การสังเคราะห์ไครัลลิแกนด์ชนิดใหม่สำหรับการเร่งปฏิกิริยาแบบอสมมาตร

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SYNTHESIS OF NOVEL CHIRAL LIGANDS FOR CATALYTIC ASYMMETRIC REACTIONS

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ได้สังเคราะห์ชุดของไครัลลิแกนด์เอ็น-ซาลิซิล-บีต้า-อะมิโนแอลกอฮอล์ด้วยปฏิกิริยาแมนนิคชนิดสามองค์ประกอบตามด้วยการเปิดวงของอนุพันธ์ออกซาโซลิดีนด้วยไฮดรอกซิลเอมีนไฮโดรคลอไรด์ ปฏิกิริยาดังกล่าวให้ชุดของไครัลเอ็น-ซาลิซิล-บีต้า-อะมิโนแอลกอฮอล์ด้วยเปอร์เซ็นต์ผลิตภัณฑ์ที่สูง (84-92 เปอร์เซ็นต์) โดยปราศจากการราซีไมซ์ ได้นำสารเหล่านี้ไปศึกษาความสามารถในการเป็นลิแกนด์สำหรับเร่งปฏิกิริยาสเตรกเกอร์แบบอสมมาตร เอ็น-เบนซไฮดริลแอลดิมีนที่สังเคราะห์มาจากอะโรมาติกและอะลิฟาติกแอลดีไฮด์ทำปฏิกิริยากับไตรเมทิลไซลิลไซยาไนด์เมื่อมี 10 โมลเปอร์เซ็นต์ของสารประกอบเชิงซ้อนของไทเทเนียม-ลิแกนด์เป็นตัวเร่งปฏิกิริยา ซึ่งจะให้ผลิตภัณฑ์เป็นแอลฟาอะมิโนไนไตรล์ โดยมีปริมาณผลผลิตที่สูงและอิแนนชิโอเมอริกเอ็กเซส (ee) สูงถึง >98 เปอร์เซ็นต์ นอกจากนี้ยังสามารถลดปริมาณของตัวเร่งปฏิกิริยาเหลือเพียง 2.5 โมลเปอร์เซ็นต์ซึ่งมีประสิทธิภาพและง่ายอย่างมากสำหรับการสังเคราะห์สเกลใหญ่ บทบาทของ 2-โพรพานอลมีความสำคัญอย่างยิ่งต่อความสมบูรณ์ของการเกิดผลิตภัณฑ์และอัตราเร็วของปฏิกิริยา สเตอริโอเคมีของผลิตภัณฑ์ที่ได้จากลิแกนด์ที่มีคอนฟิกุเรชัน (เอส) ถูกยืนยันว่าเป็น เอส กรดอ่อนเช่น ซิลิกาหรือแม้แต่เมทานอลสามารถเร่งการราซีไมซ์ของ แอลฟา-อะมิโนฟีนิลอะซีโตไนไทรล์ได้ อย่างไรก็ตามสามารถยับยั้งการราซีไมซ์ได้ด้วยการเติมเบสเช่น ไตรเอทิลลามีนหรือกรดแก่เช่น กรดไฮโดรคลอริก ที่สำคัญออพติคอลลี แอคทีฟแอลฟา-อะมิโนฟีนิลอะซีโตไนไทรล์สามารถถูกเปลี่ยนเป็นเอริลไกลซีนด้วยการไฮโดรไลซีสอย่างสมบูรณ์ด้วยการราซีไมซ์น้อยที่สุด(80 เปอรเซ็นต์, มากกว่า 90 เปอร์เซ็นต์อีอี) และได้เสนอแบบจำลองแทรนซิชันสเตตเพื่อทำนายอิแนนชิโอซีเลคติวิตีของปฏิกิริยา ตัวเร่งปฏิกิริยาไครัลชนิดนี้ยังแสดงความสามารถในการเร่งปฏิกิริยาพูโดวิครวมทั้งปฏิกิริยาการเติมแบบไมเคิลแบบอสมมาตรด้วย

ภาควิชา.....เคมี.....ลายมือชื่อนิสิต.....วรวิทย์ บรรพวิจิตร.....

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

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VORAWIT BANPHAVICHIT: SYNTHESIS OF NOVEL CHIRAL LIGANDS FOR CATALYTIC ASYMMETRIC REACTIONS
THESIS ADVISOR:ASSOC. PROF. TIRAYUT VILAIVAN, D.Phil.
THESIS CO-ADVISOR:ASST. PROF. WORAWAN BHANTHUMNAVIN, Ph.D.
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A series of *N*-salicyl-β-aminoalcohol ligands had been synthesized by three-component Mannich type reaction followed by ring opening of oxazolidine derivatives with hydroxylamine hydrochloride. The reactions provided a series of chiral *N*-salicyl-β-aminoalcohol ligands in high yields (84-92%) without any racemization. These synthesized compounds were evaluated as ligands for catalytic asymmetric Strecker reactions. *N*-Benzhydrylaldimines derived from aromatic and aliphatic aldehydes reacted with TMSCN in the presence of 10 mol% of Ti-ligand complex to give the α-aminonitriles in excellent yields and in up to >98 % ee. In addition, the catalyst loading was successfully reduced to 2.5 mol% which is very effective and extremely simple for large scale synthesis. The presence of 2-propanol is essential to ensure good conversion and reaction rate. The absolute configuration of all products derived from the (*S*)-ligand was confirmed to be *S*. Racemization of α-aminophenylacetonitriles is catalyzed by weak acids such as silica (SiO_2) or even methanol. However, the racemization can be suppressed by addition of either a base such as triethylamine (NEt_3) or strong acid such as hydrochloric acid (HCl). Importantly, optically active α-aminoacetonitriles can be easily converted to arylglycines by complete hydrolysis with minimal racemization. (>80% and >90% ee). A transition state model to explain the enantioselectivity of the reaction is proposed. The present chiral catalysts showed their catalytic ability in not only asymmetric strecker reaction but also asymmetric Pudovic reaction as well as asymmetric Michael addition.

Department……Chemistry……..…Student's signature.....Vorawit Banphavichit…
Field of study.....Chemistry……Advisor's signature.....T. Vilaivan……
Academic year……2006…….....…Co-Advisor's signature……...

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List of Abbreviations

Å	angstrom	mL	milliliter (s)
br	broad	NMR	nuclear magnetic resonance
Boc	*tert*-butoxycarbonyl	^{i}Pr	isopropyl
°C	degree celsius	^{i}Bu	isobutyl
$CDCl_3$	deuterated chloroform	OAc	acetate
c	concentration	OTf	triflate
DMSO-d_6	deuterated dimethyl sulfoxide	Ph	phenyl
d	doublet (NMR)	ppm	part per million
dd	doublet of doublet	q	quartet (NMR)
ee	enantiomeric excess	RNA	ribonucleic acid
EtOAc	ethyl acetate	rt	room temperature
equiv	equivalent (s)	s	singlet (NMR)
Fig	Figure	μL	microliter
g	gram (s)	δ	chemical shift
h	hour (s)	%	percent
Hz	hertz	$[\alpha]_D$	specific rotation
J	coupling constant	^{sec}Bu	secondary butyl
lit	literature	THF	tetrahydrofuran
MeOH	methanol	TLC	thin layer chromatography
m	multiplet (NMR)	^{t}Bu	tertiary butyl
min	minute (s)	TFA	trifluoroacetic acid
mg	milligram (s)	t	triplet (NMR)
mmol	millimole	T_R	retention time
mp	melting point	NEt_3	triethylamine

CHAPTER I

INTRODUCTION

1.1 Chiral molecules and chiral building blocks

Chirality is a fundamental symmetry property of three-dimensional objects and is applied to three-dimensional structure of molecules which is called chiral molecules. Many compounds may be obtained in two different forms in which the molecular structures are constitutionally identical but differ in the three-dimensional arrangement of atoms such that they are related as mirror images. Stereoisomers which are related to each other as nonsuperimposable mirror image are called enantiomers (Figure 1.1). In the absence of an external chiral environment, enantiomers have identical chemical and physical properties such as melting point, solubility and NMR spectra. This is a reason why enantiomers can not be separated or distinguished by conventional separation or analytical methods including chromatography and spectroscopy. However, there are at least two properties in which enantiomers differ. These are the rotation of the plane of plane-polarized light which is the origin of the phenomenon called "optical activity" and interactions with other chiral molecules - just like a right hand will only fit with the corresponding right-hand glove but not the left-hand glove.[1]

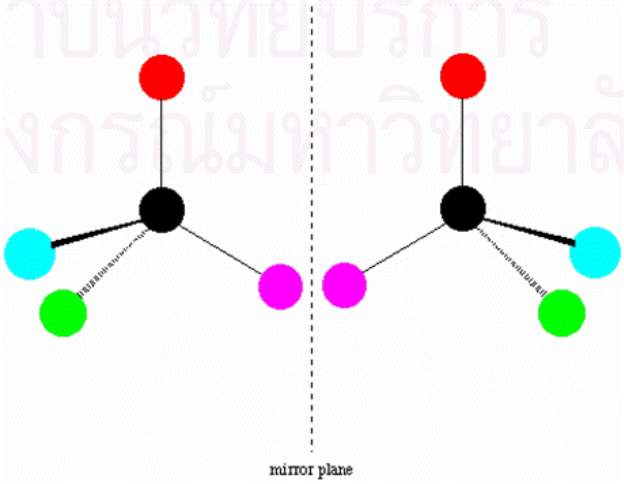
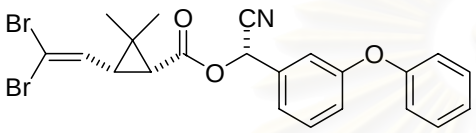
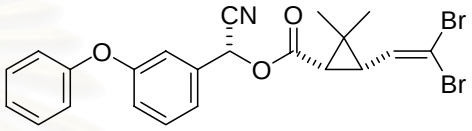


Figure 1.1 A model of enantiomers

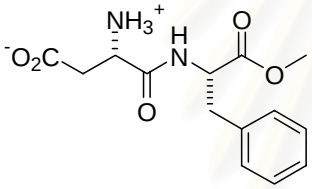
Biological molecules, which constitute a fundamental structure and perform vital functions in living organisms such as proteins and enzymes, are produced from chiral building blocks. Naturally occurring compounds are generally optically active because living organisms tend to produce only a single enantiomer of these molecules through the action of enzymes. Since living organisms are chiral, they usually respond to different enantiomers in different ways. There are many examples of pharmaceuticals, agrochemicals and other chemical compounds where the desired biological property is related to the absolute configuration (Figure 1.2).



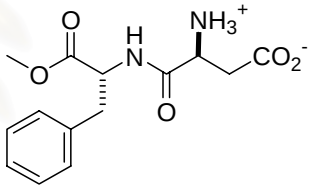
(*R*,*R*,*S*)-Deltamethrin (1)



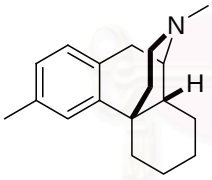
(*S*,*S*,*R*)-Deltamethrin (2)



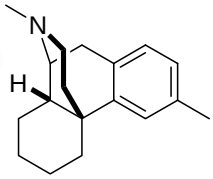
(*S*,*S*)-Aspartame (3)



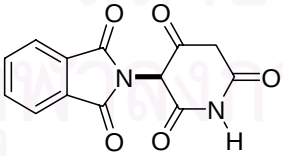
(*S*,*R*)-Aspartame (4)



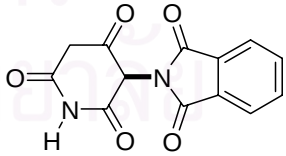
(-)-Levorphanol (5)



(+)-Dextrophan (6)



(*S*)-Thalidomide (7)



(*R*)-Thalidomide (8)

Figure 1.2 Chiral compounds having different biological activities

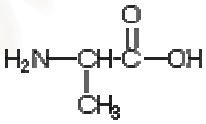
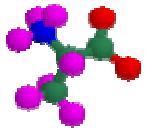
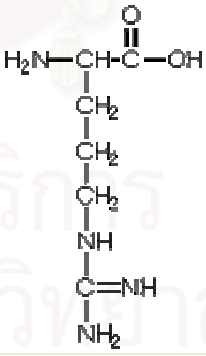
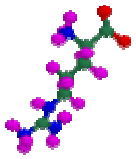
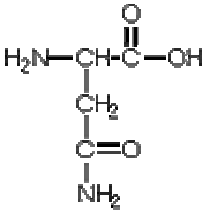
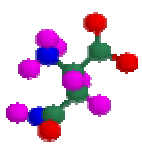
As an example,[2] in a series of eight possible stereoisomers of delthamethrin, the (*R*,*R*,*S*)-**(1)** is the most powerful insecticide whereas the enantiomer (*S*,*S*,*R*)-**(2)** is inactive. In food additives, aspartame (*S*,*S*)-**(3)** is used as an artificial sweetener whilst the (*S*,*R*)-**(4)** tastes bitter and must be avoided in the manufacturing process. In drugs, (-)-levorphanol **(5)** is a powerful narcotic analgaesic whereas its enantiomer, (+)-dextrorphan **(6)** is active as a cough suppressant. Perhaps the most well-known example is the well-known example of thalidomide. While the (*R*) enantiomer **(8)** was used as a sedative, the (*S*) enantiomer **(7)** exhibits teratogenic activity. Unfortunately, the drug had been administrated as a racemate until many tragedies occurred. As a result, the racemic mixture had to be withdrawn from the market (Figure 1.2). Consequently, the preparation of optically active compounds as a single enantiomer is very important in chemical industries especially for production of pharmaceuticals which requires chiral building blocks**.** Economic, environmental and pharmacodynamic considerations are all points to the need for enantiomerically pure drugs and agrochemicals.

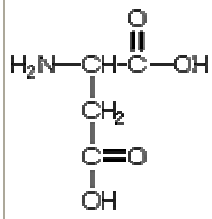
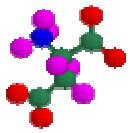
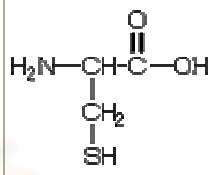
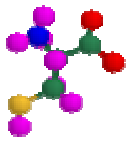
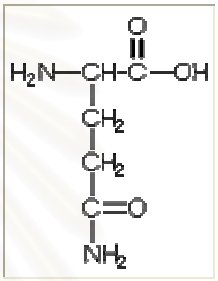
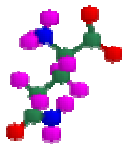
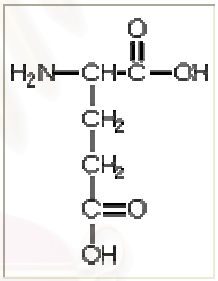
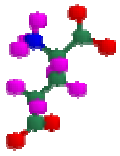
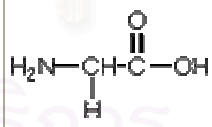
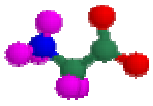
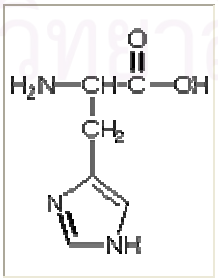
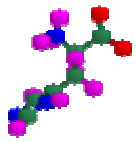
1.1.1 α-Amino acids

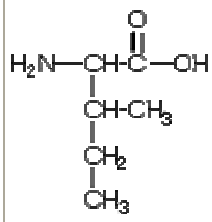
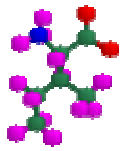
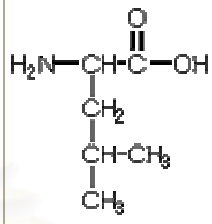
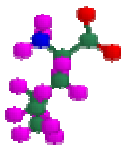
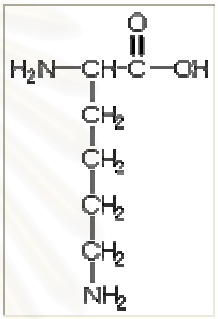
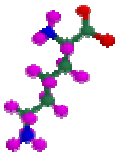
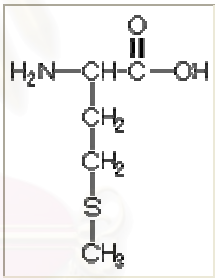
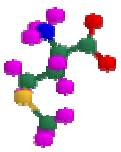
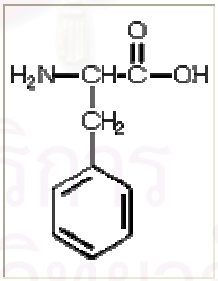
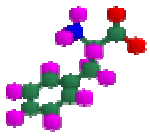
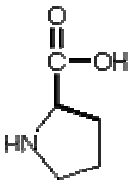
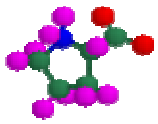
Amino acids are one of the main classes of natural product. They are very small biomolecules with an average molecular weight of about 135 daltons. These organic acids exist naturally in a zwitterion state where the carboxylic acid moiety is ionized and the basic amino group is protonated. The most important class of amino acids is the α-amino acids which have a common backbone consisting of a carboxylic acid group and an amino group attached to the same saturated (sp^3) carbon atom. The simplest member of this group is glycine, where the saturated carbon atom is unsubstituted, rendering it optically inactive. The rest of the 19 most common amino acids are optically active existing as both D and L stereoisomers. Naturally occurring amino acids that are incorporated into proteins are, for the most part, the levorotary (L) isomer. Substituents on the alpha (or saturated) carbon atom vary from lower alkyl groups to amines, and alcohols and aromatic group. There are also acidic and basic side chains as well as thiol chains that can be oxidized to disulfide linkages which play an important role in holding the peptide chains together in a well-defined.[3]

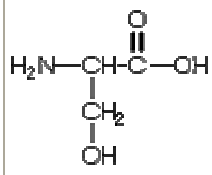
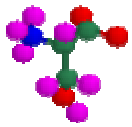
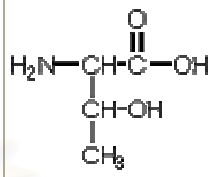
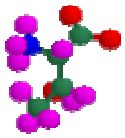
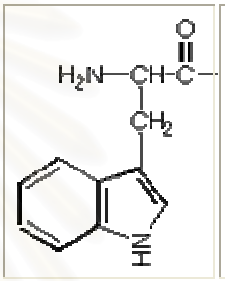
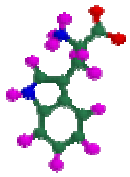
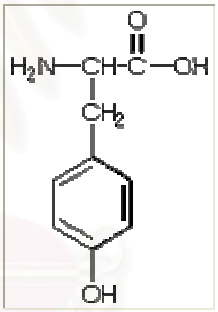
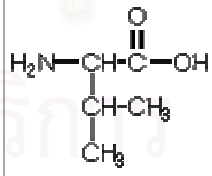
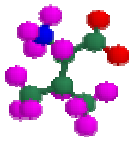
Alpha-amino acids are the "building blocks" of the body. Besides building cells and repairing tissue, they form antibodies to combat invading bacteria and viruses; they are part of the enzyme and hormonal system; they build nucleic acids (RNA and DNA); they carry oxygen throughout the body and participate in muscle activity and also extensively used as food additives,[4] agrochemicals,[5] and pharmaceuticals.[6] When protein is broken down by digestion the result is 20 known amino acids. In human, eight are essential (can be manufactured by the body with proper nutrition), tryptophan, lysine, methionine, phenylalanine, threonine, valine, leucine and isoleucine, and the rest are non-essential.[7] All of the structures of α-amino acids are different at the α-side-chain as shown in Table 1.1.

Table 1.1 The proteinogenic amino acids [3]

Amino Acid	**3-Letter code**	**1-Letter code**	**Properties**	**2D Structure (un-ionized form)**	**3D Structure**
Alanine	Ala	A	aliphatic hydrophobic neutral		
Arginine	Arg	R	polar hydrophilic charged (+)		
Asparagine	Asn	N	polar hydrophilic neutral		

Aspartate	Asp	D	polar hydrophilic charged (-)		
Cysteine	Cys	C	polar hydrophobic neutral		
Glutamine	Gln	Q	polar hydrophilic neutral		
Glutamate	Glu	E	polar hydrophilic charged (-)		
Glycine	Gly	G	aliphatic neutral		
Histidine	His	H	aromatic polar hydrophilic charged (+)		

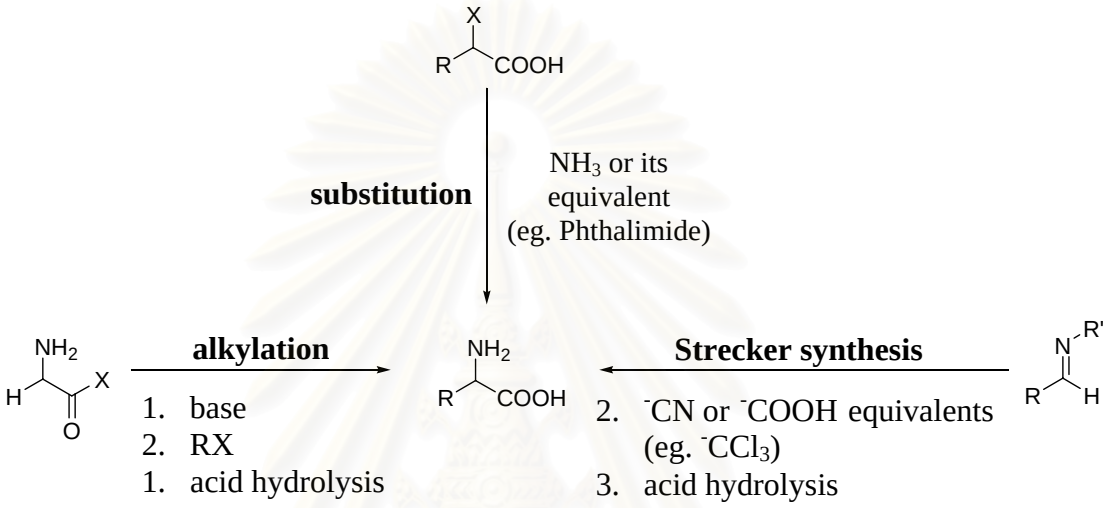
Isoleucine	Ile	I	aliphatic hydrophobic neutral		
Leucine	Leu	L	aliphatic hydrophobic neutral		
Lysine	Lys	K	polar hydrophilic charged (+)		
Methionine	Met	M	hydrophobic neutral		
Phenylalanine	Phe	F	aromatic hydrophobic neutral		
Proline	Pro	P	hydrophobic neutral		

Serine	Ser	S	polar hydrophilic neutral		
Threonine	Thr	T	polar hydrophilic neutral		
Tryptophan	Trp	W	aromatic hydrophobic neutral		
Tyrosine	Tyr	Y	aromatic polar hydrophobic		
Valine	Val	V	aliphatic hydrophobic neutral		

In many syntheses of complex chiral compounds in recent years, α-amino acids are increasingly becoming the first starting point to be considered. Their structural features were employed as the starting point for the synthesis of value of this readily-available pool of compounds such as synthetic targets, a source of chiral materials and constituents for reagents or catalysts in asymmetric synthesis. The α-amino acids syntheses and their applications therefore have been developed and rapidly grown in many other areas of organic synthesis.

1.1.2 Retro-synthesis of α-amino acids synthesis

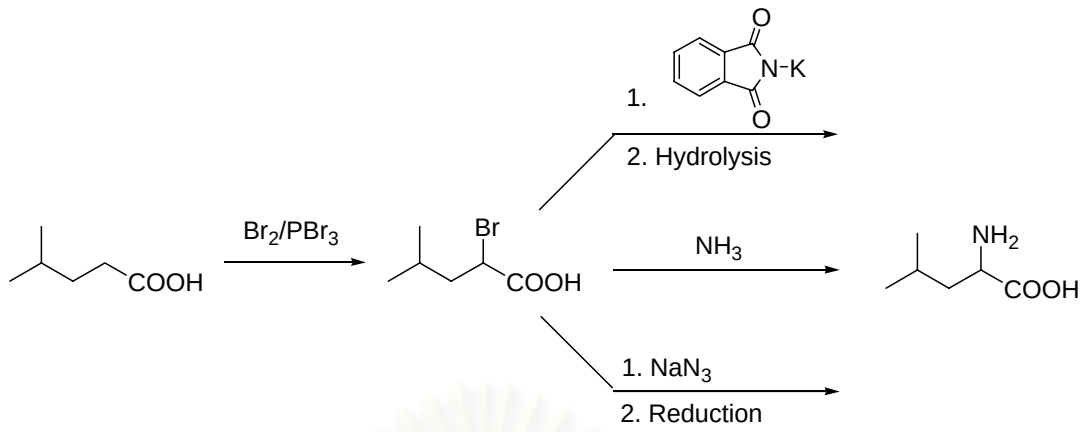
There are several methods successfully employed in the synthesis of α-amino acids. Only some general methods for the synthesis of α-amino acids including substitution reactions of halogen in α-halo acids, alkylation of glycine anion or equivalents and the Strecker reaction will be described.[8]



Scheme 1.1 Retro-synthesis of α-amino acids

Substitution reactions of halogen in α-halo acids

The substitution reactions on α-halo acids with ammonia or its equivalents are very convenient methods for the synthesis of α-amino acids with no chiral center such as glycine. Simple α-bromo acids can be synthesized from the reaction of carboxylic acid and bromine in the presence of phosphorous tribromide. Ammonia is a simple reagent and works well in conversion of simple α-halo acids to α-amino acids. In addition, its equivalents as potassium phthalimide and sodium azide are superior reagents and can also react with α-halo acids to provide α-amino acids after hydrolysis (phthalimide, the Gabriel synthesis) and reduction (azide) respectively.

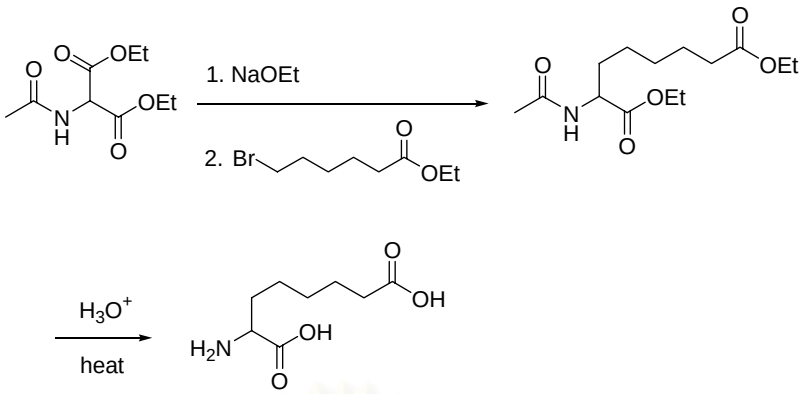


Scheme 1.2 Synthesis of α-amino acids by substitution reactions of bromine in α-halo acid

The substitution reaction is S_N2 in nature, which means that obtaining optically active α-amino acid should be possible by this method. Unfortunately, the optically active α-bromoacids required as the starting materials are not readily available. In fact, they are usually obtained from the corresponding α-amino acid by nitrosation in aqueous HBr.

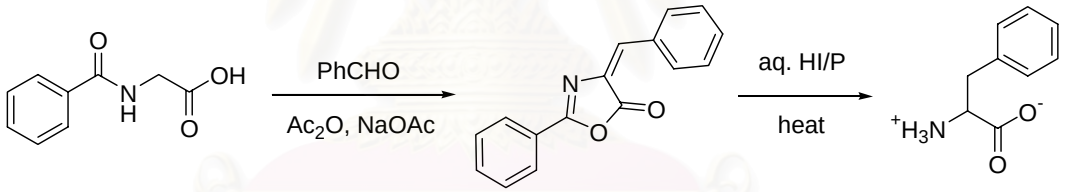
Alkylation of glycine anion or equivalents

The reaction which is applied to *N*-acetylaminomalonic ester is called Sorensen synthesis. The concept of this method is α-carbon deprotonation of *N*-acetylaminomalonic ester which is a glycine equivalent stabilized by another carboxylic group. It can be alkylated in the same way as malonate esters. Decarboxylation of the α-substituted aminomalonate ester provided amino acids.



Scheme 1.3 Sorensen synthesis of α-amino acid

Another one is synthesis of amino acids from glycine equivalents by α-carbon deprotonation to form stabilized carbanion followed by alkylation with a suitable alkylating agent such as aldehyde provides unsaturated substituted azalactone. It can be transformed to the α-amino acids by reduction and hydrolysis.

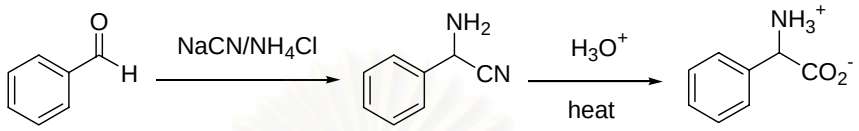


Scheme 1.4 Synthesis of α-amino acid by alkylation of glycine anion

The Strecker reaction

The Strecker synthesis is a well-known classical procedure for the synthesis of α-aminonitriles. These can be prepared in one step by the treatment of aldehydes or ketones with alkali cyanides such as sodium or potassium cyanide and salt of amine as ammonium salt such as NH_4Cl.[9] The reaction has also been carried out with NH_3/HCN and with NH_4CN. Salts of primary and secondary amines can be used instead of NH_4^+ to obtain *N*-substituted and *N*,*N*-disubstituted α-aminonitriles. It may be considered as a special case of the Mannich reaction. Since the nitrile function

(CN) of α-aminonitriles can be easily hydrolyzed to the carboxylic acid, it is a convenient and atom-economy method for the preparation of α-amino acids.[10] The amino acids obtained from conventional Strecker synthesis are generally racemic mixtures.



Scheme 1.5 The conventional Strecker synthesis

From the information described above, there are several methods for α-amino acids synthesis. These examples, including many others that cannot be mentioned due to the limited space available, are important models for finding alternative synthetic approaches to obtain useful α-amino acids for various applications.

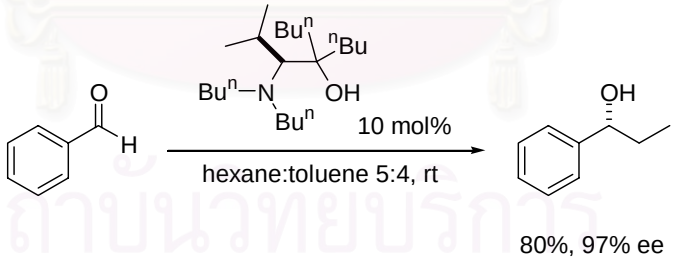
1.2 Catalytic asymmetric synthesis

Since the early 1970s, there has been a dramatic increase in research on new methods for the preparation of chiral compounds in the form of single enantiomers. The most widely used procedure in the past are called "resolution" of the enantiomer pairs ("racemate") using an appropriate enantiomerically pure chiral resolving agent or using an enzyme which can recognize only one enantiomer out of the pair. One of the main drawbacks of this method is that the process is lengthy since the racemate must be made first and resolved later. The more important drawback is its inefficiency. The maximum recovery of the pure enantiomer is only 50 % and the remaining incorrect enantiomer must be discarded or recycled. More recently, due to economic and environmental reasons, there are a lot of interests in synthesizing the chiral compound as a single enantiomer - the process called "asymmetric synthesis".

Asymmetric synthesis [11-12] is a reaction in which an achiral unit in an ensemble of substrate molecules is transformed into a chiral unit in such a manner that

the stereoisomers which may be enantiomers or diastereomers are produced in unequal amounts. This can be accomplished by using a stereogenic center in the chiral substrate or a chiral auxiliary attached to an achiral substrate (stoichiometric asymmetric synthesis).[11] A breakthrough in the field of asymmetric synthesis has initiated since the early 1980s when catalytic asymmetric synthesis has been developed and since then has progressed rapidly. The use of only small amounts of the highly efficient catalyst could enantioselectively induce the formation of chiral compounds as a single enantiomer in large quantities when compared to amount of the used catalyst. The preparation of single enantiomer in this way is economically attractive because the expensive chiral auxiliaries are not required in large quantities.

For catalytic asymmetric synthesis, a chiral catalyst is allowed to react with an achiral substrate to produce a chiral product. The advantages over stoichiometric asymmetric synthesis are two-fold: the range of starting materials is far wider because it needs no longer to come from the chiral pool, and there are no two complicated steps for the attachment and removal of a chiral auxiliary.[13] For instance, Scheme 1.6 shows the asymmetric diethylzinc addition to benzaldehyde catalyzed by chiral β-aminoalcohol derived from (*S*)-valinol to give (*R*)-1-phenyl-1-propanol in high yield and excellent enantioselectivity.[14]



Scheme 1.6 Asymmetric diethylzinc addition to aldehyde

The understanding of the mechanism of asymmetric reaction led to the belief that the difference between racemic reaction and enantioselective reaction lies in differentiating the two transition states, leading to the production of '*R*' and '*S*' isomers. In a racemic reaction, $\Delta G^{\#}_{S} = \Delta G^{\#}_{R}$, both the transition states are of the equal energy. Consequently, both *R* and *S* isomers are produced in equal amounts to yield a

racemic product. In other words, $\Delta G^{\#}_{S} \neq \Delta G^{\#}_{R}$, the catalyst facilitates one of the transition states to be at lower energy than the others, leading to the reaction which is called enantioselective reaction (Figure 1.3). The catalyst interacts with achiral substrate in which transition state leading to '*R*'product has been lowered by $\Delta G^{\#}$, whereas transition state for the formation of '*S*' product may remain unaffected or decrease. In an enantioselective reaction, the value of $\Delta\Delta G^{\#}$ plays a crucial role in determining the selectivity of the reaction. The value of $\Delta\Delta G^{\#}$ between 2.5 and 3.0 k cal/mol may result in 98-100% ee, depending upon the reaction (temperature was also considered).[12]

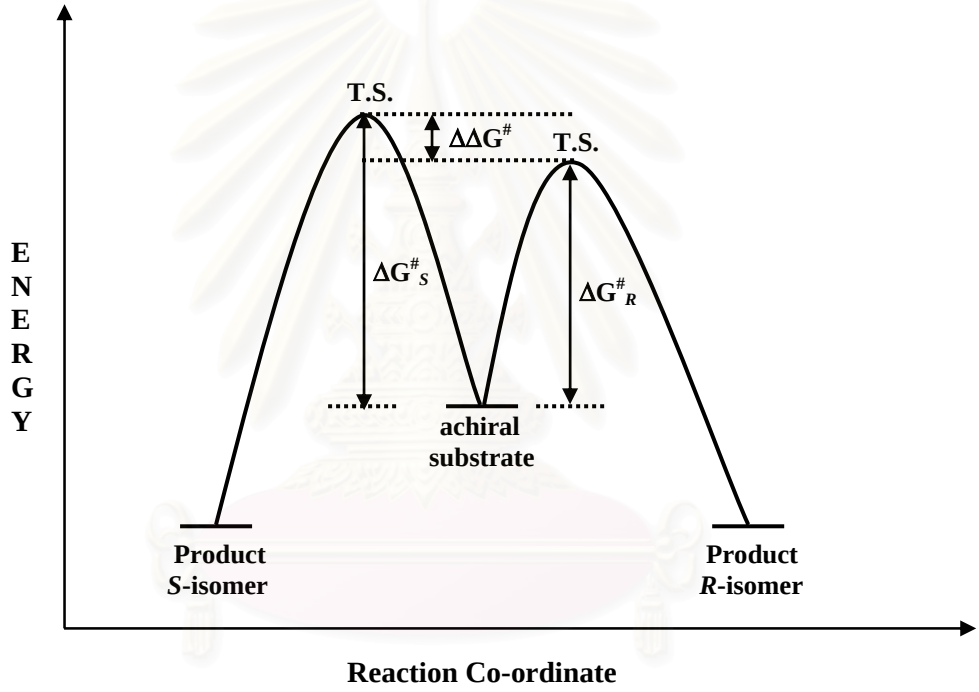


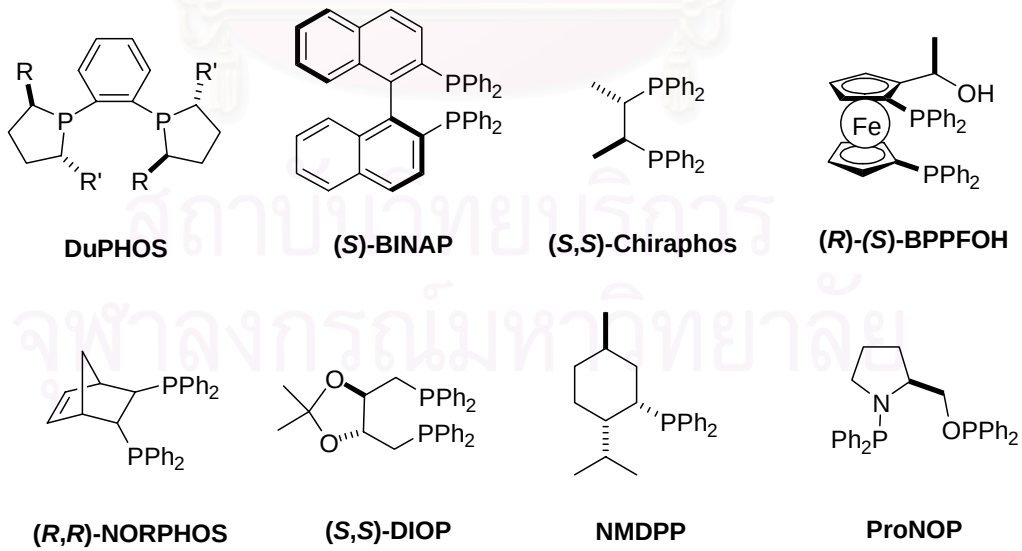
Figure 1.3 Reaction coordinates for asymmetric synthesis from prochiral substrate

In the field of asymmetric catalysis spectacular progress has been made by using homogeneous catalysts based on transition metal complexes modified by chiral ligands. Chiral ligands may be mono- or polydentate. Often bidentate chiral ligands are the most effective, both in terms of catalytic activity and stereoselectivity. The increase in stereoselectivity could be related to the decrease in the number of the ligand conformations that can assume in the cooridination sphere of the metal.[15] A good chiral ligand should meet several conditions as follow:

1. It must be coordinated to the metal during the step in which the chiral center on the substrate is created and not exert merely a chiral medium effect.
2. The catalytic ability when the chiral ligand is present should be reasonably good relative to the achiral catalyst.
3. The structure of the ligand should contain functional groups that can be easily modified.
4. The synthesis of the ligand must be relatively easy. If possible, resolution is to be avoided, the starting material should be commercially available and inexpensive.
5. It is desirable to be able to get both antipodes of the ligand.

Although there are many reports about new chiral ligands for asymmetric catalysis during the past 20 years,[16-17] the methodology will be continuously developed especially for the syntheses of new chiral ligands which are inexpensive, practical to use, highly efficient, easily synthesized and can be customly modified to suit any desired reactions. For the most popular or “privileged” chiral ligands,[18] these can be classified into four simple families.

Chiral phosphorous ligands

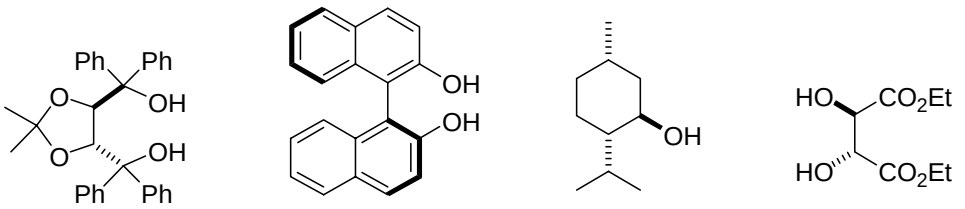


DuPHOS **(*S*)-BINAP** **(*S*,*S*)-Chiraphos** **(*R*)-(*S*)-BPPFOH**

(*R*,*R*)-NORPHOS **(*S*,*S*)-DIOP** **NMDPP** **ProNOP**

Figure 1.4 Chiral phosphorus ligands [15, 18-19]

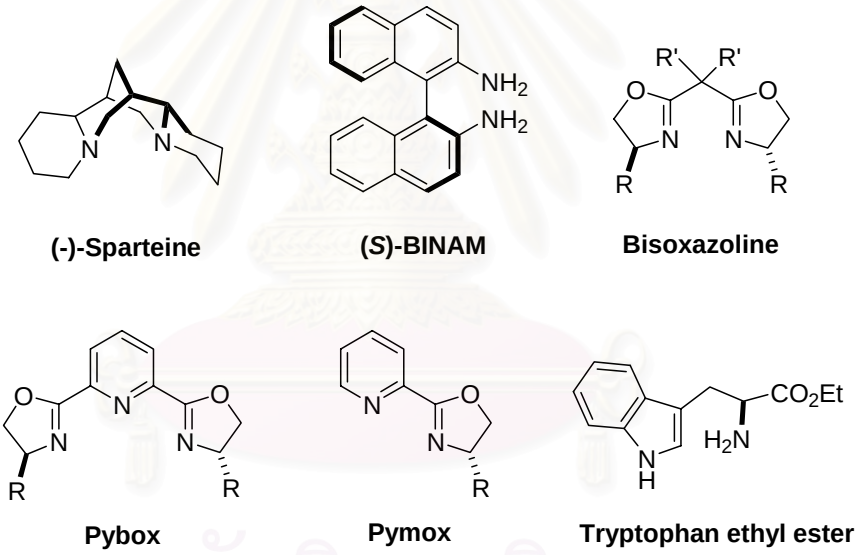
Chiral oxygen ligands



(*S*,*S*)-TADDOL **(*S*)-BINOL** ***l*-Menthol** **(+)-DET**

Figure 1.5 Chiral oxygen ligands [15, 18]

Chiral nitrogen ligands



(-)-Sparteine **(*S*)-BINAM** **Bisoxazoline**

Pybox **Pymox** **Tryptophan ethyl ester**

Figure 1.6 Chiral nitrogen ligands [15, 18]

Chiral amino alcohol ligands and related compounds

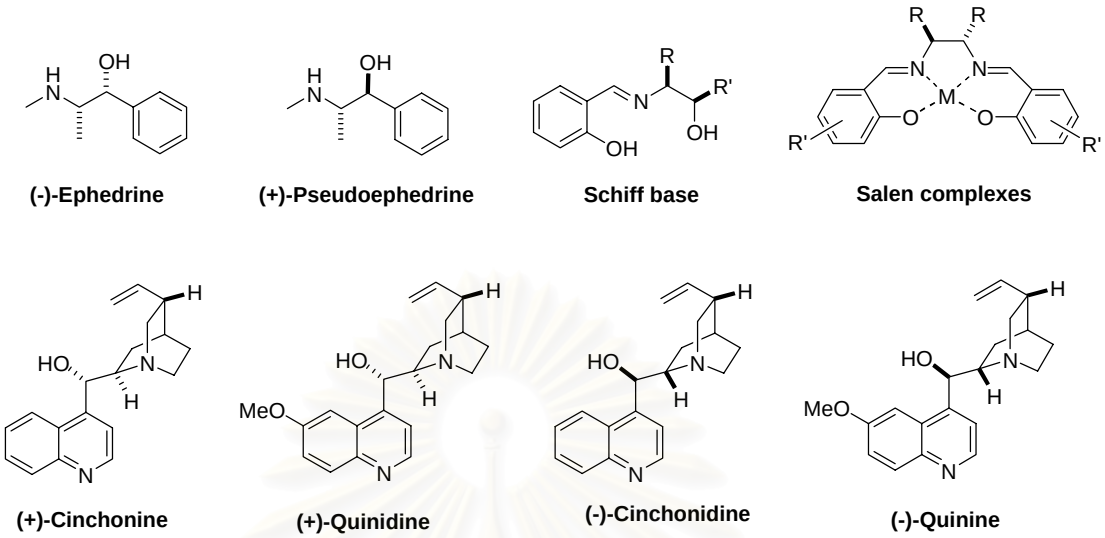


Figure 1.7 Chiral amino alcohol lagands and related compounds [15, 18, 20]

The development of novel chiral ligands is crucial to the advancement of asymmetric catalysis. Classification of ligands that have been successfully used in enatioselective catalysis can be informative.[21] Many of the most common ligands are bidentate and neutral. These ligands are attached to metal ions to form chiral metal complexes acting as chiral catalysts. Most of them are employed in catalytic asymmetric reactions and some chiral catalysts can be also recoverable.[22]

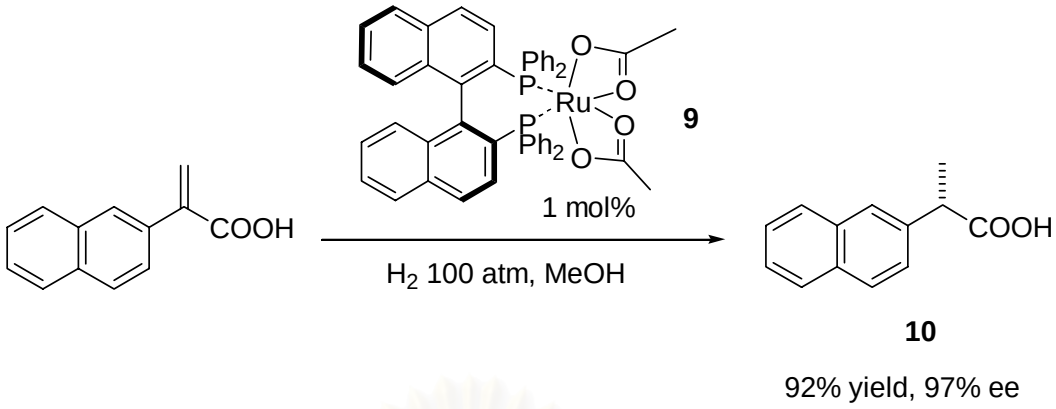
1.3 Chiral catalysts

Many examples of the well-known and very synthetically important catalytic asymmetric reactions are nucleophilic addition to carbonyl compounds,[23] polarized double bonds [24] and imines.[25] These catalytic asymmetric reactions [26] need an effective chiral catalyst which may be an organic molecule containing appropriate functional groups for catalyzing the reaction that can be called *chiral organocatalyst* or a complex between a metal ion and a chiral ligand that can be called *chiral Lewis acid*.[27-28]

1.3.1 Chiral Lewis acids

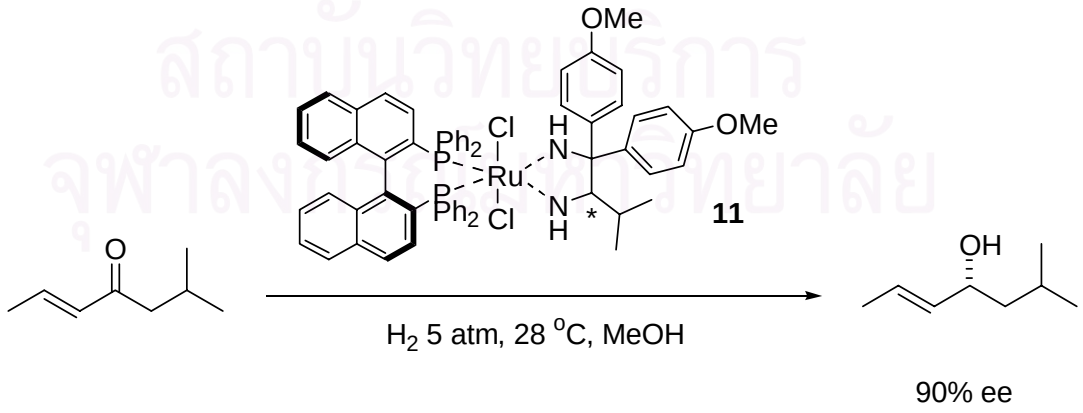
The widely utilized class of chiral catalysts in catalytic asymmetric synthesis is chiral Lewis acids consisting of a metal ion and a chiral ligand. The metal accelerates the reaction while the ligand provides the chiral environment.[29-32] Most often stoichiometric amounts of Lewis acids such as BF_3, $AlCl_3$, $SnCl_4$, $TiCl_4$ or lanthanide metal ions [33-34] with different counter anions such as 2-propoxide (O^iPr^-) and triflate (OTf^-) have been employed for a variety of carbon-carbon bond formation in asymmetric synthesis. Undoubtedly, an economically efficient way to perform enantioselective carbon-carbon bond formation would be to use only catalytic amounts of chiral Lewis acids. There are many reports about the use of chiral Lewis acids in catalytic asymmetric reactions; however, some specific examples which will be mentioned are the use of well-known utilized catalysts.

The development of efficient chiral phosphorus catalysts [35] has played an important role in development of asymmetric hydrogenation. In fact, the exploration of chiral phosphorus catalyts for asymmetric hydrogenation is a continuous effort which started in the late 1960s.[36] In 1980, Noyori and co-workers published the synthesis of both enantiomers of the BINAP which has been successfully used in asymmetric hydrogenations.[37] Later, Noyori exchanged rhodium, Rh(I), for another transition metal, ruthenium, Ru(II), in an attempt to find more general catalysts with broader applications. The ruthenium(II)-BINAP complex catalyze hydrogenation of many types of molecules with other functional groups. These reactions give high enantiomeric excess and high yields and can be scaled up for industrial use. Noyori's Ru-BINAP is used a catalyst **(9)** in the industrial production of an anti-inflammatory, (*S*)-naproxen **(10)** (Scheme 1.7).[38]



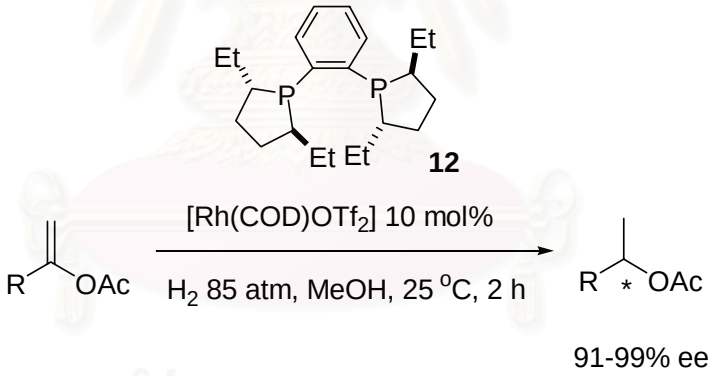
Scheme 1.7 Catalytic asymmetric synthesis of (*S*)-naproxen

Recently, Noyori reported a remarkable enhancement in the reactivity of the Ru(II) catalysts by the addition of ethylene diamine and KOH in 2-propanol. The addition of very small amounts of these basic agents entirely reverse the chemoselectivity from olefin-selective to carbonyl-selective.[39] Effective asymmetric hydrogenation of α,β-unsaturated ketones has been an enduring problem in organic chemistry. In the example in Scheme 1.8, the combined use of chiral Ru(II) complex and the weak base K_2CO_3 transforms a simple enone by enantioselective hydrogenation into a chiral allylic alcohol. The substrate/catalyst ratio approaches 100,000. This chemoselectivity is remarkable in view of the large catalytic activity of diamine-free BINAP-Ru complexes **(11)** for hydrogenation of carbon-carbon double bonds in allylic alcohols.



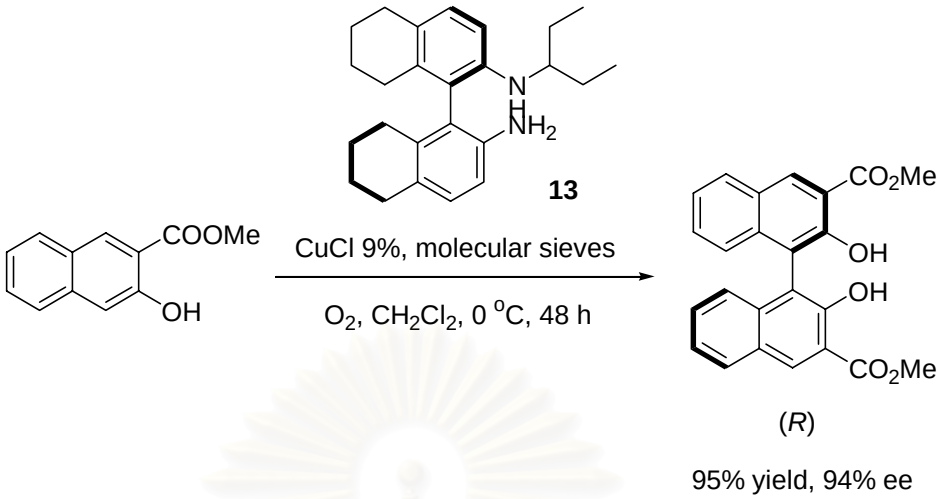
Scheme 1.8 Asymmetric hydrogenation of enone catalyxed by diamine-BINAP-Ru complexe (11)

One of the most interesting examples is hydrogenation of functionalized ketones. Optically active secondary alcohols bearing a functional group are extremely useful starting matherials for the synthesis of various biologically active compounds. Diphosphine complexes of Rh and Ru have been used as catalysts for this reaction. α-Amino ketones and β-keto esters were hydrogenated with high enantioselectivities by using a high substrate/catalyst ratio to give the corresponding amino alcohols with up to 96% ee.[40-41] In addition, enol esters are interesting substrates for asymmetric hydrogenation because the products can easily be converted to optically active alcohols. Several enol esters have been used in asymmetric hydrogenation catalyzed by Rh complexes with chiral diphosphine ligands. Substrates having an additional functional group are hydrogenated with high enantiomeric excess. Chiral Et-DuPHOS **(12)** were reported to be the excellent ligands for the asymmetric hydrogenation of enol acetates. Several aromatic and aliphatic enol acetates were hydrogenated by using a complex of rhodium and Et-DuPHOS **(12)** to give the corresponding esters with high enantioselectivities.[42]



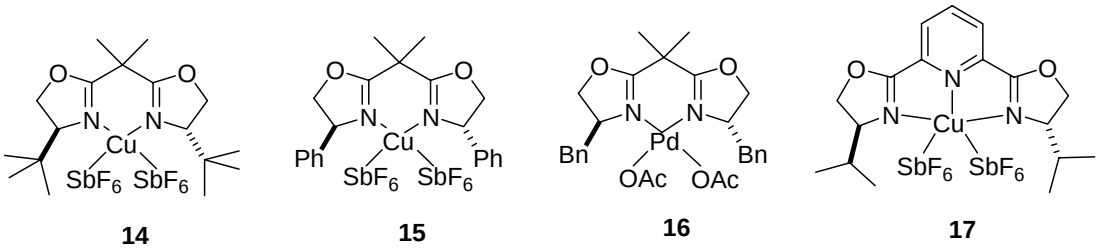
Scheme 1.9 Asymmetric hydrogenation of enol esters using Rh-Et-DuPHOS complex

The chiral amines previously employed for the biaryl coupling reaction were mostly aliphatic diamines, and the use of chiral diaryldiamines derived from 1,1′-naphtyl-2,2′-diamine (BINAM) has been reported.[43] These chiral ligands were complexed with Cu^{+} and employed in the catalytic asymmetric oxidative coupling of 3-hydroxy-2-naphthanoate to the corresponding binaphthol derivative. The diamine with one N-(3-pentyl) group **(13)** shows highest enantioselectivity in the biaryl coupling.

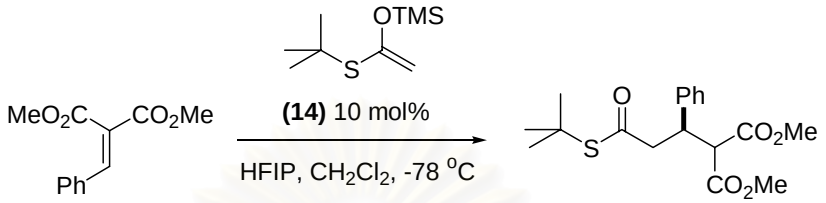


Scheme 1.10 Enantioselective oxidative coupling of metyl-3-hydroxy-2-naphthanoate

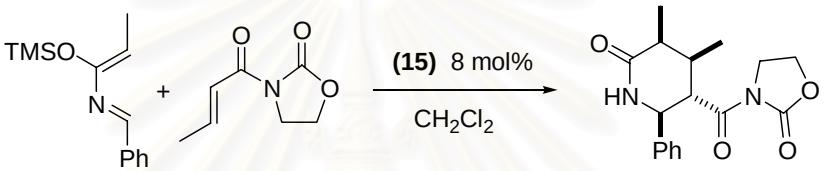
Chiral Lewis acids formed by complexation of a copper salt by a chiral bisoxazoline are C_2-symmetric complexes (BOX). These ligand-metal complexes have emerged as an effective catalyst for carrying out a wide range of enantioselective reactions such as Mukaiyama aldol reaction,[44] Michael addition,[45] Diels-Alder reaction [46] and annulation of allene [47] (Scheme 1.11). The presence of a C_2-symmetric axis in the bisoxazoline and Pybox complexes **(14-17)** minimizes the number of possible transition states in a particular reaction. The selectivity was observed due to the fact that the bisoxazoline catalysts form six membered metal chelates which are conformationally constrained and the chiral centers in these catalysts are located in close proximity to the nitrogen donor, thereby imposing a strong directing effect on the catalytic sites.



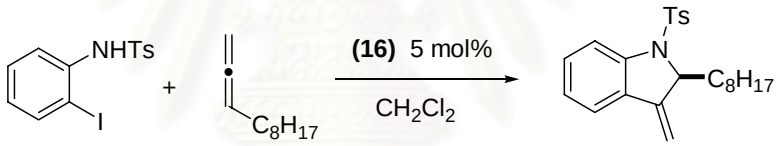
14 **15** **16** **17**



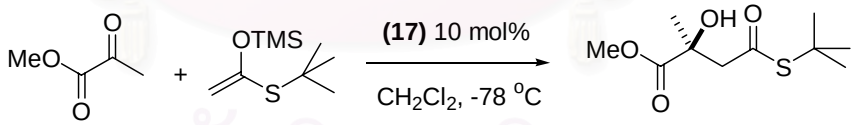
91% yield, 93% ee



80% yield, 95% ee



94% yield, 82% ee

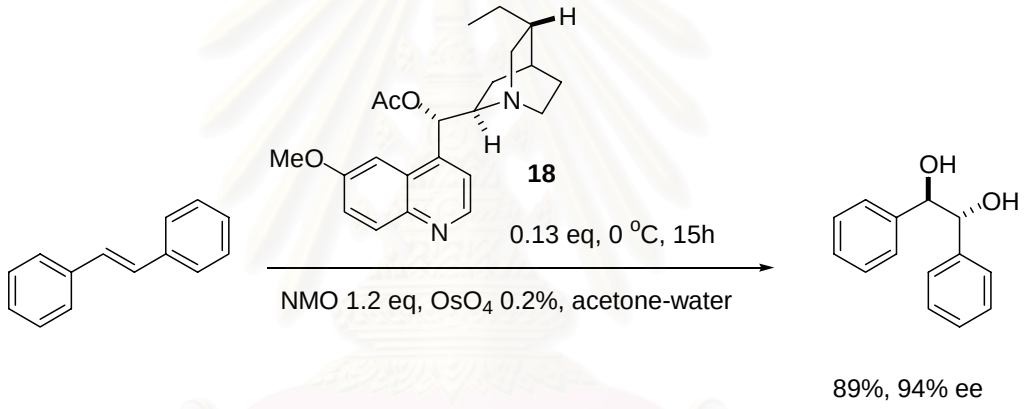


92% yield, 95% ee

Scheme 1.11 Various enantioselective reactions catalyzed by bisoxazoline and Pybox complexes

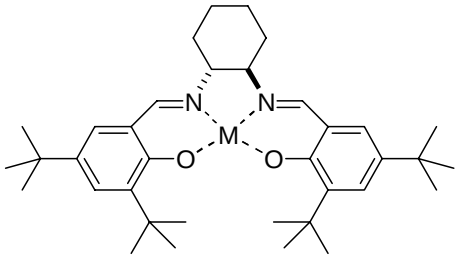
Asymmetric *cis*-dihydroxylation of the olefins is the reaction that converts an olefin to a vicinol diol present in many natural products and unnatural molecules. The original dihydroxylation reaction used stoichiometric amount of osmium tetroxide (OsO_4), which is expensive, volatile and toxic, with the result that even small-scale reactions were inconvenient. However, the hydroxylation shows specificity for double

bonds and has no particular substrate requirements, which were advantages. Over the years, the original dihydroxylation procedure has been modified to operate catalytically, more rapidly, and in better yield. It was observed that the addition of amines, such as pyridine, to the dihydroxylation reaction increases its rate. Presumably this is due to the formation of an electron-rich coordination complex with the osmium atom. A useful stoichiometric co-oxidant is *N*-methylmorpholine *N*-oxide (NMO). In 1988, Sharpless discovered the first catalytic asymmetric dihydroxylation. The cinchona alkaloid ligand **(18)** was proved to have more balanced properties and gave more pronounced "ligand accelerated catalysis". The sharpless cinchona alkaloid catalytic dihydroxylation process with the practical quantities of NMO resulted in good yields and good enantiomeric excess.[48]



Scheme 1.12 Catalytic asymmetric dihydroxylation developed by Sharpless

Chiral salen ligands firstly reported by Jacobsen are tetradentate ligands prepared by condensation of two equivalents of a salicylaldehyde derivative with chiral 1,2-diamines. Chiral salen ligands have several attractive features which constitute the basis for their utility in asymmetric reactions. Metal complexes of salen ligands are readily prepared from a variety of first row and second row transition metal salts as well as main group metals. Although a large number of ligand structures are accessible, it is striking that the salen complex **(19)** has often been found to be the optimum complexes for a broad range of reactions catalyzed by several different metals (Figure 1.8) such as Mn-complexes for epoxide, Co- and Cr-complexes for ring-opening of epoxide and Diels-Alder reaction, and Al-complxes for conjugate addition.

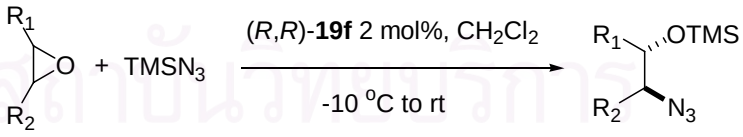


19a M=Mn-Cl
19b M=Co-OAc
19c M=Co-SbF_6
19d M=Co-Cl
19e M=Cr-Cl
19f M=Cr-N_3
19g M=Cr-BF_4
19h M=Cr-SbF_6
19i M=Al-Cl
19j M=Al-N_3

Figure 1.8 Metal salen complexes utilized in catalytic asymmetric reactions

As an example, asymmetric epoxide ring opening by $TMSN_3$ was found to be catalyzed by (salen) metal complexes. Meso epoxides undergo desymmetrization catalyzed by complex **(19f)** with good to excellent enantioselectivity. This reaction was extended to the kinetic resolution of racemic terminal epoxides to provide 1-azido-2-trimethylsiloxyalkane derivatives in high enantiomeric excess (Table 1.2 and 1.3).[49] Epoxide ring-opening with $TMSN_3$ has also been demonstrated to show a high degree of catalyst control in the regioselective opening of enantiopure dissymmetrically substituted epoxides.[50]

Table 1.2 The asymmetric ring opening of meso epoxides with $TMSN_3$

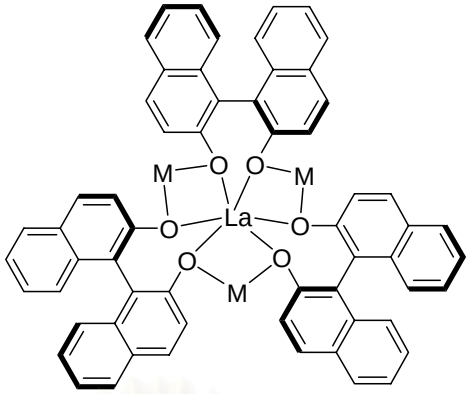


Entry	R^1	R^2	Yield(%)	Ee(%)
1	$-(CH_2)_3-$		97	93
2	$-(CH_2)_4-$		96	85
3	$-CH_2OCH_2-$		96	97
4	$-CH_2N(C(O)CF_3)CH_2-$		96	97
5	$-CH_2CH=CHCH_2-$		85	93
6	$-CH_2C(O)CH_2-$		77	94

Table 1.3 The kinetic resolution of racemic epoxides via ring opening with $TMSN_3$

Entry	R^1	R^2	Yield(%)	Ee(%)
1	Me	H	49	97
2	Et	H	41	97
3	*n*-Bu	H	45	97
4	CH_2Cl	H	47	95
5	CH_2OTBS	H	48	96
6	*c*-C_6H_{11}	H	42	97
7	Bn	H	47	93
8	$(CH_2)_2CH=CH_2$	H	47	98
9	$CH(OEt)_2$	H	48	89
10	CH_2CN	H	40	92

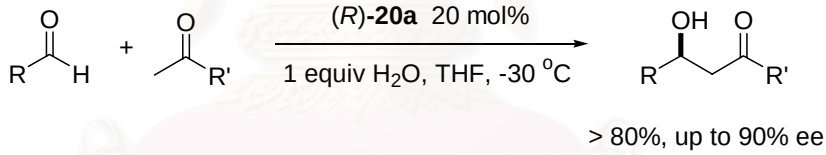
Chiral ligands containing oxygen atoms in the molecules and previously developed as a highly efficient catalysts are diol compounds such as TADDOL,[51] and BINOL,[52] both being bidentate ligands. Shibasaki reported the use of various chiral heterobimetallic complexes derived from lanthanide metals, alkaline metals and (*S*) of (*R*)-BINOL as chiral catalysts [53] in Michael reaction,[54-55] Aldol reaction,[56] and Pudovik reaction.[57-58] Heterobimetallic complexes **(20a-c)** (Figure 1.9) developed by Shibasaki are the well-known catalysts for many reactions especially for aldol-type reactions. These catalysts function as both Lewis acids and Bronsted bases. The central metal acts as the Lewis acids, and the alkali metal binaphthoxide moieties act as Bronsted bases. The balance and co-orperation between these functionalities are important to asymmetric induction. After testing a series of lanthanides (La, Ga, Gd, Sm, Pr, Dy, Yb), lanthanum-derived catalysts have been found to give the best results.



20a M = Li^+ (*R*-LLB) **20b** M = Na^+ (*R*-LSB) **20c** M = K^+ (*R*-LPB)

Figure 1.9 Heterobimetallic complexes developed by Shibasaki

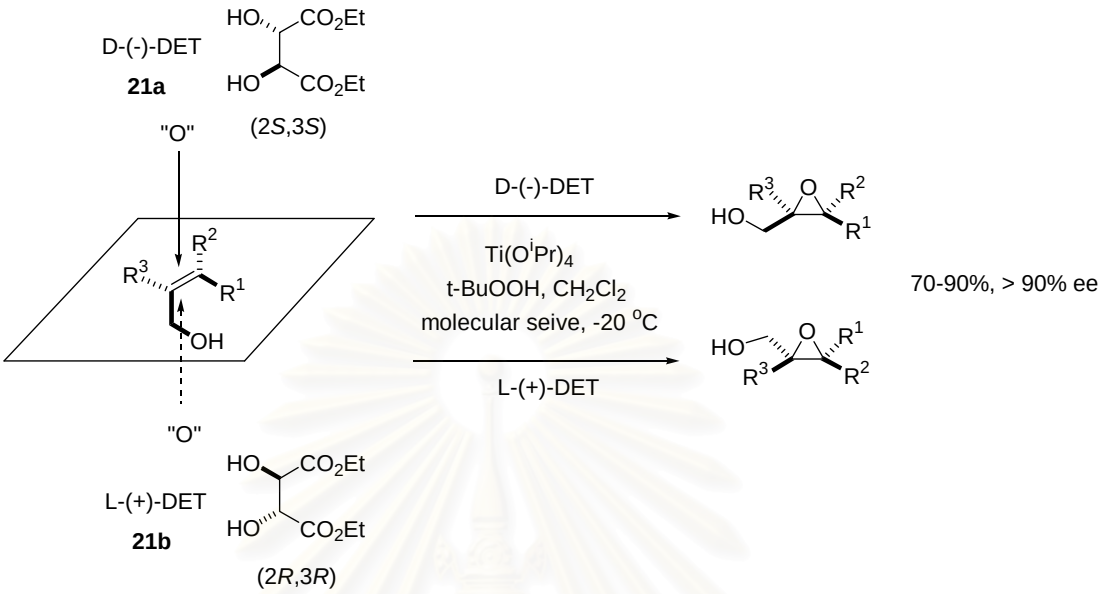
For example, In 1997, Shibasaki employed the heterobimetallic complex **(20a)** in catalytic enantioselective aldol reaction between aromatic or aliphatic aldehydes and methylketone. The reaction gave β-hydroxyketone as the major product with high yields and enantioselectivities.[56]



Scheme 1.13 Asymmetric aldol reaction catalyzed by heterobimetallic complex (20a)

In addition, Sharpless discovered an asymmetric epoxidation reaction of allylic alcohols in 1980. This reaction is a classic in asymmetric catalyst development. Using titanium(IV) tetraisopropoxide, *tert*-butyl hydroperoxide and an enantiomerically pure dialkyl tartrate, the Sharpless epoxidation accomplishes with excellent stereoselectivity. This powerful reaction is very predictable. When the D-(-)-tartrate ligand (D-(-)-DET) **(21a)** is used in epoxidation, the oxygen atom is delivered to the top face of the allylic alcohol as depicted. The L-(+)-tartrate ligand L-(+)-DET) **(21b)**, on the other hand, allows the bottom face of the olefin to be epoxidized. When achiral allylic alcohols are employed, the Sharpless reaction exhibits exceptional

enantiofacial selectivity (ca. 100:1) and provides convenient access to synthetically versatile glycidol derivatives.[59]

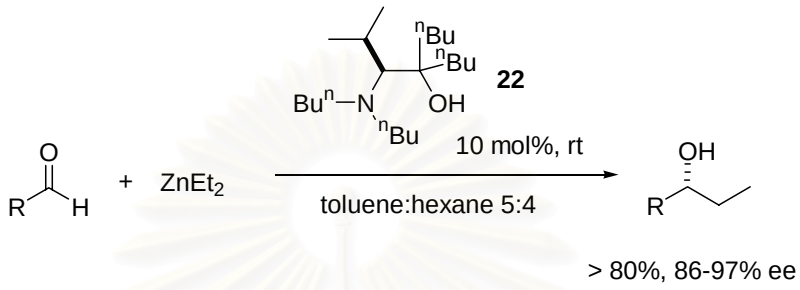


Scheme 1.14 The predictive stereoselectivity of the Sharpless epoxidation

It was found that metal complexes of TADDOL, BINOL and tartrate are the powerful and efficient catalysts for several asymmetric reactions. Interestingly, when the one hydroxy group in the structure of TADDOL or BINOL or tartrate is replaced by an amino group, the new chiral aminoalcohol ligands having related structure will be obtained. The use of such chiral aminoalcohols [60-61] is mainly limited to only a few types of reaction such as alkylation of aldehydes [62-65] and imines.[66-68]

Asymmetric organozinc additions to carbonyl compounds have grown dramatically and a large number of chiral catalysts have been developed. The diethylzinc addition to aldehydes has also become a classical test in the design of new ligands for catalytic enantioselective syntheses. The chiral ligands do not only control the stereochemistry of the orgnozinc addition, but also activate the zinc reagents. A number of chiral ligands developed for the asymmetric organozinc additions are derived from amino alcohols. These compounds react with dialkylzincs to generate a zinc-based chiral Lewis acid omplex which can further coordinate with both the aldehyde substrates and the dialkylzinc reagents to induce the catalytic addition. Thus the *in situ* generated zinc complex is a multifunctional catalyst. It acts as a Lewis acid

to activate the carbonyl substrates and also as a Lewis base to activate the organozinc reagents. The chiral environment of the ligand controls the stereoselectivity. For instance, Luche *et al*. disclosed the use of chiral ligand **(22)** in asymmetric diethylzinc addition to aromatic and aliphatic aldhydes. Chiral secondary alcohols were obtained in high yield and enantioselectivity.[64]



Scheme 1.15 Asymmetric diethylzinc addition catalyzed by amino alcohol (22)

1.3.2 Chiral organocatalysts

In organic chemistry, value is directly related to purity. In recent years, the number of methods available for high yielding and enantioselective transformation of organic compounds has increased tremendously. Most of the newly introduced reactions are catalytic in nature. Clearly catalytic transformation provides the best “atom economy”, because the stoichiometric introduction and removal of chiral auxiliaries can be avoided or at least minimized. Until recently, the catalysts employed for enantioselective synthesis of organic compounds such as pharmaceuticals, agrochemicals, fine chemicals, or synthetic intermediates, fell into two general categories – transition metal complexes and enzymes. Between the extremes of transition metal catalysis and enzymatic transformations, methods based exclusively on metal-free chiral catalysts have become more significant. The third approach to the catalytic production of enantiomerically pure organic compounds, organocatalysis, has recently emerged.[69]

Organocatalysts are purely organic molecules which mainly composed of carbon, hydrogen, nitrogen, sulfur and phosphorus. As opposed to organic ligands in transition metal complexes, the catalytic activity of organocatalysts resides in the low

molecular weight organic molecule itself, and no transition metals or other metals are required. Organocatalysts have several advantages over metal based catalysts. They are usually robust, inexpensive, non-toxic, and readily available. Because of their inertness toward moisture and oxygen, demanding reaction conditions, for example inert atmosphere, low temperatures and anhydrous solvents are also not required. The absence of transition metals in organocatalyses seem to be especially attractive for the preparation of compounds that do not tolerate metal contamination.[70] A selection of the typical organocatalysts is shown in Figure 1.10.

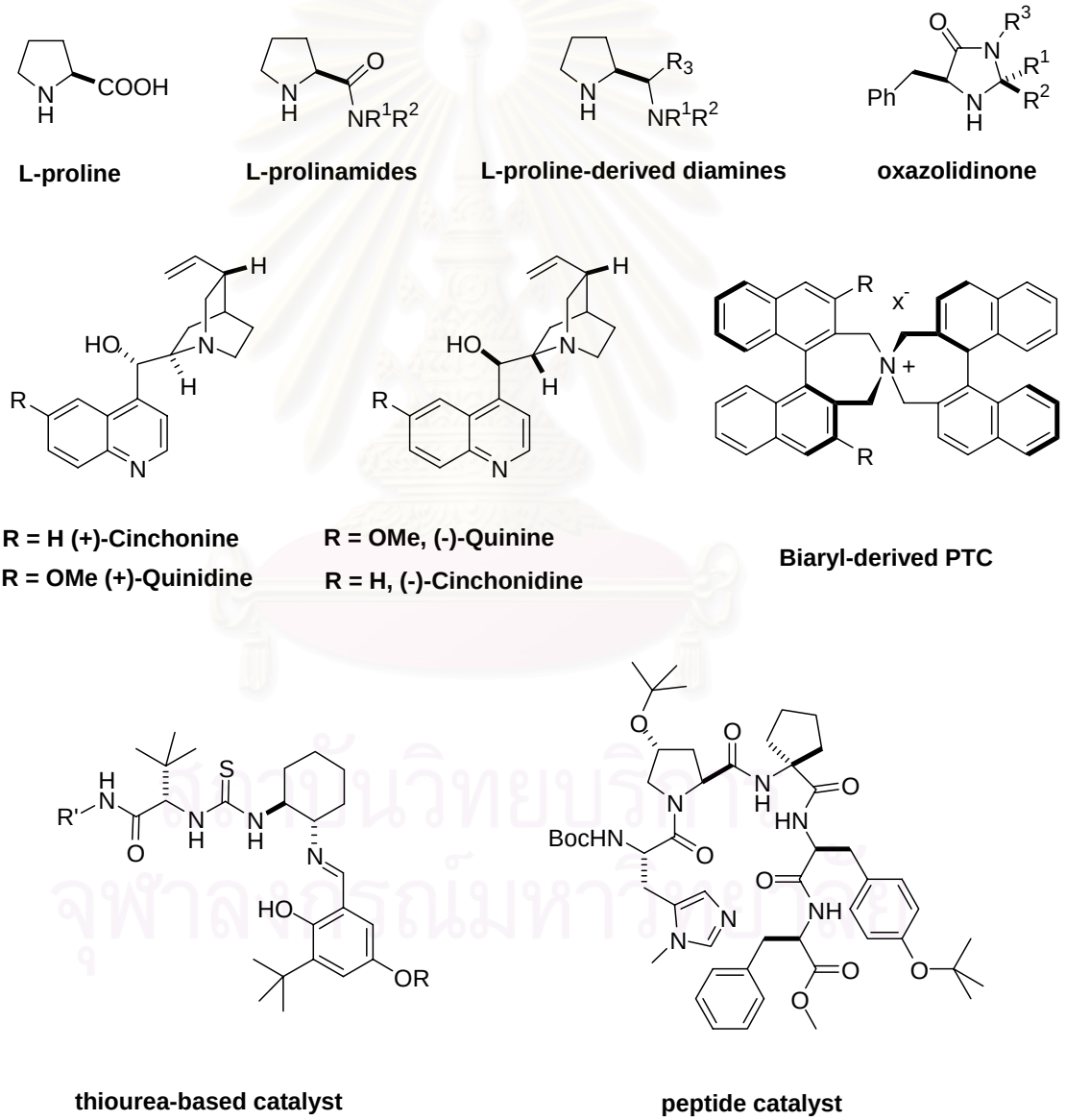


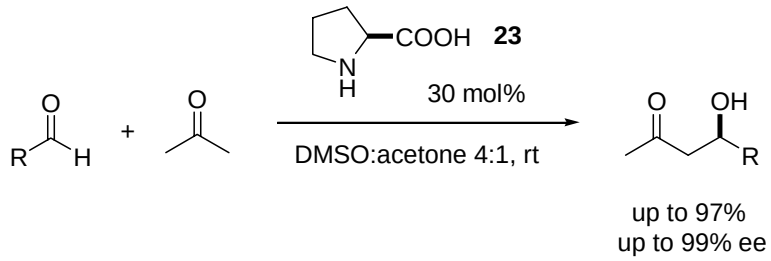
Figure 1.10 A selection of typical organocatalysts

From mechanistic considerations in metal-mediated enantioselective catalytic reactions, the metal plays an organizational role by translating chiral information and activating the reagents. In the absence of the metal, the well-organized transition state, which is required for the enantioselective transformation, can be formed either by passive or dynamic interactions. Passive binding refers to ordinary molecular recognition through hydrophobic, Van de Waals and electrostatic interactions. Dynamic binding refers to interactions between catalysts and substrates at the reaction centers. Hydrogen bonding plays a crucial role in the determination of the stereoselectivity of the reaction.[71] In many instances, the mechanism of organocatalysis can be generally distinguished between covalent catalysis and non-covalent catalysis.

1.3.2.1 Covalent catalysis

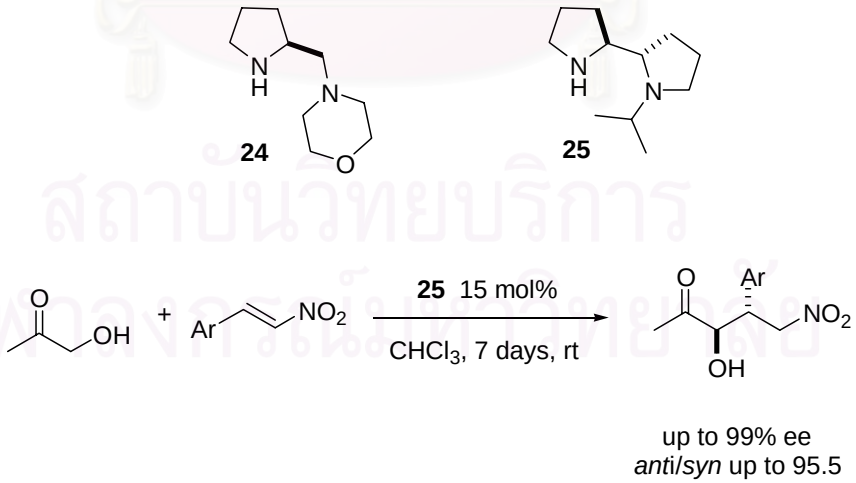
For mechanism of covalent catalysis, the formation of covalent substrate-catalyst adducts might occur by a single step Lewis-cid-Lewis-base interaction or by muitistep reactions such as the formation of enamine from aldehydes and secondary amines. Organic molecules can form reactive intermediate. The chiral catalyst is consumed in the reaction and requires regeneration in a parallel catalytic cycle. The rate acceleration of the reaction is also similar to the Lewis acid/base activation.

There have been many reports about the use of L-proline **(23)** in asymmetric aldol reaction. This reaction provides β-hydroxy carbonyl compounds. It has a broad range of applications and play a key role in the production of pharmaceuticals. The possibility of using a simple molecule from the chiral pool to act like an enzyme for the catalytic intermolecular direct aldol reaction has recently been reported by the List and Barbas group.[72-77] L-Proline **(23)** was chosen as the simple unmodified catalytic molecule from the chiral pool. The proline catalyzed reaction of acetone with aromatic and aliphatic aldehydes at room temperature resulted in the formation of the desired aldol products in satisfactory to very good yields and with enantioselectivity up to > 99% ee (Scheme 1.16). This reaction starts from acetone and L-proline. Formation of an acetone enamine *via* an iminium salt occurs in the initial step. Conversion of the enamine intermediate with an aldehyde and subsequent releases of the proline catalyst furnishes the aldol product.[72]



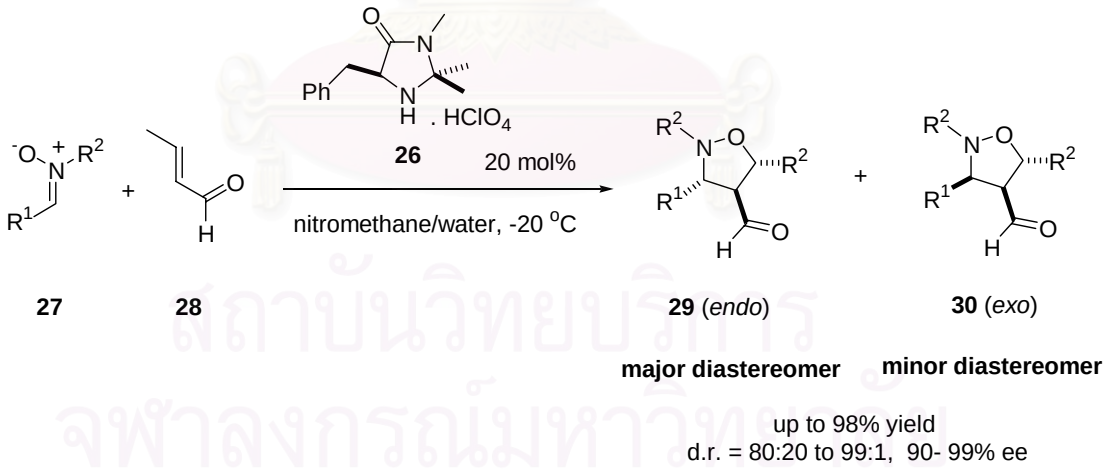
Scheme 1.16 Asymmetric direct aldol reaction catalyzed by *L*-proline (23)

In contrast to aldol-type reactions, the proline-mediated conjugate addition of various enolizable carbonyl compounds to activated olefins occurs with only modest enantioselectivity.[73,78] Excellent diastereoselectivity and higher enantioselectivity were observed with structurally similar (S)-2-(morpholinomethyl)pyrrolidine **(24)**, which was tested in the *syn*-selective addition of ketones and aldehydes to trans-β-nitrostyrene.[79] Interestingly, *N*-isopropyl-2,2′-bipyrrolidine **(25)** mediates an *anti*-selectivitive Michael addition. The reversal of the diastereoselectivity with α-hydroxyacetone can be ascribed to the formation of a *Z*-enamine intermediate, which is favored through the formation of hydrogen bonds between the OH group of α-hydroxyacetone and the tertiary nitrogen atom of catalyst (Scheme 1.7).[80]



Scheme 1.17 Asymmetric Michael addition catalyzed by chiral diamine (25)

The asymmetric 1,3-dipolar cycloaddition reaction of nitrones and electron-deficient olefins is wide of interest. The resulting isoxazolidine products are intermediates in the preparation of a wide range of biologically important compounds such as β-lactams and unusual amino acids.[81-82] Serveral asymmetric versions of cycloaddition of nitrones in the presence of optically active metal complexes as Lewis acid catalysts have been reported.[83] However, asymmetric deign of this reaction was found to be difficult when using α,β-unsaturated aldehydes as substrates because these compounds are poor substrates for metal catalysts, probably because of preferential coordination of the Lewis acid catalyst to the nitrone in the presence of the monodentate carbonyl compounds. Recently, MacMillan group successfully applied the phenylalanine-derived imidazolidinone salt **(26)** acting as iminium catalysis in organocatalytic 1,3-dipolar cycloaddition. Conversion of various *N*-oxides **(27)** with (*E*)-crotonaldehyde **(28)** to the isoxazolidine products **(29)** was investigated. The reaction can be performed under an aerobic atmosphere using wet solvents which makes this reaction even more attractive. The resulting isoxazolidines *endo*-**(30)** were obtained in yields of up to 98%, with diastereomeric ratios of d.r. (endo/exo) of 80:20 to 99:1 and with enantioselectivity of 90-99% ee (Scheme 1.18).[84]



Scheme 1.18 Asymmetric 1,3-dipolar cycloaddition catalyzed by imidazolidinone salt (26)

The Morita-Baylis-Hillman (MBH) reaction is the formation of α-methylene-β-hydroxycarbonyl compounds.[85] For the reaction to occur the presence of

catalytically active nucleophiles is required. It is now commonly accepted that MBH reaction initiated by addition of a catalytically active nucleophile to the enone **(31)** to generate enolate. The resulting enolate adds to the aldehyde **(32)** establishing the new stereogenic center at the carbon atom of aldehyde. Formation of the product **(33)** is completed by proton transfer from the α-position of the carbonyl moiety to the oxygen atom of alcohol with concomitant elimination of the nucleophile. Consequently, the nucleophile is available for the next catalytic cycle (Figure 1.11).

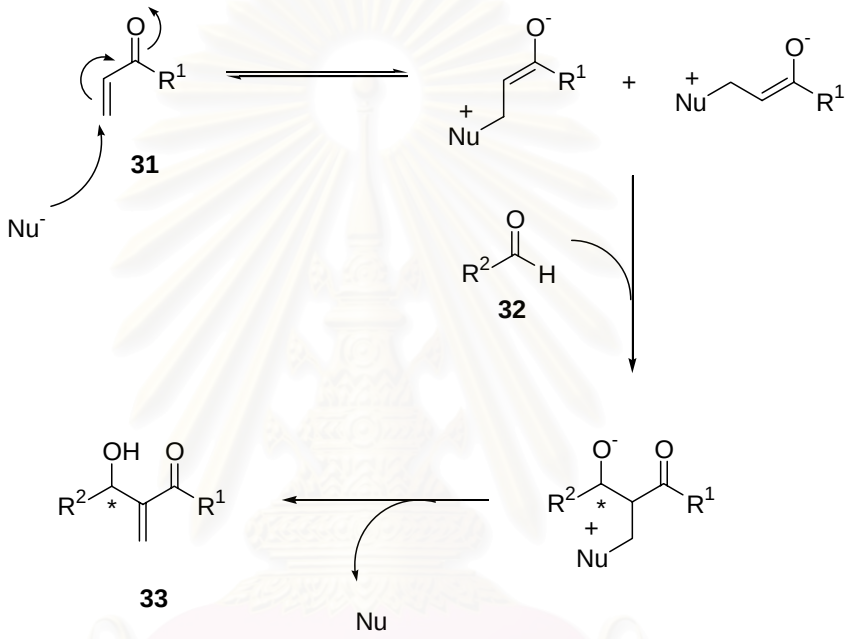
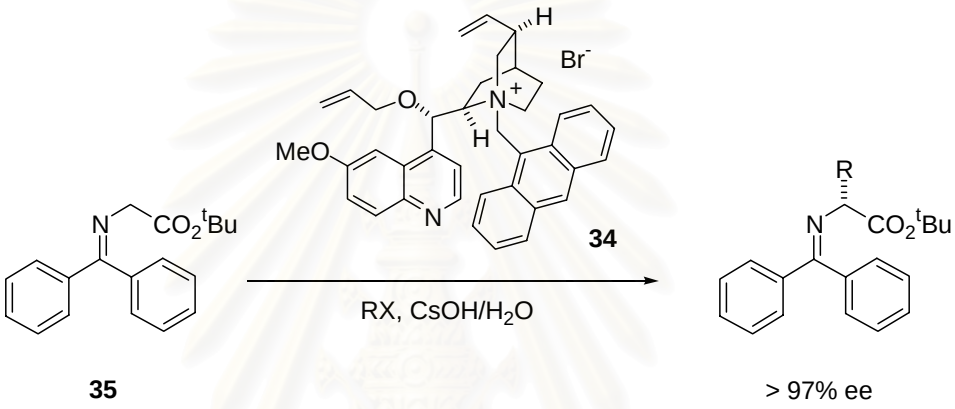


Figure 1.11 Mechanism of the Morita-Baylis-Hillman (MBH) reaction

1.3.2.2 Non-covalent catalysis

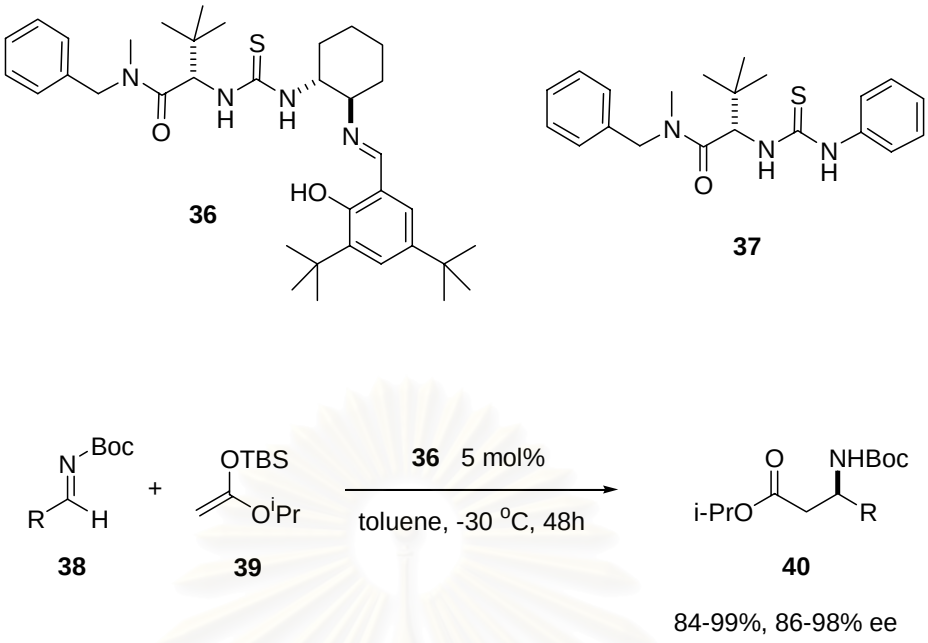
In many instances, non-covalent catalysis relies on the formation of hydrogen bonded adducts between substrate and catalyst or on protonation and deprotonation steps. Phase-transfer catalysis (PTC) by organic phase-transfer catalysts [86] also is in the non-covalent catalysis area. It is, however, mechanistically unique because PTC promotes reactivity not only by altering the chemical properties of the reactants but also involves a transport phenomenon. The chiral catalyst forms a host-guest complex with the substrate and shuttles between the standard organic solvent and a second phase such as the solid or aqueous phase, in one of which the reaction takes place.

Chiral phase-transfer catalysts are employed in several enantioselective organocatalytic reactions. One of the most important chiral phase-transfer reactions is the methods for synthesizing optically active α-amino acids from glycine derivatives by asymmetric alkylation at the α side-chain and using cinchona-based PTC. O′ Donnell and Corey reported *O*-(9)-allyl-*N*-(9-anthracenylmethyl) cinchonidinium bromide **(34)** catalyzed enantioselective alkylation of the enolate derived from the *t*-butyl glycinate benzophenone Schiff base **(35)** under phase-transfer conditions. Reactions provided the products in very high ee (> 97%) (Scheme 1.19). [87]



Scheme 1.19 The synthesis of optically active α-amino acids using cinchonidium bromide as chiral PTC

Another type of organocatalysts is chiral urea or thiourea-based catalysts developed by Jacobsen.[88-89] The molecules contain the urea or thiourea core unit as a scaffold which can donates hydrogen atoms to form strong hydrogen bonding with substrates. Besides, an optically active α-amino acid is also attached to induce chiral environment in enantioselective reactions. These organocatalysts have been found to catalyze the Manich-type reaction efficiently. Jacobsen *et. al.* developed an elegant and highly enantioselective route to *N*-Boc-β-amino acid esters *via* nucleophilic addition of enolate to *N*-Boc-protected imines.[88] Application of 5 mol% organocatalyst **(36)** in the asymmetric addition of silyl ketene acetals **(39)** to *N*-Boc-protected imines **(38)** led to a formation of β-amino acid derivatives **(40)** in both high yield and enantioselectivity (Scheme 1.20).

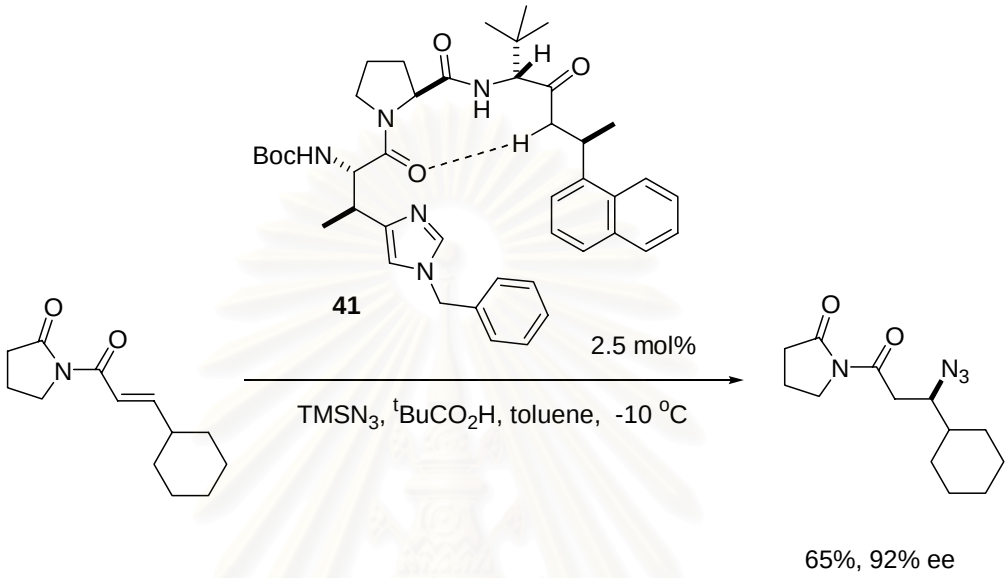


Scheme 1.20 Asymmetric Mannich-type reaction catalyzed by thiourea based catalyst (36)

Recently, Jacobsen has focused on optimization of the organocatalyst and design the simpler catalysts. A new catalyst **(37)** was found with a simple amino acid derivative and less than half the molecular weight and fewer stereogenic centers than the previous effective catalyst **(29)**. The catalyst **(30)** was also tested under the similar reaction conditions. After screening, the reaction provide the same excellent results.[89]

In the field of asymmetric organocatalysis, short peptides and peptide-based molecules have emerged as promising catalysts for a rapidly growing number of reactions.[90] Most of peptide-based catalysts are successful in kinetic resolution because these catalysts are making promising contributions through the combined advantages of secondary structural elements (α-helix and β-sheet) and their natural adaptability to diversification through combinatiorial chemistry.[91-94] For organic synthesis, peptide-based catalyst **(41)** derived from a short-chain peptide, with a histidine or modified histidine residue and a well-β-turn structure comprising a L-Pro-D-*tert*-Leu sequence catalyzed the conjugate addition of azide to α,β-unsaturated carbonyl compounds.[95] This oligopeptide was also tested earlier in asymmetric

acylation reactions.[96] Both the secondary structure and the presence of the Histidine base are necessary for the activity of the catalyst. Conformational restriction through functionalization of the β position of Histidine residue resulted in an improved selectivity in the azidation (Scheme 1.21).

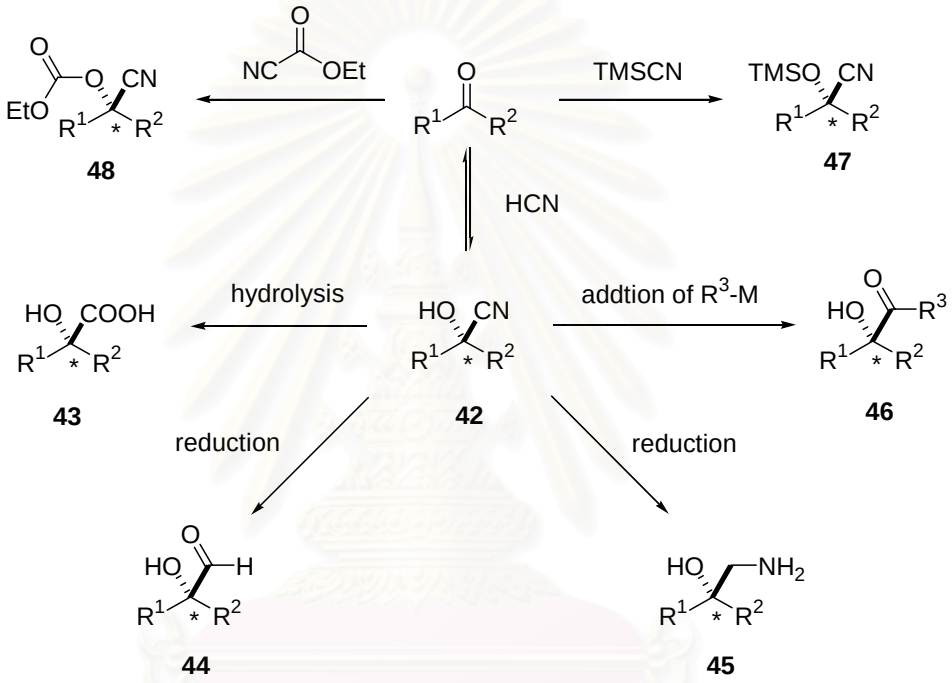


Scheme 1.21 Asymmetric 1,4-addition of azide to an enone catalyzed by the short-chain oligopeptide (41)

From all examples shown above, catalytic asymmetric synthesis has been prosperous. It is evident that the effective chiral catalysts, bearing much simpler and much smaller ligands than the proteins and natural occurring enzymes, can efficiently create molecules with extremely high enantiomeric purities. The chiral catalysts have an attractive C_2 symmetry in some cases and in other cases a fascinating dissymmetry. It is realized that such simple and beautiful small molecules can compete, practically and efficiently, with highly sophisticated enzymes that nature has created. This is a great encouragement for further studies to expand the design and continuously develop highly efficient chiral catalysts for catalytic asymmetric syntheses.

1.4 Asymmetric cyanohydrin formation

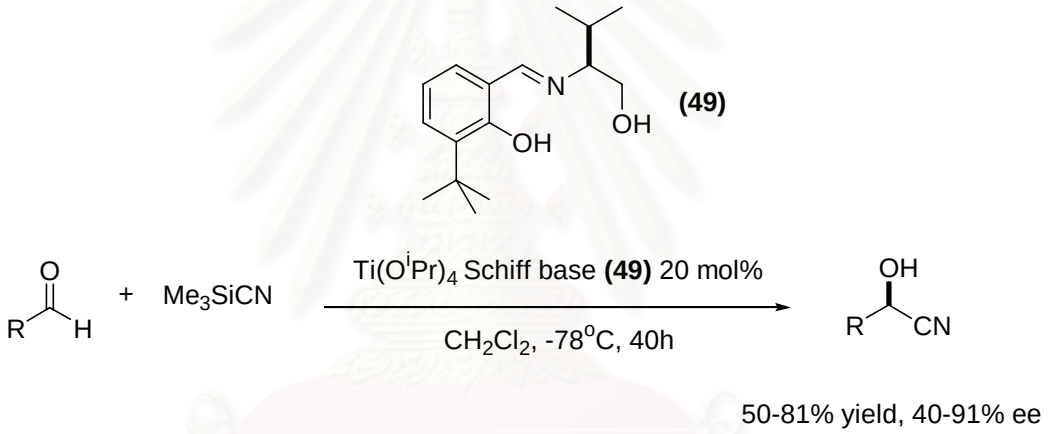
The addition of hydrogen cyanide to a carbonyl group provides the formation of an α-hydroxynitrile which is called a cyanohydrin **(42)**.[97] Compounds of this type have in many instances served as intermediates in the synthesis of α-hydroxy acids **(43)**, α-hydroxy aldehydes **(44)**, β-amino alcohols **(45)**, or α-hydroxy ketones **(46)** (Scheme 1.22).



Scheme 1.22 Hydroxy-compounds obtained from asymmetric cyanohydrin formation

In all these transformations of the cyanohydrins, the stereocenter originally introduced by HCN addition is preserved. Consequently, the catalytic asymmetric addition of HCN to aldehydes and ketone is a synthetically very valuable transformation. Besides addition of HCN, it also covers the addition of trimethylsilyl cyanide (TMSCN) and cyanoformate, generating cyanide anion equivalent, to carbonyl compounds resulting in the formation of *O*-silylated cyanohydrin **(47)** and cyanohydrin-*O*-carbonates **(48)** respectively. There have been a number of publications about the use of chiral Lewis acid catalysts and chiral organocatalysts in asymmetric hydrocyanation of aldehydes and ketones.

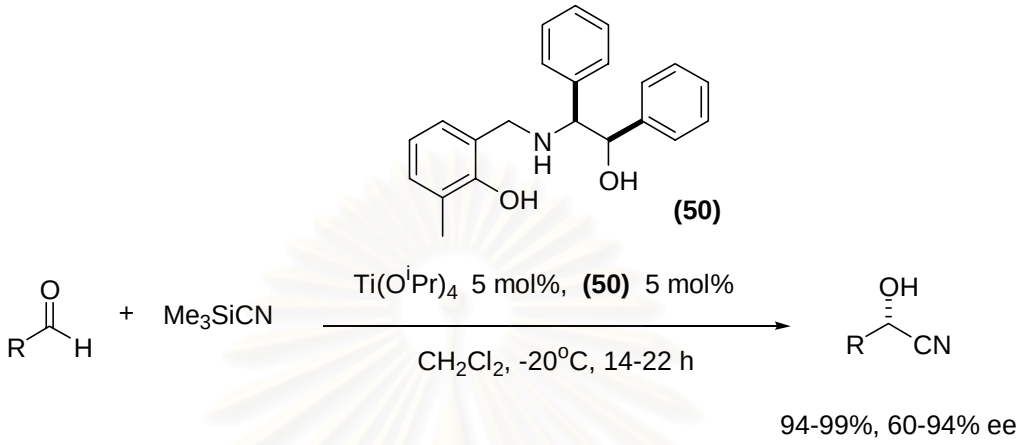
A classic research was published by Oguni and co-workers in 1993. They employed the tridentate chiral Schiff base complex **(49)** derived from 2-*tert*-butylsalicylaldehyde, a β-aminoalcohol and $Ti(OiPr)_4$ to catalyze an enantioselective trimethylsilylcyanation of a variety of aldehydes (aromatic, heteroaromatic, α,β-unsaturated and nonconjugated aliphatic aldehydes) to give silyl protected cyanohydrins in good yields and moderate to high enantioselectivities (Scheme 1.23).[98] One year later, they also reported that catalyst **(49)** also promoted the highly enantioselective reaction of diketene with various aldehydes, which led to the formation of optically active 5-hydroxy-3-oxoesters.[99] This work forms a basis of other more famous related works including those of Jacobsen and Hoveyda.[100]



Scheme 1.23 Enantioselective addition of trimethylsilyl cyanide to aldehydes catalyzed by Schiff base (49)-titanium alkoxide complex

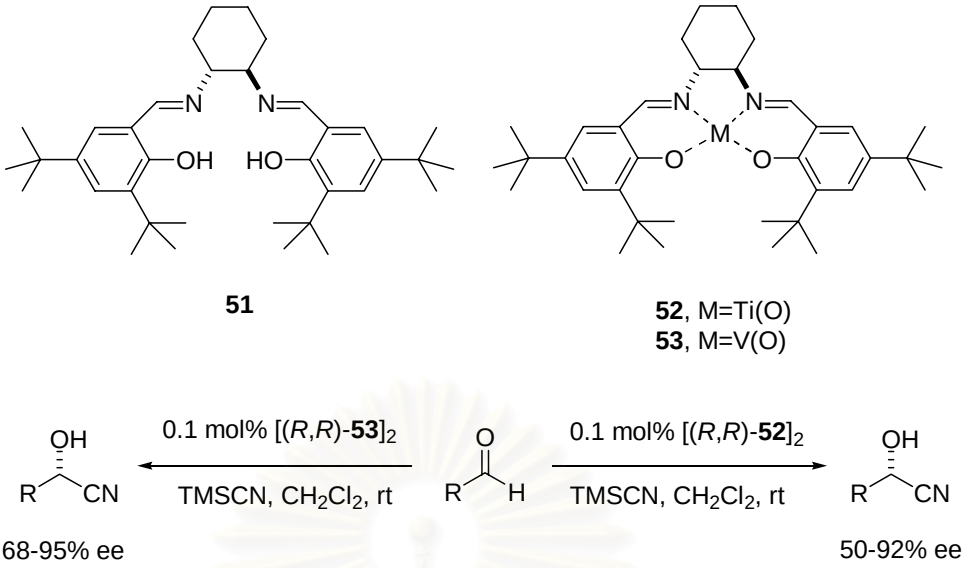
Zhang's group disclosed the achievement in asymmetric trimethylsilylcyanation of aldehydes. The β-amino alcohol **(50)**-$Ti(O^iPr)_4$ complex has been shown to efficiently catalyze the enantioselective cyanosilylation of aldehydes. They found that the backbone of (1*R*,2*S*)-1,2-diphenylaminoethanol in the ligand is a key point for high reactivity and enantioselectivity of the asymmetric cyanosilylation of aldehydes. In the presence of 5 mol % of this kind of complex catalyst, the aromatic, conjugated, heteroaromatic and aliphatic aldehydes were converted to their corresponding trimethylsilyl ethers of cyanohydrins in 94-99%

yields under mild conditions. In the sense of enantioselectivities, high ee values with up to 94% were obtained from aromatic substrates but aliphatic substrate gave the fair to good ee′s (Scheme 1.24).[101]



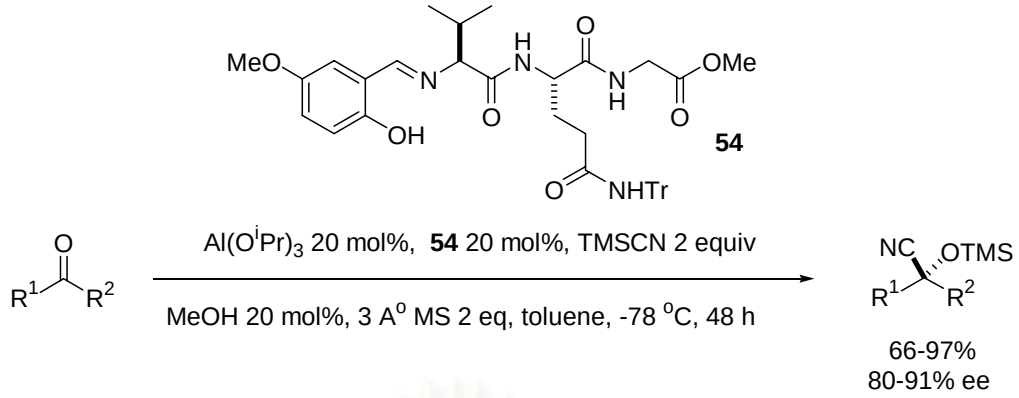
Scheme 1.24 Highly enantioselective cyanosilylation of aldehydes catalyzed by Titinium-chiral ligand (50) complex

Among the (salen)metal complexes found to be effective catalysts for several asymmetric reactions, North and Belokon have previously identified that a ligand **(51)** complexed with $TiCl_4$ is an asymmetric catalyst for the addition of TMSCN to aldehydes [102] and ketone.[103] In a limited screening of salen ligand with substituents, the ligand **(51)** was found to be optimal for this transformation as well. Subsequently, the Ti(IV)oxo-dimeric **(52)** and the V(IV)oxo-dimeric **(53)** complexes of **(51)** were determined as improved catalysts in terms of reactivity **(52)** and selectivity **(53)** for all substrates investigated (Scheme 1.25).[104] The results showed that aromatic aldehydes were the best substrates, although a greater range of selectivities was observed.



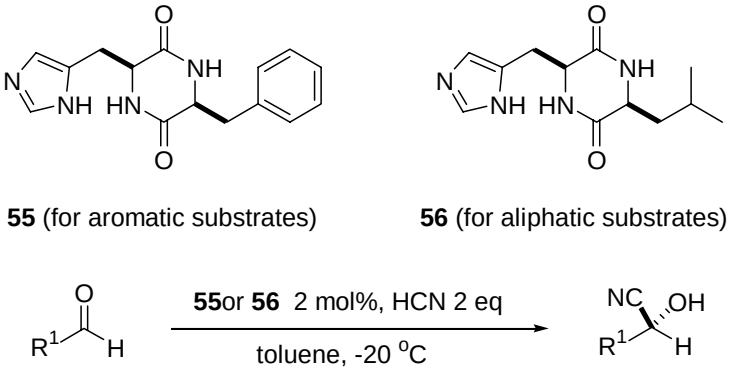
Scheme 1.25 Asymmetric hydrocyanation of various aldehydes catalyzed by salen-catalysts (52) and (53)

Snapper and Hoveyda have developed a number of asymmetric carbon-carbon bond forming reactions that are promoted by chiral peptidic ligands in the presence of early or late transition metals. In 2002, they reported a new approach to asymmetric cyanation of ketones that is Al-catalyzed, utilizes a peptidic chiral ligand, and delivers high enantioselectivity with both aromatic and aliphatic ketones.[105] Furthermore, this method provides several practical advantages, it requires a recyclable chiral ligand **(54)** that is readily modifiable and can be easily synthesized in six steps in 75% overall yields. The chiral ligand **(54)** and $Al(O^iPr)_3$ were employed in the enantioselective addition of TMSCN to various ketones including cyclic, acyclic, saturated and unsaturated substrates. In all cases, optically active cyanohydrins were obtained in high yields and enantioselectivities (Scheme 1.26).



Scheme 1.26 Asymmetric hydrocyanation of various ketones catalyzed by peptidic ligand (54)-Al complex

The first asymmetric hydrocyanation catalyzed by organocatalyst was discovered some twenty years ago. In 1982, Inoue *et al.* reported that a peptide catalyst **(55)**, readily available from L-histidine and L-phenylalanine, catalyzed the addition of HCN to benzaldehyde with up to 90% ee.[106] Later reaction conditions were optimized and many aromatic and aliphatic aldehyde were tested as substrates. The desired cyanohydrins produced by **(55)** generally possess *R* configuration with high yield and enantioselecivity for aromatic substrates. In case of aliphatic substrates, poor enantioselectivityies (<50% ee) were observed with the same catalyst. However, a catalyst **(56)** which is available from L-histidine and L-leucine afforded an enantioselectivity as high as 81% ee for aliphatic aldehydes (Scheme 1.27).[107-108]



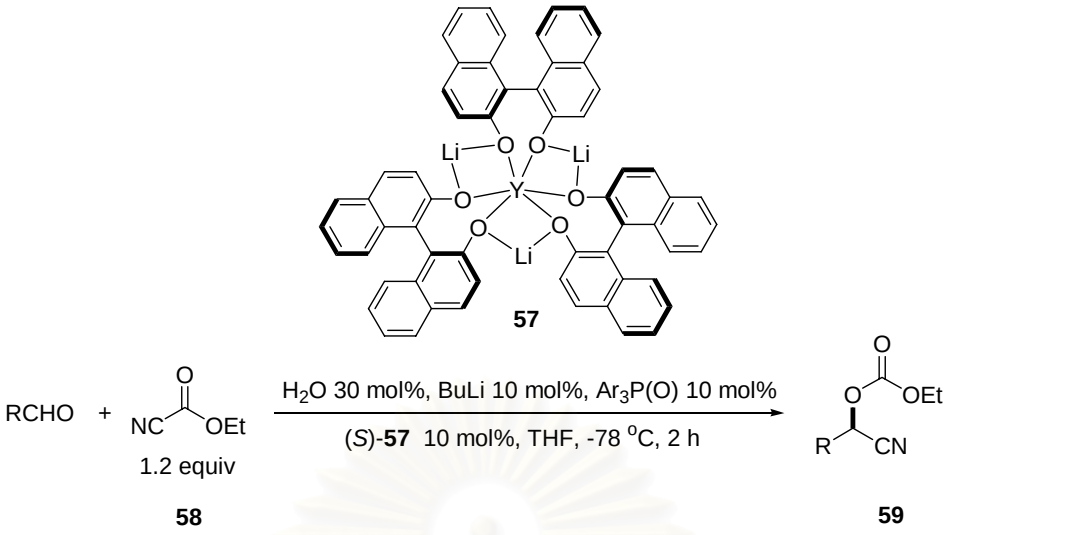
55 (for aromatic substrates) **56** (for aliphatic substrates)

50-97% and 84-98% ee, aromatic substrates

83-99% and 61-81% ee, aliphatic substrates

Scheme 1.27 Asymmetric hydrocyanation of various aldehydes catalyzed by cyclic peptide (55) or (56)

Recently, Shibasaki developed an enantioselective cyano-ethoxycarbonylation reaction of aldehydes with ethyl cyanoformate **(58)** catalyzed by heterobimetallic YLi_3tris(binaphthoxide) complex (YLB) **(57)**. The cyanation of aldehydes was carried out in the presence of (*S*)-**(58)** 10 mol% and 1.2 equiv of ethyl cyanoformate in THF at -78 °C for 2 hours. In addition, they also found that H_2O, tris(2,6-dimehoxyphenyl)phosphine oxide and BuLi, which are achiral additives, played crucial roles in achieving high reactivity and enantioselectivity. The reactions provided cyanohydrin *O*-carbonates **(59)** in up to > 99% yield and up to 98% ee (Scheme 1.28).[109]

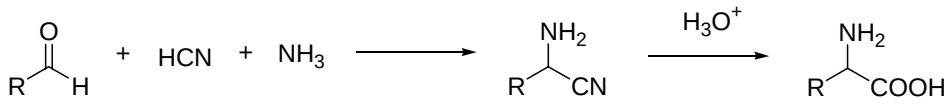


Scheme 1.28 Enantioselective cyano-ethoxycarbonylation reactions catalyzed by (*S*)-YLB **(57)**

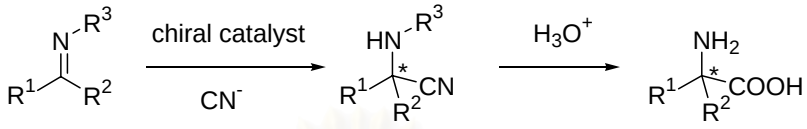
Asymmetric hydrocyanation is a reaction of high synthetic importance. The development of preparatively viable methodology has seen a continuous between chiral Lewis acid catalysts and organocatalysts. Likewise, its related reaction, which is called Strecker reaction, is the well-known classical procedure for the preparation of α-aminonitriles which are also key intermediates for natural products syntheses and preparation of several biologically active compounds.

1.5 Asymmetric Strecker reaction

The classical Strecker reaction,[9] a three-component reaction, starting from an aldehyde, ammonia and a cyanide source is one of the most atom-economical method for the synthesis of α-amino acids. A popular version for asymmetric Strecker reactions is based on the use of performed imines **(60)** and a subsequent nucleophilic addition of HCN or TMSCN in the present of a chiral catalysts.[110-112] The resulting α-aminonitriles **(61)** are important precursor of α-amino acids and other nitrogen-containing compounds (Scheme 1.29).



Classical Strecker synthesis

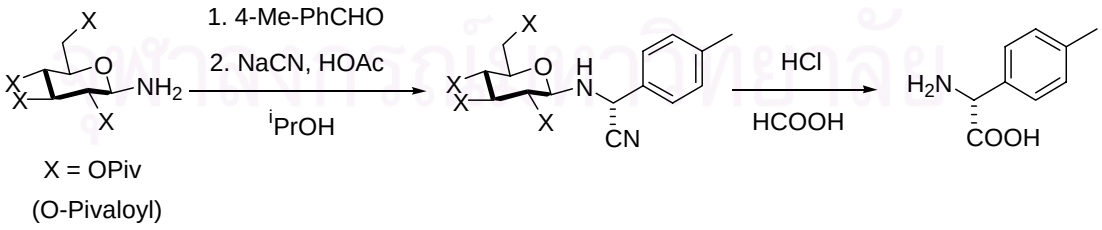


60 **61**

Addition of cyanide to imines

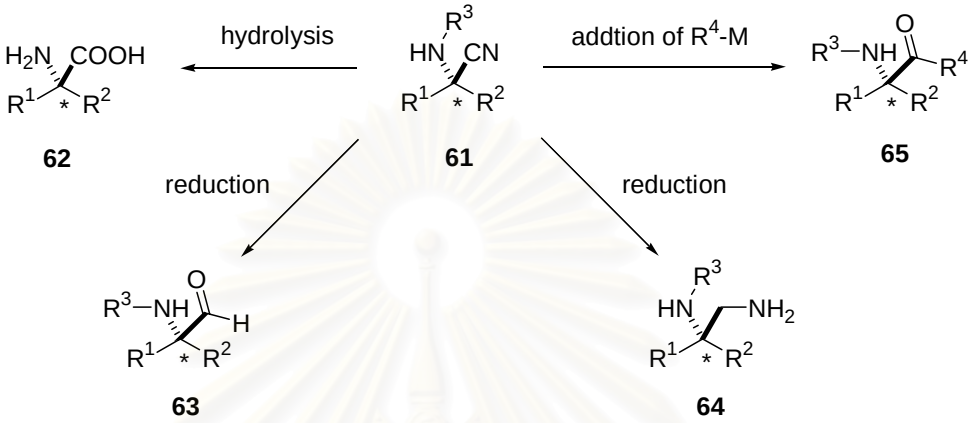
Scheme 1.29 General reactions of Strecker synthesis

Traditionally, optically pure α-amino acids can be obtained via the Strecker reaction with the use of chiral auxiliaries (Scheme 1.30).[113-117] However, this requires extra steps for the introduction of the auxiliary into the substrate and its removal from the product. Morover, these chiral auxiliaries are often expensive and difficult to recover. These limitations substantially hinder the use of this method for large-scale synthesis of α-amino acids. On the other hand, catalytic Strecker-type reactions require only a small, reliable 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 more economical.



Scheme 1.30 Chiral Auxiliary approach

In addition, α-aminonitriles obtained from Strecker reaction can serve as starting maerials for useful intermediates in organic synthesis [118-119] such as of α-amino acids **(62)**, α-amino aldehydes **(63)**, chiral diamines **(64)**, or α-amino ketones **(65)** (Scheme 1.31).

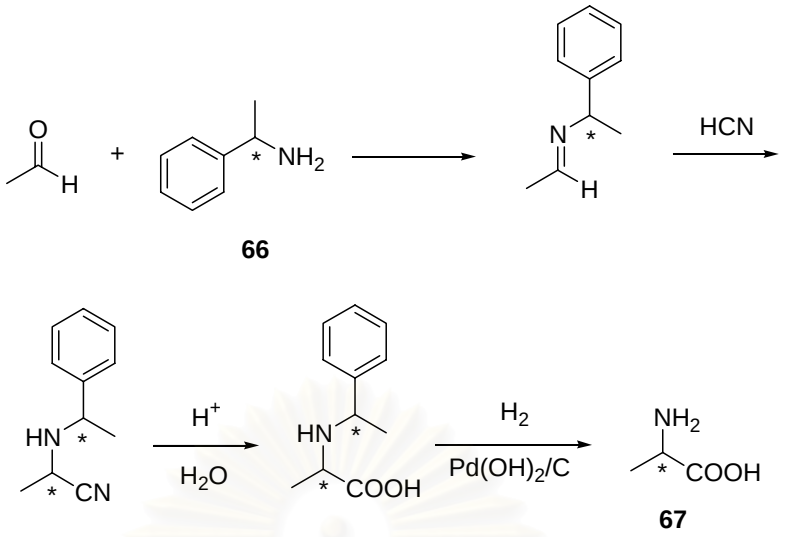


Scheme 1.31 Several useful intermediates obtained from asymmetric Strecker synthesis

1.6 Literature reviews of the asymmetric Strecker synthesis

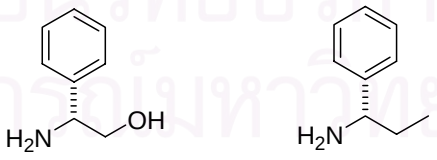
1.6.1 Non-catalytic asymmetric reactions

Asymmetric Strecker reactions using chiral auxiliaries are known for more than 50 years. In 1963, Harada reported the first asymmetric Strecker synthesis by using chiral imines as substrates.[120] This reaction provides an optically active α-aminonitrile which is then hydrolyzed to the amino acid. For instance, the optically active α-methylbenzylamine **(66)**, acetaldehyde, and hydrogen cyanide reacted to form *N*-α-methylbenzylaminoacetonitrile. Optically active alanine **(67)** with high optical purity (98%) was obtained after hydrolysis and hydrogenolysis (Scheme 1.32).[121-122]



Scheme 1.32 The first asymmetric Strecker synthesis

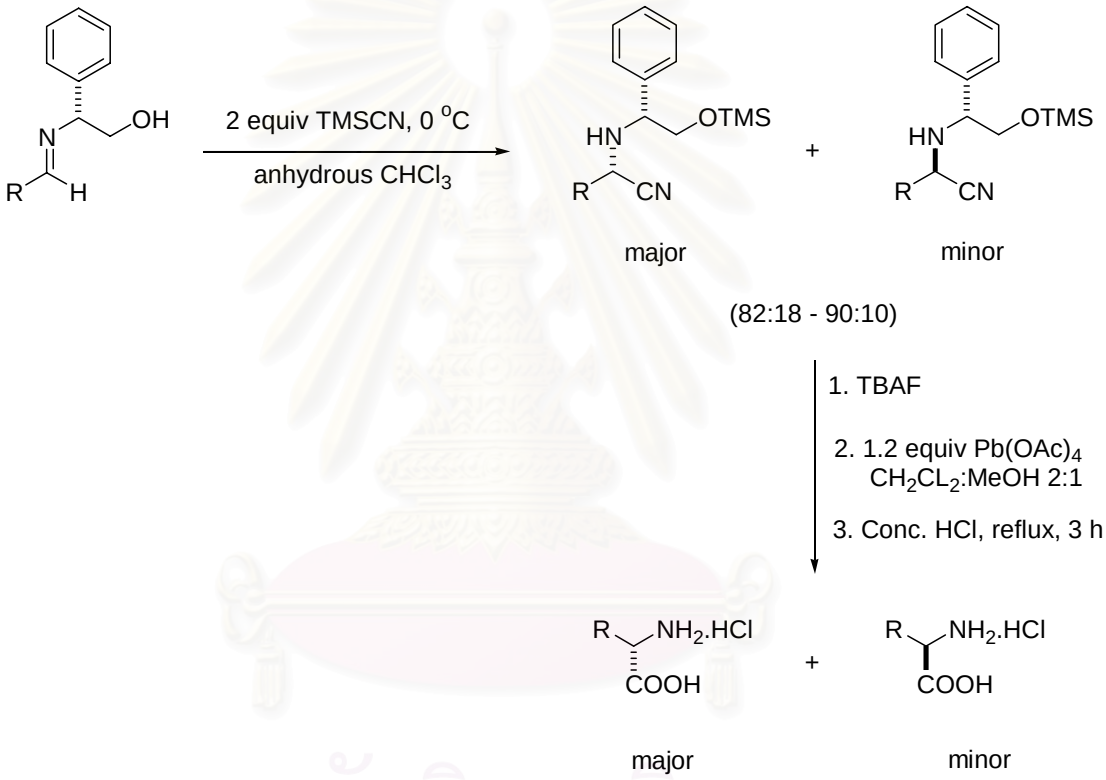
In 1970, Patel and Worsely disclosed an asymmetric synthesis of several α-amino acids including unusual amino acids such as the L(+) and D(-) enantiomers of norvaline and norleucine by addition of hydrogen cyanide to the carbon-nitrogen double bond of Schiff bases prepared from optically active *S*-(-) and *R*-(+)-α-methylbenzylamine and various aldehydes. The desired amino acids were obtained with high enantioselectivity up to 99% ee and fair overall yield 40-60% ee.[123] Afterwards, other optically active amines have been used as chiral auxiliaries in asymmetric Strecker synthesis such as *R*-(-)-2-phenylglycinol **(68)**,[124-126] *S*-(-)-1-phenylpropylamine **(69)** (Figure 1.12)**.** Nevertheless, *S*-(-)-methylbenzylamine **(66),** has been still employed until recently.



68 **69**

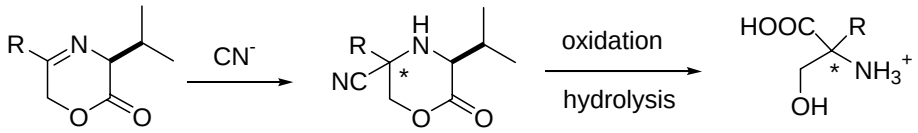
Figure 1.12 Optically active amines successfully used as chiral auxiliaries for α-amino acids syntheses

Reddy and colleagues reported highly diastereoselective Strecker reaction using α-phenylglycinol as chiral auxiliary, which is easily removed by oxidative cleavage. Reactions of romatic and aliphatic aldimines derived from *S*-(-)-1-phenylpropylamine **(69)** were carried out in the presence of 2 equiv of TMSCN in anhydrous $CHCl_3$ at 0 ^oC. The reactions provided *O*-silylated-α-aminonitriles in high yield and diastereoselectivity. After oxidative cleavage with $Pb(OAc)_4$ and hydrolysis with concentrated HCl, α-amino acids were obtained as hydrochloride salt (Scheme 1.33). [124]



Scheme 1.33 Diastereoselective Strecker reaction using α-phenylglycinol as chiral auxiliary,

In addition, Ohfune has reported an asymmetric Strecker reaction of kitimine by addition of cyanide ion to the imine double bond of an optically active oxazinone **(70)** prepared from (*S*)-valyl ester of α-hydroxy ketone. The optically active α-substituted serines were obtained after oxidation and hydrolysis (Scheme 1.34).[119]



70

Scheme 1.34 Asymmetric Strecker reaction *via* a cyanide addition to an optically active imine

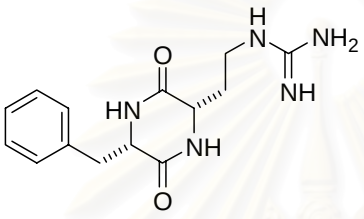
From the reactions mentioned above, the auxiliary control strategy has seemed to be quite successful in the asymmetric synthesis of many amino acids. However, the one reason that makes auxiliary control inferior is the difficulty in removing the chiral auxiliary. Furthermore, the optically active chiral auxiliaries have to be stoichiometrically used. Therefore, this is an economically unacceptable. To evade the inherent problems for using of chiral auxiliaries, chiral catalysts must be developed instead.

1.6.2 Catalytic asymmetric Strecker reactions

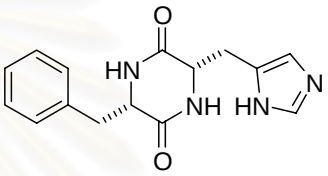
Catalysis is accomplished by electrophilic activation of the imine, either by a Lewis acid or *via* noncovalent interaction such as hydrogen bonds. In order for these processes to be catalytic, the species that is involved in the imine activation must be released after the addition of the cyanide. In some cases, an additive is needed to enhance the rate of this final step. Finally, the asymmetric induction is achieved through the chiral environment provided by the catalyst. Currently, the catalysts are categorized into two general classes: metal complexes (chiral Lewis acid catalysts) and organocatalysts. The former act as Lewis acids, whereas the latter involve noncovalent activation. Highly enantiomericaly enriched α-aminonitrile adducts of various imines have been obtained in good yields with these two catalyst systems.

1.6.2.1 Chiral organocatalysts catalyzed asymmetric Strecker reactions

The first catalytic asymmetric Strecker reaction was reported by Lipton using a cyclic peptide **(71)** as an organocatalyst.[127] This diketopiperazine **(71)** was prepared starting from (*S*)-phenylalanine and (*S*)-α-amino-γ-guanidinobutyric acid. The design of **(71)** was based on **(72),** a cyclic peptide which has been previously shown the great catalytic ability in enantioselective formation of cyanohydrin from aldehydes.[106-108,128]



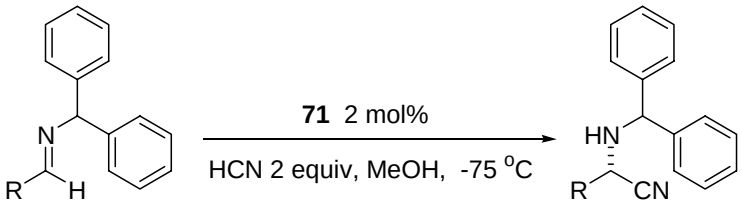
71



72

The presence of the basic guanidine side-chain was found to be a prerequisite for asymmetric induction. It is noteworthy that replacing the guanidine moiety by an imidazole moiety led to a non-enantioselective reaction. The reaction was performed only at 2 mol% catalyst loading. A broad variety of *N*-substituted imines **(72)** were found to be suitable as a substrate. Good to excellent enantioselectivity in the range 80-99% ee of α-amino nitriles **(73)** was usually obtained when imines derived from benzaldehyde and electron-deficient aldehydes were used. In contrast, heteroatom-substituted aromatic imines resulted in substantially lower enantioselectivity. Indeed, the reactions of imines derived from alphatic aldehydes were also nonselective (Table 1.4).

Table 1.4 Enantioselective Strecker reaction catalyzed by cyclic peptide (71)

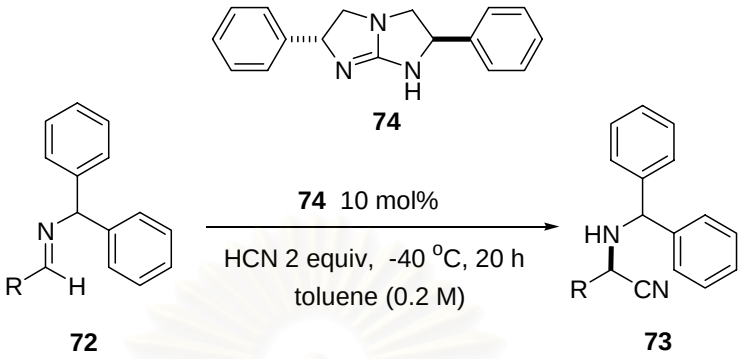


72 **73**

Entry	R^1	Yield (%)	Ee (%)
1	Ph	97	>99
2	4-$MeOC_6H_4$	90	96
3	4-ClC_6H_4	94	>99
4	2-Furyl	94	32
5	3-Pyridyl	86	<10
6	^{i}Pr	81	<10
7	^{t}Bu	80	17

There was no mechanism proposal at the time of discovery of this catalyst. However, a few years later, another guanidine-based catalyst for Strecker reactions was reported by Corey group with a full mechanistic proposal.[129] They developed an efficient chiral C_2-symmetric guanidine **(74)** that is a completely different type of guanidine, in which the guanidine functionality is embedded in a bicyclic framework. In the presence of this catalyst, high enanioselectivity was obtained when imines bearing an *N*-benzhydryl substituent were used as substrate. The choice of *N*-substituent is important, because *N*-benzyl or *N*-(9-fluorenyl)-substituted imine substrates gave substantially lower % ee. The hydrocyanation is typically performed with 10 mol% of **(74)** and has been shown the generality for a wide range of substituted aromatic imines. Enantioselectivity was in the range 80-88% ee for *p*-substituted benzaldimines whereas the *o*-substituted methylbenzaldimine and 1-naphthylaldimine gave somewhat lower enantioselectivity. Futhermore, the catalyst **(74)** can be recovered for re-using in 80-90% yields by extraction with oxalic acid. The α-aminonitriles were easily transformed into the corresponding α-amino acids by removing the benzhydryl group with hydrolysis in aqueous HCl (Table 1.5).

Table 1.5 Enantioselective Strecker reaction catalyzed by cyclic guanidine (74)



Entry	R^1	Yield (%)	Ee (%)
1	Ph	96	86
2	4-$MeOC_6H_4$	99	84
3	4-ClC_6H_4	88	81
4	4-FC_6H_4	97	86
5	4-$^tBuC_6H_4$	80	85
6	4-$TBSOC_6H_4$	98	88
7	*p*-tolyl	96	80
8	*o*-tolyl	88	50
9	3,5-xylyl	96	79
10	1-Naphthyl	90	76

For a proposed mechanism (Figure 1.13), a guanidinium cyanide complex **(75)** is formed in the initial step. This is followed by the generation of a ternary complex **(76)**. In this complex, both cyanide and imine are attached to the cyclic guanidine by hydrogen bonds. Subsequent steps are the formation and release of the optically active α-aminonitriles possessing *R* configuration.

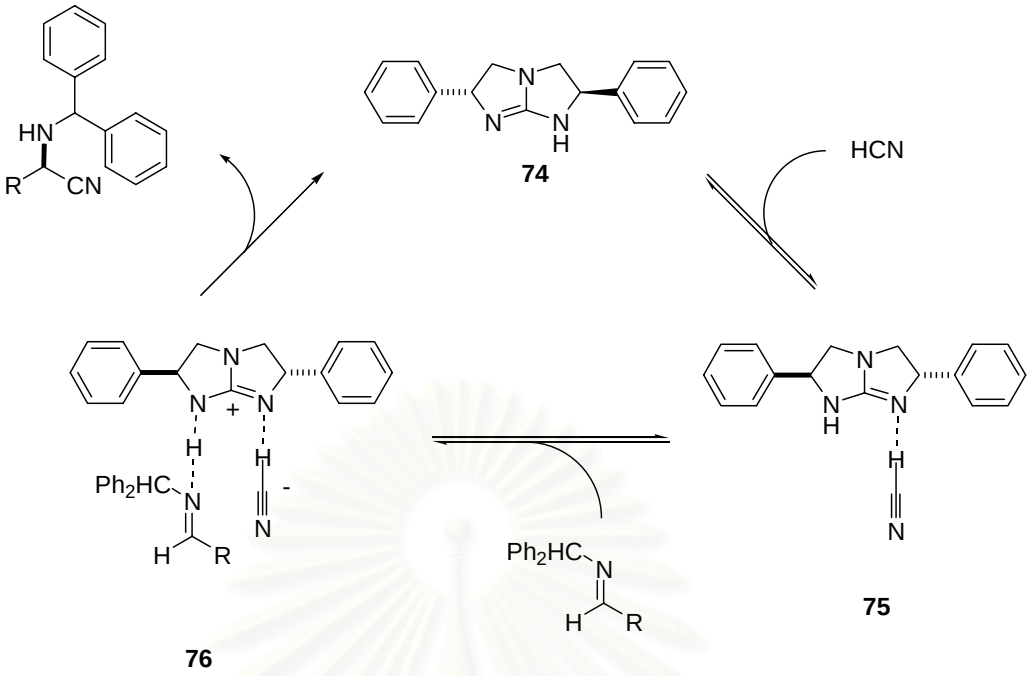
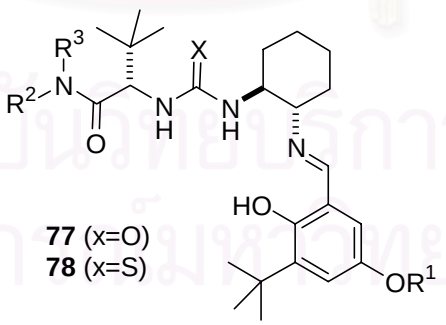


Figure 1.13 Proposed mechanism of cyclic guanidine (74) catalyzed Corey's enantioselective Strecker reaction

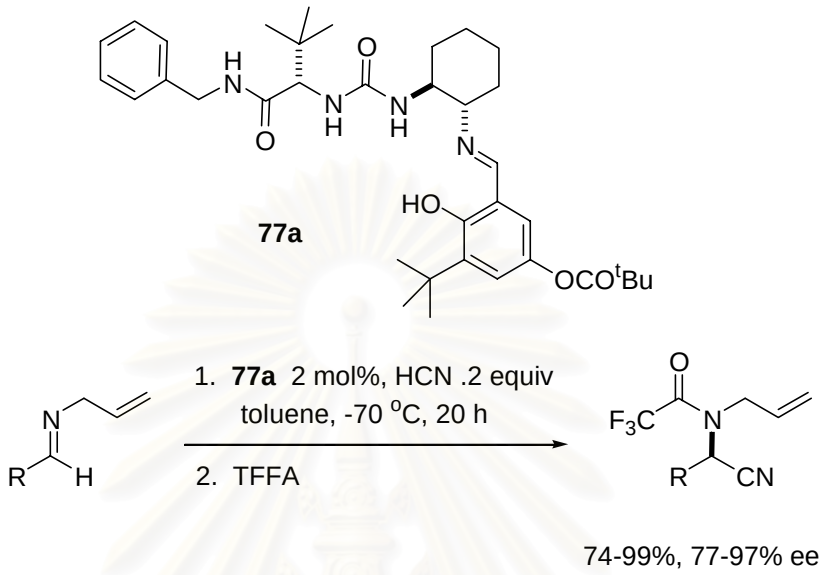
In 1998, Jacobsen developed a very efficient method for hydrocyanation of aldimines and ketimines catalyzed by a new chiral Schiff base catalysts derived from a substituted salicylaldehyde, an enantiomerically pure 1,2-cyclohexanediamine and a urea or thiourea that bonded with α-amino acids in their molecules **(77 and 78)**.



77 (x=O)
78 (x=S)

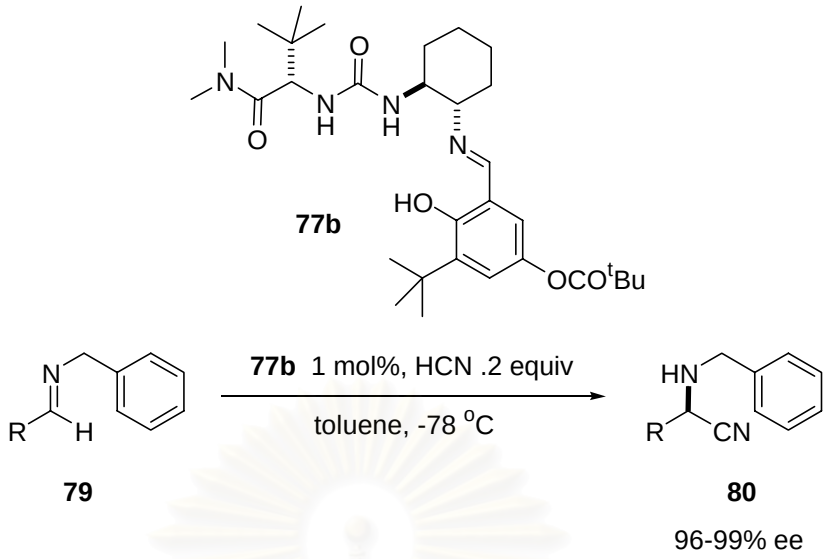
This new type of organocatalyst was discovered from a parallel screening.[130] Investigation of numerous variants of Schiff base organoatalysts led to an optimized catalyst bearing substituents on the salicyl moiety and thiourea functionality. Enantioselective strecker reaction was carried out in the presence of 2 mol% of catalyst **(77a)** to give the α-aminonitriles in high yield and excellent enantioselectivity

when both aromatic and aliphatic *N*-allyl aldimines were employed as substrates.[131] An optimized procedure for the preparation of the catalyst **(77a)** has recently been reported (Scheme1.35).[132]



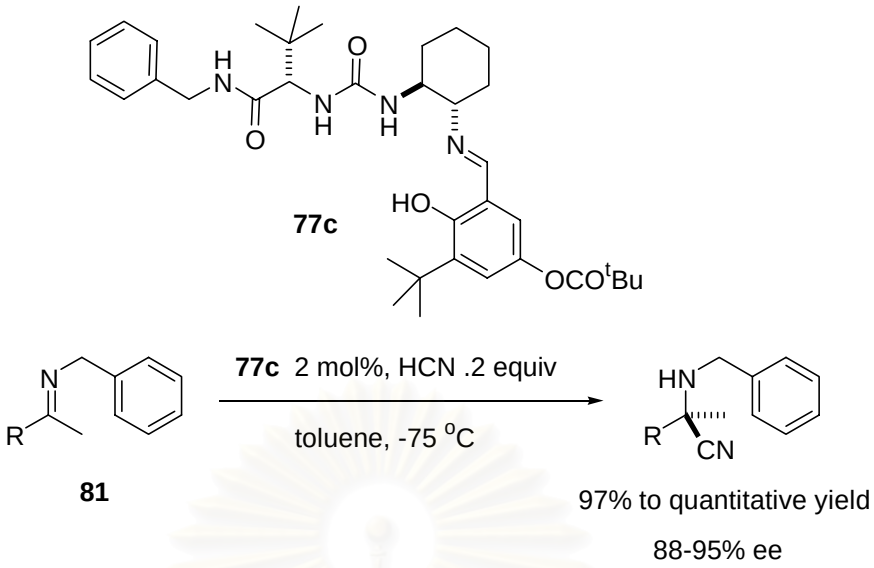
Scheme 1.35Asymmetric hydrocyanation of *N*-allyl imines catalyzed by catalyst (77a)

Further optimization of the organocatalyst **(77a)** was also made based on molecular modeling. The resulting, improved catalyst **(77b)** was found to be the superior to **(77a)** and is the most effective Strecker catalyst. Starting from both aromatic and aliphatic *N*-benzyl aldimines **(79)**, Excellent enantioselectivity was obtained in range 96-99% ee of α-aminonitriles **(80)** even in the the presence of only 1 mol% catalyst loading (Scheme 1.36).[133]



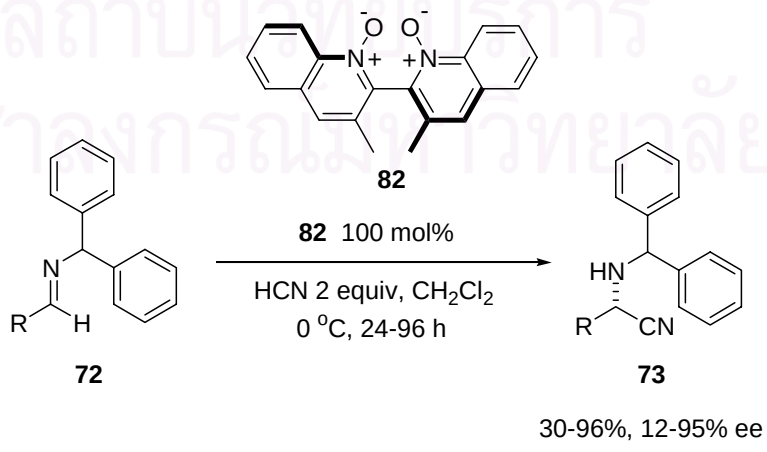
Scheme 1.36 Asymmetric hydrocyanation of *N*-benzyl imines catalyzed by catalyst (77b)

In addition, they successfully extended the range of application of these organocalysts to the first highly enantioselective hydrocyanation of ketimines.[156] This reaction gives α-aminonitriles bearing a stereogenic quaternary carbon center which are suitable precursors for preparation of α,α-disubstituted-α-amino acids. The optimum system consists of 2 mol% of the soluble orgnocatalyst **(77c)** in combination with *N*-benzyl-substituted ketimines **(81)**. It was found that the enantioselectivity was usually high for a variety of aromatic substrates. Some α-aminonitriles were obtained in the crystalline forms so that further enhancement of enantiopurity by recrystallization was possible. Quaternary amino acids were easily prepared by subsequent formylation and hydrolysis of the α-aminonitriles (Scheme 1.37).



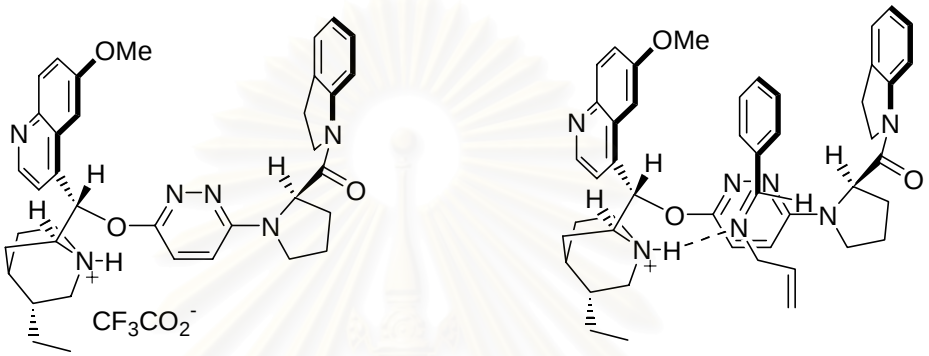
Scheme 1.37 Asymmetric hydrocyanation of *N*-benzyl ketimines catalyzed by catalyst (77c)

Recently, Feng group showed that an organic molecule without an imine moeity also seems to be able to catalyze the cyanation of imines.[134] Stoichiometric amount of the "catalyst" **(82)** was still required to achieve moderate to good enantioselectivity. The catalyst was believed to act as a Lewis base to coordinate with the silicon atom in TMSCN before transferring the cyanide moiety to the imine. A transition state model to explain the sense of asymmetric induction was proposed. The reactions of TMSCN addition to several types of aldimine were carried out in the presence of stoichiometric amount of a chiral *N*-oxide **(82)** to give the desired α-aminonitriles with enantioselectivity up to 95 % ee (Scheme 1.38).[135]

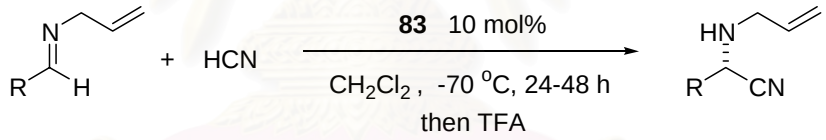


Scheme 1.38 Asymmetric Strecker reaction catalyzed by chiral *N*-oxide (82)

Huang and Corey has synthesized a new chiral ammonium salt **(83)** derived from a cinchona alkaloid as a catalyst for asymmetric Strecker reaction. The U-shaped molecule was designed to hold the aromatic part of the aldimine while the ammonium salt formed a hydrogen bond with nitrogen, leaving only the re-face of the imine exposed to the attack by cyanide. The *N*-substituent must be small like allyl group to achieve good enantioselectivities. (Scheme 1.39).[136]



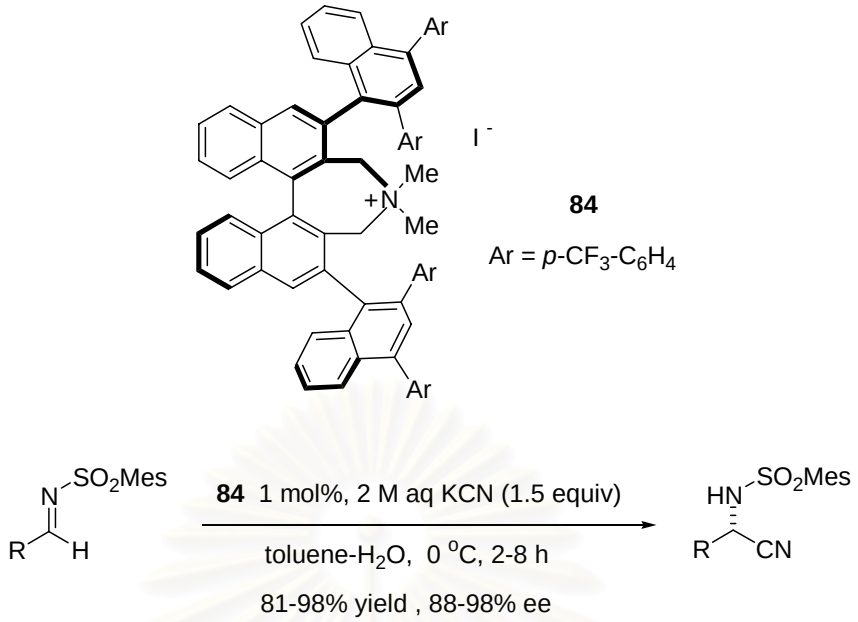
83 **83**-imine complex



R = Ph, substituted phenyl, 2-naphthyl
yield = 88-96%, ee = 77-99%

Scheme 1.39 Asymmetric Strecker reaction catalyzed by chiral ammonium salt (83)

Very recently in 2006, Maruoka and colleagues disclosed the first example of highly enantioselective Strecker reaction of aliphatic aldimines using a phase-transfer catalyst **(84)** derived from a chiral quaternary ammonium salt bearing a binaphthyl backbone, and aqueous KCN as the cyanide source.

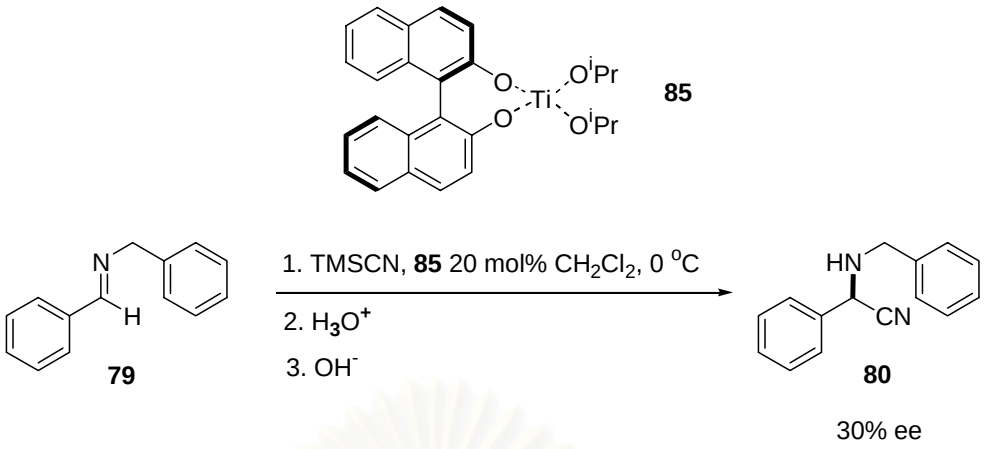


Scheme 1.40 Asymmetric Strecker reactions catalyzed by chiral phase-transfer catalyst (84)

The newly developed chiral quaternary ammonium iodide **(84)** possessed the hydrophilic ammonium cation part linked to the stereochemically defined hydrophobic tetranaphthyl backbone. The *ortho*-naphthyl groups caused rotational restriction around the reaction center providing the α-aminonitriles possessing *S* configuration with high yield and excellent enantioselectivity in the range 88-98% ee (Scheme 1.40).[137]

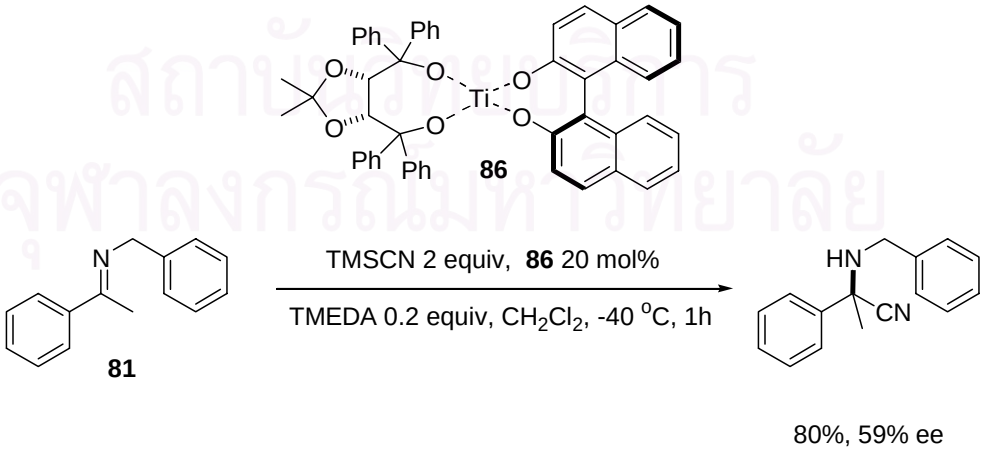
1.6.2.2 Chiral Lewis acids catalyzed asymmetric Strecker reactions

In 1997, Nakai *et al.* presented symmetric Strecker reaction catalyzed by a Ti-BONOL complex **(85)**. The reaction of *N*-benzylimine derived from bezaldehyde and benzylamine with TMSCN was carried out in the present of 20 mol% of the complex **(85)**. It was found to catalytically proceed to afford the α-aminonitrile in good yield although the selectivity was quite low (Scheme 1.41).[138]



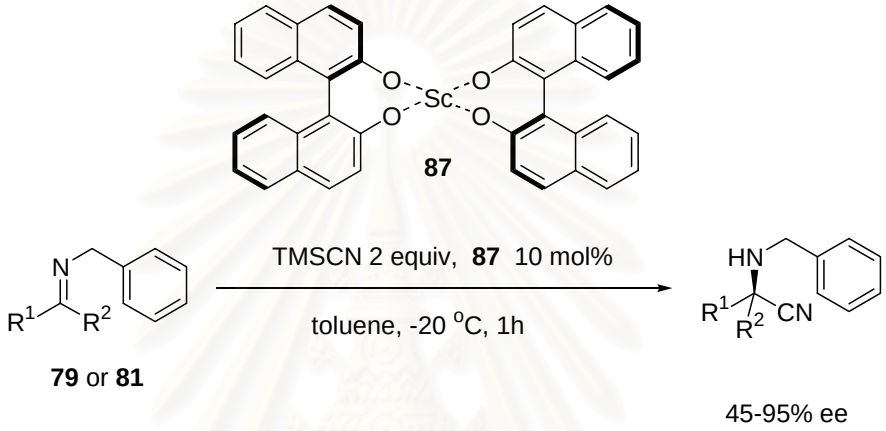
Scheme 1.41 Asymmetric Strecker reaction catalyzed by the complex (85)

In 2000, Vallee and co workers has achieved an asymmetric addition of TMSCN to ketimines by using catalytic amount of a chiral titanium complex **(86)** prepared from (*R*,*R*)-TADDOL and (*R*)-BINOL. The reactions of the *N*-benzyl-phenyl-methyl-imine with TMSCN in the present of 0.1 equiv of the complex **(86)** were examined. Several reaction conditions and simple non-chiral ether or amine additives were also tested. An 80% yield and enantiomeric excesses as high as 59% were achieved when tetramethylethylenediamine (TMEDA) was used as the additive (Scheme 1.42).[139]



Scheme 1.42 Asymmetric hydrocynation of ketimine catalyzed by complex (86)

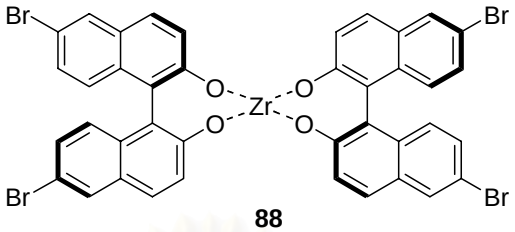
Moreover, they later reported a new chiral heterobimetallic complex **(87)** behaving as a Lewis acid and also as a Brönsted base. The complex also enantioselectively catalyzes reactions involving deprotonation of a weakly acidic site in the presence of a carbonyl compound as in Michael reactions. The heterobimetallic complex **(87)** was prepared and employed in the enantioselctive addition of cyanide to three samples of *N*-benzyl aromatic aldimines and ketimines. High conversion rates and enantiomeric excesses as high as 95% were obtained (Scheme 1.43).[140]



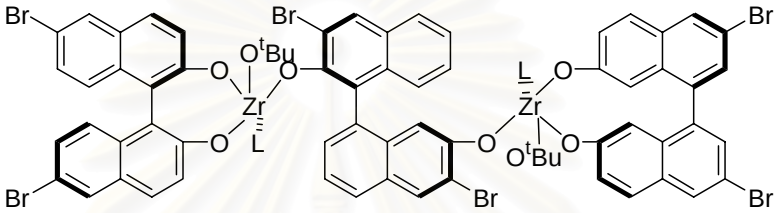
Scheme 1.43 Asymmetric Strecker reaction catalyzed by heterobimetallic complex (87)

Recently, chiral zirconium catalysts have been shown to catalyze enantioselective Mannich-type reactions [141-142] and aza Diels-Alder reactions.[143] Studies of ligand modification around the zirconium center [144] have led to the discovery of a zirconium catalyst **(88)**. The Strecker reaction between aldimines derived from 2-hydroxyaniline and Bu_3SnCN underwent in the presence of 10 mol% of the zirconium catalyst **(88)** in dichloromethane at -45 ^oC. The best results (92% yield, 91% ee) were obtained when the reaction was carried out in benzene:toluene (1:1) using 10 mol% of the zirconium catalyst **(88)** at -45 to 0^oC. In addition, they found that the use of a mixture of (*R*)-6-Br-BINOL and (*R*)-3-Br-BINOL provided the best results. The structure of the zirconium catalyst was carefully identified and it was evident from NMR studies that a zirconium binuclear complex **(89)** was formed under catalytic condition used. The binuclear complex

consists of 2 equiv of zirconium, (*R*)-6-Br-BINOL, and NMI, and 1 equiv of (*R*)-3-Br-BINOL.[145]



88



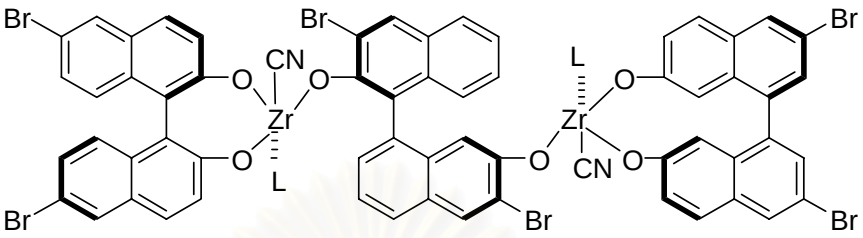
89

L = *N*-methylimidazole

Figure 1.14 A zirconium catalyst (88) and the binuclear zirconium complex (89)

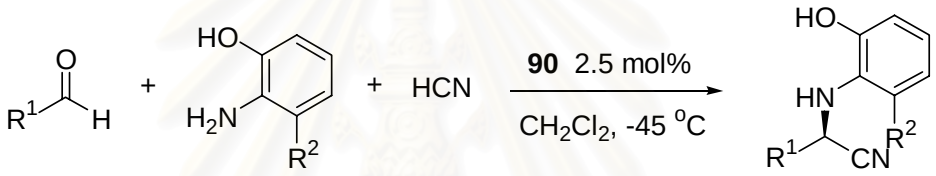
Two years later, Kobayashi *et al* disclosed a three-component asymmetric Strecker process which is a significant improvement upon the original Strecker reaction. They also found that HCN was successfully used instead of Bu_3SnCN as the cyanide source. Addition of a mixture of aldehyde and 2-amino-3-methyl phenol **(91)** to the solution of **(90)** in dichloromethane produced the α-aminonitriles derivatives. Excellent yields and enantioselectivities were obtained with aromatic and aliphatic aldehydes (Table 1.6). The mechanism of this zirconium catalyzed Strecker reactions is still under investigation.[146]

Table 1.6 Catalytic asymmetric Strecker reactions catalyzed by the binuclear complex (90)



90

L = *N*-methylimidazole

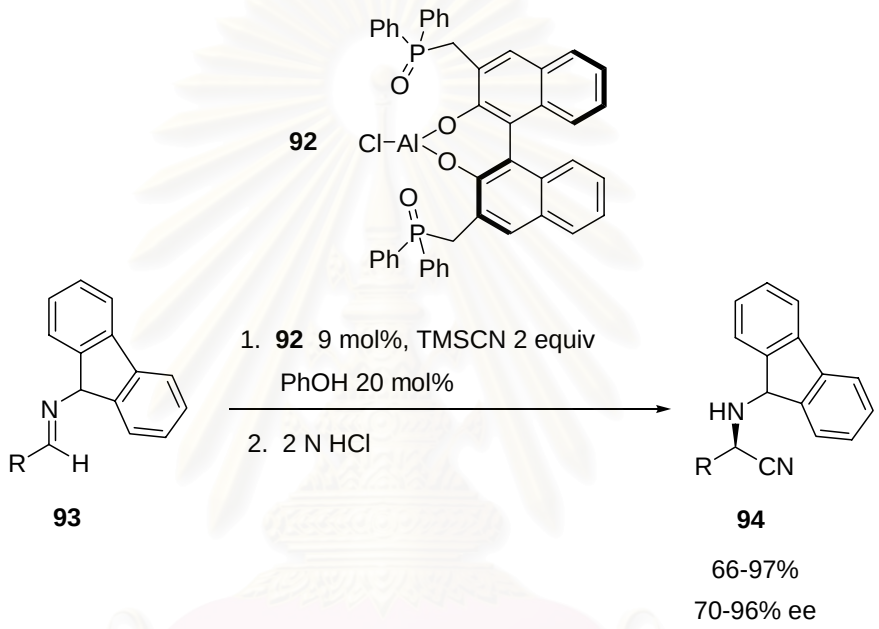


91

Entry	R^1	R^2	Yield (%)	Ee (%)
1	Ph	H	80	86
2	1-Naph	H	83	85
3	$Ph(CH_2)_2$	CH_3	85	94
4	C_8H_{17}	CH_3	93	91
5	^{i}Bu	CH_3	99	94
6	*c*-C_6H_{11}	CH_3	95	86
7	^{t}Bu	CH_3	quant	88

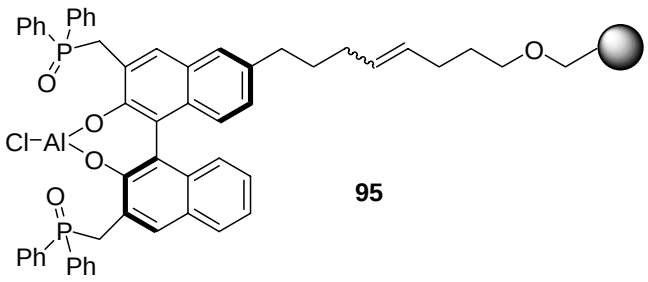
An aluminium complex **(92)** has been identified as a bifunctional Lewis acid-Lewis base catalyst because of its proposed dual activation of both the electrophile and nucleophile in the asymmetric cyanosilylation of aldehydes. by Shibasaki *et al.* [147] As a result, the use of this catalyst has been extended to the enantioselective Strecker-type reaction.[148-149] It was found that the addition of phenol and TMSCN to the fluorenyl imines **(93)** in the presence of the catalyst **(88)** at -40 ^{o}C affords the

corresponding α-aminonitriles **(94)**. Good yields and enantioselectivities were obtained with aromatic amines. α-Aminonitriles adducts of enolizable and non-enolizable aliphatic imines were also obtained in good yields although only in moderate %ee (Scheme 1.44). α-Aminonitriles **(94)** (R = Ph) could be converted into α-aminoamide in several steps.[149]



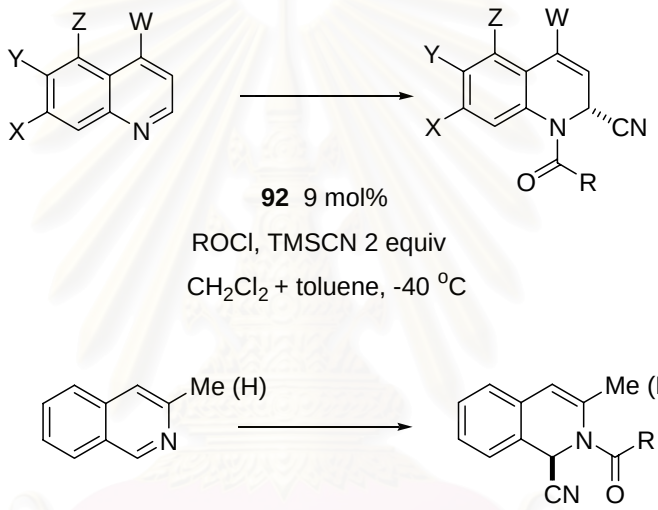
Scheme 1.44 Asymmetric Strecker reaction catalyzed by bifunctional Lewis acid-Lewis base catalyst (92)

In all cases, the use of a fluorenyl group on the imines and slow addition of phenol to the reaction mixture were found to be crucial for achieving high enantioselectivities. The addition of phenol was also found to have a beneficial effect on the reaction rates, presumably by converting TMSCN to HCN which is a more reactive cyanating agent. They also reported that a Janda*JEL*^{TM}-supported bifunctional catalyst **(95)** (10 mol%), the heterogeneous analogue of **(92)**, is able to promote the Strecker-type reaction of aromatic and α,β-unsautarated imines in excellent yields with 83-83% ee in the presence of 1.1 equiv of ^{t}BuOH. The catalyst **(95)** could be recycled at least four times.[150]



95

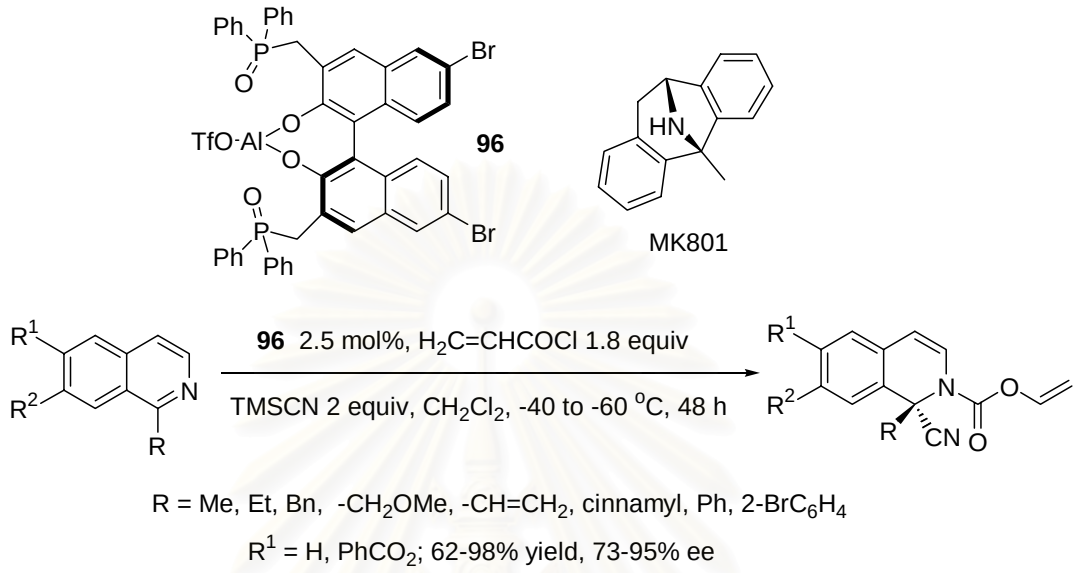
Interestingly, a variety of substituted quinolines and isoquinolines could undergo asymmetric Reissert-type reaction with TMSCN in the presence of the same bifunctional Al-phosphine oxide-BINOL complex **(92)** (Scheme 1.45).[151-152]



Scheme 1.45 Asymmetric Riessert-type reactions catalyzed by catalyst (92)

In addition, Shibasaki has demonstrated that 2-substituted isoquinolines could be enantioselectively cyanated at the 2-position in the presence of the catalyst **(96)** and vinylchloroformate/TMSCN.[153] The degree of substrate tolerance was remarkable. By this route, a potent anticonvulsant MK801 was obtained in only a few steps from 2-bromophenylisoquinoline, demonstrating the potential of this

methodology in constructing quarternary stereocenters that could not be obtained by other routes such as hydrogenations (Scheme 1.46).

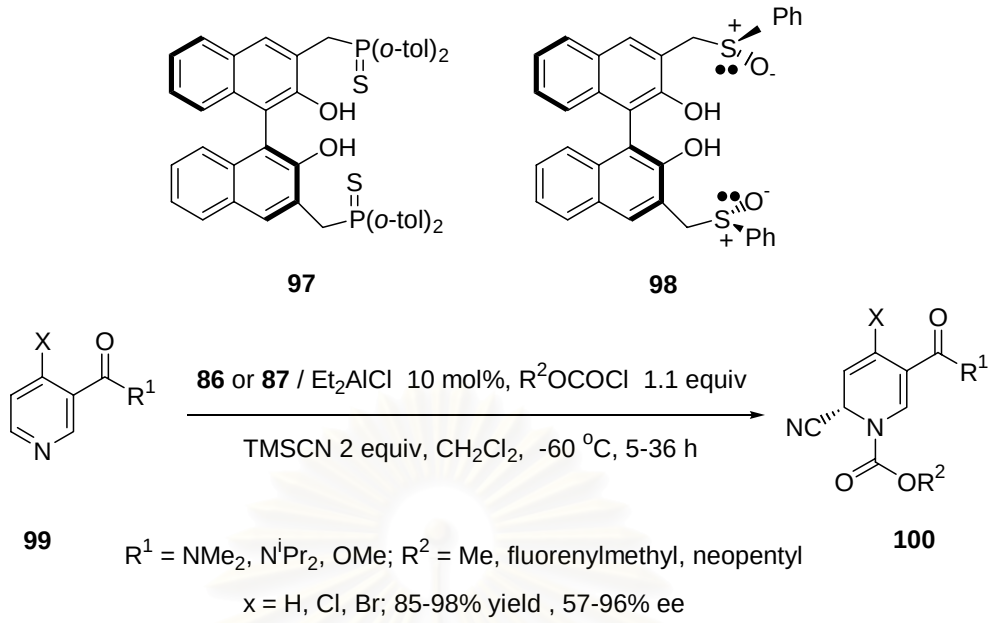


R = Me, Et, Bn, $-CH_2OMe$, $-CH=CH_2$, cinnamyl, Ph, $2\text{-}BrC_6H_4$

R^1 = H, $PhCO_2$; 62-98% yield, 73-95% ee

Scheme 1.46 Asymmetric hydrocyanation of isoquinolines derivatives catalyzed by complex (96)

The analogous Reissert-type reaction of pyridines has been achieved only recently using related bifunctional catalysts carrying substituents with less Lewis basicity than phosphine oxide such as **(97)** and **(98)**. Under optimal conditions, nicotinic acid derivatives **(99)** underwent a highly regio- and enantioselective addition to provide the Reissert compounds **(100)** which are useful building blocks for pharmaceutical substances (Scheme 1.47).[154]

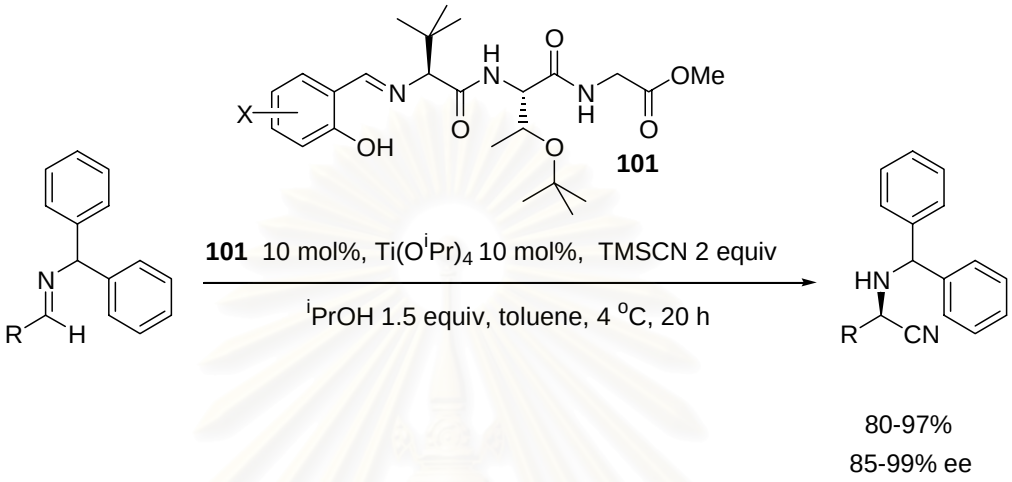


Scheme 1.47 Asymmetric hydrocyanation of nicotinic acid derivatives catalyzed by complex (97) or (98)

Although HCN and TMSCN have almost always been the only cyanide sources for asymmetric Strecker reactions, (In some cases, Bu_3SnCN was used as a cyanide source for asymmetric Strecker reaction).[145-146] asymmetric cyanation of *N*-substituted benzaldimines have been performed by using diethylaluminium cyanide (Et_2AlCN) in the presence of chiral ligands such as BINOL, TADDOL and bisoxazolines. The best enantioselectivity was achieved with (*R*)-BINOL as the ligands but was still only moderate (up to 70 % ee). The reaction could not yet be regarded as catalytic since an equivalent of the chiral ligand was required. The nature of nitrogen substituents and the number of equivalent of the ligand exerted dramatic influences on the absolute configuration of the product.[155]

In 1999, Snapper and Hoveyda employed a combination of a salicylimine Schiff base ligand **(97)** and titanium isopropoxide ($Ti(O^iPr)_4$), and 2-isopropanol as additive, as a catalyst for asymmetric Strecker reaction of *N*-benzhydrylimines. It was found that catalyst turnover was significantly facilitated by HCN which is generated by the reaction between 2-isopropanol and TMSCN. The addition of TMSCN to the aldimines in the presence of **(101)** and $Ti(O^iPr)_4$, followed by a slow addition of 2-propanol provides the α-aminonitriles. Good yields and moderate to high

enantioselectivities were obtained with both aromatic and non-enolizable aliphatic imines. The α-aminonitriles can be readily converted to the corresponding α-amino acids by hydrolysis with 6 N HCl with concomitant amine deprotection (Scheme 1.48). [156]



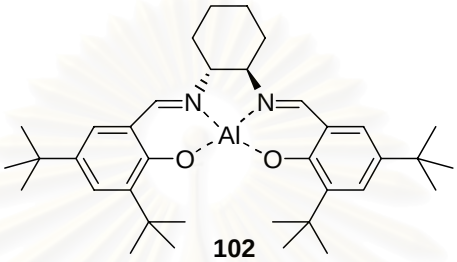
Scheme 1.48 Asymmetric Strecker reaction catalyzed by Ti-Schiff base ligand (101) complex

In addition, they also studied the mechanism of the Ti-peptide Schiff-base **(101)** complex catalyzed Strecker reaction. The results obtained from kinetic, structural, and streochemical data showed that this reaction is first order. These non-C_2 symmetric catalysts likely operate in a bifunctional manner. The Ti-Schiff base coordinates with the substrate, while an amide moiety within the peptide segment associates and delivers cyanide to the activated imine. It is indicated that ligand structure allows the Ti-Schiff base and amide carbonyls to provide complementary functions, giving rise to high yields and enantioselectivities.[157]

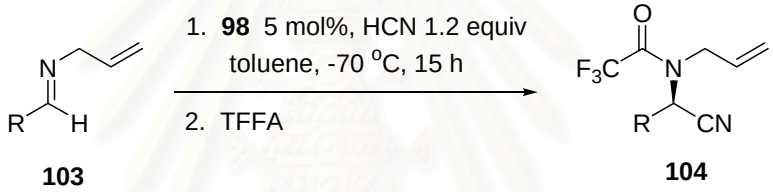
Jacobsen *et al.* reported another type of chiral aluminium complex that catalyzes enantioselectivie addition of cyanide ion to *N*-allyl imines **(103)**. Screening of a series of metal complexes revealed the aluminium catalyst **(102)** as the best catalyst.[158] α-aminonitriles derivatives of aromatic imines **(104)** were obtained in good yields and high enantioselectivites by treating the *N*-allyl imines **(103)** with HCN in the presence of the catalyst **(102)** at -70 ^{o}C. However, α-aminonitriles

adducts of imines of enolizable and non-enolizable aliphatic aldehydes were obtained in moderate yields with low to satisfactory enantioselectivities. They also prepared the enantiomerically enriched α-amino acid derivative in high yield and excellent % ee.[159]

Table 1.7 Jacobsen's catalytic enantioselective Strecker reaction



102

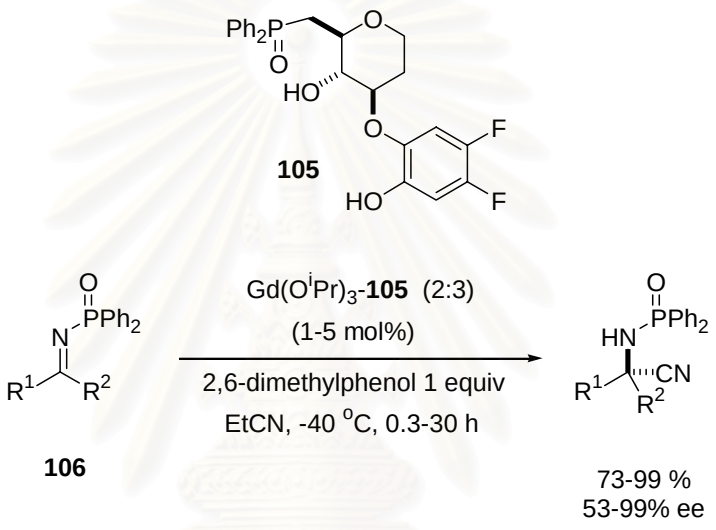


103 **104**

Entry	R^1	Yield (%)	Ee (%)
1	Ph	91	95
2	1-Naph	93	91
3	$Ph(CH_2)_2$	93	93
4	C_8H_{17}	77	57
5	^{i}Bu	69	37
6	*c*-C_6H_{11}	88	86

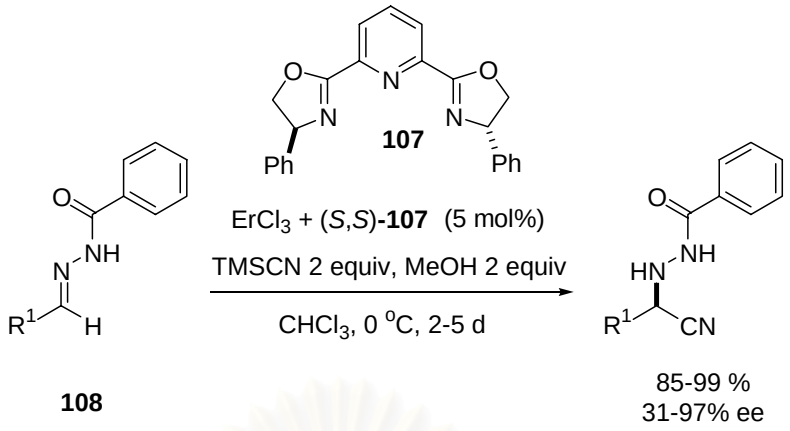
In case of catalytic asymmetric Strecker reaction of ketimines, there were much less successful instances compared to that of aldimines. Only a few examples have been reported to date.[110,140,160-161] The most recent advancement in this field was accomplished in 2003. Shibasaki developed a chiral lanthanide complex as 2:3 complex of gadolinium-chiral ligand **(105)** derived from D-glucose [162] for catalyic enantioselective strecker reaction of *N*-diphenylphosphinoylketimines **(106)**.[163] High enantioselectivity was obtained (83-95 % ee at 2.5-5 mol % catalyst

loading) from a wide range of ketimines derived from aromatic methyl ketone, aliphatic methyl ketones and cyclic ketones. In case of cyclic aliphatic and heteroaromatic ketimines, the reaction time was significantly decreased and enantioselectivities were also improved when adding 2,6-dimethylphenol (1 equiv) as a catalyst modulator (Scheme 1.49).[164] To employ a catalytic amount of TMSCN and stoichiometric amount of HCN allowed the catalyst loading to be decreased to 1.0 mol % while still maintaining the high degree of enantioselectivity.[165]



Scheme 1.49 Asymmetric Strecker reaction of ketimines catalyzed by Gd-chiral ligand (105) complex

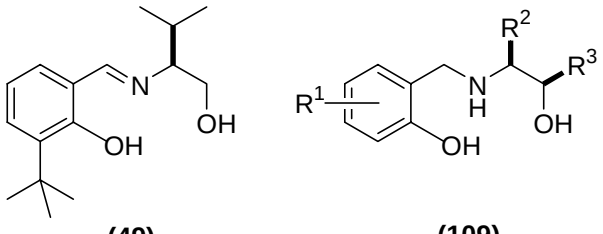
An asymmetric hydrocyanation of hydrazone **(108)** has been reported by Jacobsen.[166] Very high yield and enantioselectivity for a range of *N*-benzoylhydrazones investigated were achieved with an $ErCl_3$-(*S*,*S*)-PyBox **(107)** catalyst (Scheme 1.50). Substrates bearing electron-withdrawing group reacted sluggishly, suggesting that complexation of the hydrazone to the catalyst might be the rate limiting step.



Scheme 1.50 Asymmetric hydrocyanation of hydrozone catalyzed by $ErCl_3$-(*S*,*S*)-PyBox (107) complex

1.7 Background and objectives

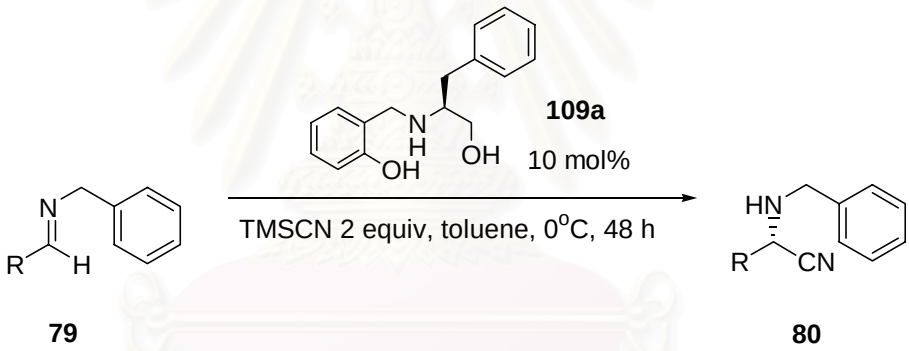
The first utilizing of the tridentate chiral Schiff base complex **(49)** was accomplished in the enantioselective trimethylsilylcyanation of a variety of aldehydes by Oguni. [98] However, the inherent instability of Schiff bases towards many nucleophilic reagents makes it not ideal as a catalyst for nucleophilic addition reactions to C=O or C=N. It is quite likely, although not yet systematically verified, that the real active catalyst species in these reactions might be the adduct formed from the ligand and the nucleophile. Thus, it is envisaged that the reduced form of Schiff such as **(109)**, which should be more stable towards nucleophiles, should be an interesting candidate for development of chiral ligand. In the view of the similar mechanistic aspects of trimethylsilylcyanation of aldehydes and imines, it is surprising that no equivalent cyanation reactions of imines using this class of ligands have been reported.



(49) **(109)**

Until 2003, Mansawat *et al*.firstly disclosed an enantioselective Strecker reaction that was catalyzed by titanium-*N*-salicyl-β-aminoalcohol complexes.[167] The reaction conditions were also optimized. *N*-Benzylidenebenzylamine **(79a)** underwent catalytic asymmetric Strecker reactions with 2 equiv of TMSCN in the presence of 10 mol% of titanium-*N*-salicyl-β-aminoalcohol **(109a)** derived from (*S*)-phenylalaninol complex to give the corresponding α-aminonitriles **(80)** in good to excellent yield and high enantioselectivity with (*S*)-configuration. Similar reactions with various *N*-benzyl aromatic aldimines resulted in moderate to good enantioselectivities (Table 1.8). It is interesting to observe that the Ti complex of the corresponding Schiff base ligands provided the α-aminonitriles in less than 10% ee.

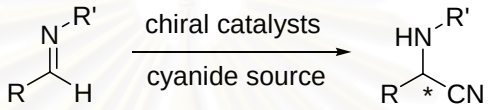
Table 1.8 Enantioselective Strecker reactions catalyzed by chiral *N*-salicyl-β-aminoalcohol (109a).[167]



79 **80**

Entry	Substrate	R	% Yield	% Ee
1	**79a**	Ph	98	76
2	**79b**	4-Cl-C_6H_4	84	72
3	**79c**	4-Br-C_6H_4	86	71
4	**79d**	4-MeO-C_6H_4	98	44
5	**79e**	4-Me-C_6H_4	>99	67
6	**79f**	3-Cl-C_6H_4	98	80
7	**79g**	3-Br-C_6H_4	98	81
8	**79h**	3-NO_2-C_6H_4	>99	64
9	**79i**	2-MeO-C_6H_4	92	51

Apart from the ability to behave as a ligand for asymmetric Strecker reaction, ligands related to **(109)** have been successfully employed in other catalytic asymmetric reactions including reduction,[168] Michael addition [169] and cyanosilylation of aldehydes.[98,101] Consequently, one objective of this research is to develop, design and modify a synthetic methodology for syntheses of novel *N*-salicyl-β-aminoalcohol ligands. Another is to develop a novel catalyst for catalytic asymmetric Strecker reaction from the ligand synthesized (Scheme 1.51) in order to study their catalytic ability in details.



Scheme 1.51 General synthesis of optically active α-aminonitriles from imines using chiral catalysts.

The resulting α-aminonitriles are potentially useful starting materials for synthesis of bioactive natural products such as α-amino acids and chiral diamines. In addition, Mechanistic aspects and applications to other asymmetric synthesis will be also investigated.

CHAPTER II

EXPERIMENTAL

2.1 General

All reactions were performed in oven-dried glasswares. The weight of all chemical substances was determined on a Mettler AE200 electrical balance. Evaporation of solvents was carried out on a Büchi Rotavapor R-114 equipped with a Büchi B-480 water bath. The progress of the reaction was monitored by thin layer chromatography (TLC) performed on Merck D.C. silica gel 60 F_{254} 0.2 mm precoated aluminium plates and visualized by using short wavelength UV light (254 nm), $KMnO_4$ solution, ninhydrin solution, 2,4-DNP reagent, $FeCl_3$ solution, iodine, $Co(SCN)_2$ solution or anisaldehyde reagent. Column chromatography was performed on 60-400 mesh silica gel for flash column chromatography or activated neutral aluminum oxide 90 (Activity I).

Chiral high performance liquid chromatography (HPLC) experiments were performed on Water 600^{TM} equipped with UV/VIS detector in normal phase mode using hexanes:^{i}PrOH as eluent. A Daicel Chiralcel OD® column and a Chiralpak AD® column were used for the separation of enantiomers. Melting points were measured on an Electrothermal 9100 melting point apparatus and were uncorrected. The optical rotations were measured at the ambient temperature with a Jasco P-1010 Polarimeter. Elemental analysis results were analyzed on CHNS/O Analyzer (Perkin Elmer PE2400 Series II) at Scientific and Technological Research Equipment Centre, Chulalongkorn University.

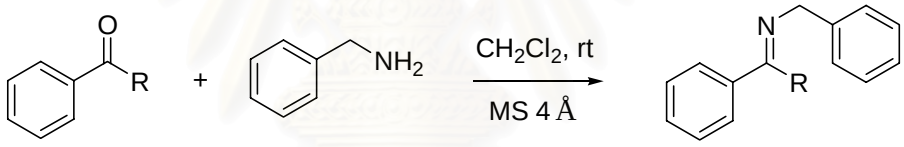
Proton (^{1}H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury-400 plus operating at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or using the residual protonated solvent signal as a reference. Coupling constant (*J*) are proton-proton coupling unless otherwise noted and reported in hertz (Hz). Multiplicities were abbreviated as followed: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

2.2 Materials and methods

All chemicals were purchased from Fluka, Merck or Aldrich Chemical Co., Ltd. and were used as received without purification. Commercial grade solvents for column chromatography were distilled before use. THF was distilled from sodium benzophenone ketyl radical prior to use. Toluene for the reactions was AR grade and dried with activated 4 Å molecular sieves. HPLC grade hexanes and 2-propanol for HPLC experiments on a chiral column were obtained from Merck and filtered through a membrane filter before use. Other solvents for the reactions were AR grade and used without further purification. High purity nitrogen and hydrogen gas for the experiments were purchased from TIG.

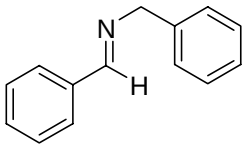
2.3 General procedure for the synthesis of imines

2.3.1 Synthesis of *N*-benzyl aldimines (106) and *N*-diphenylmethyl ketimine



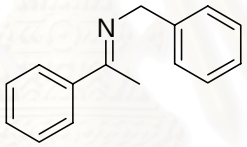
N-Benzyl aldimines or *N*-benzyl ketimines were prepared according to the procedure by Jacobsen *et al.*[131] Activated 4 Å molecular sieves and 5 mL dichloromethane were added into round bottom flask. Benzylamine (1.0 equiv) and aldehyde or ketone (1.0 equiv) were then added. The reaction mixture was left at room temperature for 18 hours without stirring. The sieves were removed by filtration. The filtrate was collected and organic solvent was evaporated *in vacuo* to obtain the desired product.

2.3.1.1 *N*-Benzylidene benzylamine (79a)



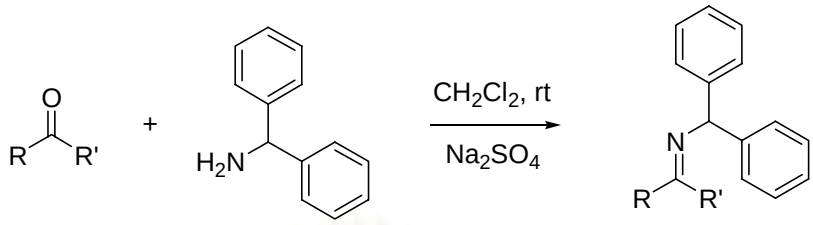
N-Benzylidene benzylamine was prepared according to the general procedure using benzaldehyde (1.06 g, 10.0 mmol) and benzylamine (1.70 g, 10.0 mmol). The product was obtained as yellow oil (1.91 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.88 (2H, s, C<u>H</u>$_2$Ph), 7.25-7.50 (8H, m, Ar), 7.82-7.86 (2H, m, Ar), 8.46 (1H, s, <u>H</u>C=N); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 65.3 (<u>C</u>H$_2$Ph), 127.1, 128.1, 128.4, 128.6, 128.8, 130.8, 136.2, 139.4 (Ar), 162.3 (H<u>C</u>=N).

2.3.1.2 *N*-(1-Methylbenzylidene)benzylamine (81a)



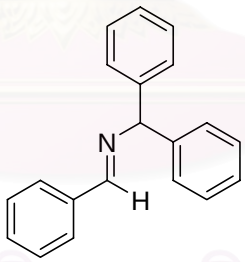
N-(1-Methylbenzylidene)benzylamine was prepared according to the general procedure using acetophenone (1.20 g, 10.0 mmol) and benzylamine (1.70 g, 10.0 mmol). The product was obtained as colorless oil (1.58 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (3H, s, C<u>H</u>$_3$), 4.85 (2H, s, C<u>H</u>Ph$_2$), 7.23-7.43 (7H, m, Ar), 7.62-7.76 (3H, m, Ar).

2.3.2 Synthesis of *N*-diphenylmethyl aldimines (72) and *N*-diphenylmethyl ketimine (81b)



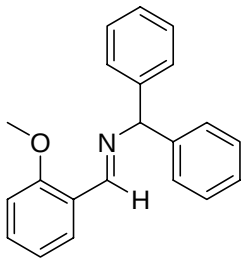
N-Diphenylmethyl aldimines or *N*-diphenylmethyl ketimines were prepared by adapting from the method of Krueger *et al*.[156] Aldehyde or ketone (1.0 equiv) was added to a solution of diphenylmethylamine (1.0 equiv) in dichloromethane. Then anhydrous Na_2SO_4 was added and the reaction mixture was left at room temperature for 18 hours without stirring. The Na_2SO_4 was removed by filtration. The filtrate was collected and the solvent was removed *in vacuo*. The crude products were purified by recrystallization from hexanes to afford the pure products.

2.3.2.1 *N*-Benzylidene diphenylmethylamine (72a)



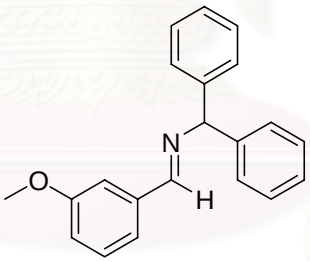
N-Benzylidene diphenylmethylamine was prepared according to the general procedure using benzaldehyde (1.06 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.47 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.64 (1H, s, C<u>H</u>Ph_2), 7.25-7.38 (13H, m, Ar), 7.82-7.91 (2H, m, Ar), 8.47 (1H, s, <u>H</u>C=N); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 78.0 (<u>C</u>HPh_2), 127.1, 127.7, 128.5, 128.6, 128.8, 129.0 130.8, 136.2, 139.4, 143.9 (Ar), 160.9 (H<u>C</u>=N).

2.3.2.2 *N*-(2-Methoxybenzylidene)diphenylmethylamine (72b)



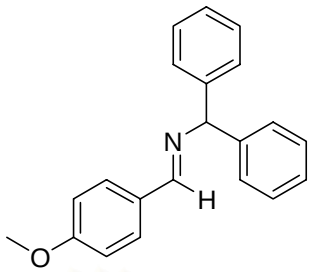
N-(2-Methoxybenzylidene)diphenylmethylamine was prepared according to the general procedure using 2-methoxybenzaldehyde (1.36 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.71 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.92 (3H, s, $OC\underline{H}_3$), 5.65 (1H, s, $C\underline{H}Ph_2$), 7.22-7.43 (12H, m, Ar), 7.48-7.56 (2H, m, Ar), 8.49 (1H, s, $\underline{H}C{=}N$).

2.3.2.3 *N*-(3-Methoxybenzylidene)diphenylmethylamine (72c)



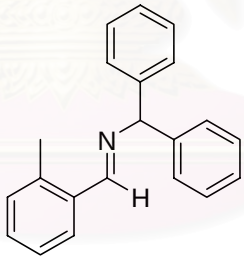
N-(3-Methoxybenzylidene)diphenylmethylamine was prepared according to the general procedure using 3-methoxybenzaldehyde (1.36 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.70 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.73 (3H, s, $OC\underline{H}_3$), 5.65 (1H, s, $C\underline{H}Ph_2$), 7.13 (1H, s, Ar), 7.28-7.42 (11H, m, Ar), 7.44-7.52 (2H, m, Ar), 8.49 (1H, s, $\underline{H}C{=}N$).

2.3.2.4 *N*-(4-Methoxybenzylidene)diphenylmethylamine (72d)



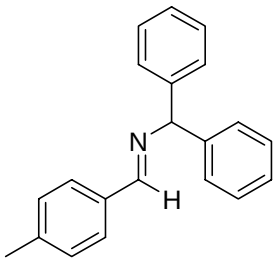
N-(4-Methoxybenzylidene)diphenylmethylamine was prepared according to the general procedure using *p*-anisaldehyde (1.36 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.8 g, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.72 (3H, s, OC<u>H</u>$_3$), 5.64 (1H, s, C<u>H</u>Ph_2), 6.78 (2H, d, *J* = 8.8 Hz, Ar) 7.02-7.22 (6H, m, Ar), 7.29 (4H, m, Ar), 7.40 (2H, d, *J* = 7.6 Hz, Ar), 8.48 (1H, s, <u>H</u>C=N).

2.3.2.5 *N*-(2-Methylbenzylidene)diphenylmethylamine (72e)



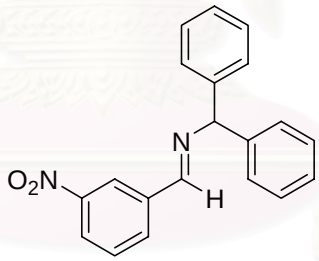
N-(2-Methylbenzylidene)diphenylmethylamine was prepared according to the general procedure using *o*-tolualdehyde (1.20 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.63 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (3H, s, C<u>H</u>$_3$), 5.62 (1H, s, C<u>H</u>Ph_2), 7.22-7.36 (7H, m, Ar), 7.40 (2H, m, Ar), 7.48 (2H, m, Ar), 7.60 (3H, m, Ar), 8.47 (1H, s, <u>H</u>C=N).

2.3.2.6 *N*-(4-Methylbenzylidene)diphenylmethylamine (72f)



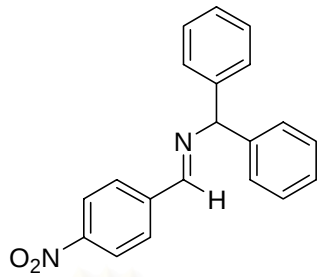
N-(4-Methylbenzylidene)diphenylmethylamine was prepared according to the general procedure using *p*-tolualdehyde (1.20 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.59 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (3H, s, C<u>H</u>$_3$), 5.63 (1H, s, C<u>H</u>Ph$_2$), 6.78 (2H, d, *J* = 8.6 Hz, Ar),7.10-7.32 (7H, m, Ar), 7.36 (3H, m, Ar), 7.41 (2H, d, *J* = 7.5 Hz, Ar), 8.47 (1H, s, <u>H</u>C=N).

2.3.2.7 *N*-(3-Nitrobenzylidene)diphenylmethylamine (72g)



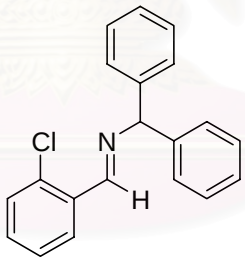
N-(3-Nitrobenzylidene)diphenylmethylamine was prepared according to the general procedure using 3-nitrobenzaldehyde (1.51 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a light yellow crystalline solid (2.62 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.66 (1H, s, C<u>H</u>Ph$_2$), 7.32-7.41 (6H, m, Ar), 7.50-7.59 (5H, m, Ar), 8.05-8.14 (2H, m, Ar), 8.49 (1H, s, <u>H</u>C=N), 8.57 (1H, s, Ar).

2.3.2.8 *N*-(4-Nitrobenzylidene)diphenylmethylamine (72h)



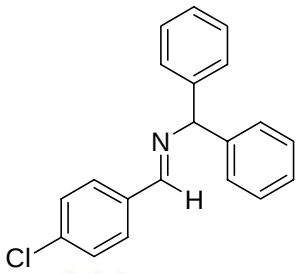
N-(4-Nitrobenzylidene)diphenylmethylamine was prepared according to the general procedure using 4-nitrobenzaldehyde (1.51 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a light yellow crystalline solid (2.67 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.65 (1H, s, C<u>H</u>Ph_2), 7.22-7.41 (6H, m, Ar), 7.59 (4H, m, Ar), 7.88 (2H, m, Ar), 8.22 (2H, m, Ar), 8.47 (1H, s, <u>H</u>C=N).

2.3.2.9 *N*-(2-Chlorobenzylidene)diphenylmethylamine (72i)



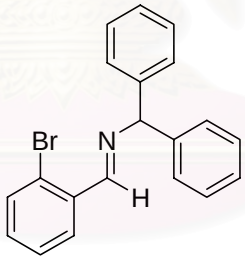
N-(2-Chlorobenzylidene)diphenylmethylamine was prepared according to the general procedure using 2-chlorobenzaldehyde (1.40 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.63 g, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.65 (1H, s, C<u>H</u>Ph_2), 7.22-7.42 (8H, m, Ar), 7.28 (2H, m, Ar), 7.60 (4H, m, Ar), 8.48 (1H, s, <u>H</u>C=N).

2.3.2.10 *N*-(4-Chlorobenzylidene)diphenylmethylamine (72j)



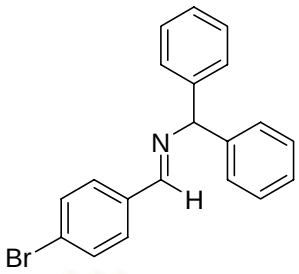
N-(4-Chlorobenzylidene)diphenylmethylamine was prepared according to the general procedure using 4-chlorobenzaldehyde (1.40 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.69 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.64 (1H, s, C<u>H</u>Ph_2), 7.22-7.42 (6H, m, Ar), 7.28 (2H, d, *J* = 7.2 Hz, Ar), 7.52 (2H, d, *J* = 8.2 Hz, Ar) 7.60 (4H, m, Ar), 8.48 (1H, s, <u>H</u>C=N).

2.3.2.11 *N*-(2-Bromobenzylidene)diphenylmethylamine (72k)



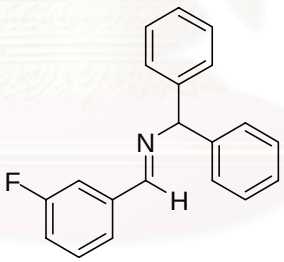
N-(2-Bromobenzylidene)diphenylmethylamine was prepared according to the general procedure using 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (3.15 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (1H, s, C<u>H</u>Ph_2), 7.22-7.45 (8H, m, Ar), 7.50 (2H, m, Ar), 7.58-7.68 (4H, m, Ar); 8.49 (1H, s, <u>H</u>C=N).

2.3.2.12 *N*-(4-Bromobenzylidene)diphenylmethylamine (72l)



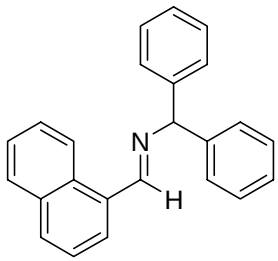
N-(4-Bromobenzylidene)diphenylmethylamine was prepared according to the general procedure using 4-bromobenzaldehyde (1.85 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.90 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.64 (1H, s, C<u>H</u>Ph_2), 7.20-7.42 (6H, m, Ar), 7.46 (2H, d, *J* = 7.5 Hz, Ar), 7.52 (2H, d, *J* = 8.3 Hz, Ar) 7.59 (4H, m, Ar), 8.48 (1H, s, <u>H</u>C=N).

2.3.2.13 *N*-(3-Fluorobenzylidene)diphenylmethylamine (72m)



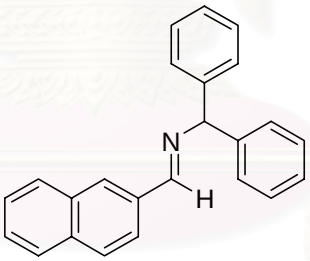
N-(3-Fluorobenzylidene)diphenylmethylamine was prepared according to the general procedure using 3-fluorobenzaldehyde (1.24 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.46 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.64 (1H, s, C<u>H</u>Ph_2), 7.05 (2H, m, Ar), 7.20-7.42 (4H, m, Ar), 7.46 (2H, m, Ar), 7.52 (2H, m, Ar) 7.59 (4H, m, Ar), 8.48 (1H, s, <u>H</u>C=N).

2.3.2.14 *N*-(Naphthalen-1-ylmethylene)diphenylmethylamine (72n)



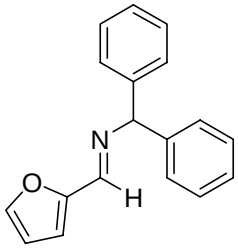
N-(Naphthalen-1ylmethylene)diphenylmethylamine was prepared according to the general procedure using 1-naphthaldehyde (1.56 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.89 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.65 (1H, s, C<u>H</u>Ph_2), 7.21-7.60 (11H, m, Ar), 7.66 (2H, m, Ar), 7.82-7.91 (2H, m, Ar), 7.95 (2H, m, Ar), 8.65 (1H, s, <u>H</u>C=N).

2.3.2.15 *N*-(Naphthalen-2-ylmetylene)diphenylmethylamine (72o)



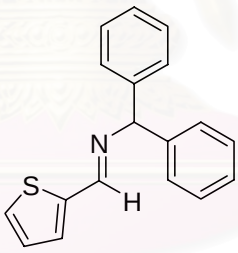
N-(Naphalen-2-ylmethylene)diphenylmethylamine was prepared according to the general procedure using 2-naphthaldehyde (1.56 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.92 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.65 (1H, s, C<u>H</u>Ph_2), 7.20-7.60 (11H, m, Ar), 7.64 (2H, m, Ar), 7.82-7.90 (2H, m, Ar), 7.95 (2H, m, Ar), 8.64 (1H, s, <u>H</u>C=N).

2.3.2.16 *N*-(Furan-2-ylmethylene)diphenylmethylamine (72p)



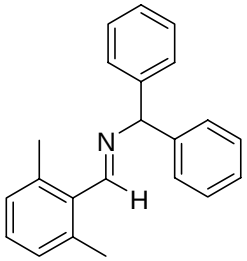
N-(Furan-2-ylmethylene)diphenylmethylamine was prepared according to the general procedure using furfural (0.96 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as an orange crystalline solid (2.10 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.64 (1H, s, C<u>H</u>Ph_2), 6.42 (1H, dd, *J* = 3.2, 2.0 Hz, C<u>H</u>-furan), 6.49 (1H, d, *J* = 3.2 Hz, C<u>H</u>-furan), 7.24-7.42 (6H, m, Ar), 7.48 (3H, m, C<u>H</u>-furan and Ar), 7.55 (2H, m, Ar), 8.55 (1H, s, <u>H</u>C=N).

2.3.2.17 *N*-(Thiophen-2-ylmethylene)diphenylmethylamine (72q)



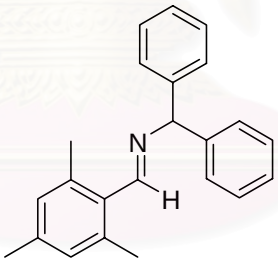
N-(Thiophen-2-ylmethylene)diphenylmethylamine was prepared according to the general procedure using thiophene-2-carboxaldehyde (1.12 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as a white crystalline solid (2.43 g, 88%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.65 (1H, s, C<u>H</u>Ph_2), 6.84 (1H, dd, *J* = 5.2, 3.6 Hz, C<u>H</u>-thiophene), 7.05-7.28 (8H, m, C<u>H</u>-thiophene and Ar), 7.30 (2H, m, Ar), 7.40 (2H, m, Ar), 8.53 (1H, s, <u>H</u>C=N).

2.3.2.18 *N*-(2,6-Dimethylbenzylidene)diphenylmethylamine (72r)



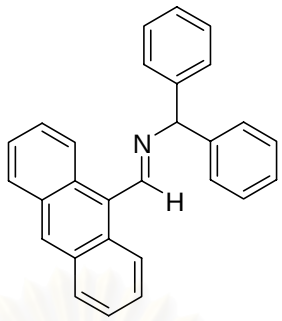
N-(2,6-Dimethylbenzylidene)diphenylmethylamine was prepared according to the general procedure using 2,6-dimethylbenzaldehyde (1.34 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as yellow viscous oil (2.87 g, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (3H, s, C<u>H</u>$_3$), 2.36 (3H, s, C<u>H</u>$_3$), 5.63 (1H, s, C<u>H</u>Ph$_2$), 6.90-7.05 (3H, m, Ar), 7.20-7.42 (8H, m, Ar), 7.54 (2H, m, Ar), 8.45 (1H, s, <u>H</u>C=N).

2.3.2.19 *N*-(2,4,6-Trimethylbenzylidene)diphenylmethylamine (72s)



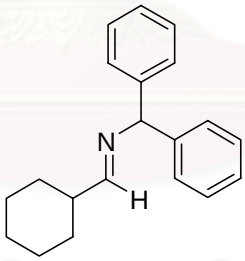
N-(2,4,6-Trimethylbenzylidene)diphenylmethylamine was prepared according to the general procedure using 2,4,6-trimethylbenzaldehyde (1.48 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as yellow viscous oil (2.97 g, 95%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (6H, s, 2xC<u>H</u>$_3$), 2.36 (3H, s, C<u>H</u>$_3$), 5.64 (1H, s, C<u>H</u>Ph$_2$), 6.70 (1H, s, Ar), 6.92 (1H, s, Ar), 7.23-7.41 (6H, m, Ar), 7.56 (4H, m, Ar), 8.44 (1H, s, <u>H</u>C=N).

2.3.2.20 *N*-(Anthracen-9-ylmethylene)diphenylmethylamine (72t)



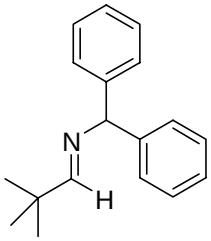
N-(Anthracen-9-ylmethylene)diphenylmethylamine was prepared according to the general procedure using 9-anthracenecarboxaldehyde (2.06 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as an orange crystalline solid (1.92 g, 52%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.65 (1H, s, C<u>H</u>Ph_2), 7.26-7.41 (10H, s, Ar), 7.56-7.62 (4H, m, Ar), 7.81-7.92 (4H, m, Ar), 8.52 (1H, s, <u>H</u>C=N), 8.63 (1H, m, Ar).

2.3.2.21 *N*-(Cyclohexylmethylene)diphenylmethylamine (72u)



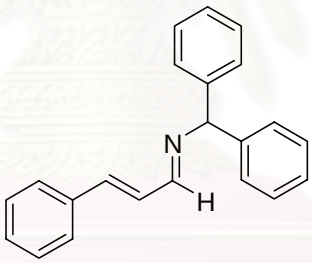
N-(Cyclohexylmethylene)diphenylmethylamine was prepared according to the general procedure using cyclohexane carboxaldehyde (1.12 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as an orange crystalline solid (1.24 g, 55%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04-1.19 (3H, m, C<u>H</u>cyclohexyl), 1.22-1.37 (2H, m, C<u>H</u>cyclohexyl), 1.54 (1H, m, C<u>H</u>cyclohexyl), 1.63 (2H, m, C<u>H</u>cyclohexyl), 1.78 (2H, m, C<u>H</u>cyclohexyl), 2.17 (1H, m, C<u>H</u>cyclohexyl), 4.13 (1H, s, C<u>H</u>Ph_2), 7.12-7.36 (10H, s, Ar), 8.22 (1H, s, <u>H</u>C=N).

2.3.2.22 *N*-(2,2-Dimethyl-propylidene)diphenylmethylamine (72v)



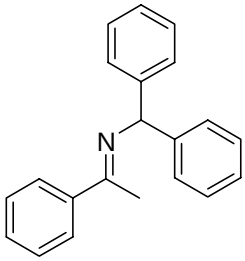
N-(2,2-Dimethyl-propylidene)diphenylmethylamine was prepared according to the generalprocedure using pivalaldehyde (0.86 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as yellow oil (1.28 g, 51%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.10 (9H, s, $C(C\underline{H}_3)_3$), 4.08 (1H, s, $C\underline{H}Ph_2$), 7.22-7.38 (10H, s, Ar), 8.31 (1H, s, $\underline{H}C{=}N$).

2.3.2.23 *N*-(3-Phenyl-propenylidene)diphenylmethylamine (72w)



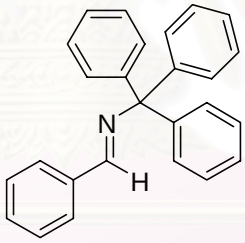
N-(3-Phenyl-propenylidene)diphenylmethylamine was prepared according to the general procedure using cinnamaldehyde (1.32 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as an orange crystalline solid (1.78 g, 60%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.16 (1H, s, $C\underline{H}Ph_2$), 5.61 (1H, dd *J* = 6.0 and 16.0 Hz, C<u>H</u>CHPh), 6.62 (1H, d *J* = 16.0 Hz, CHC<u>H</u>Ph), 7.26-7.41 (10H, s, Ar), 7.56-7.62 (5H, m, Ar), 8.51 (1H, s, $\underline{H}C{=}N$)

2.3.2.24 *N*-(1-Phenylethylidene)diphenylmethylamine (81b)



N-(1-Phenylethylidene)diphenylmethylamine was prepared according to the generalprocedure using acetophenone (1.20 g, 10.0 mmol) and diphenylmethylamine (1.83 g, 10.0 mmol). The product was obtained as colorless oil (2.22 g, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (3H, s, C$\underline{H}_3$), 5.63 (1H, s, C$\underline{H}Ph_2$), 7.21-7.38 (7H, m, Ar), 7.42 (2H, m, Ar), 7.48 (2H, m, Ar), 7.56 (4H, m, Ar).

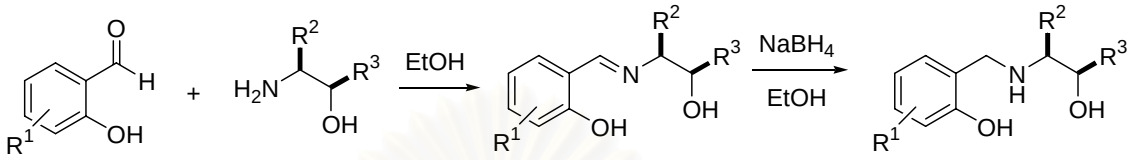
2.3.3 Synthesis of *N*-benzylidene tritylamine (110)



N-Benzylidene tritylamine was prepared according to the general procedure using benzaldehyde (1.06 g, 10.0 mmol) and tritylamine (2.59 g, 10.0 mmol). The product was obtained as a white crystalline solid (3.44 g, 92%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21-7.32 (6H, m, Ar), 7.38-7.46 (6H, m, Ar), 7.51-7.72 (6H, m, Ar), 7.85 (2H, m, Ar), 8.65 (1H, s, $\underline{H}$C=N).

2.4 General procedure for the synthesis of chiral *N*-salicyl-β-aminoalcohol ligands

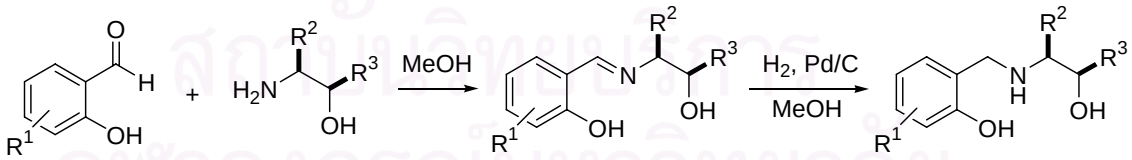
Synthesis of chiral-*N*-salicyl-β-aminoalcohol by $NaBH_4$ reduction [167,170] **(Method A)**



109

A mixture of ethanol (5 mL), an appropriate amino alcohol (1.0 mmol), and salicylaldehyde (1.0 mmol) was stirred at 30 °C for 12 hours. Then sodium borohydride (1.0 mmol) was added into the yellow solution with vigorous stirring to give a colorless solution. The reaction mixture was quenched with dil. HCl and then neutralized with saturated $NaHCO_3$. The solution was concentrated under reduced pressure and the residue was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation. The crude products were purified by flash column chromatography using hexanes and ethyl acetate as eluent.

Synthesis of chiral-*N*-salicyl-β-aminoalcohol by hydrogenation [171-172] **(Method B)**

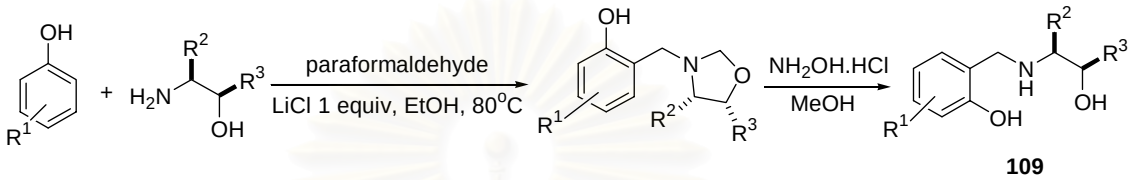


109

A mixture of methanol (5 mL), an appropriate amino alcohol (1.0 mmol), salicylaldehyde (1.0 mmol) was stirred at 30 °C for 6 hours. Then Pd/C (10 mol% by weight) was added. The reaction mixture was vigorously stirred under hydrogen atmosphere (1 atm) until the yellow solution turned to colorless (monitored by TLC). The reaction mixture was filtered through celite to remove the Pd/C. Organic solvent

was evaporated under reduced pressure. The crude products were purified by flash column chromatography using hexanes and ethyl acetate as eluent.

Synthesis of chiral-*N*-salicyl-β-aminoalcohol by three-component Mannich type reaction followed by ring opening of oxazolidene derivatives with hydroxylamine hydrochloride (Method C)

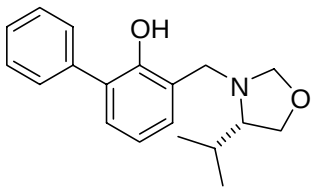


109

A mixture of phenol (0.5 mmol), paraformaldehyde (250 mg, 10 equiv), an appropriate amino alcohol (0.5 mmol) and LiCl (0.5 mmol) were weighed and dissolved with ethanol 3 mL in a screw-capped test tube. The reaction mixture was heated at 80 °C for 18 hours. Ethanol was removed *in vacuo* and the crude products (oxazolidines) were purified by flash column chromatography using hexanes and ethyl acetate as eluent. Oxazolidines **111a**, **111b**, **111c**, and **111d** were successfully isolated while others were contaminated with the phenol starting materials.

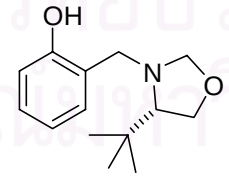
The purified oxazolidine which may be contaminated by the phenol was dissolved in methanol 5 mL and treated with hydroxylamine hydrochloride (5.0 mmol, 10 equiv). The reaction mixture was vigorously stirred for 2 hours or until the reaction went completely (monitored by TLC). Organic solvent was removed by evaporation. The residue (ligand) was dissolved in ethyl acetate 20 mL and washed with water 10 mL. The organic layer was dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash column chromatography using hexanes and ethyl acetate as eluent to obtain chiral-*N*-salicyl-β-aminoalcohols.

2.4.1 *N*-(2′-Hydroxy-3′-biphenyl)methyl-(*S*)-4-isopropyl-oxazolidine (111a)



N-(2′-Hydroxy-3′-biphenyl)methyl-(*S*)-4-isopropyl-oxazolidine was prepared according to *Method C* using 2-phenylphenol (85 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), and LiCl (22.0 mg, 0.5 mmol). The product was obtained as colorless oil (134 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.99 and 1.15 (6H, 2×d, *J* = 6.8 Hz, CH($C\underline{H}_3$)$_2$), 1.82 (1H, m, C$\underline{H}$(CH_3)$_2$), 2.84 (1H, quartet, *J* = 7.6 Hz, NC$\underline{H}$ CH(CH_3)$_2$), 3.60 (1H, apparent t, *J* = 8.4 Hz, CHC$H_a\underline{H}_b$O), 3.98 (1H, A$\underline{B}$, *J* = 13.6 Hz, ArC$H_a\underline{H}_b$N), 4.10 (1H, $\underline{A}$B, *J* = 13.6 Hz, ArC$\underline{H}_aH_b$N), 4.21 (1H, apparent t, *J* = 8.4 Hz, CHC$\underline{H}_aH_b$O), 4.24 (1H, A$\underline{B}$, *J* = 6.4 Hz, NC$H_a\underline{H}_b$O), 4.45 (1H, $\underline{A}$B, *J* = 6.4 Hz, NC$\underline{H}_aH_b$O), 6.97 (1H, apparent t, *J* = 7.2 Hz, Ar), 7.07 (1H, d, *J* = 6.8 Hz, Ar), 7.40 (2H, m, Ar), 7.55 (3H, m, Ar), 7.73 (1H, d, *J* = 6.8 Hz, Ar), 10.4 (br s, ArO$\underline{H}$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9, 20.4, 31.0, 50.3, 59.5, 68.5, 70.8, 84.5, 116.0, 119.5, 120.8, 122.7, 127.0, 127.4, 128.2, 128.4, 129.4, 130.4, 138.4, 154.7.

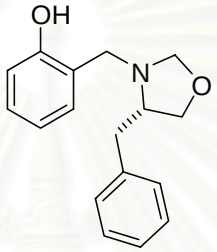
2.4.2 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine (111b)



N-(2′-Hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine was prepared according to *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-*tert*-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), and LiCl (22.0 mg, 0.5 mmol). The product was obtained as colorless oil (106 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03 (9H, s, C($C\underline{H}_3$)$_3$), 2.81 (1H, apparent t, *J* = 7.6 Hz, NC$\underline{H}CH_2$), 3.28 (1H, apparent

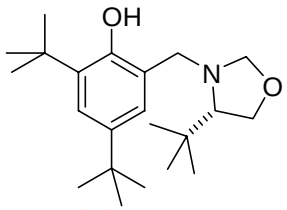
t, J = 8.0 Hz, CHCH$_a$H$_b$O), 3.94 (1H, AB, J = 13.6 Hz, ArCH$_a$H$_b$N), 4.06 (1H, AB, J = 13.6 Hz, ArCH$_a$H$_b$N), 4.08 (1H, AB, J = 6.8 Hz, NCH$_a$H$_b$O), 4.15 (1H, apparent t, J = 8.4 Hz, CHCH$_a$H$_b$O), 4.38 (1H, AB, J = 6.8 Hz, NCH$_a$H$_b$O), 6.83 (1H, apparent t, J = 7.6 Hz, Ar), 6.90 (1H, d, J = 8.0 Hz, Ar), 7.00 (1H, d, J = 7.2 Hz, Ar), 7.23 (1H, apparent t, J = 7.2 Hz, Ar), 10.3 (br s, ArOH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.4, 33.8, 61.3, 67.2, 74.2, 85.1, 116.4, 119.4, 122.4, 128.8, 129.2, 157.6.

2.4.3 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-4-benzyl-oxazolidine (111c)



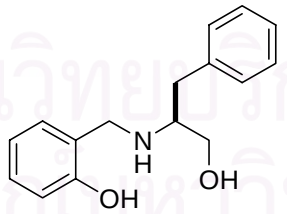
N-(2′-Hydroxyphenyl)methyl-(*S*)-4-benzyl-oxazolidine was prepared according to *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-phenylalaninol (76 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), and LiCl (22.0 mg, 0.5 mmol). The product was obtained as colorless oil (123 mg, 91%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.79 (1H, ABX, J_{AB} = 13.6, J_{BX} = 8.0 Hz, CHCH$_a$H$_b$Ph), 2.97 (1H, ABX, J_{AB} = 13.6, J_{AX} = 7.2 Hz, CHCH$_a$H$_b$Ph) 3.41 (1H, m, NCHCH$_2$Ph), 3.62 (1H, ABX, J_{AB} = 8.8, J_{BX} = 5.6 Hz, CHCH$_a$H$_b$O), 3.86 (1H, AB, J = 13.6 Hz, ArCH$_a$H$_b$N), 3.92 (1H, AB, J = 13.6 Hz, ArCH$_a$H$_b$N), 4.11 (1H, ABX, J_{AB} = 8.4, J_{AX} = 6.8 Hz, CHCH$_a$H$_b$O), 4.40 (1H, AB, J = 6.0 Hz, NCH$_a$H$_b$O), 4.43 (1H, AB, J = 6.0 Hz, NCH$_a$H$_b$O), 6.86 (2H, m, Ar), 7.00 (1H, d, J = 6.8 Hz, Ar), 7.18-7.30 (4H, m, Ar), 7.37 (2H, m, Ar), 10.4 (br s, ArOH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 39.7, 58.2, 65.2, 69.6, 84.5, 115.3, 116.6, 119.5, 121.9, 126.8, 128.9, 129.3, 129.7, 137.8, 157.3.

2.4.4 *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine (111d)



N-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine was prepared according to *Method C* using 2,4-di-*tert*-butylphenol (103 mg, 0.5 mmol), (*S*)-*tert*-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), and LiCl (22.0 mg, 0.5 mmol). The product was obtained as colorless oil (156 mg, 90%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03 (9H, s, $C(C\underline{H}_3)_3$), 1.32 (9H, s, $C(C\underline{H}_3)_3$), 1.47 (9H, s, $C(C\underline{H}_3)_3$), 2.82 (1H, apparent t, *J* = 8.0 Hz, $NC\underline{H}C(CH_3)_3$), 3.65 (1H, apparent t, *J* = 8.4 Hz, $CHCH_a\underline{H}_bO$), 3.90 (1H, A<u>B</u>, *J* = 13.2 Hz, $ArCH_a\underline{H}_bN$), 4.04 (1H, <u>A</u>B, *J* = 13.6 Hz, $ArC\underline{H}_aH_bN$), 4.08 (1H, A<u>B</u>, *J* = 6.4 Hz, $NCH_a\underline{H}_bO$), 4.15 (1H, apparent t, *J* = 8.4 Hz, $CHC\underline{H}_aH_bO$), 4.43 (1H, <u>A</u>B, *J* = 6.4 Hz, $NC\underline{H}_aH_bO$), 6.87 (1H, s, Ar), 7.28 (1H, s, Ar), 10.3 (br s, Ar<u>O</u>H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.5, 29.6, 31.7, 33.8, 34.1, 34.9, 62.1, 67.1, 74.0, 85.2, 121.9, 123.3, 123.7, 136.0, 140.8, 154.1.

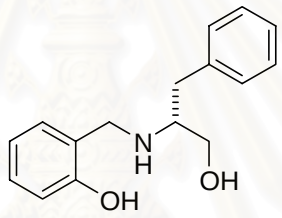
2.4.5 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (109a)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-phenylalaninol (151 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method B* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-phenylalaninol (151 mg, 1.0 mmol) and Pd/C 26 mg. *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-phenylalaninol (76 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$

(348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (190, 213 and 113 mg; 74, 83 and 88% respectively); m.p. 133.2-134.5 °C; $[\alpha]^{24}_{D}$ = -23.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.89 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 7.6 Hz, $CH_a\underline{H}_bPh$), 2.91 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 6.4 Hz, $C\underline{H}_aH_bPh$), 3.02 (1H, m, C<u>H</u>NH), 3.58 (1H, A<u>B</u>X, J_{AB} = 11.0, J_{BX} = 5.0 Hz , $CH_a\underline{H}_bOH$), 3.78 (1H, <u>A</u>BX, J_{AB} = 11.0, J_{AX} = 3.8 Hz, $C\underline{H}_aH_bOH$), 4.05 (2H, s, $C\underline{H}_2NH$), 6.82 (1H, appaprent t, *J* = 7.2 Hz, Ar), 6.87 (1H, d, *J* = 8.0 Hz, Ar), 7.01 (1H, d, *J* = 7.2 Hz, Ar), 7.19-7.38 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.3, 50.3, 59.7, 62.6, 116.6, 119.2, 122.7, 126.7, 128.3, 128.7, 128.9, 129.2, 138.0, 158.0; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.66; H, 7.41; N, 5.43 %.

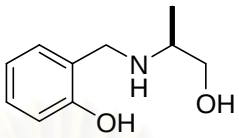
2.4.6 *N*-(2′-Hydroxyphenyl)methyl-(*R*)-2-amino-3-phenyl-propanol (109a)



N-(2′-Hydroxyphenyl)methyl-(*R*)-2-amino-3-phenyl-propanol was prepared according to <u>*Method A*</u> using salicylaldehyde (122 mg, 1.0 mmol), (*R*)-phenylalaninol (151 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). <u>*Method B*</u> using salicylaldehyde (122 mg, 1.0 mmol), (*R*)-phenylalaninol (151 mg, 1.0 mmol) and Pd/C 26 mg. <u>*Method C*</u> using phenol (47 mg, 0.5 mmol), (*R*)-phenylalaninol (76 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (185, 206 and 112 mg; 72, 80 and 87% respectively); m.p. 133.5-134.8 °C; $[\alpha]^{24}_{D}$ = +24.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.85 (1H, A<u>B</u>X, J_{AB} = 13.6 Hz, J_{BX} = 7.6 Hz, $CH_a\underline{H}_bPh$), 2.94 (1H, <u>A</u>BX, J_{AB} = 13.6 Hz, J_{AX} = 6.4 Hz, $C\underline{H}_aH_bPh$), 3.03 (1H, br, C<u>H</u>NH), 3.57 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 4.8 Hz, $CH_a\underline{H}_bOH$), 3.76 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 3.2 Hz, $C\underline{H}_aH_bOH$), 4.04 (2H, s, $C\underline{H}_2NH$), 6.80 (1H, appaprent t, *J* = 7.2 Hz, Ar), 6.85 (1H, d, *J* = 8.0 Hz, Ar), 7.00 (1H, d, *J* = 7.2 Hz, Ar), 7.19-7.38 (6H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.1, 50.1, 59.7, 62.5, 116.6, 119.3, 122.6,

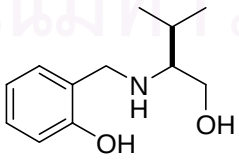
126.7, 128.4, 128.8, 129.0, 129.2, 137.9, 157.9; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.43; H, 7.29; N, 5.41 %.

2.4.7 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-propanol (109b)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-propanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-alaninol (75 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-alaninol (38 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as yellow viscous oil (92 and 56 mg; 51 and 62% respectively); $[\alpha]^{24}_D$ = +64.0 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.17 (3H, d, *J* = 6.4 Hz, C$\underline{H}_3$), 2.92 (1H, m, C$\underline{H}$CH$_3$), 3.54 (1H, A$\underline{B}$X, J_{AB} = 10.9, J_{BX} = 6.6 Hz, CH$_a\underline{H}_b$OH), 3.75 (1H, $\underline{A}$BX, J_{AB} = 10.9, J_{AX} = 3.6 Hz, C$\underline{H}_a$H$_b$OH), 4.00 and 4.10 (2H, AB, *J* = 13.8 Hz, C$\underline{H}_2$NH), 4.20 (br s, N$\underline{H}$ and O$\underline{H}$) 6.81 (1H, apparent t, *J* = 7.4 Hz, Ar), 6.86 (1H, d, *J* = 8.0 Hz, Ar), 7.03 (1H, d, *J* = 7.2 Hz, Ar), 7.19 (1H, apparent t, *J* = 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz); δ 16.1, 49.8, 53.9, 65.6, 116.5, 119.1, 121.7, 128.4, 128.9, 158.0; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.11; H, 8.50; N, 7.75 %.

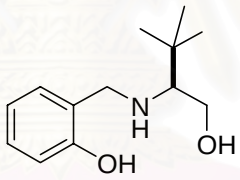
2.4.8 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109c)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-valinol (103 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method B* using salicylaldehyde (122

mg, 1.0 mmol), (*S*)-valinol (103 mg, 1.0 mmol) and Pd/C 26 mg. *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (157, 157 and 91 mg; 75, 75 and 87% respectively); m.p. 52.2-53.6 °C; $[\alpha]^{24}_D$ = +16.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 and 1.04 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 1.99 (1H, m, C$\underline{H}(CH_3)_2$), 2.54 (1H, m, C$\underline{H}$NH), 3.69 (1H, A$\underline{B}$X, J_{AB} = 11.1, J_{BX} = 6.0 Hz, $CH_a\underline{H}_bOH$), 3.87 (1H, $\underline{A}$BX, J_{AB} = 11.1, J_{AX} = 3.8 Hz, C$\underline{H}_aH_bOH$), 4.05 (2H, s, C$\underline{H}_2$NH), 6.82 (1H, apparent t, *J* = 7.4 Hz, Ar), 6.88 (1H, d, *J* = 8.0 Hz, Ar), 7.03 (1H, d, *J* = 7.6 Hz, Ar), 7.21 (1H, apparent t, *J* = 7.7 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 19.2, 28.7, 51.0, 61.2, 64.0, 116.5, 119.1, 123.1, 128.2, 128.8, 158.1; Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69; Found: C, 68.65; H, 9.39; N, 6.73 %.

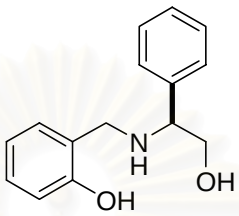
2.4.9 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol (109d)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3,3-methyl-butanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-*tert*-leucinol (117 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method B* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-*tert*-leucinol (117 mg, 1.0 mmol) and Pd/C 26 mg. *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-*tert*-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (165, 174 and 95 mg; 74, 78 and 85% respectively); m.p. 58.2-59.6 °C; $[\alpha]^{24}_D$ = +5.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (9H, s, 3×C$\underline{H}_3$), 2.41 (1H, AB$\underline{X}$, J_{AX} = 3.6, J_{BX} = 5.8 Hz, C$\underline{H}C(CH_3)_3$), 3.74 (1H, A$\underline{B}$X, J_{AB} = 10.9, J_{BX} = 5.8 Hz, $CH_a\underline{H}_bOH$), 4.00 (1H, $\underline{A}$BX, J_{AB} = 10.9, J_{AX} = 3.6, C$\underline{H}_aH_bOH$), 4.02 and 4.10 (2H, AB, *J* = 13.3 Hz, C$\underline{H}_2$NH), 6.82 (1H, apparent t, *J* = 7.4 Hz, Ar), 6.89 (1H, d, *J* = 8.0 Hz, Ar), 7.04 (1H, d, *J* = 7.2 Hz, Ar), 7.21 (1H, apparent t, *J* = 7.8 Hz, Ar); ^{13}C NMR

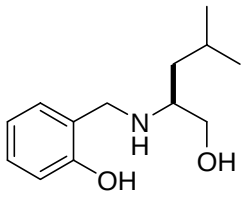
($CDCl_3$, 100 MHz) δ 27.5, 34.2, 53.1, 61.2, 67.8, 116.4, 119.3, 123.7, 128.5, 128.8, 157.9; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.95; H, 9.52; N, 6.27 %.

2.4.10 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-2-phenyl-ethanol (109e)



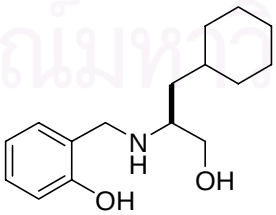
N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-2-phenyl-ethanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-phenylglycinol (137 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-phenylglycinol (69 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (177 and 105 mg;73 and 86% respectively); m.p. 119.4-121.1 °C; $[\alpha]^{24}_D$ = +64.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.74 (1H, AB, *J* = 13.6 Hz, CH_aH_bNH), 3.76-3.87 (3H, m, CH_2OH and CHNH), 3.97 (1H, AB, *J* = 13.6 Hz, CH_aH_bNH), 5.05 (br s, NH and OH), 6.79 (1H, apparent t, *J* = 7.2 Hz, Ar), 6.87 (1H, d, *J* = 8.0 Hz, Ar), 6.92 (1H, d, *J* = 6.4 Hz, Ar), 7.19 (1H, apparent t, *J* = 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.1, 63.9, 66.5, 116.4, 119.4, 122.8, 127.5, 128.2, 128.6, 128.9, 129.0, 138.7, 157.8; Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.07; H, 7.03; N, 5.79 %.

2.4.11 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-4-methyl-pentanol (109f)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-4-methyl-pentanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-leucinol (117 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a light yellow crystalline solid (112 and 95 mg; 50 and 85% respectively); .mp. 87.2-88.7 °C; $[\alpha]^{24}_D$ = +15.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (6H, t, *J* = 6.2 Hz, 2×C$\underline{H}_3$), 1.36 and 1.44 (2H, 2×m, C$\underline{H}_2$CH$(CH_3)_2$), 1.74 (1H, m, C$\underline{H}(CH_3)_2$), 2.81 (1H, m, C$\underline{H}$NH), 3.56 (1H, A$\underline{B}$X, J_{AB} = 11.1, J_{BX} = 5.6 Hz, $CH_a\underline{H}_bOH$), 3.84 (1H, $\underline{A}$BX, J_{AB} = 11.1, J_{AX} = 3.4 Hz, C$\underline{H}_aH_bOH$), 4.04 (2H, s, C$\underline{H}_2$NH), 4.90 (br s, N$\underline{H}$ and O$\underline{H}$), 6.79 (1H, apparent t, *J* = 6.4 Hz, Ar); 6.87 (1H, d, *J* = 8.0 Hz, Ar) 7.02 (1H, d, *J* = 6.8 Hz, Ar), 7.19 (1H, apparent t, *J* = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 22.8, 25.0, 40.2, 49.8, 56.2, 63.2, 116.5, 119.1, 122.8, 128.3, 128.7, 158.1; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.74; H, 9.55; N, 6.04 %.

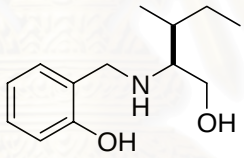
2.4.12 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-cyclohexyl-propanol (109g)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-cyclohexyl-propanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-cyclohexylalaninol hydrochloride (193 mg, 1.0 mmol), triethylamine (100 µL, 1.0

mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method C* using phenol (47 mg, 0.5 mmol), (*S*)-cyclohexylalaninol hydrochloride (97 mg, 0.5 mmol), triethylamine (50 µL, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a light yellow crystalline solid (187 and 110 mg; 71 and 84% respectively); m.p. 82.3-84.1 °C; $[\alpha]^{24}_D$ = +12.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 0.85−1.78 (13H, m, ^{c}Hex ring protons and ^{c}HexC$\underline{H}_2$), 2.83 (1H, m, C$\underline{H}$NH), 3.55 (1H, A$\underline{B}$X, J_{AB} = 11.1, J_{BX} = 5.2 Hz, $CH_a\underline{H}_bOH$), 3.82 (1H, $\underline{A}$BX, J_{AB} = 11.1, J_{AX} = 3.4 Hz, $C\underline{H}_aH_bOH$), 4.03 (2H, s, C$\underline{H}_2$NH), 5.02 (br s, N$\underline{H}$ and O$\underline{H}$), 6.81 (1H, apparent t, *J* = 7.2 Hz, Ar), 6.87 (1H, d, *J* = 8.0 Hz, Ar), 7.02 (1H, d, *J* = 7.2 Hz, Ar), 7.19 (1H, apprent t, *J* = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 26.5, 33.6, 34.5, 38.6, 49.7, 55.5, 63.2, 116.5, 119.1, 122.8, 128.4, 128.9, 158.1; Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found: C, 73.16; H, 9.49; N, 5.46 %.

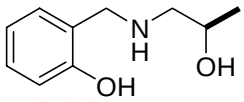
2.4.13 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-(*S*)-3-methyl-pentanol (109h)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-(*S*)-3-methyl-pentanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*S*)-isoleucinol (117 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method C* using phenol (47 mg, 0.5 mmol), (*S*,*S*)-isoleucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as yellow viscous oil (165 and 96 mg; 74 and 86% respectively); $[\alpha]^{24}_D$ = +54.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 0.95 (6H, m, C$\underline{H}_3$CH$_2$ and C$\underline{H}_3$CH), 1.22 and 1.50 (2H, 2×m, CH$_3$C$\underline{H}_2$), 1.75 (1H, m, CH$_3$C$\underline{H}$), 2.66 (1H, m, C$\underline{H}$NH), 3.63 (1H, A$\underline{B}$X, J_{AB} = 11.2, J_{BX} = 6.8 Hz, $CH_a\underline{H}_bOH$), 3.83 (1H, $\underline{A}$BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, $C\underline{H}_aH_bOH$), 3.98-4.09 (2H, AB, J = 13.6 Hz, C$\underline{H}_2$NH), 4.85 (br s, N$\underline{H}$ and O$\underline{H}$), 6.81 (1H, apparent t, *J* = 7.4 Hz, Ar), 6.87 (1H, d, *J* = 8.0 Hz, Ar), 7.03 (1H, d, *J* = 7.2 Hz, Ar), 7.20 (1H, apparent t, *J* = 7.8 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.9, 14.8, 26.2, 35.2, 50.7, 61.0, 62.7, 116.5, 119.2,

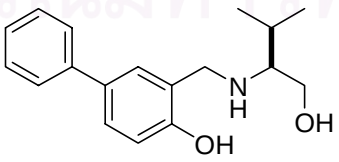
123.0, 128.4, 128.9, 158.0; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.85; H, 9.42; N, 6.20 %.

2.4.14 *N*-(2′-Hydroxyphenyl)methyl-(*R*)-1-amino-propanol (109i)



N-(2′-Hydroxyphenyl)methyl-(*R*)-1-amino-propanol was prepared according to *Method A* using salicylaldehyde (122 mg, 1.0 mmol), (*R*)-1-amino-propan-2-ol (75 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). *Method C* using phenol (47 mg, 0.5 mmol), (*R*)-1-amino-propan-2-ol (38 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a light yellow crystalline solid (87 and 59 mg; 49 and 65% respectively); m.p. 87.4-88.6 °C; $[\alpha]^{24}_D$ = -24.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 1.13 (3H, d, *J* = 6.4 Hz, C$\underline{H}_3$CH), 2.50 (1H, A$\underline{B}$X, J_{AB} = 12.0, J_{BX} = 8.4 Hz, CH$_a\underline{H}_b$CH), 2.62 (1H, $\underline{A}$BX, J_{AB} = 12.0, J_{AX} = 3.2 Hz, C$\underline{H}_a$H$_b$CH), 3.91 (1H, m, C$\underline{H}$OH), 3.90 and 3.99 (2H, AB, *J* = 14.0 Hz, C$\underline{H}_2$NH), 5.03 (br s, N$\underline{H}$ and O$\underline{H}$), 6.71 (1H, apparent t, *J* = 7.4 Hz, Ar), 6.75 (1H, d, *J* = 8.2 Hz, Ar), 6.91 (1H, d, *J* = 7.2 Hz, Ar), 7.09 (1H, apparent t, *J* = 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 52.5, 55.6, 66.5, 116.4, 119.1, 122.4, 128.5, 128.8, 158.1; Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.14; H, 8.30; N, 7.67 %.

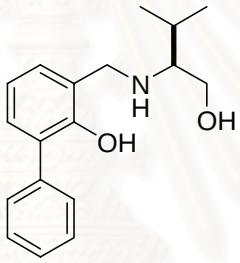
2.4.15 *N*-(2′-Hydroxy-5′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109j)



N-(2′-Hydroxy-5′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using 4-phenylphenol (85 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol)

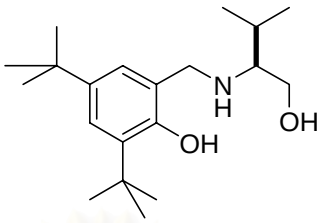
and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (121 mg, 85%); m.p. 132-133 °C; $[\alpha]^{24}_D$ = -19.4 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 and 1.05 (6H, 2×d, *J* = 6.8 Hz, 2×C<u>H</u>$_3$), 2.05 (1H, m, C<u>H</u>$(CH_3)_2$), 2.65 (1H, m, C<u>H</u>NH), 3.73 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 6.4 Hz, $CH_a\underline{H}_bOH$), 3.87 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, C<u>H</u>$_a$H$_b$OH), 4.15 (1H, A<u>B</u>, *J* = 13.6 Hz, $CH_a\underline{H}_bNH$), .4.18 (1H, <u>A</u>B, *J* = 13.6 Hz, C<u>H</u>$_a$H$_b$NH), 7.01 (1H, d, *J* = 8.4 Hz, Ar), 7.32 (2H, m, Ar), 7.45 (3H, m, Ar), 7.55 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 19.3, 28.6, 51.2, 61.1, 64.1, 116.0, 119.1, 123.5, 126.7, 127.5, 128.0, 129.1, 129.3, 138.5, 155.3; Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; Found: C, 75.78; H, 8.22; N, 4.75 %.

2.4.16 *N*-(2′-Hydroxy-3′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109k)



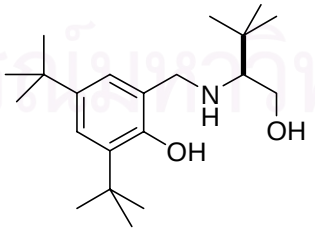
N-(2′-Hydroxy-3′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to <u>*Method C*</u> using 2-phenylphenol (85 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (123 mg, 86%); m.p. 135-136 °C; $[\alpha]^{24}_D$ = +19.6 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.03 and 1.05 (6H, 2×d, *J* = 6.8 Hz, 2×C<u>H</u>$_3$), 2.05 (1H, m, C<u>H</u>$(CH_3)_2$), 2.65 (1H, m, C<u>H</u>NH), 3.73 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 6.4 Hz, $CH_a\underline{H}_bOH$), 3.87 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, C<u>H</u>$_a$H$_b$OH), 4.16 (2H, s, C<u>H</u>$_2$NH), 7.01 (1H, d, *J* = 8.4 Hz, Ar), 7.32 (2H, m, Ar), 7.45 (3H, m, Ar), 7.55 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 19.3, 28.6, 51.2, 61.1, 64.1, 119.1, 123.7, 126.8, 127.7, 128.1, 129.2, 129.4, 130.0, 138.6, 155.1; Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91; Found: C, 75.74; H, 8.11; N, 5.15 %.

2.4.17 *N*-(3′,5′-Di-*tert*-butyl-2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109l)



N-(3′,5′-Di-*tert*-butyl-2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using 2,4-di-*tert*-butylphenol (103 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (140 mg,87%); m.p. 55-57 °C; $[\alpha]^{24}_D$ = +17.3 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 and 1.09 (6H, 2×d, *J* = 7.2 Hz, 2×C$\underline{H}_3$), 1.38 (9H, s, C(C$\underline{H}_3$)$_3$), 1.52 (9H, s, C(C$\underline{H}_3$)$_3$) 2.03 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 2.56 (1H, m, C$\underline{H}$NH), 3.72 (1H, A$\underline{B}$X, J_{AB} = 11.2, J_{BX} = 5.6 Hz, CH$_a\underline{H}_b$OH), 3.88 (1H, $\underline{A}$BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, C$\underline{H}_a$H$_b$OH), 4.05 (1H, A$\underline{B}$, *J* = 13.6 Hz, CH$_a\underline{H}_b$NH), .4.12 (1H, $\underline{A}$B, *J* = 13.6 Hz, C$\underline{H}_a$H$_b$NH), 6.98 (1H, s, Ar), 7.33 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 19.2, 28.7, 29.7, 31.8, 34.2, 35.0, 51.8, 61.3, 64.0, 122.7, 123.1, 123.2, 136.1, 140.7, 154.5; Anal. Calcd for $C_{20}H_{35}NO_2$: C, 74.72; H, 10.97; N, 4.36; Found: C, 74.90; H, 10.97; N, 4.48 %.

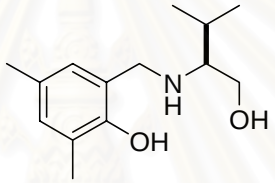
2.4.18 *N*-(3′,5′-Di-*tert*-butyl-2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl- butanol (109m)



N-(3′,5′-Di-*tert*-butyl-2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol was prepared according to *Method C* using 2,4-di-*tert*-butylphenol (103 mg, 0.5 mmol), (*S*)-*tert*-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10

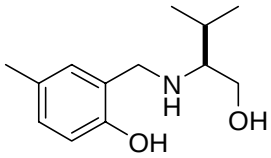
equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (143 mg, 85%); m.p. 57-59 °C; $[\alpha]^{24}_D$ = +16.7 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.34 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.49 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.40 (1H, AB<u>X</u>, J_{AX} = 3.6, J_{BX} = 5.2 Hz, C<u>H</u>C(CH$_3$)$_3$), 3.77 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 5.2 Hz, CH$_a$<u>H</u>$_b$OH), 4.02 (1H, <u>A</u>BX, J_{AB} = 12.0, J_{AX} = 3.6 Hz, C<u>H</u>$_a$H$_b$OH), 4.19 (2H, d, *J* = 13.2 Hz, C<u>H</u>$_2$NH), 6.95 (1H, s, Ar), 7.29 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6, 29.7, 31.7, 34.2, 34.3, 35.0, 53.6, 61.6, 67.5, 122.9, 123.1, 123.3, 136.1, 140.6, 154.6; Anal. Calcd for $C_{21}H_{37}NO_2$: C, 75.17; H, 11.12; N, 4.17; Found: C, 75.18; H, 11.04; N, 4.15 %.

2.4.19 *N*-(3′,5′-Dimethyl-2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109n)



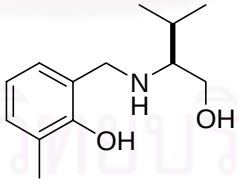
N-(3′,5′-Dimethyl-2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to <u>*Method C*</u> using 2,4-dimethylphenol (61 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as colorless oil (98 mg, 83%); $[\alpha]^{24}_D$ = +13.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (6H, apparent t, *J* = 7.2 Hz, 2×C<u>H</u>$_3$), 2.14 and 2.16 (6H, 2×s, 2×C<u>H</u>$_3$), 2.58 (1H, m, C<u>H</u>NH), 3.60 (1H, A<u>B</u>X, J_{AB} = 11.6, J_{BX} = 6.8 Hz, CH$_a$<u>H</u>$_b$OH), 3.74 (1H, <u>A</u>BX, J_{AB} = 11.6, J_{AX} = 3.6 Hz, C<u>H</u>$_a$H$_b$OH), 3.91 (1H, A<u>B</u>, *J* = 13.2 Hz, CH$_a$<u>H</u>$_b$NH), 4.00 (1H, <u>A</u>B, *J* = 13.2 Hz, C<u>H</u>$_a$H$_b$NH), 6.67 (1H, s, Ar), 6.83 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 18.3, 19.3, 20.3, 27.9, 49.7, 60.1, 64.1, 120.5, 125.9, 127.5, 128.9, 131.6, 153.6; Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90; Found: C, 70.69; H, 9.77; N, 5.90 %.

2.4.20 *N*-(2′-Hydroxy-5′-methyl-phenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109o)



N-(2′-Hydroxy-5′-methylphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using *p*-cresol (54 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (96 mg, 86%); m.p. 58-59 °C; $[\alpha]^{24}_D$ = +18.0 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 and 1.02 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 1.95 (1H, m, C$\underline{H}$(CH_3)$_2$), 2.27 (1H, s, C$\underline{H}_3$) 2.50 (1H, m, C$\underline{H}$NH), 3.62 (1H, A$\underline{B}$X, J_{AB} = 11.2, J_{BX} = 6.4 Hz, $CH_a\underline{H}_bOH$), 3.81 (1H, $\underline{A}$BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, C$\underline{H}_aH_bOH$), 3.97 (2H, s, C$\underline{H}_2$NH), 5.22 (br s, N$\underline{H}$ and O$\underline{H}$), 6.76 (1H, d, *J* = 8.0 Hz, Ar), 6.82 (1H, s, Ar), 6.99 (1H, d, *J* = 8.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 19.2, 20.5, 28.6, 50.8, 60.9, 64.0, 116.5, 116.1, 123.0, 128.3, 128.9, 129.1, 155.5; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.62; H, 9.46; N, 6.27 %.

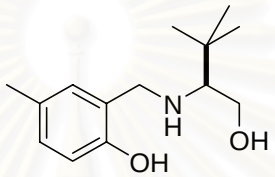
2.4.21 *N*-(2′-Hydroxy-3′-methyl-phenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109p)



N-(2′-Hydroxy-3′-methylphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using *o*-cresol (54 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (98 mg, 88 %); m.p. 56-57 °C $[\alpha]^{24}_D$ = +17.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 and 1.04 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 1.98 (1H, m, C$\underline{H}$(CH_3)$_2$), 2.29 (1H, s, C$\underline{H}_3$) 2.51 (1H, m, C$\underline{H}$NH), 3.64 (1H, A$\underline{B}$X, J_{AB} = 11.2, J_{BX} = 6.0 Hz,

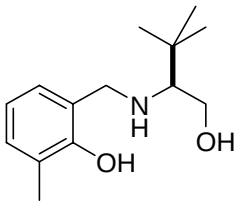
CH_aH_bOH), 3.82 (1H, ABX, J_{AB} = 11.2, J_{AX} = 4.0 Hz, CH_aH_bOH), 4.00 (2H, s, CH_2NH), 5.24 (br s, NH and OH), 6.74 (1H, apparent t, J = 7.2 Hz, Ar), 6.88 (1H, d, J = 7.2 Hz, Ar), 7.03 (1H, d, J = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.8, 18.8, 19.2, 28.6, 51.0, 61.0, 64.2, 116.5, 118.8, 122.6, 125.3, 125.9, 130.0, 156.1; Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; Found: C, 69.93; H, 9.47; N, 6.20 %.

2.4.22 *N*-(2′-Hydroxy-5′-methyl-phenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol (109q)



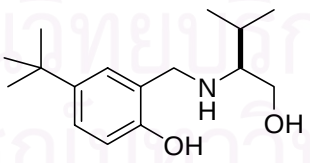
N-(2′-Hydroxy-5′-methylphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol was prepared according to *Method C* using *p*-cresol (54 mg, 0.5 mmol), (*S*)-*tert*-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (100 mg, 84%); m.p. 62-64 °C; $[\alpha]^{24}_D$ = +7.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (9H, s, 3×CH_3), 2.27 (1H, s, CH_3), 2.41 (1H, ABX, J_{AX} = 3.6, J_{BX} = 5.6 Hz, $CHC(CH_3)_3$), 3.72 (1H, ABX, J_{AB} = 11.2, J_{BX} = 6.0 Hz, CH_aH_bOH), 3.98 (1H, ABX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, CH_aH_bOH), 4.14 (2H, d, J = 13.6 Hz, CH_2NH), 4.76 (br s, NH and OH), 6.79 (1H, d, J = 8.0 Hz, Ar), 6.85 (1H, s, Ar), 7.01 (1H, d, J = 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 27.5, 34.2, 53.0, 61.4, 67.7, 116.1, 123.0, 128.2, 129.0, 129.2, 155.6; Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90; Found: C, 70.89; H, 9.80; N, 5.98 %.

2.4.23 *N*-(2′-Hydroxy-3′-methyl-phenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol (109r)



N-(2′-Hydroxy-3′-methylphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol was prepared according to *Method C* using *o*-cresol (54 mg, 0.5 mmol), (*S*)-*tert*-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (106 mg, 89%); m.p. 60-62 °C; $[\alpha]^{24}_D$ = +6.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (9H, s, 3×C$\underline{H}_3$), 2.31 (1H, s, C$\underline{H}_3$), 2.38 (1H, AB$\underline{X}$, J_{AX} = 3.6, J_{BX} = 6.0 Hz, C$\underline{H}$C(CH$_3$)$_3$), 3.68 (1H, A$\underline{B}$X, J_{AB} = 11.2, J_{BX} = 6.0 Hz, CH$_a\underline{H}_b$OH), 3.97 (1H, $\underline{A}$BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, C$\underline{H}_a$H$_b$OH), 4.03 (1H, A$\underline{B}$, *J* = 13.6 Hz, CH$_a\underline{H}_b$NH), 4.15 (1H, $\underline{A}$B, *J* = 13.6 Hz, C$\underline{H}_a$H$_b$NH), 5.21 (br s, N$\underline{H}$ and O$\underline{H}$), 6.76 (1H, apparent t, *J* = 7.6 Hz, Ar), 6.89 (1H, d, *J* = 7.2 Hz, Ar), 7.10 (1H, d, *J* = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.9, 27.5, 34.2, 53.3, 61.5, 67.9, 118.8, 122.9, 125.3, 126.0, 130.0, 156.2; Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90; Found: C, 70.72; H, 9.90; N, 5.85 %.

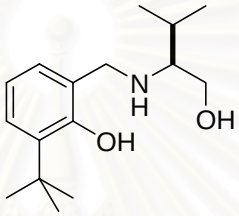
2.4.24 *N*-(5′-*tert*-Butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109s)



N-(5′-*tert*-Butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using 4-*tert*-butylphenol (75 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as colorless oil (115 mg, 87%); $[\alpha]^{24}_D$ = +18.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 and 1.03 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 1.31 (9H, s, 3×C$\underline{H}_3$), 1.98 (1H, m,

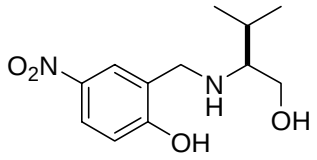
C<u>H</u>$(CH_3)_2$), 2.55 (1H, m, C<u>H</u>NH), 3.66 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 6.4 Hz, $CH_a\underline{H}_bOH$), 3.83 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 4.0 Hz, $C\underline{H}_aH_bOH$), 4.03 (2H, s, $C\underline{H}_2NH$), 5.24 (br s, N<u>H</u> and O<u>H</u>), 6.81 (1H, d, *J* = 8.4 Hz, Ar), 7.04 (1H, s, Ar), 7.22 (1H, d, *J* = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 19.2, 28.6, 31.6, 34.0, 51.2, 61.0, 64.2, 115.8, 122.3, 125.2, 125.6, 141.9, 155.5; Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28; Found: C, 72.30; H, 10.23; N, 5.14%.

2.4.25 *N*-(3′-*tert*-Butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109t)



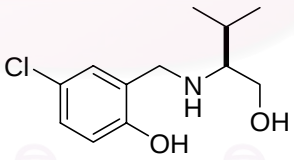
N-(3′-*tert*-Butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to <u>*Method C*</u> using 2-*tert*-butylphenol (75 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as colorless oil (111 mg, 84%); $[\alpha]^{24}_D$ = +15.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 and 1.05 (6H, 2×d, *J* = 6.8 Hz, 2×C<u>H</u>$_3$), 1.48 (9H, s, 3×C<u>H</u>$_3$), 1.99 (1H, m, C<u>H</u>$(CH_3)_2$), 2.55 (1H, m, C<u>H</u>NH), 3.68 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 5.6 Hz, $CH_a\underline{H}_bOH$), 3.84 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 4.0 Hz, $C\underline{H}_aH_bOH$), 4.03 (1H, A<u>B</u>, *J* = 13.6 Hz, $CH_a\underline{H}_bNH$), 4.08 (1H, <u>A</u>B, *J* = 13.6 Hz, $C\underline{H}_aH_bNH$), 6.78 (1H, apparent t, *J* = 7.6 Hz, Ar), 6.94 (1H, d, *J* = 7.2 Hz, Ar), 7.25 (1H, d, *J* = 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 19.3, 28.7, 29.6, 34.7, 51.2, 61.0, 63.8, 118.5, 123.4, 126.1, 126.7, 137.1, 157.0; Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28; Found: C, 72.24; H, 10.34; N, 5.28%.

2.4.26 *N*-(2′-Hydroxy-5′-nitrophenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109u)



N-(2′-Hydroxy-5′-nitrophenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method A* using 2-hydroxy-5-nitrobenzaldehyde (167 mg, 1.0 mmol), (*S*)-valinol (103 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). The product was obtained as a yellow crystalline solid (223 mg; 88%); m.p. 122-123 °C; $[\alpha]^{24}_D$ = +8.4 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.94 and 0.97 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 2.00 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 2.68 (1H, m, C$\underline{H}$NH), 3.54 (1H, A$\underline{B}$X, J_{AB} = 11.6, J_{BX} = 6.0 Hz, CH$_a\underline{H}_b$OH), 3.67 (1H, $\underline{A}$BX, J_{AB} = 11.6, J_{AX} = 3.6 Hz, C$\underline{H}_a$H$_b$OH), 4.98 (br s, N$\underline{H}$ and O$\underline{H}$),), 6.41 (1H, d, *J* = 9.2 Hz, Ar), 7.93 (1H, d, *J* = 9.2 Hz, Ar), 8.01 (1H, s, Ar); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 18.7, 19.2, 27.5, 48.5, 58.4, 63.5, 118.1, 121.6, 126.5, 126.8, 133.2, 174.6; Anal. Calcd for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02; Found: C, 56.71; H, 7.40; N, 11.06%.

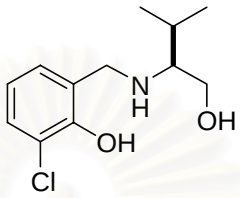
2.4.27 *N*-(5′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109v)



N-(5′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using 4-chlorophenol (65 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (107 mg, 88%); m.p. 98-100 °C, $[\alpha]^{24}_D$ = +18.5 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 and 1.02 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 1.95 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 2.53 (1H, m, C$\underline{H}$NH), 3.65 (1H, A$\underline{B}$X, J_{AB} = 11.2, J_{BX} = 6.4 Hz, CH$_a\underline{H}_b$OH), 3.83 (1H, $\underline{A}$BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, C$\underline{H}_a$H$_b$OH), 4.00 (2H, s, C$\underline{H}_2$NH), 5.13 (br s, N$\underline{H}$ and O$\underline{H}$), 6.78 (1H, d, *J* = 8.8 Hz, Ar), 6.99 (1H, s, Ar), 7.25

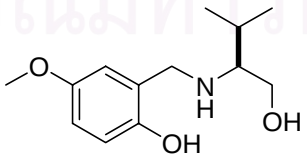
(1H, d, J = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 19.3, 28.5, 50.2, 60.7, 64.0, 117.7, 123.6, 124.2, 128.2, 128.7, 156.8; Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.54; N, 5.75; Found: C, 59.13; H, 7.62; N, 5.77%.

2.4.28 *N*-(3′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109w)



N-(3′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using 2-chlorophenol (65 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (102 mg, 84%); m.p. 90-92 °C, $[\alpha]^{24}_D$ = +13.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 and 0.95 (6H, 2×d, J = 6.8 Hz, 2×C$\underline{H}_3$), 1.94 (1H, m, C$\underline{H}(CH_3)_2$), 2.56 (1H, m, C$\underline{H}$NH), 3.62 (1H, A$\underline{B}$X, J_{AB} = 11.6, J_{BX} = 6.8 Hz, $CH_a\underline{H}_bOH$), 3.77 (1H, $\underline{A}$BX, J_{AB} = 11.2, J_{AX} = 3.2 Hz, C$\underline{H}_aH_bOH$), 4.01 (2H, s, C$\underline{H}_2$NH), 6.50 (1H, apparent t, J = 7.6 Hz, Ar), 6.90 (1H, d, J = 7.6 Hz, Ar), 7.19 (1H, d, J = 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.4, 19.4, 28.2, 49.9, 60.3, 64.4, 119.6, 121.5, 123.1, 127.6, 129.6, 153.7; Anal. Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.44; N, 5.75; Found: C, 59.14; H, 7.49; N, 5.62 %.

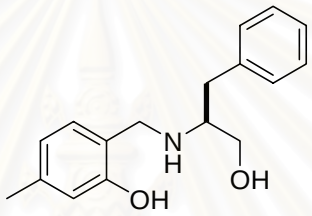
2.4.29 *N*-(2′-Hydroxy-5′-methoxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109x)



N-(2′-Hydroxy-5′-methoxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to *Method C* using 4-methoxyphenol (62 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5

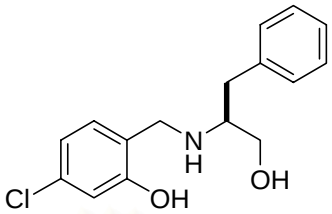
mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as yellow viscous oil (110 mg, 92%); $[\alpha]^{24}_D$ = +7.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 and 1.00 (6H, 2×d, *J* = 6.8 Hz, 2×C<u>H</u>$_3$), 1.94 (1H, m, C<u>H</u>$(CH_3)_2$), 2.49 (1H, m, C<u>H</u>NH), 3.61 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 6.4 Hz, $CH_a\underline{H}_bOH$), 3.74 (3H, s, OC<u>H</u>$_3$), 3.80 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 3.6 Hz, C<u>H</u>$_a$H$_b$OH), 3.98 (2H, s, C<u>H</u>$_2$NH),4.98 (br s, N<u>H</u> and O<u>H</u>), 6.59 (1H, s, Ar), 6.74 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.7, 19.2, 28.5, 50.8, 55.8, 60.8, 64.1, 113.6, 114.3, 116.7, 123.8, 151.6, 152.5; Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85; Found: C, 64.96; H, 8.75; N, 5.85%.

2.4.30 *N*-(2′-Hydroxy-4′-methylphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (109y)



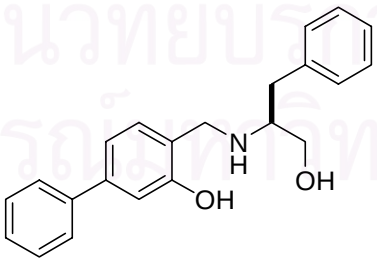
N-(2′-Hydroxy-4′-methylphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to <u>*Method C*</u> using 3-methylphenol (54 mg, 0.5 mmol), (*S*)-phenylalaninol (76 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (116 mg, 86%); m.p. 136.3-137.5 °C; $[\alpha]^{24}_D$ = +28.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (1H, s, C<u>H</u>$_3$), 2.80 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 7.6 Hz, $CH_a\underline{H}_bPh$), 2.88 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 6.4 Hz, C<u>H</u>$_a$H$_b$Ph), 2.97 (1H, m, C<u>H</u>NH), 3.52 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 5.2 Hz , $CH_a\underline{H}_bOH$), 3.71 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 4.0 Hz, C<u>H</u>$_a$H$_b$OH), 3.95 (2H, s, C<u>H</u>$_2$NH), 5.07 (br s, N<u>H</u> and O<u>H</u>), 6.75 (2H, m, Ar), 6.96 (1H, d, *J* = 8.0 Hz, Ar), 7.18 (2H, m, Ar), 7.24 (1H, m, Ar), 7.31 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.7, 37.5, 50.2, 59.6, 62.4, 116.5, 122.2, 126.4, 128.3, 128.6, 129.1, 129.5, 138.2, 155.6; Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16; Found: C, 75.23; H, 7.78; N, 5.25 %.

2.4.31 *N*-(4′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (109z)



N-(4′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to *Method C* using 3-chlorophenol (64 mg, 0.5 mmol), (*S*)-phenylalaninol (76 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a white crystalline solid (121 mg, 83%); m.p. 143.6-144.5 °C; $[\alpha]^{24}_D$ = +35.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.80 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 7.6 Hz, $CH_a\underline{H}_bPh$), 2.88 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 6.4 Hz, $C\underline{H}_aH_bPh$), 2.97 (1H, m, C<u>H</u>NH), 3.54 (1H, A<u>B</u>X, J_{AB} = 10.8, J_{BX} = 4.8 Hz , $CH_a\underline{H}_bOH$), 3.71 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 4.0 Hz, $C\underline{H}_aH_bOH$), 3.98 (2H, s, $C\underline{H}_2NH$), 6.74 (2H, d, *J* = 8.0 Hz, Ar), 6.84 (2H, m, Ar), 7.17 (2H, m, Ar), 7.24 (1H, m, Ar), 7.31 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.3, 49.8, 59.5, 62.4, 116.9, 119.2, 121.1, 126.7, 128.6, 128.9, 129.1, 134.0, 137.8, 158.9.

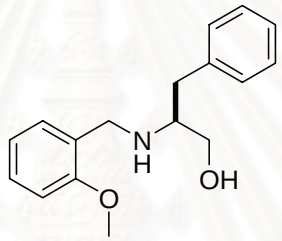
2.4.32 *N*-(2′-Hydroxy-4′-phenyl-phenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (109aa)



N-(2′-Hydroxy-4′-phenyl-phenyl)methyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to *Method C* using 3-phenylphenol (85 mg, 0.5 mmol), (*S*)-phenylalaninol (76 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol) and $NH_2OH.HCl$ (348 mg, 5.0 mmol). The product was obtained as a

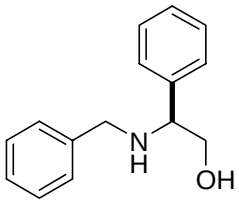
white crystalline solid (145 mg, 87%); m.p. 134.8-136.3 °C; $[\alpha]^{24}_{D}$ = +26.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.83 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 7.2 Hz, $CH_a\underline{H}_bPh$), 2.92 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 6.4 Hz, $C\underline{H}_aH_bPh$), 3.01 (1H, m, C<u>H</u>NH), 3.55 (1H, A<u>B</u>X, J_{AB} = 11.2, J_{BX} = 5.2 Hz, $CH_a\underline{H}_bOH$), 3.75 (1H, <u>A</u>BX, J_{AB} = 11.2, J_{AX} = 4.0 Hz, $C\underline{H}_aH_bOH$), 4.04 (2H, s, $C\underline{H}_2NH$), 5.16 (br s, N<u>H</u> and O<u>H</u>), 7.03 (2H, m, Ar), 7.12 (1H, s, Ar), 7.20 (2H, m, Ar), 7.26 (1H, m, Ar), 7.34 (3H, m, Ar), 7.43 (2H, m, Ar), 7.59 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.2, 49.8, 59.3, 62.4, 115.1, 118.0, 121.8, 126.7, 126.9, 127.3, 128.7, 129.2, 138.0, 140.8, 142.0, 158.2.

2.4.33 *N*-(2′-Methoxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol (109ab)



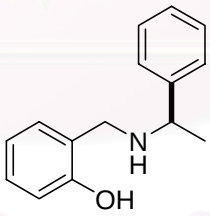
N-(2′-Methoxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to <u>*Method A*</u> using 2-methoxybenzaldehyde (136 mg, 1.0 mmol), (*S*)-phenylalaninol (151 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). The product was obtained as a white crystalline solid (203 mg, 75%); m.p. 118.2-119.5 °C; $[\alpha]^{24}_{D}$ = -20.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.60 (br s, N<u>H</u> and O<u>H</u>), 2.89 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 7.6 Hz, $CH_a\underline{H}_bPh$), 2.91 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 6.4 Hz, C<u>H</u>aHbPh), 2.96 (1H, m, C<u>H</u>NH), 3.43 (1H, A<u>B</u>X, J_{AB} = 10.8, J_{BX} = 4.8 Hz , $CH_a\underline{H}_bOH$), 3.70 (1H, s, $OC\underline{H}_3$), 3.74 (1H, <u>A</u>BX, J_{AB} = 10.8, J_{AX} = 3.6 Hz, $C\underline{H}_aH_bOH$), 3.77 (1H, A<u>B</u>, J = 12.8 Hz, $CH_a\underline{H}_bNH$), 3.86 (1H, <u>A</u>B, J = 13.2 Hz, $C\underline{H}_aH_bNH$), 6.83 (1H, d, J = 8.0 Hz, Ar 6.92 (1H, appaprent t, J = 7.6 Hz, Ar), 7.16 (3H, m, Ar), 7.23-7.34 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 38.2, 46.8, 55.0, 58.8, 62.2, 110.2, 120.4, 126.3, 127.5, 128.5, 128.6, 129.2, 130.0, 138.6, 157.6.

2.4.34 *N*-Benzyl-(*S*)-2-amino-2-phenyl-ethanol (109ac)



N-Benzyl-(*S*)-2-amino-2-phenyl-ethanol was prepared according to *Method A* using benzaldehyde (106 mg, 1.0 mmol), (*S*)-phenyglycinol (137 mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). The product was obtained as a white crystalline solid (193 mg, 85%); m.p. 111.2-112.5 °C; $[\alpha]^{24}_D$ = +60.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.62 (1H, m, C<u>H</u>NH), 3.74 (1H, A<u>B</u>X, J_{AB} = 10.8, J_{BX} = 4.4 Hz, $CH_a\underline{H}_bOH$), 3.80 (1H, d, *J* = 13.2 Hz, C<u>H</u>$_2$NH), 3.86 (1H, <u>A</u>BX, J_{AB} = 8.8, J_{AX} = 4.4 Hz, C<u>H</u>aH_bOH), 7.30-7.45 (10H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 51.2, 63.8, 66.7, 127.2, 127.4, 127.8, 128.4, 128.5, 128.8, 139.8, 140.2.

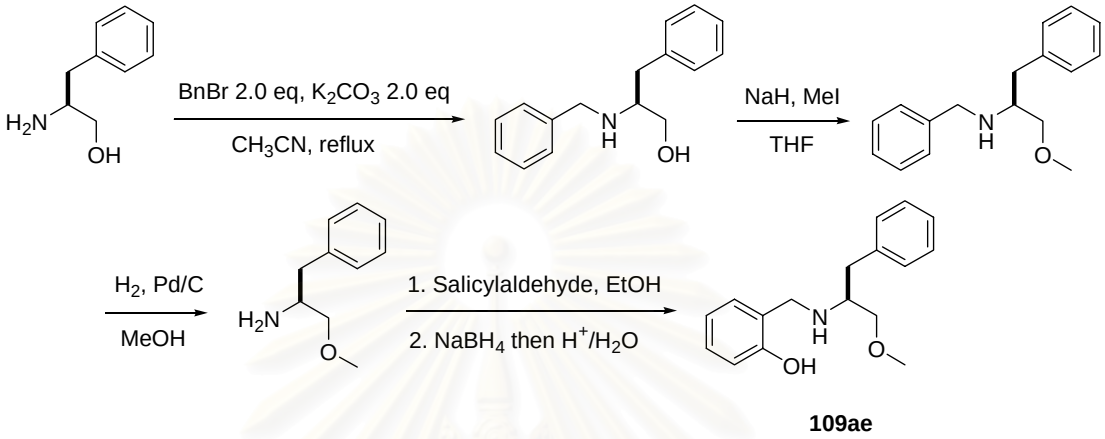
2.4.35 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-1-amino-1-phenyl-ethane (109ad)



N-(2′-Hydroxyphenyl)methyl-(*S*)-1-amino-1-phenyl-ethane was prepared according to *Method A* using salicylaldehyde (106 mg, 1.0 mmol), (*S*)-methyl benzylamine (121) mg, 1.0 mmol) and $NaBH_4$ (38 mg, 1.0 mmol). The product was obtained as yellow viscous oil (204 mg, 90%); $[\alpha]^{24}_D$ = -43.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (3H, d, *J* = 6.8 Hz,CHC<u>H</u>$_3$), 3.86 (1H, quartet, *J* = 6.8 Hz, C<u>H</u>CH_3), 3.77 (1H, A<u>B</u>, *J* = 14.0 Hz, $CH_a\underline{H}_bNH$), 3.92 (1H, <u>A</u>B, *J* = 13.6 Hz, C<u>H</u>$_a$$H_b$NH), 6.81 (1H, apparent t, *J* = 7.6 Hz, Ar), 6.92 (1H, apparent t, *J* = 8.4 Hz, Ar), 7.22 (1H, apparent t, *J* = 7.6 Hz, Ar), 7.34 (3H, m, Ar), 7.43 (3H, m, Ar); ^{13}C

NMR ($CDCl_3$, 100 MHz): δ 23.3, 50.3, 57.2, 116.4, 119.2, 122.7, 126.2, 127.7, 128.5, 128.8, 128.9, 143.2, 158.2; Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16.

2.5 Synthesis of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl propane (109ae)



Scheme 2.1 Synthesis of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane (109ae)

Step 1 (*S*)-Phenylalaninol (232 mg, 2.0 mmol), benzyl bromide (684 mg, 2.0 mmol) and K_2CO_3 (552 mg, 2.0 mmol) were weighed into a round bottom flask. Then acetonitrile 10 mL was added and reaction mixture was refluxed until starting materials were completely consumed (monitored by TLC). The volatile was removed by evaporation and the residue was dissolved in CH_2Cl_2 10 mL and extracted with 1N HCl (2 × 10 mL). Aqueous phase was collected and neutralized with saturated $NaHCO_3$ then extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was used in the next step without further purification.

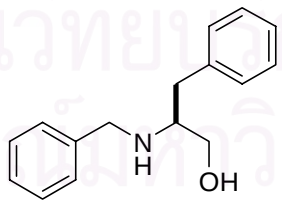
Step 2 *N*-Benzyl-(*S*)-2-amino-3-phenyl-propanol (467 mg) prepared from step 1 was dissolved in anhydrous THF 10 mL. Then sodium hydride (50 mg, 2.0 mmol) was added and the reaction mixture was stirred for 15 minutes under nitrogen. Methyl iodide (210 μL, 2.0 mmol) was syringed and the reaction mixture was vigorously stirred until starting materials disappeared (monitored by TLC). Organic solvent was reduced in *vacuo*. Then the residue was dissolved in CH_2Cl_2 10 mL and washed with water (2 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4 and removed

by evaporation. The crude product was used in the next step without further purification.

Step 3 *N*-Benzyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane (459 mg) prepared from step 2 was dissolved in absolute methanol 10 mL. Then Pd/C (46 mg, 10% by weight) was added and the reaction mixture was stirred under hydrogen atmosphere until the starting material was completely consumed (monitored by TLC). The reaction mixture was filtered through celite to remove the Pd/C. The organic solvent was evaporated under reduced pressure. The crude product was used in the next step without further purification.

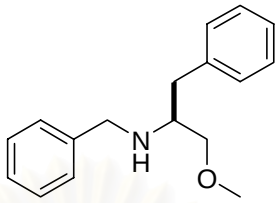
Step 4 (*S*)-2-Amino-1-methoxy-3-phenyl-propane (276 mg) prepared from step 3 was mixed with salicylaldehyde (204 mg, 1.0 equiv) in absolute ethanol (10 mL). The reaction mixture was stirred at room temperature until the starting materials were totally consumed (monitored by TLC). Then $NaBH_4$ (67 mg, 1.0 equiv) was added into the light yellow solution with vigorous stirring to give a colorless solution. The reaction mixture was quenched with dil. HCl and then neutralized with saturated $NaHCO_3$. The solution was concentrated under reduced pressure and the residue was extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation. The crude products were purified by flash column chromatography using hexanes and ethyl acetate as eluent.

2.5.1 *N*-Benzyl-(*S*)-2-amino-3-phenyl-propanol (112)



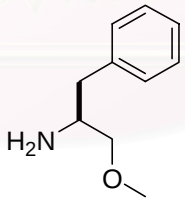
N-Benzyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to Step 1. The product was obtained as colorless oil (467 mg, 97%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.43 (1H, m, C<u>H</u>$_2$Ph), 2.95-3.20 (2H, m, C<u>H</u>$_2$Ph and C<u>H</u>NH), 3.35 (br s, N<u>H</u> and O<u>H</u>), 3.98 (2H, s, C<u>H</u>$_2$NH), 3.78 (1H, <u>A</u>BX, J_{AB} = 11.0, J_{AX} = 3.8 Hz, C<u>H</u>$_a$H$_b$OH), 4.05 (2H, s, C<u>H</u>$_2$NH), 7.03-7.42 (10H, m, Ar).

2.5.2 *N*-Benzyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane (113)



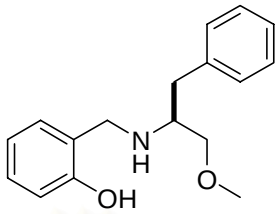
N-Benzyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to Step 2. The product was obtained as a white crystalline solid (459 mg, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.81 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 7.6 Hz, $CH_a\underline{H}_bPh$), 2.90 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 7.2 Hz, $C\underline{H}_aH_bPh$), 3.10 (1H, m, C<u>H</u>NH), 3.30 (3H, s, $OC\underline{H}_3$), 3.44 (1H, A<u>B</u>X, J_{AB} = 10.0, J_{BX} = 4.8 Hz , $CH_a\underline{H}_bOH$), 3.52 (1H, <u>A</u>BX, J_{AB} = 10.0, J_{AX} = 6.0 Hz, $C\underline{H}_aH_bOH$), 3.76 (2H, s, $C\underline{H}_2NH$), 7.07 (2H, m, Ar), 7.18-7.27 (8H, m, Ar).

2.5.3 (*S*)-2-Amino-1-methoxy-3-phenyl-propane (114)



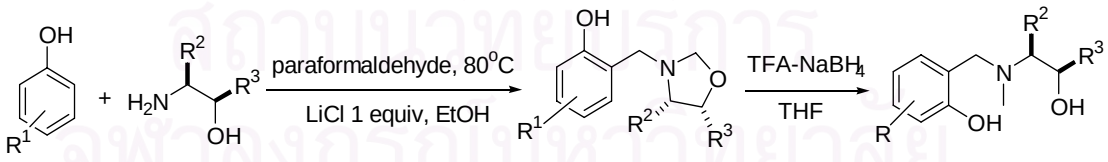
(*S*)-2-Amino-3-phenyl-propanol was prepared according to Step 3. The product was obtained as colorless oil (276 mg, 93%); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.02 (br s, N<u>H</u> and O<u>H</u>), 2.56 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 7.6 Hz, $CH_a\underline{H}_bPh$), 2.76 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 4.8 Hz, $C\underline{H}_aH_bPh$), 3.20 (2H, m, C<u>H</u>NH and $C\underline{H}_2OCH_3$), 3.42 (3H, s, $OC\underline{H}_3$), 3.55 (1H, <u>m</u>, $C\underline{H}_2OH$), 7.17-7.21 (3H, m, Ar), 7.26-7.30 (2H, m, Ar).

2.5.4 *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane (109ae)



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane was prepared according to Step 4. The product was obtained as colorless oil (379 mg, 82%); $[\alpha]^{24}_{D}$ = -21.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.81 (1H, A<u>B</u>X, J_{AB} = 13.6, J_{BX} = 8.0 Hz, $CH_a\underline{H}_bPh$), 2.92 (1H, <u>A</u>BX, J_{AB} = 13.6, J_{AX} = 6.4 Hz, $C\underline{H}_aH_bPh$), 3.05 (1H, m, C<u>H</u>NH), 3.28 (1H, A<u>B</u>X, J_{AB} = 9.6, J_{BX} = 5.2 Hz , $CH_a\underline{H}_bOH$), 3.36 (3H, s, $OC\underline{H}_3$), 3.45 (1H, <u>A</u>BX, J_{AB} = 9.6, J_{AX} = 4.0 Hz, $C\underline{H}_aH_bOH$), 4.02 (2H, s, $C\underline{H}_2NH$), 6.80 (1H, apparent t, *J* = 7.6 Hz, Ar), 6.87 (1H, d, *J* = 8.4 Hz, Ar), 7.18 (3H, m, Ar), 7.25 (1H, m, Ar), 7.33 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.5, 50.2, 58.1, 59.0, 72.4, 116.5, 119.1, 122.8, 126.6, 128.3, 128.6, 128.8, 129.3, 138.1, 158.1; Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16.

2.6 Synthesis of chiral-*N*-methyl-*N*-salicyl-β-aminoalcohol by three-component Mannich type reaction followed by reductive ring opening of oxazolidene derivatives with TFA-$NaBH_4$ [173]

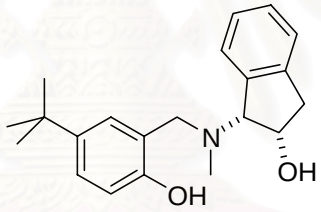


A mixture of phenol (0.5 mmol), paraformaldehyde (250 mg, 10 equiv), an appropriate amino alcohol (0.5 mmol) and LiCl (0.5 mmol) were weighed and dissolved with ethanol 3 mL in a screw-capped test tube. The reaction mixture was heated at 80 °C for 18 hours. Ethanol was removed *in vacuo* and the crude products

(oxazolidines) were purified by flash column chromatography using hexanes and ethyl acetate as eluent.

Sodium borohydride (2.5 mmol) was dissolved in anhydrous THF 10 mL at 0 °C with vigorous stirring. Then trifluoroacetic acid (2.5 mmol) was added dropwise to a suspension of metal hydride. A solution of the purified oxazolidines in anhydrous THF 3 mL was added dropwise to a cooled mixture. After the addition, the reaction mixture was stirred for 1 hour at room temperature. The suspension was cooled and decomposed cautiously by 10% sodium hydroxide aqueous solution. The mixture was concentrated and extracted with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The oily residue was purified by flash column chromatography using hexanes and ethyl acetate as eluent to obtain chiral-*N*-methyl-*N*-salicyl-β-aminoalcohols.

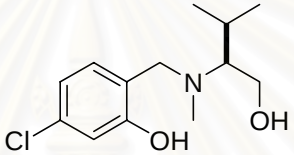
2.6.1 *N*-(5′-*tert*-Butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(1*R*,2*S*)-indan-2-ol (115a)



N-(5′-*tert*-Butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(1*R*,2*S*)-indan-2-ol (major isomer) was prepared according to the general procedure using 4-*tert*-butylphenol (75.0 mg, 0.5 mmol), (1*R*,2*S*)-indan-2-ol (74.6 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol), $NaBH_4$ (95 mg, 2.5 mmol) and TFA (198 μL, 2.5 mmol). The major isomer was obtained as a white crystalline solid (57 mg, 52%); m.p. 82-84 °C; $[\alpha]^{24}_D$ = +18.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.34 (9H, s, C(C$\underline{H}_3$)$_3$), 2.37 (3H, s, NC$\underline{H}_3$), 3.19 (1H, A$\underline{B}$X, J_{AB} = 17.6, J_{BX} = 4.8 Hz, ArCH$_a\underline{H}_b$CHOH), 3.42 (1H, $\underline{A}$BX, J_{AB} = 17.6, J_{AX} = 8.8 Hz, ArC$\underline{H}_a$H$_b$CHOH), 4.30 (2H, s, C$\underline{H}_2$N), 4.80 (1H, d, *J* = 7.6 Hz, NC$\underline{H}$CHOH), 5.29 (1H, m, NCHC$\underline{H}$OH), 6.93 (1H, d, *J* = 8.8 Hz, Ar), 7.05 (1H, s, Ar), 7.30 (3H, m, Ar), 7.41 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 34.0, 40.7, 44.0, 57.9, 70.0, 77.9, 114.5, 118.4, 123.5, 126.2, 126.3, 126.9, 127.0, 130.4, 133.8, 141.5, 144.8, 153.1.

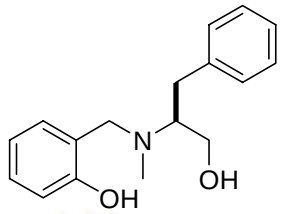
The minor isomer was obtained as colorless oil (20 mg, 8%); $[\alpha]^{24}_{D}$ = +15.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.37 (3H, s, NC<u>H</u>$_3$), 3.03 (1H, A<u>B</u>X, J_{AB} = 17.6, J_{BX} = 4.8 Hz, ArCH$_a$<u>H</u>$_b$CHOH), 3.28 (1H, <u>A</u>BX, J_{AB} = 17.6, J_{AX} = 8.8 Hz, ArC<u>H</u>$_a$H$_b$CHOH), 4.17 (2H, AB, *J* = 13.8 Hz, C<u>H</u>$_2$NH), 4.46 (1H, d, *J* = 7.6 Hz, NC<u>H</u>CHOH), 4.93 (1H, m, NCHC<u>H</u>OH), 6.95 (1H, d, *J* = 8.8 Hz, Ar), 7.08 (1H, s, Ar), 7.34 (3H, m, Ar), 7.45 (2H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 34.0, 38.1, 40.5, 58.8, 68.5, 73.1, 115.9, 120.3, 125.6, 125.8, 125.9, 126.5, 127.2, 129.0, 137.4, 141.2, 142.2, 155.2.

2.6.2 *N*-(4′-Chloro-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol (115b)



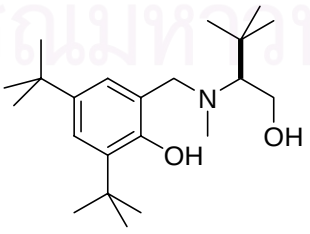
N-(4′-Chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to the general procedure using 3-chlorophenol (65 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol), $NaBH_4$ (95 mg, 2.5 mmol) and TFA (198 μL, 2.5 mmol). The product was obtained as a white crystalline solid (59 mg, 61%); m.p. 78-80 °C, $[\alpha]^{24}_{D}$ = +16.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 and 1.08 (6H, 2×d, *J* = 6.8 Hz, 2×C<u>H</u>$_3$), 2.02 (1H, m, C<u>H</u>(CH$_3$)$_2$), 2.43 (3H, s, NC<u>H</u>$_3$), 2.67 (1H, m, C<u>H</u>N), 3.84 (1H, A<u>B</u>X, J_{AB} = 12.0, J_{BX} = 7.6 Hz, CH$_a$<u>H</u>$_b$OH), 3.92 (1H, <u>A</u>BX, J_{AB} = 12.0, J_{AX} = 3.2 Hz, C<u>H</u>$_a$H$_b$OH), 4.05 (2H, d, *J* = 4.4 Hz, C<u>H</u>$_2$NH), 6.76 (1H, d, *J* = 8.0 Hz, Ar), 6.92 (1H, s, Ar), 6.95 (1H, d, *J* = 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.9, 21.5, 26.5, 35.9, 58.6, 58.8, 70.4, 116.6, 119.1, 119.4, 130.1, 134.7, 158.4.

2.6.3 *N*-(2′-Hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-phenyl-propanol (115c)



N-(2′-Hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to the general procedure using phenol (47 mg, 0.5 mmol), (*S*)-phenylalaninol (76 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol), $NaBH_4$ (95 mg, 2.5 mmol) and TFA (198 μL, 2.5 mmol). The product was obtained as a white crystalline solid (84 mg, 62%); m.p. 63-65 °C; $[\alpha]^{24}_{D}$ = -35.5 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (3H, s, NC$\underline{H}_3$), 2.60 (1H, A$\underline{B}$X, J_{AB} = 13.6, J_{BX} = 9.2 Hz, $CH_a\underline{H}_bPh$), 2.98 (1H, $\underline{A}$BX, J_{AB} = 13.6, J_{AX} = 4.8 Hz, C$\underline{H}_aH_bPh$), 3.19 (1H, m, C$\underline{H}$NH), 3.71 (2H, m, C$\underline{H}_2$OH), 3.88 (1H, A$\underline{B}$, *J* = 13.6 Hz, $CH_a\underline{H}_bN$), 4.01 (1H, A$\underline{B}$, *J* = 13.6 Hz, $CH_a\underline{H}_bNH$), 6.83 (2H, m, Ar), 7.01 (1H, d, *J* = 8.0 Hz, Ar), 7.20 (2H, m, Ar), 7.27 (2H, m, Ar), 7.34 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.7, 35.7, 57.9, 60.9, 66.2, 116.2, 119.2, 121.9, 126.5, 128.7, 128.8, 128.9, 129.0, 129.1, 138.9, 157.7; Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.29; H, 7.90; N, 4.88 %.

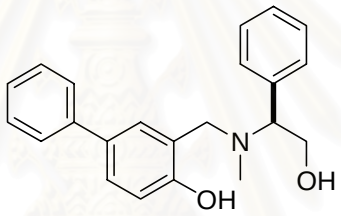
2.6.4 *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3,3-dimethyl-butanol (115d)



N-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3,3-dimethyl-butanol was prepared according to the general procedure using 2,4-di-*tert*-

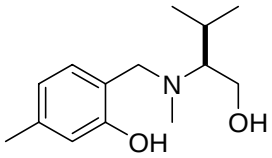
butylphenol (103 mg, 0.5 mmol), (*S*)-*tert*-leucinol (59 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol), $NaBH_4$ (95 mg, 2.5 mmol) and TFA (198 μL, 2.5 mmol).The product was obtained as colorless oil (63 mg, 60%); $[\alpha]^{24}_D$ = +8.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.08 (9H, s, C(C$\underline{H}_3$)$_3$), 1.32 (9H, s, C(C$\underline{H}_3$)$_3$), 1.47 (9H, s, C(C$\underline{H}_3$)$_3$), 2.49 (3H, s, NC$\underline{H}_3$), 2.71 (1H, AB$\underline{X}$, J_{AX} = 3.6, J_{BX} = 11.6 Hz, C$\underline{H}$C(CH$_3$)$_3$), 4.02 (1H, A$\underline{B}$X, J_{AB} = 11.6, J_{BX} = 3.6 Hz, CH$_a\underline{H}_b$OH), 4.10 (1H, $\underline{A}$BX, J_{AB} = 11.6, J_{AX} = 6.4 Hz, C$\underline{H}_a$H$_b$OH), 4.14 (1H, A$\underline{B}$, *J* = 13.2 Hz, CH$_a\underline{H}_b$N), 4.21 (1H, $\underline{A}$B, *J* = 13.6 Hz, C$\underline{H}_a$H$_b$N), 6.91 (1H, s, Ar), 7.25 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.6, 29.6, 31.7, 34.2, 34.9, 35.2, 38.2, 60.2, 62.0, 73.3, 121.6, 122.7, 123.8, 135.3, 140.4, 154.3.

2.6.5 *N*-(2′-Hydroxy-5′-phenyphenyl)methyl-*N*-methyl-(*S*)-2-amino-2-phenyl-ethanol (115e)



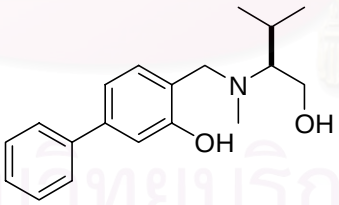
N-(2′-Hydroxy-5′-phenylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-phenyl-propanol was prepared according to the general procedure using 4-phenylphenol (85 mg, 0.5 mmol), (*S*)-phenylglycinol (69 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol), $NaBH_4$ (95 mg, 2.5 mmol) and TFA (198 μL, 2.5 mmol). The product was obtained as a white crystalline solid (70 mg, 60%); m.p. 136-138 °C; $[\alpha]^{24}_D$ = -96.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.33 (3H, s, NC$\underline{H}_3$), 3.76 (1H, A$\underline{B}$, *J* = 13.6 Hz, CH$_a\underline{H}_b$NH), 3.91 (1H, A$\underline{B}$, *J* = 13.6 Hz, CH$_a\underline{H}_b$NH), 3.96 (1H, AB$\underline{X}$, J_{AX} = 5.6, J_{BX} = 8.0 Hz, PhC$\underline{H}$N), 4.02 (1H, A$\underline{B}$X, J_{AB} = 11.2, J_{BX} = 5.4 Hz, CH$_a\underline{H}_b$OH), 4.23 (1H, $\underline{A}$BX, J_{AB} = 11.6, J_{AX} = 8.4 Hz, C$\underline{H}_a$H$_b$OH), 6.97 (1H, d, *J* = 8.4 Hz, Ar), 7.22 (1H, s, Ar), 7.33 (3H, m, Ar), 7.44 (5H, m, Ar), 7.55 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 37.4, 58.0, 62.1, 69.2, 115,9, 116.6, 122.0, 126.5, 126.6, 126.7, 127.4, 127.5, 128.5, 128.7, 129.1, 132.4, 134.9, 140.9, 157.4.

2.6.6 *N*-(2′-Hydroxy-5′-methylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol (115f)



N-(2′-Hydroxy-5′-methylpheny)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to the general procedure using 4-methylphenol (54 mg, 0.5 mmol), (*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol), $NaBH_4$ (95 mg, 2.5 mmol) and TFA (198 μL, 2.5 mmol). The product was obtained as colorless oil (51 mg, 57%); $[\alpha]^{24}_D$ = +12.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03 and 1.11 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 2.06 (1H, m, C$\underline{H}(CH_3)_2$), 2.32 (3H, s, C$\underline{H}_3$Ar), 2.39 (3H, s, NC$\underline{H}_3$), 2.58 (1H, m, C$\underline{H}$N), 3.88 (1H, A$\underline{B}$X, J_{AB} = 12.0, J_{BX} = 7.2 Hz, $CH_a\underline{H}_bOH$), 3.95 (1H, $\underline{A}$BX, J_{AB} = 11.6, J_{AX} = 3.2 Hz, C$\underline{H}_aH_bOH$), 4.02 (2H, s, C$\underline{H}_2$NH), 6.64 (1H, d, *J* = 7.2 Hz, Ar), 6.71 (1H, s, Ar), 6.91 (1H, d, *J* = 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1, 21.2, 21.4, 26.7, 35.9, 59.2, 70.3, 116.6, 118.6, 119.9, 128.6, 138.9, 157.2.

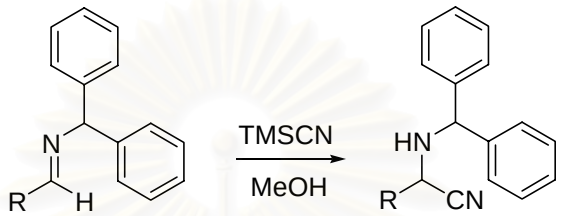
2.6.7 *N*-(2′-Hydroxy-4′-phenylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol (115g)



N-(2′-Hydroxy-4′-phenylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol was prepared according to the general procedure using 4-phenylphenol (85 mg, 0.5 mmol),(*S*)-valinol (52 mg, 0.5 mmol), paraformaldehyde (250 mg, 10 equiv), LiCl (22.0 mg, 0.5 mmol), $NaBH_4$ (95 mg, 2.5 mmol) and TFA (198 μL, 2.5 mmol). The product was obtained as a white crystalline solid (60 mg, 58%); m.p. 126-128 °C $[\alpha]^{24}_D$ = -11.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 and 1.13 (6H, 2×d, *J* = 6.8 Hz, 2×C$\underline{H}_3$), 2.06 (1H, m, C$\underline{H}(CH_3)_2$), 2.45 (3H, s, NC$\underline{H}_3$), 2.66 (1H, m, C$\underline{H}$N), 3.91 (1H, A$\underline{B}$X, J_{AB} = 11.6, J_{BX} = 7.2 Hz, $CH_a\underline{H}_bOH$), 3.98 (1H, $\underline{A}$BX, J_{AB} =

11.6, J_{AX} = 3.2 Hz, C$\underline{H}_a$H$_b$OH), 4.11 (2H, s, C$\underline{H}_2$NH), 7.06-7.15 (3H, m, Ar), 7.28 (1H, s, Ar), 7.36 (1H, m, Ar), 7.45 (1H, apparent t, J = 7.2 Hz, Ar), 7.61 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.2, 21.2, 21.5, 26.8, 36.0, 59.3, 70.5, 114.7, 118.0, 120.6, 127.0, 127.3, 128.7, 129.3, 140.8, 142.2, 158.0.

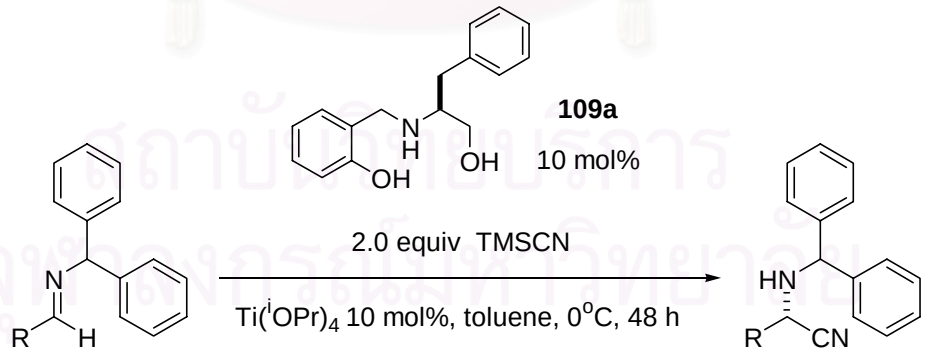
2.7 General procedure for the preparation of racemic 2-aminonitriles



72 **73**

An imine was dissolved in absolute methanol at room temperature. Then 1.5-2.0 equiv of trimethylsilyl cyanide was added with vigorous stirring. Upon completion of the reaction which is usually very rapid (4 hours), the organic solvent was removed by evaporation to obtain the desired product as racemic 2-aminonitriles.

2.8 General procedure for Ti-catalyzed addition of TMSCN to imines (small scale)

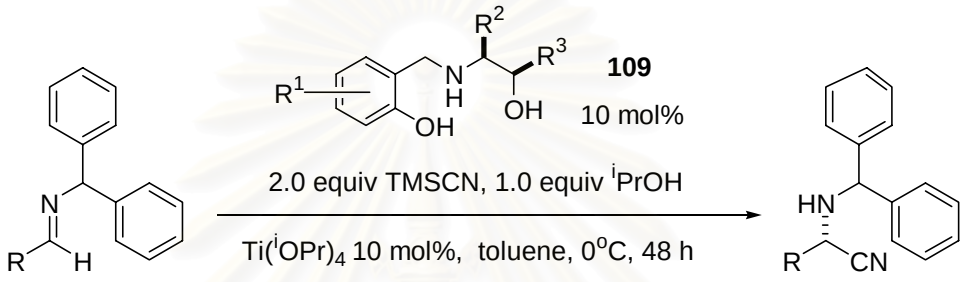


72 **73**

The chiral ligand **(109)** (0.02 mmol) was weighed into a dried NMR tube and dissolved with anhydrous toluene (0.3 mL). Ti(O^iPr)$_4$ (6.0 μL, 0.02 mmol) was added to the reaction and left for 10 minutes at ambient temperature to give a clear yellow

solution. The selected imine (0.2 mmol) was added and then cooled to 0 °C in ice-salt bath for 15 minutes. TMSCN (50 μL, 0.4 mmol) was then added using a syringe. After 48 hours at 0 °C, a sample for NMR was prepared by sampling from NMR tube. Toluene was removed by blowing with N_2. Percent conversion and enantioselectivity of the crude product was analyzed by ^{1}H NMR spectroscopy.

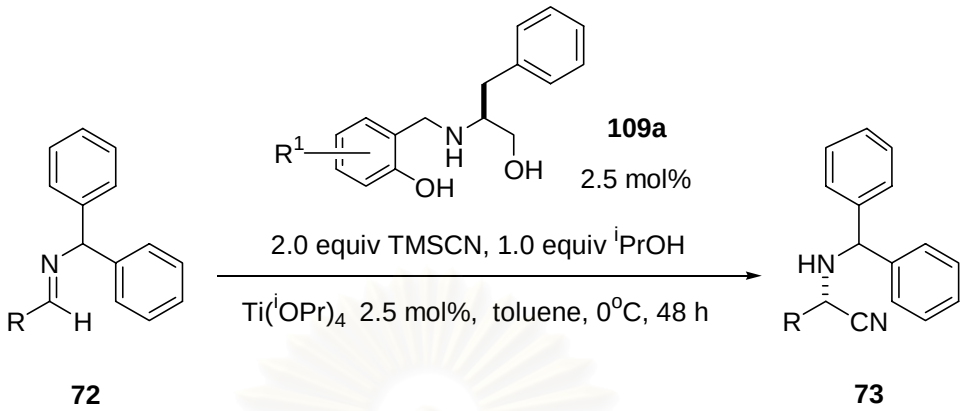
2.9 General procedure for Ti-catalyzed addition of TMSCN + 2-propanol to imines (small scale)



72 **73**

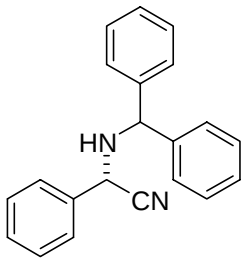
The chiral ligand **(109)** (0.02 mmol) was weighed into a dried NMR tube and dissolved with anhydrous toluene (0.3 mL). $Ti(O^iPr)_4$ (6.0 μL, 0.02 mmol) was added to the reaction and shook for 10 minutes at ambient temperature to give a clear yellow solution. 2-Propanol (15.3 μL, 1.0 mmol) was added and left for another 10 minutes. The selected imine (0.2 mmol) was added and then cooled to 0 °C in ice-salt bath for 15 minutes. TMSCN (50 μL, 0.4 mmol) was then added using syringe. After 48 hours, percent conversion and enantioselectivity was analyzed by ^{1}H NMR spectroscopy.

2.10 General procedure for Ti-catalyzed addition of TMSCN + 2-propanol to imine (large scale)



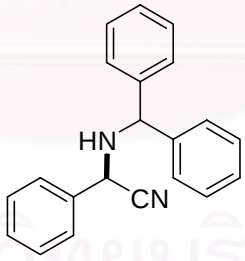
N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (*S*)-**(109a)** (6.43 mg, 0.025 mmol) was weighed in a dried screw-cap test tube and dissolved with anhydrous toluene (1.5 mL). $Ti(O^iPr)_4$ (7.44 μL, 0.025 mmol) was added to the reaction and left for 10 minutes at ambient temperature to give a clear yellow solution. 2-Propanol (76.5 μL, 1.0 mmol) was added by a syringe and left for another 10 minutes. The selected imine (1.0 mmol) was then added and cooled to 0 °C in ice-salt bath for 15 minutes. Finally, TMSCN (250 μL, 2.0 mmol) was quickly added in one portion using syringe. After 8 hours, toluene was removed *in vacuo* and the crude product was purified by passing through a plug of neutral alumina eluting with ethyl acetate-hexanes plus 0.1% triethylamine to yield the corresponding α-aminonitriles and analyzed for enantioselectivity by ^{1}H NMR spectroscopy.

2.10.1 (*S*)-Diphenylmethylamino-phenylacetonitrile (73a)



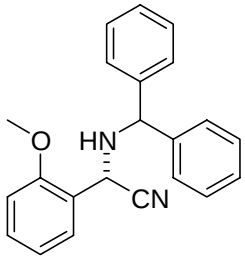
(*S*)-Diphenylmethylamino-phenylacetonitrile was prepared according to the general procedure using *N*-benzylidene diphenylmethylamine (271 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.257 g, 95%); m.p. 94-96 °C, 98% ee: $[\alpha]^{22}_{D}$ = -63.0 (*c* 1.0, $CHCl_3$) {lit.[156] $[\alpha]^{24}_{D}$ (97 % ee, *c* 5.0, $CHCl_3$) = -64.2}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.18 (1H, d, *J* = 12.0 Hz, NHCH), 4.63 (1H, d, *J* = 12.0 Hz, CHCN), 5.28 (1H, s, $CHPh_2$), 7.23-7.55 (11H, m, Ar), 7.60 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.4, 65.6, 118.8, 127.2, 127.3, 127.5, 127.8, 128.0, 128.8, 129.0, 129.1, 129.2, 135.0, 141.2, 142.8.

2.10.2 (*R*)-Diphenylmethylamino-phenylacetonitrile (73a)



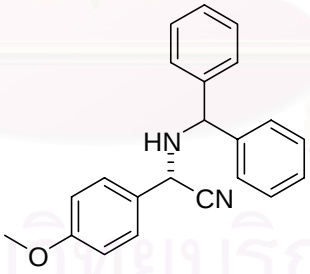
(*S*)-Diphenylmethylamino-phenylacetonitrile was prepared according to the general procedure using *N*-benzylidene diphenylmethylamine (271 mg, 1.0 mmol) and ligand (*R*)-**109a**. The product was obtained as a white crystalline solid (0.257 g, 95%); m.p. 94-96 °C, 98% ee: $[\alpha]^{22}_{D}$ = +63.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.15 (1H, d, *J* = 12.0 Hz, NHCH), 4.65 (1H, d, *J* = 12.0 Hz, CHCN), 5.29 (1H, s, $CHPh_2$), 7.21-7.52 (11H, m, Ar), 7.62 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.4, 65.6, 118.8, 127.2, 127.3, 127.5, 127.8, 128.0, 128.8, 129.0, 129.1, 129.2, 135.0, 141.2, 142.8.

2.10.3 (*S*)-Diphenylmethylamino-2-methoxyphenylacetonitrile (73b)



(*S*)-Diphenylmethylamino-2-methoxyphenylacetonitrile was prepared according to the general procedure using *N*-(2-methoxybenzylidene)diphenylmethyl-amine (301 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.253 g, 84%); m.p. 98-100 °C, 83% ee: $[\alpha]^{24}_{D}$ = -57.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 (3H, s, OC<u>H</u>$_3$), 4.71 (1H, s, C<u>H</u>CN), 5.23 (1H, s, C<u>H</u>Ph$_2$), 7.03 (2H, m, Ar), 7.28-7.43 (8H, m, Ar), 7.48 (2H, d, *J* = 7.6 Hz, Ar), 7.56 (2H, d, *J* = 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.6, 55.7, 65.4, 111.5, 119.2, 121.1, 123.5, 127.4, 127.6, 127.7, 127.8, 128.8, 128.9, 129.0, 130.7, 141.6, 143.0, 157.1.

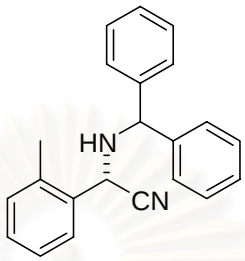
2.10.4 (*S*)-Diphenylmethylamino-4-methoxyphenylacetonitrile (73d)



(*S*)-Diphenylmethylamino-4-methoxyphenylacetonitrile was prepared according to the general procedure using *N*-(4-methoxybenzylidene)diphenylmethyl-amine (301 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.256 g, 85%); m.p. 102-103 °C, 91% ee; $[\alpha]^{24}_{D}$ = -38.0 (*c* 1.0, $CHCl_3$) {lit. [156] $[\alpha]^{22}_{D}$ (94 % ee, *c* 0.54, $CHCl_3$) = -27.7}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.94 (1H, d, *J* = 12.0 Hz, N<u>H</u>CH), 3.66 (3H, s, OC<u>H</u>$_3$), 4.39 (1H, d, *J* = 12.0 Hz, C<u>H</u>CN), 5.06 (1H, s, C<u>H</u>Ph$_2$), 6.78 (2H, d, *J* = 8.8 Hz, Ar) 7.02-7.22 (6H, m, Ar), 7.29 (4H, m, Ar),

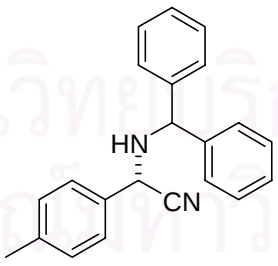
7.40 (2H, d, *J* = 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.9, 55.4, 65.6, 114.4, 119.1, 127.1, 127.2, 127.5, 127.7, 128.0, 128.6, 128.8, 129.1, 141.3, 142.9, 160.1.

2.10.5 (*S*)-Diphenylmethylamino-2-methylphenylacetonitrile (73e)



(*S*)-Diphenylmethylamino-2-methylphenylacetonitrile was prepared according to the general procedure using *N*-(2-methylbenzylidene)diphenylmethylamine (285 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.282 g, 99%); m.p. 106-108 °C, 98% ee: $[\alpha]^{24}_D$ = -161.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (1H, br, NHCH), 2.33 (3H, s, CH_3), 4.62 (1H, s, CHCN), 5.32 (1H, s, $CHPh_2$), 7.22-7.36 (7H, m, Ar), 7.40 (2H, m, Ar), 7.48 (2H, d, *J* = 7.2 Hz, Ar), 7.60 (3H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 50.4, 65.9, 118.9, 126.8, 127.1, 127.6, 127.7, 128.0, 128.2, 128.9, 129.0, 129.3, 131.2, 133.3, 136.6, 141.1, 142.9.

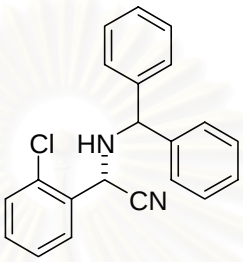
2.10.6 (*S*)-Diphenylmethylamino-4-methylphenylacetonitrile (73f)



(*S*)-Diphenylmethylamino-4-methylphenylacetonitrile was prepared according to the general procedure using *N*-(4-methylbenzylidene)diphenylmethylamine (285 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.276 g, 97%); m.p. 100-102 °C, >98% ee; $[\alpha]^{28}_D$ = -54.0 (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.16 (1H, br s, NHCH), 2.42 (1H, s, CH_3), 4.60 (1H, s, CHCN), 5.30 (1H, s,

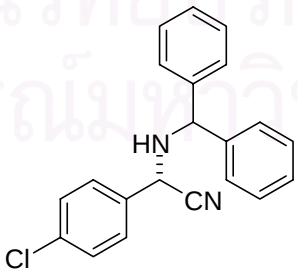
C<u>H</u>Ph_2), 7.26 (3H, d, *J* = 7.2 Hz, Ar), 7.34 (3H, d, *J* = 7.2 Hz, Ar) 7.37-7.52 (6H, m, Ar), 7.62 (2H, d, *J* = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 52.2, 65.6, 119.0, 127.1, 127.2, 127.5, 127.7, 128.0, 128.8, 129.1, 129.7, 132.0, 139.0, 141.2, 142.8.

2.10.7 (*S*)-Diphenylmethylamino-2-chlorophenylacetonitrile (73i)



(*S*)-Diphenylmethylamino-2-chlorophenylacetonitrile was prepared according to the general procedure using *N*-(2-chlorobenzylidene)diphenylmethylamine (305.5 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.300 g, 84%); m.p. 100-102 °C, >98% ee: $[\alpha]^{22}_D$ = -118.0 (*c* 1.0, $CHCl_3$) {lit.[156] $[\alpha]^{24}_D$ (>99 % ee, *c* 3.5, $CHCl_3$) = -122} ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.93 (1H, s, C<u>H</u>CN), 5.26 (1H, s, C<u>H</u>Ph_2), 7.22-7.42 (8H, m, Ar), 7.28 (2H, d, *J* = 7.2 Hz, Ar), 7.60 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.3, 65.8, 118.2, 127.2, 127.6, 127.7, 127.8, 128.0, 128.8, 128.9, 129.3, 130.4, 130.6, 132.8, 133.5, 140.7, 142.6.

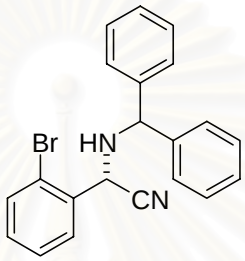
2.10.8 (*S*)-Diphenylmethylamino-4-chlorophenylacetonitrile (73j)



(*S*)-Diphenylmethylamino-4-chlorophenylacetonitrile was prepared according to the general procedure using *N*-(4-chlorobenzylidene)diphenylmethylamine (305.5 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.287 g, 94%);

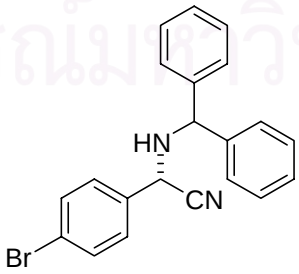
m.p. 105-107 °C, 98 % ee; $[\alpha]^{28}_D$ = -34.6 (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.12 (1H, br s, NHCH), 4.85 (1H, s, CHCN), 5.24 (1H, s, $CHPh_2$), 7.23-7.34 (4H, m, Ar), 7.39 (4H, m, Ar), 7.45 (2H, d, *J* = 7.2 Hz, Ar), 7.50 (2H, d, *J* = 8.4 Hz, Ar), 7.56 (2H, d, *J* = 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.8, 65.6, 118.4, 127.1, 127.4, 127.8, 128.0, 128.6, 128.8, 129.1, 129.2, 133.4, 135.1, 140.8, 142.5.

2.10.9 (*S*)-Diphenylmethylamino-2-bromophenylacetonitrile (73k)



(*S*)-Diphenylmethylamino-2-bromophenylacetonitrile was prepared according to the general procedure using *N*-(2-bromobenzylidene)diphenylmethylamine (350 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.340 g, 97%); m.p. 101-103 °C, >98% ee: $[\alpha]^{22}_D$ = -121.0 (*c* 1.0, $CHCl_3$) {lit.[156] $[\alpha]^{24}_D$ (>99 % ee, *c* 5.0, $CHCl_3$) = -122}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92 (1H, s, CHCN), 5.24 (1H, s, $CHPh_2$), 7.22-7.45 (8H, m, Ar), 7.50 (2H, d, *J* = 7.2 Hz, Ar), 7.58-7.68 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.6, 65.7, 118.3, 123.4, 127.2, 127.8, 127.9, 128.0, 128.3, 128.8, 128.9, 129.4, 130.8, 133.8, 134.5, 140.7, 142.6.

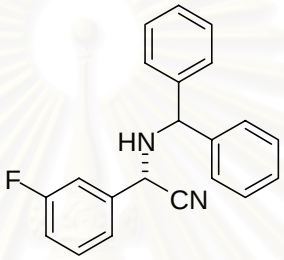
2.10.10 (*S*)-Diphenylmethylamino-4-bromophenylacetonitrile (73l)



(*S*)-Diphenylmethylamino-4-bromophenylacetonitrile was prepared according to the general procedure using *N*-(4-bromobenzylidene)diphenylmethylamine (350

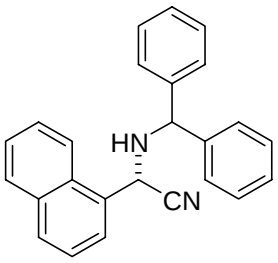
mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.343 g, 98%); m.p. 104-106 °C, 96% ee; $[\alpha]^{28}_{D}$ = -32.9 (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.21 (1H, br s, NHCH), 4.58 (1H, s, CHCN), 5.27 (1H, s, $CHPh_2$), 7.26-7.36 (4H, m, Ar) 7.42-7.50 (6H, m, Ar), 7.56-7.61 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.9, 65.6, 118.3, 123.2, 127.1, 127.5, 127.8, 128.1, 128.8, 128.9, 129.1, 132.2, 134.0, 140.9, 142.6.

2.10.11 (*S*)-Diphenylmethylamino-3-fluorophenylacetonitrile (73m)



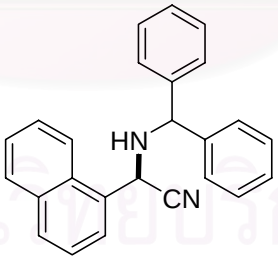
(*S*)-Diphenylmethylamino-3-fluorophenylacetonitrile was prepared according to the general procedure using *N*-(3-fluorobenzylidene)diphenylmethylamine (289.4 mg, 1.0 mmol). The product was obtained as colorless oil (0.286 g, 99%); 96% ee; $[\alpha]^{28}_{D}$ = -59.8 (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (1H, s, NHCH), 4.63 (1H, s, CHCN), 5.28 (1H, s, $CHPh_2$), 7.09 (1H, m, Ar) 7.25-7.44 (9H, m, Ar), 7.49 (2H, d, *J* = 7.6 Hz, Ar), 7.60 (2H, d, *J* = 7.6 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.9, 65.6, 114.4, 114.6 ($J_{13C\text{-}19F}$ = 22.9 Hz, Ar), 116.0, 116.2 ($J_{13C\text{-}19F}$ = 21.0 Hz, Ar), 118.3, 122.8, 127.1, 127.5, 127.8, 128.1, 128.9, 129.1, 130.6, 130.7 ($J_{13C\text{-}19F}$ = 8.2 Hz, Ar), 137.2, 137.3 ($J_{13C\text{-}19F}$ = 8.2 Hz, Ar), 140.9, 142.5, 161.7, 164.2 ($J_{13C\text{-}19F}$ = 246.2 Hz, Ar).

2.10.12 (*S*)-Diphenylmethylamino-1-naphthylacetonitrile (73n)



(*S*)-Diphenylmethylamino-1-naphthylacetonitrile was prepared according to the general procedure using *N*-(naphthalen-1-ylmethylene)diphenylmethylamine (321 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.316 g, 91%); m.p. 118-120 °C, >98% ee: $[\alpha]^{23}_{D}$ = -186.0 (*c* 1.0, $CHCl_3$) {lit.[24] $[\alpha]^{22}_{D}$ (>99 % ee, *c* 2.0, $CHCl_3$) = -182.2}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (1H, br, NHCH), 5.20 (1H, s, CHCN), 5.41 (1H, s, $CHPh_2$), 7.21-7.60 (11H, m, Ar), 7.66 (2H, d, *J* = 7.2 Hz, Ar), 7.82-7.91 (2H, m, Ar), 7.95 (2H, d, *J* = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.5, 66.1, 118.9, 123.1, 125.3, 125.9, 126.3, 126.9, 127.0, 127.7, 128.1, 128.3, 128.7, 128.9, 129.0, 130.2, 130.4, 130.6, 134.0, 141.1, 142.6.

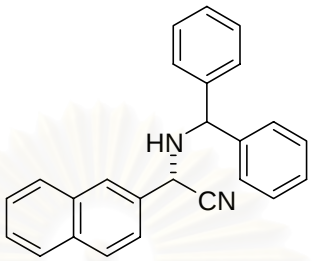
2.10.13 (*R*)-Diphenylmethylamino-1-naphthylacetonitrile (73n)



(*R*)-Diphenylmethylamino-1-naphthylacetonitrile was prepared according to the general procedure using *N*-(naphthalen-1-ylmethylene)diphenylmethylamine (321 mg, 1.0 mmol) and ligand (*R*)-**109a**. The product was obtained as a white crystalline solid (0.303 g, 89%); m.p. 118-120 °C, > 98% ee: $[\alpha]^{23}_{D}$ = +185.0 (*c* 1.0, $CHCl_3$) {lit.[24]}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.20 (1H, br, NHCH), 5.20 (1H, s, CHCN), 5.40 (1H, s, $CHPh_2$), 7.20-7.60 (11H, m, Ar), 7.64 (2H, d, *J* = 7.2 Hz, Ar), 7.82-7.90 (2H, m, Ar), 7.95 (2H, d, *J* = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.5, 66.1,

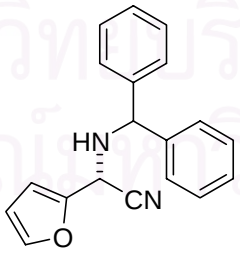
118.9, 123.2, 125.3, 125.9, 126.3, 126.9, 127.0, 127.7, 128.1, 128.3, 128.8, 128.9, 129.0, 130.2, 130.4, 130.7, 134.0, 141.1, 142.7.

2.10.14 (*S*)-Diphenylmethylamino-2-naphthylacetonitrile (73o)



(*S*)-Diphenylmethylamino-2-naphthylacetonitrile was prepared according to the general procedure using *N*-(naphthalen-1-ylmethylene)diphenylmethylamine (321 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.315 g, 98%); m.p. 126-128 °C, 96% ee: $[\alpha]^{28}_{D}$ = -12.4 (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.14 (1H, br, NHCH), 4.77 (1H, s, CHCN), 5.32 (1H, s, $CHPh_2$), 7.25 (1H, m, Ar), 7.33 (3H, m, Ar), 7.42 (2H, m, Ar), 7.49 (2H, d, *J* = 7.6 Hz, Ar), 7.54 (2H, m, Ar), 7.62 (3H, m, Ar), 7.88 (3H, m, Ar), 8.03 (1H, s, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.5, 65.7, 118.7, 124.8, 126.3, 126.8, 127.1, 127.5, 127.7, 128.0, 128.2, 128.8, 129.0, 129.1, 133.0, 133.4, 141.0, 142.6.

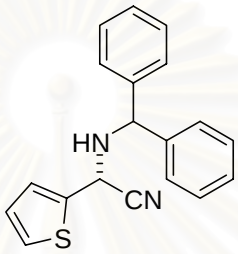
2.10.15 (*R*)-Diphenylmethylamino-furan-2-ylacetonitrile (73p)



(*S*)-Diphenylmethylamino-furan-2-ylacetonitrile was prepared according to the general procedure using *N*-(furan-2-ylmethylene)diphenylmethylamine (261 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.214 g, 82%); m.p. 99-101 °C, 91% ee: $[\alpha]^{21}_{D}$ = -25.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37

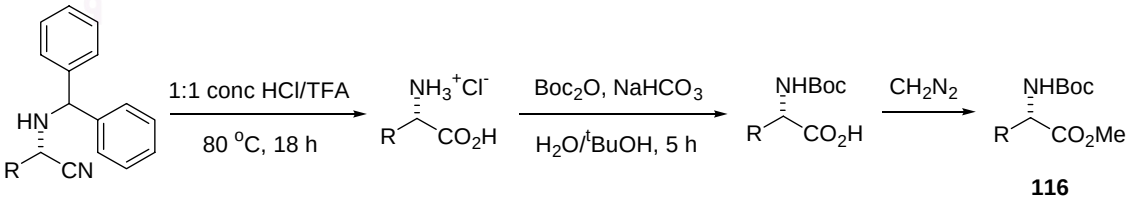
(1H, br, NHCH), 4.65 (1H, s, CHCN), 5.20 (1H, s, CHPh$_2$), 6.42 (1H, dd, *J* = 3.2 and 2.0 Hz, CH-furan), 6.49 (1H, d, *J* = 3.2 Hz, CH-furan), 7.24-7.42 (6H, m, Ar), 7.48 (3H, d, *J* = 7.6 Hz, CH-furan and Ar), 7.55 (2H, d, *J* = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.2, 65.2, 109.0, 110.7, 117.1, 127.3, 127.4, 127.9, 128.0, 128.9, 129.1, 140.9, 142.4. 143.7, 147.3.

2.10.16 (*R*)-Diphenylmethylamino-thiophen-2-ylacetonitrile (73q)



(*S*)-Diphenylmethylamino-thiophen-2-ylacetonitrile was prepared according to the general procedure using *N*-(furan-2-ylmethylene)diphenylmethylamine (277 mg, 1.0 mmol). The product was obtained as a white crystalline solid (0.239 g, 83%); m.p. 98-100 °C, 98% ee: $[\alpha]^{24}_D$ = -76.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22 (1H, d, *J* = 12.0 Hz, NHCH), 4.62 (1H, d, *J* = 12.0 Hz, CHCN), 5.08 (1H, s, CHPh$_2$), 6.84 (1H, dd, *J* = 5.2 and 3.6 Hz, CH-thiophene), 7.05-7.28 (8H, m, CH-thiophene and Ar), 7.30 (2H, d, *J* = 7.2 Hz, Ar), 7.40 (2H, d, *J* = 7.2 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.3, 65.5, 118.2, 126.2, 126.8, 127.0, 127.2, 127.4, 127.9, 128.2, 128.9, 129.2, 138.4, 140.9, 142.6.

2.11 General procedure for the preparation of *N*-Boc-arylglycine methyl ester derivatives



116

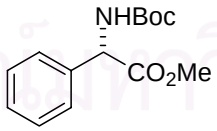
Step 1 The optically pure α-aminonitrile (0.5 mmol) was weighed into a dried screw-cap test tube. Then 1:1 mixture of concentrated aqueous HCl and trifluoroacetic

acid (2 mL/mmol) was added. The reaction mixture was heated at 80 °C for 18 hours. Upon the completion, the solvent was extraction with hexanes and then removed by evaporation to afford the crude products as hydrochloride salt.

Step 2 The mixture of crude arylglycine hydrochloride salt obtained from step 1 and 2 equiv of $NaHCO_3$ were dissolved in water (2 mL). The resulting mixture was stirred and 1.2 equiv of Boc_2O in ^tBuOH (2 mL) was added dropwise to prevent the heat. The homogeneous solution was vigorously stirred for 5 hours. Upon completion, of the reaction, the solvent was removed under reduced pressure. The solution was acidified to pH = 2 and extracted with ethyl acetate (3 × 10 mL). The organic phase was combined, dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was used for the next step without further purification.

Step 3 *N*-Methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) [175] (250 mg, 1 mmol of diazald provided diazomethane 3 mmol) was dissolved with absolute ethanol 6 mL in test tube with a side-arm directly connected to N_2 line. Diazomethane was generated from a solution of diazald in ethanol by slow addition of sodium hydroxide in water (10.0 M) dropwise at room temperature. Diazomethane was liberated and carried into the solution of the crude *N*-Boc-arylglycine dissolved in ethyl acetate by a steam of N_2 gas. Upon completion of the reaction (monitored by TLC or permanent color changed), the organic solvent was removed by evaporation. The crude product was purified by flash column chromatography using hexanes and ethyl acetate as eluent.

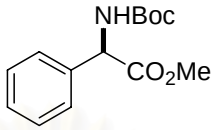
2.11.1 *N*-Boc-(*S*)-phenylglycine methyl ester (116a)



(*S*)-*N*-Boc-phenylglycine methyl ester was prepared according to the general procedure The product was obtained as a white crystalline solid (123.3 mg, 92%); 93% ee analyzed by chiral HPLC: $[\alpha]^{28}_D$ = +120.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (9H, s, $C(C\underline{H}_3)_3$), 3.72 (3H, s, $OC\underline{H}_3$), 5.31 (1H, d, *J* = 7.2 Hz,

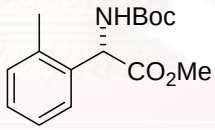
C<u>H</u>CO_2Me), 5.55 (1H, d, *J* = 5.2 Hz, N<u>H</u>Boc), 7.33 (5H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.7, 57.6, 80.2, 127.1, 128.4, 128.9, 136.8, 154.8, 171.7.

2.11.2 *N*-Boc-(*R*)-phenylglycine methyl ester (116a)



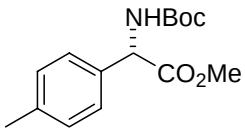
(*R*)-*N*-Boc-phenylglycine methyl ester was prepared according to the general procedure The product was obtained as a white crystalline solid (122.1 mg, 89%); 93% ee analyzed by chiral HPLC: $[\alpha]^{28}_D$ = -120.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 5.33 (1H, d, *J* = 7.2 Hz, C<u>H</u>CO_2Me), 5.55 (1H, d, *J* = 5.6 Hz, N<u>H</u>Boc), 7.35 (5H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.7, 57.7, 80.2, 127.1, 128.4, 128.8, 136.8, 154.8, 171.5.

2.11.3 *N*-Boc-(*S*)-2-methylphenylglycine methyl ester (116e)



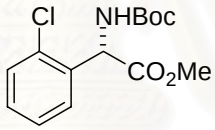
N-Boc-(*S*)-2-methylphenylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (107.6 mg, 76%); 95% ee analyzed by chiral HPLC: $[\alpha]^{28}_D$ = +132.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.47 (3H, s, ArC<u>H</u>$_3$), 3.71 (3H, s, OC<u>H</u>$_3$), 5.43 (1H, d, *J* = 6.4 Hz, C<u>H</u>CO_2Me), 5.54 (1H, d, *J* = 7.6 Hz, N<u>H</u>Boc), 7.19 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 28.3, 52.6, 54.2, 80.1, 126.3, 126.5, 128.4, 130.9, 135.4, 136.7, 154.9, 172.2.

2.11.4 *N*-Boc-(*S*)-4-methylphenylglycine methyl ester (116f)



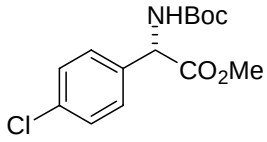
N-Boc-(*S*)-4-methylphenylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (83.3 mg, 60%); 93% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = +129.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.33 (3H, s, ArC<u>H</u>$_3$), 3.71 (3H, s, OC<u>H</u>$_3$), 5.27 (1H, d, *J* = 6.8 Hz, C<u>H</u>CO_2Me), 5.50 (1H, d, *J* = 5.2 Hz, N<u>H</u>Boc), 7.15 (2H, d, *J* = 8.0 Hz, Ar), 7.24 (2H, d, *J* = 8.0 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 28.3, 52.6, 57.3, 80.1, 127.0, 129.7, 133.9, 138.3, 154.8, 171.8.

2.11.5 *N*-Boc-(*S*)-2-chlorophenylglycine methyl ester (116i)



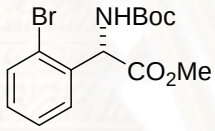
N-Boc-(*S*)-2-chlorophenylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (125.5 mg, 85%); 91% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = +117.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 5.68 (2H, m, C<u>H</u>CO_2Me and N<u>H</u>Boc), 7.26 (2H, m, Ar), 7.37 (2H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.9, 55.6, 80.3, 127.2, 129.6, 129.8, 130.1, 133.6, 135.2, 154.8, 171.1.

2.11.6 *N*-Boc-(*S*)-4-chlorophenylglycine methyl ester (116j)



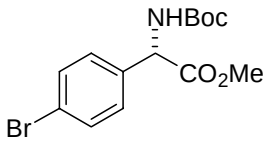
N-Boc-(*S*)-4-chlorophenylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (129.0 mg, 86%); 94% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = +102.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.71 (3H, s, OC<u>H</u>$_3$), 5.28 (1H, d, *J* = 6.8 Hz, C<u>H</u>CO_2Me), 5.62 (1H, d, *J* = 5.6 Hz, N<u>H</u>Boc), 7.31 (4H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.9, 56.9, 80.4, 128.4, 129.0, 134.3, 135.6, 154.7, 171.2.

2.11.7 *N*-Boc-(*S*)-2-bromophenylglycine methyl ester (116k)



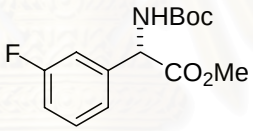
N-Boc-(*S*)-2-bromophenylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (152.4 mg, 87%); 93% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = +95.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.72 (3H, s, OC<u>H</u>$_3$), 5.65 (1H, d, *J* = 5.6 Hz, C<u>H</u>CO_2Me), 5.70 (1H, d, *J* = 7.2 Hz, N<u>H</u>Boc), 7.18 (1H, m, Ar), 7.27-7.34 (2H, m, Ar), 7.57 (1H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.9, 57.5, 80.3, 123.7, 127.9, 129.7, 129.8, 133.5, 136.8, 154.8, 171.1.

2.11.8 *N*-Boc-(*S*)-4-bromophenylglycine methyl ester (116l)



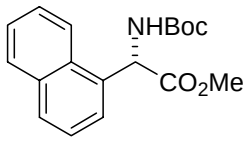
N-Boc-(*S*)-4-bromophenylglycine methyl ester was prepared according to the general procedure The product was obtained as a white crystalline solid (144.0 mg, 81%); No separation by chiral HPLC: $[\alpha]^{28}_{D}$ = +102.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.71 (3H, s, OC<u>H</u>$_3$), 5.27 (1H, d, *J* = 6.8 Hz, C<u>H</u>CO_2Me), 5.62 (1H, d, *J* = 5.6 Hz, N<u>H</u>Boc), 7.23 (2H, d, *J* = 8.4 Hz, Ar), 7.24 (2H, d, *J* = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.9, 56.9, 80.3, 122.5, 128.8, 132.0, 136.1, 154.7, 171.1.

2.11.9 *N*-Boc-(*S*)-3-fluorophenylglycine methyl ester (116m)



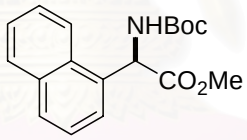
N-Boc-(*S*)-3-fluorophenylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (132.6 mg, 91%); 94% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = +89.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 5.32 (1H, d, *J* = 6.8 Hz, C<u>H</u>CO_2Me), 5.70 (1H, d, *J* = 4.8 Hz, N<u>H</u>Boc), 7.00 (1H, m, Ar), 7.07 (1H, d, *J* = 9.6 Hz, Ar), 7.15 (1H, d, *J* = 7.6 Hz, Ar), 7.32 (1H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.9, 57.1, 80.4, 114.0, 114.2 ($J_{13C\text{-}19F}$ = 22.3 Hz, Ar), 115.3, 115.5 ($J_{13C\text{-}19F}$ = 21.1 Hz, Ar), 122.8, 130.3, 130.4 ($J_{13C\text{-}19F}$ = 8.2 Hz, Ar), 139.4, 154.7, 161.7, 164.1 ($J_{13C\text{-}19F}$ = 250.0 Hz, Ar), 171.1.

2.11.10 *N*-Boc-(*S*)-1-naphthylglycine methyl ester (116n)



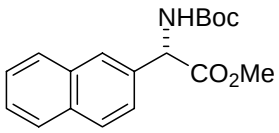
N-Boc-(*S*)-1-naphthylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (122.6 mg, 78%); 98% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = +160.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.72 (3H, s, OC<u>H</u>$_3$), 5.52 (1H, d, *J* = 6.8 Hz, C<u>H</u>CO_2Me), 6.07 (1H, d, *J* = 8.0 Hz, N<u>H</u>Boc), 7.44 (2H, m, Ar), 7.52 (1H, apparent t, *J* = 6.8 Hz, Ar), 7.59 (1H, apparent t, *J* = 7.6 Hz Ar), 7.86 (2H, m, Ar), 8.17 (1H, d, *J* = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.7, 54.7, 80.3, 123.3, 125.3, 125.5, 126.0, 127.0, 128.9, 129.3, 131.0, 132.8, 134.0, 155.0, 172.3.

2.11.11 *N*-Boc-(*R*)-1-naphthylglycine methyl ester (116n)



N-Boc-(*R*)-1-naphthylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (121.4 mg, 77%); 98% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = -160.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.72 (3H, s, OC<u>H</u>$_3$), 5.54 (1H, d, *J* = 6.8 Hz, C<u>H</u>CO_2Me), 6.05 (1H, d, *J* = 7.6 Hz, N<u>H</u>Boc), 7.43 (2H, m, Ar), 7.54 (1H, apparent t, *J* = 6.8 Hz, Ar), 7.60 (1H, apparent t, *J* = 7.6 Hz Ar), 7.86 (2H, m, Ar), 8.18 (1H, d, *J* = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.7, 54.7, 80.3, 123.5, 125.3, 125.5, 126.0, 127.0, 129.0, 129.3, 131.0, 132.8, 133.9, 155.0, 172.3.

2.11.12 *N*-Boc-(*S*)-2-naphthylglycine methyl ester (116o)



N-Boc-(*S*)-2-naphthylglycine methyl ester was prepared according to the general procedure The product was obtained as colorless oil (117.8 mg, 74%); 90% ee analyzed by chiral HPLC: $[\alpha]^{28}_{D}$ = +133.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.72 (3H, s, OC<u>H</u>$_3$), 5.48 (1H, d, *J* = 6.8 Hz, C<u>H</u>CO_2Me), 5.68 (1H, d, *J* = 6.4 Hz, N<u>H</u>Boc), 7.11 (1H, m, Ar), 7.48 (3H, m, Ar), 7.84 (3H, m, Ar); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3, 52.8, 57.7, 80.2, 124.6, 126.4, 126.5, 127.7, 128.0, 128.4, 128.8, 129.6, 133.1, 133.2, 154.8, 171.6.

2.12 Determination of enantiomeric excess and optical purity of α-aminonitriles and α-amino acids

2.12.1 ^{1}H-NMR spectroscopy (for α-aminonitriles)

Diastereomers may be distinguished in a chiral media by their NMR because certain resonances are chemical shift non-equivalent (anisochronous). Nevertheless, enantiomers cannot be distinguished in achiral medium by their NMR spectra because their resonances are chemical shift equivalent (isochronous).[174] Determination of enantiomeric excess using ^{1}H-NMR requires an intervension of a chiral auxiliary to convert the enantiomeric mixture into a mixture of diastereomers. The magnitude of the observed signals having the chemical shift non-equivalence should be sufficient to give baseline resolution so that an integration of the appropriate signals gives an accurate measurement of diastereomeric mixture. The three types of chiral auxiliaries commonly used are chiral derivatizing agents (CDAs) [127,176-177] forming discrete diastereomers *via* a covalent bond, chiral lanthanide shift reagents (CLSRs) [178] forming diastereomeric association complexes with enantiomeric substrate in solution and chiral solvating agents (CSAs) forming diastereomeric salvation complexes with the enantiomers *via* rapidly reversible equilibria in competition with the bulk solvent. (1*R*)-Camphor-10-sulfonic acid which is an effective CSAs has been used to

determine the enantiomeric excess of the optically active α-aminonitriles by ^{1}H NMR spectroscopy in $CDCl_3$.[179] The percent enantiomeric excess (enantiomeric purity) can be calculated by equation (1) by using the integrations of the compared peak areas of (*R*) and (*S*) enantiomers after base line was corrected and the minor isomer's peak area was adjusted to one.

$$\% ee = \frac{|R\text{-}S| \times 100}{|R+S|} \qquad (1)$$

% *ee* = percent enantiomeric excess
R = integration of *R* enantiomer
S = integration of *S* enantiomer

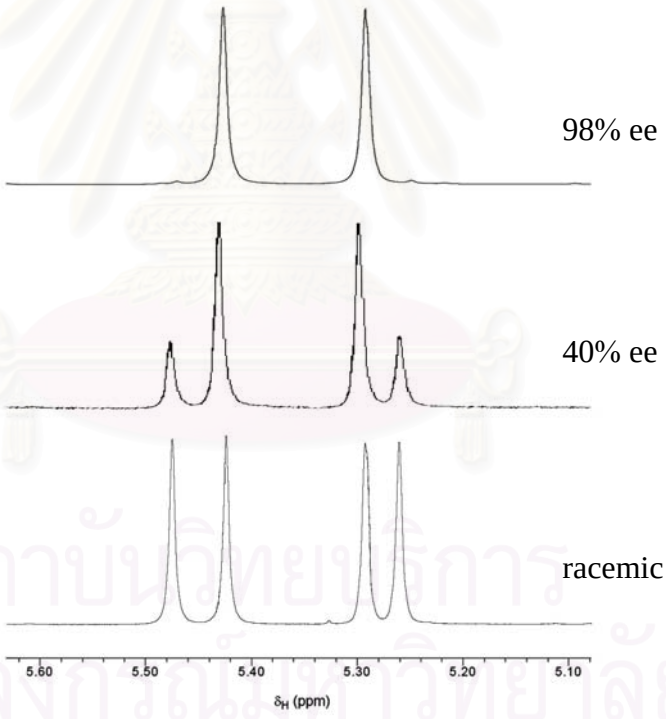


Figure 2.1 ^{1}H spectra of crude aminonitrile **(73a)** with different %ee

2.12.2 Normal phase chiral HPLC (for *N*-Boc-arylglycine methyl esters)

The separation of enantiomers by chiral HPLC has proven to be the most useful method for the analysis of chiral substances**.** Chiral HPLC columns are made by immobilizing single enantiomers onto the stationary phase. Resolution directly related to the efficiency of the chiral column relies on flow rate, pressure, particle size, and quality of packing and the formation of transient diastereoisomers on the surface of the column packing. The compound which forms the most stable diastereoisomer will be most retained, whereas the opposite enantiomer will form a less stable diastereoisomer and will elute first.[174]

A Daicel Chiralcel OD® column and a Chiralpak AD® column were selected for the enantiomeric separation of *N*-Boc-arylglycine methyl esters. Absolute configuration can be determined if the same sample with known configuration is available for reference. The percent enantiomeric excess (enntiomeric purity) can be calculated by equation (2) by using the peak areas of the (*R*) and (*S*) enantiomers.

$$\%\ ee = \frac{|A_R - A_S| \times 100}{|A_R + A_S|} \qquad (2)$$

% *ee* = percent enantiomeric excess

A_R = peak area of *R* enantiomer

A_S = peak area of *S* enantiomer

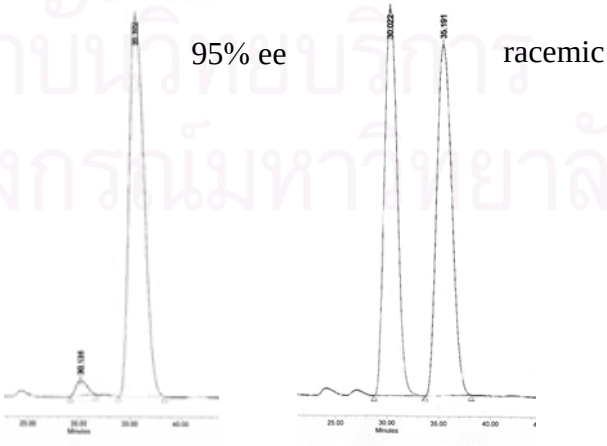


Figure 2.2 HPLC chromatograms of **116f** separated by a Daicel Chiralcel OD® column

2.12.3 Polarimetry (for α-aminonitriles and α-amino acids)

Optical rotation of chemical substance at a single wavelength is an important physical property for the study of a chiral system primarily because it allows one to make reference to the comparable data accumulated in the literatures. Samples containing an excess of one enantiomer of a chiral molecule can rotate the orientation of plane-polarized light. Such substances have optical activity. Measurement of this change in polarization orientation is called polarimetry, and the measuring instrument is called a polarimeter. These measurements are useful for checking the optical purity of chiral mixtures. A sample containing only one enantiomer of a chiral molecule is said to be optically pure. The enantiomer rotating light to the right, or clockwise when viewing in the direction of light propagation is called the dextrorotatory (d) or (+) enantiomer, and the enantiomer rotating light to the left, or counterclockwise, is called the levorotatory (l) or (-) enantiomer.[174]

Optical rotation occurs because optically active samples have different refractive indices for left- and right-circularly polarized light. When an optically active substance is present in the beam, it rotates the polarization of the light reaching the analyzer so that there is a component that reaches the detector. The angle that the analyzer must be rotated to return to the minimum detector signal is the optical rotation (α). The amount of optical rotation depends on the number of optically active species through which the light passes, and thus depends on both the sample path length (*l*, the length which the light travels through a sample) and the analyte concentration (*c*, how much of the sample is present that will rotate the light).[180]

Measuring and determining optical activity

When rotation is quantified using a polarimeter, it is known as an observed optical rotation. Whenever these effects are eliminated, a standard for comparison of all molecules is obtained as the specific rotation, [α], which is a physical property like the boiling point of a sample an can be calculated by equation (3) by using an observed optical rotation

$$[\alpha]^{t}_{\lambda} = \frac{\alpha \times 100}{c \times l} \qquad (3)$$

$[\alpha]$ = the specific optical rotation

t = temperature (Celsius)

λ = wave length of incident light (nm)

α = an observed optical rotation

l = cell path length (dm)

c = analyte concentration expressed as g sample /100 cm^3 of solvent

Determining optical purity

The optical purity or the enantiomeric excess (% ee) of a sample can be calculated by equation (4)

$$\text{Optical purity} = \frac{[\alpha]_{\text{mixture}} \times 100}{[\alpha]_{\text{pure sample}}} \qquad (4)$$

$[\alpha]_{\text{mixture}}$ = the specific optical rotation of mixture

$[\alpha]_{\text{pure sample}}$ = the specific optical rotation of pure sample

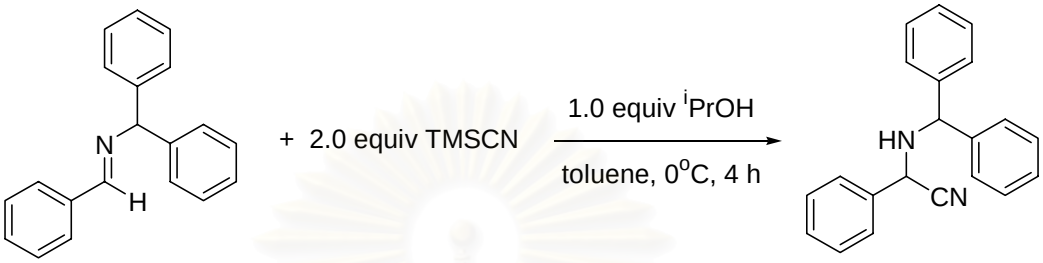
2.13 Study of the role of protic additives

N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (*S*)-**(109a)** (5.14 mg, 0.02 mmol) was weighed into a dried NMR tube and dissolved with anhydrous toluene (0.3 mL). $Ti(O^{i}Pr)_4$ (6.0 μL, 0.02 mmol) was added to the reaction and left for 10 minutes at ambient temperature to give a clear yellow solution. 2-Propanol (0, 7.65, 15.3 or 150.3 μL), (0, 0.2, 1.0 or 10 mmol) was added and left for another 10 minutes. The *N*-benzylidene diphenymethylamine (54.2 mg, 0.2 mmol) was added and then cooled to 0 °C in ice-salt bath for 15 minutes. TMSCN (50 μL, 0.4 mmol) was then added using syringe. The reaction mixture was sampled every hour. Percent conversion and enantioselectivity was analyzed by ^{1}H-NMR spectroscopy at 1 hour intervals.

2.14 Study of the composition of catalyst system

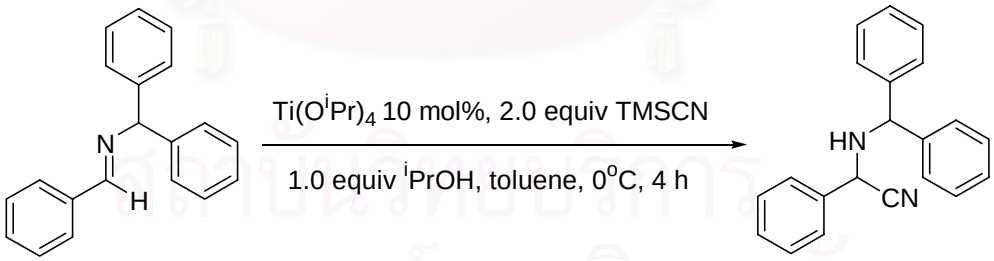
The different four Strecker reactions were carried out as follows:

2.14.1 The Strecker reaction without chiral catalyst



The *N*-benzylidene diphenylmethylamine (54.2 mg, 0.2 mmol) was weighed into a dried NMR tube and dissolved with anhydrous toluene (0.3 mL). 2-Propanol (15.3 μL, 1.0 mmol) was added and then cooled to 0 °C in ice-salt bath for 15 minutes. TMSCN (50 μL, 0.4 mmol) was then added using syringe. The reaction mixture was sampled every hour. Percent conversion and enantioselectivity was analyzed by ^{1}H NMR spectroscopy at 1 hour intervals.

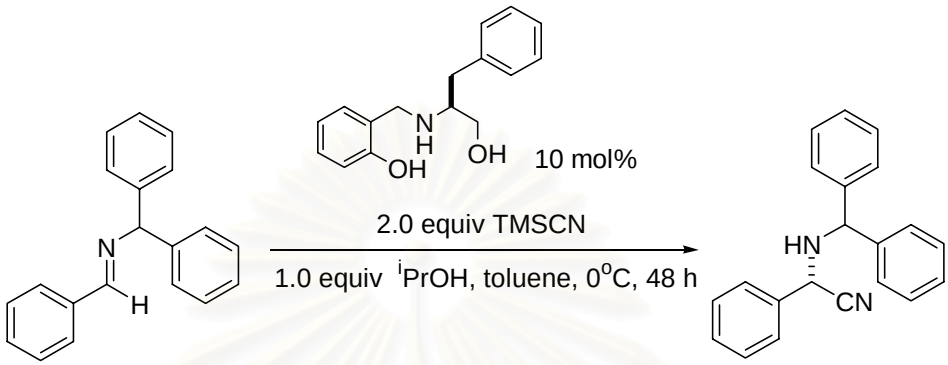
2.14.2 The Strecker reaction with only Ti(O^{i}Pr)$_4$



The *N*-benzylidene diphenylmethylamine (54.2 mg, 0.2 mmol) was weighed into a dried NMR tube and dissolved with anhydrous toluene (0.3 mL). Ti(O^{i}Pr)$_4$ (6.0 μL, 0.02 mmol) was then added to the reaction and left for 10 minutes at ambient temperature. 2-Propanol (15.3 μL, 1.0 mmol) was added and left for another 10 minutes. The reaction mixture was cooled to 0 °C in ice-salt bath for 15 minutes. TMSCN (50 μL, 0.4 mmol) was then added using syringe. The reaction mixture was

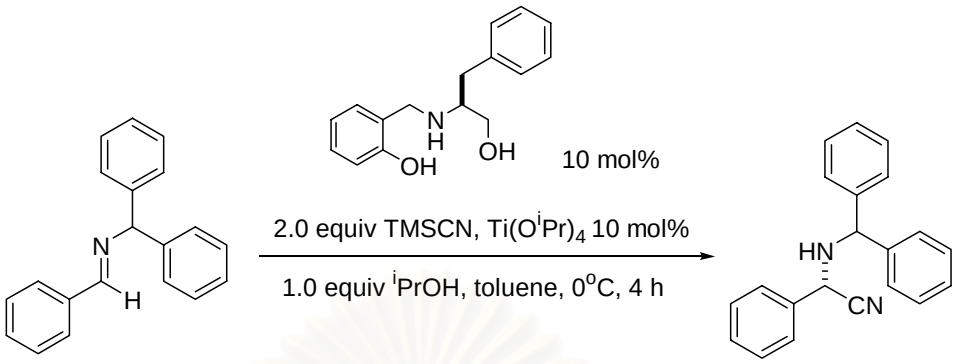
sampled every hour. Percent conversion and enantioselectivity was analyzed by ^{1}H NMR spectroscopy at 1 hour intervals.

2.14.3 The Strecker reaction with chiral ligand only



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (*S*)-**(109a)** (5.14 mg, 0.02 mmol) was weighed into a dried NMR tube and dissolved with anhydrous toluene (0.3 mL). 2-Propanol (15.3 μL, 1.0 mmol) was added and left for another 10 minutes. The *N*-benzylidene diphenylmethylamine (54.2 mg, 0.2 mmol) was added and then cooled to 0 °C in ice-salt bath for 15 minutes. TMSCN (50 μL, 0.4 mmol) was then added using syringe. The reaction mixture was sampled every hour. Percent conversion and enantioselectivity was analyzed by ^{1}H NMR spectroscopy at 1 hour intervals.

2.14.4 The Strecker reaction with $Ti(O^iPr)_4$ and chiral ligand



N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (*S*)-**(109a)** (5.14 mg, 0.02 mmol) was weighed into a dried NMR tube and dissolved with anhydrous toluene (0.3 mL). $Ti(O^iPr)_4$ (6.0 μL, 0.02 mmol) was added to the reaction and shook for 10 minutes at ambient temperature to give a clear yellow solution. 2-Propanol (15.3 μL, 1.0 mmol) was added and left for another 10 minutes. The *N*-benzylidene diphenylmethylamine (54.2 mg, 0.2 mmol) was added and then cooled to 0 °C in ice-salt bath for 15 minutes. TMSCN (50 μL, 0.4 mmol) was then added using syringe. The reaction mixture was sampled every hour. Percent conversion and enantioselectivity was analyzed by ^{1}H-NMR spectroscopy at 1 hour intervals.

2.15 Study of nonlinear effects

A mixture of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (*S*)-**(109a)** and of *N*-(2′-hydroxyphenyl)methyl-(*R*)-2-amino-3-phenyl-propanol (*R*)-**(109a)** (12.85 mg, 0.05 mmol) was weighed in a dried screw-cap test tube and dissolved with anhydrous toluene (1.5 mL). $Ti(O^iPr)_4$ (14.95 μL, 0.05 mmol) was added to the reaction and left for 10 minutes at ambient temperature to give a clear yellow solution. 2-Propanol (38.25 μL, 0.5 mmol) was added and left for another 10 minutes. The *N*-benzylidene diphenylmethylamine (135.5 mg, 0.5 mmol) was then added and cooled to 0 °C in ice-salt bath for 15 minutes. Finally, TMSCN (125 μL, 1.0 mmol) was quickly added in one portion using syringe. After 8 hours, percent conversion and enantioselectivity was analyzed by ^{1}H NMR spectroscopy. Upon the completion, toluene was removed *in vacuo* and the crude product was purified by passing through a plug of neutral alumina eluting with ethyl acetate-hexanes plus

0.1% triethylamine to yield the corresponding α-aminonitriles and analyzed again for enantioselectivity by ^{1}H NMR spectroscopy. All data were recorded and plotted the graph showing the relation between % ee of product and % ee of chiral ligand.

Table 2.1 % Ee, ratio and weight of ligand *S*:*R* for the study of nonlinear effect

% Ee	**Ratio of ligand *S*:*R***	**Weight of ligand *S*:*R* (mg)**
0	1:1	6.43:6.43
10	1.22:1	7.06:5.79
25	1.67:1	8.04:4.81
50	3:1	9.64:3.21
75	7:1	11.25:1.60
100	1:0	12.85:0

2.16 Study of % catalyst loading

N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol (1.29, 2.57, 3.21, 6.43 or 12.85 mg; 1.0, 2.0, 2.5, 5.0 or 10 mol% respectively) was weighed in a dried screw-cap test tube and dissolved with anhydrous toluene (1.5 mL). $Ti(O^{i}Pr)_4$ (14.95 μL, 0.05 mmol) was added to the reaction and shook for 10 minutes at ambient temperature to give a clear yellow solution. 2-Propanol (38.25 μL, 0.5 mmol) was added and left for another 10 minutes. The *N*-benzylidene diphenylmethylamine (135.5 mg, 0.5 mmol) was then added and cooled to 0 °C in ice-salt bath for 15 minutes. Finally, TMSCN (125 μL, 1.0 mmol) was quickly added in one portion using syringe. After 8 hours, toluene was removed *in vacuo* and the crude product was purified by passing through a plug of neutral alumina eluting with ethyl acetate-hexanes plus 0.1% triethylamine to yield the corresponding α-aminonitriles and analyzed for enantioselectivity by ^{1}H-NMR spectroscopy.

2.17 Measurement of kinetic racemization of α-aminonitriles

2.17.1 Conditions for racemization

(*S*)-Diphenylmethylamino-phenylacetonitrile 70% ee (20 mg) was dissolved in 2 mL volumetric flask with the several solvents as follows:

1. MeOH	4. MeOH + 10 μL NEt_3	7. THF+ 10 μL NEt_3
2. MeOH + 10 μL CH_3COOH	5. THF	8. CH_3COOH
3. MeOH +10 μL conc.HCl	6. THF + 10 μL TFA	9. 1,1,1-trifluoroethanol

The optical rotations were measured every 30 minutes at the ambient temperature (28 °C) with Jasco P-1010 Polarimeter with a period of 3 hours. The optical rotation values were recorded and plotted against time.

2.17.2 Electronic effect on substrate structure

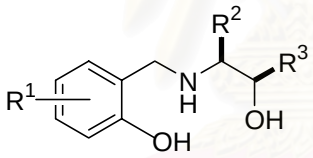
(*S*)-Diphenylmethylamino-phenylacetonitrile 70% ee, (*S*)-diphenylmethyl amino-4-chlorophenylacetonitrile 90% ee or (*S*)-diphenylmethylamino-4-methoxyphenyl acetonitrile 80% ee (20 mg) was dissolved in 2 mL volumetric flask with MeOH or MeOH + 10 μL conc.HCl. The optical rotations were measured every 30 minutes at the ambient temperature (28 °C) with Jasco P-1010 Polarimeter with a period of 3 hours. The optical rotation values were recorded and plotted against time.

CHAPTER III

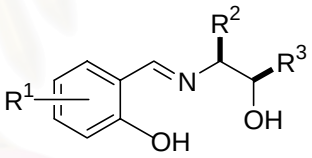
RESULTS AND DISSCUSSION

3.1 Design of the ligand

Asymmetry is one of the most important aspects of nature. Chiral molecules play essential roles in physiological process. In the last few decades, brilliant achievements have been made to synthesize optically pure or enantiomer-enriched products by employing specific ligand-metal complexes, as a remarkable consequence of the coordination chemistry of transition metals,[181] to catalyze or promote some asymmetric reactions. Titanium compounds, in the presence of chiral ligands, has been extensively applied to asymmetric synthesis as chiral Lewis acid.[182-183]



(109)



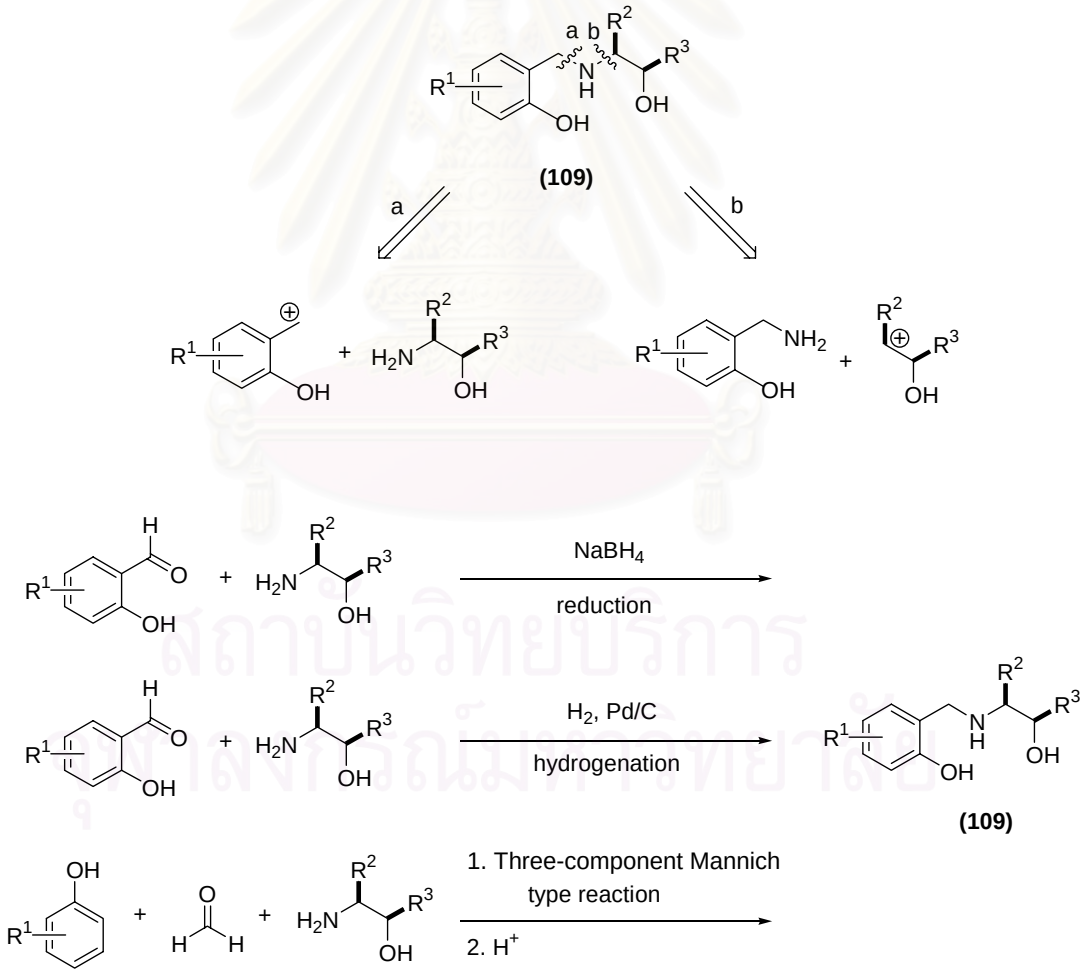
(117)

The chiral ligands we are interested would be small molecules possessing as few stereogenic centers as possible. Good reactivity and enantioselectivity should be obtained when those ligands complexed with metal ion to form the effective catalysts. The tridentate *N*-salicyl-β-aminoalcohol **(109)** and its parent Schiff base **(117)** should form chelating complexes with metal ions such as titanium or aluminium. These complexes should behave as Lewis acids whilst providing a rigid asymmetric environment and, therefore, be potentially useful for catalyzing various types of asymmetric reactions. In decades, these ligands, **(109)** and **(117)**, have become interesting and there also have been several reports about the use of this type of catalyst in, for instance, the Michael addition, [169] cyanohydrin formation, [98] and Strecker reaction.[167] However, the chiral *N*-salicyl-β-aminoalcohol **(109)**

complexes, which are small molecule catalysts possessing only one stereogenic center, still appear to be a promising ligands for catalytic asymmetric reaction that has not yet been studied and utilized extensively enough.

3.2 Synthesis of novel chiral ligands

Although many disconnections are possible, the disconnection at the benzylic C-N bond appears to be the most convenient since β-aminoalcohols are readily available (e.g. by reduction of α-amino acids). On the other hand, disconnection between the chiral C-N bond are not ideal because the bond formation must be stereocontrolled and the substrates are not quite as readily available. In this work, we shall focus only disconnation via route a (Scheme 3.1).

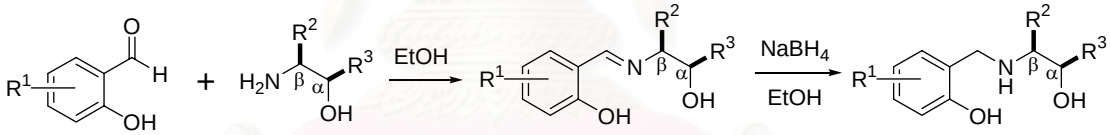


Scheme 3.1 Retrosynthesis of the tridentate *N*-salicyl-β-aminoalcohols **(109)** by disconnection

Regarding to benzylic C-N disconnection, reactive alkylation of β-aminoalcohols via Schiff base **(114)** is usually the method of choice and indeed is the only method available in the literature.[170] The reducing agents used include $LiAlH_4$, BH_3, $ZnBH_4$, $NaBH_4$ and dibutylchlorotin hydride-HMPA. It is also possible to start from a Schiff base of amino acids or ester and use strong reducing agent such as $LiAlH_4$ to effect both reduction of the Schiff base and the ester simultaneously. We began the synthesis of the ligand in this way using the readily available $NaBH_4$ as a reducing agent (Method A, title 3.2.1). Later we have developed a related reductive alkylation using catalytic hydrogenation (Method B, title 3.2.2). Ultimately, we have developed a novel three component Mannich type reaction between phenol, formaldehyde and β-aminoalcohols routing to the ligand **(109)** (Method C, title 3.2.3). Details of each method will be disclosed in details as follows:

3.2.1 Synthesis of novel chiral ligands by $NaBH_4$ reduction (Method A)

Table 3.1 Structure and yield of the ligands synthesized by $NaBH_4$ reduction



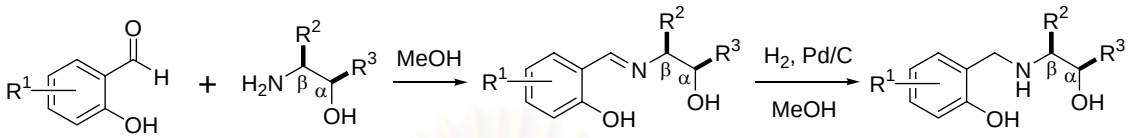
(109)

Entry	Ligand	Amino alcohols	R^1	R^2 (β)	R^3 (α)	Yield (%)
1	(*S*)-**109a**	(*S*)-phenylalaninol	H	$PhCH_2$	H	74
2	(*R*)-**109a**	(*R*)-phenylalaninol	H	$PhCH_2$	H	72
3	(*S*)-**109b**	(*S*)-alaninol	H	Me	H	51
4	(*S*)-**109c**	(*S*)-valinol	H	^{i}Pr	H	75
5	(*S*)-**109d**	(*S*)-*tert*-leucinol	H	^{t}Bu	H	74
6	(*S*)-**109e**	(*S*)-phenylglycinol	H	Ph	H	73
7	(*S*)-**109f**	(*S*)-leucinol	H	^{i}Bu	H	50
8	(*S*)-**109g**	(*S*)-cyclohexyl-alaninol	H	$^{c}HexCH_2$	H	71
9	(*S*)-**109h**	(*S,S*)-isoleucinol	H	^{sec}Bu	H	74
10	(*R*)-**109i**	(*R*)-1-aminopropan-2-ol	H	H	CH_3	49

A series of *N*-salicyl-β-aminoalcohol ligand **(109)** were synthesized by reduction of the salicylimines prepared *in situ* from the corresponding β-aminoalcohol and salicylaldehyde.[167,170] By this method, imines derived from β-aminoalcohols and salicyaldehyde derivatives which are commercially available and inexpensive were initially formed in alcoholic solvent as ethanol. It was supposed that the alcoholic solvent provides a driving force for the forward reaction by protonation of imine initially formed and also increase solubility of $NaBH_4$.[184] Then the imine C=N bond was reduced to C-N bond by $NaBH_4$ via a nucleophilic addition. After work up and purification by column chromatography, the ligands **109a-i** were obtained in poor to moderate yields (50-75% in Table 3.1). Some ligands **(109a**, **109b**, **109e**, **109g** and **109h)** are stable white crystalline solids which can be kept for years at room temperature (30 ^{o}C) without detectable degradation. The important disadvantages of this method is the requirement for an extraction step in which the yield is lost to a considerable extent. Another disadvantage is the limited variety of aldehydes. Because ring-substituted salicylaldehyde derivatives are not always commercially available, variation at the salicyl moiety is quite limited.

3.2.2 Synthesis of novel chiral ligands by catalytic hydrogenation (Method B)

Table 3.2 Structure and yield of the ligands synthesized by catalytic hydrogenation



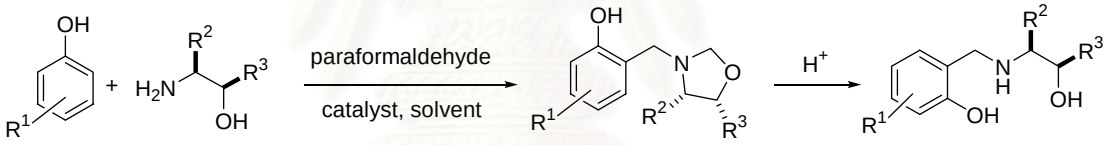
(109)

Entry	Ligand	Amino alcohols	R^1	R^2 (β)	R^3 (α)	Yield (%)
1	(*S*)-**109a**	(*S*)-phenylalaninol	H	$PhCH_2$	H	83
2	(*R*)-**109a**	(*R*)-phenylalaninol	H	$PhCH_2$	H	81
3	(*S*)-**109c**	(*S*)-valinol	H	^{i}Pr	H	75
4	(*S*)-**109d**	(*S*)-*tert*-leucinol	H	^{t}Bu	H	78
6	(*S*)-**109e**	(*S*)-phenylglycinol	H	Ph	H	74

The same series of *N*-salicyl-β-aminoalcohol ligand **(109)** were also synthesized by hydrogenation of the salicylimines over palladium catalyst.[171-172] By this method, hydrogen atoms were concomitantly added to C=N bond of imine. The reaction occurred at the surface of paladium. The ligands **(109a**, **109c-e)** were obtained in good yields (74-83% in Table 3.2). This method gave better yields when compared to reductive amination because the work up procedure involved only simple filtration of the Pd/C instead of extraction. However, since the products **(109)** still contain a benzylic C-N bond, over-reduction was still a problem which may occur when the reaction was left for too long especially for (*S*)-**109c** and (*S*)-**109d**. The induction period of the reaction was also inconveniently slow. Hence while the early rate of hydrogenation was slow, after 3 hours the rate became rapid and it proved difficult to stop the reaction at exactly the right time (i.e. complete reduction of the C=N without cleavage of the benzylic C-N bond). The method also relies on the availability of the substituted salicylaldehyde hence the same problem as the previous $NaBH_4$ reduction method was found.

3.2.3 Synthesis of chiral-*N*-salicyl-β-aminoalcohol by three-component Mannich type reaction followed by hydrolysis of oxazolidine derivatives (Method C)

Ultimately, we have found a new route to eliminate the major problems for synthesis of chiral *N*-salicyl-β-aminoalcohol ligands: namely the limited variety of salicylaldehydes, the requirement for extractive work-up and the over-reduction problems. This method is divided into 2 steps. The first step is a three-component Mannich type reaction which is a condensation reaction between three substrates: a phenol, a β-aminoalcohol and paraformaldehyde using a Lewis acid as catalyst.[185-187] Instead of the expected β-aminoalcohol product, an oxazolidine derivative was first obtained as an isolable intermediate. The structure of which was characterized by NMR spectroscopy. An additional step of ring opening of the oxazolidine under acidic conditions was necessary to give the desired chiral *N*-salicyl-β-aminoalcohol ligands as the final product (Scheme 3.2).

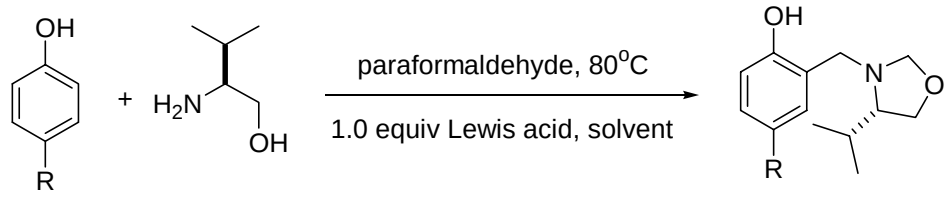


Scheme 3.2 General synthetic scheme for three-component Mannich type reaction

3.2.3.1 The optimization of three-component Mannich type reaction

The condition for the three-component Mannich type reaction was optimized by reacting 4-phenylphenol or phenol as a representative phenol, (*S*)-valinol as a representative β-aminoalcohol and paraformaldehyde in the presence of 1.0 equiv of Lewis acid catalysts in various solvents at 80 ^{o}C. The results were shown in Table 3.3.

Table 3.3 Optimized condition for three-component Mannich type reaction



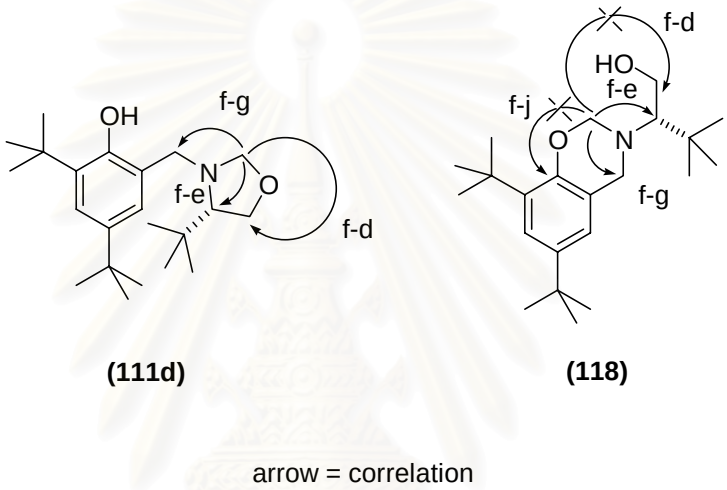
(111)

Entry	R	Lewis acid	Solvent	% Yield
1	C_6H_5	-	EtOH	46
2	C_6H_5	-	CH_3CN	31
3	C_6H_5	LiCl	EtOH	86
4	C_6H_5	LiCl	CH_3CN	45
5	C_6H_5	LiBr	EtOH	72
6	C_6H_5	LiOTf	EtOH	81
7	C_6H_5	$LiClO_4$	EtOH	83
8	C_6H_5	$MgCl_2$	EtOH	58
9	C_6H_5	$ZnCl_2$	EtOH	47
10	C_6H_5	$CuCl_2$	EtOH	38
11	H	-	EtOH	42
12	H	-	CH_3CN	28
13	H	LiCl	EtOH	86
14	H	LiCl	CH_3CN	48

The results showed that the optimum Lewis acid was LiCl. In addition, the effect of counter ion was investigated. The results showed only slight difference in yield with all lithium salts tested although the nature of these anions was quite different (Table 3.3, entries 3, 5, 6 and 7). Furthermore, bivalent metals Lewis acids like $MgCl_2$, $ZnCl_2$ and $CuCl_2$ were also tested and the same oxazolidine product was obtained in poor to moderate yields (Table 3.3, entries 8-10). Importantly, a very high *ortho*-selectivity was observed since only *ortho*-product was obtained even when unsubstituted phenol with the free *para*-position was used as substrate (Table 3.3, entries 11-14). The reaction performed in EtOH afforded higher yield than CH_3CN in all cases regardless of the Lewis acid used.

3.2.3.2 Structure of the oxazolidine intermediate

The Mannich reaction was repeated with other substrates under the optimal condition obtained above. Generally, most of the oxazolidine derivatives cannot be separated from the unreacted phenols due to their similar polarity. Fortunately, the oxazolidine derived from 2,4-di-*tert*-butylphenol and (*S*)-*tert*-leucinol can be obtained pure by flash column chromatography as a stable white solid. Based on ^{1}H NMR data, the two structures **(111d)** and **(118)** are possibities.



(111d) **(118)**

arrow = correlation

The oxazolidine structure **(111d)** was suggested by the presence of a sharp singlet signal of H-bonded phenolic O<u>H</u> group on phenol at 10.00 ppm in its ^{1}H NMR spectrum. ^{1}H-^{1}H-HSQC spectrum showed correlations between NC<u>H</u>C$(CH_3)_3$ signal at 2.78 ppm and N<u>C</u>HC$(CH_3)_3$ signal 73.4 ppm. Ar<u>C</u>H_2N signals at 3.84 and 4.20 ppm correlated with Ar<u>C</u>H_2N signal at 61.6 ppm. CHC<u>H_2</u>O signals at 3.60 and 4.13 ppm correlated with CH<u>C</u>H_2O signal at 66.8 ppm. NC<u>H_2</u>O signals at 4.04 and 4.40 ppm correlated with N<u>C</u>H_2O at 85.2 ppm. C<u>H</u>Ar at 6.85 ppm correlated with <u>C</u>HAr at 123.4 ppm and C<u>H</u>Ar at 7.25 ppm correlated with <u>C</u>HAr at 123.7 ppm (Figure 3.1). In addition, ^{1}H-^{1}H-COSY spectrum showed no correlation between C<u>H_2</u>N and C<u>H</u>-Ar was observed. There is also a correlation between NC<u>H</u>C$(CH_3)_3$ signal at 2.78 ppm and CHC<u>H_2</u>O signals at 3.60 and 4.13 ppm (Figure 3.2). Importantly, there are three key correlations shown by ^{1}H-^{13}C-HMBC. The first is the correlation between NC<u>H</u>C$(CH_3)_3$ (e) signal at 2.78 ppm, and NC<u>H_2</u>O (f, f′) signals at 4.04 and 4.40 ppm, and Ar<u>C</u>H_2N (g, g′) signal at 61.6 ppm. In addition, NC<u>H_2</u>O (f, f′) signals at 4.04 and

4.40 ppm, Ar$C\underline{H}_2$N (g, g′) signals at 3.84 and 4.20 ppm, and NC$\underline{H}$C$(CH_3)_3$ (e) signal at 2.78 ppm correlated with CH$\underline{C}H_2$O signals at 66.8 ppm. The other is the correlation between CHC$\underline{H}_2$O (d, d′) signals at 3.60 and 4.13 ppm, NC$\underline{H}_2$O (f, f′) signals at 4.04 and 4.40 ppm, NC$\underline{H}$C$(CH_3)_3$ (e) signal at 2.78 ppm and N$\underline{C}H_2$O (f, f′) at 85.2 ppm. Importantly, no correlation between NC$\underline{H}_2$O (f, f′) signals at 4.04 and 4.40 ppm and Ar$C\underline{H}_2$ (j) at 154.1 ppm was observed (Figure 3.3). Consequently, it can be inferred that oxazoline **(111d)** was formed as the product in this step.

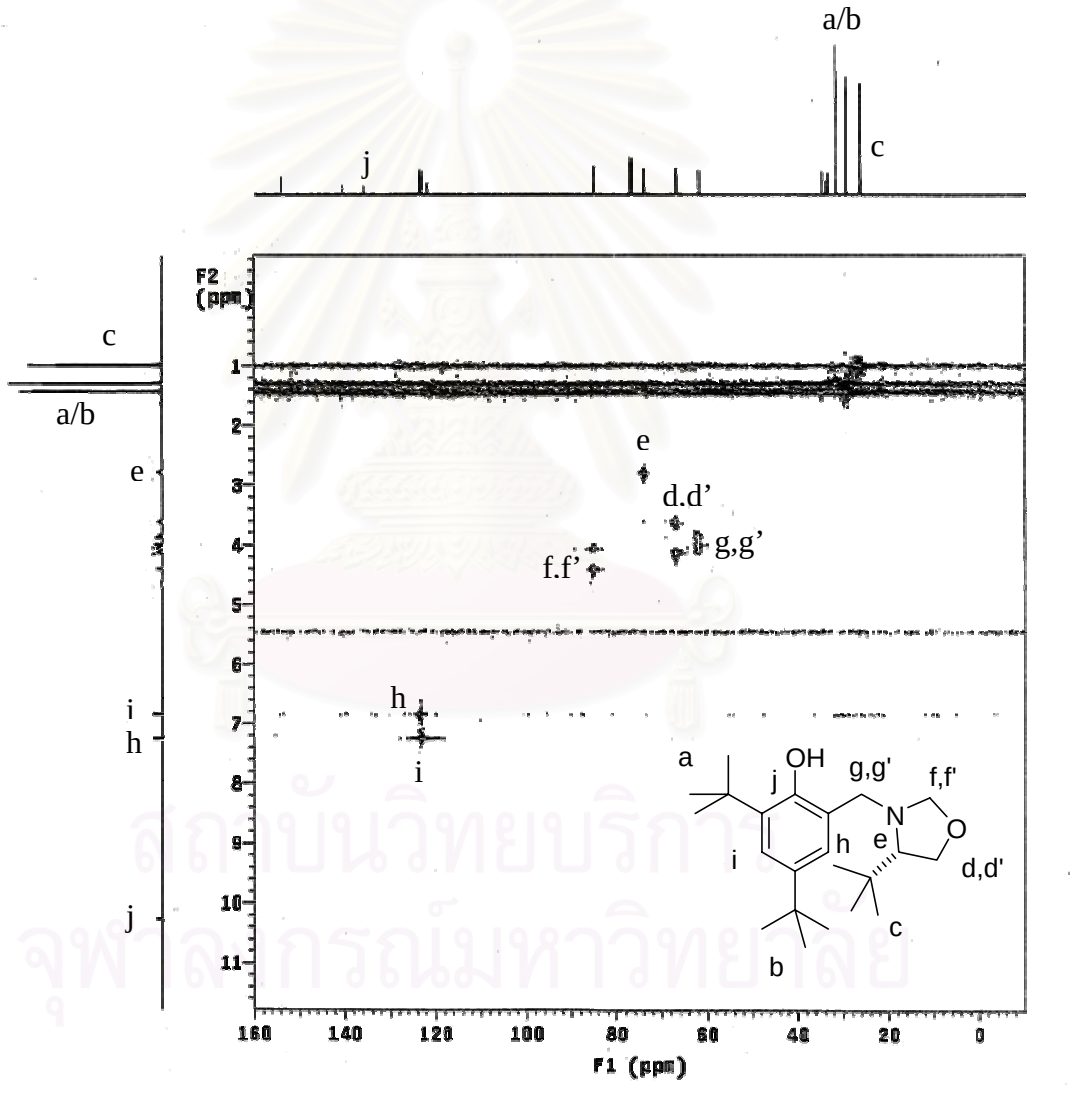


Figure 3.1 ^{1}H-^{13}C-HSQC spectrum of oxazolidine **(111d)**

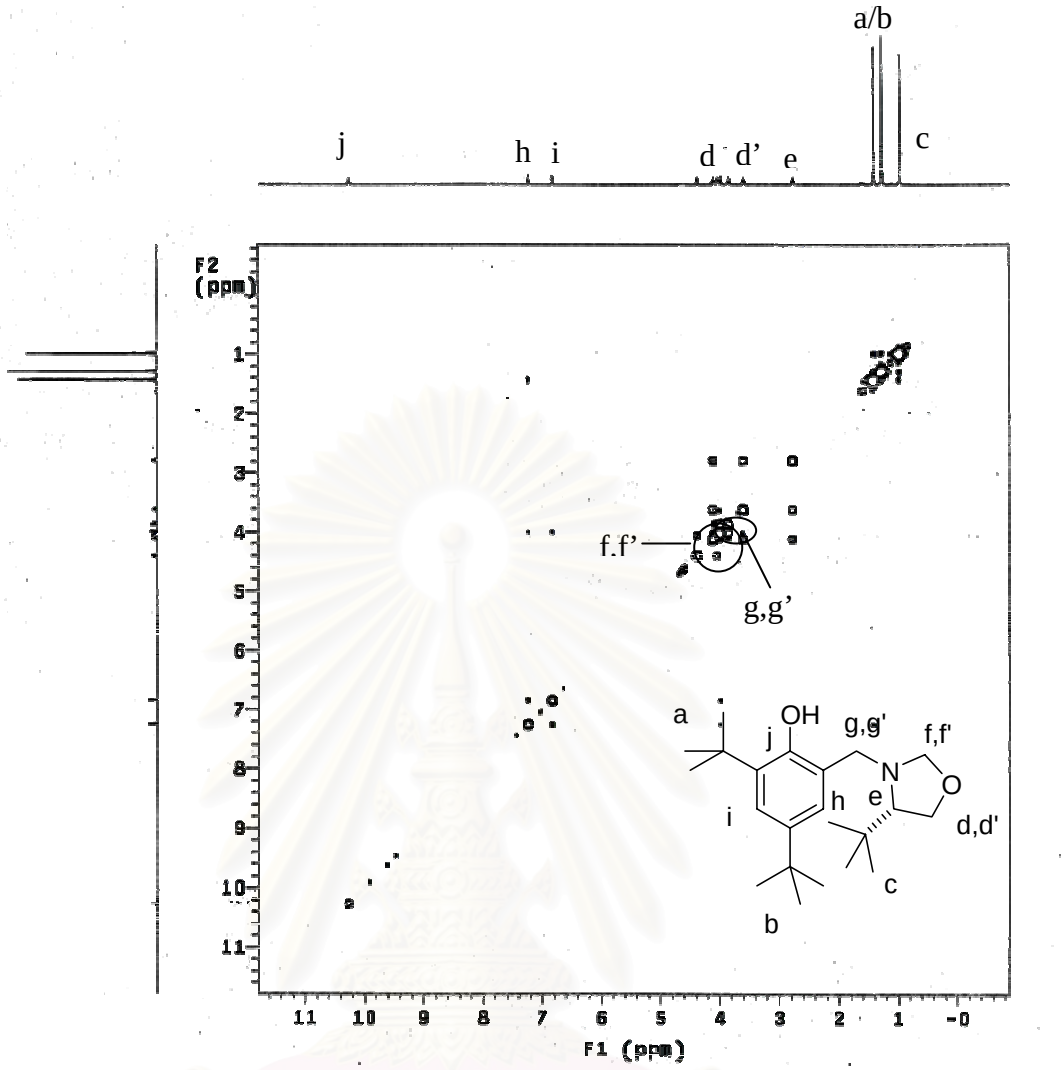


Figure 3.2 ^{1}H-^{1}H-COSY spectrum of oxazolidine **(111d)**

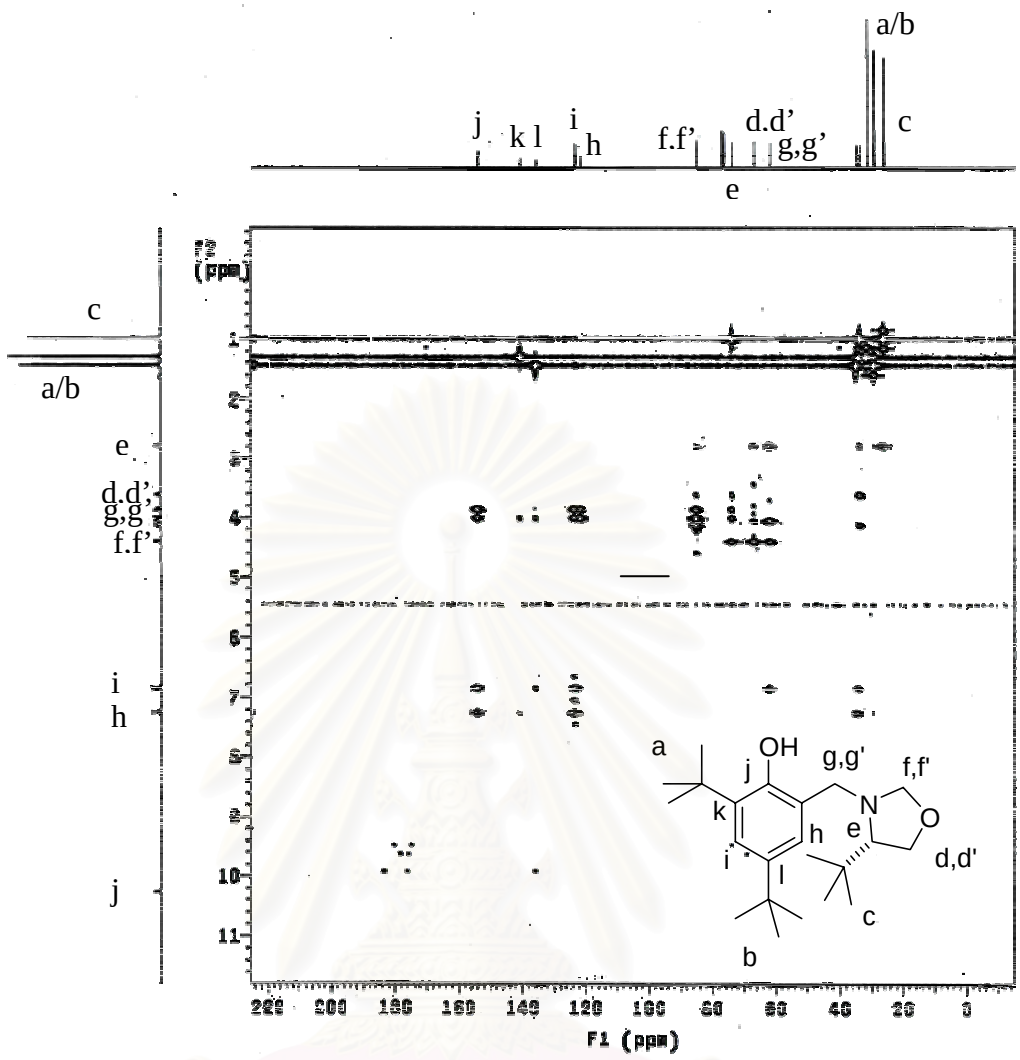
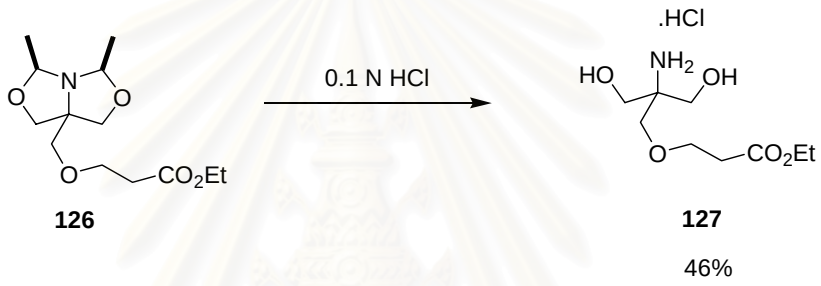


Figure 3.3 ^{1}H-^{13}C-HMBC spectrum of oxazolidine **(111d)**

3.2.3.3 Hydrolytic cleavage of the oxazolidine

The next step is the ring opening of the oxazolidine derivatives or 1,3-*N*,*O* ring to provide the desired aminoalcohol ligands. Oxazolidine cleavage requires the presence of a Brönsted or a Lewis acid. The general protocol for cleavage of the oxazolidine ring by acid hydrolysis using aq. HCl or PTSA in MeOH.[10] It is indicated strong anomeric effect occurring in the O-C-N bond is a key reason for achieving the oxazolidine ring-opening. For instance, Pavia reported the use of 0.1 N aq. HCl to hydrolyze oxazolidine **(126)**. The open chain derivative **(127)** was readily obtained with moderate yield (Scheme 3.4).[173]

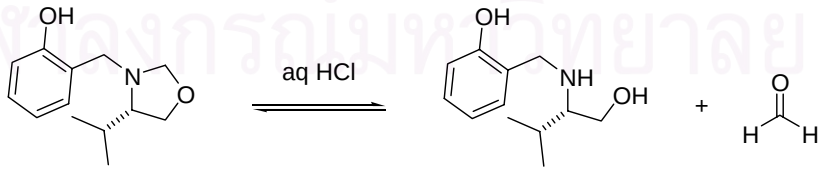


126 **127**

46%

Scheme 3.3 Acid hydrolysis of oxazolidine **(116)**

Although hydrolysis of cyclic hemiaminal under acidic condition is simple, there is still the important drawback of this method. Cleavage of oxazolidine with acid is a reversible reaction. Formaldehyde will be generated during hydrolysis. The liberated formaldehyde is a driving force for the backward reaction by condensation with free amino group. This results in an incomplete reaction (Scheme 3.5).



Scheme 3.4 Acid hydrolysis of oxazolidine

However, this problem was figured out by Broxterman *et al*. They reported an effective route for cleavage of the imines using hydroxylamine hydrochloride.[188]

The method has been employed to cleave the imine derived from $Pb(OAc)_4$ oxidation of the aminoalcohol.[189] We have applied this effective method to cleave the oxazolidine rings which is a molecule containing active methylene. A large excess (10 equiv) of hydroxylamine hydrochloride, which is a source of acid in methanol, plays a crucial role to trap formaldehyde by-product so that the reversible oxazolidine formation is not possible. Gratifyingly, the condition works very well for oxazolidine ring opening in our case. By this route, a series of chiral *N*-salicyl-β-aminoalcohol ligands were obtained in high yields and without racemization.

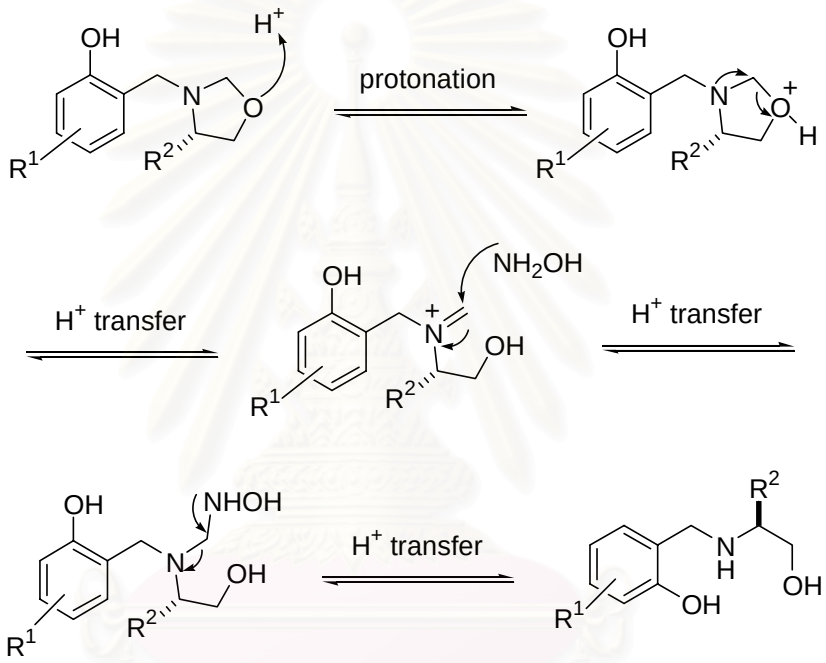
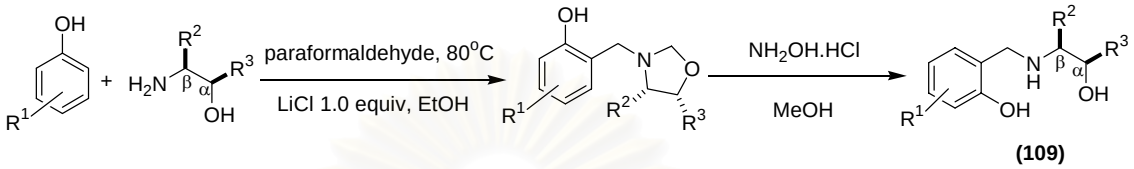


Figure 3.4 Mechanism of ring opening of oxazolidines by hydroxylamine hydrochloride

For the mechanistic pathway, the *ortho*-selective product was protonated and eletron pair of nitrogen atom was shifted to active methylene to form iminium salt and alcohol functional group. Then hydroxylamine hydrochloride nucleophilically attacked at the carbon of generated iminium species to form an aminal intermediate. Then an eletron pair of nitrogen on hydroxylamine moiety was moved to active methylene carbon and amino group was consecutively released. Finally, the chiral-*N*-salicyl-β-aminoalcohol was obtained as the product (Figure 3.5).

3.2.3.4 Application in synthesis of a variety of *N*-salicyl-β-aminoalcohol ligands

Table 3.4 Ligands synthesized from phenol and β-aminoalcohols by three-component Mannich type reaction followed by ring opening of oxazolidine derivatives by hydroxylamine hydrochloride



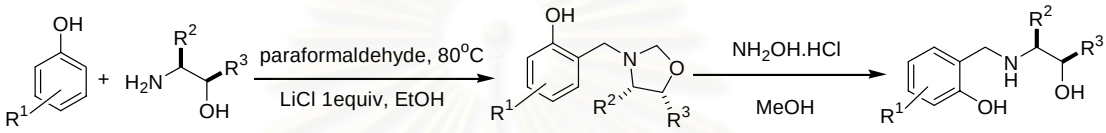
(109)

Entry	Ligand	Amino alcohols	R^1	R^2 (β)	R^3 (α)	Yield (%)
1	(*S*)-**109a**	(*S*)-phenylalaninol	H	$PhCH_2$	H	88
2	(*R*)-**109a**	(*R*)-phenylalaninol	H	$PhCH_2$	H	85
3	(*S*)-**109b**	(*S*)-alaninol	H	Me	H	62
4	(*S*)-**109c**	(*S*)-valinol	H	^{i}Pr	H	87
5	(*S*)-**109d**	(*S*)-*tert*-leucinol	H	^{t}Bu	H	85
6	(*S*)-**109e**	(*S*)-phenylglycinol	H	Ph	H	86
7	(*S*)-**109f**	(*S*)-leucinol	H	^{i}Bu	H	85
8	(*S*)-**109g**	(*S*)-cyclohexyl-alaninol	H	$^{c}HexCH_2$	H	84
9	(*S*)-**109h**	(*S*,*S*)-isoleucinol	H	^{sec}Bu	H	86
10	(*R*)-**109i**	(*R*)-1-aminopropan-2-ol	H	H	CH_3	60

The conditions were applied to synthesize a number of chiral *N*-salicyl-β-aminoalcohol ligands previously synthesized by other methods for comparison. In all cases the ligands were obtained in high yields (>85%) except for (*S*)-**109b** and (*S*)-**109i** which are relatively polar than other ligands hence are difficult to purify by column chromatography. The results suggested that the three-component Mannich type reaction is a highly efficient route to these chiral ligands (Table 3.4). Furthermore, various phenol derivatives bearing substituents with both electronic and steric nature and several β-aminoalcohols were also investigated. The results showed that various chiral *N*-salicyl-β-aminoalcohol ligands were obtained in high yield (>85%, Table 3.5). Exceptions were substrates bearing strong electron-withdrawing

groups like 4-nirophenol which could not form oxazolidine under this condition due to the low reactivity of the phenol. However, the chiral *N*-salicyl-β-aminoalcohol ligand bearing with 4-nitro substituent on salicyl moiety **(109u)** can be synthesized by reduction of $NaBH_4$.

Table 3.5 Ligands synthesized from phenol derivatives and β-aminoalcohols by three-component Mannich type reaction followed by ring opening of oxazolidine derivatives by hydroxylamine hydrochloride

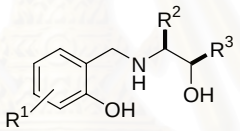


(109)

Entry	Ligand	R^1	R^2	R^3	% Yield (2 steps)
1	(*S*)-**109j**	4-C_6H_5	^{i}Pr	H	85
2	(*S*)-**109k**	2-C_6H_5	^{i}Pr	H	86
3	(*S*)- **109l**	2,4-di^{t}Bu	^{i}Pr	H	87
4	(*S*)- **109m**	2,4-di^{t}Bu	^{t}Bu	H	85
5	(*S*)- **109n**	2,4-diMe	^{i}Pr	H	83
6	(*S*)- **109o**	4-Me	^{i}Pr	H	86
7	(*S*)- **109p**	2-Me	^{i}Pr	H	88
8	(*S*)- **109q**	4-Me	^{t}Bu	H	84
9	(*S*)- **109r**	2-Me	^{t}Bu	H	89
10	(*S*)- **109s**	4-^{t}Bu	^{i}Pr	H	87
11	(*S*)- **109t**	2-^{t}Bu	^{i}Pr	H	84
12	(*S*)- **109u**	4-NO_2	^{i}Pr	H	-
13	(*S*)- **109v**	4-Cl	^{i}Pr	H	88
14	(*S*)- **109w**	2-Cl	^{i}Pr	H	84
15	(*S*)- **109x**	4-OMe	^{i}Pr	H	92
16	(*S*)- **109y**	3-C_6H_5	$PhCH_2$	H	86
16	(*S*)- **109z**	3-Cl	$PhCH_2$	H	85
17	(*S*)- **109aa**	3-Me	$PhCH_2$	H	88

The reactions provided the chiral ligands in high yields without any racemization. The reaction is widely applicable because a variety of phenol is commercially available therefore a great diversity of the salicyl moiety can be easily made. It was emphasized that only *ortho*-selective products were obtained in all cases although substrates with free *para*-position were employed. Especially for *meta*-substituted phenols, which contain two different *ortho*-positions with different steric effect, the reaction ocured only at the less sterically hindered position. Importantly, this method is beneficial for synthesis of chiral *N*-salicyl-β-aminoalcohol bearing three sterically hindered *tert*-butyl groups **(109l)** and **(109m)** which were not successfully synthesized by other method.

Table 3.6 Ligands synthesized by $NaBH_4$ reduction, catalytic hydrogenation and three-component Mannich type reaction followed by ring opening of oxazolidine derivatives by hydroxylamine hydrochloride



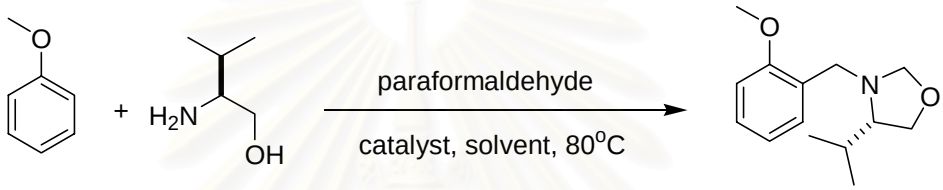
(109)

Entry	Ligand	R^1	R^2 (β)	R^3 (α)	% Yield (Method)		
					A	B	C
1	(*S*)-**109a**	H	$PhCH_2$	H	74	83	88
2	(*R*)-**109a**	H	$PhCH_2$	H	72	80	85
3	(*S*)-**109b**	H	Me	H	51	0	62
4	(*S*)-**109c**	H	^{i}Pr	H	75	75	87
5	(*S*)-**109d**	H	^{t}Bu	H	74	78	85
6	(*S*)-**109e**	H	Ph	H	73	0	86
7	(*S*)-**109f**	H	^{i}Bu	H	50	0	85
8	(*S*)-**109g**	H	$^{c}HexCH_2$	H	72	0	84
9	(*S*)-**109h**	H	^{sec}Bu	H	74	0	86
10	(*R*)-**109i**	H	H	CH_3	49	0	60
11	(*S*)- **109l**	2,4-di^{t}Bu	^{i}Pr	H	0	0	87
12	(*S*)- **109m**	2,4-di^{t}Bu	^{t}Bu	H	0	0	85

It was noticed that a series of chiral *N*-salicyl-β-aminoalcohol ligands obtained from three-component Mannich type reaction reaction followed by ring opening of oxazolidine derivatives by hydroxylamine hydrochloride (Method C) was obtained with much better yields (Table 3.6) when compared to $NaBH_4$ reduction (Method A) and catalytic hydrogenation (Method B).

3.2.3.5 Mechanistic aspects

Table 3.7 The role of hydroxyl group of phenol



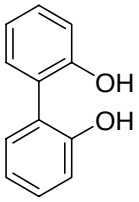
(119)

Entry	Catalyst	Solvent	% Yield
1	-	EtOH	-
2	-	CH_3CN	-
3	LiCl	EtOH	-
4	LiCl	CH_3CN	-

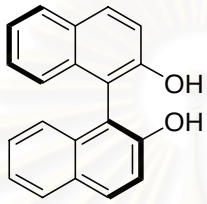
The active role of the hydroxyl group of the phenol was next investigated by using anisole as substrate under various conditions (Table 3.7). Although the reaction is carried out in alcoholic solvent which can act as a proton source, no reactions were observed in both with and without catalyst. It can be inferred that hydroxyl group of phenol played a crucial role in mediating the reaction and perhaps to induce the high *ortho*-selectivity.

In addition, phenol like substrate such as 2,2′-dihydroxybiphenyl **(120)**, (*S*)-BINOL **(121)**, α-naphthol **(122)** and β-naphthol **(123)** were investigated. Reactions of biphenol and (*S*)-BINOL gave a tailing spot on TLC which is difficult to separate and

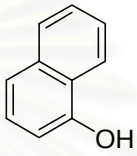
purify by flash column chromatography. The product gave complex ^{1}H-NMR spectrum which cannot be characterized the product structures. In case of naphthols, a highly colored product obtained gave complex ^{1}H-NMR spectrum whereas no reactions with β-naphthol was observed. It can be implied that α-naphthol is too reactive and β-naphthol is not reactive enough. Furthermore, secondary aminoalcohol, such as (*S*)-prolinol **(124)** and amide-like carbamic acid *tert*-butyl ester **(125)** were not substrates for this reaction since the desired product were not formed.



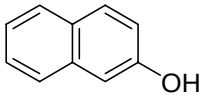
(120)



(121)



(122)



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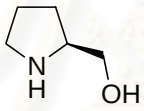

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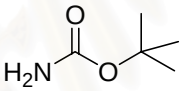
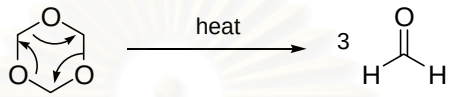


(125)

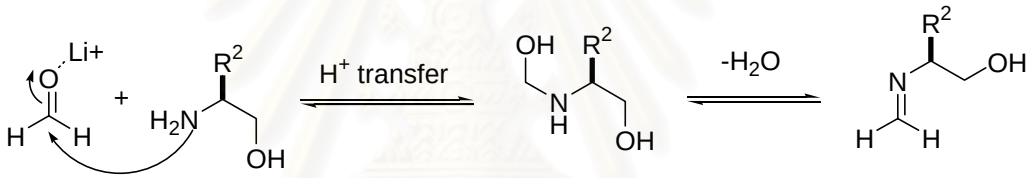
The mechanism of the oxazolidine formation is proposed to consist of three steps. **Step 1**, the paraformaldehyde was initially decomposed to formaldehyde (3 equiv). **Step 2**, the imine derived from β-aminoalcohol and paraformaldehyde generated from step 1 was formed. Lithium ion then coordinated at oxygen atom of carbonyl group. The nitrogen atom of β-aminoalcohol nucleophilically attacked at the carbon atom of the carbonyl group followed by dehydration to give an imine. **Step 3**, there are two possible mechanistic pathways for oxazolidine formation. *Type a* an imine and phenol were coordinated with lithium ion as three-component. Then nucleophilic carbon of phenol at *ortho*-position attacked at the carbon of imine to form *C*-alkylated intermediate after tautomerization. Next, the *C*-alkylated product was intramolecular cyclized by alcoholic OH to give oxazolidine ring. *Type b*, an oxazolidine ring was first formed and condensed with formaldehyde to provide an iminium ion. Then an iminium ion was nucleophilically attacked by the hydroxyl group of phenol to form an *O*-alkylated phenol. An oxazolidine ring was then

coordinated with lithum ion and followed by 1,3-*N*,*O* ring opening with lone pair electron of nitrogen atom to provide an iminium ion species. Cope rearrangement consecutively occurred and followed by tautomerization to form the *ortho*-selective iminium ion. Finally, *ortho*-selective oxazolidine was formed *via* intramolecular cyclization of alcoholic OH.

Step 1 Decomposition of paraformaldehyde

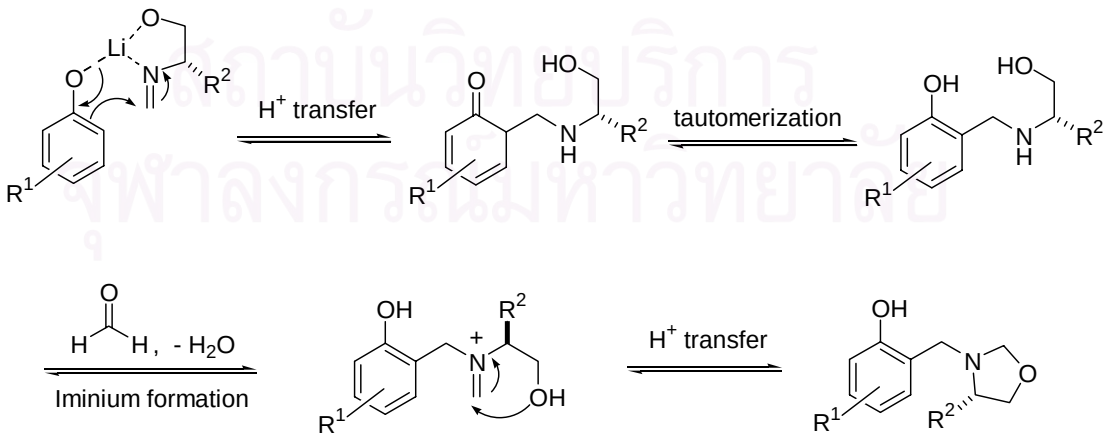


Step 2 Imine formation



Step 3 Mannich reaction

a



b

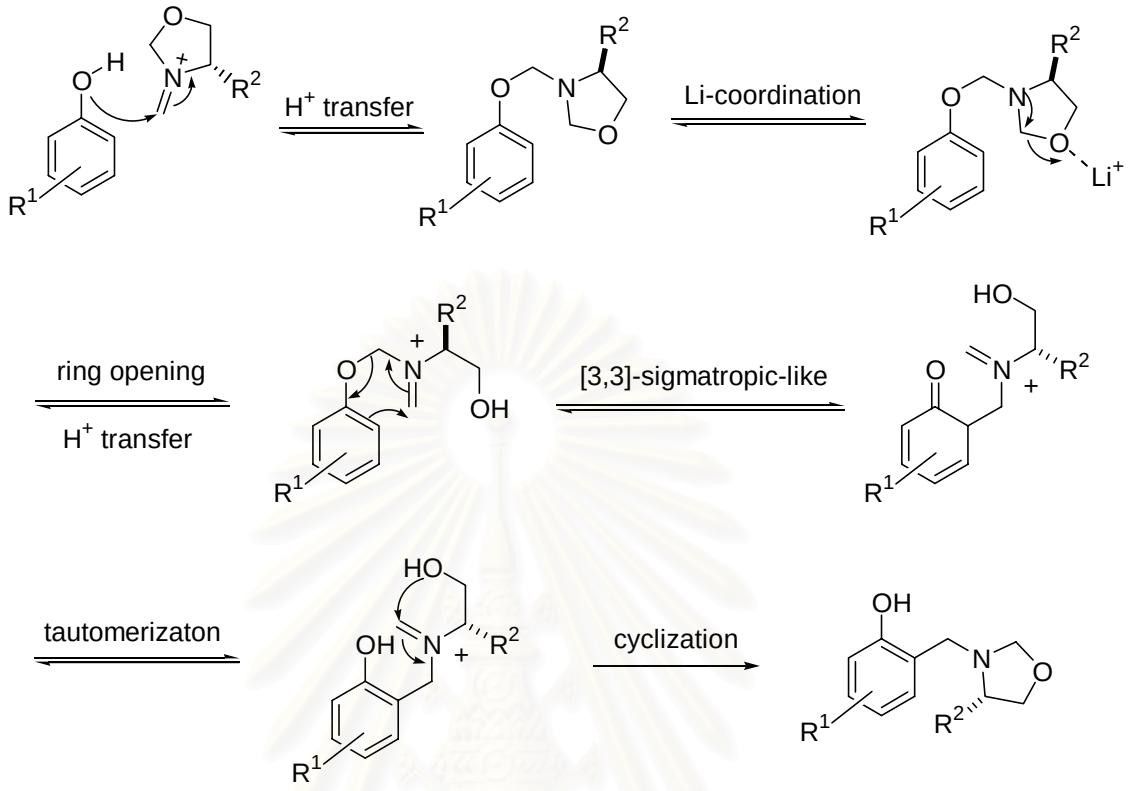


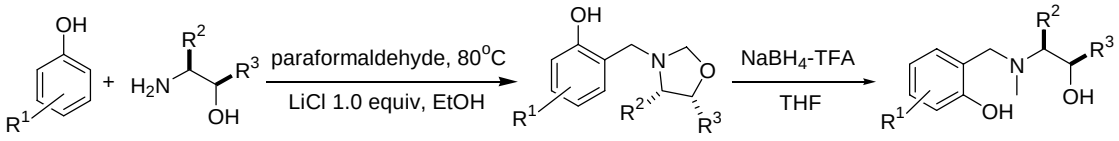
Figure 3.5 Mechanism of oxazolidine formation by three-component Mannich type reaction

3.2.4 Synthesis of selectively *O*- and *N*-methylated ligands for structure-activity relationship study.

3.2.4.1 *N*-Methylated ligands

Oxazolidine intermediate may undergo reactive ring opening to provide the *N*-methylated ligand.[173] However, we also utilized the oxazolidines derived from several phenol derivatives and β-aminoalcohols in the regioselective ring opening of oxazolidines for preparation of chiral *N*-methyl-*N*-salicyl-β-aminoalcohols.

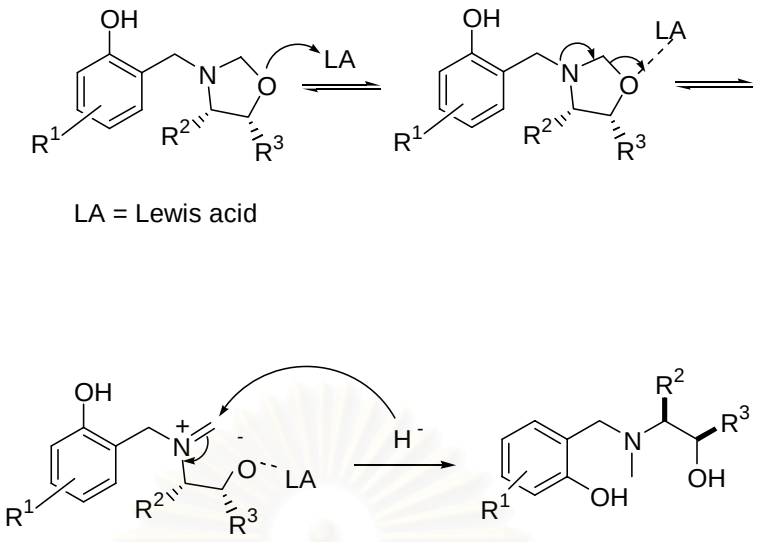
Table 3.8 *N*-Methylated ligands synthesized from phenol derivatives and several β-aminoalcohols by three-component Mannich type reaction followed by ring opening of oxazolidine derivatives by TFA-$NaBH_4$



(115)

Entry	Ligand	R^1	R^2	R^3	% Yield (2 steps)
1	(*S*)-**115a**	^{t}Bu	-$C_6H_4CH_2$-		61
2	(*S*)-**115b**	3-Cl	^{i}Pr	H	61
3	(*S*)-**115c**	H	CH_2Ph	H	62
4	(*S*)-**115d**	2,4-di ^{t}Bu	^{t}Bu	H	60
5	(*S*)-**115e**	4-Ph	Ph	H	60
6	(*S*)-**115f**	3-Me	^{i}Pr	H	57
7	(*S*)-**115g**	3-Ph	^{i}Pr	H	58

The reductive ring opening of oxazolines was observed as soon as the reducing reagent is added in the presence of a Brönsted or Lewis acid. Most probably, the Lewis acid acts by coordinating the oxygen atom, which in turn weakens the C-O bond and therefore increases the rate of reduction. Boron and aluminum are known to have high affinity for oxygen.[173] Ring opening occurred on the treatment with $NaBH_4$ previously reacted with TFA. One can postulate that in the condition, Lewis acid species such as BH_3 was formed *in situ* and generated on reaction of metal hydrides with TFA. Anomeric effect seemed to be a stereoelectronic preference for ring opening of oxazolidines in the indicated direction (Scheme 3.5). However, the reaction gave chiral *N*-methyl-*N*-salicyl-β-aminoalcohols in only fair yields (Table 3.8). Nevertheless, it provides a very concise access to *N*-methylated ligands, which might be useful for other reactions.



Scheme 3.5 Mechanism of ring opening of oxazolidine catalyzed by TFA-$NaBH_4$

In case of **(115a),** there were two spots on TLC. The more polar spot was the major product, **(115a)**, (52% yield) and less polar spot was the minor product (8% yield). ^{1}H-^{1}H-COSY of **(115a)** showed the correlation between ArC$\underline{H}_2$CHOH signal at 3.19 and 3.42 ppm and NCHC$\underline{H}$OH signal at 5.29 ppm including the correlation between NC$\underline{H}$CHOH signal at 4.80 ppm and NCHC$\underline{H}$OH signal at 5.29 ppm. For the minor product, its ^{1}H-^{1}H-COSY showed a similar pattern of signals but different in chemical shifts. In addition, ^{1}H-^{13}C-HSQC spectrum of **(115a)** (Figure 3.7) showed the important correlations as follows: 1) signals of ArC$\underline{H}_2$CHOH at 3.19 and 3.42 ppm, and Ar$\underline{C}H_2$CHOH at 34.0 ppm, 2) signal of NC$\underline{H}$CHOH at 4.80 ppm and N$\underline{C}$HCHOH at 70.0 ppm, 3) signal of NCHC$\underline{H}$OH at 5.29 and NCH$\underline{C}$HOH) at 77.9 ppm. Surprisingly, the similar correlations was also observed in ^{1}H-^{13}C-HSQC spectrum of the minor product (Figure 3.8) which is shown as follows: 1) signals of ArC$\underline{H}_2$CHOH at 3.03 and 3.28 ppm, and Ar$\underline{C}H_2$CHOH at 34.0 ppm. 2) signal of NC$\underline{H}$CHOH at 4.46 ppm and N$\underline{C}$HCHOH at 68.5 ppm. 3) signal of NCHC$\underline{H}$OH at 4.93 and NCH$\underline{C}$HOH) at 73.1 ppm.

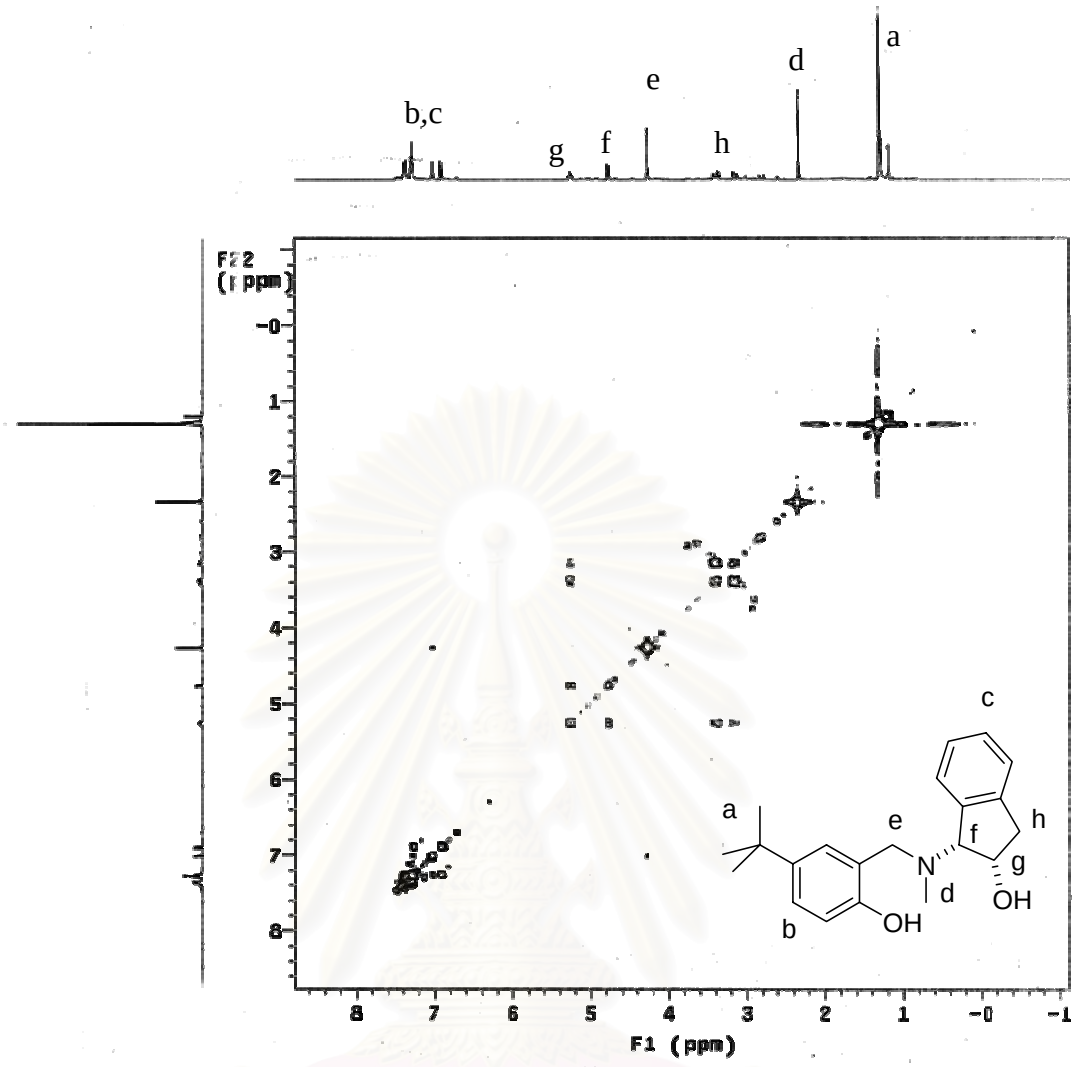


Figure 3.6 ^{1}H-^{1}H-COSY spectrum of **(115a)**

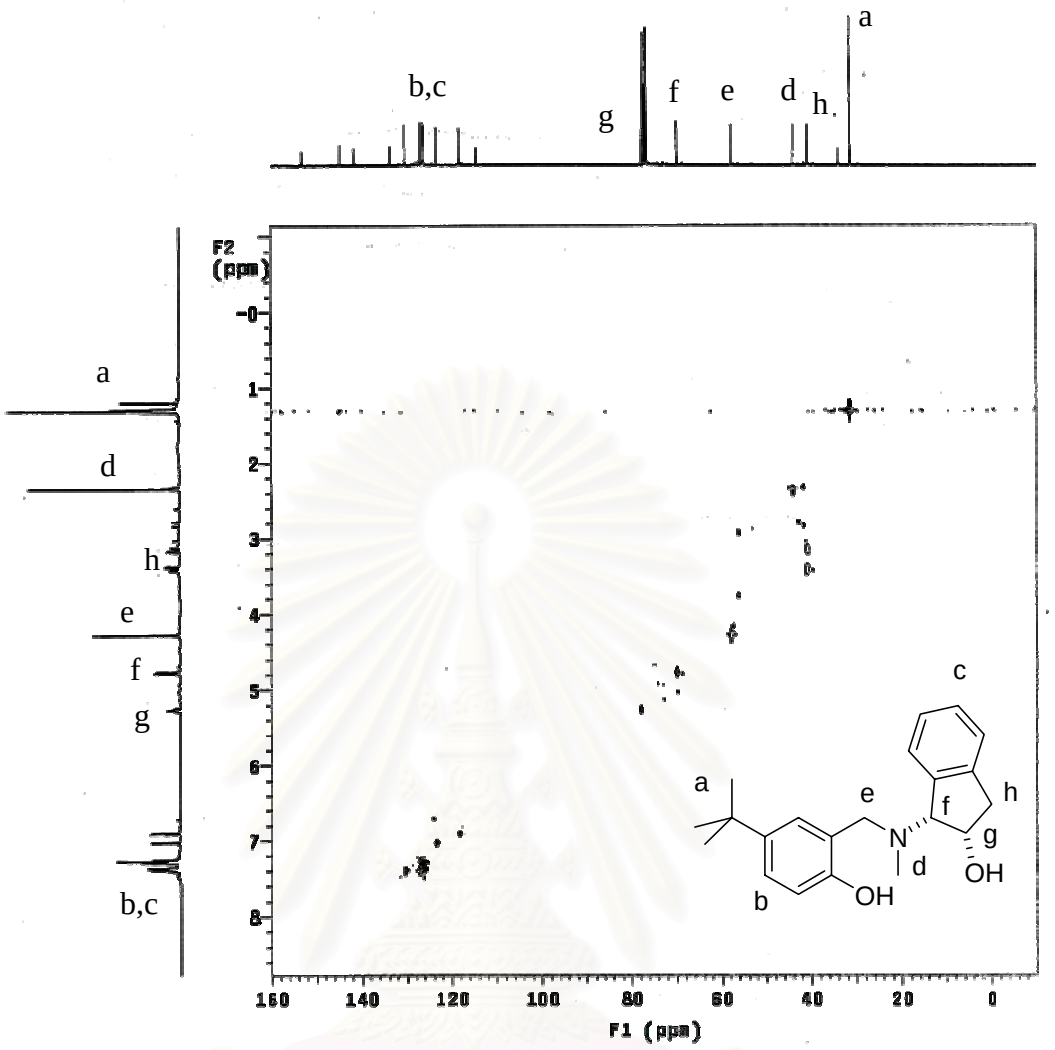


Figure 3.7 ^{1}H-^{13}C-HSQC spectrum of **(115a)**

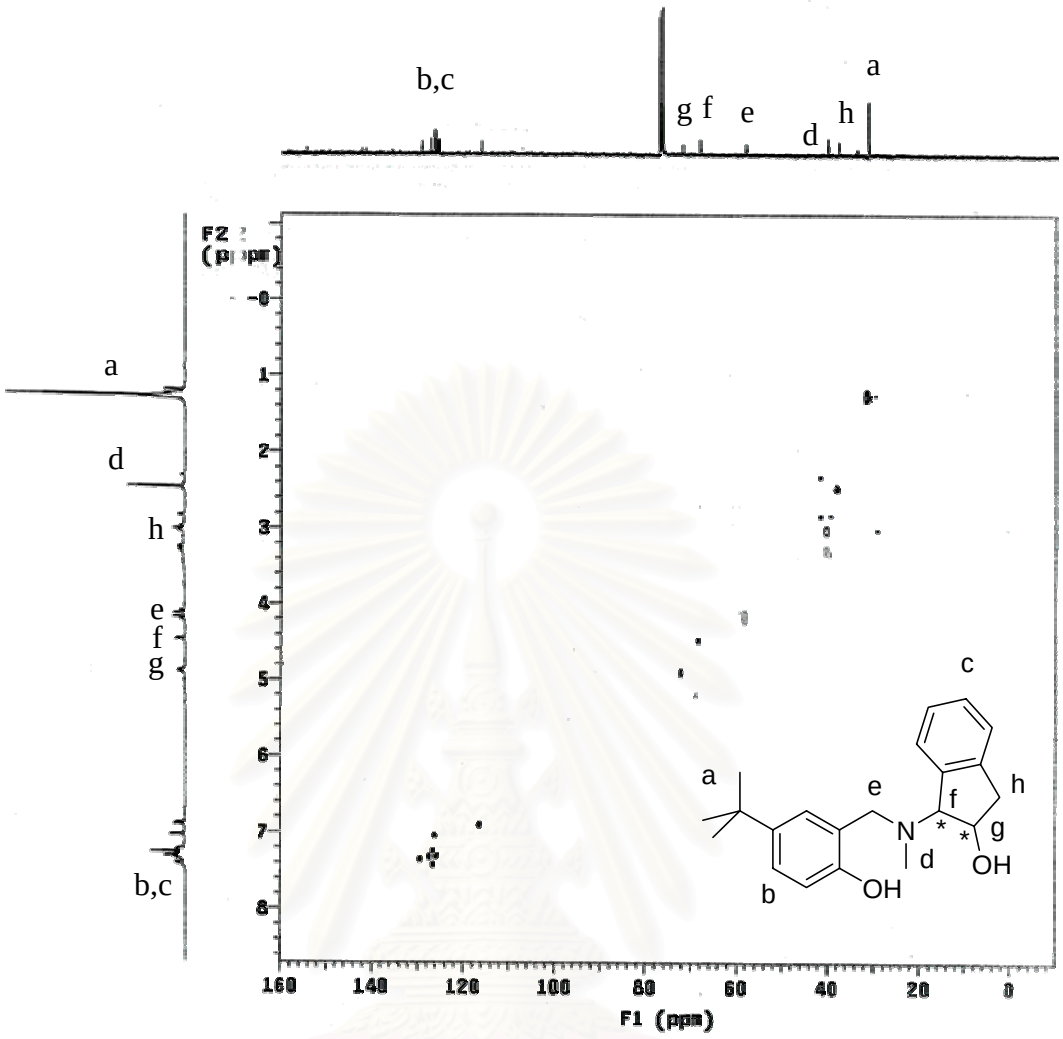
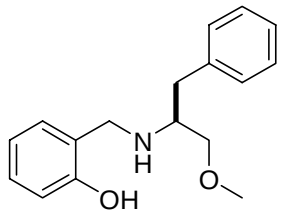


Figure 3.8 ^{1}H-^{1}H-HSQC spectrum of the possible diastereomer of **(115a)**

From the NMR experiments, it can be confirmed that **(115a)** is a correct structure. The minor product was supposed to be diastereomer of **(115a)**.

3.2.4.2 Alcoholic *O*-methylated ligand

Synthesis of the ligand **(109ae)** was attempted so as to use it as a control to evaluate the role of alcoholic OH group in the ligand **(109)**. Initially, we attempted to synthesize 1-methoxy-3-phenyl-2-propylamine **(114)**, which is a synthetic precursor for synthesis of ligand **(109ae)** by ring opening of *N*-Boc-aziridine **(128)** with NaOMe followed by Boc-deprotection (Scheme 3.6).



(109ae)

The aziridine was synthesized from (*S*)-phenylalaninol according to a literature procedure.[190] Several reaction conditions were examined. No reactions of *N*-Boc-aziridine **(128)** with sodium methoxide were observed at both room temperature and elevated temperature. Surprisingly, ring opening of aziridine with MeOH at room temperature with Lewis acid catalyst either $Cu(OTf)_2$ or $LiClO_4$ gave small amount of product (32%) which was shown to be the undesired regioisomer **(130)** by NMR (Figure 3.9). The exact structure of the product **(129)** was elucidated by ^{1}H-NMR and ^{1}H-^{13}C-HSQC (Figure 3.9). Two significant correlations which allowed unambiguous determination of the structure was observed. The first one is the correlation between $\underline{C}H_2NH$ at 57.4 ppm and $C\underline{H}_2NH$ at 3.05 and 3.30 ppm. Another one is the correlation between $\underline{C}HO$ at 81.3 ppm and $C\underline{H}O$ at 3.47 ppm. It can be concluded that **(130)** is the correct structure of the product obtained. Therefore, the synthetic plan was not successful (Scheme 3.6).

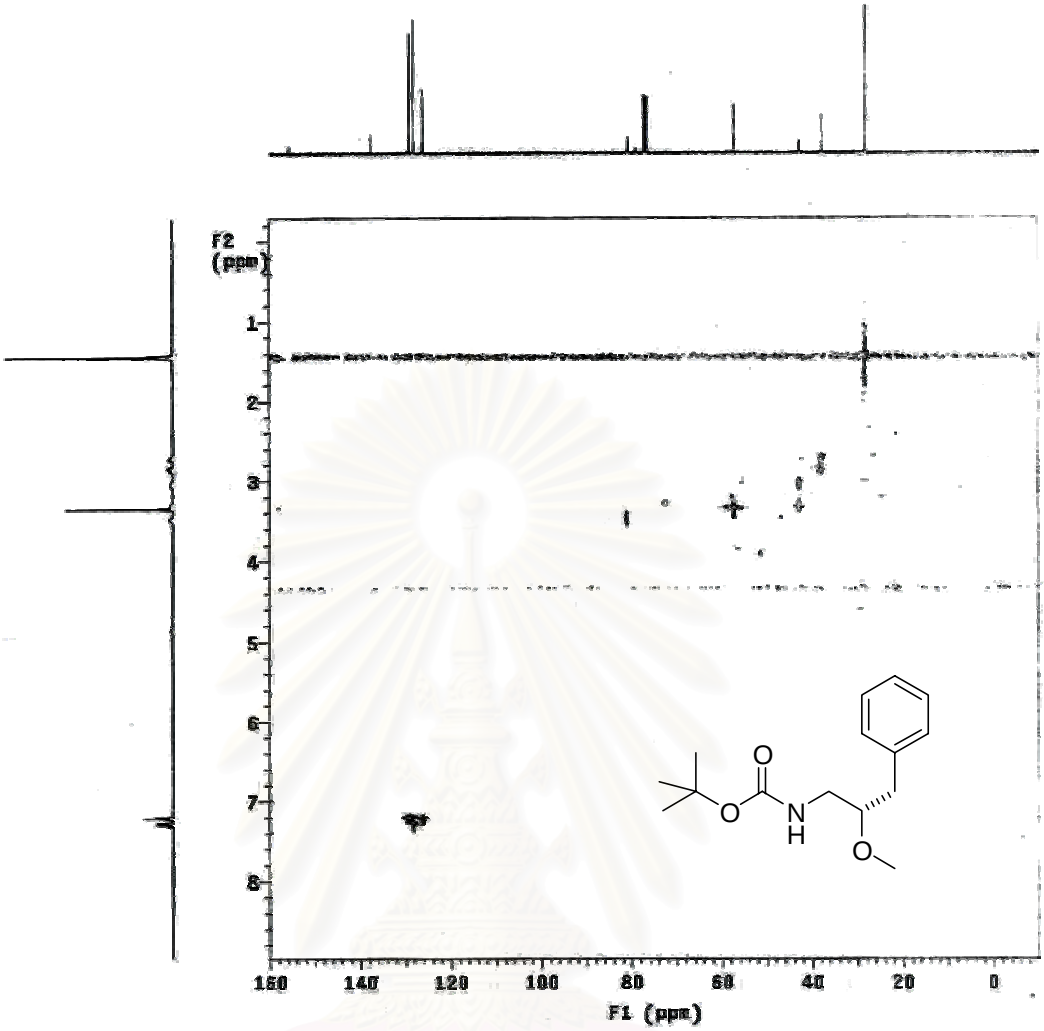
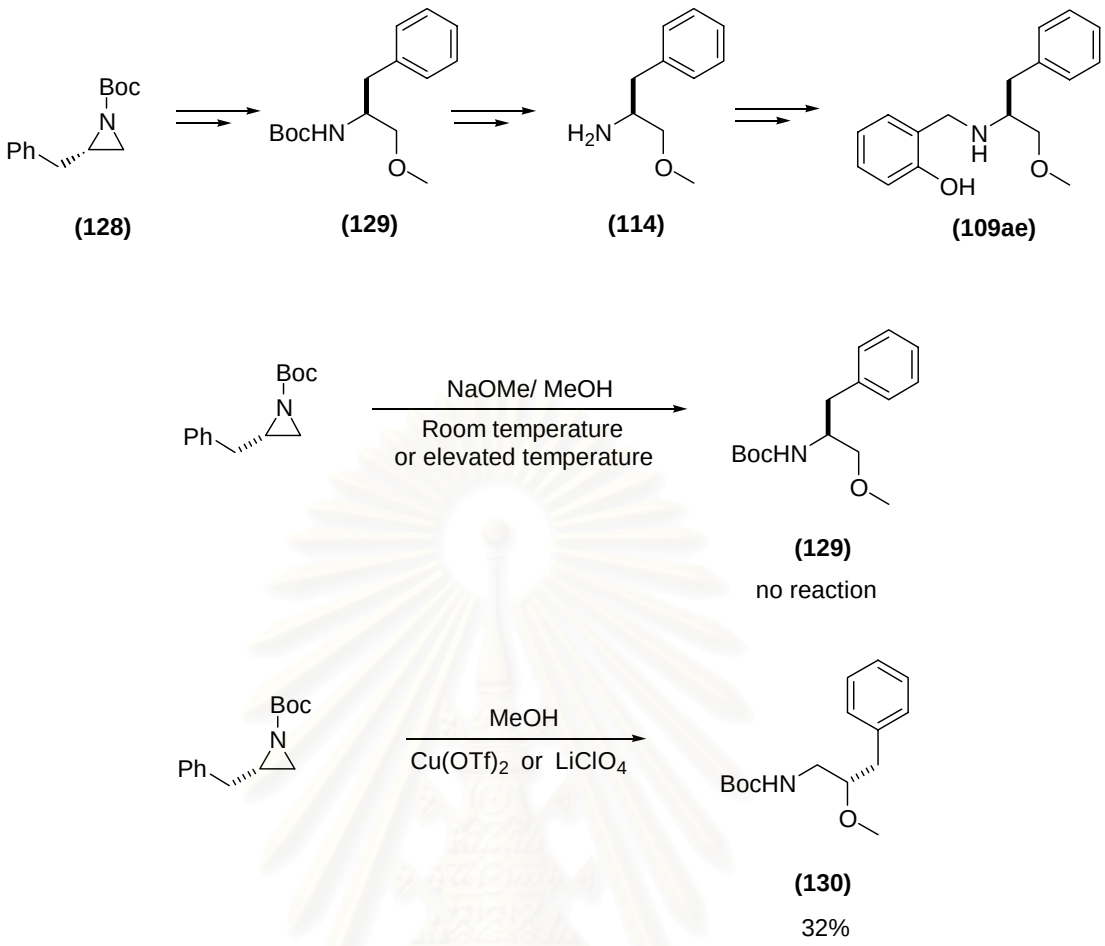


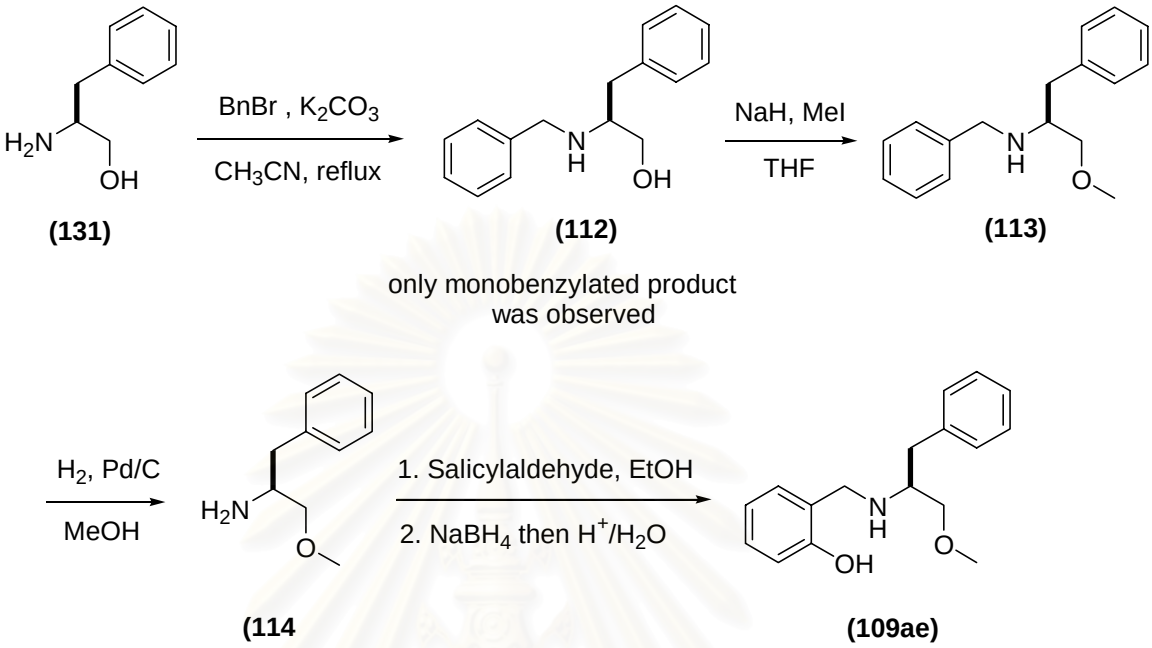
Figure 3.9 ^{1}H-^{13}C-HSQC spectrum of regioisomer **(130)**



Scheme 3.6 Synthesis of precursor **(114)** by ring opening of *N*-Boc-aziridine **(128)**

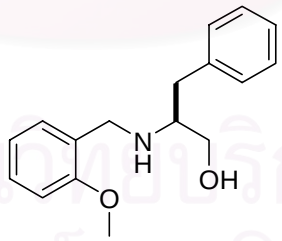
Next, we attempted to find a new method for preparation of the chiral ligand **(109ae)**. It can be divided to four steps. **Step 1**, the nucleophilic amino group of (*S*)-phenylalaninol **(131)** was protected with benzyl group using 2 equiv of benzylbromide under basic condition. Theory and literature precedence showed that this should provide *N*,*N*-dibenzylated product, but the result from ^{1}H-NMR spectrum showed that only monobenzylated product **(112)** was obtained. **Step 2**, the hydroxyl group of monobenzylated product **(112)** was deprotonated by sodium hydride to generate an alkoxy species which underwent S_N2 reaction with methyl iodide to give intermediate **(113)**. **Step 3**, the benzyl group of the intermediate **(113)** was removed by catalytic hydrogenation to provide 1-methoxy-3-phenyl-2-propylamine **(114)** as a key synthetic precursor. **Step 4**, the **(114)** was condensed with salicyaldehyde followed by reduction with $NaBH_4$ to give the desired ligand, *N*-(2′-

hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane **(109ae)**, after purified by flash column chromatography in 52% overall (Scheme 3.7).



Scheme 3.7 Synthesis of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane **(109ae)**

3.2.4.3 Phenolic *O*-methylated ligand



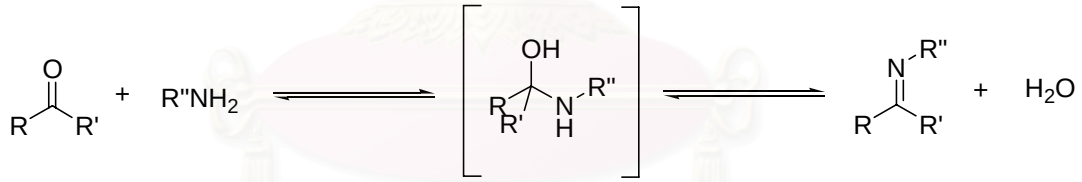
(109ab)

N-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane **(109ab)** was attempted to synthesize by condensation of 2-methoxybenzaldehyde followed by $NaBH_4$ reduction to evaluate the role of phenolic OH group in the ligand. The phenolic *O*-methylated ligand **(109ab)** was obtained in 82%.

3.3 Asymmetric Strecker reactions

3.3.1 Synthesis of imines

Imines or Schiff bases are generally prepared from the reaction of aldehydes or ketones and amines. Imines formation is acid-catalyzed reaction. The acid protonates at oxygen atom of carbonyl group followed by attacking of amine and dehydration to give imine as product (Scheme 3.8). Drying agents, for instance, anhydrous sodium sulfate, anhydrous magnesium sulfate or molecular sieve are generally added as water scavenger to ensure the forward equilibrium. All imine employed in this study could be easily prepared by mixing an equivalent amount of the amine and aldehydes or ketones in the presence of anhydrous sodium sulfate in dichloromethane at room temperature overnight. Filtration followed by evaporation of the solvent gave the imines characterized by sharp singlet signals of C<u>H</u>=N around 8.50 ppm in their ^{1}H-NMR spectra. The imines, being easily hydrolyzed, are not stable enough to withstand silica gel column chromatography. Fortunately, imines prepared from 1,1-diphenylmethylamine are crystalline solids. They can be easily purified by recrystallization from hexane.



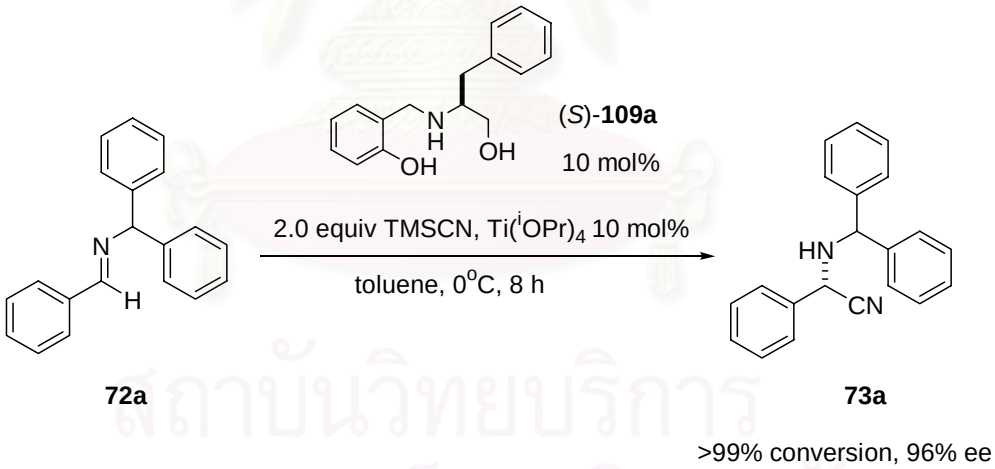
Scheme 3.8 Formation of imines

Imines can exist in two geometric isomers, namely *E*- and *Z*- isomer (Figure 3.10). Regarding the preferred isomer, the *Z*- form is especially less favorable than the *E*- form due to the steric repulsion between both R and R′ locating on the same side of C=N bond. On the other hand, the *E*- form possesses both R and R′ opposite to each other, therefore it should be the more stable isomer.

Figure 3.10 Two possible geometric isomers of imines

3.3.2 Effects of reaction parameters

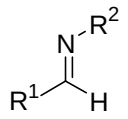
Initially, the reaction between **(72a)** and trimethylsilyl cyanide (TMSCN) was carried out in the presence of 10 mol% of the ligand (*S*)-**109a** and 10 mol% of $Ti(O^iPr)_4$ in toluene at -5 to 0 ^oC as described by Mansawat *et al*. [167] was attempted. However, the maximum ee of only 86% was obtained. Gratifyingly, upon changing the substrate to *N*-benzylidenebenzhydrylimine **(72a)** using the optimal condition above, over 90% ee was observed. The imine **(72a)** was therefore chosen for further studies.



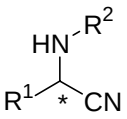
Scheme 3.9 Enantioselective Strecker reaction of *N*-benzylidenebenzhydrylamine catalyzed by chiral *N*-salicyl-β-aminoalcohol **(109a)**

Next, the determination of enantiomeric purity by ^1H-NMR was investigated.

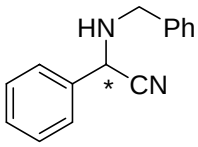
3.3.2.1 Development of an NMR method for determination of enantiomeric purity



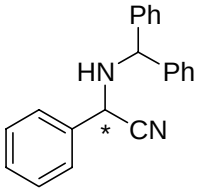
(72 or 79)



(73 or 80)



(80a)



(73a)

Optical purity could be expressed in the term of %ee which is defined as (%*R*-%*S*)/(%*R*+%*S*). Ee values approaching 100% are desirable. In the worst cases, when no enantioselectivity is observed, the ee value would be zero. To calculate the ee, one needs to know the ratio of the *R* and *S* enantiomers in the mixture. This can be done by chromatographic or spectroscopic methods. Although chiral HPLC is usually employed as the method of choice for analysis of optical purity of Strecker adducts **(73** or **80)**, unfortunately α-aminonitrile cannot be distinguished with both a Daicel Chiralcel OD® and a Chiralpack AD®. We, therefore, envisioned that ^{1}H NMR spectroscopy should be a potential alternative technique since it should require only a short analysis time, consume less solvent, require no expensive accessories such as chiral columns, and most importantly, the sample can be analyzed without any pre-treatment apart from removal of the reaction solvents. However, enantiomers cannot be distinguished in an achiral environment by their NMR spectra alone. Consequently, determination of enantiomeric purity using NMR requires a chiral additive to convert an enantiomeric mixture into a diastereomeric mixture, either transiently as a complex (by the use of chiral solvating agent) or permanently as a covalent compound (by the use of chiral derivatizing agent).

After several attempts it was found that (*S*)-camphorsulfonic acid (*S*-CSA) was the most effective chiral solvating agents (CSAs) in resolving the signals of the racemic *N*-benzyl α-aminonitrile **(73a)** and **(80a)**.[179] The splitting of the $C_{\alpha}H$ signal by up to 0.14 ppm was observed on a 200 MHz NMR spectrometer upon addition of 1-2 eq of (*S*)-CSA to a 0.1 M solution of **(80a)** in $CDCl_3$. The $C_{\alpha}H$ and Ph_2CH peaks of *N*-benzhydryl substituted α-aminonitrile **(73a)** also split in the presence of CSA although the resolution was of a lesser magnitude than that of the *N*-benzyl analogues (up to 0.03 ppm for $C_{\alpha}H$ signal and 0.05 ppm for Ph_2CH signal).

Nevertheless, a baseline resolution was obtained on a 400 MHz NMR spectrometer. Only a single $C_\alpha H$ peak was detected when enantiomerically pure (*S*)-**(73a)** was treated with CSA. The "satellite" peaks can be easily detected in enantiomerically enriched samples containing as little as 1% of the other enantiomer (98% ee) prepared by addition of racemic **(73a)** to enantiomerically pure **(73a)**. No racemization was observed after the CSA-treated optically pure sample was left at room temperature for several days. As expected, the position of the enantiomeric $C_\alpha H$ peaks reversed if the opposite enantiomer of CSA was added. Importantly, CSA is very general in inducing a chiral environment for many other racemic *N*-benzyl and *N*-benzhydryl substituted α-aminonitriles **(73** or **80)** carrying different aromatic and aliphatic α-substituents. Therefore, we conclude that ^1H NMR is indeed a very reliable method for the determination of enantiomeric purity of a variety of Strecker adducts.

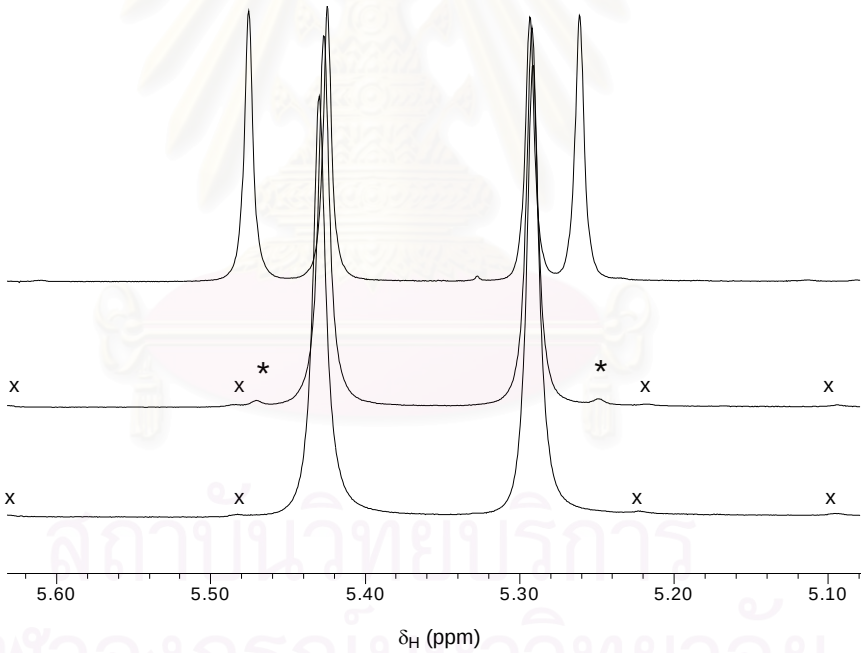
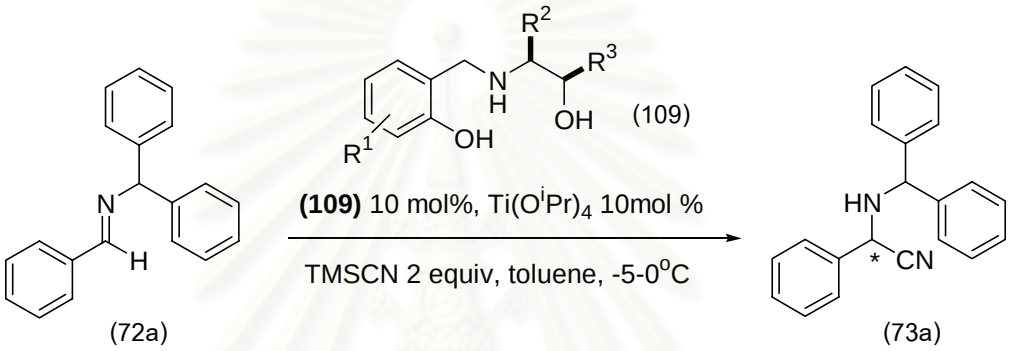


Figure 3.11 Partial ^1H-NMR spectra of aminonitrile **(73a)** (400 MHz, $CDCl_3$) in the presence of (*S*)-CSA showing the Ph_2CH (δ*R*: 5.48; δ*S*: 5.42 ppm) and $C_\alpha H$ signals (δ*R*: 5.26; δ*S*: 5.29 ppm): racemic (top); 98% ee (middle); and enantiomerically pure (*S*)-**(73a)** (bottom). The humps marked by "x" denote satellites due to ^1H-^{13}C couplings ($^1J_{1H\text{-}13C}$ ~ 140 Hz) and "*" denote the opposite isomer.

3.3.2.2 Evaluation of the ligands for asymmetric Strecker reaction

To study the effect of ligand structure on the enantioselectivities, the reactions of imine **(72a)** with TMSCN in the presence of **109**-Ti(O^iPr)$_4$ complexes were repeated using the optimized condition obtained for (*S*)-**109a** that was previously mentioned by Mansawat *et al*. [167] (Table 3.9).

Table 3.9 Evaluation of the ligands for asymmetric Strecker reaction



Entry	Ligand	R^1	R^2	R^3	% Conversion	% Ee (method of the ligand synthesis)		
						A	B	C
1	(*S*)-**109a**	H	CH_2Ph	H	>99	98	98	98
2	(*S*)-**109b**	H	Me	H	>99	73	-	75
3	(*S*)-**109c**	H	^{i}Pr	H	>99	97	97	98
4	(*S*)-**109d**	H	^{t}Bu	H	>99	98	98	98
5	(*S*)-**109e**	H	Ph	H	>99	89	88	89
6	(*S*)-**109f**	H	^{i}Bu	H	>99	84	-	85
7	(*S*)-**109g**	H	^{c}HexCH$_2$	H	>99	85	-	85
8	(*S*)-**109h**	H	^{sec}Bu	H	>99	98	-	98
9	(*S*)-**109i**	H	H	Me	>99	0	-	0
10	(*S*)-**109j**	4-C_6H_5	^{i}Pr	H	>99	-	-	97
11	(*S*)-**109k**	2-C_6H_5	^{i}Pr	H	>99	-	-	41

Entry	Ligand	R^1	R^2	R^3	% Conversion	% Ee (method of the ligand synthesis)		
						A	B	C
12	(*S*)-**109l**	2,4-di^{t}Bu	^{i}Pr	H	82	-	-	11
13	(*S*)-**109m**	2,4-di^{t}Bu	^{t}Bu	H	78	-	-	14
14	(*S*)-**109n**	2,4-diMe	^{i}Pr	H	>99	-	-	47
15	(*S*)-**109o**	4-Me	^{i}Pr	H	>99	-	-	97
16	(*S*)-**109p**	2-Me	^{i}Pr	H	>99	-	-	79
17	(*S*)-**109q**	4-Me	^{t}Bu	H	>99	-	-	97
18	(*S*)-**109r**	2-Me	^{t}Bu	H	>99	-	-	83
19	(*S*)-**109s**	4-^{t}Bu	^{i}Pr	H	>99	-	-	93
20	(*S*)-**109t**	2-^{t}Bu	^{i}Pr	H	>99	-	-	5
21	(*S*)-**109u**	4-NO_2	^{i}Pr	H	>99	-	-	60
22	(*S*)-**109v**	4-Cl	^{i}Pr	H	>99	-	-	93
23	(*S*)-**109w**	2-Cl	^{i}Pr	H	>99	-	-	43
24	(*S*)-**109x**	4-OMe	^{i}Pr	H	>99	-	-	94
25	(*S*)-**109y**	3-C_6H_5	CH_2Ph	H	>99	-	-	82
26	(*S*)-**109z**	3-Cl	CH_2Ph	H	>99	-	-	78
27	(*S*)-**109aa**	3-Me	CH_2Ph	H	>99	-	-	90

A = $NaBH_4$ reduction, B = catalytic hydrogenation, C = Three-component Mannich type reaction

Several 1:1 metal complexes of (*S*)-**109** were prepared *in situ* and tested as catalysts for enantioselective Strecker reactions. The reaction between imine **(72a)** and TMSCN was performed in toluene at 0 ^{o}C in the presence of 10 mol% of the catalyst. Excess TMSCN (2 equiv) was essential to assure a complete reaction. Interestingly, the presence of TMS groups was not observed in the Strecker adduct, presumably due to the cleavage of the rather labile *N*-Si bond by trace of moisture during work-up. A good correlation, at least in a qualitative sense, between the size of the alkyl side-chain on aminoalcohol moiety and the degree of enantioselectivity was observed. Only ligands bearing a relatively sterically hindered substituent at the β-position such as (*S*)-**109a** (R = $PhCH_2$), (*S*)-**109c** (R = ^{i}Pr), (*S*)-**109d** (R = ^{t}Bu), and

(*S*)-**109** (R = ^{sec}Bu) provided excellent enantioselectivities (Entries 1, 3, 4 and 8). It is evident that the bulkiness of the substituent on the chiral *N*-salicyl-β-aminoalcohol plays a significant role in determining the degree of selectivity because these highly branched groups having rigid structure can certainly be steric around reaction center. On the other hand, smaller group like methyl group, (*S*)-**109b** (R = Me)**,** gave somewhat lower %ee (Entry 2). In case of (*S*)-**109e** (R = Ph), phenyl group is a flat molecule that can sometimes flip or rotate to reduce bulkiness around reaction center. Thus, the enantioselectivity were slightly decreased. For (*S*)-**109f** and **109g** (R = ^{i}Bu and ^{c}HexCH$_2$), both alkyl side-chains are quite far from reaction center, consequently, steric effect may not much affect the enantioselectivities therefore resulted in lower %ee (Entries 6-7). Moving the substituent to the α-position, (*S*)-**109i** resulted in a racemic product (Entry 9). It can be inferred that substituent at the β-position has less effect on the enantioselectivity of reaction.

In addition, a series of chiral *N*-salicyl-β-aminoalcohols bearing substituents on the salicyl moiety were also investigated. Attempts to increase the steric bulk of salicyl part by using Ti-complexes of (*S*)-**109j**, **109o**, **109q**, and **109s** bearing different bulky substituents at *para*-position on salicyl moiety resulted in slightly decreased enatioselectivities (Entries 10, 15, 17 and 19). Enantioselectivities were dramatically decreased when Ti-complexes of the ligands, (*S*)-**109k**, **109p**, **109r**, and **109t** bearing bulkier subtituents (R^1 = Me, Ph and ^{t}Bu) at *ortho*-position on the salicyl part were employed (Entries 11, 16, 18 and 20). The Ti-complexes (*S*)-**109l**, **109m**, and **109n** bearing bulky groups like Me and ^{t}Bu at both *ortho*- and *para*-positions on the salicyl moiety not only showed the drastically dropped ee but also resulted in very slow reaction rate (Entries 12, 13, and 14). It is evident that the bulkiness of the substituent on the chiral *N*-salicyl-β-aminoalcohol has negative effect to both the degree of enantioselectivity and reaction rate. Poor ee value was also obtained from the reaction catalyzed by Ti-complexes of (*S*)-**109u** bearing strongly electron-withdrawing substituent (a nitro group) (Entry 21). On the other hand, Ti-complexes of the ligands (*S*)-**109v**, (*S*)-**109o** and (*S*)-**109x** bearing weakly electron withdrawing, weakly electron donating and strongly electron-donating substituents (a chloro, a methyl and a methoxy group respectively) catalyzed asymmetric Strecker reactions with high enantioselectivities (Entries 15, 22 and 24). However, the presence of chlorine atom

to *para*-position as in (*S*)-**109v** resulted in a rather poor ee. Furthermore, Ti-complexes of the ligands (*S*)-**109y**, (*S*)-**109z** and (*S*)-**109aa** bearing weakly electron withdrawing and weakly electron donating substituents (a phenyl, a chloro and a methyl group respectively) at *meta*-position also catalyzed the reactions with somewhat lower enantioselectivities (Entries 25-27). Figures 3.12 and 3.13 shown below is the examples of partial ^{1}H-NMR spectra of crude aminonitrile **(73a)** catalyzed by Ti(O^{i}Pr)4-(*S*)-**109** with good and poor enantioselectivity respectively.

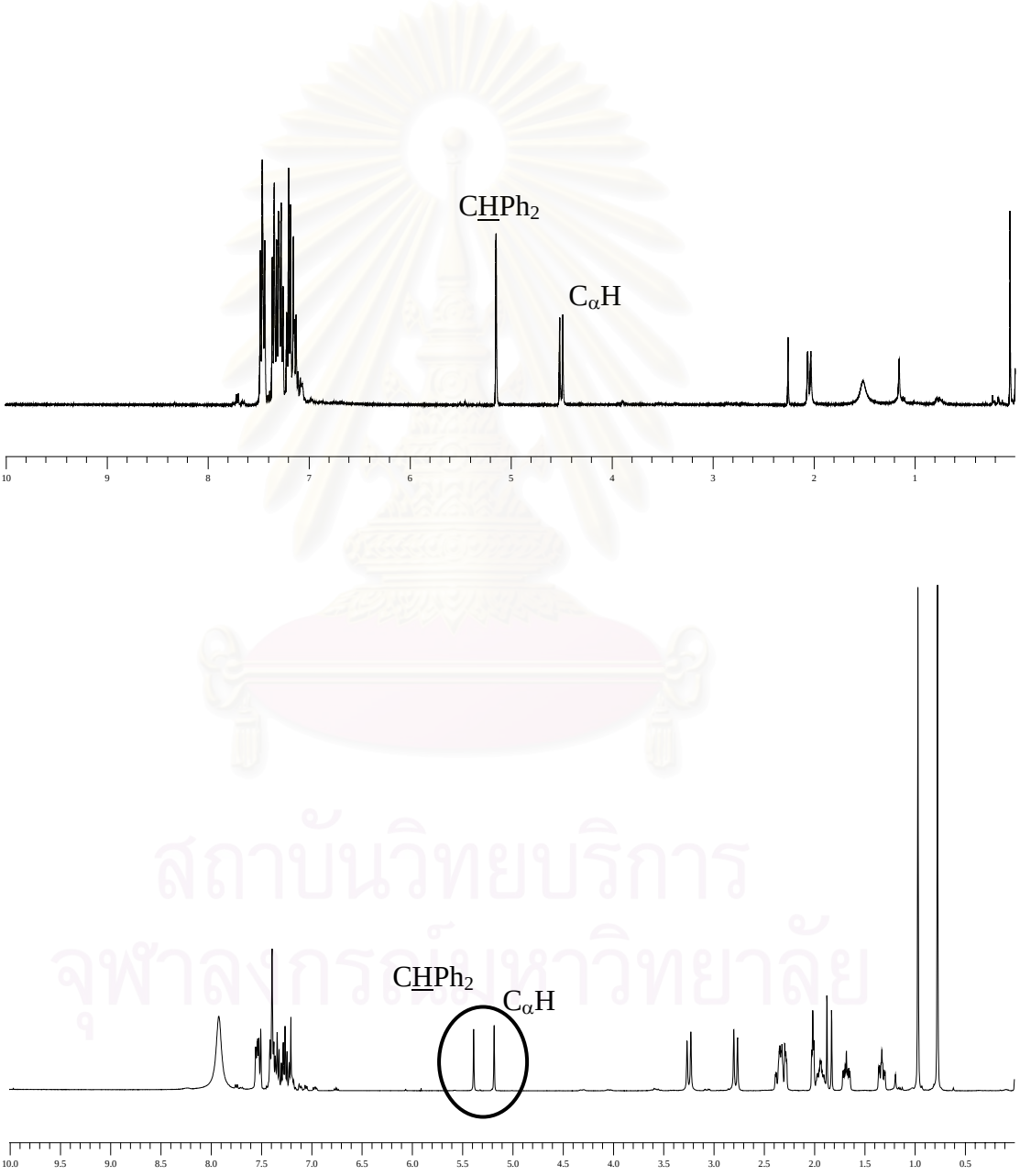


Figure 3.12 Partial ^{1}H-NMR spectra of crude aminonitrile **(73a)** catalyzed by Ti(O^{i}Pr)$_4$-(*S*)-**109a** (400 MHz, $CDCl_3$) (top); in the presence of (*S*)-CSA showing 98% ee (bottom)

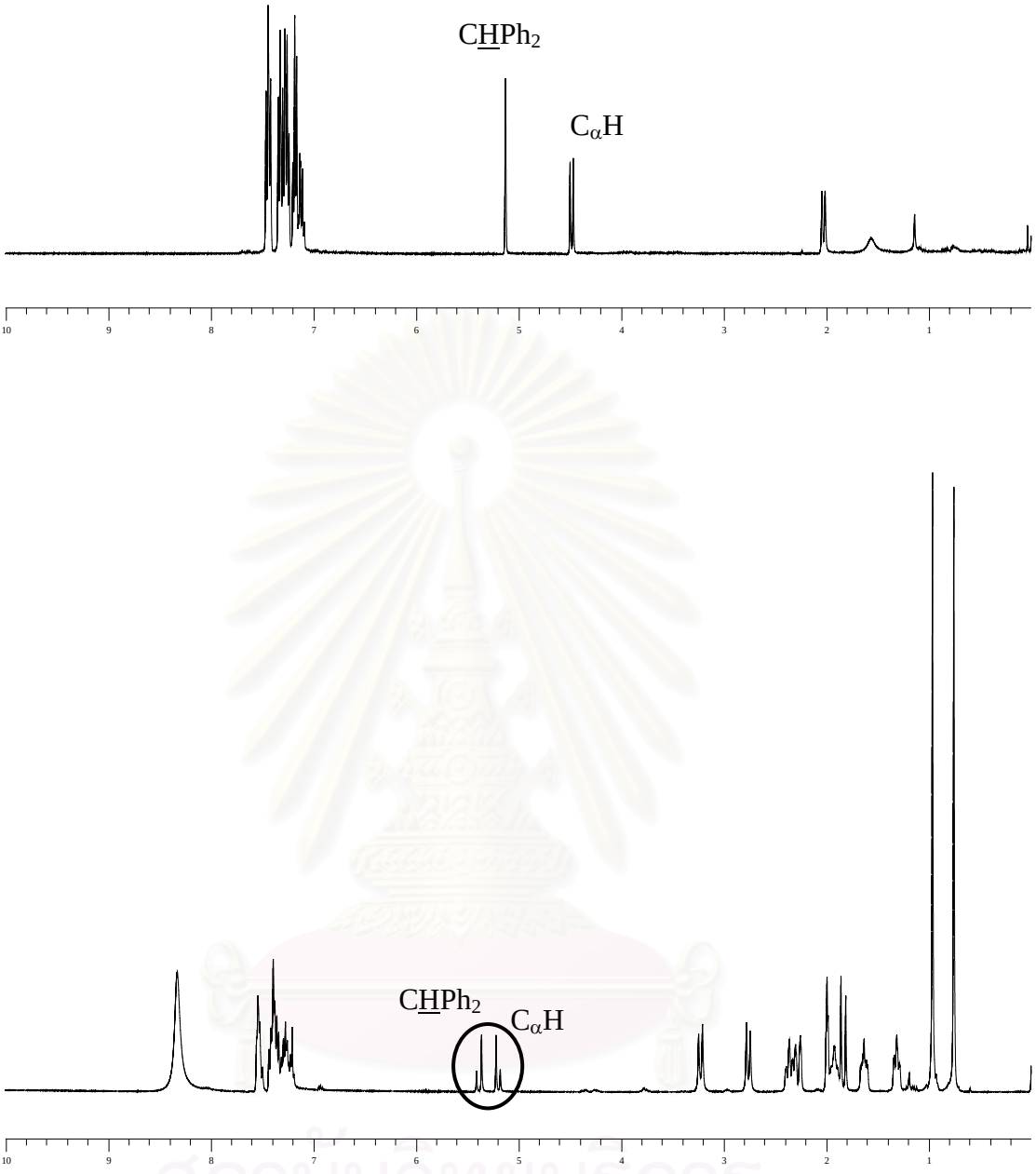


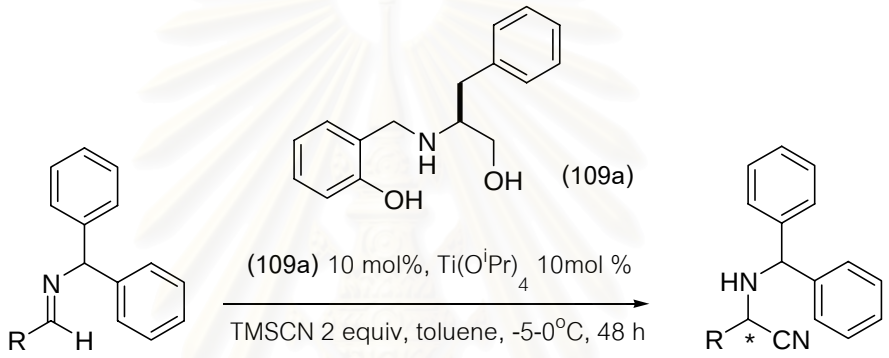
Figure 3.13 Partial ^{1}H-NMR spectra of crude aminonitrile **(73a)** catalyzed by Ti($O^{i}Pr$)$_4$-(*S*)-**109k** (400 MHz, $CDCl_3$) (top); in the presence of (*S*)-CSA showing 41% ee (bottom)

From the results shown above, the effective chiral *N*-salicyl-β-aminoalcohol ligands should only have a sterically hindered substituent at the α-position and without any substituents on the salicyl moiety. Incidentally, the ligand (*S*)-**109a** derived from the commercially available and inexpensive (*S*)-phenylalaninol and

salicylaldehyde, apart from providing excellent yield and ee of the Strecker product, is a stable crystalline solid which can be kept for years at room temperature without detectable degradation. Hence, the ligand (*S*)-**109a** was chosen as the ligand of choice for next experiment.

3.3.2.3 Effect of substrate structure: the nature of aromatic substrates

Table 3.10 Enantioselective Strecker reaction of aromatic benzhydrylimine **(72)** catalyzed by $Ti(O^iPr)_4$-(*S*)-**109a** complexes



(72) (73)

Entry	Substrate	R	% Conversion	% Ee
1	**72a**	Ph	>99	98
2	**72a**	Ph	>99 (15h, rt)	97
3	**72a**	Ph	>99	-98 [a]
4	**72b**	2-MeO-C_6H_4	>99	90
5	**72c**	3-MeO-C_6H_4	>99	94
6	**72d**	4-MeO-C_6H_4	>99	91
7	**72e**	2-Me-C_6H_4	>99	97
8	**72f**	4-Me-C_6H_4	>99	96
9	**72g**	3-NO_2-C_6H_4	>99	98
10	**72h**	4-NO_2-C_6H_4	53 (3 weeks)	51
11	**72i**	2-Cl-C_6H_4	>99	>98
12	**72j**	4-Cl-C_6H_4	>99	95
13	**72k**	2-Br-C_6H_4	>99	>98
14	**72l**	4-Br-C_6H_4	>99	94

Entry	Substrate	R	% Conversion	% Ee
15	**72m**	3-F-C_6H_4	>99	96
16	**72n**	1-naphthyl	98	98
17	**72o**	2-naphthyl	97	96
18	**72p**	2-furyl	>99	98
19	**72q**	2-thienyl	>99	98
20	**72r**	2,6-diMe-C_6H_3	96	71
21	**72s**	2,4,6-triMe-C_6H_2	>99	42
22	**72t**	anthryl	-	-

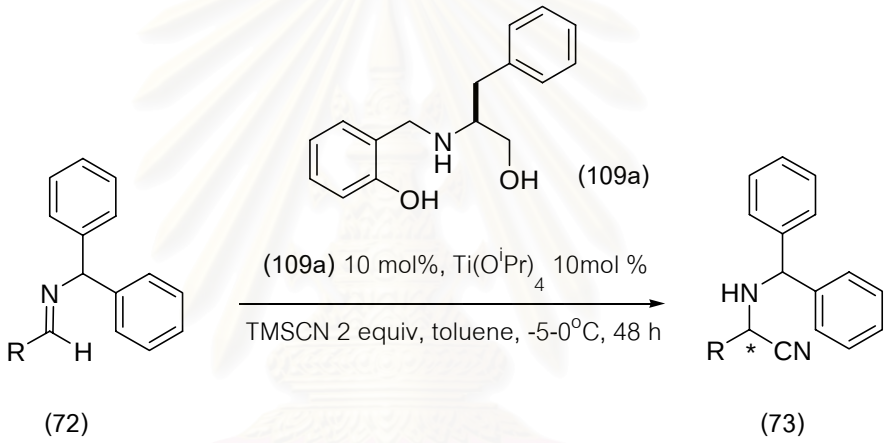
[a] $Ti(O^iPr)_4$-(*R*)-**109a** was the catalyst employed

The substrate generality of enantioselective Strecker reactions employing this class of ligand was investigated. Various *N*-benzhydryl substituted aldimines **(72a-72t)** were subjected to cyanide addition under the optimized conditions obtained thus far using the Ti complex of the crystalline ligand (*S*)-**109a**. It was found that optically active α-aminonitriles **73** were generally obtained in excellent yields and with high enantioselectivities. High percent conversion and enantiomeric excess were routinely observed (usually >99% yield and >90% ee respectively) for various imine substrates derived from aromatic aldehydes bearing electron donating and withdrawing groups and benzhydrylamine (Table 3.10). The Strecker reaction of *N*-benzhydrylimine **(72a)** in the presence of either $Ti(O^iPr)_4$-(*S*)-**109a** or $Ti(O^iPr)_4$-(*R*)-**109a** provided the corresponding optically active α-aminonitriles in 98% ee with opposite absolute stereochemistry (Entries 1 and 3). The reaction proceeded faster at room temperature and still gave α-aminonitrile in excellent enantioselectivity (97% ee) (Entry 2). Substituents with various steric (entries 4, 7, 11, 13, 16-17 and 20-22) and electronic (entries 1, 5-6, 8-10, 12, and 14-15) natures appeared to be well-tolerated. Substrates bearing strongly electron donating group (Entry 5-6) and ortho substituents such as 2-OMe-derivative (Entry 4) gave slightly lower % ee. Surprisingly, the reaction of substrates bearing strongly electron withdrawing group at *para*-position such as 4-NO_2-derivative took place with a very slow reaction rate and resulted in poor enantioselectivity (Entry 10). Heteroaromatic imines derived from fufural and thiophene-2-carboxaldehyde still gave the excellent conversion and with high enantioselectivities (Entries 18-19). Attempt to increase the steric bulk of the R^1

group by using substrates derived from 2,6-dimethylbenzaldehyde and 2,4,6-trimethylbenzaldehyde resulted in a dramatically decreased % ee (Entries 20-21). In another extreme case, no reaction was observed with an imine derived from 9-anthracenaldehyde as a result of the sterically bulkiest group of R^1 part on the substrate (Entry 22).

3.3.2.4 Effect of substrate structure: the nature of aliphatic substrates

Table 3.11 Enantioselective Strecker reaction of aliphatic benzhydrylimine **(72)** catalyzed by $Ti(O^iPr)_4$-(*S*)-**109a** complexes

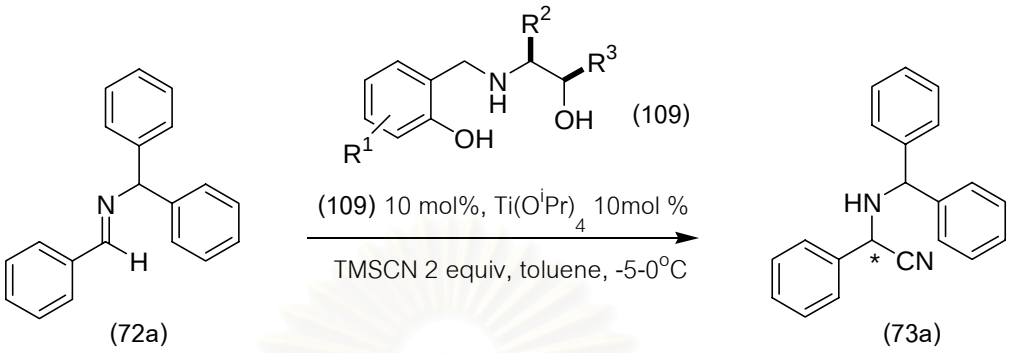


(72) (73)

Entry	Substrate	R	% Conversion	% Ee
1	**72u**	cyclohexyl	>99	0
2	**72v**	^{t}Bu	>99	23
3	**72w**	cinnamyl	>99	61

Aliphatic substrates such as those derived from cyclohexane carboxaldehyde, pivalaldehyde and cinnamaldehyde were also investigated (Table 3.11). While the conversion was still very good, the reactions gave much poorer ee's at similar conversion when compared to aromatic substrates (Entries 2-3). Only racemic α-aminonitrile was especially obtained in case of imine derived from cyclohexane carboxaldehyde (Entry 1). Nevertheless, a much better %ee can be obtained with other more sterically bulky ligand.

Table 3.12 Enantioselective Strecker reaction of aliphatic benzhydrylimine **(72)** catalyzed by $Ti(O^iPr)_4$-(*S*)-**109** complexes



(72a) (73a)

Entry	Ligand	R^1	R^2	R^3	R	% Conversion	% Ee
1	(*S*)-**109a**	H	CH_2Ph	H	^tBu	>99	23
2	(*S*)-**109d**	H	^tBu	H	^tBu	>99	47
3	(*S*)-**109h**	H	^{sec}Bu	H	^tBu	>99	51
4	(*S*)-**109a**	H	CH_2Ph	H	cinnamyl	>99	61
5	(*S*)-**109d**	H	^tBu	H	cinnamyl	>99	88
6	(*S*)-**109h**	H	^{sec}Bu	H	cinnamyl	>99	91

Enantioselectivities of α-aminonitrile obtained from aliphatic aldimines can be significantly improved by employing the ligands bearing bulkier substituents such as (*S*)-**109d** and (*S*)-**109h** (Table 3.12). It can be inferred that a good correlation between the size of alkyl side-chain at β-position and degree of enantioselectivity is on the same trend. Ligands bearing a relatively sterically hindered substituent at β-position provided substantially increased higher %ee (R^2 = Bn < ^tBu < ^{sec}Bu). Nevertheless, it is clear that aliphatic substrates are not quite as good substrate as aromatic ones.

3.3.2.5 Effects of protic additives

From screening results obtained, there are two points that should be concerned. These are % conversion and % enantiomeric excess. In some cases, the reaction rate were slow (substrates bearing strongly electron withdrawing group) and % ee were low (substrates bearing strongly electron donating group). Indeed, in most cases, the reaction did not proceed to completion when the reactions were scaled up from 0.1 mmol to 0.5 or 1 mmol. The same phenomenon was observed in other Strecker reactions [147-148, 156-157] and there was several reports on the beneficial effect of protic additives such as 2-propanol in such cases. Previous works [147,156] in this area have demonstrated the importance of proton sources in similar reactions. It is the fact that alcohols react with TMSCN to afford HCN.[191] Therefore the proton source can generate HCN from TMSCN, which is believed to be the actual cyanating species.[156] Furthermore, since the catalyst contains free hydroxylic functions which should be susceptible to silylation by TMSCN under the reaction conditions, a proton source should increase the catalyst turnover by preventing silylation of, or by regenerating, the hydroxylic function of the catalyst. To address the efficiency problem based on our experimental observations that is aforementioned, we were pleased to find that addition of a proton source as 2-propanol (^{i}PrOH) completely restored the catalytic activity in larger scale reactions.

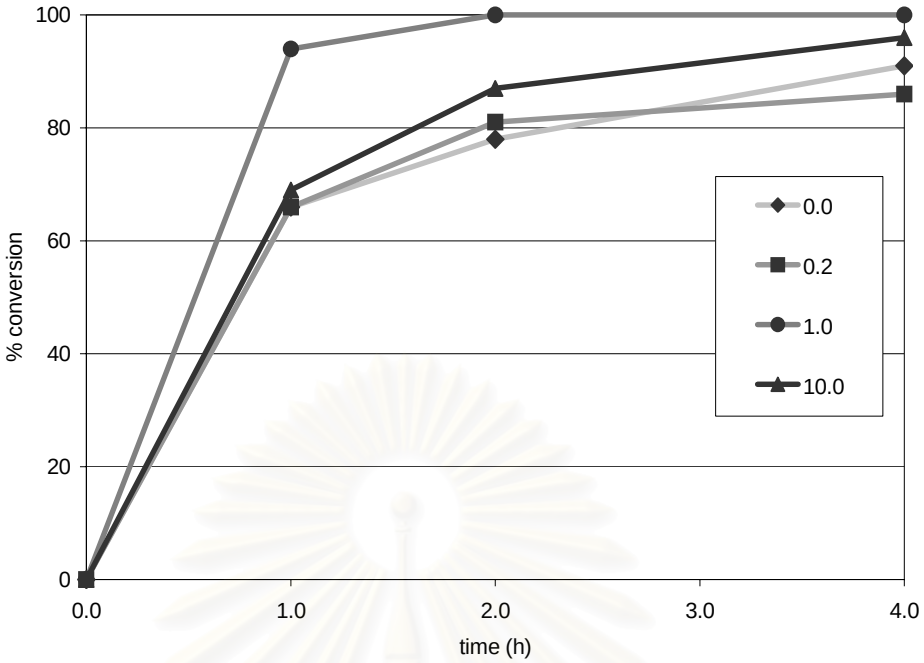


Figure 3.14 The rate of cyanation of imine **(72a)** at 0 ^{o}C in the presence of 10 mol% Ti($O^{i}Pr$)$_4$-(*S*)-**109a** complex and 0, 0.2, 1.0 or 10 equiv of 2-propanol

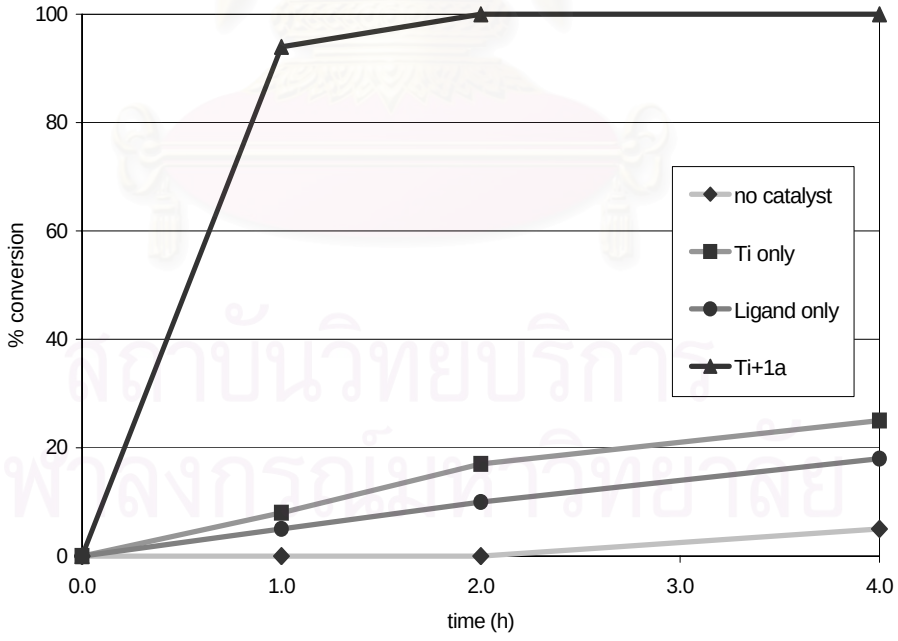


Figure 3.15 The rate of cyanation of imine **(72a)** at 0 ^{o}C in the presence of 10 mol% Ti($O^{i}Pr$)$_4$-(*S*)-**109a** complex and 1.0 equiv of 2-propanol and with or without Ti($O^{i}Pr$)$_4$ and/or (*S*)-**109a** (10 mol%)

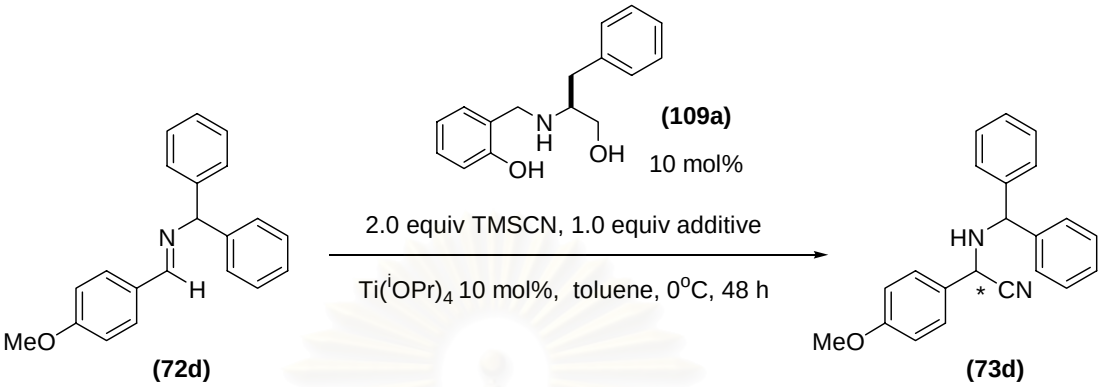
Kinetic analysis by ^{1}H NMR spectroscopy of the Ti-(*S*)-**109a** complex catalyzed cyanation of imine **(72a)** conducted in the presence of different amounts of 2-propanol additive suggested that the reaction rate was significantly enhanced compared to the reaction without the additive (Figure 3.14). The reaction rate was faster when the equivalent amount of added ^{i}PrOH is increased from 0.0 to 0.2 and 1.0 and reaches a maximum when an amount of the additive is used in equal to the amount of substrate under these conditions. The reaction was completed within 2 hours at 0 ^{o}C. Interestingly, a large excess of 2-propanol (10 equiv) caused not only a significantly slower reaction rate, but also provided almost racemic product. It appears that only an appropriate equivalent amount of ^{i}PrOH would effectively accelerate the rate of reaction.

The reactions in the presence of 1.0 equiv ^{i}PrOH but without the Ti-(*S*)-**109a** catalyst or either of its components were very slow (Figure 3.15). In all cases the conversion was < 20% after 2 h at 0 ^{o}C. This suggested that the background hydrocyanation is almost insignificant under the experimental conditions. Consequently, the slow addition of ^{i}PrOH or performing the reaction at very low temperatures employed by other investigators may not be essential to ensure good enantioselectivities, at least for this particular substrate. This would greatly simplify the synthetic procedure. Indeed, we have found that the additive can be added at the beginning of the reaction without any adverse effects on the yield and the total exclusion of all adventitious moisture was difficult which explains why the reaction proceeded to completion without the need for the protic additive in small scale (0.2 mmol).

3.3.2.6 Attempts to improve ee values for reactive starting materials

To screen for other suitable protic additives that might provide even better ee, the Strecker reaction of *N*-benzhydrylimine derived from 4-methoxy benzaldehyde **(72)** was chosen as a model reaction (Table 3.13).

Table 3.13 Enantioselective Strecker reaction of 4-methoxy-benzhydrylimine **(72d)** catalyzed by $Ti(O^iPr)_4$-(*S*)-**109a** complexes with additives

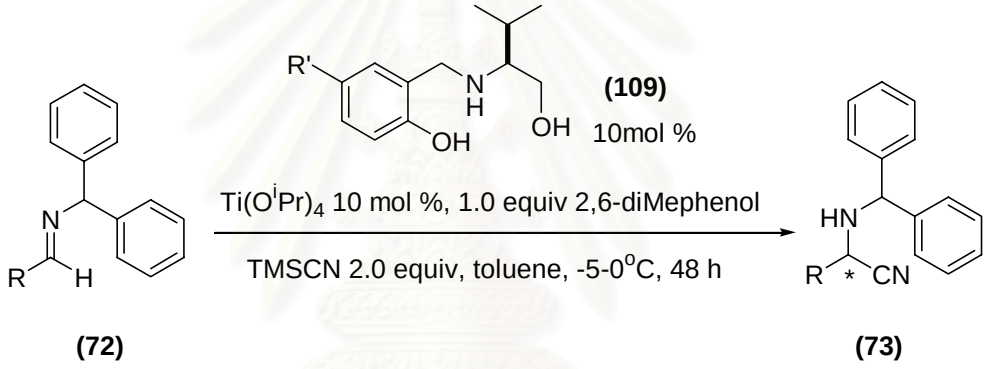


Entry	additive	% Conversion	% Ee
1	-	>99	91
2	H_2O	>99	7
3	^{i}PrOH	>99	91
4	HFIP	>99	42
5	PhOH	>99	88
6	2-methylphenol	>99	88
7	2,6-dimethylphenol	>99	92
8	2,4-di-*tert*-butylphenol	>99	40

Reaction of this imine is very fast and usually gave high % conversion but low % ee. H_2O as additive resulted in very poor %ee (Entry 2). Addition of HFIP, phenol, 2-methylphenol or 2,4-di-*tert*-butylphenol showed fair to good enantioselectivities (Entries 4-6 and 8). Gratifyingly, an almost equally high %ee were obtained when ^{i}PrOH and 2,6-dimethylphenol were employed (Entries 3 and 7). It can be implied that the rate of HCN generation or proton releasing is sufficiently slow in both cases. For 2,6-dimethylphenol, the sterically bulky group at both *ortho*-positions on phenol might be a cause of slower rate of HCN generation and improvement of enantioselectivity. However, ^{i}PrOH is an inexpensive, non-toxic and readily vailable, its use as additive is preferred.

With the hope of improving the results with both strongly electron-donating and electron-withdrawing substituted imines, we evaluate the effect of the catalyst structure on reaction rate and enantioselectivity. Difficult substrates such as 4-OMe benzhydrylimine **(72d)** and 4-NO_2 benzhydrylimine **(72h)** which react too fast and too slow respectively were carried out in the presence of 10 mol% different catalysts and 1 equiv of 2,6-dimethylphenol under the optimized condition obtained previously (Table 3.14).

Table 3.14 Enantioselective Strecker reaction of 4-OMe benzhydrylimine **(72d)** and 4-NO_2 benzhydrylimine **(72h)** catalyzed by Ti(O^iPr)$_4$-(*S*)-**109** complexes with 2,6-dimethylphenol



(72) **(73)**

Entry	Substrate	Ligand	R	R′	% Conversion	% Ee
1	**72d**	(*S*)-**109c**	4-MeO-C_6H_4	H	>99	97
2	**72d**	(*S*)-**109p**	4-MeO-C_6H_4	Me	>99	95
3	**72d**	(*S*)-**109x**	4-MeO-C_6H_4	OMe	>99	96
4	**72d**	(*S*)-**109v**	4-MeO-C_6H_4	Cl	>99	92
5	**72d**	(*S*)-**109u**	4-MeO-C_6H_4	NO_2	>99	13
6	**72h**	(*S*)-**109c**	4-NO_2-C_6H_4	H	67	80[a]
7	**72h**	(*S*)-**109p**	4-NO_2-C_6H_4	Me	77	92[a]
8	**72h**	(*S*)-**109x**	4-NO_2-C_6H_4	OMe	81	71[a]
9	**72h**	(*S*)-**109v**	4-NO_2-C_6H_4	Cl	62	63[a]
10	**72h**	(*S*)-**109u**	4-NO_2-C_6H_4	NO_2	56	56[a]

[a] The reaction time for 4-NO_2 substrate is 3 weeks

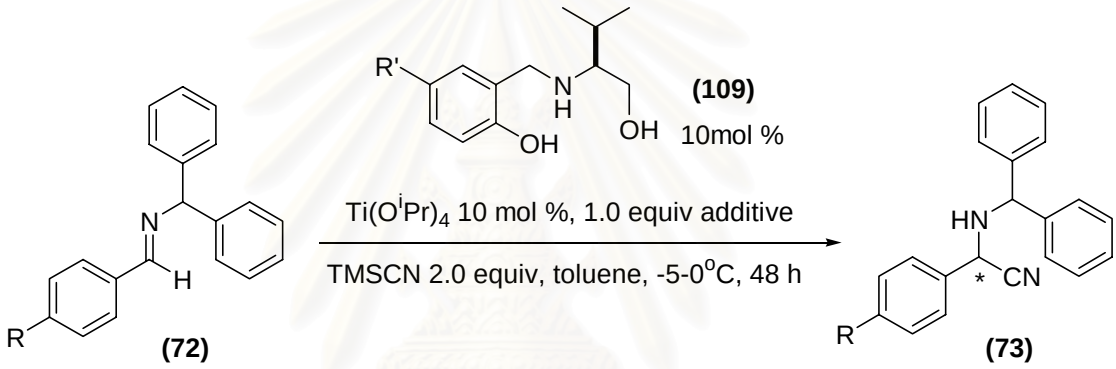
The asymmetric Strecker reaction of 4-OMe benzhydrylimine **(72d)** catalyzed by Ti(O^iPr)$_4$-(*S*)-**109c** complex which has no substituent on salicyl moiety provided excellent enantioselecivity (Entry 1). Ti(O^iPr)$_4$-(*S*)-**109p and 109x** complexes bearing electron-donating groups at *para*-position on salicyl part catalyzed the similar reactions with slightly lower enantioselectivities (Entries 2-3). A significantly, reduced ee values were obtained in the reaction of 4-OMe benzhydrylimine **(72d)** catalyzed by Ti(O^iPr)$_4$-(*S*)-**109v** and **109u** complexes bearing electron-withdrawing groups at *para*-position on salicyl part (Entries 2 and 3). Only 13 %ee of α-aminonitrile almost being a racemic poduct were acquired with employing of Ti(O^iPr)$_4$-(*S*)-**109u** complex bearing strongly electron-withdrawing group like nitro (-NO_2) as catalyst (Entries 3).

In the next series, substrate with very slow reaction rate as 4-NO_2 benzhydrylimine **(72h)** was investigated. Asymmetric strecker reaction of this type of substrate with 10 mol% Ti(O^iPr)$_4$-(*S*)-**109c** complex under the similar condition gave the poor %conversion and only moderate %ee (Entry 6). The good results in term of reaction rate and enantioselectivity were obtained (77% conversion, 92% ee) when Ti(O^iPr)$_4$-(*S*)-**109p** complex bearing electron-donating group as methyl (Me) at para-position on salicyl part was employed (Entry 7). Unexpectedly, % ee was substantially decreased in the reaction catalyzed by Ti(O^iPr)$_4$-(*S*)-**109x** bearing strongly electron-donating group as methoxy (OMe). Nevertheless, the reaction rate was still increased (81% conversion and 71% ee, entries 8). The similar trend was observed with the employing Ti(O^iPr)$_4$-(*S*)-**109v** and **109k** complexes bearing electron-withdrawing group at *para*-position on the salicyl part (Entries 9-10). Both poor % conversion and % ee were obtained especially for the reaction catalyzed by Ti(O^iPr)$_4$-(*S*)-**109u**. For substrate with very slow reaction as 4-NO_2 benzhydrylimine **(72h)**, it can be noticed that Ti(O^iPr)$_4$-(*S*)-**109** complexes bearing weakly electron-donating group as methyl catalyzed the asymmetric strecker reaction with faster reaction rates and higher enantioselectivities. Ti(O^iPr)$_4$-(*S*)-**109** complexes bearing strongly electron-donating group as methoxy catalyzed also the reaction with fastest reaction rate but showed a lower enantioselectiviy. On the other hand, Ti(O^iPr)$_4$-(*S*)-**109** complexes bearing electron-withdrawing groups were not only catalyzed the reactions with very slow reaction rate but also resulted in the poor enantioselectivities.

3.3.2.7 Protic additives: 2,6-dimethylphenol vs ^{i}PrOH

The previous results from several asymmetric Strecker reactions of 4-OMe benzhydrylimine **(72d)** and 4-NO_2 benzhydrylimine **(72h)** catalyzed by Ti($O^{i}Pr)_4$-(*S*)-**109c** complexes in the presence of 1 equiv 2,6-dimethylphenol were compared to the results of the similar reactions that 1 equiv ^{i}PrOH was used instead (Table 3.15).

Table 3.15 Enantioselective Strecker reaction of 4-OMe benzhydrylimine **(72d)** and 4-NO_2 benzhydrylimine **(72h)** catalyzed by Ti($O^{i}Pr)_4$-(*S*)-**109** complexes with ^{i}PrOH or 2,6-dimethylphenol



Entry	Substrate	Ligand	Additive	R	R′	% Conversion	% Ee
1	**72d**	**3c**	^{i}PrOH	MeO	H	>99	97
2	**72d**	**3c**	2,6-diMe-phenol	MeO	H	>99	97
3	**72d**	**3x**	^{i}PrOH	MeO	OMe	>99	96
4	**72d**	**3x**	2,6-diMe-phenol	MeO	OMe	>99	96
5	**72d**	**3u**	^{i}PrOH	MeO	NO_2	>99	13
6	**72d**	**3u**	2,6-diMe-phenol	MeO	NO_2	>99	9
7	**72h**	**3x**	^{i}PrOH	NO_2	H	>99	80[a]
8	**72h**	**3x**	2,6-diMe-phenol	NO_2	H	67	79[a]

[a] The reaction time for 4-NO_2 substrate is 3 weeks

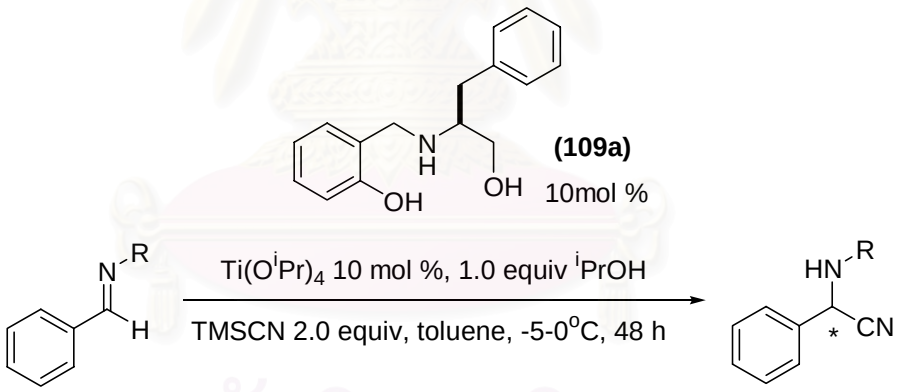
Practically the same results were obtained in the most cases (Entries 1-6). Except for reactions of 4-NO_2 benzhydrylimine **(72h)**, complete reaction and equal ee value were observed when ^{i}PrOH was used, compared to the use of 2,6-

dimethylphenol as additive (Entries 7-8). This experiment double confirmed that ^{i}PrOH can be used instead of 2,6-dimethylphenol. Indeed, 2,6-dimethylphenol is actually quite difficult to remove from the scaled-up reactions and also not as environmentally friendly. Therefore, ^{i}PrOH is finally selected to be the most appropriate additive for asymmetric Strecker reactions.

3.3.2.8 Effect of substrate structure: the nature of *N*-substituents

In order to investigate the effect of the structure of various *N*-substituted imines on the enantioselectivity of the reaction, the related *N*-substituted imines were prepared by condensation of benzaldehyde and various amines. These imines were then screened under the best conditions (Table 3.16).

Table 3.16 Enantioselective Strecker reaction of *N*-substituted imine derived from benzaldehyde catalyzed by Ti(O^{i}Pr)$_4$-(*S*)-**109a** complex with ^{i}PrOH



Entry	Substrate	R	% Conversion	% Ee
1	**79a**	Bn	>99	79
2	**72a**	Ph_2CH	>99	98
3	**110**	Ph_3C	-	-
4	**125**	^{t}Bu	>99	37

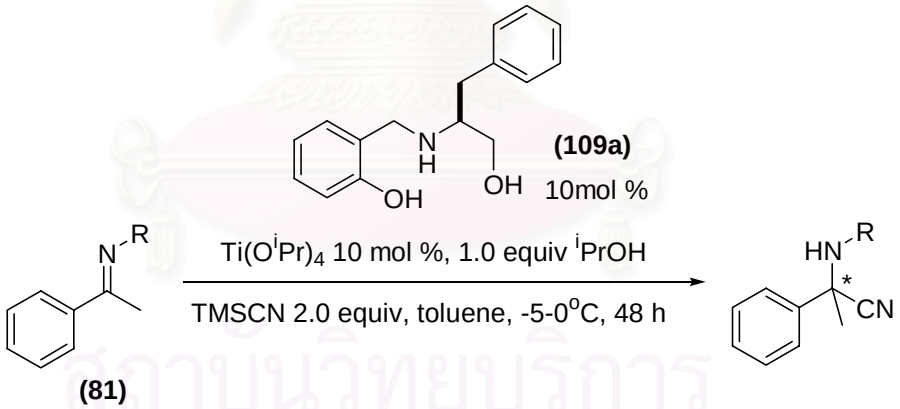
The reaction of *N*-benzylidenebenzylamine **(79a)** catalyzed by the Ti(O^{i}Pr)$_4$-(*S*)-**109a** complex under the best condition showed a moderate enantioselectivity. Attempt to increase the steric bulk of the *N*-substituent from benzyl group to

diphenylmethyl group **(72a)** resulted in excellent enantioselectivity. Unfortunately, no reaction was observed when *N*-benzylidenetritylamine **(110)** was employed. Moreover, replacement of the the *N*-substituent with in *N*-benzylidene-^{t}butylamine **(125)** resulted in considerably lower ee′s. the *N*-substituent exert a very significant influence on the enantioselectivity of the reaction. It can be concluded that too much bulkiness of substituents at *N*-position on imines inhibited the reaction and *N*-benzhydryl substituents was the optimal.

3.3.2.9 Effect of substrate structure: ketimines

We also attempted to extend the scope of the reaction by employing ketimines derived from acetophenone as substrates. The substrates were screened under the best condition (Table 3.17).

Table 3.17 Enantioselective Strecker reaction of ketimines **(81)** derived from acetophenone catalyzed by Ti(O^{i}Pr)$_4$-(*S*)-**109a** complex with ^{i}PrOH



Entry	Substrate	R	% Conversion	% Ee
1	**81a**	Bn	88	0
2	**81b**	Ph_2CH	>99	0

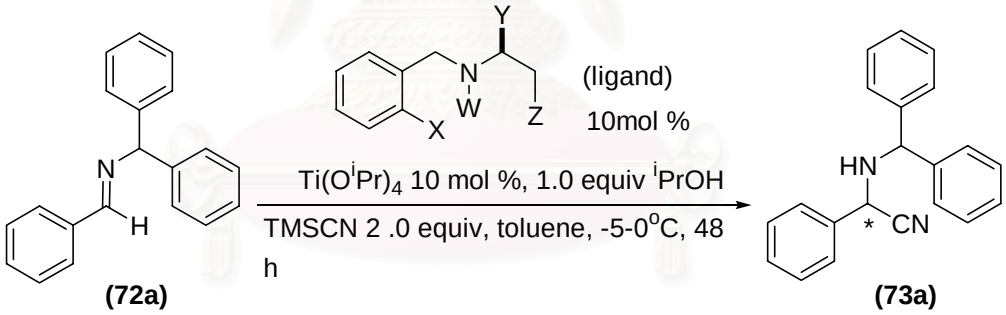
Ketimines derived from acetophenone and benzylamine **(81a)** or diphenylmethylamine **(82b)** were evaluated using Ti(O^{i}Pr)$_4$-(*S*)-**3a** complex. Complete conversion of ketimine **(82b)** occurred within 48 h to give the corresponding Strecker adduct, but only 88% conversion was observed for ketimine

(81a). Even more disappointingly, racemic products were observed in both cases. It is therefore concluded that ketimines are not good substrate for enantioselective Strecker reaction using this particular catalysts. It is possible that these substrates undergo a facile reversible addition of cyanide due to a highly stabilized iminium ion compared to those of aldimines (see 3.4.2)

3.3.2.10 Effect of ligand structure

To investigate the effect of the structure of ligands on the enantioselectivity of the reaction, the related *N*-salicyl-β-aminoalcohol ligands **(109a-109e)** were synthesized by aforementioned methods. These ligands were screened under the best condition (Table 3.18).

Table 3.18 Enantioselective Strecker reaction of *N*-benzylidenebenzhydrylamine **(72a)** catalyzed by several $Ti(O^iPr)_4$-(*S*)-**109** complexes with ^iPrOH for study of the effect of ligand structure



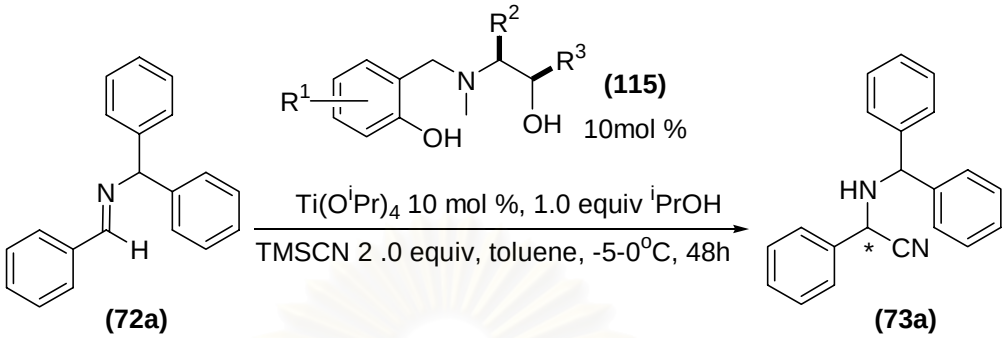
(72a) **(73a)**

Entry	Ligand	W	X	Y	Z	% Conversion	% Ee
1	**109a**	H	OH	Bn	OH	>99	98
2	**109ab**	H	OMe	Bn	H	11	0
3	**109ae**	H	OH	Bn	OMe	>99	16
4	**115c**	Me	OH	Bn	OH	>99	24
5	**109e**	H	OH	Ph	OH	>99	91
6	**109ac**	H	H	Ph	OH	78	3
7	**109ad**	H	OH	Ph	H	69	7

First, it was aimed to investigate the ability of the ligands which were blocked at one of the coordinating atom by methylation or by removing the oxygen atom, can still catalyze the asymmetric Strecker reactions or not. The reactions catalyzed by $Ti(O^iPr)_4$-(*S*)-**109ae** and **115c**, resulted from methylation of *N* and *O* atom on β-amino alcohol moiety, resulted in complete reactions but very poor enantioselectivities (Entries 3-4) when compared to the unmodified (*S*)-**109a** (Entry 1). Interestingly, both very low % conversion and racemic product were obtained from the reaction catalyzed by $Ti(O^iPr)_4$-(*S*)-**109ab**, the phenolic OH of which was methylated (Entry 2). It can be concluded that this phenolic oxygen is crucial for catalytic activities as well as enantioselectivity while the NH and alcoholic OH are only essential for enantioselectivity.

The next purpose for the synthesis of ligands **(109e**, **109ac** and **109ad)** is also to prove whether the Ti complex of ligands containing only two coordinating atoms can still catalyze the asymmetric Strecker reactions as well or not. The standard reaction catalyzed by $Ti(O^iPr)_4$-(*S*)-**109e** proceeded to completion with high enantioselectivity (Entry 5). On the other hand, the $Ti(O^iPr)_4$-(*S*)-**109ac** and **109ad** complexes**,** which contained only two coordinating sites, apart from providing low conversion, very low enantioselectivities were obtained. These experiments emphasize that the presence of two free O<u>H</u> (×2) and one N<u>H</u> in the ligand **(109)** are essential for both catalytic activity. It is most likely that the ligand bind to Ti in a tridentate fashion.

Table 3.19 Enantioselective Strecker reaction of *N*-benzylidenebenzhydrylamine **(72a)** catalyzed by several $Ti(O^iPr)_4$-(*S*)-**115** complexes



Entry	Ligand	R^1	R^2	R^3	% Conversion	% Ee
1	(*S*)-**115a**	^{t}Bu	-$C_6H_4CH_2$-		>99	0
2	(*S*)-**115b**	3-Cl	^{i}Pr	H	>99	12
3	(*S*)-**115c**	H	CH_2Ph	H	>99	24
4	(*S*)-**115d**	2,4-di ^{t}Bu	^{t}Bu	H	>99	0
5	(*S*)-**115e**	4-Ph	Ph	H	>99	11
6	(*S*)-**115f**	3-Me	^{i}Pr	H	>99	14
7	(*S*)-**115g**	3-Ph	^{i}Pr	H	>99	8

All *N*-methylated ligands catalyzed asymmetric Strecker reaction with very poor enantioselectivities (Table 3.19). It was clarified that presence of phenolic and alcoholic OH and NH in the ligand plays significant role in the enantioselection.

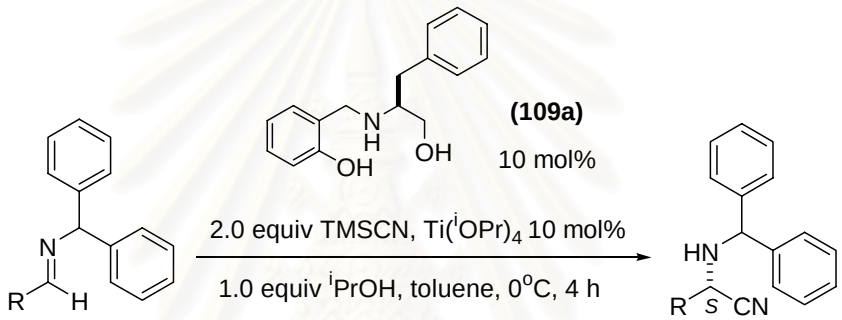
3.4 Development of practical Strecker reactions

3.4.1 Decreasing the amount of catalyst

To ascertain that the protic additive was generally beneficial for large scale reactions with other substrates, a few more representative reactions were performed at 1 mmol scale in the presence of 10 mol% catalyst prepared from ligand (*S*)-**109a** (25 mg of the ligand/mmol of substrate) with 1.0 equiv of 2-propanol added at the beginning and 2.0 equiv of TMSCN in toluene at 0 ^oC. The results were shown in Table 3.20. ^1H NMR analysis of the crude reaction mixture revealed that most

reactions were completed within 4 hours, and that the enantioselectivities were comparable to the small scale reactions. Interestingly, after attempted purification by passing through silica gel or alumina column, a significant racemization was observed especially for products bearing electron donating substituents (e.g., 2-furyl, 2-thienyl, 2- and 4-methoxyphenyls) so that the final products were obtained only in 50-75% ee. Fortunately, addition of a small amount of triethylamine 1% to the eluent largely suppressed the racemization.

Table 3.20 Enantioselective Strecker reaction of aromatic benzhydrylimine **(72)** catalyzed by $Ti(O^iPr)_4$-(*S*)-**109** complex with ^{i}PrOH at 1 mmol scale



(72) **(73)**

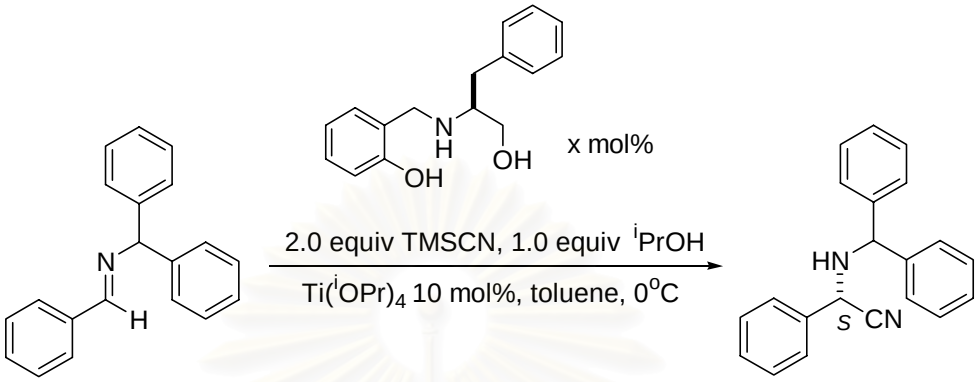
Entry	Substrate	R	% yield	% Ee
1	**72a**	Ph	85	96
2	**72a**	Ph	85	96[a]
3	**72b**	2-OMe-C_6H_4	84	83
4	**72d**	4-OMe-C_6H_4	85	91
5	**72e**	2-Me-C_6H_4	84	>98
6	**72i**	2-Cl-C_6H_4	84	>98
7	**72k**	2-Br-C_6H_4	80	>98
8	**72n**	1-Naphthyl	91	>98
9	**72n**	1-Naphthyl	87	>98[a]
10	**72p**	2-furyl	82	91
11	**72q**	2-thienyl	83	98

[a] The reaction was catalyzed by $Ti(O^iPr)_4$-(*R*)-**109a**

In all cases, the isolated yields of the crystalline products were > 80% and the enantioselectivities were good to excellent (Entries 1-10). The absolute configuration of all products derived from the ligand (*S*)-**109a** was confirmed to be *S* by comparison of the optical rotations with literature values.[157] It should be noted that for R = 2-thienyl and 2-furyl, although the sense of asymmetric induction is the same, the absolute configuration must be designated as *R* according to Cahn-Ingold-Prelog sequence rules. The stereoselectivity of the enantioselective Strecker reaction induced by the Ti-**109** catalyst is, therefore, fully controlled by the absolute configuration of the ligand **109**. It is obvious that aminonitriles with opposite configuration should be obtained simply by switching to the enantiomeric ligand. The presence of only one stereogenic center in the ligand moiety means that the other enantiomer would be much more easily obtained than those with multiple stereogenic centers. Gratifyingly, the enantioselective reaction of aromatic benzhydrylimine **(72n)** catalyzed by $Ti(O^iPr)_4$-(*S*)- and (*R*)-**109a** for 10 mmol scale provided α-aminonitriles with 90% yield and >98% ee. The results showed that this enantioselective Strecker reaction catalyzed by $Ti(O^iPr)_4$-**109** was definitely successful for practically huge scale synthesis.

Although the scaled-up asymmetric Strecker reactions were achieved with good isolated yields of corresponding α-aminonitriles and excellent enantioselecivities. The catalyst loading was still fairly high (10 mol%). We believed that % catalyst loading can be reduced. This reduction of catalyst loading will be beneficial to practical scale synthesis and also can be indicated how efficient the catalyst has. To develop the most practically useful process, the protocol for our previously reported asymmetric Strecker reaction catalyzed by Ti-*N*-salicyl β-aminoalcohol was further optimized. The ligand (*S*)-**109a** derived from (*S*)-phenylalaninol was still the ligand of choice due to its low cost and good crystallinity in addition to excellent *ee* provided for most substrates. A protic additive 2-propanol (1 equiv) is required to ensure complete and reproducible results. At 1 mmol scale, weighing of as little as 1 mol% of the catalyst was quite practical. The results were summarized in Table 3.21.

Table 3.21 Enantioselective Strecker reaction of *N*-benzylidenebenzhydrylamine **(72a)** catalyzed by different loading of Ti(O^iPr)$_4$-(*S*)-**109a** complex with ^{i}PrOH at 1 mmol scale

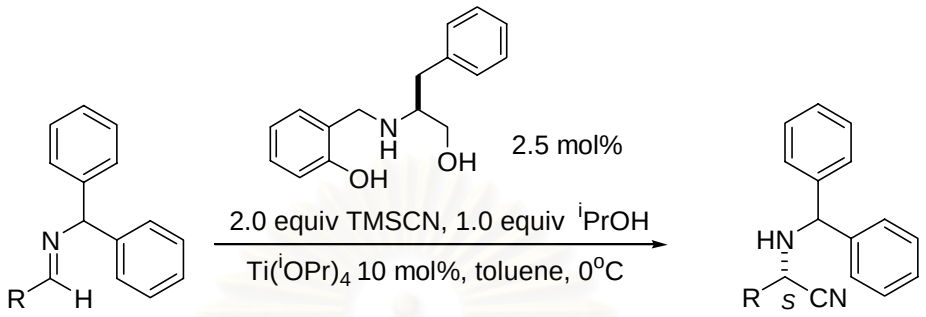


(72a) **(73a)**

Entry	x	% Conversion	Time (h)	% ee
1	10	>99	24	98
2	5.0	>99	24	98
3	2.5	>99	24	98
4	2.0	>99	24	90
5	1.0	72	24	70

After several attempts to reduce the catalyst loading from 10 mol% previously employed (Entry 1), it was found that lower % catalyst loading as 5.0 and 2.5 % still provided the excellent enantioselecitivity (Entries 2-3). A fairly good level of ee of the α-aminonitriles could still be obtained at only 2 mol% (Entry 4) Unacceptably poor % conversion and ee, (72% and 70%), were obtained at 1 mol% (Entry 5). The 2.5 mol% catalyst loading was preferably used for scaled-up synthesis because it seemed to exhibit more substrate tolerance. It was surprising to note that even at such a low catalyst loading, there was no need to slowly add the protic additive to the reaction, which greatly simplified the reaction procedure. In fact, slow addition of the additive did not improve the ee of the product. The optimal temperature was found to be at 0 ^{o}C. Attempts to decrease the temperature further results in very slow reaction rate and the *ee* was not improved.

Table 3.22 Enantioselective Strecker reaction of aromatic benzhydrylimine **(72)** catalyzed by 2.5 mol % Ti(O^iPr)$_4$-(*S*)-**109a** complex with ^{i}PrOH at 1 mmol scale



Entry	Substrate	R	% yield	% Ee
1	**72a**	Ph	95	98
2	**72a**	Ph	95	-98[a]
3	**72e**	2-Me-C_6H_4	99	98
4	**72f**	4-Me-C_6H_4	97	>98
5	**72i**	2-Cl-C_6H_4	98	>98
6	**72j**	4-Cl-C_6H_4	94	98
7	**72k**	2-Br-C_6H_4	97	>98
8	**72l**	4-Br-C_6H_4	98	96
9	**72m**	3-F-C_6H_4	99	96
10	**72n**	1-Naphthyl	91	98
11	**72n**	1-Naphthyl	89	-98[a]
12	**72o**	2-Naphthyl	96	98

[a] The reaction was catalyzed by Ti(O^iPr)$_4$-(*R*)-**109a**

The new optimized conditions were tested with a variety of benzaldimine substrates containing alkyl and halogen substituents at various positions on the aromatic ring (Table 3.22). The reactions were carried out at 1-2 mmol scales in screw-capped test tube, which required only 6.4-12.8 mg of the ligand (2.5 mol%). Once all the reagents were completely added, the tube was capped and left at 0 ^{o}C for 72 hours. Under these optimized conditions, the reaction proceeded smoothly to give

the desired α-aminonitrile as the sole product. Some α-aminonitriles derivatives such as (*S*) or (*R*)-diphenylmethylamino-1-naphthylacetonitrile **(72n)** even crystallized from the toluene solution, in such cases, cold hexanes was added and the precipitated products collected by suction filtration. When the product was not crystallized out, the solvent was removed (CAUTION: Toxic HCN vapour can evolve, use fume hood!) and the residue purified by flash column chromatography if necessary. Hence, the reaction was usually complete within 8-48 hours, depending on the type of substrates. The imines carrying electron withdrawing groups reacted more slowly than those containing electron donating groups. Nevertheless, all substrates reacted more or less completely (>95 % conversion) after 72 hours.

3.4.2 Racemization of optically active aminonitriles

It should be noted that optically active α-aminonitriles are very prone to racemization - the fact that many investigators has not yet realized. We have previously observed that the racemization is catalyzed by weak acids such as silica (SiO_2). The effect is more pronounced for aminonitriles containing an electron donating substituent on the aromatic ring. The exact cause of the racemizaion was investigated by utilizing the Strecker reactions of *N*-benzylidenebenzhydrylamine **(72a)** catalyzed by $Ti(O^iPr)_4$-(*S*)-**109a** complex under the best condition. These reactions, resulting in complete conversion and excellent enantioselectivities (98% ee), were sampled in a NMR tube and either added with several additives or put on under elevated temperature. After 16 hours, enantiomeric excess was determined by treating the solution with (*S*)-CSA after the screening was finished. The results were summarized in Table 3.23.

Table 3.23 Investigation of the exact cause of the racemization

Entry	Additives	Condition	Time (h)	% Ee
1	-	30 ^{o}C	16	98
2	-	40 ^{o}C	16	98
3	NEt_3	30 ^{o}C	16	98
4	silica gel (SiO_2)	30 ^{o}C	16	0
5	TFA	30 ^{o}C	16	0

No racemization was observed at both room and elevated temperature in the absence of any additive, although the reactions were left for over a day (Entries 1-2). The results showed that the α-aminonitriles are thermally stable. Surprisingly, racemization also did not occur under basic condition (Entries 3), eventhough α-aminonitriles contain α-CH and NH both should be quite, acidic position, and therefore are expected to be base-labile. Obviously, NEt_3 is not a strong enough base to cause such deprotonation. In contrast, racemic products were obtained under weakly acidic conditions (Entries 4-5). Interestingly, weak acids experimentally employed such as SiO_2 and TFA were found to be the actual cause for racemization.

3.4.3 Study of racemization

Preliminary results showed that α-aminonitriles are easily racemized under weakly acidic conditions. To exactly understand the racemization in detail, the following experiments were performed. First, we sought to confirm that the racemization occurred under acidic condition by measurement of optical rotation. Experimentally, optical rotation of a solution of 70% ee of (*S*)-diphenylmethylamino-phenylacetonitrile **(72a)**, which is readily available in our laboratory, under a variety of conditions (neutral, acidic and basic) were measured every 30 minutes for a period of 3 hours. The relationships between the observed specific rotation and time are shown in Figure 3.16.

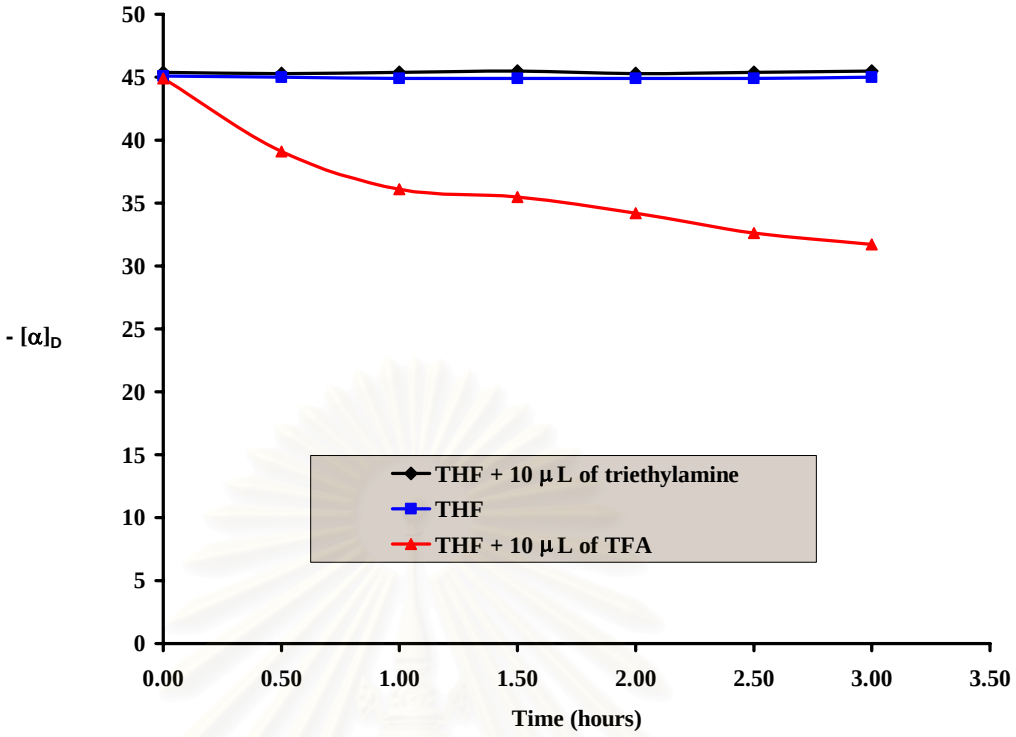


Figure 3.16 Kinetics of racemization of α-aminonitrile **(72a)** in THF with/without TFA 10 µL or triethylamine 10 µL

The optical rotation of **(72a)** in THF did not change over a three-hour period (Blue line). Under basic condition, no racemization was also found (Black line). This result is in line with our preliminary observation. On the other hand, the optical rotation was slowly but progressively deteriorated as shown in Figure 3.16 as a result of TFA (Red line). It is evident that the racemization of α-aminonitrile is catalyzed by acid.

Next, several organic solvents with different acidities were examined to determine the effect of solvent acidity on the rate of racemization. Experimentally, the optical rotation of a solution of the α-aminonitrile **(72a)** (70% ee) in each solvent were measured over the same period.

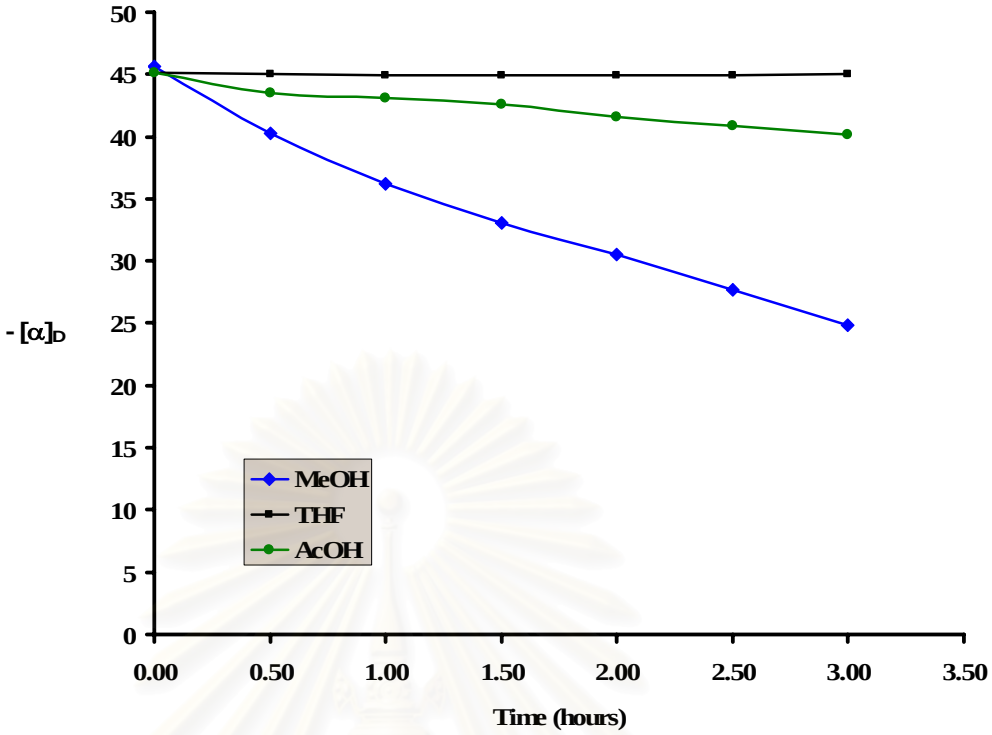


Figure 3.17 Kinetics of racemization of α-aminonitrile **(72a)** in several solvents

An interesting effect of solvent to the rate of racemization was observed. Significant racemization was observed in all protic solvent tested. Quantitatively, the rate of racemization was in order of MeOH >> AcOH > THF. The racemization in methanol was complete after leaving overnight as confirmed by both optical activity measurement and ^{1}H-NMR analysis in the presence of (*S*)-CSA. Consequently, a solution of the α-aminonitrile **(72a)** (70% ee) in methanol with several additives was chosen as models for investigation of the possibility to suppress the racemization in alcoholic media. The results are shown in Figure 3.18.

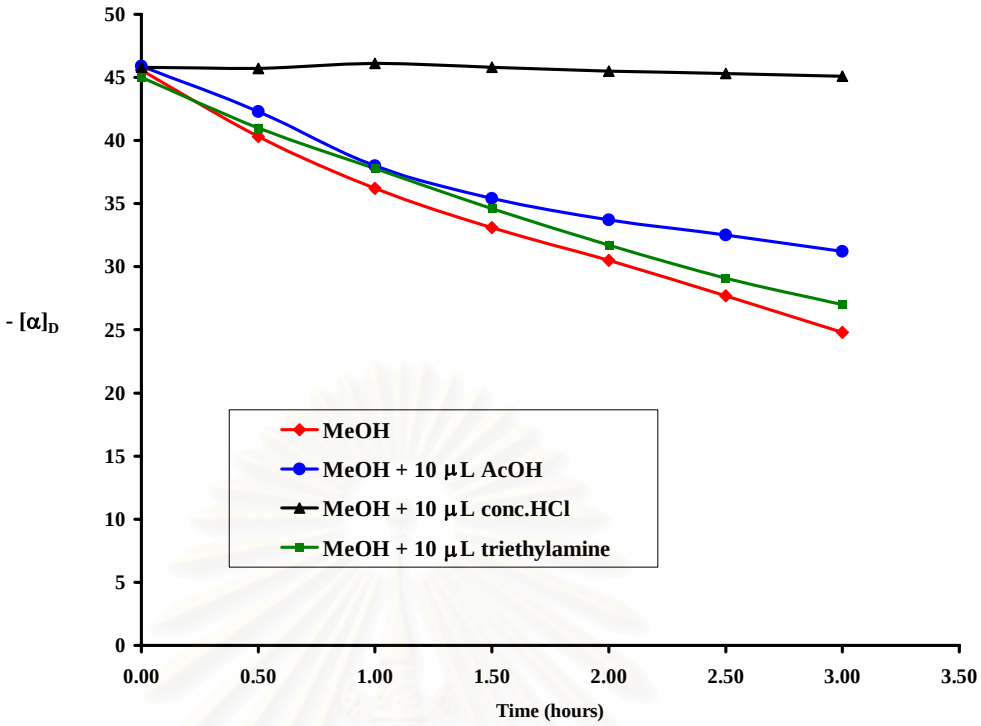


Figure 3.18 Kinetics of racemization of α-aminonitrile **(72a)** in MeOH with/without several additives

A solution of 70% ee of the unsubstituted α-aminonitrile **(72a)** in reagent grade methanol lost its optical activity rapidly with a half-life ($t_{1/2}$) of around 3 hours at 20 ^{o}C at a concentration of 0.0035 M (red line). Upon addition of 10 µL triethylamine, the rate of racemization was slightly reduced (green line). Despite its sensitivity towards racemization in weak acid, it is more surprising that the racemization of α-aminonitrile is inhibited in the presence of acids. A slower rate of racemization was obtained upon addition of 10 µL acetic acid (blue line). Surprisingly, addition of concentrated HCl in methanol to a concentration of 0.1 M completely suppressed the racemization (black line). No change in the optical rotation was observed over a period of 12 hours while a complete racemization was observed in MeOH alone under the same period of time. For all information obtained from Figure 3.16-3.18, it can be concluded that the racemization of α-aminonitriles is catalyzed by weak acids or protic solvents. The addition of strong acid can completely suppress racemization. It is evident that α-aminonitrile is easily racemized under weakly acidic condition, and even in protic solvents under essentially neutral condition. This suggested that even seemingly harmless reactions such as

hydrogenation (usually in alcohols) or recrystallization from protic solvents should be avoided. This finding has a significant impact on choosing conditions for subsequent hydrolysis and other reactions of the optically active α-aminonitriles to give α-amino acids.

Furthermore, electronic nature of substrate on the racemization rate was also studied. The optical rotation of (*S*)-diphenylmethylamino-phenylacetonitrile **(72a)** (70% ee), or (*S*)-diphenylmethylamino-4-chlorophenylacetonitrile **(72j)** (90% ee), or (*S*)-diphenylmethylamino-4-methoxy phenylacetonitrile **(72d)** (80% ee) in reagent grade methanol with or without 10 μL concentrated HCl were experimented. Their optical rotations were measured over a period of 3 hours. The data were as shown in Figure 3.19.

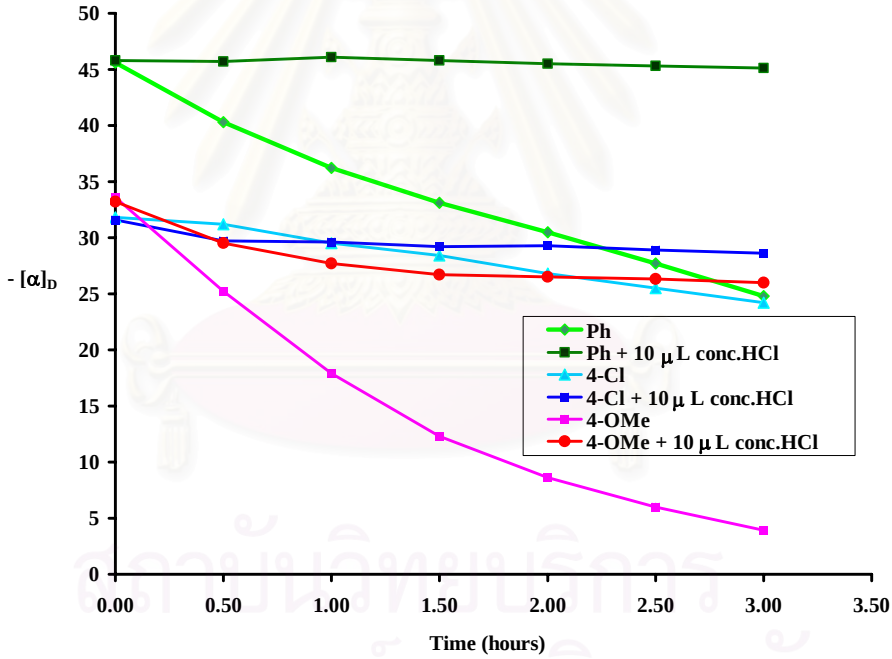


Figure 3.19 Kinetics of racemization of several α-aminonitriles **(72)** in MeOH with/without 10 μL conc.HCl

Without the addition of 10 μL conc HCl, the results showed a clear electronic effect on the racemization. Qualitatively the racemization rate were fastest for

electron donating substituent (4-OMe) and slowest for electron withdrawing substituent (4-Cl). In all cases, no change in the optical activities was observed when 10 μL conc. HCl was added in methanol (Red, Dark blue and Dark green lines). It was confirmed the racemization was suppressed by addition of a strong acid, which implied that the usual hydrolysis conditions by strong acid should be safe for these racemization-prone α-aminonitriles.

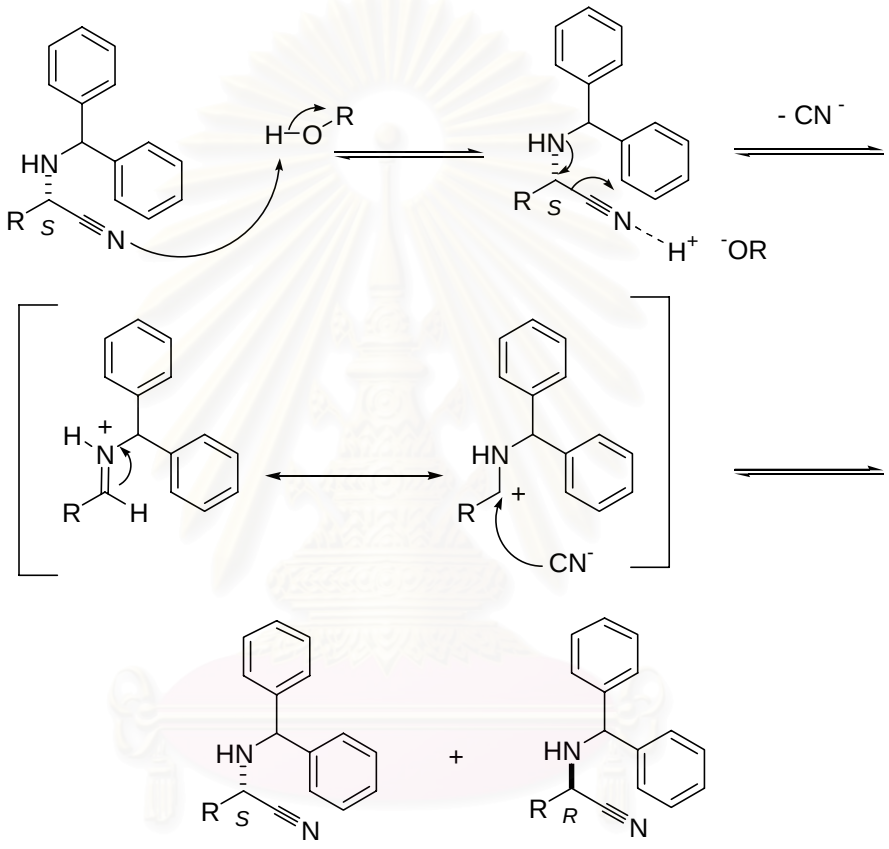


Figure 3.20 Weak acid catalyzed racemization of α-aminodiphenylmethyl acetonitrile

A mechanism of racemization which is consistent with the experimental results are as shown in Figure 3.20. Hard-Soft theory is the key for this racemization. Initially, nitrogen atom of nitrile group, which is a softer atom when compared to nitrogen atom of amine group, was activated with hydrogen ion, which came from weak acid, to form hydrogen bonding. Then electron pair of nitrogen atom of amine donated to chiral carbon center and left the cyanide ion as leaving group. Iminium ion was formed and the resonance led its structure be carbocation intermediate. The stability of this carbocation should increase by the presence of electron donating

groups on the aromatic moiety. This carbocation, being planar structure, after nucleophilic reattacking of cyanide ion resulted in the formation of both enantiomers and losing its optical activity. At equilibrium a racemic product is obtained.

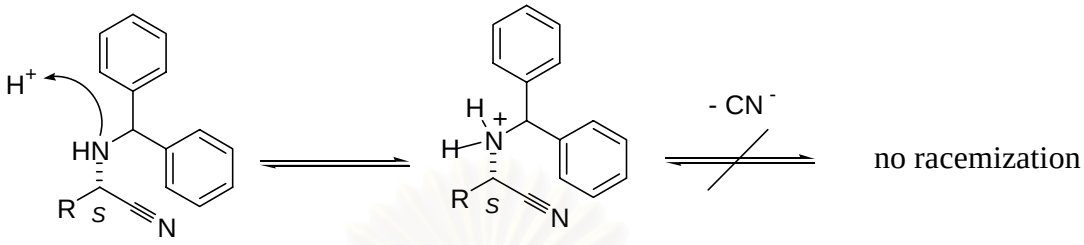


Figure 3.21 Strong acid suppressed racemization

The role of strong acid in suppressing the racemization is also explained by Hard-Soft theory (Figure 3.21). It is proposed that hydrogen ion coming from strong acid possibly behaved as hard hydrogen ion. Consequently, nitrogen atom of amine group was initially protonated to form an ammonium ion which does not have electron pair at the nitrogen atom, hence cannot participate in the carbocation formation. The racemization is therefore not possible. By this reason, it can be explained why the addition of HCl to the methanol solution can completely suppress the racemization.

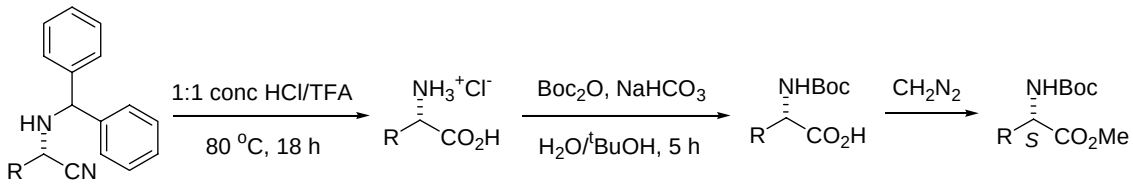
3.4.4 Hydrolysis and determination of % ee and absolute configuration of α-aminoacids by chiral HPLC

There are some literature examples of successful hydrolysis of optically active α-aminonitriles without racemization since the hydrolysis is usually carried out under strongly acidic conditions.[146-147,156-160] In order to illustrate the usefulness of optically active α-aminonitriles as a versatile intermediate, the α-aminonitriles were hydrolyzed to provide the arylglycines, which are non-proteinogenic amio acids that are useful as agrochemical, pharmaceutical.[192] Initial attempts according to a literature procedure using 6 N HCl at reflux temperature were unsuccessful. Most of the α-aminonitrile starting materials did not react and was almost completely recovered due to its low solubility in the reaction medium. Better results were

obtained when a water-miscible co-solvents was used. Among co-solvents tested (methanol, acetic acid, trifluoroacetic acid), it was clear that trifluoroacetic acid was the most efficient. Complete hydrolysis of all α-aminonitriles tested was achieved in a 1:1 mixture of concentrated aqueous HCl and trifluoroacetic acid within 12 h at 80 ^{o}C (2 mL/mmol). It should be noted that due to the sensitivity of α-aminonitrile towards racemization in weak acid as discussed above, the acids should mix before addition of the nitrile. If the order of addition is changed, ie, the nitrile was first dissolved in TFA followed by addition of HCl, a significant racemization took place. We have been demonstrating this by dissloving the nitrile in TFA and leave for 30 minutes before addition of HCl. HPLC analysis of the crude material revealed that an extensive racemization has occurred (From 98% to 0% ee for Ph-substrate **73a**). In case of substrates being not tolerant under strongly acidic condition as 4-OMe of heteroaromatic substrates, the reactions provide the decomposed products.

In order to determine the optical purity of the crude arylglycines obtained, they were converted to *N*-Boc-arylglycines by reacting with Boc_2O under basic condition. Then crude *N*-Boc-arylglycines were methylated with diazomethane to provide *N*-Boc-arylglycine methyl esters **(116)**. The % ee of which was determined by chiral HPLC. The racemic samples were also analyzed in parallel. In all cases the enantiomeric purity was almost completely preserved (Table 3.24). Importantly, it should be noted that prolonged heating in strong acid solution caused partial racemization (78% yield, from 98% to 90% ee for 1-naphthyl-substrate **73n**) and too short reaction time resulted in incomplete hydrolysis (64% yield, 98% ee for 1-naphthyl-substrate **73n**). Consequently, prolonged heating is required for complete hydrolysis providing higher yield. On the other hand, higher % ee requires shorter reaction time.

Table 3.24 Enantiomeric excess determination of optically active *N*-Boc-arylglycine methyl esters by chiral HPLC



73 **116**

Entry	Substrate	R	% yield	% Ee (73)	% Ee (116)
1	**73a**	Ph	92	98	93
2	**73a**	Ph	89	98[a]	93[a]
3	**73e**	2-Me-C_6H_4	76	98	95
4	**73f**	4-Me-C_6H_4	60	>98	93
5	**73i**	2-Cl-C_6H_4	85	>98	91
6	**73j**	4-Cl-C_6H_4	86	98	94
7	**73k**	2-Br-C_6H_4	87	>98	93
8	**73l**	4-Br-C_6H_4	81	96	ND[b]
9	**73m**	3-F-C_6H_4	91	96	94
10	**73n**	1-Naphthyl	78	98	98
11	**73n**	1-Naphthyl	77	98[a]	98[a]
12	**73o**	2-Naphthyl	74	98	90

[a] The reaction was catalyzed by $Ti(O^iPr)_4$-(*R*)-**109a**
[b] not determined because the peaks do not resolve by chiral HPLC

Absolute configuration of *N*-Boc-phenylglycine methylesters **(113a)** was determined by HPLC with comparison to standard sample prepared from optically active L-phenylglycine. Absolute configuration of other α-aminonitriles **(73a)** was determined by comparison the optical specific rotation to the literature values. For these methods, It is therefore confirmed that absolute configuration of all optically active α-aminonitriles obtained from the lignd **(109a)** is *S* configuration.

3.5 Mechanistic aspects and transition state model

After a practical synthesis of the α-aminonitrile and its hydrolysis was accomplished, we performed some preliminary experiments towards understanding of the reaction mechanism. The selectivity and stereochemical outcome could be explained based on the analogous transition state model for the corresponding cyanosilylation of aldehyde by Oguni′s model (Figure 3.22).[98] This model assumed that the catalytic asymmetric trimethylsilylcyanation of imines was initiated by the coordination of coordinately unsaturated chiral Schiff base-titanium isopropoxide complex. Trimethylsilyl cyanide would then react with the aldehyde coordinated to the titanium from the *si* face of the activated aldehyde leading to the preferable formation of *R*-cyanohydrin, since the *re* face of aldehydes would be blocked by the *tert*-butyl substituent (Figure 3.22, top). On the other hand, when Ti-(*S*)-**109c** complex was employed in the reaction, the *re* face would be less hindered than the *si* face due to the iso-propyl group. Therefore, the cyanating reagent will attack from the *re* face of aldehydes to produce the *S*-cyanohydrin (Figure 3.22, bottom).

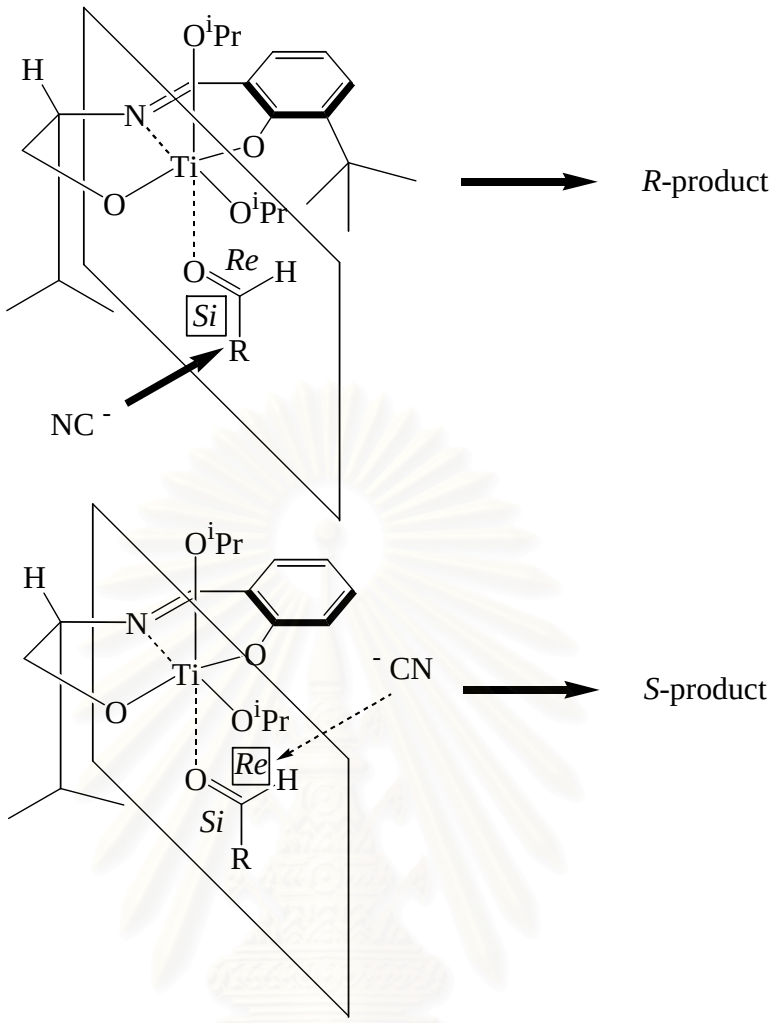


Figure 3.22 Transition state models of trimethylsilylcyanation of aldehyde as proposed by Oguni

In a related Zhang′s model (Figure 3.23) for cyanation of the aldehydes using a related Ti-*N*-salicyl, [101] the *Re* face of the aldehyde is much more accessible for nucleophilic addition than *Si* face due to strong shielding by the phenyl group (Figure 3.23, top). On the other hand, aldehyde could not coordinate with Ti-complex because of large steric hindrance between the two phenyl groups. Consequently, cyanide ion will attack the carbonyl group from a less hindered trajectory (*Re* face) to provide the product possessing (*S*)-configuration.

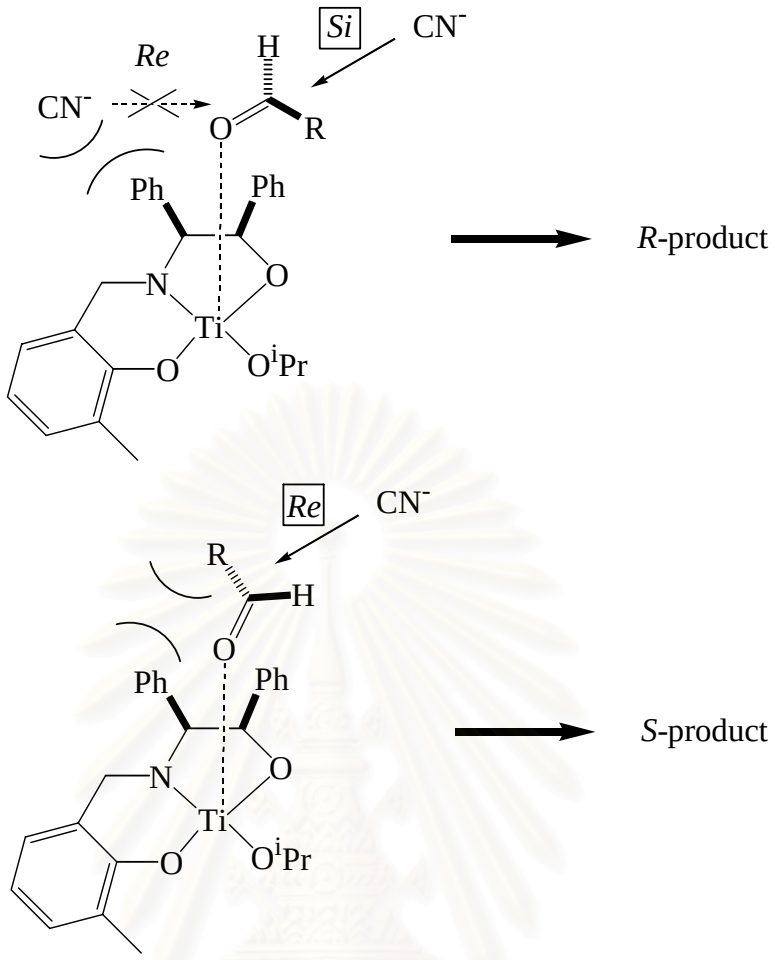


Figure 3.23 Transition state models of trimethylsilylcyanation of aldehyde as proposed by Zhang

Among the catalyst systems systematically examined, the combination of $Ti(^{i}OPr)_4$ and chiral ligands **109a**, **109c**, **109d**, or **109h** derived from highly branched α-alkyl side-chains as (*S*)-phenylalaninol, (*S*)-valinol, (*S*)-*tert*-leucinol, or (*S*)-leucinol provided the best resulted wherein the *S*-aminonitriles were obtained in excellent yield and enantioselectivity (up to > 98% ee). For our Strecker reaction, several important experimental results, which are the keys for depicting the transition state model, are described. Chiral *N*-salicyl-β-aminoalcohol ligands bearing bulky groups, Me or ^{t}Bu, especially at *ortho*-positions on salicyl moiety not only showed the drastically dropped ee but also resulted in very slow reaction. The most effective one should only have highly branched groups at β-position without any substituents on salicyl moiety. In addition, the steric bulk of the substituent imines directly affects to enantioselectivity. Dramatically decreased % ee was observed with the reaction of

imines derived from bulky aldehydes such as 9-anthracenaldehyde and 2,6-dimethylbenzaldehyde. Too much bulkiness of substituents at *N*-position on imines exhibited no reaction. Moreover, the reaction of ketimines resulted in no enantioselectivity. Enantioselectivity was observed with only aromatic substrates. It's supposed to be π-stacking effect between the aromatic moiety on substrate and the salicyl part on chiral ligand. Furthermore, the effective chiral *N*-salicyl-β-aminoalcohol ligands for asymmetric Strecker reactions are tridentate ligands and must not have any substituents on each heteroatom. (*S*)-ligands provide α-aminonitrile products with *S* configuration. A transition state model, which is consistent with all the facts described above, is therefore shown in Figure 3.24.

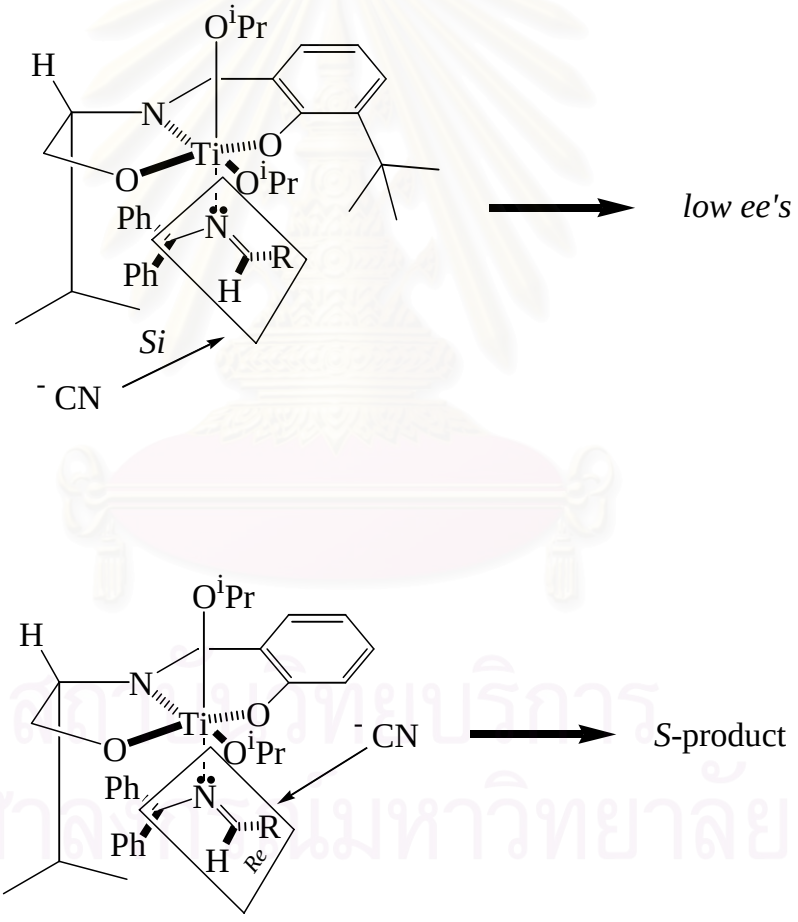


Figure 3.24 Transition state models of Strecker reaction catalyzed by Ti-chiral *N*-salicyl-β-aminoalcohol **109c** complex

We proposed a possible asymmetric induction pathway of asymmetric strecker reaction shown in Figure 3.24. The enantioselectivity and stereochemical outcome could be also explained based on the similar transition state model for the related cyanosilylation of aldehyde by Oguni's model.[98] This model supposed that the catalytic asymmetric Strecker reaction was initiated by the coordination of coordinately chiral *N*-salicyl-β-aminoalcohol-titanium-^{i}PrOH complex. *E*-imine was established by arranging diphenylmethyl group below the catalyst structure to avoid steric repulsion between diphenylmethyl group and ^{i}Pr group (alkyl side-chain) on aminoalcohol. There possibly is π-π stacking between diphenylmethyl group and aromatic part on salicyl moiety to explain the good enantioselection otained in case of aromatic substrates. The *si* face of imine is almost comparably hindered to the *re* face when ligands bearing ^{t}Bu group at the *ortho*-position was employed (Figure 3.24, top). This resulted in almost no selectivity which explained why % ee almost dropped to zero when chiral ligands bearing bulky substituents at *ortho*-position on salicyl part were employed. In contrast, when unsubstituted ligand as **109a**, **109c**, **109d** or **109h** was employed for the reaction, the *Re* face is much more accessible to a cyanide the the *Si* face since the latter is strongly shielded by the highly branched alkyl side-chain of the ligand (Figure 3.24, bottom and Figure 3.25). Thus, the nucleophilic cyanide will attacked the polarized C=N of imine at the carbon atom from a less stereohindered direction, *Re* face, to give the α-amnonitrile possessing *S* configuration with excellent enantioselectivity.

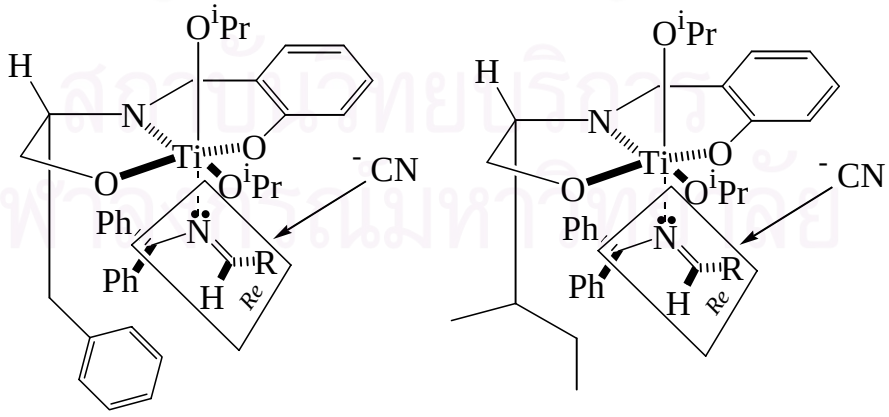


Figure 3.25 Transition state models of Strecker reaction catalyzed by Ti-chiral *N*-salicyl-β-aminoalcohol **109a** or **109h** complex

However, the models were only theoretically proposed based on the assumption that the catalytic species is monomeric. There is not much information to support how correct it is. We also investigated the nonlinear effect (NLE) in asymmetric Strecker reactions catalyzed by chiral $Ti(O^iPr)_4$-*N*-salicyl-β-aminoalcohol complexes. The reactions of *N*-benzylidenebenzhydrylamine **(72a)** with 2 equiv TMSCN and 10 mol% of several ratios of $Ti(O^iPr)_4$-**(*S*)-109a**:**(*R*)-109a** complexes were carried out in the presence of 1 equiv of 2-propanol. These reactions provided α-aminonitriles with complete conversion but with different enantiomeric excess. The data were shown in Figure 3.26.

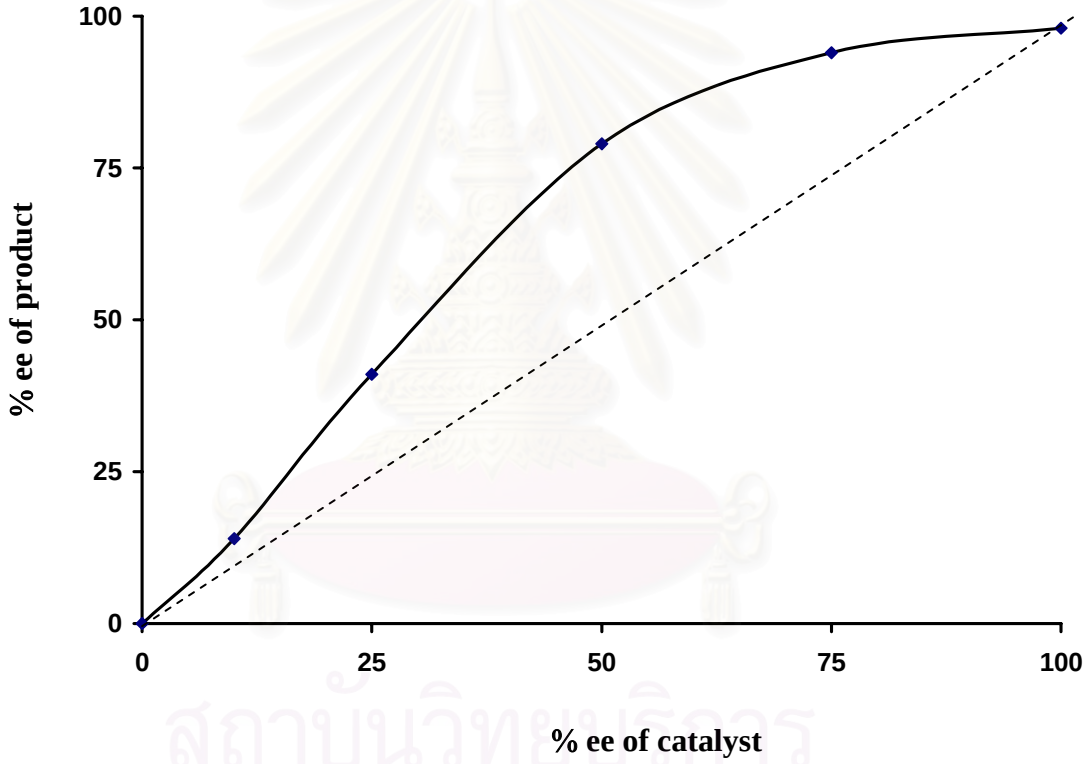
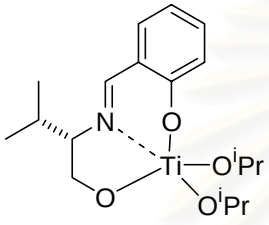


Figure 3.26 (+)-NLE in the asymmetric Strecker reactions catalyzed by chiral $Ti(O^iPr)_4$-**3a** complexes (10 mol%)

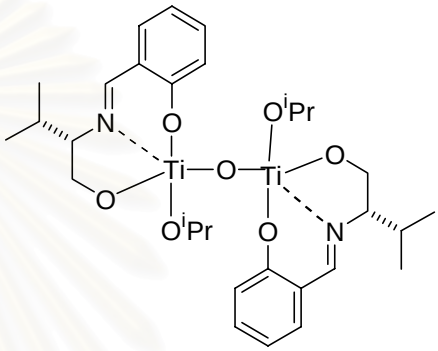
The result suggested a positive non-linear effect [193] in this asymmetric Strecker reaction. Asymmetric reactions with positive NLE usually involve aggregrated catalysts. It implied that the proposed model based on monomeric catalytic species might be an oversimplification. However, the reactions with a positive nonlinear effect are particularly attractive. Starting from an optically impure

catalyst in a reaction displaying a positive nonlinear effect, it is possible to obtain reaction products with a higher enantiomeric excess than is expected from the catalyst's optical purity. Indeed, the nonlinear effect also suggests a higher order molecularity of the catalytically active species. The active and inactive species might be 1:1 ratio of titanium ion:chiral ligands and one proposed to be **(126)** and **(127)** according to Oguni's work.[98]. However, it was suggested that the dimeric catalyst was infact the inactive species in such case.



Active species

(126)



Inactive species

(127)

Furthermore, we attempted to investigate the catalyst structure by ^{1}H-NMR spectroscopy. The 1:1 ratio of ligand **(109a)**:Ti(O^{i}Pr)$_4$ was prepared using toluene-d$_8$ as solvent at room temperature in a NMR tube. The catalyst formation was mornitored every 10 minutes over a period of 40 minutes. ^{1}H-NMR spectra were shown in Figure 3.27.

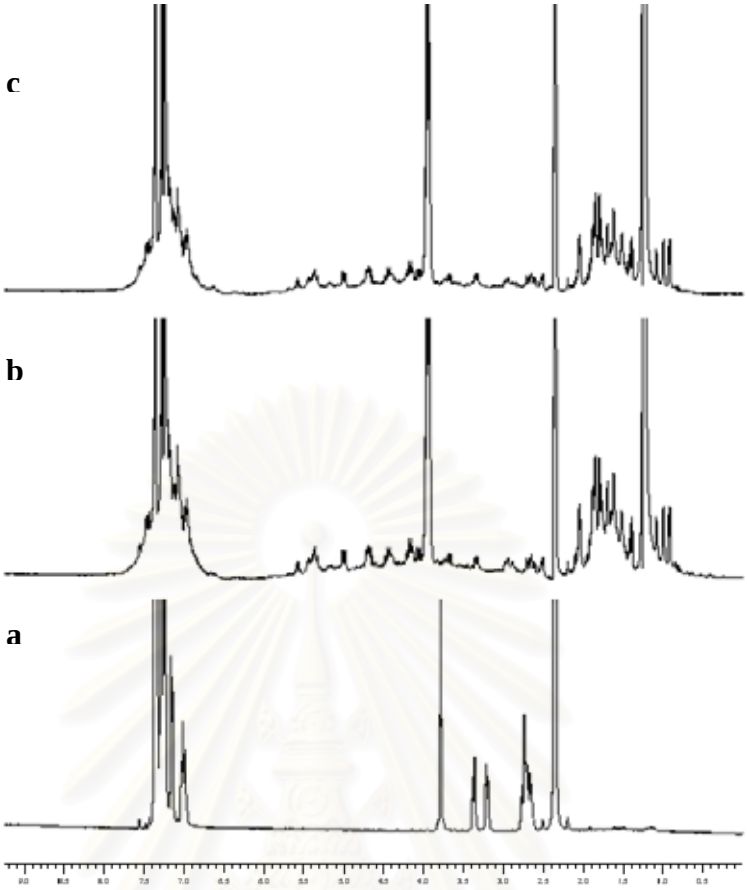


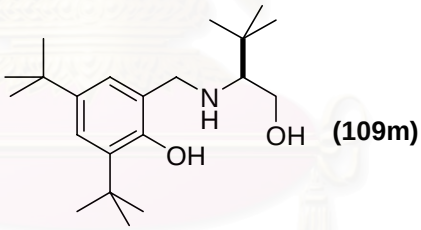
Figure 3.27 Spectra of ligand **(109a) (a)**; complex of Ti(O^iPr)$_4$–(*S*)-**109a** promptly formed **(b)**; complex of Ti(O^iPr)$_4$ –**109a** formed for 40 minutes **(c)**

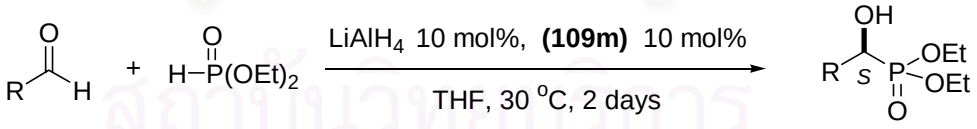
The results showed that the complex of Ti(O^iPr)$_4$ -(*S*)-**109a** was formed rapidly when Ti(O^iPr)$_4$ was mixed with chiral ligand. After a period of 40 minutes, the same species was observed. The complex NMR spectra suggested that no single major comlex was obtained and it was not possible to determine the structure of the complex in this way.

3.6 Other reactions

Screening of chiral *N*-salicyl-β-aminoalcohols synthesized in this work on other asymmetric reactions has been gratifyingly successful. Nammoonnoy *et al.* [194] disclosed the first report of asymmetric hydrophosphonylation of imines (Pudovic reactions) catalyzed by this class of ligands (Table 3.25). It was found that the effective catalyst is a heterobimetallic complex formed from the ligand and $LiAlH_4$. In contrast to Strecker reaction, steric bulk of substituents on the salicyl moiety plays beneficial role to the enantoselectivity of the reaction. The reactions of aromatic and aliphatic aldehydes with diethylphosphite were carried in the present of 10 mol% of chiral ligand **(109m)** and $LiAlH_4$ in THF at 30 ^oC. The reaction of aromatic aldehydes resulted in high yields and good enantioselectivities. Aliphatic substrates showed fair to good yields and % ee.

Table 3.25 Enantioselective Pudovic reactions catalyzed by heterobimetallic Li-Al-chiral ligands **(109m)** complex

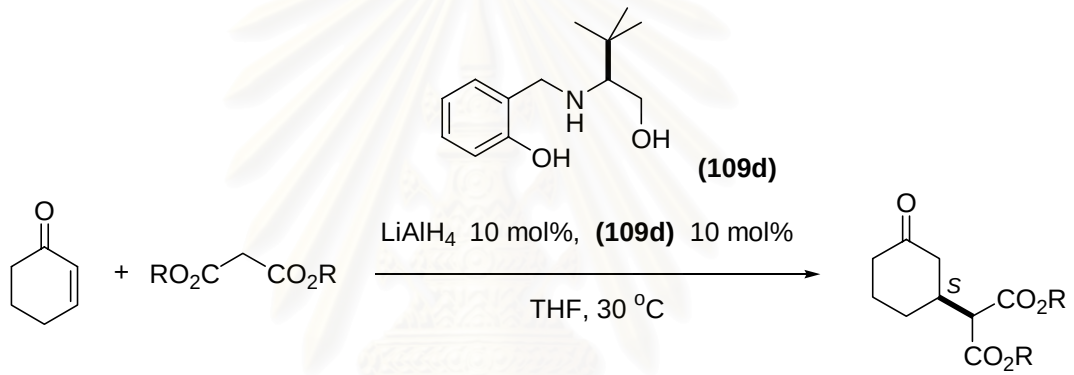




Entry	R	% yield	% Ee
1	Ph	89	60
2	4-OMe-C_6H_4	69	72
3	n-Pr	49	63
4	^{i}Pr	55	70
5	^{t}Bu	54	70

In addition, Srikaenjun *et al.* has shown that the heterobimeallic complex prepared from chiral *N*-salicyl-β-aminoalcohol **(109d)** and $LiAlH_4$ is also an effective catalyst in asymmetric Michael addition reactions of dialkyl malonate to cyclic enones (Table 3.26).[195] The reactions of cyclic enones with several dilkyl malonates were carried in the present of 10 mol% of chiral ligand **(109d)** at 30 ^{o}C. The reaction of cyclic enones with bulkier dilkyl malonates as di-*tert*-butyl malonate resulted in high yields and enantioselectivities.

Table 3.26 Enantioselective Michael additions catalyzed by heterobimetallic Li-Al-chiral ligands **(109d)** complex



Entry	R	% yield	% Ee
1	Et	88	67
2	^{i}Pr	90	70
3	^{t}Bu	90	88

CHAPTER IV

CONCLUSION

The investigation had been carried out to search for novel chiral ligands complexed with metal ion to form novel optically active Lewis acid catalysts for the asymmetric reactions. This work contains four major parts which are novel chiral ligands syntheses, catalytic asymmetric Strecker reactions, practical synthesis of arylglycines and mechanistic aspect. Synthetic methodology of *N*-salicyl-β-aminoalcohol ligands had been developed. The best method for the synthesis of this type of ligand is the three-component Mannich type reaction followed by ring opening of oxazolidine derivatives with hydroxylamine hydrochloride. It was found that the hydroxyl group of the phenol played significant role in mediating the reaction and to induce *ortho*-selectivity. The reactions provided a series of chiral *N*-salicyl-β-aminoalcohol ligands **(109)** in high yields (84-92%) without any racemization.

These synthesized ligands were complexed with $Ti(O^iPr)_4$ to form the $Ti(O^iPr)_4$-(*S*)- or (*R*)-**(109)** complexes as the effective catalysts in catalytic asymmetric Strecker reactions. This part has demonstrated that the Ti complexes of tridentate *N*-salicyl-β-aminoalcohols **(109)**, which do not have any substituents on salicyl moiety and substituents on each heteroatom, are highly effective catalysts for enantioselective Strecker reactions of aldimines. It has been clearly shown that the configuration as well as the bulkiness of the β-substituent exerts a direct influence on both the absolute stereochemical outcome and enantioselectivity of the Strecker product. High percent conversion and enantiomeric excess of optically active α-aminonitriles **(73)** were routinely observed (usually >99% yield and >90% ee respectively) for various imine substrates derived from heteroaromatic and aromatic aldehydes bearing electron donating and withdrawing groups and benzhydrylamine. Attempts to increase the steric bulk of the aldehyde part resulted in a dramatically decreased % ee. In addition, some aliphatic substrates were also investigated. The

reactions gave much poorer ee values at similar conversion when compared to aromatic substrates. It was found that ligands **(109)** bearing a relatively sterically hindered substituent at the β-position provided a substantially increased % ee in this case. Furthermore, we have illustrated that excellent yields accompanied by extremely high degrees of enantioselectivity can be obtained when a substrate with a more sterically demanding *N*-aromatic substituent was employed. The absolute configuration of all products derived from the ligand (*S*)-**(109)** was confirmed to be *S* by comparison of the optical rotations with literature values and also chiral HPLC. The stereoselectivity of the enantioselective Strecker reaction induced by the Ti-**(109)** catalyst is, therefore, fully controlled by the absolute configuration of the ligand.

For a practical synthesis of arylglycines, a protic additive such as ^{i}PrOH was found to be beneficial for large scale synthesis. It has been shown that the best reaction conditions with equivalence of ^{i}PrOH and 2.5 mol% catalysts loading are extremely simple. This catalyst system offered a very practical access to optically active α-aminonitriles **(73)** with excellent yields and enantioselectivities. Importantly, the racemization of α-aminonitriles **(73)** is shown to be catalyzed by weak acids or alcohols. Fortunately, the racemization can be suppressed by addition of either a base such as triethylamine (NEt_3) or strong acid such as hydrochloric acid (HCl). The optically active α-aminonitriles **(73)** have been successfully converted to arylglycines by complete hydrolysis in a 1:1 mixture of concentrated aqueous HCl and trifluoroacetic acid within 12 h at 80 ^{o}C and with minimal racemization. In addition, the positive non-linear effect, (+)-NLE, was observed in catalytic asymmetric Strecker reactions catalyzed by $Ti(O^{i}Pr)_4$-**109** complexes. We have also proposed the transition state that the nucleophilic cyanide will attacked the polarized C=N of imine at the carbon atom on *Re* face to give the α-amnonitrile possessing *S* configuration with excellent enantioselectivity.

The last conclusion drawn from this work has been described with other asymmetric reactions. Successfully, chiral catalysts we synthesized proudly showed their catalytic ability in not only asymmetric strecker reaction but also asymmetric Pudovic reaction and asymmetric Micheal addition. Gratifyingly, the superiority of this class of optically active ligands we synthesized can be emphasized due to their low molecular weights and the fact that they possess only one stereogenic center, the starting precursor of which is readily available with any desirable absolute stereochemistry.

REFERENCES

1. Stephenson, G. R. *Advanced Asymmetric Synthesis*, Blackie Academic & Professional: New York, **1996**.
2. Bentley, R. *in Stereochemistry*, C. H. Tamm (ed.), Elsevier: Amsterdam, **1982**.
3. Barrett, G. C. *Amino Acid Derivatives*, Oxford University Press: Oxford, **1999**.
4. Cervinka, O. *Enantioselective Reactions in Organic Chemistry*, Publishing House of the Academy of Sciences of the Czech Republic: Prague, **1995**.
5. Baker, D. R.; Fenyes, J. G.; Basarab, G. S.; Hunt, D. A. *ACS Symposium Series: Synthesis and Chemistry of Agrochemicals V*, American Chemical Society: Washington D. C., **1998**.
6. Wagner, I.; Musso, H. New Naturally Occurring Amino Acids. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.
7. Barrett, G. C.; Elmore, D. T. *Amino Acids and Peptides*, Cambridge University Press: Cambridge, **1998**.
8. Jones, J. *Amino Acid and Peptide Synthesis*, Oxford University Press: Oxford, **1992**.
9. Strecker, A. Strecker Amino Acid Synthesis. *Ann. Chem. Pharm.* **1850**, *75*, 27.
10. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part B: Reactions and Synthesis, 4th ed.* Kluwer Academic/Plenum Publishers: New York**,** **2001**.
11. Mark, A. R.; Michael, P. *Stoichiometric Asymmetric Synthesis*, Sheffield Academic Press: Sheffield, **2000**.
12. Ojima, I. *Catalytic Asymmetric Synthesis*, Wiley-VCH, Inc: New York, **2000**.
13. Feringa, B. L.; Delden, R. A. Absolute Asymmetric Synthesis: The Origin, Control, and Amplification of Chirality. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418.
14. Luche, J. L.; Delair, P.; Einhorn, C.; Dinhorn, J. New β-Amino Alcohols Derived from L-Valine as Chiral Inductors for Enantioselective Reductions of and Nucleophilic Additions to Carbonyl Compounds. *Tetrahedron* **1995**, *51*, 165.
15. Morrison, J. D. *Asymmetric Synthesis Volume 5 Chiral catalysis*, Academic Press, Inc: Durham, **1983**.

16. Gennari, C.; Piarulli, U. Combinatorial Libraries of Chiral Ligands for Enantioselective Catalysis. *Chem. Rev*. **2003**, *103*, 3071.
17. Walsh, P. J.; Lurain, A. E.; Balsells, J. Use of Achiral and Meso Ligands to Convey Asymmetry in Enantioselective Catalysis. *Chem. Rev*. **2003**, *103*, 3297.
18. Jacobsen, E. N.; Yoon, T. P. Privileged Chiral Catalysts. *Science* **2003**, *299*, 1691.
19. Hayashi, T. Chiral Monodentate Phosphine Ligand MOP for Transition-Metal-Catalyzed Asymmetric Reactions. *Acc. Chem. Res*. **2000**, *33*, 354.
20. Ooi, T.; Maruoka, K. Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis. *Chem. Rev*. **2003**, *103*, 3013.
21. Ronchi, A. U.; Bandini, M.; Cozzi, P. G. Asymmetric Synthesis with "Privileged" Ligands. *Pure Appl. Chem*. **2001**, *73*, 325.
22. Fan, Q.; Li, Y.; Chan, S. C. Recoverable Catalysts for Asymmetric Organic Synthesis. *Chem. Rev*. **2002**, *102*, 3385.
23. Duthaler, R. O.; Hafner, A. Chiral Titanium Complexes for Enantioselective Addition of Nucleophiles to Carbonyl Groups. *Chem. Rev*. **1992**, *92*, 807.
24. Rodero, A. S.; Krause, N. An Exceptional P-H Phosphonite: Biphenyl-2,2'-Bisfenchylchlorophosphite and Derived Ligands (BIFOPs) in Enantioselective Copper-Catalyzed 1,4-Addition. *Synthesis* **2001**, *2*, 171.
25. Ender, D.; Reinhold, U. Asymmetric Synthesis of Amines by Nucleophilic 1, 2-Addition of Organometallic Reagents to the C-N Double Bond. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.
26. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons: Chichester, **1993**.
27. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. E. *Comprehensive Asymmetric Catalysis*, Springer: Berlin, **1999**.
28. Williams, J. M. J. *Catalysis in Asymmetric Synthesis*, Sheffield Academic Press: Sheffield, **1999**.
29. Shibasaki, M.; Naoki, Y. Lanthanide Complexes in Multifunctional Asymmetric Catalysis. *Chem. Rev*. **2002**, *102*, 2187.
30. Junji, I.; Hiroshi, F.; Tetsuji, H. Asymmetric Catalysis and Amplification with Chiral Lanthanide Complexes. *Chem. Rev*. **2002**, *102*, 2211.

31. Kobayashi, S.; Sagiura, M.; Kitagawa, H. Rare-Earth Metal Trifates in Organic Synthesis. *Chem. Rev*. **2002**, *102*, 2227.

32. Chen, Y.; Yekta, S.; Yudin, A. K. Modified BINOL Ligands in Asymmetric Catalysis. *Chem. Rev*. **2003**, *103*, 3155**.**

33. Aspinall, H. Chiral Lanthanide Complexes: Coordination Chemistry and Application. *Chem. Rev*. **2002** *103*, 3155**.**

34. Imamoto, T. *Lanthanides in Organic Synthesis*, Academic Press: London, **1994**.

35. Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. Modified BINAP: The How and the Why. *Chem. Rev*. **2005**, *105*, 1801.

36. Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. *Chem. Rev*. **2003**, *103*, 3029**.**

37. Miyashita, A.; Yasuda, H.; Takaya, H.; Toriumi, T.; Ito, T.; Souchi, T.; Noyori, R. Synthesis of 2,2'-Bis(diphenylphosphino)-1,1'-Binaphthyl (BINAP), An Atropisomeric Chiral Bis(triaryl)phosphine, and Its Use in the Rhodium(I)-Catalyzed Asymmetric Hydrogenation of α-(Acylamino)acrylic Acids. *J. Am. Chem. Soc*. **1980**, *102*, 7933.

38. Ohta, T.; Takaya, H.; Kitamaru, M.; Nagai, K.; Noyori, R. Asymmetric Hydrogenation of Unsaturated Carboxylic Acids Catalyzed by BINAP-ruthenium(II) Complexes. *J. Org. Chem*. **1987**, *52*, 3174.

39. Ohkuma, T.; Ooka, H.; Hashigychi, S.; Ikariya, T.; Noyori, R. Practical Enantioselective Hydrogenation of Aromatic Ketones. *J. Am. Chem. Soc*. **1995**, *117*, 2675.

40. Takahashi, H.; Sakurba, S.; Takeda, H.; Achiwa, K. Asymmetric Reactions Catalyzed by Chiral Metal Complexes: Highly Efficient Asymmetric Hydrogenation of Amino Ketone Derivatives Leading to Practical Syntheses of (*S*)-Propanolol and Related Compounds. *J. Am. Chem. Soc*. **1990**, *112*, 5876.

41. Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. Homogeneous Asymmetric Hydrogenation of Functionalized Ketones. *J. Am. Chem. Soc*. **1988**, *110*, 629.

42. Burk. M. J. C_2-Symmetric Bis(phospholanes) and Their Use in Highly Enantioselective Hydrogenation Reactions. *J. Am. Chem. Soc*. **1991**, *113*, 8518.

43. Kim, K. H.; Lee, D. W.; Lee, Y. S.; Ko, D. H.; Ha, D. Enantioselective Oxidative Coupling of Methyl-3-hydroxy-2-naphthoate Using Mono-*N*-alkylated Octahydro binaphthyl-2,2-Diamine Ligand. *Tetrahedron* **2004**, *60*, 9037.

44. Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids. Scope and Mechanism of the Catalytic Enantioselective Aldol Additions of Enolsilanes to Pyruvate Esters. *J. Am. Chem. Soc*. **1999**, *121*, 686.

45. Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. C_2-Symmetric Cu(II) Complexes as Chiral Lewis Acids. Catalytic Enantioselective Michael Addition of Silylketene Acetals to Alkylidene Malonates. *J. Am. Chem. Soc*. **1999**, *121*, 1994.

46. Jnoff, E.; Ghosez, L. Asymmetric Diels-Alder Reactions of 2-Azadienes Catalyzed by a Chiral Copper(II) Complex. A General Route to Enantiomerically Pure Piperidones. *J. Am. Chem. Soc*. **1999**, *121*, 2617.

47. Zenner, J. M.; Larock, R. C. Palladium-Catalyzed Asymmetric Hetero- and Carboannulation of Allenes Using Functionally-Substituted Aryl and Vinylic Iodides. *J. Org. Chem.* **1999**, *64*, 7312.

48. Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. Asymmetric Dihydroxylation via Ligand-accelerated Catalysis. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

49. Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. Kinetic Resolution of Terminal Epoxides via Highly Regioselective and Enantioselective Ring Opening with $TMSN_3$. An Efficient Catalytic Route to 1,2-Amino Alcohols. *J. Am. Chem. Soc*. **1996**, *118*, 7420.

50. Brandes, B. D.; Jacobsen, E. N. Regioselective Ring Opening of Enantiomerically Enriched Epoxides via Catalysis with Chiral (Salen)Cr(III) Complexes. *Synlett* **2001**, 1013.

51. Seebach, D.; Beck, A. K.; Heckel, A. TADDOLs, Their Derivatives, and TADDOL Analogues: Versatile Chiral Auxiliaries. *Angew. Chem. Int. Ed.* **2001**, *40*, 92.

52. Brunel, J. M. BINOL: A Versatile Chiral Reagent. *Chem. Rev*. **2005**, *105*, 857.

53. Shibasaki, M.; Sasai, H.; Arai, T. Asymmetric Catalysis with Heterobimetallic Compounds. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1236.

54. Sasai, H.; Arai, T.; Satow, Y.; Shibasaki, M. The First Heterobimetallic Multifunctional Asymmetric Catalyst. *J. Am. Chem. Soc*. **1995**, *117*, 6194**.**

55. Saida, Y.; Fubabashi, K.; Sasai, H.; Arai, T.; Shibasaki, M. Catalytic Asymmetric Michael Addition of Nitromethane to Enones Controlled by (*R*)-LPB. *Tetrahedron Lett*. **1998**, *39*, 7557.

56. Shibasaki, M.; Sasai, H.; Yoshikawa, N. Direct Catalytic Asymmetric Aldol Reactions of Aldehydes and Unmodified Ketones. *Angew. Chem. Int. Ed. Engl*. **1997**, *36*, 1871.

57. Sasai, H.; Arai, S.; Tahara, Y.; Shibasaki, M. Catalytic Asymmetric Synthesis of α-Amino Phosphonates Using Lanthanoid-Potassium-BINOL Complexes. *J. Org. Chem*. **1995**, *60*, 656.

58. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. Enantioselective Synthesis of α-Hydroxyphosphonates through Asymmetric Pudovik Reactions with Chiral Lanthanoid and Titanium Alkoxides. *J. Chem. Soc., Perkin Trans. I* **1997**, 1527.

59. Katsuki, T.; Sharpless, K. B. The First Practical Method for Asymmetric Epoxidation. *J. Am. Chem. Soc*. **1980**, *102*, 5974.

60. Bergmeier, S. C. The Synthesis of Vicinal Amino Alcohols. *Tetrahedron* **2000**, *56*, 2561.

61. Ager, D. J.; Prakash, I.; Schaad, D. R. 1,2-Amino Alcohols and Their Heterocyclic Derivatives as Chiral Auxiliaries in Asymmetric Synthesis. *Chem. Rev*. **1996**, *96*, 835.

62. Yu, H.; Pu, L. Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds. *Chem. Rev*. **2001**, *101*, 757.

63. Singer, R. D.; Knochel, P. Preparation and reactions of polyfunctional Organozinc Reagents in organic Synthesis. *Chem. Rev*. **1993**, *93*, 2117.

64. Luche, J. L.; Delair, P.; Einhorn, C.; Dinhorn, J. New β-Amino Alcohols Derived from L-Valine as Chiral Inductors for Enantioselective Reductions of and Nucleophilic Additons to Carbonyl Compounds. *Tetrahedron* **1995**, *51*, 165.

65. Zhang, F. Y.; Chan, A. Enantioselective Addition of Diethylzinc to Aromatic Aldehydes Catalyzed by Titanium-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol Complex. *Tetrahedron: Asymmetry* **1997**, *8*, 3651.

66. Bloch, R. Additions of Organometallic Reagents to C=N Bonds: Reactivity and Selectivity. *Chem. Rev*. **1998**, *98*, 1407.

67. Kobayashi, S.; Ishitani, H. Catalytic Enantioselective Addition to Imines. *Chem. Rev*. **1999**, *99*, 1069.

68. Soai, K.; Hatanaka, T. Highly Enantioselective Alkylation of Carbon-Nitrogen Double Bonds. Catalytic and Stoichiometric Asymmetric Synthesis of Optically Active Amines by the Enantioselective Addition of Dialkylzinc Reagents to *N*-Diphenylphosphinoylimines. *J. Chem. Soc. Chem., Commun*. **1992**, 1097.

69. Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2005**.

70. Dalko, P, I.; Moisan, L. In the Golden Age of Organocatalysis. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

71. Dalko, P, I.; Moisan, L. Enantioselective Organocatalysis. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

72. List, B.; Lerner, R. A.; Barbas III, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

73. Sakthivel, K.; Notz, W.; Bui, T.; Barbas III, C. F. Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon-Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

74. List, B. Asymmetric Aminocatalysis. *Synlett* **2001**, 1675.

75. List, B. Proline-Catalyzed Asymmetric Reactions. *Tetrahedron* **2002**, *58*, 5573.

76. List, B. Enamine Catalysis is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents. *Acc. Chem. Res*. **2004**, *37*, 548.

77. Movassaghi, M.; Jacobsen, E. N. The Simplest Enzyme. *Science* **2002**, *298*, 1904.

78. List, B.; Pojarliev. P.; Martin, H. J. Efficient Proline-Catalyzed Michael Additions of Unmodified Ketones to Nitro Olefins. *Org. Lett*. **2001**, *3*, 2423.

79. Betancort, J. M.; Barbas III, C. F. Catalytic Direct Asymmetric Michael Reactions: Taming Naked Aldehyde Donors. *Org. Lett*. **2001**, *3*, 3737.

80. Andrey, O.; Alexakis, A.; Bernardinelli, G. Asymmetric Michael Addition of α-Hydroxyketones to Nitro Olefins Catalyzed by Chiral Diamine. *Org. Lett.* **2003**, *5*, 2559.

81. Gothelf, K. V.; Jorgensen, K. A. Asymmetric 1,3-Dipolar Cycloaddition Reactions. *Chem. Rev*. **1998**, *98*, 863.

82. Frederickson, M. Optically Active Isoxazolidines *via* Asymmetric Cycloaddition Reactions of Nitrones with Alkenes: Applications in Organic Synthesis**.** *Tereahedron* **1997**, *53*, 403.

83. Viton, F.; Bernardinelli, G.; Kundig, E. P. Iron and Ruthenium Lewis Acid Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions between Nitrones and Enals. *J. Am. Chem. Soc*. **2002**, *124*, 4968.

84. Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Enantioselective Organocatalytic 1,3-Dipolar Cycloaddition. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

85. France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. Nucleophilic Chiral Amines as Catalysts in Asymmetric Synthesis. *Chem. Rev*. **2003**, *103*, 2985.

86. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Recent Advances in the Baylis-Hillman Reaction and Applications. *Chem. Rev*. **2003**, *103*, 811.

87. Calmes, M.; Daunis, J. How to Build Optically Active α-Amino Acids. *Amino Acids* **1999**, *16*, 215.

88. Wenzel, A. G.; Jacobsen, E. N. Asymmetric Catalytic Mannich Reactions Catalyzed by Urea Derivatives: Enantioselective Synthesis of β-Aryl-β-Amino Acids. *J. Am. Chem. Soc.* **2002**, *124*, 12964.

89. Wenzel, A. G.; Lalonde, M. P.; Jacobsen, E. N. Divergent Stereoinduction Mechanisms in Urea-Catalyzed Additions to Imines. *Synlett* **2003**, 1919.

90. Elizabeth, R.; Jarvo, J. M. Amino acids and Peptides as Asymmetric Organocatalysts. *Tetrahedron* **2002**, *58*, 2481.

91. Jarvo, E. R.; Evans, C. A.; Copeland, G. T.; Miller, S. J. Fluorescence-Based Screening of Asymmetric Acylation Catalysts through Parallel Enantiomer Analysis. Identification of a Catalyst for Tertiary Alcohol Resolution. *J. Org. Chem*. **2001**, *66*, 5522.

92. Papaioannou, N.; Evans, C. A.; Blank, J. T.; Miller, S. J. Enantioselective Synthesis of a Mitosane Core Assisted by Diversity-Based Catalyst Discovery. *Org. Lett*. **2001**, *3*, 2879.

93. Sculimbrene, B. R.; Miller, S. J. Discovery of a Catalytic Asymmetric Phosphorylation through Selection of a Minimal Kinase Mimic: A Concise Total Synthesis of D-myo-Inositol-1-phosphate. *J. Am. Chem. Soc*. **2001**, *123*, 10125.

94. Sculimbrene, B. R.; Miller, S. J. Enantiodivergence in Small-Molecule Catalysis of Asymmetric Phosphorylation: Concise Total Syntheses of the Enantiomeric D-myo-Inositol-1-phosphate and D-myo-Inositol-3-phosphate. *J. Am. Chem. Soc.* **2002**, *124*, 11653.

95. Guerin, D. J.; Miller, S. J. Asymmetric Azidation-Cycloaddition with Open-Chain Peptide-Based Catalysts. A Sequential Enantioselective Route to Triazoles. *J. Am. Chem. Soc.* **2002**, *124*, 2134.

96. Horstmann, T. E.; Guerin, D.; Miller, S. J. Asymmetric Conjugate Addition of Azide to *α,β*-Unsaturated Carbonyl Compounds Catalyzed by Simple Peptides. *Angew. Chem. Int. Ed.* **2000**, *39*, 3635.

97. Smith, M. B.; March, J. *Advanced Organic Chemistry. Reactions, Mechanisms, and Structure*.-*5th Edition*, John Wiley & Sons, Inc.: New York, **2001**.

98. Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. Enantioselective Trimethylsilylcyanation of Some Aldehydes Catalyzed by Chiral Schiff Base-Titanium Alkoxide Complexes. *J. Org. Chem*. **1993**, *58*, 1515.

99. Hayashi, M.; Inoue, T.; Miyamoto, Y.; Oguni, N. Asymmetric Carbon-Carbon Bond Forming Reactions Catalyzed by Chiral Schiff Base-Titanium Alkoxide Complexes. *Tetrahedron* **1994**, *50*, 4385.

100. Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. Discovery of Chiral Catalysts through Ligand Diversity: Ti-Catalyzed Enantioselective Addition of TMSCN to *meso* Epoxides. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1668.

101. Li, Y.; He, B.; Qin, B.; Feng, X.; Zhang, G. Highly Enantioselective Cyanosilylation of Aldehydes Catalyzed by Novel β-Amino Alcohol-Titanium Complexes. *J. Org. Chem*. **2004**, *69*, 7910.

102. Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. The Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Chiral (Salen)Titanium Complexes. *J. Am. Chem. Soc.* **1999**, *121*, 3968.

103. Belokon, Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. I. Chiral Salen-metal Complexes as Novel Catalysts for Asymmetric Phase Transfer Alkylations. *Tetrahedron Lett*. **1999**, *40*, 6105.

104. Belokon, Y. N.; North, M.; Parsons, T. Vanadium-Catalyzed Asymmetric Cyanohydrin synthesis. *Org. Lett*. **2000**, *2*, 1617.

105. Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. Aluminium-Catalyzed Asymmetric Addition of TMSCN to Aromatic and Aliphatic Ketones Promoted by an Easily Accessible and Recyclable Peptide Ligand. *Angew. Chem. Int. Ed.* **2002**, *41*, 1009.

106. Oku, J.; Inoue, S. Asymmetric Cyanohydrin Synthesis Catalyzed by a Synthetic Cyclic Dipeptide. *J. Chem. Soc., Chem. Commun*. **1981**, 229.

107. Tanaka, K.; Mori, A.; Inoue, S. The Cyclic Dipeptide Cyclo[(*S*)-phenylalanyl-(*S*)-histidyl] as a Catalyst for Asymmetric Addition of Hydrogen Cyanide to Aldehydes. *J. Org. Chem*. **1990**, *55*, 181.

108. Matthews, B. R.; Jackson, W. R.; Jayatilake, G. S.; Wilshire, C.; Jacobs, H. A. Asymmetric Hydrocyanation of a Range of Aromatic and Aliphatic Aldehydes. *Aust. J. Chem.* **1988**, *41*, 1697.

109. Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. Catalytic Asymmetric Cyano-Ethoxycarbonylation Reaction of Aldehydes using a YLi_3Tris(binaphthoxide) (YLB) Complex: Mechanism and Roles of Achiral Additives. *J. Am. Chem. Soc.* **2005**, *127*, 3413.

110. Groger, H. Catalytic Enantioselective Strecker Reactions and Analogous Syntheses. *Chem. Rev*. **2003**, *103*, 2795.

111. Yet, L. Recent Developments in Catalytic Asymmetric Strecker-Type Reacions. *Angew. Chem. Int. Ed.* **2001**, *40*, 875.

112. Vilaivan, T.; Bhanthumnavin, W.; Sritana-anant, Y. Recent Advances in Catalytic Asymmetric Addition to Imines and Related C=N Systems. *Curr. Org. Chem.* **2005**, *9*, 1315.

113. Calmes, M.; Daunis, J. How to Build Optically Active α-Amino Acids. *Amino Acids*, **1999**, *16*, 215.

114. Kunz, H.; Sager, W. Diastereoselective Strecker Synthesis of α-aminonitriles on Carbohydrate Templates. *Angew. Chem. Int. Ed. Engl*. **1987**, *26*, 557.

115. Kunz, H.; Pfrengle, W. Asymmetric Synthesis on Carbohydrate Templates: Stereoselective Ugi Synthesis of α-Amino Acid Derivatives. *J. Am. Chem. Soc*. **1988**, *110*, 651.

116. Kunz, H.; Sager, W.; Pfrengle, W.; Schanzenbach, D. Reversal of Asymmetric Induction in Stereoselective Strecker Synthesis on Galactosyl Amine as the Chiral Matrix. *Tetrahedron Lett*. **1988**, *29*, 4397.

117. Kunz, H.; Pfrengle, W. Carbohydrates as Chiral Templates: Asymmetric Ugi-Synthesis of α-Amino Acids using Galactosylamines as the Chiral Matrices. *Tetrahedron* **1988**, *44*, 5487.

118. Williams, R. M. *Synthesis of Optically Active α-amino acids*, Pergamon Press: Oxford, **1989**.

119. Duthaler, R. O. Recent Developments in the Stereoselective Synthesis of α-amino acids. *Tetrahedron* **1994**, *50*, 1539.

120. Harada, K. Asymmetric Synthesis of α-amino acids by the Strecker Synthesis. *Nature* **1963**, *200*, 1201.

121. Stout, D. M.; Black, L. A.; Matier, W. L. Asymmetric Strecker Synthesis: Isolation of Pure Enantiomers and Mechanistic Implications. *J. Org. Chem*. **1983**, *48*, 5369.

122. Weinges, K.; Gries, K.; Stemmle, B.; Scharank, W. Uber die Asymmetrische Strecker-Syntheses mit (*S*)-(-)-1-Phenylethylamin als Chiralem Hilfsreagens. *Chem. Ber*. **1997**, *110*, 2098.

123. Patel, M. S.; Worsely, M. Asymmetric Syntheses of Optically Active α-Amino Acids by Hydrocyanic Acid Addition to the Optically Active Schiff Bases. *Can. J. Chem*. **1970**, *48*, 1881.

124. Chakraborty, T. K.; Reddy. G. V.; Hussain, K. A. Diastereoselective Strecker Synthesis using α-Phenylglycinol as Chiral Auxiliary. *Tetrahedron Lett*. **1995**, *51*, 9197.

125. Inaba, T.; Kozono, I.; Fujita, M.; Ogura, K. An Efficient and Practical Synthesis of L-α-Amino Acids Using (*R*)–Phenylglycinol as a Chiral Auxiliary. *Bull. Chem. Soc. Jpn*. **1992**, *65*, 2359.

126. Chakraborty, T. K.; Hussain, K. A.; Reddy. G. V. α-Phenylglycinol as Chiral Auxiliary in Diastereoselective Strecker Synthesis of α-Amino Acids. *Tetrahedron* **1995**, *51*, 9179.

127. Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. Asymmetric Catalysis of the Strecker Amino Acid Synthesis by a Cyclic Dipeptide. *J. Am. Chem. Soc*. **1996**, *118*, 4910.

128. Danda, H.; Nishikawa, H.; Otaka, K. Enantioselective Autoinduction in the Asymmetric Hydrocyanation of 3-Phenoxybenzaldehyde Catalyzed by *Cyclo*[(*R*)-phenylalanyl-(*R*)-histidyl]. *J. Org. Chem*. **1991**, *56*, 6740.

129. Corey, E. J.; Grogan, M. J. Enantioselective Synthesis of α-Amino Nitriles from *N*-Benzhydryl Imines and HCN with a Chiral Bicyclic Guanidine as Catalyst. *Org. Lett*. **1999**, *1*, 157.

130. Sigman, M. S.; Jacobsen, E. N. Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries. *J. Am. Chem. Soc*. **1998**, *120*, 4901.

131. Sigman, M. S.; Vachal, P.; Jacobsen, E. N. A General catalyst for the Asymmetric Strecker Reaction. *Angew. Chem. Int. Ed*. **2000**, *39*, 1279.

132. Su, J. T.; Vachal, P.; Jacobsen, E. N. Practical Synthesis of a Soluble Schiff Base Catalyst for the Asymmetric Strecker Reaction. *Adv. Synth. Catal*. **2001**, *343*, 197.

133. Vachal, P.; Jacobsen, E. N. Structure-Based Analysis and Optimization of a Highly Enantioselective Catalyst for the Strecker Reaction. *J. Am. Chem. Soc*. **2002**, *124*, 10012.

134. Liu, B.; Feng, X.; Chen, F.; Zhang, G.; Cui, X.; Jiang, Y. Enantioselective Strecker Reactions Promoted by Chiral *N*-oxides. *Synlett* **2001**, 1551.

135. Jiao, Z.; Feng, X.; Liu, B.; Chen, F.; Zhang, G.; Jiang, Y. Enantioselective Strecker Reactions between Aldimines and Trimethylsilyl Cyanide Promoted by Chiral *N*,*N*′-Dioxides. *Eur. J. Org. Chem*. **2003**, 3818.

136. Huang, J.; Corey, E. J. A New Chiral Catalyst for the Enantioselective Strecker Synthesis of α-Amino Acids. *Org. Lett*. **2004**, *6*, 5027.

137. Ooi, T.; Uematsu, Y.; Maruoka, K. Asymmetric Strecker Reaction of Aldimines Using Aqueous Potassium Cyanide by Phase-Transfer Catalysis of Chiral Quaternary Ammonium Salts with a Tetranaphthyl Backbone. *J. Am. Chem. Soc.* **2006**, *128*, 2548.

138. Mori, M.; Imma, H.; Nakai, T. Asymmetric Catalytic Cyanosilylation of Aldehydes Using a Chiral Binaphthol-Titanium Complex. *Tetrahedron Lett.* **1997**, *38*, 6229.

139. Vallee, Y.; Byrne, J. J.; Chavarot, M. Asymmetric Strecker Reactions of Ketimines Catalyzed by Titanium-based Complexes. *Tetrahedron Lett*. **2000**, *41*, 873.

140. Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Vallee, Y. $Sc(BINOL)_2Li$: A New Heterobimetallic Catalyst for the Asymmetric Strecker Reaction. *Tetrahedron: Asymmetry* **2001**, *12*, 1147.

141. Ishihara, K.; Miyata, M.; Hattori, K.; Tada, T.; Yamamoto, H. A New Chiral BLA Promoter for Asymmetric Aza Diels-Alder and Aldol-Type Reactions of Imines. *J. Am. Chem. Soc.* **1994**, *116*, 10520.

142. Kobayashi, S.; Ishitani, H.; Ueno, M. Catalytic Asymmetric Synthesis of Both Syn- and Anti-β-Amino Alcohols. *J. Am. Chem. Soc.* **1998**, *120*, 431.

143. Kobayashi, S.; Komiyama, S.; Ishitani, H.; The first enantioselective Aza Diels-Alder Reactions of Imino Dienophiles on Use of a Chiral Zirconium Catalyst. *Angew. Chem. Int. Ed.* **1998**, *37*, 979.

144. Kobayashi, S.; Ishitani, H. Novel Binuclear Chiral Zirconium Catalysts Used in Enantioselective Strecker Reactions. *Chirality* **2000**, *12*, 540.

145. Ishitani, H.; Komiyama, S.; Kobayashi, S. Catalytic, Enantioselective Synthesis of α-Aminonitriles with a Novel Zirconuim Catalyst. *Angew. Chem. Int. Ed.* **1998**, *37*, 3186.

146. Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. Catalytic Asymmetric Strecker Synthesis. Preparation of Enantiomerically Pure α-Amino Acid Derivatives from Aldimines and Tributyltin Cyanide or Achiral Aldehydes, Amines, and Hydrogen Cyanide Using a Chiral Zirconium Catalyst. *J. Am. Chem. Soc.* **2000**, *122*, 762.

147. Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. A Catalytic Asymmetric Strecker-Type Reaction: Interesting Reactivity

Difference between TMSCN and HCN. *Angew. Chem. Int. Ed.* **2000**, *39*, 1650.

148. Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. A Catalytic Asymmetric Strecker-Type Reaction Promoted by Lewis Acid-Lewis Base Bifunctional Catalyst. *Chem. Pharm. Bull*. **2000**, *48*, 1586.
149. Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. A New Bifunctional Asymmetric Catalysis: An Efficient Catalytic Asymmetric Cyanosilylation of Aldehydes. *J. Am. Chem. Soc*. **1999**, *121*, 2641.
150. Nogami, H.; Matsunaga, S.; Nakai, M.; Shibasaki, M. Enantioselective Strecker-Type Reaction Promoted by Polymer-Supported Bifunctional Catalyst. *Tetrahedron Lett*. **2001**, *42*, 279.
151. Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. Asymmetric Reissert-type Reaction Promoted by Bifunctional Catalyst. *J. Am. Chem. Soc.* **2000**, *122*, 6327.
152. Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. Catalytic Enantioselective Reissert-Type Reaction: Development and Application to the Synthesis of a Potent NMDA Receptor Antagonist (-)-L-689,560 Using a Solid-Supported Catalyst. *J. Am. Chem. Soc.* **2001**, *123*, 6801.
153. Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. Enantioselective Construction of Quaternary Stereocenter through a Reissert-Type Reaction Catalyzed by an Electronically Tuned Bifunctional Catalyst: Efficient Synthesis of Various Biologically Significant Compounds. *J. Am. Chem. Soc*. **2001**, *123*, 10784.
154. Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. New Entries in Lewis Acid-Lewis Base Bifunctional Asymmetric Catalyst: Catalytic Enantioselective Reissert Reaction of Pyridine Derivatives. *J. Am. Chem. Soc.* **2004**, *126*, 11808.
155. Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. A New Approach to Enantioselective Cyanation of Imines with Et_2AlCN. *Tetrahedron: Asymmetry* **2004**, *15*, 1513.
156. Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. Ti-Catalyzed Enantioselective Addition of

Cyanide to Imines. A Practical Synthesis of Optically Pure α-Amino Acids. *J. Am. Chem. Soc.* **1999**, *121*, 4284.

157. Josephsohn, N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. Mechanism of Enantioselective Ti-Catalyzed Strecker Reaction: Peptide-Based Metal Complexes as Bifunctional Catalysts. *J. Am. Chem. Soc.* **2001**, *123*, 11594.
158. Sigman, M. S.; Jacobsen, E. N. Schiff Base Catalysts for the Asymmetric Strecker Reaction Identified and Optimized from Parallel Synthetic Libraries. *J. Am. Chem. Soc.* **1998**, *120*, 4901.
159. Sigman, M. S.; Jacobsen, E. N. Enantioselective Addition of Hydrogen Cyanide to Imines Catalyzed by a Chiral (Salen)Al(III) Complex. *J. Am. Chem. Soc.* **1998**, *120*, 5315.
160. Vachal, P.; Jacobsen, E. N. Enantioselective Catalytic Addition of HCN to Ketoimines. Catalytic Synthesis of Quaternary Amino Acids. *Org. Lett.* **2000**, *2*, 867.
161. Spino, C. Recent Developments in the Catalytic Asymmetric Cyanation of Ketimines. *Angew. Chem. Int. Ed.* **2004**, *43*, 1764.
162. Kato, N.; Tomita, D.; Maki, K.; Kanai, M.; Shibasaki, M. Practical Synthesis of Chiral Ligands for Catalytic Enantioselective Cyanosilylation of Ketones and Ketoimines. *J. Org. Chem.* **2004**, *69*, 6128.
163. Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. Catalytic Enantioselective Strecker Reaction of Ketoimines. *J. Am. Chem. Soc.* **2003**, *125*, 5634.
164. Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. General and Practical Catalytic Enantioselective Strecker Reaction of Ketoimines: Significant Improvement through Catalyst Turning by Protic Additives. *Tetrahedron Lett.* **2004**, *45*, 3147.
165. Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. Catalytic Enantioselective Strecker Reaction of Ketoimines using Catalytic Amount of TMSCN and Stoichiometric Amount of HCN. *Tetrahedron Lett*. **2004**, *45*, 3153.
166. Keith, J. M.; Jacobsen, E. N. Asymmetric Hydrocyanation of Hydrazones Catalyzed by Lanthanide-PYBOX Complexes. *Org. Lett*. **2004**, *6*, 153.

167. Mansawat, W.; Bhanthumnavin, W.; Vilaivan, T. *N*-Salicyl-β-Aminoalcohols as A New Class of Ligand for Catalytic Asymmetric Strecker Reactions. *Tetrahedron Lett* **2003**, *44*, 3805.

168. Narasimhan, S.; Velmathi, S.; Balakumar, R.; Radhakrishnan, V. Novel Enantiomer-Switching Catalysts for Asymmetric Reductions and Michael Reactions. *Tetrahedron Lett*. **2001**, *42*, 719.

169. Velmathi, S.; Swarnalakshmi, S.; Narasimhan, S. Novel Heterobimetallic Catalysts for Asymmetric Michael Reactions. *Tetrahedron: Asymmetry* **2003**, *14*, 113.

170. Suwa, T.; Sugiyama E.; Shibata, I.; Baba, A. Chemoselectively Reductive Amination of Aldehydes and Ketones by Dibutylchlorotin Hydride-HMPA Complex. *Synthesis* **2000**, 789.

171. Gomez, S.; Peters, J. A.; Maschmeyer, T. The Reductive Amination of Aldehydes and Ketones and the Hydrogenation of Nitriles: Mechanistic Aspects and Selectivity Control. *Adv. Synth. Catal*. **2002**, *344*, 1037.

172. Yoshida, T.; Harada, K. Asymmetric Hydrogenation of the C=N Bond. Factors Controlling the Stereoselectivity. *Bull. Chem. Soc. Jpn*., **1972**, *54*, 3706.

173. Selambarom, J.; Monge, S.; Carre, F.; Roque, J. P.; Pavia, A. A. Stereoelectronic Control of Oxazolidine Ring-Opening: Structural and Chemical Evidences. *Tereahedron* **2002**, *58*, 9559.

174. Morrison, J. D. *Asymmetric Synthesis Volume 1 Analytical Methods*, Academic Press, Inc: Durham, 1983.

175. Fusan, R. C.; Wolf, D. E. The Methylation of β-Ketonitriles. *J. Chem. Soc*. **1939**, *61*, 1940.

176. Dale, J. A.; Dull, D. L.; Mosher, H. S. α-Methoxy-α-trifluoromethylphenylacetic Acid, a Versatile Reagent for the Determination of Enantiomeric Composition of Alcohols and Amines. *J. Org. Chem*. **1969**, *34*, 2543.

177. Marvell, C. S.; Noyes, W. A. A Study of the Possible Asymmetry of the Aliphatic Diazo Compounds. *J. Am. Chem. Soc*. **1920**, *42*, 2266.

178. Aitken, R. A.; Kilenyi, S. N. *Asymmetric Synthesis*, Blackie Academic & Professional: Glasgow, **1992**.

179. Hassan, N. A.; Bayer, E.; Jochims, J. C. Syntheses of Optically Active α-Aminonitriles by Asymmetric Transformation of the Second Kind Using a Principle of O. Dimroth. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3747.

180. Blaha, K.; Cervinka, O.; Kovar, J. *Fundamentals of Stereochemistry and Conformational Analysis*, Illiffe: Prague, **1992**.

181. Lin, G.; Chen, X.; Li, Y. *Principle and Application of Asymmetric Reactions*. Science Press: Bejing, **2000**.

182. Clark, R. J. H. *The Chemistry of Titanium and Vanadium*. Elsevier: Amsterdam, **1968**.

183. Bradley, D. C.; Methrotra, R. C.; Gaur, D. P. *Metal Alkoxides*. Academic Press: London, **1978**.

184. Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. Indium Mediated Barbier-Type Allylation of Aldimines in Alcoholic Solvents. *Tetrahedron Lett.* **2001**, *42*, 9073.

185. Huang, T.; Li, C. Synthesis of Amino Acids via a Three-component Reaction of Phenols, Glyoxylates and Amines. *Tetrahedron Lett* **2000**, *41*, 6715.

186. Katritzky, A. R.; Abdel-Fat-tah, A. A. A.; Tymoshenko, D. O.; Steel, P. J. Amino(hetero)arylmethylation of Phenols with *N*-[α-Amino(hetero)arylmethyl]benzo triazoles. *J. Org. Chem.* **1999**, *64*, 6071.

187. Skattebol, L.; Hofslokken, N. U. Convenient Method for the *ortho*-Formylation of Phenols. *Acta. Chem. Scand*. **1999**, *53*, 258.

188. Sluis, M. V. D.; Dalmolen, J.; Lange, B. D.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. Diastereoselective Addition of Allylzinc Bromide to Imines Derived from (*R*)-Phenylglycine Amide. *Org. Lett*. **2001**, *3*, 3943.

189. Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. Indium-Mediated Asymmetric Barbier-Type Allylation of Aldimines in Alcoholic Solvents: Synthesis of Optically Active Homoallylic Amines. *J. Org. Chem.* **2005**, *70*, 3464.

190. Kwon, S. J.; Ko, S. Y. Stereoselective Synthesis of Triply-stereogenic *syn*, *anti*-Amino Diols: the Abbott Amino Diol. *Bull. Korean Chem. Soc*. **2003**, *24*, 1053.

191. Mai, K.; Patil, G. Alkylsilyl Cyanides as Silylating Agents. *J. Org. Chem.* **1986**, *51*, 3545.

192. Williams, R. M.; Hendrix, J. A. Asymmetric Synthesis of Arylglycines. *Chem. Rev.* **1992**, *92*, 889.

193. Heller, D.; Drexler, H.; Christine, F.; Buschmann, H.; Buamann, W.; Heller, B. How Long Have Nonlinear Effects Been Known in the Field of Catalysis? *Angew. Chem. Int. Ed.* **2000**, *39*, 495.

194. Nammoonoy, J. The Degree of Master of Science in Chemistry Thesis.

195. Srikaenjun, P. The Degree of Master of Science in Chemistry Thesis.

APPENDICES

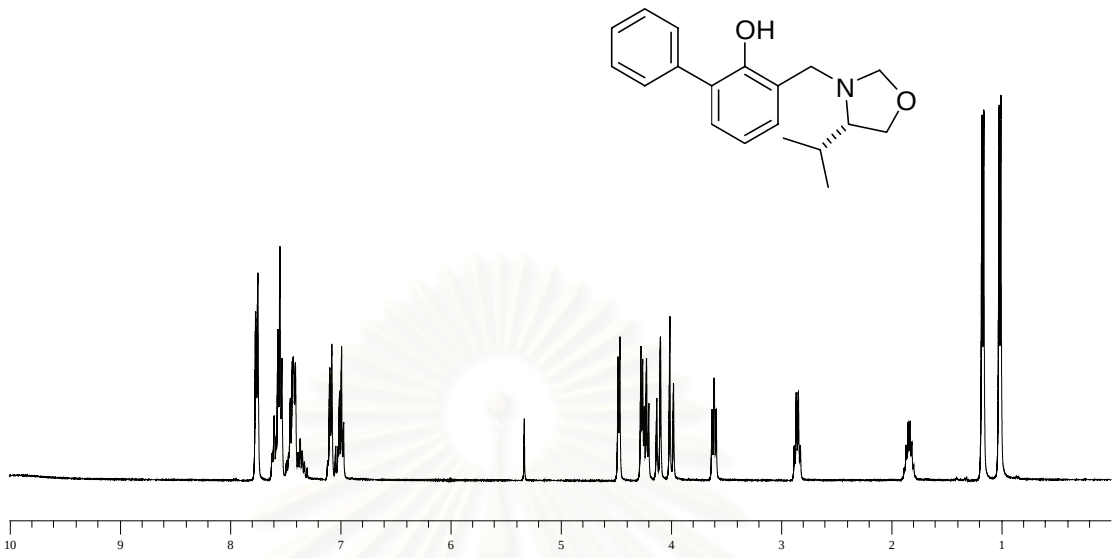


Figure 1 ^{1}H NMR of *N*-(2′-hydroxy-3′-biphenyl)methyl-(*S*)-4-isopropyl-oxazolidine **(111a)**

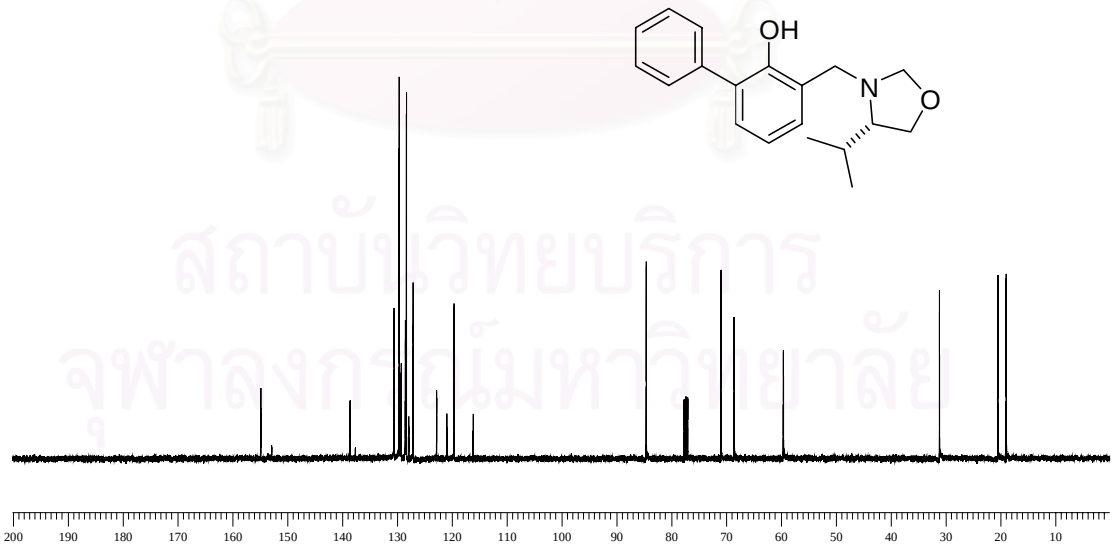


Figure 2 ^{13}C NMR of *N*-(2′-hydroxy-3′-biphenyl)methyl-(*S*)-4-isopropyl-oxazolidine **(111a)**

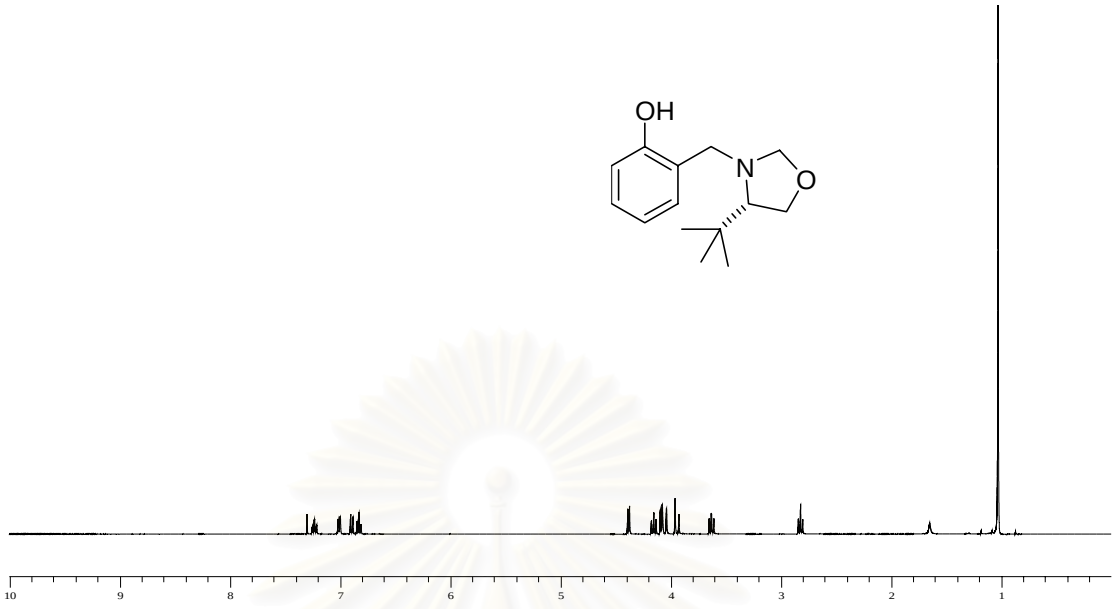


Figure 3 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine **(111b)**

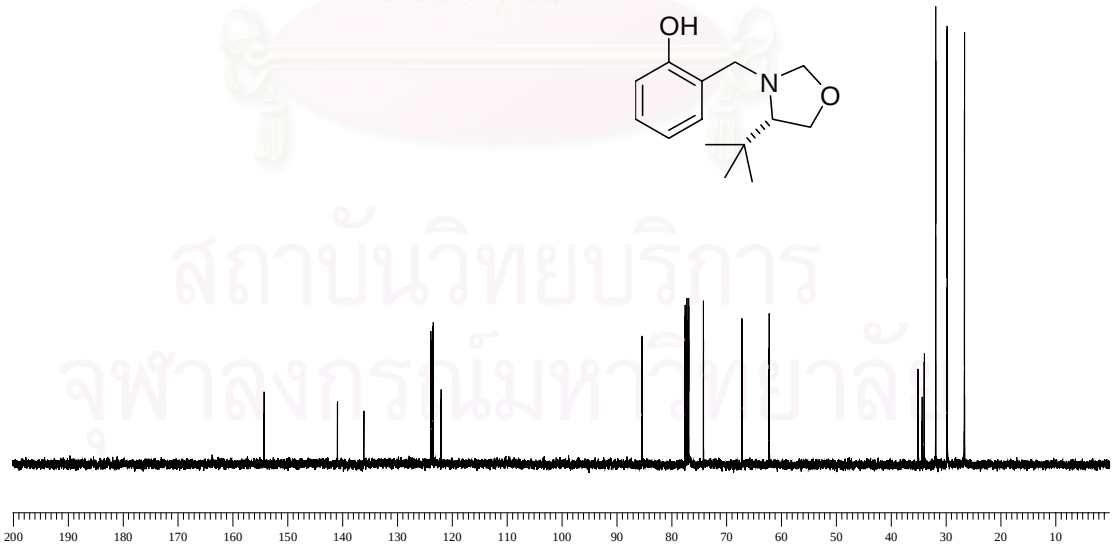


Figure 4 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine **(111b)**

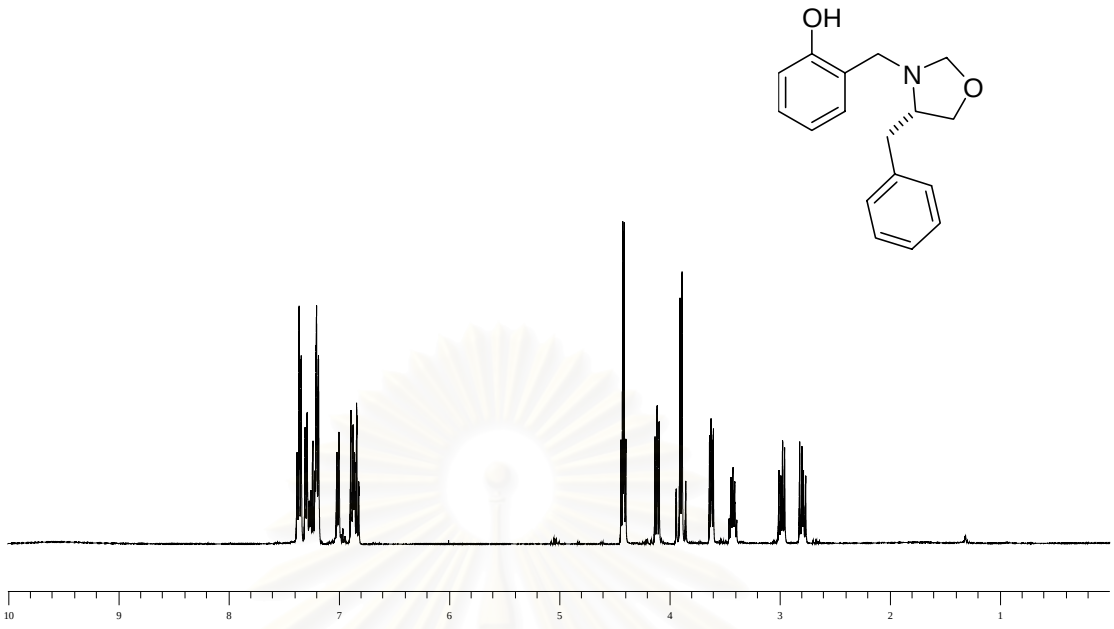


Figure 5 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-4-benzyl-oxazolidine **(111c)**

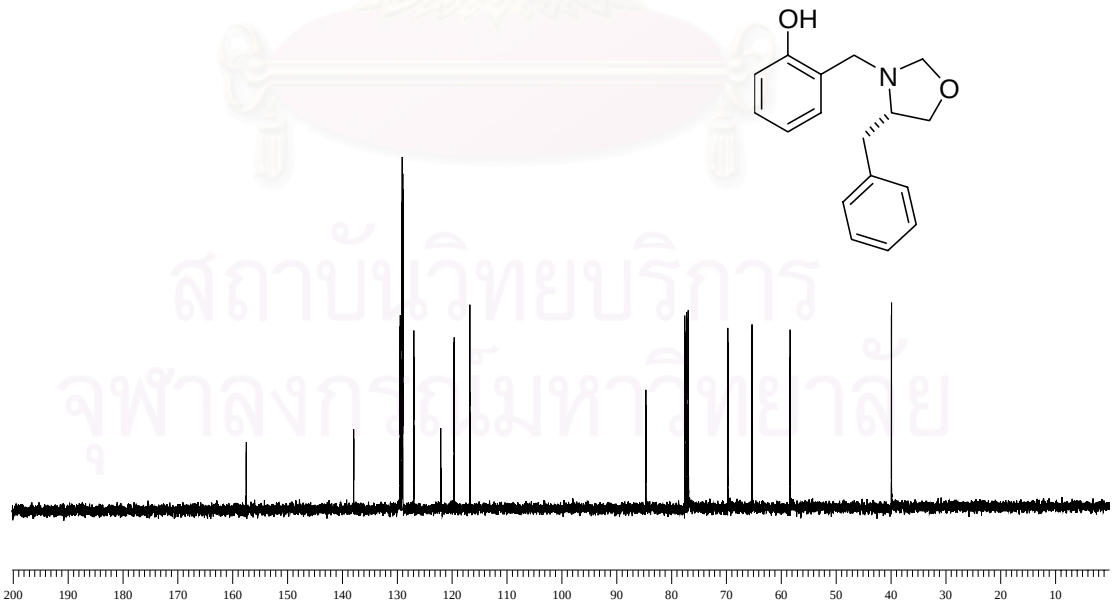


Figure 6 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-4-benzyl-oxazolidine **(111c)**

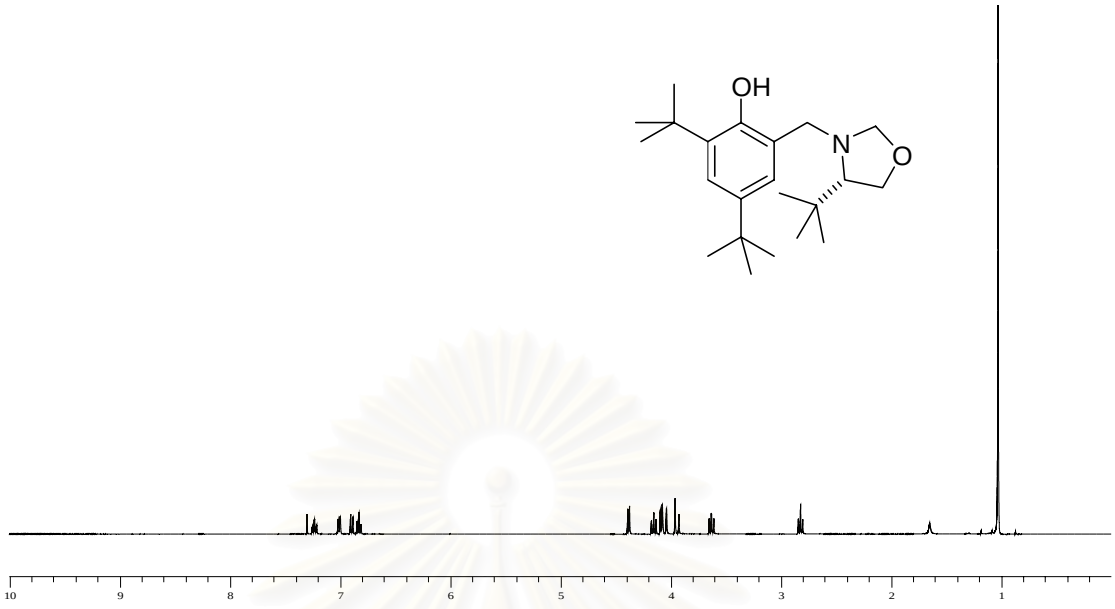


Figure 7 ^{1}H NMR of *N*-(3′,5′-Di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine **(111d)**

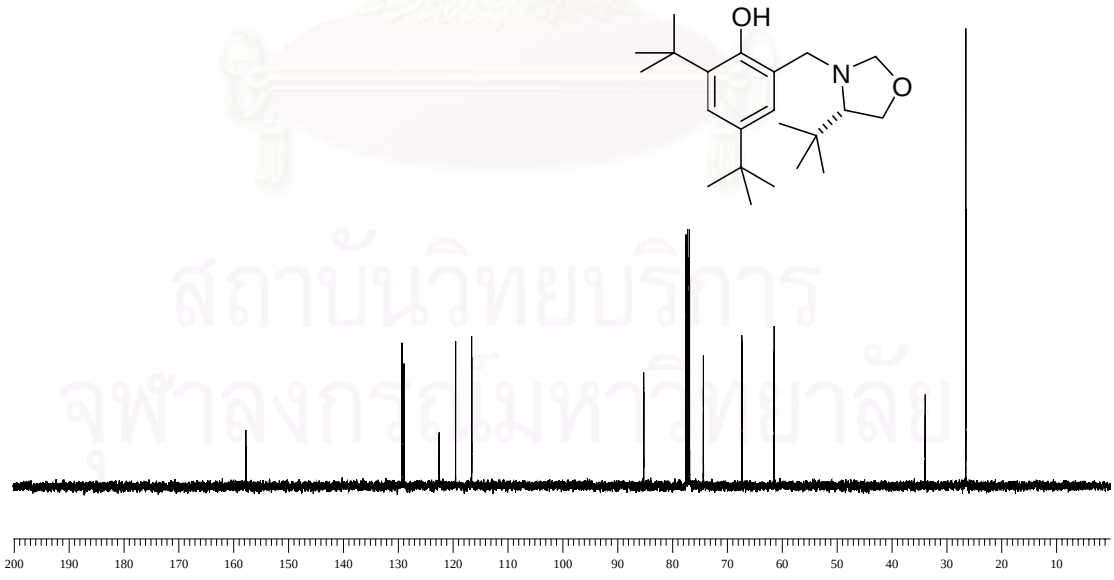


Figure 8 ^{13}C NMR of *N*-(3′,5′-di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-4-*tert*-butyl-oxazolidine **(111d)**

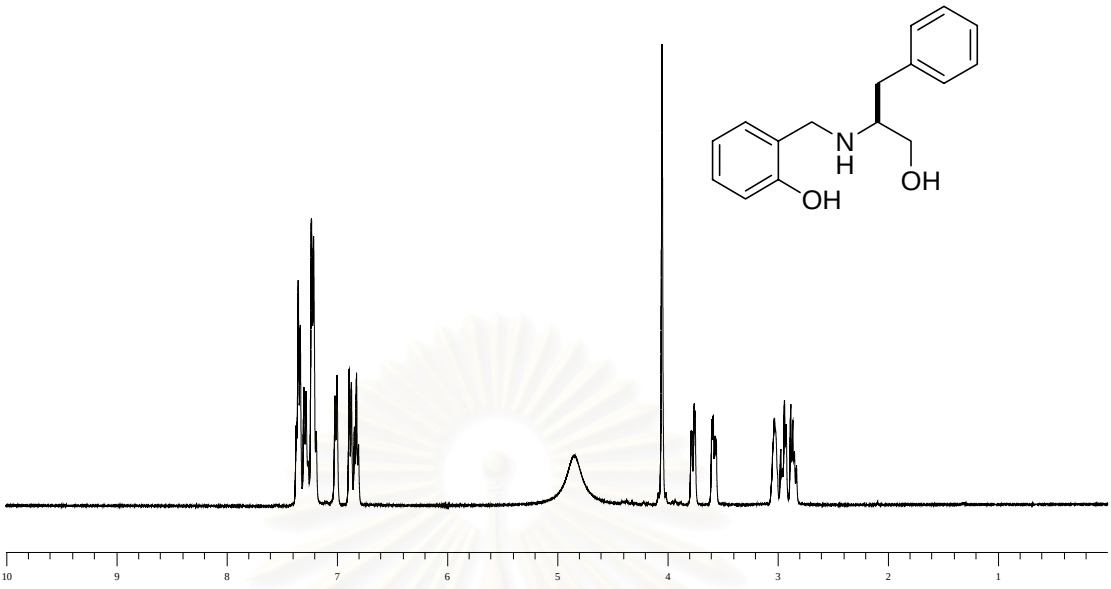


Figure 9 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl- propanol **(109a)**

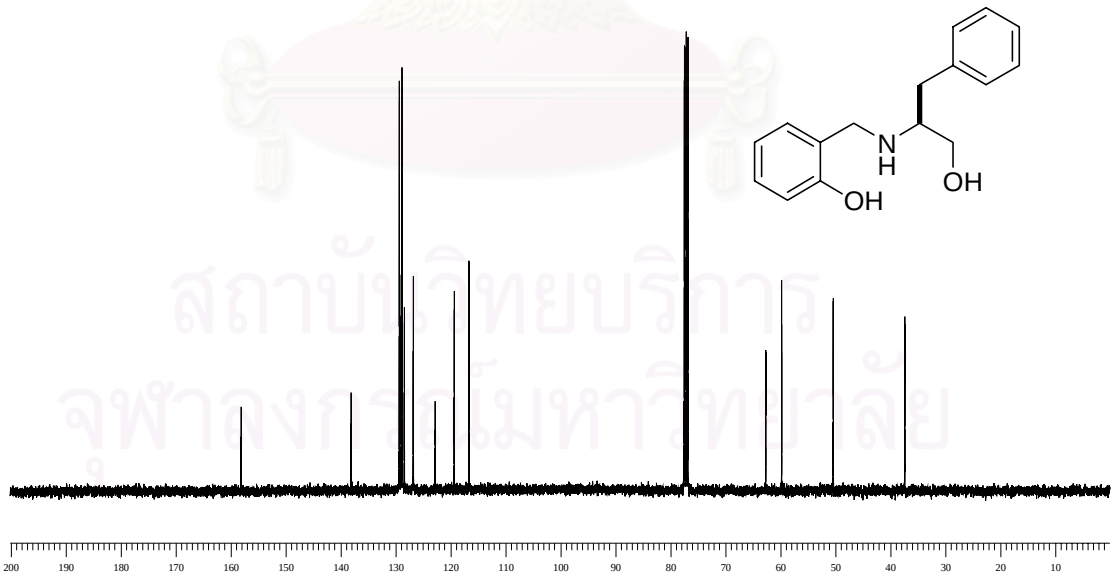


Figure 10 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol **(109a)**

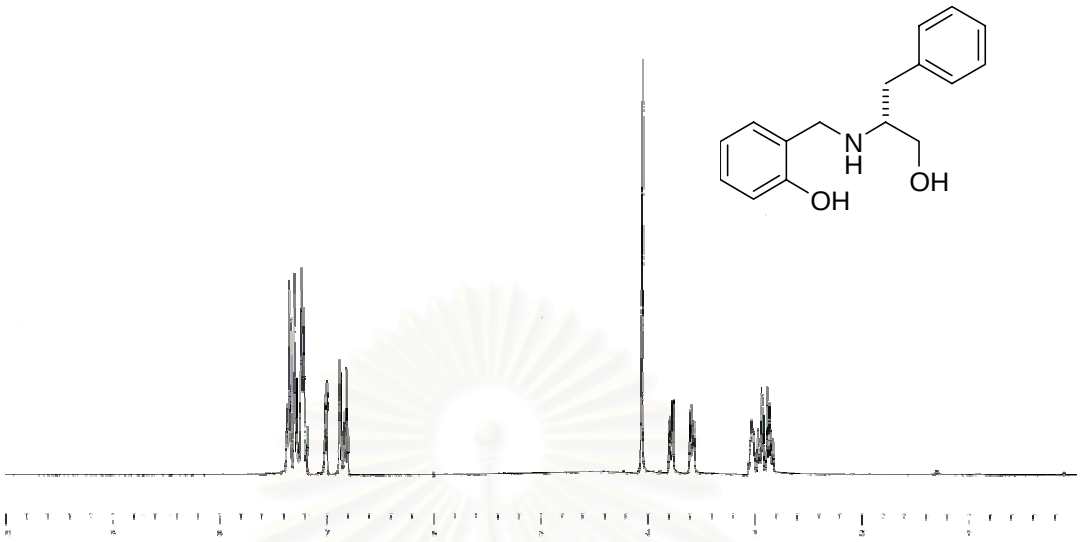


Figure 11 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*R*)-2-amino-3-phenyl-propanol **(109a)**

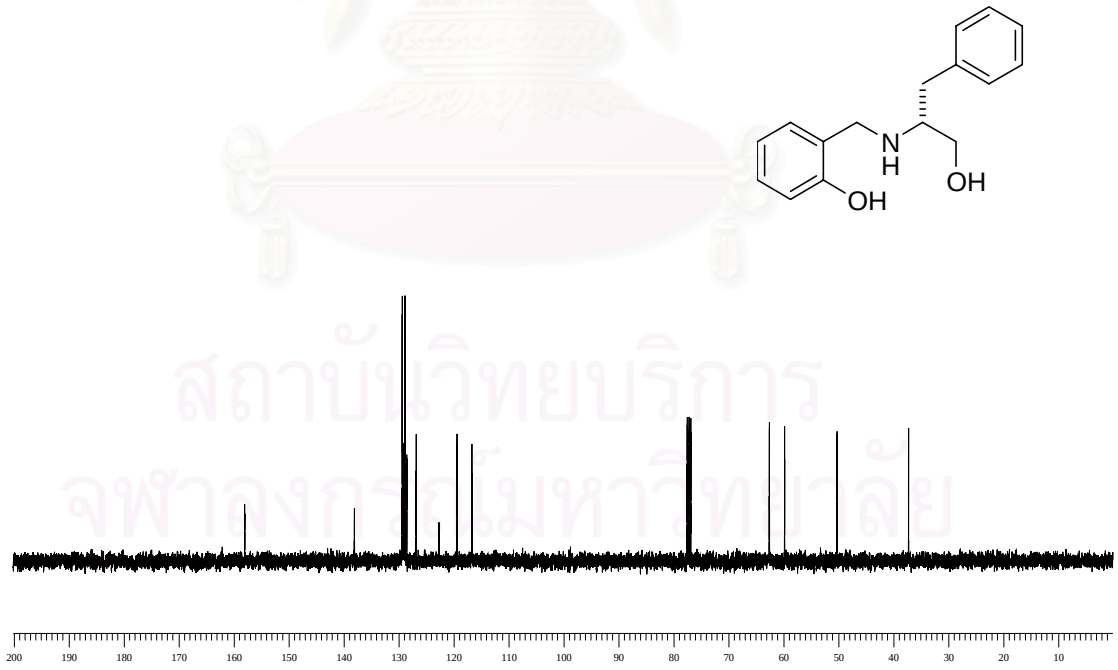


Figure 12 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*R*)-2-amino-3-phenyl-propanol **(109a)**

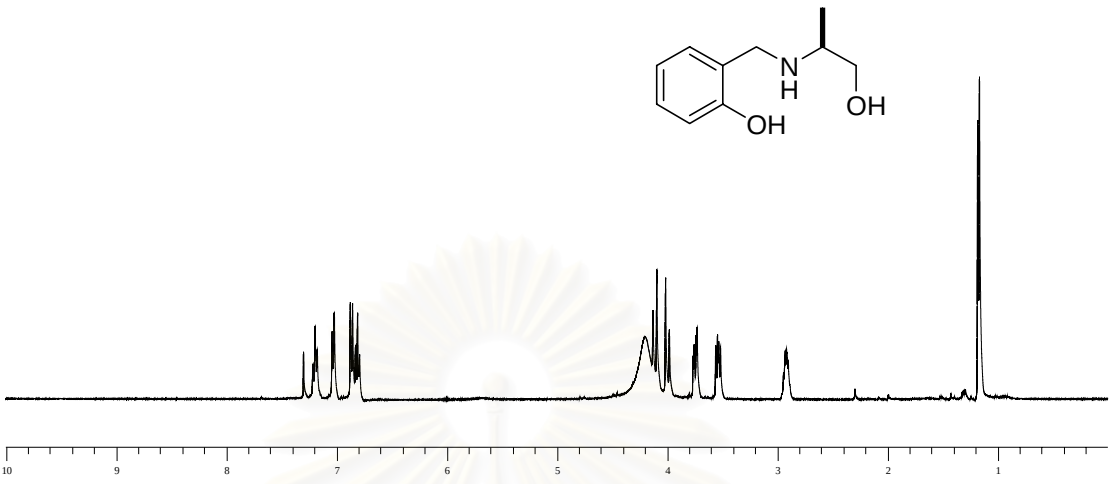


Figure 13 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-propanol **(109b)**

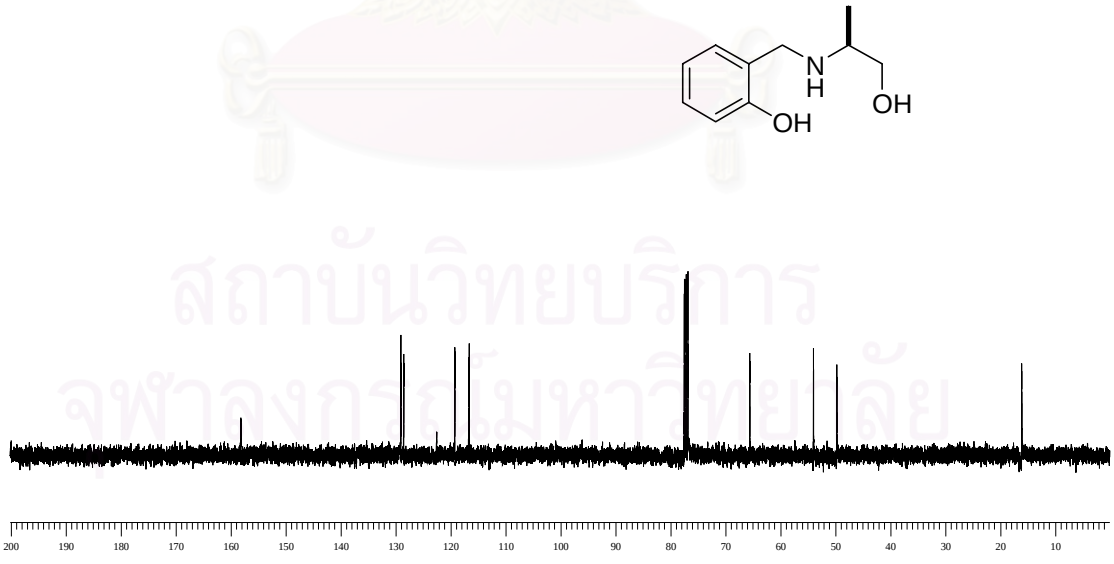


Figure 14 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-propanol **(109b)**

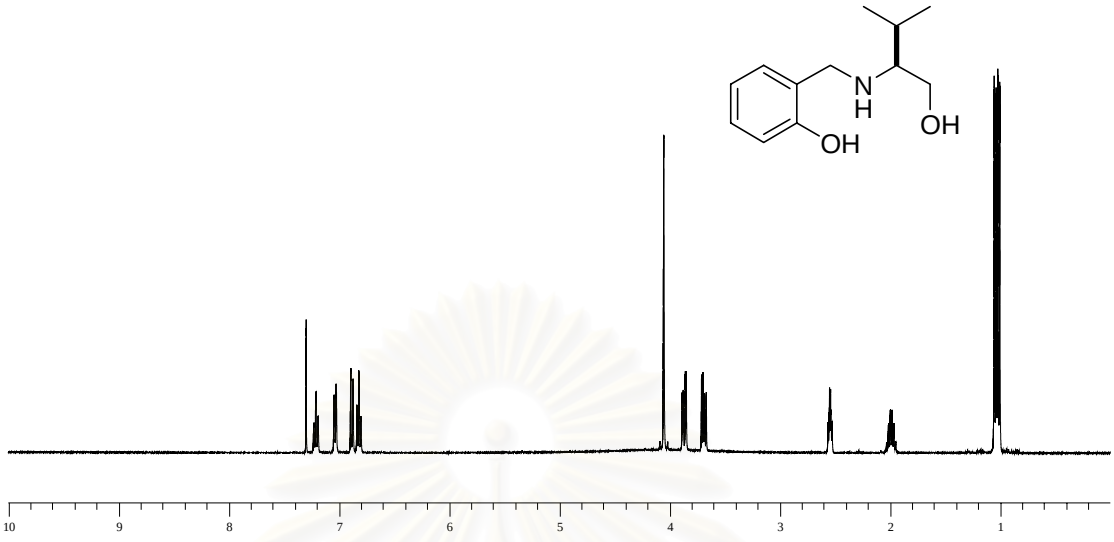


Figure 15 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109c)**

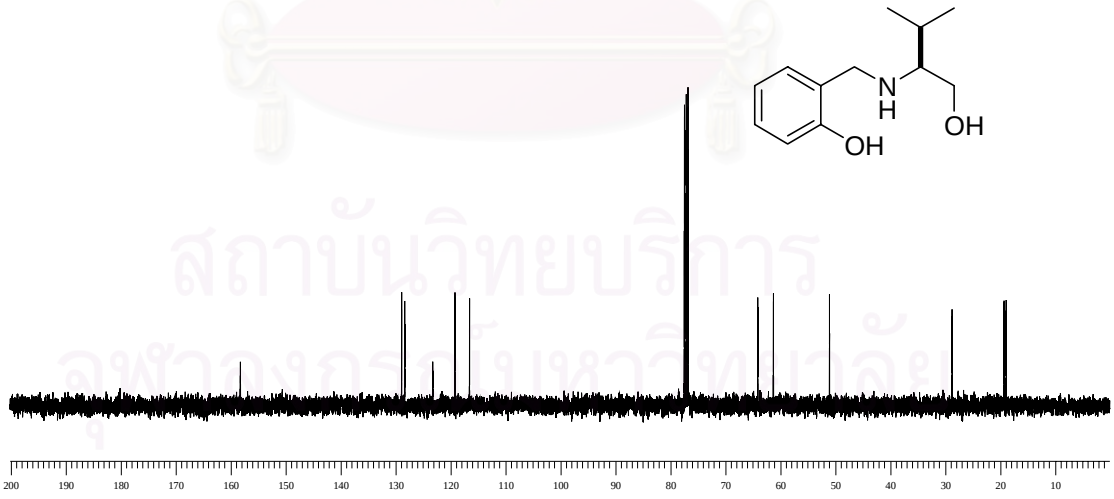


Figure 16 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109c)**

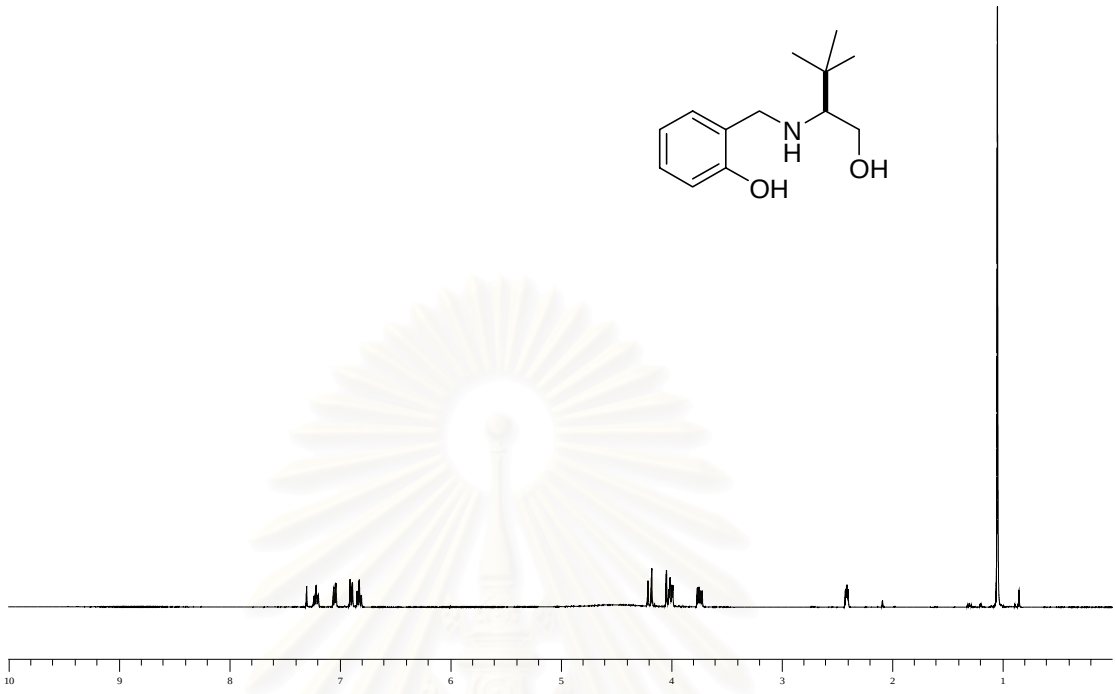


Figure 17 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109d)**

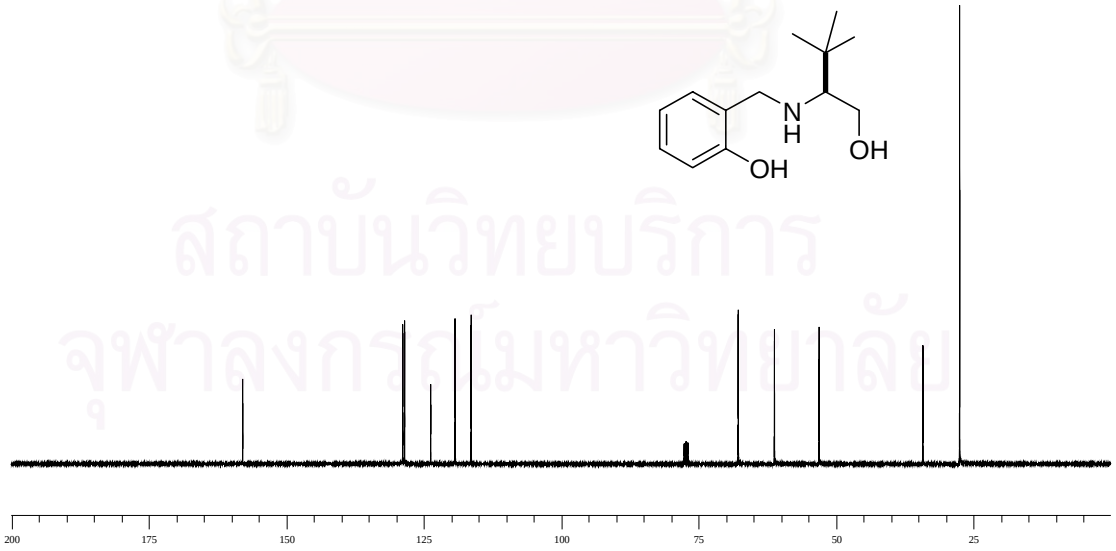


Figure 18 ^{13}C NMR of ***N***-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109d)**

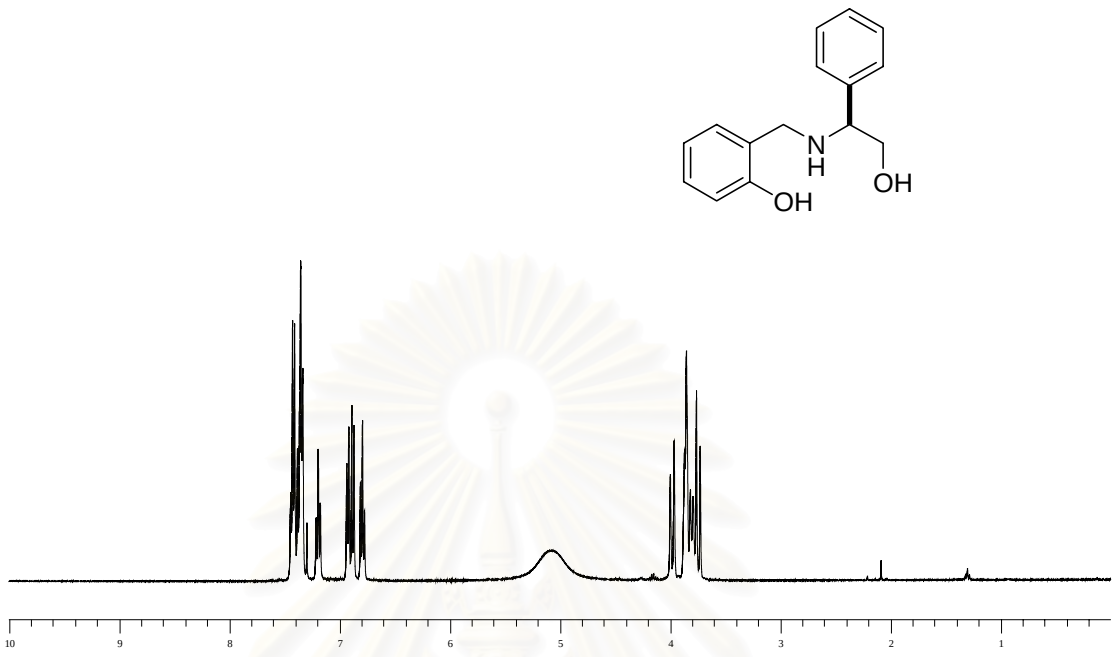


Figure 19 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-2-phenyl-ethanol **(109e)**

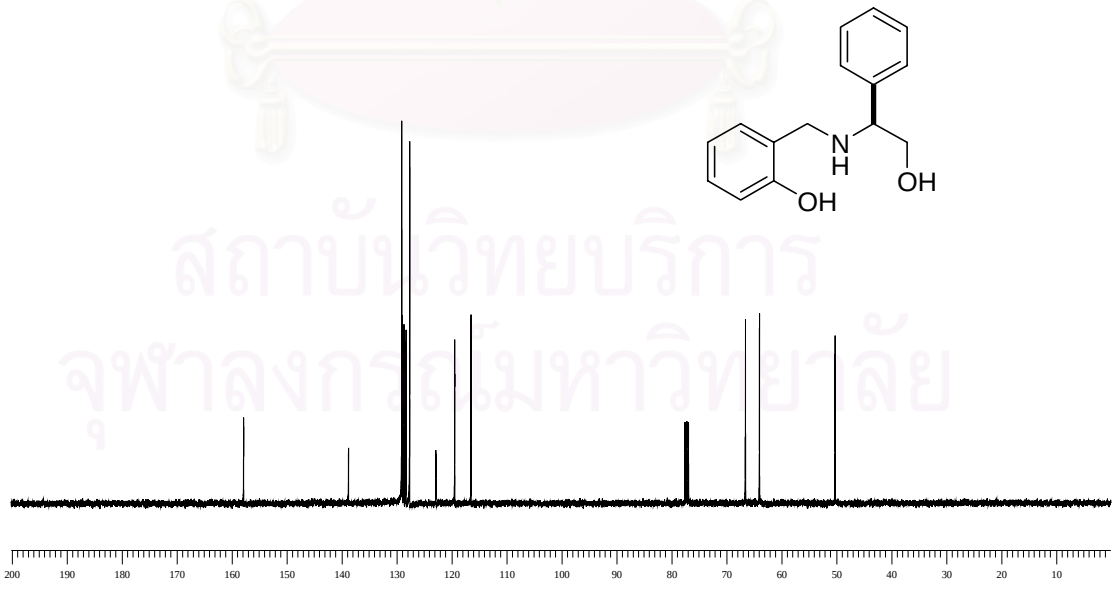


Figure 20 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-2-phenyl-ethanol **(109e)**

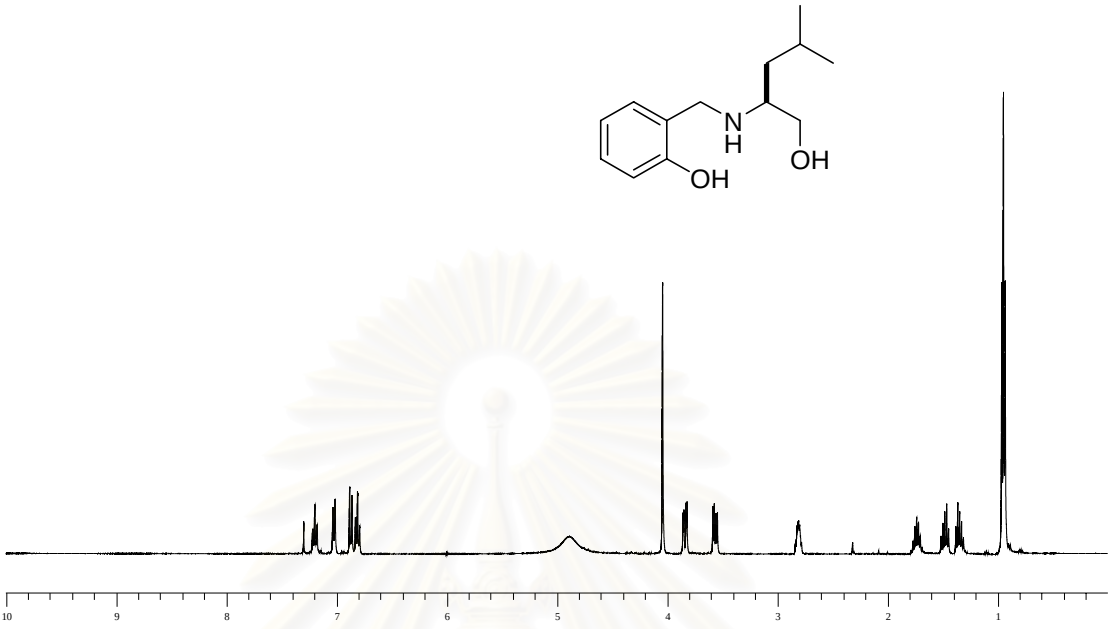


Figure 21 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-4-methyl-pentanol **(109f)**

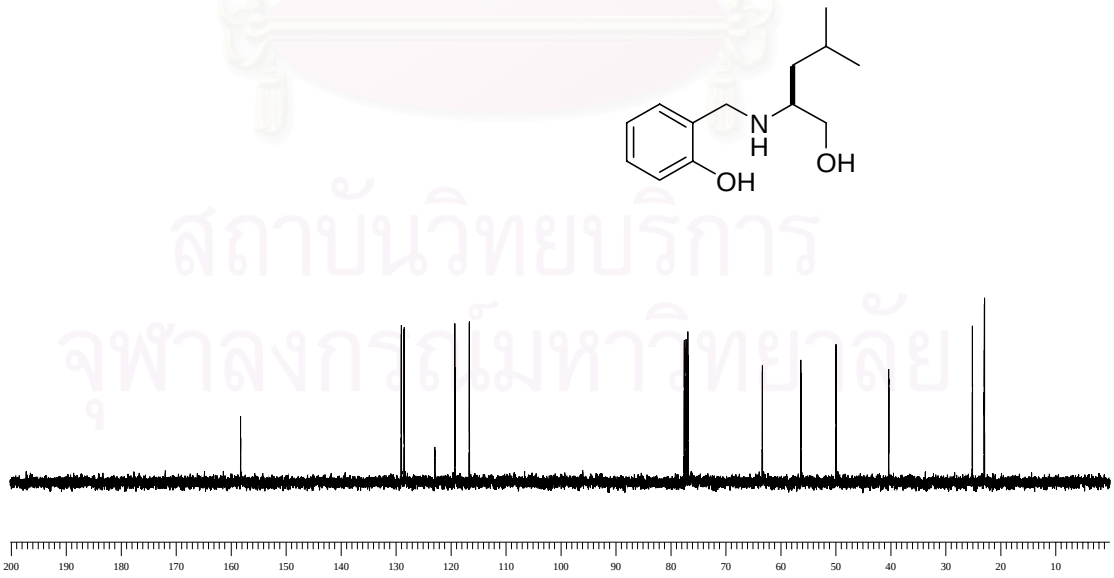


Figure 22 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-4-methyl-pentanol **(109f)**

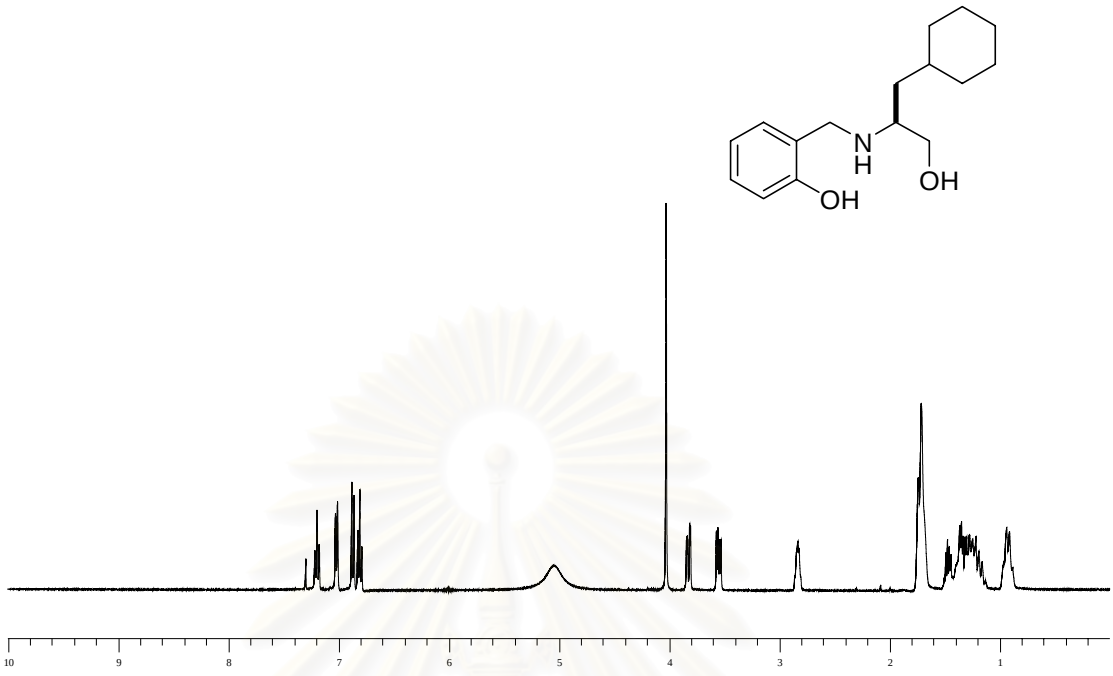


Figure 23 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-cyclohexyl-propanol **(109g)**

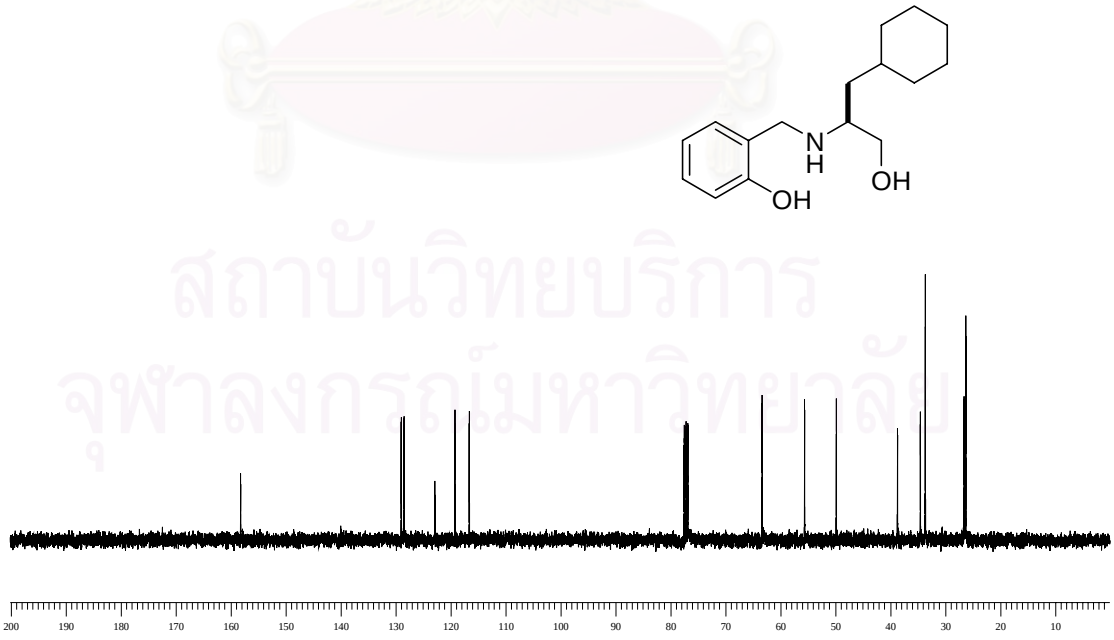


Figure 24 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-cyclohexyl-propanol **(109g)**

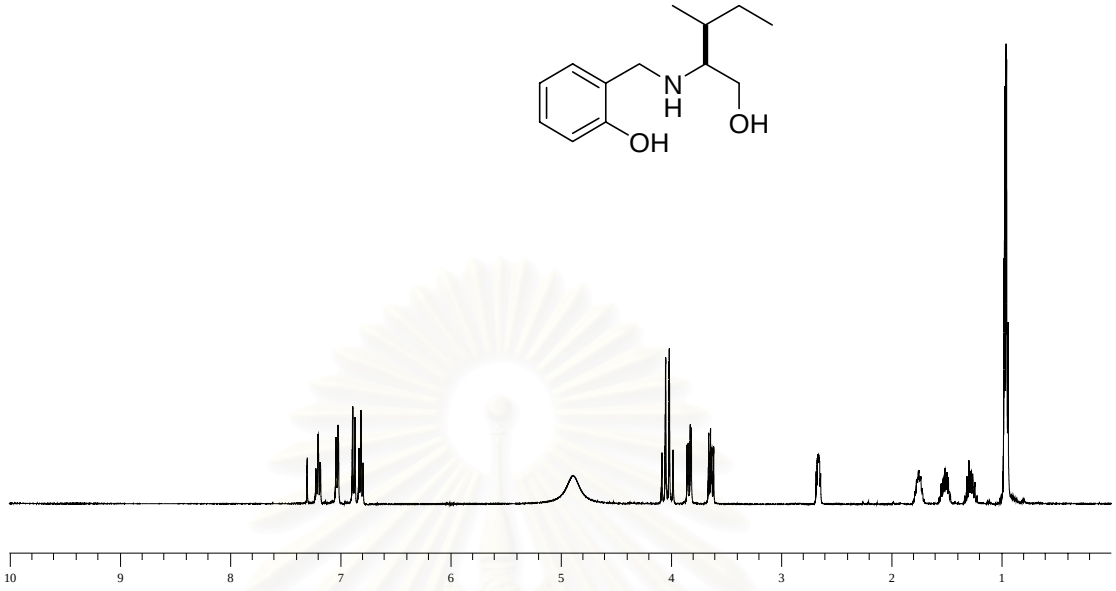


Figure 25 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-(*S*)-3-methyl-pentanol **(109h)**

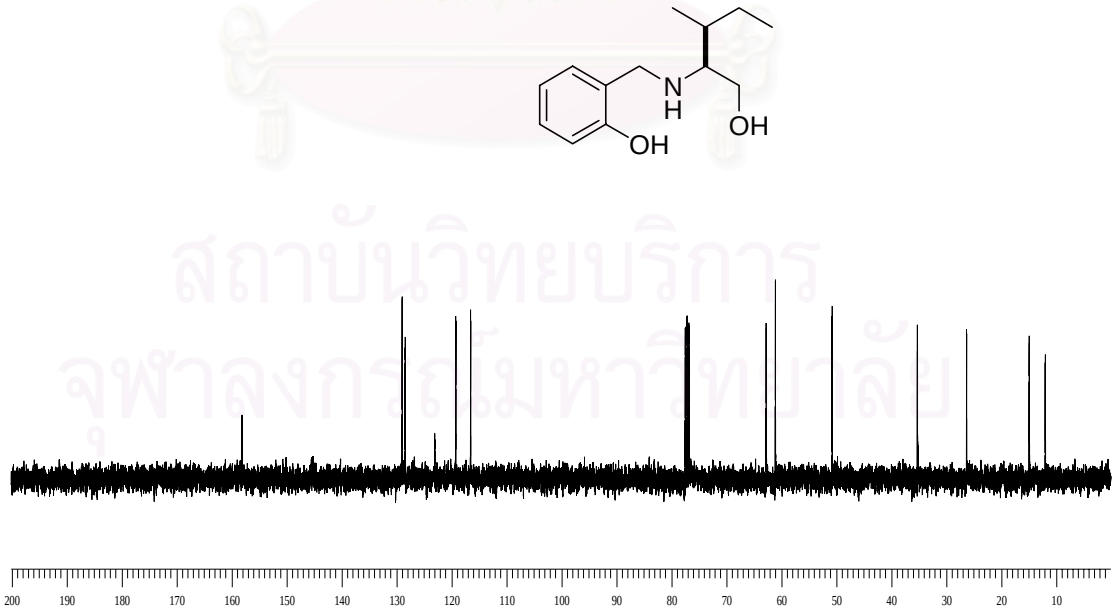


Figure 26 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-(*S*)-3-methyl-pentanol **(109h)**

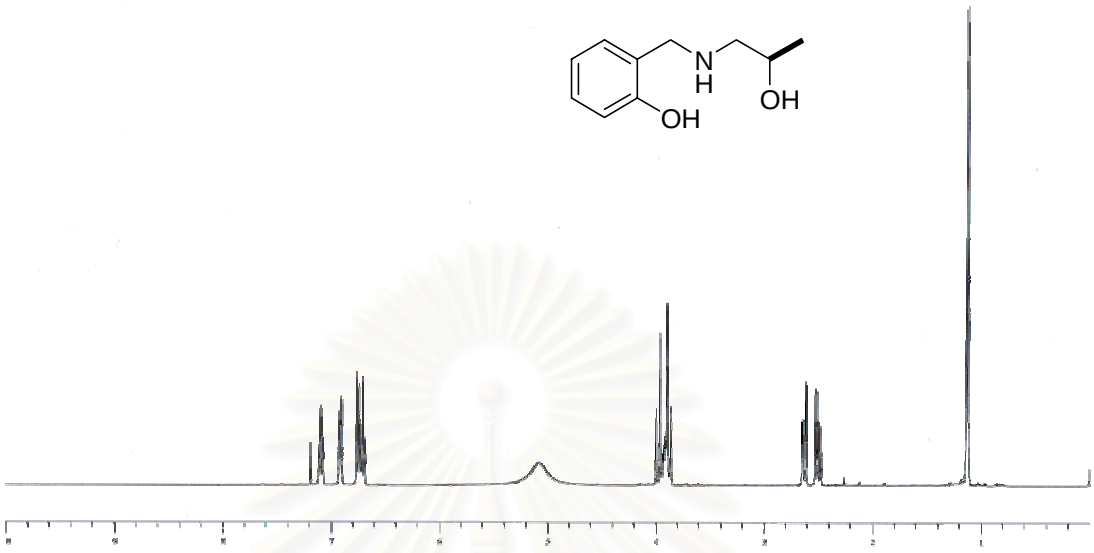


Figure 27 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*R*)-1-amino-propanol **(109i)**

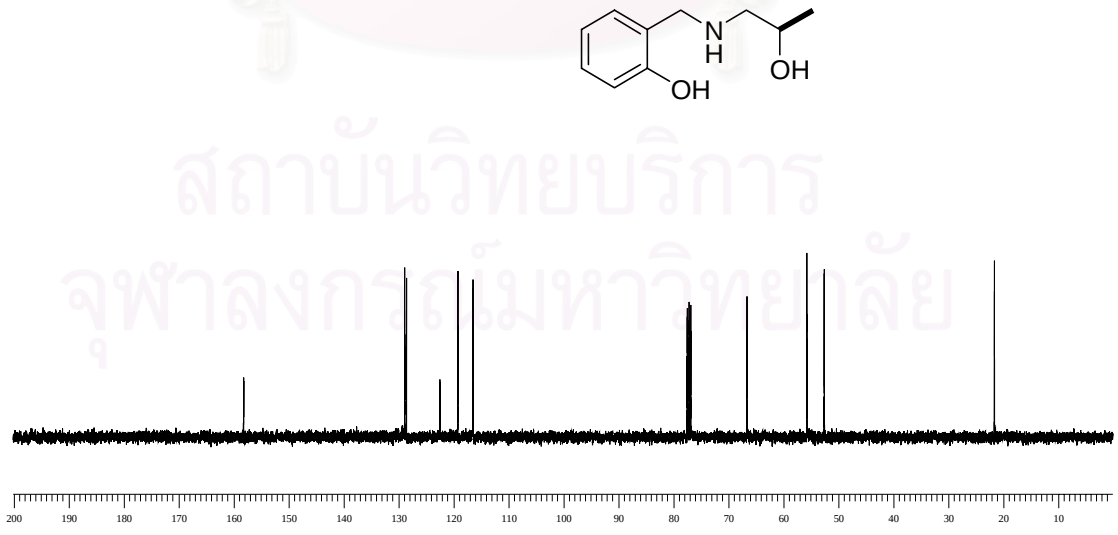


Figure 28 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*R*)-1-amino-propanol **(109i)**

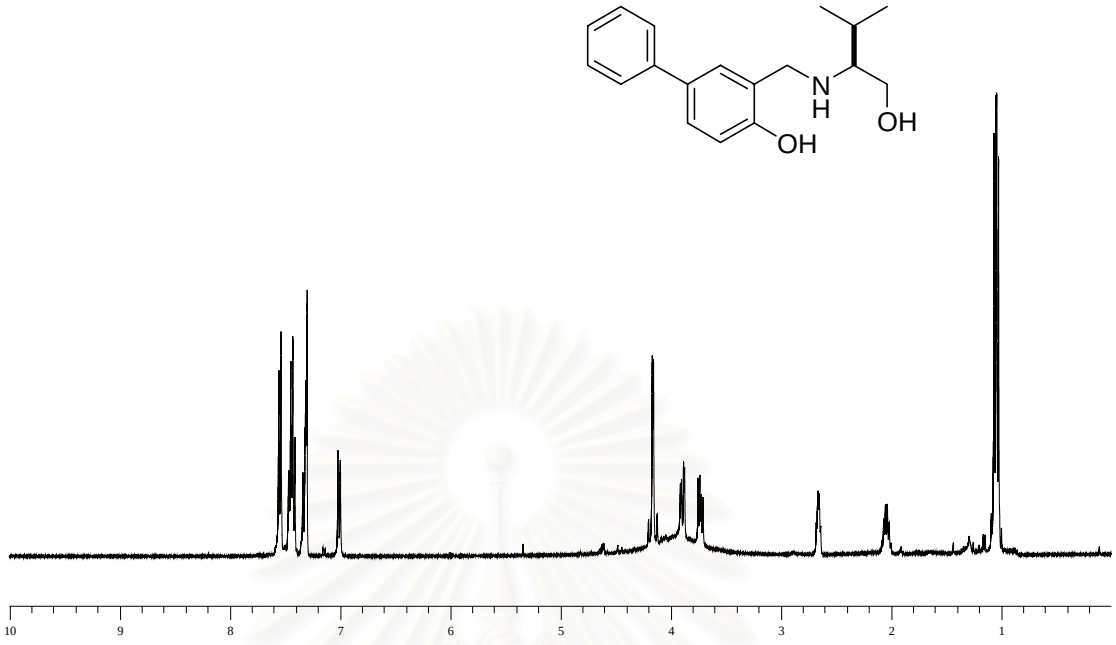


Figure 29 ^{1}H NMR of *N*-(2′-hydroxy-5′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109j)**

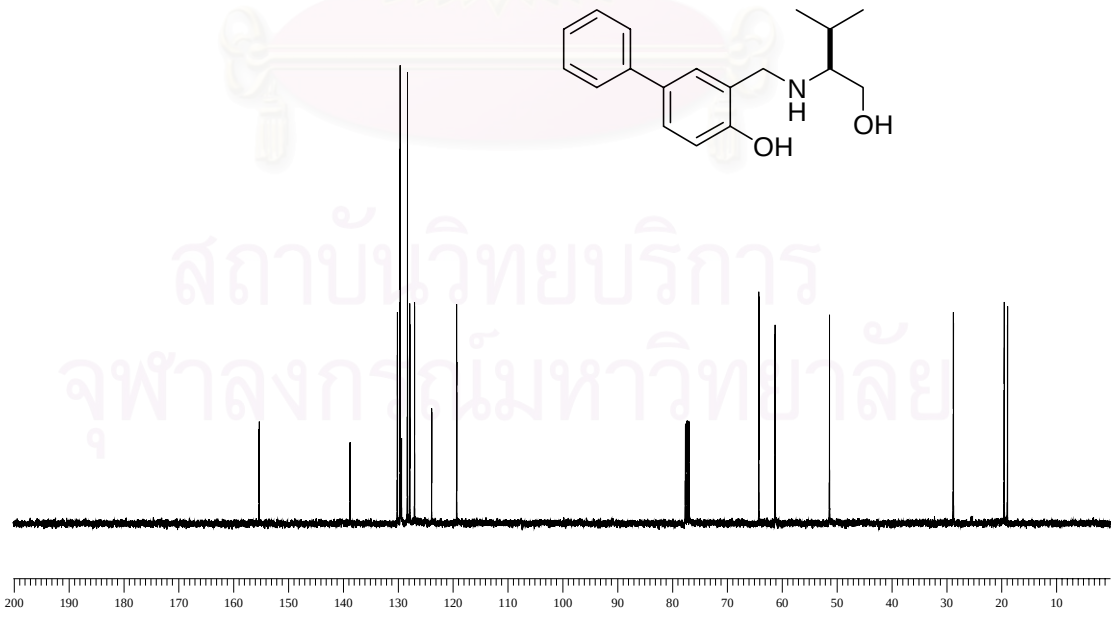


Figure 30 ^{13}C NMR of *N*-(2′-hydroxy-5′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109j))**

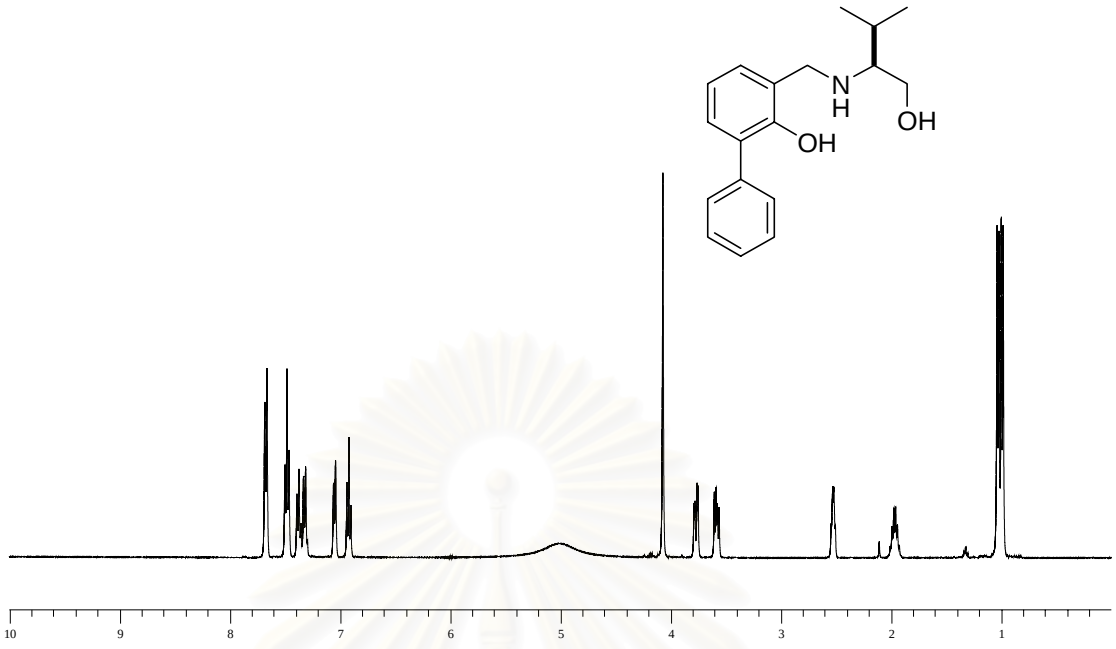


Figure 31 ^{1}H NMR of *N*-(2′-hydroxy-3′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109k)**

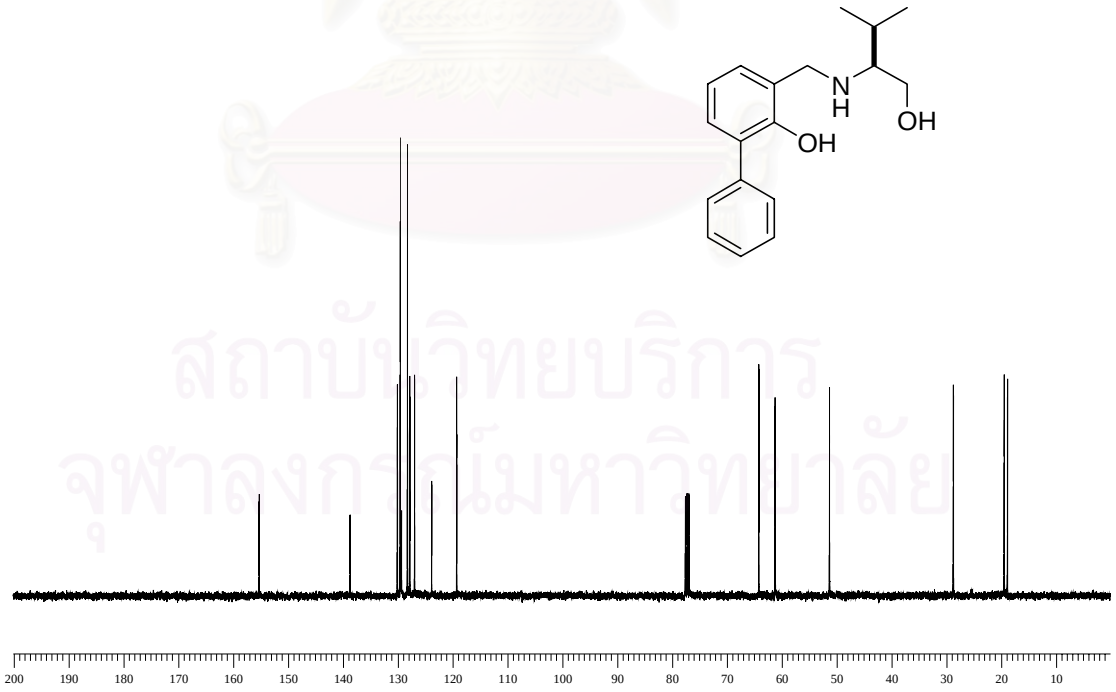


Figure 32 ^{13}C NMR of *N*-(2′-hydroxy-3′-biphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109k)**

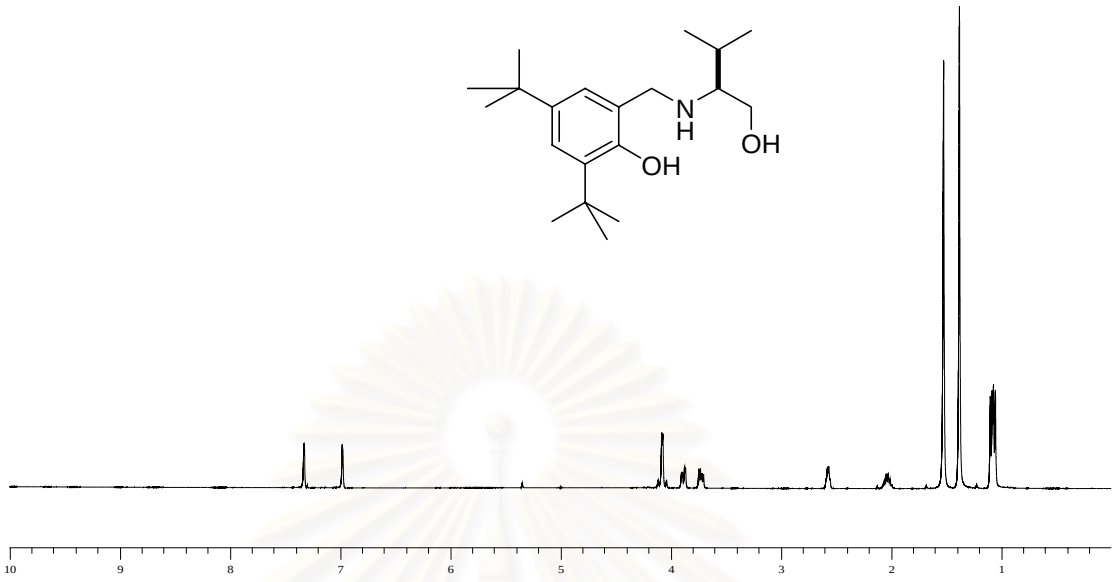


Figure 33 ^{1}H NMR of *N*-(3′,5′-di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109l)**

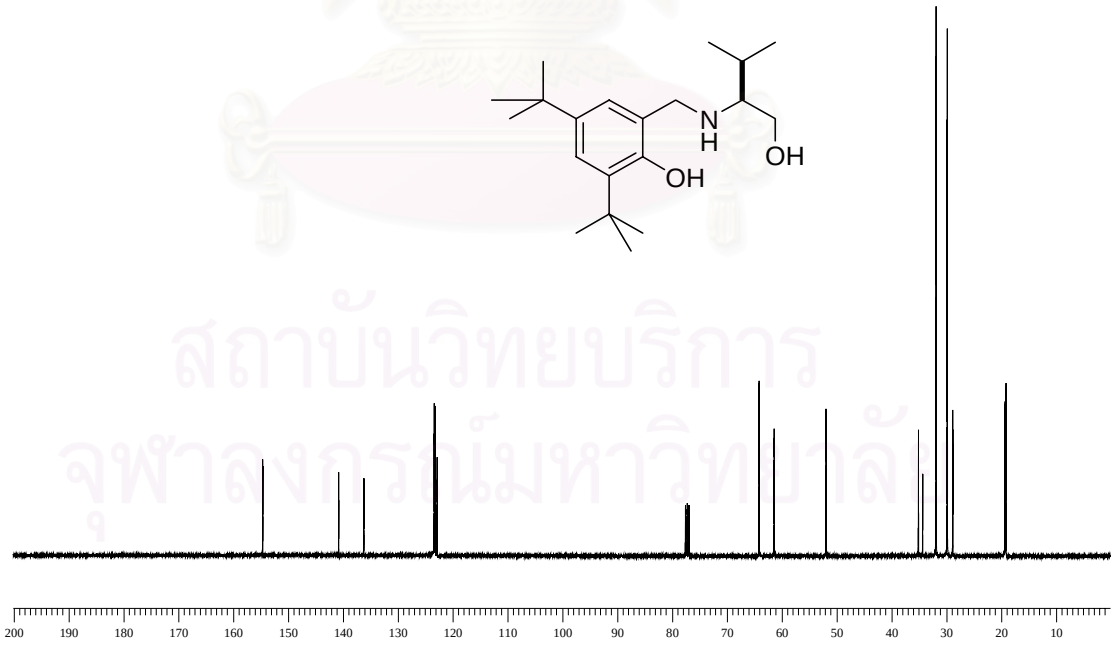


Figure 34 ^{13}C NMR of *N*-(3′,5′-di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109l)**

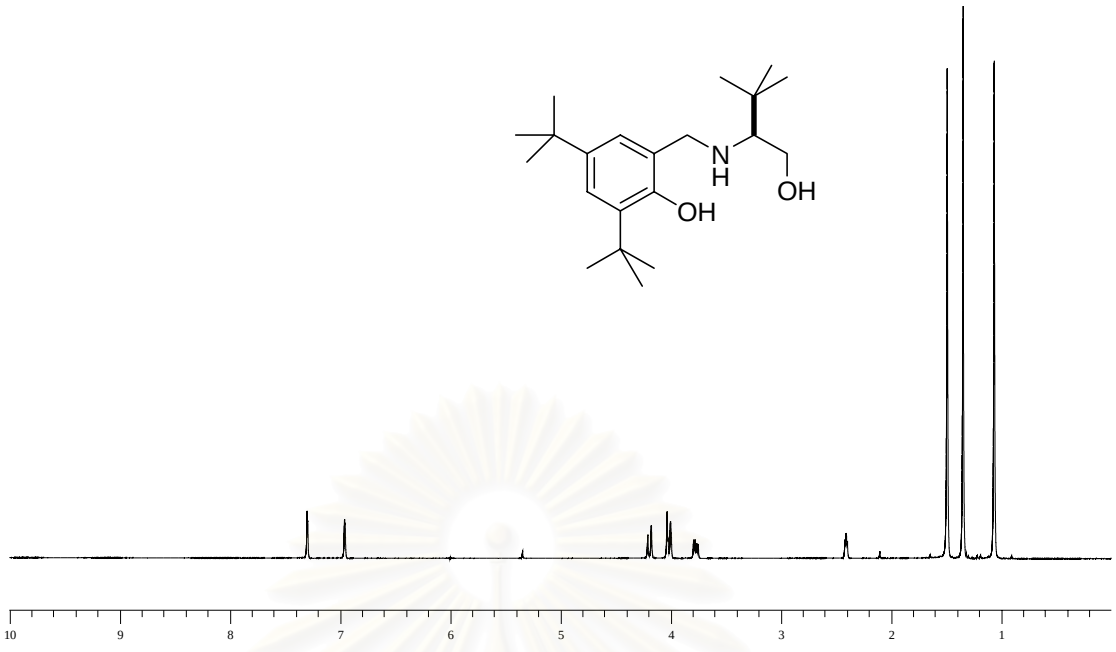


Figure 35 ^{1}H NMR of *N*-(3′, 5′-di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl- butanol **(109m)**

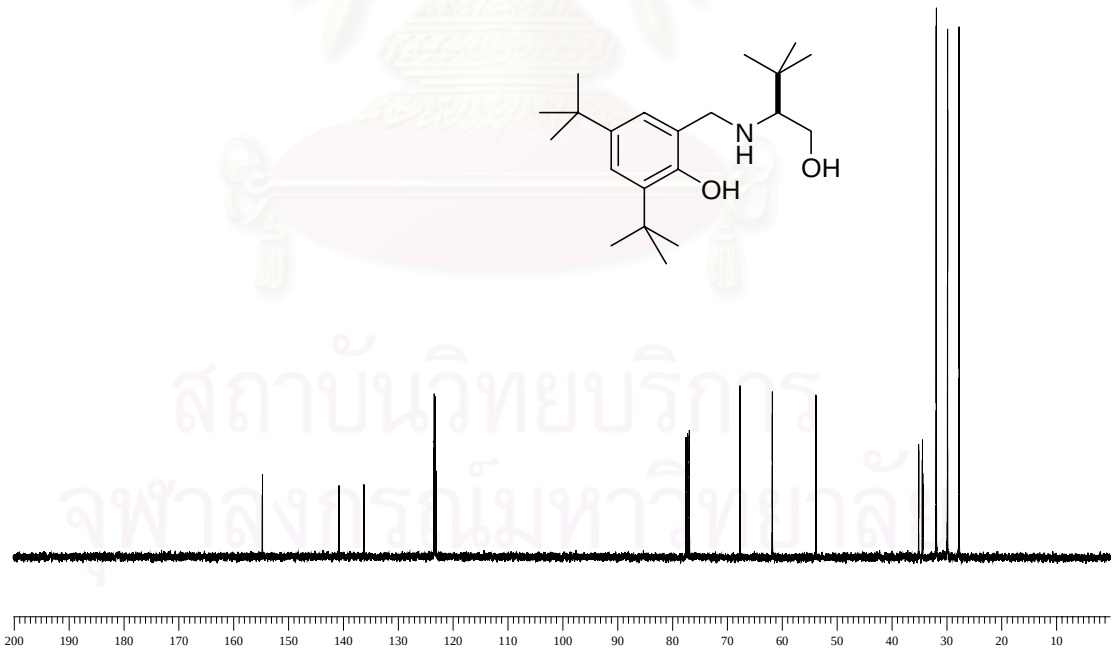


Figure 36 ^{13}C NMR of *N*-(3′, 5′-di-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109m)**

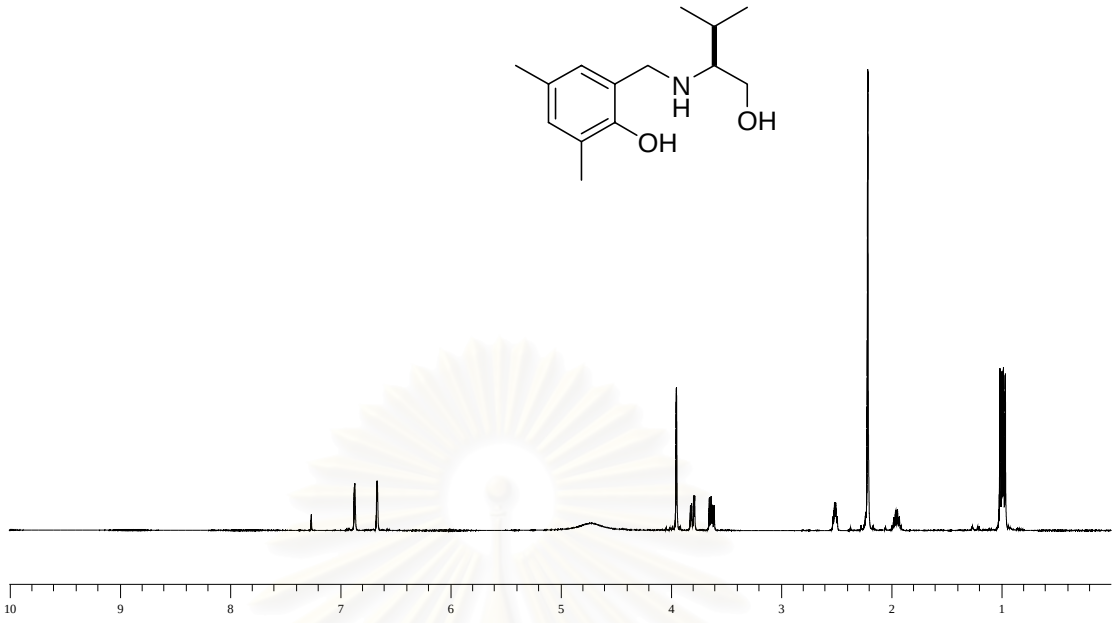


Figure 37 ^{1}H NMR of *N*-(3′,5′-dimethyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109n)**

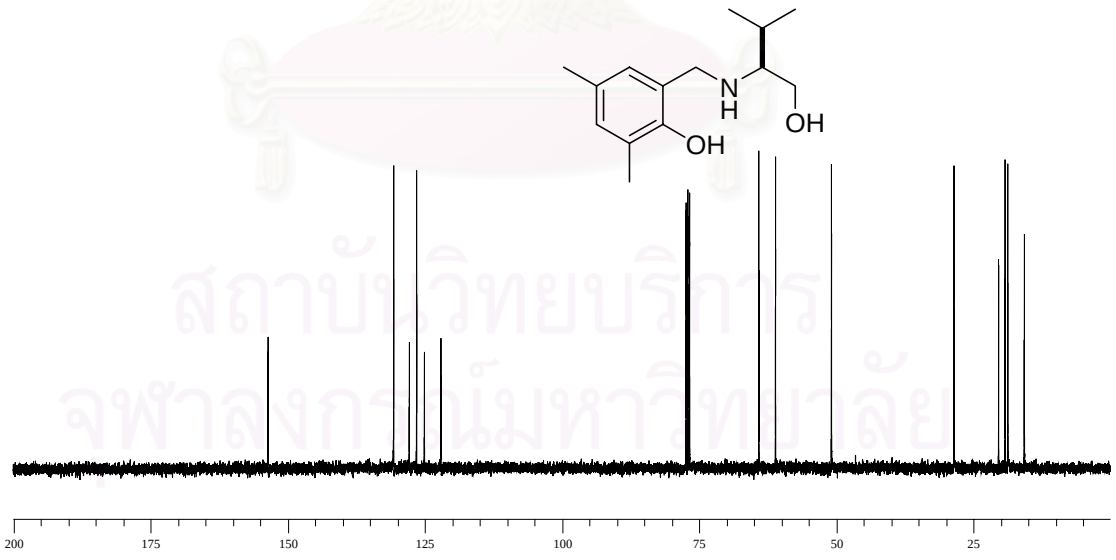


Figure 38 ^{13}C NMR of *N*-(3′,5′-dimethyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109n)**

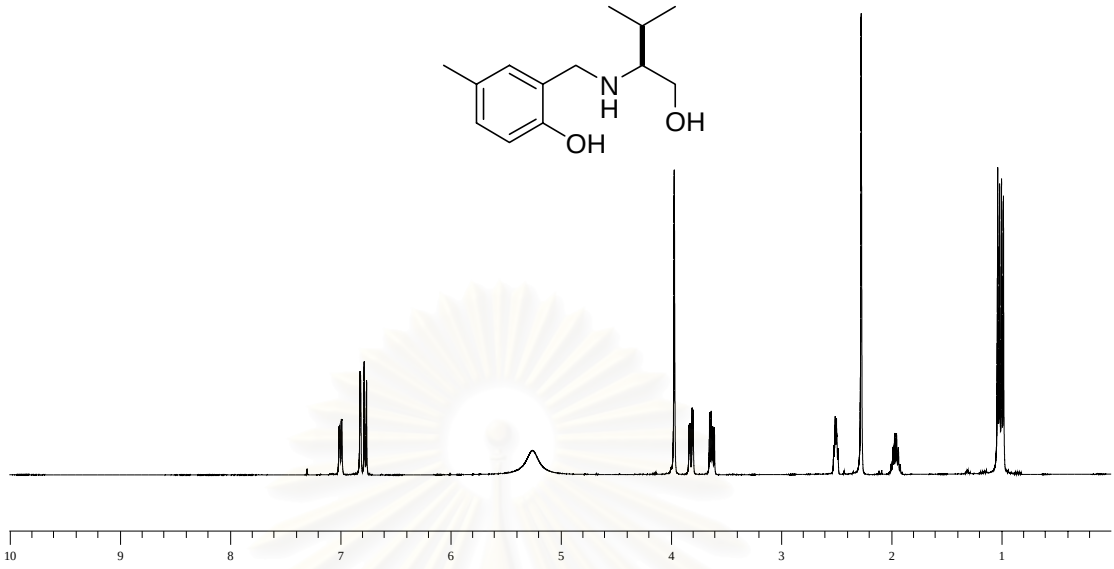


Figure 39 ^{1}H NMR of *N*-(2′-hydroxy-5′-methyl-phenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109o)**

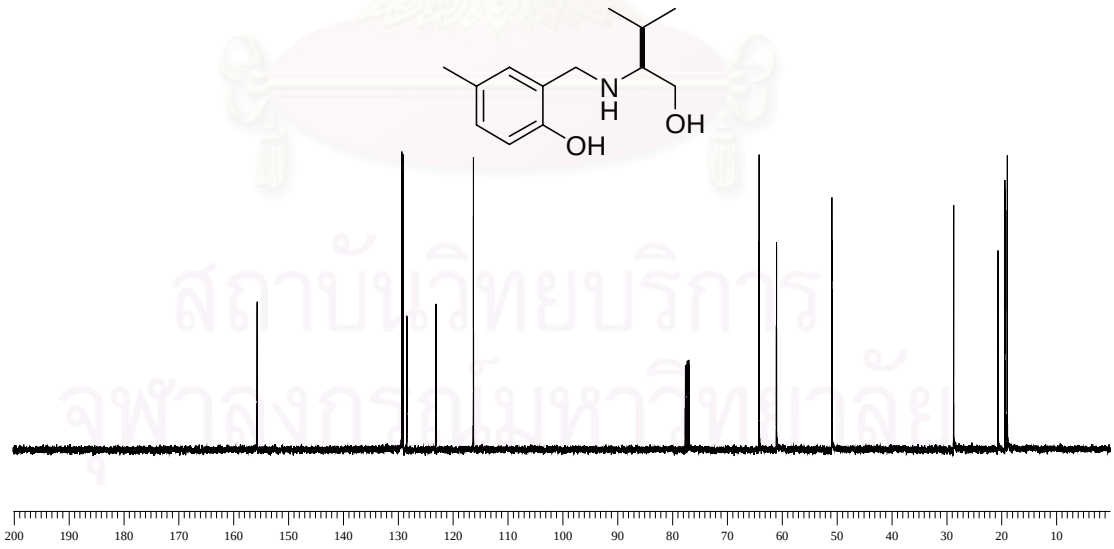


Figure 40 ^{13}C NMR of *N*-(2′-hydroxy-5′-methyl-phenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109o)**

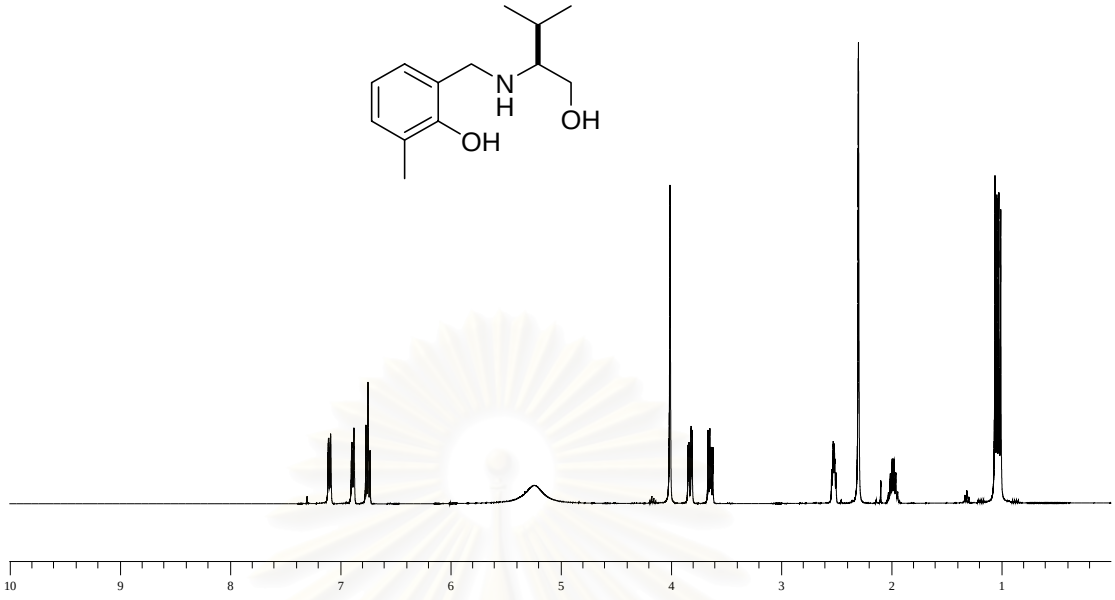


Figure 41 ^{1}H NMR of *N*-(2′-hydroxy-3′-methyl-phenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109p)**

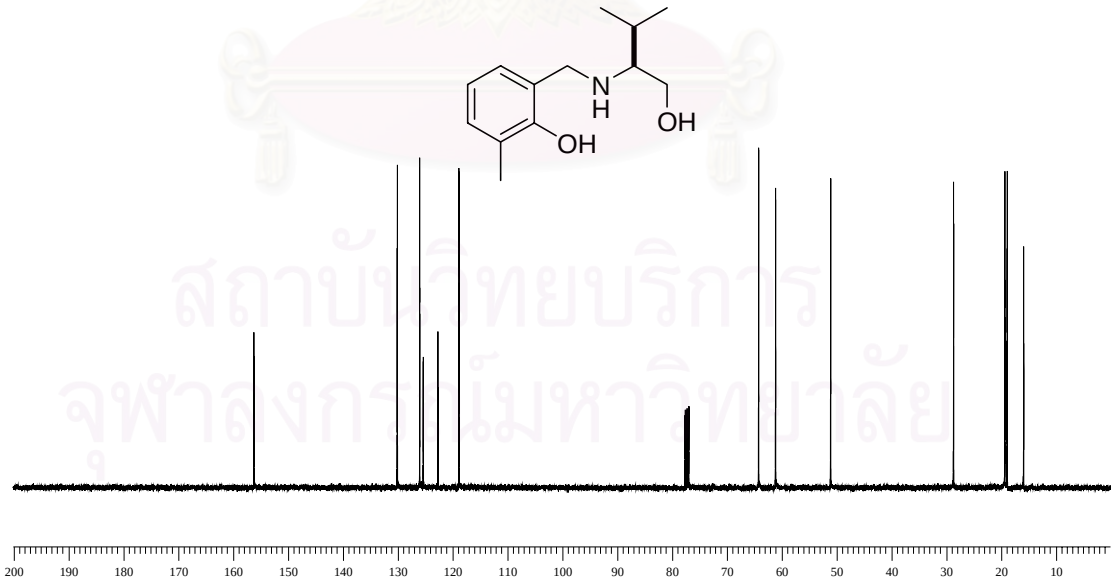


Figure 42 ^{13}C NMR of *N*-(2′-hydroxy-3′-methyl-phenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109p)**

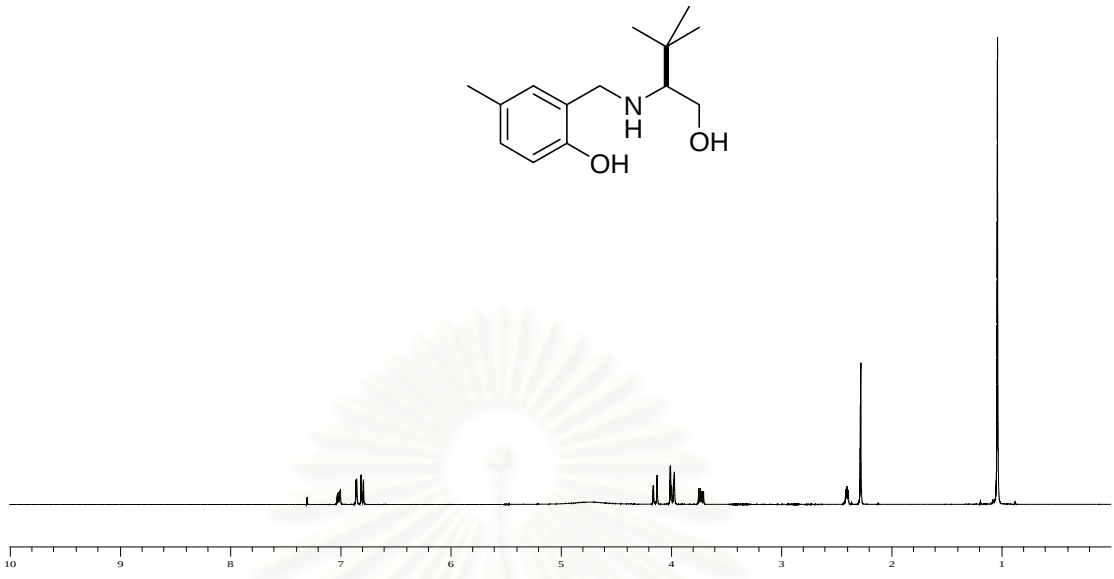


Figure 43 ^{1}H NMR of *N*-(2′-hydroxy-5′-methyl-phenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109q)**

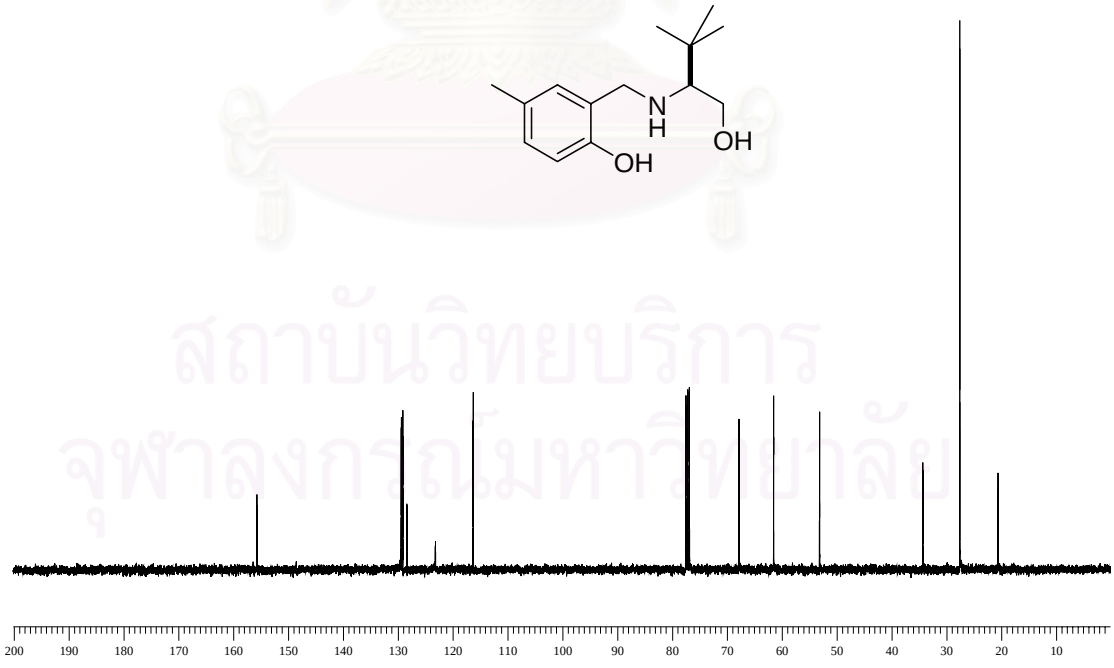


Figure 44 ^{13}C NMR of *N*-(2′-hydroxy-5′-methyl-phenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109q)**

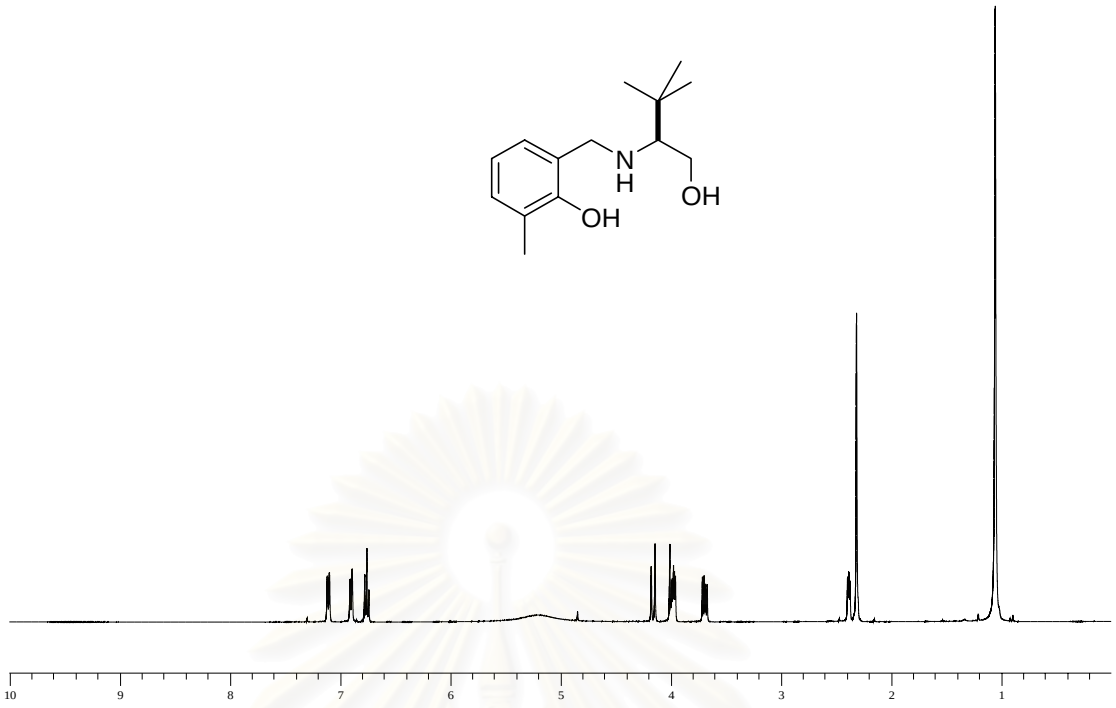


Figure 45 ^{1}H NMR of *N*-(2′-hydroxy-3′-methyl-phenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109r)**

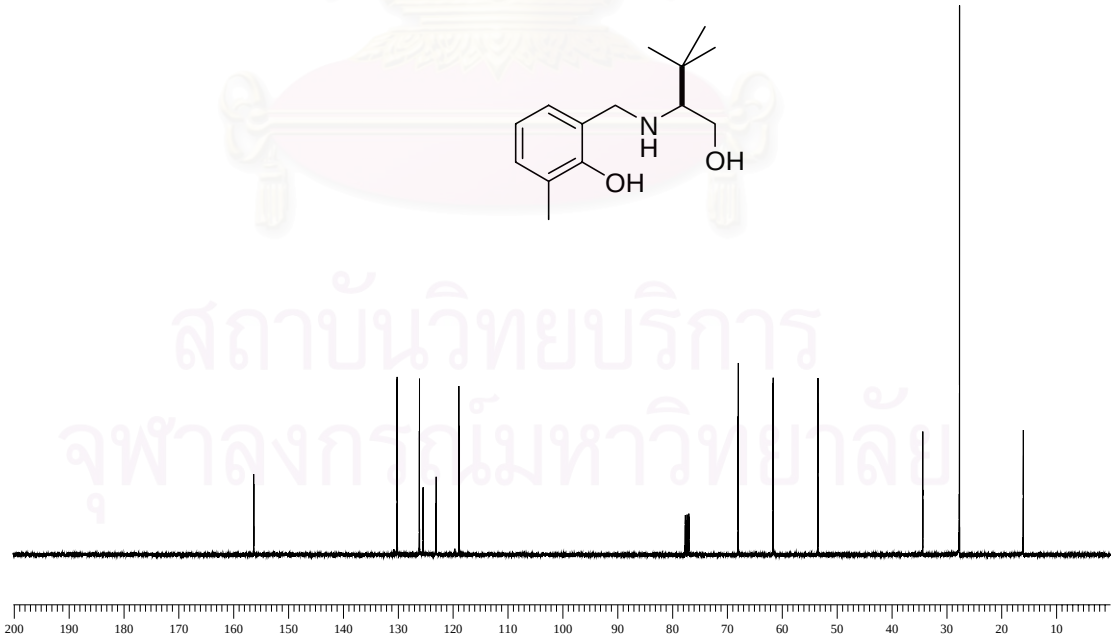


Figure 46 ^{13}C NMR of *N*-(2′-hydroxy-3′-methyl-phenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109r)**

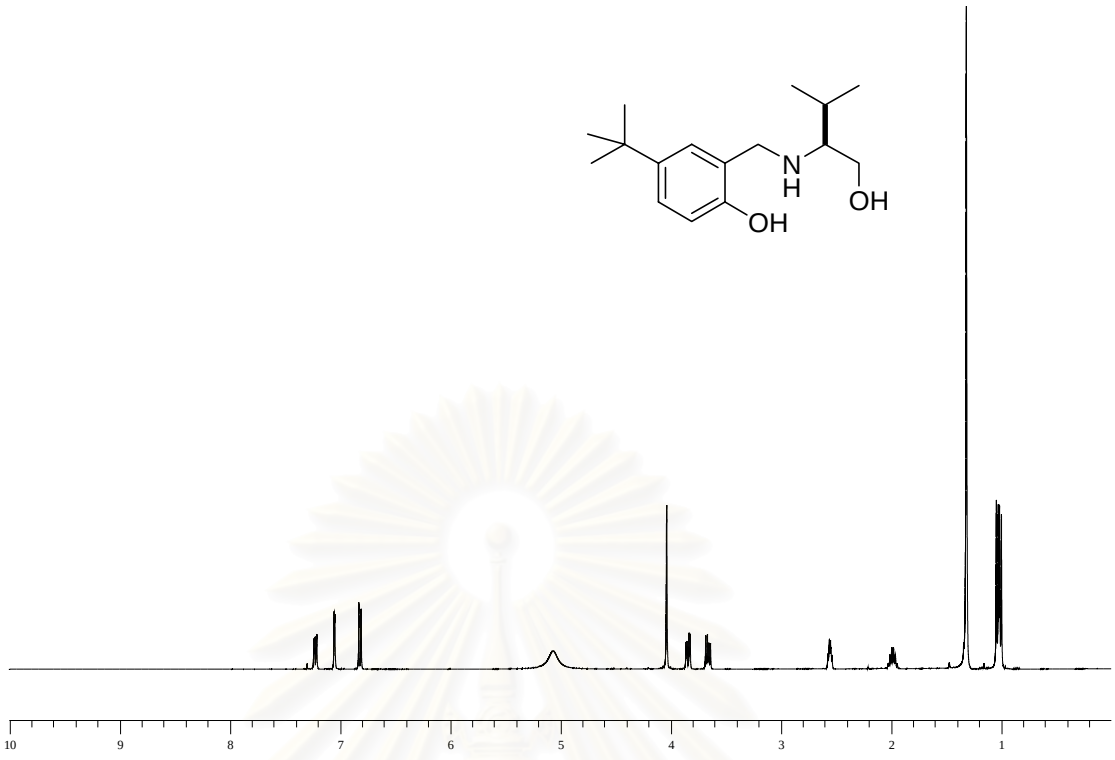


Figure 47 ^{1}H NMR of *N*-(5′-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-buta**nol (109s)**

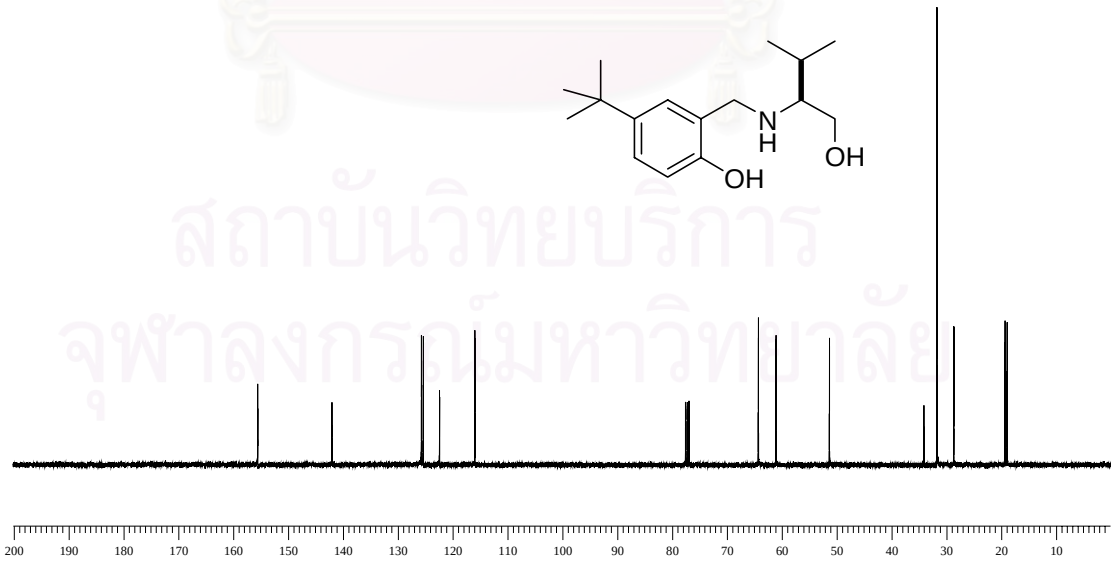


Figure 48 ^{13}C NMR of *N*-(5′-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109s)**

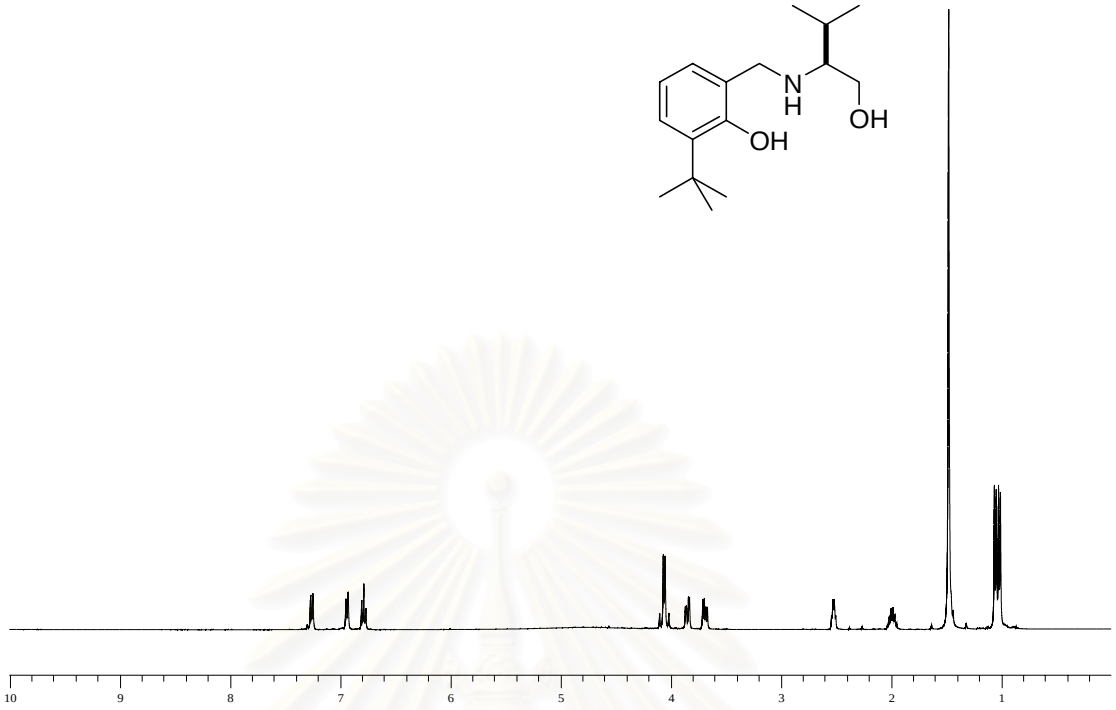


Figure 49 ^{1}H NMR of *N*-(3′-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109t)**

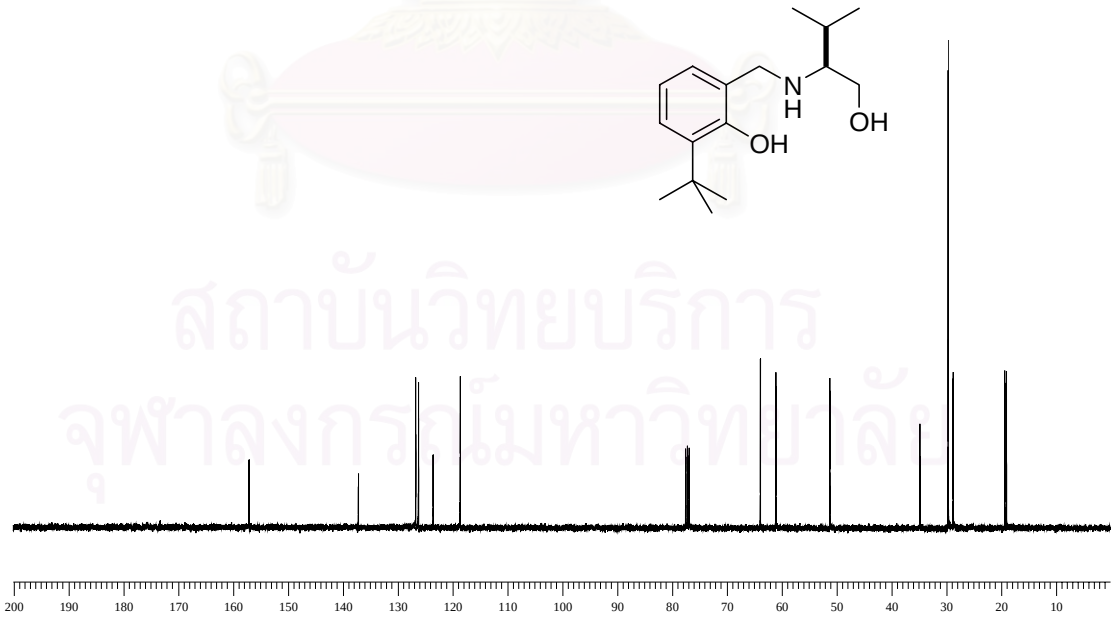


Figure 50 ^{13}C NMR of *N*-(3′-*tert*-butyl-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109t)**

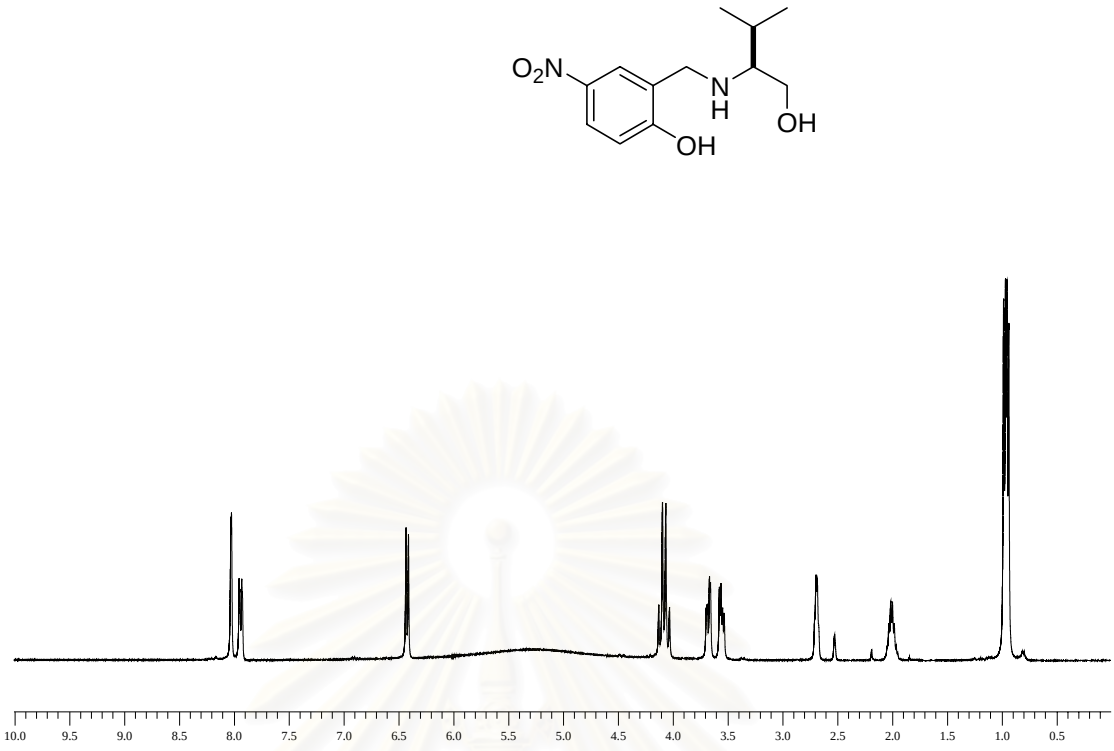


Figure 51 ^{1}H NMR of *N*-(2′-hydroxy-5′-nitrophenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109u)**

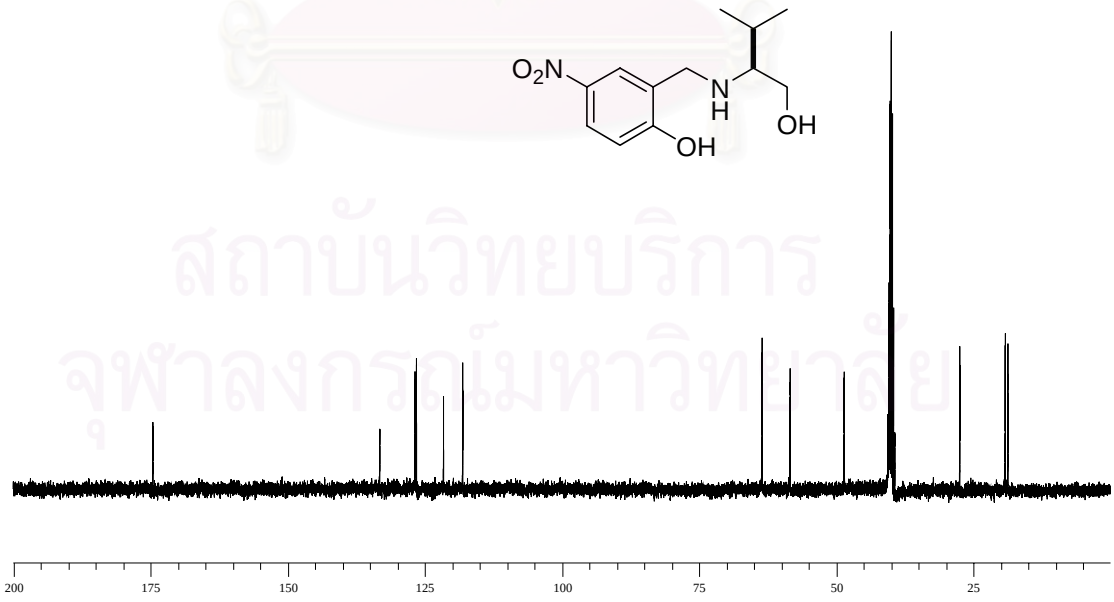


Figure 52 ^{13}C NMR of *N*-(2′-hydroxy-5′-nitrophenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109u)**

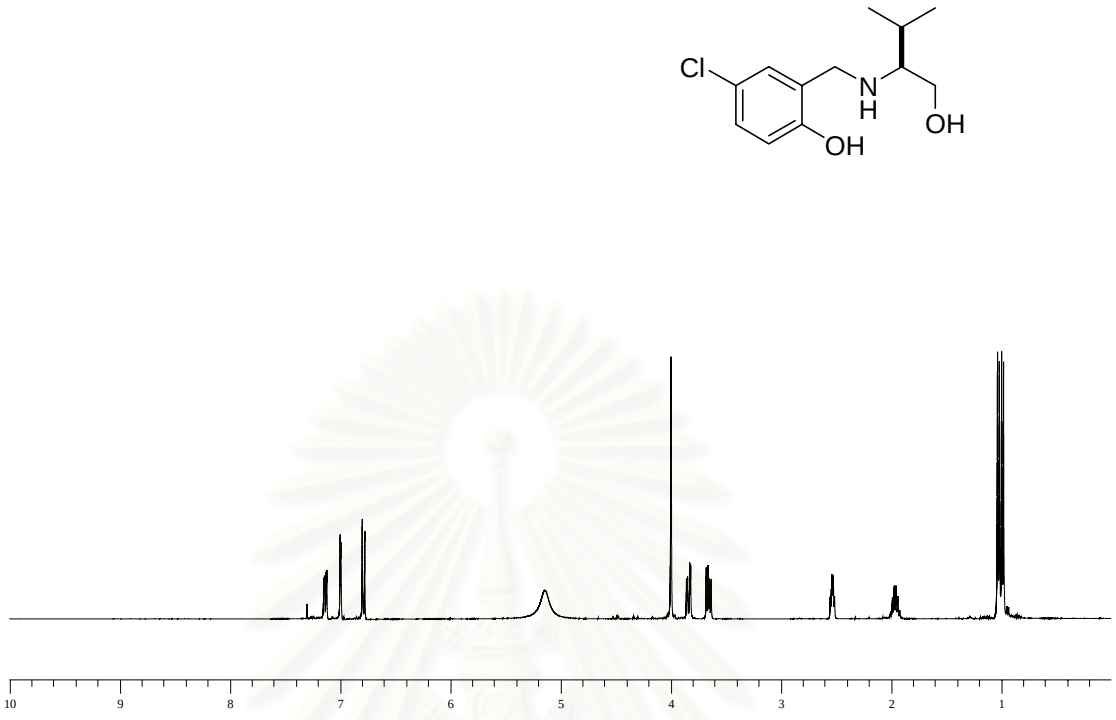


Figure 53 ^{1}H NMR of *N*-(5′-chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109v)**

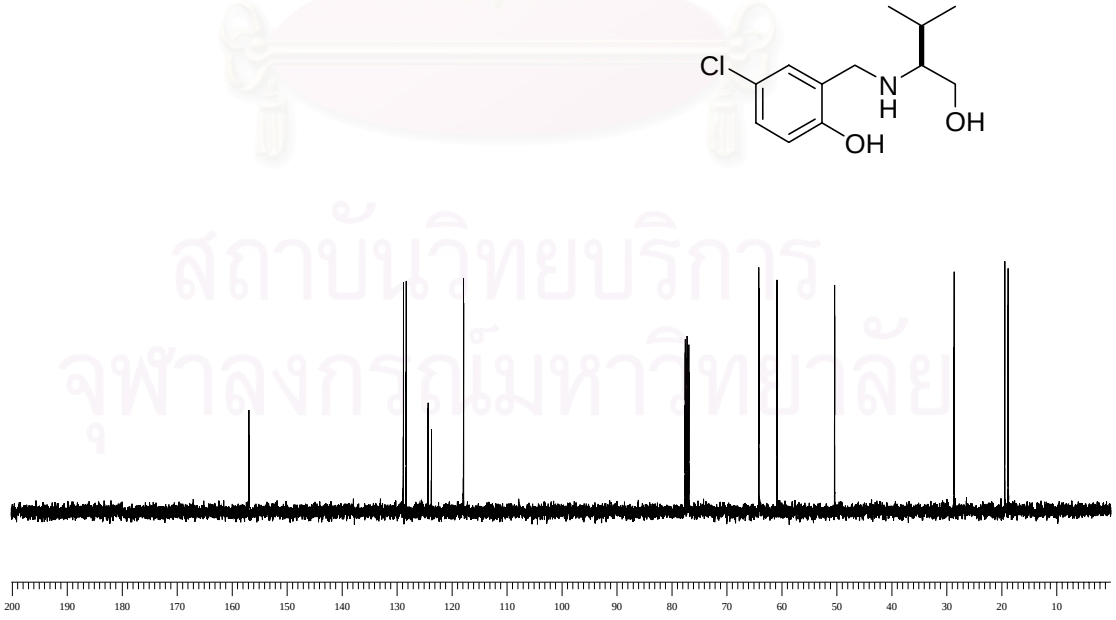


Figure 54 ^{13}C NMR of *N*-(5′-chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109v)**

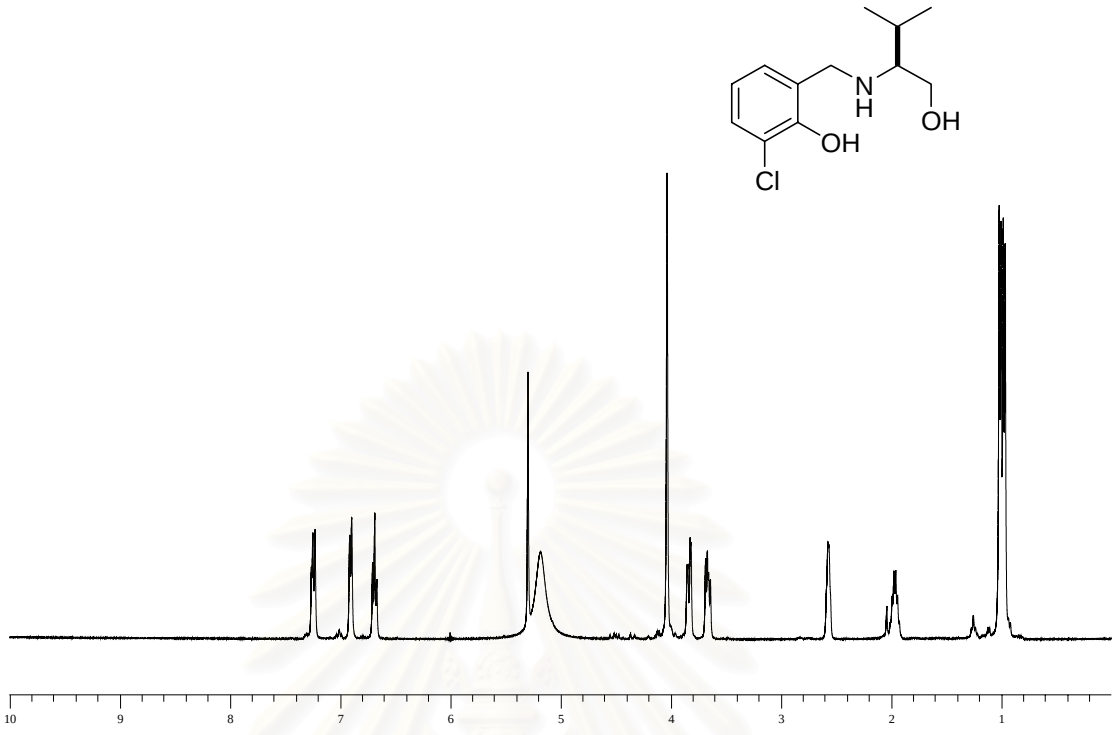


Figure 55 ^{1}H NMR of *N*-(3′-chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109w)**

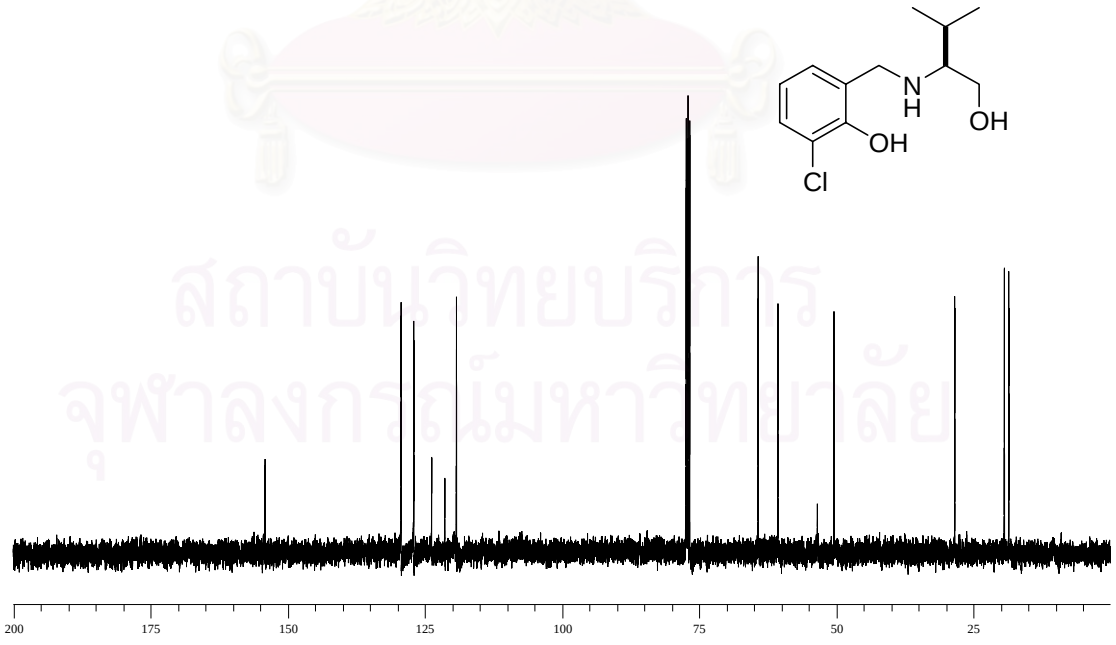


Figure 56 ^{13}C NMR of *N*-(3′-chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109w)**

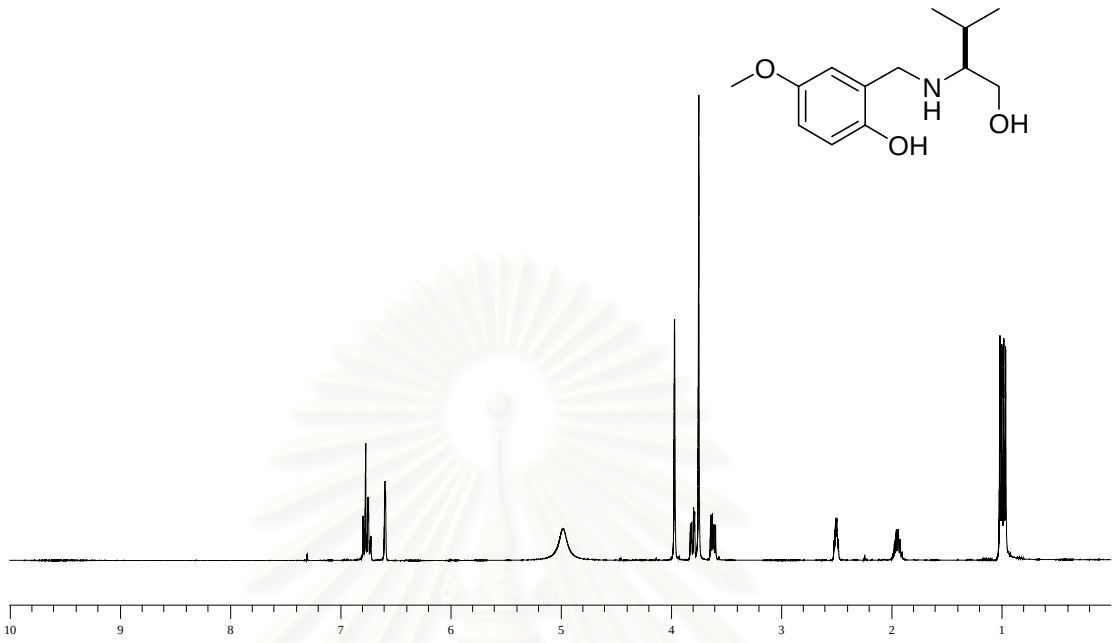


Figure 57 ^{1}H NMR of *N*-(2′-hydroxy-5′-methoxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109x)**

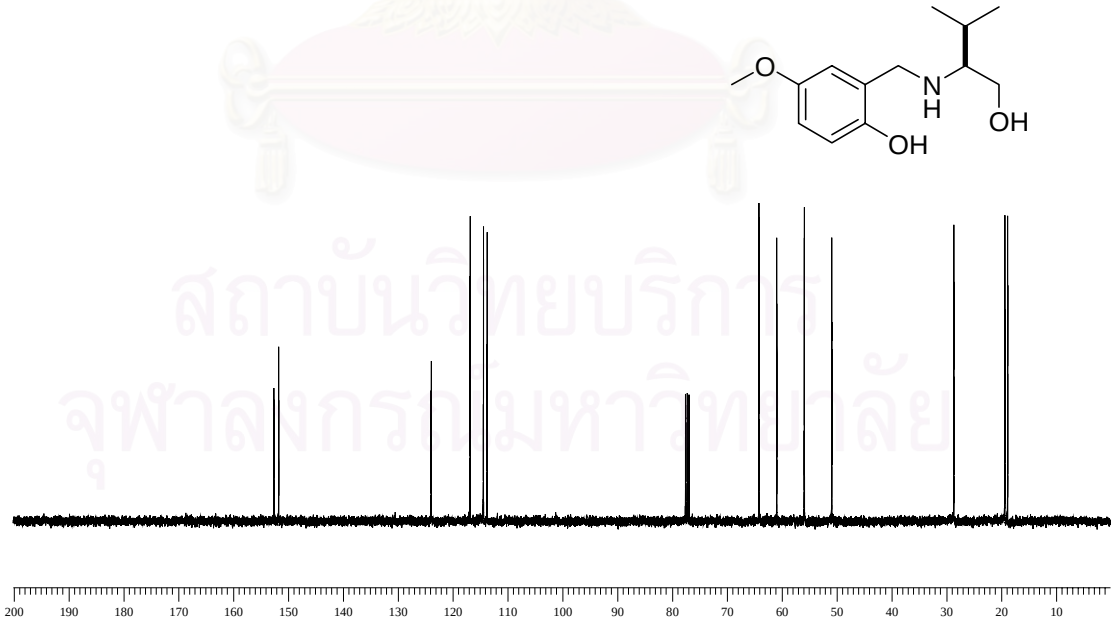


Figure 58 ^{13}C NMR of *N*-(2′-hydroxy-5′-methoxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109x)**

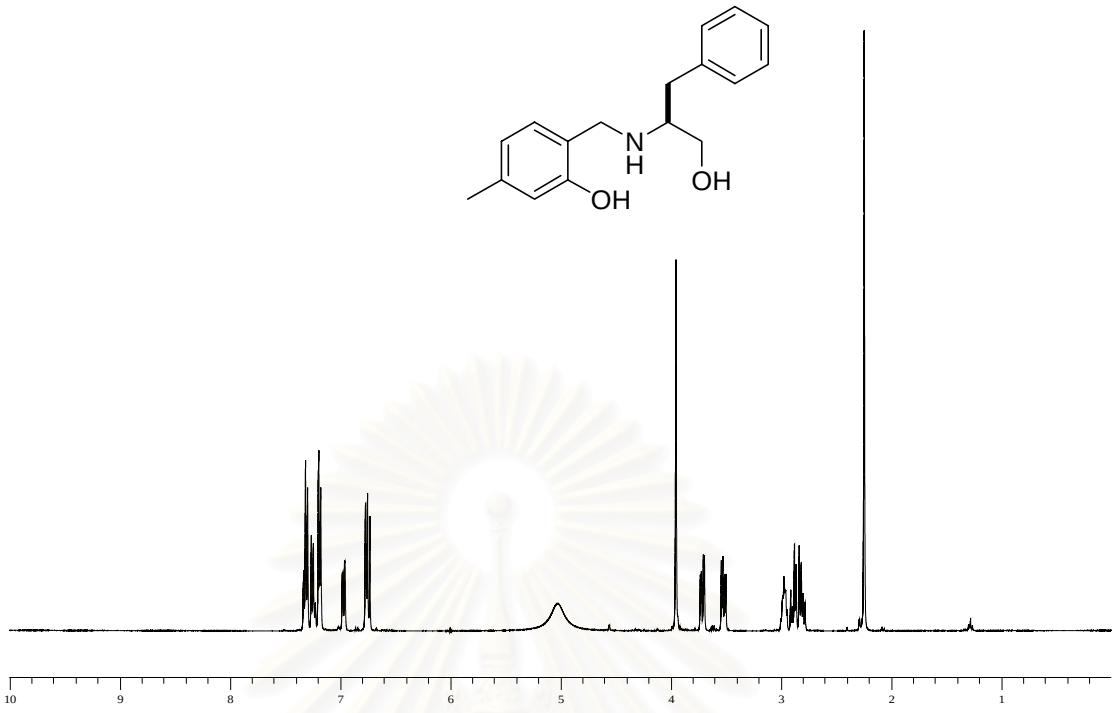


Figure 59 ^{1}H NMR of *N*-(2′-hydroxy-4′-methylphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol **(109y)**

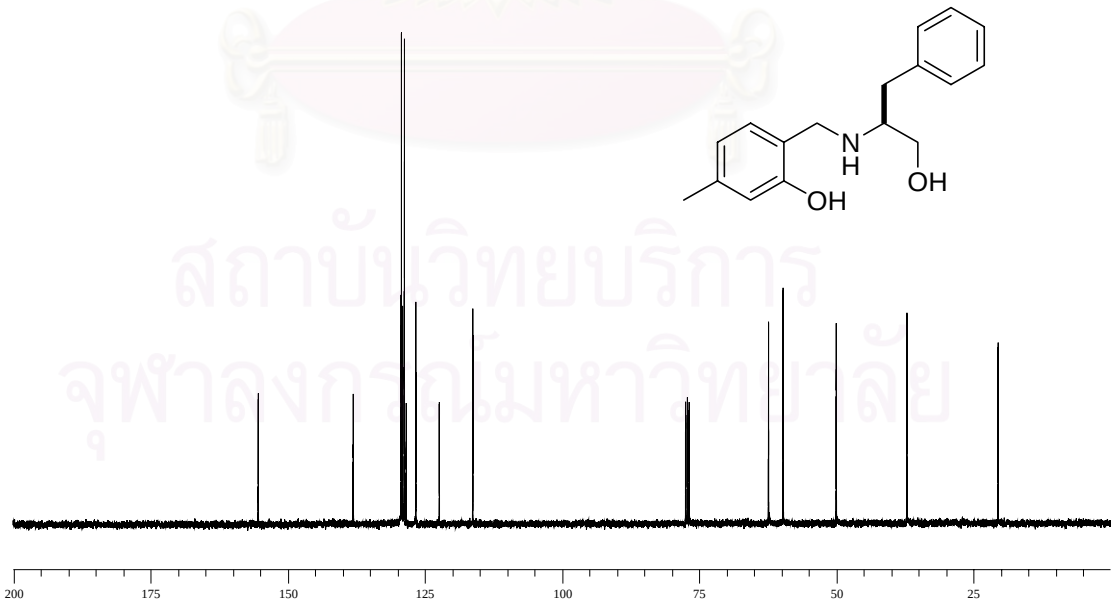


Figure 60 ^{13}C NMR of *N*-(2′-hydroxy-4′-methylphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol **(109y)**

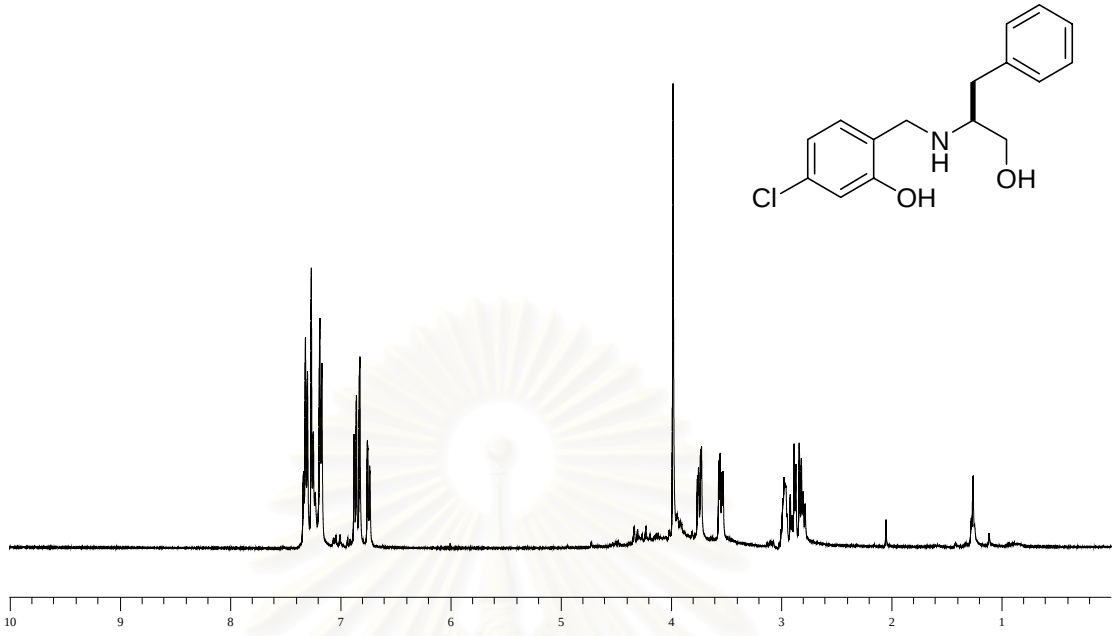


Figure 61 ^{1}H NMR of *N*-(4′-chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol **(109z)**

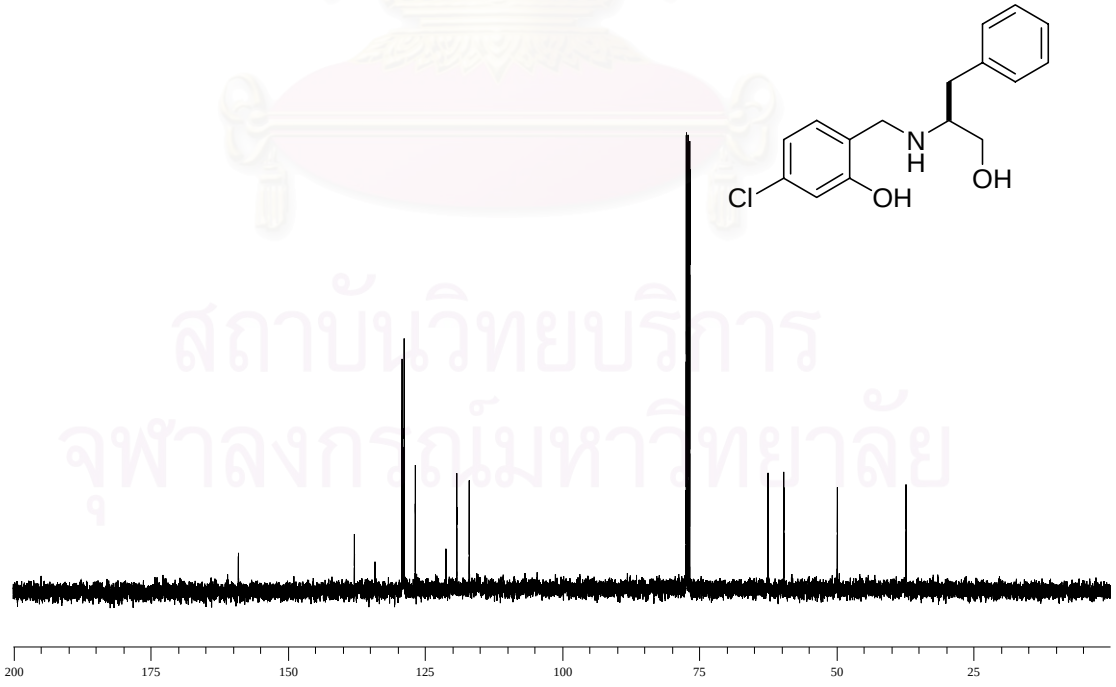


Figure 62 ^{13}C NMR of *N*-(4′-chloro-2′-hydroxyphenyl)methyl-(*S*)-2-amino-3-phenyl-propanol **(109z)**

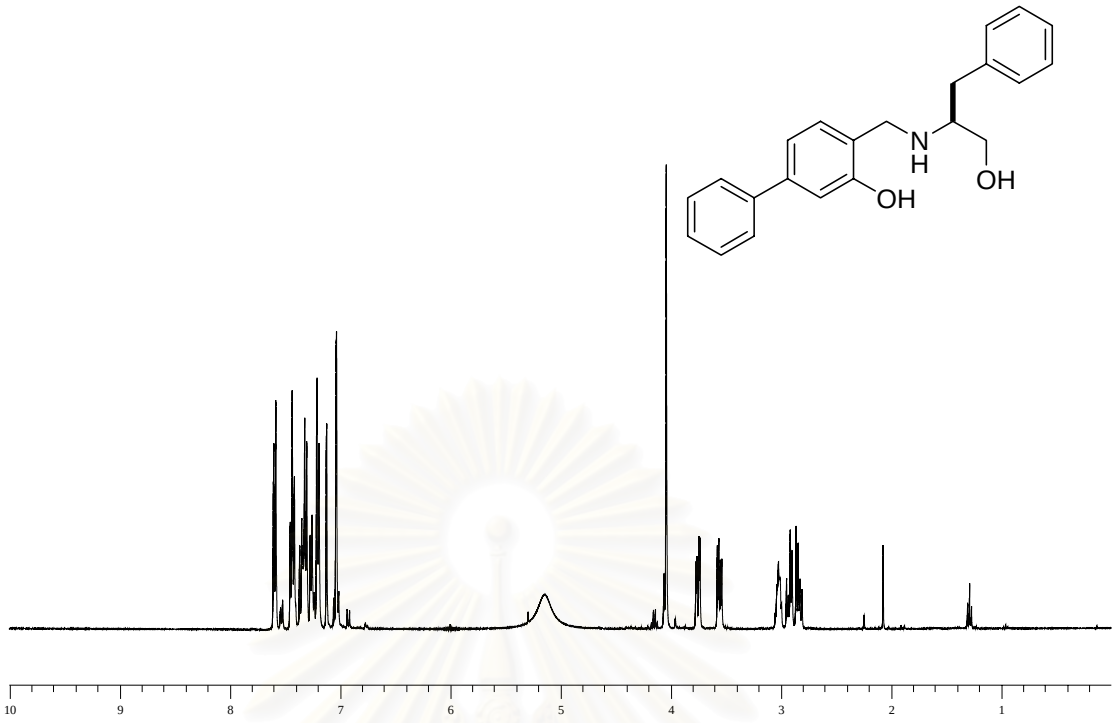


Figure 63 ^{1}H NMR of *N*-(2′-hydroxy-4′-phenyl-phenyl)methyl-(*S*)-2-amino-3-phenyl-propanol **(109aa)**

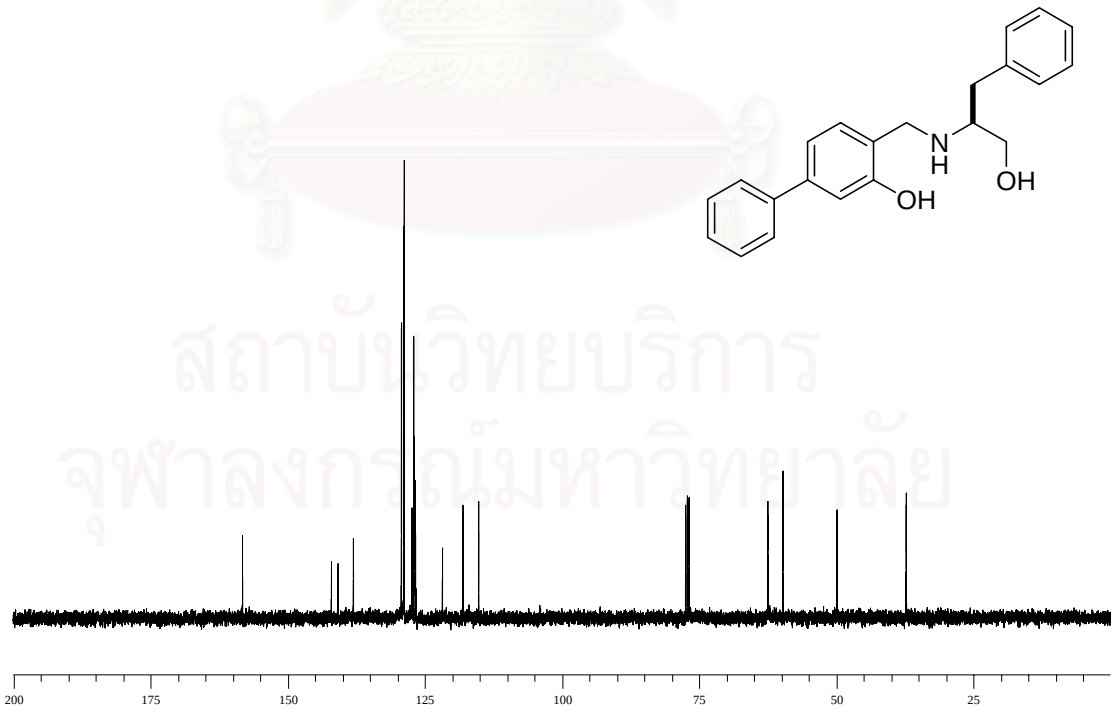


Figure 64 ^{13}C NMR of *N*-(2′-hydroxy-4′-phenyl-phenyl)methyl-(*S*)-2-amino-3-phenyl-propanol **(109aa)**

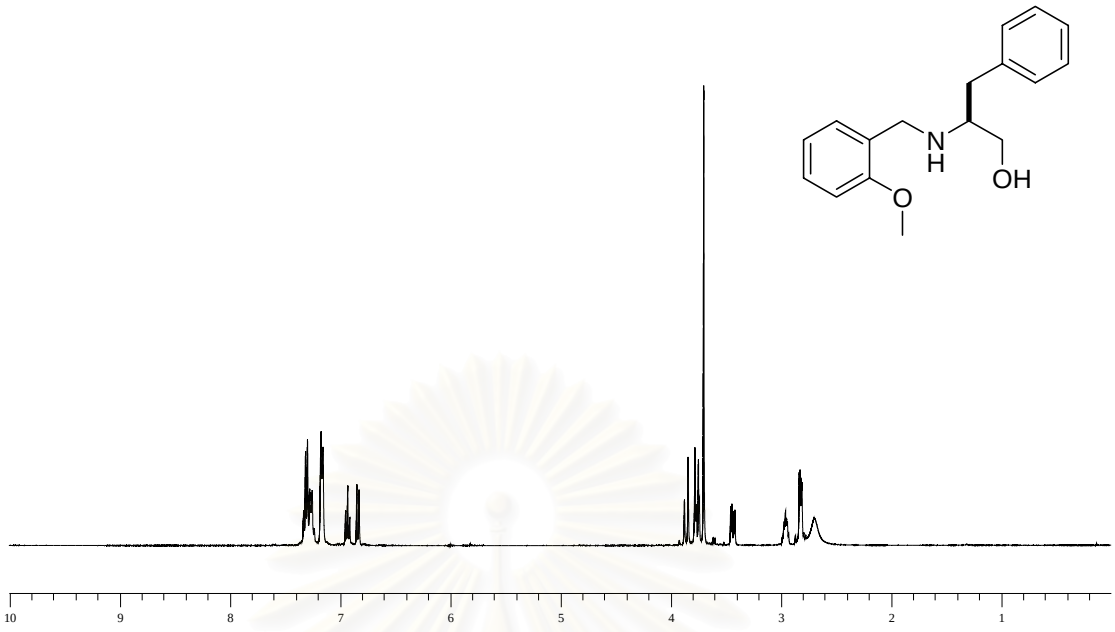


Figure 65 ^{1}H NMR of *N*-(2′-methoxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109ab)**

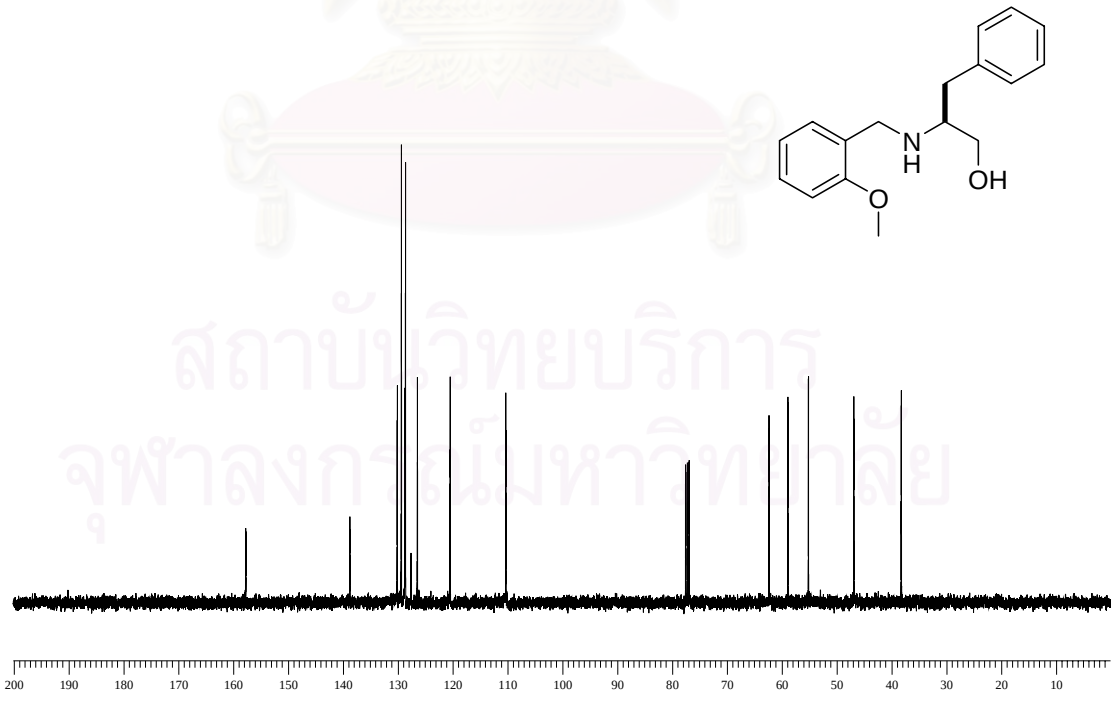


Figure 66 ^{13}C NMR of *N*-(2′-methoxyphenyl)methyl-(*S*)-2-amino-3-methyl-butanol **(109ab)**

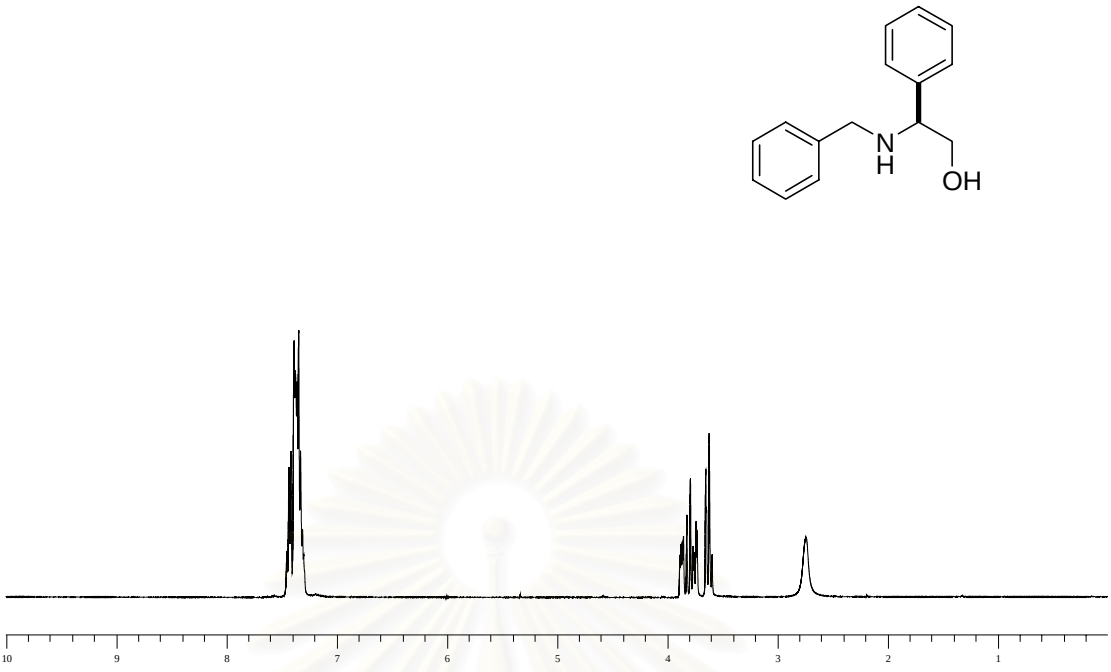


Figure 67 ^{1}H NMR of *N*-benzyl-(*S*)-2-amino-2-phenyl-ethanol **(109ac)**

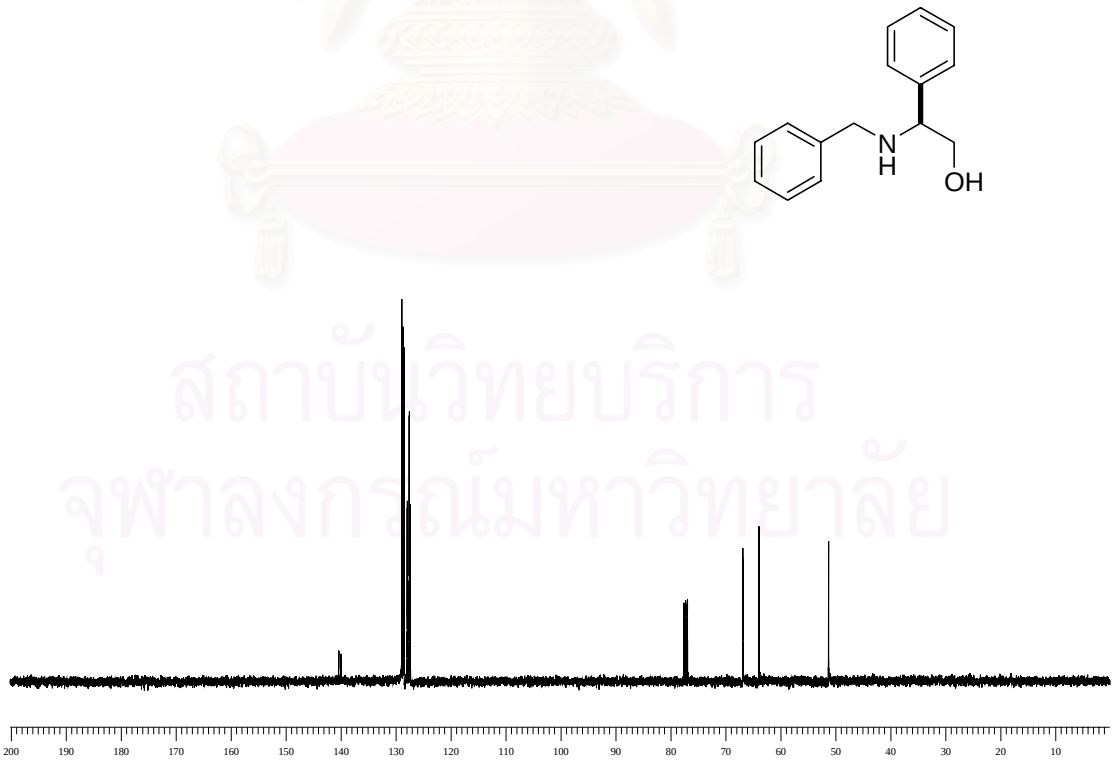


Figure 68 ^{13}C NMR of *N*-benzyl-(*S*)-2-amino-2-phenyl-ethanol **(109ac)**

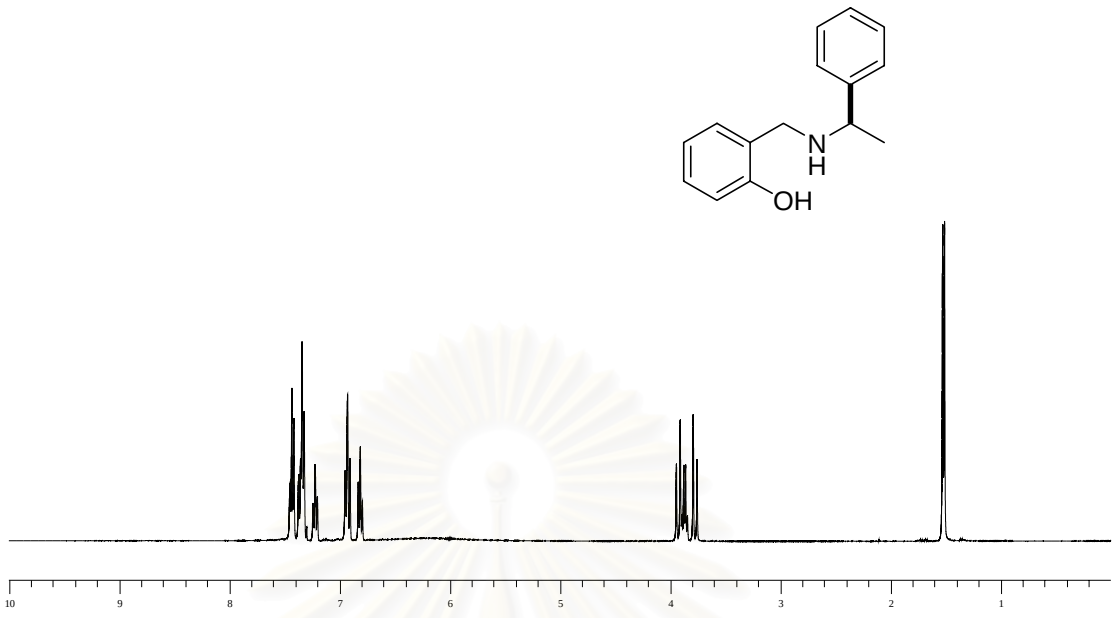


Figure 69 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109ad)**

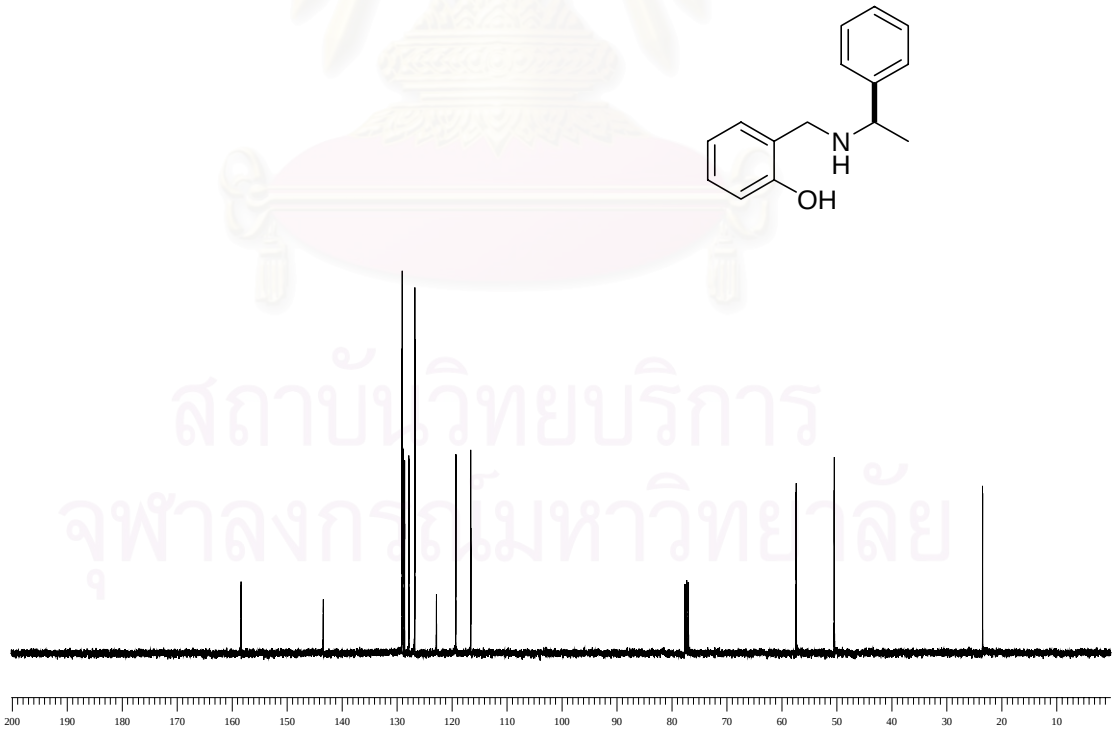


Figure 70 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(109ad)**

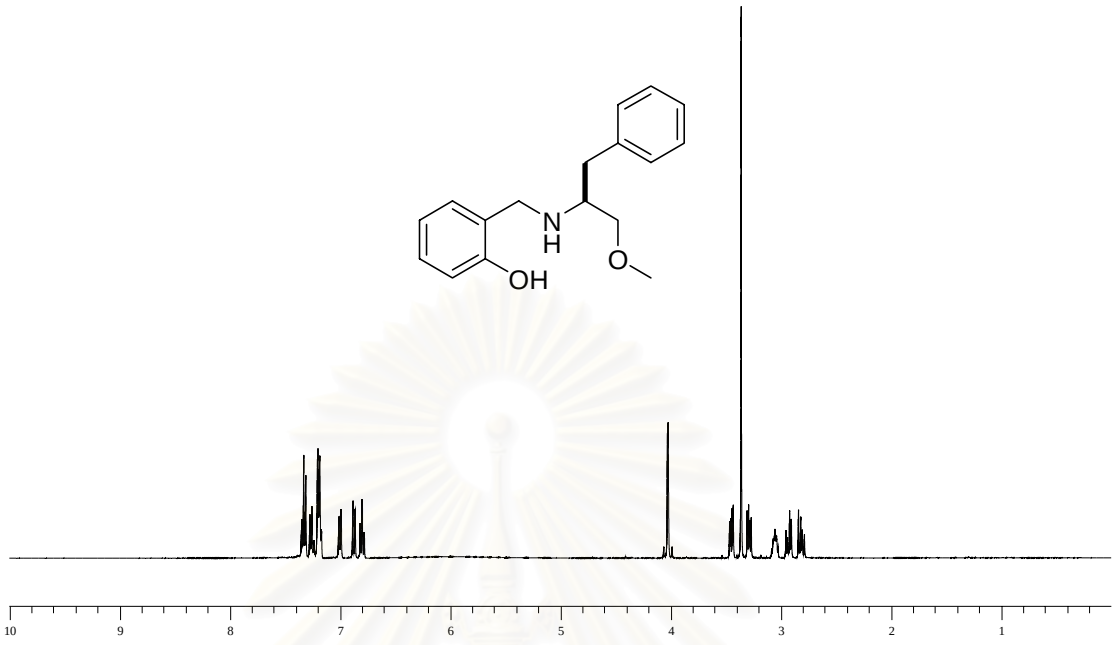


Figure 71 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane **(109ae)**

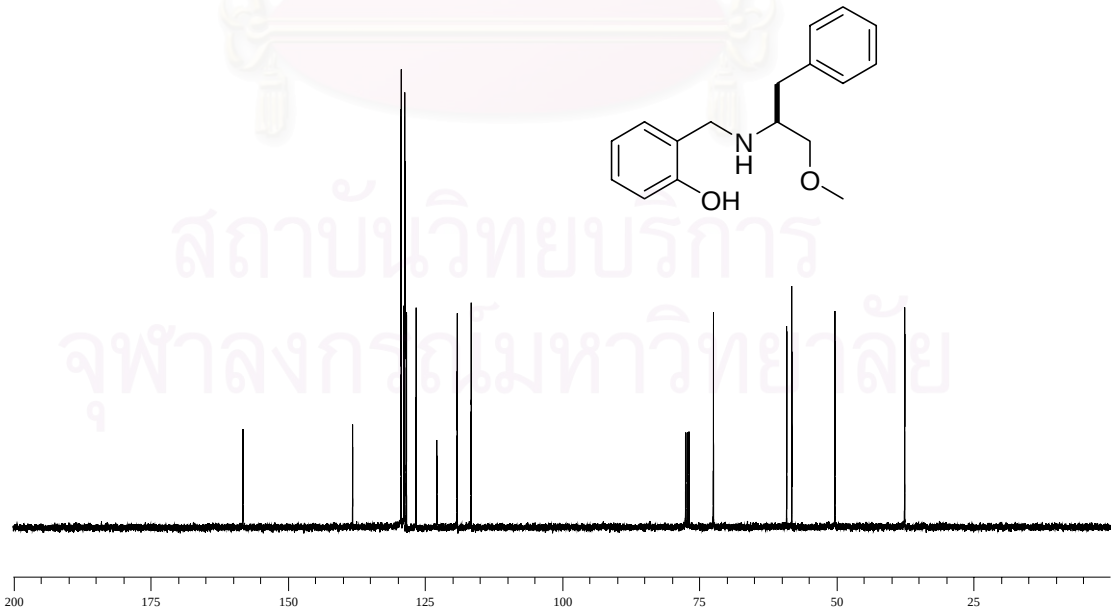


Figure 72 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane **(109ae)**

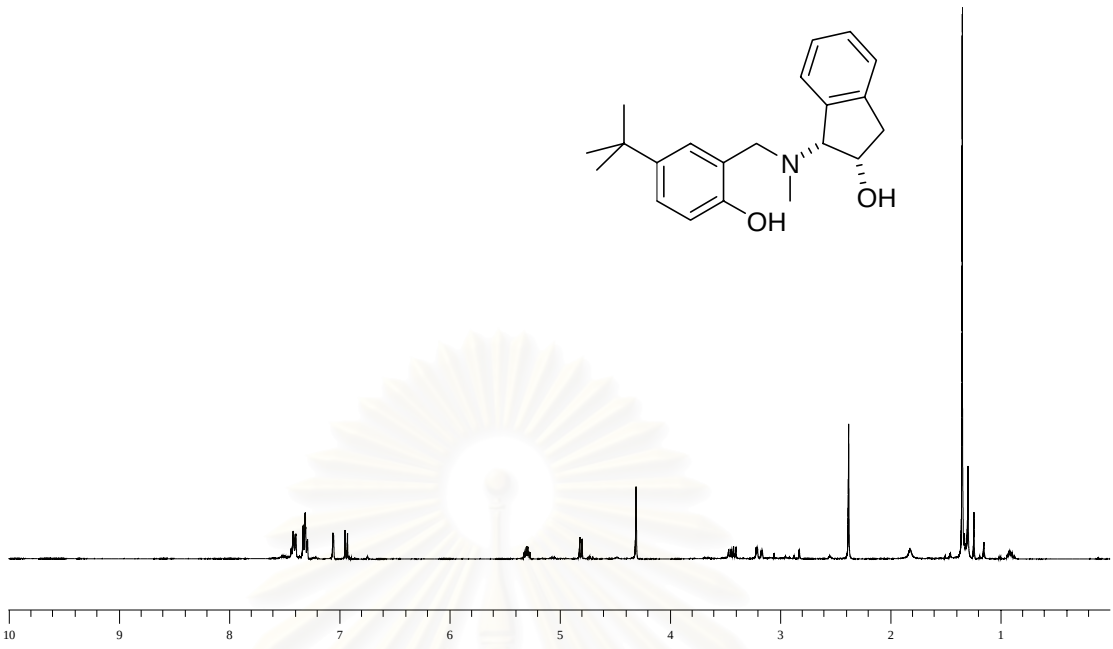


Figure 73 ^{1}H NMR of *N*-(5′-*tert*-butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(1*R*,2*S*)-indan-2ol **(115a)**

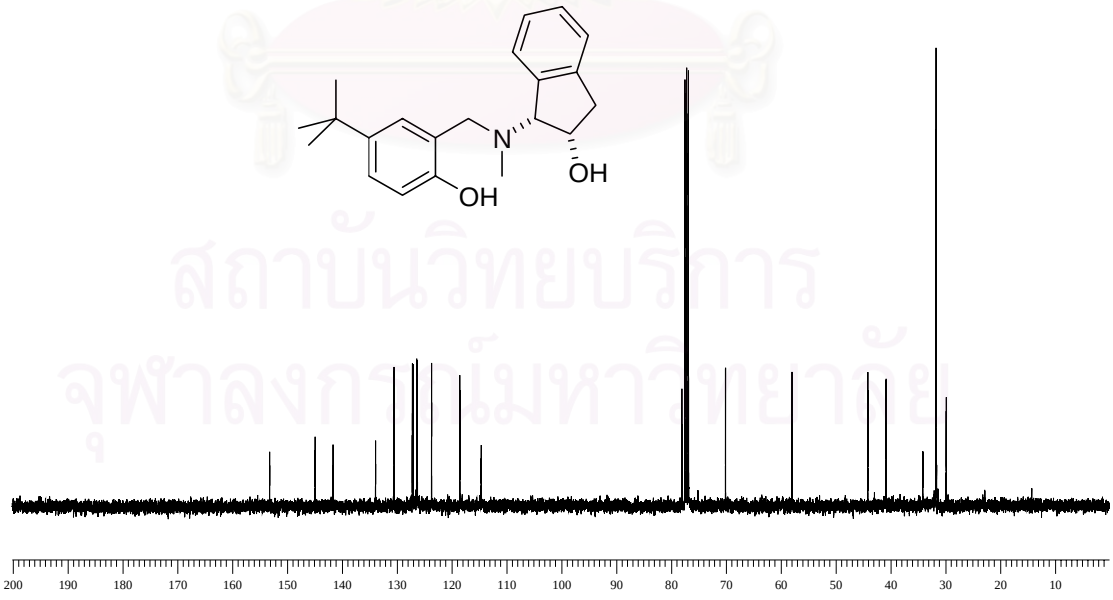


Figure 74 ^{13}C NMR of *N*-(2′-Hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane **(109ae)**

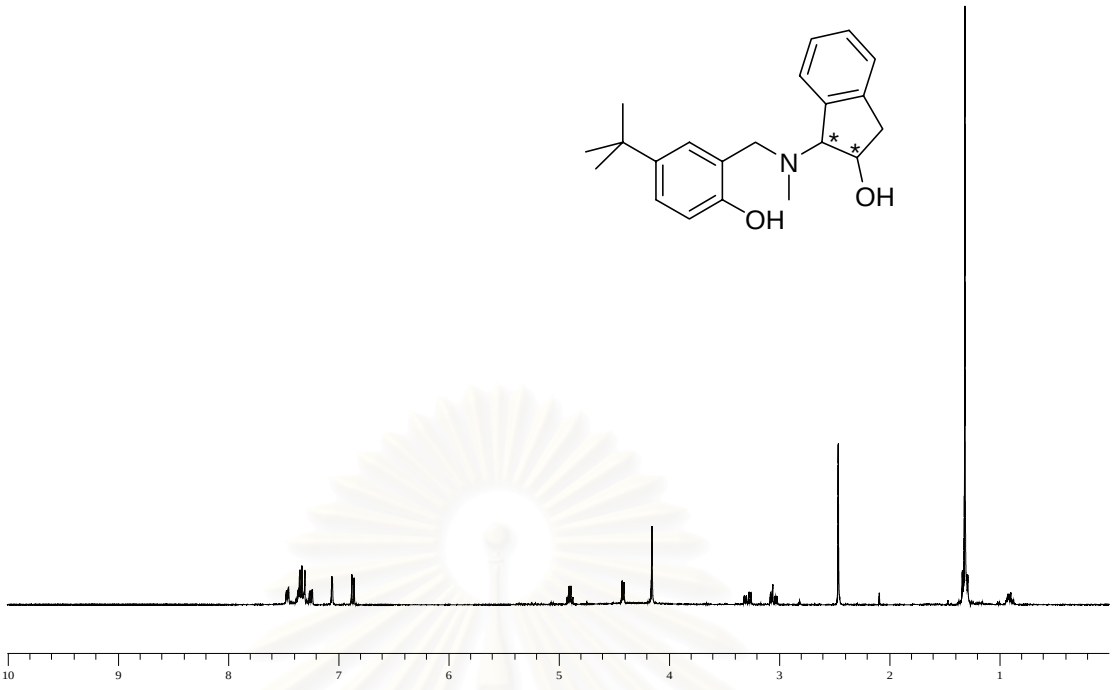


Figure 75 ^{1}H NMR of diastereomer of *N*-(5′-*tert*-butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(1*R*,2*S*)-indan-2ol **(115a)**

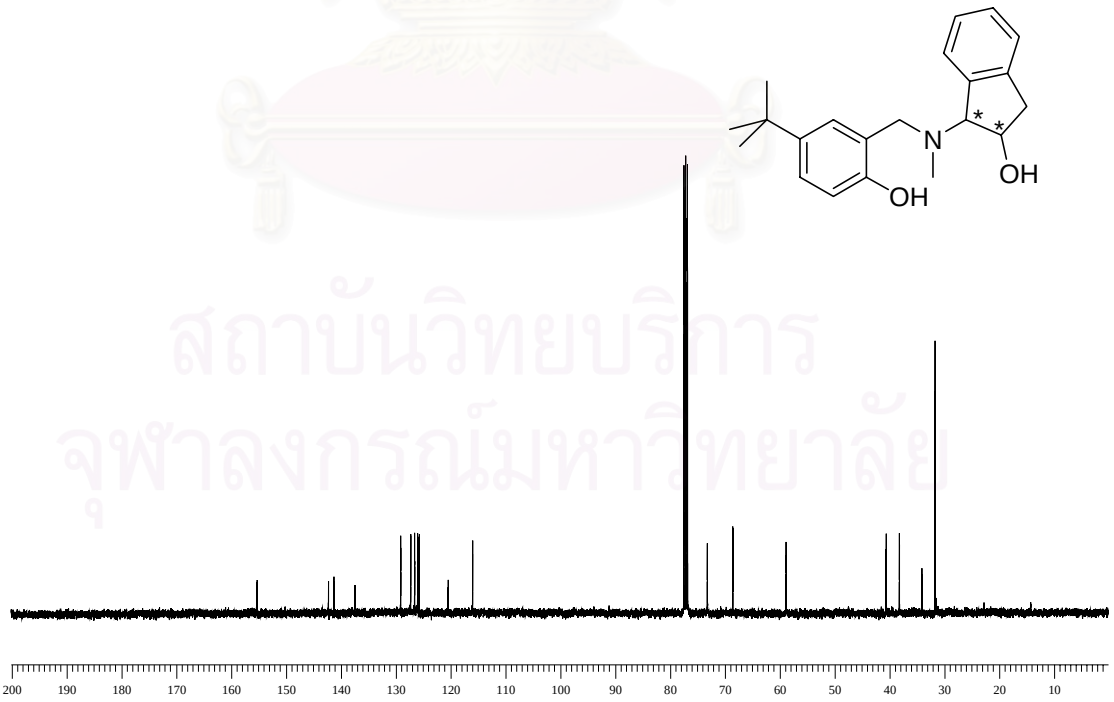


Figure 76 ^{13}C NMR of diastereomer of *N*-(2′-hydroxyphenyl)methyl-(*S*)-2-amino-1-methoxy-3-phenyl-propane **(109ae)**

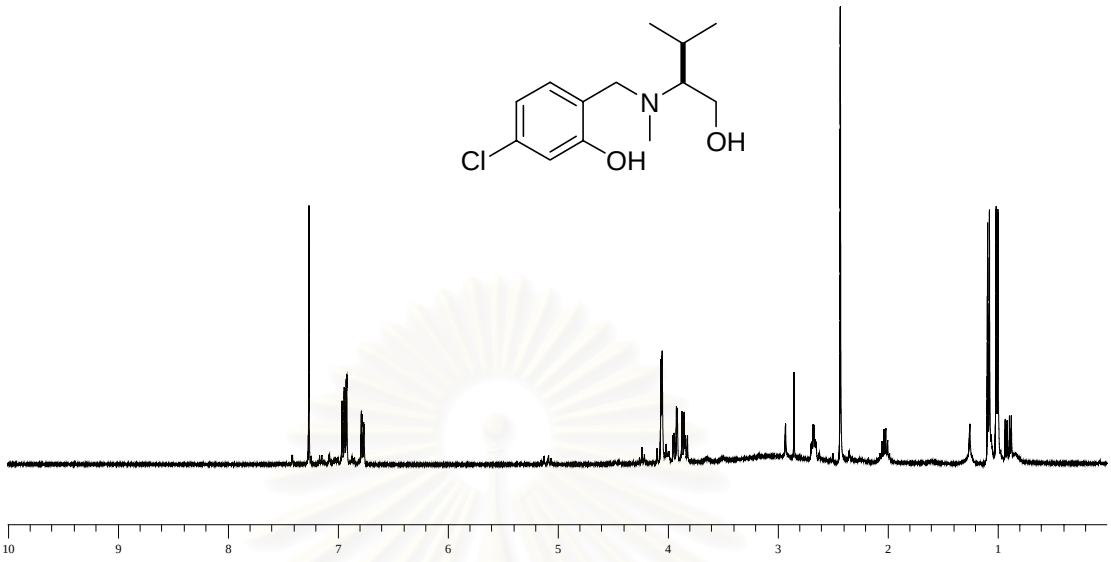


Figure 77 ^{1}H NMR of *N*-(4′-chloro-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol **(115b)**

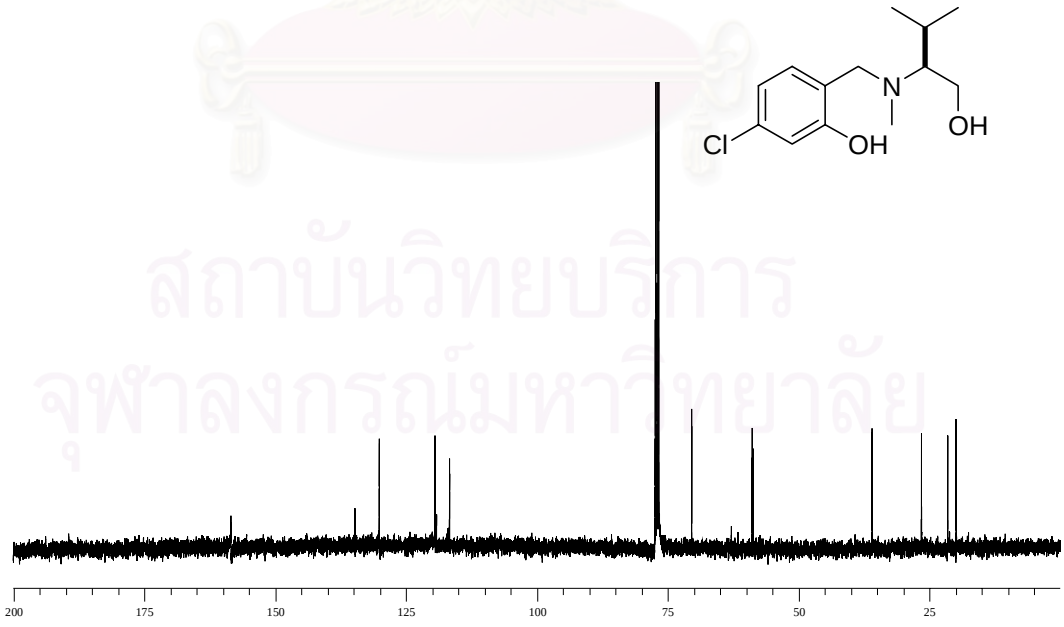


Figure 78 ^{13}C NMR of *N*-(4′-chloro-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol **(115b)**

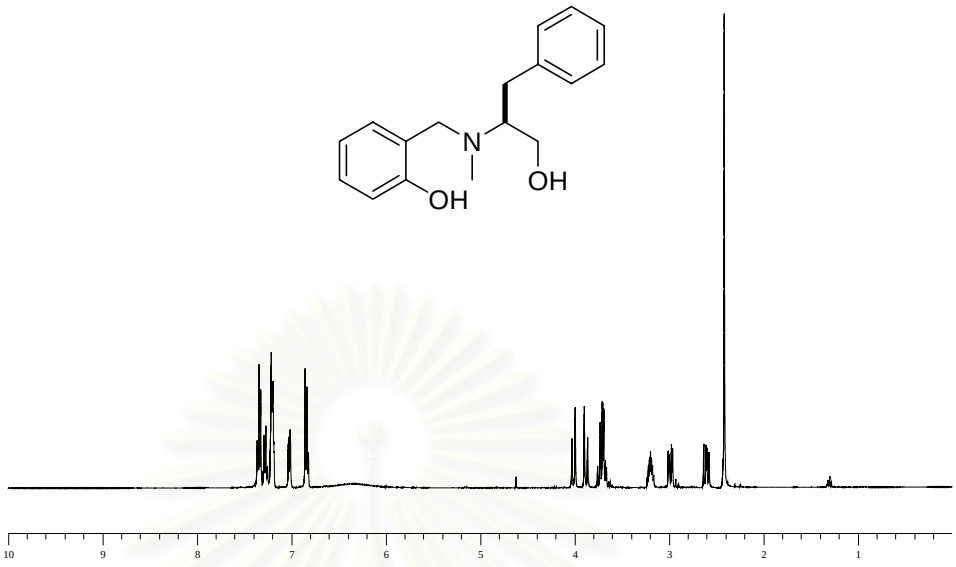


Figure 79 ^{1}H NMR of *N*-(2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-phenyl-propanol **(115c)**

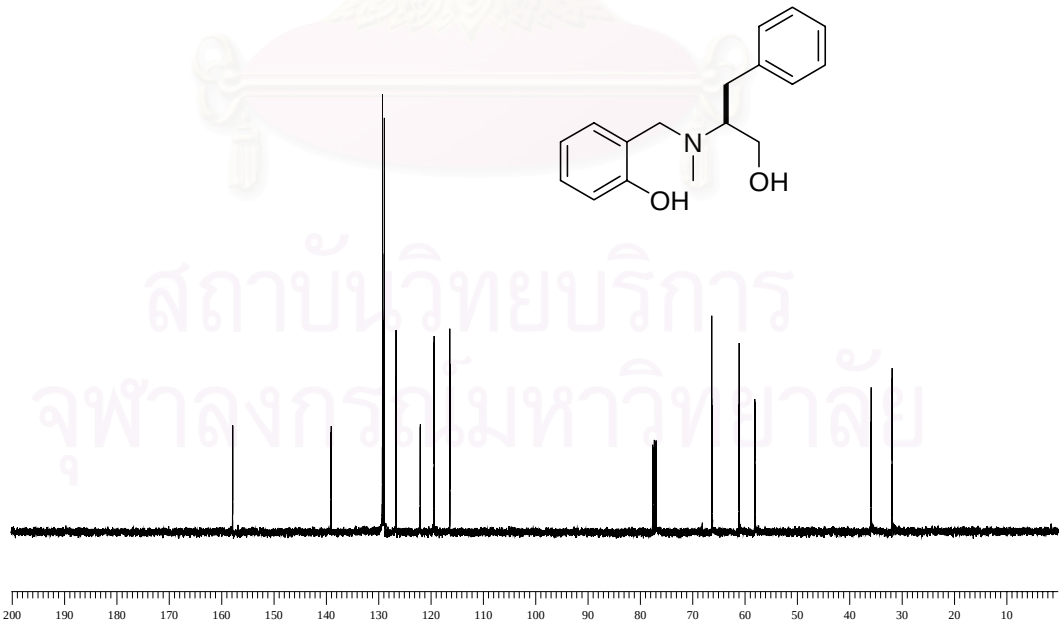


Figure 80 ^{13}C NMR of *N*-(2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-phenyl-propanol **(115c)**

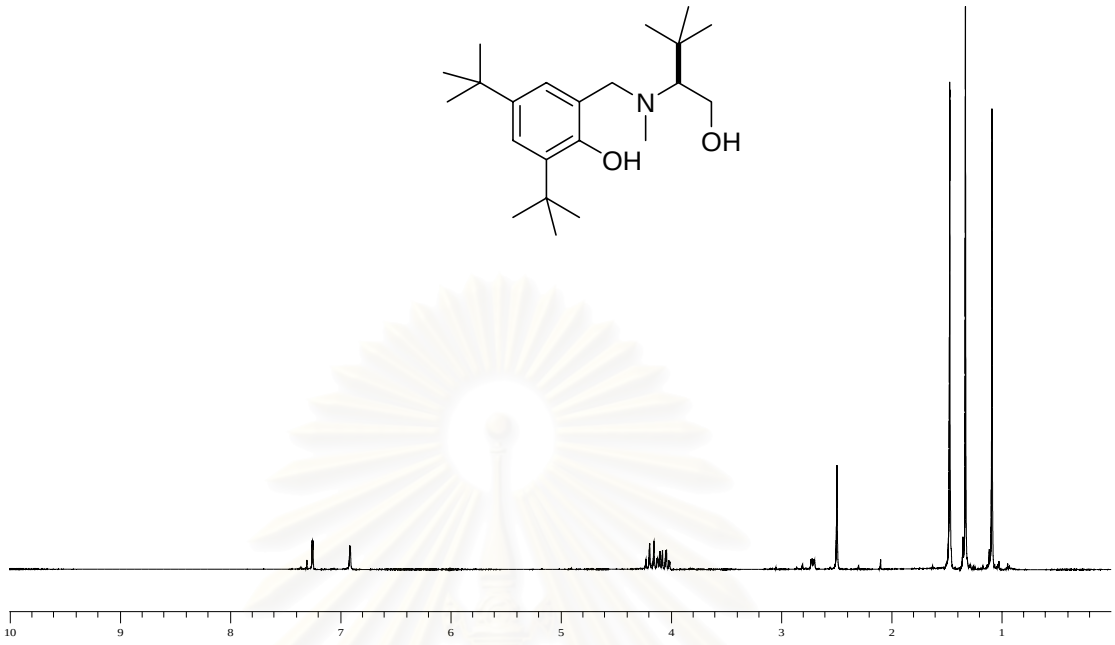


Figure 81 ^{1}H NMR of *N N*-(3′,5′-di-*tert*-butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(115d)**

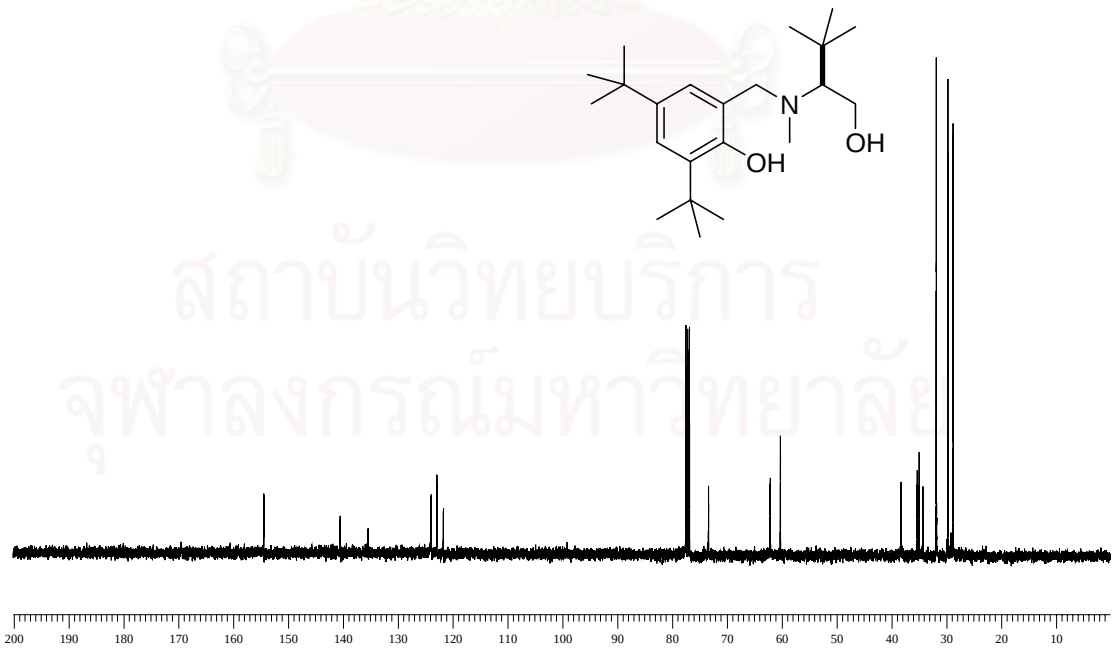


Figure 82 ^{13}C NMR of *N*-(3′,5′-di-*tert*-butyl-2′-hydroxyphenyl)methyl-*N*-methyl-(*S*)-2-amino-3,3-dimethyl-butanol **(115d)**

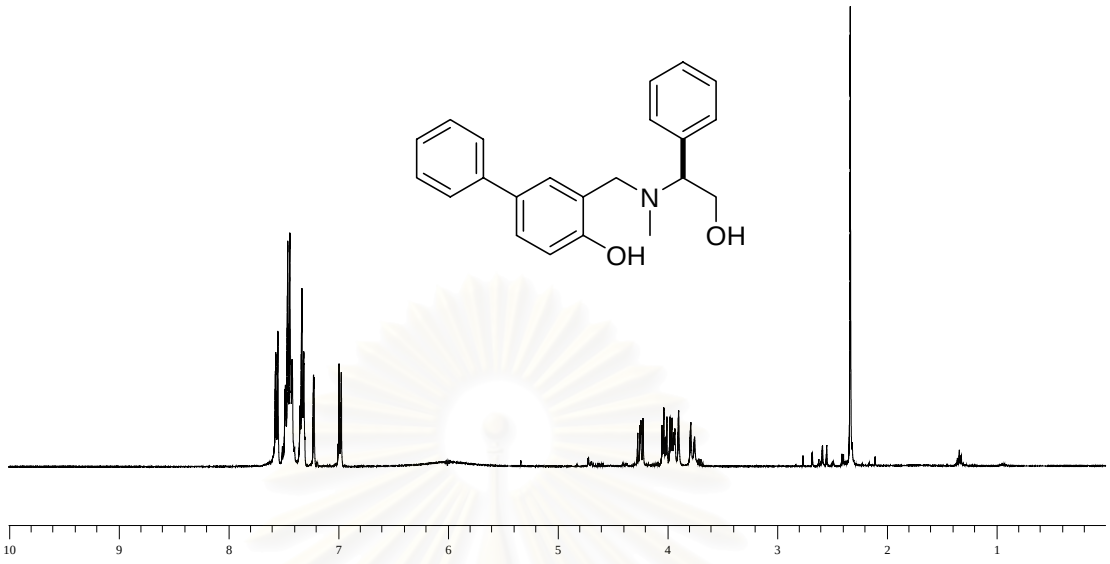


Figure 83 ^{1}H NMR of *N*-(2′-hydroxy-5′-phenyphenyl)methyl-*N*-methyl-(*S*)-2-amino-2-phenyl-ethanol **(115e)**

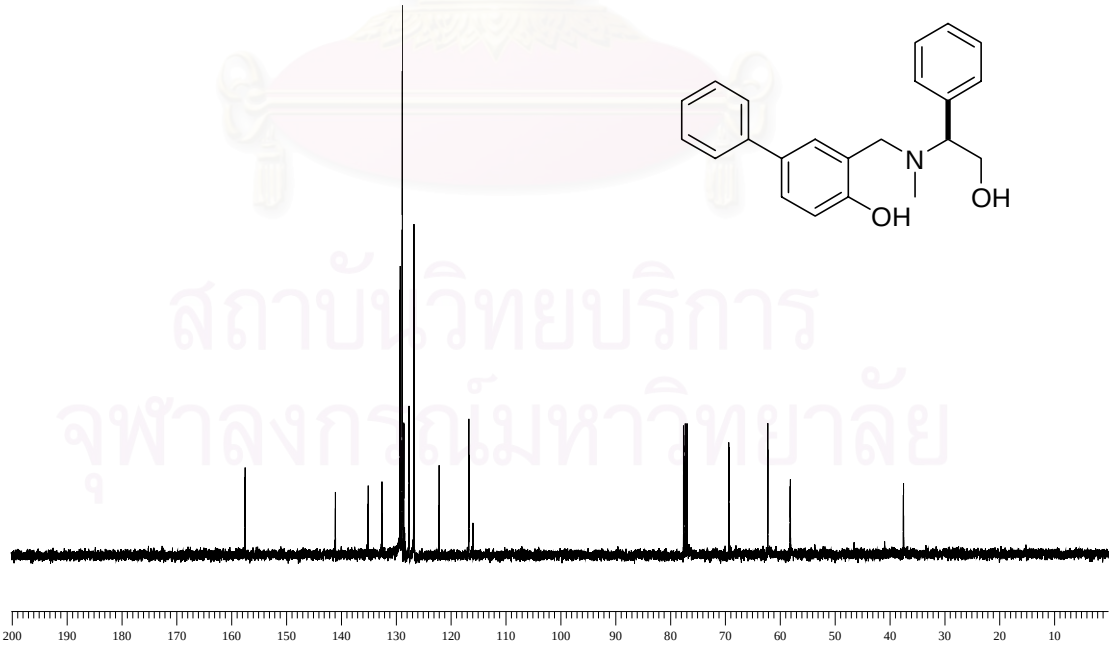


Figure 84 ^{13}C NMR of *N*-(2′-hydroxy-5′-phenyphenyl)methyl-*N*-methyl-(*S*)-2-amino-2-phenyl-ethanol **(115e)**

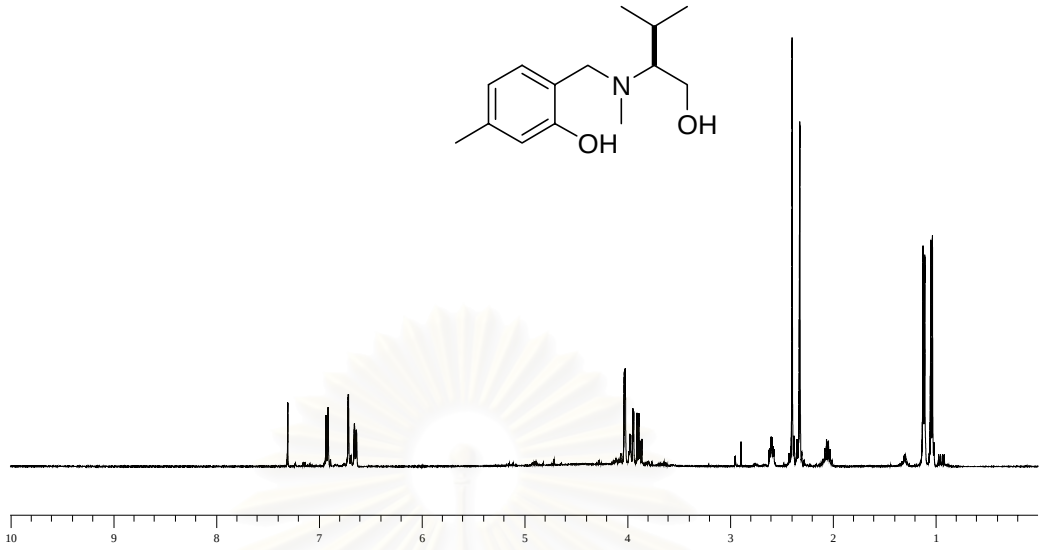


Figure 85 ^{1}H NMR of *N*-(2′-hydroxy-5′-methylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol **(115f)**

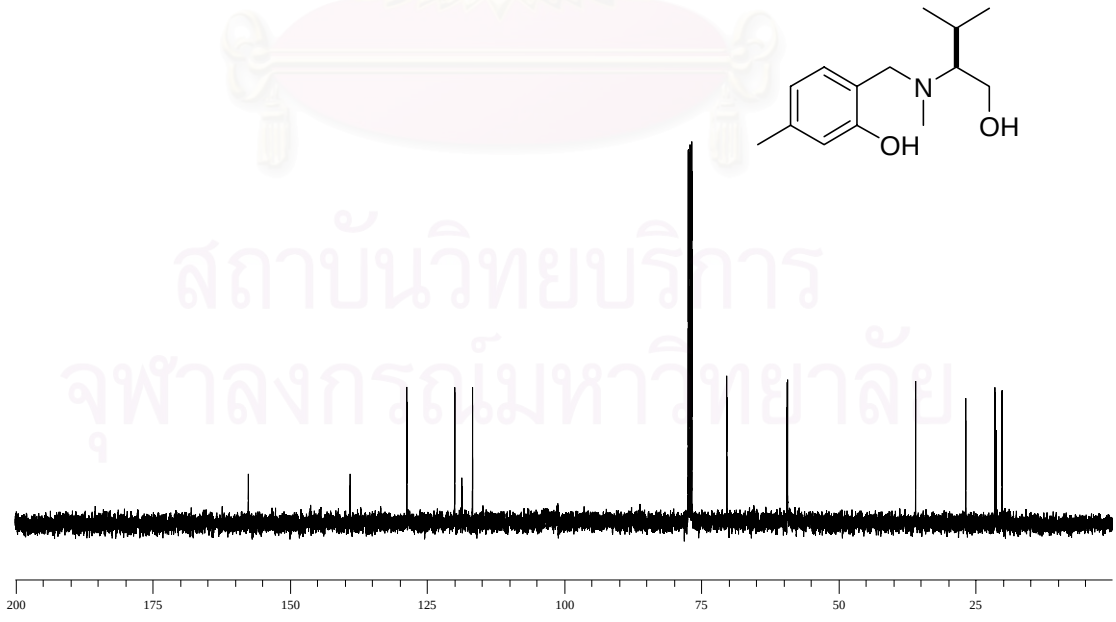


Figure 86 ^{13}C NMR of *N*-(2′-hydroxy-5′-methylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol **(115f)**

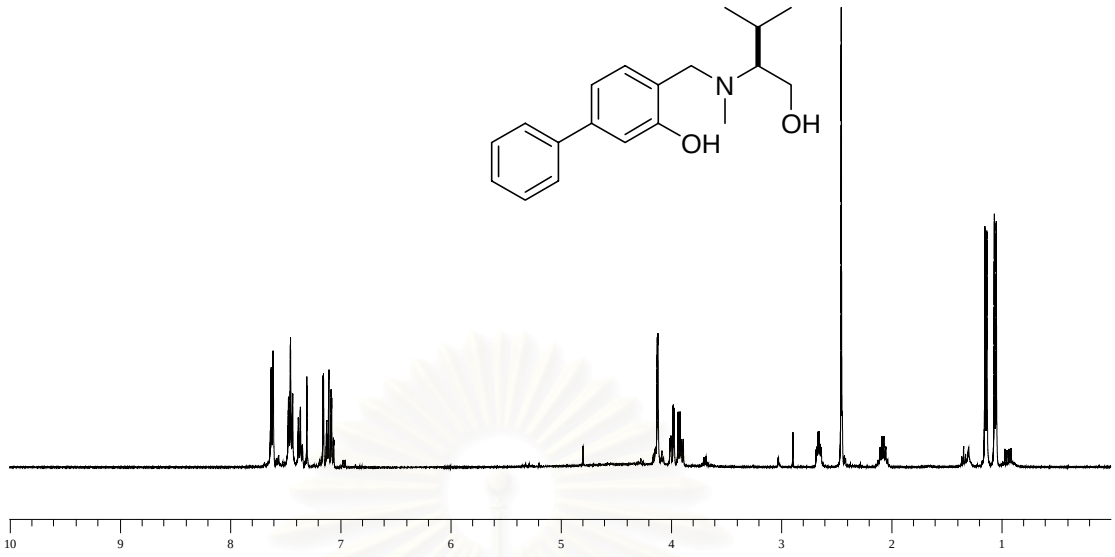


Figure 87 ^{1}H NMR of *N*-(2′-hydroxy-4′-phenylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol **(115g)**

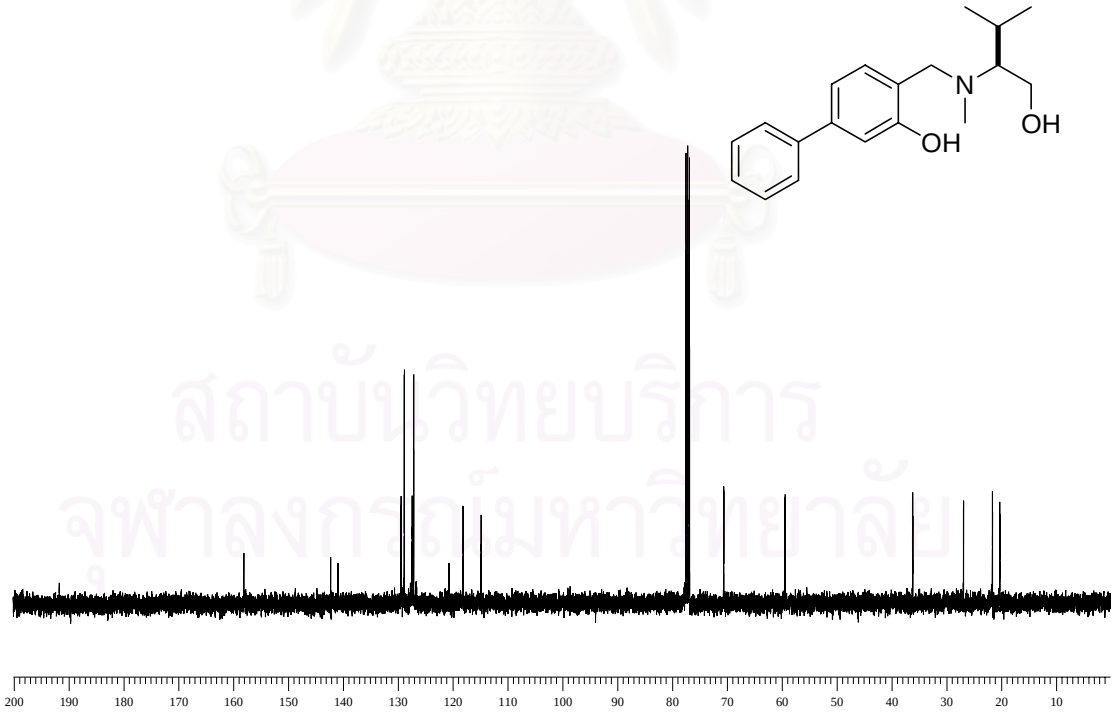


Figure 88 ^{13}C NMR of *N*-(2′-hydroxy-4′-phenylphenyl)methyl-*N*-methyl-(*S*)-2-amino-3-methyl-butanol **(115g)**

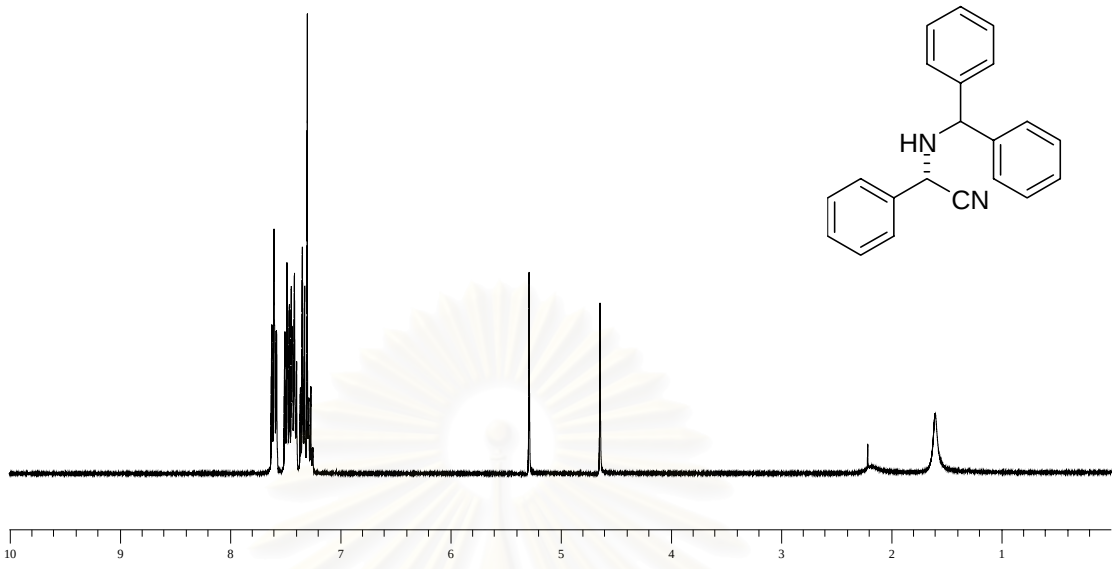


Figure 89 ^{1}H NMR of **(***S***)**-diphenylmethylamino-phenylacetonitrile **(73a)**

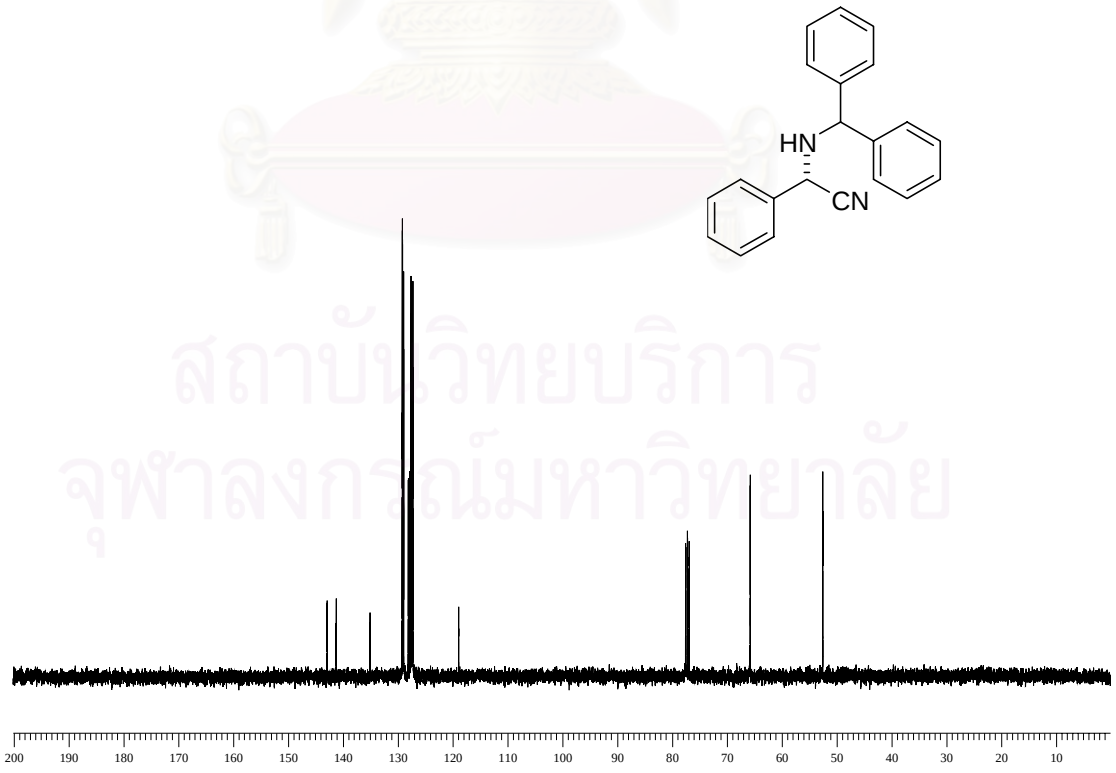


Figure 90 ^{13}C NMR of (*S*)-diphenylmethylamino-phenylacetonitrile **(73a)**

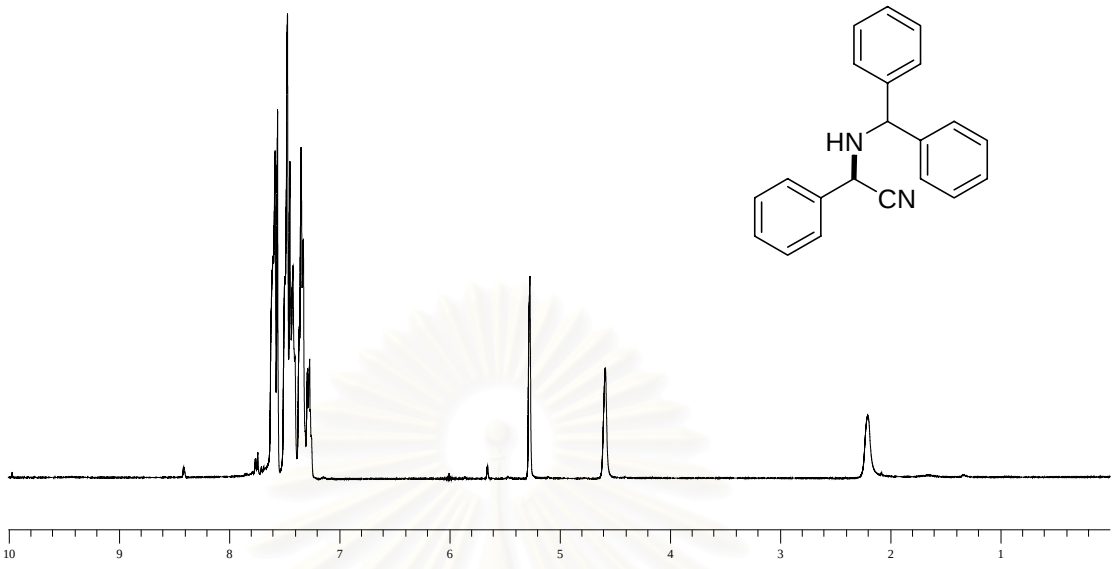


Figure 91 ^{1}H NMR of (*R*)-diphenylmethylamino-phenylacetonitrile **(73a)**

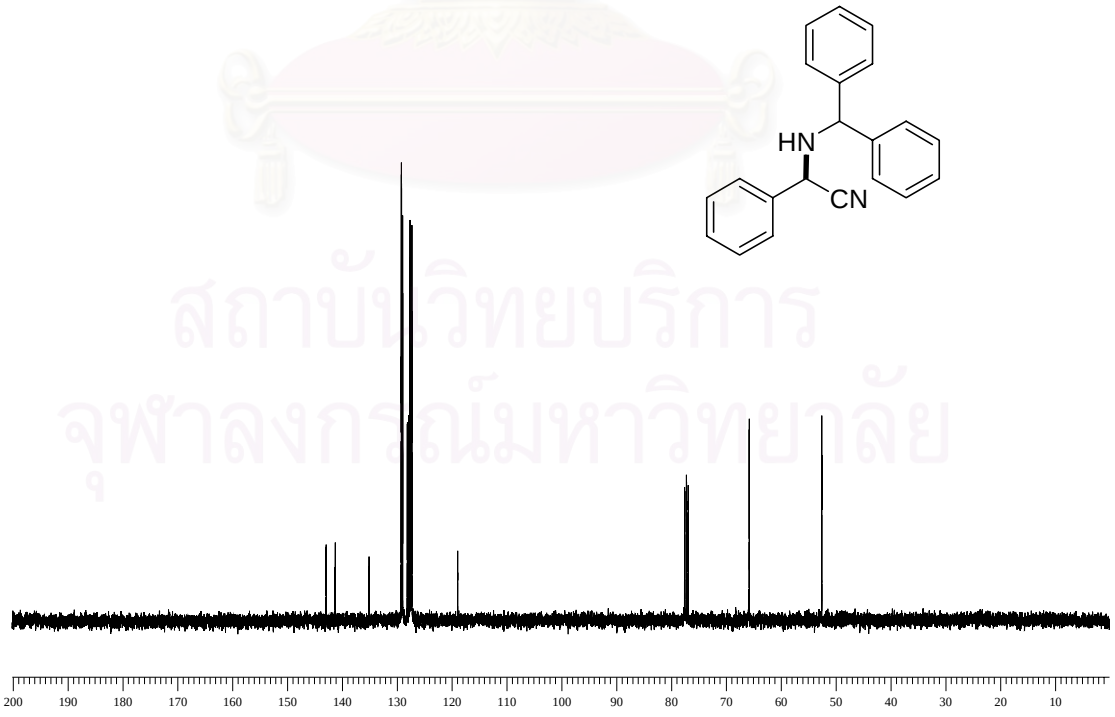


Figure 92 ^{13}C NMR of (*R*)-diphenylmethylamino-phenylacetonitrile **(73a)**

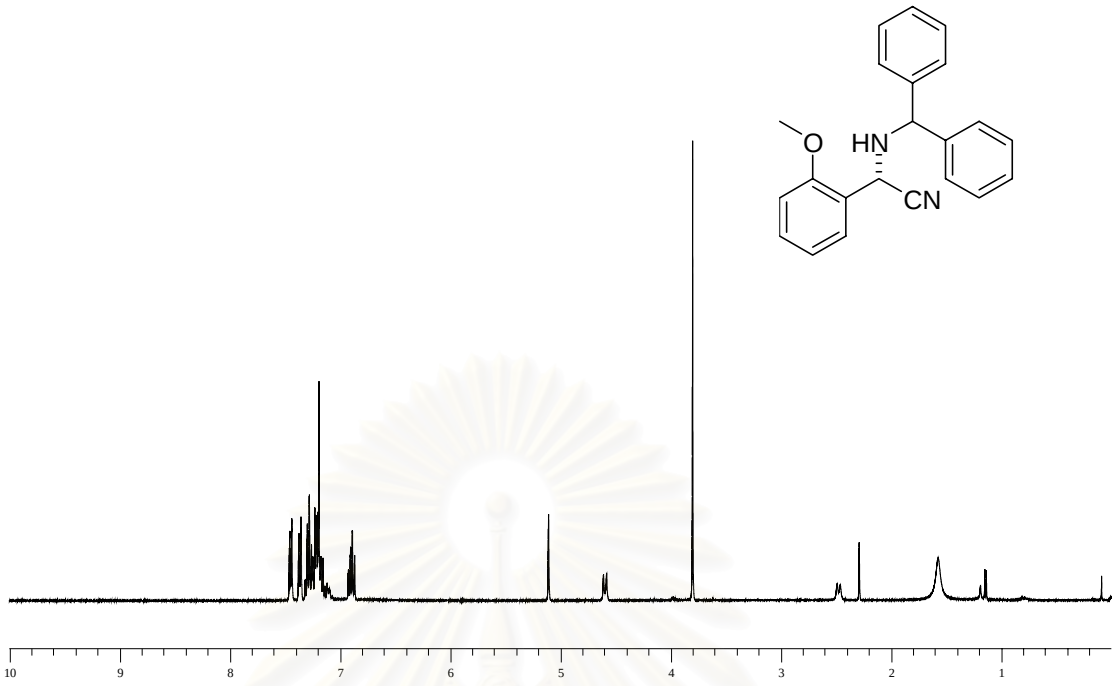


Figure 93 ^{1}H NMR of (*S*)-diphenylmethylamino-2-methoxyphenylacetonitrile **(73b)**

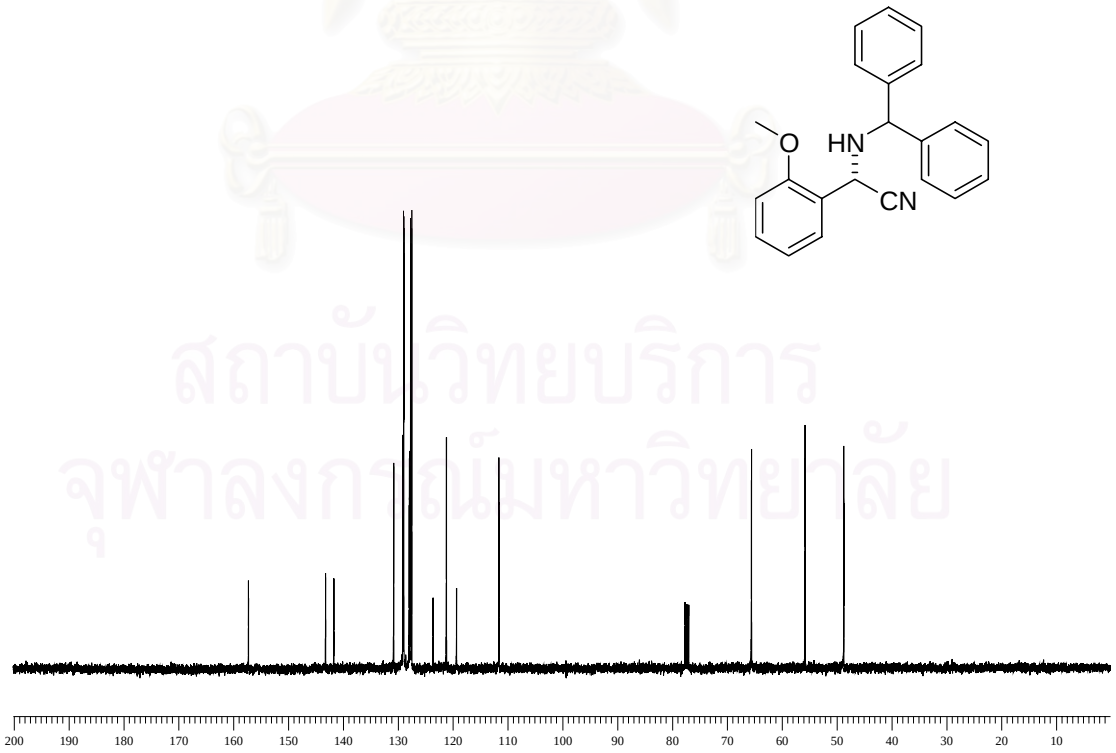


Figure 94 ^{13}C NMR of (*S*)-diphenylmethylamino-2-methoxyphenylacetonitrile **(73b)**

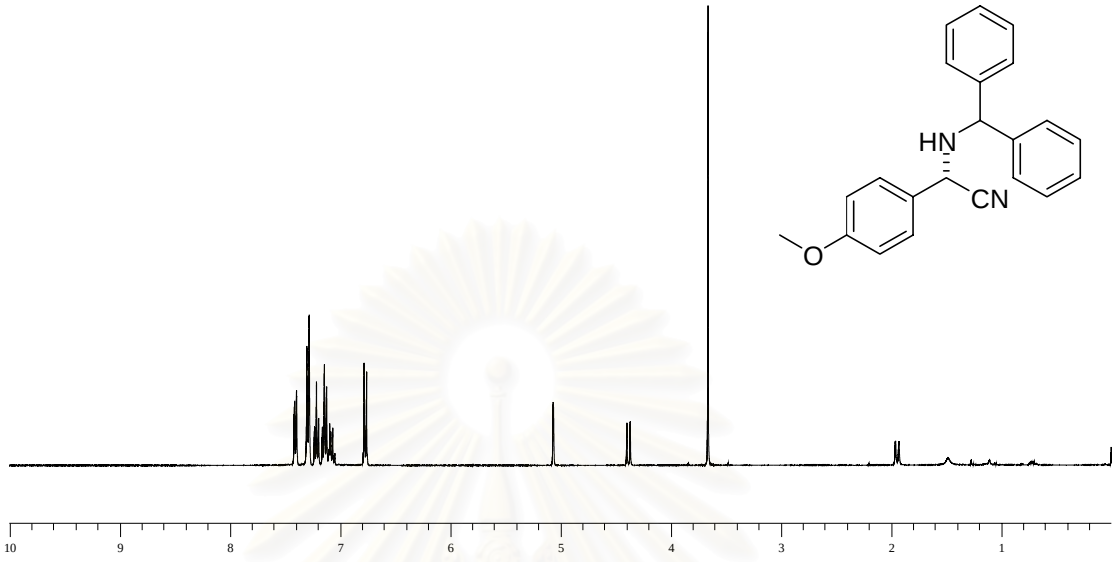


Figure 95 ^{1}H NMR of (*S*)-diphenylmethylamino-4-methoxyphenylacetonitrile **(73d)**

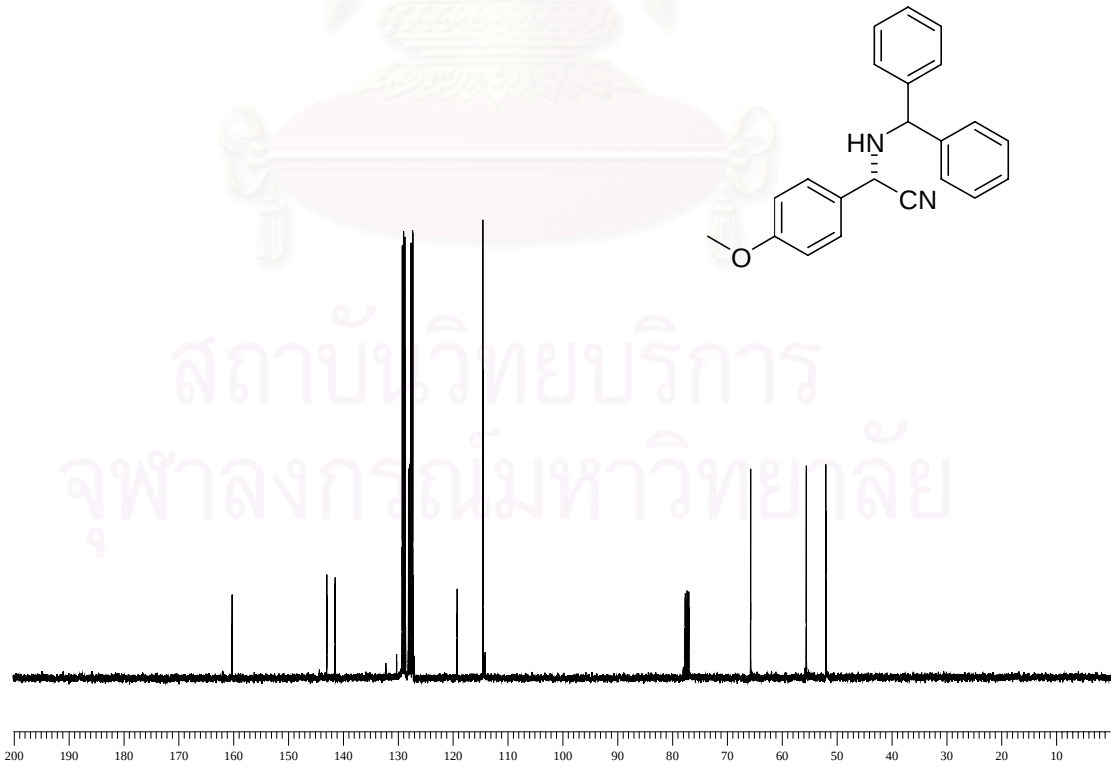


Figure 96 ^{13}C NMR of (*S*)-diphenylmethylamino-4-methoxyphenylacetonitrile **(73d)**

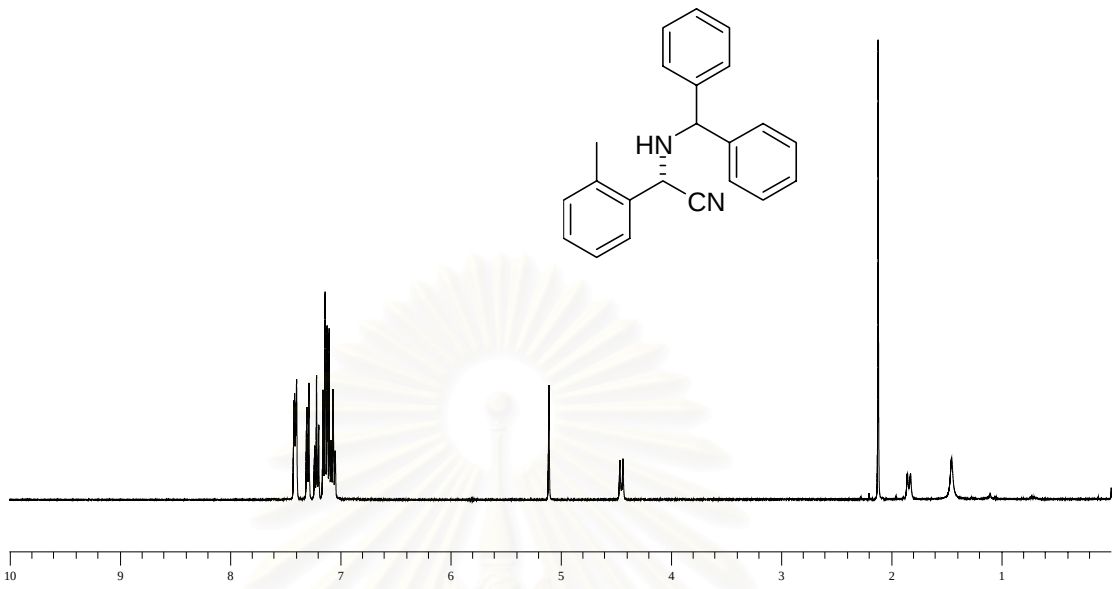


Figure 97 ^{1}H NMR of (*S*)-diphenylmethylamino-2-methylphenylacetonitrile **(73e)**

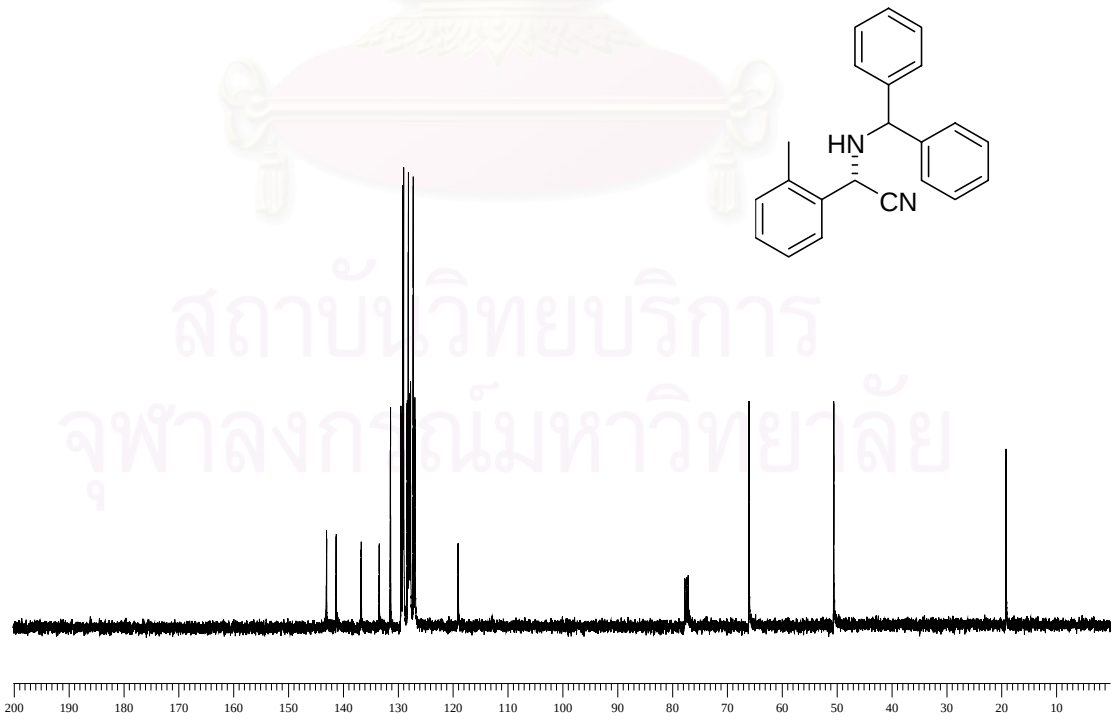


Figure 98 ^{13}C NMR of (*S*)-diphenylmethylamino-2-methylphenylacetonitrile **(73e)**

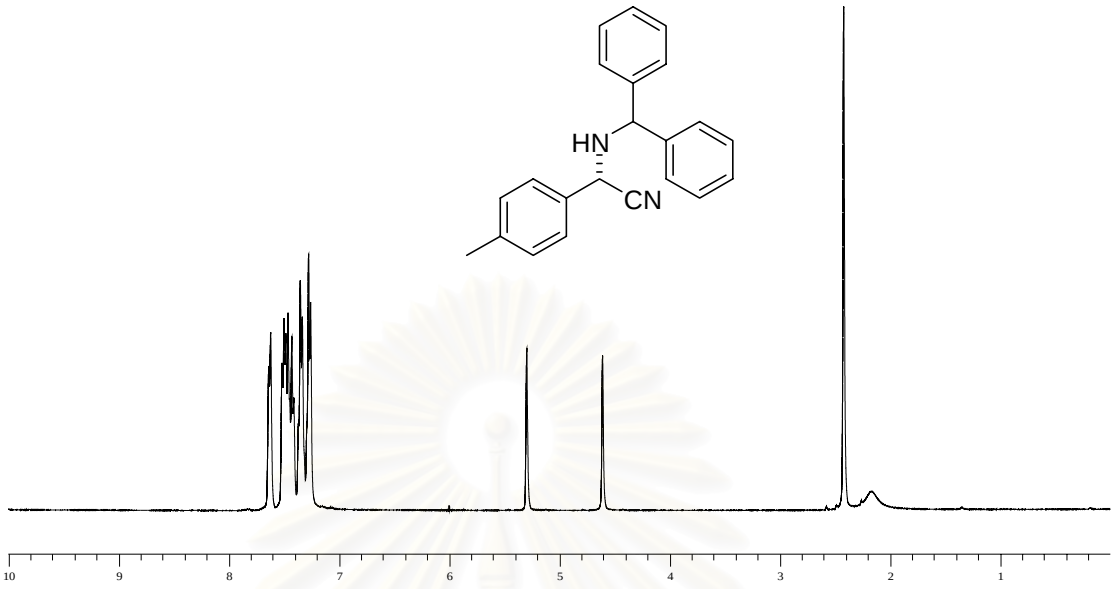


Figure 99 ^{1}H NMR of (*S*)-diphenylmethylamino-4-methylphenylacetonitrile **(73f)**

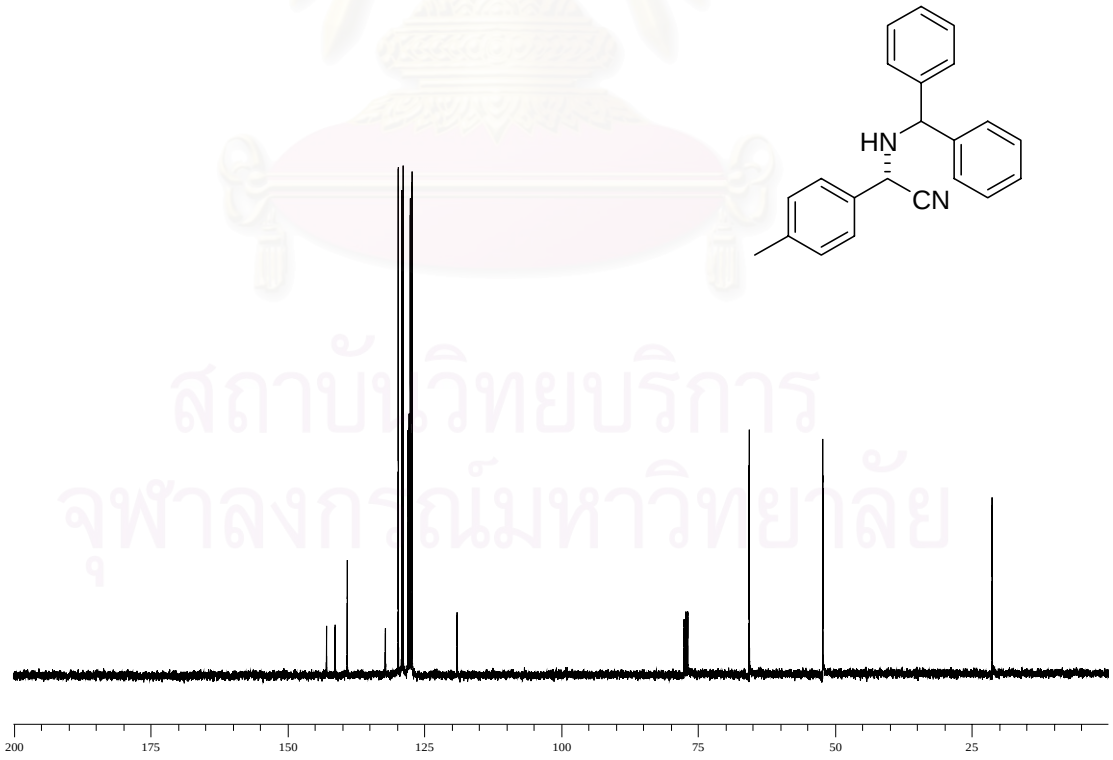


Figure 100 ^{13}C NMR of (*S*)-diphenylmethylamino-4-methylphenylacetonitrile **(73f)**

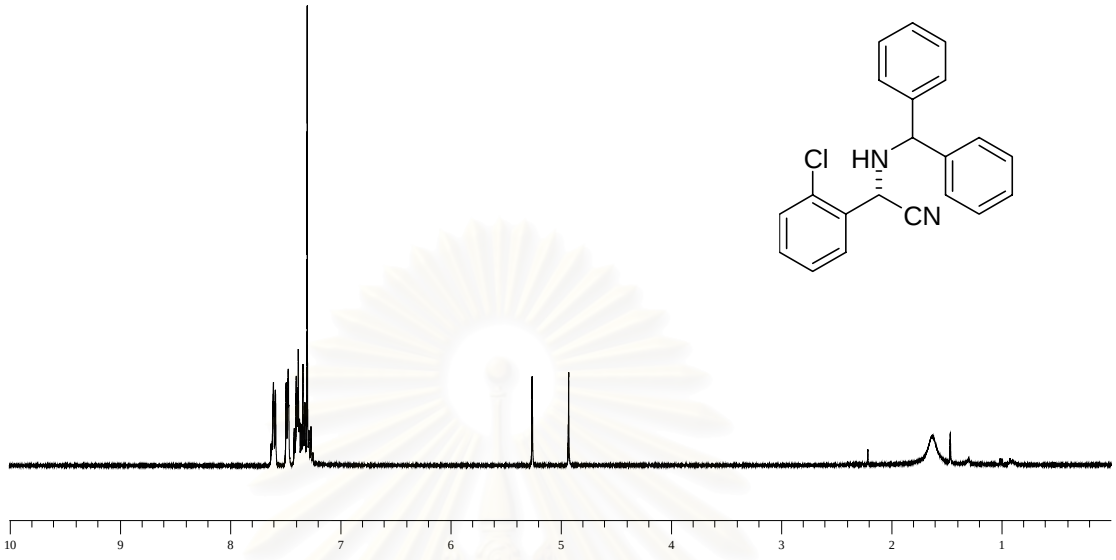


Figure 101 ^{1}H NMR of (*S*)-diphenylmethylamino-2-chlorophenylacetonitrile **(73i)**

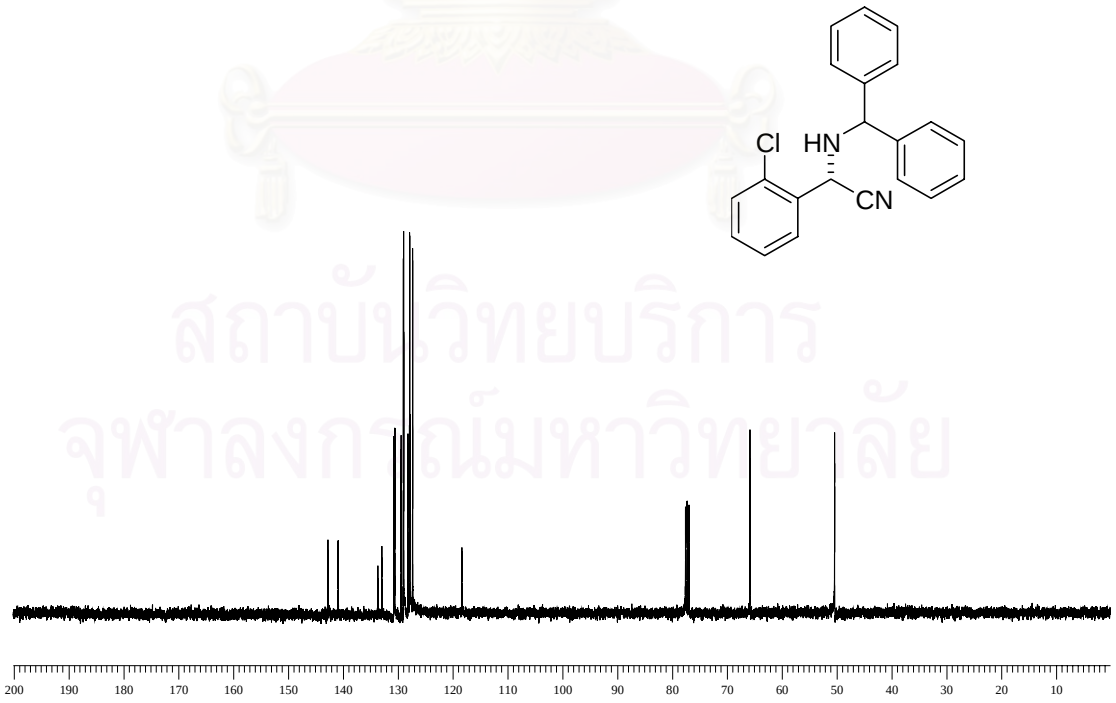


Figure 102 ^{13}C NMR of (*S*)-diphenylmethylamino-2-chlorophenylacetonitrile **(73i)**

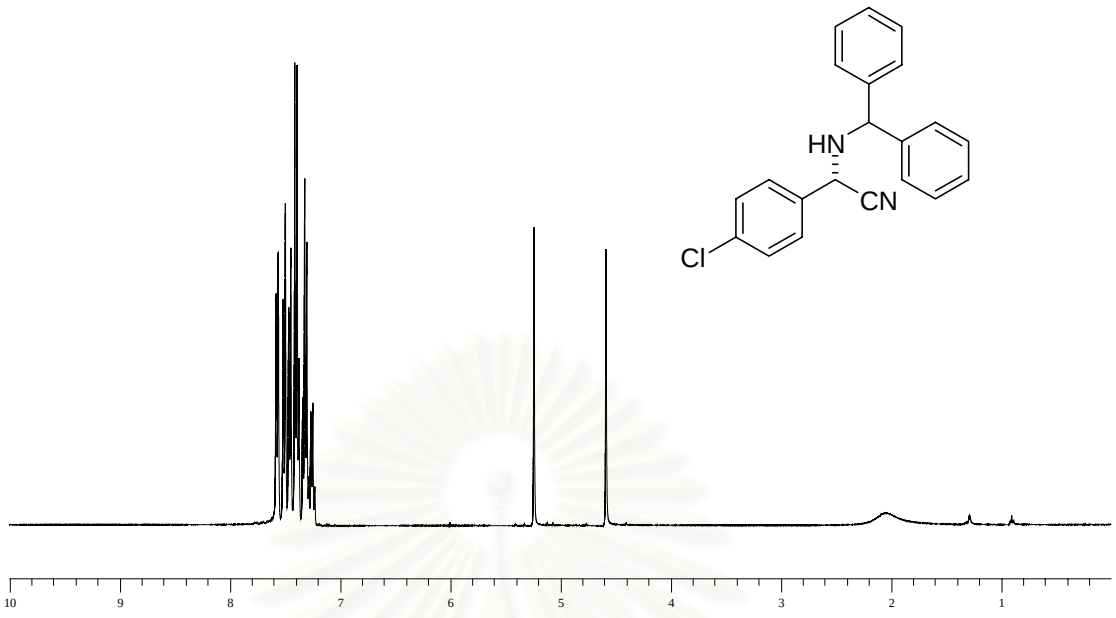


Figure 103 ^{1}H NMR of (*S*)-diphenylmethylamino-4-chlorophenylacetonitrile **(73k)**

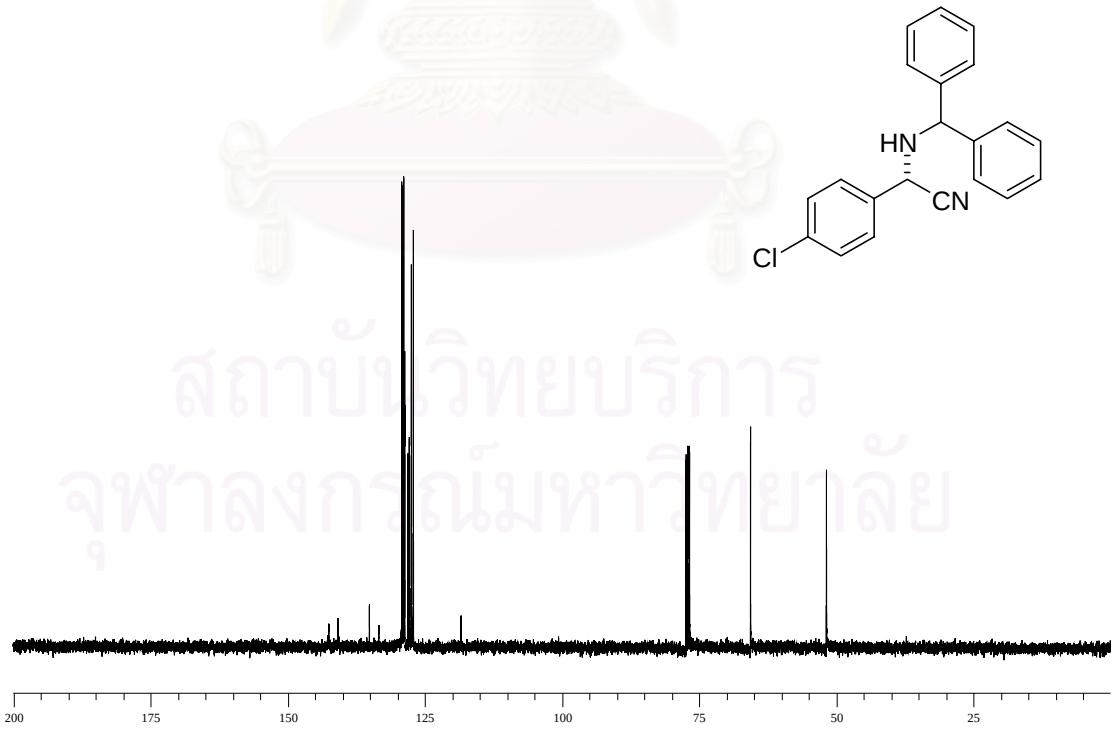


Figure 104 ^{13}C NMR of (*S*)-diphenylmethylamino-4-chlorophenylacetonitrile **(73k)**

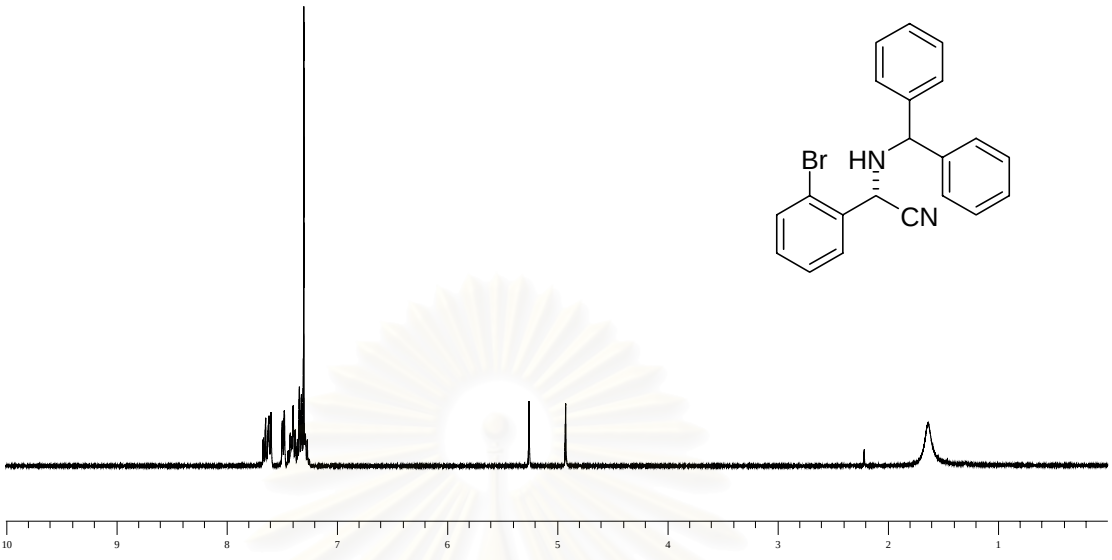


Figure 105 ^{1}H NMR of (*S*)-diphenylmethylamino-2-bromophenylacetonitrile **(73k)**

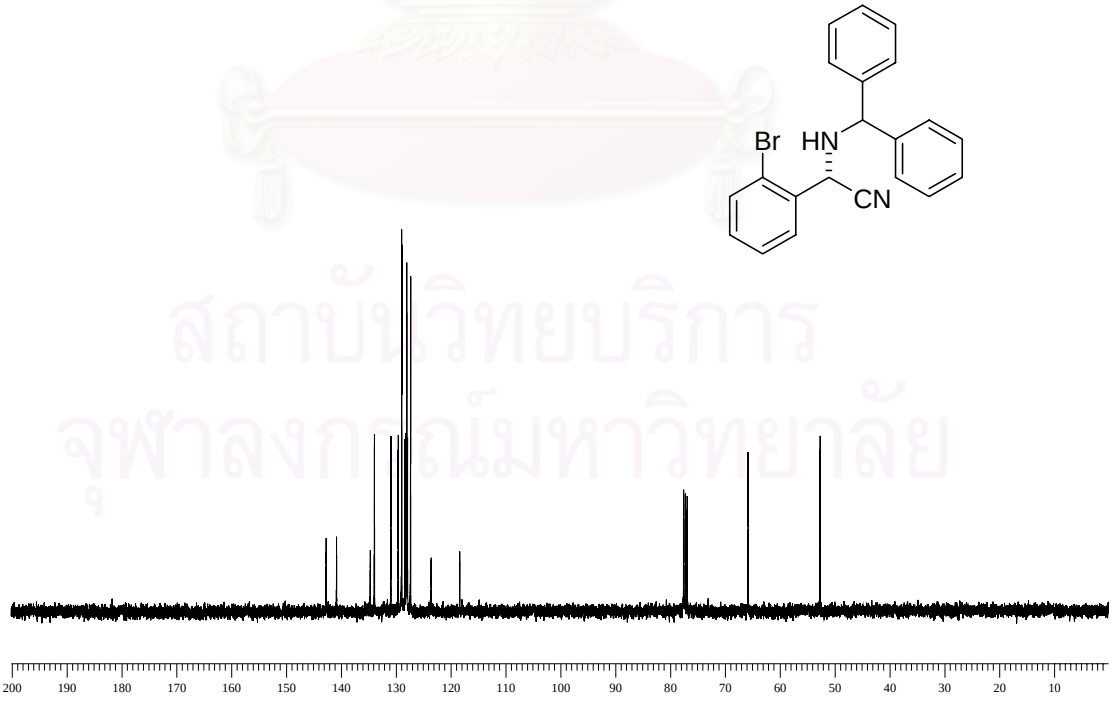


Figure 106 ^{13}C NMR of (*S*)-diphenylmethylamino-2-bromophenylacetonitrile **(73k)**

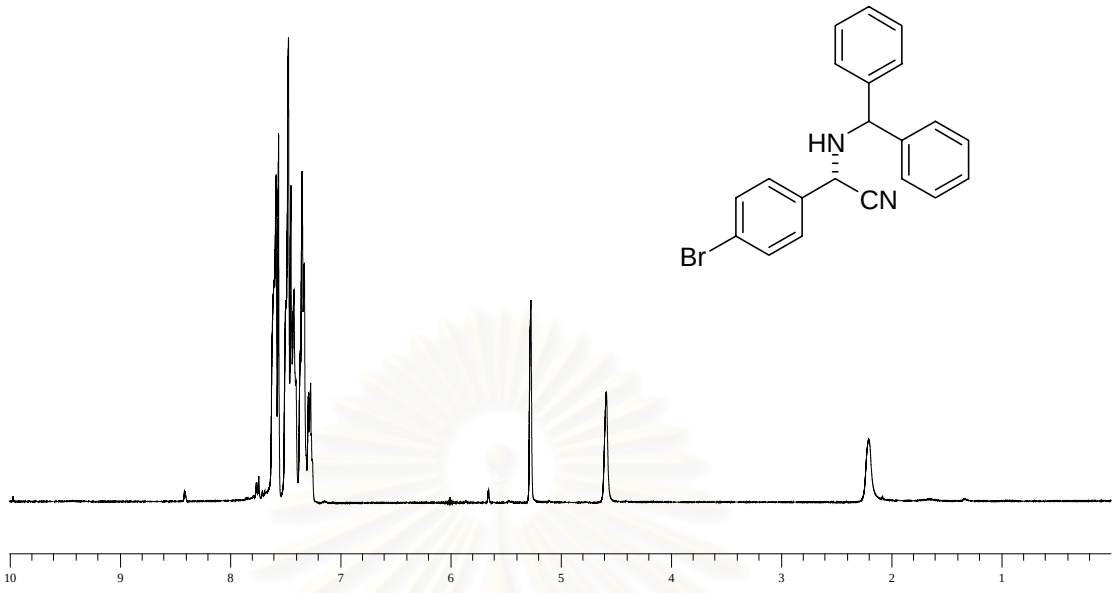


Figure 107 ^{1}H NMR of (*S*)-diphenylmethylamino-4-bromophenylacetonitrile **(73l)**

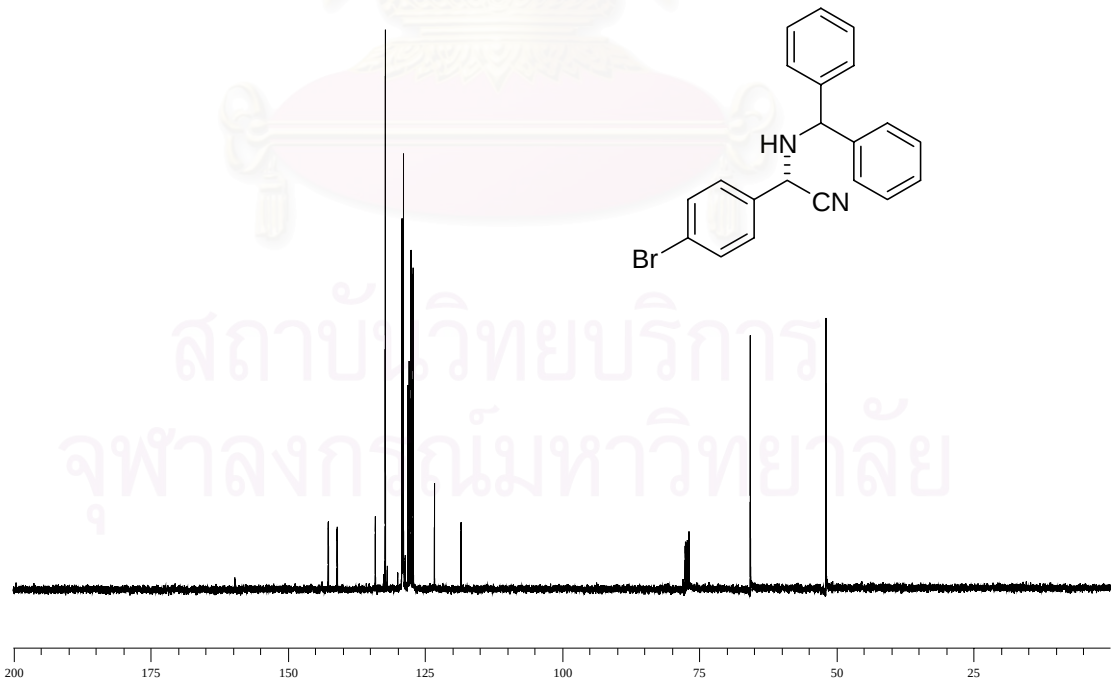


Figure 108 ^{13}C NMR of (*S*)-diphenylmethylamino-4-bromophenylacetonitrile **(73l)**

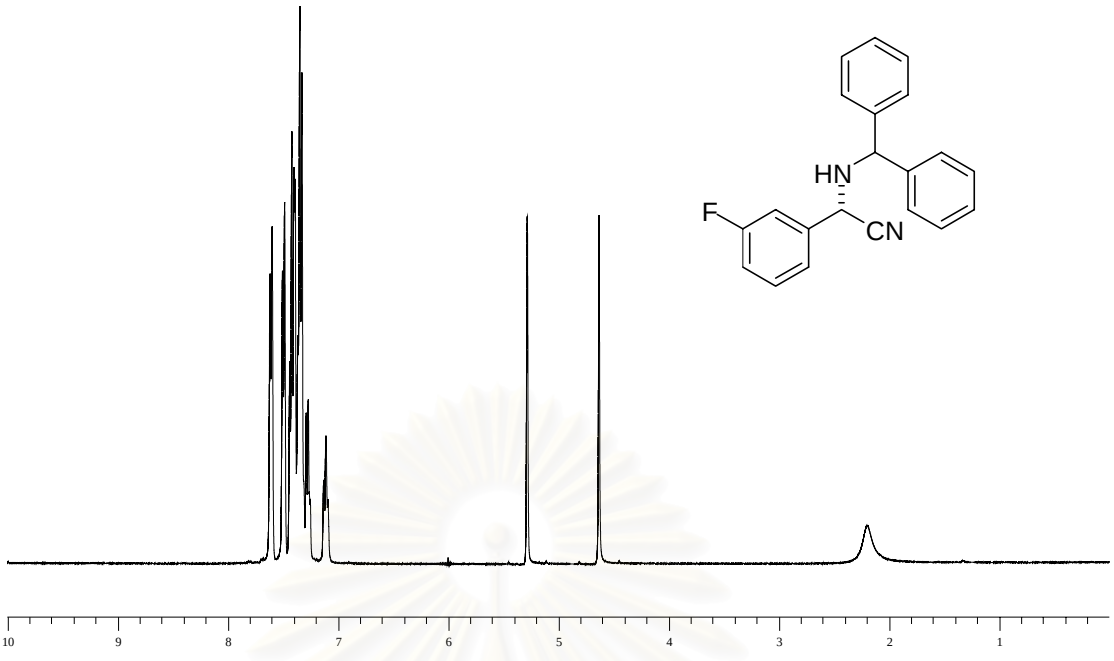


Figure 109 ^{1}H NMR of (*S*)-diphenylmethylamino-3-fluorophenylacetonitrile **(73m)**

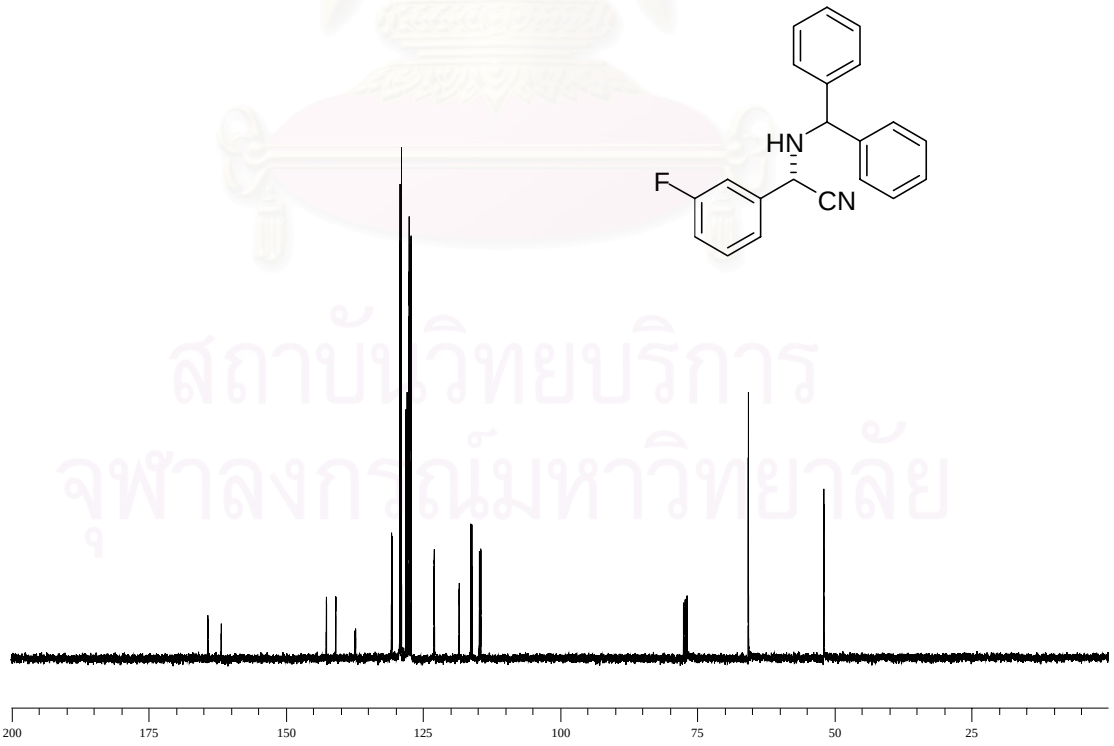


Figure 110 ^{13}C NMR of (*S*)-diphenylmethylamino-3-fluorophenylacetonitrile **(73m)**

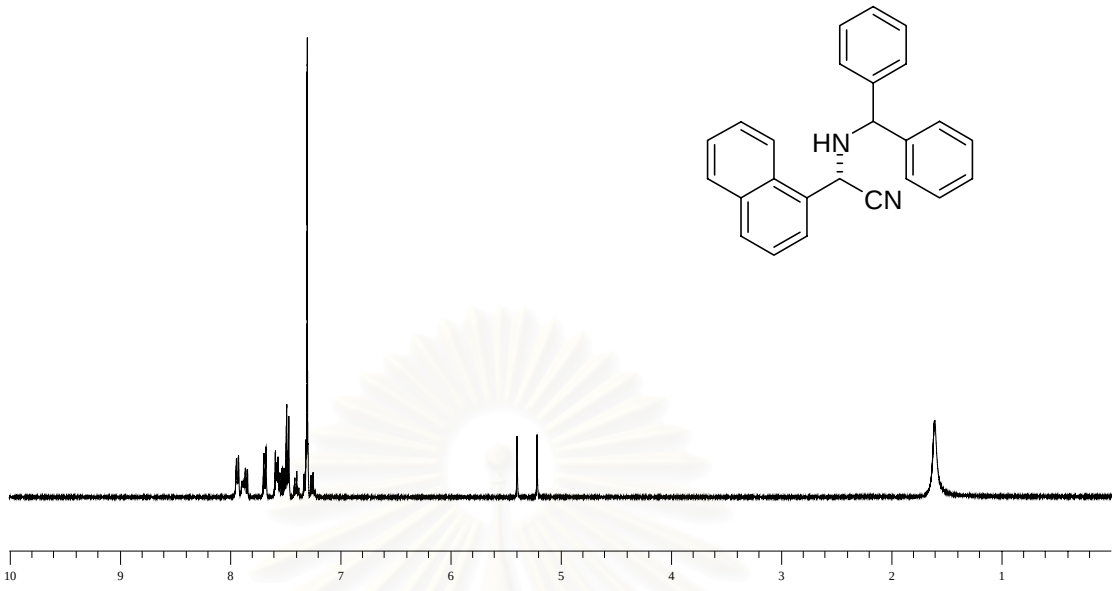


Figure 111 ^{1}H NMR of (*S*)-diphenylmethylamino-1-naphthylacetonitrile **(73n)**

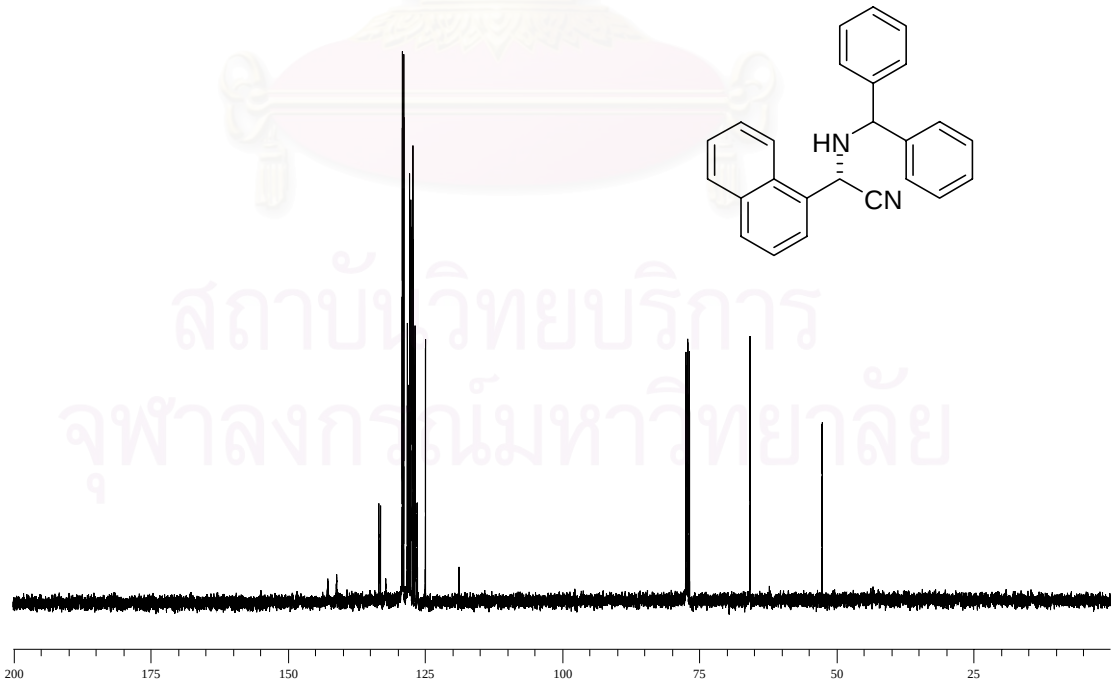


Figure 112 ^{13}C NMR of (*S*)-diphenylmethylamino-1-naphthylacetonitrile **(73n)**

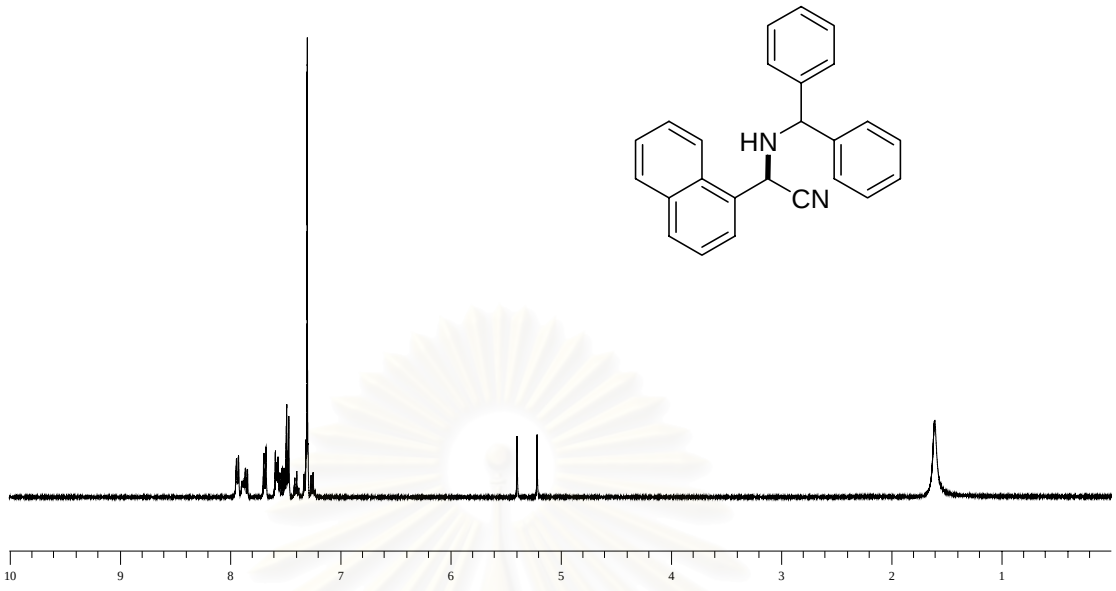


Figure 113 ^{1}H NMR of (*R*)-diphenylmethylamino-1-naphthylacetonitrile **(73n)**

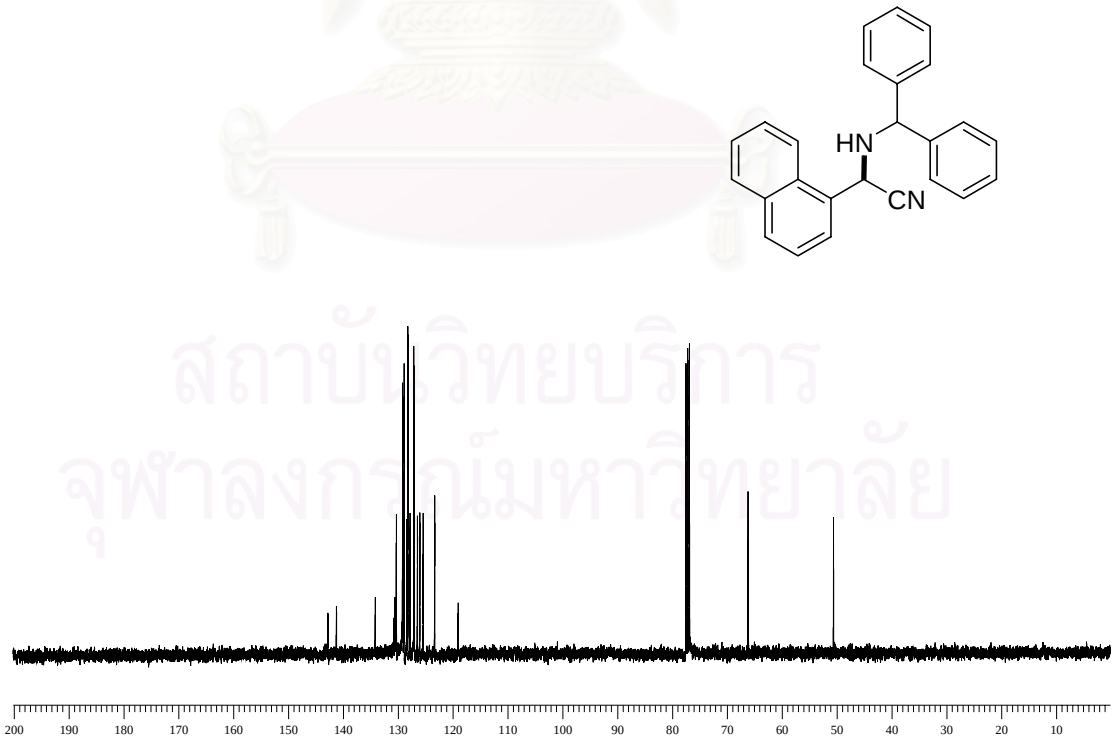


Figure 114 ^{13}C NMR of (*R*)-diphenylmethylamino-1-naphthylacetonitrile **(73n)**

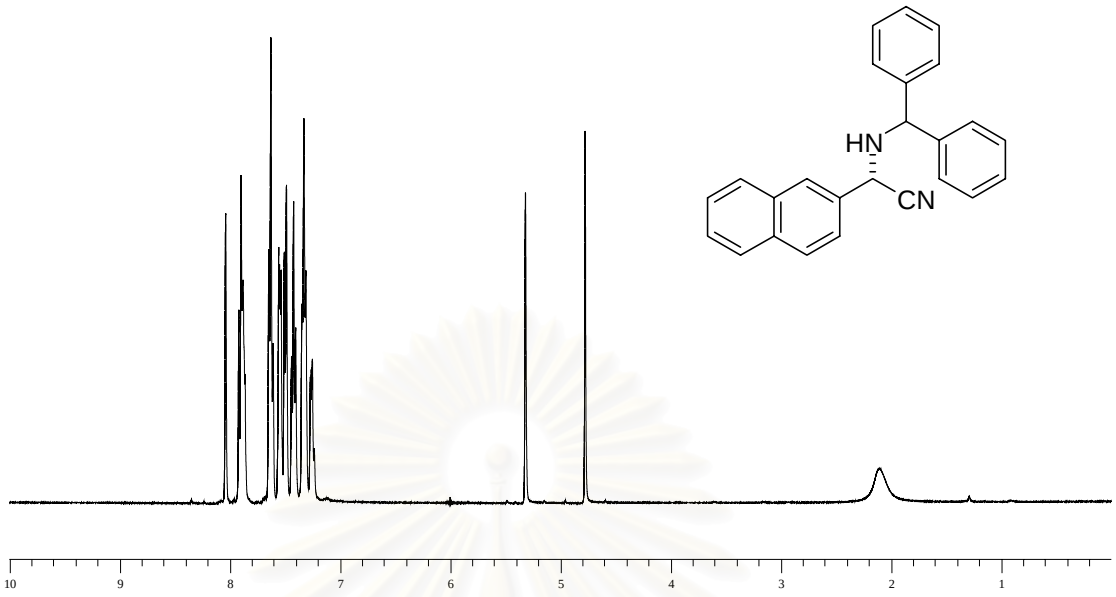


Figure 115 ^{1}H NMR of (*S*)-diphenylmethylamino-2-naphthylacetonitrile **(73o)**

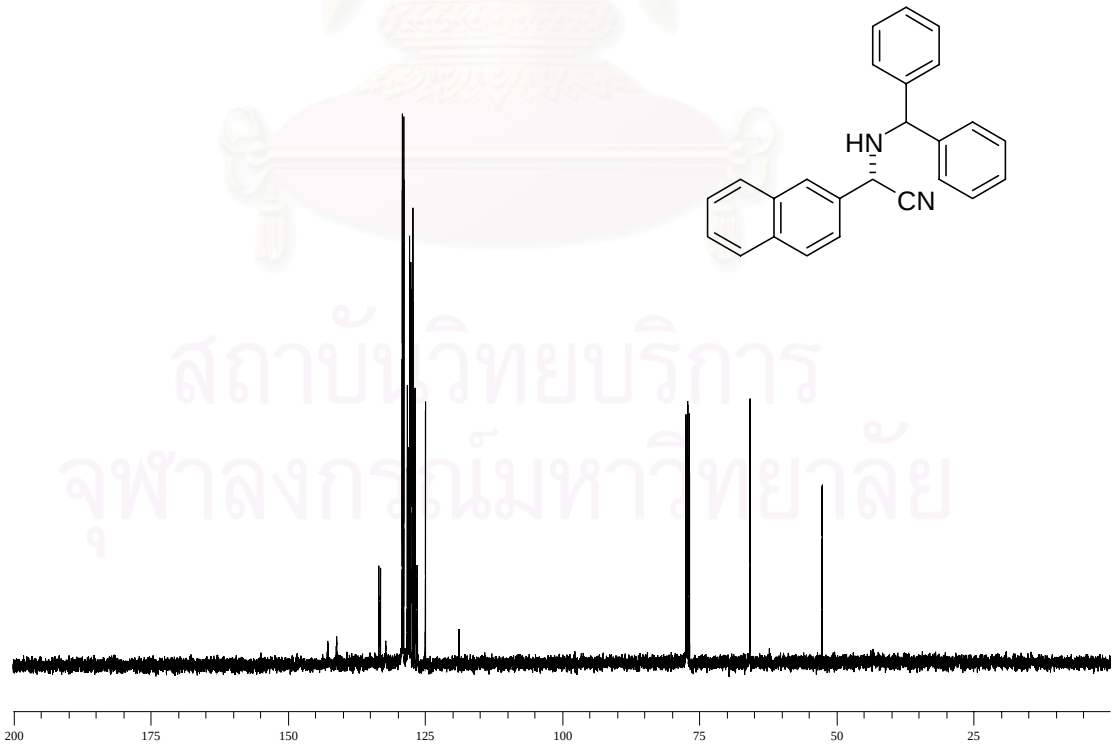


Figure 116 ^{13}C NMR of (*S*)-diphenylmethylamino-2-naphthylacetonitrile **(73o)**

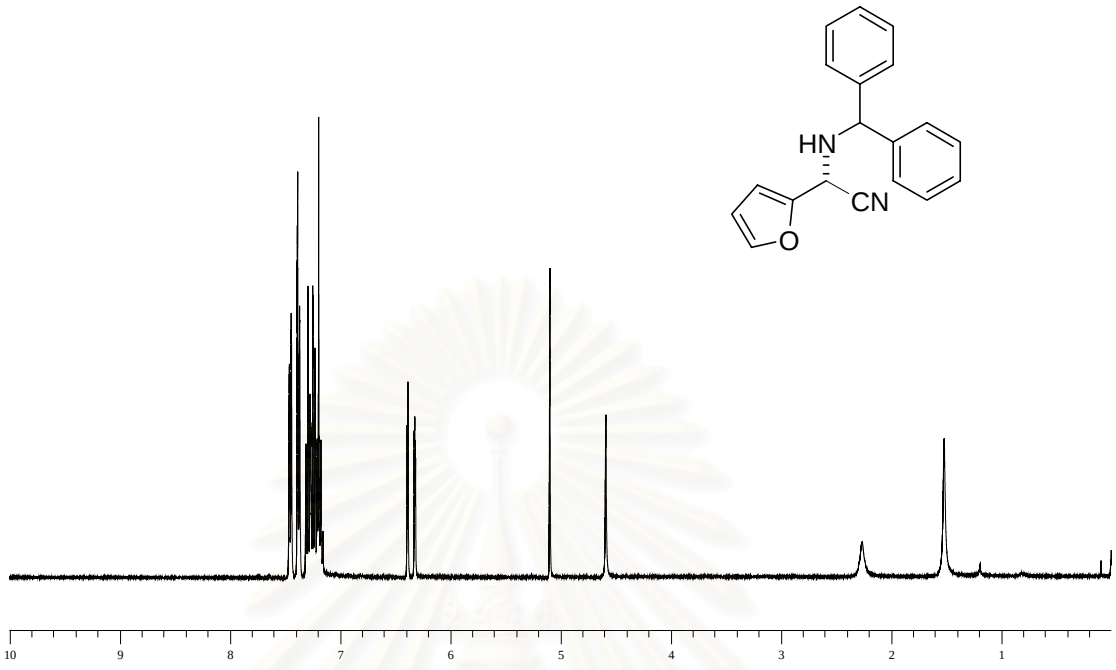


Figure 117 ^{1}H NMR of (*R*)-diphenylmethylamino-furan-2-ylacetonitrile **(73p)**

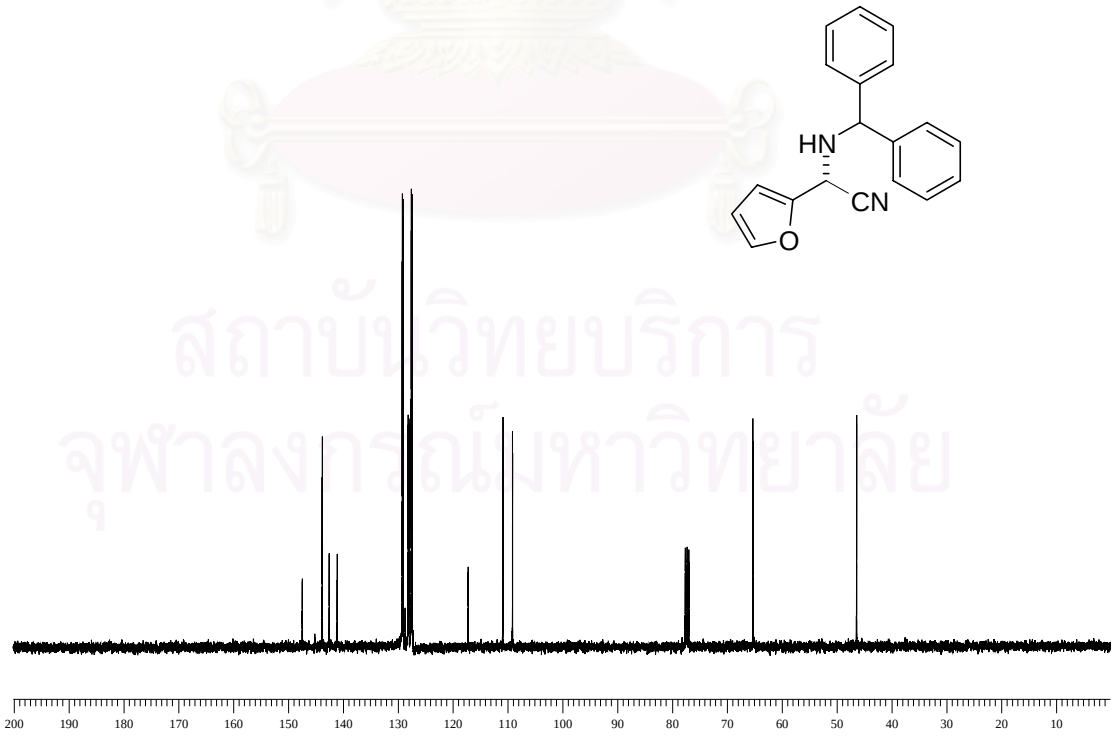


Figure 118 ^{13}C NMR of (*R*)-diphenylmethylamino-furan-2-ylacetonitrile **(73p)**

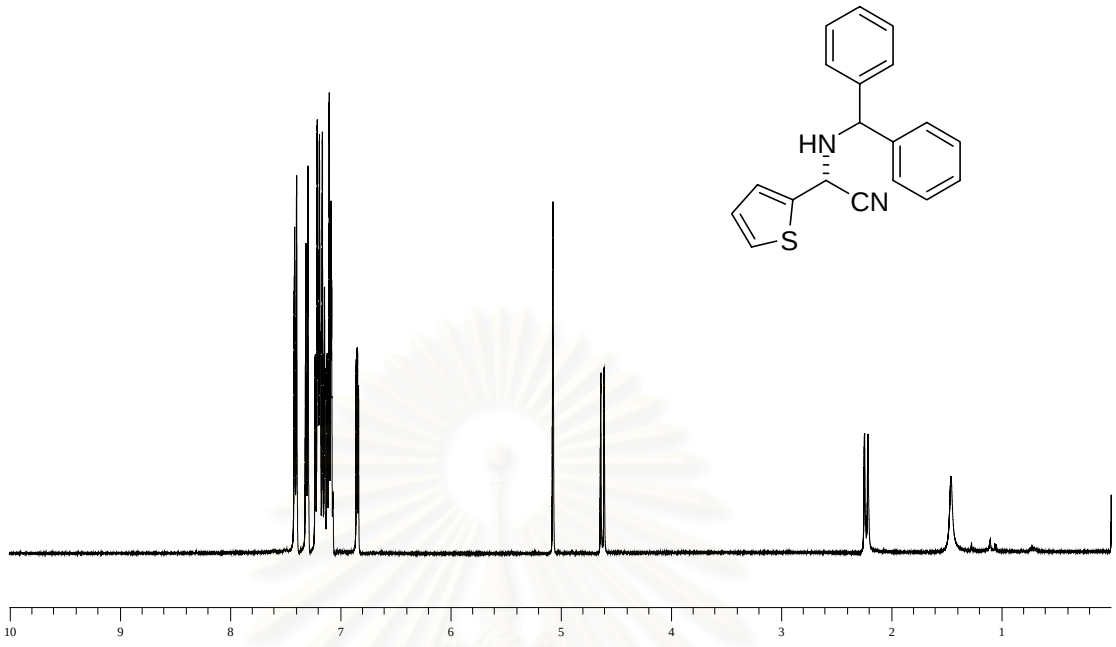


Figure 119 ^{1}H NMR of (*R*)-diphenylmethylamino-thiophen-2-ylacetonitrile **(73q)**

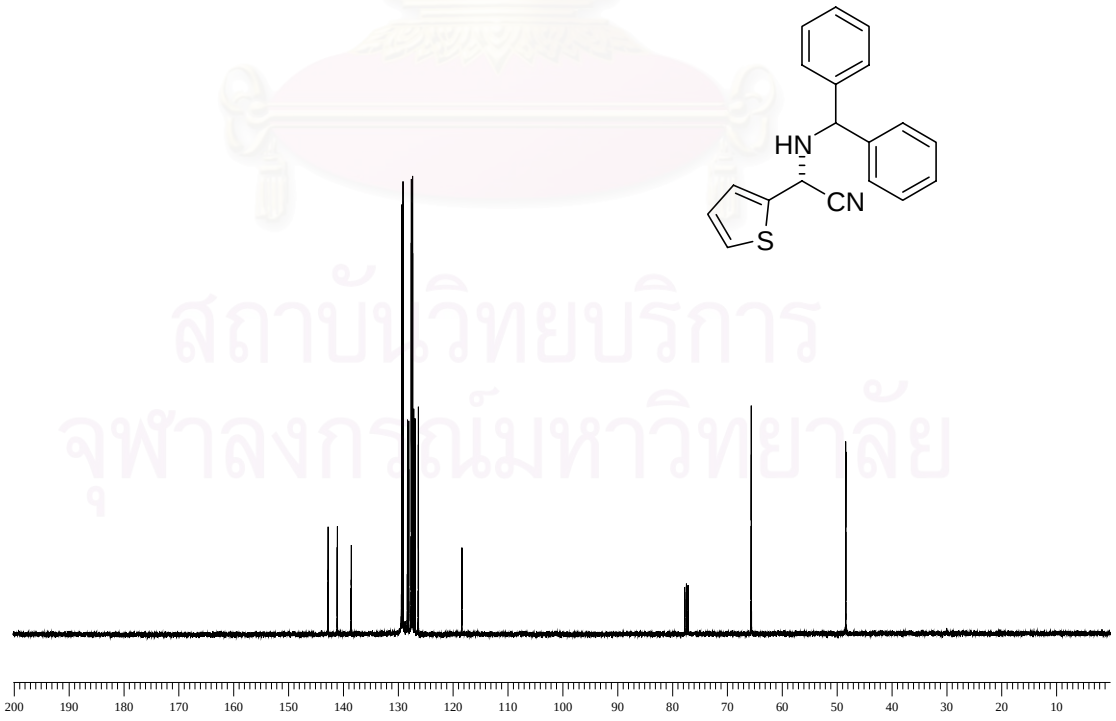


Figure 120 ^{13}C NMR of (*R*)-diphenylmethylamino-thiophen-2-ylacetonitrile **(73q)**

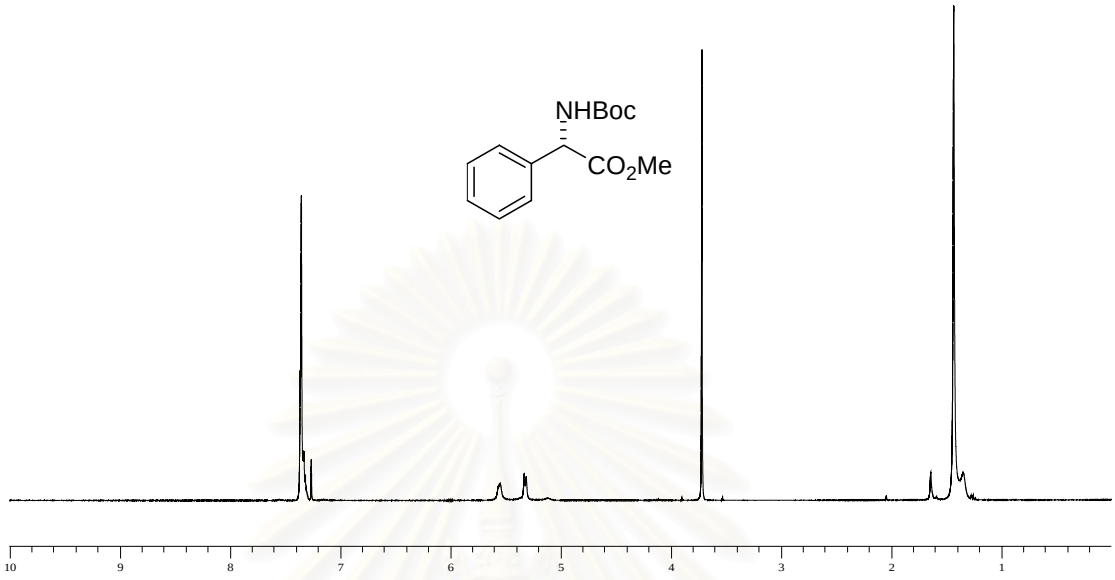


Figure 121 ^{1}H NMR of *N*-Boc-(*S*)-phenylglycine methyl ester **(116a)**

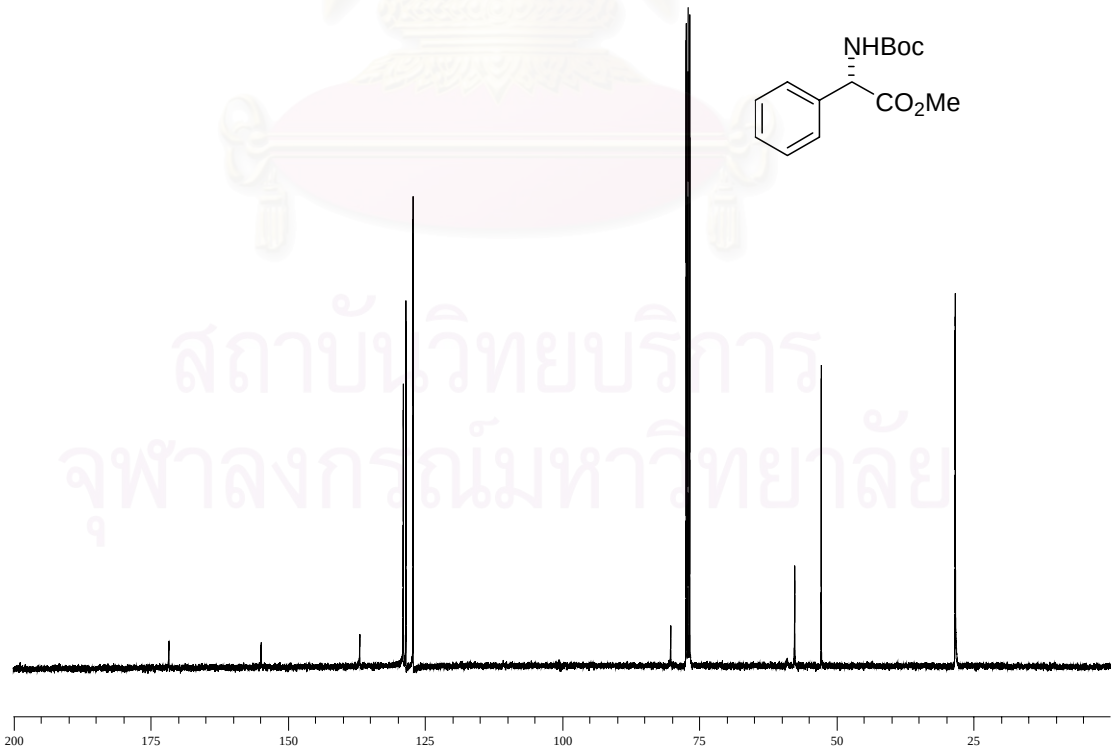


Figure 122 ^{13}C NMR of *N*-Boc-(*S*)-phenylglycine methyl ester **(116a)**

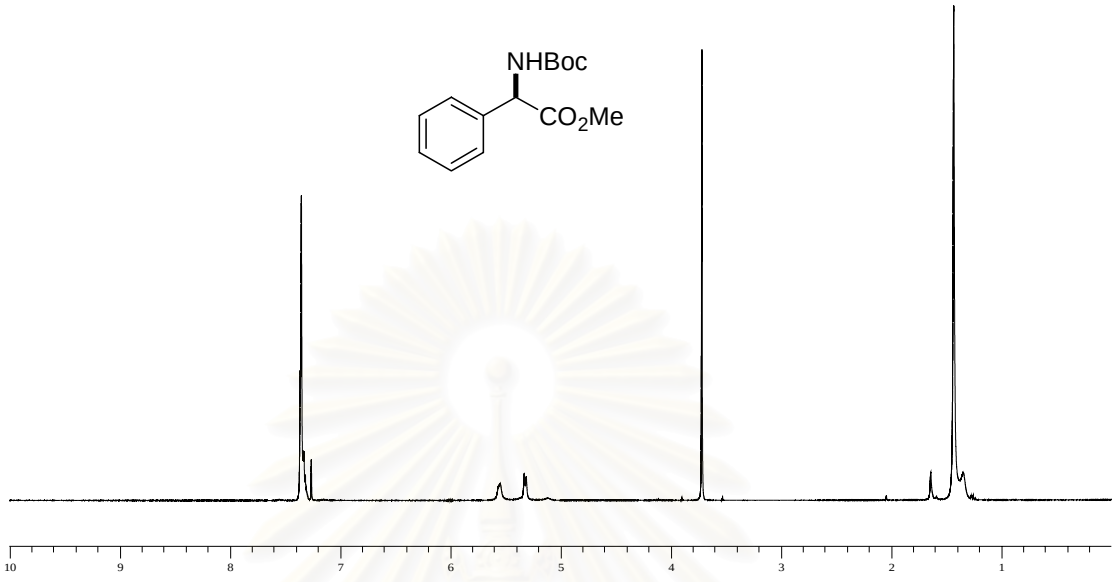


Figure 123 ^{1}H NMR of *N*-Boc-(*R*)-phenylglycine methyl ester **(116a)**

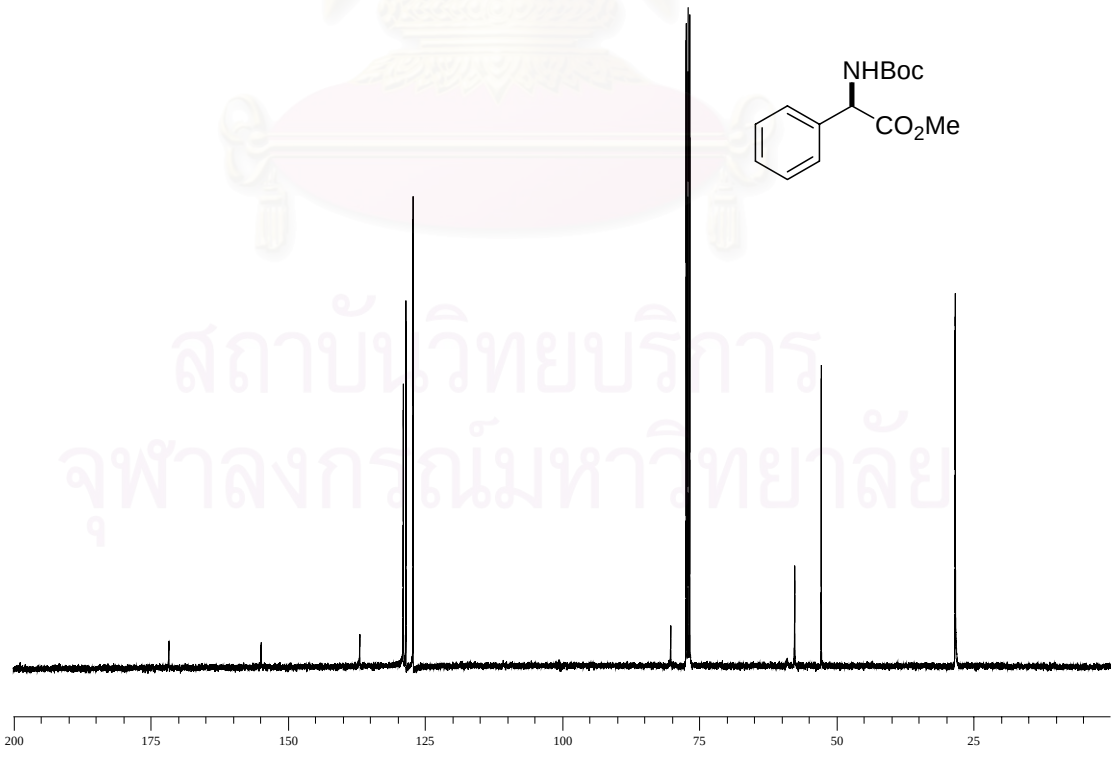


Figure 124 ^{13}C NMR of *N*-Boc-(*R*)-phenylglycine methyl ester **(116a)**

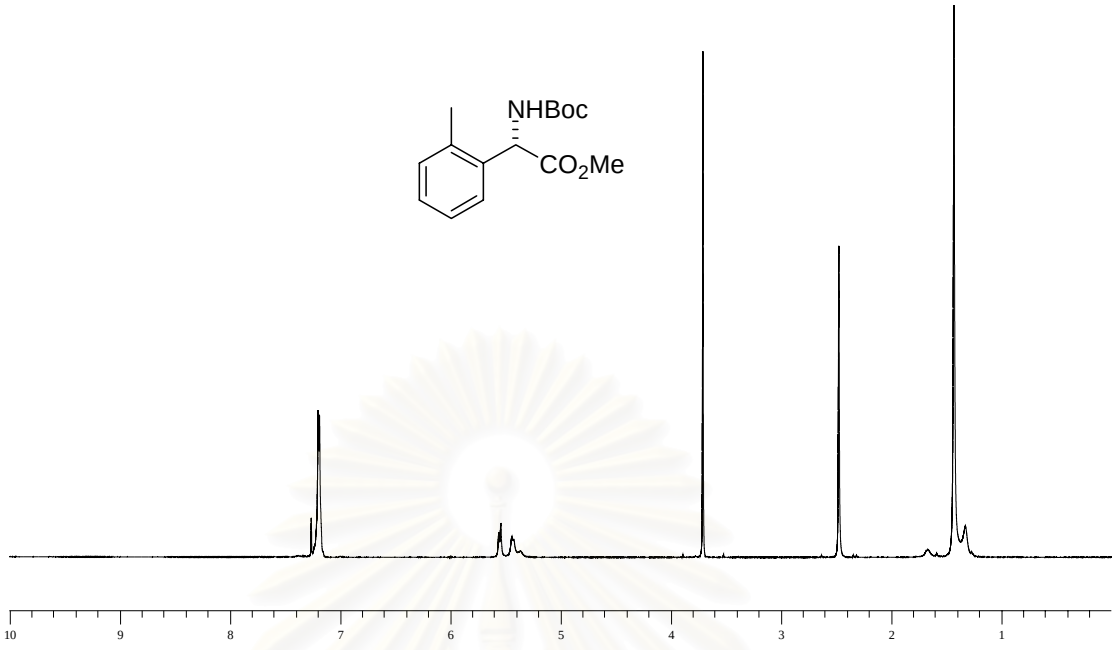


Figure 125 ^{1}H NMR of *N*-Boc-(*S*)-2-methylphenylglycine methyl ester **(116e)**

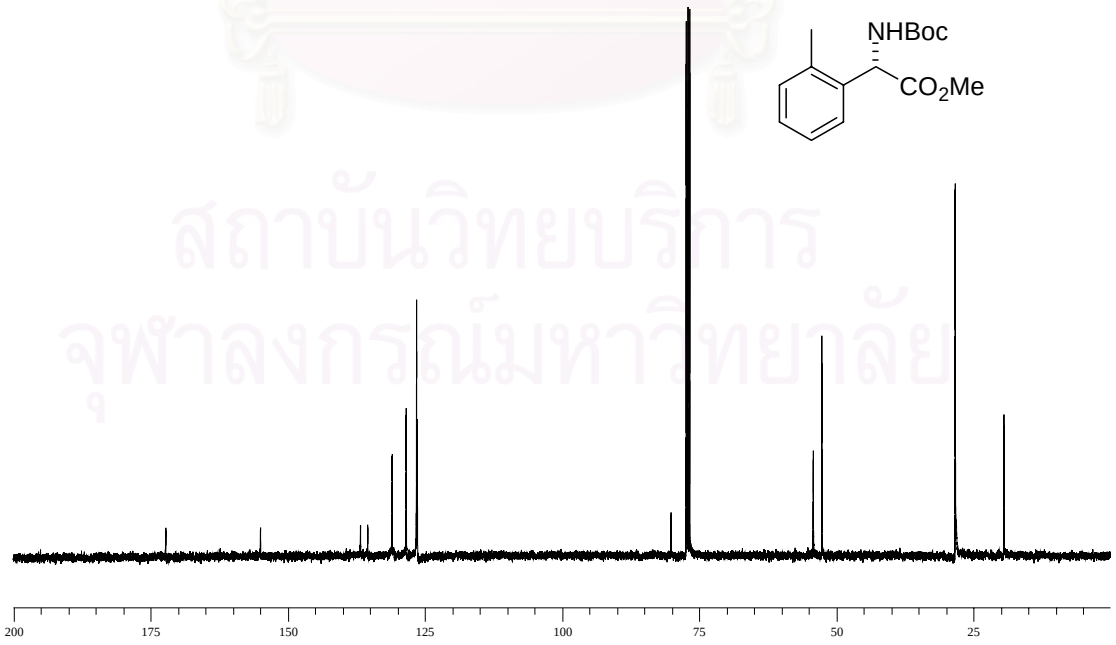


Figure 126 ^{13}C NMR of *N*-Boc-(*S*)-2-methylphenylglycine methyl ester **(116e)**

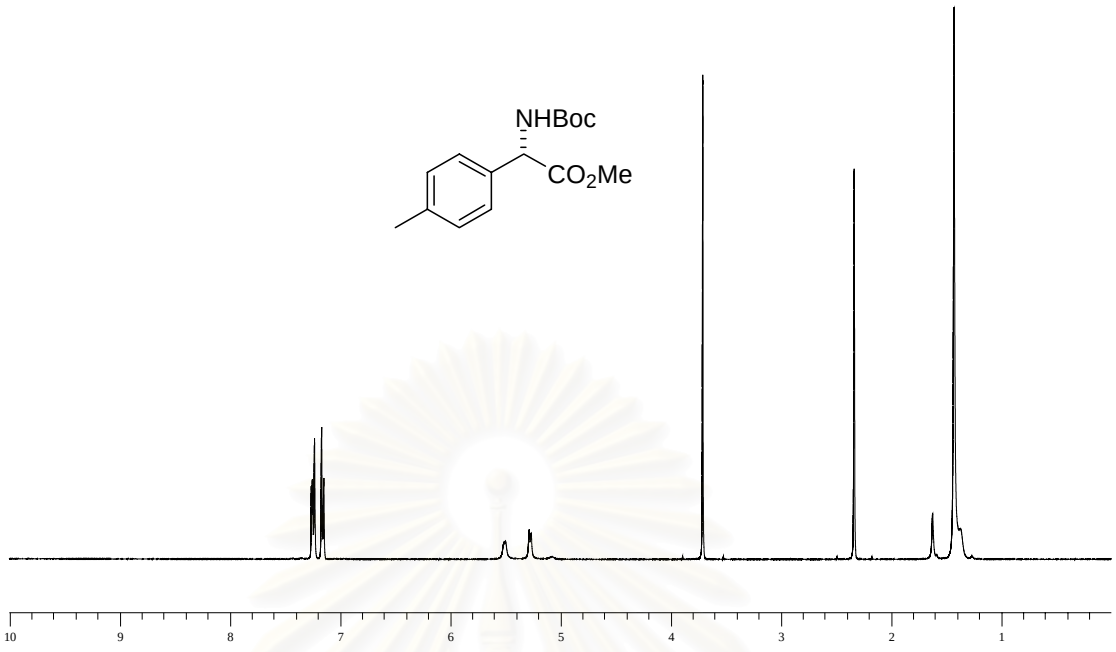


Figure 127 ^{1}H NMR of *N*-Boc-(*S*)-4-methylphenylglycine methyl ester **(116f)**

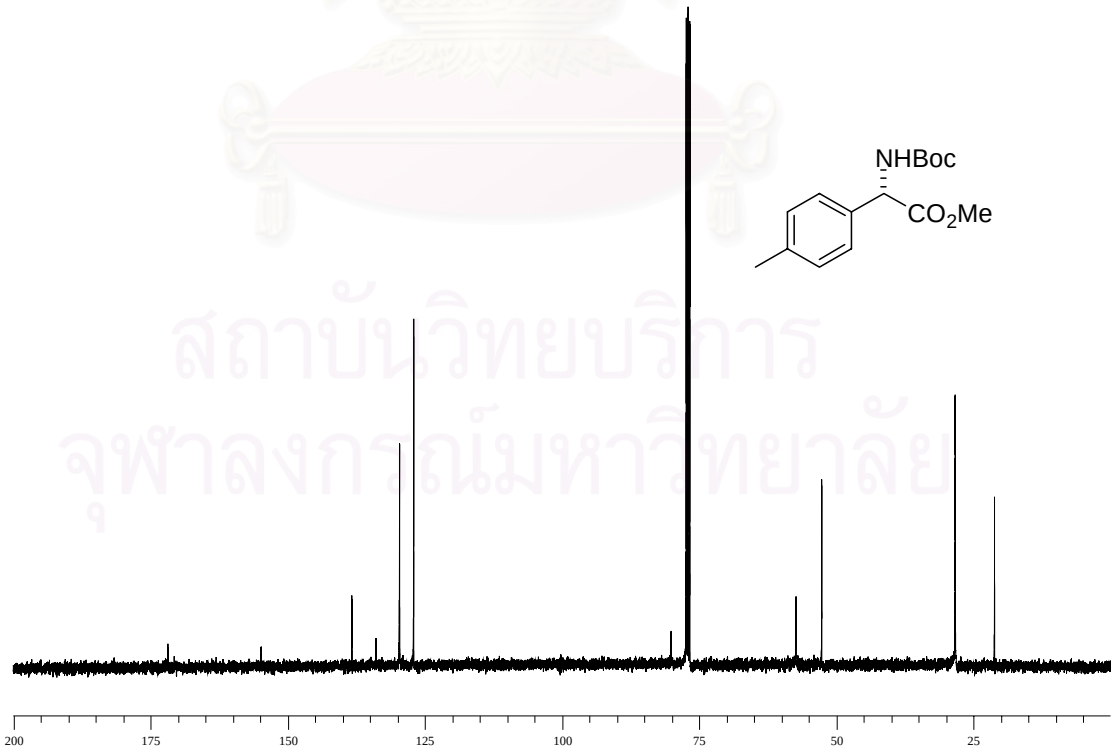


Figure 128 ^{13}C NMR of *N*-Boc-(*S*)-4-methylphenylglycine methyl ester **(116f)**

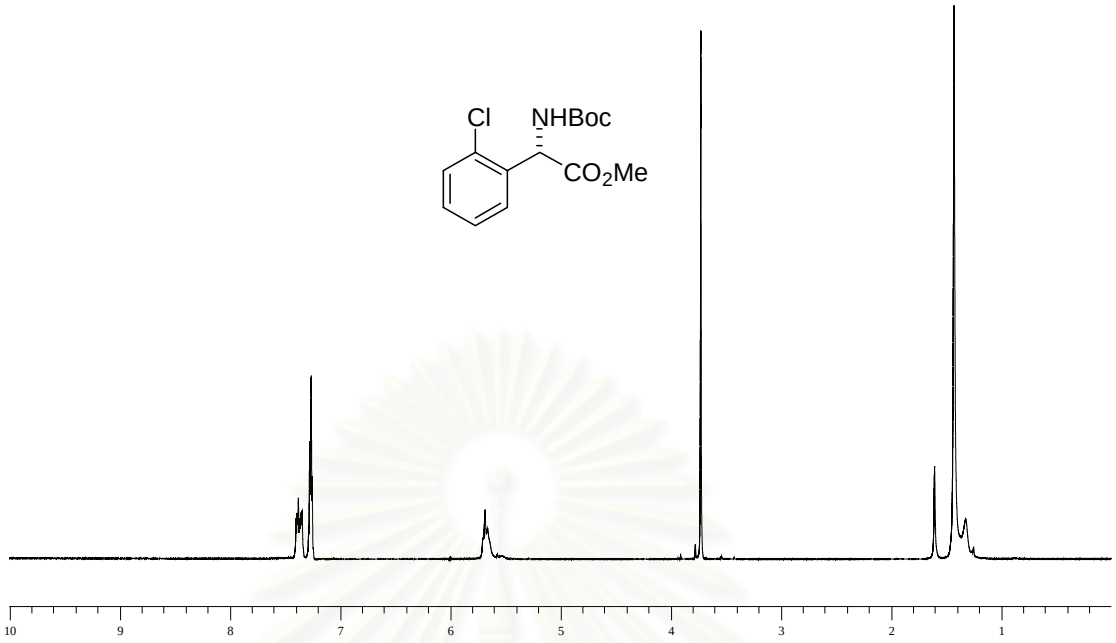


Figure 129 ^{1}H NMR of *N*-Boc-(*S*)-2-chlorophenylglycine methyl ester **(116i)**

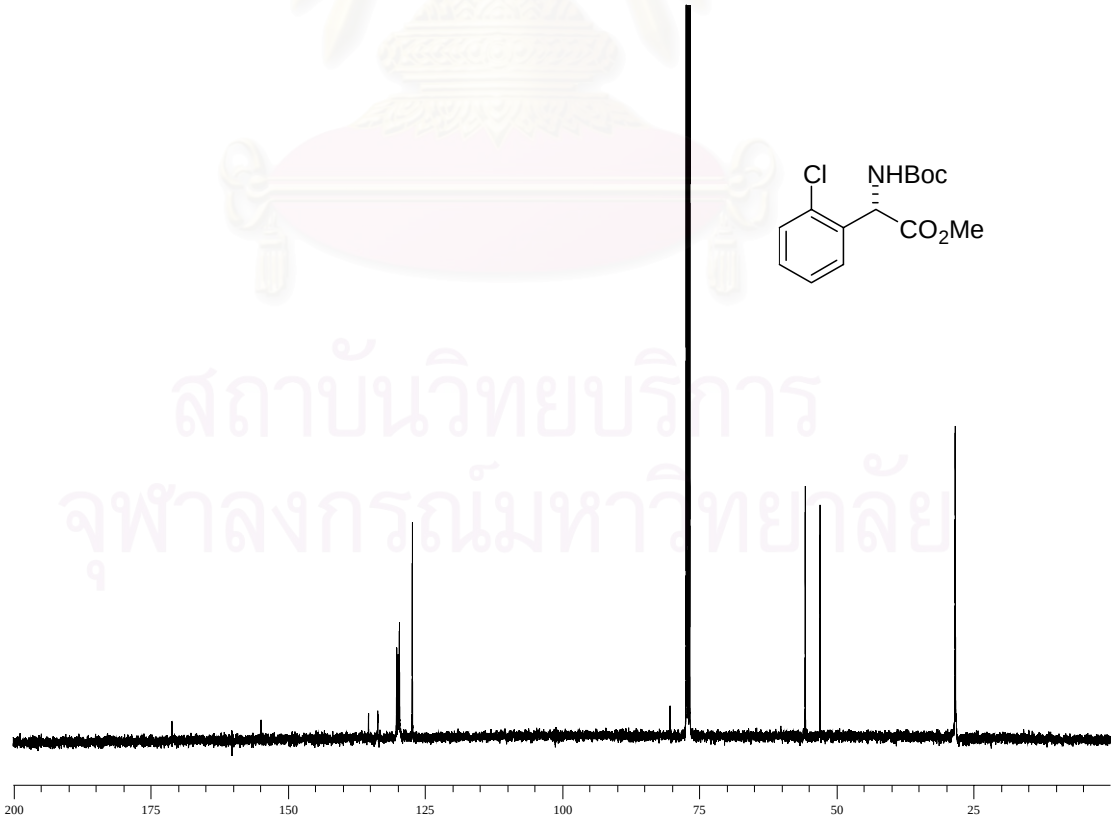


Figure 130 ^{13}C NMR of *N*-Boc-(*S*)-2-chlorophenylglycine methyl ester **(116i)**

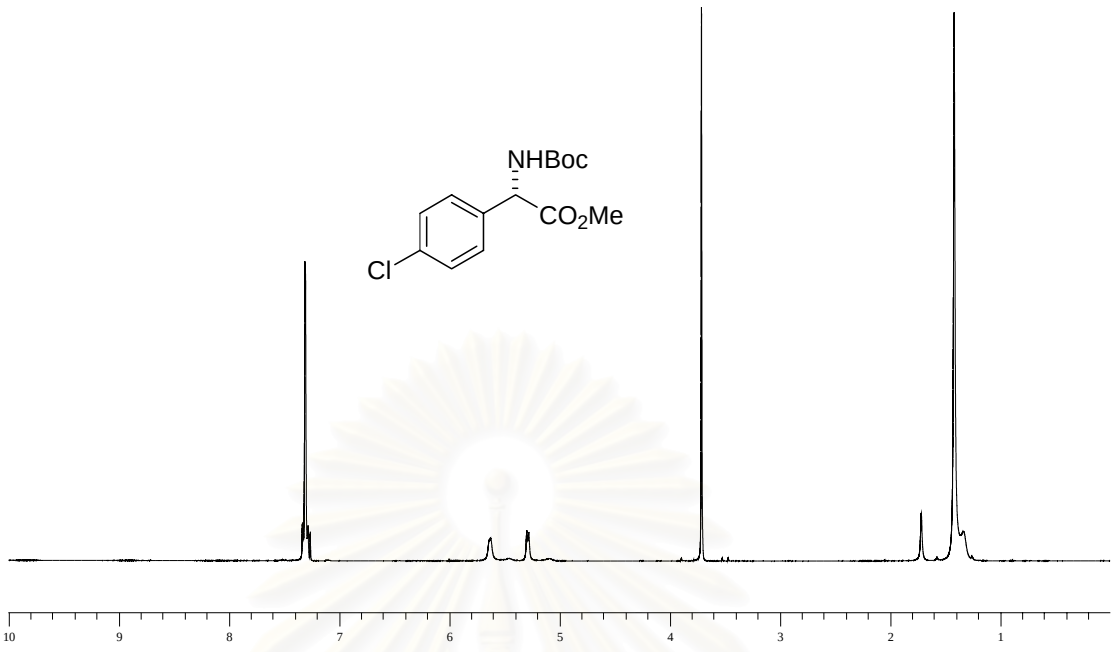


Figure 131 ^{1}H NMR of *N*-Boc-(*S*)-4-chlorophenylglycine methyl ester **(116j)**

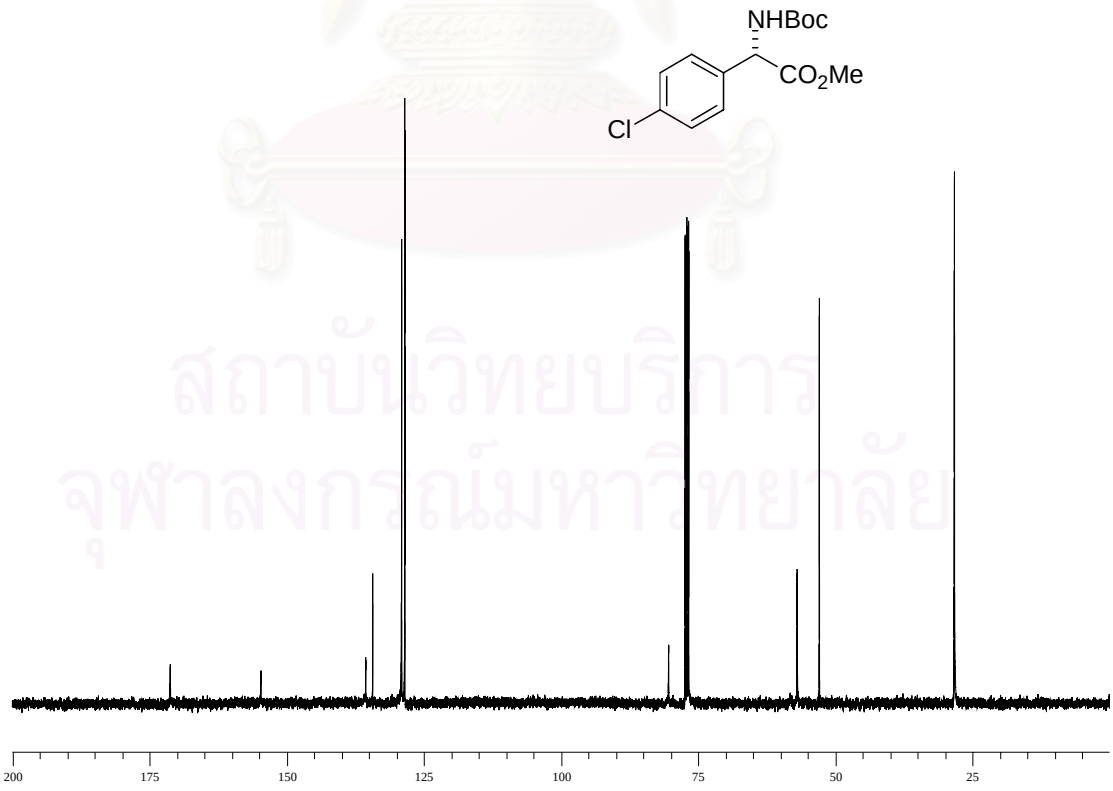


Figure 132 ^{13}C NMR of *N*-Boc-(*S*)-4-chlorophenylglycine methyl ester **(116j)**

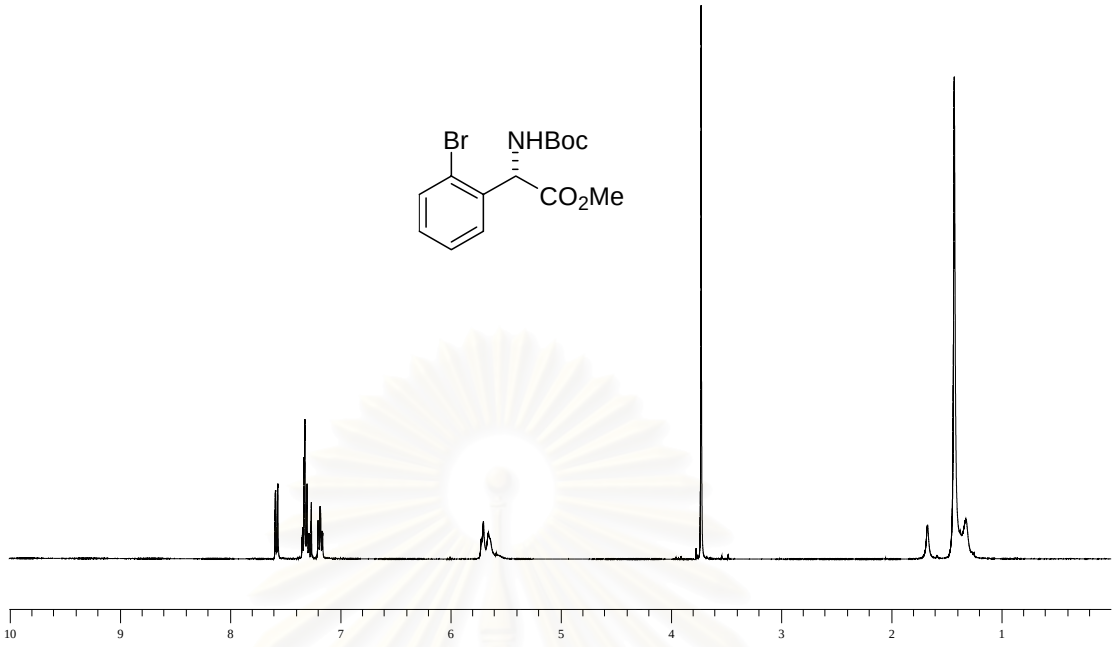


Figure 133 ^{1}H NMR of *N*-Boc-(*S*)-2-bromophenylglycine methyl ester **(116k)**

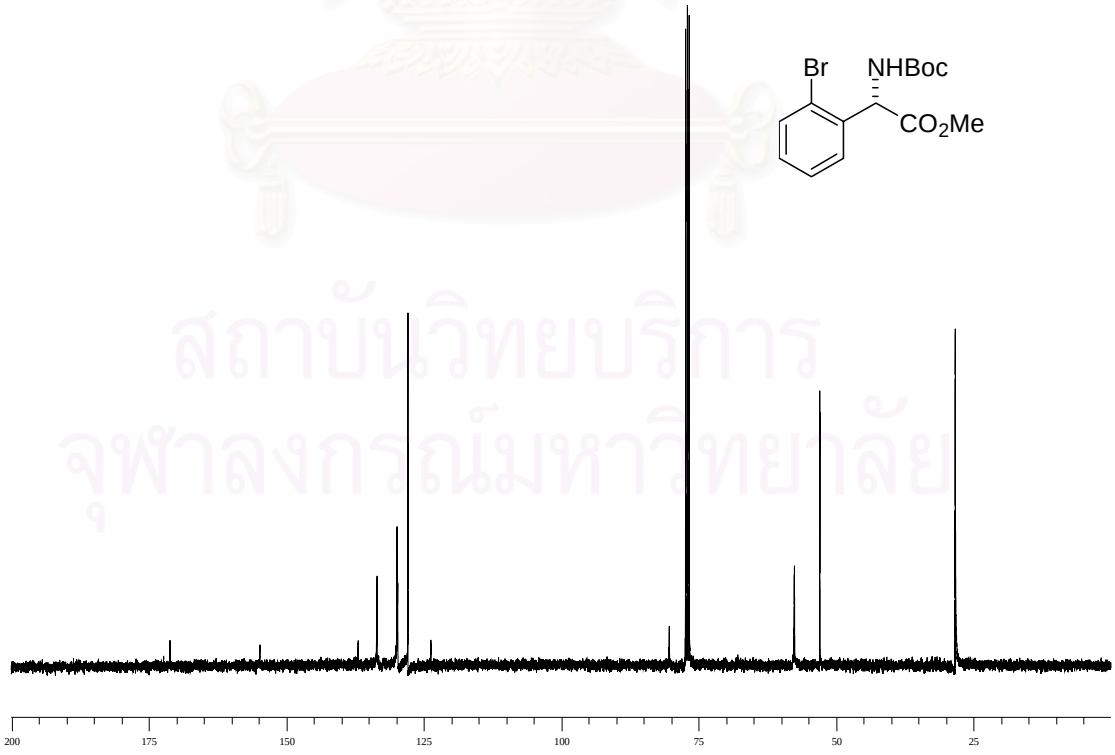


Figure 134 ^{13}C NMR of *N*-Boc-(*S*)-2-bromophenylglycine methyl ester **(116k)**

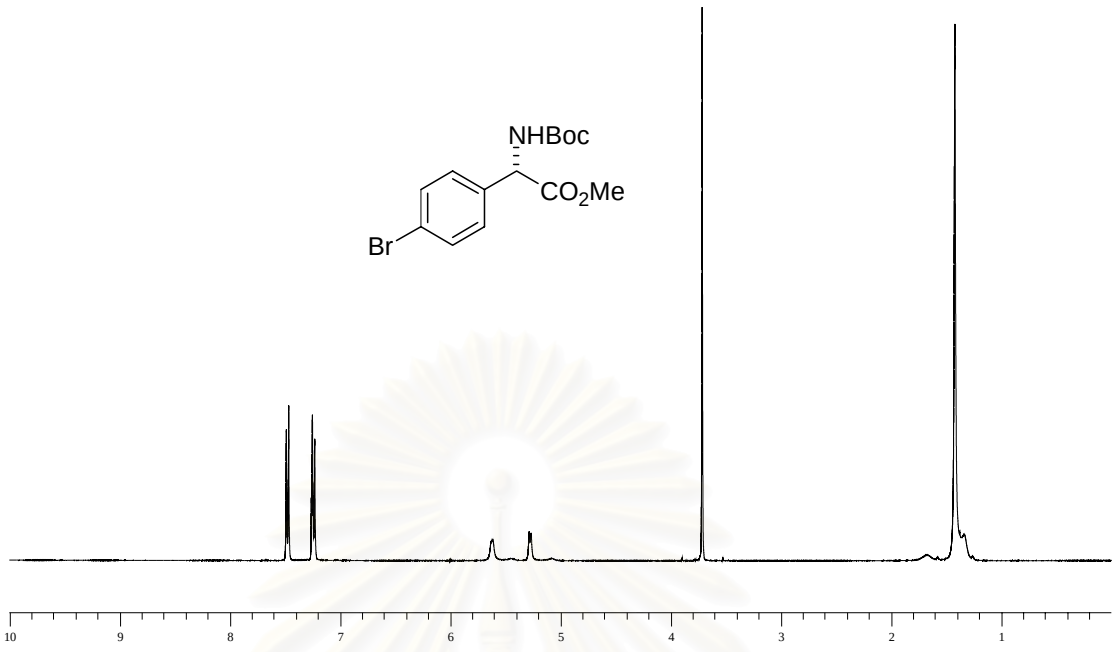


Figure 135 ^{1}H NMR of *N*-Boc-(*S*)-4-bromophenylglycine methyl ester **(116l)**

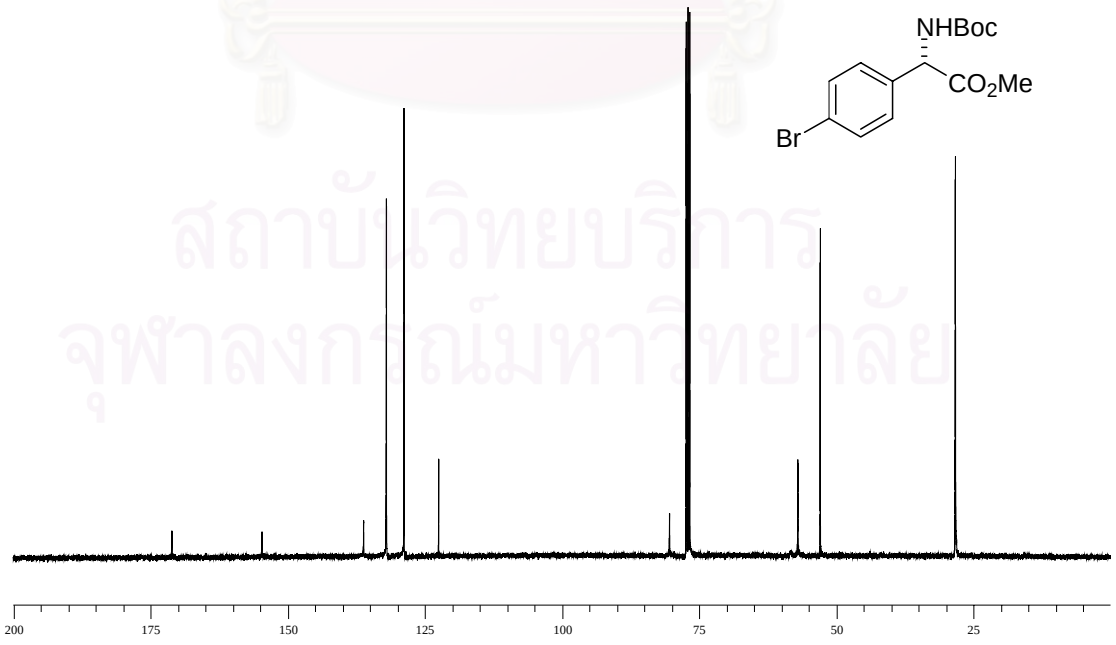


Figure 136 ^{13}C NMR of *N*-Boc-(*S*)-4-bromophenylglycine methyl ester **(116l)**

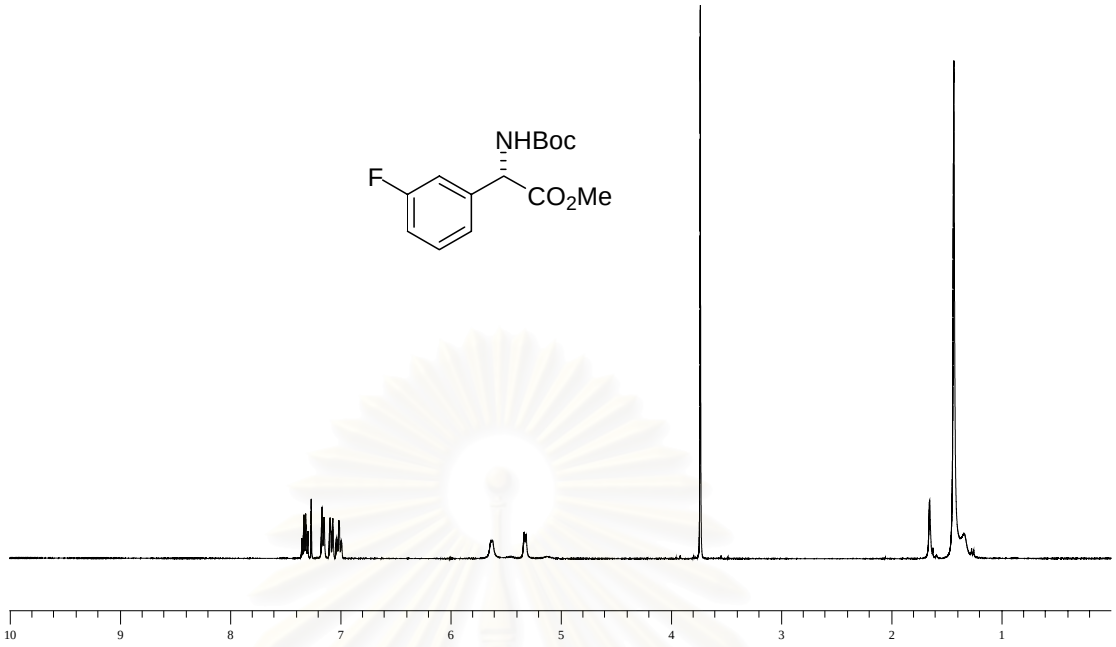


Figure 137 ^{1}H NMR of *N*-Boc-(*S*)-3-fluorophenylglycine methyl ester **(116m)**

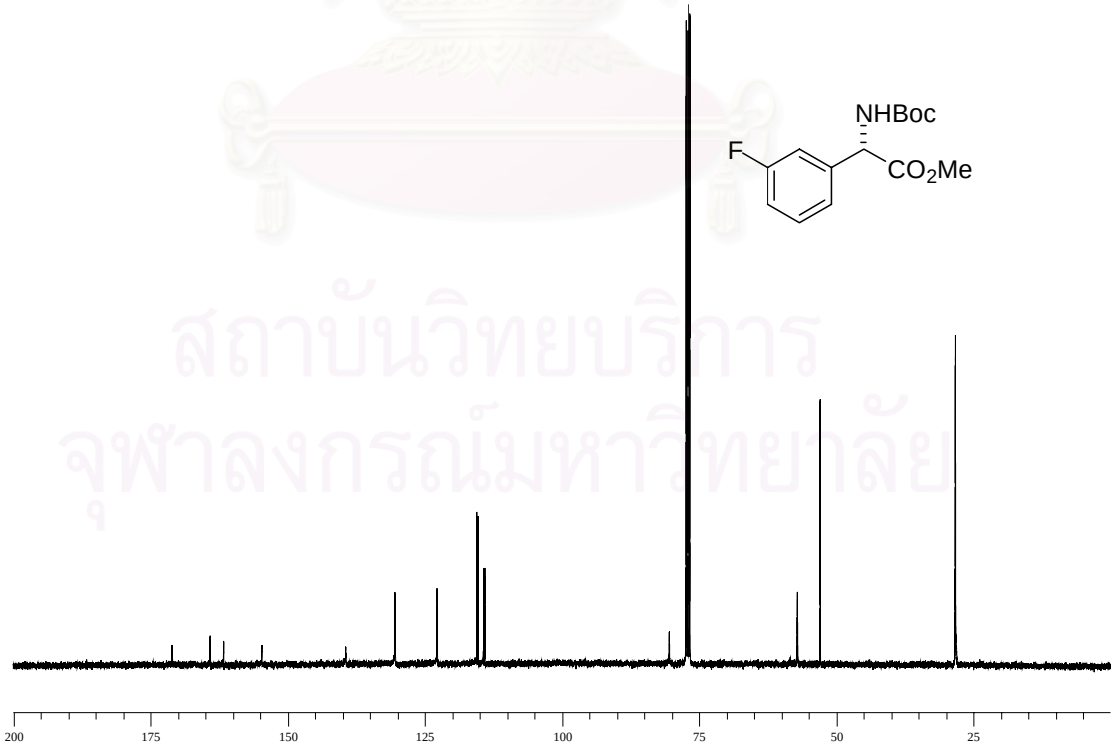


Figure 138 ^{13}C NMR of *N*-Boc-(*S*)-3-fluorophenylglycine methyl ester **(116m)**

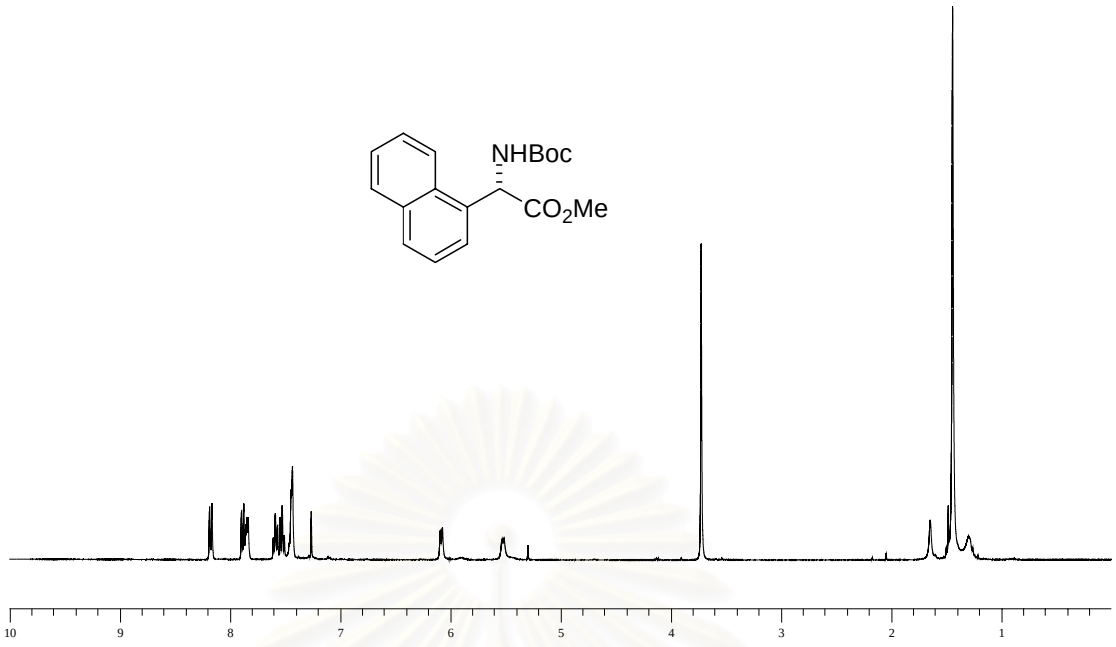


Figure 139 ^{1}H NMR of *N*-Boc-(*S*)-1-naphthylglycine methyl ester **(116n)**

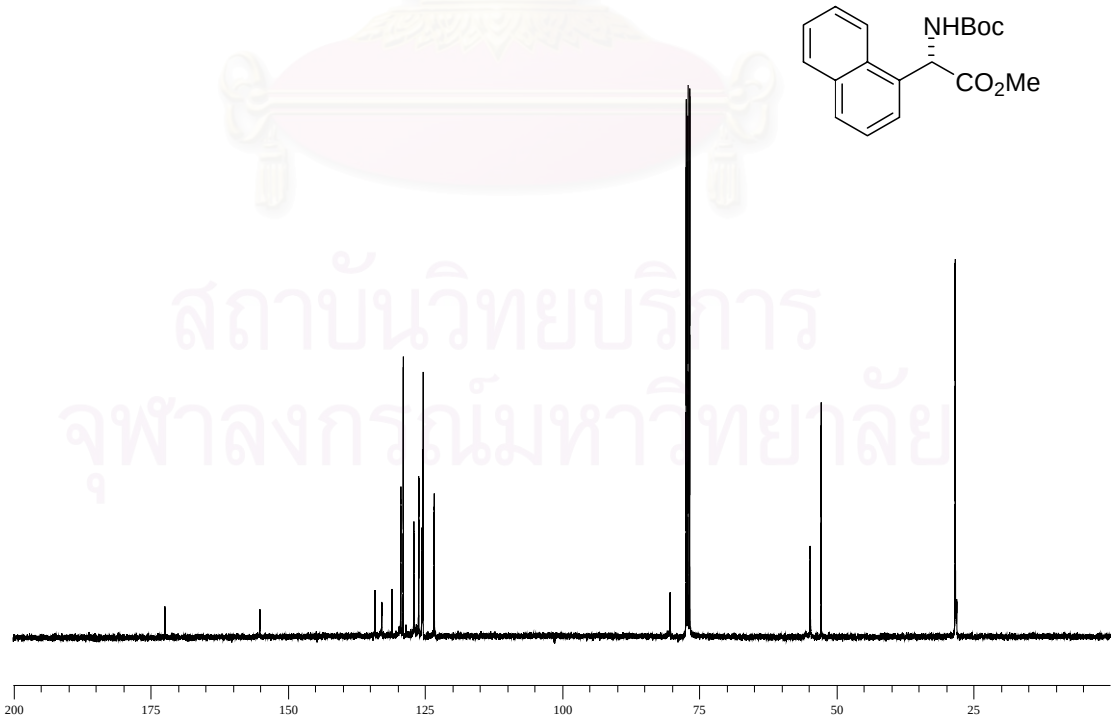


Figure 140 ^{13}C NMR of *N*-Boc-(*S*)-1-naphthylglycine methyl ester **(116n)**

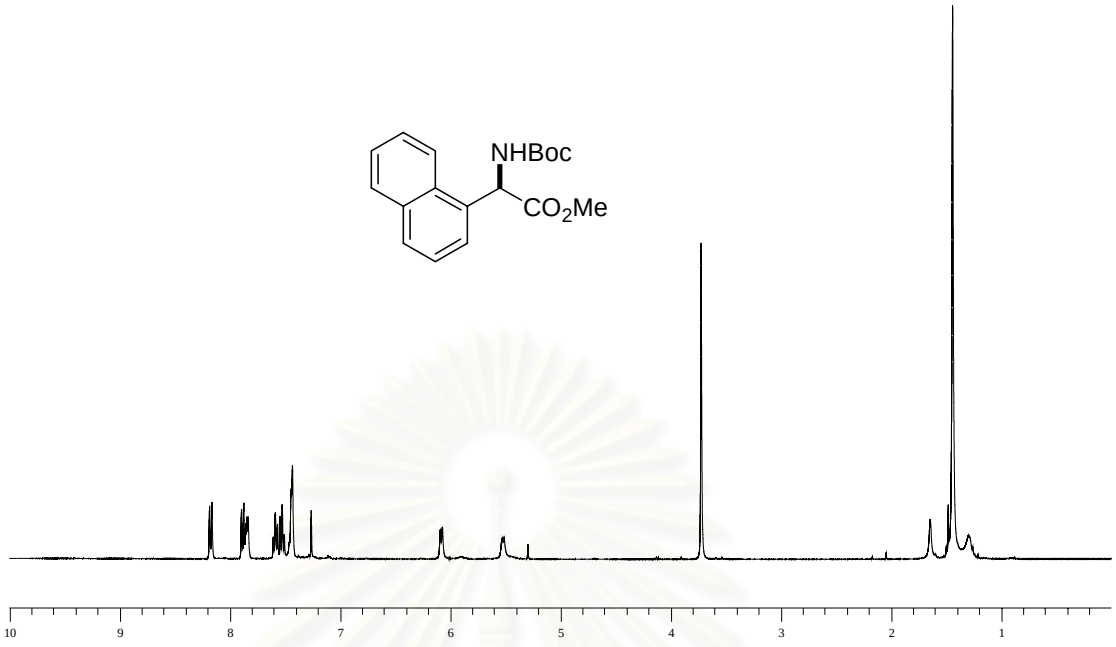


Figure 141 ^{1}H NMR of *N*-Boc-(*R*-1-naphthylglycine methyl ester **(116n)**

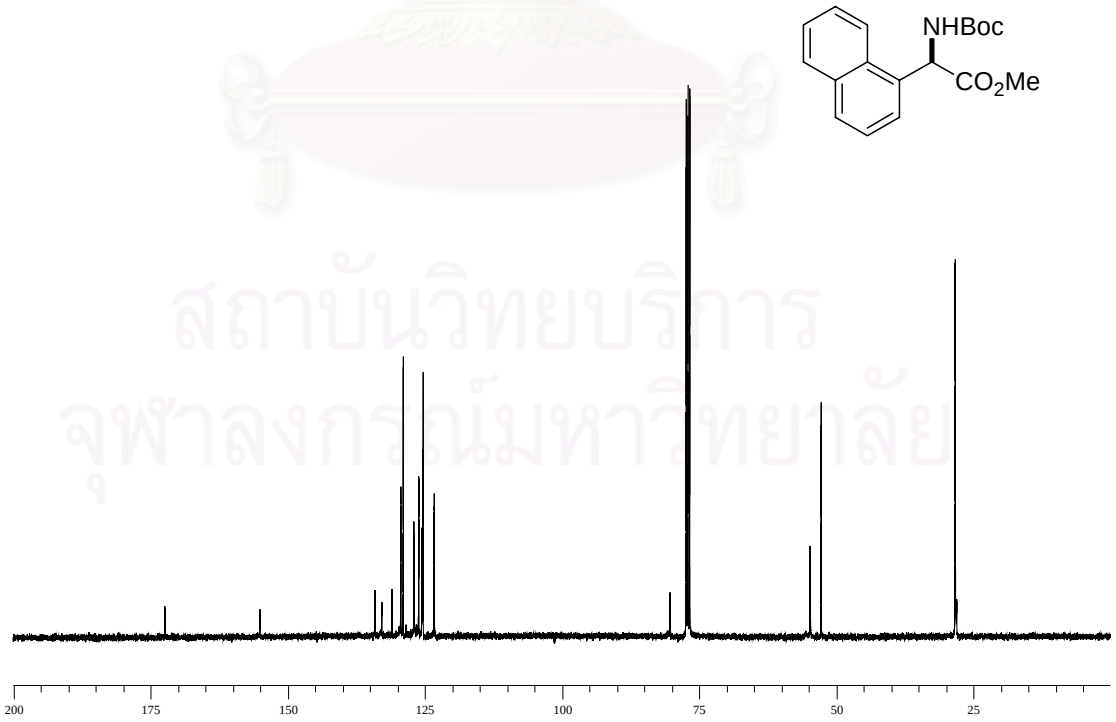


Figure 142 ^{13}C NMR of *N*-Boc-(*R*)-1-naphthylglycine methyl ester **(116n)**

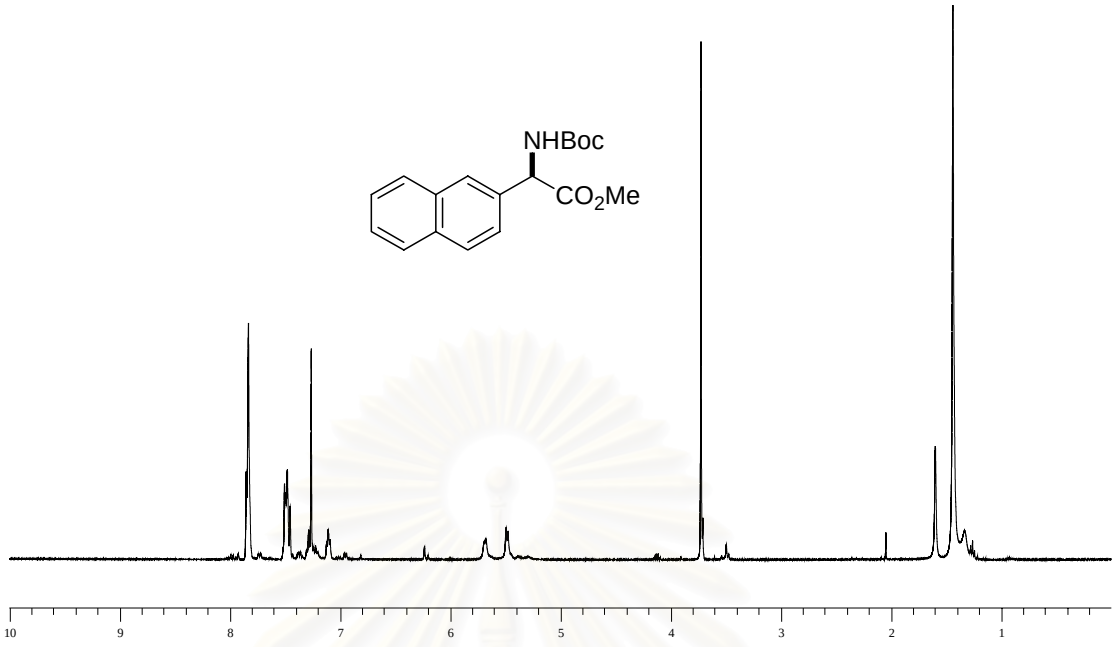


Figure 143 ^{1}H NMR of *N*-Boc-(*S*)-2-naphthylglycine methyl ester **(116o)**

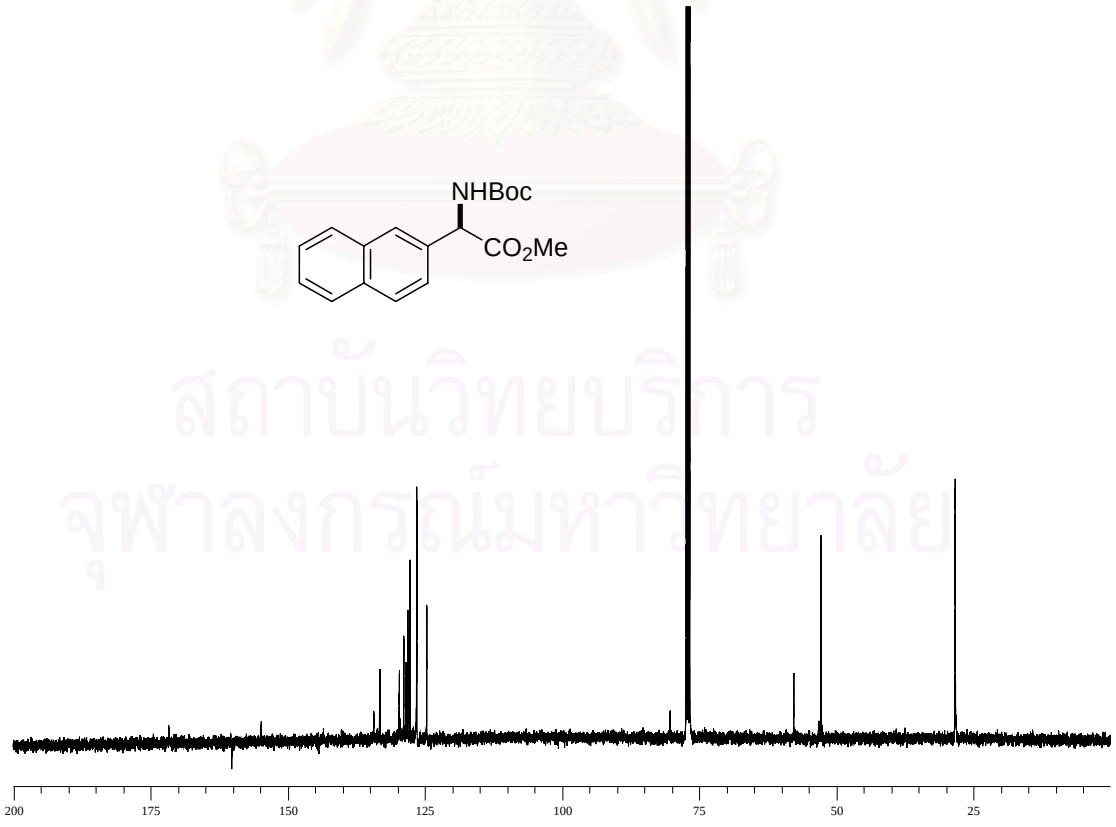


Figure 144 ^{13}C NMR of *N*-Boc-(*S*)-2-naphthylglycine methyl ester **(116o)**

CURRICULUM VITAE

Mr. Vorawit Banphavichit was born on January 31st, 1980 in Bangkok, Thailand. He received a Bachelor Degree of Science with second class honors, majoring in Chemistry from Chulalongkorn University in 2001. Since 2001, he has been graduate student studying Organic Chemistry as his major course at Chulalongkorn University. During his studies towards the Ph.D. program, he has been awarded the Royal Golden Jubilee Scholarship by Thai government during 2004-2006 and supported by a research grant for his Ph.D. program from the Graduate School, Chulalongkorn University, Chulalongkorn University's Radchadapisek Endowment fund and The Thailand Toray Science Foundation. In 2002, he received The Tab foundation Scholarship. He has also been an author of textbooks in Chemistry for high school students since 2003. His research was presented in Associate, the 30th "Science and Technology for Society and Knowledge-based Economy", October 2004. He has collaborated with Professor Kevin Burgess as visiting scholar at Texas A&M University, United State of America during 2005-2006. In 2006-2008, he has received the post doctoral scholarship and collaborated with Professor Yasufumi Ohfune at Osaka University, Japan.

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