UNIVERSITY OF OKLAHOMA
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SYNTHESIS OF SYMMETRICAL AND OPTICALLY ACTIVE α-AMINO ACIDS VIA HOMOLOGATION OF Ni(II) COMPLEXED GLYCINE SCHIFF BASES

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By

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Acronyms/Abbreviations

AA	Amino Acid
Ac	Acetyl ($CH_3C=O$)
Aib	Aminoisobuturic acid
Alk	Alkyl
Atc	2-Aminotetraline-2-carboxylic acid
aq	aqueous
Bn	Benzyl ($-CH_2-C_6H_5$)
Boc	*t*-Butyloxycarbonyl ($CO-t-C_4H_9$)
BOP	Benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluoro-phosphate
Bu	Butyl ($-C_4H_9$)
br.	broad (NMR)
^oC	Degrees Celsius
Calcd.	Calculated
Cbz	Carbobenzyloxy ($BnOC=O$)
d	doublet (NMR)
d	day (time)
3D	Three Dimensional
DBU	1,8-Diazabicyclo[5.4.0]-undec-7-ene
DCH	dicyclohexyl
de	Diastereomeric excess
decomp.	decomposed
DIEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)-pyridine
DMeG	α,α-Dimethylglycine
DMF	Dimethylformamide
Dmt	2',6'-Dimethyltyrosine
DOPA	3,4-Dihydroxy-L-phenylalanine
E	Entgegen (opposite, trans)
ee	enantiomeric excess
Et	Ethyl
et al.	et alia (a number of people)
ESI	Electrospray ionization
equiv	equivalent
g	gram(s)
h	hour

HIV	Human immunodeficiency virus
HMW	High molecular weight
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution MassSpectrometry
Hz	Hertz
i	iso
J	Coupling constant (NMR)
KHMDS	Potassium Hexamethyldisilazane
LDA	Lithium Diisopropylamide
L	Liter(s)
m	multiplet (NMR)
m	meta
M	Molecular mass
Me	Methyl (-CH_3)
mg	milligram(s)
MHz	Megahertz
min	minute(s)
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
M.P.	Melting Point
m/z	mass tocharge
n	normal
N	Normal (Concentration)
NaHMDS	Sodium Hexamethyldisilazane
n-BuLi	normal butyl lithium (LiC_4H_9)
N.D.	not determined
NGE	nucleophilic glycine equivalent
nm	nanometer
NMR	Nuclear Magnetic Resonance
NOBIN	2-Amino-2'-hydroxy-1,1'-binaphthyl
o	ortho
p	para
PA	Picolinic Acid
PAAP	2-(Picolinoylamino)-acetophenone
PABP	2-(Picolinoylamino)-benzophenone

Ph	Phenyl (C_6H_5)
Phe	Phenylalanine
ppm	parts per million
prop	propyl
PT	Phase Transfer
PTC	Phase Transfer Conditions/ Phase Transfer Catalyst
q	quartet (NMR)
UV	Ultraviolet
R_f	Retention factor
r.t.	room temperature
s	singlet (NMR)
S_N1	Nucleophilic substitution reaction with a unimolecular rate determining step
S_N2	Nucleophilic substitution reaction with a bimolecular rate determining step
sym	symmetrical
t	triplet (NMR)
t, *tert*	tertiary
TBAB	Tetrabutyl Ammonium Bromide
TBDMS	*tert*-butyldimethylsiloxyl
TEA	Triethylamine
THF	Tetrahydrofuran
Tic	Tetrahydroisoquinoline
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
Tol	Toluene (CH_3-C_6H_5)
Tr	Triphenylmethyl
Ts	Tosyl (*p*-CH_3-C_6H_4-SO_2)
TS	Transition State
Tyr	Tyrosine
Z	Zusammen (together, cis)
δ	Chemical Shift
λ	Wavelength
$[\alpha]_D^{25}$	Specific Rotation at 25 ^oC
Δ	Heat

ABSTRACT

The focus of this research project is the synthesis of a variety of sterically constrained and chemically unique α-amino acids. Picolinic acid derived Ni(II) complexes of glycine Schiff bases proved to be a practical and efficient platform for the synthesis of a variety of sterically constrained α,α-disubstituted α-amino acids via homogeneous alkyl halide alkylation reactions. In particular the homologation of this picolinic acid derived Ni(II) complexed nucleophilic glycine equivalent (NGE) in dimethylformamide (DMF) with sodium *t*-butoxide and electrophiles such as benzyl, cinnamyl, or allyl bromide, as well as methyl, ethyl, propyl, butyl, and pentyl iodides, has proven useful for the preparation of the corresponding α,α-disubstituted α-amino acid derivatives in high chemical yields (>90%).

In order to overcome some of the limitations associated with the previously described Ni(II) complexed NGE a new generation of modular Ni(II) complexed NGE were introduced. The flexibility of this modular design has allowed for unprecedented methodological adaptability allowing the unification of at least four currently orthogonal methods for the preparation or resolution of α-amino acids. Of particular interest was the application of the Ni(II) complex of the glycine Schiff base with *N*-(2-acetyl-phenyl)-2-piperidylacetamide for the preparation of optically active β-substituted pyroglutamic acids via 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) catalyzed Michael additions of the NGE and optically active β-substituted acrylic acid derivatives in DMF. This robust process results in the formation of the β-substituted pyroglutamic acid precursors in diastereomerically pure form and can tolerate acrylic acid derived

Michael acceptors which contain a variety of sterically constraining and/or electron rich groups, such as 3,4-dichlorophenyl, *i*-propyl, 2-methoxyphenyl, *N*-tosyl-indolyl moieties, in the beta position.

Furthermore, optically active alkylamine containing ligands, such as (*R*)-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide, have demonstrated potential for the separation of enantiomers of racemic α-amino acids via Ni(II) complex formation and chromatographic separation of the diastereomeric complexes. This procedure has proven useful for a variety of α-amino acids such as, alanine, valine, phenyl glycine, α-aminobuteric acid, and α-aminopentanoic acid. The metal complexed glycine equivalents required for the preparation of the α-amino acids described within are available via simple and concise synthetic approaches on the large scale and are extremely economical given the recyclable ligands utilized.

CHAPTER 1

Importance and Classical Synthesis of α-Amino Acids

1.1: Introduction

It would be difficult to overstate the biological importance of α-amino acids, the building blocks of life, and perhaps the most studied class of organic compounds.[1] Besides their primary function as structural units of peptides and proteins, they also serve countless biological functions in most living things. Non-proteinogenic α-amino acids are frequently found in the peptides of cell walls and capsules of numerous bacteria and fungi as well as in various natural antibiotics.[2] Naturally occurring amino acids have been extensively used as a "chiral pool" for the preparation of a plethora of biologically and pharmacologically active compounds and are widely used in the pharmaceutical, agrichemical and food industries.[3] Unnatural, tailor-made α-amino acids are increasingly employed in the preparation of new synthetic enzymes, hormones and immunostimulants. More recently, sterically constrained α-amino acids have found indispensable applications in the rational de novo design of peptides and peptidomimetics with enhanced bio-stability and physiological functions.[4] The structural diversity, biological activity and application of α-amino acids in medicine and health related sciences are far too broad to be discussed in detail in this section. Briefly discussed below are the most general and commonly used approaches for the asymmetric synthesis of α-amino acids.

1.2: Asymmetric Synthesis of α-Amino Acids

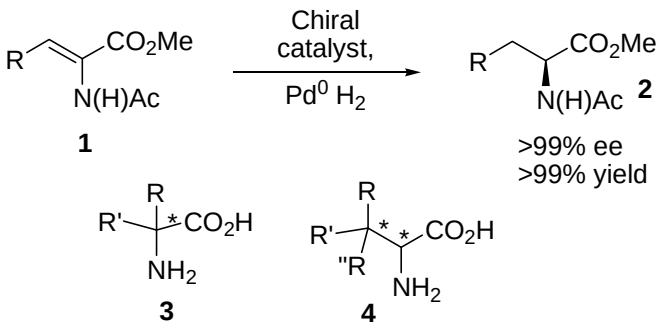
The unique role of α-amino acids in biology and chemistry has fueled a large amount of attention within the synthetic community aimed towards the development of efficient methods for the preparation of α-amino acids. From the middle of the last century, countless reports have been dedicated to the asymmetric synthesis of natural as well as various structurally diverse, tailor-made α-amino acids.[5] Analysis of the relevant literature reveals three major and general approaches which are outlined below.

1.2.1: Asymmetric Hydrogenation

One of the general approaches to the synthesis of α-amino acids is a catalytic asymmetric hydrogenation of properly protected α,β-dehydro-α-amino acid derivatives **1** (Scheme 1). Over the last decade,[6] this field has witnessed truly spectacular achievements. Currently available methods allow for the hydrogenation step to proceed with virtually complete (>99%) chemical yield and enantioselectivity.

While the asymmetric hydrogenation might be the method of choice for preparation of some structurally simple amino acids, it suffers several methodological drawbacks. For example, the starting dehydro-α-amino acids **1** must be individually prepared, usually by multi-step methods, for each new amino acid that is desired. Most importantly, this methodology is much less useful for synthesis of highly biologically valuable sterically constrained and/or polyfunctional amino acids and not applicable for the preparation of α- or β-quaternary derivatives of general structures **3** and **4**.

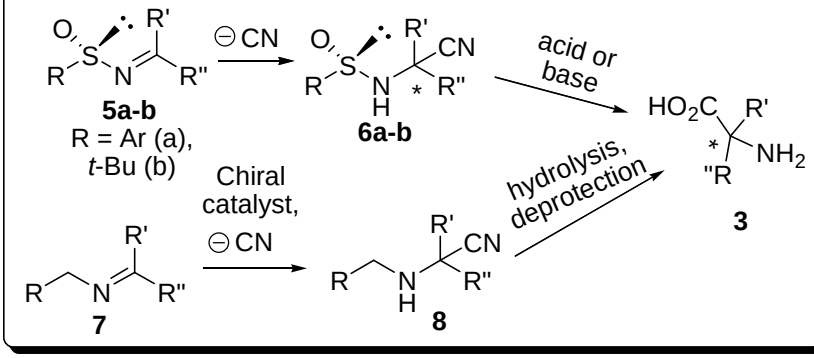
Scheme 1. Asymmetric Hydrogenation of α,β-Unsaturated α-Amino Acids



1.2.2: Asymmetric Strecker Synthesis

Another general method for the synthesis of α-amino acids is a hydrocyanation of imines (the second step in the Strecker reaction). Both stoichiometric and catalytic approaches for this reaction have been intensively studied over the past several years. The Davis[7] and Ellman[8] groups have developed convenient and highly diastereoselective approaches using chiral sulfinimines as starting compounds (Scheme 2).

Scheme 2. Asymmetric Strecker Reaction of Chiral Sulfinimines



Truly impressive protocols for catalytic asymmetric hydrocyanation have been reported by the Lipton,[9] Jacobsen,[10] Snapper-Hoveyda,[11] Corey,[12] Kobayashi[13] and Shibasaki[14] laboratories. While the Strecker synthesis provides a simple and reliable approach for many types of amino acids, it still has several serious methodological drawbacks. For instance, the hydrocyanation cannot be directly used for simultaneous formation of two stereogenic centers as required in the synthesis of β-substituted natural and numerous biologically and synthetically important unnatural α-amino acids. Moreover, the sometimes problematic removal of the *N*-protecting groups, harsh conditions for hydrolysis of the nitrile function, and lethal properties of the hydrogen cyanide or its derivatives present some additional disadvantages of this approach.

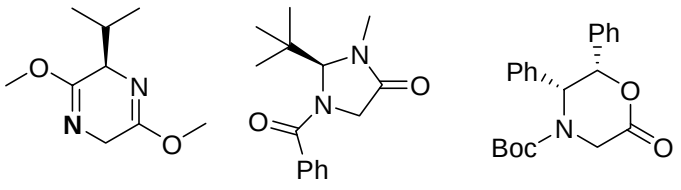
1.2.3: Asymmetric Homologation of Glycine

The third major approach for the asymmetric synthesis of α-amino acids is the homologation of glycine derivatives. It is methodologically the most straightforward, practical, and so far the most reliable and general method for preparing various amino acids, in particular, structurally complex and sterically constrained derivatives. Analysis of the relevant literature, dealing with the asymmetric homologation approach, revealed two general orthogonal directions.

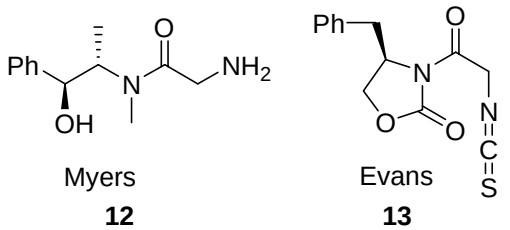
1.2.3.1: Chiral Equivalents of Nucleophilic Glycine Equivalents

The first approach to the synthesis of α-amino acids via homologation of nucleophilic glycine equivalents involves the design of properly protected glycine equivalents that incorporate an element of chirality into their framework. This approach has enjoyed a great deal of creativity producing a wealth of methodologies for the asymmetric synthesis of α-AA via the diastereoselective homologation of chiral glycine templates. Among the chiral derivatives of glycine that have been developed are the bis-lactim ether **9** introduced by the group of Professor Schollkopf[15], the optically active imidazolidinone derivative **10** introduced by Professor Seebach's group[16], the diastereomeric lactone **11** introduced by Professor Williams and co-workers[17], pseudoephedrine glycinate **12** developed by Professor Myeres[18], as well as the optically active isothiocyanate **13** by Professor Evans and associates[19] (Figure 1).

Figure 1. Optically Active Nucleophilic Glycine Equivalents



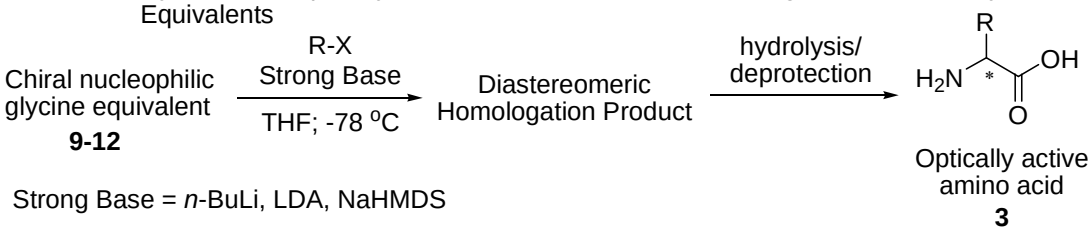
9 **10** **11**



12 **13**

The chiral derivatives of glycine **9-13** have received widespread attention for the laboratory-scale asymmetric synthesis of various α-amino acids, due to their ability to provide virtually complete control over the stereochemistry of the α-stereogenic carbon of target amino acids. However, the major drawback of templates **9-12**, as well as most of the other currently available chiral glycine equivalents, is the low C-H acidity of the glycine moiety, making it necessary to use strong bases. The application of bases such as *n*-BuLi, LDA, or NaHMDS, at low temperature (-78 ^{o}C) in order to generate the corresponding enolate makes their application problematic and impractical even on the relatively large scale (Scheme 3). Furthermore, usually incomplete chemical yields, liberation and isolation of the target amino acid, as well as various synthetic problems related to the preparation of derivatives **9-13** render these multistep methods synthetically unattractive.

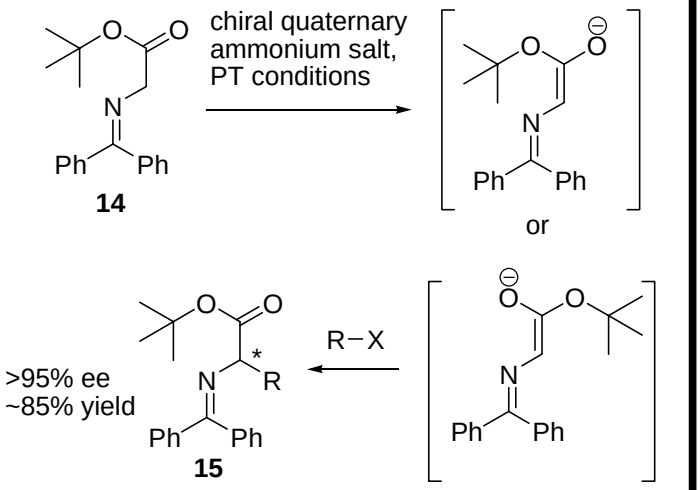
Scheme 3. Synthesis of Optically Active α-Amino Acids Via Homologation of Chiral Glycine Equivalents



1.2.3.2: Enantioselective Homologation of Achiral Glycine Schiff Base Esters under Phase Transfer Catalyzed Conditions

The second approach for the synthesis of α-amino acids via homologation of protected glycine equivalents centers around the homologation of Schiff base **14** (Scheme 4) under phase transfer conditions using a catalytic amount of chiral quaternary ammonium salts. Since the seminal report by Professor O'Donnell[20a] on the enantioselective alkylation of Schiff base **14** using *Cinchona* alkaloid-derived phase transfer catalysts, the focus of creative efforts in this area were concentrated on the development of new chiral catalysts. Truly impressive reports from the laboratories of O'Donnell,[20b] Lygo,[21] Jew-Park,[22] Najera,[23] Maruoka,[24] Shibasaki[25] and others[26] offer a wealth of structural modifications of the *Cinchona* alkaloids as well as the design of catalysts possessing elements of C_2-symmetry and axial chirality, which have been recently reviewed in the excellent texts of O'Donnell,[20b] Lygo[27] and Maruoka.[24a,28] Some of the catalysts can be used in an amount as low as 1 mol % providing a stereochemical outcome as high as 99% ee. Over the past several years, design of new phase transfer catalysts for homologation of achiral glycine equivalents has become one of the most intensively studied subjects in the field of asymmetric catalysis.[29] However, room remains for further improvement in the catalyst design, for instance, the major disadvantages of the currently available catalysts are their very large molecular weights and low-yield multistep synthesis.

Scheme 4. Asymmetric Phase Transfer Catalyzed Homologation of Glycine Equivalent 14



By contrast, since its introduction by O'Donnell in 1978,[30] not a single attempt has been made to improve on the structure of Schiff base **14**. While compound **14** features excellent solubility in most organic solvents and high CH acidity of the glycine moiety, its application is generally plagued by the hydrolytic instability of **14** as well as the products of its homologation. Thus, while excellent enantioselectivity (99% ee) can be achieved with the current catalysts, the products are usually obtained in low chemical yields (80%). Moreover, the controversial issue of the corresponding enolate geometry, (*Z*) or (*E*), hampers the elucidation of the stereochemical outcome, and thus the truly rational design of new and more efficient catalysts. Finally, the Schiff base **14** is rather expensive, and due to its hydrolytic instability cannot be stored in the open air. Therefore, the need for alternative, improved and generally applicable achiral glycine equivalents represents an unsolved and general problem in the asymmetric synthesis of α-amino acids via phase transfer catalyzed conditions.

1.4 Project Objectives

Although there have been numerous unique methodologies investigated, the lack of a general process for the efficient preparation of structurally and chemically diverse α-amino acids has spawned interest into the development of a general and practical approach for their synthesis. Therefore, the principal aim of this research project is to develop a practical methodology for the synthesis of α-amino acids via a scalable chemical process which could be conducted under operationally convenient conditions with an attractive cost structure.

After analyzing the generality and limitations of various approaches for the synthesis of α-amino acids, it was found that among the most practical and general is the homologation of nucleophilic glycine equivalents. It is envisioned that the homologation of nucleophilic glycine equivalents could unify a variety of currently orthogonal and conceptually different approaches to the synthesis of sterically constrained and/or enantiomerically pure α-amino acids under one synthetically powerful, flexible, and efficient methodology.

The major focus of this research project will be the identification, synthesis and exploitation of a synthetically versatile and robust nucleophilic glycine equivalent(s). Of particular interest is the relatively unstudied picolinic acid derived Ni(II) complex of glycine due to its increased stability and relatively high chemical reactivity, compared with other glycine equivalents. The initial investigations of this research project will center around the application of this Ni(II) complexed nucleophilic glycine equivalent, however as its limitations become apparent and/or complications resulting from its

implementation arise, the design of a new nucleophilic glycine equivalent(s) may become necessary.

The primary homologation methods employed will include, but are not limited to, alkyl halide alkylations and Michael addition reactions. Although the Michael addition reactions will primarily be conducted in polar solvents such as DMF with organic bases, while the alkyl halide alkylation reactions will be studied in a variety of solvents under homogeneous and heterogeneous (phase-transfer) reaction conditions. With respect to the synthesis of optically active α-amino acids via the asymmetric homologation of the nucleophilic glycine equivalent, the results obtained from the application of various reaction conditions and stereocontrolling elements will be carefully analyzed to elucidate the factors that aid in the asymmetric induction. The latter analysis will lead to an enhanced understanding of the molecular recognition, facilitating the further rational design of improved recyclable ligands for the metal complexes and experimental procedures.

1.5 List, by Chapter, of Previously Published Manuscripts Which Have Been Utilized Within the Text of This Dissertation

The material discussed within the text of this dissertation has been previously published in the following peer reviewed professional journals.

Chapter 2:

1) Ueki, Hisanori; Ellis, Trevor K.; Martin, Collin H.; Soloshonok, Vadim A. **Efficient Large-scale Synthesis of Picolinic Acid-derived Nickel(II) Complexes of Glycine.** *E. J. Org. Chem.* **2003**, *10*, 1954.
2) Ellis, Trevor K.; Martin, Collin H.; Ueki, Hisanori; Soloshonok, Vadim A. **Efficient, Practical Synthesis of Symmetrically α,α-disubstituted α-amino Acids.** *Tetrahedron Lett.*. **2003**, *44*, 1063.
3) Reproduced in part with permission from Ellis Trevor K; Martin Collin H; Tsai Gary M; Ueki Hisanori; Soloshonok Vadim A **Efficient Synthesis of Sterically Constrained Symmetrically α,α-Disubstituted α-amino Acids Under Operationally Convenient Conditions**. *J. Org. Chem.*. **2003**, *68*, 6208. Copyright 2003 American Chemical Society.
4) Reproduced in part with permission from Ellis Trevor K; Hochla Veronica M; Soloshonok Vadim A **Efficient Synthesis of 2-aminoindane-2-carboxylic Acid Via Dialkylation of Nucleophilic Glycine Equivalent**. *J. Org. Chem*. **2003**, *68*, 4973. Copyright 2003 American Chemical Society.

Chapter 3:

1) Ellis, Trevor K.; Ueki, Hisanori; Soloshonok, Vadim A. **New Generation of Nucleophilic Glycine Equivalents.** *Tetrahedron Lett*. **2005**, *46*, 941.
2) Soloshonok, Vadim A.; Ueki, Hisanori; Ellis, Trevor K.; Yamada, Takeshi; Ohfune, Yasufumi. **Application of Modular Nucleophilic Glycine Equivalents for Truly Practical Asymmetric Synthesis of β-Substituted Pyroglutamic Acids.** *Tetrahedron Lett*. **2005**, *46*, 1107.
3) Ellis, Trevor K.; Soloshonok, Vadim A. **Synthesis of A New Generation of Ni(II) "NH" Complexes, And Examples of Their Unusual Chemoselectivity**. *Synlett.* **2006**, *4*, 533.
4) Reproduced in part with permission from Soloshonok, Vadim A.; Ueki, Hisanori; Ellis, Trevor K.; Yamada, Takeshi; Ohfune, Yasufumi. **The Design, Synthesis and Evaluation of a New Generation of Modular Nucleophilic Glycine Equivalents for the Efficient Synthesis of Sterically Constrained Amino Acids**. *J. Org. Chem.* **2006**, *71*, 8572. Copyright 2006 American Chemical Society.

Chapter 4:

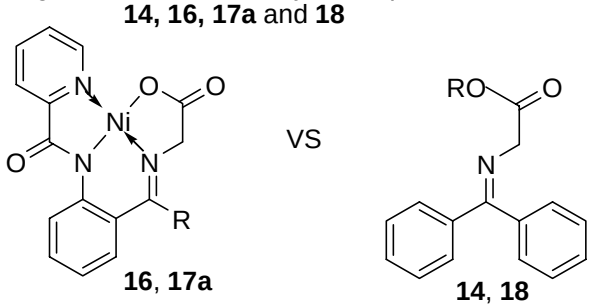
1) Ueki, Hisanori; Ellis, Trevor K.; Khan, Masood A.; Soloshonok, Vadim A. **Highly Diastereoselective Synthesis of New, Carbostyril-based Type of Conformationally-constrained β-phenylserines.** *Tetrahedron*. **2003**, *59*, 7301.

Chapter 2

Preparation of Picolinic Acid Derived Ni(II) Complexes of Glycine Schiff Bases and Their Application as Achiral Nucleophilic Glycine Equivalents.

2.1: Introduction

Figure 2. Schiff Base Glycine Equivalents **14, 16, 17a** and **18**



16, **17a**

R = Me (**16**)
R = Ph (**17a**)

14, **18**

R = Et (**18**)
R = *t*-Bu (**14**)

Picolinic acid-derived (PA-derived) Ni (II) complexes **16** and **17a** (Figure 2) have emerged as new types of highly efficient achiral nucleophilic glycine equivalents.[31-32] Their superior qualities in relation to conventional *N*-(phenylmethylene) glycine derivatives **14** and **18** include chemical stability and predictable formation of the corresponding (*Z*) geometrically homogeneous enolates,[33] a feature of paramount importance for highly enantioselective homologation of the glycine moieties in **16** and **17a**. Thus, the application of complexes **16** and **17a** as glycine equivalents has been

demonstrated in asymmetric Michael addition reactions[31] and catalytic alkylations under phase-transfer conditions.[32]

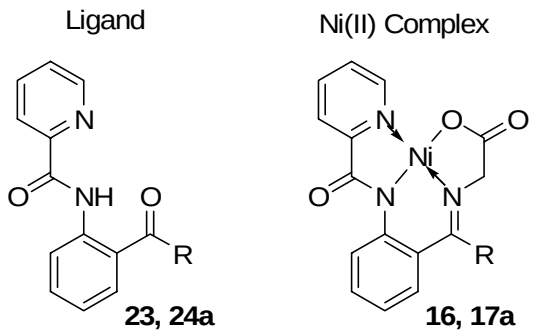
2.2: Synthesis of 2-[*N*-(α-picolyl)amino]-aceto/benzophenone Ligands 23, 24a-c

2.2.1: Previous Synthetic Approaches

It was previously reported that the synthesis (95% yield) of 2-[*N*-(α-picolyl)amino]acetophenone (PAAP, **23**; Figure 3), the ligand for complex **16**, could be accomplished starting from PA and 2-aminoacetophenone and with the use of BOP (benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate) as a condensing reagent.[33] On the other hand, 2-[*N*-(α-picolyl)amino]benzophenone (PABP, **24a**), the ligand for complex **17a**, was prepared in 85% yield from 2-aminobenzophenone and thionyl chloride through the in situ formation of the corresponding chloroanhydride of PA **19**.[32] It was found that the literature methods,[2,4] although successful, are unattractive as expeditious and reliable methods for large-scale preparation of **16** and **17a**. For instance, the synthesis of **23** and **24a** by application of peptide coupling reagents such as BOP is a very simple and convenient approach and could be effectively used for relatively small scale preparations, however the high molecular weights and cost of these coupling reagents render this method economically unattractive for the large-scale synthesis. On the other hand, application of thionyl chloride has serious synthetic

disadvantages, such as substantial formation of byproducts, necessitating laborious purification of ligands **23** and **24a**.

Figure 3. Picolinic Acid Derived Ligands **23** and **24a** and Ni(II) Complexes **16** and **17a**



23, 24a **16, 17a**

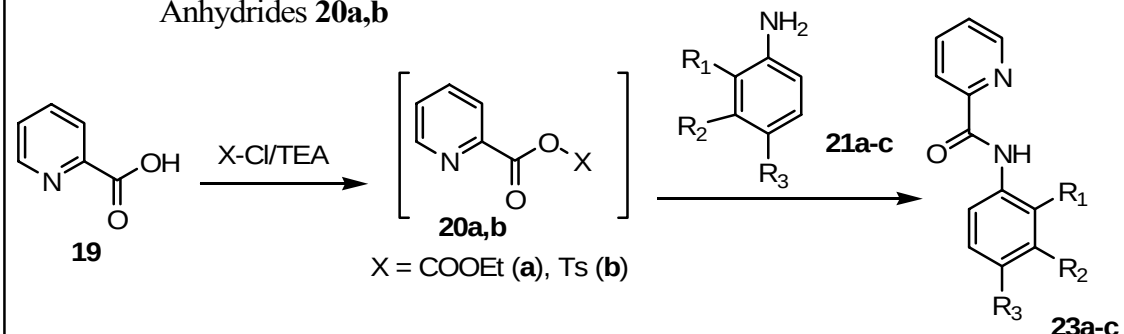
R = Me (**16, 23**)
R = Ph (**17a, 24a**)

2.2.2: Improved Synthesis of the 2-[*N*-(*α*-picolyl)amino]aceto- and Benzophenone Derived Ligands 23, 24a-c

Amidation of carboxylic acids in general and formation of a peptide bond in particular has been an area of intense research and is well documented.[34] The reagents most commonly used to increase the electrophilicity of the carboxylic function are carbodiimides,[35] 1,1'-(carbonyldioxy)dibenzotriazole,[36] sulfuryl chloride fluoride,[37] arylsulfonyl chlorides,[38] alkyl chloroformates,[39] and others.[40] In these publications, the synthetic power and generality of the methods is demonstrated by the use of a wide range of amines, however there are few examples which apply to a sterically hindered or weakly nucleophilic amino function. Therefore, amidation of acids with *o*-aminoaceto- and –benzophenone derivatives **21a-c**, and **22a-c** is a rather challenging task, as these

compounds possess the undesirable features of steric constraint and low nucleophilicity of the amino group. Of the methods cited above, activation of the carboxylic function by in situ formation of the corresponding mixed carboxylicsulfonic or -carbonic anhydrides was shown to be effective for amidation reactions with sterically hindered or weakly nucleophilic amines.[38,39]

Scheme 5. Amidation of Picolinic Acid with Amines **21a-c** via Intermediate Mixed Anhydrides **20a,b**



21, 23	R_1 = Acetyl; R_2 = H; R_3 = H (a) R_1 = H; R_2 = Acetyl; R_3 = H (b) R_1 = H; R_2 = H; R_3 = Acetyl (c)

Table 1. Amidation of Picolinic Acid with Amines **21a-c** via Intermediate Mixed Anhydrides **20a,b**

Entry[a]	Amine **21a-c**	X in **20**	Ratio[b] **21a-c/23a-c**	% Yield[c] **23a-c**
1	a	COOEt	34/66	N.D.
2	c	COOEt	4/96	92
3	b	COOEt	>1/99	98
4	a	Ts	11/89	>85
5	a	Ts[d]	>1/99	>94

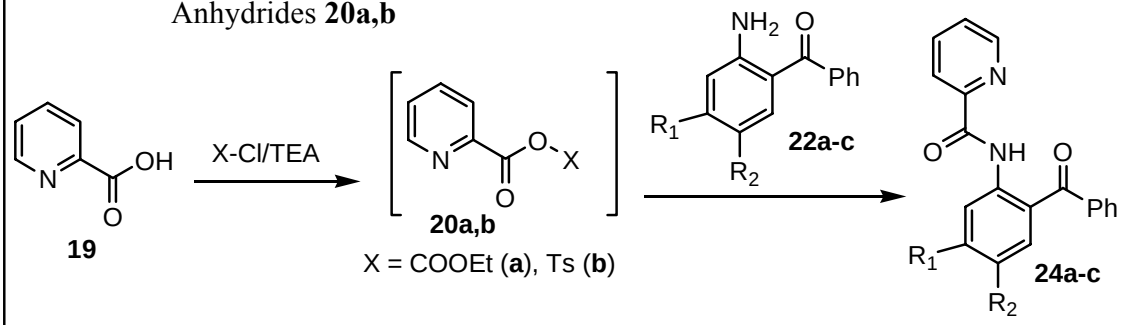
[a]All reactions were run in commercial grade dichloromethane overnight in the presence of TEA (PA/**21a-c** = 1.1/1). [b]Determined by NMR (300 MHz) analysis of the crude reaction mixtures. [c]Isolated yield of pure products based on **21a-c**. [d]PA/**21a-c** = 1.2/1

Therefore the amidation of picolinic acid with acetophenone **21a** by the application of ethyl chloroformate and triethylamine (TEA) to form the intermediate mixed anhydride **20a** was initially investigated (Scheme 5).[41] Unfortunately, the reaction proceeded sluggishly, giving rise to a mixture of the target product **23a** and the starting amine **21a** in a ratio of 66/34 (Table 1, Entry 1). Under the same reaction conditions, PA **19** was treated with *p*- and *m*-aminoacetophenones **21b-c**, which afforded the corresponding products **23b-c** in high chemical yields (Entries 2 and 3). These results clearly suggested that electron-withdrawing and shielding effects, more pronounced with the *ortho*-substituted analine derivative **21a,** impart unfavorable consequences on the reactivity of the amino function. In subsequent attempts, *p*-toluenesulfonyl chloride was substituted for ethyl chloroformate, since the *p*-tosyloxy group is generally a better leaving group. The result was fairly satisfactory, as up to 89% conversion of the starting amine **21a** was observed (Entry 4), however complete conversion was achieved when 1.2 equivalents of the intermediate anhydride was used (Entry 5). Without additional purification, compound **23a** was used to prepare the corresponding Ni(II) complex **16.** To demonstrate the reliability and efficiency of this procedure, the preparation of ligand **23a** and its Ni(II) complex **16** was repeated on a > 100 g scale with >93% overall yield.

With these results in hand, the focus was turned to the amidation of PA with *o*-aminobenzophenone derivatives **22a-c**. A reaction between PA **19** and amine **22a** was conducted under the conditions previously found to give the best result for the amidation with **21a-c** (Scheme 6). The reaction proceeded at a substantially faster rate, affording the target compound **24a** in quantitative chemical yield (Table 2, Entry 1). Taking advantage of the higher reactivity of *o*-aminobenzophenone **22a**, the amidation was

performed with ethyl chloroformate instead of *p*-toluenesulfonyl chloride. The reaction proceeded smoothly, affording virtually complete chemical conversion, as was also observed with the more reactive *p*-toluenesulfonyl chloride (Entry 1 vs. 2).

Scheme 6. Amidation of Picolinic Acid with Amines **22a-c** via Intermediate Mixed Anhydrides **20a,b**



22, 24	R_1 = H; R_2 = H (a) R_1 = Me; R_2 = H (b) R_1 = H; R_2 = NO_2 (c)

Table 2. Amidation of Picolinic Acid with Amines **22a-c** via Intermediate Mixed Anhydrides **20a,b**

Entry[a]	Amine **22a-c**	X in **20**	Ratio[b] **22a-c/24a-c**	% Yield[c] **24a-c**
1	a	Ts[d, e]	>1/99	99
2	a	COOEt[d]	>1/99	99
3	b	Ts[d]	>1/99	99
4	b	COOEt	7/93	91
5	b	COOEt[d]	>1/99	97
6	c	Ts	46/54	N.D.
7	c	COOEt	49/51	N.D.
8	c	Ts[f]	20/80	78
9	c	Ts[f, g]	>1/99	99

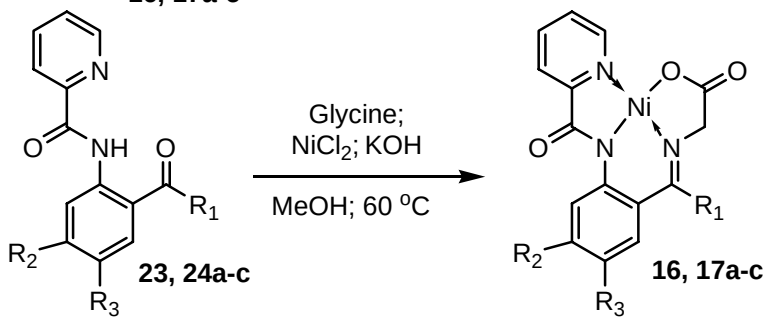
[a]All reactions were run in commercial grade dichloromethane overnight in the presence of TEA (PA/**22a-c** = 1.1/1). [b]Determined by NMR (300 MHz) analysis of the crude reaction mixtures. [c]Isolated yield of pure products based on **22a-c**. [d]PA/**21, 22a-c** = 1.2/1. [e]Reaction time was 4h. [f]Reaction was conducted in the presence of DMAP. [g]Reaction was conducted in dichloroethane.

This procedure, using ethyl chloroformate, was also successfully reproduced on a >100 g scale, thus proving its efficiency and practicality. Under the same reaction conditions, 4-methyl-substituted amine **22b** was used to prepare the new ligand **24b** with virtually complete chemical conversion both with *p*-toluenesulfonyl chloride (Entry 3) and with ethyl chloroformate (Entry 4, 5). In contrast, application of these standard conditions for the preparation of ligand **22c** starting from the nitro-containing amine **22c** gave unsatisfactory results (Entries 6, 7). To improve these results it was decided to use 4-(dimethylamino)pyridine (DMAP) as a catalyst, as it has been utilized to improve the outcomes of many similar reactions, including acylations on amino groups.[42] After several attempts it was found that the application of DMAP in stoichiometric amounts could have a noticeable effect on the chemical outcome (Entry 8). To improve the results further, the amidation was conducted in dichloroethane, allowing the reaction to be run at a higher temperature and to obtain the target compound in quantitative chemical yield (Entry 9).

2.2.3: Preparation and Chemical Properties of the Picolinic Acid Derived Ni(II) Complexes of Glycine 16, 17a-c

The corresponding Ni(II) complexes **16, 17a-c** were prepared from ligands **23, 24a-c** in high chemical yields under previously reported conditions utilizing potassium hydroxide to catalyze the Schiff base formation as well as the complexation of the Ni(II) ion by deprotonation of the amide nitrogen of the ligand and the carboxylic acid moiety of glycine in warm methanol.[32] (Scheme 7) In the ^{1}H NMR spectra of complexes **17a-c**, the protons of the glycine methylene moiety were found to be sensitive to the effect of the

Scheme 7. Assembly of Picolinic Acid Derived Glycine Equivalents



16, 23	R_1 = Me; R_2 = H; R_3 = H
17, 24	R_1 = Ph; R_2 = H; R_3 = H (**a**) R_1 = Ph; R_2 = Me; R_3 = H (**b**) R_1 = Ph; R_2 = H; R_3 = NO_2 (**c**)

aryl substituent(s). Thus, relative to that of the unsubstituted complex **17a** (δ = 3.83 ppm), chemical shift of the glycine methylene group protons in **17c** was found to be shifted downfield (δ = 3.88 ppm), and in **17b** shifted upfield (δ = 3.79 ppm),. This data suggested that the glycine methylene moiety in **17c** is more, and **17b** less, CH acidic than the known complex **17a**. This observation provides grounds for a rational design of these type of complexes with controlled reactivity of the glycine methylene group.

2.3: Application of 2-[*N*-(α-picolyl)amino]-aceto/benzophenone Derived Ni(II) Complexes of Glycine 17a

2.3.1: Synthesis of Sterically Constrained Symmetrical α,α-Disubstituted α-Amino Acids 3

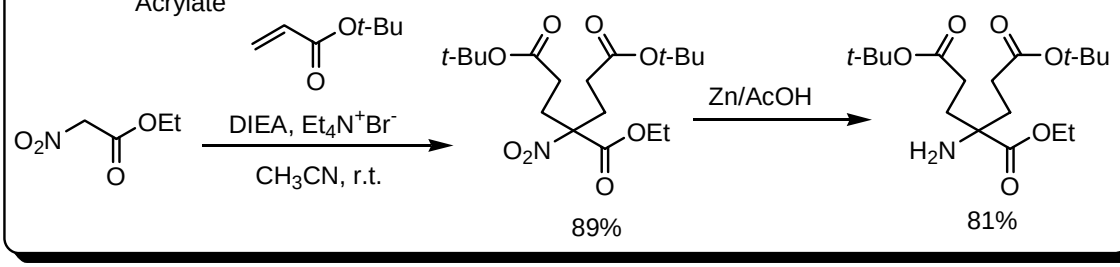
With completion of the first draft of the human genome and the completion or near completion of the genomes of several other animals, plants, and bacteria,[43] the de novo design of peptides and peptidomimetics with a presupposed three-dimensional structure rapidly becomes a subject of major interest and importance in the multidisciplinary areas of organic, bioorganic, peptide chemistry, biology, and medicine.[44] The availability of synthetic methods allowing for the design and synthesis of novel sterically constrained amino acids and related compounds will be a critical component of any effort to understand the proteome and its relation to life, health, and disease.[45] In particular, identification of α,α-dimethylglycine (DMeG) [α-methylalanine, α-aminoisobuturic acid (Aib)] and its higher homologues in natural peptides[46] as well as the discovery of its propensity to predictably influence three-dimensional structure of peptides[47,48] generated a great deal of interest. Therefore, the development of new synthetic methods for preparation of various symmetrically α,α-disubstituted α-amino acids **3** to satisfy the increasing demand in these sterically constrained tailor-made amino acids[49,50] for biological studies[51] has garnered a large amount of attention.

However, α,α-disubstituted amino acids other than DMeG are not readily available, therefore their biological properties and applications as sterically constrained scaffolds for the rational design of peptides and proteins are still awaiting systematic studies. Analysis of the relevant literature has revealed that, despite substantial interest in *sym*-α,α-amino acids, there has not been a single generalized and practical method[52] for their preparation developed to date.

2.3.1.1: Elaboration of Representative Synthetic Approaches for the Synthesis of Symmetrical α,α-Disubstituted α-Amino Acids 3

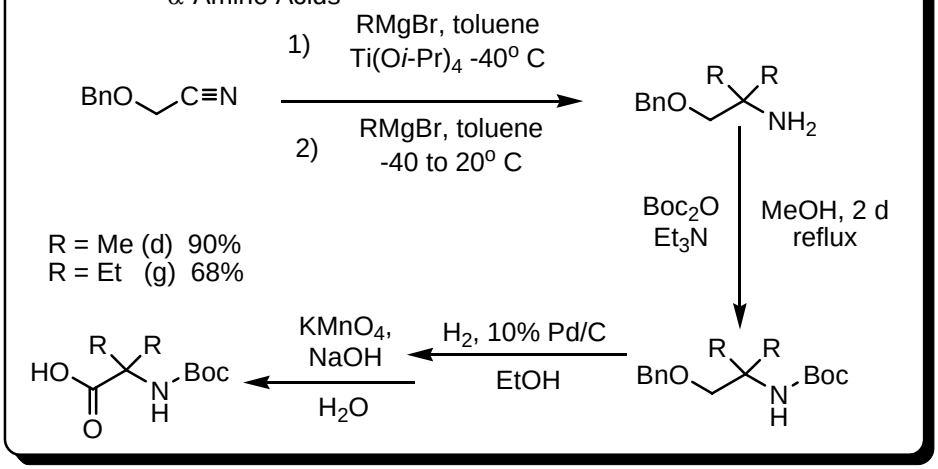
One of the traditional and widely used approaches to *sym*-α,α-amino acids **3** is the Bucherer-Bergs or Strecker reactions of *sym*-dialkyl ketones with cyano derivatives as a source of an amino function.[53] This explains the high availability of DMeG as a consequence of the abundance of acetone. However, as shown by Mclaughlin and Hammer,[54,55] these methods, besides the application of lethally toxic potassium cyanide, are not suitable for preparation of some sterically bulky *sym*-α,α-amino acids **3**, as, for instance, dibenzylglycine. These synthetic limitations and the overall impracticality of the classical methods for generalized and efficient[52] synthesis of *sym*-α,α-amino acids **3** led to the development of various alternative approaches.

Scheme 8. Phase Transfer Catalyzed Michael Addition Reaction of α-Nitroacetate With *tert*-Butyl Acrylate



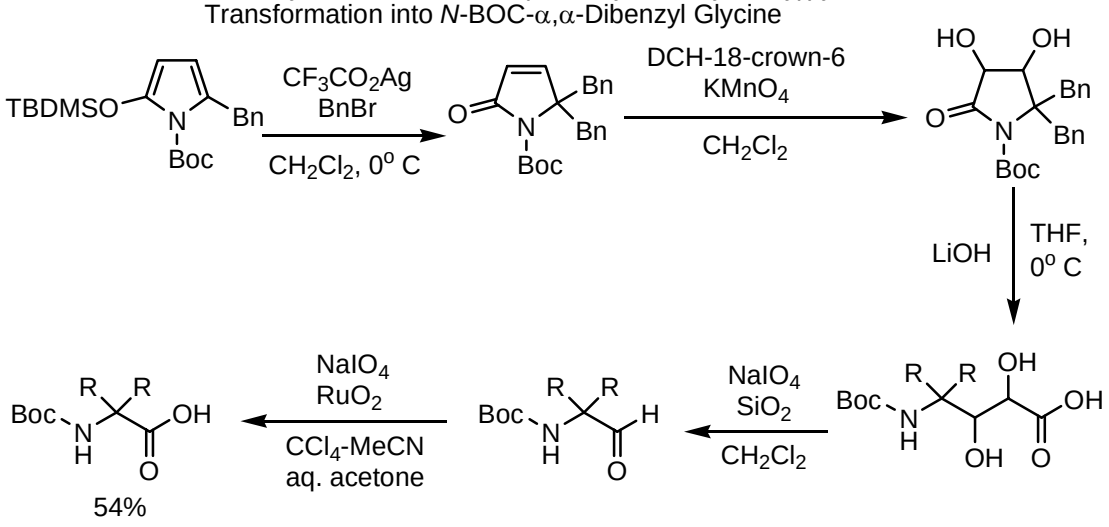
Most recently, Mclaughlin and Hammer reported a methodologically interesting approach to the synthesis of *sym*-α,α-amino acid **3** using the dialkylation of ethyl α-nitroacetate as a masked nucleophilic glycine equivalent (Scheme 8).[54] This method was shown to be successful for preparing various functionalized *sym*-α,α-amino acids **3** via Michael addition reactions. Unfortunately, application of alkyl halides for dialkylation of the ethyl α-nitroacetate was found to be limited to activated reagents such as benzyl bromides, *tert*-butyl-2-bromoacetate, and allyl iodide.[54]

Scheme 9. Double Nucleophilic Grignard Addition to Alkoxy Acetonitriles and Further Transformation into Symmetrical α,α-Disubstituted α-Amino Acids



Another methodologically different approach to the preparation of *sym*-α,α-amino acids **3**, reported by Charette,[56] is based on the double nucleophilic addition of Grignard reagents to alkoxy-(methoxy, benzyloxy) acetonitriles followed by the deprotection and oxidation of the primary alcohol moiety (Scheme 9). From a synthetic standpoint, this approach has many drawbacks, including the multistep procedure, which results in low overall yield of the target products, protection-deprotection manipulations, operationally inconvenient conditions (-40 °C), and sensitivity of the reaction outcome to some additives and promoters.[56]

Scheme 10. Dibenzylation of *N*-BOC-2-(*tert*-butyldimethylsiloxy)pyrrole and Further Transformation into *N*-BOC-α,α-Dibenzyl Glycine

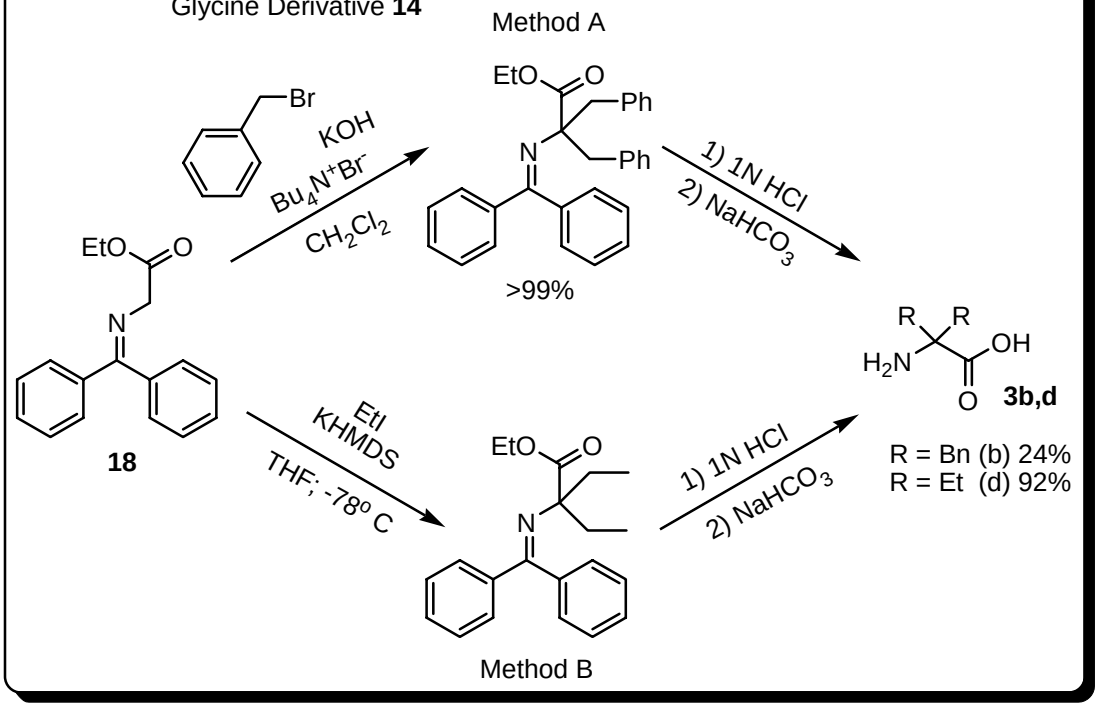


Another example of synthetic organic chemists' ingenuity is provided by Rassu-Casiraghi's group, who studied the *N*-BOC-2-(*tert*-butyldimethylsiloxy)pyrrole as a deeply masked α-amino acid enolate equivalent and showed its potential application for synthesis of *sym*-α,α-amino acids **3**, including dibenzylglycine **3b** (Scheme 10).[57] Unfortunately, this method suffers from methodological deficiencies such as a multistep

(at least five transformations) procedure, inconvenient reaction conditions, and low overall yields of the target products.

Of particular interest was the report by Ezquerra-Moreno-Manas's group who studied the dialkylation of the glycine Schiff base **18** under the convenient phase-transfer conditions (Scheme 11).[58] The authors demonstrated that the methylene moiety in derivative **18** can be dialkylated under mild conditions (0 °C) using benzyl and allyl bromides (Scheme 11, Method A). Unfortunately, low yields of the target products cannot render this method synthetically useful.

Scheme 11. Homogeneous and Heterogeneous Homologation of *N*-(phenylmethylene) Glycine Derivative **14**



More recently, Denmark et al. reported one example of the dialkylation of Schiff base **18** with nearly quantitative chemical yield.[59] In this case, diethylation of **18** with ethyl iodide was conducted as a stepwise procedure using KHMDS to generate the

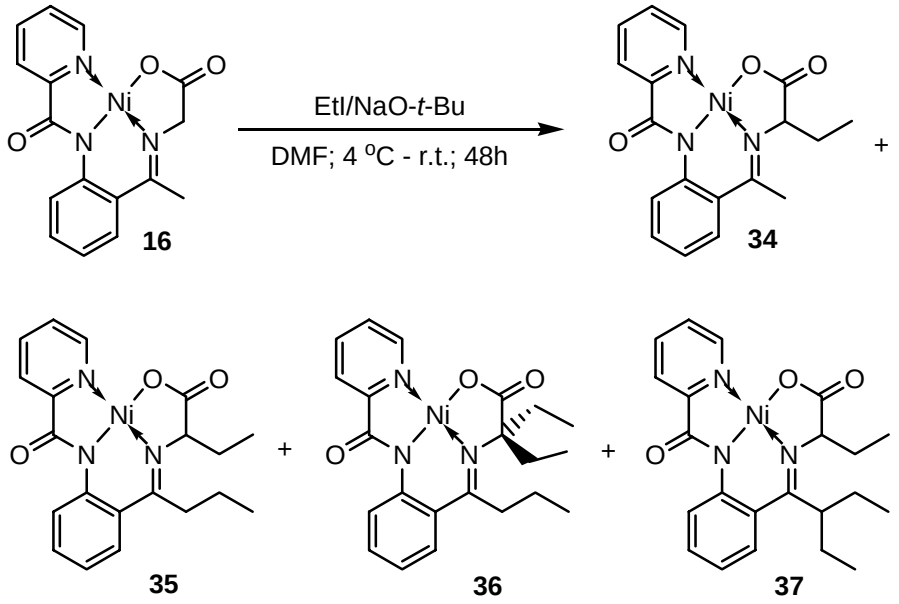
corresponding enolate at -78 °C (Scheme 11, Method B). Though successful, this procedure does not enjoy advantages of operationally convenient conditions and thus is unattractive to scale-up. On the other hand, from the methodological standpoint, dialkylation of a properly protected glycine derivative might be the most straightforward and generalized approach to the synthesis of *sym*-α,α-amino acids **3**.

2.3.1.2: Application of Ni (II) Complexed Schiff Bases of Glycine 17a for the Synthesis of Acyclic Symmetrical α,α-Disubstituted α–Amino Acids 3

Taking advantage of the previous experience of our group in the chemistry of Ni(II) complexes of amino acid Schiff bases,[60] it was envisioned that the Ni(II) complexes **16**, introduced by Professor Soloshonok,[61] and **17a**, designed by Belokon's group[32] (Figure 2, page 10), might be ideal starting glycine equivalents for the preparation of *sym*-α,α-amino acids via their dialkylation. Complexes **16** and **17a** are stable yet highly reactive nucleophilic glycine equivalents, and their homologation can be carried out at ambient temperature and without recourse to inert atmosphere or rigorously dried and/or degassed solvent. Moreover, generation of the corresponding enolates from **16** and **17a** can be effectively achieved by using common inorganic bases (KOH, NaOH) or alkoxides. All these advantageous features render **16** and **17a** more synthetically appealing compared to the traditionally used Schiff base **18** (Figure 2, page 10) for the particular purpose of preparing *sym*-α,α-amino acids **3** via dialkylation.

Taking into account the highly sterically constrained nature of the expected α,α-dialkylation products, it was first decided to study the dialkylation of Ni(II) complex **16**, which is derived from the less sterically bulky 2-[*N*-(α-picolyl)amino]-acetophenone (PAAP) **23** (Scheme 12).[62]

Scheme 12. Homogeneous Diethylation of the Picolinic Acid Derived Glycine Equivalent **16**

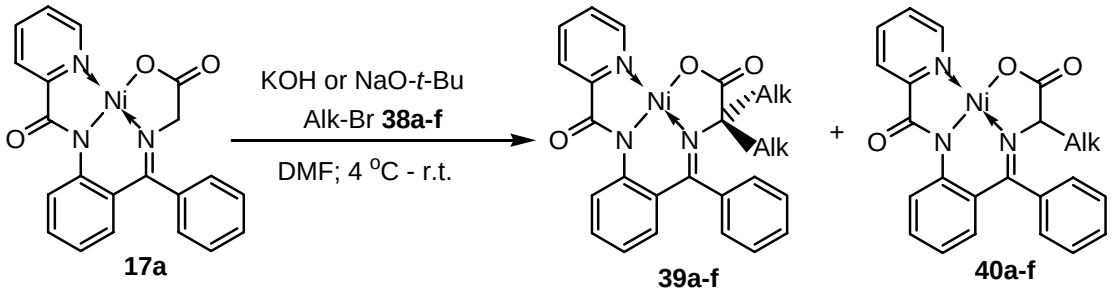


A series of experiments were conducted to investigate the dialkylation of **16** using commercial-grade DMF as a solvent, sodium hydroxide or sodium *tert*-butoxide as a base, and several activated and inactivated alkyl halides as alkylating reagents. The results obtained, though interesting, did not render the dialkylation of the acetophenone-derived complex **16** as a synthetically useful method for preparing the target *sym*-α,α-amino acid **3**. The most representative example is given in Scheme 12. Thus, depending on the reaction conditions used (reaction time and amount of the alkylating reagent), up

to four products **34-37** could be isolated from the reaction mixture. Monoalkylated product **34** was observed as a major product on the initial stage (15 min). Completion of the second alkylation required about one hour and was exclusively directed on the acetimino group to yield complex **35**. Interestingly, the third alkylation, observed after 12-24 hours, occurred on the aminobuturic acid moiety and in the α-position to the ketimine group with comparable rates. Compounds **34** and **35** were isolated in analytically pure form by column chromatography and fully characterized, while products **36** and **37** were obtained as an inseparable mixture.

By contrast, the first attempt to dialkylate complex **17a**, derived from a glycine Schiff base with 2-[*N*-((*R*)-picolyl)-amino]benzophenone (PABP) **24a** (Scheme 13), gave synthetically promising results. Thus, treatment of **17a** in commercial-grade DMF with allyl bromide (**38a**) (2.5 equiv.) in the presence of KOH (10 equiv.) at ambient temperature resulted in an exothermic reaction, giving rise to the target dialkylated product **39a** in high chemical yield (Scheme 13; Table 3, entry 1). Under the same conditions, the reaction of complex **17a** with benzyl bromide (**38b**) occurred at a slower rate but resulted in complete dibenzylation of the glycine moiety in **17a** affording product **39b** as an individual product (entry 2). Attempts to reduce the amount of the base resulted in incomplete dialkylation, giving rise to a mixture of the major products **39a**,**b** and monoalkylated derivatives **40a**,**b** (5-10%). It was also noticed that an increase in the reaction time lowered the yields of the target products due to the formation of some unidentified dark-colored high molecular weight byproducts. Therefore, it was decided to use commercially available and inexpensive sodium *tert*-butoxide as the base which allowed the reactions to be conducted under homogeneous conditions. The resulting

Scheme 13. Homogeneous Dialkylation of Glycine Equivalent **17a** with Activated Alkyl Bromides **38a-f**



17a **39a-f** **40a-f**

Alk = allyl (a), benzyl (b), *trans*-cinnamyl (c), ethyl (d), propyl (e), butyl (f),

Table 3. Homogeneous Dialkylation of Glycine Equivalent **17a** with Activated Alkyl Bromides **38a-f**

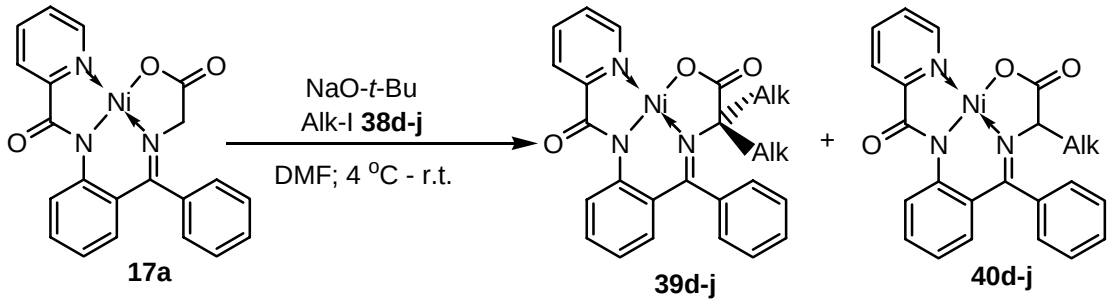
Entry[a]	**38a-f**	Base	Ratio base/**38a-f**	Time	Products **39** and **40** Yield[b] %	Ratio **39/40**[c]
1	**a**	KOH	10/2.5	30 min	83	>99/1
2	**b**	KOH	10/2.5	1 h	90	>99/1
3	**a**	NaO-*t*-Bu	3.0/3.0	15 min	94	>99/1[d]
4	**b**	NaO-*t*-Bu	3.0/3.0	15 min	89	>99/1
5	**c**	NaO-*t*-Bu	3.0/3.0	15 min	94	>99/1
6	**d**	NaO-*t*-Bu	3.5/3.5	20 min	94	76/24
7	**d**	NaO-*t*-Bu	4.0/4.0	2 h	92	90/10
8	**d**	NaO-*t*-Bu	4.5/4.5	2 h	91	98/2
9	**e**	NaO-*t*-Bu	4.0/4.0	2 h	90	91/9
10	**f**	NaO-*t*-Bu	4.0/4.0	2 h	91	94/6

[a]All reactions were conducted in commercial-grade DMF. [b]Isolated yield of the crude product. [c]Determined by NMR (300 MHz) analysis of the crude reaction mixture. [d]The reaction was conducted on a >10 g scale.

experiment with allyl bromide (**38a**) and **17a**, in the presence of only three equivalents of the base, which occurred at a substantially higher reaction rate, and afforded the diallylated complex **39a** as an individual product with improved chemical yield (entry 3). This reaction was conducted on >10 g scale to prepare free amino acid **3a**. Under the same conditions, reactions of **17a** with benzyl (**38b**) and cinnamyl bromide (**38c**)

occurred at similar rates and virtually complete dialkylation, giving rise to the target compounds **39b**,**c** in high isolated yields (entries 4 and 5).

Scheme 14. Homogeneous Dialkylation of Glycine Equivalent **17a** with Alkyl Iodides **38d-j**



17a **39d-j** **40d-j**

Alk = ethyl (d), propyl (e), butyl (f), methyl (g), pentyl (h), *i*-propyl (i), *i*-butyl (j)

Table 4. Homogeneous Dialkylation of Glycine Equivalent **17a** with Alkyl Iodides **38d-j**

					Products **39** and **40**	
Entry[a]	**38d-j**	Base	Ratio base/**38d-j**	Time	Yield[b] %	Ratio **39/40**[c]
1	**g**	NaO-*t*-Bu	3.5/3.5	15 min	91	>99/1
2	**d**	NaO-*t*-Bu	3.5/3.5	15 min	92	>99/1
3	**e**	NaO-*t*-Bu	3.5/3.5	15 min	91	>99/1[d]
4	**f**	NaO-*t*-Bu	3.5/3.5	15 min	91	>99/1
5	**h**	NaO-*t*-Bu	3.5/3.5	15 min	93	>99/1
6	**i**	NaO-*t*-Bu	3.5/3.5	20 min	97	<1/99
7	**j**	NaO-*t*-Bu	3.5/3.5	15 min	98	<1/99

[a]All reactions were conducted in commercial-grade DMF. [b]Isolated yield of the crude product. [c]Determined by NMR (300 MHz) analysis of the crude reaction mixture. [d]The reaction was conducted on a >10 g scale.

Next it was decided to explore the generality of this method for the dialkylation of complex **17a** using nonactivated alkyl halides. Under the same conditions, except for an increase in the amounts of the alkylating reagent and base (3.5 equiv. each), the reaction

between **17a** and ethyl bromide (**38d**) yielded a mixture of di- (**39d**) and monoalkylated (**40d**) products in a ratio of 76/24 (entry 6). Continuation of this reaction for up to two hours did not result in a noticeable increase of **39d**. However, a further increase in the amounts of the alkylating reagent and base allowed improvement in the ratio of products **39d** and **40d** to a satisfactory level of 98/2 (entries 7 and 8). Similar results were obtained in the reactions of **17a** with propyl (**38e**) and butyl bromides (**38f**) (entries 9 and 10).

Critical analysis of the results obtained suggested that application of the activated alkyl bromides **38a-c** for dialkylation of the glycine equivalent **17a** might be rendered as an efficient and synthetically useful approach for preparing products **39a-c** and thus the target amino acids **3a-c**. On the other hand the dialkylation of **17a** with nonactivated bromides **38d-f**, though successful, still needed improvement to achieve complete dialkylation. Therefore, it was decided to use nonactivated alkyl iodides as alkylating reagents. It was found that only 3.5 equiv. of methyl iodide (**38g**) and sodium *t*ert-butoxide is enough for complete, fast, and clean dimethylation of **17a** to afford compound **39g** in high isolated yield (Scheme 14, Table 4, entry 1). Inspired by these results, the reaction of complex **17a** with ethyl (**38d**), propyl (**38e**), butyl (**38f**), and pentyl (**38h**) iodides were conducted, all of which gave similarly excellent chemical outcomes affording their respective dialkylated complexes **39d-f**,**h** as individual products with yields of 91-93% (entries 2-5). As the prices of alkyl bromides and alkyl iodides are very close, the application of the alkyl iodides verses alkyl bromides becomes practical and useful considering the decreased amount of reagent needed and the enhanced chemical outcome obtained. On the other hand, attempts to use α- or *β*-branched alkyl halides exposed some limitations of this method. For instance, alkylation of complex **17a**

with isopropyl **38i** and isobutyl **38j** bromides or iodides, even under increased temperature, resulted in quantitative formation of only monoalkylated products **40i**,**j** (entries 6 and 7).

Scheme 15. Phase Transfer Catalyzed Homologation of Glycine Equivalent **17a** with Propargyl Bromide **38k**, Acrylonitrile **38l**, and Ethyl Acrylate **38m**

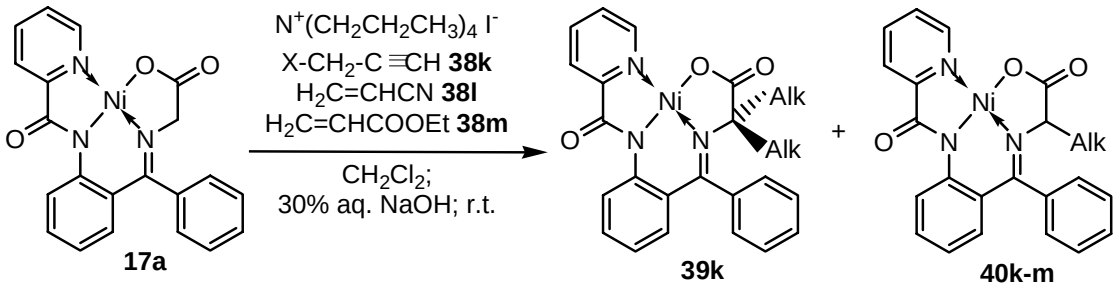


Table 5. Phase Transfer Catalyzed Homologation of Glycine Equivalent **17a** with Propargyl Bromide **38k**, Acrylonitrile **38l**, and Ethyl Acrylate **38m**

Entry	**38k-m**	X	Base	Ratio **17a/38k-m**	Time	Products **39** and **40** Yield[a] %	Ratio **39/40**[b]
1	**k**	Br	30% aq. NaOH	1/3.5	45 min	97	5/95
2	**k**	Br	30% aq. NaOH	1/3.5	24 h	>98	>99/1
3	**l**	—	30% aq. NaOH	1/3.5	15 min	93	<1/99
4	**m**	—	30% aq. NaOH	1/3.5	15 min	95	<1/99

[a]Isolated yield of the crude product. [b]Determined by NMR (300 MHz) analysis of the crude reaction mixtures.

Taking into account the synthetic versatility of terminal alkyne groups, dialkylation of complex **17a** with propargyl bromide (**38k**) was of particular interest. Unfortunately, all attempts to alkylate glycine equivalent **17a** with propargyl bromide **38k** in a DMF solution using NaO-*t*-Bu or NaOH as bases resulted in the formation of a substantial amount of unidentified byproducts rather than affording the target dialkylated

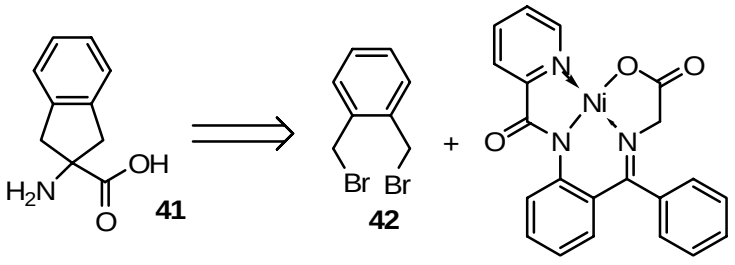
products. Perhaps the strongly basic reaction conditions used were incompatible with the reactivity of the propargyl group. Therefore, it was decided to try the dialkylation under much milder phase-transfer conditions (PTC). The reaction of complex **17a** with propargyl bromide **38k** was conveniently carried out at room temperature in dichloromethane using tetrapropylammonium iodide as the phase transfer catalyst and 30% aqueous NaOH as the base (Scheme 15). To our satisfaction, quantitative conversion of complex **17a** to the monosubstituted intermediate product **40k** took place within 45 min (Table 5, entry 1), with further clean conversion of **40k** to the target disubstituted complex **39k** occurring in >98% yield after allowing the reaction to stirr overnight (entry 2).

Finally, the dialkylation of glycine equivalent **17a** was investigated via Michael addition reactions using acrylonitrile **38l** and ethyl acrylate **38m** as Michael acceptors. It was found that application of strongly basic homogeneous conditions (DMF/NaOH or NaO-*t*-Bu) was incompatible with the high reactivity of Michael acceptors **38l** and **38m**, leading to a substantial amount of unidentified byproducts along with the monoalkylated complexes **40l** and **40m**. Therefore the reactions were conducted using the milder PTC with the intent of obtaining the target disubstituted products. However, despite the quick and clean monoalkylation (Table 5, entries 3 and 4), the reactions did not proceed further, affording only the monosubstituted derivatives **40l** and **40m** in high chemical yields.

2.3.1.3: Application of Ni (II) complexed Schiff Base of Glycine 17a for the Synthesis of Cyclic Symmetrical α,α-Disubstituted α-Amino Acids

The successful synthetic application of complex **17a** for dialkylation of the glycine moiety prompted the study of its reactions with dibromoxylylene **42** to develop a more practical approach for preparing 2-aminoindane-2-carboxylic acid **41** (Figure 4).[63] Since dibromide **42** is an analogue of benzyl bromide, initially the reaction between complex **17a** and **42** was conducted under the conditions that were previously used for the dialkylation of **17a** with activated alkyl halides. The reaction, which was carried out

Figure 4. Retrosynthetic Analysis of the Synthesis of 2-Aminoindane-2-Carboxylic Acid **41** with **17a**



at ambient temperature in commercial-grade DMF (8.3 mL per 1 mmol of **17a**) and NaOH, occurred with a relatively high reaction rate affording the target cyclic derivative **44** along with a substantial amount of high molecular weight (HMW) byproducts, the latter formed presumably due to the bis-mono-alkylation and further cross-dialkylation reactions (Scheme 16; Table 6, entry 1). Application of three equivalents of NaO-*t*-Bu as a base resulted in a decreased amount of the HMW by-products, however the formation

of cyclic complex **44** was incomplete because the mono-alkylated derivative **43** and target **44** were isolated in approximately a 1:1 ratio (entry 2). An increased amount of base led to the complete consumption of **43**, however unfortunately, an increased amount of the HMW byproducts was also produced. Next, a series of reactions were conducted with less concentrated solutions of the starting complex **17a** in DMF, which allowed the suppression but not the elimination of the undesired HMW byproducts. Utilization of other solvents, bases, as well as low temperatures led to some improvements in the overall reaction outcome but not the complete elimination of the HMW byproducts. The results obtained were successful (as great as 70% yield of **44**) but suggested that the direct dialkylation of glycine equivalent **17a** with dibromide **42** is generally plagued by the formation of undesired dimers or short polymers. Therefore, the use of very low concentrations of the starting compounds may be the only procedure to increase the chemical yield of product **44** under the conditions for the direct alkylation.

Alternatively, application of low concentrations of the starting compounds, as in the literature procedures,[5a,8] automatically leads to lower volume yields than desired. Therefore, a two-step approach including a selective preparation of the monoalkylated product **43** and its further cyclization into the target **44** was envisioned. For the first step, application of mild PTC was found to give the desired result. Thus, the reaction between complex **17a** and dibromide **42** conducted under the PTC with dichloromethane, saturated aqueous NaOH, and tetrapropylammonium bromide as the catalyst, afforded the mono- alkylated **43** in 87% yield along with less than 10% of the HMW byproducts (entry 3). Application of the less concentrated base was found to give a better yield of **43** and a decreased amount of the HMW byproducts (entry 4). The optimum results were

Scheme 16. Two Step Synthesis of 2-Aminoindane-2-Carboxylic Acid **41** From Glycine Equivalent **17a** and *o*-Xylylene Dibromide **42**

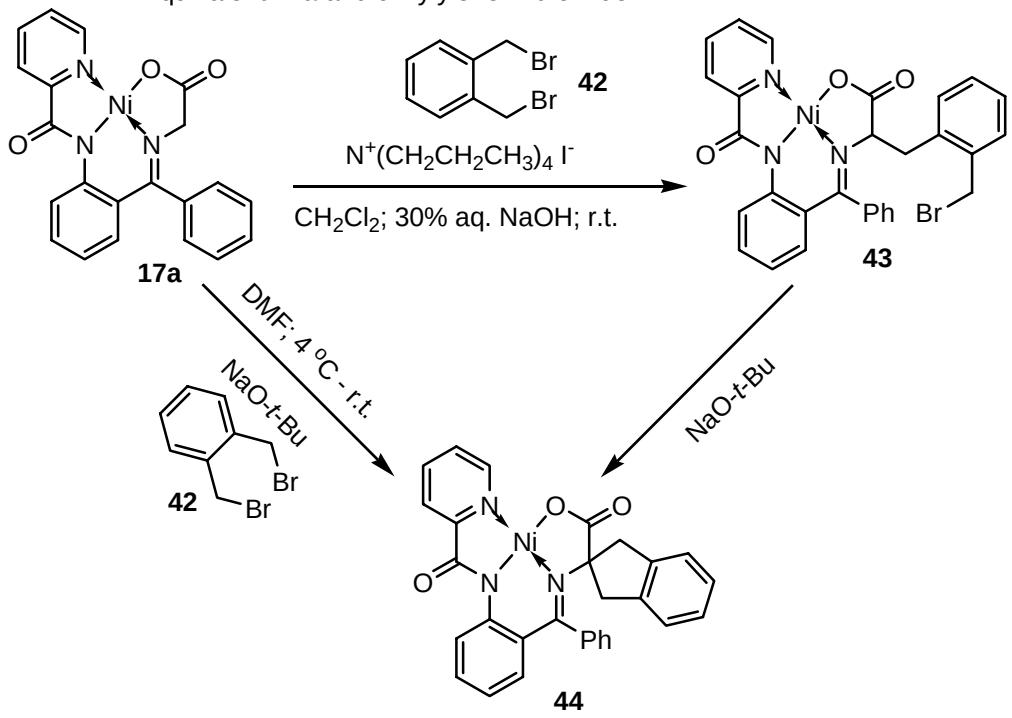


Table 6. Two Step Synthesis of 2-Aminoindane-2-Carboxylic Acid **41** From Glycine Equivalent **17a** and *o*-Xylylene Dibromide **42**

					Products **43** and **44**	
Entry[a]	Solvent	Base (equiv)	Reactant	Time	Yield[b] %	Ratio[c] **43**/**44**
1	DMF	NaOH (10)	**17a**	30 min	67	>1/99
2	DMF	NaO-*t*-Bu (3)	**17a**	45 min	41	48/52
3	CH_2Cl_2/H_2O[d]	50% aq. NaOH	**17a**	1 h	87	>99/1
4	CH_2Cl_2/H_2O[d]	30% aq. NaOH	**17a**	1 h	91	>99/1
5	CH_2Cl_2/H_2O[d]	30% aq. NaOH[e]	**17a**	2 h	97	>99/1
6	DMF	NaO-*t*-Bu (3)	**43**	10 min	67	31/69
7	DMF	NaO-*t*-Bu (3.5)	**43**	5 min	93	>1/99

[a]All reactions were conducted at ambient temperature under the indicated conditions using a 1:1.1 ratio of **17a** and **42**. [b]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixtures. [c]Isolated yield of pure **43** or **44**. [d]The reaction was conducted under PTC with the concentration of base indicated and 15 mol % of tetrapropyl-ammonium bromide.[e]Tetrapropylammonium iodide was used as the phase transfer catalyst.

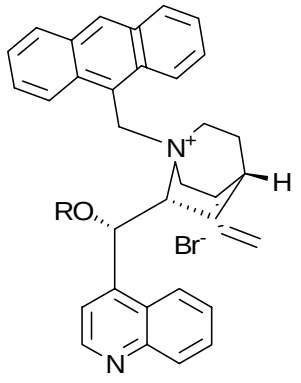
obtained by employing tetrapropylammonium iodide as a catalyst, allowing isolation of product **43** in 97% yield (entry 5). The product **43** was isolated in a crystalline state by evaporation of the organic phase and without purification was used directly for the cyclization step. The first attempts to convert **43** to **44** in a DMF solution with NaOH as a base gave rather satisfactory results. However, the application of NaO-*t*-Bu allowed the acceleration of the cyclization rate and achieved a complete, fast, and clean transformation of **43** to **44** in 93% yield (entry 7).

2.3.2: Application of the Picolinic Acid Derived Ni (II) Complex 17a for the Synthesis of Optically Active α-Amino Acids Via Chiral Phase Transfer Catalyzed Homologations

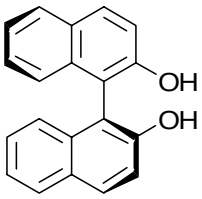
2.3.2.1: Commercially Available Chiral Phase Transfer Catalysts

Phase transfer catalysis has slowly developed into an integral part of synthetic chemistry for numerous reasons. These reasons include the cost efficient nature of the methodology, due in large part to the application of substoicheometric amounts of the source of optical activity, which is in many cases the most costly part of a reaction, as well as the convenience of the reaction conditions, which allows for the scalability of these processes.

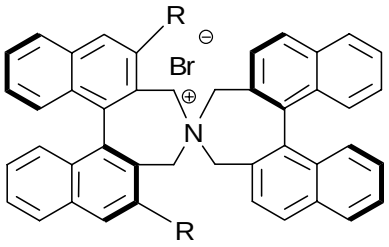
Figure 5. Commercially Available Optically Active Phase Transfer Catalyst **45-49**



R = allyl **45**
R = H **46**
cinchonidinium derived catalysts



(*S*)-(-)-1, 1'-bi-2-naphthol catalyst **47**



R = 3,4,5-trifluorophenyl **48**
R = β-naphthyl **49**

(*S*,*S*)-NAS bromide catalysts

Over the past two decades significant strides have been made to enhance the understanding and applicability of chiral phase transfer catalyzed reactions. However in the realm of asymmetric phase transfer catalyzed synthesis of amino acids the major focus has been devoted to the design and discovery of new chiral catalysts. The result of these studies is the commercialization of several catalysts such as the two catalysts **45** and **46** which were derived from natural cinchona alkaloids, the *N*-spiro C_2 symmetrical catalysts **48** and **49** designed by Professor Maruoka, as well as the optically active bi-2-naphthol catalyst **47** (Figure 5).[64,65]

Each of these catalysts have their own advantages and disadvantages such as the availability and economic cost structure of the cinchona alkaloid inspired catalysts **45** and **46** as well as the bi-2-naphthol catalyst **47**. However, although the *N*-spiro catalysts **48** and **49** are more expensive than catalysts **45** and **46**, one must also keep in mind that much less of the *N*-spiro catalyst are necessary for most reactions due to the lack of the Hoffman Elimination pathway which is present in catalysts **45** and **46**.

2.3.2.2: Investigation of Reaction Conditions

Although asymmetric phase transfer catalyzed reactions are rather widespread and a commonly used synthetic tool, optimization of the reaction conditions remains a critical and time consuming task. A large number of variables need to be considered when devising a synthetic plan utilizing asymmetric phase transfer catalysis such as: selection of the catalyst to be employed, the reaction medium, as well as the source of the base. Critical analysis of literature examples can supply many ideas for initial experiments, however to be truly successful, in most cases a series of experiments are necessary to find the most favorable conditions for the specific application.

2.3.2.2.1: Catalyst Screening

It was decided to begin the investigation of the asymmetric homologation of the Ni(II) complex **17a** by screening the previously mentioned commercially available chiral catalysts **45-49**. After reviewing the literature for similar processes with the diphenylmethylene glycinate Schiff base **14** mentioned earlier, it was decided to conduct the initial screening experiments in a toluene:methylene chloride mixed solvent system due to the outcome of the optical activities of the previous systems as well as the rather limited solubility of the Ni(II) complex **17a**. The base that was chosen for these initial reactions was 30% aqueous sodium hydroxide, due to the previous studies, and benzyl bromide **38b** was selected for the alkylating reagent because of its eletrophilic nature and

the commercial availability of the corresponding optically pure phenyl alanine derivatives, which are useful for references during the determination of the enantiomeric excess of the catalyzed products (Scheme 17).

Scheme 17. Asymmetric Benzylation of Glycine Equivalent **17a** with Commercially Available Chiral Phase Transfer Catalysts **45-49**

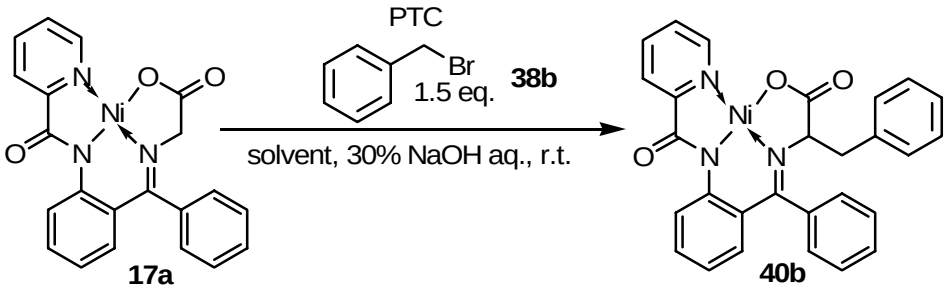


Table 7. Asymmetric Benzylation of Glycine Equivalent **17a** with Commercially Available Chiral Phase Transfer Catalysts **45-49**

Entry	Time h	Catalyst	mol % catalyst	Solvent	Ratio[a] **17a/40b**	Yield[b] %	% ee[c] (Abs. conf.)
1	2	**45**	15	70% Tol:30% CH_2Cl_2	10/90	88.5	20.13 (*S*)
2	2	**45**	15	70% CH_2Cl_2: 30 % Tol	1/>99	94.2	15.2 (*S*)
3	2.25	**46**	15	70% Tol:30% CH_2Cl_2	2/92	95.2	11.10 (*S*)
4	2.25	**46**	15	70% CH_2Cl_2: 30 % Tol	1/>99	99.3	1.62 (*S*)
5	48	**47**	15	70% Tol:30% CH_2Cl_2	7/93	84.3	12.60 (*S*)
6	48	**47**	15	70% CH_2Cl_2: 30 % Tol	1/>99	89.4	10.80 (*S*)
7	2	**48**	2	70% Tol:30% CH_2Cl_2	63/37	33.7	21.65 (*R*)
8	2	**48**	2	70% CH_2Cl_2: 30 % Tol	2/98	96.6	14.11 (*R*)
9	3	**49**	2	70% Tol:30% CH_2Cl_2	13/87	78.2	3.54 (*R*)

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 95:5 Hexane:*i*-propanol) of the corresponding *N*-CBz-phenylalanine ethyl ester.

The first experiment conducted, utilized the *O*-allyl cinchonidinium derived catalyst **45** with a solvent system of 70% toluene:30% dichloromethane (solvent system A) and resulted in the nearly complete conversion to the corresponding product (90%) in

2 hours and yielded the monoalkylated product **40b** in 88.5% yield and 22.13 % ee (Table 7, entry 1). Altering the solvent system to 30% toluene:70% dichloromethane (solvent system B) resulted in the complete conversion (>99%) to the corresponding product **40b** in the same amount of time as the previous reaction, however the optical purity of the product **40b** was decreased (15.20% ee) (entry 2). The application of catalyst **46** which contains the unprotected hydroxyl group, or the bi-2-naphthol catalyst **47** resulted in nearly complete conversion of the starting complex **17a** to the corresponding product **40b** (92 % or greater) however, regardless of the solvent system, there was a substantial decrease in the control of the enantioselectivity as the products were obtained in 11.10, 1.62, 12.60, and 10.80% ee respectively (entries 3-6). The most promising results of these experiments came from utilizing the *N*-spiro catalyst **48** in the more lipophilic solvent system A, which yielded product **40b** with the highest optical purity (21.65% ee) within this series of experiments, however the 2 hour reaction yielded only 33.7% of the expected product **40b**. (entry 7) Again a noticeable decrease in enantiomeric excess was noticed for the application of the slightly more polar solvent system which yielded nearly 97% of the expected product **40b** in 14.11% ee (entry 8). It was also found that the nature of the substituents on the *N*-spiro catalysts **48** and **49** played a large role in the enantioselective process as application of the β-napthyl containing catalyst **49** provided the product **40b** in a nearly racemic form (3.54% ee) however the reaction nearly proceeded to completion (87% conversion) (entry 9). After reviewing these results it was rather easy to see that a more systematic study would be necessary to realize the goal of a high yielding process for the synthesis of optically pure α-amino acids with this Ni(II) complex **17a**. It should also be mentioned that the

absolute configuration of the phenylalanine product obtained from the homologation of this picolinic acid derived Ni(II) complex **17a** corresponded with those reported in the literature for the diphenylmethylene glycinate Schiff base **14** with all catalysts studied.

2.3.2.2.2: Solvent Screening

It was gathered from the previous experiments that there is a strong dependence on the organic solvent system employed and the optical purity of the product. Therefore, it was decided to explore one of the most promising reaction conditions from the previous series of reactions, which was the benzylation of the Ni (II) complex **17a** with the trifluorophenyl derived *N*-spiro catalyst **48** with 30% aqueous sodium hydroxide. The organic solvent system was varied in order to confirm the solvent dependence of the reaction and identify any possible trend for increasing the optical purity of the products (Scheme 18). Employing somewhat polar solvents such as dichloromethane and 1,2-dichloroethane for these phase transfer catalyzed reactions resulted in rapid conversion of the starting materials to the corresponding product **40b** which was obtained in high chemical yield, however the optical purities of the monoalkylated product **40b** were quite low (7.88%, 8.77% ee respectively) (Table 8, entries 1 and 2).

Decreasing the polarity of the solvents by utilizing benzene or toluene accomplished little with respect to increasing the optical purity of the product **40b**, although the reaction rates were decreased requiring 24 hours to reach more than 50% conversion (85.4%, 51.9% respectively). These results may be more complex than the previous examples due to the incomplete solubility of the Ni (II) complex **17a** (entries 3

and 4). Therefore, it was concluded that the mixed solvent system utilized during the catalyst screening experiments remains the most promising candidate, due in large part to the balance between polarity of the system and the solubility of the Ni (II) complex **17a** (entries 5 and 6).

Scheme 18. Asymmetric Phase Transfer Catalyzed Benzylation of Glycine Equivalent **17a** with (*S*,*S*)-3,4,5-Trifluorophenyl-NAS Bromide **48** in Various Organic Reaction Mediums

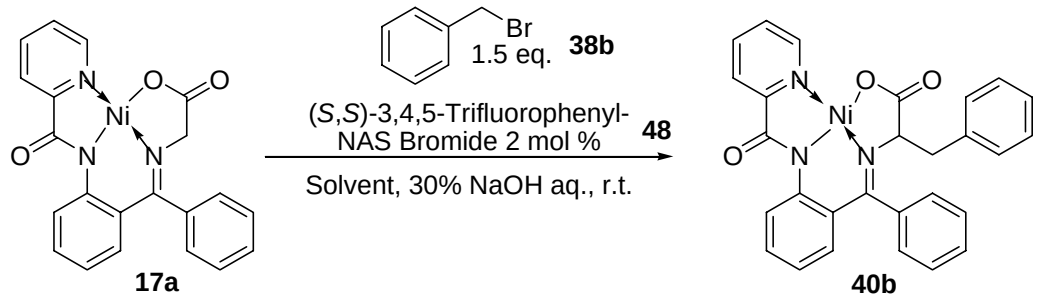


Table 8. Asymmetric Phase Transfer Catalyzed Benzylation of Glycine Equivalent **17a** with (*S*,*S*)-3,4,5-Trifluorophenyl-NAS Bromide **48** in Various Organic Reaction Mediums

Entry	Time	Solvent	Ratio[a]	Yield[b]	ee[c]
	h		**17a/40b**	%	%
1	2	CH_2Cl_2	1/>99	95.6	7.88
2	1	CH_2Cl-CH_2Cl	1/>99	98.3	8.77
3	24	Benzene	8/92	85.4	6.01
4	24	Toluene	43/57	51.9	8.68
5	2	70% Tol:30% CH_2Cl_2	63/37	33.7	21.65
6	2	70% CH_2Cl_2: 30 % Tol	2/98	96.6	14.11

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 95:5 Hexane:isopropanol as the eluant) of the corresponding *N*-CBz-phenylalanine ethyl ester.

2.3.2.2.3: Base Screening

Following the identification of the optimum catalyst and solvent system, the focus of further investigation was directed toward the concentration as well as the counter ion of the hydroxide base, as both of these variables have been shown to impact the outcome of phase transfer reactions.[20, 27] Therefore, these reactions were conducted using catalyst **48** and 70% toluene:30% dichloromethane, solvent system A, at room temperature (Scheme 19). The first change to the system was the application of the potassium ion in place of sodium which was demonstrated earlier in this chapter. The outcome of this experiment revealed that employing the hydroxide base with the potassium ion resulted in a slight increase in the enantioselectivity of the process as the product was isolated in 23.5% ee, however the rate of the reaction was increased by almost three fold (Table 9, entries 1 and 2). Given the positive correlation between the enantioselectivity of the reaction with the counter ion of the hydroxide base, the use of aqueous cesium hydroxide was investigated, however only minor improvements in the optical purities of the product **40b** were realized (entry 3).

Scheme 19. Asymmetric Phase Transfer Catalyzed Benzylation of Glycine Equivalent **17a** with (*S*,*S*)-3,4,5-Trifluorophenyl-NAS Bromide **48** in Toluene with Various Hydroxide Bases

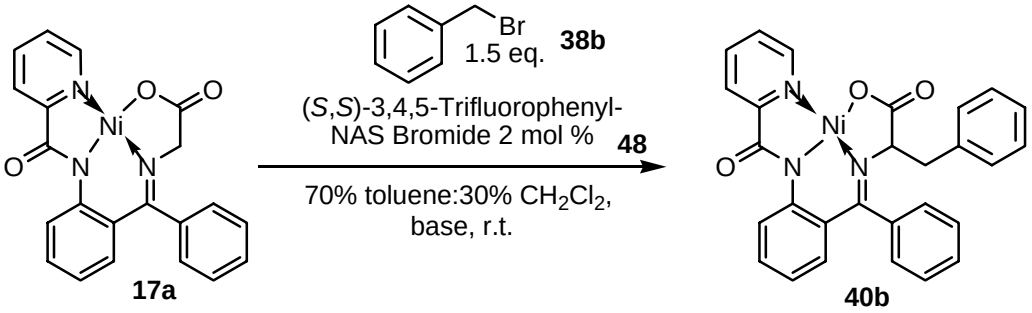


Table 9. Asymmetric Phase Transfer Catalyzed Benzylation of Glycine Equivalent **17a** with (*S*,*S*)-3,4,5-Trifluorophenyl-NAS Bromide **48** in Toluene with Various Hydroxide Bases

Entry	Time	Base	Ratio[a]	Yield[b]	ee[c]
	h		**17a/40b**	%	%
1	2	30% aq. NaOH	63/37	33.7	8.77
2	2	30% aq. KOH	9/91	86.3	23.5
3	2	50% aq. CsOH	11/89	87.6	24.2
4	2.5	NaOH (s) 5 eq.	26/74	68.3	66.2
5	2.5	KOH (s) 5 eq.	17/83	78.4	39.3

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 95:5 hexane:isopropanol as the eluant) of the corresponding *N*-CBz-phenylalanine ethyl ester.

Although alteration of the counter ion of the base only led to minor improvements in the asymmetric homologation of this glycine equivalent **17a**, altering the concentration of the base seemed to have a dramatic effect. It was found that utilizing a biphasic system employing solid (crushed) sodium hydroxide for this reaction could increase the enantioselectivity of this process to yield the appropriate product in 68.3% yield and 66.2% ee (entry 4). However, contrary to the application of aqueous bases, increasing the size of the counter ion by utilizing potassium hydroxide instead of sodium hydroxide

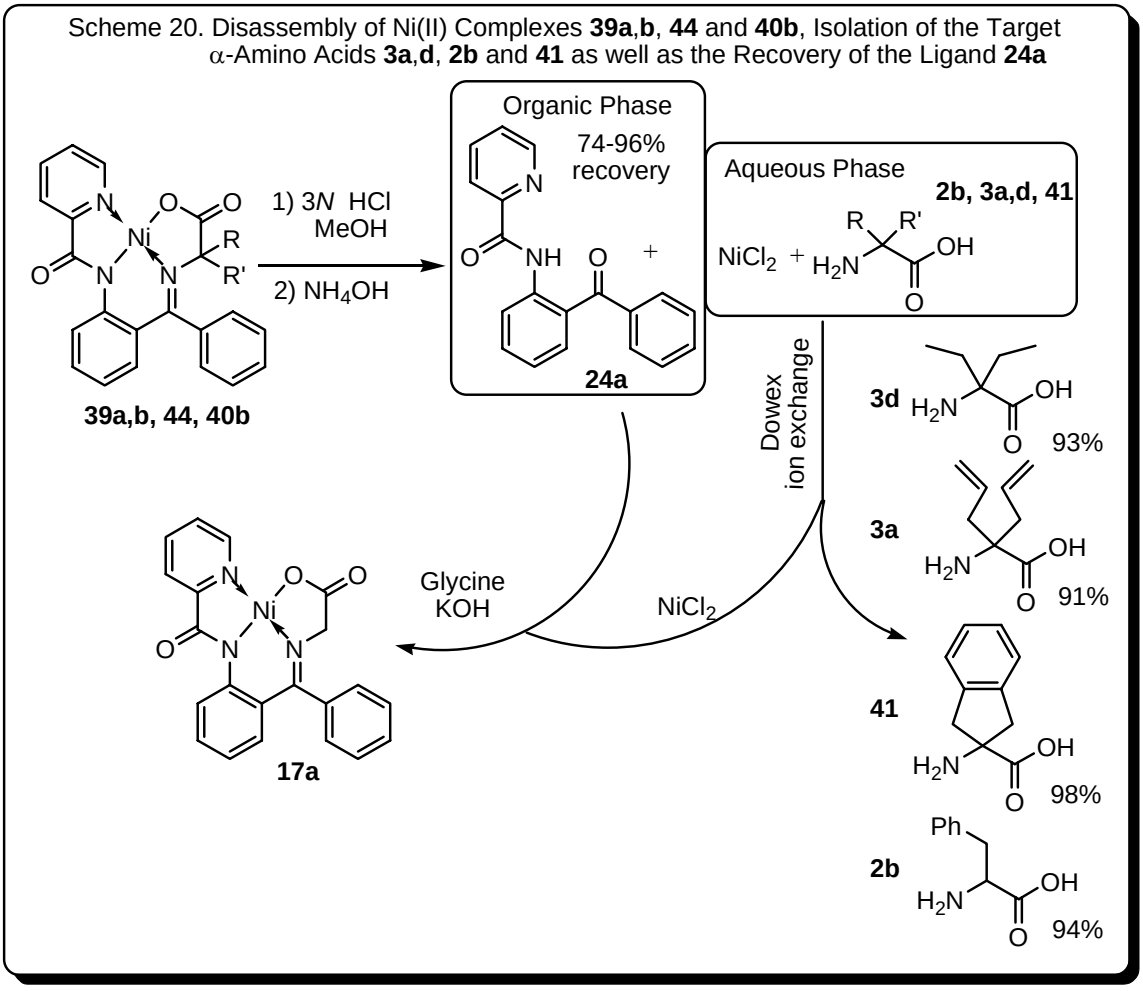
resulted in diminished optical purity of the monoalkylated product **40b** (3.93% ee), although the rate of the reaction was slightly increased (entry 5).

2.3.2: Disassembly of the Ni(II) complex 17a, recovery of the free α-amino acids 2b, 3a, 3d, 41, and the recyclable organic ligand 24a

The disassembly of these picolinic acid derived Ni (II) complexes **39a, 39d**, **44**, **40b** is very facile and can be accomplished with the addition of 3*N* HCl to a warm methanol solution of the complex which may be observed by the fading of the red color and the appearance of the deep green color associated with $NiCl_2$ (Scheme 20).

Following the complete disassembly of the complex **17a** and evaporation of the methanolic solution, ammonium hydroxide was added to liberate the hydrochloric salt of the ligand. The solution was then extracted with dichloromethane to separate the hydrophilic amino acid and nickel (II) chloride from the organic soluble ligand **24a** (recovered in 73-96% yield) which may be reconverted to the starting Ni (II) complex **17a** by the synthetic procedure described earlier (Chapter 2, section 2.3). The corresponding aqueous phase was evaporated to reveal a mixture of the corresponding amino acids **2b**, **3a**, **3d**, **41** and nickel(II) chloride which can be separated on a Dowex ion exchange resin. This was accomplished by loading the mixture on the neutral column liberating hydrochloric acid. The appropriate amino acid **2b**, **3a**, **3d**, and **41** was then washed from the column with 8% ammonium hydroxide which was evaporated to afford the appropriate amino acid in greater than 95% purity and greater than 90% yield.[62,63]

Scheme 20. Disassembly of Ni(II) Complexes **39a**,**b**, **44** and **40b**, Isolation of the Target α-Amino Acids **3a**,**d**, **2b** and **41** as well as the Recovery of the Ligand **24a**



2.4: Summary

In summary, within this chapter a convenient and scalable procedure for the synthesis of the picolinic acid derived Ni(II) complexes of glycine Schiff bases **16**, **17a-c** has been introduced, as well as the identification of complex **17a** as a practical nucleophilic glycine equivalent for the general and convenient synthesis of α,α-symmetrically disubstituted α-amino acids. However, after a systematic study the asymmetric synthesis of α-amino acids via homologation of complex **17a**, under chiral

phase transfer conditions, remains impractical, which is probably due to the limited solubility of the starting Ni(II) complex.

2.5: Experimental Section

2.5.1: General Considerations

Unless specified, all reactions were carried out under an atmosphere of nitrogen with magnetic stirring, using commercially available solvents. TLC was performed using aluminum backed TLC plates with Silica Gel 60 F_{254} from Merck. Column chromatography was performed using Silica Gel 300-300 mesh from Natland International Corporation. HPLC analysis was performed on a Shimadzu LC-10AT liquid chromatograph with a Shimadzu SPD-10AV UV/Vis detector (λ = 254 nm) or a Jasco PU-1580 Intelligent HPLC pump with a Jasco UV-1575 Intelligent UV/Vis detector (λ = 254 nm). Optical rotation was assigned by an AutoPol III automatic polarimeter by Rudolph Research. Exact masses were obtained with a micromass Q-TOF electrospray ionization (ESI) instrument (Waters, UK) and processed using the MassLynx 3.5 software package. ^{1}H, ^{13}C, and spectra were recorded on a Varian Mercury 300 or Varian Unity Inova-400 spectrometer, and were referenced with an internal standard of TMS, for ^{1}H and ^{13}C spectra. Melting points were obtained with a Mel-Temp apparatus with a Fluke 50S digital thermometer and are uncorrected.

2.5.2: Picolinic Acid Derived Ni(II) Complexes of Glycine Schiff Base Synthesis

Large-Scale Preparation of Ligand 24a and 24b by the Use of Ethyl Chloroformate; Typical Procedure: Ethyl chloroformate (87.48 g, 0.81 mol) was added at 0 °C under N_2 to a flask containing picolinic acid (99.65 g, 0.81 mol), triethylamine (81.91 g, 0.81 mol), and CH_2Cl_2 (1.36 L). After the mixture had been stirred at room temperature for 20 min, **22a** (134.02 g, 0.68 mol) was added and the mixture was kept stirring at 40-50 °C overnight. Water was then added to quench the reaction, and the organic phase was washed three times with water. After evaporation of the CH_2Cl_2, washing of the crude precipitate with ether afforded the target product **24a** (200.73 g, 97.61%), which was used for preparing the corresponding Ni(II) complex **17a** without further purification.

Large-Scale Preparation of Ligand 23 by Use of TsCl: TsCl (45.60 g, 0.24 mol) and **21** (27.02 g, 0.20 mol) were added, in that order, at 0 °C under N_2 to a flask containing picolinic acid (29.53 g, 0.24 mol), triethylamine (40.45 g, 0.40 mol), and CH_2Cl_2 (200 mL), and the mixture was stirred at 40-50 °C overnight. Acetic acid (5% aq.) was then added to quench the reaction, and the organic phase was washed three times with water. After evaporation of the CH_2Cl_2, washing of the crude precipitate with ether furnished the desired ligand **23** (46.51 g, 96.84%), which was used without further purification for preparation of the corresponding Ni (II) complex **16**. This procedure was successfully reproduced for the preparation of ligand **24b**.

Preparation of Ligand 24c: Triethylamine (5.41 mL, 38.50 mmol), DMAP (4.28 g, 35.06 mmol), $ClCH_2CH_2Cl$ (100 mL), TsCl (7.34 g, 38.63 mmol), and 2-amino-5-nitrobenzophenone (8.48 g, 35.03 mmol) were added in that order at 0 °C under N_2 to a flask containing picolinic acid (4.74 g, 38.53 mmol). The mixture was then heated at 60-70 °C and stirred overnight. The reaction was quenched by addition of aqueous AcOH (5%) and the organic phase was washed three times with water. After evaporation of the CH_2Cl_2, washing of the crude precipitate with ethyl acetate afforded the desired product **24c** (12.43 g, 98.95% yield), which was used without further purification for preparation of the corresponding Ni (II) complex **17c**.

2-(Picolinoylamino)acetophenone (PAAP) 23a:[41] M.p. 112.4 °C. ^{1}H NMR δ 2.73 (3 H, s), 7.16-7.21 (1 H, m), 7.47-7.51 (1 H, m), 7.60-7.66 (1 H, m), 7.90 (1 H, dt, *J* = 8.7 Hz, 1.7 Hz), 7.97 (1 H, dd, *J* = 7.8 Hz, 1.5 Hz), 8.29 (1 H, d, *J* = 8.1 Hz), 8.80-8.82 (1 H, m), 9.03 (1 H, dd, *J* = 8.5 Hz, 1.0 Hz), 13.5 (1 H, br. s).

3-(Picolinoylamino)acetophenone 23b: [41] M.p. 78.5 °C. ^{1}H NMR δ 2.64 (3 H, s), 7.48 (1 H, t, *J* = 7.7 Hz), 7.50 (1 H, ddd, *J* = 7.6, 4.76, 1.22 Hz), 7.73 (1 H, ddd, *J* = 7.8, 1.7, 1.1 Hz), 7.92 (1 H, td, *J* = 7.8, 1.7 Hz), 8.08 (1 H, ddd, *J* = 7.1, 2.2, 1.1 Hz), 8.28 (1 H, ddd, *J* = 7.8, 1.1, 1.0 Hz), 8.32 (1 H, dd, *J* = 2.1, 1.7 Hz), 8.61 (1 H, ddd, *J* = 4.8, 1.7, 0.9 Hz), 10.2 (1 H, br. s). ^{13}C NMR δ 26.8, 119.1, 122.2, 123.8, 123.9, 126.5, 129.2, 137.5, 137.6, 138.0, 147.8, 149.1, 162.0, 197.5. HRMS [M + Na^+] found *m*/*z* 263.0713, calcd. For $C_{14}H_{12}N_2NaO_2$ 263.0796.

4-(Picolinoylamino)acetophenone 23c: [41] M.p. 173.2 °C. ^{1}H NMR δ 2.60 (3 H, s), 7.51 (1 H, ddd, *J* = 6.6, 4.8, 1.2 Hz), 7.76-8.04 (5 H, m), 8.30 (1 H, ddd, *J* = 7.8, 1.2, 1.0 Hz), 8.62 (1 H, ddd, *J* = 4.8, 1.7, 1.0 Hz), 10.2 (1 H, br. s). ^{13}C NMR δ 26.6, 118.8,

122.4, 126.7, 129.7, 132.7, 137.6, 141.8, 147.8, 149.0, 162.0, 196.6. HRMS [M + Na^+] found *m*/*z* 263.0981, calcd. for $C_{14}H_{12}N_2NaO_2$ 263.0796.

2-(Picolinoylamino)benzophenone (PABP) 24a: [41] M.p. 154.9 °C. ^{1}H NMR δ 7.07 (1 H, m), 7.35-7.43 (3 H, m), 7.43-7.60 (3 H, m), 7.65-7.71 (2 H, m), 7.81 (1 H, td, *J* = 7.7, 1.71 Hz), 8.21 (1 H, d, *J* = 7.8 Hz), 8.68 (1 H, ddd, *J* = 4.8, 1.7, 0.9 Hz), 8.82 (1 H, d, *J* = 8.3 Hz), 12.6 (1 H, br. s).

4-Methyl-2-(picolinoylamino)benzophenone (4-Me-PABP) 24b: [41] M.p. 182.9 °C. ^{1}H NMR δ 2.47 (3 H, s), 6.94 (1 H, dq, *J* = 4.9, 0.9 Hz), 7.40-7.60 (5 H, m), 7.70-7.80 (2 H, m), 7.88 (1 H, td, *J* = 7.8, 1.7 Hz), 8.28 (1 H, d, *J* = 7.8 Hz), 8.72-8.86 (2 H, m), 12.9 (1 H, br. s). ^{13}C NMR δ 22.3, 121.8, 121.9, 122.4, 123.1, 126.2, 128.0, 129.7, 131.9, 133.7, 137.2, 138.9, 139.9, 145.1, 148.5, 150.0, 163.4, 198.6. HRMS [M + Na^+] found *m*/*s* 339.1007, calcd. for $C_{20}H_{16}N_2NaO_2$ 339.1010.

5-Nitro-2-(picolinoylamino)benzophenone (5-NO_2-PABP) 24c: [41] M.p. 236.4 °C. ^{1}H NMR δ 7.48 (3 H, m), 7.62-7.70 (1 H, m), 7.76-7.86 (2 H, m), 7.93 (1 H, td, *J* = 7.8, 1.7 Hz), 8.30 (1 H, ddd, *J* = 7.8, 1.2, 0.9 Hz), 8.45-8.52 (2H, m), 8.78 (1 H, dd, *J* = 0.9, 1.6 Hz), 9.17 (1 H, d, *J* = 9.3 Hz), 13.0 (1 H, br. s). ^{13}C NMR δ 121.2, 122.7, 123.8, 126.8, 128.3, 128.4, 128.5, 129.7, 137.1, 137.1, 137.3, 141.2, 144.8, 148.5, 148.8, 163.5, 196.7. HRMS [M + Na^+] found *m*/*s* 370.0924, calcd. for $C_{19}H_{13}N_3NaO_4$ 370.0804.

Preparation of Ni(II) complexes of Glycine Schiff bases from ligands 23, 24a-c. General Procedure: To a warm methanolic (3L/mol of **23, 24a-c**) solution of ligand **23, 24a-c** (1 eq.) was added $NiCl_2$ hexahydrate (2 eq.), glycine (5 eq.), and KOH (7 eq). The reaction is allowed to proceed at 60-70 ^{o}C until complete consumption of the ligand, which is monitored by TLC. Upon complete consumption of the ligand the methanolic

solution is gently poured over icy 5% acetic acid (acetic acid:methanol 10:1). Once the ice has been allowed to melt the precipitate should be filtered and washed with water, followed by drying in a low temperature oven.

Ni(II) Complex of Glycine Schiff Base with 2-(Picolinoylamino)acetophenone 16: [41] Yield 97.35%. M.p. 290 °C (decomp.). ^{1}H NMR δ 2.43 (3 H, s), 4.20 (2 H, s), 7.01 (1 H, m), 7.32-7.43 (2 H, m), 7.63 (1 H, d, *J* = 8.6 Hz), 7.81 (1 H, d, *J* = 7.3 Hz), 7.95 (1 H, t, *J* = 7.6 Hz), 8.18 (1 H, d, *J* = 4.9 Hz), 8.69 (1 H, d, *J* = 8.8 Hz).

Ni(II) Complex of Glycine Schiff Base with 2-(Picolinoylamino)benzophenone 17a:[41] Yield 99.07%. M.p. 270 °C (decomp). ^{1}H NMR δ 3.83 (2 H, s), 6.83 (1 H, t, *J* = 7.6 Hz), 6.91 (1 H, d, *J* = 7.8 Hz), 7.11 (2 H, d, *J* = 7.1 Hz), 7.34-7.47 (2 H, m), 7.50-7.60 (2 H, m), 7.89 (1 H, d, *J* = 6.8 Hz), 7.99 (1 H, m), 8.29 (1 H, d, *J* = 5.4 Hz), 8.99 (1 H, d, *J* = 8.1 Hz).

Ni(II) Complex of Glycine Schiff Base with 4-Methyl-2-(picolinoylamino)benzophenone 17b:[41] Yield 92.78%. M.p. 270 °C (decomp.). ^{1}H NMR δ 2.33 (3 H, s), 3.79 (2 H, s), 6.61 (1 H, m), 6.78 (1 H, d, *J* = 8.3 Hz), 7.09 (2 H, m), 7.43 (1 H, ddd, *J* = 7.1 Hz), 7.48-7.60 (3 H, m), 7.87 (1 H, m), 7.98 (1 H, td, *J* = 7.6, 1.22 Hz), 8.26 (1 H, m), 8.85 (1 H, br. s). ^{13}C NMR δ 61.7, 122.7, 123.3, 123.8, 124.2, 125.9, 126.8, 129.4, 134.3, 134.6, 140.3, 142.8, 144.4, 146.7, 153.2, 170.2, 172.4, 177.2. HRMS [M + Na^+] found *m*/*z* 452.0668, calcd. for $C_{22}H_{17}N_3NaNiO_3$ 452.0521.

Ni(II) Complex of Glycine Schiff Base with 5-Nitro-2-(picolinoylamino)benzophenone 17c:[41] Yield 95.43%. M.p. 300 °C (decomp.). ^{1}H NMR δ 3.88 (2 H, s), 7.00-7.38 (4 H, m), 7.54 (1 H, m), 7.62 (1 H, m), 7.85 (1 H, d, *J* = 2.4 Hz), 7.95 (1 H, d, *J* = 7.8 Hz), 8.06 (1 H, dd, *J* = 7.7, 7.6 Hz), 8.16 (1 H, dd, *J* = 9.3,

2.2 Hz), 8.34 (1 H, d, *J* = 4.9 Hz), 9.13 (1 H, d, *J* = 9.6 Hz). HRMS [M + Na^+] found *m*/*z* 485.0386, calcd. for $C_{21}H_{15}N_4NaNiO_5$ 485.0509.

2.5.3: Synthesis of α,α-Symmetrically Disubstituted α-Amino Acids Via Homologation of Picolinic Acid Derived Ni(II) Complexes of Glycine Schiff Bases 16 and 17a.

Alkylation of Complex 16 with Ethyl Iodide. To a solution of 0.950 g (9.887 mmol) of sodium *tert*-butoxide in DMF (10 mL/0.95 g), cooled in an ice bath to 4 °C, were added 1.005 g (2.834 mmol) of complex **16** and 1.542 g (9.887 mmol) of ethyl iodide (**38d**), and the reaction was stirred at 4 °C for 5 min, after which time the ice bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction was quenched by pouring the reaction mixture over ice water. The resulting crystalline precipitate was filtered off and washed with water and *n*-hexane to yield the products **34-37**, which were separated by column chromatography.

Ni(II) Complex of 2-Aminobuturic Acid Schiff Base with PAAP 34.[62a] Obtained by quenching the reaction after 15 min (monitored by TLC): *Rf* = 0.17. M.p. >200 °C; ^{1}H NMR δ 1.50 (3 H, t, *J* = 7.5 Hz), 2.10 (1 H, dq, *J* = 7.5, 3.9 Hz), 2.21 (1 H, dq, *J* = 13.8, 7.5 Hz), 2.51 (3 H, s), 4.29 (1 H, q, *J* = 7.5, 3.9 Hz), 7.02 (1 H, m), 7.26-7.45 (2 H, m), 7.69 (1 H, dd, *J* = 8.4, 1.5 Hz), 7.87 (1 H, dm, *J* = 5.4 Hz), 7.97 (1 H, td, *J* = 7.5, 1.5 Hz), 8.22 (1 H, dm, *J* = 3.6 Hz), 8.79 (1 H, dd, *J* = 8.7, 1.2 Hz); ^{13}C NMR δ 9.81, 18.68, 28.23, 71.73, 121.75, 123.77, 123.95, 126.60, 126.75, 129.91, 132.54,

140.25, 141.67, 146.80, 153.07, 169.21, 169.46, 179.42; HRMS [M + Na^+] calcd for $C_{18}H_{17}N_3NaNiO_3$ 405.0292, found 405.0101.

Ni(II) Complex of 2-Aminobuturic Acid Schiff Base with 1-[2'-[*N*-(α-Picolyl)amino]phenyl]butan-1-one (35).[62a] Obtained by quenching the reaction after 1 h (monitored by TLC): *Rf* = 0.28; M.p. >200 °C; ^{1}H NMR δ 1.13 (3 H, t, *J* = 7.2 Hz), 1.58 (3 H, t, *J* = 7.4 Hz), 1.70 (2 H, s, *J* = 7.7 Hz), 2.13 (1 H, m), 2.31 (1 H, m), 2.69-2.88 (2 H, m), 4.23 (1 H, dd, *J* = 3.8, 7.4 Hz), 7.02 (1 H, m), 7.36 (1 H, m), 7.41 (1 H, m), 7.61 (1 H, d, *J* = 8.1 Hz), 7.87 (1 H, m), 7.97 (1 H, m), 8.19 (1 H, d, *J* = 5.1 Hz), 8.76 (1 H, d, *J* = 8.4 Hz); ^{13}C NMR δ 10.1, 14.3, 22.8, 29.2, 33.0, 71.5, 121.7, 123.7, 124.0, 125.4, 126.6, 129.9, 132.4, 140.2, 142.3, 146.8, 153.1, 169.3, 172.7, 178.9; HRMS [M + H^+] calcd for $C_{20}H_{22}N_3NiO_3$ 411.1006, found 411.1209.

Ni(II) Complex of 2-Amino-2-ethylbuturic Acid Schiff Base with 1-[2'-[*N*-(α-picolyl)amino]phenyl]butan-1-one (36) and Ni(II) Complex of 2-Aminobuturic acid Schiff Base with 2-Ethyl-1-[2'-[*N*-(α-picolyl)amino]phenyl]butan-1-one 37.[62a] Obtained as an inseparable mixture by column chromatography by quenching the reaction after 24 h (monitored by TLC): *Rf* = 0.41. Compound **10**: ^{1}H NMR δ 0.98 (3 H, t, *J* = 7.5 Hz), 1.28 (6 H, t, *J* = 7.5 Hz), 1.44 (2 H, m), 2.18 (4 H, m), 3.13 (2 H, m), 7.0 (1 H, m), 7.34-7.42 (2 H, m), 7.41 (1 H, m), 7.88 (1 H, m), 7.97 (1 H, m), 8.29 (1 H, m), 8.52 (1 H, m). Compound **11**: ^{1}H NMR δ 0.83 (3 H, t, *J* = 7.5 Hz), 1.10 (3 H, t, *J* = 7.5 Hz), 1.46 (2 H, m), 1.70 (3 H, t, *J* = 7.5), 1.75-2.10 (3 H, m), 2.67 (1 H, s, *J* = 13.8, 6.3 Hz), 2.95 (1 H, m), 4.16 (1 H, dd, *J* = 8.1, 3.3 Hz), 6.94 (1 H, m), 7.34 (1 H, m), 7.42 (1 H, m), 7.68 (1 H, m), 7.87 (1 H, m), 7.97 (1 H, m), 8.13 (1 H, m), 8.61 (1 H, m). HRMS [M + H^+] calcd for $C_{22}H_{25}N_3NaNiO_3$ 461.1147, found 461.0996.

Dialkylation of Ni(II) Complex 17a with Activated Bromides 38a-c Yielding Complexes 39a-c. **General Procedure.** To a solution of sodium *tert*-butoxide (3 equiv.) in DMF (10 mL/1 g of complex **17a**) were added complex **17a** (1 equiv.) and the corresponding alkylating reagent **38a-c** (3 equiv.). The reaction was stirred at ambient temperature (room temperature water bath) for 15 min, and upon completion (monitored by TLC), the reaction mixture was poured into ice water and the resulting solid was filtered, washed with water and *n*-hexane to afford the products **39a-c** in yields ranging from 89 to 94% and of greater than 99% purity. For the chemical yields, see Table 1, entries 3-5. The corresponding monoalkylated products **40a-c** were prepared under the same conditions except that the base and the alkylating reagent were used in a ratio of 1.5/1.1, respectively.

Ni(II) Complex of α,α-Diallylglycine Schiff Base with PABP 39a:[62] *Rf* = 0.60; M.p. 247.3 °C; ^{1}H NMR δ 2.31 (2 H, ddt, *J* = 15.5, 6.8, 1.5 Hz), 2.50 (2 H, ddt, *J* = 15.5, 6.8, 1.5 Hz), 5.24-5.35 (4 H, m),6.19-6.33 (2 H, m), 6.67 (1 H, m), 6.71 (1 H, m), 7.26-7.35 (3 H, m), 7.41-7.57 (4 H, m), 7.89 (1 H, m), 7.99 (1 H, m), 8.36 (1 H, m), 8.70 (1 H, m); ^{13}C NMR δ 43.16, 82.43, 119.14, 121.04, 123.45, 123.47, 124.85, 126.55, 127.34, 127.74, 128.59, 129.60, 131.89, 132.53, 133.39, 134.25, 136.38, 140.10, 140.45, 142.12, 144.43, 147.02, 152.81, 169.64, 173.49, 180.34; HRMS [M + H^{+}] calcd for $C_{27}H_{23}N_3NiO_3$ 497.1810, found 497.1416.

Ni(II) Complex of 2-amino-pent-4-enoic Acid Schiff Base with PABP 40a:[62] *Rf* = 0.47; M.p. 232.5 °C; ^{1}H NMR δ 2.48-2.53 (2 H, m), 4.11 (1 H, dd, *J* = 5.4, 4.5 Hz), 5.15 (1 H, m), 5.32 (1 H, m), 6.44 (1 H, m), 6.75-6.82 (2 H, m), 7.10 (1 H, m), 7.32 (1 H, m), 7.43-7.56 (5 H, m), 7.90 (1 H, m), 8.01 (1 H, m), 8.22 (1 H, d, *J* = 4.8 Hz), 8.92 (1 H,

d, J = 8.4 Hz). ^{13}C NMR δ 38.9, 71.1, 119.6, 121.3, 123.3, 123.9, 126.6, 126.8, 127.0, 127.8, 128.7, 129.1, 129.8, 131.9, 133.3, 133.8, 134.4, 140.4, 143.0, 146.8, 153.1, 169.7, 171.8, 178.6; HRMS [M + Na^+] calcd for $C_{24}H_{19}N_3NaNiO_3$ 479.1093, found 479.0992.

Ni(II) Complex of α,α-Dibenzylglycine Schiff Base with PABP 39b:[62] *Rf* = 0.62; M.p. 295.2 °C. ^{1}H NMR δ 2.78 (2 H, d, J = 15.9 Hz), 3.37 (2 H, d, J = 15.9 Hz), 6.65- 6.67 (2 H, m), 6.82-6.85 (2 H, m), 6.96-7.02(2 H, m), 7.20-7.34 (12 H, m) 7.50 (1 H, m), 7.75 (1 H, m), 7.82-7.92 (2 H, m), 8.52 (1 H, m). ^{13}C NMR δ 30.88, 82.70, 120.95, 122.94, 123.46, 125.86, 126.26, 127.22, 127.40, 127.70, 128.01, 128.28, 128.67, 129.35, 129.59, 132.37, 134.17, 135.70, 136.40, 139.42, 142.13, 146.59, 152.75, 168.70, 171.53, 178.48. HRMS [M + Na^+] calcd $C_{36}H_{30}N_3NiO_3$ 597.3014, found 597.1463.

Ni(II) complex of 2-Amino-3-phenylpropionic Acid Schiff Base with PABP 40b:[62] *Rf* = 0.65; M.p. 262.7 °C. ^{1}H NMR δ 2.86, 3.13 (2 H, ABX, J = 13.5, 5.9, 3.2 Hz), 4.36 (1 H, dd, J = 5.9, 3.2 Hz), 6.76-6.88 (3 H, m), 7.13-7.26 (3 H, m), 7.28-7.42 (5 H, m), 7.52-7.61 (3 H, m), 7.68 (1 H, m), 7.77 (1 H, m), 7.90 (1 H, m), 8.71 (1 H, d, J = 8.7 Hz). ^{13}C NMR δ 40.1, 72.9, 121.3, 123.4, 123.5, 126.2, 127.0, 127.1, 127.3, 127.5, 128.0, 129.0, 129.2, 130.0, 131.0, 133.2, 133.5, 134.2, 135.6, 139.7, 143.0, 146.5, 153.0, 169.0, 171.0, 177.8. HRMS [M + H^+] calcd for $C_{28}H_{21}N_3NaNiO_3$ 529.1680, found 529.0767.

Ni(II) Complex of α,α-Di-(*trans*)-cinnamylglycine Schiff Base with PABP 39c:[62] *Rf* = 0.79. M.p. 247.5 °C. ^{1}H NMR δ 2.46 (2 H, dd, J = 15.2, 6.0 Hz), 2.73 (2 H, dd, J = 15.2, 6.0 Hz), 6.63-6.76 (7 H, m), 7.12-7.41 (13 H, m), 7.49-7.58 (4 H, m), 7.76 (1 H, m), 8.13 (1 H, m) 8.61 (1 H, m). ^{13}C NMR δ 42.13, 83.56, 121.11, 123.22, 123.52, 123.74, 125.91, 126.15, 127.00, 127.52, 127.60, 128.15, 128.94, 129.68, 132.52, 134.04,

134.10, 136.13, 136.72, 139.58, 142.22, 146.55, 152.42, 169.14, 172.76, 179.46. HRMS [M + H^+] calcd for $C_{39}H_{34}N_3NiO_3$ 649.3753, found 649.1760.

Ni(II) Complex of 2-Amino-5-phenylpent-4-enoic Acid Schiff Base with PABP 40c:[62] *Rf* = 0.43. M.p. 182.1 °C. ^{1}H NMR δ 2.56-2.71 (2 H, br. m), 4.22 (1 H, m), 6.69-6.81 (3 H, m), 7.04-7.06 (3 H, m), 7.12 (1 H, m), 7.24-7.39, (5 H, m), 7.53-7.56 (4 H, m), 7.77 (1 H, t, *J* = 7.5 Hz), 7.97 (1 H, m), 8.79 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 30.10, 71.07, 121.68, 123.79, 124.07, 126.35, 126.72, 127.08, 127.44, 127.58, 127.75, 127.98, 128.67, 128.78, 129.28, 129.58, 130.29, 133.63, 133.82, 134.66, 135.86, 136.97, 140.25, 143.44, 146.92, 153.00, 169.65. HRMS [M + Na^+] calcd for $C_{30}H_{23}N_3NaNiO_3$ 555.2052, found 555.0589.

Dialkylation of Ni(II) Complex 17a with Nonactivated Alkyl Iodides 38d-h Yielding Complexes 39d-h. General Procedure. To a solution of sodium *tert*-butoxide (3.5 equiv) in DMF (10mL per 1 g of complex **17a**), cooled in an ice bath to 4 °C, was added complex **17a** (1 equiv) and the corresponding alkylating reagent **38d-h** (3.5 equiv). The reaction was stirred at 4 °C for 5 min, after which time the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After an additional 10 min (monitored by TLC), the reaction was poured into ice water, and the resulting solid was filtered and washed with water and *n*-hexane to afford the products **39d-h** of greater than 99% purity. The corresponding monoalkylated products **40d-h** were prepared under the same conditions except that the base and the alkylating reagent (bromides) were used in a ratio of 1.5/ 1.1, respectively.

Ni(II) Complex of α,α-Diethylglycine Schiff Base with PABP 39d:[62] *Rf* = 0.52. M.p. 322.1 °C. ^{1}H NMR δ 1.27 (6 H, t, *J* = 7.2 Hz), 1.52 (2 H, dq, *J* = 14.7, 7.2 Hz),

1.71 (2 H, dq, *J* = 14.7,7.2 Hz), 6.68 (1 H, m), 6.72 (1 H, m), 7.24-7.34 (3 H, m), 7.42-7.55 (4 H, m), 7.90 (1 H, m), 7.99 (1 H, m), 8.40 (1 H, m), 8.71 (1 H, m). ^{13}C NMR δ 9.54, 32.79, 84.53, 121.04, 123.46, 123.48, 126.55, 127.31, 127.33, 128.71, 129.40, 132.40, 134.19, 136.49, 140.10, 142.01, 147.00, 152.88, 169.65, 173.17, 181.72. HRMS [M + H^+] calcd for $C_{25}H_{24}N_3NiO_3$ 473.1626, found 473.1322.

Ni(II) Complex of 2-Aminobutyric Acid Schiff Base with PABP 40d:[62] *Rf* = 0.45. M.p. 265.4 °C. ^{1}H NMR δ 1.39 (3 H, t, *J* = 7.5 Hz), 1.73 (1 H, m), 1.97 (1 H, m), 3.99 (1 H, dd, *J* = 7.5; 3.3 Hz), 6.74-6.81 (2 H, m), 7.06 (1 H, m), 7.32 (1 H, m), 7.43-7.52 (5 H, m), 7.91 (1 H, m), 8.01 (1 H, m), 8.24 (1 H, d, *J* = 4.8 Hz), 8.93 (1 H, d, *J* = 8.1 Hz). ^{13}C NMR δ 9.7, 28.4, 72.0, 121.1, 123.2, 123.8, 126.5, 126.7, 126.7, 127.5, 128.5, 128.9, 129.5, 133.1, 133.6, 134.2, 140.2, 142.7, 146.6, 153.0, 169.6, 171.5, 179.0. HRMS [M + Na^+] calcd for $C_{23}H_{19}N_3NaNiO_3$ 467.0986, found 467.2276.

Ni(II) Complex of α,α-Di-*n*-propylglycine Schiff Base with PABP 39e:[62] *Rf* = 0.63. M.p. 282.5 °C. ^{1}H NMR δ 0.91 (6 H, t, *J* = 7.5 Hz), 1.35-1.45 (2 H, m), 1.57-1.95 (6 H, m), 6.69-6.74 (2 H, m), 7.19-7.23 (2 H, m), 7.30 (1 H, m), 7.41-7.56 (4 H, m), 7.89 (1 H, m), 7.98 (1 H, m), 8.38 (1 H, m), 8.70 (1 H, m). ^{13}C NMR δ 14.27, 18.62, 42.32, 83.78, 121.51, 123.93, 123.97, 127.02, 127.79, 127.84, 129.13, 129.93, 132.87, 134.67, 136.98, 140.57, 142.46, 147.44, 153.36, 170.12, 173.43. HRMS [M + H^+] calcd for $C_{27}H_{28}N_3NiO_3$ 501.2158, found 501.1381.

Ni(II) Complex of 2-Aminopentanoic Acid Schiff Base with PABP 40e:[62] *Rf* = 0.63. M.p. 252.1 °C. ^{1}H NMR δ 0.80 (3 H, t, *J* = 7.2 Hz), 1.57-1.69 (2 H, m), 2.02 (1 H, m), 2.17 (1 H, m), 4.02 (1 H, dd, *J* = 8.4; 3.0 Hz), 6.75-6.81 (2 H, m), 7.07 (1 H, m), 7.32 (1 H, m), 7.42-7.52 (5 H, m), 7.91 (1 H, m), 8.01 (1 H, m), 8.23 (1 H, d, *J* = 5.4 Hz), 8.92

(1 H, d, *J* = 8.1 Hz). ^{13}C NMR δ 13.7, 18.4, 37.3, 70.9, 121.1, 123.2, 123.8, 126.5, 126.7, 126.8, 127.5, 128.5, 128.8, 129.5, 133.0, 133.6, 134.2, 140.2, 142.7, 146.6, 153.0, 169.6, 171.2, 179.1. HRMS [M + H^+] calcd for $C_{24}H_{22}N_3NiO_3$ 459.1361, found 459.0934.

Ni(II) Complex of α,α-Di-*n*-butylglycine Schiff Base with PABP 39f:[62] *Rf* = 0.67. M.p. 221.7 °C. ^{1}H NMR δ 0.93 (6 H, t, *J* = 7.4 Hz), 1.21-1.34 (4 H, m), 1.39-1.49 (2 H, m), 1.59-1.87 (6 H, m), 6.65-6.74 (2 H, m), 7.19-7.23 (2 H, m), 7.31 (1 H, m), 7.42-7.55 (4 H, m), 7.90 (1 H, m), 7.99 (1 H, m), 8.39 (1 H, m), 8.72 (1 H, m). ^{13}C NMR δ 14.46, 23.10, 27.33, 40.20, 83.75, 121.49, 123.93, 123.96, 127.02, 127.79, 127.87, 129.12, 129.92, 132.87, 134.71, 136.96, 140.58, 142.51, 147.47, 153.36, 170.19, 173.41, 182.60. HRMS [M + Na^+] calcd for $C_{29}H_{32}N_3NaNiO_3$ 529.2680, found 529.1837.

Ni(II) Complex of 2-Aminohexanoic Acid Schiff Base with PABP 40f:[62] *Rf* = 0.62. M.p. 250.6 °C. ^{1}H NMR δ 0.82 (3 H, t, *J* = 7.2 Hz), 1.11-1.32 (2 H, m), 1.49-1.70 (2 H, m), 1.96-2.09 (2 H, m), 4.00 (1 H, q, *J* = 3.7 Hz), 6.74-6.80 (2 H, m), 7.06 (1 H, m), 7.27-7.37 (2 H, m), 7.41-7.54 (4 H, m), 7.90 (1 H, m), 8.00 (1 H, m), 8.23 (1 H, d, *J* = 5.4 Hz), 8.92 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 14.16, 22.73, 27.41, 35.46, 71.53, 121.62, 123.65, 124.26, 127.01, 127.16, 127.32, 128.00, 128.96, 129.35, 130.00, 133.53, 134.10, 134.69, 140.70, 143.19, 147.14, 153.50, 170.13, 171.76, 179.66. HRMS [M + Na^+] calcd for $C_{25}H_{23}N_3NaNiO_3$ 495.1517, found 495.1092.

Ni(II) Complex of α,α-Dimethylglycine Schiff Base with PABP 39g:[62] *Rf* = 0.36. M.p. 328.9 °C. ^{1}H NMR δ 1.25 (3 H, s), 1.44 (3 H, s), 6.72-6.74 (2 H, m), 7.21-7.25 (2 H, m), 7.31 (1 H, m), 7.43-7.52 (4 H, m), 7.91 (1 H, m), 8.00 (1 H, m), 8.38 (1 H, m), 8.72 (1 H, m). ^{13}C NMR δ 29.07, 75.21, 121.06, 123.38, 123.51, 126.58, 127.34, 128.35,

128.94, 129.15, 132.50, 134.29, 136.27, 140.15, 141.83, 146.75, 152.94, 169.53, 173.08, 182.63. HRMS [M + H^+] calcd for $C_{23}H_{20}N_3NiO_3$ 445.1095, found 445.0939.

Ni(II) Complex of 2-Aminopropionic Acid Schiff Base with PABP 40g:[62] *Rf* = 0.44. M.p. 259.1 °C. ^{1}H NMR δ 1.58 (3 H, d, *J* = 7.1 Hz), 4.03 (1 H, q, *J* = 7.1 Hz), 6.74-6.78 (2 H, m), 7.08 (1 H, m), 7.27-7.36 (2 H, m), 7.42-7.55 (4 H, m), 7.90 (1 H, m), 8.00 (1 H, m), 8.23 (1 H, d, *J* = 5.1 Hz), 8.92 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 21.56, 67.18, 121.20, 123.31, 123.84, 126.42, 126.76, 126.83, 127.67, 128.54, 128.96, 129.58, 133.16, 133.46, 134.25, 140.32, 142.71, 146.64, 153.04, 169.70, 171.65, 180.36. HRMS [M + Na^+] calcd for $C_{22}H_{17}N_3NaNiO_3$ 454.0720, found 454.0523.

Ni(II) Complex of α,α-Di-*n*-pentylglycine Schiff Base with PABP 39h:[62] *Rf* = 0.81. M.p. 223.4 °C. ^{1}H NMR δ 0.89 (6 H, t, *J* = 7.1 Hz), 1.19-1.47 (10 H, m), 1.58-1.88 (6 H, m), 6.66-6.74 (2 H, m), 7.19-7.22 (2 H, m), 7.31 (1 H, m), 7.42- 7.53 (4 H, m), 7.89 (1 H, m), 7.99 (1 H, m), 8.39 (1 H, m), 8.72 (1 H, m). ^{13}C NMR δ 14.67, 23.00, 24.99, 32.20, 40.43, 83.80, 121.51, 123.93, 123.96, 127.03, 127.81, 127.85, 129.14, 129.91, 132.86, 134.70, 136.98, 140.58, 142.50, 147.49, 153.36, 170.18, 173.40, 182.55. HRMS [M + Na^+] calcd for $C_{32}H_{39}N_3NaNiO_3$ 571.2345, found 571.2650.

Ni(II) Complex of 2-Aminoheptanoic Acid Schiff Base with PABP 40h:[62] *Rf* = 0.63. M.p. 248.3 °C. ^{1}H NMR δ 0.80 (3 H, t, *J* = 6.9 Hz), 1.13-1.32 (4 H, m), 1.53-1.66 (2 H, m), 1.68-2.11 (2 H, m), 3.99 (1 H, m), 6.74-6.78 (2 H, m), 7.06 (1 H, m), 7.26-7.37 (2 H, m), 7.42-7.52 (4 H, m), 7.90 (1 H, m), 8.00 (1 H, m), 8.23 (1 H, d, *J* = 5.4 Hz), 8.91 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 14.31, 22.59, 25.02, 31.70, 35.70, 71.44, 121.54, 123.57, 124.18, 126.93, 127.08, 127.26, 127.92, 128.90, 129.26, 129.91, 133.44, 134.00, 134.60,

140.62, 143.10, 147.06, 153.42, 170.04, 171.65, 179.58. HRMS [M + Na^+] calcd for $C_{26}H_{25}N_3NaNiO_3$ 509.1783, found 509.0991.

Dialkylation of Ni(II) Complex 17a with Propargyl Bromide 38k under PTC. Synthesis of 40k and 39k. To a solution of 1.013 g (2.435 mmol) of complex **17a** in 10 mL of CH_2Cl_2 (10 mL /1.013 g) at room temperature was added tetrapropylammonium iodide 0.188 g (0.600 mmol), 10 mL of 30% aqueous sodium hydroxide solution (1 mL/1 mL of CH_2Cl_2), and 1.250 g (10.51 mmol) of propargyl bromide (80%) **38k**. The resultant mixture was rigorously stirred for 18 h at room temperature. To the resultant slurry were added additional amounts of water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and then evaporated in a vacuum to yield a crystalline compound. This compound was washed with water and hexane and then dried to yield the final product **39k**. The monoalkylated complex **40k** was the major product if the reaction was worked up after 20 min.

Ni(II) Complex of α,α-Dipropargylglycine Schiff Base with PABP 39k:[62a] *Rf* = 0.56. M.p. 258.2 °C. ^{1}H NMR δ 2.19, 2.86 (4 H, ABX, *J* = 17.1, 2.7, 2.7 Hz), 2.43 (2 H, t, *J* = 2.6 Hz), 6.74 (2 H, d, *J* = 3.9 Hz), 7.34 (1 H, m), 7.46 (1 H, m), 7.50-7.56 (5 H, m), 7.88-7.91 (1 H, dm, *J* = 1.5 Hz), 7.99 (1 H, m), 8.38 (1 H, d, *J* = 5.1 Hz), 8.74 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 30.1, 30.1, 73.8, 73.8, 77.1, 78.2, 78.6, 121.1, 123.5, 123.6, 126.7, 127.8, 127.8, 128.4, 128.6, 129.9, 130.7, 132.9, 134.5, 133.9, 140.2, 142.5, 147.2, 152.9, 167.7, 174.6, 179.4. HRMS [M + Na^+] calcd for $C_{27}H_{19}N_3NaNiO_3$ 515.1414, found 515.0762.

Ni(II) Complex of 2-Aminopent-4-ynoic Acid Schiff Base with PABP 40k:[62a] *Rf* = 0.37. M.p. 244.5 °C. ^{1}H NMR δ 2.28-2.55 (2 H, m), 4.02 (1 H, m), 6.74-6.79 (2 H,

m), 7.31 (1 H, m), 7.43 (1 H, m), 7.49-7.54 (5 H, m), 7.88 (1 H, m), 7.99 (1 H, dm, *J* = 1.4 Hz), 8.20 (1 H, d, *J* = 5.4 Hz), 8.92 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 24.3, 68.9, 121.2, 123.4, 123.8, 126.5, 126.6, 126.8, 128.9, 129.1, 129.9, 133.4, 133.5, 134.4, 140.2, 143.3, 146.9, 153.0, 169.7, 172.5, 177.8. HRMS [M + Na^+] calcd for $C_{24}H_{17}N_3NaNiO_3$ 477.0934, found 477.0460.

Michael Addition Reactions of Ni(II) Complex 17a with Acrylonitrile (38l) and Ethyl Acrylate (38m). To a solution of complex **17a** (1 equiv) in CH_2Cl_2 (10 mL/1 g) at room temperature were added tetrapropylammonium iodide (0.25 equiv), 30% aqueous sodium hydroxide (1 mL/1 mL CH_2Cl_2), and Michael acceptor **38l** or **38m**(3.5 equiv). The resultant mixture was rigorously stirred for 15 min (monitored by TLC) at room temperature. To the resultant slurry were added additional amounts of water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and then evaporated in a vacuum to yield a crystalline compound. The compound was washed with water and hexane then dried to yield the final product **40l** and **40m**.

Ni(II) Complex of 2-Amino-4-cyanobutyric Acid Schiff Base with PABP 40l:[62a] *Rf* = 0.33. M.p. 229.4 °C. ^{1}H NMR δ 2.37-2.60 (2 H, m), 2.82-2.91 (2 H, m), 4.01 (1 H, m), 6.74-6.83 (2 H, m), 7.10 (1 H, m), 7.45 (1 H, m), 7.51-7.58 (4 H, m), 7.92 (1 H, m), 8.02 (1 H, m), 8.02 (1 H, m), 8.19 (1 H, d, *J* = 4.8 Hz), 8.20 (1 H, d, *J* = 6.0), 8.92 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 13.6, 30.9, 69.0, 77.1, 121.4, 123.4, 124.1, 126.1, 126.7, 126.9, 127.0, 127.3, 129.0, 129.4, 130.1, 133.1, 133.8, 134.5, 140.5, 143.0, 146.6, 152.9, 169.7, 173.1, 177.7, 206.6. HRMS [M + Na^+] calcd for $C_{24}H_{18}N_4NaNiO_3$ 492.1081, found 492.0830.

Ni(II) Complex of 2-Aminopentanedioic Acid 5-Ethyl Ester Schiff Base with PABP 40m:[62a] *Rf* = 0.36. M.p. 239.8 °C. ^{1}H NMR δ 1.16 (3 H, t, *J* = 7.2 Hz), 1.88-1.99 (2 H, m), 3.22-3.32 (2 H, m), 2.32-2.57 (2 H, m), 3.98-4.08 (3 H, m), 6.74-6.81 (2 H, m), 7.26 (1 H, m), 7.34 (1 H, m), 7.48 (1 H, m), 7.52-7.54 (4 H, m), 7.91 (1 H, m), 8.01 (1 H, m), 8.22 (1 H, d, *J* = 4.5 Hz), 8.95 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 14.1, 29.4, 29.9, 61.0, 70.2, 121.3, 123.2, 123.9, 126.4, 126.6, 126.8, 127.8, 128.7, 128.9, 129.7, 133.4, 133.6, 134.5, 140.4, 142.8, 146.7, 153.0, 169.7, 172.3, 172.7, 178.6. HRMS [M + Na^{+}] calcd for $C_{26}H_{23}N_3NaNiO_5$ 539.1612, found 539.0834.

2.5.4: Synthesis of Cyclic α,α-Symmetrically Disubstituted α-Amino Acids Via Homologation of Picolinic Acid Derived Ni(II) Complexes of Glycine Schiff Bases 17a.

Monoalkylation of Ni(II) Complex 17a with *o*-Xylylene Dibromide 42 under PTC. Synthesis of Complex 43. To a solution of 5.08 g (12.2 mmol) of complex **17a**, 3.55 g (13.1 mmol) of *o*-xylylene dibromide **42**, and 0.573 g (1.83 mmol) of tetrapropylammonium iodide in 50 mL of CH_2Cl_2 (4 mL/1 mmol of complex **17a**) was added 30 mL of 30% aq. NaOH (2.5 mL/1 mmol of complex **17a**). The reaction was vigorously stirred at room temperature for 2 h, and upon completion (monitored by TLC) 100 mL of water was added and the aqueous layer extracted with CH_2Cl_2 (3 X 50 mL). Combined organic fractions were dried over $MgSO_4$ and evaporated to afford 7.10 g (97.2% yield) of complex **43**.

Ni(II) Complex of 2-amino-3-(2-bromomethyl-phenyl)-propanoic Acid Schiff Base with PABP 43:[63] *Rf* = 0.47. M.p. 242.0 °C. ^{1}H NMR δ 3.33 (2 H, ABX, *J* = 14.4, 6.0, 4.2 Hz), 4.37 (1 H, dd, *J* = 6.0, 4.2 Hz), 4.42 (2 H, AB, *J* = 10.5 Hz), 6.85-6.82 (2 H, m), 6.88 (1 H, d, *J* = 4.2 Hz), 6.90 (1 H, d, *J* = 4.2 Hz), 7.13 (1 H, m), 7.20 (2 H, t, *J* = 1.2 Hz), 7.30-7.40 (4 H, m), 7.56-7.60 (3 H, m), 7.71 (1 H, d, *J* = 5.1 Hz), 7.83 (1 H, m), 7.94 (1 H, td, *J* = 7.5, 1.2 Hz), 8.80 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 32.56, 37.19, 73.18, 121.83, 123.85, 124.03, 126.84, 127.15, 127.68, 128.00, 128.96, 129.60, 129.65, 130.41, 130.77, 133.12, 133.55, 133.89, 134.83, 135.04, 138.12, 140.33, 143.36, 146.74, 153.27, 159.82, 169.51, 171.90, 178.11. HRMS [M + H^+] calcd for $C_{29}H_{22}BrN_3NiO_3$ 598.0205, found 598.0273.

Cyclization of Ni(II) Complex 43 to 44. To a solution of 1.44 g (15.0 mmol) of sodium *tert*-butoxide and 26 mL of DMF (18 mL/1 g of *tert*-butoxide) was added 2.57 g (4.30 mmol) of complex **43**. After the solution was stirred at room temperature for 5 min, the reaction mixture was poured into 600 mL of ice water. The resulting crystals were filtered and washed with water and hexane, affording 2.07 g (93.1% yield) of complex **44**.

Ni(II) complex of 2-amino-indan-2-carboxylic acid Schiff base with PABP 44:[63] *Rf* = 0.41. M.p. 308.3 °C. ^{1}H NMR δ 3.67 (4 H, AB, *J* = 17.9 Hz), 6.58 (1 H, m), 6.65-6.70 (3 H, m), 6.88-7.00 (7 H, m), 7.30 (1 H, m), 7.47 (1 H, m), 7.93 (1 H, m), 8.02 (1 H, m), 8.45 (1 H, d, *J* = 5.1 Hz), 8.71 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 50.71, 121.06, 123.32, 123.53, 125.85, 126.35, 126.61, 128.47, 128.64, 128.73, 132.47, 133.68, 134.55, 139.72, 140.19, 141.87, 146.90, 148.20, 152.91, 169.61, 174.26, 184.53. HRMS [M + H^+] calcd for $C_{29}H_{21}N_3NiO_3$ 518.0943, found 518.1301.

2.5.5: Disassembly of Picolinic Acid Derived Ni(II) Complexes of Amino Acid Schiff Bases, Recovery of the Organic Ligand 24a, and Isolation of the Corresponding α-Amino Acid.

Decomposition of Ni(II) Complex 44. Recovery of PABP 24a and Amino Acid 41. To a solution of 22 mL (14.5 mL/1 g of complex **44**) of MeOH and 11 mL (7.25 mL/1 g of complex **44**) of 3*N* HCl at 70 °C was added 1.508 g (2.912 mmol) of complex **44**. The solution was stirred for 30 min. Upon the complete loss of red color the solution was evaporated. The acid **41** and $NiCl_2$ were dissolved in 50 mL of deionized water and the HCl salt of ligand **24a**, 0.724 g (73.4%), was collected on a filter. The aqueous phase was evaporated and the residue was loaded on an ion-exchange column with the use of Dowex 50X2-100 resin. The column was first washed with deionized water until the pH was neutral followed by 8% aq. ammonium hydroxide (500 mL) to elute acid **41**. Evaporation of the solution afforded 0.506 g (2.85 mmol, 97.9% yield) of acid **41**. The $NiCl_2$ was eluted with concentrated HCl after the column was returned to neutral pH with deionized water.

2-Amino-indan-2-carboxylic acid 41:[63] M.p. 261.1 °C (decomp.). ^{1}H NMR (CD_3OD) δ 3.09 (2 H, d, *J* = 17.4 Hz), 3.49 (2 H, d, *J* = 17.4 Hz), 7.109-7.183 (4 H, m). HRMS [M + H^+] calcd for $C_{10}H_{11}NO_2$ 178.0797, found 178.0918.

Decomposition of Compounds 39a and 39d and Isolation of Free Amino Acids 3a,d. General Procedure: A solution of complex **39a**,**d** (22.5 mmol) in MeOH (90 mL) was slowly added to a mixture of aqueous 3*N* HCl and MeOH (180 mL, ratio

1/1) at 70 °C with stirring. The reaction mixture was evaporated in a vacuum to dryness after it was determined that the decomposition was complete by TLC ($CHCl_3$/acetone 5/1). Water (120 mL) was added, and the resultant mixture was treated with an excess of NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated in a vacuum to afford free PABP **24a** (5.92-6.33 g, 87-93%). The aqueous phase was evaporated under vacuum, redissolved in the minimum amount of water, and loaded on a Dowex 50X2 100 ion-exchange column, which was washed with water until neutral. The column was then washed with 8% aqueous NH_4OH. This fraction (350 mL) was collected and evaporated under vacuum to afford the corresponding amino acids **3a** (3.18 g, 91%) and **3d** (2.74 g, 93%).

α,α-Diallylglycine 3a:[62a] M.p. 217.8 °C (decomp.). ^{1}H NMR (CD_3OD) δ 2.46 (2 H, dd, *J* = 7.2, 14.3 Hz), 6.67 (2 H, dd, *J* = 7.2, 14.3 Hz), 5.20-5.28 (4 H, m), 5.75-5.89 (2 H, m). ^{13}C NMR (CD_3OD) δ 40.66, 63.51, 119.95, 131.27, 173.48. HRMS [M + H^+] calcd for $C_8H_{14}NO_2$ 156.1024, found 156.1021.

α,α-Diethylglycine 3d:[62a] M.p. 252.6 °C (decomp.). ^{1}H NMR (CD_3OD) δ 0.98 (6 H, t, *J* = 7.5 Hz), 1.76 (2 H, dq, *J* = 14.7, 7.5 Hz), 1.91 (2 H, dq, *J* = 14.7, 7.5 Hz). ^{13}C NMR (CD_3OD) δ 7.62, 29.42, 66.04, 174.64. HRMS [M + H^+] calcd for $C_6H_{14}NO_2$ 132.1024, found 132.0945.

Synthesis of Optically Active Phenylalanine via Asymmetric Phase Transfer Catalyzed Homologation of Ni(II) Complex of Glycine Schiff Base 17a. General Procedure: To a solution of Ni(II) complex **17a** (1 eq.) in solvent (1 g of 17a/15 mL solvent) was added the chiral phase transfer catalyst **45-49** (1-15 mol%), benzyl bromide **38b** (1.5 eq.), and base. The reaction was vigorously stirred under a N_2 atmosphere and

monitored by TLC. In order to quench the reaction excess brine was added and the organic portion was extracted with the same solvent that the reaction was conducted under. The aqueous phase was washed with the organic solvent at least three times before the organic fractions were combined and dried over $MgSO_4$. After the organic fraction was filtered to remove the $MgSO_4$ the organic solvent was evaporated to dryness under vacuum.

Disassembly of Complex 39b, Recovery of Ligand 24a, and Transformation of the Corresponding Phenylalanine Product 2b for the Determination of Optical Purity. Representative Example: Aqueous 12*N* HCl was slowly added (dropwise until all red color disappears) to a solution of complex **39b** in MeOH (1 mL/100 mg) with stirring. The reaction mixture was evaporated in a vacuum to dryness after it was determined that the decomposition was complete by TLC ($CHCl_3$/acetone 5/1). Water (1 mL/100 mg of starting complex) was added, and the resultant mixture was treated with an excess of NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated in a vacuum to afford free PABP **24a** (89-96%). The aqueous phase was evaporated under vacuum to provide the corresponding mixture of the free phenylalanine and $NiCl_2$, which was treated with thionyl chloride (7 eq.) in ethanol and allowed to react at 60 ^oC for four hours. Following the reaction, the excess thionyl chloride, alcohol, and water were removed under vacuum. Without purification methylene chloride (1 mL/200 mg of the starting Ni(II) complex **39b**) was added to the corresponding mixture of the $NiCl_2$ and ethyl ester of phenylalanine. Triethylamine (1.2 eq.) was added to the previously described emulsion and cooled to 4 ^oC with an ice water bath. After the temperature had been equilibrated the emulsion was treated with benzyl chloroformate

(1.2 eq.), and allowed to warm to room temperature by removal of the water bath. After allowing the reaction to proceed for one hour excess water was added to quench the reaction, followed by the extraction of the organic fraction with methylene chloride. This extraction was performed three times and all of the organic fractions were collected and dried with $MgSO_4$. Following the filtration of the drying reagent, the methylene chloride was evaporated under vacuum until dry. The corresponding *N*-CBz-phenylalanine ethyl ester was purified by a preparative TLC with ethyl acetate:hexane (1:4**)** as the eluant. The determination of optical purity of the phenyl alanine derivatives was accomplished by HPLC employing a Chiralcel OD column with a hexane:isopropanol (95:5) eluant.

Chapter 3

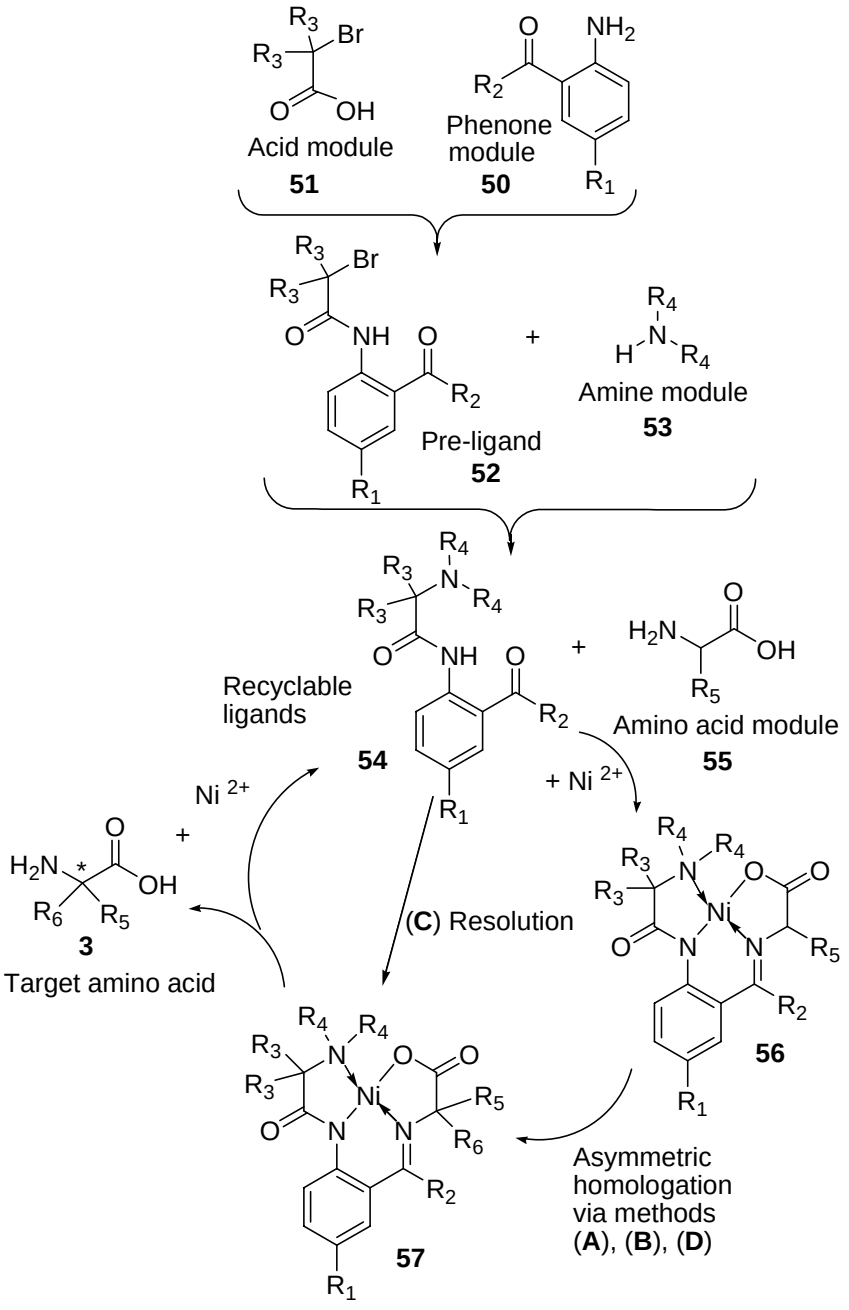
The Design, Synthesis and Application of a New Generation of Modular Nucleophilic Glycine Equivalents

3.1. Modular Approach to the Design of Nucleophilic Equivalents of Glycine and Various Other α-Amino Acids.

The concept of the modular design for nucleophilic equivalents of glycine and its homologues was devised as an alternative to the previously reviewed glycine derivatives **16** and **17a**, in which the physical properties and chemical reactivity could be altered. The general principle of the modular approach to the design of nucleophilic glycine equivalents is represented in Scheme 21. The design of amino acid derivatives **56** with the desired physical properties and chemical reactivity involves four basic modules: the phenone module **50**, the acid module **51**, amine module **53** and the amino acid module **55**.

The success of this design begins with the correct choice of the phenone module **50**, which allows for the control of C-H acidity for the glycine moiety as well as its steric availability. Thus, depending on the application and the reaction conditions required to induce the desired transformation, five types of phenone modules **50** have been investigated. The choice of the acid module **51** allows for the control of the rigidity of the chelate rings (influences stereocontrol in some reactions) in complex **56** as well as

Scheme 21. Synthesis of Modular Glycine Equivalents and a Summary of Thier Application



configurational stability of the chiral nitrogen which may be incorporated in **56**. Following the design of the pre-ligand **52**, the next step is deciding on the appropriate amine module **53**, which allows for the alteration of the physical and chemical properties of complexes **56**. In particular, the choice of amino module **53** allows for the control of the solubility of **56** which could range from hexane to water. With the properly designed ligand **54**, the subsequent choice is the proper amino acid module **55**. In most of cases, the module **55** is glycine, however, when quaternary α-alkyl amino acids are needed or methods **C** and **D** will be applied, then module **55** can be any higher amino acids depending on the synthetic needs.

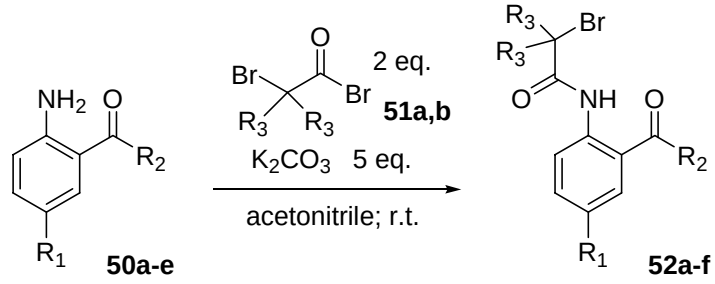
With the vast number of points of structural flexibility incorporated into this modular design, virtually complete control over the reactivity and physical properties of compounds **56** may be realized by the proper choice of the corresponding modules. As a result of this structural flexibility, the modular design gains unprecedented methodological flexibility allowing the unification of at least four currently orthogonal methods **A**-**C** using one generalized approach. Within the following sections the results for each of the homologation approaches **A** (asymmetric catalytic homologation via application of optically active phase transfer catalysts in particular), **B** (asymmetric stoicheometric homologation with the application of Michael acceptors with a removable chiral auxiliary), as well as method **C** (resolution of racemic α-amino acids via Schiff base formation and metal complexation with optically pure ligands followed by chromatographic separation of the diastereomeric products) will be discussed in detail while method **D** (homologation of diastereomerically pure Ni(II) complexes formed from optically pure α-amino acids and ligands containing a secondary, rather than tertiary

amine) will require further investigation. The efficiency of the complexes **56** should be emphasized as they are very inexpensive and can be stored at room temperature in an open atmosphere while retaining high chemical reactivity, and the homologation products **57** can be easily disassembled releasing the target amino acids **3** along with complete recovery and reuse of the ligands **54** and Ni(II).

3.2 Synthesis of Modular Ni(II) Glycine Equivalents and the Associated Ligands.

3.2.1 Synthesis of the Modular Ligands 54a-s.

Scheme 22. Condensation of Amines **50a-e** and Bromoacetyl Bromides **51a,b**



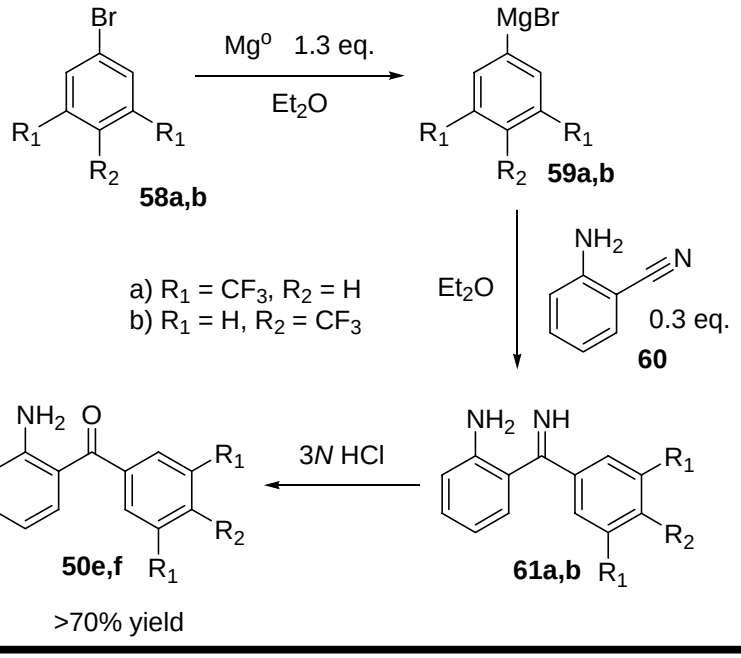
50
a) R_1 = H, R_2 = Ph
b) R_1 = H, R_2 = Me
c) R_1 = Cl, R_2 = Ph
d) R_1 = H, R_2 = 3,5-$(CF_3)_2$-C_6H_3
e) R_1 = H, R_2 = 4-(CF_3)-C_6H_4

51
a) R_3 = H
b) R_3 = Me

52
a) R_1 = H, R_2 = Ph, R_3 = H
b) R_1 = H, R_2 = Me, R_3 = H
c) R_1 = Cl, R_2 = Ph, R_3 = H
d) R_1 = H, R_2 = 3,5-$(CF_3)_2$-C_6H_3, R_3 = H
e) R_1 = H, R_2 = 4-(CF_3)-C_6H_4, R_3 = H
f) R_1 = H, R_2 = Ph, R_3 = Me

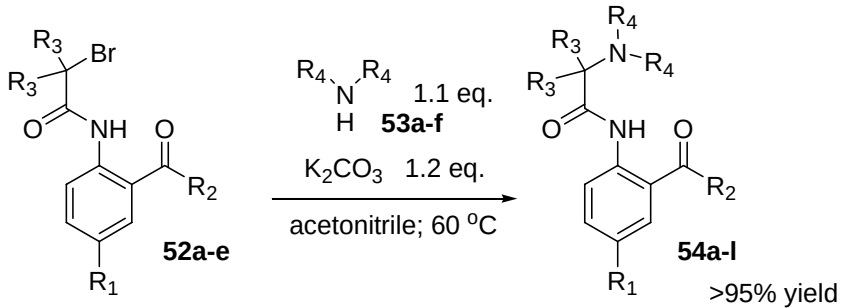
The synthesis of ligands required for construction of the modular Ni(II) complexes were realized via a two step process. The initial step involved coupling the appropriate phenone modules **50a-e** with the corresponding bromoacetyl bromides **51a** and **51b** (Scheme 22)**.** After surveying various reaction conditions, it was found that the complete consumption of the phenone modules **50a-e** could be realized by conducting the reaction in a slurry of acetonitrile and potassium carbonate at room temperature with slow addition of the corresponding bromoacetyl bromide **51a** or **51b**. This procedure was successfully repeated to synthesize the six bromo-acetamide derivatives **52a-f** in greater than 95% yield.[66]

Scheme 23. Synthesis of Trifluoromethylated *o*-Amino-benzophenones **50e**,**f** Via Aromatic Grignard Additions to *o*-Aminobenzonitrile **60**



Although both bromoacetyl bromide pre-ligands **51a** and **51b**, and phenone modules **50a-c** were commercially available,[67] the two amino-benzophenone derivatives **50d-e**, which have trifluoromethyl groups incorporated within their structure, were commercially unavailable. However they were available from a synthetic procedure utilizing commercially available reagents via nucleophilic addition to 2-aminobenzonitrile **60** with the corresponding aryl Grignard reagents **59a** and **59b**, followed by acidic hydrolysis of the intermediate imines **61a** and **61b** (Scheme 23).[68]

Scheme 24. Synthesis of Ligands *N*-(2-benzoyl-phenyl/acetyl)-2-dialkyl-acetamides **54a-l**



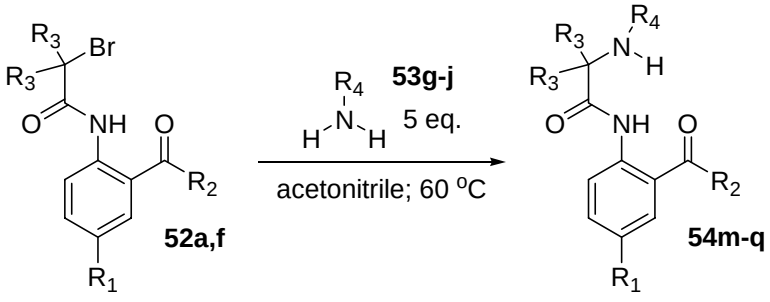
52
a) R_1 = H, R_2 = Ph, R_3 = H
c) R_1 = H, R_2 = Me, R_3 = H
d) R_1 = Cl, R_2 = Ph, R_3 = H
e) R_1 = H, R_2 = 3,5-$(CF_3)_2$-C_6H_3, R_3 = H
f) R_1 = H, R_2 = 4-(CF_3)-C_6H_4, R_3 = H

53	
a) R_4 = Me	b) R_4 = *n*-Bu
c) R_4 = Bn	d) R_4^2 = Piperidyl
e) R_4^2 = Morpholyl	f) R_4^2 = Indolyl

54
a) R_1 = H, R_2 = Ph, R_3 = H, R_4 = Me
b) R_1 = H, R_2 = Ph, R_3 = H, R_4 = *n*-Bu
c) R_1 = H, R_2 = Ph, R_3 = H, R_4 = Bn
d) R_1 = H, R_2 = Ph, R_3 = H, R_4^2 = Piperidyl
e) R_1 = H, R_2 = Ph, R_3 = H, R_4^2 = Morpholyl
f) R_1 = H, R_2 = Ph, R_3 = H, R_4^2 = Indolyl
g) R_1 = H, R_2 = Me, R_3 = H, R_4 = *n*-Bu
h) R_1 = H, R_2 = Me, R_3 = H, R_4^2 = Piperidyl
i) R_1 = Cl, R_2 = Ph, R_3 = H, R_4 = *n*-Bu
j) R_1 = Cl, R_2 = Ph, R_3 = H, R_4^2 = Piperidyl
k) R_1 = H, R_2 = 3,5-$(CF_3)_2$-C_6H_3, R_3 = H, R_4 = *n*-Bu
l) R_1 = H, R_2 = 4-CF_3-C_6H_4, R_3 = H, R_4 = *n*-Bu

The dialkylamine containing ligands **54a-l** may be obtained via a nucleophilic substitution of the bromine atom in the pre-ligand **52a-e** with various dialkyl amines **53a-f** in acetonitrile at 60 ^{o}C with potassium carbonate to trap the hydrobromic acid generated during the reaction (Scheme 24). This procedure has been utilized to synthesize a large number of ligands **54a-l** by varying both the dialkyl amine **53a-f**, as well as the bromo-acetamide pre-ligands **52a-e** employed. All of these reactions were successful in obtaining the ligand **54a-l** in high chemical yield, >95%.

Scheme 25. Synthesis of *N*-(2-benzoylphenyl)-2-alkylamino-acetamides **54m-q**



60-95% Yield

52
a) R_1 = H, R_2 = Ph, R_3 = H f) R_1 = H, R_2 = Ph, R_3 = Me

53	
g) R_4 = Bn	h) R_4 = *i*-Prop
i) R_4 = *t*-Bu	j) R_4 = (*R*)-1-Ph-ethyl

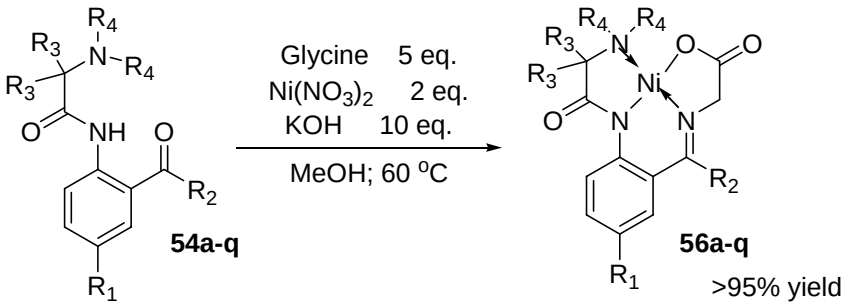
54
m) R_1 = H, R_2 = Ph, R_3 = H, R_4 = Bn n) R_1 = H, R_2 = Ph, R_3 = H, R_4 = *i*-Prop o) R_1 = H, R_2 = Ph, R_3 = H, R_4 = *t*-Bu p) R_1 = H, R_2 = Ph, R_3 = Me, R_4 = (*R*)-1-Ph-ethyl

Although the previously described reaction conditions, described for the synthesis of the dialkyl amine containing ligands **54a-l** could be employed for the synthesis of the monoalkyl amine ligands **54m-p**, it was found that the most convenient and reliable approach was the nucleophilic substitution of the bromide atom of the bromo-acetamide derived pre-ligands **52a** and **52f** with alkyl amines **53g-j** while the excess amine could be employed as a base to trap the hydrobromic acid (Scheme 25). These reactions were conducted in acetonitrile at 60 ^{o}C and obtained the corresponding products in high yield for the S_N2 substitution of the bromo-acetamide preligand **52a**,[69] and moderate yield, for the S_N1 substitution of the dimethylated bromo-acetamide preligand **52f**. The decrease in yield for the synthesis of the dimethyl containing ligands **54p** could be contributed to the change in reaction mechanism as well as the enhanced steric bulk of the product.

3.2.2 Preparation of Modular Ni(II) Glycine Equivalents 56a-q

The corresponding Ni (II) complexes **56a-p** were prepared in a single reaction, which is similar to the previously described synthesis of the picolinic acid derived Ni(II) complexes **17a-c** described in Chapter 2 (section 2.2.3), from ligands **54a-p** in methanol at 60 ^{o}C (Scheme 26). The potassium hydroxide is utilized to deprotonate the amide nitrogen of the ligand and the carboxyl moiety of glycine, which is followed by complexation via ligand substitution of the Ni (II) ion, as well as catalyzing the Schiff base from the amine moiety of glycine and the ketone of the appropriate ligand. All of the complexes described in Scheme 26 were synthesized in greater than 95% yield except for complex **56p** (86%) due to a slight solubility in water which is utilized during the workup.

Scheme 26. Assembly of Modular Glycine Equivalents **56a-q**



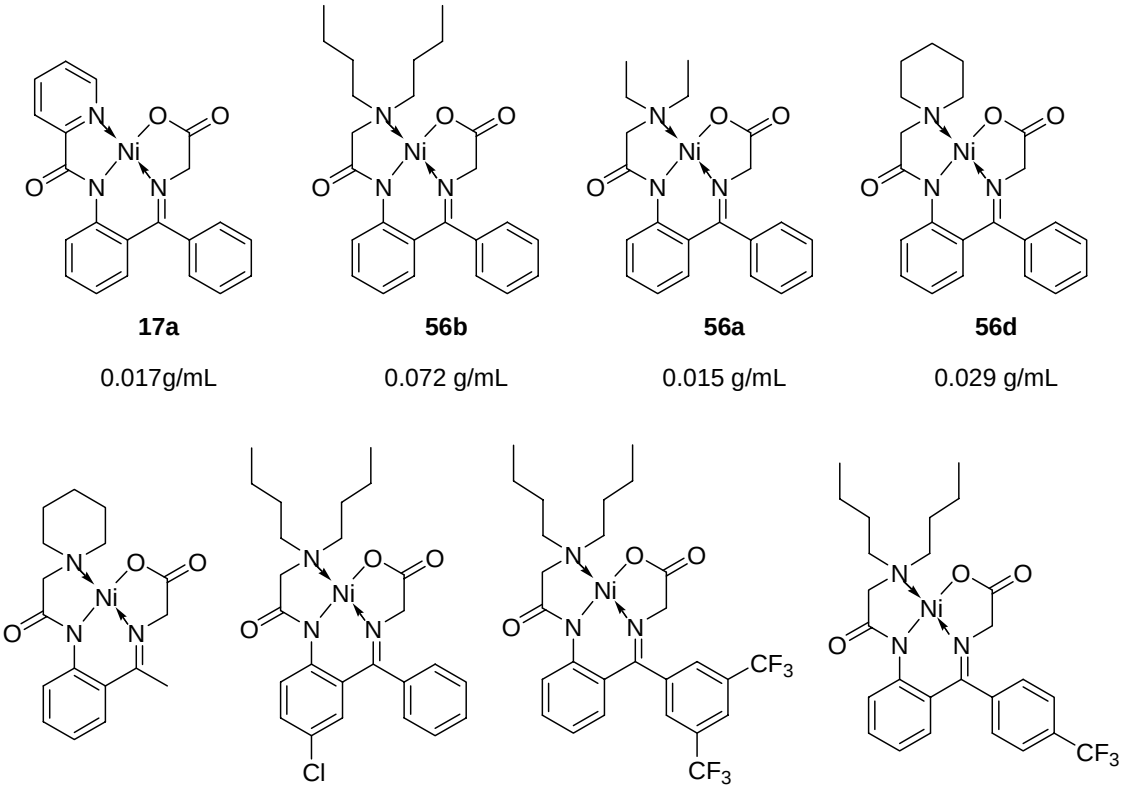
a) R_1 = H, R_2 = Ph, R_3 = H, R_4 = Me
b) R_1 = H, R_2 = Ph, R_3 = H, R_4 = *n*-Bu
c) R_1 = H, R_2 = Ph, R_3 = H, R_4 = *n*-Bu
d) R_1 = H, R_2 = Ph, R_3 = H, R_4^2 = Piperidyl
e) R_1 = H, R_2 = Ph, R_3 = H, R_4^2 = Morpholyl
f) R_1 = H, R_2 = Ph, R_3 = H, R_4^2 = Indolyl
g) R_1 = H, R_2 = Me, R_3 = H, R_4 = *n*-Bu
h) R_1 = H, R_2 = Me, R_3 = H, R_4^2 = Piperidyl
i) R_1 = Cl, R_2 = Ph, R_3 = H, R_4 = *n*-Bu
j) R_1 = Cl, R_2 = Ph, R_3 = H, R_4^2 = Piperidyl
k) R_1 = H, R_2 = 3,5-$(CF_3)_2$-C_6H_4, R_3 = H, R_4 = *n*-Bu
l) R_1 = H, R_2 = 4-CF_3-C_6H_4, R_3 = H, R_4 = *n*-Bu
m) R_1 = H, R_2 = Ph, R_3 = H, R_4 = Bn
n) R_1 = H, R_2 = Ph, R_3 = H, R_4 = *i*-Pr
o) R_1 = H, R_2 = Ph, R_3 = H, R_4 = *t*-Bu
p) R_1 = H, R_2 = Ph, R_3 = Me, R_4 = (*R*)-1-Ph-Et

3.3 Examination of the Chemical Stability and Relative Reactivity of Various Modular Glycine Equivalents 56a-n

Now that an established synthesis for the production of modular glycine equivalents has been identified, their solubility, chemical stability, and chemical reactivity need to be evaluated. The variety of Ni(II) complexes of glycine available allows for the selection of the Ni(II) complex that possesses the most favorable chemical and physical properties for the corresponding homologation method which will be

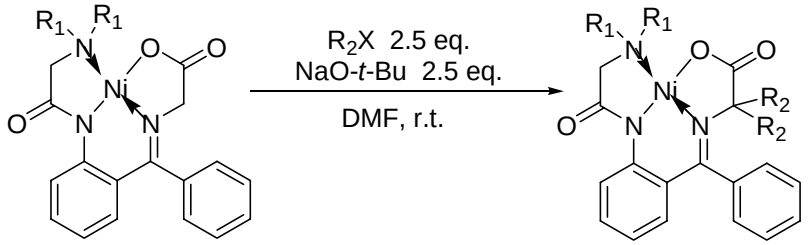
applied. However, in order to determine which Ni(II) complex is the most appropriate for the corresponding homologation approach, some basic information about the complexes is necessary. Therefore, it was decided to explore the solubility of a variety of the Ni(II) complexes available. As one can see from Figure 6 many of the modularly designed glycine equivalents are significantly more soluble in toluene compared to the picolinic acid derivative **17a**. The complex with the highest solubility (0.127 g/mL) in toluene, of the variations shown is the complex containing two trifluoromethyl groups **56k** as well as dibutyl amine for the amine moiety, however its mono-trifluoromethylated and non-trifluoromethylated derivatives **56l** and **56b** have demonstrated adequate solubility to justify their application in reactions with toluene as the organic medium.

Figure 6. Solubility of Ni(II) Complexes of Glycine in Toluene



With the enhanced solubility of a variety of modular glycine equivalents identified, attention was shifted to address their chemical stability. Therefore, it was determined that a variety of modular glycine equivalents **56a-f** should be subjected to extreme conditions in order to confirm the stability of the complex as well as to ensure that the methylene moiety, introduced into the ligands **54a-f** via the addition of bromoacetyl bromide **51a**, is not reactive under basic conditions and therefore would not interfere with the overall atom economy of the process or the recyclable nature of the ligand **54a-f**.

Scheme 27. Homogeneous Dialkylation of Modular Glycine Equivalents **56b-d** with Alkyl Halides **38a-c,g,k**



56b-d **62a-f, 63, 64**

Table 10. Homogeneous Dialkylation of Modular Glycine Equivalents **56b-d** With Alkyl Halides **38a-c,g,k**

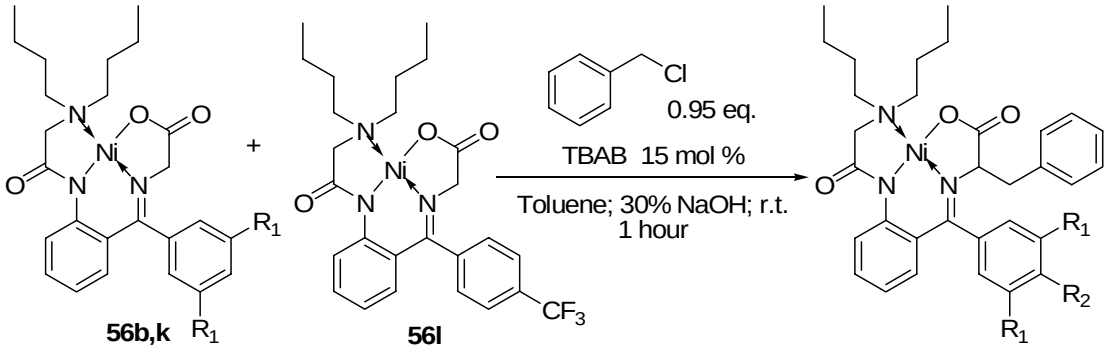
entry	R_1	R_2	X	time	product	conversion[a]	yield[b]
1	Bu (**56b**)	Bn	Br	15 min	**62a**	>99/1	93
2	Bn (**56c**)	Bn	Br	15 min	**63**	>99/1	90
3	Piperidyl (**56d**)	Bn	Br	15 min	**64**	>99/1	91
4	Bu (**56b**)	Allyl	Br	15 min	**62b**	>99/1	92
5	Bu (**56b**)	Cinnamyl	Br	15 min	**62c**	>99/1	88
6	Bu (**56b**)	Me	I	25 min	**62d**	>99/1	87
7	Bu (**56b**)[c]	Propargyl	Br	24 h	**62e/62f**	33/67	30

[a]Determined by NMR analysis of the crude reaction mixtures. [b]Isolated yield of the crude product. [c]Phase transfer conditions were used with TBAB as the catalyst, dichloromethane as the organic solvent, and 30% aq. NaOH as the base.

Therefore, to evaluate the possibility of the fore-mentioned as well as any unforeseen complications, homologation reactions of the complexes **56b-d** were attempted in the presence of sodium *tert*-butoxide and benzyl bromide (Scheme 27).[66a,71] The initial experiment conducted, with the dibutylated complex **56b** as the glycine equivalent, was found to be successful with the application of 3.5 equivalents of the base and the electrophile. The corresponding α,α–dibenzylated glycine-containing complex was found in greater than 90% yield with no other observable products. It was later discovered that the excess of the base and benzyl bromide could be decreased to 2.5 equivalents each with similar outcomes, contrary to the results obtained with the application of their picolinic acid containing predecessors (Table 10; entry 1).[62] These reactions were then repeated using various alkyl groups on the amino function of the Ni(II) complexes **56** to ensure some generality. It was found that the complexes incorporating either a piperidine **56d** or dibenzylamine **56c** moiety yielded similar results as both reactions resulted in greater than 90% yield and greater than 99% conversion to the desired products **63** or **64** (entries 2 and 3). These experiments were complimented by two more reactions that were conducted to demonstrate that these results were reproducible with various other alkyl halides. Therefore, it was found that the dibutylated Ni(II) complex **56b** would also react with allyl or cinnamyl bromide in the presence of the sodium *tert*-butoxide with success similar to the earlier example generating the corresponding products **62b** or **62c** in high chemical yield (92 and 88% respectively) (entries 4 and 5). It was also found that the introduction of two unactivated alkyl groups could be accomplished; however, the application of the more reactive alkyl iodide was

necessary for the reaction to reach completion, such as the synthesis of **62d** via homologation with methyl iodide (entry 6). Although the direct alkylation of the complex **56b** with propargyl bromide was unsuccessful due to the production of various byproducts, seemingly from the reactivity of the alkyl halide, slightly milder phase-transfer conditions were more appropriate for this process. However, longer reaction times or more concentrated aqueous bases are necessary to complete the reaction which only proceeded to 33% conversion to the bis-alkylated product **62e** in 24 h while 67% of the monoalkylated product **62f** remained (entry 7).

Scheme 28. Competitive Phase Transfer Benzylation of Modular Glycine Equivalents **56b,k,l**



65	R_1 =H, R_2 = H
66	R_1 = H, R_2 = CF_3
67	R_1 = CF_3, R_2 = H

Table 11. Competitive Phase Transfer Benzylation of Modular Glycine Equivalents **56b,k,l**

Entry	Glycine Equivalents	Starting Ratio[a]	Products	Product Ratio[b]
1	**56b/56l**	1/1.09	**65/66**	<1/100
2	**56k/56l**	1/0.93	**66/67**	1/2.49

[a]Determined by ^{1}H NMR (300 MHz) analysis of the starting reaction mixture.
[b]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture after 1 hour.

Another area of interest was the relative reactivity of these modular glycine equivalents, especially the complexes which include the electron withdrawing trifluoromethyl groups. The impact on the solubility of the glycine equivalents by the introduction of one or two trifluoromethyl groups was immediately apparent, however, the influence of the electronegative trifluoromethyl groups on the reactivity of the Ni(II) complexes required examination. This was accomplished by the direct comparisons of the glycine equivalents via their homologation utilizing benzyl chloride as the limiting reagent, the symmetrical phase transfer catalyst tetrabutyl ammonium bromide, and 30% aqueous sodium hydroxide as the base in toluene (Scheme 28). The initial comparison explored was between the dibutyl/benzophenone glycine equivalent **56b**, and the *para*-trifluoromethylated dibutyl/benzophenone Ni(II) complex **56l** which resulted in the nearly complete conversion of the trifluoromethylated Ni(II) complex **56l** to the corresponding product **66** while none of the non-trifluoromethylated phenyl alanine derivative **65** could be detected, thus demonstrating a drastic increase in reactivity (Table 11, entry 1). However, direct comparison between the mono- and di-trifluoromethylated glycine equivalents **56l** and **56k** demonstrated more similar reactivities as both products were obtained, although approximately 2.5 times more of the bis trifluormethylated product **67** was produced (entry 2).

3.4 The Application of Modular Glycine Equivalents for the Asymmetric Synthesis of α-Amino Acids Via Their Phase Transfer Catalyzed Homologation

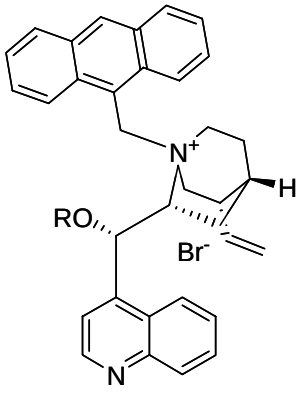
Application of the new modular glycine equivalents **56** for the asymmetric synthesis of α-amino acids via chiral phase transfer catalysis provides an added variable to the already intricate process, given the ability to alter the physical properties as well as the reactivity of the glycine equivalents. However it was the potential adaptability of the modular glycine equivalents **56** that prompted an interest in their alkylation under chiral phase transfer catalyzed conditions. Therefore the following studies of the asymmetric homologation of the modular glycine equivalents will consist of a variety of sections which will represent alteration of each of the variables in the reaction with the goal of optimizing the overall reaction conditions. The variables that will be investigated include the catalyst, the glycine equivalent, solvent, and the base utilized.

3.4.1 Identification of the Most Appropriate Optically Active Phase Transfer Catalyst

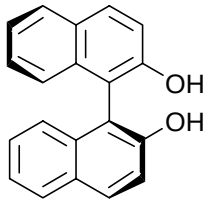
For these studies six optically active catalysts were utilized for the homologation process (Figure 7), four of which (**45**-**48**) were utilized during the phase transfer alkylation of the picolinic acid derived complex **17a** (Chapter 2, Section 2.3.2.2.1, pages

33-36). However, for the study of these modular glycine equivalents **56** one commercially available catalyst **68**,[71] and one catalyst **69** which was synthesized within the laboratory were also investigated.

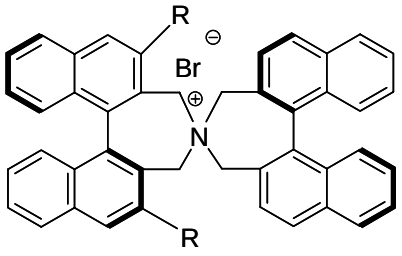
Figure 7. Optically Active Phase Transfer Catalysts **45-49,68,69**



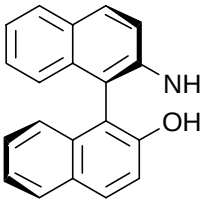
R = allyl **45**
R = H **46**
cinchonidinium derived catalysts



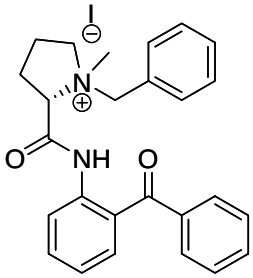
(*S*)-(-)-1, 1'-Bi-2-naphthol
Catalyst **47**



R = 3,4,5-trifluoro-C_6H_2 **48**
R = β-naphthyl **49**
(*S*,*S*)-NAS bromide Catalysts



(*R*)-2-Amino-2'-hydroxy-1,1'-binaphthyl **68**



(*S*)-2-[*N*-(*N*-benzylprolyl)-amino]-benzophenone derivative **69**

The dibutylamino/benzophenone derived complex **56b** was selected as the glycine equivalent for the initial catalyst screening studies because of its solubility in various organic solvents (Scheme 29). Due to the dramatic increase in solubility of the new glycine equivalent **56b** in less polar solvents compared to the picolinic acid complex **17a**, toluene was selected as the solvent for the initial reactions while potassium hydroxide, as

a fine crushed powder or as an aqueous solution, was chosen as the base. The initial reactions with the *O*-allyl cinchonidine derived catalyst **45** produced the corresponding benzylated product in moderate yield (65.9-71.3%) with both, aqueous and solid, forms of the base in 12 hours. However the asymmetric induction for the homologation process was quite low as the reaction with the aqueous base yielded racemic product **65** while the reaction with the solid potassium hydroxide yielded the product **65** in 7.8% ee (Table 12, entries 1 and 2). Application of the nonallylated cinchonidine derived catalyst **46** again provided the product **65** in high chemical yield (86.4-88.2%), however it was obtained in virtually racemic form in either case, 0.1 and 3.1% ee respectively (entries 3 and 4). The reactions with both the optically active binaphthol catalyst **47** and the *N*-benzyl proline derived catalyst **69** required 36 hours to produce only nominal yields of the appropriate product (22.3, 14.1, 17.2, and 10.9% respectively) with either form of potassium hydroxide employed, while the asymmetric induction of the process was poor providing the product in a maximum of 11.7% ee (entries 5-8). Although the catalysts that have been investigated to this point have been rather unsuccessful in controlling the stereochemical outcome of the reaction, a significant improvement was noticed with the application of the fluorinated *N*-spiro catalyst **48**, as the benzylated product **65** could be obtained in 45.1-62.4% ee in 12 hours with the application of the aqueous or solid potassium hydroxide respectively, although in modest yields (entries 9 and 10). Utilizing (*R*)-2-amino-2'-hydroxy-1,1'-binaphthyl (*R*-NOBIN) **68** as the catalyst for this reaction resulted in the synthesis of the appropriate product **65** in moderate to high chemical yields (87.6 and 79.7%) however with slightly diminished optical purities compared to the results of the reactions with the *N*-spiro catalyst (entries 11 and12). The absolute

configuration of the phenylalanine derived product **65** was the same as described for the picolinic acid derivative described in Chapter 2, as well as those for the phenylmethylene glycinate **14**.

Scheme 29. Asymmetric Phase Transfer Benzylation of Modular Glycine Equivalent **56b** With Optically Active Catalysts **45-49,68,69**

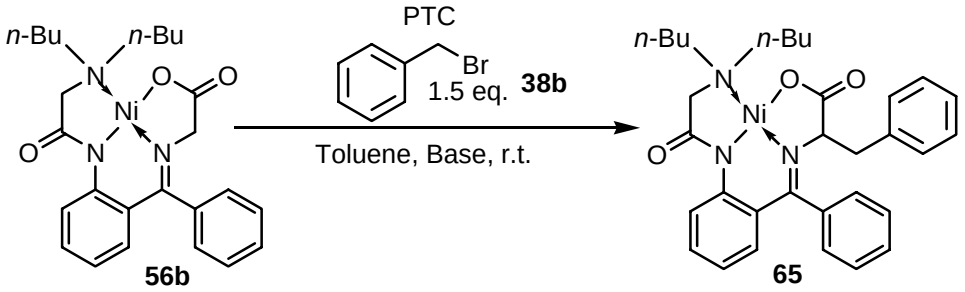


Table 12. Asymmetric Phase Transfer Benzylation of Modular Glycine Equivalent **56b** With Optically Active Catalysts **45-49,68,69**

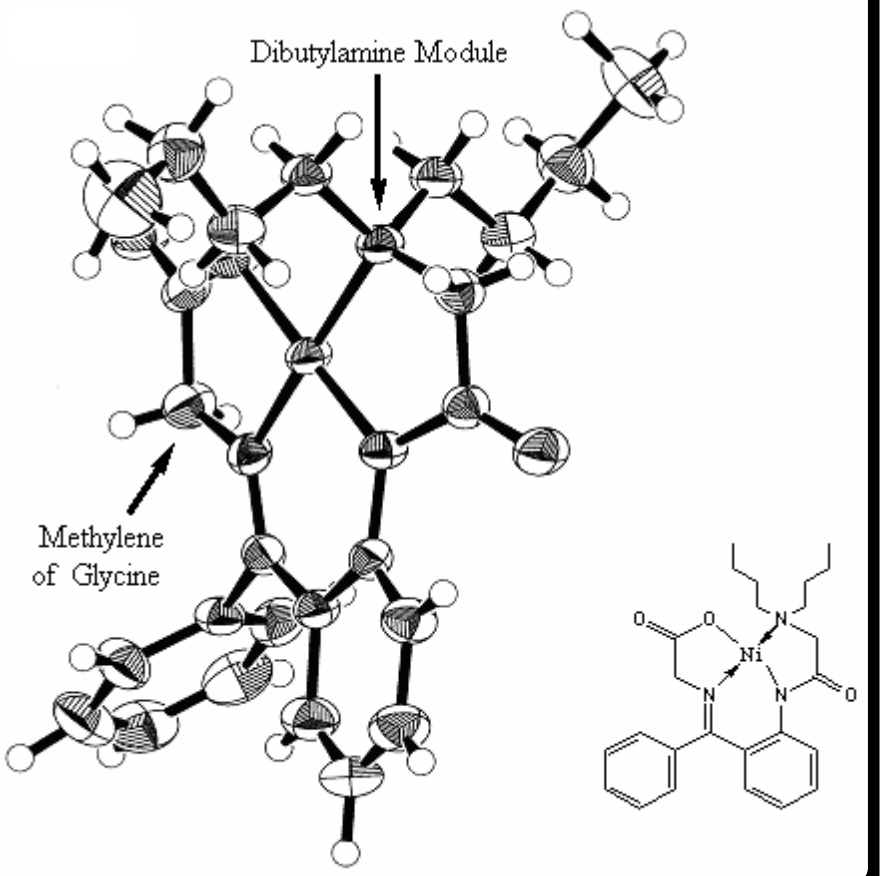
Entry	Time h	Catalyst	Mol % Catalyst	Base	Ratio[a] **65**/**56b**	Yield[b] %	ee[c] %
1	12	**45**	15	50% KOH Aq.	78/22	71.3	0.0
2	12	**45**	15	KOH (5 eq.)	67/33	65.9	7.8
3	12	**46**	15	50% KOH Aq.	94/6	88.2	0.1
4	12	**46**	15	KOH (5 eq.)	88/12	86.4	3.1
5	36	**47**	15	50% KOH Aq.	30/70	22.3	0.5
6	36	**47**	15	KOH (5 eq.)	15/85	14.1	2.8
7	36	**69**	15	50% KOH Aq.	18/82	17.2	0.2
8	36	**69**	15	KOH (5 eq.)	15/85	10.9	11.7
9	12	**48**	2	50% KOH Aq.	64/36	60.7	45.1
10	12	**48**	2	KOH (5 eq.)	59/41	54.5	62.4
11	12	**68**	10	50% KOH Aq.	90/10	87.6	28.6
12	12	**68**	10	KOH (5 eq.)	84/16	79.7	36.8

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 9:1 Hexane:isopropanol as the eluant) of the corresponding Ni(II) complex.

3.4.2 Screening Various Versions of the Modular Glycine Equivalent 56 to Identify the Most Suitable Candidate for Further Investigation

Following the identification of the most promising catalyst candidate **48**, the focus of the investigation into this asymmetric phase transfer catalyzed homologation process

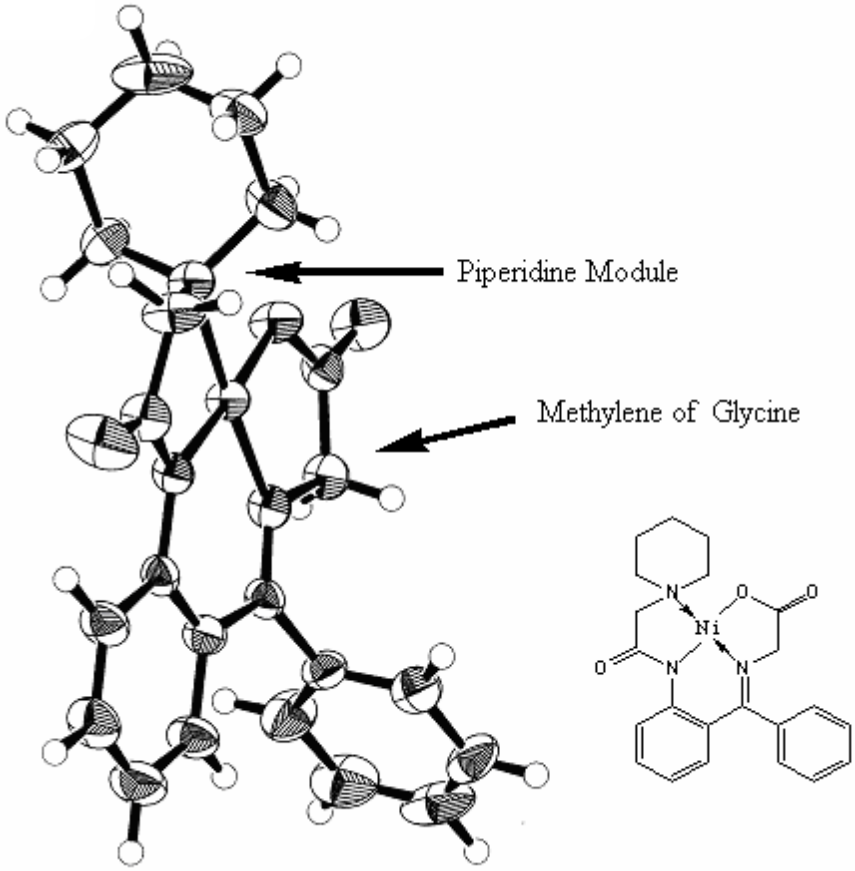
Figure 8. X-Ray Crystal Structure of Modular Glycine Equivalent **56b**



shifted to the variation of the glycine equivalent itself. Although there are numerous possible variations of the modular glycine equivalent, the major interest was directed toward decreasing the possible steric interactions of the glycine equivalent while maintaining reasonable solubility in various fairly lipophilic solvents. The rational for these alterations stem from the possibility of steric interference contributed by the *n*-butyl

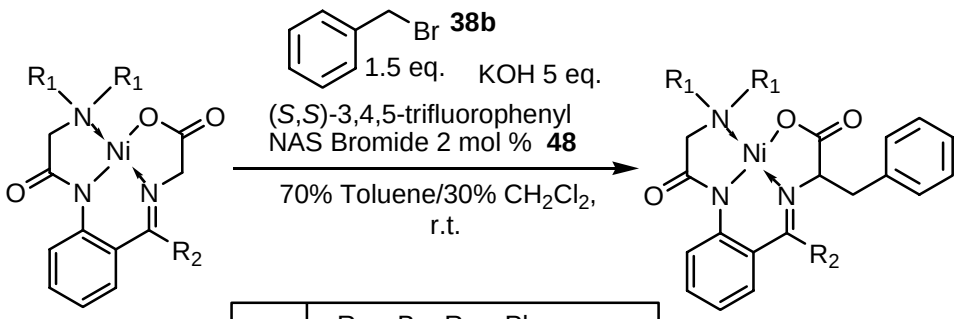
groups from the amine module of the glycine equivalent **56b** which could influence the alignment of the ion pair between the enolate and the ammonium ion of the optically active phase transfer catalyst. The X-ray crystal structure of the dibutyl amine/benzophenone complex confirms that the dibutyl groups could provide interference due to the amount of space that they occupy (Figure 8). Therefore two alternative glycine equivalents were studied in which the dibutyl amine module was replaced with piperidine or a diethylamine moiety, as the X-ray crystal structure of the piperidine derived glycine equivalent **56d** indicates, the steric interference posed by the alkyl groups of the amino function would be significantly decreased (Figure 9).

Figure 9. X-Ray Crystal Structure of Modular Glycine Equivalent **56d**



Therefore a series of reactions were conducted utilizing the most successful catalyst **48** from the previous experiments in a 7:3 solution of toluene/dichloromethane (due to the decreased solubility of glycine equivalents **56a,d,g**) with solid potassium hydroxide as the stoicheometric base and benzyl bromide as the electrophile (Scheme 30). The initial reaction studied was similar to the most promising reaction conditions described earlier with the dibutylamine/benzophenone glycine equivalent **56b**. However given the alteration in solvent from the previous attempt, the enantiomeric excess decreased to 56.3% while the product was obtained in fairly low chemical yield (28.2%) although the reaction time was only 4.5 hours (Table 13, entry 1). The subsequent reaction was conducted with the dibutyl amine/acetophenone derived glycine derivative **56g**, thereby decreasing the possibility of interference of the benzo/acetophenone moiety. Although the reaction was slightly more complete than the previous experiment (38% conversion, 31.1% yield), the enantioselectivity of the process diminished, providing the corresponding product **71** in 14.3% ee (entry 2). Given the decrease in enantioselectivity with the exchange of the benzophenone module for the acetophenone module, the following experiments were conducted with variations of the amine module while utilizing the benzophenone module exclusively. Therefore the following experiment employed the piperidine derived complex **56d** which led to high conversion and chemical yield (67% and 65.4% respectively) under decreased reaction times (3.0 hours), however the enantioselectivity (48.2% ee) of the process was not increased compared to the dibutyl amine derived complex **56b** (entry 3). Application of the diethylamine derived glycine equivalent **56a** yielded similar results as the product **72** could be obtained in 56.8% yield following the three hour reaction while its optical purity (44.8% ee) was

Scheme 30. Asymmetric Phase Transfer Benzylation of Modular Glycine Equivalents **56a,b,d,g** With Optically Active Catalyst **48**



56a,b,d,g

65	R_1 = Bu, R_2 = Ph
71	R_1 = Bu, R_2 = Me
70	R_1 = Piperidine, R_2 = Ph
72	R_1 = Et, R_2 = Ph

65, 70, 71, 72

Table 13. Asymmetric Phase Transfer Benzylation of Modular Glycine Equivalents **56a,b,d,g** With Optically Active Catalyst **48**

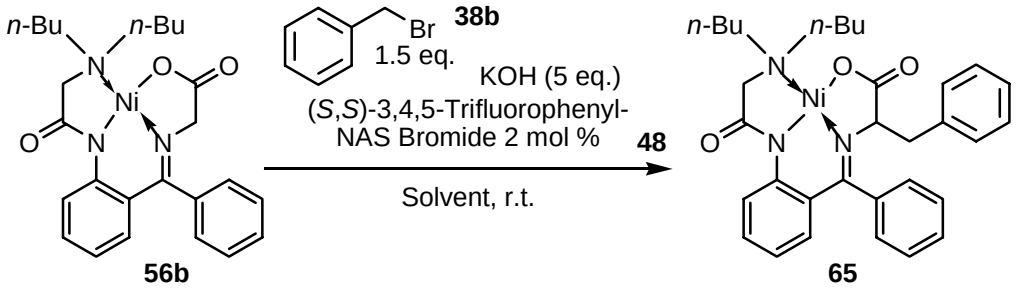
Entry	Starting Complex	Time h	Product	Ratio[a] Prod./Start	Yield[b] %	ee %
1	**56b**	4.5	**65**	33/67	28.2	56.3[c]
2	**56g**	4.5	**71**	38/62	31.1	14.3[d]
3	**56d**	3.0	**70**	67/33	65.4	48.2[d]
4	**56a**	3.0	**72**	59/41	56.8	44.8[d]

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 90:10 hexane:isopropanol as the eluant). [d]Determined by HPLC analysis (Chiralcel ODcolumn with 95:5 hexane:isopropanol as the eluant) of the corresponding *N*-CBz-phenylalanine ethyl ester.

rather moderate (entry 4). Although decreasing the steric hindrance provided by the alkyl groups on the amine module resulted in increased reactivity compared to the dibutylamine derived complex **56b**, they were unable to improve the enantioselectivity of the homologation process. However several variables remain to be investigated such as the solvent and base employed for the reaction.

3.4.3 Investigations into the Effects Rendered by the Alteration of the Organic Reaction Medium

Scheme 31. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56b** With Optically Active Catalyst **48** in Various Organic Solvents



56b **65**

Table 14. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56b** With Optically Active Catalyst **48** in Various Organic Solvents

Entry	Time	Solvent	Ratio[a]	Yield[b]	ee[c]
	h		**65**/**56b**	%	%
1	4	CH_2Cl_2	98/2	97.4	6.3
2	4	CH_2Cl-CH_2Cl	98/2	93.8	10.3
3	12	Benzene	46/54	43.5	3.2
4	12	Toluene	59/41	54.7	62.4
5	12	70% Tol:30% CH_2Cl_2	91/9	87.9	52.6
6	12	Xylenes	50/50	48.4	48.3
7	12	70% Xylenes:30% CH_2Cl_2	87/13	86.6	51.6

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 90:10 Hexane:isopropanol as the eluant) of the complex.

Following the identification of the most promising catalyst candidate **48** as well as the most compatible modular glycine equivalent **56b**, an investigation into the relationship between the organic reaction medium employed and the enantioselectivity of the homologation process was conducted. Utilizing the dibutylamine derived glycine equivalent **56b**, trifluoronated *N*-spiro catalyst **48** and solid potassium hydroxide, a series

of reactions were conducted in various solvent systems (Scheme 31). The initial experiment conducted employed dichloromethane as the solvent and provided the product **65** in excellent chemical yield (97.4%) in four hours, however the optical purity of this product **65** was rather low (6.3% ee) (Table 14, entry 1). The solvent selected in the subsequent reaction was dichloroethane which provided a slight decrease in the polarity of the organic reaction medium and resulted in a slight increase in the enantioselectivity of the benzylation procedure (10.3% ee) while providing the product in high chemical yield (93.8%) (entry 2). The trend of decreasing polarity of the reaction medium and increasing the enantioselectivity of the homologation process, which became apparent during the optically active phase transfer catalyzed homologation of the picolinic acid derived Ni(II) complex **17a**, has also been true to the modular glycine equivalent **56b** thus far. However, the application of benzene as the solvent for the reaction provided a decrease in the optical purity of the target product **65** (3.2 % ee) while decreasing the reaction rate, as 43.5% yield of the product can be obtained following the twelve hour reaction (entry 3). Given the results from this experiment it was somewhat unexpected that the outcome obtained by utilizing toluene as the solvent would be as successful as it was, yielding the product in 54.7% chemical yield and with an enantiomeric excess of 62.4% (entry 4). Another solvent system that was explored was the 7:3 mixture of toluene and dichloromethane. The application of this solvent system was intended to optimize the reaction rate while retaining the enantioselectivity of the benzylation, which resulted in nearly complete conversion (91%) of the starting glycine equivalent to the target product **65**, which had an enantiomeric excess of 52.6% after twelve hours (entry 5). Altering the conditions of the reaction, by using xylenes as the solvent, decreased the

reaction rate (50% conversion in 12 hours) as well as the optical purity of the product **65** (48.3% ee). However, somewhat unexpectedly the application of the 7:3 mixed solution of xylenes and dichloromethane increased the rate of the reaction as well as the enantioselectivity of the process yielding the product in 86.6% chemical yield and 51.6% ee (entries 6 and 7).

Although a variety of solvents were explored for the benzylation of the modular glycine equivalent **56b**, toluene seems to remain as the most efficient with respect to enantioselectivity. Therefore to this point the most successful homologation of the dibutylamine derived glycine equivalent **56b** has been found to involve the trifluoronated *N*-spiro catalyst **48** with solid potassium hydroxide as the base and toluene as the solvent, however one more variable remains to be investigated, the base.

3.4.4 Alteration of the Stoicheometric Base and its Consequences on the Asymmetric Phase Transfer Catalyzed Homologation of the Modular Glycine Equivalent 56b

An essential element of these asymmetric phase transfer catalyzed alkylation reactions is the stoicheometric base, the source of the hydroxide anion, which is responsible for the formation of the enolate, via deprotonation of the glycine equivalent, which forms the ion pair with the ammonium catalyst. There are various modifications that can be made to the base such as the counter ion, which could influence the exchange between the halogen anion and hydroxide across the interface of the two phases, as well as its concentration. Therefore a number of experiments were conducted in order to

Scheme 32. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56b** With Optically Active Catalyst **48** and Various Hydroxide Bases

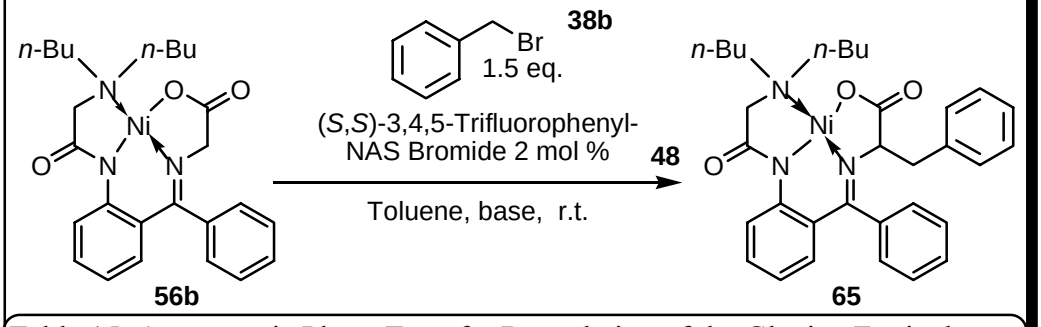


Table 15. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56b** With Optically Active Catalyst **48** and Various Hydroxide Bases

Entry	Time	Base	Ratio[a]	Yield[b]	ee[c]
	h		**65**/**56b**	%	%
1	12	50% KOH (aq.)	64/36	60.3	45.1
2	12	30% NaOH (aq.)	66/34	64.4	41.3
3	12	50% CsOH (aq.)	73/27	72.2	60.1
4	12	NaOH (5 eq.)	51/49	48.7	57.3
5	12	KOH (5 eq.)	59/41	54.9	62.4

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 90:10 hexane:isopropanol as the eluant) of the complex.

evaluate the relationship between the base and the enantioselectivity of the benzylation. Again the dibutylamine derived glycine equivalent **56b**, trifluoronated *N*-spiro catalyst **48**, and benzyl bromide **38b** were utilized to examine this dependence with toluene as the solvent (Scheme 32). The first reaction to be discussed employed an aqueous solution of potassium hydroxide (50%) as the base and provided the benzylated target **65** in moderate chemical yield (60.3%), and rather low optical purity (45.1% ee) (Table 15, entry 1). The application of an 30% aqueous solution of sodium hydroxide provided similar results as the asymmetric induction provided by the catalyst allowed for 41.3% ee and 64.4% chemical yield of the phenyl alanine derivative **65**. However the use of

cesium as the cation of the aqueous hydroxide base improved the enantioselectivity of the benzylation procedure providing the corresponding product **65** in 60.1% ee and 72.2% chemical yield (entries 2 and 3). Although the application of aqueous cesium hydroxide increased the enantioselectivity for the liquid:liquid reaction medium, the best results emerged from the exclusion of the majority of water from the reaction allowing for a solid:liquid biphasic system. The use of solid bases such as sodium or potassium hydroxide allowed for the synthesis of the product in moderate chemical yields (48.7 and 54.9% respectively) while the maximum enantiomeric excess of this process remains 62.4% at room temperature (entries 4 and 5). Although numerous variables associated with this asymmetric phase transfer catalyzed reaction have been investigated, it seems as if room for improvement remains. One such possibility would be to decrease the reaction temperature, which could aid in differentiating between or increasing the organization of the transition states by decreasing the free energy of the system, therefore increasing the stereoselectivity of the homologation process.

3.4.5 Decreasing the Reaction Temperature of the Phase Transfer Catalyzed Homologation of Glycine Equivalent 56b and its Correlation with the Optical Purity of the Benzylated Product 65

Reproducing the most successful reaction conditions found thus far, for the chiral phase transfer catalyzed benzylation of the modular glycine equivalent **56b**, while decreasing the temperature did little to improve the enantioselectivity of the reaction

Scheme 33. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56b** With Optically Active Catalyst **48** Under Reduced Temperature

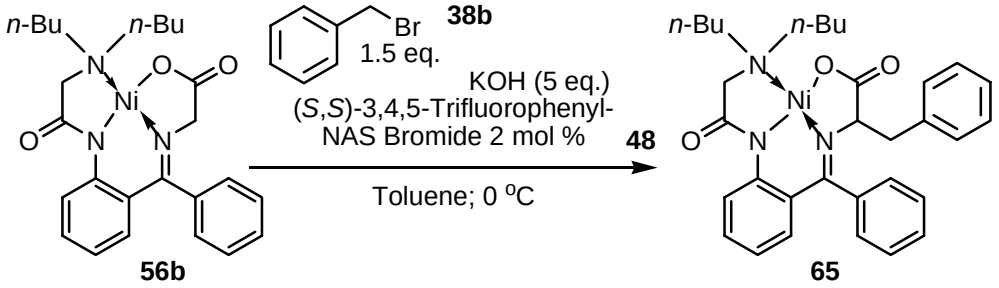


Table 16. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56b** With Optically Active Catalyst **48** Under Reduced Temperature

Entry	Time	Ratio[a]	ee[b]
	h	**65**/**56b**	%
1	1.5	27/73	76.8
2	3	38/62	73.9
3	6	44/56	70.1
4	9	49/51	67.3
5	12	51/49	65.9
6	12	10/90	0[c]

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Determined by HPLC analysis (Chiralcel OD column with 90:10 hexane:isopropanol as the eluant) of the complex. [c]The reaction was conducted without the phase transfer catalyst.

(Scheme 33), however it did lead to the discovery of some interesting results. Although the optical purity of the product **65** was increased to 76.8% ee following the 1.5 hourreaction, only 27% conversion to the appropriate product could be realized (Table 16, entry 1). Allowing the reaction to proceed for a longer period of time resulted in a decrease in the optical purity of the product **65**, which culminated with the isolation of the product following 51% conversion to the product in twelve hours, however the product was obtained in 65.9% ee (entry 5). It became evident that the length of the reaction time drastically influenced the optical purity of the product **65**. It was later

discovered that this could be attributed to the presence of a background reaction which provides the product **65** in racemic form without the need for a catalyst. In an independent reaction conducted without the catalyst under the same conditions as the previously described catalyzed reaction, the racemic product was obtained in approximately 10% yield (entry 6) which would account for approximately half of the undesired enantiomer in the catalyzed reaction. Therefore it became evident that a change in the reaction conditions would be necessary in order to suppress this background reaction. The approach that was envisioned to suppress or eliminate the background reaction involved increasing the lipophilicity of the glycine equivalent as well as increasing its reactivity to minimize the reaction time.

3.4.6 Increasing the Reactivity of the Modular Glycine Equivalents by the Strategic Incorporation of Electron Withdrawing Trifluoromethyl Groups to Improve the Stereochemical Outcome of the Asymmetric Phase Transfer Catalyzed Benzylation of the Modular Glycine Equivalents

With the increase in reactivity and lipophilicity provided by the previously described trifluoromethyl containing modular glycine equivalents **56k** and **56m**, a series of experiments were conducted to evaluate the efficiency of the chiral phase transfer catalysts, with respect to their ability to influence the stereochemical outcome of the homologation process. This investigation yielded results similar to the previously studied non-trifluoromethylated glycine equivalent **56b** except for the increased reaction rate

Scheme 34. Asymmetric Phase Transfer Benzylation of Modular Glycine Equivalent **56k** With Optically Active Catalysts **45-49**

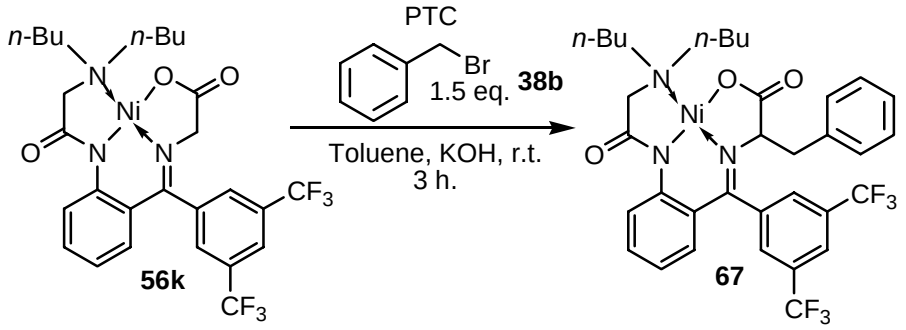


Table 17. Asymmetric Phase Transfer Benzylation of Modular Glycine Equivalent **56k** With Optically Active Catalysts **45-49**

Entry	Time h	Catalyst	Mol % Catalyst	Ratio[a] **67/56k**	Yield[b] %	ee[c] %
1	3	**45**	15	95/5	93.4	19.8
2	3	**46**	15	98/2	95.8	1.8
3	3	**47**	50	69/31	65.7	0.8
4	3	**49**	2	86/14	80.3	3.5
5	3	**48**	2	89/11	85.7	20.3

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 95:5 hexane:isopropanol as the eluant) of the corresponding Ni(II) complex .

(89% conversion in 3 hours) and slightly lower enantioselectivity. The most promising catalyst candidate was identified as the fluorine containing *N*-spiro catalyst **48** which provided the target product **67** in 85.7% yield and 20.3% ee in toluene with aqueous potassium hydroxide as the base, and benzyl bromide **38b** as the alkylating reagent (Scheme 34, Table 17, entry 5). However the allyl containing cinchonidine derivative **45** provided the product **67** in a similar optical purity, 19.8% ee, in higher chemical yield, 93.4%, with the same reaction time (entry 1). Unfortunately the three other catalysts

Scheme 35. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56k** With Optically Active Catalyst **48** in Various Organic Solvents

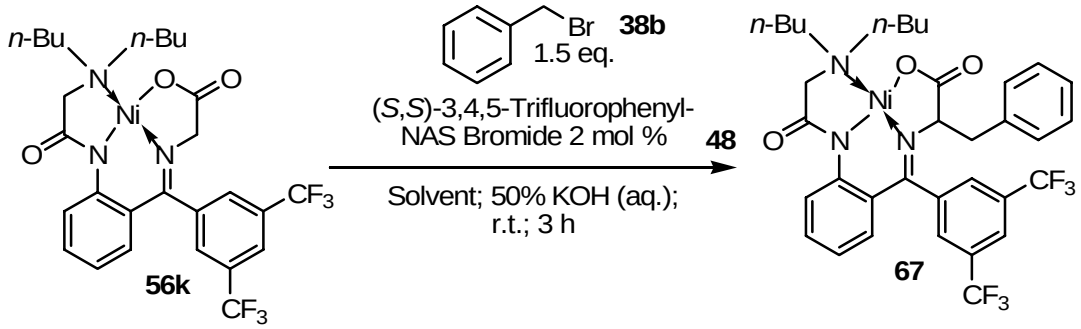


Table 18. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56k** With Optically Active Catalyst **48** in Various Organic Solvents

Entry	Solvent	Ratio[a] **56k/67**	Yield[b] %	ee[c] %
1	CH_2Cl_2	2/98	96.3	5.3
2	CH_2Cl-CH_2Cl	2/98	97.1	7.5
3	Benzene	2/98	91.9	0.4
4	Toluene	11/89	85.7	20.3
5	70% Tol:30% CH_2Cl_2	2/98	93.5	25.4
6	Xylenes	10/90	87.4	15.6
7	70% Xylenes:30% CH_2Cl_2	8/92	89.9	21.1
8	70% Hexanes:30% CH_2Cl_2	2/98	95.7	29.7

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 90:10 hexane:isopropanol as the eluant) of the complex.

investigated, **46**, **47**, and **49**, provided the benzylated target product **67** in nearly racemic form, although it could be obtained in high chemical yield (entries 2-4).

Utilizing the fluorinated *N*-spiro derived phase transfer catalyst **48** and 50% aqueous potassium hydroxide, the benzylation of the dibutylamine derived ditrifluoromethylated glycine equivalent **56k** was investigated utilizing various solvent systems (Scheme 35). As with previous investigations, the products obtained from the previously described phase transfer catalyzed homologation reactions in somewhat polar

organic solvents, such as dichloromethane and 1,2-dichloroethane, are nearly racemic (5.3 and 7.5% ee respectively). However they can be isolated in nearly complete chemical yield (Table 18, entries 1 and 2). Decreasing the polarity of the solvent system, by the application of benzene or toluene, resulted in conflicting results as the reaction in benzene provided the benzylated product **67** in nearly racemic form (0.4% ee), while utilizing toluene as the organic reaction medium resulted in increased enantiomeric excess, 20.3%, of the product **67**. However both reactions progressed to near completion (98% and 89% conversion respectively) in their corresponding three hour reactions (entries 3 and 4). Contrary to the previous studies, with the non-fluorinated glycine equivalent **56b**, mixed solvent systems such as 7:3 toluene:dichloromethane, or 7:3 xylenes:dichloromethane, demonstrated superior qualities as the reaction medium for this phase transfer catalyzed process when compared to any of the individual solvents themselves (entries 5 and 7 versus entries 1, 4, and 6). This resulted in the synthesis of the corresponding phenyl alanine derivatives **67** with enantiomeric excesses of 25.4 and 21.1% respectively following the nearly complete consumption of the initial glycine equivalent **56k** (entries 5 and 7). However the most promising result, with respect to enantioselectivity of the process, was obtained with the application of the mixed solvent system comprised of 7:3 hexanes:dichloromethane (entry 8). The outcome of this experiment was the isolation of the corresponding benzylated product **67** in 29.7% ee and 95.7% chemical yield which represents the most promising system for further investigations which include varying the hydroxide anion source.

Variation of the corresponding cation of the hydroxide base as well as its concentration has yielded dramatic effects on the enantioselectivity of the previous

Scheme 36. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56k** With Optically Active Catalyst **48** and Various Hydroxide Bases

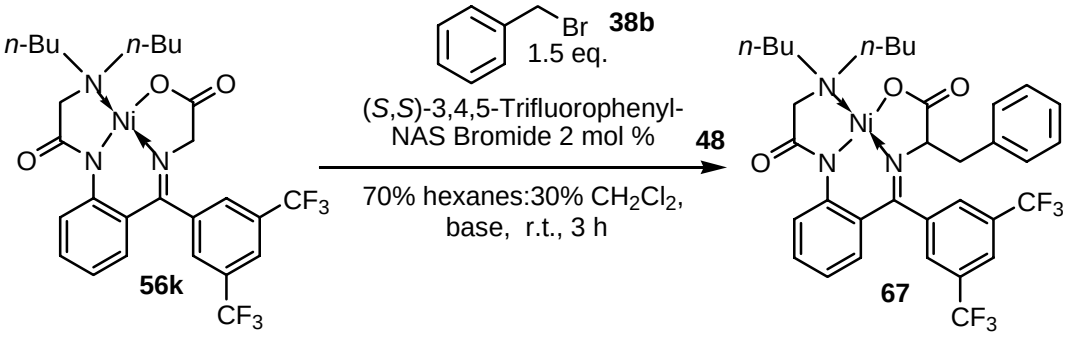


Table 19. Asymmetric Phase Transfer Benzylation of the Glycine Equivalent **56k** With Optically Active Catalyst **48** and Various Hydroxide Bases

Entry	Base	Ratio[a] **67/56k**	Yield[b] %	ee[c] %
1	50% KOH (aq.)	98/2	95.7	29.7
2	30% KOH (aq.)	94/6	91.3	27.9
3	30% NaOH (aq.)	98/2	94.7	27.1
4	50% CsOH (aq.)	96/4	92.1	25.3
5	KOH (5 eq.)	96/4	86.0	22.3
6	NaOH (5 eq.)	95/5	89.7	24.8
7	LiOH (5 eq.)	5/95	4.3	3.8
8	Cs_2CO_3 (5 eq.)	26/74	22.8	31.9

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixture. [b]Isolated yield of the pure product. [c]Determined by HPLC analysis (Chiralcel OD column with 95:5 hexane:isopropanol as the eluant) of the complex.

asymmetric phase transfer catalyzed reactions, however with regard to the trifluoromethyl containing glycine equivalent **56k**, very little effect could be observed.

The reactions conducted to determine the influence of the hydroxide source on the enantioselectivity of the glycine homologation process utilized the *N*-spiro catalyst **48**, and benzyl bromide **38b** in toluene at room temperature (Scheme 36). The application of aqueous potassium hydroxide yielded the corresponding benzylated product **67** in excellent chemical yield (95.7 and 91.3%), however, the optical purity of these products

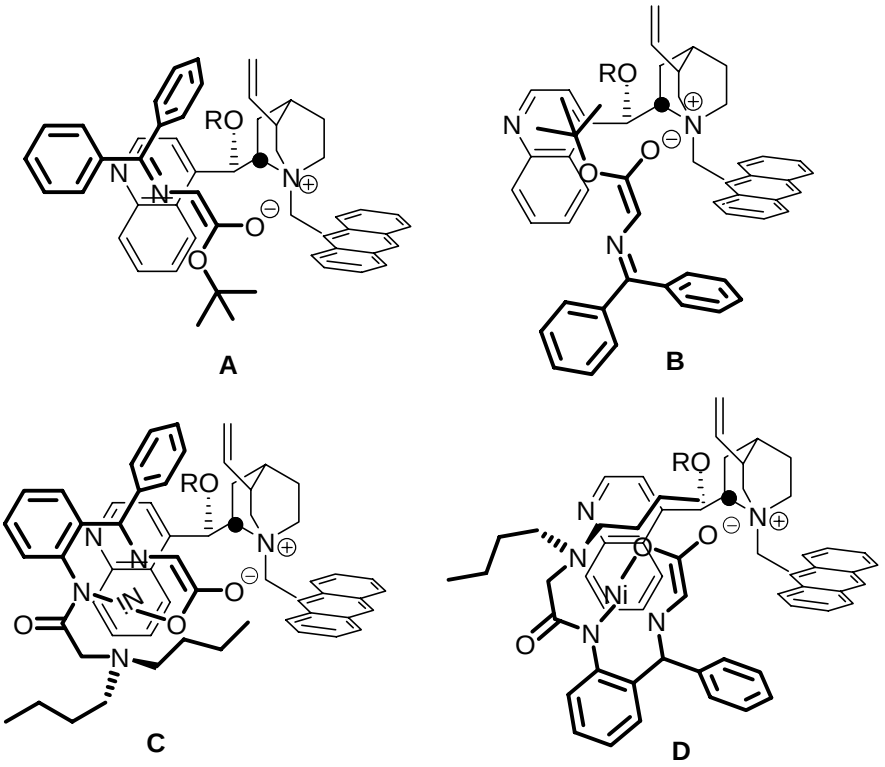
were only 29.7 and 27.9% ee, respectively (Table 19, entries 1 and 2). It was also found that altering the cation associated with the hydroxide anion had little effect on the enantioselectivity. The application of aqueous sodium or cesium hydroxide yielded the product **67** in similar optical purities (27.1% and 25.3% ee) to those previously described with the application potassium hydroxide as the base, although the product **67** was obtained in high chemical yields (94.7, and 92.1% respectively) in each reaction (entries 3 and 4). However, contrary to the results of the previous experiments utilizing solid bases, such as sodium or potassium hydroxide, their application in these experiments seemed to have a negative impact on the optical purity of the homologation product **67** providing it with enantiomeric excesses of 22.3 and 24.8% respectively, albeit in nearly complete chemical yield (entries 5 and 6). It was also found that using solid lithium hydroxide as the base resulted in the formation of nearly racemic product (3.8% ee) and a dramatic decrease in the reaction rate, as the product could be realized in 4.3% yield following the three hour reaction (entry 7). The highest optical purity of the phenyl alanine derived product **67** could be obtained by the application of crushed cesium hydroxide as the base. However the reaction rate was significantly lower, providing only 26% conversion of the glycine equivalent **56k** to the corresponding product **67** in three hours (entry 8). The results from these investigations indicate that aqueous solutions of the hydroxide base seem to provide higher enantioselectivity than the corresponding crushed base. However, contrary to the outcomes from previous investigations, the cation of the corresponding base seemed to have little effect.

3.4.7 Evaluation and Rationalization of the Results Obtained From the Investigation Involving the Asymmetric Homologation of 56 Under Phase Transfer Catalyzed Reaction Conditions

Unfortunately, despite the application of various reaction conditions for the asymmetric phase transfer catalyzed benzylation of the modular glycine equivalent **56**, further investigation will be required to identify a general and efficient method for the synthesis of optically active α-amino acids via this methodology. It appears that the largest issue that needs to be resolved is the compatibility of the glycine equivalent and the ammonium ion of the phase transfer catalysts. For instance, in the literature there have been two arrangements suggested for the ion pairs formed from the enolate of the *N*-(phenylmethylene) glycine derivative **14** and the *O*-allylated cinchonidine derived phase transfer catalyst **45** which were utilized to explain the stereocontrol of the homologation.[72]

Ion pair arrangement **A** has been proposed as the reactive intermediate in the enantioselective alkylation of this glycine equivalent **14** and is consistent with the observed stereochemistry (Figure 10). While ion pair **B** would favor the formation of the opposite enantiomer, it is less likely due to the increased separation of charges resulting from the accommodation of the *tert*-butyl ester group within the *N*-(phenylmethylene) derivative **14**. However if the dibutylamine derived Ni(II) complex **56b** is substituted for the *N*-(phenylmethylene) derivative **14**, it becomes evident that formation of either ion pair **C** or **D** could be possible due to the decrease in steric effects contributed by the

Figure 10. Stereopair Representations of the Three-Dimensional Arrangement of the Ion Pair From Catalyst **45** and the enolates of **14** and **56b**



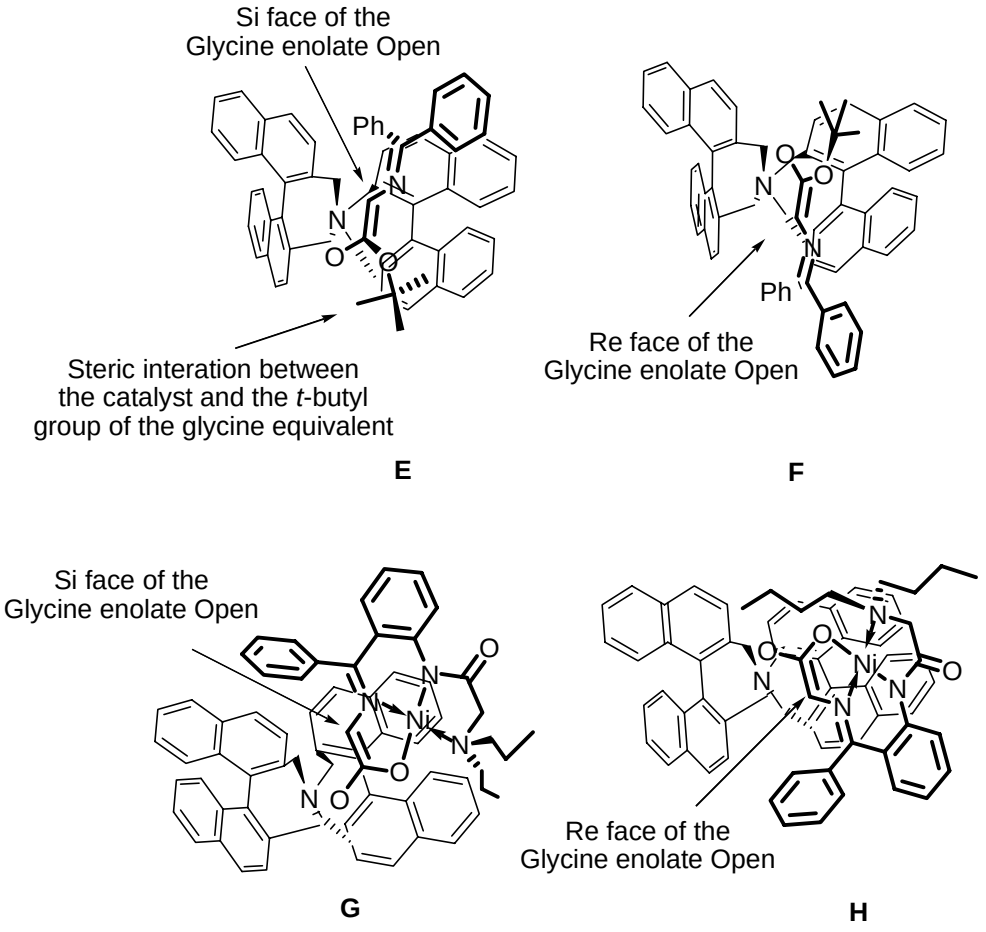
A and **B** are two possible stereopair representations of the three-dimensional arrangement of the ion pair from catalyst **45** and the enolate of **14**. **C** and **D** are two possible stereopair representations of the three-dimensional arrangement of the ion pair from catalyst **45** and the enolate of **56b**.

metal complexed anionic ester moiety of the complex, which could explain the decrease in enantioselectivity of the benzylation of **56b** with these cinchonidine derived catalysts.

A similar explanation could be invoked to explain the decreased selectivity in the reactions between the glycine equivalent **56b** and the *N*-spiro catalyst **48**. There has been an arrangement suggested for the ion pair formed between the catalyst **48** and the *N*-(phenylmethylene) derivative **14** which could explain the stereochemical outcome of these catalyzed reactions (Figure 11, **F**).[73] The formation of an ion pair that would seem to favor the opposite enantiomer **E**, although as in the previous case, the *tert*-butyl ester

group of the *N*-(phenylmethylene) derived glycine equivalent **14** could greatly decrease the probability of this ion pair due to steric interactions. However, by decreasing the steric demand of the ester functionality with the application of the Ni(II) complexed glycine equivalent **56b**, it seems more likely that either of the ion pairs **G** or **H** could form, thus leading to decreased optical purity of the benzylated product.

Figure 11. Stereopair Representations of the Three-Dimensional Arrangement of the Ion Pair From Catalyst **48** and the Enolates of **14** and **56b**



E and **F** are two possible stereopair representations of the three-dimensional arrangement of the ion pair from catalyst **48** and the enolate of **14**. **G** and **H** are two possible stereopair representations of the three-dimensional arrangement of the ion pair from catalyst **48** and the enolate of **56b**.

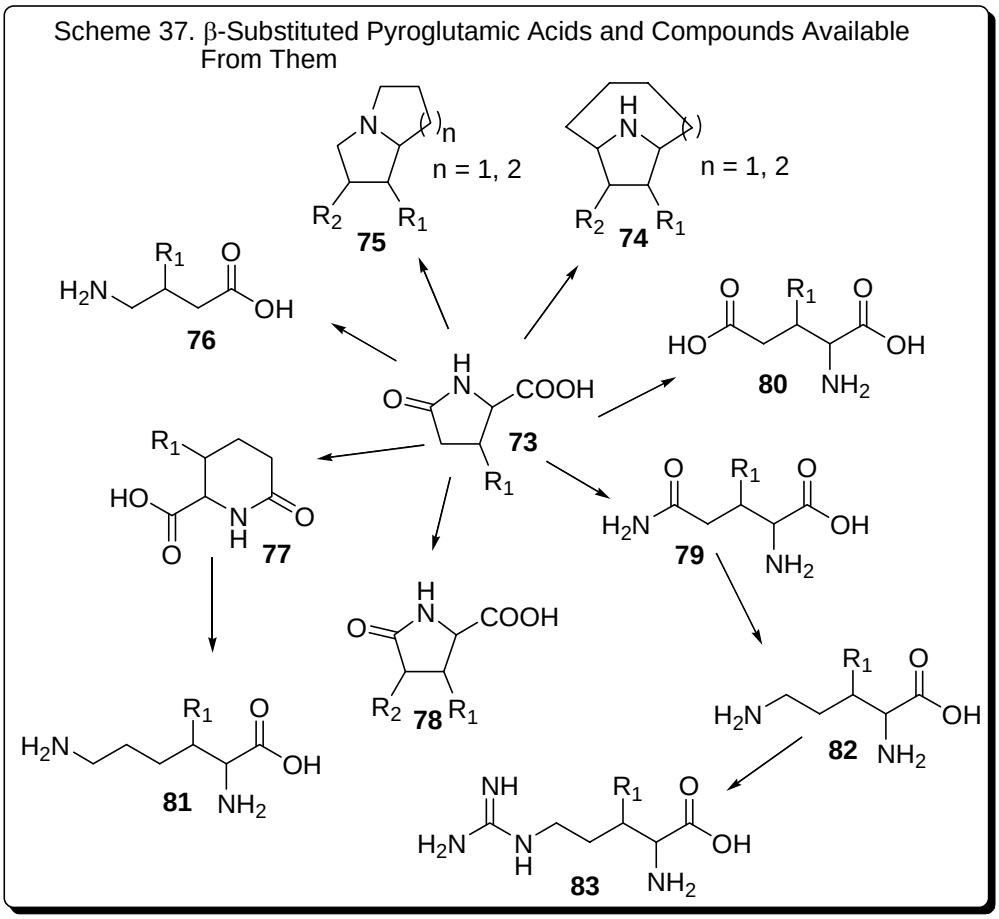
The asymmetric synthesis of α-amino acids, via asymmetric phase transfer catalysis, will require more investigation before being rendered as practical, however in the mean time there are various other methods that the modular glycine equivalent **56** could be utilized for, such as the synthesis of optically active β-substituted pyroglutamic acids.

3.5 The Synthesis of β-Substituted Pyroglutamic Acids Via the Homologation of Modular Glycine Equivalents 56 With Optically Active α,β-Unsaturated Carboxylic Acid Derivatives Under Mild Organic Base Catalyzed Conditions

3.5.1 The Importance of Optically Active Substituted Pyroglutamic Acids as well as Previous Synthetic Methodologies Devised for Their Production

Although the catalytic application of the chiral source for the asymmetric homologation of the modular glycine equivalents **56** will require further investigation, the use of (*R* or *S*)-4-phenyloxazolidin-2-ones as a stoicheometric source of optical activity has allowed for the asymmetric synthesis of various β-substituted pyroglutamic acids.[66] The asymmetric synthesis of β-substituted pyroglutamic acids have garnered a considerable amount of attention in the literature,[74,75] as they can be utilized as optically active building blocks for the preparation of a variety of compounds including *N*-bridged

Scheme 37. β-Substituted Pyroglutamic Acids and Compounds Available From Them



bicyclic compounds **74**,[76,77] pyrolizidines, indolizidines,[77,78] and assorted fused azabicyclic derivatives **75**.[77,79] Another significant group of compounds available from the elaboration of **73** is the β-substituted γ-amino acid derivatives **76**, of which Baclofen and Rolipram are recognized commercial pharmaceuticals.[80] Of significant interest to those investigating the proteome are transformations of β-substituted pyroglutamic acids to a class of sterically hindered β-substituted amino acids **77-83** that serve as crucial χ-constrained[81-83] skeletons in the de novo design of peptides and peptidomimetics with predetermined three-dimensional structures.[83]

Although a variety of methods for the synthesis of optically active β-substituted pyroglutamic acids are available from the literature, the Michael addition of nucleophilic

glycine equivalents with β-substituted acrylic acid derivatives serves as a methodologically concise and synthetically attractive approach to the synthesis of the desired β-substituted pyroglutamic acids **73**. The asymmetric version of this reaction has been investigated by numerous research groups, which has led to the development of methods useful for the control of the concurrently formed two stereogenic centers.[74,75] However, drawbacks of these methods include the incomplete stereochemical control of the products (<95% ee), incomplete chemical conversion, the application of strong bases such as *n*-butyl lithium, and the necessity to perform the reactions at low temperatures (-78 ^{o}C), all of which diminish the attractiveness of these methods. Critical analysis of the relevant literature associated with these methods reveals that the majority of focus has been directed toward reactions between chiral glycine equivalents and α,β-unsaturated carboxylic acid derivatives in which reasonable stereochemical control could be realized at both the α and β-positions of the resultant glutamic acids.[74,75,77] However, more recently, Professor Soloshonok and coworkers have introduced an alternative strategy, utilizing chiral derivatives of α,β-unsaturated amides with achiral glycine equivalents for the synthesis of β-substituted pyroglutamic acids **73**.[31,74,84]

Motivated by the previous investigations involving the Michael addition of the picolinic acid derived glycine equivalents **16** and **17a**[31,74,84] to (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidinones **84**,[85] application of the new modular glycine equivalents **56** became an interesting topic given the amount of flexibility of the modular framework. The reaction conditions employed for the synthesis of the β-substituted pyroglutamic acids are undoubtedly more mild compared to the homologation methods discussed to this point. However, the level of intricacy is multiplied as two stereogenic centers will be

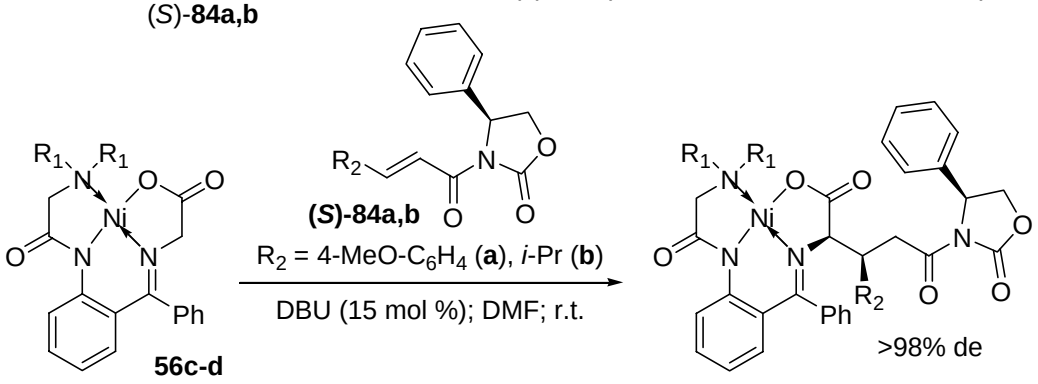
established by the formation of one bond. Therefore, the homogeneity of the enolate formed from the glycine structure, provided by the Ni(II)-complexed glycine equivalent, as well as the steric constraints surrounding the site of addition becomes of paramount importance to aid in the organization of the transition state, thereby providing the potential for increased yields as well as enhanced diastereoselectivities.

3.5.2 Evaluation of Various Modular Glycine Equivalents by Variation of the Corresponding Amine Module to Identify the Most Reactive Candidate With Respect to the Synthesis of β-Substituted Pyroglutamic Acid Precursors

Given the complex nature of these reactions, compounded by the application of milder bases, they provide an excellent platform to compare the reactivity of various derivatives within the series of the new glycine equivalents **56**. This is especially true given the simple workup procedures utilized, which were established from previous efforts and include pouring the crude reaction mixtures over a solution of icy 5% acetic acid to quench the reactions which is followed by simple filtration.

The initial reactivity comparison studies were conducted to determine the effect of the alkyl group of the amino moiety of the complexes with respect to their differences in lipophilicity, as well as their electronic and steric properties. The two (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **16a**,**b** chosen for these experiments included a *para*-methoxyphenyl or an *iso*-propyl substituent in the β-position to limit the rate, by virtue of

Scheme 38. Michael Additon Reations of Ni(II) Complexes **56c-d** and Michael Acceptors (*S*)-**84a,b**



56c-d

R_1 = Benzyl (**c**)
R_1^2 = Piperidyl (**d**)

(2*R*, 3*S*)-**85c-d** R_2 = 4-MeO-C_6H_4
(2*R*, 3*S*)-**86c-d** R_2 = *i*-Pr

Table 20. Michael Additon Reations of Ni(II) Complexes **56c-d** and Michael Acceptors (*S*)-**84a,b**

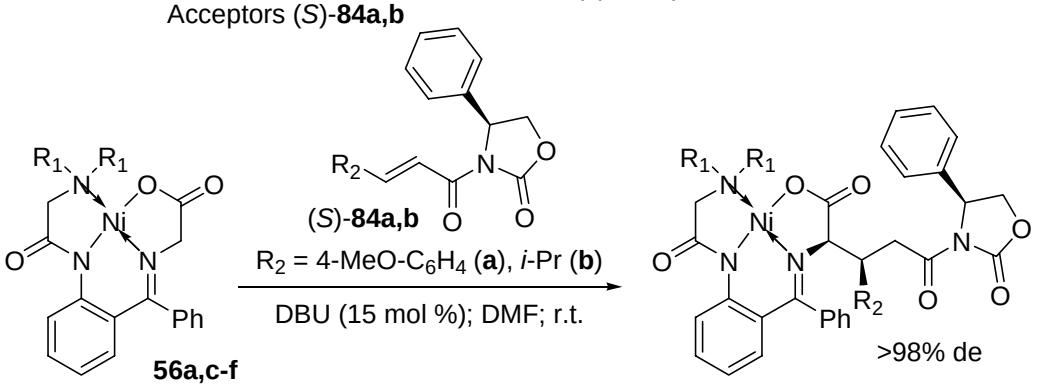
Entry	Substrate	Acceptor	Product	Time	Conversion[a] %	Yield %
1	**56d**	**84a**	**85d**	20 min	>99	>95
2	**56d**	**84b**	**86d**	25 min	>99	>99
3	**56c**	**84a**	**85c**	2.5 h	>99	>99
4	**56c**	**84b**	**86c**	26 h	88	>86

[a]Determined by ^{1}H NMR (300 Mhz) of the crude reaction mixtures.

their corresponding electronic and steric contributions, of the corresponding reactions to increase the accuracy while determining the relative reactivity of each of the complexes **56a**,**c-f**. Each of the following reactions discussed in this section was conducted under a set of standard conditions at ambient temperature, which included the use of commercial-grade DMF as the solvent and 15 mol % of DBU as the catalyst (Scheme 38). The initial experiments involving the application of the piperidine derived Ni(II) complex **56d** were impressive, as in both examples explored, the corresponding products **85d** and **86d** were obtained in high chemical yield (>95 and >99%, respectively) and high diastereoselectivity (>98% de) following the complete conversion from the starting

material **56d** in 20-25 min (Table 20, entries 1 and 2). Although the reaction rate was decreased from the previous example, the complete conversion of the dibenzylamine containing complex **56c** to the product **85c** was realized for the application of the aromatic substituted Michael acceptor **84a** in 2.5 hours (entry 3). However, after 26 hours, the reaction of the Michael acceptor bearing the *iso*-propyl group **84b** was limited to 88% conversion to the appropriate product **86c** (entry 4). The decrease in the reaction rates of the dibenzylated Ni(II) complex **56c** could be accounted for by the increase in the free rotation of the benzyl groups coupled with the enhanced size of the substituents.

Scheme 39. Michael Addition Reactions With Ni(II) Complexes **56a,c-f** and Michael Acceptors (*S*)-**84a,b**



56a,c-f

R_1 = Methyl (**a**)
$R_1{}^2$ = Morpholyl (**e**), Indolyl (**f**)

(2*R*, 3*S*)-**85a**, **e-f** R_2 = 4-MeO-C_6H_4
(2*R*, 3*S*)-**86a**, **e-f** R_2 = *i*-Pr

Table 21. Michael Addition Reactions With Ni(II) Complexes **56a,c-f** and Michael Acceptors (*S*)-**84a,b**

Entry	Substrate	Acceptor	Product	Time	Conversion[a] %	Yield %
1	**56a**	**84a**	**85a**	2 h	>99	>99
2	**56a**	**84b**	**86a**	26 h	62	>60
3	**56e**	**84a**	**85e**	2.25 h	>99	>95
4	**56e**	**84b**	**86e**	18 h	>99	>79
5	**56f**	**84a**	**85f**	2.5 h	83	>78
6	**56f**	**84b**	**86f**	26 h	60	>58

[a]Determined by ^{1}H NMR (300 Mhz) of the crude reaction mixtures.

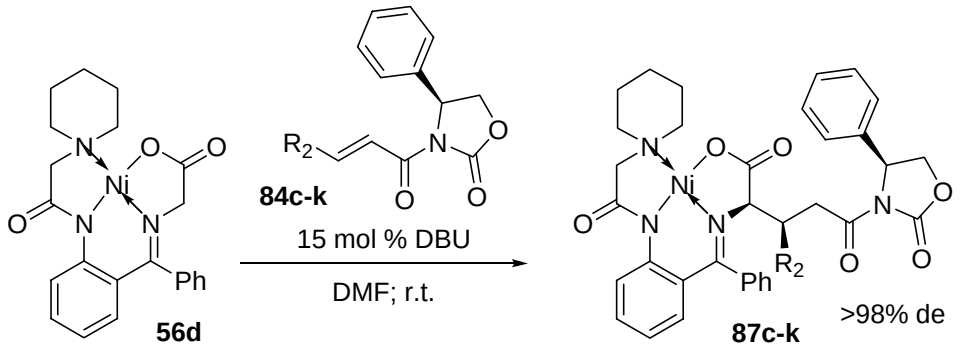
With these preliminary results in mind, the remaining reactions were conducted utilizing complexes that contained amino groups which were expected to also demonstrate optimal reactivity (Scheme 39); therefore, the results of the following experiment were initially unexpected. The incorporation of a dimethylamino group into the Ni(II) complex framework **56a** was expected to increase the reactivity by eliminating the steric considerations while not seeming to effect the overall electronic nature of the complex. Although the reaction with the aromatic containing Michael acceptor **84a** proceeded, it required two hours for the reaction to progress to completion providing the corresponding product **85a** in 99% chemical yield (Table 21, entry 1), whereas the reaction with the sterically challenged *iso*-propyl containing Michael acceptor **84b** did not achieve complete conversion (62%) even after two hours (entry 2). However, the unexpected outcomes from these reactions could be easily explained by observing the reaction as it progressed, because it was evident that the Ni(II) complex **56a** was not completely soluble at the standard concentration utilized for these experiments, 0.1 g in 2 mL, intrinsically decreasing the reaction rate. Application of the morpholyl derived Ni(II) complex **56e** proved synthetically useful as reactions with both of the Michael acceptors **84a**,**b** proceeded to completion and provided acceptable chemical yields of the products **85e** and **86e**, >95 and >79%, respectively. The rates of the reactions were drastically slower, requiring 2.25 hours for the *para*-methoxyphenyl derived acceptor **84a** and 18 hours for the *iso*-propyl containing acceptor **84b** (entries 3 and 4), when compared with their cyclic counterpart, the piperidyl derived complex **56d** (Table 20, entries 1 and 2). There seems to be little to no rationale to explain how this effect could arise from steric interations; however, the introduction of the oxygen atom into the ring could introduce a

number of electronic differences. In the last example investigated within this series, the indolyl group incorporated into the structure of the modular glycine equivalent **56f** is cyclic; however, it may be the overall size of this group that could account for the dismal reactivity, as neither reaction proceeded to completion given the time allotted for the reaction. The reaction which included the Michael acceptor bearing the aromatic substituent **84a** obtained 83% conversion to **85f** in 2.5 hours (entry 5), and the reaction with the *iso*-propyl-derived acceptor **84b** achieved a dismal 60% conversion to **86f** within 26 hours (entry 6).

3.5.3 Exploring the Generality and Limitations Associated With the Michael Addition of Various Optically Active *N*-(*E*-Enoyl)-4 Phenyl-1,3-Oxazolidin-2-Ones to the Glycine Equivalent 56d for the Synthesis of β-Substituted Pyroglutamic Acids

After analyzing the information obtained by the relative reactivity experiments, it was not difficult to identify the most likely candidate for further investigation. The piperidine moiety proved to be the most compatible amine module to incorporate into the Ni(II) complex for enhanced reactivity under the conditions necessary for these Michael addition reactions. Its reactivity far surpasses that of the previously published glycine equivalents including the picolinic acid derived Ni(II) complexes **16** and **17a**.[16] Therefore, the generality and limitations for the application of this modular glycine equivalent, with respect to this type of chiral Michael addition reactions, were of great

Scheme 40. Michael Addition Reactions With Modular Glycine Equivalent **56d** and Michael Acceptors **84c-k**



R_2 = Me (**c**), Ph (**d**), 2-MeO-C_6H_4 (**e**), 2-CF_3-C_6H_4 (**f**), 2,6-F_2-C_6H_3 (**g**), *N*-Bn-Indolyl (**h**), *N*-Ts-Indolyl (**i**), *N*-Tr-Imidazolyl (**j**), *t*-Bu (**k**)

Table 22. Michael Addition Reactions With Modular Glycine Equivalent **56d** and Michael Acceptors **84c-k**

Entry	R_2	Product	Time	Conversion[a] %	Yield %
1	Me	**87c**	3 min	>99	86[b]
2	Ph	**87d**	3 min	>99	>99
3	2-MeO-C_6H_4	**87e**	1.75 h	>98	>98
4	2-CF_3-C_6H_4	**87f**	1 h	>98	>98
5	2,6-F_2-C_6H_3	**87g**	4 min	>99	>99
6	*N*-Bn-Indolyl	**87h**	20 h	16	14
7	*N*-Ts-indolyl[c]	**87i**	30 min	>99	81[b]
8	*N*-Tr-Imidazolyl[c]	**87j**	24 h	0	0
9	*t*-Bu	**87k**	24 h	0	0

[a]Determined by ^{1}H NMR (300 Mhz) of the crude reaction mixture. [b]The yield was low because of incomplete filtration due to the particle size. [c]The absolute configuration of the Michael acceptor was *R*.

interest. The first two experiments that were investigated were fairly straightforward as both of the Michael acceptors were not as electron-rich or bulky as the previous two that were employed for the reactivity study. As expected, the crotonyl- and cinnamic acid-derived Michael acceptors **84c** and **84d** were successfully incorporated into the glycine equivalent to produce the corresponding β-substituted glutamic acid derivatives **87c** and

87d in high chemical yield, 86% and >99%, respectively, with a diastereomeric purity greater than 98% in both cases (Scheme 40, Table 22, entries 1 and 2). The Michael acceptor with the 2-methoxyphenyl moiety incorporated into the structure **84e** was explored as an interesting example which includes two key features that would decrease the reactivity of the acceptor due to the electron-donating nature of the substituent as well as to its location on the phenyl ring which would also serve to increase the steric constraint around the active site. Although the electronic and steric factors contributed by the Michael acceptor **84e** slowed the reaction rate, the reaction did proceed to completion providing the corresponding product **87e** in high chemical yield without compromising the stereochemical outcome (entry 3). As evidenced from the outcome from the previous reactions, the rate of these 1,4-addition reactions is effected by both the electronic and steric bulk contributed by the Michael acceptor; however, it was rather difficult to determine the effect of each factor independently. From the following experiment, conducted with a Michael acceptor containing an *ortho*-trifluoromethyl-phenyl group, introduced to retain the steric effects from the previous example while reversing the electronic contribution of the acceptor, **84f**, it was evident that the steric factor seemed to play a large role in determining the rate of the reaction. Although the reaction proceeded to completion providing the corresponding product **87f** in excellent yield (>98%) and diastereomeric purity (>98% de), one hour was necessary to complete the reaction (entry 4). The experiment to follow involved the application of an electron-poor Michael acceptor which included a 2,6-difluoro-phenyl group incorporated into the structure **84g**. Again, the reaction proceeded to completion providing the corresponding product **87g** in a diastereomerically pure form (>98% de) and very high chemical yield (>99%);

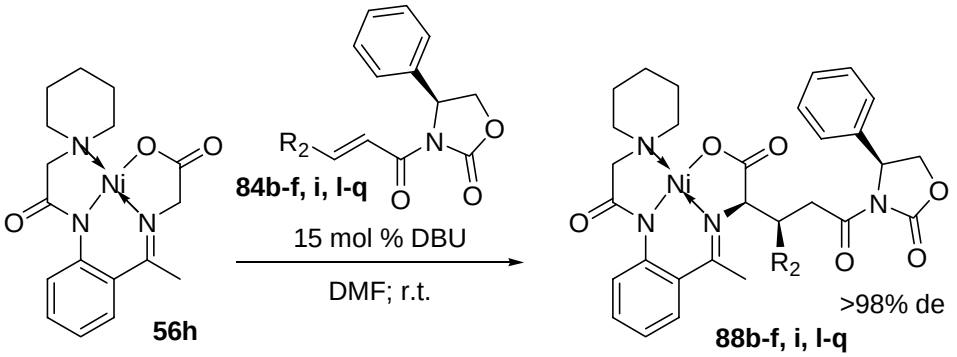
however, only four minutes were required for this reaction to be completed (entry 5). Despite the electronic donation of the 2-methoxy-phenyl moiety, the Michael acceptor **84e** did not prevent the progression of the reaction, however it was found that the electronic contributions of a *N*-benzyl-indolyl moiety into the skeleton of the reactive site of the Michael acceptor proved too much as the reaction between the complex **56d** and the Michael acceptor **84h** progressed sluggishly only providing 16% conversion to the corresponding product **87h** in 20 hours (entry 6). However, by employing the electron-withdrawing capabilities of a tosyl group, the electron-donating character of the indolyl moiety could be sufficiently reduced to allow the Michael addition reaction to proceed as evidenced by the completion (>99% conversion) of the reaction between the piperidine-containing Ni(II) complex **56d** and the corresponding Michael acceptor **84i** in 30 minutes (entry 7). Although the piperidine derived complex **56d** has proven to be quite useful to this point, it does seem that limitations do exist, as no products could be obtained from the reaction conducted with the *N*-tritylimidazolyl-substituted Michael acceptor **84j** even after 24 hours. This, however, is not so unexpected given the shear bulk of the *N*-tritylimidazolyl group coupled with the electron-releasing nature of the substituent. Presumably, because of the massive steric demands of the group, similar results could be obtained with the incorporation of a *tert*-butyl group into the Michael acceptor **84k** as no products were observed within the 24 hour reaction time.

3.5.4 Investigating the Possibility of Increasing the Reactivity of the Modular Glycine Equivalents Via the Application of the Less Sterically Demanding 2-Aminoacetophenone Module to Expand its Generality for the Production of β-Substituted Pyroglutamic Acids

Although the superior reactivity demonstrated by the piperidine-derived Ni(II) complex **56d** has far surpassed expectations, it seems that there remains some room for improvement. As discussed earlier, the transition state of these Michael addition reactions is extremely crowded, therefore one may assume that relieving some of the possible steric interactions could lead to favorable increases in reactivity. So far in this study, only the substituents of the amino module of the Ni(II) complexes have been evaluated for this purpose; however, previous investigations have demonstrated that utilizing an *ortho*-aminoacetophenone module rather than the *ortho*-aminobenzophenone one in the construction of the Ni(II) complexes can lead to increased reactivity without risking any adverse effects on the stereochemical outcome or complications from their preparation.[84d]

Therefore, the following reactions will involve the study of the 2-aminoacetophenone derived, piperidine containing complex **56h** (Scheme 41). As expected from previous experiments, the Michael addition reactions involving this new complex **56h**, and crotonyl or cinnamic acid derived chiral Michael acceptors **84c**,**d** were limited only by the time necessary to conduct the first TLC analysis (Table 23, entries 1 and 2). The reactions both proceeded to completion, >99% conversion, in under two minutes providing the corresponding products **88c**,**d** in greater than 98% yield. However,

Scheme 41. Michael Addition Reactions With Modular Glycine Equivalent **56h** and Michael Acceptors **84b-f,i,l-q**



R_2 = *i*-Pr (**b**), Me (**c**), Ph (**d**), 2-MeO-C_6H_4 (**e**), 2-CF_3-C_6H_4 (**f**), *N*-Ts-Indolyl (**i**), 4-Cl-C_6H_4 (**l**), 3,4-Cl_2-C_6H_3 (**m**), 3,5-F_2-C_6H_3 (**n**), 3-CF_3-C_6H_4 (**o**), Et (**p**), 2,6-Me_2-4-MeO-C_6H_2 (**q**)

Table 23. Michael Addition Reactions With Modular Glycine Equivalent **56h** and Michael Acceptors **84b-f,i,l-q**

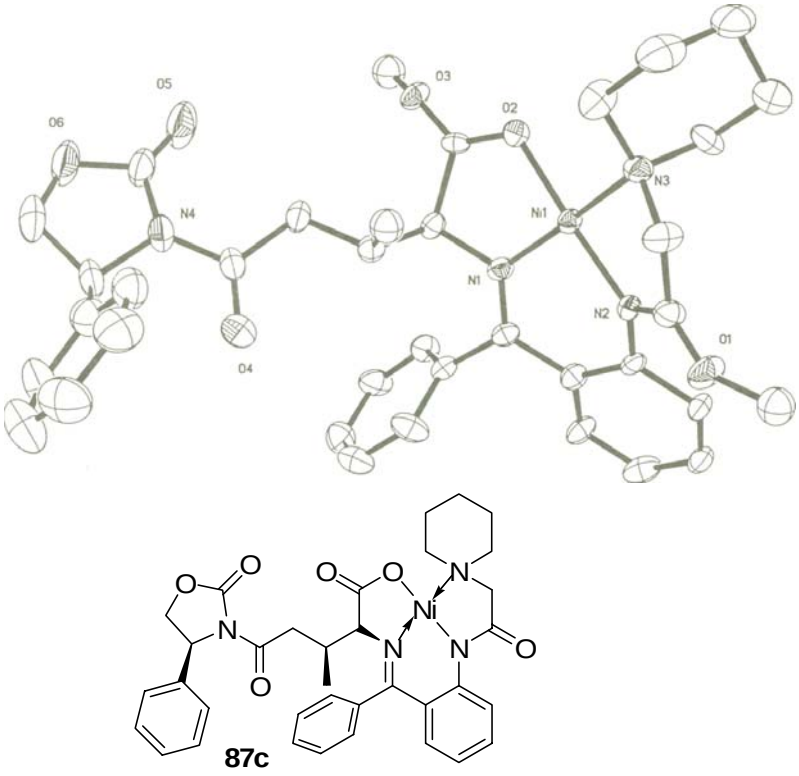
Entry	R_2	Product	Time	Conversion[a] %	Yield %
1	Me	**88c**	2 min	>99	98
2	Ph	**88d**	2 min	>99	98
3	4-Cl-C_6H_4	**88l**	3 min	>99	92
4	3,4-Cl_2-C_6H_3	**88m**	3 min	>99	96
5	3,5-F_2-C_6H_3	**88n**	3 min	>99	91
6	2-CF_3-C_6H_4	**88f**	20 min	>99	89
7	3-CF_3-C_6H_4	**88o**	2 min	>99	92
8	Et	**88p**	7 min	>99	95
9	i-Pr	**88b**	15 min	>99	70
10	2-MeO-C_6H_4	**88e**	30 min	>99	94
11	*N*-Ts-indolyl[b]	**88i**	10 min	>99	98
12	2,6-Me_2-4-MeO-C_6H_2[b,c]	**88q**	24 h	38	35

[a]Determined by ^{1}H NMR (300 Mhz) of the crude reaction mixture. [b]The absolute configuration of the Michael acceptor was *R*. [c]A stoicheometric amount of DBU was used.

the first bit of promising information came with the conclusion of the following reaction, as the Michael acceptor bearing the *iso*-propyl group **84b** reacted with the acetophenone-derived complex **56h** (entry 3) at a faster rate than the benzophenone complex utilized

earlier (Scheme 38, Table 20, entry 4) providing complete consumption of the starting material **56h** in 15 minutes. The reaction of the Michael acceptor which included the *ortho*-methoxyphenyl substituent **84e** for this reaction also provided exciting results as the reaction rate was cut from 1.75 to 0.5 hours merely by the application of the Ni(II) complex **56h**, whereas the complete chemical conversion (>99%) and yield of the products **88e** (94%) were not effected by the modification of the Ni(II) complex (Table 23, entry 4). The presence of an electron-withdrawing *para*-trifluoromethylphenyl in the Michael acceptor **84f** did not break with the trend for this set of reactions, as the reaction proceeded approximately six times faster with the acetophenone-derived complex **56h** (20 minutes) compared to the more bulky benzophenone-containing complex **56d** (entry

Figure 12. X-ray Crystallographic Structure of **87c**



5). Revisiting the application of the *N*-Ts-indolyl-containing Michael acceptor **84i** with the improved glycine equivalent **56h** also proved useful as the complete conversion of the starting material **56h** to products **88i** was observed in approximately 10 minutes (entry 6), whereas in the previous case, nearly 30 minutes was necessary to obtain similar results. The stereochemical assignments of these diastereomeric Ni(II) complexes were based on analysis of X-ray crystal structures of various products such as **87c** which is depicted in Figure 12.

In summary, this new series of modular achiral glycine equivalents has been evaluated with respect to their synthetic utility for the production of tailor-made, sterically constrained, and functionalized amino acids. Among the series of modular achiral glycine equivalents, the piperidine derived, 2-aminoacetophenone containing Ni(II) complex **56h** was found to be a superior glycine derivative for the Michael additions with various (*R*)- or (*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **84a-l** representing a general and practical synthesis of sterically constrained β-substituted pyroglutamic acids. In particular, the application of these complexes allowed for the preparation of several β-substituted pyroglutamic acids which include electron-releasing and sterically demanding substituents in the structure thus increasing the synthetic efficiency and expanding the generality of these Michael addition reactions.

3.6 The Application of Modular Glycine Equivalents Derived from Primary Rather Than Secondary Amine Modules

The design of modular glycine equivalents with primary rather than secondary amine modules was envisioned to provide the opportunity for additional pathways for the preparation of optically active α-amino acids which have been relatively unexplored via the application of metal coordinated glycine derivatives.[86,87] Such additional pathways could include the deracemization of racemic α-amino acids, and the asymmetric synthesis of α, α-asymmetrically substituted α-amino acids from optically active α-amino acids due to the incorporation of a chiral center in the Ni(II) complex.

3.6.1 Investigation of the Reactivity, Chemoselectivity and Stereoselectivity Associated With the Primary Amine Module Containing 'NH' Complexes

Prior to the application of these new complexes for the synthesis of α-amino acids via the alternative pathways, it was decided to investigate their reactivity, chemoselectivity ("CH" versus "NH" chemoselectivity of the metal coordinated secondary amine and an activated methylene moiety), stereochemical characteristics, as well as their potential as less sterically restricted nucleophilic glycine equivalents.[69] This was accomplished by the homologation of these modular glycine equivalents via phase

transfer catalyzed alkylations as well as organic base catalyzed Michael additions with optically active α,β-unsaturated acid derivatives.

3.6.1.1 Application of the Phase Transfer Catalyzed Homologation of the 'NH' Glycine Equivalents 56m-o

Scheme 42. Phase Transfer Benzylation of the "NH" Benzyl Glycine Equivalent **56m**

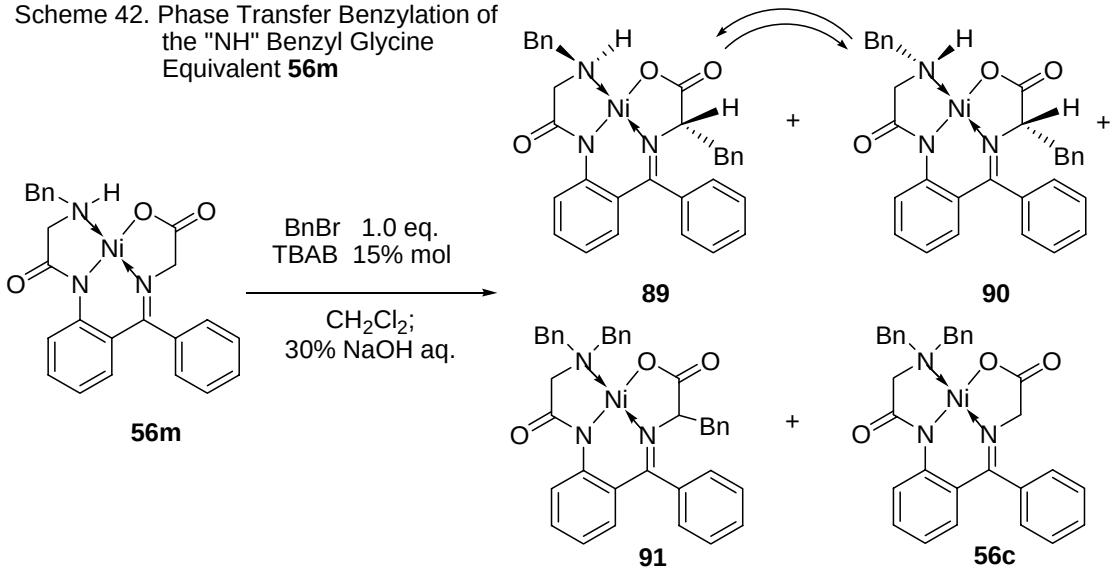


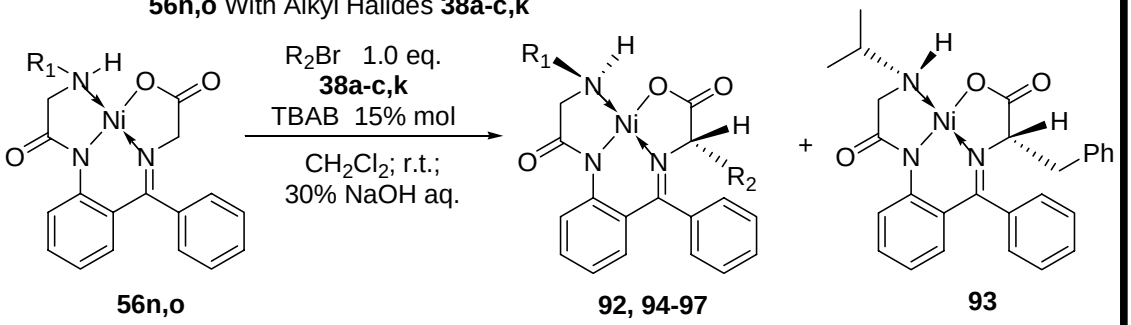
Table 24. Phase Transfer Benzylation of the "NH" Benzyl Glycine Equivalent **56m**

Entry	Temp. °C	Time (h)	Ratio[a] **89,90/56c/91**
1	25	2	1/0/0.58
2	0	2	1/0.2/0.29
3	-10	2	1/0.2/0

[a]Determined by ^{1}H NMR (300 Mhz) of the crude reaction mixtures.

The alkylation of complex **56m** with one equivalent of benzyl bromide **38b** under phase transfer catalyzed conditions (Scheme 42) unexpectedly produced three isolatable products **89**–**91** as well as an amount of the initial starting material **56m** (Table 24, entry 1). Further analysis of these products revealed that the *N*,*N*-dibenzylamine derived glycine equivalent **56c** was not obtained at all. Instead, a pair of diastereomers **89** and **90**, containing a phenylalanine residue, and the dibenzylated complex **91** were isolated in approximately equal amounts. Intrigued by the outcome of this experiment and the unique chemoselectivity observed, a series of experiments were conducted in order to investigate this system in more detail. Lowering the temperature of the reaction to 0 °C provided all three of the products **89**–**91** isolated from the room temperature reaction as well as one more, complex **56c** (entry 2). Decreasing the reaction temperature further eliminated the formation of the *N*,*N*-dibenzyl phenylalanine complex **91**, although provided the *N*,*N*-dibenzyl derivative **56c** as a minor product and the diastereomers **89** and **90** as the major products (entry 3). However, it was interesting to note that compounds **89** and **90** undergo slow interconversion in solution at room temperature. This process seems to occur from inversion of the secondary nitrogen atom resulting in the epimerization of the nitrogen stereogenic center. However, in the solid phase, this process was not observed, allowing for the isolation of each of the diastereomeric compounds. It was also observed that polar solvents as well as higher temperatures increase the interconversion rates. Intrigued by the highly unusual preferential *C*-alkylation vs. *N*-alkylation observed, the relevant literature was searched for precedents, however only one example was found and was reported by Hegedus[88] on the minimally chemoselective *O*- vs. *N*-acylation of Ni(II)-coordinated cyclams.

Scheme 43. Phase Tranfer Catalyzed Alkylation of Ni(II) Complexed "NH" Glycine Equivalents **56n,o** With Alkyl Halides **38a-c,k**



56n,o **92, 94-97** **93**

Table 25. Phase Tranfer Catalyzed Alkylation of Ni(II) Complexed "NH" Glycine Equivalents **56n,o** With Alkyl Halides **38a-c,k**

Entry	R_1	R_2	Product	Time (h)	Yield %	de[a]
1	*i*-Pr	Bn	**92/93**	1.5	91	67
2	*t*-Bu	Bn	**94**	3	93	>98
3	*t*-Bu	allyl	**95**	1	96	>98
4	*t*-Bu	cinnamyl	**96**	1	94	>98
5	*t*-Bu	propargyl	**97**	3	90	>98

[a]Determined by ^{1}H NMR (300 Mhz) of the crude reation mixtures.

Therefore it was decided to investigate the homologations of these 'NH' complexes in detail with two goals in mind: to find an example with complete CH chemoselectivity and also to put this unprecedented phenomenon to synthetic use. As follows from the data obtained, decreasing the temperature of the reaction did provide a small increase in the chemoselectivity of the reaction, it seems that very low temperatures would be necessary in order to completely eliminate the formation of the *N*,*N*-dibenzyl product **56c**, or its phenyl alanine analogue **91**. Therefore it was decided to explore how the steric bulk on the secondary amine residue could influence the chemoselectivity. To this end complexes **56n**, containing an isopropyl moiety, and **56o** with a *tert*-butyl group were investigated. Under the same phase transfer conditions utilized in the previous

reaction, with one equivalent of benzyl bromide **38b**, the alkylation of the *iso*-propyl derived complex **56n** was found to be completely chemoselective, as only the diastereomeric complexes **92** and **93** containing phenylalanine residue were produced (Scheme 43, Table 25, entry 1) in a ratio of 1:5.2. Further increase in the steric constraint provided by application of the complex containing a *tert*-butylamine module **56o** was found to have an even more profound effect on the stereochemical outcome of the alkylation. Thus, alkylation of the complex **56o** was accomplished in three hours with one equivalent of benzyl bromide **38b**, providing the phenylalanine complex **94** in 93% yield and virtually complete (>98%) diastereoselectivity (entry 2). After successfully identifying the conditions necessary to achieve complete chemo- and diastereoselectivity for the benzylation reaction, the alkyl halide was varied in order to establish the presence of some generality for this procedure. Under the same phase-transfer conditions described for the previous reaction, the *tert*-butyl containing complex **56o** reacted with complete chemo- and diastereoselectivity when allyl **38a**, cinnamyl **38c**, or propargyl bromide **38k** were employed. The application of allyl **38a**, or cinnamyl bromide **38c** significantly increased the reaction rate as the corresponding homologated products **94** and **95** were obtained in 96 and 94% yield respectively and in diastereomerically pure form, in less than one hour (entries 3 and 4). Although slightly slower, the allylated product **96** was obtained as a single diastereomer in 90% yield in three hours (entry 5).

These results demonstrate that the coordination of a secondary amine to Ni(II), along with the appropriate steric effects, allows for complete prevalence of C–H chemoselectivity versus that of the N–H, as demonstrated by the alkylations of complexes **56n** and **56o**. In fact, the coordination of nucleophilic nitrogen to a metal

could be considered as the equivalent of a protecting group without the need of introducing a transient N–C substituent.

3.6.1.2 Organic Base Catalyzed Michael Additions Between the 'NH' Complexes and Optically Pure Michael Acceptors 76c and 76d

Scheme 44. Michael Addition Reactions of "NH" Ni(II) Complexes of Glycine **56m-o** and Michael Acceptors (R)-**84c,d**

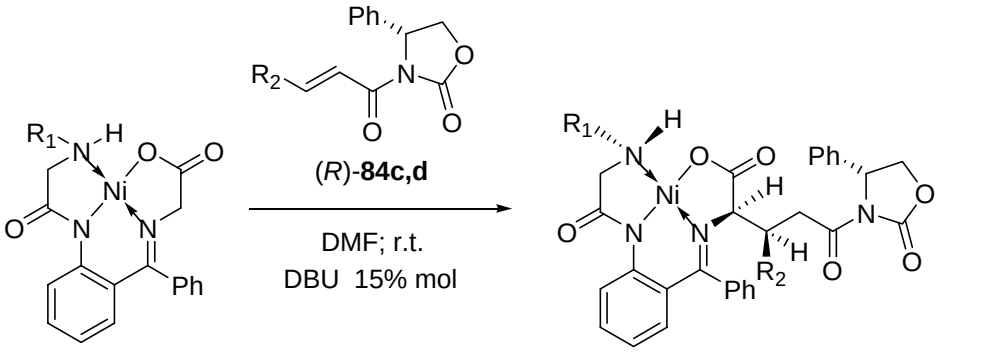


Table 26. Michael Addition Reactions of "NH" Ni(II) Complexes of Glycine **56m-o** and Michael Acceptors (R)-**84c,d**

Entry	R_1	R_2	Product	Time (h)	Conversion[a] %	Yield %	de
1	*t*-Bu	Me	**97**	2	>99	95	>98
2	*t*-Bu	Ph	**98**	2	>85	84	>98
3	*i*-Pr	Ph	**99**	1	>99	92	>98
4	Bn	Ph	**100**	1	>99	89	>98

[a]Determined by ^{1}H NMR (300 MHz) of the crude reaction mixtures.

To realize the synthetic opportunity provided by the unusual chemoselectivity of 'NH' complexes **56m-o**, their application as nucleophilic glycine equivalents in the highly diastereoselective, organic-base catalyzed Michael addition reactions were explored. The reactions between compounds **56m-o** and chiral (*R*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones **84c,d** were conducted in commercial grade DMF at room temperature in the presence of 15 mol% of DBU (Scheme 44). The reaction of the *tert*-butylamine-containing complex **56o** and the crotonyl derived Michael acceptor **84c** produced the glutamic acid derivative **97** in high chemical yield (95%) and >98% de in two hours (Table 26, entry 1). Remarkably, not even a trace of the product, corresponding to the possible addition of the secondary amino group in **56o** to the Michael acceptor **84c**, was detected in the crude reaction mixture. The application of a more sterically demanding Michael acceptor, such as the phenyl-containing **84d**, slowed the reaction rate therefore decreasing the conversion and the chemical yield of product **98** (entry 2). On the other hand, decreasing the steric bulk on the amino moiety in the starting complex with the application of *iso*-propyl containing complex **56n** provided increased reactivity. Thus, the reaction between **56n** and the phenyl-containing Michael acceptor **84d** proceeded to completion cleanly, providing the corresponding product **99** in 92% yield and >98% de in one hour (entry 3). Impressed by the increased diastereoselectivity obtained from this reaction, the benzyl-derived complex **56m** was also applied as a Michael donor. The reaction between **56m** and the phenyl-containing Michael acceptor **84d** provided the corresponding product **100** in high chemical yield (89%) and high diastereomeric purity (>98%) in less than one hour (entry 4).

It should be mentioned that the application of these modular Ni(II) complexes have proven to be synthetically useful for this transformation. The overall decrease in the steric bulk provided by the secondary rather than tertiary amines serves as an advantageous feature as well as the improved separation and reuse of the chiral auxiliary and the corresponding ligands due to the physical properties of the new generation of ligands.

3.6.2 Deracemization of α-Amino Acids With the Aid of Optically Active Primary Amine Containing Ligands Via Diastereomeric Ni(II) Complex Formation Followed by Chromatographic Separation

The methodology which will be discussed within this section will not be a synthetic procedure for the preparation of α-amino acids, rather the focus will be directed toward a chromatographic separation process for previously synthesized racemic α-amino acids. Despite the potential of the asymmetric synthesis,[89,90] resolution of racemates remains the most favorable approach to the large-scale preparation of enantiomerically pure compounds.[91,92] While the enzymatic resolution of racemates is more economically feasible for the large-scale production of α-amino acids[91], certain substrate limitations, as well as the time required to identify the selective enzyme, or the most appropriate enzyme catalyzed transformation could render it less attractive to many research facilities that require only small amounts of a large number of various unnatural α-amino acids thereby making the application of chemical approaches, via the formation of diastereomeric derivatives, more practical. In the latter approach, application of a

resolving reagent with one stereogenic center is a well established and routine technique.[93,94] Alternatively, application of chiral resolving agents which include multiple stereogenic centers remains virtually unstudied.[95] Therefore it remains unclear what advantages may be contributed to the practical resolution of racemates with the

Scheme 45. Evaluation of the Percentage ofStereochemical Differnce in Resolving Reagents With a Variable Number of Stereogenic Centers

Equation	Resolving Reagent	Substrate	Diastereomeric Products	Stereochemical Difference
1)	*R*	*R*/*S* →	*R*,*R* + *R*,*S*	50%
2)	*R*,*R*	*R*/*S* →	*R*,*R*,*R* + *R*,*R*,*S*	33%
3)	*R*,*S*	*R*/*S* →	*R*,*S*,*R* + *R*,*S*,*S*	33%
4)	*R*,(*R*/*S*)	*R*/*S* →	*R*,*S*,*R* + *R*,*R*,*S*	66%
			R,*R*,*R* + *R*,*S*,*S*	66%

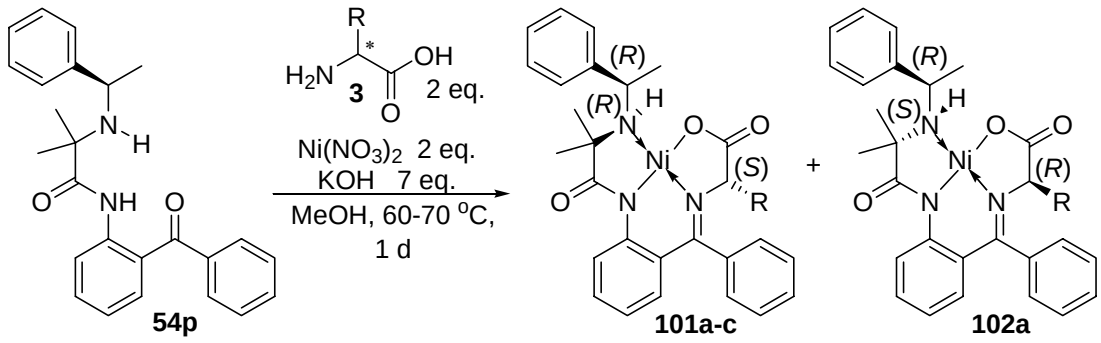
application of optically active resolving agents with more than one stereogenic center. For instance, application of a resolving agent with two stereogenic centers will produce two different stereochemical combinations of the corresponding diastereomeric derivatives. As shown in Scheme 45, if both stereogenic centers of the resolving reagent are set, *R*,*R* (equation 2) or *R*,*S* (equation 3), it will lead to diastereomeric products with the absolute configurations of *R*,*R*,*R* and *R*,*R*,*S*, or *R*,*S*,*R*, and *R*,*S*,*S* respectively. Considering the degree of stereochemical difference (33.33%) in these products, one may agree that it might be a less advantageous combination compared with the traditional approach (equation 1) dealing with only two stereogenic centers in the diastereomeric products which have a stereochemical difference of 50%. On the other hand, if an alternative combination of the stereogenic centers, such as *R*,*R*,*R* and *R*,*S*,*S*, or *R*,*S*,*R* and

R,*R*,*S* (eq. 4) can be obtained, then the increased stereochemical difference (66.67%) of the products may represent a substantial advantage over the traditional approach (equation 1). However, to realize the potential of this approach, for practical separations, at least two challenges must be addressed. First, the design of such a resolving agent must allow for one of the stereogenic centers be configurationally unstable. Second, to make this approach practical, the stereochemistry, either *R* or *S*, of the configurationally unstable stereocenter must be totally controlled by absolute configuration of the substrate, thus leading to the formation of only two diastereomers, either *R*,*R*,*R* and *R*,*S*,*S*, or *R*,*S*,*R*, and *R*,*R*,*S*, not all four of them. A search of the current literature failed to reveal any reports that such a methodology employing the stereochemically favorable combination of the three stereogenic centers for separations of enantiomers has ever been investigated.

3.6.2.1 Diastereomeric Ni(II) Complex Formation From Racemic α-Amino Acids and the (*R*)-1-Phenyl-Ethylamine Derived Modular Ligand 54p

Therefore it was decided to investigate the application of the (*R*)-1-phenyl-ethylamine derived modular 'NH' ligand, which contains a configurationally stable carbon and a configurationally unstable nitrogen stereogenic center as a resolving agent for natural and unnatural α-amino acids via formation and separation of the corresponding Ni(II) complexes. These diastereomeric complexes contain three stereogenic centers of favorable stereochemistry thus providing for their easy separation.

Scheme 46. Assembly of Diastereomeric Ni(II) Complexes **101a-c** and **102a**



R = Methyl (**a**), Ethyl (**b**), Propyl (**c**)

Table 27. Assembly of Diastereomeric Ni(II) Complexes **101a-c** and **102a**

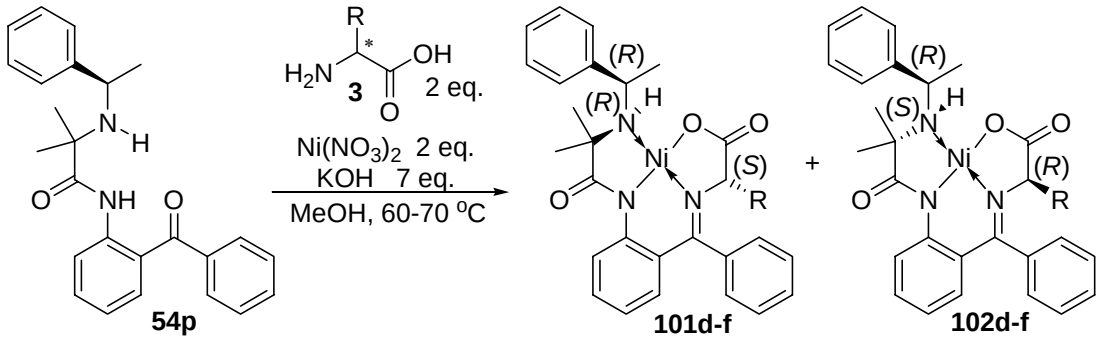
Entry	R	Ratio **101/102**[a]	Yield %
1	Methyl	73/27	38
2	Ethyl	>98/2	89
3	Propyl	>98/2	84

[a]Determined by ^{1}H NMR (300 MHz) analysis of crude reaction mixtures.

The conditions employed for the Ni(II) complex formation differ from those described earlier for the synthesis of the glycine containing derivatives **56** as the quantity of the amino acid was decreased in order to increase the efficiency of this methodology (Scheme 46). The initial investigation involved the application of the (*R*)-1-phenyl-ethylamine derived ligand **54p** and racemic alanine to produce the corresponding diastereomeric products **101a** and **102a** in methanol with potassium hydroxide (7 eq.) and nickel nitrate (2 eq.). The products obtained were a pair of diastereomers which were obtained in a ratio of 73:27 and 38% chemical yield (Table 27, entry 1). Although this process was somewhat selective in favor of the diastereomer which contained the amino acid residue in the *S* absolute configuration, the diastereomeric products required separation in order to obtain the optically pure amino acids. It was found that this

separation could easily be accomplished via column chromatography on silica gel utilizing a mixture of dichloromethane and acetone as the eluant. The experiment to follow involved the application of 2-aminobutyric acid as the racemic amino acid and was found to be extremely selective for the formation of the Ni(II) complex which contains the (*S*)-aminobyteric acid **102b** (entry 2). With respect to the ligand, the nearly pure diastereomeric product **102b** was obtained in high chemical yield (89%) and could be easily purified on silica gel. Extending the *n*-alkyl chain of the amino acid to three carbons by the use of norvaline for the synthesis of the Ni(II) complex again resulted in the nearly complete formation of the product **102c** as a single diastereomer in high chemical yield allowing for the efficient isolation of (*S*)-norvaline (entry 3).

Scheme 47. Assembly of the Diastereomeric Ni(II) Complexes **101d-f**, and **102d-f**



R = Benzyl (**d**), *i*-Propyl (**e**), Phenyl (**f**)

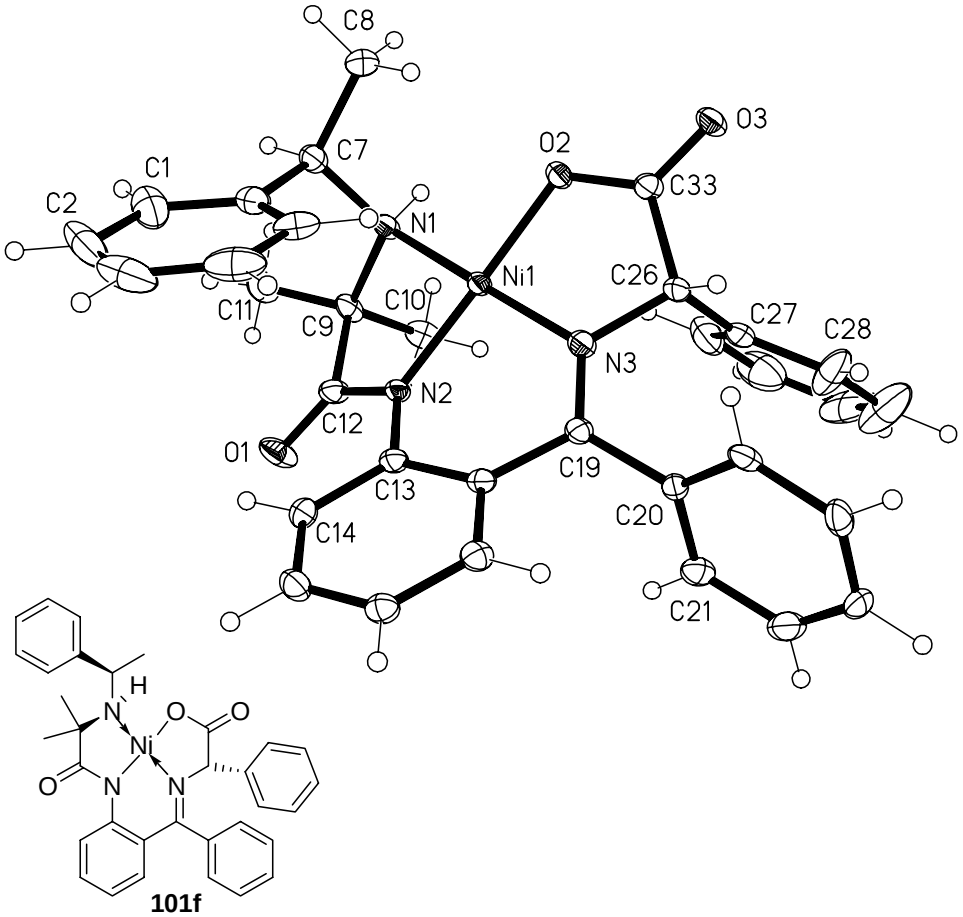
Table 28. Assembly of the Diastereomeric Ni(II) Complexes **101d-f**, and **102d-f**

Entry	R	Time d	Ratio **101**/**102**[a]	Yield %
1	Benzyl	1	88/12	71
2	*i*-Propyl	1	54/46	79
3	*i*-Propyl	3	60/40	99
4	Phenyl	1	59/41	64
5	Phenyl	3	59/41	80

[a]Determined by ^{1}H NMR (300 MHz) analysis of crude reaction mixtures.

Given the successful application of this optically active modular ligand for the resolution of racemic amino acids bearing *n*-alkyl side chains via chromatographic separation, it was decided to investigate the generality of this process to include amino acids with branched side chains (Scheme 47). The first amino acid investigated for this purpose was phenylalanine. The result of this inquiry was the synthesis of Ni(II) complexes **101d** and **102d** in a ratio of 88:12 respectively and nearly complete chemical yield following the 24 hour reaction (Table 28, entry 1). The increased steric bulk contributed by the *iso*-propyl group of valine resulted in decreased chemical yield for the 24 hour reaction, however, prolonging the reaction to 72 hours resulted in nearly complete conversion of the ligand to the corresponding Ni(II) complexes **101e** and **102e** (entries 2 and 3). Although the reaction could be optimized to proceed to completion, the process was only slightly selective providing two diastereomeric products **101e** and **102e**, however they could be easily separated on a silica gel column utilizing the same eluent system described earlier for the alanine derived complexes **101a** and **102a**. As with the previous example, the steric contributions from the α-branched amino acid phenyl glycine prohibited the reaction from progressing to completion in 24 hours, however extension of the reaction time provided for increased chemical yield (64-80%) of the two diastereomeric products **101f** and **102f** in a ratio of 59:41 which were subsequently chromatographically separated (entries 4 and 5).

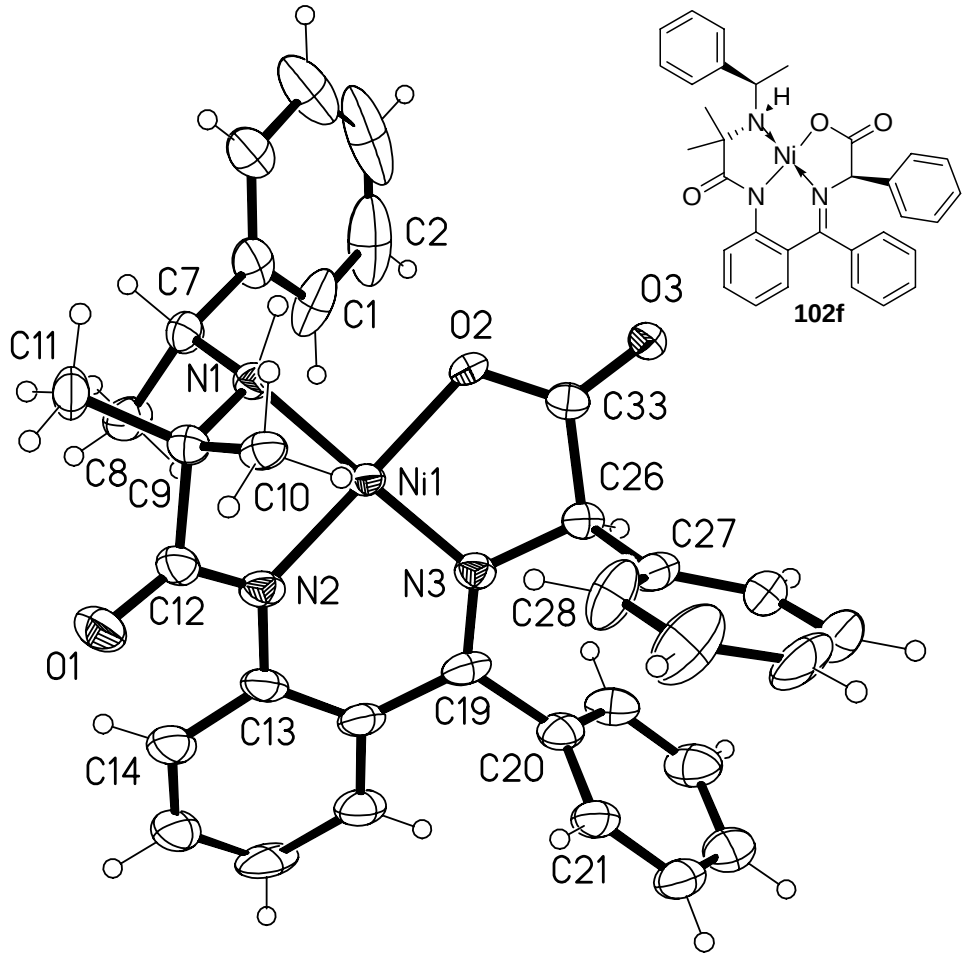
Figure 13. X-Ray Crystal Structure of Ni(II) Complex **101f**



101f

The stereochemical assignments were made according to analysis of the X-ray crystal structure of the major **101f** and minor **102f** diastereomers of the Ni(II) complexes derived from the *R*-1-phenyl-ethylamine derived modular 'NH' ligand and phenyl glycine (Figures 13 and 14).

Figure 14. X-Ray Crystal Structure of Ni(II) Complex **102f**

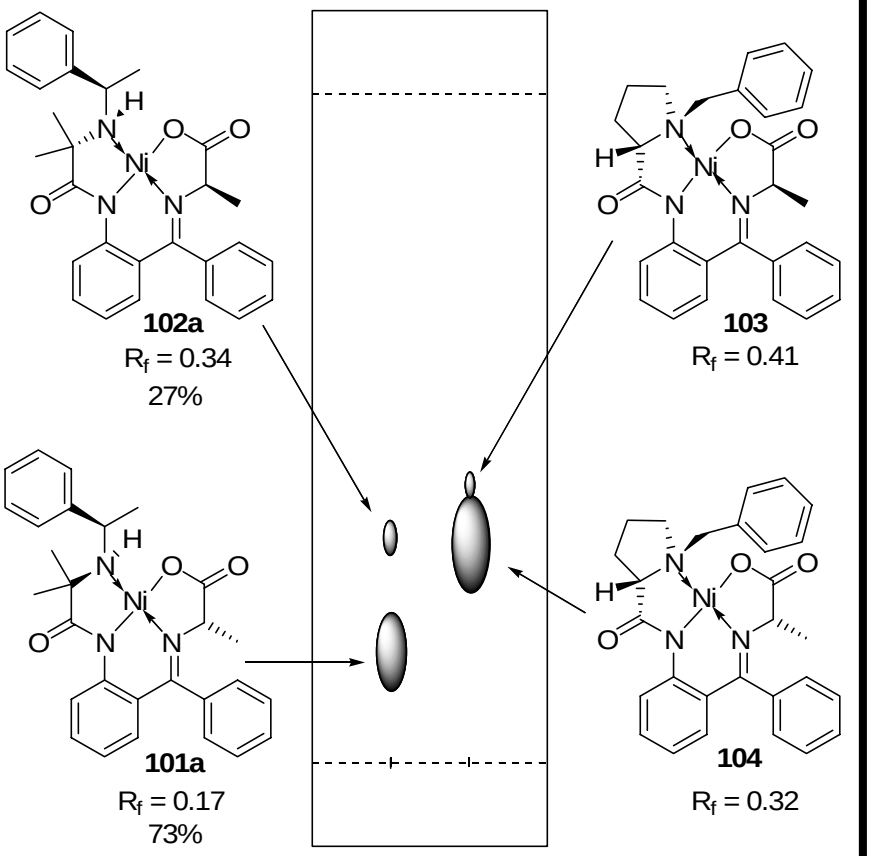


3.6.2.2 Chromatographic Separation of Diastereomeric Ni(II) Complexes of Racemic α-Amino Acids and the Optically Active 'NH' Derived (*R*)-1-Phenyl-Ethylamine Ligand and Their Comparisons With an Alternative Resolving Agent With Multiple Stereogenic Centers

Although the separation of some of the racemic amino acids into their optically pure form was extremely straightforward given the selectivity of the Ni(II) complex formed (Table 26, entries 2 and 3), others required further chromatographic separation of the diastereomeric products to complete their resolution. The ease of these separations is of paramount importance when considering the practicality of this process. However in all examples studied, the difference in retention factor (R_f) values of each of the diastereomers was substantial thus providing for their separation without complication. Moreover, when compared to similar α-amino acid resolving agents with two fixed stereogenic centers, the advantageous qualities of these modular resolving agents which employ the most favorable stereochemical characteristics becomes apparent. As a representative example, the diastereomeric Ni(II) complexes derived from *N*-benzyl-proline and phenyl alanine **103** and **104** were subjected to thin layer silica gel chromatography using 4:1 chloroform:acetone[86] and compared with the chromatograph provided by the separation of the diastereomers of the (*R*)-1-phenyl-ethylamine derived Ni(II) complex of phenyl alanine **101a** and **102a** with 4:1 dichloromethane:acetone as the eluent. As one can see the from Figure 15, the difference in R_f for the diastereomers of the (*R*)-1-phenyl-ethylamine derived Ni(II) complex of phenylalanine **101a** and **102a** is

significantly greater than that of the analogous diastereomers from the *N*-benzyl-proline derived Ni(II) complexes **103** and **104**.

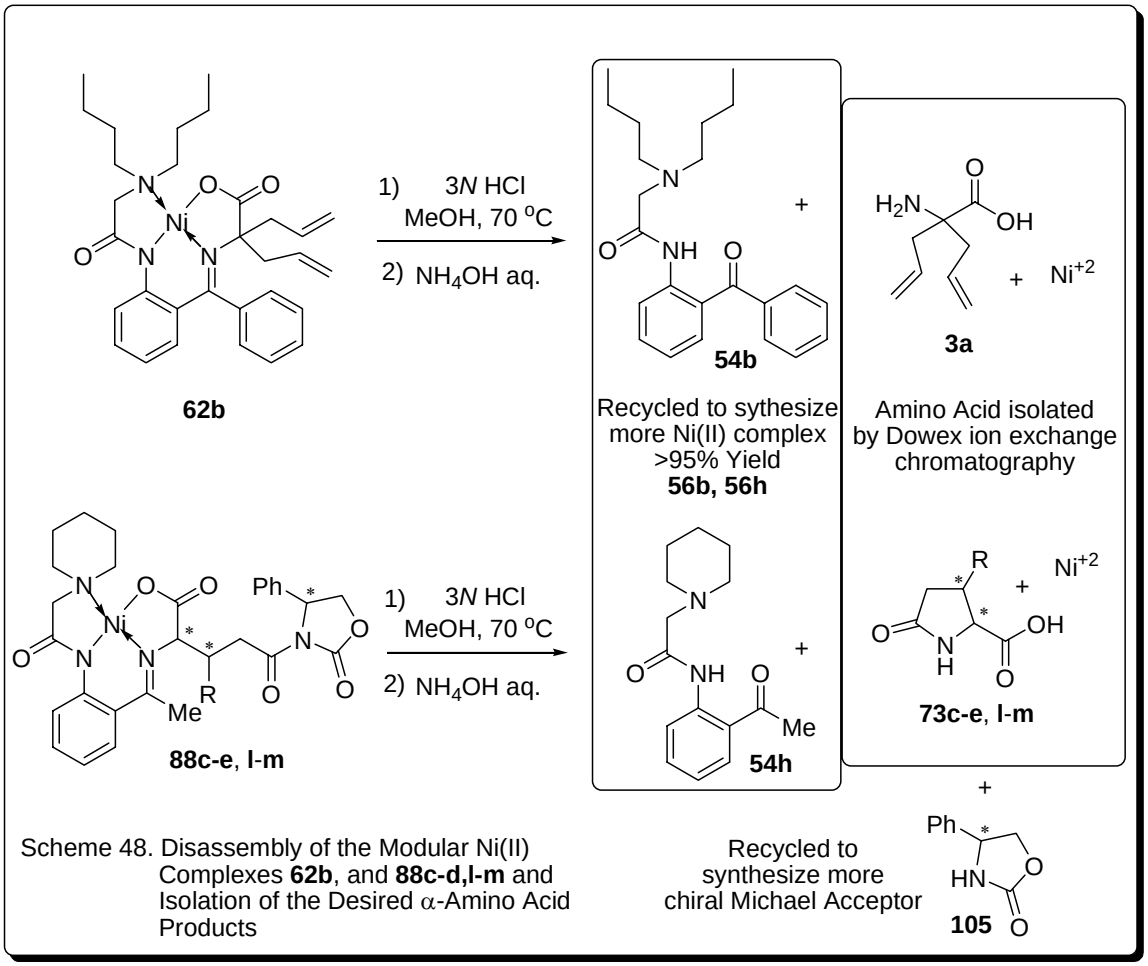
Figure 15. Thin Layer Chromatographic Separation of Diastereomeric Resolving Reagents **101a**,**102a** and **103**,**104**



In summary, a new optically active resolving agent has been investigated for the resolution of α-amino acids via stereoselective transformation to the corresponding diastereomeric Ni(II) complex or the chromatographic separation of the corresponding diastereomers. The chiral resolving agent contains a configurationally stable carbon and a configurationally unstable nitrogen stereogenic center, which has been shown to lead to the formation of diastereomeric products with optimal stereochemical differences,

therefore providing a general and practical approach to the chemical resolution of enantiomers of various α-amino acids with limited difficulty.

3.7 Disassembly of the Modular Ni(II) Complexes and Isolation of the Desired α-Amino Acid Products



Scheme 48. Disassembly of the Modular Ni(II) Complexes **62b**, and **88c-d,l-m** and Isolation of the Desired α-Amino Acid Products

Although the chemical stability that has been referred to throughout this manuscript might lead one to believe that the disassembly of the modular Ni(II)

complexes **56** might be difficult, however it turns out to be rather simple and straightforward assuming the appropriate conditions are employed, as the Ni(II) complex will disassemble under sufficiently concentrated aqueous acids. Therefore, 3 N hydrochloric acid will suffice to disassemble the complexes which are typically in a solution of warm methanol for purposes of solubility (Scheme 48). Once the complex has been disassembled into its individual pieces (the target amino acid, metal ions, and the ligand), the solution is treated with ammonium hydroxide to quench the hydrochloric salt of the organic soluble ligand which can be recovered by extraction into methylene chloride and reused to form a new potion of the modular Ni(II) complexes **56** in nearly quantitative yield, extinguishing any concern about the poor atom economy of this methodology. The addition of the ammonium hydroxide solution plays an additional role in the case of the disassembled Michael adducts as it catalyzes the ring closure and release of the chiral auxiliary **105** which can be reused to form a new portion of chiral Michael acceptors **84**. The resulting aqueous solution of the amino acids and Ni(II) ions may be subjected to ion-exchange chromatography for purposes of isolation of the free amino acid **3a**, **73c-e**,**l-m** in 82-94% yield.

3.8 Experimental Section

3.8.1 General Considerations

Unless specified all reactions were carried out under an atmosphere of nitrogen with magnetic stirring, using commercially available solvents. TLC was performed using

aluminum backed TLC Plates with Silica Gel 60 F_{254} from Merk. Column chromatography was performed using Silica Gel 300-300 mesh from Natland International Corporation. HPLC analysis was performed on a Shimadzu LC-10AT liquid chromatograph with a Shimadzu SPD-10AV UV/Vis detector (λ = 254 nm) or a Jasco PU-1580 Intelligent HPLC pump with a Jasco UV-1575 Intelligent UV/Vis detector (λ = 254 nm). Optical rotation was assigned by an AutoPol III automatic polarimeter by Rudolph Research. Exact masses were obtained with a micromass Q-TOF electrospray ionization (ESI) instrument (Waters, UK) and processed using the MassLynx 3.5 software package. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian Mercury 300 or Varian Unity Inova-400 spectrometers, and were referenced with an internal standard of TMS, for ^{1}H and ^{13}C spectra or $CFCl_3$, and C_6F_6 for ^{19}F NMR spectra. Melting points were obtained with a Mel-Temp apparatus with a Fluke 50S digital thermometer and are uncorrected.

3.8.2 Synthesis of Modular Ni(II) Glycine Equivalents and Associated Ligands

Condensation of phenone module 50a-e and acid module 51a,b Yielding *N*-(2-benzoyl/acetyl-phenyl)-2-bromo-acetamides 52a-f. General Procedure: A solution of acid module **51a,b** (104.64 mmol) in Acetonitrile (2 mL/1 g of **51a,b**) was slowly added to a slurry of phenone module **50a-e** (102.32 mmol) and potassium carbonate 70.71 g (511.6 mmol) in Acetonitrile 240 mL. The reaction was stirred at ambient temperature (room temperature water bath) for one hour, and upon completion (monitored by TLC),

the acetonitrile was evaporated under vacuum. Water 200 mL was then added to the crude mixture and extracted with dichloromethane 200 mL three times. The organic portions were combined, dried and concentrated under vacuum to afford the corresponding α-bromoamide product **52a-f** in 98% yield and greater than 99% chemical purity.

***N*-(2-benzoyl-phenyl)-2-bromo-acetamide 52a:**[66,70] M.p. 71.7 °C. ^{1}H NMR δ 4.20 (2 H, s), 7.15 (1 H, m), 7.43-7.53 (2 H, m), 7.53-7.63 (3 H, m), 7.63-7.75 (2 H, m), 8.61 (1 H, dd, *J* = 8.80, 1.17 Hz), 11.6 (1 H, bs). ^{13}C NMR δ 43.0, 121.3, 122.9, 124.0, 128.1, 129.8, 132.4, 133.3, 133.9, 138.1, 139.0, 165.1, 198.8. HRMS [M+Na^{+}] found *m/z* 339.9955, calcd for $C_{15}H_{12}BrNNaO_2$ 339.9949. mp 105.8 °C.

***N*-(2-acetylphenyl)-2-bromoacetamide 52b:**[66,70] M.p. 75.1 °C. ^{1}H NMR δ 2.69 (3 H, s), 4.19 (2 H, s), 7.19 (1 H, m), 7.59 (1 H, m), 7.93 (1 H, dd, *J* = 7.91, 1.61 Hz), 8.73 (1 H, dd, *J* = 8.50, 1.17 Hz), 12.5 (1 H, bs). ^{13}C NMR δ 28.5, 43.2, 120.6, 122.3, 123.2, 131.4, 134.8, 139.5, 165.5, 202.2. HRMS [M+Na^{+}] found *m/z* 277.9784, calcd for $C_{10}H_{10}BrNNaO_2$ 277.9793.

***N*-(2-benzyol-4-chlorophenyl)-2-bromoacetamide 52c:** M.p. 84.9 °C. ^{1}H NMR δ 4.05 (2 H, s), 7.53-7.61 (4 H, m), 7.64 (1 H, tt, *J* = 7.5, 1.5 Hz), 7.75-7.79 (2 H, m), 8.61 (1 H, d, *J* = 9.9 Hz). ^{13}C NMR δ 29.4, 123.1, 125.5, 128.4, 128.7, 130.1, 132.7, 133.2, 133.9, 137.6, 137.9, 165.0, 197.9. HRMS [M+Na^{+}] found *m/z* 373.9427, calcd for $C_{16}H_{12}BrClNNaO_2$ 372.9601.

***N*-(2-(3,5-di(1,1,1-trifluoromethyl)-benzoyl)-phenyl)-2-bromoacetamide 52d:** M.p. 58.2 ^{o}C. ^{1}H NMR δ 4.04 (2 H, s), 7.22 (2 H, m), 7.49 (1 H, dd, *J* = 7.2, 1.2 Hz), 7.70 (1 H, td, *J* = 8.7, 1.2 Hz), 8.11 (1 H, s), 8.17 (2 H, s), 8.66 (1 H, d, *J*= 8.7 Hz), 11.37 (1

H, s). ^{13}C NMR δ 29.4, 122.1, 122.8 (2 C, q, *J* = 271.28 Hz), 125.8, 129.8, 132.5 (2 C, q, *J* = 75.25 Hz), 132.6, 133.0, 135.5, 140.0, 140.41, 165.1, 196.1. ^{19}F NMR δ -62.92. HRMS [M+Na$^+$] found *m/z* 475.9710, calcd for $C_{17}H_{10}BrF_6NNaO_2$ 475.9691.

***N*-(2-(4-(1,1,1-trifluoromethyl)-benzoyl-phenyl)-2-bromoacetamide 52e:** M.p. 67.3 ^{o}C. ^{1}H NMR δ 4.03 (2 H, s), 7.17 (1 H, td, *J* = 8.1, 0.6 Hz), 7.54 (1 H, dd, *J* = 8.1, 1.8 Hz), 7.65 (1 H, td, *J* = 8.4, 1.2 Hz), 7.75-7.88 (4 H, m), 8.69 (1 H, dd, *J* = 8.1, 0.6 Hz), 11.50 (1 H, s). ^{13}C NMR δ 121.8, 123.2, 123.3, 125.4, 125.5, 125.6, 130.1, 130.3, 133.5, 134.0 (1 C, q, *J* = 32.85 Hz), 134.9, 139.9, 141.6, 165.1, 198.2. ^{19}F NMR δ -63.08. HRMS [M+Na$^+$] found *m/z* 407.9932, calcd for $C_{16}H_{11}BrF_3NNaO_2$ 407.9817.

***N*-(2-benzyolphenyl)-2,2-dimethyl-2-bromoacetamide 52f:** M.p. 79.8 °C. ^{1}H NMR δ 2.08 (6 H, s), 2.70 (3 H, s), 7.17 (1 H, ddd, *J* = 8.00, 7.32, 1.17 Hz), 7.59 (1 H, dddd, *J* = 8.50, 7.32, 1.57, 0.39 Hz), 7.94 (1 H, dd, *J* = 8.01, 1.57 Hz), 8.74 (1 H, dd, *J* = 8.50, 1.17 Hz), 12.5 (1 H, bs). ^{13}C NMR δ 28.5, 31.8, 60.1, 120.6, 122.3, 122.9, 131.7, 135.1, 140.6, 171.3, 202.7. HRMS [M+H$^+$] found *m/s* 284.1122, calcd for $C_{12}H_{15}BrNO_2$ 284.0286.

Alkylation of Secondary Amines With *N*-(2-benzyoly/acetyl-phenyl)-2-bromo-acetamide 52a-f, Yielding the Corresponding *N*-(2-benzoyl/acetyl-phenyl)-2-dialkylamino-acetamide 54a-l. General Procedure. To a slurry of *N*-(2-benzoyl/acetyl-phenyl)-2-bromo-acetamide **52a-f** (1 equiv) and potassium carbonate (1.2 equiv) in Acetonitrile (10 mL/1g of *N*-(2-benzoyl/acetyl-phenyl)-2-bromo-acetamide) was added the corresponding secondary amine **53a-f** (1.1 equiv). The reaction was allowed to proceed for 2 hours at 60-70^o C (monitored by TLC) before the reaction mixture was concentrated under vacuum. Water was added to the viscous liquid,

followed by extraction with dichloromethane. The organic portions were combined, dried with magnesium sulfate, and concentrated in a vacuum to afford the corresponding *N*-(2-benzoyl/acetyl-phenyl)-2-dialkylamino-acetamide **54a-l** in nearly quantitative yield and high chemical purity >99%.

***N*-(2-benzoyl-phenyl)-2-dimethylamino-acetamide 54a:**[66] M.p. 96.2 °C. ^{1}H NMR δ 2.38 (6 H, s), 3.10 (2 H, s), 7.08 (1 H, m), 7.40-7.65 (6 H, m), 7.70-7.80 (2 H, m), 8.64 (1 H, d, *J* = 8.30 Hz), 11.5 (1 H, bs). ^{13}C NMR δ 45.9, 63.9, 121.4, 122.0, 124.5, 128.0, 129.6, 132.1, 132.6, 133.3, 138.3, 138.9, 170.0, 197.8. HRMS [M] found *m/z* 283.1358, calcd for $C_{17}H_{18}N_2O_2$ 283.1368.

***N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 54b:**[66,70] ^{1}H NMR δ 0.78 (6 H, t, *J* = 7.5 Hz), 1.25 (4 H, s, *J* = 7.5 Hz), 1.46 (4 H, p, *J* = 7.5 Hz), 2.51 (4 H, t, *J* = 7.5 Hz), 3.17 (2 H, s), 7.09 (1 H, dt, *J* = 8.1, 1.2 Hz), 7.45-7.61 (4 H, m), 7.77 (1 H, d, *J* = 8.7 Hz), 8.63 (1H, d, *J* = 8.7 Hz), 11.38 (1H, bs). ^{13}C NMR δ 14.2, 20.8, 29.5, 55.7, 59.9, 122.0, 122.5, 126.1, 128.5, 130.3, 132.3, 132.8, 133.3, 138.6, 139.0, 172.3, 197.9. HRMS [M+H^{+}] found *m/z* 367.2251, calcd for $C_{23}H_{31}N_2O_2$ 367.2380.

***N*-(2-benzoyl-phenyl)-2-dibenzylamino-acetamide 54c:**[66,70] M.p. 136.9 °C. ^{1}H NMR δ 3.20 (2 H, s), 3.61 (4 H, s), 6.93 (1 H, t, *J* = 8.57 Hz), 7.03-7.16 (6 H, m), 7.34-7.44 (4 H, m), 7.44-7.54 (5 H, m), 7.76-7.83 (2 H, m), 8.67 (1 H, d, *J* = 8.79 Hz) 11.5 (1 H, bs). ^{13}C NMR δ 58.2, 59.0, 120.9, 121.4, 124.3, 126.7, 127.7, 128.7, 129.6, 131.6, 132.1, 132.6, 136.9, 137.6, 138.5, 170.0, 197.1. HRMS [M+H^{+}] found *m/z* 435.1925, calcd for $C_{29}H_{27}N_2O_2$ 435.1994.

***N*-(2-benzoyl-phenyl)-2-piperidino-acetamide 54d:**[66,70] M.p. 111.5 °C. ^{1}H NMR δ 1.40-1.50 (2 H, m), 1.72 (4 H, m), 2.50 (4 H, m), 3.09 (2 H, s), 7.09 (1 H, dd, *J* =

7.82, 7.32 Hz), 7.40-7.65 (5 H, m), 7.70-7.80 (2 H, m), 8.63 (1 H, dd, *J* = 8.31, 1.10 Hz), 11.5 (1 H, bs). ^{13}C NMR δ 23.8, 25.8, 54.9, 63.1, 121.4, 121.9, 125.0, 127.9, 129.7, 132.1, 132.1, 132.9, 138.1, 138.7, 170.4, 197.1. HRMS [M+Na$^+$] found *m/z* 345.1472, calcd for $C_{20}H_{22}N_2NaO_2$ 345.1579.

***N*-(2-benzoyl-phenyl)-2-morphalino-acetamide 54e:**[66] M.p. 93.8 °C. ^{1}H NMR δ 2.60 (4 H, m), 3.17 (2H, s), 3.87 (4 H, m), 7.10 (1 H, m), 7.40-7.65 (5 H, m), 7.70-7.80 (2 H, m), 8.66 (1 H, dd, *J* = 8.42, 1.22 Hz), 11.7 (1 H, bs). ^{13}C NMR δ 53.7, 62.6, 66.7, 121.3, 122.0, 124.5, 128.0, 129.8, 132.3, 132.4, 133.2, 138.1, 138.7, 169.4, 197.5 HRMS [M+Na$^+$] found *m/z* 347.0980, calcd for $C_{19}H_{20}N_2NaO_3$ 324.3738.

***N*-(2-benzoyl-phenyl)-2-indolylamino-acetamide 54f:**[66] M.p. 152.4 °C. ^{1}H NMR δ 3.56 (2 H, s), 4.13 (4 H, s), 7.09 (1 H, ddd, *J* = 7.82, 7.32, 1.22 Hz), 7.12-7.25 (4 H, m), 7.35-7.43 (2 H, m), 7.46-7.59 (3 H, m), 7.62-7.68 (2 H, m), 8.61 (1 H, dd, *J* = 8.43, 1.10 Hz), 11.4 (1 H, bs). ^{13}C NMR δ 59.8, 60.8, 121.6, 122.0, 122.2, 125.0, 126.5, 127.9, 129.6, 132.1, 132.3, 133.1, 138.0, 138.6, 139.2, 169.9, 197.5. HRMS [M+Na$^+$] found *m/z* 379.1281, calcd for $C_{23}H_{20}N_2NaO_2$ 379.1423.

***N*-(2-acetyl-phenyl)-2-dibutylamino-acetamide 54g:** ^{1}H NMR δ 0.89 (3 H, t, *J* = 7.2 Hz), 1.32 (4 H, s, *J* = 7.2 Hz), 1.48-1.58 (4 H, m), 2.55-2.64 (4 H, m), 2.65 (3 H, s), 3.22 (2 H, s), 7.12 (1 H, td, *J* = 8.4, 1.2 Hz), 7.54 (1 H, td, *J* = 8.7, 1.5 Hz), 7.88 (1 H, dd, *J* = 8.4, 1.5 Hz), 8.84 (1 H, dd, *J* = 8.4, 1.2 Hz), 12.42 (1 H, s). ^{13}C NMR δ 14.1, 20.1, 28.6, 29.2, 55.5, 59.9, 121.0, 122.4, 123.2, 131.3, 134.5, 139.9, 172.8, 201.1. HRMS [M+Na$^+$] found *m/z* 327.2008, calcd for $C_{18}H_{28}N_2NaO_2$ 327.2048.

***N*-(2-acetyl-phenyl)-2- piperidino-acetamide 54h:**[66] M.p. 59.2 °C. ^{1}H NMR δ 1.43-1.47 (2 H, m), 1.76 (4H, quin., *J* = 5.7 3.12 (2 H, s), 7.11 (1 H, dt, *J* = 1.2, 6.9 Hz),

7.53 (1 H, dt, *J* = 1.2, 7.5 Hz), 7.87 (1 H, dd, *J* = 1.2, 8.3), 8.84 (1 H, dd, *J* = 0.9, 8.5 Hz), 12.45 (1 H, bs). ^{13}C NMR δ 23.76, 25.66, 28.53, 29.54, 54.96, 63.59, 120.79, 122.24, 122.88, 131.20, 134.36, 139.80, 171.24, 200.99. HRMS [M+Na$^+$] found *m/s* 283.1403, calcd for $C_{15}H_{20}N_2NaO_2$ 283.1423.

***N*-(2-benzoyl-4-chlorophenyl)-2-dibutylamino-acetamide 54i:** ^{1}H NMR δ 0.80 (3 H, t, *J* = 1.5 Hz), 1.16 (4 H, s, *J* = 7.5 Hz), 1.41-1.51 (4 H, m), 2.52 (4 H, t, *J* = 7.5 Hz), 3.18 (2 H, s), 7.44 (1 H, d, *J* = 2.7 Hz), 7.49-7.54 (3 H, m), 7.63 (1 H, t, *J* = 7.2 Hz), 7.79 (2 H, dd, *J* = 6.9, 1.8 Hz), 8.63 (1 H, d, *J* = 8.7 Hz), 11.29 (1 H, s). ^{13}C NMR δ 14.0, 20.5, 29.3, 55.4, 59.6, 123.2, 127.2, 127.4, 128.5, 130.1, 131.2, 132.8, 133.1, 137.2, 137.6, 172.0, 196.3. HRMS [M+Na$^+$] found *m/s* 423.1559, calcd for $C_{23}H_{29}ClN_2NaO_2$ 423.1815.

***N*-(2-benzoyl-4-chlorophenyl)-2-piperidinamino-acetamide 54j:** M.p. 132.6 ^{o}C. ^{1}H NMR δ 1.49-1.53 (2 H, m), 1.68-1.76 (4 H, m), 2.50-2.54 (4 H, m), 3.11 (2 H, s), 7.48-7.57 (4 H, m), 2.66 (1 H, m), 2.79-2.82 (2 H, m), 8.65 (1 H, d, *J* = 9.0 Hz), 11.47 (1 H, s). ^{13}C NMR δ 23.8, 25.9, 55.1, 63.2, 123.2, 126.7, 127.4, 128.6, 130.1, 131.6, 133.0, 137.5, 137.7, 170.9, 196.4. HRMS [M+Na$^+$] found *m/s* 379.1568, calcd for $C_{20}H_{21}ClN_2NaO_2$ 379.1189.

***N*-(2-(3,5-(1,1,1-trifluoromethyl)benzoyl)-phenyl)-2-dibutylamino-acetamide 54k:** ^{1}H NMR δ 0.85 (6 H, t, *J* = 7.2 Hz), 1.31 (4 H, s, *J* = 7.2 Hz), 1.47-1.57 (4 H, m), 2.58 (4 H, t, *J* = 7.5 Hz), 3.23 (2 H, s), 7.19 (1 H, td, *J* = 7.2, 0.9 Hz), 7.42 (1 H, dd, *J* = 6.3, 0.9 Hz), 7.67 (1 H, td, *J* = 8.7, 1.5 Hz), 8.13 (1 H, s), 8.24 (2 H, s), 8.69 (1 H, dd, *J* = 8.7, 0.9 Hz), 11.49 (1 H, s). ^{13}C NMR δ 14.0, 20.6, 29.4, 55.5, 59.7, 122.3, 122.7, 122.9 (2 C, q, *J* = 271.28 Hz), 124.1, 125.6, 125.7, 129.8, 131.9, 132.1 (2 C, q, *J* = 33.75 Hz),

134.5, 139.4, 140.4, 172.2, 194.5. 19F NMR δ -161.74. HRMS [M+H^+] found *m/s* 503.2115, calcd for $C_{25}H_{29}F_6N_2O_2$ 503.2129.

***N*-(2-(4-(1,1,1-trifluoromethyl)-benzoyl-phenyl)-2-dibutylamino-acetamide 54l:** ^{1}H NMR δ 0.83 (3 H, t, *J* = 7.2 Hz), 1.29 (4 H, s, *J* = 7.2 Hz), 1.45-1.55 (4 H, m), 2.56 (4 H, t, *J* = 7.2 Hz), 3.22 (2 H, s), 7.13 (1 H, td, *J* = 7.5, 0.6 Hz), 7.46 (1 H, dd, *J* = 7.5, 1.8 Hz), 7.61 (1 H, td, *J* = 8.4, 1.5 Hz), 7.77 (2 H, d, *J* = 8.4 Hz), 7.89 (2 H, d, *J* = 8.7 Hz), 8.69 (1 H, d, *J* = 8.7 Hz), 11.56 (1 H, s). ^{13}C NMR δ 14.0, 20.5, 55.4, 59.7, 121.9, 122.4, 125.1, 125.3, 125.4, 125.5, 130.1, 132.3, 133.8 (1 C, q, *J* = 32.3 Hz), 134.0, 139.3, 141.7, 172.2, 196.6. HRMS [M+Na^+] found *m/s* 457.2078, calcd for $C_{24}H_{29}F_3N_2NaO_2$ 457.2073.

Alkylation of Primary Amines With *N*-(2-benzyolphenyl)-2-bromo-acetamide 52a or *N*-(2-benzyolphenyl)-2,2-dimethyl-2-bromo-acetamide 52f, Yielding the Corresponding *N*-(2-benzoylphenyl)-2-alkylamino-acetamides 54m-o or *(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 54q. General Procedure: To a solution of **52a,f** (1 equiv) and Acetonitrile (10 mL/1g of **52a,f**) was added the corresponding primary amine **53g-j** (5 equivalents). The reaction was allowed to proceed for 24 hours at 60-70 ^{o}C (monitored by TLC) before the reaction mixture was concentrated under vacuum. Water was added to the viscous liquid, followed by extraction with dichloromethane. The organic portions were combined, dried with magnesium sulfate, and concentrated in a vacuum to afford the corresponding alkylamino-acetamide product **54m-o** in nearly quantitative yield and high chemical purity >99% or *(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide **54p** in moderate chemical yield and purity.

***N*-(2-benzoylphenyl)-2-benzylamino-acetamide 54m**:[69] ^{1}H NMR δ 1.95 (1 H, bs), 3.45 (2 H, s), 3.86 (2 H, s), 7.10 (1 H, t, *J* = 7.2 Hz), 7.13-7.29 (3 H, m), 7.03-7.43 (2 H, m), 7.46-7.60 (5 H, m), 7.77 (2 H, d, *J* = 8.4 Hz), 8.64 (1 H, d, *J* = 8.4 Hz), 11.66 (1 H, bs). ^{13}C NMR δ 52.9, 54.1, 121.7, 122.3, 124.8, 125.6, 125.7, 127.3, 127.4, 128.3, 128.5, 128.5, 130.2, 132.6, 132.8, 133.7, 138.5, 139.1, 139.3, 171.2, 198.3. HRMS [M+Na^{+}] *m/s* expected for $C_{22}H_{20}N_2NaO_2$ is 367.1417, found 367.1103.

***N*-(2-benzoylphenyl)-2-*iso*-propylamino-acetamide 54n**:[69] ^{1}H NMR δ 1.24 (6 H, d, *J* = 6.3 Hz), 3.09 (1 H, hept., *J* = 6.3 Hz), 3.63 (2 H, s), 7.12 (1 H, t, *J* = 7.8 Hz), 7.45-7.62 (5 H, m), 7.74 (2 H, d, *J* = 8.1 Hz), 8.51 (1 H, d, *J* = 8.4 Hz), 11.46 (1 H, bs). ^{13}C NMR δ 22.9, 49.6, 51.2, 121.6, 122.2, 125.0, 128.3, 128.4, 130.0, 130.1, 132.5, 132.7, 133.5, 138.5, 139.2, 172.4, 198.1. HRMS [M+H^{+}] *m/s* expected for $C_{18}H_{21}N_2O_2$ is 297.1598, found 297.1601.

***N*-(2-benzoylphenyl)-2-*tert*-butylamino-acetamide 54o**:[69] ^{1}H NMR δ 1.16 (9 H, s), 3.42 (2 H, s), 7.09 (1 H, t, *J* = 8.1 Hz), 7.44-7.61 (5 H, m), 7.75 (2 H, d, *J* = 6.9 Hz), 8.61 (1 H, d, *J* = 8.4 Hz), 11.67 (1 H, bs). ^{13}C NMR δ 28.8, 47.1, 51.2, 121.5, 122.2, 125.2, 128.3, 130.1, 132.5, 132.6, 133.5, 138.6, 139.1, 173.0, 198.0. HRMS [M+H^{+}] *m/s* expected for $C_{19}H_{23}N_2O_2$ is 311.1754, found 311.1715.

***(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 54p:** ^{1}H NMR δ 1.36 (3 H, d, J = 6.6 Hz), 1.37 (3 H, s), 1.43 (3 H, s), 1.75 (1 H, s), 4.00 (1 H, q, J = 6.6 Hz), 7.12 (1 H, td, J = 7.8, 1.2 Hz), 7.18 (1 H, m), 7.24-7.30 (2 H, m), 7.47-7.51 (2 H, m), 7.56-7.58 (4 H, m), 7.64 (1 H, m), 7.84 (2 H, d, J = 6.9 Hz), 8.65 (1 H, d, J = 8.7 Hz), 11.84 (1 H, s). ^{13}C NMR δ 24.2, 25.3, 28.4, 54.4, 59.8, 121.2, 121.9, 124.7, 126.7, 126.8, 128.3, 128.4, 130.2, 132.6, 132.8, 133.6, 138.6, 139.8, 147.0, 177.6,

198.0. HRMS [M+H$^+$] found *m/s* 387.2021, calcd for $C_{25}H_{27}N_2O_2$ 387.2068. $[\alpha]_D^{25}$ +3053 (*c* 0.02, $CHCl_3$).

Synthesis of the Ni(II) complexes of glycine Schiff bases with N-(2-benzyoly/acetyl-phenyl)-2-alkylamino-acetamides 56a-o. General Procedure. A solution of potassium hydroxide (10 equivalents) in methanol (7 mL/1 g of KOH) was added to a suspension of *N*-(2-benzyoly/acetyl-phenyl)-2-alkylamino-acetamides **54a-o** (1 equiv), glycine (5 equivalents), nickel nitrate hexahydrate (2 equivalnets) in methanol (10 mL/1 g of **54a-o**) at 60-70^o C. Upon complete consumption of the *N*-(2-benzyoly/acetyl-phenyl)-2-alkylamino-acetamides **54a-o**, monitored by TLC, the reaction mixture was poured over slurry of ice and 5% acetic acid. After the complete precipitation, product **56a-o** was filtered and dried, in an low temp oven (50^o C) overnight. The product was obtained in high chemical yield (99%) and high chemical purity without further purification.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-benzyoly-phenyl)-2-methylamino-acetamide 56a:[66] M.p. >290 °C. ^{1}H NMR δ 2.60 (6 H, s), 3.44 (2 H, s), 3.71 (2 H, s), 6.80 (1 H, ddd, *J* = 8.06, 7.08, 1.10 Hz), 6.89 (1 H, dd, *J* = 8.06, 1.46 Hz), 7.02-7.08 (2 H, m), 7.35 (1 H, ddd, *J* = 8.67, 7.08, 1.71 Hz), 7.48-7.56 (3 H, m), 8.64 (1 H, dd, *J* = 8.54, 1.10 Hz). ^{13}C NMR δ 49.6, 61.1, 67.7, 121.3, 124.1, 125.2, 125.8, 129.5, 129.6, 132.6, 133.5, 134.4, 142.3, 171.9, 176.0, 177.2. HRMS [M+Na$^+$] found *m/s* 418.0825, calcd for $C_{19}H_{19}N_3NaNiO_3$ 418.0678.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-benzyoly-phenyl)-2-dibutylamino-acetamide 56b:[66,70] M.p. 174.9 °C. ^{1}H NMR δ 1.08 (6 H, t, *J* = 7.2 Hz), 1.44-1.64 (4 H, m), 2.17-2.37 (4 H, m), 2.86 (2 H, dt, *J* = 12.6, 4.5 Hz), 3.04-3.17 (2 H,

m), 3.38 (2 H, s), 3.74 (2 H, m), 6.80 (1 H, m), 6.90 (1 H, dd, *J* = 8.1, 1.8 Hz), 7.08-7.11 (2H, m), 7.36 (1H, m), 7.51-7.57 (3H, m), 8.70 (1H, d, *J* = 8.4 Hz). ^{13}C NMR δ 14.3, 21.0, 29.3, 60.5, 61.5, 62.2, 121.4, 124.5, 125.5, 126.2, 129.8, 132.8, 133.8, 135.0, 142.8, 172.0, 177.5, 179.0. HRMS [M+H$^+$] found *m/s* 480.1779, calcd for $C_{25}H_{31}N_3NaNiO_3$ 480.1792.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-benzyoly-phenyl)-2-dibenzylamino-acetamide 56c:[66,70] M.p. 278.9 °C (decomp.). ^{1}H NMR δ 3.43 (2 H, s), 3.53 (2 H, d, *J* = 12.7 Hz), 3.79 (2 H, s), 4.53 (3 H, d, *J* = 12.5 Hz), 6.66 (1 H, ddd, *J* = 8.18, 6.96, 1.22 Hz), 6.77 (1 H, dd, *J* = 8.30, 1.71 Hz), 7.00-7.06 (2 H, m), 7.14 (1 H, ddd, *J* = 8.79, 6.84, 1.71 Hz), 7.35-7.55 (9 H, m), 8.02-8.10 (4 H, m), 8.23 (1 H, dd, *J* = 8.79 Hz). ^{13}C NMR δ 59.4, 61.2, 63.3, 120.5, 123.7, 124.5, 125.7, 128.7, 129.0, 129.3, 129.3, 131.9, 131.9, 132.3, 132.8, 134.2, 141.9, 171.3, 176.7, 177.6. HRMS [M+Na$^+$] found *m/s* 570.1669, calcd for $C_{31}H_{27}N_3NaNiO_3$ 570.1304.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-benzyoly-phenyl)-2-piperidino-acetamide 56d:[66,70] M.p. 243.4 °C (decomp.). ^{1}H NMR δ 1.36-1.80 (6 H, m), 3.08-3.22 (2 H, m), 3.28-3.43 (2 H, m), 3.66 (2 H, s), 3.70 (2 H, s), 6.78 (1 H, ddd, *J* = 8.30, 6.96, 1.10 Hz), 6.87 (1 H, dd, *J* = 8.30, 1.71 Hz), 7.00-7.06 (2 H, m), 7.33 (1 H, ddd, *J* = 8.66, 6.84, 1.71 Hz), 7.46-7.58 (3 H, m), 8.53 (1 H, dd, *J* = 8.66, 1.10 Hz). ^{13}C NMR δ 19.7, 22.8, 55.8, 60.5, 61.0, 120.9, 124.0, 125.0, 125.5, 129.2, 132.1, 133.0, 134.2, 142.0, 171.4, 176.4, 176.7. HRMS [M+Na$^+$] found *m/s* 458.1283, calcd for $C_{22}H_{23}N_3NaNiO_3$ 458.0991.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-benzyoly-phenyl)-2-morpholylamino-acetamide 56e:[66] M.p. >240 °C (decomp.). ^{1}H NMR δ 2.59 (2 H, m), 3.55 (2 H, m), 3.68 (2 H, s), 3.78-3.88 (2 H, m), 3.82 (2 H, s), 4.04 (2 H, m), 6.80 (1 H, ddd, *J* = 8.18, 6.96, 1.22 Hz), 6.88 (1 H, dd, *J* = 8.21, 1.83 Hz), 7.00-7.08 (2 H, m), 7.34 (1 H, ddd, *J* = 8.54, 6.83, 1.71 Hz), 7.48-7.58 (3 H, m), 8.42 (1 H, dd, *J* = 8.55, 1.10 Hz). ^{13}C NMR δ 56.2, 60.8, 62.1, 63.7, 121.3, 124.0, 125.2, 125.5, 129.4, 129.4, 132.4, 133.2, 134.0, 141.5, 171.8, 174.0, 176.7. HRMS [M+Na$^+$] found *m/s* 460.0680, calcd for $C_{21}H_{21}N_3NaNiO_4$ 460.0886.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-benzyoly-phenyl)-2-indolylamino-acetamide 56f:[66] M.p. >240 °C (decomp.). ^{1}H NMR δ 3.58 (2 H, s), 3.76 (2 H, s), 3.94 (2 H, d, *J* = 14.7 Hz), 5.03 (2 H, d, *J* = 14.7 Hz), 6.82 (1 H, ddd, *J* = 8.18, 6.96, 1.22 Hz), 6.92 (1 H, dd, *J* = 8.30 1.71 Hz), 7.02-7.10 (2 H, m), 7.18-7.31 (4 H, m), 7.37 (1 H, ddd, *J* = 8.79, 7.08, 1.71 Hz), 7.46-7.58 (3 H, m), 8.62 (1 H, dd, *J* = 8.54 1.10 Hz). ^{13}C NMR δ 61.3, 63.1, 66.3, 121.1, 122.6, 124.0, 125.2, 125.6, 127.9, 129.3, 129.4, 132.4, 133.3, 134.1, 134.6, 142.1, 171.7, 175.8, 176.6. HRMS [M+Na$^+$] found *m/s* 492.0774, calcd for $C_{25}H_{21}N_3NaNiO_3$ 492.0834.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 56h:[66a] M.p. >246.7 °C (decomp.). ^{1}H NMR δ 1.36-1.84 (6H, m), 2.38 (3H, s), 3.10 (2H, d, *J* = 12.9 Hz), 3.31 (2H, t, *J* = 12.3 Hz), 3.60 (2H, s), 4.10 (2H, s), 7.02 (1H, t, *J* = 7.5 Hz), 7.35 (1H, t, *J* = 7.5 Hz), 7.59 (1H, d, *J* = 8.4 Hz), 8.36 (1H, d, *J* = 8.4 Hz). ^{13}C NMR δ 19.05, 19.78, 22.84, 30.89, 55.94, 59.86, 60.66, 121.74, 124.83, 126.51, 129.23, 131.97, 141.38, 169.63, 176.18, 177.05. HRMS [M+Na$^+$] found *m/s* 396.0864, calcd for $C_{17}H_{21}N_3NaNiO_3$ 396.0834.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-benzyoly-4-chlorophenyl)-2-dibutylamino-acetamide 56i: M.p. 203.4 °C. ^{1}H NMR δ 1.09 (6 H, t, *J* = 7.5 Hz), 1.48-1.63 (4 H, m), 2.20-2.36 (4 H, m), 2.89 (2 H, td, *J* = 12.0, 4.5 Hz), 3.12-3.18 (2 H, m), 3.36 (2 H, s), 3.74 (2 H, s), 6.86 (1 H, d, *J* = 2.7 Hz), 7.08-7.11 (2 H, m), 7.30 (1 H, td, *J* = 7.5, 2.7 Hz), 7.57-7.59 (3 H, m), 8.73 (1 H, d, *J* = 9.0 Hz). ^{13}C NMR δ 14.0, 20.8, 29.2, 60.4, 61.5, 61.8, 125.6, 125.8, 125.9, 126.5, 129.9, 130.0, 132.2, 132.4, 134.1, 141.4, 171.1, 177.0, 179.0. HRMS [M+Na^{+}] found *m/s* 536.1405, calcd for $C_{25}H_{30}{}^{Cl}N_3NaNiO_3$ 536.1221.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-(3,5-di(1,1,1-trifluoromethyl)-benzoyl-phenyl)-2-dibutylamino-acetamide 56k: M.p. 153.6 °C. ^{1}H NMR δ 1.05 (6 H, t, *J* = 7.2 Hz), 1.51 (4 H, s, *J* = 7.2 Hz), 2.17-2.32 (4 H, m), 2.81-2.89 (2 H, m), 3.10-3.17 (2 H, m), 3.32 (2 H, s), 3.65 (2 H, s), 6.64 (1 H, d, *J* = 8.1 Hz), 6.81 (1 H, td, *J* = 6.9, 1.2 Hz), 7.36 (1 H, td, *J* = 6.9, 1.5 Hz), 7.63 (2H, s), 8.06 (1 H, s), 8.74 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 14.01, 20.75, 29.20, 60.47, 61.35, 61.81, 121.52, 123.91, 124.04, 124.32, 124.74, 126.50, 132.67, 133.28, 133.44, 133.74, 136.73, 143.32, 168.00, 176.24, 179.04. ^{19}F NMR δ -161.9. HRMS [M+H^{+}] found *m/s* 616.1918, calcd for $C_{27}H_{30}F_6N_3NiO_3$ 616.1540.

Ni(II) Complex of Glycine Schiff Base with *N*-(2-(4-1,1,1-trifluoromethyl)-benzoyl-phenyl)-2-dibutylamino-acetamide 56l: M.p. 167.2 °C. ^{1}H NMR δ 1.09 (6 H, t, *J* = 7.5 Hz), 1.55 (4 H, s, *J* = 7.5 Hz), 2.22-2.38 (4 H, m), 2.85-2.93 (2 H, m), 3.11-3.17 (2 H, m), 3.39 (2 H, s), 3.70 (2 H, s), 6.82 (2 H, m), 7.29 (2 H, d, *J* = 7.2 Hz), 7.39 (1 H, m), 7.85 (2 H, d, *J* = 8.1 Hz), 8.73 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 121.3, 124.5, 124.6, 126.7, 127.0 (2 C, q, *J* = 272.0 Hz), 131.9, 133.2, 138.3, 142.9, 170.1, 176.8, 179.0. ^{19}F

NMR δ -161.7. HRMS [M+Na^+] found *m/s* 570.1329, calcd for $C_{26}H_{30}F_3N_3NaO_3$ 570.1485.

Ni(II) Complex of Glycine Schiff base with *N*-(2-benzoyl-phenyl)-2-benzylamino-acetamide 56m:[69] M.p. >300° C (decomp.). ^{1}H NMR δ 1.95 (1 H, bs), 3.45 (2 H, s), 3.86 (2 H, s), 7.01 (1 H, td, *J* = 7.65, 0.72 Hz), 7.13-7.29 (3 H, m), 7.30-7.60 (7 H, m), 7.62-7.78 (2 H, m), 8.64 (1 H, dd, *J* = 8.4, 0.3 Hz), 11.66 (1 H, bs). ^{13}C NMR δ 52.90, 54.10, 121.68, 122.32, 124.82, 125.55, 125.71, 127.30, 127.40, 128.32, 128.45, 128.48, 130.17, 132.62, 132.82, 133.66, 138.47, 139.12, 139.26, 171.19, 198.32. HRMS expected for $C_{22}H_{20}N_2NaO_2$ is 367.1417, found 367.1103.

Ni(II) Complex of Glycine Schiff base with *N*-(2-benzoyl-phenyl)-2-*iso*-propylamino-acetamide 56n:[69] M.p. 292.3° C (decomp.). ^{1}H NMR δ 1.56 (3 H, d, *J* = 6.3 Hz, 1.66 (3 H, d, *J* = 6.3 Hz), 2.76 (1 H, bs), 3.12 (1 H, dq, *J* = 13.2, 6.3 Hz), 3.29 (1 H, d, *J* = 17.7 Hz), 3.75 (2 H, s), 3.99 (1 H, dd, *J* = 17.7, 7.5 Hz), 6.83 (1 H, m), 6.93 (1 H, m), 7.01 (1 H, m), 7.19 (1 H, m), 7.35 (1 H, m), 7.53-7.59 (3 H, m), 8.55 (1 H, d, *J* = 7.8 Hz). ^{13}C NMR δ 20.57, 21.74, 51.70, 53.33, 60.60, 121.28, 128.34, 125.69, 125.82, 136.24, 129.45, 129.75, 129.88, 132.66, 133.60, 134.66, 142.62, 173.23, 177.88, 177.91, 178.18. HRMS expected for $C_{20}H_{21}N_3NaNiO_3$ is 432.0828, found 432.0837.

Ni(II) Complex of Glycine Schiff base with *N*-(2-benzoyl-phenyl)-2-*tert*-butylamino-acetamide 56o:[69] M.p. >300° C (decomp.). ^{1}H NMR δ 1.54 (9 H, s), 2.60 (1 H, d, *J* = 7.8 Hz), 3.41 (1 H, d, *J* = 17.1 Hz), 3.73 (2 H, d, *J* = 3.9 Hz), 4.17 (1 H, dd, *J* = 17.1, 7.5 Hz), 6.84 (1 H, m), 6.93 (1 H, dd, *J* = 8.1, 1.8 Hz), 6.99 (1 H, m), 7.23 (1 H, m), 7.38 (1 H, m), 7.53-7.60 (3 H, m), 8.37 (1 H, d, *J* = 7.5 Hz). ^{13}C NMR δ 28.02, 50.98, 58.25, 60.42, 121.33, 124.24, 125.71, 126.27, 129.41, 129.79, 129.90, 132.72,

133.50, 134.54, 142.38, 171.74, 177.36, 177.72. HRMS expected for $C_{21}H_{23}N_3NaNiO_3$ is 446.0985, found 446.1015.

3.8.3 Synthesis of α,α-Dialkyl Amino Acids Utilyzing Modular Glycine Equivalents 56b-d

Dialkylation of Ni(II) complexes 56b-d with Activated Alkyl Bromides, 38a-c,g,k, Yielding Complexes 62a-f,63,64. General Procedure. To a solution of sodium *tert*-butoxide (2.5 equiv) in DMF (10 mL/1 g of complex **56b-d**) were added complex **56b-d** (1 equiv) and the corresponding alkylating reagent **38a-c,g,k** (2.5 equiv). The reaction was stirred at ambient temperature (room temperature water bath) for 15 minutes, and upon completion (monitored by TLC), the reaction mixture was poured into ice-water and the resulting precipitate was filtered, washed with water to afford the products **62a-f,63,64** in yields ranging from 92 to 96% and of greater than 99% purity.

Ni(II) Complex of α,α-dibenzylglycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 62a:[66a,70] M.p. 216.8 °C. ^{1}H NMR δ 1.03 (6 H, t, *J* = 7.2 Hz), 1.36-1.52 (4 H, m), 1.59-1.68 (2 H, m), 2.05 (2 H, td, *J* = 12.0, 4.5 Hz), 2.04-2.20 (2 H, m), 2.43 (2 H, td, *J* = 12.0, 4.5 Hz), 2.80 (2 H, AB, *J* = 15.6 Hz), 3.03 (2 H, s), 3.29 (2 H, AB, *J* = 15.6 Hz), 6.68 (2 H, m), 6.89 (2 H, d, *J* = 9.3 Hz), 7.26-7.53 (14H, m), 8.34 (1H, d, *J* = 9.3 Hz). ^{13}C NMR δ 14.1, 20.8, 26.8, 45.8, 56.6, 63.4, 80.9, 121.0, 123.8, 126.8, 127.7, 127.7, 128.5, 128.6, 129.7, 130.2, 132.2, 134.0, 136.3, 137.0, 142.2, 171.6, 176.0, 179.2. HRMS [M+Na$^+$] found *m/s* 660.2764, calcd for $C_{39}H_{44}N_3NiO_3$ 660.2731.

Ni(II) Complex of α,α-diallylglycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 62b:[66a,70] M.p. 176.3 °C. ^{1}H NMR δ 1.05 (6 H, t, *J* = 7.5 Hz), 1.53 (4 H, sp, *J* = 7.5 Hz), 2.16-2.29 (6 H, m), 2.44 (2 H, dd, *J* = 8.1, 7.2 Hz), 2.8 (2 H, dt, *J* = 13.5, 3.7 Hz), 2.98-3.05 (2 H, m), 3.32 (2 H, s), 5.28 (2 H, dd, J = 25.2, 1.5), 5.33 (2 H, dd, *J* = 18.6, 1.5 Hz), 6.10-6.23 (2 H, m), 6.63-6.72 (2 H, m), 7.25-7.30 (3H, m), 7.43-7.55 (3H, m), 8.45 (1H, d, *J* = 9.0 Hz). ^{13}C NMR δ 13.0, 19.8, 28.2, 42.1, 59.2, 60.9, 76.2, 80.4, 118.2, 119.9, 122.9, 126.6, 127.0, 127.4, 128.8, 131.0, 131.3, 132.8, 135.7, 141.0, 171.8, 177.3, 179.7. HRMS [M+Na^{+}] found *m/s* 582.2278, calcd for $C_{31}H_{39}N_3NiO_3$ 582.2237.

Ni(II) Complex of α,α-dicinnamylglycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 62c:[66a, 70] M.p. 184.6 °C. ^{1}H NMR δ 0.83 (6 H, t, *J* = 7.2 Hz), 1.26 (4 H, s, *J* = 7.2 Hz), 1.99-2.14 (4 H, m), 2.31 (2 H, td, *J* = 11.2, 5.1 Hz), 2.43 (4 H, dp, *J* = 11.2, 5.1 Hz), 2.68 (2 H, dd, *J* = 15.0, 5.7 Hz), 2.98 (2 H, s), 6.60-6.62 (3 H, m), 6.69-6.79 (2 H, m), 7.24-7.37 (10 H, m), 7.47-7.59 (7 H, m), 8.41 (1H, d, *J* = 9.3 Hz). ^{13}C NMR δ 14.0, 20.8, 28.0, 42.5, 58.9, 62.6, 77.5, 82.5, 121.3, 124.1, 126.6, 127.9, 128.0, 128.2, 128.9, 130.1, 132.5, 134.0, 134.4, 136.8, 137.5, 142.4, 172.8, 177.4, 180.5. HRMS [M+Na^{+}] found *m/s* 734.2824, calcd for $C_{43}H_{47}NaN_3NiO_3$ 734.2863.

Ni(II) Complex of α,α-dimethylglycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 62d:[66a] M.p. 196.2 °C. ^{1}H NMR δ1.05 (6 H, t, *J* = 7.5 Hz), 1.44 (6 H, s), 1.47-1.59 (4 H, m), 2.21-2.34 (4 H, m), 2.79-2.88 (2 H, m), 2.95-3.05 (2 H, m), 3.39 (2 H, s), 6.71 (1 H, td, *J* = 8.1, 0.9 Hz), 6.80 (1 H, dd, *J* = 8.1, 1.5 Hz), 7.17-7.20 (2 H, m), 7.27 (1 H, td, *J* = 8.7, 1.5 Hz), 7.41-7.49 (3 H, m), 8.43 (1 H, d, *J* = 7.8 Hz). ^{13}C NMR δ 14.03, 20.81, 29.19, 29.23, 60.05, 61.63, 74.36, 120.99, 123.86,

127.58, 128.40, 129.12, 129.33, 131.95, 133.65, 136.36, 141.53, 171.93, 177.98, 182.43. HRMS [M+H$^+$] found *m/s* 508.2090, calcd for $C_{27}H_{36}N_3NiO_3$ 508.2106.

Ni(II) Complex of α,α-dibenzylglycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibenzylamino-acetamide 63:[66a,70] M.p. 332.6 °C (decomp.). ^{1}H NMR δ 2.85 (2 H, d, *J* = 15.7 Hz), 3.06 (2 H, s), 3.28 (2 H, d, *J* = 15.8 Hz), 3.36 (2 H, d, *J* = 13.3 Hz), 3.42 (2 H, d, *J* = 13.3 Hz), 6.52-6.56 (2 H, m), 6.81-6.86 (2 H, m), 7.00 (1 H, m), 7.23-7.60 (19 H, m), 7.69 (1 H, dt, *J* = 7.62, 0.73 Hz), 7.74-7.82 (4 H, m). ^{13}C NMR δ 45.6, 62.6, 62.7, 80.7, 120.4, 123.6, 126.7, 127.3, 127.4, 127.9, 128.5, 128.6, 128.6, 129.4, 130.2, 131.2, 131.3, 132.4, 133.0, 135.7, 137.0, 141.2, 171.1, 175.3, 178.6. HRMS found *m/s* 755.2686, calcd for $C_{47}H_{43}N_3NiO_3$ 755.2703.

Ni(II) Complex of α,α-dibenzylglycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidino-acetamide 64:[66a,70] M.p. 278.2 °C (decomp.). ^{1}H NMR δ 1.23-1.60 (6 H, m), 2.48 (2 H, bd, *J* = 13.6 Hz), 2.71 (2 H, d, *J* = 15.7 Hz), 2.91-3.04 (2 H, m), 3.12 (2 H, s), 3.30 (2 H, d, *J* = 15.7 Hz), 6.58-6.67 (2 H, m), 6.74-6.81 (2 H, m), 7.18-7.50 (14 H, m), 8.27 (1 H, d, *J* = 8.21 Hz). ^{13}C NMR δ 19.7, 22.8, 45.9, 55.3, 60.0, 81.0, 120.7, 123.5, 126.6, 127.3, 127.4, 128.3, 128.5, 129.4, 130.0, 131.9, 133.7, 135.8, 136.8, 142.0, 171.1, 175.2, 178.7. HRMS [M+Na$^+$] found *m/s* 638.1874, calcd for $C_{36}H_{35}N_3NiO_3$ 638.1930.

Phase transfer homologation of Ni(II) Complex of glycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 56b with propargyl bromide 38k. General Procedure: To a solution of **56b** in CH_2Cl_2 (1mL /g) at room temperature was added tetrapropylammonium bromide (0.25 equivalents), 30% sodium hydroxide solution (1mL / mL CH_2Cl_2), and propargyl bromide **38k** (3.5 equivalents). The resultant mixture

was rigorously stirred overnight at room temperature. To the resultant slurry, additional water and CH_2Cl_2 was added and the water was extracted several times with CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered, and evaporated in vacuum to yield a crystalline compound. This compound was washed first with water and then with hexane and then dried completely to yield the final products **62e,f**.

Ni(II) complex of 2-amino-2-prop-2-ynyl-pent-4-ynoic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 62e:[66a] M.p. 101.6 °C. ^{1}H NMR δ 1.05 (6 H, t, *J* = 7.5 Hz), 1.56 (4H, p, *J* = 7.5 Hz), 2.14 (2 H, ABX, *J* = 17.1, 2.7 Hz), 2.21-2.31 (4 H, m), 2.45 (2 H, m), 2.66 (2 H, ABX, *J* = 17.1, 2.7 Hz), 2.79-2.89 (2 H, m), 3.14-3.20 (2 H, m), 3.34 (2 H, s), 6.67 (2 H, m), 7.29 (1 H, m), 7.47-7.54 (5 H, m), 8.52 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 14.08, 20.82, 29.22, 30.19, 60.29, 62.12, 73.40, 76.89, 79.15, 120.83, 123.95, 127.93, 128.07, 130.03, 132.25, 134.06, 136.29, 142.38, 173.86, 178.35, 179.93. HRMS [M+H$^+$] found *m/s* 556.2052, calcd for $C_{31}H_{36}N_3NiO_3$ 556.2106.

Ni(II) complex of 2-amino-pent-4-ynoic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 62f:[66a] M.p. 112.5 °C. ^{1}H NMR δ 1.00 (3 H, t, *J* = 7.5 Hz), 1.05 (3 H, t, *J* = 7.2 Hz), 1.39 (2 H, p, *J* = 7.5 Hz), 1.55 (2 H, p, *J* = 6.3 Hz), 1.81 (2 H, m), 2.19-2.47 (4 H, m), 2.51-2.74 (5 H, m), 2.92 (1 H, td, *J* = 8.4, 1.2 Hz), 3.03 (1 H, d, *J* = 16.2 Hz), 3.98 (1 H, m), 6.75-6.77 (2 H, m), 7.05 (1 H, m), 7.25 (1 H, m), 7.33 (1 H, m), 7.46-7.53 (3 H, m), 8.58 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 13.94, 14.02, 20.64, 20.86, 23.67, 26.73, 29.27, 57.02, 60.48, 62.72, 67.49, 74.21, 79.57, 121.05, 123.79, 126.62, 126.73, 127.73, 129.14, 129.17, 130.00, 132.86, 133.75, 133.81, 142.92, 171.79, 177.00, 178.30. HRMS [M+H$^+$] found *m/s* 518.1943, calcd for $C_{28}H_{34}N_3NiO_3$ 518.1949.

3.8.4 Reactivity Comparisons of Modular Glycine Equivalents 56

Competitive phase transfer homologation of Ni(II) Complex of glycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 56b and Ni(II) Complex of glycine Schiff Base with *N*-(2-(4-(1,1,1-trifluoromethyl)benzoyl)-phenyl)-2-dibutylamino-acetamide 56l with benzyl chloride. To a solution of tetrabutyl ammonium bromide (0.0101 g, 0.0314 mmol), complexes **56b** (0.1007 g, 0.2097 mmol) and **56l** (0.1253 g, 0.2286 mmol) in toluene (50 mL/1 g of **56b**) was added benzyl chloride (0.0259 g, 0.2046 mmol), and 5 mL of 30% aqueous sodium hydroxide. The reaction mixture was vigorously stirred for one hour at room temperature before the adding an additional amount of water (10 mL) and toluene (5 mL). After diluting the reaction mixture the organic fraction is extracted and this procedure is repeated three times. The organic fractions are combined, dried with $MgSO_4$, filtered, and evaporated under vacuum which yielded the crude reaction mixture for further ^{1}H NMR analysis.

Ni(II) Complex of Phenylalanine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 65: M.p. 159.7 °C. ^{1}H NMR δ 0.92 (3 H, t, *J* = 5.7 Hz), 0.98 (3 H, t, *J* = 5.7 Hz), 1.16-1.31 (4 H, m), 1.41 (1 H, s, *J* = 2.4 Hz), 1.52 (1 H, s, *J* = 2.4 Hz), 1.89-2.00 (2 H, m), 2.08-2.19 (2 H, m), 2.69 (1 H, m), 2.75 (1 H, ABX, *J* = 10.2, 3.9 Hz), 2.81 (1 H, AB, *J* = 12.0 Hz), 3.04 (1 H, ABX, *J* = 10.2, 3.9 Hz), 3.38 (1 H, AB, *J* = 12.0 Hz), 4.12 (1 H, q, *J* = 5.4 Hz), 6.79 (2 H, d, *J* = 2.7 Hz), 7.05 (1 H, dd, *J* = 5.4, 0.6 Hz), 7.30-7.33 (2 H, m), 7.43-7.45 (2 H, m), 7.51-7.57 (6 H, m), 8.45 (1 H, dd, *J* = 6.6, 0.6 Hz). ^{13}C NMR δ 13.9, 14.1, 20.4, 20.8, 23.5, 29.4, 39.3, 54.9, 57.9, 63.7, 71.4, 121.2, 123.7, 127.0, 127.3, 127.7, 128.9, 129.1, 129.2, 130.0, 131.5, 132.8, 133.7, 133.8, 136.3,

142.8, 170.7, 176.0, 178.1. HRMS [M+Na^+] found *m/s* 592.2239, calcd for $C_{32}H_{37}N_3NaNiO_3$ 592.2080.

Ni(II) Complex of Phenylalanine Schiff Base with *N*-(2-(4-(1,1,1-trifluoromethyl)-benzoyl)-phenyl)-2-dibutylamino-acetamide 66: M.p. 207.6 °C. ^1H NMR δ 0.93 (3 H, t, *J* = 5.4 Hz), 0.98 (3 H, t, *J* = 5.4 Hz), 1.17-1.54 (6 H, m), 1.94-2.02 (2 H, m), 2.11-2.20 (2 H, m), 2.48 (1 H, td, *J* = 9.3, 3.3 Hz), 2.71 (1 H, m), 2.72 (1 H, ABX, *J* = 10.2, 3.9 Hz), 2.83 (1 H, AB, *J* = 12.0 Hz), 3.13 (1 H, ABX, *J* = 10.2, 3.9 Hz), 3.42 (1 H, AB, *J* = 12.0 Hz), 4.11 (1 H, m), 6.67 (1 H, dd, *J* = 6.3, 1.2 Hz), 6.81 (1 H, td, *J* = 6.3, 0.9 Hz), 7.13 (1 H, d, *J* = 6.0 Hz), 7.35 (1 H, td, *J* = 5.4, 1.5 Hz), 7.40-7.43 (2 H, m), 7.49 (1 H, d, *J* = 6.3 Hz), 7.54-7.58 (3 H, m), 7.77 (1 H, d, *J* = 6.0 Hz), 7.84 (1 H, d, *J* = 6.0 Hz), 8.49 (1 H, dd, *J* = 5.4, 0.9 Hz). ^{13}C NMR δ 13.9, 14.0, 20.4, 20.8, 23.8, 29.4, 29.7, 55.1, 58.2, 63.6, 71.6, 121.3, 124.0, 125.2, 126.2, 126.3, 126.4, 127.8, 128.0, 128.3, 129.0, 131.4, 132.0 (1 C, q, *J* = 32.9 Hz), 133.2, 133.3, 135.9, 137.3, 137.4, 143.1, 169.0, 176.3, 177.7. HRMS [M+H^+] found *m/s* 638.2449, calcd for $C_{33}H_{36}F_3N_3NiO_3$ 638.2135.

Competitive phase transfer homologation of Ni(II) Complex of glycine Schiff Base with *N*-(2-(4-(1,1,1-trifluoromethyl)benzoyl)-phenyl)-2-dibutylamino-acetamide 56l and Ni(II) Complex of glycine Schiff Base with *N*-(2-(3,5-di(1,1,1-trifluoromethyl)benzoyl)-phenyl)-2-dibutylamino-acetamide 56k with benzyl chloride. To a solution of tetrabutyl ammonium bromide (0.0090 g, 0.0278 mmol), complexes **56l** (0.1015 g, 0.1851 mmol) and **56k** (0.1150 g, 0.1866 mmol) in toluene (50 mL/1 g of **56l**) was added benzyl chloride (0.0223 g, 0.1758 mmol), and 5 mL of 30% aqueous sodium hydroxide. The reaction mixture was vigorously stirred for one hour at room temperature before the adding an additional amount of water (10 mL) and toluene

(5 mL). After diluting the reaction mixture the organic fraction is extracted and this procedure is repeated three times. The organic fractions are combined, dried with $MgSO_4$, filtered, and evaporated under vacuum which yielded the crude reaction mixture for further ^1H NMR analysis.

Ni(II) Complex of Phenylalanine Schiff Base with *N*-(2-(3,5-di(1,1,1-trifluoromethyl)-benzoyl)-phenyl)-2-dibutylamino-acetamide 67: M.p. 145.7 °C. ^1H NMR δ 0.94 (3 H, t, *J* = 5.4 Hz), 0.99 (3 H, t, *J* = 5.4 Hz), 1.20-1.44 (6 H, m), 2.01-2.05 (2 H, m), 2.15-2.19 (2 H, m), 2.47 (1 H, td, *J* = 6.8, 1.2 Hz), 2.65 (1 H, m), 2.67 (1 H, ABX, *J* = 10.2, 3.9 Hz), 2.85 (1 H, AB, *J* = 12.0 Hz), 3.24 (1 H, ABX, *J* = 10.2, 3.9 Hz), 3.44 (1 H, AB, *J* = 12.0 Hz), 4.01 (1 H, t, *J* = 3.0 Hz), 6.51 (1 H, dd, *J* = 6.3, 1.2 Hz), 6.83 (1 H, td, *J* = 5.4, 1.2 Hz), 7.35-7.44 (4 H, m), 7.82 (1 H, s), 8.08 (1 H, s), 8.54 (1 H, dd, *J* = 6.6, 0.9 Hz). ^{13}C NMR δ 13.9, 14.0, 20.4, 20.8, 23.9, 29.4, 40.2, 55.3, 58.3, 63.5, 71.6, 121.5, 122.5 (2 C, q, *J* = 203.7 Hz), 123.8, 123.9, 124.1, 124.2, 125.7, 127.5, 127.9, 128.0, 129.1, 131.2, 132.7, 132.8,133.0, 133.2, 133.5, 135.3, 135.9, 143.4, 166.9, 176.2, 177.0. HRMS [$M+H^+$] found *m/s* 706.2025, calcd for $C_{34}H_{36}F_6N_3NiO_3$ 706.2009.

3.8.5 Asymmetric Phase Transfer Catalyzed Homologation of Modular Glycine Equivalents 56

Synthesis of Optically Active Phenylalanine via Asymmetric Phase Transfer Catalyzed Homologation of Modular Ni(II) Complex of Glycine Schiff Bases 56. General Procedure: To a solution on Ni(II) complex **56a,b,d,g,k** (1 eq.) in solvent (1 g of **56a,b,d,g,k** /15 mL solvent) was added the chiral phase transfer catalyst **45-49,68-69**

(1-15 mol%), benzyl bromide **38b**(1.5 eq.), and base. The reaction was vigorously stirred under a N_2 atmosphere and monitored by TLC. In order to quench the reaction excess brine was added and the organic portion was extracted with the same solvent that the reaction was conducted under. The aqueous phase was washed with the organic solvent at least three times before the organic fractions were combined and dried over $MgSO_4$. After the organic fraction was filtered to remove the $MgSO_4$ the organic solvent was evaporated to dryness under vacuum.

Ni(II) Complex of Phenylalanine Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidinamino-acetamide 70: M.p. 142.6 °C. ^{1}H NMR δ 1.28-1.35 (4 H, m), 1.45-1.56 (2 H, m), 1.99 (1 H, m), 2.43 (1 H, p, *J* = 7.2 Hz), 2.71 (1 H, ABX, *J* = 13.5, 5.7 Hz), 2.99-3.01 (2 H, m), 3.12 (1 H, AB, *J* = 14.7 Hz), 3.28 (1 H, ABX, *J* = 13.5, 5.7 Hz), 3.36 (1 H, AB, *J* = 14.7 Hz), 4.29 (1 H, m), 6.79-6.82 (2 H, m), 7.12 (1 H, m), 7.30-7.38 (3 H, m), 7.50-7.65 (7 H, m), 8.47 (1 H, d, *J* = 5.7 Hz). ^{13}C NMR δ 19.5, 19.8, 22.9, 39.2, 54.6, 55.7, 60.4, 71.5, 121.2, 123.7, 126.9, 127.3, 127.6, 127.7, 128.9, 129.1, 129.3, 130.0, 131.6, 132.8, 133.7, 133.8, 136.3, 139.5, 142.9, 170.7, 175.6, 178.1. HRMS [M+Na^+] found *m/s* 548.1467, calcd for $C_{29}H_{29}N_3NaNiO_3$ 548.1454.

Ni(II) Complex of Phenylalanine Schiff Base with *N*-(2-acetyl-phenyl)-2-dibutylamino-acetamide 71: M.p. 265.1 °C. ^{1}H NMR δ 0.96 (3 H, t, *J* = 7.5 Hz), 0.97 (3 H, t, *J* = 7.5 Hz), 1.25 (2 H, s, *J* = 7.2 Hz), 1.30-1.55 (4 H, m), 1.95-2.06 (2 H, m), 2.08-2.22 (2 H, m), 2.40 (3 H, s), 2.42 (1 H, m), 2.61 (1 H, m), 2.82 (1 H, AB, *J* = 15.6 Hz), 3.25 (1 H, ABX, *J* = 13.5, 4.5 Hz), 3.42 (1 H, AB, *J* = 15.6 Hz), 3.63 (1 H, ABX, *J* = 13.5, 4.5 Hz), 4.45 (1 H, t, *J* = 4.5 Hz), 7.04 (1 H, m), 7.38 (1 H, m), 7.46-7.49 (2 H, m), 7.53-7.57 (3 H, m), 7.67 (1 H, dd, *J* = 8.1, 1.8 Hz), 8.44 (1 H, dd, *J* = 8.7, 1.2 Hz).

^{13}C NMR δ 13.9, 14.1, 18.1, 20.5, 20.8, 24.1, 29.4, 40.1, 55.3, 58.1, 63.6, 71.5, 121.6, 124.1, 126.6, 127.7, 129.0, 129.5, 131.5, 132.3, 133.0, 136.2, 141.8, 165.1, 167.7, 175.9, 178.1. HRMS [M+Na$^+$] found *m/s* 781.2156, calcd for $C_{27}H_{35}N_3NaNiO_3$ 530.1924.

Ni(II) Complex of Phenylalanine Schiff Base with *N*-(2-benzoyl-phenyl)-2-diethylamino-acetamide 72: M.p. 193.2 °C. ^{1}H NMR δ 0.85 (3 H, t, *J* = 7.5 Hz), 1.77 (3 H, t, *J* = 7.5 Hz), 2.09 (1 H, m), 2.16-2.29 (2 H, m), 2.68 (1 H, m), 2.70 (1 H, ABX, *J* = 13.5, 3.3 Hz), 2.79 (1 H, AB, *J* = 15.9 Hz), 3.06 (1 H, ABX, *J* = 13.5, 3.3 Hz), 3.38 (1 H, AB, *J* = 15.9 Hz), 4.28 (1 H, m), 6.80-6.82 (2 H, m), 7.06-7.09 (1 H, m), 7.30-7.37 (2 H, m), 7.43-7.46 (2 H, m), 7.50-7.61 (6 H, m), 8.47 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 6.6, 12.9, 39.3, 48.7, 51.7, 62.7, 71.3, 121.2, 123.7, 126.9, 127.2, 127.6, 127.7, 128.9, 129.1, 129.3, 130.0, 131.5, 132.8, 133.8, 133.8, 136.2, 142.8, 170.8, 175.8, 178.1. HRMS [M+Na$^+$] found *m/s* 536.1577, calcd for $C_{28}H_{29}N_3NaNiO_3$ 536.1454.

Procedure for Determination of Optical Purity of Modular Ni(II) Complexes of Phenylalanine 65,67. General Procedure: The corresponding modular Ni(II) complexes **65,67** were purified by a silica gel column chromatography with a 2:1 solution of ethyl acetate and hexane as the eluent. The determination of optical purity of these Ni(II) complexes **65,67** were accomplished by HPLC employing a Chiralcel OD column with a hexane:isopropanol eluent (90:10 for **65** and 95:5 for **67**).

Disassembly of Complexes 70-72, Recovery of the Corresponding Ligands 54a,d,g, and Transformation of the Corresponding Phenylalanine Product 2b to the *N*-CBz-phenylalanine ethyl ester for the Determination of Optical Purity. General Procedure: Aqueous 12*N* HCl was slowly added (dropwise until all red color disappears) to a solution of the appropriate Ni(II) complex **70-72** in MeOH (1 mL/100

mg) while stirring. Following the completion of the acid catalyzed disassembly (confirmed by TLC with $CHCl_3$/acetone 5/1 as the eluent), the reaction mixture was evaporated in a vacuum to dryness. Water (1 mL/100 mg of starting complex) was added, and the resultant mixture was treated with an excess of NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried over $MgSO_4$ and evaporated in a vacuum to afford the free modular ligand **54a,d,g** (92-98%). The aqueous phase was evaporated under vacuum to provide the corresponding mixture of free phenylalanine and $NiCl_2$, which was treated with thionyl chloride (7 eq.) in ethanol and allowed to react at 60 ^oC for four hours. Following the reaction the excess thionyl chloride, alcohol, and water were removed under vacuum. Without purification, methylene chloride (1 mL/200 mg of the starting Ni(II) complex **70-72**) was added to the corresponding mixture of the $NiCl_2$ and ethyl ester of phenylalanine. Triethylamine (1.2 eq.) was added to the previously described emulsion and cooled to 4 ^oC with an ice water bath. After the temperature had been equilibrated, the emulsion was treated with benzyl chloroformate (1.2 eq.), and allowed to warm to room temperature by removal of the water bath. After allowing the reaction to proceed for one hour, excess water was added to quench the reaction, followed by the extraction of the organic fraction with methylene chloride. This extraction was reproduced three times and all of the organic fractions were collected and dried with $MgSO_4$. Following the filtration of the drying reagent the methylene chloride was evaporated under vacuum until dryness. The corresponding *N*-CBz-phenylalanine ethyl ester was purified by a preparative TLC with ethyl acetate:hexane (1:4**)** as the eluent. The determination of optical purity of the phenyl alanine derivatives was

accomplished by HPLC employing a Chiralcel OD column with a hexane:isopropanol (95:5) eluent.

3.8.6 Michael Addition Reactions of Modular Glycine Equivalents and (*R*,*S*)-*N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones

The Michael addition of the oxazolidinone derived amides of unsaturated acids 84a,b and nucleophilic glycine equivalent 56a,c-f. General Procedure. To a flask containing **56a, c-f** (0.10 g), 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one **84a,b** (1.05 eq.) and 1.5 ml of DMF, DBU (15 mol%) was added to the reaction mixture, which was stirred at room temperature and monitored by TLC. After disappearance of starting glycine equivalent by TLC, the reaction mixture was poured into a beaker containing 100 mL ice water. After the ice had melted the corresponding product **85a, c-f, or 86a, c-f**, was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high chemical yields.

Ni(II) Complex of 3-(*p*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidino-acetamide 85d:[66] M.p. >200 °C (decomp.). ^{1}H NMR δ 1.20-1.70 (6 H, m), 2.10-2.24 (1 H, m), 2.43 (1 H, m), 2.87-3.00 (1 H, m), 3.07 (1 H, d, *J* = 16.1 Hz), 3.16-3.36 (4 H, m), 3.70-3.80 (1 H, m), 3.89 (3 H, s), 4.13 (1 H, dd, *J* = 8.79, 3.66 Hz), 4.31 (1 H, d, *J* = 4.15 Hz), 4.56 (1 H, dd, *J* = 8.79, 8.55 Hz), 5.14 (1 H, dd, *J* = 8.55, 3.66 Hz), 6.71-6.78 (2 H, m), 6.92-7.01 (4 H, m), 7.06-7.13 (2 H, m), 7.20-7.54 (9 H, m), 8.39 (1 H, d, *J* = 8.55 Hz). ^{13}C NMR δ 19.4, 19.7, 22.7, 30.9, 36.3, 44.3, 54.4, 55.4, 57.3, 59.9, 69.5, 73.3, 113.8, 120.6, 122.9, 125.4,

126.5, 126.9, 127.6, 127.9, 128.5, 128.7, 128.8, 129.5, 130.5, 131.2, 132.4, 133.3, 133.6, 138.4, 142.4, 152.9, 159.2, 169.6, 170.6, 174.8, 176.4. HRMS [M+Na^+] found *m/s* 781.2156, calcd for $C_{42}H_{42}N_4NaNiO_6$ 781.2148. $[\alpha]_D^{25}$ +1863 (*c* 0.109, CH_3Cl).

Ni(II) Complex of 3-*i*-propyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidino-acetamide 86d:[66] M.p. >190 °C (decomp.). ^1H NMR δ 0.25 (3 H, d, *J* = 6.84 Hz), 0.88 (3 H, d, *J* = 6.84 Hz), 1.20-1.84 (7 H, m), 2.34 (1 H, m), 2.51 (1 H, dd, *J* = 19.0, 1.47 Hz), 2.92 (1 H, m), 3.10 (1 H, dd, *J* = 19.0, 10.0 Hz), 3.14 (1 H, m), 3.26-3.45 (2 H, m), 3.61 (1 H, m), 3.64-3.76 (2 H, m), 3.90-4.03 (2 H, m), 5.32 (1 H, dd, *J* = 6.14, 3.35 Hz), 6.79 (1 H, ddd, *J* = 8.30, 6.96, 1.22 Hz), 6.87 (1 H, dd, *J* = 8.30, 1.71 Hz), 7.12-7.59 (11 H, m), 8.73 (1 H, dd, *J* = 8.66, 1.22 Hz). ^{13}C NMR δ 15.6, 19.1, 19.8, 21.6, 22.9, 27.4, 31.5, 45.3, 53.7, 56.1, 57.2, 60.6, 70.5, 72.1, 121.1, 122.7, 125.3, 125.7, 127.8, 128.4, 128.8, 128.9, 129.1, 129.1, 129.7, 132.6, 133.3, 134.3, 139.0, 142.4, 153.5, 171.1, 172.3, 176.5, 178.0. HRMS [M+Na^+] found *m/s* 717.2361, calcd for $C_{38}H_{42}N_4NaNiO_5$ 717.2199. $[\alpha]_D^{25}$ -2187 (*c* 0.104, CH_3Cl).

Ni(II) Complex of 3-(*p*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibenzylamino-acetamide 85c:[66] M.p. 305.2 °C (decomp.). ^1H NMR δ 2.61 (1 H, d, *J* = 16.4 Hz), 2.97 (1 H, d, *J* = 12.2 Hz), 3.14 (1 H, dd, *J* = 17.4, 7.44 Hz), 3.27 (1 H, m), 3.36 (1 H, d, *J* = 14.0 Hz), 3.52 (1 H, d, *J* = 14.0 Hz), 3.66 (1 H, d, *J* = 16.4 Hz), 3.82 (1 H, d, *J* = 12.2 Hz), 3.89 (3 H, s), 3.95 (1 H, dd, *J* = 167.3, 7.57 Hz), 4.13 (1 H, dd, *J* = 8.80, 3.91 Hz), 4.32 (1 H, d, *J* = 3.90 Hz), 4.57 (1 H, t, *J* = 8.79 Hz), 5.15 (1 H, dd, *J* = 8.55, 3.91 Hz), 6.57-6.63 (2 H, m), 6.87-7.40 (6 H, m), 7.08-7.56 (17 H, m), 7.75 (1 H, d, *J* = 8.55 Hz), 8.18-8.25 (2 H, m). ^{13}C NMR

δ 36.5, 44.5, 55.3, 57.3, 62.3, 62.7, 62.9 ,69.5, 73.6, 113.9, 120.3, 123.1, 125.3, 125.7, 126.0, 127.0, 127.6, 128.0, 128.3, 128.3, 128.5, 128.5, 128.6, 128.7, 128.8, 129.0, 129.2, 129.4, 130.0, 130.6, 131.0, 131.4, 131.5, 131.7, 131.9, 131.9, 132.9, 133.3, 134.0, 138.3, 141.8, 152.9, 159.2, 169.5, 170.6, 175.2, 176.3. HRMS [M+Na^+] found *m/s* 894.3173, calcd for $C_{51}H_{46}N_4NaO_6$ 894.5903. $[\alpha]_D^{25}$ +1330 (*c* 0.039, CH_3Cl).

Ni(II) Complex of 3-*i*-propyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibenzylamino-acetamide 86c:[66] M.p. >160 °C (decomp.). ^{1}H NMR δ 0.18 (3 H, d, *J* = 6.71 Hz), 0.90 (3 H, d, *J* = 6.72 Hz), 2.30 (1 H, m), 2.57 (1 H, d, *J* = 19.1 Hz), 2.90 (1 H, d, *J* = 16.4 Hz), 2.90-3.15 (1 H, m), 3.11 (1 H, d, *J* = 12.0 Hz), 3.65-3.80 (2 H, m), 3.90-4.10 (4 H, m), 4.40 (1 H, d, *J* = 16.6 Hz), 5.13 (1 H, d, *J* = 13.9 Hz), 5.14 (1 H, dd, *J* = 6.84, 4.64 Hz), 6.60-6.74 (2 H, m), 6.96-7.06 (2 H, m), 7.10-7.60 (17 H, m), 7.97 (1 H, d, *J* = 8.79 Hz), 8.29-8.37 (2 H, m). ^{13}C NMR δ 15.5, 21.5, 27.6, 31.6, 45.3, 57.4, 62.6, 62.9, 64.0, 70.3, 71.8, 120.5, 122.7, 125.3, 125.3, 127.9, 128.3, 128.4, 128.4, 128.4, 128.4, 128.7, 128.8, 128.9, 129.2, 129.6, 130.4, 131.2, 131.7, 131.9, 133.2, 133.6, 134.1 139.0, 141.8, 153.5, 170.7, 172.5, 176.6, 178.2. HRMS [M+Na^+] found *m/s* 829.2483, calcd for $C_{47}H_{46}N_4NaNiO_5$ 829.2512. $[\alpha]_D^{25}$ -1318 (*c* 0.112, CH_3Cl).

Ni(II) Complex of 3-(*p*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-dimethylamino-acetamide 85a:[66a] M.p. 274.2 °C (decomp.). ^{1}H NMR δ 1.75 (3 H, s), 2.48 (3 H, s), 2.66 (1 H, d, *J* = 15.9 Hz), 3.17-3.36 (3 H, m), 3.75 (1 H, dd, *J* = 16.8, 6.35 Hz), 3.89 (3 H, s), 4.15 (1 H, dd, *J* = 8.79, 3.66 Hz), 4.34 (1 H, d, *J* = 4.15 Hz), 4.57 (1 H, t, *J* = 8.79 Hz), 5.14 (1 H, dd, *J* = 8.54, 3.66 Hz), 6.74-6.80 (2 H, m), 6.94-7.03 (3 H, m), 7.08-7.14 (2 H, m), 7.20-7.56 (10

H, m), 8.48 (1 H, dt, *J* = 8.54, 0.86 Hz). ^{13}C NMR δ 36.3, 44.3, 47.4, 49.6, 55.4, 57.3, 66.9, 69.5, 73.4, 113.9, 120.8, 122.9, 125.5, 126.5, 126.9, 127.6, 128.0, 128.5, 128.8, 128.8, 129.5, 130.5, 131.2, 132.5, 133.3, 133.8, 138.4, 142.4, 152.9, 159.2, 169.6, 170.7, 174.3, 176.5. HRMS [M+Na$^+$] found *m/s* 741.16.49, calcd for $C_{39}H_{38}N_4NaNiO_6$ 741.1835. $[\alpha]_D^{25}$ +1865 (*c* 0.105, CH_3Cl).

Ni(II) Complex of 3-*i*-propyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-dimethylamino-acetamide 86a:[66a] M.p. 141.9 °C (decomp.). ^{1}H NMR δ 0.24 (3 H, d, *J* = 6.83 Hz), 0.89 (3 H, d, *J* = 6.84 Hz), 2.30-2.45 (1 H, m), 2.40 (3 H, m), 2.46-2.65 (1 H, m), 2.61 (3 H, s), 3.04 (1 H, d, *J* = 15.6 Hz), 3.12 (1 H, dd, *J* = 19.1, 11.5 Hz), 3.52 (1 H, m), 3.70 (1 H, d, *J* = 9.28 Hz), 3.96 (1 H, d, *J* = 8.67 Hz), 4.00 (1 H, d, *J* = 8.79 Hz), 4.20 (1 H, d, *J* = 15.6 Hz), 5.31 (1 H, dd, *J* = 6.35, 4.15 Hz), 6.81 (1 H, ddd, *J* = 8.18, 6.83, 1.22 Hz), 6.88 (1 H, dd, *J* = 8.30, 1.95 Hz), 7.13-7.56 (11 H, m), 8.79 (1 H, dd, *J* = 8.54, 1.22 Hz). ^{13}C NMR δ 15.6, 21.6, 27.5, 31.5, 45.2, 48.4, 49.2, 57.2, 67.9, 70.4, 72.0, 121.2, 122.6, 125.3, 125.7, 127.8, 128.4, 128.8, 128.9, 129.1, 129.1, 129.7, 132.7, 133.2, 134.4, 139.0, 142.3, 153.5, 171.2, 172.3, 175.7, 178.3. HRMS [M+Na$^+$] found *m/s* 677.1802, calcd for $C_{35}H_{38}N_4NaNiO_5$ 677.1886. $[\alpha]_D^{25}$ -2094 (*c* 0.085, CH_3Cl).

Ni(II) Complex of 3-(*p*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-morpholyl-acetamide 85e:[66] M.p. >190 °C (decomp.). ^{1}H NMR δ 1.85-2.00 (1 H, m), 2.32 (1 H, m), 2.60-2.70 (1 H, m), 3.08 (1 H, d, *J* = 15.6 Hz), 3.19 (1 H, m), 3.33 (1 H, dd, *J* = 17.8, 8.06 Hz), 3.38 (1 H, d, *J* = 15.9 Hz), 3.40-3.52 (2 H, m), 3.66-3.92 (3 H, m), 3.90 (3 H, s), 3.95-4.95 (1 H, m), 4.14 (1 H, dd, *J* = 8.79, 3.67 Hz), 4.31 (1 H, d, *J* = 4.88 Hz), 4.58 (1 H, t, *J* = 8.79 Hz), 5.15 (1 H,

dd, *J* = 8.67, 3.66 Hz), 6.73-6.80 (2 H, m), 6.93-7.00 (3 H, m), 7.07-7.14 (2 H, m), 7.20-7.40 (8 H, m), 7.46 (1 H, tt, *J* = 7.57, 1.34 Hz), 7.53 (1 H, td, *J* = 7.57, 1.34 Hz), 8.28 (1 H, d, *J* = 8.30 Hz). ^{13}C NMR δ 36.3, 44.3, 54.6, 55.4, 56.5, 57.3, 61.9, 62.3, 63.6, 69.5, 72.8, 113.8, 120.9, 122.9, 125.5, 126.7, 126.8, 127.7, 128.0, 128.5, 128.8, 128.8, 129.6, 130.5, 131.3, 132.6, 133.1, 133.7, 138.4, 141.9, 152.8, 159.3, 169.5, 170.9, 172.8, 176.4. HRMS [M+Na$^+$] found *m/s* 783.1940, calcd for $C_{41}H_{40}N_4NaNiO_7$ 783.1941. $[\alpha]_D^{25}$ +1985 (*c* 0.103, CH_3Cl).

Ni(II) Complex of 3-*i*-propyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-morpholyl-acetamide 86e:[66] M.p. >180 °C (decomp.). ^{1}H NMR δ 0.25 (3 H, d, *J* = 6.83 Hz), 0.87 (3 H, d, *J* = 6.84 Hz), 2.37 (1 H, m), 2.53 (1 H, dd, *J* = 19.2, 1.47 Hz), 2.60-2.70 (1 H, m), 2.84 (1 H, m), 3.10 (1 H, dd, *J* = 19.3, 10.3 Hz), 3.29 (1 H, ddd, *J* = 12.0, 8.30, 3.54 Hz), 3.47-3.98 (8 H, m), 4.01 (2 H, d, *J* = 5.37 Hz), 4.38 (1 H, d, *J* = 15.6 Hz), 5.36 (1 H, t, *J* = 5.37 Hz), 6.81 (1 H, ddd, *J* = 8.30, 6.83, 1.22 Hz), 6.87 (1 H, dd, *J* = 8.30, 1.95 Hz), 7.15-7.60 (11 H, m), 8.64 (1 H, dd, *J* = 8.54, 1.10 Hz). ^{13}C NMR δ 15.6, 21.5, 27.4, 31.5, 45.1, 55.1, 55.3, 57.1, 60.9, 61.7, 63.2, 70.4, 71.7, 121.3, 122.6, 125.3, 125.9, 127.7, 128.4, 128.9, 128.9, 129.1, 129.2, 129.8, 132.7, 133.1, 134.3, 138.9, 141.9, 153.5, 171.3, 172.2, 174.6, 177.9. HRMS [M+H$^+$] found *m/s* 697.2001, calcd for $C_{37}H_{41}N_4NiO_6$ 697.2094. $[\alpha]_D^{25}$ -1856 (*c* 0.154, CH_3Cl).

Ni(II) Complex of 3-(*p*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-indolylamino-acetamide 85f:[66] M.p. 322.2 °C (decomp.). ^{1}H NMR δ 2.96 (1 H, d, *J* = 5.87 Hz), 3.13 (1 H, d, *J* = 5.62 Hz), 3.19-3.32 (2 H, m), 3.39 (1 H, dd, *J* = 17.8, 8.30 Hz), 3.65-3.78 (2 H, m), 3.90 (3 H, s),

3.95 (1 H, d, *J* = 15.6 Hz), 4.15 (1 H, dd, *J* = 8.78, 3.66 Hz), 4.39 (1 H, d, *J* = 4.88 Hz), 4.57 (1 H, t, *J* = 8.79 Hz), 5.12 (1 H, d, *J* = 14.7 Hz), 5.15 (1 H, dd, *J* = 8.54, 3.66 Hz), 6.73-6.82 (2 H, m), 6.95-7.56 (19 H, m), 8.49 (1 H, d, *J* = 8.79 Hz). ^{13}C NMR δ 36.3, 44.2, 55.4, 57.3, 60.9, 63.6, 65.5, 69.5, 73.6, 113.9, 120.8, 122.4, 122.6, 123.1, 125.5, 126.6, 127.0, 127.5, 127.6, 127.9, 128.0, 128.5, 128.8, 128.8, 129.5, 130.6, 131.4, 132.5, 133.2, 133.8, 136.0, 138.5, 142.5, 152.9, 159.2, 169.5, 170.6, 174.8, 176.2. HRMS [M+Na$^+$] found *m/s* 815.2503, calcd for $C_{45}H_{40}N_4NaNiO_6$ 815.1992. $[\alpha]_D^{25}$ +1838 (*c* 0.113, $CHCl_3$).

Ni(II) Complex of 3-*i*-propyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-indolylamino-acetamide 86f:[66] M.p. >200 °C (decomp.). ^{1}H NMR δ 0.32 (3 H, d, *J* = 6.83 Hz), 0.92 (3 H, d, *J* = 6.84 Hz), 2.46 (1 H, m), 2.56 (1 H, d, *J* = 17.8 Hz), 3.17 (1 H, dd, *J* = 19.2, 10.4 Hz), 3.35 (1 H, d, *J* = 15.8 Hz), 3.53 (1 H, m), 3.77 (1 H, d, *J* = 9.27 Hz), 3.88 (1 H, d, *J* = 14.4 Hz), 3.90-4.10 (3 H, m), 4.16 (1 H, d, *J* = 15.4 Hz), 4.42 (1 H, d, *J* = 15.11 Hz), 5.11 (1 H, d, *J* = 14.4 Hz), 5.32 (1 H, dd, *J* = 5.83, 3.90 Hz), 6.82 (1 H, ddd, *J* = 8.18, 6.96, 1.22 Hz), 6.91 (1 H, dd, *J* = 8.30, 1.70 Hz), 7.25-7.52 (15 H, m), 8.80 (1 H, dd, *J* = 8.64, 1.22 Hz),. ^{13}C NMR δ 15.6, 21.6, 27.4, 31.5, 45.0, 57.2, 61.9, 63.3, 66.7, 70.3, 72.2, 121.2, 122.4, 122.7, 122.8, 125.4, 125.8, 127.5, 127.8, 127.9, 128.4, 128.8, 128.9, 129.1, 129.1, 129.7, 132.7, 133.2, 133.5, 134.4, 136.1, 139.0, 142.3, 153.5, 171.2, 172.1, 175.9, 177.9. HRMS [M+Na$^+$] found *m/s* 751.2099, calcd for $C_{41}H_{40}N_4NaNiO_5$ 751.2043. $[\alpha]_D^{25}$ -1856 (*c* 0.154, CH_3Cl).

The Michael addition of the oxazolidinone derived amides of unsaturated acids 84c-k and nucleophilic glycine equivalent 56d. General Procedure. To a flask containing **56d** (0.10 g), 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one **84c-k** (1.05 eq.) and 1.5 ml of DMF, DBU (15 mol%) was added to the reaction mixture, which was stirred at room temperature and monitored by TLC. After disappearance of starting glycine equivalent by TLC, the reaction mixture was poured into a beaker containing 100 mL ice water. After the ice had melted the corresponding product **87c-k**, was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high chemical yields.

Ni(II) Complex of 3-methyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 87c:[66] M.p. 286.5 °C (decomp.). ^{1}H NMR δ 1.20-2.10 (6 H, m), 1.95 (3 H, d, *J* = 6.83 Hz), 2.59 (1 H, m), 2.70-3.50 (5 H, m), 3.40 (1 H, m), 3.67 (1 H, d, *J* = 16.6 Hz), 3.84 (1 H, d, *J* = 16.6 Hz), 4.00 (1 H, d, *J* = 5.13 Hz), 4.17 (1 H, dd, *J* = 8.79, 3.17 Hz), 4.51 (1 H, t, *J* = 8.79 Hz), 5.24 (1 H, dd, *J* = 8.80, 3.18 Hz), 6.69-6.78 (2 H, m), 6.94 (1 H, bd, *J* = 7.33 Hz), 7.13-7.52 (10 H, m), 8.57 (1 H, d, *J* = 8.54 Hz). ^{13}C NMR δ 17.1, 19.3, 19.9, 22.8, 34.1, 38.8, 54.2, 56.8, 57.3, 60.6, 69.8, 73.5, 120.9, 123.1, 125.7, 126.5, 126.9, 127.9, 128.2, 128.6, 128.7, 128.7, 129.4, 132.4, 133.2, 133.7, 138.8, 142.2, 153.0, 170.0, 171.0, 175.8, 176.7. HRMS [M+Na^+] found *m/s* 689.1902, calcd for $C_{36}H_{38}N_4NaNiO_5$ 689.1886. $[\alpha]_D^{25}$ +2320 (*c* 0.105, CH_3Cl).

Ni(II) Complex of 3-phenyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 87d:[66] M.p. >200 °C (decomp.). ^{1}H NMR δ 1.20-1.68 (6 H, m), 1.98-2.10 (1 H, m), 2.39 (1 H, m), 2.89 (1 H,

bd, *J* = 12.8 Hz), 3.05 (1 H, d, *J* = 16.0 Hz), 3.15-3.35 (4 H, m), 3.79 (1 H, m), 4.12 (1 H, dd, *J* = 8.80, 3.81 Hz), 4.35 (1 H, d, *J* = 4.25 Hz), 4.55 (1 H, t, *J* = 8.79 Hz), 5.12 (1 H, dd, *J* = 8.65 Hz), 6.69-6.76 (2 H, m), 6.90-7.10 (3 H, m), 7.17-7.37 (6 H, m), 7.38-7.60 (7 H, m), 8.40 (1 H, d, *J* = 8.50 Hz). ^{13}C NMR δ 19.3, 19.7, 22.7, 36.3, 44.9, 54.4, 55.3, 57.3, 60.0, 69.6, 73.3, 120.7, 123.0, 125.4, 126.6, 126.9, 127.7, 127.8, 128.0, 128.6, 128.7, 128.8, 129.6, 130.3, 132.4, 133.3, 133.7, 138.4, 138.8, 142.6, 153.0, 169.6, 171.0, 174.9, 176.3. HRMS [M+Na$^+$] found *m/s* 751.2044, calcd for $C_{41}H_{40}N_4NaNiO_5$ 751.2043. $[\alpha]_D^{25}$ +1960 (*c* 0.108, CH_3Cl).

Ni(II) Complex of 3-(*o*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 87e:[66] M.p. >190 °C (decomp.). ^{1}H NMR δ 1.24-1.70 (7 H, m), 2.00-2.20 (1 H, m), 2.40 (1 H, m), 2.83-3.05 (2 H, m), 3.15-3.40 (1 H, m), 3.24 (3 H, s), 3.40 (1 H, dd, *J* = 18.3, 8.54 Hz), 3.58 (1 H, dd, *J* = 18.3 6.59 Hz), 4.03 (1 H, m), 4.13 (1 H, dd, *J* = 8.79, 3.42 Hz), 4.33 (1 H, d, *J* = 4.64 Hz), 4.56 (1 H, t, *J* = 8.79 Hz), 5.11 (1 H, dd, *J* = 8.55, 3.42 Hz), 6.68-6.78 (2 H, m), 6.93-7.02 (2 H, m), 7.08 (1 H, d, *J* = 8.05 Hz), 7.15-7.34 (8 H, m), 7.40-7.61 (3 H, m), 7.68 (1 H, bd, *J* = 7.33 Hz), 8.37 (1 H, d, *J* = 8.54 Hz). ^{13}C NMR δ 19.4, 19.7, 22.8, 35.5, 36.1, 54.5, 54.6, 55.2, 57.2, 60.0, 69.5, 73.4, 109.9, 120.5, 121.0, 122.8, 125.6, 126.7, 126.8, 127.8, 127.9, 128.4, 128.5, 128.7, 128.9, 129.3, 129.9, 131.9, 133.4, 133.6, 138.6, 142.1, 152.9, 158.0, 169.5, 171.3, 174.9, 176.7. HRMS [M+H$^+$] found *m/s* 759.2089, calcd for $C_{42}H_{42}N_4NaNiO_6$ 759.2251. $[\alpha]_D^{25}$ +1607 (*c* 0.097, CH_3Cl).

Ni(II) Complex of 3-(*o*-trifluoromethyl-phenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 87f:[66] M.p. >200 °C (decomp.). ^{1}H NMR δ 1.19-1.80 (7 H, m), 2.50-2.74 (2 H, m), 2.99 (1 H, m), 3.29 (1 H, m), 3.44 (1 H, d, *J* = 16.1 Hz), 3.50-3.67 (2 H, m), 4.13 (1 H, dd, *J* = 8.79, 3.42 Hz), 4.23 (1 H, m), 4.33 (1 H, d, *J* = 4.89 Hz), 4.49 (1 H, t, *J* = 8.79 Hz), 5.16 (1 H, dd, *J* = 8.54, 3.42 Hz), 6.56 (1 H, bs), 6.66-6.75 (2 H, m), 6.94-7.20 (2 H, m), 7.10-7.30 (6 H, m), 7.40-7.57 (5 H, m), 7.72 (1 H, d, *J* = 7.62 Hz), 8.62 (1 H, d, *J* = 8.55 Hz). ^{19}F NMR δ -57.6 (3 F, s). ^{13}C NMR δ 19.5, 20.0, 22.9, 38.3, 40.7, 54.4, 55.7, 57.3, 60.4, 69.9, 74.0, 120.6 122.6, 123.8 (q, *J* = 273.7 Hz), 125.4, 126.4, 126.4, 126.4 (q, *J* = 5.92 Hz), 127.2, 127.4, 127.9, 128.1, 128.6, 128.7, 129.0, 129.5, 129.8 (q, *J* = 29.4 Hz), 130.2, 132.0, 132.8, 133.1, 134.1, 138.0, 138.3, 142.8, 153.3, 168.6, 172.5, 175.3, 176.3. HRMS [M+Na^{+}] found *m/s* 819.1591, calcd for $C_{42}H_{39}F_3N_4NaNiO_5$ 819.1916. $[\alpha]_D^{25}$ +1810 (*c* 0.106, CH_3Cl).

Ni(II) Complex of 3-(2,6-difluorophenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 87g:[66] M.p. 290.2 °C (decomp.). ^{1}H NMR δ 1.15-1.70 (7 H, m), 2.43 (1 H, bd, *J* = 13.8 Hz), 2.66 (1 H, m), 3.00 (1 H, bd, *J* = 12.6 Hz), 3.09 (1 H, d, *J* = 16.1 Hz), 3.25-3.45 (2 H, m), 3.74 (1 H, dd, *J* = 18.6, 6.01 Hz), 3.65-3.84 (1 H, m), 4.17 (1 H, dd, *J* = 8.80, 3.52 Hz), 4.32 (1 H, d, *J* = 6.01 Hz), 4.53 (1 H, t, *J* = 8.80 Hz), 5.13 (1 H, dd, *J* = 8.65, 3.52 Hz), 6.67-6.78 (2 H, m), 6.90-7.36 (11 H, m), 7.40-7.53 (3 H, m), 8.44 (1 H, d, *J* = 8.36 Hz). ^{19}F NMR δ -104.1 (1 F, s), -109.6 (1 F, s). ^{13}C NMR δ 19.3, 19.8, 22.8, 35.0, 35.2, 54.4, 55.6, 57.3, 60.0, 69.7, 71.5, 111.3 (d, *J* = 25.9 Hz), 112.4 (d, *J* = 20.2 Hz), 120.7, 122.8, 125.9, 126.5, 127.0, 128.0, 128.0, 128.2, 128.6, 128.7, 129.0, 129.4 (t, *J* = 10.5 Hz), 129.6, 132.5,

133.1, 133.9, 138.6, 142.6, 152.9, 162.1 (dd, *J* = 257.3, 10.4 Hz), 163.0 (dd, *J* = 251.9, 6.04 Hz), 169.5, 172.1, 174.8, 176.2. HRMS [M+Na^+] found *m/s* 787.2065, calcd for $C_{41}H_{38}F_2N_4NaNiO_5$ 787.1854. $[\alpha]_D^{25}$ +1839 (*c* 0.102, CH_3Cl).

Ni(II) Complex of 3-(*N*-benzyl-indolyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 87h:[66] M.p. >180 °C (decomp.). ^{1}H NMR δ 0.70-1.60 (2 H, m), 1.99 (1 H, m), 2.88 (1 H, m), 3.01 (1 H, d, *J* = 16.3 Hz), 3.11 (1 H, m), 3.66 (1 H, m), 3.90-4.10 (1 H, m), 4.00 (1 H, m), 4.29 (1 H, d, *J* = 3.52 Hz), 4.49 (1 H, t, *J* = 8.80 Hz), 5.10 (1 H, dd, *J* = 8.88, 3.90 Hz), 5.26 (1 H, d, *J* = 5.53 Hz), 5.30 (1 H, d, *J* = 5.54 Hz), 6.68-6.82 (4 H, m), 6.90-7.58 (18 H, m), 7.73 (1 H, m), 8.44 (1 H, d, *J* = 8.36 Hz). ^{13}C NMR δ 19.1, 19.3, 22.7, 29.6 37.0, 39.1, 50.2, 53.9, 54.7, 57.3, 59.4, 69.4, 109.4, 112.7, 120.1, 120.6 121.4, 122.3, 123.3, 125.1, 126.4, 127.0, 127.1, 127.4, 127.8, 127.9, 128.3, 128.4, 128.5, 128.8, 129.0, 129.4, 132.4, 133.5, 133.6, 136.6, 138.2, 142.6, 153.0, 170.0, 170.5, 175.3, 177.2. HRMS [M+Na^+] found *m/s* 880.2409, calcd for $C_{50}H_{47}N_5NaNiO_5$ 880.2621. $[\alpha]_D^{25}$ +1350 (*c* 0.099, CH_3Cl).

Ni(II) Complex of 3-(*N*-tosyl-indolyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide 87i:[66] M.p. >200 °C (decomp.). ^{1}H NMR δ 0.80-1.60 (6 H, m), 1.69 (1 H, m), 2.10-2.30 (1 H, m), 2.21 (3 H, s), 2.49 (1 H, bd, *J* = 15.8 Hz), 2.80-3.00 (2 H, m), 3.10-3.20 (1 H, m), 3.11 (1 H, d, *J* = 16.1 Hz), 3.68 (1 H, m), 4.00-4.30 (1 H, m), 4.04 (1 H, dd, *J* = 8.79, 3.67 Hz), 4.30 (1 H, d, *J* = 3.08 Hz), 4.55 (1 H, t, *J* = 8.79 Hz), 5.13 (1 H, dd, *J* = 8.50, 3.52 Hz), 6.66-6.79 (4 H, m), 6.89-6.98 (2 H, m), 7.02-7.16 (5 H, m), 7.18-7.28 (2 H, m), 7.33-7.55 (5 H, m), 7.76-7.87 (3 H, m), 8.12 (1 H, d, *J* = 8.21 Hz), 8.48 (1 H, d, *J* = 8.51 Hz). ^{13}C NMR δ 19.0, 19.4, 21.5, 22.7, 36.9, 38.3, 53.9, 55.2, 57.3, 59.4, 69.7, 74.6, 113.2, 119.9, 120.5,

120.6, 123.3, 123.4, 124.8, 125.1, 125.5, 126.0, 126.9, 127.0, 127.6, 127.9, 128.5, 129.0, 129.1, 129.5, 129.8, 131.4, 132.7, 133.4, 133.7, 134.5, 134.9, 137.9, 142.9, 144.7, 153.0, 169.6, 171.3, 175.5, 176.3. HRMS [M+Na^+] found *m/s* 944.2324, calcd for $C_{50}H_{47}N_5NaNiO_7S$ 944.2240. $[\alpha]_D^{25}$ -1350 (*c* 0.082, CH_3Cl).

The Michael addition of the oxazolidinone derived amides of unsaturated acids 84b-f, i, l-q and nucleophilic glycine equivalent 56h. General Procedure. To a flask containing **56h** (0.10 g), 3-((*E*)-3-phenylacryloyl)oxazolidin-2-one **84b-f, i, l-q** (1.05 eq.) and 1.5 ml of DMF, DBU (15 mol%) was added to the reaction mixture, which was stirred at room temperature and monitored by TLC. After disappearance of starting glycine equivalent by TLC, the reaction mixture was poured into a beaker containing 100 mL ice water. After the ice had melted the corresponding product **88b-f, i, l-q** was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high chemical yields.

Ni(II) Complex of 3-methyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88b:[66a] M.p. 212.1 °C (decomp.). ^{1}H NMR δ 1.25-1.77 (6H, m), 2.40 (3H, d, *J* = 6.9 Hz), 2.53 (3H, s), 2.66 (1H, m), 2.92-3.15 (4H, m), 3.34 (1H, t, *J* = 12.3 Hz), 3.59-3.85 (3H, m), 4.21 (1H, dd, *J* = 2.7, 9.0 Hz), 4.27 (1H, d, *J* = 4.8 Hz), 4.60 (1H, t, *J* = 8.4 Hz), 5.38 (1H, dd, *J* = 2.7, 8.4 Hz), 6.99 (1H, dt, *J* = 1.5, 7.5 Hz), 7.27-7.42 (6H, m), 7.63 (1H, dd, *J* = 1.5, 8.4 Hz), 8.42 (1H, dd, *J* = 1.2, 8.7 Hz). ^{13}C NMR δ 17.5, 18.4, 19.2, 19.9, 22.7, 29.2, 33.4, 38.6, 54.2, 56.9, 57.3, 60.7, 70.1, 72.3, 121.5, 123.9, 125.6, 126.8, 128.5, 129.1, 129.5, 131.9, 139.2, 141.3, 153.5, 168.7, 171.5, 175.5, 177.2. HRMS [M+Na^+] found *m/s* 627.1711, calcd for $C_{30}H_{34}N_4NaNiO_6$ 627.1730. $[\alpha]_D^{25}$ -1428 (CH_3Cl).

Ni(II) Complex of 3-phenyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88d:[66a] M.p. 212.1 °C (decomp.). ^{1}H NMR δ 1.26-1.61 (6H, m), 1.98 (1H, m), 2.31 (1H, m), 2.68 (3H, s), 2.85 (1H, m), 2.98 (1H, m), 3.13-3.23 (2H, m), 3.46-3.57 (2H, m), 4.26 (1H, dd, *J* = 2.7, 8.7 Hz), 4.48-4.58 (2H, s), 4.76 (1H, t, *J* = 8.4 Hz), 5.42 (1H, dd, *J* = 2.4, 8.4 Hz), . ^{13}C NMR δ 17.5, 18.4, 19.2, 19.9, 22.7, 29.2, 33.4, 38.6, 54.2, 56.9, 57.3, 60.7, 70.1, 72.3, 121.5, 123.9, 125.6, 126.8, 128.5, 129.1, 129.5, 131.90, 139.2, 141.3, 153.5, 168.7, 171.5, 175.5, 177.2. HRMS [M+Na^{+}] found *m/s* 627.1711, calcd for $C_{30}H_{34}N_4NaNiO_6$ 627.1730. $[\alpha]_D^{25}$ -1428 (CH_3Cl).

Ni(II) Complex of 3-(*o*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88e:[66a] M.p. 183.6 °C. ^{1}H NMR δ 1.25-1.58 (6H, m), 2.10 (1H, m), 2.37 (1H, m), 2.71 (3H, s), 2.89 (2H, m), 3.11 (3H, s), 3.22 (3H, t, *J* = 16.2 Hz), 4.25 (1H, d, *J* = 8.7 Hz), 4.39 (1H, m), 4.46-4.56 (2H, m), 4.75 (1H, t, *J* = 8.4 Hz), 5.43 (1H, d, *J* = 8.4 Hz), 6.98 (1H, t, *J* = 6.9 Hz), 7.03 (1H, d, *J* = 8.1 Hz), 7.25-7.40 (7H, m), 7.58 (1H, t, *J* = 7.6 Hz), 7.68 (1H, d, *J* = 8.1 Hz), 7.78 (1H, d, *J* = 7.2 Hz), 8.23 (1H, d, *J* = 8.4 Hz). ^{13}C NMR δ 18.3, 19.4, 19.7, 22.8, 33.6, 37.0, 54.5, 54.7, 55.4, 57.4, 60.1, 70.2, 72.3, 110.0, 121.2, 121.3, 123.6, 125.6, 126.8, 128.5, 128.6, 129.1, 129.3, 130.6, 131.6, 132.0, 139.3, 141.4, 153.4, 157.8, 169.2, 171.8, 174.8, 177.4. HRMS [M+Na^{+}] found *m/s* 719.1912, calcd for $C_{36}H_{38}N_4NaNiO_7$ 719.1992. $[\alpha]_D^{25}$ +1301.3 (CH_3Cl).

Ni(II) Complex of 3-(*o*-trifluoromethyl-phenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88f:[66a] M.p. 172.1 °C. ^{1}H NMR δ 1.18-1.73 (6H, m), 2.38 (1H, m), 2.48 (3H, s), 2.59 (1H, m), 2.99 (1H, m), 3.10-3.28 (3H, m), 3.62 (1H, dd, *J* = 4.2, 17.7 Hz), 4.17-4.26 (2H, m), 4.40 (1H, m), 4.61 (1H, d, *J* = 4.5 Hz), 4.69 (1H, t, *J* = 8.7 Hz), 5.39 (1H, dd, *J* = 3.0, 8.7 Hz), 6.95 (1H, m), 7.20-7.37 (6H, m), 7.61-7.68 (2H, m), 7.80-7.87 (2H, m), 8.05 (1H, d, *J* = 7.5 Hz), 8.34 (1H, dd, *J* = 1.2, 8.4 Hz). ^{13}C NMR δ18.3, 19.6, 20.0, 22.8, 38.6, 38.7, 54.6, 55.9, 57.5, 60.5, 70.3, 72.0, 121.3, 122.1, 123.2, 125.5, 125.8, 126.5, 126.8, 126.9, 128.0, 128.6, 129.2, 129.4, 129.7, 129.7, 130.1, 131.4, 132.2, 132.4, 138.6, 138.9, 141.6, 153.7, 170.4, 174.4, 177.5. HRMS [M+Na$^+$] found *m/s* 757.1716, calcd for $C_{36}H_{35}F_3N_4NaNiO_6$ 757.1760. $[\alpha]_D^{25}$ +1752.4 (CH_3Cl).

Ni(II) Complex of 3-(*N*-tosyl-indolyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88i:[66a] M.p. >200 °C (decomp.). ^{1}H NMR δ 1.14-1.36 (4H, m), 1.42-1.61 (2H, m), 2.02 (1H, m), 2.35 (3H, s), 2.39-2.50 (2H, m), 2.72 (3H, s), 2.81 (1H, m), 3.03-3.12 (2H, m), 3.49 (1H, dd, *J* = 3.3, 18.3 Hz), 3.90 (1H, m), 4.26 (1H, dd, *J* = 2.7, 8.7 Hz), 4.46-4.55 (2H, m), 4.75 (1H, t, *J* = 8.7 Hz), 5.41 (1H, dd, *J* = 2.7, 8.4 Hz), 6.93-7.07 (3H, m), 7.19-7.38 (9 H, m), 7.67 (1H, dd, *J* = 1.2, 8.4 Hz), 7.87 (1H, s), 7.91 (2H, d, *J* = 4.8 Hz), 8.15 (1H, d, *J* = 8.4 Hz), 8.30 (1H, d, *J* = 7.8 Hz). ^{13}C NMR δ 18.4, 19.0, 19.3, 21.6, 22.7, 29.6, 35.6, 37.4, 58.9, 55.4, 57.5, 59.3, 70.2, 73.1, 113.4, 120.2, 121.1, 121.2, 123.7, 123.8, 125.6, 126.1, 127.1, 128.6, 129.1, 129.5, 130.0, 131.4, 132.2, 134.6, 134.9, 139.0, 142.0, 145.2, 153.5, 168.8, 171.2, 175.0, 176.9. HRMS [M+Na$^+$] found *m/s* 882.2130, calcd for $C_{44}H_{43}N_5NaNiO_8S$ 882.2084. $[\alpha]_D^{25}$ -1094.9 (CH_3Cl).

Ni(II) Complex of 3-(*p*-Chlorophenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88l:[66a] M.p. 203.7 °C. ^{1}H NMR δ 1.24 (1 H, m), 1.33-1.41 (3 H, m), 1.50 (1 H, m), 1.62 (1 H, m), 1.98 (1 H, d, *J* = 14.7 Hz), 2.33 (1 H, m), 2.65 (3 H, s), 2.89 (1 H, d, *J* = 6.2 Hz), 3.05 (1 H, AB, *J* = 16.2 Hz), 3.17 (1 H, t, *J* = 12.3 Hz), 3.32 (1 H, AB, *J* = 16.2 Hz), 3.48-3.56 (2 H, m), 4.25 (1 H, dd, *J* = 9.01, 3.0 Hz), 4.44 (1 H, q, *J* = 10.8 Hz), 4.45 (1 H, d, *J* = 4.2 Hz), 4.74 (1 H, t, *J* = 9.0 Hz), 5.42 (1 H, dd, *J* = 8.7, 2.7 Hz), 6.98 (1 H, td, *J* = 7.2, 1.2 Hz), 7.22-7.27 (2 H, m), 7.29-7.37 (4 H, m), 7.38-7.42 (2 H, m), 7.56 (1 H, d, *J* = 8.4 Hz), 7.68 (1 H, dd, *J* = 8.4, 1.2 Hz), 8.35 (1 H, dd, *J* = 8.4, 1.2 Hz). ^{13}C NMR δ 18.5, 19.3, 19.7, 22.8, 36.8, 43.9, 54.4, 55.6, 57.5, 60.1, 70.3, 72.6, 121.5, 123.8, 125.8, 126.5, 128.7, 128.9, 129.2, 129.8, 132.1, 132.3, 134.3, 137.9, 139.1, 141.8, 153.6, 169.1, 171.3, 175.0, 176.7. HRMS [M+H$^+$] found *m/s* 701.1627, calcd for $C_{35}H_{36}N_4NiO_6$ 701.1673. $[\alpha]_D^{25}$ +1096.81 (CH_2Cl_2).

Ni(II) Complex of 3-(*m*,*m*--Dichlorophenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88m:[66a] M.p. 192.5 °C. ^{1}H NMR δ 1.24 (1 H, m), 1.36-1.42 (3 H, m), 1.51 (1 H, m), 1.62 (1 H, m), 2.00 (1 H, d, *J* = 13.6 Hz), 2.39 (1 H, m), 2.65 (3 H, s), 2.92 (1 H, d, *J* = 12.8 Hz), 3.01 (1 H, AB, *J* = 16.0 Hz), 3.16 (1 H, t, *J* = 10.8 Hz), 3.35 (1 H, AB, *J* = 16.0 Hz), 3.49-3.55 (2 H, m), 4.25 (1 H, dd, *J* = 8.4, 2.8 Hz), 4.38 (1 H, q, *J* = 10.8 Hz), 4.44 (1 H, d, *J* = 2.0 Hz), 4.74 (1 H, t, *J* = 8.8 Hz), 5.42 (1 H, dd, *J* = 8.8, 2.8 Hz), 6.99 (1 H, t, *J* = 8.4 Hz), 7.18-7.38 (7 H, m), 7.62 (1 H, d, *J* = 4.0 Hz), 7.67-7.70 (2 H, m), 8.39 (1 H, d, *J* = 9.2 Hz). ^{13}C NMR δ 18.5, 19.2, 22.7, 36.6, 43.7, 54.4, 55.8, 57.5, 60.1, 70.3, 72.4, 121.5, 123.8, 125.7, 126.3, 128.7, 129.2, 130.5, 132.4, 132.5, 133.3, 139.0, 139.7,

141.9, 153.5, 169.4, 171.0, 175.0, 176.4. HRMS [M+H$^+$] found *m/s* 735.1605, calcd for $C_{35}H_{35}Cl_2N_4NiO_6$ 735.1282. $[\alpha]_D^{25}$ +588.7 (CH_2Cl_2).

Ni(II) Complex of 3-(*m*,*m*--Difluorophenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88n:[66a] M.p. 188.3 °C. ^{1}H NMR δ 1.22 (1 H, m), 1.33-1.37 (3 H, m), 1.48 (1 H, m), 1.58 (1 H, m), 2.29 (1 H, m), 2.46 (1 H, m), 2.57 (3 H, s), 2.89 (1 H, d, *J* = 12.8 Hz), 3.12 (1 H, AB, *J* = 16.4 Hz), 3.17 (1 H, t, *J* = 12.0 Hz), 3.32 (1 H, AB, *J* = 16.4 Hz),

3.46-3.54 (2 H, m), 4.20 (1 H, dd, *J* = 8.8, 2.8 Hz), 4.33 (1 H, q, *J* = 8.4 Hz), 4.43 (1 H, d, *J* = 4.0 Hz), 4.69 (1 H, t, *J* = 8.4 Hz), 5.39 (1 H, dd, *J* = 8.8, 2.8 Hz), 6.92-7.03 (4 H, m), 7.20-7.34 (6 H, m), 7.63 (1 H, dd, *J* = 8.4, 1.2 Hz), 8.36 (1 H, dd, *J* = 8.4, 0.8 Hz). ^{13}C NMR δ 18.5, 19.3, 19.8, 22.8, 36.8, 44.1, 54.4, 55.9, 57.5, 60.2, 70.3, 72.0, 121.5, 123.7, 125.7, 126.2, 128.7, 129.2, 129.8, 132.4, 139.0, 141.9, 143.4, 143.5, 143.6, 153.6, 163.1 (1 C, d, *J* = 186.6 Hz), 163.2, (1 C, d, *J* = 186.6 Hz), 169.4, 170.9, 175.0, 176.6. ^{19}F NMR δ –108.57, –108.62. HRMS [M+H$^+$] found *m/s* 703.1892, calcd for $C_{35}H_{35}F_2N_4NiO_6$ 703.1874. $[\alpha]_D^{25}$ +396.01 (CH_2Cl_2).

Ni(II) Complex of 3-(*m*—1,1,1-trifluoromethyl-phenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88o:[66a] M.p. 190.2 °C. ^{1}H NMR δ 1.23-1.38 (4 H, m), 1.47-1.57 (2 H, m), 1.89 (1 H, d, J = 13.8 Hz), 2.34 (1 H, td, J = 13.8, 3.6 Hz), 2.67 (3 H, s), 2.85-2.95 (1 H, m), 2.90 (1 H, AB, *J* = 16.2 Hz), 3.14 (1 H, t, *J* = 10.5 Hz), 3.26 (1 H, AB, *J* = 16.2 Hz), 3.56 (1 H, dd, J = 18.6, 3.6 Hz), 3.65 (1 H, m), 4.25(1 H, dd, *J* = 8.7, 3.0 Hz), 4.50 (1 H, q, *J* = 10.2 Hz), 4.51 (1 H, d, *J* = 4.2 Hz), 4.74 (1 H, t, *J* = 8.7 Hz), 5.43 (1 H, dd, *J* = 8.4,

2.7 Hz), 6.99 (1 H, dd, J = 8.4, 1.2 Hz), 7.22-7.25 (2 H, m), 7.27-7.35 (4 H, m), 7.55 (1 H, d, *J* = 7.5 Hz), 7.68-7.76 (3 H, m), 7.87 (1 H, d, J = 7.5 Hz), 8.39 (1 H, dd, *J* = 8.4, 0.9 Hz). ^{13}C NMR δ 18.6, 19.3, 19.5, 22.7, 36.8, 44.3, 54.3, 55.7, 57.6, 60.1, 70.3, 72.5, 121.5, 123.8, 125.1, 125.2, 125.7, 126.3, 125.5, 126.6, 128.7, 129.2, 129.2, 129.8, 131.6, 132.4, 134.7, 139.0, 140.7, 141.9. ^{19}F NMR δ –261.8. HRMS [M+H$^+$] found *m/s* 735.1985, calcd for $C_{36}H_{36}F_3N_4NiO_6$ 735.1935. $[\alpha]_D^{25}$ +381.76 (CH_2Cl_2).

Ni(II) Complex of 3-ethyl-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88p:[66a] M.p. 158.2 °C. ^{1}H NMR δ 1.22 (3 H, t, J = 7.2 Hz), 1.36-1.50 (3 H, m), 1.57-1.67 (2 H, m), 1.75 (1 H, m), 2.11 (1 H, m), 2.53 (3 H, m), 2.58 (1 H, m), 2.95-3.14 (4 H, m), 3.32 (1 H, t, J = 9.9 Hz), 3.63 (1 H, AB, J = 15.6 Hz), 3.67 (1 H, q, J = 8.4 Hz), 3.76 (1 H, AB, J = 15.6 Hz), 4.15-4.22 (3 H, m), 4.45 (1 H, t, J = 8.4 Hz), 5.36 (1 H, dd, J = 6.3, 1.2 Hz), 6.99 (1 H, td, J = 6.9, 1.2 Hz), 7.27-7.42 (6 H, m), 7.65 (1 H, dd, J = 8.4, 1.2 Hz), 8.44 (1 H, dd, J = 8.4, 1.2 Hz). ^{13}C NMR δ 12.4, 18.6, 19.3, 20.0, 22.9, 34.7, 40.5, 54.3, 57.0, 57.4, 60.9, 70.3, 72.2, 121.7, 124.0, 125.8, 126.8, 128.7, 129.2, 129.8, 132.0, 139.4, 141.5, 153.6, 168.7, 172.3, 175.8, 177.7. HRMS [M+H$^+$] found *m/s* 619.2073, calcd for $C_{31}H_{37}N_4NiO_6$ 619.2062. $[\alpha]_D^{25}$ -909.45 (CH_2Cl_2).

Ni(II) Complex of 3-(*o*,*o*-dimethyl-*p*-methoxyphenyl)-5-[3'-(2'-oxazolidinonyl)]glutamic acid Schiff Base with *N*-(2-acetyl-phenyl)-2-piperidyl-acetamide 88q:[66a] M.p. 174.3 °C. ^{1}H NMR δ 1.40-1.70 (6 H, m), 2.07 (3 H, s), 2.59 (3 H, s), 2.60 (3 H, s), 2.66 (1 H, m), 2.89-2.96 (2 H, m), 3.25 (1 H, t, J = 12.6 Hz), 3.35-3.46 (2 H, m), 3.81 (3 H, s), 4.13 (1 H, dd, J = 8.7, 2.4 Hz), 4.34 (1 H, d, J = 6.9 Hz), 4.35-4.52 (2 H, m), 4.96 (1 H, t, J = 8.1 Hz), 5.34 (1 H, dd, J = 8.7, 2.4 Hz), 6.69 (1 H, d,

J = 2.7 Hz), 6.79 (1 H, d, J = 2.7 Hz), 6.99 (1 H, td, J = 8.1, 1.2 Hz), 7.21-7.39 (6 H, m), 7.64 (1 H, dd, J = 8.1, 1.5 Hz), 8.37 (1 H, dd, J = 8.7, 1.2 Hz). ^{13}C NMR δ 18.4, 19.4, 20.0, 22.2, 22.9, 22.9, 37.08, 39.1, 54.2, 55.5, 57.4, 60.3, 70.3, 72.9, 113.5, 117.2, 121.5, 123.6, 125.7, 126.6, 128.7, 129.2, 129.9, 132.3, 139.2, 140.7, 141.2, 141.9, 153.7, 158.2, 168.1, 172.0, 175.3, 178.2. HRMS [M+H$^+$] found *m/s* 725.2576, calcd for $C_{38}H_{43}N_4NiO_6$ 725.2481. $[\alpha]_D^{25}$ -482.35 (CH_2Cl_2).

3.8.7 Homologation of 'NH' Glycine Equivalents 56m-o

Alkylation of Ni(II) Complexes 56m-o Under Achiral Phase Transfer Conditions. General Procedure. To a flask containing the corresponding Ni(II) complex **56m-o** (0.10 g), tetrapropylammonium iodide (25 mol%), 15 ml of dichloromethane and 5 ml of 30% aqueous sodium hydroxide, alkyl bromide (1.0 equiv) was added and the reaction mixture was stirred at room temperature. After disappearance of **56m-o** by TLC, 10 mL of water was added and the organic layer was extracted with $CHCl_3$ three times. The combined organic layer was dried over magnesium sulfate, and concentrated under vacuum to afford the corresponding products **56c, 89-97**.

Ni(II) Complex of Phenylalanine Schiff base with N-(2-benzoyl-phenyl)-2-benzylamino-acetamide (upper diasteriomer) 89:[69] M.p. 219.7^o C (decomp.). ^{1}H NMR δ 2.0 (1 H, t, *J* = 7.5 Hz), 2.72-2.84 (2 H, m), 3.08-3.16 (2 H, m), 3.66 (1 H, ABX, *J* = 13.8, 10.2 Hz), 4.04 (1 H, AB, *J* = 13.8 Hz), 4.37 (1 H, m), 6.84 (1 H, m), 7.08-7.19 (2 H, m), 7.23-7.48 (6 H, m), 7.49 (1 H, m), 7.52-7.65 (6 H, m), 7.74 (1 H, dd, *J* = 6.6, 2.4 Hz), 8.42 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 39.54, 53.14, 54.68, 71.34, 121.03,

124.32, 127.11, 127.41, 127.83, 128.78, 128.96, 129.10, 129.32, 129.74, 130.12, 131.67, 132.54, 133.77, 133.86, 134.43, 136.47, 142.99, 170.39, 176.81, 178.34. HRMS expected for $C_{21}H_{27}N_3NaNiO_3$ is 570.1298, found 570.1312.

Ni(II) Complex of Phenylalanine Schiff base with *N*-(2-benzoyl-phenyl)-2-benzylamino-acetamide (lower diasteriomer) 90:[69] M.p. 219.7° C (decomp.). ^{1}H NMR δ 2.43 (1H, m), 2.75-2.91 (2 H, m), 3.12-3.23 (2 H, m), 3.65 (1 H, ABX, *J* = 13.5, 9.6 Hz), 3.96 (1 H, AB, *J* = 13.5 Hz), 4.35 (1 H, m), 6.77-6.83 (2 H, m), 7.08-7.16 (2 H, m), 7.26-7.37 (5 H, m), 7.42-7.48 (2 H, m), 7.51-7.63 (6 H, m), 7.72 (1 H, dd, *J* = 5.7, 2.4 Hz), 8.38 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 39.57, 52.75, 55.38, 71.23, 121.02, 123.69, 126.94, 127.40, 127.69, 127.80, 128.71, 128.85, 128.92, 128.95, 129.15, 129.70, 130.12, 131.46, 132.70, 133.37, 133.80, 136.22, 142.98, 170.37, 176.73, 179.08. HRMS expected for $C_{21}H_{27}N_3NaNiO_3$ is 570.1298, found 570.1307.

Ni(II) Complex of Phenylalanine Schiff base with *N*-(2-benzoyl-phenyl)-2-dibenzylamino-acetamide 91:[69] M.p. 295.2 °C (decomp.). ^{1}H NMR δ 2.64 (1 H, d, *J* = 16.4 Hz), 2.73 (1 H, dd, *J* = 13.5, 5.29 Hz), 3.02 (1 H, d, *J* = 12.3 Hz), 3.04 (1 H, dd, *J* = 13.3, 3.37 Hz), 3.17 (1 H, d, *J* = 14.1 Hz), 3.49 (1 H, d, *J* = 14.2 Hz), 3.58 (1 H, d, *J* = 16.3 Hz), 3.83 (1 H, d, *J* = 12.3 Hz), 4.31 (1 H, dd, *J* = 5.28, 3.38 Hz), 6.60-6.68 (2 H, m), 6.96-7.09 (3 H, m), 7.17-7.80 (17 H, m), 8.20-8.28 (2 H, m). ^{13}C NMR δ 39.0, 62.3, 62.7, 62.8, 71.3, 120.5, 123.5, 126.2, 127.1, 127.3, 127.5, 128.4, 128.5, 128.6, 128.7, 128.9, 129.7, 130.2, 131.2, 131.6, 131.8, 132.8, 133.5, 134.0, 136.3, 142.0, 170.2, 175.5, 177.6. HRMS expected for $C_{38}H_{33}N_3NaNiO_3$ is 660.1768, found 660.1781.

Ni(II) Complex of Phenylalanine Schiff base with *N*-(2-benzoyl-phenyl)-2-*iso*-propylamino-acetamide 92:[69] M.p. 245.9° C (decomp.). ^{1}H NMR δ 1.28 (3 H, d, *J* = 6.3 Hz), 1.46 (3 H, d, *J* = 6.3 Hz), 1.74 (1 H, bs), 2.67-2.73 (2 H, m), 2.93 (1 H, d, *J* = 16.5 Hz), 3.08 (1 H, dd, *J* = 13.5, 3.0 Hz), 3.32 (1 H, dd, *J* = 16.5, 7.2 Hz), 4.33 (1 H, dd, *J* = 5.4, 3.0 Hz), 6.82 (2 H, d, *J* = 3.6 Hz), 7.14 (1 H, m), 7.31-7.37 (2 H, m), 7.43-7.46 (2 H, m), 7.55-7.62 (6 H, m), 8.39 (1 H, d, *J* = 9.0 Hz). ^{13}C NMR δ 20.37, 21.75, 39.25, 52.02, 53.08, 71.23, 121.07, 123.59, 127.27, 127.35, 127.71, 127.86, 128.71, 129.14, 129.34, 130.14, 131.54, 132.81, 133.78, 133.83, 136.24, 142.93, 170.26, 176.77, 178.76. HRMS expected for $C_{27}H_{27}N_3NaNiO_3$ is 522.1298, found 522.1375.

Ni(II) Complex of Phenylalanine Schiff base with *N*-(2-benzoyl-phenyl)-2-*tert*-butylamino-acetamide 94:[69] M.p. 272.9° C (decomp.).^{1}H NMR δ 1.30 (9 H, s), 1.78 (1 H, d, *J* = 7.2 Hz), 2.66 (1 H, dd, *J* = 13.5, 6.0 Hz), 3.03 (1 H, d, *J* = 16.5 Hz), 3.07 (1 H, dd, *J* = 13.5, 2.7 Hz), 3.37 (1 H, dd, *J* = 16.5, 7.2 Hz), 4.33 (1 H, dd, *J* = 5.4, 3.0 Hz), 6.84 (2 H, d, *J* = 3.9 Hz), 7.14 (1 H, m), 7.32-7.43 (4 H, m), 7.55-7.63 (6 H, m), 8.26 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 27.76, 29.75, 39.02, 50.88, 57.74, 70.80, 121.04, 123.34, 127.33, 127.61, 127.76, 128.02, 128.80, 129.14, 129.35, 130.19, 131.40, 132.94, 133.73, 133.88, 136.09, 142.82, 170.40, 176.33, 178.73. HRMS expected for $C_{28}H_{29}N_3NaNiO_3$ is 536.1454, found 536.1472.

Ni(II) Complex of (*E*)-2-amino-5-phenylpent-4-enoic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-*tert*-butylamino-acetamide 95:[69] M.p. 198.3° C (decomp.). ^{1}H NMR δ 1.37 (9 H, s), 2.26 (1 H, d, *J* = 7.5 Hz), 2.34 (1 H, m), 2.64 (1 H, m), 2.98 (1 H, d, *J* = 16.8 Hz), 3.23 (1 H, dd, *J* = 16.8, 7.5 Hz), 4.19 (1 H, dd, *J* = 5.7, 3.3 Hz), 6.72 (1 H, d, *J* = 15.9 Hz), 6.82 (1 H, d, *J* = 4.2 Hz), 7.04-7.15 (2 H, m), 7.30-7.38 (3 H, m), 7.44 (2

H, t, *J* = 7.2 Hz), 7.50-7.60 (3 H, m), 7.66 (2 H, d, *J* = 7.5 Hz), 8.34 (1 H, d, *J* = 8.4 Hz). ^{13}C NMR δ 27.89, 36.65, 50.66, 58.00, 69.92, 121.04, 123.23, 124.01, 126.40, 127.20, 127.72, 127.97, 128.03, 129.07, 129.26, 130.07, 132.96, 133.69, 133.85, 135.38, 137.32, 142.89, 170.54, 176.86, 178.96. HRMS expected for $C_{30}H_{31}N_3NaNiO_3$ is 562.1611, found 562.1620.

Ni(II) Complex of 2-amino-4-enoic acid Schiff base with *N*-(2-benzoyl-phenyl)-2-*tert*-butylamino-acetamide 96:[69] M.p. 116.3° C (decomp.). ^{1}H NMR δ 1.46 (9 H, s), 2.32 (1 H, m), 2.48 (1 H, m), 2.73 (1 H, d, *J* = 7.5 Hz), 3.41 (1 H, d, *J* = 16.8 Hz), 4.08 (1 H, dd, *J* = 6.3, 3.6 Hz), 4.28 (1 H, dd, *J* = 16.8, 7.5 Hz), 5.26 (1 H, dd, *J* = 17.1, 1.5 Hz), 5.56 (1 H, dd, *J* = 10.1, 1.5 Hz), 6.63 (1 H, m), 6.81 (1 H, m), 6.99 (1 H, m), 7.32-7.38 (2 H, m), 7.48-7.55 (3 H, m), 8.33 (1 H, d, *J* = 8.1 Hz). ^{13}C NMR δ 27.96, 38.12, 51.36, 58.05, 69.43, 120.01, 121.12, 123.31, 127.13, 127.72, 127.98, 129.02, 129.20, 130.03, 132.32, 132.88, 133.67, 133.83, 142.63, 170.64, 176.78, 179.05. HRMS expected for $C_{24}H_{27}N_3NaNiO_3$ is 486.1298, found 486.1308.

Ni(II) Complex of 2-aminopent-4-ynoic Acid Schiff base with *N*-(2-benzoyl-phenyl)-2-*tert*-butylamino-acetamide 97:[69] M.p. 236.7° C (decomp.). ^{1}H NMR δ 1.47 (9 H, s), 2.28 (1 H, dq, *J* = 19.8, 2.7 Hz), 2.67 (1 H, dt, *J* = 17.4, 2.7 Hz), 2.81-2.86 (2 H, m), 3.41 (1 H, d, *J* = 16.5 Hz), 4.05 (1 H, dd, *J* = 6.3, 3.0 Hz), 4.27 (1 H, dd, *J* = 16.5, 7.2 Hz), 6.81 (2 H, m), 7.05 (1 H, m), 7.31-7.39 (2 H, m), 7.48-7.58 (3 H, m), 8.32 (1 H, d, *J* = 8.1 Hz). ^{13}C NMR δ 23.89, 27.95, 51.50, 57.97, 67.25, 74.24, 79.54, 121.10, 123.52, 126.86, 127.70, 127.74, 129.27, 130.18, 133.03, 133.64, 133.70, 142.92, 171.37, 176.90, 178.46. HRMS expected for $C_{24}H_{25}N_3NaNiO_3$ is 484.1141, found 484.1172.

The Michael addition of the oxazolidinone derived amides of cinnamic acid 84c,d and nucleophilic glycine equivalents 56m-o. General Procedure. To a flask containing **56m-o** (0.10 g), 3-((*E*)-3-alkylacryloyl)oxazolidin-2-one **84c,d** (1.05 eq.) and 3 ml of DMF, DBU (15 mol%) was added to the reaction mixture, which was stirred at room temperature and monitored by TLC. After disappearance of starting glycine equivalent by TLC, the reaction mixture was poured into a beaker containing 100 mL ice water. After the ice had melted the corresponding product **97-100**, was filtered from the aqueous solution and dried in an oven to afford the appropriate product in high chemical yields.

Ni(II) Complex of (2*S*, 3*R*, 4'*R*)-3-methyl-5-[3'-(4'-phenyl-2'-oxazolidinonyl)]Glutamic Acid Schiff base with *N*-(2-benzoyl-phenyl)-2-*tert*-butylamino-acetamide 97:[69] M.p. 153.7^{o} C. ^{1}H NMR δ 1.43 (9 H, s), 1.91 (3 H, s), 3.04 (1 H, dd, J = 18.3, 7.2 Hz), 3.24 (1 H, dd, J = 18.3, 7.2 Hz), 3.39 (1 H, d, J = 17.1 Hz), 4.16 (1 H, d, J = 4.5 Hz), 4.22 (1 H, dd, J = 9.0, 3.6 Hz), 4.39 (1 H, q, J = 17.1, 7.2 Hz), 4.61 (1H, t, J = 8.7 Hz), 5.28 (1H, dd, J = 8.7, 3.3 Hz), 6.78 (2 H, d, J = 4.8 Hz), 6.94 (1 H, d, J = 7.8 Hz), 7.25 (2 H, m), 7.30-7.47 (7 H, m), 7.53 (1 H, t, J = 7.8 Hz), 8.37 (1 H, d, J = 8.4 Hz). ^{13}C NMR δ 16.85, 27.97, 33.75, 38.94, 51.51, 57.50, 57.89, 69.93, 72.32, 120.98, 123.04, 126.09, 127.33, 127.81, 128.59, 128.83, 129.03, 129.09, 129.85, 132.88, 133.68, 134.00, 139.23, 142.73, 153.55, 170.46, 171.24, 177.12, 177.78. HRMS expected for $C_{34}H_{36}N_4NiO_6$ is 677.1880, found 677.1918.

Ni(II) Complex of (2*S*, 3*R*, 4'*R*)-3-phenyl-5-[3'-(4'-phenyl-2'-oxazolidinonyl)]Glutamic Acid Schiff base with *N*-(2-benzoyl-phenyl)-2-*tert*-butylamino-acetamide 98:[69] M.p. 183.1° C. ^{1}H NMR δ 1.28 (9 H, s), 2.67 (1 H, s), 2.97 (1 H, d, J = 16.8 Hz), 3.20-3.37 (2 H, m), 3.51 (1 H, dd, J = 17.7, 8.4 Hz), 3.74 (1 H, dd, J = 17.7, 8.4 Hz), 4.17 (1 H, dd, J = 9, 3.9 Hz), 4.46 (1 H, d, J = 4.5 Hz), 4.61 (1 H, t, J = 8.7 Hz), 5.18 (1 H, dd, J = 8.7, 3.6 Hz), 6.79 (1 H, m), 6.98-7.03 (3 H, m), 7.26-7.38 (7 H, m), 7.43-7.49 (3 H, m), 7.54-7.63 (4 H, m), 8.23 (1 H, d, J = 8.4 Hz). ^{13}C NMR δ 27.78, 36.55, 44.93, 50.81, 57.45, 59.70, 69.72, 72.53, 120.89, 123.10, 125.81, 127.34, 127.63, 128.24, 128.32, 128.82, 128.87, 129.03, 129.18, 129.97, 130.62, 132.88, 133.62, 133.94, 138.83, 139.11, 142.79, 153.29, 169.99, 170.83, 176.36, 177.20. HRMS expected for $C_{39}H_{39}N_4NiO_6$ is 739.2037, found 739.2078.

Ni(II) Complex of (2*S*, 3*R*, 4'*R*)-3-phenyl-5-[3'-(4'-phenyl-2'-oxazolidinonyl)]Glutamic Acid Schiff base with *N*-(2-benzoyl-phenyl)-2-*iso*-propylamino-acetamide 99:[69] M.p. 183.1° C. ^{1}H NMR δ 1.29 (3 H, d, *J* = 6.6 Hz), 1.37 (3 H, d, *J* = 6.6 Hz), 2.67 (1 H, s), 2.74 (1 H, h, *J* = 6.6 Hz), 2.86 (1 H, d, *J* = 16.5 Hz), 3.18-3.30 (2 H, m), 3.56 (1 H, dd, *J* = 18.6, 8.7 Hz), 3.72 (1 H, dd, *J* = 18.6, 8.7 Hz), 4.20 (1 H, dd, *J* = 8.7, 3.9 Hz), 4.49 (1 H, d, *J* = 4.5 Hz), 4.63 (1 H, t, *J* = 9.0 Hz), 5.18 (1 H, dd, *J* = 8.7, 3.9Hz), 6.74 (1 H, d, *J* = 2.7 Hz), 6.99-7.05 (3 H, m), 7.24 (1 h, d, *J* = 2.7 Hz), 7.27 (1 H, d, *J* = 2.7 Hz), 7.28-7.33 (5 H, m), 7.37 (1 H, t, *J* = 7.2 Hz), 7.47-7.52 (3 H, m), 7.56-7.62 (3 H, m), 8.40 (1 H, d, *J* = 9.3 Hz). ^{13}C NMR δ 20.22, 21.44, 29.30, 44.95, 52.75, 53.779, 57.47, 69.77, 73.29, 124.67, 125.66, 125.91, 127.27, 127.95, 128.31, 128.42, 128.49, 128.75, 128.88, 129.33, 129.42, 130.32, 130.80, 132.57, 132.70,

132.86, 138.82, 139.21, 141.57, 153.35, 169.80, 169.98, 176.94, 177.08. HRMS expected for $C_{38}H_{36}N_4NaNiO_6$ is 759.1501, found 759.1584.

Ni(II) Complex of (2*S*, 3*R*, 4'*R*)-3-phenyl-5-[3'-(4'-phenyl-2'-oxazolidinonyl)]Glutamic Acid Schiff base with *N*-(2-benzoyl-phenyl)-2-benzylamino-acetamide 100:[69] M.p. 146.3° C. ^{1}H NMR δ 2.66-2.89 (4 H, m), 3.25-3.42 (3 H, m), 3.85 (1 H, dd, *J* = 16.2, 6.0 Hz), 4.18 (1 H, dd, *J* = 8.7, 3.9 Hz), 4.43 (1 H, d, *J* = 4.2 Hz), 4.60 (1 H, t, *J* = 8.7 Hz), 5.18 (1 H, dd, *J* = 8.7, 3.9 Hz), 6.71-6.84 (3 H, m), 6.97-7.01 (2 H, m), 7.05 (1 H, d, *J* = 6.9 Hz), 7.11-7.14 (2 H, m), 7.23-7.47 (10 H, m), 7.56-7.59 (2 H, m), 7.67-7.73 (3 H, m), 8.38 (1 H, d, *J* = 8.7 Hz). ^{13}C NMR δ 36.44, 45.18, 53.08, 54.69, 57.47, 69.75, 73.38, 121.04, 123.85, 125.72, 125.86, 126.88, 126.96, 127.24, 127.97, 128.28, 128.37, 128.74, 128.89, 129.14, 129.62, 129.79, 130.72, 132.57, 133.53, 133.61, 133.98, 138.72, 132.84, 139.24, 142.93, 169.89, 171.02, 175.94, 176.60, 177.47. HRMS expected for $C_{42}H_{36}N_4NaNiO_6$ is 773.1880, found 773.1813.

3.8.8 Application of a Modular 'NH' Ligand as a Chiral Resolving Agent

Synthesis of Diastereomers from Ni(II) Complexes of Schiff bases with various amino acids and *(R)-N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 54p: To a flask containing ligand **54p** (0.50 g, 1.3 mmol), $Ni(NO_3)_2 \cdot 6H_2O$ (0.75 g, 2.6 mmol), racemic amino acid (2.0 eq) and 5 mL of MeOH, was added KOH (0.51 g, 9.1 mmol), and the reaction mixture was stirred at 60-70 °C for 1 day. After removal of the solvent, under reduced pressure, water was added to the

residue. Then, the organic layer was extracted with CH_2Cl_2 and washed with water several times to remove the unreacted amino acid. The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated under vaccuum. After evaporation of the solvents and silica-gel column chromatography, the desired complexes **101a-f** and **102a,d-f** were obtained in moderate yields.

Ni(II) Complex of (S)-alanine Schiff Base with *(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 101a: M.p. 269.4 °C (decomp.). ^{1}H NMR δ 1.42 (3 H, d, *J* = 7.03 Hz), 1.58 (3 H, s), 1.67 (3 H, d, *J* = 6.74 Hz), 2.53 (1 H, bs), 2.95 (3 H, s), 3.80 (1 H, q, *J* = 7.03 Hz), 3.89 (1 H, m), 6.58 (1 H, m), 6.65 (1 H, m), 6.84 (1 H, bd, *J* = 7.91 Hz), 7.04-7.15 (2 H, m), 7.18-7.28 (4 H, m), 7.39-7.57 (3 H, m), 8.03 (1 H, d, *J* = 8.79 Hz), 8.20 (2 H, bd, *J* = 7.32 Hz). ^{13}C NMR δ 21.0, 22.1, 22.6, 33.3, 57.5, 64.9, 65.1, 120.2, 123.4, 126.8, 127.4, 127.6, 128.2, 128.6, 128.7, 129.2, 129.4, 131.7, 132.8, 133.5, 140.3, 142.2, 169.6, 180.4, 180.9. HRMS [M+Na^+] found *m/s* 536.1418, calcd for $C_{28}H_{29}N_3NaNiO_3$ 536.1460. $[\alpha]_D^{25}$ +747.1 (*c* 1.08, $CHCl_3$).

Ni(II) Complex of (*R*)-alanine Schiff Base with *(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 102a: ^{1}H NMR δ 1.12 (3 H, s), 1.51 (3 H, d, *J* = 7.32 Hz), 2.75-2.90 (1 H, m), 2.82 (3 H, d, *J* = 7.04 Hz), 3.80 (1 H, dq, *J* = 8.50, 7.04 Hz), 3.99 (1 H, q, *J* = 7.32 Hz), 6.76-6.85 (2 H, m), 6.98-7.04 (1 H, m), 7.20-7.60 (10 H, m), 8.55 (1 H, d, *J* = 8.50 Hz). ^{13}C NMR δ 21.2, 24.2, 27.5, 33.1, 59.4, 65.5, 66.7, 121.0, 123.8, 125.6, 127.0, 127.3, 127.7, 127.8, 128.8, 128.9, 129.1, 129.7, 132.5, 133.4, 133.7, 142.4, 143.2, 170.1, 180.5, 180.8.

Ni(II) Complex of (*S*)-2-Aminobutyric Acid Schiff Base with *(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 101b: M.p. 281.0 °C (decomp.). ^{1}H NMR δ 1.36 (3 H, m), 1.56 (3 H, s), 1.60-1.75 (2 H, m), 1.65 (3 H, d, *J* = 6.93 Hz), 2.70-3.00 (1 H, m), 2.87 (3 H, s), 3.81 (1 H, dd, *J* = 6.80, 4.15 Hz), 3.87 (1 H, dd, *J* = 6.93, 3.12 Hz), 6.54-6.66 (2 H, m), 6.85 (1 H, m), 7.00-7.12 (2 H, m), 7.13-7.25 (3 H, m), 7.35-7.56 (3 H, m), 8.07 (1 H, dd, *J* = 8.69, 1.68 Hz), 8.24 (2 H, bd, *J* = 7.52 Hz). ^{13}C NMR δ 9.58, 22.3, 23.3, 27.5, 33.3, 57.8, 65.3, 69.9, 120.4, 123.4, 126.8, 127.1, 127.6 127.9, 128.5, 128.8, 128.9, 129.3, 129.6, 132.0, 133.2, 134.1, 140.4, 142.5, 170.1, 179.8, 180.4. HRMS [M+H^{+}] found *m/s* 528.1666, calcd for $C_{29}H_{32}N_3NiO_3$ 528.1797. $[\alpha]_D^{25}$ +2909 (*c* 0.05, $CHCl_3$).

Ni(II) Complex of (*S*)-Phenylalanine Schiff Base with *(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 101d: M.p. 289 °C (decomp.). ^{1}H NMR δ 1.58 (3 H, d, *J* = 7.02 Hz), 2.17 (6 H, s), 2.21 (1 H, bs), 2.68 (1 H, dd, *J* = 13.8, 5.57 Hz), 3.08 (1 H, dd, *J* = 13.8, 4.40 Hz), 3.75 (1 H, qd, *J* = 7.03, 3.22 Hz), 4.10 (1 H, dd, *J* = 5.57, 4.40 Hz), 6.59 (1 H, dd, *J* = 8.21, 2.05 Hz), 6.64 (1 H, ddd, *J* = 8.20, 6.45, 1.17 Hz), 7.00-7.60 (14 H, m), 8.09 (2 H, bd, *J* = 7.32 Hz), 8.17 (1 H, dd, *J* = 8.79, 1.17 Hz). ^{13}C NMR δ 22.1, 23.1, 32.8, 39.1, 57.4, 64.9, 70.1, 120.1, 123.0, 126.7, 126.9, 127.2, 127.7, 127.8, 128.3, 128.7, 128.9, 129.1, 129.6, 130.1, 132.1, 133.3, 134.1, 135.5, 140.3, 142.9, 170.5, 179.0, 180.2. HRMS [M+Na^{+}] found *m/s* 612.1725, calcd for $C_{34}H_{33}N_3NaNiO_3$ 612.1773. $[\alpha]_D^{25}$ +482.2 (*c* 1.03, $CHCl_3$).

Ni(II) Complex of (*R*)-Phenylalanine Schiff Base with *(R)*-*N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 102d: ^{1}H NMR δ 0.95 (3 H, s), 2.11 (3 H, s), 2.53 (1 H, d, *J* = 8.80 Hz), 2.65-2.85 (1 H, m), 2.73 (3 H, d, *J*

= 7.04 Hz), 3.08 (1 H, dd, *J* = 13.8, 3.82 Hz), 3.66 (1 H, dq, *J* = 8.50, 7.04 Hz), 3.35 (1 H, dd, *J* = 6.86, 4.11 Hz), 6.74-6.87 (2 H, m), 6.96-7.76 (19 H, m), 8.62 (1 H, dd, *J* = 8.50, 1.17 Hz). ^{13}C NMR δ 24.2, 27.4, 30.8, 38.7, 59.3, 66.3, 70.5, 120.8, 123.4, 125.6, 127.0, 127.0, 127.3, 127.7, 128.0, 128.8, 129.0, 129.1, 129.8, 130.1, 132.7, 133.9, 134.1, 135.5, 143.1, 170.9, 179.1, 180.6.

Ni(II) Complex of (*S*)-Valine Schiff Base with *(R)-N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 101e: M.p. 309.3 °C (decomp.). ^{1}H NMR δ 0.73 (3 H, d, *J* = 6.73 Hz), 1.56 (3 H, s), 1.65-1.85 (1 H, m), 1.69 (3 H, d, *J* = 6.94 Hz), 1.75 (3 H, d, *J* = 6.25 Hz), 2.83 (3 H, s), 3.08 (1 H, bd, *J* = 2.34 Hz), 3.66 (1 H, d, *J* = 3.12 Hz), 3.86 (1 H, m), 6.56-6.65 (2 H, m), 6.85 (1 H, bd, *J* = 7.72 Hz), 7.03 (1 H, m), 7.06 (1 H, m), 7.13-7.20 (2 H, m), 7.22 (1 H, bd, *J* = 7.23 Hz), 7.41 (1 H, m), 7.44-7.55 (2 H, m), 8.15 (1 H, d, *J* = 8.50 Hz), 8.21 (2 H, bd, *J* = 7.42 Hz). ^{13}C NMR δ 17.7, 19.8, 22.1, 23.1, 32.8, 34.1, 57.7, 65.0, 73.8, 120.1, 123.0, 126.9, 129.9, 127.6, 127.9, 128.2, 128.5, 128.8, 129.3, 129.3, 131.9, 133.2, 134.1, 140.6, 142.6, 170.0, 178.1, 180.8. HRMS [M+H^{+}] found *m/s* 542.1964, calcd for $C_{30}H_{34}N_3NiO_3$ 542.1954. $[\alpha]_D^{25}$ +2424 (*c* 0.09, $CHCl_3$).

Ni(II) Complex of (*R*)-Valine Schiff Base with *(R)-N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 102e: M.p. 303.5 °C (decomp.). ^{1}H NMR δ 0.73 (3 H, d, *J* = 6.54 Hz), 1.12 (3 H, s), 1.79 (3 H, s), 2.77 (1 H, d, *J* = 8.79 Hz), 2.82 (3 H, s), 2.84 (3 H, d, *J* = 6.93 Hz), 3.80 (1 H, d, *J* = 2.54 Hz), 3.88 (1 H, m), 6.77 (1 H, m), 6.81 (1 H, dd, *J* = 8.20, 2.05 Hz), 6.99 (1 H, m), 7.20-7.60 (11 H, m), 8.64 (1 H, m). ^{13}C NMR δ 17.7, 19.8, 22.1, 23.1, 32.8, 34.1, 57.7, 65.0, 73.8, 120.1, 123.0, 126.9,

126.9, 127.6, 127.9, 128.2, 128.5, 128.8, 129.3, 129.3, 131.9, 133.2, 134.1, 140.6, 142.6, 170.0, 178.1, 180.8. HRMS [M+H$^+$] found *m/s* 542.1996, calcd for $C_{30}H_{34}N_3NiO_3$ 542.1954. $[\alpha]_D^{25}$ -2791 (*c* 0.06, $CHCl_3$).

Ni(II) Complex of (*S*)-Phenylglycine Schiff Base with *(R)-N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 101f: M.p. 263.1 °C (decomp.). ^{1}H NMR δ 1.41 (3 H, s), 1.73 (3 H, d, *J* = 6.84 Hz), 2.61 (3 H, s), 3.03 (1 H, bd, *J* = 2.83 Hz), 3.89 (1 H, m), 4.66 (1 H, s), 6.01 (1 H, m), 6.55-6.65 (2 H, m), 6.95 (1 H, m), 7.03-7.12 (2 H, m), 7.16-7.38 (8 H, m), 7.45-7.55 (2 H, m), 8.00 (1 H, m), 8.32 (2 H, bd, *J* = 7.52 Hz). ^{13}C NMR δ 22.1, 22.5, 32.9, 57.9, 64.9, 73.0, 120.3, 123.6, 126.0, 126.4, 126.5, 127.1, 127.7, 127.8, 128.2, 128.3, 128.3, 129.1, 129.5, 132.1, 133.1, 134.2, 138.0, 140.5, 142.8, 171.7, 178.4, 181.2. HRMS [M+H$^+$] found *m/s* 576.1746, calcd for $C_{33}H_{32}N_3NiO_3$ 576.1797. $[\alpha]_D^{25}$ +1734 (*c* 0.05, $CHCl_3$).

Ni(II) Complex of (*R*)-Phenylglycine Schiff Base with *(R)-N*-(2-benzoylphenyl)-2,2-dimethyl-2-(1-phenyl-ethylamino)-acetamide 102f: M.p. 264.5 °C (decomp.). ^{1}H NMR δ 1.15 (3 H, s), 2.89 (3 H, d, *J* = 6.93 Hz), 2.93 (3 H, s), 2.98 (1 H, d, *J* = 8.60 Hz), 3.86 (1 H, m), 4.89 (1 H, s), 6.09 (1 H, m), 6.74 (1 H, ddd, *J* = 8.10, 6.93, 1.17 Hz), 6.80 (1 H, dd, *J* = 8.20, 1.66 Hz), 6.97 (1 H, m), 7.14-7.60 (14 H, m), 8.63 (1 H, dd, *J* = 8.59, 1.07 Hz). ^{13}C NMR δ 24.2, 27.3, 32.8, 59.5, 66.4, 73.4, 120.9, 123.8, 125.6, 125.9, 126.4, 126.9, 127.2, 127.6, 127.7, 127.7, 128.2, 128.3, 128.9, 129.1, 132.6, 133.7, 134.0, 137.9, 142.8, 143.0, 172.1, 178.2, 181.0. HRMS [M+H$^+$] found *m/s* 576.1746, calcd for $C_{33}H_{32}N_3NiO_3$ 576.1797. $[\alpha]_D^{25}$ -2069 (*c* 0.05, $CHCl_3$).

8.3.9 Disassembly of Modular Glycine Equivalents and Isolation of the Corresponding Free α-Amino Acids

Decomposition of Ni(II) Complex of α,α-diallylglycine Schiff Base with *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 57a yielding α,α-diallylglycine 3a and *N*-(2-benzoyl-phenyl)-2-dibutylamino-acetamide 54b. To a solution of 22mL (14.5mL/1g of complex **57a**)of MeOH and 11mL(7.25mL/1g of complex **57a**) of 3*N* HCl at 70^{o} C was added 1.471g (2.527 mmol) of complex **57a**. The solution was stirred for 30 min. and evaporated. The acid **3a** and Ni(II) were extracted in 50mL of DI water from ligand **54b** and CH_2Cl_2 then evaporated. Following the evaporation the crystalline compounds were dissolved in the minimum amount of DI water and placed on a ion-exchange column using Dowex 50x2-100 resin. The column was first washed with DI water until neutral and followed by 8% aq. ammonium hydroxide 500mL to elute acid **3a**. This solution was evaporated to afford 0.3843g (2.476 mmol, 98% yield) of acid **3a**. The Ni(II) was eluted with concentrated HCl after the column was returned to neutral with DI water. Ligand **54b** was recovered by the evaporation of the organic layer from the fore mentioned separation.

Decomposition of complexes 88c-e, l-m; Isolation of (2*S*, 3*S*)-3-alkyl-, (2*S*, 3*R*)-3-arylpyroglutamic acids 73c-e, l-m, recovery of ligand 54h, and starting chiral auxillary (*S*)-105. (General Procedure). A solution of pure complex **88c-e**, **l-m** (25 mmol) in MeOH (50 mL) was slowly added to a stirring solution of aqueous 3*N* HCl in MeOH (90 mL, ratio 1:1, acid:MeOH) at 70 ^{o}C. Upon disappearance of the red color, the reaction mixture was evaporated in vacuum until dryness. Water (85 mL) was added and

the resultant mixture was treated with an excess of concentrated ammonium hydroxide and extracted with methylene chloride. The methylene chloride extracts were dried over magnesium sulfate and evaporated in vacuum to afford 10.59g of a 1:1 mixture (99%) of ligand **54h**, and chiral auxillary (*S*)-**105**. The aqueous solution was evaporated in vacuum, dissolved in a minimum amount of water, and loaded on a cation exchange resin Dowex 50X2 100 column. The column was washed with water and the acidic fraction was collected to give the pyroglutamic acid **73c-e**, **l-m**. An analytically pure sample of the product was obtained by crystallization of the compound from THF/*n*-hexane.

(2*S*,3*S*)-3-Methylpyroglutamic acid 73c:[66a] Yield 96%. M.p. 111.5 °C. ^{1}H-NMR (CD_3OD) δ 1.27 (3H, d, *J* = 6.4 Hz), 1.99 (1H, dd, *J* = 8.5, 20.0 Hz), 2.54 (1H, dd, *J* = 9.3, 20.0 Hz), 2.50-2.59 (1H, m), 3.82 (1H, d, *J* = 4.9 Hz). ^{13}C-NMR (CD_3OD) δ 20.1, 34.8, 38.4, 63.1, 174.0, 178.3. HRMS $[M+H]^+$ found *m*/*s* 144.0660, calcd. for $C_6H_{10}NO_3$ 144.0661. $[\alpha]_D^{25}$ +41.0 (*c* 1.16, CH_3OH).

(2*S*,3*R*)-3-Phenylpyroglutamic acid 73d:[66a] Yield 95%. M.p. 140.0 °C. ^{1}H-NMR (CD_3OD) δ 2.31 (1H, dd, *J* = 6.1, 17.1 Hz), 2.73 (1H, dd, *J* = 9.3, 17.1 Hz), 3.58 (1H, ddd, *J* = 4.9, 6.1, 9.3 Hz), 4.10 (1H, d, *J* = 4.9 Hz), 7.12-7.26 (5H, m). ^{13}C-NMR (CD_3OD) δ 39.3, 45.6, 64.6, 127.9, 128.4, 130.0, 143.9, 174.9, 179.7. HRMS $[M+H]^+$ found *m*/*s* 206.0809, calcd. for $C_{11}H_{12}NO_3$ 206.0817. $[\alpha]_D^{25}$ +75.6 (*c* 0.74, CH_3OH).

(2*S*,3*R*)-3-(3-Methoxyphenyl)pyroglutamic acid 73e:[66a] Yield 85%. M.p. 150.0 °C. ^{1}H-NMR (CD_3OD) δ 2.42 (1H, dd, *J* = 5.9, 17.1 Hz), 2.83 (1H, dd, *J* = 9.3, 17.1 Hz), 3.66 (1H, ddd, *J* = 4.6, 5.9, 9.8 Hz), 3.78 (3H, s), 4.21 (1H, d, *J* = 4.9 Hz), 6.81-6.90 (3H, m), 7.23-7.28 (1H, m). ^{13}C-NMR (CD_3OD) δ 39.2, 45.5, 55.7, 64.5, 113.6, 113.7, 119.9,

131.0, 145.4, 161.5, 174.9, 179.7. HRMS $[M+H]^+$ found *m/s* 236.0922, calcd. for $C_{12}H_{14}NO_4$: 236.0923. $[\alpha]_D^{25}$ +78.8 (*c* 0.96, CH_3OH).

(2*S*,3*R*)-3-(4-Chlorophenyl)pyroglutamic acid 73l:[66a] Yield 83%. M.p. 192.0 °C. ^{1}H-NMR (CD_3OD) δ 2.43 (1H, dd, *J* = 6.3, 17.1 Hz), 2.84 (1H, dd, *J* = 9.3, 17.1 Hz), 3.70 (1H, ddd, *J* = 5.4, 6.3, 9.3 Hz), 4.21 (1H, d, *J* = 5.4 Hz), 7.33 (4H, dd, *J* = 9.2, 11.1 Hz). ^{13}C-NMR (CD_3OD) δ 39.2, 45.0, 64.3, 129.7, 130.0, 134.1, 142.4, 174.7, 179.4. HRMS $[M+H]^+$ found *m/s* 240.0428, calcd. for $C_{11}H_{11}ClNO_3$ 240.0427. $[\alpha]_D^{25}$ +88.4 (*c* 2.1, $CHCl_3$).

(2*S*,3*R*)-3-(3,4-Dichlorophenyl)pyroglutamic acid 73m:[66a] Yield 84%. M.p. 217.0 °C. ^{1}H-NMR (CD_3OD) δ 2.32 (1H, dd, *J* = 6.8, 17.3 Hz), 2.71 (1H, dd, *J* = 9.3, 17.3 Hz), 3.60 (1H, ddd, *J* = 5.4, 6.8, 9.3 Hz), 4.12 (1H, d, *J* = 5.4 Hz), 7.18 (1H, dd, *J* = 2.2, 8.3 Hz), 7.39 (1H, d, *J* = 8.3 Hz), 7.42 (1H, d, *J* = 2.2 Hz). ^{13}C-NMR (CD_3OD) δ 39.1, 44.8, 64.0, 128.0, 130.5, 132.0, 132.2, 133.6, 144.4, 174.3, 178.9. HRMS $[M+H]^+$ found *m/s* 274.0033, calcd. for $C_{11}H_{10}Cl_2NO_3$ 274.0038. $[\alpha]_D^{25}$ +60.7 (*c* 0.22, CH_3OH).

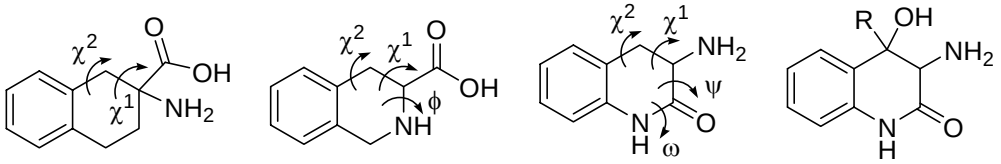
Chapter 4

Highly Diastereoselective Synthesis of a New, Carbostyril-Based Type of Conformationally Constrained β-Phenylserines

4.1 Importance of Conformationally Constrained Analogs of Aromatic Amino Acids

As mentioned in previous chapters, the application of specifically designed sterically/conformationally constrained amino acids[45] has resulted in remarkable progress toward the understanding of peptide three-dimensional (3D) structure and its relationship to biological activity via the rational modification of native peptide secondary structures.[96] In particular, considerable effort has been focused on developing conformationally constrained analogs of aromatic amino acids because of their importance in protein folding and recognition.[82] In the case of phenylalanine (Phe) and structurally related amino acids, such as tyrosine and 3,4-dihydroxy-phenylalanine (DOPA), the design considerations may include restriction of the torsional angles ϕ (phi), ψ (psi) and ω (omega), which determine the 3D structure of peptide backbone,[97] as well as the χ (chi) torsional angles, which define the position of side-chain functional groups (Figure 16).[82]

Figure 16. Literature Examples of Confomationally Constrained Derivatives of Phenyl Serine



Act-**106** Tic-**107** **108** **109**

Of the various conformationally constrained derivatives of Phe reported in the literature,[82] cyclic models **106**[98-104] and **107**[105-107] were found to be extremely useful conformationally constrained scaffolds in the de novo peptide design. For instance, the tetraline-based constrained Phe-model Atc-**106**, allowing for the restriction of both χ^1 and χ^2, has been successfully used in the design of various opioid peptides (dynorphin A[99], deltorphin,[100] enkephalins[101]), peptidic α-adrenergic agonists[102] and enzyme inhibitors,[103] as well as in the study of protein folding.[104] Application of the tetrahydroisoquinoline-based model Tic-**107**, as a Phe analog with restricted χ^1, χ^2, as well as ϕ torsional angles, has been found to be even more successful. Thus, a systematic study of Tic-**107** for peptide design led to the development of potent, yet highly selective angiotensin-converting enzyme inhibitor "Quinapril",[106] a tripeptide currently under clinical trials, as well as dipeptide Dmt-Tic,[107] a potent pharmacophore, representing a conformationally constrained Tyr-Phe moiety. The most conformationally constrained in this series, the 3,4-dihydro-1*H*-quinolin-2-one (carbostyril)-based model **108**[108] with four restricted torsional angles, χ^1, χ^2, ψ and ω, has also been useful as an analog of Phe in the design of di- and tripeptides. In particular, very promising results have been reported on the application of model **108** in the design of HIV-1 reverse transcriptase inhibitors,[109] dopamine D2/D4 receptor antagonists,[110] metalloproteinase inhibitors[111] as well as other

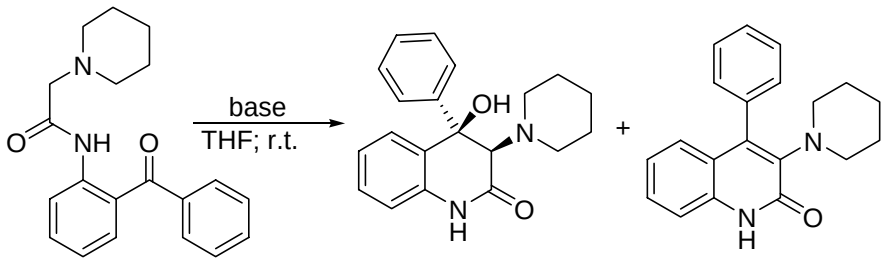
biologically active peptides and peptidomimetics.[112] Besides Phe, scaffolds **106-108** have been used for preparing structurally similar aromatic amino acid derivatives such as tyrosine and DOPA.[99-104,106] On the other hand the application of models **106-108** as conformationally constrained analogs of other amino acids with substituents on the aliphatic moiety of **106-108** is not straightforward and might require the development of new approaches methodologically different to those applicable for preparing Phe and its derivatives. Thus, no carbostyril-based models of β-hydroxyphenylalanine (phenylserine) **109** have been reported in the literature to date. However within this chapter a highly diastereoselective (>99/1) synthesis of new types of conformationally constrained phenylserine derivatives **109a,c,d,f,g** will be described. This synthetic transformation involves an intermolecular aldol addition reaction of the readily available amides **54a,c,d,f,g** (Scheme 49) which contain a glycine moiety and keto group, thus prearranged for the intermolecular aldol addition reaction.

4.2 Cyclization of Acetamides 54a,c,d,f,g for the Diastereoselective Synthesis of Constrained β-Phenylserines

Therefore with ready access to a variety of *N*-(2-benzoyl-phenyl)-2-dialkylamino-acetamides **54a,c,d,f,g** (for preparation see Chapter 3, Section 3.2), it was envisioned that they could be utilized for the synthesis of carbostyril-based types of conformationally constrained β-phenylserines via cyclization under basic conditions. The cyclization step was initially studied using compound **54d** due its high crystallinity and solubility in various organic solvents. Taking into account the presence of the amide hydrogen in

54a,c,d,f,g, it was assumed that the cyclization might require formation of the corresponding di-anion. Therefore, at least two equivalents of relatively strong base was utilized in order to effect the cyclization.

Scheme 49. Cyclization of the *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide **54d**



54d **109d** **110d**

Table 29. Cyclization of the *N*-(2-benzoyl-phenyl)-2-piperidyl-acetamide **54d**

Entry	Base	Equivalents Base	Time h	Conversion %[a]	Ratio **109d**/**110d**[a,b]
1	NaOMe	2	24	10	>99/1
2	KOH	2	24	25	>99/1
3	KO-*t*-Bu	2	24	54	89/11
4	KO-*t*-Bu	2	24	67	88/12
5	KO-*t*-Bu	2	72	77	53/47
6	KO-*t*-Bu[c]	2	2	>99	30/70
7	KO-*t*-Bu[c]	2	48	>99	8/92
8	KO-*t*-Bu	4	12	>99	86/14

[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixtures. [b]Compound **109d** was isolated as a single diastereomer. [c]The reaction was conducted in refluxing THF.

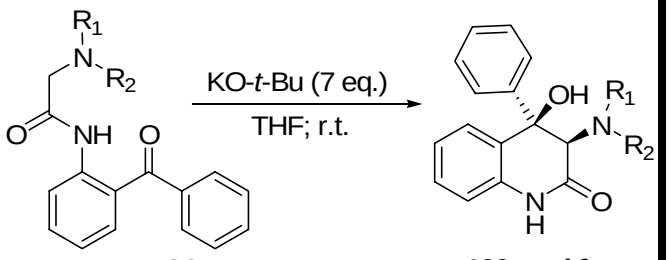
The first attempt, using sodium methoxide as a base and THF as a solvent, was rather unsuccessful. The sluggish reaction proceeded overnight at room temperature to afford only 10% conversion giving rise to the target compound **109d** (Table 29, entry 1). On the other hand, compound **109d** was obtained as a single product in

diastereomerically pure form, which encouraged the search for optimal reaction conditions. Application of potassium hydroxide as the base increased the conversion of the amide **54d** (entry 2), but the result was still unsatisfactory. The use of the stronger bases allowed for a substantial increase in the conversion without compromising the diastereoselectivity of the reaction. However, the target **109d** was obtained along with the product of its dehydration **109d** (entries 3, 4). Continuation of the reaction for up to three days resulted in the increased conversion of the starting **54d**, but led to increased amounts of the dehydration product **110d** as well (entry 5). Further attempts to improve the reaction outcome by varying solvents did little to improve the results. For instance, the reactions conducted in ether or acetonitrile, using potassium *tert*-butoxide as the base, furnished **109d** as the individual product with virtually complete diastereoselectivity, however the conversion of the starting **54d** to the corresponding product was very low. On the other hand, it was discovered that increasing the reaction temperature and the amount of base used, had a considerable effect on the reaction outcome. Thus, the reaction conducted in THF at reflux was completed in two hours affording a mixture of **109d** and **110d** in a ratio of 30/70 (entry 6). Continuation of the reaction for two days resulted in the formation of **110d** as the major product isolated in 87% yield (entry 7).

Further experiments revealed that elevating the temperature generally accelerated the reaction rates of both the desired aldol addition and the undesired dehydration, suggesting that room temperature reactions may be a better option. However, it was found that increasing the base/substrate ratio led to a substantial acceleration of the aldol addition reaction allowing preparation of the target **109d** as an individual product in quantitative chemical yield (entries 8). Thus, application of seven equivalents of the base

for cyclization of **54d** resulted in a clean and fast reaction giving rise to the product **109d** with virtually complete chemical and stereochemical outcome (Scheme 50, Table 30, entry 1).

Scheme 50. Cyclization of *N*-(2-benzoyl-phenyl)-2-dialkylamino-acetamides **54a,c,d,f,g**



54a,c,d,f,g **109a,c,d,f,g**

a	R_1 = Et, R_2 = Et
c	R_1 = Bn, R_2 = Bn
d	R_1,R_2 = Piperidyl
f	R_1,R_2 = Indolyl
g	R_1 = Bn, R_2 = H

Table 30. Cyclizationof *N*-(2-benzoyl-phenyl)-2-dialkylamino-acetamides **54a,c,d,f,g**

Entry	Starting Amide	Product	Conversion %[a]	Yield %[b,c]
1	**54d**	**109d**	>99	98
2	**54a**	**109a**	>99	97
3	**54c**	**109c**	95	89
4	**54g**	**109g**	>99	97
5	**54f**	**109f**	>99	97

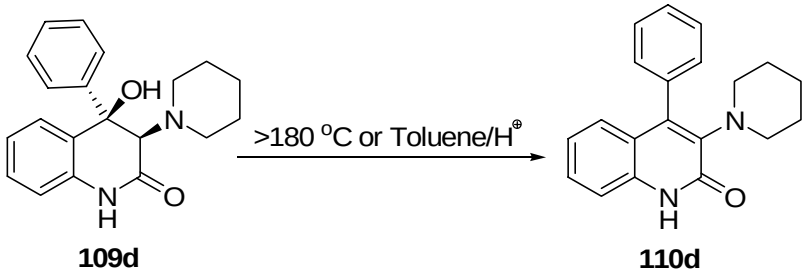
[a]Determined by ^{1}H NMR (300 MHz) analysis of the crude reaction mixtures. [b]Isolated yield of the crude product. [c]Compounds **109a,c,d,f,g** was isolated as a single diastereomer.

With these results in hand it was decided to study the generality of the stereochemical outcome of this cyclization reaction using compounds **54a,d,f,g** which bear various substituents on the amino function of the glycine moiety. The diethyl

derivative **54a** was converted to the cyclized product **109a**, and isolated as a pure diastereomer in 97% yield (Table30, entry 2). From the point of the view of potential application of products **109** as conformationally constrained phenylserine derivatives, the cyclizations of compounds **54c,f,g**, with removable substituents on the amino group were of particular interest. The reaction of the dibenzylated **54c** occurred at a slightly lower rate allowing for 95% conversion of the starting compound to the product **109c** under the standard conditions (2 h), presumably due to the increased steric bulk of two benzyl groups (entry 3). On the other hand, the reaction of indolyl derivative **54f** occurred with a similar reaction rate and chemical yield, compared to the alkyl series of reactions (entry 4 vs 1, and 2). Interestingly, the *mono*-benzyl substituted derivative **54g**, possessing an unprotected N-H group, easily underwent the cyclization to afford the diastereomerically pure product **109g** in high chemical yield, suggesting a wider than expected generality of this reaction.

4.3 Dehydration of Diastereomerically pure 109d for the Production of 3-Amino-4-Phenylquinolin-2(1*H*)-one 110d

Scheme 51. Dehydration of the Carbostyril **109d** and Preparation of 3-Amino-4-Phenylquinolin-2(1*H*)-one **110d**



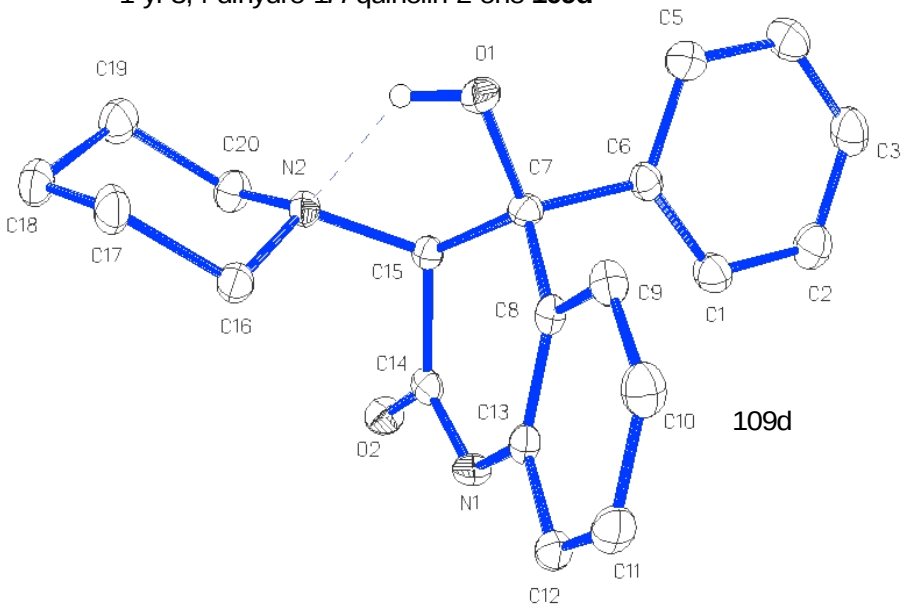
109d **110d**

Since compound **109a** was obtained as the major product in some of the earlier experiments (entries 6 and 7), it was decided to explore the possibility of a selective process for preparation of the derivatives of this type.[113] 1*H*-Quinolin-2-one and in particular its amino derivatives have been used as pharmacophore units in the design of various biologically active compounds, for instance with oxytocin antagonist activity, antidepressant, and antiallergenic activity.[114] It was discovered that complete dehydration of **109d** to **110d** could be achieved by simply heating the former at temperatures above 180 ^{o}C or the application of classical dehydration methods such as refluxing a toluene solution of **109d** and an acidic catalyst. Using these methods compound **109d** was cleanly dehydrated to afford **110d** in high chemical yields (96-98%) rendering the cyclization reactions reported here synthetically versatile and useful for preparing biologically relevant compounds of types **109** and **110**.

4.4 Stereochemical Determination of Diastereomer 109d and the Rational for its Diastereomerically Pure Preparation

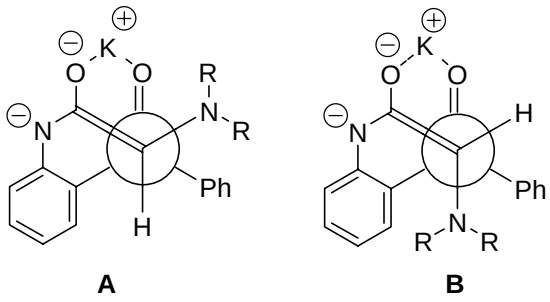
It should be emphasized that in all reactions studied, using different bases, solvents, reaction times and temperatures, product **109d** was always obtained as a single diastereomer. The robust diastereoselectivity obtained was really a remarkable feature of this reaction. The relative stereochemistry of the diastereomer **109d** was found to be (3*R**,4*R**) by single crystal X-ray analysis (Figure 17). It is interesting to note that the crystals of compound **109d** are made of successive layers of enantiomerically pure (3*R*,4*R*) and (3*S*,4*S*) diastereomers.

Figure 17. X-Ray Crystallographic Structure of 4-Hydroxy-4-phenyl-3-piperidin-1-yl-3,4-dihydro-1*H*-quinolin-2-one **109d**



To account for the diastereoselectivity observed, two transition states (TS) **A** and **B** have been proposed, leading to the (3*R**,4*R**) and (3*R**,4*S**) diastereomers, respectively (Fig. 18). In both TS **A** and **B** the enolate and the carbonyl oxygens are located in close proximity to each other allowing the reaction to occur with a thermodynamically advantageous minimum charge separation.[115] On the other hand, considering the steric interactions in the TS **A** and **B**, one could assume that the latter might be less favorable relative to TS **A**. Thus, in TS **B** the substituted amino group experiences unfavorable repulsive interactions with the two phenyl rings, while in the TS **A** these steric interactions are minimized. Moreover, in TS **A** the amino group and the oxygen of the enolate are in the *cis* position allowing the nitrogen to be involved in stabilizing the transition state via coordination to the metal.

Figure 18. Transition States Proposed for the Diastereoselective Cyclization of **54a,c,d,g,f**



In summary, it has been demonstrated that the readily available amido-keto compounds **54a,c,d,f,g**, with prearranged carbonyl and glycine moieties, under strongly basic conditions, easily undergo a complete and highly diastereoselective cyclization, affording a generalized and practical synthesis for the conformationally constrained phenylserine derivatives **109** as well as amino substituted carbostyrils **110**.[116] High chemical yields and virtually complete diastereoselectivity, combined with the operational convenience of the experimental procedures render this method worth consideration for the multi-gram scale preparation of these diastereomerically pure derivatives.

4.5: Experimental Section

4.5.1: General Considerations

Unless specified all reactions were carried out under an atmosphere of nitrogen with magnetic stirring using commercially available solvents. Thin layer chromatography

was performed using aluminum backed TLC Plates with Silica Gel 60 F_{254} from Merk. Column chromatography was performed using Silica Gel 300-300 mesh from Natland International Corporation. Exact masses were obtained with a micromass Q-TOF electrospray ionization (ESI) instrument (Waters, UK) and processed using the MassLynx 3.5 software package. ^{1}H, ^{13}C NMR and spectra were recorded on a Varian Mercury 300 or Varian Unity Inova-400 spectrometers, and were referenced with an internal standard of TMS, for ^{1}H and ^{13}C NMR spectra. Melting points were obtained with a Mel-Temp apparatus with a Fluke 50S digital thermometer and are uncorrected.

4.5.2 Preparation of Diastereomerically Pure 4-Hydroxy-4-phenyl-3-dialkylamino-1-yl-3,4-dihydro-1*H*-quinolin-2-ones 109a,c,d,f,g

Cyclization of acetamides 54a,c,d,f,g for the preparation of diastereomerically pure 4-Hydroxy-4-phenyl-3-dialkylamino-1-yl-3,4-dihydro-1*H*-quinolin-2-ones 109a,c,d,f,g. General Procedure: To a flask containing one equivalent of **54a,c,d,f,g** and three mL of THF, KO-*t*-Bu (7.0 eq.) was added at room temperature under a nitrogen atmosphere. After stirring the reaction for two hours at room temperature, aqueous ammonium chloride and ethyl acetate were added and the organic phase was extracted with ethyl acetate three times. The combined organic fractions were dried over anhydrous magnesium sulphate. After evaporation of the solvents and washing with hexane:ethyl acetate (2:1), the desired products **109a,c,d,f,g** were afforded in high yield.

4-Hydroxy-4-phenyl-3-piperidin-1-yl-3,4-dihydro-1*H*-quinolin-2-one 109d [116]

M.p. 186.6 ^{o}C. ^{1}H NMR δ 1.34-1.44 (2 H, m), 1.46-1.60 (4 H, m), 2.48-2.60 (2 H, m),

2.66-2.78 (2 H, m), 3.34 (1 H, s), 6.03 (1 H, s), 6.76 (1 H, dd, *J* = 7.77, 1.18 Hz), 7.10 (1 H, td, *J* = 7.62, 1.17 Hz), 7.14-7.28 (5 H, m), 7.60 (1 H, dd, *J* = 7.62, 1.46 Hz), 8.43 (1 H, bs). ^{13}C NMR δ 23.6, 26.5, 52.1, 72.2, 74.1 114.7, 124.3, 125.2, 127.1, 127.3, 128.3, 128.6, 129.7, 134.5, 145.4, 167.0. HRMS [M+Na$^+$] found *m/s* 345.1491, calcd for $C_{20}H_{22}N_2NaO_2$ 345.1579.

3-Diethylamino-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one 109a.[116] M.p. 174.6 °C. ^{1}H NMR δ 1.09 (6 H, t, *J* = 7.2 Hz), 2.65 (2H, dtq, *J* = 19.8, 13.5, 6.9 Hz) 2.73 (2H, dtq, *J* = 19.8, 13.5, 6.9 Hz) 3.58 (1 H, s), 5.94 (1 H, s), 6.80 (1 H, d, *J* = 8.1 Hz), 7.11 (1 H, t, *J* = 7.5 Hz), 7.17-7.26 (5 H, m), 7.60 (1 H, d, *J* = 7.8 Hz), 9.10 (1 H, bs). ^{13}C NMR δ 14.0, 45.6, 69.3, 72.5, 115.0, 124.8, 125.8, 127.8, 127.8, 128.7, 129.1, 130.0, 135.0, 146.0, 168.7. HRMS [M+H$^+$] found *m/s* 311.1830, calcd for $C_{19}H_{23}N_2O_2$ 311.1688.

3-Dibenzylamino-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one 109c.[116] M.p. 241.2 °C. ^{1}H NMR δ 3.62 (2 H, d, *J* = 12.3 Hz), 3.70 (1 H, s), 3.83 (2 H, d, *J* = 12.5 Hz), 5.78 (1 H, s), 6.52-6.60 (2 H, m), 6.82 (1 H, d, *J* = 7.33 Hz), 7.00-7.40 (15 H, m), 7.62 (1 H, dd, *J* = 7.72, 1.17 Hz), 8.46 (1 H, bs). ^{13}C NMR δ 55.3, 65.9, 72.6, 114.5, 124.5, 125.7, 127.3, 127.4, 127.5, 128.0, 128.4, 128.9, 129.5, 134.7, 137.5, 144.9, 167.1. HRMS [M+H$^+$] found *m/s* 435.1910, calcd for $C_{29}H_{27}N_2O_2$ 435.1994.

3-(1,3-Dihydro-isoindol-2-yl)-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one 109g.[116] ^{1}H NMR δ 3.87 (1 H, s), 4.06 (2 H, d, *J* = 11.7 Hz), 4.13 (2 H, d, *J* = 11.7 Hz), 5.37 (1 H, bs), 6.83 (1 H, dd, *J* = 8.77, 1.17 Hz), 7.0-7.45 (11 H, m), 7.63 (1 H, dd, *J* = 7.62, 1.17 Hz), 9.74 (1 H, bs). ^{13}C NMR δ 55.8, 69.4, 73.5, 115.3, 122.1, 124.7, 125.9,

126.9, 126.9, 127.8, 128.4, 129.0, 129.4, 134.6, 138.4, 143.5, 167.9. HRMS [M+H$^+$] found *m/s* 357.1518, calcd for $C_{23}H_{21}N_2O_2$ 357.1525.

3-Benzylamino-4-hydroxy-4-phenyl-3,4-dihydro-1*H*-quinolin-2-one 109f.[116] ^{1}H NMR δ 1.25 (1 H, m), 3.10, 3.35 (2 H, AB, *J* = 13.5 Hz), 3.84 (1 H, s), 6.83 (1 H, d, J = 7.8 Hz), 6.91 (2 H, m), 7.07 (2 H, d, J = 6.6 Hz), 7.17-7.27 (4 H, m), 7.30-7.46 (5 H, m), 9.35 (1H, s). ^{13}C NMR δ 52.7, 65.1, 75.8, 116.0, 124.0, 127.3, 127.4, 127.5, 127.7, 127.9, 128.4, 128.5, 128.6, 128.8, 129.9, 130.2, 136.2, 139.3, 143.3, 170.1. HRMS [M+H$^+$] found *m/s* 345.1383, calcd for $C_{23}H_{23}N_2O_2$ 345.1532.

4.5.3 Dehydration of 4-Hydroxy-4-phenyl-3-piperidin-1-yl-3,4-dihydro-1*H*-quinolin-2-ones 109d for the Production of 4-Phenyl-3-piperidin-1-yl-1*H*-quinolin-2-one 110d.

4-Phenyl-3-piperidin-1-yl-1*H*-quinolin-2-one 110d.[116] M.p. 233.0 °C (decomp.). ^{1}H NMR δ 1.41 (6 H, bs), 2.90 (4 H, bs), 7.03 (1 H, m), 7.18 (1 H, ddd, *J* = 8.21, 1.91, 0.88 Hz), 7.23-7.52 (7 H, m), 11.9 (1 H, bs). ^{13}C NMR δ 24.2, 26.4, 51.7, 115.2 121.5, 121.7, 125.8, 127.2, 127.7, 127.8, 129.7, 135.5, 136.6, 139.8, 141.5, 163.1. HRMS [M+Na$^+$] found *m/s* 327.1374, calcd for $C_{20}H_{20}N_2NaO$ 327.1473.

Chapter 5

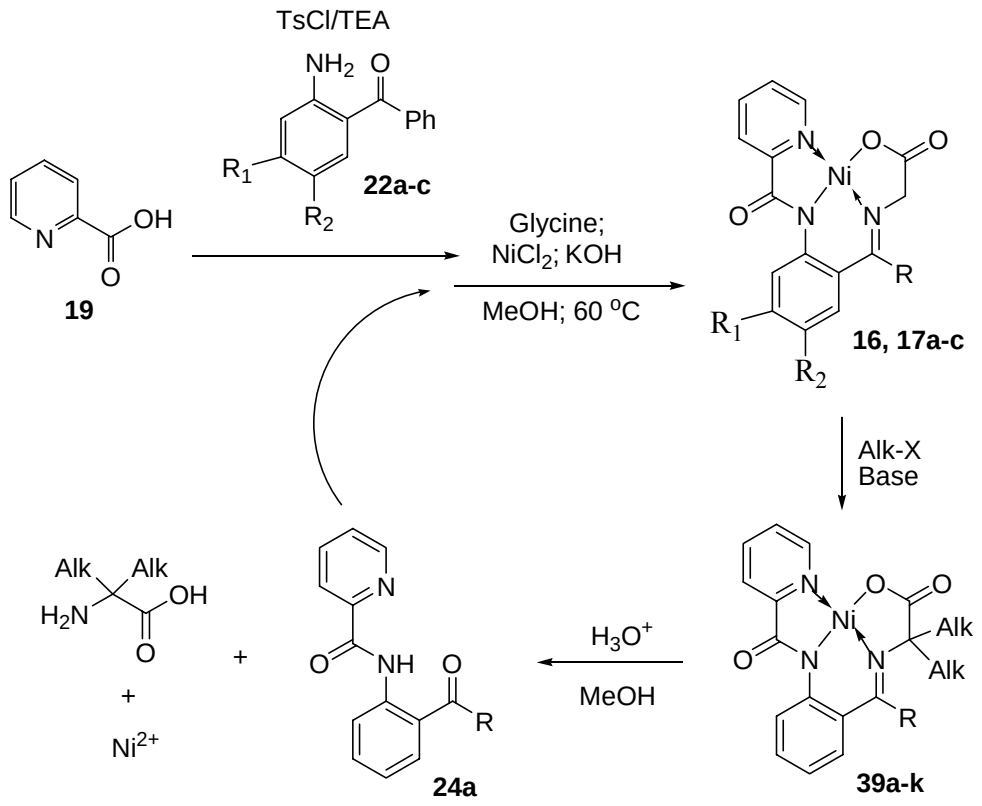
Summary, Future Directions, and Conclusions

5.1 Summary

Efficient synthetic methodologies associated with the preparation of a variety of unique α-amino acids under operationally convenient conditions have been chronicled and discussed within this dissertation. To this end, the compatibility of an assortment of nucleophilic glycine equivalents have been evaluated with respect to various homologation methods such as Michael addition reactions and alkyl halide alkylations under homogeneous as well as heterogeneous conditions.

Following the development of an efficient large scale synthetic approach for the production of the picolinic acid derived Ni(II) complexed nucleophilic glycine equivalents **16** and **17a-c**, it was found that they represented a excellent platform for the preparation of sterically constrained symmetrical α,α-disubstituted α-amino acids (Scheme 52). Alkyl halide alkylations of this achiral nucleophilic glycine equivalent **17a** allowed for the preparation of a variety of α,α-disubstituted α-amino acids which contain *n*-alkyl, unsaturated alkyl, aromatic, and cyclic side chains. However, despite their success as nucleophilic glycine equivalents for the synthesis of symmetrical α,α-dialkyl α-amino acids, the picolinic acid derived Ni(II) complex of glycine **17a** was found to be

Scheme 52. Summary of the Synthesis and Application of the Picolinic Acid Derived Ni(II) Complexed Glycine Equivalents **16**, **17a-c**



inefficient for the synthesis of optically active α-alkyl α-amino acids via asymmetric phase transfer catalyzed alkyl halide alkylations. Although the incomplete stereochemical control of these phase transfer reactions was initially attributed to an increased charge separation of the ions in the reaction intermediate due to the application of somewhat polar organic reaction mediums stemming from the solubility limitations of the glycine equivalent, it now seems that their incompatibility with commercially available phase transfer catalysts is a more viable rationale.

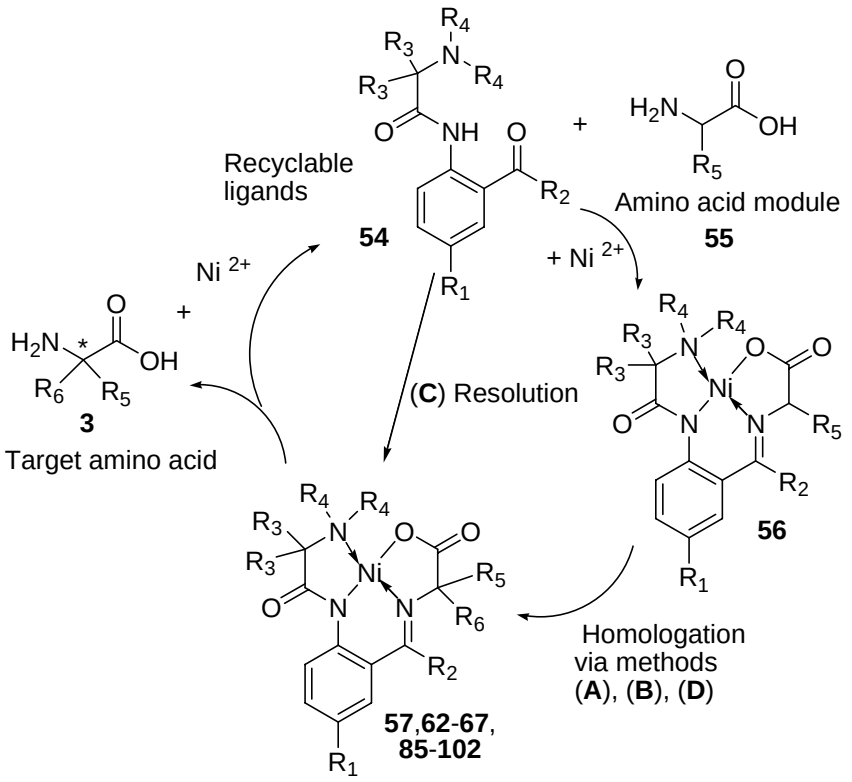
Subsequently, a new generation of modularly designed Ni(II) complexed nucleophilic glycine equivalents **56a-p** has been developed. Simple, convenient, and

reliable synthetic approaches have been established and reproduced for their preparation on a relatively large scale. The flexible framework of the modular glycine equivalents **56a-p** was found to be beneficial for the alteration of the physical (solubility), and chemical (reactivity and methodological adaptability) properties. Their simple and efficient synthesis as well as the recyclability of the corresponding ligands **54a-p** allow for their application within an attractive cost structure.

Modular glycine equivalents containing dialkylamine modules, like their picolinic acid derived counterparts, were found to be useful for the preparation of symmetrical α,α-disubstituted α-amino acid precursors and were chemically stable under the strongly basic conditions used for the homogeneous alkyl halide alkylations with DMF as the solvent (Scheme 53). Despite the inherent flexibility of the modular glycine equivalents, and the numerous alterations of the reaction conditions employed, their asymmetric phase transfer homologation remains unresolved. However, stereopair representations of the three-dimensional arrangements of the enolate, resulting from the deprotonation of the Ni(II) complexed modular glycine equivalent **56b** and two of the most prominent commercially available chiral phase transfer catalysts, have been proposed to explain the incomplete stereoselectivity observed from the corresponding alkylations. These ion pair models have resulted in further evaluation of the modular glycine equivalent which will be discussed in more detail in the future plans section of this chapter. Conversely, Michael addition reactions of the modular glycine equivalents **56a,c-d** with various optically active *N*-(*E*-enoyl)-4-phenyl-1,3-oxazolidin-2-ones resulted in significant advances in the area of asymmetric synthesis of β-substituted pyroglutamic acids and their precursors. In particular, the piperidine derived modular glycine equivalents **56d,h**

were found to be extremely reactive in the DBU catalyzed Michael addition reactions with optically active

Scheme 53. Summary of the Synthesis and Application of the Modular Glycine Equivalent **56**



Michael acceptors **84a-i,l-q** resulting in the efficient and robust preparation of various enantiomerically pure β-substituted pyroglutamic acids which were previously unknown in literature.

While the dialkylamine containing modular glycine equivalents **56a-l** have proven useful for the preparation of symmetrical and optically active sterically constrained α-

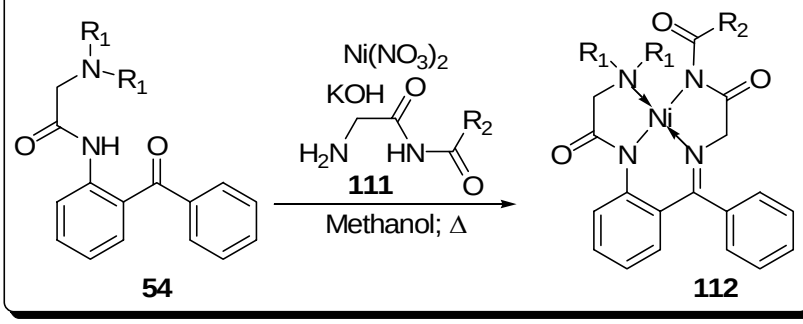
amino acids, their alkylamine containing counterparts have demonstrated potential for the separation of enantiomers of racemic α-amino acids. Although in some cases the selectivity of the optically active "NH" ligands has provided for the resolution of racemic α-amino acids following complexation, the majority of cases required further chromatography in order to separate the enantiomerically pure diastereomeric complexes. The unique stereochemical properties of the ligand **54q** employed has resulted in Ni(II) complexes **92-97** which contain a stereochemically favorable combination of the three stereogenic centers thereby allowing for their simple chromatographic separations.

5.2 Future Directions

Three major areas of interest remain relatively unstudied or unresolved with respect to the application of metal complexed nucleophilic glycine equivalents despite the large amount of success that has been accomplished. Among them is the asymmetric phase transfer catalyzed homologation of achiral metal complexed glycine equivalents, homologation of optically active metal complexed glycine equivalents, as well as the alkylation of optically active α-amino acids via the formation of stable diastereomeric metal complexes. The remainder of this chapter will focus on the future directions in which this project could proceed in order to investigate the areas of interest that are currently being considered.

5.2.1 Ni(II) Complexes Containing Schiff Bases of α-Aminoacetamides

Scheme 54. Assembly of Amide Derived Ni(II) Complexes



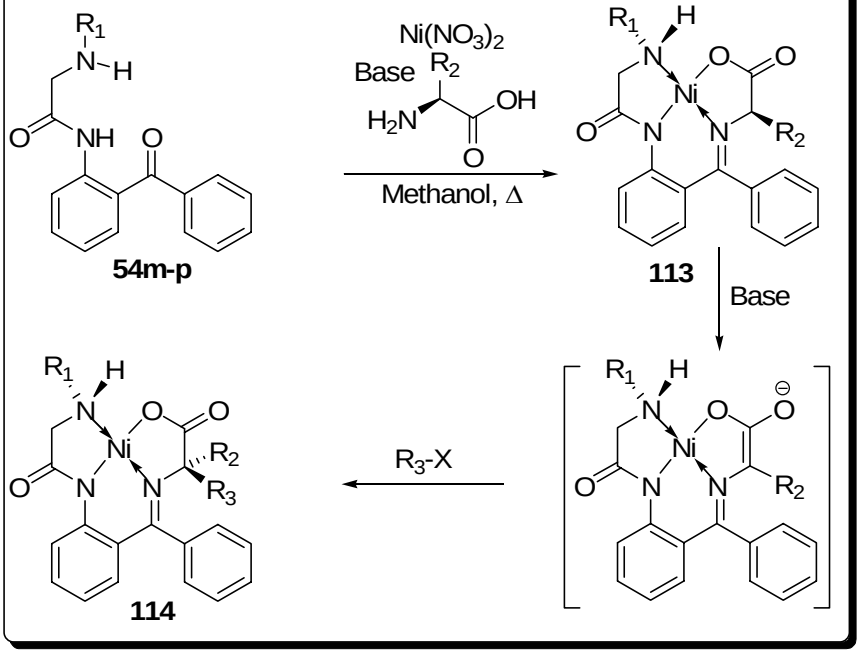
Although a variety of adjustments have been made in order to establish an efficient, reproducible, and general method for the asymmetric phase transfer catalyzed homologation of the Ni(II) complexed glycine equivalents, all efforts to this point have been unsuccessful. However, these investigations have led to the development of an increased understanding of the overall process as well as a model which may be able to rationalize the results which have been obtained to this point. Building off of the information obtained from the model, it would seem logical to increase the steric bulk around the Ni(II) complexed ester function so the chances of successfully alkylating the glycine subunit of the complex with high enantioselectivity would be more probable. Although adding a bulky group to the oxygen of the ester function would sacrifice the stability, rigidity, and enolate homogeneity established by the ionic bond between the anionic acid moiety and the nickel cation, employing a sterically constrained α-amino amide **111** rather than the customary α-amino acid could achieve the effect desired.

Although this concept seems fairly straightforward, potential for a few complications remain. The first of which could be the competitive esterification of the α-amino amides **111** during the assembly of the Ni(II) complex **112**. The highly basic conditions employed in methanol during the Ni(II) complex assembly could result in the formation of the methyl ester of glycine potentially decreasing the yield and overall efficiency of the glycine equivalent synthesis. The second potential problem involves the decrease of the reactivity of the methylene unit of the glycine moiety due to the electronic contributions of the amide function. However, this may be overcome by the application of electron withdrawing *N*-acylated amines for the preparation of the glycine amides. Although this modification would add an additional step to the preparation of the corresponding glycine equivalents, the results obtained could outweigh the cost.

5.2.2 Synthesis of Optically Active α,α-Disubstituted α-Amino Acids Via a Chiral Relay Process

Another interesting and potentially viable application of these metal complexed nucleophilic glycine equivalents is the synthesis of optically active α,α-disubstituted α-amino acids from optically pure α-alkyl α-amino acids via a chiral relay process with alkylamine derived ligands **54m-q**. The inspiration for this approach was the excellent regio- and diastereoselectivity obtained from the alkylation of the "NH" glycine equivalents **54m-p**. Therefore, given the results from previous investigations, it is envisioned that Ni(II) complexes assembled from optically active α-alkyl α-amino acids and alkyl amine derived ligands would produce an enantiomerically and diastereomerically pure Ni(II) complex **113**. This complex would then be subjected to

Scheme 55. Synthesis of Optically active α,α-Disubstituted α-Amino Acids Via a Chiral Relay Process



basic conditions to deprotonate the methylene moiety of the amino acid subunit thereby forming the planar enolate intermediate, however the stereochemistry of the amino module of the Ni(II) complex would retain the stereochemical information necessary to control the approach of the corresponding alkyl halide thereby determining the stereochemistry of the new optically active product **114**. However, as with any future project plans possible, complications exist.

Among the possible complications that may become apparent during these investigations would be the difficulty associated with assembly of the corresponding Ni(II) complexes **113** with racemization of the optically pure α-amino acid utilized. Although further investigation will be necessary, it has been found that Ni(II) complexes such as the ones envisioned could be formed under mildly basic conditions such as the application of triethylamine or *N*,*N*-diisopropyl-ethylamine. Another possible

complication that may necessitate further attention will be the stereochemical stability of the amine module of the Ni(II) complex **113**. Despite these possible obstacles, the enormous potential for this methodology makes this an interesting project for further investigation.

5.2.3 Application of Alternative Metal Ions for the Metal Complex Assembly of α-Amino Acid Schiff Bases

The third and final direction that will be discussed in this section will be the substitution of the metal ion employed. To this point Ni (II) has been the metal of choice for these investigations due to the square planar complex obtained as well as the paramagnetic nature of the metal which allows for NMR analysis of the complexes. However, it has been demonstrated that metal ions such as copper (II) are also capable of forming crystalline complexes with the previously described ligands and α-amnio acid Schiff bases, although analysis of such Cu(II) complexes by NMR spectroscopy is not convenient due to the diamagnetic properties of the metal ion. However, there may be some positive aspects that may arise from the application of metals other than nickel for the preparation of nucleophilic glycine equivalents. One such possibility would be to exploit the increased apical coordination affinity of the Cu(II) ions by including a nucleophilic atom such as an oxygen or nitrogen atom into the alkylamine module of the "NH" ligands.[117] This could aid in the conformational stability of the complex and increase the number of possibilities for asymmetric induction on the α-amino acid subunit. This approach could be useful for stabilization of the nitrogen stereogenic center

of the "NH" complexes during the chiral relay process as well as provide more rigid optically active nucleophilic glycine equivalents.

5.3 Overall Conclusions

In conclusion, Ni(II) complexed glycine equivalents have proven synthetically useful for the preparation of various symmetrical and optically active sterically constrained α-amino acids. In particular, a large variety of symmetrical α,α-disubstituted α-amino acids and β-substituted pyroglutamic acids are available via the methodologies described within this dissertation. Although certain limitations exist and further room for improvement for the asymmetric phase transfer catalyzed homologations remain, the synthetic utility of these glycine equivalents is general, reliable and robust. Furthermore, optically active alkylamine containing ligands and complexes have demonstrated potential for the separation of enantiomers of racemic α-amino acids. The metal complexed glycine equivalents required for the preparation of the α-amino acids described within are available via simple and concise synthetic approaches on the large scale and are extremely economical given the recyclable ligands utilized.

Chapter 6

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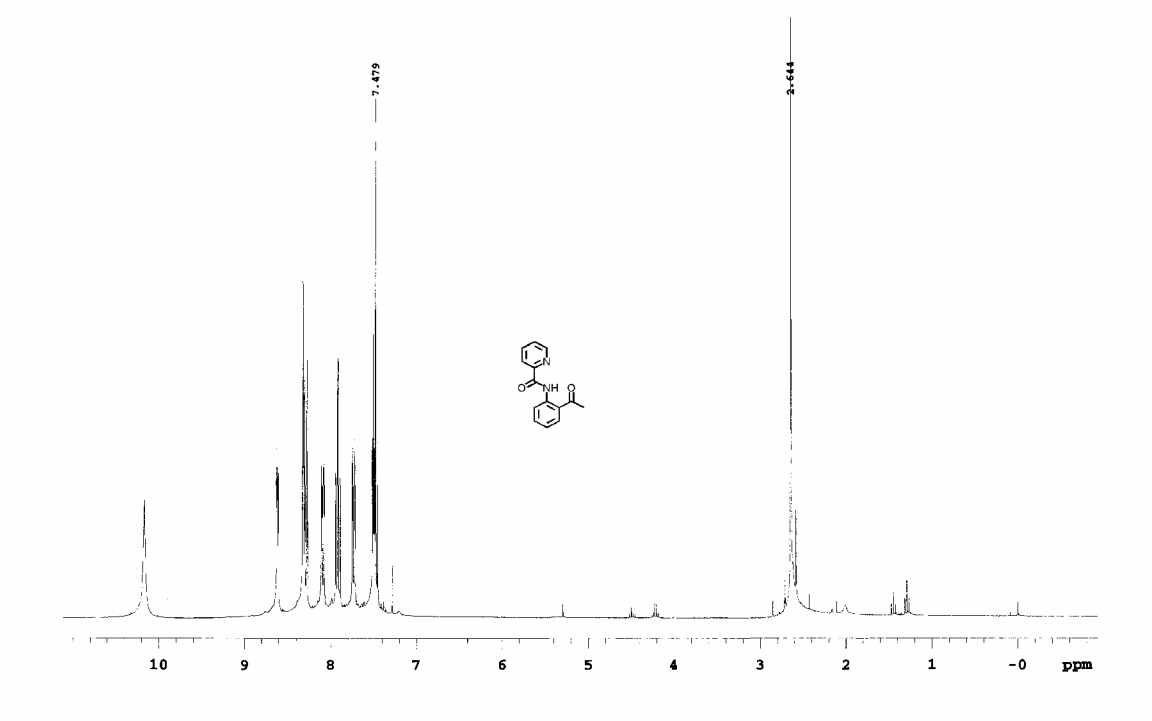
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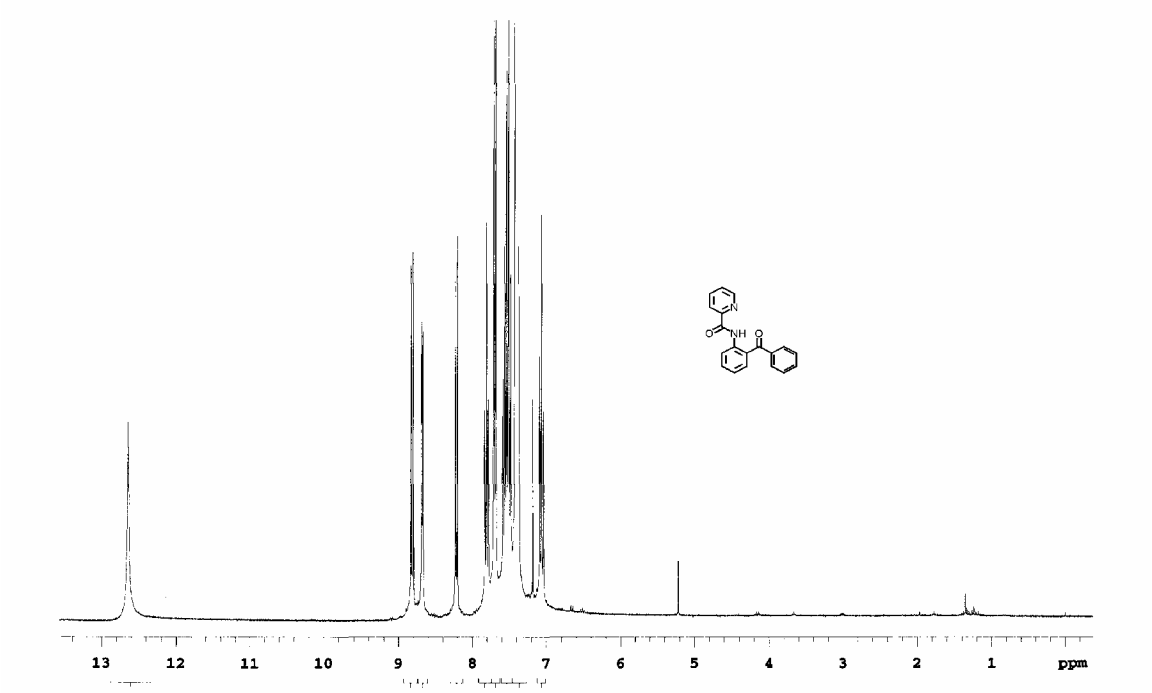
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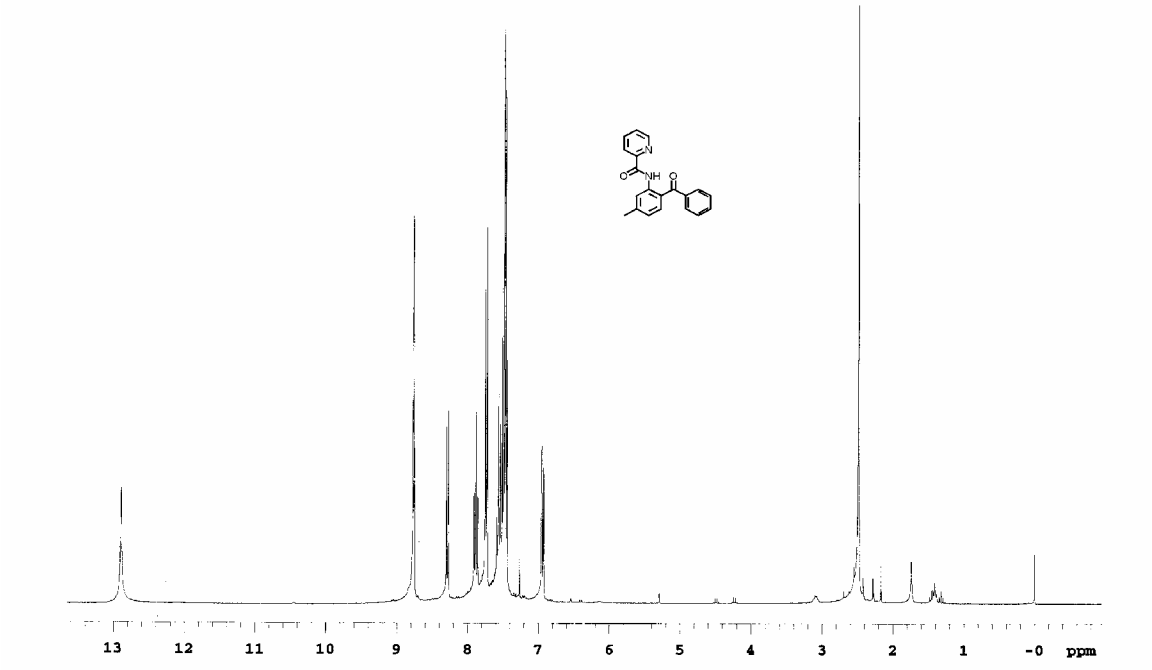
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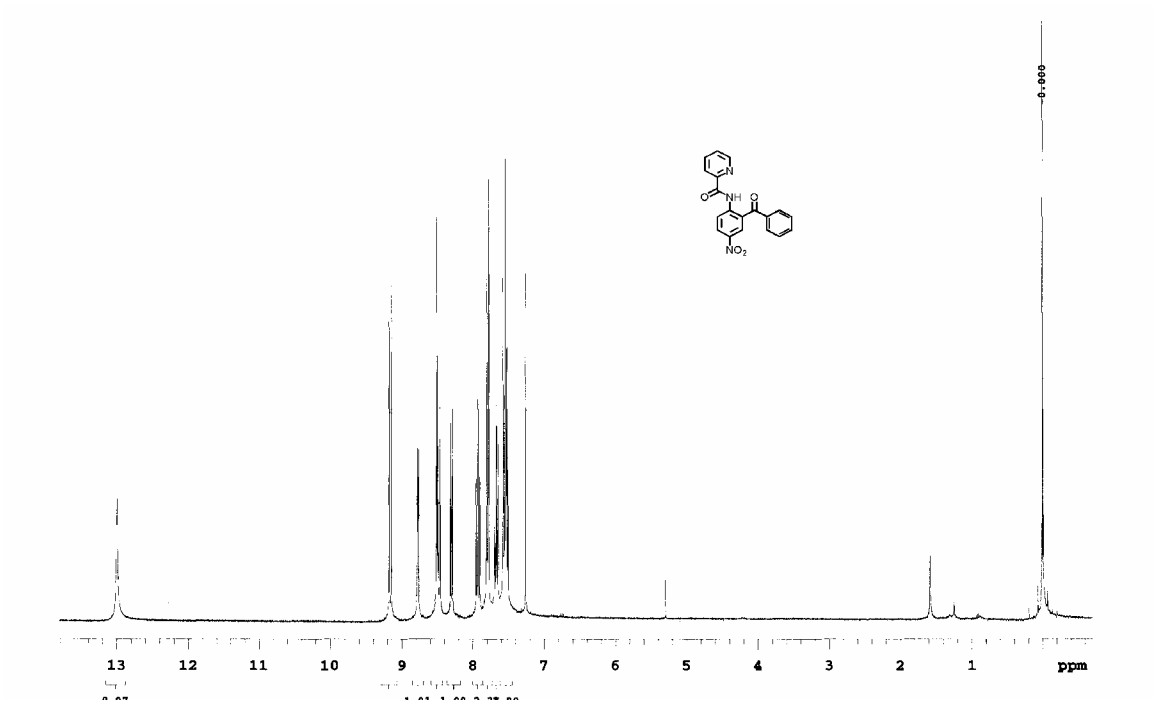
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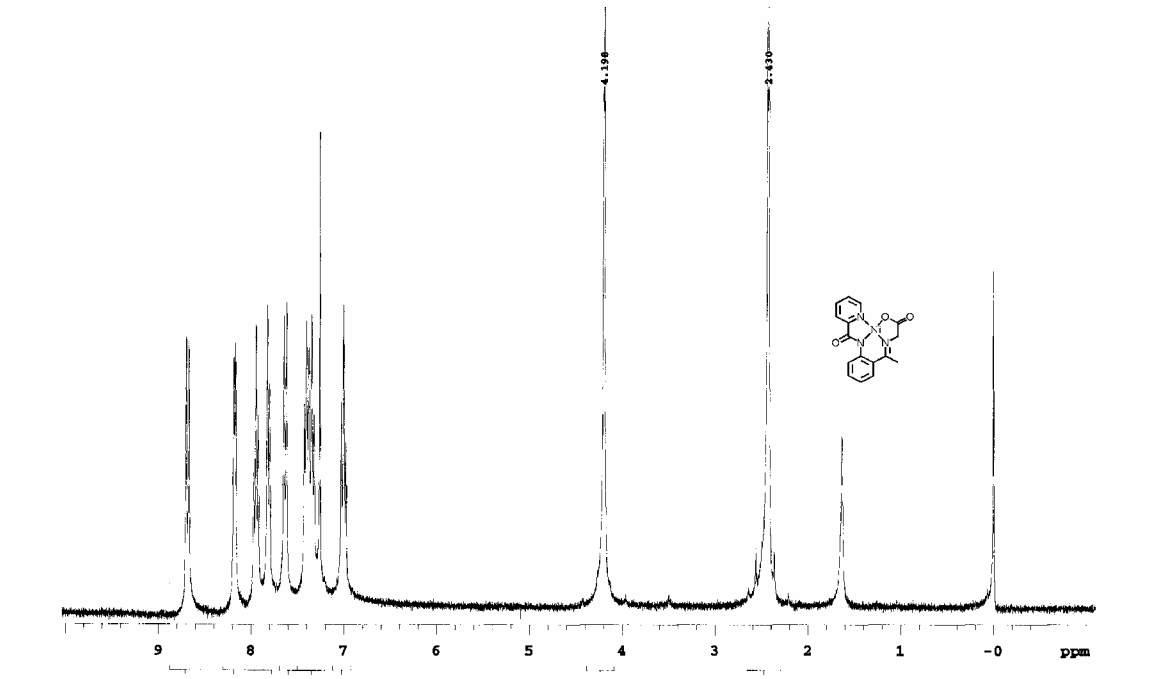
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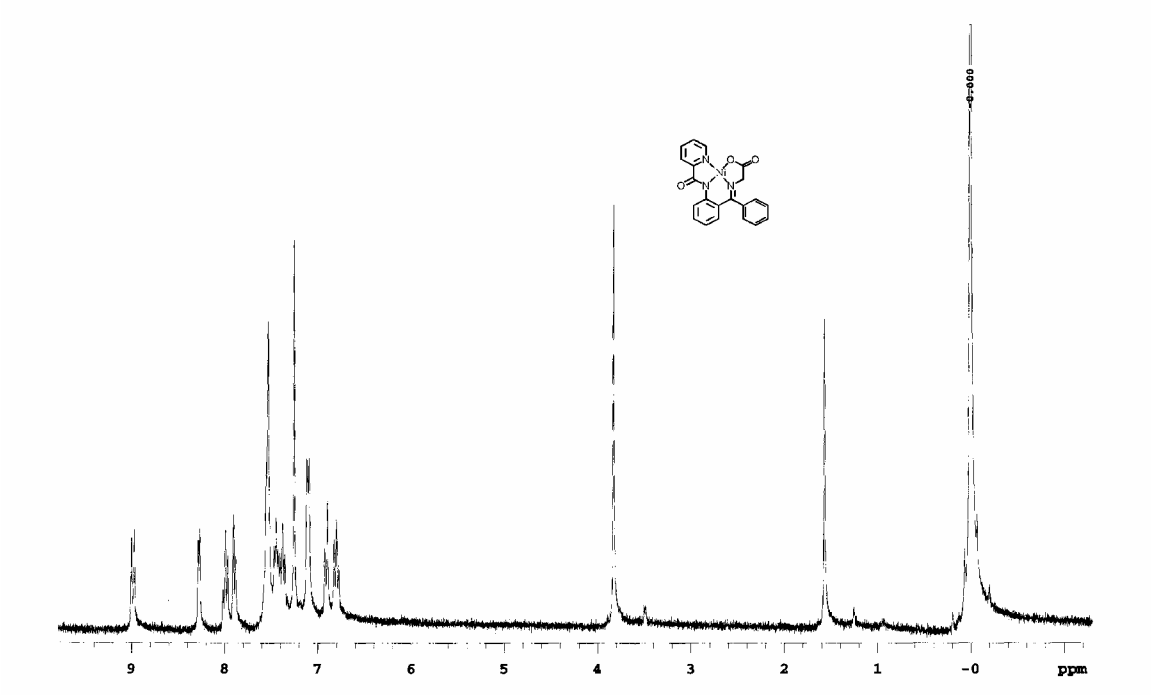


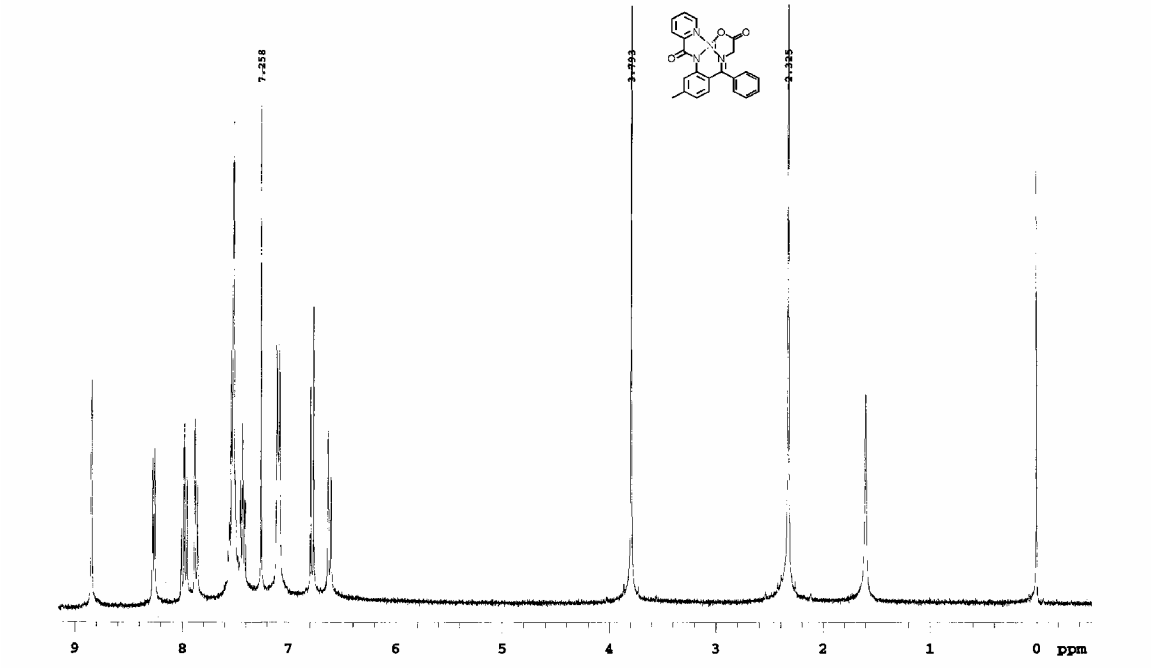

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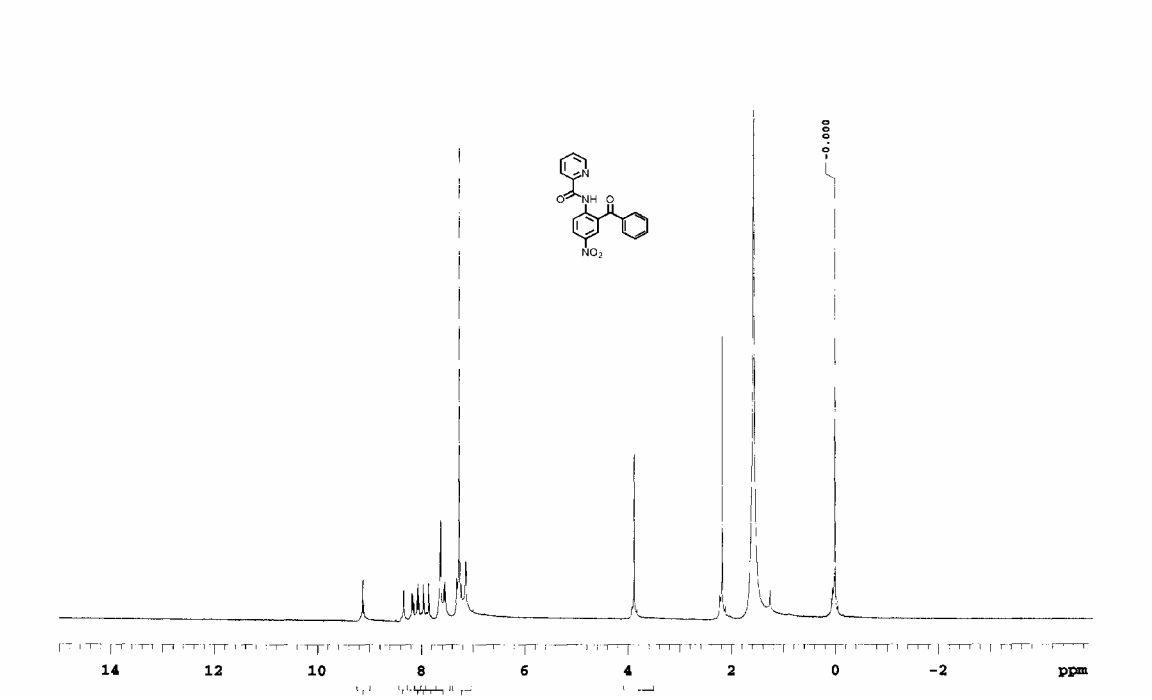

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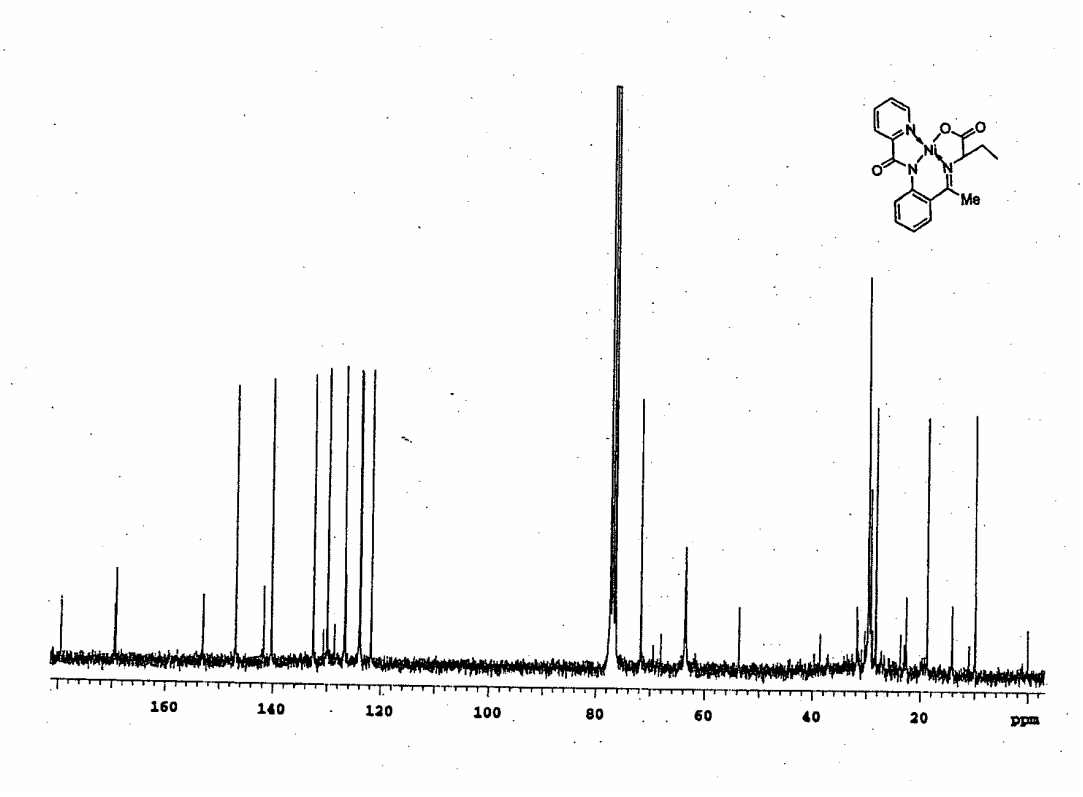

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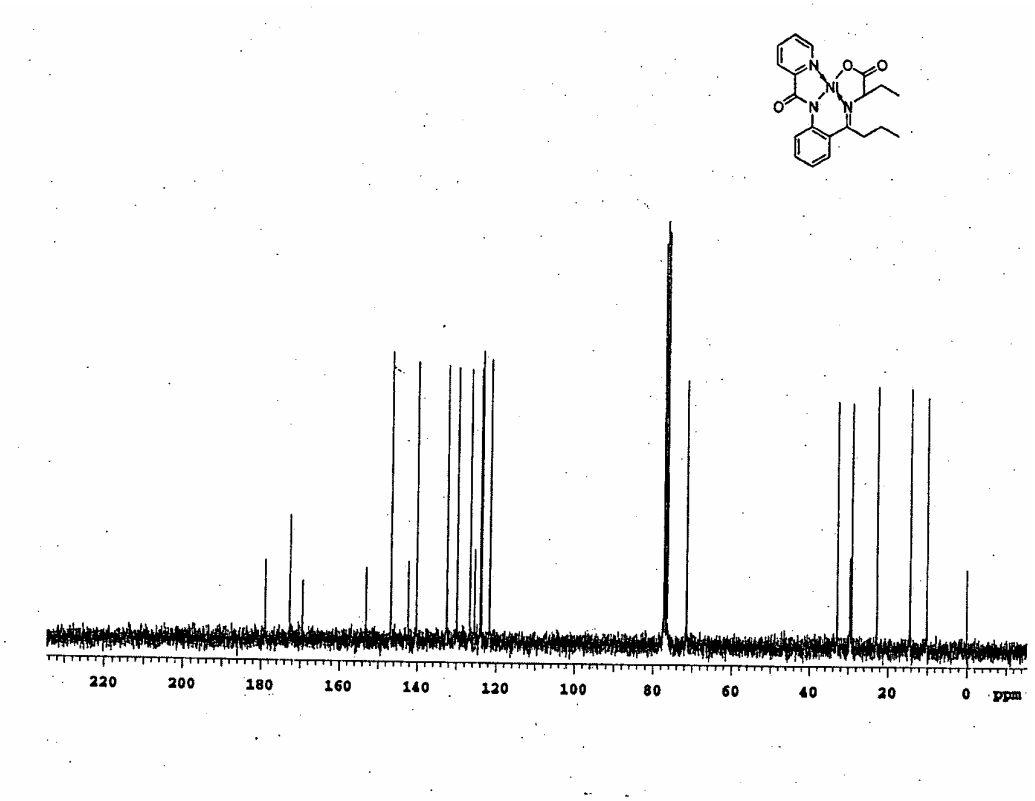

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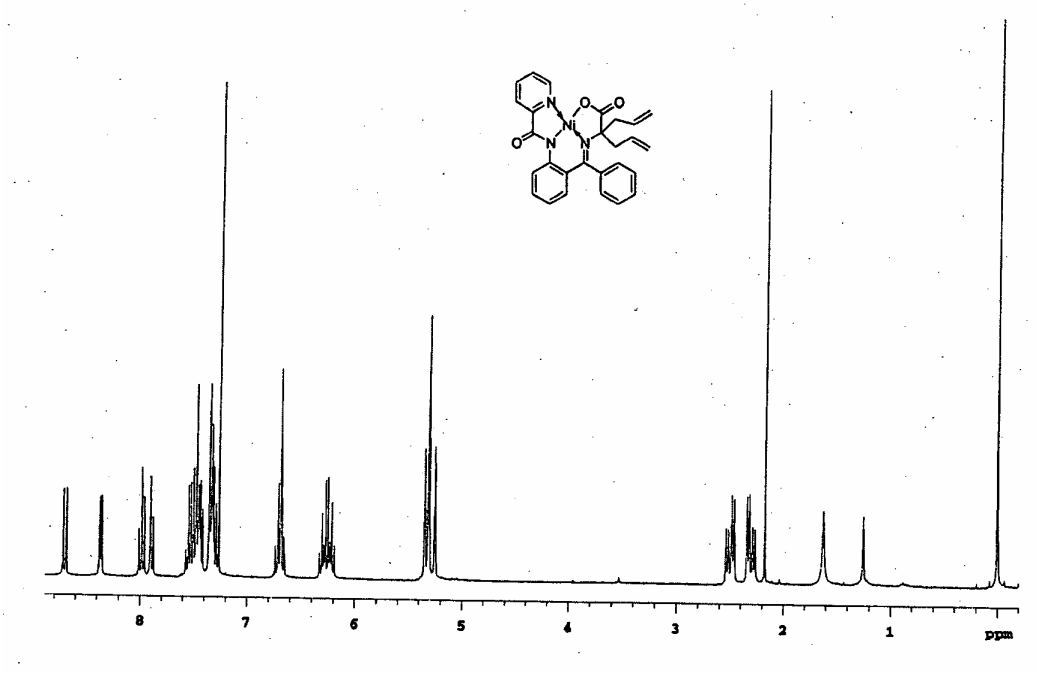

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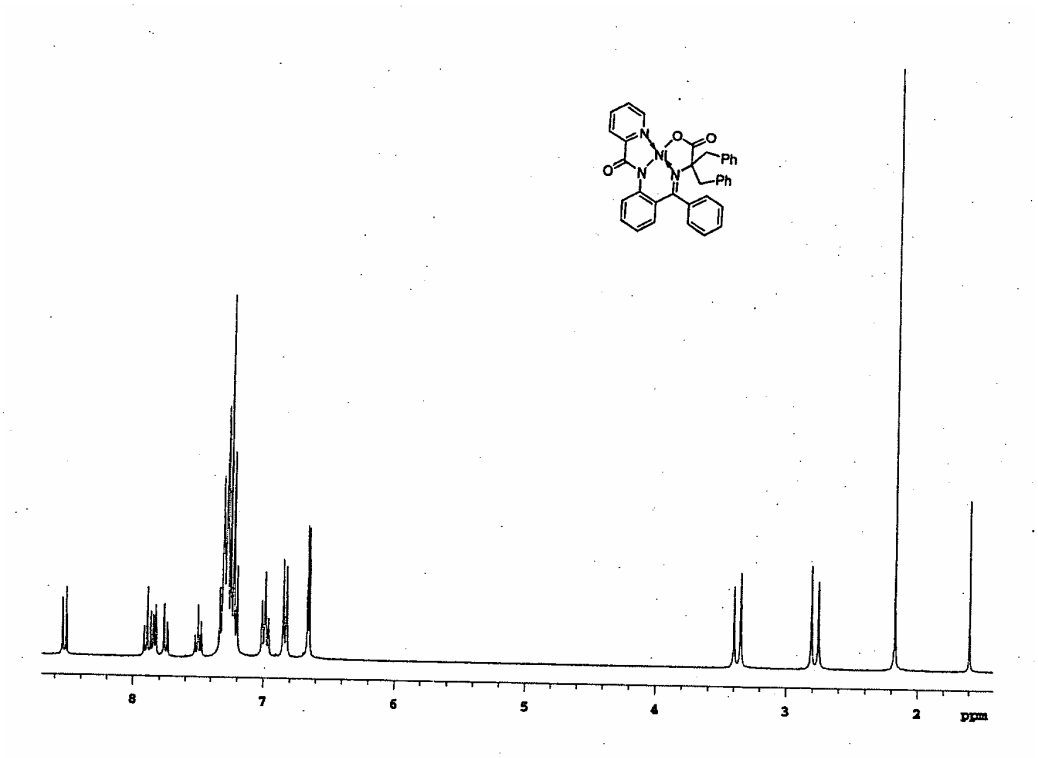

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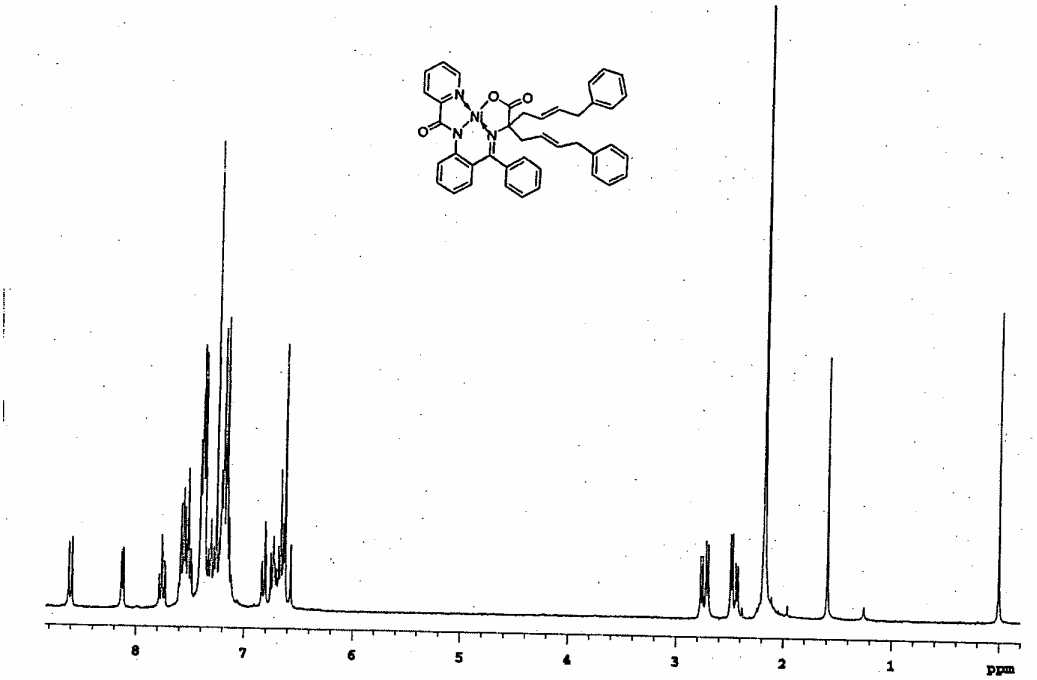

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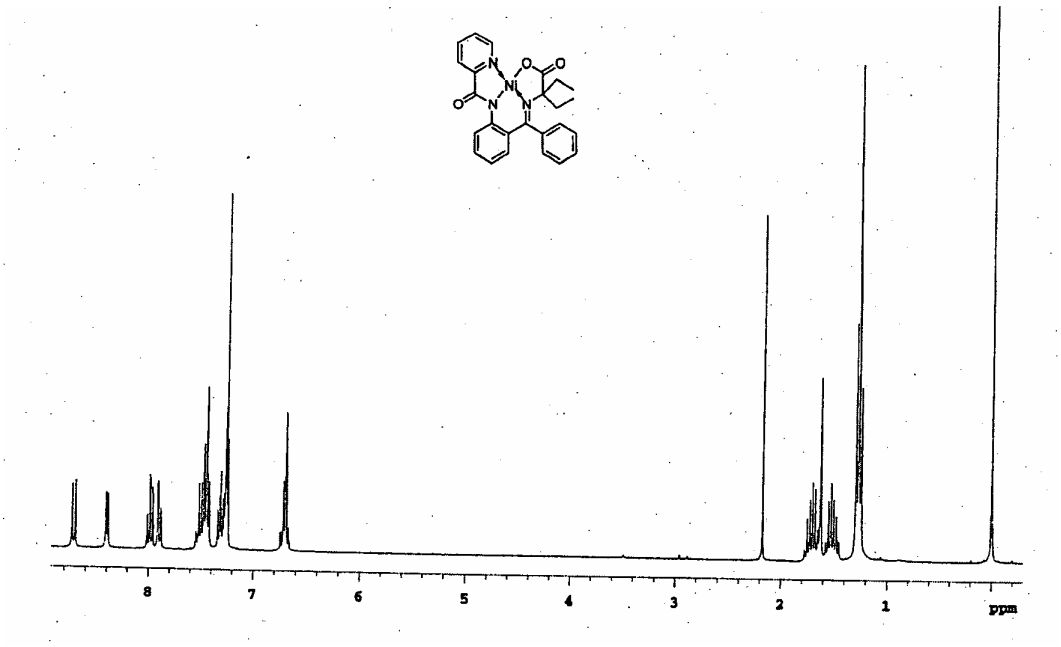

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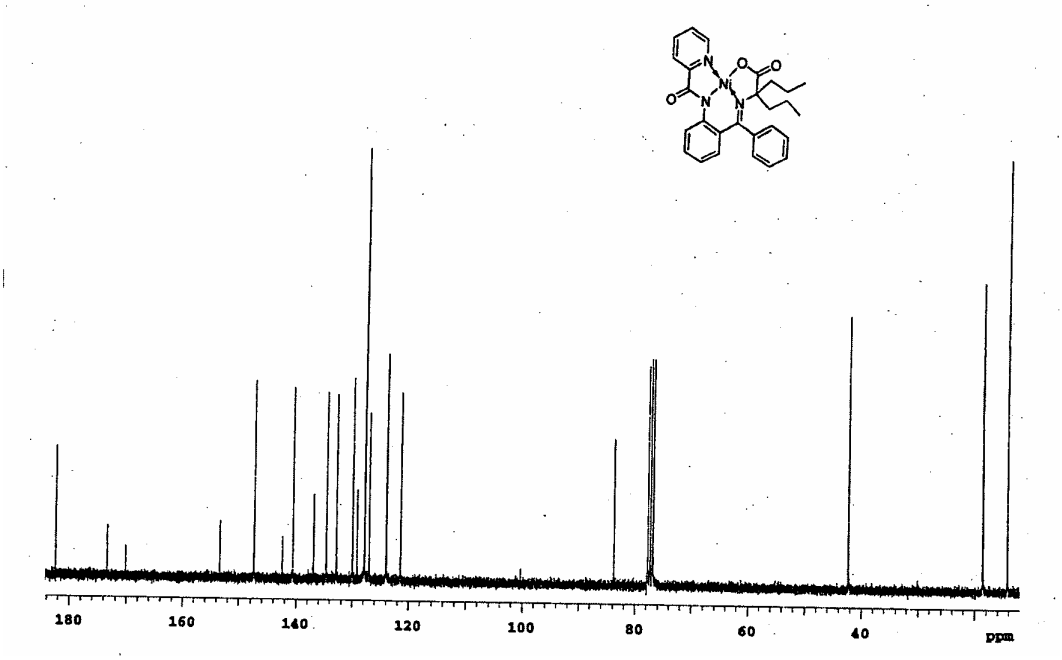

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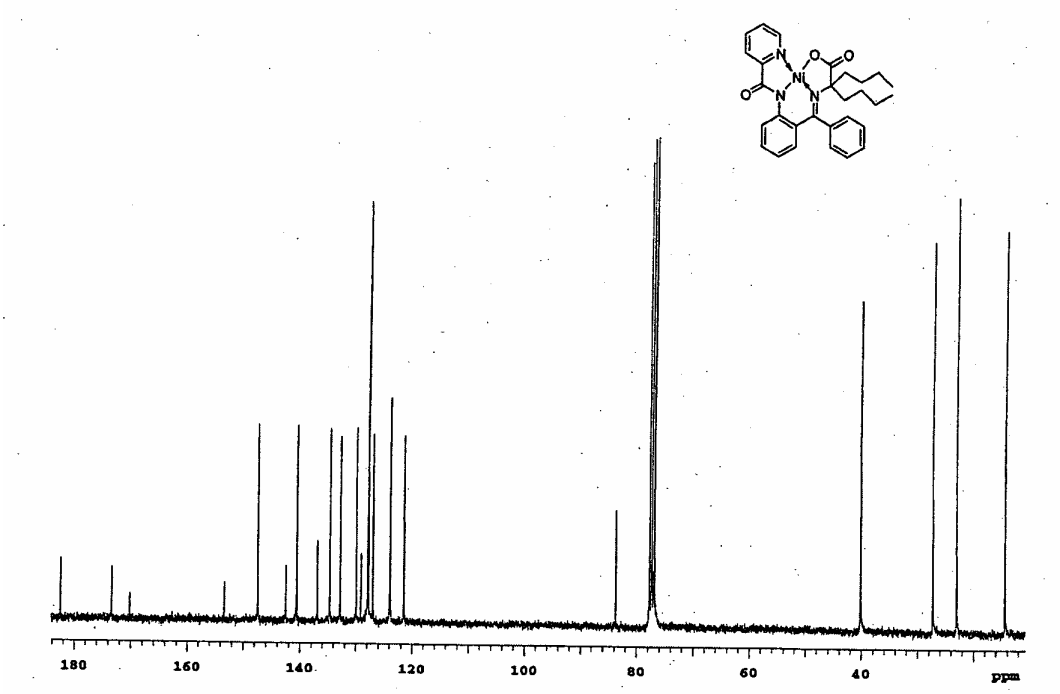

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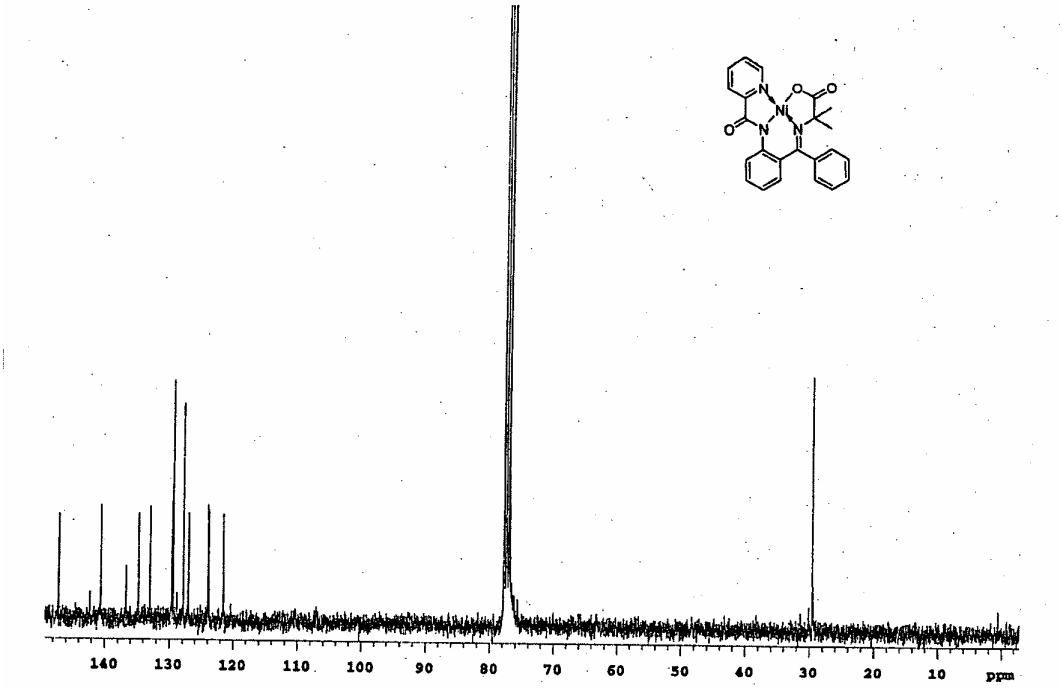

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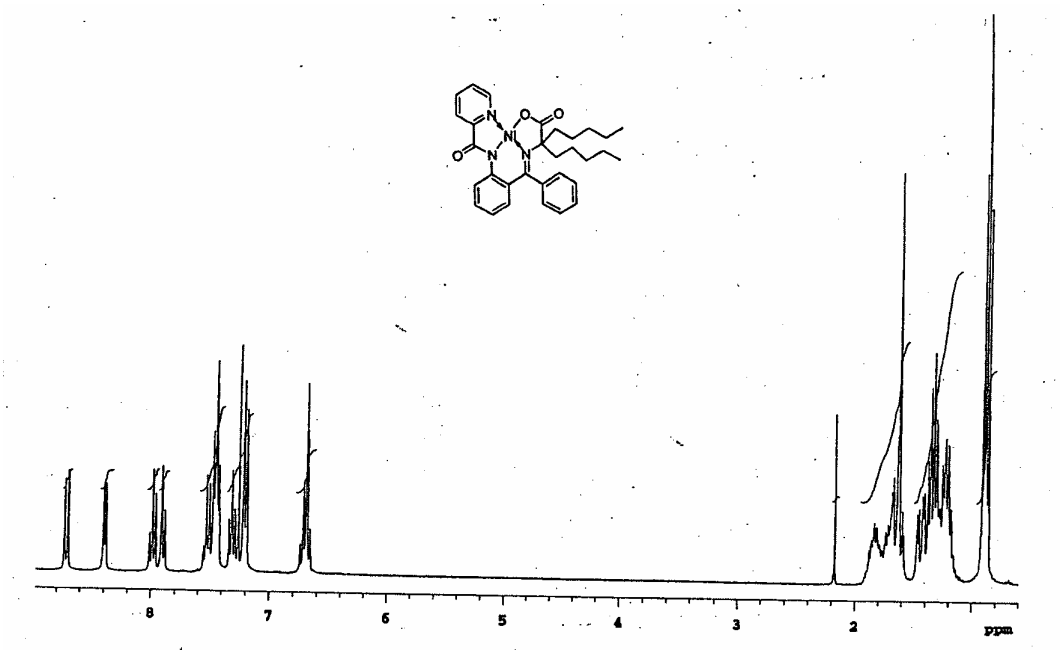

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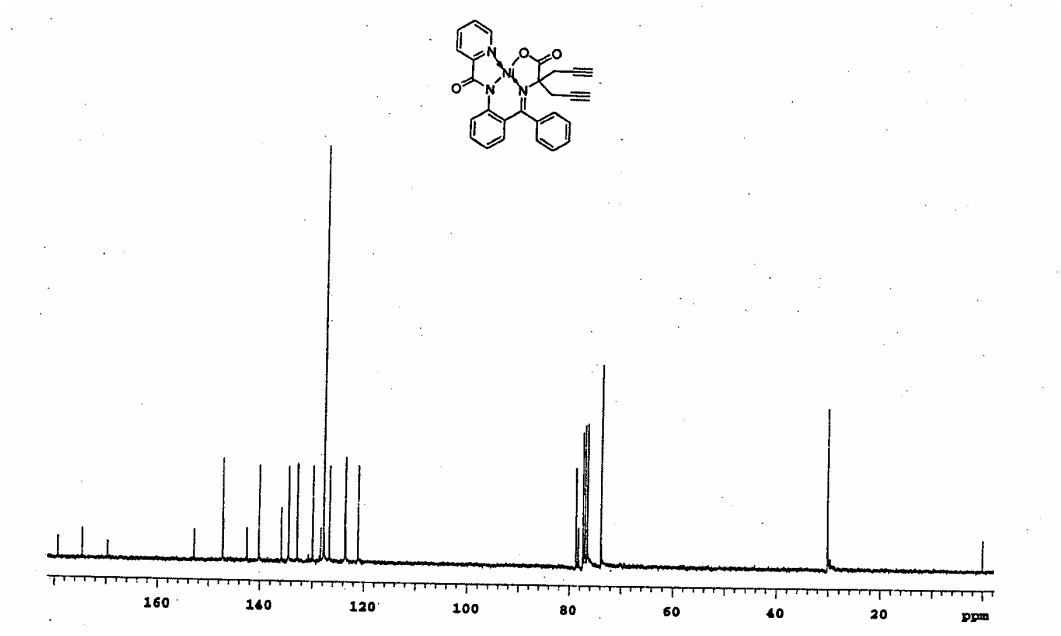

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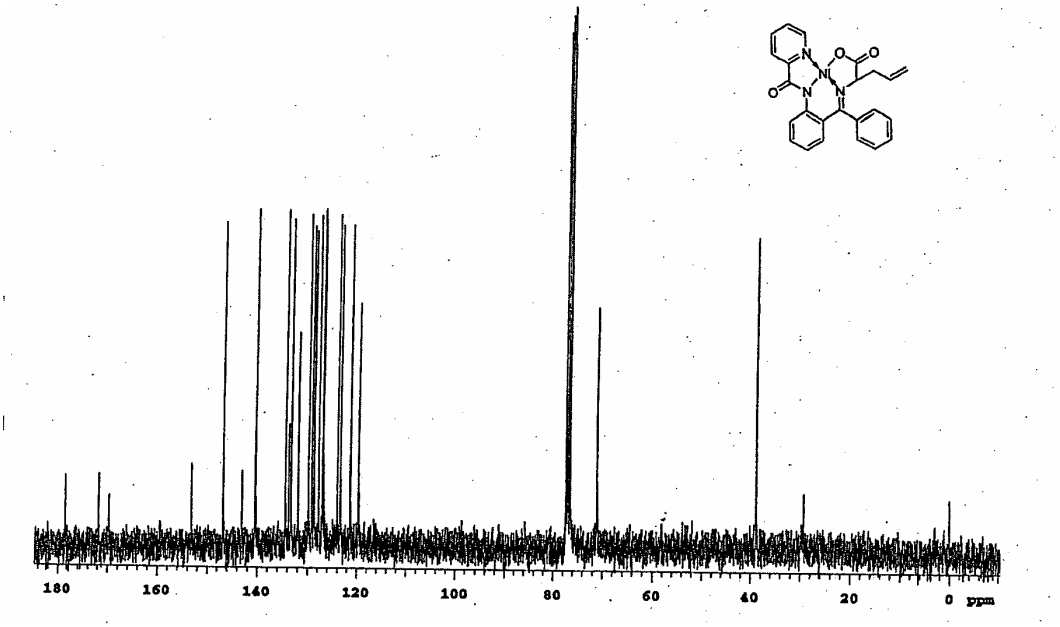

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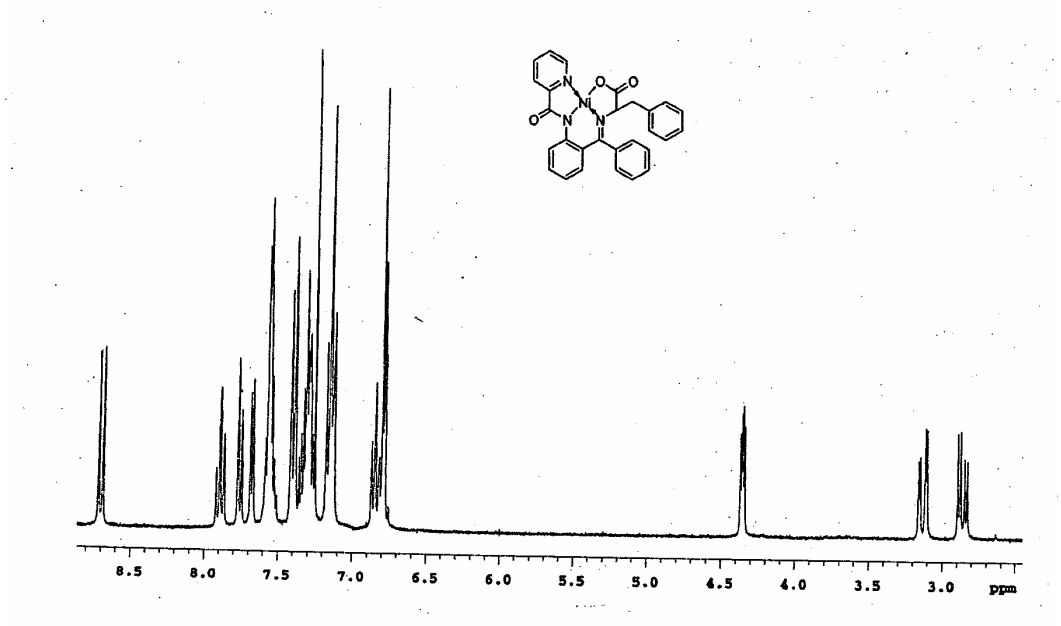

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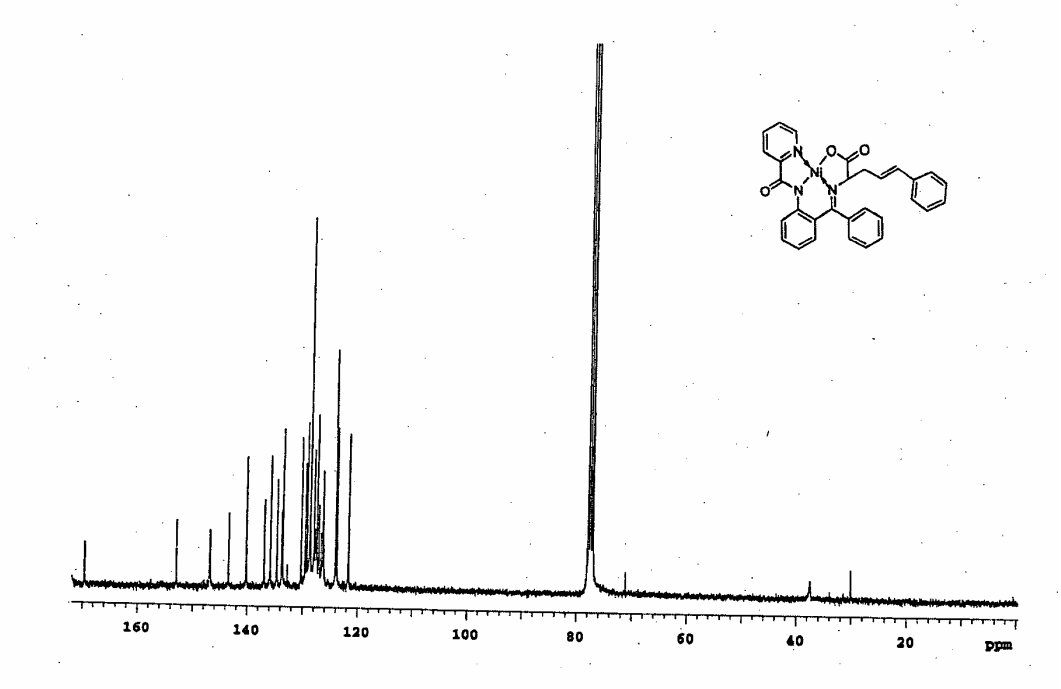

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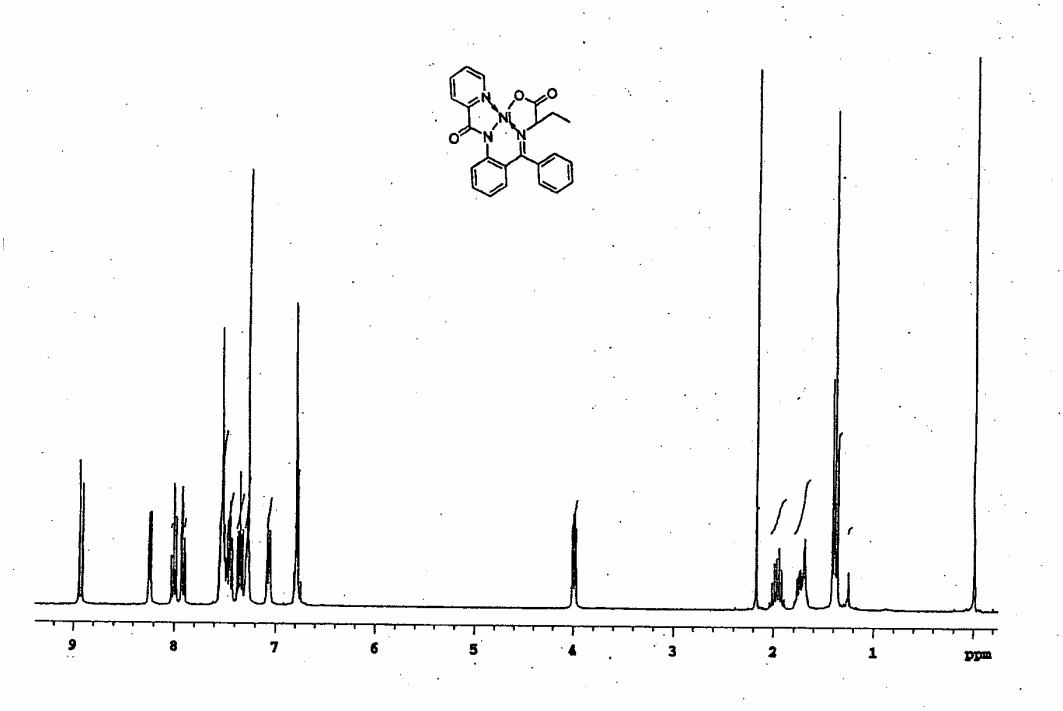

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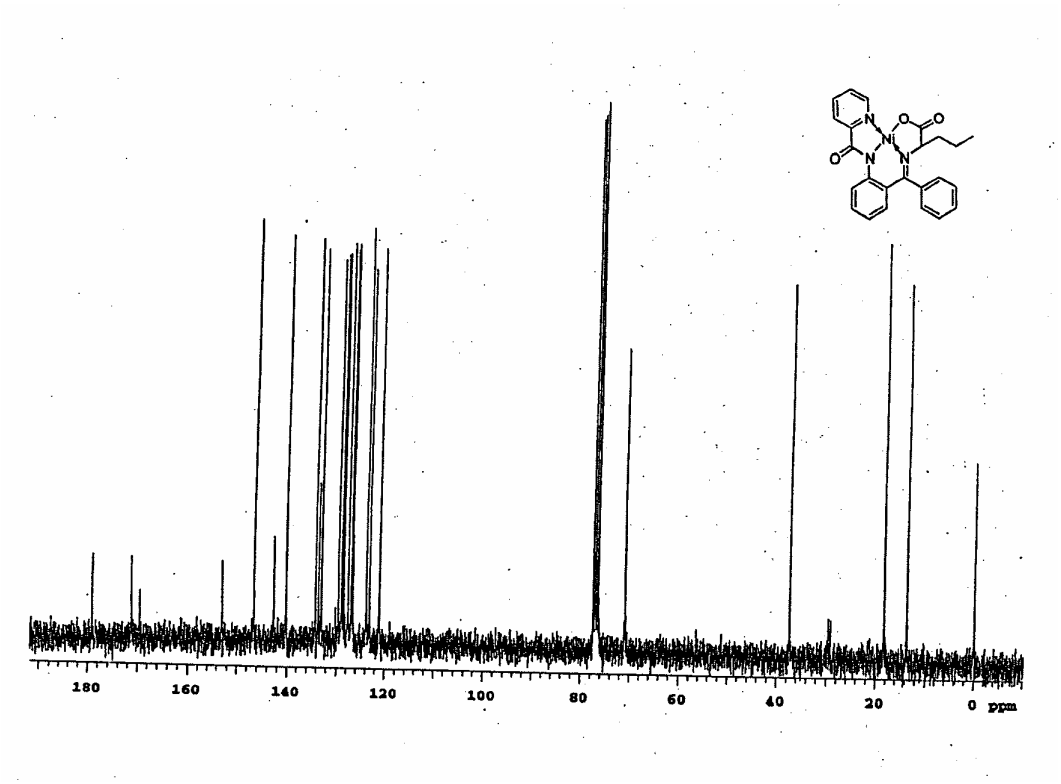

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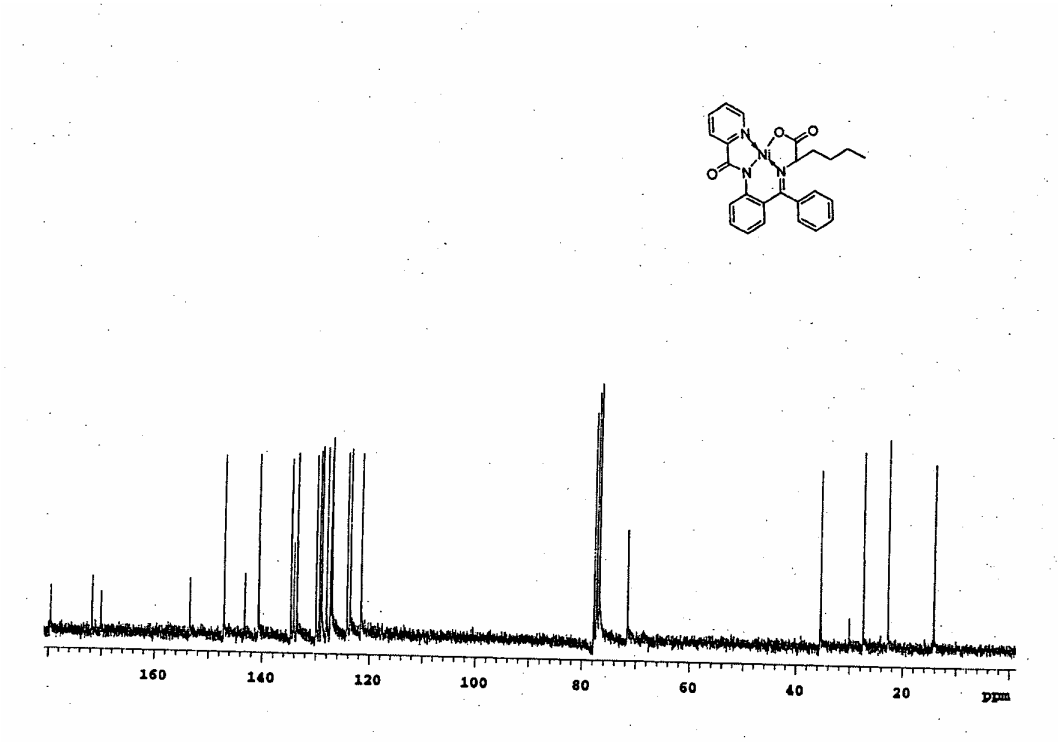

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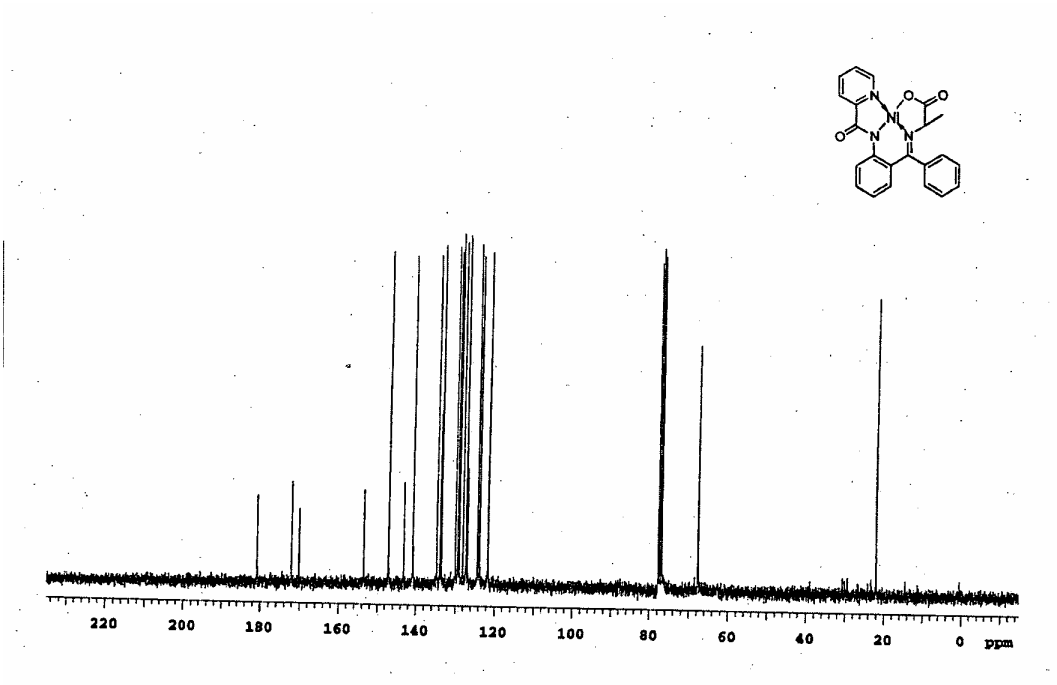

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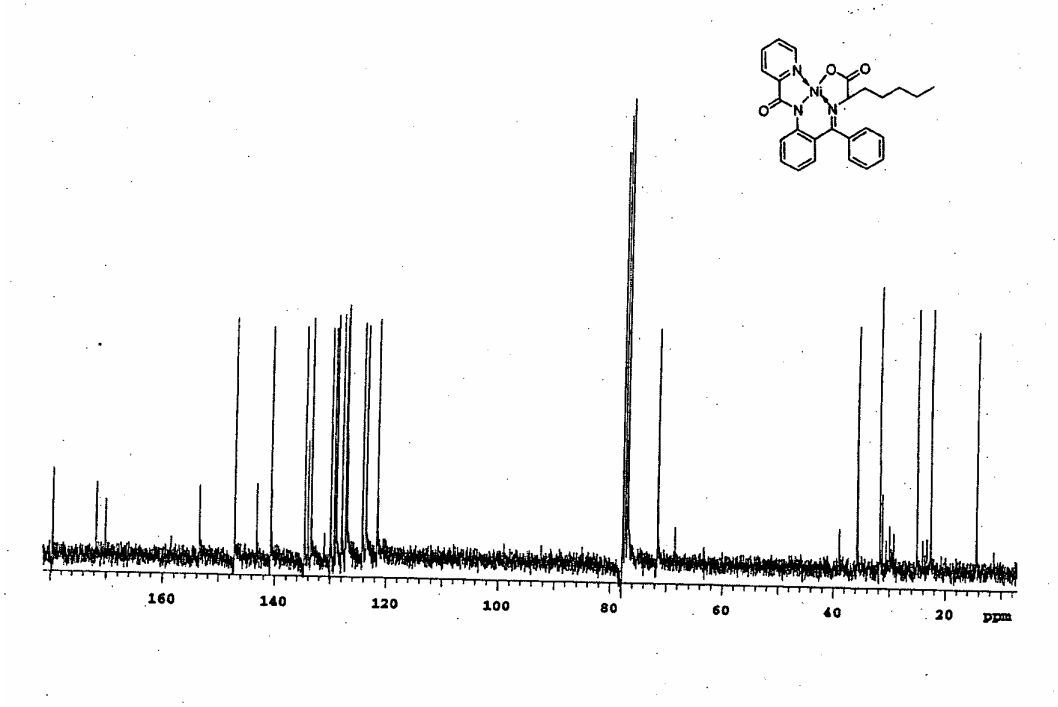

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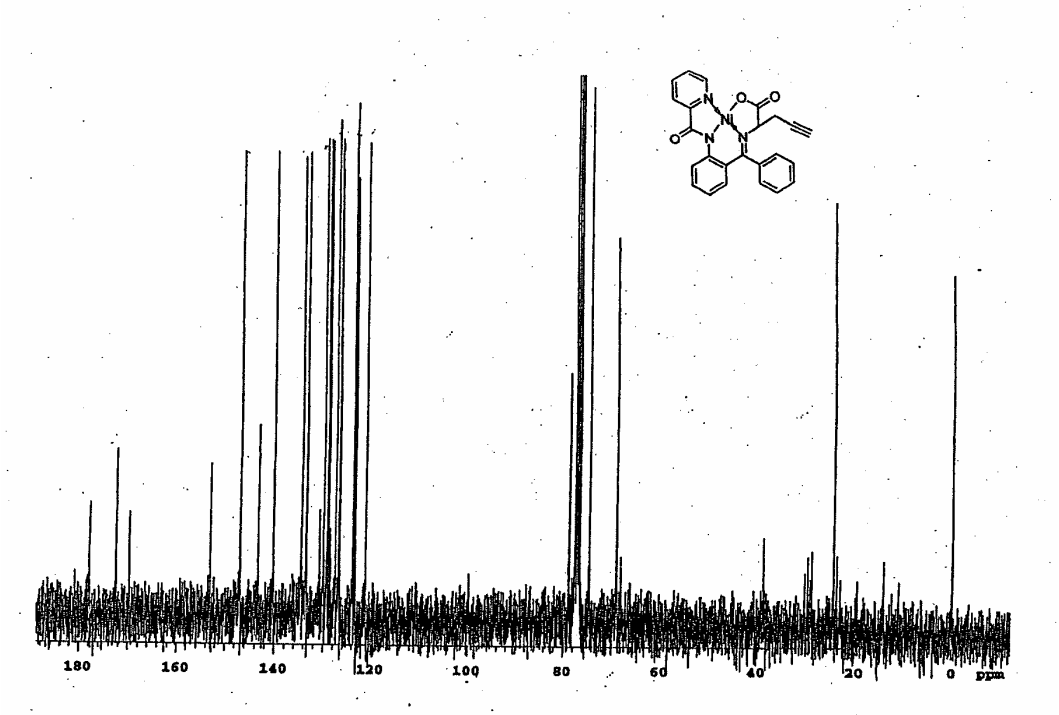

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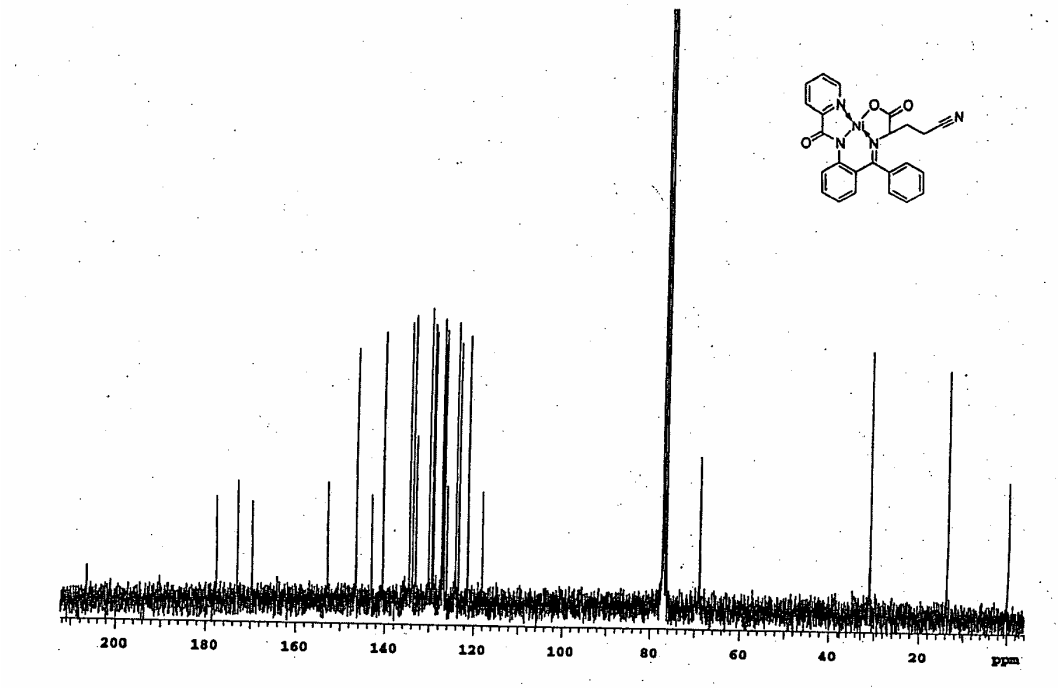

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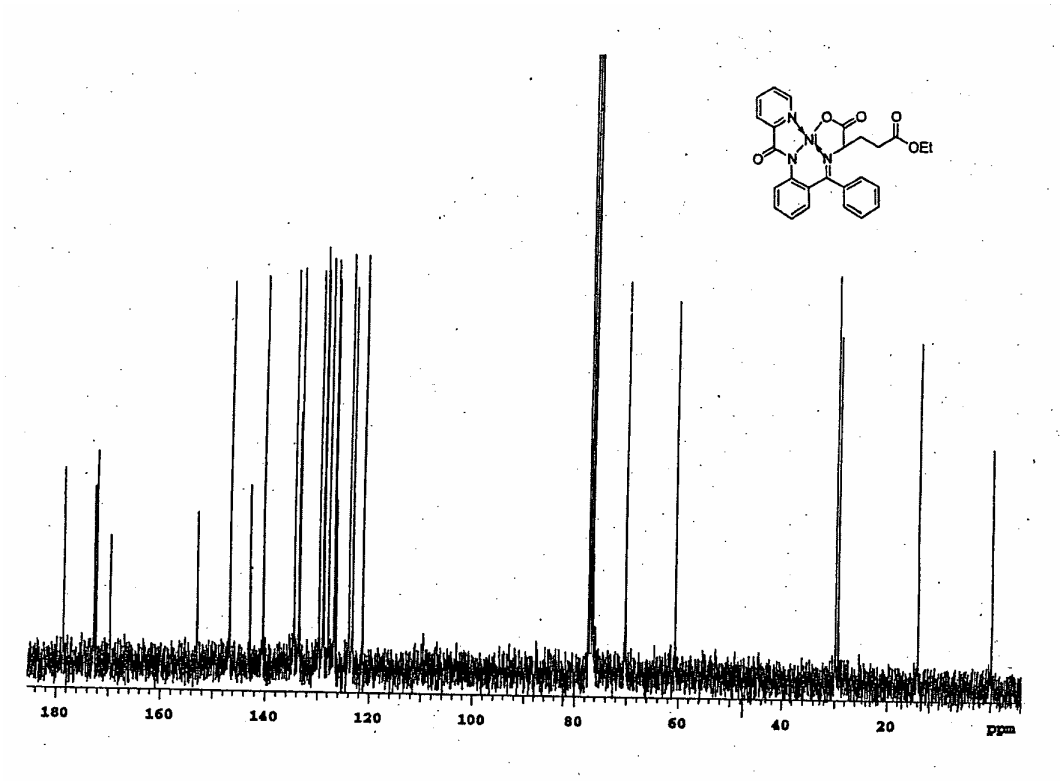

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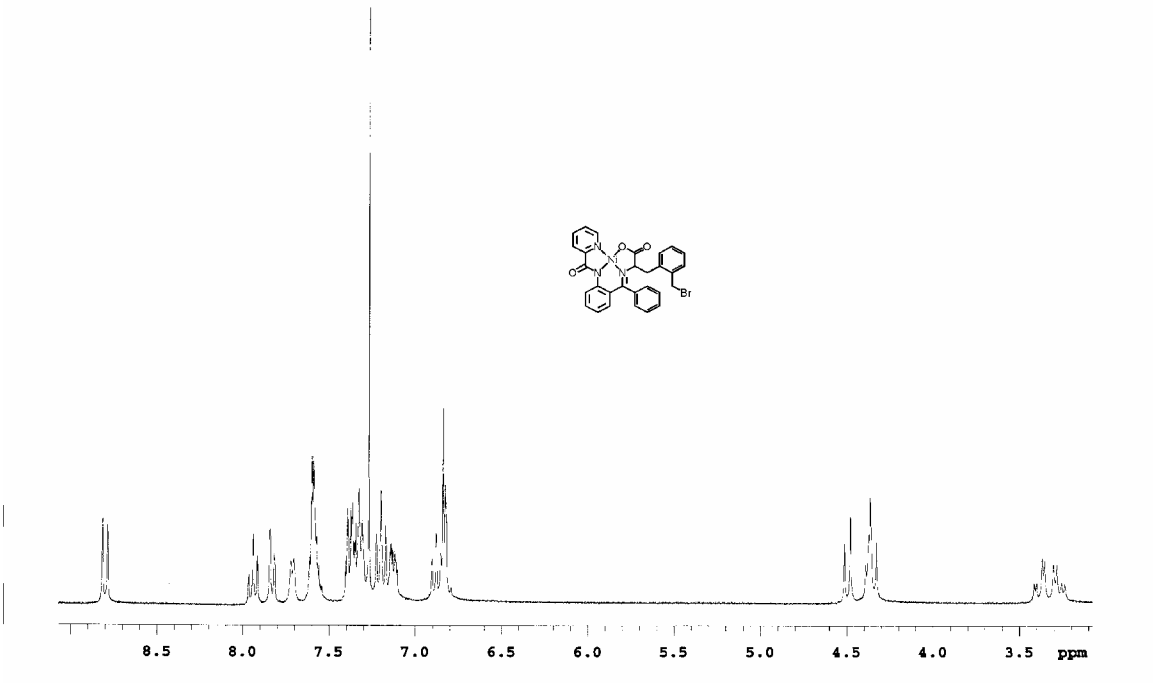

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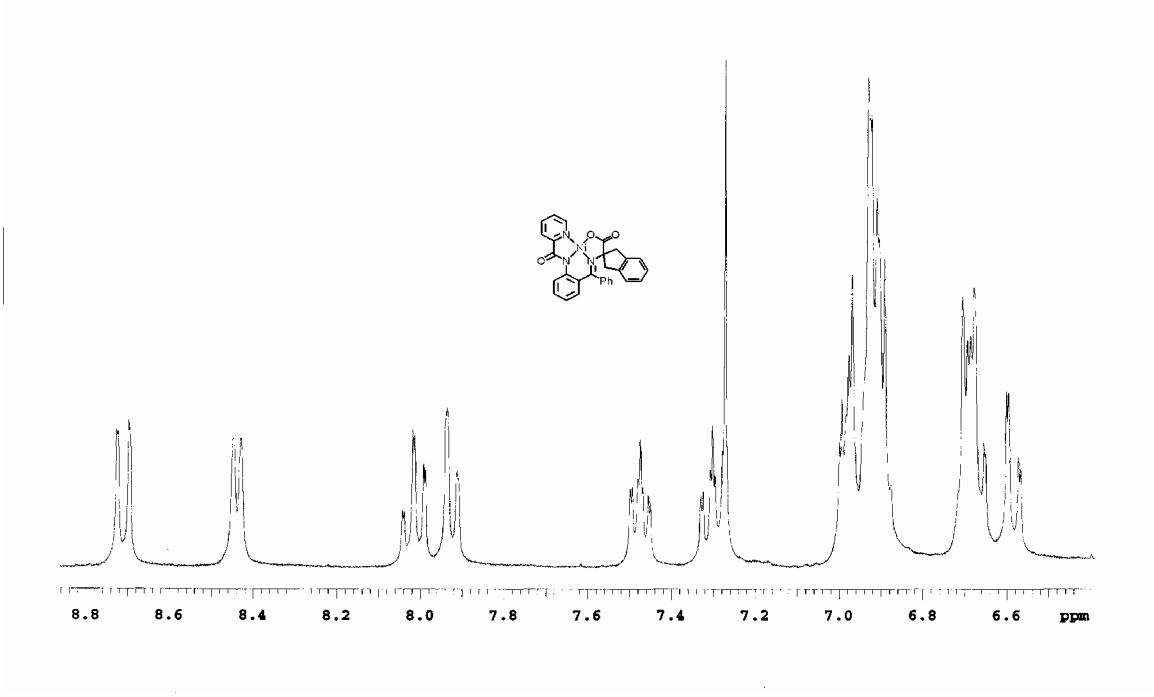

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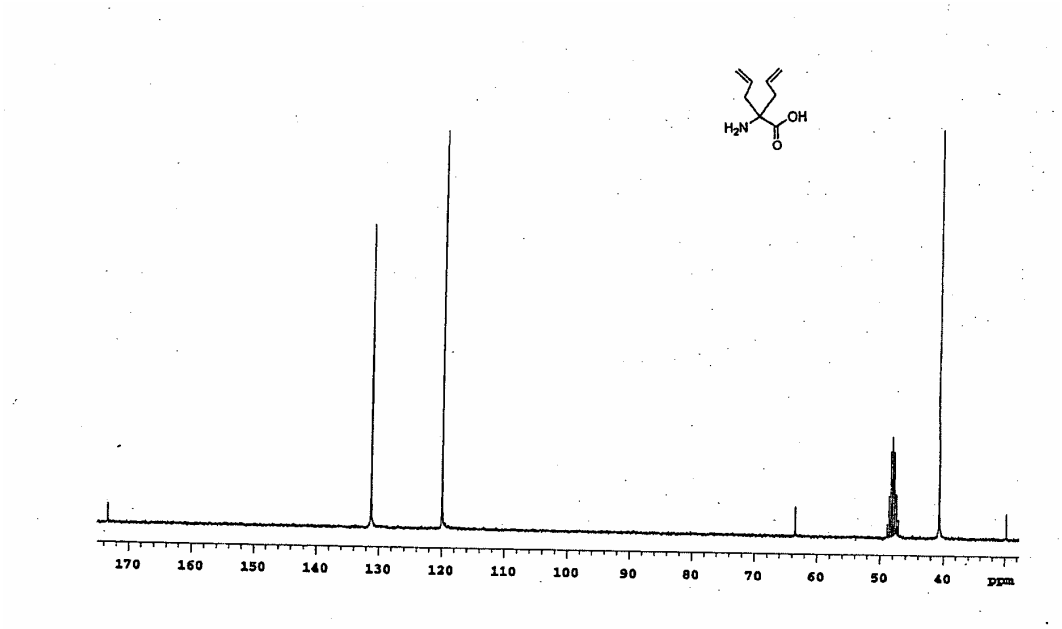

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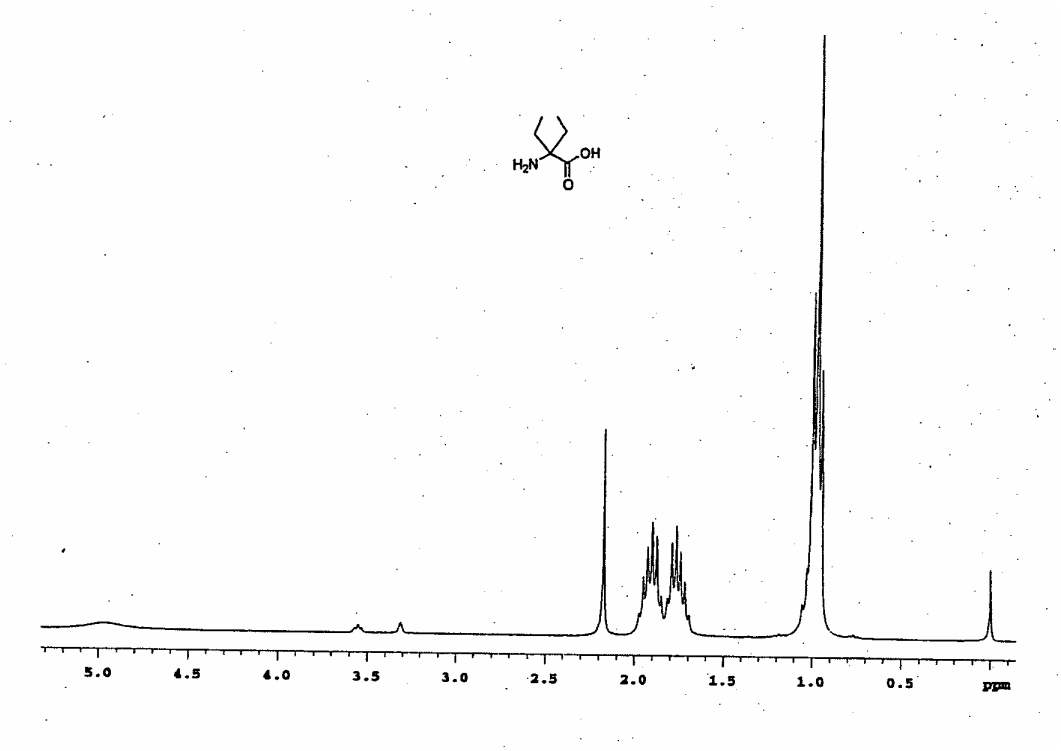

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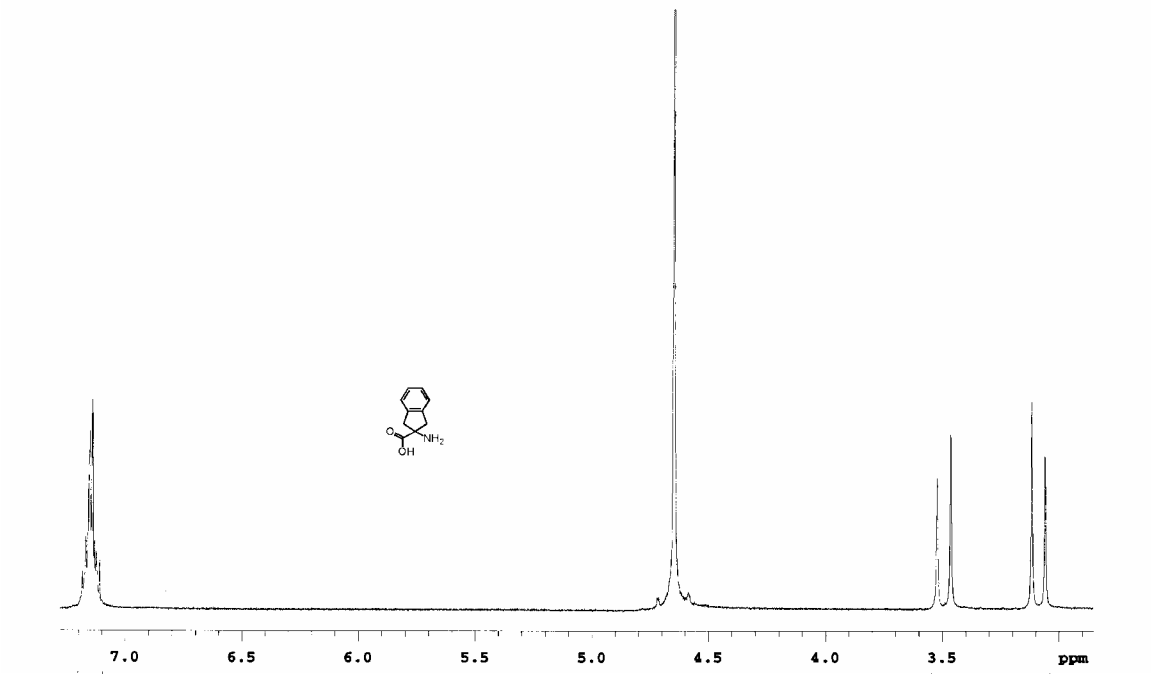

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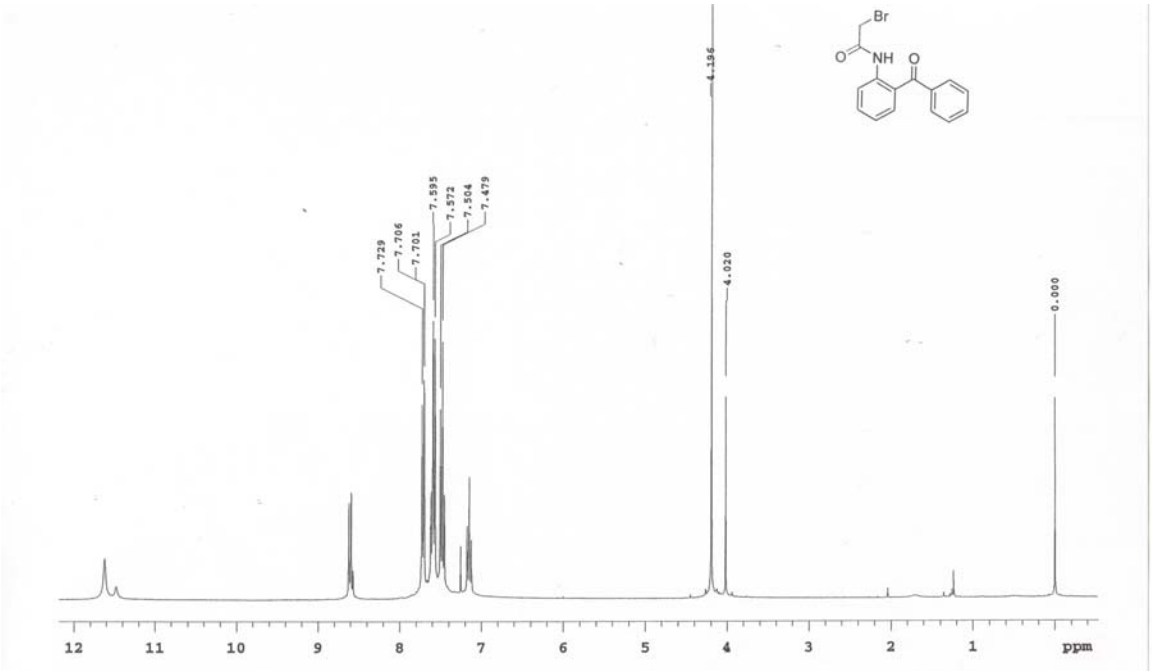

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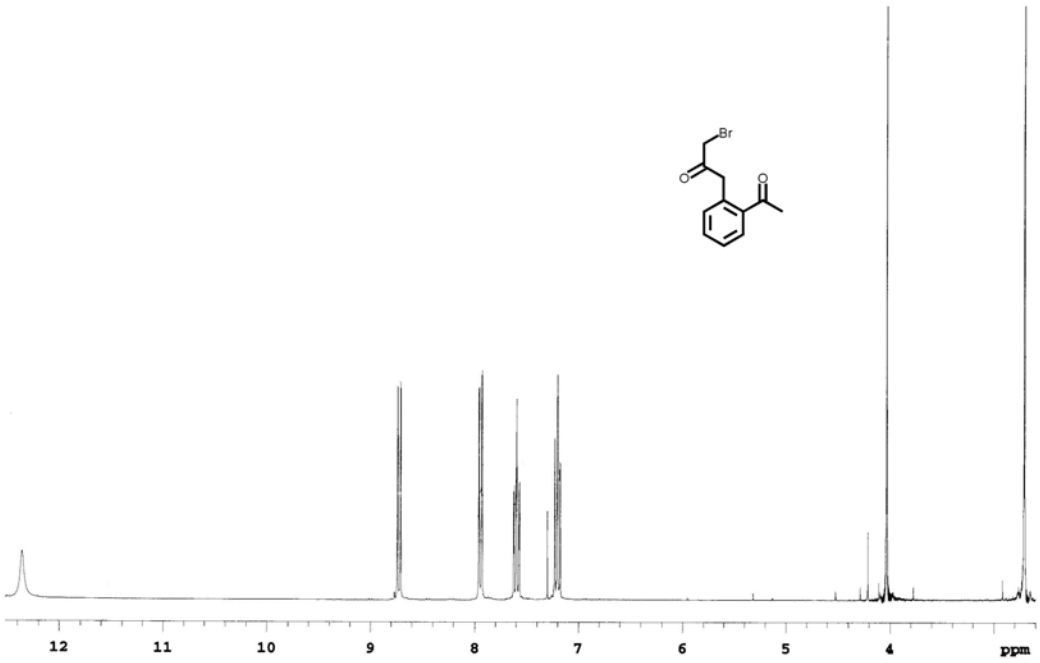

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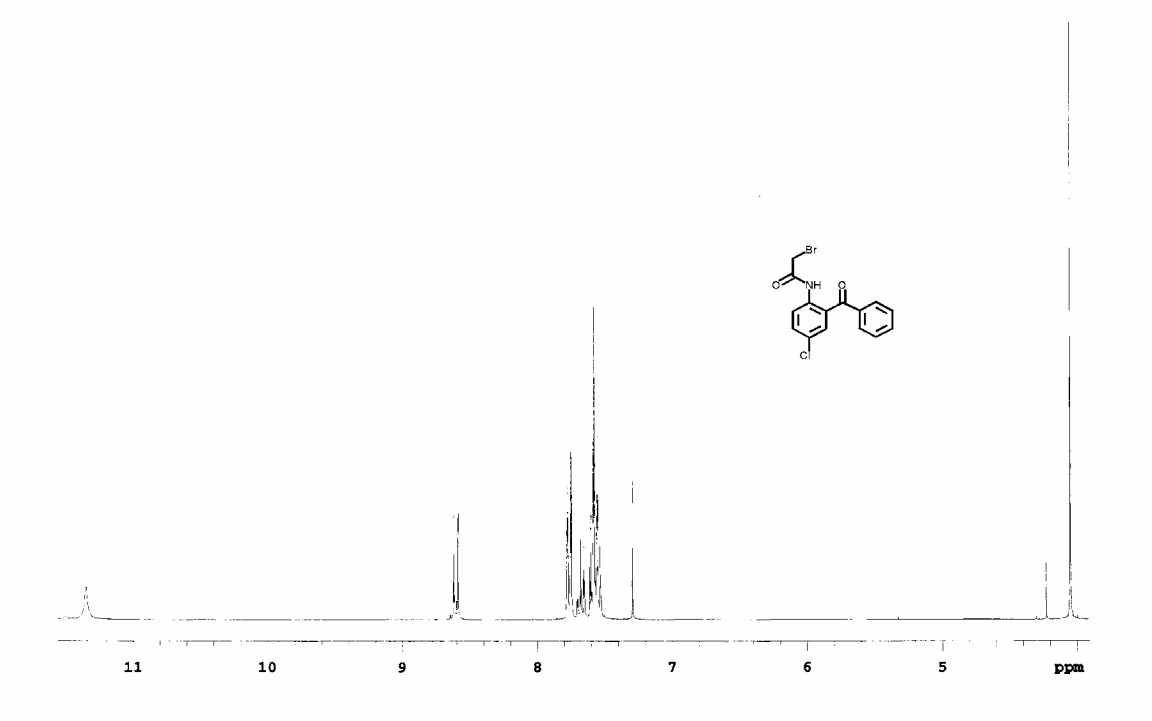

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100
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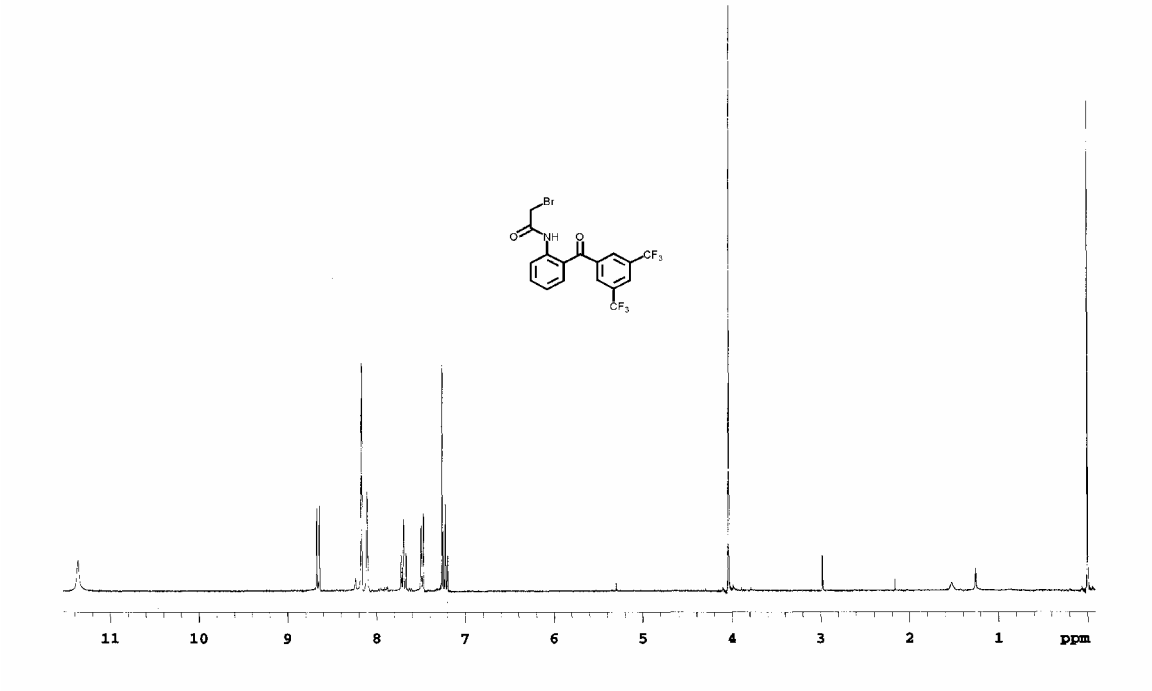

OH
H2N
O
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1.0
0.5
ppm

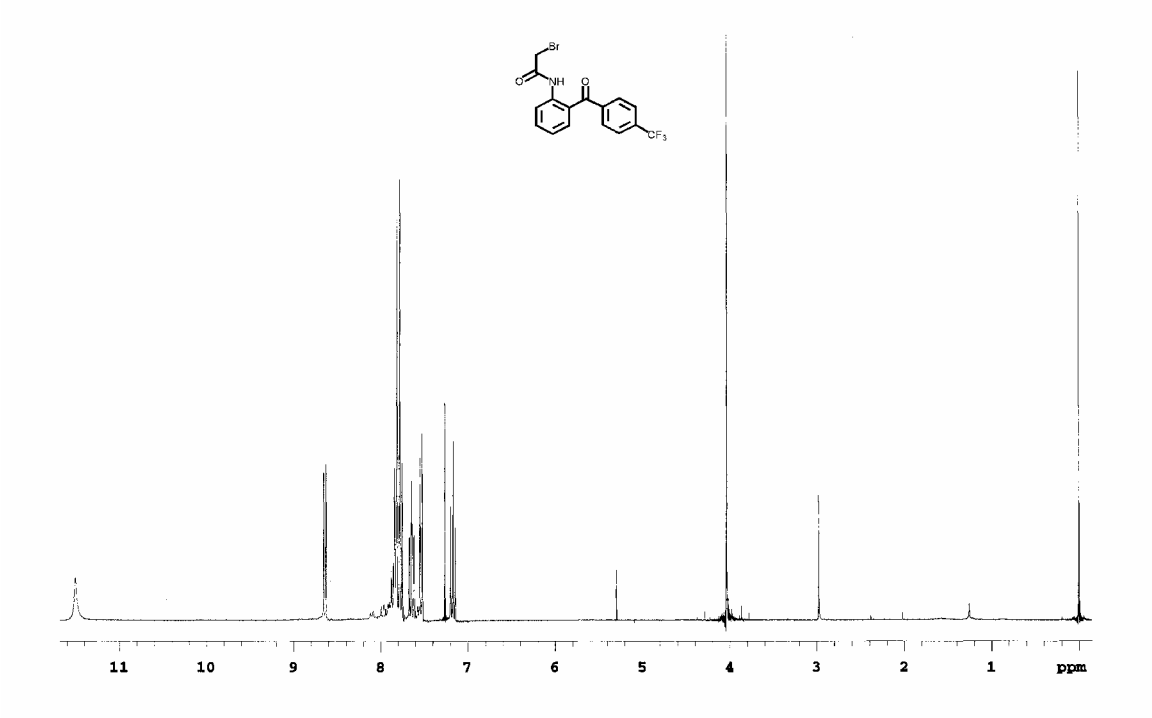

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OH
NH2
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5.0
4.5
4.0
3.5
ppm

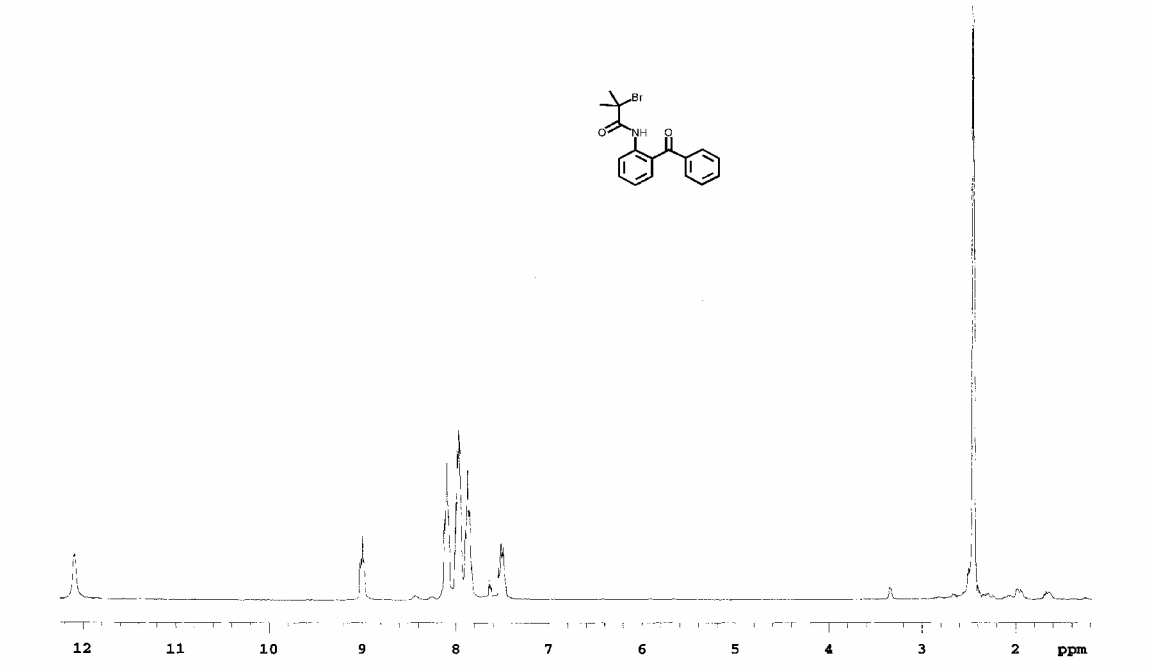

Br
NH
O
O
7.729
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7.701
7.595
7.572
7.504
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0.000
12
11
10
9
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7
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3
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1
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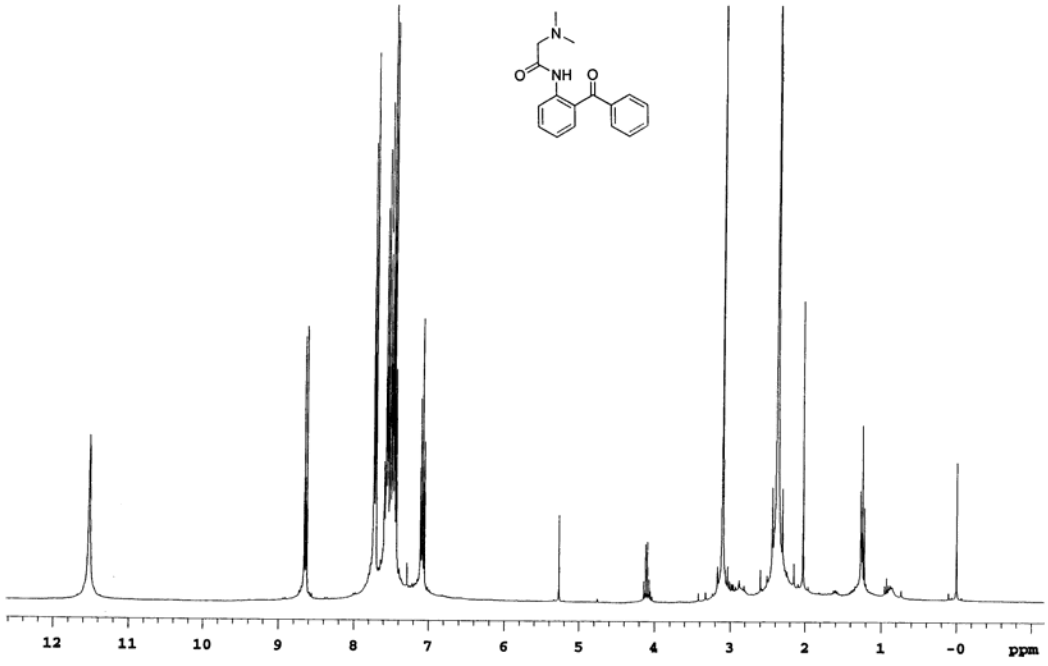

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O
O
12
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6
5
4
ppm

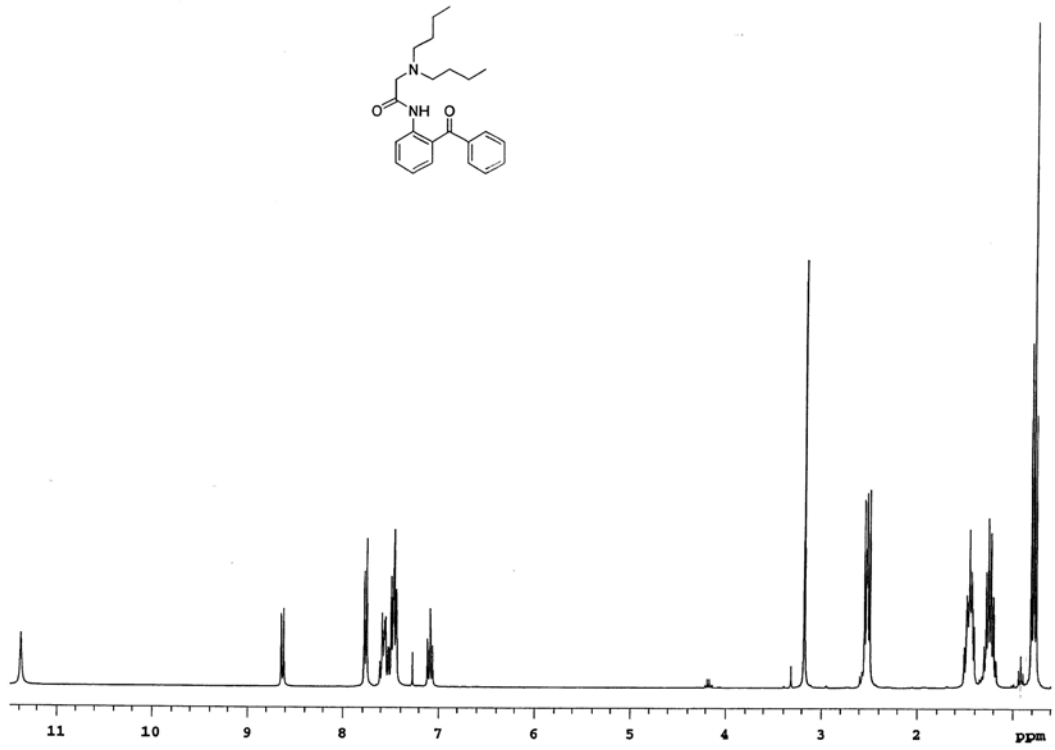

Br
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NH
O
Cl
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7
6
5
ppm

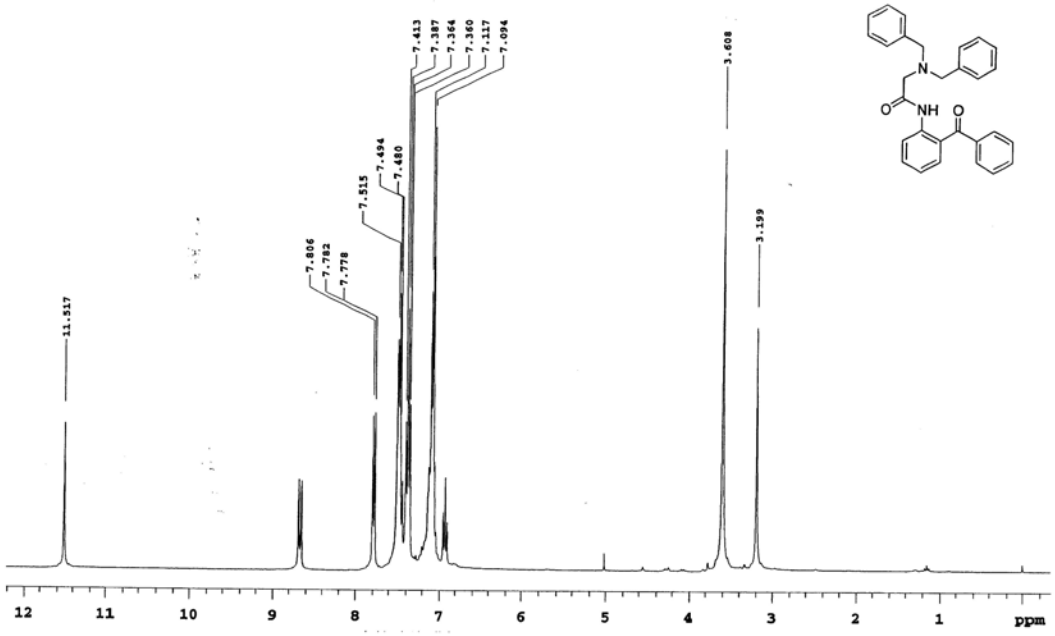

Br
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NH
O
CF3
CF3
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1
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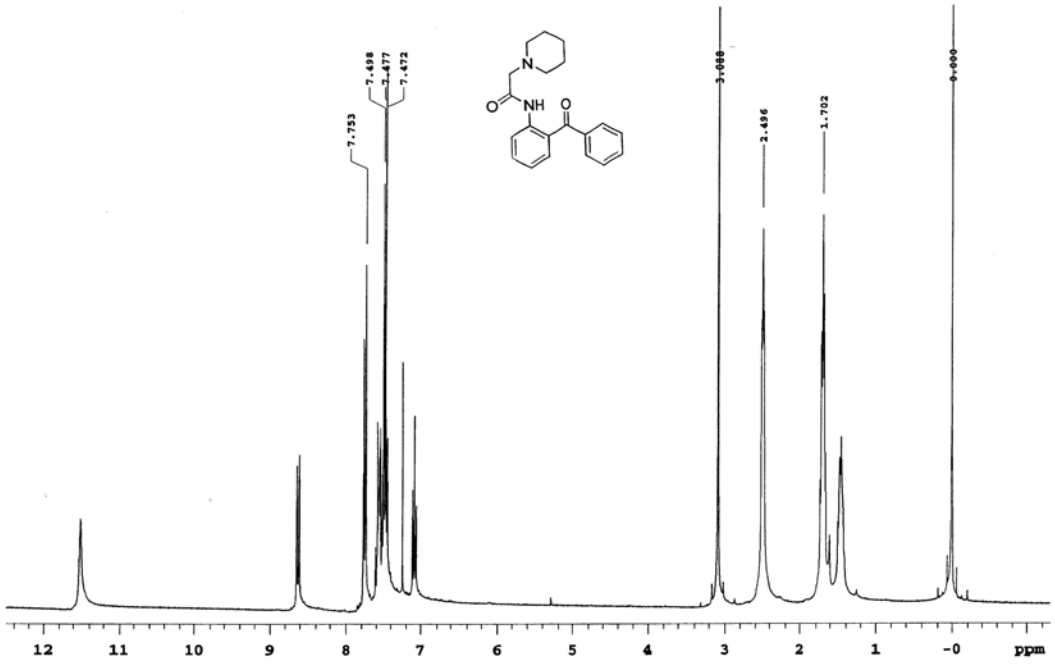

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O
CF3
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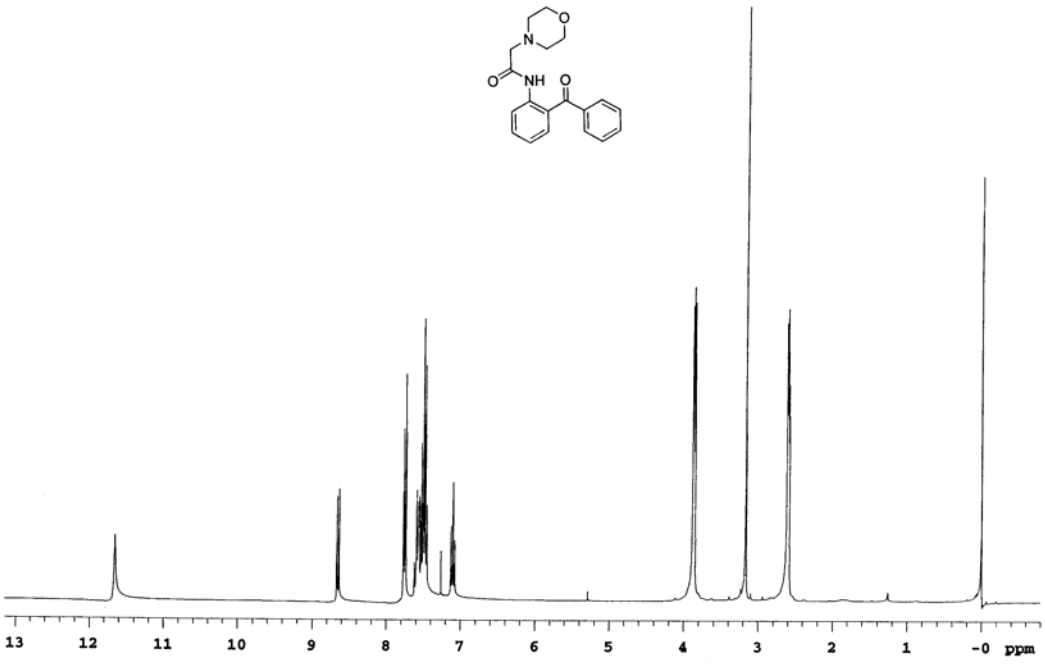

Br
NH
O
O
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ppm

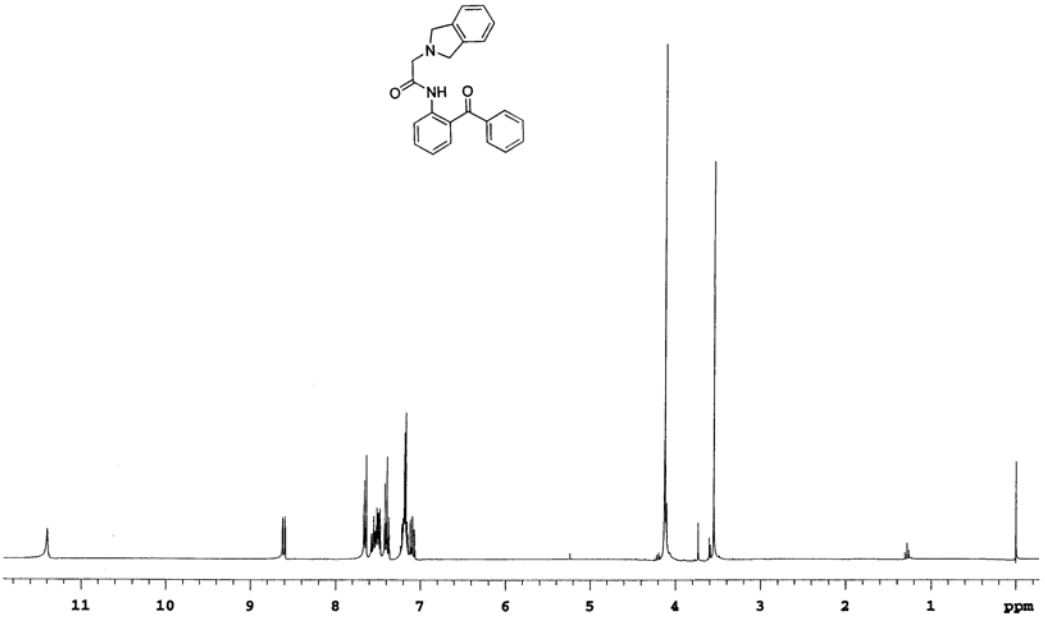

N
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O
O
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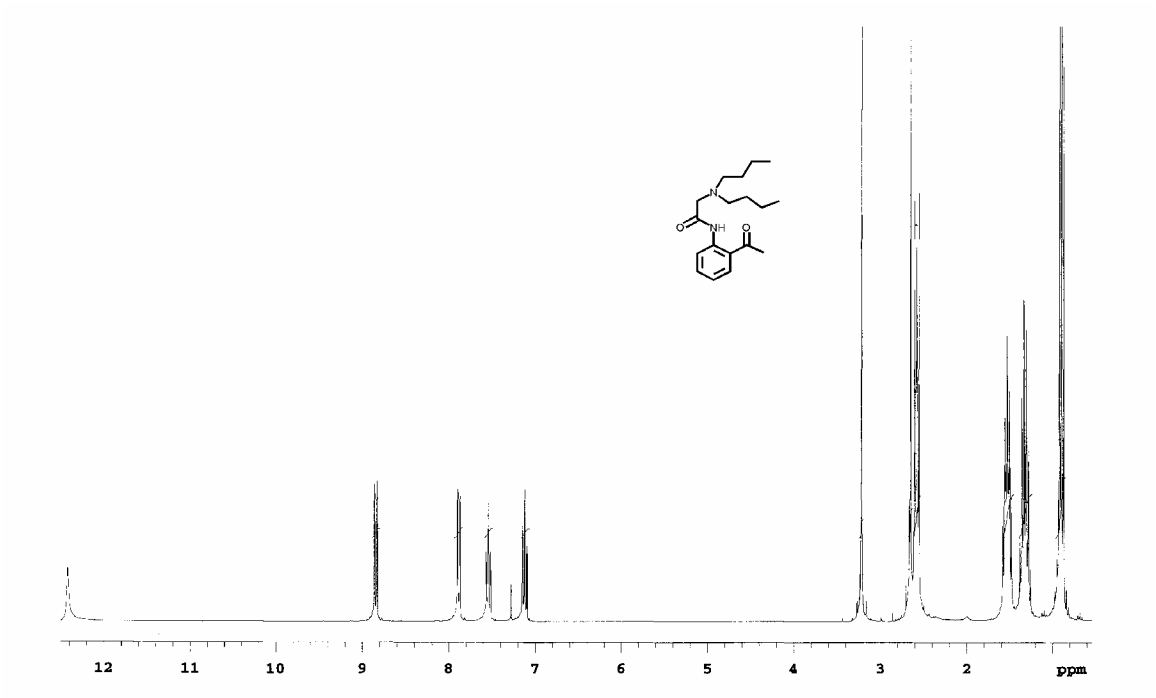

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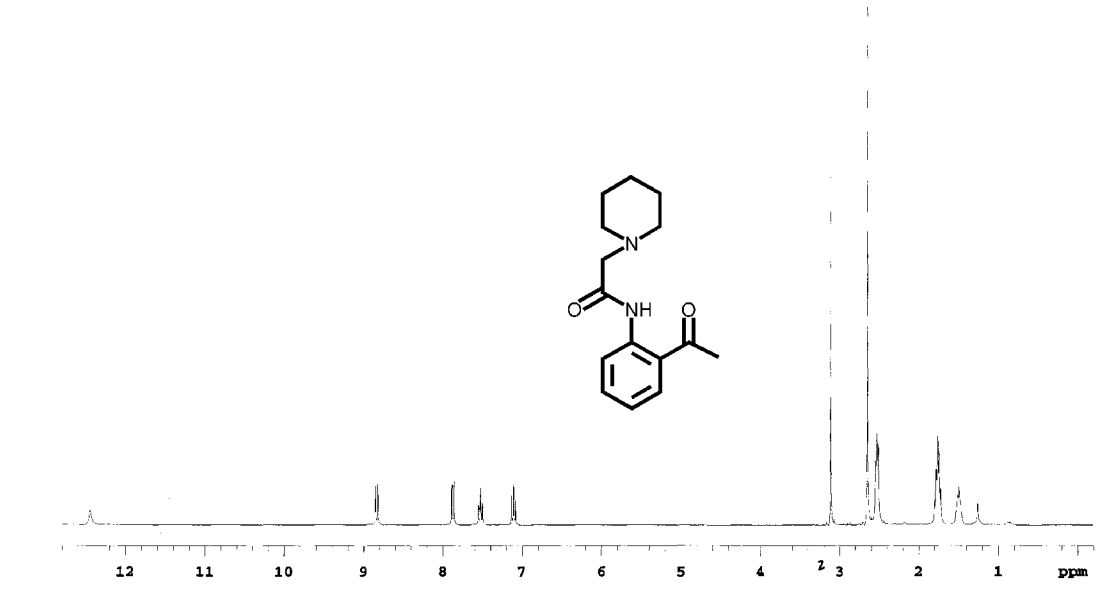

11.517
7.806
7.782
7.778
7.515
7.494
7.480
7.413
7.387
7.364
7.360
7.117
7.094
3.608
3.199
NH
O
O
12
11
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3
2
1
ppm

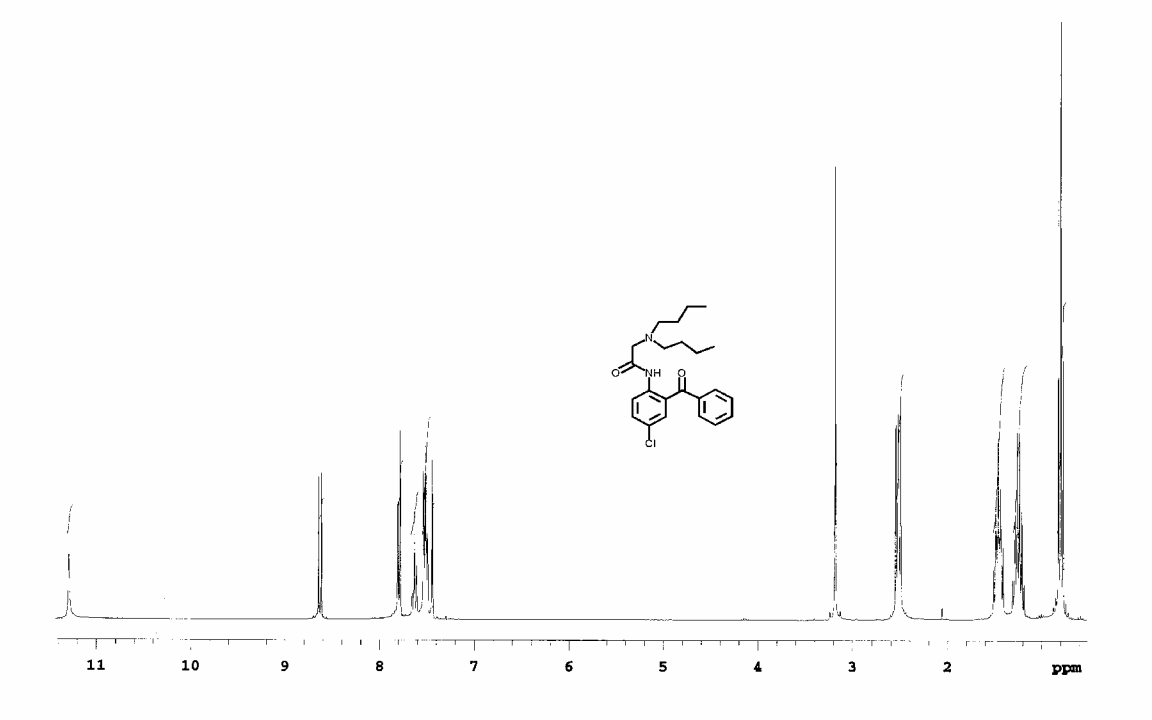

7.753
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7.477
7.472
3.080
2.496
1.702
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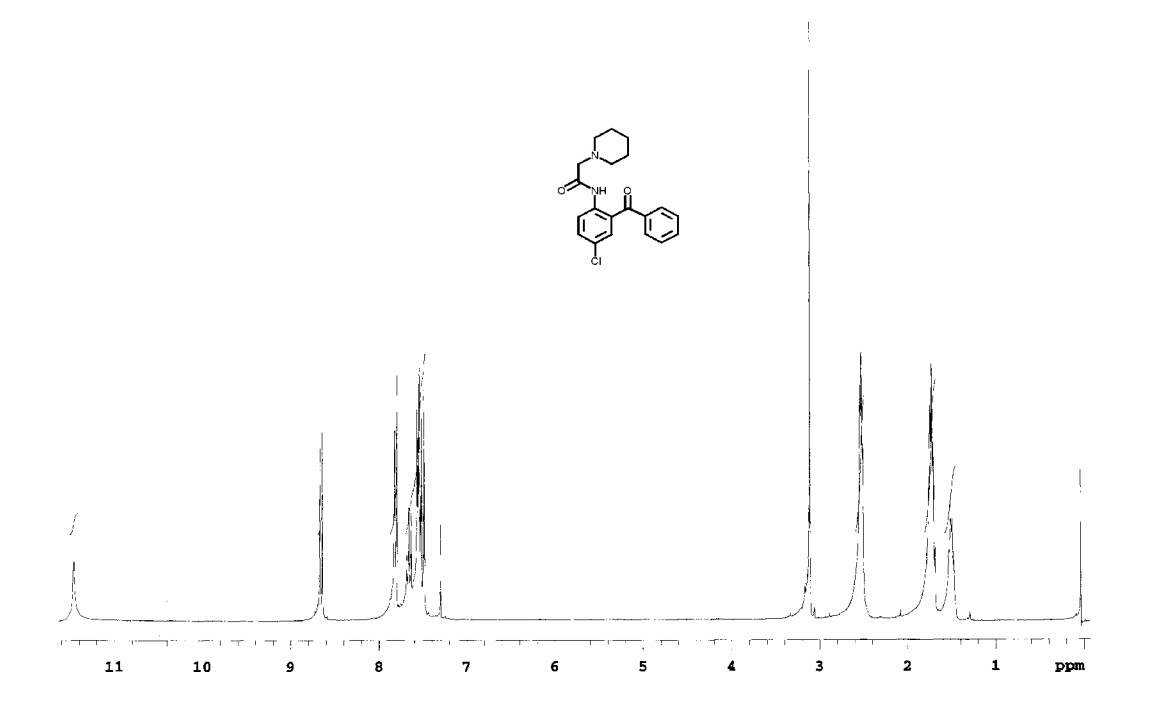

O
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O
NH
O
13
12
11
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9
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6
5
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2
1
-0
ppm

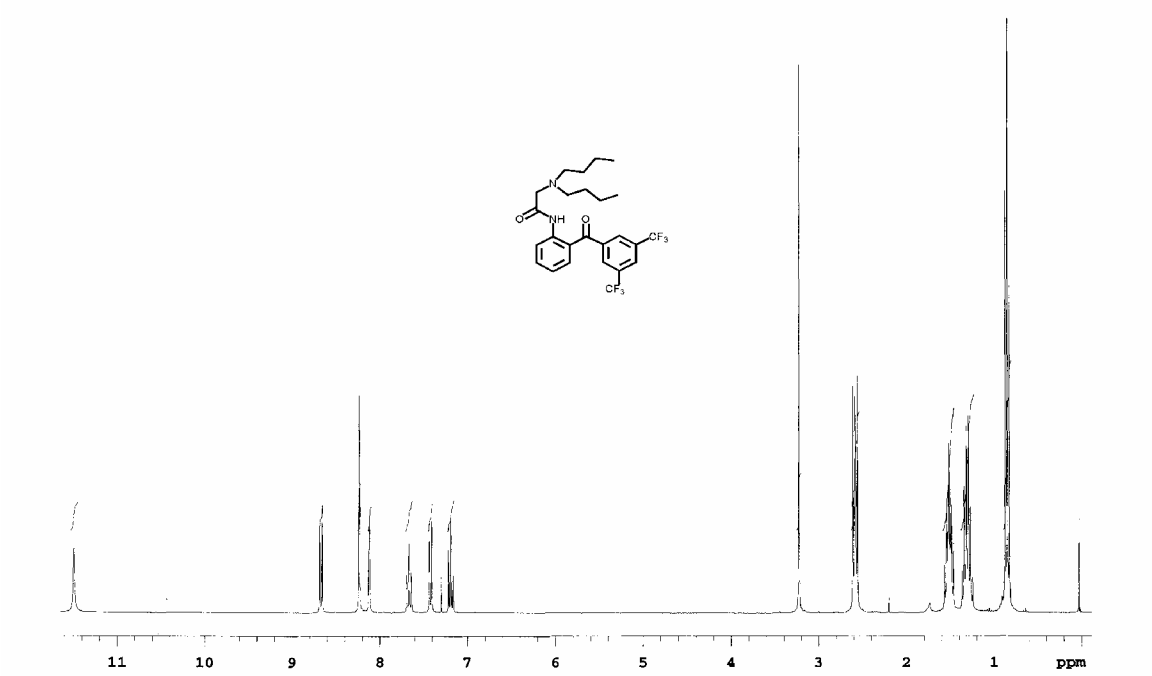

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NH
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3
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ppm

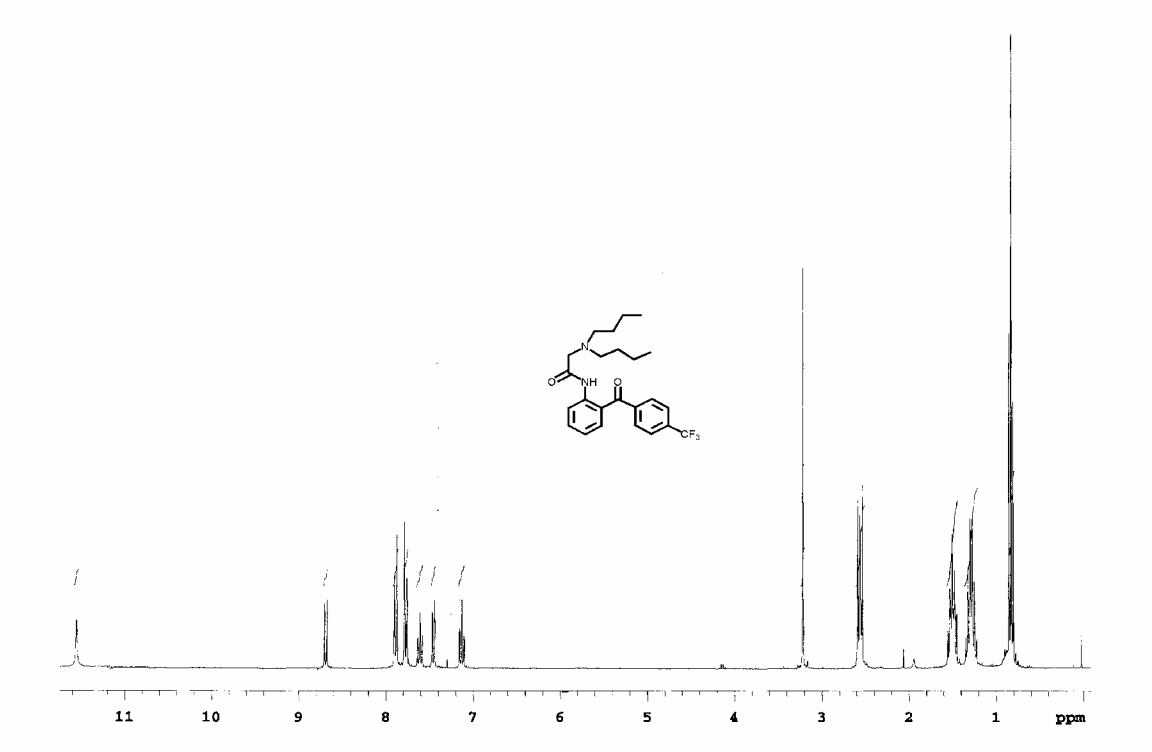

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4
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2
ppm

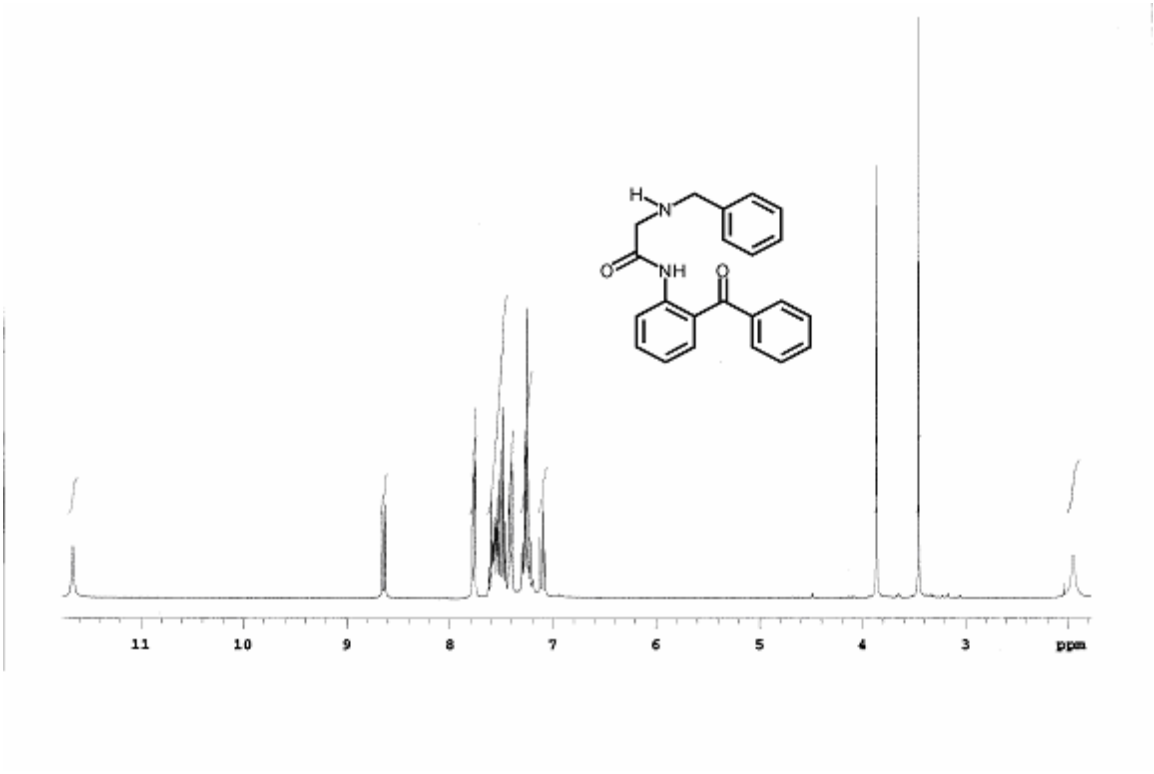

N
O
NH
O
12
11
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1
ppm

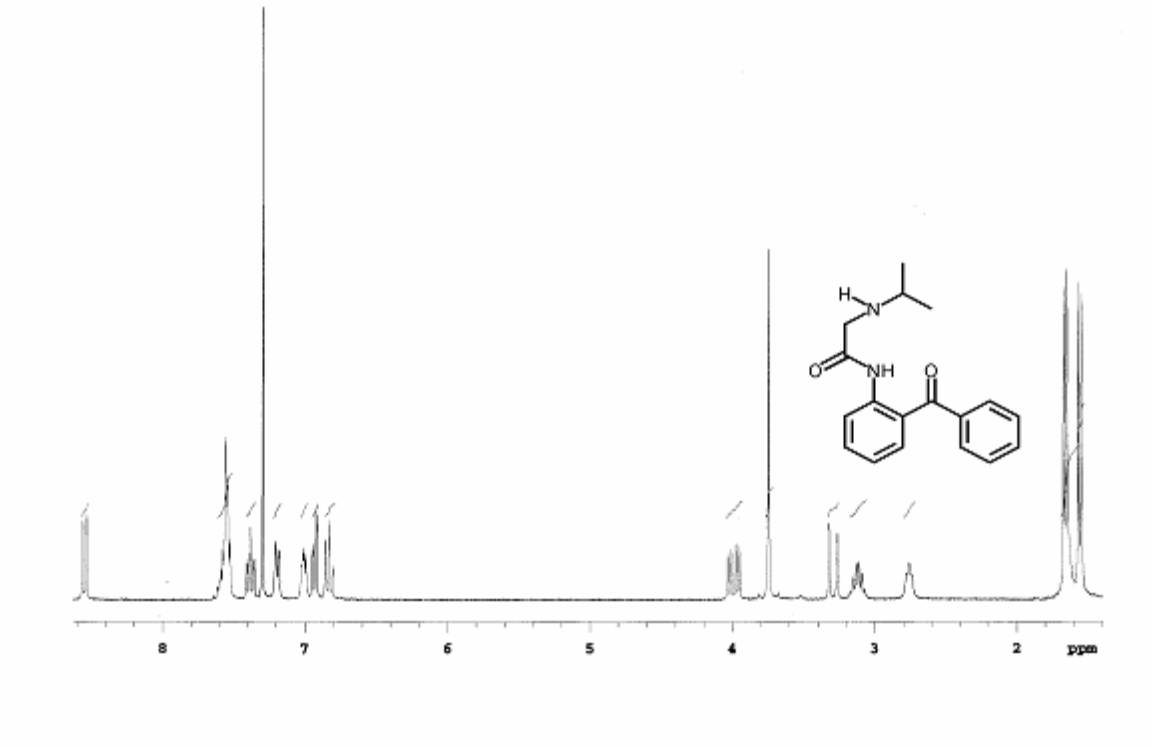

N
NH
O
O
Cl
11
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8
7
6
5
4
3
2
ppm

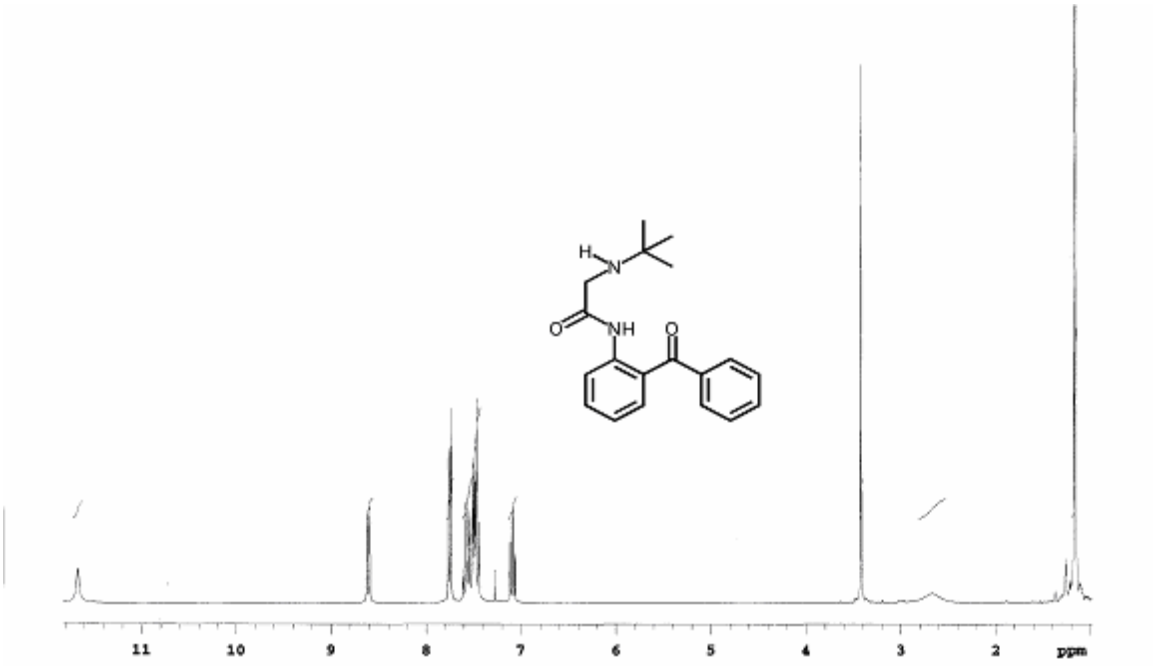

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O
O
Cl
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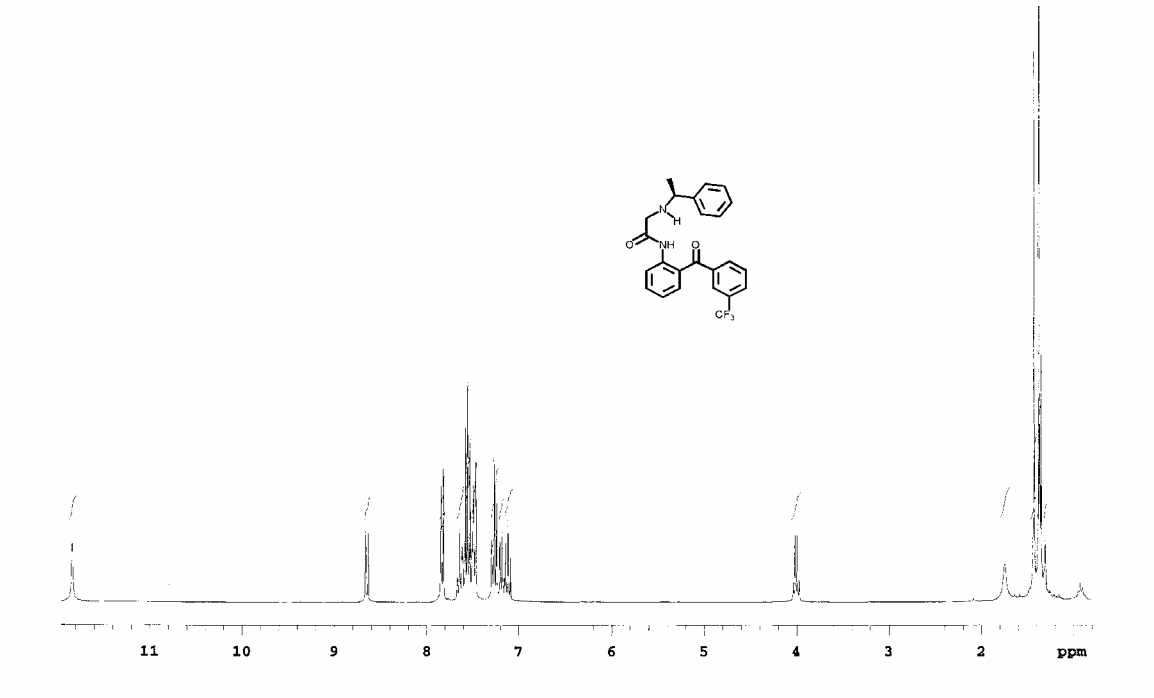

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O
O
CF3
CF3
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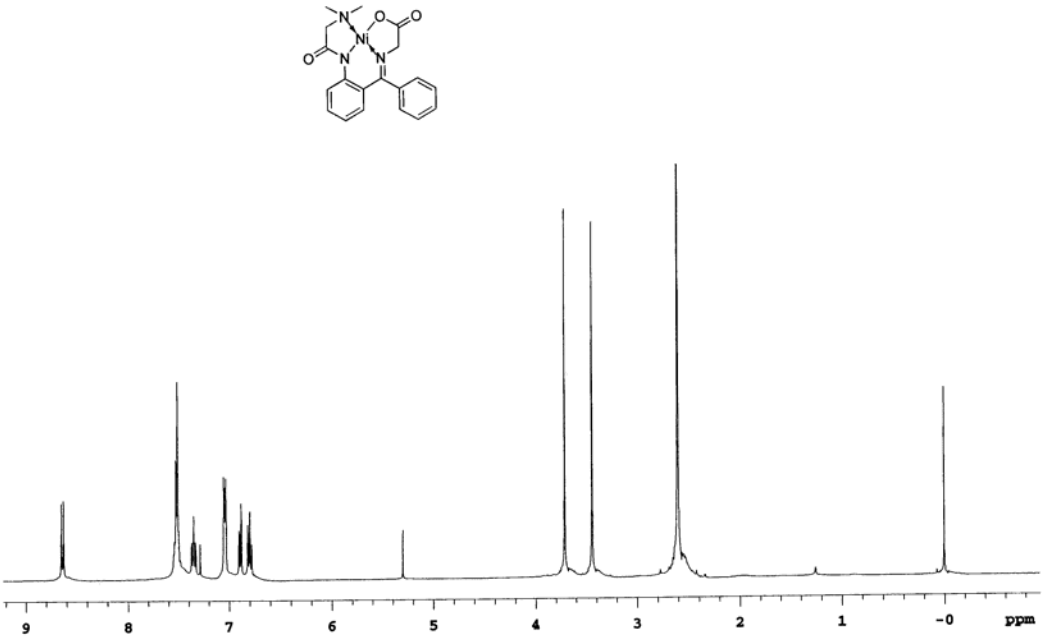

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O
O
CF3
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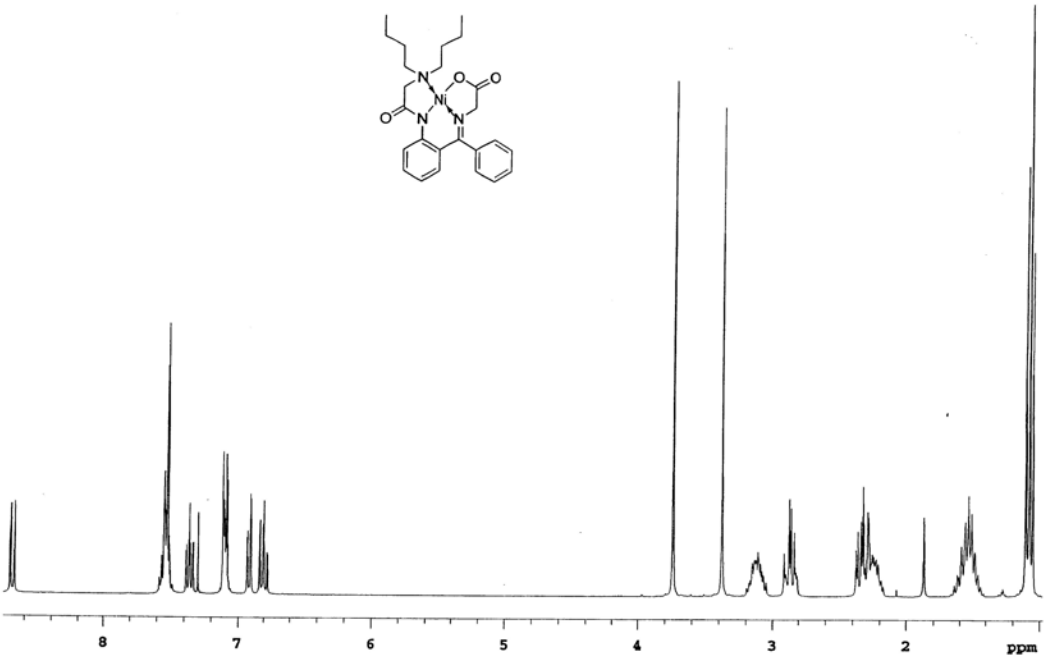

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NH
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3
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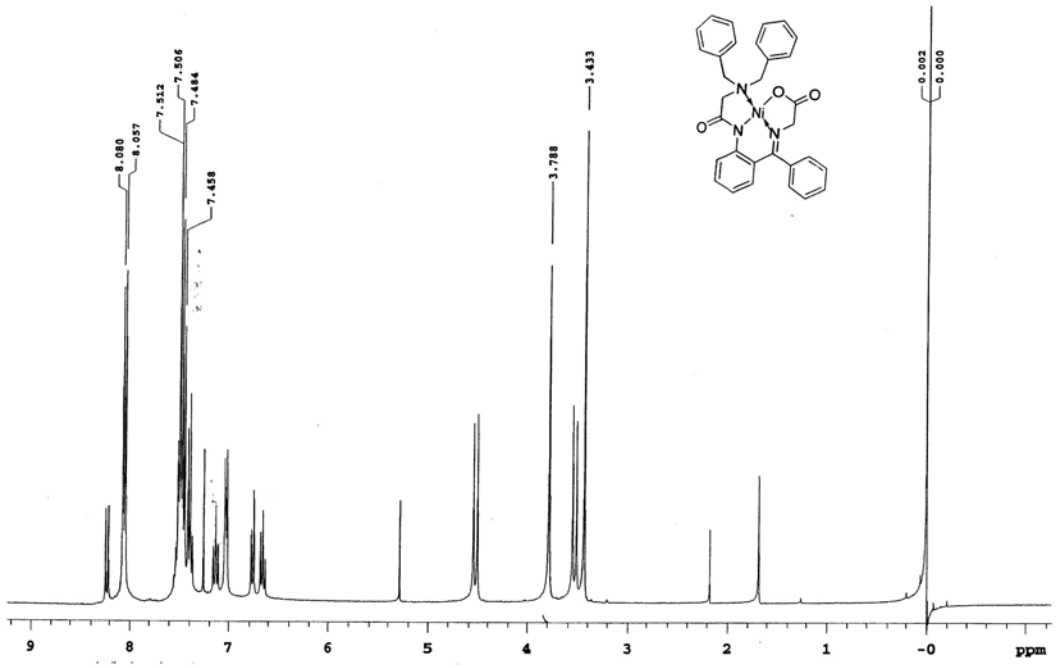

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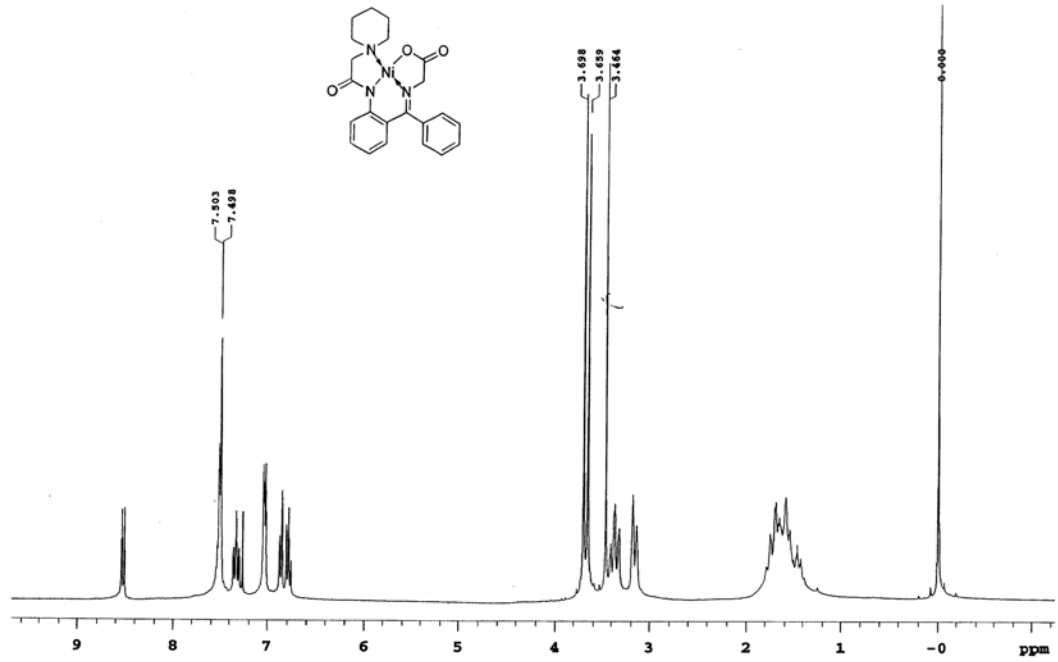

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NH
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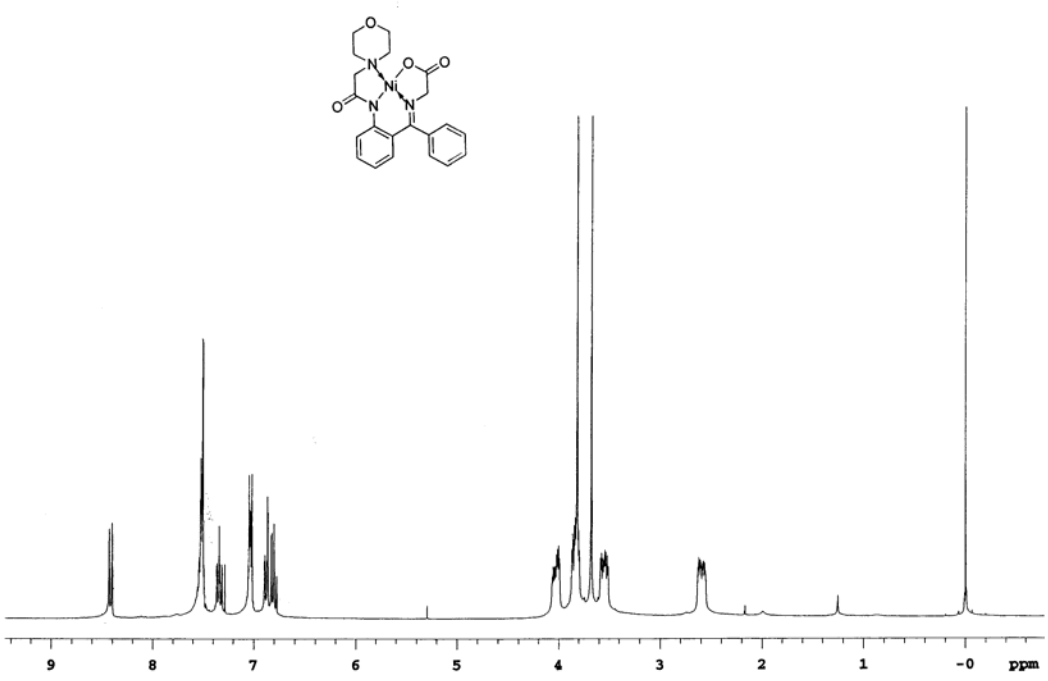

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NH
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CF3
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2
ppm

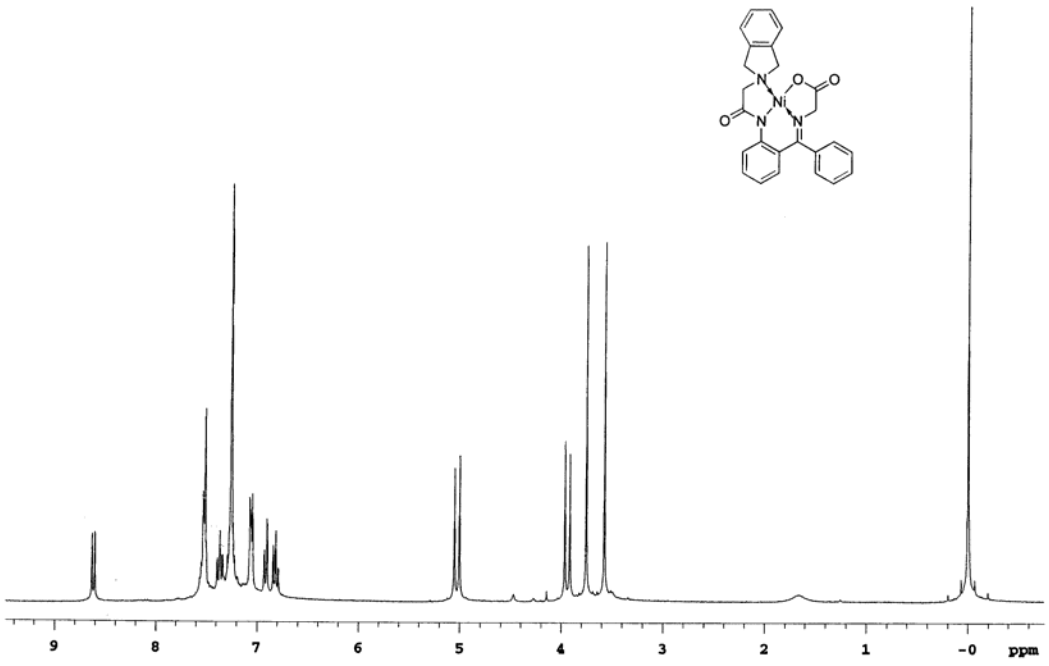

9
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6
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4
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2
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-0
ppm

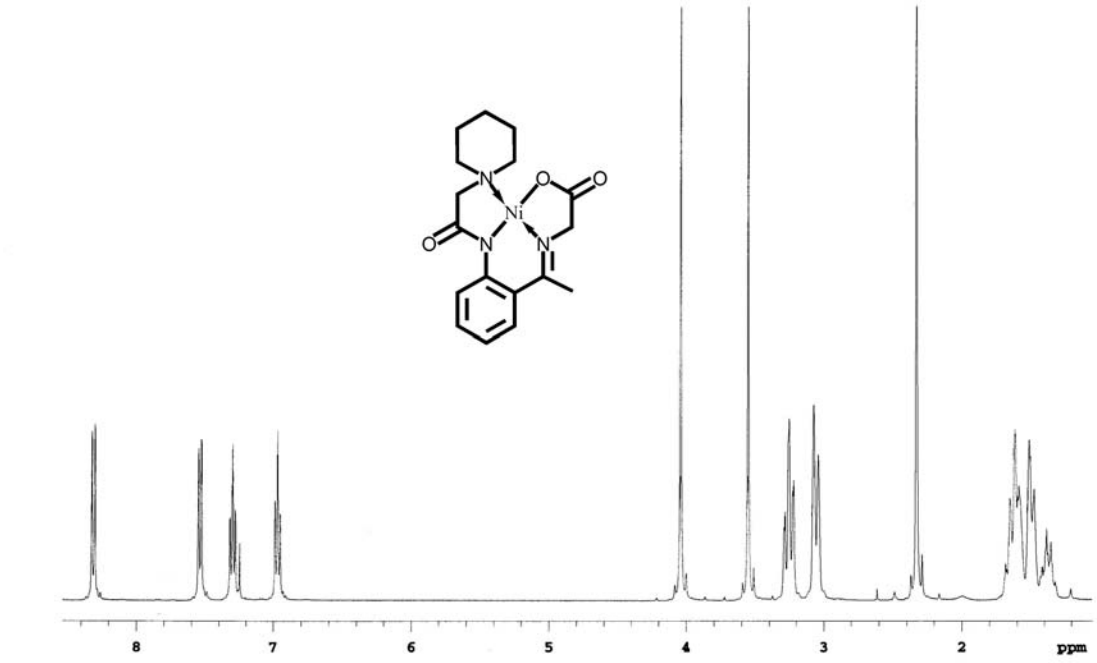

8
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4
3
2
ppm

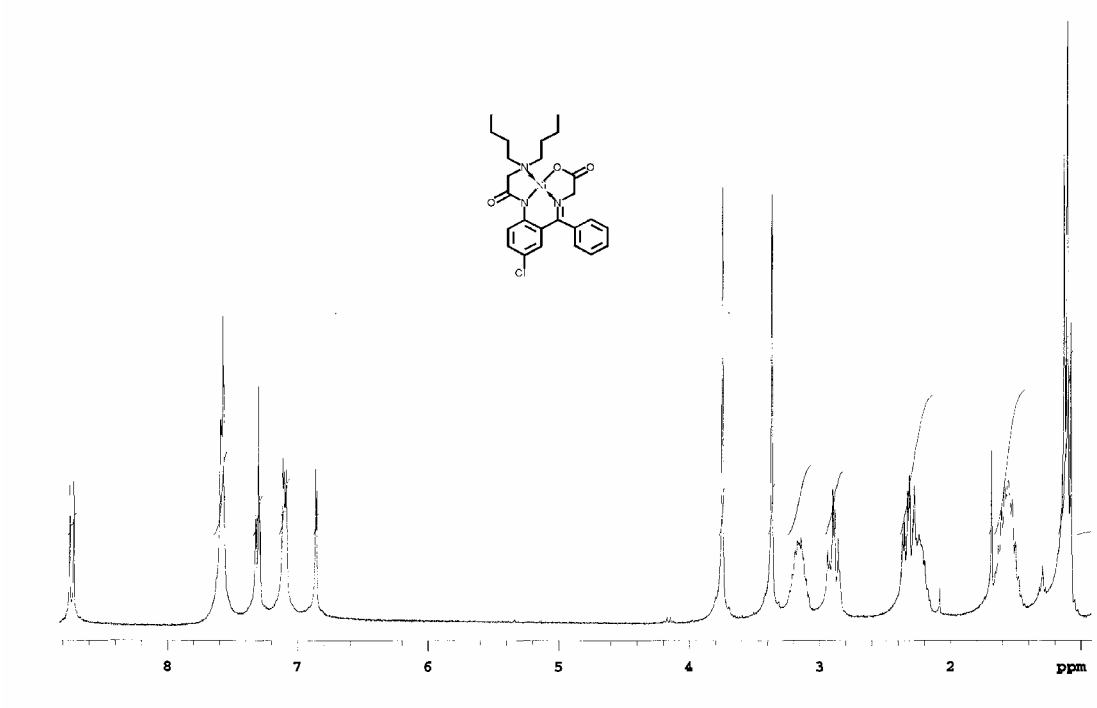

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3.433
0.002
0.000
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ppm

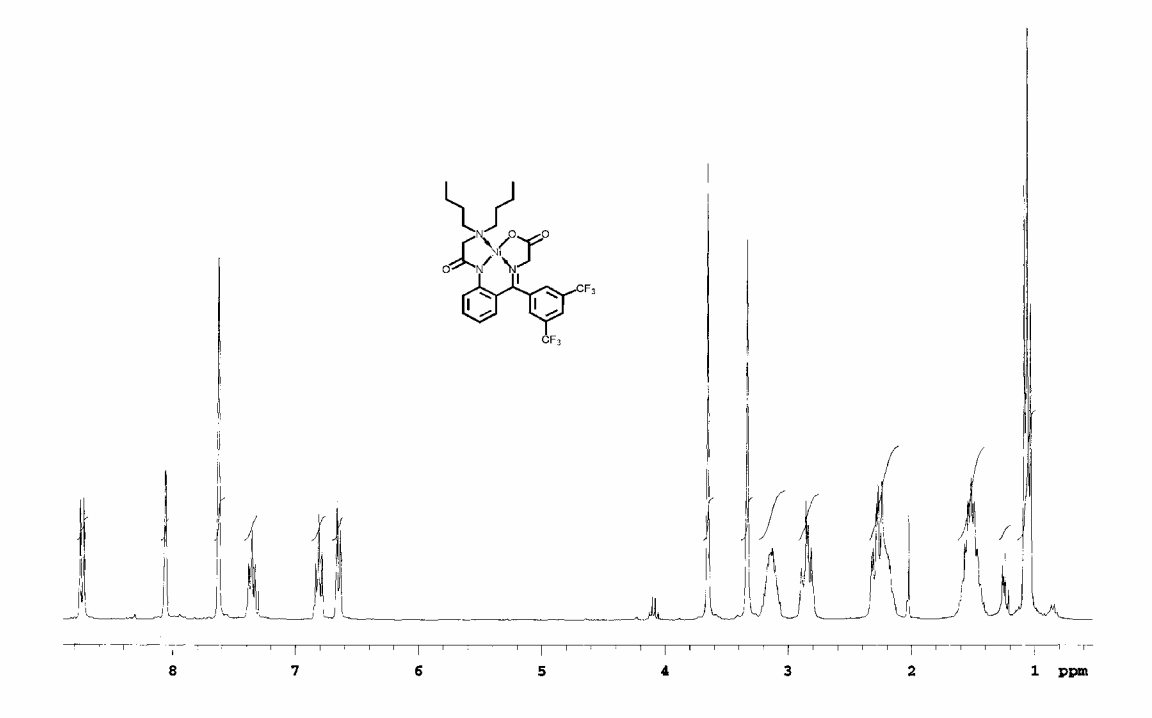

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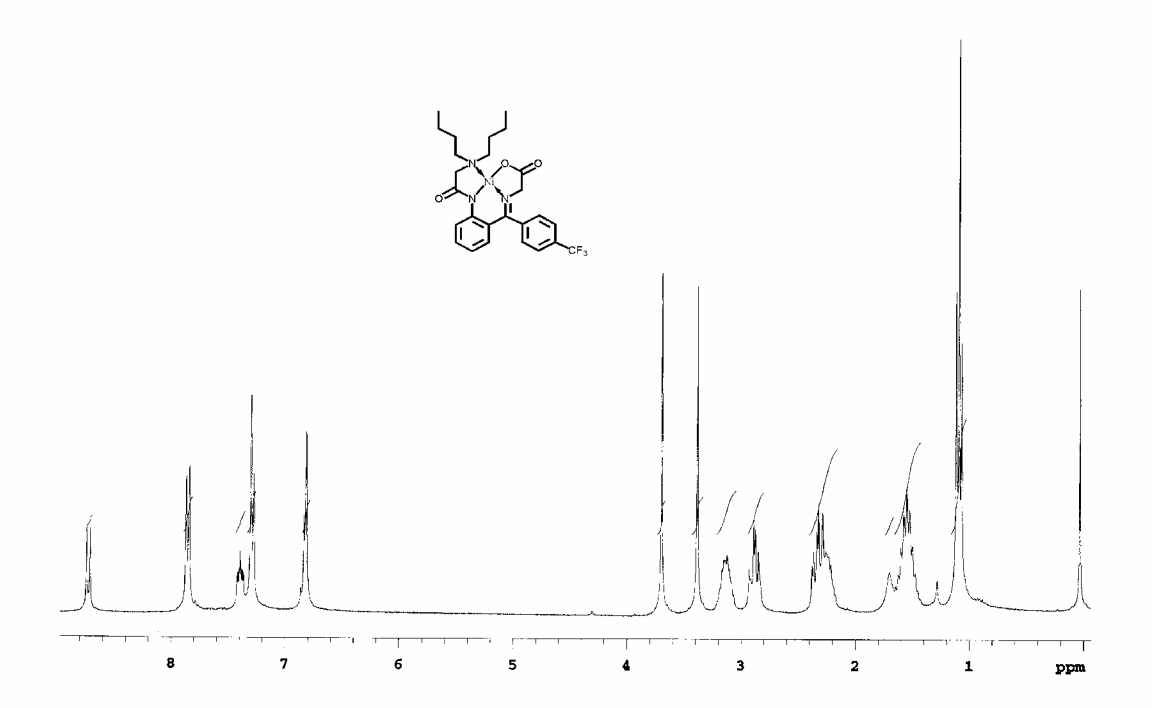

O
N
Ni
O
O
O
N
N
9
8
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6
5
4
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2
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-0
ppm

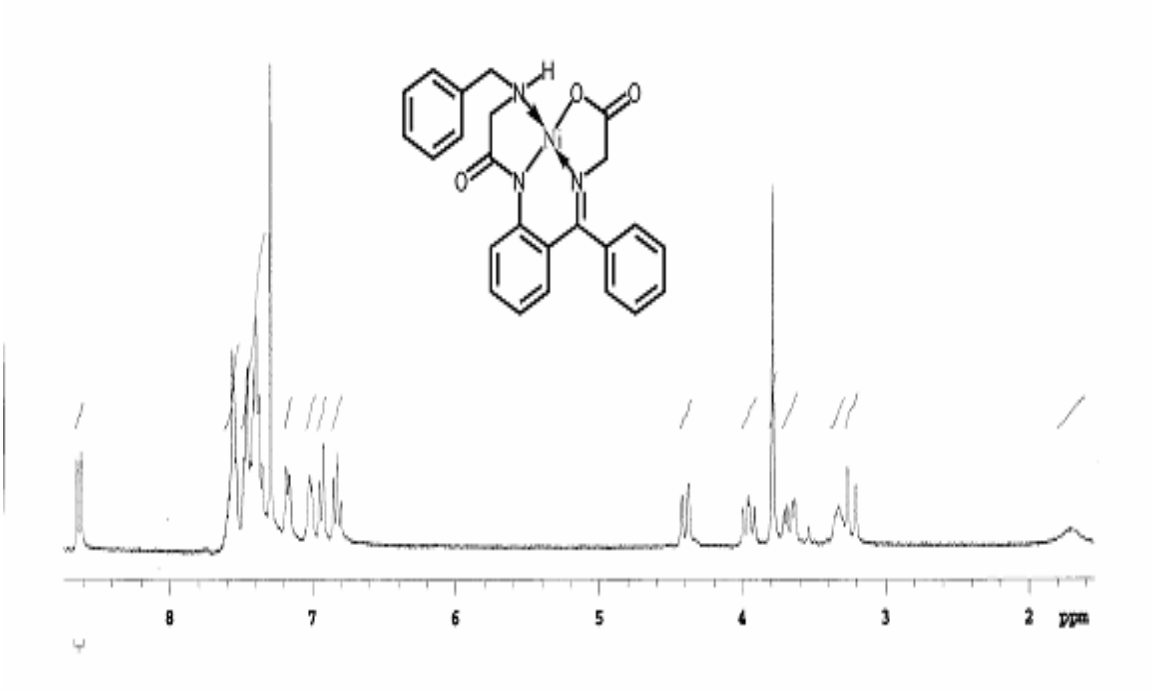

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O
O
N
N
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6
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4
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-0
ppm

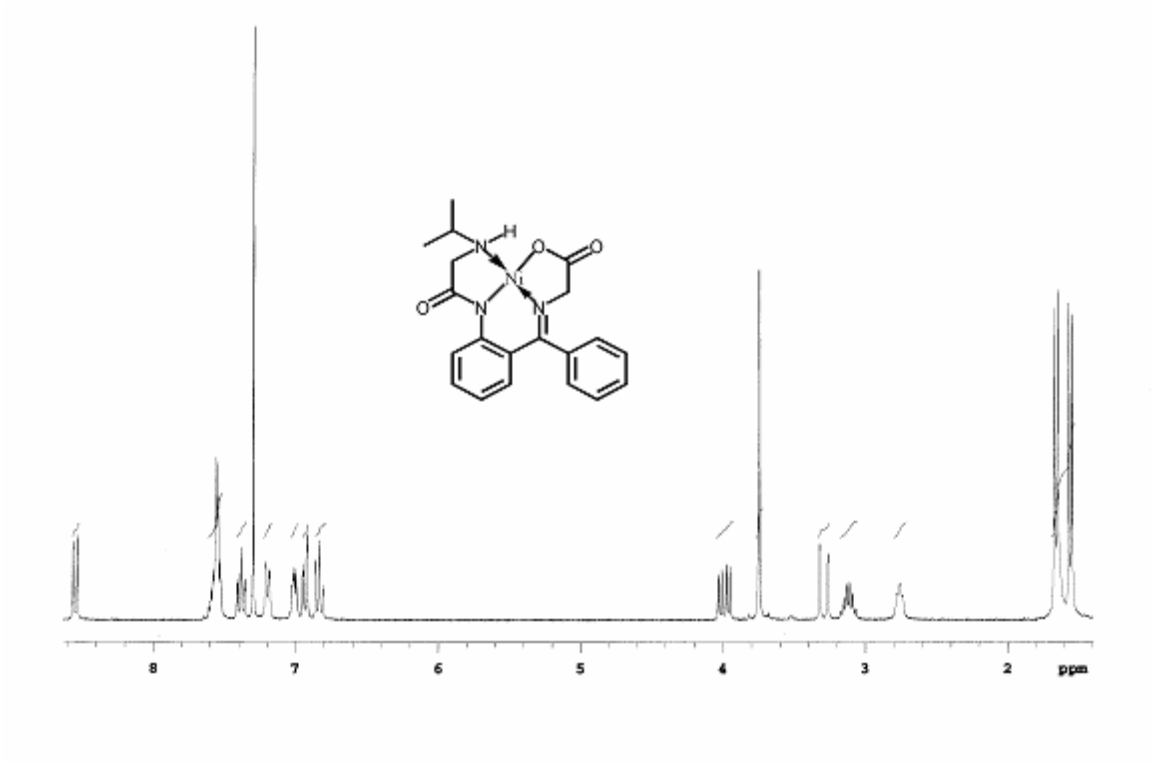

Ni
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4
3
2
ppm

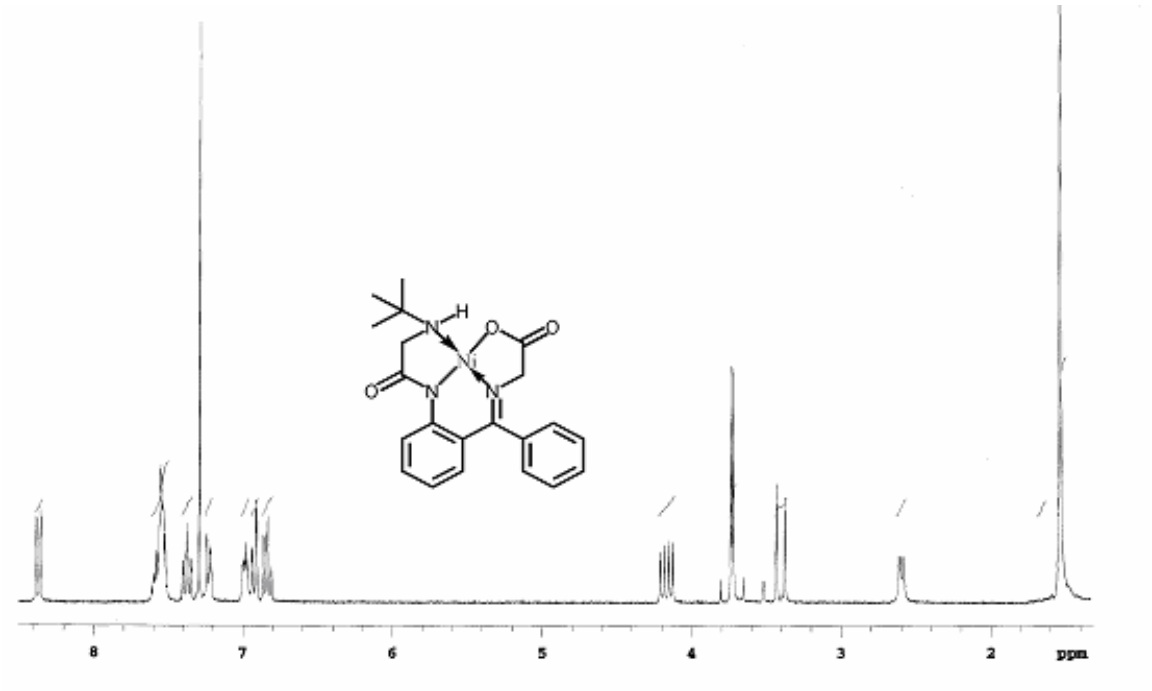

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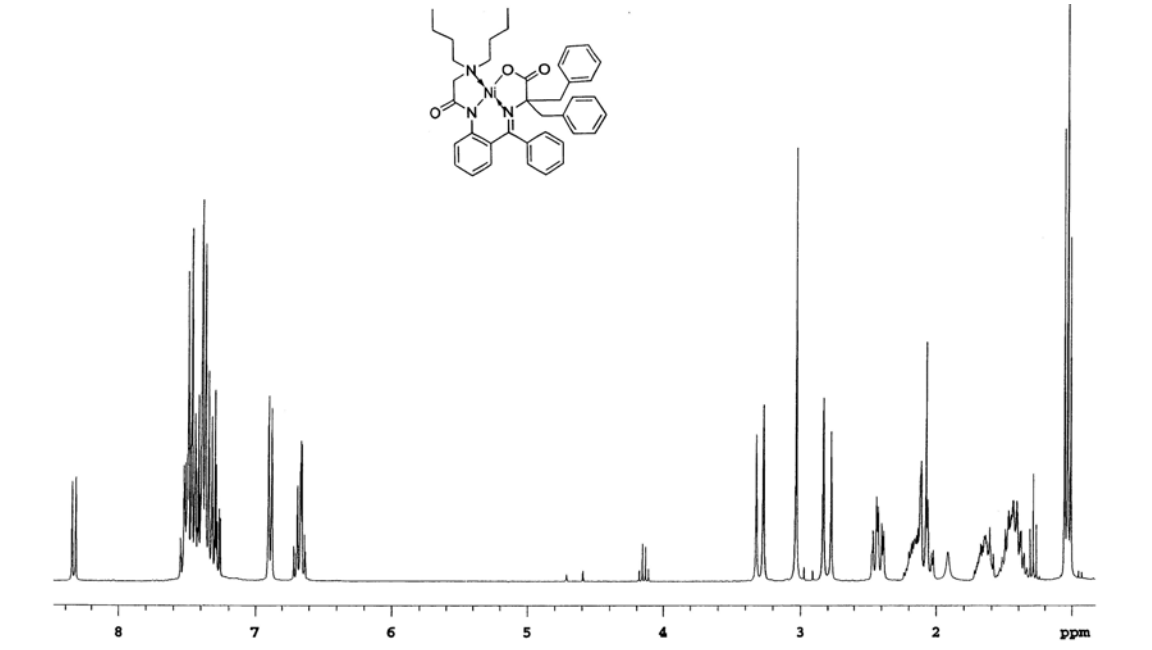

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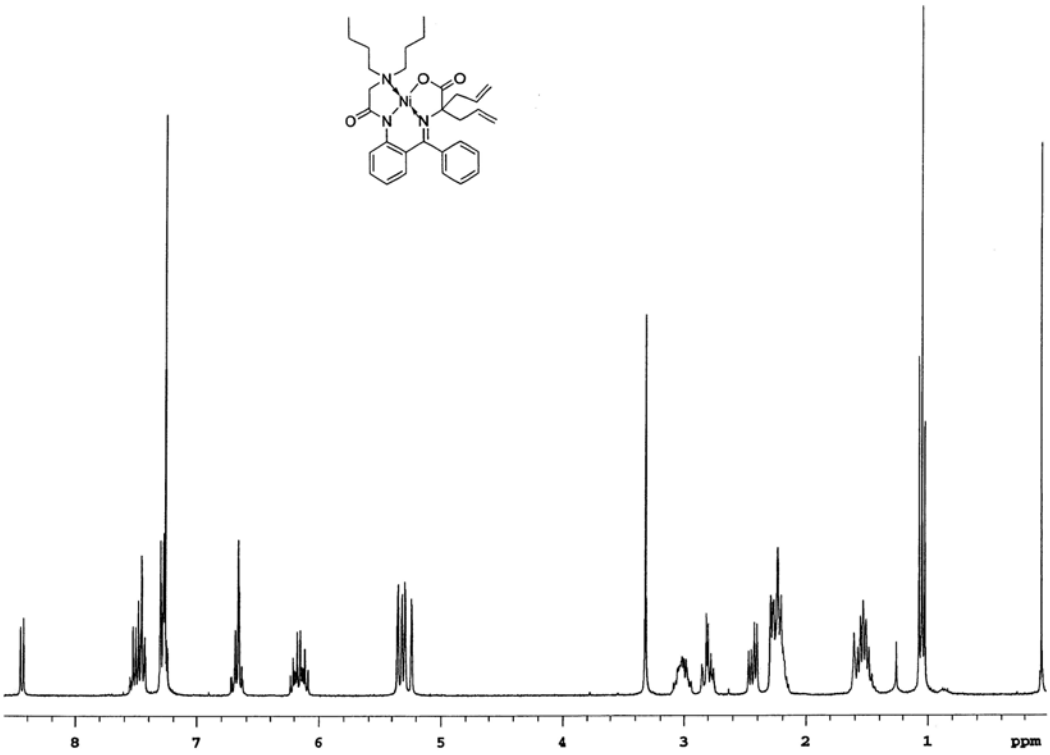

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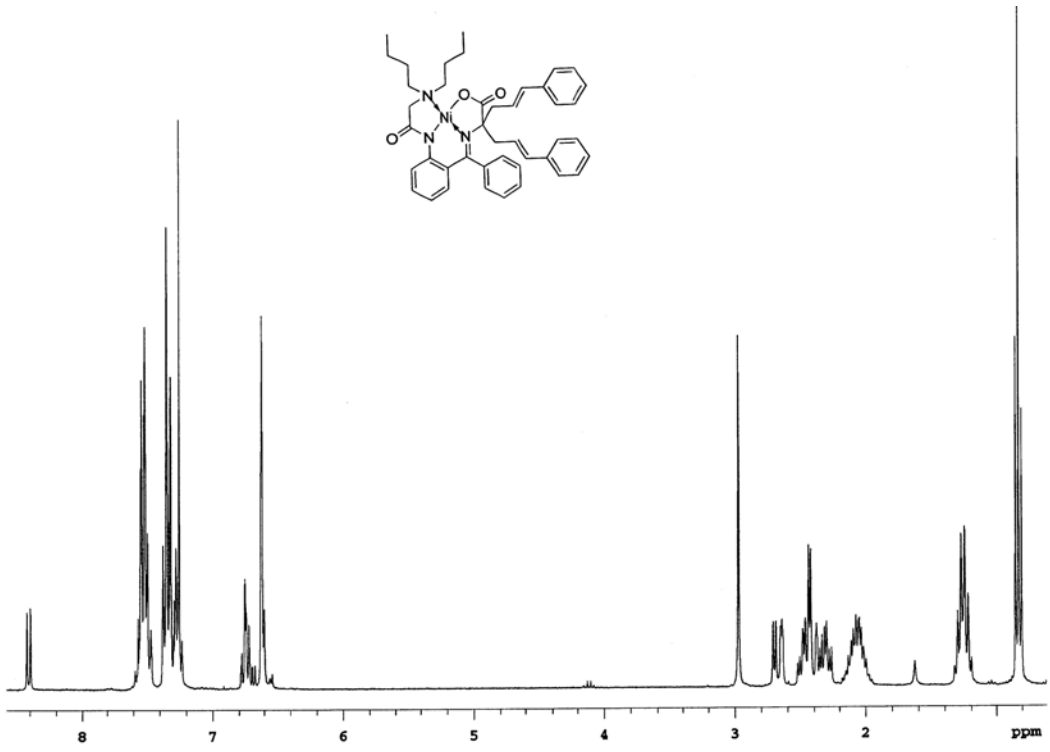

H
N
O
O
Ni
O
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8
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4
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2
ppm

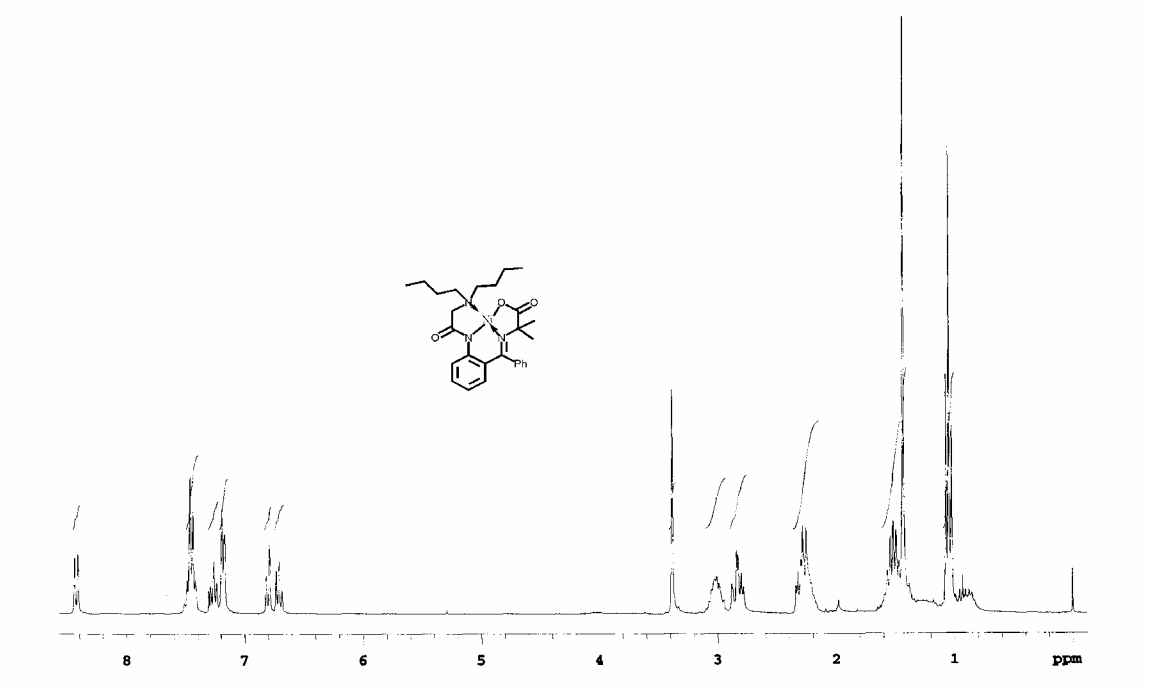

H
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O
Ni
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ppm

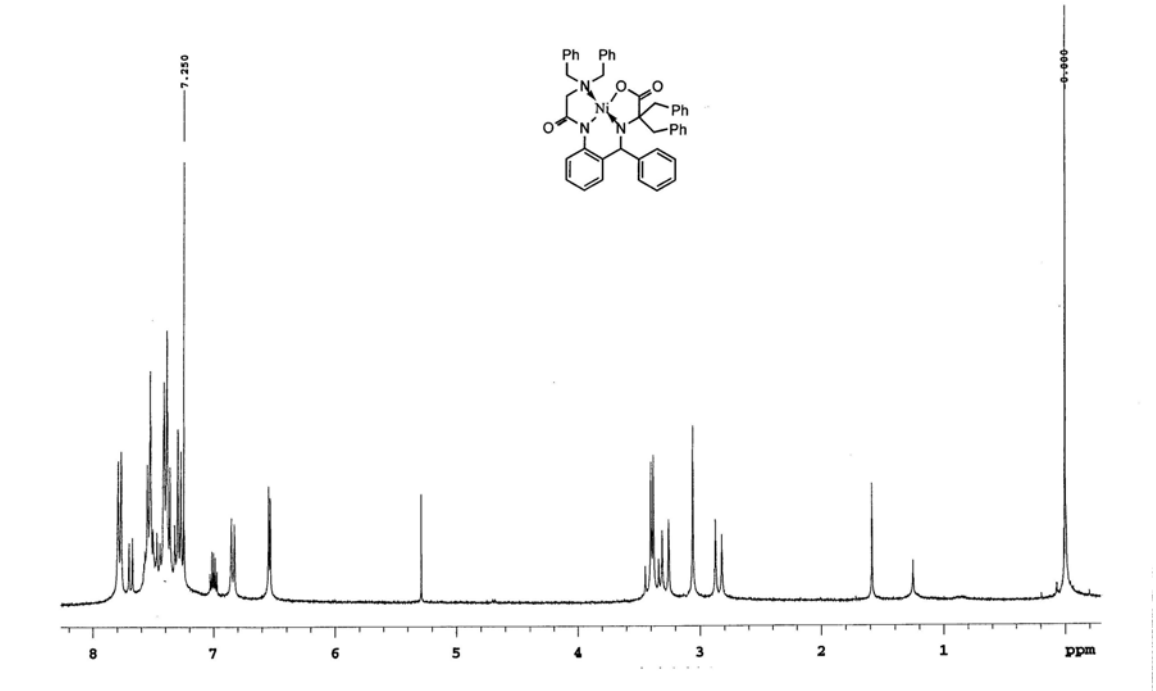

H
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4
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2
ppm

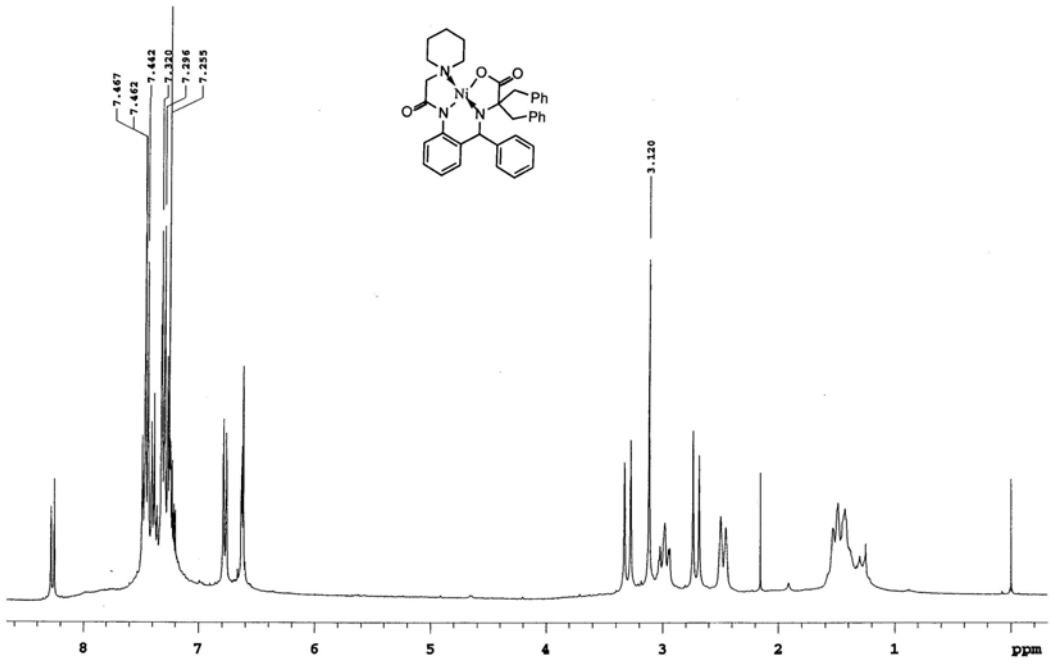

N
O
O
Ni
O
N
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8
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6
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4
3
2
ppm

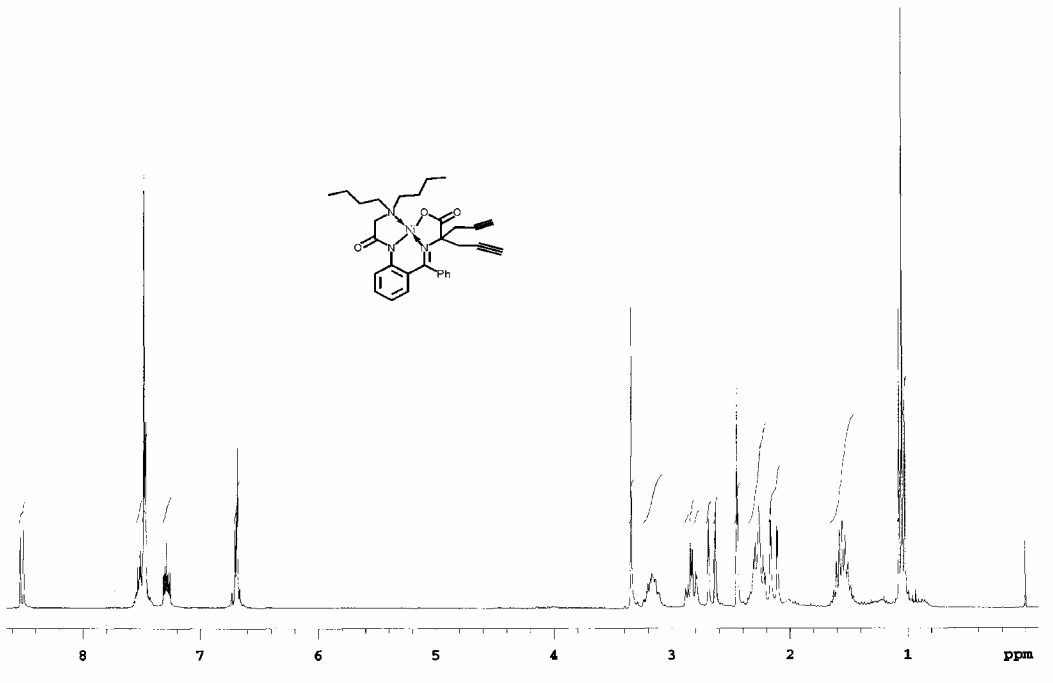

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5
4
3
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ppm

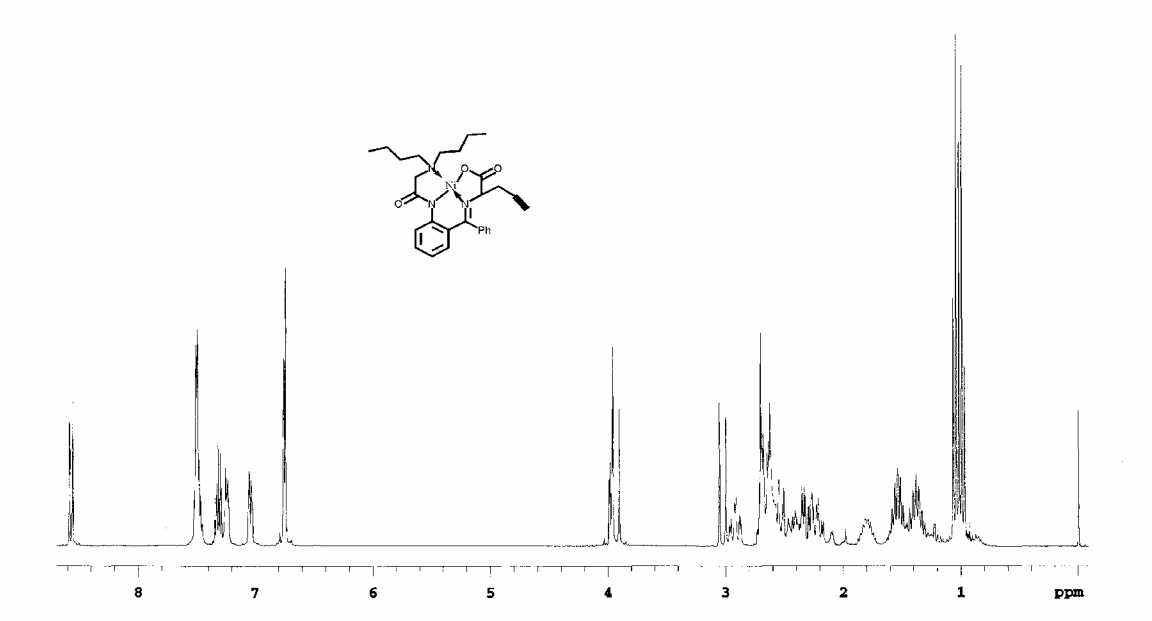

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4
3
2
ppm

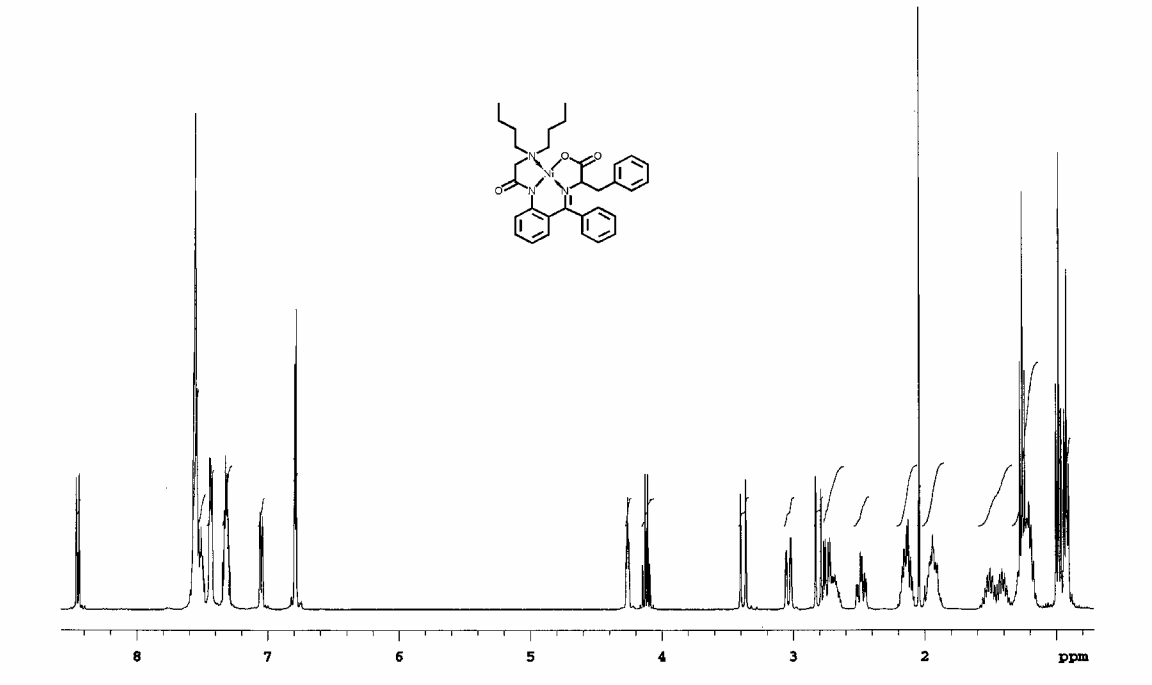

Ph
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4
3
2
1
ppm

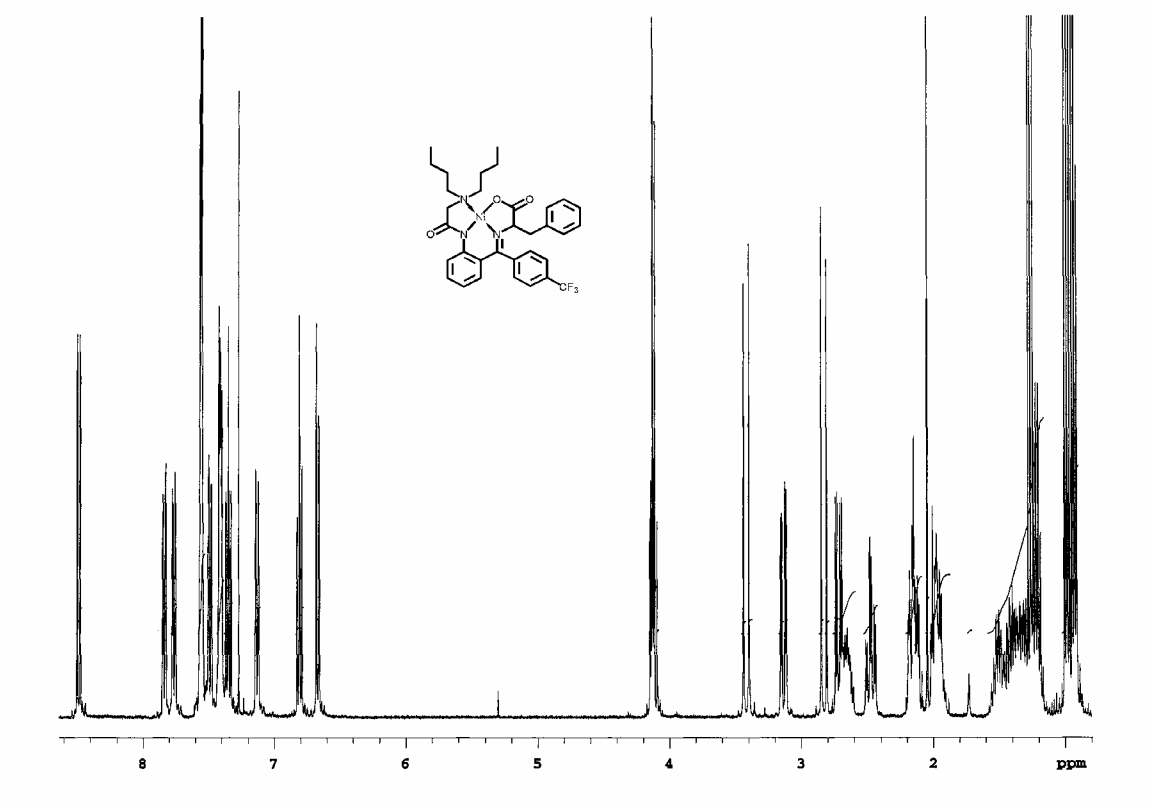

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Ph
Ni
Ph
Ph
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0.000
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7
6
5
4
3
2
1
ppm

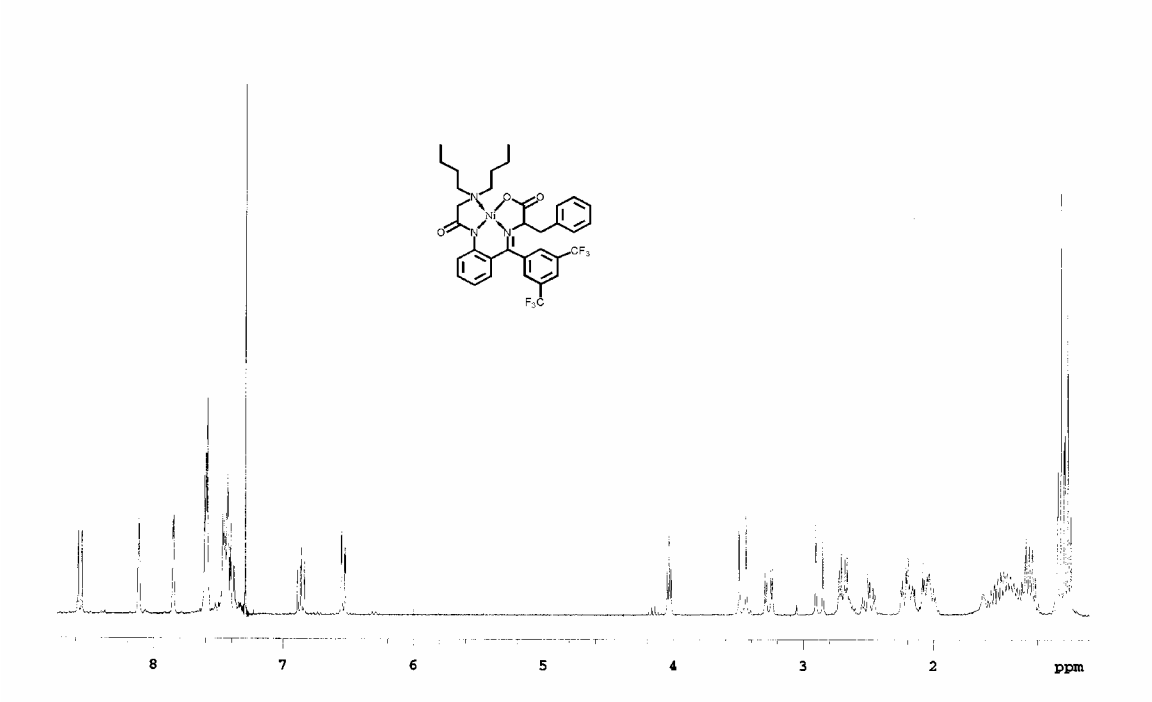

7.467
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3.120
Ni
O
N
Ph
Ph
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7
6
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4
3
2
1
ppm

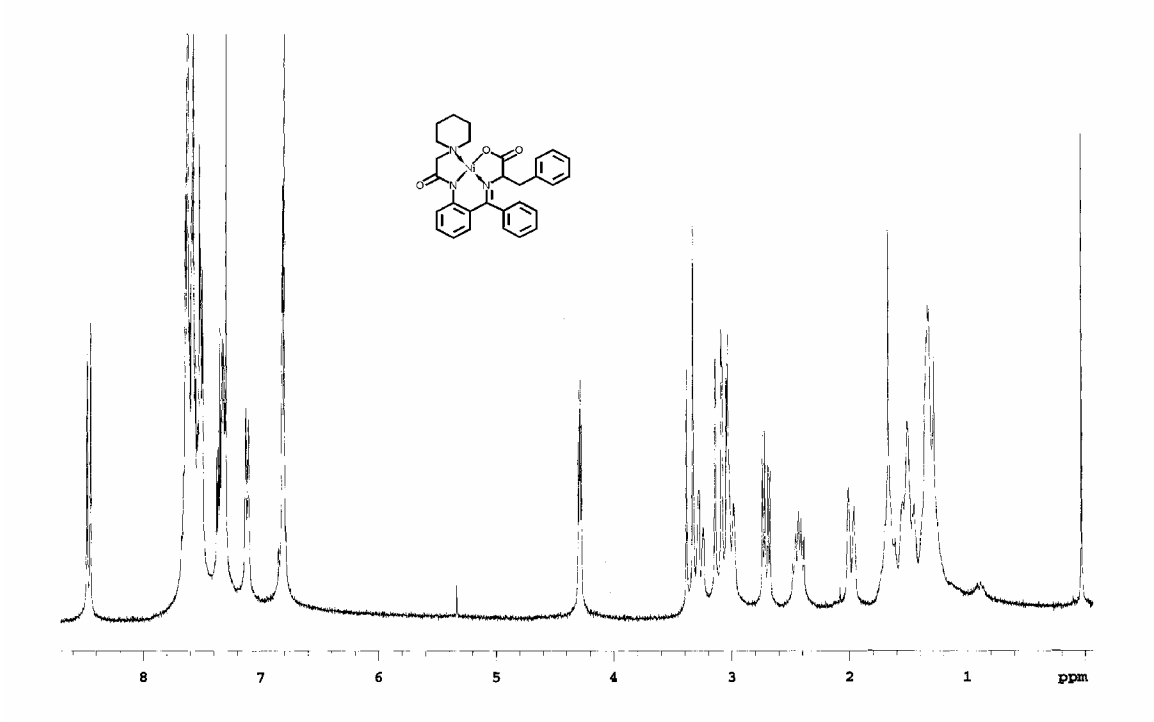

Ni
O
N
Ph
8
7
6
5
4
3
2
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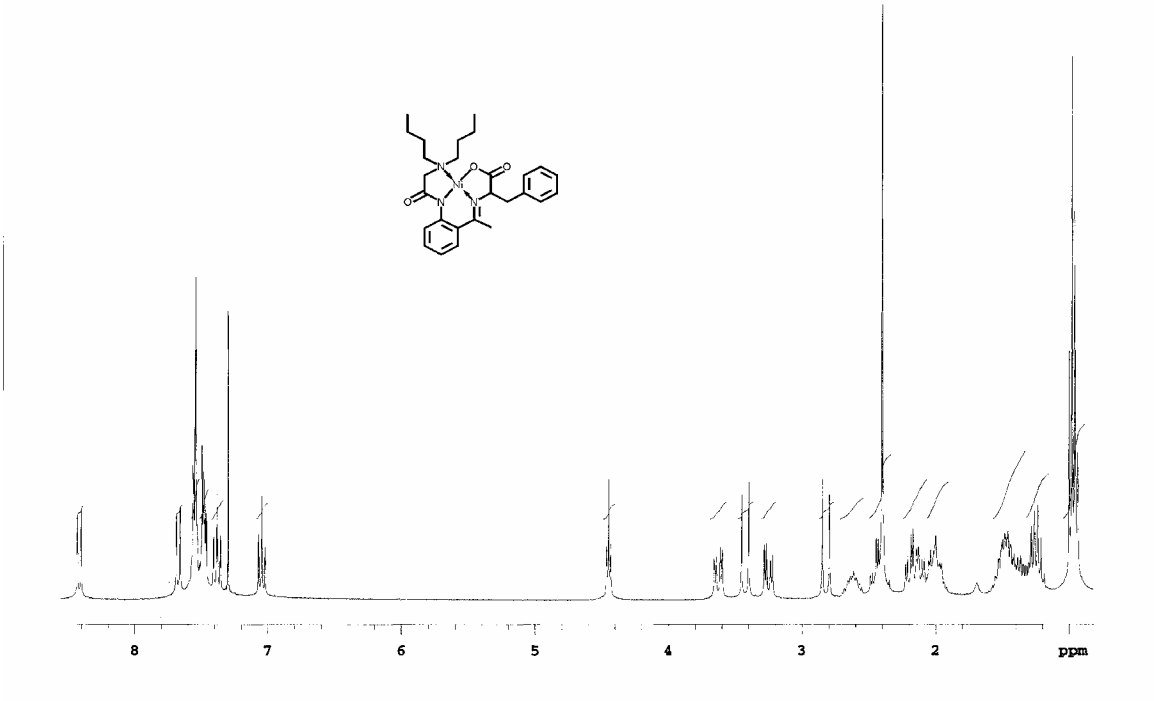

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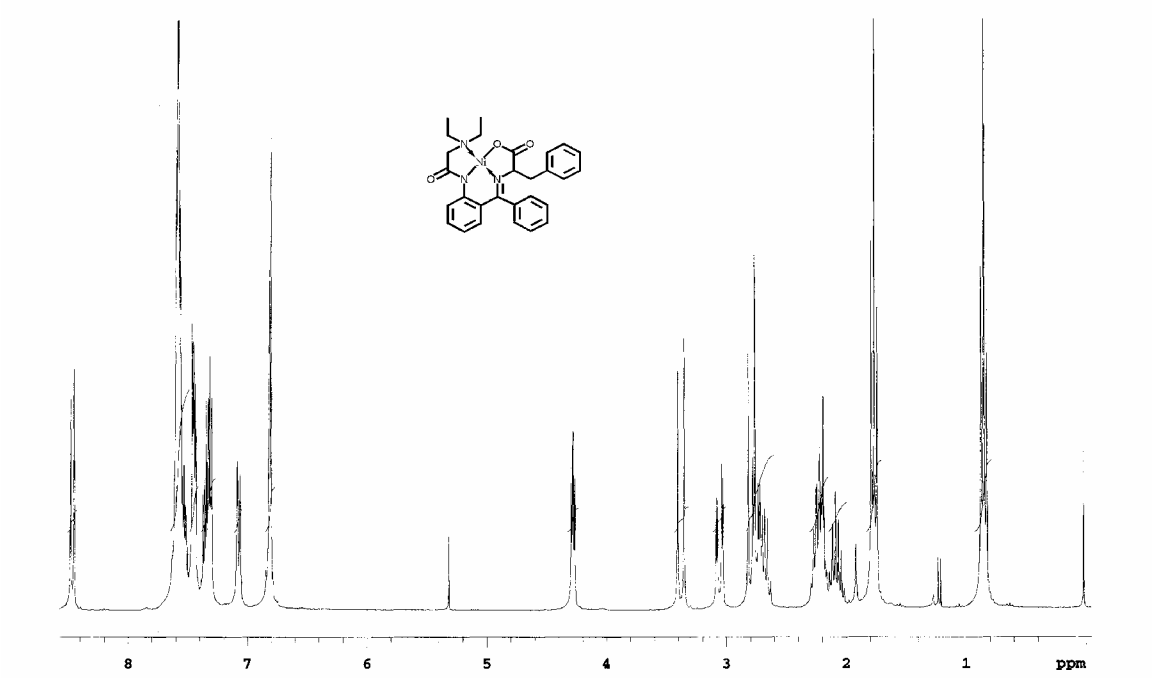

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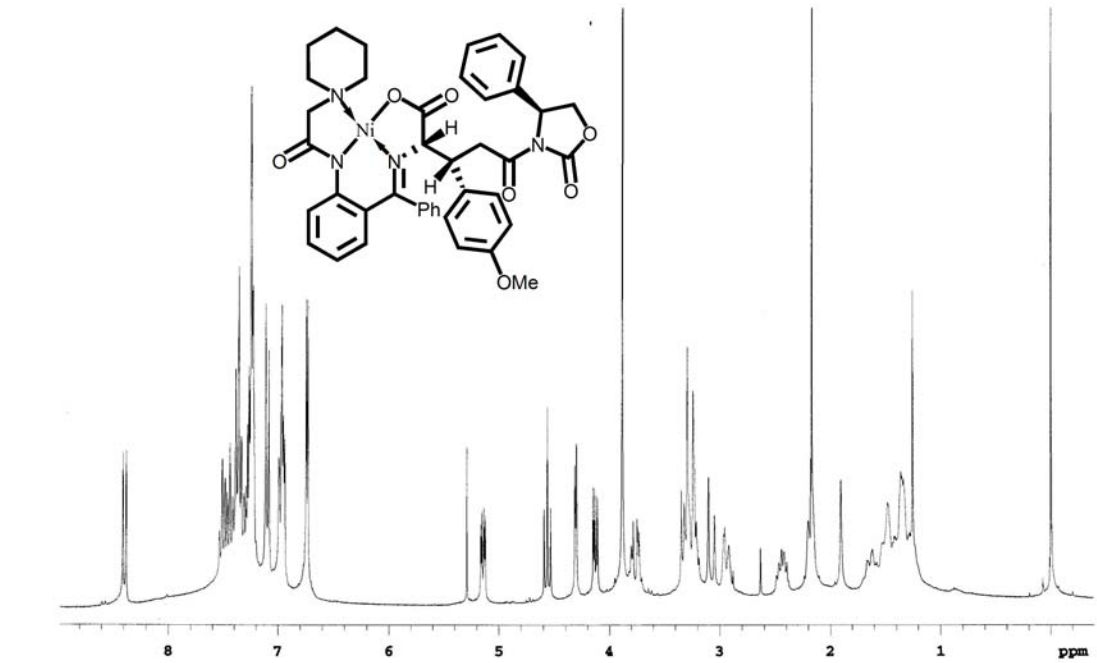

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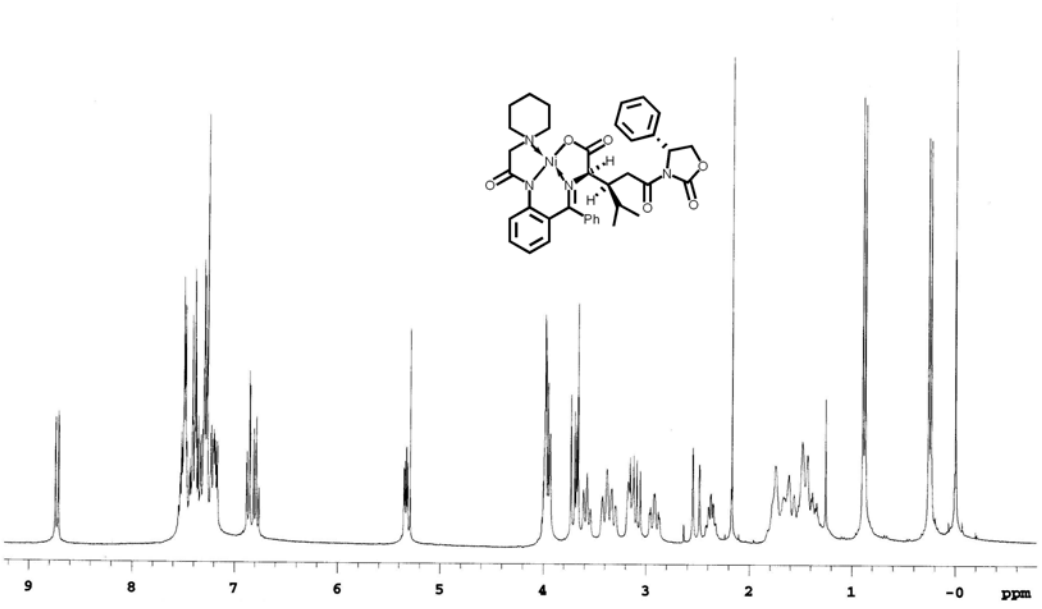

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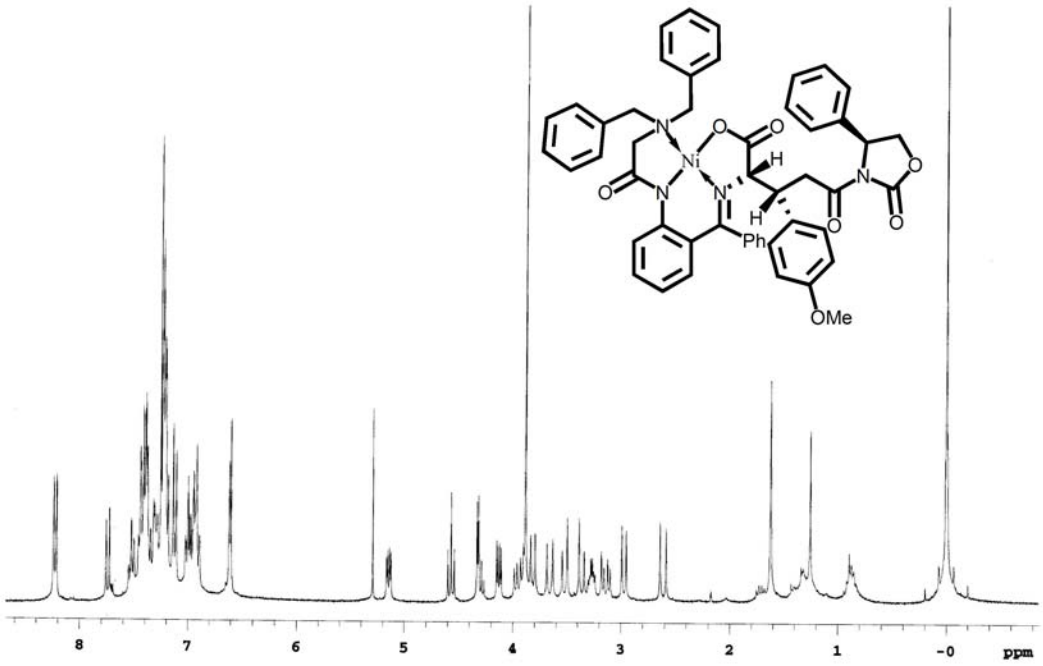

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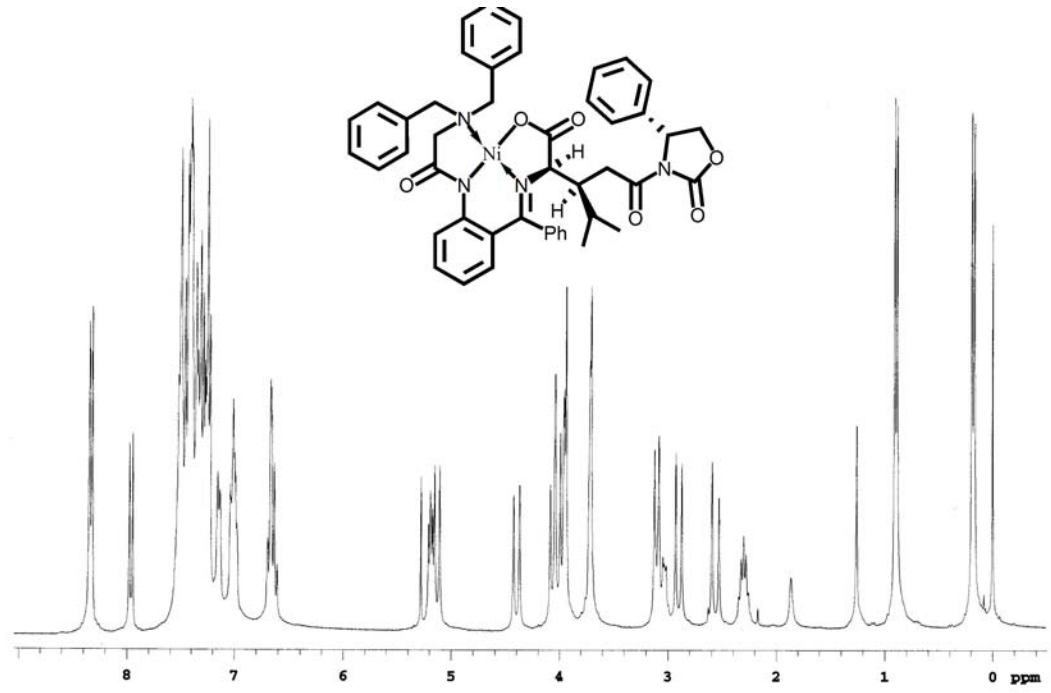

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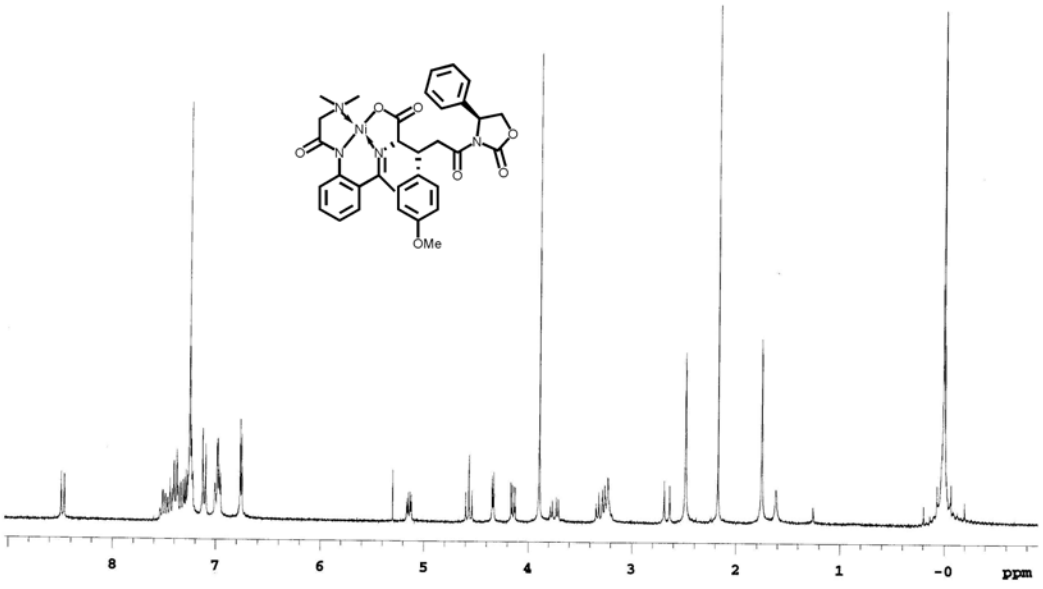

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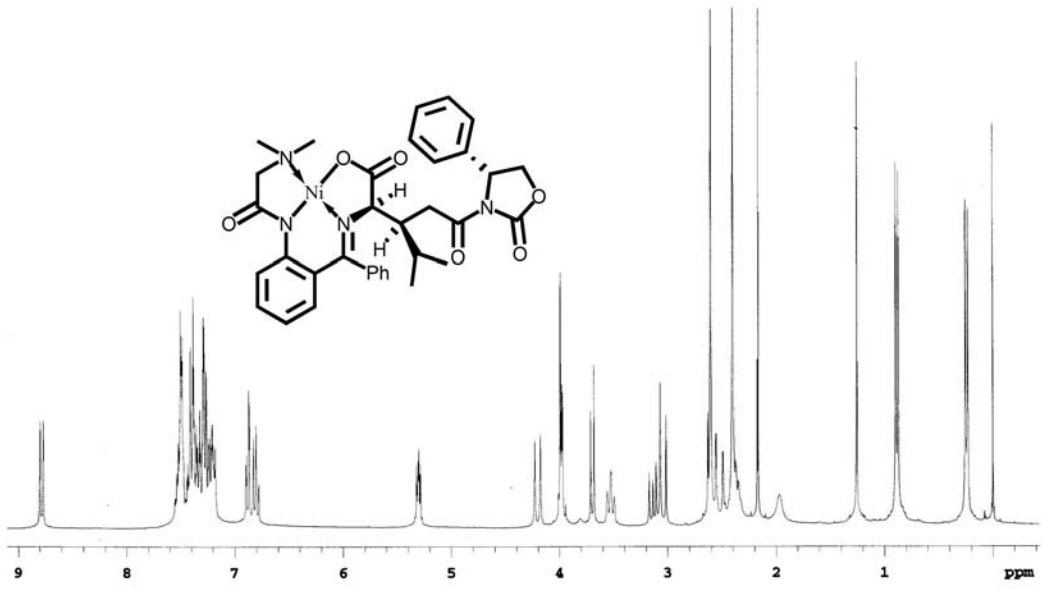

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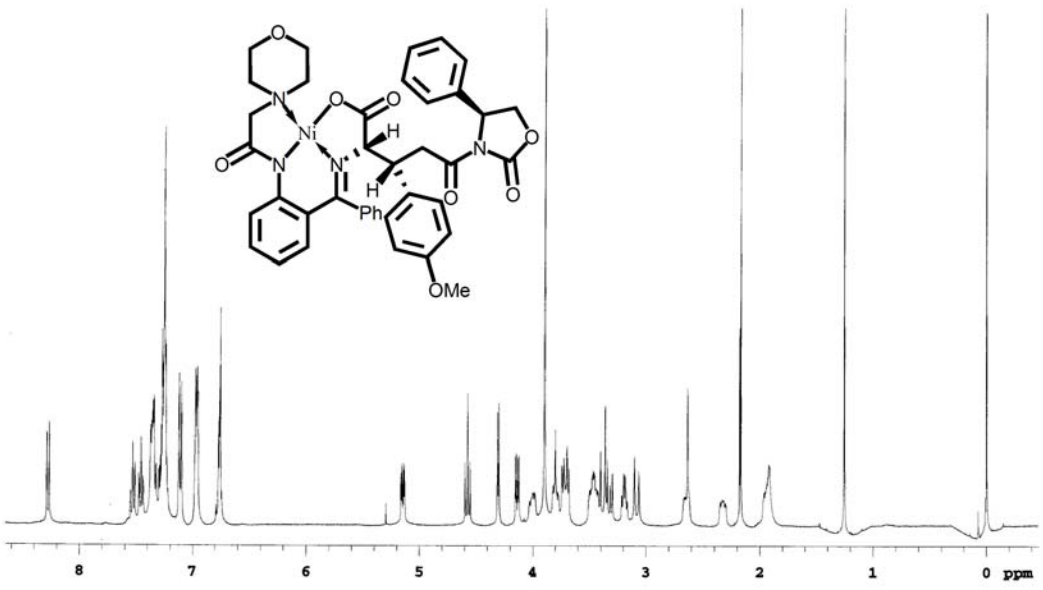

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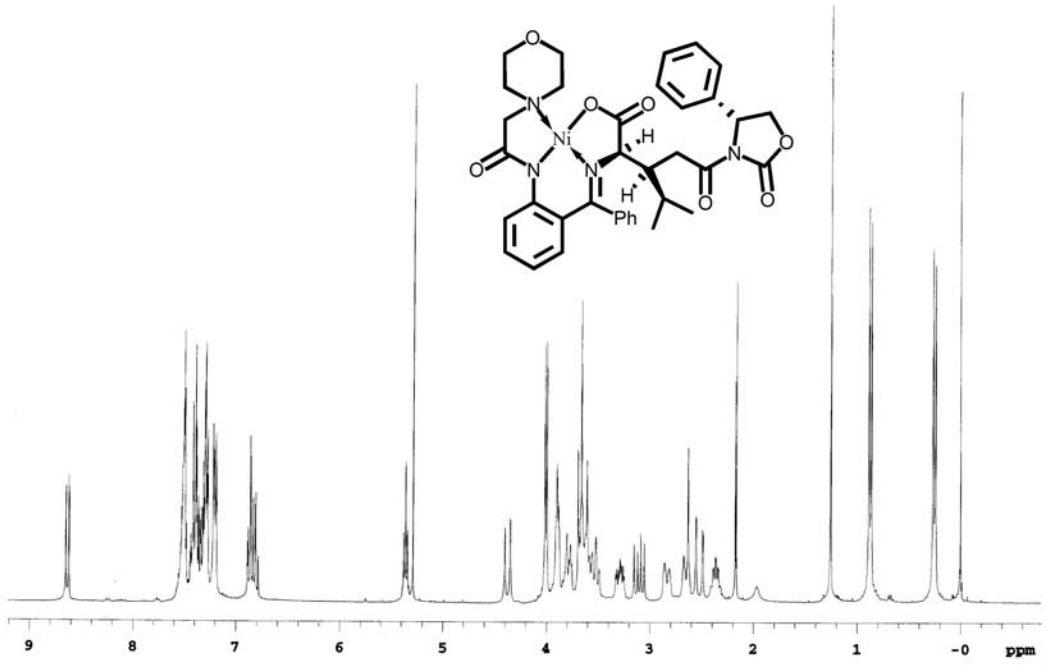

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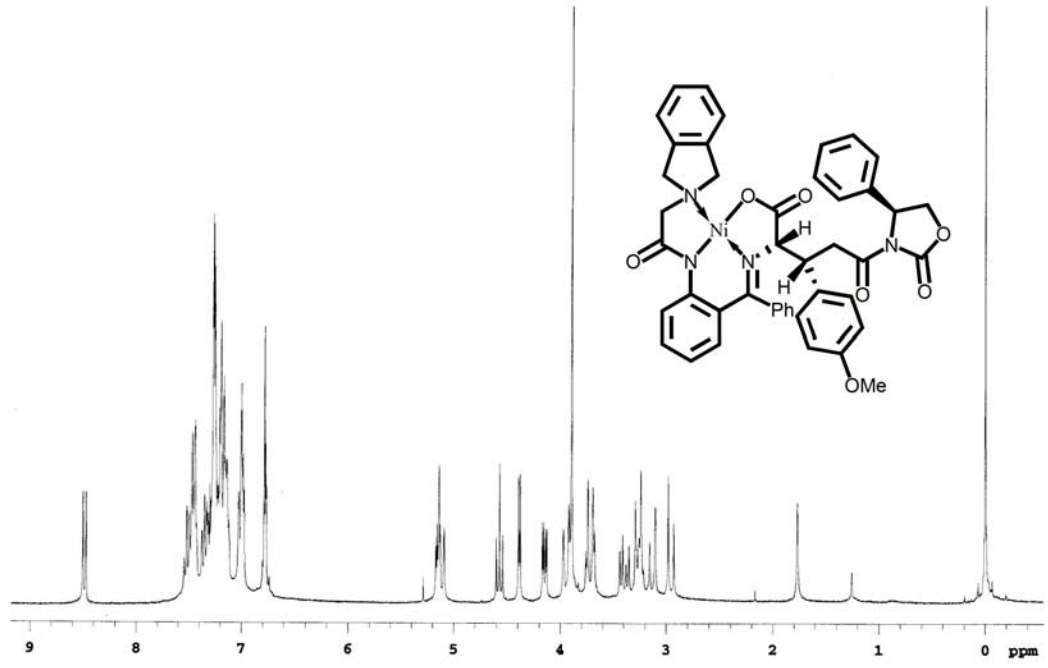

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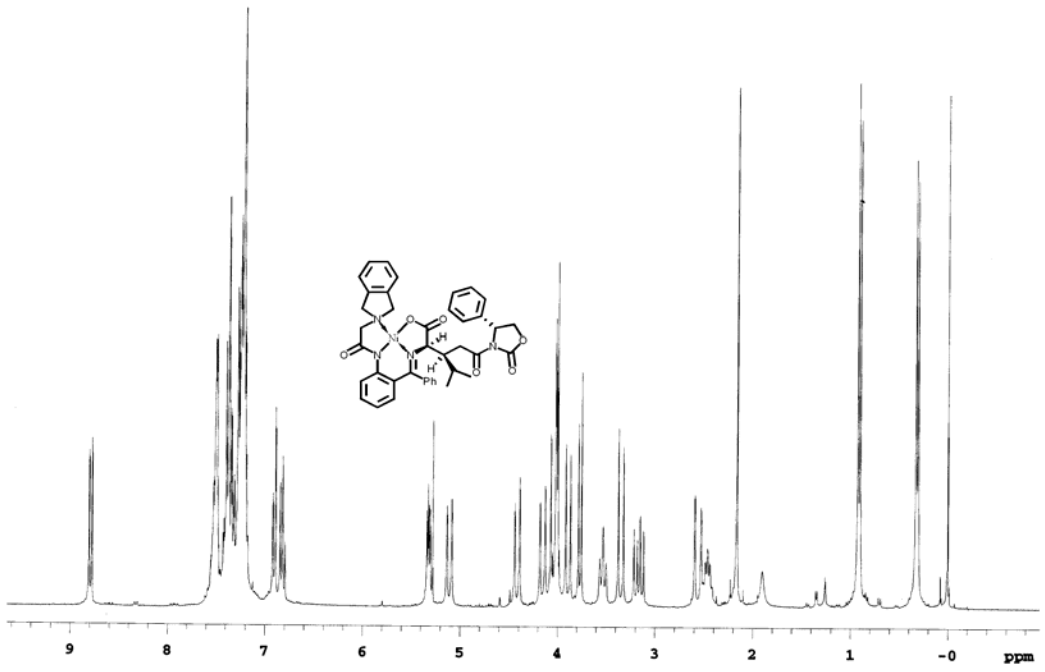

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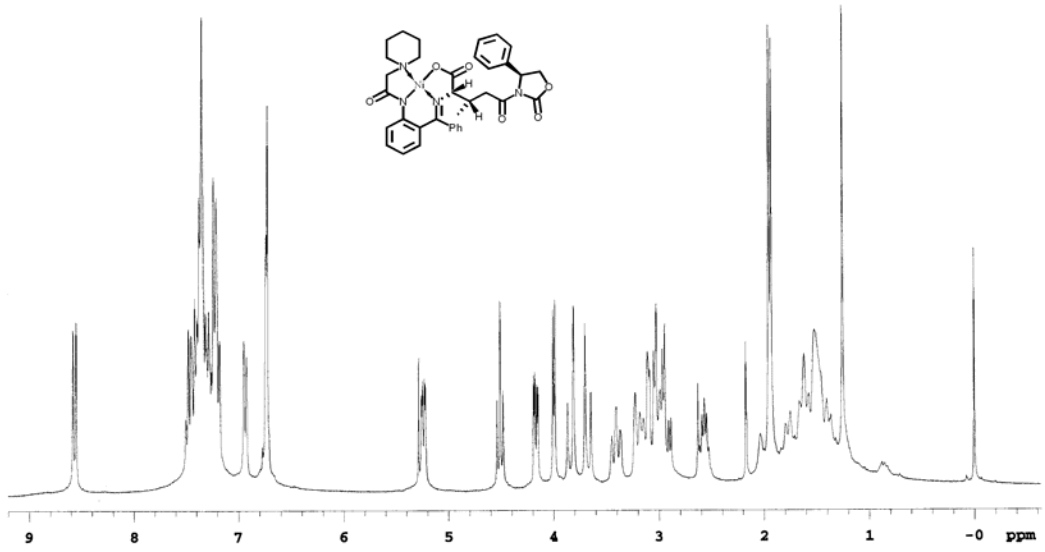

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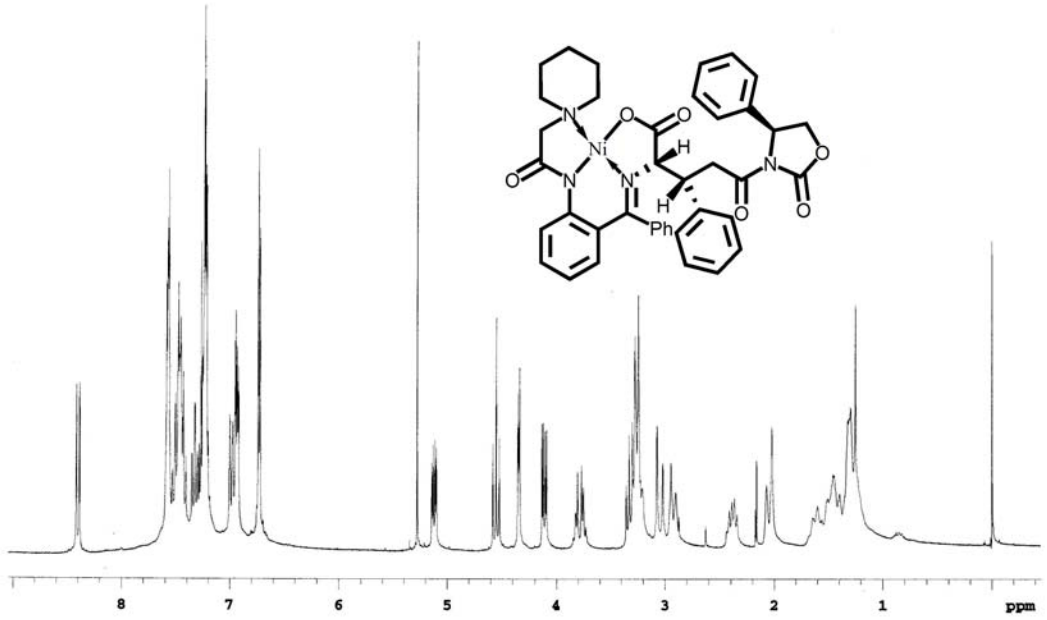

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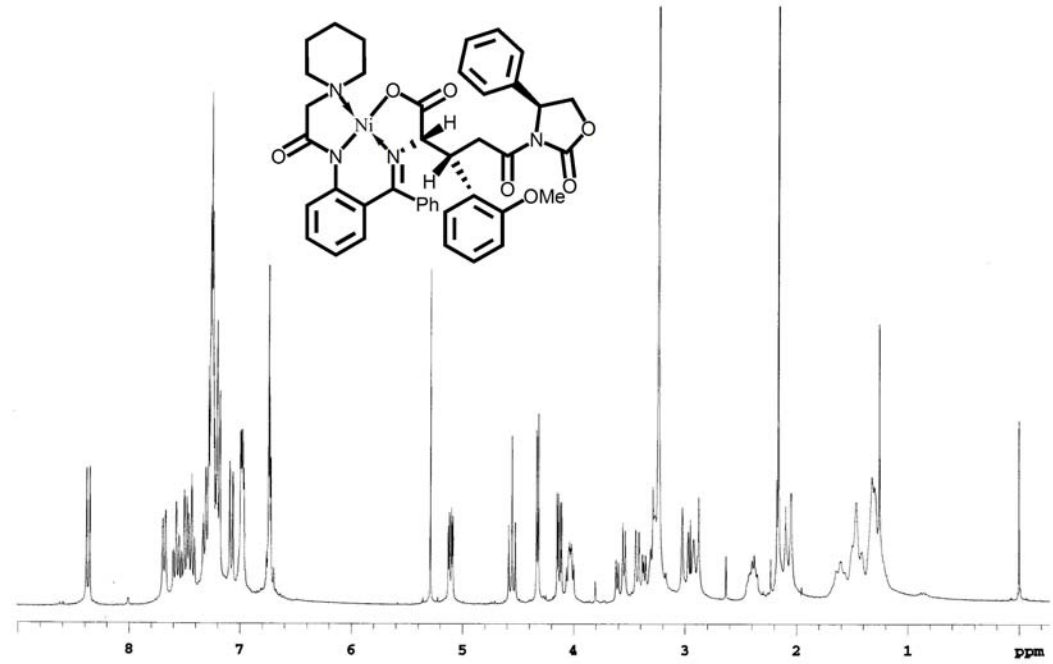

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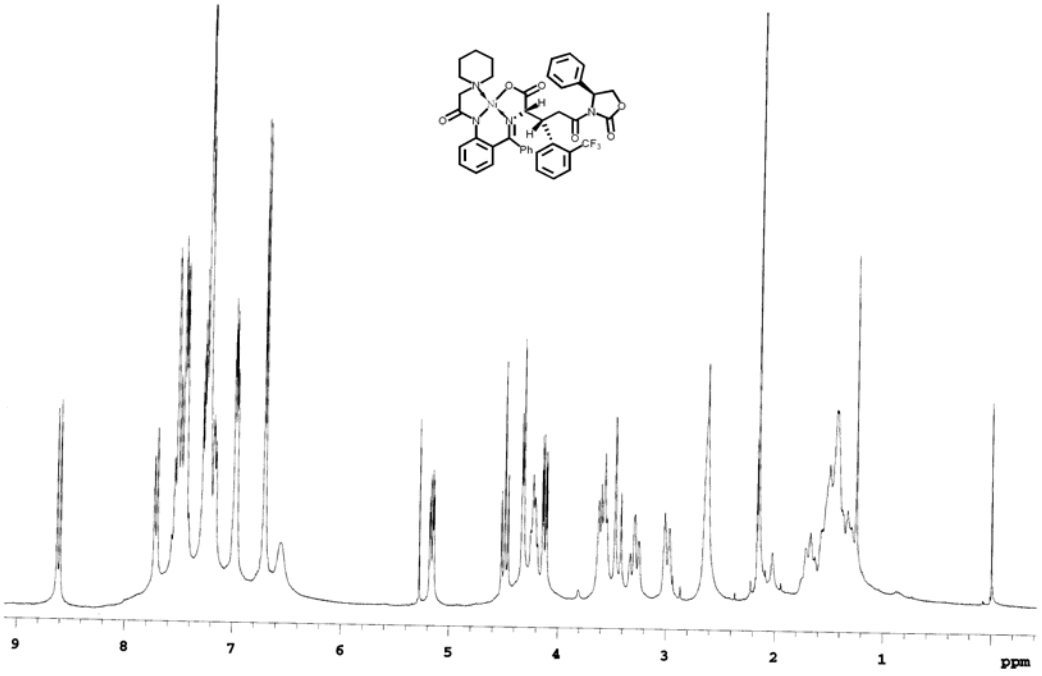

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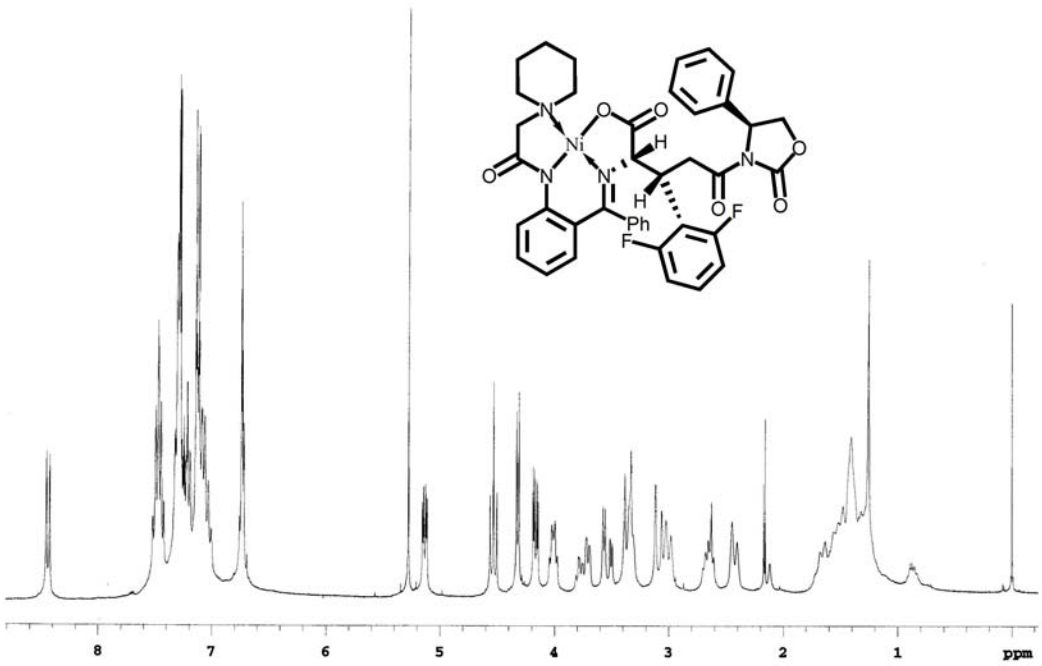

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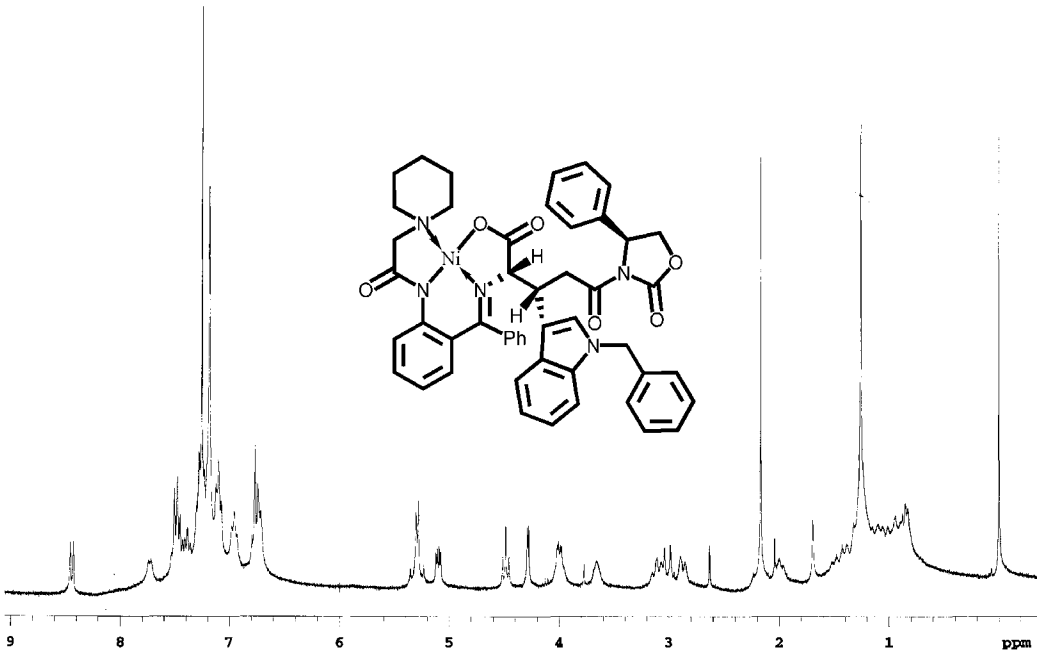

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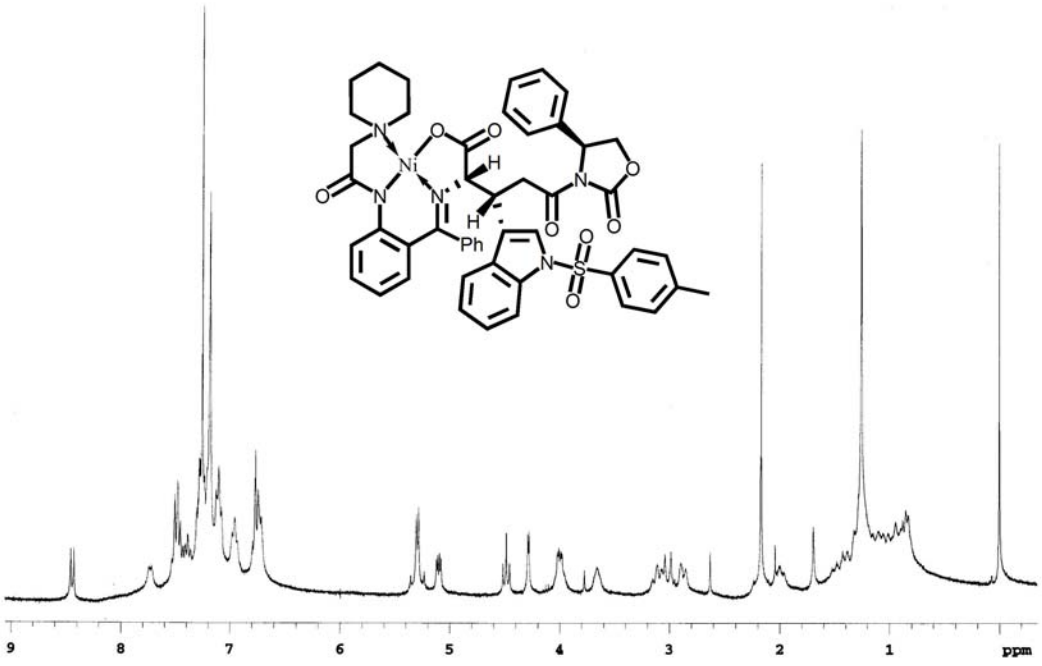

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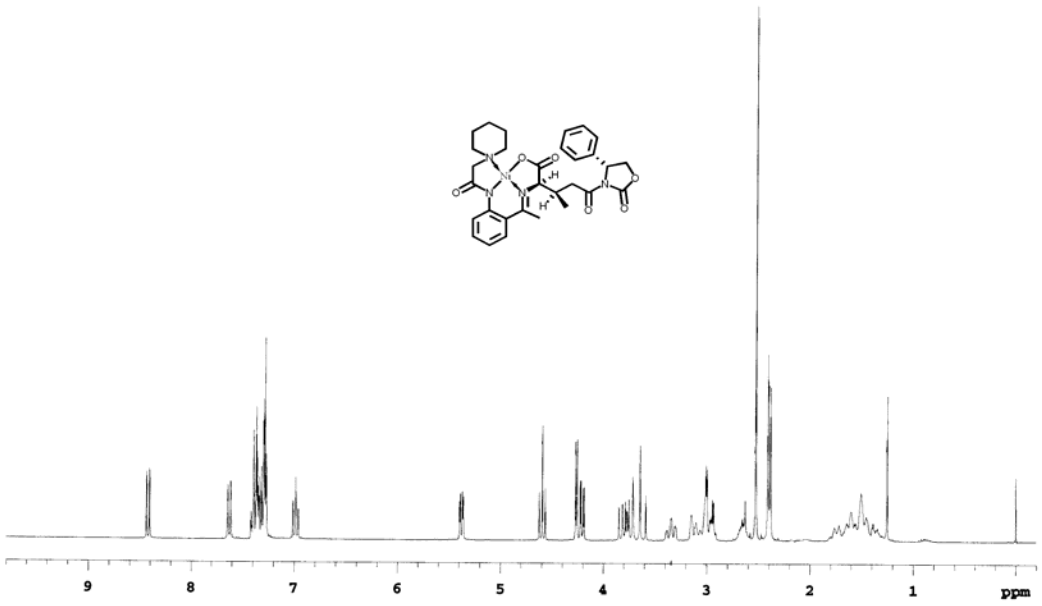

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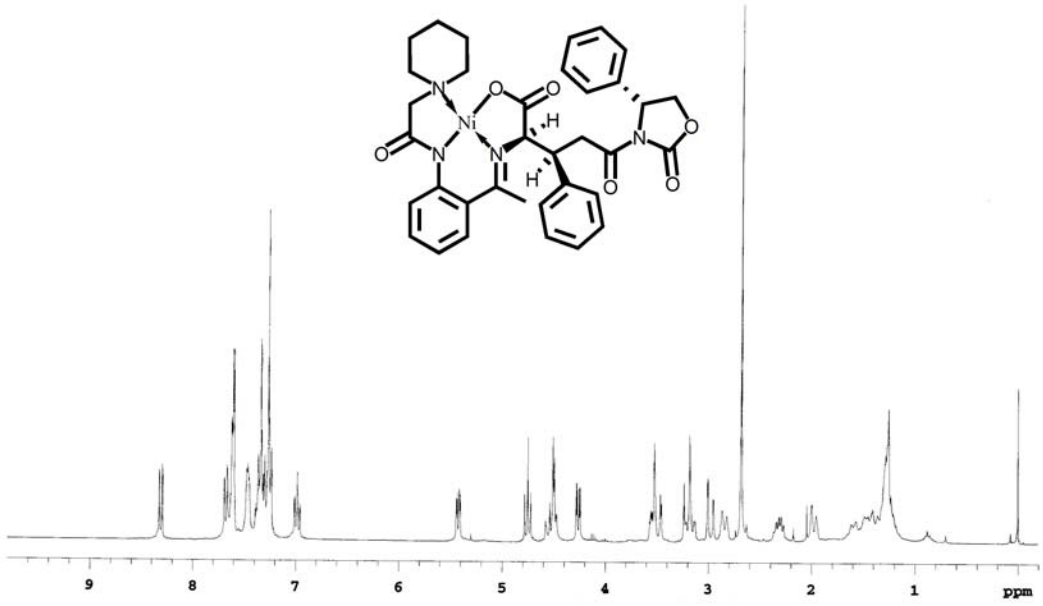

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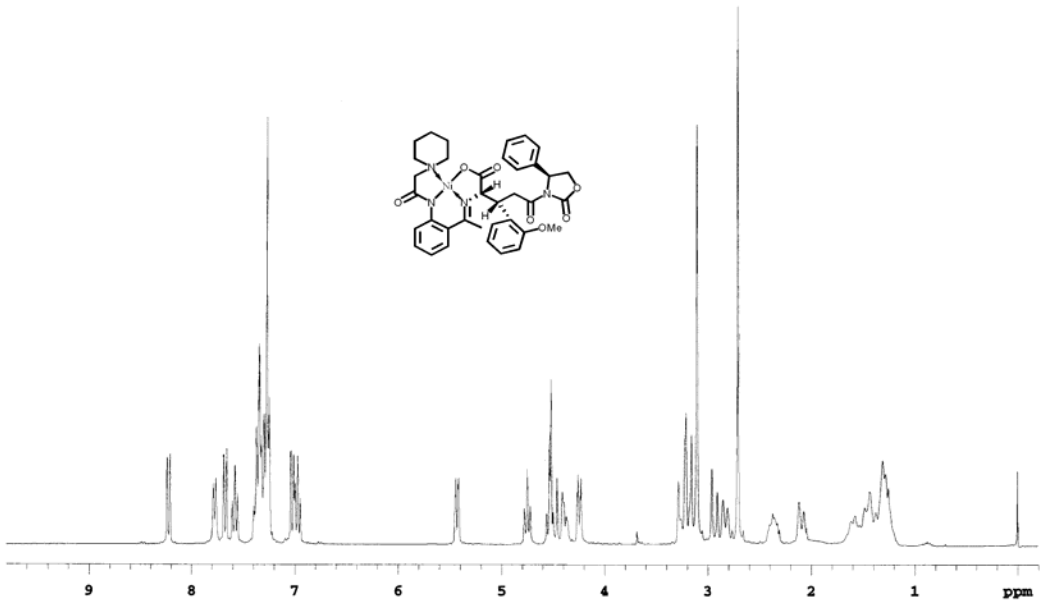

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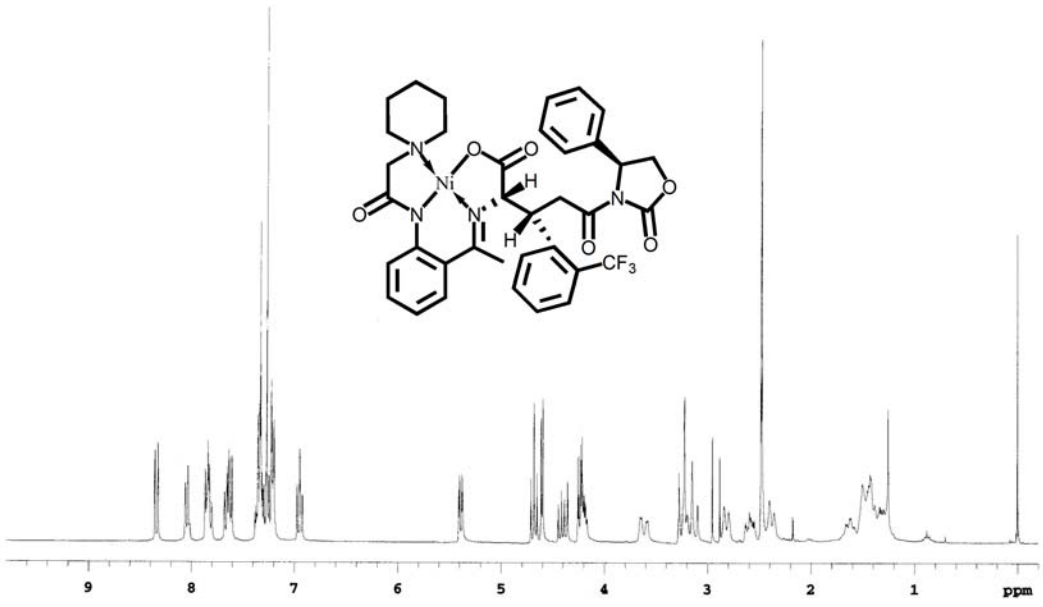

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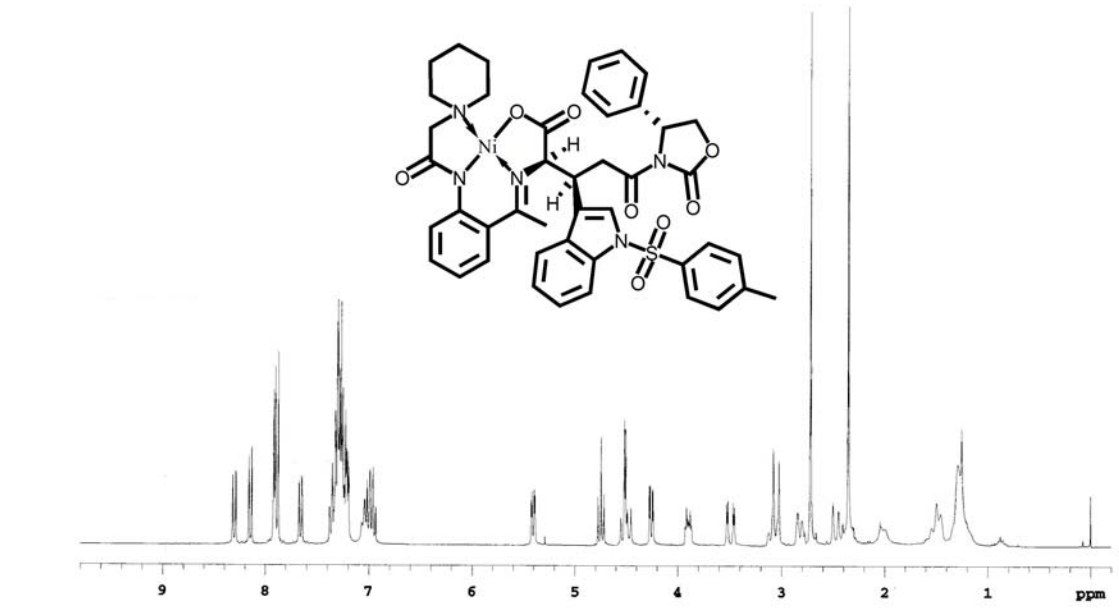

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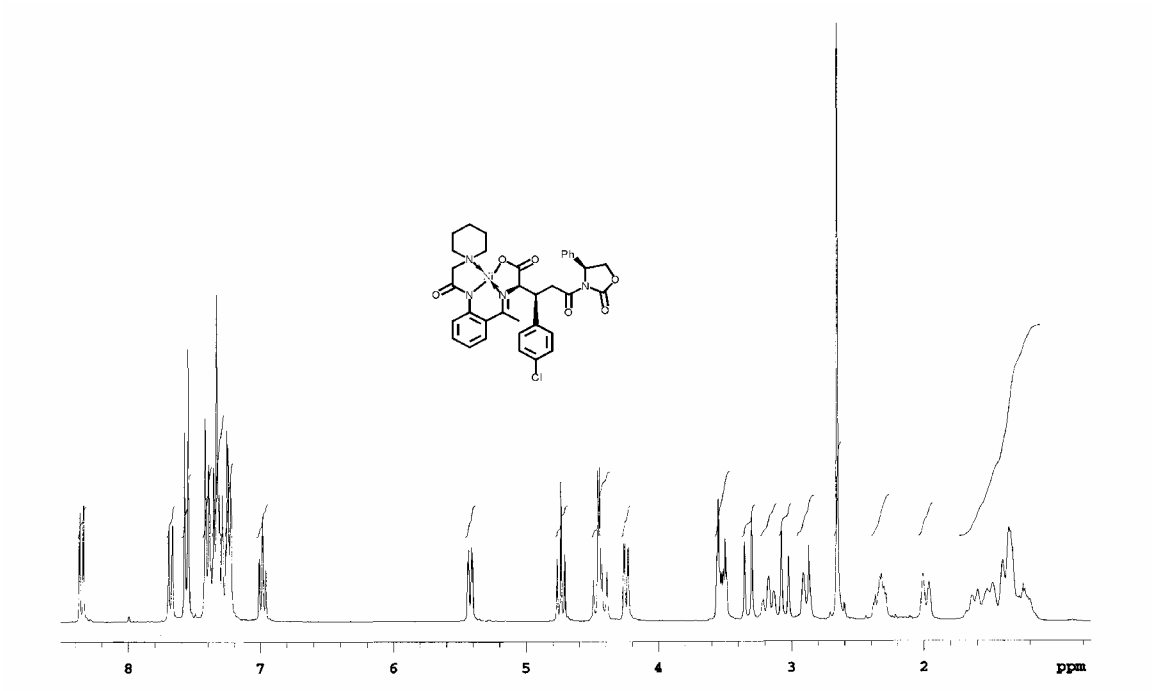

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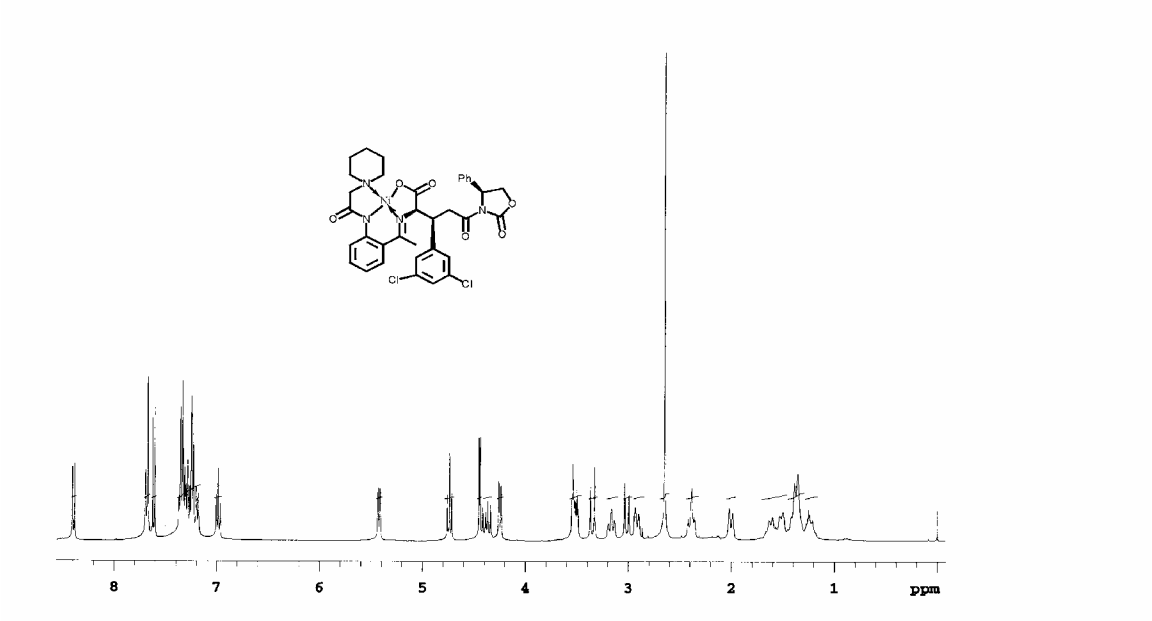

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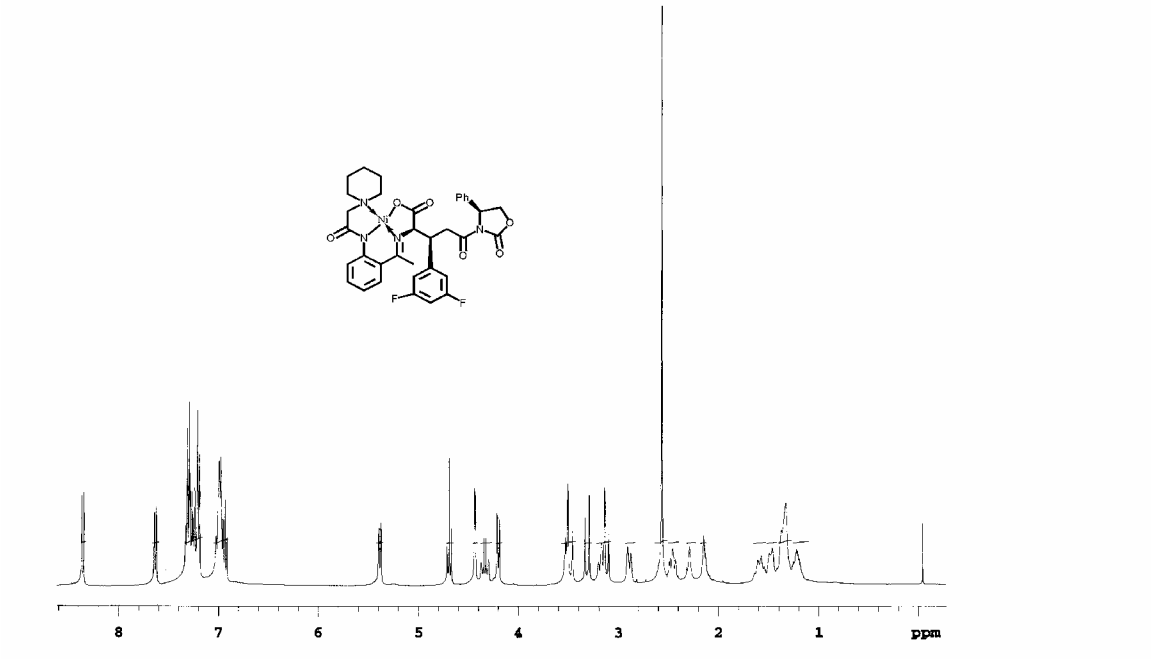

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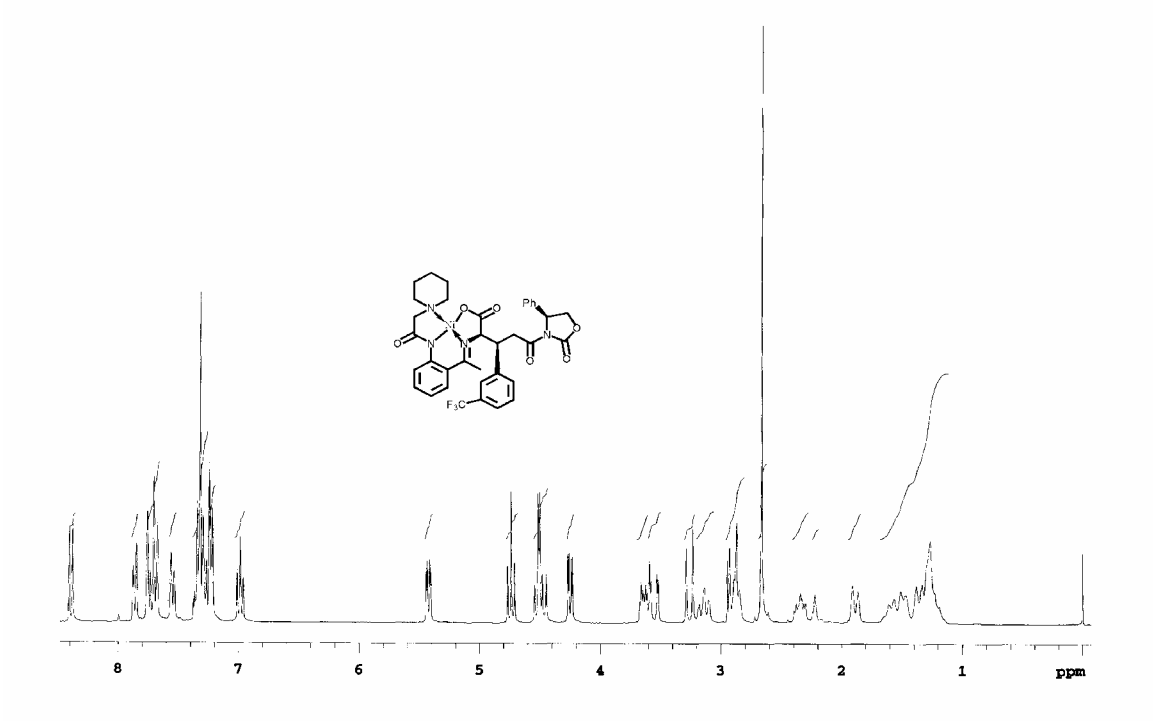

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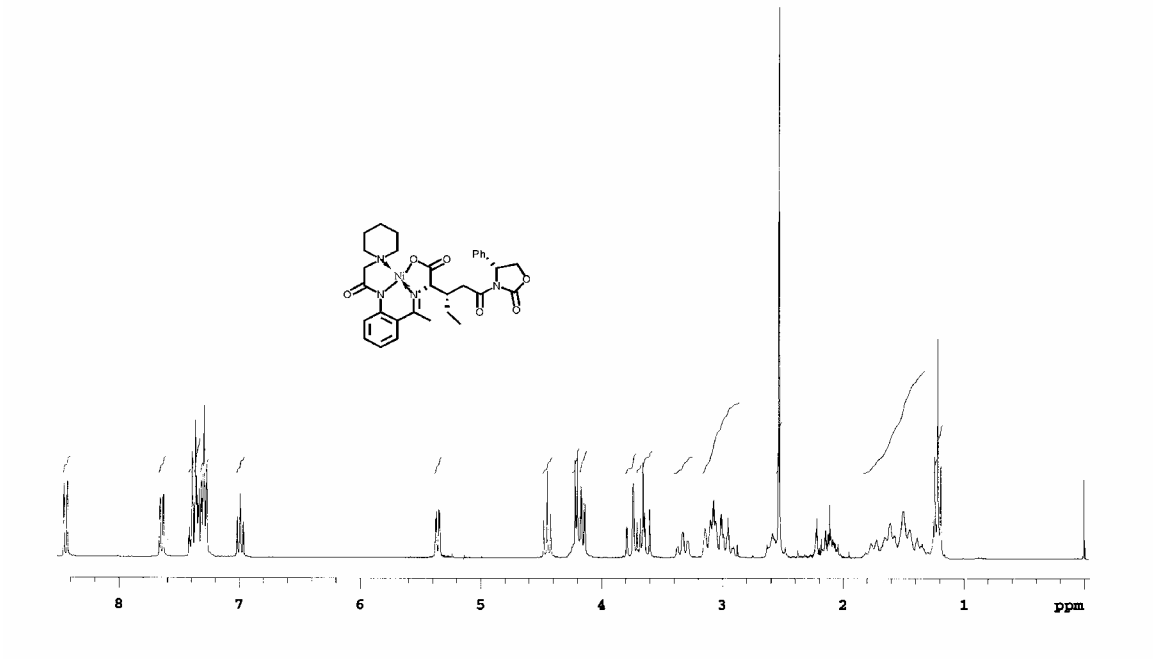

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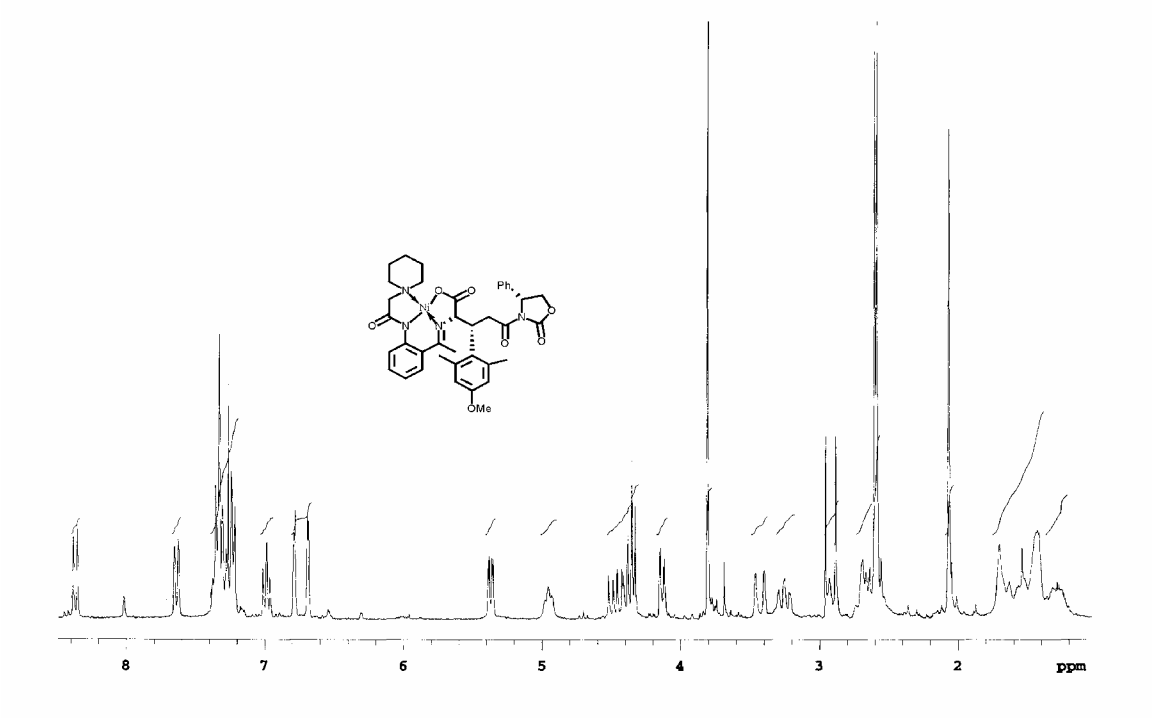

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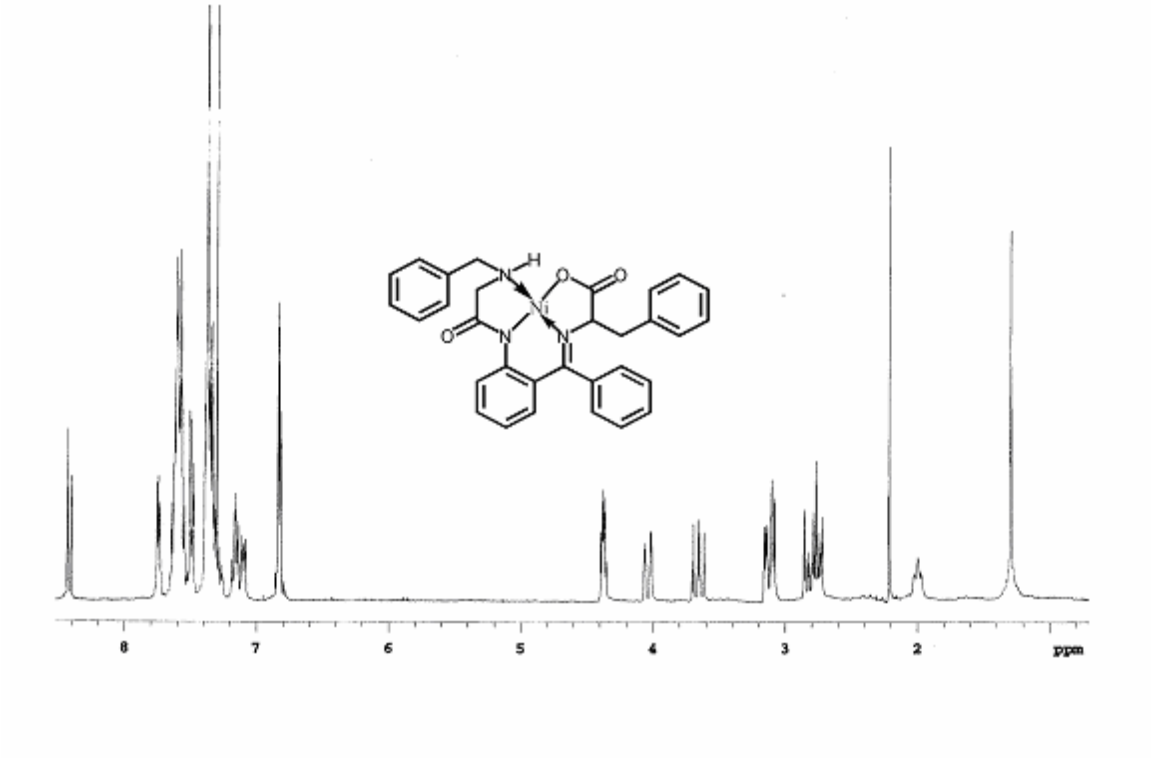

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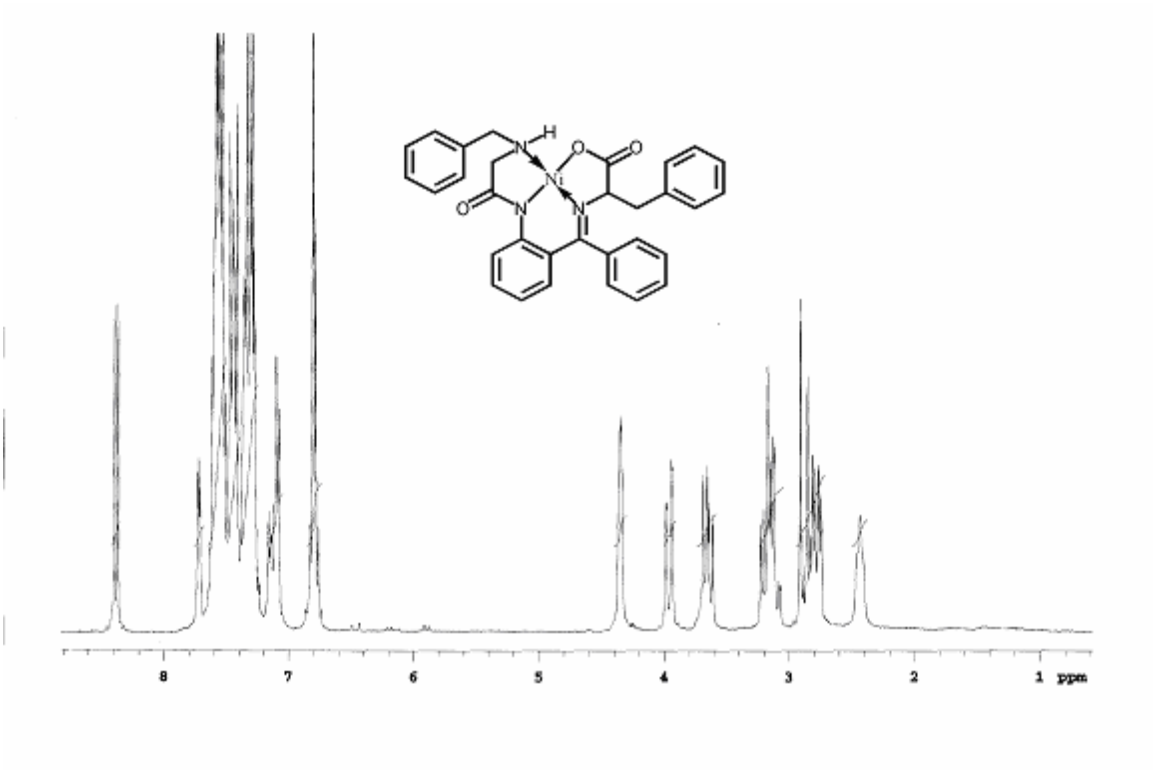

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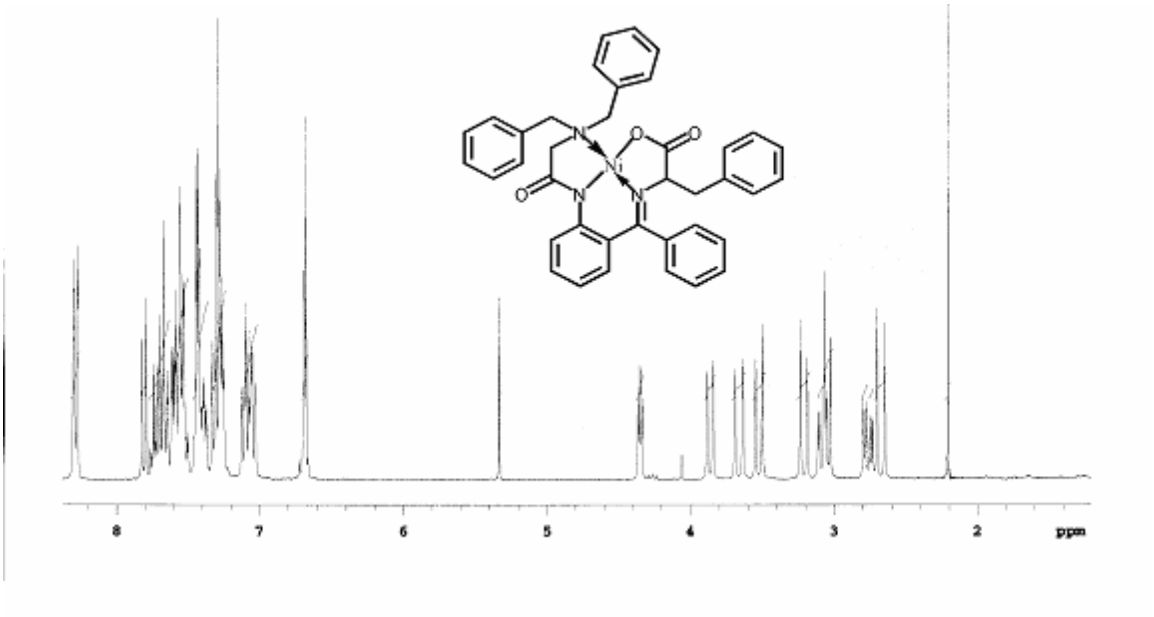

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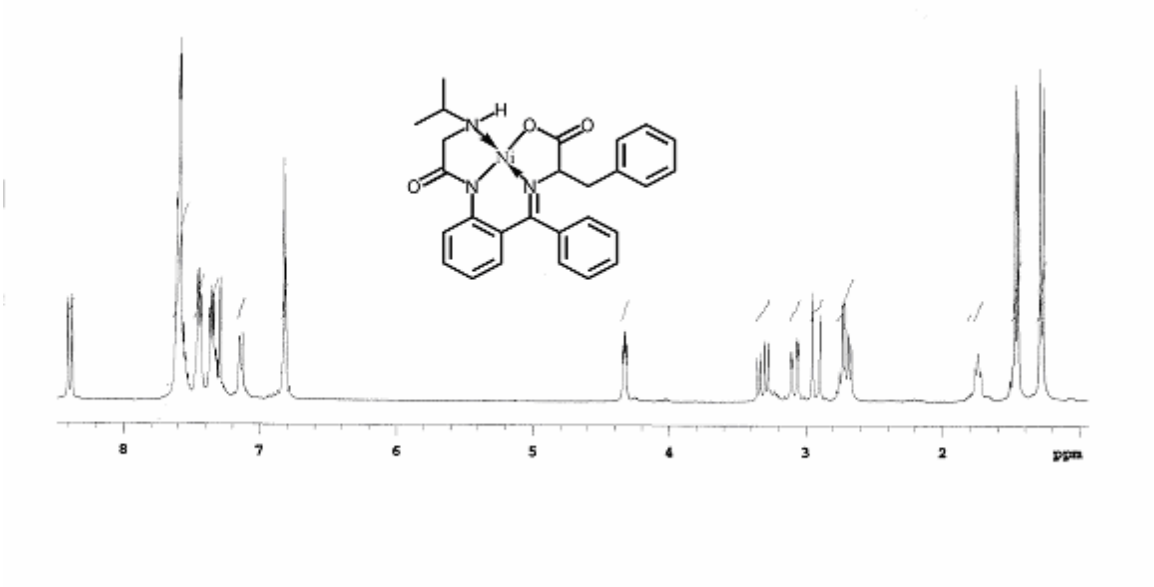

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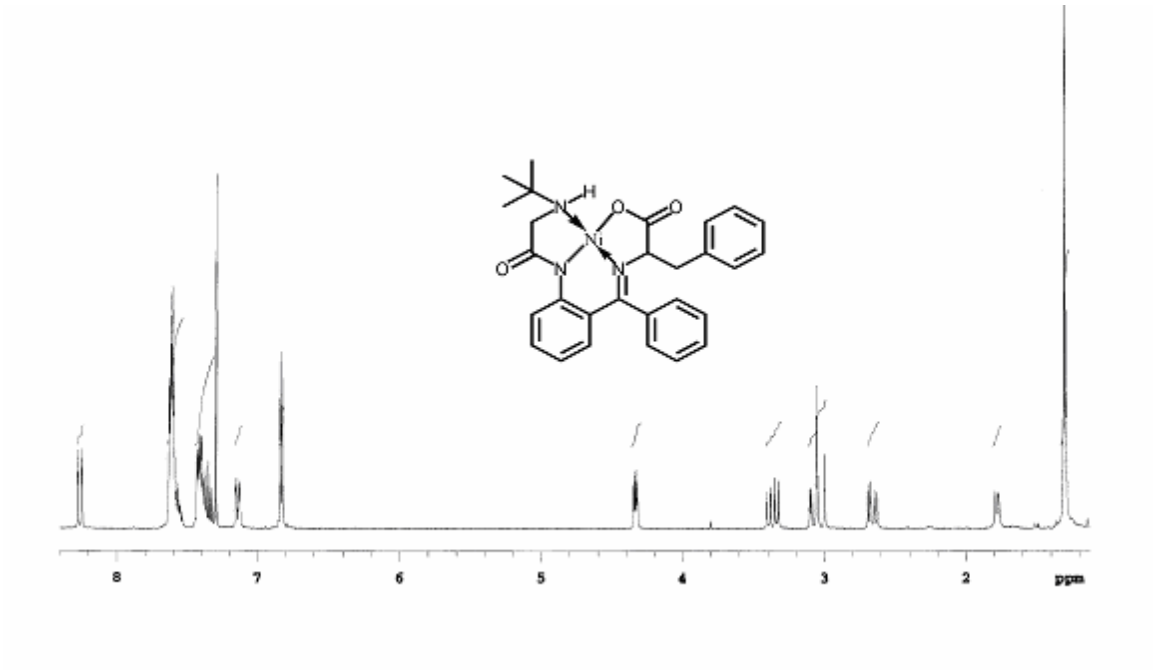

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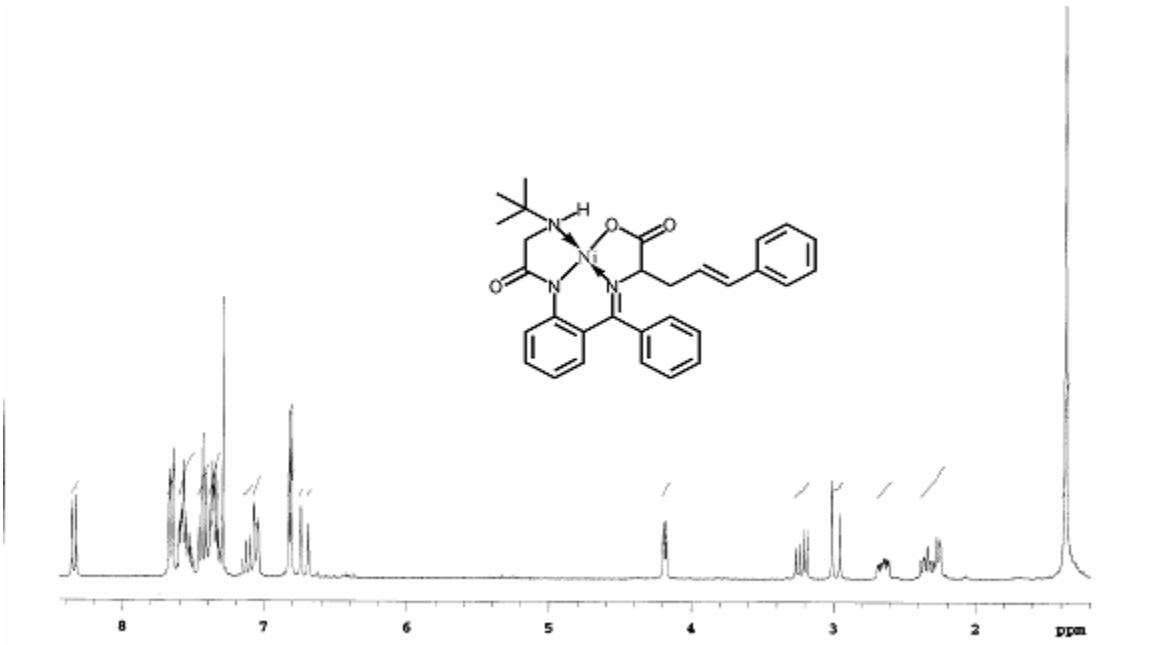

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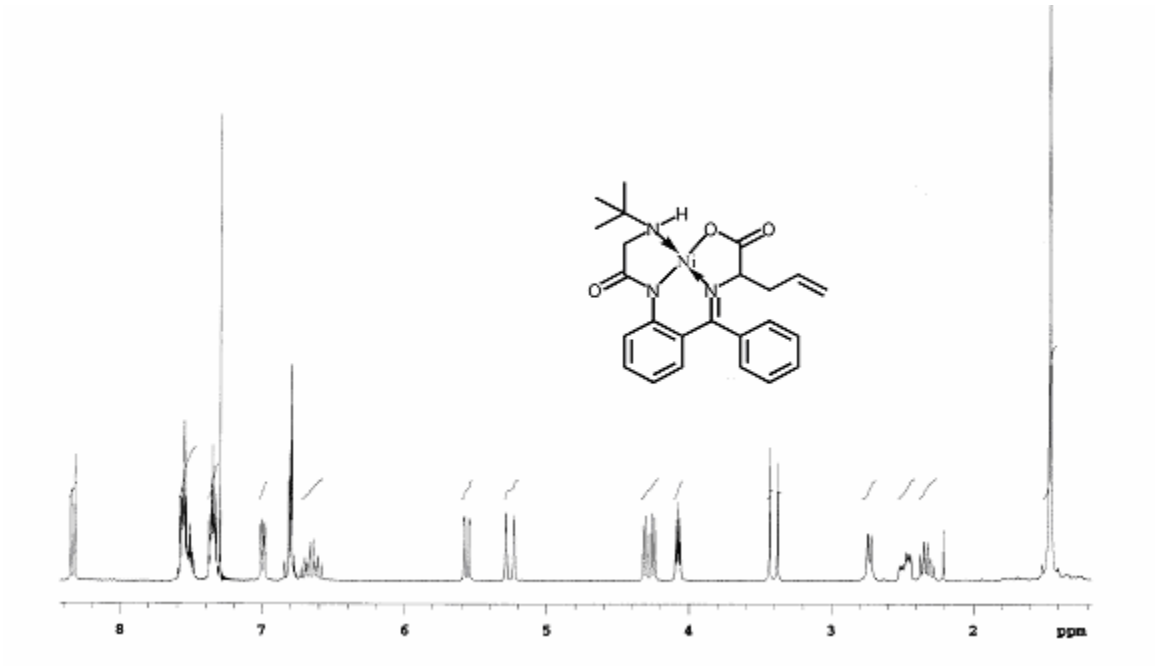

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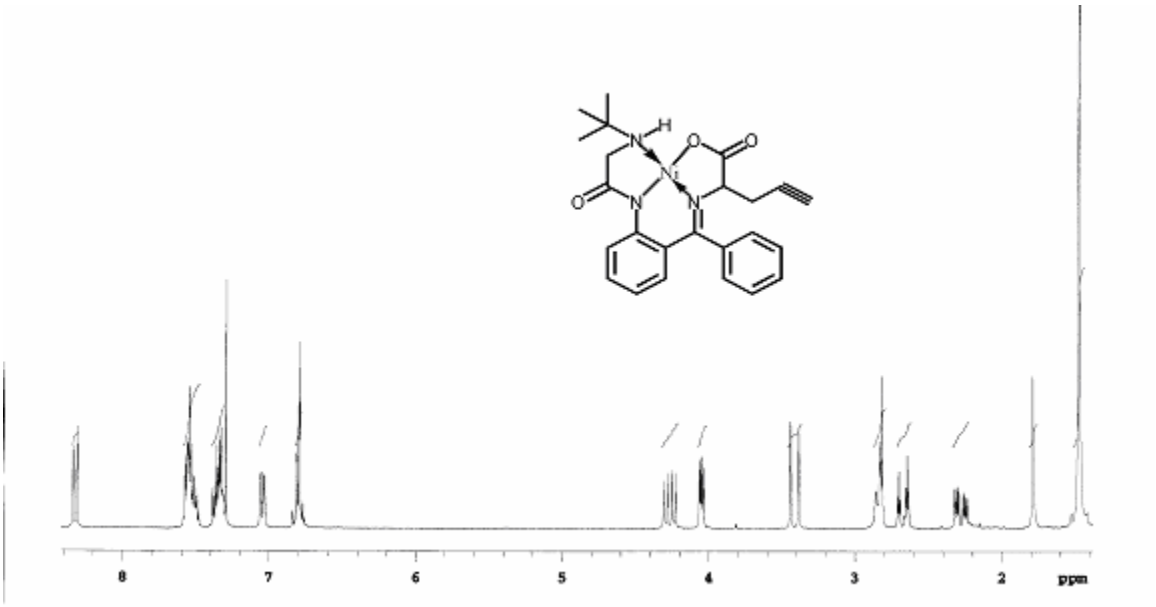

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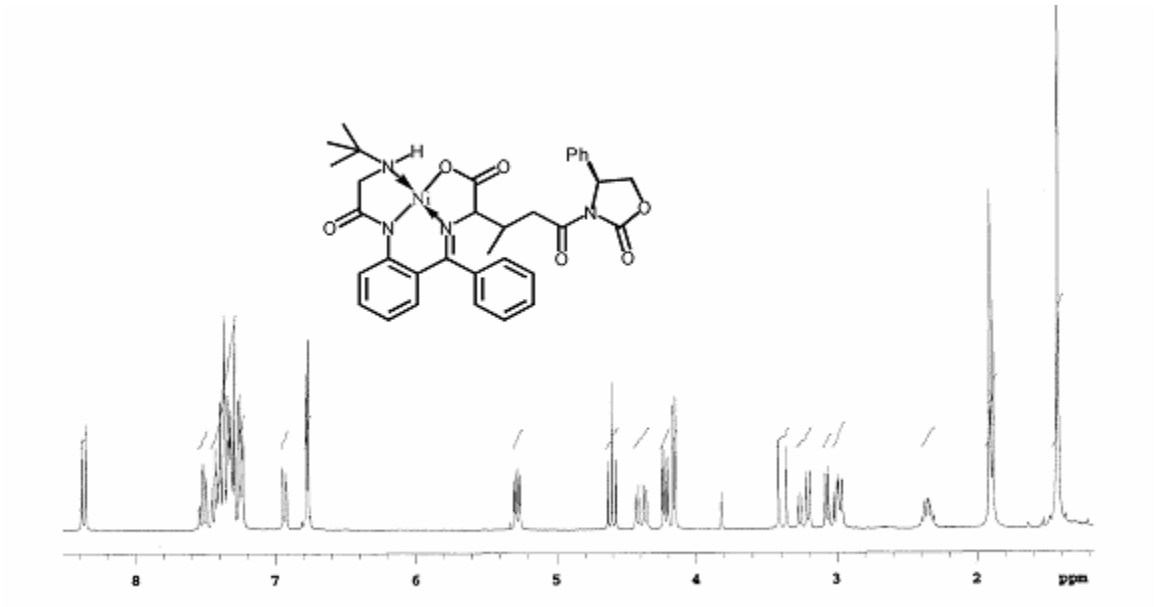

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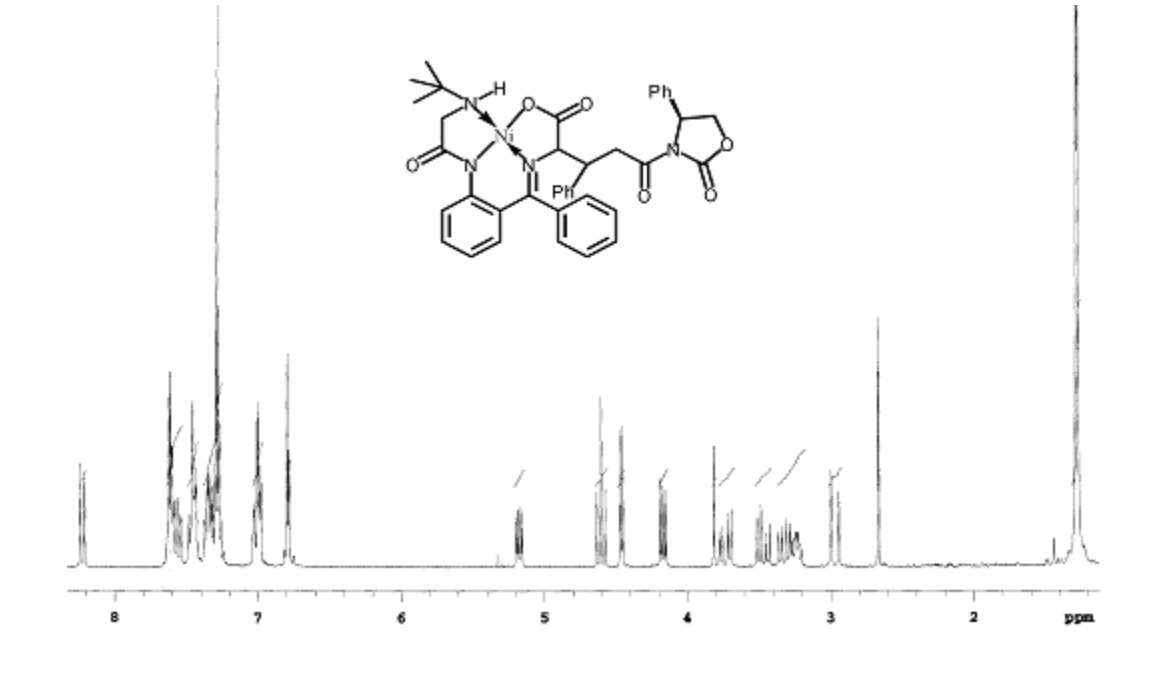

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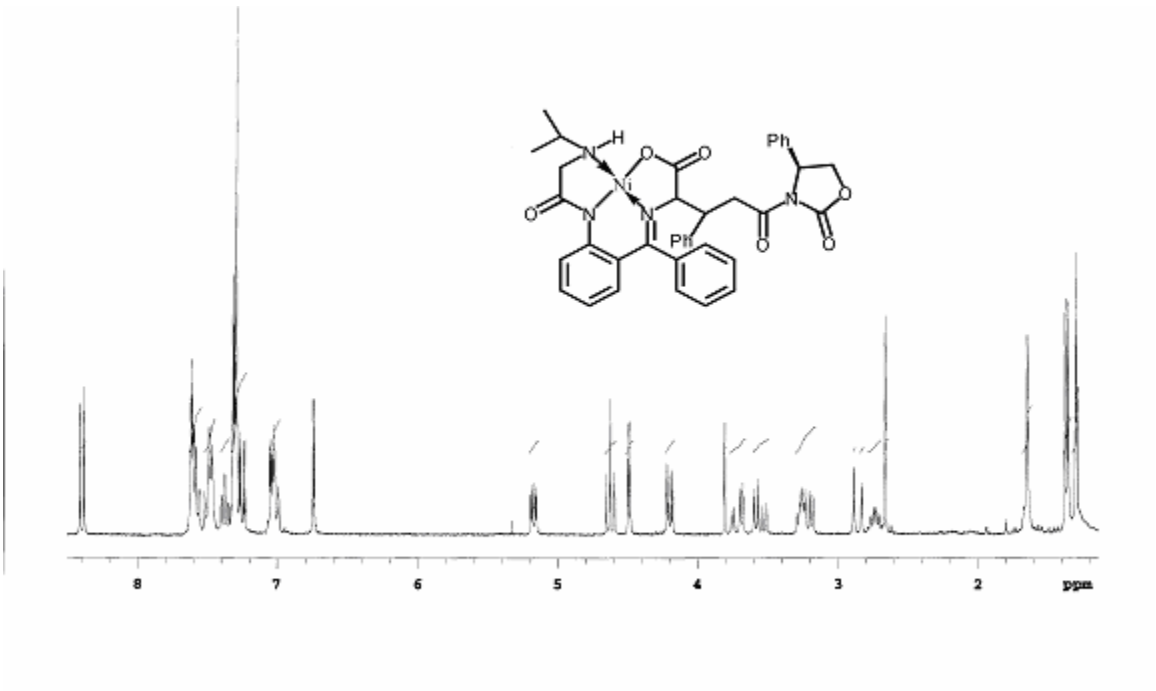

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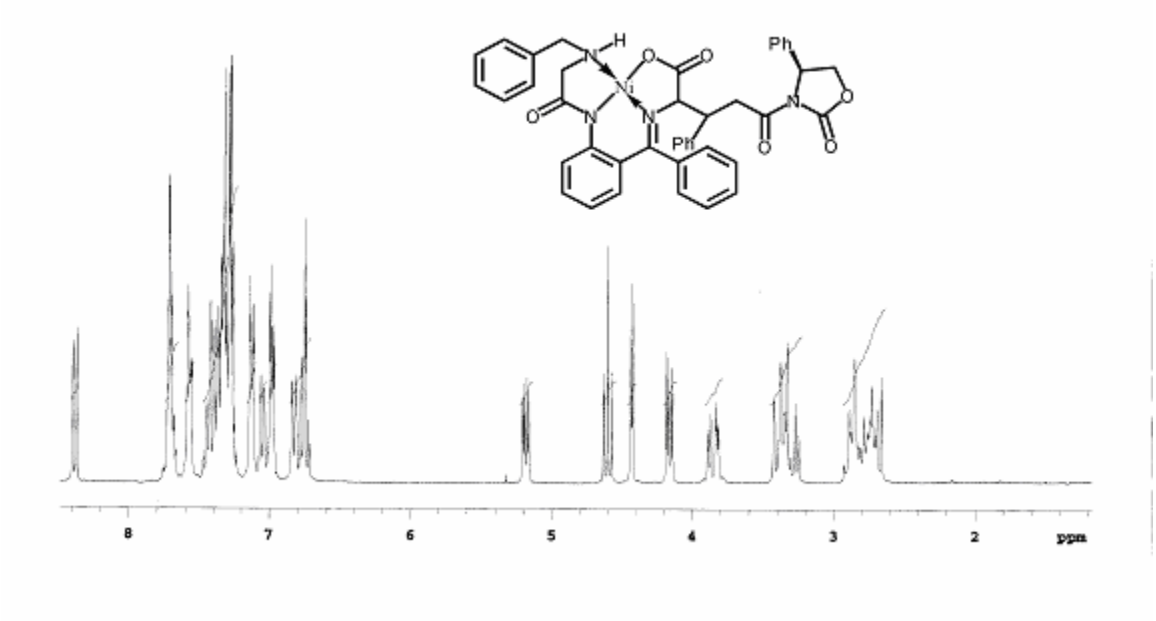

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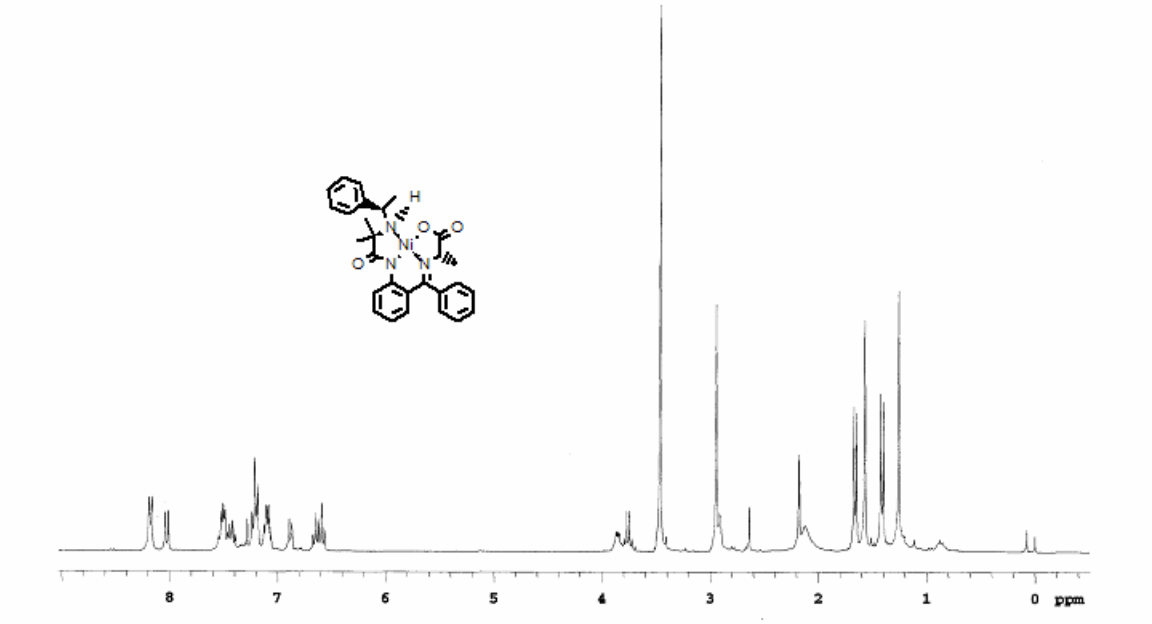

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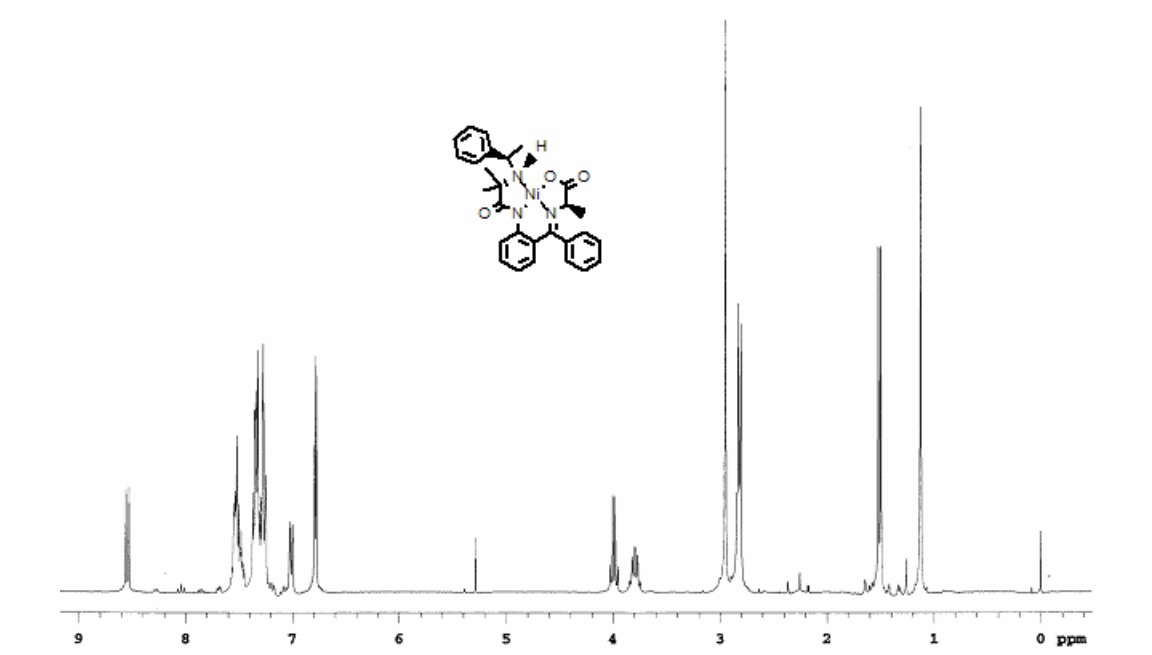

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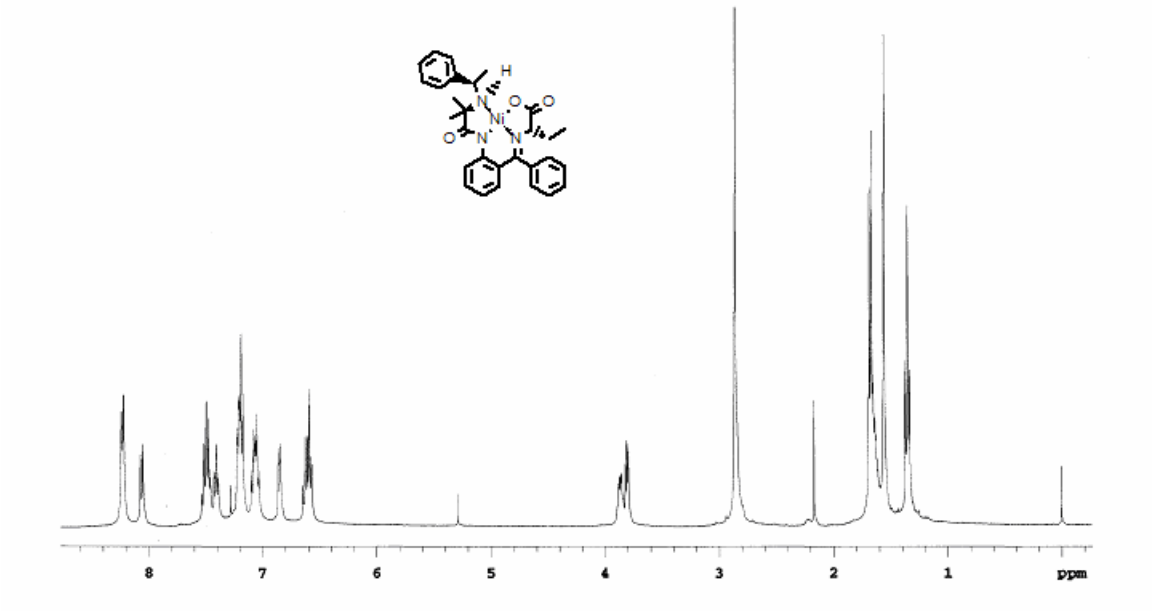

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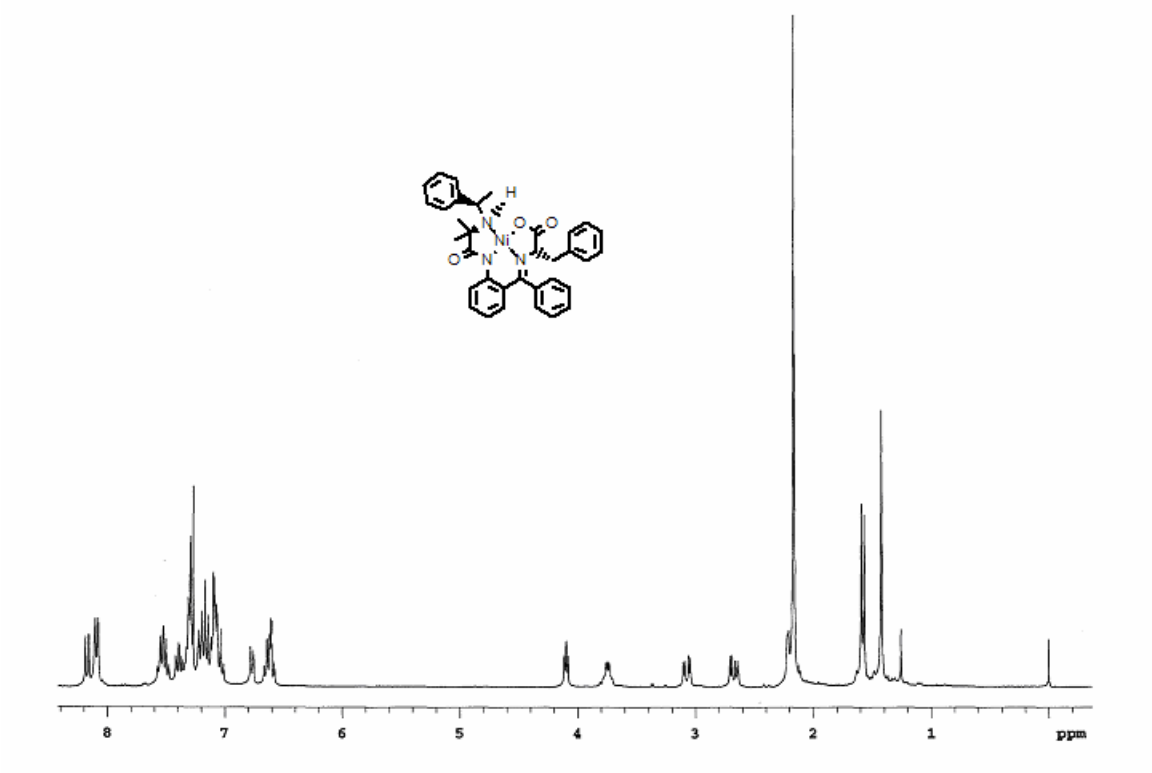

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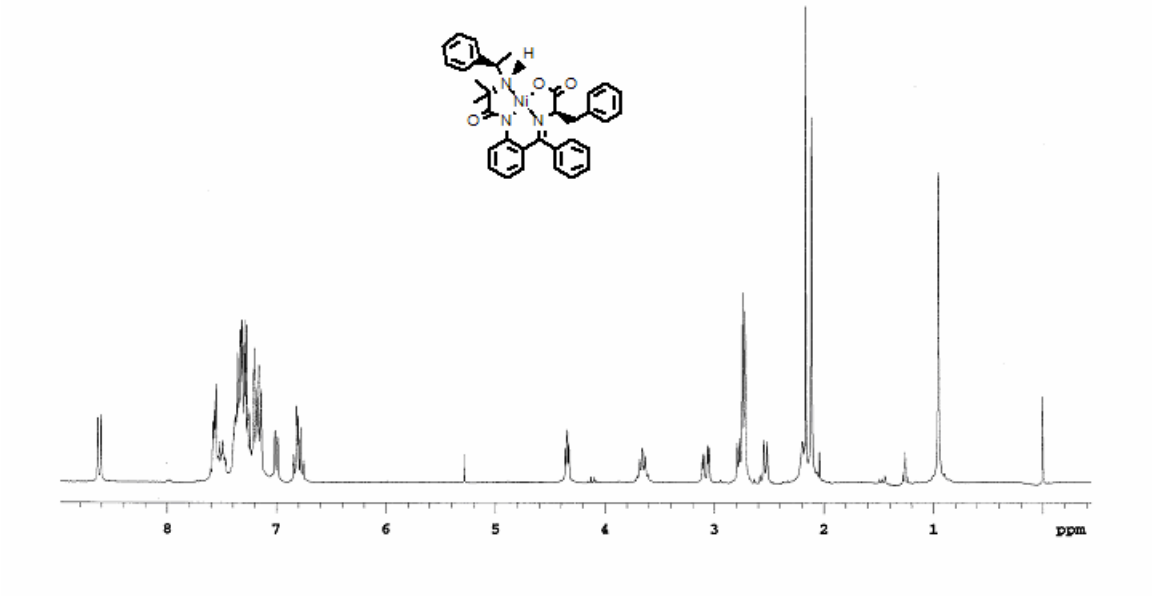

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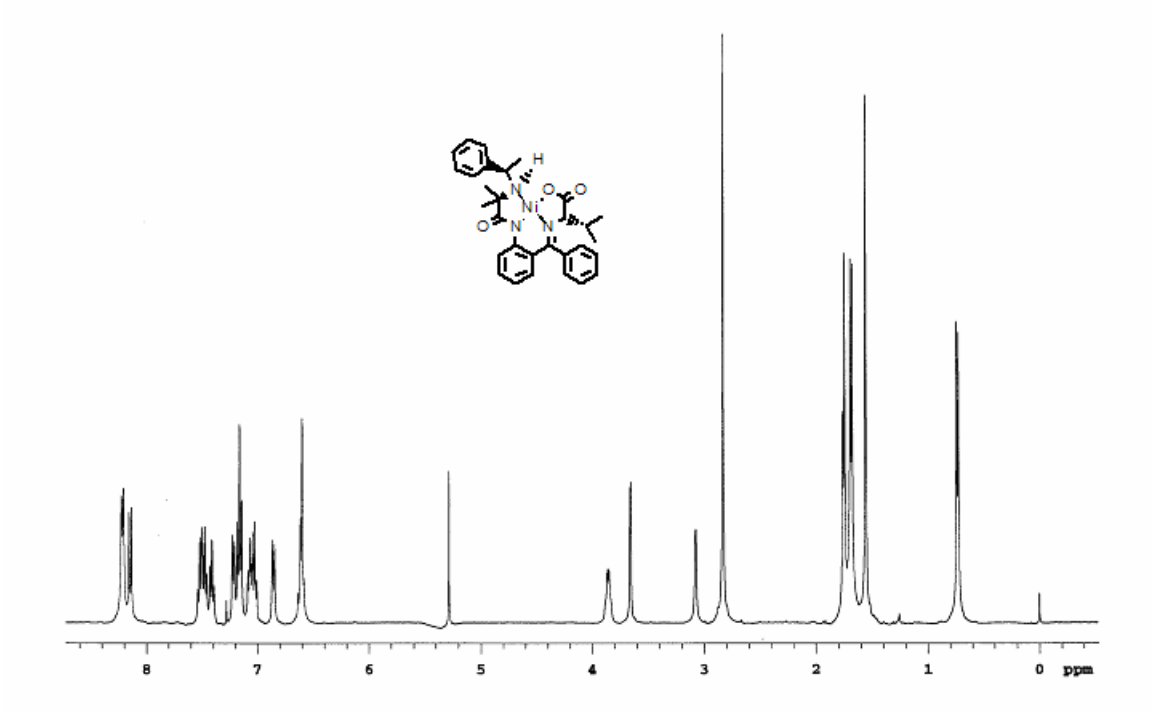

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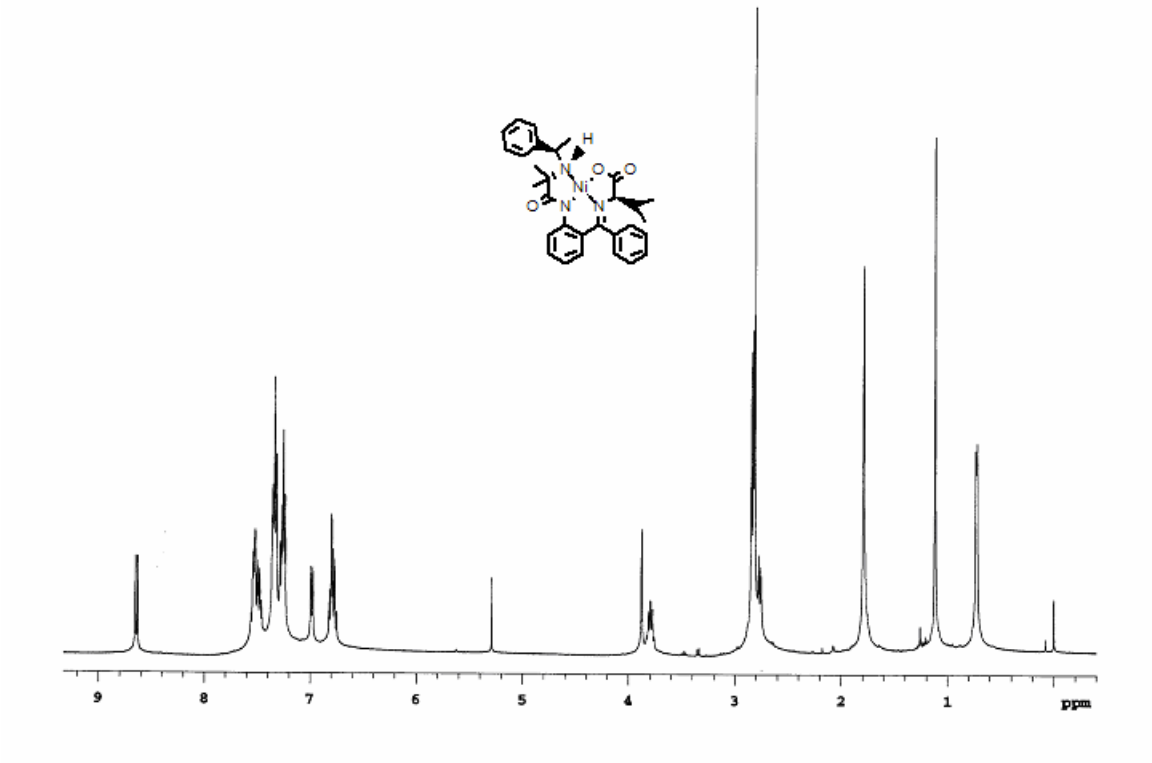

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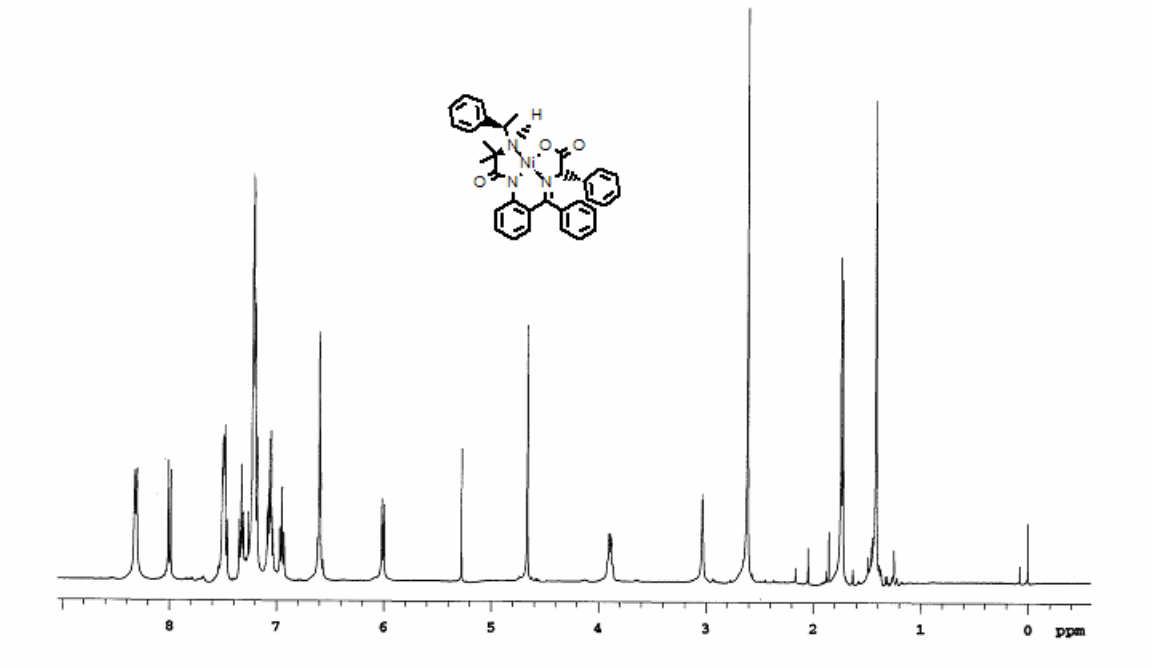

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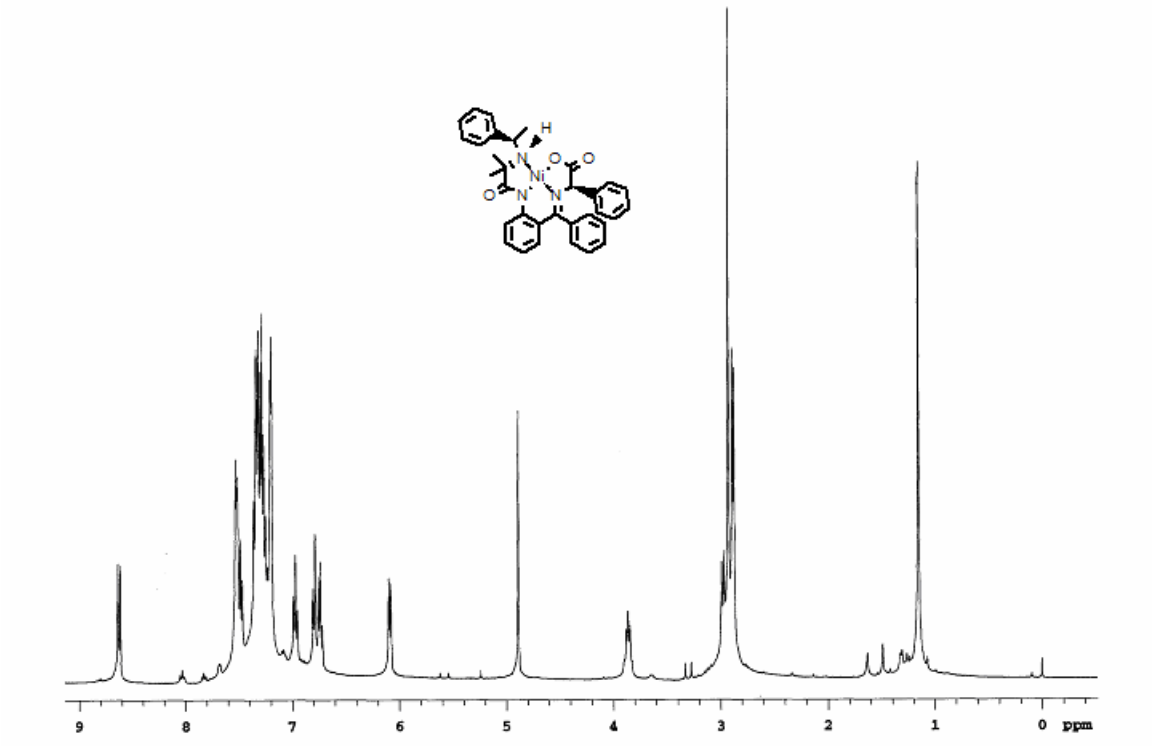

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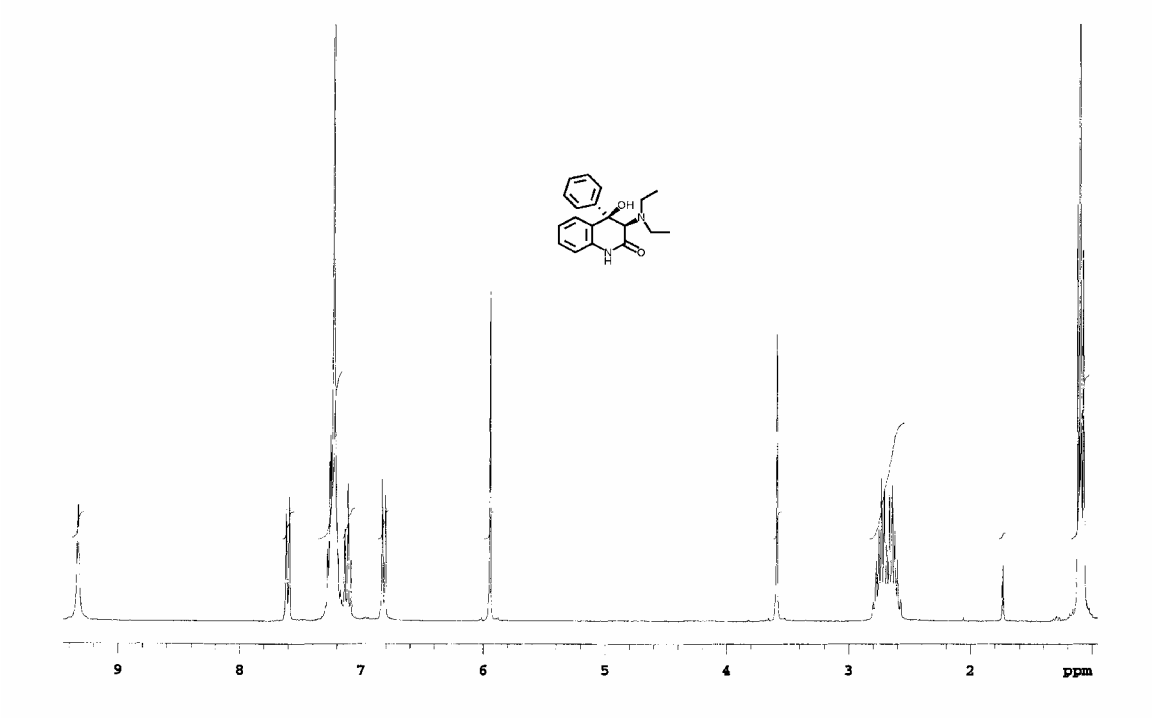

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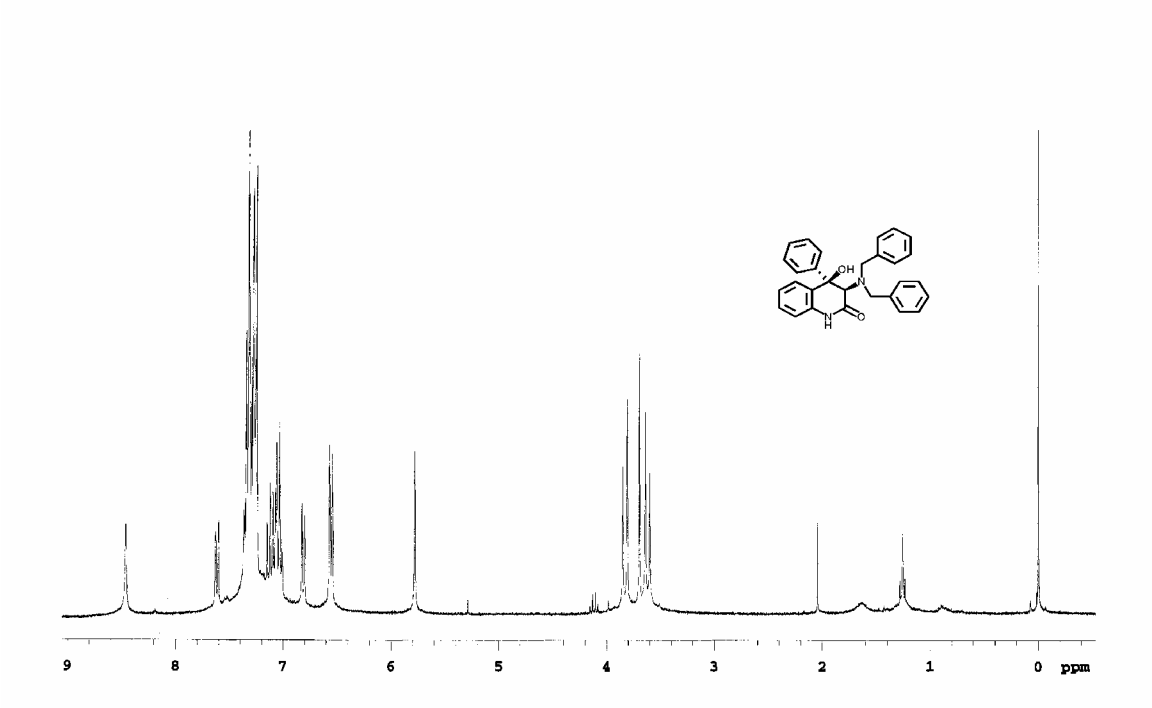

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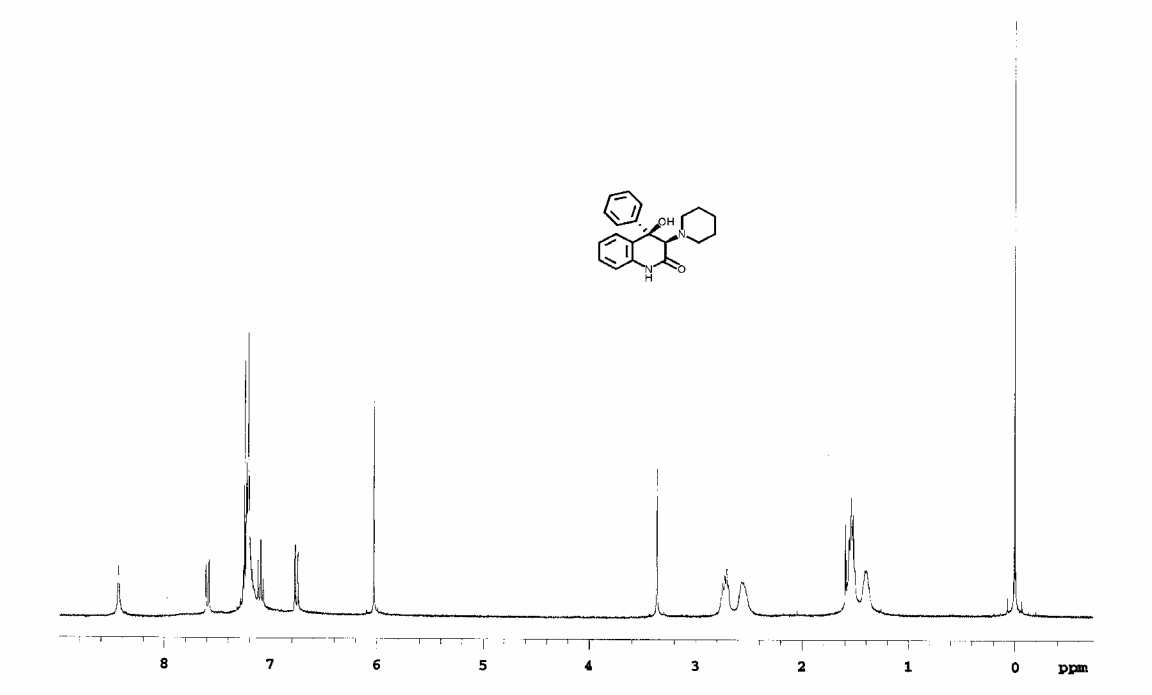

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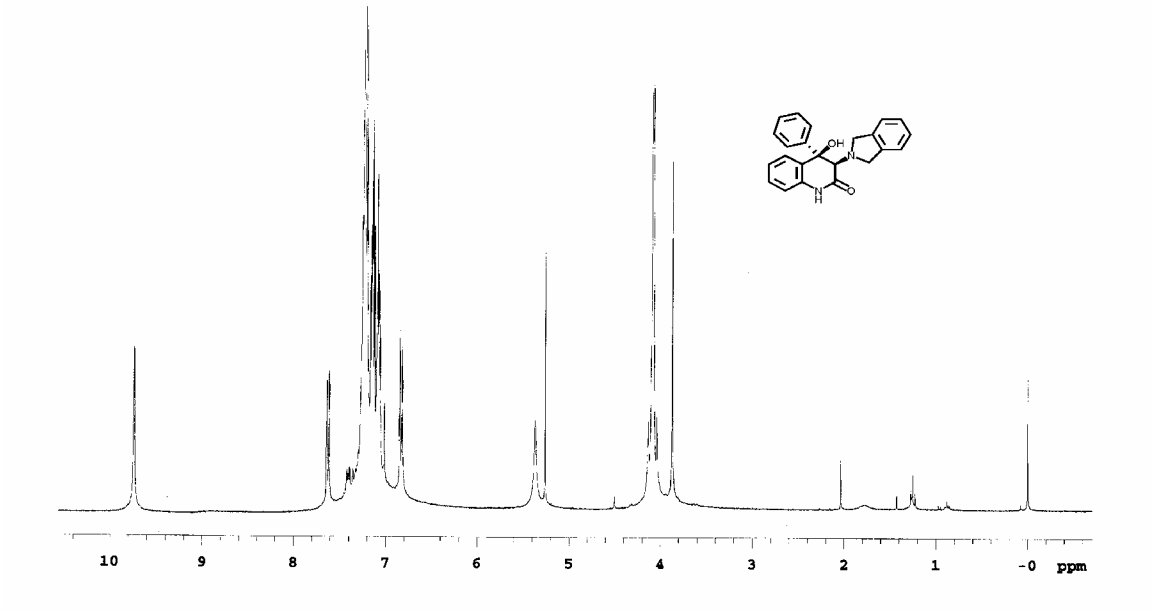

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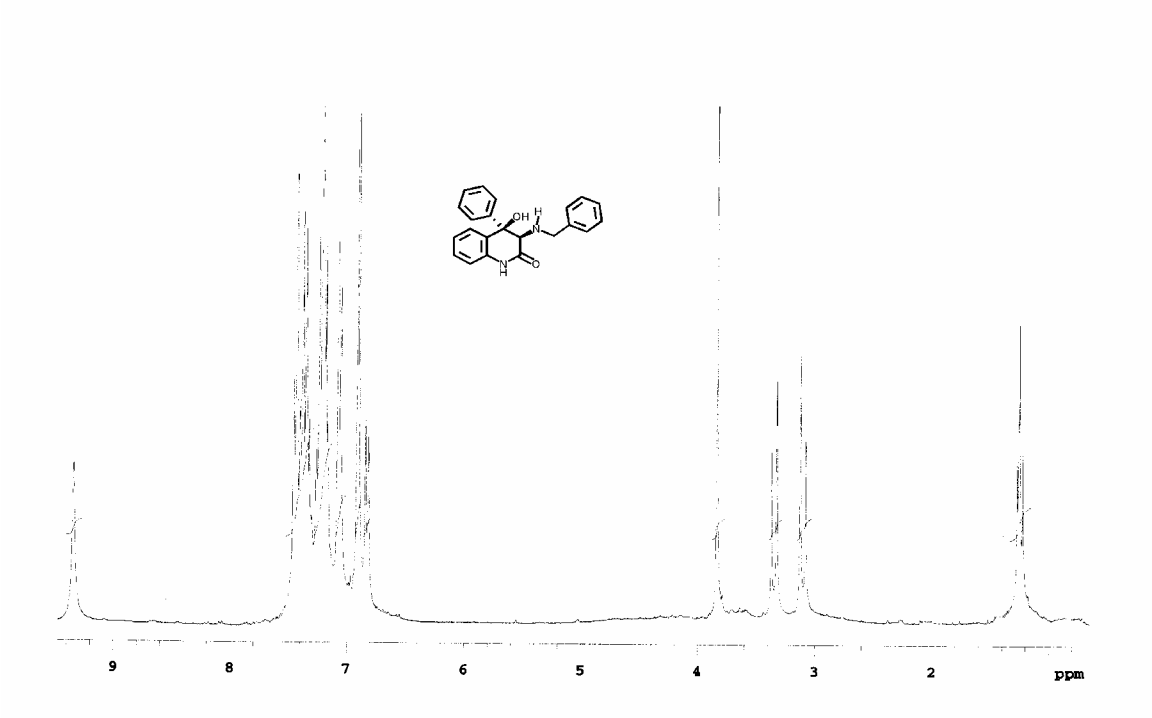

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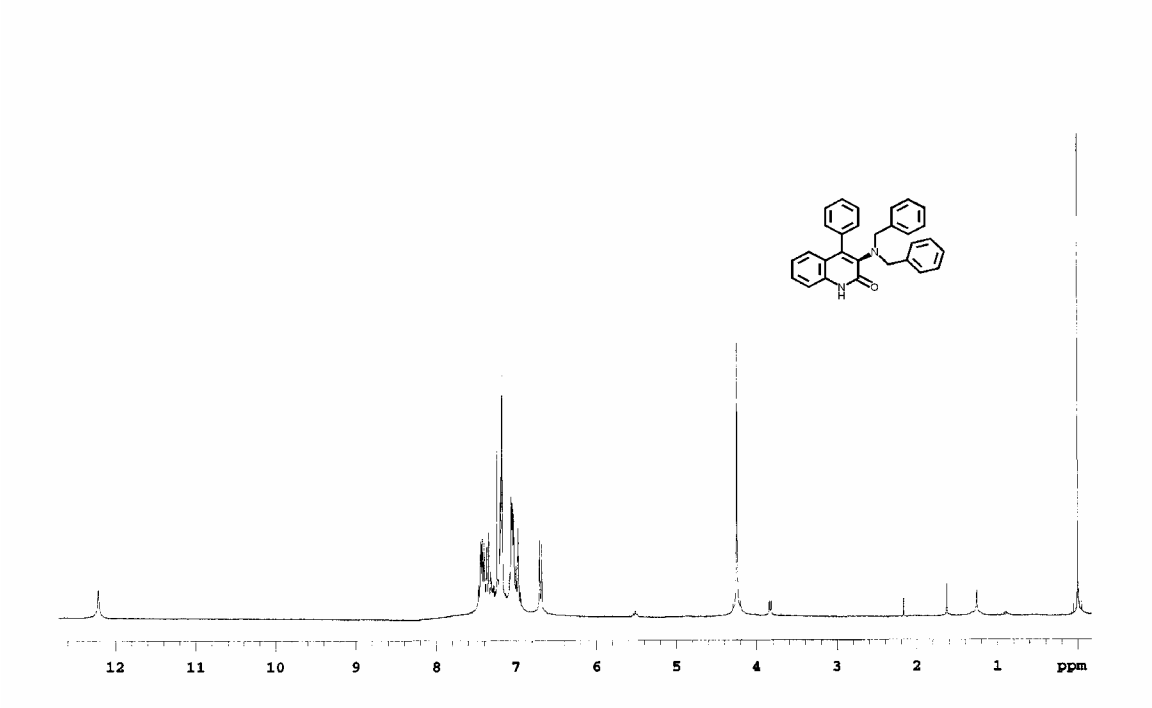

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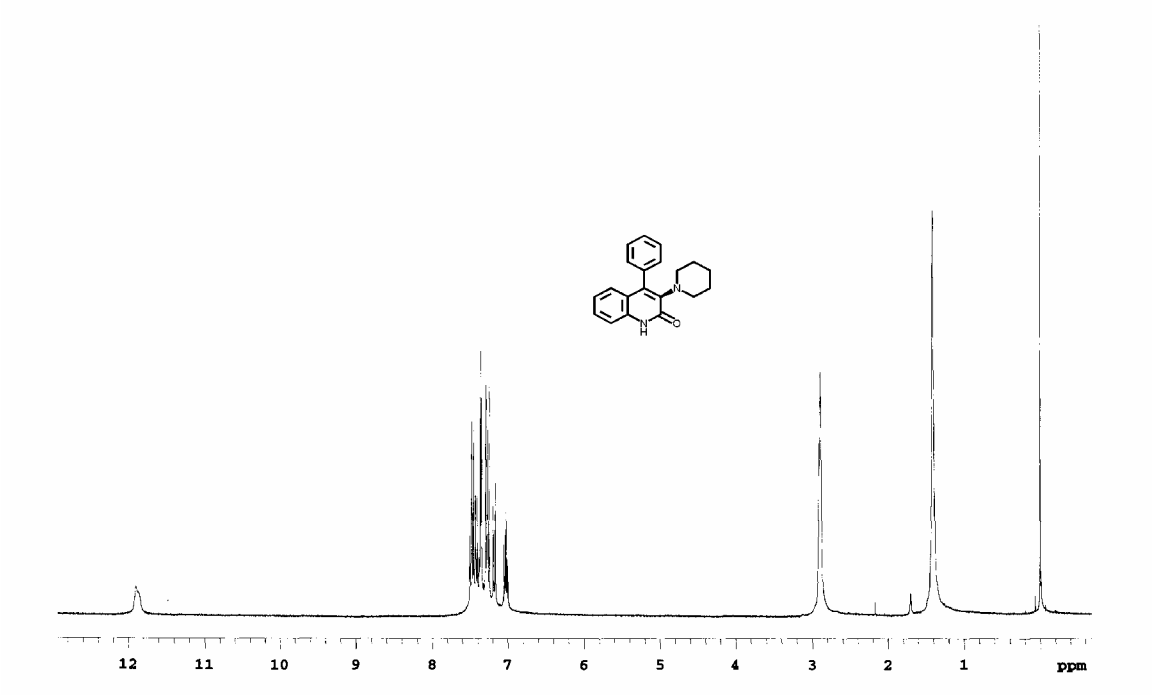

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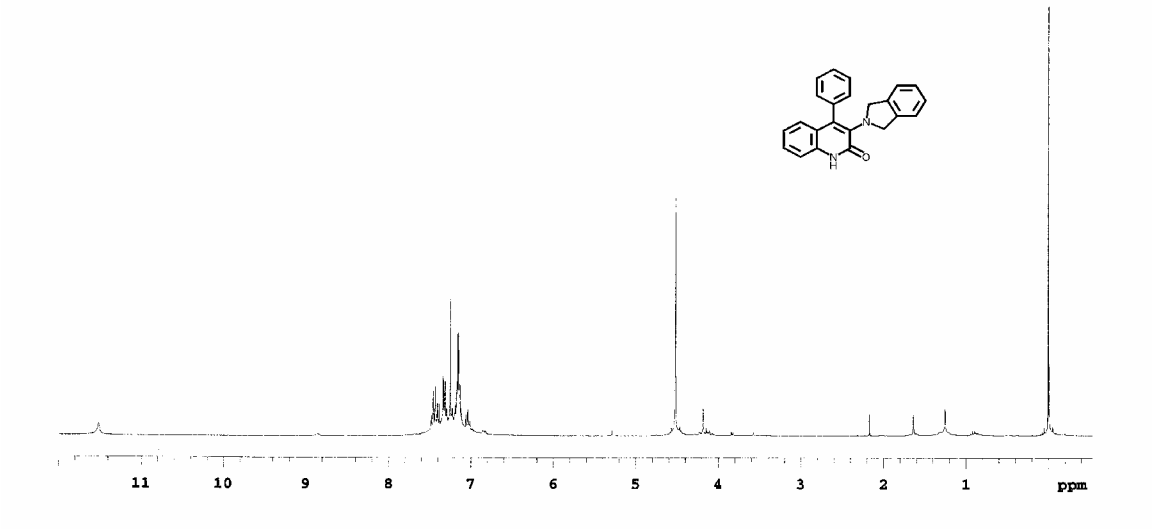

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ppm


OH
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N
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O
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6
5
4
3
2
ppm


N
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ppm