รายงานวิจัยฉบับสมบูรณ์

โครงการ

ปฏิกิริยาการเติมด้วยนิวคลีโอไฟล์ของสารประกอบอิมมีนแบบอะซิมเมตริก

(Asymmetric Nucleophilic Addition to Imines)

โดย

นางสาววรวรรณ พันธุมนาวิน

ภาควิชาเคมี คณะวิทยาศาสตร์

จุฬาลงกรณ์มหาวิทยาลัย

17 มีนาคม 2551

สัญญาเลขที่ TRG4580050

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สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

กิตติกรรมประกาศ

ผู้วิจัยขอกราบขอบพระคุณ ศาสตราจารย์ ดร. สมศักดิ์ รุจิรวัฒน์ นักวิจัยที่ปรึกษาที่ได้กรุณาให้ข้อคิดเห็น ให้การสนับสนุนทั้งทางด้านวิชาการ การบริหารโครงการ การสร้างเครือข่ายวิจัย และด้านอื่นๆ ตลอดมา และขอขอบคุณสำนักงานกองทุนสนับสนุนการวิจัย (สกว.) ที่ได้จัดสรรทุนให้ รวมทั้งกรุณาชี้แนะและติดตามการทำวิจัยมาโดยตลอด แม้เมื่อผู้วิจัยมีข้อขัดข้อง ทาง สกว. ก็ยังคงให้การสนับสนุนเสมอมา

นอกจากนี้ ขอขอบคุณจุฬาลงกรณ์มหาวิทยาลัยที่อนุเคราะห์สถานที่ และปัจจัยสนับสนุนด้านเครื่องมือ รวมถึงสาธารณูปโภคทุกด้าน และขอขอบคุณผู้ร่วมวิจัยทุกท่านทั้งคณาจารย์และนิสิตบัณฑิตศึกษา

บทคัดย่อ

รหัสโครงการ : TRG4580050

ชื่อโครงการ : ปฏิกิริยาการเติมด้วยนิวคลีโอไฟล์ของสารประกอบอิมมีนแบบอะซิมเมตริก

ชื่อนักวิจัย : ผู้ช่วยศาสตราจารย์ ดร. วรวรรณ พันธุมนาวิน
ภาควิชาเคมี คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

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ได้สังเคราะห์อนุพันธ์ของซาลิซิลิมีนลิแกนด์ชนิดใหม่ ซึ่งประกอบด้วยส่วนของซาลิซิลัลดีไฮด์ แอลฟาอะมิโนแอซิด และไครัลเอมีน และได้ศึกษาสมบัติการเร่งปฏิกิริยาและการเลือกเกิดอิแนนทิโอเมอร์ของลิแกนด์เหล่านี้ในปฏิกิริยาสเตรคเกอร์แบบอสมมาตร พบว่า *N*-(3,5)-di-*tert*-butylsalicylyl-(*S*)-leucyl-(*S*)-(1-phenyl-ethyl)amine (**(S,S)-S2-Leu-A1**) และ *N*-(3,5)-di-*tert*-butylsalicylyl-(*S*)-leucyl-(*S*)-(1-naphthyl-ethyl)amine (**(S,S)-S2-Leu-A2**) เป็นลิแกนด์ที่ให้การเลือกเกิดอิแนนชิโอเมอร์สูงสุดเมื่อใช้เร่งปฏิกิริยาการเติมไซยาไนด์ของอะโรมาติกอิมมีนที่ไม่มีหมู่แทนที่แบบให้อิเล็กตรอนที่ตำแหน่งออร์โทและพาราโดยมีไทเทเนียมเตตระไอโซโพรพอกไซด์อยู่ร่วมในปฏิกิริยาด้วย กลไกการเร่งปฏิกิริยาเชื่อว่าเกิดผ่านสารประกอบเชิงซ้อนระหว่างซาลิซิลิมีนกับไทเทเนียม ซึ่งมีหมู่แทนที่ที่อยู่บนซาลิซิลัลดีไฮด์และไครัลเอมีนวางตัวในตำแหน่งที่สามารถควบคุมการเข้าชนของไซยาไนด์ไอออน โดยที่คอนฟิกุเรชันของผลิตภัณฑ์ถูกกำหนดโดยคอนฟิกุเรชันของส่วนไครัลเอมีนมากกว่าส่วนที่เป็นอะมิโนแอซิด และความเกะกะของหมู่แทนที่บนวงซาลิซิลัลดีไฮด์มีผลต่อการเลือกเกิดอิแนนชิโอเมอร์อย่างมาก

นอกจากนั้นยังได้ทดลองใช้ตัวเร่งปฏิกิริยากลุ่มดังกล่าวในการสังเคราะห์สารประกอบแอลฟ่าอะมิโนฟอสโฟเนตแบบอะซิมเมตริกผ่านปฏิกิริยาไฮโดรฟอสโฟนิเลชัน แม้ว่าตัวเร่งปฏิกิริยาจะสามารถทำให้ปฏิกิริยาเกิดได้เร็วขึ้นและมีปริมาณผลผลิตในระดับปานกลาง แต่ไม่พบว่าสามารถเหนี่ยวนำให้ปฏิกิริยาดำเนินไปโดยมีการเลือกเกิดอิแนนชิโอเมอร์เดี่ยวได้เลย

คำหลัก : สเตรกเกอร์ / ไฮโดรฟอสโฟนิเลชัน / ซาลิซิลิมีน / ตัวเร่งปฏิกิริยาอสมมาตร

Abstract

Project Code : TRG4580050

Project Title : Asymmetric Nucleophilic Addition to Imines

Investigator : Worawan Bhanthumnavin
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Project Period : 1 July 2002 – 30 June 2004

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

In addition, this class of catalyst had been employed in the synthesis of α-aminophophonates *via* asymmetric hydrophosphonylation. Although the catalyst can accelerate the reaction to a higher rate, no detectable enantioselectivity was observed in the product.

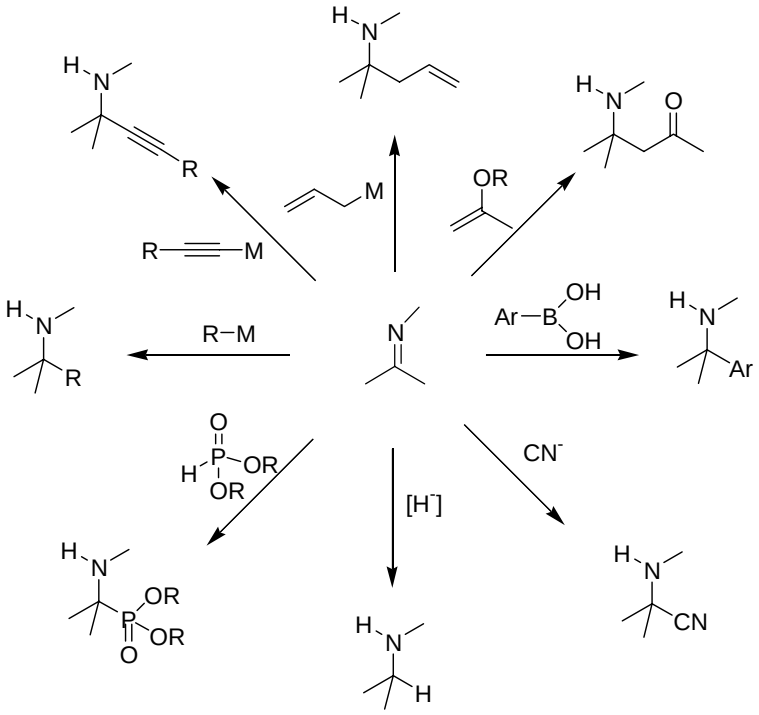
Keywords : Strecker / hydrophosphonylation / Salicylimine / Asymmetric Catalyst

Output จากโครงการวิจัยที่ได้รับทุนจาก สกว.

1. ผลงานตีพิมพ์ในวารสารวิชาการนานาชาติ – อยู่ในระหว่างการส่งเพื่อพิจารณาที่วารสาร Molecule
2. การนำผลงานวิจัยไปใช้ประโยชน์
   - เชิงสาธารณะ – ได้สร้างความร่วมมือกับนักวิจัยที่สถาบันวิจัยจุฬาภรณ์
   - เชิงวิชาการ – ได้นำองค์ความรู้ที่ได้ไปบรรจุเป็นเนื้อหาส่วนหนึ่งในรายวิชา Asymmetric Synthesis
3. อื่นๆ (เช่น หนังสือ การจดสิทธิบัตร) – ไม่มี

1. INTRODUCTION

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



This work deals mainly with the synthesis and applications of a new class of optically active dipeptide ligands on asymmetric addition of cyanide ion to imines as well as asymmetric hydrophosphonylation to imines. Focus will be placed upon this particular class of ligands and these two types of reaction to generate chiral α-amino acids and α-aminophosphonates. Other topics, such as organocatalysis and other types of nucleophiles, are beyond the scope of this work.

1.1 α-amino acids

Proteins are main constituents of body organs such as muscles, skin, hair, and nails. They carry all vital life processes in the human system. The basic chemical units of proteins are α-amino acids. The structures of most α-amino acids consist of a chiral carbon atom (the α-carbon), which is bonded to an amino group (-NH_2), a carboxyl group (-COOH), and a hydrogen atom. Because the α-carbon of an α-amino acid is an asymmetric carbon, each α-amino acid

can exist as two enantiomers. The two mirror images are called the L-isomer and the D-isomer. The amino acids present in living systems are almost exclusively L-isomers. The exceptions are a few D-amino acids present in the antibiotics produced by fungi.

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

1.1.2 Strecker α-amino acid synthesis

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

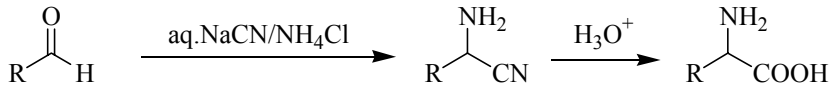


Figure 1.1 Classical Strecker synthesis of α-amino acids.

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

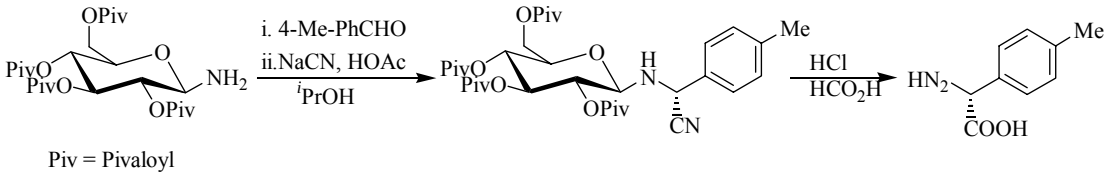


Figure 1.2 A chiral auxiliary for the Strecker synthesis of (*S*)-configured amino acid.

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

1.1.3 Literature review on asymmetric Strecker synthesis

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

1.1.3.1 Guanidine-Based Catalysts

An analogue of guanidine has been shown to catalyze the asymmetric cyanation of aldehydes. In 1990, Inoue and co-workers designed the use of cyclo[(*S*)-phenylalanyl-(*S*)-histidyl], **1** as a chiral catalyst with a histidine imidazole moiety. It was an excellent catalyst for the hydrocyanation reaction of various aldehydes giving good yields of cyanoalcohols with high enantiopurities.[4] However, it failed to afford any asymmetric induction in Strecker synthesis. This

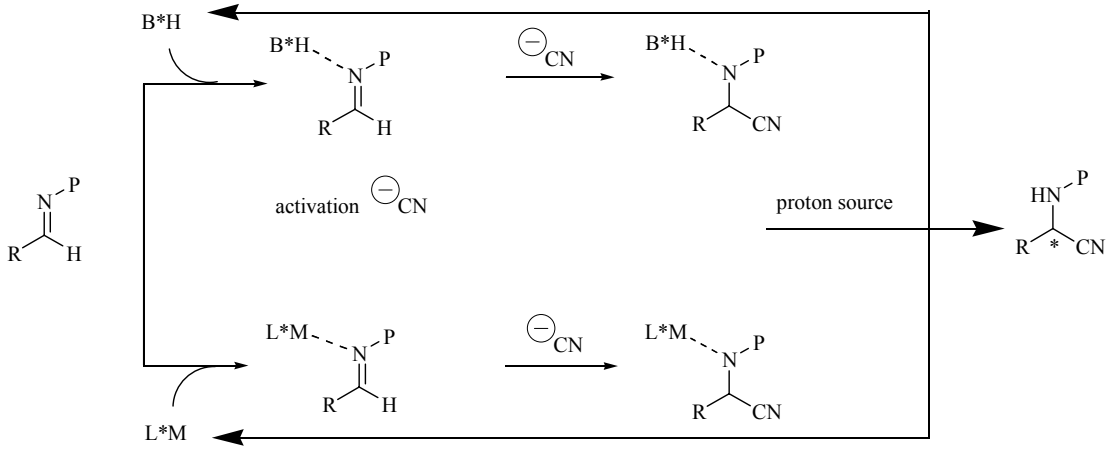
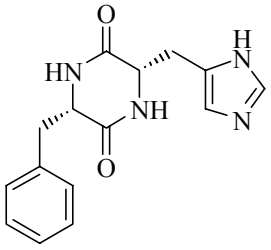
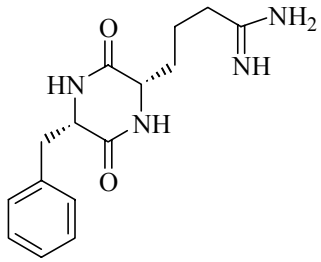


Figure 1.3 Concept of imine activation.

is because the imidazole side chain of **1** accelerated a proton transfer in the reaction of HCN with the putative aldimine intermediate in the Strecker reaction. In 1996, Lipton first demonstrated the use of **2** in a catalytic enantioselective Strecker-type reaction.[5] α-amino nitrile derivative **4** was obtained from *N*-benzhydryl imine **3** by using 2 mol % of (*S*)-α-amino-γ-guanidinobutyric acid **2** (Table 1.1). Excellent % *ee* and yields were obtained with aromatic imine, but low % *ee* was obtained with aliphatic substrates.

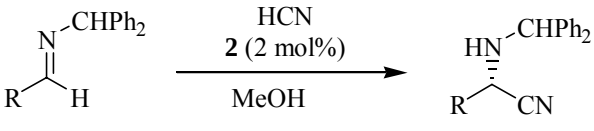


1 cyclo[(*S*)-phenylalanyl-(*S*)-histidyl]



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

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



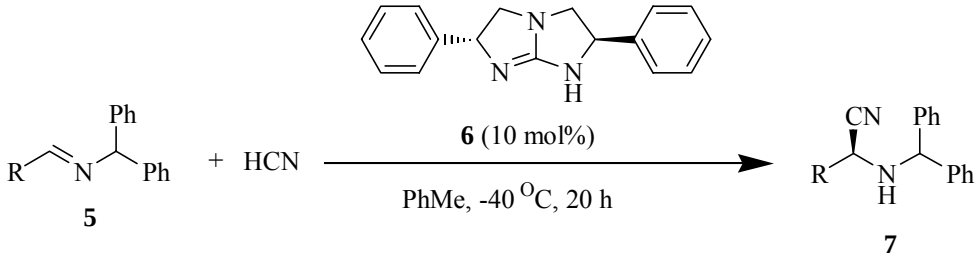
3 **4**

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

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

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

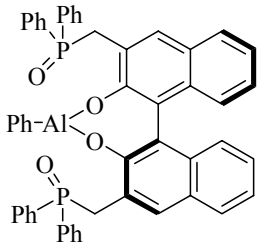
Table 1.2 Conversion of *N*-benzhydryl imines to α-amino nitrile in the presence of **6**.



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

1.1.3.2 BINOL-based Catalysts

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



8

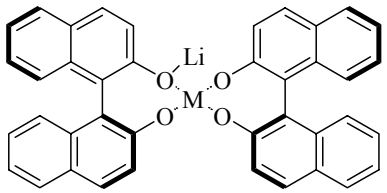
With this catalyst system, *N*-allyl- and *N*-benzhydryl- imines generally gave lower enantioselectivities. The addition of phenol was found to have a beneficial effect on the reaction rates.

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

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

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

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

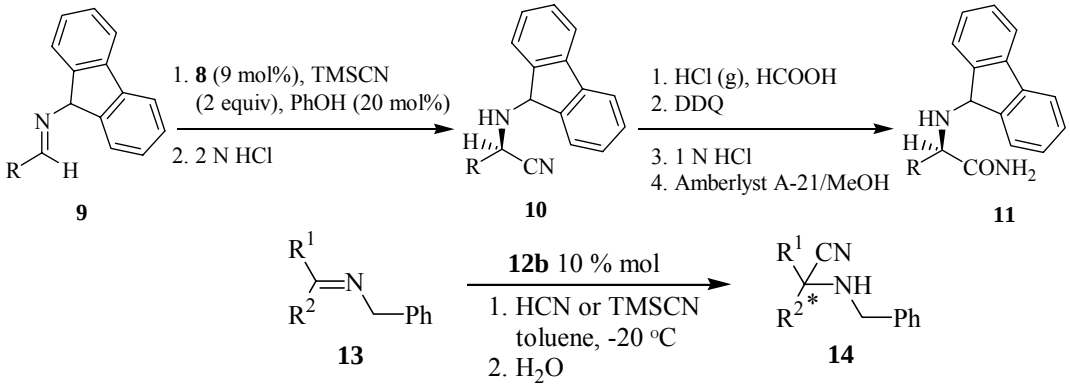


12a : M = Al^{III}
12b : M = Sc^{III}

12

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

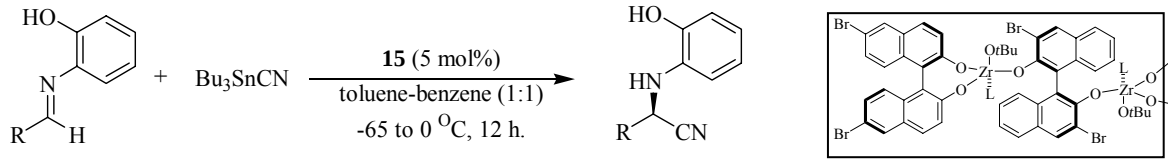
Table 1.4 Asymmetric hydrocyanation of imines catalyzed by Sc[(R)-BINOL]$_2$Li **12b**.



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

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

Table 1.5 Catalytic Asymmetric Strecker-Type Reaction Using Bu_3SnCN.

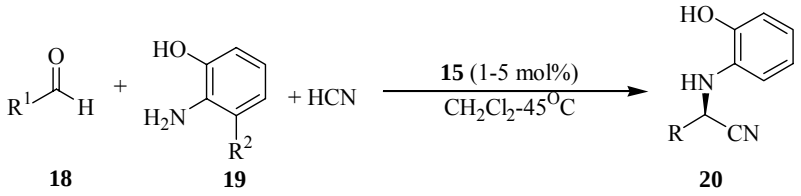


Imine	R	Yield (%)	*ee* (%)
16a	Ph	92	91
16b	1-Nap	98	91
16c		89	92
16d	C_8H_{17}	79	83[a]

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

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

Table 1.6. Catalytic asymmetric Strecker reactions using HCN.



18 **19** **20**

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

1.1.3.3 Salen based catalysts.

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

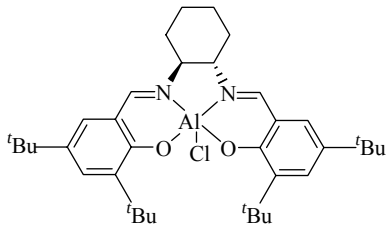


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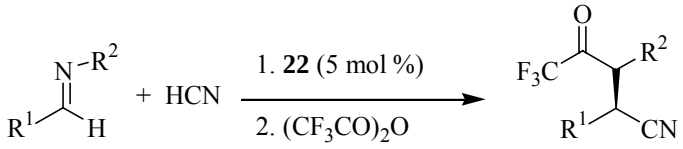
Table 1.7 Jacobsen's catalytic enantioselective Strecker-type reactions.

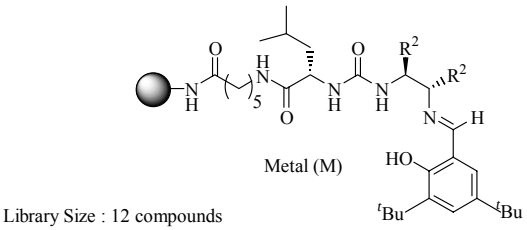


21 **23**

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

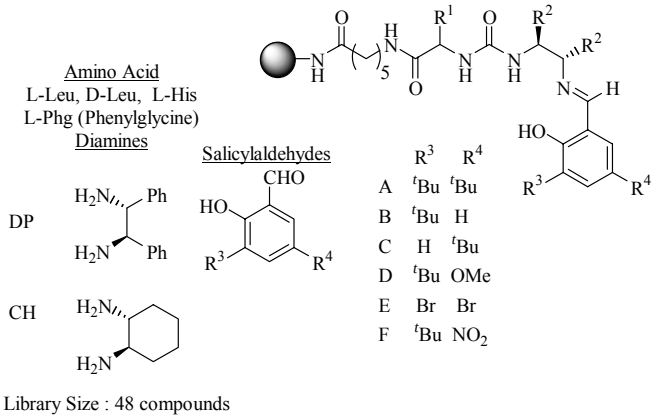
In 1998, Jacobsen and co-workers showed three parallel libraries techniques for screening a known class of chiral half salen ligands which were more effective for the Strecker-type reaction (Figure 1.4).[14] Library 1 was used for evaluating catalytic properties of a series of different metal ions. From this library, it was found that the Schiff base ligand without metal complex provided the best enantioselectivity (19 % *ee*). Libraries 2 and 3 were used to screen the ligand components, amino acid units, stereochemistry, and substituents. From the library screening they found **24** to be the best ligand with the highest enantioselectivity (Table 1.8).

Library 1



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

Library 2



Library 3

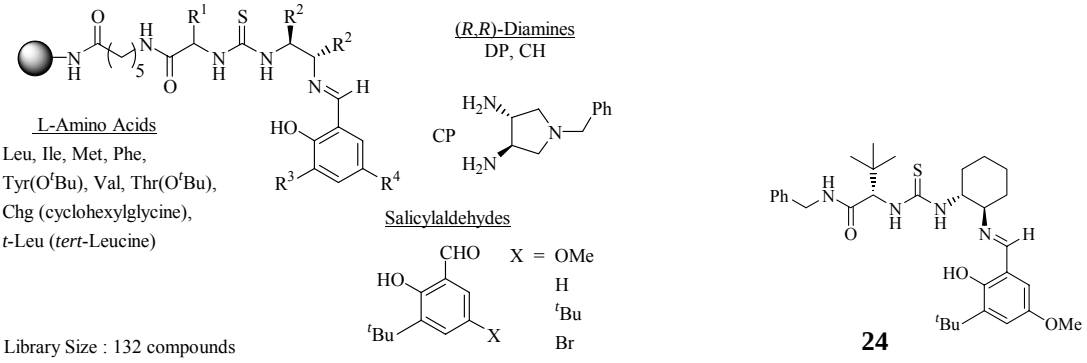
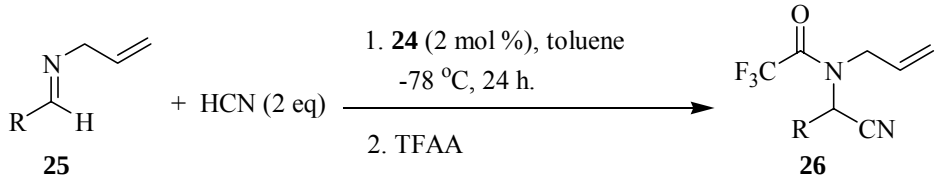


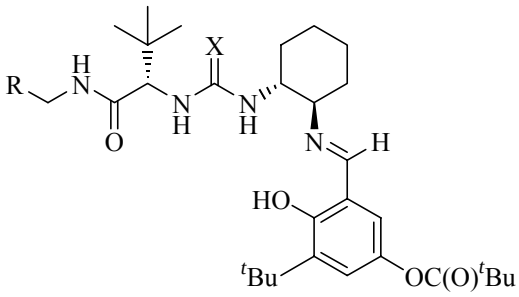
Figure 1.4 Ligand library for catalytic enantioselective Strecker-type reaction.

Table 1.8. Enantioselectivities obtained with Library 3.



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

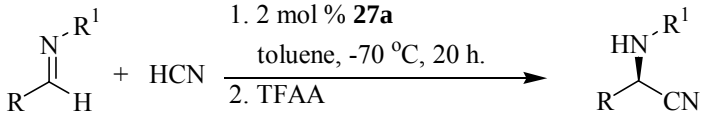
Moreover, Jacobsen and co-worker developed a new catalyst **27**, which gave good yield and high enantioselectivity on the addition of cyanide to either aromatic or aliphatic imines (Table 1.9).[15] These catalysts can be used either in solution or covalently linked to polystyrene resin. The key elements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



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

In 2002, Jacobsen and co-workers reported the structural and mechanistic studies for rational catalyst optimization.[16] The structure elucidated for the catalyst – substrate complex sheded substantial light on the basis for the scope and selectivity of asymmetric Strecker reactions with **27a**.

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



28 **29**

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

(1) The large group on the imine carbon is directed away from the catalyst and into the solvent (Figure 1.5B). (2) The small group (H for aldimines, Me for methylketoimines) is aimed directly into the catalyst. (3) The *N*-substituent is also directed away from the catalyst (Figure 1.5 B, C). (4) On the basis of the observed sense of stereoinduction, addition of HCN takes place over the diaminocyclohexane portion of the catalyst (*i.e.*, from the right-hand side in Figure 1.5C) and away from the amino acid/amide portion. The combination of the Schiff base ligand **30** and titanium isopropoxide as a catalyst was identified through screening by Snapper and Hoveyda in 1999.[17] The addition of TMSCN to the imine **31** in the presence of **30** and titanium isopropoxide ($Ti(O^iPr)_4$), followed by a slow addtion of isopropanol (^iPrOH) provided the α-amino nitrile **32** which may then be converted to optically pure α-amino acid. Good yields and moderate to high *ee* are obtained with both aromatic and non-enolizable aliphatic aldehydes (Table 1.10).

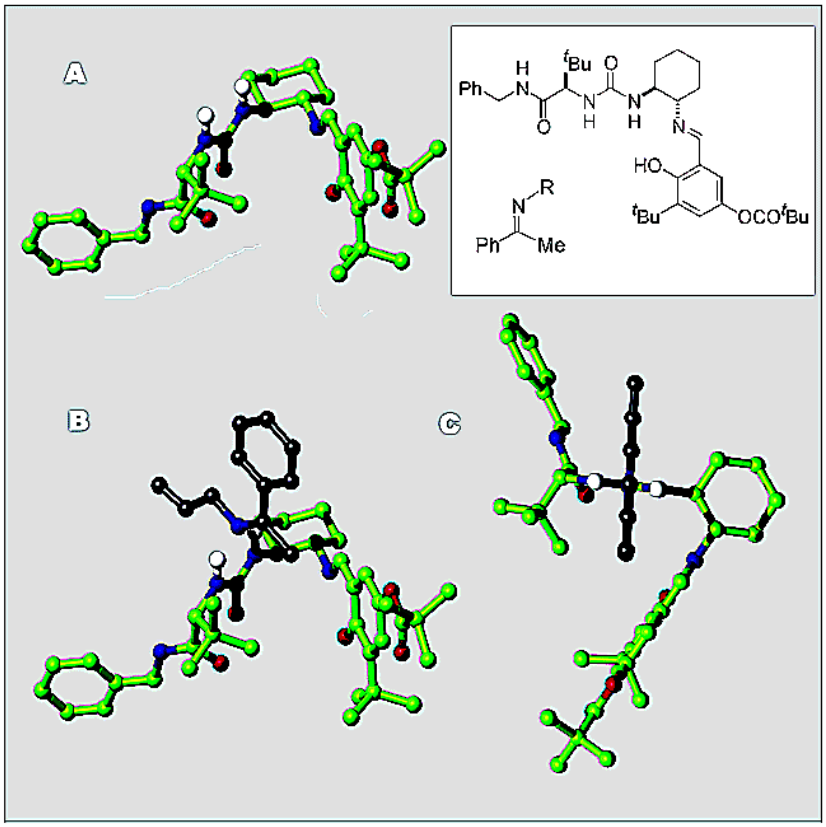
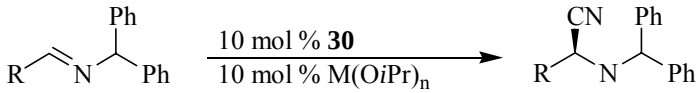
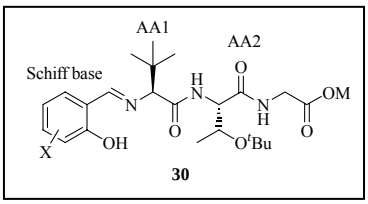


Figure 1.5 (A) Solution structure of catalyst **27b** and (B, C) two views of the complex generated upon binding of Z-imine, as determined by NMR analysis.

Table 1.10 Ti-catalyzed enantioselective cyanide addition to imines.



31 **32**



30

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

In 2001, Hoveyda and co-worker disclosed kinetic and structural data that, for the first time, shed light on one of the key transformations promoted by this class of chiral ligands.[18] The results showed that in affecting the Ti-catalyzed addition, these non-C_2 symmetric catalysts were

likely to operate in a bifunctional manner. The Ti-Schiff base (**SB**) coordinates with the substrate, while an amide moiety within the peptide segment associates and delivers cyanide to the activated imine (Figure 1.6).

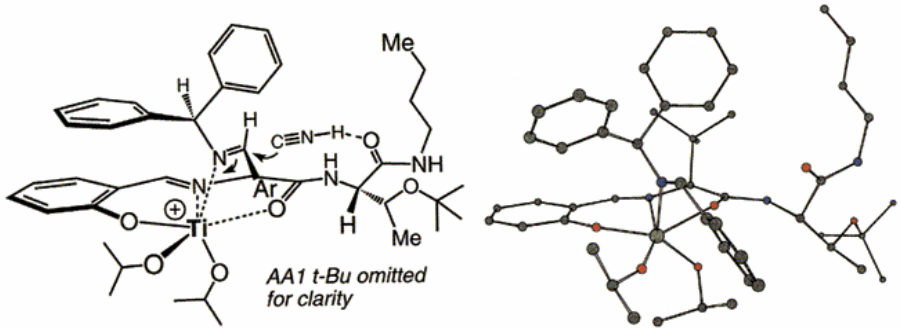


Figure 1.6 Cyanide addition catalyzed by Ti-tripeptide Schiff base complexes.

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

In 2001, Mansawat *et al.* revealed the use of a new class of catalytic asymmetric Strecker-type reaction employing a structurally simple salicylimine derived from peptide amide (**33**).[19] Noncomplex structure of salicylimine catalyst which included the peptide and Schiff base group **33** was observed for catalytic activities. The addition of TMSCN to *N*-benzylimine **34** in the presence of **33** and Ti(^{i}OPr)$_4$ provides optically active α-aminonitrile **35** which preferred *S*-configuration in good yield and moderate enantiomeric excess (Figure 1.7).

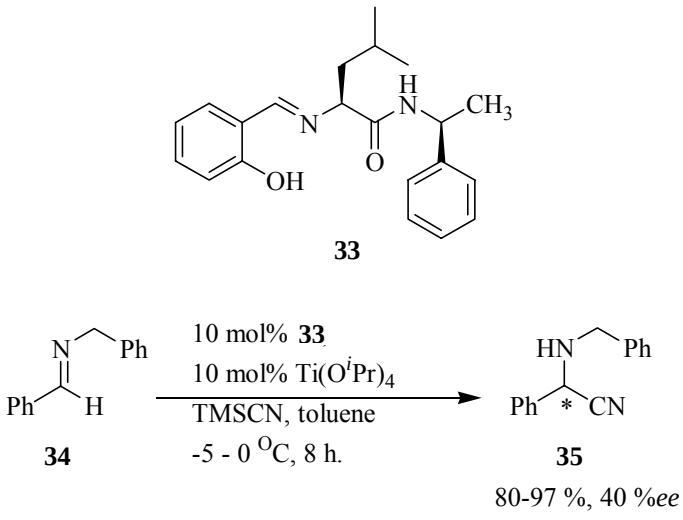
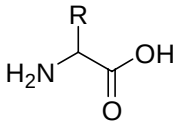


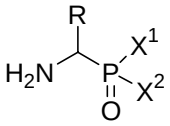
Figure 1.7 Asymmetric Strecker synthesis using Ti-peptide Schiff base catalyst.

1.2 α-Aminophosphonic acids

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



α-amino acids



36

36a : $X^1 = X^2 = OH$ α-aminoalkylphosphonic acids

36b : $X^1 = OH$, X^2 = alkyl, aryl α-aminoalkylphosphinic acids

36c : $X^1 = OH$, $X^2 = H$ α-aminoalkylphosphonous acids

36d : $X^1 = OR$, $X^2 = OR$ α-aminophosphonates

Figure 1.8 α-Amino acids and their phosphonic analogues.

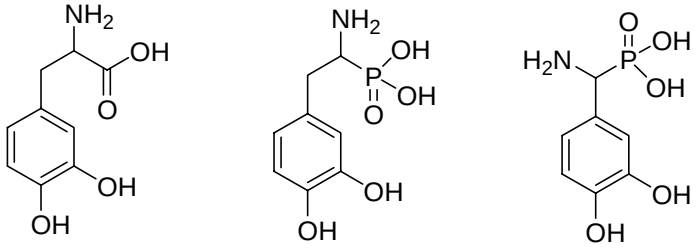
The replacement of the carbonyl carbon by a phosphorus atom has a number of important consequences as an additional substituent group is present in the molecule. The phosphorus atom has a tetrahedral configuration whereas the carbonyl carbon atom is planar, and there are significant differences in steric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

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

1.2.1 Mode of action

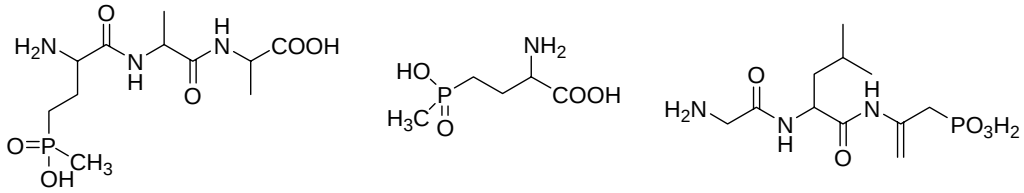
Inhibition of enzymes: Many of the enzymes are involved in the metabolism of amino acids. The inhibition frequently observed indicates that there is a structural antagonism between amino acids and their phosphonic acid counterparts, and numerous enzymes do recognize α-aminophosphonic acids as being similar to the respective α-amino carboxylic acids. A good example is the interaction of the phosphonic analogues of 3,4-dihydroxyphenylalanine (dopa, **37**) with tyrosinase.[19] A replacement of carboxyl group of dopa by a phosphonic moiety

and a shortening of the alkyl chain lead to compounds **38** and **39** serving as synthetic substrates for tyrosinase.



37 **38** **39**

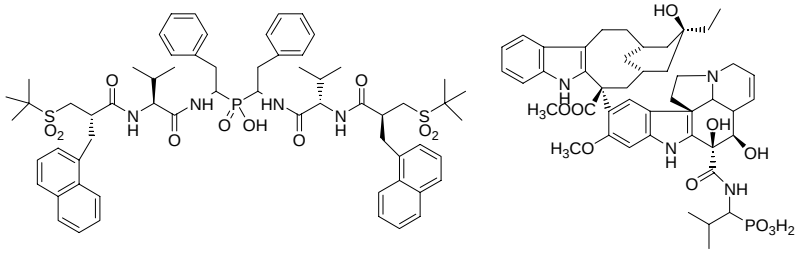
Antibiotic activities: Phosphorus-containing antibiotics, especially phosphonic acids, represent an interesting group of antimicrobial agents which is steadily increasing in number. Some of these compounds are produced by total chemical synthesis but many represent products of microbial origin. The most important among these compounds is bialaphos (**40**), an antibacterial metabolite produced by *Steptomyces hygroscopicus.* This tripeptide contains an analogue of glutamic acid, *L*-phosphinothricin (**41**), a potent inhibitor of glutamine synthetase. The tripeptide (**40**) is highly active *in vitro* against Gram-positive and Gram-nagative bacteria and also exerts strong herbicidal properties. Antimicrobial and immunostimulating phosphonotripeptide **42** was isolated as a component of a complex mixture of antibiotics produced by a soil microorganism.



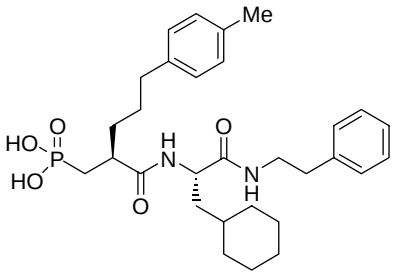
40 **41** **42**

Figure 1.10 Examples of antibiotic agents

Other biological activities of α-aminophosphonic acids and derivatives include Neuroactive activities, Plant growth regulating activities, and the compounds also exhibit possible applications on specifically targeted research examples of which include compounds related to HIV protease inhibitor **43**,[20] anticancer (**44**), antithrombin (**45**), and human collagnease inhibitor (**46**).



43 **44**



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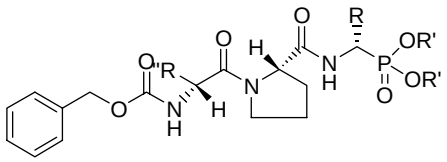

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1.2.2 α-Aminophosphonate synthesis

Although α-aminophosphonic acids were first mentioned in the literature in the early 1940s, for about three decades they received only marginal attention. Today, α-aminophosphonic acids attract considerable interest because of their diverse and useful biological activities, therefore, a wide variety of approaches for their preparation are currently being developed. More importantly, they can be use as synthetic precursors. A simple route to α-aminophosphonate diesters, therefore, held the promise of considerable utility.

1.2.3 General synthetic methods

There are many methods successfully employed in the synthesis of α-aminophosphonates that all details can not be covered here. Only general methods for the synthesis of α-aminophosphonates (Scheme 1.1) including the neucleophilic addition of di- or trialkyl phosphate derivatives to C=N bond (C-P bond forming, a), alkylation of phosphonate imines (C-C bond forming, b), electrophilic amination of α-alkyl phosphonamides or nucleophilic amination of α-hydroxy phosphonate derivatives (C-N bond forming, c).[21]

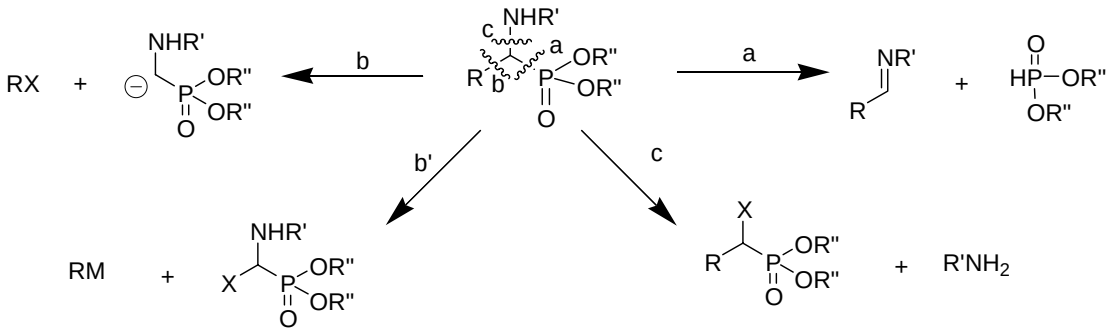


Figure 1.11 General methods for α-aminophosphonate synthesis

1.2.3.1 The nucleophilic addition to the C=N bond

The standard synthesis of α-aminophosphonates involves addition of a trivalent phosphorus acid or ester to an imines, which itself may be generated *in situ* from aldehydes and amines,[22-24] alkyl carbamates,[25-26] or ammonium acetate.[27] There are reports on the use of phosphorus trichloride or dichlorophosphine,[28] as well as trialkylphosphite[25] as starting materials. Figure 1.12 illustrates the reaction of nucleophilic addition of dialkyl phosphite to an imines.

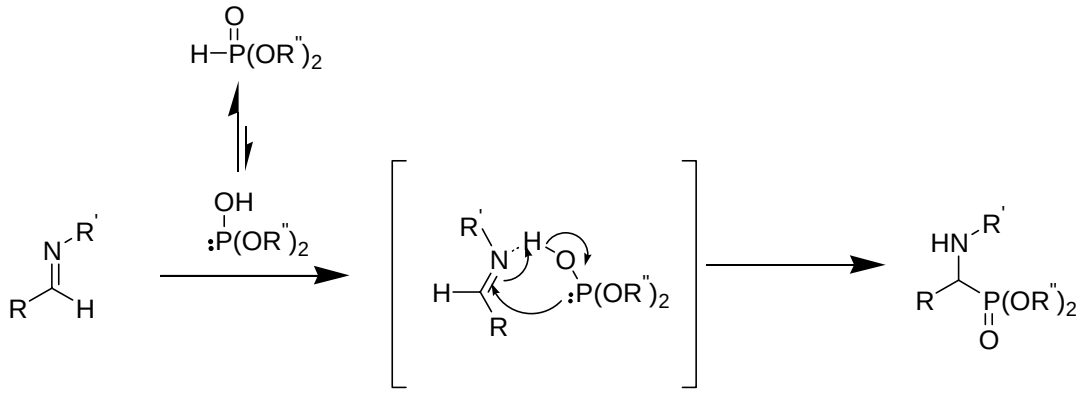


Figure 1.12 C-P bond formation through a nucleophilic addition of dialkyl phosphate to imine

Alkylation of a Schiff base[29] obtained from a dialkyl aminomethanephosphonate and benzaldehyde or benzophenone is a general method for the preparation of a wide variety of α-aminoalkanephosphonic acids.[30-31] A quite different approach is to convert *N*-acyl-aminoalkanephosphonates and phosphinates into their α-bromo derivatives by *N*-bromosuccinimide. These compounds are then reacted *in situ* with Grignard or organocopper reagents affording diethyl 1-(*N*-acylamino)alkanephosphonates. Nucleophilic amination seems at first sight to be the simplest method for the preparation of 1-aminoalkanephosphonic acids. However, this reaction proceeded with difficulty and gave only a low yield of the desired product. Nevertheless, this reaction was used as a method for the preparation of aminophosphonates in some special cases.[29]

1.2.4 Asymmetric synthesis

The biological activity of α-aminophosphonates is influenced by the absolute configuration of the stereogenic carbon α to the phosphorus atom. For example, the *S*-enantiomer of 2-amino-4-phosphobutanic acid is 20-40 times more active than the *R*-enantiomer in the suppression of glutamate-mediated nervous transmission.[29]

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

The first synthesis of an optically active α-aminophosphonic acid by C-P bond formation was reported by Gilmore and McBride in 1972.[32] The reaction of Schiff base derivative of an appropriate aldehyde and enantiomerically pure α-phenylethylamine, as chiral auxiliary. The acid-catalyzed addition of dialkyl phosphites to aldimines proceeds with high diastereoselectivity only on the case of bulky groups on the aldehyde residue of the aldimine and decrease markedly when small aliphatic groups are present. Attempts to improve the diastereoselectivity

of the reaction by increasing the bulkiness of the phosphite, for instance, by the use of bis(trimethylsilyl) phosphite, failed.[29]

1.2.5 Literature reviews of hydrophosphonylation of imines

As mentioned earlier that enantiomerically pure amines bearing a stereogenic center at the α-position play a crucial role as a characteristic structural feature in bioactive natural products and pharmaceutically important compounds. Ironically, the development of stereoselective syntheses of enantiopure amines by nucleophilic addition to imines has been investigated to a lesser extent. Some general problems include poor electrophilicity of the azomethine carbon which results in a difficulty in nucleophilic addition to the C=N bonds compared to the addition to the C=O bonds. In addition, the possibility of imine-enamine tautomerism can be problematic especially in the presence of strong bases such as organometallic reagents.[33-35]

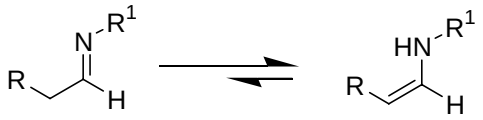
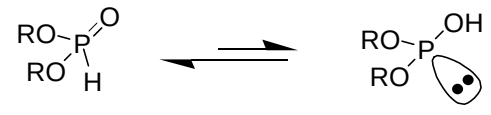


Figure 1.13 Imine-enamine tautomerism

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

Hydrophosphonylation reaction is based on addition of an appropriate phosphorus nucleophile to imines. In most cases, esters of phosphorus acid **34**, which can also be called dialkyl phosphites, have been used as phosphorus nucleophiles. These compounds are known to undergo a phosphite-phosphonate tautomerism with the phosphite tautomer as the nucleophile (active) form and the phosphonate tautomer as the almost exclusively favored but non-nucleophilic (resting) form. (Figure 1.14) This tautomerism has an equilibrium constant for diethyl H-phosphonate (**47**) of 10^7 in favor of the H-phosphonate (**48**) form.[36] Apparently, this adds more difficulties to the efficiency of the addition of imines.



Phosphonate tautomer **47**

Phosphite tautomer **48**

Figure 1.14 Phosphite-phosphonate tautomer

1.2.5.1 Non asymmetric synthesis of α-amino phosphonates

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

In recent years, the development of synthetic approaches to α-amino phosphonates using a variety of catalysts has been reported. The pioneering work of Pudovik using NaOEt and a Lewis acid such as $SnCl_2$, $SnCl_4$, and $BF_3.Et_2O$ has also been found to be effective. However, the reaction using these reagents and catalysts resulted in unsatisfactory yields of α-amino phosphonates. Later work by Zon demonstrated that the reaction can be strongly promoted by $ZnCl_2$ or $MgBr_2$ in high yields.[37]

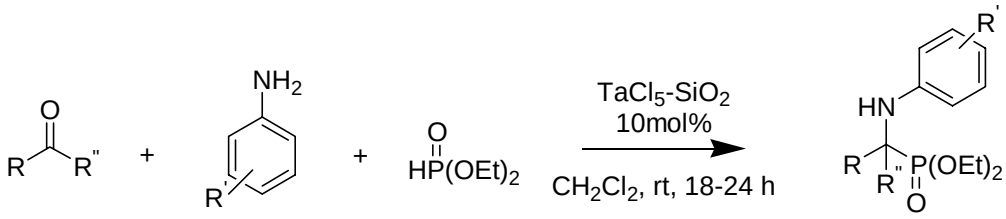
In 1998, Qian and Huang[37] proposed that a one-pot synthesis of α-amino phosphonates from aldehydes was effectively activated by rare earth metal triflates such as ytterbium triflate ($Yb(OTf)_3$) and scandium triflate ($Sc(OTf)_3$). They used them as catalysts in the reaction of diethyl phosphite with imines in order to overcome the drawbacks of classical Lewis acids sensitivity to moisture. Normally, water resulting from a one-pot reaction of aldehyde and amine during the *in situ* formation of imine can decompose or deactivate regular Lewis acids. These lanthanide triflates are, however, stable in water and can be recovered and also reused after the reaction is complete. It was found that this reaction provided excellent yields of the desired α-aminophosphonates in the case of aromatic aldehydes and moderate yields from the reaction of aliphatic aldehydes in the presence of 10 mol% of $Yb(OTf)_3$.

In addition, Ranu and coworkers[38] employed indium (III) chloride as a catalyst for the synthesis of α-amino phosphonates from both aldehydes and ketones with aliphatic as well as aromatic amines. One of the remarkable features, similarly observed in lanthanide triflate of $InCl_3$ is its effectiveness in an aqueous medium. A wide range of structurally varied carbonyl compounds were subjected to this procedure and converted to products in high yields (75-93%).

In 2000, Kobayashi and Manabe[39] proposed the use of a Lewis acid-surfactant combined catalysts (LASC) as a new type of Lewis acid. LASC consists of Lewis acidic metal cations such as scandium (III) and amphiphilic anions such as dodecyl sulfate, which form stable colloidal dispersions in the presence of organic substrates in water. They reported that scandium tris(dodecyl sulfate), a representative LASC, creates excellent hydrophobic reaction

fields to realize the rapid three component reaction of aldehydes, amine, and triethyl phosphite (PO_3Et_3) in water.

Recently, Chandrasekhar and coworkers[40] initiated the use of $TaCl_5$ and $TaCl_5$-SiO_2 for Lewis acid promoted three component coupling of carbonyl compounds, amines and diethyl phosphite for the synthesis of various amino phosphonates.



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

1.2.5.2 Asymmetric hydrophosphonylation

In 1992, Laschat and Kunz[41] reported an asymmetric synthesis of α-aminophosphonates in which *O*-pivaloylated glycosylamine serves as the stereodifferentiating auxiliary. By this method, both series of enantiomers of α-aminophosphonic acids can be obtained in high stereoselectivity. The *N*-galactosylimine prepared by reacting *O*-pivaloylated glycosylamines with 4-chlorobenzaldehyde reacted with diethyl phosphate in the presence of tin (IV) chloride catalyst and furnished four diastereomeric *N*-glycosyl-4-chlorophenyl phosphonoglycine esters in high yield (83%).

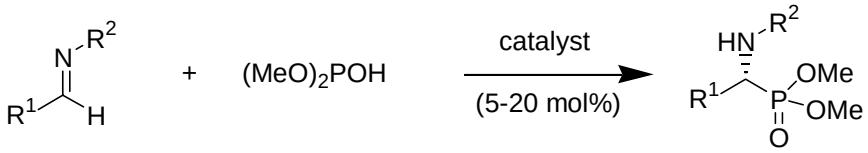
Shibuya and Yokomatsu [42] disclosed a route for an asymmetric synthesis of α-amino phosphonic acids. This involves a stereoselective opening of homochiral dioxane acetals with triethyl phosphite in the presence of a Lewis acid such as $BF_3.Et_2O$, $TiCl_4$-$Ti(O^iPr)_4$, or TMSOTf as a key reaction. They examined Lewis acid mediated cleavage of homochiral acetals by using triethyl phosphite as nucleophile to obtain chiral phosphono alcohols useful intermediates for the synthesis of α-amino phosphonic acids.

Hanessian and coworkers[43-44] developed two complementary approaches to the synthesis of enantioenriched α-amino phosphonic acids. Alkylation of scalemic bicyclic phosphonamides of either absolute configuration with carbon electrophiles furnished α-amino phosphonodiamides in 80-98% de. Acidic hydrolysis then yields the α-aminophosphonic acids with moderate to excellent enantiopurities (81-98% *ee*). Because this method relies on alkylation, however, derivatives containing branched or aromatic α substituents are inaccessible. The second strategy, based on an amination or azidation of chiral α-alkyl

phosphonamides, provides adducts with moderate diastereoselectivities (64-80% de). Acidic hydrolysis and catalytic hydrogenolysis again furnishes the α-amino phosphonic acids in 63-99% *ee*.

Only, a few examples of synthesis by enantiomeric catalysis have been published. In 1995, Shibasaki et al.[45-46] developed the first practical method to synthesize α-amino phosphonates by using chiral heterobimetallic rare earth catalysts. It was found that the lanthanum-potassium-BINOL complex (LPB) was the most efficient in this type of reaction. In the presence of 5-20 mol% of chiral catalyst **49**, the reaction of imine **50** with dimethyl phosphite proceeded to afford the corresponding α-amino phosphonate **51** in high yields with high enantioselectivities as illustrated on Table 1.11.

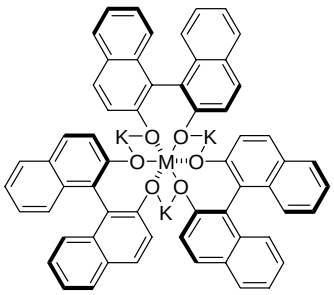
Table 1.11 Shibasaki's catalytic enantioselective hydrophosphonylation of imines **50**



50 **51**

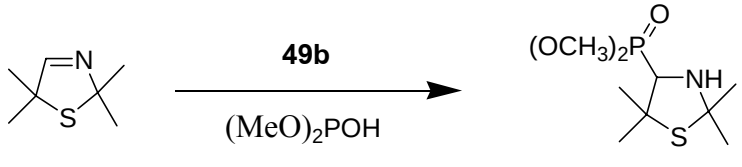
entry	aldimine	catalyst **49a** (mol%)	yield %	ee (%)
1	R^1 = ^{i}Pr, R^2 = $CHPh_2$	5	82	92
2	R^1 = Et, R^2 = $CHPh_2$	20	80	91
3	R^1 = Me, R^2 = $CHPh_2$	20	73	75

Catalyst =



49a : M=La, **49b** : M=Yb

Furthermore, They applied this group of catalyst to the synthesis of cyclic imines **50**.[46-48] The best result (97% yield, 98% *ee*) obtained is when the reaction was carried out in THF-toluene (1:7) using 5 mol% of the chiral ytterbium catalyst **49b** at 50°C.



50

1.4 Objectives of this research

Among the wide range of synthetic routes to α-amino acids, catalytic asymmetric Strcker-type reaction offers one of the most direct and viable methods. Salicylimine catalyst (Figure 1.12), the new class for catalytic asymmetric Strecker-type reaction showed interesting catalytic properties.

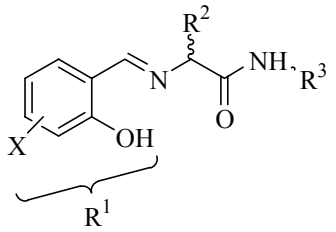


Figure 1.12 Salicylimine catalyst.

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

An additional objective of this research was to develop an asymmetric synthetic method of α-aminophosphonates involving nucleophilic addition of phosphorus nucleophiles to imines utinlizing the same class of chiral salicylimine ligands. The phosphorus nucleophile used in this study is a diethyl phosphite reagent and the substrates chosen are unactivated *N*-alkyl aldimines.

It is envisaged that the use of this type of catalyst to activate Strecker and hydrophosphonylation reactions would give high yields and stereoselectivity.

2. EXPERIMENTAL

2.1 General procedures and materials

Air-sensitive materials were transferred *via* syringe or cannula under a nitrogen atmosphere. Solvents for the reaction were used as received unless otherwise noted. All commercial solvents for column chromatography were distilled prior to use. Dichloromethane and toluene were dried over molecular sieves UOP type 4A prior to use. Tetrahydrofuran was dried over sodium/benzophenone. HPLC grade hexanes and 2-propanol for HPLC experiments on a chiral column were obtained from J.T. Baker and Merck, respectively. Chiral amines, amino acids, di-*tert*-butyl dicarbonate, (+)-camphor-10-sulfonic acid, 1-hydroxybenzotriazole, *N*,*N*'-dicyclohexylcarbodiimide, *N*-benzyloxycarbonylglycine and analytical solvents were purchased from Fluka. Trimethylsilylcyanide, $Ti(O^iPr)_4$, chloroform-d and [*S*-(*R**,*R**)]-(-)-bis(α-methylbenzyl)amine were purchased from Aldrich Chemical Co.. Fmoc-Thr(^{t}Bu)-OH was purchased from Nova biochem. All chemical reagents were used as received without further purification.

Melting points were measured on an Electrothermal 9100 melting point apparatus and were uncorrected. Optical rotations were measured at 26.2 $^{\circ}$C with a Bellingham+ stanley Ltd. ADP220 polarimeter. The progress of all reactions was followed by thin layer chromatography (TLC) performed on Merck D.C. siliga gel 60 F254 0.2 mm precoated aluminium plate and visualized by using either UV light (254 nm), iodine, ninhydrin, potassium permanganate, or $Co(SCN)_2$. Column chromatography was performed on the 230-400 mesh silica gel for flash column chromatography, 63-200 mesh silica gel for gravimetric chromatography or activated neutral aluminium oxide 90, purchased from Merck.

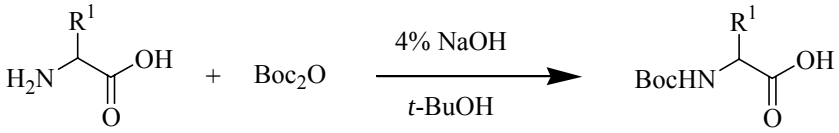
Proton (^{1}H), carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$, DMSO or D_2O on a Bruker ACF200 spectrometer operating at 200 MHz (^{1}H) and 50 MHz (^{13}C), a Mercury Varian 400 spectrometer operating at 400 MHz (^{1}H) at the chemistry department, Faculty of Science, Chulalongkorn University, or a Varian Gemini 2000 YH200 spectrometer operating at 200 MHz (^{1}H) at Chulabhorn Research Institute (CRI). Phosphorus (^{31}P) nuclear magnetic resonance spectra were recorded in $CDCl_3$ on a Jeol JNM A-500 spectrometer operating at 202.35 MHz at the Scientific and Technology Research Equipment Center, Chulalongkorn University. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) (0.00) or with the solvent as an internal reference for ^{1}H and ^{13}C NMR. A phosphoric acid (H_3PO_4) capillary in an appropriate solvent was used as an external reference (0.00) for the ^{31}P spectra. Multipicities are abbreviated as followed: s =

singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (*J*) are reported as proton-proton (J_{HH}) and proton-phosphorus (J_{HP}) coupling and are reported in Hertz (Hz).

High performance liquid chromatography (HPLC) separation of products were performed on a Gilson HPLC system equipped with a 112 UV/Vis detector. A Daicel Chiralcel OD® column (cellulose tris(3,5-dimethylphenyl carbamate) on a 10 μm silica gel substrate, 250 mm × 4.6 mm) and a Daicel Chiralpak AD® column (amylase tris-(3,5-dimethylphenylcarbamate) on 10 μm silica gel substrate, 250 mm × 4.6 mm) were used in attempts for separation of enantiomers. HPLC solvents were filtered through a membrane filter (0.5 μm Millipore®-FH) before use. Each sample was filtered through a 0.45 μm Millex®-HV syringe filter unit prior to injection onto the liquid chromatograph.

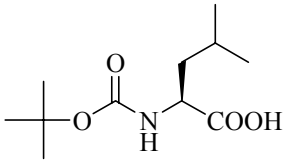
Mass spectra (MS) were recorded on GC-MS GCQ Mas Finnigan Mat by using the Fast Atom Bombardment ionization (LR-FAB+) method or in the electron impact (EI) mode (70 eV). Masses are reported in units of mass over charge (*m/z*). Intensities are reported as a percent of the base peak intensity. The molecular ion is indicated by $[MH]^+$ or $[M]^+$. Elemental analyses were conducted on a Perkin Elmer PE 2400 Series II.

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



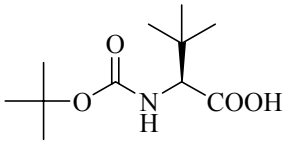
The amino acid (10 mmol) was dissolved with 4% NaOH (25 mL) in a 250 mL round bottomed flask. The solution was stirred and cooled to room-temperature then *tert*-butanol (10 mL) was added. To this mixture, a solution of Boc_2O (2.40 g, 11 mmol) in *tert*-butyl alcohol (5 mL) was added dropwise to give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

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



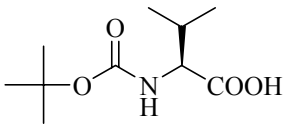
This compound was prepared from a reaction of (*S*)-leucine (1.31 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acids described in section 2.2. The crude product was recrystallized from hexanes to give **(*S*)-Boc-Leu-OH** as clear plates (1.94 g, 8.4 mmol, 84% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.93 (6H, d, *J* = 6.0, $CH(C\underline{H}_3)_2$), 1.41 (9H, s, $CC\underline{H}_3$), 1.38-1.46 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 4.20-4.32 (1H, m, α-C<u>H</u>), 4.95 (1H, d, *J* = 8.5, N<u>H</u>), 6.45 (1H, br, O<u>H</u>).

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



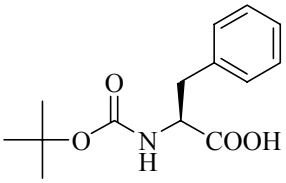
This compound was prepared from a reaction of (*S*)-*tert*-leucine (1.31 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (1.83 g, 8.6 mmol, 86% yield). ^{1}H NMR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

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



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

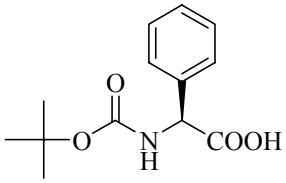
2.2.4 *N-tert*-butoxycarbonyl-(*S*)-phenylalanine ((*S*)-Boc-Phe-OH).



This compound was prepared from the reaction of (*S*)-phenylalanine (0.65 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (2.25 g, 9.1 mmol, 91% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (9H, s, $C\underline{H}_3$), 3.05-3.30 (2H, br, $C\underline{H}_2$), 4.57-

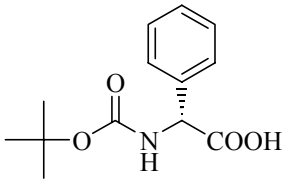
4.61 (1H, d, *J* = 7.0, α-CH), 5.05-5.09 (1H, br, NH), 6.10-6.25 (1H, br, OH), 7.15-7.33 (5H, m, ArH).

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



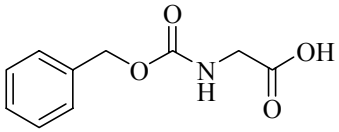
This compound was prepared from a reaction of (*S*)-phenylglycine (1.51 g, 10 mmol) and Boc_2O (2.40 g, 11 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (2.20 g, 8.8 mmol, 88% yield). ^{1}H NMR (200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

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



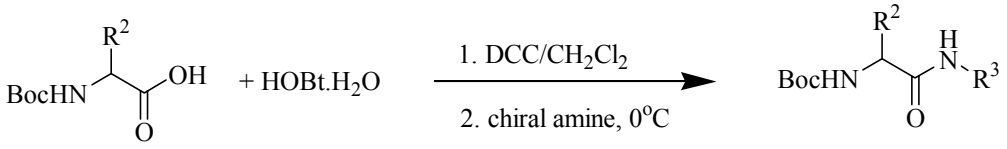
This compound was prepared from the reaction of (*R*)-phenylglycine (0.76 g, 5 mmol) and Boc_2O (1.20 g, 5 mmol) following the general procedure for the preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (1.2 g, 4.7 mmol, 94% yield). ^{1}H NMR (200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

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



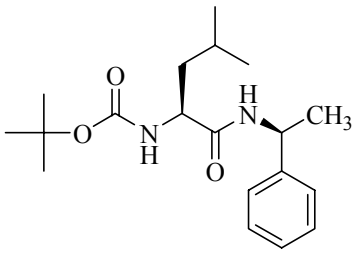
This compound was prepared from a reaction of glycine (0.37 g, 5 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (ZOSu) (1.23 g, 5 mmol) following the general procedure for preparation of Boc-amino acid described in section 2.2. The desired product was obtained as a white solid (0.20 g, 0.96 mmol, 19%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

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



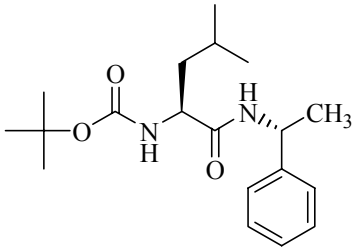
To a solution of *N*-Boc-amino acid (1 mmol) and HOBt•H_2O (1 mmol) in CH_2Cl_2 (2 mL), DCC (1 mmol) in CH_2Cl_2 (1 mL) was added dropwise under N_2 gas. White precipitates were formed during the addition. The mixture was cooled to -5 - 0 ^{o}C and then chiral amine (1 mmol) was added through a micro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

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



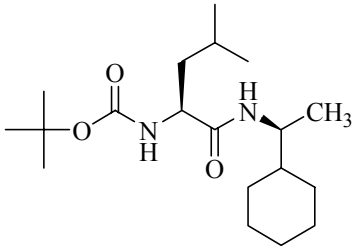
This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.231g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure for the condensation between *N*-Boc-amino acid and chiral amine described in section 2.4. The desired product was obtained as a white solid (0.26 g, 0.73 mmol, 73 %), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.0, CH(C<u>H</u>$_3$)$_2$), 0.89 (3H, d, *J* = 6.0, CH(C<u>H</u>$_3$)$_2$), 1.41 (9H, s, OC(C<u>H</u>$_3$)$_3$), 1.65 (3H, d, *J* = 7.0, CHPhC<u>H</u>$_3$), 1.53-1.68 (3H, m, C<u>H</u>(CH$_3$)$_2$ and C<u>H</u>$_2$), 4.04-4.06 (1H, m, α-C<u>H</u>), 4.93-4.96 (1H, br, N<u>H</u>Boc), 5.03-5.10 (1H, m, C<u>H</u>Ph), 6.57 (1H, d, *J* = 7.0, N<u>H</u>CHPh), 7.19-7.35 (5H, m, Ar<u>H</u>).

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



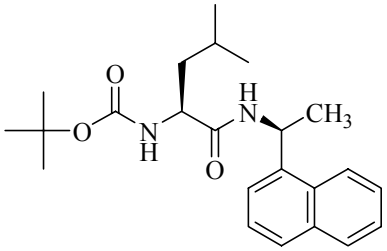
This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), HOBt•H_2O (0.14 g, 1 mmol), DCC (0.21 g, 1 mmol) and (*R*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.27 g, 0.77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

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



This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), HOBt•H_2O (0.14 g, 1 mmol), DCC (0.21g, 1 mmol) and (*S*)-cyclohexylethylamine (149 μL, 1 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.23 g, 0.68 mmol, 68 %), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (6H, d, *J* = 8.5, CH($C\underline{H}_3$)$_2$), 0.93-1.28 (11H, m, cyclohexyl), 1.08 (3H, d, *J* = 9.0, CH(cyclo)$C\underline{H}_3$), 1.41 (9H, s, C($C\underline{H}_3$)$_3$), 1.61-1.73 (3H, m, $C\underline{H}(CH_3)_2$ and $C\underline{H}_2$), 3.73-3.84 (1H, m, C<u>H</u>(cyclo)CH_3), 3.94-4.05 (1H, m, α-C<u>H</u>), 4.85-4.90 (1H, br, N<u>H</u>), 6.00 (1H, d, *J* = 8.5, N<u>H</u>Boc).

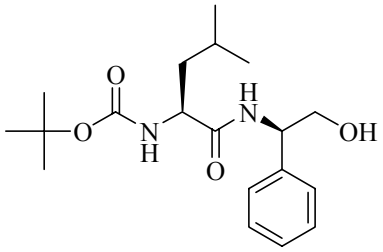
2.4.4 *N*-Boc-(*S*)-leucyl-(*S*)-(1-naphthylethyl)amine ((*S*,*S*)-Boc-Leu-A2).



This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), HOBt•H_2O (0.14 g, 1 mmol), DCC (0.21 g, 1 mmol) and (*S*)-napthylethylamine (160 μL, 1 mmol)

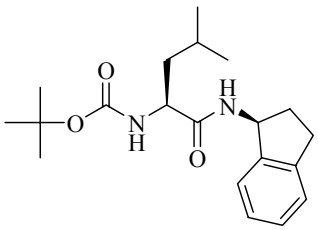
following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.25 g, 0.68 mmol, 68%), ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (6H, d, *J* = 5.0, CH(C<u>H</u>$_3$)$_2$), 1.41 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.63 (3H, d, *J* = 6.7, CH(1-naph)C<u>H</u>$_3$), 1.69-1.71 (3H, m, C<u>H</u>(CH$_3$)$_2$) and C<u>H</u>$_2$), 3.95-4.02 (1H, m, α-C<u>H</u>) 4.85-5.00 (1H, br, N<u>H</u>Boc), 5.81-5.95 (1H, m, *J* = 8.0, C<u>H</u>(1-naph)CH$_3$), 6.46 (1H, d, *J* = 8.0, N<u>H</u>), 7.39-7.52 (4H, m, Ar<u>H</u>), 7.75-7.86 (2H, m, Ar<u>H</u>), 8.05 (1H, d, *J* = 9.0, Ar<u>H</u>).

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



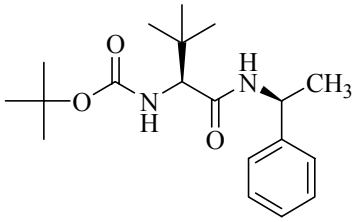
This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.15 g, 0.7 mmol), HOBt•H$_2$O (0.09 g, 0.7 mmol), DCC (0.14 g, 0.7 mmol) and (*S*)-phenylglycinol (0.09 g, 0.7 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.15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

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



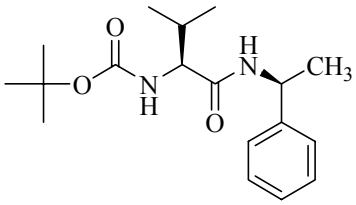
This compound was prepared from the reaction of **(*S*)-Boc-Leu-OH** (0.23 g, 1 mmol), HOBt•H$_2$O (0.13 g, 1 mmol), DCC (0.21 g, 1 mmol) and (*S*)-1-aminoindane (85 μL, 1 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.27 g, 0.79 mmol, 79 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94-0.95 (6H, m, CH(C<u>H</u>$_3$)$_2$), 1.42 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.51-1.68 (3H, m, C<u>H</u>(CH$_3$)$_2$ and C<u>H</u>$_2$), 2.54-2.63 (2H, m, CHCH$_2$C<u>H</u>$_2$), 2.82-2.90 (1H, m, α-C<u>H</u>), 2.94-3.02 (2H, m, CHC<u>H</u>$_2$), 5.43-5.48 (1H, m, C<u>H</u> (indane)), 6.31-6.41 (1H, br, N<u>H</u>), 7.19-7.24 (4H, m, Ar<u>H</u>).

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



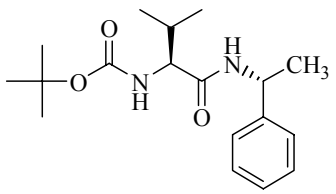
This compound was prepared from the reaction of **(*S*)-Boc-*t*Leu-OH** (0.693 g, 3 mmol), HOBt•H_2O (0.406 g, 3 mmol), DCC (0.619 g, 3 mmol) and (*S*)-methylbenzylamine (381 μL, 3 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.19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

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



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

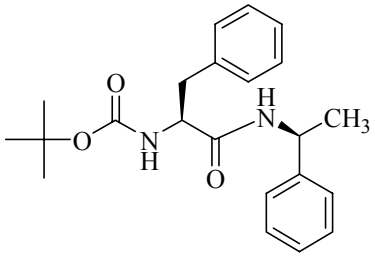
2.4.9 *N*-Boc-(*S*)-Valyl-(*R*)-(1-phenylethyl)amine ((*S*, *R*)-Boc-Val-A1).



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

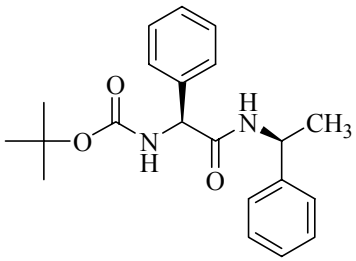
7.0, CH(Ph)C<u>H</u>$_3$), 1.95-2.20 (1H, m, C<u>H</u>(CH$_3$)$_2$), 3.83 (1H, dd, *J* = 6.5, 8.5, α-C<u>H</u>), 5.06-5.13 (1H, m, C<u>H</u>(Ph)CH$_3$), 6.31-6.34 (1H, br, N<u>H</u>), 7.19-7.33 (5H, m, Ar<u>H</u>).

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



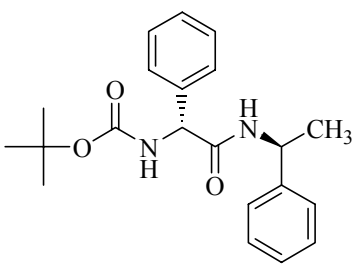
This compound was prepared from the reaction of **(*S*)-Boc-Phe-OH** (0.269 g, 1 mmol), HOBt•H$_2$O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure. The desired product was obtained as a white solid (0.29 g, 0.79 mmol, 79 %). ^{1}H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

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



This compound was prepared from the reaction of **(*S*)-Boc-Phg-OH** (0.251 g, 1 mmol), HOBt•H$_2$O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.18 g, 0.51 mmol, 51%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.38 (9H, s, OC(C<u>H</u>$_3$)$_3$), 1.45 (3H, d, *J* = 7.0, CH(Ph)C<u>H</u>$_3$), 5.02-5.12 (2H, m, α-C<u>H</u> and C<u>H</u>(Ph)CH$_3$), 5.88 (1H, d, *J* = 7.5, N<u>H</u>), 6.98-7.03 (2H, m, Ar<u>H</u>), 7.18-7.35 (8H, m, Ar<u>H</u>).

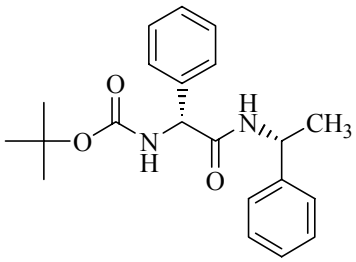
2.4.12 *N*-Boc-(*R*)-phenylglycyl-(*S*)-(1-phenylethyl)amine ((*R*,*S*)-Boc-Phg-A1).



This compound was prepared from the reaction of **(*R*)-Boc-Phg-OH** (0.251 g, 1 mmol), HOBt•H$_2$O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1

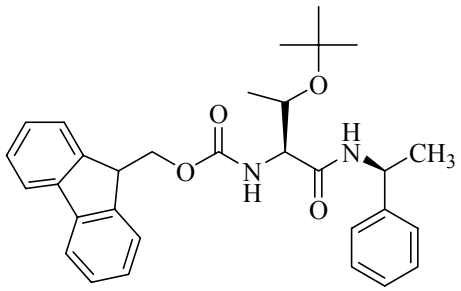
mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.16 g, 0.4 mmol, 40 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (9H, s, OC(C<u>H</u>$_3$)$_3$), 1.44 (3H, d, *J* = 7.0, CH(Ph)C<u>H</u>$_3$), 5.02-5.11 (2H, m, α-C<u>H</u> and C<u>H</u>(Ph)CH$_3$), 6.00 (1H, d, *J* = 7.5, N<u>H</u>), 6.98-7.03 (2H, m, Ar<u>H</u>), 7.16-7.35 (8H, m, Ar<u>H</u>).

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



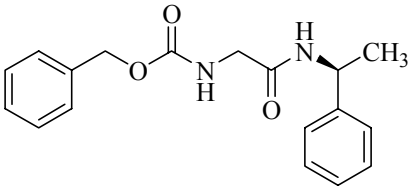
This compound was prepared from the reaction of **(*R*)-Boc-Phg-OH** (0.251 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*R*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.27 g,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

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



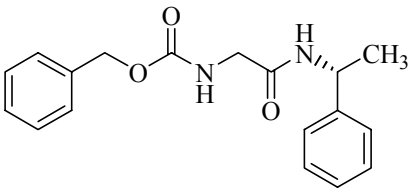
This compound was prepared from the reaction of **(*S*)-Fmoc-Thr(^{t}Bu)-OH** (0.39 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.43 g, 0.86 mmol, 86%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (3H, d, *J* = 6.0, CH(O^{t}Bu)C<u>H</u>$_3$), 1.26 (9H, s, OC(C<u>H</u>$_3$)$_3$), 1.48 (3H, d, *J* = 7.0, CHPhC<u>H</u>$_3$), 1.63 (1H, d, *J* = 4.5, C<u>H</u>$_2$), 4.09-4.23 (2H, m, C<u>H</u>CH$_2$ and α-C<u>H</u>), 4.35 (1H, d, *J* = 6.0, C<u>H</u>(O^{t}Bu)), 5.05 (1H, m, *J* = 7.0, C<u>H</u>PhCH$_3$), 6.02 (1H, d, *J* = 4.5, N<u>H</u>), 7.26-7.76 (13H, m, Ar<u>H</u>).

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



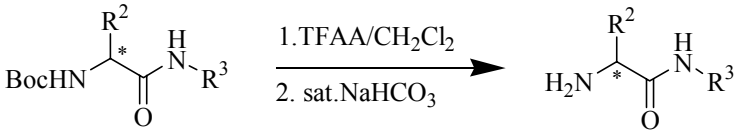
This compound was prepared from the reaction of **Cbz-Gly-OH** (0.21 g, 1 mmol), HOBt•H_2O (0.135 g, 1 mmol), DCC (0.206 g, 1 mmol) and (*S*)-methylbenzylamine (127 μL, 1 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.23 g, 0.73 mmol,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

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



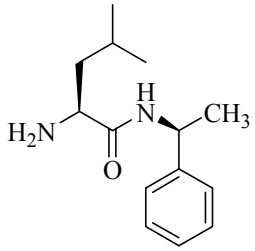
This compound was prepared from the reaction of **Cbz-Gly-OH** (0.10 g, 0.5 mmol), HOBt•H_2O (0.070 g, 0.5 mmol), DCC (0.103 g, 0.5 mmol) and (*S*)-methylbenzylamine (64 μL, 0.5 mmol) following the general procedure described in section 2.4. The desired product was obtained as a white solid (0.14 g, 0.49 mmol, 98 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (3H, d, *J* = 7.0, C<u>H</u>$_3$), 3.81 (2H, d, *J* = 5.5, α-C<u>H</u>$_2$), 5.06 (1H, m, C<u>H</u>), 5.07 (2H, s, C<u>H</u>$_2$Ph), 5.45-5.60 (1H, br, N<u>H</u>), 6.45-6.60 (1H, br, N<u>H</u>), 7.23-7.32 (10H, m, Ar<u>H</u>).

2.5 General procedure for *N*-deprotection



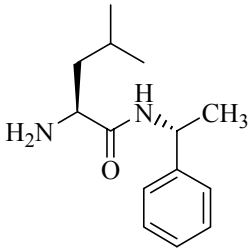
N-Boc-aminoamide was dissolved in CH_2Cl_2 (0.5 mL). TFAA (0.5 mL, 5 mmol) was added. The mixture was stirred for 30 minutes at room temperature. The mixture was then extracted with saturated $NaHCO_3$ solution (3×2 mL) and dried over anhydrous $MgSO_4$. The solvent was removed by a rotary evaporator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

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



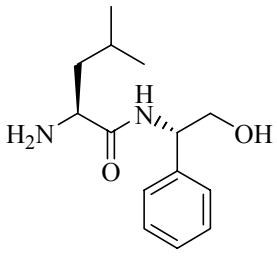
This compound was prepared from the reaction of **(*S*,*S*)-Boc-Leu-A1** (0.20 g, 0.57 mmol) and TFA (0.5 mL) following the general procedure described in section 2.5. The desired product was obtained as clear oil (0.11 g, 0.47 mmol, 83 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 9.0, CH(C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

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



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

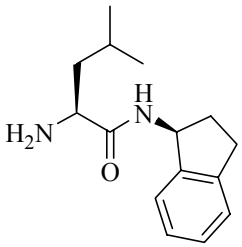
2.5.3 (*S*)-Leucyl-(*R*)-(1-phenyl-2-hydroxyethyl)amine ((*S*,*R*)-Leu-A3).



This compound was prepared from the reaction of **(*S*,*R*)-Boc-Leu-A3** (0.15 g, 0.43 mmol) and TFA (0.25 mL) following the general procedure described in section 2.5. The desired product was obtained as clear oil (0.03 g, 0.13 mmol, 30 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 4.5, CH(C<u>H</u>$_3$)$_2$), 0.91 (3H, d, *J* = 6.0, CH(C<u>H</u>$_3$)$_2$), 1.54-1.67 (3H, m, C<u>H</u>(CH$_3$)$_2$ and

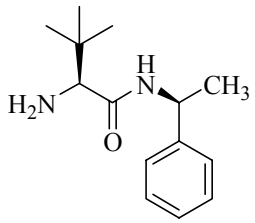
C$\underline{H}_2$CH(CH$_3$)$_2$), 2.92-3.35 (1H, br, OH), 3.45 (1H, d, *J* = 5.5, α-C$\underline{H}$), 3.77 (2H, d, *J* = 5.0, C$\underline{H}_2$OH), 4.97-5.02 (1H, m, C$\underline{H}$Ph), 7.21-7.32 (5H, m, Ar$\underline{H}$), 8.08 (1H, d, *J* = 7.5, N$\underline{H}$).

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



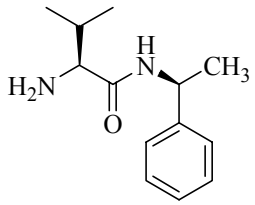
This compound was prepared from the reaction of **(*S*,*S*)-Boc-Leu-A5** (0.27 g, 0.79 mmol) and TFA (0.25 mL) following the general procedure described in section 2.5. The desired product was obtained as a clear oil (0.14 g, 0.60 mmol, 76 %). ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.93-0.96 (6H, m, CH$_3$), 1.60-1.81 (3H, m, C$\underline{H}$(CH$_3$)$_2$ and C$\underline{H}_2$), 1.89-1.92 (2H, m, CHCH$_2$C$\underline{H}_2$), 2.49-2.60 (2H, m, CHC$\underline{H}_2$), 3.37-3.58 (1H, br, α-C$\underline{H}$), 5.38-5.49 (1H, m, C$\underline{H}$ (indane)), 7.18-7.26 (4H, m, Ar$\underline{H}$).

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



This compound was prepared from the reaction of **(*S*,*S*)-Boc-*t*Leu-A1** (0.19 g, 0.5 mmol) and TFA (0.5 mL) following the general procedure for deprotection of Boc protecting group described in section 2.5. The desired product was obtained as clear oil (0.11 g, 0.48 mmol, 96 %). ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.94 (9H, s, C(C$\underline{H}_3$)$_3$), 1.43 (3H, d, *J* = 8.0, CHC$\underline{H}_3$), 3.78-3.82 (1H, br, α-C$\underline{H}$), 4.95-5.20 (1H, m, C$\underline{H}$Ph), 7.18-7.33 (5H, m, Ar$\underline{H}$).

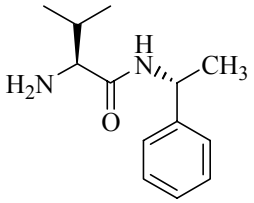
2.5.6 (*S*)-Valyl-(*S*)-(1-phenylethyl)amine ((*S*,*S*)-Val-A1).



This compound was prepared from the reaction of **(*S*,*S*)-Boc-Val-A1** (0.26 g, 0.8 mmol) and TFA (0.5 mL) following the general procedure described in section 2.5. The desired product was obtained as clear oil (0.07 g, 0.33 mmol, 41%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.80 (3H, d, *J* = 7.0, CH(C$\underline{H}_3$)$_2$), 0.92 (3H, d, *J* = 7.0, CH(C$\underline{H}_3$)$_2$), 1.43 (3H, d, *J* = 7.0, CH(Ph)C$\underline{H}_3$), 1.95-2.20

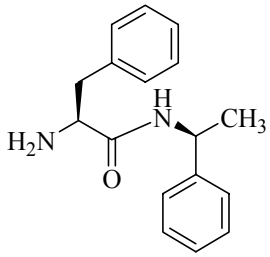
(1H, m, C<u>H</u>$(CH_3)_2$), 3.05-3.20 (1H, m, α-C<u>H</u>), 5.07 (1H, m, *J* = 7.0, C<u>H</u>(Ph)CH_3), 7.17-7.33 (5H, m, Ar<u>H</u>), 7.60-7.68 (1H, br, N<u>H</u>).

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



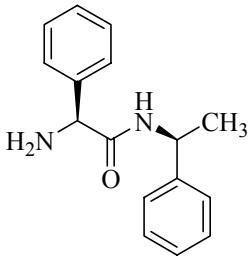
This compound was prepared from the reaction of **(*S*,*R*)-Boc-Val-A1** (0.23 g, 0.7 mmol) and TFA (0.5 mL) following the general procedure described in section 2.5. The desired product was obtained as clear oil (0.04 g, 0.33 mmol, 47%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.72 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3)_2$), 0.92 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3)_2$), 1.41 (3H, d, *J* = 7.0, CH(Ph)C<u>H</u>$_3$), 1.95-2.20 (1H, m, C<u>H</u>$(CH_3)_2$), 3.05-3.20 (1H, m, α-C<u>H</u>), 5.07 (1H, q, *J* = 7.0, C<u>H</u>(Ph)CH_3), 7.17-7.33 (5H, m, Ar<u>H</u>), 7.59-7.63 (1H, br, N<u>H</u>).

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



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

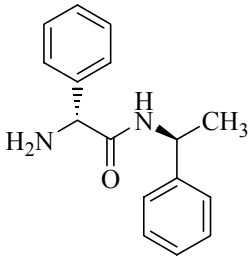
2.5.9 (*S*)-Phenylglycyl-(*S*)-(1-phenylethyl)amine ((*S*,*S*)-Phg-A1)



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

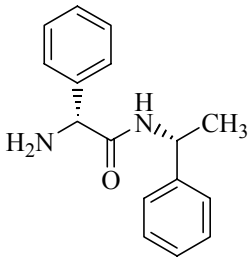
7.5, CH(Ph)C<u>H</u>$_3$), 4.44 (1H, br, α-C<u>H</u>), 5.07 (1H, q, *J* = 7.5, C<u>H</u>(Ph)CH$_3$), 7.19-7.34 (10H, m, Ar<u>H</u>), 7.49 (1H, d, *J* = 7.5, N<u>H</u>).

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



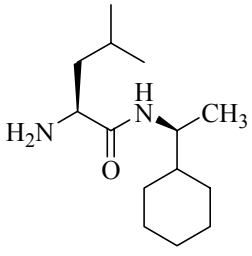
This compound was prepared from the reaction of **(*R*)-Boc-Phg** (0.16 g, 0.47 mmol) and TFA (0.5 mL) following the procedure described in section 2.5. The desired product was obtained as clear oil (0.11 g, 0.42 mmol, 99%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.43 (3H, d, *J* = 7.5, CH(Ph)C<u>H</u>$_3$),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

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



This compound was prepared from the reaction of **(*R*,*R*)-Boc-Phg-A1** (0.27 g, 0.76 mmol) and TFA (0.5 mL) following the procedure described in section 2.5. The desired product was obtained as clear oil (0.17 g, 0.67 mmol, 88%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 1.42 (3H, d, *J* = 7.0, CH(Ph)C<u>H</u>$_3$), 4.42 (1H, s, α-C<u>H</u>), 5.06 (1H, q, *J* = 7.0, C<u>H</u>(Ph)CH$_3$), 7.18-7.35 (10H, m, Ar<u>H</u>), 7.59 (1H, d, *J* = 7.0, N<u>H</u>).

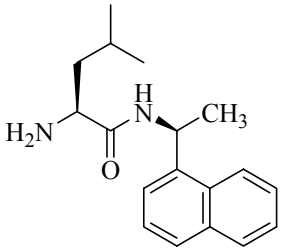
2.5.12 (*S*)-Leucyl-(*S*)-(1-cyclohexylethyl)amine ((*S*,*S*)-Leu-A4)



This compound was prepared from the reaction of **(*S*,*S*)-Boc-Leu-A4** (0.23 g, 0.68 mmol) and TFA (0.5 mL) following the general procedure described in section 2.5. The desired product was obtained as clear oil (0.16 g, 0.68 mmol, 99 %). ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.81-

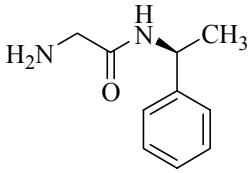
1.16 (17H, m, *J* = 8.5, CH(C<u>H</u>$_3$)$_2$ and cyclohexyl), 1.53-1.89 (6H, m, C<u>H</u>(CH$_3$)$_2$, C<u>H</u>$_2$, CH(cyclo)C<u>H</u>$_3$), 3.60-3.80 (1H, br, C<u>H</u>(cyclo)CH$_3$), 5.13-5.22 (1H, m, α-C<u>H</u>).

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



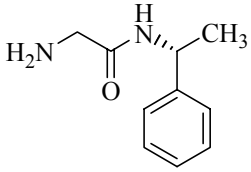
This compound was prepared from the reaction of **(*S*,*S*)-Boc-Leu-A2** (0.26 g, 0.68 mmol) and TFA (0.5 mL) following the procedure for deprotection of Boc protecting group. The desired product was obtained as a clear oil (0.16, 0.55 mmol, 81%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.84 (6H, d, *J* = 6.0, CH(C<u>H</u>$_3$)$_2$), 1.20-1.41 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.54 (3H, d, *J* = 10, CH(1-naph)C<u>H</u>$_3$), 1.60-1.65 (2H, m, C<u>H</u>$_2$), 2.00-2.20 (2H, br, N<u>H</u>$_2$), 3.21-3.40 (1H, br, α-C<u>H</u>) 5.78-5.90 (1H, m, *J* = 10.0, C<u>H</u>(1-naph)CH$_3$), 7.31-7.50 (4H, m, Ar<u>H</u>), 7.70-7.90 (3H, m, Ar<u>H</u>), 8.07 (1H, d, *J* = 10.0, N<u>H</u>).

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



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

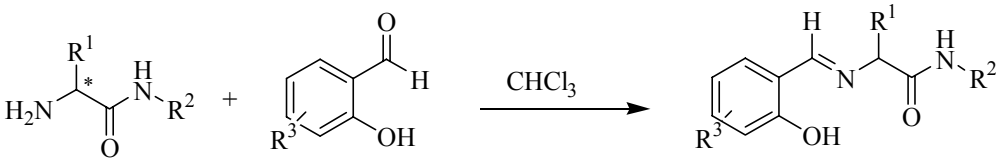
2.5.15 Glycyl-(*R*)-(1-phenyletyl)amine ((*R*)-Gly-A1).



This compound was prepared from the **(*R*)-Cbz-Gly-A1** (0.15 g, 0.50 mmol) following the procedure for the synthesis of glycyl-(*S*)-(1-phenylethyl)amine described in section 2.5.14. The desired product was obtained as a clear oil (0.08 g, 0.45 mmol, 89%). ^{1}H NMR (200 MHz,

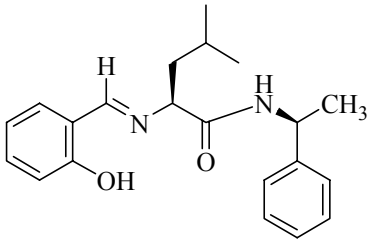
$CDCl_3$) δ 1.37 (3H, d, *J* = 7.0, C<u>H</u>$_3$), 3.33-3.58 (2H, br, α-C<u>H</u>), 4.96-5.05 (1H, m, C<u>H</u>(Ph)CH_3), 7.10-7.35 (5H, m, Ar<u>H</u>), 7.74 (1H, d, *J* = 7.0, N<u>H</u>).

2.6 General procedure for preparation of salicylimine ligands.



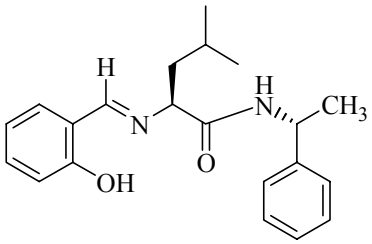
An amine was dissolved in $CHCl_3$ (2 mL) and then salicylaldehyde was added. After stirring for 24 h at room temperature, the solvent was removed by a rotary evaporator to give yellow residue. The residue was dissolved in dichloromethane and eluted through a silica gel column by ethyl acetate in hexanes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

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



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

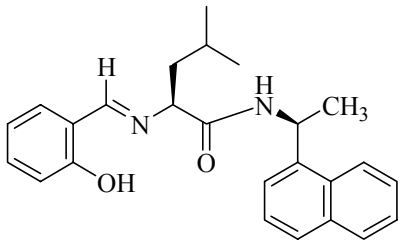
2.6.2 *N*-salicylidene-(*S*)-leucyl-(*R*)-(1-phenylethyl)amine ((*S*,*R*)-Leu-A1).



This compound was prepared from the reaction of **(*S*,*R*)-Leu-A1** (0.11 g, 0.49 mmol) and salicylaldehyde (42.1 μL, 0.49 mmol) following the procedure for the preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.11 g, 0.33 mmol,

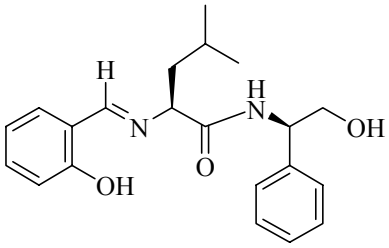
83%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3$)$_2$), 0.87 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3$)$_2$), 1.42 (3H, d, *J* = 7.0, CHPhC<u>H</u>$_3$), 1.75-1.85 (3H, m, C<u>H</u>$_2$ and C<u>H</u>(CH$_3$)$_2$), 3.80-3.95 (1H, m, α-C<u>H</u>), 5.08-5.20 (1H, m, C<u>H</u>PhCH$_3$), 6.20 (1H, d, *J* = 8.0, N<u>H</u>), 6.80-7.0 (4H, m, Ar<u>H</u>), 7.17-7.29 (5H, m, Ar<u>H</u>), 8.30 (1H, s, <u>H</u>C=N).

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



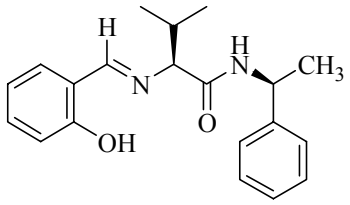
This compound was prepared from the reaction of **(*S*,*S*)-Leu-A2** (0.20 g, 0.71 mmol) and salicylaldehyde (75 μL, 0.71 mmol) following the general procedure for the preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.19 g, 0.49 mmol, 69 %) δ 0.84-0.92 (6H, t, *J* = 7.5, CH(C<u>H</u>$_3$)$_2$), 1.58-1.71 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.65 (3H, d, *J* = 7.0, CH(1-naph)C<u>H</u>$_3$), 1.78-1.97 (2H, m, CH$_2$), 3.92 (1H, dd, *J* = 9.0, 4.5, α-C<u>H</u>), 5.87-6.01 (1H, m, C<u>H</u>(1-naph)CH$_3$), 6.25 (1H, d, *J* = 8.0, N<u>H</u>), 6.84-6.95 (4H, m, Ar<u>H</u>), 7.20-7.50 (4H, m, Ar<u>H</u>), 7.70-7.82 (2H, m, Ar<u>H</u>), 8.06 (1H, d, *J* = 10.0, Ar<u>H</u>), 8.25 (1H, s, <u>H</u>C=N).

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



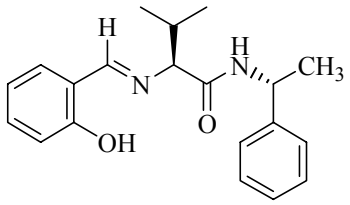
This compound was prepared from the reaction of **(*S*,*S*)-Leu-A3** (0.03 g, 0.13 mmol) and salicylaldehyde (13.5 μL, 0.13 mmol) following the general procedure for the preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.02 g, 0.05 mmol, 38 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 6.5, CH(C<u>H</u>$_3$)$_2$), 0.93 (3H, d, *J* = 6.5, CH(C<u>H</u>$_3$)$_2$), 1.52-1.60 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.86 (2H, t, *J* = 7.0, C<u>H</u>$_2$CH(CH$_3$)$_2$), 3.02-3.50 (1H, br, OH), 3.84 (2H, d, *J* = 5.0, C<u>H</u>$_2$OH), 3.93-4.00 (1H, m, α-C<u>H</u>), 5.03-5.06 (1H, m, C<u>H</u>Ph), 6.87-6.98 (4H, m, ArH), 7.22-7.39 (5H, m, Ar<u>H</u>), 8.33 (1H, d, *J* = 7.5, <u>H</u>C=N).

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



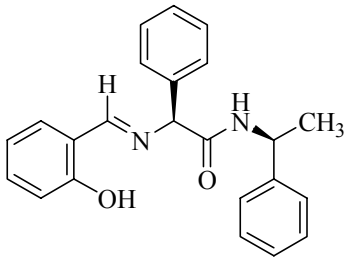
This compound was prepared from the reaction of **(*S*,*S*)-Val-A1** (0.12 g, 0.53 mmol) and salicylaldehyde (55 μL, 0.52 mmol) following the general procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.11 g, 0.35 mmol, 67 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (3H, d, *J* = 7.0, CH(C$\underline{H}_3$)$_2$), 0.98 (3H, d, *J* = 7.0, CH(C$\underline{H}_3$)$_2$), 1.50 (3H, d, *J* = 7.0, CH(Ph)C$\underline{H}_3$), 2.40-2.60 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 3.75 (1H, d, *J* = 4.0, α-C$\underline{H}$), 5.15 (1H, m, *J* = 7.0, C$\underline{H}$(Ph)CH$_3$), 6.30 (1H, d, *J* = 7.0, N$\underline{H}$), 6.88-6.97 (4H, m, Ar$\underline{H}$), 7.29-7.48 (5H, m, Ar$\underline{H}$), 8.27 (1H, s, $\underline{H}$C=N).

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



This compound was prepared from the reaction of **(*S*,*R*)-S1-Val-A1** (0.11 g, 0.49 mmol) and salicylaldehyde (51 μL, 0.49 mmol) following the general procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.15 g, 0.45 mmol, 91 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (6H, d, *J* = 7.0, CH(C$\underline{H}_3$)$_2$), 1.41 (3H, d, *J* = 7.0, CH(Ph)C$\underline{H}_3$), 2.37-2.43 (1H, m, C$\underline{H}$(CH$_3$)$_2$), 3.67 (1H, d, *J* = 4.0 α-C$\underline{H}$), 5.15 (1H, m, *J* = 7.0, C$\underline{H}$(Ph)CH$_3$), 6.40 (1H, d, *J* = 7.0, N$\underline{H}$), 6.88-6.97 (4H, m, Ar$\underline{H}$), 7.29-7.48 (5H, m, Ar$\underline{H}$), 8.30 (1H, s, $\underline{H}$C=N).

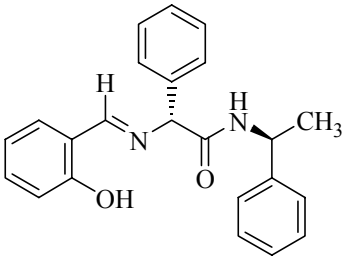
2.6.7 *N*-salicylidene-(*S*)-phenyl-glycyl-(*S*)-(1-phenylethyl)amine ((*S*,*S*)-S1-Phg-A1).



This compound was prepared from the reaction of **(*S*,*S*)-Phg-A1** (0.07 g, 0.29 mmol) and salicylaldehyde (30 μL, 0.29 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.08 g, 0.23 mmol, 81 %) ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (3H, d, *J* = 7.0, CH(Ph)C$\underline{H}_3$),

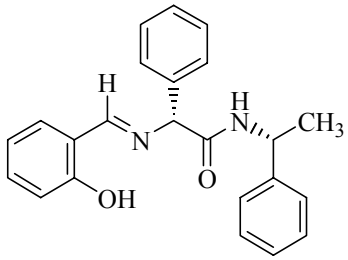
5.02 (1H, s, α-CH), 5.13-5.20 (1H, m, CH(Ph)CH_3), 6.44 (1H, d, *J* = 7.0, NH), 6.86-7.02 (4H, m, ArH), 7.17-7.45 (10H, m, ArH), 8.42 (1H, s, HC=N).

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



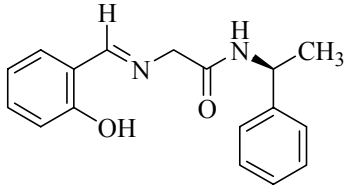
This compound was prepared from the reaction of **(*R*,*S*)-Phg-A1** (0.11 g, 0.42 mmol) and salicylaldehyde (44 μL, 0.42 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.12 g, 0.33 mmol, 80 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (3H, d, *J* = 7.0, CH(Ph)CH_3), 5.02 (1H, s, α-CH), 5.13-5.20 (1H, m, CH(Ph)CH_3), 6.44 (1H, d, *J* = 7.0, NH), 6.86-7.02 (4H, m, ArH), 7.17-7.45 (10H, m, ArH), 8.42 (1H, s, HC=N).

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



This compound was prepared from the reaction of **(*R*,*R*)-Phg-A1** (0.17 g, 0.67 mmol) and salicylaldehyde (70 μL, 0.68 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.18 g, 0.50 mmol, 74 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (3H, d, *J* = 7.0, CH(Ph)CH_3), 4.28 (1H, s, α-CH), 5.11-5.23 (1H, m, CH(Ph)CH_3), 6.44 (1H, d, *J* = 7.5, NH), 6.86-7.02 (4H, m, ArH), 7.17-7.45 (10H, m, ArH), 8.41 (1H, s, HC=N).

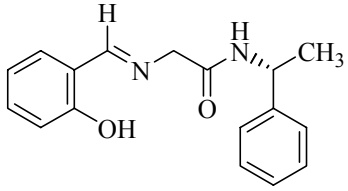
2.6.10 *N*-salicylidene-glycyl-(*S*)-(1-phenylethyl)amine ((*S*)-S1-Gly-A1).



This compound was prepared from the reaction of **(*S*)-Gly-A1** (0.17 g, 0.67 mmol) and salicylaldehyde (70 μL, 0.68 mmol) following the general procedure in section 2.6. The desired product was obtained as a yellow solid (0.18 g, 0.50 mmol, 74 %). ^{1}H NMR (200

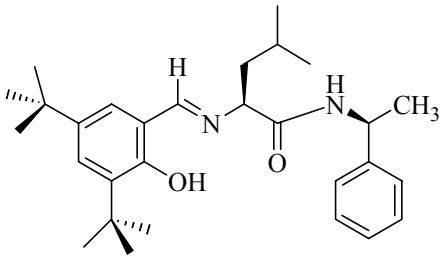
MHz, $CDCl_3$) δ 1.50 (3H, d, *J* = 6.0, C<u>H</u>$_3$), 4.30 (2H, s, α-C<u>H</u>), 5.05-5.20 (1H, m, C<u>H</u>(Ph)CH_3), 6.80-7.00 (4H, m, Ar<u>H</u>), 7.26-7.30 (5H, m, Ar<u>H</u>), 8.33 (1H, s, <u>H</u>C=N).

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



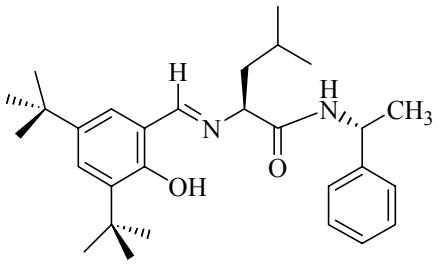
This compound was prepared from the reaction of **(*R*)-Gly-A1** (0.05 g, 0.28 mmol) and salicylaldehyde (29 μL, 0.28 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.06 g, 0.22 mmol, 78 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 (3H, d, *J* = 6.0, C<u>H</u>$_3$), 4.30 (2H, s, α-C<u>H</u>), 5.05-5.20 (1H, m, C<u>H</u>(Ph)CH_3), 6.80-7.00 (4H, m, Ar<u>H</u>), 7.26-7.30 (5H, m, Ar<u>H</u>), 8.33 (1H, s, <u>H</u>C=N).

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



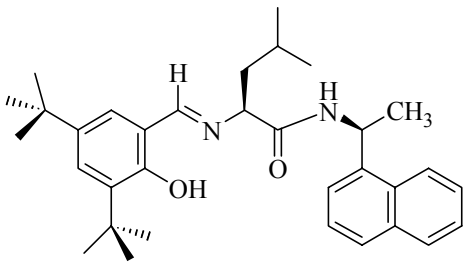
This compound was prepared from the reaction of **(*S*,*S*)-Leu-A1** (0.12 g, 0.51 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.12 g, 0.51 mmol) following the procedure described in section 2.6. The desired product was obtained as a yellow solid (0.17 g, 0.37 mmol, 72 %). mp: 152.7-153.9 °C. $[\alpha]_D^{26.2}$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

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



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

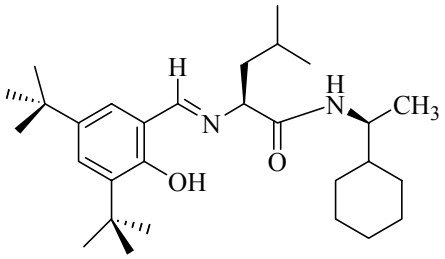
2.6.14 *N*-(3, 5)-*tert*-butyl-salicylidine-(*S*)-leucyl-(*S*)-(1-naphthylethyl)amine ((*S*,*S*)-S2-Leu-A2).



This compound was prepared from the reaction of **(*S*,*S*)-Leu-A2** (0.16 g, 0.55 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.13 g, 0.55 mmol) following the general procedure for preparation of salicylimine ligands described in section 2.6. The desired product was obtained as a yellow solid (0.12 g, 0.25 mmol, 46%) mp: 162.7-163.4 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +145.7°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 6.5, CH(C<u>H</u>$_3$)$_2$), 0.94 (3H, d, *J* = 6.5, CH(C<u>H</u>$_3$)$_2$), 1.26 (9H, s, *p*-C(C<u>H</u>$_3$)$_3$), 1.41 (9H, s, *o*- C(C<u>H</u>$_3$)$_3$), 1.64-1.67 (3H, d, *J* = 8, CH(1-naph)C<u>H</u>$_3$), 1.85-1.98 (3H, m, C<u>H</u>(CH$_3$)$_2$ and C<u>H</u>$_2$), 3.85-4.00 (1H, m, α-C<u>H</u>), 5.85-5.95 (1H, m,

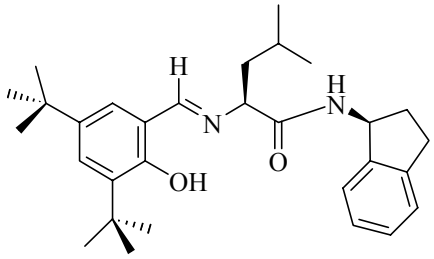
C<u>H</u>(1-naph)CH_3), 6.51 (1H, d, *J* = 8.0, N<u>H</u>), 7.05 (1H, d, *J* = 6.0, Ar<u>H</u>), 7.41 (5H, d, *J* = 2.4, Ar<u>H</u>), 7.65-7.85 (2H, m, Ar<u>H</u>), 8.06 (1H, d, *J* = 2.3, Ar<u>H</u>), 8.30 (1H, s, C<u>H</u>=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.1 (CH(<u>C</u>H_3)$_2$), 22.6 (<u>C</u>H_3CHPh), 23.4 (CH(<u>C</u>H_3)$_2$), 24.3 (<u>C</u>H$(CH_3)_2$), 29.4 (C(<u>C</u>H_3)$_3$), 31.4 (<u>C</u>$(CH_3)_3$), 35.0 (<u>C</u>$(CH_3)_3$), 43.2 (<u>C</u>H_2), 44.9 (<u>C</u>HNH), 72.0 (α-<u>C</u>H), 117.5, 122.4, 123.2, 125.7, 126.4, 126.6 127.9, 128.2, 128.8, 138.3, 140.8, 143.0 (Ar), 157.7 (C-OH), 168.2 (C=N), 171.2 (C=O). MS (FAB+) *m/z* (relative intensity) 501 $[M+H]^+$ (40), 316 (18), 301 (10), 288 (7), 258 (7), 244 (7), 233 (9), 219 (9), 218 (7), 155 $[CH(1\text{-napthyl})CH_3]^+$ (100). Anal. Calcd for $C_{33}H_{44}N_2O_2$: C, 79.16; H, 8.86; N, 5.59. Found: C, 79.19; H, 8.88; N, 5.57.

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



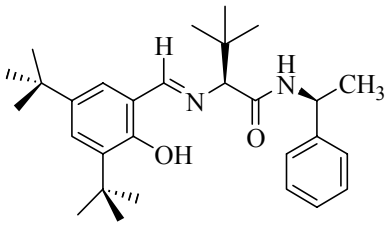
This compound was prepared from the reaction of **(*S*,*S*)-Leu-A4** (0.16 g, 0.68 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.16 g, 0.68 mmol) following the procedure for preparation of salicylimine ligands. The desired product was obtained as a yellow solid (0.22 g, 0.49 mmol, 72 %) mp: 172.9-173.7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

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



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

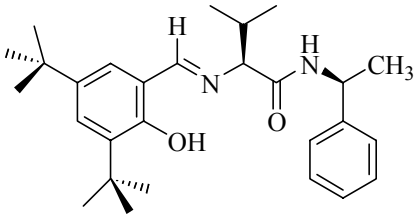
2.6.17 *N*-(3,5)-di-*tert*-butylsalicylidene-(*S*)-*tert*-leuyl-(*S*)-(1-phenyleythyl)amine ((*S*,*S*)-S2-*t*Leu-A1).



This compound was prepared from the reaction of **(*S*,*S*)-tLeu-A1** (0.11 g, 0.48 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.11 g, 0.48 mmol) following the general procedure. The desired product was obtained as a yellow solid (0.14 g, 0.32 mmol, 67 %), mp: 151.4-152.5 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +109.3°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (9H, s, CH(C<u>H</u>$_3$)$_3$), 1.31 (9H, s, *p*-C(C<u>H</u>$_3$)$_3$), 1.46 (9H, s, *o*-C(C<u>H</u>$_3$)$_3$), 1.52 (3H, d, *J* = 7.0, CHC<u>H</u>$_3$), 3.54 (1H, s, α-C<u>H</u>), 4.95-5.20 (1H, m, C<u>H</u>Ph), 6.35 (1H, d, *J* = 8.0, NH), 7.11 (1H, d, J = 2.5, Ar<u>H</u>), 7.10-7.27 (5H, m, Ar<u>H</u>), 7.43 (1H, d, *J* = 2.5, Ar<u>H</u>), 8.26 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.8 (NHCH<u>C</u>H$_3$), 27.3 (CHC(<u>C</u>H$_3$)$_3$), 29.4 (*o*-C(<u>C</u>H$_3$)$_3$), 31.4 (*p*-C(<u>C</u>H$_3$)$_3$), 34.2 (<u>C</u>(CH$_3$)$_3$), 35.1 (<u>C</u>(CH$_3$)$_3$), 48.7 (<u>C</u>HNH), 83.6 (α-<u>C</u>H), 117.6, 125.8, 126.7, 127.3, 127.9,

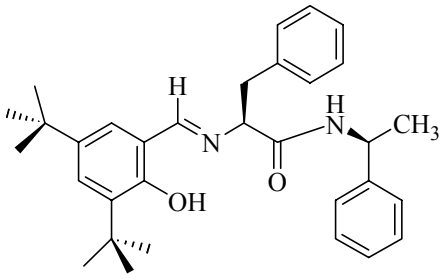
128.7, 136.9, 140.8, 142.9 (Ar), 157.8 (C-OH), 167.1 (C=N), 171.3 (C=O). MS (FAB+) *m/z* (relative intensity) 451 $[M+H]^+$ (100), 435 (12), 395 (10), 302 (20), 105 $[CHCH_3Ph]^+$ (34). Anal. Calcd for $C_{29}H_{42}N_2O_2$: C, 77.29; H, 9.39; N, 6.22. Found: C, 77.19; H, 9.42; N, 6.29.

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



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

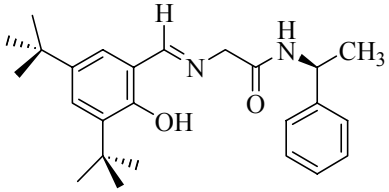
2.6.19 *N*-(3,5)-di-*tert*-butylsalicylidene-(*S*)-phenyl-alanyl-(*S*)-(1-phenyleythyl)amine ((*S*,*S*)-S2-Phe-A1).



This compound was prepared from the reaction of **(*S*,*S*)-Phe-A1** (0.15 g, 0.59 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.14 g, 0.59 mmol) following the procedure described in section 2.6. The desired product was obtained as a yellow solid (0.21 g, 0.41 mmol, 72 %). mp:

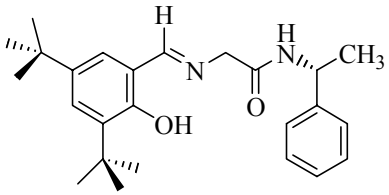
142.1-142.7 °C. $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = -34.9°. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (9H, s, *p*-C(C<u>H</u>$_3$)$_3$), 1.42 (3H, d, *J* = 7.5, C<u>H</u>$_3$), 1.44 (9H, s, *o*-C(C<u>H</u>$_3$)$_3$), 3.13 (1H, dd, *J* = 13.5, 8.0, C<u>H</u>$_2$), 3.39 (1H, dd, *J* = 13.5, 4.0, C<u>H</u>$_2$), 4.01 (1H, dd, *J* = 8.0, 4.0, α-C<u>H</u>), 5.08 (1H, q, *J* = 7.5, C<u>H</u>(Ph)CH$_3$), 6.33 (1H, d, *J* = 7.5, N<u>H</u>), 6.91 (1H, d, *J* = 2.5, Ar<u>H</u>), 7.14-7.28 (10H, m, Ar<u>H</u>), 7.39 (1H, d, *J* = 2.5, Ar<u>H</u>), 7.94 (1H, s, <u>H</u>C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3 (<u>C</u>H$_3$), 29.4 (*o*-C(<u>C</u>H$_3$)$_3$), 31.4 (*p*-C(<u>C</u>H$_3$)$_3$), 34.1 (<u>C</u>(CH$_3$)$_3$), 35.1 (<u>C</u>(CH$_3$)$_3$), 41.1 (<u>C</u>H$_2$), 49.0 (<u>C</u>HNH), 75.0 (α-<u>C</u>H), 117.5, 125.9, 126.6, 127.3, 128.0, 128.4, 128.7, 129.8, 136.8, 137.0, 140.7, 142.8 (Ar), 157.7 (<u>C</u>-OH), 168.5 (<u>C</u>=N), 170.0 (<u>C</u>=O). MS (FAB+) *m/z* (relative intensity) 485 $[M+H]^+$ (100), 469 (10), 429 (3), 381 (3), 336 (15), 288 (5), 269 (5), 244 (7), 234 (10), 218 (9), 105 $[CHCH_3Ph]^+$ (38). Anal. Calcd for $C_{29}H_{42}N_2O_2$: C, 79.30; H, 8.32; N, 5.78. Found: C, 79.28, H, 8.32; N, 5.79.

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



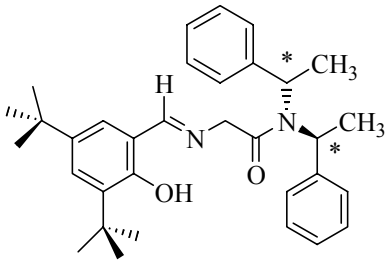
This compound was prepared from the reaction **(*S*)-Gly-A1** (0.08 g, 0.43 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.10 g, 0.43 mmol) following the procedure described in section 2.6. The product was obtained as a yellow solid (0.09 g, 0.23 mmol, 57 %). mp: 146.1-146.4 °C. $[\alpha]_D^{26.2}$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

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



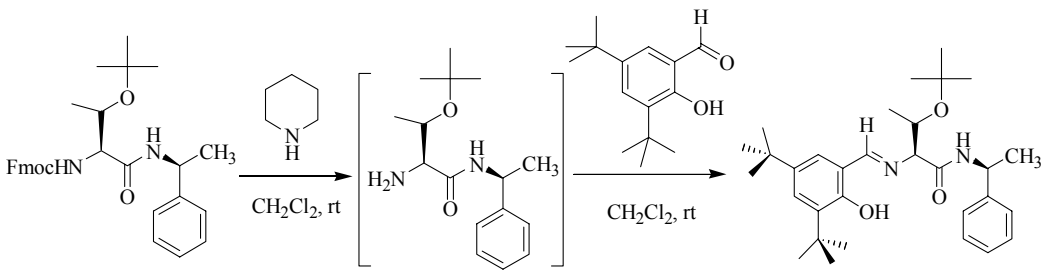
This compound was prepared from the reaction **(*R*)-Gly-A1** (0.09 g, 0.50 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.11 g, 0.50 mmol) following the general procedure described in section 2.6. The desired product was obtained as a yellow solid (0.13 g, 0.33 mmol, 66 %). mp: 142.5-144.7 °C. $[\alpha]_D^{26.2}$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

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



This compound was prepared from the reaction **(*S*)-Gly-A6** (1.02 g, 3.62 mmol) and 3,5-di-*tert*-butylsalicylaldehyde (0.85 g, 3.62 mmol) following the procedure described in section 2.6. The desired product was obtained as a yellow solid (0.20 g, 0.40 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (9H, s, *p*-C(C$\underline{H}_3$)$_3$), 1.43 (9H, s, *o*-C(C$\underline{H}_3$)$_3$), 1.74 (3H, br, CH(Ph)C$\underline{H}_3$), 1.86 (3H, br, CH(Ph)C$\underline{H}_3$), 4.00 (2H, d, *J* = 12.0 α-C$\underline{H}$), 4.28 (2H, d, *J* = 14.0, C$\underline{H}$(Ph)CH_3), 7.36 (1H, d, *J* = 2.5, Ar$\underline{H}$), 7.19-7.21 (5H, m, Ar$\underline{H}$), 8.27 (1H, s, $\underline{H}$C=N). ^{13}C NMR (50 MHz, $CDCl_3$) δ 29.2 (*o*-C(C$\underline{H}_3$)$_3$), 29.4 (C$\underline{H}_3$), 31.3 (*p*-C(C$\underline{H}_3$)$_3$), 31.5 (C$\underline{H}_3$), 34.1 (C$\underline{(CH_3)_3}$), 35.0 (C$\underline{(CH_3)_3}$), 53.1 (C$\underline{H}$N), 62.4 (α-C$\underline{H}_2$), 117.9, 126.4, 127.3, 127.5, 127.8, 127.9, 128.0, 128.2, 128.3, 128.5, 131.9, 136.5, 140.0, 140.6 (Ar), 157.9 (C$\underline{-}$OH), 168.9 (C$\underline{=}$N), 169.6 (C$\underline{=}$O). MS (FAB+) *m/z* (relative intensity) 499 $[M+H]^+$ (30), 395 (15), 219 (11), 105 $[CHCH_3Ph]^+$ (100).

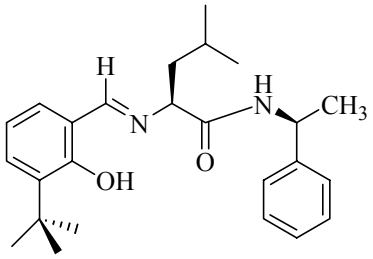
2.6.23 *N*-(3,5)-di-*tert*-butylsalicylidene -(*S*)-Thr(*tert*-butyl)-(*S*)-(1-phenylethyl)amine ((*S*, *S*)-S2-Thr(^{t}Bu)-A1).



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

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

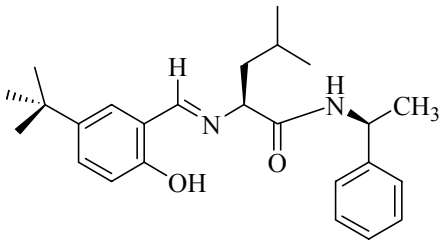
2.6.24 *N*-3-*tert*-butylsalicylidene -(*S*)-leucyl-(S)-(1-phenylethyl)amine ((*S*,*S*)-S3-Leu-A1).



This compound was prepared from the reaction of **(*S*,*S*)-Leu-A1** (0.16 g, 0.67 mmol) and 3-*tert*-butylsalicylaldehyde (0.12 g, 0.67mmol) following the procedure described in section

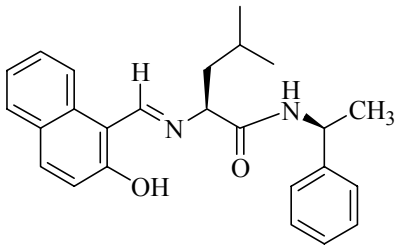
2.6. The desired product was obtained as a yellow solid (0.17 g, 0.43 mmol, 64%). mp: 151.2-152.2 °C $[\alpha]_D^{26.2}$ (c 1.0, $CHCl_3$) = +138.9 °. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3$)$_2$), 0.94 (3H, d, *J* = 7.0, CH(C<u>H</u>$_3$)$_2$), 1.44 (9H, s, *o*-C(C<u>H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

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



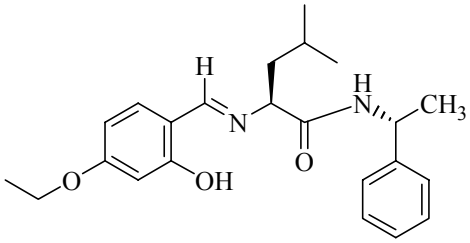
This compound was prepared from the reaction of **(*S*, *S*)-Leu-A1** (0.16 g, 0.67 mmol) and 3-*tert*-butylsalicylaldehyde (0.12 g, 0.67mmol) following the general procedure described in section 2.6. The desired product was obtained as a yellow solid (0.17 g, 0.43 mmol, 64%). mp: 90.7-92.5 °C. $[\alpha]_D^{26.2}$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

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



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

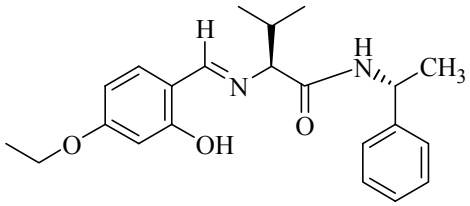
2.6.27 *N*-4-ethoxy-salicylidene-(*S*)-leucyl-(*R*)-(1-phenyleythyl)amine ((*S*,*R*)-S6-Leu-A1).



This compound was prepared from the reaction of **(*S*, *R*)-Leu-A1** (0.11 g, 0.49 mmol) and 4-ethoxysalicylaldehyde (0.08 g, 0.49 mmol) following the general procedure described in section 2.6. The desired product was obtained as a yellow solid (0.13 g, 0.34 mmol, 70 %). mp: 113.6-118.0 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (6H, d, *J* = 6.5, CH(C<u>H</u>$_3$)$_2$), 1.44 (3H, t, *J* = 7.0, CH$_2$C<u>H</u>$_3$), 1.46 (3H, d, *J* = 7.0, CH(Ph)C<u>H</u>$_3$), 1.73-1.80 (3H, m, C<u>H</u>$_2$ and C<u>H</u>(CH$_3$)$_2$), 3.88 (1H, dd, *J* = 9.0, 4.5, α-C<u>H</u>), 4.05 (2H, q, *J* = 7.0, C<u>H</u>$_2$CH$_3$), 5.12 (1H, m, C<u>H</u>(Ph)CH$_3$), 6.26 (1H, d, *J* = 8.0, N<u>H</u>), 7.11 (1H, d, *J* = 8.5, Ar<u>H</u>), 7.16-7.32 (7H, m, Ar<u>H</u>), 8.23 (1H, s, <u>H</u>C=N).

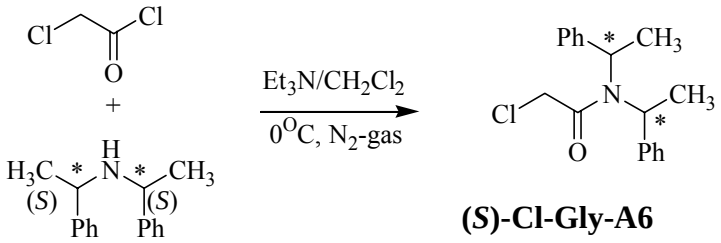
^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6 ($OCH_2\underline{C}H_3$), 21.0 ($CH_2CH(\underline{C}H_3)_2$), 22.0 ($NHCH\underline{C}H_3$), 23.3 ($CH_2CH(\underline{C}H_3)_2$), 24.3 ($CH_2\underline{C}H(CH_3)_2$), 43.3 ($\underline{C}H_2$), 48.9 ($\underline{C}HNH$), 63.8 ($O\underline{C}H_2CH_3$), 72.0 (α-$\underline{C}H$), 101.5, 107.4, 112.1, 125.8, 127.3, 128.7, 133.3, 136.1, 143.0 (Ar), 163.2 ($\underline{C}$-OH), 166.1 ($\underline{C}$=N), 171.4 ($\underline{C}$=O).

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



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

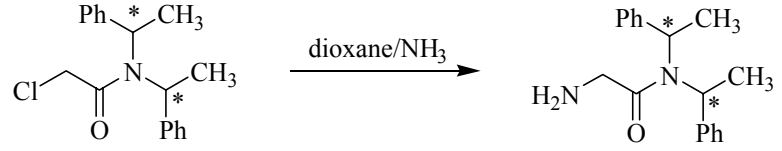
2.7 Preparation of 2-chloro-[*S*-(*R,*R**)]-*N*,*N*-bis (phenylethyl)acetamide ((*S*)-Cl-Gly-A6).**



(*S*)-Cl-Gly-A6

Chiral amine -[*S*-(*R**,*R**)]-*N*,*N*-bis (phenylethyl)amine (288 μL, 1 mmol) was dissolved in Et_3N (279 μL, 2 mmol) at room temperature. After stirring for 10 min., the mixture was cooled down to 0 ^{O}C then the 1-chloroacetylchloride was added dropwise under N_2-atmosphere. The mixture was stirred for 6 h The mixture was treated with 5% HCl and washed with 10% aqueous $NaHCO_3$. The organic layer was washed with water and dried over anhydrous $MgSO_4$. The solid was filtered and the filtrate was evaporated by a rotary evaporator to give the crude product. The product was further purified by column chromatography on silica gel with 20% ethyl acetate in hexanes to give the desired product as a white solid (0.24 g, 0.8 mmol, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71-1.88 (6H, br, $C\underline{H}_3$), 3.77 (1H, d, *J* = 12.0, α-$C\underline{H}$), 3.92 (1H, d, *J* = 12.0, α-$C\underline{H}$), 4.82-5.18 (1H, br, $C\underline{H}$Ph), 5.38-5.60 (1H, br, $C\underline{H}$Ph), 6.90-7.35 (10H, m, ArH).

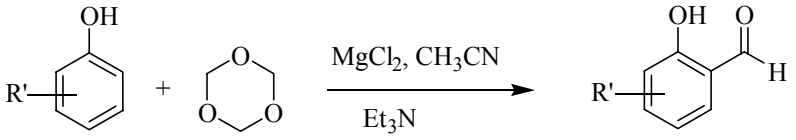
2.8 Preparation of 2-amino-[*S*-(*R,*R**)]- *N*,*N*-bis(phenylethyl)acetamide ((*S*)-Gly-A6).**



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

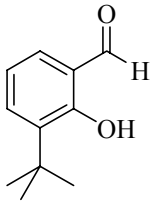
To a solution of **(*S*)-Cl-Gly-A6** (0.24 g, 0.8 mmol) in dioxane (2 mL) and concentrated ammonia solution (2 mL) was stirred and gently warmed (not over 50 °C) in a closed system (scaled test tube). The reaction was completed in 2 h The solvent was removed by a rotary evaporator to give the desired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

2.9 General procedure for preparation of salicylaldehyde.



Salicylaldehyde derivative was prepared according to the method by Skattebol *et al*.[20] with a slight modification. Phenol derivative (20 mmol) and anhydrous magnesium chloride (30 mmol) were dissolved in acetonitrile 100 mL in a 250 mL round bottomed flask then triethylamine (10 mL) (dried over molecular sieves) was added. To the mixture, paraformaldehyde (135 mmol) was added to give a yellow solution. After refluxing for 3 h, the mixture was cooled down to room-temperature then acidified with 2 M HCl. The mixture was extracted with ether (20×3 mL). The organic layer was dried over anhydrous $MgSO_4$. The solid was filtered and the filtrate was evaporated by a rotary evaporator to give the crude product. The product was further purified by column chromatography on silica gel with 10% ethyl acetate in hexanes to give the desired product.

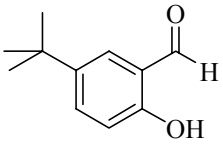
2.9.1 3-*tert*-butylsalicylaldehyde (S3).



This compound was prepared from the reaction of 2-*tert*-butylphenol (3.06 mL, 20 mmol) following the general procedure for preparation of salicylicylaldehyde described in section 2.9. The desired product was obtained as a yellow oil (1.96 g, 11 mmol, 55%). ^{1}H NMR (400 MHz,

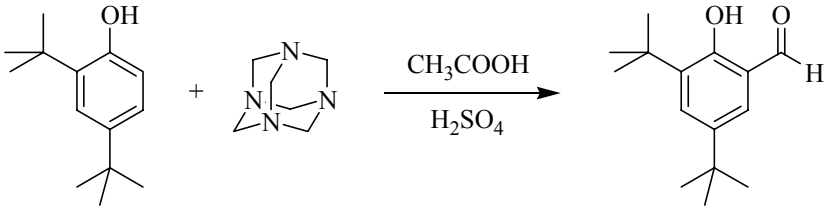
$CDCl_3$) δ 1.41 (9H, s, C<u>H</u>$_3$), 6.93 (1H, t, *J* = 7.5, Ar<u>H</u>), 7.39 (1H, d, *J* = 7.0, Ar<u>H</u>), 7.48 (1H, d, *J* = 7.0, Ar<u>H</u>), 9.86 (1H, s, C<u>H</u>O), 11.77 (1H, s, O<u>H</u>).

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



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

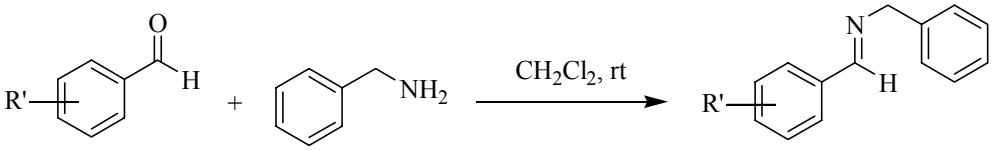
2.10 Preparation of 3,5-*tert*-butylsalicylaldehyde (S2).



S2

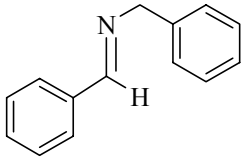
Salicylaldehyde derivative was prepared according to the method described by Jacobsen *et al*.[21] with a slight modification. Hexamine (17 g, 120 mmol), 2,4-di-*tert*-butylphenol (12.5 g, 60 mmol) and glacial acetic acid (30 mL) were combined in 250 round bottomed flask. The mixture was heated to 130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

2.11 General procedure for preparation of imine.



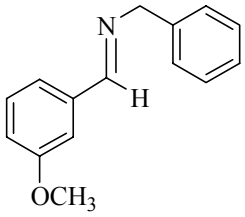
Imine was prepared according to the method reported by Jocobsen et al.[15] To a 25 mL round bottomed flask was added activated 3 Å molecular sieves and 5 mL dichloromethane. To this solution, benzylamine (0.55 mL, 5 mmol) was added followed by slow syringe addition of aldehyde (5 mmol). When all the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

2.11.1 *N*-benzylidene benzylamine (1).



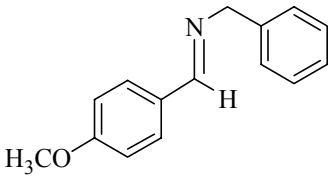
This compound was prepared from the reaction of benzaldehyde (1.02 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as a yellow oil (1.70 g, 8.7 mmol, 87%). ^{1}H NMR (200 MHz, $CDCl_3$)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

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



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

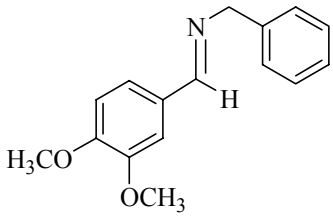
2.11.3 4-Methoxy-*N*-benzylidene benzylamine (4).



This compound was prepared from the reaction of 4-methoxybenzaldehyde (1.20 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (1.37 g, 50

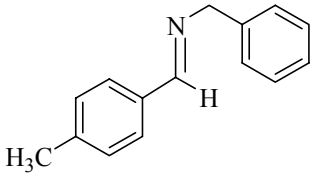
mmol, >95%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.93 (3H, s, OC<u>H</u>$_3$), 4.88 (2H, s, C<u>H</u>$_2$), 7.02 (1H, d, *J* = 8.5, Ar<u>H</u>), 7.35-7.45 (5H, m, Ar<u>H</u>), 8.42 (1H, s, <u>H</u>C=N).

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



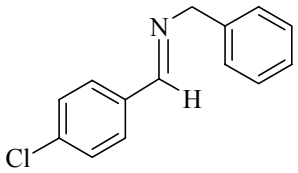
This compound was prepared from the reaction of 3,4-di-methoxybenzaldehyde (0.8 g, 5 mmol) and benzylamine (0.35 mL, 5 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (1.27 g, 5 mmol, >95%). ^{1}H NMR (200 MHz, $CDCl_3$)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

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



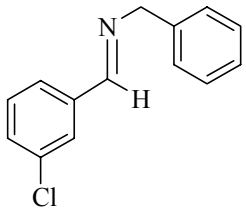
This compound was prepared from the reaction of *p*-tolualdehyde (1.18 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (2.04 g, 10 mmol, 98%). ^{1}H NMR (200 MHz, $CDCl_3$)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

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



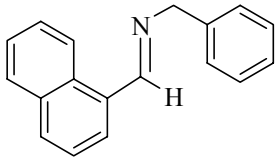
This compound was prepared from the reaction of 4-chlorobenzaldehyde (1.40 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (1.82 g, 8 mmol, 79%). ^{1}H NMR (200 MHz, $CDCl_3$)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

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



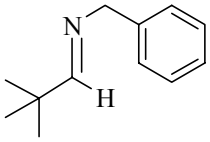
This compound was prepared from the reaction of 3-chlorobenzaldehyde (1.14 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (2.53 g, 10 mmol, 99%). ^{1}H NMR (200 MHz, $CDCl_3$)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

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



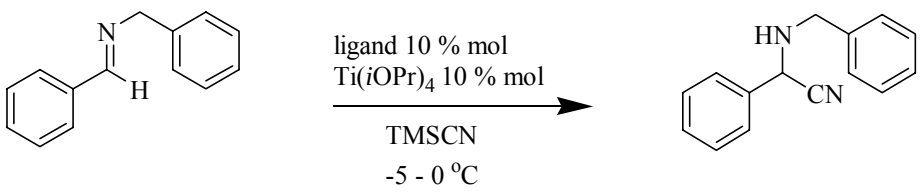
This compound was prepared from the reaction of 1-naphthylaldehyde (1.36 mL, 10 mmol) and benzylamine (0.69 mL, 10 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (2.35 g, 9.6 mmol, 96%). ^{1}H NMR (200 MHz, $CDCl_3$) 4.97 (2H, s, C<u>H</u>$_2$), 7.35-7.44 (7H, m, Ar<u>H</u>), 7.51-7.60 (5H, m, Ar<u>H</u>), 9.06 (1H, s, <u>H</u>C=N).

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



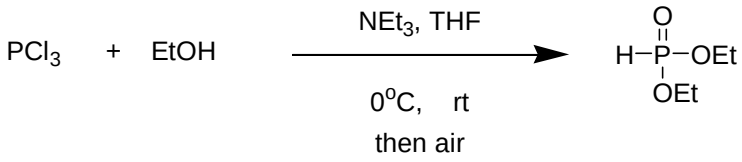
This compound was prepared from the reaction of pivalaldehyde (0.55 mL, 5 mmol) and benzylamine (0.55 mL, 5 mmol) following the general procedure for preparation of imine described in section 2.11. The desired product was obtained as yellow oil (0.69 g, 4 mmol, 79%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.88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

2.12 General procedure for catalysis screening in the asymmetric Strecker reactions.



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

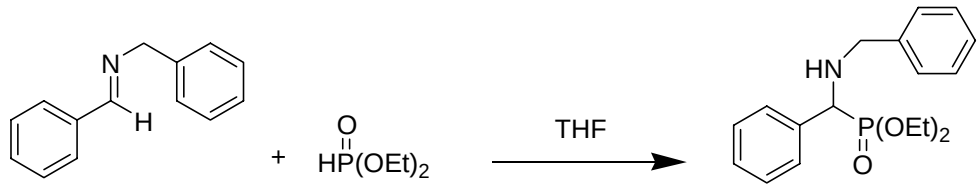
2.13 Synthesis of diethyl phosphite



A solution of ethanol (29 mL, 0.495 mol) in dry THF (500 mL) was placed in a three-neck round bottom flask cooled in an ice bath. A solution of phosphorus trichloride (13 mL, 0.15 mol) in dry THF (50 mL) was added dropwise with vigorous stirring under a nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for additional for 2-3 h. Air was passed through the mixture. After 0.5 h, triethylamine (46 mL, 0.33 mol) in THF (100 mL) was added to the flask at 0°C (ice bath). The mixture was let stand at room temperature for 2 h. The precipitates were then removed by filtration. The THF was removed to afford a colorless liquid (60-65%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (s, $^3J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 4.05 (dq, $^3J_{HH}$ = 7.1 Hz, $^2J_{HP}$ = 9.0 Hz, 2H, $OC\underline{H}_2CH_3$), 4.11 (dq, $^3J_{HH}$ = 7.1 Hz, $^2J_{PH}$ = 9.0 Hz, 2H, $OC\underline{H}_2CH_3$), 6.75 (d, $^1J_{HP}$ = 692.4 Hz, 1H, C<u>H</u>P).

2.14 Catalytic asymmetric synthesis of α-aminophosphonates

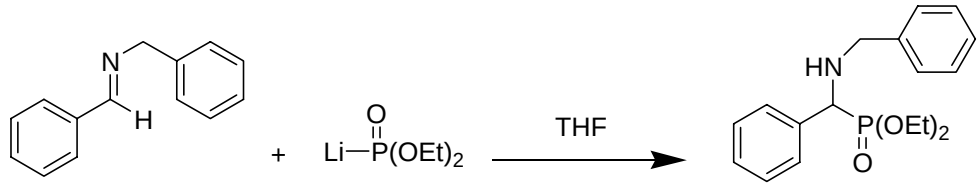
2.14.1 Procedures for the preparation of racemic α-aminophosphonates



I-1 **II-1**

Method A: To an oven-dried 10 mL round bottom flask equipped with a stirrer bar was added a solution of imine **I-1** (0.0975 g, 0.5 mmol) in 4 mL of dry THF, and a solution of 10 mol% of $Ti(O^iPr)_4$ in 1 mL of dry THF. A reaction was stirred for 10 min then diethyl phosphite (225 μL, 1.75 mmol) was added *via* syringe. The solution was allowed to stir for 3d at 70°C under a nitrogen atmosphere. The mixture was quenched with H_2O (2 mL). Most of the THF

was removed *in vacuo* and the product was extracted with EtOAc. The organic layer was dried with anhydrous sodium sulfate and then concentrated. Analytically pure **II-1** was then obtained by column chromatography (gradient elution, 10%-25% EtOAc/hexanes) as a yellow oil (0.1184 g, 0.36 mmol, 71%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H, $OCH_2C\underline{H}_3$), 1.25 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 3.55-4.05 (m, 7H, $OC\underline{H}_2CH_3$, $C\underline{H}_2Ph$, $C\underline{H}P$), 7.21-7.39 (m, 10H, Ar); ^{13}C NMR ($CDCl_3$, 50 MHz, {^{1}H}) δ 16.28 (d, $^{3}J_{CP}$ = 9.5 Hz, $OCH_2\underline{C}H_3$), 16.44 (d, $^{3}J_{CP}$ = 5.9 Hz, $OCH_2\underline{C}H_3$), 51.15 (d, $^{3}J_{CP}$ = 17.3 Hz, $\underline{C}H_2Ph$), 59.51 (d, $^{1}J_{CP}$ = 152.8 Hz, $\underline{C}HP$), 62.86 (d, $^{2}J_{CP}$ = 8.0 Hz, $O\underline{C}H_2CH_3$), 63.01 (d, $^{2}J_{CP}$ = 7.7 Hz, $O\underline{C}H_2CH_3$), 127.14, 127.98, 128.37, 128.47, 128.62, 128.75, 135.65, 139.25.



I-1 **II-1**

Method B: *n*-Butyl lithium (1.64 M in hexanes, 0.30 mL, 0.5 mmol) was added *via* syringe to a solution of diethyl phosphite (1 mmol, 0.128 mL) in dry THF (1 mL) at -78°C under a nitrogen atmosphere. The reaction was stirred for 0.5 h then warmed to room temperature. This mixture was then added to a solution of imine **I-1** (0.0975 g, 0.5 mmol) in dry THF (1 mL). After 1d, the mixture was quenched with water (1 mL). Solvent was removed and the aqueous layer was extracted with EtOAc (4 × 2 mL). The combined extracts were dried ($NaSO_4$), filtered, and concentrated. Purification of crude material by column chromatography (gradient elution, 10% to 25% EtOAc/Hexane) resulted in the desired α-aminophosphonates **II-1** (0.063 g, 0.19 mmol, 38%).

2.14.2 General procedure for asymmetric synthesis of α-aminophosphonate (II-1)

Method A : A chiral ligand (0.025 mmol) and $Ti(O^{i}Pr)_4$ (0.025 mmol) were placed in an oven-dried 10 mL round bottom flask. The mixture was dissolved in dry THF (1 mL) and stirred for 15 min at room temperature. Subsequently, a solution of imine **I-1** (0.25 mmol) in 1 mL of dry THF was added by syringe. Diethyl phosphite (0.064 mL, 2 eq) was added to the mixture and was stirred for 3 d at 70ºC. The solvent was then removed by distillation at reduced pressure to give a crude product. Purification of the crude material by column chromatography (gradient elution, 10% to 25% EtOAc/hexanes) yielded the desired α-aminophosphonate **II-1**.

Method B : In an oven-dried round bottom flask, a solution of diethyl phosphite (0.128 mL, 1 mmol) in dry THF (1 mL) was cooled to -78ºC and treated dropwise with *n*-butyl lithium (1.64 M in hexanes, 0.30 mL, 0.5 mmol). After 0.5 h, the mixture was warmed to room temperature and added *via* syringe to a solution of a chiral ligand (0.5 mmol) in dry THF (1 mL)

at room temperature. The reaction mixture was stirred for 0.5 h and then treated with a solution of imine **I-1** (0.0975 g, 0.5 mmol) in dry THF (1 mL). The reaction was let stand for 1 d at room temperature, quenched with water (2 mL) and extracted with Et_2O (4 × 2 mL). The organic layer was dried over Na_2SO_4. Evaporation of the solvent followed by purification with column chromatography gave **II-1**.

2.15 General methods for optical purity determination of α-aminophosphonates

2.15.1 Analysis of α-aminophosphonates II-1 using a chiral HPLC column

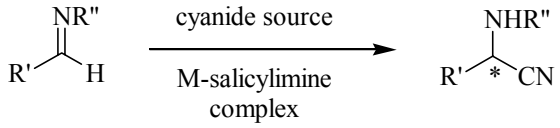
α-Aminophosphonates were dissolved in an appropriate solvent composition (9:1 hexanes/2-propanol) and filtered through a membrane filter. An aliquot of the solution was injected into the Daicel Chiralcel OD® column. Elution with the mobile phase 95:5 to 90:10 (hexanes/2-propanol) resulted in no separation. An alternative Daicel Chiralpak AD® column was employed. Elution of an α-aminophosphonate mixture by the mobile phase 90:10 to 98:2 (hexanes/2-propanol) gave a satisfactory separation of enantiomeric peaks of α-aminophosphonate **II-1**.

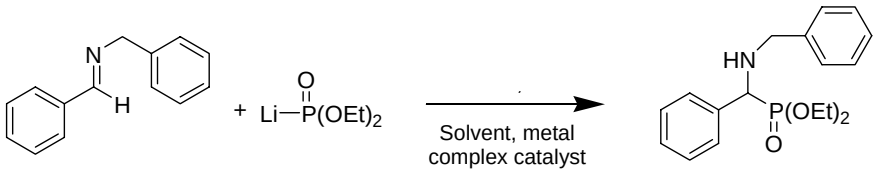
2.15.2 Analysis of α-aminophosphonates II-1 using ^{1}H NMR spectroscopy

The enantiomeric purities of the optically active α-aminophosphonates were determined by ^{1}H NMR spectroscopy at 200 MHz from a solution in $CDCl_3$ upon an addition of chiral solvating agents such as *R*-(-)-α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's acid), (*1S*)-(+)-camphor-10-sulfonic acid (CSA), *R*-(-)-α-acetoxyphenylacetic acid (APA), *R*-(+)-1,1'-binaphthalene-2,2'-diyl hydrogenphosphate (BNP), and *R*-(+)-1,1'-bi(2-naphthol). The ^{1}H NMR spectra were recorded at intervals of each 1 eq of chiral solvating agent added.

3. RESULTS AND DISCUSSION

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





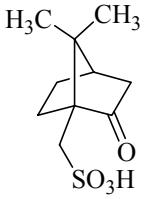
3.1 RESULTS ON STRECKER REACTION

3.1.1 Analytical method: Determination of yield and enantiomeric excess of α-aminonitriles

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

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

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



(*S*)-CSA

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

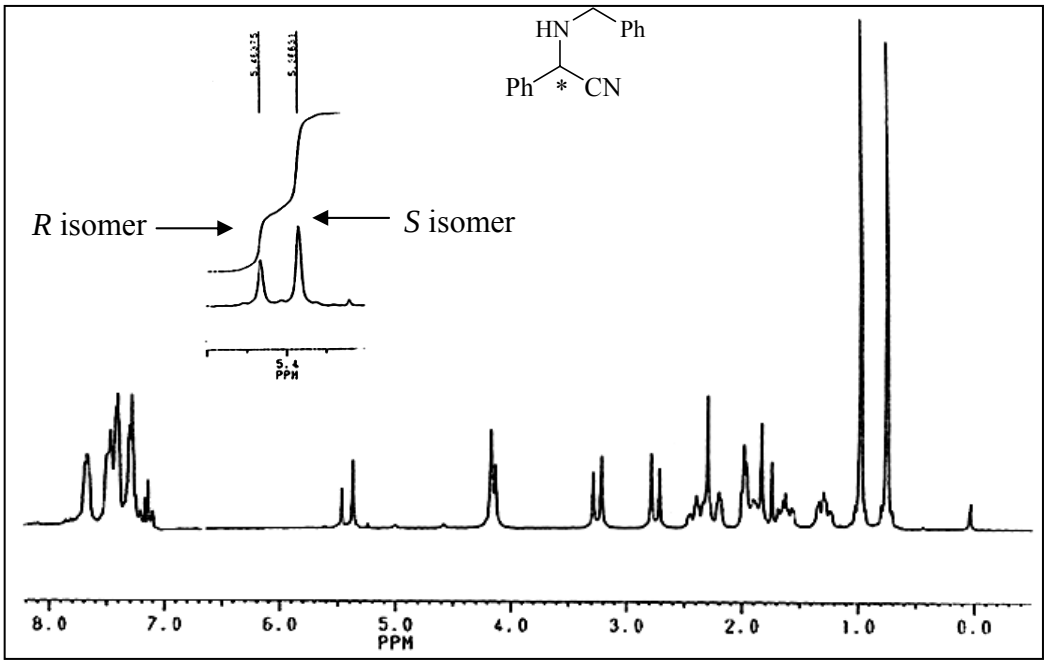
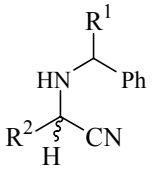


Figure 3.1 Spectrum of 2-benzylamino-2-phenylacetonitrile in the presence of CSA.

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



α-aminonitrile

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

[a]condition: 2 eq of TMSCN, 0.3 mL MeOH, rt, 30 min. [b]Only relative configuration was assigned except for the first entry that the absolute configuration was known. [c] δ of $C\underline{H}_2$ (not an α-H)

3.1.2 Synthesis

3.1.2.1 Imine substrates

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

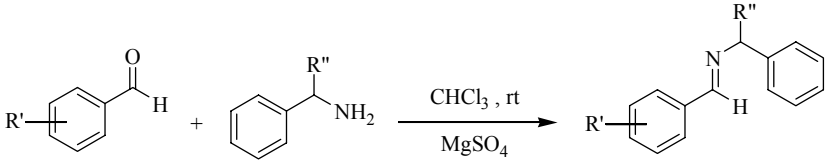


Figure 3.2 Imine substrate synthesis

Table 3.2 Percent yield of imine substrate.

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

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

3.1.2.2 Salicylimine ligands

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

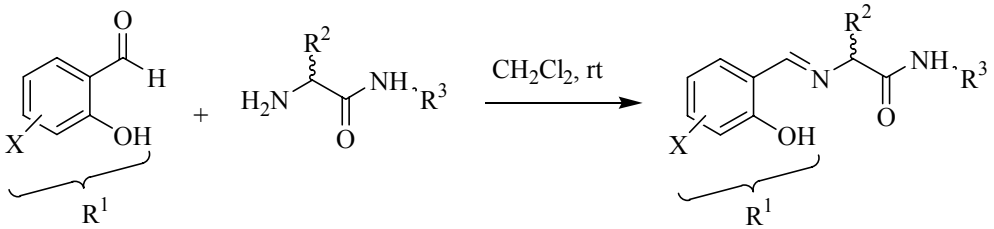
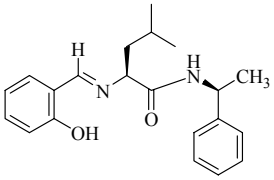
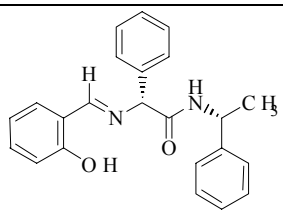
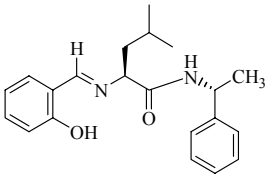
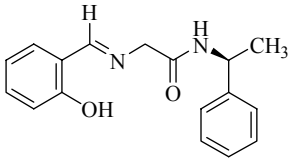
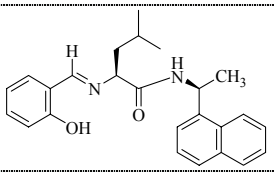
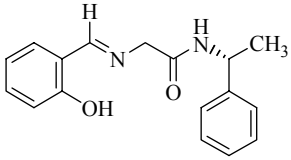
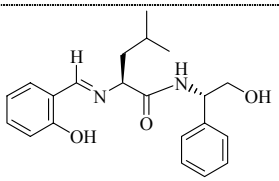
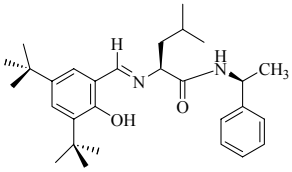
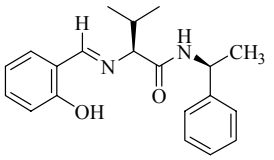
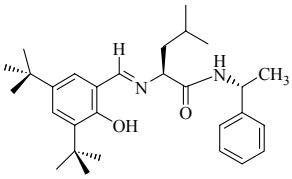
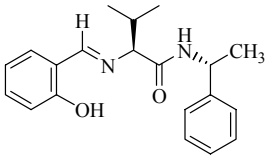
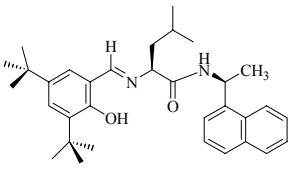
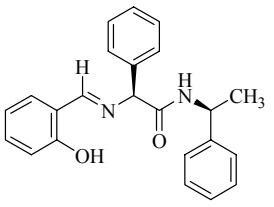
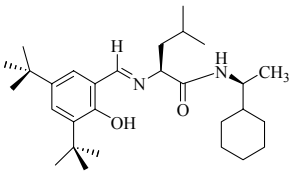
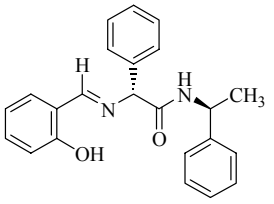
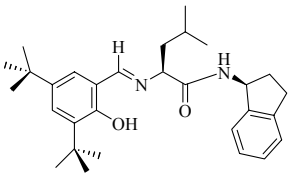


FIgure 3.3 Salicylimine ligand synthesis

All of target salicylimine ligands were shown in Table 3.3.

Table 3.3 Structure of the target salicylimine ligand.

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

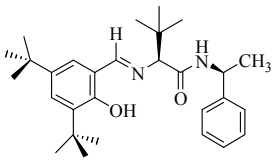
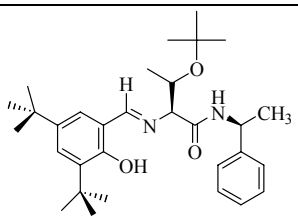
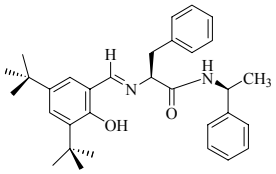
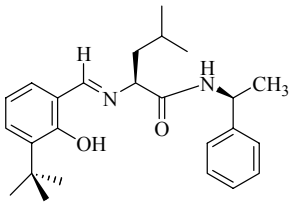
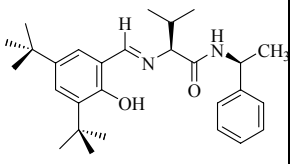
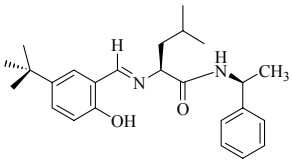
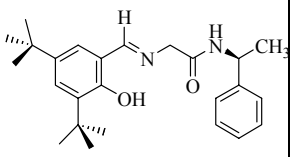
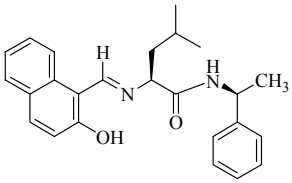
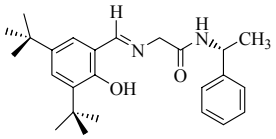
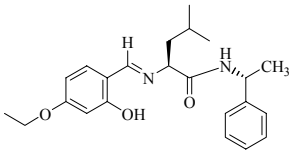
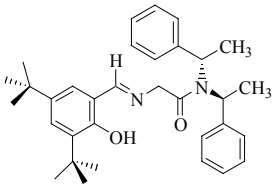
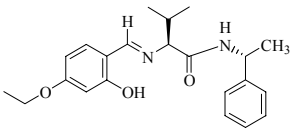
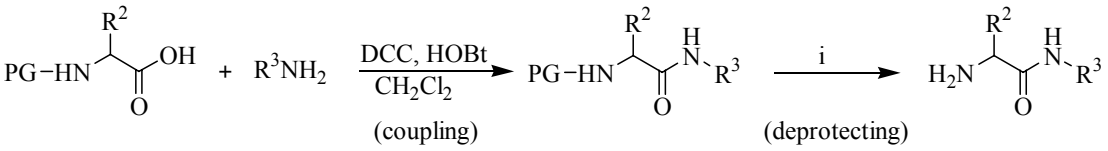
	**(*S,S*)-S2-*t*Leu-A1**		**(*S,S*)-S2-Thr-A1**
	**(*S,S*)-S2-Phe-A1**		**(*S,S*)-S3-Leu-A1**
	**(*S,S*)-S2-Val-A1**		**(*S,S*)-S4-Leu-A1**
	**(*S*)-S2-Gly-A1**		**(*S,S*)-S5-Leu-A1**
	**(*R*)-S2-Gly-A1**		**(*S,R)*-S6-Leu-A1**
	**(*S*)-S2-Gly-A6**		**(*S,R*)-S6-Val-A1**

Table 3.4 The percent yield of salicylimine synthesis.

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

3.1.2.3 Chiral amines

Seventeen chiral α-aminoamides were used in the synthesis of the salicylimine ligands decribed in section 2.2. These α-aminoamides were obtained from 8 α-amino acids and 6 chiral amines applying protecting-coupling-deprotecting chemistry commonly used in the peptide synthesis (Figure 3.4). The coupling and deprotecting steps gave satisfactory yields of the desired α-aminoamides (Table 3.5).



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

Figure 3.4 Chiral amine synthesis

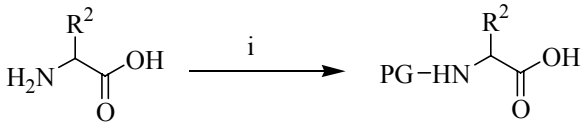
Table 3.5 The percent yield of amide coupling and deprotection.

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

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

For the protecting step, 6 amino acids were protected with Boc and one amino acid (Gly) was protected with Cbz and one (Thr(^{t}Bu)) with Fmoc. This protecting step gave excellent

yields except for the protection of glycine (Table 3.6). The last protected amino acid, Fmoc-Thr(^{t}Bu), was purchased from Nova biochem.



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

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

Figure 3.5 Protection of amino acid

Table 3.6 The percent yield of amino acid protection.

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

*t*Leu = *tert*-Leucine

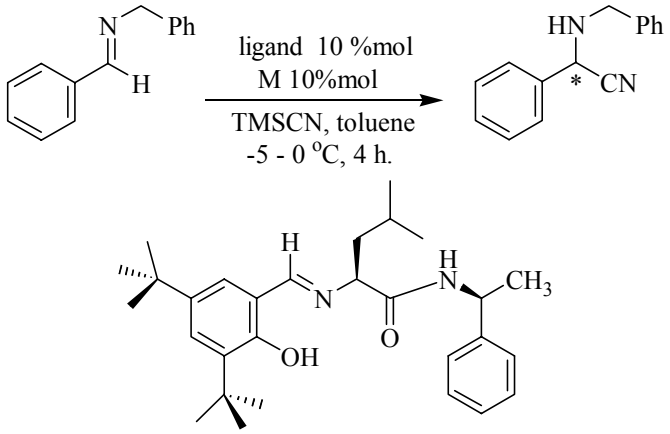
3.1.3 Catalytic properties of salicylimine ligands and condition for asymmetric Strecker reaction

3.1.3.1 Ligands and metal ions

The addition of cyanide to *N*-benzylidenebenzylamine was evaluated at –5 to 0 °C for 4 hours in the presence of Ti(O^iPr)$_4$ at 10% mol and the absence of the salicylimine ligand. The reaction gave the expected α-aminonitrile product with >95% conversion and 0% *ee* (entry 1, Table 3.7). When the reaction was carried out in the presence of the salicylimine ligand **(*S*,*S*)-S2-Leu-A1** alone, the enantiomeric excess was improved to 36% with 34% conversion of the product (entry 2). These results indicated that salicylimine ligand itself was able to catalyze the reaction to a certain extent as well as inducing asymmetry in the product. When the reaction was carried out in the presence of both Ti(^{i}OPr)$_4$ and the ligand (entry 3), the reaction proceeded with very high % conversion and good % *ee*. The reaction was likely to be catalyzed by the Ti-salicylimine complex generated in the reaction. Ti(^{i}OPr)$_4$ itself also catalyzed the reaction (entry 1), however the reaction proceeded without stereoselectivity. $ZrCl_4$-salicylimine catalytic system was less effective in catalyzing the reaction (entry 4), especially in terms of

enantioselectivity. These results are in agreement of the observation reported by Jacobsen that the salicylimine-type ligands can catalyze the addition of cyanide ion to the imine. The results observed here, however, present a sharp contrast to Jacobsen's work in that this salicylimine can catalyze the reaction more effectively in the presence of $Ti(^{i}OPr)_4$ while Jacobsen's salicylimine catalyzed the reaction better without any metal ion.

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



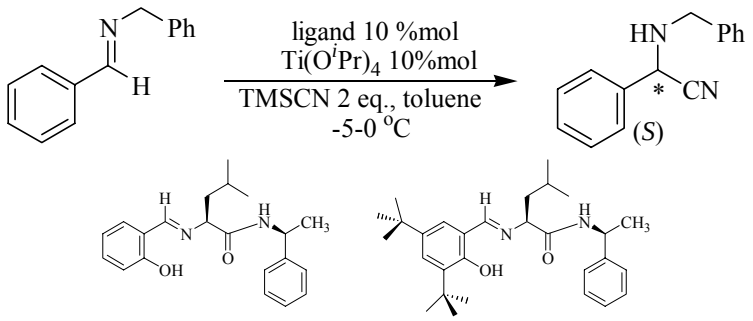
Ligand

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

3.1.3.2 Reaction time

In the study of catalytic properties of the synthesized salicylimine ligands, the addition of cyanide to the imines was initially performed at –5 to 0 °C using TMSCN as a cyanide source in the presence of a catalytic amount of $Ti(^{i}OPr)_4$ and a salicylimine ligand. Due to the difficulties encountered in controlling the temperature throughout the unnecessarily long reaction time while satisfactory conversion and comparable %*ee* can still be achieved, the reaction was instead performed for 4 hours only (Table 3.8, entry 2).

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



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

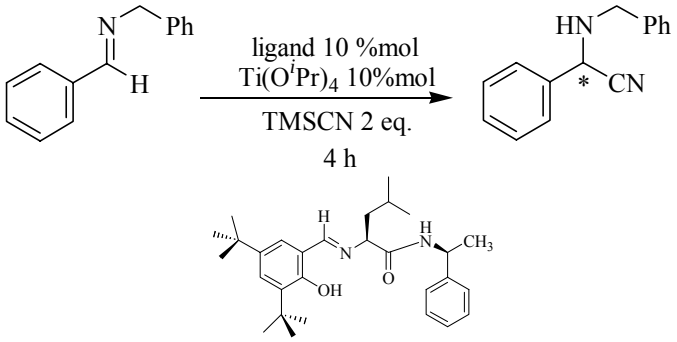
entry	ligand	Time (h.)	Conv. (%)	*ee* (%)
1	**(*S,S*)-S1-Leu-A1**	6	94	40
2	**(*S,S*)-S1-Leu-A1**	4	42	33
3	**(*S,S*)-S2-Leu-A1**	4	92	74

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

3.1.3.4 Temperature

A strategy most frequently used for improving selectivity of a reaction is to lower the reaction temperature. The reaction was thus performed at – 40 °C by using dry-ice acetonitrile (1:1) cold bath. The results were, however, rather discouraging as the reaction went so sluggishly at – 40 °C (Table 3.9). The rate of the reaction was too slow and no product was observed when using toluene as a solvent at –40 °C.

Table 3.9 Catalytic asymmetric Strecker reaction using ligand (**(*S*,*S*)-S2-Leu-A1**) at different temperature.



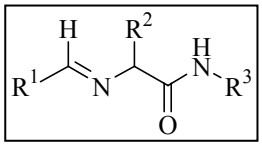
(*S, S*)-S2-Leu-A1

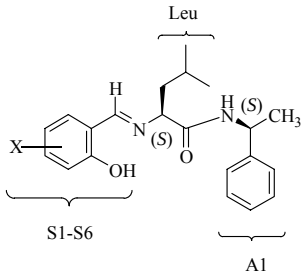
entry	solvent	Temp. ($^{\circ}$C)	Conv. (%)	*ee* (%)
1	toluene	-5 – 0	92	74
2	toluene	-40	0	-
3	toluene(anh.)/*i*PrOH (2 equiv.)	-5 – 0	98	54
4	toluene(anh.)/*i*PrOH (2 equiv.)	-40	29	41

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

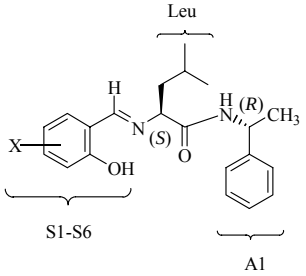
In order to find ligands with high asymmetric catalytic efficiency, effect of R^1 substituent on ligand was investigated first. Effect of R^1 substituent (**S1**, **S2**, **S3**, **S4**, **S5** and **S6**) on the catalytic properties of the ligands was studied by fixing R^2 as isobutyl group and R^3 as 1-phenylethyl which were derived from (*S*)-Leucine (Leu) and methylbenzylamine (A1) building blocks, respectively (Table 3.10). The reactions were carried out in the presence of the catalytic complex formed *in situ* from Ti(^{i}OPr)$_4$ and a salicylimine ligand (10 % mol each) with various R^1.

Table 3.10 Catalytic asymmetric Strecker reaction using salicylimine ligand bearing various R^1(salicyl) substituents.

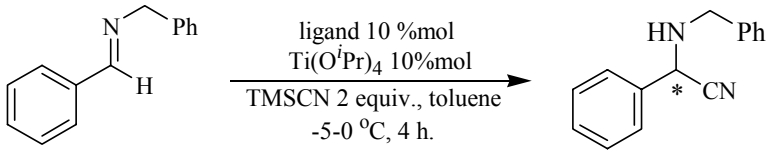


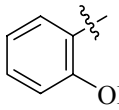
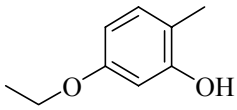
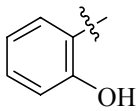
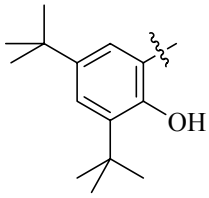
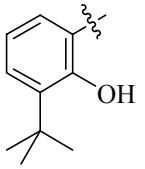
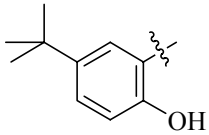
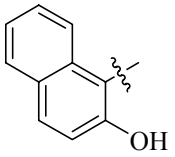


(*S, S*)-(S1-S6)-Leu-A1



(*S, R*)-(S1-S6)-Leu-A1



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

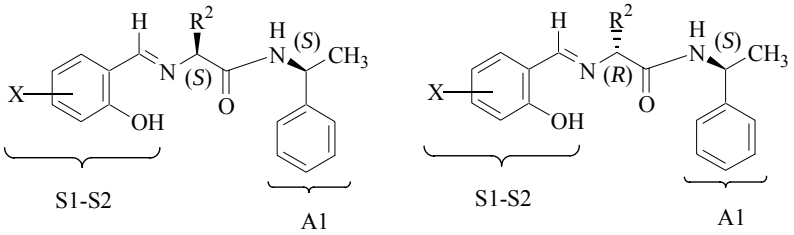
[a] Reaction time was 6 hours. [b] Structures of all ligands are presented in Table 4.

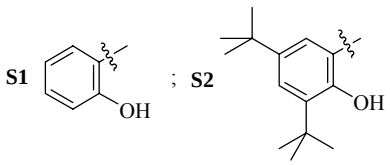
The first ligand tested in this reaction was **(*S*,*R*)-S1-Leu-A1** in which R^1 was 2-hydroxyphenyl group derived from unsubstituted salicyladehyde. With this ligand the reaction proceeded with high conversion to give virtually quantitative yield of the (*R*)-aminonitrile in six hours. This ligand,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

3.1.3.6 Effect of R^2 substituent on ligand

Effect of R^2 substituent on catalytic properties of salicylimine ligands was investigated by varying R^2, and fixing R^3 as 1-phenylethyl and R^1 as either 2-hydroxyphenyl (**S1**) or 2-hydroxy-3,5-di-*tert*-butylphenyl (**S2**). As mentioned in the previous section that the **S1** series gave lower % *ee* than **S2** series and the variation of R^2 by using different types of α-amino acids, Gly, Val, Leu, and Phg, in **S1** series did not improved the % *ee* to the satisfactory level. However, it showed that Gly was the worst and Leu or Val were the best in contributing the enantioselective control of the ligands (Table 3.11, entries 1-4). The effect of R^2 on the enantioselective control of the ligands was more clearly seen in the **S2** series (entries 6-10) and again the best ligand was the one with R^2 = isobutyl derived from Leu amino acid (entry 9). It is interesting to point out here that, unlike the R^1 group, the R^2 group played the more complicated secondary role in stereoselectivity of the ligands as the observed % *ee* did not related directly to the bulkiness of the R^2 substituent.

Table 3.11 Catalytic asymmetric Strecker reaction using salicylimine ligand with various R^2.





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

[a]Reaction time was 6 hours.

In addition, a variety of R^2 moieties were employed in order to optimize the enantioselectivity with 3,5-di-*tert*-butylsalicylaldehyde **S2** (R^1) and (*S*)-methylbenzylamine **A1** (R^3). The results showed that leucine was the best substituent at R^2 position of the ligand (entries 7-12). In entry 11, ligand **(*S*,*S*)-S2-Thr(^{t}Bu)-A1** constituted the most sterically hindered R^2 but the enantioselective induction of this ligand was not as good as **(*S*,*S*)-S2-Leu-A1**. The results showed that the configuration at R^2 was not the major factor to determine the configuration of the product. This is evidenced when the ligand with *S*-configuration and *R*-configuration at R^2 were compared (entries 4 and 5). Both of R^2 configuration gave the same preferred configuration of the product, i.e. *S*-configuration is preferred. The configuration of the

product was not directly affected by the configuration of the R^2 part but more affected by the R^3 part.

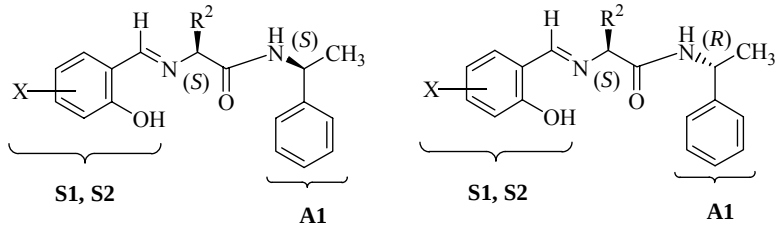
3.1.3.7 Effect of R^2 and R^3 configurations on the outcome of the reaction.

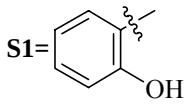
Effect of R^3 substituent on the stereoselectivity of the ligands such as (*S*)-phenylethylamine, (*R*)-phenylethylamine, (*S*)-1-naphthylethylamine, (*R*)-phenylethoxylamine, (*S*)-cyclohexylethylamine, aminoindane and *S*(*R**,*R**)-bis(pheylethyl)amine was also studied. The results indicated that the configuration (*R* and *S*) of R^3, derived from chiral amine, directly affected the configuration of the aminonitrile product (Table 3.12). The ligands with (*R*) R^3 preferably gave the (*R*) aminonitrile product, while ligands with (*S*) R^3 preferably yielded the (*S*) aminonitrile product. The R^3 substituents, like the R^1 substituents, may thus directly involve with the attacking cyanide ion and play a primary role in governing the stereoselectivity of the reaction. It is also important to point out here that the change of configuration of R^2 did not affect the configuration of the aminonitrile product but it affected cooperatively with R^3 (entries 11-12) as shown by the decreased selectivity for not matched pair (*S*, *R*) compared to the matched pair ((*R, R*), (*S, S*)) (entries 5, 6 and 9, 10). These results confirmed that R^2 played only the secondary role in governing the enantioselectivity of the ligands. These results presented intriguingly different hypothesis from what was proposed in literatures using ligands with a related structure.

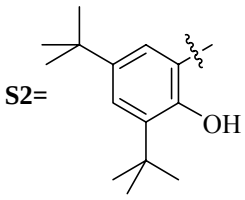
3.1.3.8 Effect of R^3 bulkiness

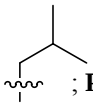
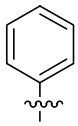
With the previous hypothesis about the role of R^3 substituents in mind, increasing the bulkiness of R^3 should improve the enantioselectivity of the ligands. Generally, higher enantioselectivity was obtained from the reaction with the ligands containing bulkier R^3 substituent (Table 3.13). Ligand **(*S, S*)-S2-Leu-A2** constituted 3,5-di-*tert*-butylsalicylimine moiety and dipeptides derived from L-leucine, and (*S*)-1-napthylethylamine showed the best enantiomeric selectivity. The ligand gave 84 % *ee* of product with *S* configuration. It is interesting to note that **(*S, S*)-S1-Leu-A3,** in which the R^3 substituent contained a hydroxy group, displayed no enantioselectivity (entry 5). There is no clear explanation, which can be deduced from this observation at present. Nevertheless, these results clearly showed that the steric hindrance of R^1 and R^3 worked cooperatively in enhancing the enantioselectivity of the ligands. Although, the bulkiest R^3 substituent showed promising and interesting results in ligand **(*S*)-S2-Gly-A6** (entry 2 compared to entry 1) in terms of %*ee* and yield of the product, it was unfortunate that this substituent (**A6**) which have extremely high steric hindrance could not be synthetically incorporated into the **S2-Leu** moiety to confirm the hypothesis.

Table 3.12 Effect of R^2 and R^3 configurations on catalytic asymmetric Strecker reaction.



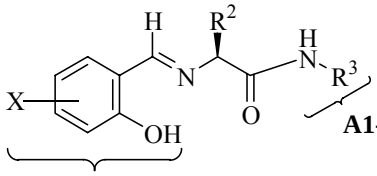




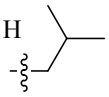
R^2: **Gly** = H; **Val** =  ; **Leu** =  ; **Phg** = 

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

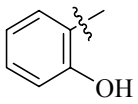
Table 3.13 Catalytic asymmetric Strecker reaction using ligand in various R^3.



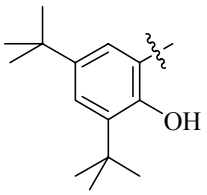
Gly: $R^2 = H$

Leu: $R^2 =$ 

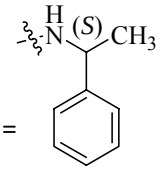
S1



S2



A1 =



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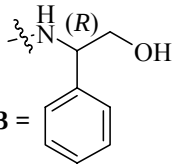

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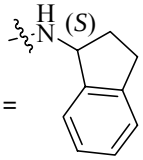
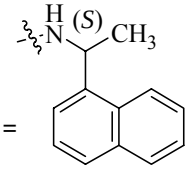
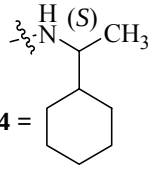


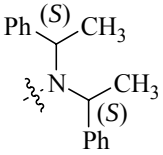
A2 =



A4 =



A6 =

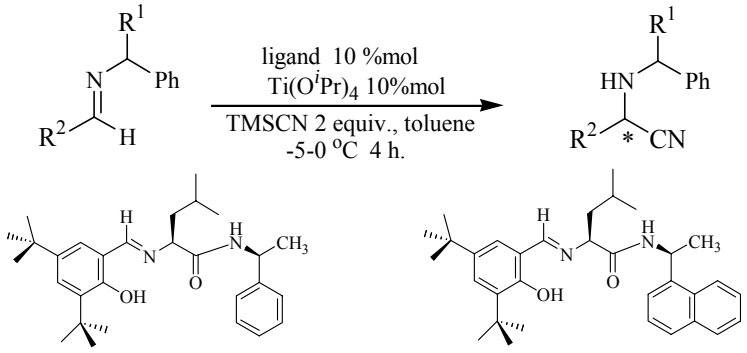


entry	Ligand	Conv. (%)	*ee* (%)
1	**(*S*)-S2-Gly-A1**	92	23 (*S*)
2	**(*S*)-S2-Gly-A6**	>99	39 (*R*)
3	**(*S*, *S*)-S1-Leu-A1**	94	40 (*S*)
4	**(*S*, *S*)-S1-Leu-A2**	95	37 (*S*)
5	**(*S*, *R*)-S1-Leu-A3**	80	0
6	**(*S*, *S*)-S2-Leu-A1**	92	74 (*S*)
7	**(*S*, *S*)-S2-Leu-A2**	92	84 (*S*)
8	**(*S*, *S*)-S2-Leu-A4**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

3.1.3.9 Substrate dependence

Various imines were reacted with TMSCN in the presence of **(*S*, *S*)-S2-Leu-A1** or **(*S*, *S*)-S2-Leu-A2** salicylimine ligands. Most of the aromatic imines (entries 1-5, 7 and 9-12, Table 3.14) gave satisfactory results except for those bearing strong electron donating group at the *ortho* or *para* position of the benzene ring (entries 6 and 8).

Table 3.14 Asymmetric addition of cyanide to various imines using salicylimine ligands.



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

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

(*S*,*S*)-S2-Leu-A1 did not show any enantioselectivity in the cyanation of the sterically hindered aliphatic imine, *t*-butylmethylene imine (entry 13). Similar results have been reported in the literatures. Surprisingly though, the cyanation of *N*-benzylidenebenzhydrylimine gave essentially racemic product (entry 14). This highly steric aromatic imine has been reported to be one of the best substrates in the enantioselective addition of cyanide with various types of catalysts. This and other results, discussed previously, implied that the ligands synthesized in this work catalyzed the addition of cyanide to the imines through a transition state with a

structure quite different from what was proposed for the related ligands reported in the literatures.

3.2 RESULTS ON HYDROPHOSPHONYLATION REACTIONS

3.2.1 Analytical methods for the determination of enantiomeric purity of α-aminophosphonates

3.2.1.1 Chromatographic method

Due to the highly polar nature of aminophosphonates, GC-based separation is not quite practical. However, rapid progress in developing sensitive and accurate HPLC methods of analysis of enantiomeric α-aminophosphonates has been made in the past years. Most of the reported works employ enantiomeric chromatographic analysis techniques on chiral HPLC columns such as Daicel ChiralPak AD®, Chiralcel OD®, or Chiralpak AS® to determine the optical purity of α-aminophosphonates.[37,42,50] Efficient chiral HPLC systems offer good separations for two components having $\alpha \geq 1.05$. The principle of enantiomer separation by chiral chromatography involves short-term diastereomeric interactions of the two enantiomers with a chiral stationary phase. The diastereoisomeric complexes formed will have non-identical stabilities and hence elute at different times.

3.2.1.2 NMR spectroscopy

Although enantiomers cannot be distinguished in an achiral medium because the resonances of enantiotopic nuclei are isochronous (equivalent), diastereoisomers may be distinguished because the resonances are anisochronous (non-equivalent). The determination of the enantiomeric purity using NMR, therefore, requires the use of a chiral auxiliary that converts the mixture of enantiomers into a diastereoisomeric mixture. As long as there is a large enough chemical shift nonequivalence to give baseline resolution of the appropriate signals, the integration gives a direct measure of diastereomeric composition which can be related directly to the enantiomeric composition of the original mixture.

In general, there are three types of chiral auxiliary that are widely used. Chiral lanthanide shift reagents and chiral solvating agents form diastereoisomeric complexes *in situ* with substrate enantiomers and may be used directly. Chiral derivatizing agents (CDAs) require the separate formation of discrete diastereoisomers prior to NMR analysis and care has to be taken to ensure that neither kinetic resolution of the substrate to be analyzed nor racemization of the derivatizing agent occurs during derivatization. A control experiments using racemic substrates must always be performed in order to validate the derivatizing procedure.

Chiral derivatizing agents (CDAs)

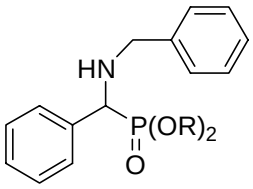
A CDA forms discrete diastereoisomers for which the observed chemical shift nonequivalence ($\Delta\delta$), is typically several times greater than for related complexes with a CSA. Smith[15] used (*S*)-Mosher's amides to derivatize α-aminophosphonates to form diastereoisomeric amides. A comparison of the ^{1}H or ^{19}F NMR spectrum of the derivatized crude product with that of a derivatized authentic racemate would yield information on the preference of the enantiomer being formed.

Chiral solvating agents (CSAs)

Chiral solvating agents form diastereoisomeric solvation complexes with enantiomeric solute *via* rapidly reversible equilibria in competition with the bulk solvent. One of the advantages of this method is quick and simple to perform with no problem associated with kinetic resolution or sample recemization provided that the complexes formed remain in the solution. Furthermore, in contrast to the method using CDA, the enantiomeric purity of the CSA is not critical. If it is less than 100% then only the degree of the chemical shift nonequivalence is reduced. However, the relative signal integrations remain unchanged. The main drawback of the method is that $\Delta\delta$ values tend to be small, but with high modern field NMR instrumentation widely available nowadays, this is no longer critical. In addition, another disadvantage is that only a limited range of cosolvents may be used. Nonpolar solvents ($CDCl_3$, CCl_4, and C_6D_6) tend to maximize the observed anisochrony between the diastereoisomeric complexes while more polar solvents preferentially solvate the solute and the $\Delta\delta$ falls to zero. An example of successful enantiopurity determination of α-hydroxyphosphonates by ^{31}P NMR spectroscopy where quinine was employed as a chiral solvating agent was demonstrated by Kee.

Chiral lanthanide shift reagents (CLSRs)

Addition of a lanthanide shift reagent to an organic compound may result in shifts of resonance to higher (or lower) frequencies, the size of which is determined primarily by the distance of the given type of proton from the donor group. The six-coordinate lanthanide complex forms a weak addition complex with a large variety of organic compounds that is in fast exchange with the unbound organic substrate on the NMR time scale. The magnitude of the chemical shift non-equivalence depends on the strength of the complexation. The association the complexes formed are especially moisture sensitive. One drawback of this technique is the severe line broadening which occurs as a result of paramagnetic properties of lanthanide shift reagents.



II-1 : R = Et; **II-2** : R = Me

In order to find a suitable method for determination of %*ee*, two analytical techniques were compared in this study. A normal phase chiral HPLC as well as NMR methods by using chiral solvating agents (CSAs) and lanthanide shift reagents were used.

3.2.2 The results of analytical methods

Initial experiments involved a search for suitable model substrates for the study. The imine substrates themselves can be formed by the conventional aldehyde-amine condensation. What needs to be taken into consideration include the ease to manipulate the reaction as well as to analyze dialkyl phosphonates, the product resulting from the reaction of the so-formed imine substrate and dialkyl phosphite. In general, dimethyl phosphite and diethyl phosphite are common commercially available phosphonylating agents. Unfortunately, such phosphorus reagents could not be obtained due to export regulations by the US government. Therefore, they need to be synthesized. It turned out that diethyl phosphite can be synthesized with higher purity than that of dimethyl phosphite. In addition, solubility problem in non-polar solvent such as toluene was encountered when dimethyl phosphite was used. Therefore, racemic diethyl phosphonates **II-1** was chosen as model α-aminophosphonates to be tested with various analytical methods. There are precedent reports on liquid chromatographic enantiomeric separation of these compounds on chiral columns for comparison.

3.2.2.1 Chiral HPLC analysis

As reported by Sasai and coworkers,[42] commercially available chiral HPLC columns efficiently used in the determination of enantiomeric composition of α-aminophosphonates include Daicel ChiralPak AD® and Chiralpak AS® columns. In the present work, analysis of racemic mixtures of α-aminophosphonate **II-1** on a readily available Chiralcel OD® and ChiralPak AD® HPLC columns was carried out. A pure sample of product to be analyzed was prechromatographed on silica gel column prior to injection to either of the chiral columns to avoid ambiguity of peak assignment. After exhaustive attempts to separate the racemic mixture on the Chiralcel OD® HPLC column (mobile phase: hexanes/2-propanol at various ratio), it was found that no separation was obtained. While the chiralcel OD® column failed to give any peak separation, the ChiralPak AD® column gave satisfactory separations of the racemic α-aminophosphonates **II-1** (hexanes/2-propanol) provided that the sample loadings were small. A

representative chromatogram obtained from the best conditions for separation of the racemic α-aminophosphonate **II-1** is shown in Figure 1 (Appendix). It clearly shows that the enantiomeric pair was separated and eluted as two peaks of equal peak area. However, due to a time-consuming prechromatography requirement as well as the limited timeslot for the HPLC machine, this method seems a little less practical. Therefore, we had turned our focus from chromatographic resolving technique towards classical NMR techniques.

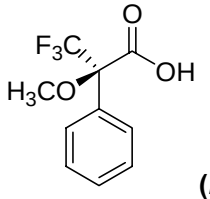
3.2.2.2 ^{1}H NMR spectroscopic analysis

In theory, determination of enantioselectivity of the reaction by ^{1}H-NMR spectroscopy can be achieved by monitoring the integral ratios of the proton at the α position to the phosphonyl group. This is successful under a circumstance where adequate asymmetric environment is experienced by the enantiomeric α protons of the 2 isomers.

For α-aminophosphonic acid derivatives, the α-proton NMR signal appears as a doublet due to the phosphorus-proton coupling ($^2J_{PH}$ = 19.7 Hz). In a regular ^{1}H-NMR spectrum of **II-1**, this doublet appears in the same region as the methylene proton multiplets of the ethoxy groups (3.60-4.00 ppm) as illustrated in Figure 4 (Appendix). However, in some cases the doublet will shift further downfield upon an addition of an acidic chiral solvating agent as the environment is altered by protonation of the amino group. This results in a clear doublet peak with no interference by the ethoxy protons. Whether or not this doublet of enantiomeric protons would split into 2 sets of doublet depends on the type of chiral solvating agent and/or chiral Lanthanide shift reagent employed which will be discussed next (*vide infra*).

3.2.2.3 Analysis employing chiral solvating agents

Chiral solvating agents offer a more practical and economical way to the determination of enantiomeric compositions of a mixture. In order to screen for a good CSA, the sample aminophosphonate **II-1** was chosen as the representative model compound. At the beginning, one of the most widely used chiral solvating agent for the determination of enantiomeric composition of alcohols and amines by the NMR method, α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA or Mosher's acid, **51**), was tested as a CSA.



(*R*)-65

At the beginning *R*-(-)-Mosher's acid was employed for analysis of racemic α-aminophosphonate **II-1**. After 2 eq of **51** were added to a $CDCl_3$ solution of **II-1**, the peak of the enantiomeric proton, H-C_α-P, were separated into two signals of doublet peaks of equal

intensity at 4.18, 4.23, 4.28, and 4.32 ppm. It was not possible at this stage to assign which doublet belongs to which diastereomeric complex. Although MTPA could give good peak separation, the analysis method may be too costly due to the price of MTPA (**51**). Baseline-to-baseline separation is not absolutely required at the initial stage. The more important thing is the speed and convenience of the screening method. Once a selectivity is observed, a more reliable means can later be used to determine percent enantiomeric excess of the reaction. We have, therefore, attempted to investigate other CSAs for alternatives.

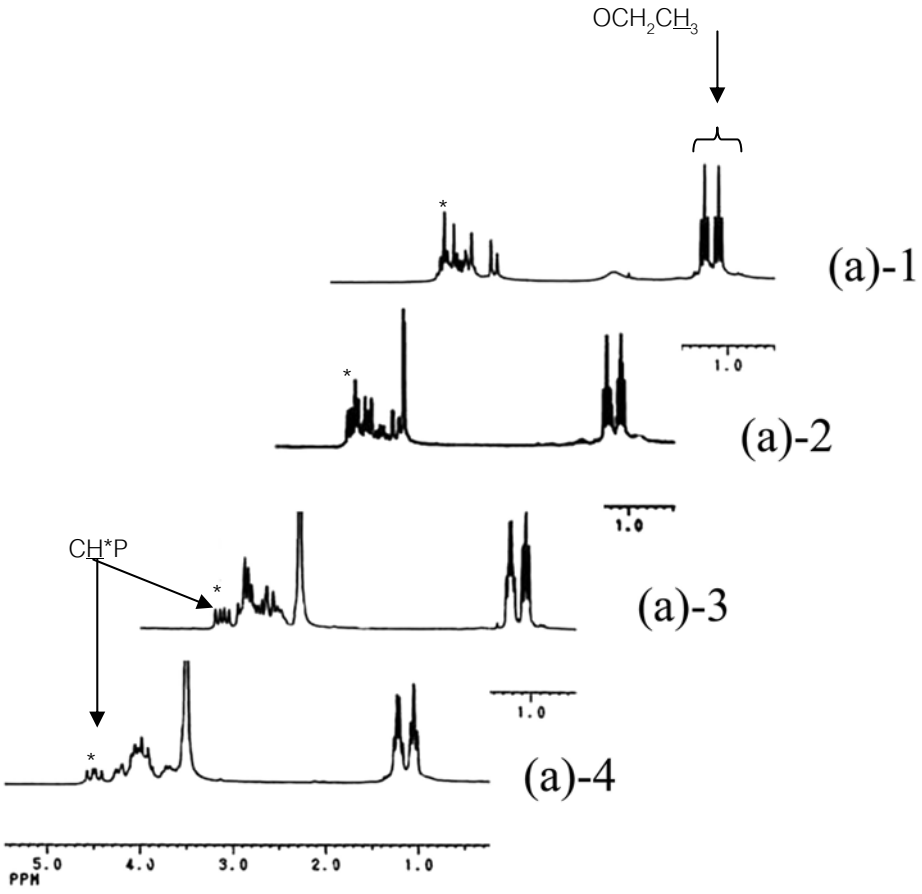
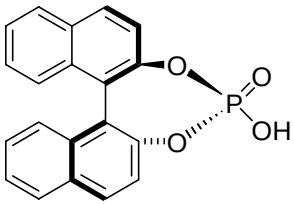


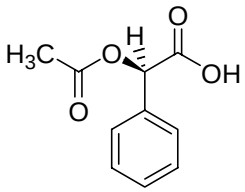
Figure 3.6 The ^{1}H NMR spectra of α-aminophosphonate **II-1** in the presence of **51** as CSA: (a)-1 Before adding **51**; (a)-2 After adding 1 eq of **51**; (a)-3 After adding 2 eq of **51**; (a)-4 After adding 3 eq of **51**.

Next, the separation of an enantiomeric pair of **II-1** was examined using *R*-(-)-1,1'-binaphthalene-2,2'-diylhydrogen phosphate (BNP, **(*R*)-52**). Although upto 2 eq of **52** was added in a $CDCl_3$ solution of **II-1**, no sign of splitting of the H_α signal was detectable. Due to the low solubility of **52** in $CDCl_3$, a higher amount of **52** could not be added. Therefore, **52** was not a good CSA to distinguish **II-1** enantiomeric protons.

R-(-)-α-acetoxyphenylacetic acid (APA, **(*R*)-53**) was next employed as an alternative CSA in the NMR analysis of racemic α-aminophosphonate **II-1**. It was found that addition of 2 eq of **53** to a solution of **II-1** in $CDCl_3$ resulted in a marked downfield shift of a doublet signal of enantiomeric proton. Although this doublet shifted downfield further from the multiplet peak of the ethoxy proton, no sign of splitting of the signal at 4.20 and 4.14 ppm was observed. When another 1 eq of **53** was added, the peak characteristics remained unchanged.



(*R*)-52



(*R*)-53

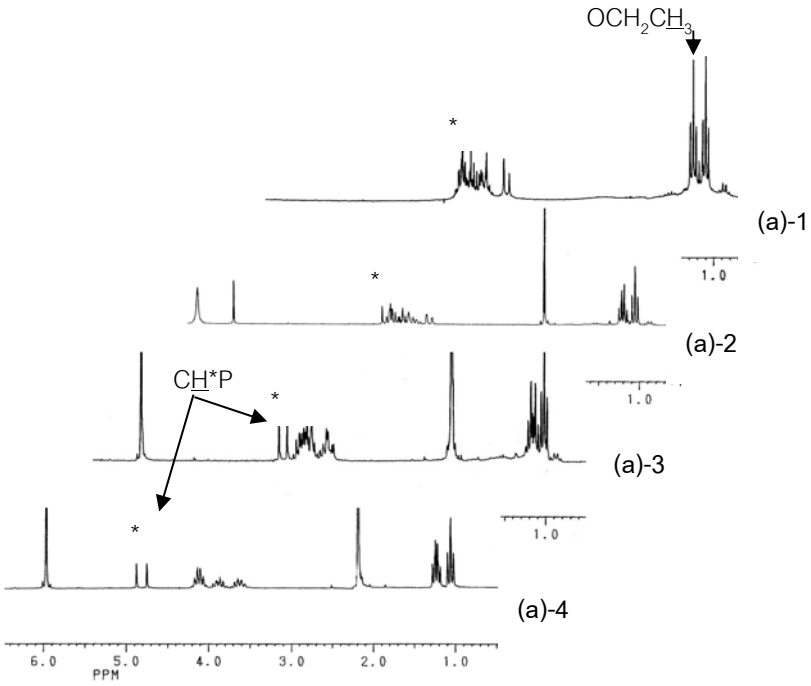
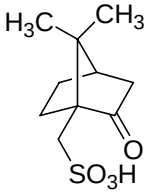


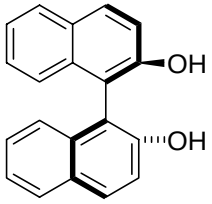
Figure 3.7 The ^{1}H NMR spectra of α-aminophosphonate **II-1** in the presence of **53** as CSAs: (a)-1 Before adding **53**; (a)-2 After adding 1 eq of **53**; (a)-3 After adding 2 eq of **53**; (a)-4 After adding 3 eq of **53**.

Another CSA, (*1S*)-(+)-camphor-10-sulfonic acid (**(*R*)-54**), was tested for analysis of racemic α-aminophosphonate **II-1**. Addition of 1 eq of **54** to a solution of **II-1** did not show any separation. It was found that an increased amount of **54** may provide a better separation. However, its low solubility in $CDCl_3$ had prevented further addition to the sample.

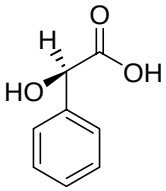
In addition, (*R*)-(+)-1,1'-bi(2-naphthol) (**(*R*)-55**), D-(-)-mandelic acid (**56**), and quinine (**57**) were tested for use in an enantiomeric determination of **II-1**. Due to the low solubility of **55** and **56** only about 1 eq could be added to the mixture. Disappointingly, separation of enantiomeric α-proton signals was not observed in both cases. Even though a solubility problem was not encountered in an attempt to utilize **57** as a CSA, addition of **57** to the NMR sample resulted in no hint of separation of the signal of interest.



(*S*)-54



(*R*)-55



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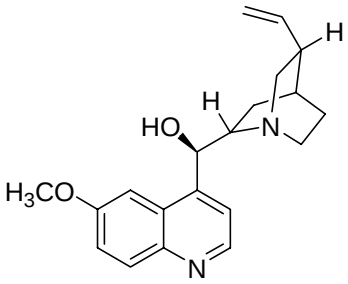

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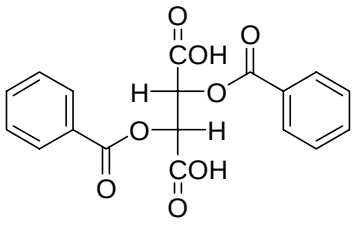
(-)-*O,O'*-dibenzoyl tartaric acid (**58**) was also investigated as a potential CSA. When 1 eq of **58** was added, two sets of doublet peak appeared at 4.10 and 4.19 ppm but not a satisfactory baseline separation. As its solubility in $CDCl_3$ is low, it was anticipated that an increased amount of **58** would not result in a better separation.

The chiral lanthanide shift reagent, Europium (III) tris [3-(heptafluoropropyl hydroxymethylene)-d-camphorate], $Eu(hfc)_3$ (**59**) was employed as alternative to CSAs. When **59** was added to a $CDCl_3$ solution of **II-1**, separation of H_α-C-P peak was not achieved before broadening of the peaks was observed. All of ^1H NMR spectroscopic analysis results were summarized in Table 3.15.



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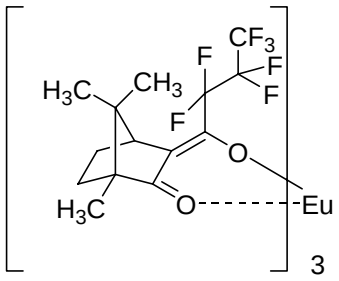

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Table 3.15 Summary of the ^{1}H NMR spectroscopic analysis of α-aminophosphonate **II-1** using various chiral solvating agents at 200 MHz in $CDCl_3$

CSA	amount added (eq)	Δδ (ppm)[b]
51	2	0.096
52	2[a]	0
53	2	0
54	2[a]	0
55	2[a]	0
56	2[a]	0
57	2	0
58	2[a]	splitting but not baseline-baseline separation
59	2	0

[a] low solubility. [b] Δδ of H_α of **II-1**.

All results described above indicated that among all methods tested, enantiomeric analysis of α-aminophosphonate **II-1** by means of ^{1}H NMR spectroscopy employing Mosher's acid (**51**) as a chiral solvating agent is the suitable method available at hands. Although **51** is relatively expensive, it was the only choice. Therefore, the ^{1}H NMR spectroscopy was chosen as the method for the determination of enantiomeric compositions described herein.

3.2.3 The results of asymmetric synthesis of α-aminophosphonate

In principle, imines can exist in two geometric isomers, namely *E*- and *Z*-isomers, (Figure 3.8). Regarding the preferred isomer, the *Z*- form should be sterically less favorable than the *E*-form because of the repulsion of the R and R′ groups locating on the same side of the C=N bond. On the other hand, the more stable E form possesses R and R′ opposite to each other, hence the more stable isomer.

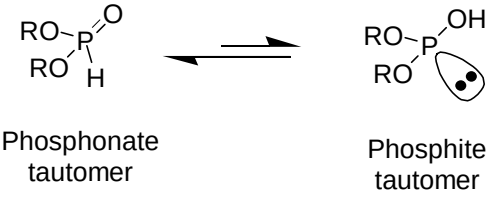
E-form *Z*-form

Figure 3.8 Possible geometric isomers of imines

3.2.3.2 Asymmetric synthesis of α-aminophosphonate:

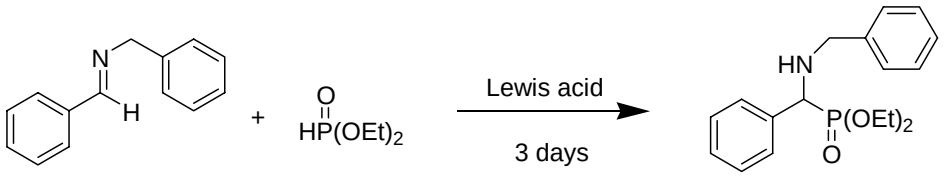
Method A: A chiral Lewis acid approach

Qian[26] reported the reaction of imines with diethyl phosphite to afford α-aminophosphonates in good yields (62-93%), by using $Yb(OTf)_3$ or $Sc(OTf)_3$ as a catalyst. As mentioned earlier that the keto form is the unreactive form of this phosphorus species, it is encouraging to see from Qian's results that diethyl phosphite can still be used as a reagent for such a preparation. Apparently, the keto (inactive) form has been converted to the active enol form in an adequate amount to drive the reaction forward. In general, dialkyl phosphites are more stable than its three-coordinate enol counterpart (or trialkyl phosphites) which are air-sensitive. Therefore, it is easier to handle. Encouraged by these findings, we first investigated the preparation of α-aminophosphonate **II-1** from imine **I-1** and diethyl phosphite in the presence of 1 eq of a Lewis acid in CH_2Cl_2.



In order to search for suitable Lewis acids for the system, various metal salts namely $SnCl_4$, $TiCl_4$, $Ti(O^iPr)_4$, and $Al(O^iPr)_3$ were used in the reaction. At the beginning a full equivalent of the metal salt was used in dichloromethane at room temperature for 3 d. The results are summarized in Table 3.16. As shown, the reaction in the presence of $Al(O^iPr)_3$ gave a higher amount of product than that with $Ti(O^iPr)_4$ (Table 3.16, entries 4 and 3). It was originally expected that the result would be in the opposite direction since the Ti(IV) complex of chiral ligands of interest tends to give better selectivity for a related Strecker reaction than the corresponding Al(III) complexes. Therefore, $Ti(O^iPr)_4$ was chosen as a catalyst.

Table 3.16 Hydrophosphonylation of **I-1** by diethyl phosphite with various Lewis acid catalysts.



I-1 **II-1**

entry	Lewis acid	mol%	solvent	yield (%)[a]
1	$SnCl_4$	100	CH_2Cl_2	-[b]
2	$TiCl_4$	100	CH_2Cl_2	5
3	$Ti(O^iPr)_4$	100	CH_2Cl_2	18
4	$Al(O^iPr)_3$	100	CH_2Cl_2	40

[a] Isolated yield. [b] No reaction.

Next, solvent effect on the reaction was examined. The reaction of imine **I-1** and diethyl phosphite in the presence of 100%mol $Ti(O^iPr)_4$ was carried out in various solvents at room temperature for 3 d. The results suggested that dichloromethane and tetrahydrofuran were the best solvents among those tested, such as toluene (13%), and THF:toluene (1:7) (5%). THF was selected as the solvent for the reaction during condition optimization because the reaction can be performed at higher temperatures due to its higher boiling point (67 ºC).

Table 3.17 Hydrophosphonylation of diethyl phosphite and imine **I-1** in different solvents

entry	Solvent	yield (%)[a]
1	CH_2Cl_2	18
2	THF	16
3	CH_3CN	-[b]
4	Toluene	13
5	THF/Toluene	5

[a] Isolated yield. [b] No reaction.

In order to search for preliminary suitable conditions, reactions probing for the influence of various factors, *i.e.*, reaction time, temperature, and amount of diethyl phosphite, on the course of the reaction were carried out. Selected results are listed in Table 3.18. First, the reaction time was taken into consideration. The reactions of imine **I-1** with 1.2 eq of diethyl phosphite were performed at room temperature for 3 and 6 days (entries 1 and 2) to determine the effect of reaction time. The yields were, however, comparable. A similar trend can be seen when the reactions were carried out at 65°C for 3 and 5 days (entries 5 and 6). These representative results suggest that there is no significant difference in the length of time the reaction was carried out.

Table 3.18 Hydrophosphonylation of diethyl phosphite and imine **I-1** under various conditions

entry	DEP (eq)	time	temp	yield (%)[a]
1	1.2	3d	rt	36
2	1.2	6d	rt	23
3	3.5	3d	rt	43
4	5.0	3d	rt	42
5	1.2	3d	65ºC	44
6	1.2	5d	65ºC	43
7	3.5	3d	65ºC	71
8	5.0	3d	65ºC	54

DEP : diethyl phosphite. [a] Isolated yield.

Next, the effect of temperature on the outcome of the reaction was studied. Entries 1 and 5 represent reactions of imine **I-1** with 1.2 eq of diethyl phosphite at room temperature and 65°C (refluxing THF), respectively. As shown in Table 3.4, at room temperature the reaction proceeded with marginal yields. An increase in reaction temperature resulted in a slightly improved yield. The same trend is observed when 3.5 eq of diethyl phosphite was used in the reactions at room temperature and 65°C (3 and 7), although the yields were significantly improved.

In theory, only one equivalent of dialkyl phosphite should be adequate for the reaction. However, as illustrated by Shibasaki[43] that a hydrophosphonylation using heterobimetallic catalyst systems afford much higher yields (without affecting the percent enantiomeric excesses) when a significantly higher amount of diethyl phosphite (5 eq) was used. Therefore, an influence of the amount of diethyl phosphite on yields was studied. The reactions were performed at room temperature with increased amounts of diethyl phosphite from 1.2 eq to 3.5 and 5 eq (entries 1, 3, and 4) to give product **65** in 36, 44, and 43%, respectively. It can be seen that an increase from 1.2 to 3.5 eq gave higher yields, whereas increasing the amount to 5 eq did not improve the yields. Likewise, at 65°C, an increase in product yields from 43 to 71% was achieved when the amount of diethyl phosphite was increased from 1.2 eq to 3.5 eq, while when 5 eq was used **II-1** was obtained in even lower yield of 54%. Apparently, higher amounts of phosphonylating agent could not significantly drive the equilibrium further in the forward direction in this case.

A report by Qian[26] showed that a one-pot reaction of benzaldehyde, benzylamine, and diethyl phosphite in CH_2Cl_2 at ambient temperature for 15-30 h gave only a trace amount of the desired product. This strongly suggests that no background reaction is involved, *i.e.*, a catalyst is needed for the reaction.

A series of experiments have been carried out to search for an adequate amount of metal ion catalyst for the reaction. It was found that only 10 mol% of $Ti(O^iPr)_4$ can still catalyze the reaction. Therefore, the optimum condition of the reaction under study requires the use of 10 mol% $Ti(O^iPr)_4$, 3.5 eq of diethyl phosphite under reflux at 65°C in THF for 3 days. Under this developed condition α-aminophosphonate **II-1** can be prepared in 71% yield. This condition was used for the rest of the reactions of imine **I-1** and diethyl phosphite.

3.1.3.3 Attempted catalytic asymmetric synthesis of α-aminophosphonate:

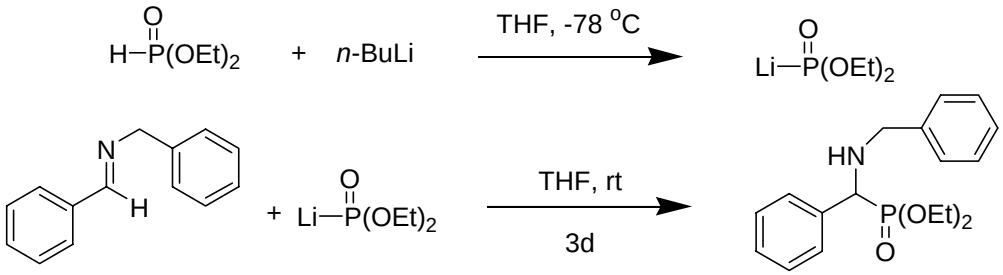
Method B: A chiral Lithium phosphonate approach

This method is based on the fact that $(RO)_2P(O)H$ exists in two tautomeric forms, namely, H-phosphonate **47** and phosphite **48**. The anionic form of the phosphite tautomer **48**

would be the most nucleophilic and would make the main contribution to the formation of the carbon-phosphorus bond under the basic conditions of the hydrophosphonylation.

Therefore, it is anticipated that appropriate bases should act as an activator to drive the equilibrium forward and convert the phosphonate tautomer to its thermodynamically less stable anionic form of phosphite tautomer. As shown by Smith's report lithium salt of diethyl phosphite ($LiPO_3Et_2$) indeed gave much higher product yields.

With this idea in mind, attempts to utilize a more reactive species of phosphonylating agent were carried out following Smith's procedure. The lithium salt of diethyl phosphite ($LiPO_3Et_2$) was generated *in situ* by using diethyl phosphite and *n*-butyllithium. Tetrahydrofuran emerged as the solvent of choice offering minimal inhomogeneity. The reaction was carried out in THF at the 1.2 eq of diethyl phosphite and *n*-BuLi (10 mol%). Disappointingly, a very poor yield (3%) was obtained. The efficiency of the reaction was somewhat improved by increasing the amount of diethyl phosphite to 2 eq and the reaction time to 3 days. Under this condition the product was obtained in 36% yield. (Table 3.19, entries 5)



I-1 **II-1**

Table 3.19 Attempted asymmetric addition of $LiPO_3Et_2$ to imine **I-1**

entry	eq of DEP	time	temp	yield (%)[a]
1	1.2	1d	rt	3
2	2	1d	rt	30
3	3.5	1d	rt	20
4	5	1d	rt	10
5	2	3d	rt	36

DEP : diethyl phosphite. [a] Isolated yield.

All results obtained thus far suggested that the catalyst group of chiral Schiff base, amino alcohols, and peptide Schiff base series were not capable of inducing enantioselectivity of asymmetric hydrophosphonylation under the conditions employed.

4. CONCLUSIONS

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

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

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

Furthermore, the work had focus on the synthesis of α-aminophosphonates *via* nucleophilic addition of diethyl phosphite to imines including asymmetric and non-asymmetric synthesis. For asymmetric synthesis, unfortunately, the enantiomeric composition of the resulting α-aminophosphonates could be monitored by ^1H NMR spectroscopy. It was found that although acceptable yield of the product was obtained, none of the chiral catalysts based on metal-salen and related ligands could induce stereoselectivity in the hydrophosphonylation of *N*-benzylidenebenzylamine.

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