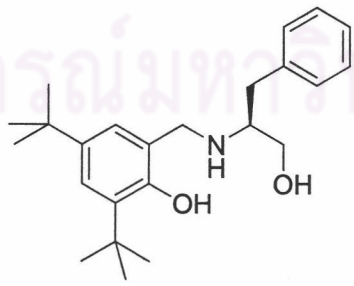
(*S, R*)-**71i**



(*S*)-**71j**



(*S*)-**71k**



(*S*)-**71l**

Figure 3.9 Amino alcohol ligands synthesized in this laboratory.

The reactions of dialkyl phosphite and two representative aldehydes namely, benzaldehyde and 4-nitrobenzaldehyde, were carried out in THF at room temperature to screen for potential catalysts. Selected results are shown in Table 3.4. The catalysts were prepared *in situ* by the addition of the metal salts to a solution of ligand and allowed to stir for 1 h under nitrogen atmosphere for the complex to form.

Table 3.4 Asymmetric hydrophosphonylation of dimethyl phosphite to aldehyde with titanium-complex catalyst.

50a: R = Me, R′ = Ph
50b: R = Et, R′ = Ph
50d: R = Et, R′ = 4-$NO_2C_6H_4$

entry	product	chiral catalyst		solvent	temp. (°C)	time	yield (%)[a]	*ee* (%)
		metal	ligand					
1	**50d**	$Al(O^iPr)_3$	**68**	toluene	rt	2 d	41	0
2	**50d**	$Al(O^iPr)_3$	(*S*)-**71a**	toluene	rt	2 d	31	0
3	**50d**	$Ti(O^iPr)_4$	**68**	toluene	rt	2 d	-	-
4	**50d**	$Ti(O^iPr)_4$	**70**	THF	rt	5 d	-	-
5	**5od**	$Ti(O^iPr)_4$	(*S*)-**71a**	THF	rt	2 d	0	0
6	**50b**	$Ti(O^iPr)_4$	(*S*)-**71a**	THF	rt	1 d	38	0
7	**50b**	$Ti(O^iPr)_4$	(*R*)-**66**	THF	0	1 d	39	0
8	**50b**	$Ti(O^iPr)_4$	(*S*)-**67**	THF	0	1 d	34	0
9	**50b**	$Ti(O^iPr)_4$	(*R*)-**71a**	THF	rt	1 d	34	0
10	**50b**	$Ti(O^iPr)_4$	(*S*)-**71a**	THF	0	1 d	46	8
11	**50b**	$Ti(O^iPr)_4$	(*S*)-**71e**	THF	0	1 d	33	7
12	**50b**	$Ti(O^iPr)_4$	(*S*)-**71c**	THF	0	1 d	41	2
13	**50a**	$Ti(O^iPr)_4$	**69**	THF	rt	3 d	-	-
14	**50a**	$Ti(O^iPr)_4$	**70**	THF	rt	2 d	-	-
15	**50a**	$Ti(O^iPr)_4$	(*S*)-**71a**	THF	rt	2 d	-	-
16	**50a**	$Ti(O^iPr)_4$	(*S*)-**71a**	THF	rt	3 d	-	-

[a] Isolated yield.

As shown, the yield of **50d** obtained from the reaction in the presence of $Al(O^iPr)_3$ were moderate, however, no enantioselectivity was observed. Several attempts to utilize $Ti(O^iPr)_4$ to screen for good ligands were also performed, but none of the reactions yielded the enantioselective products. It can be deduced at this stage that these catalysts are not suitable for enantioselective induction in Pudovik reaction. There is a need to find catalyst systems which can efficiently facilitate the reaction while inducing asymmetry in the product.

3.3.2.2 Asymmetric Pudovik reactions promoted by heterobimetallic complexes. It has been recognized that the Pudovik reaction is a base-catalyzed reaction. From the viewpoint of methodology, an enantioselective Pudovik reaction catalyzed by a catalytic amount of chiral base would be both highly desirable and efficient. In this context, Wynberg examined an asymmetric Pudovik reaction using chiral amines derived from quinine as chiral base.[58] However, the enantiomeric excesses of products through this method was reported to be rather low (10-21% *ee*). To obtain more efficient asymmetric catalysts for the Pudovik reaction, Shibasaki and co-workers[38] reported the catalytic asymmetric synthesis of α-hydroxyphosphonates using the Al-Li-BINOL complex (ALB). Independently, Shibuya had reported a catalytic asymmetric Pudovik reaction using La-Li-BINOL complex (LLB) as well.[50]

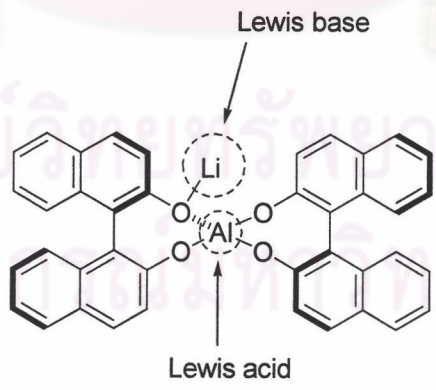


Figure 3.10 The heterobimetallic complex of aluminium lithium BINOL (ALB).

According to Shibasaki's work, it can be implied that the use of a heterobimetallic catalyst exhibiting both Lewis acid and Lewis base character was an effective method for Pudovik reaction. An additional report by Narashimhan and co-

workers revealed heterobimetallic complexes of amino alcohol chiral ligands **72** and **73** which were shown to be effective catalysts in the Michael addition reaction resulting in the production of the products in good chemical and enantiomeric yields (65-86%, 37-84% *ee*) (Figure 3.11).[49] In his report, Narasimhan also stated that different lithium aluminium hydride (LAH):ligand ratios of 1:1 and 1:2, giving proposed active catalyst structures of **72** and **73**, respectively, would yield products with different stereochemistry.

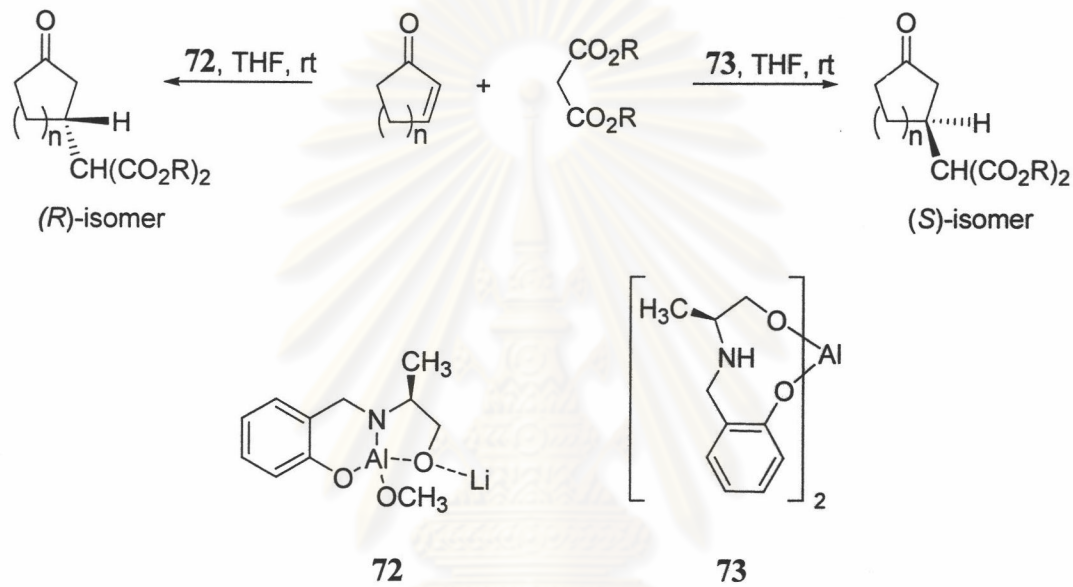


Figure 3.11 The Michael addition reaction of cyclic enone and malonate.

With the basis of Shibasaki's and Narasimhan's heterobimetallic results, we would like to find other heterobimetallic catalyst systems bearing different kinds of metals or chiral ligands other than BINOL. Narasimhan's system is especially of high interest since they employed chiral amino alcohols, structurally similar to the systems extensively studied in our laboratory.[48] It is, therefore, envisaged that this type of catalyst may be applied to Pudovik reaction.

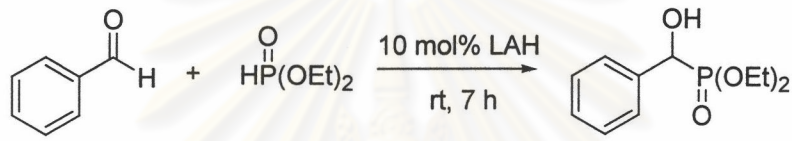
Synthesis of racemic α-hydroxyphosphonates using lithium aluminium hydride.

We first examined the possibility of using lithium aluminium hydride, $LiAlH_4$, LAH, as an activator for the Pudovik reaction. Although, the reaction proceeded rather slowly, after a completion in 2 days the racemic α-hydroxyphosphonates was obtained in 84% yield on the treatment of benzaldehyde with diethyl phosphite in the

presence of 10 mol% of $LiAlH_4$ in THF at room temperature. This reaction under the condition used was far more efficient than what had been observed thus far.

Preliminary investigation of solvent effects was performed to screen for the best medium. As shown in Table 3.5, the reaction proceeded smoothly in many solvents including tetrahydrofuran, toluene, dichloromethane, and diethyl ether. All reactions gave comparable yields with that in diethyl ether at a slightly lower yield. As the result, slightly higher chemical yield was obtained when used tetrahydrofuran as solvent. Tetrahydrofuran was chosen as solvent in this reaction.

Table 3.5 Hydrophosphonylation of diethyl phosphite and benzaldehyde in difference solvents.

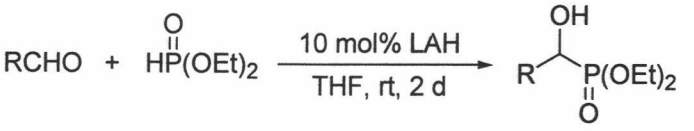


entry	solvent	Yield (%)[a]
1	THF	84
2	toluene	83
3	CH_2Cl_2	83
4	Et_2O	73

[a] Isolated yield.

Encouraged by this result, we continued to examine the reaction of diethyl phosphite with various aldehydes covering both aliphatic and aromatic ones using the reaction condition mentioned earlier. Initially, general scope of reaction with regard to effect of substrate aldehyde on product yields were examined in the absence of a chiral ligand. Under the condition which used tetrahydrofuran as solvent and reaction performed at room temperature, poor to high chemical yields were obtained. The results are summarized in Table 3.6. As for aromatic aldehydes, several 4-substituted aromatic aldehydes were subjected to the LAH-catalyzed reaction. In general product yields in the case where R is an electron withdrawing group were slightly higher than the yield product from aldehyde having electron-donating groups at the *para* position. The lower chemical yield was obtained (36%) when cinnamaldehyde was a substrate. One explanation may be that 1,4-addition of phosphorus nucleophile to the aldehyde had occurred. An alternative is a possibility of an LAH reduction at the unsaturated moiety of the molecule.

Table 3.6 Synthesis of racemic α-hydroxyphosphonates using $LiAlH_4$.



50

entry	Product	R	yield (%)[a]
1	**50b**	C_6H_5	84[b]
2	**50i**	$C_6H_5CH=CH$	36
3	**50c**	4-$MeOC_6H_4$	75
4	**50j**	2-MeC_6H_4	71
5	**50k**	4-MeC_6H_4	62
6	**50l**	4-MeC_6H_4[b]	49
7	**50m**	4-$Me_2NC_6H_4$	6
8	**50n**	2-BrC_6H_4	76
9	**50o**	3-BrC_6H_4	67
10	**50p**	3-ClC_6H_4	42
11	**50g**	4-ClC_6H_4	58
12	**50q**	2-FC_6H_4	70
13	**50r**	3-FC_6H_4	66
14	**50s**	4-FC_6H_4	59
15	**50t**	4-CNC_6H_4	77
16	**50u**	4-$^{i}PrC_6H_4$	79
17	**50v**	4-$^{t}BuC_6H_4$	83
18	**50w**	cyclohexyl	55
19	**50x**	$CH_3(CH_2)_2$	13
20	**50y**	$CH_3(CH_2)_3$	53
21	**50z**	$CH_3(CH_2)_6$	15
22	**50aa**	$(CH_3)_2CHCH_2$	83
23	**50bb**	$(CH_3)_2CH$	43
23	**50cc**	$(CH_3)_3C$	48

[a] Isolated yield. [b] Reaction time 7 h.

One general trend which can clearly be observed is that reactions of aromatic aldehydes were consistently more efficient than those of aliphatic aldehydes (13-

83%). It is noticeable that lower yields were observed when aliphatic aldehydes were used except for the case where R was a tertiary butyl group. Self-Aldol condensation in the presence of hydride or lithium base may account for a lower degree of α-hydroxyphosphonate formation in the case of these aliphatic aldehydes.

All the preliminary results show a good sign that a catalytic Pudovik reaction catalyzed by lithium aluminium hydride can be an efficient alternative method for the synthesis α-hydroxyphosphonates, especially, for aromatic aldehydes.

Asymmetric Pudovik reaction using LAH-chiral aminoalcohol complexes.

The moderate to high yields on the formation of α-hydroxyphosphonates *via* an LAH catalyzed reaction promoted us to explore the possibility of catalytic asymmetric hydrophosphonylation with the incorporation of chiral ligands to such a system.

Ligand screening.

The ligand in the *N*-salicyl-β-aminoalcohol (**71**) group which can be synthesized by a reduction of imine derived from amino alcohols and a salicyladehyde derivatives were of the main focus for our asymmetric studies. These ligands which form chelating complexes with metals such as lithium and aluminium as heterobimetallic Li-Al complexes **72** and **73** were reported to catalyze Michael addition reaction of cyclic enones and malonates.[59] In addition, these ligands also can catalyze an asymmetric Strecker reaction in high enantiomeric excess (>98% *ee*).[60]

In order to investigate the effect of the ligand structure on the introduction of enantioselectivity in hydrophosphonylation reaction, reactions of benzaldehyde and diethyl phosphite in the presence of several LAH-**71** complexes were carried out at various temperatures. Representative data are summarized in Table 3.7.

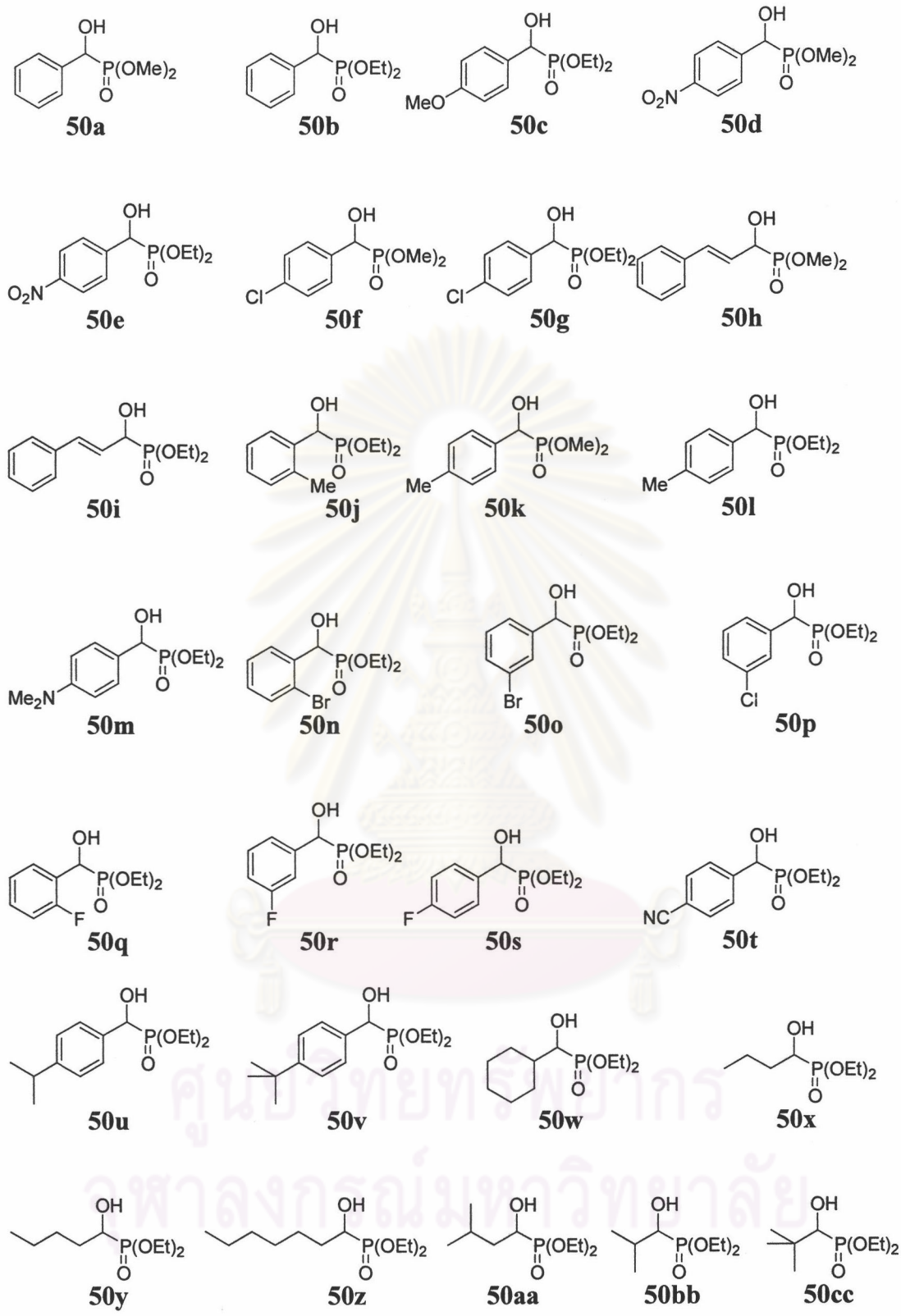
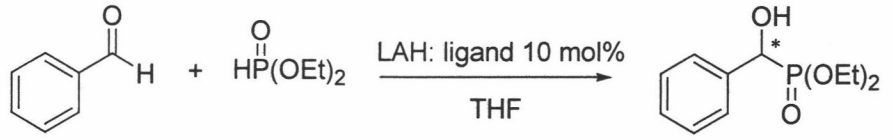


Figure 3.12 racemic α-hydroxyphosphonates.

Table 3.7 Reactions of benzaldehyde and diethyl phosphite with various catalysts.



50b

entry	ligand[a]	ratio	temp (°C)	time[b]	yield (%)[c]	*ee* (%)[d]
1	(*S*)-**71a**	1 : 1	rt	7 h	70	0
2	(*R*)-**71a**	1 : 1	rt	7 h	65	0
3	(*S*)-**71a**	1 : 1	0	2 d	85	1
4	(*S*)-**71a**	1 : 2	0	2 d	78	4
5	(*R*)-**71a**	1 : 2	0	2 d	77	-4
6	(*R*)-**71a**	1 : 2	-78	2 d	84	4
7	(*S*)-**71b**	1 : 1	rt	17 h	83	0
8	(*S*)-**71c**	1 : 1	rt	17 h	80	9
9	(*S*)-**71c**	1 : 2	0	2 d	87	2
10	(*S*)-**71d**	1 : 1	rt	17 h	67	0
11	(*S*)-**71e**	1 : 1	rt	17 h	81	3
12	(*S*)-**71e**	1 : 2	0	2 d	91	0
13	(*S*)-**71f**	1 : 2	rt	4 h	60	3
14	(*S*)-**71f**	1 : 2	0	7 h	80	0
15	(*S,R*)-**71i**	1 : 1	rt	17 h	72	3
16	(*S, R*)-**71i**	1 : 2	0	7 h	55	1
17	(*S*)-**71j**	1 : 2	rt	7 h	91	1
18	(*S*)-**71h**	1 : 2	0	4 d	88	3
19	(*S*)-**71g**	1 : 2	0	7 h	57	10
20	(*S*)-**71l**	1 : 2	0	4 d	76	40
21	(*S*)-**71k**	1 : 2	rt	17 h	75	54
22	(*S*)-**71k**	1 : 1	rt	17 h	89	60
23	(*S*)-**71k**	1 : 2	0	4 d	78	54
24	(*S*)-**71k**	1 : 1	-78	2 d	47	59

[a] ligand starting from derivative of salicylaldehydes and amino alcohols, **71a-i** were obtained from salicylaldehyde, **71j** was obtained from biphenylsalicyladehyde, and **71k** was obtained from 3,5-di-*tert*-butylsalicyladehyde. [b] The reaction progress was monitored by TLC until the consumption of all aldehyde. [c] Isolated yield. [d] Enantiomeric excess determined by chiral gas chromatography.

At the beginning, the LAH complexes of ligands derived from L-phenylalaninol (*S*)-**71a** and D-phenylalaninol (*R*)-**71a** were used as catalysts, no enantiomeric excess was detected.

In order to study any substituent effect of the ligand on the enantioselectivity of the reaction, changing of the R group at the alpha position to the nitrogen atom was carried out. Starting from different aminoalcohols, the ligands were synthesized and employed in the reaction. In the case where R was benzyl (entry 1) and phenyl (entry 7) no enantioselectivity was observed. The enantioselectivity was slightly improved when the more steric group such as that present in (*S*)-**71c** ligand was employed. Disappointingly, in an attempted to use the more bulky substituents, such as isobutyl group ((*S*)-**71d**, entry 10) and *tert*-butyl group ((*S*)-**71e**, entries 11, and 12), no enantioselectivity was observed. Addition of a phenyl group on the aminoalcohol moiety and methyl group on amino alcohol moiety resulted in low enantioselectivity (3% *ee*, entry 18). Moreover, changing to a more rigid substituent on aminoalcohol moiety yielded low enantiomeric excess (10% *ee*, entry 19). Regarding the effect of substituents on aromatic ring in the salicyl moiety, it was found upon changing of the R′ group from H (entry 1) to biphenyl (entry 17) that low enantioselectivity was observed.

Ligand (*S*)-**71k** (entry 22), bearing two tertiary butyl groups on the 3 and 5 position of the aromatic ring of the salicyl group, afforded the highest enantioselectivity of the reaction at 60% *ee*. This implies that ligands bearing a relatively sterically hindered substituent on the salicyl moiety provide much higher enantioselectivity in the reaction. In order to prove the effect of the substituent bulkiness on salicyl moiety, synthesis of a ligand derived from 3,5-di-*tert*-butylsalicylaldehyde and L-*tert*-leucinol, aiming to magnify the bulkiness to the extreme, was attempted to synthesize. Unfortunately, no ligand was obtained.

As it is well known that the selectivity achieved from asymmetric reaction largely depends on the reaction temperature, many asymmetric reactions are carried out well below room temperature in order to achieve maximum selectivity. Therefore, an effect of temperature on the outcome of the reaction was also studied. In addition to reactions performed at room temperature, the reactions in the presence of ligands **71a** and **71k** were subsequently screened at 0 °C and –78 °C. The results are also presented in Table 3.7. As for **71a**, low enantioselectivity were obtained in all cases.

Even with very low percent enantioselectivity, entries 4 and 5 illustrate the fact that ligands with opposite stereochemistry gave opposite (relative) enantiomers. As observed in the case of **71k**, comparable yields and enantioselectivities were obtained even at lower temperatures. The suitable temperature which will be used throughout the rest of the reactions is, therefore, the room temperature.

As far as the LAH-ligand ratio is concerned, the 1:1 ratio seems to have given the products in a shorter reaction time and, in some cases higher yields, while comparable enantioselectivity can still be obtained. Therefore, the higher ratio of 1:2, where more costly ligands would be consumed, were not necessary.

The most important observation is that the LAH-*N*-salicyl-β-aminoalcohol complex is capable of inducing enantioselective Pudovik reaction and that (*S*)-**71k** was the best ligand in the series tested.

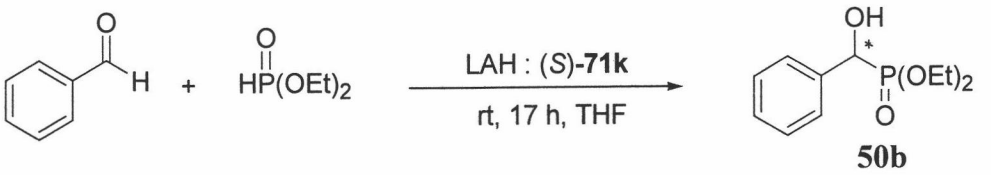
The effects of the metal:ligand ratio.

As observed by Narasimhan, LAH-aminoalcohol complexes **72** and **73**, proposed to have been formed from 1:1 and 1:2 of the LAH:ligand ratios, respectively, gave Michael addition product with opposite stereochemistry.[59] Highly aware of this report, reactions in the presence of different ratios of LAH to (*S*)-**71k** ligand were examined. This was performed in order to find the most suitable metal to ligand ratio as well. The results are shown in Table 3.8.

One trend which can be observed is that when the amount of ligand increased (entries 1-4), both chemical yield and enantioselectivity decreased. It may be deduced that when the amount of the ligand increases, the non-coordinated ligand, present in higher concentration, would block the coordination of diethyl phosphite and lithium complex, populating the non-activated phosphite than when the 1:1 ratio is used. An exception was found in the case where the ratio was 1:0.5 when only 12% *ee* was observed. This could very well be because the chiral environment observed by the substrates is low.

In order to investigate the effect of amount of catalyst on the outcome of the reaction, an experiment in the presence of 20 mol% of the catalyst was also performed, the enantioselectivity was lower when compared with that resulting from a reaction with 10 mol% catalyst. One possible rationale could be that the high amount of LAH present in the reaction mixture may have caused the reaction to proceed at a

Table 3.8 Enantioselective additions of diethyl phosphite to benzaldehyde with the complex of LAH and (*S*)-**71k** ligand.



50b

entry	catalyst		yield (%)[a, b]	*ee* (%)[c]
	ratio	mol%		
1	1 : 0.5	10	91	12
2	1 : 1	10	89	60
3	1 : 2	10	66	51
4	1 : 4	10	49	40
5	1 : 1	5	55	46
6	1 : 1	20	74	3

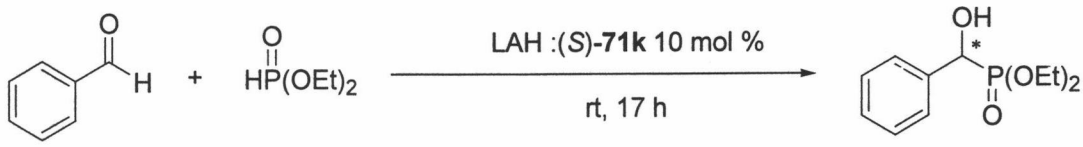
[a] the reaction progress was monitored by TLC until the consumption of all aldehyde.
[b] Isolated yield. [c] Enantiomeric excess was determined by chiral gas chromatography.

higher rate, hence enantiodifferentiation occurs to a lesser degree. Therefore, the appropriate amount of catalyst added is at 10 mol%.

It is obvious that the highest enantioselectivity was observed when the LAH and ligand ratio of 1:1 was used (entry 2). However, similar observation to Narasimhan's report, on reversed stereochemistry in the product when 1:1 and 1:2 ratios were compared, was not experienced. The major enantiomer with the same relative stereochemistry was always observed regardless of the LAH:ligand ratios. Since the issue was not quite clearly resolved at the time, we decided to carry out experiments with the catalyst presence in both 1:1 and 1:2 ratios when available. Only the 1:1 ratio was used when the problem with an inadequate amount of ligand was encountered.

To fine-tune the condition, possible solvent effect in the presence of chiral ligand was also determined. It may affect reaction yields. This was performed to ensure that THF was the best choice available. The reactions were carried out in the presence of a representative ligand **71k** in THF, toluene, dichloromethane, and diethyl ether, respectively. The yields as well as enantiomeric compositions of the products were determined and the results are presented in Table 3.9.

Table 3.9 Hydrophosphonylation of diethyl phosphite and benzaldehyde in difference solvents in the presence of chiral ligand (*S*)-**71k**.



entry[a]	solvent	yield (%)[b]	*ee* (%)[c]
1	THF	89	60
2	toluene	51	31
3	CH_2Cl_2	52	30
4	Et_2O	55	46

[a] The reaction progress was monitored by TLC until the consumption of all aldehyde.
[b] Isolated yield. [c] Enantiomeric excess was determined by chiral gas chromatography.

When the reaction was conducted in toluene which is a low polar solvent, low enantioselectivity accompanying the low chemical yield (51 %, 31 % *ee*, entry 2) was observed. When higher polar solvent such as dichloromethane, was used, the same level of both chemical yield and enantioselectivity were observed. Changing solvent to an electron donor solvent such as diethyl ether and tetrahydrofuran, the enantioselectivity was slightly improved when diethyl ether was used (46% *ee*, entry 4). When THF was used, the chemical yield and the enantioselectivity increased to 89% and 60% *ee*, respectively. THF appeared to be the best solvent giving highest yield and selectivity. These data show that efficient incorporation of the chiral catalyst into diethyl phosphite by increasing the basicity of catalyst through tuning the donor ability of the solvent used was critical to induce the asymmetric hydrophosphonylation reaction. These results correspond with the studies of asymmetric Pudovik reaction using titanium alkoxide as catalyst which enantio-discrimination depend on donor ability of the solvent used.[50]

Order of addition of reagents.

As Shibasaki and co-workers proposed in their mechanism of catalytic asymmetric Pudovik reaction catalyzed by heterobimetallic catalysts, the enantioselectivity was greatly dependent on the incorporation of the substrate aldehyde and phosphonylating agent to the catalyst.[38] As previously proposed in Figure 3.7, the favorable aldehyde that afforded good enantioselectivity in the product

was the aldehyde which coordinates with the aluminium atom. On the other hand, no enantioselectivity was observed when the activated phosphite reacted with the unactive aldehyde which not coordinate with aluminium complex.

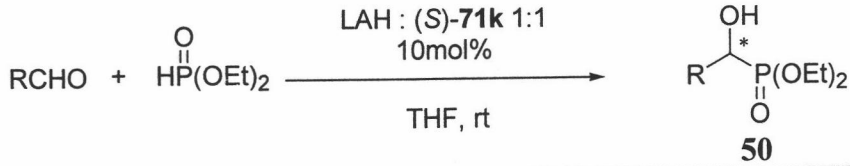
In light of this concept, the order of addition of reagents was also investigated in this preliminary study. The hydrophosphonylation using the representative catalyst, the complex of LAH-**71k**, prepared *in situ* from *N*-salicyl-β-aminoalcohol and lithium aluminium hydride was examined. It was found that the change in the order to which the substrate and the nucleophile were added to the solution of the catalyst indeed gave a drastic contrast in the enantioselectivity observed while the product yields were comparable. In the experiment, the organometalic complex was always preformed in THF by a reaction of LAH and the ligand and stirred for 0.5 h. In the case where the dialkyl phosphite was activated by its addition to the solution of the complex prior to an addition of the aldehyde, a high product yield was accompanied with a relatively high enantioselectivity (89%, 60% *ee*). In contrast, the reaction in which the aldehyde was added before diethyl phosphite gave comparable product yield but with much lower enantioselectivity (85%, 2% *ee*). Therefore, we chose to add the phosphite before the aldehyde. The answer as to why this gives higher enantioselectivity is not clear at present.

Effect of ligand on the reaction with various aldehydes.

The substrate generality of (*S*)-**71k**, the best ligand obtained thusfar, was investigated. Hydrophosphonylation reactions of various aldehydes including both aromatic and aliphatic ones were examined under the best conditions using the LAH complex of (*S*)-**71k**. Under the the reaction of aldehydes and diethyl phosphite were reacted in the presence of 10 mol% of LAH: (*S*)-**71k** ligand (at 1:1 ratio) at room temperature. The results are presented in Table 3.10.

Having improved an effective catalytic asymmetric hydrophosphonylation of aromatic aldehydes, we then turned attention to hydrophosphonylation of aliphatic and cyclic aldehyde. First, the reaction of butyraldehyde was examined (entry 11). Unexpectedly, the reaction yielded slightly higher enantiomeric excess than aromatic aldehyde (63% *ee*). Moreover, reactions of other aliphatic aldehydes such as 1-heptaldehyde and isovaleraldehyde were also examined, affording same level of

Table 3.10 Catalytic asymmetric hydrophosphonylation of various aldehydes catalyzed by LAH -(*S*)-**71k** complex.



50

entry	R	product no.	time	yield (%)[a, b]	*ee* (%)[c]
1	C_6H_5	**50b**	17 h	89	60
2	4-$MeOC_6H_4$	**50c**	2 d	69	72
3	2-MeC_6H_4	**50j**	16 h	79	-[d]
4	4-MeC_6H_4	**50l**	2 d	59	54
5	4-$Me_2NC_6H_4$	**50m**	2 d	22	55
6	4-$^{i}BuC_6H_4$	**50u**	2 d	54	60
7	4-FC_6H_4	**50s**	4 d	59	41
8	4-ClC_6H_4	**50g**	2 d	47	34
9	4-NCC_6H_4	**50t**	4 d	66	39
10	C_6H_5CH=CH	**50i**	2 d	72	32
11	$CH_3(CH_2)_2$	**50x**	2 d	49	63
12	$CH_3(CH_2)_5$	**50z**	2 d	15	65
13	$(CH_3)_2CHCH_2$	**50aa**	2 d	20	63
14	$(CH_3)_2CH$	**50bb**	2 d	55	70
15	$(CH_3)_3C$	**50cc**	2 d	54	70
16	cyclohexyl	**50w**	2 d	15	66

[a] the reaction progress was monitored by TLC until the consumption of all aldehyde. [b] Isolated yield. [c] Enantiomeric excess determined by chiral gas chromatography. [d] No separation by chiral GC

enantioselectivity (65% *ee*, entry 12; and 63% *ee*, entry 13). Nevertheless, the use of more steric substrate such as pivaldehyde gave significantly improved result (70% *ee*, entry 15). Saturated aldehyde such as cyclohexanecarboxaldehyde was converted to the corresponding α-hydroxyphosphonates in good enantiomeric excess (66% *ee*, entry 16).

To our surprise, reactions of aliphatic aldehydes gave the corresponding α-hydroxyphosphonates in comparable, or in some cases higher, enantioselectivities compared to results from the aromatic counterparts, albeit with low chemical yield

ranging from 15 to 55%. The results from the aliphatic series are very satisfying since the only report in the literatures on hydrophosphonylation of aliphatic aldehydes showed only marginal enantioselectivities (3-24% *ee*).[38] Apparently, multifunctional heterobimetallic catalysts, bearing *N*-salicyl-β-aminoalcohol ligand, in which two different metals play different roles to enhance the reactivity and selectivity of both substrate and nucleophile can be efficiently applied to our system.