CHAPTER I

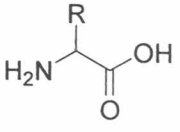
INTRODUCTION

1.1 α-Aminophosphonic acids

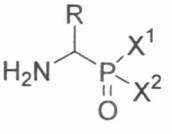
Organophosphorus compounds are essential constituents of protoplasm and play important roles in the maintenance of life, for example as nucleic acids, nucleotide coenzymes, metabolic intermediates, and phosphatides. Moreover, many organophosphorus compounds are artificially produced for practical applications, for instance, as agricultural chemicals including insecticides, herbicides, and plant growth regulators or as medicinal compounds such as anticancer, antiviral, and antibacterial agents. In addition, the metal-coordinated phosphine complexes are widely used as catalyst systems in many industrial processes, e.g., oxo hydroformylation, olefin hydrogenation, Reppe olefin polymerization, etc.. Alternative applications include its use as flame retardants for fabrics and plastics, plasticizing and stabilizing agents in the plastics industry, selective extractants of metal salts from ores, as well as, additives in the petroleum products fields, and corrosion inhibitors.[1]

α-Amino acids are one of the most fundamental groups of molecule of life. They exhibit important and diverse biological functions, for example, they are building blocks of peptides, proteins, peptidoglycans in bacterial cell-walls and many other natural products.

α-Amino phosphonic acids are broadly defined as phosphorus analogues of the α-amino acids in which the carboxylic acid group is replaced by a phosphonic or related function.



α-amino acids



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1a : $X^1 = X^2 = OH$	α-aminoalkylphosphonic acids
1b : $X^1 = OH$, X^2 = alkyl, aryl	α-aminoalkylphosphinic acids
1c : $X^1 = OH$, $X^2 = H$	α-aminoalkylphosphonous acids
1d : $X^1 = OR$, $X^2 = OR$,	α-aminophosphonates

Figure 1.1 α-Amino acids and their phosphonic analogues

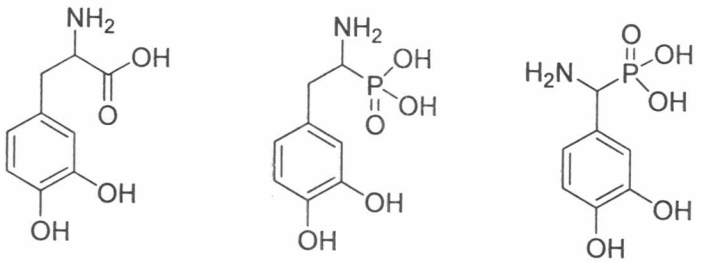
The replacement of the carbonyl carbon by a phosphorus atom has a number of important consequences as an additional substituent group is present in the molecule. The phosphorus atom has a tetrahedral configuration whereas the carbonyl carbon atom is planar, and there are significant differences in steric bulk and in acidity (p*K* difference of at least three units). These differences each has a bearing on the behavior of the phosphorus analogue, compared to that of the corresponding amino carboxylic acid. The tetrahedral configuration of phosphorus has important implications in the design of transition state-analogue enzyme-inhibitors which have wide-ranging potential in medicinal chemistry.

Being the structural analogues of α-amino acids, α-aminophosphonic acids usually act as their antagonists and compete with their carboxylic counterparts for the active site of enzymes or other cell receptors. The fact that they bear a very close resemblance to aminocarboxylic acids makes them extremely important antimetabolites of the latter. As inhibitors of metabolic processes, they exert physiological activity as antibacterial agents, neuroactive compounds, anticancer drugs or herbicides, possible application of which range from medicinal to agricultural.

1.1.1 Mode of action

- Inhibition of enzymes

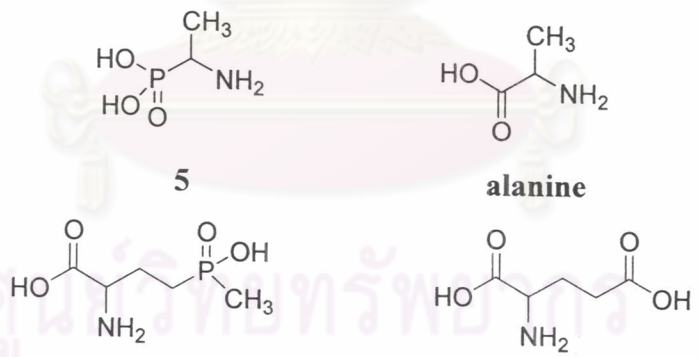
Many of the enzymes are involved in the metabolism of amino acids. The inhibition frequently observed indicates that there is a structural antagonism between amino acids and their phosphonic acid counterparts, and numerous enzymes do recognize α-aminophosphonic acids as being more or less similar to the respective α-amino carboxylic acids. A good example is the interaction of the phosphonic analogues of 3,4-dihydroxyphenylalanine (dopa, **2**) with tyrosinase.[2] A simple replacement of carboxylic acid group of dopa by a phosphonic moiety and a shortening of the alkyl chain lead to compounds **3** and **4** which serve as synthetic substrates for tyrosinase.



2 3 4

Figure 1.2 3,4-dihydroxyphenylalanine (dopa, **2**), and the phosphonic analogues of dopa (**3, 4**)

Strong electrostatic binding of phosphonate positively charged carboxylate-binding site of the enzyme to the dianion by the appropriate portion of enzyme accounts significantly for the inhibitory action of most of the phosphonic acid analogues of amino acids including substrate **3** and inhibitor **4**. The representative examples of these inhibitors are illustrated in Figure 1.3. The phosphonic analogue **5** of alanine is a potent inhibitor of alanine racemases. Phosphonothricin (**6**), phosphonic acid mimetic of glutamic acid, is a potent inhibitor of glutamine synthetase which catalyzes a reaction of central importance in nitrogen metabolism.[2]



5 **alanine**

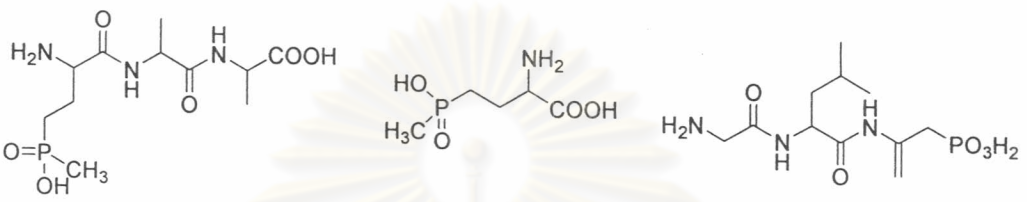
6 **glutamic acid**

Figure 1.3 Examples of the enzyme inhibitors

- Antibiotic activities

Phosphorus-containing antibiotics, especially phosphonic acids, represent an interesting group of antimicrobial agents which is steadily increasing in number. Some of these compounds are produced by total chemical synthesis but many represent products of microbial origin. The most important among these compounds is bialaphos (**7**), an antibacterial metabolite produced by *Steptomyces hygroscopicus.*

This tripeptide contains an analogue of glutamic acid, *L*-phosphinothricin (**8**), a potent inhibitor of glutamine synthetase. The tripeptide (**7**) is highly active *in vitro* against Gram-positive and Gram-nagative bacteria and also exerts strong herbicidal properties. Antimicrobial and immunostimulating phosphonotripeptide **9** was isolated as a component of a complex mixture of antibiotics produced by a soil microorganism.



7 **8** **9**

Figure 1.4 Examples of antibiotic agents

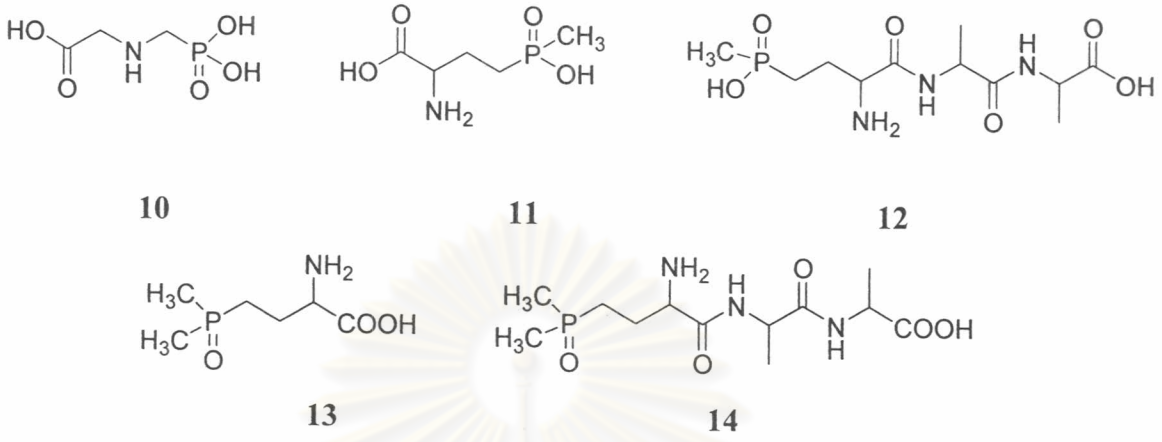
- Plant growth regulations

Since its initial discovery in 1970, glyphosate (**10**) represents a major breakthrough in herbicide research and development. In soil it is readily broken down by microbes to aminomethylphosphonic acid. It is widely accepted that glyphosate kills plants by inhibiting the enzyme EPSPS (5-enolpyruvoylshikimate-3-phosphate synthease). EPSPS is a critical enzyme in the biosynthesis of essential aromatic amino acids and other aromatic compounds. This pathway is present in all plants and microorganisms, but is completely absent on mammals, birds, fish and insect.

The disclosure of herbicidal activity of glyphosate initiated the extensive research concerned with the design, synthesis and evaluation of biological properties of new aminophosphonates. Numerous aminophosphonic and aminophosphinic acids and their derivatives have been synthesized and tested as potential agrochemicals. Many have shown plant-growth regulating or herbicidal activity to varying degrees. Some have shown fungicidal activity and in a few cases there have been indications of limited insecticidal activity. For example, glyfosinate (**11**), bilanafos (**12**), are used commercially in agriculture. Both are environmentally friendly herbicides.

There are a number of examples which display fungicidal activity. Phosphinothricin (**13**), and its tripeptide, phosphinothricyl-*L*-alanyl-*L*-alanine (**14**), referred not to herbicidal activity (although both were subsequently developed

commercially as herbicides) but to activity against Gram-positive and Gram-negative bacteria and against a number of fungal pathogens on rice.



10 **11** **12**

13 **14**

Figure 1.5 Examples of aminophosphonic acid-based plant growth regulators

- Neuroactive activities

The involvement of various amino acids in neurotransmission process is well recognized. It appears as a natural development that aminophosphonates are included among various amino acid analogues examined for neurophysiological effects. Among all the neuromodulators, *L*-glutamic acid a common transmitter in central nervous system, is of special importance. It plays a crucial role in the development of long term potentiation and certain forms of memory. Thus, it is not surprising that preliminary studies were focused on the neuroactivity of the simple phosphonic acid analogue **15** of glutamic acid. This analogue appears to be remarkable for its manifold and potent effects in various kinds of nervous tissue.[2]

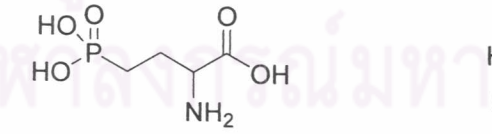


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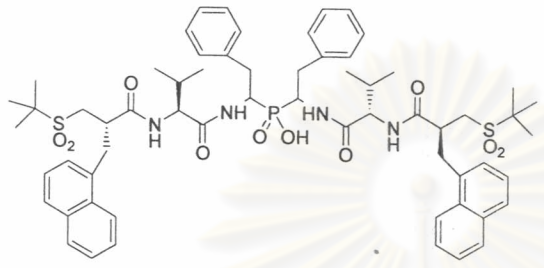
Figure 1.6 Example of neuroactive agents

- Other activities

There is a growing recognition that aminophosphonic acids affect living organisms in many ways as mentioned above and exhibit possible applications on specifically targeted research related to the HIV protease inhibitor (**16**),[3] anticancer (**17**), antithrombin (**18**), and human collagnease inhibitor (**19**).



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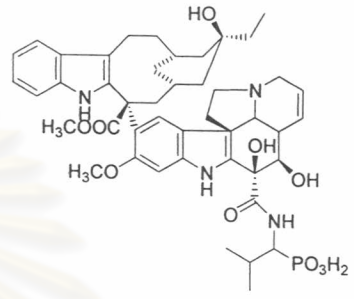

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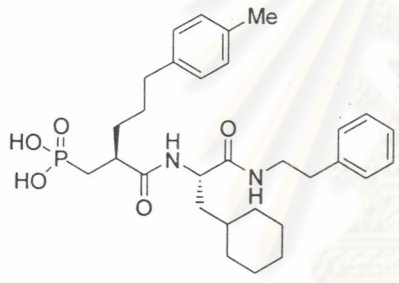

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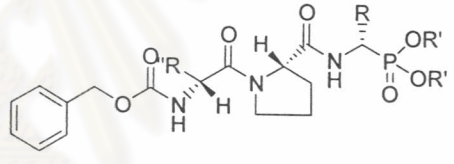

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Figure 1.7 Examples of the HIV protease inhibitor (**16**), anticancer (**17**), antithrombin (**18**), and human collagnease inhibitor (**19**)

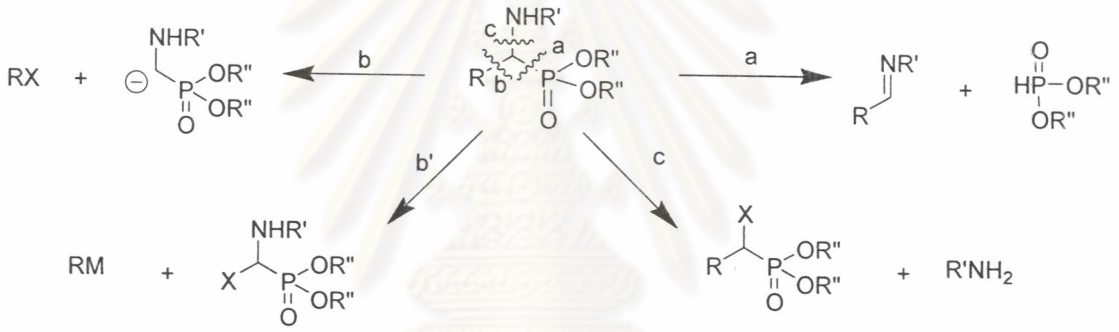
1.2 α-Aminophosphonate synthesis

Although α-aminophosphonic acids were first mentioned in the literature in the early 1940s, for about two decades they received only marginal attention. Today, α-aminophosphonic acids attract considerable interest because of their diverse and useful biological activities, therefore, a wide variety of approaches for their preparation are currently being developed. More importantly, they can be use as synthetic precursors. For example, α-aminophosphonate diesters are more attractive as intermediates for multistep syntheses than the corresponding phosphonic acids, as the insolubility of the latter in both organic and neutral aqueous media complicates

derivatization of both the amine and acid functionalities. A simple route to α-aminophosphonate diesters, therefore, held the promise of considerable utility.

1.2.1 General synthetic methods

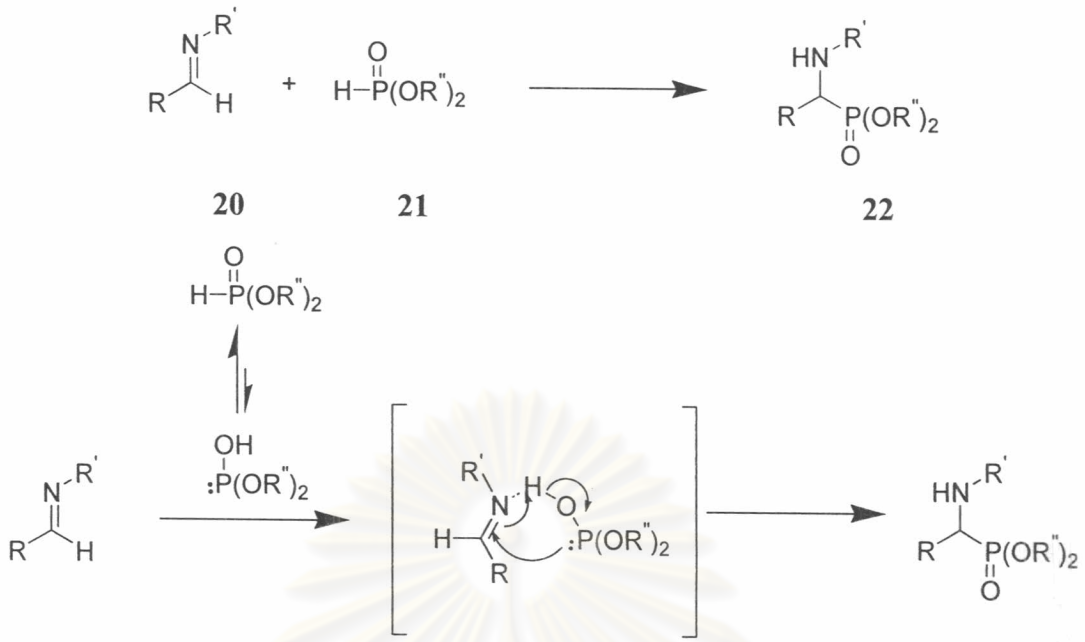
There are so many methods successfully employed in the synthesis of α-aminophosphonates that all details can not be covered here. Only general methods for the synthesis of α-aminophosphonates (Scheme 1.1) including the neucleophilic addition of di- or trialkyl phosphite derivatives to C=N bond (C-P bond forming, a), alkylation of phosphonate imines (C-C bond forming, b), electrophilic amination of α-alkyl phosphonamides or nucleophilic amination of α-hydroxy phosphonate derivatives (C-N bond forming, c).[4]



Scheme 1.1 General methods for α-aminophosphonate synthesis

1.2.1.1 The nucleophilic addition to the C=N bond

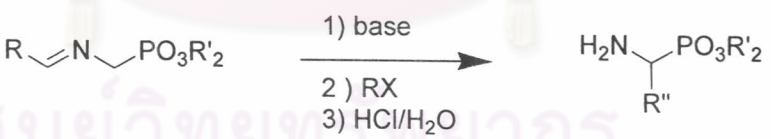
The standard synthesis of α-aminophosphonates involves addition of a trivalent phosphorus acid or ester to an imines, which itself may be generated *in situ* from aldehydes and amines,[5-7] alkyl carbamates,[8-9] or ammonium acetate.[10] There are reports on the use of phosphorus trichloride or dichlorophosphine,[11] as well as trialkylphosphite[8] as starting materials. Scheme 1.2 illustrates the reaction of nucleophilic addition of dialkyl phosphite to an imines.



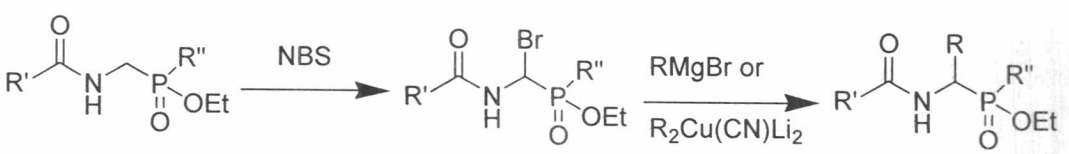
Scheme 1.2 C-P bond formation through a nucleophilic addition of dialkyl phosphite to an imine

1.2.1.2 Alkylation of phosphonate imines[12]

Alkylation of a schiff base obtained from a dialkyl aminomethanephosphonate and benzaldehyde or benzophenone is a general method for the preparation of a wide variety of α-aminoalkanephosphonic acids. The alkylation was carried out either by the classical approach (*i.e.* by generation of an intermediate carbanion by the use of LDA) or under solid-liquid phase transfer catalysis conditions.[13-14]

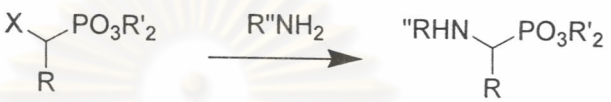


A quite different approach is to convert *N*-acyl-aminoalkanephosphonates and –phosphinates into their α-bromo derivatives by *N*-bromosuccinimide. These compounds are then reacted *in situ* with Grignard or organocopper reagents affording diethyl 1-(*N*-acylamino)alkanephosphonates.

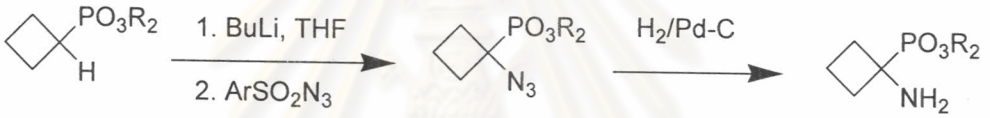


1.2.1.3 Amination[12]

Nucleophilic amination, a nuclephilic attack of ammonia or of amines on an electrophilic carbon bearing a halogen in readily available 1-halogenoalkanephosphonates, seems at first sight to be the simplest method for the preparation of 1-aminoalkanephosphonic acids. However, this reaction proceeded with difficulty and gave only a low yield of the desired product. Nevertheless, this reaction was used as a method for the preparation of aminophosphonates in some special cases.



Electrophilic amination has been the least explored method for the synthesis of these compounds. An example is given below.



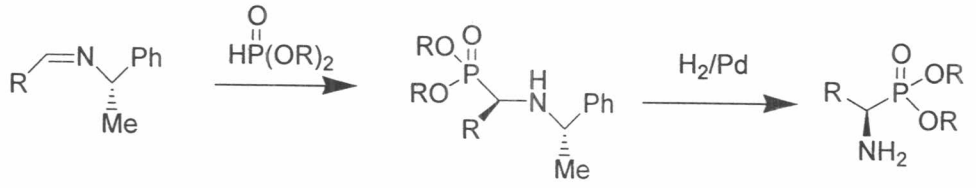
1.2.2 Asymmetric synthesis

The biological activity of α-aminophosphonates is influenced by the absolute configuration of the stereogenic carbon α to the phosphorus atom. For example, the *S*-enantiomer of 2-amino-4-phosphobutanic acid is 20-40 times more active than the *R*-enantiomer in the suppression of glutamate-mediated nervous transmission.[12]

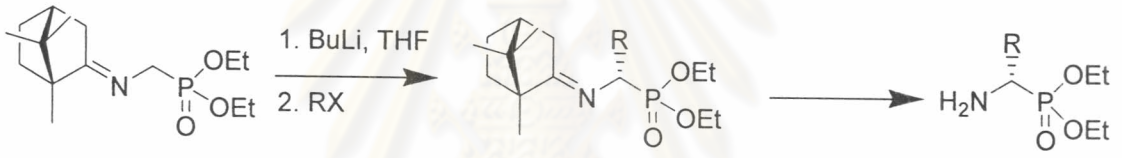
For the preparation of asymmetric aminophosphonic acids it is possible to use methods involving stereoselective formation of the amino functionality, transformations of chiral amino acids, and stereoselective substitution of appropriate substituents in enantiomeric substrates containing an amino function.

The first synthesis of an optically active α-aminophosphonic acid by C-P bond formation was reported by Gilmore and McBride in 1972.[15] The reaction of Schiff base derivative of an appropriate aldehyde and enantiomerically pure α-phenylethylamine, as chiral auxiliary. The acid-catalyzed addition of dialkyl phosphites to aldimines proceeds with high diastereoselectivity only on the case of bulky groups on the aldehyde residue of the aldimine and decrease markedly when small aliphatic groups are present. Attempts to improve the diastereoselectivity of the

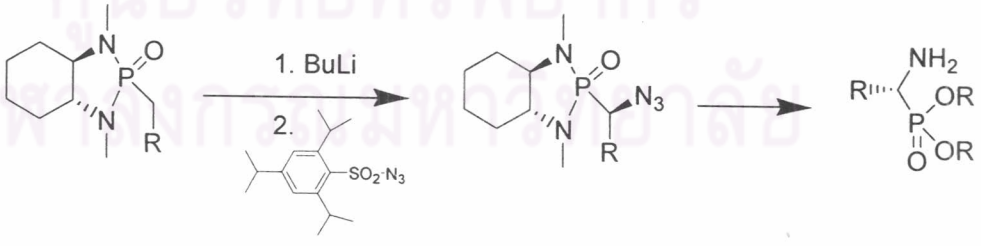
reaction by increasing the bulkiness of the phosphite, for instance, by the use of bis(trimethylsilyl) phosphite, failed.[12]



In the part of enantioselective C-C bond forming reactions, Camphor and its derivatives are most commonly used as chiral auxiliary due to the availability of their enantiomerically pure forms, and their low cost. For example, the lithium derivative of schiff base, from (*R*)-camphor and diethylaminomethanephosphonate, reacts with different alkyl, allyl and benzyl halides to yield the corresponding esters of (*S*)-α-aminoalkanephosphonic acids, with 11-95% diastereomeric excess.



One of the most promising approaches to the asymmetric synthesis of α-aminophosphonates is the stereoselective electrophilic amination of chiral α-phosphonate carbanions. Diazaphosphole **23**, derived from 1,2-diaminocyclohexane was successfully used as the substrate in electrophilic amination with trisylazide. After deprotonation and reduction of the azido group, various chiral α-aminophosphonic acids were obtained in good enantiomeric excess (63-99%).[12]



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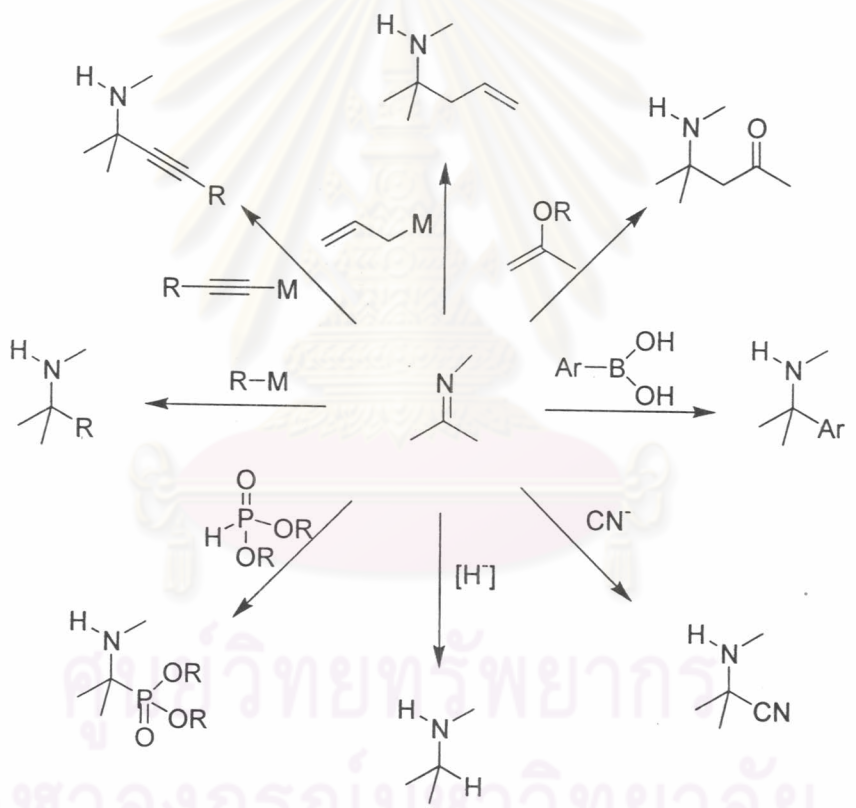
1.3 Literature reviews of hydrophosphonylation of imines

1.3.1 Nucleophilic Addition to imines

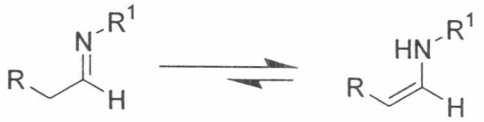
The amine group is one of the fundamental structures in organic compounds. An addition of a nucleophile to the C=N bond of imines or imine derivatives is a well known reaction yielding amino compound. Several nucleophiles add of C=N bonds to imines or imine derivatives such as oximes, nitrones, hydrazones. These reactions include alkylation of organometallic reagents, reductive amination of hydride reagents, Strecker reaction of cyanide ions, and hydrophosphonylation of dialkyl phosphite, etc. (Scheme 1.3)



Scheme 1.3 Various types of nucleophilic addition to imine or imine derivatives

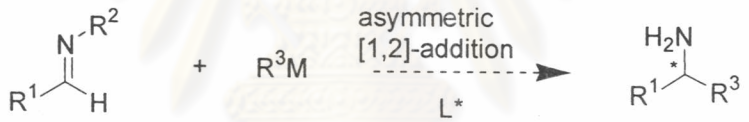
Enantiomerically pure amines bearing a stereogenic center at the α-position play a crucial role as a characteristic structural feature in bioactive natural products and pharmaceutically important compounds. Ironically, the development of stereoselective syntheses of enantiopure amines by nucleophilic addition to imines has been investigated to a lesser extent. Some general problems include poor

electrophilicity of the azomethine carbon which results in a difficulty in nucleophilic addition to the C=N bonds compared to the addition to the C=O bonds. In addition, the possibility of imine-enamine tautomerism can be problematic especially in the presence of strong bases such as organometallic reagents.[16-18]



Scheme 1.4 Imine-enamine tautomerism

Some improvements have been reached in overcoming these problems by activation of the imino group. The electrophilicity of carbon atom of the C=N bond can be increased by *N*-substitution with an electron-withdrawing groups such as *N*-alkylation, *N*-oxidation, *N*-acylation, or *N*-sulfonylation to give iminium salts, reactive nitrones, acylimines, and sulfonimines, respectively. However, this method requires an additional removal step of the activating groups to generate free amines.

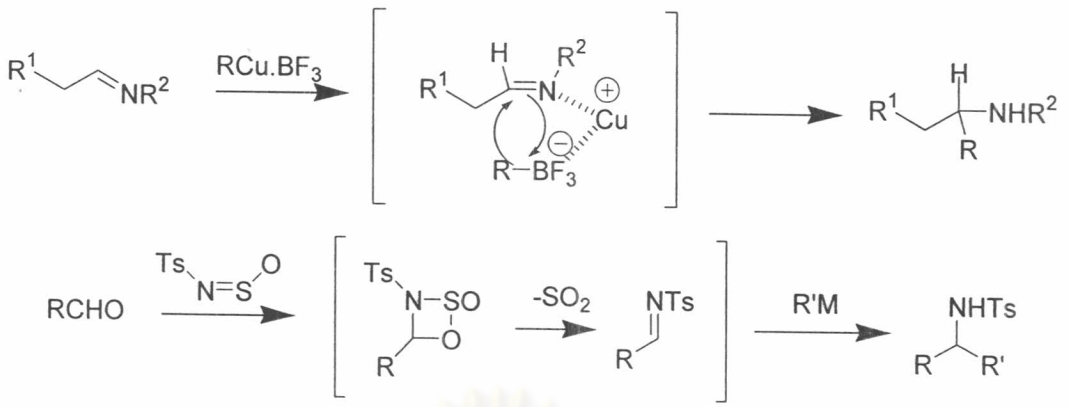


$R^1 = R^3$ = alkyl, aryl, allyl, vinyl,etc.
R^2 = alkyl, aryl, $-SiR_3$, $-NR_2$, POR_2, -OR, $-S(O)_xR$, $-BR_2$, etc.
M = Li, Mg, Ba, B, Sn, Si, Ce, Yb, Cd, Cu, Zn, Zr, etc.
L*= external chiral ligands

Scheme 1.5 General equation of asymmetric 1,2 addition of nucleophiles to imines

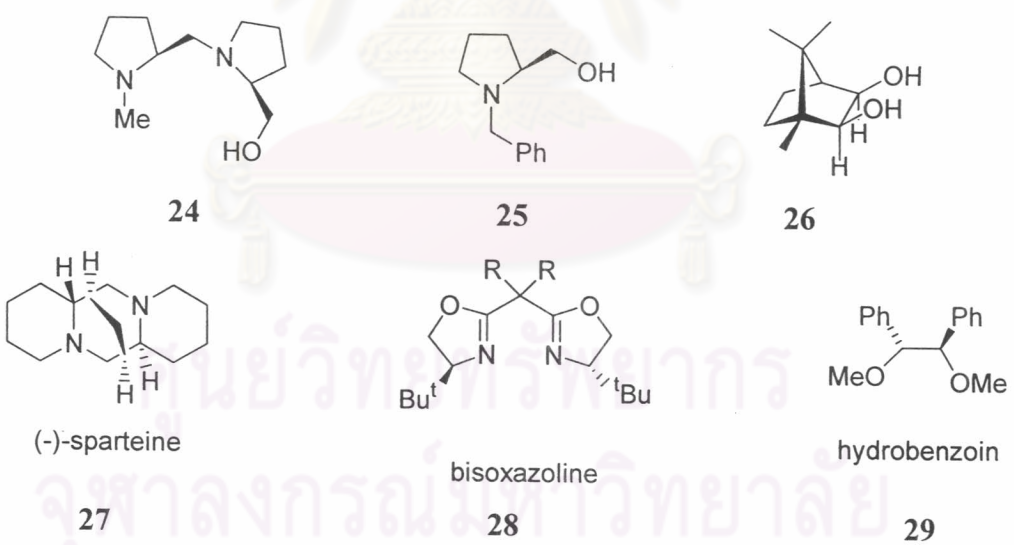
Another strategy involves activation of the C=N bond of imines or imine derivatives by coordination of a Lewis acid with the nitrogen lone pair or by addition of external promoters. The chirality information can be incorporated into the amine part of the imino substrate, in the nucleophilic reagent or in external chiral ligands as is depicted in the general equation (Scheme 1.5).[16]

An example includes the use of $RCu.BF_3$, a reagent with low basicity, which can activate imines by coordination and makes simultaneous addition possible. Another example is the use of *N*-Tosyl aldimines generated *in situ* from aldehydes and *N*-sulfinyl sulfonamides which are highly electrophilic.[19]



yield 60 to 90%

A number of reviews on various amine synthetic routes have appeared in the literature.[16-18] In the 1990s, the addition of carbanions to imines and imine derivatives has increasingly attracted organic chemists' attention. There have been reports on asymmetric 1,2-addition of organolithium to imines by using an external chiral ligands such as chiral alcohols, diols and amino alcohols (**24, 25, 26**),[20] (-)-sparteine (**27**), chiral bisoxazoline (**28**),[21-24] and chiral hydrobenzoin (**29**)[25] as a stereocontroller.



24 **25** **26**

(-)-sparteine

bisoxazoline

hydrobenzoin

27 **28** **29**

Figure 1.8 Examples of chiral ligands used in asymmetric synthesis of amino compounds

Strecker reaction is also well recognized as a versatile route for α-amino acids synthesis *via* α-amino nitrile intermediates by nucleophilic addition of cyanide ion to imines. A recent review by Kobayashi and Ishitani offers many reports on asymmetric Strecker reactions.[18] Examples of ligands used as stereocontrollers in the

Strecker reactions which provide excellent enantiomeric excess are illustrated in Figure1.9. Hydrophosphonylation is one of the reactions based on nucleophilic addition to imines. Even though phosphorus nucleophile is more labile than cyanide ion (Strecker reaction), or organometallic reagent (alkylation), it is interesting to try the same group of chiral ligand which selectively catalyzed a Strecker reaction or alkylation on the hydrophosphonylation.

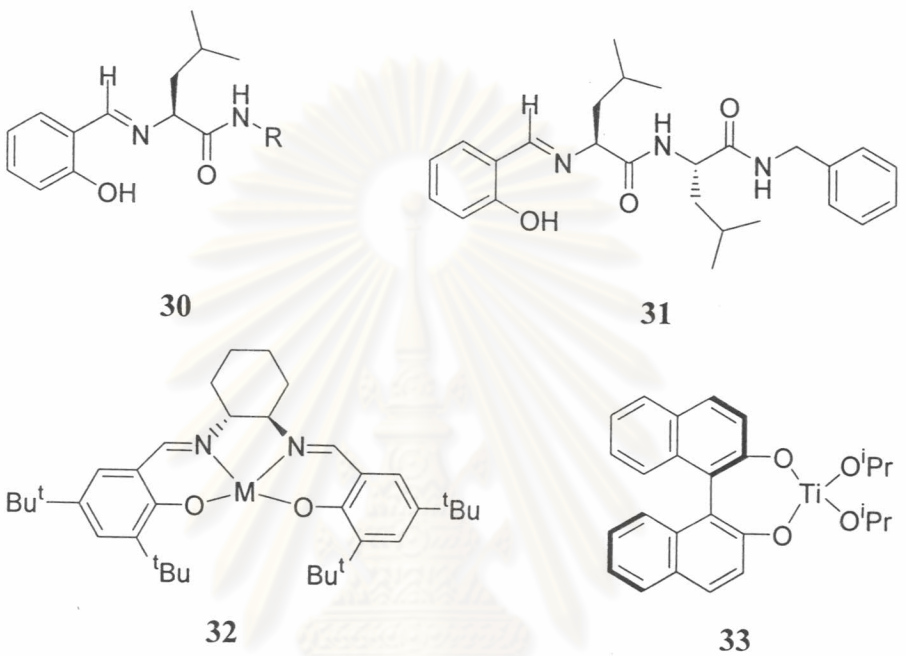


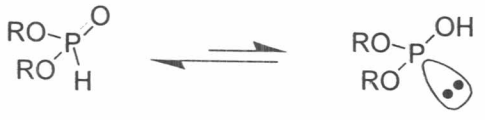
Figure 1.9 Example for chiral ligand in Strecker reaction

1.3.2 Non asymmetric synthesis of α-amino phosphonates

A variety of synthetic approaches to α-amino phosphonates are available. Among these methods, nucleophilic addition of phosphites to imines is one of the most convenient protocols. Hydrophosphonylation of imines provides a possible route for synthesis of biologically interesting α-aminophosphonates. However, only a few reports on α-aminophosphonate syntheses are precedented. This could be due in part to the fact that this strategy faces a lack of powerful driving forces rising from both the poor electrophilicity of imines and poor nucleophilicity of phosphites.

Hydrophosphonylation reaction is based on addition of an appropriate phosphorus nucleophile to imines. In most cases, esters of phosphorus acid **34**, which can also be called dialkyl phosphites, have been used as phosphorus nucleophiles. These compounds are known to undergo a phosphite-phosphonate tautomerism with the phosphite tautomer as the nucleophile (active) form and the phosphonate tautomer

as the almost exclusively favored but non-nucleophilic (resting) form. (Scheme 1.6) This tautomerism has an equilibrium constant for diethyl H-phosphonate (**34**) of 10^7 in favor of the H-phosphonate (**35**) form.[1]

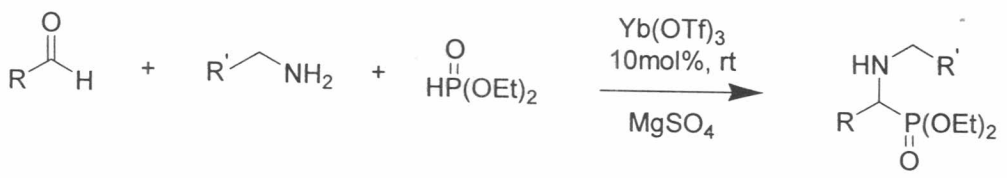


Phosphonate tautomer — **34** ⇌ Phosphite tautomer — **35**

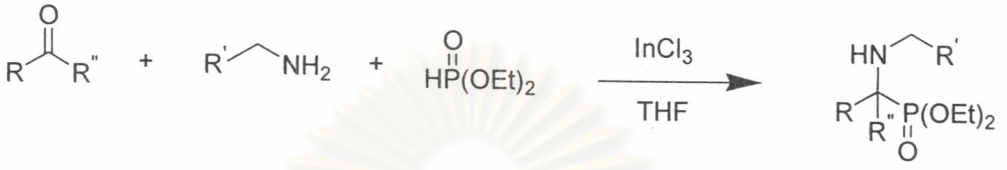
Scheme 1.6 Phosphite-phosphonate tautomer

In recent years, the development of synthetic approaches to α-amino phosphonates using a variety of catalysts has been reported. The pioneering work of Pudovik using NaOEt and a Lewis acid such as $SnCl_2$, $SnCl_4$, and $BF_3.Et_2O$ has also been found to be effective. However, the reaction using these reagents and catalysts resulted in unsatisfactory yields of α-amino phosphonates. Later work by Zon demonstrated that the reaction can be strongly promoted by $ZnCl_2$ or $MgBr_2$ in high yields.[26]

In 1998, Qian and Huang[26] proposed that a one-pot synthesis of α-amino phosphonates from aldehydes was effectively activated by rare earth metal triflates such as ytterbium triflate ($Yb(OTf)_3$) and scandium triflate ($Sc(OTf)_3$). They used them as catalysts in the reaction of diethyl phosphite with imines in order to overcome the drawbacks of classical Lewis acids sensitivity to moisture. Normally, water resulting from a one-pot reaction of aldehyde and amine during the *in situ* formation of imine can decompose or deactivate regular Lewis acids. These lanthanide triflates are, however, stable in water and can be recovered and also reused after the reaction is complete. It was found that this reaction provided excellent yields of the desired α-aminophosphonates in the case of aromatic aldehydes and moderate yields from the reaction of aliphatic aldehydes in the presence of 10 mol% of $Yb(OTf)_3$.



In addition, Ranu and coworkers[27] employed indium (III) chloride as a catalyst for the synthesis of α-amino phosphonates from both aldehydes and ketones with aliphatic as well as aromatic amines. One of the remarkable features, similarly observed in lanthanide triflate of $InCl_3$ is its effectiveness in an aqueous medium. A wide range of structurally varied carbonyl compounds were subjected to this procedure and converted to products in high yields (75-93%).



In 2000, Kobayashi and Manabe[28] proposed the use of a Lewis acid-surfactant combined catalysts (LASC) as a new type of Lewis acid. LASC consists of Lewis acidic metal cations such as scandium (III) and amphiphilic anions such as dodecyl sulfate, which form stable colloidal dispersions in the presence of organic substrates in water. They reported that scandium tris(dodecyl sulfate) (**36**), a representative LASC, creates excellent hydrophobic reaction fields to realize the rapid three component reaction of aldehydes, amine, and triethyl phosphite (PO_3Et_3) in water.

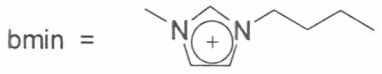
36

Figure 1.10 Structure of scandium tris(dodecyl sulfate)

Although, this catalyst was effective to catalyze three-component reactions of aldehyde, amine, and triethyl phosphite to give high yields of various α-amino phosphonates in water at high reaction rates, an excess (2.5-4 eq) of triethyl phosphite $P(OEt)_3$ is needed since it is gradually hydrolyzed to diethyl phosphite $(HP(O)(OEt)_2$ in water. It is noted that the use of diethyl phosphite instead of triethyl phosphite on organic solvent hardly proceeded.

Lee *et.al.*[29] presented that lanthanide triflate catalyzed three component reactions in room temperature ionic liquids, [bmin][X], to give α-amino phosphonates. It has been found by using anhydrous lanthanide triflates as catalysts the reaction in $[bimn][PF_6]$ proceeded efficiently. Among the anhydrous lanthanide triflate catalysts tested, $Sm(OTf)_3$ is superior to other catalysts in an ionic liquid. The

use of $P(OEt)_3$ instead of diethyl phosphate changed the catalytic activities of the lanthanide triflates. In this reaction system, $Sc(OTf)_3$ exhibited the highest catalytic activity.

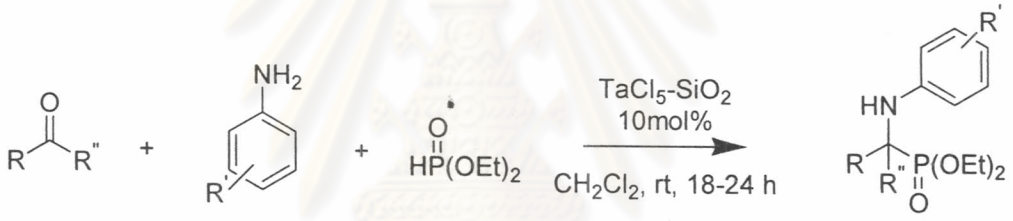


X = PF_6^-, SbF_6^-, BF_6^-, OTf^-

37

Figure 1.11 Ionic liquid, [bmin][X]

Recently, Chandrasekhar and coworkers[30] initiated the use of $TaCl_5$ and $TaCl_5$-SiO_2 for Lewis acid promoted three component coupling of carbonyl compounds, amines and diethyl phosphite for the synthesis of various amino phosphonates.



Furthermore, Kaboudin and Nazari[31] described a novel approach for the synthesis of α-aminoalkyl phosphonates through a one-pot reaction of aldehydes with amines in the presence of acidic alumina under solvent-free conditions using microwave irradiation. It was also found that this method was capable of producing high yield of α-amino phosphonates under mild conditions.

1.3.3 Asymmetric hydrophosphonylation

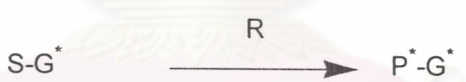
An asymmetric synthesis involves the formation of chiral molecules or it may be defined as a synthesis in which an achiral unit in an ensemble of substrate molecules is converted to a chiral unit such that the possible stereoisomer are formed in unequal amounts. In the simplest case an achiral substrate is converted to an unequal mixture of the two enantiomers of a chiral product containing only one streogenic unit. The aim 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 that of the minor enantiomer and is commomly expressed as a percentage.

$$\%\,ee \quad = \quad \frac{|\,\%R \;-\; \%S|}{|\,\%R \;+\; \%S|}$$

If there are n stereogenic units in a molecule, there can be anywhere up to 2^n stereoisomers. In comparing any two of these stereoisomers two possibilities arise: either they are mirror images of each other, in which case they are enantiomers, or they are not in which case they are called diastereomers. An asymmetric reaction leads to a pair of diastereomers when one of the reactant is chiral. Several different measures of the diastereoselectivity can be given. In general, asymmetric synthetic methods can be conveniently divided into four major classes depending on how the influence of chiral environment is exerted.[32]

(a) First-generation or substrate-controlled methods: In this category, a reaction is directed intramolecularly by a stereogenic unit already present in the chiral substrate. The formation of the new stereogenic unit most often occurs by reaction with an achiral reagent at a diastereotopic site controlled by a nearby stereogenic unit.



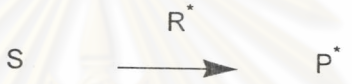
S : substrate
G : chiral directing group
R : reagent
P-G : product
* : chirality

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

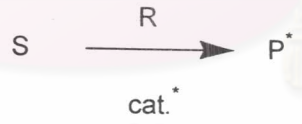
(b) Second-generation or auxiliary-controlled methods: This approach is similar to the first-generation method in that control is again achieved intramolecularly by a chiral group in the substrate. The difference is that the directing group, the chiral auxiliary, is now deliberately attached to an achiral substrate in order to direct the reaction and can be removed once it has served its purpose.

An additionally 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 addition stereogenic center of the auxiliary. Therefore, separation of these diastereomers should be trivial. However, the addition and removal of the auxiliary group make the synthesis at least 2 steps longer.

(c) Third-generation or reagent-controlled methods: An achiral substrate is directly converted to the chiral product by the use of a chiral reagent. In contrast to the first- and second-generation methods, the control is now intermolecular. This is obviously an attractive procedure but the range of reactions for which effective chiral reagents exist is somewhat limited at present.

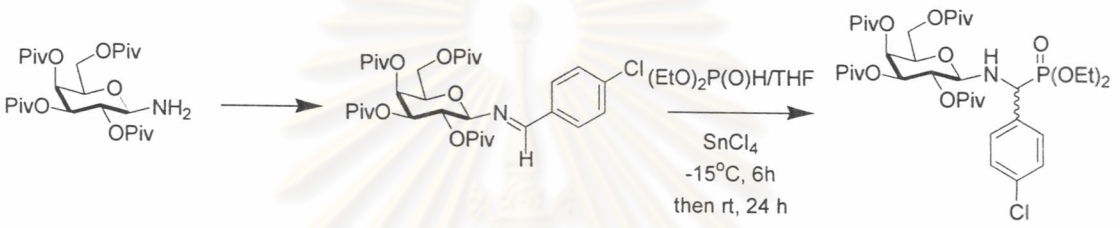


(d) Fourth-generation or catalyst-controlled methods: In each of the previously mentioned three classes, an enantiomerically pure compound is required in stoichiometric amounts. The final refinement, possible in the fourth-generation methods, is to use a chiral catalyst to direct the conversion of an achiral substrate to a chiral product with an achiral reagent. Again the control here is intermolecular.



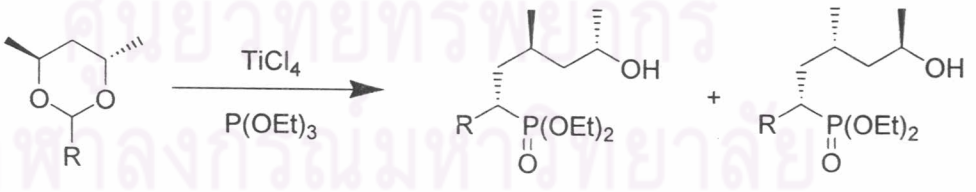
Recent trends show that α-aminophosphonic acid and their derivatives play an important role in modern medicine. In addition, pharmaceutical and biological activities of α-amino phosphonic acids strongly depend on the stereogenicity at the carbon center α to the phosphorus atom. As a consequence, an increasing number of industrial demand on the synthesis of enantiomerically pure α-aminophosphonic acid and their derivatives is in sight. The development of methods for the preparation of optically active aminophosphonate is important and has currently attracted growing interest. Several reviews have recently been published which are devoted to asymmetric syntheses of α-aminophosphonic acid and their derivatives. These have covered methods where chirality is introduced by the use of chiral auxiliaries or by catalytic asymmetric synthesis.

In 1992, Laschat and Kunz[33] reported an asymmetric synthesis of α-aminophosphonates in which *O*-pivaloylated glycosylamine (**38**) serves as the stereodifferentiating auxiliary. By this method, both series of enantiomers of α-aminophosphonic acids can be obtained in high stereoselectivity. The *N*-galactosylimine (**39**) prepared by reacting *O*-pivaloylated glycosylamines with 4-chlorobenzaldehyde reacted with diethyl phosphate in the presence of tin (IV) chloride catalyst and furnished four diastereomeric *N*-glycosyl-4-chlorophenyl phosphonoglycine esters (**40**) in high yield (83%).



38 **39** **40** (83%)

Shibuya and Yokomatsu [34] disclosed a route for an asymmetric synthesis of α-amino phosphonic acids. This involves a stereoselective opening of homochiral dioxane acetals (**41**) 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. They examined Lewis acid mediated cleavage of homochiral acetals by using triethyl phosphite as nucleophile to obtain chiral phosphono alcohols (**42** and **43**), useful intermediates for the synthesis of α-amino phosphonic acids.

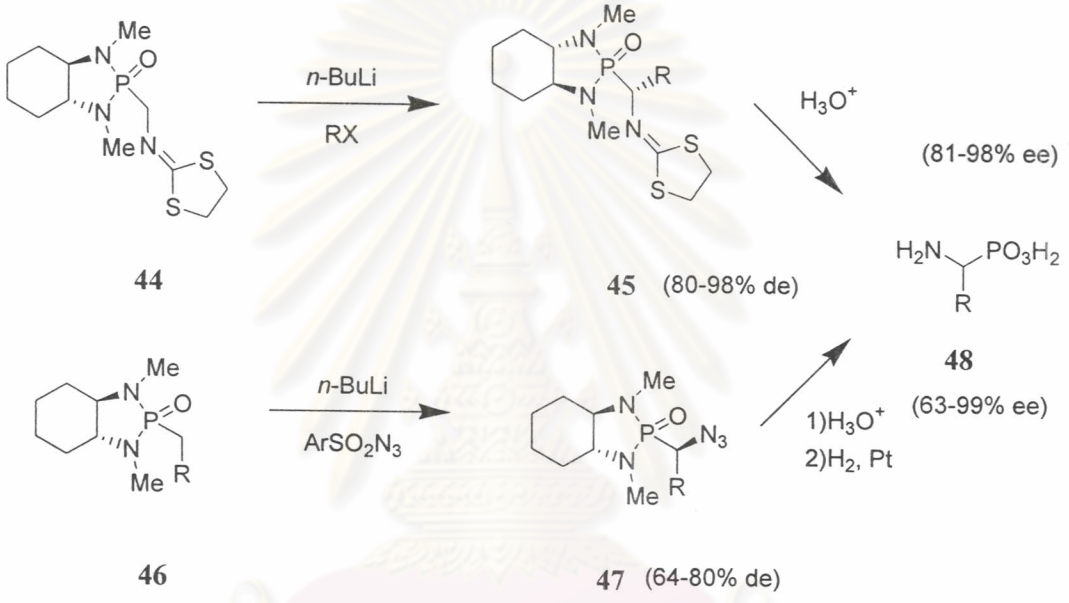


41 **42** **43**

a : R = ^{i}Pr
b : R = ^{t}Bu
c : R = CH_2Ph

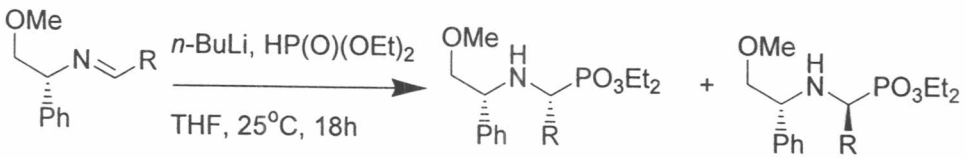
Hanessian and coworkers[35-36] developed two complementary approaches to the synthesis of enantioenriched α-amino phosphonic acids. Alkylation of scalemic bicyclic phosphonamides (**44**) of either absolute configuration with carbon electrophiles furnished α-amino phosphonodiamides in **45** 80-98% de. Acidic

hydrolysis then yields the α-aminophosphonic acids **48** with moderate to excellent enantiopurities (81-98% *ee*). Because this method relies on alkylation, however, derivatives containing branched or aromatic α substituents are inaccessible. The second strategy, based on an amination or azidation of chiral α-alkyl phosphonamides **46**, provides adducts **47** with moderate diastereoselectivities (64-80% de). Acidic hydrolysis and catalytic hydrogenolysis again furnishes the α-amino phosphonic acids **48** in 63-99% *ee*.

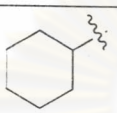
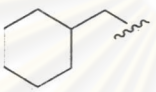


In 1994, Smith[15,37] explored the generality of the phosphite addition with a variety of imines. Authentic mixtures of **50** and **51** were prepared by treatment of each imine prepared from (*R*)-(-)-1-amino-1-phenyl-2-methoxyethane (**49**) and each aldehyde in Table 1.1. Most substrates reacted with excellent diastereoselectivity (95-98% ds).

Table 1.1 Asymmetric addition of $LiPO_3Et_2$ to imines **49** derived from chiral auxiliary



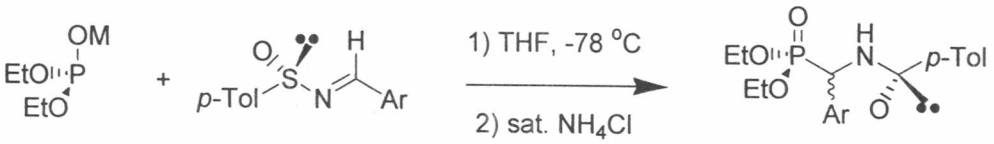
49 **50** **51**

entry	R	yield(%)	de (%)
1		68	96.0
2		70	98.3
3		82	96.5
4		78	96.0

Hydrogenolysis of the chiral directing group in **50** with catalytic palladium hydroxide on carbon in absolute ethanol (25°C, 22-24 h) afforded the amino ester in 83-100% yields.

Moreover, Lefebvre and coworkers[38] illustrated an enantioselective approach to α-amino phosphonic acids which involved the addition of metallo phosphite **52** to enantiomerically homogeneous and configurationally restricted sulfinimines **53**, used as activated imine acceptors in the conjugate addition of metallo phosphite to enantiopure sulfnimines. It was found that the product was obtained in excellent diastereoselectivity of **54** in all cases as shown in Table 1.2.

Table 1.2 Diastereoselective addition of metallo phosphite **52** to sulfinimines **53** at -78°C in THF



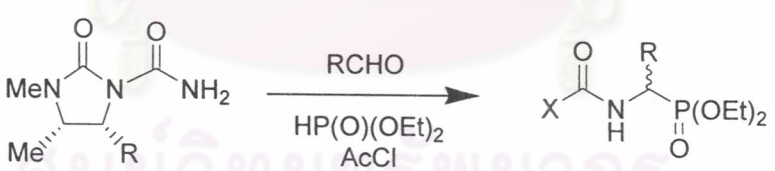
52 **53a** : Ar = Ph **54**

53b : Ar = *p*-MeOPh

entry	M	sulfinimines (**53**)	yield %	de (%)
1	Li	**53a**	85	84
2	Na	**53a**	80	93
3	Li	**53b**	50	84
4	Na	**53b**	50	90

In 1998, Balasubramaniam and Roos[39] modified the stereoselective synthesis of α-amino phosphonates by using urea derivatives **54** of the (4*R*, 5*S*)-imidazolidine-2-one chiral auxiliary in the stereoselective, one-pot formation of product. The results of these reactions are collected in the Table 1.3.

Table 1.3 Diastereoselective synthesis of α-amino phosphonates by use the analogue urea derivatives **55**



55a R = Ph **56**

55b R = *cyc*C_6H_{11}

entry	urea	R	yield **56** (%)	d.r.
1	**55a**	Ph	70	>100:1
2	**55b**	Ph	52	>100:1
3	**55a**	Me	42	66:34
4	**55a**	*p*-NO_2Ph	68	>100:1

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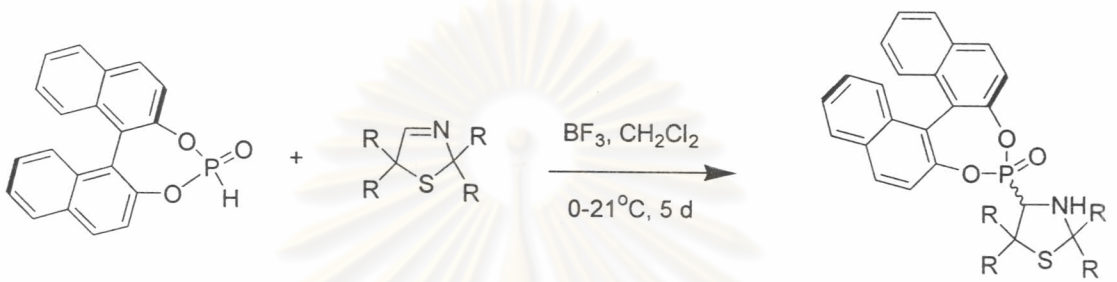
Only a few chiral phosphorus nucleophiles have been reported to be diastereoselective phosphonylating reagents. Recently, Martens *et al.*[40-41] presented for the first time a highly diastereoselective hydrophosphonylation of heterocyclic imine of type **57** using BINOL-phosphite in BF_3-activated media leading to the pharmaceutically interesting 4-thiazolidinylphosphonates **58**. The chiral BINOL-phosphonate **57** was found to be a highly stereoselective phosphonylating agent towards 3-thiazolines.



57 **58** **59**

Only, a few examples of synthesis by enantiomeric catalysis have been published. In 1995, Shibasaki *et al.*[42-43] developed the first practical method to synthesize α-amino phosphonates by using chiral heterobimetallic rare earth catalysts. It was found that the lanthanum-potassium-BINOL complex (LPB) was the most efficient in this type of reaction. In the presence of 5-20 mol% of chiral catalyst **62**, the reaction of imine **60** with dimethyl phosphite proceeded to afford the corresponding α-amino phosphonate **61** in high yields with high enantioselectivities as illustrated on Table 1.4.

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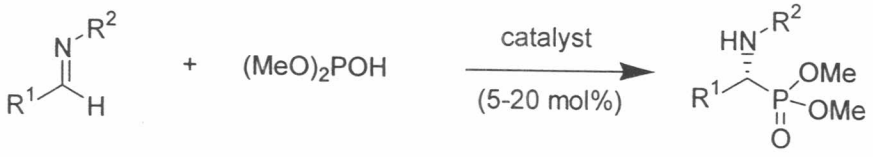
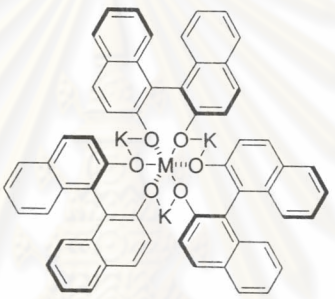
Table 1.4 Shibasaki's catalytic enantioselective hydrophosphonylation of imines **60**



60 **61**

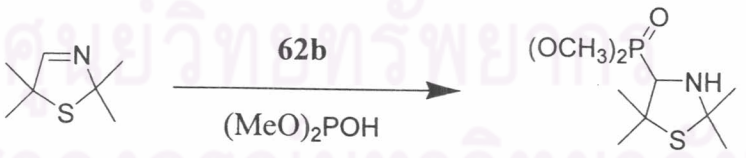
entry	aldimine	catalyst **62a** (mol%)	yield %	ee (%)
1	$R^1 = {}^iPr$, $R^2 = CHPh_2$	5	82	92
2	$R^1 = Et$, $R^2 = CHPh_2$	20	80	91
3	$R^1 = Me$, $R^2 = CHPh_2$	20	73	75

Catalyst =



62a : M=La
62b : M=Yb

Furthermore, They applied this group of catalyst to the synthesis of cyclic imines **63**[41,43-44] The best result (97% yield, 98% *ee*) obtained is when the reaction was carried out in THF-toluene (1:7) using 5 mol% of the chiral ytterbium catalyst **62b** at 50°C.



63 **64**

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1.4 Objectives of this research

The objective of this research was to develop a synthetic method of α-aminophosphonates involving nucleophilic addition of phosphorus nucleophiles to imines. The phosphorus nucleophile used in this study is a diethyl phosphite reagent and the substrates chosen are unactivated *N*-alkyl aldimines.

Interestingly, a novel efficient chiral catalyst was disclosed for asymmetric cyanation of imines (Strecker reaction) such as chiral Schiff bases, amino alcohols, and peptide-Schiff base in our research group. Since only a few reports on asymmetric hydrophosphonylation of imines has been presented, this has prompted us to study the efficiency of such systems in asymmetric hydrophosphonylation. We expected that the use of this catalyst to activate hydrophosphonylation would give high yields and stereoselectivity.

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