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Asymmetric Synthesis of Stereochemically-Defined and Conformationally-Constrained Novel Amino Acids *via* Direct Alkylation of Chiral Ni(II)-Coordinated Schiff Bases of Glycine and alanine, and Design and Synthesis of Selective Peptide and Non-Peptide Ligands for the Delta-Opioid Receptor

by

Xue-jun Tang

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF CHEMISTRY

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2002

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and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy

Victor J. Hruby	Date 1/12/02
Robert B. Bates	Date 1/8/02
Jon D. Rainier	Date 01/08/02
Michael Barfield	Date 01/08/02
Bradley S. Moore	Date 1/8/02

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Dissertation Director	Date 1/12/02

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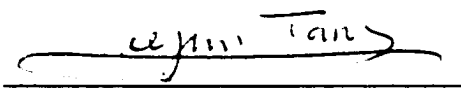
SIGNED: 

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Dedicated to

my wife Rong Tang

my parents Mingzhong Tang and Yibi Mo

my parents-in-law Shijin Tang and Qize Liu

my grandfather Shangyuan Tang

my sisters Jinrong Tang and Cui Tang, my brother Xuguang Tang, and their families

for their whole-hearted support

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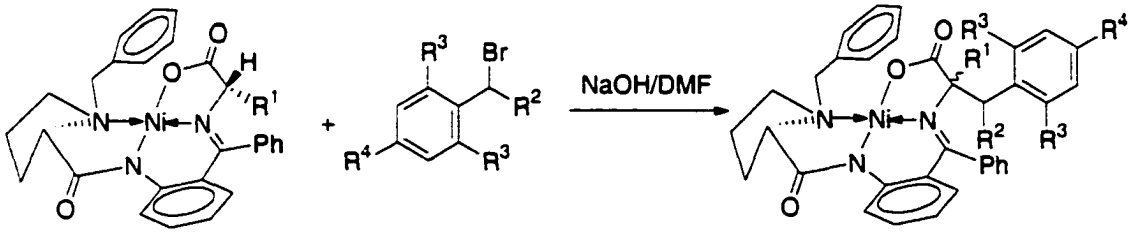
ABSTRACT

A systematic practical method to prepare highly chi (χ)-constrained amino acids has been developed. It was found that increasing the size of R^1 (see figure) from H to Me to Et to *n*-Pr led to decreased reactivity of the starting complexes. In the case of R^1 as *i*-Pr, no alkylation was observed. With an increase of the size of R^2 from H to Me to Et to *i*-Bu, the reactivities of the alkyl bromides decreased. The starting Schiff bases had more effective stereocontrol at the α-carbon center than at the β-carbon center. The starting Schiff bases showed differential reactivity toward the racemic electrophile (kinetic resolution). Satisfactory differentiations were obtained at room temperature which makes this method synthetically useful. In the case of R^1 as H (NiGlyBPB), the thermodynamically-controlled stereoselectivity of alkylation was as high as 30:1.



A series of dipeptide analogues (TMT-Tic and DMT-Tic) were designed and synthesized to mimic the potent and highly selective δ-opioid receptor pentapeptide ligand-[(2*S*, 3*R*)TMT[1]]-DPDPE and thus to explore the topographical requirements for recognition of ligands at the opioid receptor through bioassays and NMR studies to

facilitate the design of non-peptide compounds to be used as therapeutic agents for pain. (2*S*, 3*R*)-TMT-L-Tic was found to have best binding affinities at the δ-opioid receptor in TMT-Tic series. In preliminary NMR studies, it was found that these designed peptide ligands have their own distinct conformations in the aqueous media. Meanwhile some modified non-peptide analogues of SL-3111 were prepared to continue our efforts to find effective non-peptide ligands for the δ-opioid receptor. More systematic studies are still ongoing using NMR and computational methods.

Chapter 1. Asymmetric Synthesis of Unnatural α-Amino Acids *via* Direct Alkylation

1.1. Introduction

1.1.1 Peptide Structures and their Biological Functions

Two hundred years ago proteins were found to be the primary materials of life systems. Not until 1902 were α-amino acids found to be the constituents of proteins by Emil Fischer and Franz Hofmeister.[1-4] The shorter analogues of proteins are called peptides. There is no clear-cut line to distinguish peptides and proteins. But generally speaking, peptides contain less than 50 amino acid residues.

Individual α-amino acids in peptides and proteins are linked to each other through peptide bonds (Figure 1-1). The peptide bond is an amide bond formed between the carboxyl group from one amino acid residue and amino group in another amino acid. Even though so far hundreds of thousands of peptides have been discovered, they are mainly constructed from the 20 natural L-amino acids.

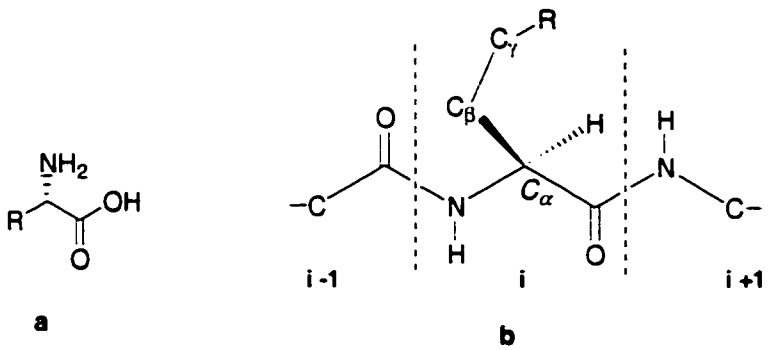


Figure 1-1. General structures of amino acids (**a**) and peptides (**b**)

Peptide chemistry was not established as an independent discipline until Emil Fisher and Franz Hofmeister's ground-breaking discovery. The last century has witnessed the rapid explosion in the discovery of biologically active peptides and development of synthetic methods for peptides. Some of these monumental works include du Vigneaud's isolation, characterization and synthesis of oxytocin and vassopressin,[5-7] Sanger's elucidation of the sequence of bovin insulin,[8-11] Merrifield's invention of solid-phase peptide synthesis (SPPS),[12,13] and Watson and Crick's discovery of the double helix of DNA revealing the connection between nucleotide sequences and peptide sequences.[14,15]

Peptides play a variety of functions in biological systems. They can work as hormones, neurotransmitters, enzyme substrates or inhibitors, immune system modulators, growth factors, antibiotics, antigens, cytokine modulators of transcription and translation, or many other effectors. These functions of peptides are known to influence essentially all vital physiological process *via* inter- and intracellular communication and signal transduction mediated through various classes of receptors.[16]

The biological functions of peptides are determined by their chemical, structural, conformational, topographical and dynamic properties. The conformations of peptides and proteins can be described by their backbone conformations and side chain conformations. The backbone conformations are characterized by the dihedral angles ϕ, φ, and ω. The side chain conformations are characterized by dihedral angles χ^1, χ^2, etc (Figure 1-2).

To achieve certain types of backbone conformations (secondary structures) such as α-helix, β-sheet, extended and β-turn structures, the general torsional angles ϕ and φ

must be controlled. The ω angles for peptide bonds are generally *trans* except for the peptide bond with Pro, which can be either *cis* or *trans*. During the past 30 years, much effort has been directed to develop strategies for the design and synthesis of peptides with specific backbone conformations.[17] Evaluation of the favored low energy conformations of the ϕ and φ angles was first examined by Ramachandran and co-workers about 30 years ago,[18] and subsequent studies by many other workers have shown that only certain regions of ϕ, φ space (often referred to as Ramachandran space) are actually acceptable to most L-amino acids. These regions correspond to the classical secondary structures of peptides and proteins.

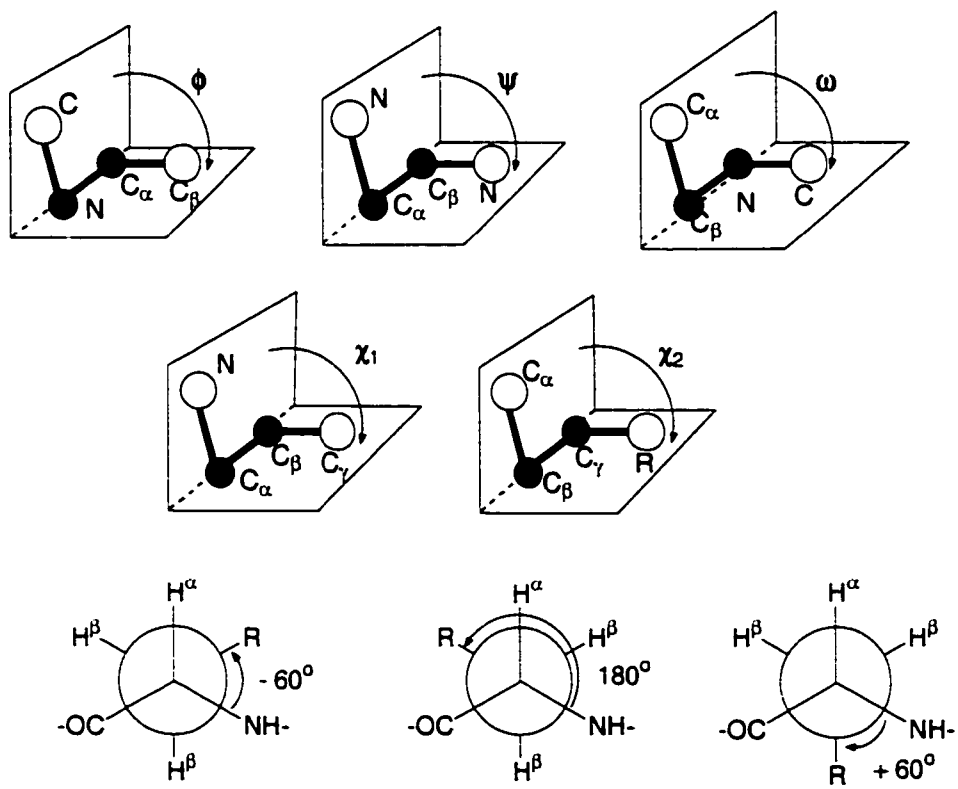


Figure 1-2. Definitions of ϕ, φ, ω, χ^1 and χ^2

An equally critical area for design of peptides with pre-defined structures is the three-dimensional structures of the side chain moieties. The side chain groups in α-amino acids that make up peptides and proteins possess a wide variety of chemical-physical properties, and include acids (carboxylic acids), bases (amine, guanidyl, and imidazole), alcohols, phenols, thiols, thioethers, amides, aromatics, heteroaromatics, and alkanes). In the case of de novo design of peptide and protein conformations (Ramachandran space), the major consideration is to use various structural constraints to achieve predictable backbone dihedral angles (φ and ψ, and maybe ω) that would strengthen, or fix or highly bias the secondary structures (α-helix, β-sheet, etc.) to obtain the desired template. In the same manner, the approach to design peptides and proteins in χ space is to introduce side chain constraints to bias or freeze the side chain torsional angles to specific ranges thus to gain insights on binding conformations of peptides when they interact with their corresponding receptors. That will benefit the design of peptide mimics with enhanced biological functions and optimized structural features.

Peptides can be constrained locally in Ramachandran space, topographically in χ space, and globally. The local backbone conformations can be constrained to favor certain secondary structures by 1) replacement of amide bonds (O=C-N) with olefinic double bonds (C=C or other "amide bond replacements"); 2) systematic replacement of L-amino acids with D-amino acids; 3) substitution of amino acid residues with N^{α}-alkylated amino acids or C_{α}-alkylated amino acids.[17,19,20] The global structures of peptides can be biased by cyclization through amide bonds (backbone to backbone,

backbone to side chain or side chain to side chain) and disulfide bonds or tethers to limit both Ramachandran and χ spaces. So far many well-developed strategies have been developed to achieve backbone and global conformation constrains. But there still is much space left to explore in χ space conformational constraint because for all natural amino acids χ space is still highly flexible. Generally, χ space constraints can be achieved by incorporating substitutents into the β-position in amino acids. For aromatic amino acids, the χ^1 in topographical space can be further constrained by substitutents at *ortho*-positions.[21-24]

1.1.2. Methods for Asymmetric Synthesis of Non-Proteinogenic Amino Acids

It is clear that the control of the conformation of peptides can be realized through the control of the key individual amino acid residues. Therefore the design and synthesis of biologically active peptides or peptidomimetics with pre-defined conformations rely on the synthesis of amino acids with pre-defined conformational preferences. So far there are several well-established direct or indirect methods to generate non-proteinogenic amino acids.[25] The direct methods usually begin with a starting material with a moiety of lower amino acids such as glycine and alanine. Manipulation (alkylation or Michael addition) of these simple amino acid-derivatized substrates leads to target amino acids with designed substitution patterns, stereochemistry and functional groups. On this topic, more discussion will be carried on in the next section. The indirect method usually starts from a non-amino acid structure. The stereochemistry of the target amino acids is realized through chiral auxiliaries or non-racemic catalysts. Of these chiral auxiliaries used so far,

the Hruby chiral auxiliary, 4-(*R/S*)-4-phenyl-2-oxozolidinone has been demonstrated to be the most efficient to achieve the steric control at both α- and β-positions. Usually it gives a diastereomeric ratio of over 95:5 at the β-position and stereospecific control at the α-carbon. This auxiliary has been used to synthesize many novel amino acids with controlled stereochemistry and constrained conformation at the topographical space (Figure 1-3).[26-38] These amino acids have been introduced into some biologically active peptides such DPDPE,[21,22] deltorphin[23] and oxytocin.[24] These constrained peptides have demonstrated enhanced biological properties, which led to systematic exploration of the bioactive conformation of these peptides at their corresponding receptors.

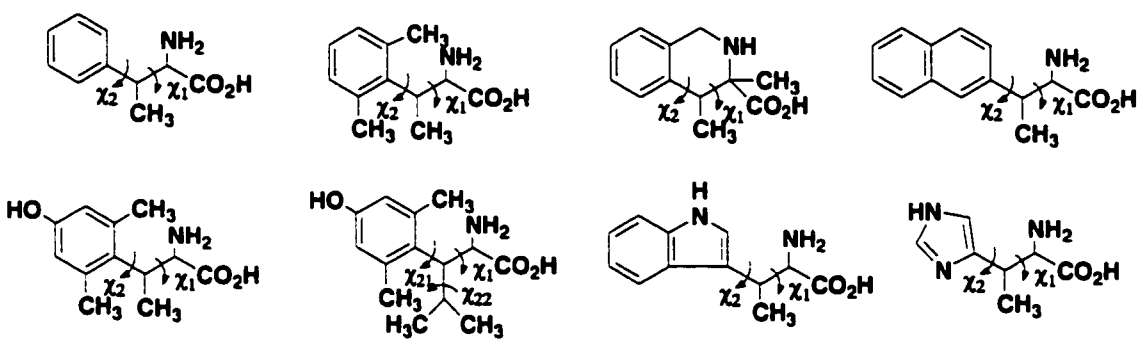


Figure 1-3. Amino acids prepared through Hruby chiral auxiliary

1.2. Reported Synthetic Methods for α-Amino Acids *via* Direct Alkylation

The essence of direct alkylation is the replacement of one or two α-protons of the starting amino acid substrates with functionalized electrophiles such as alkyl halides (Figure 1-4). The alkylation of glycine or other lower amino acid anion chiral equivalents is one of the most convenient general methodologies for the synthesis of non-racemic

amino acids and, in particular, α-alkylamino acids. In order to carry out alkylation at the α-carbon center, the α-proton(s) has to be activated by transforming them into Schiff bases or other activated amino acid derivatives, and other functional groups of simple amino acids which perturb alkylation should be masked. This approach is based on the following concepts.[39,40] A chiral amino acid equivalent is built up from a racemic lower amino acid (or synthetic equivalent) and a chiral auxiliary; this compound possesses an

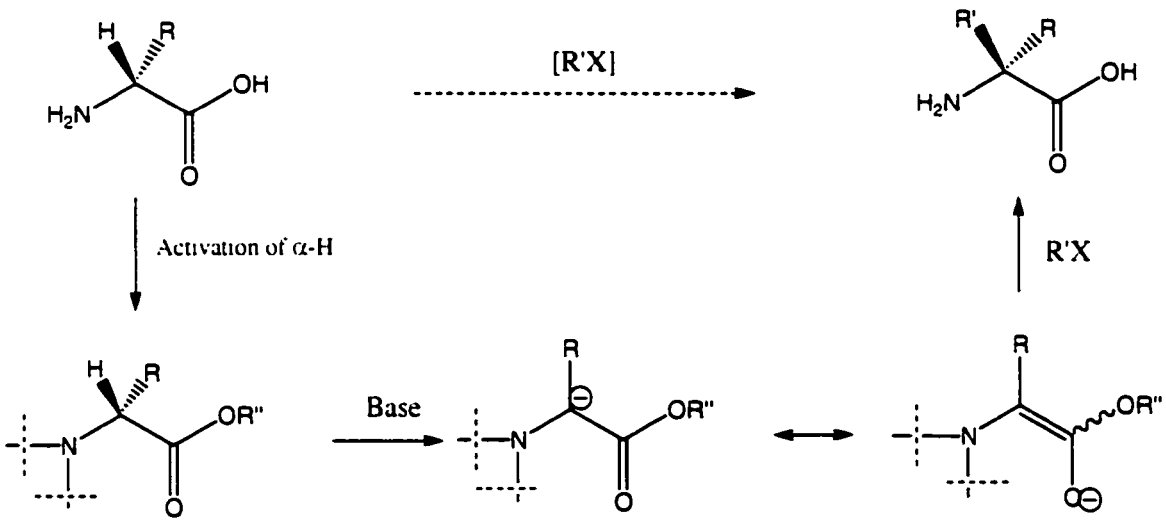


Figure 1-4. General steps of direct alkylation methods

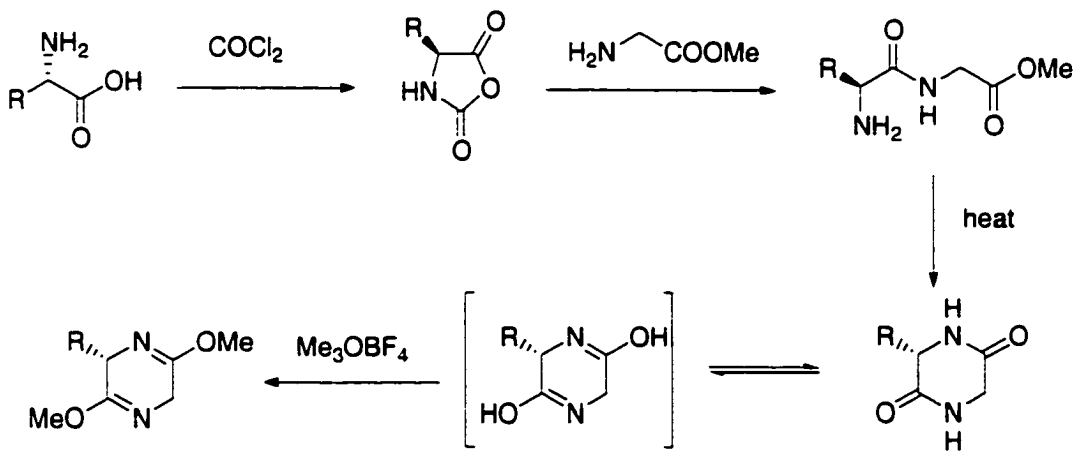
acidic α-proton adjacent to the potential amino group. Treatment with base generates an anionic intermediate that is neutralized with an electrophile to diastereoselectively afford a higher amino acid. Subsequent hydrolysis of this alkylated intermediate liberates the chiral auxiliary and the newly formed optically active amino acids. So far several

methods have been employed to prepare unnatural amino acids *via* direct alkylation. The most popular include Schollkopf's method *via* *bis*-lactim, Seebach's method *via* imidazolidione, O'Donnell's catalytic alkylation, and Williams' method. These methods differ from each other due to their different starting templates.

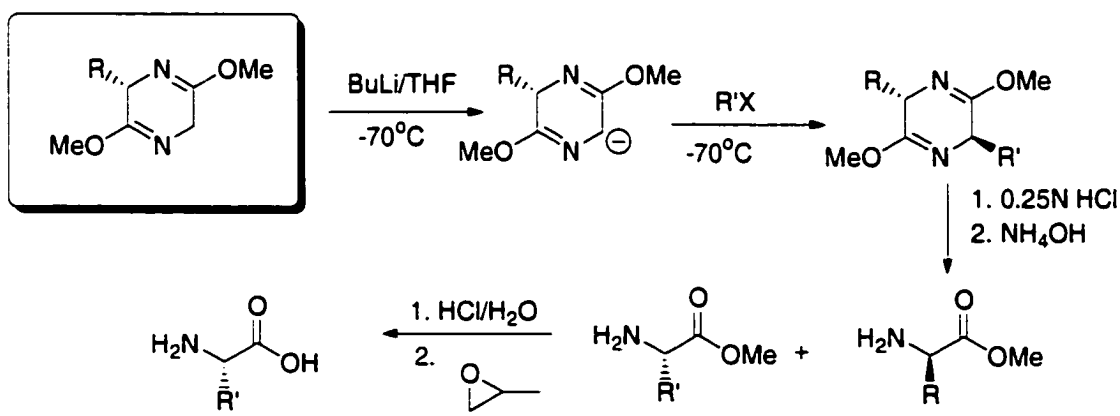
1.2.1. Schollkopf's Method (*bis*-Lactim)

Schollkopf's method is one of the most notable. It involves a *bis*-lactim ether template which was generated form diketopiperazine (Scheme 1-1).[41-57] The pioneering work began with condensation of L-alanine methyl ester on heating to give a diketopiperazine that was converted 2,5-dimethoxy-3,6-dimethyl-3,6-dihydropyrazine upon treatment with trimethyloxonium tetrafluoroborate. The generated *bis*-lactim ether was deprotonated by butyllithium at -70 °C in THF (Scheme 1-2). Then the enolate was attacked by the electrophile (R'X) from the opposite side of the anchor group (R) to avoid the steric hindrance. The nucleophilic substitution gave high diastereoselectivity (de >95%). The alkylated *bis*-lactim ether was hydrolyzed by dilute hydrochloric acid to give two amino methyl esters after work-up with ammonium hydroxide. The target amino ester was isolated by distillation. Treatment with hydrochloric acid and propylene oxide gave the free amino acids. With this way different α-amino acids with *R* or *S* configurations can be obtained by appropriate selection of the starting templates. Of course with 3,6-dialkyl-3,6-dihydropyrazines α-alkylamino acids can be prepared. This method has also been employed to generate some cyclic amino acids through bisalkylation. In addition to alkylation, the *bis*-lactim ether can also be used for aldol

reactions or Michael additions to give amino acids with different side chain functional groups.



Scheme 1-1. Preparation of Schollkopf's *bis*-lactim ether



Scheme 1-2. Substitution of Schollkopf's intermediates with electrophiles

The procedure was subsequently improved with the use of mixed *bis*-lactim ethers derived from a chiral amino acid (e.g. L-valine) and racemic alanine, obtained from

dipeptide L-Val-D/L-Ala-OCH_3. The mixed *bis*-lactim ether was metallated regioselectively in the alanine moiety by treatment with butyllithium at -70 °C and subsequently alkylated with excellent diastereoselectivity (de >95%). This procedure has been applied to the synthesis of several amino acids such as (*R*)-α-methylphenylalanine, (*R*)-α-methyldopa, several (*R*)-α-methyl-a-allylglycines,(*R*)-α-methylserine, (*R*)-α-methyl-*S*-alkylcysteines, (*R*)-α-methyltryptophan and (*R*)-isovaline.[47,58-61]

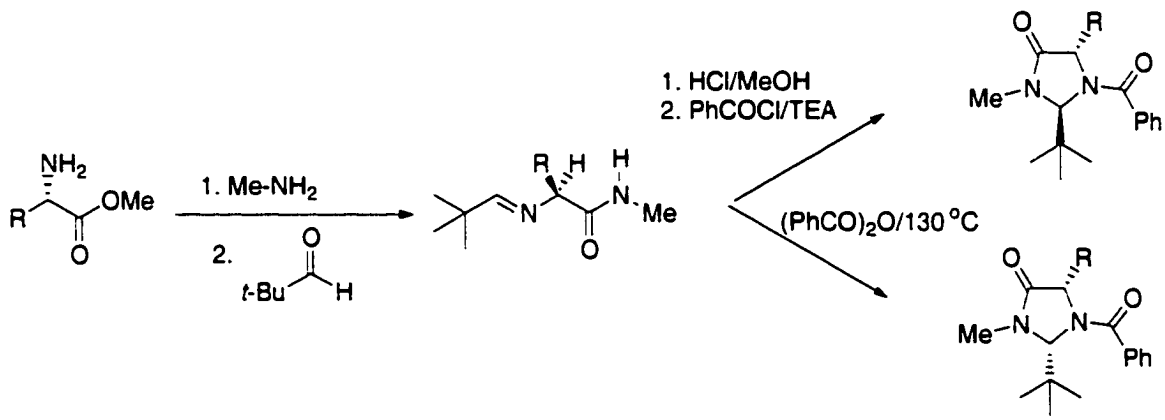
Even though this method gave very high stereoselectivity, the reaction has to be done at very low reaction temperature and with strong base like BuLi. Also the decomposition of alkylated *bis*-lactim ether gave two amino esters which might not be separable under normal conditions. Schollkopf's method could achieve high stereochemical purity and yields with primary alkyl halide to generate certain types of amino acids, but so far no example of alkylation with *secondary* alkyl halides to reach β-substituted amino acids, which are extremely important to achieve control of the topographical space in peptides, has been observed by this method.

1.2.2. Seebach's Method

α-Amino acid derivatives can be alkylated stereoselectively with retention or inversion of configuration through *cis*- or *trans*-imidazolidinones, respectively, without an external chiral auxiliary in a synthetic route developed by Seebach and called self-production of the center of chirality.[62-77]

In order to obtain *cis*- or *trans*-imidazolidiones, methyl or ethyl esters of amino acid hydrochlorides were converted into *N*-methylamides which were condensed with

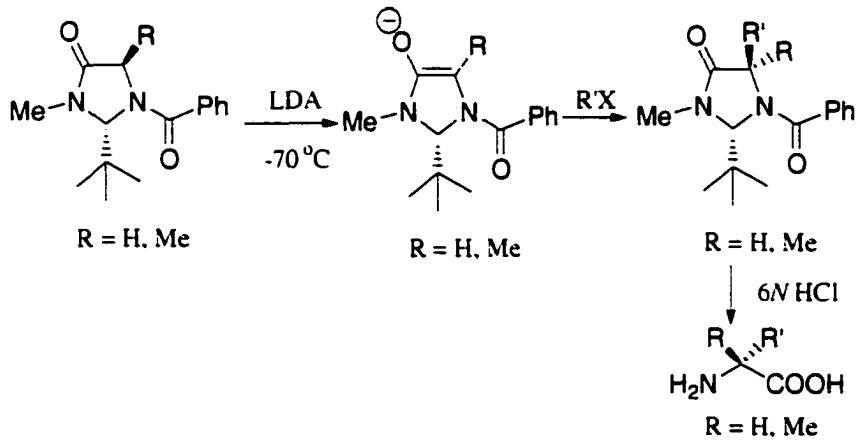
pivalaldehyde to give the corresponding Schiff bases (Scheme 1-3). Subsequent cyclization gave either *cis*- or *trans*-imidazolidiones as major products under different reaction conditions in the presence of either benzoic anhydride or benzoyl chloride. Usually a simple recrystallization is required to obtain the desired starting materials with high purity.



Scheme 1-3. Synthesis of *cis*- or *trans*-imidazolidinones

The nucleophilic substitution of Seebach's *cis*- or *trans*-imidazolidinones began with deprotonation with lithium diisopropylamide (LDA) to give chiral enolates (Scheme 1-4). The facial selectivity of products was controlled by the *t*-butyl group. The incoming electrophiles approached the enolate from the face opposite the bulky *t*-butyl group. This stereochemical behavior has been explained by Seebach et al.[68] in the case of imidazolidinones by taking into account the steric requirements of the C_2 substituent, which hinders the approach to the *cis*-face and favors the attack of electrophiles at the *anti*-face, as well as invoking stereoelectronic effects that lower the transition-state energy of the approach of the electrophile from the face opposite to the C_2 substituent.

Moreover, the aggregation state of the reagent, as well as the chelation of the metal, may play an important role in controlling the stereochemical course of the reaction and must also be taken into account. The stereochemical outcome is excellent from this method. The diastereomeric excess can be greater than 95%.



Scheme 1-4. Nucleophilic substitution on the Seebach intermediate

This general and elegant asymmetric synthesis of α-alkylamino acids has been applied by Seebach and co-workers to the synthesis of a wide variety of highly valuable compounds such as both enantiomers of α-methyldopa from (*S*)-alanine, (*S*)-α-methylvaline from (*S*)-valine, (*R*)-α-methylmethionine from (*S*)-methionine, (*S*)-α-methylaspartic acid from (*S*)-aspartic acid, (*R*)-α-methyl and (*S*)-α-benzylglutamic acid from (*S*)-glutamic acid, (*R*)- and (*S*)-α-methyl- and (*R*)-α-benzyllysine from (*S*)-lysine, (*R*)-α-methylornithine from (*S*)-ornithine and, more recently, to the stereoselective synthesis of (*S*)-α-methyl-4-carboxyphenylglycine, (*S*)-α-methyl-4-

phosphonophenylglycine, and (*S*)-α-methyl-4-(tetrazol-5-yl)phenylglycine, from (*R*)-4-hydroxyphenylglycine.[70,78-81] This synthetic method has been used to prepare α-substituted-β–unsubstituted amino acids (Figure 1-5) and some other amino acids which cannot be readily obtained by other methods. This method also is applicable to generate β-substituted amino acids.

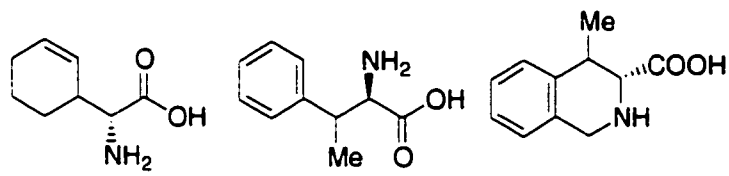


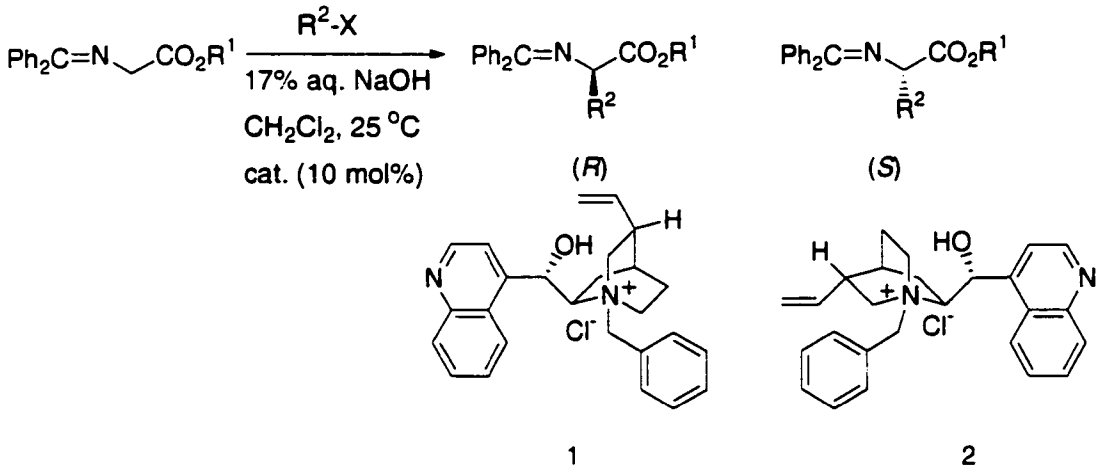
Figure 1-5. Some amino acids prepared through Seebach's method

Usually *cis*-imidazolidinones are less readily available than *trans*-imidazolidiones. Still, this method has to employ very strong bases like LDA to deprotonate the α-proton in imidazolidiones. In order to obtain the free amino acids, hydrolysis is required in concentrated acid at 175-180 °C in a sealed tube. This limits this synthetic method to amino acids without acid-labile substitutents.

1.2.3. Catalytic Alkylation

In 1989, O'Donnell successfully synthesized optically active amino acids *via* direct alkylation of the benzophenone Schiff base of glycine *t*-butyl ester under chiral phase transfer catalyst.[82] This method differs from the previous method in that the substrate is achiral. The asymmetric induction on the glycine Schiff base is realized by

chiral catalysts. The catalysts used for this method are derivatives of cinchonine- or cinchonidine-related alkaloids.

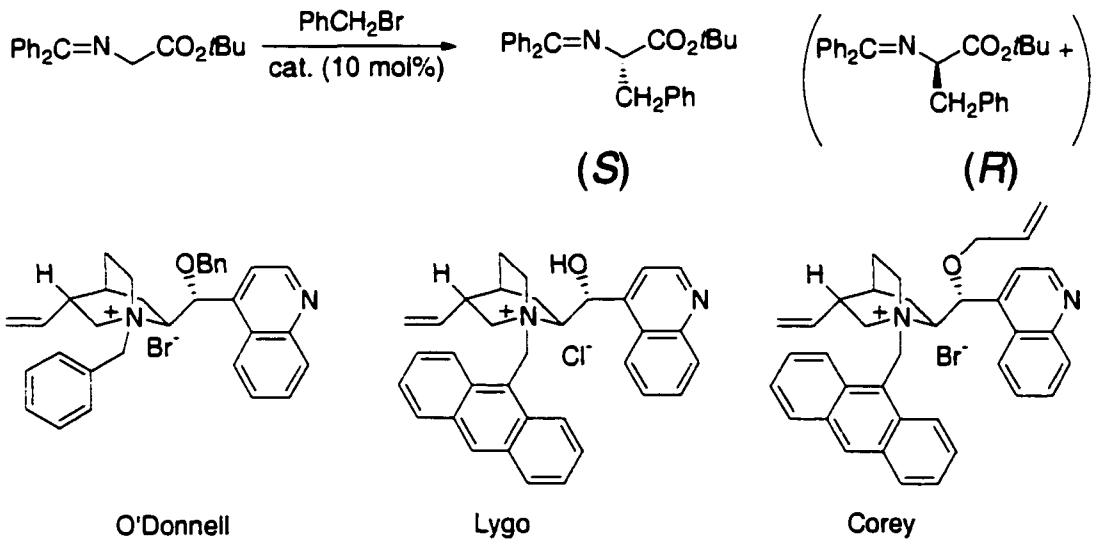


Scheme 1-5. Alkylation of O'Donnell Schiff bases using the first generation catalysts

Table 1-1. Alkylation of O'Donnell Schiff bases using the first generation catalysts

R^1	R^2	catalyst	major	% ee
Bn	Allyl	1	*R*	28
Me	Allyl	1	*R*	30
Et	Allyl	1	*R*	36
t-Bu	Allyl	1	*R*	56
t-Bu	Allyl	2	*S*	62
t-Bu	Bn	1	*R*	66
t-Bu	Bn	2	*S*	64
t-Bu	4-Cl-Bn	1	*R*	66
t-Bu	4-Cl-Bn	2	*S*	62

In the early stage of this method, with the first generation catalysts derived from cinchonine the enantiomeric excess could reach 66% in favor of *R*-amino acids. Under the same conditions the *S*-amino acids could become the major product by switching to the cinchonidine-derived catalysts (Scheme 1-5 and Table 1-I). Optimization of the catalyst was carried out by O'Donnell et al. by converting the OH group into a benzyl ether. In this way, the enantiomeric excess could be up to 81% (Scheme 1-6 and Table 1-2).[83-85] With further increase of the steric size of ammonium salts by Lygo[86,87] and Corey,[88-91] the catalysts have demonstrated excellent enantiomeric excesses up to 99.5%.

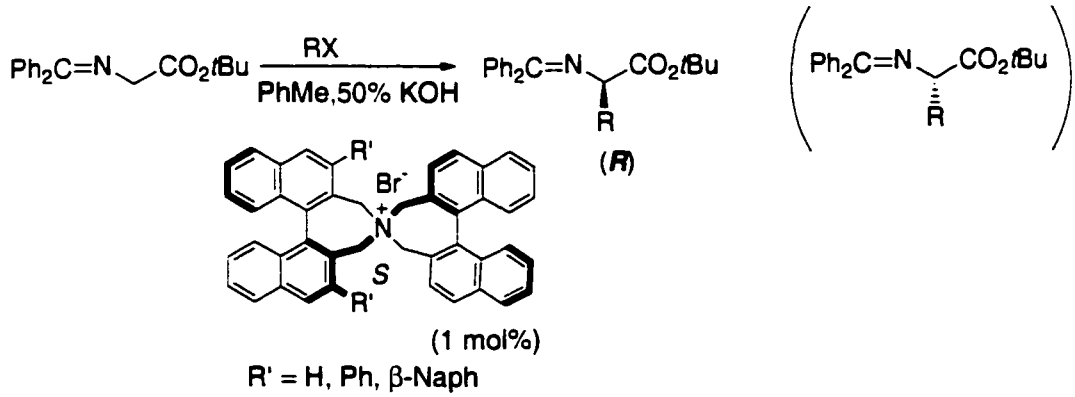


Scheme 1-6. Catalytic alkylations of O'Donnell Schiff base using improved catalysts

Table 1-2. Comparison of alkylation using cinchona-related catalysts

method	yield, %	ee, %	condition	temperature & time
O'Donnell	87	81	50% NaOH, CH_2Cl_2/PhMe	+5 °C, 0.5 h
Lygo	68	91	50% NaOH, PhMe	RT, 18h
Corey	87	99.5	$CsOH.H_2O$, CH_2Cl_2	-78 °C, 22h

In addition to these alkaloid catalysts that share a common feature of β-hydroxyammonium salts, a β-naphthalene ammonium salt catalyst has been developed by Maruoka and co-workers.[92-94] These types of catalysts are C_2-symmetric. The asymmetric induction on the achiral Schiff base is very efficient. The enantiomeric excess can reach over 98% with excellent yields in some cases (Table1-3 and Scheme 1-7). The stereochemistry of the major products can be alternated by using the enantiomers of the catalysts.



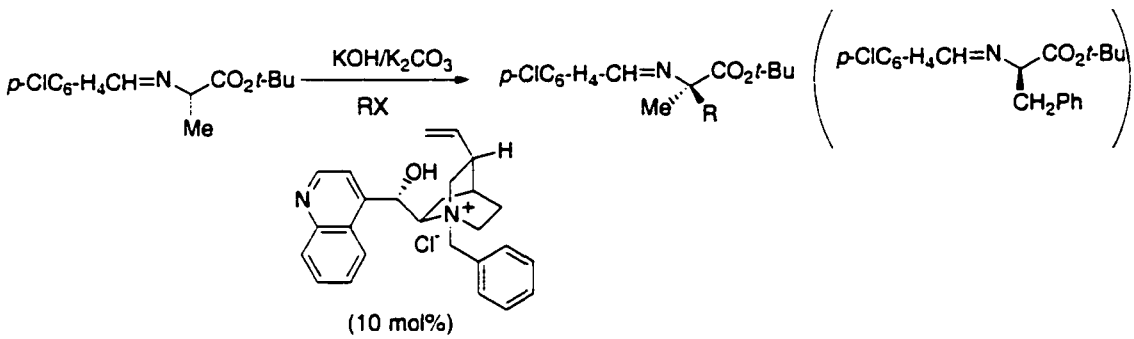
Scheme 1-7. Asymmetric alkylation of Schiff bases catalyzed by β-naphthalene ammonium salts

Table 1-3. Alkylation of Schiff base using β-naphthalene ammonium salts

RX	condition(°C, h)	yield(%)	% ee (config.)
$PhCH_2Br$	0, 0.5	95	96 (*R*)
MeI	0, 8	64	90 (*R*)
EtI	0, 10	41	95 (*R*)
4-Me-BnBr	0, 0.5	80	96 (*R*)

In addition to alkylation of ketone-derived glycine Schiff bases (ketimines), those cinchonine-derived catalyst can also be applied to control the stereochemical outcome of double alkylation of aldehyde-derived glycine Schiff bases (aldimines) and alkylation of alanine-derived Schiff bases (Table 1-4 and Scheme 1-8). O'Donnell et al. have also developed an enantioselective route to α-alkylamino acids based on the well known strategy developed by him and his colleagues and applied to the asymmetric synthesis of monoalkylamino acids. Asymmetric synthesis of α-methylamino acids is performed by phase-transfer catalytic alkylation, using cinchonine or cinchonidine as a chiral catalyst, of Schiff bases derived from aromatic aldehydes and alanine *tert*-butyl ester.[83,95] Optimal results were obtained using KOH/K_2CO_3 as the base and the *p*-chlorobenzaldehyde-derived imine as the substrate. Under these reaction conditions alkylation with several alkyl halides gave the corresponding alkylation products in good yields and with enantiomeric excesses in the range of 36-50% in favor of the enantiomer of *R* configuration when the *cinchonine*-derived chiral catalyst was used. With the use of

pseudoenantiomeric cinchonidine-derived catalyst, the corresponding enantiomer of *S* configuration is obtained as the major compound. Purification of the major enantiomer by crystallization and subsequent deprotection releases the α,α-dialkylamino acid.



Scheme 1-8. Catalytic alkylation on the aldimines

Table 1-4. Catalytic alkylation of the aldimines

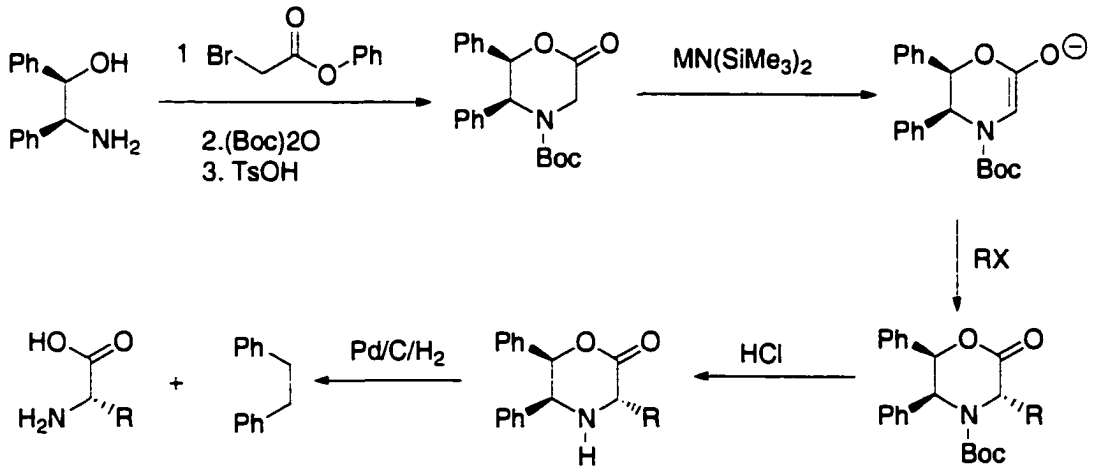
Entry	RX	ee%
1	4-$FC_6H_4CH_2Br$	50
2	4-$ClC_6H_4CH_2Br$	48
3	4-$BrC_6H_4CH_2Br$	44
4	$C_6H_5CH_2Br$	44
5	2-naphthylCH_2Br	42
6	CH_2=$CHCH_2Br$	36

Generally, asymmetric catalytic alkylation is a very useful method for practical synthesis. But so far the electrophiles used are only limited to primary alkyl halides. No

example with a secondary alkyl halide has been observed. Therefore this method has not yet been applied to generate β-substituted amino acids.

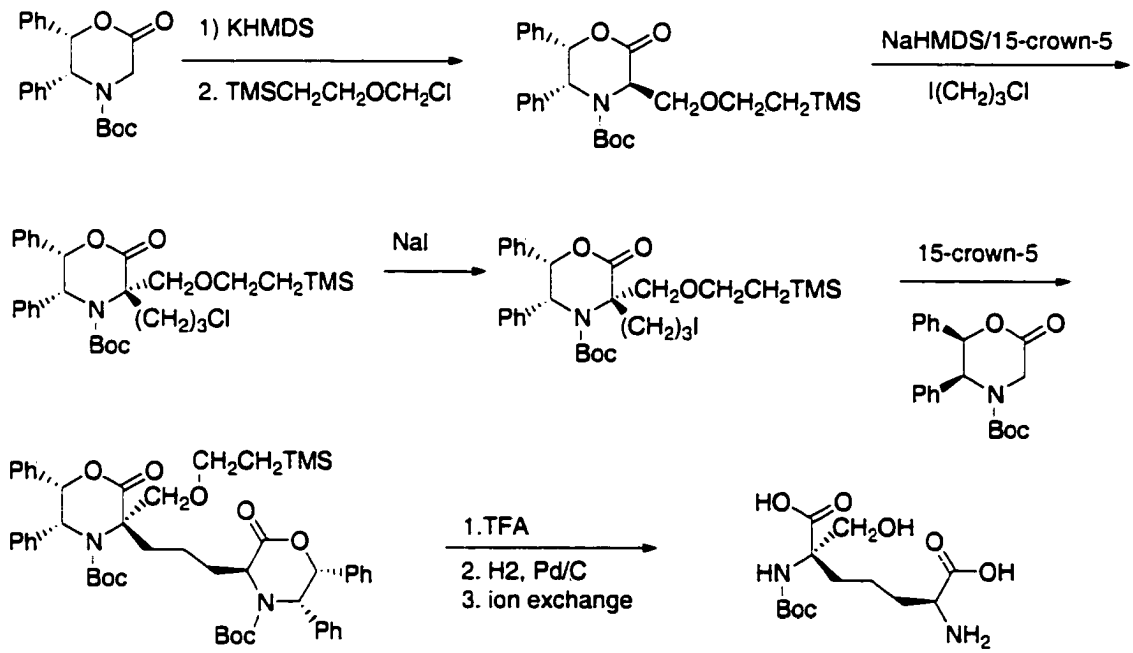
1.2.4. Williams' Homologation

Chiral *N-tert*-butoxycarbonyl- or *N*-benzyloxycarbonyl-5,6-diphenyltetrahydro-1,4-oxazin-2-ones initially obtained from chiral 1,2-diphenyl-2-hydroxyethylamine and ethyl bromoacetate, and whose syntheses have been recently improved, have proven to be extremely useful starting materials for the synthesis of α-alkylamino acids with high enantiomeric purity.[96-101] Generation of the enolate with lithium or sodium hexamethyldisilylamide followed by addition of an alkyl halide results in the formation of alkylation products *anti* to the two phenyl substituents on the oxazinone ring (Scheme 1-9), with high diastereoselectivity. To perform alkylation of 3-monosubstituted



Scheme 1-9. General steps of Williams' homologation of amino acids

oxazinones it is necessary to generate the enolate in the presence of the electrophile using potassium hexamethyldisilylamide as base and to avoid the use of HMPA as co-solvent. Alkylation of highly hindered 3-substituted oxazinones requires the use of a large excess of base to promote the reaction.

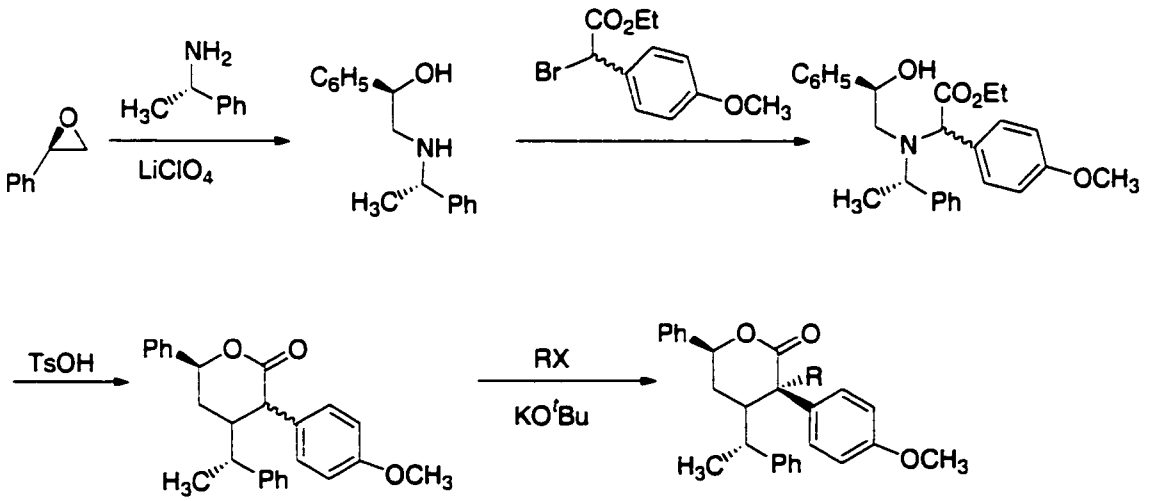


Scheme 1-10. Double alkylation of Williams' template

As an alternative to this procedure, Baldwin has recently described generation of the sodium enolate in the presence of 15-crown-5, which results in the formation of alkylation compounds, even when non-activated alkyl halides were used to trap the enolate (Scheme 1-10). In all of the cases described, bisalkylation occurs with total

diastereoselectivity and, as expected, the second alkylation also proceeded *anti* to the two phenyl rings of the oxazinone. The Baldwin protocol has proven to be very useful in the synthesis of (2*S*,6*S*)-2,6-diamino-6-(hydroxymethyl)pimelic acid and led to an improvement on the results described by Williams for the synthesis of the same compound.[102,103]

In a related approach, Remuzon et al. obtained (6*R*)-*N*-*tert*-butoxycarbonyl- and *N*-benzyloxycarbonyl-3,6-diphenyl-1,4-oxazin-2-ones and tested their methylation under a variety of reaction conditions. However, all attempts to obtain the dialkylated compounds in high yields and stereoselectivities were unsuccessful. Nevertheless, when the starting compound possesses an additional chiral substituent at the *N*-atom, e.g. a phenylethyl group, and a 4-methoxyphenyl group at C3, alkylation occurs with acceptable yields and excellent diastereoselectivity (Scheme 1-11 and Table 1-5). Yields



Scheme 1-11. Remuzon modification of Williams' type template

were better when the electrophile was added prior to the addition of base and an increase in the size of the electrophile resulted in an increase in the stereoselectivity of the alkylation reaction. Final hydrolyses to afford 2-alkyl-2-(4-methoxyphenyl)glycine derivatives have proved to be troublesome as undesired by-products also are obtained.[104]

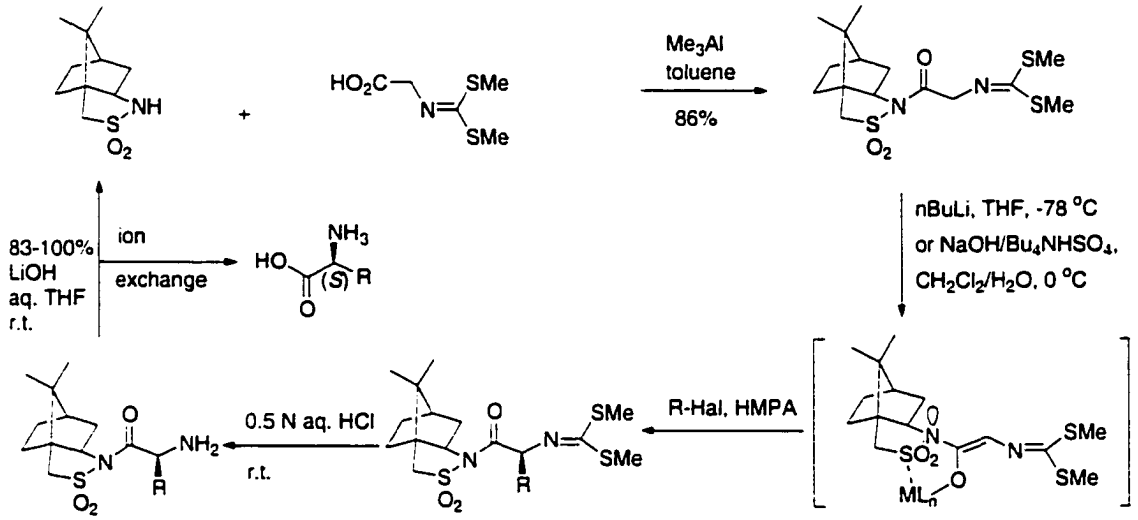
Table 1-5. Remuzon modification of Williams' type template

entry	RX	de%
1	MeI	84
2	EtI	98
3	Allyl Br	100
4	BnBr	94

1.2.5. Oppolzer's Method

This method involves a glycine Schiff base containing a camphor sultam auxiliary.[105-107] Me_3Al-Mediated acylation of sultam with *N*-[*bis*(methylthio)methylene]glycinate furnished the chiral Schiff base with high purity after a simple crystallization (Scheme 1-12). The deprotonation was carried out by BuLi at -78 °C and alkylation followed in HMPA in favor of (*S*)-isomer in the case of the (*R*)-camphor auxiliary due to the π-facial selectivity (Table 1-6). The amino group was restored after treatment with 0.5 *N* aqueous hydrochloric acid. The free amino acids were obtained by basic hydrolysis and the chiral auxiliary was recovered. Interestingly, this simple alkylation could also be carried out under phase-transfer conditions (entry 5 in

Table 1-6). Bansal[108] and Roques[109] used this method to prepare some functionalized amino acids *via* direct alkylation.



Scheme 1-12. Direct alkylation of Oppolzer glycine Schiff base

Table 1-6. Direct alkylation of Oppolzer's glycine Schiff base

Entry	R-Hal	Base	de (% in alkylation)
1	MeI	BuLi	>99
2	BnI	BuLi	>99
3	Allyl-I	BuLi	>99
4	*i*-BuI	BuLi	>99
5	BnI	NaOH/PTC	>99

Lavielle extended this chemistry by preparing the benzophenone and 4-chlorobenzaldehyde Schiff base derivatives (**a** and **b** in Figure 1-6). The aldehyde-derived Schiff bases (aldimines, **b** in Figure 1-6) have been successfully used for

preparation of $C_{\alpha\alpha'}$-disubstituted amino acids with excellent diastereoselectivity (Scheme 1-13 and Table 1-7). Recrystallization and hydrolysis led to pure amino acids.[110]

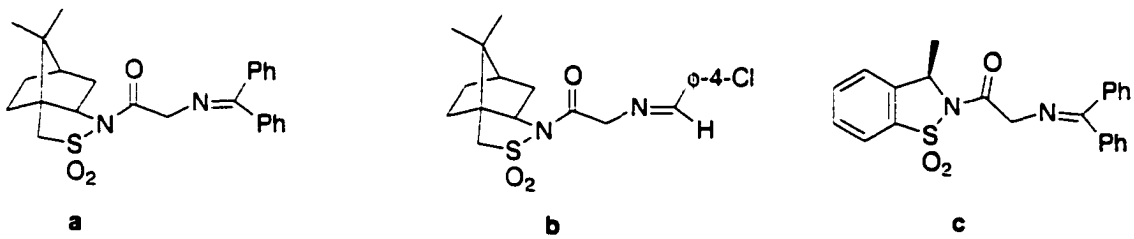
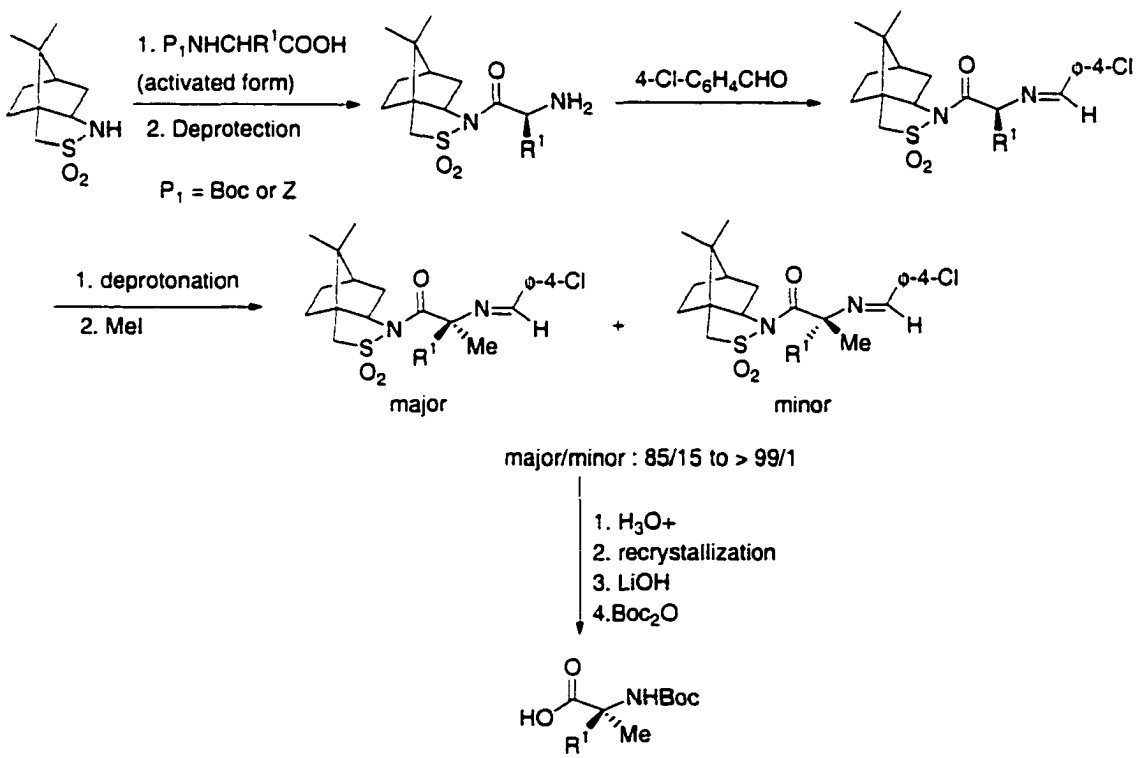


Figure 1-6. Structures of other Schiff bases with a sultam auxiliary



Scheme 1-13. Alkylation of aldimines containing a sultam auxiliary

Table 1-7. Alkylation of aldimines with sultam auxiliary

Entry	R1	Base	de in alkylation
1	CH_3SCH_2	BuLi	> 99 : 1
2	i-Bu	BuLi	87 : 13
3	Bn	BuLi	85 : 15
4	Me	BuLi	97 : 3

In addition to camphor Schiff base, Oppolzer also tried another sultam Schiff base (**c** in Figure 1-6) but this compromised stereoselectivity. Generally, the glycine Schiff bases with the camphor sultam auxiliary as chiral inducer are very useful to generate simple functionalized amino acids. But it has not yet been demonstrated to be viable for generating β-substituted amino acids.

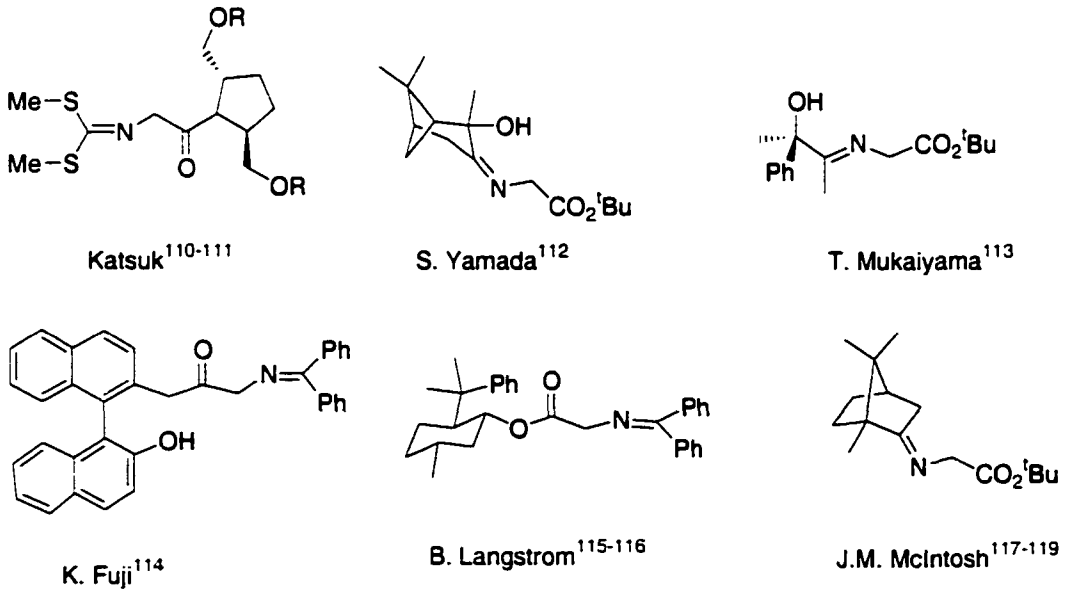


Figure 1-7. Chiral aldimines and ketimines of glycine equivalents

In addition to these amino acid derivatives mentioned above which can be used to prepare new amino acids by alkylation, there are many other simple amino acid substrates as listed in Figure 1-7.[111-120] Generally, all these methods have been successfully used to prepare unnatural amino acids with designed functional groups. Only a few methods *via* direct alkylation lead to β-substituted amino acids. But none of these methods have been demonstrated to be useful for preparing conformationally constrained amino acids with α,β-disubstitution, 2',6',α,β-tetrasubstitution, or 2',6',β-trisubstitution.

In this research, a systematic method for the synthesis of α-substituted, β-substituted, α,β-disubstituted, α,2',6'-trisubstituted, β,2',6'-trisubstituted, and α,β,2',6'-tetrasubstituted amino acids has been developed.

Chapter 2. Asymmetric Synthesis of Stereochemically Defined and Conformationally Constrained Novel Amino Acids *Via* Direct Alkylation of Chiral Ni(II) Schiff Bases of Lower Amino Acids with Functionalized Alkyl Halides

The concept of global and local constrains for *de novo* peptide design, introduced and developed by our group,[17,121-123] has proven to be one of the most fruitful and promising methodologies for the rational design of peptides and peptide mimics with a pre-supposed pattern of biological properties. In particular, introduction of the chi-(χ)-constrained[17,124] α-amino acids in strategic positions of peptides (local side-chain constraints) allows for a substantial reduction of the corresponding side-chain conformers, and thus usually leads to the increased biological activity of the target peptide. [21,22,24,42,43] Systematic studies conducted by our group into the chemical-physical basis for peptide-mediated biological information transfer, as a function of topographical properties and three-dimensional structure of peptides, have led to a uniquely fruitful approach to the *de novo* design of peptides *via* rational introduction of global and local constraints to the peptide's geometry.[20] Since phenylalanine (Phe) often plays a pivotal role as a pharmacophore element in biologically active peptides such as enkephalin, much attention had been paid by us[36,37,125-127] and others[75,124,128-134] to the development of sterically constrained analogues of this essential amino acid and related tyrosine (Tyr) analogues to be used as building blocks in the rational design of peptides.

2.1. Design of Ni(II)-Coordinated Schiff Bases of Amino Acids

We envisioned that the highly-substituted amino acids (Figure 2-1) can be assembled from two moieties through nucleophilic substitution. One moiety carries all the designed structural features on the side chains (function groups and substituents) required to achieve the biased conformations of the target amino acids. Usually this part is designed as an electrophile. For the purpose of alkylation, they are introduced in a form of alkyl halides which can be reached through appropriate manipulations. Another moiety carries the basic structural features, α-amino group and carboxyl group, without significant side chain structures. This part is usually considered as the parental part of the target amino acids and can be generated from some simple amino acids such as glycine and alanine. These types of substrates have significant advantages because they already have the basic structural features of amino acids in position. Since one or more asymmetric centers are generated, the stereochemical control becomes an issue for direct alkylation of amino acid substrates. Generally, the electrophile part is not used to control stereochemistry. Instead the substrates are designed to influence the stereochemistry of the newly-created steric center(s). To fulfill this goal, the substrates for alkylation would possess at least one existing stereochemical control mechanism to define the stereochemistry of potential stereogenic center(s). No matter what forms the substrates require for a specific alkylation route, the alkylation of the substrates occurs *via* the corresponding enolate forms produced *in situ* with strong bases. The enolates can potentially exist in different geometries which might lead to different stereochemistries at the newly-created stereogenic center(s) which might compromise the stereoselectivity in

alkylation reactions (Figure 2-2). In order to achieve high stereochemical control or stereospecificity from alkylation, it is necessary to control the geometry of the enolates, in addition to the assistance of existing asymmetric anchor groups. The geometry of enolates can be controlled by fixing the carboxyl group and amino group of substrates in a cyclic form. Actually most of the methods mentioned in Chapter 1 utilized this strategy to specify the enolate geometry.

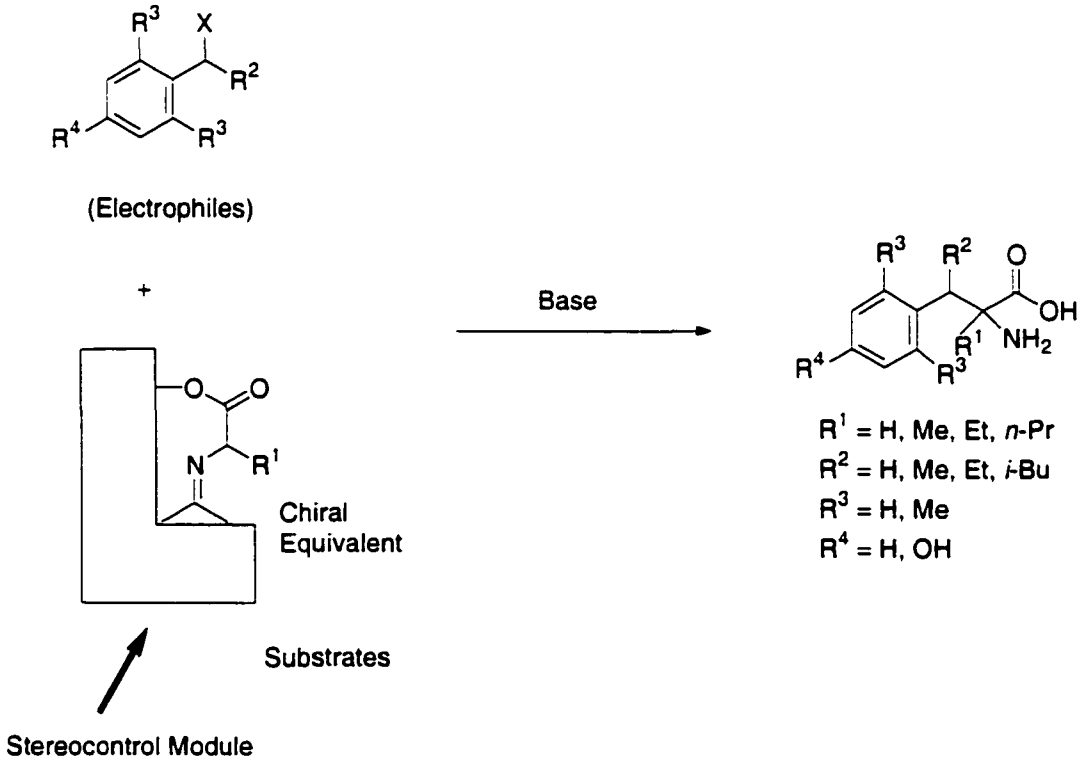


Figure 2-1. Assembly of highly substituted amino acids

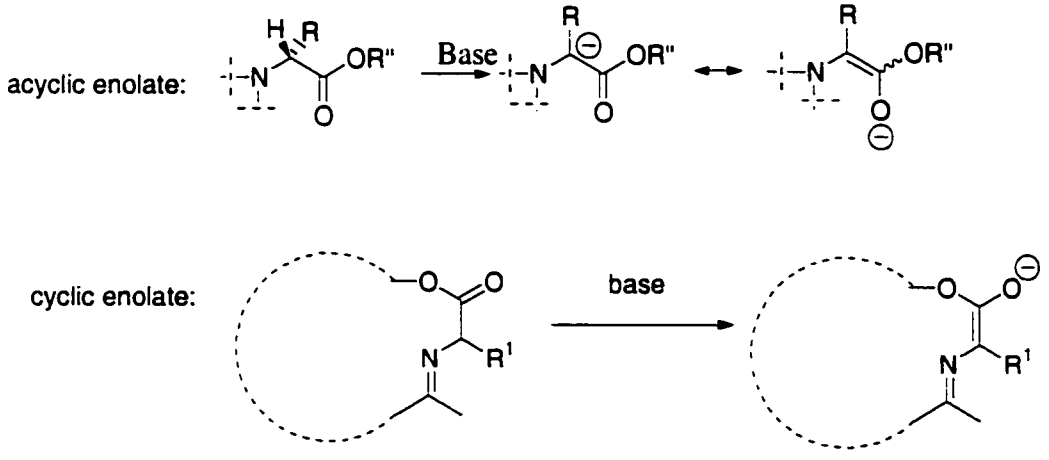


Figure 2-2. Acyclic enolates and cyclic enolates

In addition to stereochemical control, many practical aspects such as reaction temperature, expense of starting materials, reaction conditions, and the scale-up of preparations, should also be considered in asymmetric synthesis of novel amino acids.

Aiming to discover efficient non-peptide therapeutics for human pain, a series of highly conformationally-constrained phenylalanine and tyrosine derivatives with designated substitution patterns are needed for the design and synthesis of novel opioid peptide ligands with distinct conformation preferences to aid our further investigations on the interaction mechanism between the opioid receptors and their ligands. A systematically useful method has to be utilized to generate these desired unnatural amino acids with novel structural features.

After a systematic search, it was found that direct alkylation of Ni(II)-coordinated Schiff bases (Figure 2-3) might meet our needs because of their unique advantages. These chiral Schiff bases were first introduced and modified by Belokon.[135-148] After a careful

search of the metal center to coordinate the Schiff bases, Ni(II) was found to be the best choice for the chelated center. Many aspects of the chemistry involving these complexes have been investigated and they have been successfully employed for the synthesis of β-hydroxy amino acids *via* stereoselective aldol reactions by Belokon and co-workers,[142,149-153] and for β,γ-substituted glutamic acids *via* Michael additions in our laboratory.[154-167] Some simple aromatic substituted phenylalanines have been prepared *via* simple alkylation reactions.[141,168-175] However, many interesting aspects in the alkylation of the Schiff bases were unexplored.

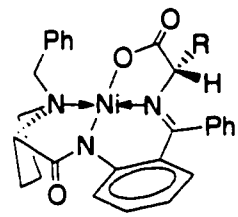


Figure 2-3. Structures of Ni(II)-coordinated Schiff bases

The Schiff base we selected to prepare highly substituted amino acids was a type of cyclic Ni(II)-coordinated Schiff base which solidifies the geometry of enolates in alkylation. After deprotonation, there is only one enolate form because of its cyclic structure, thus fixing the geometry of the enolate. It contains a rigid proline moiety which is the origin of the facial selectivity in nucleophilic substitution. Since it is coordinated to Ni, this robust structure has high C-H acidity at the α-position. In case of NiGlyBPB with R^1 as H in Figure 2-3, the pK_a of the first proton is around 11. It can even be extracted by a weak base like K_2CO_3 or a weak organic base such as DBU. The pK_a of the second

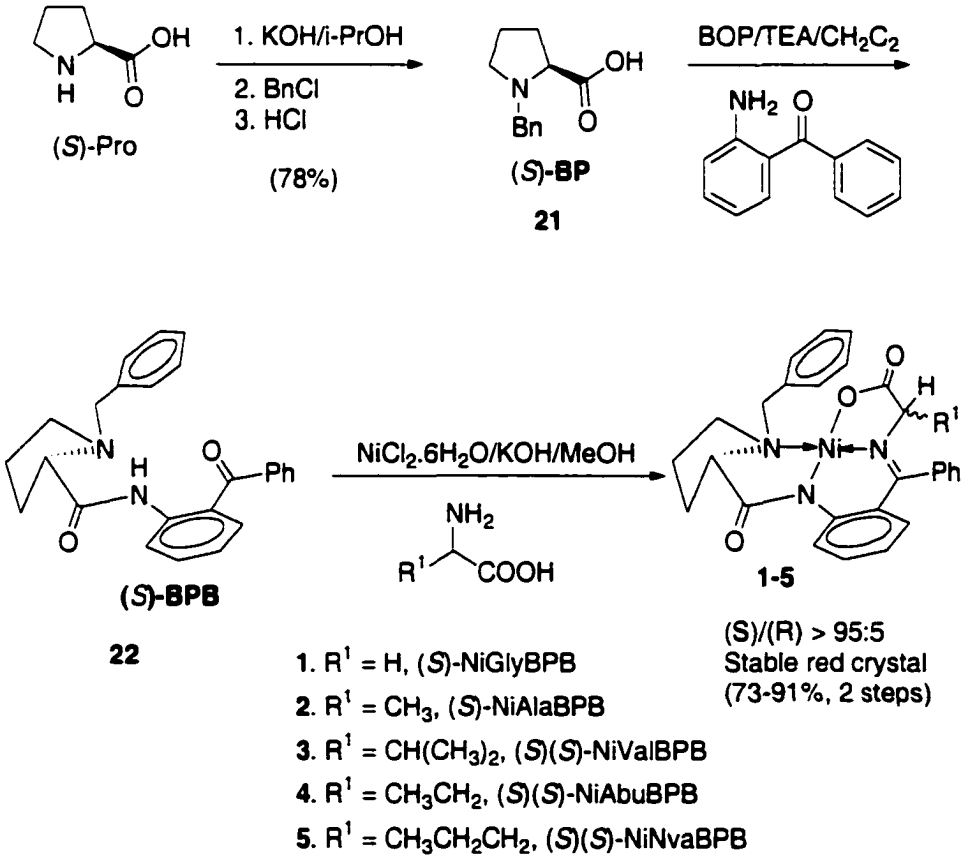
proton is around 15. It cannot be removed by K_2CO_3, but it can by NaOH or KOH. The difference in acidity of the two protons in the glycine moiety may provide exclusive advantages of this type of complex for preparation of α,β-cyclized amino acids as demonstrated later. Even though deprotonation can potentially happen at two α-H positions (one is the α-position of proline and the other is the α-position of the Schiff base), alkylation of these Schiff bases exclusively goes to the α-position of the amino acids of the Schiff base moiety because of the rigidity of the proline moiety. These Ni(II) complexes are highly soluble in polar solvents like DMF, and this can be utilized to ensure a homogenous reaction medium. Usually ordinary inorganic bases such as KOH and NaOH were used to generate the enolate instead of exotic bases. More significantly, the alkylation of these Ni(II)-coordinated Schiff bases can proceed at room temperature or higher to achieve high stereoselectivity. Furthermore, it had been demonstrated that the chiral ligand can be recycled after release of free amino acids to generate a new batch of starting complexes.

2.2. Preparation of the Ni(II)-Coordinated Schiff Bases

2.2.1 Preparation of (*S*)-Proline Complexes

Following Belokon's procedure,[176] in addition to (*S*)-NiGlyBPB and (*S*)-NiAlaBPB a series of new Ni(II)-coordinated Schiff bases were prepared with our modifications (Scheme 2-1). First the amination of (*S*)-proline with benzyl chloride was conducted at 40 °C in *i*-PrOH/KOH in 78% yield to give *N*-benzylproline (**BP**, **21**) in hydrochloric salt form. Then *N*-benzylproline (**21**) was coupled with 2-

aminobenzophenone to give the chiral ligand *N*-(*N*-benylprolyl)-2- aminobenzophenone (**BPB**, **22**). After simple work-up by washing with deionized water, the ligand was used in the next step without further purification. The Ni-coordinated Schiff bases were formed between the chiral ligand and simple amino acids in the presence of $NiCl_2.6H_2O$ with strong bases in MeOH at 55 °C for about 4 hours. The reactions gave 73-91% yield

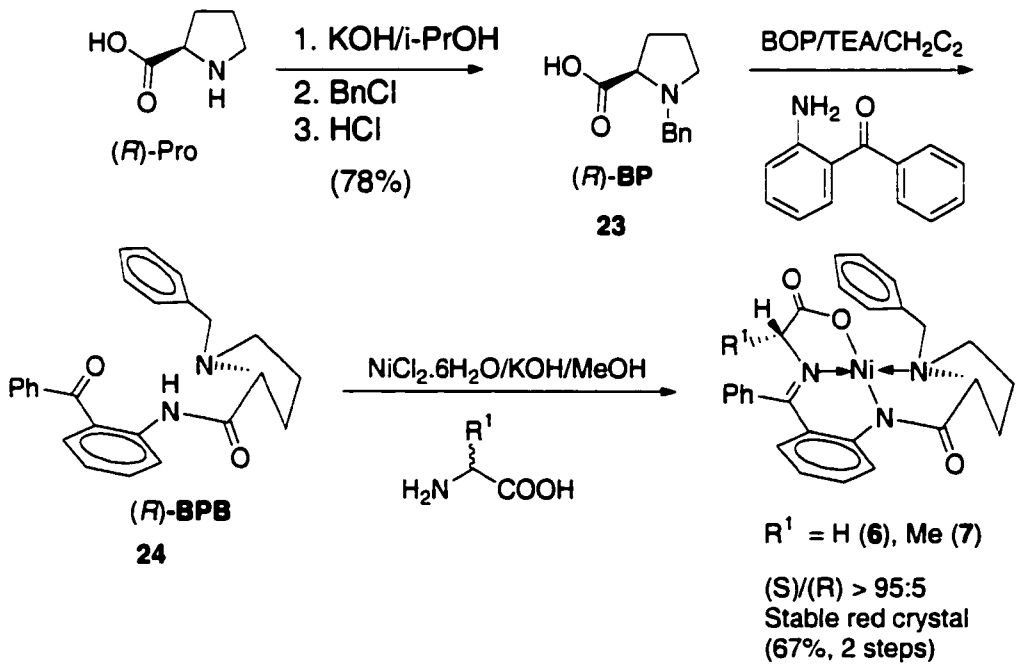


Scheme 2-1. Synthesis of (*S*)-proline Ni(II)-coordinated Schiff bases

of **1-5** in 2 steps from (*S*)-benzylproline (**21**). All the formed Schiff bases were red crystals. They were stable and could be stored in the air with prolonged exposition

without any significant decomposition. The Schiff bases were formed in 3 steps, which is fewer than in the formation of other Schiff bases used so far, with inexpensive starting materials. The workup in these steps is easy. Also no drastic reaction condition was required to form the target complexes. All these features make this method very attractive for large-scale synthesis of tailer-made amino acids.

Even though for the complexes other than (*S*)-NiGlyBPB racemic, simple amino acids were used, the formed complexes had a ratio of 2*S* to 2*R* of over 95:5 in case of (*S*)-proline as chiral control moiety in these complexes. At this stage the complexes already had demonstrated their first application. They can be used to "resolve" some precious amino acids which can only be obtained in racemic form.



Scheme 2-2. Synthesis of (*R*)-proline Ni(II)-coordinated Schiff bases

2.2.2. Preparation (*R*)-Proline Complexes

Following the same procedure for preparation of (*S*)-proline complexes, (*R*)-NiGlyBPB (**6**) and (*R*)-NiAlaBPB (**7**) were synthesized starting with (*R*)-proline (Scheme 2-2).

2.3. Preparation of Electrophiles-Alkyl Halides

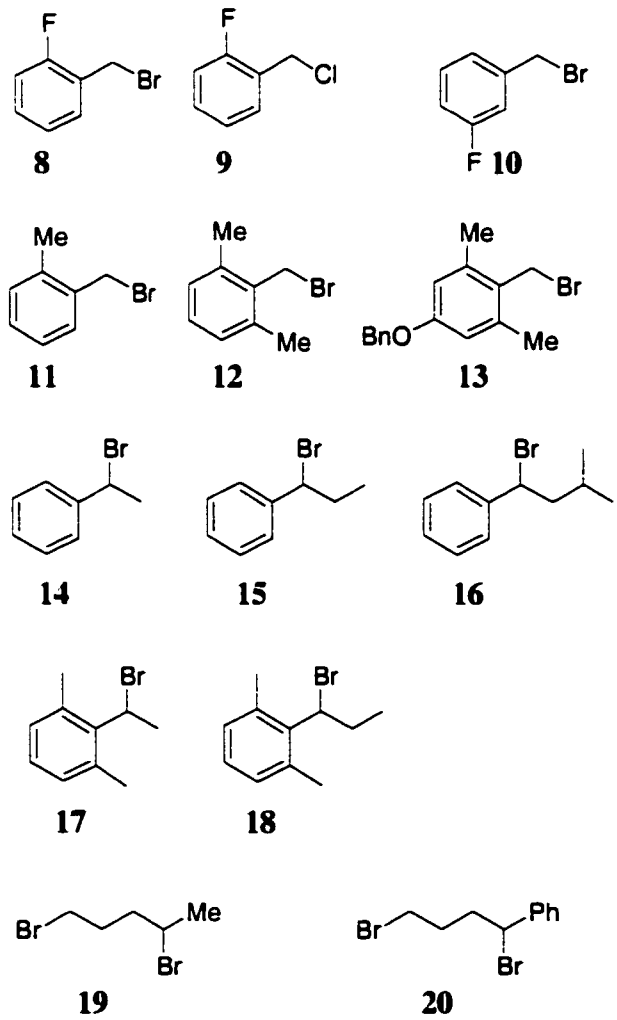
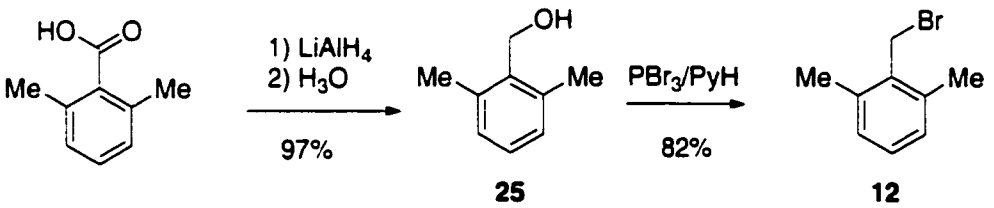


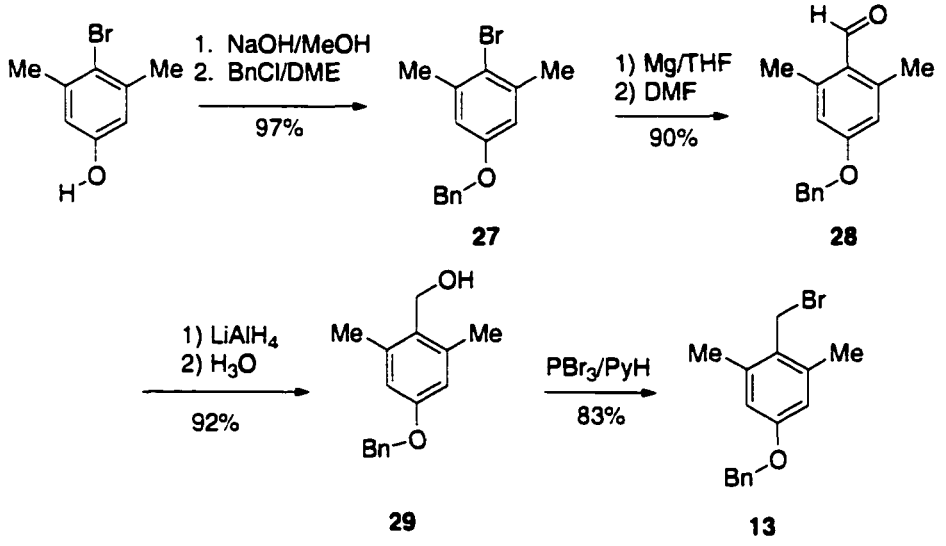
Figure 2-4. Structures of electrophiles investigated

The electrophiles **8-20** (Figure 2-4) were used to investigate the nucleophilic substitution of Ni(II)-coordinated Schiff bases. Of the eletrophiles **8-20**, **8-11**, **14** and **19** are commercially available. **12**, **13**, and **15-20** were prepared with the help from literature.[177] The preparation of **12** (Scheme 2-3) started from 2,6-dimethylbenzoic acid. 2,6-Dimethylbenzoic acid was first reduced by lithium aluminum hydride to 2,6-dimethylbenzyl alcohol (**25**), which was turned into 2,6-dimethylbenzyl bromide by phosphorus tribromide in anhydrous ethyl ether with pyridine as base. The preparation of **12** can also begin with 2,6-dimethylbenzaldehyde following the exact same procedure.



Scheme 2-3. Preparation of **12**

The preparation of **13** (Scheme 2-4) started from 4-bromo-3,5-dimethylphenol, the phenol group of which was first protected as the benzyl **27** ether in dimethoxyethane (DME) at 40 °C for 48 hours following neutralization with NaOH in 85% aqueous methanol at 0 °C. Instead of benzyl bromide, benzyl chloride, a weaker electrophile, was used to avoid any unwanted electrophilic substitution on the aromatic ring.[178] Later it was found that the benzylation of 4-bromo-3,5-dimethylphenol can be simply carried out

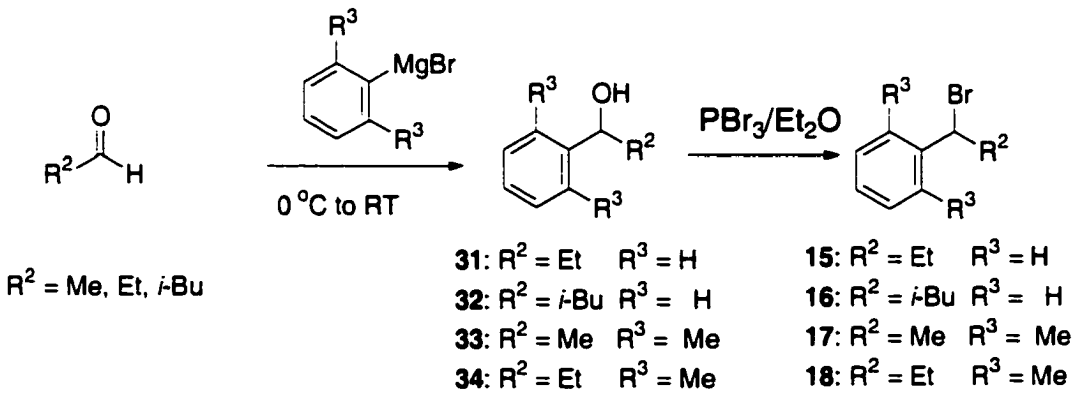


Scheme 2-4. Synthesis of **13**

in DME with benzyl bromide or chloride in the presence of Na_2CO_3. Either method gave excellent yields. Then 4-benzyloxy-2,6-dimethylbenzaldehyde (**28**) was prepared from DMF and the Grignard reagent, which was generated *in situ* by refluxing **27** and magnesium turnings in THF.[33] Aldehyde **28** was reduced by $LiAlH_4$ to the corresponding alcohol **29**, which was transformed into bromide **13** with PBr_3 in the presence of pyridine.

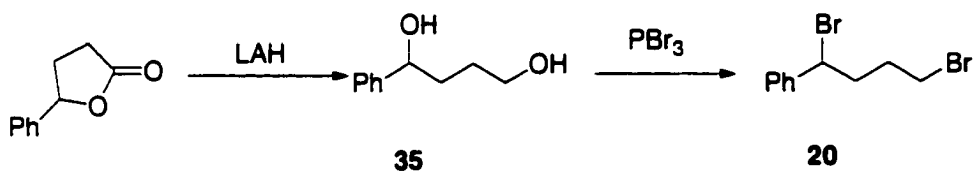
Electrophiles **15-18** were prepared as shown in Scheme 2-5. Reaction of aldehydes with phenylmagnesium bromide or 2,6-dimethylphenylmagnesium bromide gave the secondary α-alkylbenzyl alcohols **31-34**. Bromination of the alcohols **31-34** to bromides **15-18** was conducted in anhydrous ether by PBr_3. Literature suggested the use of pyridine as base to accelerate the bromination process at 5 °C,[177] but it was found that with the presence of pyridine elimination became a serious concern. In order to avoid

elimination, we chose not to use base for this transformation but to conduct the reaction at room temperature. With our modification eliminations significantly diminished.



Scheme 2-5. Synthesis of **15-18**

1-Phenyl-1,4-dibromobutane (**20**) was prepared from γ-phenylbutyrolactone which was reduced to 1-phenyl-1,4-butanediol **35** by LAH (Scheme 2-6). Double bromination gave the dibromobutane **20**.



35 **20**

Scheme 2-6. Synthesis of **20**

In all of these bromination steps, 1.1 equivalents of PBr_3 were used to achieve a reasonable reaction rate. Generally, 2.2 equivalents of pyridine were used to neutralize the formed HBr for the bromination of primary alcohols. All reactions were started at -78

°C and were stirred overnight at room temperature. For bromination of secondary alcohols no base was used in order to suppress elimination.

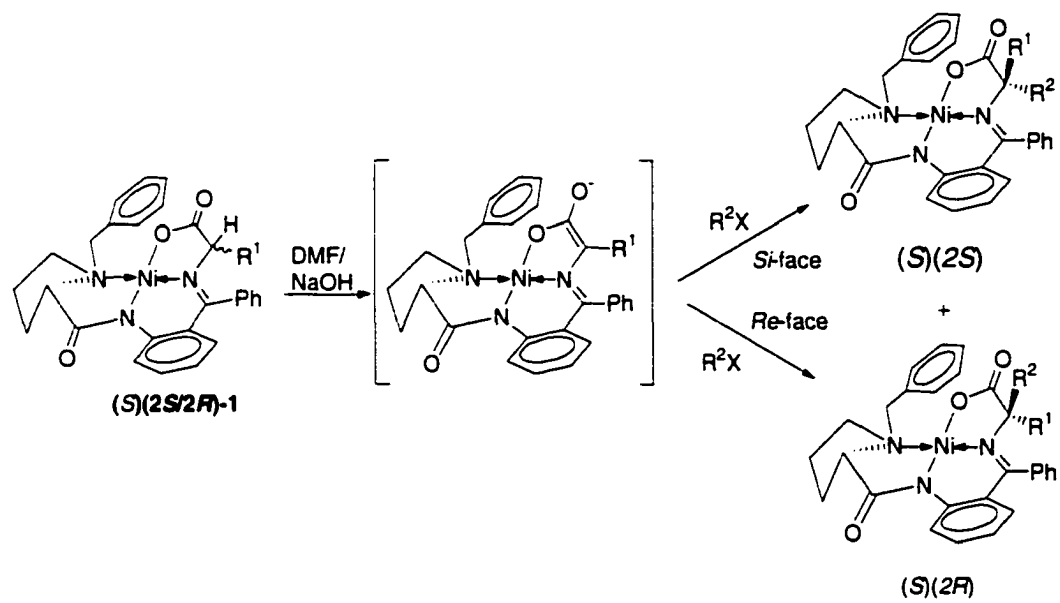
2.4. General Considerations on Asymmetric Alkylation of Chiral Ni(II) Schiff Bases

2.4.1. Experimental Aspects

The nucleophilic substitution of Ni(II)-coordinated Schiff bases **1-7** with electrophiles (alkyl halides) can be dissected into 2 steps (Scheme 2-7). First the Schiff bases were deprotonated by NaOH or KOH to generate cyclic enolates with a single geometry. Then the incoming electrophiles approach the formed enolates from their *Si*- or *Re*-face to give alkylated products with a 2*S* or 2*R* configuration at the α-carbon, respectively. In case of (*S*)-proline complexes, due to the steric shield of the *Re*-face from the *N*-benzyl group in proline, the formed enolates will be preferentially attacked from the *Si*-face to avoid steric hindrance. Thus the nucleophilic substitution will give mainly the 2*S* as the major product. But with (*R*)-proline complexes, the major product will have a 2*R* configuration.

Although the stereochemistry of the major products at the α-carbon center is predictable, it is much more difficult to predict the configuration at the β-carbon in cases when a secondary alkyl halide used. Usually the stereochemistry at the β-carbon center was determined by X-ray crystallography and by comparison of high resolution NMR with similar compounds with known stereochemistry.

The 2.5 equivalents of electrophile were used for secondary bromides **14-18** in light of the different reactivity of the two enantiomers in the racemic electrophiles. But



Scheme 2-7. General steps in the nucleophilic substitution of Ni-coordinated Schiff bases

for **12** and **13**, 1.05 equivalents were used. The excessive eletrophiles were used to drive the reaction to completion. Due to the severe bisalkylation with primary benzyl bromides **8-11**, **19**, and **20**, only one equivalent was used.

The reaction temperature was controlled by an oil bath for 50 °C, ice/methanol mediated by dry ice for -10 °C, or ice water for 0 °C. The reaction at 25 °C was conducted at room temperature without fine control.

Usually the base NaOH was ground and used in 10-fold excess due to the limited solubility of NaOH in DMF. The whole reaction system, including powdered NaOH and starting complexes, was purged with argon at least twice before anhydrous DMF was added *via* syringe. The nucleophilic substitution was conducted in anhydrous DMF under argon to avoid side reactions such as oxidation of the enolate which can be observed on the top and bottom of the TLC plate.

For either (*R*)- or (*S*)-NiGlyBPB, once the enolate was formed the DMF solution turned dark green from bloodish red and back to red once the reaction was completed. Sometimes we could determine the end point with glycine complexes by observing the color change. But in all cases the end point was monitored by TLC with either acetone/chloroform (1:10, v:v) or acetone/hexanes (1:1, v:v) as eluent. The reaction end point was reached upon the complete disappearance of the starting Ni (II)-complexes on TLC. Once the reaction was complete, it was quenched by pouring the reaction mixture into 3% icy aqueous acetic acid with violent stirring. The product was isolated as a precipitate, thoroughly washed with deionized water, and dried under vacuum. A complete wash of the dried crude product with chloroform can further get rid of inorganic salts. The yield reported is the combined yield of all products.

With or without preliminary purification, the diastereomeric ratios were determined by ^{1}H-NMR (DRX500 or DRX600). In particular, characteristic and well-resolved signals of aromatic protons of the phenyl group in the ketimine of complexes in the region 9.00-7.50 ppm were used for the determination.

2.4.2. Factors Considered in Nucleophilic Substitution

For nucleophilic substitution of Ni(II)-coordinated Schiff bases, there are several factors contributing to reactivity and stereoselectivity. They include the steric features of the electrophiles (alkyl bromides), reaction temperature, and the structure of the starting complexes. To study the effects of these factors on the substitutions systematically, a series of controlled experiments were designed and conducted.

In the case of secondary alkyl halides, two steric centers were generated simultaneously. It was be very interesting to learn how the stereoselectivity at the β-carbon center was controlled by the starting complexes and the incoming electrophiles, though the steric preference at the α-carbon centers was known. Since the formed enolates are chiral, it was reasonable to believe that they exhibit different reaction rates toward the enantiomers of the racemic electrophiles. It was very important to learn which enantiomer shows better reactivity toward the starting complexes. Fundamentally, the kinetic resolution of starting complexes on the electrophiles became a serious issue for practical synthesis to achieve stereocontrol in the nucleophilic substitution.

Reaction temperature plays a very important role on reaction rates and even facial selectivity in the process. To evaluate this issue, reactions under different temperature were conducted.

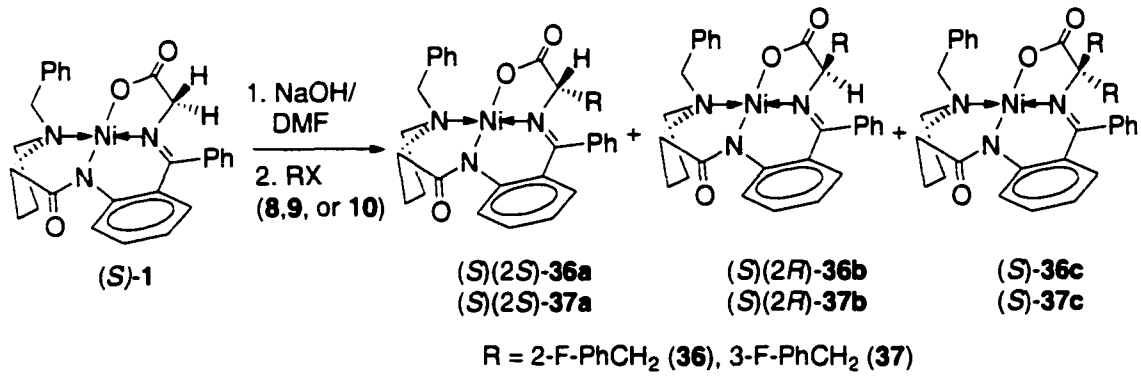
Another important issue for nucleophilic substitution is the structure of the starting complexes. What effect R^1 (Scheme 2-7) has on the stereoselectivity and reactivity is of key importance.

2.5. Reaction of (*S*)- or (*R*)-NiGlyBPB with Halo-Substituted Benzyl Halides

2.5.1. Reaction with (*S*)-NiGlyBPB

The first series of substitutions of (*S*)-NiGlyBPB (**1**) were conducted with 2-fluorobenzyl bromide (**8**), 2-fluorobenzyl chloride (**9**) and 3-fluorobenzyl bromide (**10**) at 25 °C (Scheme 2-8 and Table 2-1). With 10 equivalents of NaOH, all three reactions

were very fast. The starting complexes were completely consumed within 5 minutes either by visualization or by TLC. The yields were excellent (92-97%).



Scheme 2-8. Nucleophilic substitution of (*S*)-NiGlyBPB (**1**) with **8-10**

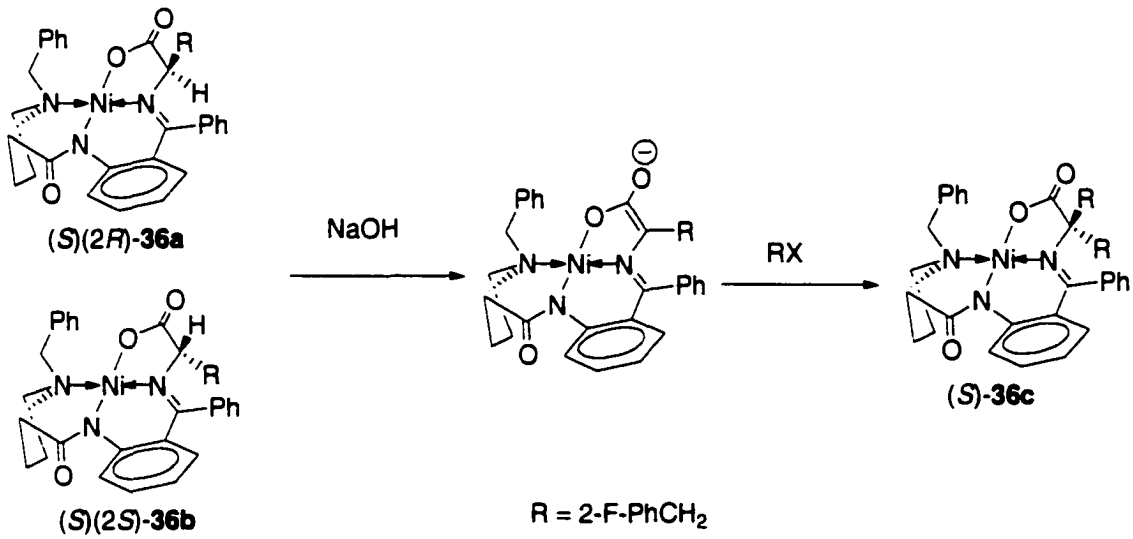
Table 2-1. Alkylation of (*S*)-NiGlyBPB with **8-10**

Entry	RX	time (min)	(*S*)(2*S*)/(*S*)(2*R*)	yield (%)
1	**8**	< 5	4.5 : 1	95
2	**9**	< 5	3.5 : 1	92
3	**11**	< 5	6.4 : 1	97

In the cases of **8** and **9**, there is no significant difference in reactivity or stereoselectivity between benzyl chloride and benzyl bromide at room temperature, and no differences were observable at elevated reaction temperatures. This observation is different than what has been observed at very low temperatures like -78 °C in Belokon's work.

As expected, these reactions gave isomers with a 2*S* configuration as major products, which lead to *S*-amino acids. The facial selectivities are about 4:1 of 2*S* to 2*R*. The 3-fluorobenzyl bromide gave slightly higher selectivity which was around 6:1.

It was observed that when more than one equivalent of electrophiles was used, bisalkylation products (**36c**) were detected on TLC with significantly higher R_f values which could be isolated and well characterized (Scheme 2-9). Actually with greater than two equivalents of **8**, **9**, or **10** used, the reactions gave exclusively bisalkylation products because the second proton at the α-carbon was deprotonated by excess NaOH and the product after the first nucleophilic substitution was not bulky enough to prevent another



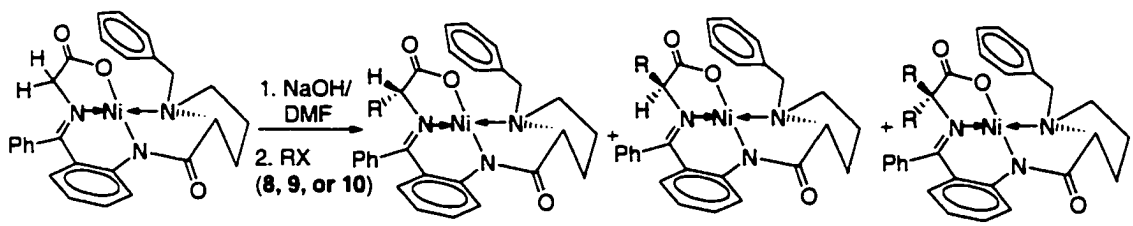
Scheme 2-9. Formation of bisalkylation products

electrophile attacking. At this stage we envisioned that the double alkylation could be excluded by: 1) using a base strong enough to extract the first proton but not strong enough to remove the first α-proton after alkylation and/or 2) using more sterically

demanding electrophiles. Our first assumption was confirmed by the reactions with K_2CO_3 as base from which no bisalkylation products were detected. The second assumption was found to be true by the following reactions with electrophiles with certain steric constraints like 2,6-disubstituted benzyl bromides or α-alkylbenzyl bromides (secondary). According to the literature, bisalkylation can also be curbed by lowering the reaction temperature, but this idea was not examined in our studies.

2.5.2. Reaction with (*R*)-NiGlyBPB

The (*R*)-NiGlyBPB (**6**), the enantiomer of (*S*)-NiGlyBPB (**1**), was used to conduct asymmetric alkylation with the same electrophiles (Scheme 2-10 and Table 2-2). The (*R*)-proline complexes showed almost the same reaction profiles as the (*S*)-proline complexes, but the reaction gave the 2*R* isomers as the major products, which lead to *R*-amino acids. This would facilitate the preparation of enantiomerically pure D-amino acids.



R = 2-F-PhCH$_2$ (**38**), 3-F-PhCH$_2$ (**39**)

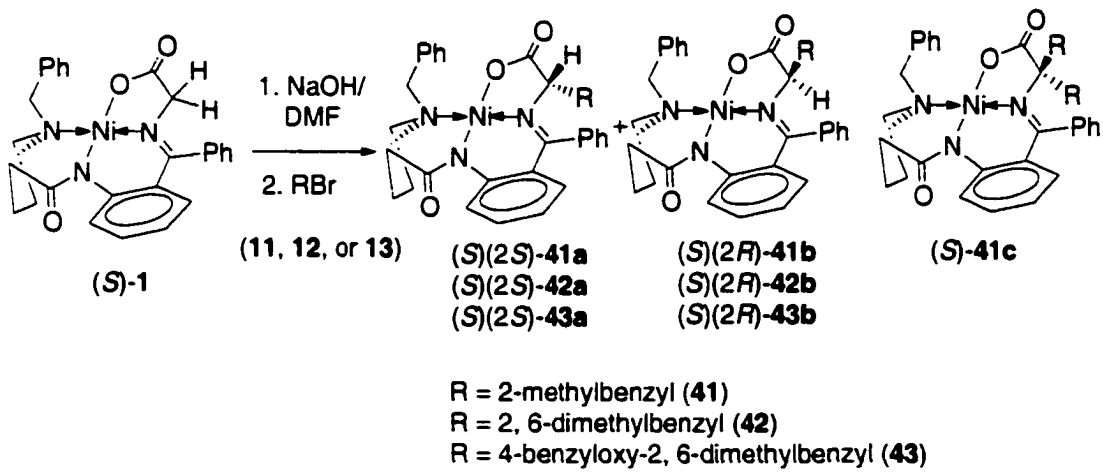
Scheme 2-10. Nucleophilic substitution of (*R*)-NiGlyBPB with **8-10**

Table 2-2. Alkylation of (*R*)-NiGlyBPB with **8-10**

entry	RX	time (min)	(*R*)(2*R*)/(*R*)(2*S*)	yield (%)
1	**8**	< 5	5.8 : 1	94
2	**9**	< 5	3.7 : 1	92
3	**11**	< 5	5.0 : 1	96

2.6. Reaction of (*S*)- or (*R*)-NiGlyBPB with 2-Methyl-, 2,6-Dimethylbenzyl, or 4-Benzoxy-2,6-dimethylbenzyl Bromides (**11-13**)

After gaining some basic knowledge on the alkylation of (*S*)-NiGlyBPB (**1**) with *mono*-halo-substituted electrophiles, we considered other electrophiles with different substitution patterns and steric size (Scheme 2-11 and Table 2-3). Using these considerations, electrophiles **11-13** were investigated. In order to understand the contribution of temperature to the stereochemical outcome, all electrophiles were studied



Scheme 2-11. Nucleophilic substitution of (*S*)-NiGlyBPB with **11-13**

at three different reaction temperatures (25, 0, and -10 °C). NaOH was used to generate enolates *in situ*. All these reactions were fast and completed in 5 min except for 2,6-dimethylbenzyl bromide at -10 °C, which took about 15 minutes. The yields from all the reactions were excellent.

Table 2-3. Nucleophilic substitution of (*S*)-NiGlyBPB with **11-13**

entry	RBr	temp (°C)	Base	time (min)	(*S*)(2*R*)/(*S*)(2*S*)	yield (%)
1	**11**	25	NaOH	< 5	1 : 4.5	93
2	**11**	0	NaOH	5	1 : 3.5	90
3	**11**	-10	NaOH	5	1: 4.0	92
4	**12**	25	NaOH	< 5	1 : 8.2	98
5	**12**	0	NaOH	5	1 : 6.2	99
6	**12**	-10	NaOH	15	1 : 6.5	99
7	**13**	25	NaOH	< 5	1 : 8.0	94
8	**13**	0	NaOH	5	1 : 4.0	95
9	**13**	-10	NaOH	5	1 : 4.5	93

For 2-methylbenzyl bromide (**11**), the facial selectivity of the starting Schiff base was around 1:4.5 at room temperature (entry 1, Table 2-3). With a decrease of reaction temperature, the diastereoselectivity decreased only slightly. With *ortho*, *ortho*-disubstituted electrophiles **12** and **13**, reactions gave a ratio of 1:8 of 2*R* to 2*S* at 25 °C. But more interestingly, the stereoselectivity decreased with a decrease of reaction temperature. This observation is completely different than the usual case in which the stereoselectivity increases with a decrease in reaction temperature. To explore the origin of this observation, a series of experiments at an elevated temperature were designed and

conducted (Table 2-4). The reactions were conducted at 50 °C under argon with NaOH as base. Even though we knew the reaction was done in less than a minute, the reaction mixture was keeping stirring for 5 minutes at the designated temperature (Scheme 2-11 and Table 2-4). It was observed that the stereoselectivity at 50 °C is much better than that at room temperature or lower. For electrophile **11**, no 2*R* product was observed on the NMR level sensitivity. For **12** and **13**, the ratios of 2*R* to 2*S* were 1:29. These high diastereomeric ratios make this method synthetically meaningful for unnatural amino acids. In light of the fact that the second proton can be deprotonated by strong inorganic bases like KOH and NaOH, it is reasonable to believe that the epimerization makes a significant contribution to such high stereoselectivity because the 2*S* isomer is thermodynamically favored. At high temperatures the epimerization of the 2*R* isomer to the 2*S* isomer is fast, so very high diastereoselectivities were observed at the α-carbon center.

Table 2-4. Nucleophilic substitution of (*S*)-NiGlyBPB with **11-13** at 50 °C for 5 min

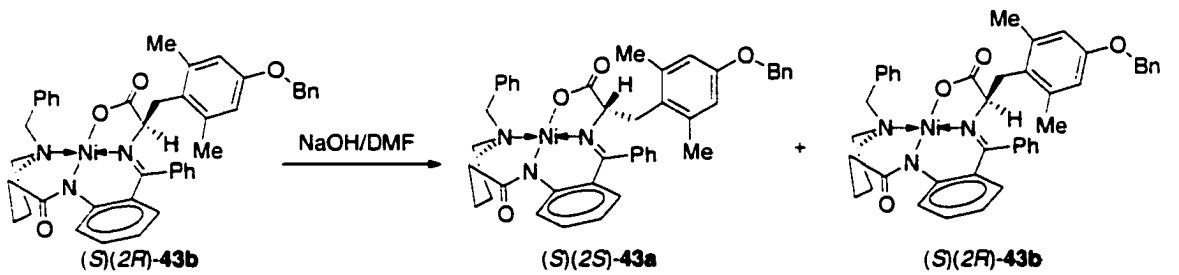
entry	RBr	(*S*)(2*R*)/(*S*)(2*S*)	yield (%)
1	**11**	Only (*S*)(2*S*)	94
2	**12**	1: 29	96
3	**13**	1: 29	96

The kinetic diastereoselectivities for **11-13** at 25 °C were measured with a slow base, K_2CO_3. The observed facial discrimination of the chiral enolate for 2-methylbenzyl bromide was 1:2.1, which is significantly lower than that at 25 °C with NaOH as base

(entry 1 in Table 2-3 and entry 1 in Table 2-5). For disubstituted bromides **12** and **13**, the kinetic diastereomeric ratio is 1:6.6 and 1:4.0, respectively. These ratios are very close to the diastereoselectivities at low reaction temperatures (0 and -10 °C). But as shown in Table 2-5, the reactions proceeded much slower with K_2CO_3. After 24 hours, only about 60-65% of the starting complexes were converted.

Table 2-5. Alkylation of (*S*)-NiGlyBPB with **11-13** at 25 °C with K_2CO_3 for 24 hr

entry	RBr	(*S*)(2*R*)/(*S*)(2*S*)	yield (%)
1	**11**	1 : 2.1	65
2	**12**	1 : 6.6	60
3	**13**	1 : 4.0	60



Scheme 2-12. Epimerization of **43b**

In order to have a direct understanding of isomerization of the α-carbon center, the epimerization was carried out by submitting the diastereomerically pure α-(*R*) isomer **43b** under the same conditions for nucleophilic substitution at 25 °C (Scheme 2-12). We

did observe the transformation of the α-(*R*) isomer **43b** into the α-(*S*) isomer **43a**, but the process was slow at room temperature. The observed ratio of α-(*R*) to α-(*S*) after one hour was 6:1.

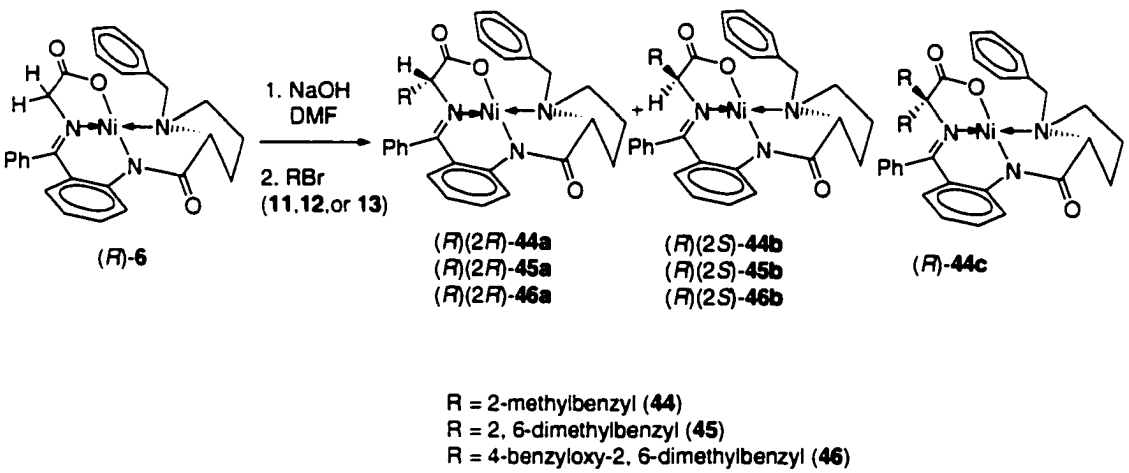
The differences between the diastereomeric ratios observed at 25 °C under NaOH and K_2CO_3 are attributed to the epimerization at the α-carbon because NaOH can cause redistribution of two isomers to favor thermodynamically more stable product-2*S* isomer after the alkylation was done but K_2CO_3 can not. Therefore we believe the observed stereoselectivity at 25 °C is a ratio mediated by both kinetic and thermodynamic factors, but it is not the real thermodynamic ratio because it contains only part of thermodynamic contribution. It is more reasonable to believe the ratios measured at 50 °C may still not be the real thermodynamically-controlled ratios but are very close to them. The stereoselectivities observed at lower temperatures may not be the kinetically-controlled ratios but should be very close to the kinetic ratios because they contain much less contribution of epimerization at the α-carbon center.

Additionally it is interesting to notice that 2,6-dimethylbenzyl bromide (**12**) at (*S*)-NiGlyBPB showed slightly higher stereoselectivity than 4-benzyloxy-2,6-dimethylbenzyl bromide (**13**) (entries 5 and 8 vs. 6 and 9 in Table 2-3, entries 2 and 3 in Table 2-5). This is probably because the electrophile **13** is more reactive than **12**, leading to lower stereoselectivity.

It is clear that the stereocontrol at the α-carbon can be easily improved by raising the reaction temperature to accelerate the epimerization process, giving high diastereoselectivity in the nucleophilic substitution of glycine complexes. It makes this

method very useful for preparation of novel amino acids without tedious work-ups and purifications.

With (*R*)-NiGlyBPB (**6**), the substitution showed the same reaction profile under the same conditions (Scheme 2-13 and Table 2-6). The stereochemical selectivity went up to 24:1, favoring the 2*R* product at 50 °C (entry 7 in Table 2-6).



Scheme 2-13. Nucleophilic substitution of (*R*)-NiGlyBPB with **11-13**

As we envisioned, asymmetric synthesis of enantiomerically pure DMT could be achieved *via* alkylation of an appropriate chiral equivalent of nucleophilic glycine with the corresponding 2',6'-dimethylbenzyl halide. This simple and most methodologically straightforward approach had not been reported previously. Most of the methods developed for the asymmetric homologation of glycine equivalents involved the

kinetically controlled reaction between lithium-derived enolates of the latter and alkyl halides under very mild conditions at –78 °C.[25,179] However, the highly sterically hindered nature of the corresponding 2',6'-dimethylbenzyl halides could interfere with a successful chemical and/or stereochemical reaction outcome. Indirect support for this comes from the fact that all attempts to conduct a standard Erlenmeyer condensation between 2',6'-dimethyl-4-*O*-protected benzaldehyde and *N*-acetylglycine were unsuccessful, which was attributed to the highly sterically hindered nature of the corresponding aldehyde.[180]

Table 2-6. Nucleophilic substitution of (*R*)-NiGlyBPB with **11-13**

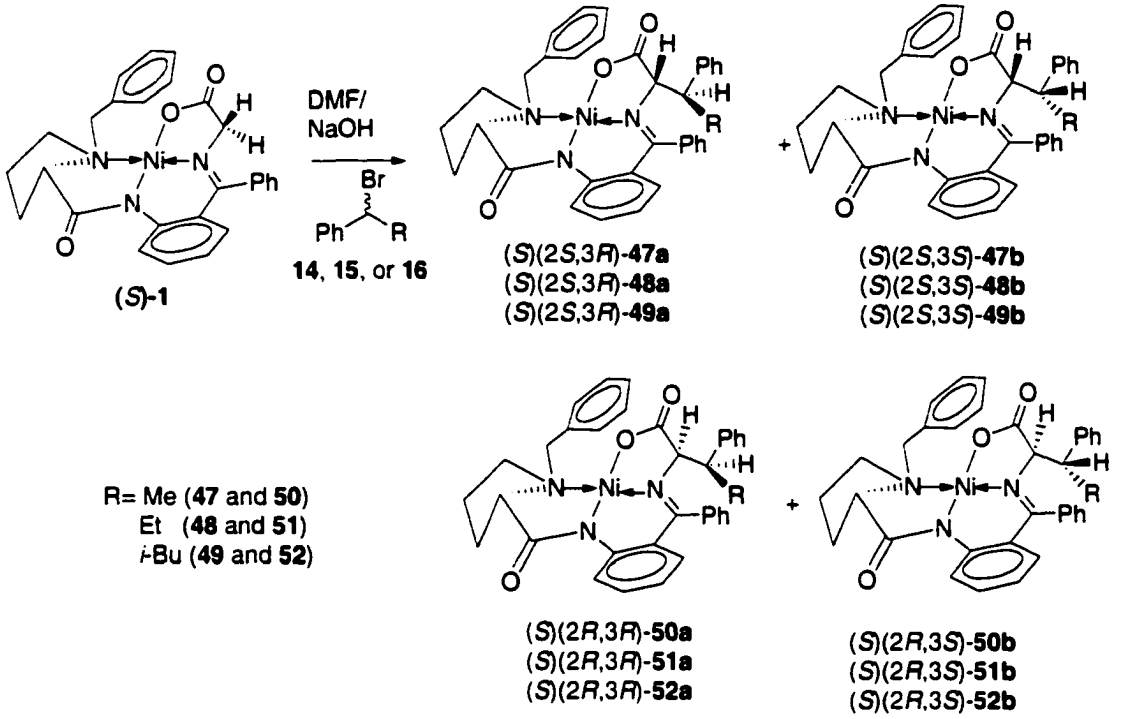
entry	RBr	temp (°C)	time (min)	(*S*)(2*R*)/(*S*)(2*S*)	yield (%)
1	**11**	25	< 5	5.9 : 1	91
2	**11**	0	5	5.0 : 1	95
3	**11**	-10	10	5.0 : 1	90
4	**12**	25	<5	7.4 : 1	95
5	**12**	0	5	6.5 : 1	96
6	**12**	-10	10	7.4 : 1	94
7	**13**	50	5	24 : 1	90
8	**13**	25	<5	6.7 : 1	93
9	**13**	0	5	7.0 : 1	95
10	**13**	-10	5	5.3 : 1	93

Analysis of the relevant literature surprisingly revealed only one report on the asymmetric synthesis of DMT.[180,181] The method utilized an asymmetric hydrogenation protocol using methyl (*Z*)-2-acetamido-3-(4-acetoxy-2,6-dimethylphenyl)-2-propenoate as a starting compound and [Rh(1,5)-COD)(*R*,*R*-DIPAMP)]BF_4 as a catalyst (1-5 mole

%). Due to the sterically congested nature of the starting dehydroamino acid, the hydrogenation step proceeded very slowly requiring 12-24 hours for completion at 60 °C under 60 psig of hydrogen to afford (*S*)-4-acetoxy-*N*-acetyl-2,6-dimethyltyrosine methyl ester in 87% yield with 92% ee. We believed that the development of an alternative method featuring simple experimental procedures and providing a fast and reliable protocol for preparing gram-quantities of DMT would be highly desirable. We developed such a method using, for the first time, a methodologically straightforward and general approach, an alkylation of the readily available chiral equivalent of a nucleophilic glycine **1** (Schemes 2-12 and 2-13) with the corresponding 4'-benzyloxy-2',6'-dimethylbenzyl bromide (**13**). More importantly, we can reach both (*S*)- and (*R*)-DMT by appropriate selection of starting Schiff bases with over 95% de in alkylation *via* thermodynamic control. Decomposition of **43a** and **46b** gave (*S*)-2,6-dimethyltyrosine and **43b** and **46a** led to (*R*)-2,6-dimethyltyrosine as will be demonstrated later.

2.7. Reaction of (*S*)-NiGlyBPB with α-Alkyl Benzyl Bromides (**14-16**)

Nucleophilic substitutions of (*S*)-NiGlyBPB ((*S*)-**1**) with racemic secondary alkyl bromides **14-16** were conducted under argon with NaOH as base at three different reaction temperatures (Scheme 2-14 and Table 2-7). Electrophiles **14-16** were used in 2.5 equivalents to facilitate enantiomeric discrimination. The reactions were monitored and quenched as usual. All gave excellent yields (81-97%).



Scheme 2.14. Nucleophilic substitution of (*S*)-NiGlyBPB with **14-16**

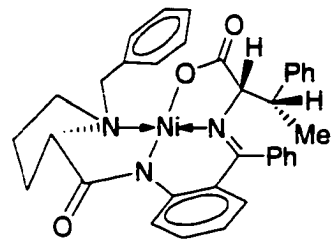
Table 2-7. Nucleophilic substitution of (S)-NiGlyBPB with **14-16**

entry	RBr	temp (°C)	time (min)	(*S*)(2*S*,3*R*)/ (*S*)(2*S*,3*S*)	2*R*/2*S*	yield (%)
1	**14**	25	< 5	1.0 : 1	1 : 5.3	93
2	**14**	0	5	1.3 : 1	1 : 5.5	95
3	**14**	-10	10	1.3 : 1	1 : 8.2	97
4	**15**	0	5	7.7 : 1	1 : 15.5	92
5	**15**	-10	10	5.0 : 1	1 : 12.0	95
6	**16**	25	5	5.0 : 1	1 : 5.0	93
7	**16**	0	20	4.0 : 1	1 : 7.3	94
8	**16**	-10	90	11.3: 1	1 : 7.2	81

In this process two asymmetric carbon centers were created simultaneously. A pair of 2*S* isomers and a pair of 2*R* isomers were generated. With (*S*)-proline complexes, due to the facial selectivity of the starting complexes the 2*S* isomers should be the major products and the 2*R* isomers would be the minor products. Since the enolate for alkylation was chiral, it showed differential reactivity toward the enantiomers of the racemic α-alkylbenzyl bromides. Therefore it is reasonable to believe the two 2*S* isomers would not exist in the same amount after the reaction. The same is true for the two 2*R* isomers.

The stereochemistry of the products was determined by X-crystallography. It was found that the minor isomer of the pair of 2*S* isomers had the 2*S*,3*S* configuration (Figure 2-5). Therefore the major one should have 2*S*,3*R* stereochemistry. The inversion of the α-carbon center of the major one in the pair of 2*R* products with NaOH gave the minor one of the pair of 2*S* products. So the major 2*R* product was determined to be 2*R*,3*S*. Then the minor one of the two 2*R* isomers should be 2*R*,3*R*. This assignment of stereochemistry can be evidenced by what was observed in the NMR spectra. For the 2*S*,3*R* isomer, the β-methyl group stays right above the phenyl group in the ketimine. It absorbs at higher field than that in the 2*S*,3*S* isomer, in which the methyl group points away from the phenyl group.

In case of α-methylbenzyl bromide (**14**), the stereoselectivities at the α-position with secondary benzyl bromides were around 1:5. With an increase in the size of the side chain of electrophile from Me to Et, the observed diastereoselectivities at the α-carbon increased. At 0 °C the ratio of 2*S* to 2*R* was about 16:1 with **15**. But with further



(*S*)(2*S*,3*S*)-**47b**

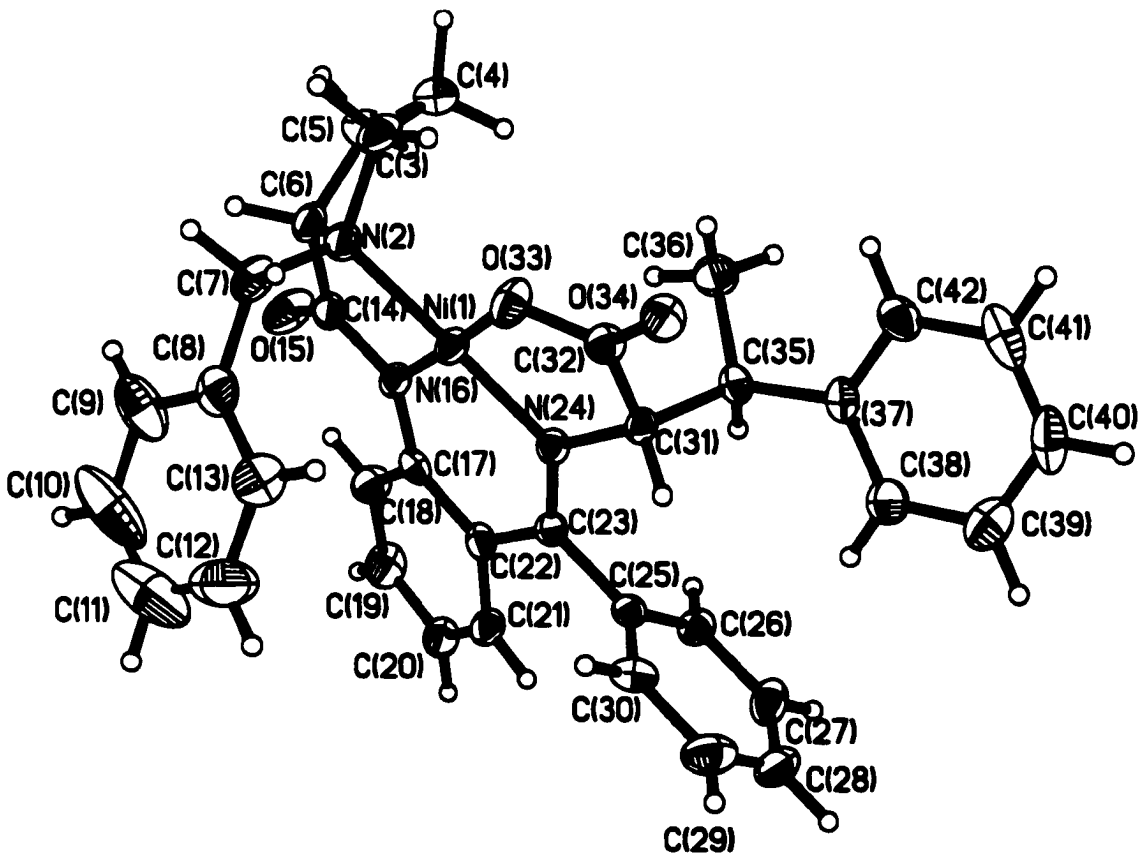


Figure 2-5. X-ray structure of 47b

extension of the side chain of electrophiles from Et to *iso*-butyl, the facial discrimination of the enolate became worse: the selectivity of 2*S* to 2*R* was lowered to about 7:1. The diastereoselectivities at the α-carbon may not be critical because the stereoselectivities can always be improved by isomerization at elevated temperature to suppress the proportion of α-*R* isomers.

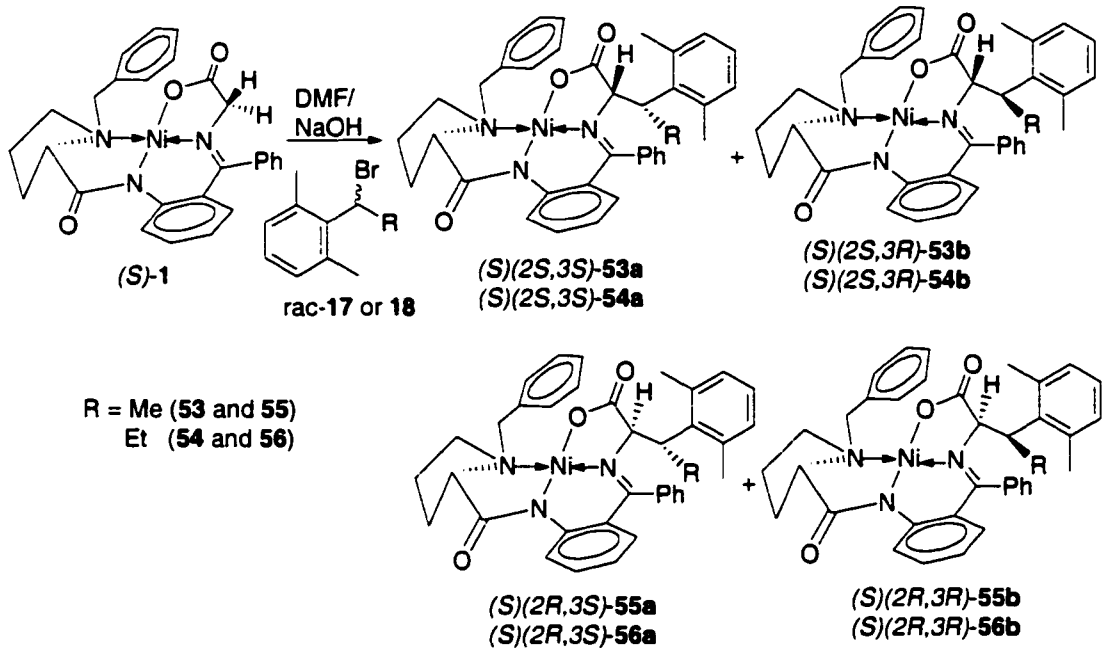
The most critical selectivity is at the β-carbon. In the case of **14**, the chiral enolates have no significant discrimination on the two enantiomers of the racemic electrophile. The two 2*S* isomers with either 3*R* or 3*S* configuration were formed in almost equal amounts. Basically there is significant kinetic resolution of (*S*)-NiGlyBPB on the racemic α-methylbenzyl bromide (**14**). In case of ethyl (**15**), the chiral enolates had much better kinetic resolution of the racemic electrophiles. The (2*S*,3*R*)-isomer was formed in a larger amount than the (2*S*,3*S*)-isomer. That means the *S*-isomer of e racemic **15** is sterically favorable for nucleophilic substitution in the case of the *S*-proline glycine complex. The stereoselectivity at the β-position reached 7.7:1 in favor of the 3*R* product. With an *i*-Bu side chain, the best steric selectivity at the β-position, reached at -10 °C, was 11.3:1 between 3*R* and 3*S*. Based on what was observed, extension of the side chain of electrophiles leads to increased stereoselectivities at the β-carbon center.

It is noticeable that with the extension of the side chain, the electrophiles showed decreased reactivity. For **14** and **15** the reaction still proceeded pretty fast. It took about 10 minutes even at -10 °C. But for α-*iso*-butylbenzyl bromide, the reaction took about 90 minutes at -10 °C which was much longer that for **14** and **15** under the same nucleophilic substitution conditions (entry 8 in Table 2-7). Significantly, with the decrease of reaction

temperature, the reaction slowed down from 5 min at 25 °C to 20 min at 0 °C to 90 min at -10 °C (entries 6-8 in Table 2-7). This sluggishness may present some practical problems for the reactions.

2.8. Reaction of (*S*)- and (*R*)-NiGlyBPB with α-Alkylbenzyl Bromides (17 and 18)

As a combined case of the primary electrophiles with 2,6-disubstituion and secondary electrophiles without 2,6-substitution, the electrophiles **17** and **18** were systematically investigated for their reactivities and stereoselectivities with Ni(II)-coordinated glycine Schiff bases (Scheme 2-15). The nucleophilic substitution with this type of electrophiles would lead to β,2',6'-trisubstituted phenylalanines that are not easily accessible by other alkylation methods. With (*S*)-NiGlyBPB, the reactions with **17** and **18** took slightly longer than that with the corresponding primary electrophile (**12** and **13**) and secondary electrophiles without substitution at positions 2 and 6 on the aromatic ring. The yields were excellent. In both the cases of **17** and **18**, α-(*R*) isomers were still detected on both TLC and NMR. In spite of the increase of steric bulkiness of electrophiles, the α-*R* isomer could not be excluded. But as demonstrated (entry 5 in Table 2-8) the selectivity at the α-position can be markedly increased by the method mentioned above.



Scheme 2-15. Alkylation of (*S*)-NiGlyBPB with **17** and **18**

Table 2-8. Alkylation of (*S*)-NiGlyBPB with **17** and **18**

entry	RBr	temp (°C)	time (min)	2*R*/2*S*	(*S*)(2*S*, 3*S*)/(*S*)(2*S*,3*R*)	yield (%)
1	**17**	50	5	1:23.2	2.2:1	95
2	**17**	25	< 5	1:7.1	2.3:1	94
3	**17**	0	10	1:6.1	2.0:1	96
4	**17**	-10	20	1:10.6	2.4:1	92
5	**18**	50	5	1:28.1	1.8:1	95
6	**18**	25	10	1:8.4	2.7:1	94
7	**18**	0	25	1:7.5	2.1:1	96

Surprisingly, it was observed that the diastereoselectivity at the β-position stayed around 1:2 at all temperatures for both **17** and **18**, though the reaction showed a slightly increased kinetic resolution with racemic 2,6-methyl-α-methylbenzyl bromide (**17**)

compared to α-methylbenzyl bromide (**14**; entries 1-3 in Table 2-7 vs. entries 2-4 in Table 2-8, respectively). For racemic 2,6-dimethyl-α-ethylbenzyl bromide (**18**), the kinetic discrimination became worse in comparison with α-ethylbenzyl bromide (**15**) (entry 4 in Table 2-7 vs. entry 7 in Table 2-8). Therefore it can be inferred that the increase of steric hindrance on the aromatic ring interferes with the stereoselectivity because it destabilizes the transition state leading to the (2*S*,3*S*) isomer.

53b was found to be the minor isomer of the pair of 2*S* isomers. It was determined to have the 2*S*,3*R* configuration by X-ray (Figure 2-6). This observation is different than what was observed with unsubstituted *secondary* bromides in which the minor α-*S* isomer had a 2*S*,3*S* configuration.

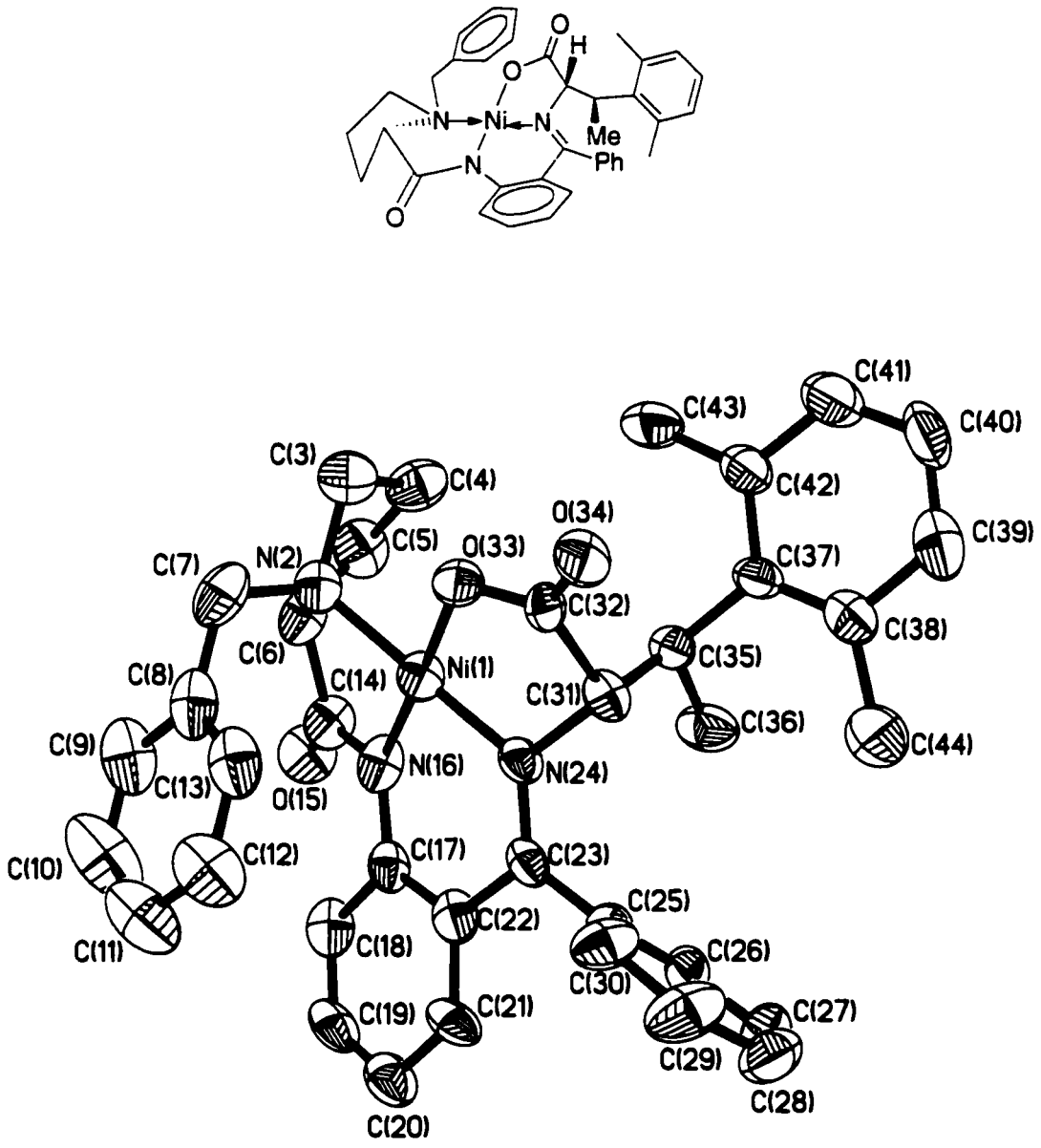
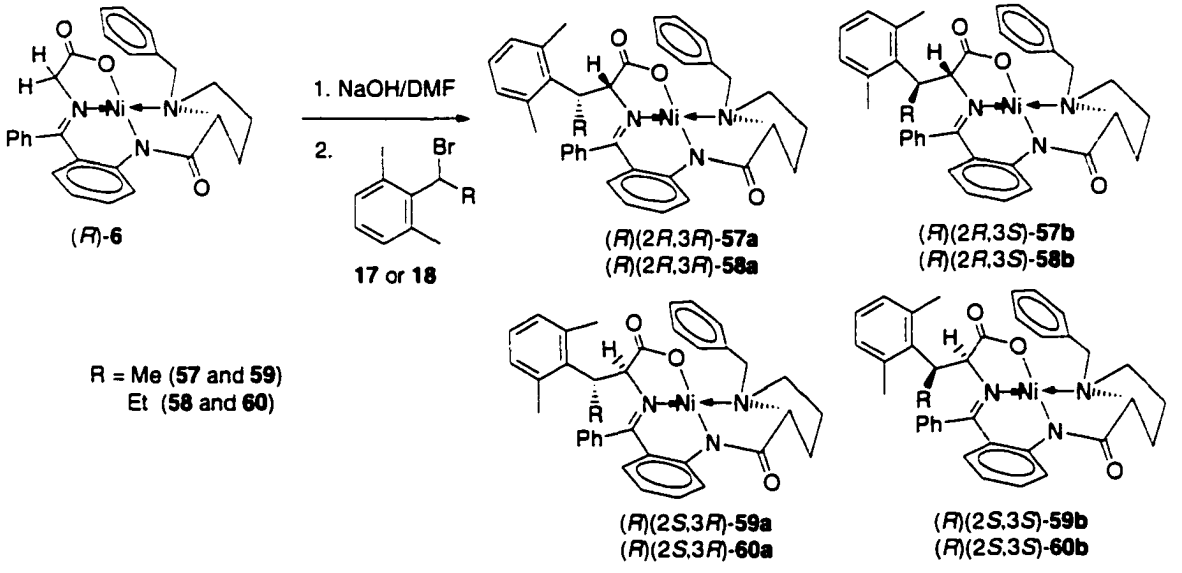


Figure 2-6. X-ray structure of **53b**

Reactions of **17** and **18** with (*R*)-NiGlyBPB showed the same reaction profiles (Scheme 2-16 and Table 2-9). With both (*R*)-NiGlyBPB and (*S*)-NiGlyBPB, we obtained all four isomers of β,2',6'-trimethylphenylalanines (TMP) with excellent enantiomeric and diastereomeric purity.



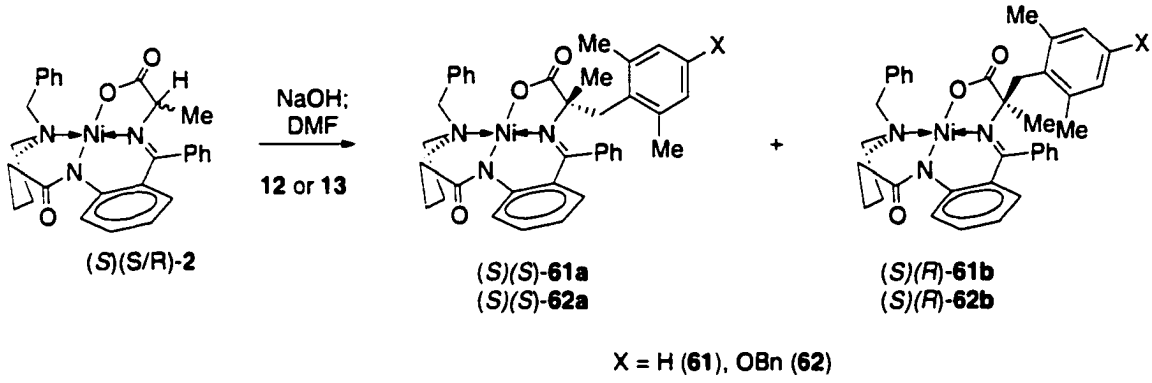
Scheme 2-16. Reaction of (*R*)-NiGlyBPB with **17** and **18**

Table 2-9. Reaction of (*R*)-NiGlyBPB with **17** and **18**

entry	RBr	temp (°C)	time (min)	2*S*/2*R*	(*R*)(2*R*, 3*R*)/(*R*)(2*R*,3*S*)	yield (%)
1	**17**	50	5	1:29.2	2.3:1	94
2	**17**	25	< 5	1:7.4	1.9:1	93
3	**17**	0	5	1:5.7	2.1:1	96
4	**17**	-10	20	1:6.6	2.4:1	92
5	**18**	50	5	1:19.3	2.6:1	95
6	**18**	25	10	1:13.2	3.3:1	94
7	**18**	0	20	1:5.4	2.2:1	97

2.9. Reaction of (*S*)-NiAlaBPB with *Primary* Benzyl Bromides (**12** and **13**)

The reactions between alanine Ni(II)-complex (*S*)(*S*/*R*)-**2** and benzyl bromides **12** and **13** were conducted at various temperatures in DMF using powdered NaOH as a base (Scheme 2-17). The results are summarized in Table 2-10. The benzylations occurred at lower reaction rates as compared with the rates of glycine complex (*S*)-**1**. In these reactions the observed stereochemical outcome was kinetically controlled as there was no possibility for equilibration of the resultant products (*S*,2*S*)-**61a**, **62a** and (*S*,2*R*)-**61b**, **62b**. The reaction temperature had little effect on the diastereoselectivity of the benzylation and was in the range of 5.5:1 to 6.6:1 (70-74% de) which is in a good agreement with the kinetically controlled stereochemical outcome of the glycine complex (*S*)-**1** with bromides **12** and **13** (Table 2-3). Due to the substantial difference in the chromatographic behavior of products (*S*,2*S*)-**61a**, **62a** and (*S*,α-*R*)-**61b**, **62b**, they were easily separated by column chromatography and isolated in diastereomerically pure form. Decomposition of the tyrosine-containing complex products (*S*,2*S*)-**62a** gave the intermediate *O*-benzyl protected amino acid which was hydrogenated under standard conditions to afford a mixture of the target (*S*)-α-TMT and its methyl ester. The mixture was treated with concentrated hydrochloric acid at 70 °C to afford upon evaporation enantiomerically pure (*S*)-α-TMT. Decomposition of **61a** led to α-TMP.



Scheme 2-17. Reaction of (*S*)-NiAlaBPB with **12** and **13**

Table 2-10. Reaction of (*S*)-NiAlaBPB with **12** and **13**

entry	RBr	temp (°C)	time (min)	(*S*)(2*R*) : (*S*)(2*S*)	yield (%)
1	**12**	25	20	1:6.6	93
2	**12**	0	80	1:5.9	94
3	**13**	-10	210	1:5.5	92
4	**13**	25	20	1:6.3	96
5	**13**	0	60	1:5.5	95
6	**13**	-10	210	1:5.7	93

2.10. Reaction of (*S*)-NiAlaBPB with *Secondary* Benzyl Bromides (**14-16**)

Even though the synthesis of α-alkylamino acids (quaternary amino acids) had been successfully demonstrated, asymmetric synthesis of α-alkyl-β-substituted amino acids was virtually undeveloped, however. To the best of our knowledge only a recent

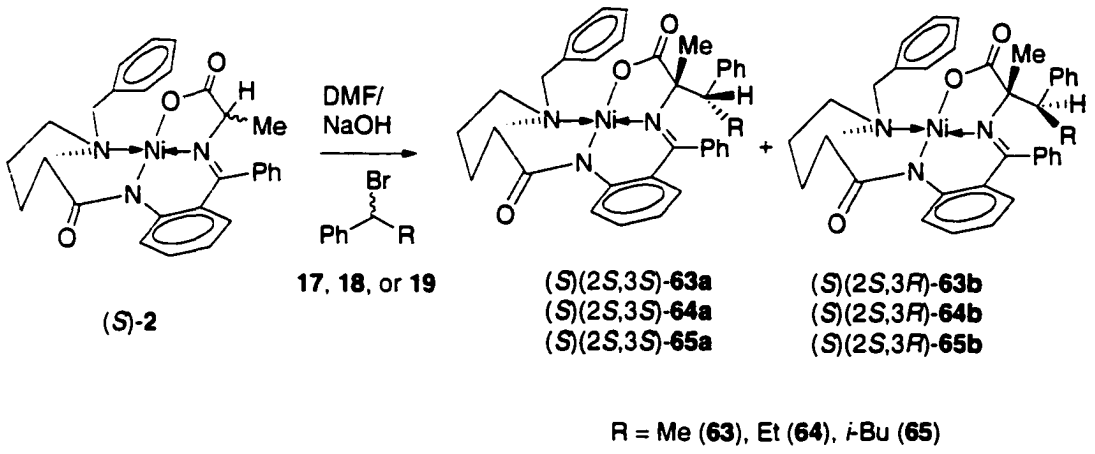
report by the Davis group offered a relatively generalized approach to α,β-dialkyl-substituted α-amino acids *via* stepwise introduction of the required functionalities.[131,182]

A more methodologically concise approach to the target amino acids would be by direct alkylation of chiral derivatives of alanine with racemic *sec*-alkyl halides.[30] Thus a series of reactions between a chiral Ni(II)-complex of alanine (*S*)(*S*/*R*)-**2** (Scheme 2-18) with a series of racemic 1-bromo-1-phenylalkanes **14-16** were conducted. This method provided a fast, generalized and synthetically efficient access to the target α,β-dialkyl substituted α-amino acids.

A central issue for the stereochemical outcome of the reactions between chiral derivatives of alanine with racemic *sec*-alkyl halides was the enantiomer-differentiating ability of the former. A handful of reports describing high enantiomer-differentiation in the reactions between chiral derivatives of alanine[30] or glycine[75,77] utilized reactions conducted at low temperatures (-78 °C). Therefore, we were most interested in developing a process which could be conducted at synthetically more convenient, higher temperatures, ultimately, at room temperature.

The alkylations of the alanine complex (*S*)(*S*/*R*)-**2** with *rac*-**14-16** (ratio 1/2.5, respectively) were conducted under our standard conditions: in DMF solutions using powdered NaOH as a base. The temperature of the reactions was varied to study its influence on the stereochemical outcome. The results obtained are given in Table 2-11. First, we were pleased to find that even at room temperature (25 °C), the alkylation of the alanine complex (*S*)(*S*/*R*)-**2** with racemic α-methylbenzyl bromide (**14**) occurred with substantial stereoselectivity giving rise to a mixture of diastereomeric products

(*S*)(2*S*,3*S*)-**63a** and (*S*)(2*S*,3*R*)-**63b** in a ratio of 5.7 to 1 (entry 1 in Table 2-11). Lowering the reaction temperature decreased the rate of the alkylation (entries 2, 3 vs. 1) as expected, but noticeably increased the enantiomer stereo-differentiation process allowing preparation of (*S*)(2*S*,3*S*)-**63a** with synthetically meaningful diastereoselectivity (90% de; entry 3). The major product (*S*)(2*S*,3*S*)-**63a** was isolated in diastereomerically pure form simply by washing the reaction mixture with diethyl ether, and could be decomposed to give the target (2*S*,3*S*)-α,β-dimethylphenylalanine (**72**) in 70% overall yield, along with the recovered chiral ligand (*S*)-**22** (96%; Scheme 2-25). Alkylation of alanine complex (*S*)(*S*/*R*)-**2** at room temperature with the more sterically demanding α-ethylbenzyl bromide (**15**) gave more impressive results, affording the major product (*S*)(2*S*,3*S*)-**64a** with 93.7% diastereoselectivity (entry 4 vs. 1). As observed in the reaction between (*S*)(*S*/*R*)-**2** with **14** (entries 1-3 in Table 2-11), lowering the temperature (to -10 °C) increased the selectivity of the enantiomer-differentiation process in the alkylation of (*S*)(*S*/*R*)-**2** with **15** (entry 6 in Table 2-11). However, the observed diastereoselectivity was lower than that obtained in the reaction between (*S*)(*S*/*R*)-**2** and **14** (entry 5 vs. 3 in Table 2-11). Unexpectedly, a further increase in the steric bulk of the alkylating agent resulted in decreased diastereoselectivity. Thus, alkylation of (*S*)(*S*/*R*)-**2** with α-*i*sobutylbenzyl bromide (**16**) at room temperature gave a mixture of the corresponding diastereomeric products (2*S*,3*S*)-**65a** and (*S*)(2*S*,3*R*)-**65b** in a ratio of 3 to 1, respectively (entry 6). While a decrease of the reaction temperature allowed us to reach a respectable level of diastereoselectivity (92.3%; entries 8, 9), the results of the



Scheme 2-18. Reaction of (*S*)-NiAlaBPB with **14-16**

Table 2-11. Reaction of (*S*)-NiAlaBPB with **14-16**

Entry	RBr	temp (°C)	time (min)	(2*S*,3*S*):(2*S*,3*R*)	yield (%)
1	**14**	25	60	5.7 :1	92
2	**14**	0	90	6.2 : 1	91
3	**14**	-10	240	18.8 : 1	94
4	**15**	25	40	14.9 : 1	90
5	**15**	0	60	8.1 : 1	95
6	**15**	-10	140	17.0 : 1	97
7	**16**	25	240	3.0 : 1	90
8	**16**	0	360	5.9 : 1	93
9	**16**	-10	480	11.9 : 1	90

enantiomer-differentiation process obtained in this series were noticeably lower as compared with the data observed in the alkylations of (*S*)(*S*/*R*)-**2** with **14** and **15** (entries 7-9 vs. 1-3 and 4-6). These data allow us to arrive at the surprising conclusion that an increase in the steric bulk of the alkylating agents **14-16** results in a lowering of the enantiomer-differentiation selectivity. On the other hand, the high level of the diastereoselectivity, especially at room temperature, observed in the reactions, suggests

that the present methodology is definitely synthetically superior to the previously described methods, providing a reliable access to this family of α,β-dialkyl amino acids.

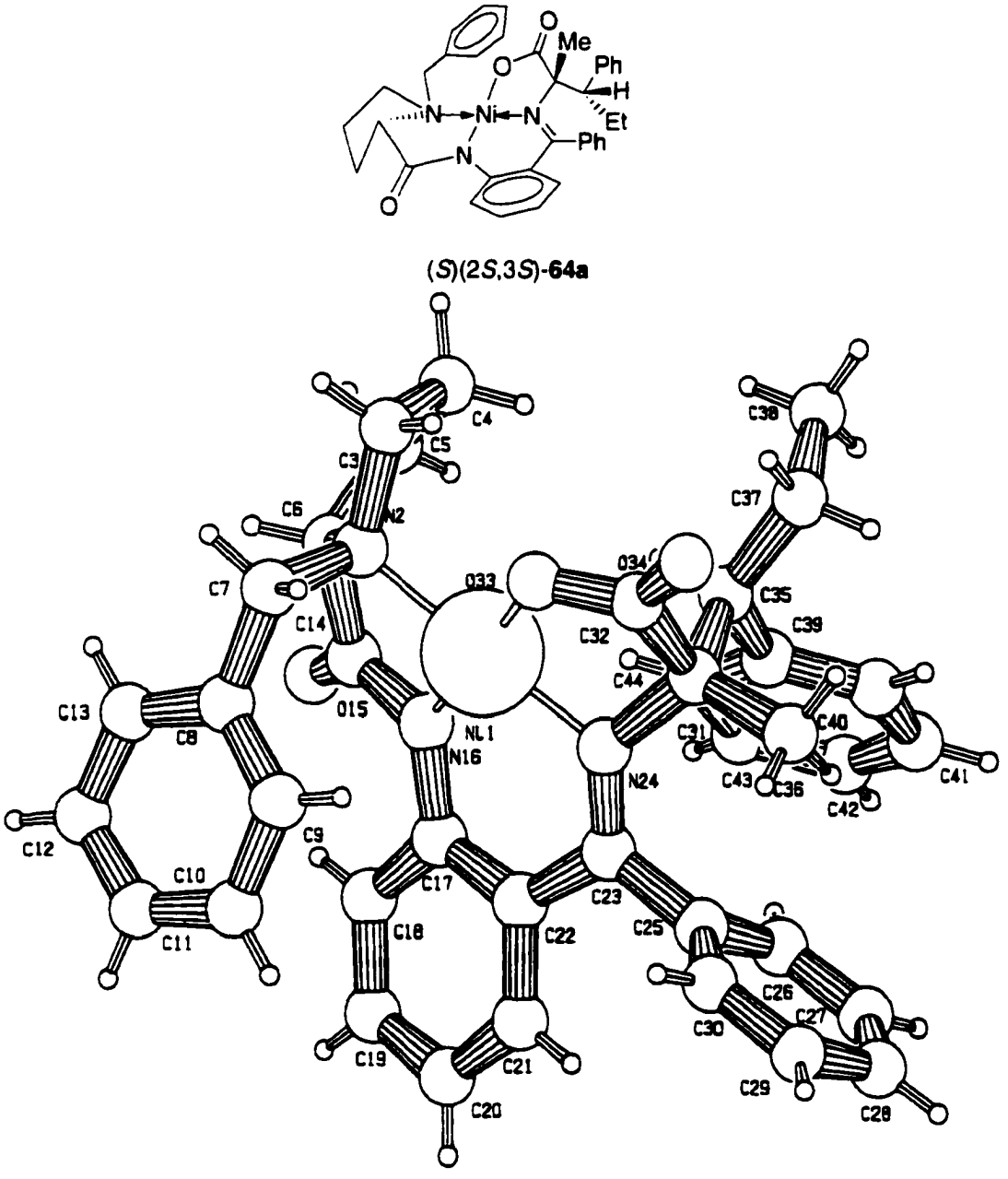
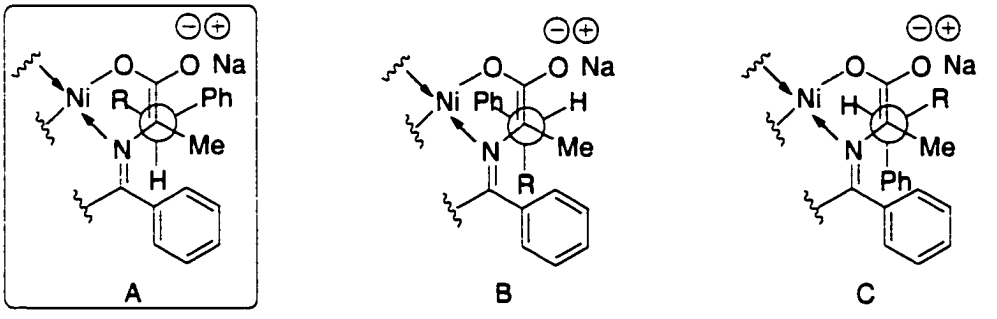


Figure 2-7. X-Ray Structure of **64a**

The absolute configuration of the α-stereogenic center of the newly formed amino acids in products **64a** and **64b** was determined to be *S* on the basis of their chiroptical properties and NMR data. Accordingly, complexes **64a** and **64b** could be considered as diastereomers, differing in absolute configuration at the β-stereogenic center. It follows that the attack by the alkylating agent **14-16** occurs almost exclusively on the *si*-face of the enolate derived from the complex **2**. As mentioned above, decomposition of the complex **63a** to the free amino acid (2*S*,3*S*)-**72** allowed us to determine the 2*S*,3*S* stereochemistry of the former. Moreover, taking into account the surprising observation that an increase in the steric bulk of the alkylating agent reduced the stereodifferentiation between the enantiomers of **14-16**, we performed a single crystal X-ray analysis of the major product **64a** obtained in the reaction between (*S*)(*S*/*R*)-**2** and **15** which confirmed its 2*S*,3*S* absolute configuration. On the basis of the obvious similarity in the ^{1}H-NMR spectra between **63a**, **64a** and **65a**, and on the other hand between **63b**, **64b** and **65b**, we confidently assigned a 2*S*,3*S* configuration to **63a** and **65a**, and 2*S*,3*R* stereochemistry to **63b** and **65b**.

With the stereochemistry of the products assigned we explored the mechanism of these alkylation reactions. Considering the three possible transition states (TSs) **A-C** (Figure 2-8), with the approach geometry *unlike*, leading to the products of 2*S*,3*S* absolute configuration **63a**, **64a** and **65a**, and three TSs **D-F**, of approach geometry *like*, affording the (*S*)(2*S*,3*R*) configured products **63b**, **64b** and **65b**, we suggest that the TSs **A** and **F** are the most plausible to account for the formation of products (*S*)(2*S*,3*S*)-**63a**,

approach geometry *unlike* to afford (2*S*,3*S*) configured products



approach geometry *like* to afford (2*S*,3*R*) configured products

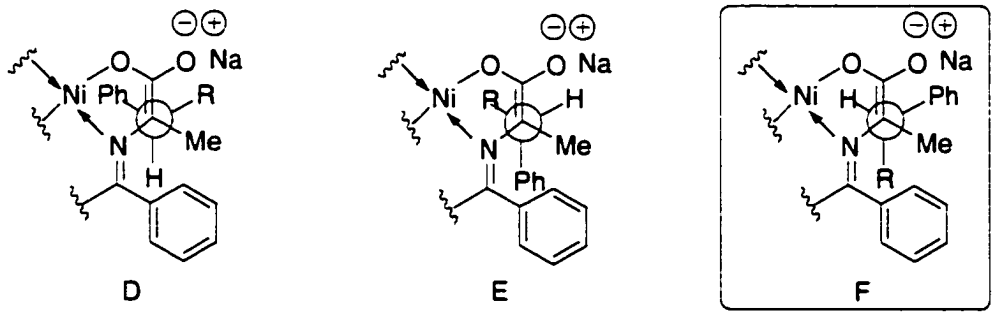
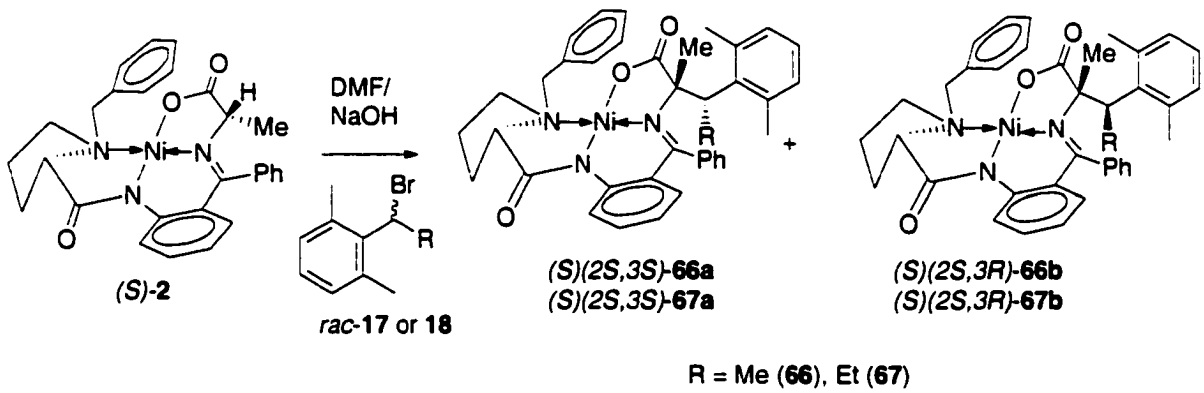


Figure 2-8. Proposed mechanism of the stereoselectivity

64a and **65a** and (*S*)(2*S*,3*R*)-**63b**, **64b** and **65b**, respectively. Thus, in the TSs **A** and **F** the phenyl of the alkylating agent occupies the position of the largest group avoiding unfavorable steric interactions with the ketimine phenyl and the Ni atom of the alanine complex (TSs **A** and **F** vs. **B**-**E**). On the other hand, TS **A** should be regarded more thermodynamically favorable relative to **F**, as in the latter the substituent R experiences a direct unfavorable non-bonding steric interaction with the ketimine phenyl of the complex. Moreover, TS **A** perfectly accounts for the unexpected observation that an increase in the steric bulk of the substituent R interferes with a high level of an

enantiomer-differentiation process. Thus, in TS **A** the substituent R points directly to the Ni ion and thus increases in the steric bulk of R should destabilize TS **A**. Based on the results obtained, we conclude that while the steric bulk of methyl and ethyl groups are accommodated by TS **A**, the stereochemical requirements of the *i*sobutyl substituent are definitely larger, decreasing the thermodynamic difference between TSs **A** and **F**.

2.11. Reaction of (*S*)-NiAlaBPB with Racemic Secondary 2,6-Dimethyl-α-alkylbenzyl Bromides (**17** and **18**)



Scheme 2-19. Reaction of (*S*)-NiAlaBPB with **17** and **18**

Electrophiles **17** and **18** have the combined structural features of primary benzyl bromide with 2,6-disubstitution (**12** and **13**) and secondary α-alkylbenzyl bromides (**14-16**). The nucleophilic substitution of (*S*)-NiAlaBPB with them gave good chemical yields (Scheme 2-19 and Table 2-12) and the stereoselectivity at the α-carbon center was exclusively α-(*S*). No α-*R* isomer was observed either on TLC or NMR. But surprisingly, the diastereomeric discrimination with these electrophiles at the β-carbon center was far less efficient that with secondary benzyl bromides without *ortho,ortho*-disubstitution.

With 2,6-dimethyl-α-methylbenzyl bromides, the reactions gave slightly more 2*S*,3*S* isomers than 2*S*,3*R* isomers. Temperature did not have notable effects on the kinetic resolution. In case of **18**, (*S*)(*S*/*R*)-2 showed virtually no steric discrimination on the racemic electrophile.

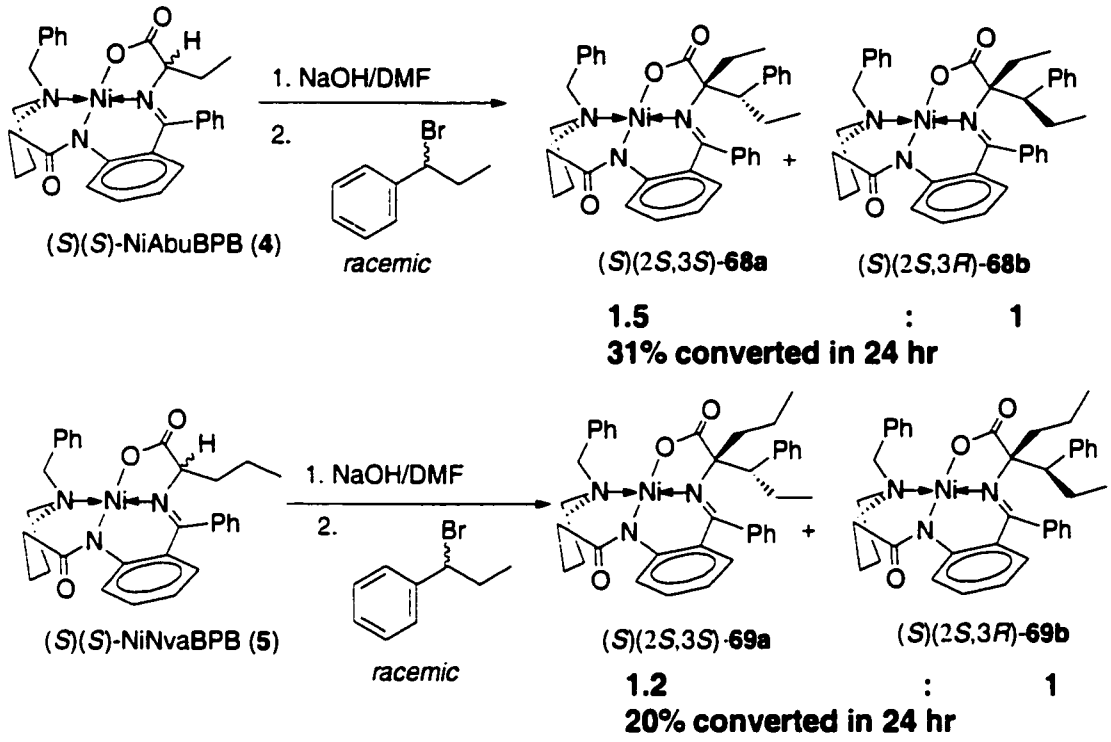
Table 2-12. Reaction of (*S*)-NiAlaBPB with **17** and **18**

Entry	RBr	temp (°C)	time (min)	(*S*)(2*S*,3*S*)/(*S*)(2*S*,3*R*)	yield (%)
1	**17**	25	25	1.4 : 1	90
2	**17**	0	60	2.0 : 1	92
3	**17**	-10	80	1.5 : 1	87
4	**18**	25	60	1.1 : 1	85
5	**18**	0	120	1.1 : 1	89

Therefore substitution on the *ortho*-position compromised the stereochemical selectivity at the β-position.

2.12. Reaction of (*S*)(*S*)-NiAbuBPB (**4**), (*S*)(*S*)-NiNvaBPB (**5**) and (*S*)(*S*)-NiValBPB (**3**) with **17** and **18**

With the same electrophiles from glycine to alanine complexes, increased stereoselectivity at the α-carbon was observed. With further extension of the side chain of the starting complexes, the same trend was observed but decreased reactivity and stereoselectivity at the β-position were also observed. With (*S*)(*S*)-NiAbuBPB (**4**), the reaction proceeded extremely slowly. After 24 hours, only 31% of the starting complexes were converted (Scheme 2-20). There was no significant discrimination on the racemic



Scheme 2-20. Alkylation of (*S*)(*S*)-NiAbuBPB (**4**) and (*S*)(*S*)-NiNvaBPB (**5**) with **15**

electrophiles. From (*S*)(*S*)-NiAbuBPB (**4**) to (*S*)(*S*)-NiNvaBPB (**5**), the situation got even worse. Clearly the extension of side chains on the starting complexes benefited neither the reactivity nor the diastereoselectivity of the reaction. Instead, it interfered with the chemical selectivity. Due to these problems, these two complexes were not synthetically meaningful.

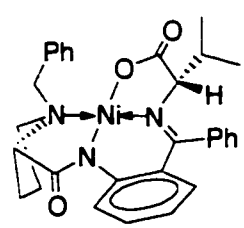


Figure 2-9. (*S*)-NiValBPB (**3**)

In the case of (*S*)(*S*)-NiValBPB (**3**) (Figure 2-9), the reaction did not proceed using different bases (NaOH and potassium *t*-butoxide), prolonged reaction times (up to 24 hours), and different types of alkyl bromides (Table 2-13). Apparently this is due to the β-branching of the *iso*propyl group which totally blocked electrophiles from approaching the corresponding enolate of the complexes for alkylation. Here the nucleophilic substitution of Ni(II)-coordinated Schiff bases reached an end.

Table 2-13. Reaction of (*S*)-NiValBPB with **17** and benzyl bromide

entry	RBr	Base	time	result
1	**17**	NaOH	1h	N. R.
2	**17**	NaOH	24h	N. R.
3	**17**	*t*-BuOK	24h	N. R.
4	BnBr	NaOH	24h	N. R.
5	BnBr	*t*-BuOK	24h	N. R.

2.13. Discussion

From what was observed, it was found that, generally, primary bromides were more reactive than secondary bromides with similar structures. It took shorter times for reactions of primary bromides than secondary bromides. The observed reactivity of electrophiles was determined by reaction temperature, the structure of the starting complexes and the structure of the electrophiles. Usually at elevated reaction temperature, the difference in reactivity between primary electrophiles and secondary primary electrophiles was not significant. As seen in entry 4 in Table 2-3 and entry 2 in Table 2-8 at 25 °C, the recorded reaction time did not have a significant effect. But at

lower reaction temperatures, the reactivity difference was magnified and could be clearly observed. Another controlling factor in the nucleophilic substitution which could magnify the reactivity difference of electrophiles was the structures of the starting complexes. At designated temperatures, the difference in reaction time with glycine complexes between primary and secondary alkyl halides was far less significant than that with alanine complexes as demonstrated in entries 4-6 in Table 2-3 vs. entries 1-3 in Table 2-10; entries 7-9 in Table 2-3 vs. entries 4-6 in Table 2-10). Even for the secondary electrophiles, the extension of the α-alkyl group from H to methyl to ethyl to *iso*butyl slows the reaction (Table 2-11). But as to the stereoselectivities, in the case of α-alkylbenzyl bromides without 2,6-disubstitution, the reactions showed increased stereoselectivity at the β-carbon center. But for the α-alkylbenzyl bromides with 2,6-disubstitution, no such trend was observed. Also as shown in Tables 2-8, 2-9 and 2-12, the 2,6-disubstitutions on the aromatic ring were detrimental to stereoselectivity at the β-carbon center.

Reaction temperature played a very important role in the diastereoselectivity of the alkylation of NiGlyBPB (**1** and **6**) with electrophiles, specifically at the α-carbon due to the potential isomerization at the α-carbon. However, epimerization at the α-carbon center was usually slow at room temperature but much faster at higher reaction temperatures. This feature could result in very high facial selectivity which makes this method synthetically useful. But reaction temperature had very little effect either on the reactivity or stereochemical outcome for starting Schiff bases with side chains like the alanine, α-aminobutyric acid, and norvaline complexes. In all cases, reaction temperature

directly affected the reaction time. Usually at higher temperatures, nucleophilic substitution proceeded much faster than at lower temperatures, though in some cases high reaction temperature compromised the stereoselectivity.

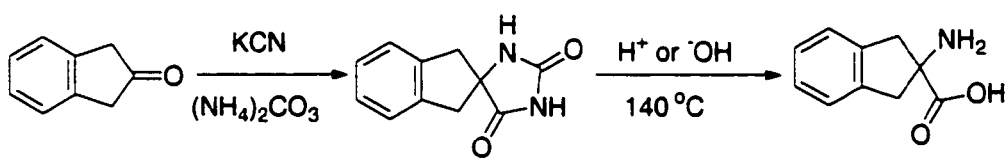
As shown in Tables 2-9, 2-12 and 2-13 and Scheme 2-20, from glycine to alanine complexes to α-aminobutyric acid to norvaline to valine complexes, the reactivity of the complexes decreased with the extension of the side chain. But the stereochemical selectivity situation was more complicated. From a slight increase of side chain from glycine to alanine, the stereoselectivity at both the α- and β-positions increased. More importantly, the stereochemical selectivity at the β-carbon increased, which led to a very high ratio between the β-position isomers. These features make this method very useful for the preparation of α,β-disubstituted amino acids. But with further increase of side chain bulk, the stereochemical outcome suffered. Basically, there was no steric discrimination at the β-position when secondary electrophiles were used. Valine complexes could not be used because the valine complex did not exhibit any reactivity due to its steric size which completely blocked the electrophiles.

2.14. Double Alkylation at α-Carbon Center of Glycine Complexes

In the previous study, double alkylation at the α-carbon of glycine complexes was observed with simple primary alkyl halides. It was a serious concern with sterically less hindered electrophiles. It was predicted and demonstrated that the bisalkylation could be curbed by lowering the reaction temperature, controlling the amount of electrophiles used and using weaker bases such as K_2CO_3 instead of NaOH or KOH. This feature led to a

way to generate α,β-cyclized amino acids, which are a type of conformationally constrained amino acids, which constrain not only the χ-space but also the backbone conformation. The most feasible rings should be 5- or 6-membered.

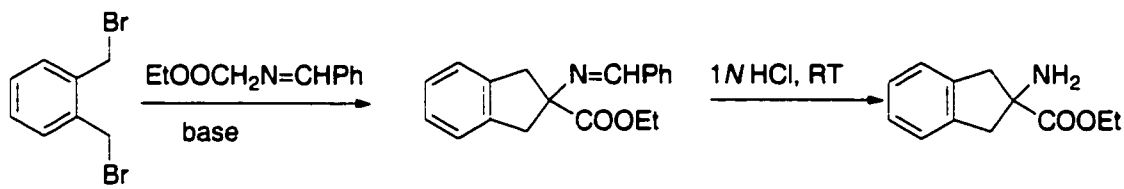
The conventional method for the preparation of cyclic amino acid derivatives involves a Bucherer-Berg synthesis using an indane-2-one derivative as the starting material (Scheme 2-21). Although the Bucherer-Berg synthesis continues to provide new amino acids, there are still many limitations to this approach. The synthesis of indane-2-one derivatives requires a multistep sequence. The hydrolysis of the intermediate spiro-hydantoins further requires drastic reaction conditions (excess barium hydroxide, 140 °C or 60% concentrated sulfuric acid, 140 °C) which often induce side reactions. Consequently it is very difficult to prepare amino acids with sensitive side-chain functionalities by the Bucherer-Berg method.[183-186]



Scheme 2-21. Synthesis of cyclic amino acids *via* Bucherer-Berg method

Stork and others have shown that the benzylidene derivative of glycine esters can be selectively α-alkylated with one or two electrophiles in a stepwise sequence leading to non-cyclic mono- and dialkylated amino esters (Scheme 2-22). These alkylated derivatives can be further hydrolyzed to amino esters or amino acids depending on the

reaction conditions. However there has been no report on the efficacy of the alternative intramolecular dialkylation of this glycine enolate to generate cyclic amino acids. Towards this end several different substrates have been examined and good results were obtained to give cyclic dialkylated benzylidene derivatives of glycine ethyl ester.[187,188]



Scheme 2-22. Synthesis of cyclic amino acids *via* double alkylation

Even though several methods have been developed, none of them can lead to optically active, substituted α,β-cyclized amino acids. In our efforts to obtain α,β-cyclized amino acids with structures in Figure 2-10, Ni(II)-coordinated glycine Schiff bases were used. In order to form a ring, obviously an electrophile with two functional points was necessary. In our case it was a dihaloalkane. Technically preparation of di-haloalkanes should not present any problems. We envisioned that the double alkylation wwould proceed stepwise. The cyclization would follow after the first alkylation. Since

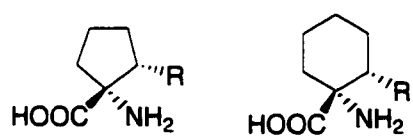
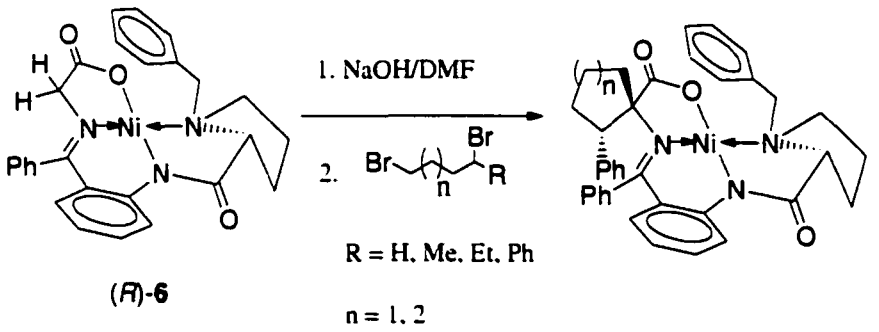


Figure 2-10. Examples of α,β-cyclized amino acids

Based on Belokon's work, one way that could be considered for our needs was to use different halide groups at these two functional points. But generally with our experimental conditions no appreciable difference in reactivity has been observed between alkyl chlorides and alkyl bromides, though Belokon demonstrated that alkyl bromides were more reactive than alkyl chlorides. Additionally, technically it is not easy to incorporate two different halide groups in the same electrophile. Based on what we have known from the previous study, primary alkyl bromides generally have faster reaction rates that secondary alkyl bromides with the same type of substrates. Therefore electrophiles with both primary and secondary alkyl halide structure features were designed and prepared with simple transformations as shown in Scheme 2-23.

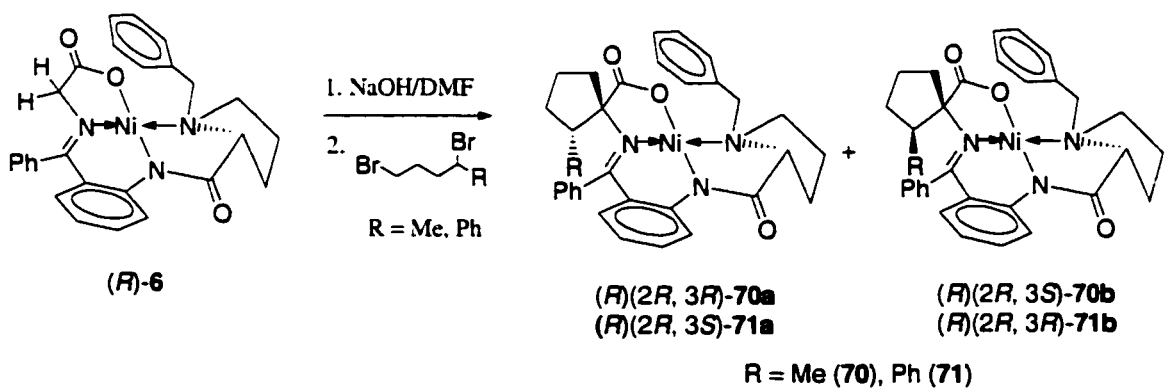


Scheme 2-23.General approach for α,β-cyclized amino acids *via* Ni(II) Schiff bases

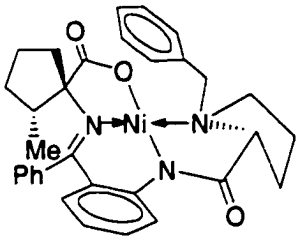
The second alkylation should be designed to take place intramolecularly. With the potential of unwanted intermolecular double alkylation, only one equivalent of electrophiles was used to favor the second nucleophilic substitution happening intramolecularly.

Following these general considerations and design, a series of reactions were conducted (Scheme 2-24). As always, the reaction was conducted in DMF under argon. The reaction end point was monitored by TLC. The reactions were quenched only after both the starting complexes and the products after first alkylation had completely disappeared. Usually the reaction took about 40 minutes by constant TLC monitoring. The products were separated with 1:1 acetone/ hexanes. Based on what was observed on TLC two products in equal amounts were detected as expected. At this stage we had no sense of the stereochemistry at the β-stereogenic center of these two observed products. We resorted to X-ray to determine the absolute configuration. Thus a product with R_f value of 0.36 from **19** was assigned as (2*R*, 3*R*)-**70a** (Figure 2-11). Another product with R_f value of 0.40 was assigned as (2*R*,3*S*)-**70b**. From **20**, the product with R_f value of 0.45 was assigned as (2*R*,3*S*)-**71a** (Figure 2-12). Another with R_f value of 0.25 was assigned as (2*R*,3*R*)-**71b**.

The decomposition of these separated complexes led to enantiomerically and diastereomerically pure cyclic amino acids.



Scheme 2-24. Reaction of (*R*)-NiGlyBPB with 1-substituted-1,4-dibromobutanes



(*R*)(2*R*, 3*R*)-**70a**

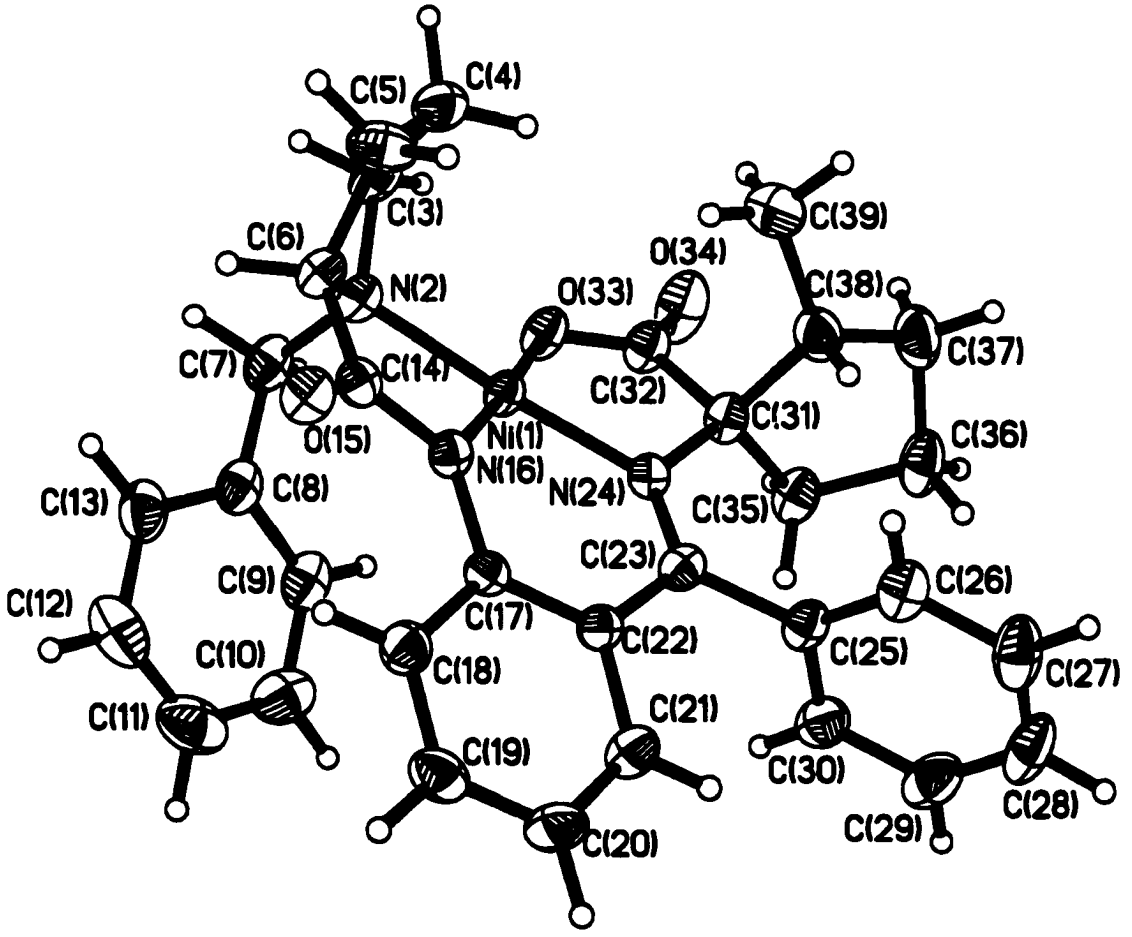
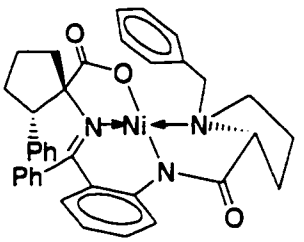


Figure 2-11. X-Ray Structure of **70a**



(*R*)(2*R*, 3*S*)-**71a**

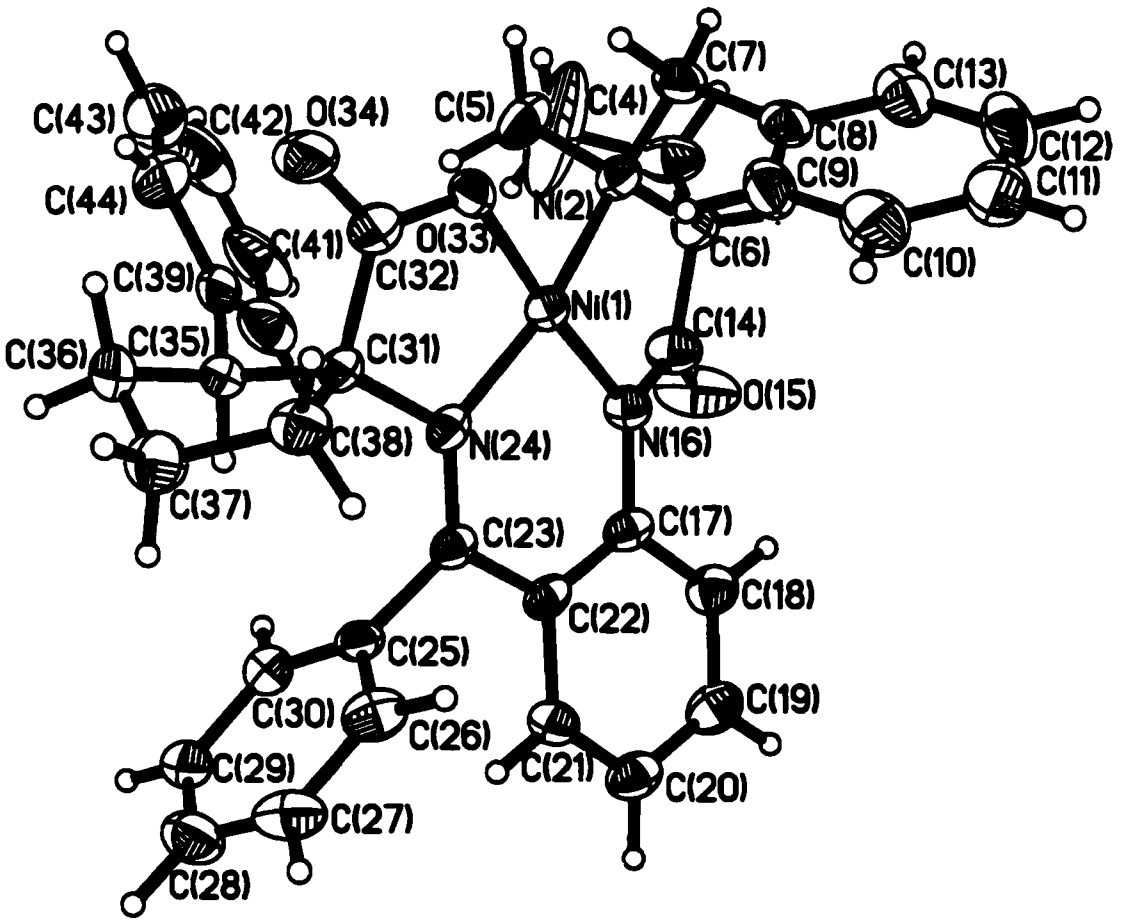
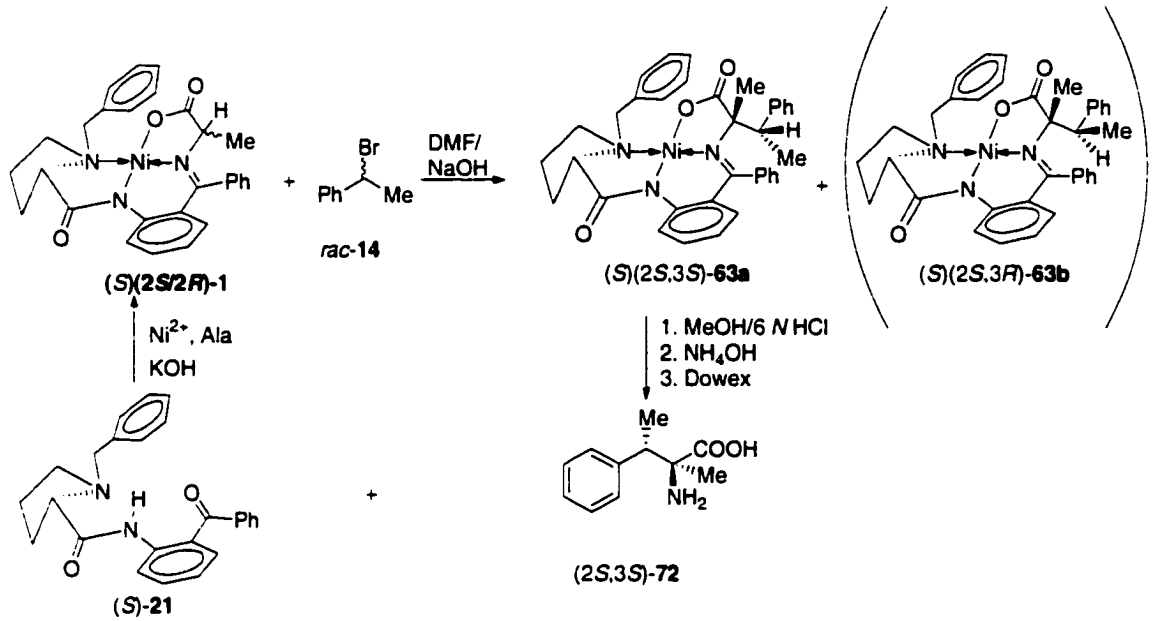


Figure 2-12. X-Ray Structure of **71a**

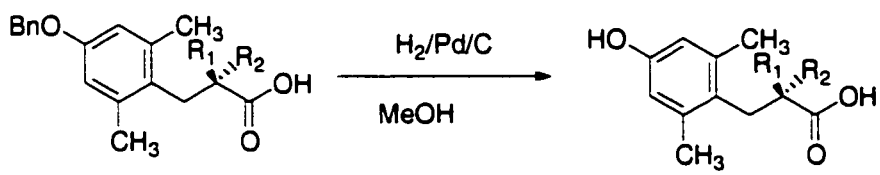
2.15. Isolation of Free Amino Acids



Scheme 2-25. Example of isolation of free amino acids

To obtain the free amino acids, the separated alkylated Ni(II) complexes were decomposed at 70 °C in MeOH with 3*N* HCl for 35 min. When the methanolic solutions turned completely green, the volatiles were evaporated under vacuum. The solid residue was triturated with deionized water (3 x 50 mL) to remove HCl. The residue was converted into its basic form with 20 mL of concentrated ammonium hydroxide. The solvent was eveporated and the residue was triturated with water (3 x 50 mL). Water (100 mL) and $CHCl_3$ (100 mL) were added to the residue. (Sometimes, part of the product stayed at the interface between the aqueous phase and organic phase due to the limited solubility of the product in water. This undissolved product was filtered and washed

with water and $CHCl_3$. This product was combined with the rest of product that was obtained later. The washings were also combined with the filtrate.) The $CHCl_3$ layer was separated from the aqueous layer and the aqueous layer was washed with $CHCl_3$ (2 x 100 mL). The chloroform layers were dried over anhydrous $MgSO_4$ and evaporated to recover chiral ligand (**BPB**). The aqueous part was concentrated to obtain the crude product. The product was dissolved in a minimal amount of 1:1 ethanol/water and the solution applied to a Dowex 50X2 100 ion-exchange column. It was washed with water until the eluent was neutral and then washed with 1:4 water/concentrated ammonium hydroxide and the eluent was collected and evaporated off to obtain the product. (If necessary, a mixture of 2:3:5 concentrated ammonium hydroxide/ethanol/water was used as eluent). For **73-75**, debenzylation were carried out in methanol with Pd/C in the presence of 40 *psi* of H_2 (Scheme 2-26).



73: $R^1 = H$, $R^2 = NH_2$
74: $R^1 = NH_2$, $R^2 = H$
75: $R^1 = CH_3$, $R^2 = NH_2$

79: $R^1 = H$, $R^2 = NH_2$
80: $R^1 = NH_2$, $R^2 = H$
81: $R^1 = CH_3$, $R^2 = NH_2$

Scheme 2-26. Hydrogenolysis of *O*-protected tyrosine analogues

With this method, a series of amino acids (**72**, **76-81**) with different substitution patterns and functional groups were prepared as shown in Figure 2-14.

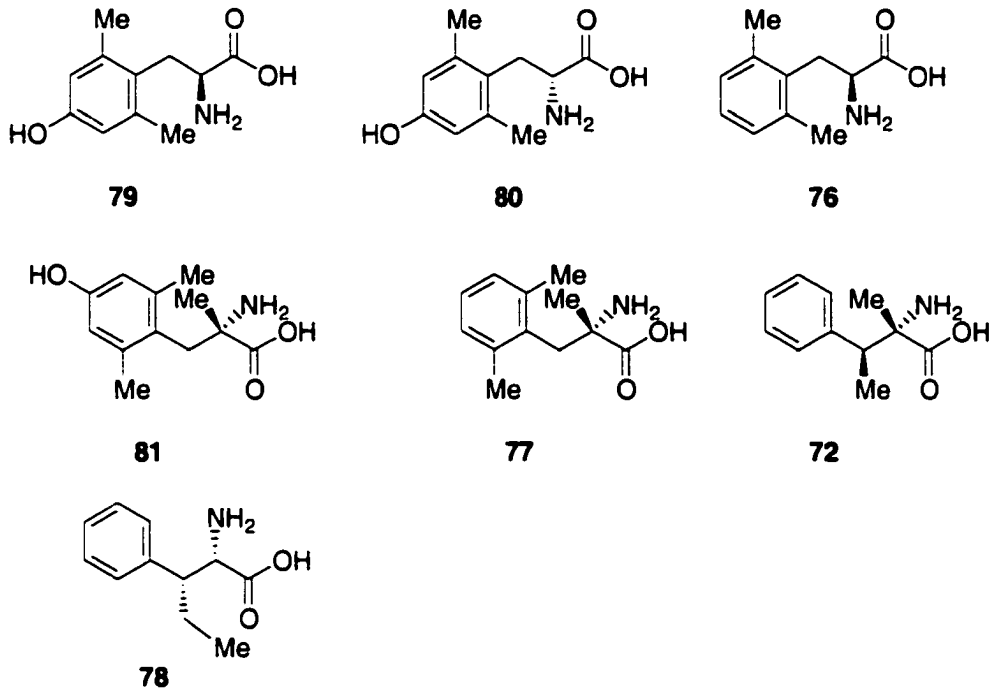
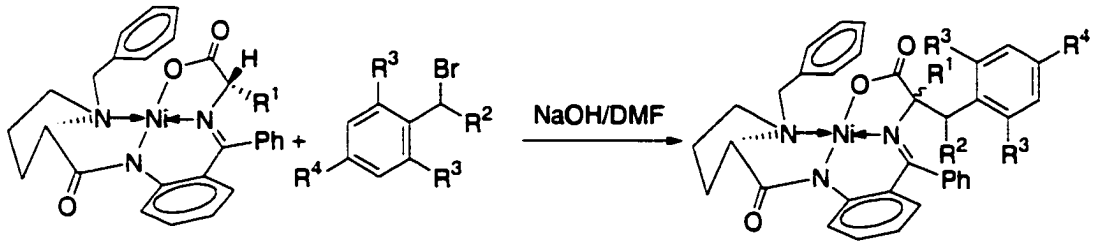


Figure 2-13. Amino acids prepared *via* direction alkylation

2.16. Summary



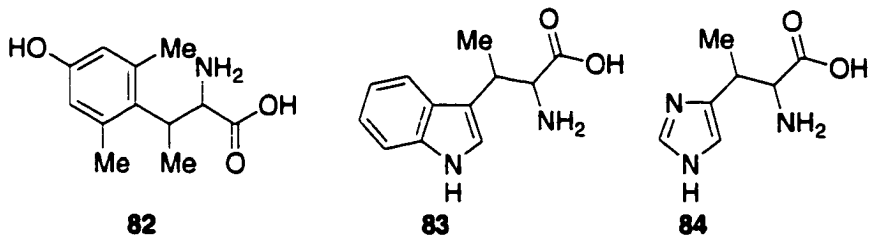
Scheme 2-27. General representation of alkylation of Ni (II)-coordinated Schiff bases

A systematically practical method to prepare highly constrained amino acids was developed (Scheme 2-27). With an increase in the size of R^1 from H to Me to Et to *n*-Pr, decreased reactivity of starting complexes was observed. In the case of R^1 as *i*-Pr, no alkylation was observed. With an increase in the size of R^2 from H to Me to Et to *i*-Bu, the reactivities of alkyl bromides decreased. The starting Schiff bases had more effective stereocontrol at the α-carbon center than at β-carbon center. The starting Schiff bases showed differential reactivity toward the racemic electrophiles (kinetic resolution) with (*S*)-NiAlaBPB and (*S*)-NiGlyBPB. Satisfactory differentiations were obtained at room temperature, makeing this method synthetically useful. In the cases of (*R*)- and (*S*)-NiGlyBPB), thermodynamically-controlled stereoselectivity of alkylation was as high as 30:1.

2.17. Future Work

Generally speaking, the nucleophilic substitution developed here is applicable to generate derivatives of the 20 proteinogenic amino acids with a variety of substitution patterns if the corresponding nucleophiles are available. Specifically, there are several candidate amino acids of key importance in our research (**82-84**, Figure 2-15). Even though synthetic methods have been developed for some of them, it is still highly desirable to develop a large-scale synthetic approach with reduced number of steps for them. We think it is possible to obtain these amino acids using our method, but we have experienced some difficulties in reaching the corresponding electrophiles (alkyl halides or tosylates) due to significant elimination in their preparation. We still think this

approach is promising, but we do need to generate the appropriate electrophiles. The future work in this area could be toward this goal.



82 **83** **84**

Figure 2-14. Some important amino acids to be prepared by this method

There are some unexplored aspects as to the mechanism of this type of nucleophilic substitutions, for example S_N2 vs. S_N2' and the origin of stereoselectivity in some specific cases. More systematic work is needed to elucidate these issues.

2.18 Experimental

General. ^1H and ^{13}C NMR were performed on Bruker-250, DRX-500, DRX-600 and Varian-300 spectrometers using TMS and $CDCl_3$ as internal standards. High resolution mass spectra (HRMS) were recorded on a JEOL HX110A instrument. Optical rotations were measured on a JASCO P-1010 polarimeter. Melting points (mp) are uncorrected and were obtained in open capillaries. All reagents and solvents, unless otherwise stated, are commercially available and were used as received. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated

by ^{1}H and ^{13}C NMR spectrometry. All new compounds were characterized by ^{1}H, ^{13}C NMR and HRMS.

X-ray structures: A red block of examined Ni-coordinated Schiff base having approximate dimensions of 0.30 x 0.10 x 0.10 mm was mounted on a glass fiber in a random orientation. Examination of the crystal on a Bruker SMART 1000 CCD detector X-ray diffractometer at 170(2)K and a power setting of 50KV, 40mA showed measurable diffraction to at least $\theta = 24°$. Data were collected on a SMART1000 system using graphite monochromated Mo-Kα radiation (λ =0.71073Å).

***N*-Benzylproline (BP) (21 and 23).** To a clear solution of 173.0 g of (*R*)- or (*S*)-proline (1.5 mol, 1.0 eq) and 252.5 g of potassium hydroxide (4.5 mol, 3.0 eq) in 1 L of *i*-PrOH at 40 °C was added 207.4 mL of benzyl chloride (1.8 mol, 1.2 eq) dropwise over 3 hours. The resulting reaction mixture was stirred at 40 °C overnight, acidified to pH 5-6 with concentrated hydrochloric acid, mixed with 200 mL of chloroform and allowed to stand overnight. The white precipitate (KCl) was filtered and washed thoroughly with chloroform. The filtrate was evaporated *in vacuo* to give crude product that was dispersed in acetone and allowed to stand overnight. The pure product was obtained after filtration, washing with a small amount of cold acetone and drying in vacuum.

(*S*)-**BP.HCl (21)**. Yield: 78%. m.p. 193-195 °C. $[\alpha]_D^{25}$ -26.3 (*c* 1.021, EtOH). ^{1}H-NMR (CD_3OD) δ 1.96-2.00 (m, 1H), 2.11-2.20 (m, 2H), 2.51-2.59 (m, 1H), 3.29-3.36 (m, 1H), 3.53-3.56 (m, 1H), 4.20 (dd, 1H, J_1 = 7.3 Hz and J_2 = 9.3 Hz), 4.34 (part of AB, d, 1H, J = 12.8 Hz), 4.54 (part of AB, d, 1H, J = 12.8 Hz), 7.45-7.48 (m, 3H), 7.53-7.55

(m, 2H). ^{13}C-NMR (CD_3OD) δ 23.6, 29.5, 55.6, 59.6, 68.5, 130.3, 131.2, 131.7, 131.8, 171.7. HRMS (FAB) $[M+H]^+$ calcd. for $C_{12}H_{15}NO_2$ 206.1181, found 206.1190.

(*R*)-**BP.HCl** (**23**). Yield: 78%. M.P. 194-196 °C. $[\alpha]_D^{25}$ +26.5 (*c* 1.173, EtOH). ^{1}H-NMR (CD_3OD, DRX500M) δ 1.95-2.00 (m, 1H), 2.11-2.20 (m, 2H), 2.51-2.59 (m, 1H), 3.29-3.36 (m, 1H), 3.52-3.56 (m, 1H), 4.20 (dd, 1H, J_1 = 7.3 Hz and J_2 = 9.3 Hz), 4.33 (part of AB, d, 1H, J = 12.8 Hz), 4.54 (part of AB, d, 1H, J = 12.8 Hz), 7.45-7.48 (m, 3H), 7.53-7.55 (m, 2H). ^{13}C-NMR (CD_3OD, DRX500M) δ 23.6, 29.5, 55.5, 59.6, 68.5, 130.3, 131.1, 131.7, 131.8, 171.7. HRMS (FAB) $[M+H]^+$ calcd. for $C_{12}H_{15}NO_2$ 206.1181, found 206.1190.

(*R*)- and (*S*)-BPB (22 and 24). To a solution of 50.0 g of (*S*)- or (*R*)-BP (0.2069 mol, 10 eq), 40.8 g of 2-aminobenzophone (0.2069 mol, 1.0 eq) and 91.5 g of BOP (0.2069) mol, 1.0 eq) in 300 mL of freshly distilled dichloromethane was added 87 mL of triethylamine (0.6207 mol, 3.0 eq). The reaction mixture was stirred at room temperature until the 2-aminobenzophone completely disappeared. The reaction was quenched by adding 1.0 *N* of hydrochloric acid with strong agitation. The aqueous layer was separated from the organic layer and washed with methylene chloride (2 x 100 mL). The combined methylene chloride layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to afford the crude product. Only a small amount of crude product was purified by column chromatography on silica gel with 1:9 EtOAc/hexanes as eluent to collect experimental data. The rest was used to carry out the next step without purification.

(*S*)-**BPB** (**22**). m.p. 98-100 °C. $[\alpha]_D^{25}$ -135.8 (*c* 0.9541, MeOH). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 1.74-1.86 (m, 2H), 1.93-1.99 (m, 1H), 2.24-2.29 (m, 1H), 2.37-

2.43 (m, 1H), 3.19-3.23 (m, 1H), 3.32 (dd, 1H, J_1 = 10.0 Hz and J_2 = 5.5 Hz), 3.59 (d, 1H, J = 13.0 Hz), 3.92 (d, 1H, J = 13.5 Hz), 7.07 (t, 1H, J = 7.8 Hz), 7.12-7.14 (m, 2H), 7.36-7.38 (m, 2H), 7.47-7.56 (m, 4H), 7.59 (t, 1H, J = 7.8 Hz), 7.78 (d, 2H, J = 7.0 Hz), 8.75 (d, 1H, J = 8.5 Hz), 11.5 (s, 1H). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 24.3, 29.8, 31.0, 53.9, 68.4, 121.5, 122.1, 125.4, 127.0, 128.3, 128.3, 129.2, 130.1, 132.5, 132.6, 133.5, 138.1, 138.6, 139.3, 174.6, 198.1. HRMS (FAB) $[M+H]^+$ calcd. for $C_{25}H_{26}N_2O_2$ 385.1916, found 385.1918.

(*R*)-**BPB** (**24**). m.p. 98-100 °C. $[\alpha]_D^{25}$ +133.3 (*c* 0.8522, MeOH). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 1.73-1.86 (m, 2H), 1.93-1.99 (m, 1H), 2.21-2.29 (m, 1H), 2.37-2.43 (m, 1H), 3.19-3.23 (m, 1H), 3.32 (dd, 1H, J_1 = 10.0 Hz and J_2 = 5.0 Hz), 3.59 (d, 1H, J = 13.0 Hz), 3.91 (d, 1H, J = 13.0 Hz), 7.07 (t, 1H, J = 7.8 Hz), 7.12-7.14 (m, 2H), 7.36-7.38 (m, 2H), 7.47-7.54 (m, 4H), 7.59 (t, 1H, J = 7.5 Hz), 7.78 (d, 2H, J = 7.0 Hz), 8.75 (d, 1H, J = 8.5 Hz), 11.5 (s, 1H). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 24.2, 29.8, 31.0, 53.9, 68.2, 121.5, 122.2, 125.3, 127.0, 128.1, 128.3, 129.1, 130.1, 132.5, 132.6, 133.4, 138.1, 138.5, 139.2, 174.6, 198.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{25}H_{26}N_2O_2$ 385.1916, found 385.1918.

Ni(II) Complex of Schiff base of (*R*) or (*S*)-BPB with simple amino acids (1-7). The solution of (*S*)- or (*R*)-BPB generated above, $NiCl_2.6H_20$ (2.0 eq), potassium (7.0 eq) and amino acids **1-5** (5.0 eq for **1**, 2.0 eq for the others) in methanol was stirred at 40 °C until the staring ligand (*S*)- or (*R*)-**BPB** was completely consumed as monitored by TLC (1:1 acetone/hexanes). Then the reaction mixture was poured into ice water (four times the volume of methanol) with 1% acetic acid. The precipitate was filtered, washed

with water and dried in vacuum to afford the crude product. The crude product was dissolved in a large quantity of chloroform and the precipitate was filtered and washed with chloroform. The filtrate was evaporated *in vacuo* and dried under vacuum to afford the product. Recrystallization from acetone/hexanes gave the pure product. The yields are reported for the 2 steps from **21** or **23**.

(*S*)-NiGlyBPB (1). Yield: 75%. R_f = 0.25 (1:1 acetone/hexanes). m.p. 219-221 °C. $[\alpha]_D^{25}$ +2117 (*c* 0.01452, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 2.06-2.10 (m, 1H), 2.13-2.18 (m, 1H), 2.40-2.47 (m, 1H), 2.56-2.59 (m, 1H), 3.32-3.38 (m, 1H), 3.47 (dd, 1H, J_1 = 5.5 Hz and J_2 = 11.0 Hz), 3.66-3.80 (m, 4H), 4.48 (d, 1H, *J* = 12.5 Hz), 6.69-6.72 (m, 1H), 6.80 (d, 1H, *J* = 8.5 Hz), 6.97-6.99 (m, 1H), 7.10 (d, 1H, *J* = 7.0 Hz), 7.19-7.23 (m, 1H), 7.30-7.33 (m, 1H), 7.41-7.44 (m, 2H), 7.49-7.53 (m, 3H), 8.07 (d, 2H, *J* = 8.0 Hz), 8.29 (d, 1H, *J* = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 23.7, 30.7, 57.5, 61.3, 63.1, 69.9, 120.8, 124.2, 125.1, 125.7, 126.2, 128.9, 129.1, 129.3, 129.6, 129.7, 129.8, 132.2, 133.1, 133.3, 134.6, 142.5, 171.6, 177.3, 181.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{27}H_{25}N_3O_3Ni$ 498.1328, found 498.1328.

(*S*)-NiAlaBPB (2). Yield: 84%. R_f = 0.30 (1:1 acetone/hexanes). m.p. 268-270 °C. $[\alpha]_D^{25}$ = +2984 (*c* 0.01365, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 1.65 (d, 3H, *J* = 7.3 Hz), 2.04-2.14 (m, 1H), 2.19-2.29 (m, 1H), 2.51-2.55 (m, 1H), 2.72-2.76 (m, 1H), 3.47-3.50 (m, 1H), 3.53-3.58 (m, 2H), 3.70-3.73 (m, 1H), 3.90-3.93 (m, 1H), 4.41 (d, 1H, *J* = 12.4 Hz), 6.62-6.66 (m, 1H), 6.95-6.96 (m, 1H), 7.13-7.15 (m, 1H), 7.19-7.27 (m, 4H), 7.35-7.38 (m, 2H), 7.44-7.53 (m, 3H), 8.06-8.11 (m, 2H). HRMS (FAB) $[M+H]^+$ calcd. for $C_{28}H_{27}N_3O_3Ni$ 512.1484, found 512.1484.

(*S*)(*S*)-NiValBPB (3). Yield: 73%. R_f = 0.40 (1:1 acetone/hexanes). m.p. 245-247 °C. $[\alpha]_D^{25}$ = +2522 (*c* 0.02232, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 0.76 (d, 3H, *J* = 6.5 Hz), 1.80-1.81 (m, 1H), 1.94 (d, 3H, *J* = 6.0 Hz), 2.06-2.08 (m, 2H), 2.51-2.55 (m, 1H), 2.81-2.86 (m, 1H), 3.34-3.36 (m, 1H), 3.46-3.53 (m, 2H), 3.63 (d, 1H, *J* = 12.5 Hz), 3.81-3.83 (m, 1H), 4.49 (d, 1H, *J* = 12.5 Hz), 6.64-6.66 (m, 2H), 6.92 (d, 1H, *J* = 7.0 Hz), 7.14-7.18 (m, 2H), 7.22-7.30 (m,1H), 7.31-7.34 (m, 2H), 7.45-7.46 (m, 1H), 7.50-7.52 (m, 2H), 8.02 (d, 2H, *J* = 7.0 Hz), 8.25 (d, 1H, *J* = 9.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 18.0, 19.7, 23.0, 30.7, 34.1, 56.6, 63.2, 70.3, 75.3, 120.5, 123.3, 126.3, 127.1, 127.9, 128.7, 128.8, 128.9, 129.5, 131.5, 132.2, 133.1, 133.4, 134.0, 142.4, 170.7, 177.8, 180.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{30}H_{31}N_3O_3Ni$ 540.1797, found 540.1802.

(*S*)(*S*)-NiAbuBPB (4). Yield: 85%. R_f = 0.33 (1: 1 acetone/hexanes). m.p. 265-267 °C. $[\alpha]_D^{25}$ = +1769 (*c* 0.03710, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 1.36 (t, 3H, *J* = 7.5 Hz), 1.67-1.75 (m, 1H), 1.96-1.98 (m, 1H), 2.04-2.08 (m, 1H), 2.10-2.17 (m, 1H), 2.48-2.56 (m, 1H), 2.73-2.79 (m, 1H), 3.47 (q, 1H, *J* = 5.8 Hz), 3.57 (d, 1H, *J* = 12.5 Hz), 3.51-3.54 (m, 2H), 3.89 (dd, 1H, J_1 = 4.0 Hz), J_2 = 8.0 Hz), 4.42 (d, 1H, *J* = 12.5 Hz), 6.62-6.66 (m, 2H), 6.92 (d, 1H, *J* = 7.5 Hz), 7.11-7.14 (m, 1H), 7.18 (t, 1H, *J* = 7.5 Hz), 7.25-7.26 (m, 1H), 7.34 (t, 2H, *J* =7.5 Hz), 7.42-7.44 (m, 1H), 7.45-7.53 (m, 2H), 8.07 (d, 2H, *J* = 7.5 Hz), 8.16 (d, 1H, *J* = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 9.7, 23.3, 28.2, 30.5, 56.8, 62.9, 70.1, 71.1, 120.4, 123.4, 126.2, 126.9, 127.3, 128.6, 128.7, 129.4, 131.3, 131.8, 133.0, 133.1, 133.7, 142.1, 170.3, 179.1, 180.1. HRMS (FAB) $[M+H]^+$ calcd. for $C_{29}H_{29}N_3O_3Ni$ 526.1641, found 526.1641.

(*S*)(*S*)-NiNvaBPB (5). Yield: 91%. R_f = 0.24 (2:3 acetone/hexanes). m.p. 228-230 °C. $[\alpha]_D^{25}$ = +2345 (*c* 0.04388, $CHCl_3$). HRMS (FAB) $[M+H]^+$ calcd. for $C_{30}H_{32}N_3O_3Ni$ 540.1797, found 540.1815. ^{1}H-NMR ($CDCl_3$, DRX500M) δ 0.78 (t, 3H, *J* = 5.8 Hz), 1.58-1.64 (m, 2H), 1.98-2.10 (m, 3H), 2.14-2.19 (m, 1H), 2.49-2.56 (m, 1H), 2.74-2.78 (m, 1H), 3.46-3.53 (m, 2H), 3.53-3.59 (m, 3H), 3.91 (dd, 1H, J_1 = 2.5 Hz and J_2 = 7.0 Hz), 4.42 (d, *J* =10.5 Hz), 6.62-6.67 (m, 2H), 1.93 (d, *J* = 6.5 Hz), 7.12-7.15 (m, 1H), 7.19 (t, 1H, *J* = 6.3 Hz), 7.26-7.28 (m, 1H), 7.35 (t, 2H, *J* = 6.5 Hz), 7.44-7.47 (m, 1H), 7.49-7.53(m, 2H), 8.06 (d, 2H, *J* = 6.2 Hz), 8.12 (d, 1H, *J* = 9.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 13.6, 18.7, 23.6, 30.7, 37.5,57.0,63.1, 70.1, 70.2, 120.7, 123.6, 126.5, 127.2, 127.5, 128.6,128.7,128.8, 128.9, 129.6, 131.5, 132.0, 133.1, 133.2, 133.8, 142.1, 170.2, 179.5, 180.3.

(*R*)-NiGlyBPB (6). Yield: 67%. R_f = 0.25 (1:1 acetone/hexanes). M.P. 219-221 °C. $[\alpha]_D^{25}$ = -1739 (*c* 0.01176, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 2.06-2.10 (m, 1H), 2.13-2.18 (m, 1H), 2.40-2.47 (m, 1H), 2.56-2.59 (m, 1H), 3.32-3.38 (m, 1H), 3.47 (dd, 1H, J_1 = 5.5 Hz and J_2 = 11.0 Hz), 3.66-3.80 (m, 4H), 4.48 (d, 1H, *J* = 12.5 Hz), 6.69-6.72 (m, 1H), 6.80 (d, 1H, *J* = 8.5 Hz), 6.97-6.99 (m, 1H), 7.10 (d, 1H, *J* = 7.0 Hz), 7.19-7.22 (m, 1H), 7.30-7.33 (m, 1H), 7.41-7.44 (m, 2H), 7.49-7.53 (m, 3H), 8.07 (d, 2H, *J* = 8.0 Hz), 8.29 (d, 1H, *J* = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 23.7, 30.7, 57.5, 61.3, 63.1, 69.9, 120.8, 124.2, 125.1, 125.7, 126.2, 128.9, 129.1, 129.3, 129.6, 129.7, 129.8, 132.2, 133.1, 133.3, 134.6, 142.5, 171.6, 177.3, 181.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{27}H_{25}N_3O_3Ni$ 498.1328, found 498.1328.

(*R*)-NiAlaBPB (7). R_f = 0.31 (1:1 acetone/hexanes). m.p. 264-266 °C. $[\alpha]_D^{25}$ = -2206 (*c* 0.01468, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500M) δ 1.59 (d, 3H, *J* = 6.6 Hz), 2.05-2.20 (m, 1H), 2.17-2.23 (m, 1H), 2.50-2.57 (m, 1H), 2.72-2.77 (m, 1H), 3.48 (dd, 1H, J_1 = 6.0 Hz and J_2 = 11.4 Hz), 3.54-3.57 (m, 2H), 3.69-3.76 (m, 1H), 3.89-3.93 (m, 1H), 4.41 (d, 1H, *J* = 13.2 Hz), 6.62-6.67 (m, 2H), 6.95 (d, 1H, *J* = 7.2 Hz), 7.12-7.15 (m, 1H), 7.19-7.22 (m, 1H), 7.25-7.27 (m, 1H), 7.35-7.44 (m, 2H), 7.44-7.46 (m, 1H), 7.50-7.53 (m, 2H), 8.07 (d, 2H, *J* = 7.8 Hz), 8.10 (d, 1H, *J* = 9.0Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 21.8, 24.0, 30.7, 57.2, 63.0, 66.5, 70.2, 120.7, 123.8, 126.4, 127.1, 127.4, 128.8, 128.9, 129.6, 131.5, 132.0, 133.0, 133.3, 133.4, 142.0, 170.2, 180.3, 180.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{28}H_{27}N_3O_3Ni$ 512.1484, found 512.1482.

2',6'-Dimethylbenzyl alcohol (25). To a solution of 20.0 g of 2,6-dimethylbenzoic acid (0.133 mol) in 150 mL of freshly distilled THF at –78 °C, 10.1 g of $LiAlH_4$ (0.266 mole, 2 eq.) was slowly added. The solution was stirred for 2 hours at –78 °C, warmed to room temperature and refluxed for 10 hours. The reaction was quenched with 200 mL of 3*N* HCl. The aqueous layer was separated from the organic layer and washed with diethyl ether (2 x 200 mL). The combined ether layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to provide product. Yield: 97%. m.p. 82-84 °C. R_f = 0.56 (EtOAc/hexanes, 3:7). ^{1}H-NMR ($CDCl_3$) δ 2.42 (s, 6H), 4.72 (s, 2H), δ 7.02-7.11 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ 19.4, 59.3, 128.0, 128.4, 136.5, 137.3. HRMS (FAB) $[M + H]^+$ calcd. for $C_9H_{12}O$ 137.0966, found 137.0963. Elemental analysis: for $C_9H_{12}O$ calcd C: 79.37, H: 8.88, found: C: 79.31, H: 9.09.

2',6'-Dimethylbenzyl bromide (12). To a solution of 5.45 g of 2,6-dimethylbenzyl alcohol (40 mmol) and 7.13 mL of anhydrous pyridine (88 mmole, 2.2 eq.) in 150 mL of anhydrous diethyl ether, 4.14 mL of PBr_3 (44 mmol, 1.1 eq.) was added dropwise over 1 hr via a syringe at –78 °C. The resulted white slurry was stirred under Ar for 2 hours at –78 °C and overnight at room temperature. The reaction progress was monitored with TLC. Upon the complete disappearance of the starting material, the reaction was quenched by slowly adding ice-water. The reaction mixture was stirred at 0 °C for 30 min, the ether layer was separated from the aqueous layer and the aqueous phase was washed with ether (3 x 100 mL). The combined ether solution was washed with ice-cold 1*N* HCl (2 x 100 mL), saturated sodium bicarbonate (2 x 100 mL) and distilled water (2 x 100 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to afford the product. Yield: 82%. m.p. 36-38 °C. R_f = 0.82 (EtOAc/hexanes, 1:9). ^{1}H-NMR ($CDCl_3$) δ 2.37(s, 6H), 4.51 (s, 2H), 6.97-7.08 (m, 3H). ^{13}C-NMR($CDCl_3$) δ 19.1, 29.2, 128.4, 128.5, 134.0, 137.4. HRMS (FAB) [M + H]+ calcd. for $C_9H_{11}Br$ 199.0122, found 199.0115.

4-Bromo-3,5-dimethylphenyl benzyl ether (27). To a solution of 10.0 g of 4-bromo-3,5-dimethylphenol (49.7 mmol) in a minimal amount of anhydrous methanol (ca. 13 mL) at 0 °C was added 2.0 g of NaOH (50 mmol, 1 eq.) dissolved in a minimal amount of methanol. After 2 hr, the solvent was removed *in vacuo* to afford sodium 4-bromo-3, 5-dimethyl phenoxide. This was dispersed in 80 mL of DME, treated with 5.7 mL of benzyl chloride dissolved in 20 mL of DME, heated at 35 °C for 24 hr and quenched with 100 mL of water. The reaction mixture was extracted with diethyl ether

(3 x 200 mL). The combined organic layer was dried over magnesium sulfate and evaporated *in vacuo*. The residue was recrystallized from methanol to give compound **6** in 97% yield: m.p. 52-54 °C; ^{1}H-NMR ($CDCl_3$) δ 7.42-7.25 (m, 5H), 1.16 (s, 2H), 4.77 (s, 2H), 2.26 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 152.4, 137.2, 133.4, 131.4, 128.6, 128.1, 127.8, 116.5, 74.1, 16.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{15}H_{15}BrO$ 290.0306, found 290.0304.

4-Benzyloxy-2,6-dimethylbenzaldehyde (28). To a solution of 10.7 g (36.5 mmol) of 4-bromo-3,5-dimethylphenyl benzyl ether (**6**) in 100 mL of freshly distilled THF, 0.2 g of I_2 and 3.5 g of Mg (146 mmol, 4 eq.) were added. The reaction mixture was refluxed under Ar atmosphere for 4 hr. To the Grignard reagent, 11.4 mL (146 mmol, 4 eq.) of anhydrous DMF was slowly added at 0 °C. The reaction mixture was stirred for 2 hours at 0 °C and overnight at room temperature. It was quenched with saturated ammonium chloride and the organic layer was separated from the aqueous layer. The aqueous layer was washed with diethyl ether (2 x 100 mL). The combined organic layer was dried over magnesium sulfate and evaporated *in vacuo* to afford a crude product which was purified by column chromatography (hexanes/ethyl acetate 7:3). Yield: 90%; m.p. 54-56 °C; ^{1}H-NMR ($CDCl_3$) δ 10.51 (s, 1H), 7.42-7.30 (m, 5H), 6.68 (s, 2H), 5.09 (s, 2H), 2.59 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 191.5, 161.8, 144.4, 136.1, 128.6, 128.2, 127.4, 126.1, 115.6, 69.8, 21.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{16}H_{16}O_2$ 241.1229, found 241.1226.

4-Benzyloxy-2,6-dimethylbenzyl alcohol (29). To a solution of 6.2 g (21.4 mmol) of **7** in 100 mL freshly distilled THF 1.47 g (25.8 mmol, 1.2 eq.) of lithium

aluminum hydride was added at –78 °C. The reaction mixture was stirred at –78 °C for 2 hr, warmed to room temperature and refluxed for 4 hr. The reaction was quenched with 1*N* HCl and the THF layer was separated from the aqueous phase. The aqueous layer was washed with ethyl ether (2 x 100 mL). The combined organic layer was dried over magnesium sulfate and evaporated *in vacuo* to afford the product **8** which was not further purified. Yield: 92%; mp 77-79 °C; ^{1}H-NMR ($CDCl_3$) δ 7.45-7.30 (m, 5H), 6.66 (s, 2H), 5.02 (s, 2H), 4.66 (d, 2H, *J* = 3 Hz), 2.39 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 158.1, 139.0, 137.1, 129.6, 128.6, 127.9, 127.4, 114.5, 69.8, 59.0, 19.7. HRMS (FAB) $[M+H]^+$ calcd. for $C_{16}H_{18}O_2$ 242.1307, found 243.1305.

4-Benzyloxy-2,6-dimethylbenzyl bromide (13). To a solution of 4.84 g (20 mmol) of **8** in 100 mL of anhydrous ethyl ether and under Ar, 2.1 mL (44 mmol, 2.2 eq.) of anhydrous pyridine was added via a syringe at –78 °C. After 5 min, 2.1 mL (22 mmol, 1.1 eq.) of phosphorus tribromide was slowly dropped into the solution over one hour. Formation of a white slurry was observed. The mixture was stirred for 2 hr at –78 °C and overnight at room temperature. Completion of the reaction was monitored by TLC. The reaction was quenched by slowly adding an ice-water mixture with stirring at 0 °C, and the mixture was stirred for 30 min at 0 °C. The ether layer was separated from the aqueous layer and the aqueous phase was washed with diethyl ether (2 x 150 mL). The combined ethyl ether solution was washed with ice-cold 85% phosphorus acid (50 mL), saturated sodium bicarbonate (2 x 100 mL) and water (2 x 100 mL). The ether solution was dried over magnesium sulfate and evaporated *in vacuo* to yield a white solid residue. No further purification of compound **4** was necessary. Yield: 83%; mp 99-101 °C; ^{1}H-

NMR ($CDCl_3$) δ 7.40 (m, 5H), 6.67 (s, 2H), 5.03 (s, 2H), 4.58 (s, 2H), 2.39 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 158.7, 139.3, 136.9, 128.5, 127.9, 127.4, 126.6, 114.7, 69.8, 30.1, 19.6. HRMS (FAB) $[M+H]^+$ calcd. for $C_{16}H_{17}BrO$ 305.0538, found 305.0541.

General procedure for 31-34. The reactions were conducted on a 100 mmol scale. To a solution of propionaldehyde or isobutaldehyde in 100 mL of anhydrous ethyl ether at –78 °C, phenylmagnesium bromide (3M in Et_2O, 1.1 eq) was slowly added via a syringe. The mixture was stirred for 1 hr at –78 °C, overnight at room temperature, and quenched with saturated ammonium chloride at 0°C. The ether layer was separated from the aqueous layer. The aqueous layer was washed with ethyl ether (3 x 100 mL). The combined ether layers were washed with 5% $NaHCO_3$ (2 x 100 mL) and distilled water (2 x 100 mL). The ether solution was dried over $MgSO_4$ and evaporated *in vacuo* to afford the crude product, which was purified by column chromatography with ethyl acetate/hexanes (3:7) as eluent.

1-Phenyl-1-propanol (31). Colorless oily liquid. Yield: 88%; ^{1}H-NMR ($CDCl_3$) δ 0.84 (t, 3H, J = 6.8 Hz), 1.53-1.76 (m, 2H), 4.40 (t, 1H, J = 6.6 Hz), 7.10-7.30(m, 5H). ^{13}C-NMR ($CDCl_3$) δ 9.9, 31.6, 75.5, 125.8, 127.0, 127.7, 144.5. HRMS (FAB) $[M+H]^+$ calcd. for $C_9H_{12}O$ 137.0968, found 137.0971.

3-Methyl-1-phenyl-1-butanol (32). Pale yellow oil. Yield: 81%; ^{1}H-NMR ($CDCl_3$) δ 0.9 (dd, 6H, J = 1.7 Hz, J = 6.3Hz), 1.40-1.55 (m, 1H), 1.60-1.83 (m, 2H), δ 4.70 (dd, 1H, J = 5.5 Hz, J = 7.8 Hz), 7.10-7.50 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 22.2, 23.0, 24.6, 48.2, 72.5, 125.8, 127.9, 128.3, 142.5. HRMS (FAB) $[M+H]^+$ calcd. for $C_{11}H_{16}O$ 165.1281, found 165.1277.

33. White solid recrystallized from EtOAc/hexanes. Yield: 79%. R_f = 0.30 (1:9 EtOAc/hexanes). m.p.: 55-57 °C. ^{1}H-NMR ($CDCl_3$) δ 1.52 (d, 3H, J = 7.0 Hz), 2.44 (s, 6H), 5.35-5.38 (m, 1H), 6.97-7.05 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ 20.6, 21.4, 67.4, 126.9, 129.4, 135.7, 140.5. Anal: Calcd for C_{10} $H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.27; H, 9.32.

34. Oily liquid. Yield: 85%. R_f = 0.45 (1:9 EtOAc/hexanes). ^{1}H-NMR ($CDCl_3$) δ 0.98 (t, 3H, J = 7.5 Hz), 1.74-1.82 (m, 2H), 1.94-2.03 (m, 1H), 2.42 (s, 6H), 5.07 (dd, 1H, J_1 = 6.0Hz and J_2 = 8.0 Hz), 6.97 (d, 2H, J = 7.0 Hz), 7.02-7.05 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ 11.0, 20.8, 28.6, 73.1, 126.9, 129.3, 136.1, 139.7.

General procedure for bromides 15-18. To a solution of 20 mmole of **31**, **32**, 33, or **34** in 100 mL of anhydrous ethyl ether and under Ar, 2.1 mL (44 mmol, 2.2 eq.) of anhydrous pyridine was added via a syringe at –78 °C. After 5 min, 2.1 mL (22 mmol, 1.1 eq.) of phosphorus tribromide was slowly dropped into the solution over 1 hr. Formation of a white slurry was observed. The mixture was stirred for 2 hr at –78 °C and overnight at room temperature. Completion of the reaction was monitored by TLC. The reaction was quenched by slowly adding an ice-water mixture with stirring at 0 °C, and the mixture was stirred for 30 min at 0 °C. The ether layer was separated from the aqueous layer and the aqueous phase was washed with diethyl ether (2 x 150 mL). The combined ethyl ether solution was washed with ice-cold 85% phosphorus acid (50 mL), saturated sodium bicarbonate (2 x 100 mL) and water (2 x 100 mL). The ether solution was dried over magnesium sulfate and evaporated *in vacuo* to afford product **15**, **16**, **17** or **18**. No further purification of compounds **15-18** was necessary.

15. Pale yellow oil. Yield: 72%; ^{1}H-NMR ($CDCl_3$) δ 0.97(t, 3H, J = 7.5 Hz), 2.08-2.40 (m, 2H), 4.85 (t, 1H, J = 7.5 Hz), 7.15-7.35 (m, 5H). ^{13}C-NMR($CDCl_3$) δ 12.9, 33.1, 57.4, 127.1, 127.6, 128.1, 142.9. HRMS (FAB) $[M+H]^+$ calcd. for $C_9H_{11}Br$ 198.0044, found 198.0036.

16. Colorless oil. Yield: 83%; ^{1}H-NMR ($CDCl_3$) δ 0.93 (d, 3H, J = 6.2 Hz), 1.00 (d, 3H, J = 6.9 Hz), 1.75-1.85 (m, 1H), 2.00-2.11 (m, 1H), 2.24-2.36 (m, 1H), 5.14 (dd, 1H, J = 7.0 Hz, J = 8.4 Hz), 7.20-7.50 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 21.8, 22.0, 26.6, 48.7, 53.9, 127.2, 128.1, 129.1, 139.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{11}H_{15}Br$ 226.0357, found 226.0340.

17 Colorless oil. Yield: 70%. R_f = 0.90 (1: 9 EtOAc/hexanes). ^{1}H-NMR ($CDCl_3$) δ 2.8 (d, 3H, *J* = 5.5 Hz), 2.39 (s, 3H), 2.61 (s. 3H), 5.74 (q, 1H, *J* = 7.3 Hz), 6.99-7.09 (m, 3H).^{13}C-NMR ($CDCl_3$) δ 20.6, 21.3, 24.9, 46.1, 128.0, 128.4, 130.9, 138.2.

18 Oil-like liquid. Yield: 62%. R_f = 0.9 (1: 9 EtOAc/hexanes). ^{1}H-NMR ($CDCl_3$) δ 0.97 (t, 3H, *J* = 7.3 Hz), 2.21-2.29 (m, 1H), 2.37 (s, 3H), 2.39-2.48 (m, 1H), 2.56 (s, 3H), 5.42 (dd, 1H, J_1 = 7.0 Hz and J_2 = 8.5 Hz), 6.97-7.08 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ 13.3, 20.9, 21.3, 31.0, 53.9, 128.0, 128.4, 130.8, 138.2.

1-Phenyl-1,4-butanediol (35). To a solution of 9.73 g of γ-phenylbutyrolactone (0.060 mol) in 50 mL of freshly distilled THF at –78 °C, 4.56 g of $LiAlH_4$ (0.120 mol, 2.0 eq.) was slowly added. The solution was stirred for 2 hr at –78 °C, warmed to room temperature, refluxed for 10 hr, and quenched with 50 mL of 3*N* HCl. The aqueous layer was separated from the organic layer and washed with diethyl ether (2 x 200 mL). The combined ether layer was dried over $MgSO_4$ and evaporated *in vacuo* to provide product. Yield: 81%. m.p. 62-64 °C. R_f = 0.59 (3:7, EtOAc/hexanes, v:v). ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.56-1.68 (m, 2H), 1.78-1.83 (m, 2H), 3.60-3.71 (m, 2H), 4.66 (t, 1H, *J* = 6.3 Hz), 7.23-7.33 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 29.1, 36.3, 62.6, 74.2, 125.8, 127.3, 128.3, 144.7. HRMS (FAB) $[M + H]^+$ calcd. for $C_{10}H_{14}O_2$ 167.1072, found 167.1076. Elemental analysis: for $C_{10}H_{14}O_2$ calcd C: 72.26, H: 8.61, found: C: 72.22, H: 8.49.

1-Phenyl-1,4-dibromobutane (20). To a solution of 20 mmol of 1-phenyl-1,4-butanediol (35) in 40 mL of anhydrous ethyl ether and under Ar at –78 °C, 3.76 mL (40 mmol, 2.0 eq.) of phosphorus tribromide was slowly added in 1 hr. The mixture was stirred for 2 hr at -78 °C and overnight at room temperature. Completion of the reaction

was monitored by TLC. The reaction was quenched by slowly adding an ice-water mixture with stirring at 0 °C, and the resulting mixture was stirred for 30 min at 0 °C. The ether layer was separated from the aqueous layer and the aqueous phase was washed with diethyl ether (2 x 40 mL). The combined ethyl ether solution was washed with ice-cold 85% phosphorus acid (50 mL), saturated sodium bicarbonate (2 x 100 mL) and water (2 x 100 mL). The ether solution was dried over anhydrous magnesium sulfate and evaporated *in vacuo* to afford product 20 as an oily liquid which was not purified further.. Yield: 78%. R_f = 0.83 (1:9 EtOAc/hexanes, v:v) ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.87-1.94 (m, 1H), 2.06-2.14 (m, 1H), 2.38-2.40 (m, 1H), 2.41-2.54 (m, 1H), 3.41-3.45 (m, 1H), 4.96 (dd, 1H, J_1 = 6.5 Hz and J_2 = 8.5 Hz), 7.26-7.41 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 31.2, 32.5, 38.4, 54.1, 127.2, 128.5, 128.8, 141.7. Anal. Calcd for $C_{10}H_{12}Br_2$: C, 41.60; H, 4.24. Found: C, 41.13; H, 4.14.

General procedure for reaction of Ni(II)-complex with electrophiles. A 100 mL round-bottom flask with 10 mmol of Schiff base and 4.0 g (100 mmol, 10 eq.) of NaOH was purged with Ar and 20 mL of anhydrous DMF was added to dissolve the complex and the base. Electrophile (dissolved in 20 mL of anhydrous DMF was dropped into the solution *via* a syringe. The mixture was stirred under Ar and the reaction progress was monitored by TLC. Upon completion, the reaction was quenched by addition of 500 mL of ice-water and the precipitated material was filtered off and dried *in vacuo*. The diastereomerically pure products were isolated by column chromatography on silica gel using acetone/hexanes 1:1 as an eluent.

36a. R_f = 0.35 (1:1 acetone/hexanes). m.p. 208-210 °C. $[\alpha]_D^{25}$ +2125 (*c* 0.04144, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 1.68-1.71 (m, 1H), 1.92-1.97 (m, 1H), 2.30-2.40 (m, 3H), 2.95 (dd, 1H, J_1 = 3.6 Hz and J_2 = 13.8Hz), 3.09-3.11 (m, 1H), 3.17 (dd, 1H, J_1 = 6.0 Hz and J_2 = 13.8 Hz), 3.31 (t, 1H, *J* = 8.4 Hz), 3.49 (d, 1H, *J* = 12.6 Hz), 4.27-4.29 (m, 2H), 6.63-6.66 (m, 2H), 6.98 (d, 1H, *J* = 7.8Hz),7.12-7.19 (m, 4H), 7.26-7.31 (m, 4H), 7.33-7.39 (m, 1H), 7.42-7.44 (m, 1H), 7.48-7.55 (m, 1H), 8.00 (d, 2H, *J* = 7.8 Hz), 8.28 (d, 1H, *J* = 9.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX600M) δ 23.1, 30.7, 33.3, 57.0, 63.2, 70.3, 70.8, 115.5, 115.7, 120.5, 123.2, 124.124.6, 124.7, 126.2, 127.1, 128.1, 128.2, 128.7, 128.8, 128.9, 129.3, 129.4, 129.7, 131.5, 132.3, 182.8, 132.9, 133.2, 133.5, 134.0, 142.9,161.2, 162.8, 171.9, 178.4, 180.2. HRMS (FAB) $[M+H]^+$ calcd. for $C_{34}H_{30}FN_3O_3Ni$ 606.1703, found 606.1708.

36b. R_f = 0.47 (1:1 acetone/hexanes). m.p. 150-152 °C. $[\alpha]_D^{25}$ +1944 (*c* 0.01807, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 1.53-1.60 (m, 1H), 1.97-2.00 (m, 1H), 2.31-2.37 (m, 1H), 2.45-2.50 (m, 1H), 2.85 (dd, 1H, J_1 = 3.0 Hz and J_2 = 13.2 Hz), 3.22 (dd, 1H, J_1 = 6.6 Hz and J_2 = 13.8 Hz), 3.39 (dd, 1H, J_1 = 3.0 Hz and J_2 = 9.0 Hz), 3.54 (d, 1H, *J* = 13.8 Hz), 3.81-3.85 (m, 1H), 3.91 (d, 1H, *J* = 13.8 Hz), 4.26 (dd, 1H, J_1 = 3.6 Hz and J_2 = 5.4 Hz), 6.74 (t, 1H, *J* = 7.5 Hz), 6.81 (d, 1H, *J* = 7.8 Hz), 7.14 (t, 1H, *J* = 7.5 Hz), 7.18 (d, 1H, *J* = 7.2 Hz), 7.25-7.29 (m, 4H), 7.36-7.40 (m, 6H), 7.51-7.54 (m, 3H), 8.52 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR ($CDCl_3$, DRX600M) δ 23.5, 31.1, 33.5, 53.9, 55.9, 59.9, 68.4, 71.0, 115.6, 115.7, 120.6, 123.5, 124.6, 124.7, 126.1, 127.0, 128.3, 128.8, 128.9, 129.0, 129.1, 129.3, 129.4, 129.7, 131.9, 132.0, 132.6, 133.1, 133.2, 133.8, 134.2,

143.2, 161.4, 163.1, 172.2, 178.4, 181.9. HRMS (FAB) $[M+H]^+$ calcd. for $C_{34}H_{30}FN_3O_3Ni$ 606.1703, found 606.1701.

36c. R_f = 1.41 (1:1 acetone/hexanes). m.p. 230-232 °C. $[\alpha]_D^{25}$ +2105 (*c* 0.01448, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 1.62-1.67 (m, 1H), 2.04-2.13 (m, 2H), 2.17-2.27 (m, 2H), 2.54 (d, 1H, J = 17.4 Hz), 3.02 (d, 1H, J = 14.4 Hz), 3.18 (d, 1H, J = 17.4 Hz), 3.22 (d, 1H, J = 6.0 Hz), 3.32-3.36 (m, 1H), 3.40 (d, 1H, J = 7.2 Hz), 3.42 (d, 1H, J = 5.4 Hz), 4.34 (d, 1H, J = 12.6 Hz), 6.50-6.55 (m, 2H), 6.62 (d, 1H, J 7.8 Hz), 7.05-7.09 (m, 2H), 7.16-7.23 (m, 4H), 7.30-7.37 (m, 6H), 7.42-7.50 (m, 2H), 7.74-7.76 (m, 1H), 7.83-7.85 (m, 1H), 7.98 (d, 1H, J = 8.4 Hz), 8.05 (d, 2H, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, DRX600M) δ 23.0, 30.6, 39.4, 40.5, 58.0, 63.9, 69.9, 79.6, 115.1, 115.2, 115.7, 115.8, 120.3, 123.5, 124.1, 124.6, 124.7, 126.8, 126.9, 127.3, 127.9, 128.0, 128.1, 128.2, 128.9, 129.2, 129.3, 129.5, 129.7, 129.8, 131.5, 131.6, 133.0, 133.1, 133.5, 133.8, 136.4, 142.2, 160.1, 161.3, 161.7, 163.0, 173.5, 179.5, 180.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{41}H_{36}F_2N_3O_3Ni$ 714.2078, found 714.2084.

38a. R_f = 0.35 (1:1 acetone/hexanes). m.p. 190-192 °C. $[\alpha]_D^{25}$ -2418 (*c* 0.02293, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 1.68-1.71 (m, 1H), 1.92-1.97 (m, 1H), 2.30-2.40 (m, 3H), 2.94-2.97 (m, 1H), 3.09-3.11 (m, 1H), 3.15-3.22 (m, 1H), 3.31 (t, 1H, *J* = 7.8 Hz), 3.49 (d, 1H, *J* = 13.2 Hz), 4.27-4.30 (m, 2H), 6.65-6.66 (m, 1H), 6.98 (d, 1H, *J* = 7.2 Hz), 7.11-7.16 (m, 4H), 7.27-7.31 (m, 3H), 7.34-7.39 (m, 1H), 7.42-7.44 (m, 1H), 7.50-7.55 (m, 2H), 8.06 (d, 2H, *J* = 7.2 Hz), 8.28 (d, 1H, *J* = 9.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 23.1, 30.7, 33.3, 57.0, 63.2, 70.3, 70.8, 115.5, 115.7,120.5, 123.2, 124.7, 124.8, 126.2, 127.1, 128.1, 128.2, 128.7, 128.8, 128.9, 129.0, 129.2, 129.3, 129.7, 131.5,

132.3, 132.8, 132.9, 133.2, 133.5, 134.0, 142.9, 161.2, 162.8, 172.0, 178.4, 180.2. HRMS (FAB) $[M+H]^+$ calcd. for $C_{XX}H_{XX}FN_3O_3Ni$ 606.1703, found 606.1711.

38b R_f = 0.47 (1:1 acetone/hexanes). m.p. 220-222 °C. $[\alpha]_D^{25}$ +1643 (*c* 0.01090, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 1.53-1.60 (m, 1H), 1.97-2.00 (m, 1H), 2.31-2.38 (m, 1H), 2.45-2.49 (m, 1H), 2.85 (dd, 1H, J_1 = 3.6 Hz and J_2 = 13.8 Hz), 3.22 (dd, 1H, J_1 = 6.0 Hz and J_2 = 13.8 Hz), 3.39 (dd, 1H, J_1 = 3.6 Hz and J_2 = 9.0 Hz), 3.54 (d, 1H, J = 13.8 Hz), 3.81-3.84 (m, 1H), 3.90 (d, 1H, J = 13.8Hz), 4.26 (dd, 1H, J_1 4.2 Hz and J_2 = 6.0 Hz), 6.73-6.76 (m, 1H), 6.80-6.81 (m, 1H), 7.13-7.16 (m, 1H), 7.19 (d, 1H, J = 7.2 Hz), 7.25-7.30 (m, 4H), 7.37-7.42 (m, 6H), 7.50-7.55 (m, 3H), 8.51 (d, 1H, J = 8.4 Hz). ^{13}C-NMR ($CDCl_3$, DRX600M) δ 23.6, 31.1, 33.4, 55.8, 59.9, 68.4, 71.0,115.6, 115.7, 120.6, 123.3, 123.4, 123.5, 124.6, 124.7, 126.1, 127.0, 128.3, 128.8, 128.9, 129.0, 129.1, 129.2, 129.3, 129.7, 131.9, 132.0, 132.6, 133.1, 133.2, 133.8, 134.2, 143.2, 161.4, 163.1, 172.2, 178.4, 181.9. HRMS (FAB) $[M+H]^+$ calcd. for $C_{34}H_{30}FN_3O_3Ni$ 606.1703, found 606.1697.

38c. R_f = 0.41 (1:1 acetone/hexanes). m.p. 230-232 °C. $[\alpha]_D^{25}$ -1420 (*c* 0.01800, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 1.62-1.67 (m, 1H), 2.03-2.14 (m, 1H), 2.17-2.29 (m, 1H), 2.54 (d, 1H, J = 17.4 Hz), 3.02 (d, 1H, J = 15.0 Hz), 3.19 (d, 1H, J = 18.0 Hz), 3.22 (d, 1H, J = 5.4 Hz), 3.34 (dd, 1H, J_1 = 7.2 Hz and J_2 = 9.6 Hz), 3.40 (d, 1H, J = 7.8 Hz), 3.42 (d, 1H, J = 6.0 Hz), 4.34 (d, 1H, J = 12.6 Hz), 6.50-6.55 (m, 2H), 6.62 (d, 1H, J = 7.2 Hz), 7.05-7.09 (m, 2H), 7.16 (d, 1H, J = 7.8 Hz), 7.20-7.23 (m, 3H), 7.29-7.32 (m, 3H), 7.34-7.37 (m, 3H), 7.42-7.45 (m, 1H), 7.45 (t, 1H, J = 7.5 Hz), 7.74-7.76 (m, 1H), 7.83-7.86 (m, 1H), 7.98 (d, 1H, J = 8.4 Hz), 8.05 (d, 2H, J = 7.2 Hz). ^{13}C-NMR

($CDCl_3$, DRX600M) δ 23.0, 30.6, 39.3, 40.4, 57.9, 63.8, 69.9, 115.0, 115.2, 115.7, 115.8, 120.3, 123.5, 124.0, 124.6, 124.7, 126.8, 126.9, 127.3, 127.8, 128.0, 128.1, 128.2, 128.8, 129.2, 129.3, 129.5, 129.7, 129.8, 131.5, 131.6, 133.0, 133.5, 133.7, 136.4, 142.2, 160.0, 161.3, 161.7, 162.9, 173.5, 179.5, 180.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{41}H_{36}F_2N_3O_3Ni$ 714.2078, found 714.2084.

41a. R_f = 0.50 (1:1 acetone/hexanes). m.p. 180-182 °C. $[\alpha]_D^{25}$ +1157 (*c* 0.01994, $CDCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.93-2.00 (m, 1H), 2.04 (s, 3H), 2.04-2.07 (m, 1H), 2.44-2.52 (m, 1H), 2.60-2.66 (m, 1H), 3.04-3.09 (m, 1H), 3.27-3.31 (m, 1H), 3.32 (dd, 1H, J_1 = 5.5 Hz and J_2 = 14.0 Hz), 3.48 (d, 1H, J = 13.0 Hz), 3.54 (dd, 1H, J_1 = 7.5 Hz and J_2 = 14.0 Hz), 4.23 (dd, 1H, J_1 = 5.0Hz and J_2 = 7.0 Hz), 4.35 (d, 1H, J = 13.0 Hz), 6.27 (d, 1H, J = 8.0 Hz), 6.55-6.57 (m, 1H), 6.62-6.65 (m, 1H), 7.08-7.20 (m, 6H), 7.21-7.24 (m, 2H), 7.26-7.31 (m, 2H), 7.40-7.49 (m, 2H), 8.05 (d, 2H, J = 7.0 Hz), 8.24 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.3, 23.7, 30.9, 39.3, 57.3, 63.2, 70.6, 71.2, 120.6, 123.3, 126.1, 126.3, 127.4, 127.5, 127.9, 128.7, 128.8, 129.5, 130.8, 131.4, 131.5, 132.3, 133.3, 133.6, 134.1, 137.7, 142.7, 170.9, 178.5, 180.3. HRMS (FAB) [M+H] calcd. for $C_{35}H_{33}N_3O_3Ni$ 602.1954, found 602.1960.

41b. R_f = 0.64 (1:1 acetone/hexanes). mp. 240-242 °C. $[\alpha]_D^{25}$ -1680 (*c* 0.0105, $CDCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.61-1.70 (m, 1H), 2.02-2.05 (m, 1H), 2.06 (s, 3H), 2.25-2.33 (m, 1H), 2.60-2.66 (m, 1H), 3.11 (dd, 1H, J_1 = 5.5 Hz and J_2= 14.0 Hz), 3.26 (dd, 1H, J_1 = 6.0 Hz and J_2 = 14.0 Hz), 3.49 (d, 1H, J = 13.5 Hz), 3.57 (dd, 1H, J_1 = 3.0 Hz and J_2 = 9.0 Hz), 3.98 (d, 1H, J = 13.5 Hz), 4.01-4.05 (m, 1H), 4.22 (t, 1H, J = 6.0 Hz), 6.53-6.56 (m, 1H), 6.70-6.73 (m, 2H), 7.08-7.10 (m, 1H), 7.13-7.23 (m, 4H), 7.27-7.31

(m, 2H), 7.32-7.36 (m, 1H), 7.38-7.52 (m, 4H), 7.64 (d, 2H, J = 8.0 Hz), 8.55 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.5, 23.5, 31.0, 38.2, 57.0, 60.2, 69.0, 71.4, 120.7,123.4, 126.0, 126.1, 127.3, 127.5, 128.0, 128.8, 129.0, 129.6, 130.9, 131.6, 131.9, 132.7, 132.9, 133.9, 134.0, 134.4, 138.2, 143.1, 171.1, 178.7, 181.9. HRMS (FAB) [M+H] calcd. for $C_{35}H_{33}N_3O_3Ni$ 602.1954, found 602.1946.

41c. Bisalkylation product: R_f = 0.70 (1:1 acetone/hexanes). mp. 282-284 °C. $[\alpha]_D^{25}$ +2603 (*c* 0.00948, $CDCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.61-1.69 (m, 1H), 1.89 (s, 3H), 2.00-2.13 (m, 2H), 2.19-2.22 (m, 1H), 2.24-2.33 (m, 2H), 2.40 (s, 3H), 3.16-3.12 (m, 1H), 3.22 (d, 1H, J = 12.0 Hz), 3.33 (d, 1H, J = 14.5 Hz), 3.38-3.42 (m, 3H), 4.35 (d, 1H, J = 12.5 Hz), 6.30 (d, 1H, J = 7.5 Hz), 6.44-6.46 (m, 1H), 6.51-6.54 (m, 1H), 7.05-7.09 (m, 3H), 7.17-7.27 (m, 3H), 7.32-7.38 (m, 4H), 7.40-7.49 (m, 4H), 7.60-7.62 (m, 1H), 7.66 (d, 1H, J = 7.5 Hz), 7.98-8.00 (m, 1H), 8.25 (d, 2H, J = 8.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.8, 20.3, 23.0, 30.4, 43.6, 43.7, 58.3, 64.1, 70.2, 79.9, 120.2, 123.6, 125.7, 126.0, 126.1, 126.4, 127.1, 127.4, 127.5, 127.7, 128.0, 128.8, 129.1, 130.4, 131.3, 131.4, 131.6, 131.9, 133.6, 134.0, 135.0, 136.0, 136.5, 136.8, 138.7, 142.3, 171.2, 179.5, 180.4. HRMS (FAB) [M+H] calcd. for $C_{43}H_{41}N_3O_3Ni$ 706.2580, found 706.2578.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*)-2',6'-dimethyl phenylalanine (α-(*S*)-NiDmpBPB, 42a). m.p. 122-124°C. R_f = 0.35 (acetone/hexanes, 1:1). $[\alpha]_D^{25}$ +2437 (*c* 0.02002, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 2.08-2.12 (m, 1H), 2.14 (s, 6H), 2.27-2.33 (m, 1H), 2.57-2.66 (m, 1H), 2.76-2.80 (m, 1H), 3.51-3.57 (m, 2H), 3.53 (d, 1H, J = 12.9 Hz), 3.91-3.97 (m, 1H), 4.11 (dd, 1H, J = 10.5 Hz, J = 14.0 Hz), 4.30 (dd, 1H, J = 4.0 Hz, J = 10.5 Hz), 4.46 (d, 1H, J = 12.5 Hz), 5.55 (d, 1H, J = 7.4 Hz),

6.41-6.43 (m, 2H), 6.56-6.60 (m, 1H), 6.82 (d, 2H, J = 7.6 Hz), 6.93-7.00 (m, 2H), 7.06-7.16 (m, 3H), 7.28-7.38 (m, 4H), 8.07 (d, 2H, J = 7.1 Hz), 8.22 (d, 1H, J = 8.7 Hz). ^{13}C-NMR ($CDCl_3$) δ 20.0, 24.2, 30.6, 37.5, 57.1, 63.0, 70.3, 70.4, 120.6, 123.2, 126.0, 126.9, 127.4, 128.1, 128.3, 128.6, 128.8, 128.9, 129.0, 131.4, 132.3, 132.4, 133.1, 133.3, 133.8, 137.8, 142.3, 171.0, 178.8, 180.0. HRMS (FAB) $[M + H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2100.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*R*)-2',6'-dimethyl phenylalanine (α-(*R*)-NiDmpBPB, 42b). m.p. 295-297 °C. R_f = 0.47 (acetone/hexanes, 1:1). $[\alpha]_D^{25}$ −1481(*c* 0.0280, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.85-1.94 (m, 1H), 1.98 (s, 6H), 2.22-2.30 (m, 1H), 2.87-2.92 (m, 1H), 3.34 (dd, 1H, J_1 = 3.0 Hz, J_2 = 14.0 Hz), 3.43 (d, 1H, J = 13.0 Hz), 3.94 (d, part of AB, 1H, J_{AB} = 9.0 Hz), 4.02 (t, 1H, J = 13.6 Hz),), 4.29 (dd, 1H, J = 3.5 Hz, J = 10.5 Hz),), 4.29 (dd, 1H, J = 3.5 Hz, J = 10.5 Hz), 4.34 (d, 1H, J = 12.0 Hz), 5.41 (d, 1H, J = 6.5 Hz), 6.54-6.56 (d, 1H, J = 8.5 Hz), 6.62-6.65 (m, 1H), 6.81 (d, 2H, J = 7.5 Hz), 6.92-6.95 (m, 1H), 6.98-7.01 (m, 1H), 7.11-7.12 (m, 1H), 7.22-7.23 (m, 1H), 7.31-7.33 (m, 2H), 7.46-7.49 (m, 1H), 7.52-7.55 (m, 2H), 7.92 (d, 1H, J = 7.5 Hz), 8.61 (d, 1H, J = 9.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.7, 22.7, 29.6, 36.7, 58.6, 60.0, 68.5, 70.4, 120.6, 123.1, 125.7, 126.8, 127.1, 128.1, 128.5, 128.6, 128.9, 129.1, 129.2, 131.9, 132.5, 132.6, 133.2, 133.4, 134.1, 138.3, 142.7, 171.5, 179.0, 181.1. HRMS (FAB) $[M + H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2105.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*)-(4'-*O*-benzyl)-2',6'-dimethyltyrosine (α-(*S*)-NiDmtBPB, 43a). R_f = 0.43. m.p. 112-114 °C. $[\alpha]_D^{25}$ +1472° (*c* 0.01958, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 8.22(d, 1H, J = 8.4 Hz), 8.06 (d, 2H, J = 6.8 Hz),

7.41-7.25 (m, 10H), 7.14-7.02 (m, 3H), 6.90-6.78 (m, 1H), 6.62-6.54 (m, 1H), 6.57 (s, 2H), 6.42 (d, 1H, J = 8.3 Hz), 5.66 (d, 1H, J = 7.4 Hz), 4.96 (s, 2H), 4.30 (d, 1H, J = 12.6 Hz), 4.25(dd, 1H, J_1 = 9.9 Hz, J_2 = 4.3 Hz), 4.04-3.91 (m, 2H), 3.56-3.43 (m, 4H), 2.72-2.59 (m, 2H), 2.40-2.28 (m, 1H), 2.08 (s, 6H). ^{13}C-NMR ($CDCl_3$) d 179.7, 178.5, 170.5, 156.9, 142.0, 138.8, 136.8, 133.4, 133.2, 132.9, 131.9, 131.0, 128.7, 128.5, 128.4, 128.2, 128.0, 127.7, 127.5, 127.1, 127.0, 125.7, 124.6, 122.9, 120.2, 114.4, 77.2, 70.1, 69.2, 62.7, 56.9, 36.7, 30.3, 23.9, 19.9. HRMS (FAB) $[M+H]^+$ calcd. for $C_{43}H_{42}O_4N_3Ni$ 722.2529 , found 722.2524.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*R*)-(4'-*O*-benzyl)-2',6'-dimethyltyrosine (α-(*R*)-NiDmtBPB, 43b). R_f = 0.62. m.p. 130-132 °C. $[\alpha]_D^{25}$ −1094° (*c* 0.01384, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 8.61 (d, 1H, J = 8.25 Hz), 7.89 (d, 2H, J = 6.1 Hz), 7.55-7.23 (m, 12H), 7.11-7.06 (m, 1H), 6.87-6.83 (m, 1H), 6.68-6.63 (m, 1H), 6.57-6.46(m, 1H), 6.47 (s, 2H), 5.55 (s, 1H), 4.98 (s, 2H), 4.35 (d, 2H, J = 13.3 Hz), 4.23 (d, 1H, J = 7.8 Hz), 3.91-3.89 (m, 2H), 3.45 (d, 1H, J = 12.9 Hz), 3.27 (d, 1H, J = 13.6 Hz), 2.92-2.82 (m, 1H), 2.32-2.18 (m, 2H), 2.17-2.06 (m, 1H), 1.94 (s, 6H). ^{13}C-NMR ($CDCl_3$) δ 181.2, 179.1, 171.3, 157.2, 142.8, 139.7, 137.0, 134.1, 133.4, 132.6, 131.9, 129.2, 129.1, 128.9, 128.6, 128.5, 128.1,127.8, 127.3, 127.1, 125.7, 125.1, 123.1, 120.6, 114.7, 70.7, 69.5, 68.5, 60.0, 58.5, 36.2, 29.7, 22.7, 20.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{43}H_{42}N_3O_4Ni$ 722.2529, found 722.2524.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*R*)-2'-methylphenylalanine (44a). R_f = 0.36 (1:1 acetone/hexanes). m.p. 205-207 °C. $[\alpha]_D^{25}$ +1671 (*c* 0.00869, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.96-1.99 (m, 1H), 2.02-2.07 (m, 1H), 2.04 (s, 3H), 2.46-

2.51 (m, 1H), 2.59-2.65 (m, 1H), 3.04-3.08 (m, 1H), 3.27-3.29 (m, 1H), 3.30-3.33 (m, 1H), 3.41 (dd, 1H, J_1 = 5.5 Hz and J_2 = 9.0 Hz), 3.46 (d, 1H, J = 10.5 Hz), 3.53 (dd, 1H, J_1 = 6.0 Hz and J_2 = 10.5 Hz), 4.22-4.24 (m, 1H), 4.33 (d, 1H, J = 10.5 Hz), 6.27 (d, 1H, J = 6.5 Hz), 6.55-6.57 (m, 1H), 6.61-6.63 (m, 1H), 7.07-7.13 (m, 5H), 7.14-7.16 (m, 1H), 7.19-7.23 (m, 1H), 7.28-7.31 (m, 3H), 7.43-7.48 (m, 2H), 8.06 (d, 2H, J = 6.0 Hz), 8.24 (d, 1H, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.4, 23.5, 30.7, 39.1, 57.1, 63.0, 70.3, 71.0, 120.4, 122.9, 125.8, 125.9, 127.2, 127.2, 127.6, 128.4, 128.5,128.6, 128.7, 128.8, 129.1, 130.6, 131.2, 131.3, 132.0, 133.0, 133.3, 133.4, 133.9, 133.9, 137.5, 142.5, 170.7, 178.3, 180.1. HRMS (FAB) $[M+H]^+$ Calcd. For $C_{35}H_{33}N_3O_3Ni$ 602.1954, found 602.1948.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*S*)-2'-methylphenylalanine (44b). m.p. 130-132 °C. $[\alpha]_D^{25}$ -1877 (*c* 0.02809, $CHCl_3$). R_f = 0.40 (1:1 acetone/hexanes). ^{1}H-NMR ($CDCl_3$) δ 1.62-1.72 (m, 2H), 2.03-2.04 (m, 1H), 2.06 (s, 3H), 2.26-2.31 (m, 1H), 2.60-2.65 (m, 1H), 3.12 (dd, 1H, J_1 = 4.5 Hz and J_2 = 11.5 Hz), 3.26 (dd, 1H, J_1 = 5.5 Hz and J_2 = 12.0 Hz), 3.50 (d, 1H, J = 6.5 Hz), 3.57 (dd, 1H, J_1 = 2.5 Hz and J_2 = 7.5 Hz), 3.99 (d, 1H, J = 11.5 Hz), 4.01-4.05 (m, 1H), 4.21-4.23 (m, 1H), 6.54 (d, 1H, J = 6.5 Hz), 6.70-6.73 (m, 2H), 7.08 (d, 1H, J = 3.5 Hz), 7.14-7.23 (m, 4H), 7.26-7.29 (m, 1H), 7.30-7.35 (m, 1H), 7.39-7.42 (m, 1H), 7.44-7.49 (m, 4H), 7.65 (d, 2H, J = 6.5 Hz), 8.56 (d, 1H, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.4, 23.4, 30.9, 38.0, 57.0, 60.1, 68.9, 71.3, 120.6, 123.4, 125.9, 126.0, 127.2, 127.4, 127.8, 128.7, 128.9, 129.5, 130.7, 131.5, 131.8, 132.6, 132.8, 133.8, 133.9, 134.3, 138.1, 143.0, 171.1, 178.6, 181.8. HRMS (FAB) $[M+H]^+$ calcd. for $C_{35}H_{33}N_3O_3Ni$ 602.1954, found 602.1956.

Ni(II) Complex of Schiff base of (*R*)-BPB with *bis*-(2-methylbenzyl)glycine (bisalkylation product, 44c). R_f = 0.50 (1:1 acetone/hexanes). m.p. 280-282 °C. $[\alpha]_D^{25}$ -1547 (*c* 0.02581, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.57-1.53 (m, 1H), 1.85 (s, 3H), 1.99-2.09 (m, 2H), 2.13-2.16 (m, 1H), 2.19-2.26 (m, 2H), 2.37 (s, 3H), 3.11-3.15 (m, 1H), 3.20 (d, 1H, *J* = 14.5 Hz), 3.31-3.39 (m, 4H), 4.29 (d, 1H, *J* = 10.5 Hz), 6.26 (d, 1H, *J* = 6.5 Hz), 6.42 (d, 1H, *J* = 7.0 Hz), 6.49 (d, 1H, *J* = 7.5 Hz), 7.01-7.07 (m, 3H), 7.14-7.20 (m, 3H), 7.30-7.34 (m, 4H), 7.37-7.44 (m, 4H), 7.57 (d, 1H, *J* = 5.5 Hz), 7.62 (d, 1H, *J* = 6.5 Hz), 7.95 (d, 1H, *J* = 7.0 Hz), 8.22 (d, 2H, *J* = 6.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.7, 20.2, 22.9, 30.3, 43.4, 43.6, 58.2, 64.1, 70.1, 79.8, 120.2, 123.5, 125.6, 126.0, 126.2, 127.1, 127.3, 127.4, 127.6, 127.8, 128.7, 128.8, 129.1, 130.3, 131.3, 131.5, 131.8, 133.5, 134.0, 134.8, 135.8, 136.3, 136.6, 138.6, 142.1, 171.1, 179.6, 180.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{43}H_{41}N_3O_4Ni$ 706.2580, found 706.2577.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*R*)-2',6'-dimethylphenylalanine (45a) R_f = 0.36 (1:1 acetone/hexanes). m.p. 253-255 °C. $[\alpha]_D^{25}$ -2460 (*c* 0.01416, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 2.09-2.15 (m, 1H), 2.13 (s, 6H), 2.26-2.31 (m, 1H), 2.56-2.65 (m 1H), 2.72-2.77 (m, 1H), 3.46-3.56 (m, 4H), 3.90-3.96 (m, 1H), 4.06-4.11 (m, 1H), 4.29 (dd, 1H, J_1 = 4.0 Hz and J_2 = 10.0 Hz), 4.41 (d, 1H, *J* = 12.5 Hz), 5.57 (d, 1H, *J* = 7.5 Hz), 6.41-6.43 (m, 1H), 6.54-6.57 (m, 1H), 6.80 (d, 2H, *J* = 7.5 Hz), 6.93-6.98 (m, 2H), 7.03-7.15 (m, 3H), 7.27-7.38 (m, 4H), 8.10 (d, 2H, *J* = 7.0 Hz), 8.19-8.21 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ 19.6, 23.9, 30.3, 37.1, 56.9, 62.7, 69.8, 70.1, 77.3, 120.2, 122.8, 125.6, 126.5, 127.0, 127.7, 127.9, 128.2, 128.3, 128.4, 128.5, 128.6,

131.0, 131.9, 132.0, 132.7, 133.1, 133.4, 137.4, 142.0, 170.6, 178.3, 179.6. HRMS (FAB) $[M+H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2114.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*S*)-2',6'-dimethylphenylalanine (45b). R_f = 0.50 (1:1 acetone/hexanes). m.p. 280 °C (decomposed). $[\alpha]_D^{25}$ +1762 (*c* 0.01320, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.85-1.94 (m, 1H), 1.98 (s, 6H), 2.05-2.11 (m, 1H), 2.22-2.33 (m, 2H), 2.87-2.92 (m, 1H), 3.34 (dd, 1H, J_1 = 3.5 Hz and J_2 = 14.5 Hz), 3.44 (d, 1H, J = 13.0Hz), 3.94 (dd, 1H, J_1 = 2.5 Hz and J_2 = 14.5 Hz), 4.02 (dd, 1H, J_1 = 10.5 Hz and J_2 = 14.0 Hz), 4.27-4.36 (m, 1H), 4.35 (d, 1H, J = 13.0 Hz), 5.41 (d, 1H, J = 6.5 Hz), 6.54-6.57 (m, 1H), 6.63-6.67 (m, 1H), 6.81-6.83 (m, 2H), 6.52-7.02 (m, 2H), 7.12-7.14 (m, 1H), 7.22-7.25 (m, 1H), 7.32-7.38 (m, 2H), 7.48-7.50 (m, 1H), 7.52-7.56 (m, 2H), 7.93 (d, 2H, J = 6.5 Hz), 8.62 (d, 1H, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.7, 22.7, 29.2, 29.7, 36.8, 58.6, 60.1, 68.6, 70.5, 120.7, 123.2, 125.8, 126.9, 127.2, 128.1, 128.5, 128.6, 128.7, 128.9, 129.2, 129.3,131.9, 132.6, 132.7, 133.3, 133.5, 134.2, 138.3, 142.8, 171.5, 179.1, 181.1. HRMS (FAB) $[M+H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2114.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*R*)-2',6'-dimethyltyrosine (46a). R_f = 0.34 (1:1 acetone/hexanes). m.p. 195-197 °C. $[\alpha]_D^{25}$ -2119 (*c* 0.00961, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 2.05-2.12 (m ,1H), 2.12 (s, 6H), 2.25-2.30 (m, 1H), 2.58-2.63 (m, 1H), 2.74-2.79 (m, 1H), 3.45-3.56 (m, 4H), 3.87-3.94 (m, 1H), 4.00-4.04 (m, 1H), 4.24 (dd, 1H, J_1 = 4.0 Hz and J_2 = 10.0 Hz), 4.45 (d, 1H, J = 12.5 Hz), 4.96-5.02 (m, 2H), 5.65 (d, 1H, J = 6.5 Hz), 6.42-6.44 (m, 1H), 6.47 (s, 2H), 6.58-6.61 (m, 1H), 6.86 (t, 1H, J = 7.5 Hz), 7.07-7.15 (m, 3H), 7.27-7.41 (m, 9H), 8.07 (d, 2H, J = 7.0 Hz), 8.22 (d,

1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 19.8, 22.5, 29.5, 35.9, 58.4, 59.9, 68.4, 69.3, 70.4, 114.1, 114.5, 120.4, 122.9, 124.8, 125.5, 126.9, 127.1, 127.6, 127.9, 128.2, 128.3, 128.4, 128.7, 128.9, 129.0, 131.6, 132.4, 133.1, 133.3, 133.9, 136.9, 139.5, 142.5, 157.0, 171.1, 178.9, 180.9. HRMS (FAB) $[M+H]^+$ calcd. for $C_{43}H_{42}N_3O_4Ni$ 722.2529, found 722.2538.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*S*)-2',6'-dimethyltyrosine (46b). R_f = 0.50 (1:1 acetone/hexanes). m.p. 205-207 °C. $[\alpha]_D^{25}$ +1406 (*c* 0.01390, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.83-1.92 (m, 2H), 1.94 (s, 6H), 2.02-2.09 (m, 1H), 2.20-2.31 (m, 2H), 2.84-2.90 (m, 1H), 3.27 (dd, 1H, J_1 = 6.5 Hz and J_2 = 13.5 Hz), 3.45 (d, 1H, J =13.0 Hz), 3.89-3.04 (m, 2H), 4.23 (dd, 1H, J_1 = 4.0 Hz and J_2 = 10.5 Hz), 4.29-4.30 (m, 1H), 4.98 (s, 2H), 5.55 (d, 1H, J = 5.5 Hz), 6.48 (s, 2H), 6.56-6.58 (m, 1H), 6.64-6.67 (m, 1H), 6.84-6.87 (m, 1H), 7.11 (d, 1H, J = 7.5 Hz), 7.21-7.27 (m, 1H), 7.28-7.45 (m, 6H), 7.46-7.58 (m, 3H), 7.90 (d, 2H, J = 7.5 Hz), 8.62 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 20.2, 24.1, 30.5, 36.9, 57.0, 62.9, 69.5, 70.3, 70.4, 114.7, 120.4, 123.1, 124.9, 126.0, 127.2, 127.3, 127.8, 127.9, 128.2, 128.4, 128.6, 128.7, 128.8, 128.9, 131.3, 132.1, 133.1, 133.2, 133.7, 137.0, 139.1, 142.2, 157.1, 170.7, 178.7, 179.9. HRMS $[M+H]^+$ calcd. for $C_{43}H_{42}N_3O_4Ni$ 722.2529, found 722.2538.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*R*)-3-methylphenylalanine (47a). R_f = 0.53 (acetone/hexanes, 1:1), m.p. 153-155 °C. $[\alpha]_D^{25}$ +2202 (*c* 0.02862, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.15 (d, 3H, J = 7.5 Hz), 1.41-1.46 (m, 1H), 1.77-1.82 (m, 1H), 1.92-1.97 (m, 1H), 2.21-2.25 (m, 2H), 2.78-2.87 (m, 2H), 3.26 (t, 1H, J = 8.8 Hz), 3.40 (d, 1H, J = 13.0 Hz), 4.12 (d, 1H, J = 3.0 Hz), 4.24 (d, 1H, J = 12.5 Hz),

6.65-6.68 (m, 1H), 6.71-6.73 (m, 1H), 7.03 (d, 1H, J = 7.5 Hz), 7.12-7.15 (m, 2H), 7.25-7.28 (m, 2H), 7.32-7.33 (m, 1H), 7.39-7.59 (m, 8H), 8.00 (d, 2H, J = 7.5 Hz), 8.30 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 18.3, 22.9, 30.7, 44.8, 57.2, 63.4, 70.2, 75.5, 120.3, 123.0, 125.9, 127.1, 127.5, 127.9, 128.5, 128.7, 128.8, 129.0, 129.4, 129.6, 131.4, 132.2, 133.1, 133.4, 134.3, 141.1, 142.9, 171.0, 177.3, 180.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{35}H_{33}N_3O_3Ni$ 602.1954, found 602.1974.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*S*)-3-methylphenylalanine (47b). R_f = 0.38 (acetone/hexanes, 1:1), m.p. 194-196 °C. $[\alpha]_D^{25}$ +2766 (*c* 0.02022, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.99 (d, 3H, J = 7.3 Hz), 2.08-2.20 (m, 2H), 2.59-2.66 (m, 1H), 2.90-2.96 (m, 1H), 3.47-3.56 (m, 3H), 3.58 (d, 1H, J = 12.8 Hz), 3.81-3.85 (m, 1H), 4.06 (d, 1H, J = 6.0 Hz), 4.46 (d, 1H, J = 12.7 Hz), 6.19 (d, 1H, J = 7.7 Hz), 6.54-6.56 (m, 1H), 6.61-6.64 (m, 1H), 6.72-6.74 (m, 2H), 7.07-7.14 (m, 5H), 7.15-7.32 (m, 4H), 7.43-7.47 (m, 2H), 8.05 (d, 2H, J = 7.3 Hz). 8.25 (d, 1H, J = 8.6 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 16.3, 23.3, 30.7, 45.5, 56.8, 63.1, 70.5, 76.1, 120.4, 123.0, 126.2, 126.7, 127.4, 127.8, 128.1, 128.3, 128.7, 129.9, 131.4, 132.1, 133.1, 133.5, 133.6, 140.9, 142.5, 170.5, 176.7, 180.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{35}H_{33}N_3O_3Ni$ 602.1954, found 602.1937.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*R*,3*S*)-3-methylphenylalanine (50b). R_f = 0.66 (acetone/hexanes, 1:1), m.p. 210-212 °C. $[\alpha]_D^{25}$ -1419 (*c* 0.02110, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.19-1.26 (m, 1H), 1.25 (d, 3H, J = 7.0 Hz), 1.32-1.38 (m, 1H), 1.81-1.86 (m, 1H), 2.07-2.13 (m, 1H), 2.45-2.51 (m, 1H), 2.94-2.99 (m, 1H), 3.34 (d, 1H, J = 14.0 Hz), 3.34-3.38 (m, 1H), 3.47 (d, 1H, J = 14.0 Hz), 3.76-3.80

(m, 1H), 4.11 (d, 1H, J = 3.5 Hz), 6.75-6.79 (m, 1H), 6.85-6.87 (m, 1H), 7.12-7.14 (m, 2H), 7.17-7.19 (m, 1H), 7.28-7.35 (m, 5H), 7.46-7.50 (m, 1H), 7.56-7.61 (m, 7H), 8.48 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 17.5, 23.6, 31.3, 45.4, 54.9, 59.2, 68.6, 75.9, 120.6, 123.5, 126.2, 127.2, 127.8, 127.9, 128.6, 128.7, 128.8, 129.2, 129.7, 130.0, 131.7, 131.9, 132.6, 133.7, 134.2, 141.1, 143.2, 170.8, 176.9, 181.8. HRMS (FAB) $[M+H]^+$ calcd. for $C_{35}H_{33}N_3O_3Ni$ 602.1954, found 602.1981.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*R*)-3-ethylphenylalanine (48a). R_f = 0.46 (acetone/hexanes, 1:1), m.p. 232-234 °C. $[\alpha]_D^{25}$ +1778 (*c* 0.02251, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.28 (t, 3H, J = 7.3 Hz), 1.39-1.45 (m, 1H), 1.61-1.66 (m, 1H), 1.70-1.79 (m, 2H), 1.94-1.99 (m, 1H), 2.13-2.20 (m, 2H), 2.54-2.57 (m, 1H), 2.79-2.84 (m, 1H), 3.24 (t, 1H, J = 8.8 Hz), 3.37 (d, 1H, J = 12.5 Hz), 4.22 (d, 1H, J = 12.5 Hz), 4.26 (d, 1H, J = 3.5 Hz), 6.64-6.70 (m, 2H), 7.08-7.14 (m, 3H), 7.25-7.28 (m, 2H), 7.33-7.37 (m, 3H), 7.41-7.60 (m, 6H), 8.00 (d, 2H, J = 7.5 Hz), 8.26 (d, 1H, J = 9.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 11.3, 22.9, 25.0, 30.6, 52.0, 57.3, 63.5, 70.3, 73.7, 120.2, 123.0, 125.9, 127.3, 127.4, 128.1, 128.5, 128.6, 128.7, 128.8, 128.9, 129.6, 129.8, 131.4, 132.1, 133.2, 133.3, 134.3, 140.2, 142.8, 170.6, 177.4, 180.2. HRMS (FAB) $[M+H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2134.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*S*)-3-ethylphenylalanine (48b). R_f = 0.31 (acetone/hexanes, 1:1), m.p. 243-245 °C. $[\alpha]_D^{25}$ +2628 (*c* 0.02600, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.86 (t, 3H, J = 7.5 Hz), 2.02-2.21 (m, 3H), 2.60-2.66 (m, 1H), 2.89-2.95 (m, 1H), 3.13-3.18 (m, 1H), 3.46-3.52 (m, 3H), 3.56 (d, 1H, J = 12.5 Hz), 3.63-3.67 (m, 1H), 4.08 (d, 1H, J =6.0 Hz), 4.44 (d, 1H, J = 13.0 Hz), 6.19 (d,

1H, J = 7.5 Hz), 6.52-6.54 (m, 1H), 6.61-6.64 (m, 1H), 6.74 (d, 2H, J = 7.0 Hz), 7.07-7.15 (m, 5H), 7.18-7.19 (m, 1H), 7.22-7.27 (m, 1H), 7.28-7.31 (m, 2H), 7.31-7.46 (m, 2H), 8.05 (d, 2H, J = 7.5 Hz), 8.21 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 12.5, 23.4, 23.6, 30.8, 54.3, 56.8, 63.2, 70.6, 76.0, 120.5, 123.0, 126.5, 126.9, 127.6, 128.3, 128.7, 128.8, 129.4, 131.5, 132.2, 133.1, 133.6, 133.7, 138.6, 142.5, 170.4, 177.2, 180.1. HRMS (FAB) $[M+H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2134.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*R*,3*S*)-3-ethylphenylalanine (51b). R_f = 0.58 (acetone/hexanes, 1:1), m.p. 138-140 °C. $[\alpha]_D^{25}$ -2197 (*c* 0.01079, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.34 (t, 3H, J = 7.3 Hz), 1.13-1.21 (m, 1H), 1.32-1.36 (m, 1H), 1.72-1.77 (m, 2H), 1.79-1.84 (m, 1H), 1.84-2.09 (m, 1H), 2.47-2.52 (m, 1H), 2.64-2.68 (m, 1H), 3.31-3.36 (m, 1H), 3.35 (d, 1H, J = 14.0 Hz),3.43 (d, 1H, J = 14.5 Hz), 3.78-3.82 (m, 1H), 4.28 (d, 1H, J = 3.5 Hz), 6.75-6.78 (m, 1H), 6.83-6.84 (m, 1H), 7.12-7.14 (m, 2H), 7.18-7.20 (m, 1H), 7.28-7.37 (m, 5H), 7.48-7.60 (m, 8H), 8.45 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 11.5, 23.7, 24.4, 31.4, 52.7, 55.0, 59.3, 68.7, 74.1, 120.7, 123.6, 126.3, 127.5, 127.8, 128.3, 128.6, 128.7, 128.8, 128.9, 129.3, 129.9, 130.5, 131.8, 132.0, 132.6, 133.7, 134.3, 140.5, 143.2, 170.6, 177.3, 181.8. HRMS (FAB) $[M+H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2104.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*R*)-3-*iso*butylphenylalanine (49a). R_f = 0.59 (acetone/hexanes, 1:1), m.p. 288-290 °C. $[\alpha]_D^{25}$ +2815 (*c* 0.02083, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.41 (d, 3H, J = 6.5 Hz), 0.61 (d, 3H, J = 6.6 Hz), 0.70-0.76 (m, 1H), 0.87-0.92 (m, 1H), 1.39-1.44 (m, 1H), 1.75-1.78 (m, 2H), 1.94-1.99 (m, 1H), 2.15-2.22(m, 3H), 2.72-2.76 (m, 1H), 2.79-2.84 (m, 1H),

3.23 (t, 1H, J = 8.8 Hz), 3.38 (d, 1H, J = 14.4 Hz), 4.15 (d, 1H, J = 3.2 Hz), 4.25 (d, 1H, J = 14.2 Hz), 6.63-6.70 (m, 2H), 7.07-7.08 (m, 1H), 7.11-7.14 (m, 2H), 7.24-7.28 (m, 2H), 7.33-7.38 (m, 3H), 7.43-7.60 (m, 6H), 7.99 (d, 2H, J = 7.1 Hz), 8.25 (d, 1H, J = 9.4 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 20.9, 23.0, 23.6, 24.7, 30.7, 41.1, 48.4, 57.3, 63.5, 70.3, 75.7, 127.2, 127.5, 127.6, 128.2, 128.6, 128.8, 129.0, 129.1, 129.6, 129.7, 130.0, 131.5, 132.2, 133.2, 133.4, 134.5, 139.3, 142.9, 170.7, 177.6, 180.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{38}H_{39}N_3O_3Ni$ 644.2423, found 644.2412.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*R*,3*S*)-3-*iso*butylphenylalanine (52b). R_f = 0.71 (acetone/hexanes, 1:1), m.p. 144-146 °C. $[\alpha]_D^{25}$ -1224 (*c* 0.02800, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.50 (d, 3H, J = 6.5 Hz), 0.63 (d, 3H, J = 6.6 Hz), 0.82-0.88 (m,1H), 0.99-1.04 (m, 1H), 1.13-1.21 (m, 1H), 1.32-1.39 (m, 1H), 1.79-1.84 (m, 1H), 2.05-2.18 (m, 2H), 2.45-2.50 (m, 1H), 2.83-2.87 (m, 1H), 3.32 (dd, 1H, J = 3.4 Hz, J = 9.7 Hz), 3.35 (d, 1H, J = 14.2 Hz), 3.48 (d, 1H, J = 14.2 Hz), 3.75-3.80 (m, 1H), 4.14 (d, 1H, J = 6.6 Hz), 6.75-6.78 (m, 1H), 6.82-6.84 (m, 1H), 7.12-7.13 (m, 1H), 7.18-7.19 (m, 1H), 7.26-7.37 (m, 5H), 7.46-7.59 (m, 8 H), 8.46 (d, 1H, J = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 21.1, 23.6, 23.7, 24.9, 31.4, 40.4, 49.1, 55.0, 59.3, 68.6, 76.1, 120.7, 123.5, 126.4, 127.3, 127.8, 128.3, 128.7, 128.9, 129.0, 129.3, 129.7, 131.8, 131.9, 132.6, 133.7, 134.4, 139.5, 143.3, 170.6, 177.3, 181.8. HRMS (FAB) $[M+H]^+$ calcd. for $C_{38}H_{39}N_3O_3Ni$ 644.2423, found 644.2412.

Ni(II) Complexes of Schiff base of (*S*)-BPB with (2*S*,3*S*)-2',6',β-trimethylphenylalanine (53a). R_f = 0.39 (1:1 acetone/hexanes). m.p. 253-255 °C. $[\alpha]_D^{25}$ +2702 (*c* 0.01239, $CHCl_3$). ^{1}H-NMR $CDCl_3$) δ 1.61-1.73 (m, 3H), 1.76 (s, 3H), 2.11-

2.16 (m, 2H), 2.28 (s, 3H), 2.52-2.56 (m, 1H), 2.74-2.78 (m, 1H), 3.38 (d, 1H, J = 10.5 Hz), 3.47-3.51 (m, 2H), 3.53-3.57 (m, 1H), 4.33-4.37 (m, 2H), 4.46-4.53 (m, 1H), 6.40-6.50 (m, 1H), 6.62-6.64 (m, 2H), 6.81 (d, 1H, J = 6.0 Hz), 6.90-6.97 (m, 2H), 7.05-7.09 (m, 1H), 7.25-7.29 (m, 4H), 7.42-7.48 (m, 2H), 8.13 (d, 2H, J = 6.0 Hz), 8.31 (d, 1H, J = 6.0 Hz). 13C-NMR ($CDCl_3$) δ 16.9, 20.9, 21.5, 23.9, 31.1, 42.1, 57.5, 63.4, 70.8, 73.4, 120.4, 122.8, 126.2, 126.7, 128.1, 128.6, 128.7, 128.8, 128.9, 129.1, 129.6, 130.8, 131.4, 132.5, 133.8, 134.0, 134.1, 136.7, 137.4, 137.5, 142.8, 171.4, 177.8, 180.4. $[M+H]^+$ calcd. for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2258.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*R*)-2',6',β-trimethylphenylalanine (53b). R_f = 0.30 (1:1 acetone/hexanes). m.p. 273-275 °C. $[\alpha]_D^{25}$ +2406 (*c* 0.02202, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.52 (d, 3H, J = 6.5 Hz), 1.59 (s, 3H), 2.09-2.14 (m, 1H), 2.32-2.37 (m, 1H), 2.64-2.70 (m, 1H), 2.73 (s, 3H), 2.81-2.85 (m, 1H), 3.48-3.52 (m, 2H), 3.90-3.95 (m, 1H), 4.43-4.45 (m, 2H), 5.23 (d, 1H, J = 6.5 Hz), 5.51-5.57 (m, 1H), 6.34-6.36 (m, 1H), 6.53-6.59 (m, 2H), 6.79-6.85 (m, 2H), 6.90-6.93 (m, 1H), 7.01-7.05 (m, 1H), 7.07-7.14 (m, 2H), 7.26-7.34 (m, 4H), 8.08 (d, 2H, J = 7.0 Hz), 8.16 (d, 1H, J = 7.5 Hz). 13C-NMR ($CDCl_3$) δ 17.7, 19.8, 22.0, 23.9, 30.6, 42.7, 57.0, 62.9, 70.5, 73.7, 120.5, 122.9, 126.0, 126.4, 127.5, 127.7, 128.1, 128.5, 128.7, 128.8, 128.9, 131.2, 131.3, 132.1, 132.9, 133.2, 133.8, 136.6, 137.4, 137.8, 142.2, 169.6, 177.5, 179.6. $[M+H]^+$ calcd. for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2265.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*R*,3*R*)-2',6',β-trimethylphenylalanine (57a). R_f = 0.32 (1:1 acetone/hexanes). m.p. 273-275 °C. $[\alpha]_D^{25}$ -2312 (*c* 0.00884, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.60-1.72 (m, 3H), 1.75 (s, 3H), 2.12-2.18

(m, 2H), 2.28 (s, 3H), 2.53-2.59 (m, 1H), 2.74-2.80 (m, 1H), 3.39 (d, 1H, J = 12.5 Hz), 3.47-3.51(m, 2H), 3.54-3.60 (m, 1H), 4.34-4.37 (m, 2H), 4.47-4.51 (m, 1H), 6.40-6.50 (m, 1H), 6.63 (d, 2H, J = 4.0 Hz), 6.81 (d, 1H, J = 7.0 Hz), 6.91-6.98 (m, 2H), 7.06-7.10 (m, 1H), 7.25-7.30 (m, 4H), 7.43-7.49 (m, 2H), 8.13 (d, 2H, J = 7.0 Hz), 8.29 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 16.6, 20.6, 21.2, 23.7, 29.0, 41.8, 57.2, 63.1, 70.5, 73.0, 120.2, 122.5, 125.9, 126.4, 127.8, 128.3, 128.4, 128.5, 128.6, 128.8, 129.3, 130.5, 131.1, 132.2, 133.4, 133.7, 133.8, 136.4, 137.0, 137.1, 142.4, 171.1, 177.5, 180.1. $[M+H]^+$ calcd. for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2280.

Ni(II) Complex of Schiff base of (*R*)-BPB with (2*R*,3*S*)-2',6',β-trimethylphenylalanine (57b). R_f = 0.40 (1:1 acetone/hexanes). m.p. 270-272 °C. $[\alpha]_D^{25}$ -2201 (*c* 0.00994, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.52 (d, 3H, J = 7.5 Hz), 1.59 (s, 3H), 1.96-2.15 (m, 1H), 2.30-2.38 (m, 1H), 2.65-2.71 (m, 1H), 2.80-2.85 (m, 1H), 3.48-3.52 (m, 3H), 3.89-3.97 (m, 1H), 4.43-4.45 (m, 2H), 5.22 (d, 1H, J = 7.5 Hz), 5.51-5.58 (m, 1H), 6.34-6.36 (m, 1H), 6.53-6.59 (m, 2H), 6.80-6.86 (m, 2H), 6.92 (t, 1H, J = 7.5 Hz), 7.02-7.15 (m, 3H), 7.26-7.35 (m, 4H), 8.08-8.10 (m, 2H), 8.15-8.17 (m, 1H). ^{13}C-NMR ($CDCl_3$) δ 17.70, 19.8, 22.1, 23.9, 42.6, 57.0, 62.9, 70.5, 73.7, 120.5, 122.9, 125.9, 126.4, 127.4, 127.6, 128.1, 128.5, 128.7, 128.8, 131.2, 131.3, 132.1, 132.9, 133.2, 133.8, 136.3, 137.4, 137.8, 142.2, 169.6, 177.5, 179.6. $[M+H]^+$ calcd. for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2261.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*)-2',6'-dimethyl-α-methylphenylalanine (α-(*S*)-NiTmpBPB, 61a). m.p. 224-225 °C. R_f = 0.46 (acetone/ hexanes, 1:1). $[\alpha]_D^{25}$ +2253 (c, 0.01988, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.94 (s, 3H),

1.95-2.00 (m, 1H), 2.06-2.11 (m, 1H), 2.38 (s, 6H), 2.44-2.51 (m, 1H), 2.55-2.58 (m, 1H), 3.10-3.15 (m, 1H), 3.37-3.41 (m, 1H), 3.44-3.49 (m, 1H), 3.53 (d, 1H, J = 12.5 Hz), 3.68 (d, 1H, J = 14.0 Hz), 3.96 (d, 1H, J = 14.5 Hz), 4.47 (d, 1H, J = 12.5 Hz), 6.29 (d, 1H, J = 8.0 Hz), 6.58-6.52 (m, 2H), 7.02-7.18 (m, 6H), 7.21-7.22 (m, 1H), 7.30-7.33 (m, 2H), 7.36-7.39 (m, 2H), 8.08 (d, 2H, J = 7.5Hz), δ 8.11 (d, 1H, J = 9.0 Hz). ^{13}C-NMR ($CDCl_3$) δ 21.6, 23.8, 27.8, 30.5, 42.5, 57.3, 63.5, 70.1, 80.4, 120.4, 123.2, 126.7, 127.1, 127.2, 127.8, 128.1, 128.8, 128.9, 130.3, 131.6, 131.9, 133.2, 133.4, 134.0, 136.8, 139.2, 141.9, 171.7, 180.1, 180.4. HRMS (FAB) [M + H]+ calcd. for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2262.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*R*)-2',6'-dimethyl-α-methylphenylalanine (α-(*R*)-NiTmpBPB, 61b). R_f =0.36 (acetone/hexanes, 1:1). m.p. 230-232 °C. $[\alpha]_D^{25}$ -228.0 (*c* 0.06058, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.11 (s, 3H), 1.71-1.69 (m, 1H), 1.79-1.72 (m, 1H), 2.22-2.18 (m, 1H), 2.28 (s, 6H), 2.53-2.45 (m, 2H), 3.26 (d, 1H, J = 14.4 Hz), 3.41 (d, 1H, J = 14.3 Hz), 3.50 (dd, 1H, J = 3.8 Hz, J = 9.6 Hz), 3.54 (d, 1H, J = 13.4 Hz), 3.97 (d, 1H, J = 13.3 Hz), 4.00-4.02 (m, 1H), 6.63-6.66 (m, 1H), 6.68 (d, 2H, J = 7.4 Hz), 7.08 (d, 2H, J = 7.5 Hz), 7.14-7.21 (m, 3H), 7.30-7.45 (m, 5H), 7.70 (d, 2H, J = 7.3 Hz), 8.20 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 21.4, 23.3, 28.2, 30.7, 42.6, 56.8, 61.1, 69.2, 79.8, 120.4, 123.6, 127.0, 127.2, 127.6, 127.7, 128.5, 128.7, 129.0, 129.5, 131.6, 131.8, 132.9, 133.6, 134.1, 137.1, 139.2, 141.9, 172.2, 180.2, 180.7. HRMS (FAB) $[M+H]^+$ calcd. for $C_{37}H_{37}N_3O_3Ni$ 630.2267, found 630.2287.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*)-4'-benzyloxy-2',6'-dimethyl-α-methyltyrosine (α-(*S*)-NiTmtBPB, 62a). m.p. 108-110 °C, $[\alpha]_D^{25}$ +1666.7 (*c* 0.0099, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.92 (s, 3H), 1.92-1.97 (m, 1H), 2.06-2.12 (m, 1H), 2.34 (s, 6H), 2.43-2.49 (m, 1H), 2.53-2.61 (m, 1H), 3.08-3.13 (m, 1H), 3.41-3.47 (m, 2H), 3.52 (d, 1H, *J* = 12.5 Hz),3.64 (d, H, *J* = 14.5 Hz), 3.84 (d, 1H, *J* = 14.5 Hz), 4.47 (d, 1H, *J* = 14.5 Hz), 5.02 (s, 2H), 6.39 (d, 1H, *J* = 7.0 Hz), 6.53-6.59 (m, 2H), 6.69 (s, 2H), 7.05-7.08 (m, 1H), 7.11-7.17 (m, 2H), 7.20-7.22 (m, 1H), 7.30-7.33 (m, 3H), 7.24-7.43 (m, 6H), 8.08-8.11(m, 3H).^{13}C-NMR ($CDCl_3$, DRX500) δ 21.9, 23.8, 27.8, 30.5, 42.0, 57.8, 63.6, 69.6, 70.1, 80.4, 115.0, 120.3, 123.2, 125.8, 126.7, 127.2, 127.4, 127.8, 127.9, 128.1, 128.5, 128.8, 128.9, 130.3, 131.5, 131.9, 133.4, 134.0, 136.9, 137.1, 140.6, 141.9, 157.3, 171.6, 180.1, 180.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{44}H_{43}N_3O_4Ni$ 736.2685, found 736.2695.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*R*)-4'-benzyloxy-2',6'-dimethyl-α-methyltyrosine (α-(*R*)-NiTmtBPB, 62b). m.p. 243-245 °C. $[\alpha]_D^{25}$ -372.8 (*c* 0.01725, $CHCl_3$). ^{1}H-NMR($CDCl_3$) δ 1.06 (s, 3H), 1.61-1.69 (m, 2H), 2.13-2.17 (m, 1H), 2.28 (s, 6H), 2.40-2.45 (m, 1H), 2.48-2.53 (m, 1H), 3.20 (d, 1H, *J* = 14.5 Hz), 3.32 (d, 1H, *J* = 14.5 Hz), 3.46-3.52 (m, 1H), 3.57 (d, 1H, *J* =13.5 Hz), 3.96 (d, 1H, *J* = 13.5 Hz), 4.01-4.05 (m, 1H), 4.93 (d, 1H, *J* = 11.5 Hz). 5.00 (d, 1H, *J* = 11.5 Hz), 6.63-6.69 (m, 2H), 6.81 (s, 2H), 6.78-6.81 (m, 1H), 7.17-7.22 (m, 2H), 7.33-7.47 (m, 11H0, 7.62-7.63 (m, 2H), 8.21 (d, 1H, *J* = 8.5 Hz). 13C-NMR (CDCl3) d 21.8, 23.5, 28.5, 30.9, 42.5, 56.8, 61.2, 69.4, 69.5, 80.2, 114.9, 120.6, 123.7, 126.8, 127.2, 127.3, 127.4, 127.6, 127.8, 127.9, 128.5, 128.6, 128.7, 128.8, 129.1, 129.8, 131.8, 131.9, 133.0, 133.9, 137.0,

137.4, 141.0, 142.1, 157.4, 172.1, 180.4, 180.9. HRMS (FAB) [M+H]+ calcd for $C_{44}H_{43}N_3O_4Ni$ 736.2685, found 736.2695.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*S*)-2,3-dimethylphenylalanine (63a). R_f = 0.36 (acetone/hexanes, 1:1), m.p. 277-279 °C. $[\alpha]_D^{25}$ +2095 (*c* 0.01250, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.67 (s, 3H), 1.66 (d, 3H, *J* = 6.7 Hz), 2.08-2.13 (m, 1H), 2.18-2.23 (m, 1H), 2.63-2.73 (m, 1H), 2.99-3.06 (m, 1H), 3.41-3.50 (m, 1H), 3.52-3.56 (m, 3H), 4.45 (d, 1H, *J* = 12.7 Hz), 4.85 (d, 1H, *J* = 7.7 Hz), 6.09-6.13 (m, 1H), 6.30-6.32 (m, 1H), 6.48-6.51 (m, 1H), 6.83-6.87 (m, 1H), 7.00-7.03 (m, 1H), 7.07-7.11 (m, 2H), 7.17-7.33 (m, 9H), 8.13 (d, 2H, *J* = 7.2 Hz), 8.21 (d, 1H, *J* = 8.7 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 16.7, 20.6, 23.1, 30.5, 52.8, 56.6, 63.0, 70.6, 81.9, 120.0, 122.2, 125.9, 126.8, 127.0, 127.1, 127.6, 128.0, 128.3, 128.4, 128.5, 129.2, 129.6, 131.0, 131.5, 133.1, 133.5, 135.7, 139.6, 141.4, 169.7, 178.5, 179.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2106.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*R*)-2,3-dimethylphenylalanine (63b). R_f = 0.43 (acetone/hexanes, 1:1), m.p. 121-123 °C. $[\alpha]_D^{25}$ +2254 (*c* 0.01680, $CHCl_3$), ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.15 (s, 3H), 1.43 (d, 3H, *J* = 7.0 Hz), 1.49-1.56 (m, 1H), 1.94-2.03 (m, 2H), 2.11-2.22 (m, 2H), 3.02-3.05 (m, 1H), 3.25 (dd, 1H, *J* = 7.9 Hz, *J* = 9.3 Hz), 3.48 (d, 1H, *J* = 12.6 Hz), 3.47-3.51 (m, 1H), 4.27 (d, 1H, 12.6 Hz), 6.54-6.60 (m, 2H), 7.03-7.05 (m, 1H), 7.07-7.09 (m, 1H), 7.10-7.16 (m, 1H), 7.27-7.51 (m, 11H), 8.01 (d, 2H, *J* = 7.1 Hz), 8.22 (d, 1H, *J* = 8.4 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 16.3, 22.9, 28.0, 30.2, 48.8, 57.3, 63.8, 69.9, 81.3, 120.1, 122.9, 127.1, 127.3, 127.6, 127.7, 127.8, 128.6, 129.2, 129.6, 130.9, 131.5, 131.8, 133.4, 133.9,

137.3, 142.3, 142.5, 171.8, 179.7, 180.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{36}H_{35}N_3O_3Ni$ 616.2110, found 616.2106.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*S*)-3-ethyl-2-methylphenylalanine (64a). m.p. 236-238 °C. R_f = 0.60 (acetone/hexanes, 1:1); $[\alpha]_D^{25}$ +2095 (*c* 0.01250. $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.67 (s, 3H), 0.92 (t, 3H, *J* = 7.8 Hz), 1.89-1.95 (m, 1H), 2.08-2.14 (m, 1H), 2.19-2.23 (m, 1H), 2.34-2.39 (m, 1H), 2.66-2.73 (m, 1H), 3.03-3.08 (m, 1H), 3.46-3.60 (m, 3H), 3.58 (d, 1H, *J* = 12.5 Hz), 4.49 (d, 1H, *J* = 13.0 Hz), 4.81 (d, 1H, *J* = 7.3 Hz), 5.81-5.84 (m, 1H), 6.29 (d, 1H, *J* = 8.0 Hz), 6.51 (t, 1H, *J* = 7.3 Hz), 6.85-88 (m, 1H), 7.04 (t, 1H, *J* = 7.8 Hz), 7.07-7.08 (m, 1H), 7.13 (t, 1H, *J* = 7.5 Hz), 7.22-7.26 (m, 6H), 7.28-7.32 (m, 3H), 8.10 (d, 2H, *J* = 7.5 Hz), 8.20 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$) δ 13.0, 21.9, 23.4, 23.5, 30.8, 50.8, 61.4, 63.4, 70.9, 82.5, 120.4, 122.6, 126.3, 127.3, 127.4, 127.5, 128.1, 128.5, 128.7, 128.9, 129.6, 131.4, 131.9, 133.3, 133.9, 136.0, 137.4, 141.8, 170.0, 179.2, 179.7. HRMS (FAB) $[M+H]^+$ calcd. for $C_{39}H_{37}N_3O_3Ni$ 630.2267, found 630.2265.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*S*)-3-*iso*butyl-2-methylphenylalanine (65a). R_f = 0.57 (acetone/hexanes, 1:1), m.p. 129-131 °C. $[\alpha]_D^{25}$ +1710 (*c* 0.02498, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.72 (s, 3H), 0.92 (d, 3H, *J* = 6.5 Hz), 0.98 (d, 3H, *J* = 6.5 Hz), 1.36-1.42 (m, 1H), 2.02-2.20 (m, 4H), 2.61-2.68 (m, 1H), 3.00-3.05 (m, 1H), 3.39-3.44 (m, 1H), 3.49-3.53 (m, 1H), 3.59-3.65 (m, 2H), 4.49 (d, 1H, *J* = 12.7 Hz), 4.98 (d, 1H, *J* = 7.5 Hz), 5.38-5.41 (m, 1H), 6.29-6.31 (m, 1H), 6.49-6.52 (m, 1H), 6.92-695 (m, 1H), 7.02-7.32 (m, 12H), 8.10 (d, 2H, *J* = 7.9 Hz), 8.21 (d, 1H, *J* = 8.7 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 21.1, 22.8, 23.8, 24.1, 25.8, 31.0,

39.0, 56.1, 57.0, 63.6, 70.9, 82.1, 120.3, 122.4, 126.3, 127.2, 127.4, 127.6, 128.0, 128.2, 128.6, 128.7, 128.8, 129.7, 131.4, 131.9, 133.3, 133.9, 136.2, 137.5, 141.8, 170.5, 179.3, 179.8. HRMS (FAB) $[M+H]^+$ calcd. for $C_{39}H_{41}N_3O_3Ni$ 658.2580, found 658.2574.

Ni(II) Complex of Schiff base of (*S*)-BPB with (2*S*,3*R*)-3-*iso*butyl-2-methylphenylalanine (65b). R_f = 0.50 (acetone/hexanes, 1:1), m.p. 246-248 °C. $[\alpha]_D^{25}$ + 1650 (*c* 0.01244, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.56 (d, 3H, *J* = 6.4 Hz), 0.76 (d, 3H, *J* = 6.6 Hz), 1.01-1.06 (m, 1H), 1.18 (s, 3H), 1.49-1.56 (m, 3H), 2.00-2.20 (m, 3H), 2.43-2.44 (m, 1H), 3.07-3.10 (m, 1H), 3.22-3.25 (m, 1H), 3.30 (dd, 1H, *J* = 3.0 Hz , *J* = 12.5 Hz), 3.49 (d, 1H, *J* = 13.0 Hz), 4.31 (d, 1H, *J* = 13.0 Hz), 6.54-6.60 (m, 2H), 7.05-7.11 (m, 2H), 7.17-7.20 (m, 1H), 7.28-7.34 (m, 4H), 7.39-7.50 (m, 7H), 8.00 (d, 2H, *J* = 7.5 Hz), 8.22 (d, 1H, *J* = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 20.7, 23.1, 24.1, 25.0, 29.7, 30.4, 38.1, 52.5, 57.4, 63.9, 70.1, 81.7, 120.2, 122.9, 127.1, 127.4, 127.8, 128.3, 128.7, 129.2, 130.3, 131.1, 131.6, 131.9, 133.4, 134.0, 137.5, 140.2, 142.3, 171.9, 179.3, 180.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{39}H_{41}N_3O_3Ni$ 658.2580, found 658.2594.

68b. R_f = 0.57 (1:1 acetone/hexanes). m.p. 234-236 °C. $[\alpha]_D^{25}$ + 2000 (*c* 0.0192, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.39 (t, 3H, *J* = 7.3 Hz), 0.99 (t, 3H, *J* = 7.3 Hz), 1.49-1.54 (m, 2H), 1.77 -1.83 (m, 1H), 1.91-1.97 (m, 1H), 2.04-2.12 (M, 3H), 2.17-2.21 (m, 1H), 2.96-3.00 (m, 1H), 3.19-3.22 (m, 2H), 3.36 (m, 1H, *J* = 12.5 Hz), 4.21 (d, 1H), J = 12.5 Hz), 6.52-6.54 (m, 1H), 6.58 (t, 1H, *J* = 7.8 Hz), 7.06-7.11 (m, 1H), 7.18 (t, 1H, J = 7.5 Hz), 7.28-7.34 (m, 3H), 7.42-7.53 (m, 9H), 8.02 (d, 1H, *J* = 8.5 Hz), 8.15 (d, 2H, *J* = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 9.88, 12.6, 21.8, 23.0, 29.7, 30.6, 53.8, 58.2,

64.6, 70.9, 86.8, 120.3, 123.4, 127.3, 127.4, 127.6, 128.3, 128.4, 128.6, 128.7, 128.8, 128.9, 129.5, 130.3, 131.4, 131.5, 133.6, 134.3, 137.2, 140.9, 142.2, 171.3, 180.0, 180.5. HRMS (FAB) $[M+H]^+$ calcd. for $C_{38}H_{39}N_3O_3Ni$ 644.2423, found 644.2411.

68a. R_f = 0.46 (1:1 acetone/hexanes). m.p. 258-260 °C. $[\alpha]_D^{25}$ + 3413 (*c* 0.00252, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.81 (t, 3H, *J* = 7.8 Hz), 0.85 (t, 3H, *J* = 7.8 Hz), 1.09-1.17 (m, 1H), 1.63-1.69 (m, 1H), 2.03-2.08 (m, 1H), 2.13-2.18 (m, 1H), 2.43-2.50 (m, 1H), 2.52-2.63 (m, 1H), 2.71-2.77 (m, 1H), 3.19 (dd, 1H, J_1 = 2.0 Hz and J_2 = 12.5 Hz), 3.27-3.30 (m, 1H), 3.47 (dd, 1H, J_1 = 6.0 Hz) and J_2 = 11.0 Hz), 3.64 (d, 1H, *J* =12.5 Hz), 3.71-3.76 (m, 1H), 4.15-4.20 (m, 1H), 4.43 (d, 1H, *J* = 12.5 Hz), 6.61-6.66 (m, 2H), 7.06-7.14 (m, 5H), 7.18-7.22 (m, 1H), 7.34-7.39 (m, 2H), 7.44-7.48 (m, 3H), 7.52-7.60 (m, 3H), 7.92 (d, 1H, *J* = 8.0 Hz), 8.20 (d, 2H, *J* = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) d9.1, 12.8, 23.1, 29.3, 29.7, 30.6, 32.7, 53.2, 57.5, 64.4, 70.9, 85.1, 120.7, 124.0, 126.8, 127.1, 127.4, 127.9, 128.3, 128.9, 129.0, 129.4, 129.5, 131.3, 131.5, 133.2, 134.2, 136.7, 137.4, 141.3, 172.3, 179.3, 180.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{38}H_{39}N_3O_3Ni$ 644.2423, found 644.2411.

69a. R_f = 0.42 (1:1 acetone/hexanes). m.p. 276-278 °C. $[\alpha]_D^{25}$ +724.2 (*c* 0.01496, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.79 (t, 3H, *J* = 7.3 Hz), 0.84 9t, 3H, *J* = 7.3 Hz), 1.02-1.08 (m, 1H), 1.16-1.33 (m, 1H), 1.50-1.56 (m, 2H), 2.02-2.14 (m, 2H), 2.41-2.52 (m, 1H), 2.53-2.60 (m, 1H), 2.70-2.78 (m, 1H), 3.18 (dd, 1H, J_1 = 3. 0 Hz and J_2 = 12.5 Hz), 3.22-3.32 (m, 1H), 3.43 (dd, 1H, J_1 = 6.5 Hz and J_2 = 10.5 Hz), 3.55 (d, 1H, *J* = 13.0 Hz), 3.73 (dd, 1H, J_1 = 6.5 Hz and J_2 = 10.5 Hz), 4.13-4.20 (m, 1H), 4.44 (d, 1H, *J* =12.5 Hz), 6.61-6.68 (m, 2H), 7.04-7.13 (m, 6H), 7.20-7.24 (m, 1H), 7.34-7.40 (m, 4H), 7.53-

7.60 (m, 2H), 7.93 (d, 1H, J = 8.5 Hz), 8.18 (d, 2H, J = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) d 12.8, 13.5, 17.8, 24.3, 29.7, 30.6, 41.2, 53.3, 57.4, 64.3, 70.8, 84.5, 120.7, 124.0, 126.8, 127.2, 127.4, 127.9, 128.3, 128.8, 128.9, 129.0, 129.3, 129.6, 131.4, 131.5, 133.2, 134.1, 136.7, 137.4, 141.4, 172.1, 179.4, 180.5. HRMS (FAB) $[M+H]^+$ calcd. for $C_{39}H_{41}N_3O_3Ni$ 658.2580, found 658.2580.

69b. R_f = 0.52 (1:1 acetone/hexanes). m.p. 250-253 °C $[\alpha]_D^{25}$ +986.0 (*c* 0.0388, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.41 (t, 3H, J = 7.3 Hz), 0.92 (t, 3H, J = 7.0 Hz), 1.29-1.46 (m, 2H), 1.48 -1.57 (m, 2H), 1.78-1.84 (m, 1H), 1.90-1.98 (m, 2H), 2.03-2.16 (m, 2H), 2.17-2.22 (m, 2H), 2.98-3.02 (m, 1H), 3.18-3.22 (m, 1H), 3.38 (d, 1H, J = 12.0 Hz), 4.09 (d, 1H, J = 12.5 Hz), 6.52-6.64 (m, 1H), 6.57-6.60 (m, 1H), 7.08-7.11 (m, 1H), 7.20 (t, 1H, J = 7.5 Hz), 7.31-7.37 (m, 3H), 7.38-7.43 (m, 1H), 7.42-7.55 (m, 8H), 8.06 (d, 1H, J = 8.5 Hz), 8.13 (d, 1H, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 12.6, 13.6, 18.3, 21.8, 23.0, 30.4, 39.3, 54.1, 58.1, 64.5, 70.8, 86.2, 120.3, 123.5, 127.3, 127.5, 127.6, 128.2, 128.3, 128.7, 128.8, 129.5, 130.3, 131.5, 131.6, 133.7, 134.2, 137.3, 140.8, 142.2, 171.2, 180.0, 180.5. HRMS (FAB) $[M+H]^+$ calcd. for $C_{39}H_{41}N_3O_3Ni$ 658.2580, found 658.2580.

(2*R*,3*R*)-70a. R_f = 0.36 (1:1 acetone/hexanes). m.p. 228-230 °C. $[\alpha]_D^{25}$ -2614 (*c* 0.01530, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500M) δ -0.25-0.14 (m, 1H), 1.19-1.25 (m, 1H), 1.37-1.43 (m, 1H), 1.53-1.60 (m, 1H), 1.89-1.91 (m, 3H), 2.00-2.08 (m, 1H), 2.20-2.24 (m, 1H), 2.33-2.38 (m, 1H), 2.46-2.52 (m, 1H), 2.56-2.63 (m, 1H), 2.74-2.78 (m, 1H), 3.17-3.21 (m, 1H), 3.41-3.48 (m, 1H), 3.63-3.66 (m, 1H), 4.00 (d, 1H, J = 12.6 Hz), 4.57 (d, 1H, J = 12.6 Hz), 6.59 (d, 2H, J = 4.2 Hz), 7.00-7.01 (m, 1H), 7.05-7.10 (m, 1H),

7.22-7.25 (m, 1H), 7.32-7.49 (m, 6H), 7.92 (d, 1H, J = 8.4 Hz), 8.08 (d, 2H, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$, DRX600M) δ 15.3, 22.8, 23.3, 30.3, 33.0, 41.4, 49.1, 56.7, 63.3, 69.7, 86.1, 120.3, 123.4, 126.9, 127.4, 128.5, 128.6, 128.8,129.0, 130.6, 130.9, 131.4, 133.0, 135.6, 141.0, 171.5, 180.0, 182.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{32}H_{33}N_3O_3Ni$ 566.1954, found 566.1964.

(2*R*,3*S*)-70b. R_f = 0.40 (1:1 acetone/hexanes). m.p. 258-260 °C. $[\alpha]_D^{25}$ -2102 (*c* 0.01742, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 0.68-0.75 (m, 1H), 1.17-1.35 (m, 5H), 1.39-1.43 (m, 1H), 1.87-1.91 (m, 1H), 1.97-2.11 (m, 1H), 2.14-2.20 (m, 1H), 2.57-2.65 (m, 1H), 2.94-2.96 (m, 1H), 3.39-3.49 (m, 4H), 4.32-4.38 (m, 2H), 6.49 (d, 1H, J = 10.2 Hz), 6.57-6.60 (m, 1H), 6.80 (d, 1H, J = 9.0 Hz), 7.01-7.09 (m, 2H), 7.23-7.28 (m, 3H), 7.32 (d, 1H, J = 8.7 Hz), 7.40-7.49 (m, 1H), 8.09 (d, 2H, J = 8.4 Hz), 8.4 (d, 1H, J = 10.2 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 18.3, 22.0, 23.5, 29.3, 29.6, 30.8, 31.6, 49.7, 56.8, 63.2, 71.1, 87.9,120.2, 122.1, 127.8, 128.0, 128.3, 128.4, 128.5, 128.7, 128.9, 129.4, 131.2, 132.0, 133.4, 133.9, 137.2, 142.2, 168.6, 179.5, 179.8. HRMS (FAB) $[M+H]^+$ calcd. for $C_{32}H_{33}N_3O_3Ni$ 566.1954, found 566.1949.

(2*R*,3*S*)-71a. R_f = 0.45 (1:1 acetone/hexanes). m.p. 263-265 °C. $[\alpha]_D^{25}$ -4039 (*c* 0.00927, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ -0.08—0.01 (m, 1H), 1.32-1.44 (m, 2H), 1.49-1.59 (m, 2H), 1.84-1.88 (m, 1H), 2.17-2.31 (m, 2H), 2.35-2.43 (m, 2H), 2.59-2.67 (m, 2H), 3.23 (t, 1H, J = 8.7 Hz), 3.45 (d, 1H, J = 7.2 Hz), 3.76 (dd, 1H, J_1 = 5.4 Hz and J_2 = 13.2 Hz), 4.34 (d, 1H, J = 12.6 Hz), 6.61-6.66 (m, 2H), 7.07-7.10 (m, 1H), 7.19-7.22 (m, 2H), 7.30-7.33 (m, 2H), 7.40-7.43 (m, 2H), 7.47-7.56 (m, 5H), 7.68 (d, 1H, J = 7.2 Hz), 7.91 (d, 1H, J = 7.8 Hz), 8.05 (d, 2H, J = 7.2 Hz). ^{13}C-NMR ($CDCl_3$,

DRX500M) δ 22.3, 23.1, 30.3, 31.2, 41.6, 57.2, 58.5, 63.3, 69.6, 86.1, 120.1, 123.3, 127.1, 127.2, 127.4, 128.2, 128.3, 128.5, 128.6, 129.0, 129.2, 130.6, 130.8, 131.3, 132.8, 132.9, 135.6, 139.1, 141.4, 171.4, 180.0, 181.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{37}H_{36}N_3O_3Ni$ 628.2110, found 628.2101.

(2*R*,3*R*)-71b. R_f = 0.25 (1:1 acetone/hexanes). m.p. 205-207 °C. $[\alpha]_D^{25}$ -878.5 (*c* 0.01004, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 0.12-0.17 (m, 1H), 1.46-1.50 (m, 1H), 1.54-1.58 (m, 1H), 1.73-1.77 (m, 1H), 1.84-1.89 (m, 1H), 2.13-2.21 (m, 2H0, 2.29 (dd, 1H, J1 = 9.6 Hz and J2 = 13.8 Hz), 2.42-2.49 (m, 1H), 2.57-2.63 (m, 1H), 2.81-2.88 (m, 1H), 3.22 (d, 1H, J = 13.2 Hz), 3.34 (dd, 1H, J1 = 4.8 Hz and J2 = 10.8 Hz), 3.70-3.73 (m, 1H), 3.84 (d, 1H, J = 13.2 Hz), 3.94 (dd, 1H, J1 = 6.0 Hz and J2 = 12.6 Hz), 6.62-6.65 (m, 1H), 6.70 (d, 1H, J = 8.4 Hz), 7.12-7.14 (m, 1H), 7.26-7.31 (m, 3H), 7.35-7.39 (m, 2H), 7.11-7.48 (m, 6H), 7.56 (d, 2H, J = 7.8 Hz), 7.61 (d, 2H, J = 7.2 Hz), 7.98 (d, 1H, J = 8.4 Hz). ^{13}C-NMR ($CDCl_3$, DRX500M) δ 23.1, 23.4, 29.9, 30.7, 39.8, 565, 59.5, 61.3, 68.8, 86.6, 120.4, 123.8, 127.1, 127.2, 127.7, 128.2, 128.4, 128.5, 128.7, 128.8, 129.5, 129.7, 1341.1, 131.5, 132.8, 133.0, 136.1, 139.0, 131.5, 171.8, 181.1, 181.3. HRMS (FAB) $[M+H]^+$ calcd. for $C_{37}H_{36}N_3O_3Ni$ 628.2110, found 628.2106.

General procedure for decomposition of Ni(II)-coordinated Schiff bases. A solution of a diastereomerically pure Ni(II) complex after alkylation(15 mmole, 1eq.) in 20 mL of MeOH was slowly dropped into a mixture of 40 mL of 3*N* HCl and MeOH (1:1) at 70 °C. When the red color disappeared, the solvents was evaporated off. The solid residue was triturated with deionized water (3 x 50 mL) to remove HCl. The residue was

converted into its basic form with 100 mL of concentrated ammonium hydroxide. The solvent was evaporated off and the residue was triturated with water (3 x 50 mL). 100 mL of water and 100 mL of $CHCl_3$ were thoroughly mixed with the residue. (Sometimes, part of the product stayed at the interface between the aqueous phase and organic phase due to the limited solubility of the product in water. The undissolved product was filtered and washed thoroughly with water and $CHCl_3$. This part of the product was combined with the rest of product that would be obtained later. Also, the washings were combined with the main filtrate.) The $CHCl_3$ layer was separated from the aqueous layer and the aqueous layer was washed with $CHCl_3$ (2 x 100 mL). The chloroform layer was dried over $MgSO_4$ and evaporated to recover chiral ligand (BPB). Water was evaporated from the aqueous solution to obtain the crude product. The product was dissolved with minimal amount of 1:1 ethanol/water and applied to a Dowex 50X2 100 ion-exchange column. The column was washed with water until the eluent was neutral. Then it was washed with 1:4 water/concentrated ammonium hydroxide, the eluent was collected, and water was evaporated off to obtain the product. (If necessary, a mixture of 2:3:5 concentrated ammonium hydroxide/ethanol/water could be used as eluent).

(2*S*,3*S*)-2,3-Dimethylphenylalanine (72). Yield: 87%; m.p. 263-265 °C; $[\alpha]_D^{25}$ +67.42 (*c* 0.3472, MeOH); ^{1}H-NMR(d_6-DMSO/DCl) δ 0.94 (d, 3H, *J* = 5.4 Hz), 1.07 (s, 3H), 2.95 (q, 1H, *J* = 5.6 Hz), 6.84-6.91 (m, 5H). ^{13}C-NMR (d_6-DMSO/DCl) δ 17.7, 22.0, 47.5, 66.2, 131.0, 131.6, 132.2, 141.0, 174.6. HRMS (FAB) $[M+H]^+$ calcd. for $C_{11}H_{15}NO_2$ 194.1181, found 194.1186.

α-(*S*)-(4'-*O*-Benzyl)-2',6'-dimethyltyrosine (73). Yield: 85%. m.p.: 224-226 °C. $[\alpha]_D^{25}$ +58.08° (*c* 0.1927, MeOH). ^{1}H-NMR (d_6-DMSO/DCl): 7.25-7.16 (m, 5H), 6.52(s, 2H), 4.87 (s, 2H), 3.77 (dd, 1H, J_{BX} = 6.2 Hz J_{AX} = 10.4 Hz), 2.99 (ddd, ABX, 2H, J_{AX} = 10.5 Hz, J_{AB} = 14.2 Hz, J_{BX} = 8.2 Hz), 2.06 (s, 6H). ^{13}C-NMR (d_6-DMSO/DCl) δ 172.3, 158.3, 140.7, 138.6, 130.5, 129.9, 125.9, 116.2, 71.0, 53.3, 31.5, 21.5. HRMS (FAB) $[M+H]^+$ calcd. for $C_{18}H_{22}O_3N$ 300.1600, found 300.1605.

α-(*R*)-(4'-*O*-benzyl)-2',6'-dimethyltyrosine (74). Yield: 83%. m.p. 225-227 °C. $[\alpha]_D^{25}$ −56.32° (*c* 0.2968, MeOH). ^{1}H-NMR (CD_3OD/DCl) δ 7.08-6.96 (m, 5H), 6.35 (s, 2H), 4.68 (s, 2H), 3.59 (dd, 1H, J_{BX} = 6.4 Hz, J_{AX} = 10.0 Hz), 2.82 (ddd, 2H, J_{BX} = 6.4 Hz, J_{AX} = 10.0 Hz, J_{AB} = 14.0 Hz), 1.87 (s, 6H). ^{13}C-NMR (d_6-DMSO/DCl) δ 711.3, 157.3, 139.7, 137.6, 130.0, 128.4, 124.3, 114.7, 70.0, 52.0, 30.0, 19.9. HRMS (FAB) $[M+H]^+$ calcd. for $C_{18}H_{22}O_3N$ 300.1600, found 300.1605.

α-(*S*)-*O*-Benzyl-α,2',6'-trimethyltyrosine ((*S*)-75). Yield: 85%. m.p.: 210--212 °C. $[\alpha]_D^{25}$ +19.08° (*c* 0.5781, MeOH). ^{1}H-NMR (d_6-DMSO/DCl): 1.89 (s, 3H), 2.06 (s, 6H), 3.35 (d, 1H, *J* = 6.5 Hz), 3.41 (d, 1H, *J* = 6.2 Hz), 4.67 (s, 2H), 6.40(s, 2H), 7.06-7.15 (m, 5H). ^{13}C-NMR (d_6-DMSO/DCl) δ 170.3, 157.3, 138.7, 138.2, 130.0, 128.9, 127.9, 113.2, 69.0, 51.3, 31.5, 21.5, 18.2. HRMS (FAB) $[M + H]^+$ calcd. for $C_{19}H_{19}NO_3$ 314.1756, found 314.1764.

α-(*S*)-2',6'-Dimethylphenylalanine ((*S*)-76). Yield: 85%. m.p. 259-261 °C. $[\alpha]_D^{25}$ +31.12 (*c* 0.8444, MeOH). ^{1}H-NMR(d_6-DMSO/DCl) δ 2.77 (dd, another part of AB, J_{BX} = 6.5 Hz, J_{AB} = 14.5 Hz), 2.86 (dd, part of AB, 1H, J_{AX} = 11.0 Hz, J_{AB} = 14.0 Hz), 3.62

(dd, ABX, 1H, J_{AX} = 10.0 Hz, J_{BX} = 6.5 Hz), 6.62-6.56 (m, 3H). ^{13}C-NMR (d_6-DMSO/DCl) δ 23.1, 33.7, 55.2, 131.1, 132.0, 134.6, 140.9, 173.8. HRMS (FAB) [M + H]$^+$ calcd. for $C_{11}H_{15}NO_2$ 194.1181, found 194.1182.

α-(*S*)-α,2',6'-Trimethylphenylalanine ((*S*)-77). Yield: 87%. m.p. 243-245 °C. $[\alpha]_D^{25}$ +10.25 (*c* 1.026, MeOH). ^{1}H-NMR(d_6-DMSO/DCl) δ 1.13 (s, 3H), 1.86 (s, 6H), 2.95 (d, 1H, *J* = 5.5 Hz), 2.99 (d, 1H, *J* = 5.5 Hz), 6.95-7.00 (m, 3H). ^{13}C-NMR (d_6-DMSO/DCl) δ 21.3, 22.0, 36.5, 40.9, 126.6, 128.4, 133.7, 138.6, 172.2. HRMS (FAB) [M + H]$^+$ calcd. for $C_{12}H_{17}NO_2$ 208.1338, found 208.1344.

Hydrogenolysis of 73-75. **73-75** (10 mmol) was dissolved in 20 mL of concentrated HCl and 20 mL of MeOH in a hydrogenation vessel, Ar was bubbled through the solution for 5 min, 0.5 g of 10% Pd/C was added into the solution and Ar was bubbled through for 30 min more. The vessel was connected to a hydrogenator and shaken for 24 hr under H_2 of 40 psi. 24 hr later the catalyst was filtered off and washed with small amounts of methanol and water. The filtrate was evaporated and lyophilized to yield the crude product, containing the target amino acid and its methyl ester. The crude product was dissolved in 20 mL of concentrated HCl and refluxed for 6 hr. The mixture was evaporated *in vacuo* and the residue was triturated with water (3 x 50 mL) followed by lyophilization to afford quantitatively the target amino acid as a white powder.

(*S*)-α,2',6'-Trimethyltyrosine ((*S*)-α-TMT, 81). Yield: 99%. m.p. 224-226 °C. $[\alpha]_D^{25}$ +20.15 (*c* 0.9124, MeOH). ^{1}H-NMR(d_6-DMSO/DCl) δ 1.52 (s, 3H), 2.01 (s, 6H), 2.64 (d, *J* = 6.2 Hz), 2.70 (d, 1H, *J* = 6.3 Hz), 6.42 (s, 2H). ^{13}C-NMR (d_6-DMSO/DCl)

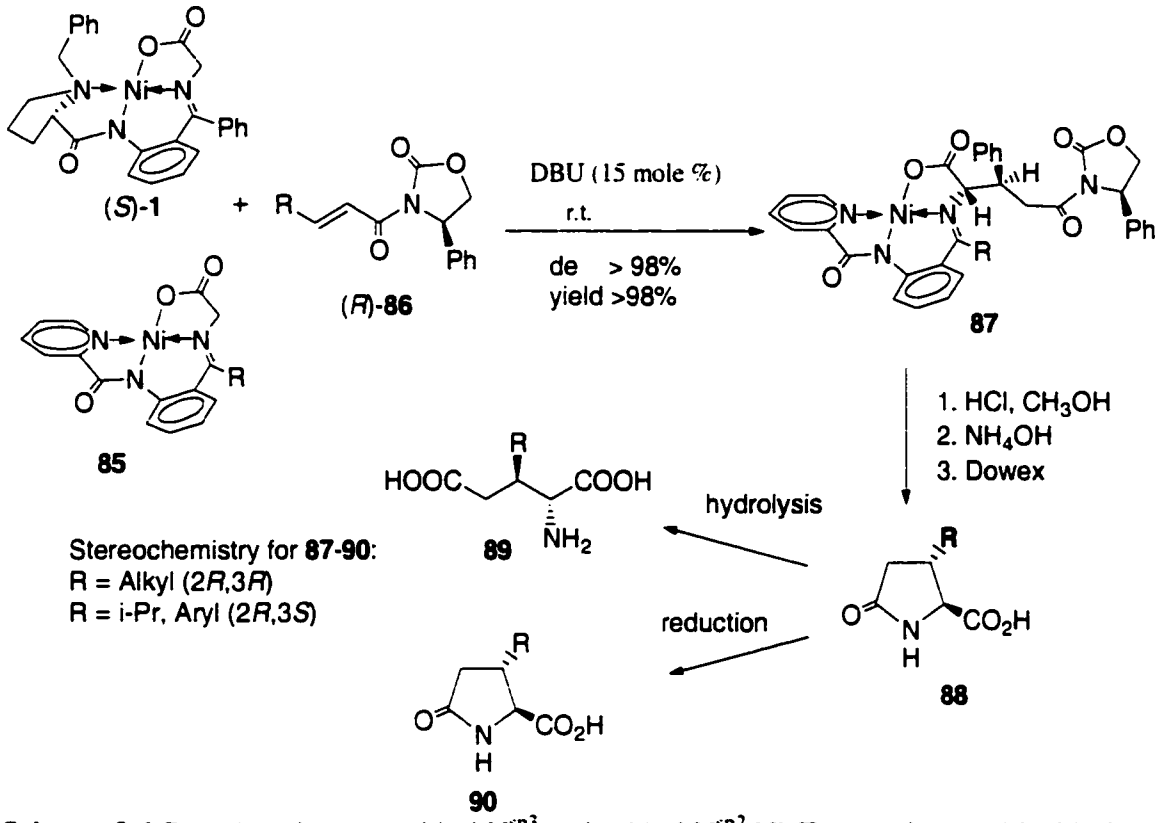
17.9, 19.4, 30.4, 53.0, 112.4, 123.6, 137.7, 155.3, 170.8, . HRMS (FAB) $[M + H]^+$ calcd. for $C_{12}H_{17}NO_3$ 224.1287, found 224.1276.

(*R*)-2',6'-Dimethyltyrosine (80). Yield: 99%. mp 248-250 °C. $[\alpha]_D^{25}$ – 40.29 (*c* 0.984, MeOH). $[\alpha]_D^{25}$ = –60.10 (*c* 0.81, AcOH). ^{1}H-NMR (CD_3OD) δ 5.51 (s, 2H), 4.00 (t, 1H, J = 8.0 Hz), 3.29 (dd, 1H, J_{BX} = 8.0 Hz, J_{AB} = 14.5 Hz), 3.08 (dd, 1H, J_{AX} = 8.0 Hz, J_{AB} = 14.5 Hz), 2.28 (s, 6H). ^{13}C-NMR (CD_3OD) δ 171.9, 157.3, 139.7, 123.6, 116.4, 54.0, 31.4, 20.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{11}H_{16}O_3N$ 210.1130, found 210.1134.

(*S*)-2',6'-Dimethyltyrosine (79). Yield: 99%. mp 247-249 °C. $[\alpha]_D^{25}$ + 39.41 (*c* 1.017, MeOH). $[\alpha]_D^{25}$ = + 60.56 (*c* 0.85, AcOH). ^{1}H-NMR (CD_3OD) δ 6.51 (s, 2H), 4.00 (t, 1H, J = 8.0 Hz). 3.29 (dd, 1H, J_{BX} = 8 Hz, J_{AB} = 14.5 Hz), 3.08(dd, J_{AX} = 8 Hz, J_{AB} = 14.5Hz), 2.28 (s, 6H). ^{13}C-NMR (CD_3OD) δ 171.8, 157.3, 139.7, 123.6, 116.4, 53.9, 31.4, 20.4. HRMS (FAB) $[M+H]^+$ for $C_{11}H_{16}O_3N$ 210.1130, found 210.1134.

Chapter 3. New Generation of Ni(II)-Complexes of Glycine Schiff Bases as Highly Reactive Nucleophilic Glycine Equivalents for Asymmetric, Organic Base-Catalyzed Michael Addition Reactions

Recently, via the rational design of a single-preferred transition state, others in our research group developed a new protocol for highly diastereoselective, room temperature, organic base-catalyzed Michael additions between nucleophilic glycine equivalents and α,β-unsaturated carboxylic acid derivatives.[166] In particular, glycine Ni(II)-complexes **1** and **85** (Scheme 3-1) readily reacted at room temperature in a DMF solution and in the presence of catalytic amounts (15 mole %) of DBU with chiral *N*-enoyl-4-phenyl-1,3-oxazolidin-2-ones **86** affording the corresponding addition products **87** in excellent chemical yields and with virtually complete diastereoselectivity. Decomposition of products **87** under mild reaction conditions afforded pyroglutamic acids **88** as well as recovery of the corresponding chiral auxiliary(ies) and glycine ligands which can be recycled and used to prepare starting complexes **1**, **85** and Michael acceptors **86**. Since pyroglutamic acids **88** can be easily transformed to glutamic acids **89** and prolines **90**, this method offers a convenient, practical and general approach to the whole family of χ-(chi)-constrained[17,124] five-carbon-atom amino acids as well as their CH_2-homologues. [189] While application of complexes **1** and **87** as nucleophilic glycine equivalents in the addition reactions with Michael acceptors **86** in some cases gave similar and synthetically useful results, there was a general noticeable difference in reactivity between **1** and **85**. Reactivity of the proline-derived complex **1** (N^{sp3}-complex) was substantially higher as

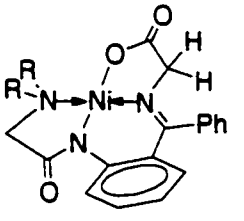


Scheme 3-1 Reactions between chiral N^{sp3} and achiral N^{sp2} Ni(II) complexes with chiral acceptors

compared with that of picolinic acid-derived complex **85** (N^{sp2}-complex), a fact that limits synthetic applications of the latter. On the other hand, the stereochemical outcome in the reactions of chiral complex **1** with chiral Michael acceptors **86** was shown to be completely controlled by the stereochemical preferences of the latter. Systematic studies of the reactions between complex **1** and Michael acceptors **86** revealed that chirality of **1** influenced only reaction rates featuring fast reactions between (*S*)-**1** and (*S*)-**86**, a match case, and slow reactions between (*S*)-**1** and (*R*)-**86**, a mismatch case. Since the chirality of the complex **1** plays no role in controlling the absolute configuration of the resultant

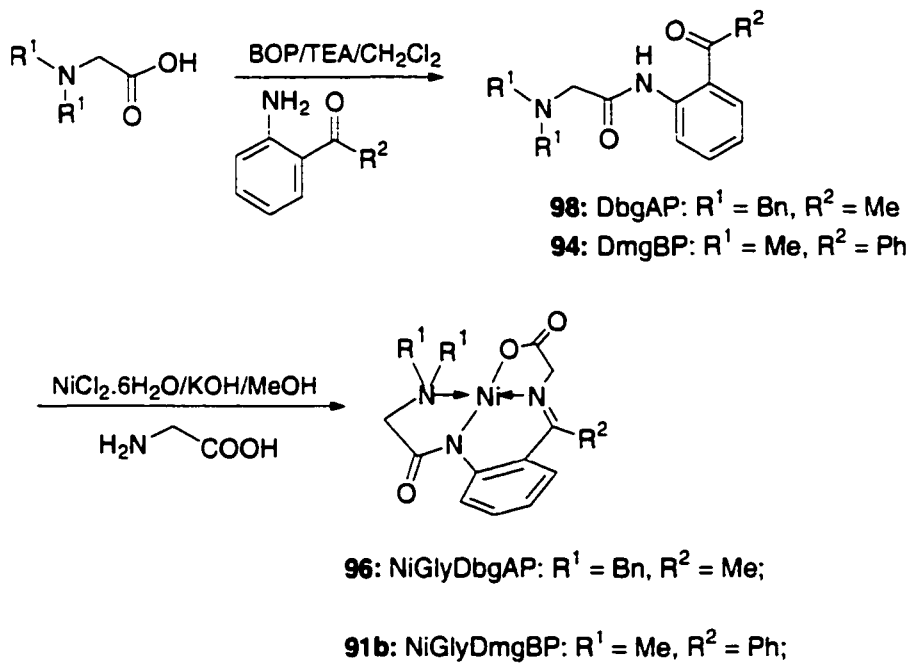
products **87** and moreover, slows down the rates of the mismatch case reactions, we felt that the application of chiral complex **1**, though extremely successful, is economically inappropriate. Therefore, we set for ourselves a goal to develop a new generation of achiral N^{sp3}-containing Ni(II)-complexes which would feature high reactivity like chiral complex **1**, but be much less expensive and synthetically more readily available. We now report our preliminary results on the design, synthesis and reactivity of such complexes which allow us to improve substantially the practicality and synthetic efficiency of our method.

One can assume that N^{sp3}-containing analogues of complex **1** could be prepared using achiral *N,N*-2,2-tetraalkyl-substituted glycine derivatives in the place of the (*S*)-proline (Fig. 3-1, complex **91a**). Unfortunately, it turned out that synthesis of these tetra-substituted glycine derivatives was far from straightforward and their commercial cost was even higher that that of (*S*)-proline. Therefore we considered a simpler, though risky, structural motif, the application of *N,N*-dialkyl-substituted glycines. Considering the structure of complex **91b**, one may expect that the methylene groups of both glycine



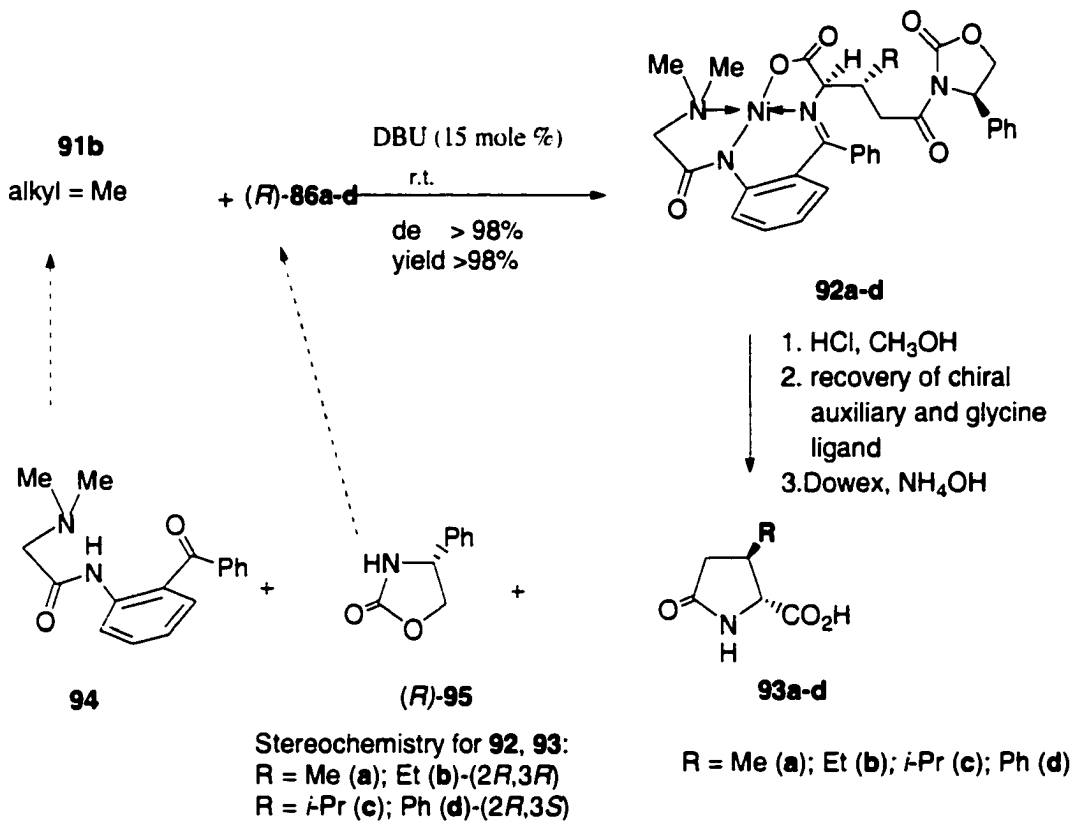
R = Bn (**91a**), R = Me (**91b**)

Figure 3-1 Design of achiral N^{sp3}-containing Ni(II)-complexes



Scheme 3-2. Synthesis of **96** and **91b**

fragments in **91b** could be involved in the addition with Michael acceptors **86**, casting a reasonable doubt on successful application of complex **91a** as a "mono-glycine" equivalent. However, taking into account the very mild reaction conditions we use in our method, we hoped that, provided by the Schiff base function, higher CH-acidity of the methylene group of the releasable glycine, as compared with that of the *N,N*-dialkyl-substituted, non-releasable, glycine, would be sufficient to achieve complete regioselectivity in the reactions of complex **91b** (Scheme 3-2) with Michael acceptors **86**. To check on this possibility we prepared the corresponding complex **91b** (alkyl = Me) (Scheme 3-3), according to our standard procedure, using the commercially available and cheap *N,N*-dimethylglycine in the place of (*S*)-proline. First we studied the reaction



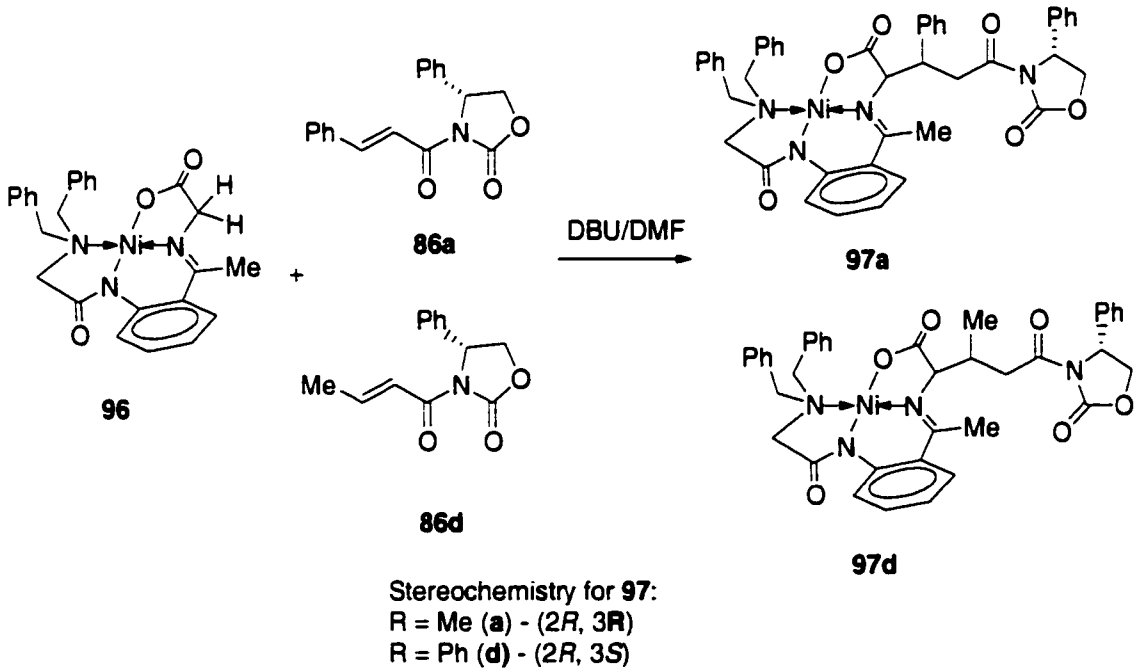
Scheme 3-3. Reactions between achiral *N,N*-dimethyl N^{sp3} Ni(II) complexes with chiral acceptors

between complex **91b** (alkyl = Me) and crotonyl-derived (*R*)-configured Michael acceptor **86a** (Scheme 2). To our satisfaction, the reaction was completed in ca. 10 min, the rate comparable to that of the addition between (*S*)-**1** and **86a**, and much faster than the reaction between **85** and **86a** (50 min). Most importantly, the regio- and stereoselectivity of the addition was found to be virtually complete and the target **92a** was isolated in 94% yield. The reaction of ethyl-containing (*R*)-**86b** with complex **91b** (Alkyl = Me) proceeded at slightly lower rate (15 min), as a result of the increased steric bulk of

(*R*)-**86b**, featuring the same virtually complete regio- and stereoselectivity (97% yield of **92b**). Of particular interest was the reaction of complex **91b** (alkyl = Me) with isopropyl-containing Michael acceptor **86c**. Previously we had shown that the picolinic acid-derived complex **85** did not react with bulky **86c** at all, while the addition between the proline-derived complex **1** and **86c**, even in the match case, occurred at a relatively low rate (30 min). Surprisingly, the reaction between **91b** (alkyl = Me) and (*R*)-**86c** proceeded at a higher rate than that of complex (*S*)-**1** reaction furnishing a single reaction product **92c** (97% yield), as determined by ^{1}H-NMR (500 MHz) on the crude reaction mixture. Successful application of complex **91b** (alkyl = Me) in the Michael addition with aromatic α,β-unsaturated acid-derived acceptors **86** was demonstrated by the reaction between **91b** (Alkyl = Me) and *N*-cinnamyl derivative **86d**. The addition occurred at a relatively high rate (20 min) affording the diastereomerically pure target **92d** in 95% yield.

Under the standard reaction conditions[160] products **92a-d** were decomposed to afford pyroglutamic acids **83a-d** as well as glycine ligand **94** and chiral auxiliary (*R*)-**95**, which were recycled and used for the preparation of the starting compounds **91b** (alkyl = Me) and **86**. These results strongly suggest that application of new achiral complexes of type **91b** could be a valuable synthetic alternative to the currently used picolinic acid-derived complex **85**. Despite the presence of two potentially reactive glycine methylene groups in **91b**, virtually complete regioselectivity can be achieved due to the mild reaction conditions. With these results in hand, we gained further success designing several other complexes of type **91b** to improve further the reactivity and synthetically

desirable physical properties, such as crystallinity and solubility of the complexes in various organic solvents. One of the most promising examples is complex **96** (Schemes 3-2 and 3-4) derived from commercially available *N*,*N*-dibenzylglycine and *o*-aminoacetophenone. The presence of the *N*,*N*-dibenzylglycine fragment in **96** was found to increase the solubility of the complex, while substitution of the ketimine phenyl by the methyl group (application of *O*-aminoacetophenone) had a dramatic effect on the reaction rates. Thus the addition reaction of complex **96** with *N*-crotonyl- and cinnamyl-derived Michael acceptors **86a,d**, conducted under the standard condition, occurred almost instantly (less then 5 min) furnishing the products **97a,d** in over 95% yield with virtually complete regio- and stereoselectivity.



Scheme 3-4. Reactions between achiral *N*,*N*-dibenzyl N^{sp3} Ni(II) complexes with chiral acceptors

The preliminary results reported here clearly demonstrate that the new generation of achiral N^{sp3}-complexes of type **91b**, **96** can be successfully used as nucleophilic glycine equivalents in the asymmetric Michael addition reactions with chiral 3-[(*E*)-*N*-enoyl]-4-phenyl-1,3-oxazolidin-2-ones (**86**). Despite the presence of two reactive glycine methylene groups in complexes **91b**, **96**, their reactions proceeded with virtually complete regioselectivity affording the corresponding addition products as sole diastereomers in excellent chemical yields. Synthetic characteristics of new complexes of type **91b**, **96** render them superior over currently in use complexes **1** and **85**, in particular in terms of reactivity, cost and thus overall practicality and efficiency of preparing χ-(chi)-constrained amino acids by our method. The general features of the Ni-complexes described here should allow rational control of the new complex's reactivity and physical properties and preparation of immobilized derivatives for solid-phase synthesis.

3.1 Experimental

Synthesis of DmgBP (94). To a solution of *N*,*N*-disubstituted glycine (100 mmol), 2-aminobenzophone or 2-aminoacetophenone (100 mmol, 1.0 eq), and 44.2 g of BOP (50 mmol, 1.0 eq) in 40 mL of freshly distilled dichloromethane was added 55.8 mL of TEA (300 mmol, 3.0 eq.). The reaction mixture was stirred at room temperature for 24 hr and quenched by adding 100 mL of 1.0*N* hydrochloric acid with agitation. The aqueous layer was separated from the organic layer and washed with methylene chloride (2 x 100 mL). The combined methylene chloride layers were dried over $MgSO_4$ and evaporated *in*

vacuo to afford the crude product. The product was purified on a silica gel column with 1:9 ethyl acetate/hexanes. Oily liquid. Yield: 50%. ^{1}H-NMR ($CDCl_3$, DRX600M) δ 2.41 (s, 6H), 3.12 (s, 3H), 7.09-7.11 (m, 1H), 7.45-7.74 (m, 4H), 8.83 (d, 1H, J = 7.0 Hz), 11.5 (s, 1H). 13C-NMR ($CDCl_3$, DRX600M) δ 46.0, 64.0, 121.8, 122.4, 128.3, 129.9, 132.4, 132.9, 133.6, 138.7, 139.2, 170.3, 198.4. HRMS (FAB) [M+H]+ calcd. for $C_{17}H_{18}N_2O_2$ 283.1447. found 283.1448

Synthesis of NiDbgAP and NiDmgBP. The solution of DbgAP or DmgBP generated above, $NiCl_2.6H_20$ (2.0 eq.), potassium (7.0 eq.) and glycine (5.0 eq.) in methanol was stirred at 40 °C until the starting ligand **94** was completely consumed as monitored by TLC (1:1 acetone/hexanes). The reaction mixture was poured into ice water (four times the volume of methanol) with 1% acetic acid. The precipitate was filtered, washed with water and dried *in vacuo* to afford the crude product. The crude product was dissolved in chloroform and the precipate was filtered and washed with chloroform. The filtrate was evaporated and dried *in vacuo* to afford the product. Recrystallization from acetone/hexanes gave the pure product.

NiGlyDbgAP (96). m.p. 233.0-234.0 °C. ^{1}H-NMR (CDCl3, 300MHz) δ 2.37 (s, 3H), 3.42 (s, 2H), 3.48 (d, 2H, J = 12.7 Hz), 4.19 (s, 2H), 4.44 (d, 2H, J = 12.7 Hz), 6.85-6.91 (m, 1H), 7.10-7.15 (m, 1H), 7.33-7.47 (m, 7H), 7.86 (d, 1H, J = 8.5 Hz), 8.08 (d, 4H, J = 8.3 Hz). ^{13}C-NMR (CDCl3, 300MHz) δ 19.0, 60.0, 60.1, 63.8, 121.2, 124.7, 126.0, 128.7, 128.9, 129.2, 131.4, 132.0, 132.7, 141.0, 169.4, 177.0. HRMS (FAB) $[M+H]^+$ calcd. for $C_{26}H_{26}N_3NiO_3$ 486.1328, found 486.1324.

NiGlyDmgBP (91b). Yield: 27%. m.p. 320 °C (decomposed). ^{1}H-NMR ($CDCl_3$, DRX600M) δ 2.61 (s, 6H), 3.44 (s, 2H), 3.71 (s, 2H), 6.79-6.82 (m, 1H), 6.89 (d, 1H, J = 8.0 Hz), 7.04 (d, 2H, J = 6.0 Hz), 7.34-7.37 (m, 1H), 7.50-7.54 (m, 3H), 8.65 (d, 1H, J = 7.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX600M) δ 49.7, 61.2, 67.8, 121.4, 124.2, 125.3, 125.9, 129.6, 129.7, 132.7, 133.6, 134.6, 142.5, 172.1, 176.1, 177.2. HRMS (FAB) $[M+H]^+$ calcd. for $C_{19}H_{19}N_3O_3Ni$ 396.0858, found 396.0859.

General procedure for the reactions of NiGlyDbgAP and NiGlyDmgBP with Michael acceptors 86a-d. To a suspension of Ni(II)-complex NiGlyDbgAP or NiGlyDmgBP (0.500 mmol) in DMF (2.0 mL) was added the Michael acceptor **86** (0.525 mmole, 1.05 eq). After stirring the mixture for 10 min at ambient temperature, DBU (13-15 mol%) was added. The reaction end point was reached when the starting complex completely disappeared. The mixture was poured into icy 5% aqueous acetic acid (80 mL). The precipitate was filtered off, thoroughly washed with water and dried *in vacuuo* to afford addition products. The stereoselectivities were determined by high resolution NMR. The pure products were obtained by column chromatography (1:1 acetone/ chloroform as eluent).

92a. Yield: 94%. R_f = 0.49 (1:1 acetone/$CHCl_3$). m.p. 286-288 °C. $[\alpha]_D^{25}$ -2455 (*c* 0.01871, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 1.90 (d, 3H, J = 7.0 Hz), 2.36 (s, 3H), 2.54-2.59 (m, 1H), 2.67 (s, 3H), 2.97 (dd, 1H, J_1 = 13.0 Hz and J_2 = 18.0 Hz), 3.03 (d, 1H, J = 16.0 Hz), 3.10 (dd, 1H, J_1 = 7.5 Hz and J_2 = 18.5 Hz), 4.02 (d, 1H, J = 5.0 Hz), 4.05 (d, 1H, J = 16.0 Hz), 4.17(dd, 1H, J_1 = 3.5 Hz and J_2 = 9.0 Hz), 4.52 (t, 1H, J = 7.8 Hz), 5.25 (dd, 1H, J_1 = 3.5 Hz and J_2 = 8.8 Hz), 6.75 (d, 2H J = 4.0 Hz), 6.95 (d, 1H, J =

8.0 Hz), 7.20-7.24 (m, 3H), 7.28-7.36 (m, 5H), 7.41-7.44 (m, 1H), 8.66 (d, 1H, J = 8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 17.0, 29.2, 34.0, 38.8, 48.9, 49.5, 57.3, 67.8, 69.8, 73.6, 121.1, 123.1, 125.9, 126.6, 127.1, 128.1, 128.4, 128.8, 128.9, 129.0, 129.6, 132.7, 133.4, 134.1, 139.1, 142.5, 153.3, 170.3, 171.5, 175.4, 177.2. HRMS (FAB) $[M+H]^+$ calcd. for $C_{32}H_{33}N_4O_6Ni$ 627.1754, found 627.1752.

92b. Yield: 97%. R_f = 0.57 (1:1 acetone/$CHCl_3$). m.p. 223-225 °C $[\alpha]_D^{25}$ -2652 (*c* 0.02227, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.81 (t, 3H, J = 7.8 Hz), 1.67-1.73 (m, 1H), 2.38 (s, 3H), 2.65 (s, 3H), 2.81-2.87 (m, 3H), 3.09 (d, 1H, J = 16.0 Hz), 3.30 (dd, 1H, J_1 = 9.5 Hz and J_2 = 19.5 Hz), 3.93 (d, 1H, J = 6.5 Hz), 4.14 (d, 1H, J = 11.5 Hz), 4.32 (t, 1H, J = 8.5 Hz), 5.24 (dd, 1H, J_1 = 3.0 Hz and J_2 = 8.5 Hz), 6.75-6.80 (m, 2H), 7.04-7.05 (m, 1H), 7.20 (d, 1H, J = 7.5 Hz), 7.25-7.26 (m, 2H), 7.29-7.50 (m, 7H), 8.71 (d, 1H, J = 9.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 11.1, 23.9, 29.2, 35.7, 40.4, 48.7, 49.4, 53.8, 57.3, 67.8, 70.1, 72.5, 121.1, 123.0, 125.8, 126.4, 127.5, 128.5, 128.6, 128.9, 129.0, 129.7, 132.8, 133.4, 134.3, 139.2, 142.5, 153.6, 171.2, 171.5, 175.6, 177.8. HRMS (FAB) [M+H]+ calcd. for $C_{33}H_{35}N_4O_6Ni$ 641.1910, found 641.1912.

92c. Yield: 97%. R_f = 0.70 (1:1 acetone/$CHCl_3$). m.p. 238-240 °C $[\alpha]_D^{25}$ +2610 (*c* 0.02390, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 0.24 (d, 3H, J = 7.0 Hz), 0.89 (d, 3H, J = 6.5 Hz), 2.34-2.39 (m, 1H), 2.41 (s, 3H), 2.53 (d, 1H, J = 18.0 Hz), 2.61 (s, 3H), 3.04 (d, 1H, J = 16.0 Hz), 3.13 (dd, 1H, J_1 = 10.5 Hz and J_2 = 19.0 Hz), 3.54 (t, 1H, J = 10.0 Hz), 3.70 (d, 1H, J =10.5 Hz), 3.96-4.00 (m, 2H), 4.11 (d, 1H, J = 15.5 Hz), 5.31 (dd, 1H, J_1 = 3.5 Hz and J_2 = 6.5 Hz), 6.81(t, 1H, J = 7.0 Hz), 7.19-7.21 (m, 1H), 7.24 (d, 1H, J = 7.5 Hz), 7.27-7.29 (m, 2H), 7.31-7.43 (m, 4H), 7.47-7.56 (m, 3H), 8.12 (d, 1H, J =

8.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 15.6, 21.6, 27.5, 29.2, 31.5, 45.3, 48.5, 49.3, 57.3, 68.1, 70.5, 72.2121.4, 122.8, 125.6, 126.0, 128.0, 128.6, 129.1, 129.2, 129.4, 129.9, 130.0, 133.5, 134.6, 139.3, 142.6, 163.8, 171.5, 172.7, 176.0, 178.6. HRMS (FAB) $[M+H]^+$ calcd. for $C_{34}H_{37}N_4O_6Ni$ 655.2067, found 655.2067.

92d. Yield: 95%. R_f = 0.42 (1:1 acetone/hexanes). m.p. 340 °C (decomposed) $[\alpha]_D^{25}$ +2256 (*c* 0.01382, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ δ 1.67 (s, 3H), 2.45 (s, 3H), 2.63 (d, 1H, 15.5 Hz), 3.24 (d, 1H, *J* = 15.5 Hz), 3.25-3.30 (m, 2H), 3.80-3.86 (m, 1H), 4.08 (dd, 1H, J_1 = 4.0 Hz and J_2 = 9.0 Hz), 4.36 (d, 1H, *J* = 4.0 Hz), 4.54 (t, 1H, *J* = 8.8 Hz), 5.12 (dd, 1H, J_1 = 3.5 Hz and J_2 = 8.5 Hz), 6.73-6.78 (m, 2H), 6.92-6.94 (m, 2H), 7.01 (d, 1H, *J* = 7.5 Hz), 7.20-7.28 (m, 4H), 7.35 (t, 1H, *J* = 7.5 Hz), 7.49-7.52 (m, 4H), 7.54-7.60 (m, 3H), 8.49 (d, 1H, *J* = 8.0 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 36.9, 44.8, 47.2, 49.3, 57.1, 66.7, 69.4, 73.3, 76.7, 120.7, 122.9, 125.3, 126.4, 126.8, 127.5, 127.8, 127.9, 128.5, 128.6, 128.8, 128.9, 129.5, 130.2, 132.5, 133.2, 133.7, 138.4, 138.8, 142.6, 153.0,169.5,171.0, 174.4, 176.4. HRMS (FAB) $[M+H]^+$ calcd. for $C_{37}H_{35}N_4O_6Ni$ 689.1910, found 689.1900.

97a. Yield: 95%. R_f = 0.79 (1:1 acetone/$CHCl_3$). m.p. 198-200 °C $[\alpha]_D^{25}$ -1689 (*c* 0.01399, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, DRX500) δ 2.26 (d, 3H, *J* = 7.0 Hz), 2.50 (s, 3H), 2.76-2.81 (m, 1H), 2.99 (d, 1H, *J* = 14.5 Hz), 3.00 (d, 1H, *J* = 18.5 Hz), 3.19 (d, 1H, *J* = 12.5 Hz), 3.83 (dd, 1H, J_1 = 10.0 Hz and J_2 = 18.5 Hz), 3.98 (d, 1H, *J* = 13.5 Hz), 4.11 (t, 1H, *J* = 13.5 Hz), 4.19 (dd, 1H, J_1 = 3.0 Hz and J_2 = 9.0 Hz), 4.29 (d, 1H, *J* = 5.0 Hz), 4.53 (t, 1H, *J* =8.8 Hz), 4.58 (d, 1H, *J* = 13.5 Hz), 5.38 (dd, 1H, *J1* = 3.0 Hz and *J2* = 8.3 Hz), 6.83-6.86 (m, 1H), 7.02-7.05 (m, 1H), 7.08-7.11 (m, 1H), 7.25-7.29 (m, 4H), 7.33-

7.43(m, 6H), 7.47-7.49 (m, 3H), 7.75 (d, 1H, J = 8.5 Hz), 8.24 (d, 2H, J = 7.5 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 17.7, 18.5, 33.8, 38.7, 57.4, 62.3, 63.1, 64.6, 70.1, 72.5, 121.1, 124.0, 125.7, 126.2, 128.6, 128.7, 128.8, 128.9, 129.1, 130.6, 131.3, 131.5, 131.9, 133.9, 139.2, 140.8, 153.5, 168.8, 171.6, 176.1, 177.5. HRMS (FAB) $[M+H]^+$ calcd. for $C_{39}H_{39}N_4O_6Ni$ 717.2223, found 717.2220.

97d. Yield: 97%. R_f = 0.76 (1:1 acetone/$CHCl_3$). m.p. 208-210 °C $[\alpha]_D^{25}$ +1303 (*c* 0.02172, CHCl3). ^{1}H-NMR ($CDCl_3$, DRX500) δ 2.55 (d, 1H, J = 16.5 Hz), 2.65 (s, 3H), 2.91 (d, 1H, J = 12.5 Hz), 3.23 (d, 1H, J = 14.5 Hz), 3.42 (d, 1H, J = 14.0 Hz), 3.55 (d, 1H, J = 16.0 Hz), 3.58-3.63 (m, 2H), 3.71 (d, 1H, J = 12.5 Hz), 4.24 (dd, 1H, J_1 = 2.5 Hz and J_2 = 8.5 Hz), 6.85 (t, 1H, J = 7.5 Hz), 6.97-7.00 (m, 2H), 7.14-7.19 (m, 4H), 7.23 (d, 2H, J = 7.0 Hz), 7.28-7.43 (m, 6H), 7.53 (t, 3H, J = 7.3 Hz), 7.62-7.67 (m, 3H), 7.74 (t, 1H, J = 7.8 Hz), 8.17 (d, 2H, J = 8.7 Hz). ^{13}C-NMR ($CDCl_3$, DRX500) δ 18.1, 36.9, 44.1, 57.4, 62.4,62.5, 62.7, 70.1, 72.6,120.8, 123.7, 125.5, 126.0, 128.0, 128.4, 128.5, 128.6, 128.7, 128.8, 129.0, 130.2, 130.9, 131.1, 131.3, 131.6, 134.1, 139.0, 139.6, 141.0, 153.4, 168.6, 171.4, 174.9, 176.7. HRMS (FAB) $[M+H]^+$ calcd. for $C_{44}H_{41}N_4O_6Ni$ 779.2380, found 779.2391.

Chapter 4. Design and Synthesis of Selective Peptide and Non-Peptide Ligands for the δ-Opioid Receptor

4.1 Introduction

4.1.1 Discovery of Opioid Receptors and their Peptide Ligands

It is now well-established and that at least three distinct subtypes of opioid receptors, designated μ, δ, and κ receptors, exist in the central nervous system and periphery[190,191] and that agonists of all receptor subtypes are known to produce antinociception. The cloning of the opioid receptors has revealed three gene products displaying pharmacological profiles consistent with the traditional classification of μ, κ, and δ receptor types. It is now well-established that opioid receptors belong to the rhodopsin subclass within the superfamily of G protein-coupled receptors (GPCRs). Structurally, GPCRs are transmembrane (TM) proteins characterized by the presence of seven transmembrane helices that are clustered in the form of a bundle. Within the family of opioid receptors, there is a high degree of sequence homology within the transmembrane region, while there is significant divergence in the sequence of the N-terminus and extracellular loops (Figure 4-1).[192-194]

The cloning of the opioid receptors has enabled two modes of investigation that greatly enhance the understanding of ligand-receptor interactions. The first is molecular modeling which can be used to generate protein models that can then be used for ligand docking experiments and identification of putative binding sites. The second mode is site-

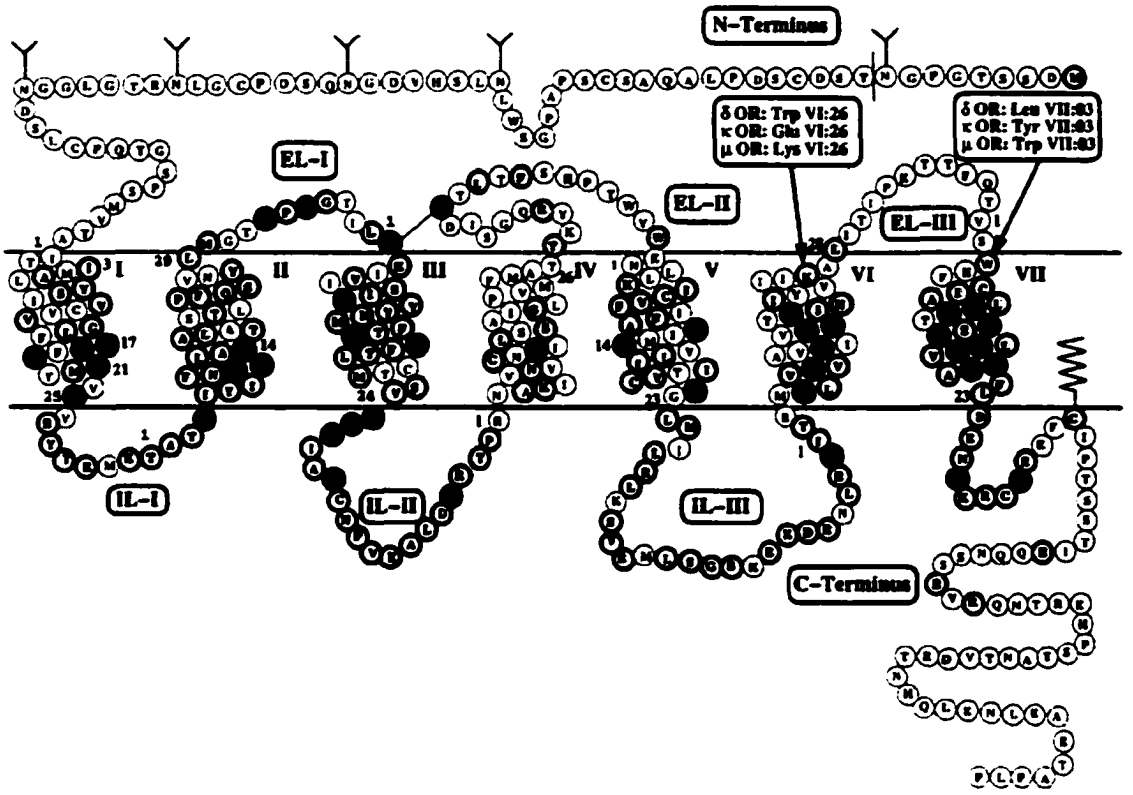


Figure 4-1. Homology between μ, δ, and κ opioid receptors and the localization of splice sites. Black lines represent the boundaries of the membrane. Circles contain the one-letter code for the given amino acid. Gray circles represent amino acids that are present in all three receptor types (μ, δ, and κ). Black circles represent residues highly conserved among the rhodopsin subclass of GPCRs. Each transmembrane region is indicated with a Roman numeral. The Arabic number in the membrane denotes the position of each residue from the N-terminal region of each helix using a generic numbering scheme (e.g. Trp VI:26 indicates the 26th position from the N-terminal end of TM VI) defined in the Experimental Section. Positions that were mutated in this study are indicated with arrows. IL = intracellular loop; EL = extracellular loop.[195]

directed mutagenesis experiments that are useful for determining the role of particular segments or amino acid residues in ligand recognition. Together, these two tools combined with ligand design and syntheses afford a powerful combination aimed at elucidating the structural basis of molecular recognition at opioid receptors.

The opioid system plays a major role in pain-control systems[196] and affects behavior, including motivation and rewarding.[197,198] It also modulates locomotor activity, learning and memory, neuroendocrine physiology, and autonomic and immune functions. The endogenous ligands for the μ, δ, and κ receptors are endorphins, enkephalins, and dynorphins, respectively. These opioid peptides share a common N-terminal sequence (NH_2-Tyr-Gly-Gly-Phe-Met/Leu-COOH), and are encoded by three different genes known as preproenkaphalin, proopiomelanocortin, and prodynorphin.[199-201] In addition to these endogenous peptide ligands, many interesting and useful selective peptide ligands for the opioid receptors have been developed and used extensively in studying the opioid biological activities. For the δ opioid receptor, the complete and highly selective agonists, DPDPE (*c*[DPen^2, DPen^5]enkephalin) and its analogues including *p*ClDPDPE (c[DPen^2, Phe(*p*Cl)^4, DPen^5]enkephalin) and [(2*S*,3*R*)TMT^1]DPDPE, have been developed. Deltrophin I (Tyr-DAla-Phe-Asp-Val-Val-Gly-NH_2) and Deltrophin II (Tyr-DAla-Phe-Glu-Val-Val-Gly-NH_2) also have been found to be potent and highly selective δ-agonists. The synthesized highly μ-selective peptide ligands include CTOP (DPhe-*c*[Cys-Tyr-DTrp-Arg-Thr-Pen]-Thr-NH_2, and TIPP[φ] (Tyr-Ticφ[CH_2NH]-Phe-Phe-OH) and its analogues. TIPP[φ] is also a potent and highly selective δ-antagonist. [D-Ala^3]Dynorphin A (Tyr-Gly-DAla-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-NH_2) was demonstrated as a highly potent and selective κ-agonist.

Opiates, the prototype of which is morphine, are potent analgesics and addictive drugs that act through opioid receptors.[202,203] Morphine and morphine-like compounds are widely used clinically as analgesics. However, it is also known that they induce

several unwanted side effects such as respiratory depression, dependence, constipation, euphoria and other toxicities. All of these side effects are primarily due to the fact that they are agonists at the μ receptor.

The development of potent and selective antagonist and agonist ligands for each of these opioid receptor subtypes has been the goal of medicinal chemists for many years because of their potential usefulness as pharmacological tools and as therapeutic agents.[204,205] The discovery of an opioid analgesic that acts at different opioid receptor subtypes may have the advantage of analgesia but without the unwanted side effects of morphine. Studies based on δ-selective opioid peptide ligands have suggested potential advantages over other opioid receptors.[206] However, the inherent inability for systemically administered peptides to be well-absorbed from the gastrointestinal tract and to cross the blood-brain barrier has encouraged the development of non-peptide δ ligands.[207]

4.1.2. Peptide and Non-Peptide Peptidomimetics: Rationales and Designs

Some classes of non-peptide ligands may have advantages as drug candidates, such as high oral bioavailability and higher permeability across the blood-brain barrier. Although native biologically active peptides have a great potential for medical application, they often need to be modified to overcome certain problems inherent in current drug delivery strategies. Some properties which are highly desired but not often present or optimized in the native ligands include: receptor/acceptor selectivity; high potency; biodistribution and bioavailability. These issues have been addressed by the

design of chemical "Trojan Horses" known as peptidomimetics.[20] Different people have different definition for them. One of the well-accepted definitions is that which Hruby gave in 1997:[208]

A peptidomimetic is an organic molecule, such as a peptide analogue or non-peptide ligand, that interacts with a receptor or acceptor in a similar chemical manner as the native peptide/protein ligand to effect the same biochemical (biological) activities. In the parlance of medicinal chemistry, both peptidomimetics and native ligands/proteins should share common pharmacophore elements.

While this term has been broadly used to describe compounds discovered through a variety of research strategies ranging from random screening and optimization to *de novo* design, the advocates of rational design do not favor its use to describe compounds found by screening. It would be more appropriate to describe a peptidomimetic at the molecular level as a designed compound whose pharmacophoric stereostructural elements mimic a peptide's pharmacophoric element in 3D space, and which mimic the binding, the biological agonist (or antagonist) activity, and the structure-activity relationships of a natural endogenous peptide ligand or peptide ligand with equivalent or superior bioactivity.[208]

A major but difficult goal of peptidomimetic design is the translation of three-dimensional (3D) pharmacophore information from a potent bioactive peptide to a small organic non-peptide ligand with the same agonist or antagonist biological properties. After advancements of many years, a *de novo* approach for peptidomimetic design has

been proposed as shown in Figure 4-2.[20] According to this approach, the very first step in the peptidomimetic design is to identify the biologically active peptides.

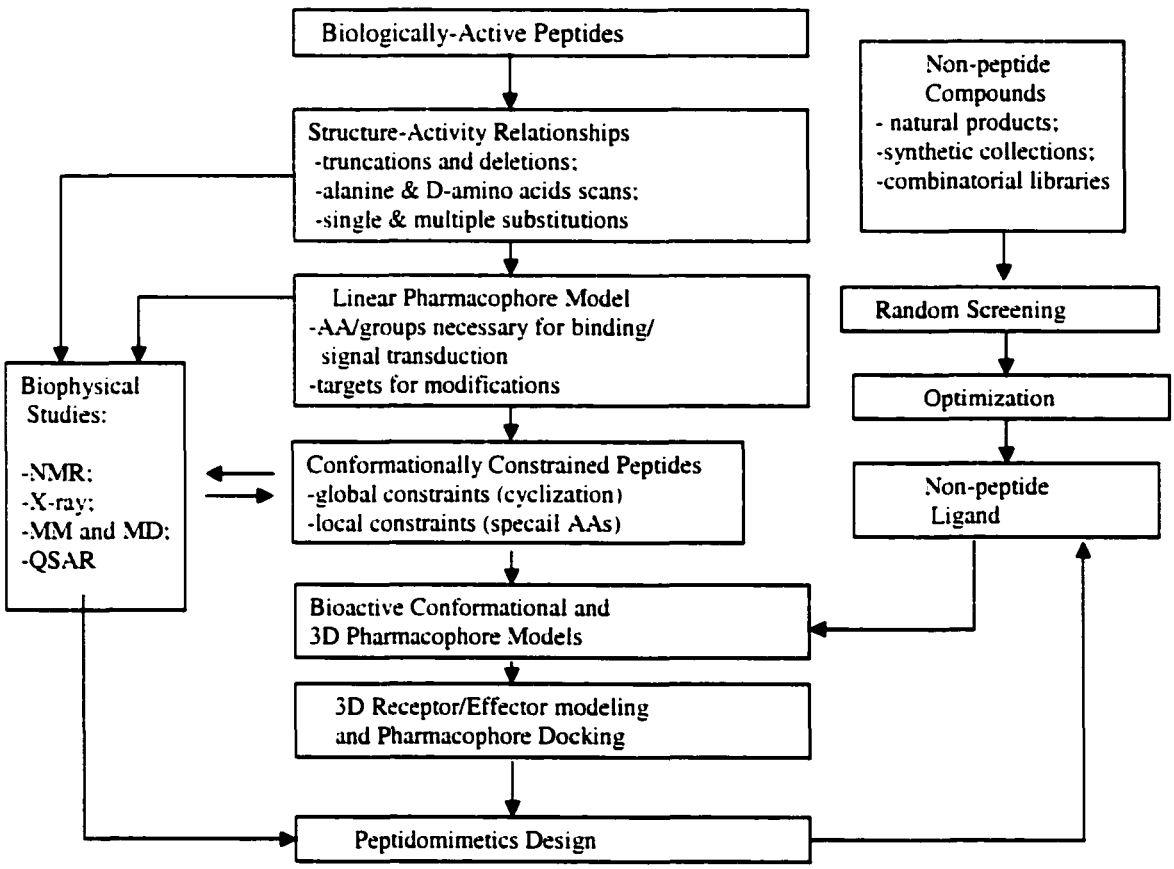


Figure 4-2. A *de novo* approach for peptidomimetic design from peptide ligands

Based on the knowledge of the structure of target peptides, the key amino acids residues necessary for receptor recognition are diagnosed *via* single amino acid modifications such as truncations, deletions, alanine and D-amino acid scans. Meanwhile, local constraints are built into the ligand so as to constrain the local backbone conformations

(ϕ, φ, and ω angles) to achieve the most appropriate local minima in a way that is compatible with molecular recognition. Alternatively, more global constraints are incorporated through cyclization to make an appropriate template for all the structural elements that make up the pharmacophore. Thus, a peptide ligand with rigid or half-rigid conformations is produced. Detailed structure-activity study will identify the most active structure that works as the surrogate of the original bioactive peptide in the later stage of the systematic studies. The next stage is to use biophysical methods to carry out the systematic analysis of the three-dimensional arrangement of critical side chain groups and backbone functionalities that are critical for bioactivity. Usually, these biophysical methods include NMR, X-ray crystallography, circular dichroism (CD) and computation. To successfully bridge the gap from peptide to non-peptide structures, a detailed development of a 3D peptide pharmacophore model based on the design, synthesis, and comprehensive evaluation of conformational (ϕ, φ) and topographical (chi[χ]) space of a peptide ligand is definitely required. On the basis of this information, the geometrical relationships of key pharmacophore elements may become clearer. Up to here a comprehensive conformational and topographical understanding has been gained on the peptide ligands. The next step is to transfer all key structural elements into an appropriate organic moiety without peptide bond features but with appropriate structural arrangements. Then the designed non-peptide structures that are expected to demonstrate the same biological profiles are prepared and tested. Sometimes screening and optimization are necessary to find the non-peptide ligand which mimics the endogenous ligand with all or most desired properties. Most likely the whole process has to be

repeated to achieve success. In many cases, these studies can lead to highly potent, selective and efficacious drug candidates.

4.1.3. From Enkephalin to SL-311: Successes, Challenges and Problems

One of the most significant health problems for the human being is the inadequate treatment of pain. Morphine, one of the opioids used extensively for the treatment of pain, is a partial μ-receptor agonist. It has good bioavailability and produces very strong analgesic effects. While opioids such as morphine remain a mainstay of therapy for the treatment of pain, the use of opioids in chronic pain states leads to a decrease in analgesic potency and efficacy. Additionally, while opioids are effective in management of acute pain, they show poor efficacy in the management of abnormal pain such as those pain states classified as neuropathic.

In the field of opioid research, selective peptide agonists for the δ-opioid receptor have shown promising therapeutic potential as analgesics without the adverse side effects associated with morphine and other opioid drugs selective for the μ-opioid receptor. Therefore, it is highly desirable to develop a therapeutic agent which shows strong analgesic efficacy but without the side effects such as addiction, depression, and tolerance based on the information of the chemical, conformational, dynamic, and structural requirements for selective agonist recognition of the δ-opioid receptors from detailed structure-activity relationship (SAR) studies of opioid peptides. The human endeavor has led to several examples of non-peptide ligands discovered either by modification of morphine-type alkaloids or by random screening approaches (Figure 4-

3). though thousands of non-peptide ligands designed for the opioid receptors have beenprepared. But even the most selective non-peptide compounds generally do not approach those of peptides and some of the more selective ligands are irreversible alkylating agents and hence unsuitable for long term *in vivo* studies. Naloxone has served for many years as the non-selective ligand for opioid receptors to define what is an opioid ligand. However, because of its lack of selectivity for any of the opioid receptors, it has only limited value for the design of non-peptide ligands. derivative of Naloxone, Naltrindole (**98**, Figure 4-3) was found to be a δ antagonist but it has only modest δ-selectivity.[209] Later, a potent δ-agonist-SIOM[210] (**99**) and partial δ-agonist oxymorphindole[209] (**100**), which are closely related to Naltrindole (**98**), were developed, but SIOM (**99**) showed only modest selectivity. A significant success was achieved in the development of the δ-opioid receptor agonist BW-373U86[211] (**102**) and SNC-80[212] (**103**) which were developed by screening. These two compounds are very close to each other. With methylation of the phenol group, BW-373U86 (**102**) was converted to the much more potent and highly selective δ-agonist, SNC-80 (**103**). SNC-80 (**103**) showed modest antinociception. Another interesting example in the development of the potent non-peptide opioid ligands is Tan-67[210] (**101**), which is a highly selective δ-agonist but showed no analgesic activities. As demonstrated above, most of these non-peptide opioids ligands are associated, as potential drug candidates, with various problems such as poor selectivity and low efficacy *in vivo* and display binding profiles different from those of typical δ-opioid-selective peptide agonists. Therefore, development of δ-opioid receptor-selective non-peptide agonists, based on peptide structure-activity relationships,

would have an important impact in understanding relationships between peptide and non-peptide ligand-receptor recognition, and signal transduction requirements, for rational drug design and for discovery of novel therapeutics.

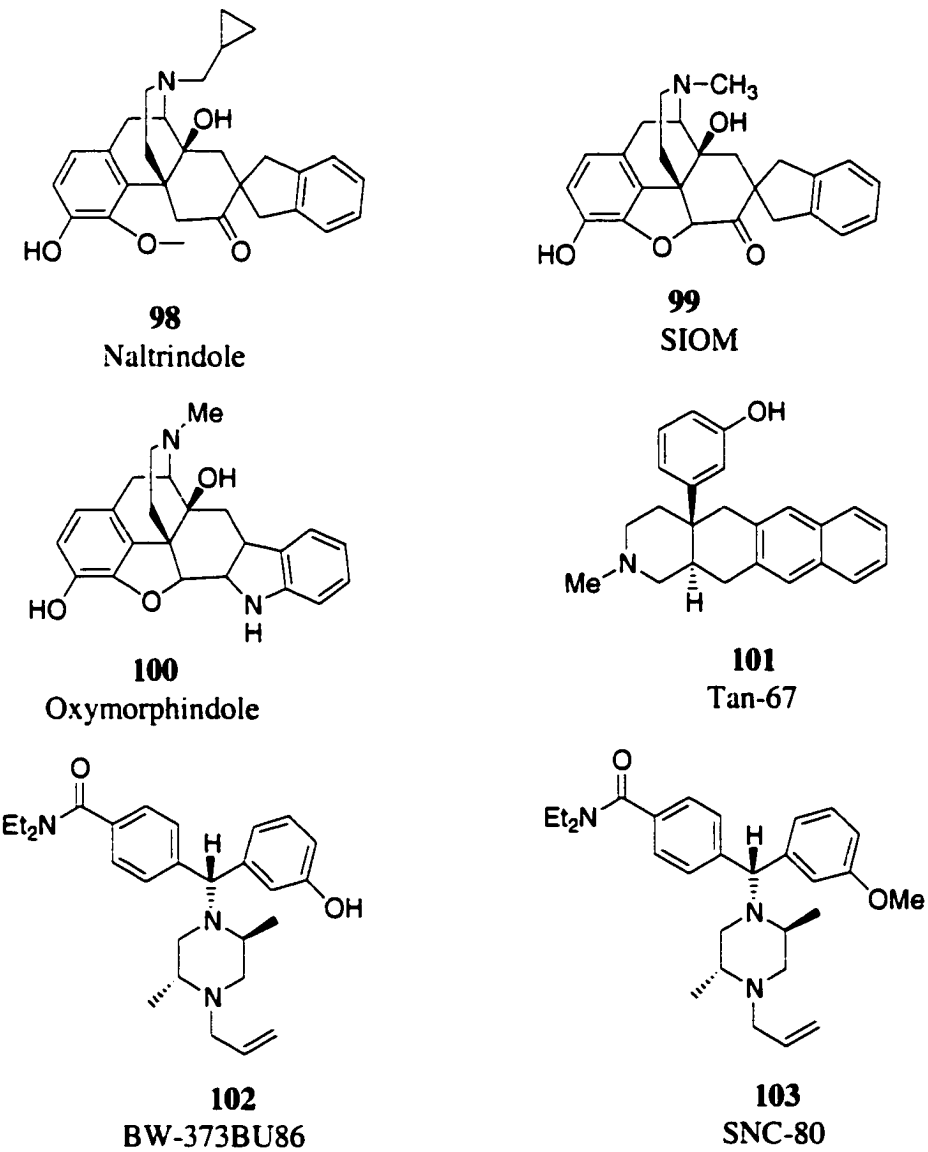


Figure 4-3. Structures of non-peptide opioid ligands

Detailed structure-activity relationship studies on the endogenous δ-opioid-selective 5-amino acid linear peptide ligands, enkephalins (H-Tyr-Gly-Gly-Phe-Met(Leu)-OH, **104**, Figure 4-4), have demonstrated that the phenol ring and the amino group in the tyrosine residue and the phenyl ring in the phenylalanine residue are the essential pharmacophores for peptide ligands to recognize δ-opioid receptor and produce physiological effects. But this linear peptide cannot provide much information on the conformational and topographical requirements on the interaction of peptide ligands with the opioid receptors. As a result of applying global constraints to the endogenous δ-opioid enkephalin peptides by the substitution of both Gly^2 and Met^5 (or Leu^5) residues in enkephalin with D-Pen (β,β-dimethylcysteine), to form a disulfide bridge, a potent and highly selective cyclic peptide Tyr-*c*[D-Pen-Gly-Phe-D-Pen]-OH (DPDPE, **105**) was developed in our laboratory.[213] The biological properties and significant constrained conformational mobility of DPDPE (**105**) have made the peptide and its analogues a popular target for structural studies aimed at determination of the three-dimensional (3D) structure of δ-opioid pharmacophore that could be used in rational design of new potent and selective δ-opioid ligands. The potent agonist DPDPE (**105**) which shows nanomolar binding affinity at the δ-opioid receptor and over 350-fold selectivity for the δ- over μ-opioid receptor.[213] In addition, DPDPE (**105**) has no inhibitory effect on gut motility, is stable to proteolytic degradation in blood, brain, and gut, and is also able to penetrate through the blood-brain barrier.[214,215] Most importantly, it was found to produce a potent, efficacious, and prolonged analgesia in several *in vivo* tests and to have low addiction potential, making it an alternative candidate for the treatment of pain without the toxicity

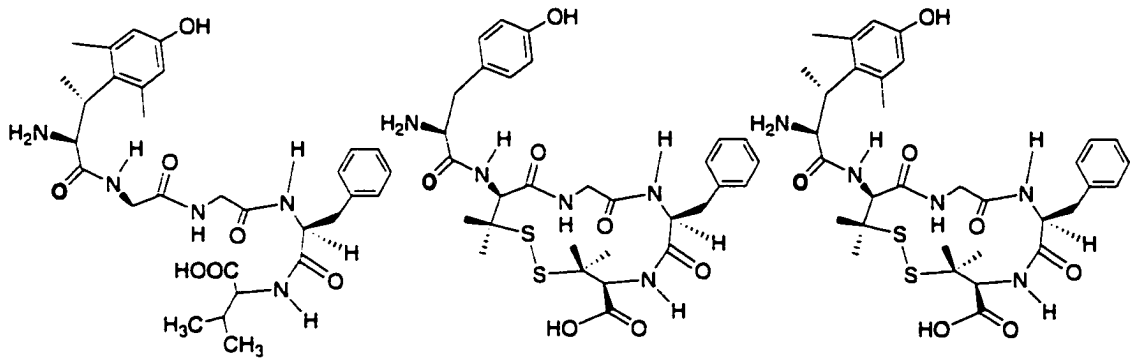


Figure 4-4. Structures of some enkephalin analogues

and side effects of current drugs. Extensive nmr,[216] X-ray,[217] and molecular modeling studies[218] have led to the conclusion that the 14-membered ring maintains a very similar conformation in solution and in the crystal form and determined favorable conformations of the 14-membered disulfide ring of DPDPE (**105**) in various environments. However, determination of the 3D pharmacophore of DPDPE (**105**) remained a challenging problem due to the unconstrained mobility of the exocyclic N-terminal residue Tyr^1 and the Phe^4 side chain group, which bear the main opioid pharmacophore groups (the α-amino group and the aromatic rings of Tyr^1 and Phe^4); they assume quite different orientations depending on environmental conditions. Therefore, a second generation of DPDPE (**105**) analogues was aimed at constraining the conformation mobility of side chains in positions 1 and 4, mainly by incorporation of cyclic and β-methyl-substituted

derivatives of the aromatic amino acids.[219,220] In one of these studies, the substitution of Phe^4 with the four isomers of β-methylphenylalanine, followed by NMR and molecular modeling studies of these derivatives, led to the conclusion that the gauche (-) conformation was required for interaction of the Phe^4 side chain with the δ-opioid receptor.[220] Recently, the highly constrained tyrosine derivatives, 2′,6′-dimethyl-β-methyltyrosine (TMT) were designed[221,222] and incorporated into position 1 of DPDPE.[21,22] The series of [TMT^1]DPDPE analogues (Table 4-1) allowed a breakthrough in determining requirements for the δ-receptor recognition of the amino acid in position 1. The four stereoisomers of TMT favor distinctly different side-chain conformations, and as expected this resulted in a wide range of affinities and biological activities, from the highly potent and highly selective [(2*S*,3*R*)-TMT^1]DPDPE (**106b**, Figure 4-4) (EC_{50} = 2 n*M* in the MVD Bioassay) to the virtually inactive [(2*R*,3*S*)TMT^1]DPDPE (**106c**) (EC_{50} > 40 μ*M*). [22] Nuclear magnetic resonance and theoretical studies have shown that the most active (2*S*,3*R*)-stereoisomer (**106b**) strongly prefers the *trans* conformation of the TMT^1 side chain (χ^1: ca.180°).[17,22] Although the ambiguity in the "bioactive" conformation of the tyramine moiety was thereby solved, a few unconstrained degrees of freedom (torsion angles φ_1, ϕ_2, and $\chi_4{}^1$) still made unequivocal determination of the 3D pharmacophore for the most constrained δ-opioid peptides, such as [TMT^1]DPDPE, difficult. Molecular modeling studies of [(2*S*,3*R*)-TMT^1]DPDPE (**106b**) and two potent non-peptide δ-opioid receptor agonists, SIOM(**99**)[223] and TAN-67 (**101**),[210] resulted in a 3D pharmacophore model for this receptor (Figure 4-5). From this model a characteristic distance of 7.0 ± 1.5 Å between the phenol and phenyl rings was observed.[224] Computer-

assisted template search indicated that two *cis* 1,4-disubstituted benzyl-like aromatic rings can be presented at such distances on a cyclohexane-like scaffold and that the hydroxyl group of the phenol ring should be in a *meta* position to overlap with the corresponding pharmacophore in the bioactive conformation of [(2*S*,3*R*)-TMT^1]DPDPE (**106b**) (Figure 4-5).

Table 4-1. Binding affinity data of the enkephalin peptide analogues

Peptide	IC_{50} (nM)		Selectivity (μ/δ)
	[3H][*p*-ClPhe4]DPDPE (δ)	[3H]CTOP (μ)	
DPDPE (**105**)	1.6	610	381
[(2*S*,3*S*)TMT^1]DPDPE (**106a**)	210	720	3
[(2*S*,3*R*)TMT^1]DPDPE (**106b**)	5.0	4300	860
[(2*R*,3*R*)TMT^1]DPDPE (**106c**)	3500	77080	22
[(2*R*,3*S*)TMT^1]DPDPE (**106d**)	9% at 10000	0% at 10000	N/A

Additionally, an amino group may be introduced on the cyclohexane scaffold to overlap the corresponding amino group of the peptide ligand as shown in Figure 4-5.[224] It also has been shown that the increased hydrophobicity of the tyrosine derivatives and the β-dimethyl groups in both D-Pen residues may contribute to the enhanced selectivity and binding affinity of the peptide ligand.[224-226] Thus additional substituents R_1, of variable size and hydrophobicity were introduced onto the benzyl carbon of the phenol side-chain

group as shown in Figure 4-5, to test how this would affect the selectivity and binding affinity of these designed peptidomimetics. To facilitate the synthetic process, 1,4-piperazine was used as a 6-membered ring scaffold for the first generation of peptidomimetics.

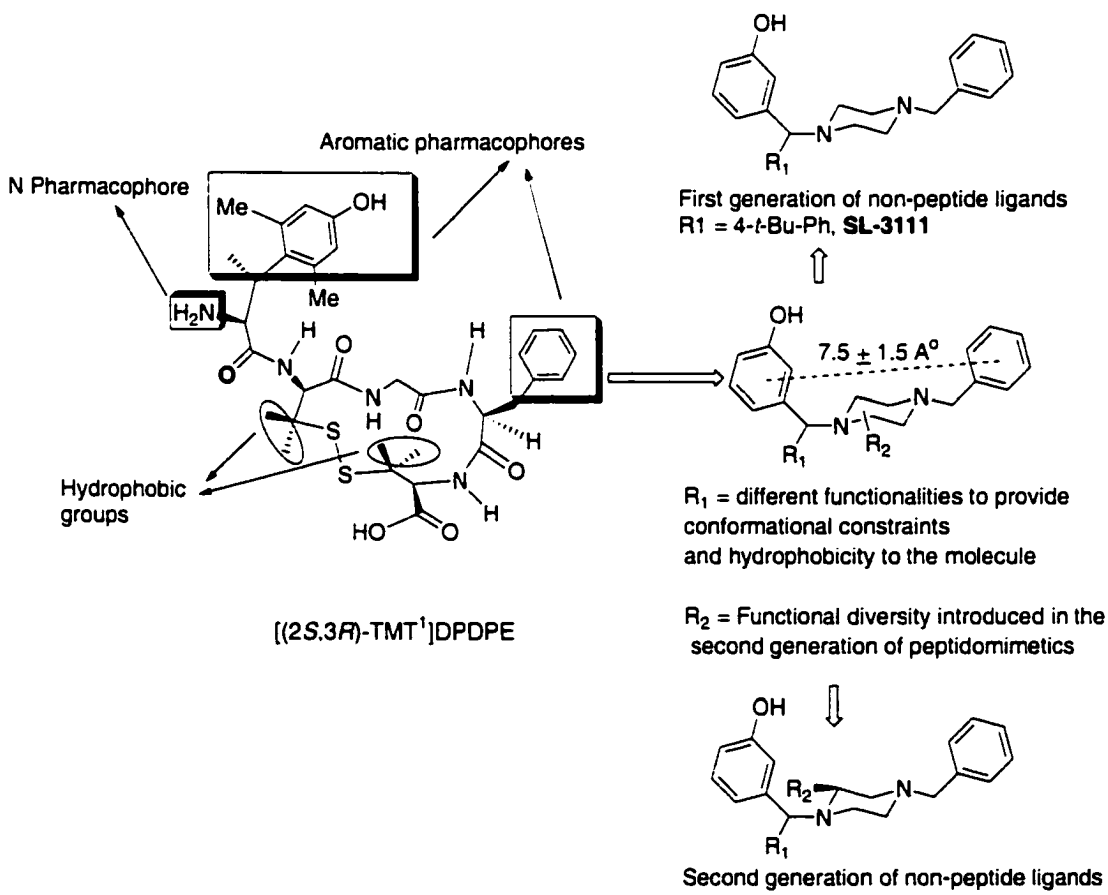
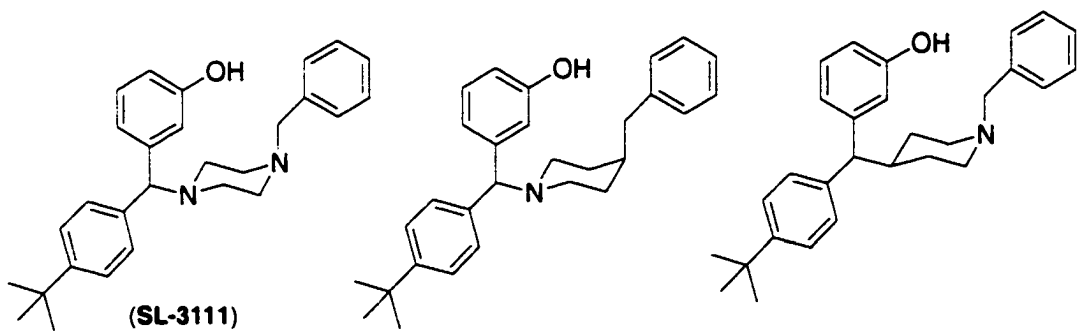


Figure 4-5. Rationale for the design of the first and second generation of peptidomimetics based on [(2*S*,3*R*)TMT¹]DPDPE (**106b**)

In this first series of non-peptide ligands, a primary amino group was omitted to simplify the synthetic work. Furthermore, the nitrogen in the piperazine ring has not been ideally positioned in 3D space to mimic the terminal amino group in the peptide lead analogue (Figure 4-5). Thus, it was postulated that with three appropriately oriented binding pharmacophore groups, high binding affinity could still be expected according to the theory proposed by Farmer.[227] Therefore, the first generation of peptidomimetic compounds based on [(2*S*, 3*R*)TMT^1]DPDPE (**106b**) was intentionally designed to explore the functional roles of the two aromatic rings and the hydrophobic group R in the ligand-receptor interaction.

Based on these assumptions, a series of analogues were generated and tested. Of them, SL-3111 (**107**, Figure 4-6) showed 8 nM binding affinity and over 2000-fold selectivity for the δ- over the μ-opioid receptor.[228] Binding studies of SL-3111 and [*p*-ClPhe^4]DPDPE on the cloned wild type and mutated human δ-opioid receptor suggested



(SL-3111)

107 **108** **109**

Figure 4-6. Some non-peptide ligands based on enkephalin

that SL-3111 has a binding profile similar to that of DPDPE, but different from that of SNC80, a potent δ-opioid selective non-peptide agonist that also contains a piperazine ring. This may suggest that SL-3111 is more like a real peptidomimetic than SNC-80. However, when tested in MVD (δ) and GPI (μ) bioassays, SL-3111, despite having a moderate selectivity of 460-fold μ/δ, showed low potency (EC_{50} = 85 n*M*) compared to the 1.8 nM binding affinity observed for the peptide lead [(2*S*,3*R*)TMT[1]]DPDPE (**106b**). Also, in contrast to the peptide lead, no *in vivo* antinociception on the classical tail flick was detected for SL-3111 before toxic side effects intervene. Even though methylation of phenol group in BW-387BU86 gave the highly potent and selective SNC-80, methylation of the phenyl group in SL-3111 led to an inactive ligand that lost both binding affinity and selectivity just as is the case for DPDPE. Compared to SNC-80, SL-3111shows lower potency (Table 4-2). SL-3111 showed high binding affinity (in *nano*-molar range)

Table 4-2. Binding affinity of some non-peptide ligands

Compound	IC_{50} (n*M*)		Selectivity (μ/δ)
	[^{3}H][*p*-ClPhe^4]DPDPE (δ)	[^{3}H]CTOP/[^{3}H]DAMGO (μ)	
SNC-80 (**103**)	1.06	2500	2300
107 (SL-3111)	8.4	1700	2020
108	12600	22900	1.3
109	33	4300	130

and selectivity, but this non-peptide ligand is toxic *in vivo* and not particularly potent in *in vivo* in MVD which is possibly attributed to the insufficient introduction of all structures necessary for a potent and efficacious δ-opioid ligand.

Table 4-3. Biological potencies of the non-peptide ligands

	Bioassay data, EC50(n*M* ± SEM)		
Compound	GPI(μ)	MVD (δ)	selectivity (μ/δ)
[(2*S*,3*R*)TMT[1]]DPDPE	0%	1.8 ± 0.3	>33000
	(antagonist, IC50 = 5 μ*M*)		
107 (SL-3111)	39000 ± 2600	85 ± 10	460
109	15600 ± 2100	390 ± 140	40

In an attempt to improve the biological profile of this peptidomimetic lead, two different routes were pursued. The first route was to search different types of scaffolds. Based on this idea, the piperazine ring in SL-3111 was substituted by two different heterocyclic systems: 1,3,5-thiadiazine-2-thione and piperidine. The second approach was to introduce diverse functional groups-R_2 (Figure 4-5) as a possible way to improve the biological properties of SL-3111 while maintaining a piperazine ring as a template. The compounds with 1,3,5-thiadiazine-2-thione showed no binding affinity and selectivity at the opioid receptors in inhibitory binding studies.[229] These observations support the idea of the scaffold having great importance for interaction with the δ-receptor. With the substitution of the nitrogen atom bearing a benzyl group with a CH, the ligand (**108**, Figure 4-6 and Table 4-2) showed a dramatic loss of binding affinity (1500-fold) compared to SL-3111 (**107**). However, when the nitrogen atom bearing the

benzyhydryl group was CH-substituted, a compound (**109**, Figure 4-6 and Table 4-2) was obtained and found to be only 4-fold less potent. These results may indicate that the nitrogen atom linked to the benzyl group in SL-3111 is the one that mimics the basic amine group known to be essential in opioid-like drugs, which is thought to imitate the amino terminus on our peptide lead [(2*S*,3*R*)TMT^1]DPDPE (**106b**). On the other hand these observations also revealed that the nitrogen at position 4 is far more important than the one at position 1 for effective recognition of ligands by the opioid receptors. This observation is contradicted what was observed in SNC-80 (**103**). In SNC-80 (**103**), it has been demonstrated that the nitrogen at position 1 is more important than the one at position 4.[230] Instead of 6-membered ring scaffolds, some 5-membered scaffolds have

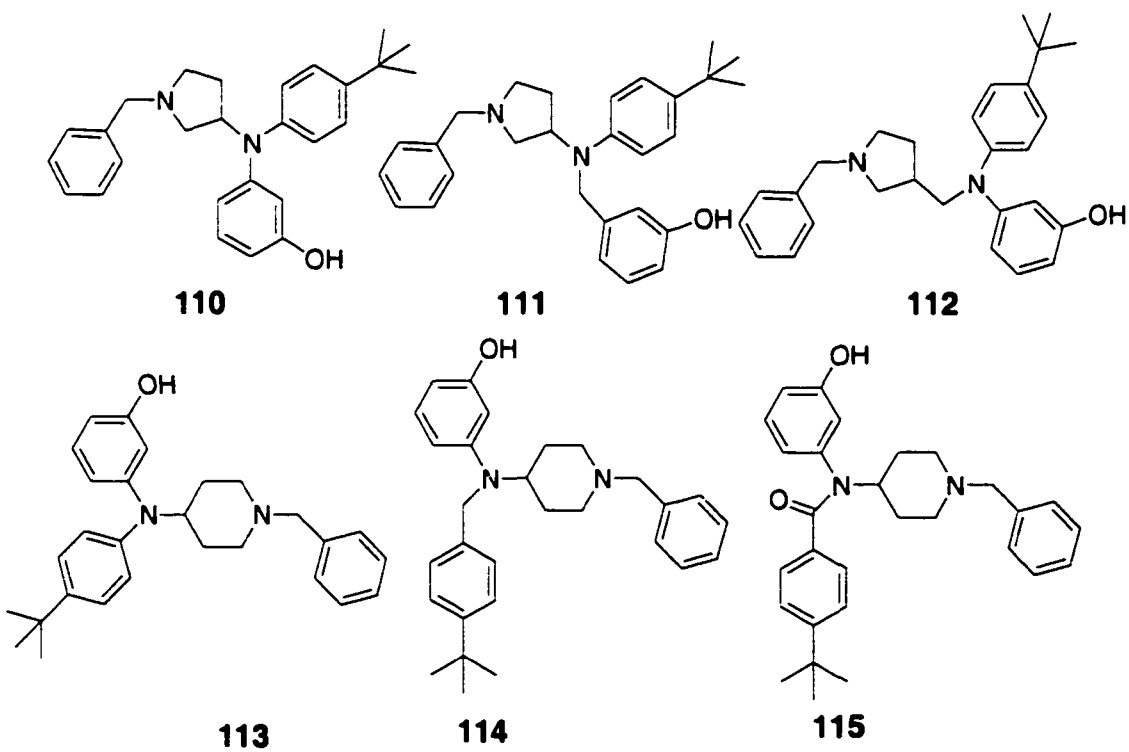


Figure 4-7. Some non-peptide analogues with modified scaffolds

also been tried (**110-112**, Figure 4-7). The binding studies showed all these ligands with 5-membered rings were inactive toward the opioid receptors or showed very low affinities. The manipulation of the relative positions of two nitrogens also led to inactive ligands (**113-115**, Figure 4-7). The introduction of side chain functional groups at position 2 through diketopiperazine only led to ligands with compromised binding affinities and selectivity.[229] From the results with modification of scaffolds, now it is well understood that it is critical to manage all pharmacophores on the 6-membered piperazine system to maintain the proper spatial arrangement of pharmacophores and other key functional groups.

4.2. General Considerations in Our Design of Peptide and Non-Peptide Ligands

Of the non-peptide peptidomimetic ligands prepared for the δ-opioid receptor so far, SL-3111 turned out to be the best. As mentioned above, this ligand is not particularly potent because of the insufficient introduction of pharmacophores, and from *in vivo* studies, it's toxic. In order to improve the now-existing non-peptide ligands, we pursued our goal from two different directions. First, instead of going directly from the bioactive peptide [(2*S*, 3*R*)-TMT^1]DPDPE (**106**) to a non-peptide ligand, we believed it was highly desirable to design some shorter intermediate peptides, which contain all or most pharmacophores from the key amino acid residues in the parental peptide [(2*S*,3*R*)TMT^1]DPDPE (**106**), to bridge the peptide lead and synthetic non-peptide ligands. These peptides would mimic the lead peptide in the topographical space. These smaller peptides would better our understanding of the interaction between the peptide

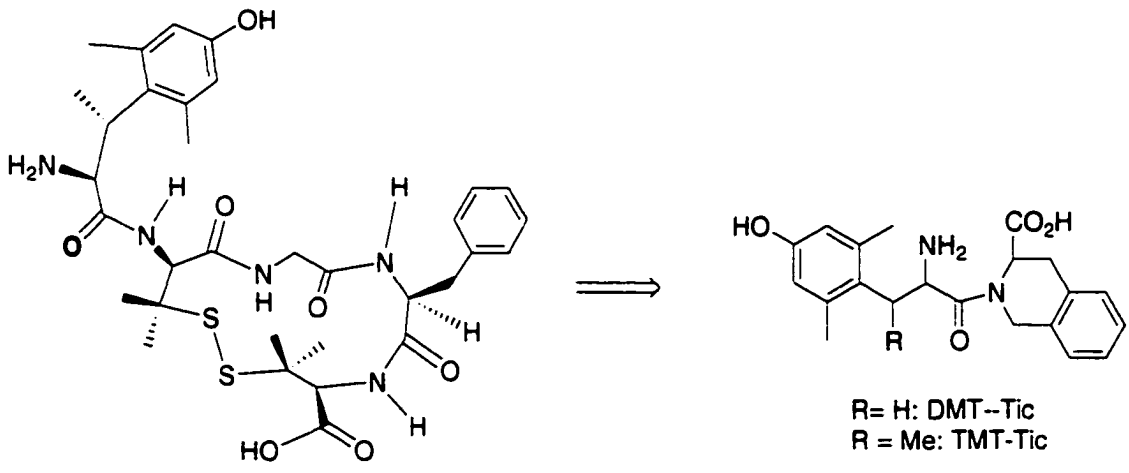
lead and its receptors through biological studies of these newly-designed peptides, and help us to identify more necessary structural features thus to benefit the design of non-peptide ligands toward efficient therapeutics. Another direction we pursued was to modify the scaffold of SL-3111 (**107**) to reduce its toxicity and thus make it suitable for *in vivo* antinociception study.

4.3. Design, Synthesis and Bioassay of Topographical Peptidomimetics

4.3.1 Design

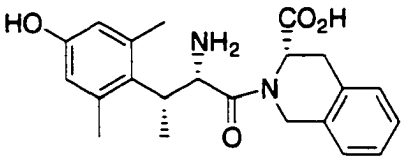
As Mentioned, the key pharmacophores in the peptide ligand [(2*S*,3*R*)-TMT^1]DPDPE reside in two key amino acid residues-(2*S*,3*R*)-β-methyl-2',6'-dimethyltyrosine (TMT) and phenylalanine. Based on systematic studies, we know that (2*S*,3*R*)-TMT has a *trans* conformation in the $\chi 1$ space[22] for effective recognition of ligands at the δ-receptor to produce corresponding pharmacological effects and that phenylalanine would take a *gauche* (-) conformation. Therefore in our consideration to design a smaller peptide based on [(2*S*,3*R*)TMT^1]DPDPE (**106b**), we believed at least it should contain TMT and Phe analogues. Since a gauche (-) conformation is required for the Phe residue, a D-Tic residue instead of Phe was used because L-Tic preferably takes a *gauche* (-) conformation (Figure 4-8).[30] In order to gain complete understanding of the steric and conformational requirements for effective recognition of peptide ligand at the δ-opioid receptor, all TMT, DMT and Tic stereoisomers were taken into consideration. Therefore there are 12 possible analogues as shown in Figure 4-9. By systematic biological and NMR studies of these compounds, we will gain more insights on the steric

and topographical requirements on the interaction between the peptide ligands and the opioid receptors.

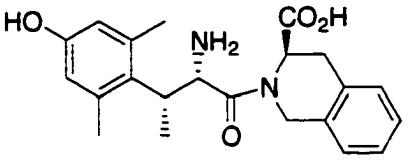


[(2*S*,3*R*)-TMT^1]DPDPE (**106b**)

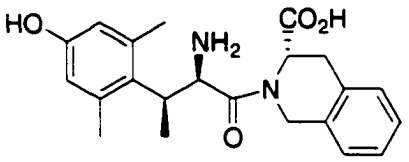
Figure 4-8. Design of dipeptide analogues based on [(2*S*,3*R*)TMT^1]DPDPE (**106b**)



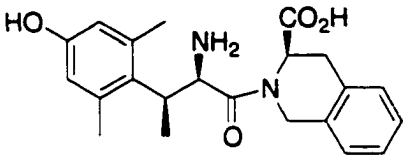
116
(2*S*, 3*R*)-TMT-L-Tic



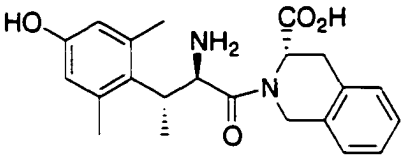
117
(2*S*, 3*R*)-TMT-D-Tic



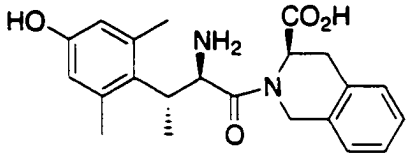
118
(2*R*, 3*S*)-TMT-L-Tic



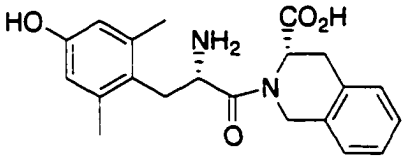
119
(2*R*, 3*S*)-TMT-D-Tic



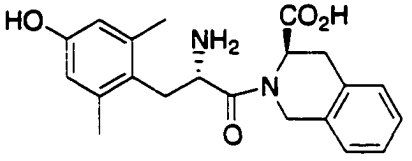
120
(2*R*, 3*R*)-TMT-L-Tic



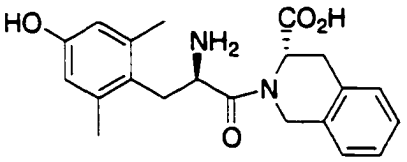
121
(2*R*, 3*R*)-TMT-D-Tic



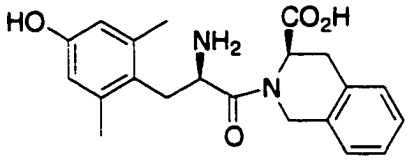
122
(2*S*)-DMT-L-Tic



123
(2*S*)-DMT-D-Tic



124
(2*R*)-DMT-L-Tic

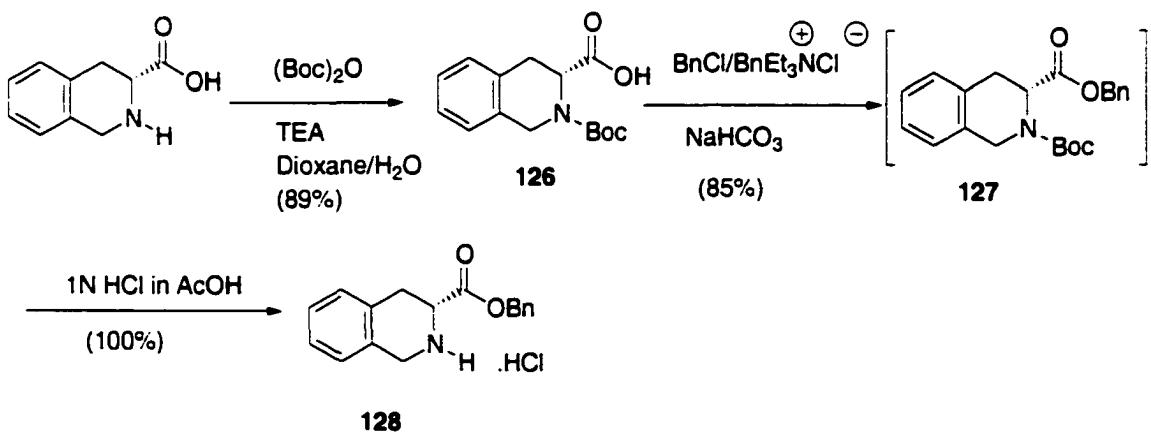


125
(2*R*)-DMT-D-Tic

Figure 4-9. Designed dipeptide peptidomimetics in topographical space

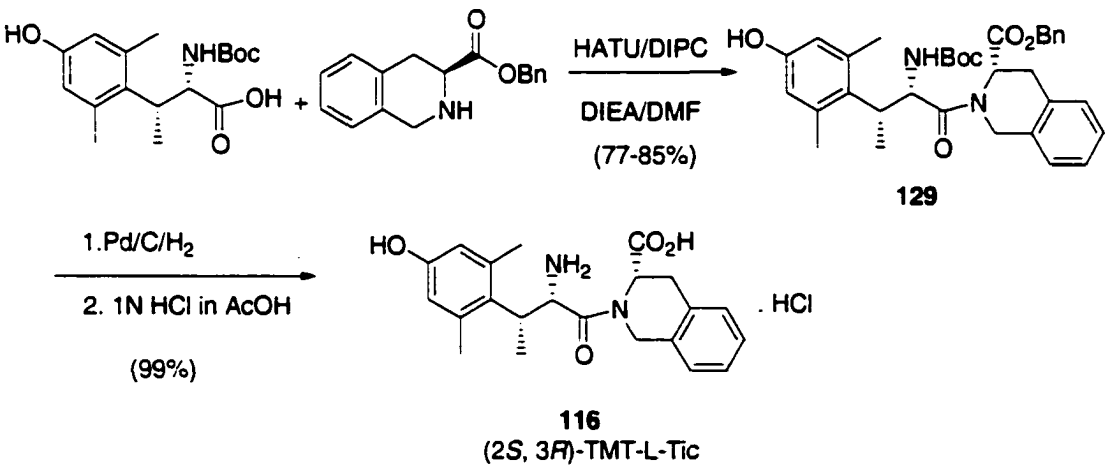
4.3.2. Synthesis of Topographical Peptidomimetics

We followed an established procedure[231] to prepare dipeptides analogues **116-125**. All TMT analogues in *N*α-Boc protected form were available in our lab. Both (*S*)- and (*R*)-DMT were prepared using our method in Chapter 2, and are protected in their N^{α}-Boc form through a known method.[232] In order to prepare DMT- or TMT-D-Tic analogues, D-Tic benzyl ester was prepared following a literature procedure starting from D-1,2,3,4-tetrahydroisoquinoline carboxylic acid (Tic, Scheme 4-1).[231] First the amino group in D-Tic was protected in 89% yield by di-*t*-butyl dicarbonate ($(Boc)_2O$) in dioxane/water in the presence of TEA. Then N^{α}-Boc-D-Tic (**126**) was converted into its corresponding benzyl ester (**127**) via reaction with benzyl bromide in the presence of phase transfer catalyst triethylbenzylammonium chloride in dichloromethane. The N^{α}-Boc group in **127** was removed by 1*N* HCl in acetic acid at 0 °C to give the benzyl ester of D-Tic (**128**) in hydrochloric acid form.



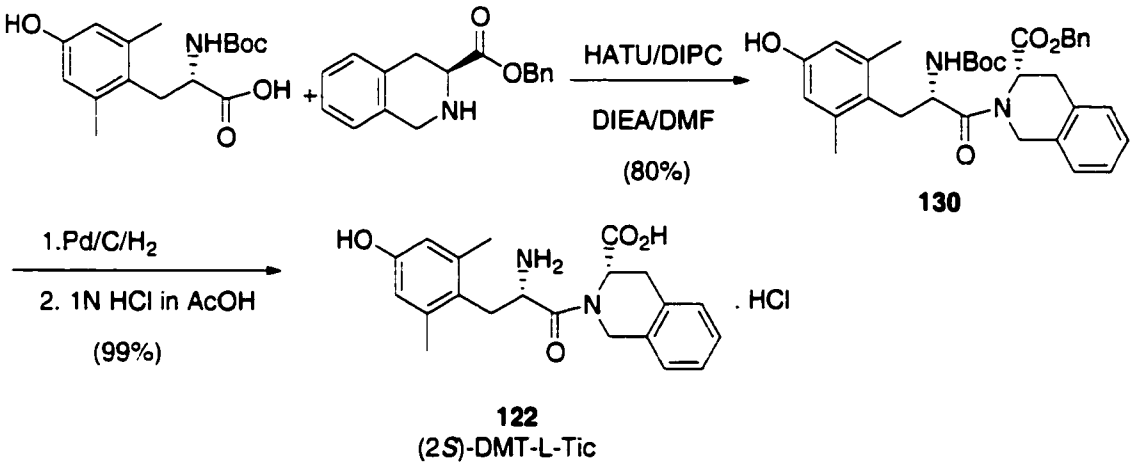
Scheme 4-1. Synthesis of D-Tic benzyl ester (**128**)

With all starting materials in hand, 8 of the designed analogues were prepared as shown in Scheme 4-2. The most difficult step in this preparation was the very first step coupling between N^{α}-Boc-protected TMTs and Tic benzyl esters. This coupling did not proceed under the standard coupling conditions with DIC/HOBt coupling reagents. But it was accomplished with HATU/DCC as coupling reagents in DMF in 48 hours. Upon completion of the reaction, it was quenched with saturated ammonium chloride and the reaction mixture was extracted with dichloromethane. The crude product was purified by column chromatograph with silica gel to give **129**. The benzyl group was removed by hydrogenolysis under 40-50 psi H_2 and Pd/C, and the N^{α}-Boc group was removed with 1*N* HCl in acetic acid to give the hydrochloric acid form of the designed dipeptide **116**



Scheme 4-2. Synthesis of TMT-Tic analogues

after purification by Prep-HPLC. All other TMT–containing peptides were prepared following this protocol without any modification. This step gave about 80% yield. The four DMT-Tic analogues are prepared following the same procedure as that of TMT-Tic (Scheme 4-3).



Scheme 4-3. Synthesis of DMT-Tic analogues

4.3.3. Bioassay of Topographical Peptidomimetics

The binding affinities of all six TMT-Tic analogues and two DMT-Tic analogues were examined using the radio-labeled opioid ligand [^{3}H]deltorphin II for the δ-opioid receptor and [^{3}H]DAMGO ([D-Ala^2, MePhe^4, Glyol]enkephalin for the μ-opioid receptor. As shown in Table 4-4, (2*S*,3*R*)-TMT-L-Tic (**116**) had a binding affinity of 13.0 n*M* at the δ-opioid receptor and 660 nM at the μ-opioid receptor, which was only

Table 4-4. Binding assay of TMT-Tic and DMT-Tic analogues

Compound	IC_{50} (nM)		Selectivity (μ/δ)
	[3H]deltorphin II (δ)	[3H]DAMGO (μ)	
(2*S*, 3*R*)-TMT-L-Tic (**116**)	12.9	657.2	51
(2*S*, 3*R*)-TMT-D-Tic (**117**)	4450	1690	0.4
(2*R*, 3*S*)-TMT-L-Tic (**118**)	1150	1,050,000	910
(2*R*, 3*S*)-TMT-D-Tic (**119**)	10200	8180	0.8
(2*R*, 3*R*)-TMT-L-Tic (**120**)	380900	1100	0.003
(2*R*, 3*R*)-TMT-D-Tic (**121**)	726	180,000	250
(2*S*)-DMT-L-Tic (**122**)	7.6	n.d.	N/A
(2*S*)-DMT-D-Tic (**123**)	2330	8180	4

medium selectivity for the δ-opioid receptor over the μ-opioid receptor. (2*S*)-DMT-L-Tic (**122**) was another of the eight prepared peptides that shows nanomolar binding affinities at the δ-opioid receptor, but it showed no binding affinity at the μ-opioid receptor. All of the other peptide ligands showed no binding affinities at either the δ-opioid receptor or the μ-opioid receptor. It is noticeable that the enantiomers of peptide analogues (**116** and **119**, **117** and **118**) showed completely different binding affinities at the opioid receptors. In the TMT-Tic series, as expected, (2*S*,3*R*)-TMT-L-Tic (**116**) showed the best binding affinity at the δ-opioid receptor because its two amino acid residues, (2*S*,3*R*)-TMT and L-Tic (**116**), maintained the appropriate conformations required for effective recognition at the δ-opioid receptor based on the parental peptide-[(2*S*, 3*R*)-TMT[1]]DPDPE (**106**). (2*R*,3*R*)-TMT-L-Tic (**120**), the 2-epimer of (2*S*,3*R*)-TMT-L-Tic (**116**), showed

significantly lower binding affinities compared to (2*S*,3*R*)-TMT-L-Tic (**116**). That substantiated that the *trans* conformation is required for the tyrosine moiety. By comparison of the binding profile of **116** and **117**, it is clear that the Tic residue must maintain a *gauch* (-) conformation in addition to the appropriate conformation arrangement for the Tyr residue.

Dipeptide analogues **116-123** were evaluated in the isolated mouse vas deferens (MVD) and guinea pig ileum (GPI) bioassays (Table 4-5). (2*S*,3*R*)-TMT-L-Tic (**116**) and (2*S*)-DMT-L-Tic (**122**) were strong δ-antagonists. They showed K_e values of 12.47 ± 6.75 and 14.87 ± 2.41 nM, respectively. Additionally, these two compounds showed weak agonism at the μ-opioid receptor. Based on (2*S*,3*R*)-TMT-L-Tic (**116**), with the reverse of the stereochemistry of the TMT moiety, compound **118**, (2*R*,3*S*)-TMT-L-Tic

Table 4-5. Biological potencies of dipeptide analogues **116-123**

	MVD (δ)		GPI (μ)	
Compound	agonist	δ-antagonism	agonist	μ-antagonism
(2*S*, 3*R*)-TMT-L-Tic (**116**)	5% at 100 n*M*	Ke = 12.47 n*M*	26% at 30 μ*M*	none at 1 μ*M*
(2*S*, 3*R*)-TMT-D-Tic (**117**)				
(2*R*, 3*S*)-TMT-L-Tic (**118**)	IC50 = 376.7 n*M*	None at 1 μ*M*	0% at 30 μ*M*	none at1μ*M*
(2*R*, 3*S*)-TMT-D-Tic (**119**)	3% at 1 μ*M*	none at 1 μM	5% at 30 μ*M*	none at 1 μ*M*
(2*R*, 3*R*)-TMT-L-Tic (**120**)			7% at 30 mM	none at 1mM
(2*R*, 3*R*)-TMT-D-Tic (**121**)	5% at 1 m*M*	none at 10 m*M*	8% at 30 n*M*	none at 1m*M*
(2*S*)-DMT-L-Tic (**122**)	0% at 1m*M*	Ke = 14.87 n*M*	13% at 30 m*M*	none at 1m*M*
(2*S*)-DMT-D-Tic (**123**)	2% at 1 m*M*	none at 1m*M*	0% at 30 m*M*	none at 1 m*M*

was turned into a weak δ-agonist. It is also very interesting to notice that compound **123** with inversed stereochemistry at the Tic moiety in (2*S*)-DMT-L-Tic (**122**), completely lost the potencies. All other compounds with different stereochemistry at either TMT or Tic moiety showed no activities at the either δ- or μ- receptor. These observations led us to believe that the stereochemistry of the dipeptide has significant effects on the agonistic/antagonistic properties of these peptide analogues.

The data in Table 4-4 clearly demonstrated that none of these dipeptide analogues can match the parental peptide-[(2*S*,3*R*)TMT^1]DPDPE (**106b**) in either binding or selectivity after several amino residues were omitted. In order to achieve the comparable binding affinity and selectivity of [(2*S*,3*R*)TMT^1]DPDPE (**106b**), it would be necessary to include more functional groups into TMT/DMT or Tic or introduce one more amino residue into the dipeptides to form tripepides.

4.3.4. Preliminary NMR Study of Topographical Peptidomimetics

1D and 2D NMR studies on a DRX600 were conducted on all the synthesized dipeptide ligands. The solvent used after several trials was a mixture of 90% (volume) of deuterated sodium acetate (3.3 mg/mL buffer in H_2O (pH 4.76) and 10% D_2O because with this solvent, the rotamers of the designed dipeptides were maximally eliminated to simplify the spectra. With other solvents such as d_4-MeOH and d_6-DMSO, the rotamers were distinctly identifiable. The 1D experiments include both ^{1}H-NMR and ^{13}C-NMR. The 2D experiments include ROESY, DQF-COSY and TOCSY. The 1D ^{1}H-NMR and

2D experiments used presaturation techniques to achieve solvent suppression at 4.76 ppm.

From the 1D-NMR spectra, it was clearly observed that for all TMT-Tic analogues the two methyl groups on the phenyl rings in the TMT moiety were not non-equivalent, though they are equivalent in the free amino acids at a slow rate. Therefore two well-resolved singlets were observed. The two aromatic protons in the TMT moiety were not non-equivalent as well, since two distinct singlets were observed between 6.0 ppm and 6.8 ppm for these two protons. These preliminary observations suggest that the dipeptides of the TMT-Tic series are fixed conformationally in this aqueous medium. Each stereoisomeric TMT-Tic analogue (**116-121**) has its own distinct conformational orientation. But for the DMT-Tic it was found that the two methyl groups and two aromatic protons in the DMT moiety showed up as two broad singlets at around 2.1 and 6.4 ppm, indicating as expected a lower barrier to rotation about the Ar-CH_2 that exists about the Ar-CH bond in TMT-Tic stereoisomers. Based on the difference in 1D NMR experiments of TMT-Tic compounds and DMT-Tic compounds, we realized that the β-substitutents has a key importance to constrained the conformation of the peptides.

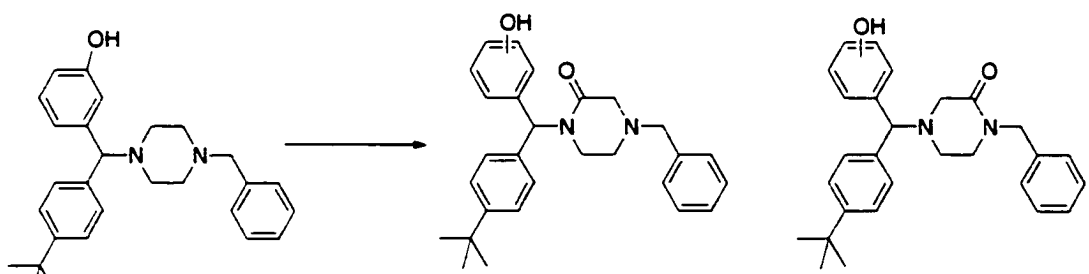
Based on all 2D experiments we hope we can generate some special distances between pharmacophores in the peptide ligands, and thus generate the distinct conformation of each peptide ligand through computational modeling to understand the "bioactive conformation" and why the *trans* conformation for Tyr and gauche (-) conformation for Phe are required in [(2*S*,3*R*)TMT^1]DPDPE (**106b**) for effective binding and high selectivity. This information would provide us unique insights on the opioid

receptor structures to facilitate our design of non-peptide analogues as potential therapeutics. So far, we still cannot generate much useful information on the spatial arrangements of pharmacophores form ROESY experiments mainly because for the dipeptides, couplings through space are highly limited, especially for these constrained peptides. We believe J-couplings may provide a viable approach to generate the special information of the pharmacophores in the dipeptides with appropriate labelings.

4.4. Synthesis of Non-Peptide Peptidomimetics

4.4.1. Design of Non-Peptide Peptidomimetics

Our second approach to improve our design of non-peptide ligands aiming to the δ-opioid was to optimize the now-existing ligand-SL-3111 (**107**), the toxicity of which compromised its extended use in spite of the fact that it had very good selectivity for the δ-opioid receptor over the μ-opioid receptor. We believed its toxicity stemed from its two basic nitrogens in the piperazine ring, but we knew that the two nitrogens were crucial for effective recognition of ligands at the δ-opioid receptor. Therefore it was highly desirable



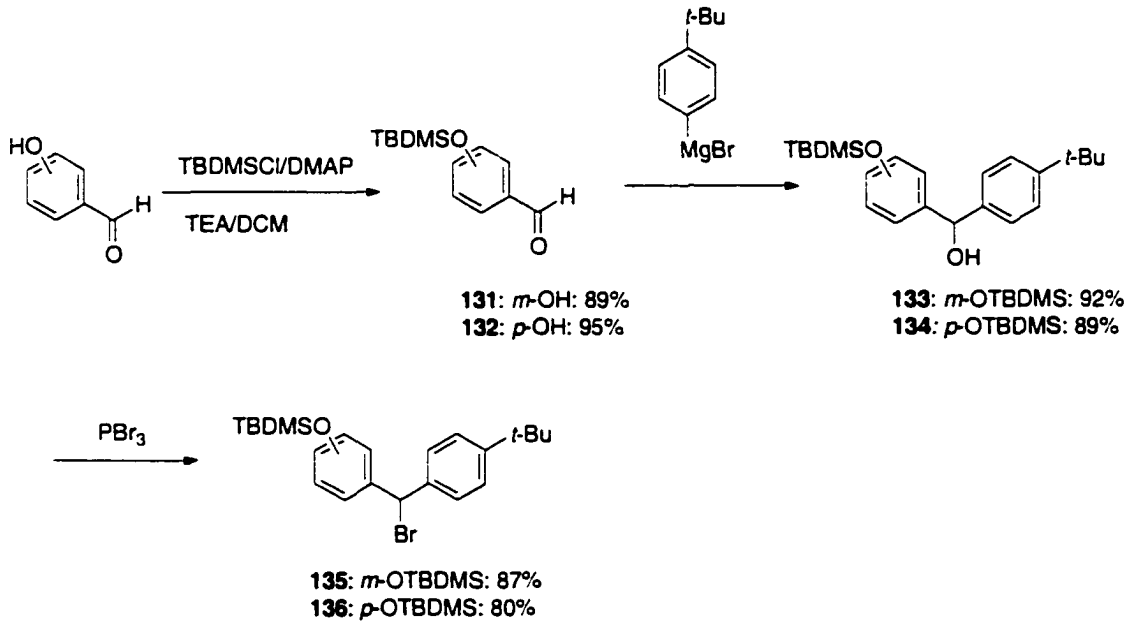
107
SL-3111

Figure 4-10. Design of modified analogues of SL-3111

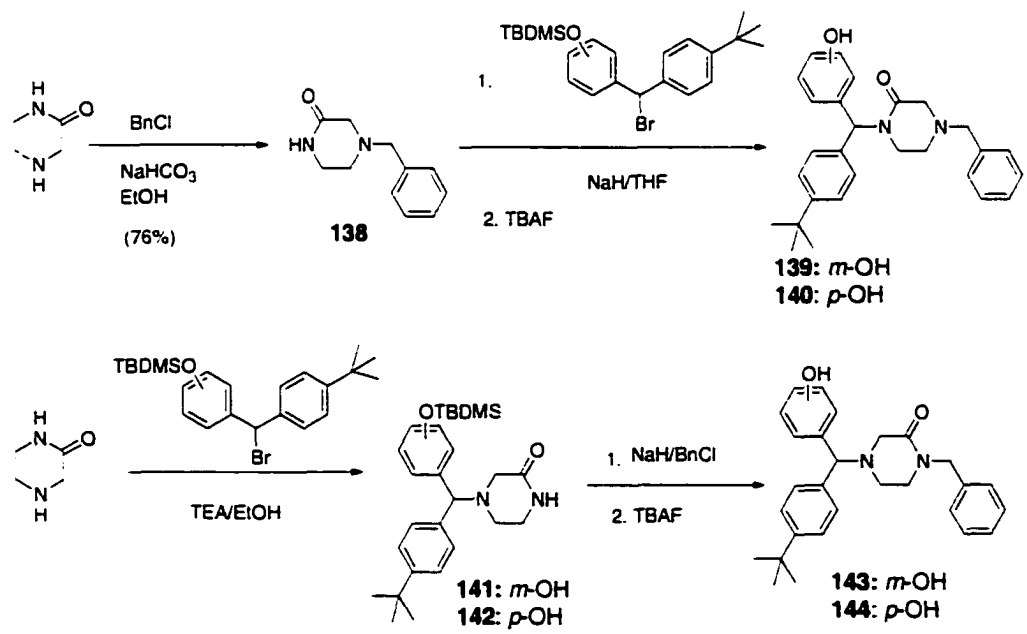
to convert one of two nitrogens to the amide form to reduce its toxicity. Therefore several analogues of SL-3111 (**107**) were designed as shown Figure 4-10. We believed that the conformation of the scaffold would expect some changes with the introduction of carbonyl group on the piperazine scaffold. Both *m*-hydroxyl and *p*-hydroxyl compounds were designed. Meanwhile, two different types of amide analogues were designed to optimize the lead compound.

4.4.2. Synthesis of Non-peptide Peptidomimetics

The preparation of new analogues began with the protection of 3- or 4-hydroxybenzaldehyde with TBDMSCl (Scheme 4-4). The protection was achieved with 89 or 95% yield with DMAP and TEA in DCM.[233] The protected **131** or **132** was reduced to its corresponding alcohol (**133** or **134**) by 4-*tert*- butylphenylmagnesium bromide. The alcohol **133** or **134** was brominated by PBr_3 in Et_2O. To reach compounds **139** and **140**, the *N*-benzyl group at position 4 was introduced by amination of 2-ketopiperazine with benzyl chloride in the presence of sodium bicarbonate[234] before the attachment of bromide **135** and **136** onto the nitrogen at position 1 (Scheme 4-5). To reach compounds **143** and **144**, benzyhydryl groups were introduced before the benzyl group as shown in Scheme 4-5. More work is still going on in this direction.



Scheme 4-4. Synthesis of **135** and **136**



Scheme 4-5. Synthesis of **139**, **140**, **143** and **144**

4.5 Summary

A series of dipeptide analogues (TMT-Tic and DMT-Tic) were designed and synthesized to mimic the potent and highly selective δ-opioid receptor pentapeptide ligand-[(2*S*,3*R*)TMT[1]]DPDPE (**106b**) and thus to explore the topographical requirements for recognition of ligands at the opioid receptor through bioassays and NMR studies to facilitate the design of non-peptide compounds to be used as therapeutic agents for pain. (2*S*,3*R*)-TMT-L-Tic (**116**) was found to have the best binding affinities at the δ-opioid receptor in the TMT-Tic series. In our preliminary NMR studies, it was found that these designed peptide ligands have their own distinct conformations in the aqueous media. Meanwhile some modified non-peptide analogues of SL-3111 (**107**) were prepared to continue our efforts to find effective non-peptide ligands for the δ-opioid receptor. NMR studies and computational work are still in progress.

4.6. Future work

Based what we know so far, in addition to TMT-Tic and DMT-Tic analogues we have prepared in our research, we think it would be very interesting to investigate the TMT-TMP and DMT-TMP analogues. These analogues would carry the same pharmacophores as DMT-Tic and TMT-Tic compounds, but compared to Tic, TMP is less rigid. In our preliminary understanding, the rigidity of Tic may present some difficulties for dipeptide ligands to form appropriate conformations to be recognized by the opioid receptors.

4.7 Experimental

General. ^{1}H and ^{13}C NMR were performed on DRX-500 and DRX600 spectrometers with TMS or solvents used as internal standard. High Resolution Mass Spectra (HRMS) were recorded on a JEOL HX110A instrument. All reagents and solvents, unless otherwise stated, are commercially available and were used as received. All new compounds were characterized by ^{1}H, ^{13}C NMR and HRMS.

N^{α}-Boc-D-Tic (126). To a solution of 2.0 g of D-Tic (11.3 mmol) and 2.4 mL of triethylamine (17.0 mmol, 1.5 eq) in 50 mL dioxane/H_2O (1:1, v:v) at 0 °C was added 2.8 g of di-*tert*-butyl dicarbonate (12.4 mmol, 1.1 eq) in a single portion. The reaction mixture was stirred for 30 min at 0 °C and overnight at room temperature. The volatiles were evaporated and 30 mL of ethyl acetate was added, and the pH was adjusted to 2 with 1*N* HCl. The aqueous layer was separated from the ethyl acetate layer and washed with ethyl acetate (2 x 25 mL). The combined ethyl acetate solution was dried over $MgSO_4$ and evaporated using a rotary evaporator to give **126**. Yield: m.p. 123-125 °C. HRMS (FAB) $[M+H]^+$ calcd. For $C_{15}H_{19}NO_4$ 278.1392, found 278.1395. ^{1}H-NMR (d_6-DMSO) δ 1.45 (s, 9H), 3.13 (d, 2H, J = 5.0 Hz), 4.43 (d, 1H, J = 16.5 Hz), 4.60 (d, 1H, J = 16.5 Hz), 4.77 (br. s, 1H), 7.14-7.21 (m, 4H). ^{13}C-NMR (d_6-DMSO) δ 29.0, 31.8, 44.9, 53.0, 80.4, 126.9, 127.3, 127.4, 128.5, 128.8, 133.3, 155.4, 173.3.

HCl·D-Tic-OBn (128). To a mixture of 3.1 g of N^{α}-Boc-D-Tic (11.3 mmol) in 11 mL of dichloromethane and 11 mL of saturated Na_2CO_3, was added 2.57 g of triethylbenzylammonium chloride (22.6 mmol, 2.0 eq.) and 1.82 mL of benzyl bromide (15.4 mmol, 1.1 eq). The mixture was vigorously stirred until completion of the reaction.

Water was added and the reaction mixture was extracted with DCM (3 x 25 mL). The combined dichloromethane solution was dried over $MgSO_4$ and evaporated *in vacuo* to give the crude product, which was purified by column chromatography on silica gel with 2:8 EtOAc/hexanes as eluent to give N^{α}-Boc-D-Tic-OBn (**127**). **127** was dissolved in 40 mL of ice-cold 1*N* HCl in acetic acid and stirred for at 0 °C for 1.5 hr. The mixture was evaporated *in vacuo*, dissolved in dichloromethane and evaporated again to give oily product which was lyophilized to give **128** as a powder. Yield: 84%. m.p.: 310 °C (decomposed). HRMS (FAB) $[M+H]^+$ calcd. For $C_{17}H_{18}NO_2$ 268.1338, found 268.1335. ^{1}H-NMR (d_6-DMSO) δ 3.14 (dd, 1H, J_1 = 11.0 Hz and J_2 = 16.5 Hz), 3.30 (dd, 1H, J_1 = 5.0 Hz and J_2 = 17.0 Hz), 4.29-4.38 (m, 1H), 4.62 (dd, 1H, J_1 = 5.0 Hz and J_2 = 11.5 Hz), 5.29 (s, 2H), 7.24-7.26 (m, 4H), 7.34-7.28 (m, 5H). ^{13}C-NMR (d_6-DMSO) δ 28.0, 43.9, 53.2, 67.4, 126.6, 127.0, 127.7, 128.1, 128.2, 128.5, 128.6, 128.8, 130.4, 135.1, 168.3.

General procedure for the coupling of N^{α}-Boc-DMT or -TMT with Tic benzyl ester. To a solution of N^{α}-Boc-TMT or –DMT, D- or L-Tic(OBn) (in hydrochloric acid form or toluenesulfonic acid from, respectively, 1.0 eq.), and HATU (1.1 eq.) in 3 mL of anhydrous DMF under Ar at 0 °C was added diisopropylethylamine (8.0 eq.). 10 min later, DCC (1.1 eq.) dissolved in 1mL of DMF was added. 1 hr later, the mixture was stirred at room temperature until the completion of the coupling reaction by TLC. The reaction was quenched by 10 mL of deionized water, stirred for 30 min, and extracted with dichloromethane (3 x 10 mL). The DCM solution was dried over $MgSO_4$ and evaporated *in vacuo* to afford crude completely protected dipeptide which was purified by column chromatography on silica gel to give N^{α}-Boc-TMT-Tic(OBn). Due to

the existence of rotamers all these completely protected dipeptides were not characterized by NMR, but HRMS and HPLC analyses were conducted.

HCl·TMT-Tic-OH and HCl·DMT-Tic-OH (116-123). N^{α}-Boc-TMT-Tic(OBn) or N^{α}-Boc-DMT-Tic(OBn) was dissolved in MeOH and shaken for 24 hr under 50 psi H_2 in the presence of Pd/C to remove the benzyl group. The Pd/C was filtered off was washed with MeOH. The filtrate was concentrated *in vacuo*, and dissolved in 10 mL of 1*N* HCl in glacial acetic acid at 0 °C. 1.5 hr later, the volatiles were evaporated to afford the crude dipeptide. After purification with Prep-HPLC, the pure dipeptide was obtained. The yield for this step is quantitative. The yield reported below includes both coupling and deprotection steps.

(2*S*,3*R*)-TMT-L-Tic (116). Yield: 77%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{22}H_{26}N_2O_4$ 383.1971, found 383.1970. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 1.40 (d, 3H, J = 6.0 Hz), 1.89 (s, 3H), 2.06 (dd, 1H, J_1 = 5.0 Hz and J_2 = 13.0 Hz), 2.38 (s, 3H), 2.67 (dd, 1H, J_1 = 5.0 Hz and J_2 = 12.5 Hz), 3.55 (t, 1H, J = 5.0 Hz), 3.64-3.67 (m, 1H), 4.13 (d, 1H, J = 13.0 Hz), 4.40 (d, 1H, J = 10.0 Hz), 4.60-4.75 (m, 1H, buried in H_2O peak), 6.01 (s, 1H), 6.11 (s, 1H), 6.96-6.97 (m, 1H), 7.07-7.09 (m, 1H), 7.14-7.16 (m, 2H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 15.9, 20.5, 21.5, 31.5, 36.2, 44.6, 53.4, 57.9, 116.0, 117.3, 126.4, 127.2, 127.9, 133.1, 134.0, 139.9, 154.7, 170.4, 177.4, 178.8.

(2*S*,3*R*)-TMT-D-Tic (117). Yield: 79%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{22}H_{26}N_2O_4$ 183.1971, found 383.1969. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O,

90:10, v:v) δ 1.44 (d, 3H, J = 4.5 Hz), 2.06 (s, 3H), 2.38 (s, 3H), 2.44 (dd, 1H, J_1 = 5.5 Hz and J_2 = 13.5 Hz), 2.97-3.00 (m, 1H), 3.68-3.74 (m, 1H), 3.85 (d, 1H, J = 13.5 Hz), 4.36 (d, 1H, J = 13.0 Hz), 4.82 (d, 1H, J = 9.5 Hz), 4.96-4.98 (m, 1H), 6.08 (s, 1H), 6.17 (s, 1H), 6.84-6.85 (m, 1H), 6.96-6.97 (s, 1H), 7.06-7.10 (m, 2H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 15.8, 20.7, 21.5, 30.4, 36.1, 45.2, 53.1, 54.4, 115.4, 117.3, 125.9, 126.7, 127.3, 127.7, 128.5, 130.8, 132.4, 138.5, 139.5, 154.4, 169.6, 178.4.

(2*R*,3*S*)-TMT-L-Tic (118). Yield: 81%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{22}H_{26}N_2O_4$ 383.1971, found 383.1970. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 1.45 (d, 3H, J = 6.0 Hz), 2.05 (s, 3H), 2.38 (s, 3H), 2.41-2.46 (m, 1H), 2.98 (d, 1H, J = 15.5 Hz), 3.69-3.73 (m, 1H), 3.85 (d, 1H, J = 13.0 Hz), 4.70-4.75 (m, 1H, buried in H_2O peak), 6.08 (s, 1H), 6.17 (s, 1H), 6.84-6.85 (m, 1H), 6.96-6.97 (m, 1H), 7.06-7.10 (m, 2H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 15.8, 20.8, 21.6, 30.5, 36.2, 45.3, 53.2, 54.6, 115.5, 117.4, 126.6, 126.8, 127.3, 127.8, 128.5, 130.9, 132.5, 138.6, 139.6, 154.5, 169.7, 179.4.

(2*R*,3*S*)-TMT-D-Tic (119). Yield: 78%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{22}H_{26}N_2O_4$ 383.1971, found 383.1968. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) d 1.46 (d, 3H, J = 6.0 Hz), 1.92 (s, 3H), 2.12 (dd, 1H, J_1 = 5.0 Hz and J_2 = 12.5 Hz), 2.41 (s, 3H), 2.72 (dd, 1H, J_1 = 5.0 Hz and J_2 = 13.0 Hz), 3.62 (t, 1H, J = 5.5 Hz), 3.70-3.72 (m, 1H), 4.18 (d, 1H, J = 12.5 Hz), 4.45 (d, 1H, J = 10.5 Hz), 4.65-4.70 (m, 1H, buried in H_2O peak), 6.08 (s, 1H), 6.54 (s, 1H), 7.01-7.03 (m, 1H), 7.16-7.22 (m,

1H), 7.14-7.16 (m, 2H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 15.8, 20.5, 21.5, 31.4, 36.2, 44.5, 53.4, 57.8, 115.9, 117.2, 126.3, 127.2, 127.8, 133.0, 134.6,139.4, 139.9, 154.6, 170.3, 178.4.

(2*R*,3*R*)-TMT-L-Tic (120). Yield: 79%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{22}H_{26}N_2O_4$ 383.1971, found 383.1972. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 1.29 (d, 3H, J = 7.2 Hz), 1.95 (s, 3H), 2.03 (s, 3H), 3.06 (dd, 1H, J_1 = 6.0 Hz and J_2 = 16.2 Hz), 3.16 (dd, 1H, J_1 = 4.2 Hz and J_2 = 16.2 Hz), 3.68-3.71 (m, 1H), 3.83-3.87 (m, 1H), 4.24 (d, 1H, J = 15.0 Hz), 4.90 (d, 1H, J = 9.0 Hz), 4.93-4.95 (m, 1H), 6.49 (s, 1H), 6.56 (s, 1H), 6.99 (d, 1H J = 7.8 Hz), 7.08-7.31 (m, 4H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) d 15.4, 25.7, 31.9, 32.4, 37.3, 46.6, 52.8, 56.2, 116.2, 117.8, 126.4, 127.7, 127.3, 128.0, 128.3, 131.9, 133.6, 139.4, 140.4, 155.0, 169.5, 178.6.

(2*R*,3*R*)-TMT-D-Tic (121). Yield: 85%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{22}H_{26}N_2O_4$ 383.1971, found 383.1971. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 1.33 (d, 3H, J = 7.2 Hz), 2.11 (s, 3H), 2.26 (s, 3H), 2.78 (dd, J_1 = 6.0 Hz and J_2 = 13.0 Hz), 2.99 (dd, 1H, J_1 = 4.8 Hz and J_2 = 13.0 Hz), 3.12-3.18 (m, 1H), 3.66-3.71 (m, 1H), 3.96-3.98 (m, 1H), 4.43 (d, 1H, J = 13.8 Hz), 4.89-4.92 (m, 1H), 6.28 (s, 1H), 6.59 (s, 1H), 7.12-7.14 (m, 1H), 7.18-7.23 (3H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 15.5, 22.0, 22.6, 33.0, 38.7, 46.1, 54.1, 59.6, 117.4, 119.2, 127.9, 128.4, 128.6, 129.1, 129.2, 133.9, 141.6, 156.1, 170.8, 179.2.

(2*S*)-DMT-L-Tic (122). Yield: 72%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{21}H_{24}N_2O_4$ 369.1814, found 369.1816. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 2.07 (s, 6H), 2.16-2.21 (m, 1H), 2.66-2.72 (m, 1H), 3.09-3.21 (m, 4H), 3.24-3.27 (m, 1H), 4.24 (d, 1H, J = 13.0 Hz), 7.08 (d, 1H, J = 6.0 Hz), 7.22 (d, 1H, J = 6.5 Hz), 7.21-7.30 (m, 2H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 19.4, 31.3, 31.4, 44.5, 49.8, 58.0, 115.7, 122.6, 126.5, 127.2, 127.9, 128.0, 133.1, 134.2, 139.9, 154.9, 169.9, 178.6.

(2*S*)-TMT-D-Tic (123). Yield: 75%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{21}H_{24}N_2O_4$ 369.1814, found 369.1817. ^{1}H-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 2.12 (s, 6H), 2.76 (dd, 1H, J_1 = 5.0 Hz and J_2 = 13.5 Hz), 3.05-3.18 (m, 4H), 3.45 (d, 1H, J = 13.0 Hz), 4.27 (d, 1H, J =13.0 Hz), 4.98 (dd, 1H, J_1 = 2.5 Hz and J_2 = 5.5 Hz), 6.20 (s, 2H), 6.65 (d, 1H, J = 6.0 Hz), 7.01-7.04 (m, 2H), 7.07 (m, 2H). ^{13}C-NMR (d_3-sodium acetate buffer in H_2O/D_2O, 90:10, v:v) δ 19.5, 21.0, 30.5, 30.9, 45.3, 49.5, 55.0, 115.4, 122.5, 126.1, 126.7, 127.4, 128.2, 130.9, 132.3, 139.4, 154.9, 169.5, 178.4.

Radiolabeled ligand binding assays. Membranes were prepared according to the following procedure: adult male Sprague-Dawley rats (200-300 g) obtained from Harlan Sprague-Dawley, Inc. (Indianapolis, IN) were sacrificed and their brains immediately removed and placed on ice. The whole brain was homogenized in 20 volumes of 50 mM Tris-HCl stock buffer (pH 7.4) with a glass-Teflon homogenizer. The homogenate was centrifuged (48000 *g* for 15 min), resuspended, and preincubated (25 °C for 30 min) to

remove endogenous opioids. The homogenate was centrifuged and resuspended (0.5% final concentration). Binding affinities of the prepared peptide ligands **116-123** were measured against deltorphin II (Tyr-DAla-Phe-Glu-Val-Val-Gly-NH_2) and [^{3}H]DAMGO ([^{3}H]Tyr-D-Ala-Gly-*N*-methyl-Phe-Gly-ol) by a rapid filtration technique. A solution of 0.75 nM deltorphin II or 1.0 nM [^{3}H]DAMGO in a total volume of 1 mL of 50 mM Tris-HCl buffer (pH 7.4) containing bovine serum albumin (1.0 mg/mL), bacitracin (50 μg/mL), bestatin (30 μg/mL), captopril (10 μM), and phenylmethanesulfonyl fluoride (0.1 mM) was used. Assays were done in duplicate with 10 μM naltrexone hydrochloride to define nonspecific tissue binding. The binding reaction was terminated by rapid filtration through presoaked (0.5% poly(ethylenimine) solution) GF/B Whatman glass fiber strips with a Brandel cell harvester followed immediately by three rapid washes with 4-mL aliquots of ice-cold saline solution. The filters were removed and soaked in 10 mL of scintillation fluid at 4 °C for at least 6 hr before bound radioactivity was measured. The data were analyzed by nonlinear least-squares regression analysis.

3-(*tert*-Butyldimethylsiloxy)benzaldehyde (131) and 4-(*tert*-butyldimethylsiloxy)benzaldehyde (132). To a solution of 4- or 3-hydroxybenzaldehyde (20 mmol), DMAP (0.8 mmol, 0.04 eq), and 22 mL of 1M TBDMSCl in THF (22 mmol, 1.1 eq) in 20 mL of freshly distilled dichloromethane was added triethylamine (22 mmol, 1.1 eq) at 0 °C. After 1 hr, the reaction mixture was warmed to room temperature, stirred until the completion of the reaction by TLC, and quenched by saturated ammonium chloride. The mixture was washed with water, dried over magnesium sulfate and

evaporated *in vacuo* to afford the crude product. After flash column chromatography on silica gel with 1:9 EtOAc/hexanes as eluent, pure **131** or **132** was obtained.

3-(*tert*-Butyldimethylsiloxy)benzaldehyde (131). Oily liquid. Yield: 89%. Elemental analysis: $C_{13}H_{20}O_2Si$ calcd. C: 70.85, H: 9.15; found C: 70.90, H: 9.12. ^{1}H-NMR ($CDCl_3$) δ 0.21 (s, 6H), 1.07 (s, 9H), 7.10-7.11 (m, 1H), 7.26-7.48 (m, 3H), 9.94 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ -4.4, 18.2, 25.6, 119.9, 123.5, 126.5, 130.1, 137.9, 156.4, 192.1.

4-(*tert*-Butyldimethylsiloxy)benzaldehyde (132). Oily liquid. Yield: 95%. Elemental analysis: $C_{13}H_{20}O_2Si$ calcd. C: 70.85, H: 9.15; found C: 70.87, H: 9.14. ^{1}H-NMR ($CDCl_3$) δ NMR ($CDCl_3$) δ 0.24 (s, 6H), 1.05 (s, 9H), 7.11-7.13 (m, 1H), 7.25-7.47 (m, 3H), 9.95 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ -4.4, 18.2, 25.6, 127.5, 131.1, 138.9, 156.7, 195.1.

133 and 134. To a solution of **131** or **132** (16 mmol) in 30 mL of freshly distilled THF was added 9 mL of 2*M* 4-tert-butylphenylmagnesium bromide in Et_2O (18 mmol, 1.1 eq) at 0 °C. 20 min later, the reaction mixture was warmed to room temperature. The reaction was quenched by saturated ammonium chloride after a 4-hr stir. The reaction mixture was extracted with diethyl ether, and the combined ether solution was dried over $MgSO_4$ and evaporated *in vacuo* to give crude product. Column chromatography on silica gel with 1:9 EtOAc/hexanes as eluent led to pure **133** or **134**.

133. Oily liquid. Yield: 95%. Elemental analysis: calcd. for $C_{23}H_{34}OSi$ C: 77.90, H: 9.66; found C: 77.99, H: 9.11. ^{1}H-NMR ($CDCl_3$) δ 0.16 (s, 6H), 0.96 (s, 9H), 1.31 (s,

9H), 2.15 (d, 1H, J = 3.5 Hz), 5.76 (d, 1H, J = 2.5 Hz), 6.72-6.74 (m, 1H), 6.86-6.87 (m, 1H), 6.95-6.97 (m, 1H), 7.18 (t, 1H, J = 7.7.8 Hz), 7.25-7.29 (m, 2H), 7.34-7.36 (m, 2H). ^{13}C-NMR ($CDCl_3$) d -4.2, 18.2, 25.7, 31.3, 34.5, 75.8, 118.2, 119.0, 119.4, 125.4, 126.3, 129.4, 140.8, 145.5, 150.5, 155.7.

134. Oily liquid. Yield: 95%. Elemental analysis: calcd. for $C_{23}H_{34}OSi$ C: 77.90, H: 9.66; found C: 77.95, H: 9.15. ^{1}H-NMR ($CDCl_3$) δ 0.19 (s, 6H), 0.99 (s, 9H), 1.31 (s, 9H), 2.11 (d, 1H, J = 3.5 Hz), 5.77 (d, 1H, J = 3.5 Hz), 6.78-6.81 (m, 2H), 7.21-7.39 (m, 6H). ^{13}C-NMR ($CDCl_3$) d -4.2, 21.4, 25.7, 31.3, 34.5, 75.7,119.9, 125.3, 126.2, 127.8, 136.7, 141.0, 150.4, 155.0.

135 and 136. To a solution of **133** or **134** in 50 mL of anhydrous ethyl ether under Ar, 1.1 mL (22 mmol, 2.2 eq.) of anhydrous pyridine was added via a syringe at –78 °C. After 5 min, 1.1 mL (11 mmol, 1.1 eq.) of phosphorus tribromide was slowly dropped into the solution over 1hr. Formation of a white slurry was observed. The mixture was stirred for 2 hr at –78 °C and overnight at room temperature. Completion of the reaction was monitored by TLC. The reaction was quenched by slowly adding an ice-water mixture with stirring at 0 °C, and the mixture was stirred for 30 min at 0 °C. The ether layer was separated from the aqueous layer and the aqueous phase was washed with diethyl ether (2 x 50mL each). The combined ethyl ether solution was washed with ice-cold 85% phosphorus acid (50 mL), saturated sodium bicarbonate (2 x 100 mL) and water (2 x 100 mL). The ether solution was dried over magnesium sulfate and evaporated *in vacuo* to yield a white solid residue. No further purification of compound **135** or **136** was necessary.

135. Oily liquid. Yield: 87%. ^{1}H-NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.94 (s, 9H), 1.29 (s, 9H), 6.2 (s, 1H), 6.72-6.73 (m, 1H), 6.92-6.93 (m, 1H), 7.00-7.01 (m, 1H), 7.14-7.16 (m, 1H), 7.31-7.35 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ -4.3, 25.7, 31.2, 34.6, 55.2, 119.7, 120.4, 121.3, 125.4, 128.1, 129.4, 138.1, 142.5, 151.1, 155.6. Elemental analysis: for $C_{23}H_{33}OBrSi$: Calcd. C: 63.73, H: 7.67; found C: 63.51, H: 7.57.

138. A reaction mixture of 2.0 g of piperazine-2-one (20 mmol), 2.0 g of $NaHCO_3$ (24 mmol, 1.2 eq.) and 2.3 mL of $PhCH_2Cl$ (20 mmol, 1.0 eq) in 25 mL of EtOH was refluxed for 5 hr. The reaction was quenched by adding deionized water, EtOH was evaporated in vacuo, and the mixture was extracted with EtOAc (5 x 30 mL). The combined EtOAc solution was dried over magnesium sulfate and evaporated *in vacuo* to give **138**. Yield: 76%. HRMS (FAB) $[M+H]^+$ calcd. For $C_{11}H_{15}N_2O$ 191.1184, found 191.1178. ^{1}H-NMR ($CDCl_3$) δ 2.64 (t, 2H, J = 5.5 Hz), 3.15 (s, 2H), 3.33-3.35 (m, 2H), 3.58 (s, 2H), 6.58 (s, 1H), 7.26-7.34 (m, 5H). ^{13}C-NMR ($CDCl_3$) δ 41.4, 48.5, 57.0, 61.8, 127.4, 128.4, 129.0, 136.9, 169.6.

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