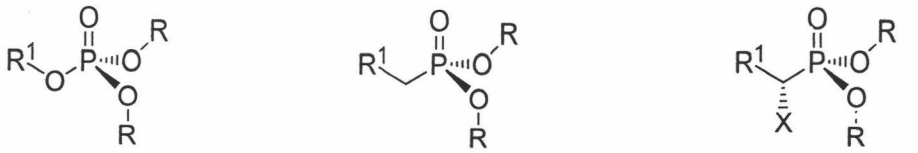
CHAPTER I

INTRODUCTION

Organophosphorus compounds are fundamentally important in the chemistry of living systems. They are involved in biological systems with the most spectacular role in life processes is as the central building block in nucleic acids. Furthermore, organophosphorus residues are attached to several coenzymes, combined with the hydroxyl groups of the serin, threonine, and tyrosine, residues of enzymes, and metabolic intermediates. Moreover, many organophosphorus compounds are artificially produced for practical applications, for instance, as medicinal compounds such as a valuable chemotherapeutic agent, antitumor, antiviral, antibacterial, and agents for the treatments of bone diseases, or as agricultural chemicals including insecticides, herbicides, and plant growth regulators. In addition, metal-coordinated tertiary phosphites are used for many industrial processes such as oxo hydroformylation, olefin hydrogenation, and Reppe olefin polymerization etc.. Alternative applications of organophosphorus compounds are flame retardants for fabrics and plastics, plasticizing and stabilizing agents in plastic industry, selective extractants of metal salts from ores, especially for those of uranium, additives in the petroleum products field, corrosion inhibitors, and catalysts in asymmetric synthesis.[1]

1.1 α-Hydroxyphosphonic acid derivatives

Phosphonic acid and their derivatives are common in literature of organic chemistry where are employed in synthetic operations leading to carbon-carbon bond formation, sought for their potential contribution to biological activities. In addition, they are used as transition state analogues in production of antibodies catalytic for a wide variety of reaction, and their ability to mimic biological phosphates **1**.[2] The introduction of fluoro (**3a**),[3-5] amino (**3b**),[6,7] and hydroxy (**3c**)[8-11] groups at the α-carbon was aimed to improve phosphate mimicry and enzyme inhibition properties.



1 R = H, organic residue

2

3a X = F
3b X = NH_2
3c X = OH

Figure 1.1 Phosphates, phosphonates, and α-substituted phosphonates.

Chiral α-hydroxyphosphonates are useful precursors for a variety of α-substituted phosphonates and especially for α-aminophosphonic acid and their derivatives which are α-amino acid analogues. They have received considerable attention over the past decade in pharmaceutical, agricultural, bioorganic and organic chemistry. In addition, α-hydroxyphosphonic acid derivatives also have biological activity as enzyme inhibitors such as rennin synthase,[12,13] tyrosine-specific protein kinase,[14-16] and HIV protease.[17-19]

1.2 Non asymmetric synthesis of α-hydroxyphosphonates

In recent years, there has been considerable interest in phosphorus-carbon (P-C) bond forming reactions. α-Hydroxyphosphonic acid esters are compounds of significant biological and pharmaceutical interests. They have been prepared by the Abramov reaction, which is an acid catalyzed addition of trialkyl phosphite to aldehydes.[20]

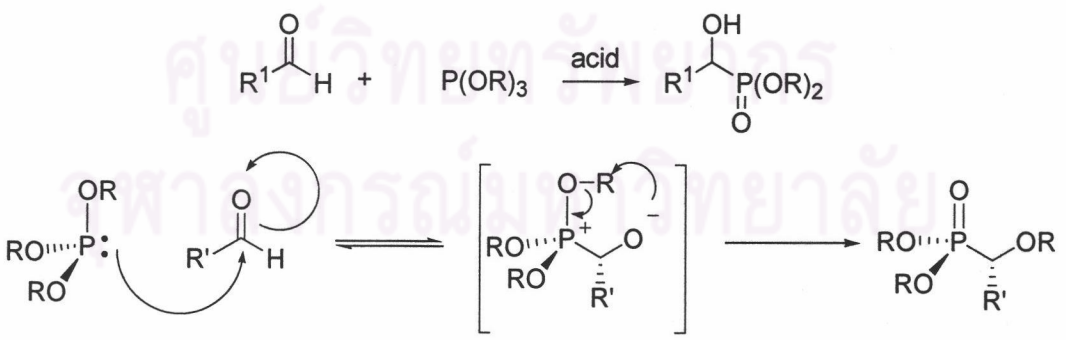


Figure 1.2 The Abramov reaction.

There was a report in which α-hydroxyphosphonic esters were obtained by an Abramov reaction between carbonyl compound and phosphorus acid triester, trialkyl phosphite, at room temperature under strong acidic conditions and dissolved in

anhydrous dioxane.[20] The reaction is quite exothermic and cooling is often needed. Ten to fifteen minute reaction time is sufficient in order to assure almost quantitative yields of the desired product. The solvent's choice is very crucial; in fact, it is imperative that it must be inert towards the starting aldehyde and should easily dissolve the reactants and the final products, including large quantities of gaseous HCl.

Another method for synthesizing α-hydroxyphosphonic esters is through a Pudovik reaction using dialkyl phosphite, which can be more easily handled than trialkyl phosphite, as a phosphorus nucleophile, under basic condition, *e.g.* triethylamine or Lewis acid catalysis.

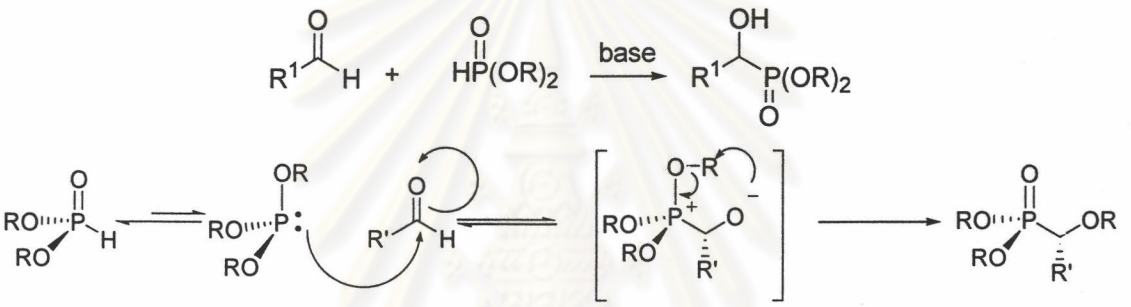
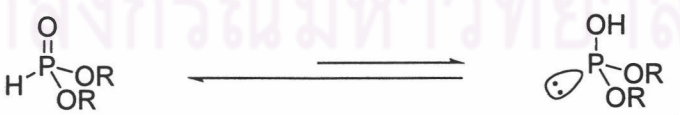


Figure 1.3 The Pudovik reaction.

However, these phosphorus compounds are known to undergo a phosphite-phosphonate tautomerism with the phosphite tautomer (**5**) as the nucleophile (active) form and the phosphonate tautomer (**4**) as the almost exclusively favored but non-nucleophilic (resting) form (Figure 1.4). This tautomerism has an equilibrium constant for dialkyl H-phosphonate (**4**) of 10^7 in favor of the H-phosphonate (**5**) form.[1]



phosphonate tautomer — phosphite tautomer

4 — **5**

Figure 1.4 Phosphite-phosphonate tautomers.

In 1982, Foucaud and Texier-Boullet[21] reported a convenient synthesis of α-hydroxyphosphonates by reactions of an aldehyde or ketones with dialkyl phosphite

in the presence of alkali metal fluorides such as potassium and cesium fluoride without solvent at room temperature. In addition, they also described the synthesis of α-hydroxyphosphonates from carbonyl compounds and dialkyl phosphites on an alumina surface, without solvent.[22]

In addition, Sardarian and Koboudin presented that magnesia (MgO) was found to be an effective catalyst for the synthesis of diethyl 1-hydroxyarylmethyl phosphonates from aromatic aldehydes and diethyl phosphite.[23] High yields were mostly obtained without side reactions.

In 1998, Simoni and co-workers demonstrated that trimethylguanidine (TMG) catalyzed the addition of dialkyl phosphites to various kinds of unsaturated molecules.[24] The very mild conditions employed, together with the short reaction times, make the procedure highly versatile and tolerant to a range of functionalities.

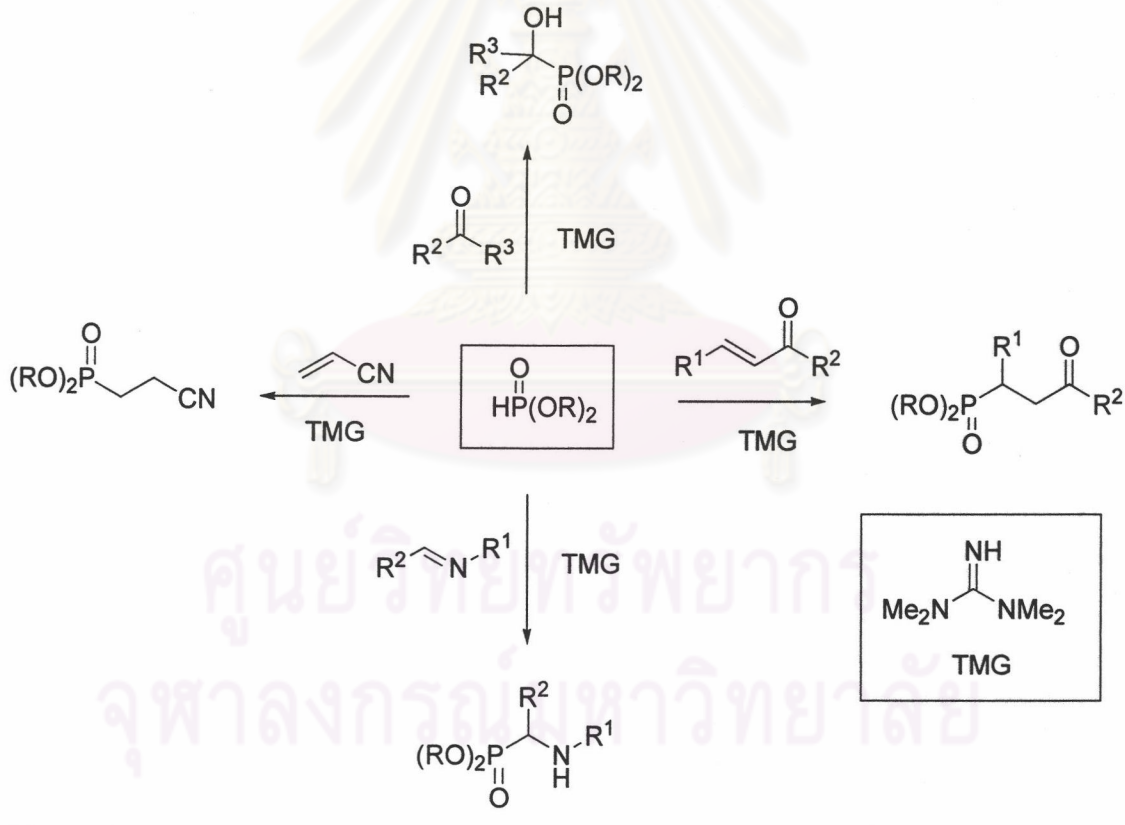


Figure 1.5 The addition of dialkyl phosphite to unsaturated molecules by using TMG as catalysts.

1.3 Asymmetric synthesis

An asymmetric synthesis may be defined as a synthesis which involves the formation of a new stereogenic unit in the substrate under the influence of a chiral

compound. The possible stereoisomers of a chiral compound are formed in unequal amounts. In the simplest case an achiral substrate is converted to an unequal mixture of the two enantiomers of chiral product containing only one stereogenic unit. The purpose of asymmetric synthesis is obviously to achieve the highest possible proportion of the desired enantiomer: to maximize the enantioselectivity. The most commonly used measure of the degree of enantioselectivity achieved is the enantiomeric excess (*ee*). This is defined as the proportion of the major enantiomer less than that of the minor enantiomer and is commonly expressed as a percentage.

$$\%\, ee = \frac{|R-S|}{|R+S|} \times 100$$

R: amount of (*R*)-enantiomer; *S*: amount of (*S*)-enantiomer

In general, asymmetric synthesis can be divided into four major classes, depending on how this influence is exerted, as follows:

1.3.1 First-generation or substrate-controlled methods

In this category, the reaction is directed intramolecularly by a stereogenic unit already present in the chiral substrate. The formation of the new stereogenic unit often occurs by reaction with an achiral reagent at a diastereotopic site controlled by a nearby stereogenic unit. Part or the entire starting chiral compound is actually built into the final product and serves to direct the formation of the new stereogenic centers.

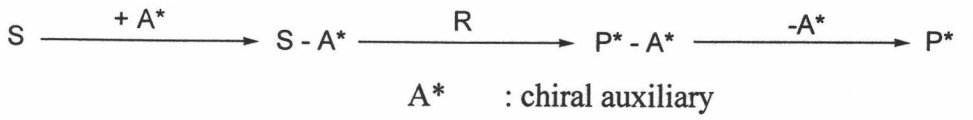
S	: substrate	P-G	: product
G	: chiral directing group	*	: chirality
R	: reagent		

The main drawback of this procedure is the need for an enantiomerically pure starting material, an amount and a specific enantiomer of which may not be readily available.

1.3.2 Second-generation or auxiliary-controlled methods

This approach is similar to the first-generation method in that control is again achieved intramolecularly by a chiral group, the chiral auxiliary. The auxiliary is now

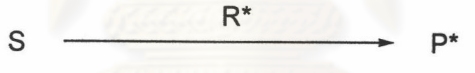
deliberately attached to an achiral substrate in order to direct the reaction and can be removed once it has served its purpose.



An additional useful feature of this approach is that the two possible products resulting from the alternative modes of reaction with R are not enantiomers but diastereomers as a result of the presence of the additional stereogenic center of the auxiliary. The separation of these diastereomers should be trivial. However, the addition and removal of the auxiliary group make the process at least 2 steps longer.

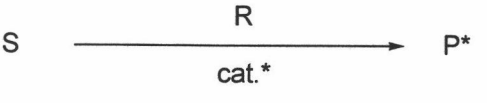
1.3.3 Third-generation or reagent-controlled methods

An achiral substrate is converted to the chiral product by the use of a chiral reagent, the control is intermolecular which is in contrast to the first- and second-generation methods. This is obviously an attractive procedure but the range of reactions for which effective chiral reagents exist is somewhat limited at present.



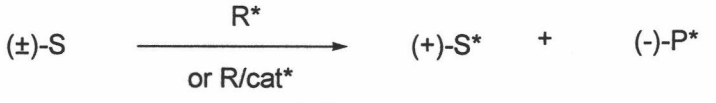
1.3.4 Fourth-generation or catalyst-controlled methods

In each of the previously mentioned three classes, an enantiomerically pure compound has been required in stoichiometric amounts, although in some cases it could be recovered for reuse. The final refinement, possible in fourth-generation methods, is to use a chiral catalyst to direct the conversion of an achiral substrate directly to a chiral product with an achiral reagent. Again the control here is intermolecular.



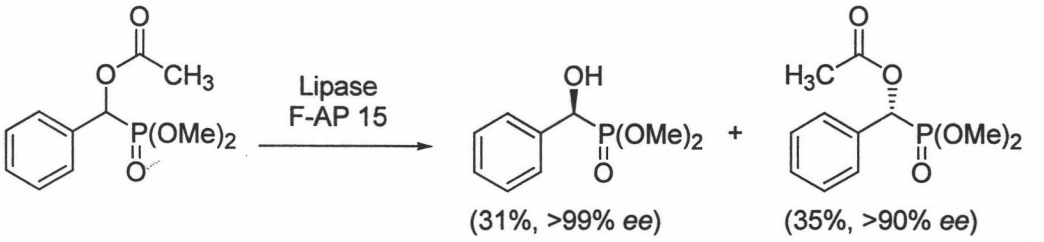
Besides four major classes of asymmetric synthesis, chiral products were obtained from kinetic resolution. This procedure involves reaction of either a racemic chiral compound or an achiral compound containing equivalent enantiotropic groups

with a chiral reagent or an achiral reagent/chiral catalyst system. In either case the two enantiomers or enantiotropic groups undergo reaction at different rates and in the ideal case one enantiomer (enantiotopic group) is converted to product while the other remains unchanged.



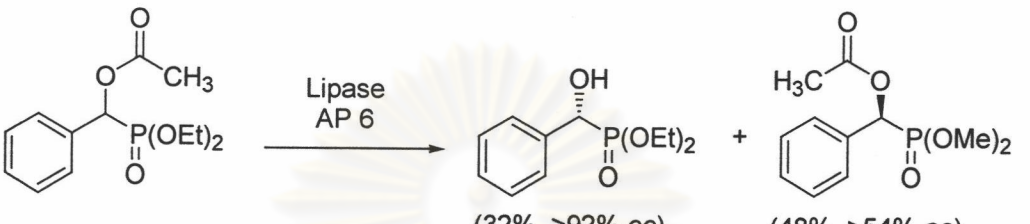
Several features of this type of reaction are notable. In the simple case shown, as in a classical resolution, maximum yield of one product is 50% and the enantiomeric excess actually varies as the reaction progresses due to the kinetics of the system. If the reaction is preformed under conditions in which the enantiomers of substrate can interconvert (racemisation), the entire substrate can in principle be converted to the enantiomerically pure product and the enantiomeric excess of the product then remains constant throughout the course of the reaction. Many of the most useful applications of enzymes in asymmetric synthesis involve kinetic resolution.

An alternative strategy for obtaining of α-hydroxyphosphonates, beside the asymmetric synthesis, is based on enzyme mediated reactions, either hydrolysis of α-acyloxy derivative or acylation of hydroxy group. In the first report on this approach, racemic substrates were prepared by Pudovik reaction followed by acylation of the resulting α-hydroxyphosphonates with acetic anhydride or an acyl chloride. Hydrolysis of the α-acyloxy group was examined with several diffcrent enzymes, including Lipases F-AP 15 and AP 6 which gave the highest enantioselectivity.[25] In some trials, the (*S*)-enantiomers were exclusively hydrolyzed to give optically pure *S* configuration alcohols and left the ester of *R* configuration virtually unreacted. For example, phosphonate **6** gave the (*S*)-α-hydroxy phosphonate **7** in 31% yield and >99% *ee*, while the *R* enantiomer was obtained in 35% yield and 90% *ee* by chemical hydrolysis of recovered ester **8**.



6 **7** **8**

In most other trails much lower yields or enantioselectivities were observed, suggesting that each substrate may require examination of a series of enzymes. This strategy was recently extended to preparation of the phosphorus analogues of phenylalanine and tyrosine, where the *R* ester **11** was recovered while the *S* enantiomers **10** was obtained as the alcohol with Lipase AP 6.[16]



9 **10** **11**

1.4 Asymmetric hydrophosphonylation

Interest in the biological activity of phosphonates has grown tremendously in recent years. If phosphonate esters represent the currency of metabolism, then the analogue phosphonates can be viewed as exquisite counterfeits. When the oxygen of a natural phosphate ester is formally replaced by the methylene group, the resulting phosphonates can be viewed as an isosteric analogue of the original phosphate with greatly enhanced metabolic stability. However, the formal substitution also effects the phosphorus acid pK_a's (with the second pK_a of the phosphonic acid about 0.5-1.5 pK_a units less acidic than that of the phosphate monoester)[26] and eliminates the possibility of enzymatic interaction with non-bonded electrons at this site. With an addition of electron withdrawing substituents such as fluorine or oxygen to the α-carbon, α-aminophosphonates that are clear analogues of α-amino acids can be constructed. Introduction of a geminal difluoromethylene group does not produce stereochemical considerations, but preparations of most α-hydroxy and α-aminophosphonates will require consideration of the stereochemistry of α-carbon if biological activity is a goal. Various α-hydroxyphosphonates already have established activity as enzyme inhibitors.[12-19] Several reviews have recently been published which are devoted to asymmetric synthesis of α-hydroxyphosphonic acid and their derivatives.[4,13,19,26-34]

In principle, nonracemic α-hydroxyphosphonates could be obtained from an addition of achiral phosphites to nonracemic aldehydes and ketones, from a reaction

of optically active phosphorus (III) reagents with a carbonyl compound, or from a condensation of an achiral phosphite with an aldehyde or prochiral ketone if mediated by a nonracemic catalyst.

Nonracemic α-hydroxyphosphonates have been obtained by resolution and prepared through stereoselective formation of each of the four bonds to a tertiary carbon, as shown in Figure 1.6.

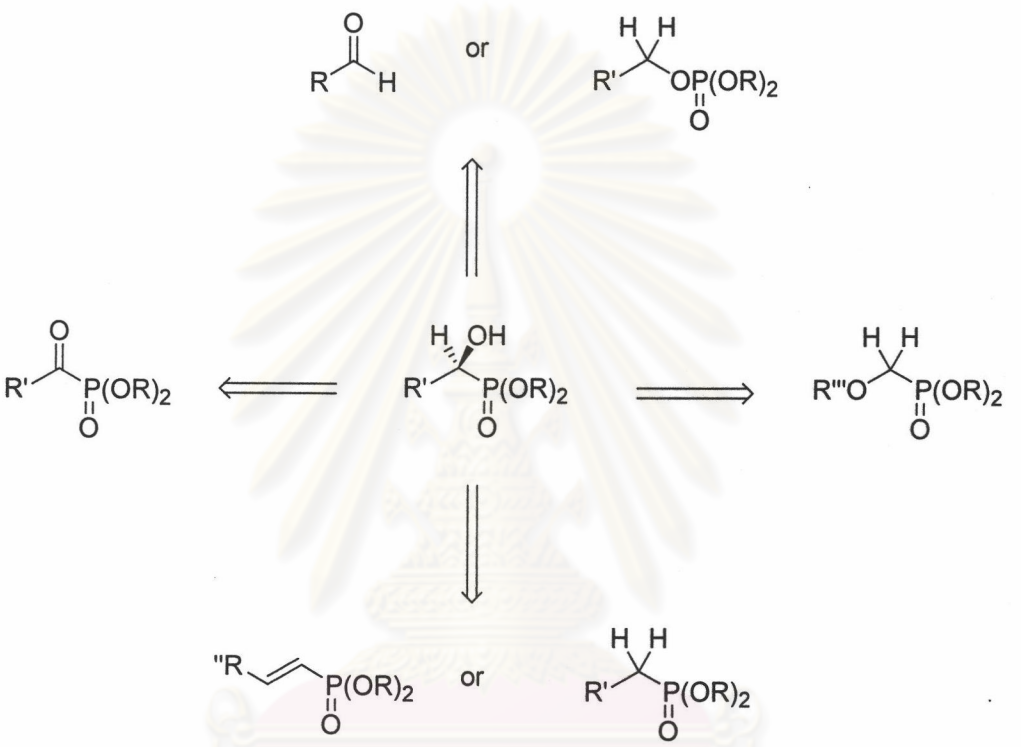


Figure 1.6 Known disconnections to nonracemic α-hydroxyphophonates.

At least in theory, nonracemic α-hydroxyphosphonates can be obtained from phosphite additions to any aldehyde or ketone drawn from the chiral pool. Several early examples involving phosphite additions to chiral aldehyde were reported. An aldehyde **12** derived from methyl lactate was reported to give the greatest erythro/threo ratio (**13**:**14** ca. 3:1) from an Abramov reaction with diisopropyl trimethylsilyl phosphite (Figure 1.7).

More recent research has extended this approach to carbonyl compounds derived from amino acids. For example, the Boc amino aldehyde **15** derived from L-phenylalanine, undergoes diastereoselective addition of dimethyl phosphite to give α-hydroxyphosphonates **16** and **17** with diastereomeric ratio as high as 12:1.[13]

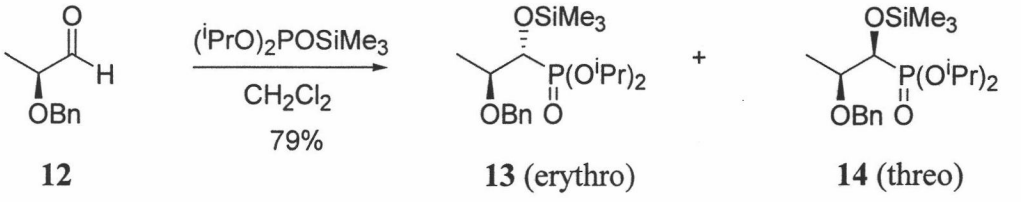


Figure 1.7 Synthesis of α-hydroxyphosphonates from *O*-benzyl lactaldehyde.

Even greater ratios (up to >98:2) were observed in the formation of α-hydroxyphosphonates **19** and **20** through the use of *tert*-butyldimethylsilyl diethyl phosphite in a $TiCl_4$ catalyzed condensation with an α-dibenzylamino aldehyde **18** derived from L-phenyalanine.[19] Furthermore, Shibuya and co-workers[10] observed that when diethyl phosphite was employed in place of the TBDMS phosphite, which was explained that the nucleophilicity of TBDMS phosphite higher than diethyl phosphite. In both studies, removal of the amino groups gave β-amino-α-hydroxyphosphonates valued as components of peptidomimetics

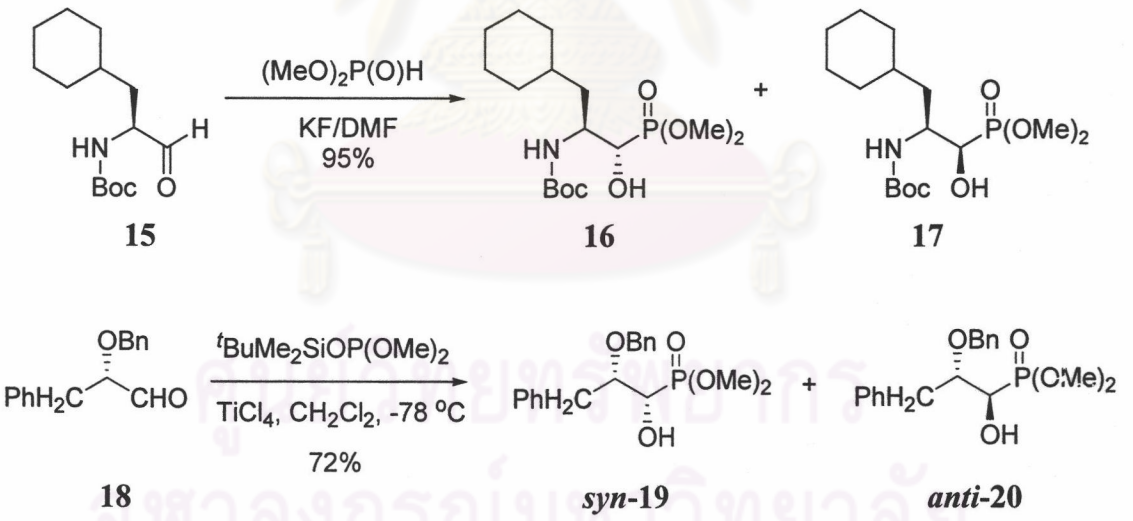
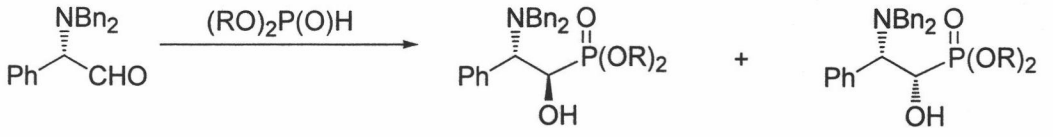


Figure 1.8 The addition of phosphorus nucleophile to aldehyde derived from amino acids.

In 2001, Pioptrowska and Wróblewski[28] reported the addition of various dialkyl phosphite derivatives to (*S*)-*N,N*-dibenzylphenylglycinal **21** which led to the preponderance of *anti* and *syn* diastereomers ranging from 80:20, when Et_3N or $Ti(O^iPr)_4$ were used, to 51:49 for Li or Mg salts.

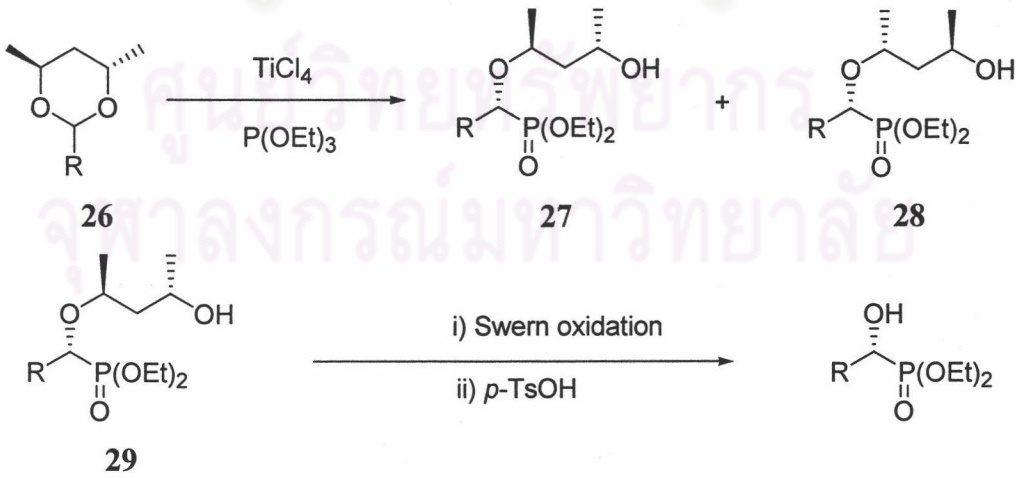
Table 1.1 Diastereoselectivity of the addition to (*S*)-**21.**



21 (1*R*,2*S*)-**22** R = Me (1*S*,2*S*)-**23** R = Me
(1*R*,2*S*)-**24** R = Et (1*S*,2*S*)-**25** R = Et

reagent	**22**	**23**	**24**	**25**
$(MeO)_2P(O)H/Et_3N$	78	22	-	-
$(EtO)_2P(O)H/Et_3N$	-	-	80	20
$(MeO)_2P(O)Li$	57	43	-	-
$(EtO)_2P(O)MgBr$	-	-	51	49
$(EtO)_2P(O)TMS$	-	-	61	39
$(EtO)_2P(O)H/Ti(O^iPr)_4$	-	-	72	28

Shibuya and Yokomatsu[29] reported the method of stereoselective ring opening of homochiral acetal **26** with triethyl phosphite, in the presence of a Lewis acid such as $BF_3.Et_2O$, $TiCl_4$-$Ti(O^iPr)_4$ or TMSOTf as a key reaction (Figure 1.9). This route was applied to the enantioselective synthesis of α-hydroxyphosphonates in good chemical yields (80-87%). The products were then successfully converted to the α-amino phosphonic diethyl esters.



26 **27** **28**

29

Figure 1.9 The stereoselective ring opening of homochiral acetal **26** with triethyl phosphite.

In 2001, Wróblewski and Balcerzak[30] disclosed the asymmetric synthesis of protected 2-amino-1,3-dihydroxypropylphosphonates which were synthesized from Garner aldehyde and dialkyl phosphites in good diastereoselectivity (9:1), when triethylamine or $Ti(O^iPr)_4$ were used as a catalyst.

Table 1.2 Enantiomeric excess of the phosphonates.[a]

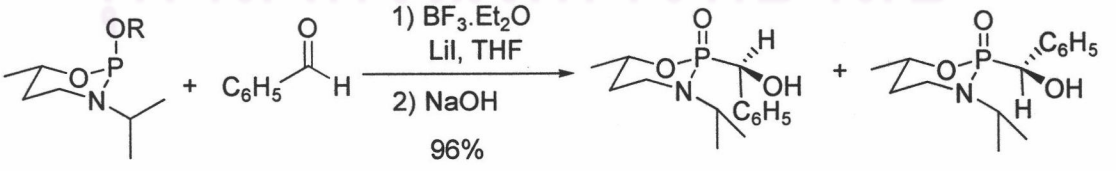
(2*S*)-**30** R = Me, Et

(1*S*,2*S*)-**31a** R = Me
(1*R*,2*S*)-**31b** R = Me
(1*S*,2*S*)-**32a** R = Et
(1*R*,2*S*)-**32b** R = Et

entry	catalyst	(1*S*,2*S*)-**31a**	(1*R*,2*S*)-**31b**	(1*S*,2*S*)-**32a**	(1*R*,2*S*)-**32b**
1	Et_3N [b]	91	94	80	82
2	Et_3N [c]	92	94	82	91
3	$Ti(O^iPr)_4$ [b]	95	97	93	95
4	$Ti(O^iPr)_4$ [c]	96	98	93	95

[a] After correction for *ee* of (*S*)-*O*-methylmandelic acid used (97.6%). [b] After chromatography on silica gel. [c] After crystallization from heptane.

Stereoselective additions of phosphoric acid derivatives to achiral aldehydes were investigated under both Pudovik and Abramov reaction conditions. Attention was focused on the chemistry of mono- and diamide derivatives of phosphoric acids. The observation is that oxazaphosphite **33a** and methyl derivative **33b** reacted with benzaldehyde to afford a moderate diastereoselective of α-hydroxyphosphonates **34** and **35**.[31]



33a R = Li
33b R = Me

34 **35**

Figure 1.10 The addition of oxazaphosphite to aldehyde.

In 1994, Spilling and co-workers have shown that the addition of the anion of the bicyclic chiral phosphorus acid diamide **36** to aldehyde gave α-hydroxy phosphonamides in good yield and good diasteroselectivity (54-93% *de*).[32] Then, the phosphonamides were hydrolyzed with aqueous HCl in dioxane to give α-hydroxyphosphonic acids. Methylation of the resulting phosphonic acids with diazomethane gave α-hydroxy dimethyl phosphonates without loss of stereochemical integrity.

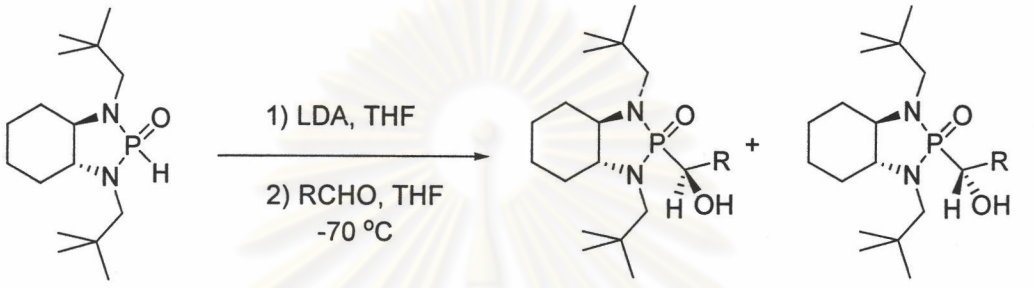


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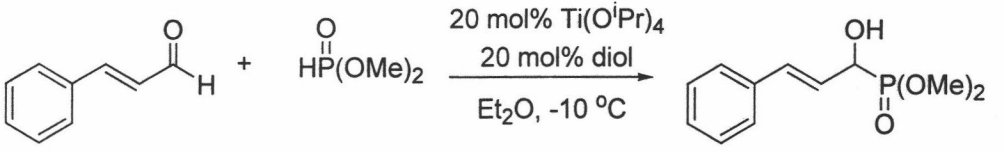
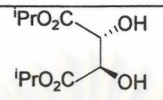
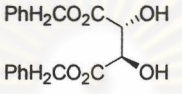
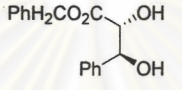
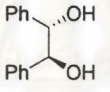
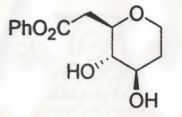
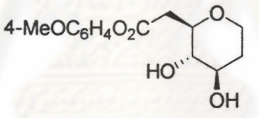
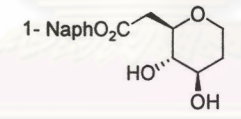
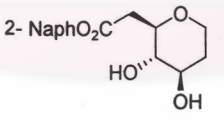
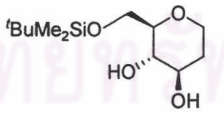
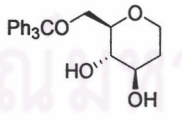
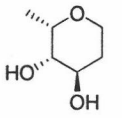
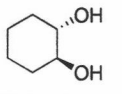
Figure 1.11 The addition of the bicyclic chiral phosphorus acid diamide to aldehyde.

In 1993, Shibuya reported that complexes of $Ti(O^iPr)_4$ and BINOL and TADDOL were effective asymmetric catalysts for hydrophosphonylation. However, the complex formed by mixing $Ti(O^iPr)_4$ and diisopropyl L-tartrate (1:1) catalyzed the addition of diethyl phosphite to benzaldehyde with 53% *ee* and 75% yield. Spilling and coworkers[35] investigated the structural effect of diol ligands on the enantioselectivity of phosphonylation of dimethyl phosphite and aldehyde. Cyclic diols, and cyclohexanediol in particular, were identified as effective ligands for titanium alkoxide catalyzed asymmetric phosphonylation (Table 1.3).

In 1995, Shibasaki and co-workers[36] reported the first example of an efficient catalytic asymmetric hydrophosphonylation of imines by the La-K-BINOL complex (lanthanum potassium binaphthol complex, LPB). As an extension of this research, they investigated the catalytic asymmetric hydrophosphonylation of aldehydes promoted by a heterobimetallic asymmetric catalyst. When they started this research, Shibuya[33] and Spilling[37] had independently reported catalytic asymmetric hydrophosphonylations of aldehydes using the La-Li-BINOL complex (lanthanum lithium binaphthol complex, LLB).

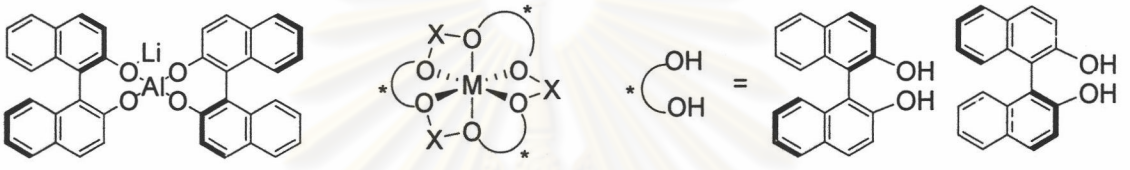
Table 1.3 The enantioselectivities in the hydrophosphonylation by using titanium alkoxides as catalysts.



entry	ligand	*ee* (%)[a]
1		13
2		43-51 (*S*)
3		38 (*S*)
4		7 (*S*)
5		49 (*S*)
6		45
7		44
8		54
9		40
10		50
11		39 (*R*)
12		67-70 (*R*)

[a] Enantiomeric excess was determined by HPLC on Whelk-O column, EtOH/hexanes.

For example, using benzaldehyde as a starting substrate, Shibuya reported the formation of **37a** (98%, 20% *ee*, 20 mol% LLB), and Spilling announced the formation of **37b** (58%, 28% *ee*, 10 mol% LLB). To improve the results, they first attempted a catalytic asymmetric hydrophosphonylation of benzaldehyde using either La-K-BINOL or the La-Na-BINOL complex (lanthanum sodium binaphthol complex, LSB). However, the enantiomeric excess of **37b** was only 2% *ee* (LPB) and 32% *ee* (LSB). In addition, they introduced the use of Al-Li-BINOL aluminium lithium binaphthol complex (ALB) as catalysts in the reaction of 1.1 equiv of dimethyl phosphite, which gave **37b** with 65% *ee* in 68% yield.



ALB

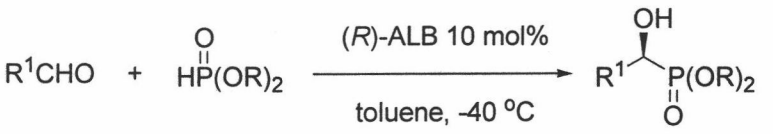
LLB X = Li, M = La
LSB X = Na, M = Na
LPB X = K, M = La

Figure 1.12 Heterobimetallic catalysts.

In 1996, Shibasaki and co-workers[38] eventually found that exposure of benzaldehyde to dimethyl phosphite (1 equiv) in toluene containing 10 mol% ALB at –40 °C for 51 h afforded **37b** with 85% *ee* in 90% yield (Table 1.4). The use of slight excess of benzaldehyde (1.2 equiv) gave rise to **37b** with 90% *ee* in 95% yield (9 mol% of ALB). Using the procedure described above, several *para*-substituted aromatic aldehydes were further subjected to catalytic asymmetric hydrophosphonylation. As shown in the Table 1.4, aromatic and α,β-unsaturated aldehydes were transformed into the corresponding α-hydroxyphosphonates in good chemical yields and high enantioselectivities.

In striking contrast to these results, even though saturated aldehyde such as hexanal and cyclohexanecarboxaldehyde were converted to the corresponding α-hydroxyphosphonates in excellent chemical yields, albeit with low enantiomeric excesses ranging from 3 to 24%.

Table 1.4 Catalytic asymmetric hydrophosphonylation of aldehydes catalyzed by ALB.



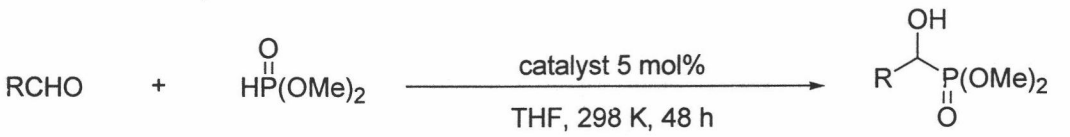
37

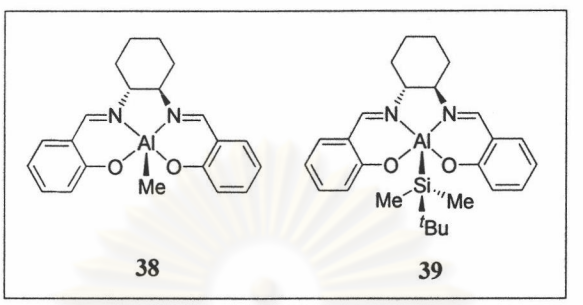
entry	R^1	R	product (**37**)	time (h)	yield (%)	*ee* (%)
1	C_6H_5	Et	**37a**	90	39	73
2	C_6H_5	Me	**37b**	51	90	85
3	C_6H_5	Me	**37b**	90	95	90
4	4-ClC_6H_4	Me	**37c**	38	80	83
5	4-MeC_6H_4	Me	**37d**	92	82	86
6	4-$MeOC_6H_4$	Me	**37e**	115	88	78
7	4-$O_2NC_6H_4$	Me	**37f**	66	85	71
8	(*E*)-C_6H_5CH=CH	Me	**37g**	83	85	82
9	(*E*)-$C_6H_5C(CH)_3$=CH	Me	**37h**	83	93	89
10	$(CH_3)_2C$=CH	Me	**37i**	94	72	68
11	(*E*)-$CH_3(CH_2)_2CH$=CH	Me	**37j**	39	53	55

During a search for new air- and water-compatible catalysts for phospho-aldol process, Kee and co-workers reported their work on a family of chiral organometallic and metallo-organic catalysts, chiral complexes of aluminium containing the salycen ligand framework, [(*R*,*R*)-salycyen]AlX (X = Me, $OSiMe_2{}^tBu$).[2] The complexes were reported to catalyze the asymmetric addition of diorgano-H-phosphonates to carbonyls, which for the first time move away from binaphthol as principal source of chiral recognition in the process. Reaction proceeded smoothly at ambient temperature in various solvents and under aerobic conditions, to afford α-hydroxyphosphonate esters $(MeO)_2P(O)CHR(OH)$, with enantiomeric excesses <50% (Table 1.5).

In 1994, Gajda[8] reported that the reduction of diethyl α-ketophosphonates **40** with borane and B-butyloxazaborolidine **41** as catalyst afforded diethyl (*S*)- or (*R*)-1-hydroxyphosphonates **42a-d** or **42e-f**, respectively, in good yields and moderate to good enantiomeric excesses (53-83% *ee*).

Table 1.5 Enantioselectivities in the reactions between DMHP (1 mmol) and ArCHO (1 mmol) catalyzed by **38** at 298 K in THF solvent.





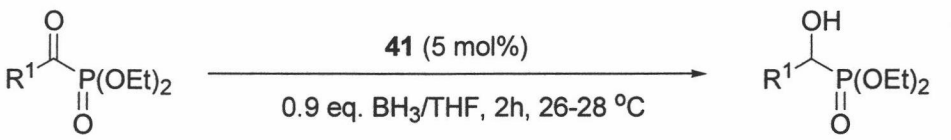
38 **39**

entry	aldehyde	*ee* (%)[a]	*ee* (%)[b]	*ee* (%)[c]
1	C_6H_5CHO	37 (*R*)	41 (*R*)	45 (*R*)
2	4-BrC_6H_4CHO	27 (*R*)	24 (*R*)	21 (*R*)
3	4-MeC_6H_4CHO	44 (*R*)	49 (*R*)	46 (*R*)
4	4-$MeOC_6H_4CHO$	39 (*R*)	46 (*R*)	49 (*R*)
5	4-$O_2NC_6H_4CHO$	15 (*R*)	10 (*R*)	
6	4-ClC_6H_4CHO	30 (*R*)	19 (*R*)	
7	2-ClC_6H_4CHO	12 (*R*)	12 (*R*)	
8	2-MeC_6H_4CHO	25 (*R*)	20 (*R*)	
9	2-$MeOC_6H_4CHO$	20 (*R*)	27 (*R*)	

[a] Reactions performed under dry inert-atmosphere conditions. [b] Reactions performed under aerobic conditions *ee*'s were determined by ^{31}P NMR using quinine as a chiral solvating agent.[39] Absolute configurations are given in parentheses. [c] Using **39** as catalyst.

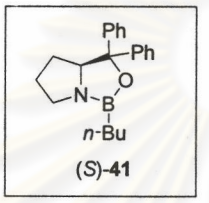
Applying (*S*)-**41** oxazaborolidine as catalyst, the diethyl (*S*)-1-hydroxyalkyl phosphonates **42a-d** was enantioselectively obtained (Table 1.6), whereas for (*R*)-**41** catalyst, the (*R*)-enantiomers of **42** was afforded. Higher values of enantiomeric excesses were achieved for aliphatic than for phenyl analogues of α-keto phosphonates **40**, probably because of comparable steric demands for phosphoryl and phenyl group flanking the carbonyl group in the last case.

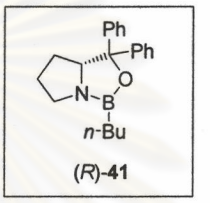
Table 1.6 Enantioselective reduction of diethyl α-ketophosphonates **40** in the presence of chiral catalyst (*S*)-**41** or (*R*)-**41** and borane.



40 **42**

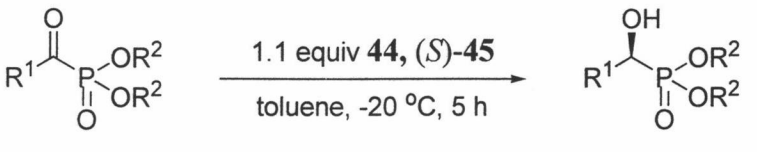
40a R^1 : Et, **40b** R^1 : Bu, **40c** R^1 : ^{i}Bu, **40d** R^1 : Ph



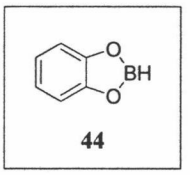


entry	catalyst (5mol%)	product **42**	yield (%)	*ee* (%)
1	(*S*)-**41**	**42a**	56	79 (*S*)
2	(*S*)-**41**	**42b**	60	82 (*S*)
3	(*S*)-**41**	**42c**	60	83 (*S*)
4	(*S*)-**41**	**42d**	85	53 (*S*)
5	(*R*)-**41**	**42e**	61	77 (*R*)
6	(*R*)-**41**	**42f**	53	83 (*R*)

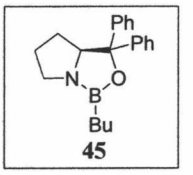
Meier *et al.* developed a highly enantioselective synthesis of dialkyl α-hydroxyphosphonates achieved by a oxazaborolidine catalyzed reduction with catecholborane starting with α-ketophosphonates.[40] The starting material α-ketophosphonates were synthesized *via* two different pathways.[41] The aromatic α-ketophosphontes were obtained by the reaction of appropriate benzoyl chlorides or alkyl chlorides and triisopropyl phosphite. The aliphatic α-ketophosphonates and aryl-α-ketophosphonates were obtained by a two step reaction sequence, first the aldehydes were reacted in the presence of sodium hydride with di-*tert*-butylphosphite to yield the racemic α-ketoalkylphosphonate di-*tert*-butyl esters.



43 **46**

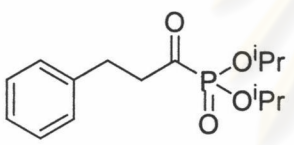


44

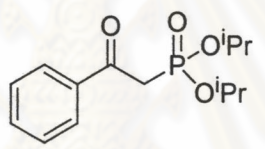


45

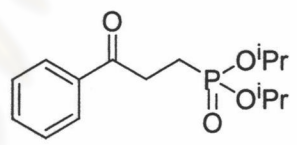
43a	R^1: C_6H_5, R^2: ^{i}Pr	**43i**	R^1: 2-$MeOC_6H_4$, R^2: ^{i}Pr
43b	R^1: 2-FC_6H_4, R^2: ^{i}Pr	**43j**	R^1: 4-MeC_6H_4, R^2: ^{t}Bu
43c	R^1: 2-ClC_6H_4, R^2: ^{i}Pr	**43k**	R^1: 4-$OMeC_6H_4$, R^2: ^{i}Pr
43d	R^1: 2-BrC_6H_4, R^2: ^{i}Pr	**43l**	R^1: 2,6-FC_6H_3, R_2: ^{i}Pr
43e	R^1: 2-IC_6H_4, R^2: ^{i}Pr	**43m**	R^1: 2,4-ClC_6H_3, R_2: ^{i}Pr
43f	R^1: 3-ClC_6H_4, R^2: ^{i}Pr	**43n**	R^1: Me, R^2: ^{t}Bu
43g	R^1: 4-ClC_6H_4, R^2: ^{i}Pr	**43o**	R^1: ^{i}Pr, R^2: ^{t}Bu
43h	R^1: 2-MeC_6H_4, R^2: ^{i}Pr	**43p**	R^1: ^{i}$PrCH_2$, R^2: ^{t}Bu



43q



43r



43s

Figure 1.13 The reduction of diethyl α-ketophosphonates with catecholborane **44** and oxazaborolidine **45**.

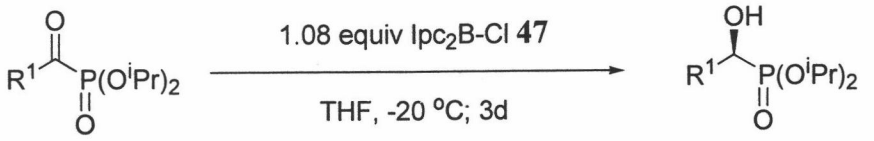
The racemic mixtures were subsequently transformed *via* the PDC-oxidation into the corresponding α-ketophosphonates.[42] Both α-aryl and α-alkylketo phosphonates were reduced using the *S*-enantiomer of catalyst **45** leading to the *S*-configuration in the products. The reaction gave good chemical yields and excellent enantiomeric excesses (up to >99% *ee*) (Table 1.7).

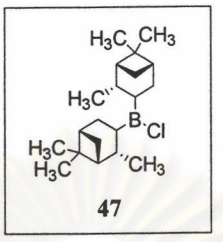
Table 1.7 Enantioselective reduction of α-ketophosphonates **43** in the presence of catecholborane **44** and (*S*)-5,5-diphenyl-2-butyl-3,4-propano-1,3,2-oxazaborolidine **45**.

entry	product **46**	yield (%)	*ee* (%)
1	**46a**	92	65 (*S*)
2	**46b**	68	91 (*S*)
3	**46c**	96	97 (*S*)
4	**46d**	82	95 (*S*)
5	**46e**	79	92 (*S*)
6	**46f**	84	77 (*S*)
7	**46g**	98	70 (*S*)
8	**46h**	89	97 (*S*)
9	**46i**	82	51 (*S*)
10	**46j**	85	76 (*S*)
11	**46k**	76	55 (*S*)
12	**46l**	96	>99 (*S*)
13	**46m**	85	94 (*S*)
14	**46n**	89	81 (*S*)
15	**46o**	91	80 (*S*)
16	**46p**	85	90 (*S*)
17	**46q**	85	95 (*S*)
18	**46r**	66	91 (*R*)
19	**46s**	58	68 (*R*)

In 1996, Meier and Laux reported the enantioselective synthesis of dialkyl α-hydroxyphosphonates using (-)-chlorodiisopinocampheylborane (Ipc_2B-Cl, **47**) to catalyze a reduction of an α-ketophophonate.[43] The reaction gave the target compounds in good yields with predictable stereochemistry and enantiomeric excesses up to 65%.

Table 1.8 Enantioselective reduction of α-ketophosphonates using (-)-Ipc_2B-Cl **47** in THF at –20 °C.



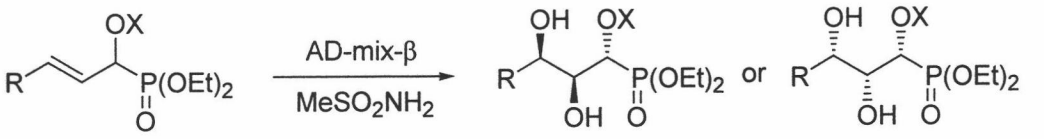


47

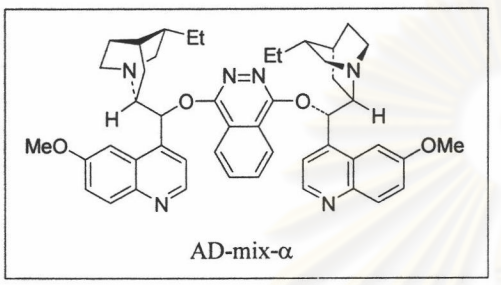
entry	R^1	yield (%)	*ee* (%)
1	C_6H_5	58	60
2	2-ClC_6H_4	89	41
3	3-ClC_6H_4	65	42
4	4-ClC_6H_4	61	42
5	2-$MeOC_6H_4$	75	54
6	3-$MeOC_6H_4$	87	52
7	4-$MeOC_6H_4$	88	65
8	4-^{t}BuC_6H_4	94	52
9	4-$MeSC_6H_4$	75	63

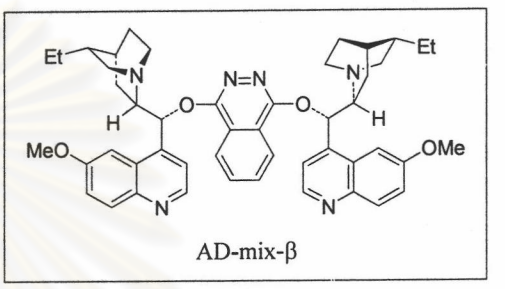
In comparison to reductive routes to nonracemic phosphonates, oxidative routes have been less studied. One example of oxidative routes is the synthesis of α,β-dihydroxy phosphonates *via* an enantioselective oxidation of vinyl phosphonates.[44] The kinetic rate of dihydroxylation was highly dependent upon the configuration of the 1-acyloxy functional group as well as the nature of substituents at the 3-position. The reagent preferentially dihydroxylated the *R*-enantiomer to leave an unreacted *S*-enantiomer of high enantiomeric purity. Double diastereoselection of the resolved diethyl 3-phenyl-1-aceloxy-2(*E*)-propenylphosphonate (**48**) in dihydroxylation was also examined.

Table 1.9 Asymmetric dihydroxylation of a racemic mixture of 2(*E*)-alkenyl phosphonates **48** with AD-*mix*-β or –α reagent.



48



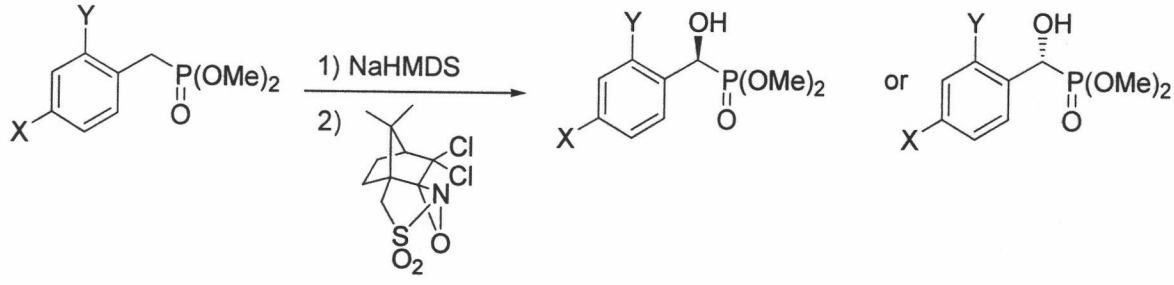


entry[a]	substrate		AD-*mix*	time	conv.[b]	product	
	R	X		(h)	(%)	yield (%)	*ee* (%)
1	C_6H_5	H	β	10	67	33	0
2	C_6H_5	Ac	β	6	65	35	99 (*S*)[c]
3	C_6H_5	Ac	α	6	87	13	99 (*R*)[c]
4	C_6H_5	Bz	β	6	40	60	42 (*S*)[c]
5	C_6H_5	Bz	β	8	87	13	98 (*S*)[c]
6	C_6H_5	Bz	α	6	50	50	49 (*R*)[c]
7	4-$MeOC_6H_4$	Ac	β	6	64	36	94 (*S*)[d]
8	H	Ac	β	6	56	44	61 (*S*)[d]
9	H	Bz	β	10	81	19	38 (*S*)[d]

[a] All reaction were carried out at 0°C on 2 mmol scale. [b] Base on consumption of racemate. [c] Determined by HPLC analysis on Chiralpak AS (Daicel). [d] Determined by ^1H and ^{31}P NMR analysis after converting to the corresponding MTPA esters.

In 1997, Wiemer and Pogatchnok studied the oxidation of achiral phosphonates to nonracemic α-hydroxyphosphonates which was based on the oxidation of phosphoryl stabilized anion with a nonracemic oxidant such as a (camphorsulfonyl)oxaziridines. Good chemical yields have been observed along with some very attractive *ee*'s (up to 93% *ee*).[45]

Table 1.10 The oxidation of phosphonates anion with oxaziridine.



entry	X	Y	yield (%)	*ee* (%)
1	H	H	70	93 (*S*)
2	NO_2	H	54	80 (*S*)
3	Cl	H	76	87 (*S*)
4	CH_3O	H	60	81 (*S*)
5	H	Cl	72	93 (*S*)
6	H	H	65	89 (*R*)

1.5 Objectives of this research

The objective of this research is to develop a catalytic asymmetric synthetic method of α-hydroxyphosphonates by the addition of phosphorus nucleophiles to aldehydes using complexes of various metal ions and chiral ligands as catalysts. The phosphorus nucleophiles used in this research are diethyl phosphite and dimethyl phosphite.

Chiral ligands of interest include chiral Schiff's bases,[46,47] peptide-Schiff's base,[46,47] and *N*-salicyl-β-aminoalcohols.[48] The last group is a rather interesting ligands as they have been shown to be a good catalysts for asymmetric cyanation of imines (Strecker reaction), and have played important role as an effective catalyst in Michael addition.[49] Mulling over an extension of application of these catalysts, we aimed at using these ligands as a catalyst in asymmetric synthesis of α-hydroxyphosphonates.