CHAPTER I
INTRODUCTION

1.1 α-Amino acids

Alpha-amino-carboxylic acids are one of the five major classes of natural products and they exhibit important and diverse biological functions. They have been of great interest in all areas of physical and life sciences for over 150 years. It is well known that they are the vital basic molecules for life. Historically, α-amino acids have been subdivided into 20 proteinogenic (RNA coded) and the non-proteinogenic representatives. These are "building blocks" of peptides, proteins, peptidoglycans in bacterial cell-walls, and many other natural products. Amino acids are also involved in neuronal signal transduction (glycine, glutamate) and are further metabolized, e.g. to polyamines. The unusual structures are mainly produced by various microorganisms and have evolved to interfere with biochemical pathways of other organisms. In close analogy a large number of man-designed unusual amino acids find pharmaceutical applications or are used to control plant growth and plant diseases. Natural occurring α-amino acids, which are constituent of proteins, are called proteinogenic amino acids. Except for glycine, all proteinogenic amino acids are chiral, belonging to the same, L-stereochemical or (2S) designation according to Cahn-Ingold-Prelog sequence rules work which makes L-[but (2R)-]-cysteine an apparent anomaly. This minor confusion has reinforced innate conservatism, and so far ensured the survival of the L-D terminology in the field. Nineteen L-α-amino acids have general structure **1** except L-proline, **2**. All of them are different at side-chain as shown in Table 1.1.[1]

1   **2**

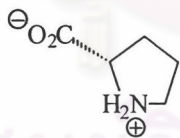**Figure 1.1** General structure of α-amino acids (**1**) and α-imino acid (**2**).

Table 1.1 The proteinogenic amino acids (**1**).

Amino acid	-R	One-letter symbol	Three-letter symbol
Alanine	$-CH_3$	A	Ala
Arginine		R	Arg
Asparagine	$-CH_2CONH_2$	N	Asn
Aspartic acid	$-CH_2CO_2H$	D	Asp
Cysteine	$-CH_2SH$	C	Cys
Glutamine	$-(CH_2)_2CONH_2$	Q	Gln
Glutamic acid	$-(CH_2)_2CO_2H$	E	Glu
Glycine	$-H$	G	Gly
Histidine		H	His
Isoleucine*	$-CH(CH_3)CH_2CH_3$	I	Ile
Leucine	$-CH_2CH(CH_3)_2$	L	Leu
Lysine	$-(CH_2)_4NH_2$	K	Lys
Methionine	$-(CH_2)_2SCH_3$	M	Met
Phenylalanine	$-CH_2Ph$	F	Phe
Proline		P	Pro
Serine	$-CH_2OH$	S	Ser
Threonine**	$-CH(CH_3)OH$	T	Thr
Tryptophan		W	Trp
Tyrosine		Y	Tyr
Valine	$-CH(CH_3)_2$	V	Val

*(2*S*, 3*S*), **(2*S*, 3*R*)

The number of known naturally occurring amino acids with unusual, *i.e.* non-proteinogenic, structures is continuously increasing, and has reached 700 when the counting was discontinued in 1985. In general, many of these non-proteinogenic amino acids are constructed by post-translational transformation of proteinogenic amino acids. For example, *trans*-4-hydroxyproline (hyp, **3**)[1] is formed by hydroxylation of proline with the enzyme prolyl-4-hydroxylase. Likewise, sarcosine (*N*-methylglycine, **4**)[1], and arylglycines (**5**)[2] are included in the class.

3   **4**   **5**
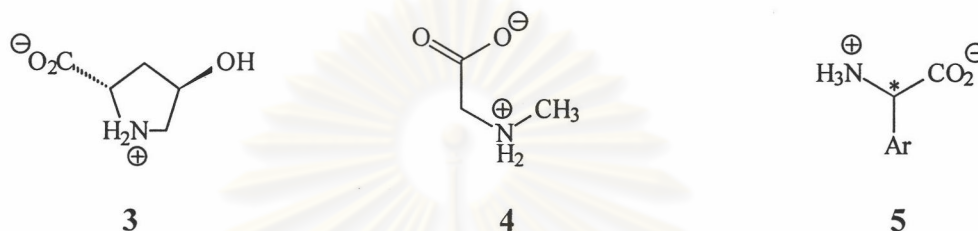
Figure 1.2 Examples of non-proteinogenic amino acids.

Beyond their fundamental role in all living organisms as constituents of proteins and other compounds, amino acids are used extensively as food additives,[3] agrochemicals,[4] and pharmaceuticals.[5] One of the well known food additives is the dipeptide ester aspartame (**6**), a low-calory sweetener (approximately 160 times sweeter than sucrose), consisting of two amino acids: L-aspartic acid, which has no taste and L-phenylalanine, which is bitter. A well known cooking ingredient, mono-sodium glutamate (MSG) is prepared from L-glutamic acid which is produced in large scale by fermentation.
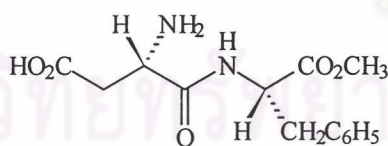

6

In the area of agrochemicals, *N*-alkylglycinate esters (**7**) have been converted to *o*-nitrohippuric esters (**8**) by *o*-nitrobenzoyl chloride (**9**). *o*-Aminohippuric esters which were readily cyclized under acidic conditions to afford 1,4-benzodiazepine-2,5-dione analogs (**10**) possess some herbicidal activity (Scheme 1.1).[4]
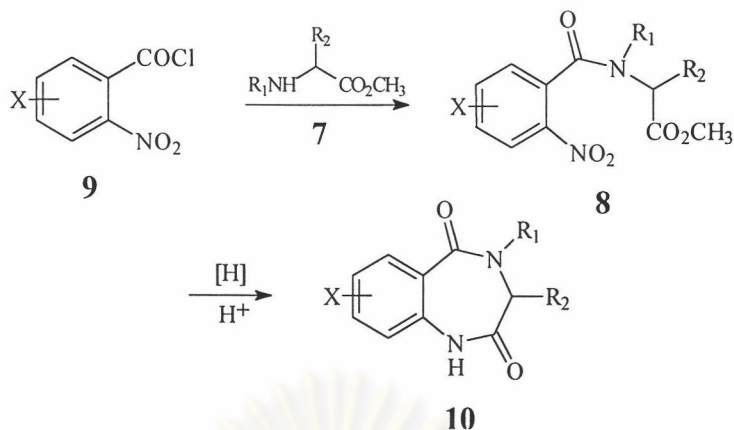
Scheme 1.1 Preparation of 1,4-benzodiazepine-2,5-dione ring system from substituted *o*-nitrohippuric esters.

In the pharmaceutical field,[2] arylglycines, isolated from natural sources, are an interesting and important non-proteinogenic class of amino acids. One of the best-studied and most interesting sources are the glycopeptide antibiotics. In 1956, the first glycopeptide antibiotic, vancomycin (**11**) was discovered. Vancomycin's structure consists of a heptapeptide in which three of the amino acid residues are arylgylcines. It is active against Gram-positive bacteria and used clinically in the treatment of severe staphylococcal infections such as endocarditis and wound septicaemia.[6] In addition, it is also used to treat pseudomembranous colitis, a potentially lethal infection usually associated with antibiotic treatment after major gastrointestinal surgery. Teicoplanin, another glycopeptide antibiotic, was approved for use in Italy and France and is under clinical trials in other European countries and the United States. Many other glycopeptide antibiotics belonging to the vancomycin group include ristocetin,[7] teicoplanin,[8] avoparcin,[9] ristomycin, and actaplanin.[10]

Furthermore, another natural source of arylglycines is the family of monocyclic β-lactam antibiotic known as the nocardicins (**12**)[11] which contain two *p*-hydroxyphenylglycine derivatives in their unusual structure (Figure 1.3).

VANCOMYCIN 11

NOCARDICINS A - G 12

R =
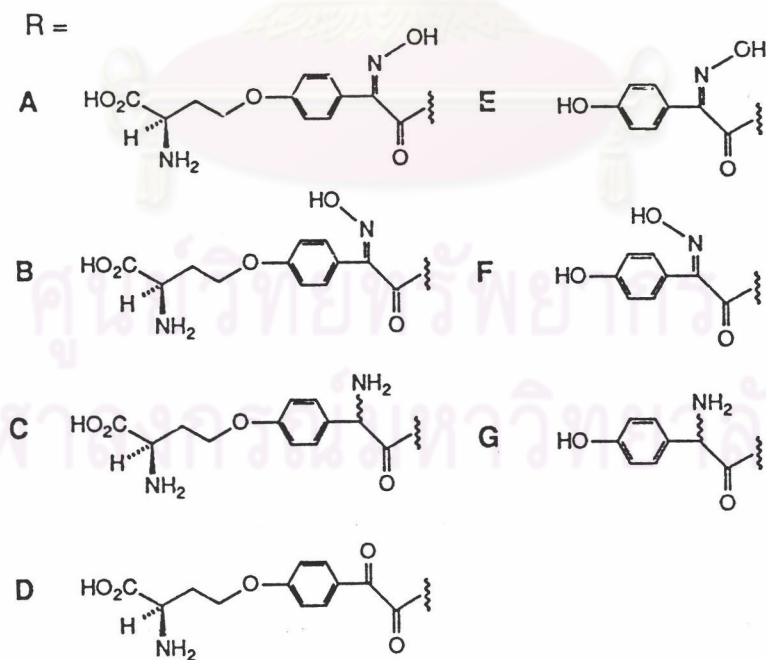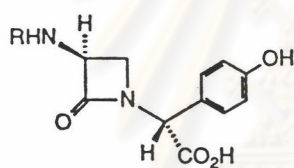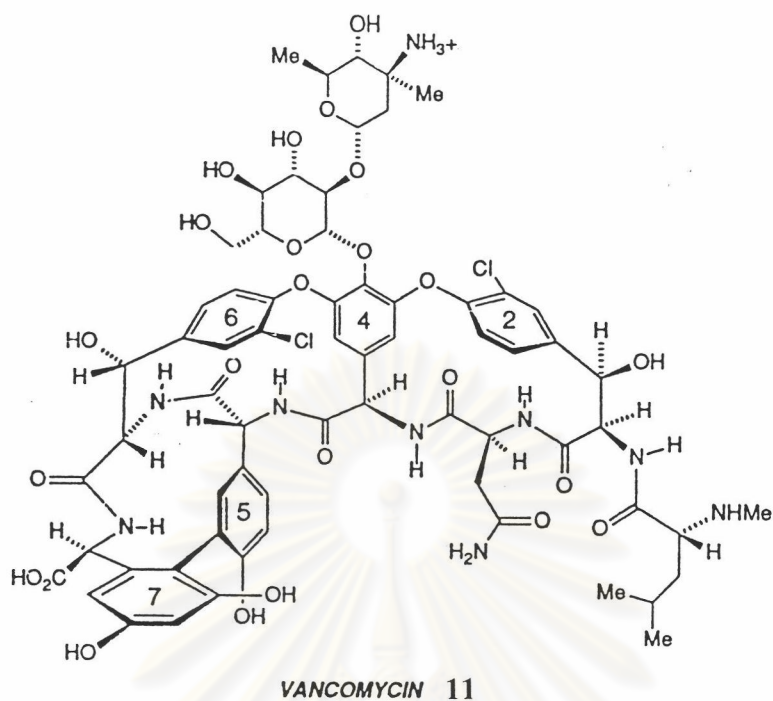
Figure 1.3 Examples of monocyclic β-lactam antibiotic arylglycines.

In addition to already numerous naturally occurring arylglycines, there are also a number of unique synthetic arylglycines. Synthetic D-arylglycines are used as a side chain moiety of semisynthetic penicillins and cephalosporins. The synthetic antibiotic cephalexin (**13**) contains phenylglycine as a side-chain constituent,[12] and *p*-hydroxyphenylglycine is used as a side chain moiety in the antibiotics cefadroxil (**14**) and amoxicillin (**15**)[13] (Figure 1.4).
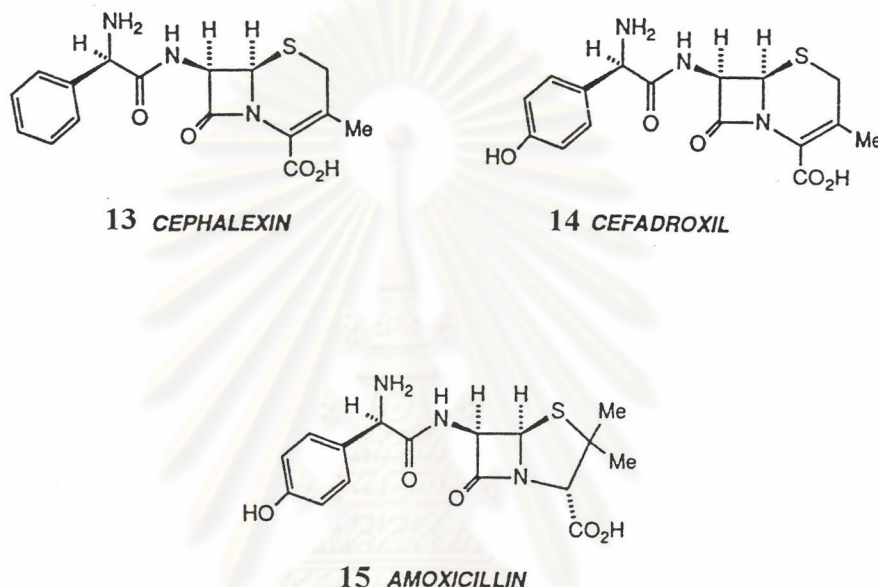
Figure 1.4 The synthetic antibiotic of arylglycines.

In addition, many α,α-disubstituted α-amino acids also possess important biological activities.[14,15] For example, some α-alkylated phenylglycine derivatives have recently been found to be selective antagonists of metabotropic glutamate receptor (mGluR).[15] Among these compounds, (*S*)-α-methyl-4-carboxyphenylglycine ((*S*)-αM4CPG)[15] and (*S*)-α-methyl-4-phosphonophenylgylcine ((*S*)-MPPG)[16] showed poor selectivity for different mGluR isoforms (Figure 1.5).
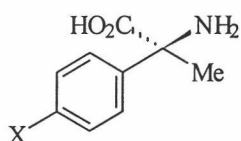

X = CO$_2$H, (*S*)-α M4CPG

X = P(O)(OH)$_2$, (*S*)-MPPG

Figure 1.5 Structures of (*S*)-α M4CPG and (*S*)-MPPG.

1.2 α-Amino acid synthesis

In general, the proteinogenic α-amino acids are produced industrially by fermentation methods and by chemical synthesis, reckoned to be in the order of hundreds of thousands of tons per annum. Their principle application is as food additives, but they are incidentally cheap starting materials for synthesizing more complex molecules. The laboratory synthesis of α-amino acids is nevertheless an active field of research because of the demand for specifically labeled unnatural and unusual amino acids. The need is almost always for homochiral products, so assembly of the target with no regard to α-chirality must be followed by resolution. Alternatively, an asymmetric synthesis must be employed or an enantiospecific conversion of a freely available homochiral compound to the required α-amino acid must be achieved. Furthermore, α,α-disubstituted α-amino acids are now popular as a replacement for proteinogenic amino acids in peptides.[2,17] Because of the tetrasubstituted asymmetric carbon atom, incorporation of these compounds into peptides results in increased proteolytic stability and conformational restrictions. They can therefore be used as enzyme inhibitors for the investigation of enzymatic mechanisms and for other purposes such as therapeutic agents.[17,18]

### 1.2.1 General synthetic methods[1]
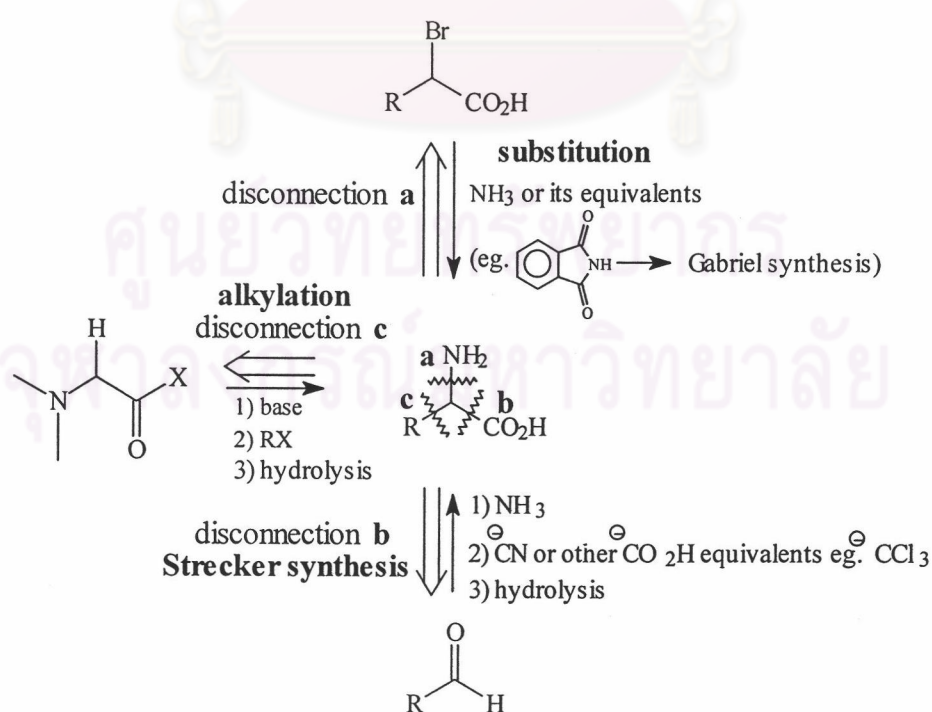
Figure 1.6 General methods for amino acids synthesis.

There are so many methods successfully employed in the synthesis of amino acids that all details can not be covered here. With the limited space available, only more general methods for the synthesis of α-amino acids, including displacement reactions on α-halo acids (e.g. Scheme 1.2), the Strecker synthesis (e.g. Scheme 1.3) *via* hydantoins (e.g. Scheme 1.4), and oxazolones (e.g. Scheme 1.5) will be discussed. Most of these methods were developed since the early days of amino acid chemistry, but still retain their importance nowadays.

-Displacement of halogen in α-halo acids

The very convenient methods for the synthesis of α-amino acids with no chiral center such as glycine are displacement reactions on α-halo acids. α-Halo acids can be synthesized from reaction of carboxylic acid, and bromine in the presence of phosphorous trihalides. Although ammonia works well enough in conversions of very simple α-halo acids to α-amino acids, potassium phthalimide (followed by hydrolysis of the intermediate phthalimido derivative with a strong acid: the Gabriel synthesis) or sodium azide (followed by reduction) are superior reagents. The reaction is stereospecific but extension to synthesize optically active amino acids is difficult since preparation of optically pure α-halo acids is not always straightforward.
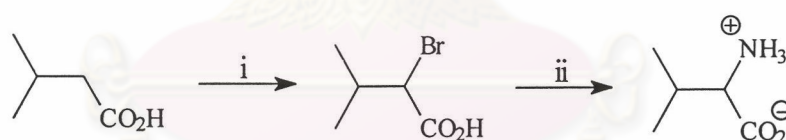
Scheme 1.2 Conditions: (i) Br_2/PCl_3; (ii) excess aq. NH_3

-The Strecker synthesis

The Strecker synthesis is a well-known classical procedure for the preparation of α-aminonitriles from aldehydes or ketones by their treatment with alkali cyanides and salt of amines.[19] Since the nitrile function of α-aminonitriles can be easily converted to the acid, this constitutes a convenient and atom-economy method for the preparation of α-amino acids.[20] The amino acids obtained from conventional Strecker synthesis are racemic mixtures.
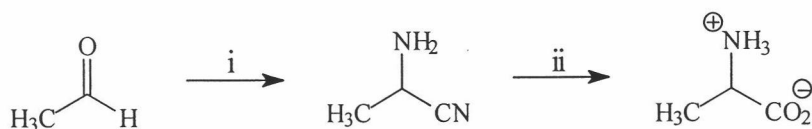
**Scheme 1.3** Conditions: (i) aq. $NaCN/NH_4Cl$; (ii) H_3O^+

A related procedure is preparation of amino acids *via* hydantoin. (The Bucherer-Berg reaction)
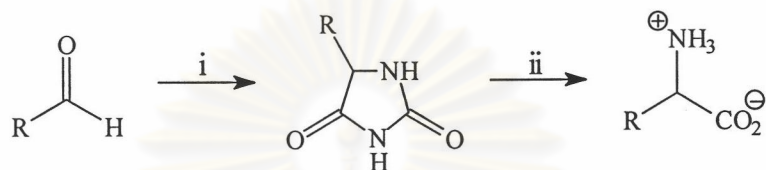
Scheme 1.4 Conditions: (i) $KCN/(NH_4)_2CO_3$ (there are several alternatives for this ring-formation); (ii) H_3O^+ or OH^-

-Alkylation of glycine anion or equivalents

Synthesis of amino acids from glycine equivalents by α-carbon deprotonation to form stabilized carbanion followed by alkylation with a suitable alkylating agent such as aldehyde provides unsaturated substituted azalactone. This can be converted to the amino acids by reduction and hydrolysis.
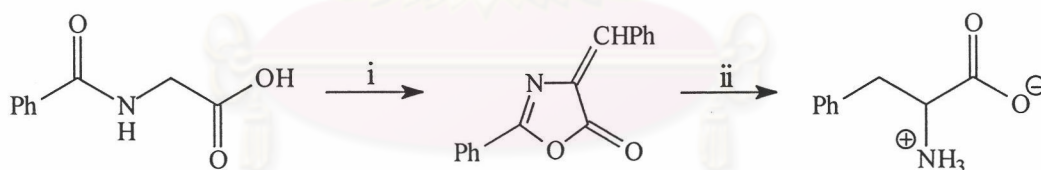
**Scheme 1.5** Conditions: (i) $PhCHO/Ac_2O/NaOAc$; (ii) aq. HI/P/heat

-via α-Acylaminomalonate ester

The concept of this method is α-carbon deprotonation of acylaminomalonate ester which is a glycine equivalent stabilized by another carboxylic group. This can be alkylated in the same way as malonate esters. Decarboxylation of the α-substituted aminomalonate provided amino acids.
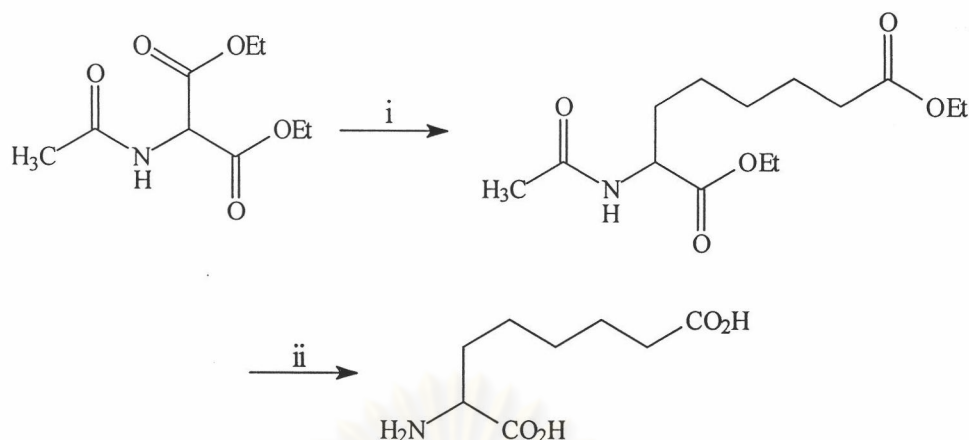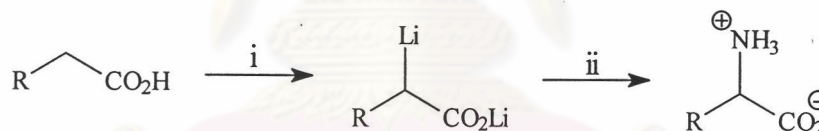
Scheme 1.6 Conditions: (i) NaOEt, then $Br(CH_2)_5CO_2Et$; (ii) H_3O^+, Δ

-Other related strategies in α-carbon alkylation are illustrated in
   Schemes1.7 and 1.8
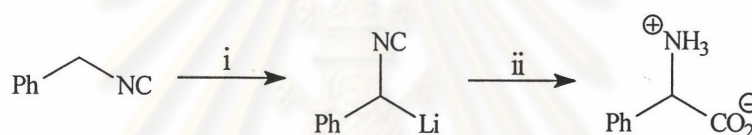
Scheme 1.7 Conditions: (i) Bu^nLi; (ii) CO_2 at $-80\ °C$, then H_3O^+

Scheme 1.8 Conditions: (i) Pr^i_2NLi; (ii) NH_2OMe

1.2.2 Resolution[1]

The reactions illustrated in Section 1.2.1 all inevitably lead to racemic products containing an equal amount of both enantiomers. Resolutions are necessary to produce the desired optically pure amino acid. The most common approach to affect the resolution of racemates of amino acids is to derivatize with an optically active reagent. Since the diastereomers formed would be differ in solubility and ease of crystallization, it is possible to separate them in a conventional manner and then reverse the derivatization. For amino acids which contain both acidic and basic functionalities, derivatization can simply be done by salt formation with a suitable optically active basic or acidic reagents. The use of enzyme for kinetic resolution of a suitable derivative is an alternative approach which is especially appropriate for α-amino acids. The principle of this method is to derivatize racemic amino acids to form

derivatives such as *N*-acylamino acids or amino acid esters, and then react with a suitable enzyme (e.g. acylase), the process of which is usually highly enantioselective. The enantiomer which is recognized by the enzyme forms free amino acid, while the other enantiomer remains in the form of derivative. At this stage, separation of the two compounds becomes trivial.

1.2.3 Enantioselective synthesis

Chirality is characteristic of nature. Naturally occurring compounds are generally optically active because living organisms tend to produce only a single enantiomer of a given molecule. Amino acids are no exception. Naturally occurring proteinogenic amino acids exist in only one enantiomer (L-isomer). Since living organisms are chiral, enantiomers often display different biological effects. As a result, synthesis of enantiomerically pure amino acids (asymmetric synthesis) is one of the most intensively studied chapter in organic synthesis.

For a reaction which creates a new chiral center, in order to lead to more of one form than the other, *i.e.* for the asymmetric reaction to take place, at least one of the reagents must be optically active. Under a suitable condition, very high selectivity can often be obtained. In the present days, there are many asymmetric methods for synthesis of both natural and non-natural amino acids. Many ingenious techniques have been devised for the efficient asymmetric synthesis of α-amino acids. Schemes 1.9 and 1.10 illustrate two classic examples.[1]
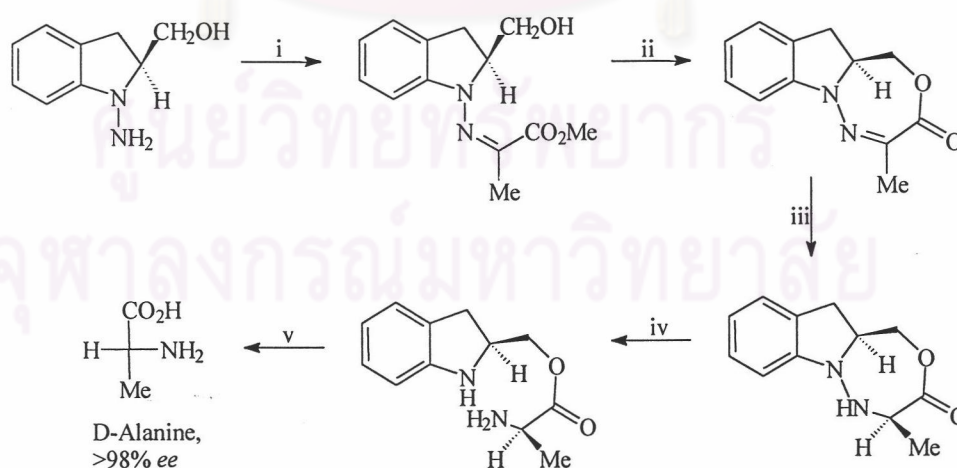

Scheme 1.9 Conditions: (i) MeCOCO$_2$Me; (ii) NaOMe/heat; (iii) Al(Hg)/ H$_2$O; (iv) H$_2$/Pd(C), followed by recrystallization to remove traces of the minor diastereoisomer; (v) H$_3$O$^+$
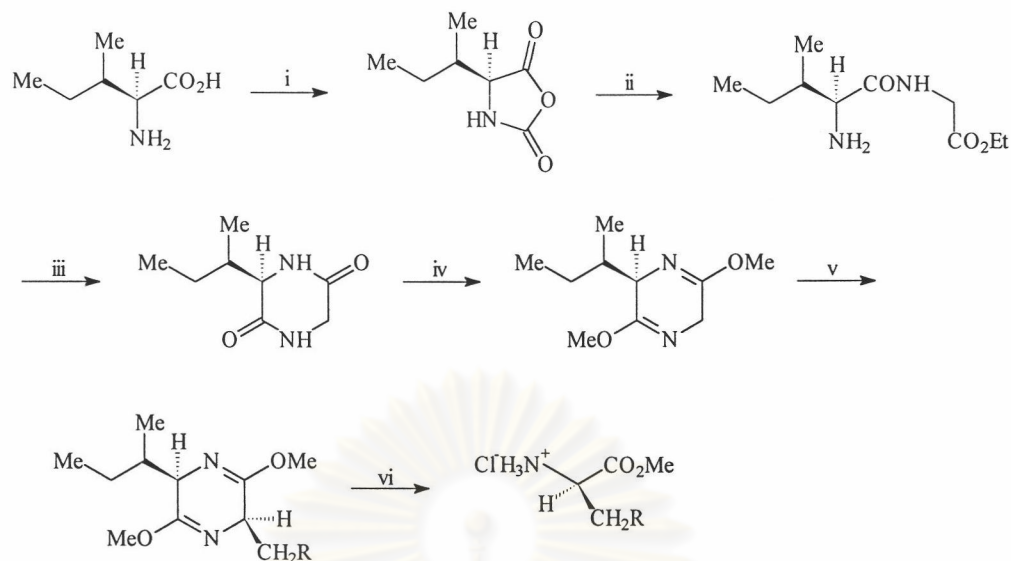
Scheme 1.10 Conditions: (i) COCl₂; (ii) NH₂CH₂CO₂Et; (iii) heat;
(iv) Me₃O⁺BF₄⁻; (v) n-BuLi, then RCH₂X; (vi) 0.25 N HCl
Products with 70-95% *ee* were obtained, depending on R

In addition, there are new procedures for synthesizing optically active *α*-amino acids from glycine derivatives, by asymmetric insertion of the side-chain. Two notable examples will be shown here. Corey reported enantioselective alkylation of the enolate derived from the *t*-butyl glycinate benzophenone Schiff base by using solid cesium hydroxide monohydrate as a base and *O*-(9)-allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide as chiral catalyst under phase transfer conditions at −60 °C to −78 °C to obtain the product in very high *ee* (up to 99.5%) (Scheme1.11).[21]
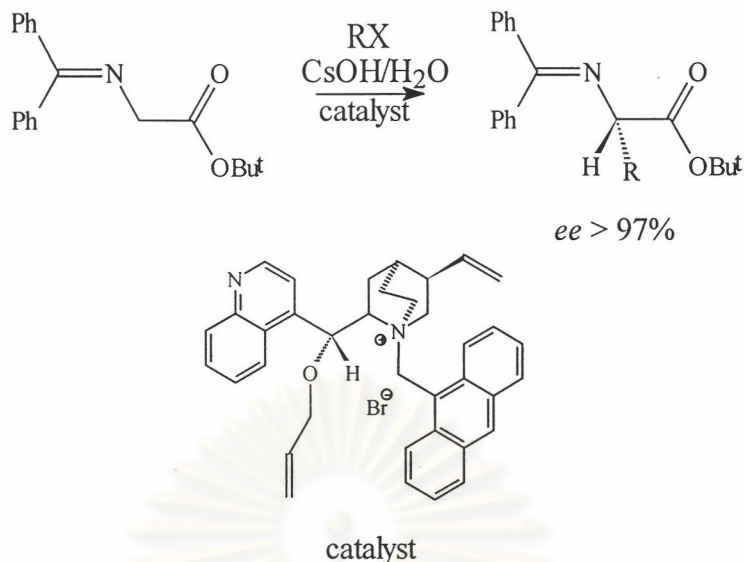
Scheme 1.11 The synthesis of optically active α-amino acids using cinchonidinium bromide as chiral catalysts.

1.2.4 Enantiospecific synthesis

In principle, the selective chemical modification of the side chains of cheap proteinogenic amino acids offers attractive access to rarer or unnatural L-α-amino acids, provided the original chirality can be preserved. L-Vinylglycine, for example, can be obtained from L-methionine or L-glutamic acid (Scheme 1.12).[1]
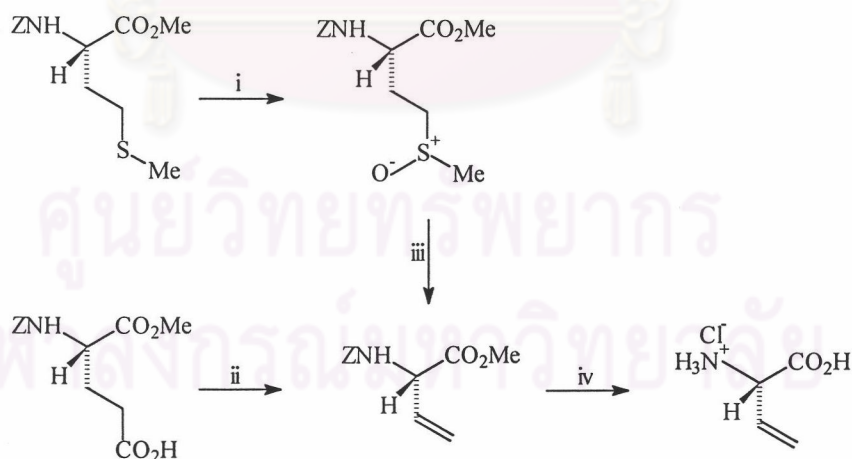
Scheme 1.12 Conditions: (i) $NaIO_4$/MeOH/H_2O/0 °C; (ii) $Pb(OAc)_4$/
$Cu(OAc)_2$/PhH/ reflux; (iii) pyrolysis 148 °C/3 mm;
(iv) 6 N HCl/reflux

Myers *et al.* also reported stereoselective eletrophilic alkylation of pseudoephedrine glycinamide or sarcosinamide at 0 °C or −78 °C to prepare *N*-protected and *N*-methyl α-amino acids with high *ee* (Scheme 1.13).[21]
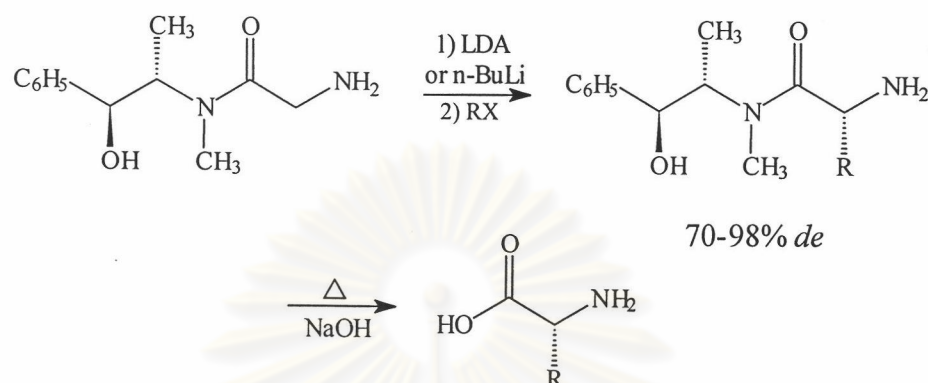
Scheme 1.13 Synthesis of optically active α-amino acids using eletrophilic alkylation of pseudoephedrine glycinamide or sarcosinamide.

From the information described above, various amino acid synthetic methods have been developed continuously. These researchs are models for finding alternative synthetic approaches to obtain useful amino acids for various applications.

1.3 Literature review of the asymmetric Strecker synthesis

1.3.1 Non-catalytic asymmetric reactions

The over-increasing interest in optically active nonproteinogenic α-amino acids in a variety of scientific disciplines has prompted the development of numerous methods for the asymmetric synthesis of α-amino acids.[22] The condensation of aldehydes with ammonia and cyanide ion (or its equivalents, e.g. trimethylsilyl cyanide, TMSCN or diethyl phosphorocyanidate, DEPC[23]) to form α-aminonitriles followed by hydrolysis of the nitrile groups (the Strecker synthesis) is one of the most simple, oldest, and most economical methods for the *de novo* synthesis of α-amino acids.[19] Among the methods developed, several enantioselective versions of the Strecker synthesis in which optically active amines replace ammonia to serve as chiral auxiliaries, with moderate to good levels of asymmetric induction, have been reported.[24,25] The first asymmetric Strecker synthesis was reported in 1963 by

Harada.[24a] By addition of a nitrile source provides an optically active α-aminonitrile which is then hydrolyzed to the amino acid. For example the optically active α-methylbenzylamine (16), acetaldehyde, and hydrogen cyanide reacted to form N-α-methylbenzylaminoacetonitrile which was hydrolyzed and hydrogenolyzed to give optically active alanine (optical purity 89-98%) (Scheme 1.14).
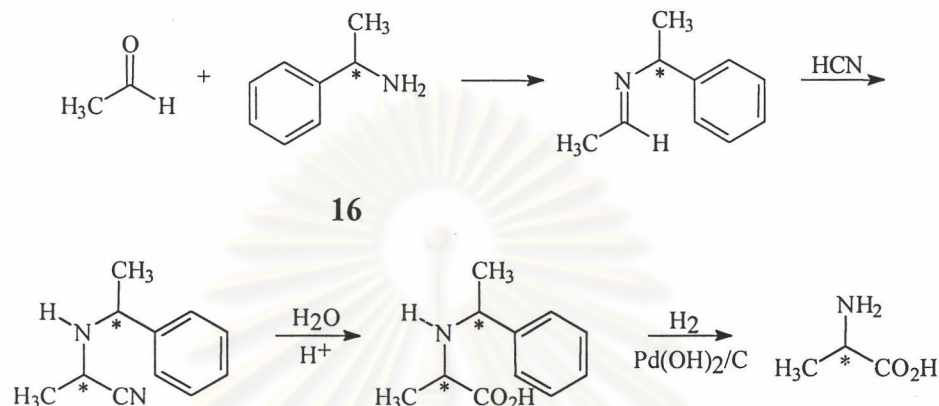

Scheme 1.14 The first report on asymmetric Strecker synthesis.

In 1970, Patel and Worsely[24c] reported an asymmetric synthesis of several α-amino acids (mostly unnatural) such as L(+) and D(−) enantiomers of norvaline and norleucine by addition of hydrogen cyanide to the carbon-nitrogen double bond of Schiff bases prepared from optically active L(−) and D(+)-α-methylbenzylamine and various aldehydes. The reported optical purities of amino acids were very high (98-99%) and the overall yield was moderate (40-60%). Subsequently, many other optically active amines have been used as chiral auxiliaries in asymmetric Strecker synthesis such as (17), (18), R-(−)-2-phenylglycinol (19), 2,3,4,6,-tetra-o-pivaloyl-β-D-galactopyranosylamine (20), and 2,3,4,6,-tetra-o-acetyl-β-D-galactopyranosylamine (21) (Figure 1.7).[24,25]
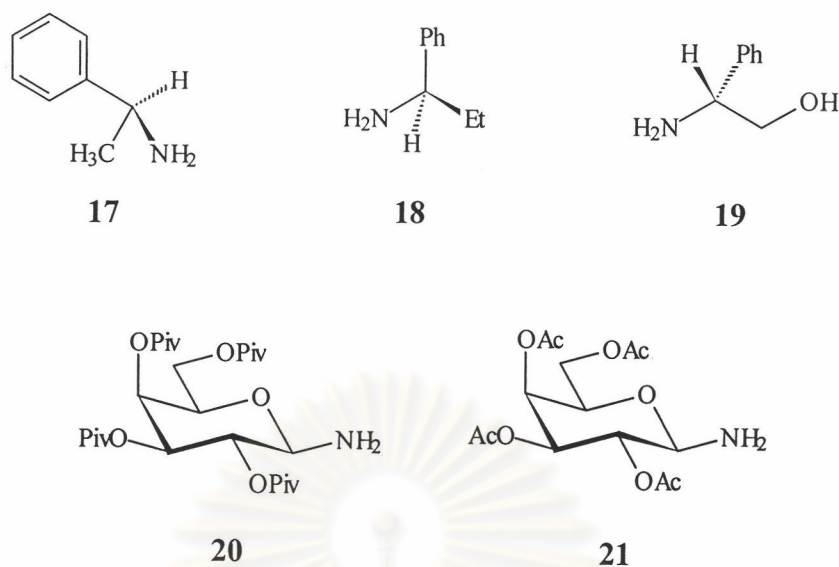
Figure 1.7 Optically active amines successfully used for synthesizing α-amino acids.

Ohfune also modified asymmetric Strecker reaction using addition of cyanide ion to the imine double bond of an optically active oxazinone prepared from L-valyl ester of α-hydroxy ketone. After oxidation and hydrolysis, optically active α-substituted serines were obtained (Scheme 1.15).[22b]
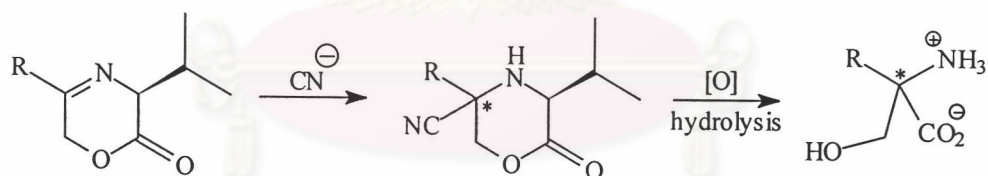

Scheme 1.15 Asymmetric Strecker reaction *via* a cyanide addition to an imine.

Although, the above-mentioned methodology has been quite successful in the synthesis of many amino acids but one reason that limits the use of such asymmetric Strecker synthesis is the difficulty in removing the chiral auxiliary. Moreover, the optically active chiral auxiliaries have to be employed stoichiometrically resulting in high cost. Consequently, this is unacceptable from economic points of view. To avoid the problems inherent to the use of chiral auxiliaries one must instead use a chiral catalyst.

### 1.3.2 Catalytic asymmetric Strecker reactions

Catalytic asymmetric strecker reactions has a relatively recent history. Only as recent as 1996 has the first catalytic asymmetric synthesis of α-aminonitriles by means of external chiral ligand-controlled additions of hydrogen cyanide to imines been reported. Lipton *et al.*[26] reported the use of cyclic dipeptide derived from (*S*)-phenylalanine (**22**) and the lower homologue of (*S*)-arginine, (*S*)-α-amino-γ-guanidinobutyric acid as chiral catalysts. The design of **22** was based on *cyclo*[(*S*)-His-(*S*)-Phe] (**23**), a cyclic dipeptide which has previously been shown to catalyze the enantioselective formation of cyanohydrins from aldehydes.[27] They examined the asymmetric synthesis of α-aminonitrile in the presence of 2 mol% of the catalyst **22** from which *N*-benzhydryl imines (**24**) derived from aromatic and aliphatic aldehydes and hydrogen cyanide reacted to afford (*S*)-α-aminonitrile (**25**). They found that imines derived from aromatic aldehydes, except for those bearing electron-deficient groups, were suitable for their reaction system. Specifically, in the presence of 2 mol% of chiral ligand **22**, imines **24a** and **24b** reacted with hydrogen cyanide in MeOH to afford the corresponding aminonitriles **25a** and **25b** in 97 and 90% yields with >99 and 96% *ee*, respectively. However, the reaction of imines derived from furfural (**24c**) and aliphatic aldehydes (**24d**) were nonselective (Table 1.2).
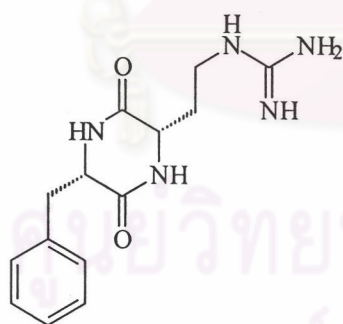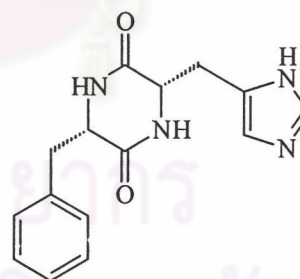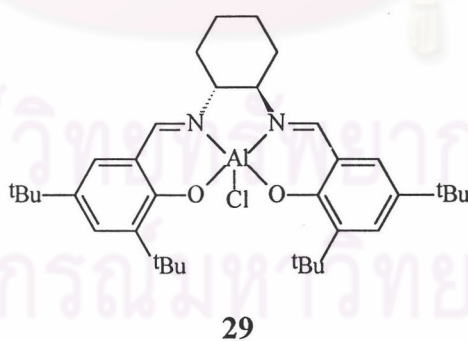

22   **23**

Table 1.2 Lipton's catalytic enantioselective Strecker-type reactions.
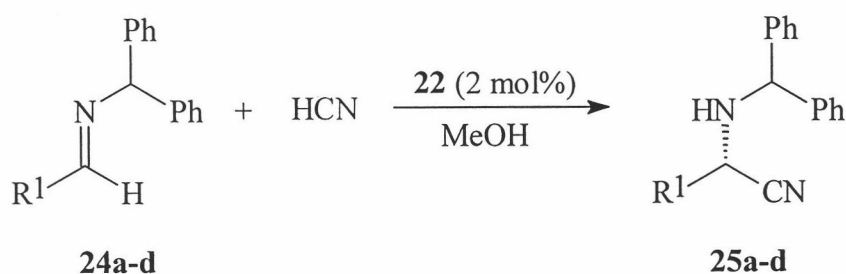
entry	imine	yield/%	ee/%
1	**24a**, R^1 = Ph	97	>99
2	**24b**, R^1 = p-MeOC$_6$H$_4$	90	96
3	**24c**, R^1 = 2-Furyl	94	32
4	**24d**, R^1 = i-Pr	81	<10

Jacobsen *et al.* reported another approach for catalytic enantioselective cyanation of imines.[28] Firstly, they screened a series of metal complexes of the readily available salen complex **26** for catalysis of the addition of TMSCN to *N*-allylbenzaldimine (**27a**). Complexes of Ti, Cr, Mn, Co, Ru, and Al were all found to catalyze the reaction at room temperature with varying degrees of conversion and enantioselectivity. The best result obtained was with Al complex **29** (Table 1.3). As a result, they evaluated the reaction of a series of imine **27** with hydrogen cyanide in the presence of 5 mol% of chiral salen aluminum complex catalyst **29**. While imines derived from aliphatic aldehydes did not give satisfactory selectivities, the selectivities were slightly improved when imine **30** was used instead of **27e** (Table 1.4).

Table 1.3 Strecker synthesis using salen complex **26** with various metals.
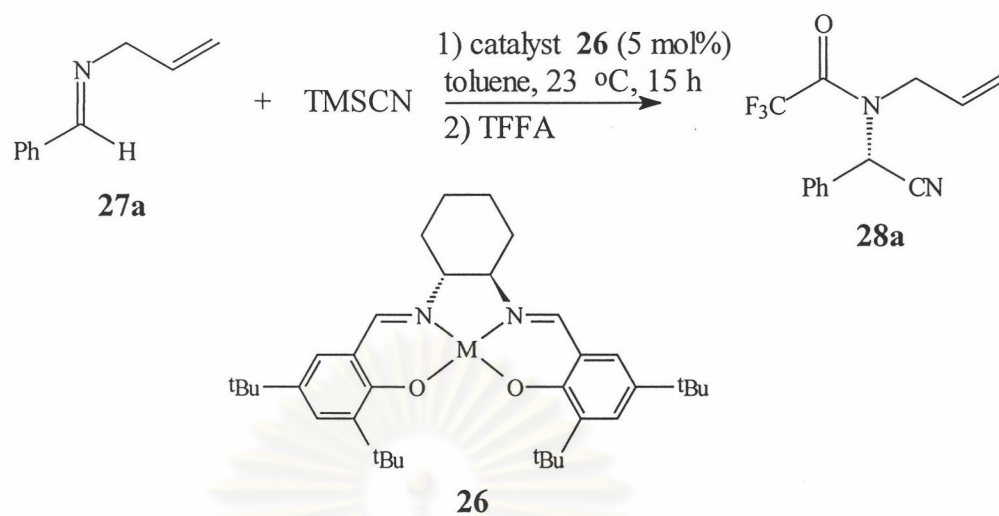
entry	M	conv/(%)	*ee*/(%)
1	H, H		
2	Ti(IV)Cl$_2$	19	24
3	Cr(III)Cl	83	0
4	Mn(III)Cl	80	20
5	Ru(III)(NO)Cl	93	6
6	Co(II)	43	0
7	Co(III)OAc	65	6
8	Al(III)Cl	100	45

29

Table 1.4 Jacobsen's catalytic enantioselective Strecker-type reactions.

entry	imine	yield/%	*ee*/%
1	**27a**, R^1 = Ph, R^2 = Allyl	91	95
2	**27b**, R^1 = *p*-MeOC$_6$H$_4$, R^2 = Allyl	93	91
3	**27c**, R^1 = 2-Nap, R^2 = Allyl	93	93
4	**27d**, R^1 = C$_6$H$_{11}$, R^2 = Allyl	77	57
5	**27e**, R^1 = *t*-Bu, R^2 = Allyl	69	37
6	**30**, R^1 = *t*-Bu, R^2 = Bn	88	49

They have also searched for more effective salen-based ligands using combinatorial techniques[29] which has been recognized as a potentially powerful tool for discovery and optimization of chiral ligands for asymmetric synthesis. They prepared three parallel libraries individually (Figure 1.8). Library 1 consisted of 12 different metal ions; however, the reaction without any metal ion gave the best result (up to 19% *ee*). Library 2 and Library 3 consisted of 48 and 132 different ligands, respectively, and it was shown that the structurally different Library 3 was more effective. It was discovered that direct attachment of the catalysts to a polystyrene matrix gave more enantiomerically enriched products than the free catalysts, and replacement of a urea-type linker to a thiourea-type linker improved the selectivity. Finally, the most effective catalyst **32** (*t*-Leu-CH-OMe type) for the reaction of imine **27a** with hydrogen cyanide was identified from the library.
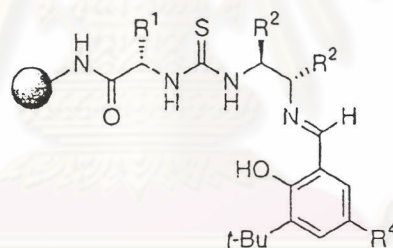
Library 1

12 Metals

Library 2

4 (R^1) x 2 (R^2) x 6 (R^3, R^4) = 48

Library 3

11 (R^1) x 3 (R^2) x 4 (R^4) = 132

t-Leu-CH OMe **32** : R^1 = t-Bu, R^2 =
R^4 = OMe
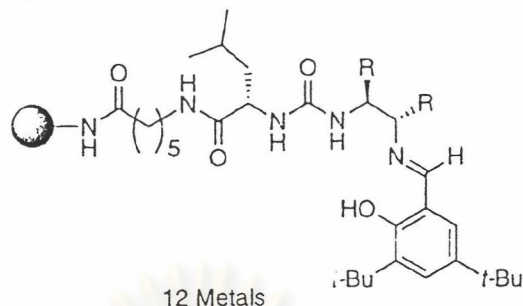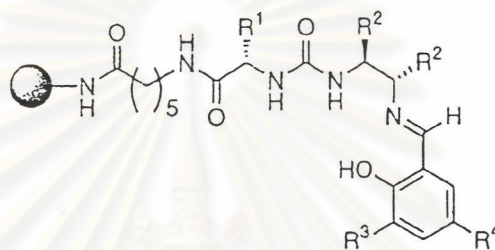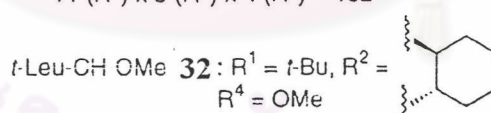
Figure 1.8 Ligand library for catalytic enantioselective Strecker-type
reactions.

On the basis of these preliminary studies, they performed solution phase
asymmetric reactions (Table 1.5). A variety of imines derived from aromatic and
aliphatic aldehydes react with hydrogen cyanide to give the corresponding
aminonitriles **28a-e** under the influence of 2 mol% of **33** in satisfactory yields and
selectivities.
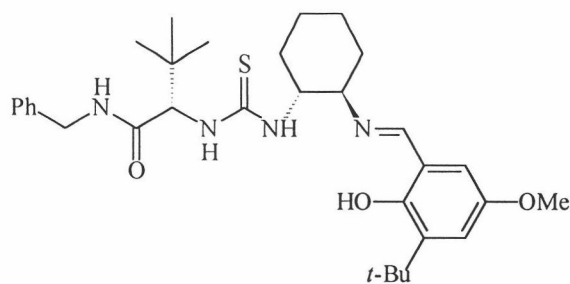
33

Table 1.5 Jacobsen's catalytic enantioselective Strecker-type reactions.

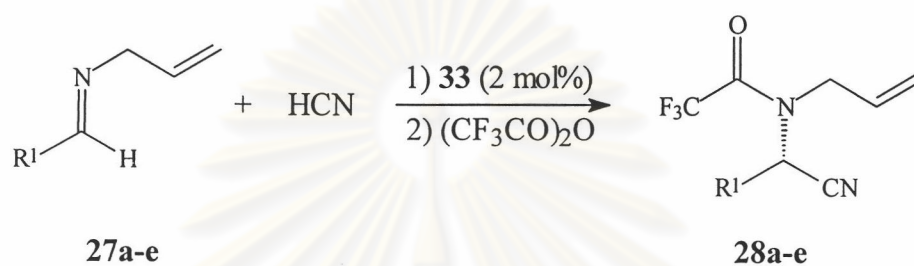| entry	imine	yield/%	ee/%
1	**27a**, R^1 = Ph	78	91
2	**27b**, R^1 = p-MeOC$_6$H$_4$	92	70
3	**27c**, R^1 = 2-Nap	88	88
4	**27d**, R^1 = C$_6$H$_{11}$	77	83
5	**27e**, R^1 = t-Bu	70	85

Furthermore, they reported new catalysts for the Strecker reaction that display high enantioselectivity and broad substrate scope for both aromatic and aliphatic imines.[30] These catalysts can be used either in solution or when covalently linked to polystyrene resins, with the latter retaining full reactivity and enantioselectivity after repeated recycling. They prepared analogues of **33**, *i.e.* catalysts **34**, **35** and found that catalyst **35** could catalyze **27e** in high enantioselectively (95% *ee*) and yield (75%). This constitutes a substantial improvement over results obtained with catalyst **33** (85% *ee*). Either *N*-benzyl or allyl imines could be used with no significant differences in yield and selectivity. In general, the soluble catalyst **35** effected hydrocyanation of imines with 2-4% higher *ee* values than the resin-bond analogue **34**. In that respect, the polymer supported catalyst **34** which is easily removed from the reaction mixtures by simple filtration offers practical advantages over the solution-phase analogue despite the slightly lower enantioselectivity.
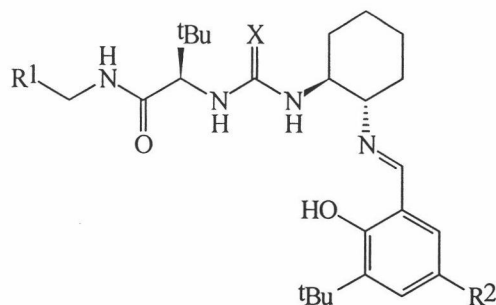
34: R^1 = polystyrene, X = S, R^2 = OCO(^{t}Bu)

35: R^1 = Ph, X = O, R^2 = OCO(^{t}Bu)

Snapper, Hoveyda and co-workers employed a related salicylimine Schiff base ligand **36** in the asymmetric titanium-catalyzed Strecker reaction of aromatic *N*-benzhydrylimines **24** to give addition products **25** (Scheme 1.16).[31] It was found that catalyst turnover was facilitated significantly in the presence of 2-propanol as an additive. The aminonitriles **25** are stable and can be directly purified by chromatography (acylation is not need) and can be readily converted into the corresponding amino acids with 6 N HCl which caused concomitant cyanide hydrolysis and amine deprotection.
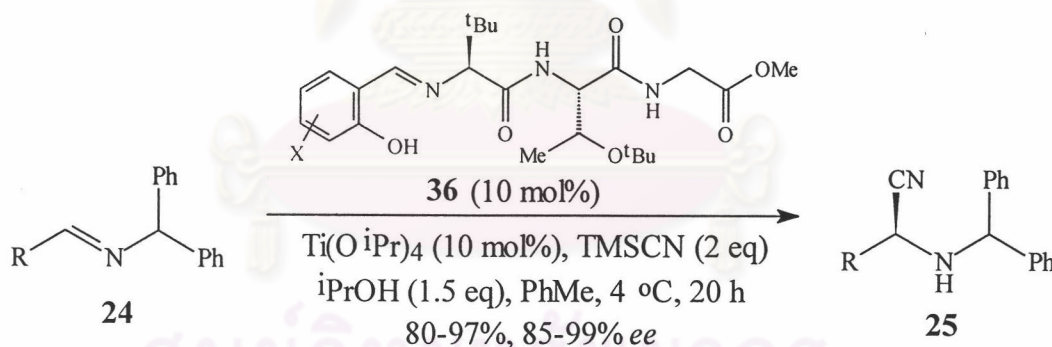
Scheme 1.16 Strecker synthesis with the chiral Schiff base ligand **36**.

TMS = trimethylsily.

In 2000, Shibasaki and co-workers disclosed a general asymmetric Strecker-type reaction that was assisted by the bifunctional Lewis acid-Lewis base catalyst **37**.[32] *N*-Fluorenylimines **38** underwent catalytic asymmetric Strecker-type reactions with TMSCN in the presence of binaphthol catalyst **37** to give α-aminonitriles **39** in good to excellent yields and enantioselectivities (Scheme 1.17). α-Aminonitriles **39** (R = Ph) could then be converted into α-aminoamide **40** in several steps. Aromatic, aliphatic, heterocyclic, and α,β-unsaturated imines **38** were the substrates employed

in these reactions. With this catalyst system, *N*-allyl- and *N*-benzhydryl- imines generally gave lower enantioselectivities. The addition of phenol was found to have a beneficial effect on the reaction rates, presumably by converting TMSCN to HCN which is a more reactive cyanating agent.

Scheme 1.17 Asymmetric Strecker synthesis with the bifunctional Lewis acid-Lewis base catalyst **37**. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Moreover, Nakai *et al.*[33] presented another asymmetric Strecker reaction catalyzed by a related Ti–BINOL complex (**41**). As shown in Scheme 1.18, the reaction of *N*-benzyl imine (**42**) with TMSCN using 20 mol% of complex **41** was found to proceed catalytically to afford the α-aminonitrile in good yield although the selectivity was quite low (30% *ee*).
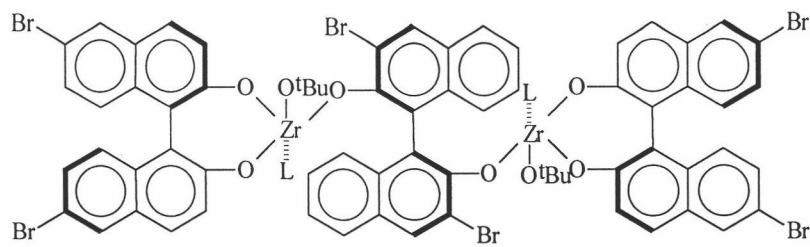
Scheme 1.18 Asymmetric Strecker reaction catalyzed by complex **41**.

In addition, zirconium catalyst **44**, which was effective in the catalytic enantioselective Mannich-type reactions[34,35] and aza Diels-Alder reactions,[36] was also used in asymmetric Strecker-type synthesis.[37] In the presence of 10 mol% of zirconium catalyst **44**, imine **45a** was treated with Bu_3SnCN in dichloromethane at − 45 °C. Zirconium catalyst **44** was prepared from 0.1 equiv of $Zr(O\text{-}t\text{-}Bu)_4$, 0.1 equiv of (R)-6-Br–BINOL and (R)-3,3′-dibromo-1,1′-bi-2-naphthol ((R)-3-Br–BINOL), and 0.3 equiv of NMI. While the reaction proceeded smoothly to afford the corresponding α-aminonitrile in 70% yield, the enantioselectivity was moderate (55% *ee*). After several reaction conditions were examined, the best results (92% yield, 91% *ee*) were obtained when the reaction was carried out in benzene-toluene (1:1) using 10 mol% of the chiral zirconium catalyst **44** at −65 to 0 °C.
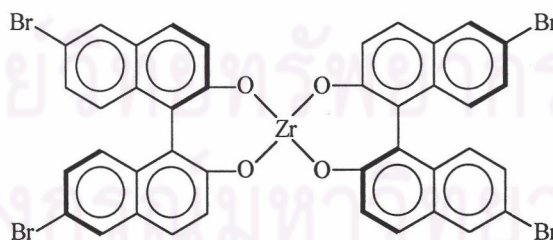
44

They found that the use of a mixture of (R)-6-Br-BINOL and (R)-3-Br-BINOL gave the best results. The structure of the zirconium catalyst was carefully examined, and it was proposed from NMR studies that a zirconium binuclear complex **46** was formed under the conditions used. The binuclear complex consists of 2 eq of zirconium, (R)-6-Br-BINOL, and NMI, and 1 eq of (R)-3-Br-BINOL.

(L = *N*-methylimidazole)

46

Several examples of asymmetric Strecker reaction catalyzed by the above chiral zirconium catalyst (**46**) are summarized in Table 1.6. Imines derived from various aromatic aldehydes as well as aliphatic and heterocyclic aldehydes reacted with Bu$_3$SnCN smoothly to afford the corresponding α-aminonitrile derivatives in high yields with high enantiomeric excess.

Table 1.6 Chiral zirconium-catalyzed enantioselective Strecker-type reactions.
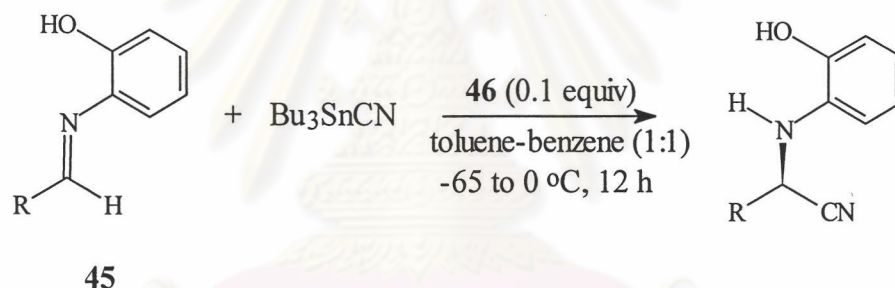
entry	R	yield/%	ee/%
1	Ph	92	91
2	p-Cl-Ph	90	88
3	1-Nap	98	91
4	p-MeOC$_6$H$_4$	97	76
5	o-Me-Ph	96	89
6	o-Me-Ph	93	89 (S)
7		85	87
8		89	80
9		89	92
10	Ph(CH$_2$)$_2$	55	83

Table 1.6 (continue)

entry	R	yield/%	ee/%
11	i-Bu	79	83
12	C_8H_{17}	72	74

Recently, Corey described a novel catalytic enantioselective Strecker reaction which utilizes the readily available chiral C_2-asymmetric guanidine **47** as a bifunctional catalyst for the addition of hydrogen cyanide to achiral *N*-benzhydrylimines (**24a**) (Scheme 1.19).[38] This reaction is quite general for *N*-benzhydrylimines of aromatic aldehydes as shown by the results which are presented in Table 1.7. The *N*-benzhydryl subunit of the aldimine substrate **24** is critical to the realization of good enantioselectivity. *N*-benzyl- or *N*-(9'-fluorenyl) aldimine analogs of **24** underwent reaction with hydrogen cyanide in the presence of 10 mol% of **47** in toluene at −10 to −20 °C to afford Strecker products of poor enantiomeric purity (0-25%). The use of Schiff bases of benzhydrylamine with aliphatic aldehydes in the Strecker process catalyzed by **47** also resulted in efficient formation of α-aminonitriles. Thus with aldimines derived from pivalaldehyde, cyclohexanecarboxaldehyde, and *n*-heptanal, (*S*)-Strecker products were formed (toluene, -40 °C, 22 h) in ~95% yield with *ee* values of 84, 76, and 63%, respectively.

47
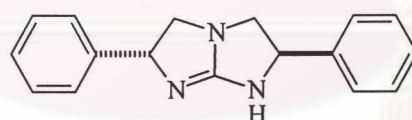
Table 1.7 Conversion of **(24)** to **(25)** by reaction with HCN in the presence of 10 mol% of **47**.

47 (0.1 eq)
HCN (2 eq)
toluene (0.2 M), -40 °C, 20 h
96% yield, 86% *ee*

24a   (*R*)-25a
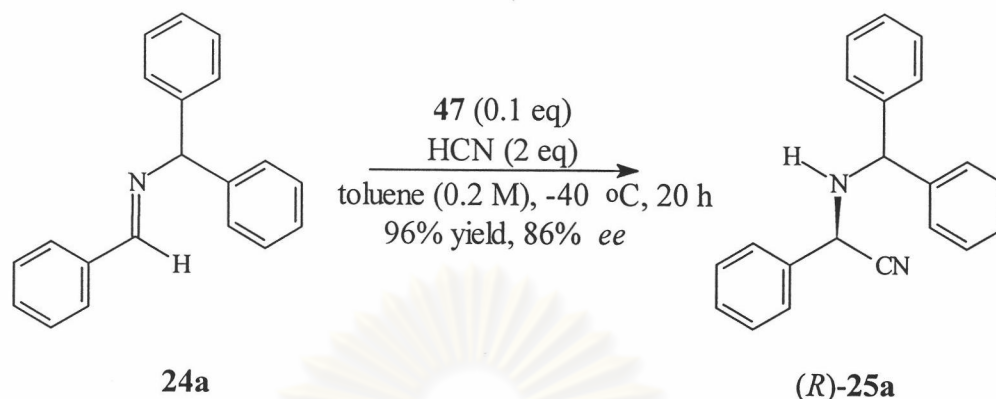
Scheme 1.19 Asymmetric Strecker synthesis with chiral guanidine catalyst **47**

24a-j	Ar	T (°C)	t (h)	% yield	% *ee*	25a-j
a	Ph	-40	20	96	86	(*R*)-25a
a	Ph	-20	8	99	82	(*R*)-25a
b	*p*-tolyl	-40	20	96	80	(*R*)-25b
c	3,5-xylyl	-40	16	96	79	(*R*)-25c
d	*o*-tolyl	-20	12	88	50	25d
e	4-*t*-Bu-Ph	-40	72	80	85	25e
f	4-TBSO-Ph	-40	38	98	88	(*R*)-25f
g	4-MeOC$_6$H$_4$	-40	28	99	84	(*R*)-25g
h	4-F-Ph	-40	23	97	86	(*R*)-25h
i	4-Cl-Ph	-20	20	88	81	(*R*)-25i
j	1-naphthyl	-20	12	90	76	(*R*)-25j

1.4 Objectives of this research

Salen ligands which could form complexes with various metals showed interesting catalytic properties in many industrially useful reactions. One most interesting application of such salen complexes includes enantioselective epoxidation of alkenes employing chiral Mn-Schiff base complex (Figure 1.9) to obtain high % *ee* in the products.[39]
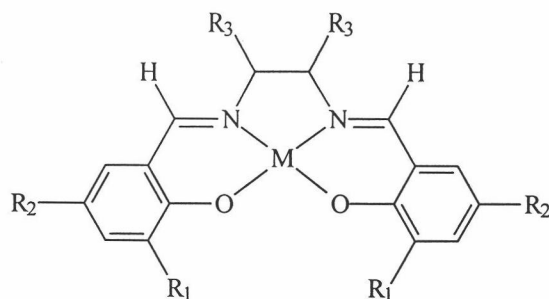
Figure 1.9 General structure of salen complex catalysts.

In addition, both polymeric salen complexes and polymer supported salen complexes have been used for asymmetric epoxidation catalyst although the selectivity was not as good as the monomeric catalyst.[40]

Due to advantages in terms of product isolation and the recycle of the expensive chiral catalysts, It is interesting to investigate other catalytic reactions using such polymeric salen catalysts. Since asymmetric cyanation of imines (Strecker reaction) has been successfully carried out in the presence of chiral salen-Al complex (**29**), and the reaction using the analogous polymeric salen complexes has never been reported, this has prompted us to study the efficiency of such systems in asymmetric Strecker reaction. It is expected that the use of polymeric salen complexes having low solubility in the reaction medium would lead to easy isolation while still giving good yield of products. Furthermore, factors affecting the catalytic efficiency including type of ligands, metals, solvents, temperature, and cyanide source will be explored.