# CHAPTER III
RESULTS AND DISCUSSION

The objectives of this research were to develop a synthetic method for non-racemic α-aminonitriles by addition of cyanide ion to imines (Strecker reaction) in the presence of chiral catalysts (Scheme 3.1). Two of the most important parameters to be considered whether the reaction is successful or not were percent yield and optical purity of the products. Optical purity could be expressed in term of % *ee* which is defined as

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

In principle, % *ee* may be determined by a variety of ways such as the use of chromatographic or spectroscopic techniques.
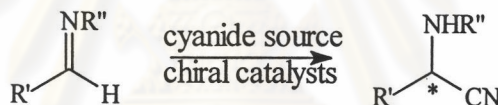
Scheme 3.1 Synthesis of optically active α-aminonitriles from imines using chiral catalysts.

3.1 Analytical methods: determination of enantiomeric purity of α-aminonitriles

3.1.1 Gas chromatographic methods

Determination of enantiomeric composition by means of chromatography on a chiral capillary GC column offers itself as a prevalent technique of separation in recent years. The method makes use of a chiral stationary phase, which contains a chiral auxiliary resolving agent of high enantiomeric purity. The enantiomers to be analyzed undergo rapid and reversible interactions with the chiral stationary phase to form transient diastereomeric complexes and hence may be eluted at different rates. Even though this is one of the best direct analytical methods for enantiomeric composition determination, there are certain limitations to the method, some of which are associated with the nature of gas chromatographic method itself. The sample should be sufficiently volatile and thermally stable, and, of course, should be

quantitatively resolved on the chiral GC phase. Occasionally this means that the enantiomeric mixtures need to be derivatized (with an achiral reagent, or a chiral reagent if achiral column is to be used) prior to GC analysis (e.g. trifluoroacetylation or silylation of amino acids). Absolute configuration can be determined if a sample of the same compound with known configuration is available for reference. In cases of enantiomers, comparison of retention time is generally not accurate enough, therefore, the spiking technique is preferred. One disadvantage of this method is due to the high cost of chiral GC column. In addition, a certain type of stationary phase might not be general enough for all compounds of interest. Therefore, it is rather difficult to predict what type of stationary phases would provide the desired separation. The success of the separation is thus highly dependent on the trial-and-error process and to the types of column available at hands. Another limitation results from the destructive nature of the GC technique itself (except in a preparative gas chromatograph where non-destructive means of detection is used).

Non-chiral GC stationary phases offer an alternative. Percent enantiomeric excess of a mixture can be obtained indirectly by the determination of diastereomeric compositions of a pair of enantiomers, after being converted to their diastereomers, on non-chiral GC columns. The problem of expensive column can thus be solved, nevertheless disadvantages associated with GC techniques are still present. There were reports where α-aminonitriles have been derivatized with trifluoroacetic anhydride before GC analysis on a γ-TA chiral GC column.[30] From a previous report,[47] the enantiomeric purity of amino compounds was determined by derivatizing with a chiral reagent (1R)-(−)-menthyl chloroformate to convert the amines into their diastereomeric, (−)-menthyl carbamates. This was followed by determination of diastereomeric composition on a GC column. There are the possibility of accidental enrichment during the derivatization process therefore control experiments should always be performed.

3.1.2 Liquid chromatographic methods

The development of rapid, simple liquid chromatographic methods for the assay of enantiomeric purity has perhaps been the most important development in the analysis of chiral compounds in the last decade. Using analytical HPLC, theseparability factor, α^*, for two components in an HPLC chromatogram depends

upon the band shape and is related directly to the efficiency of the column which is also dependent on flow rate, particle size, sample size, and quality of packing. The preferred method for chiral separation is to induce short-term diastereomeric interactions of the two enantiomers with a chiral stationary phase. An alternative is to use an achiral support and to elute with a chiral eluent. As in chiral GC, absolute configuration can be determined if the same sample of known configuration is available for reference. Most of the reported works use chiral HPLC on chiral columns such as Daicel ChiralPak AD®, Chiralcel OD®, Chiralpak AS®, or Chiralcel OJ® as a preformed method to determine the optical purity of α-aminonitriles. Although suitable for many non-volatile compounds, including highly polar ones, resolution and reproducibility of chiral HPLC still fall short of the chiral GC technique (HETP of GC >>> LC).

3.1.3 NMR spectroscopy

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

Three types of chiral auxiliary are commonly used. Chiral derivatizing agents (CDAs) form diastereomers *via* a covalent bond, thus requiring a separate derivatization step, while chiral solvating agents (CSAs) and chiral lanthanide shift reagents (CLSRs) form diastereomeric complexes *in situ* with the enantiomeric substrates, therefore, may be directly added to the substrates prior to recording the spectra. Since α-aminonitriles are basic, appropriate acidic agents are required for such resolution.

Chiral derivatizing agents (CDAs)

A CDA forms discrete diastereomers which are free from the effects of chemical exchange. As a result the magnitude of the chemical shift non-equivalence, $\Delta\delta$, is typically several times larger than that observed in the presence of a chiral solvating agent (CSA).

Lipton *et al.*[26] used R-(+)-α-methoxy-α-trifluoromethylphenylacetic acid, ((+)-MTPA) developed as a CDA by Mosher *et al.*,[48] to derivatize α-aminonitriles to form diastereoisomeric amides. A comparison of the ^{1}H or ^{19}F-NMR spectrum of the derivatized crude product with that of a derivatized authentic racemate would yield information on the preference of the enantiomer being formed. Alternatively, the enantiomeric composition of the products can be established by conversion of underivatized α-aminonitriles to phenylglycine followed by determination of the sign and magnitude of its optical rotation.[49] Other acids, in particular, camphanic acid, and O-acetyl-mandelic acid are also effectives CDAs for α-deuterated amines.[50]

Chiral solvating agents (CSAs)

Although valid in principle, the expense of using a chiral material as a bulk solvent for NMR determination of enantiomeric purity is rarely justified. Fortunately, the solvating agent may be added in between 1 to 10 mole equivalents to a solution of the solute enantiomers in an achiral bulk solvent to give the same results. Chiral solvating agents form diastereomeric solvation complexes with the substrate enantiomers *via* rapidly reversible equilibria in competition with the bulk solvent.

The advantage of the CSA technique is that it is quick and simple and there is no problem with accidental enrichment or racemization of the sample due to differential reaction rates associated with the use of CDA, provided that the sample remains in solution in the presence of the CSA. Moreover, the enantiomeric purity of the CSA is not critical. If a CSA of less than 100% *ee* is used, the magnitude of the chemical shift non-equivalence is reduced but the relative signal intensities are not affected. Non-polar solvents maximize the anisochronicity between the diastereomeric complexes while polar solvents effectively exclude the formation of these complexes with the CSA and hence reduce $\Delta\alpha$ to zero. (1R)-Camphor-10-sulfonic acid has been used to determine the enantiomeric purities of the optically

active α-aminonitriles by ^{1}H NMR spectroscopy in CDCl$_3$.[46] L-Tartaric acid could also be used for the same propose.

Chiral lanthanide shift reagents (CLSRs)

Chiral lanthanide shift reagents (CLSRs) form diastereomeric association complexes with enantiomeric substrate in solution which are subject to similar equilibria to CSA complexes. The induced shift of some particular resonances will be different in each diastereomeric complex. The magnitude of the chemical shift non-equivalence depends on the strength of the complexation. The association the complexes formed are especially moisture sensitive; the CLSR and the substrate must be dry and the solvent should be dried over molecular sieves immediately prior to use. Non-polar solvents such as carbon tetrachloride or CDCl$_3$ are preferred. The chemical shift differences of racemic α-aminonitriles could be resolved in CDCl$_3$ in the presence of chiral europium (Eu) shift reagents.[50] One drawback of this technique is the severe line broadening which occurs as a result of paramagnetic propeties of lanthanide shift reagents.

Initial experiments involved screening of the racemic α-aminonitriles of interests. Four of these were chosen from a variety of structures to find the most suitable model compound of which the enantiomeric purity could be determined by an appropriate technique (Figure 3.1). α-Aminonitriles **25a**, **43**, **55**, and **56** (Figure 3.1) contain various *N*-substituent groups benzyl, *n*-heptyl, and diphenylmethyl, as well as phenyl or *n*-heptyl group at the α-carbon position.

43

55

25a

56
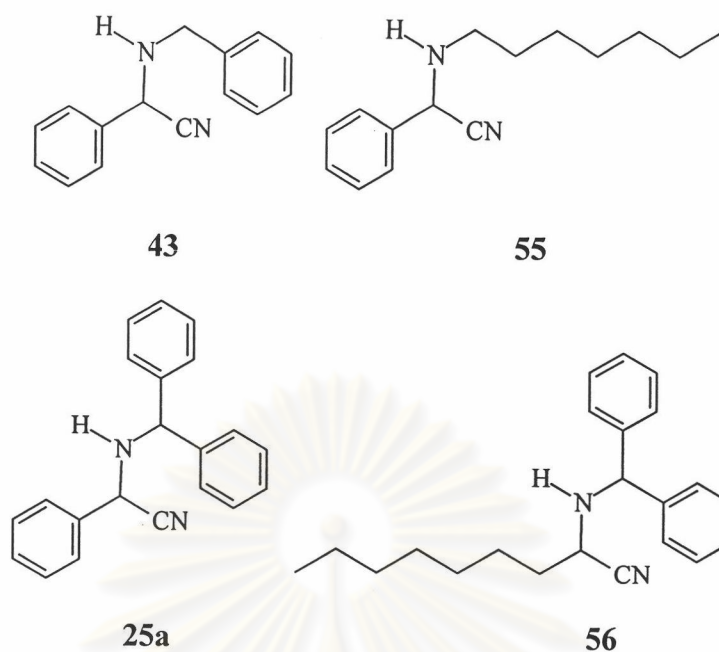
Figure 3.1 Various α-aminonitriles of interest.

In order to find a suitable method for determination of % *ee*, several analytical techniques were employed in the study including chiral GC, reverse and normal phase chiral HPLC, derivatization of α-aminonitriles by chiral derivatizing agents such as (1*R*)-(−)-menthyl chloroformate, and the use of chiral solvating agents (CSAs) for NMR analysis.

3.2 The results of analytical methods

3.2.1 Chiral GC analysis

The determination of enantiomeric composition of α-aminonitrile using a chiral γ-TA GC column was reportedly successful.[30] A pretreatment of the nitrile with trifluoroacetic anhydride to increase the volality and the thermal stability was required. Racemic α-aminonitriles had to be derivatized with trifluoroacetic anhydride prior to GC analysis prior to an attempt to resolve the pair on the chiral GC phase.

In this research, attempts to separate a racemic mixture of **25a, 43, 55**, and **56** on a chiral GC column (25.5% heptakis (2,3-di-*O*-methyl-6-*O*-tert-butyldimethylsilyl)β-cyclodextrin in OV-1701 stationary phase) was carried out. Disappointingly, no peak separation of the enantiomeric pair was observed regardless

of conditions employed. Samples were tested without trifluoroacetylation. The analysis showed that under isothermal conditions, this particular chiral GC stationary phase could not separate the racemic α-aminonitriles (Fig 11-12). The problem might also come from using non-trifluoroacylated samples which might have too high boiling point and thus not suitable for the GC technique.

Aminonitrile **25a** would have a very high boiling point due to the presence of 3 aromatic rings in its structure. As a result, GC analysis would have to be performed at a temperature far above the GC column temperature limit, therefore, it was not analyzed by this method.

3.2.2 GC analysis

Analysis of racemic mixtures of α-aminonitriles as their diastereomers on a non-chiral GC stationary phase was also carried out. There was a report where (1R)-(−)-menthyl chloroformate (**57**) was used as a chiral derivatizing agent to convert optically active alcohols, amines, α-hydroxy and α-amino acids to their diastereomers. GC analysis under isothermal conditions was subsequently carried out on a 5 ft × 1/8 in. column packed with 5% QF-1 on Aeropak 30.[47]
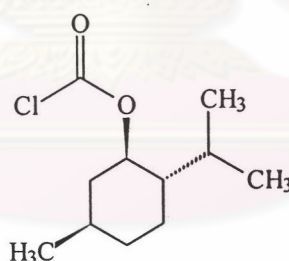
57

There was no report where **57** was used as a CDA in the separation of α-aminonitriles as their (R)-(−)-menthyl carbamate diastereomeric derivatives. In addition to the fact that **57** had been proven successful in diastereomeric composition analysis of various types of compounds, its low cost and availability had prompted us to carry out a test to see if it would be a suitable CDA for our purpose. At first, a solution of derivatized **25a** in toluene was injected into the gas chromatograph equipped with a DB™-1 column under an isothermal condition (220 °C). Such a condition resulted in a co-elution of the enantiomers (Fig 13). Subsequent attempts were exhaustively performed under various temperature programs in order to improve

the separation. Unfortunately, of the four pairs of racemic α-aminonitriles derivatized with **57**, none gave a separation under what was considered the best GC conditions obtained so far. Some ambiguities were observed. Firstly, the GC experiments showed no distinction in almost all the results because two signals of unequal intensities of what was presumed to be a diastereomeric pair were observed in the use of racemic substances. This raised the doubt of differences in rates of reaction between two enantiomers, even though this was not observed when **57** was used with other types of compound.[47] This fact was not further investigated due to the lack of an access to GC/MS facility for peak identification proposes. Furthermore, the peaks of unconverted α-aminonitriles, presumably due to incomplete derivatization, were still present in some cases. Even with excess amounts of **57** added in order to convert all the α-aminonitrile, no two peaks of equal intensity were observed (Fig 14-30). The best conditions for separation derivatized α-aminonitriles was shown in Fig 24.

^{1}H and ^{13}C NMR analysis of the profiled derivatized **25a** indicated that only one diastereomer was formed, which suggested that the derivatization process might have brought about an enantiomeric enrichment of the racemic aminonitrile. Another attractive derivatizing agent would be MTPA-Cl but its high cost discouraged any further attempts for its use as a CDA.

3.2.3 Normal phase chiral HPLC analysis

From the previous works,[26,28,30-32,37,38] commercially available chiral HPLC columns used to determine enantiomeric composition of α-aminonitriles were Daicel ChiralPak AD®, Daicel Chiralcel OD®, Chiralpak AS®, or Chiralcel OJ® column. It had been reported that % *ee* of α-aminonitriles. In the present work, analysis of racemic mixtures of α-aminonitriles on a readily available Daicel Chiralcel OD® HPLC column was attempted. The results were, however, disappointing. Neither the recommended mobile phase (hexane/^{i}PrOH in various gradients) nor modified mobile phase systems, with 0.1% *N,N*-diethylamine added, gave satisfactory separation of the racemic **25a**, **43**, **55**, and **56**. Perhaps, this particular chiral stationary phase (cellulose tris(3,5-dimethylphenyl carbamate) on a 10 μm silica-gel substrate) was not suitable for the analysis of such non-polar α-aminonitriles. Because α-aminonitriles containing the 2-hydroxyphenyl group as *N*-substituent (**45**) was successfully

determined using this chiral column.[37] Thus, the attempts to determine % *ee* of the racemic aminonitrile by a normal phase chiral HPLC were abandoned.

### 3.2.4 Reverse phase chiral HPLC analysis

We had turned our attentions towards the use of a reverse phase chiral HPLC column as a tool for enantiomeric separation. To the best of our knowledge, no report on determinations of α-aminonitriles using reverse phase chiral HPLC methods was described. It is known that reverse phase techniques were satisfactory mostly to polar substances, non-polar α-aminonitriles did not fit the reverse phase chiral HPLC methods. However, since a chiral HPLC column is available at hands, a trial attempt was performed here. Firstly, **25a** was chosen for analysis attempt on ChiralDex® (Silicagel modified by β-cyclodextrin) column eluted with acetonitrile-water but the separation was not achieved.

As shown so far, all attempts by modern chromatographic resolution were unsuccessful. Therefore, we had turned our focus towards classical NMR techniques.

3.2.5 ^{1}H NMR spectroscopic analysis

In order to screen for a good CSA, two target α-aminonitriles, **25a** and **43**, were chosen as the representatives due to their uncomplicated structures. The other α-aminonitriles **55** and **56**, containing long chain *N*-substituted alkyl group (**55**) on the other hand, was difficult to remove under mild conditions. In addition, long chain α-aminonitrile **56** might not give good enantioselectivity by asymmetric Strecker reaction due to the lack of site for interaction with the catalyst. This was supported by previous reports[26] that almost all of asymmetric Strecker reaction using chiral catalysts was rarely successful with long chain imines. As a consequence, **25a** and **43** were the preferred model structures for the analysis by spectroscopic techniques using CSAs.

Since its first introduction by Mosher *et al.*[48] *S*-(–)-α-methoxy-α-trifluoromethylphenylacetic acid, MTPA, (*S*)-**58**, had become one of the most widely used chiral solvating agent for the determination of enantiomeric composition of alcohols and amines by ^{1}H NMR spectroscopy.
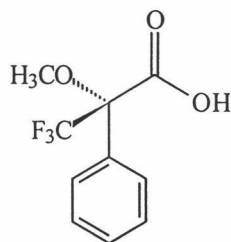
(*S*)-**58**

At the beginning, *S*-(−)-Mosher's acid (**58**) was tested for analysis of racemic α-aminonitriles **25a**. After 0.5 eq of (*S*)-**58** was added, the peak of enantiomeric proton, H-C-CN, at 4.59 ppm did not resolve into two signals of equal intensity as one might have expected. When another 0.5 eq of (*S*)-**58** was added (total of 1 eq for (*S*)-**58**), the peak characteristic remained unchanged. No further amounts of MTPA were added since although the additional amount of MTPA would result in detectable resolution, the analysis method would be too costly. Its failure to yield any enantiomeric resolution, together with its high cost, had prompted us to investigate other CSAs. Then *R*-(−)-1,1′-binaphthalene-2,2′-diyl hydrogen phosphate, BNP (**59**) was next employed in the NMR analysis of racemic **25a**. Addition of 0.25 eq of **59** to a solution of **25a** resulted in some separation of the H-C-CN signal at 4.59 ppm,
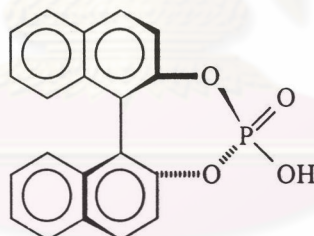
(*R*)-**59**

however it was not a satisfactory baseline separation. An additional 0.25 eq of **59** was added but the two signals of equal intensities were still obscured. It was anticipated that an increased amount of **59** would afford a better separation. However, its low solubility had prevented any further addition of **59** to the solution of **25a**. Therefore, **59** was not a good choice to distinguish **25a** enantiomeric protons. In contrast, the treatment of racemic α-aminonitriles **43** with 1 eq of **59** gave two signals of identical intensities for H-C-CN at 4.69 and 4.83 ppm with a baseline-baseline separation. The differential of δ is 0.14 ppm (Figure 3.2: (a)-1, (a)-2).

Next, the separation of an enantiomeric pair of **25a** was examined using (1*S*)-(+)-camphor-10-sulfonic acid (**60**). It was found that successive addition of two
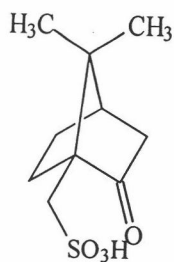
(S)-60

0.5 eq aliquots of **60** to a solution of **25a** in CDCl₃ resulted in a clear peak separation in the ^{1}H NMR spectrum. When a total of 1 eq of **60** was used the H-C-Ph₂ and H-C-CN peak shifted into one peak. On the other hand, the use of excess **60** (2 eq) with **43** did not result in the loss of separation. Although broadening of the peaks was observed (Figure 3.2).
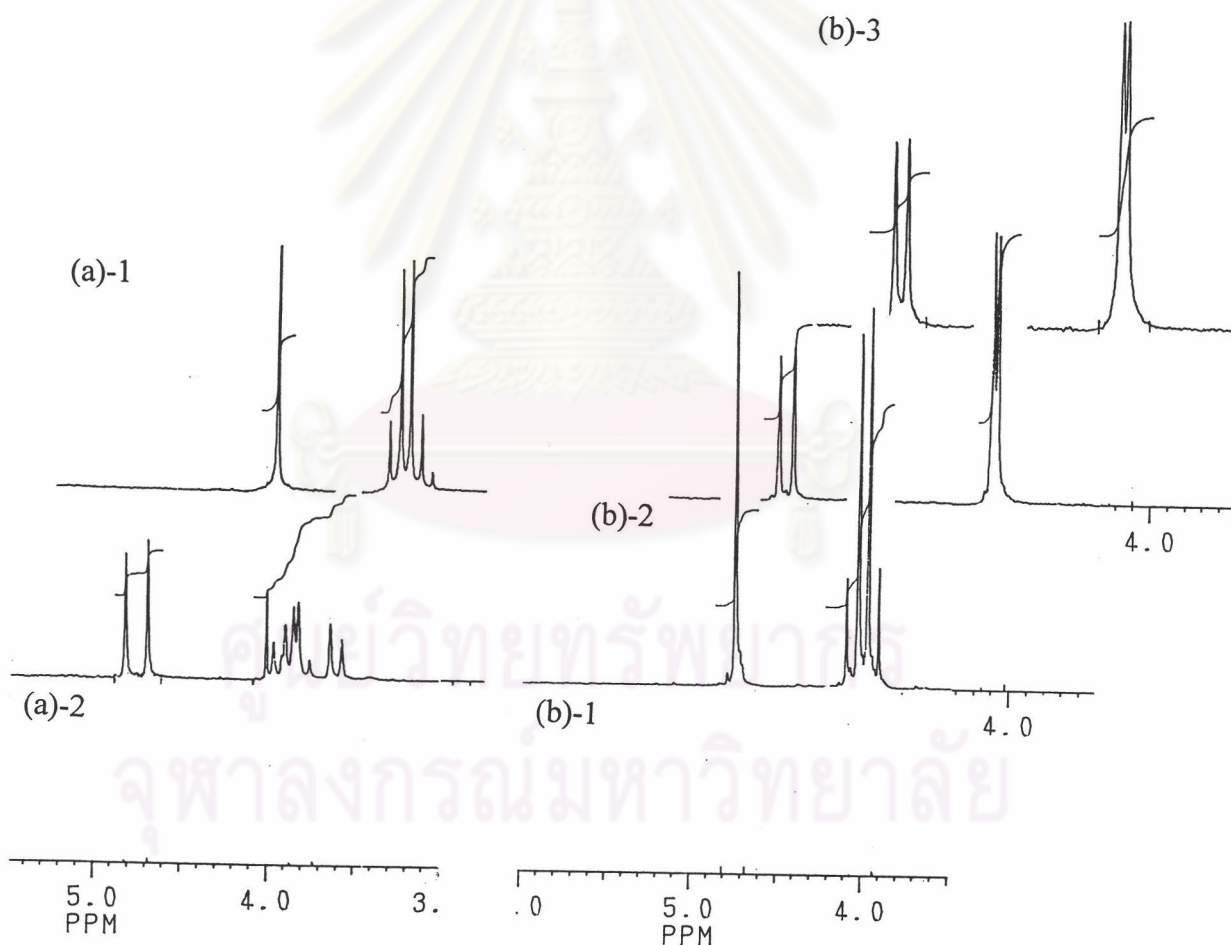
Figure 3.2 The ^{1}H nmr spectra of aminonitrile **43** in the presence of **59** and **60** as CSAs: (a)-1 Before adding **59**; (a)-2 After adding 1 eq of **59**; (b)-1 Before adding **60**; (b)-2 After adding 1 eq of **60**; (b)-3 After adding 2 eq of **60**.

In addition, R-(+)-1,1′-bi(2-naphthol) (**61**) was employed in an enantiomeric determination of **25a** and **43**. Although up to 1 eq of **61** was added to **25a**, no sign of
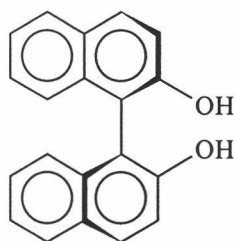
(R)-**61**

a splitting of the signal at 4.59 ppm was detectable. Due to the low solubility of **61** in CDCl$_3$, a higher amount of **61** could not be added. In contrast, enantiomeric proton peak at 4.75 ppm of **43** could be separated into two signals by an addition of 1 eq of **61**. In the case of **43**, separation using **61** was not as good as that obtained when **60** was used as a CSA.

R-(−)-α-Acetoxyphenylacetic acid (**62**) was also investigated as a potential CSA for analysis of **43**. When 1 eq of **62** was added in a CDCl$_3$ solution of **43**, no separation of the H-C-CN peak at 4.75 ppm was observed. All of ^{1}H NMR spectroscopic analysis was shown in Table 3.1.


(R)-**62**
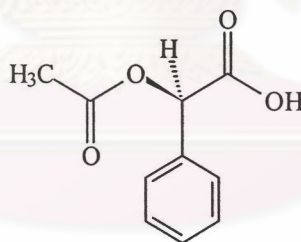
Table 3.1 Summary of the ^{1}H NMR spectroscopic analysis using various chiral solvating agents.

substrate	CSA	eq	Δδ (ppm)
aminonitrile **25a**	**58**	0.5	0
		1.0	0
	59	0.25	splitting but
		0.5	not baseline-baseline
			separation
	60	0.5	0.05
		1.0	0
	61	1.0	0
aminonitrile **43**	**59**	1.0	0.14
	60	1.0	0.10
		2.0	0.10 (peak broadening)
	61	0.5	splitting but
		1.0	not baseline-baseline
			separation
		1.5	
	62	1.0	0
		2.0	0

All results described above indicated that the suitable CSA for enantiomeric analysis of α-aminonitriles **43** determined by ^{1}H NMR spectroscopy were **59** and **60** because they could separate the peak at 4.75 (H-C-CN) into two signals of equal intensity. Although **59** gave comparable results with **25a**, it gave far better separation of **43**'s H-C-CN peak than **60**. Due to its high cost, **59** was kept only for use with the analysis of optically active α-aminonitriles **25a**. Incidentally, the use of (+)-CSA to examine % *ee* of α-aminonitrile has only recently been reported by Jochims *et al.*[46]

To prove that no racemization occurred, optically pure (*S*)-α-aminonitriles **43** (*ee* ≥ 97%) was prepared by asymmetric transformation according to Dimroth's principle as described in the literature[46] and **60** was then added into it. ^{1}H NMR spectrum showed only one signal at 5.48 ppm which is in good agreement with the literature (Figure 3.3).
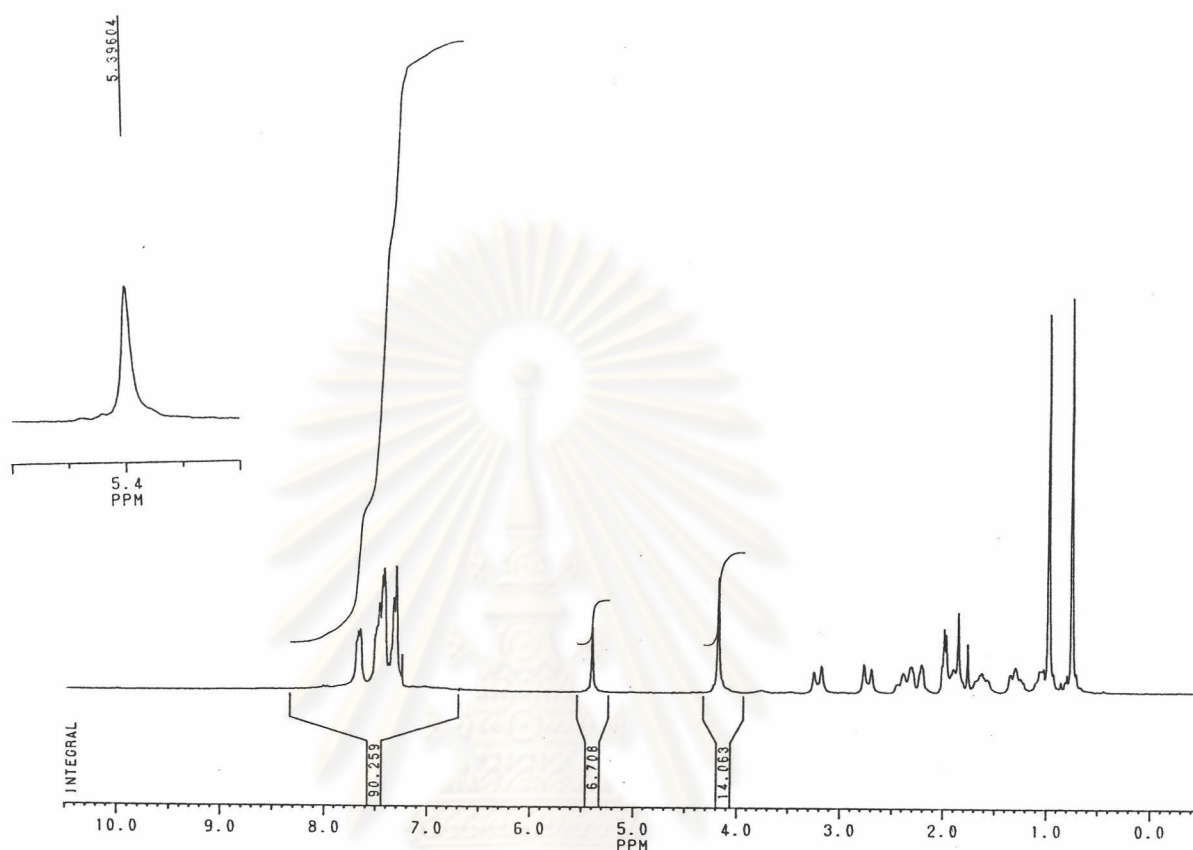
Figure 3.3 The ^{1}H nmr spectrum of optically pure aminonitrile **43**
in the presence of **60** as a CSA.

This result confirmed that the use of **60** for the determination of enantiomeric purity of α-aminonitriles took place without loss of enantiopurity. From the results described above, the use of ^{1}H NMR spectroscopic technique for the analysis enantiomeric purity of α-aminonitriles was proven a much more simple, efficient, and not too costly method compared to the chromatographic counterparts. Therefore, it was the method of choice for the rest of the determination of enantiomeric compositions described herein.

3.3 The results of asymmetric Strecker reaction

3.3.1 Synthesis of imines

Condensation of aldehydes and amines to afford imines is a well known reaction. A drying agent, for example, activated 3 Å molecular sieve or anhydrous magnesium sulfate is generally added to ensure the forward equilibrium. Imine **42** and **24a** could be easily prepared by stirring benzaldehyde and the appropriate benzylamines in the presence of MgSO$_4$. The imines are not stable enough to purify by chromatography, therefore it was used for the next reaction as such. In principle, imines can exist in two geometric isomers, namely *E*- and *Z*- isomers (Figure 3.4).

E- form   or   *Z*- form

Figure 3.4 The possible geometric isomers of imines.

Regarding the preferred isomer, the *Z*- form should be sterically less favourable than the E form because of the repulsion between both R and R′ locating on the same side of the C=N bond. On the other hand, the more stable E form possesses R and R′ opposite to each other, so it should be the more stable isomer. The fact that imines exist in *E*-isomer was supported by NOE experiment which indicated that **42** existed in the E form (anti-form) according to the significant NOE effect observed between C<u>H</u>=N and NC<u>H</u>$_2$Ph protons.

3.3.2 Jacobsen's salen and polymeric salen catalysts
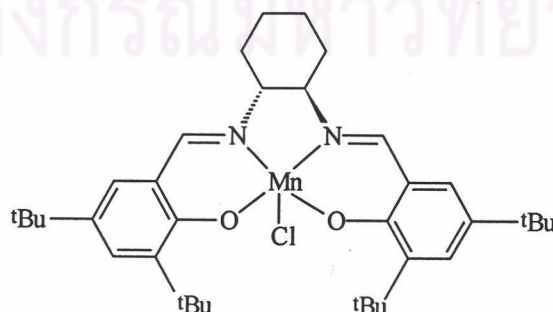
Initially, a known chiral (salen)Mn(III)Cl complex (**63**) (Jacobsen *et al.*)[51] was employed in a model asymmetric Strecker reaction of the substrate **42** using a slight modification of Jacobsen's condition. The model substrate **42** was treated with 2 eq of trimethylsilyl cyanide (TMSCN) in toluene at room temperature for 15 hours in the presence of 5 mol% **63**. This condition led to the desired product **43** with almost 100% conversion as monitored by TLC. Since the complex **63** was paramagnetic, the reaction product had to be separated from **63** before NMR spectra can be recorded otherwise line-broadening would be observed. Initially, column chromatography using silica gel absorbent was employed. However, it was found that this operation led to the decomposition of the Strecker product. In another experiment, neutral aluminium oxide 90 was used as stationary phase. A short column chromatography using hexane/ethyl acetate (9/1) as mobile phase could remove the catalyst **63** from the desired product without causing decomposition of the product. Excess (≤ 2 eq) of (1*S*)-(+)-camphor-10-sulfonic acid **60** was then added to the solution of the optically active **43** in CDCl$_3$. Encouragingly, its 200 MHz ^{1}H NMR spectrum revealed two signals of different intensities for H-C-CN at 5.37 (*S* isomer) and 5.46 ppm (*R* isomer) in 24% *ee*, (Δδ = 0.10 ppm). The relative intensity together with chemical shifts indicated that (*S*)-α-aminonitrile was formed preferentially (lit.[28] 20% *ee* prefer *S* isomer) (Figure 3.5). The shift differences depended on the amount of **60** added. This experiment indicated that within the accuracy of the 200 MHz, this method could be employed to analyze for enantiomeric purities of the optically active aminonitriles without loss of the stereochemical integrity. As a result, these operations were used throughout the course of the research.
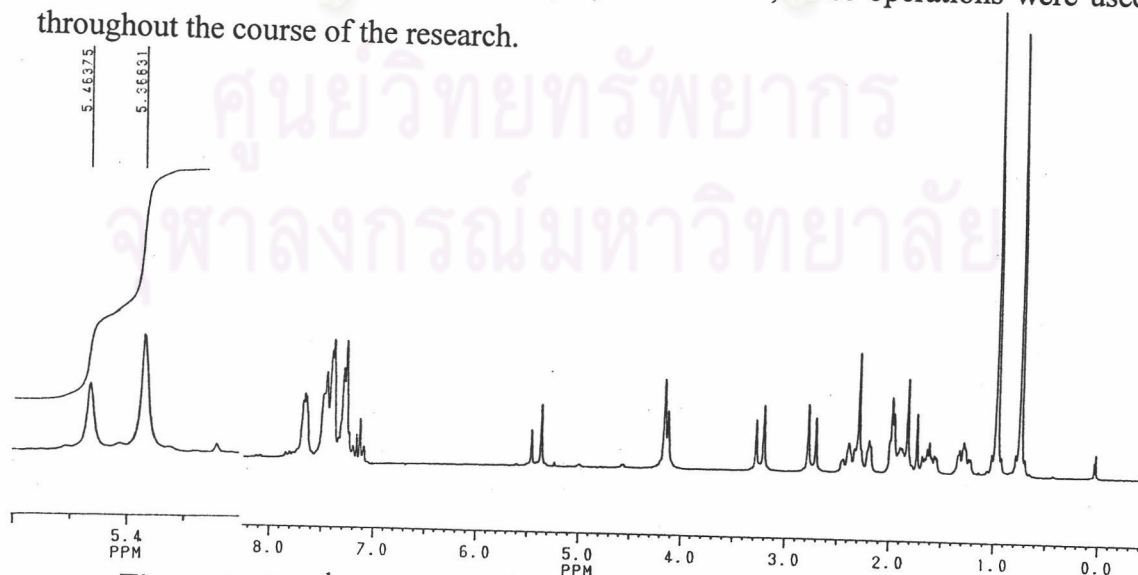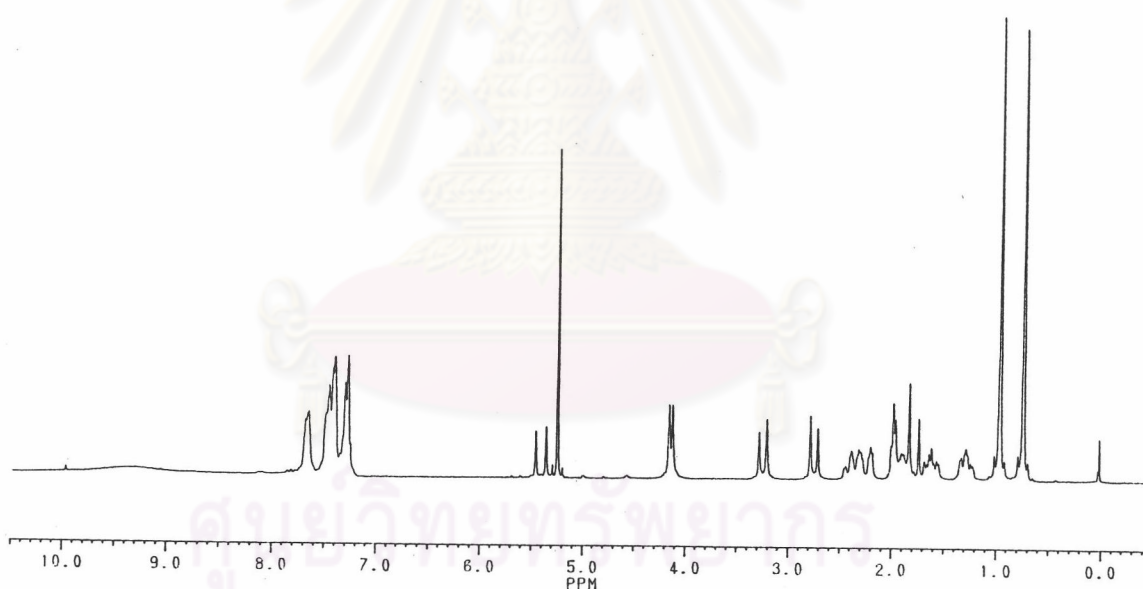

Figure 3.5 The ^{1}H nmr spectrum of **43** in the presence of **60** as a CSA.

To determine whether % enantiomeric excess might also be solvent dependent, CH_2Cl_2 was used as a solvent in place of toluene. Under similar conditions, no enantioselectivity (0% *ee*) was observed in the product (Figure 3.6). This is not surprising since enantioselectivities are generally a result of weak interactions, which are easily destroyed in polar solvents. Therefore, toluene was selected as a preferred solvent. Aliphatic hydrocarbons such as hexanes were not considered a good choice of solvent due to poor solubility of substrates.

Figure 3.6 The ^{1}H nmr spectrum of **43** in the presence of **60** as a CSA.

A variety of methods were employed in order to optimize the reaction condition with known catalyst such as **63**. These included a variation of the ways the imines were generated, cyanide sources, and reaction temperature.

Table 3.2 Percent enantiomeric excess at various reaction conditions.
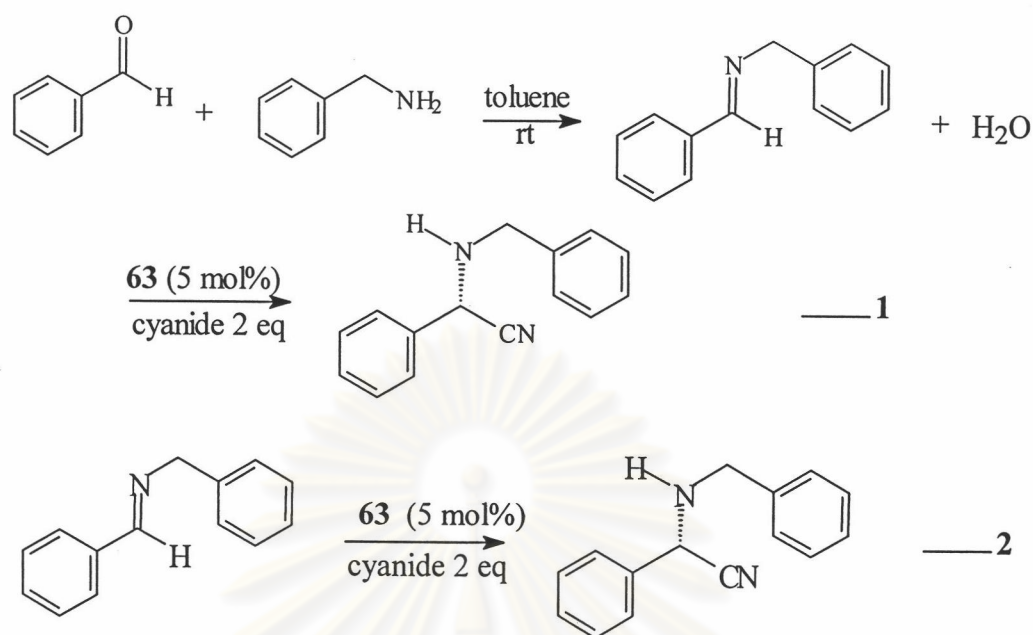
entry	method	cyanide source	temperature	time (h)	% ee (S)
1	2	TMSCN	rt	15	24
2	1	TMSCN	rt	15	22
3	2	TMSCN/MeOH	rt	15	11
4	1	TMSCN/MeOH	rt	15	10
5	2	TMSCN/MeOH	0 °C	12	27
6	1	TMSCN/MeOH	0 °C	12	30

As illustrated in Table 3.2, the aforementioned variation of conditions resulted in slight differences in observed % *ee*. At room temperature, the use of HCN (generated *in situ* from TMSCN + MeOH) caused lower % *ee* (entries 2 and 3; 11 and 10% *ee* for methods 1 and 2, respectively) than when TMSCN was used alone (22% *ee*). This suggested that at room temperature, the reaction between HCN and **42** occurred rapidly, hence resulting in low selectivity. In contrast, at low temperature, the use of HCN yielded product with higher % *ee* (entries 4 and 5, 27 and 30% *ee*). The ways the imine was generated do not appear to effect the enantioselectivity (entries 2, 3; entries 4, 5). Since **42** can be conveniently prepared and was stable enough for prolonged storage, method 2 in which imine was preformed. As a result, conditions in entries 1 and 5 were chosen as preliminary screening methods for best catalysts.

The optimized conditions were then utilized to search for the most efficient catalyst. The reactions were carried out in the presence of 10 mol% of complexes formed *in situ* from Jacobsen's ligand (**64**) and various metals including Zn, Ti, Al, Yb, and Sc in order to search for the most effective metal. The reactions of **42** and TMSCN in the presence of metal complexes of **64** generated *in situ* were carried out at room temperature (Table 3.3). In all cases quantitative conversion were observed within 15 hours.

64
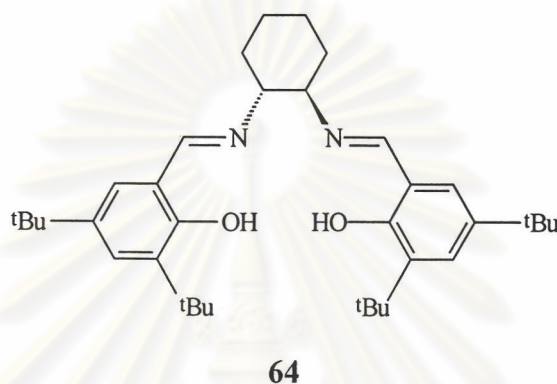
**Table 3.3** Enantioselectivity observed in the screening for suitable metals when no proton source was present.
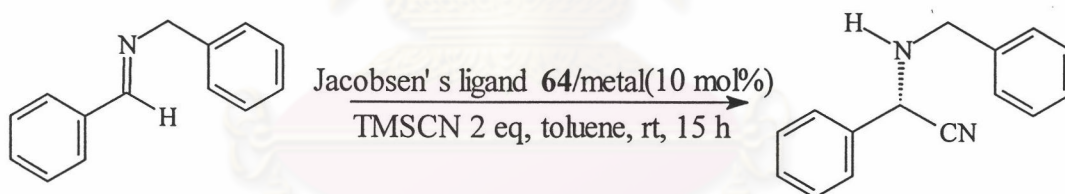
entry	metal	% ee
1	TiCl$_4$	10 (*S*)
2	Ti(O^{i}Pr)$_4$	25 (*S*)
3	Al(O^{i}Pr)$_3$	0
4	Yb(OTf)$_3$	0
5	Sc(OTf)$_3$	0

The results showed that in addition to manganese, Ti metal could induce modest enantioselectivity in the product (entries 1 and 2) while other metals failed to do so. This selectivity of the Ti complex was comparable to that of the Mn complex **63** catalyst (*S* isomer). Interestingly, Jacobsen has reported that Al-salen complex (**29**) gave very high % *ee* in asymmetric Strecker reactions. However, in our hands, Al

(O^{i}Pr)$_3$ failed to give Strecker product with any *ee*.[28] This might be attributed to the different ligands used (O^{i}Pr vs Cl).

Realizing the beneficial effect of low temperature screening, more metal salts were subsequently screened at −5 to 0 °C. In all cases quantitative conversions were observed within 12 hours. Unfortunately, all metal salts, except TiCl$_4$, yielded no enantioselectivity (Table 3.4). As expected, the % *ee* in the case of Ti was improved (10% at room temperature *vs* 19% at −5–0 °C). In this case, the (*S*) product was preferred (entry 5) which is consistent with the results obtained above. It was further confirmed that Mn and Ti were suitable metals for the reactions.

Table 3.4 Enantioselectivity observed in the screening for suitable metals with MeOH as a proton source.
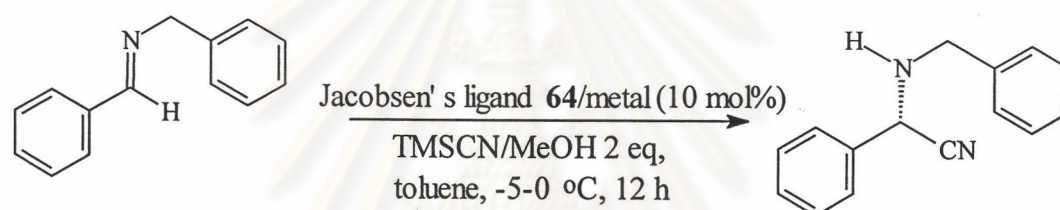
entry	metal	% *ee*
1	ZnCl$_2$	0
2	Yb(OTf)$_3$	0
3	Sc(OTf)$_3$	0
4	AlCl$_3$	0
5	TiCl$_4$	19 (*S*)

Preliminary results obtained so far indicated that salen-type complexes can induce selectivity in asymmetric Strecker reaction of **42**. In the next step, we investigated the possible use of chiral polymeric salens (**65-70**) and chiral polymeric salen-manganese complexes (**71-74**) which were polymeric analogues of **63** as catalysts in the asymmetric Strecker reaction. Unlike **63**, the substituents on the benzene ring were long chain alkyl groups (n = 2, 3, 4, 5, 6 and 12) for ligands, and n = 4, 5, 6 and 12 for Mn(OAc) complexes.
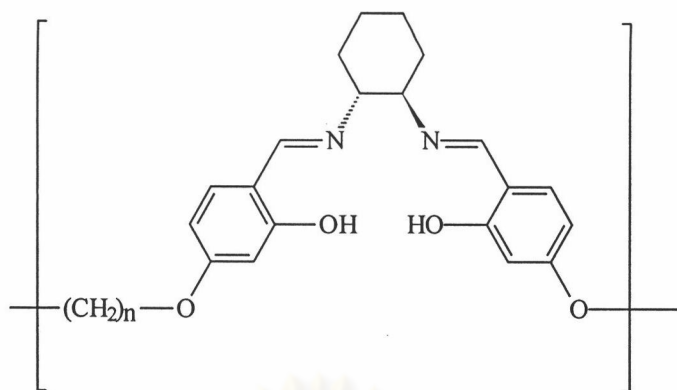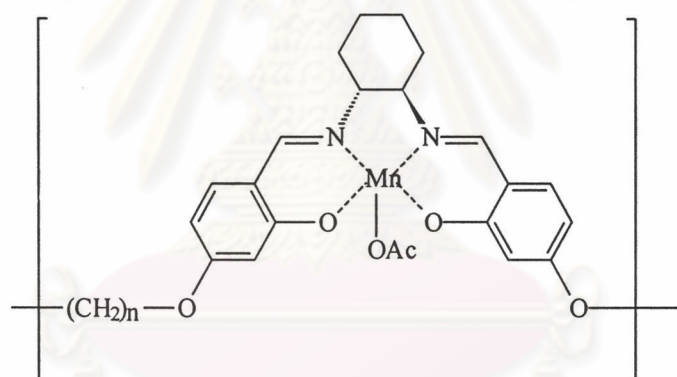
65: n = 2
66: n = 3
67: n = 4
68: n = 5
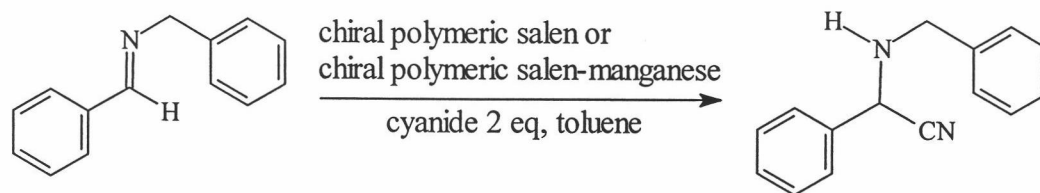**69**: n = 6
70: n = 12

71: n = 4
72: n = 5
73: n = 6
74: n = 12

The two optimized conditions using 2 eq of TMSCN at room temperature or 2 eq of TMSCN/MeOH at −5 to 0 °C were carried out find the most effective polymeric catalyst. The results were as shown in Table 3.5.

Table 3.5 Catalytic asymmetric Strecker reaction using various polymeric salens and their Mn complexes.

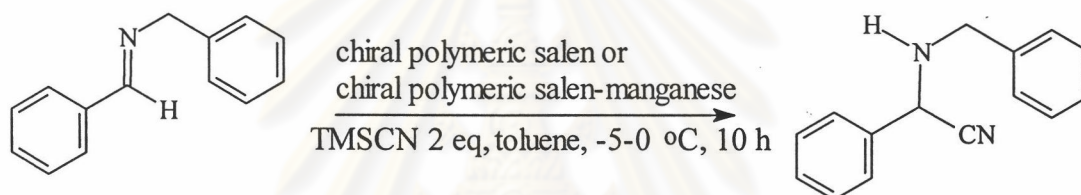| entry	ligand or complex	conv (%), *ee* (%)^a	conv (%), *ee* (%)^b
1	65	100, 0	100, 0
2	66	100, 0	100, 0
3	67	100, 0	100, 0
4	68	100, 0	100, 0
5	69	100, 0	100, 0
6	70	100, 0	100, 0
7	71	100, 0	100, 0
8	72	100, 0	100, 0
9	73	100, 0	100, 0
10	74	100, 0	100, 0

^{a} Condition: 10 mol% catalyst, 2 eq of TMSCN, toluene, rt, 15 h.

^{b} Condition: 10 mol% catalyst, 2 eq of TMSCN, 2 eq of MeOH, toluene, −5–0 °C, 6 h.

The use of chiral polymeric salen ligands as catalysts in toluene solvent revealed an unforeseen problem of decreasing solubility as the number of *n* increased. Nevertheless when TMSCN was added, the suspension became a clear solution. Disappointingly, in all cases even though conversion of the starting material approached 100%, no enantioselectivity was observed in the product. Likewise, chiral polymeric salen-metal complexes (**71-74**) were sparingly soluble and no selectivity was observed. Furthermore, the results at both room temperature and low temperature (−5 to 0 °C) were similar, *i.e.*, there was no enantioselectivity. Due to the low solubility of **65-70** in toluene, the more polar CH_2Cl_2 was also used for these systems to increase the solubility. Ligands **65-70** could dissolve well in the new solvent but again no selectivity was observed.

Having realized that the presence of methanol might be detrimental to the selectivities (*vide infra*) in the case where the chiral polymeric salen (**65-70**) and chiral polymeric salen-metal (**71-74**) were employed, some of the asymmetric Strecker reactions in the presence of chiral polymeric salen ligands, and their metal complexes were reinvestigated. The new condition; TMSCN 2 eq with no MeOH in toluene at –5–0 °C for 10 hours was used (Table 3.6). In addition, Ti complexes of **65, 67, 69** and **70** formed from the ligand and Ti(O^{i}Pr)$_4$ *in situ* were also investigated for their capability of enantioselective induction (Table 3.7).

Table 3.6 Catalytic asymmetric Strecker reaction using chiral ligands or their
Mn complexes in toluene at low temperature without
a proton source.

entry	ligand or complex	conv (%), *ee* (%)^a
1	**65**	47, 0
2	**67**	57, 0
3	**69**	32, 0
4	**70**	39, 0
5	**71**	91, 0
6	**73**	97, 3 (*S*)

^{a} Condition: 10 mol% ligand or Mn complex, 2 eq of TMSCN,
toluene, –5–0 °C, 10 h.

Table 3.7 Catalytic asymmetric Strecker reaction using Ti complexes in toluene at low temperature without a proton source.
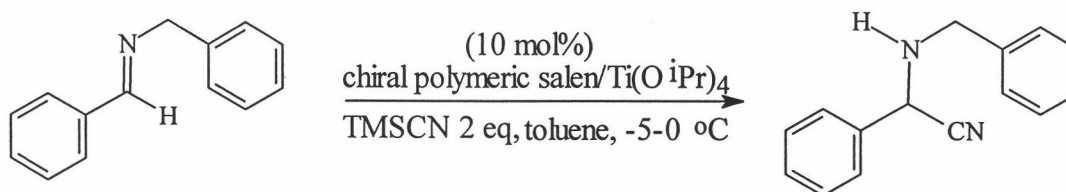
| entry	ligand	conv (%), ee (%)[b]
1	65	96, 0
2	67	96, 0
3	69	90, 0
4	70	88, 0

[b] Condition: 10 mol% Ti(OiPr)$_4$, 10 mol% ligand, 2 eq of TMSCN, toluene, −5–0 °C, 9 h.

The data shown in Table 3.6 revealed that in the presence of chiral polymeric salen ligand alone, the conversion was poor when TMSCN alone was used as cyanide source at 0 °C in toluene. On the contrary, chiral polymeric salen-metal complexes **71** and **73** yielded almost 100% conversion. In addition, 3% *ee* of *S* isomer was realized for **73** (Table 3.6, entry 6). The deep yellow complexes of ligands **65, 67, 69** and **70** with Ti(OiPr)$_4$ also gave impressive conversion although no % *ee* could be observed. These results suggested that the catalyst group of chiral polymeric salen and chiral polymeric salen-metal series were not capable of inducing enantioselectivity in asymmetric Strecker reaction under the conditions employed. In addition, attempts had been made to search for new catalysts having an intermediate structure between Jacobsen's catalyst and polymeric salen **65–70**. Ligand **75** appeared to match this concept. The structure of **75** contained two side chains of ethylene glycol on the benzene ring which were similar to chiral polymer salen catalysts.
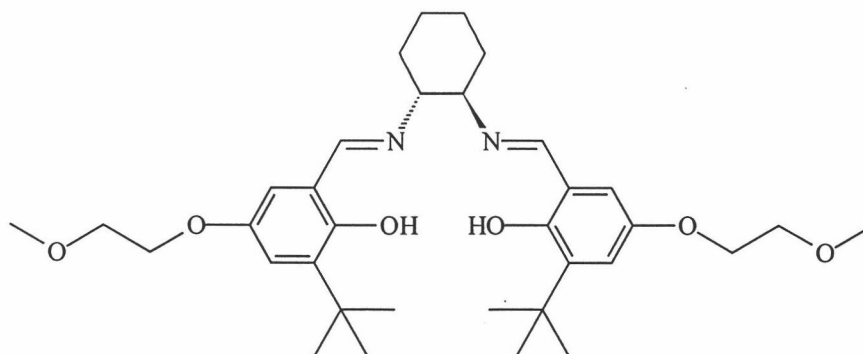
75

Ligand **75** was screened under the previous conditions (method A and C). It was found that **75** reacted with either Ti(O^{i}Pr)$_4$ and Mn(OAc)$_2$•4H$_2$O to generate *in situ* the metal complexes which could be visually observed by the color change. Complexes of **75** with Ti(O^{i}Pr)$_4$ and Mn(OAc)$_2$•4H$_2$O were orange and deep brown, respectively. The results of catalytic activity screening (10 mol%) were shown in Table 3.8.

Table 3.8 Catalytic asymmetric Strecker reaction with metal complexes of ligand **75**.
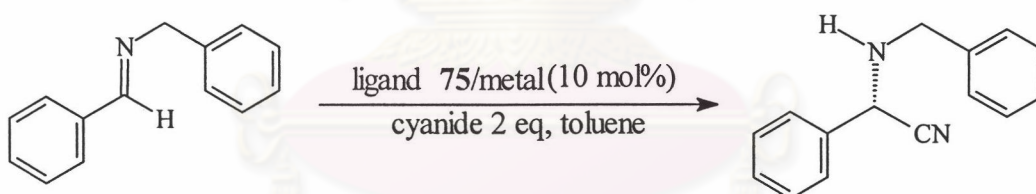
entry	Metal	conv (%), *ee* (%)^a	conv (%), *ee* (%)^b
1	–	64, 0	100, 0
2	Ti(O^{i}Pr)$_4$	93, 6 (*S*)	100, 5 (*S*)
3	Mn(OAc)$_2$ •4H$_2$O	97, 10 (*S*)	100, 0

^{a} Condition: 10 mol% metal, 10 mol% chiral ligand, 2 eq of TMSCN, toluene, rt, 15 h (method A).

^{b} Condition: 10 mol% metal, 10 mol% chiral ligand, 2 eq of TMSCN, 2 eq of MeOH, toluene, −5–0 °C, 6 h (method C).

As shown in Table 3.8, % conversion of reactions carried out at room temperature and those at low temperature when **75** was present alone (*i.e.*, no metal

salt), were 64 and 100% conversion, respectively. The reasons for this may be explained as follows: TMSCN is not reactive enough to add to the substrate completely even at room temperature while in the presence of MeOH, HCN was generated and was the active species causing observable enhancements in the reactivity. As a result, the starting material was completely consumed even at low temperature. To confirm this, the reactions of **42** with HCN generate *in situ* from TMSCN + MeOH was performed in the absence of any catalyst and the reaction rate followed by ^{1}H NMR. It was evidenced that HCN is sufficiently reactive to add to the **42** without requiring catalyst with a t1/2 of 1 h at −5 to 0 °C. It is therefore not surprising that under such condition no difference in conversion and selectivity was observed between the catalysts. On the other hand, when the metals were added to generate the complex *in situ* complete conversions were observed even when TMSCN alone was used at room temperature. The results indicated that the Ti and Mn complex were effective catalysts, in terms of conversion, even though only slight enantioselectivity was observed (lower than when **63** and **64** were used).

To investigate the temperature effect, reactions were set up again at −15 °C. It was found that although the rate of the reactions was not too sluggish to obtain high % conversion, the Mn complex was still not efficient to induce the selectivity. Likewise, the efficiency of the Ti complex under the same conditions was also not much changed, and in fact, the selectivity was decreased (Table 3.9).

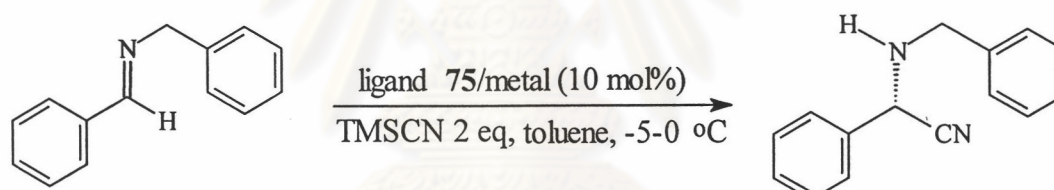**Table 3.9** Catalytic asymmetric Strecker reaction using complexes of **75** at −15 °C.
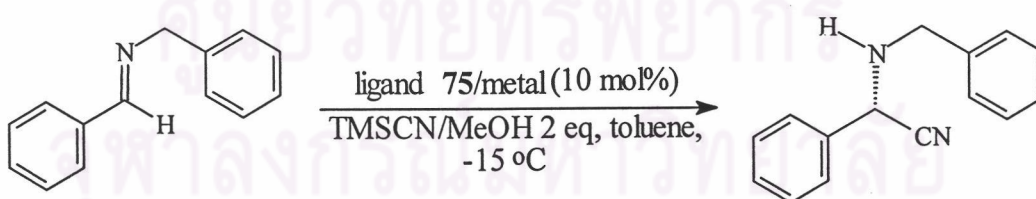
entry	metal	conv (%)	*ee* (%)
1	Ti(O^{i}Pr)$_4$	93	3
2	Mn(OAc)$_2$·4H$_2$O	95	0

Finally, the Strecker reactions catalyzed by metal complexes of ligand **75** generated *in situ* were repeated using TMSCN in toluene without MeOH at −5 to 0 °

C. It was found that after 9 hours, 85 and 97% conversion were observed for Ti and Mn complex, respectively (Table 3.10). Enantiomeric excess of the Ti complex was significantly better than what were previously obtained [15% *vs* 6% (TMSCN, at room temperature), 5% (TMSCN + MeOH, at −5 to 0 °C), and 3% (TMSCN + MeOH, −15 °C)]. When the Mn complex was used under the new condition, better enantioselectivities was also observed [11% *vs* 0% *ee* (TMSCN + MeOH, at −5 to 0 °C), 0% (TMSCN + MeOH, −15 °C)]. Again, interesting temperature effect was observed. While the enantioselectivity of the Mn complex was not very sensitive to temperature, e.g., both at room temperature and −5 to 0 °C, the *S* isomer was obtained in almost the same enantioselectivity (10 and 11% *ee*, respectively) and yield (97%). In the absence of MeOH, the Ti complex gave significantly better results at low temperature (6% at room temperature *vs* 15% at −5 to 0 °C) (Table 3.10).

Table 3.10 Catalytic asymmetric Strecker reaction using complexes of **75** at −5 to 0 °C.


entry	metal	conv (%)	*ee* (%)
1	Ti(O^{i}Pr)$_4$	85	15
2	Mn(OAc)$_2$•4H$_2$O	97	11

Since when the reactions were carried out using the better condition (TMSCN 2 eq in the absence of MeOH at −5 to 0 °C), the enantiomeric excess of the Strecker product was improved. MeOH might be out of place for the reactions which is in sharp contrast to many other published reports where *in situ* generated HCN from TMSCN and MeOH is the preferred cyanating reagent.[32] However, the difference in reactivities between the two cyanating agent, namely TMSCN and HCN have been previously noticed and utilized in the asymmetric strecker reaction using Al-BINOL complex.[32]

3.3.3 Amino alcohol Schiff base catalysts

-Synthesis of the catalysts
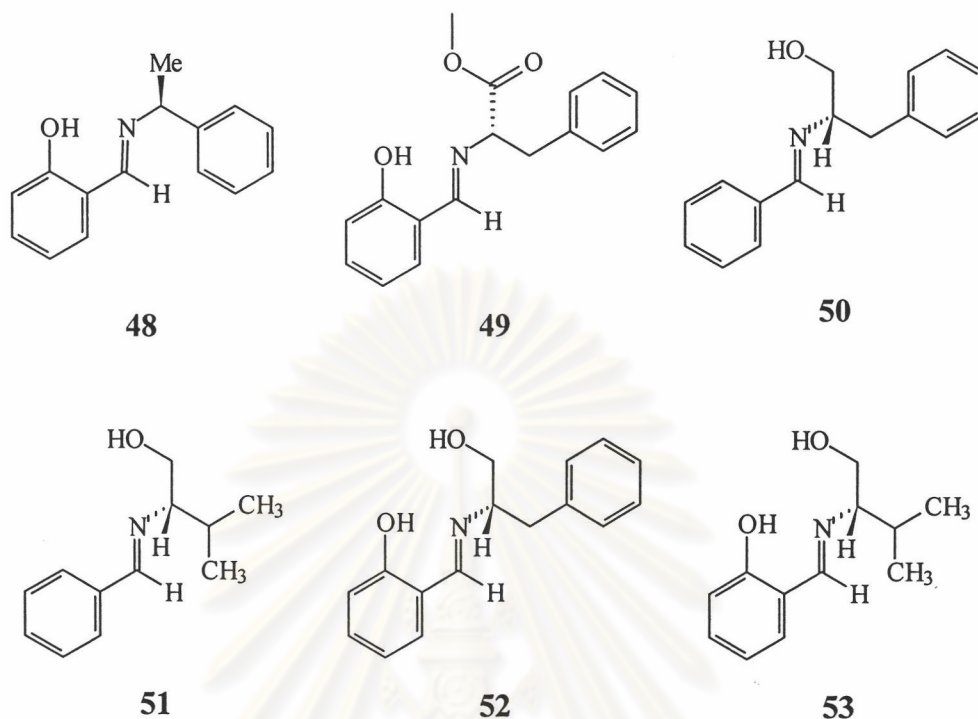
Figure 3.7 Various amino alcohol Schiff base catalysts of interest.

Similar to the synthesis of imines, synthesis of chiral Schiff base catalysts require the use of dehydrating agents. The catalysts were synthesized according to the literature procudure.[42,44,45] ^{1}H and ^{13}C NMR data indicated that the desired catalysts, **48**, **49**, **52**, and **53**, were obtained cleanly whereas additional signals was observed in the spectra of **50** and **51**. The tautomeric equilibrium between *N*-2-hydroxyethyl imines–oxazolidines is a well known phenomonon.[43] In cases of **50**, the chemical shifts of H* at 5.45, 5.60 ppm and C* at 92.0, 93.5 ppm indicated that such equilibrium existed (Figure 3.8).
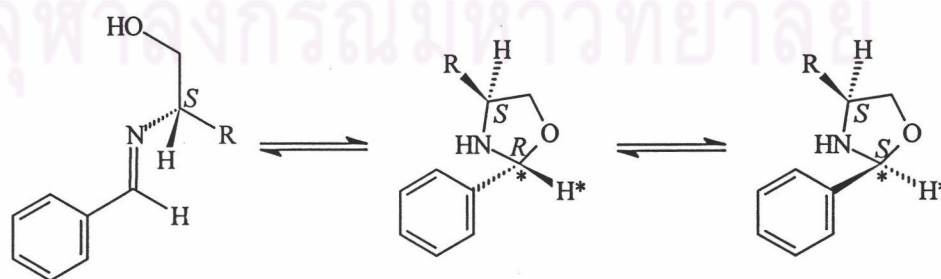

Figure 3.8 The tautomeric equilibrium between *N*-2-hydroxyethyl

imines–oxazolidines.

These tautomeric structures were in equilibrium and could not be separated by recrystallization. NMR data of **50** in CDCl$_3$ indicated that the imine form predominate the oxazolidine. NMR spectra of **51** showed the chemical shifts of ^{1}H* at 5.42, 5.44 ppm, and ^{13}C* at 92.6, 93.8 ppm, with an imine:oxazolidine peak ratio of 2:1. The cyclization is facilitated by the increased eletrophilicity of the C=N center. Therefore, similar tautomerization was not observed in **52** and **53** due to the fact that the influence of −OH on benzene ring made the C=N less electrophilic. Recognizing the origin of "impurities" observed in NMR spectra of **50** and **51**, no further attempts were made to purify the compounds.

-Asymmetric Strecker reaction

In addition to the C_2 symmetric salen catalysts and their polymeric analogues, a new chiral Schiff base group holding simple structure derived from chiral amino alcohol was investigated (**48-53**). These catalysts have been shown to be effective in asymmetric synthesis of cyanohydrins.[45] However, no use of such catalysts in asymmetric Strecker reactions have been previously reported in the literature. A preliminary reaction of TMSCN with **42** in the presence of 10 mol% of the chiral ligand (**48-53**) with Mn, Cu, Zn, Ti, Al, Yb, and Sc, generated *in situ*, were explored at room temperature. After 15 hours (method A), it was revealed that Mn(OAc)$_2$•4H$_2$O, Cu(OAc)$_2$•H$_2$O, ZnCl$_2$, TiCl$_4$, AlCl$_3$, Yb(OTf)$_3$, Sc(OTf)$_3$ and Zn(OAc)$_2$•2H$_2$O were ineffective co-catalysts, in terms of enantioselectivity. Likewise the use of **48-53** alone did not promote the desired selectivity (almost 100% conversion). Encouragingly, it was observed that chiral ligands **52** or **53** in combination with Mn(OAc)$_2$•4H$_2$O were the most effective catalyst systems in terms of conversion and enantioselectivity (the *R* isomer was preferentially formed in 7% *ee*) under −5 to 0 °C using TMSCN + MeOH (method C). In a similar procedure, reactions with a 10 mol% of complexes of **48-53** with Ti(O^{i}Pr)$_4$ generate *in situ*, were also investigated under −5 to 0 °C using TMSCN + MeOH (Table 3.11).

Table 3.11 Catalytic asymmetric Strecker reaction with metal complexes of ligand **48-53**.
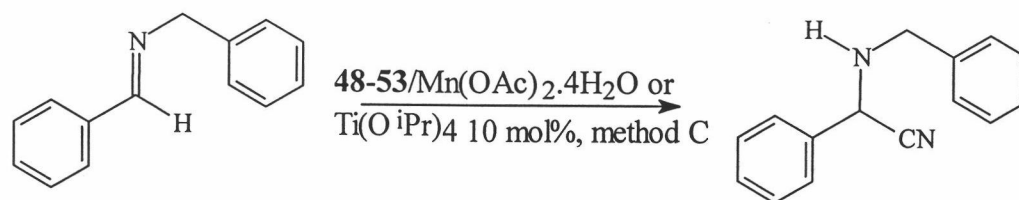
entry	ligand	ee (%)^a	ee (%)^b
1	48	0	0
2	49	0	0
3	50	0	0
4	51	0	0
5	52	7 (R)	0
6	53	7 (R)	7 (R)

^{a} using Mn(OAc)$_2$•4H$_2$O; ^{b} using Ti(O^{i}Pr)$_4$

From these preliminary results, further experiments were focused on **53** and the structurally similar **52**. Thus **52** and **53** were rescreened using Al(O^{i}Pr)$_3$ as co-catalyst at −5–0 °C using TMSCN + MeOH, unfortunately no selectivity was again observed.

To further explore the effect of very low temperature, asymmetric Strecker reaction with **52** and **53** in the presence of Mn(OAc)$_2$•4H$_2$O were repeated at −77 °C (dry ice-acetone), with the use of HCN as a cyanide source. It was found that at such very low temperature, the Strecker reaction product was not formed in a significant quantity. The results showed that this temperature was so low that the reactions could not proceed to completion. However, when the reaction mixture was warmed up to room temperature, the product was obtained in almost 100% yield. In both cases, Mn complexes of ligands **52** and **53** gave the product in 4% ee with the R isomer being the preferred enantiomer.

In light of these results, the Mn complexes of ligands **52** and **53** were also investigated at −5–0 °C by the slow addition of a solution of HCN.[31] Although quantitative conversion was obtained in both cases, no enantioselectivity was detected for **52** but a 5% ee (S isomer being preferred) was realized for **53**. In addition, catalyst **63** 5 mol% was also screen under slow addition condition by mixing 2 eq of TMSCN

in 1 mL of toluene, adding drop by drop at room temperature for 10 hours *via* syringe did not lead to increasing of % conversion and enantioselectivity. In other words, % conversion and % *ee* when adding TMSCN 2 eq all at once was the same as the slow reaction (24% *ee*).

In spite of numerous trials, the above-mentioned results revealed very poor enantioselectivity even in the most favorable cases (< 10% *ee*). We had always used the optimized conditions for cyanation which involved either using TMSCN alone at room temperature or using TMSCN + MeOH at –5–0 °C as screening protocols. Since these conditions showed moderate % *ee* with Jacobsen's catalyst **63, 64** without much difference in % *ee*, these conditions were used for all subsequent screening without realizing that the method of generating cyanide source might have profound effects on other catalyst systems. It was noticed that the condition using TMSCN alone at –5–0 ° C had never been attempted in spite of its high potential for increasing the selectivities due to the low temperature used and poorer source of CN nucleophile. Consequently, screening of catalyst **63** was again carried out under this new condition. It was found that the reaction product from this condition had enantioselectivity in 30% *ee* at 84% conversion. In terms of enantioselectivity, this was not much different from the earlier works using TMSCN + MeOH (Table 3.2, entries 5 and 6).

When the same screening condition was applied to the chiral Schiff base ligands **52** and **53** with Ti(O^{i}Pr)$_4$, a slight improvement in selectivity was observed. Under this condition, the catalyst system derived from **52, 53** and Ti(O^{i}Pr)$_4$ afforded up to 11 and 12% *ee* with *R* as the preferred enantiomer (Table 3.12).

Table 3.12 Catalytic asymmetric Strecker reaction using Ti complexes of ligand **48-53**.
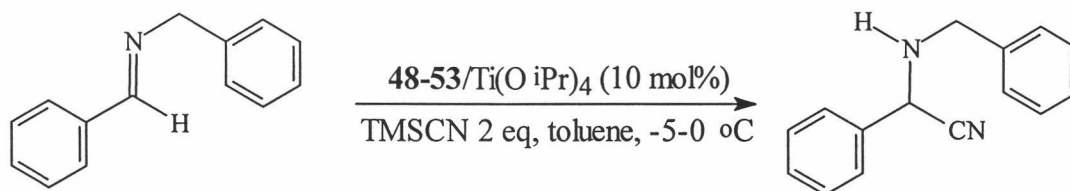
entry	ligand	time (h)	conv (%)	ee (%)
1	**48**	8	95	0
2	**49**	8	98	0
3	**50**	9	57	0
4	**51**	10	68	0
5	**52**	9	85	11 (*R*)
6	**53**	9	94	12 (*R*)

The results shown in Table 3.12 also confirmed that complexes of chiral ligands **48, 49, 50,** and **51** with $Ti(O^iPr)_4$ failed to give selectivity while the tridentate Schiff base complexes deriving from **52, 53** and $Ti(O^iPr)_4$ did.

The total results gave noteworthy attributes of the ligand structures employed in the reactions. That were **48** and **49**, each possessing a hydroxy substituent of the salicylimine moiety, were predicted to behave as bidentate ligands. While **50** and **51** possess the alcohol groups but lacking the salen-OH on benzene ring therefore they should also be capable of acting as bidentate ligands too. The structure of complexes formed from **48-51** could be depicted as follows:


possible ligand but e$^{\ominus}$ density is low because the oxygen is sp^2-hybridized

48   **49**
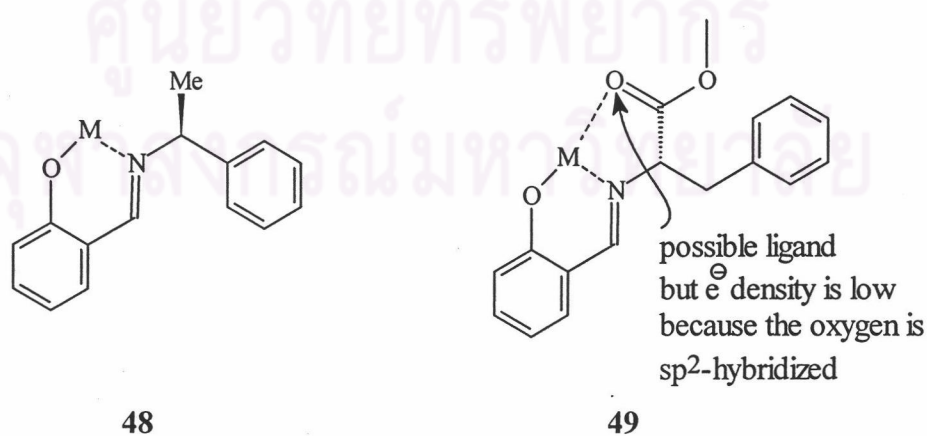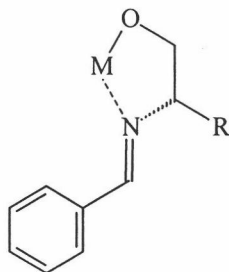
50: R = benzyl

51: R = isopropyl

In all cases, no effective complex formation would be expected when compared to the tridentate ligands **52** and **53**. In contrast to the former ligands, **52** and **53** had potential donor atoms both at the position of the salicylimine moiety and at the amino alcohol position.
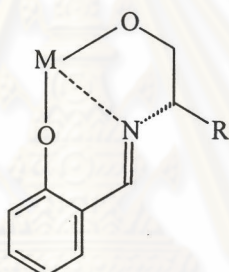

52: R = benzyl

53: R = isopropyl

The metal complexes of ligands **48**, **49**, **50**, and **51** can thus be predicted to be poor catalysts. On the other hand, tridentate Schiff base complexes derived from **52** and **53** seemed to be better from the structural point of view. There were confirmed by the observed experimental results above.

In addition, two ligands **76** and **77** containing salicylimine moiety and carboxylate group derived from L-leucine and L-valine, respectively were also investigated. The results were shown in Table 3.13.

76   **77**
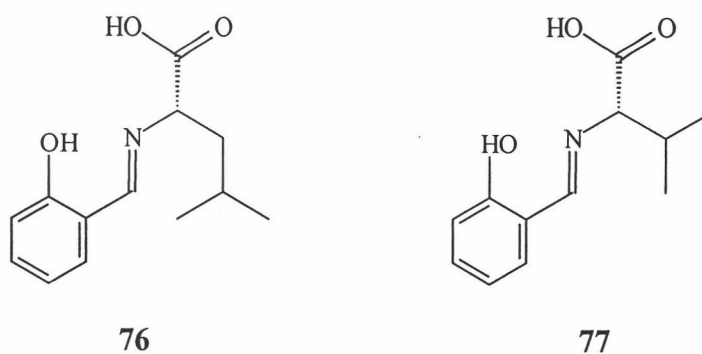
Table 3.13 Catalytic asymmetric Strecker reaction with Ti complexes of **76** and **77** using TMSCN in toluene at −5−0 °C.

| entry	ligand	time (h)	conv (%)	ee (%)
1	76	8	95	4 (R)
2	77	8	96	4 (R)

From Table 3.13, when **76** and **77** were employed, the R isomer was preferentially formed in 4% ee, although only a small selectivity was observed. It is interesting to note that the preferred isomer formed was the R which is in good agreement with the results obtained with the **52, 53** systems wherein the chiral carbon in the catalysts possessed the same S configuration. It is quite likely that the structure of the complexes formed and the mechanism of the catalytic asymmetric induction in the case of **52, 53** and **76** and **77** were the same (*vide infra*). It is therefore reasonable to propose that the presence of less electron-rich carboxylate groups as compared to the alkoxide group might be responsible for the lowered enantioselectivity.

The results indicated that the enantioselectivity was much influenced by the types of Schiff bases. Among the catalyst systems examined, the combination of Ti $(O^iPr)_4$ and the Schiff bases **52, 53** derived from salicylaldehyde and (S)-phenylalaninol (for **52**) or (S)-valinol (for **53**) gave the best results wherein the R-aminonitrile were obtained in good yield and modest selectivity (11 and 12% ee, respectively). The stereochemical outcome could be explained based on the analogous transition state model for the corresponding cyanosilylation of aldehyde.[45] This model assumed that the catalytic asymmetric trimethylsilylcyanation of imines was initiated by the coordination of imines to the coordinately unsaturated chiral Schiff base-titanium alkoxide complex. Trimethylsilyl cyanide would then react with the imine

coordinated to titanium from the *si* face of the activated imines leading to the formation of *R*-aminonitriles.

The preference of the *R* product appeared to be opposite to the cyanosilylation of aldehydes. This could be reasonably attributed to the different structure of the substrates as shown in Figure 3.9.
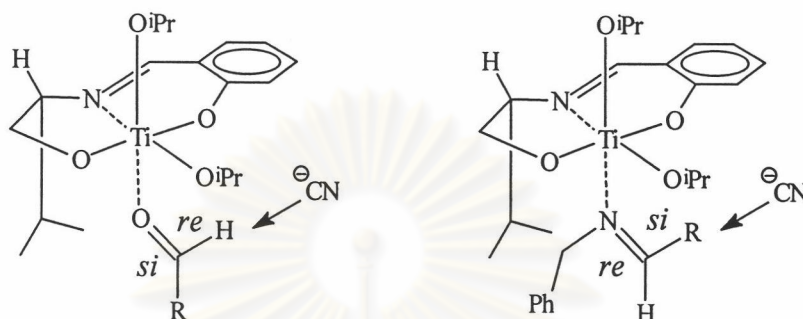

Figure 3.9 Transition state models comparing trimethylsilylcyanation to C=O and C=N.

3.3.4 Peptide Schiff base catalysts

Apart from the aforementioned Schiff base catalysts, we were also interested in novel Schiff base peptide ligands derived from amino acids and peptides **78-82**. Structures of **78-81** constituted Schiff base moiety, and peptide bond derived from sterically hindered amino acids such as L-valine and L-leucine. The Schiff base dipeptide ligands **82** contained salicylimine moiety and dipeptides derived from L-valine, L-leucine, and benzylamine (Figure 3.10).
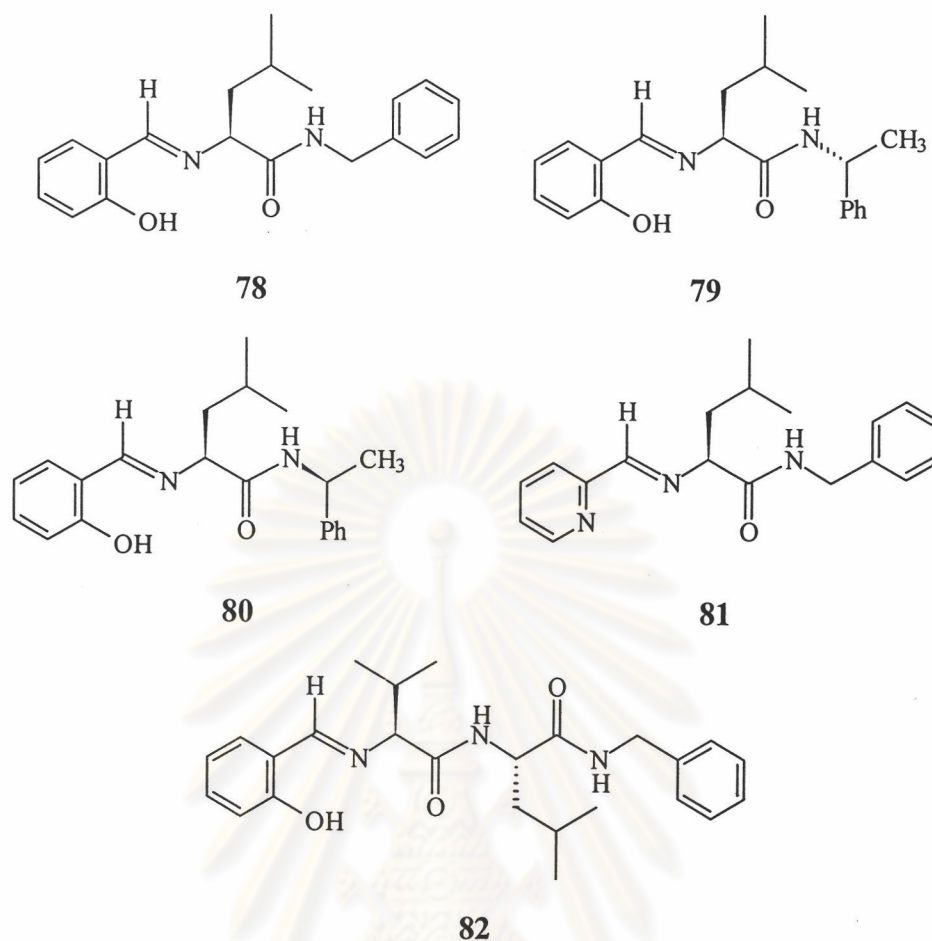
Figure 3.10 Various peptide Schiff base catalysts of interest.

Firstly, ligands **79**, **80**, and **82** were preliminary screened at room temperature using Ti(O^{i}Pr)$_4$ to generate the complex *in situ* under 2 eq of TMSCN. It was found that **79** complex slightly induced enantioselectivity in 4% *ee* with the *R* isomer being preferred and in almost quantitative conversion. Nevertheless, **80** complex differed from **79** complex. In other words, **80** complex as well as **82** complex were also able to promote enantioselectivity in 10 and 5% *ee*, respectively, with the *S* isomer being preferred and almost quantitative conversion. From these results, the reactions at low temperature were next attempted. The five Schiff base peptide ligands were examined to search for effective catalytic systems using the previously developed condition *i.e.* TMSCN 2 eq, toluene, −5 to 0 °C (Table 3.14).

Table 3.14 Catalytic asymmetric Strecker reaction using Ti complexes of **78-82**.
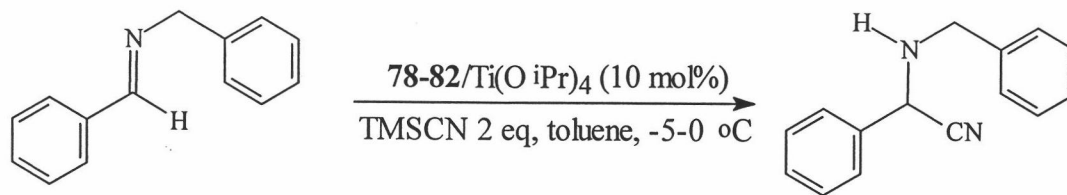
entry	ligands	conv (%)	ee (%)
1	**78**	94	7 (*S*)
2	**79**	96	23 (*R*)
3	**80**	94	40 (*S*)
4	**81**	65	0
5	**82**	91	8 (*S*)

As illustrated in the Table 3.14, **78, 79, 80,** and **82** containing salicylimine moiety could promote enantioselectivity in 7, 25, 40, and 8% *ee*, respectively. The corresponding Al complex failed to give any selectivity. Unlike Ti complex of **79**, *S*-aminonitrile was the preferred product of Strecker reactions catalyzed by **78, 80,** and **82**. The results suggested that the chiral center of the α-amino acid provide only little contribution to the enantioselectivity. At best only poor (7% *S*) selectivity was observed with the catalyst **78** derived from achiral benzylamine (Table 3.14, entry 1). It appeared that the configuration of the methylbenzylamine moiety influenced the stereoselectivity in a greater degree than the substituent at the amino acid residue. Interestingly, the sense of chiral induction depended solely on the configuration of the methylbenzylamine and not on the amino acid (Table 3.14, entries 2 and 3). With limited data available, it is difficult to draw too much conclusion and clearly further investigation is needed in order to understand the relationship of catalysts structure and their ability to induce stereoselectivity. Ligand **82** being a dipeptide gave poor selectivity and the *S* isomer was preferred while **81**, without the *ortho*-hydroxy substituent on the Schiff base moiety gave low yield and no selectivity (entry 4). We also investigated further the effect of MeOH in the reaction and found that the presence of MeOH resulted in decreased enantioselectivity and reproducibility (Table 3.15).

Table 3.15 Catalytic asymmetric Strecker reaction with metal complexes of
79-81 using TMSCN + MeOH at −5 to 0 °C.
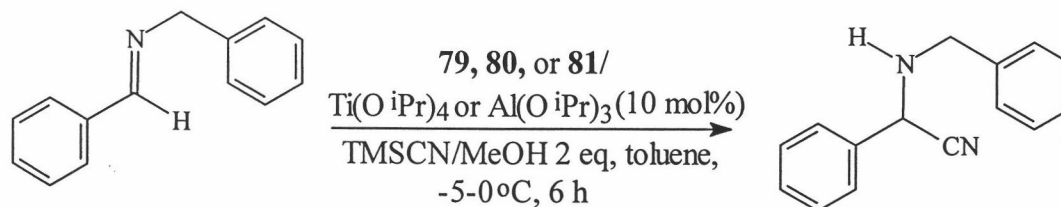
entry	ligand	conv (%), *ee* (%)^a	conv (%), *ee* (%)^b
1	**79**	97, 0	96, 0
2	**80**	95, 11 (*S*)	95, 0
3	**81**	95, 0	94, 0

^{a} using Ti(O^{i}Pr)$_4$; ^{b} using Al(O^{i}Pr)$_3$

From these preliminary results, it is shown that the metal complexes of peptide-Schiff base are another group of potential catalysts for further investigation. With suitable modification, even better *ee* would be anticipated. It should also be noted that this is the first report of successful simple monopeptide catalytic asymmetric Strecker reaction ever described. Even more so, an interesting relationship between structure of catalysts and enantioselectivity/ configuration of the products is emerging. This should lead to better understanding in design of new and more effective catalysts in the future.