ผลของหมู่แทนที่บนตัวเร่งปฏิกิริยาซาลิไซลิมีน ต่อการเลือกเกิดอิแนนทิโอเมอร์ของปฏิกิริยาสเตรคเกอร์แบบอสมมาตร

นางสาวศิริภรณ์ จิวพานิชย์

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EFFECT OF SUBSTITUENTS ON SALICYLIMINE CATALYSTS ON ENANTIOSELECTIVITY OF ASYMMETRIC STRECKER REACTION

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ศิริภรณ์ จิวพานิชย์: ผลของหมู่แทนที่บนตัวเร่งปฏิกิริยาซาลิไซลิมีนต่อการเลือกเกิดอิแนนทิโอเมอร์ของปฏิกิริยาสเตรคเกอร์แบบอสมมาตร (EFFECT OF SUBSTITUENTS ON SALICYLIMINE CATALYSTS ON ENANTIOSELECTIVITY OF ASYMMETRIC STRECKER REACTION) อ. ที่ปรึกษา: ผศ. ดร. มงคล สุขวัฒนาสินิทธิ์; อ.ที่ปรึกษาร่วม: ผศ.ดร. ธีรยุทธ วิไลวัลย์; 125 หน้า. ISBN 974-17-2518-3.

ได้สังเคราะห์อนุพันธ์ของซาลิไซลิมีนลิแกนด์ชนิดใหม่ ซึ่งประกอบด้วยส่วนของซาลิไซแลลดีไฮด์ แอลฟาอะมิโนแอซิด และไครัลเอมีน และได้ศึกษาสมบัติการเร่งปฏิกิริยาและการเลือกเกิดอิแนนทิโอเมอร์ของลิแกนด์เหล่านี้ในปฏิกิริยาสเตรคเกอร์แบบอสมมาตร พบว่า *N*-(3,5)-di-*tert*-butylsalicylyl-(*S*)-leucyl-(*S*)-(1-phenyl-ethyl)amine **((S,S)-S2-Leu-A1)** และ *N*-(3,5)-di-*tert*-butylsalicylyl-(*S*)-leucyl-(*S*)-(1-naphthyl-ethyl)amine **((S,S)-S2-Leu-A2)** เป็นลิแกนด์ที่ให้การเลือกเกิดอิแนนทิโอเมอร์สูงสุดเมื่อใช้เร่งปฏิกิริยาการเติมไซยาไนด์ของอะโรมาติกอิมมีนที่ไม่มีหมู่แทนที่แบบให้อิเล็กตรอนที่ตำแหน่งออร์โทและพารา โดยมีไทเทเนียมเตตระไอโซโพรพอกไซด์อยู่ร่วมในปฏิกิริยาด้วย กลไกการเร่งปฏิกิริยาเชื่อว่าเกิดผ่านสารประกอบเชิงซ้อนระหว่างซาลิไซลิมีนกับไทเทเนียม ซึ่งมีหมู่แทนที่ ที่อยู่บนซาลิไซแลลดีไฮด์และไครัลเอมีนวางตัวในตำแหน่งที่สามารถควบคุมการเข้าชนของไซยาไนด์ไอออน โดยที่คอนฟิกุเรชันของผลิตภัณฑ์ถูกกำหนดโดยคอนฟิกุเรชันของส่วนไครัลเอมีนมากกว่าส่วนที่เป็นอะมิโนแอซิด และความเกะกะของหมู่แทนที่บนวงซาลิไซแลลดีไฮด์มีผลต่อการเลือกเกิดอิแนนทิโอเมอร์อย่างมาก

ภาควิชา.....เคมี..... ลายมือชื่อนิสิต.....

สาขาวิชา.....เคมี..... ลายมือชื่ออาจารย์ที่ปรึกษา.....

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SIRIPORN JIWPANICH: EFFECT OF SUBSTITUENTS ON SALICYLIMINE CATALYSTS ON ENANTIOSELECTIVITY OF ASYMMETRIC STRECKER REACTION. THESIS ADVISOR: ASST. PROF. MONGKOL SUKWATTANASINITT, Ph.D.; THESIS CO-ADVISOR: ASST. PROF. TIRAYUT VILAIVAN, D.Phil., 125 pp. ISBN 974-17-2518-3.

A series of novel salicylimine ligands, constituted of salicylaldehyde, α-amino acid and chiral amine units, were synthesized. The catalytic activity and enantioselectivity of these ligands in the asymmetric Strecker reaction were explored. *N*-(3,5)-di-*tert*-butylsalicylyl-(*S*)-leucyl-(*S*)-(1-phenyl-ethyl)amine (**(*S*,*S*)-S2-Leu-A1**) and *N*-(3,5)-di-*tert*-butylsalicylyl-(*S*)-leucyl-(*S*)-(1-naphthyl-ethyl)amine (**(*S*,*S*)-S2-Leu-A2**) were proved to be the most effective ligands in catalyzing enantioselective cyanide addition to aromatic imines, containing neither *ortho*- nor *para*- electron donating substituents, in the presence of $Ti(O^iPr)_4$. The catalytic mechanism was likely to proceed through a salicylimine-Ti complex in which the substituent on salicylaldehyde and chiral amine units oriented in the direct sight of the attacking cyanide ion. The configuration of the product was largely controlled by the absolute configuration of the chiral amine moiety rather than the configuration of the α-amino acid part. The steroselectivity is strongly affected by steric effect of the substituents on the salicyl moiety.

Department……Chemistry…….Student's signature……Siriporn Jiwpanich……
Field of study….Chemistry…….Advisor's signature……Mongkol Sukwattanasinitt……
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List of Abbreviations

Å	auangstrom	Leu	leucine
Ar	aromatic	m	multiplet (NMR)
Boc	t-butoxycarbonyl	min	minute
br	broad	mL	milliliter (s)
°C	degree celsius	mmol	millimole
Cbz	benzyloxycarbonyl	mp.	melting point
cm^{-1}	unit of wave number	Nap	naphthyl
CSA	camphor-10-sulfonic acid	NMR	nuclear magnetic resonance
Conv.	conversion	OAc	acetate
d	doublet (NMR)	Ph	phenyl
dd	doublet of doublet (NMR)	Phe	phenylalanine
DCC	dicyclohexylcarbodiimide	Phg	phenylglycine
ee	enantiomeric excess	ppm	parts per million
eq.	equivalent	q	quartet (NMR)
Fig.	Figure	rt	room temperature
Fmoc	9-fluorenylmethoxycarbonyl	s	singlet (NMR)
Gly	glycine	t	triplet (NMR)
g	gram (s)	Temp.	temperature
h	hour (s)	TFAA	trifluoroacetic acid
His	histidine	Thr(^{t}Bu)	threonyl(*tert*-butyl)
HOBt	1-hydroxybenzotriazole	TMSCN	trimethylsilylcyanide
Hz	hertz	*t*Leu	*tert*-leucine
^{t}Bu	iso-butyl	Val	valine
Ile	isoleucine	μL	microliter
^{i}Pr	iso-propyl	δ	chemical shift
J	coupling constant		

CHAPTER I

INTRODUCTION

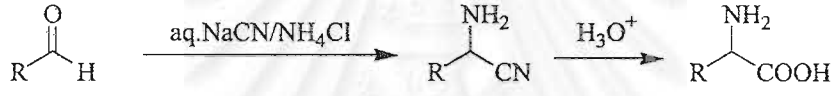
1.1 α-amino acid

Proteins are the main constituents of the body parts such as muscles, skin, hair and nails. They carry all vital life processes in the human system. The basic chemical units of proteins are α-amino acids. The structures of most α-amino acids consist of a chiral carbon atom (the α-carbon), which is bonded to an amino group ($-NH_2$), a carboxyl group (-COOH), and a hydrogen atom. Because the α-carbon of an α-amino acid is an asymmetric carbon, each α-amino acid can exist as two enantiomers. The two mirror images are called the L-isomer and the D-isomer. The amino acids present in living systems are almost exclusively L-isomers. The exceptions are a few D-amino acids present in the antibiotics produced by fungi.

To clarify the biological roles, various types of α-amino acids are desired not only in a field of organic chemistry but also in many biology-related areas. Nowadays, α-amino acid derivatives are considered to be important building blocks in the field of medicinal chemistry due to a variety of interesting biological properties. Besides, they are used as a mimicking models for studying mechanism of biological processes. For example, enzymes are catalytic proteins whose function is to accelerate chemical reactions in the body. Unnatural α-amino acids are expected to play roles in improving the original properties and functions of proteins. In addition, for a drug development, the screening of unnatural peptide or amino acid analogues is important to determine metabolic stability as well as to maximize biological response while minimizing toxicity. The synthesis of α-amino acids derivatives have thus been central to organic chemistry.

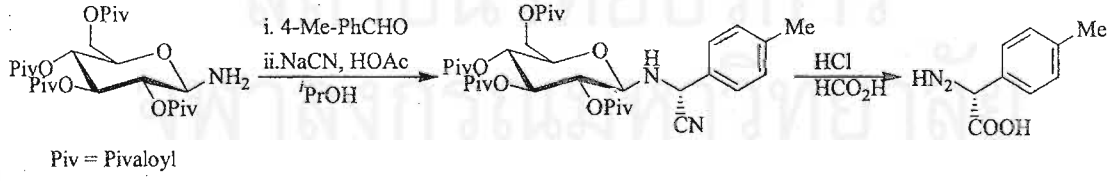
1.2 Strecker α-amino acid synthesis

There are several ways to synthesized α-amino acids, for example, by using nucleophilic substitution of α-halocarboxylic acids, alkylation of an acetamidomalonate, or Strecker synthesis. Among numerous synthetic routes to α-amino acids, the historical Strecker synthesis remains to be the most direct chemical access to this important class of compounds. The Strecker amino acid synthesis, which involves a treatment of an aldehyde or imine with ammonia and hydrogen cyanide (or its equivalent) followed by a hydrolysis of the α-amino nitrile intermediate to provide the corresponding α-amino acid (Scheme 1.1), was first reported in 1850.[1] This method has been applied on an industrial scale toward the synthesis of racemic α-amino acids due to the low cost of reagents involved.



Scheme 1.1 Classical Strecker synthesis of α-amino acids.

Optically pure α-amino acids can be obtained via the Strecker reaction with the use of chiral auxiliaries. For instance, α-arylethylamines, β-amino alcohols and derivatives, and sulfinates have been reported to provide α-amino nitriles with varying degree of diastereoselectivities (Scheme 1.2).



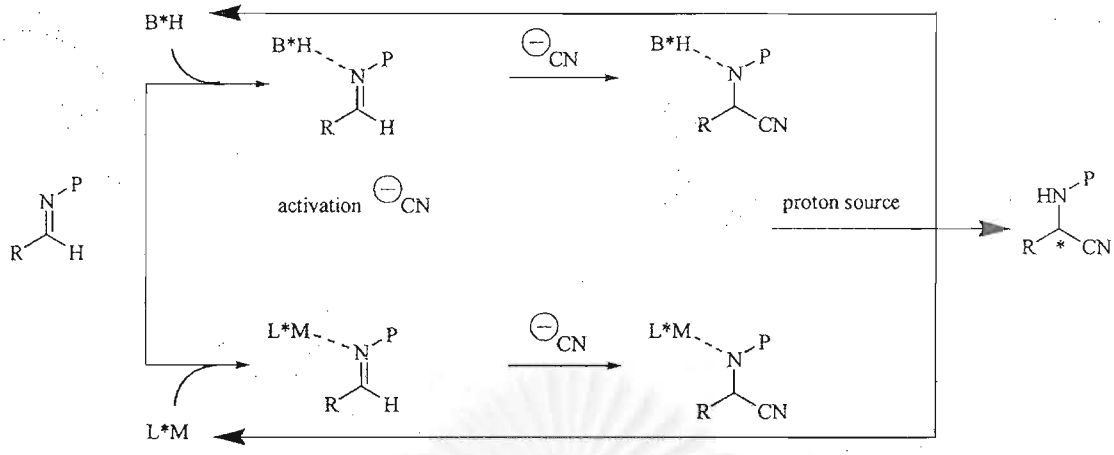
Scheme 1.2 a chiral auxiliary for the Strecker synthesis of (*S*)-configured amino acid.

Nevertheless, the use of a chiral auxiliary requires extra steps for its introduction into the substrate and removal from the product. Moreover, these chiral auxiliaries are often expensive and difficult to be recovered. These limitations

substantially hinder the use of this method for a large-scale synthesis of α-amino acids. On the other hand, catalytic Strecker type reaction requires only a small, reusable quantity of a chiral source to achieve a comparable degree of asymmetric induction. Since the chiral source is not incorporated into the substrate, not only does this approach require fewer steps, but it is also much more economical. The catalytic asymmetric Strecker-type reaction is one of the most direct and efficient methods for the asymmetric synthesis of natural and unnatural α-amino acids. This research reports new Ti-Schiff base complexes, as catalysts for improved enantioselectivity in the catalytic asymmetric Strecker reaction.

1.3 Literature review of the asymmetric Strecker synthesis

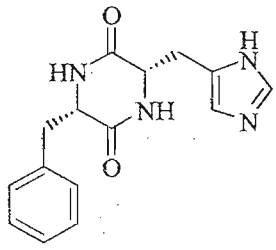
In general, catalytic, enantioselective Strecker-type reactions involve the addition of cyanide ion to an imine, either preformed or generated in situ from an amine and an aldehyde. Catalysis is accomplished by electrophilic activation of the imine, either by a Lewis acid or via noncovalent interactions such as hydrogen bonding (Scheme 1.3). In order for these processes to be catalytic, the species that is involved in the imine activation must be released after the addition of the cyanide. In some cases, an additive is needed to enhance the rate of this final step. Finally, asymmetric induction is achieved through the chiral environment provided by the catalyst. Currently, the catalysts are categorized into two general classes: guanidine-based compound and metal complexes. The former involves noncovalent activation, whereas the latter act as Lewis acid. Highly enantiomerically enriched α-amino nitrile adducts of various imines are obtained in good yields with these two catalytic systems.



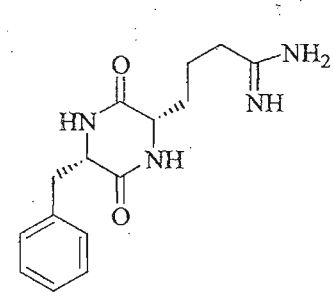
Scheme 1.3 Concept of imine activation.

1.3.1 Guanidine-Based Catalysts

An analogue of guanidine has been shown to catalyze the asymmetric cyanation of aldehydes. In 1990, Inoue and co-workers designed the use of cyclo[(*S*)-phenylalanyl-(*S*)-histidyl], **1** as a chiral catalyst with a histidine imidazole moiety. It was an excellent catalyst for the hydrocyanation reaction of various aldehydes giving good yields of cyanoalcohols with high enantiopurities.[4] However, it failed to afford any asymmetric induction in Strecker synthesis. This is because the imidazole side chain of **1** accelerated a proton transfer in the reaction of HCN with the putative aldimine intermediate in the Strecker reaction. In 1996, Lipton first demonstrated the use of **2** in a catalytic enantioselective Strecker-type reaction.[5] α-amino nitrile derivative **4** was obtained from *N*-benzhydryl imine **3** by using 2 mol % of (*S*)-α-amino-γ-guanidinobutyric acid **2** (Table 1.1). Excellent % *ee* and yields were obtained with aromatic imine, but low % *ee* was obtained with aliphatic substrates.

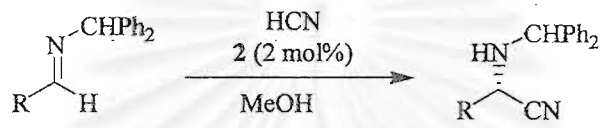


1 cyclo[(*S*)-phenylalanyl-(*S*)-histidyl]



2 (*S*)-α-amino-γ-guanidinobutyric acid

Table 1.1 Lipton's catalytic enantioselective Strecker-type reaction.



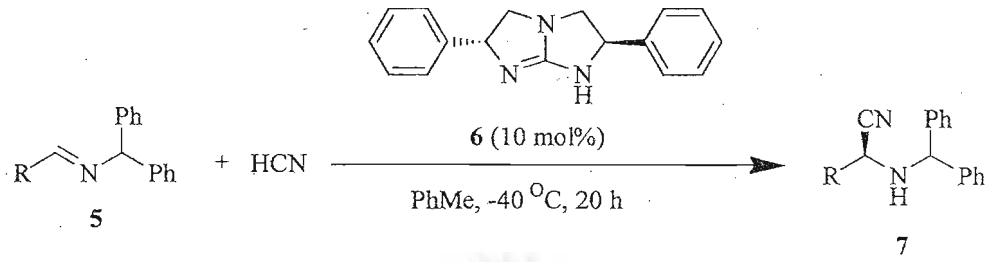
3 **4**

Imine	R	Temp, °C	Yield[a] (%)	*ee*[b] (%)
3a	Ph	-25	97	>99
3b	*p*-ClPh	-75	94	>99
3c	*p*-MeOPh	-75	90	96
3d	*t*-Butyl	-75	80	17

[a]Based on ^{1}H-NMR of crude product. [b]Determined by chiral HPLC chromatography using a Daicel ChiralPak AD column.

However, a few years later, another guanidine-based catalyst for Strecker-type reactions was reported by Corey with a full mechanistic proposal.[6] α-amino nitrile derivatives of benzhydryl imines were prepared in good yields with moderate %*ee* by using catalyst **6** (Table 1.2). The addition of hydrogen cyanide to achiral aromatic and aliphatic *N*-benzhydrylimines **5** gave *N*-benzhydryl-α-amino nitriles **7**, which were readily converted into the corresponding α-amino acids with 6 N HCl. The use of *N*-benzyl- or *N*-fluorenylimines afforded products of poor enantiomeric purity.

Table 1.2 Conversion of *N*-benzhydryl imines to α-amino nitrile in the presence of **6**.



Imines	R	Yield (%)	*ee* (%)
5a	Ph	96	86
5b	*p*-MeOPh	99	84

1.3.2 BINOL based Catalysts

Shibasaki and co-workers disclosed a general asymmetric Strecker-type reaction that was controlled by bifunctional Lewis acid-Lewis base catalyst **8**.[7] Aluminium complex **8** has been identified as a bifunctional catalyst because of its proposed dual activation of both the electrophile and nucleophile in the asymmetric cyanosilylation of aldehydes. As a result, the use of this catalyst has been extended to the enantioselective Strecker-type reaction.[8] The addition of phenol and trimethyl silyl cyanide (TMSCN) to the fluorenyl imine **9** at –40 °C in the presence of **8** afforded the corresponding α-amino nitrile **10** (Table 1.3). Good to excellent enantioselectivities and yields were obtained with aromatic imines. α-amino nitrile **10** (R = Ph) could then be converted to α-amino amide **11** in several steps. Aromatic, aliphatic, heterocyclic, and α,β-unsaturated imines **9** were used as general substrates in these reactions. The origin of the highly enantioselective catalysis by **8** was the simultaneous activation of imines and trimethylsilyl cyanide by the Lewis acid and the oxygen atom of the phosphine oxide, respectively. 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.

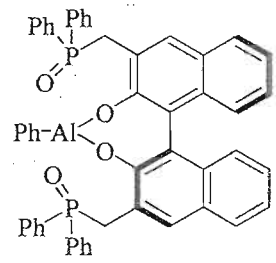


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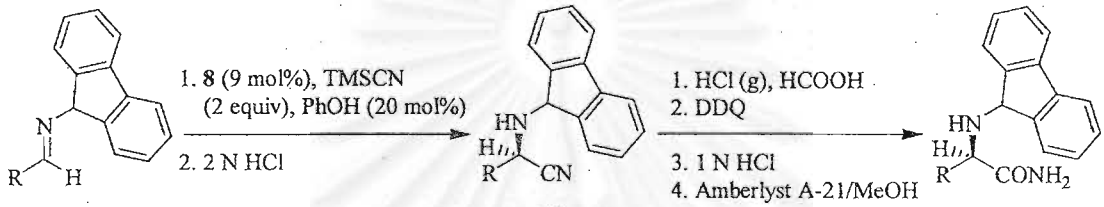
Table 1.3 Shibasaki's catalytic enantioselective Strecker-type reaction.

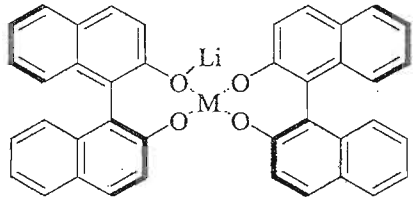


9 **10** **11**

Imines	R	Amino nitriles		Amino amides	
		Yield (%)[a]	*ee* (%)[b]	Yield (%)[a]	*ee* (%)[b]
9a	Ph	92	95	92	95
9b	3-furyl	92	90	92	87
9c	^{i}Pr	89	72	92	71
9d	^{t}Bu	97	78	98	77

[a]Yield of isolated product. [b]Determined by HPLC analysis.

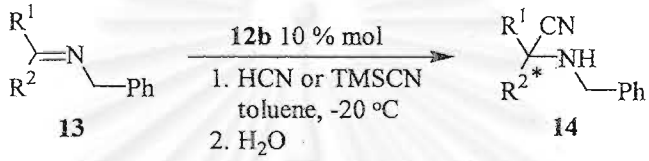
In 2001, Vallee and co-workers reported two new heterobimetallic complexes **12**, based on $BINOL_2$-lithium ligand with Al^{III} and Sc^{III} as metal centres.[9] The former using Al[(*R*)-$BINOL]_2$Li **12a** did not lead to an efficient catalytic system. Whereas, Sc[(*R*)-$BINOL)_2$Li **12b** gave 95 %*ee* when *N*-benzylidene-benzylamine was treated with TMSCN at –20 °C (Table 1.4). The enantioselectivity was slightly lower (81 %) when HCN was used as the cyanide source and when the substrate was a ketimine.



12a : M = Al^{III}
12b : M = Sc^{III}

12

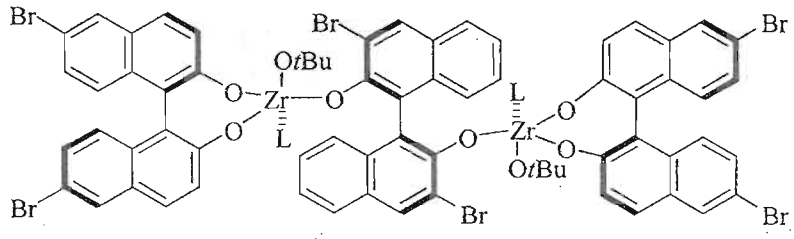
Table 1.4 Asymmetric hydrocyanation of imines catalyzed by Sc[(R)-BINOL]$_2$Li **12b**.



R^1	R^2	XCN	Time (h)	Conv. (%)[a]	*ee* (%)[b]
Ph	Me	TMSCN	1	50	95
Ph	Me	HCN	1 (-40 °C)	55	75
β-naphthyl	H	TMSCN	3	45	65
β-naphthyl	H	HCN	1	80	86

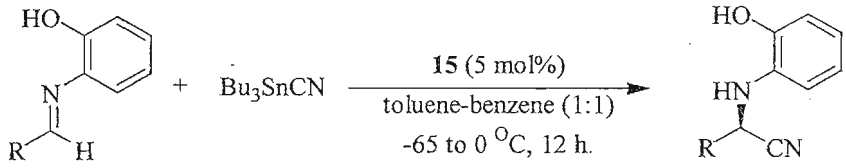
[a]Determined by ^{1}H NMR of the crude product. [b]Determined by chiral HPLC.

Recently, chiral zirconium catalysts have been shown to catalyze enantioselective Mannich-type reactions.[10] Studies of ligand modification around the zirconium center have led to the discovery of the Zirconium catalyst **15**.[11] Aromatic, aliphatic and heterocyclic aldehydes **16** reacted with Bu_3SnCN as a cyanide source produces the *α*-amino nitrile derivative **17**. Excellent *ee* and yields were obtained with aromatic, aliphatic and heterocyclic aldehydes (Table 1.5).[12]

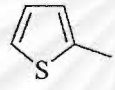


15

Table 1.5 Catalytic Asymmetric Strecker-Type Reaction Using Bu_3SnCN.



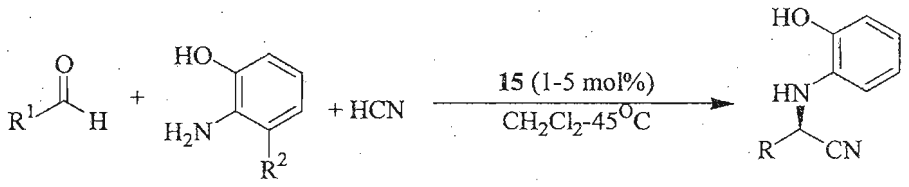
16 **17**

Imine	R	Yield (%)	*ee* (%)
16a	Ph	92	91
16b	1-Nap	98	91
16c		89	92
16d	^{t}Bu	79	83[a]
16e	C_8H_{17}	72	74[a]

[a]The imine was prepared from the corresponding aldehyde and 2-amino-3-methylphenol in situ in the presence of MS 4A.

In addition, it is noteworthy that Bu_3SnCN has been successfully used as a safe cyanide source, and that, after the reaction was completed, all tin sources were quantitatively recovered as bis(tributyltin)oxide, which has been converted to tributyltin chloride and to Bu_3SnCN. Furthermore, the catalytic asymmetric Strecker-type reaction starting from an achiral aldehydes **18**, amine **19**, and hydrogen cyanide using catalyst **15** to produce amino nitrile derivatives **20** was achieved. (Table 1.6)

Table 1.6. Catalytic asymmetric Strecker reactions using HCN.

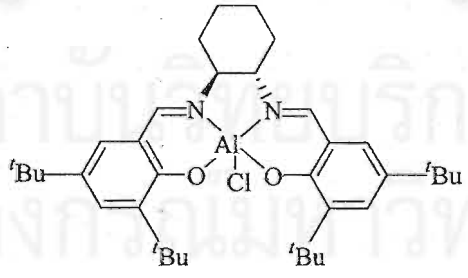


18 **19** **20**

Imine	R^1	R^2	Catalyst (mol %)	Yield (%)	*ee* (%)
20a	Ph	H	5	80	86
20b	α-Nap	H	5	83	85
20c	C_8H_{17}	CH_3	2.5	93	91
20d	^{t}Bu	CH_3	5	99	94

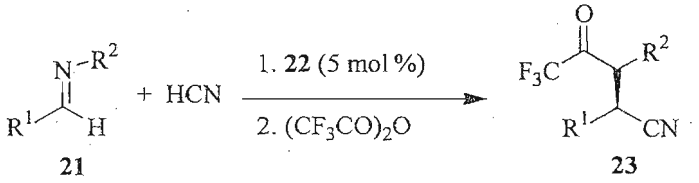
1.3.3 Salen based catalysts.

Another type of chiral metal complex that catalyzes enantioselective addition of cyanide ion to *N*-allylimine was reported by Jacobsen in 1998.[13] α-amino nitrile derivatives **23** of aromatic imines are obtained in good yields and high *ee* by treating the *N*-allyl imine **21** with HCN at –70 °C in the presence of chiral Al^{III}-salen complex **22** (salen = *N*,*N*'-bis(salicylidene)ethylenediamine dianion) (Table 1.7). However, the amino nitrile adducts of alkyl-substituted imines are obtained in moderate yields with low *ee*.



22

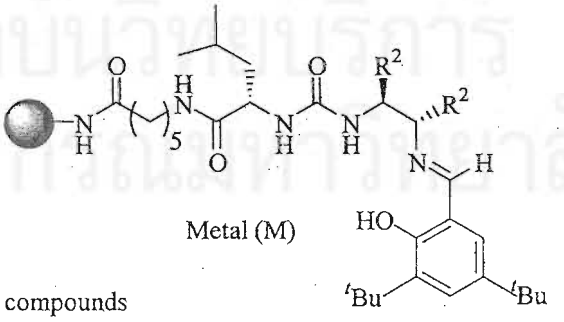
Table 1.7 Jacobsen's catalytic enantioselective Strecker-type reactions.



Imine	R^1	R^2	Yield (%)	*ee* (%)
21a	Ph	Allyl	91	95
21b	*p*-$MeOC_6H_4$	Allyl	93	91
21c	2-Nap	Allyl	93	93
21d	C_6H_{11}	Allyl	77	57
21e	^{t}Bu	Allyl	69	37
21f	^{t}Bu	Bn	88	49

In 1998, Jacobsen and co-workers showed three parallel libraries techniques for screening a known class of chiral half salen ligands which were more effective for the Strecker-type reaction (Figure 1.1).[14] Library 1 used for evaluating catalysis properties of a series of different metal ions. From this library, they found the Schiff base ligand without metal complex provided the best enantioselectivity (19 % *ee*). Library 2 and 3 are screening the ligand components, amino acid unit, stereochemistry, and substituents. From the library screening they found **24** to be the best ligand affording the highest enantioselectivity (Table 1.8).

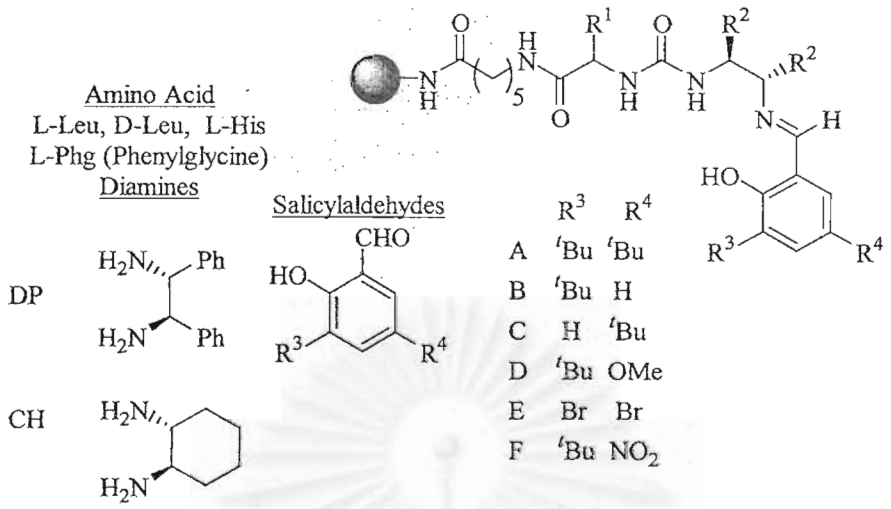
Library 1



Library Size : 12 compounds

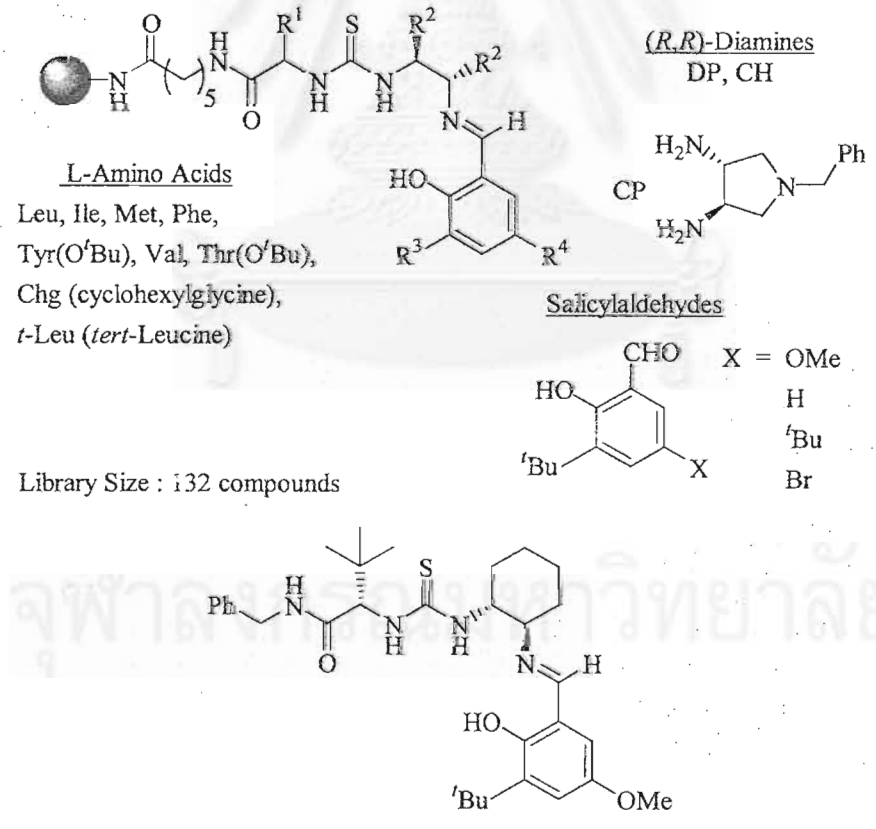
M	None	Ti	Mn	Fe	Ru	Co	Cu	Zn	Gd	Nd	Yb	Eu
ee (%)	19	4	5	10	13	0	9	1	2	3	0	5
Conv.(%)	59	30	61	69	63	68	55	91	95	84	94	34

Library 2



Library Size : 48 compounds

Library 3

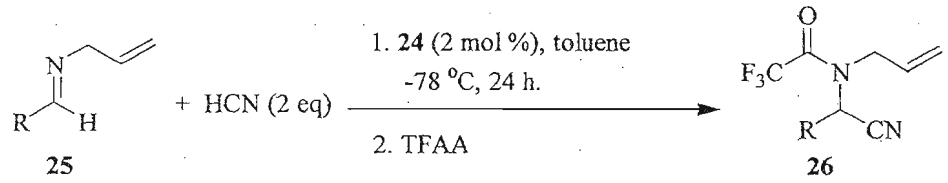


Library Size : 132 compounds

24

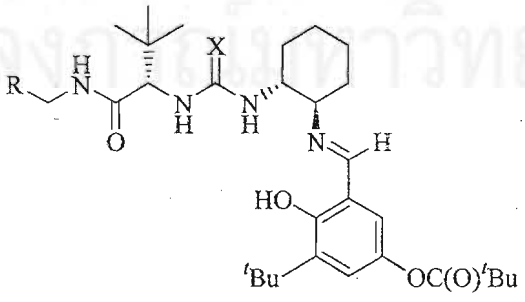
Figure 1.1 Ligand library for catalytic enantioselective Strecker-type reaction.

Table 1.8. Enantioselectivities obtained with Library 3.



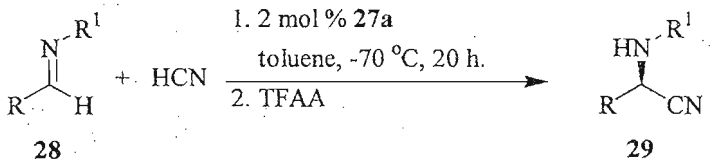
Imine	R	Yield (%)	*ee* (%)
25a	Ph	78	91
25b	*p*-$MeOC_6H_4$	92	70
25c	*p*-BrC_6H_4	65	86
25d	2-napthyl	88	88
25e	*tert*- butyl	70	85
25f	cyclohexyl	77	83

Moreover, Jacobsen and co-worker developed a new catalyst **27**, which gave good yield and high enantioselectivity on the addition of cyanide to either aromatic or aliphatic imines (Table 1.9).[15] These catalysts can be used either in solution or covalently linked to polystyrene resin. The key elements responsible for the high enantioselectivity were the presence of the bulky *tert*-butyl substituents at both the amino acid position and at the 3-position of the salicylimine moiety. Resin-bound catalyst **27b** allowed purification of the Strecker products by simple filtration and solvent removal, and the catalyst could be reused indefinitely without loss of either activity or enantioselectivity.



27a : R = polystyrene, X = S
27b : R = Ph, X = O

Table 1.9 Asymmetric catalytic Strecker reactions with catalyst **27a**.



28 **29**

Imine	R	R^1	Yield (%)	*ee* (%)
28a	Ph	allyl	74	95
28b	*tert*-butyl	allyl	75	95
28c	*p*-$MeOC_6H_4$	allyl	98	95
28d	*p*-BrC_6H_4	allyl	89	89
28e	*tert*-butyl	benzyl	88	96
28f	cyclohexyl	benzyl	85	87
28g	cyclohexyl	allyl	88	86

In 2002, Jacobsen and co-workers reported the structural and mechanistic studies for rational catalyst optimization.[16] The structure elucidated for the catalyst – substrate complex sheded substantial light on the basis for the scope and selectivity of asymmetric Strecker reactions with **27a**. (1) The large group on the imine carbon is directed away from the catalyst and into the solvent (Figure 1.2B). (2) The small group (H for aldimines, Me for methylketoimines) is aimed directly into the catalyst. (3) The *N*-substituent is also directed away from the catalyst (Figure 1.2 B, C). (4) On the basis of the observed sense of stereoinduction, addition of HCN takes place over the diaminocyclohexane portion of the catalyst (i.e., from the right-hand side in Figure 1.2C) and away from the amino acid/amide portion.

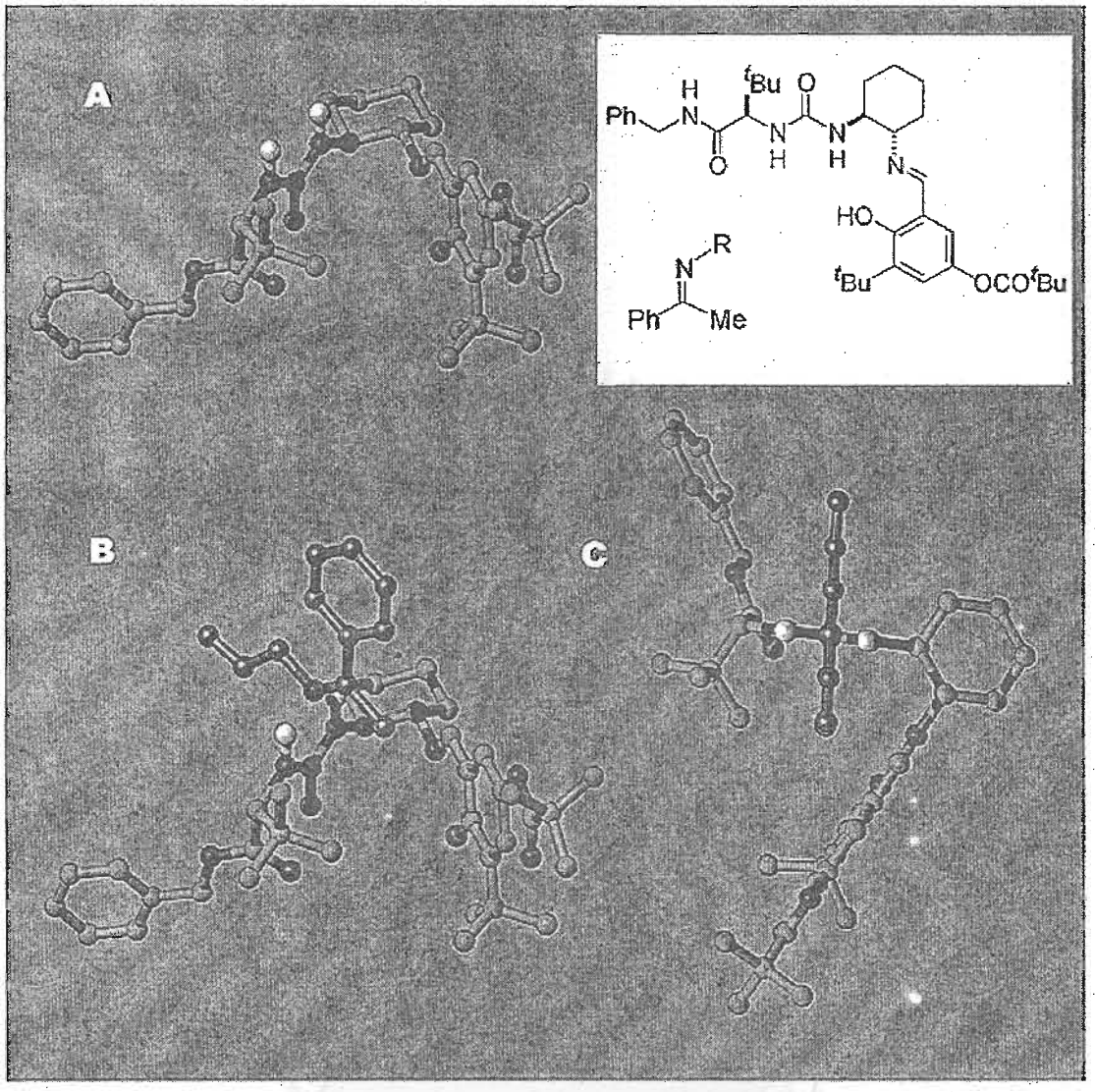
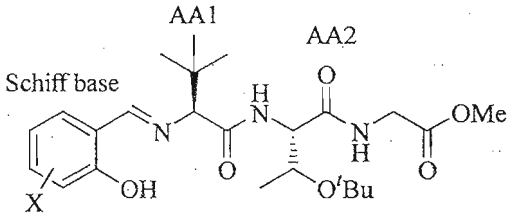


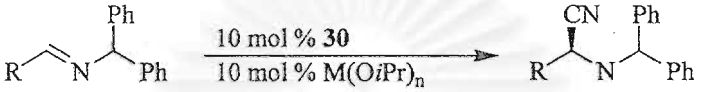
Figure 1.2 (A) Solution structure of catalyst **27b** and (B, C) two views of the complex generated upon binding of Z-imine, as determined by NMR analysis.

The combination of the Schiff base ligand **30** and titanium isopropoxide as a catalyst was identified through screening by Snapper and Hoveyda in 1999.[17] The addition of TMSCN to the imine **31** in the presence of **30** and titanium isopropoxide ($Ti(O^iPr)_4$), followed by a slow addtion of isopropanol (^iPrOH) provided the α-amino nitrile **32** which may then be converted to optically pure α-amino acid. Good yields and moderate to high *ee* are obtained with both aromatic and non-enolizable aliphatic aldehydes (Table 1.10).

Table 1.10 Ti-catalyzed enantioselective cyanide addition to imines.



30



31 **32**

Imine	R	X	Without added ^{i}PrOH Conv.(%), *ee* (%)	With added ^{i}PrOH Conv.(%), *ee* (%)
31a	Ph	5-CH_3O	30, 97	99, 97
31b	*o*-ClC_6H_4	3,5-diCl	22, 92	96, 93
31c	*o*-BrC_6H_4	3,5-diCl	15, 88	99, 94
31d	*p*-$MeOC_6H_4$	3,5-diCl	15, 84	100, 94
31e	2-Napthyl	5-CH_3O	20, 90	100, 93
31f	1-Napthtyl	5-CH_3O	25, 91	93, 90
31g	^{t}Bu	3,5-diBr	39, 88	100, 85

In 2001, Hoveyda and co-worker disclosed kinetic and structural data that, for the first time, shed light on one of the key transformations promoted by this class of chiral ligands.[18] The results showed that in affecting the Ti-catalyzed addition, these non-C_2 symmetric catalysts were likely to operate in a bifunctional manner. The Ti-Schiff base (**SB**) coordinates with the substrate, while an amide moiety within the peptide segment associates and delivers cyanide to the activated imine (Figure 1.3).

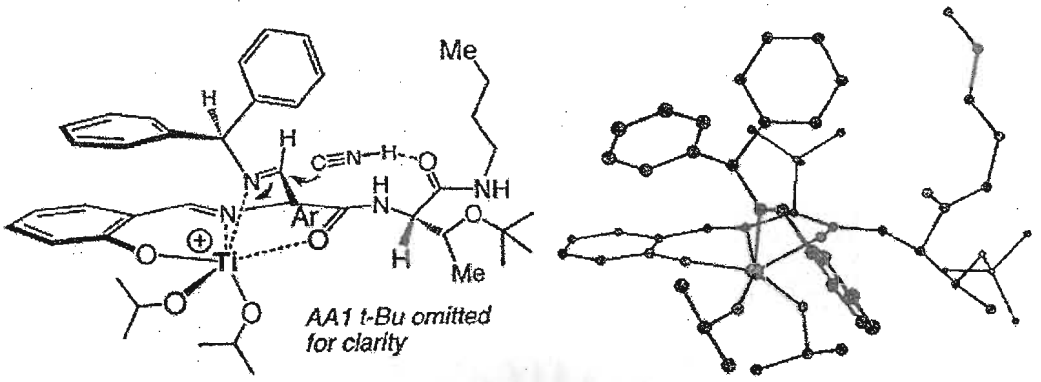
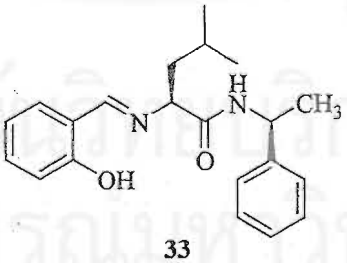


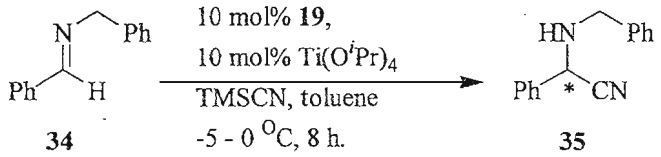
Figure 1.3 Cyanide addition catalyzed by Ti-tripeptide Schiff base complexes.

Experimental evidence and subsequent modeling studies indicate that proper disposition of different Lewis basic sites within the ligand structure allow the **SB** and amide carbonyls in **AA1** and **AA2** to provide complementary functions, giving rise to high yields and enantioselectivities.

In 2001, Mansawat showed a new class of catalytic asymmetric Strecker-type reaction employing a structurally simple salicylimine derived from peptide amide (**33**).[19] Noncomplexes structure of salicylimine catalyst which included the peptide and Schiff base group **33** was observed for catalytic activities. The addition of TMSCN to *N*-benzylimine **34** in the presence of **33** and Ti(^{i}OPr)$_4$ provides optically active α-aminonitrile **35** which preferred *S*-configuration in good yield and moderate enantiomeric excess (Scheme 1.4).



33



34 **35**

80-97 %, 40 %*ee*

Scheme 1.4 Asymmetric Strecker synthesis using Ti-peptide Schiff base catalyst.

1.4 Objectives of this research

Among the wide range of synthetic routes to α-amino acids, catalytic asymmetric Strcker-type reaction offers one of the most direct and viable methods. Salicylimine catalyst (Figure 1.4), the new class for catalytic asymmetric Strecker-type reaction showed interesting catalytic properties.

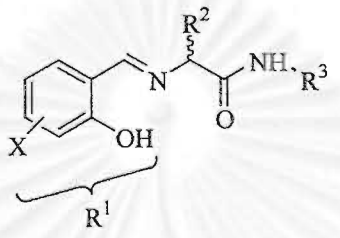


Figure 1.4 Salicylimine catalyst.

This research is aiming at synthesis of new enantioselective catalysts for strecker reaction based on salicylimines derived from α-aminoamides. Effects of substituents (R^1, R^2 and R^3) on salicylimine catalysts on enantioselectivity of the catalysts toward Strecker reaction were also investigated. We hope the results from this work will lead to efficient catalyst designs.

CHAPTER II

EXPERIMENTAL

2.1 General procedures and materials

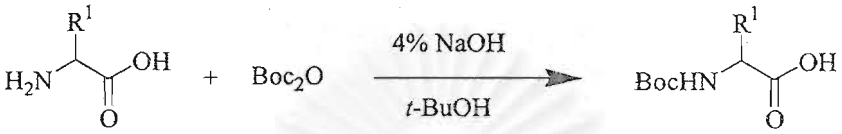
Air-sensitive materials were transferred by syringe. All commercial solvents for column chromatography were distilled prior to use. Dichloromethane and toluene were dried over molecular sieves UOP type 4A prior to use. Chiral amines, amino acids, di-*tert*-butyl dicarbonate, (+)-camphor-10-sulfonic acid, 1-hydroxybenzotriazole, *N*,*N*'-dicyclohexylcarbodiimide, *N*-benzyloxycarbonylglycine and analytical solvents were purchased from Fluka. Trimethylsilylcyanide, $Ti(O^iPr)_4$, chloroform-d and [*S*-(*R**,*R**)]-(-)-bis(α-methylbenzyl)amine were purchased from Aldrich Chemical Co.. Fmoc-Thr(*t*-Bu)-OH was purchased from Nova biochem. All chemical reagents were used as received.

The ^1H NMR spectra were acquired on a Bruker ACF200 (200 MHz) spectrometer and a Varian Mercury-400 BB (400 MHz). The chemical shifts are reported in ppm on the δ-scale with the solvent resonance ($CHCl_3$, δ 7.26) as an internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. ^{13}C NMR spectra were recorded on a Bruker ACF 200 spectrometer (at 50 MHz) with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance ($CHCl_3$, δ 77.0) as an internal reference.

The mass spectra (MS) were recorded on GC-MS GCQ Mas Finnigan Mat by using the Fast Atom Bombardment ionization (LR-FAB+) method. The melting points were measured on an Electrothermal 9100 melting point apparatus and were uncorrected. The optical rotations were measured at 26.2 °C with a Bellingham+ stanley Ltd. ADP220 polarimeter. The progress of all reactions was followed by thin layer chromatography (TLC) performed on Merck D.C. siliga gel 60 F254 0.2 mm

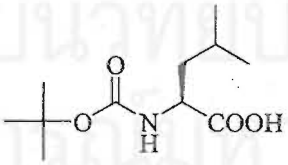
precoated aluminium plate and visualized by using either UV light (254 nm), iodine, or ninhydrin reagent. Column chromatography was performed on 63-200 mesh silica gel or activated neutral aluminium oxide 90, both purchased from Merck.

2.2 General procedure for preparation of *N-tert*-butoxycarbonyl-amino acid.



The amino acid (10 mmol) was dissolved with 4% NaOH (25 mL) in a 250 mL round bottomed flask. The solution was stirred and cooled to room-temperature then *tert*-butanol (10 mL) was added. To this mixture, a solution of Boc_2O (2.40 g, 11 mmol) in *t*-butanol (5 mL) was added dropwise to give a clear solution. Formation of an emulsion that usually gives a low yield of the desired product should be avoided. The mixture was stirred for 12 h. The solvent was removed by a rotary evaporator. The resulting thick solution was adjusted to pH 2 by addition of aq. HCl (2M) and then extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and was filtered. The filtrate was evaporated to give the crude product.

2.2.1 *N-tert*-butoxycarbonyl-(*S*)-leucine ((*S*)-Boc-Leu-OH).

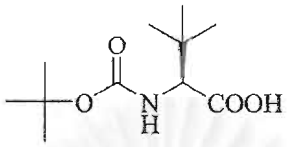


(*S*)-Boc-Leu-OH

This compound was prepared from the reaction of (*S*)-leucine (1.31 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acids described in section 2.2. The crude product was recrystallized from hexanes to give **(*S*)-Boc-Leu-OH** as clear plates (1.94 g, 8.4 mmol, 84% yield). ^1H NMR (200 MHz, $CDCl_3$) δ: 0.93 (6H, d, J = 6.0, $CH(C\underline{H}_3)_2$),

1.41 (9H, s, CC$\underline{H}_3$), 1.38-1.46 (3H, m, C$\underline{H}$(CH_3)$_2$ and C$\underline{H}_2$), 4.20-4.32 (1H, m, α-C$\underline{H}$), 4.95 (1H, d, J = 8.5, N$\underline{H}$), 6.45 (1H, br, O$\underline{H}$).

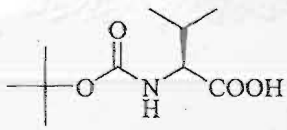
2.2.2 *N-tert*-butoxycarbonyl-(*S*)-*tert*-leucine ((*S*)-Boc-*t*Leu-OH).



(*S*)-Boc-*t*Leu-OH

This compound was prepared from the reaction of (*S*)-*tert*-leucine (1.31 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (1.83 g, 8.6 mmol, 86% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.97 (9H, s, CHC(C$\underline{H}_3$)$_3$), 1.40 (9H, s, OC(C$\underline{H}_3$)$_3$), 4.08 (1H, d, J = 9.5, α-C$\underline{H}$), 5.13-5.18 (1H, d, J = 9.5, N$\underline{H}$), 6.40 (1H, br, O$\underline{H}$).

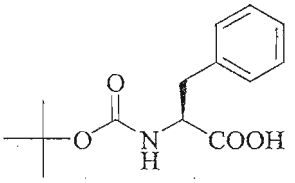
2.2.3 *N-tert*-butoxycarbonyl-(*S*)-valine ((*S*)-Boc-Val-OH).



(*S*)-Boc-Val-OH

This compound was prepared from the reaction of (*S*)-valine (1.71 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (1.95 g, 9.0 mmol, 90% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, d, J = 7.0, CH(C$\underline{H}_3$)$_2$), 0.97 (3H, d, J = 7.0, CH(C$\underline{H}_3$)$_2$), 1.40 (9H, s, OC (C$\underline{H}_3$)$_3$), 2.07-2.18 (1H, m, C$\underline{H}$(CH_3)$_2$), 4.22 (1H, dd, J = 4.5, 9.0, α-C$\underline{H}$), 5.07 (1H, d, J = 9.0, N$\underline{H}$), 7.00 (1H, br, O$\underline{H}$).

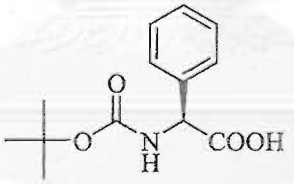
2.2.4 *N-tert*-butoxycarbonyl-(*S*)-phenylalanine ((*S*)-Boc-Phe-OH).



(*S*)-Boc-Phe-OH

This compound was prepared from the reaction of (*S*)-phenylalanine (0.65 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (2.25 g, 9.1 mmol, 91% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (9H, s, CH_3), 3.05-3.30 (2H, br, CH_2), 4.57-4.61 (1H, d, J = 7.0, α-CH), 5.05-5.09 (1H, br, NH), 6.10-6.25 (1H, br, OH), 7.15-7.33 (5H, m, ArH).

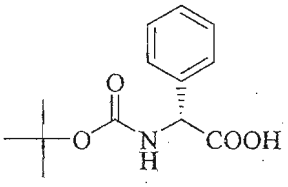
2.2.5 *N-tert*-butoxycarbonyl-(*S*)-phenyglycine ((*S*)-Boc-Phg-OH).



(*S*)-Boc-Phg-OH

This compound was prepared from the reaction of (*S*)-phenylglycine (1.51 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (2.20 g, 8.8 mmol, 88% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (9H, s, CH_3), 5.11 (1H, d, J = 5.5, α-CH), 7.24-7.39 (5H, br, ArH), 7.90 (1H, d, J = 5.5, NH).

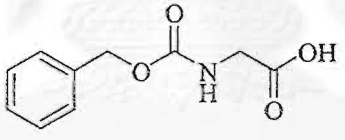
2.2.6 *N-tert*-butoxycarbonyl-(*R*)-phenylglycine ((*R*)-Boc-Phg-OH).



(*R*)-Boc-Phg-OH

This compound was prepared from the reaction of (*R*)-phenylglycine (0.76 g, 5 mmol) and Boc_2O (1.20 g, 5 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (1.2 g, 4.7 mmol, 94% yield). ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (9H, s, CH_3), 5.11 (1H, d, J = 5.0, α-CH), 7.30-7.40 (5H, br, ArH), 7.97 (1H, d, J = 4.5, NH).

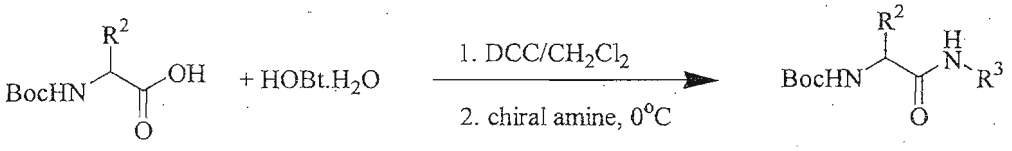
2.3 Preparation of *N*-benzyloxycarbonyl-glycine (Cbz-Gly-OH).



Cbz-Gly-OH

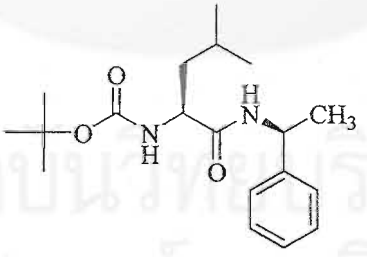
This compound was prepared from the reaction of glycine (0.37 g, 5 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (ZOSu) (1.23 g, 5 mmol) following the general procedure for preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (0.20 g, 0.96 mmol, 19% yield). ^1H NMR (200 MHz, $CDCl_3$) δ 4.02 (2H, d, J = 5.5, α-CH), 5.12 (2H, s, CH_2Ph), 5.20-5.32 (1H, br, NH), 6.25-6.40 (1H, br, OH), 7.29-7.38 (5H, m, ArH).

2.4 General procedure for condensation reaction between *N-tert*-butoxycarbonyl-amino acid and chiral amine.



To a solution of *N*-Boc-amino acid (1 mmol) and HOBt•H_2O (1 mmol) in CH_2Cl_2 (2 mL), DCC (1 mmol) in CH_2Cl_2 (1 mL) was added dropwise under N_2 gas. White precipitates were formed during the addition. The mixture was cooled to -5 - 0 °C and then chiral amine (1 mmol) was added through a micro syringe. After stirring for 3 h, the reaction mixture was filtered and the filtrate was treated with 5% HCl (3× 1 mL). The mixture was washed with 10% $NaHCO_3$ solution (3×1 mL). The organic layer was washed with water and dried over anhydrous $MgSO_4$. The solid was filtered off and the filtrate was evaporated by a rotary evaporator to give a crude product as a white solid. The product was further purified by column chromatography on silica gel (gradient from 10 % to 20 % ethyl acetate in hexanes) to give the desired product as a white solid.

2.4.1 *N*-Boc-(*S*)-leucyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Boc-Leu-A1).

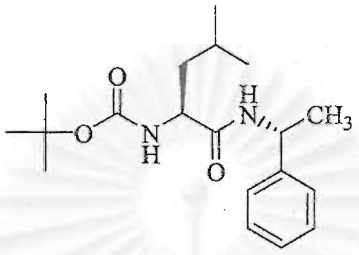


(*S*, *S*)-Boc-Leu-A1

This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.231g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.26 g, 0.73 mmol, 73 %), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 6.0, $CH(C\underline{H}_3)_2$), 0.89 (3H, d, J = 6.0, CH

($C\underline{H}_3)_2$), 1.41 (9H, s, $OC(C\underline{H}_3)_3$), 1.65 (3H, d, J = 7.0, $CHPhC\underline{H}_3$), 1.53-1.68 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 4.04-4.06 (1H, m, α-C<u>H</u>), 4.93-4.96 (1H, br, N<u>H</u>Boc), 5.03-5.10 (1H, m, C<u>H</u>Ph), 6.57 (1H, d, J = 7.0, N<u>H</u>CHPh), 7.19-7.35 (5H, m, Ar<u>H</u>).

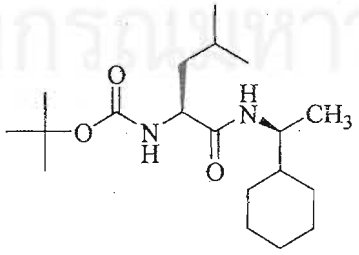
2.4.2 *N*-Boc-(*S*)-leucyl-(*R*)-(1-phenylethyl)amine ((*S*, *R*)-Boc-Leu-A1).



(*S*, *R*)-BocNH-Leu-A1

This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), $HOBt{\bullet}H_2O$ (0.14 g, 1 mmol), DCC (0.21 g, 1 mmol) and (*R*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.27 g, 0.77 mmol, 77 %), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (6H, d, J = 6.0, $CH(C\underline{H}_3)_2$), 1.40 (9H, s, $C(C\underline{H}_3)_3$), 1.45 (3H, d, J = 7.0, $CHPhC\underline{H}_3$), 1.60-1.75 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.96-4.07 (1H, m, α-C<u>H</u>), 4.93-4.96 (1H, br, N<u>H</u>Boc), 5.03-5.10 (1H, q, J = 7.0, C<u>H</u>Ph), 6.56-6.58 (1H, br, N<u>H</u>CHPh), 7.19-7.35 (5H, m, Ar<u>H</u>).

2.4.3 *N*-Boc-(*S*)-leucyl-(*S*)-(1-cyclohexylethyl)amine ((*S*, *S*)-Boc-Leu-A4).

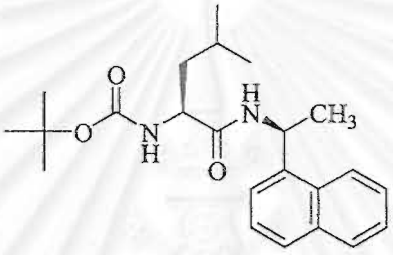


(*S*, *S*)-Boc-Leu-A4

This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), $HOBt{\bullet}H_2O$ (0.14 g, 1 mmol), DCC (0.21g, 1 mmol) and (*S*)-

cyclohexylethylamine (149 μL, 1 mmol) following the general procedure for the condensation reaction between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.23 g, 0.68 mmol, 68 %), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (6H, d, J = 8.5, $CH(C\underline{H}_3)_2$), 0.93-1.28 (11H, m, cyclohexyl), 1.08 (3H, d, J = 9.0, $CH(cyclo)C\underline{H}_3$), 1.41 (9H, s, $C(C\underline{H}_3)_3$), 1.61-1.73 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.73-3.84 (1H, m, $C\underline{H}(cyclo)CH_3$), 3.94-4.05 (1H, m, α-$C\underline{H}$), 4.85-4.90 (1H, br, $N\underline{H}$), 6.00 (1H, d, J = 8.5, $N\underline{H}Boc$).

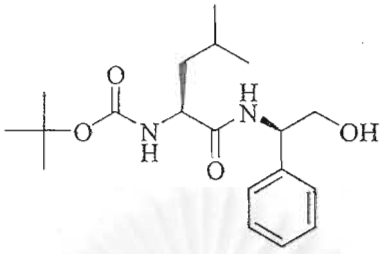
2.4.4 *N*-Boc-(*S*)-leucyl-(*S*)-(1-naphthylethyl)amine ((*S*, *S*)-Boc-Leu-A2).



(*S*, *S*)-Boc-Leu-A2

This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), $HOBt{\bullet}H_2O$ (0.14 g, 1 mmol), DCC (0.21 g, 1 mmol) and (*S*)-napthylethylamine (160 μL, 1 mmol) following the general procedure for the condensation reaction between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.25 g, 0.68 mmol, 68%), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (6H, d, J = 5.0, $CH(C\underline{H}_3)_2$), 1.41 (9H, s, $C(C\underline{H}_3)_3$), 1.63 (3H, d, J = 6.7, $CH(1\text{-naph})C\underline{H}_3$), 1.69-1.71 (3H, m, $C\underline{H}(CH_3)_2$) and $C\underline{H}_2$), 3.95-4.02 (1H, m, α-$C\underline{H}$) 4.85-5.00 (1H, br, $N\underline{H}Boc$), 5.81-5.95 (1H, m, J = 8.0, $C\underline{H}(1\text{-naph})CH_3$), 6.46 (1H, d, J = 8.0, $N\underline{H}$), 7.39-7.52 (4H, m, $Ar\underline{H}$), 7.75-7.86 (2H, m, $Ar\underline{H}$), 8.05 (1H, d, J = 9.0, $Ar\underline{H}$).

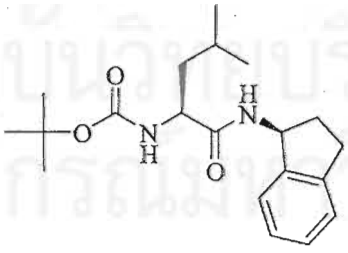
2.4.5 *N*-Boc-(*S*)-leucyl-(*S*)-(1-phenyl-2-hydroxyethyl)amine ((*S*, *S*)-Boc-Leu-A3).



(*S*, *S*)-Boc-Leu-A3

This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.15 g, 0.7 mmol), HOBt•H_2O (0.09 g, 0.7 mmol), DCC (0.14 g, 0.7 mmol) and (*S*)-phenylglycinol (0.09 g, 0.7 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.15 g, 0.43 mmol, 62 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, d, J = 5.5, CH($C\underline{H}_3$)$_2$), 0.91 (3H, d, J = 4.5, CH ($C\underline{H}_3$)$_2$), 1.41 (9H, s, C($C\underline{H}_3$)$_3$), 1.51-1.64 (3H, m, C$\underline{H}$(CH_3)$_2$ and $C\underline{H}_2$), 3.13-3.22 (1H, br, O$\underline{H}$), 3.80-3.92 (2H, m, $C\underline{H}_2$OH), 4.05-4.20 (1H, m, α-C$\underline{H}$), 5.03-5.12 (1H, m, C$\underline{H}$Ph), 6.97 (1H, d, J = 7.5, N$\underline{H}$), 7.25-7.33 (5H, m, Ar$\underline{H}$).

2.4.6 *N*-Boc-(*S*)-leucyl-(*S*)-(1-indanyl)amine ((*S*, *S*)-Boc-Leu-A5).

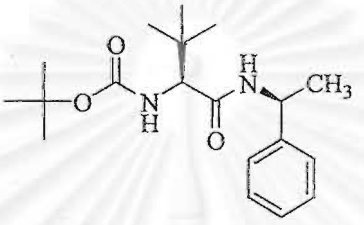


(*S*, *S*)-Boc-Leu-A5

This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), HOBt•H_2O (0.13 g, 1 mmol), DCC (0.21 g, 1 mmol) and (*S*)-1-aminoindane (85 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was

obtained as a white solid (0.27 g, 0.79 mmol, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-0.95 (6H, m, $CH(C\underline{H}_3)_2$), 1.42 (9H, s, $C(C\underline{H}_3)_3$), 1.51-1.68 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 2.54-2.63 (2H, m, $CHCH_2C\underline{H}_2$), 2.82-2.90 (1H, m, α-C<u>H</u>), 2.94-3.02 (2H, m, $CHC\underline{H}_2$), 5.43-5.48 (1H, m, C<u>H</u>(indane)), 6.31-6.41 (1H, br, N<u>H</u>), 7.19-7.24 (4H, m, Ar<u>H</u>).

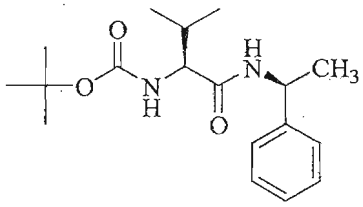
2.4.7 *N*-Boc-(*S*)-*tert*-leucyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Boc-*t*Leu-A1).



(*S*, *S*)-Boc-*t*Leu-A1

This compound was prepared from the reaction of (*S*)-Boc-*t*Leu-OH (0.693 g, 3 mmol), $HOBt{\cdot}H_2O$ (0.406 g, 3 mmol), DCC (0.619 g, 3 mmol) and (*S*)-methylbenzylamine (381 μL, 3 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.19 g, 0.5 mmol, 19 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (9H, s, $CH(C\underline{H}_3)_3$), 1.41 (9H, s, $C(C\underline{H}_3)_3$), 1.47 (3H, d, J = 7.0, $CHC\underline{H}_3$), 3.74 (1H, d, J = 9.0, α-C<u>H</u>), 5.02-5.13 (1H, m, J = 7.5, C<u>H</u>Ph), 5.25 (1H, d, J = 9.0, N<u>H</u>Boc), 5.96 (1H, d, J = 7.5, N<u>H</u>CH(Ph)CH_3), 7.20-7.36 (5H, m, Ar<u>H</u>).

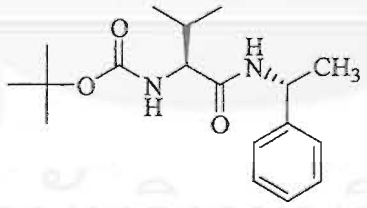
2.4.8 *N*-Boc-(*S*)-valyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Boc-Val-A1).



(*S*, *S*)-Boc-Val-A1

This compound was prepared from the reaction of **(*S*)-Boc-Val-OH** (0.217 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.27 g, 0.86 mmol, 86%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 0.88 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 1.40 (9H, s, $OC(C\underline{H}_3)_3$), 1.46 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 1.95-2.20 (1H, m, $C\underline{H}(CH_3)_2$), 3.83 (1H, dd, J = 6.5, 8.5, α-C<u>H</u>), 5.06-5.13 (1H, m, $C\underline{H}(Ph)CH_3$), 6.31-6.34 (1H, br, N<u>H</u>), 7.19-7.33 (5H, m, Ar<u>H</u>).

2.4.9 *N*-Boc-(*S*)-Valyl-(*R*)-(1-phenylethyl)amine ((*S*, *R*)-Boc-Val-A1).

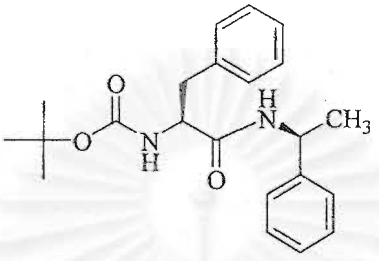


(*S*, *R*)-Boc-Val-A1

This compound was prepared from the reaction of **(*S*)-Boc-Val-OH** (0.217 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*R*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.23 g, 0.86 mmol, 86 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 0.88 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 1.40 (9H, s, $OC(C\underline{H}_3)_3$), 1.46 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 1.95-2.20 (1H, m,

C<u>H</u>(CH$_3$)$_2$), 3.83 (1H, dd, J = 6.5, 8.5, α-C<u>H</u>), 5.06-5.13 (1H, m, C<u>H</u>(Ph)CH$_3$), 6.31-6.34 (1H, br, N<u>H</u>), 7.19-7.33 (5H, m, Ar<u>H</u>).

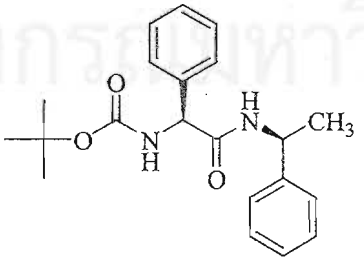
2.4.10 *N*-Boc-(*S*)-phenylalanyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Boc-Phe-A1).



(*S*, *S*)-Boc-Phe-A1

This compound was prepared from the reaction of **(*S*)-Boc-Phe-OH** (0.269 g, 1 mmol), HOBt•H$_2$O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.29 g, 0.79 mmol, 79 %). ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.30 (9H, s, OC(C<u>H</u>$_3$)$_3$), 1.40 (3H, d, J = 6.0, CH(Ph) C<u>H</u>$_3$), 3.02 (2H, t, J = 6.0, C<u>H</u>$_2$), 4.20-4.30 (1H, m, α-C<u>H</u>), 5.46-5.06 (1H, m, J = 8.0, C<u>H</u>(Ph)CH$_3$), 6.00 (1H, d, J = 8.0, N<u>H</u>), 7.09-7.26 (10H, m, Ar<u>H</u>).

2.4.11 *N*-Boc-(*S*)-phenylglycyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Boc-Phg-A1).

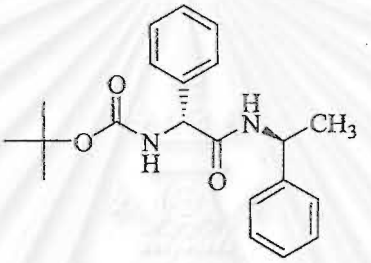


(*S*, *S*)-Boc-Phg-A1

This compound was prepared from the reaction of **(*S*)-Boc-Phg-OH** (0.251 g, 1 mmol), HOBt•H$_2$O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-

methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.18 g, 0.51 mmol, 51%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (9H, s, $OC(C\underline{H}_3)_3$), 1.45 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 5.02-5.12 (2H, m, α-C<u>H</u> and C<u>H</u>(Ph)CH_3), 5.88 (1H, d, J = 7.5, N<u>H</u>), 6.98-7.03 (2H, m, Ar<u>H</u>), 7.18-7.35 (8H, m, Ar<u>H</u>).

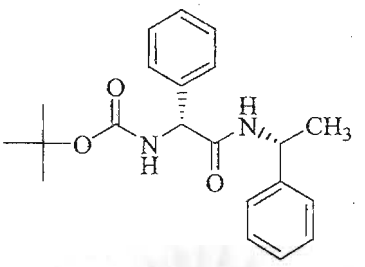
2.4.12 *N*-Boc-(*R*)-phenylglycyl-(*S*)-(1-phenylethyl)amine ((*R*, *S*)-Boc-Phg-A1).



(*R*, *S*)-Boc-Phg-A1

This compound was prepared from the reaction of **(*R*)-Boc-Phg-OH** (0.251 g, 1 mmol), $HOBt{\bullet}H_2O$ (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.16 g, 0.4 mmol, 40 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (9H, s, $OC(C\underline{H}_3)_3$), 1.44 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 5.02-5.11 (2H, m, α-C<u>H</u> and C<u>H</u>(Ph)CH_3), 6.00 (1H, d, J = 7.5, N<u>H</u>), 6.98-7.03 (2H, m, Ar<u>H</u>), 7.16-7.35 (8H, m, Ar<u>H</u>).

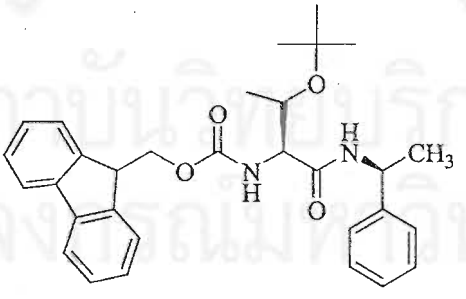
2.4.13 *N*-Boc-(*R*)-phenylglycyl-(*R*)-(1-phenylethyl)amine ((*R*, *R*)-Boc-Phg-A1).



(*R*, *R*)-Boc-Phg-A1

This compound was prepared from the reaction of **(*R*)-Boc-Phg-OH** (0.251 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*R*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.27 g, 0.77 mmol, 77 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (9H, s, $OC(C\underline{H}_3)_3$), 1.44 (3H, d, J = 7.0, CH(Ph) $C\underline{H}_3$), 5.02-5.11 (2H, m, α-C<u>H</u> and C<u>H</u>(Ph)CH_3), 6.00 (1H, d, J = 7.5, N<u>H</u>), 6.98-7.03 (2H, m, Ar<u>H</u>), 7.16-7.35 (8H, m, Ar<u>H</u>).

2.4.14 *N*-Fmoc-(*S*)-threonyl(*tert*-butyl)-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Fmoc-Thr(^{t}Bu)-A1).

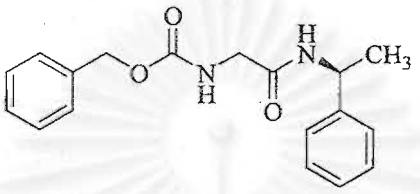


(*S*, *S*)-Fmoc-Thr(^{t}Bu)-A1

This compound was prepared from the reaction of **(*S*)-Fmoc-Thr(^{t}Bu)-OH** (0.39 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.43 g, 0.86 mmol, 86%). ^{1}H NMR

(200 MHz, $CDCl_3$) δ 0.84 (3H, d, J = 6.0, CH(O^{t}Bu)C<u>H</u>$_3$), 1.26 (9H, s, OC(C<u>H</u>$_3$)$_3$), 1.48 (3H, d, J = 7.0, CHPhC<u>H</u>$_3$), 1.63 (1H, d, J = 4.5, C<u>H</u>$_2$), 4.09-4.23 (2H, m, C<u>H</u>CH$_2$ and α-C<u>H</u>), 4.35 (1H, d, J = 6.0, C<u>H</u>(O^{t}Bu)), 5.05 (1H, m, J = 7.0, C<u>H</u>PhCH$_3$), 6.02 (1H, d, J = 4.5, N<u>H</u>), 7.26-7.76 (13H, m, Ar<u>H</u>).

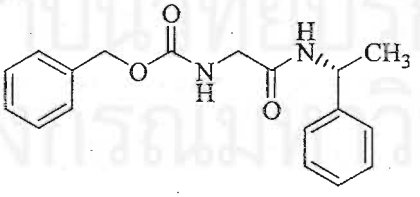
2.4.15 *N*-Cbz-glycyl-(*S*)-(1-phenylethyl)amine ((*S*)-Cbz-Gly-A1).



(*S*)-Cbz-Gly-A1

This compound was prepared from the reaction of **Cbz-Gly-OH** (0.21 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.23 g, 0.73 mmol, 73%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.45 (3H, d, J = 7.0, C<u>H</u>$_3$), 3.83 (2H, d, J = 5.5, α-C<u>H</u>$_2$), 5.08 (1H, m, C<u>H</u>), 5.09 (2H, s, C<u>H</u>$_2$Ph), 5.38-5.50 (1H, br, N<u>H</u>), 6.25-6.40 (1H, br, N<u>H</u>), 7.23-7.32 (10H, m, Ar<u>H</u>).

2.4.16 *N*-Cbz-glycyl-(*R*)-(1-phenylethyl)amine ((*R*)-Cbz-Gly-A1).

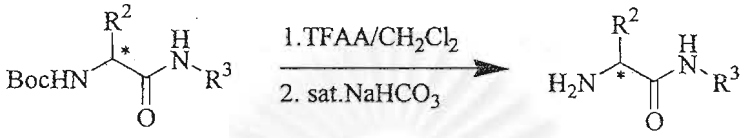


(*R*)-Cbz-Gly-A1

This compound was prepared from the reaction of **Cbz-Gly-OH** (0.10 g, 0.5 mmol), HOBt•H_2O (0.070 g, 0.5 mmol), DCC (0.103 g, 0.5 mmol) and (*S*)-methylbenzylamine (64 μL, 0.5 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.14 g, 0.49 mmol, 98 %). ^{1}H

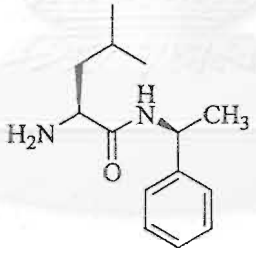
NMR (200 MHz, $CDCl_3$) δ 1.43 (3H, d, J = 7.0, $C\underline{H}_3$), 3.81 (2H, d, J = 5.5, α-$C\underline{H}_2$), 5.06 (1H, m, C<u>H</u>), 5.07 (2H, s, $C\underline{H}_2Ph$), 5.45-5.60 (1H, br, N<u>H</u>), 6.45-6.60 (1H, br, N<u>H</u>), 7.23-7.32 (10H, m, Ar<u>H</u>).

2.5 General procedure for *N*-deprotection



N-Boc-aminoamide was dissolved in CH_2Cl_2 (0.5 mL). TFAA (0.5 mL, 5 mmol) was added. The mixture was stirred for 30 minutes at room temperature. The mixture was then extracted with saturated $NaHCO_3$ solution (3×2 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by a rotary evaporator to give the desired product as a colorless oil.

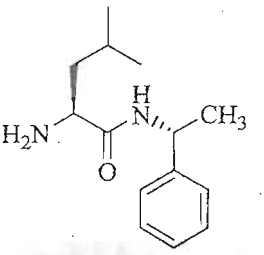
2.5.1 (*S*)-Leucyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Leu-A1).



(*S*, *S*)-Leu-A1

This compound was prepared from the reaction of **(*S*, *S*)-Boc-Leu-A1** (0.20 g, 0.57 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc group described in section 2.5. The desired product was obtained as clear oil (0.11 g, 0.47 mmol, 83 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 9.0, CH($C\underline{H}_3$)$_2$), 0.89 (3H, d, J = 9.0, CH($C\underline{H}_3$)$_2$), 1.40 (3H, d, J = 7.0, CHPh$C\underline{H}_3$), 1.56-1.66 (3H, m, $C\underline{H}_2$ and $C\underline{H}(CH_3)_2$), 3.28 (1H, dd, J = 9.0, 3.5, α-C<u>H</u>), 4.98-5.06 (1H, m, $C\underline{H}PhCH_3$), 7.17-7.29 (5H, m, Ar<u>H</u>), 7.67 (1H, d, J = 8.0, N<u>H</u>).

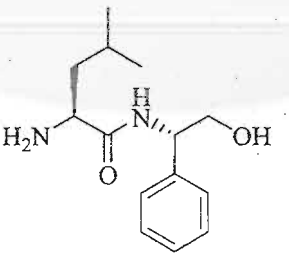
2.5.2 (*S*)-Leucyl-(*R*)-(1-phenylethyl)amine ((*S*, *R*)-Leu-A1).



(*S*, *R*)-Leu-A1

This compound was prepared from the reaction of **(*S*, *R*)-Boc-Leu-A1** (0.27 g, 0.77 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as a clear oil (0.16 g, 0.60 mmol, 78 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (6H, t, J = 5.0, $CH(C\underline{H}_3)_2$), 1.36-1.40 (3H, d, J = 5.8, $CHPhC\underline{H}_3$), 1.45-1.70 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 2.40-2.70 (2H, br, $N\underline{H}_2$), 3.30-3.50 (1H, br, α-C$\underline{H}$) 4.94-5.01 (1H, m, J = 7.1, $C\underline{H}PhCH_3$), 7.14-7.22 (5H, m, Ar$\underline{H}$), 7.83-7.85 (1H, d, J = 5.6, N$\underline{H}$).

2.5.3 (*S*)-Leucyl-(*R*)-(1-phenyl-2-hydroxyethyl)amine ((*S*, *R*)-Leu-A3).

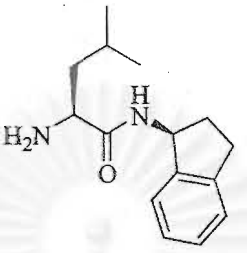


(*S*, *R*)-Leu-A3

This compound was prepared from the reaction of **(*S*, *R*)-Boc-Leu-A3** (0.15 g, 0.43 mmol) and TFA (0.25 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.03 g, 0.13 mmol, 30 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 4.5, $CH(C\underline{H}_3)_2$), 0.91 (3H, d, J = 6.0, $CH(C\underline{H}_3)_2$), 1.54-1.67 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2CH(CH_3)_2$), 2.92-3.35 (1H, br, OH), 3.45 (1H, d, J = 5.5, α-C$\underline{H}$), 3.77 (2H, d, J =

5.0, C<u>H</u>$_2$OH), 4.97-5.02 (1H, m, C<u>H</u>Ph), 7.21-7.32 (5H, m, Ar<u>H</u>), 8.08 (1H, d, J = 7.5, N<u>H</u>).

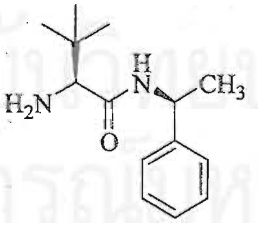
2.5.4 (*S*)-Leucyl-(*S*)-(1-indanyl)amine ((*S*, *S*)-Leu-A5).



(*S*, *S*)-Leu-A5

This compound was prepared from the reaction of **(*S*,*S*)-Boc-Leu-A5** (0.27 g, 0.79 mmol) and TFA (0.25 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as a clear oil (0.14 g, 0.60 mmol, 76 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93-0.96 (6H, m, CH_3), 1.60-1.81 (3H, m, C<u>H</u>$(CH_3)_2$ and C<u>H</u>$_2$), 1.89-1.92 (2H, m, CHCH$_2$C<u>H</u>$_2$), 2.49-2.60 (2H, m, CHC<u>H</u>$_2$), 3.37-3.58 (1H, br, α-C<u>H</u>), 5.38-5.49 (1H, m, C<u>H</u> (indane)), 7.18-7.26 (4H, m, Ar<u>H</u>).

2.5.5 (*S*)-*tert*-Leucyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-*t*Leu-A1).

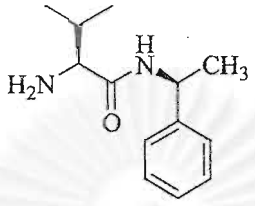


(*S*, *S*)-*t*Leu-A1

This compound was prepared from the reaction of **(*S*, *S*)-Boc-*t*Leu-A1** (0.19 g, 0.5 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.11 g, 0.48 mmol, 96 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (9H, s,

C(C$\underline{H}_3$)$_3$), 1.43 (3H, d, J = 8.0, CHC$\underline{H}_3$), 3.78-3.82 (1H, br, α-C$\underline{H}$), 4.95-5.20 (1H, m, C$\underline{H}$Ph), 7.18-7.33 (5H, m, Ar$\underline{H}$).

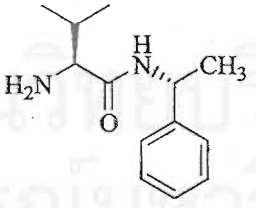
2.5.6 (*S*)-Valyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Val-A1).



(*S*, *S*)-Val-A1

This compound was prepared from the reaction of **(*S*, *S*)-Boc-Val-A1** (0.26 g, 0.8 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.07 g, 0.33 mmol, 41%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (3H, d, J = 7.0, CH(C$\underline{H}_3$)$_2$), 0.92 (3H, d, J = 7.0, CH(C$\underline{H}_3$)$_2$), 1.43 (3H, d, J = 7.0, CH(Ph)C$\underline{H}_3$), 1.95-2.20 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 3.05-3.20 (1H, m, α-C$\underline{H}$), 5.07 (1H, m, J = 7.0, C$\underline{H}$(Ph)CH$_3$), 7.17-7.33 (5H, m, Ar$\underline{H}$), 7.60-7.68 (1H, br, N$\underline{H}$).

2.5.7 (*S*)-Valyl-(*R*)-(1-phenylethyl)amine ((*S*, *R*)-Val-A1).

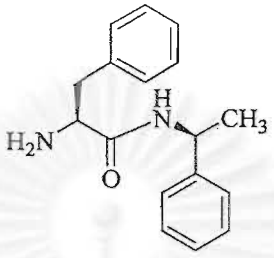


(*S*, *R*)-Val-A1

This compound was prepared from the reaction of **(*S*, *R*)-Boc-Val-A1** (0.23 g, 0.7 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.04 g, 0.33 mmol, 47%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.72 (3H, d, J = 7.0, CH(C$\underline{H}_3$)$_2$), 0.92 (3H, d, J = 7.0, CH(C$\underline{H}_3$)$_2$), 1.41 (3H, d, J = 7.0, CH(Ph)C$\underline{H}_3$), 1.95-

2.20 (1H, m, C<u>H</u>$(CH_3)_2$), 3.05-3.20 (1H, m, α-C<u>H</u>), 5.07 (1H, q, J = 7.0, C<u>H</u>(Ph) CH_3), 7.17-7.33 (5H, m, Ar<u>H</u>), 7.59-7.63 (1H, br, N<u>H</u>).

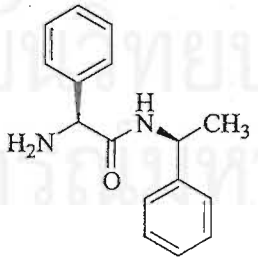
2.5.8 (*S*)-Phenylalanyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Phe-A1)



(*S*, *S*)-Phe-A1

This compound was prepared from the reaction of **(*S*)-Boc-Phe-A1** (0.27 g, 0.73 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.16 g, 0.59 mmol, 81%). ^{1}H NMR (200 MHz, $CDCl_3$) 1.43 (3H, d, J = 7.0, C<u>H</u>$_3$), 2.75 (1H, dd, J = 13.5, 8.5, C<u>H</u>$_2$), 3.20 (1H, dd, J = 13.5, 4.5, C<u>H</u>$_2$), 3.60 (1H, dd, J = 8.5, 4.5, α-C<u>H</u>), 5.08 (1H, m, C<u>H</u>(Ph)CH_3), 7.16-7.60 (10H, m, Ar<u>H</u>), 7.62 (1H, d, J = 8.0, N<u>H</u>).

2.5.9 (*S*)-Phenylglycyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-Phg-A1)

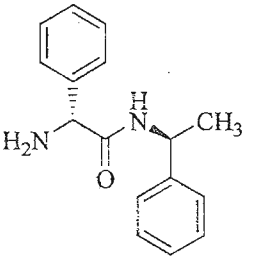


(*S*, *S*)-Phg-A1

This compound was prepared from the reaction **(*S*)-Boc-Phg** (0.18 g, 0.51 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.08 g, 0.34 mmol, 67%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 7.5, CH

(Ph)C<u>H</u>$_3$), 4.44 (1H, br, α-C<u>H</u>), 5.07 (1H, q, J = 7.5, C<u>H</u>(Ph)CH$_3$), 7.19-7.34 (10H, m, Ar<u>H</u>), 7.49 (1H, d, J = 7.5, N<u>H</u>).

2.5.10 (*R*)-Phenylglycyl-(*S*)-(1-phenylethyl)amine ((*R*, *S*)-Phg-A1)



(*R*, *S*)-Phg-A1

This compound was prepared from the reaction of **(*R*)-Boc-Phg** (0.16 g, 0.47 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.11 g, 0.42 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (3H, d, J = 7.5, CH (Ph)C<u>H</u>$_3$), 4.44 (1H, br, α-C<u>H</u>), 5.08 (1H, q, J = 7.5, C<u>H</u>(Ph)CH$_3$), 7.21-7.28 (10H, m, Ar<u>H</u>), 7.54 (1H, d, J = 7.5, N<u>H</u>).

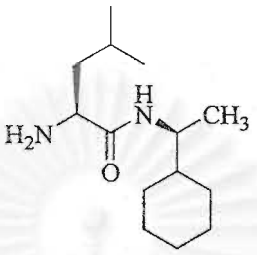
2.5.11 (*R*)-Phenylglycyl-(*R*)-(1-phenylethyl)amine ((*R*, *R*)-Phg-A1)

(*R*, *R*)-Phg-A1

This compound was prepared from the reaction of **(*R*, *R*)-Boc-Phg-A1** (0.27 g, 0.76 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.17 g, 0.67 mmol, 88%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (3H, d, J =

7.0, CH(Ph)C<u>H</u>$_3$), 4.42 (1H, s, α-C<u>H</u>), 5.06 (1H, q, J = 7.0, C<u>H</u>(Ph)CH$_3$), 7.18-7.35 (10H, m, Ar<u>H</u>), 7.59 (1H, d, J = 7.0, N<u>H</u>).

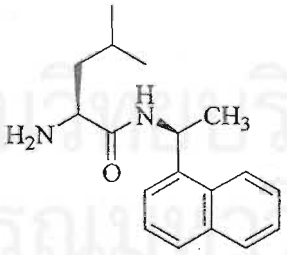
2.5.12 (*S*)-Leucyl-(*S*)-(1-cyclohexylethyl)amine ((*S*, *S*)-Leu-A4)



(*S*, *S*)-Leu-A4

This compound was prepared from the reaction of **(*S*, *S*)-Boc-Leu-A4** (0.23 g, 0.68 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.16 g, 0.68 mmol, 99 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81-1.16 (17H, m, J = 8.5, CH(C<u>H</u>$_3$)$_2$ and cyclohexyl), 1.53-1.89 (6H, m, C<u>H</u>(CH$_3$)$_2$, C<u>H</u>$_2$, CH(cyclo) C<u>H</u>$_3$), 3.60-3.80 (1H, br, C<u>H</u>(cyclo)CH$_3$), 5.13-5.22 (1H, m, α-C<u>H</u>).

2.5.13 (*S*)-Leucyl-(*S*)-(1-naphthylethyl)amine ((*S*, *S*)-Leu-A2).

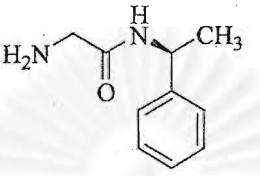


(*S*, *S*)-Leu-A2

This compound was prepared from the reaction **(*S*, *S*)-Boc-Leu-A2** (0.26 g, 0.68 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group. The desired product was obtained as a clear oil (0.16, 0.55 mmol, 81%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (6H, d, J = 6.0, CH(C<u>H</u>$_3$)$_2$), 1.20-1.41 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.54 (3H, d, J = 10, CH(1-naph)C<u>H</u>$_3$), 1.60-1.65 (2H, m,

$C\underline{H}_2$), 2.00-2.20 (2H, br, $N\underline{H}_2$), 3.21-3.40 (1H, br, α-C<u>H</u>) 5.78-5.90 (1H, m, J = 10.0, C<u>H</u>(1-naph)CH_3), 7.31-7.50 (4H, m, Ar<u>H</u>), 7.70-7.90 (3H, m, Ar<u>H</u>), 8.07 (1H, d, J = 10.0, N<u>H</u>).

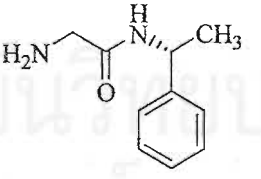
2.5.14 Glycyl-(*S*)-(1-phenylethyl)amine ((*S*)-Gly-A1).



(*S*)-Gly-A1

In 25 mL round bottomed flask, **(*S*)-Cbz-Gly-A1** (0.23 g, 0.73 mmol) was dissolved in methanol (8 mL) then 10% Pd-C was added. The reaction was stirred at room temperature under H_2 gas balloon for 3 h The mixture was filtered through a short plug of celite and washed with methanol. The solvent was removed by a rotary evaporator to give the desired product as a clear oil (0.08 g, 0.46 mmol, 64%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (3H, d, J = 6.0, $C\underline{H}_3$), 3.20-3.30 (2H, m, α-C<u>H</u>), 5.01-5.05 (1H, m, C<u>H</u>(Ph)CH_3), 7.10-7.35 (5H, m, Ar<u>H</u>), 7.70-7.85 (1H, br, N<u>H</u>).

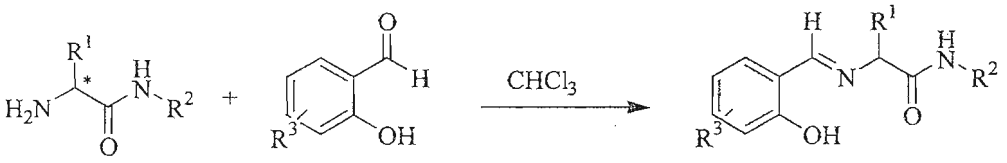
2.5.15 Glycyl-(*R*)-(1-phenyletyl)amine ((*R*)-Gly-A1).



(*R*)-Gly-A1

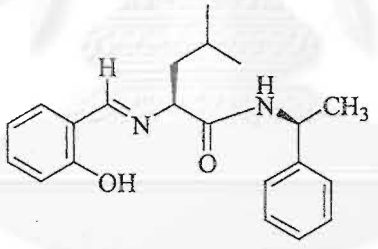
This compound was prepared from the **(*R*)-Cbz-Gly-A1** (0.15 g, 0.50 mmol) following the procedure for the synthesis of glycyl-(*S*)-(1-phenylethyl)amine described in section 2.5.14. The desired product was obtained as a clear oil (0.08 g, 0.45 mmol, 89%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (3H, d, J = 7.0, $C\underline{H}_3$), 3.33-3.58 (2H, br, α-C<u>H</u>), 4.96-5.05 (1H, m, C<u>H</u>(Ph)CH_3), 7.10-7.35 (5H, m, Ar<u>H</u>), 7.74 (1H, d, J = 7.0, N<u>H</u>).

2.6 General procedure for preparation of salicylimine ligands.



An amine was dissolved in $CHCl_3$ (2 mL) and then salicylaldehyde was added. After stirring for 24 h at room temperature, the solvent was removed by a rotary evaporator to give yellow residue. The residue was dissolved in dichloromethane and eluted through a silica gel column by ethyl acetate in hexanes gradient from 7 % to 20 % to afford a crude product as a yellow solid after evaporation. Recrystallization from hexanes provided the desired product as a yellow solid.

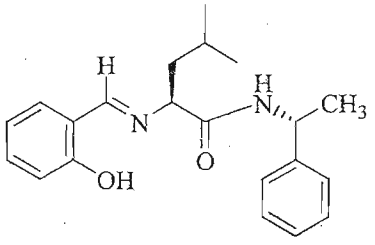
2.6.1 *N*-salicylidene-(*S*)-leucyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-S1-Leu-A1).



(*S*, *S*)-S1-Leu-A1

This compound was prepared from the reaction of **(*S*,*S*)-Leu-A1** (0.11 g, 0.38 mmol) and salicylaldehyde (39.7 μL, 0.38 mmol) following the general procedure for the preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.09 g, 0.22 mmol, 59%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, d, J = 9.0, $CH(C\underline{H}_3)_2$), 0.93 (3H, d, J = 9.0, $CH(C\underline{H}_3)_2$), 1.45 (3H, d, J = 7.0, $CHPhC\underline{H}_3$), 1.75-1.90 (3H, m, $C\underline{H}_2$ and $C\underline{H}(CH_3)_2$), 3.80-3.95 (1H, m, α-C$\underline{H}$), 5.05-5.18 (1H, m, $C\underline{H}PhCH_3$), 6.45 (1H, d, J = 8.0, N$\underline{H}$), 6.80-7.0 (4H, m, Ar$\underline{H}$), 7.17-7.29 (5H, m, Ar$\underline{H}$), 8.28 (1H, s, $\underline{H}$C=N).

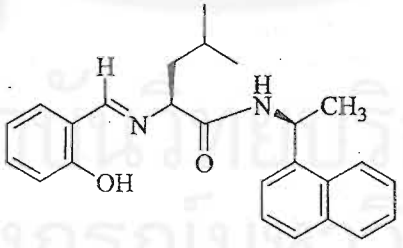
2.6.2 *N*-salicylidene-(*S*)-leucyl-(*R*)-(1-phenylethyl)amine ((*S*,*R*)-Leu-A1).



(*S*, *R*)-S1-Leu-A1

This compound was prepared from the reaction of **(*S*,*R*)-Leu-A1** (0.11 g, 0.49 mmol) and salicylaldehyde (42.1 μL, 0.49 mmol) following the general procedure for the preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.11 g, 0.33 mmol, 83%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 0.87 (3H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 1.42 (3H, d, J = 7.0, $CHPhC\underline{H}_3$), 1.75-1.85 (3H, m, $C\underline{H}_2$ and $C\underline{H}(CH_3)_2$), 3.80-3.95 (1H, m, α-C$\underline{H}$), 5.08-5.20 (1H, m, $C\underline{H}PhCH_3$), 6.20 (1H, d, J = 8.0, N$\underline{H}$), 6.80-7.0 (4H, m, Ar$\underline{H}$), 7.17-7.29 (5H, m, Ar$\underline{H}$), 8.30 (1H, s, $\underline{H}$C=N).

2.6.3 *N*-salicylidene-(*S*)-leucyl-(*S*)-(1-naphthylethyl)amine ((*S*,*S*)-S1-Leu-A2).

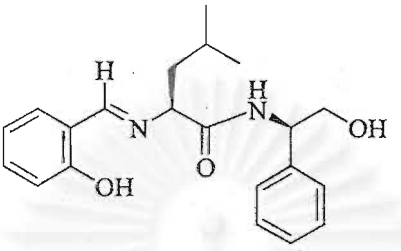


(*S*, *S*)-S1-Leu-A2

This compound was prepared from the reaction of **(*S*, *S*)-Leu-A2** (0.20 g, 0.71 mmol) and salicylaldehyde (75 μL, 0.71 mmol) following the general procedure for the preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.19 g, 0.49 mmol, 69 %) δ 0.84-0.92 (6H, t, J = 7.5, $CH(C\underline{H}_3)_2$), 1.58-1.71 (1H, m, $C\underline{H}(CH_3)_2$), 1.65 (3H, d, J = 7.0, CH(1-naph)$C\underline{H}_3$), 1.78-1.97 (2H, m, CH_2), 3.92 (1H, dd, J = 9.0, 4.5, α-C$\underline{H}$), 5.87-6.01 (1H, m, $C\underline{H}$(1-naph)CH_3), 6.25 (1H, d, J

= 8.0, NH), 6.84-6.95 (4H, m, ArH), 7.20-7.50 (4H, m, ArH), 7.70-7.82 (2H, m, ArH), 8.06 (1H, d, J = 10.0, ArH), 8.25 (1H, s, HC=N).

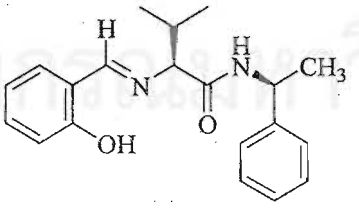
2.6.4 *N*-salicylidene-(*S*)-leucyl-(*S*)-(1-phenyl-2-hydroxyethyl)amine ((*S*, *S*)-S1-Leu-A3).



(*S*, *S*)-S1-Leu-A3

This compound was prepared from the reaction of **(*S*, *S*)-Leu-A3** (0.03 g, 0.13 mmol) and salicylaldehyde (13.5 μL, 0.13 mmol) following the general procedure for the preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.02 g, 0.05 mmol, 38 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, d, J = 6.5, $CH(CH_3)_2$), 0.93 (3H, d, J = 6.5, $CH(CH_3)_2$), 1.52-1.60 (1H, m, $CH(CH_3)_2$), 1.86 (2H, t, J = 7.0, $CH_2CH(CH_3)_2$), 3.02-3.50 (1H, br, OH), 3.84 (2H, d, J = 5.0, CH_2OH), 3.93-4.00 (1H, m, α-CH), 5.03-5.06 (1H, m, CHPh), 6.87-6.98 (4H, m, ArH), 7.22-7.39 (5H, m, ArH), 8.33 (1H, d, J = 7.5, HC=N).

2.6.5 *N*-salicylidene-(*S*)-valyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-S1-Val-A1).



(*S*, *S*)-S1-Val-A1

This compound was prepared from the reaction of **(*S*, *S*)-Val-A1** (0.12 g, 0.53 mmol) and salicylaldehyde (55 μL, 0.52 mmol) following the general procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow

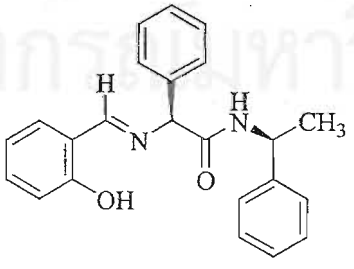
solid (0.11 g, 0.35 mmol, 67 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (3H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 0.98 (3H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 1.50 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 2.40-2.60 (1H, m, $C\underline{H}(CH_3)_2$), 3.75 (1H, d, J = 4.0, α-C<u>H</u>), 5.15 (1H, m, J = 7.0, C<u>H</u>(Ph) CH_3), 6.30 (1H, d, J = 7.0, N<u>H</u>), 6.88-6.97 (4H, m, Ar<u>H</u>), 7.29-7.48 (5H, m, Ar<u>H</u>), 8.27 (1H, s, <u>H</u>C=N).

2.6.6 *N*-salicylidene-(*S*)-valyl-(*R*)-(1-phenylethyl)amine ((*S*, *R*)-S1-Val-A1).

(*S*, *R*)-S1-Val-A1

This compound was prepared from the reaction of **(S, R)-S1-Val-A1** (0.11 g, 0.49 mmol) and salicylaldehyde (51 μL, 0.49 mmol) following the general procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.15 g, 0.45 mmol, 91 %). ^{1}H NMR (200 MHz, CDCl3) δ 0.85 (6H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 1.41 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 2.37-2.43 (1H, m, $C\underline{H}(CH_3)_2$), 3.67 (1H, d, J = 4.0 α-C<u>H</u>), 5.15 (1H, m, J = 7.0, C<u>H</u>(Ph)CH_3), 6.40 (1H, d, J = 7.0, N<u>H</u>), 6.88-6.97 (4H, m, Ar<u>H</u>), 7.29-7.48 (5H, m, Ar<u>H</u>), 8.30 (1H, s, <u>H</u>C=N).

2.6.7 *N*-salicylidene-(*S*)-phenyl-glycyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-S1-Phg-A1).

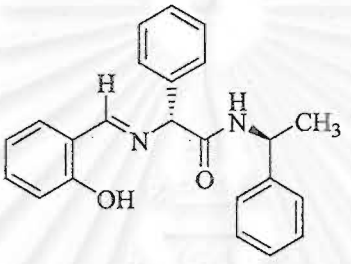


(*S*, *S*)-S1-Phg-A1

This compound was prepared from the reaction of **(*S*, *S*)-Phg-A1** (0.07 g, 0.29 mmol) and salicylaldehyde (30 μL, 0.29 mmol) following the general procedure

for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.08 g, 0.23 mmol, 81 %) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 7.0, CH(Ph)C<u>H</u>$_3$), 5.02 (1H, s, α-C<u>H</u>), 5.13-5.20 (1H, m, C<u>H</u>(Ph)CH$_3$), 6.44 (1H, d, J = 7.0, N<u>H</u>), 6.86-7.02 (4H, m, Ar<u>H</u>), 7.17-7.45 (10H, m, Ar<u>H</u>), 8.42 (1H, s, <u>H</u>C=N).

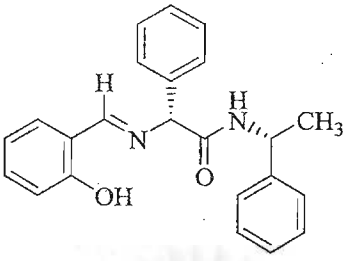
2.6.8 *N*-salicylidene-(*R*)-phenylglycyl-(*S*)-(1-phenylethyl)amine ((*R*,*S*)-S1-Phg-A1).



(*R*, *S*)-S1-Phg-A1

This compound was prepared from the reaction of **(*R*, *S*)-Phg-A1** (0.11 g, 0.42 mmol) and salicylaldehyde (44 μL, 0.42 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.12 g, 0.33 mmol, 80 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (3H, d, J = 7.0, CH(Ph)C<u>H</u>$_3$), 5.02 (1H, s, α-C<u>H</u>), 5.13-5.20 (1H, m, C<u>H</u>(Ph) CH$_3$), 6.44 (1H, d, J = 7.0, N<u>H</u>), 6.86-7.02 (4H, m, Ar<u>H</u>), 7.17-7.45 (10H, m, Ar<u>H</u>), 8.42 (1H, s, <u>H</u>C=N).

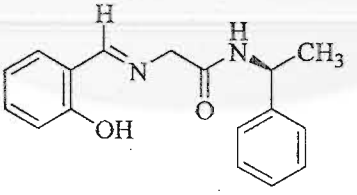
2.6.9 *N*-salicylidene-(*R*)-phenylglycyl-(*R*)-(1-phenylethyl)amine ((*R*,*R*)-S1-Phg-A1).



(*R*, *R*)-S1-Phg-A1

This compound was prepared from the reaction of **(*R*, *R*)-Phg-A1** (0.17 g, 0.67 mmol) and salicylaldehyde (70 μL, 0.68 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.18 g, 0.50 mmol, 74 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (3H, d, J = 7.0, CH(Ph)C<u>H</u>$_3$), 4.28 (1H, s, α-C<u>H</u>), 5.11-5.23 (1H, m, C<u>H</u>(Ph)CH$_3$), 6.44 (1H, d, J = 7.5, N<u>H</u>), 6.86-7.02 (4H, m, Ar<u>H</u>), 7.17-7.45 (10H, m, Ar<u>H</u>), 8.41 (1H, s, <u>H</u>C=N).

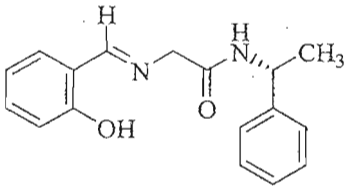
2.6.10 *N*-salicylidene-glycyl-(*S*)-(1-phenylethyl)amine ((*S*)-S1-Gly-A1).



(*S*)-S1-Gly-A1

This compound was prepared from the reaction of **(*S*)-Gly-A1** (0.17 g, 0.67 mmol) and salicylaldehyde (70 μL, 0.68 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.18 g, 0.50 mmol, 74 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 (3H, d, J = 6.0, C<u>H</u>$_3$), 4.30 (2H, s, α-C<u>H</u>), 5.05-5.20 (1H, m, C<u>H</u>(Ph)CH$_3$), 6.80-7.00 (4H, m, Ar<u>H</u>), 7.26-7.30 (5H, m, Ar<u>H</u>), 8.33 (1H, s, <u>H</u>C=N).

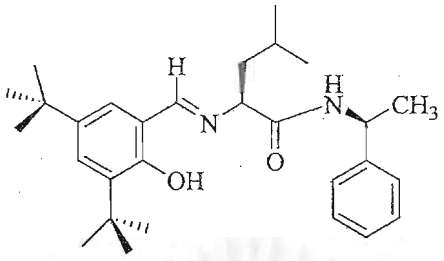
2.6.11 *N*-salicylidene-glycyl-(*R*)-(1-phenylethyl)amine ((*R*)-S1-Gly-A1).



(*R*)-S1-Gly-A1

This compound was prepared from the reaction of **(*R*)-Gly-A1** (0.05 g, 0.28 mmol) and salicylaldehyde (29 μL, 0.28 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.06 g, 0.22 mmol, 78 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 (3H, d, J = 6.0, C<u>H</u>$_3$), 4.30 (2H, s, α-C<u>H</u>), 5.05-5.20 (1H, m, C<u>H</u>(Ph)CH$_3$), 6.80-7.00 (4H, m, Ar<u>H</u>), 7.26-7.30 (5H, m, Ar<u>H</u>), 8.33 (1H, s, <u>H</u>C=N).

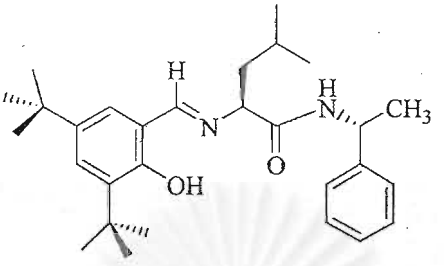
2.6.12 *N*-(3,5)-di-*tert*-butylsalicylidene-(*S*)-leucyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-S2-Leu-A1).



(*S*, *S*)-S2-Leu-A1

This compound was prepared from the reaction of **(*S*, *S*)-Leu-A1** (0.12 g, 0.51 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.12 g, 0.51 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.17 g, 0.37 mmol, 72 %). mp: 152.7-153.9 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +106.3°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, d, *J* = 7.0, $CH(C\underline{H}_3)_2$), 0.94 (3H, d, *J* = 7.0, $CH(C\underline{H}_3)_2$), 1.29 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.44 (9H, s, *o*-$C(C\underline{H}_3)_3$), 1.49 (3H, d, *J* = 8.0, $CHPhC\underline{H}_3$), 1.83-1.87 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.82-3.91 (1H, dd, *J* = 9.0, 4.5 α-C<u>H</u>), 5.05-5.12 (1H, m, $C\underline{H}PhCH_3$), 6.36 (1H, d, *J* = 6.0, N<u>H</u>), 7.09 (1H, d, *J* = 2.5, Ar<u>H</u>), 7.21-7.26 (5H, m, Ar<u>H</u>), 7.42 (1H, d, *J* = 2.5, Ar<u>H</u>), 8.30 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 ($CH_2CH(\underline{C}H_3)_2$), 22.4 ($NHCH(Ph)\underline{C}H_3$), 23.4 ($CH_2CH(\underline{C}H_3)_2$), 24.3 ($CH_2\underline{C}H(CH_3)_2$), 29.4 (*o*-$C(\underline{C}H_3)_3$), 31.4 (*p*-$C(\underline{C}H_3)_3$), 34.2 ($\underline{C}(CH_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 43.3 ($\underline{C}H_2$), 48.9 ($\underline{C}HNH$), 72.2 (α-<u>C</u>H), 117.5, 125.9, 126.6, 127.3, 128.0, 128.7, 136.9, 140.9, 142.9 (Ar), 157.8 (<u>C</u>-OH), 168.1 (<u>C</u>=N), 171.3 (<u>C</u>=O). MS (FAB+) *m/z* (relative intensity) 451 $[M+H]^+$ (100), 435 (8), 302 (18), 105 $[CHCH_3Ph]^+$ (67). Anal. Calcd for $C_{29}H_{42}N_2O_2$: C, 77.29; H, 9.39; N, 6.22. Found: C, 77.29; H, 9.39; N, 6.22.

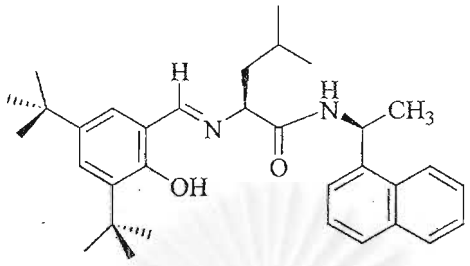
2.6.13 *N*-(3,5)-di-*tert*-butyl-salicylidene-(*S*)-leucyl-(*R*)-(1-phenylethyl) amine ((*S*, *R*)-S2-Leu-A1).



(*S*, *R*)-S2-Leu-A1

This compound was prepared from the reaction of **(*S*, *R*)-Leu-A1** (0.16 g, 0.60 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.16 g, 0.60 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.21 g, 0.46 mmol, 77 %) mp: 143.8-146.0 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +8.1°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (6H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 1.31 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.40-1.44 (3H, d, J = 8, $CHPhC\underline{H}_3$), 1.44 (9H, s, *o*-$C(C\underline{H}_3)_3$), 1.83-1.87 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.82-3.91 (1H, m, α-C<u>H</u>), 5.05-5.12 (1H, m, $C\underline{H}PhCH_3$), 6.35-6.38 (1H, d, J = 6.0, N<u>H</u>), 7.14-7.13 (1H, d, J = 2.4, Ar<u>H</u>), 7.29-7.33 (5H, m, Ar<u>H</u>), 7.44-7.45 (1H, d, J = 2.3, Ar<u>H</u>), 8.35 (1H, s, C<u>H</u>=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0 ($CH(\underline{C}H_3)_2$), 22.3 ($\underline{C}H_3CHPh$), 23.4 ($CH(\underline{C}H_3)_2$), 24.3 ($\underline{C}H(CH_3)_2$), 29.4 ($C(\underline{C}H_3)_3$), 31.5 ($\underline{C}(CH_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 43.2 ($\underline{C}H_2$), 48.7 (<u>C</u>HNH), 72.0 (α-<u>C</u>H), 117.5, 125.9, 126.6, 127.4, 128.1, 128.8, 137.0, 140.9, 143.0 (Ar), 157.8 (<u>C</u>-OH), 168.0 (<u>C</u>=N), 171.2 (C=O). MS (FAB+) *m/z* (relative intensity) 451 $[M+H]^+$ (20), 435 (2), 302 (10), 105 $[CHCH_3Ph]^+$ (100). Anal. Calcd for $C_{29}H_{42}N_2O_2$: C, 77.29; H, 9.39; N, 6.22. Found: C, 77.21; H, 9.37; N, 6.24.

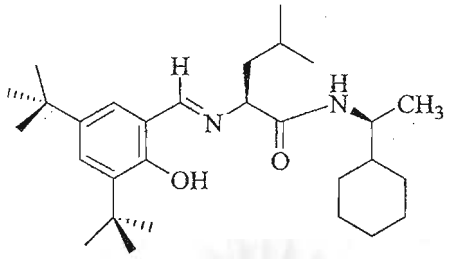
2.6.14 *N*-(3, 5)-*tert*-butyl-salicylidine-(*S*)-leucyl-(*S*)-(1-naphthylethyl) amine ((*S*, *S*)-S2-Leu-A2).



(*S*, *S*)-S2-Leu-A2

This compound was prepared from the reaction of **(*S*, *S*)-Leu-A2** (0.16 g, 0.55 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.13 g, 0.55 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.12 g, 0.25 mmol, 46%) mp: 162.7-163.4 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +145.7°. ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 0.94 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 1.26 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.41 (9H, s, *o*- $C(C\underline{H}_3)_3$), 1.64-1.67 (3H, d, J = 8, CH(1-naph)$C\underline{H}_3$), 1.85-1.98 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.85-4.00 (1H, m, α-C<u>H</u>), 5.85-5.95 (1H, m, C<u>H</u>(1-naph)CH_3), 6.51 (1H, d, J = 8.0, N<u>H</u>), 7.05 (1H, d, J = 6.0, Ar<u>H</u>), 7.41 (5H, d, J = 2.4, Ar<u>H</u>), 7.65-7.85 (2H, m, Ar<u>H</u>), 8.06 (1H, d, J = 2.3, Ar<u>H</u>), 8.30 (1H, s, C<u>H</u>=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 ($CH(\underline{C}H_3)_2$), 22.6 ($\underline{C}H_3CHPh$), 23.4 ($CH(\underline{C}H_3)_2$), 24.3 ($\underline{C}H(CH_3)_2$), 29.4 ($C(\underline{C}H_3)_3$), 31.4 ($\underline{C}(CH_3)_3$), 35.0 ($\underline{C}(CH_3)_3$), 43.2 ($\underline{C}H_2$), 44.9 (<u>C</u>HNH), 72.0 (α-<u>C</u>H), 117.5, 122.4, 123.2, 125.7, 126.4, 126.6 127.9, 128.2, 128.8, 138.3, 140.8, 143.0 (Ar), 157.7 (C-OH), 168.2 (C=N), 171.2 (C=O). MS (FAB+) *m/z* (relative intensity) 501 $[M+H]^+$ (40), 316 (18), 301 (10), 288 (7), 258 (7), 244 (7), 233 (9), 219 (9), 218 (7), 155 $[CH(1\text{-napthyl})CH_3]^+$ (100). Anal. Calcd for $C_{33}H_{44}N_2O_2$: C, 79.16; H, 8.86; N, 5.59. Found: C, 79.19; H, 8.88; N, 5.57.

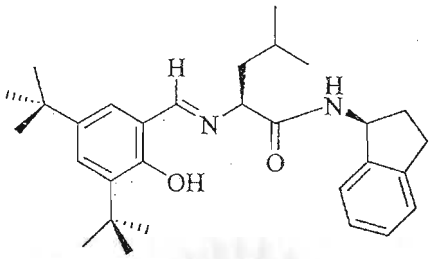
2.6.15 3, 5-di-*tert*-butylsalicylidene-(S)-leucyl-(*S*)-(1-cyclohexylethyl) amine ((*S*, *S*)-S2-Leu-A4).



(*S*, *S*)-S2-Leu-A4

This compound was prepared from the reaction of **(*S*, *S*)-Leu-A4** (0.16 g, 0.68 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.16 g, 0.68 mmol) following the general procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.22 g, 0.49 mmol, 72 %) mp: 172.9-173.7 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +100.0°. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (6H, d, J = 6.0, $CH(C\underline{H}_3)_2$), 1.10-1.12 (3H, d, J = 7.0, $NHCHC\underline{H}_3$), 1.32 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.45 (9H, s, *o*- $C(C\underline{H}_3)_3$), 1.48-1.68 (11H, m, cyclohexyl), 1.73-1.88 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.78-3.86 (1H, m, $C\underline{H}$(cyclohexyl)CH_3), 3.90 (1H, dd, J = 10, 4.0, α-$C\underline{H}$), 5.96 (1H, d, J = 8.5, $N\underline{H}$), 7.14 (1H, d, J = 2.0, Ar$\underline{H}$), 7.45 (1H, d, J = 2.0, Ar$\underline{H}$), 8.34 (1H, s, $C\underline{H}$=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.9 ($\underline{C}H_3CH$(cyclohexyl)), 21.1 ($CH(\underline{C}H_3)_2$), 23.4 ($CH(\underline{C}H_3)_2$), 24.3 ($\underline{C}H(CH_3)_2$), 26.1, 26.3, 28.7, 29.0 (cyclohexyl), 29.4 ($C(\underline{C}H_3)_3$), 31.4 ($\underline{C}(CH_3)_3$), 34.2 (cyclohexyl), 35.0 ($\underline{C}(CH_3)_3$), 42.8 ($\underline{C}H_2$), 43.4 ($\underline{C}HNH$), 49.3 (cyclohexyl), 72.5 (α-$\underline{C}H$), 117.5, 136.9, 140.8 (Ar), 157.7 (C-OH), 167.6 (C=N), 171.4 (C=O). MS (FAB+) *m/z* (relative intensity) 457 $[M+H]^+$ (100), 441 (12), 401 (8), 359 (10), 341 (8), 331 (8), 302 (12). Anal. Calcd for $C_{29}H_{48}N_2O_2$: C, 76.27; H, 10.59; N, 6.13. Found: C, 76.26; H, 10.67; N, 6.05.

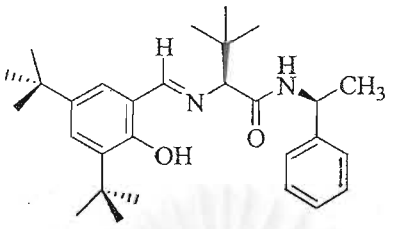
2.6.16 *N*-(3,5)-di-*tert*-butylsalicylidene-(*S*)-leucyl-(*S*)-(1-indanylethyl) amine ((*S*, *S*)-S2-Leu-A5).



(*S*, *S*)-S2-Leu-A5

This compound was prepared from the reaction **(*S*, *S*)-Leu-A5** (0.14 g, 0.6 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.14 g, 0.6 mmol) following the general procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.16 g, 0.35 mmol, 59 %). mp: 169.4-173.6 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +48.7°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, d, *J* = 2.5, $CH(C\underline{H}_3)_2$), 0.95 (3H, d, *J* = 2.5, $CH(C\underline{H}_3)_2$), 1.29 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.40 (9H, s, *o*-$C(C\underline{H}_3)_3$), 1.78-1.90 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 2.60-2.75 (2H, m, $NHCHC\underline{H}_2$), 2.85-3.00 (2H, m, $NHCHCH_2C\underline{H}_2$), 3.98 (1H, dd, *J* = 9.0, 4.5, α-C<u>H</u>), 5.46 (1H, q, *J* = 8.0, C<u>H</u> (indane), 6.25 (1H, d, *J* = 8.0, N<u>H</u>), 7.07-7.29 (5H, m, Ar<u>H</u>), 7.41 (5H, d, *J* = 2.5, Ar<u>H</u>), 8.35 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.2 ($CH(\underline{C}H_3)_2$), 23.4 (CH ($\underline{C}H_3)_2$), 24.3 ($\underline{C}H(CH_3)_2$), 27.5, 29.4 ($C(\underline{C}H_3)_3$), 30.2, 31.4 ($\underline{C}(CH_3)_3$), 34.2, 35.1 (<u>C</u> $(CH_3)_3$), 43.4 ($\underline{C}H_2$), 54.5 (<u>C</u>HNH), 72.5 (α-<u>C</u>H), 117.5, 123.8, 124.8, 126.6, 129.8, 127.9, 128.0, 136.8, 140.8, 143.0, 143.3 (Ar), 157.7 (C-OH), 168.0 (C=N), 172.1 (C=O). MS (FAB+) *m/z* (relative intensity) 463 $[M+H]^+$ (100), 447 (8), 347 (5), 302 (11), 117 $[indane]^+$ (47). Anal. Calcd for $C_{30}H_{42}N_2O_2$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.77; H, 9.15; N, 6.13.

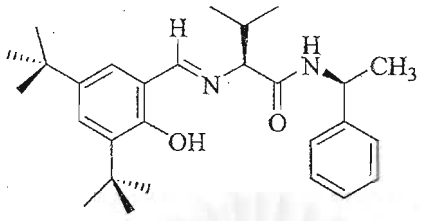
2.6.17 *N*-(3,5)-di-*tert*-butylsalicylidene-(*S*)-*tert*-leuyl-(*S*)-(1-phenyleythyl) amine ((*S*, *S*)-S2-*t*Leu-A1).



(*S*, *S*)-S2-*t*Leu-A1

This compound was prepared from the reaction of **(*S*, *S*)-tLeu-A1** (0.11 g, 0.48 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.11 g, 0.48 mmol) following the general procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.14 g, 0.32 mmol, 67 %), mp: 151.4-152.5 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +109.3°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (9H, s, $CH(C\underline{H}_3)_3$), 1.31 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.46 (9H, s, *o*-$C(C\underline{H}_3)_3$), 1.52 (3H, d, J = 7.0, $CHC\underline{H}_3$), 3.54 (1H, s, α-C<u>H</u>), 4.95-5.20 (1H, m, C<u>H</u>Ph), 6.35 (1H, d, J = 8.0, NH), 7.11 (1H, d, J = 2.5, Ar<u>H</u>), 7.10-7.27 (5H, m, Ar<u>H</u>), 7.43 (1H, d, J = 2.5, Ar<u>H</u>), 8.26 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.8 ($NHCH\underline{C}H_3$), 27.3 ($CHC(\underline{C}H_3)_3$), 29.4 (*o*-$C(\underline{C}H_3)_3$), 31.4 (*p*-$C(\underline{C}H_3)_3$), 34.2 ($\underline{C}(CH_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 48.7 (<u>C</u>HNH), 83.6 (α-<u>C</u>H), 117.6, 125.8, 126.7, 127.3, 127.9, 128.7, 136.9, 140.8, 142.9 (Ar), 157.8 (<u>C</u>-OH), 167.1 (<u>C</u>=N), 171.3 (<u>C</u>=O). MS (FAB+) *m/z* (relative intensity) 451 $[M+H]^+$ (100), 435 (12), 395 (10), 302 (20), 105 $[CHCH_3Ph]^+$ (34). Anal. Calcd for $C_{29}H_{42}N_2O_2$: C, 77.29; H, 9.39; N, 6.22. Found: C, 77.19; H, 9.42; N, 6.29.

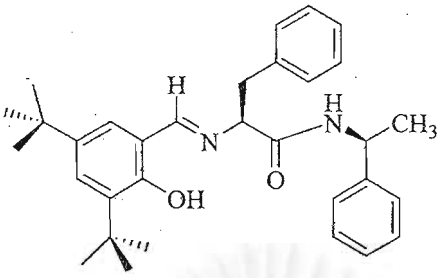
2.6.18 *N*-(3,5)-di-*tert*-butylsalicylidene-valyl-(*S*)-(1-phenyleythyl)amine ((*S*, *S*)-S2-Val-A1).



(*S*, *S*)-S2-Val-A1

This compound was prepared from the reaction of **(*S*, *S*)-Val-A1** (0.07 g, 0.33 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.07 g, 0.33 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.08 g, 0.18 mmol, 57 %) mp : 187.3-190.1 °C. $[\alpha]_D^{26}$ (c 1.0, $CHCl_3$) = +128.7°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 7.0, $CH(C\underline{H}_3)_2$), 1.05 (3H, d, *J* = 7.0, $CH(C\underline{H}_3)_2$), 1.33 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.45 (9H, s, *o*-$C(C\underline{H}_3)_3$), 1.51 (3H, d, *J* = 8.5, $CH(Ph)C\underline{H}_3$), 2.50-2.60 (1H, m, $C\underline{H}(CH_3)_2$), 3.68 (1H, d, *J* = 4.0, α-C<u>H</u>), 5.12-5.18 (1H, m, $C\underline{H}(Ph)CH_3$), 6.45-6.52 (1H, d, *J* = 8.0, N<u>H</u>), 7.14 (1H, d, *J* = 2.5, Ar<u>H</u>), 7.22-7.32 (5H, m, Ar<u>H</u>), 7.46 (1H, d, *J* = 2.5, ArH), 8.30 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.3 ($CH(CH_3)_2$), 19.7 ($CH(CH_3)_2$), 22.5 (NHCH<u>C</u>H_3), 29.4 (*o*-$C(\underline{C}H_3)_3$), 31.5 (*p*-$C(\underline{C}H_3)_3$), 32.2 ($\underline{C}H(CH_3)_2$), 34.2 (<u>C</u>$(CH_3)_3$), 35.1 ($\underline{C}(CH_3)_3$), 49.0 (<u>C</u>HNH), 79.3 (α-<u>C</u>H), 117.6, 125.9, 126.2, 126.7, 127.4, 128.0, 128.7, 136.9, 140.8, 142.9 (Ar), 157.9 (<u>C</u>-OH), 168.6 (<u>C</u>=N), 170.5 (<u>C</u>=O). MS (FAB+) *m/z* (relative intensity) 437 $[M+H]^+$ (100), 421 (13), 395 (10), 341 (7), 331 (8), 288 (20), 105 $[CHCH_3Ph]^+$ (98). Anal. Calcd for $C_{28}H_{40}N_2O_2$: C, 77.02; H, 9.23; N, 6.42. Found: C, 76.90; H, 9.29; N, 6.34.

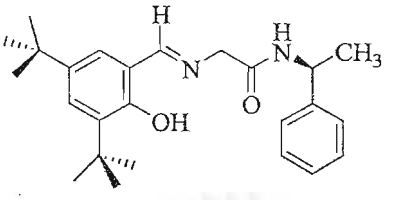
2.6.19 *N*-(3,5)-di-*tert*-butylsalicylidene-(*S*)-phenyl-alanyl-(*S*)-(1-phenyleythyl)amine ((*S*, *S*)-S2-Phe-A1).



(*S*, *S*)-S2-Phe-A1

This compound was prepared from the reaction of **(*S*, *S*)-Phe-A1** (0.15 g, 0.59 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.14 g, 0.59 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.21 g, 0.41 mmol, 72 %). mp: 142.1-142.7 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = -34.9°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (9H, s, *p*-C($C\underline{H}_3$)$_3$), 1.42 (3H, d, J = 7.5, $C\underline{H}_3$), 1.44 (9H, s, *o*-C($C\underline{H}_3$)$_3$), 3.13 (1H, dd, J = 13.5, 8.0, $C\underline{H}_2$), 3.39 (1H, dd, J = 13.5, 4.0, $C\underline{H}_2$), 4.01 (1H, dd, J = 8.0, 4.0, α-C$\underline{H}$), 5.08 (1H, q, J = 7.5, C$\underline{H}$(Ph)CH_3), 6.33 (1H, d, J = 7.5, N$\underline{H}$), 6.91 (1H, d, J = 2.5, Ar$\underline{H}$), 7.14-7.28 (10H, m, Ar$\underline{H}$), 7.39 (1H, d, J = 2.5, Ar$\underline{H}$), 7.94 (1H, s, $\underline{H}$C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3 ($\underline{C}H_3$), 29.4 (*o*-C($\underline{C}H_3$)$_3$), 31.4 (*p*-C($\underline{C}H_3$)$_3$), 34.1 ($\underline{C}$(CH_3)$_3$), 35.1 ($\underline{C}$(CH_3)$_3$), 41.1 ($\underline{C}H_2$), 49.0 ($\underline{C}$HNH), 75.0 (α-$\underline{C}$H), 117.5, 125.9, 126.6, 127.3, 128.0, 128.4, 128.7, 129.8, 136.8, 137.0, 140.7, 142.8 (Ar), 157.7 ($\underline{C}$-OH), 168.5 ($\underline{C}$=N), 170.0 ($\underline{C}$=O). MS (FAB+) *m/z* (relative intensity) 485 $[M+H]^+$ (100), 469 (10), 429 (3), 381 (3), 336 (15), 288 (5), 269 (5), 244 (7), 234 (10), 218 (9), 105 $[CHCH_3Ph]^+$ (38). Anal. Calcd for $C_{29}H_{42}N_2O_2$: C, 79.30; H, 8.32; N, 5.78. Found: C, 79.28, H, 8.32; N, 5.79.

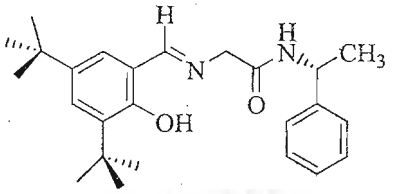
2.6.20 *N*-(3,5)-di-*tert*-butylsalicylidene glycyl-(*S*)-(1-phenyl-eythyl)amine ((*S*)-S2-Gly-A1).



(*S*)-S2-Gly-A1

This compound was prepared from the reaction **(*S*)-Gly-A1** (0.08 g, 0.43 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.10 g, 0.43 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.09 g, 0.23 mmol, 57 %). mp: 146.1-146.4 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +77.2 °. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (9H, s, *p*-C($C\underline{H}_3$)$_3$), 1.43 (9H, s, *o*-C($C\underline{H}_3$)$_3$), 1.47 (3H, d, J = 7.0, CH(Ph)$C\underline{H}_3$), 4.31 (2H, s, α-$C\underline{H}_2$), 5.12-5.20 (1H, m, $C\underline{H}$(Ph)CH_3), 6.40 (1H, d, J = 8.0, N$\underline{H}$), 7.11 (1H, d, J = 2.5, Ar$\underline{H}$), 7.23-7.34 (5H, m, Ar$\underline{H}$), 7.43 (1H, d, J = 2.5, Ar$\underline{H}$), 8.38 (1H, s, $\underline{H}$C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2 ($\underline{C}H_3$), 29.4 (*o*-C($\underline{C}H_3$)$_3$), 31.4 (*p*-C($\underline{C}H_3$)$_3$), 34.2 ($\underline{C}$(CH_3)$_3$), 35.1 ($\underline{C}$(CH_3)$_3$), 48.8 ($\underline{C}$HNH), 62.8 (α-$\underline{C}H_2$), 117.6, 126.0, 126.6, 127.5, 128.1, 128.8, 136.9, 137.0, 140.9 (Ar), 157.7 ($\underline{C}$-OH), 168.1 ($\underline{C}$=N), 169.9 ($\underline{C}$=O). MS (FAB+) *m/z* (relative intensity) 395 $[M+H]^+$ (100), 379 (10), 288 (14), 105 $[CHCH_3Ph]^+$ (80). Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69; N, 7.10. Found: C, 76.10; H, 8.57; N, 7.10.

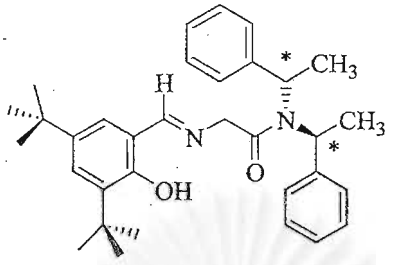
2.6.21 *N*-(3,5)-di-*tert*-butylsalicylidene glycyl-(*S*)-(1-phenyleythyl)amine ((*R*)-S2-Gly-A1).



(*R*)-S2-Gly-A1

This compound was prepared from the reaction (*R*)-**Gly-A1** (0.09 g, 0.50 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.11 g, 0.50 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.13 g, 0.33 mmol, 66 %). mp: 142.5-144.7 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = -82.2 °. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (9H, s, *p*-C($C\underline{H}_3$)$_3$), 1.40 (9H, s, *o*-C($C\underline{H}_3$)$_3$), 1.49 (3H, d, J = 7.0, CH(Ph)$C\underline{H}_3$), 4.30 (2H, s, α-C$\underline{H}_2$), 5.12-5.19 (1H, m, C$\underline{H}$(Ph)CH_3), 6.38 (1H, d, J = 8.0, N$\underline{H}$), 7.11 (1H, d, J = 2.5, Ar$\underline{H}$), 7.23-7.34 (5H, m, Ar$\underline{H}$), 7.43 (1H, d, J = 2.5, Ar$\underline{H}$), 8.38 (1H, s, $\underline{H}$C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.2 ($\underline{C}H_3$), 29.5 (*o*-C($\underline{C}H_3$)$_3$), 31.4 (*p*-C($\underline{C}H_3$)$_3$), 34.2 ($\underline{C}$(CH_3)$_3$), 35.1 ($\underline{C}$(CH_3)$_3$), 48.9 ($\underline{C}$HNH), 62.8 (α-$\underline{C}H_2$), 117.6, 126.0, 126.6, 127.5, 128.1, 128.8, 137.0, 140.9, 142.8 (Ar), 157.7 ($\underline{C}$-OH), 168.1 ($\underline{C}$=N), 169.9 ($\underline{C}$=O). MS (FAB+) *m/z* (relative intensity) 395 $[M+H]^+$ (100), 379 (10), 351 (3), 339 (5), 291 (8), 275 (8), 246 (7), 244 (6), 234 (8), 218 (6), 219 (6), 105 $[CHCH_3Ph]^+$ (80). Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69; N, 7.10. Found: C, 76.36; H, 8.52; N, 7.11.

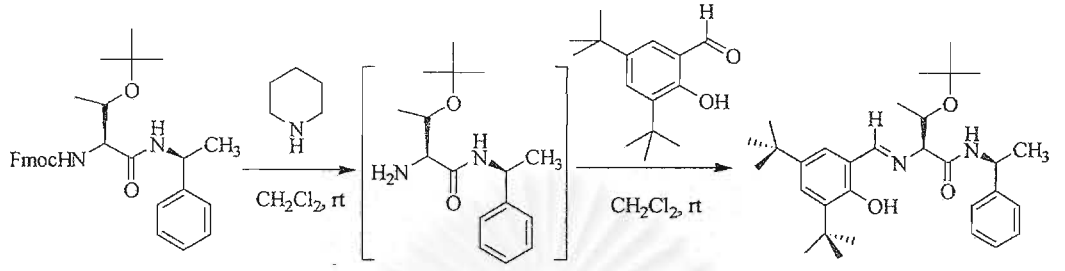
2.6.22 *N*-(3,5)-di-*tert*-butylsalicylidene-glycyl-(*S*)-[(*R, *R**)-bisphenyl-eythyl]amine ((*S*)-S2-Gly-A6).**



(S)-S2-Gly-A6

This compound was prepared from the reaction **(*S*)-Gly-A6** (1.02 g, 3.62 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.85 g, 3.62 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.20 g, 0.40 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (9H, s, *p*-C(C$\underline{H}_3$)$_3$), 1.43 (9H, s, *o*-C(C$\underline{H}_3$)$_3$), 1.74 (3H, br, CH(Ph)C$\underline{H}_3$), 1.86 (3H, br, CH(Ph)C$\underline{H}_3$), 4.00 (2H, d, J = 12.0 α-C$\underline{H}$), 4.28 (2H, d, J = 14.0, C$\underline{H}$(Ph)CH_3), 7.36 (1H, d, J = 2.5, Ar$\underline{H}$), 7.19-7.21 (5H, m, Ar$\underline{H}$), 8.27 (1H, s, $\underline{H}$C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.2 (*o*-C($\underline{C}H_3$)$_3$), 29.4 ($\underline{C}H_3$), 31.3 (*p*-C($\underline{C}H_3$)$_3$), 31.5 ($\underline{C}H_3$), 34.1 ($\underline{C}$(CH$_3$)$_3$), 35.0 ($\underline{C}$(CH$_3$)$_3$), 53.1 ($\underline{C}$HN), 62.4 (α-$\underline{C}H_2$), 117.9, 126.4, 127.3, 127.5, 127.8, 127.9, 128.0, 128.2, 128.3, 128.5, 131.9, 136.5, 140.0, 140.6 (Ar), 157.9 ($\underline{C}$-OH), 168.9 ($\underline{C}$=N), 169.6 ($\underline{C}$=O). MS (FAB+) *m/z* (relative intensity) 499 $[M+H]^+$ (30), 395 (15), 219 (11), 105 $[CHCH_3Ph]^+$ (100).

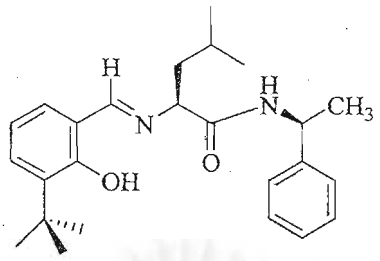
2.6.23 *N*-(3,5)-di-*tert*-butylsalicylidene -(*S*)-Thr(*tert*-butyl)-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-S2-Thr(^{t}Bu)-A1).



(*S*, *S*)-Fmoc-Thr(^{t}Bu)-A1 **(*S*, *S*)-Thr(^{t}Bu)-A1** **(*S*, *S*)-S2-Thr(^{t}Bu)-A1**

(*S*,*S*)-Fmoc-Thr(^{t}Bu)-A1 (0.43 g, 0.86 mmol) was dissolved in dried dichloromethane (1.5 mL) then piperidine (0.08 mL, 0.86 mmol) was added. After stirring at room-temperature for 1 h, the reaction was complete then the solvent was removed by rotary evaporator. The crude product was dissolved in methylene chloride then 3,5-di-*tert*-butylsalicylaldehyde was added. Stirred at room temperature for 24 h, the solvent was removed by rotary evaporator. The crude product was further purified by column chromatography on silica gel (20 % ethyl acetate in hexanes) to give the desired product as a clear oil (gradient from 7 % to 20 % ethyl acetate in hexanes) to give the desired product as a yellow solid (0.18 g, 0.36 mmol, 36%). mp: 143.4-145.6 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +42.5°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (3H, d, J = 4.5, C<u>H</u>$_3$ (Thr)), 1.20 (9H, s, *p*-C(C<u>H</u>$_3$)$_3$), 1.30 (9H, s, OC(C<u>H</u>$_3$)$_3$), 1.42 (3H, d, J = 7.5, CH(Ph)C<u>H</u>$_3$), 1.44 (9H, s, *o*-C(C<u>H</u>$_3$)$_3$), 1.51 (3H, d, J = 7.0, CH(Ph) C<u>H</u>$_3$), 3.76 (1H, d, J = 4.5, *α*-C<u>H</u>), 4.07-4.12 (1H, m, C<u>H</u>(O^{t}Bu)), 5.11 (1H, m, J = 7.5, C<u>H</u>(Ph)CH$_3$), 6.94 (1H, d, J = 7.5, N<u>H</u>), 7.10 (1H, d, J = 2.5, Ar<u>H</u>), 7.21-7.34 (5H, m, Ar<u>H</u>), 7.40 (1H, d, J = 2.5, Ar<u>H</u>), 8.29 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8 (<u>C</u>H$_3$ (Thr)), 22.6 (CH(Ph)<u>C</u>H$_3$), 28.5 (OC(<u>C</u>H$_3$)$_3$), 29.4 (*o*-C(<u>C</u>H$_3$)$_3$), 31.5 (*p*-C(<u>C</u>H$_3$)$_3$), 34.1 (<u>C</u>(CH$_3$)$_3$), 35.1 (<u>C</u>(CH$_3$)$_3$), 48.9 (<u>C</u>HNH), 69.0 (O<u>C</u>(CH$_3$)$_3$), 74.6 (<u>C</u>H (Thr)), 78.1 (*α*-<u>C</u>H), 117.8, 125.9, 126.6, 127.2, 127.5, 128.6, 136.7, 140.3, 143.4 (Ar), 157.9 (<u>C</u>-OH), 168.9 (<u>C</u>=N), 169.2 (<u>C</u>=O). MS (FAB+) *m/z* (relative intensity) 495 $[M+H]^+$ (100), 479 (6), 439 (20), 423 (8), 274 (10), 258 (9), 244 (12), 234 (20), 105 $[CHCH_3Ph]^+$ (55). Anal. Calcd for $C_{31}H_{46}N_2O_3$: C, 75.26; H, 9.37; N, 5.66. Found: C, 75.21; H, 9.44; N, 5.66.

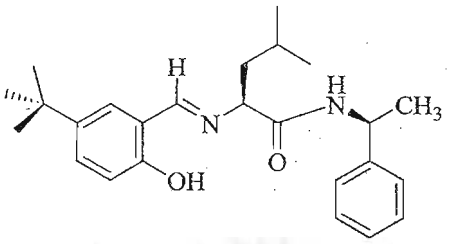
2.6.24 *N*-3-*tert*-butylsalicylidene -(*S*)-leucyl-(S)-(1-phenylethyl)amine ((*S*, *S*)-S3-Leu-A1).



(*S*, *S*)-S3-Leu-A1

This compound was prepared from the reaction of **(*S*, *S*)-Leu-A1** (0.16 g, 0.67 mmol) and 3-*tert*-butylsalicylaldehyde (0.12 g, 0.67mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.17 g, 0.43 mmol, 64%). mp: 151.2-152.2 °C $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +138.9 °. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (3H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 0.94 (3H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 1.44 (9H, s, *o*-$C(C\underline{H}_3)_3$), 1.50 (3H, d, J = 7.0, $CHPhC\underline{H}_3$), 1.81-1.90 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.90 (1H, dd, J = 9.0, 5.0, α-C<u>H</u>), 5.05-5.12 (1H, m, $C\underline{H}PhCH_3$), 6.36 (1H, d, J = 6.0, N<u>H</u>), 6.85 (1H, t, J = 2.5, Ar<u>H</u>), 7.11-39 (7H, m, Ar<u>H</u>), 8.30 (1H, s, C<u>H</u>N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 ($CH_2CH(\underline{C}H_3)_2$), 22.3 ($NHCH\underline{C}H_3$), 23.3 ($CH_2CH(\underline{C}H_3)_2$), 24.3 ($CH_2\underline{C}H(CH_3)_2$), 29.3 (*o*-$C(\underline{C}H_3)_3$), 34.8 ($\underline{C}(CH_3)_3$), 43.3 ($\underline{C}H_2$), 48.8 (<u>C</u>HNH), 72.1 (α-<u>C</u>H), 118.3, 118.5, 125.8, 127.3, 128.7, 130.4, 137.5, 142.9 (Ar), 160.0 (<u>C</u>-OH), 167.6 (<u>C</u>=N), 171.1 (<u>C</u>=O). MS (FAB+) *m/z* (relative intensity) 395 $[M+H]^+$ (100), 379 (6), 359 (10), 341 (3), 331 (12), 313 (6), 246 (15), 105 $[CHCH_3Ph]^+$ (34). Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69; N, 7.10. Found: C, 76.00; H, 8.70; N, 7.13.

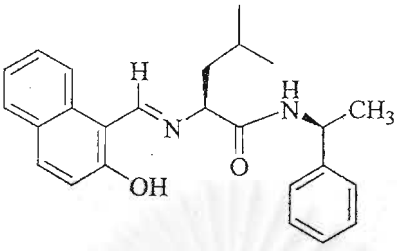
2.6.25 *N*-5-*tert*-butylsalicylidene -(*S*)-Leucyl-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-S4-Leu-A1).



(*S*, *S*)-S4-Leu-A1

This compound was prepared from the reaction of **(*S*, *S*)-Leu-A1** (0.16 g, 0.67 mmol) and 3-*tert*-butylsalicylaldehyde (0.12 g, 0.67mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.17 g, 0.43 mmol, 64%). mp: 90.7-92.5 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +57.7°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, d, J = 5.0, $CH(C\underline{H}_3)_2$), 0.93 (3H, d, J = 5.0, $CH(C\underline{H}_3)_2$), 1.29 (9H, s, *p*-$C(C\underline{H}_3)_3$), 1.48 (3H, d, J = 7.0, $CHPhC\underline{H}_3$), 1.81-1.90 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.90 (1H, dd, J = 8.0, 4.0, α-C<u>H</u>), 5.08-5.16 (1H, m, $C\underline{H}PhCH_3$), 6.26 (1H, d, J = 7.0, N<u>H</u>), 6.85 (1H, d, J = 8.5, Ar<u>H</u>), 7.11-42 (7H, m, Ar<u>H</u>), 8.30 (1H, s, C<u>H</u>N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 ($CH_2CH(\underline{C}H_3)_2$), 22.1 ($NHCH\underline{C}H_3$), 23.4 ($CH_2CH(\underline{C}H_3)_2$), 24.3 ($CH_2\underline{C}H(CH_3)_2$), 31.4 (*p*-$C(\underline{C}H_3)_3$), 34.1 ($\underline{C}(CH_3)_3$), 43.3 ($\underline{C}H_2$), 48.7 (<u>C</u>HNH), 72.2 (α-<u>C</u>H), 116.7, 117.6, 126.1, 127.3, 128.5, 130.7, 142.1, 142.9 (Ar), 158.4 (<u>C</u>-OH), 167.6 (<u>C</u>=N), 171.2 (<u>C</u>=O). Anal. Calcd for $C_{25}H_{34}N_2O_2$: C, 76.10; H, 8.69; N, 7.10. Found: C; 76.14, H, 8.66; N, 7.19.

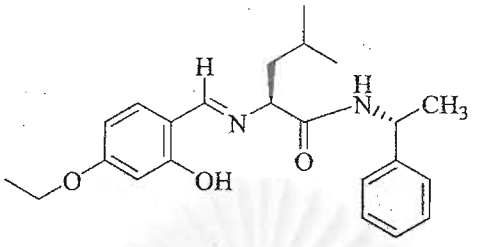
2.6.26 *N*-2'-hydroxy-1-naphthylidene-(S)-leucyl-(S)-(1-phenylethyl)amine ((*S*, *S*)-S5-Leu-A1)



(*S*, *S*)-S5-Leu-A1

This compound was prepared from the reaction **(*S*, *S*)-Leu-A1** (0.11 g, 0.47 mmol) and 2-hydroxy-naphthaldehyde (0.08 g, 0.47 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.11 g, 0.29 mmol, 62 %). mp: 152.4-154.8 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +84.16 °. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 0.95 (3H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 1.49 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 1.85-1.95 (3H, m, $C\underline{H}_2$ and $C\underline{H}(CH_3)_2$), 4.11 (1H, dd, J = 9.0, 5.0, α-C$\underline{H}$), 5.13 (1H, m, J = 7.0, $C\underline{H}(Ph)CH_3$), 6.40 (1H, d, J = 7.0, N$\underline{H}$), 7.11 (1H, d, J = 8.5, Ar$\underline{H}$), 7.16-7.37 (5H, m, Ar$\underline{H}$), 7.46-7.51 (1H, m, Ar$\underline{H}$), 7.71 (1H, d, J = 9.0, Ar$\underline{H}$), 7.76 (1H, d, J = 9.0, Ar$\underline{H}$), 7.98 (1H, d, J = 9.0, Ar$\underline{H}$), 9.07 (1H, s, $\underline{H}$C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 ($CH_2CH(\underline{C}H_3)_2$), 22.0 ($NHCH\underline{C}H_3$), 23.2 ($CH_2CH(\underline{C}H_3)_2$), 24.5 ($CH_2\underline{C}H(CH_3)_2$), 43.0 ($\underline{C}H_2$), 48.9 ($\underline{C}HNH$), 69.8 (α-$\underline{C}$H), 108.3, 118.9, 121.2, 123.6, 126.0, 127.3, 127.4, 128.1, 128.7, 129.3, 132.8, 136.1, 142.9 (Ar), 161.1 ($\underline{C}$-OH), 167.5 ($\underline{C}$=N), 170.7 ($\underline{C}$=O). MS (FAB+) *m/z* (relative intensity) 389 $[M+H]^+$ (100), 316 (4), 288 (5), 240 (30), 105 $[CHCH_3Ph]^+$ (50). Anal. Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.28; H, 7.26; N, 7.21.

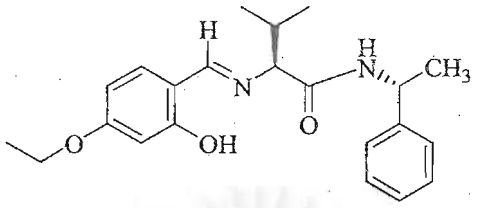
2.6.27 *N*-4-ethoxy-salicylidene-(*S*)-leucyl-(*R*)-(1-phenyleythyl)amine ((*S*, *R*)-S6-Leu-A1).



(*S*, *R*)-S6-Leu-A1

This compound was prepared from the reaction of **(*S*, *R*)-Leu-A1** (0.11 g, 0.49 mmol) and 4-ethoxysalicylaldehyde (0.08 g, 0.49 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.13 g, 0.34 mmol, 70 %). mp: 113.6-118.0 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (6H, d, J = 6.5, $CH(C\underline{H}_3)_2$), 1.44 (3H, t, J = 7.0, $CH_2C\underline{H}_3$), 1.46 (3H, d, J = 7.0, $CH(Ph)C\underline{H}_3$), 1.73-1.80 (3H, m, $C\underline{H}_2$ and $C\underline{H}(CH_3)_2$), 3.88 (1H, dd, J = 9.0, 4.5, α-C<u>H</u>), 4.05 (2H, q, J = 7.0, $C\underline{H}_2CH_3$), 5.12 (1H, m, $C\underline{H}(Ph)CH_3$), 6.26 (1H, d, J = 8.0, N<u>H</u>), 7.11 (1H, d, J = 8.5, Ar<u>H</u>), 7.16-7.32 (7H, m, Ar<u>H</u>), 8.23 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6 ($OCH_2\underline{C}H_3$), 21.0 ($CH_2CH(\underline{C}H_3)_2$), 22.0 ($NHCH\underline{C}H_3$), 23.3 ($CH_2CH(\underline{C}H_3)_2$), 24.3 ($CH_2\underline{C}H(CH_3)_2$), 43.3 ($\underline{C}H_2$), 48.9 (<u>C</u>HNH), 63.8 ($O\underline{C}H_2CH_3$), 72.0 (α-<u>C</u>H), 101.5, 107.4, 112.1, 125.8, 127.3, 128.7, 133.3, 136.1, 143.0 (Ar), 163.2 (<u>C</u>-OH), 166.1 (<u>C</u>=N), 171.4 (<u>C</u>=O).

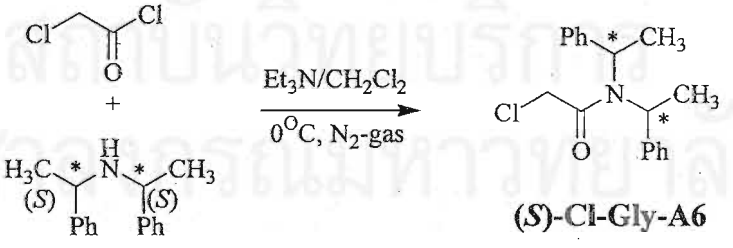
2.6.28 *N*-4-ethoxy-salicylidene-(*S*)-valyl-(*R*)-(1-phenyleythyl)amine ((*S*, *R*)-S6-val-A1).



(*S*, *R*)-S6-val-A1

This compound was prepared from the reaction **(*S*, *S*)-Val-A1** (0.06 g, 0.26 mmol) and 4-ethoxy-salicylaldehyde (0.04 g, 0.26 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.08 g, 0.22 mmol, 83 %). $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = -59.3 ° ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (6H, d, J = 7.0, $CH(C\underline{H}_3)_2$), 1.40 (3H, s, $OCH_2C\underline{H}_3$), 1.51 (3H, d, J = 8.0, $CH(Ph)C\underline{H}_3$), 2.22-2.50 (1H, m, $C\underline{H}(CH_3)_2$), 3.68 (1H, d, J = 4.0, α-C<u>H</u>), 3.98-4.20 (2H, m, $OC\underline{H}_2CH_3$), 5.05-5.20 (1H, m, C<u>H</u>(Ph) CH_3), 6.45-6.52 (1H, d, J = 8.0, N<u>H</u>), 7.14 (1H, d, J = 2.5, Ar<u>H</u>), 7.22-7.32 (7H, m, Ar<u>H</u>), 7.46 (1H, d, J = 2.5, ArH), 8.30 (1H, s, <u>H</u>C=N).

2.7 Preparation of 2-chloro-[*S*-(*R,*R**)]-*N*,*N*-bis (phenylethyl)acetamide ((*S*)-Cl-Gly-A6).**

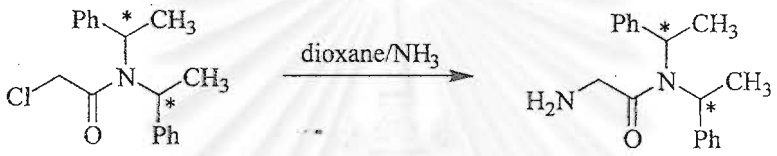


(*S*)-Cl-Gly-A6

Chiral amine -[*S*-(*R**,*R**)]-*N*,*N*-bis (phenylethyl)amine (288 μL, 1 mmol) was dissolved in Et_3N (279 μL, 2 mmol) at room temperature. After stirring for 10 min., the mixture was cooled down to 0 °C then the 1-chloroacetylchloride was added dropwise under N_2-atmosphere. The mixture was stirred for 6 h The mixture was treated with 5% HCl and washed with 10% aqueous $NaHCO_3$. The organic layer was

washed with water and dried over anhydrous $MgSO_4$. The solid was filtered and the filtrate was evaporated by a rotary evaporator to give the crude product. The product was further purified by column chromatography on silica gel with 20% ethyl acetate in hexanes to give the desired product as a white solid (0.24 g, 0.8 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.88 (6H, br, C<u>H</u>$_3$), 3.77 (1H, d, J = 12.0, α-C<u>H</u>), 3.92 (1H, d, J = 12.0, α-C<u>H</u>), 4.82-5.18 (1H, br, C<u>H</u>Ph), 5.38-5.60 (1H, br, C<u>H</u>Ph), 6.90-7.35 (10H, m, Ar<u>H</u>).

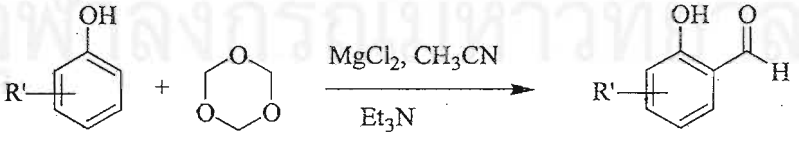
2.8 Preparation of 2-amino-[*S*-(*R,*R**)]- *N*,*N*-bis(phenylethyl)acetamide ((*S*)-Gly-A6).**



(*S*)-Cl-Gly-A6 **(*S*)-Gly-A6**

To a solution of **(*S*)-Cl-Gly-A6** (0.24 g, 0.8 mmol) in dioxane (2 mL) and concentrated ammonia solution (2 mL) was stirred and gently warmed (not over 50 ° C) in a closed system (scaled test tube). The reaction was completed in 2 h The solvent was removed by a rotary evaporator to give the desired product (0.15 g, 0.5 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, d, J = 7.0, C<u>H</u>$_3$), 1.26 (3H, d, J = 7.0, C<u>H</u>$_3$), 3.62-3.70 (2H, m, α-C<u>H</u>), 4.12 (2H, d, J = 7.0, C<u>H</u>Ph), 7.08-7.22 (10H, m, Ar<u>H</u>).

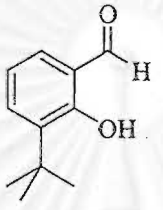
2.9 General procedure for preparation of salicylaldehyde.



Salicylaldehyde derivative was prepared according to the method by Skattebol *et al.*[20] with a slight modification. Phenol derivative (20 mmol) and anhydrous magnesium chloride (30 mmol) were dissolved in acetonitrile 100 mL in a 250 mL round bottomed flask then triethylamine (10 mL) (dried over molecular sieves) was added. To the mixture, paraformaldehyde (135 mmol) was added to give a yellow

solution. After refluxing for 3 h, the mixture was cooled down to room-temperature then acidified with 2 M HCl. The mixture was extracted with ether (20×3 mL). The organic layer was dried over anhydrous $MgSO_4$. The solid was filtered and the filtrate was evaporated by a rotary evaporator to give the crude product. The product was further purified by column chromatography on silica gel with 10% ethyl acetate in hexanes to give the desired product.

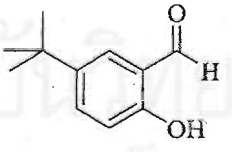
2.9.1 3-*tert*-butylsalicylaldehyde (S3).



S3

This compound was prepared from the reaction of 2-*tert*-butylphenol (3.06 mL, 20 mmol) following the general procedure for preparation of salicylicylaldehyde described in section 2.9. The desired product was obtained as a yellow oil (1.96 g, 11 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (9H, s, C<u>H</u>$_3$), 6.93 (1H, t, J = 7.5, Ar<u>H</u>), 7.39 (1H, d, J = 7.0, Ar<u>H</u>), 7.48 (1H, d, J = 7.0, Ar<u>H</u>), 9.86 (1H, s, C<u>H</u>O), 11.77 (1H, s, O<u>H</u>).

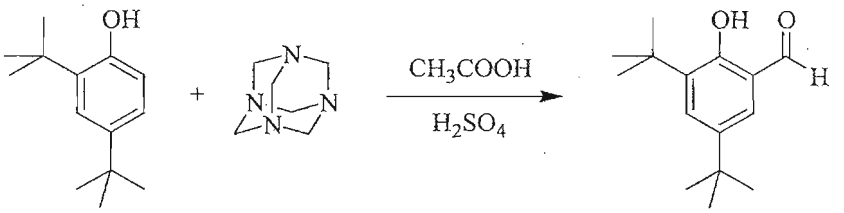
2.9.2 5-*tert*-butylsalicylaldehyde (S4).



S4

This compound was prepared from the reaction of 4-*tert*-butylphenol (3.06 mL, 20 mmol) following the general procedure for preparation of salicylicylaldehyde described in section 2.9. The desired product was obtained as a yellow oil (0.98 g, 5.5 mmol, 28%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (9H, s, C<u>H</u>$_3$), 6.90 (1H, d, J = 8.5, Ar<u>H</u>), 7.55 (2H, dt, J = 8.5, 2.0, Ar<u>H</u>), 9.87 (1H, s, C<u>H</u>O), 10.84 (1H, s, O<u>H</u>).

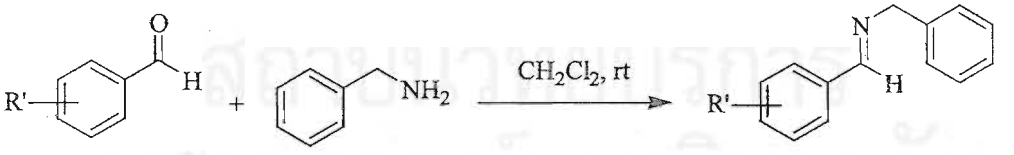
2.10 Preparation of 3,5-*tert*-butylsalicylaldehyde (S2).



S2

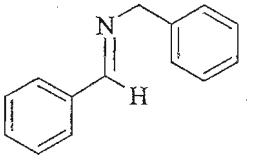
Salicylaldehyde derivative was prepared according to the method described by Jacobsen *et al.*[21] with a slight modification. Hexamine (17 g, 120 mmol), 2,4-di-*tert*-butylphenol (12.5 g, 60 mmol) and glacial acetic acid (30 mL) were combined in 250 round bottomed flask. The mixture was heated to 130 °C and refluxed for 3 h and 33 % (w/w) aqueous sulfuric acid (30 mL) was added after the mixture was cooled down to 75 °C. After refluxing at 105-110 °C for 1 h, the mixture was cooled to 75 °C and then the organic layer was separated in warm separation funnel. The solvent was removed by a rotary evaporator to give the crude product. The product was further purified by column chromatography on silica gel with 10% ethyl acetate in hexanes to give the desired product (6.73 g, 28 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (9H, s, *p*-C(C<u>H</u>$_3$)), 1.42 (9H, s, *o*-C(C<u>H</u>$_3$)), 7.34 (1H, d, J = 1.5, Ar<u>H</u>), 7.58 (1H, d, J = 1.5, Ar<u>H</u>), 9.87 (1H, s, C<u>H</u>O), 11.64 (1H, s, O<u>H</u>).

2.11 General procedure for preparation of imine.



Imine was prepared according to the method reported by Jocobsen et al.[15] To a 25 mL round bottomed flask was added activated 3 Å molecular sieves and 5 mL dichloromethane. To this solution, benzylamine (0.55 mL, 5 mmol) was added followed by slow syringe addition of aldehyde (5 mmol). When all the starting materials were consumed, the sieves were removed by filtration. The sieves were washed with dichloromethane, the filtrate was collected and the solvent was removed by a rotary evaporator to obtain the desired product.

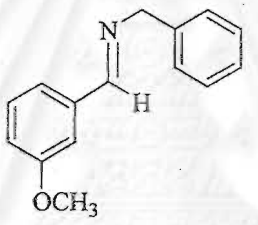
2.11.1 *N*-benzylidene benzylamine (1).



1

This compound was prepared from the reaction of benzaldehyde (1.02 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as a yellow oil (1.70 g, 8.7 mmol, 87%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.86 (2H, s, C$\underline{H}_2$), 7.32-7.50 (5H, m, Ar$\underline{H}$), 7.81-7.87 (5H, m, Ar$\underline{H}$), 8.42 (1H, s, $\underline{H}$C=N).

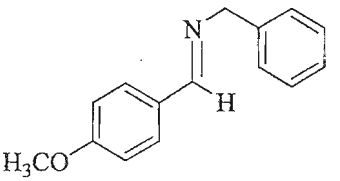
2.11.2 3-Methoxy-*N*-benzylidene benzylamine (3).



3

This compound was prepared from the reaction of 3-methoxybenzaldehyde (1.22 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as a yellow oil (1.90 g, 8 mmol, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.85 (3H, s, OC$\underline{H}_3$), 4.83 (2H, s, C$\underline{H}_2$), 6.99 (4H, d, J = 8.0, Ar$\underline{H}$), 7.31-7.40 (5H, m, Ar$\underline{H}$), 8.37 (1H, s, $\underline{H}$C=N).

2.11.3 4-Methoxy-*N*-benzylidene benzylamine (4).

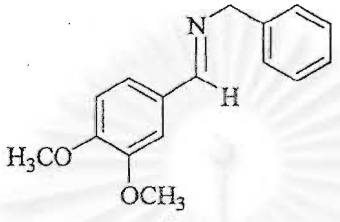


4

This compound was prepared from the reaction of 4-methoxybenzaldehyde (1.20 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general

procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (1.37 g, 50 mmol, >95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.93 (3H, s, $OC\underline{H}_3$), 4.88 (2H, s, $C\underline{H}_2$), 7.02 (1H, d, J = 8.5, Ar$\underline{H}$), 7.35-7.45 (5H, m, Ar$\underline{H}$), 8.42 (1H, s, $\underline{H}C$=N).

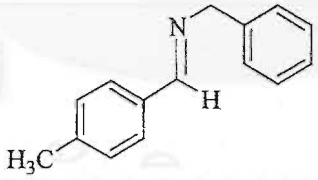
2.11.4 3,4-Dimethoxy-*N*-benzylidene benzylamine (5).



5

This compound was prepared from the reaction of 3,4-dimethoxybenzaldehyde (0.8 g, 5 mmol) and benzylamine (0.35 mL, 5 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (1.27 g, 5 mmol, >95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.85 (3H, s, $OC\underline{H}_3$), 3.93 (3H, s, $OC\underline{H}_3$), 4.88 (2H, s, $C\underline{H}_2$), 7.02 (1H, d, J = 8.5, Ar$\underline{H}$), 7.35-7.45 (5H, m, Ar$\underline{H}$), 8.42 (1H, s, $\underline{H}C$=N).

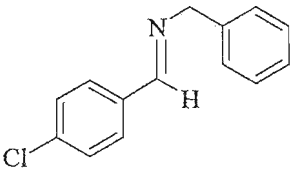
2.11.5 4-Methyl-*N*-benzylidene benzylamine (6).



6

This compound was prepared from the reaction of *p*-tolualdehyde (1.18 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (2.04 g, 10 mmol, 98%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (3H, s, $OC\underline{H}_3$), 4.88 (2H, s, $C\underline{H}_2$), 7.20-7.40 (5H, m, Ar$\underline{H}$), 7.62-7.75 (4H, m, Ar$\underline{H}$), 8.38 (1H, s, $\underline{H}C$=N).

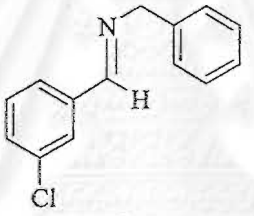
2.11.6 4-Chloro-*N*-benzylidene benzylamine (7).



7

This compound was prepared from the reaction of 4-chlorobenzaldehyde (1.40 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (1.82 g, 8 mmol, 79%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.82 (2H, s, C$\underline{H}_2$), 7.27-7.43 (7H, m, Ar$\underline{H}$), 7.72 (2H, d, J = 8.5, Ar$\underline{H}$), 8.36 (1H, s, $\underline{H}$C=N).

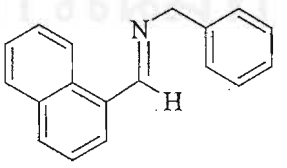
2.11.7 3-Chloro-*N*-benzylidene benzylamine (8).



8

This compound was prepared from the reaction of 3-chlorobenzaldehyde (1.14 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (2.53 g, 10 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.88 (2H, s, C$\underline{H}_2$), 7.20-7.40 (5H, m, Ar$\underline{H}$), 7.62-7.75 (4H, m, Ar$\underline{H}$), 8.38 (1H, s, $\underline{H}$C=N).

2.11.8 *N*-1-napthylidene benzylamine (9).

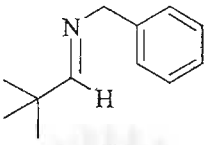


9

This compound was prepared from the reaction of 1-naphthylaldehyde (1.36 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained

as yellow oil (2.35 g, 9.6 mmol, 96%). ^{1}H NMR (200 MHz, $CDCl_3$) 4.97 (2H, s, $C\underline{H}_2$), 7.35-7.44 (7H, m, Ar$\underline{H}$), 7.51-7.60 (5H, m, Ar$\underline{H}$), 9.06 (1H, s, $\underline{H}$C=N).

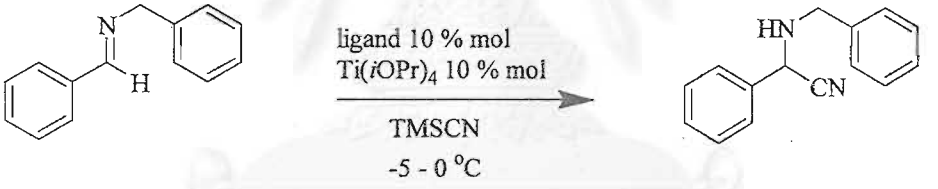
2.11.9 *N-tert*-butylmethylidene benzylamine (10).



10

This compound was prepared from the reaction of pivalaldehyde (0.55 mL, 5 mmol) and benzylamine (0.55 mL, 5 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (0.69 g, 4 mmol, 79%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88 (9H, s, $C\underline{H}_3$), 4.83 (2H, s, $C\underline{H}_2$), 7.20-7.40 (5H, m, Ar$\underline{H}$), 8.40 (1H, s, $\underline{H}$C=N).

2.12 General procedure for catalysis screening.

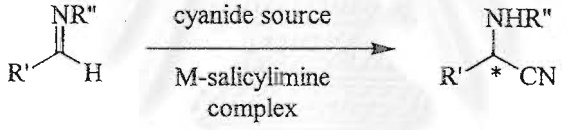


The chiral ligand (0.02 mmol) and $Ti(O^iPr)_4$ (0.02 mmol) were stirred together in toluene (dried over molecular sieve) in a round bottomed flask for 10 minutes then the imine (0.2 mmol) was added. To the mixture, cooled in an ice bath, was added TMSCN (50μL, 0.4 mmol). The mixture was then stirred at –5 to 0 °C for 4 h. The solvent was removed by rotary evaporator to afford the crude product which was filtered through a short plug of alumina. The enantiomeric excess was determined by ^{1}H NMR in the presence of (1*S*)-(+)-camphor-10-sulfonic acid (*S*-CSA) as a chiral solvating agent.[19,22]

CHAPTER III

RESULTS AND DISCUSSION

The objectives of this research are to synthesize and study new series of salicylimine ligands designed as catalysts for asymmetric Strecker-type reaction (Scheme 3.1). The effect of substituents of salicylimine ligands on the efficiency of the catalysts was investigated. Two important parameters used in the determination of the efficiency of the catalysts were percent conversion and percent enantiomeric excess ($\%\ ee = |\%R - \%S| / |\%R + \%S|$).



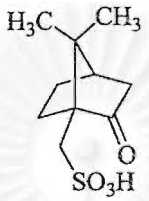
Scheme 3.1 Asymmetric Strecker-type reaction

3.1 Analytical method: Determination of yield and enantiomeric excess of α-aminonitrile product.

There are a number of analytical techniques, which may be used for determination of % *ee* such as chiral GC, chiral HPLC and NMR. NMR technique is the most informative and convenient to be used where the instrument is available, although the technique is normally limited by its accuracy of no better than ± 5 % errors.

The determination of % *ee* using NMR requires an introduction of a chiral auxiliary, which can convert an enantiomeric mixture into a mixture of diastereomers. Provided that the observed non-equivalent chemical shifts of the diastereotopic protons are baseline separated and integration can be determined, the ratio of these integrations can be directly related to the enantiomeric composition of the original mixture.

(*1S*)-(+)-camphor-10-sulfonic acid ((*S*)-CSA) was successully used as a chiral solvating agent for the determination of the enantiomeric purity of α-aminonitriles as it showed satisfactory separation of the α-proton (~ 4.75 ppm) of the enatiomeric mixture of α-aminonitrile (Table 3.1) bearing a variety of substituents.[19] Therefore, (*S*)-CSA was used in ^{1}H NMR analysis of the % *ee* throughout this work.



(*S*)-CSA

The assignment of the chemical shift of *S* and *R* isomer of 2-benzylamino-2-phenylacetonitrile was validated by using a known chiral (salen)Mn(III)Cl complex (Jacobsen *et al.*)[21] to generate a known enantiomeric mixture which was analyzed by ^{1}H NMR in the presence of (*S*)-CSA (Figure 3.1).[19] For other α-aminonitrile products, only the relative configuration could be assigned (Table 3.1).

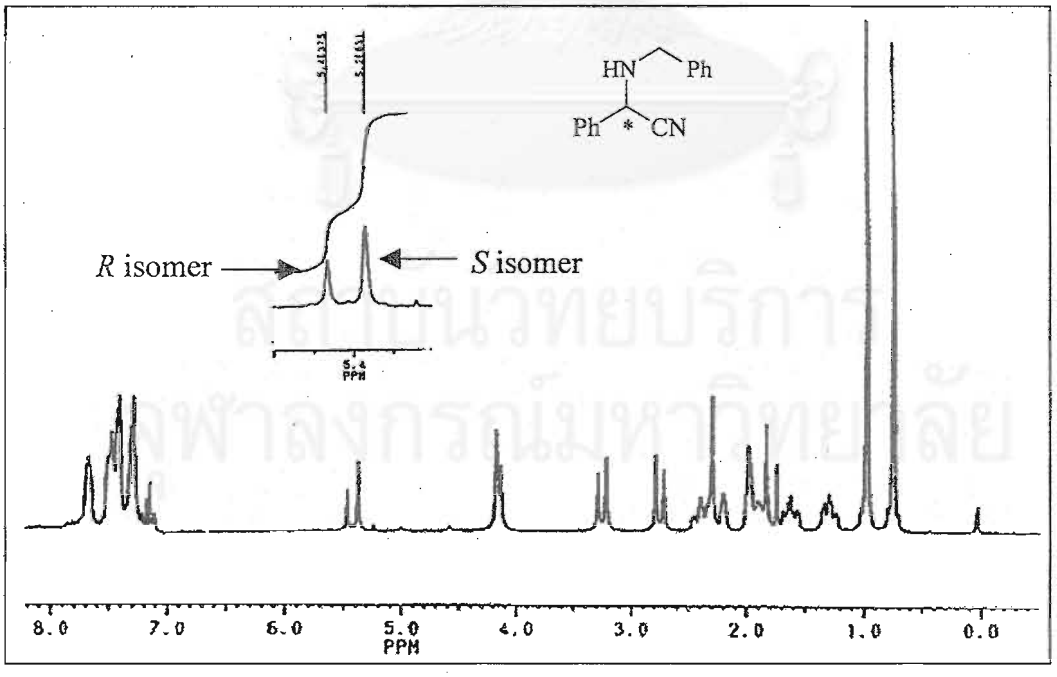
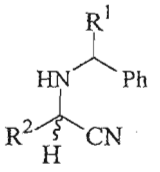


Figure 3.1 Spectrum of 2-benzylamino-2-phenylacetonitrile in the presence of CSA.

Table 3.1 Chemical shifts of α-protons of the crude α-aminonitriles obtained from the reaction in the presence of (*S*)-CSA.



α-aminonitrile

aminonitrile product[a]		δ (ppm)	
R^1	R^2	before addition of CSA	after addtion of CSA (R^*, S^*)[b]
H	Ph	4.48	5.46, 5.37
H	4-Cl C_6H_4	4.49	5.48, 5.40
H	3-ClC_6H_4	4.68	5.42, 5.37
H	2-$MeOC_6H_4$	4.80	5.27, 5.30
H	3,4-$(CH_3O)_2C_6H_3$	4.68	5.38, 5.26
H	4-$MeOC_6H_4$	4.46	5.42, 5.35
H	3-$MeOC_6H_4$	4.49	5.46, 5.39
H	4-$CH_3C_6H_4$	4.51	5.38, 5.32
H	1-Naphthyl	5.15	5.74, 5.71
H	$(CH_3)_3C$	3.10	4.97-4.90, 4.33-4.26[c]
Ph	Ph	5.01	5.47, 5.42

[a]condition: 2 eq of TMSCN, 0.3 mL MeOH, rt, 30 min.

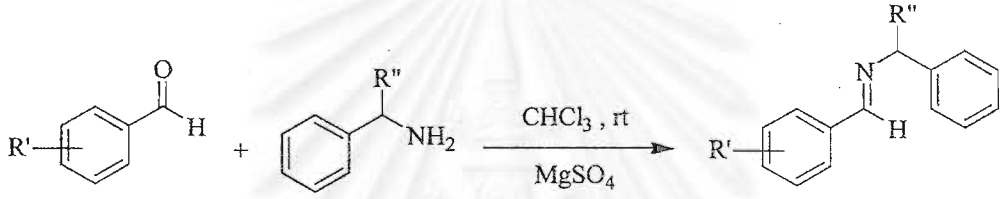
[b]Only relative configuration was assigned except for the first entry that the absolute configuration was known.

[c] δ of $C\underline{H}_2$ (not an α-H)

3.2 Synthesis

3.2.1 Imine substrates

Condensation of aldehydes with amines to afford imines is a well-known reaction. A drying agent, anhydrous magnesium sulfate was added to drive the equilibrium forward (Scheme 3.2). The imines were not sufficiently stable to be purified by chromotography or distillation. Fortunately, the reactions generally proceeded cleanly to give the product in high yield with less than 10% of the aldehyde remained in the mixture (Table 3.2). These imines were thus used as obtained without further purification.



Scheme 3.2 Imine substrate synthesis

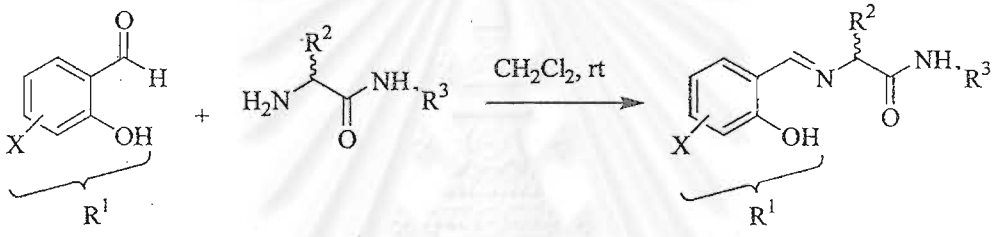
Table 3.2 Percent yield of imine substrate.

aldehyde	amine	Imine	Yield (%)
Benzaldehyde	Benzylamine	**1**	87
2-methoxybenzaldehyde	Benzylamine	**2**	-[a]
3-methoxybenzaldehyde	Benzylamine	**3**	80
anisaldehyde	Benzylamine	**4**	76
3,4-methoxybenzaldehyde	Benzylamine	**5**	>95
p-tolualdehyde	Benzylamine	**6**	98
4-chlorobenzaldehyde	Benzylamine	**7**	79
3-chlorobenazldehyde	Benzylamine	**8**	>95
1-napthaldehyde	Benzylamine	**9**	96
Pivaladehyde	Benzylamine	**10**	79
Benzaldehyde	Benzhydrylamine	**11**	-[b]

[a]**2** was supplied by Mansawat, W.[b]**11** was supplied by Banphavichit, V.

3.2.2 Salicylimine ligands

The target ligands in this work are Schiff bases of salicyladehydes called salicylimines. Twenty-eight salicylimines were synthesized from the condensation reactions of 6 salicyladehydes and 17 chiral amines derived from amino acids (Scheme 3.3). The reaction generally gave satisfactory yields (Table 3.3). The reaction was completed within 24 hours. The ligands which have R^1 as 2-hydroxy-3,5-di-*tert*-butylphenyl (**S2**), 2-hydroxy-3–*tert*-butyl-phenyl (**S3**), 2-hydroxy-5–*tert*-butyl-phenyl (**S4**), and 2-hydroxynaphthyl (**S5**) were purified by column chromatography. Washing with hexane purified the others, including those with R^3 = 2-hydroxyphenyl and 4-ethoxy-2-hydroxyphenyl.



Scheme 3.3 Salicylimine ligand synthesis

All of target salicylimine ligands were shown in Table 3.3.

Table 3.3 Structure of the target salicylimine ligand.

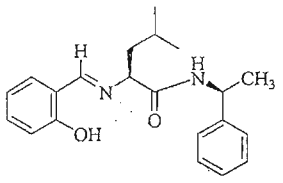
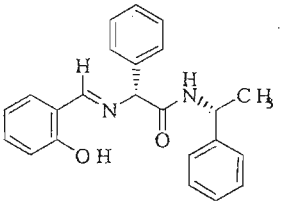
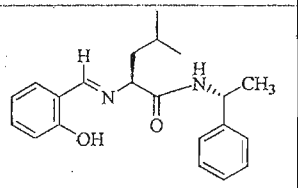
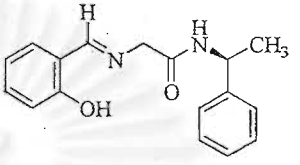
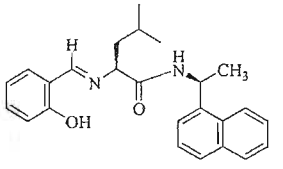
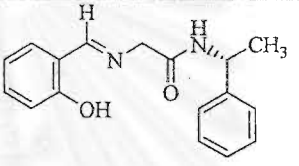
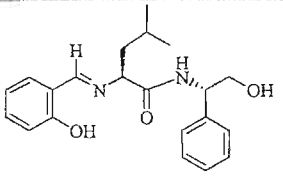
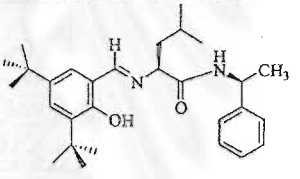
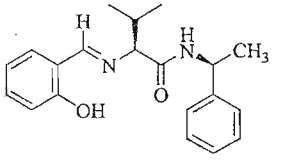
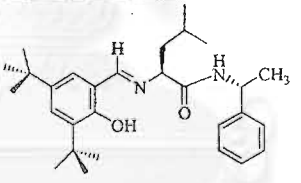
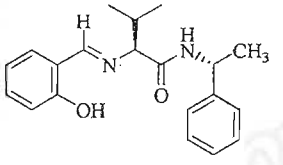
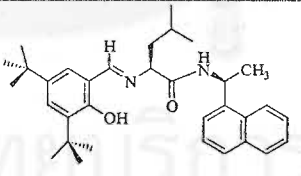
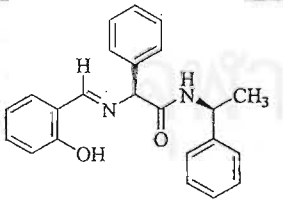
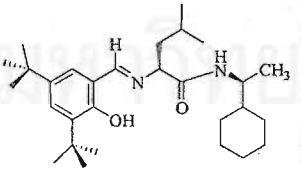
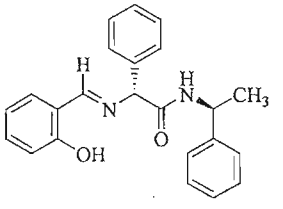
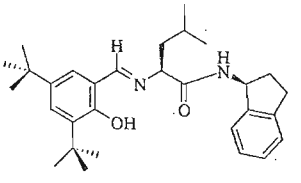
Salicylimine	Code	Salicylimine	Code
	**(*S*,*S*)-S1-Leu-A1**		**(*R*,*R*)-S1-Phg-A1**
	**(*S*,*R*)-S1-Leu-A1**		**(*S*)-S1-Gly-A1**
	**(*S*,*S*)-S1-Leu-A2**		**(*R*)-S1-Gly-A1**
	**(*S*,*S*)-S1-Leu-A3**		**(*S*,*S*)-S2-Leu-A1**
	**(*S*,*S*)-S1-Val-A1**		**(*S*,*R*)-S2-Leu-A1**
	**(*S*,*R*)-S1-Val-A1**		**(*S*,*S*)-S2-Leu-A2**
	**(*S*,*S*)-S1-Phg-A1**		**(*S*,*S*)-S2-Leu-A4**
	**(*R*,*S*)-S1-Phg-A1**		**(*S*,*S*)-S2-Leu-A5**

Table 3.3 Structure of the target salicylimine ligand (continued).

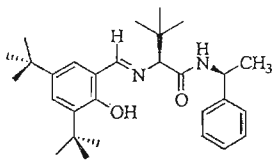
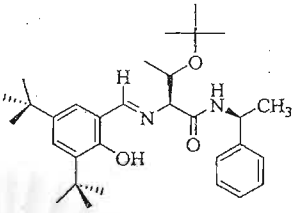
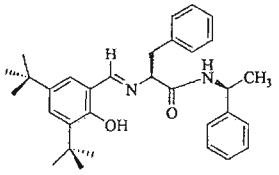
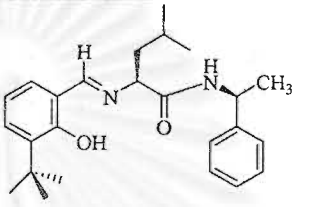
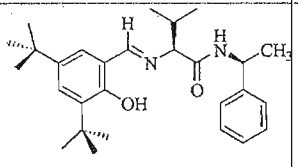
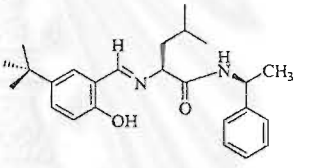
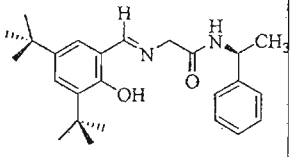
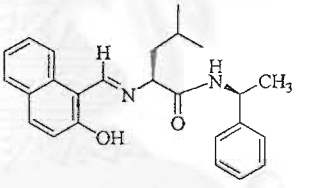
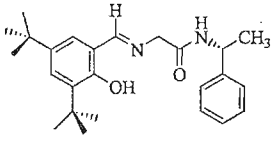
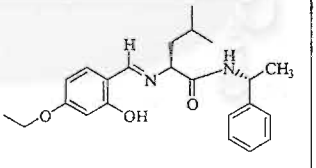
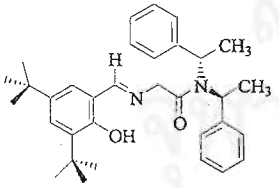
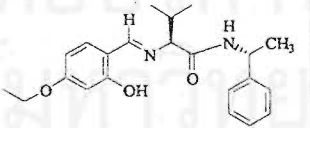
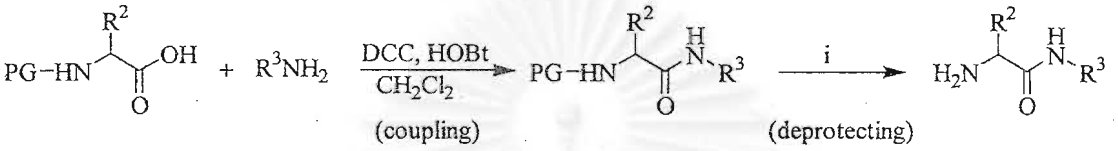
Salicylimine	Code	Salicylimine	Code
	(*S,S*)-S2-*t*Leu-A1		(*S,S*)-S2-Thr-A1
	(*S,S*)-S2-Phe-A1		(*S,S*)-S3-Leu-A1
	(*S,S*)-S2-Val-A1		(*S,S*)-S4-Leu-A1
	(*S*)-S2-Gly-A1		(*S,S*)-S5-Leu-A1
	(*R*)-S2-Gly-A1		(*S, R*)-S6-Leu-A1
	(*S*)-S2-Gly-A6		(*S, R*)-S6-Val-A1

Table 3.4 The percent yield of salicylimine synthesis.

Starting materials		Salicylimine
aldehyde	amine	Yield (%)
Salicylaldehyde	**(*S*, *S*)-Leu-A1**	59
	(*S*, *R*)-Leu-A1	83
	(*S*, *S*)-Leu-A2	69
	(*S*, *S*)-Leu-A3	38
	(*S*, *S*)-Val-A1	67
	(*S*, *R*)-Val-A1	91
	(*S*, *S*)-Phg-A1	81
	(*R*, *S*)-Phg-A1	80
	(*R*, *R*)-Phg-A1	74
	(*S*)-Gly-A1	74
	(*R*)-Gly-A1	78
3, 5–di-*tert*-butyl-salicylaldehyde	**(*S*, *S*)-Leu-A1**	72
	(*S*, *R*)-Leu-A1	77
	(*S*, *S*)-Leu-A2	46
	(*S*, *S*)-Leu-A4	72
	(*S*, *S*)-Leu-A5	59
	(*S*, *S*)-*t*Leu-A1	67
	(*S*, *S*)-Val-A1	57
	(*S*, *S*)-Phe-A1	72
	(*S*)-Gly-A1	57
	(*R*)-Gly-A1	66
	(*S*)-Gly-A6	80
	(*S*, *S*)-Thr(^{t}Bu)-A1	36
3–*tert*-butyl-salicylaldehyde	**(*S*, *S*)-Leu-A1**	64
5–*tert*-butyl-salicylaldehyde	**(*S*, *S*)-Leu-A1**	46
1-napthylsalicyladehyde	**(*S*, *S*)-Leu-A1**	62
4-ethoxysalicyladehyde	**(*S*, *R*)-Leu-A1**	70
	(*S*, *R*)-Val-A1	83

3.2.3 Chiral amines

Seventeen chiral α-aminoamides were used in the synthesis of the salicylimine ligands decribed in section 3.2.2. These α-aminoamides were obtained from 8 α-amino acids and 6 chiral amines applying protecting-coupling-deprotecting chemistry commonly used in the peptide synthesis (Scheme 3.4). The coupling and deprotecting steps gave satisfactory yields of the desired α-aminoamides (Table 3.5).



[1]PG = Boc, i = TFA/CH_2Cl_2 (1:1), rt, 30 min; [2]PG = Cbz, i = H_2, Pd-C/MeOH, rt; [3]PG = Fmoc, i = piperidine, CH_2Cl_2, rt.

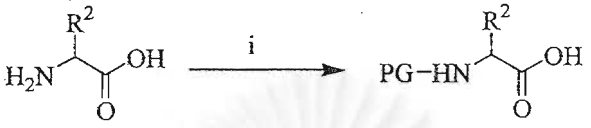
Scheme 3.4 Chiral amine synthesis

Table 3.5 The percent yield of amide coupling and deprotection.

α-aminoamide	% yield of coupling step	% yield of deprotecting step
(*S*, *S*)-Leu-A1	73	83
(*S*, *R*)-Leu-A1	77	78
(*S*, *S*)-Leu-A2	68	81
(*S*, *S*)-Leu-A3	62	30
(*S*, *S*)-Leu-A4	68	99
(*S*, *S*)-*t*Leu-A1	19	96
(*S*, *S*)-Val-A1	86	41
(*S*, *R*)-Val-A1	86	47
(*S*, *S*)-Phe-A1	79	81
(*S*, *S*)-Phg-A1	51	67
(*R*, *S*)-Phg-A1	40	99
(*R*, *R*)-Phg-A1	54	88
(*S*, *S*)-Thr(^{t}Bu)-A1	86	-[a]
(*S*)-Gly-A1	73	64
(*R*)-Gly-A1	89	89

[a]The product was not isolated before the next reaction.

For the protecting step, 6 amino acids were protected with Boc and one amino acid (Gly) was protected with Cbz and one (Thr(^{t}Bu)) with Fmoc. This protecting step gave excellent yields except for the protection of glycine (Table 3.6). The last protected amino acid, Fmoc-Thr(^{t}Bu), was purchased from Nova biochem.



PG = Boc, i = Boc_2O, *t*-BuOH, 4% aq. NaOH

PG = Cbz, i = ZOSu, dimethoxyethane, 4% aq. NaOH

Scheme 3.5 Protection of amino acid

Table 3.6 The percent yield of amino acid protection.

Product (PG-R^2)	Yield (%)
(*S*)-Boc-Leu	84
(*S*)-Boc-*t*Leu	86
(*S*)-Boc-Val	90
(*S*)-Boc-Phe	91
(*S*)-Boc-Phg	88
(*R*)-Boc-Phg	94
Cbz-Gly	19

*t*Leu = *tert*-Leucine

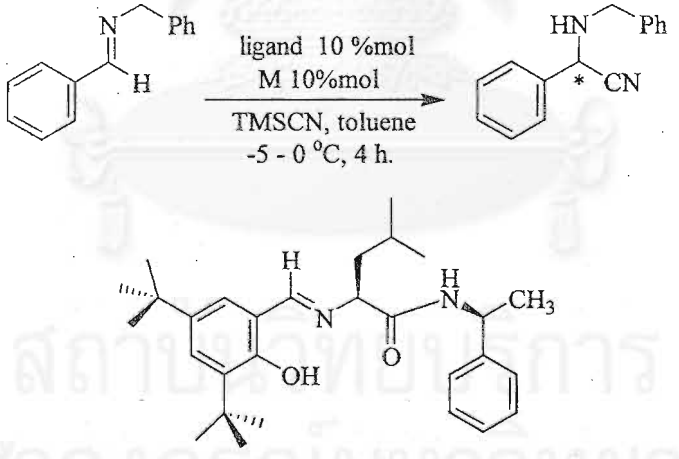
3.3 Catalytic properties of salicylimine ligands and condition for asymmetric Strecker reaction

3.3.1 Ligands and metal ions

The addition of cyanide to *N*-benzylidenebenzylamine was evaluated at –5 to 0 °C for 4 hours in the presence of $Ti(O^iPr)_4$ at 10% mol and the absence of the salicylimine ligand. The reaction gave the expected α-aminonitrile product with >95% conversion and 0% *ee* (entry 1, Table 3.7). When the reaction was carried out in the presence of the salicylimine ligand **(*S*,*S*)-S2-Leu-A1** alone, the enantiomeric

excess was improved to 36% with 34% conversion of the product (entry 2). These results indicated that salicylimine ligand itself was able to catalyze the reaction to a certain extent as well as inducing asymmetry in the product. When the reaction was carried out in the presence of both Ti(^{i}OPr)$_4$ and the ligand (entry 3), the reaction proceeded with very high % conversion and good % *ee*. The reaction was likely to be catalyzed by the Ti-salicylimine complex generated in the reaction. Ti(^{i}OPr)$_4$ itself also catalyzed the reaction (entry 1), however the reaction proceeded without stereoselectivity. $ZrCl_4$-salicylimine catalytic system was less effective in catalyzing the reaction (entry 4), especially in terms of enantioselectivity. These results are in agreement of the observation reported by Jacobsen[14] that the salicylimine-type ligands can catalyze the addition of cyanide ion to the imine. The results observed here, however, present a sharp contrast to Jacobsen's work in that this salicylimine can catalyze the reaction more effectively in the presence of Ti(^{i}OPr)$_4$ while Jacobsen's salicylimine catalyzed the reaction better without any metal ion.

Table 3.7 Catalytic asymmetric Strecker reaction using Ti and Zr metal ion



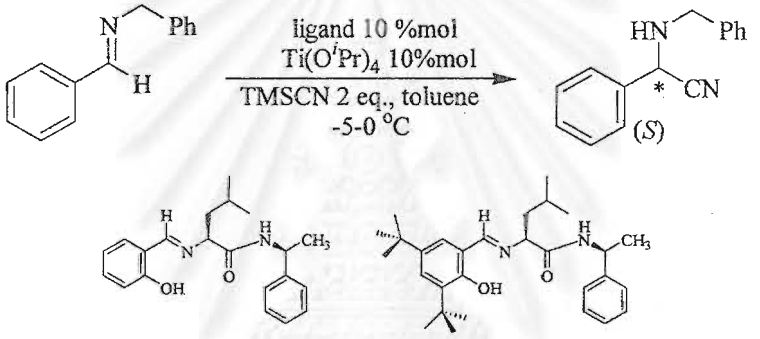
Ligand

entry	M	ligand	Conv. (%)	*ee* (%)
1	Ti(^{i}OPr)$_4$	none	>95	0
2	none	**(*S*,*S*)-S2-Leu-A1**	34	36
3	Ti(^{i}OPr)$_4$	**(*S*,*S*)-S2-Leu-A1**	92	74
4	$ZrCl_4$	**(*S*,*S*)-S2-Leu-A1**	86	21

3.3.2 Reaction time

In the study of catalytic properties of the synthesized salicylimine ligands, the addition of cyanide to the imines was initially performed at –5 to 0 °C using TMSCN as a cyanide source in the presence of a catalytic amount of $Ti(^{i}OPr)_4$ and a salicylimine ligand. Due to the difficulties encountered in controlling the temperature throughout the unnecessarily long reaction time while satisfactory conversion and comparable %*ee* can still be achieved, the reaction was instead performed for 4 hours only (Table 3.2, entry 2).

Table 3.8 Catalytic asymmetric Strecker reaction at 6 and 4 hours for screening time.



(*S*, *S*)-S1-Leu-A1 **(*S*, *S*)-S2-Leu-A1**

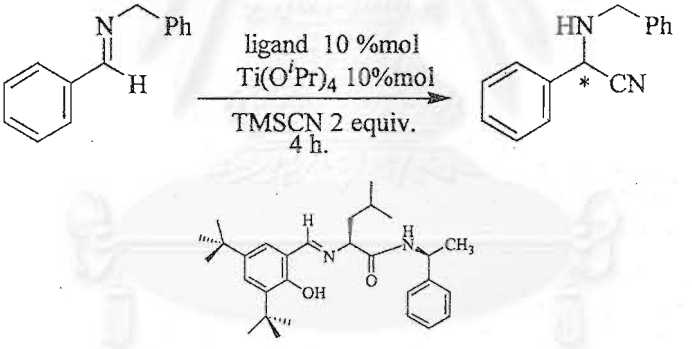
entry	ligand	Time (h.)	Conv. (%)	*ee* (%)
1	**(*S*, *S*)-S1-Leu-A1**	6	94	40
2	**(*S*, *S*)-S1-Leu-A1**	4	42	33
3	**(*S*, *S*)-S2-Leu-A1**	4	92	74

Although the percent conversion dropped significantly when the reaction time was reduced, % *ee* was decreased only slightly. Since the % conversion can usually be improved by extending the reaction time and the 4 hours reaction period provide a fair % conversion with medium level of % *ee*, this reaction period seemed appropriate for further catalyst screening of the other ligands, especially when the experimental expedience was taken into consideration. In fact, further screening showed that both % conversion and % *ee* improved when a ligand with good catalytic activity was used (Table 3.8, entry 3). In later experiments the reaction were thus carried out for only 4 hours unless stated otherwise.

3.3.3 Moisture and proton sources

During catalyst test, reproducibility presented an annoying problem when the reaction was carried out under rigorously anhydrous conditions. Both % conversion and % *ee* dropped sharply from those observed in the reaction using toluene stored over molecular sieves which was suspected to contain some moisture (compare entries 1, 2 and 3, Table 3.9). In fact, a proton source was reported to be necessary in this type of reaction[17] and it is confirmed here that an addition of a protic solvent to the anhydrous condition can improve both % conversion and % *ee* (compare entries 2, 4 and 5, Table 3.9). However, % *ee* slightly lower (entries 4 and 5) than when toluene stored over molecular sieve was used (entry 1). This suggested that, the reaction between HCN and *N*-benzylidenebenzylamine occurred rapidly hence resulting in low selectivity.

Table 3.9 Catalytic asymmetric Strecker reaction under various conditions.



(*S*, *S*)-S2-Leu-A1

entry	condition	Conv. (%)	*ee* (%)
1	toluene[a]	92	74
2	toluene[a]/under N_2	86	38
3	toluene(anh.)/under N_2	21	20
4	toluene(anh.)/H_2O (2 eq.)	98	54
5	toluene(anh.)/*i*PrOH (2 eq.)	98	54
6	toluene[a,b]	96	74

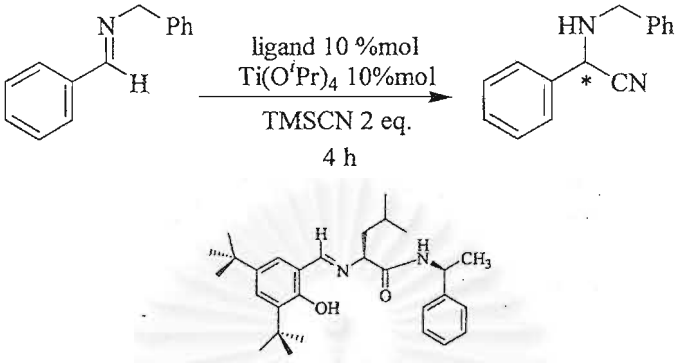
[a]stored over molecular sieve. [b]A solution of TMSCN 50 μL in toluene 150 μL was added slowly in 4 portions of 50 μL every 30 min.

The addition of cyanide in this type of reaction was proposed to proceed through HCN generated *in situ* from TMSCN and a trace amount of protic solvent present in the reaction mixture.[17] There was also report that slow addition of TMSCN into the reaction could increase enantioselectivity due to gradual formation of the reactive HCN hence reducing the background rate.[17] However, in this study, the slow addition of TMSCN did not give different results from the single addition (compare entries 1 and 6).

3.3.4 Temperature

A strategy most frequently used for improving selectivity of a reaction is to lower the reaction temperature. The reaction was thus performed at – 40 °C by using dry-ice acetonitrile (1:1) cold bath. The results were, however, rather discouraging as the reaction went so sluggishly at – 40 °C (Table 3.10). The rate of the reaction was too slow and no product was observed when using toluene as a solvent at –40 °C. However, when the reaction was carried out at –40 °C in the presence of ^{i}PrOH, the *ee* was 41% at 29% conversion. This may because the ^{i}PrOH was good proton source, therefore, HCN was generated and was the active species at the low temperature. Nevertheless, lowering the temperature provided no further advantage in terms of conversion and selectivity, therefore, the reaction temperature was kept between –5 and 0 °C for next experiments.

Table 3.10 Catalytic asymmetric Strecker reaction using ligand (**(*S*,*S*)-S2-Leu-A1**) at different temperature.



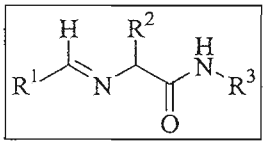
(*S*, *S*)-S2-Leu-A1

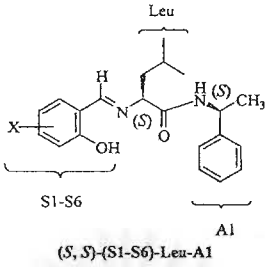
entry	solvent	Temp. (°C)	Conv. (%)	*ee* (%)
1	toluene	-5 – 0	92	74
2	toluene	-40	0	-
3	toluene(anh.)/*i*PrOH (2 equiv.)	-5 – 0	98	54
4	toluene(anh.)/*i*PrOH (2 equiv.)	-40	29	41

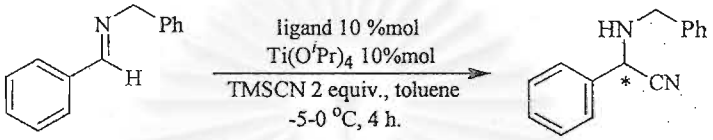
3.3.5 Effect of R^1 substituent (the salicyl moiety) on ligand

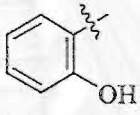
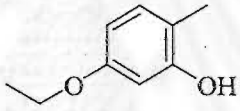
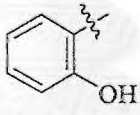
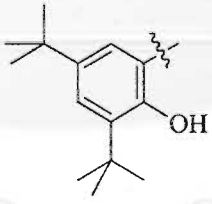
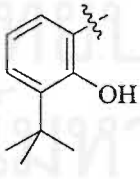
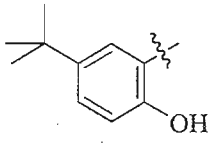
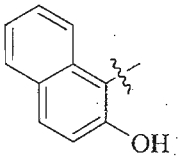
In order to find ligands with high asymmetric catalytic efficiency, effect of R^1 substituent on ligand was investigated first. Effect of R^1 substituent (**S1**, **S2**, **S3**, **S4**, **S5** and **S6**) on the catalytic properties of the ligands was studied by fixing R^2 as isobutyl group and R^3 as 1-phenylethyl which were derived from (*S*)-Leucine (Leu) and methylbenzylamine (A1) building blocks, respectively (Table 3.11). The reactions were carried out in the presence of the catalytic complex formed *in situ* from Ti(^{i}OPr)$_4$ and a salicylimine ligand (10 % mol each) with various R^1.

Table 3.11 Catalytic asymmetric Strecker reaction using salicylimine ligand bearing various R^1(salicyl) substituents.







entry	Ligand[b]	R^1	Conv. (%)	*ee* (%)
1[a]	**(*S*, *R*)-S1-Leu-A1**		96	23 *(R)*
2[a]	**(*S*, *R*)-S6-Leu-A1**		91	4 *(R)*
3	**(*S*, *S*)-S1-Leu-A1**		94	40 *(S)*
4	**(*S*, *S*)-S2-Leu-A1**		92	74 *(S)*
5	**(*S*, *S*)-S3-Leu-A1**		80	52 *(S)*
6	**(*S*, *S*)-S4-Leu-A1**		79	57 *(S)*
7	**(*S*, *S*)-S5-Leu-A1**		>99	47 *(S)*

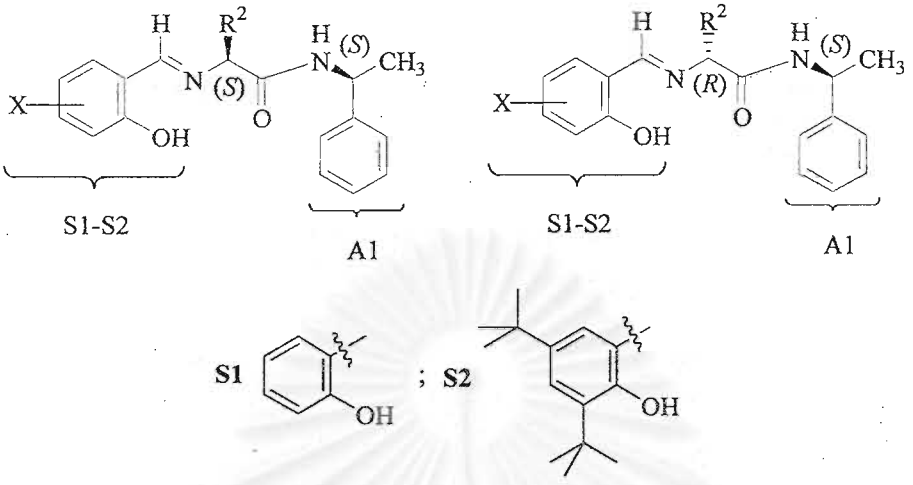
[a] Reaction time was 6 hours. [b] Structures of all ligands are presented in Table 3.4.

The first ligand tested in this reaction was **(*S*,*R*)-S1-Leu-A1** in which R^1 was 2-hydroxyphenyl group derived from unsubstituted salicyladehyde. With this ligand the reaction proceeded with high conversion to give virtually quantitative yield of the (*R*)-aminonitrile in six hours. This ligand, however, provided only moderate enantioselectivity of the reaction (entry 1). When the ligand was changed to **(*S*,*R*)-S6-Leu-A1** in which R^1 was 4-ethoxy-2-hydroxyphenyl group, enantioselectivity of the reaction almost disappeared (entry 2). In the next experiment, the diastereomer of **(*S*, *R*)-S1-Leu-A1**, namely **(*S*,*S*)-S1-Leu-A1**, was tested. This diastereomer gave the α-aminonitrile with opposite configuration (*S*) with significantly higher % *ee* (entry 3). In the subsequent experiments, the effect of R^1 substituent was thus studied based on the (*S*,*S*) isomers. Among six different types of R^1 derived from six different salicylaldehydes (**S1-S6**), the 2-hydroxy-3, 5-di-*tert*-butylphenyl group (S6, entry 4) gave the highest % *ee*. All ligands gave good to virtually quantitative conversion of the imine to the corresponding α-aminonitrile. As the observed % *ee* of the product increased with the increasing steric hindrance of the R^1 group, R^1 was likely to play a primary role in the steroselectivity of the ligands.

3.3.6 Effect of R^2 substituent on ligand

Effect of R^2 substituent on catalytic properties of salicylimine ligands was investigated by varying R^2, and fixing R^3 as 1-phenylethyl and R^1 as either 2-hydroxyphenyl (**S1**) or 2-hydroxy-3,5-di-*tert*-butylphenyl (**S2**). As mentioned in the previous section that the **S1** series gave lower % *ee* than **S2** series and the variation of R^2 by using different types of α-amino acids, Gly, Val, Leu, and Phg, in **S1** series did not improved the % *ee* to the satisfactory level. However, it showed that Gly was the worst and Leu or Val were the best in contributing the enantioselective control of the ligands (Table 3.12, entries 1-4). The effect of R^2 on the enantioselective control of the ligands was more clearly seen in the **S2** series (entries 6-10) and again the best ligand was the one with R^2 = isobutyl derived from Leu amino acid (entry 9). It is interesting to point out here that, unlike the R^1 group, the R^2 group played the more complicated secondary role in stereoselectivity of the ligands as the observed % *ee* did not related directly to the bulkiness of the R^2 substituent.

Table 3.12 Catalytic asymmetric Strecker reaction using salicylimine ligand with various R^2.



entry	Ligand	R^2	Conv. (%)	*ee* (%)
1[a]	**(*S*)-S1-Gly-A1**	-H	84	0
2[a]	**(*S*, *S*)-S1-Val-A1**	$-CH(CH_3)_2$	82	38 (*S*)
3[a]	**(*S*, *S*)-S1-Leu-A1**	$-CH_2CH(CH_3)_2$	42 (94)[a]	33 (40)[a] (*S*)
4	**(*S*, *S*)-S1-Phg-A1**	-Ph	56	29 (*S*)
5	**(*R*,*S*)-S1-Phg-A1**	-Ph	31	15 (*S*)
6	**(*S*)-S2-Gly-A1**	-H	92	23 (*S*)
7	**(*S*, *S*)-S2-Val-A1**	$-CH(CH_3)_2$	>99	58 (*S*)
8	**(*S*, *S*)-S2-*t*Leu-A1**	$-C(CH_3)_3$	70	38 (*S*)
9	**(*S*, *S*)-S2-Leu-A1**	$-CH_2CH(CH_3)_2$	92	74 (*S*)
10	**(*S*, *S*)-S2-Phe-A1**	$-CH_2Ph$	85	46 (*S*)
11	**(*S*, *S*)-S2-Thr(*t*Bu)-A1**	$-CH(CH_3)(O^tBu)$	83	54 (*S*)

[a]Reaction time was 6 hours.

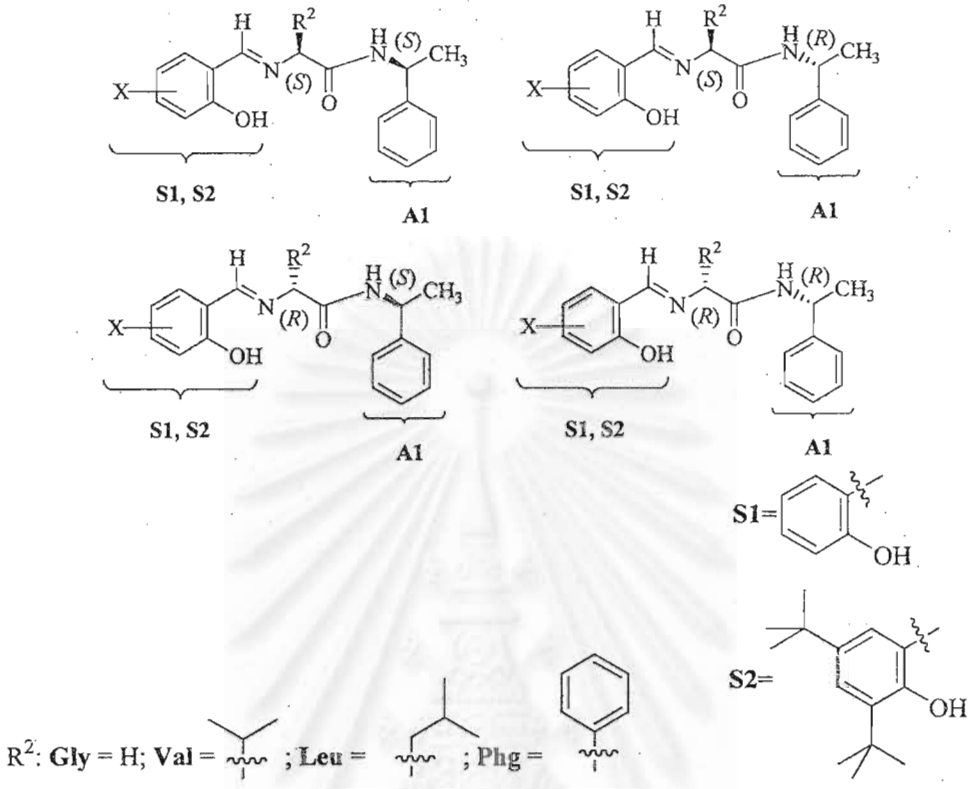
In addition, a variety of R^2 moieties were employed in order to optimize the enantioselectivity with 3,5-di-*tert*-butylsalicylaldehyde **S2** (R^1) and (*S*)-methylbenzylamine **A1** (R^3). The results showed that leucine was the best substituent at R^2 position of the ligand (entries 7-12). In entry 11, ligand **(*S*,*S*)-S2-Thr(tBu)-A1** constituted the most sterically hindered R^2 but the enantioselective induction of this ligand was not as good as **(*S*,*S*)-S2-Leu-A1**. The results showed that the configuration at R^2 was not the major factor to determine the configuration of the product. This is

evidenced when the ligand with *S*-configuration and *R*-configuration at R^2 were compared (entries 4 and 5). Both of R^2 configuration gave the same preferred configuration of the product, i.e. *S*-configuration is preferred. The configuration of the product was not directly affected by the configuration of the R^2 part but more affected by the R^3 part.

3.3.7 Effect of R^2 and R^3 configurations

Effect of R^3 substituent on the stereoselectivity of the ligands such as (*S*)-phenylethylamine, (*R*)-phenylethylamine, (*S*)-1-naphthylethylamine, (*R*)-phenylethoxylamine, (*S*)-cyclohexylethylamine, aminoindane and *S*(*R**,*R**)-bis (pheylethyl)amine was also studied. The results indicated that the configuration (*R* and *S*) of R^3, derived from chiral amine, directly affected the configuration of the aminonitrile product (Table 13.13). The ligands with (*R*) R^3 preferably gave the (*R*) aminonitrile product, while ligands with (*S*) R^3 preferably yielded the (*S*) aminonitrile product. The R^3 substituents, like the R^1 substituents, may thus directly involve with the attacking cyanide ion and play a primary role in governing the stereoselectivity of the reaction. It is also important to point out here that the change of configuration of R^2 did not affect the configuration of the aminonitrile product but it affected cooperatively with R^3 (entries 11-12) as shown by the decreased selectivity for not matched pair (*S*, *R*) compared to the matched pair ((*R*, *R*), (*S*, *S*)) (entries 5, 6 and 9, 10). These results confirmed that R^2 played only the secondary role in governing the enantioselectivity of the ligands. These results presented intriguingly different hypothesis from what was proposed in literatures using ligands with a related structure.[15]

Table 3.13 Effect of R^2 and R^3 configurations on catalytic asymmetric Strecker reaction.

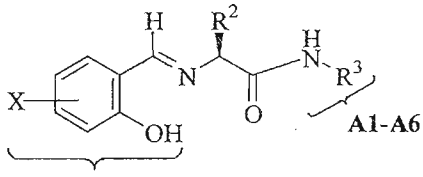


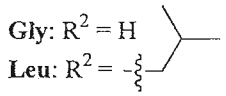
entry	Ligand	Conv. (%)	*ee* (%)
1	(*S*)-S1-Gly-A1	84	0
2	(*R*)-S1-Gly-A1	95	6 (*R*)
3	(*S*)-S2-Gly-A1	92	23 (*S*)
4	(*R*)-S2-Gly-A1	79	20 (*R*)
5	(*S*, *S*)-S1-Val-A1	82	38 (*S*)
6	(*S*, *R*)-S1-Val-A1	77	10 (*R*)
7	(*S*, *S*)-S1-Leu-A1	94	40 (*S*)
8	(*S*, *R*)-S1-Leu-A1	96	23 (*R*)
9	(*S*, *S*)-S2-Leu-A1	92	74 (*S*)
10	(*S*, *R*)-S2-Leu-A1	55	43 (*R*)
11	(*S*, *S*)-S1-Phg-A1	56	29 (*S*)
12	(*R*, *S*)-S1-Phg-A1	31	15 (*S*)

3.3.8 Effect of R^3 bulkiness

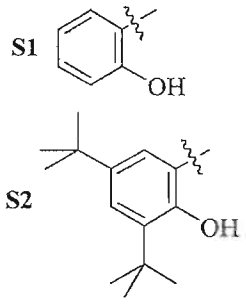
With the previous hypothesis about the role of R^3 substituents in mind, increasing the bulkiness of R^3 should improve the enantioselectivity of the ligands. Generally, higher enantioselectivity was obtained from the reaction with the ligands containing bulkier R^3 substituent (Table 3.14). Ligand **(*S*, *S*)-S2-Leu-A2** constituted 3,5-di-*tert*-butylsalicylimine moiety and dipeptides derived from L-leucine, and (*S*)-1-napthylethylamine showed the best enantiomeric selectivity. The ligand gave 84 % *ee* of product with *S* configuration. It is interesting to note that **(*S*, *S*)-S1-Leu-A3,** in which the R^3 substituent contained a hydroxy group, displayed no enantioselectivity (entry 5). There is no clear explanation, which can be deduced from this observation at present. Nevertheless, these results clearly showed that the steric hindrance of R^1 and R^3 worked cooperatively in enhancing the enantioselectivity of the ligands. Although, the bulkiest R^3 substituent showed promising and interesting results in ligand **(*S*)-S2-Gly-A6** (entry 2 compared to entry 1) in terms of %*ee* and yield of the product, it was unfortunate that this substituent (A6) which have extremely high steric hindrance could not be synthetically incorporated into the **S2-Leu** moiety to confirm the hypothesis.

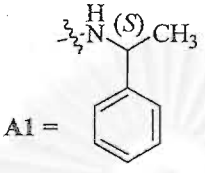
Table 3.14 Catalytic asymmetric Strecker reaction using ligand in various R^3

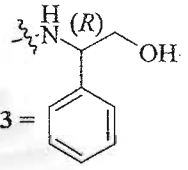


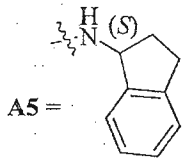


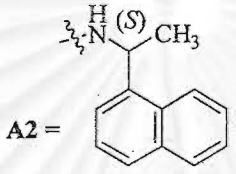
S1, S2

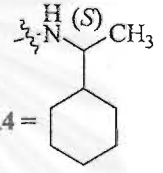


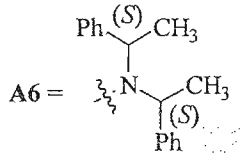










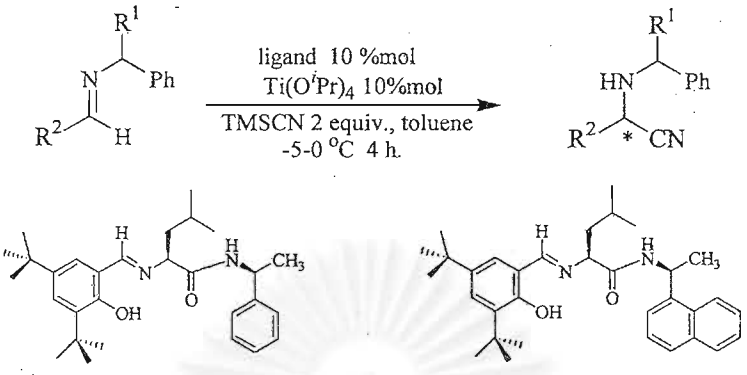


entry	Ligand	Conv. (%)	*ee* (%)
1	**(*S*)-S2-Gly-A1**	92	23 (*S*)
2	**(*S*)-S2-Gly-A6**	>99	39 (*R*)
3	**(*S*, *S*)-S1-Leu-A1**	94	40 (*S*)
4	**(*S*, *S*)-S1-Leu-A2**	95	37 (*S*)
5	**(*S*, *R*)-S1-Leu-A3**	80	0
6	**(*S*, *S*)-S2-Leu-A1**	92	74 (*S*)
7	**(*S*, *S*)-S2-Leu-A2**	92	84 (*S*)
8	**(*S*, *S*)-S2-Leu-A4**	94	77 (*S*)
9	**(*S*, *S*)-S2-Leu-A5**	71	49 (*S*)

3.3.9 Substrate dependence

Various imines were reacted with TMSCN in the presence of **(*S*, *S*)-S2-Leu-A1** or **(*S*, *S*)-S2-Leu-A2** salicylimine ligands. Most of the aromatic imines (entries 1-5, 7 and 9-12, Table 3.15) gave satisfactory results except for those bearing strong electron donating group at the *ortho* or *para* position of the benzene ring (entries 6 and 8).

Table 3.15 Asymmetric addition of cyanide to various imines using salicylimine ligands.



(*S*, *S*)-S2-Leu-A1 **(*S*, *S*)-S2-Leu-A2**

entry	salicylimine ligand	imine		Conv. (%)	*ee* (%)
		R^1	R^2		
1	**(*S*, *S*)-S2-Leu-A1**	H	Ph	92	74
2	**(*S*, *S*)-S2-Leu-A2**	H	Ph	92	84
3	**(*S*, *S*)-S2-Leu-A1**	H	4-ClC_6H_4	96	76
4	**(*S*, *S*)-S2-Leu-A2**	H	4-ClC_6H_4	97	89
5	**(*S*, *S*)-S2-Leu-A1**	H	3-ClC_6H_4	>99	63
6	**(*S*, *S*)-S2-Leu-A1**	H	2-$MeOC_6H_4$	>95	10
7	**(*S*, *S*)-S2-Leu-A1**	H	3, 4-$(MeO)_2C_6H_3$	75	73
8	**(*S*, *S*)-S2-Leu-A1**	H	4-$MeOC_6H_4$	98	0
9	**(*S*, *S*)-S2-Leu-A1**	H	3-$MeOC_6H_4$	90	84
10	**(*S*, *S*)-S2-Leu-A2**	H	3-$MeOC_6H_4$	97	88
11	**(*S*, *S*)-S2-Leu-A1**	H	4-$CH_3C_6H_4$	95	64
12	**(*S*, *S*)-S2-Leu-A1**	H	1-Naphthyl	>99	63
13	**(*S*, *S*)-S2-Leu-A1**	H	$(CH_3)_3C$	94	0
14	**(*S*, *S*)-S2-Leu-A1**	Ph	Ph	61	0

The **(*S*, *S*)-S2-Leu-A1** did not show any enantioselectivity in the cyanation of the sterically hindered aliphatic imine, *t*-butylmethylene imine (entry 13). Similar results have been reported in the literatures.[5,6] Surprisingly though, the cyanation of *N*-benzylidenebenzhydrylimine gave essentially racemic product (entry 14). This highly steric aromatic imine has been reported to be one of the best substrates in the

enantioselective addition of cyanide with various types of catalysts.[13,15] This and other results, discussed previously, implied that the ligands synthesized in this work catalyzed the addition of cyanide to the imines through a transition state with a structure quite different from what was proposed for the related ligands reported in the literatures.[18]

CHAPTER IV

CONCLUSION

The investigation had been carried out to search for novel optically active catalysts for the asymmetric Strecker reaction. The work had focused on the utilization of various salicylimine ligands with appropriate metal as active catalysts. The twenty-eight salicylimine ligands constituted of salicylaldehyde derivatives, optically amino acids and chiral amine moieties were synthesized successfully by using protection-condensation-deprotection techniques commonly used in peptide synthesis.

The catalytic properties of these salicylimine ligands and condition for asymmetric Strecker reaction were investigated. The results revealed that salicylimine ligand in the presence of $Ti(O^iPr)_4$ was an active catalyst to produce α-aminonitrile. The best condition for the catalytic system involved HCN derived from TMSCN and a protic solvent as a cyanide source in toluene at –5-0 °C. High conversion was observed in 4 hours for good catalytic system. Effect of substituents on salicylimine ligands was explored. The bulkiness of salicylaldehyde moiety was an important factor controlling the degree of asymmetric induction. In addition, the optimum steric hindrance of optically active amino acids was required to improve the enantioselectivity. The configuration of product was controlled by stereochemistry of chiral amine unit for instance, (*R*)-chiral amine gives (*R**)-product and *vice versa*.

High conversion (75-99%) and high enantiomeric excess (63-89%) were observed for the cyanide addition to various aromatic imines in the presence of **(*S*, *S*)-S2-Leu-A1** or **(*S*, *S*)-S2-Leu-A2** salicylimine ligands and $Ti(O^iPr)_4$ except the imines bearing strong electron donating group at the *ortho* or *para* position.

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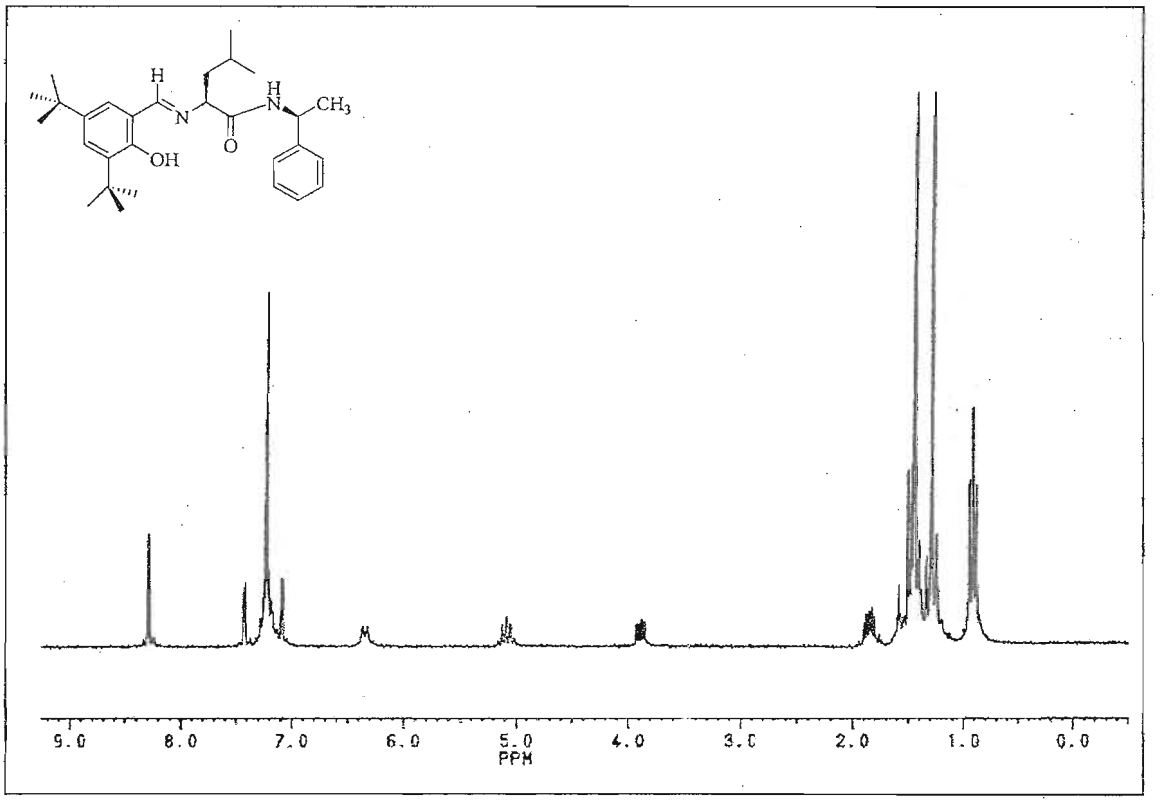
APPENDIX



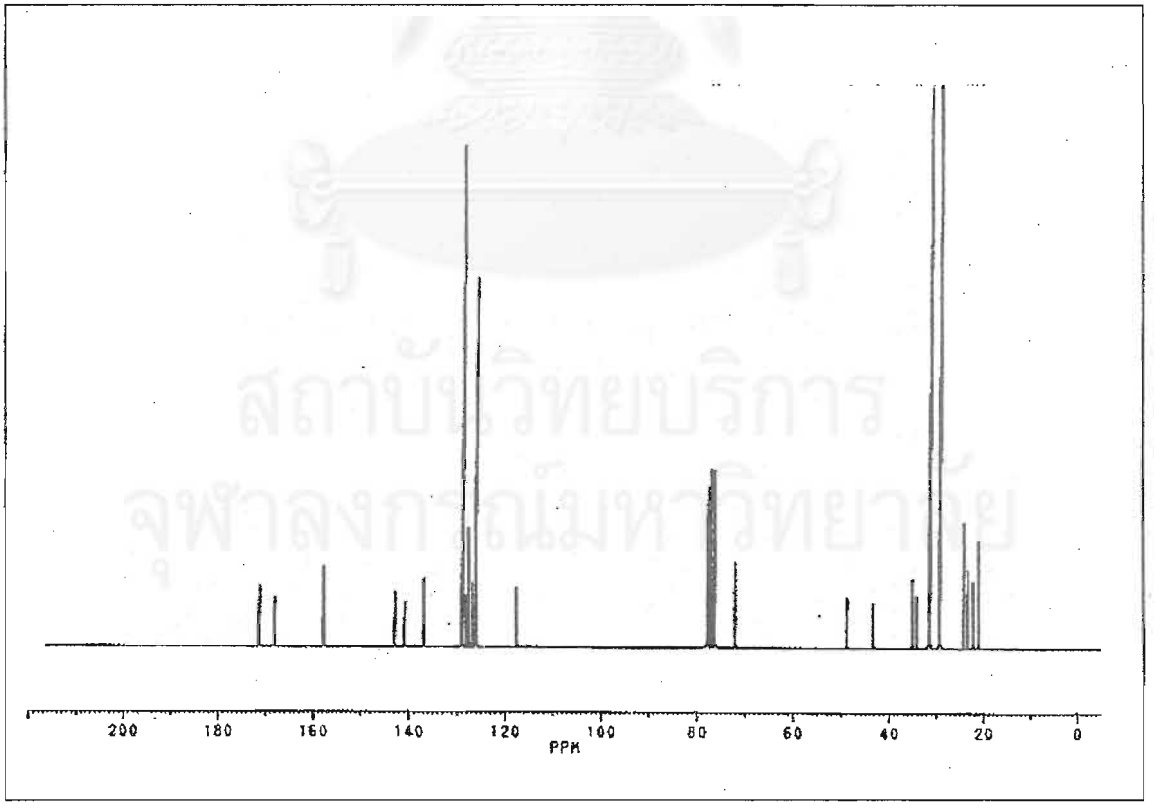


Figure 1 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-Leu-A1**.

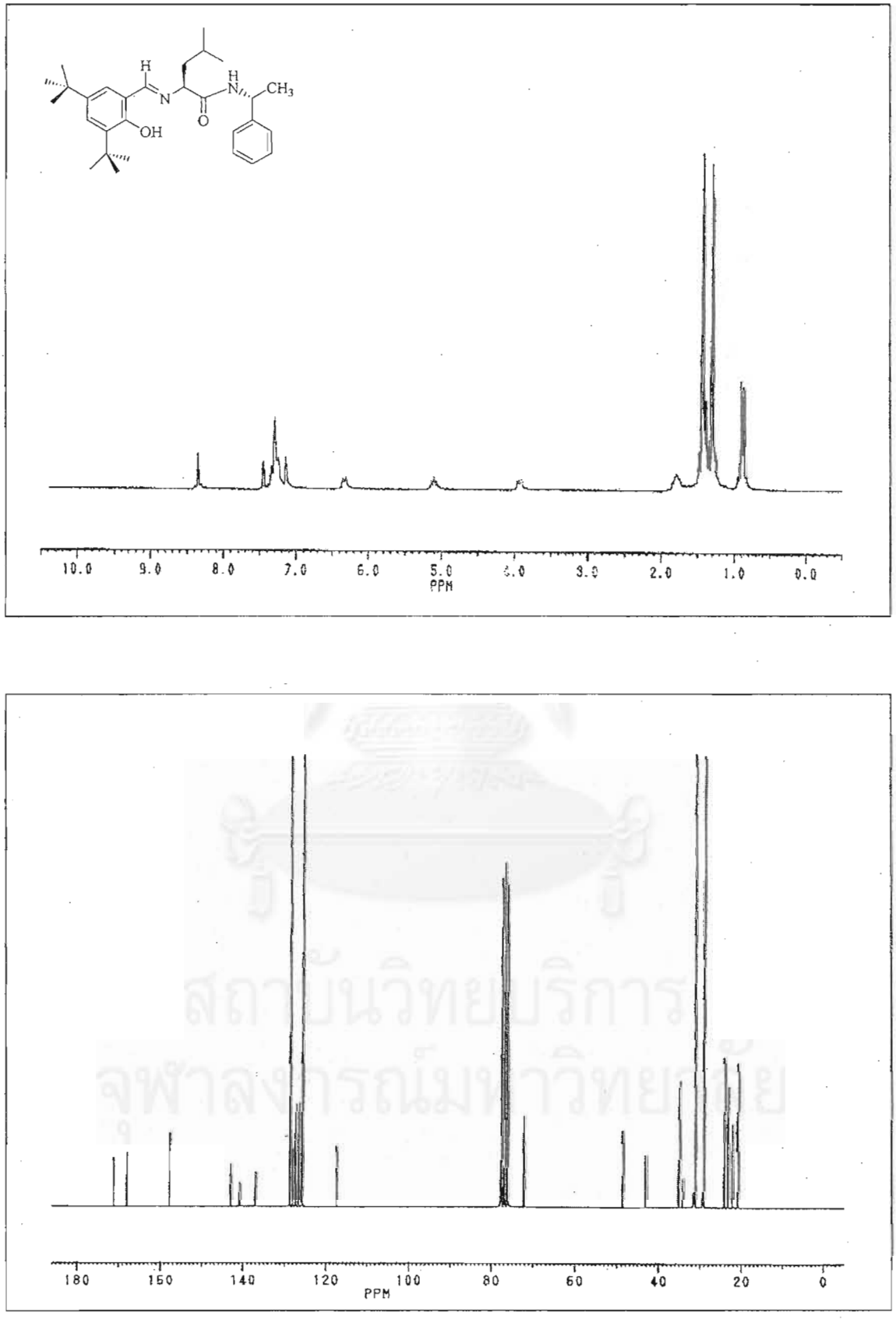
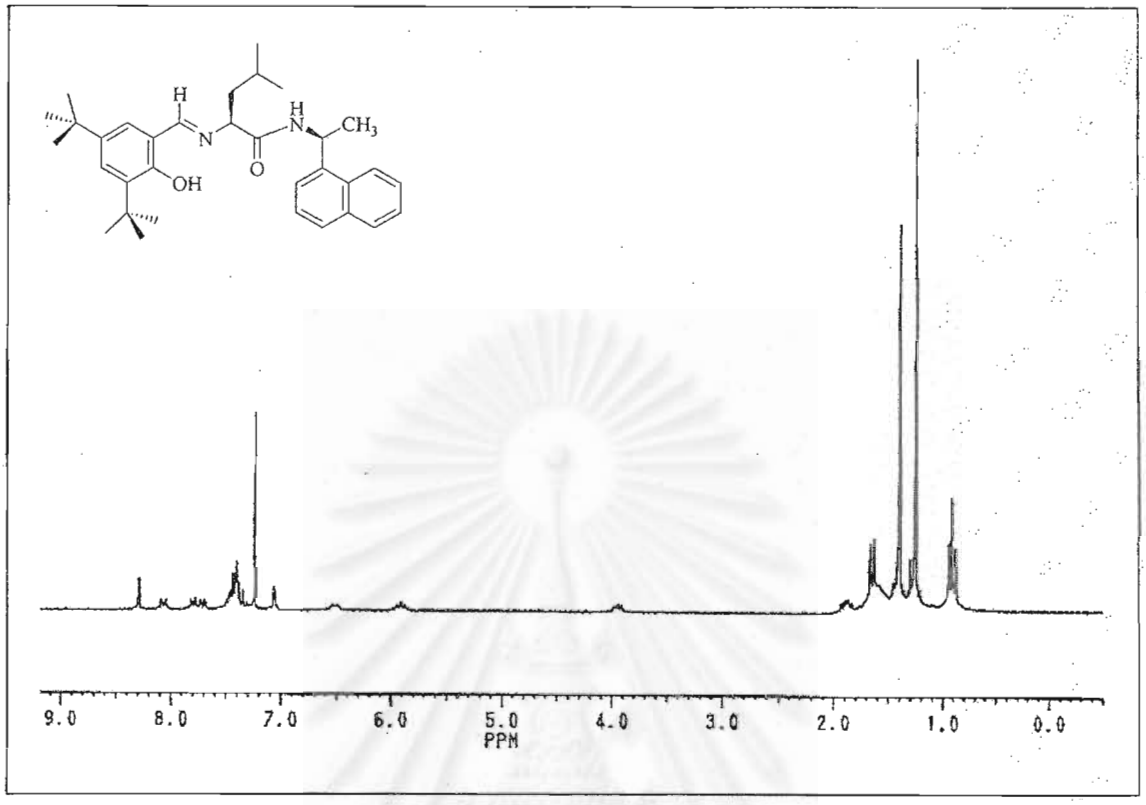


Figure 2 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *R*)-S2-Leu-A1**.



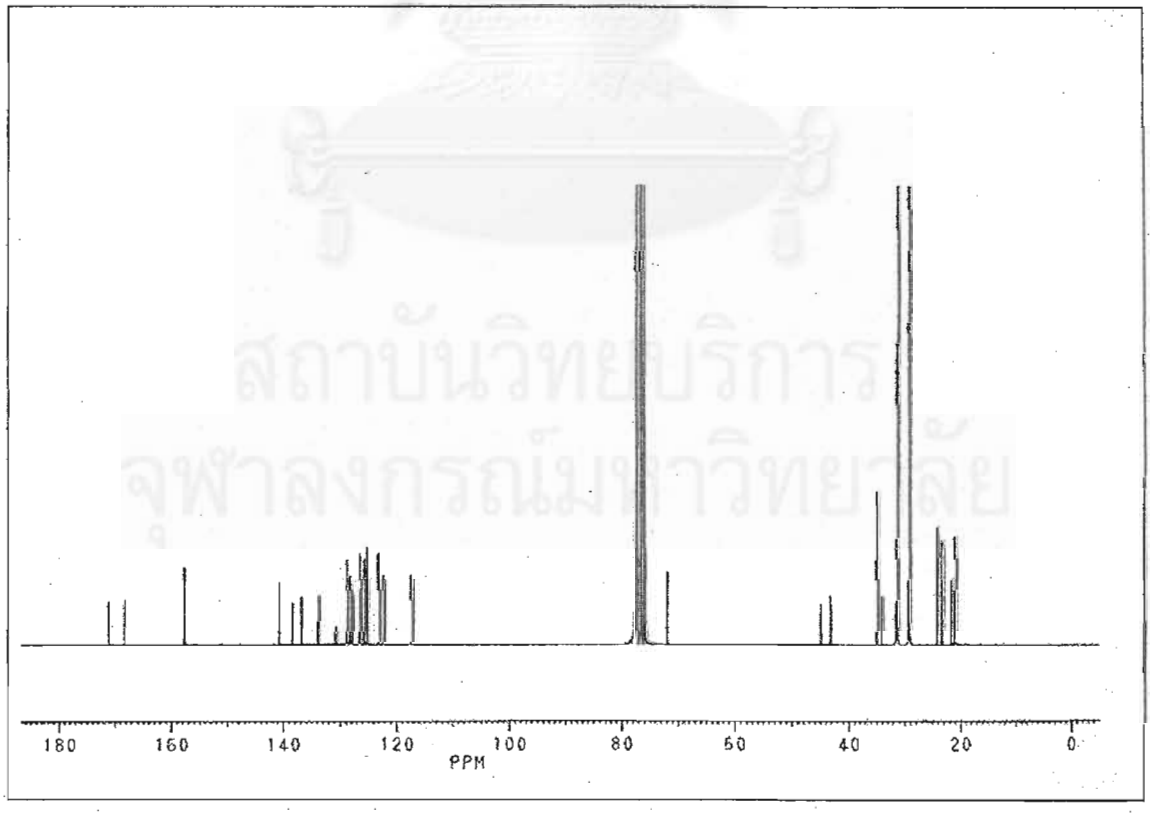


Figure 3 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-Leu-A2**.

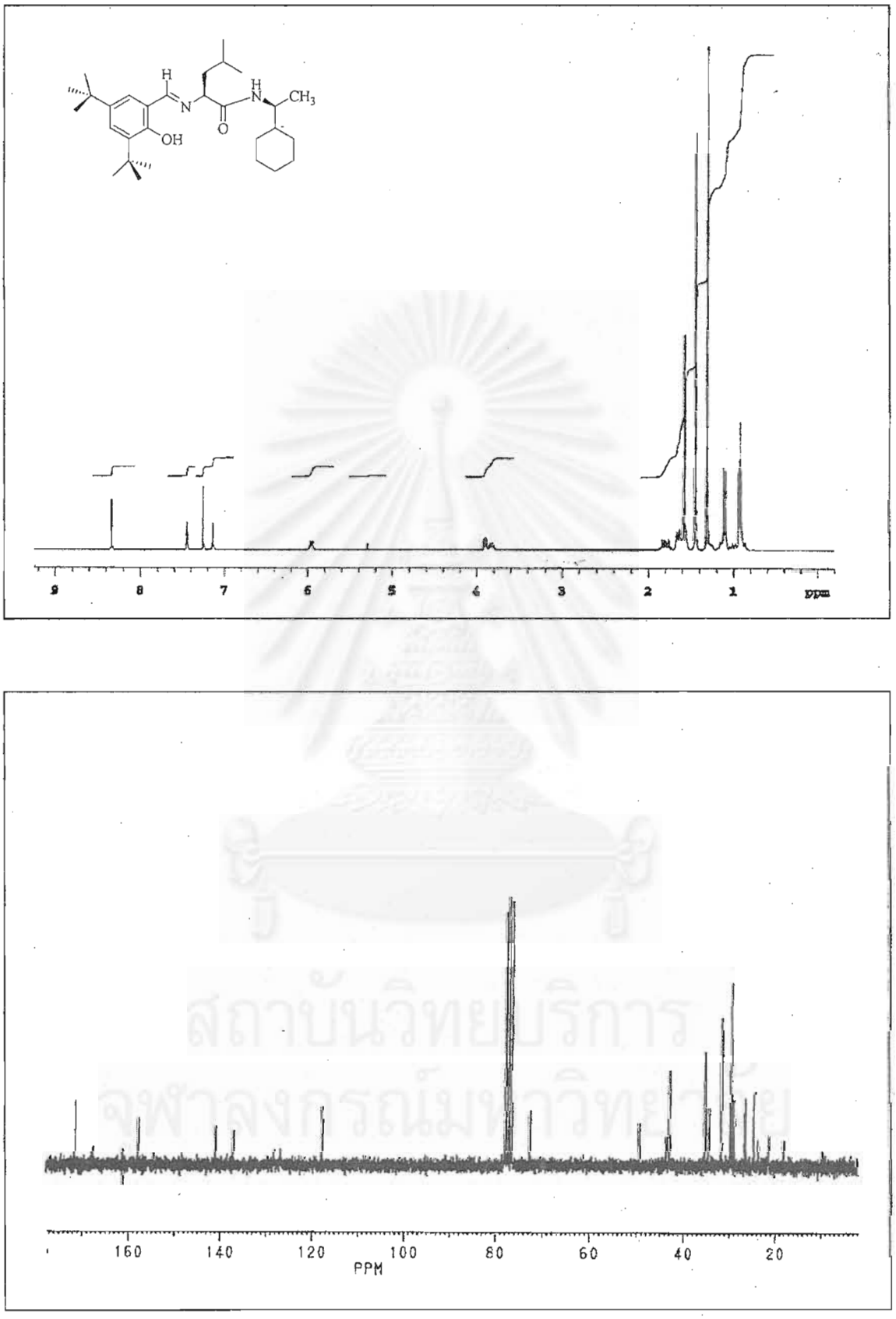


Figure 4 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-Leu-A4**.

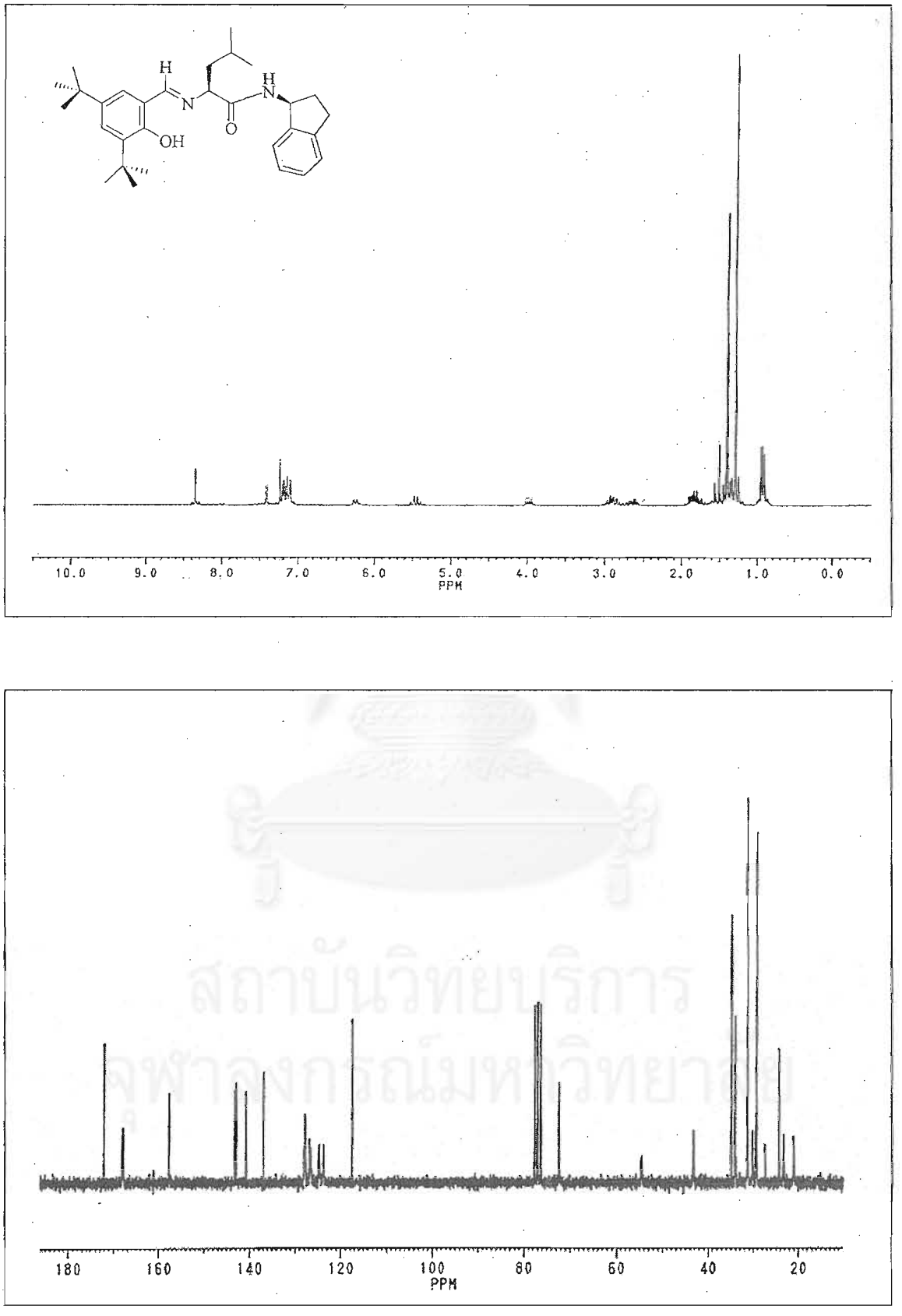


Figure 5 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-Leu-A5**.

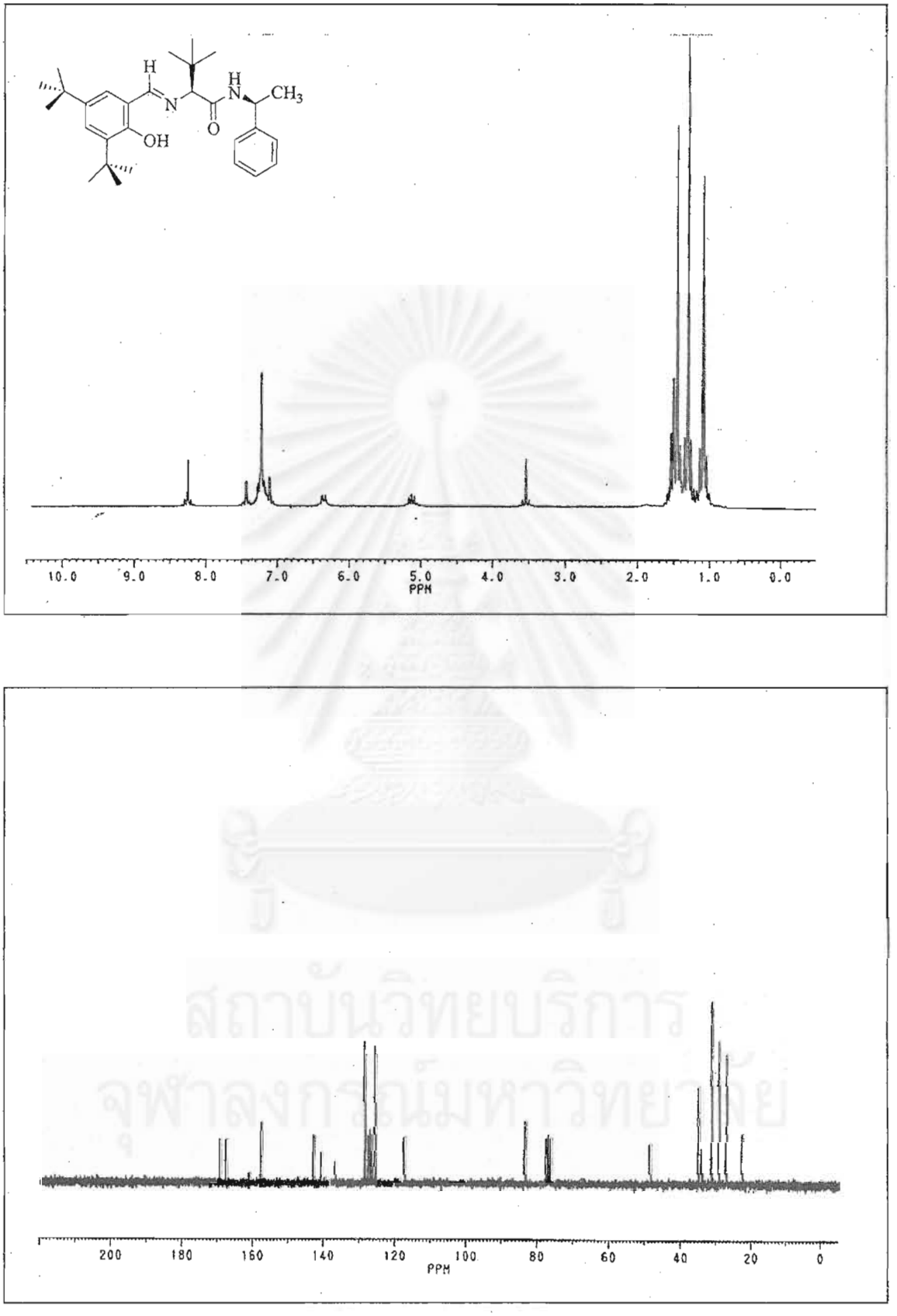


Figure 6 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-*t*Leu-A1**.

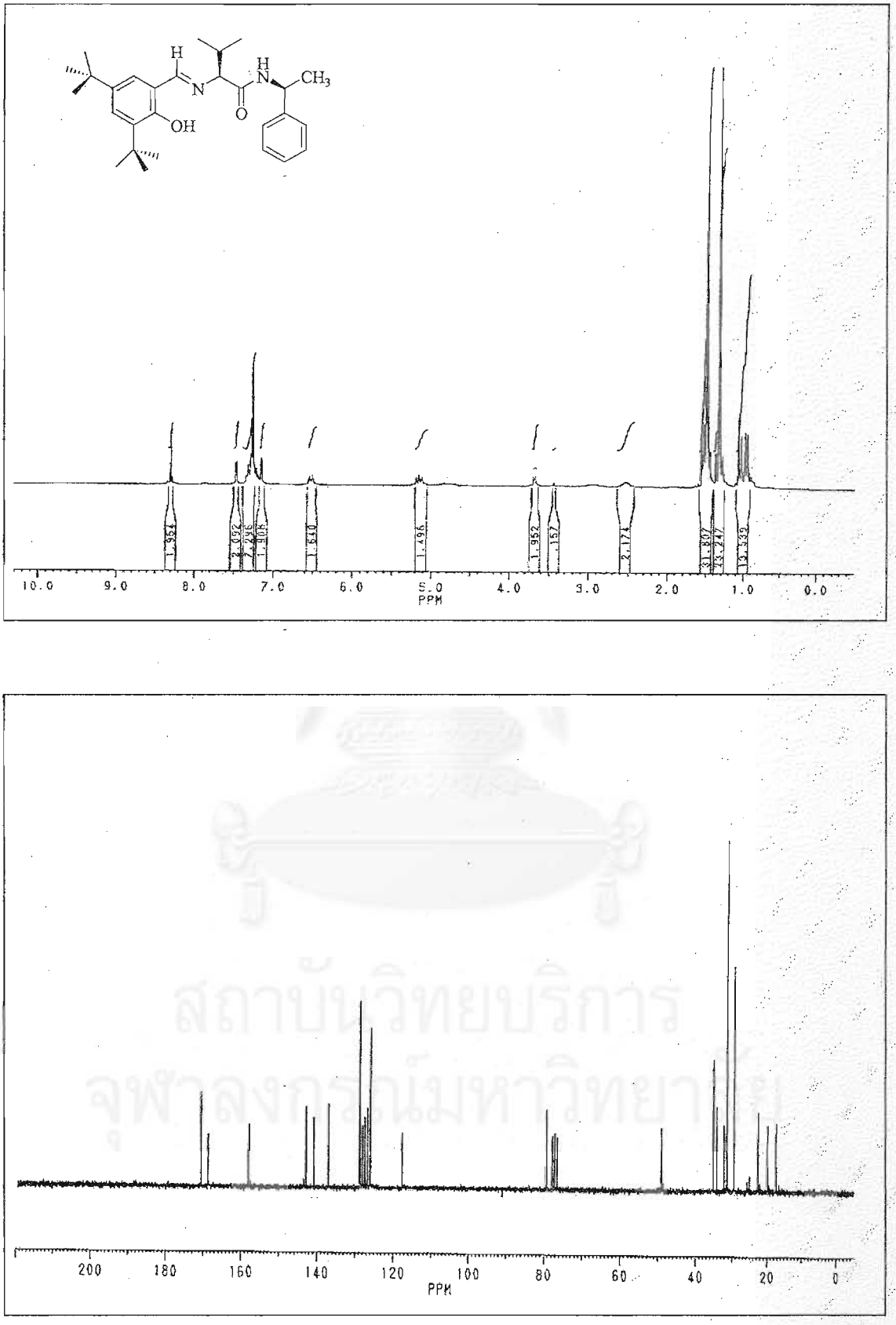


Figure 7 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-Val-A1**.

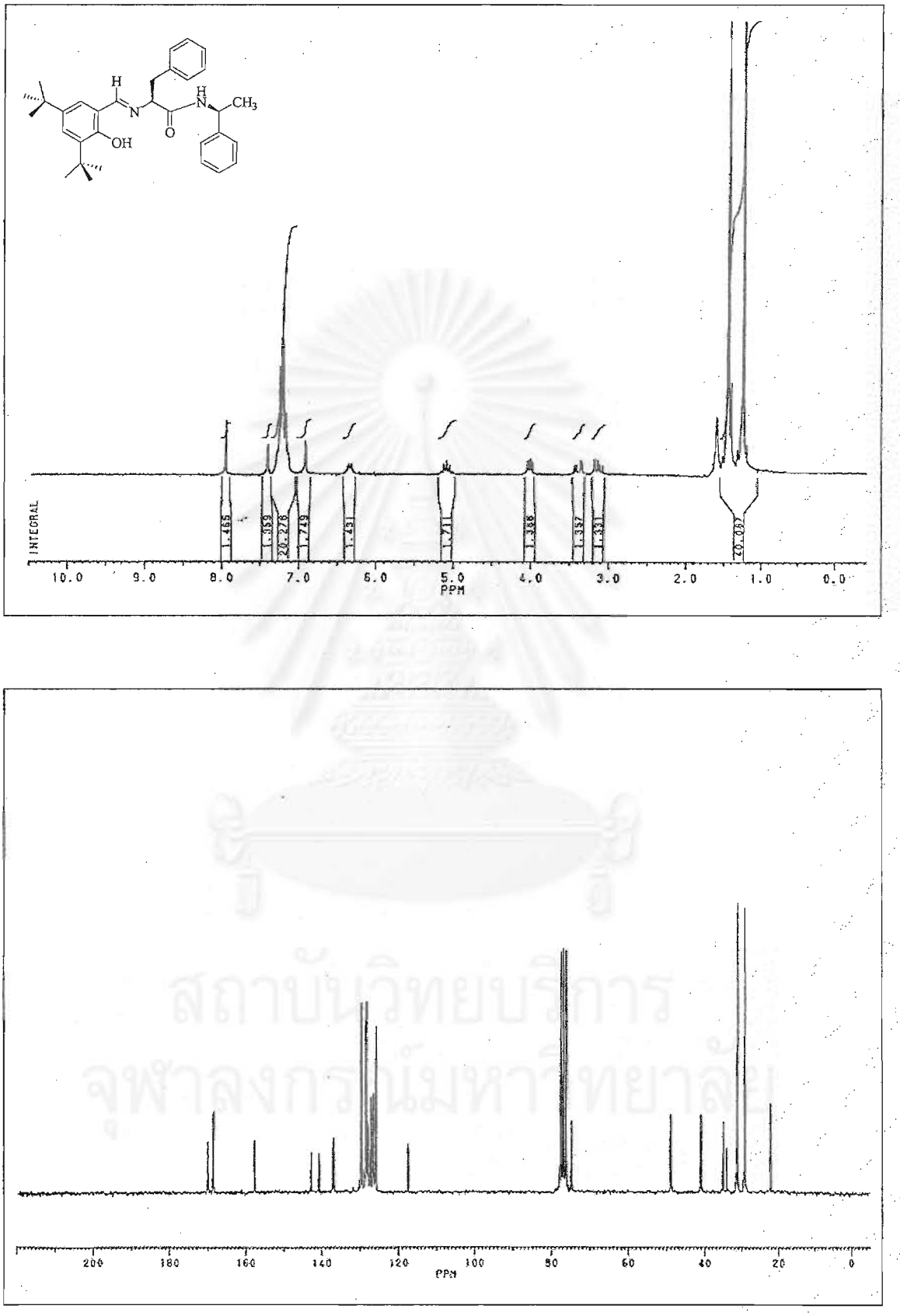


Figure 8 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-Phe-A1**.

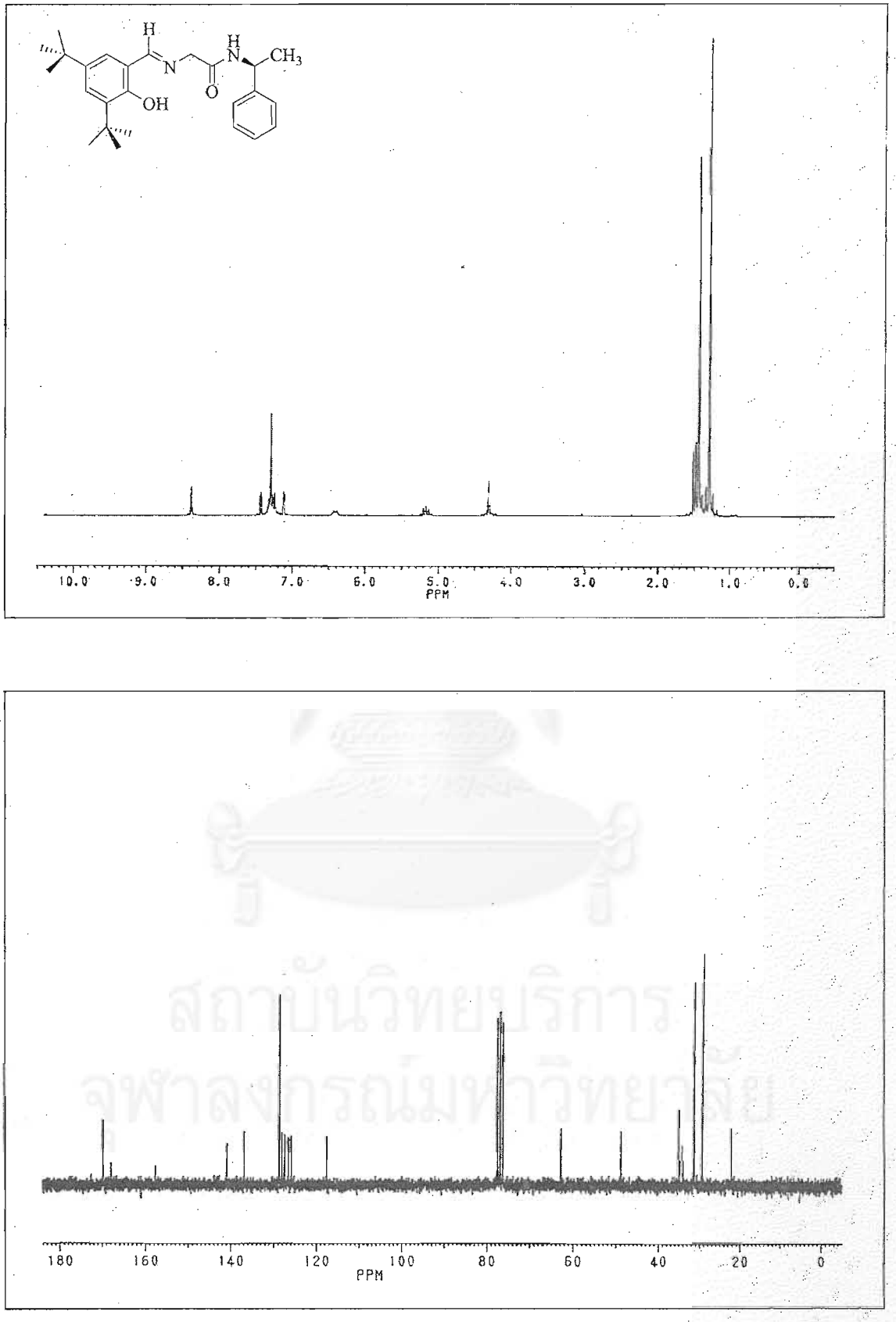
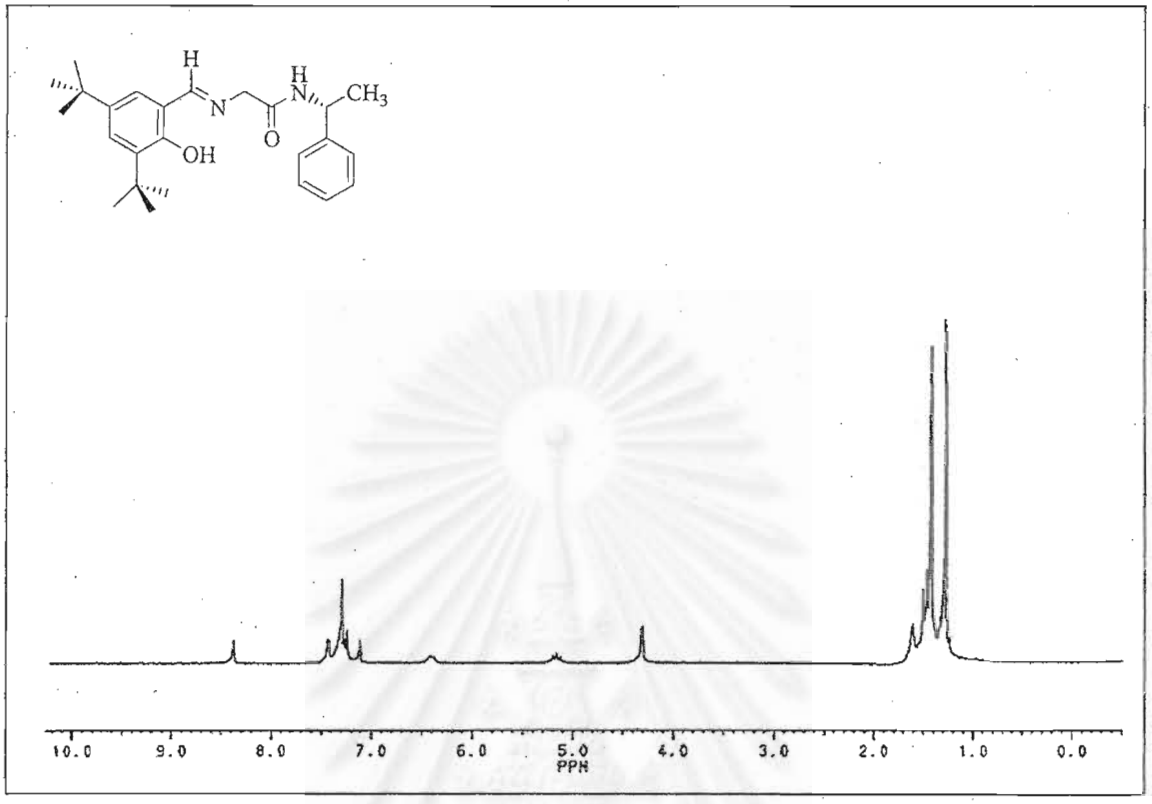


Figure 9 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*)-S2-Gly-A1**.



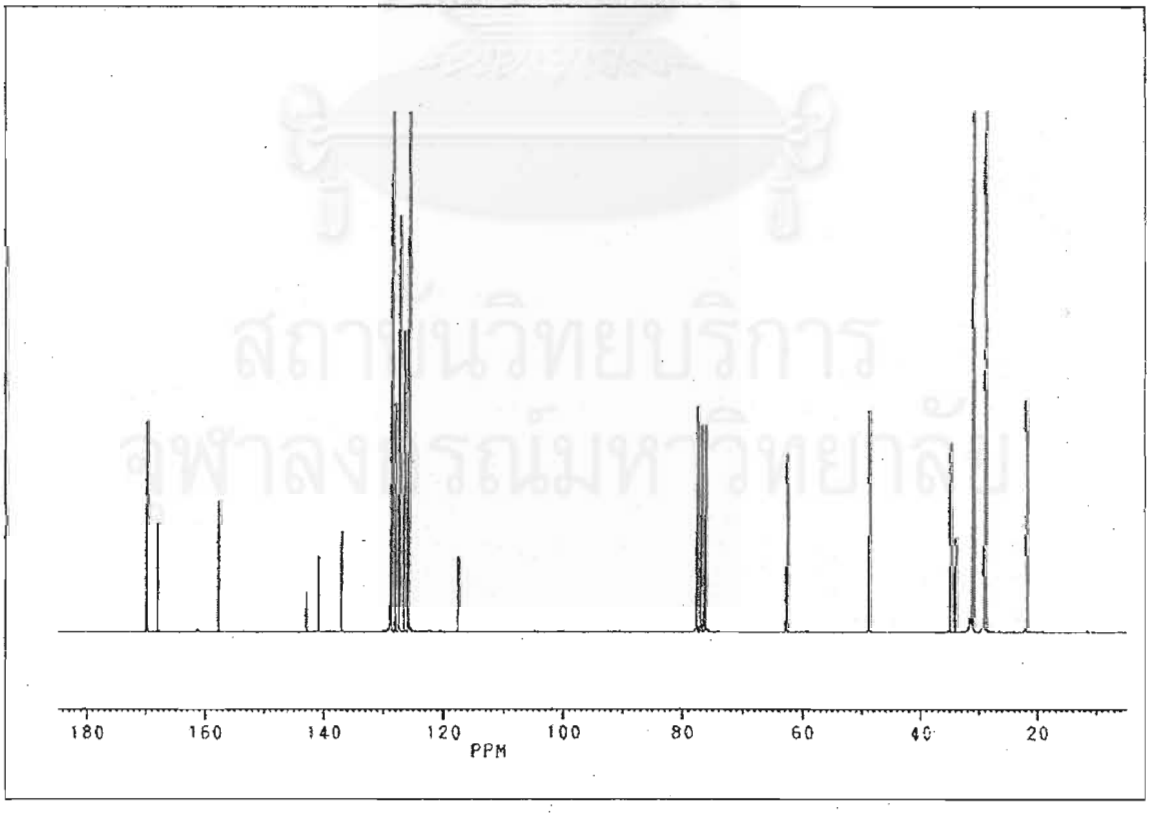
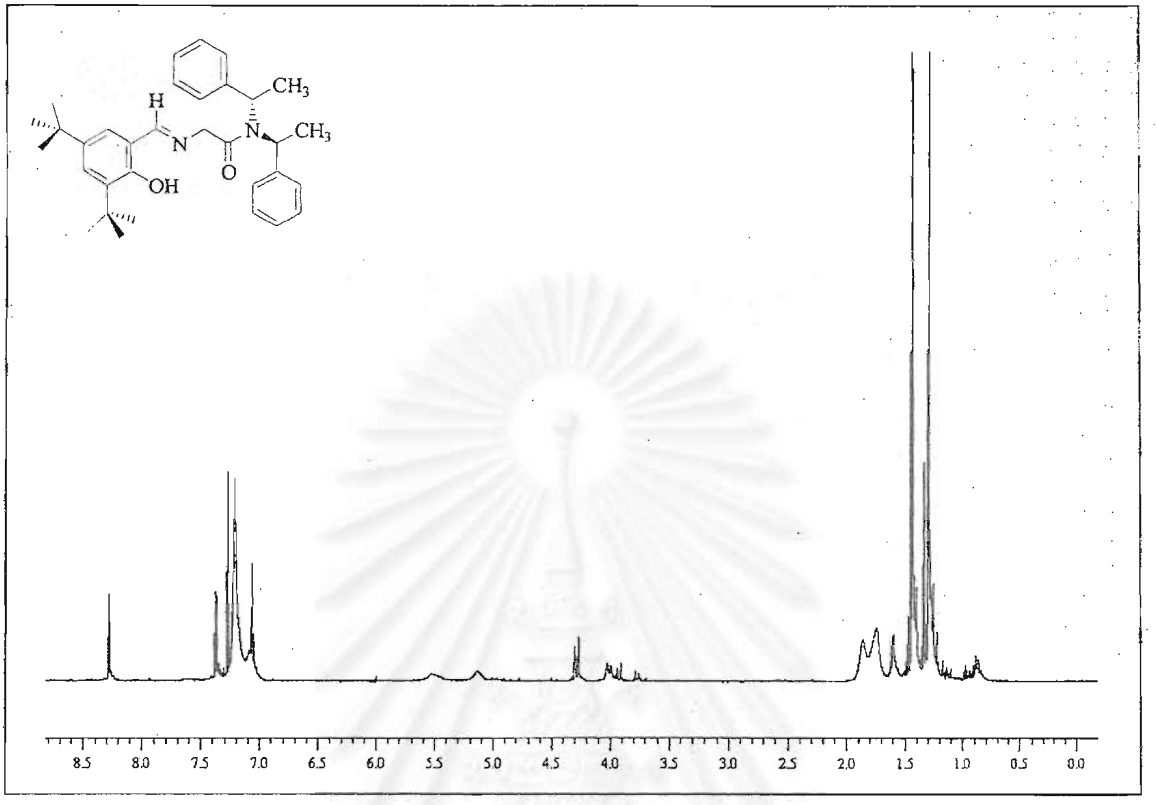


Figure 10 The ^{1}H NMR and ^{13}C NMR spectra of **(*R*)-S2-Gly-A1**.



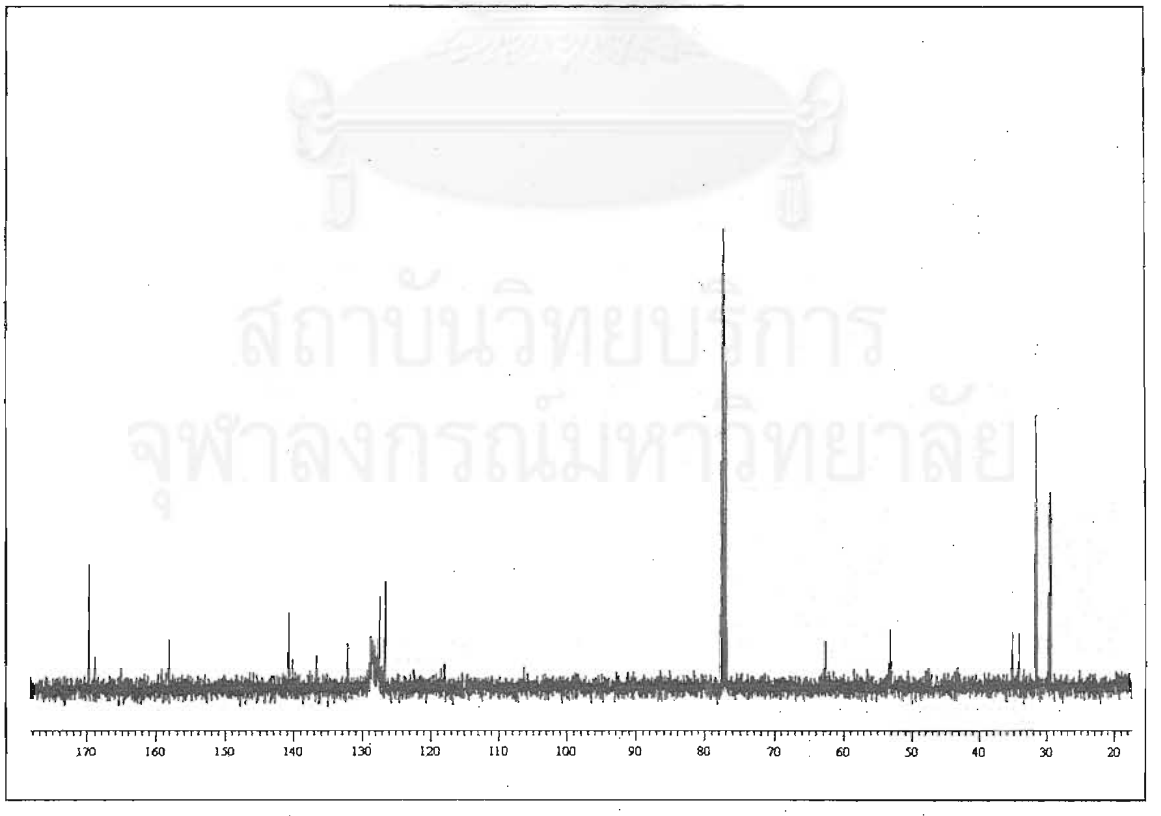
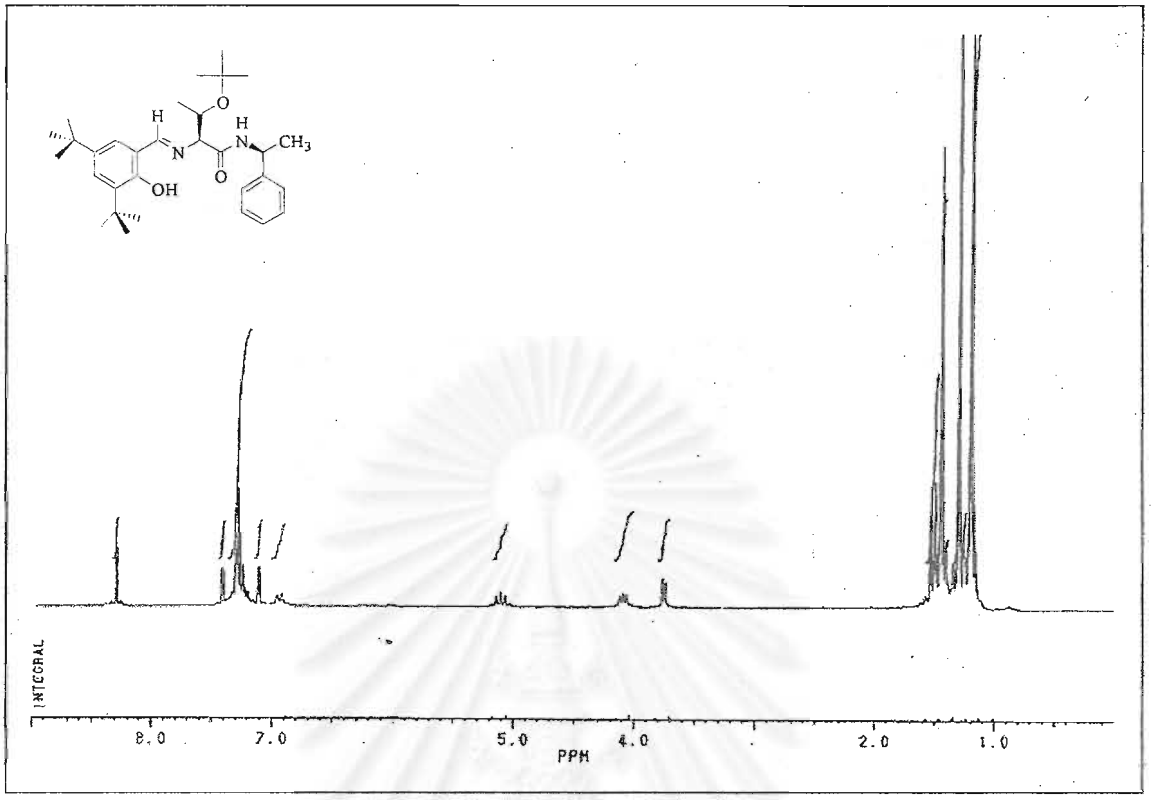


Figure 11 The ^{1}H NMR and ^{13}C NMR spectra of **(S)-S2-Gly-A6**.



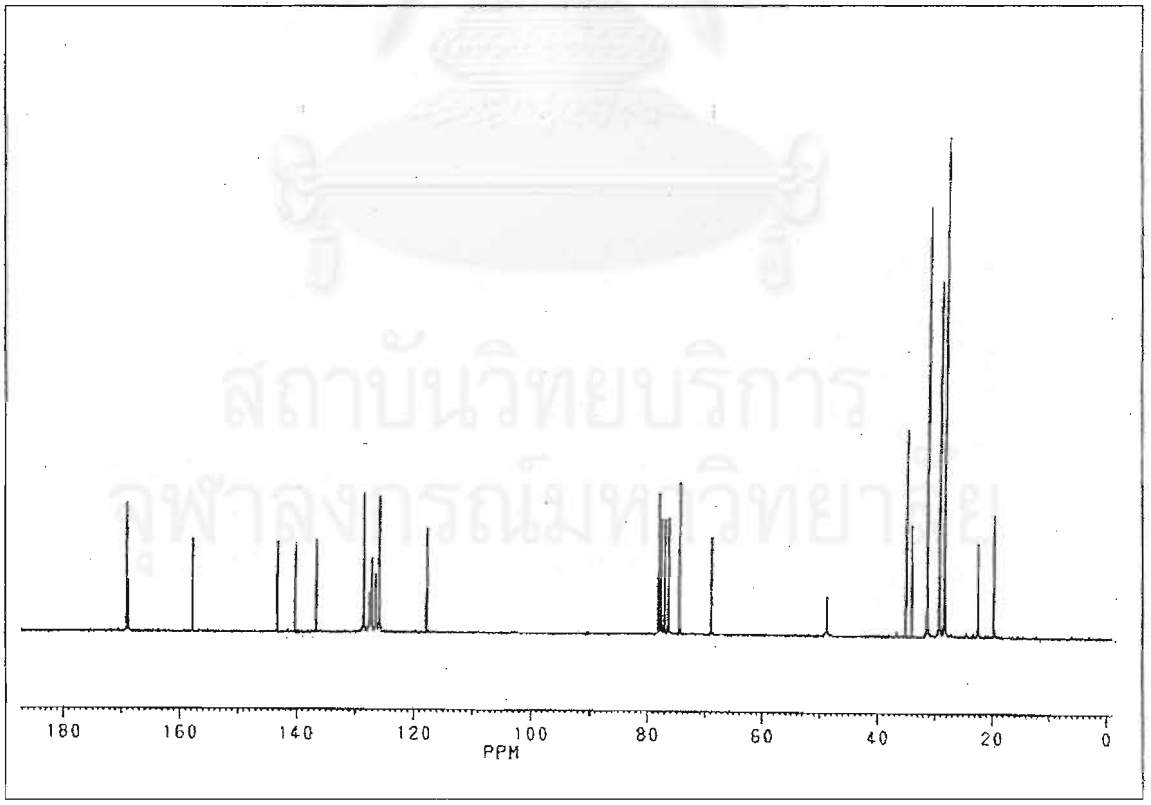


Figure 12 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S2-Thr(ᵗBu)-A1**.

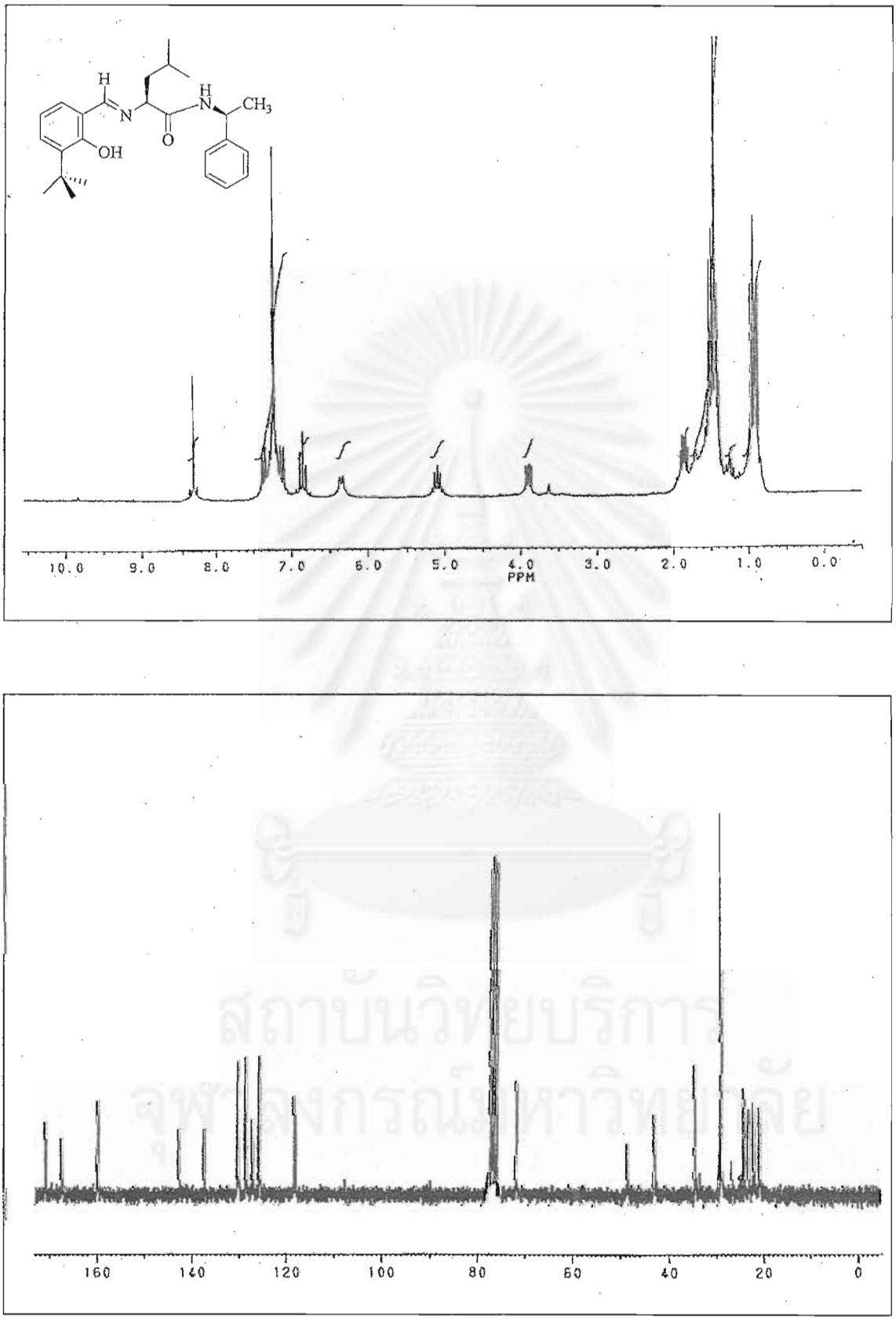
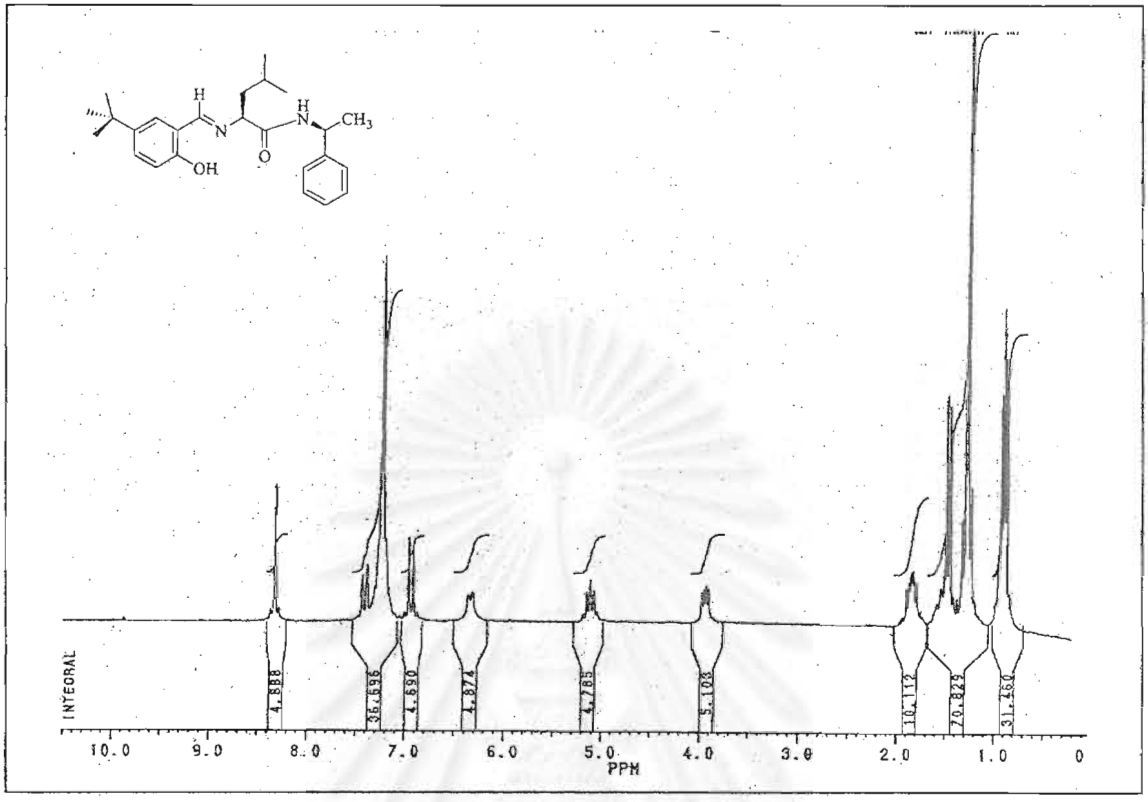


Figure 13 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S3-Leu-A1**.



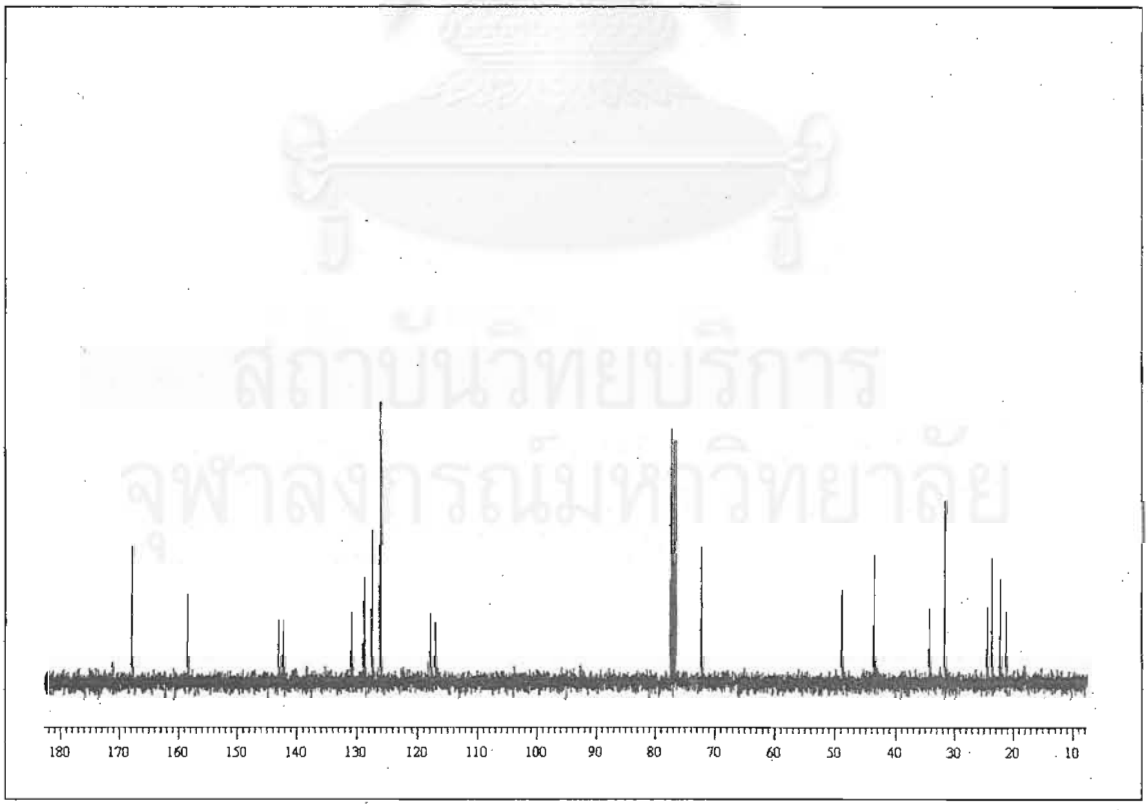


Figure 14 The ^{1}H NMR and ^{13}C spectra of **(*S*, *S*)-S4-Leu-A1**.

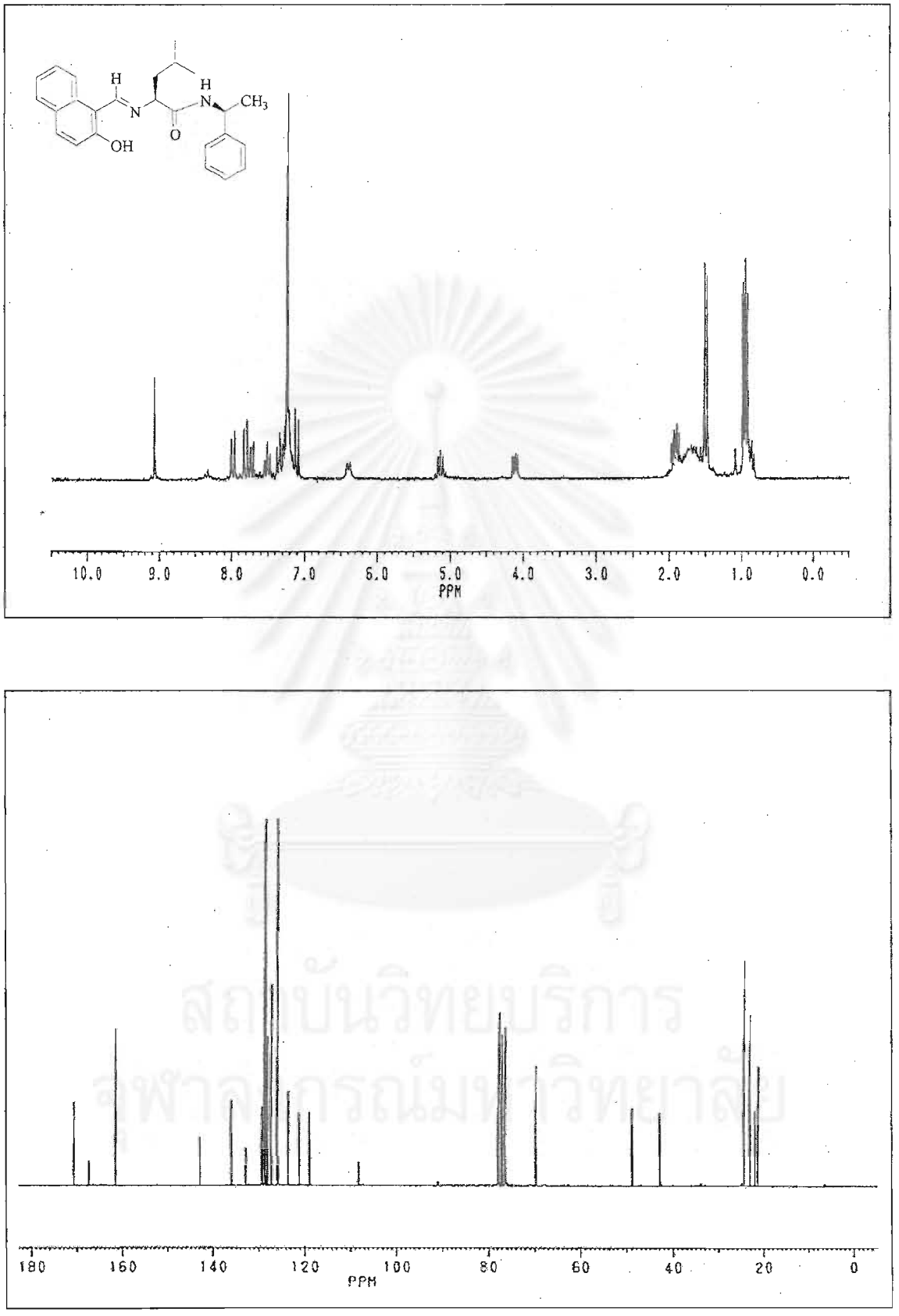


Figure 15 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *S*)-S5-Leu-A1**.

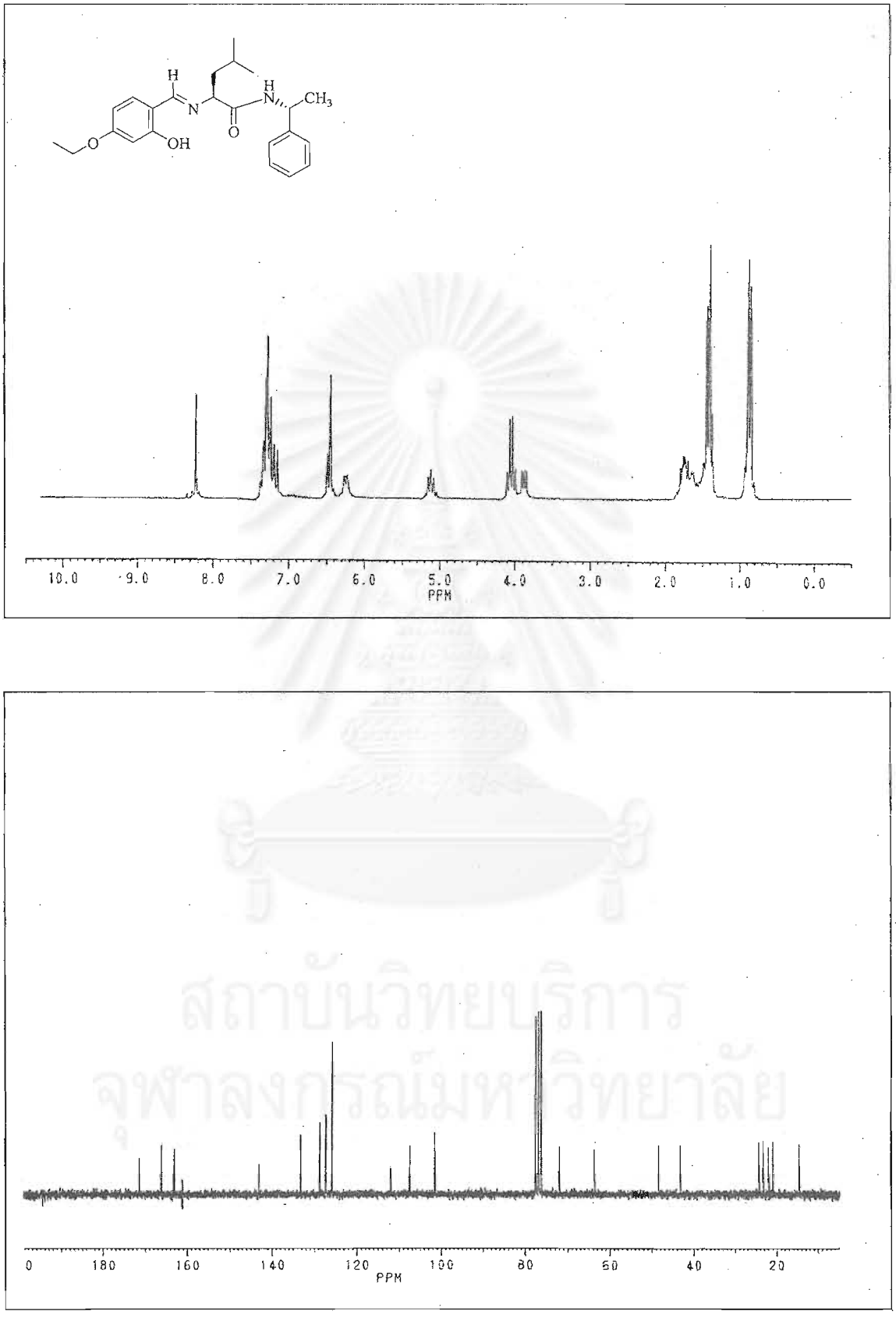


Figure 16 The ^{1}H NMR and ^{13}C NMR spectra of **(*S*, *R*)-S6-Leu-A1**.

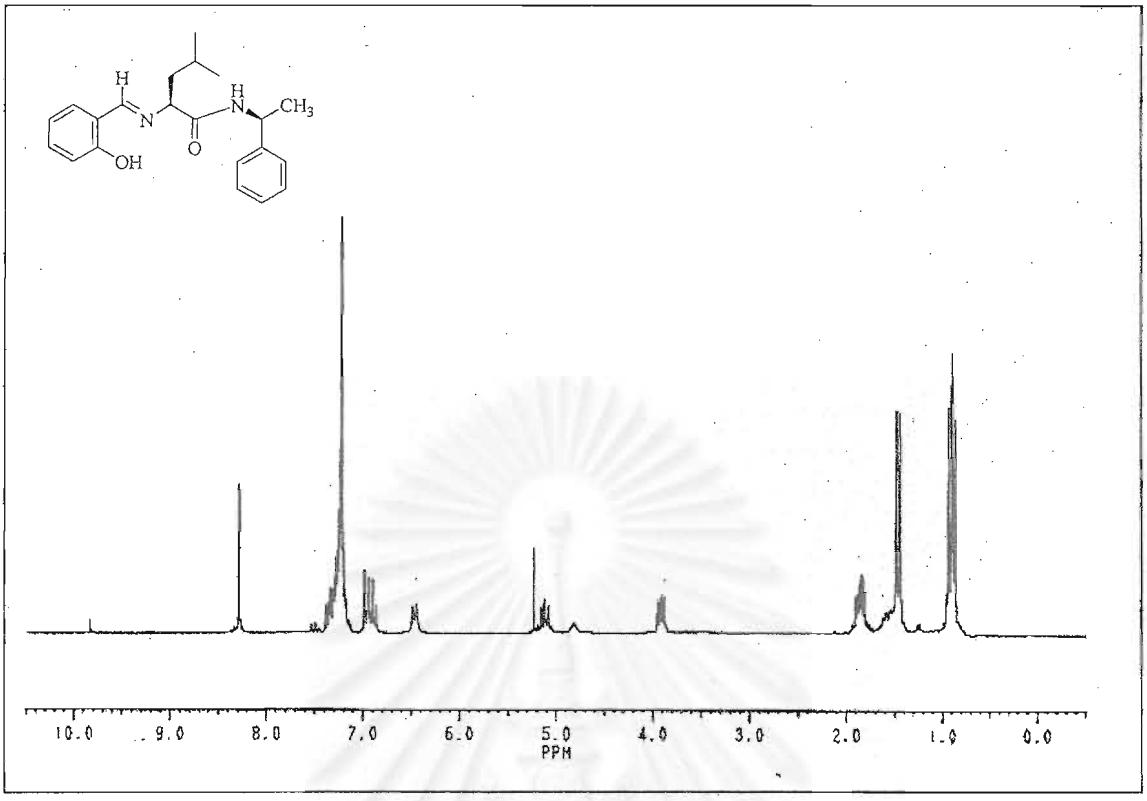


Figure 17 The ^{1}H NMR spectra of **(*S*, *S*)-S1-Leu-A1.**

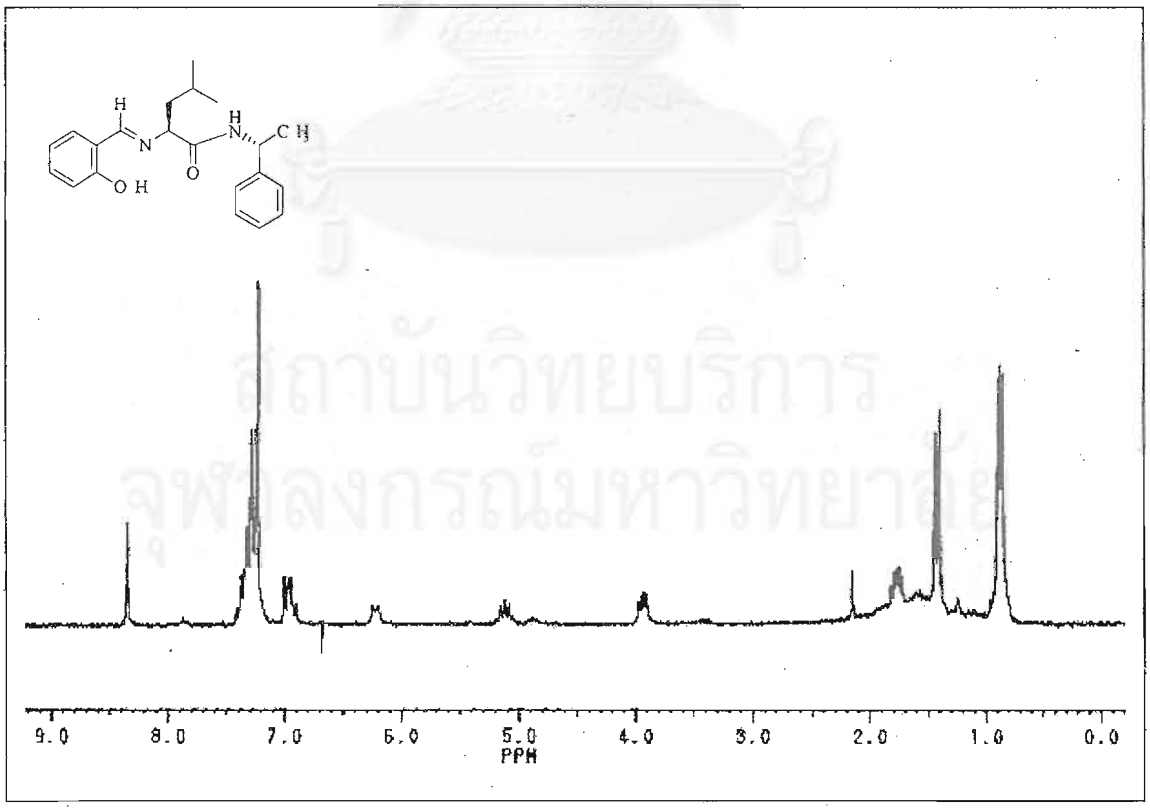


Figure 18 The ^{1}H NMR spectra of **(*S*, *R*)-S1-Leu-A1.**

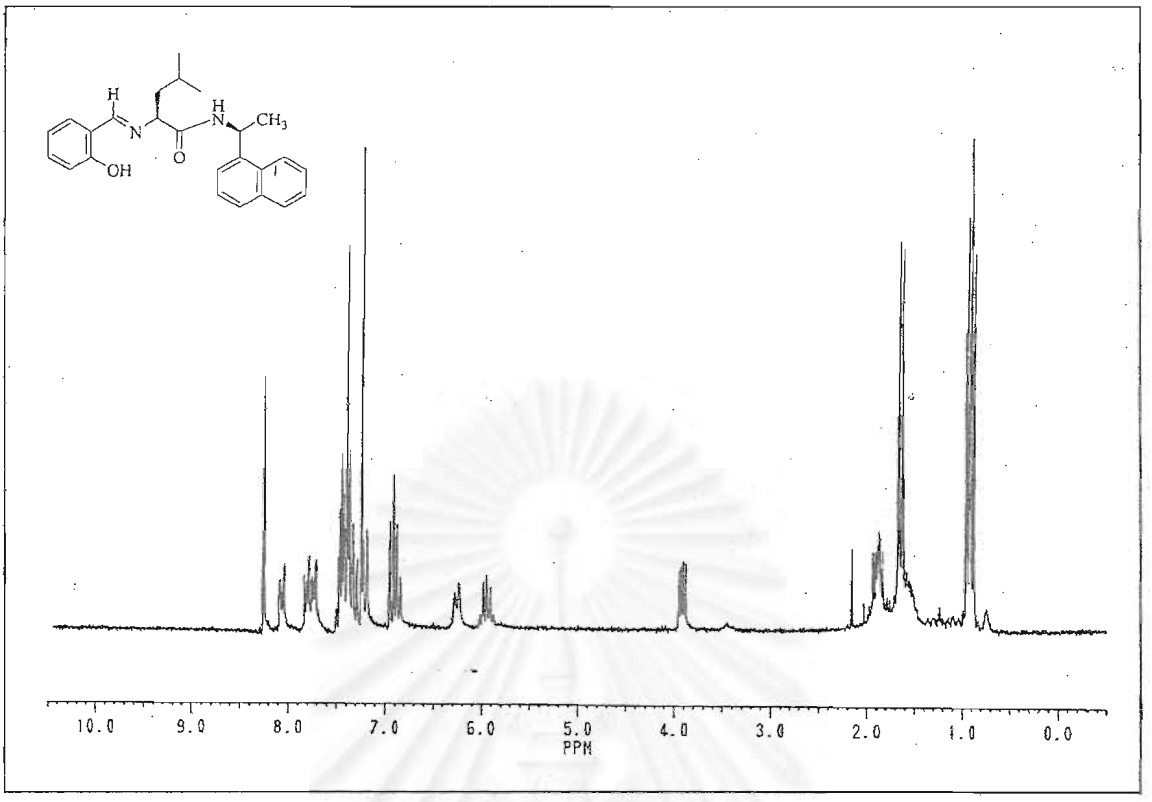


Figure 19 The ^{1}H NMR spectra of **(*S*, *S*)-S1-Leu-A2.**

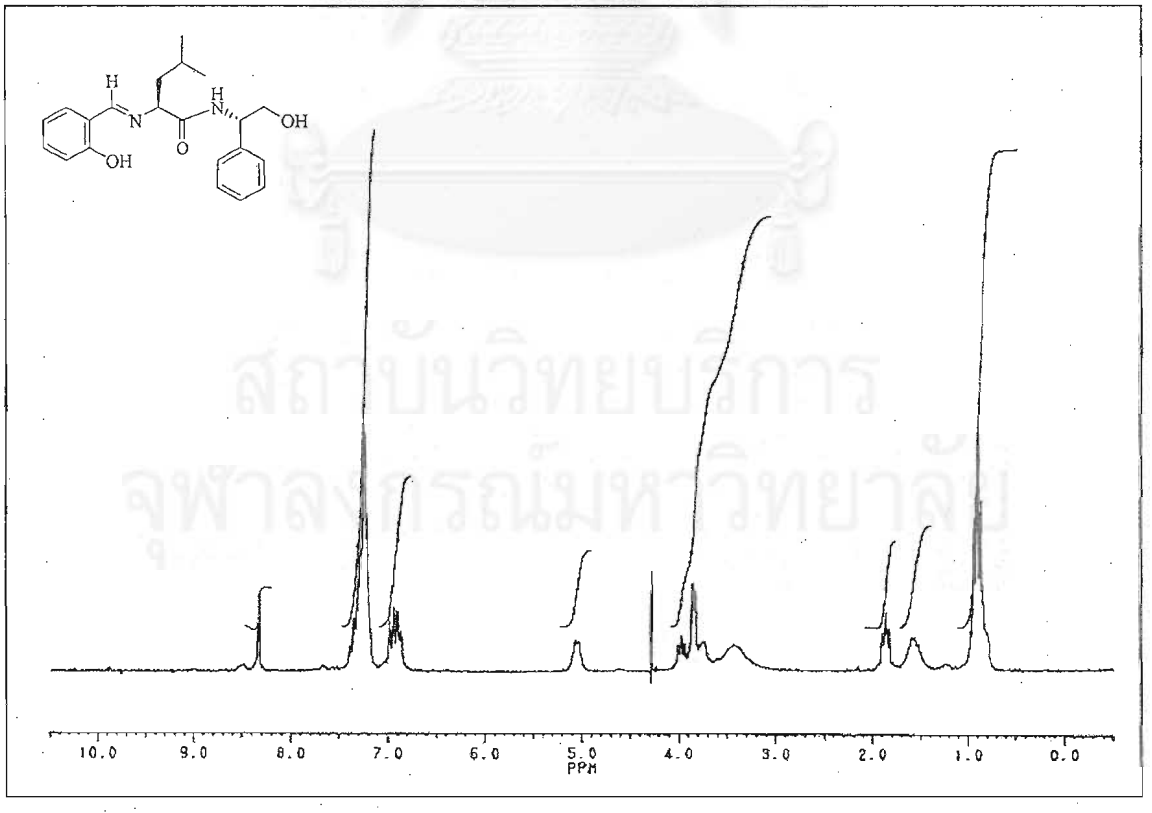


Figure 20 The ^{1}H NMR spectra of **(*S*, *R*)-S1-Leu-A3.**

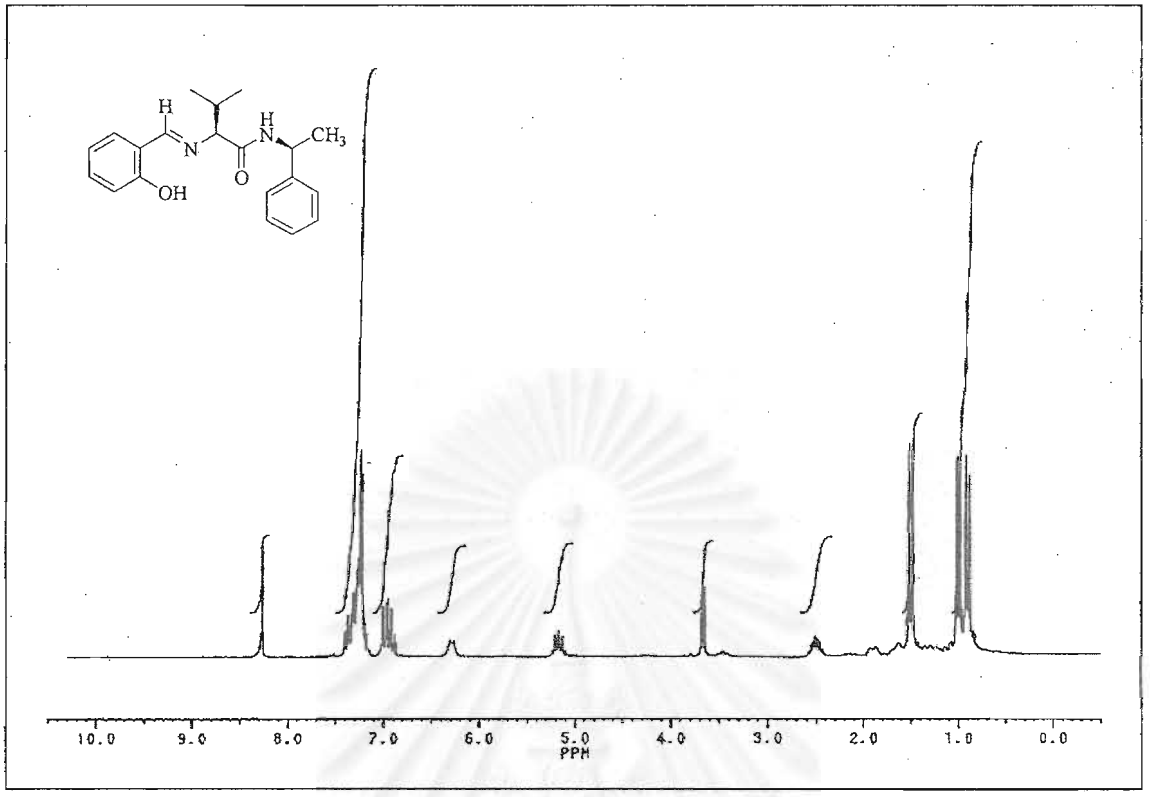


Figure 21 The ^{1}H NMR spectra of **(*S*, *S*)-S1-Val-A1.**

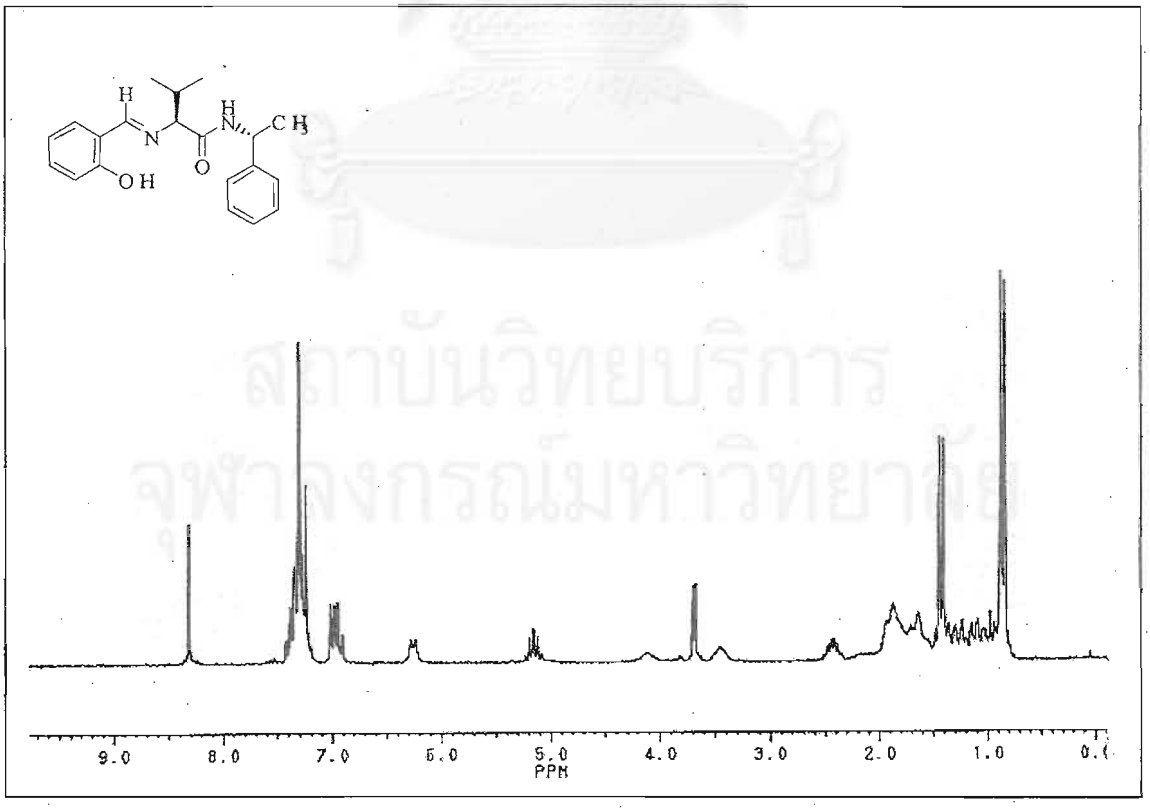


Figure 22 The ^{1}H NMR spectra of **(*S*, *R*)-S1-Val-A1.**

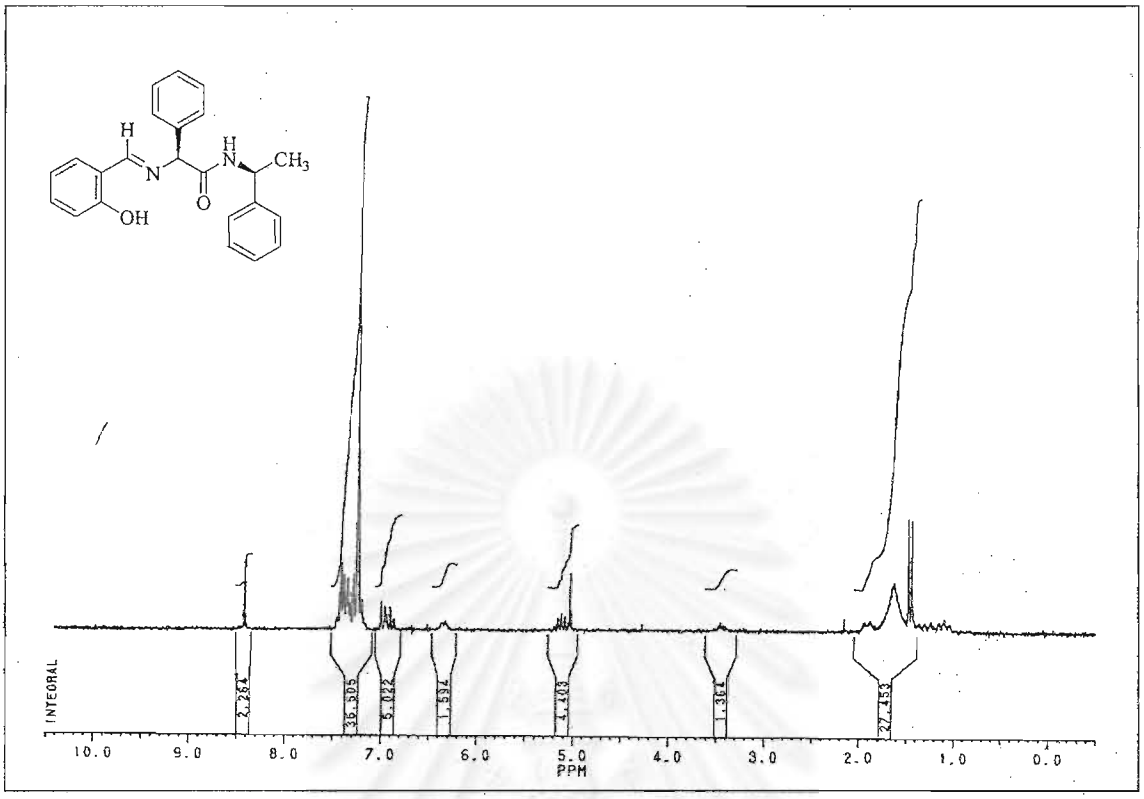


Figure 23 The ^{1}H NMR spectra of (*S*, *S*)-**S1-Phg-A1.**

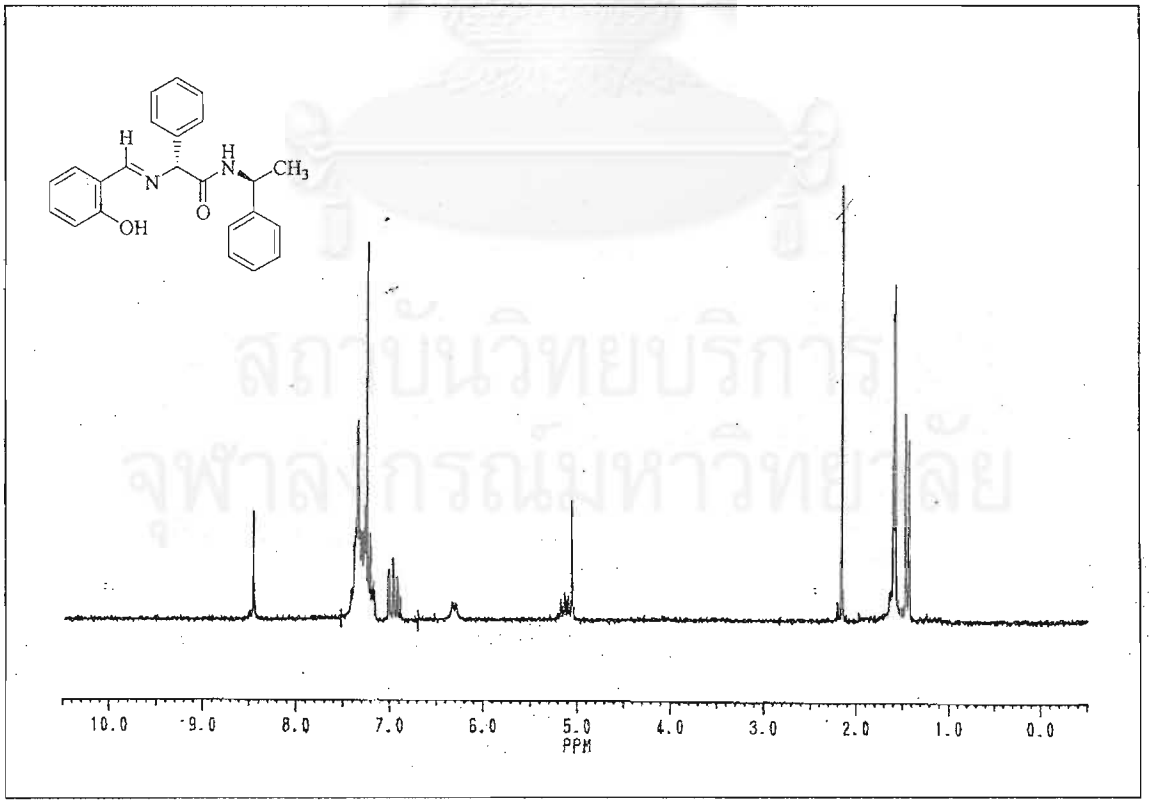
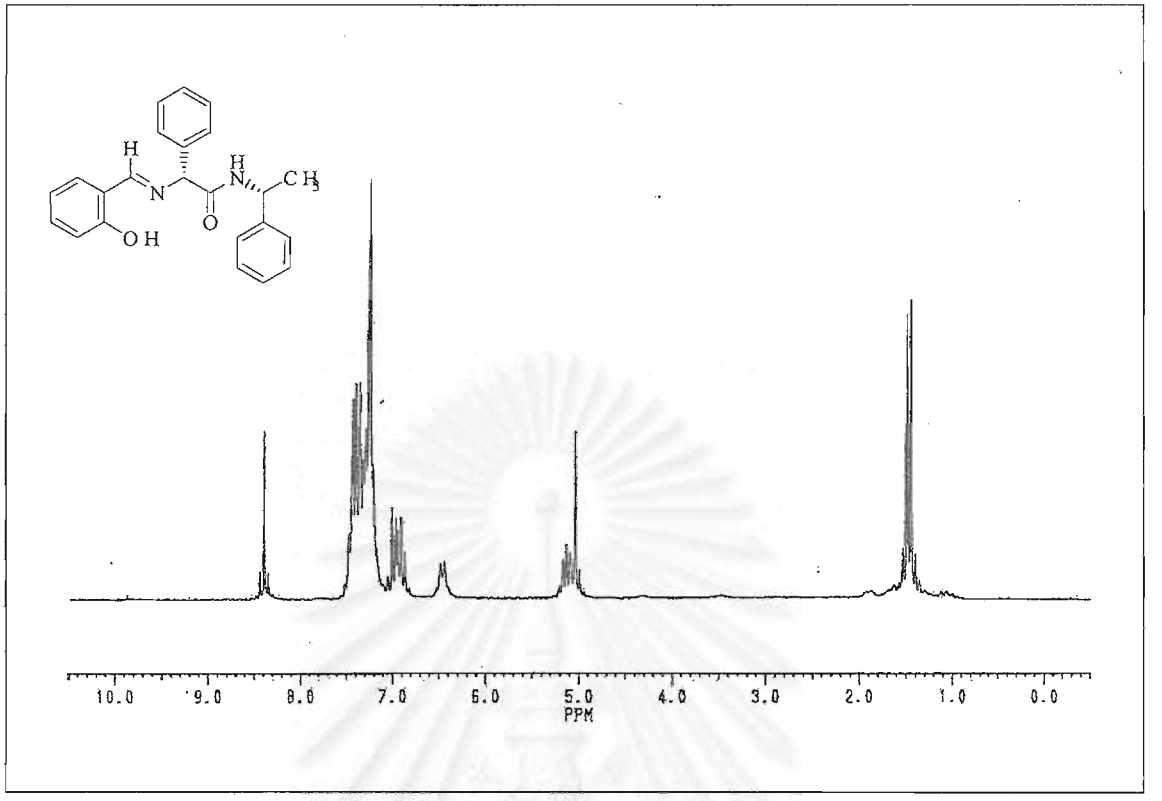


Figure 24 The ^{1}H NMR spectra of (*R*, *S*)-**S1-Phg-A1.**



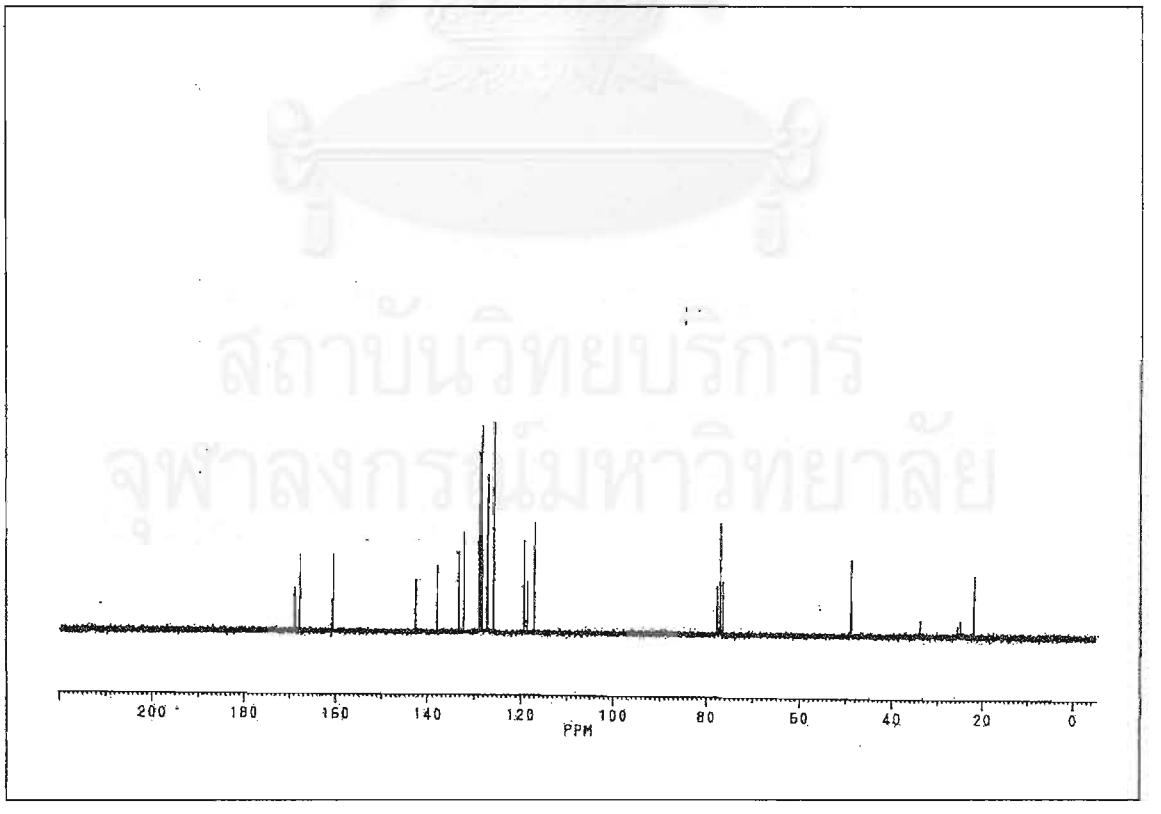


Figure 25 The ^{1}H NMR and ^{13}C NMR spectra of ***(R,R)*-S1-Phg-A1.**

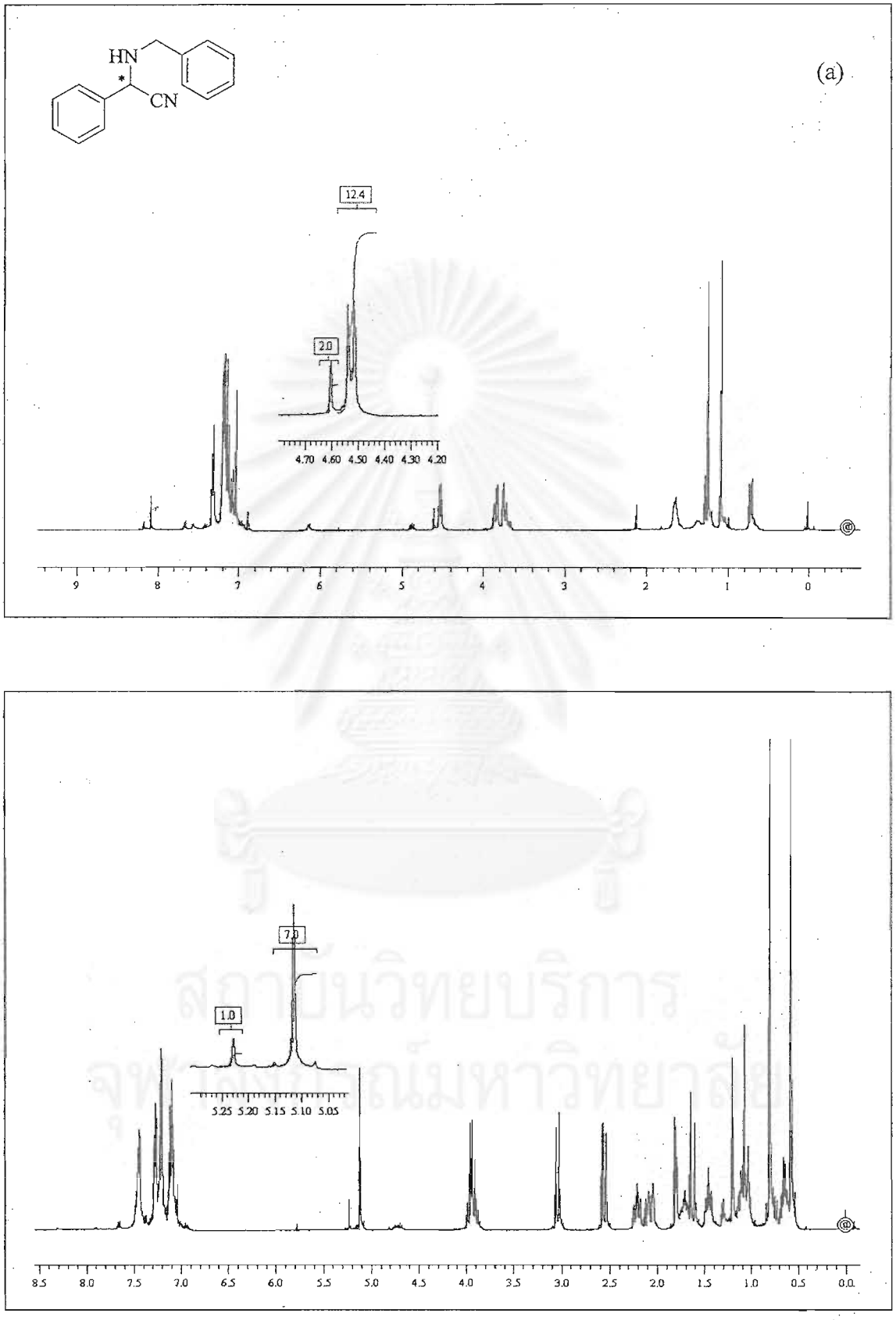


Figure 26 The ^{1}H NMR of % conv.(a), % *ee* (b)of α-aminonitrile product using **(S, S)-S2-Leu-A1**.

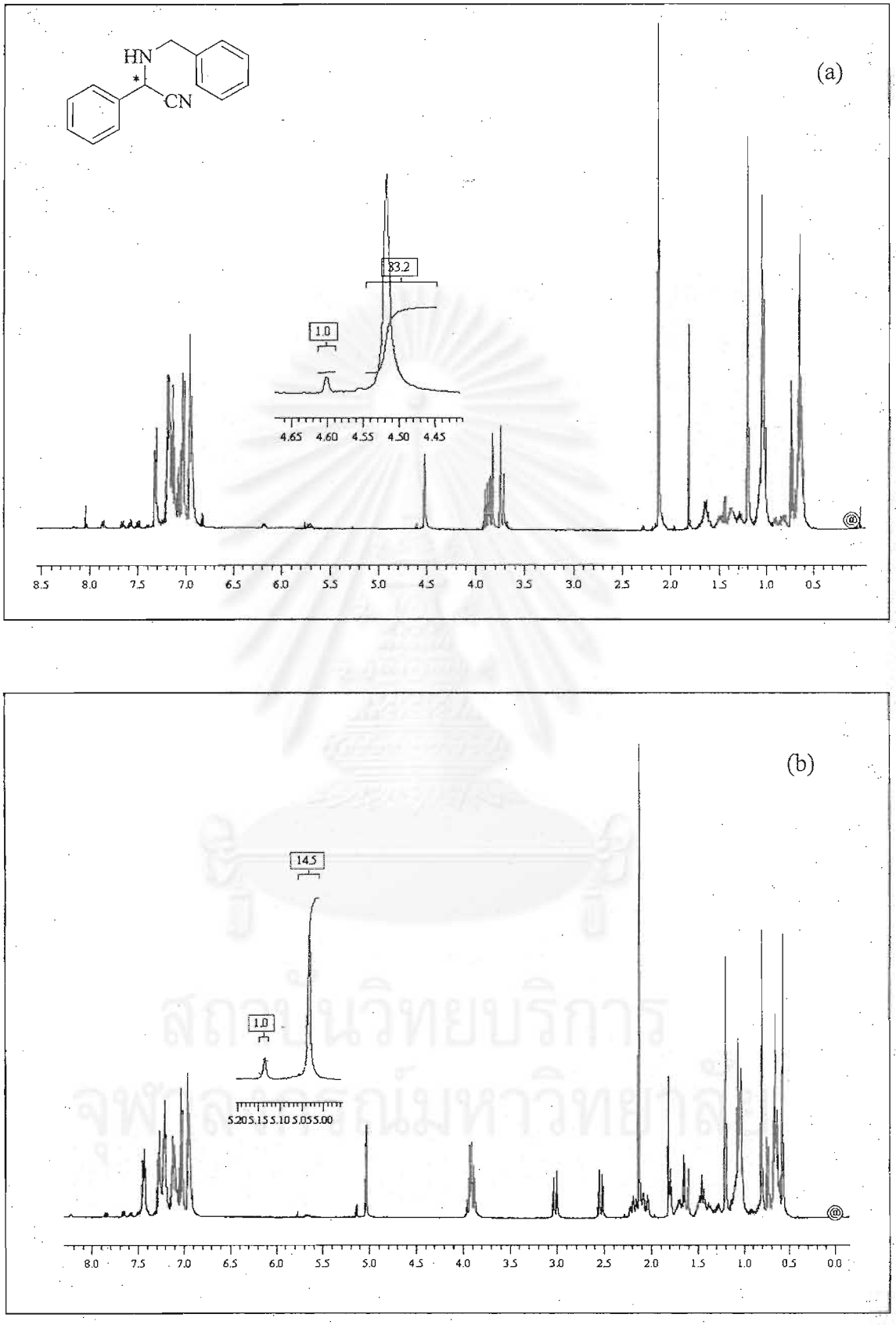


Figure 27 The ^{1}H NMR of % conv.(a), % *ee* (b)of α-aminonitrile product using **(S, S)-S2-Leu-A2**.

VITAE

Miss Siriporn Jiwpanich was born on June 10th, 1977 in Nakhonpathom, Thailand. She received a Bachelor Degree of Science, majoring in Chemistry from Chulalongkorn University in 2000. Since 2000, she has been a graduate student studying Organic Chemistry as her major course at Chulalongkorn University. During her studies towards the Master's degree, she was awarded a teaching assistant scholarship by the Faculty of Science during 2001-2003 and was spported by a research grant for her Master degree's thesis from the Graduate School, Chulalongkorn University.

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