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Development and Applications of Chiral Phosphorus Ligands to Transition-Metal Catalyzed Asymmetric Reactions

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CE SHI

We, the dissertation committee for the above candidate
for the Doctor of Philosophy degree, hereby recommend
acceptance of this dissertation.

Professor Iwao Ojima
Department of Chemistry

Professor Kathlyn A. Parker
Department of Chemistry

Professor Joanna S. Fowler
Department of Chemistry
and
Brookhaven National Laboratory

Professor Derek S. Tan
Molecular Pharmacology & Chemistry Program
Memorial Sloan-Kettering Cancer Center

This dissertation is accepted by the Graduate School

Lawrence Martin
Dean of the Graduate School

Abstract of the Dissertation

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Transition-metal catalyzed reactions have arisen as one of the most valuable synthetic methods since they often provide simple, economical and efficient ways to the synthesis of structurally complex compounds or molecules of great biological interests. Most particularly, transition-metal mediated asymmetric catalysis has attracted considerable amount of interests as it offers a highly practical access to enantiopure products that are of critical importance in the pharmaceutical or agrochemical industry.

Chiral ligands play an important role in developing highly efficient transition metal complexes for asymmetric catalysis. For nearly three decades, bidentate ligands bearing C_2 symmetry have been the dominant choices in the field. Recently, with the successful applications in various asymmetric transformations, the newly designed chiral monodentate phosphorus ligands have re-emerged as valuable tools in asymmetric synthesis.

In our laboratory, we have developed a library of axially chiral 3,3'-disubstituted-5,5',6,6'-tetramethylbiphenyl-2,2'-diols. Based on these chiral biphenols, a library of monodentate phosphoramidite and phosphite ligands and a library of bidentate diphosphonite ligands have been designed and synthesized. The salient feature of these ligands is their fine-tuning capabilities that allow a practical combinatorial approach to finding the most efficient ligand for a particular asymmetric reaction.

To demonstrate the efficacy of the newly designed ligands, we will present an efficient synthesis of 1-vinyltetrahydroisoquinoline via a Pd-catalyzed intramolecular allylic amination using monodentate phosphoramidite ligands. The diphosphonite ligands were applied to a Pd-catalyzed intermolecular allylic amination reaction, the key step in the total synthesis of *Strychnos* Indole Alkaloids, which led to high enantioselectivity and chemoselectivity. Progress towards the enantiomeric synthesis of tricyclic core of Schulzeines using Pd-diphosphonite catalyzed intramolecular allyic amination as key step will also be presented. Mechanistic study of the catalytic system using ^{31}P NMR and molecular modeling will be included as well.

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Ac	acetyl
acac	acetylacetonate
atm	atmosphere
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
BINAPO	2,2’-bis(diphenylphosphinoxy)-1,1’-binaphthyl
BINAPHOS	2-biphenylphosphino-1,1’-binaphthalen-2’yl-(1,1’-binaphthalen-2,2’-yl)phosphite
BINOL	1,1’-bis(2-naphthol)
BIPHEPHOS	2,2’-bis(dibenzo[d,f][1,3,2]dioxaphosphepinyloxy)-3,3’-(1,1-dimethyl)-5,5’-dimethoxybiphenyl
Bn	benzyl
br s	broad singlet
t-Bu	*tert*-butyl
calcd.	calculated
Celite®	diatomaceous earth filter agent, ®Celite Corp.
COD (cod)	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet
dd	doublet of doublet
de	diastereomeric excess
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane

DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
ee	enantiomeric excess
EI	electron impact (MS)
Equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
h	hour
HEPT	hexaethylphosphorus triamide
HMPT	hexamethylphosphorus triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
Im.	imidazole
J	coupling constant
LDA	lithium diisopropylamide
m	multiplet
Me	methyl
min	minute
mp	melting point
MS	mass spectrometry

NBD	norbornadiene
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic reasonance
Ph	phenyl
ppm	parts per million
i-Pr	isopropyl
psi	pounds per square inch
pyr.	pyridine
q	quartet
Red-Al®	sodium bis(2-methoxyethoxy)aluminium hydride
rt	room temperature
s	singlet
t	triplet
TADDOL	α,α,α',α'-tetraphenyl-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
tert	tertiary
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl

TMSI	iodotrimethylsilane
tol	toluene
p-TsOH	*p*-toluenesulfonic acid
Ts	*p*-toluenesulfonyl
	chemical shift

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Chapter I

Introduction and Design of Phosphorus Ligands for Catalytic Asymmetric Reactions

§1.1 General Introduction to Asymmetric Synthesis

Organic compounds are playing an important role in the area of pharmaceutilcals, agrochemicals, and other materials possessing useful physical or biological activities.[1] One of the interesting properties of organic molecules is the possession of chirality in molecular structures. For example, biological systems recognize a pair of enantiomers as different substances in most cases. The two enantiomers will probably exhibit a different level of biological activity, or even quite different types of activity. Thus, how to obtain chiral compounds with high optical purity is of great importance in modern organic synthesis.

Currently, several methods have been developed for the preparation of optically pure compounds, including the classical optical resolution via diastereomers, chromatographic separation of enantiomers, enzymatic resolutions, chemical kinetic resolutions and asymmetric synthesis. Asymmetric synthesis refers to the conversion of a prochiral starting material to a chiral product in a chiral environment. Over the past decades, asymmetric synthesis has been developed rapidly and extensively. It is growing

into the most powerful and commonly used method for the preparation of chiral non-racemic molecules. Nowadays, the importance of asymmetric synthesis has been highly acknowledged by chemists in synthetic organic chemistry, medicinal chemistry, agricultural chemistry, natural product chemistry and material chemistry.

The current asymmetric synthesis is usually realized by chiral pool technology, chiral-auxiliary method, enzymatic catalysis and chemocatalysis. Among these methods, chemocatalysis using a chiral (non-racemic) catalyst has been proven effective to solve many problems in asymmetric synthesis and is characterized by generality and flexibility. A survey by Frost & Sullivan estimated that in 2002, 55% of the world wide $7 billion revenues from chiral (non-racemic) products was generated by traditional technologies (chiral pool and separation), 35% by chemocatalysis and 10% by biocatalysis.[2]

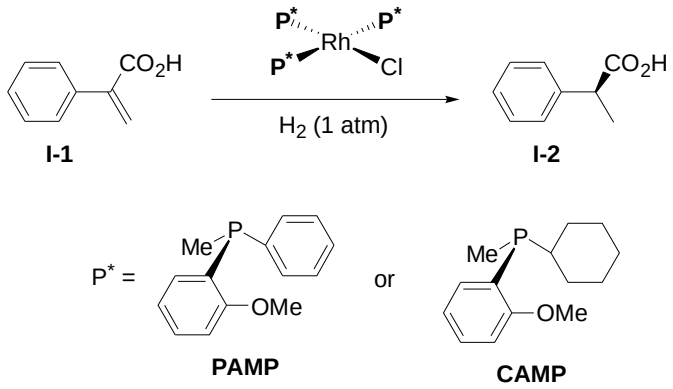
By far, the number of catalysts that can give high enantioselectivity and be applied to a wide range of substrates is still limited. The development of new asymmetric synthetic methods, especially more efficient and powerful chiral catalysts, is still required to meet the increasing demand for the optically active compounds.

§1.2 Development of Phosphorus Ligands

The design of efficient chiral ligands has played an important role in the development of effective chiral transition-metal catalysts for asymmetric synthesis. Today, thousands of chiral ligands with diverse structures have been applied to the catalytic asymmetric synthesis. Among the effective ligands, chiral phosphorus-based ligands are

the most common and useful in organic syntheses. The development of chiral phosphorus ligands in asymmetric transition metal catalysis will be briefly introduced.

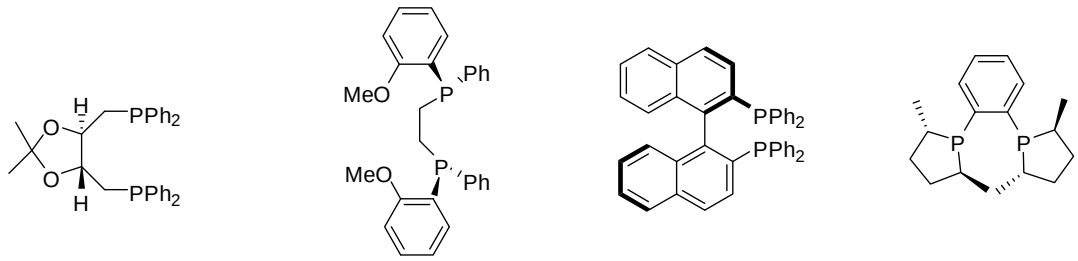
The first successful attempts of homogeneous metal-catalyzed asymmetric transformations involving chiral phosphorus ligands were made in the hydrogenation of carbon–carbon double bonds. In 1965, Wilkinson and co-workers reported the first homogeneous rhodium catalyst $RhCl(PPh_3)_3$ for hydrogenation of olefins.[3] In 1968, Horner suggested the application of chiral monodenate phosphanes for the asymmetric hydrogenation of prochiral olefins.[4] A few months later, Knowles et al. at Monsanto reported the use of rhodium complexes with the chiral ligands PAMP and CAMP for the asymmetric hydrogenation of atropic acid (**I-1**), affording hydratropic acid (**I-2**) with up to 15% ee.[5] (**Scheme I-1**) Although the enantioslectivity was moderate, the results encouraged chemists to develop more effective ligands for transition metal catalysis.



Scheme I-1 Asymmetric hydrogenation with PAMP and CAMP

The development of monodentate phosphorus ligands almost ceased at the time of its beginning. In 1971, Kagan et al. reported the first chiral bidentate diphosphane ligand, (*R*,*R*)-DIOP. The hydrogenation of (*Z*)-*N*-acetylaminocinnamic acid with the rhodium(I) complex of DIOP gave the desired product with almost quantitative conversion and 72% ee.[6] With the impressive success of DIOP ligand, bidentate ligands, especially C_2-

symmetrical diphosphorus ligands have become the dominated choices of ligands in the catalytic asymmetric transformations. In the following years, a large number of diphosphanes ligands were developed for asymmetric hydrogenation of different types of prochiral substrates containing C=C, C=O and C=N bonds.[7-9] Successful diphosphane ligands, including DIPAMP[10], BINAP[11] and DuPHOS[12] (**Figure I-1**) have also shown their efficacy in various other types of asymmetric reactions.



DIOP
Kagan, 1971

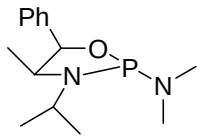
DIPAMP
Knowles, 1972

BINAP
Noyori, 1980

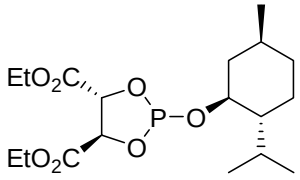
Du-PHOS
Burk, 1981

Figure I-1 Represnetative bidentate phosphane ligands

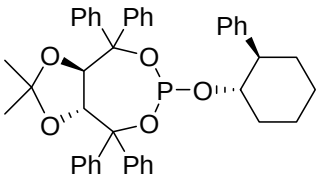
After sinking into almost complete oblivion for about thirty years, a revival of monodentate phosphorus ligands took place when easily prepared novel enantiopure ligands with P–O and/or P-N bonds revealed very promising results in various catalytic asymmetric transformations.[13-19] In 1993, Alexakis et al. reported the pioneering work on the use of a monodentate phosphorus ligand (**I-3**) based on chiral 1,2-hydroxylamine for the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone.[20-22] Although the enantioselectivity was only moderate (32% ee) at the beginning, this study disclosed a new choice of ligands for the copper-catalyzed conjugate addition reactions. This new trend of monodentate ligands has gained an increasing popularity and several new types of monodentate phosphorus ligands have been developed since then by Alexakis' and other groups (**Figure I-2**).



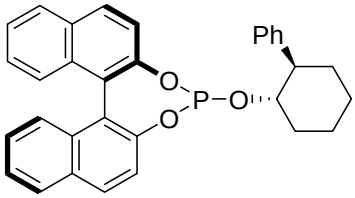
I-3, Alexakis 1993



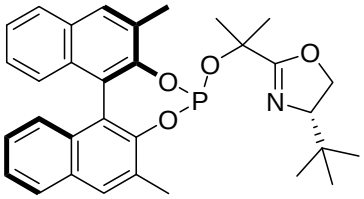
I-4, Alexakis 1997



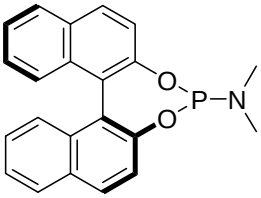
I-5, Alexakis 1998



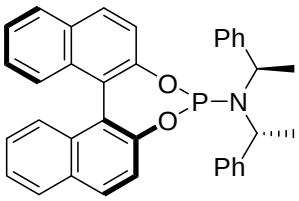
I-6, Alexakis 1999



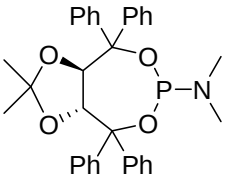
I-7, Pfaltz 1997



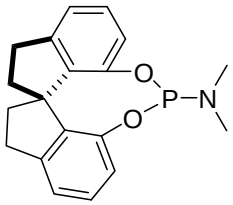
I-8, "MonoPhos"
Feringa 1996



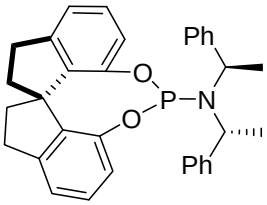
I-9, Feringa 1997



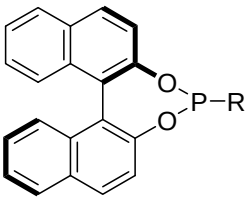
I-10, Feringa 1998



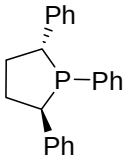
I-11, "SIPHOS"
Zhou 2002



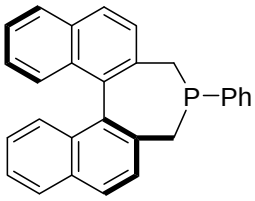
I-12, Zhou 2003



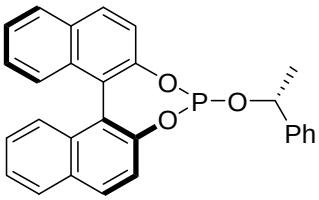
I-13a: R = *t*-Bu
I-13b: R = Et
Pringle 2000



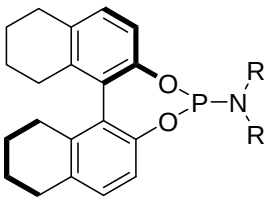
I-14, Fiaud
1999



I-15, Beller 2002



I-16, Reetz 2000



I-17a: R = Me
I-17b: R = Et
Chan 2002

Figure I-2 Representative monodentate phosphorus ligands

This large number of monodentate phosphorus ligands have been applied to a variety of metal catalyzed asymmetric reactions, e.g., hydrogenation,[14,17,22,23] 1,4-addition to enones,[16,18,24] hydrovinylation,[25] hydrosilylation,[26] intramolecular Heck reaction,[27] allylic alkylation,[28,29] amination[30] and etherification[31]. Most of these monodentate phosphorus ligands are derived from enantiomerically pure binaphthol (BINOL) or TADDOL.[32]

In the meantime, concept of modularity has also been introduced into the design of bidentate ligands. Various modular ligands have been developed and proved to be highly efficient in different asymmetric transformations, including hydrogenation,[33-35] allylic substitution,[36-39] etc..(**Figure I-3**)

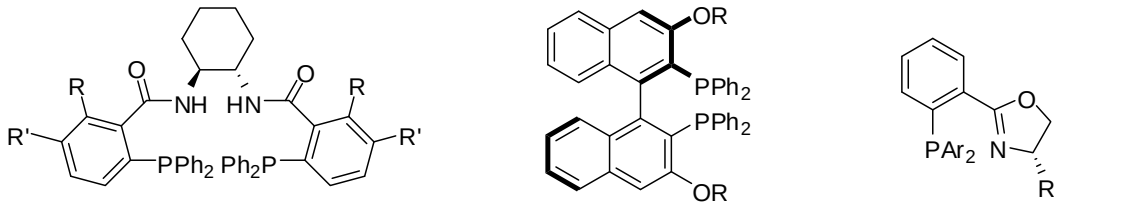


Figure I-3 Representative modular bidentate ligands

Synthetic chemists have come to realize that there are no universal ligands and catalysts for asymmetric transformations. In many cases, reactions are substrate-dependent and hence developing new ligands tailor-made to specific reaction types may turn out to be the most effective strategy to obtain high reactivity and enantioselectivity. For practical reasons, newly designed ligands need to be prepared easily, preferably in both enantiomeric forms. Catalysts derived from them should be both active and highly enantioselective. Following this trend, the development of fine-tunable phosphorus

ligands may not only provide best-fit ligands for specific asymmetric transformations, but also stimulate the understanding of new principles for chiral ligand design.

§1.3 Design of Fine-tunable Monodentate Phosphorus Ligands

In the course of our studies on monodentate phosphorus ligands, we focused on the syntheses and applications of monodentate ligands from enantiomerically pure biphenols with axial chirality (**Figure I-4**, only *S* isomer shown). These ligands include phosphite, phosphoramidite and phosphonite.

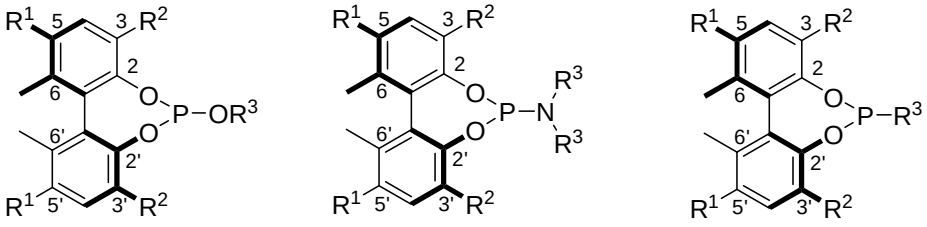


Figure I-4 Fine-tunable monodentate phosphorus ligands

The objective for the development of these new chiral ligands was to design a new class of readily accessible biphenol-based monodentate phosphorus ligands, the structures of which can be easily modified. It is believed that two molecules of monodentate phosphorus ligand will form the active catalyst complex *in situ* with one molecule of metal species. The catalyst complex arising from the monodentate ligands is considered to be more flexible than the one obtained from a bidentate ligand. Therefore, it is crucial for the monodentate ligands to have fine-tuning capability, which can play an important role to form appropriate catalyst complexes. What determines the most optimized structure of the ligands may vary with the substrates and the types of

asymmetric reactions.

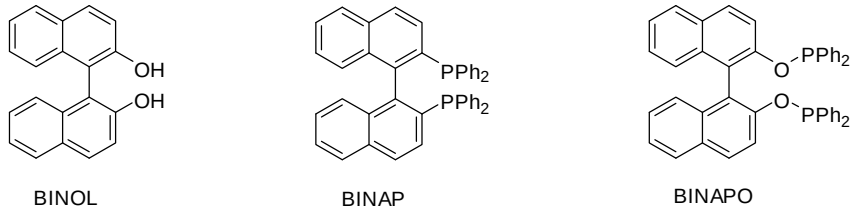
The designed ligands have two methyl groups at the 6 and 6' positions of the biphenol skeleton as the stereochemical "lock". The R^1 group at the 5 and 5' positions of the biphenol can be methyl, methoxy or a *tert*-butyl group having different electronic effects. The R^2 group at the 3 and 3' positions of the biphenol can be hydrogen, halogen, methyl, phenyl, isopropyl, *tert*-butyl, etc.. These different groups will exert different electronic and steric effects on the catalyst complex. The R^3 group can be chiral or achiral, alkyl or aryl groups. These types of monodentate phosphorus ligands are expected to have the fine-tuning capability through systematic modifications of R^1 and R^2 groups at the 3, 3', 5, 5', 6 and 6' positions of the biphenol moiety, and R^3 groups. This fine-tuning capability plays a crucial role in the applications to a variety of catalytic asymmetric transformations.

This wave of designing simple and modifiable chiral structures, which are easy to be synthesized, is fitting very well to the practical combinatorial approaches to develop the most suitable chiral ligand for a particular catalytic asymmetric process instead of a universally powerful chiral ligand for different types of catalytic asymmetric transformation.

§1.4 Introduction and Design of Fine-Tunable BINAPO Type Ligands

The design and synthesis of chiral ligands is of great importance in transition metal-catalyzed asymmetric transformations.[7,40] Among the design of chiral ligands, a large number of bidentate phosphorus ligands have proven to be effective in various

asymmetric reactions.[41] Generally, effective metal-complexes of the chiral bidentate phosphorus ligands as mentioned above bear 5, 6 or 7-membered rings.[42] There are only limited precedents where metal complexes with large chelating rings (8 or 9-membered rings) turned out to be effective.[43-47]



BINOL BINAP BINAPO

Figure I-5 Representatives of atropisomeric biaryl-based bidentate ligands

With the successful applications of BINAP ligands to transition metal catalysis, atropisomeric biaryls have become the most popular chiral scaffolds for design of effective chiral bidentate ligands (**Figure I-5**).[40] In 1977, Grubbs et al. reported the design and synthesis of chiral BINOL-based diphosphonite ligands, BINAPO, with the intention to offer an alternative choice of ligands for transition metal-catalyzed asymmetric hydrogenation processes.[43] BINAPO turned out to be not as effective as BINAP for asymmetric hydrogenation due to the conformational flexibility caused by the large chelating ring (9-membered ring) of metal-BINAPO complex. The plausible explanations for the observation are 1) the oxygen unit in the structure increases the distance between BINOL moiety and PAr_2 moieties, thus reducing the influence of chiral moiety to the orientation of PAr_2 moieties; 2) the oxygen unit also increase the flexibility of the structure in a C-O-P bond.

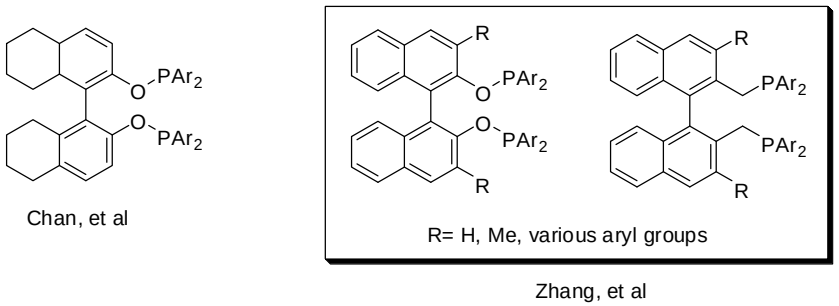


Figure I-6 Effectively modified BINAPO-type Ligands for asymmetric hydrogenation

To address the problems associated with BINAPO-type ligands in asymmetric hydrogenation, two groups have come up with different strategies to expand the scope of the applications. Chan et al. decided to use H_8-binaphthol instead of BINOL as the chiral skeleton (**Figure I-6**).[48,49] As the result of steric and electronic modulation of the BINOL moiety, the H_8-BINAPO did lead to higher efficiency and enantioselectivity compared to the original BINAPO ligand in certain asymmetric hydrogenation processes.[48,49] Zhang et al. chose to introduce substituents on the 3, 3' positions of the BINOL moiety, with the intention to improve the conformational rigidity, thus having better control of the orientation of PAr_2 moiety (**Figure I-6**).[50,51] The 3, 3' moidified BINAPO ligands turned out to be much better than the original BINAPO ligands in several asymmetric hydrogenation processes.[50,51]

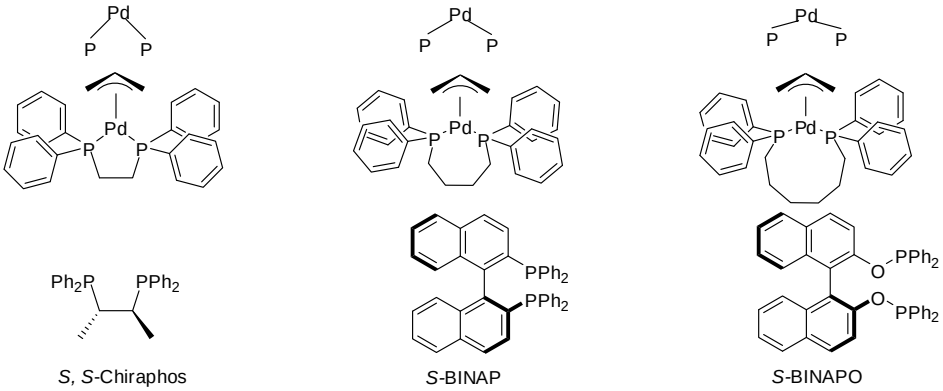
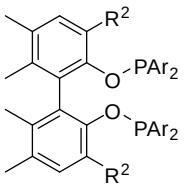


Figure I-7 Schematic model for chiral barriers

On the other hand, BINAPO ligand has also proven to be effective in Pd-catalyzed allylic substitution reactions.[44-47] Despite the formation of a larger chelating ring of a metal-ligand complex, BINAPO was found to be a superior ligand than BINAP in asymmetric allylic substitutions due to the larger bite angel (P-M-P), which increases the influence of sterically hindrant moieties to improve the chiral environment around an allylic moiety, as illustrated in **Figure I-7**. However, no ee greater than 95% has been reported so far, possibly because of the limitation in the conformational rigidity.

To address this problem, a new class of BINAPO-type diphosphonite ligands based on the 3,3'-disubstituted chiral biphenols developed in our lab has been designed. We hope that, with the introduction of proper substituents at the 3 and 3' positions of the biphenol moiety, the conformational rigidity can be greatly improved, thus making them superior ligands in the Pd-catalyzed asymmetric allylic substitution reactions (**Figure I-8**). In this design, a variety of substituents, including H, Me, Br, Ph, Bn, CH_2Ar, etc., will be introduced to the 3,3'-positions of the biphenol moiety. The Ar groups on the phosphine moieties can also be modified to adjust the steric influence. The applications of the newly designed diphosphonite ligands to asymmetric allylic substitutions will be discussed in Chapter V.



R^2= H, Me, Br, Ph, t-Bu, CH_2Ar, etc.

Ar= Ph, p-Tolyl, 3,5-m-Xylyl, etc.

Figure I-8 Design of 3, 3'-disubstituted-biphenol-based diphosphonite ligands

Chapter II

Synthesis of Enantiomerically Pure Biphenols

§2.1 Introduction

In the course of investigating the fine-tunable monodentate phosphorus ligands (phosphite, phosphoramidite, phosphonite) from enantiopure biphenols for catalytic asymmetric reactions, We focused on the modifications of the chiral biphenols at the 3 and 3' positions, i.e., R^2 group in the general structure of ligands described in Chapter I, wherein R^2 can be H, Me, Br, *t*-Bu, Ph, CH_2Ar, C≡CPh, etc. (**Figure II-1**).

(*S*)-**II-1** (*R*)-**II-1**

R^2 = H, Me, Br, Ph, *t*-Bu, etc.

Figure II-1 Enantiomerically pure biphenols

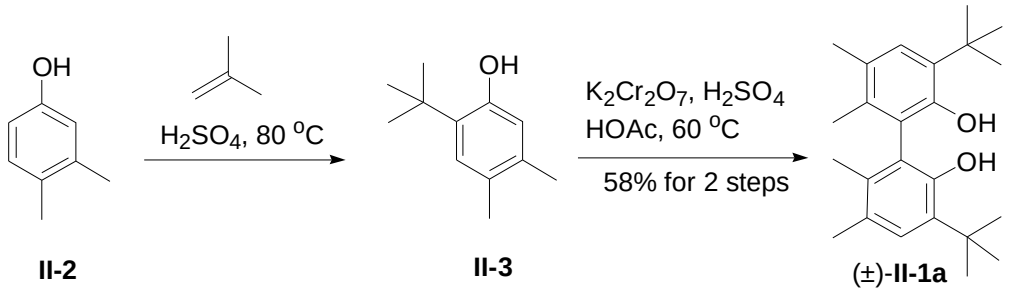
The racemic 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-2,2'-biphenol (**II-1a**) can be readily synthesized from commercially available materials, and both *R* and *S* enantiomers can be efficiently resolved by following the literature methods.[52] Starting from enantiopure biphenols (*S*)-**II-1a** and (*R*)-**II-1a**, a series of enantiopure biphenols having

different R^2 group (i.e., H, Me, Br, Ph, t-Bu, CH_2Ar, C≡CAr, etc..) at the 3 and 3' positions were prepared.[53]

§2.2 Results and Discussion

§2.2.1 Synthesis of Enantiopure 3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol

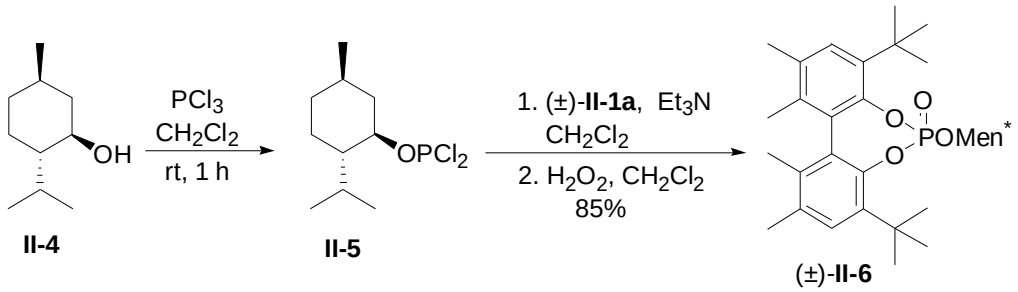
Racemic 3,3'-di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diols ((±)-**II-1a**) were prepared from 3,4-dimethylphenol (**II-2**) in two steps using literature procedures with slightly modified.[52] Treatment of 3,4-dimethylphenol (**II-2**) at 80 °C under 20 psi of 2-methylpropene in the presence of a catalytic amount of sulfuric acid gave **II-3** as crude product, which was converted to the desired biphenol (±)-**II-1a** by oxidative coupling with potassium dichromate in a mixture of acetic acid and sulfuric acid at 60 ^oC. The product was purified by washing with water and methanol to give (±)-**II-1a** as a white solid in 58% overall yield (**Scheme II-1**).



Scheme II-1 Synthesis of racemic biphenol (±)-**II-3**[52]

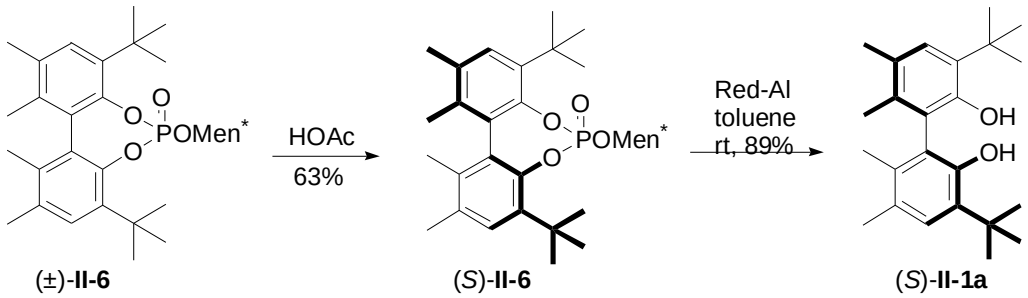
Enantiomerically pure biphenols were prepared via optical resolution through readily prepared phosphate with (-)-menthol.[1] (-)-Menthyl dichlorophosphite (**II-5**) was prepared by addition of (-)-menthol (**II-4**) to a dichloromethane solution of excess phosphorous trichloride followed by removal of the solvent and excess phosphorous

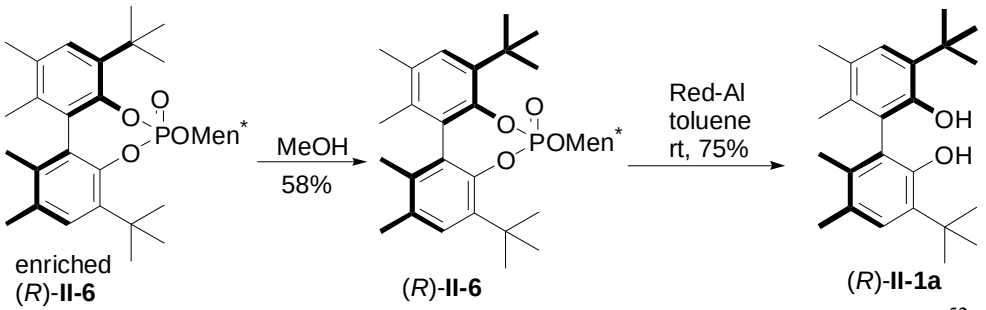
trichloride under reduced pressure. Addition of a mixture of (±)-**II-1a** and triethylamine to the dichloromethane solution of crude **II-5** followed by treatment with hydrogen peroxide afforded a diastereomeric mixture of phosphates (±)-**II-6** (**Scheme II-2**).



Scheme II-2 Synthesis of diastereomeric phosphate (±)-**II-6**[52]

Phosphate (*S*)-**II-6** was selectively crystallized from acetic acid with >99% de by ^{31}P NMR. The acetic acid mother liquor was evaporated to give a solid enriched with (*R*)-**II-6**. The solid residue was then recrystallized from methanol twice to give phosphate (*R*)-**II-6** with >99% de by ^{31}P NMR. Red-Al® reduction of the resolved phosphates (*S*)-**II-6** and (*R*)-**II-6** afforded enantiomerically pure biphenol (*S*)-**II-1a** and (*R*)-**II-1a**, respectively. The biphenol products were easily purified by trituration using cold methanol (**Scheme II-3**).

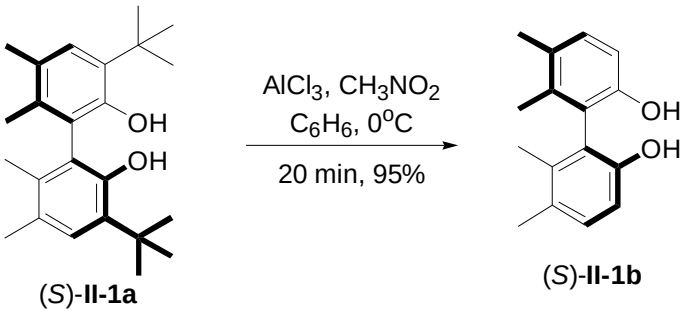




Scheme II-3 Synthesis of enantiopure biphenols (*S*)-**II-1a** and (*R*)-**II-1a**[52]

§2.2.2 Synthesis of Enantiopure 5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol

The *tert*-butyl group at the 3 and 3' positions of (*S*)-**II-1a** can be removed by treatment with aluminum trichloride in nitromethane-benzene via a Friedel-Crafts transfer reaction to provide biphenol (*S*)-**II-1b** without any loss of enantiopurity (**Scheme II-4**).[3] (*R*)-**II-1b** was obtained in identical yield following the same procedure. Then, a series of enantiopure biphenols having different groups at the 3 and 3' positions were prepared from **II-1b** as the common intermediate.

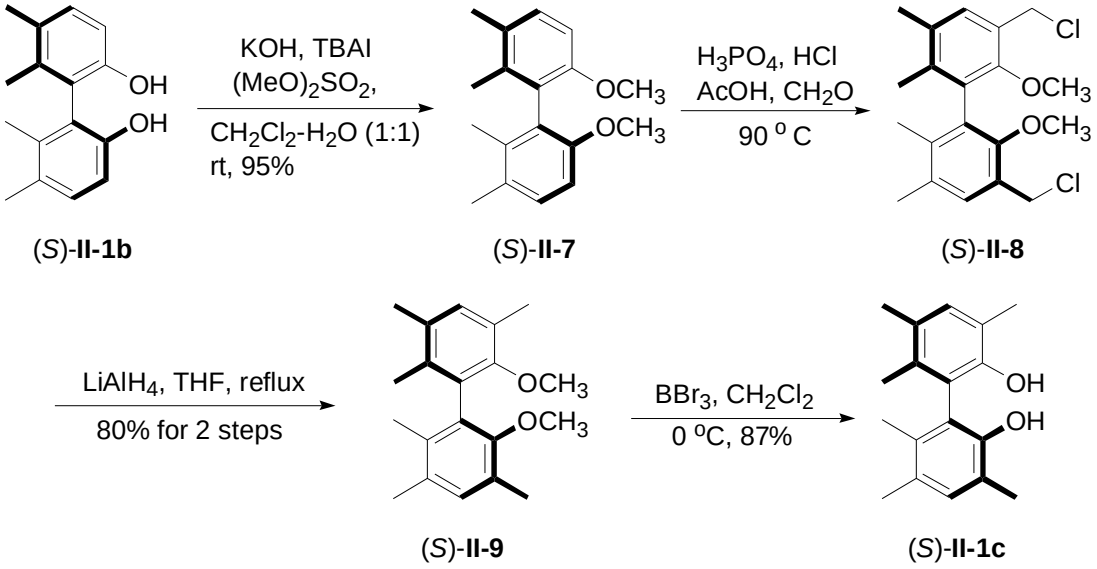


Scheme II-4 Synthesis of biphenol (*S*)-**II-1b**[53]

§2.2.3 Synthesis of Enantiopure 3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diol

Enantiomerically pure biphenol (*S*)-**II-1c** was synthesized from (*S*)-**II-1b** as shown in **Scheme II-5**. (*S*)-**II-7** was prepared through methylation of (*S*)-**II-1b** with dimethyl sulfate in the presence of potassium hydroxide and tetrabutylammonium iodide

(TBAI) in excellent yield. Subsequently, (*S*)-**II-7** was chloromethylated at the 3 and 3' positions to give crude (*S*)-**II-8**, which was reduced with lithium aluminum hydride to afford (*S*)-**II-9** in 80% yield for two steps. Final deprotection of (*S*)-**II-9** with boron tribromide gave the desired enantiopure biphenol (*S*)-**II-1c** in 87% yield. (*R*)-**II-1c** was prepared from (*R*)-**II-1b** using the same protocols.[53]

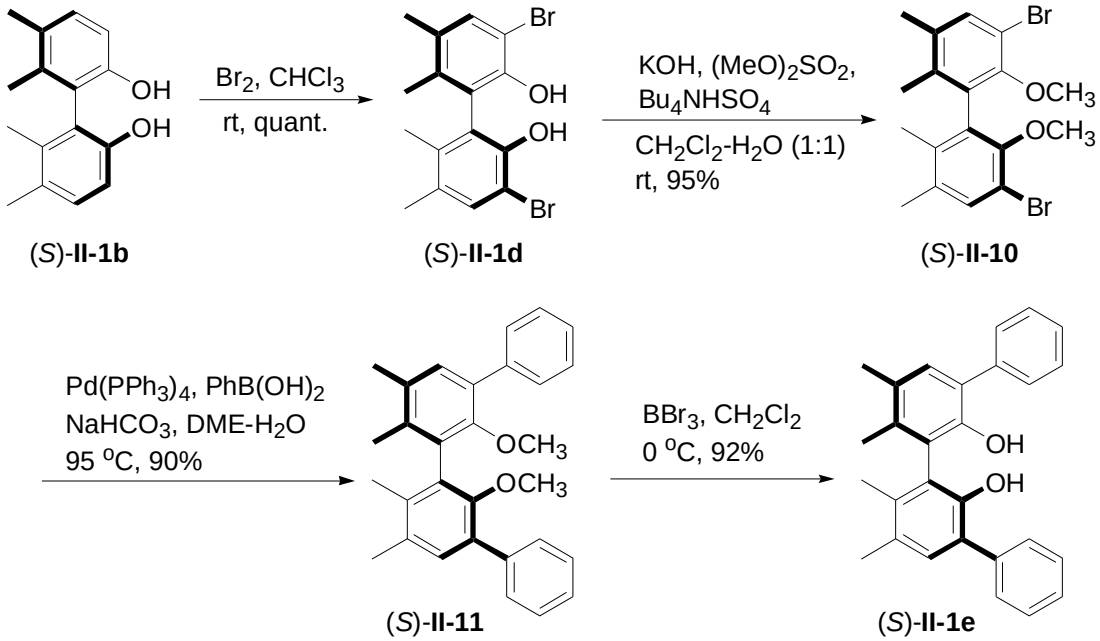


Scheme II-5 Synthesis of biphenol (*S*)-**II-1c**[53]

§2.2.4 Synthesis of Enantiopure 3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl -2,2'-diol and 3,3'-Diphenyl-5,5',6,6'-tetramethyl -1,1'-bi phenyl-2,2'-diol

Enantiomerically pure (*S*)-3,3'-dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl -2,2'-diol ((*S*)-**II-1d**) was synthesized from (*S*)-**II-1b** via bromination in quantitative yield. The attempted synthesis of **II-1e** through direct Suzuki coupling of unprotected **II-1d** with phenylboronic acid under several reported procedures for Suzuki coupling reaction gave the desired product **II-1e** in very low yield. Alternatively, biphenol (*S*)-**II-1d** was methylated with dimethyl sulfate to afford (*S*)-**II-10**, which was then submitted to a

Suzuki coupling with phenylboronic acid catalyzed by $Pd(PPh_3)_4$ to give (*S*)-**II-11**in 90% yield.[2] Subsequent removal of the methyl group with boron tribromide proceeded smoothly to give biphenol (*S*)-**II-1e** in 92% yield (**Scheme II-6**). (*R*)-**II-1d** and (*R*)-**II-1e** were also prepared from (*R*)-**II-1b** following the same procedure.[53]

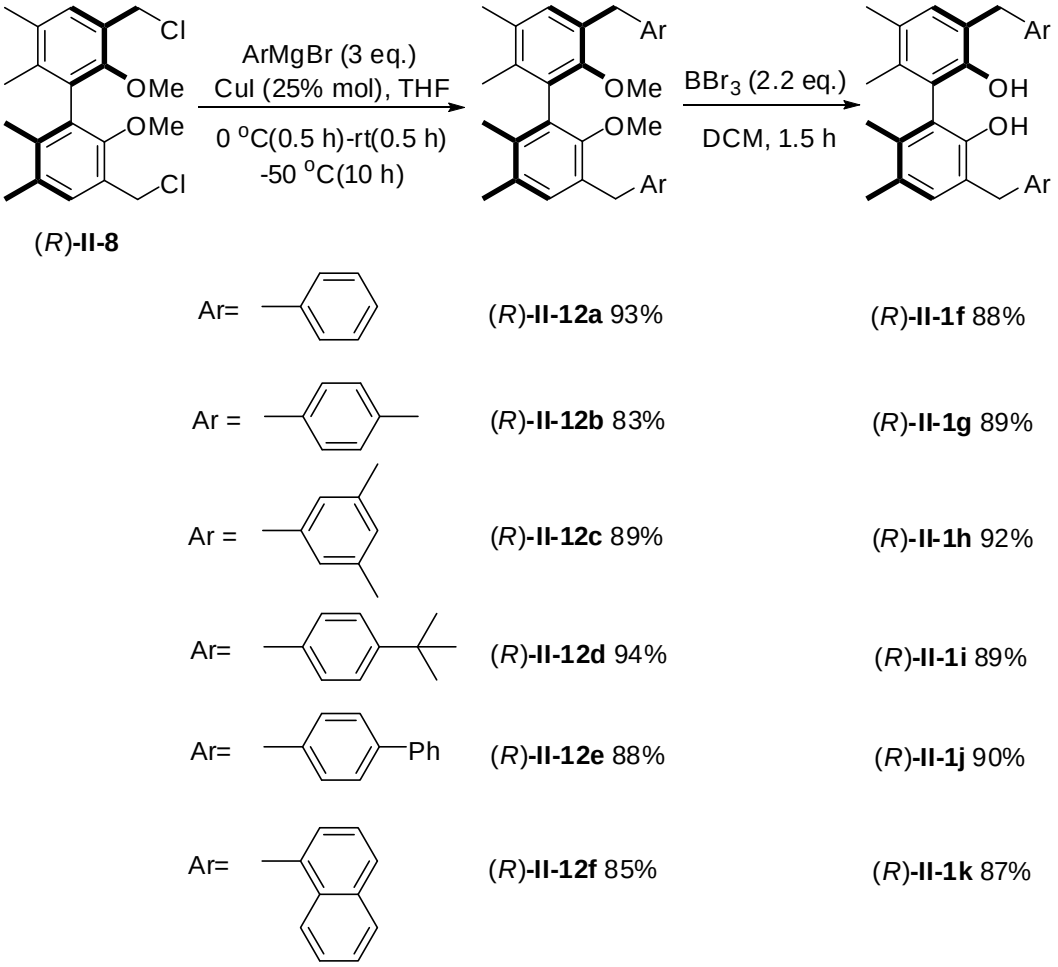


Scheme II-6 Synthesis of biphenols (*S*)-**II-1d** and (*S*)-**II-1e**[53]

§2.2.5 Synthesis of (*R*)-3,3'-Bis(substituted-benzyl)-5,5',6,6'-tetramethyl-1,1'-biphen -yl-2,2'-diols

Starting from the chloromethlated intermediate (*R*)-**II-8,** (*R*)-3,3'-bis(substituted benzyl)-2,2'-dimethoxy-5,5',6,6'-tetramethylbiphenyl intermediates (*R*)-**II-12a-f** were obtained under cross-coupling conditions using CuI and the corresponding aryl Grignard reagents generated *in situ*, giving (*R*)-**II-12a** (93%), (*R*)-**II-12b** (83%), (*R*)-**II-12c** (89%), (*R*)-**II-12d** (94%), (*R*)-**II-12e** (88%) and (*R*)-**II-12f** (85%) isolated yields respectively.[54] Subsequent removal of the methyl group with boron tribromide proceeded smoothly to give biphenols (*R*)-**II-f-k** in 88%, 89%, 92%, 89%, 90% and 87% isolated

yields respectively. (**Scheme II-7**)

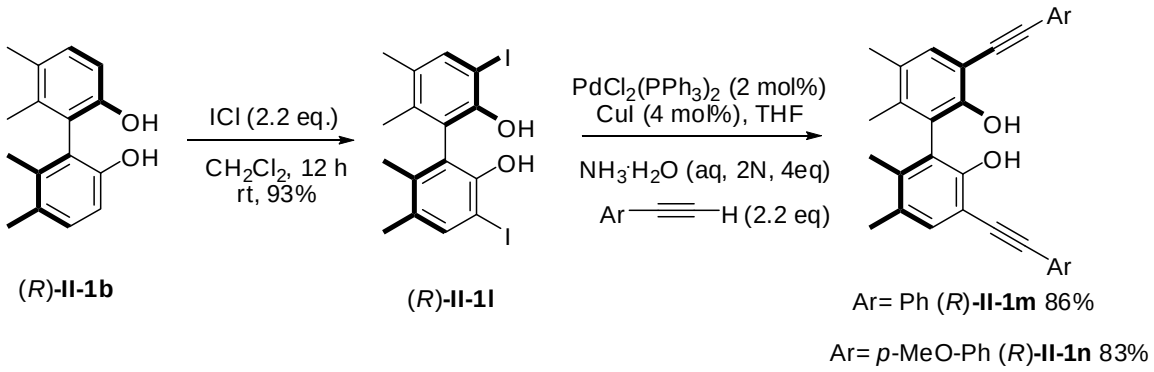


Scheme II-7 Synthesis of biphenols (*R*)-**II-1f-k**

§2.2.6 Synthesis of (*R*)-3,3'-Diiodo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol and (*R*)-5,5',6,6'-Tetramethyl-3,3'-bis(arylethynyl)-1,1'-biphenyl-2,2'-diols

Enantiomerically pure (*R*)-3,3'-diiodo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((*R*)-**II-1l**) was synthesized from (*R*)-**II-1b** using ICl as the iodination reagent in 93% isolated yield. The synthesis of (*R*)-**II-1m/n** through direct Sonogashira coupling of unprotected (*R*)-**II-1l** with aryl acetylenes using aqueous ammonia solution as the activator turned out to be an efficient process, giving the desired product (*R*)-**II-1m** and

(*R*)-**II-1n** in 86% and 83% isolated yields respectively.[55] (**Scheme II-8**)



Scheme II-8 Synthesis of biphenols (*R*)**-II-1l,** (*R*)-**II-1m** and (*R*)-**II-1n**

In conclusion, a series of enantiomerically pure 5,5',6,6'-tetramethyl -2,2'-biphenols having different substituents (i.e., H, Me, Br, Ph, *t*-Bu, CH_2Ar, C≡CAr) at the 3 and 3' positions were prepared efficiently. These axially chiral biphenols were used in the development of libraries of fine-tunable monodentate and bidentate phosphorus ligands for catalytic asymmetric reactions as described in the following chapters.

§2.3 Experimental Section

General Method. ^{1}H, ^{31}P and ^{13}C NMR spectra were measured on a Varian Inova-400 NMR (^{1}H, 400 MHz; ^{13}C, 100 MHz; ^{31}P, 162 MHz) or a Varian Gemini-2300 (^{1}H, 300 MHz; ^{13}C, 75 MHz; ^{31}P, 121 MHz) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P, 0.0 ppm). Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was

performed on Merck DC-alufolien with Kieselgel 60F-254 and column chromatography was carried out on silica gel 60 (Merck; 230-400 mesh ASTM).

Materials. All solvents used as reaction media were purified using the Manual Solvent Purification System purchased from Innovative Technology Inc.. Solvents for extraction and chromatography were reagent grade and used as received. Chemicals and reagents were purchased from Aldrich or Fischer Scientific, and were used without further purification unless otherwise noted.

2-*tert*-Butyl-4, 5-dimethylphenol (**II-3**):[52]

A 300 mL autoclave with a glass liner and stirring bar was charged with 3,4-dimethylphenol (**II-2**) (81 g, 0.66 mol) and concentrated H_2SO_4 (0.5 mL), and the autoclave was pressurized with 2-methylpropene (20 psi) and heated with stirring at 80 ^oC for 6 h. The autoclave was cooled to room temperature and the contents were analyzed by GC-MS (until no **II-2** observed). The resulting brown oil (containing oligomer of 2-methylpropene) was used directly for the next step without further purification.

3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol ((±)-**II-1a**):[52]

Potassium dichromate (60 g, 0.204 mol) in sulfuric acid (120 mL) and water (400 mL) (Hot solution!) was carefully added over a period of 10 min to an acetic acid (650 mL) solution of 3,4-dimethyl-2-*tert*-butylphenol (**II-3**) (crude product from the previous step). The reaction was exothermic and temperature reached 60 °C. The color changed from orange to green and a tan precipitate formed. The reaction mixture was stirred for

30 min at elevated temperature and then cooled to room temperature. The mixture was filtered, and the brown solid was washed with water (250 mL x 2) and methanol (200 mL x 3). The off-white solid was stirred in methanol at 0 ^{o}C, filtered, dried *in vacuo* to give (±) -**II-1a** as white solid (69 g, 58%) in two steps : ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 18H), 1.80 (s, 6H), 2.24 (s, 6H), 4.79 (s, 2H), 7.12 (s, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 16.4, 20.5, 30.19, 35.2, 121.6, 128.8, 127.7, 134.1, 134.6, 151.2. All data were consistent with literature results.[52]

Preparation and Resolution of Phosphate (*R*)**-II-6 and** (*S*)**-II-6**:[52]

A solution of (1*R*,2*S*,5*R*)-(-)-menthol (**II-4**) (44 g, 282 mmol) in CH_2Cl_2(80 mL) was added to a solution of (58 g, 423 mmol) in CH_2Cl_2 (160 mL) over 30 min at 0 °C. The ice bath was removed and the mixture was stirred for 1 h at room temperature. The volatiles were removed *in vacuo*. The resultant oil (**II-5**) was redissolved in CH_2Cl_2 (150 mL) and a solution of Et_3N (118 mL, 847 mmol) and (±)-**II-1a** (100 g, 282 mmol) in CH_2Cl_2 (300 mL) was added over 30 min. After stirring at room temperature for 2 h the white solid was filtered off and the solution was cooled to 0 ^{o}C. To this solution was added H_2O_2 (35% in water, 172 mL) slowly (CAUTION: extremely vigorous reaction) with stirring. The biphasic mixture was stirred for 2 h and then the layers were separated. The organic layer was washed with water and brine (200 mL) and dried over anhydrous $MgSO_4$. The solution was filtered and then concentrated under vacuum to give an off-white solid. The solid was dried *in vacuo* to afford (±)-**II-6** (124 g, 85%). ^{31}P NMR (121.5 MHz, C_6D_6) (*S*)-**II-6**: -2.86; (*R*)-**II-6**: -4.31. All data were consistent with literature results.[52]

The diastereomeric mixture of phosphates ((±)-**II-6**) was dissolved in a minimum amount of hot acetic acid (~300 mL). After standing at room temperature overnight, white crystals formed. These were collected by filtration and washed with cold acetic acid (50 mL x 2). The solid was then dried *in vacuo* to give (*S*)-**II-6** (56 g, 93% de). This solid was recrystallized from hot acetic acid again affording pure (*S*)-**II-6** (49.5 g, >99% de, 63%).The mother liquor from the first crystallization was concentrated *in vacuo* to give a solid enriched with (*R*)-**II-6**. This solid was recrystallized from MeOH (260 mL) to give pure (*R*)-**II-6** as white crystals (42.2 g, >99% de, 54%).

(*S*)-**3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-diphenyl-2,2'-diol** ((*S*)-**II-1a**):[52]

Resolved (*S*)-**II-6** (42.11 g, 75.93 mmol) was dissolved in toluene (340 mL) in a two-necked flask equipped with an addition funnel. Red-Al® (54.6 mL, 70 % wt. in toluene) was added into the addition funnel and then added dropwise to the phosphate solution at 0 °C. The reaction was stirred at room temperature for 16 h and then carefully quenched with water (80 mL) and bleach (80 mL). The slurry was filtered through Celite®, the pad was washed with toluene (250 mL), and the layers were separated. The toluene layer was washed with bleach and brine (200 mL each) and then dried over anhydrous $MgSO_4$. The drying agent was removed by filtration and the toluene was evaporated under reduced pressure to give a white solid. The menthol was removed by repeated washing with cold MeOH until the minty odor disappeared. The (*S*)-**II-1a** was collected by filtration and dried *in vacuo* (24.12 g, 89%, >99% ee). The enantiomeric purity of (*S*)-**II-1a** was determined on the basis of ^{31}P NMR spectra of the phosphite

derivative of (*S*)-**II-1a** with (-)-menthol. (*S*)-**II-1a**: mp 165.0-167.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 18H), 1.80 (s, 6H), 2.24 (s, 6H), 4.79 (s, 2H), 7.12 (s, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 16.3, 20.5, 30.2, 35.2, 121.6, 128.8, 127.7, 134.1, 134.6, 151.2. All data were consistent with literature results.[52]

(*R*)-**3,3'-Di-*tert*-butyl-5,5',6,6'-tetramethyl-1,1'-diphenyl-2,2'-diol** ((*R*)-**II-1a**):[52]

The preparation of (*R*)-**II-1a** from (*R*)-**II-6** followed an identical procedure: 75% yield; mp 165.0-166.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 18H), 1.80 (s, 6H), 2.24 (s, 6H), 4.79 (s, 2H), 7.12 (s, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 16.4, 20.5, 30.2, 35.2, 121.6, 128.8, 127.7, 134.1, 134.6, 151.2. All data were consistent with literature results.[53]

(*S*)-**5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol** ((*S*)-**II-1b**): [53]

To a solution of (*S*)-**II-1a** (5.53 g, 15.6 mmol) in C_6H_6 (80 mL) at 0 ^{o}C, $AlCl_3$ (3.33 g, 25.0 mmol) in C_6H_6 (15 mL) and CH_3NO_2 (30 mL) were added dropwise by cannula over 30 min. The mixture was stirred at 0 ^{o}C for 20 min. The reaction was quenched by addition of water. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to give the crude product, which was recrystallized from hexanes-CH_2Cl_2 (5:1) to afford (*S*)-**II-1b** as a white solid (3.49 g, 92%): mp 198.5-200.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 6H), 2.26 (s, 6H), 4.52 (s, 2H), 6.82 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 20.0, 112.8, 120.4, 129.4, 131.5, 137.1, 152.0; All data were consistent with literature results. [53]

(*R*)-**5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1b**): [53]

White solid; 92% yield; mp 200.0-201.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (s, 6H), 2.26 (s, 6H), 4.55 (s, 2H), 6.82 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.8, 112.6, 120.2, 129.2, 131.2, 136.9, 151.8. All data were consistent with literature results.[53]

(*S*)-**5,5',6,6'-Tetramethyl-2,2'-dimethoxy-1,1'-biphenyl** ((*S*)-**II-7**)**:** [53]

To a mixture of (*S*)-**II-1b** (0.49 g, 2.0 mmol), potassium hydroxide (0.33 g, 5.9 mmol) and tetrabutylammonium iodide (40 mg, 0.1 mmol) in CH_2Cl_2-water (26 mL, 1:1) was added dimethyl sulfate (0.57 mL, 6 mmol) and the biphasic mixture was stirred at room temperature overnight. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water (30 mL), ammonium hydroxide (30 mL) and brine (30 mL), and dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:ethyl acetate = 10:1) to afford (*S*)-**II-7** as a white solid (0.46 g, 86%): mp 111.0-112.0 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.26 (s, 6H), 3.66 (s, 6H), 6.74 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 16.4, 20.0, 55.9, 108.1, 126.8, 128.5, 128.9, 136.4, 155.2. All data were consistent with literature results. [53]

(*S*)-**3,3'-Dichloromethyl-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl** ((*S*)-**II-8**): [53]

To a mixture of 85% H_3PO_4 (16 mL), concentrated HCl (16 mL), glacial acetic acid (16 mL) and (*S*)-**II-7** (1.74 g, 6.44 mmol) was added paraformaldehyde (4.25 g). The mixture was heated to 90 ^oC and stirred for 42 h. The solution was allowed to cool to room temperature and then extracted with benzene. The combined organic layers were washed with water, saturated Na_2CO_3 and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford crude (*S*)-**II-8** as a white solid, which was pure enough for the next step: mp 98.0-101.0 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 6H), 2.30 (s, 6H), 3.38 (s, 6H), 4.58 (d, *J*= 11.0 Hz, 2H), 4.81(d, *J*= 11.2 Hz, 2H), 7.27 (s, 1H), 7.37 (s, 1H); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 16.9, 20.2, 41.7, 60.9, 127.9, 128.2, 131.2, 131.4, 132.7, 137.4, 154.0. All data were consistent with literature results. [53]

(*S*)-**3,3',5,5',6,6'-Hexamethyl-2,2'-dimethoxy-1,1'-biphenyl** ((*S*)-**II-9**)**:** [53]

To a stirred suspension of $LiAlH_4$ (0.64 g, 16.9 mmol) in THF (8 mL) was added a solution of (*S*)-**II-8** in THF (16 mL) dropwise. The stirred mixture was refluxed for 3.5 h and then cooled to 0 ^oC. The reaction was carefully quenched with THF/water (6 mL, 3:1). The mixture was poured into a dilute solution of H_2SO_4 (8 mL, 1:1) and stirred for 30 min. The mixture was extracted with ether and the combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:ethyl acetate = 10:1) to afford (*S*)-**II-9** as a white solid (1.53 g, 80% yield for 2

steps): mp 74.0-75.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (s, 6H), 2.25 (s, 6H), 2.28 (s, 6H), 3.31 (s, 6H), 7.00 (s, 2H); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 16.1, 16.6, 20.1, 59.5, 127.4, 131.3, 131.5, 131.7, 133.4, 154.1. All data were consistent with literature results.[53]

(*R*)-**3, 3', 5, 5', 6, 6'-Hexamethyl-2, 2'-dimethoxy-1, 1'-biphenyl** ((*R*)-**II-9**): [53]

White solid; 65% yield for three steps; mp 76.0-77.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.24 (s, 6H), 2.24 (s, 6H), 3.33 (s, 6H), 7.00 (s, 2H); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 16.4, 16.8, 20.3, 59.8, 127.8, 131.7, 131.9, 132.0, 133.8, 154.1. All data were consistent with literature results.[53]

(*S*)-**3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diol** ((*S*)-**II-1c**)**:** [53]

To a solution of (*S*)-**II-9** (1.45 g, 4.87 mmol) in CH_2Cl_2 (2 mL) was added BBr_3 (10 mL, 1.0 M solution in CH_2Cl_2) with stirring at 0 °C. The mixture was stired at 0 °C for 1 h and then slowly quenched by addition of water. The reaction mixture was extracted with CH_2Cl_2 and then the combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:ethyl acetate = 10:1) to give (*S*)-**II-1c** as a white solid (1.14 g, 87%): mp 136.0-137.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.23 (s, 12H), 4.53 (s, 2H), 7.00 (s, 2H); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 15.8, 16.2, 19.7, 119.9, 121.3, 128.4, 132.6, 133.8, 149.8. All data were consistent with literature results.[53]

(*R*)-**3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1c**): [53]

White solid; 90% yield; mp 135.5-137.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 2.23 (s, 12H), 4.54 (s, 2H), 7.01 (s, 2H); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 16.1, 16.4, 20.0, 120.2, 121.7, 128.8, 133.0, 134.2, 150.1. All data were consistent with literature results.[53]

(*S*)-**3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol** ((*S*)-**II-1d**):[53]

To a solution of (*S*)-**II-1b** (3.47 g, 14.3 mmol) in $CHCl_3$ (100 mL), was added Br_2 (1.7 mL, 32.2 mmol) in $CHCl_3$ (20 mL) dropwise over 20 min. The mixture was stirred at room temperature for 1 h. The reaction was quenched by saturated aqueous Na_2SO_3. The layers were separated and the aqueous layer was extracted with Et_2O, the combined organic layers were washed with water and brine and then dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to afford (*S*)-**II-1d** as an off-white solid (5.71 g, 99.7%): mp 171.0-172.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.25 (s, 6H), 5.11(s, 2H), 7.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 20.0, 106.9, 123.7, 130.8, 133.0, 136.8, 148.0. All data were consistent with literature results.[53]

(*R*)-**3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1d**): [53]

White solid; mp 172.0-173.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.25(s, 6H), 5.11(s, 2H), 7.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.1, 106.8, 123.6, 130.9, 133.1, 136.7, 148.1. All data were consistent with literature results.[53]

(*S*)-**3,3'-Dibromo-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl** ((*S*)-**II-10**):[53]

To a mixture of (*S*)-**II-1d** (5.60 g, 14.0 mmol), KOH (2.41 g, 42.0 mmol) and Bu_4NHSO_4 (515 mg, 1.4 mmol) in CH_2Cl_2-H_2O (100 mL, 1:1) was added dimethyl sulfate (3.92 mL, 42.0 mmol) dropwise. The biphasic mixture was stirred at room temperature overnight. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solution was concentrated under reduced pressure and the resulting crude product was triturated with methanol to afford (*S*)-**II-10** as a white solid (5.68 g, 94.8%): mp 150.0-151.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 6H), 2.26 (s, 6H), 3.50 (s, 6H), 7.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 20.1, 60.5, 113.9, 133.2, 133.6, 134.2, 136.0, 152.7. All data were consistent with literature results.[53]

(*R*)-**3,3'-Dibromo-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl** ((*R*)-**II-10**): [53]

White solid; 95% yield; mp 150.5-152.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 2.26 (s, 6H), 3.50 (s, 6H), 7.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 20.2, 60.6, 114.0, 133.3, 133.7, 134.4, 136.1, 152.7. All data were consistent with literature results.[53]

(*S*)-**3,3'-Diphenyl-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl** ((*S*)-**II-11**)**:** [53]

A suspension of (*S*)-**II-10** (1.18 g, 2.76 mmol) and $Pd(PPh_3)_4$ (191 mg, 0.17 mmol) in DME (25 mL) was stirred at room temperature for 30 min to give a light green solution. To this solution was added a mixture of $C_6H_5B(OH)_2$ (741 mg, 6.08 mmol) and $NaHCO_3$ (1.39 g, 16.56 mmol) in water (16 mL). The mixture was heated to reflux with stirring

and maintained at this temperature for 16 h. The reaction mixture was cooled to room temperature and diluted with ether. The organic layer was separated and washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:EtOAc = 15:1) to afford (*S*)-**II-11** (0.96 g, 82%) as a white solid: mp 56.5-58.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.33 (s, 6H), 3.19 (s, 6H), 7.18 (s, 2H), 7.30-7.42 (m, 6H), 7.60-7.63(m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 20.4, 60.4, 126.9, 128.4, 129.3, 131.5, 131.6, 132.2, 132.6, 135.7, 139.5, 153.5. All data were consistent with literature results.[53]

(*R*)-**3,3'-Diphenyl-5,5',6,6'-tetramethyl-2,2'-dimethoxy-1,1'-biphenyl** ((*R*)-**II-11**):[53]

White solid; 80% yield; mp 56.0-58.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 6H), 2.35 (s, 6H), 3.21 (s, 6H), 7.20 (s, 2H), 7.29-7.44 (m, 6H), 7.63-7.66 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 20.5, 60.5, 127.0, 128.5, 129.4, 131.6, 131.7, 132.3, 132.7, 135.9, 139.6, 153.6. All data were consistent with literature results.[53]

(*S*)-**3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol** ((*S*)-**II-1e**)**:** [53]

To a stirred solution of (*S*)-**II-11** (0.92 g, 2.17 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC was added BBr_3 (4.57 mL, 1.0 M solution in CH_2Cl_2) dropwise. The mixture was stirred at 0 ^oC for 1 h. The reaction was quenched by the slow addition of water. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:EtOAc = 5:1) to give (*S*)-**II-1e** (0.78 g, 91.2%) as white solid: mp

153.0-154.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 6H), 2.32 (s, 6H), 4.88 (s, 2H), 7.23 (s, 2H), 7.30-7.35 (m, 2H), 7.41-7.45 (m, 4H), 7.58-7.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 121.6, 125.6, 127.1, 128.4, 129.2, 129.3, 132.1, 136.4, 137.9, 148.4. All data were consistent with literature results.[53]

(*R*)-3,3'-Dibenzyl-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-II-12a):[54]

1.5 mL of phenyl Grignard solution in THF (1M, 3eq.) was added at 0 ^{o}C to a solution of the chloromethylated intermediate (*R*)-**II-8** (183 mg, 0.5 mmol, 1 eq.) in 5 ml THF containing CuI (24 mg, 0.125 mmol, 0.25 eq.) under nitrogen over 30 mins. The mixture was then warmed up to rt and kept stirred for additional 30 mins and at 50 ^{o}C for 10 h. The reaction mixture was then quenched with aqueous NH_4Cl solution (10 mL) and the mixture was extracted with CH_2Cl_2 (10 mL X 3). The combined organic layer was washed with water (20 mL) and brine (20 mL), and then dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (hexanes:EtOAc = 30:1 to 10:1) to afford (*R*)-**II-12a** (209 mg, 93%) as colorless oil. $[\alpha]_D^{22}$ +45.6 (CH_2Cl_2, *c* 0.8); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95 (s, 6H), 2.27 (s, 6H), 3.27 (s, 6H), 4.08 (q, *J*= 6.8 Hz, 4H)7.23 (s, 2H), 7.30-7.35 (m, 2H), 7.41-7.45 (m, 4H), 7.58-7.61 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 19.8, 121.6, 125.6, 127.1, 128.4, 129.2, 129.3, 132.1, 136.4, 137.9, 148.4. HRMS (EI) calcd. for $C_{32}H_{34}O_2$ $[M]^+$ 450.2559, found 450.2560 (Δ = + 0.1 ppm). Compounds (*R*)-**II-12b-f** were synthesized following the same protocol.

(*R*)-2,2'-Dimethoxy-5,5',6,6'-tetramethyl-3,3'-bis(4-methylbenzyl)-1,1'-biphenyl ((*R*)-

II-12b):

Colorless oil; 83% yield; $[\alpha]_D^{22}$ -160.8 (CH_2Cl_2, *c* 2.4);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.25 (s, 6H), 2.35 (s, 6H), 3.27 (s, 6H), 4.02 (q, *J*= 5.6 Hz, 4H), 6.95 (s, 2H), 7.13 (q, *J*= 8.0 Hz, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 20.1, 21.0, 35.3, 60.0, 128.8, 128.9, 129.0, 131.0, 131.1, 131.8, 134.3, 135.0, 138.6, 153.9; HRMS (ESI) calcd. for $C_{34}H_{39}O_2$ $[M+H]^+$ 479.2950, found 479.2932 (Δ = -3.8 ppm).

(*R*)**-3,3'-Bis(3,5-dimethylbenzyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl** ((*R*)**-II-12c**):

Colorless oil; 89% yield; $[\alpha]_D^{22}$ +140.1 (CH_2Cl_2, *c* 2.8);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.29 (s, 6H), 2.34 (s, 12H), 3.35 (s, 6H), 4.02 (S, 4H), 6.89 (s, 2H), 6.92 (s, 2H), 6.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5, 20.1, 21.3, 35.6, 60.0, 126.7, 127.3, 130.9, 131.1, 131.8, 131.9, 134.3, 137.5, 141.5, 154.0; HRMS (ESI) calcd. for $C_{36}H_{43}O_2$ $[M+H]^+$ 507.3263, found 507.3256 (Δ = -1.4 ppm).

(*R*)**-3,3'-Bis(4-*tert*-butylbenzyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl** ((*R*)**-II-12d**):

Colorless oil; 94% yield; $[\alpha]_D^{22}$ +7.3 (CH_2Cl_2, *c* 2.8);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.95 (s, 6H), 2.26 (s, 6H), 3.30 (s, 6H), 4.04 (q, *J*= 5.2 Hz, 4H), 6.98 (s, 2H), 7.20 (d, *J*= 11.6 Hz, 2H), 7.34 (d, *J*= 11.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 20.1, 31.4, 34.3, 35.1, 60.1, 125.1, 128.5, 130.9, 131.2, 131.8, 134.3, 138.5, 148.4, 154.1; HRMS (ESI) calcd. for $C_{40}H_{51}O_2$ $[M+H]^+$ 563.3889, found 563.3881

(Δ = -1.4 ppm).

(*R*)-**3,3'-Bis(4-phenyl-benzyl)-2,2'-dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl** ((*R*)-**II-12e**):

White foam; 88% yield; mp 66-68 ^{o}C; $[\alpha]_D^{22}$ +51.7 (CH_2Cl_2, *c* 1.0);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.25 (s, 6H), 3.27 (s, 6H), 4.08 (q, *J*= 4.4 Hz, 4H), 6.99 (s, 2H), 7.33 (m, 6H), 7.43 (m, 4H), 7.56 (d, *J*= 16.4 Hz, 4H), 7.59 (d, *J*= 16.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 20.2, 35.5, 60.1, 126.9, 127.0, 128.7, 129.3, 130.7, 131.2, 131.9, 132.0, 134.6, 138.6, 140.9, 141.1, 154.1; HRMS (ESI) calcd. for $C_{44}H_{43}O_2$ $[M+H]^+$ 603.3263, found 603.3278 (Δ = +2.5 ppm).

(*R*)-**1,1'-(2,2'-Dimethoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl-3,3'-diyl)bis(methylene) di-naphthalene** ((*R*)-**II-12f**):

Colorless oil; 85% yield; $[\alpha]_D^{22}$ +246.0 (CH_2Cl_2, *c* 0.4);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98 (s, 6H), 2.19 (s, 6H), 3.47 (s, 6H), 4.55 (q, *J*= 6.8 Hz, 4H), 6.87 (s, 2H), 7.37 (d, *J*= 6.8 Hz, 2H), 7.50 (m, 6H), 7.79 (d, *J*= 8.4 Hz, 2H), 7.90 (m, 2H), 8.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 20.1, 22.6, 60.3, 124.5, 125.3, 125.5, 125.8, 126.8, 126.9, 128.5, 130.2, 130.8, 131.8, 132.0, 132.3, 133.8, 134.4, 137.5, 153.7; HRMS (ESI) calcd. for $C_{40}H_{39}O_2$ $[M+H]^+$ 551.2950, found 551.2943 (Δ = -1.3 ppm).

(*R*)-**3,3'-Dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1f**):

To a stirred solution of (*S*)-**II-12a** (225 mg, 0.5 mmol) in CH_2Cl_2 (20 mL) at 0 ^{o}C was added BBr_3 (1.1 mL, 1.0 M solution in CH_2Cl_2) dropwise over 20 mins. The mixture

was stirred at 0 °C for 1.5 h. The reaction was quenched by the slow addition of water. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexanes:EtOAc = 15:1 to 5:1) to give (*R*)-**II-1f** (186 mg, 88% isolated yield) as colorless oil. $[\alpha]_D^{22}$ +141.7 (CH_2Cl_2, *c* 2.4);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 6H), 2.26 (s, 6H), 4.04 (q, *J*= 6.8 Hz, 4H), 4.69 (s, 2H), 7.00 (s, 2H), 7.24 (m, 4H), 7.33 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 35.8, 120.3, 124.7, 125.8, 128.3, 128.7, 128.8, 132.4, 134.7, 141.0, 149.5; HRMS (EI) calcd. for $C_{30}H_{30}O_2$ $[M]^+$ 422.2246, found 422.2248 (Δ = +0.2 ppm). Compounds (*R*)-**II-1g-k** were synthesized following the same protocol.

(*R*)-**5,5',6,6'-tetramethyl-3,3'-bis(4-methylbenzyl)-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1g**):

Colorless oil; 89% yield; $[\alpha]_D^{22}$ +13.6 (CH_2Cl_2, *c* 2.2);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (s, 6H), 2.22 (s, 6H), 2.34 (s, 6H), 3.96 (q, *J*= 5.2 Hz, 4H), 4.63 (S, 2H), 6.97 (s, 2H), 7.13 (q, *J*= 11.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 21.0, 35.4, 120.4, 124.9, 128.6, 128.8, 129.0, 132.3, 134.5, 135.2, 138.0, 149.5; HRMS (ESI) calcd. for $C_{32}H_{35}O_2$ $[M+H]^+$ 451.2637, found 451.2642 (Δ = +1.1 ppm).

(*R*)-**3,3'-bis(3,5-dimethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1h**):

White foam; 92% yield; mp 48-50 °C; $[\alpha]_D^{22}$ -131.1 (CH_2Cl_2, *c* 2.5);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.27 (s, 6H), 2.33 (s, 12H), 3.97 (q, *J*= 8.4 Hz, 4H), 4.69 (s,

2H), 6.88 (s, 2H), 6.92 (s, 4H), 7.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 21.3, 35.6, 120.4, 124.8, 126.5, 127.5, 128.8, 132.4, 134.5, 137.7, 140.9, 149.5; HRMS (ESI) calcd. for $C_{34}H_{39}O_2$ $[M+H]^+$ 479.2950, found 479.2955 (Δ = +1.0 ppm).

(*R*)-**3,3'-Bis(4-tert-butylbenzyl)-5,5',6,6'-tetramethylbiphenyl-2,2'-diol** ((*R*)-**II-1i**):

Colorless oil; 92% yield; $[\alpha]_D^{22}$ -9.1 (CH_2Cl_2, *c* 3.3);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.92 (s, 6H), 2.26 (s, 6H), 4.15 (q, *J*= 3.6 Hz, 4H), 4.69 (s, 2H), 7.03 (s, 2H), 7.23 (d, *J*= 11.2 Hz 4H), 7.36 (d, *J*= 11.2 Hz 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 19.7, 31.4, 34.3, 35.2, 120.4, 124.7, 125.3, 128.3, 128.8, 132.5, 134.6, 137.9, 149.5; HRMS (ESI) calcd. for $C_{38}H_{47}O_2$ $[M+H]^+$ 535.3576, found 535.3564 (Δ = -2.2 ppm).

(*R*)-**3,3'-Bis(biphenyl-4-ylmethyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1j**):

White foam; 90% yield; mp 81.5-83.5 ^{o}C; $[\alpha]_D^{22}$ -113.2 (CH_2Cl_2, *c* 2.0);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 6H), 2.27 (s, 6H), 4.07 (q, *J*= 6.8 Hz, 4H), 4.71 (s, 2H), 7.05 (s, 2H), 7.36 (m, 6H), 7.46 (t, *J*= 7.6 Hz, 4H), 7.56 (d, *J*= 8.0 Hz, 4H), 7.62 (d, *J*= 8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 19.7, 35.5, 120.4, 124.6, 126.9, 127.0, 127.1, 128.7, 129.0, 129.1, 132.5, 134.8, 138.8, 140.2, 141.1, 149.6; HRMS (ESI) calcd. for $C_{42}H_{39}O_2$ $[M+H]^+$ 575.2950, found 575.2955 (Δ = +0.9 ppm).

(*R*)-**5,5',6,6'-Tetramethyl-3,3'-bis(naphthalen-1-ylmethyl)-1,1'-biphenyl-2,2'-diol** ((*R*)-**II-1k**):

Colorless oil; 87% yield; $[\alpha]_D^{22}$ -268.4 (CH_2Cl_2, *c* 3.1);^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.93 (s, 6H), 2.15 (s, 6H), 4.47 (q, *J*= 20.4 Hz, 4H), 4.84 (s, 2H), 6.85 (s, 2H), 7.37 (d, *J*= 6.8 Hz, 4H), 7.48 (m, 6H), 7.79 (d, *J*= 8.0 Hz, 4H), 7.89 (m, 2H), 8.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 19.7, 32.4, 120.2, 124.1, 124.3, 125.5, 125.6, 125.8, 126.8, 126.9, 129.0, 132.1, 132.3, 133.9, 134.6, 136.9, 149.2; HRMS (ESI) calcd. for $C_{38}H_{35}O_2$ $[M+H]^+$ 523.2637, found 523.2619 (Δ = -2.0 ppm).

(*R*)-**3,3'-Diiodo-5,5',6,6'-tetramethylbiphenyl-2,2'-diol** ((*R*)-**II-1l**):

To a solution of (*R*)-**II-1b** (121 mg, 0.5 mmol, 1 eq) in 5 mL CH_2Cl_2 at rt, was added a solution of ICl (1.1 mL, 1M in CH_2Cl_2, 2.2 eq.) dropwise over 20 mins. The solution was then kept stirred for additional 12 h. The reaction was quenched by addition of saturated Na_2SO_3 solution (25 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (15 mL X 3). The combined organic layer was washed with water (30 mL), brine (30 mL) and dried over $MgSO_4$. The solution was concentrated *in vacuo* and the crude product was purified by flash chromatography on silica gel (hexanes:EtOAc = 30:1 to 15:1) to give (*R*)-**II-1l** (230 mg, 93%) as white solid. mp 213-214.5 ^{o}C; $[\alpha]_D^{22}$ +57 (CH_2Cl_2, *c* 0.05);^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (s, 6H), 2.22 (s, 6H), 2.23 (s, 6H), 4.95 (S, 2H), 7.56 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3, 19.4, 80.6, 122.1, 131.4, 137.6, 139.3, 150.4; HRMS (EI) calcd. for $C_{16}H_{16}I_2O_2$ $[M]^+$ 494.1060, found 494.1067 (Δ = +0.8 ppm).

(*R*)-**5,5',6,6'-Tetramethyl-3,3'-bis(phenylethynyl)biphenyl-2,2'-diol** ((*R*)-**II-1m**):[55]

To $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol), CuI (3.8 mg, 0.02 mmol), and iodinated biphenol (*R*)-**II-1l** (247 mg, 0.5 mmol) in 3 mL of THF was added phenylacetylene (0.12

mL, 1.1 mmol) at rt under nitrogen atmosphere. A 0.5 M solution of aqueous ammonia (4 mL, 2 mmol) was then added dropwise and stirring was continued for 12 h at room temperature. Two phases of the resulting mixture were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel (hexanes:EtOAc= 25:1 to 15:1) to furnish the desired product (*R*)-**II-1m** as white solid in 86% yield. mp 73-75 ^{o}C; $[\alpha]_D^{22}$ +132.2 (CH_2Cl_2, *c* 1.5);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (s, 6H), 2.29 (s, 6H), 5.53 (s, 2H), 7.35 (m, 8H), 7.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 20.0, 21.0, 84.3, 95.4, 107.1, 122.6, 123.1, 128.7, 129.2, 131.7, 132.4, 138.8, 152.3; HRMS (EI) calcd. for $C_{32}H_{26}O_2$ $[M]^+$ 442.1933, found 442.1933 (Δ = -0.0 ppm). Compound (*R*)-**II-1n** was synthesized following the same protocol.

(*R*)-**3,3'-Bis((4-methoxyphenyl)ethynyl)-5,5',6,6'-tetramethylbiphenyl-2,2'-diol** ((*R*)-**II-1n**):

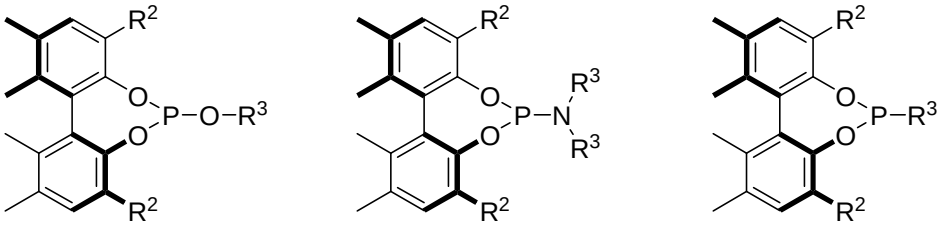
White solid; 83% yield. mp 112-113 ^{o}C; $[\alpha]_D^{22}$ +63.7 (CH_2Cl_2, *c* 0.5);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.95 (s, 6H), 2.27 (s, 6H), 3.82 (s, 6H), 5.53 (s, 2H), 6.87 (d, *J*= 12 Hz, 4H), 7.29 (s, 2H), 7.45 87 (d, *J*= 12 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 19.8, 55.3, 82.6, 95.2, 107.1, 114.0, 115.0, 122.3, 128.8, 132.0, 133.0, 138.1, 151.9, 159.7; HRMS (ESI) calcd. for $C_{34}H_{31}O_4$ $[M+H]^+$ 503.2222, found 503.2238 (Δ = +3.2 ppm).

Chapter III

Synthesis of Fine-Tunable Phosphorus Ligands

§3.1 Introduction

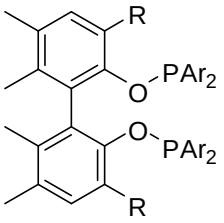
In the course of our ongoing research for the development of monodentate phosphorus ligands, libraries of monodentate phosphite, phosphoramidite and phosphonite ligands have been designed and synthesized from a series of enantiopure biphenols bearing different substituents (R^2) at the 3 and 3' positions, wherein the R^3 group is also varied with chiral or achiral groups (**Figure III-1**, only *S* biphenol shown). The fine-tuning capabilities rely on the easy and systematic modifications of the ligand structure. Substituents on the modifiable positions are usually in the vicinity of the catalytic center, thus are more inclined to play a critical effect on the catalytic reaction. The effectiveness of the monodentate ligands with different substitution pattern, especially on the 3,3' position of the biphenol moiety has been demonstrated in various transition-metal catalyzed asymmetric transformations.[53,56-60] In this chapter, the synthesis of the monodentate phosphoramidite ligands will be discussed exclusively.



Monophosphite **Monophosphoramidite** **Monophosphonite**

Figure III-1 Fine-tunable monodentate phosphorus ligands

In addition to the monodentate ligands, a small library of BINAPO-type diphosphonite ligands based on a series of enantiopure biphenols having different substituents (R^2) at the 3 and 3' positions (**Figure III-2**) have been designed and synthesized. The main purpose here is to provide a novel class of bidentate ligands which are effective in asymmetric allylic substitution reactions. The efficacy of the newly designed ligands has been demonstrated in different types of allylic amination reactions that are of importance to natural product synthesis, which will be discussed later in Chapter V.



R= H, Me, Br, Ph, t-Bu, CH_2Ar, etc.

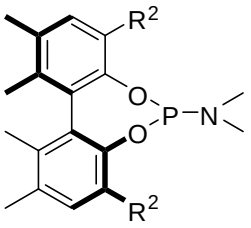
Ar= Ph, p-Tolyl, 3,5-m-Xylyl, etc.

Figure III-2 Fine-tunable bidentate diphosphonite ligands

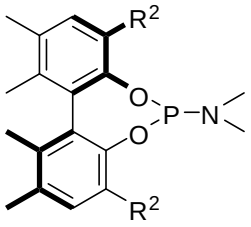
§3.2 Results and Discussion

§3.2.1 Monodentate Phosphoramidite Ligands

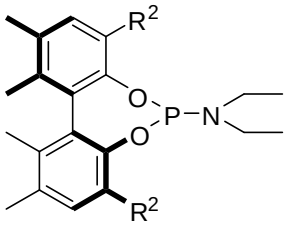
The monodentate phosphoramidite ligands prepared from the enantiomerically pure biphenols are shown in **Figure III-3**. Currently the modifications for ligands have been focused on the 3 and 3' substituents of the biphenol moiety and the amine moiety. As **Figure III-3** shows, H, Me, Br, Ph, Bn, *t*-Bu, TES and C≡CR (R= TMS or Ph) have been used as the substituents at the 3 and 3' positions of the biphenol moiety, and a variety of symmetrical or unsymmetrical, chiral or achiral amines have been used as the amine moiety. It is worthy of note that the majority of these ligands are stable in air at room temperature and can be conveniently purified by column chromatography on silica gel or basic alumina, or recrystallization from an appropriate solvent in air.



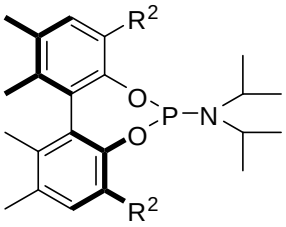
(*S*)-**III-MPN-1a** R^2= H
(*S*)-**III-MPN-1b** R^2= Me
(*S*)-**III-MPN-1c** R^2= Br
(*S*)-**III-MPN-1d** R^2= Ph
(*S*)-**III-MPN-1e** R^2= *t*-Bu
(*S*)-**III-MPN-1f** R^2= Bn
(*S*)-**III-MPN-1g** R^2= CCTMS
(*S*)-**III-MPN-1h** R^2= CCPh



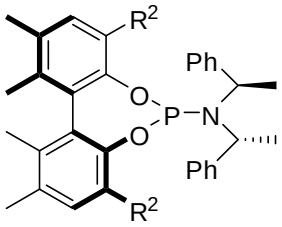
(*R*)-**III-MPN-1a** R^2= H
(*R*)-**III-MPN-1b** R^2= Me
(*R*)-**III-MPN-1c** R^2= Br
(*R*)-**III-MPN-1d** R^2= Ph
(*R*)-**III-MPN-1e** R^2= *t*-Bu
(*R*)-**III-MPN-1i** R^2= $SiEt_3$



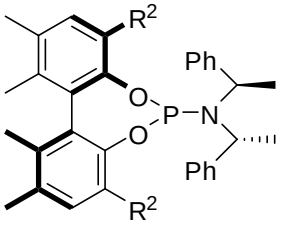
(*S*)-**III-MPN-2a** R^2= H
(*S*)-**III-MPN-2b** R^2= Me
(*S*)-**III-MPN-2c** R^2= Br
(*S*)-**III-MPN-2d** R^2= Ph
(*S*)-**III-MPN-2e** R^2= *t*-Bu



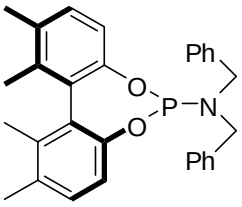
(*S*)-**III-MPN-3a** R= H
(*S*)-**III-MPN-3e** R= *t*-Bu



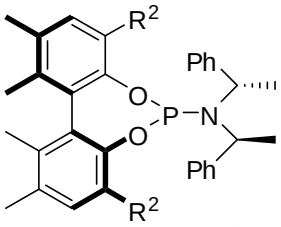
(*S,R,R*)-**III-MPN-4a** R= H
(*S,R,R*)-**III-MPN-4b** R= Me
(*S,R,R*)-**III-MPN-4c** R= Br
(*S,R,R*)-**III-MPN-4d** R= Ph
(*S,R,R*)-**III-MPN-4e** R= *t*-Bu



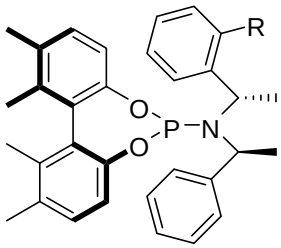
(*R,R,R*)-**III-MPN-5a** R= H
(*R,R,R*)-**III-MPN-5b** R= Me



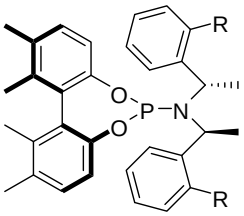
(*S*)-**III-MPN-6a**



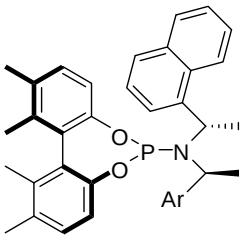
(*S,S,S*)-**III-MPN-7a** R^2= H
(*S,S,S*)-**III-MPN-7b** R^2= Me
(*S,S,S*)-**III-MPN-7c** R^2= Br
(*S,S,S*)-**III-MPN-7d** R^2= Ph



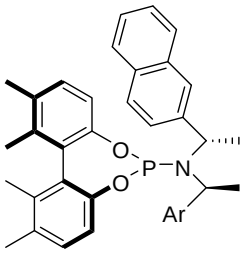
(*S,S,S*)-**III-MPN-8a** R= Me
(*S,S,S*)-**III-MPN-9a** R= OMe



(*S, S, S*)-**III-MPN-10a** R= Me
(*S, S, S*)-**III-MPN-11a** R= OMe



(*S, S, S*)-**III-MPN-12a** Ar= 1-Np
(*S, S, S*)-**III-MPN-13a** Ar= 2-MeO-Ph



(*S, S, S*)-**III-MPN-14a** Ar= 2-Np
(*S, S, S*)-**III-MPN-15a** Ar= 2-MeO-Ph

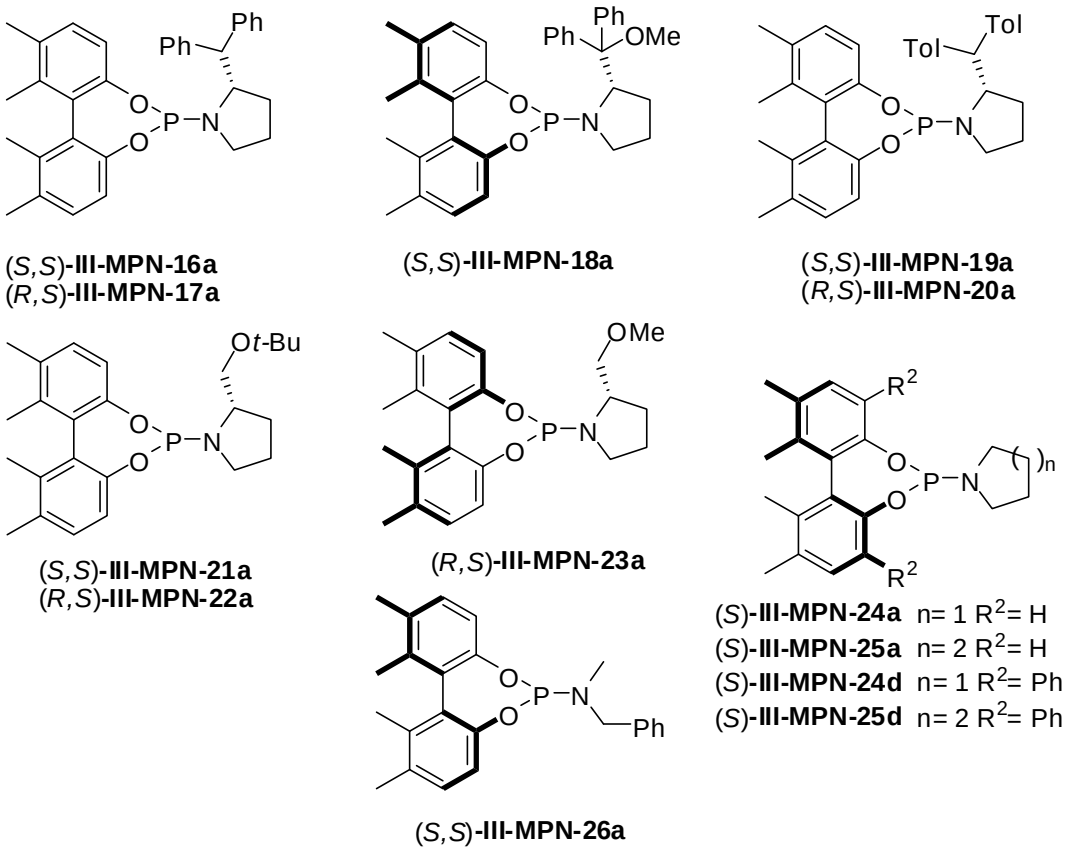
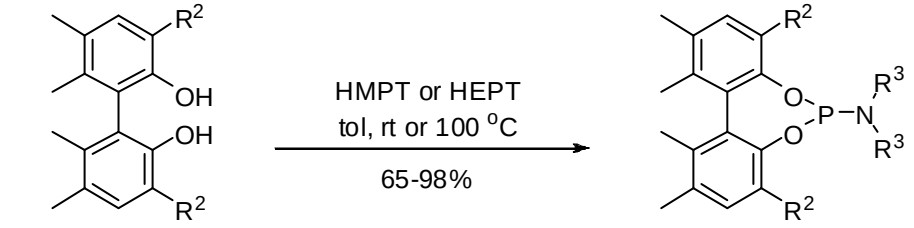


Figure III-3 Monodentate phosphoramidite ligands

Several different methods have been used for the synthesis of monodentate phosphoramidite ligands shown in **Figure III-3**. The selection of a synthetic method for a certain ligand is mainly dependent on the steric size of R^2 groups and amine moieties, as well as the availability of reagents.

The simplest method is to react enantiomerically pure biphenol (**II-1**, racemic form is shown) with hexamethylphosphorous triamide (HMPT) or hexaethylphosphorous triamide (HEPT) at room temperature or at 100 ^{o}C (**Method A**). (**Scheme III-1**) Generally, a bulkier R^2 group requires a higher temperature for complete conversion than a smaller R^2 group. The reactions are very clean with complete conversion. No

significant by-product was observed. The desired ligands can be easily purified by passing the crude product through a short silica gel column to remove excess HMPT or HEPT. This method is used for all the ligands bearing dimethylamine or diethylamine moieties (**III-MPN-1a-d and f-i**, **III-MPN-2a-d**) except for the ligand having a *tert*-butyl group at the 3 and 3' positions of the biphenol unit (**III-MPN-1e** and **III-MPN-2e**).[56]



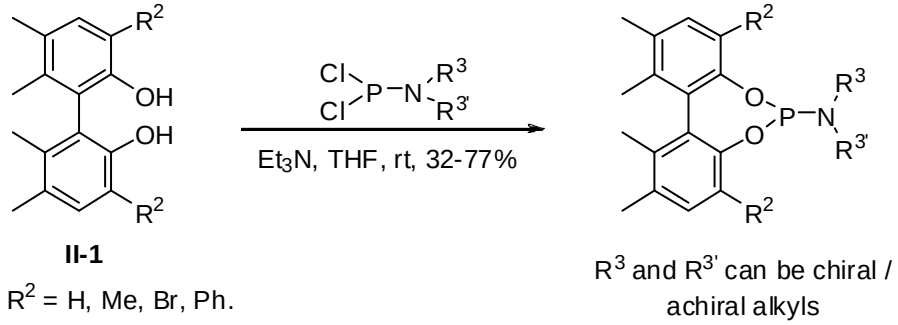
II-1
R^2= H, Me, Br, Ph, Bn, $SiEt_3$, CCTMS, CCPh

III-MPN-1a-d and f-i, R^3 = Me
III-MPN-2a-d , R^3 = Et

Scheme III-1 Synthesis of monodentate phosphoramidites (1)

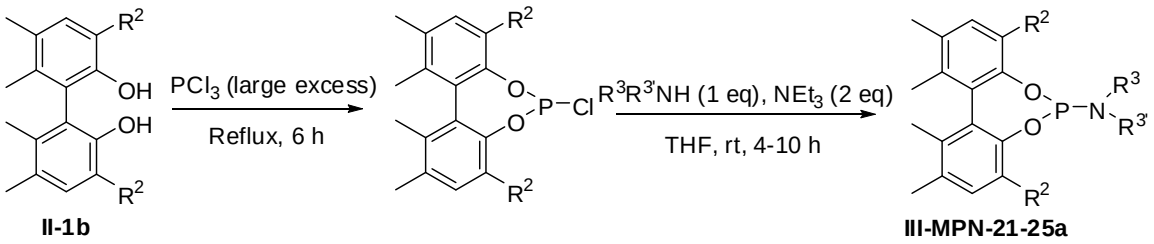
The second method involves the coupling reaction of enantiomerically pure biphenol (**II-1**) with dialkylaminophosphorus dichloride in the presence of triethylamine at room temperature (**Method B**). (**Scheme III-2**) The dialkylaminophosphorus dichloride ($R^3R^{3'}NPCl_2$) is either commercially available (R^3= $R^{3'}$= *i*-Pr), or generated *in situ* by mixing phosphorous trichloride, a secondary amine (chiral or achiral, symmetrical or unsymeetrical) and triethylamine in THF, yielding a product that can be used without purification. When using the $R^3R^{3'}NPCl_2$ generated *in situ*, ^{31}P NMR has to be monitored carefully to ensure the complete consumption of PCl_3 to avoid unnecessary side reactions in the following coupling with biphenols (**II-1**). The coupling reactions proceeded smoothly at room temperature to give the desired phosphoramidites in moderate to good

yields. This method was used for the synthesis of ligand **III-MPN-5a-b, III-MPN-4/7a-d, III-MPN-3/6/8-20,26a**. The coupling reaction of biphenol with $R^3{}_2NPCl_2$ did not proceed when R^2 is a bulky *tert*-butyl group. In those cases (**III-MPN-3/4e**), *n*-butyllithium was used instead of triethylamine to generate the dianion species before the addition of $R^3R^{3'}NPCl_2$.[56]



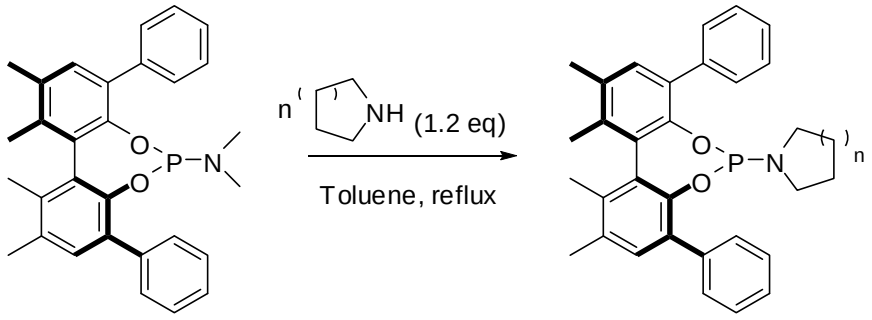
Scheme III-2 Synthesis of monodentate phosphoramidites (2)

Another strategy to synthesize phosphoramidite ligands is to synthesize the chlorophosphite from the corresponding biphenols first, then coupling with amines to afford the desired phosphoramidite ligands (**Method C**). (**Scheme III**) This method has been found very effective in the synthesis of phosphoramidite ligands with cyclic amine moiety (**III-MPN-21-25a**).



Scheme III-3 Synthesis of monodentate phosphoramidites (3)

Phosphoramidite ligands can also be synthesized from the existing ligands bearing small amine moieties (ie, **III-MPN-1a-d**, etc.). In fact, the synthesis of (*S*)-**III-MPN-24d** and (*S*)-**III-MPN-25d** proceeded smoothly when mixing the ligand (*S*)-**III-MPN-1d** with the cyclic amines in excess under reflux conditions (**Method D**). (**Scheme III-4**)



(*S*)-**III-MPN-1d**

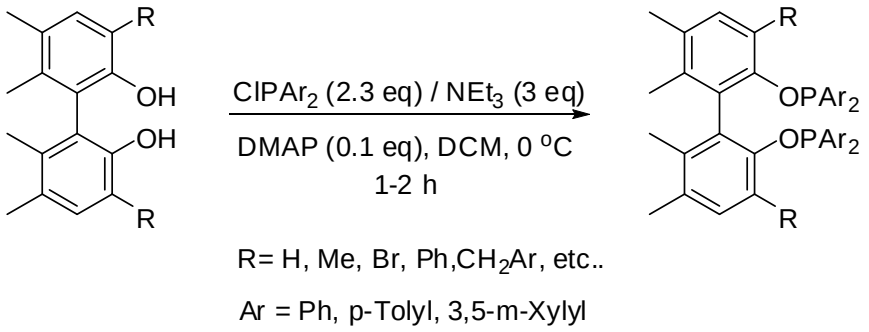
n= 1 (*S*)-**III-MPN-24d**
n= 2 (*S*)-**III-MPN-25d**

Scheme III-4 Synthesis of monodentate phosphoramidites (4)

In the course of ligand screening studies for various catalytic reactions, ligands **III-MPN-1a-d,f,h**, **III-MPN-2a-d**, (*S,R,R*)-**III-MPN-4a/b**, (*R,R,R*)-**III-MPN-5a/b**, (*S*)-**III-MPN-6a**, (*S,S,S*)-**III-MPN-7a,** (*S*)-**III-MPN-24a/d** and (*S*)-**III-MPN-25a/d** were synthesized according to the methods described in this chapter.

§3.2.2 Bidentate Diphosphonite Ligands

The 3, 3'-disustituted-biphenol-based diphosphonite Ligands (BOPs) were synthesized following the synthesis protocol as described for BINAPO ligand (**Scheme III-5**).[61] In the scheme, we design to have fine-tuning capability of both 3,3' positions of biphenol moiety and Ar groups on the phosphorus moieties.



Scheme III-5 Synthesis of 3,3'-disubstituted-biphenol-based diphosphonite ligand (BOP)

Most of the 3,3'-disustituted-biphenols were synthesized according to the procedures reported by our lab,[53] and the rest were included in Chapter II. The coupling reaction between biphenol **II-1** and chlorodiarylphosphine ($ClPAr_2$) proceeded smoothly, affording the desired products in good to excellent yields. The products had to be purified through column chromatography on neutral/basic alumina or silica gel pretreated with NEt_3. The ligand library created so far is shown in **Figure III-4**.

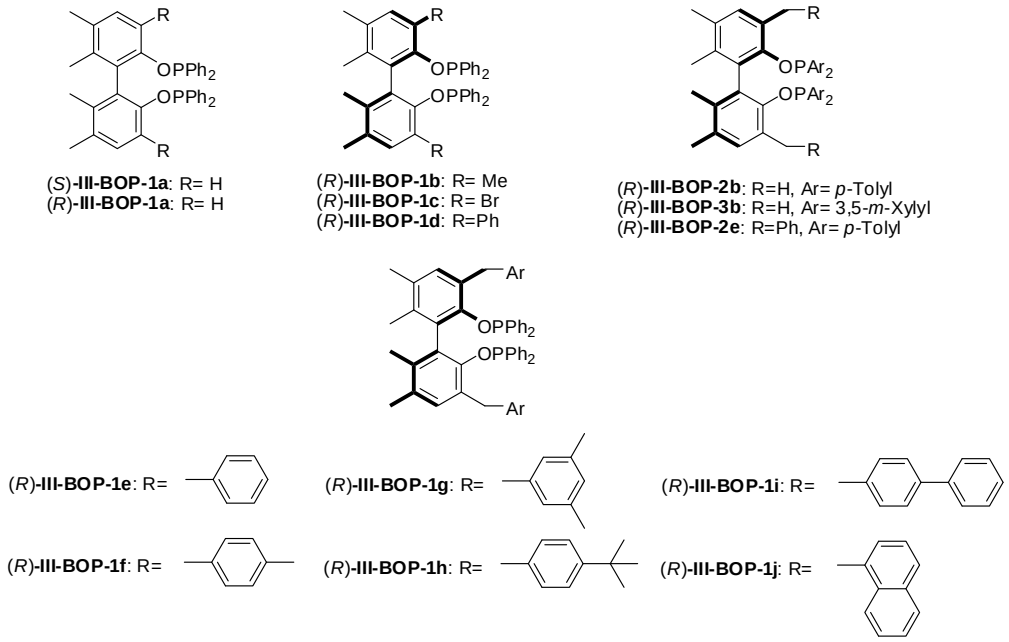


Figure III-4 Library of bidentate diphosphonite ligands

§3.3 Experimental Section

General Method. ^{1}H, ^{31}P and ^{13}C NMR spectra were measured on a Varian Inova-400 NMR (^{1}H, 400 MHz; ^{13}C, 100 MHz; ^{31}P, 162 MHz) or a Varian Gemini-2300 (^{1}H, 300 MHz; ^{13}C, 75 MHz; ^{31}P, 121 MHz) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^{1}H, 7.15 ppm) as the internal standard or phosphoric acid as the external reference (^{31}P, 0.0 ppm). Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and column chromatography was carried out on silica gel 60 (Merck; 230-400 mesh ASTM). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL.

Materials. All solvents were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. All chemicals were purchased from Aldrich and Acros Chemical Co. unless otherwise noted. All reactions were carried out under nitrogen or argon atmosphere.

General procedures for preparations of phosphoramidite ligands:

Method A: To a solution of the biphenol (1.0 mmol) in toluene (5 mL) was added HMPT (248 mg, 1.5 mmol) under nitrogen. The resulting solution was stirred at room temperature or elevated temperature until TLC indicated full conversion of the biphenol. The solvent was then evaporated under reduced pressure to afford a white solid, which

was purified by washing with Et_2O to give the desired phosphoramidite as a white solid, or column chromatography on silica gel pretreated with NEt_3 (eluent: hexanes). Ligands **III-MPN-1a-d,f**, (*S*)-**III-MPN-2a-d** were synthesized using **Method A**.

***O,O'*-(*S*)-(5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*S*)-**III-MPN-1a**): White solid; mp 166.0-168.0 ^oC; $[\alpha]_D^{22}$ +271.5 (CH_2Cl_2, *c* 0.63); ^1H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.05 (s, 3H), 2.30 (s, 6H), 2.49 (s, 3H), 2.52 (s, 3H), 6.84 (d, J = 7.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 142.7; All data were consistent with reported values.[56]

***O,O'*-(*R*)-(5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*R*)-**III-MPN-1a**): White solid (227 mg, 72.1%): mp 161.0-163.5 ^oC; $[\alpha]_D^{22}$ -267.1 (CH_2Cl_2, *c* 1.55); ^1H NMR (300 MHz, C_6D_6) δ 1.81 (s, 3H), 1.92 (s, 3H), 1.99 (s, 3H), 2.07 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 6.95 (d, J = 1.5 Hz, 4H); ^{31}P NMR (121.5 Hz, C_6D_6) δ 143.1; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*S*)-**III-MPN-1b**): White solid; 75% yield; mp 121.0-121.5 ^oC; $[\alpha]_D^{22}$ +488 (CH_2Cl_2, *c* 0.50); ^1H NMR (300 MHz, C_6D_6) δ 1.87 (s, 3H), 1.99 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 2.27 (s, 3H), 2.34 (s, 3H), 2.37 (s, 3H), 2.43 (s, 3H), 6.88 (s, 1H), 6.92 (s, 1H); ^{31}P NMR (121.5 Hz, C_6D_6) δ 138.8; All data were consistent with reported values. [56]

***O,O'*-(*R*)-(3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethyl-phosphoramidite** ((*R*)-**III-MPN-1b**): White solid; 65% yield; mp 117.0-118.0 ^{o}C; $[\alpha]_{D}^{22}$ -381.1 (CH_2Cl_2, *c* 0.62); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3H), 1.99 (s, 3H), 2.21 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.32 (s, 3H), 2.45 (s, 3H), 2.48 (s, 3H), 6.95 (s, 1H), 7.02 (s, 1H); ^{31}P NMR (121.5 Hz, $CDCCl_3$) δ 138.7; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*S*)-**III-MPN-1c**): White solid; 78% yield; mp 160.0-161.5 ^{o}C; $[\alpha]_{D}^{20}$ +473.8 (CH_2Cl_2, *c* 0.80); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H), 1.98 (s, 3H), 2.27 (s, 3H), 2.28 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 7.36 (s, 1H), 7.42 (s, 1H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 141.3; All data were consistent with reported values. [56]

***O,O'*-(*R*)-(3,3'-Dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*R*)-**III-MPN-1c**): White solid; 95% yield; mp 170.0-171.5 ^{o}C; $[\alpha]_{D}^{22}$ -496.9 (CH_2Cl_2, *c* 0.53); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (s, 3H), 1.98 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 2.51 (s, 3H), 2.54 (s, 3H), 7.36 (s, 1H), 7.42 (s, 1H); ^{31}P NMR (121.5 Hz, $CDCCl_3$) δ 141.2; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*S*)-**III-MPN-1d**): White solid; 70% yield; mp 109.5-112.5 ^{o}C; $[\alpha]_{D}^{20}$ +466.7 (CH_2Cl_2, *c* 0.45); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (s, 3H), 1.94 (s,

3H), 2.13 (s, 3H), 2.16 (s, 3H), 2.39 (s, 3H), 2.40 (s, 3H), 7.30-7.70 (m, 12H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 140.5; All data were consistent with reported values. [56]

***O,O'*-(*R*)-(3,3'-Diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*R*)-**III-MPN-1d**): White solid; 98% yield; mp 88.5-91.0 °C; $[\alpha]_D^{22}$ -420.0 (CH_2Cl_2, *c* 0.35); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87 (s, 3H), 1.90 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 7.22-7.66 (m, 12H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 140.5; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3'-Dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-dimethylphosphoramidite** ((*S*)-**III-MPN-1f**): White solid; 65% yield; mp 110.0-112.0 °C; $[\alpha]_D^{22}$ +176.2 (CH_2Cl_2, *c* 0.5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.01 (s, 3H), 2.22 (s, 3H), 2.23 (s, 3H), 2.52 (s, 3H), 2.55 (s, 3H); 3.70 (d, *J*= 15.2 Hz, 1H), 4.17 (m, 3H), 6.86 (s, 1H), 6.91 (s, 1H), 7.28 (m, 10H); ^{31}P NMR (162 Hz, $CDCl_3$) δ 140.8; ; HRMS (EI) calcd for $C_{24}H_{26}NO_2P$ $[M]^+$ 391.1701, found 391.1703 (Δ= 0.5 ppm).

***O,O'*-(*S*)-(5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-diethylphosphoramidite** ((*S*)-**III-MPN-2a**): White solid; 85% yield; mp 123.0-124.0 °C; $[\alpha]_D^{22}$ +213.9 (CH_2Cl_2, *c* 0.38); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, J = 6.9 Hz, 6H), 1.98 (s, 3H), 2.04 (s, 3H), 2.29 (s, 6H), 2.76-2.84 (m, 2H), 2.93-3.02 (m, 2H), 6.83 (d, J = 8.1 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 144.1; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3'-Dimethyl-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-diethylphosphoramidite** ((*S*)-**III-MPN-2b**): White solid; 75% yield; mp 103.0-105.0 ^{o}C; $[\alpha]_D^{22}$ +337.8 (CH_2Cl_2, *c* 0.77); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, J = 6.0 Hz, 6H), 1.92 (s, 3H), 1.98 (s, 3H), 2.25 (s, 9H), 2.32 (s, 3H), 2.78-3.12 (m, 4H), 6.95 (s, 1H), 7.02 (s, 1H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 139.9; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3'-Dibromo-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-diethylphosphoramidite** ((*S*)-**III-MPN-2c**): White solid; 90% yield; mp 153.0-155.0 ^{o}C; $[\alpha]_D^{22}$ +396.0 (CH_2Cl_2, *c* 0.33); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J = 7.1 Hz, 6H), 1.90 (s, 3H), 1.97 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 2.78-3.10 (m, 4H), 7.36 (s, 1H), 7.41 (s, 1H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 141.9; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3'-Diphenyl-5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-diethylphosphoramidite** ((*S*)-**III-MPN-2d**): White solid; 84% yield; mp 172.0-174.5 ^{o}C; $[\alpha]_D^{22}$ +450.0 (CH_2Cl_2, *c* 0.50); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (t, J = 7.2 Hz, 6H), 2.08 (s, 3H), 2.12 (s, 3H), 2.35 (s, 3H), 2.36 (s, 3H), 2.26-2.38 (m, 2H), 2.45-2.60 (m, 2H), 7.22-7.63 (m, 12H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 140.3; All data were consistent with reported values. [56]

Method B: Phosphorous trichloride (0.197 mL, 2.26 mmol) was added to Et_3N (1.56 mL, 11.30 mmol) dropwise at 0 ^oC. To this mixture, was added a solution of the secondary amine (2.26 mmol) in THF (4 mL). The mixture was stirred at room temperature for 1-6 h until ^{31}P NMR indicated full conversion of PCl_3. The mixture was cooled to 0 ^oC again, and to this mixture was added a solution of the biphenol (2.26 mmol) in THF (5 mL) dropwise over 20 mins. The resulting mixture was allowed to warm to room temperature slowly and stirred at that temperature overnight. The solid was filtered off over a pad of celite and washed with toluene, and the combined solution was concentrated *in vacuo* to give the crude product. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 30:1 to 15:1) to afford the desired product as white solid. (*S,R,R*)-**III-MPN-4a/b**, (*R,R,R*)-**III-MPN-5a/b**, (*S*)-**III-MPN-6a** and (*S,S,S*)-**III-MPN-7a** were synthesized using **Method B**.

***O,O'*-(*S*)-(5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-di-(*R,R*)-1-phenylethylphosphoramidite** ((*S,R,R*)-**III-MPN-4a**): White foam; 66% isolated yield; mp 160.0-162.5 ^oC; $[\alpha]_D^{23}$ +240.0 (*c* 0.28, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) δ 1.67 (d, J = 7.2 Hz, 6H), 1.97 (s, 3H), 2.02 (s, 3H), 2.26 (s, 3H), 2.27 (s, 3H), 4.40-4.46 (m, 2H), 6.92-7.14 (m, 14H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 140.4; HRMS (EI) calcd. for $C_{32}H_{33}NO_2P$ $[M-H]^+$ 494.2249, found 494.2256 (Δ = 1.4 ppm). All data were consistent with reported values. [56]

***O,O'*-(*S*)-(3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-di-(*R,R*)-1-phenylethylphosphoramidite** ((*S,R,R*)-**III-MPN-4b**): White solid; 50% yield; mp 133.5-

134.5 °C; $[\alpha]_D^{21}$ +302.0 (CH_2Cl_2, *c* 0.50); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 1.6 (brs, 6H), 1.88 (s, 3H), 2.00 (s, 3H), 2.16 (s, 3H), 2.24 (s, 3H), 2.25 (s, 3H), 2.45 (s, 3H), 4.40-4.58 (m, 2H), 7.02 (s, 1H), 7.03-7.17 (m, 11H); ^{31}P NMR (121.5 Hz, C_6D_6) δ 136.8; All data were consistent with reported values. [56]

***O,O'*-(*R*)-(5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-di-(*R,R*)-1-phenyl ethylphosphoramidite** ((*R,R,R*)-**III-MPN-5a**): White solid; 71% yield; mp 60.0-62.5 °C; $[\alpha]_D^{23}$ +174.2 ($CHCl_3$, *c* 0.52); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (d, J = 7.2 Hz, 6H), 2.03 (s, 3H), 2.08 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 4.40-4.46 (m, 2H), 6.84-7.28 (m, 14H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 146.0; All data were consistent with reported values. [56]

***O,O'*-(*R*)-(3,3',5,5',6,6'-Hexamethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-di-(*R,R*)-1-phenyl ethylphosphoramidite** ((*R,R,R*)-**III-MPN-5b**): White solid; 67% yield; mp 74.0-76.5 °C; $[\alpha]_D^{23}$ +289.7 (CH_2Cl_2, *c* 0.48); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.67 (d, J = 6.6 Hz, 6H), 1.87 (s, 3H), 1.99 (s, 3H), 2.24 (s, 6H), 2.42 (s, 3H), 4.52-4.55 (m, 2H), 6.92-7.17 (m, 12H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 140.8; All data were consistent with reported values. [56]

***O,O'*-(*S*)-(5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N*-benzyl-*N*-methyl phosphoramidite** ((*S*)-**III-MPN-6a**): White solid; 75% yield; mp 106.5-108 °C; $[\alpha]_D^{22}$ 242.9 (*c* 0.40, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.93 (s, 3H), 1.96 (s, 3H), 2.17 (d, *J* = 6.0 Hz, 3H), 2.20 (s, 3H), 2.23 (s, 3H), 3.80 (dd, *J* = 12.6 Hz, 15 Hz, 1H), 4.21 (dd, *J*

= 8.7 Hz, 15.7 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.95-7.28 (m, 8H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 141.9; HRMS (EI) calcd for $C_{24}H_{26}NO_2P$ $[M]^+$ 391.1701, found 391.1703 (Δ= 0.5 ppm).

***O,O'*-(*S*)-(5,5',6,6'-Tetramethyl-1,1'-biphenyl-2,2'-diyl)-*N,N*-di-(*S,S*)-1-phenylethylphosphoramidite** ((*S,S,S*)-**III-MPN-7a**): White solid; 71% yield; mp 60.0-62.5 ^{o}C; $[\alpha]_D^{23}$ -168.2 ($CHCl_3$, *c* 0.4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (d, J = 7.2 Hz, 6H), 2.03 (s, 3H), 2.08 (s, 3H), 2.27 (s, 3H), 2.35 (s, 3H), 4.40-4.46 (m, 2H), 6.84-7.28 (m, 14H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 146.0; All data were consistent with reported values.[56]

Method C: The biphenol (1 mmol) was dissolved in THF (3 mL). PCl_3 (0.9 mL) was added dropwise and the solution was reflux under N_2 for 24 h. The mixture was evaporated and toluene (2 mL) was added to the residue. Evaporation of the solvent was then repeated. The residue was put *in vacuo* for 3 h. ^{31}P NMR monitoring showed the sole presence of the chlorophosphite. The residue was then dissolved into THF (2 mL) and put at 0 ^{o}C under nitrogen atmosphere. The amine (1 eq.) was dissolved in THF (1 mL) and added via cannula to the chlorophosphite solution. The reaction mixture was further stirred for additional 6-12 h before dry ether (5 mL) was added to precipitate the triethylamine salt. The precipitate was then filtered out and the filtrate was concentrated *in vacuo*. The crude product was then purified on alumina column (pretreated with NEt_3) using hexanes:CH_2Cl_2:NEt_3 (50:10:0.1) as the eluent. Ligands (*S*)-**III-MPN-24/25a** were synthesized using **Method C**.

1-((*11aS*)-1,2,10,11-Tetramethyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)pyrrolidine ((S)-**III-MPN-24a**): White foam; 66% yield; mp 112.5-114 ^{o}C; $[\alpha]_{D}^{22}$ 256 ($CHCl_3$, *c* 0.75); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (m, 2H), 1.69 (m, 2H), 1.98 (s, 3H), 2.03 (s, 3H), 2.27 (s, 3H), 2.29 (s, 3H), 2.89 (m, 2H), 3.11 (m, 2H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 143.8; LRMS (EI) calcd for $C_{20}H_{22}NO_2P$ $[M]^+$ 341.4 found 341.4.

1-((11*aS*)-1,2,10,11-Tetramethyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)piperidine ((*S*)-**III-MPN-25a**): White foam; 57% yield; mp 116-119 ^{o}C; $[\alpha]_{D}^{22}$ 147 ($CHCl_3$, *c* 0.5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (m, 3H), 1.50 (m, 3H), 1.98 (s, 3H), 2.03 (s, 3H), 2.26 (s, 3H), 2.29 (s, 3H), 2.99 (m, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 140.0; LRMS (EI) calcd for $C_{21}H_{26}NO_2P$ $[M]^+$ 355.4, found 355.4.

Method D: To a solution of phosphoramidite ligand (*S*)-**III-MPN-1d** (1 mmol) in 2 mL toluene at room temperature, was added a solution of amine (1.2 mmol) in 1 mL toluene. The mixture was refluxed for 12 h and monitored by TLC. The reaction was then cooled down and concentrated in vacuo. The crude product was then purified on alumina column (pretreated with NEt_3) using hexanes:NEt_3 (100:1) as the eluent. Ligands (*S*)-**III-MPN-24/25d** were synthesized using **Method D**.

1-((11*aS*)-1,2,10,11-Tetramethyl-4,8-diphenyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)pyrrolidine ((*S*)-**III-MPN-24d**): White foam; 60% yield; mp 114-117 ^{o}C; $[\alpha]_{D}^{23}$ +99.5 ($CHCl_3$, *c* 0.05); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 2H), 1.85 (m, 2H),

2.09 (s, 3H), 2.11 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 2.42 (m, 2H), 3.75 (m, 2H), 7.33 (m, 8H), 7.59 (m, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 143.3; LRMS (EI) calcd for $C_{32}H_{32}NO_2P$ $[M]^+$ 393.6, found 393.6.

1-((11*aS*)-1,2,10,11-Tetramethyl-4,8-diphenyldibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)piperidine ((*S*)-**III-MPN-25d**): White foam; 43% yield; mp 112-115 ^oC; $[\alpha]_D^{23}$ +78.4 ($CHCl_3$, *c* 0.05); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (m, 3H), 1.83 (m, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 2.37 (s, 6H), 2.38 (m, 2H), 3.75 (m, 2H), 7.28 (m, 8H), 7.62 (m, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 141.3; LRMS (EI) calcd for $C_{33}H_{34}NO_2P$ $[M]^+$ 507.6, found 507.6

General procedures for preparations of diphosphonite ligands:[43]

To a solution of the biphenol (1 mmol), DMAP (10 mol%) and NEt_3 (0.8 mL, 6 mmol) in 10 mL CH_2Cl_2 at 0 ^oC, was added a solution of chloro diarylphosphine (2.5 mmol) in 5 mL CH_2Cl_2 over 20 min. The mixture was kept stirred at the same temperature for additional 2 h. The mixture was then concentrated in vacuo. The residue was redissolved in toluene 10 mL and filtered through a pad of celite. The filtrate was concentrated again and crude product was purified on a silica gel column pretreated with NEt_3 using (hexanes: NEt_3= 100: 1) as the eluent. All diphosphonite ligands were synthesized using this method.

(*S*)-2,2'-Bisdiphenylphosphinoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*S*)-**III-BOP-1a**): colorless oil; 77% yield; $[\alpha]_D^{23}$ +173.5 ($CHCl_3$, *c* 0.5); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 2.03 (s, 6H), 2.12 (s, 6H), 7.07 (m, 14H), 7.27 (m, 2H), 7.46 (m, 8H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 110.8; HRMS (EI) calcd for $C_{40}H_{36}O_2P_2$ $[M]^+$ 610.2191, found 610.2189 (Δ= -0.3 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-**III-BOP-1a**): colorless oil; 68% yield; $[\alpha]_D^{23}$ -178.4 ($CHCl_3$, *c* 0.5); ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 6H), 2.12 (s, 6H), 7.07 (m, 14H), 7.27 (m, 2H), 7.46 (m, 8H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 110.8; HRMS (EI) calcd for $C_{40}H_{36}O_2P_2$ $[M]^+$ 610.2191, found 610.2189 (Δ= -0.3 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3',5,5',6,6'-hexamethyl-1,1'-biphenyl ((*R*)-**III-BOP-1b**): White foam; 77% yield; mp 61-63 °C; $[\alpha]_D^{23}$ +143 ($CHCl_3$, *c* 0.5); ^1H NMR (300 MHz, $CDCl_3$) δ 1.78 (s, 6H), 1.83 (s, 6H), 1.96 (s, 6H), 6.52 (s, 2H), 7.18 (m, 12H), 7.48 (m, 8H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 109.2; HRMS (EI) calcd for $C_{42}H_{40}O_2P_2$ $[M]^+$ 638.2504, found 638.2500 (Δ= -0.6 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-dibromo-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-**III-BOP-1c**)): White foam; 81% yield; mp 79-82 °C; $[\alpha]_D^{23}$ +77 ($CHCl_3$, *c* 1.0); ^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 6H), 1.85 (s, 6H), 6.96 (s, 2H), 7.29 (m, 16H), 7.53 (m, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 114.1; HRMS (EI) calcd for $C_{40}H_{34}Br_2O_2P_2$ $[M]^+$ 766.0401, found 766.0412 (Δ= 1.4 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-diphenyl-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-**III-BOP-1d**): White foam; 81% yield; mp 69-71 ^{o}C; $[\alpha]_D^{23}$ +177 ($CHCl_3$, *c* 1.0); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (s, 6H), 1.99 (s, 6H), 6.88 (s, 2H), 7.24 (m, 30H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 112.4; HRMS (EI) calcd for $C_{52}H_{44}O_2P_2$ $[M]^+$ 762.2817, found 762.2821 (Δ= 0.5 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-dibenzyl-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-**III-BOP-1e**): White foam; 74% yield; mp 75-77 ^{o}C; $[\alpha]_D^{23}$ +187 ($CHCl_3$, *c* 2.2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 6H), 1.90 (s, 6H), 3.54 (d, *J*= 16 Hz, 2H), 3.70 (d, *J*= 16 Hz, 2H), 6.45 (s, 2H), 7.23 (m, 30H); ^{31}P NMR (162 Hz, $CDCl_3$) δ 110.9; HRMS (EI) calcd for $C_{54}H_{48}O_2P_2$ $[M]^+$ 790.3130, found 790.3136 (Δ= 0.8 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(4-methylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-**III-BOP-1f**): Colorless oil; 68% yield; $[\alpha]_D^{23}$ +145 (CH_2Cl_2, *c* 1.5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 6H), 1.87 (s, 6H), 2.32 (s, 6H), 3.47 (d, *J*= 16 Hz, 2H), 3.63 (d, *J*= 16 Hz, 2H), 6.40 (s, 2H), 6.88 (d, *J*= 8 Hz, 4H), 7.02 (d, *J*= 8 Hz, 4H), 7.22 (m, 20H); ^{31}P NMR (162 Hz, $CDCl_3$) δ 110.7; HRMS (EI) calcd for $C_{56}H_{52}O_2P_2$ $[M]^+$ 819.9, found 819.9.

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(3,5-dimethylbenzyl)-5,5',6,6'-tetramethyl-1,1'-biphenyl ((*R*)-**III-BOP-1g**): Colorless oil; $[\alpha]_D^{23}$ +145 (CH_2Cl_2, *c* 1.5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (s, 6H), 1.87 (s, 6H), 2.25 (s, 12H), 3.49 (d, *J*=15.6 Hz, 2H), 3.64 (d, *J*=15.6 Hz, 2H), 6.44 (s, 2H), 6.64 (s, 4H), 6.80 (s, 2H), 7.19 (m, 20H) ^{31}P

NMR (162 Hz, $CDCl_3$) δ 110.2; HRMS (EI) calcd for $C_{58}H_{56}O_2P_2$ $[M]^+$ 846.3756, found 846.3750 (Δ= -0.7 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(4-*tert*butylbenzyl)-5,5',6,6'-tetra-methyl-1,1'-biphenyl ((*R*)-**III-BOP-1h**): Colorless oil; $[\alpha]_D^{23}$ +145 (CH_2Cl_2, *c* 1.5); ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 18H), 1.84 (s, 6H), 1.94 (s, 6H), 3.56 (d, *J*= 17.6 Hz, 2H), 3.72 (d, *J*= 17.6 Hz, 2H), 6.50 (s, 2H), 7.00 (d, J= 10.8 Hz, 4H), 7.33 (m, 24H); ^{31}P NMR (162 Hz, $CDCl_3$) δ 110.2; HRMS (EI) calcd for $C_{62}H_{64}O_2P_2$ $[M]^+$ 902.4382, found 902.4388 (Δ= 0.7 ppm).

(*R*)-2,2'-Bisdiphenylphosphinoxy-3,3'-bis(4-phenylbenzyl)-5,5',6,6'-tetra-methyl-1,1'-biphenyl ((*R*)-**III-BOP-1i**): Colorless oil; $[\alpha]_D^{23}$ +171 (CH_2Cl_2, *c* 0.3); ^1H NMR (300 MHz, $CDCl_3$) δ 1.85 (s, 6H), 1.95 (s, 6H), 3.60 (d, *J*= 15.9 Hz, 2H), 3.77 (d, *J*= 15.9 Hz, 2H), 6.53 (s, 2H), 7.07 (d, *J*= 8.1 Hz, 4H), 7.23 (m, 14H), 7.43 (m, 16H), 7.64 (d, *J*= 8.1 Hz, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 110.4; HRMS (EI) calcd for $C_{66}H_{56}O_2P_2$ $[M]^+$ 942.3756, found 942.3743 (Δ= -1.4 ppm).

(*R*)**-1,1'-(2,2'-Bisdiphenylphosphinoxy-5,5',6,6'-tetramethylbiphenyl-3,3'-diyl) bis(methylene)dinaphthalene** ((*R*)-**III-BOP-1j**): Colorless oil; $[\alpha]_D^{23}$ +256 (CH_2Cl_2, *c* 1.2); ^1H NMR (300 MHz, $CDCl_3$) δ 1.83 (s, 6H), 1.85 (s, 6H), 3.97 (d, *J*= 16.5 Hz, 2H), 4.16 (d, *J*= 16.5 Hz, 2H), 6.37 (s, 2H), 7.09 (m, 14H), 7.34 (m, 14H), 7.71 (d, J= 8.1 Hz, 2H), 7.81 (m, 4H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 109.8; LRMS (EI) calcd for $C_{62}H_{52}O_2P_2$ $[M]^+$ 890.3443, found 890.3436 (Δ= -0.8 ppm).

(*R*)-2,2'-Bis[bis(*p*-tolyl)phosphinoxy]-3,3',5,5',6,6'-hexamethyl-1,1'-biphenyl ((*R*)-**III-BOP-2b**): Colorless oil; $[\alpha]_D^{23}$ -68 (CH_2Cl_2, *c* 0.8); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73 (s, 6H), 1.86 (s, 6H), 1.95 (s, 6H), 2.29 (s, 6H), 2.32 (s, 6H), 6.57 (s, 2H), 7.33 (m, 16H); ^{31}P NMR (121.5 Hz, $CDCl_3$) δ 110.5; HRMS (EI) calcd for $C_{46}H_{48}O_2P_2$ $[M]^+$ 694.3130, found 694.3131 (Δ= 0.1 ppm).

(*R*)-2,2'-Bis[bis(3,5-dimethylphenyl)phosphinoxy]-3,3',5,5',6,6'-hexamethyl-1,1'-biphenyl ((*R*)-**III-BOP-3b**): Colorless oil; $[\alpha]_D^{23}$ -167 (CH_2Cl_2, *c* 1.3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 6H), 1.83 (s, 6H), 1.96 (s, 6H), 2.26 (s, 12H), 2.27 (s, 12H), 6.55 (s, 2H), 6.83 (d, *J*= 12.3 Hz, 4H), 7.04 (d, *J*= 8.0 Hz, 4H), 7.12 (d, *J*= 7.2 Hz, 4H); ^{31}P NMR (162 Hz, $CDCl_3$) δ 111.2; HRMS (EI) calcd for $C_{50}H_{56}O_2P_2$ $[M]^+$ 750.3756, found 750.3758 (Δ= 0.3 ppm).

(*R*)-2,2'-Bis[bis(*p*-tolyl)phosphinoxy]-3,3'-dibenzyl-5,5',6,6'-hexamethyl-1,1'-biphenyl ((*R*)-**III-BOP-2e**): Colorless oil; $[\alpha]_D^{23}$ -167 (CH_2Cl_2, *c* 1.3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 6H), 1.90 (s, 6H), 2.29 (s, 6H), 2.33 (s, 6H), 3.58 (d, *J*= 16 Hz, 2H), 3.70 (d, *J*= 16 Hz, 2H), 6.41 (s, 2H), 6.92 (d, J= 7.6 Hz, 4H), 6.93 (m, 10H), 7.19 (m, 10H), 7.33 (m, 4H); ^{31}P NMR (162 Hz, $CDCl_3$) δ 112.2; LRMS (EI) calcd for $C_{58}H_{56}O_2P_2$ $[M]^+$ 847.0, found 847.0.

Chapter IV

Palladium(0)-Catalyzed Asymmetric Allylic Substitutions with Monodentate Phosphoramidite Ligands

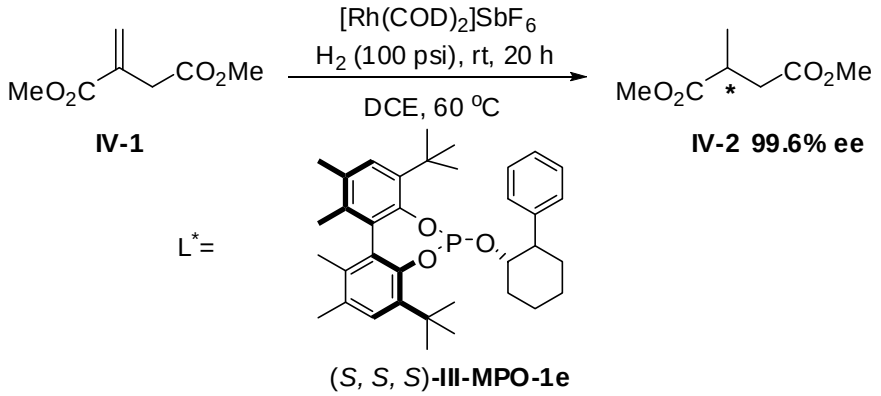
§4.1 Introduction

§4.1.1 Chiral Biphenol-Based Monodentate Phosphorus Ligands in Catalytic Asymmetric Reactions

We have proved the efficacy of our fine-tunable monodentate phosphorus ligands in various asymmetric transformations.[53,56-60] The results clearly showed that the substituents at the 3 and 3' positions of the biphenol moiety in the ligand structure did play an important role in controlling the reactivity and enantioselectivity. Excellent enantioselectivities (and regioselectivities in some cases) have been achieved through systematic optimization of ligand structures using combinatorial approach in various reactions, including asymmetric hydrogenation,[53] hydroformylation,[56] conjugate additions[56,57] and allylic alkylation[58-60].

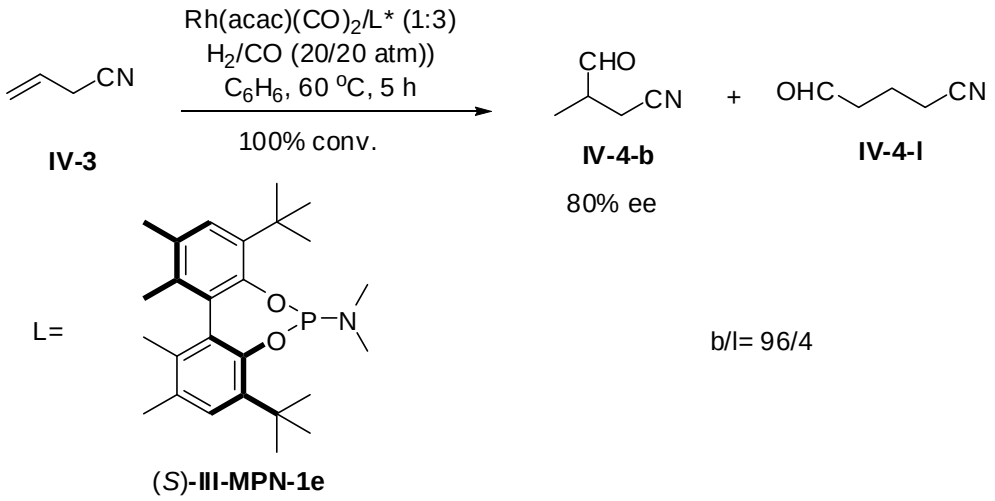
In 2003, asymmetric hydrogenation of dimethyl itaconate (**IV-1**) was screened with a library of biphenol-based phosphite ligands.[53] Thus when the reaction was run with $[Rh(COD)_2]SbF_6$/Ligand (*S,S,S*)-**MPO-1e** bearing *t*Bu on the 3,3'-position of the biphenol moiety in $ClCH_2CH_2Cl$ under hydrogen (100 psi) at 50 ^oC, the corresponding

(*S*)-dimethyl succinate (**IV-2**) was obtained in 100% conversion with 99.6% ee (**Scheme IV-1**).



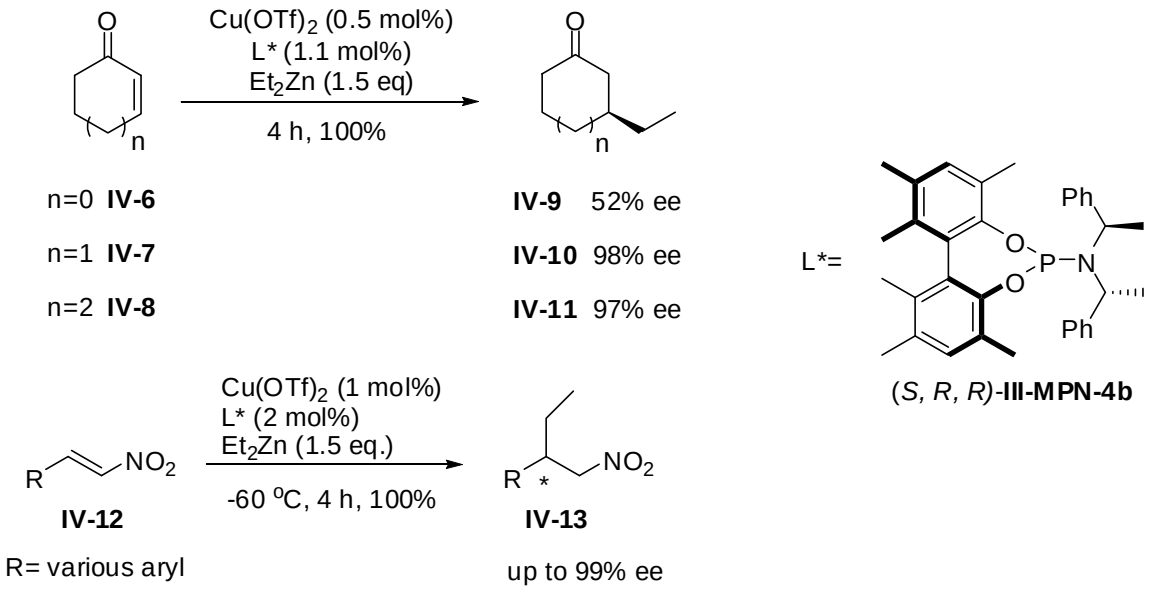
Scheme IV-1 Asymmetric hydrogenation of dimethyl itaconate (**IV-1**) catalyzed by $[Rh(COD)_2]SbF_6$ with (*S,S,S*)-**MPO-1e**[53]

Phosphoramidite ligands were tested in the hydroformylation of allyl cyanide (**IV-3**).[56] The dramatic effect of the substituents at the 3,3'-positions of the biphenol moiety to the regio- and enantioselectivity of the reaction was also observed in this case. The initial structure-activity relationship study revealed that ligand (*S*)-**III-MPN-1e** bearing *t*-Bu at the 3, 3' positions of the biphenol moiety and small amine moiety (dimethylamino) turned out to be the best ligand in terms of regioselectivity and enantioselectivity of the branched product. Optimization of the reaction conditions when using ligand (*S*)-**III-MPN-1e** permitted to achieve excellent high regioselectivity, i.e., branched to linear product ratio of 96:4, and 80% ee for the branched product (**IV-4-b**) (**Scheme IV-2**).



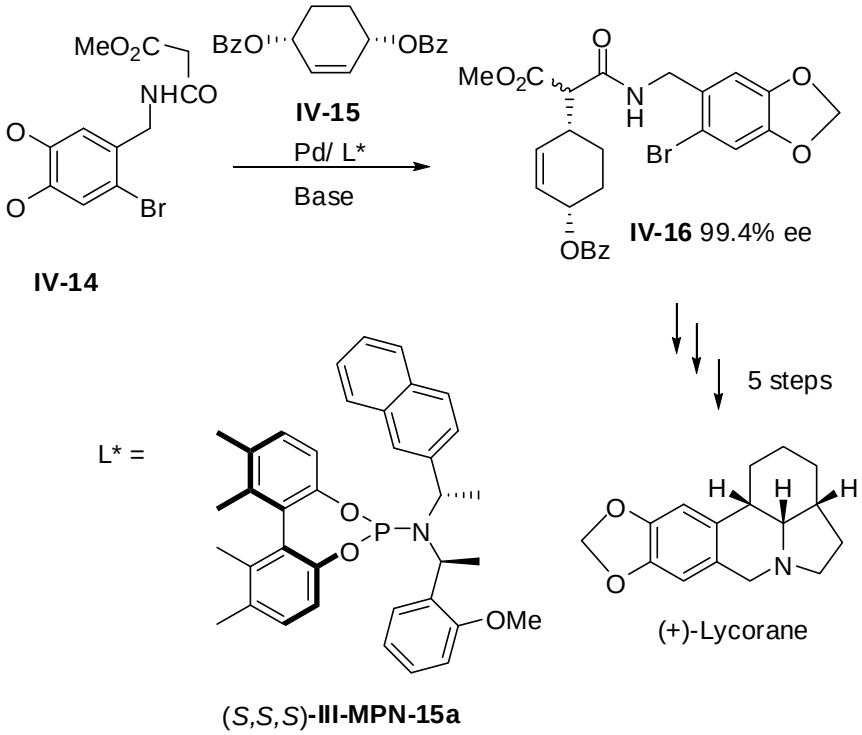
Scheme IV-2 Asymmetric hydroformylation of allyl cyanide (**IV-3**)[56]

The library of the phosphoramidite ligands was also tested in the $Cu(OTf)_2$-catalyzed conjugated addition of diethylzinc to cyclic enones and nitroalkenes.[56,57] In each case, after ligand screening, ligand (*S,R,R*)-**III-MPN-4b** bearing Me groups at the 3,3' positions of the biphenol moiety and a bulky C_2-symmetrical amine moiety was proved to be the best ligand, affording good to excellent ee (**Scheme IV-4**). Even for challenging substrate like 1-cyclopetenone (**IV-6**), 52% ee was observed for the product **IV-9**.



Scheme IV-3 Asymmetric conjugated addition of Et_2Zn to cycloenones and nitroalkenes[56,57]

Recently, our monodentate phosphoramidite ligands have also proven to be very effective in asymmetric allylic substitution reactions.[1-3] In Scheme **IV-4**, the intermolecular allylic alkylation reaction, which is the key step in the total synthesis of (+)-γ-Lycorane reported by Mori et al.,[62] was remarkablyimproved in terms of reactivity and enantioselectivity using our monodentate phosphoramidite ligand.[58,59] More than 99% ee was achieved for the desired product (**IV-16**), when ligand (*S,S,S*)**-III-MPN-15a** was applied in the reaction.

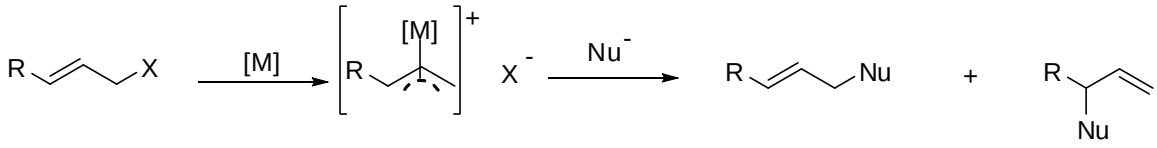


Scheme IV-4 Asymmetric allylic alkylation as the key step in the total synthesis of (+)-γ-Lycorane [58,59]

Encouraged by the successful application of our monodentate phosphoramidite ligands to the Pd-catalyzed asymmetric allylic alkylation, we decided to explore the possibility of our phosphoramidite ligands in other types of allylic substitutions.

§4.1.2 Transition Metal-Catalyzed Asymmetric Allylic Substitutions

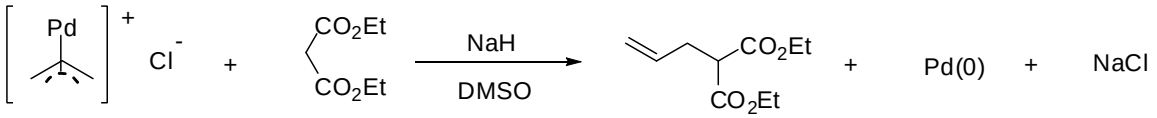
Transition-metal catalyzed allylic substitution reactions certainly stand as one of the most powerful methods for the controlled formation of carbon-carbon, carbon-heteroatom bonds. The reaction involves the formation of a π-allyl metal species that can be employed for the formation of new chemical bonds with different chemo-, regio-and stereoselectivities (**Scheme IV-5**).



IV-17 **IV-18-l** **IV-18-b**

Scheme IV-5 Allylic substitution reaction

The first example of the formation of a carbon-carbon bond through this process was accomplished by Tsuji and coworkers in 1965 (**Scheme IV-6**).[63] This discovery opened the door to numerous possibilities in the formation of new chemical bonds. Since then, great efforts have been dedicated to the study of the mechanism and the scope of the type of reaction, and especially making the reaction a catalytic enantioseletive process.

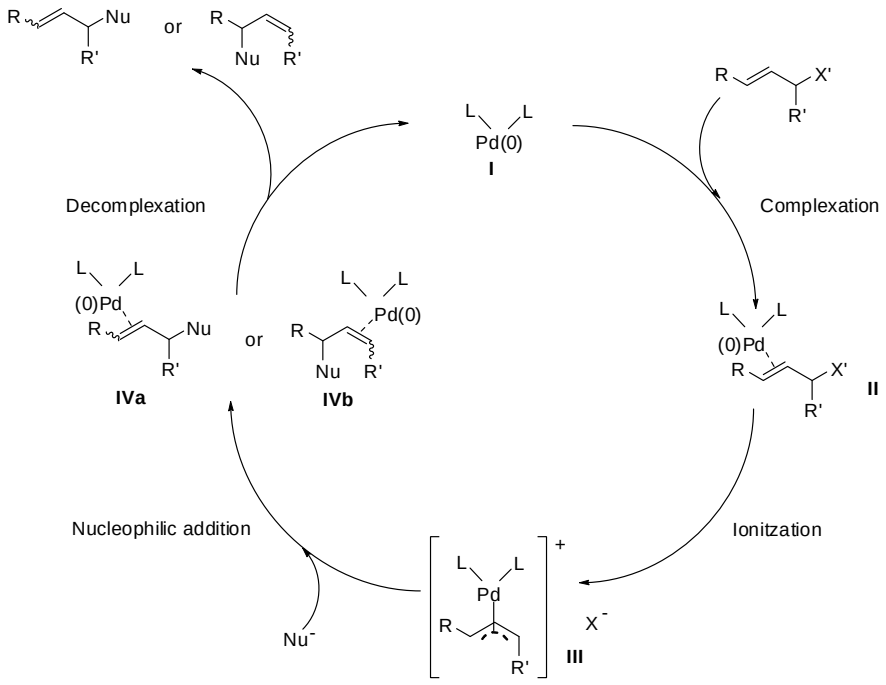


Scheme IV-6 First example of allylic alkylation reaction[63]

The first example of asymmetric allylic alkylation reaction was reported by Trost et al. in 1977.[64] Since then efforts have been made on the study of the mechanism of enantioselectivity to direct the design of ligands capable of reaching the exterior of the metal-allyl complex, creating unsymmetrical environment around the allyl substrate.

The generally accepted mechanism for the palladium-catalyzed allylic substitution, follows the scheme presented below (**Scheme IV-7**).[65,66] The catalytic cycle starts with the complexation step where the olefin moiety of the allylic substrate coordinates to $Pd(0)L_2$ (**I**) , followed by the ionization step where X' is detached from the allyl moiety, leading to the formation of a Pd(II)-allyl intermediate (**III**). It is generally observed that the ionization step occurs with the leaving group being at a position *anti* to the metal. The

third step is the nucleophilic addition to the Pd(II)-allyl complex (**III**) to form the corresponding Pd(0)-olefin complexes (**IVa** or **IVb**). In the case of soft nucleophiles which genrally refer to stabilized nucleophiles, the attack occurs on the π-allyl group *anti* to the metal. In contrast, hard nucleophiles (pKa>25), such as alkylmetals, bind to the palladium metal first, thus leading to a *syn*-attack on the allylic substrate. The final step is the decomplexation to release the newly formed compounds and regenerate $Pd(0)L_2$ (I) species for the next cycle.



Scheme IV-7 Mechanism of the Pd(0)-catalyzed allylic substitution[65]

From the mechanism, we can see that except the last step, each step in the catalytic cycle could play a key role in enantiomeric discrimination.[66] Thus, identification of the reaction type in terms of mechanism of enatiodiscrimination becomes crucial in obtaining high level of enantioselectivity.

Another challenge associated with the reaction is the control of regioselectivity (branched vs linear). It was found that a palladium catalyst generally leads to the formation of the linear product, while iridium, rhodium, molybdenum, tungsten or platinum usually give the branched product with high retention of configuration.[66] However, the reactions that favor the formation of the branched product are usually limited in reaction scope due to the nature of the catalyst. Palladium catalysts are still the most versatile catalysts in catalytic allylic substitutions. Therefore, the design of ligands that can both reverse the regioselectivity and induce high enantioselectiviy becomes very important in palladium-catalyzed asymmetric allylic substitutions.

It is only the last decades that major accomplishments have been made in the development of effective chiral ligands for palladium-catalyzed asymmetric allylic substitutions. So far, a variety of bidentate ligands have been found effective, which can be classified into C_2-symmetrical ligands and nonsymmetrical ligands (**Figure IV-1**). The C_2-symmetrical ligands generally provide large bite angle (L-M-L) when palladium-L_2 complex is formed, which extends the chiral influence beyond the π-allyl species and transfer their chriality to the substrate. The most popular C_2-symmetrical bidentate ligands are the so-called "Trost ligands" (**IV-19-21** in **Figure IV-1**), which were developed by the Trost group. Those ligands have shown their utility in various Pd-catalyzed asymmetric allylic alkylations, which are the key steps in total syntheses of natural products.[36] On the other hand, the nonsymmetrical ligands usually take the advantage of the differences between the two ligand donors to control the regioselectivity. For example, Pfaltz et al. developed a library of P-N ligands containing a phosphorus ligand donor moiety and a chiral oxazolidine moiety (**IV-22/23** in **Figure IV-1**).[37] Such

ligands displayed remarkable potencies for the regioselectivity of the process as nucleophilic attack on a π-allyl group has a tendency to occur *trans* to the phosphorus.[66]

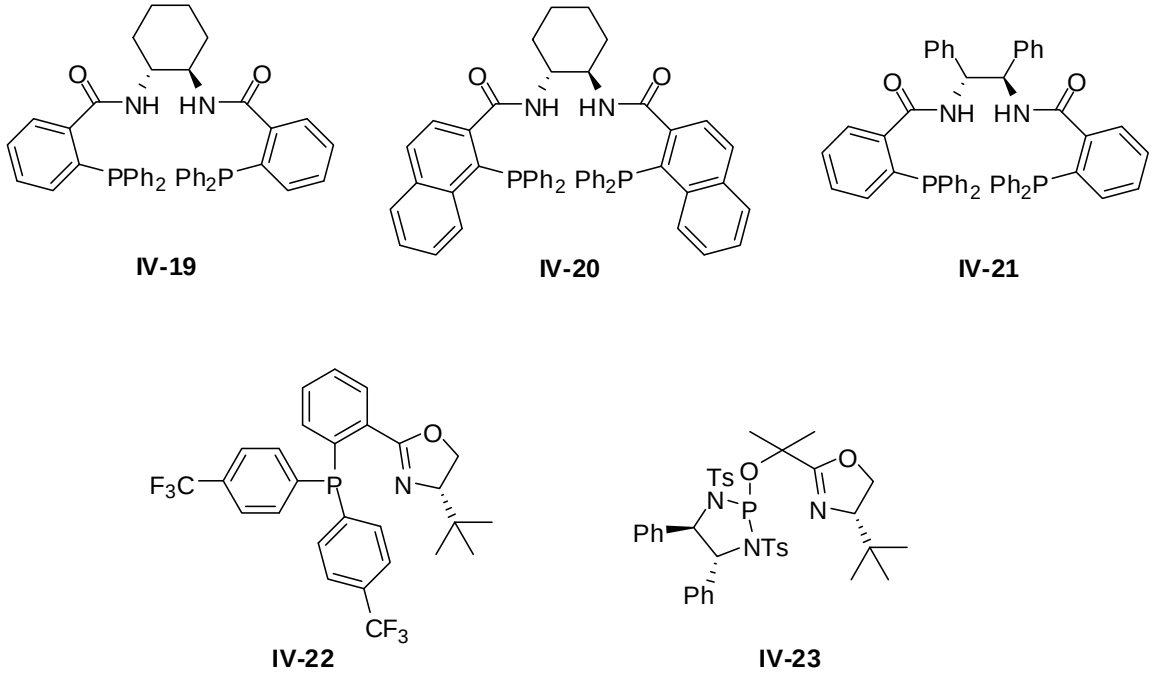


Figure IV-1 Effective bidentate ligands for Pd-catalyzed asymmetric allylic substitution

Despite the success of monodentate phosphoramidite ligands in iridium-catalyzed allylic substitutions, the applications of mondentate ligands in palladium- catalyzed asymmetric allylic substitutions are still very limited.[58-60,67] With the success of our monodentate phosphoramidite ligands in a Pd-catalyzed allylic alkylation reaction, we decided to explore other types of palladium-catalyzed allylic substitutions.

§4.2 Asymmetric Synthesis of 1-Vinyltetrahydroisoquinoline through Pd-Catalyzed Intramolecular Allylic Amination

§4.2.1 Asymmetric Synthesis of Natural Products Bearing C1-Substituted Tetrahydroisoquinolines

C1-Substituted tetrahydroisoquinolines are abundantly found in nature, especially in a variety of plants, soils, and marine microorganisms, and provide important synthetic targets because of their pharmacological properties (**Figure IV-2**).[4] Members of this family have shown diverse activities,[68] e.g., cytotoxicity,[69] antagonist activity to D1 and NMDA receptors,[70] analgesic activity,[71] pathogenesis of Parkinson's disease,[72] and enzyme inhibitory activities for glucosidases[73] and monoamine oxidases.[74] Thus, the synthesis of this class of compounds in optically pure forms is very important for the study of their biological and pharmacological activities, hence has attracted much interest in developing efficient methods and methodologies among synthetic organic chemists.[75,76]

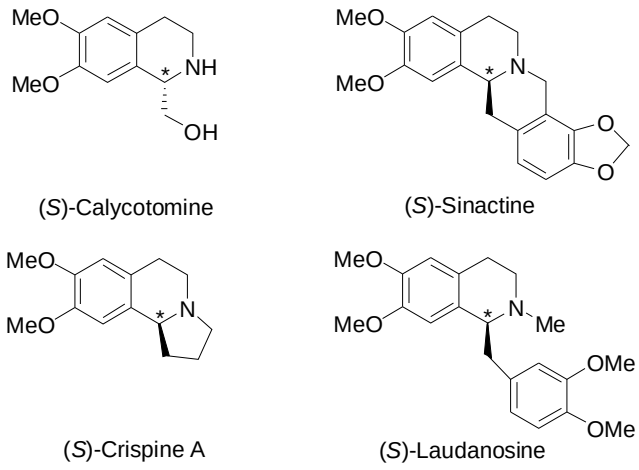
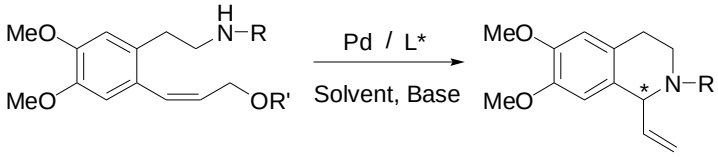


Figure IV-2 Natural products bearing C1-substituted tetrahydroisoquinoline skeleton

Traditionally, the synthesis of optically active C1-substituted tetrahydroiso-quinolines relied largely on the diastereoselective reactions to introduce the chirality at the C1 position.[77] Several enantioseletive catalytic approaches have recently been

developed for the introduction of chirality at the C1 position, e.g., enantioseletive Pictet-Spengler reaction,[78] enantioseletive alkylation, vinylation or cyanation of 3,4-dihydroisoquinolines,[79-81] asymmetric hydrogenation of 3,4-dihydroisoquinolines[82,83] as well as 1-alkylidenetetrahydroisoquinolines,[84] etc.[75]

In 2003 a Pd-catalyzed intramolecualr asymmetric allylic amination approach was reported by Katsuki and coworkers, which was able to construct the heterocycle by introducing the chirality at the C1 position simultaneously in a single step (**Scheme IV-8**).[85] The reaction led to the formation of a highly versatile C1-substituted tetrahydroisoquinoline, which can be easily transformed into various tetrahydroisoquinoline alkaloids. This could be a highly efficient approach if excellent reaction rate and enantioselectivity *were* attained. The chiral Pd catalyst system used in this process was, however, not able to achieve high catalytic activity (12-23 days were needed to reach synthetically meaningful conversions) although very good enantioselectivity (82-88% ee under the optimized conditions) was achieved.[85] Accordingly, the development of a more efficient chiral Pd catalyst systems is apparently necessary to make this process highly efficient and synthetically useful.



Scheme IV-8 Pd-catalyzed intramolecular allylic amination approach to 1-vinyltetra-hydroisoquinolines[85]

In order to achieve high efficiency in the reaction rate and enantioselectivity, the development of suitable chiral ligands for this process is crucial. As described earlier, we have been developing a library of novel enantiopure monodentate phosphoramidite and

phosphite ligands based on axially chiral biphenols, which can be readily prepared and modified, for a variety of catalytic asymmetric reactions.[56,57] Also, as described earlier, we have successfully applied our monodentate phosphoramidite ligands to a Pd-catalyzed asymmetric allylic alkylation which led to the total synthesis of (+)-*γ*-lycorane.[58,59] Since a couple of these chiral monodentate phosphoramidite ligands were found to be extremely effective (up to 99.7% ee) in the Pd-catalyzed asymmetric allylic alkylation, we thought this type of ligands would be effective for the asymmetric allylic amination process as well and optimization could be done through systematic modifications through library synthesis.

§4.2.2 Results and Discussion

§4.2.2.1 Monodentate Phosphoramidite Ligand Library

A library of enantiopure monodentate phosphoramidite ligands consisting of various biphenol moieties and amine moieties were prepared according to the procedures reported previously by our laboratory[2,22,23] (**Figure IV-3**) and used for the intramolecular allylic amination reactions.

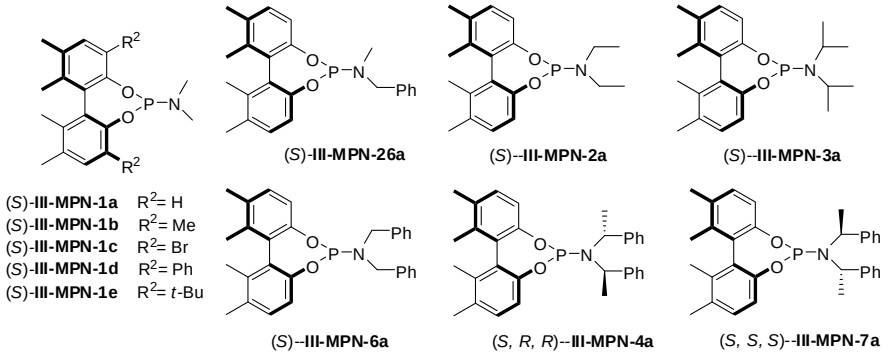
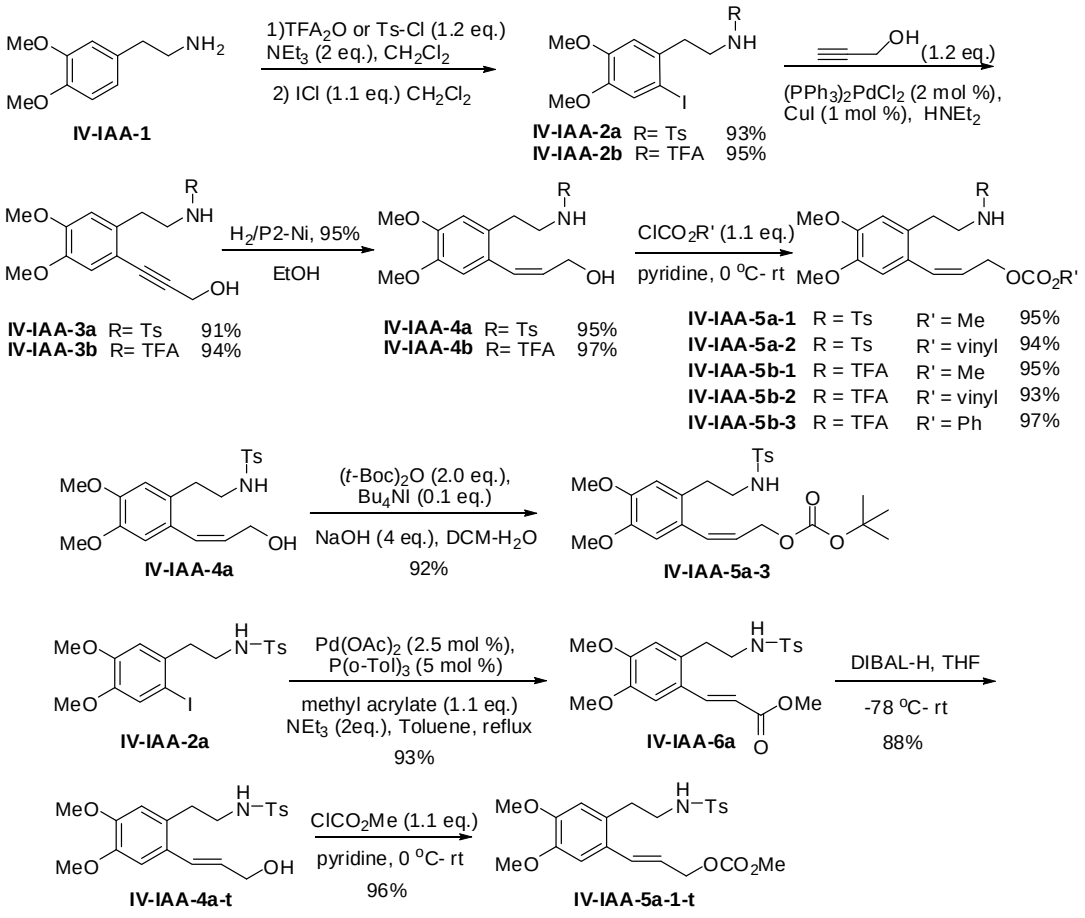


Figure IV-3 Library of enantiopure monodentate phosphoramidite ligands used in this study

§4.2.2.2 Preparation of 2-(Amidoethylphenyl)prop-2-enyl Carbonate Substrates

A series of 2-(amidoethylphenyl)prop-2-enyl carbonates **IV-IAA-5** were prepared, largely following the procedure reported by Katsuki and coworkers for two substrates,[85] with modifications. **Scheme IV-9** illustrates the syntheses of these substrates **IV-IAA-5**, starting from commercially available 3,4-dimethoxyphenylethylamine (**IV-IAA-1**). For the preparation of **IV-IAA-5a1,2** and **IV-IAA-5b1-3**, the amine moiety of **IV-IAA-1** was converted to tosylamide and trifluoroacetamide first and then iodinated to give **IV-IAA-2a** and **IV-IAA-2b**, respectively. Katsuki and coworkers used HIO_3/I_2 for this iodination in the preparation of **IV-IAA-2b** (66% yield). We used ICl in place of HIO_3/I_2 and obtained **IV-IAA-2b** in 95% yield. Sonogashira coupling of **IV-IAA-2a** and **IV-IAA-2b** with propargyl alcohol gave **IV-IAA-3a** and **IV-IAA-3b**, which were subsequently hydrogenated over P2-Ni to afford the corresponding *Z*-alcohols **IV-IAA-4a** and **IV-IAA-4b**, respectively, in excellent overall yields. The *Z*-allylic alcohols **IV-IAA-4**, thus obtained, were acylated with chloroformates (Me, vinyl, Ph) to give the carbonates **IV-IAA-5a1,2** and **IV-IAA-5b1-3** in excellent yields. Katsuki and coworkers used (trifluoroacetamidoethylphenyl)prop-2-enyl acetate and pivaloate, but we found that the intramolecular allyic amination reaction using our ligands proceeded much faster when the corresponding carbonates were used in a preliminary feasibility study. Thus, we employed only carbonates in this work. In addition, we used tosyl besides trifluoroacetyl for the amide moiety. The *tert*-butyl carbonate **IV-IAA-5a-3** was prepared by using $(t\text{-Boc})_2O$ in the acylation of **IV-IAA-4a**. For the preparation of *E*-allylic carbonate **IV-IAA-5a-1-t**, **IV-IAA-2a** was subjected to the Heck reaction with methyl acrylate to give

IV-IAA-6a, which was subsequently reduced by DIBAL-H to afford *E*-allylic alcohol **IV-IAA-4a-t**. Then, **IV-IAA-4a-t** was reacted with methyl chloroformate to give *E*-allylic carbonate substrate **IV-IAA-5a-1-t** in high overall yield.

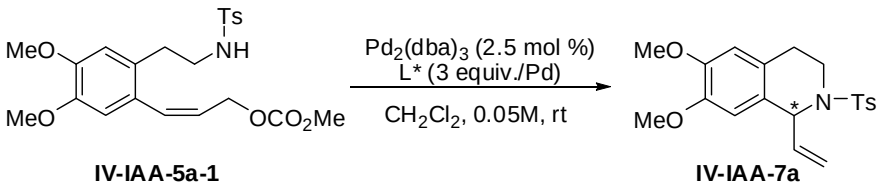


Scheme IV-9 Preparation of substrates **IV-IAA-5**

§4.2.2.3 Pd-Catalyzed Intramolecular Asymmetric Allylic Amination of Substrates IV-IAA-5

The screening of the best chiral ligand among the small library of monodentate phosphoramidite ligands shown in **Figure IV-4** was conducted in two steps. First, we examined the effect of the amine moiety on the catalyst activity and enantioselectivity, using **IV-IAA-5a-1** as the substrate (**Scheme IV-10**). For this comparison, we used ligands (*S*)-**III-MPN-1-4,6,7 and 26a**, which do not have any susbtituents at the 3 and 3'

positions of the biphenyl moiety. The reactions were carried out in CH_2Cl_2 using $Pd_2(dba)_3$ (2.5 mol%) and 3 equivalents of a chiral ligand to Pd at the 0.05 M concentration of **IV-IAA-5a-1** at room temperature (25 ºC). Results are summarized in **Table IV-1**.



Scheme IV-10 Intramolecular asymmetric allylic amination of **IV-IAA-5a-1**

As **Table IV-1** shows, all reactions completed within 5-12 hours to give the desired cyclization product (*R*)-**IV-IAA-7a** in quantitative yield based on the ^{1}H NMR and HPLC analyses. It is noteworthy that this catalyst/reaction system does not require any additional base, e.g., Cs_2CO_3, K_2CO_3, and Na_2CO_3, which is essential for Katsuki's catalyst/reaction system in CH_2Cl_2,[85] It is clear from the results shown in **Table IV-1** that bulkier the amine moiety, slower the reaction. Also, bulkier amine moieties give lower enantioselectivity as exemplified by the use of (*S*)-**III-MPN-3a** bearing a diisopropylamine moiety (Entry 4). Only exception for this general observation is ligand (*S,R,R*) **-III-MPN-4a**, which bears a bulky bis(1-phenylethyl)amine moiety (Entry 6). However, ligand (*S,S,S*)-**III-MPN-7a**, which is a diastereomer of (*S,R,R*)-**III-MPN-4a**, induces virtually no asymmetric induction (Entry 7). These results clearly indicate that (*S,R,R*)-**III-MPN-4a** is a matching pair and (*S,S,S*)-**III-MPN-7a** a mismatching pair. It is of interest to note that ligand (*S,S,S*)-**III-MPN-7a** was one of the better ligands in the asymmetric allylic alkylation reaction for (+)-lycorane synthesis, achieving 92.6% ee.[58]

The observed sharp contrast indicates how different these two reaction systems are even though both are asymmetric allylic substitution reactions. After the first screening, we selected (*S*)-**III-MPN-1a** bearing a small dimethylamine moiety as our lead ligand in terms of the catalyst activity and enantioselectivity.

Table IV-1 Ligand screening: effect of the amine moiety

Entry	Ligand (**III-MPN**)	Time (h)	Conv.[a,b] (%)	% ee [b]
1	(*S*) **-1a**	5	100	45(*R*)
2	(*S*) **-26a**	5	100	25(*R*)
3	(*S*) **-2a**	7	100	42(*R*)
4	(*S*) **-3a**	7	100	0.5(*R*)
5	(*S*) **-6a**	7	100	13(*R*)
6	(*S,R,R*) **-4a**	12	100	45(*R*)
7	(*S,S,S*) **-7a**	12	100	0.1(*R*)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralpak AD-RH, CH_3CN/H_2O.

Next, the effect of the substituent R^2 at the 3 and 3' positions of the biphenyl moiety on the catalytic activity and enantioselectivity was examined under the same reaction conditions as those for the first ligand screening mentioned above. Thus, ligands (*S*)-**III-MPN-1a-e** were examined for their efficacy in the formation of tetrahydro-isoquinoline **IV-IAA-7a**. Results are shown in **Table IV-2**. Apparently, the enantioselectivity increases (45% ee →74% ee) as the bulkiness of the substituent at the 3 and 3' positions increases, i.e., H < Me < Br < Ph (**Entries 1-4**), but *t*-Bu is so bulky that it causes negative effect (Entry 5). However, the most dramatic effect of the 3,3'-substituents is the direction of asymmetric induction, i.e., (*S*)-**III-MPN-1a** (R^2 = H)

induces *R* configuration in the product **IV-IAA-7a**, while (*S*)-**III-MPN-1b** (R^2 = Me), (*S*)-**III-MPN-1c** (R^2 = Br), (*S*)-**III-MPN-1d** (R^2 = Ph) and (*S*)-**III-MPN-1e** (R^2 = *t*-Bu) give **IV-IAA-7a** with *S* configuration. Thus, the substituent R^2 at the 3 and 3' positions exert a significant influence on the extent and direction of asymmetric induction, as anticipated from our experience in the previous catalytic asymmetric transformations using this type of ligands.[53,56-59] After two-step ligand screenings, we selected (*S*)-**III-MPN-1d** (R^2 = Ph) as the ligand of choice for the intramolecular asymmetric allylic amination of the substrates of this type.

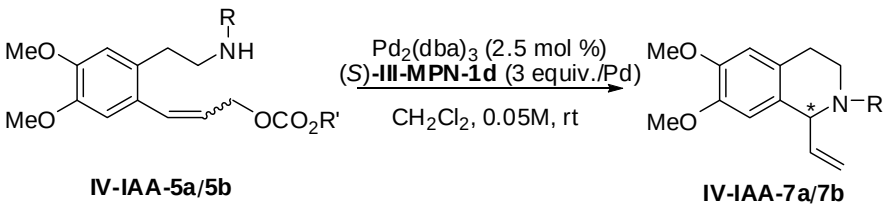
Table IV-2 Ligand screening: effect of the substituent R^2

Entry	Ligand(**III-MPN**)	Time (h)	Conv.[a, b] (%)	% ee[b]
1	(*S*)-**1a** (R^2 = H)	5	100	45(*R*)
2	(*S*)-**1b** (R^2 = Me)	7	100	48(*S*)
3	(*S*)-**1c** (R^2 = Br)	10	100	59(*S*)
4	(*S*)-**1d** (R^2 = Ph)	10	100	74(*S*)
5	(*S*)-**1e** (R^2 = *t*-Bu)	16	100	23(*S*)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralpak AD-RH, CH_3CN/H_2O

Although the enantioselectivity attained by (*S*)-**III-MPN-1d** was only 74% ee in the reaction of **IV-IAA-5a-1**, we hypothesized that much higher enantioselectivity could be achieved through modification of the substrate structure. In fact, as described below, excellent enantioselectivity (95% ee) has been achieved through substrate structure modifications. As described above, we have prepared six substrates bearing an *N*-tosyl moiety (**IV-IAA-5a**) and an *N*-trifluoroacetyl moiety (**IV-IAA-5b**) as well as methyl, vinyl, *tert*-butyl, and phenyl in the carbonate moiety. In addition to the six substrates

bearing a *Z* olefin moiety, a substrate with *E* olefin geometry, **IV-IAA-5a-1-t**, was also prepared and examined. The reactions were run under the same conditions as those used for the screening of the ligands described above, using **L1d** as the chiral ligand (**Scheme IV-11**). Results are summarized in **Table IV-3**.



Scheme IV-11 Reactions of **5a** and **5b** using **L1d** as the chiral ligand

As **Table IV-3** shows, the bulkiness of the carbonate substituent R' does not have much influence on the reaction in the **IV-IAA-5a** series of substrates (R = Ts) although *t*-Bu-carbonate **IV-IAA-5a-3** gives a slightly better enantioselectivity (77% ee) and slower reaction rate (**Entry 3**) than Me-carbonate **IV-IAA-5a-1** (Entry 1). The introduction of a vinyl group to the carbonate moiety accelerates the reaction, but lowers enantioselectivity (**Entry 2**). The geometry of the olefin moiety is critical for the direction of asymmetric induction, i.e., the substrate bearing an *E* olefin geometery, **IV-IAA-5a-1-t**, gives **IV-IAA-7a** with opposite configuration (*R*) (**Entry 4**), but the enantiopurity of the product (71% ee) is only slightly lower than the **IV-IAA-7a**(*S*) obtained in the reaction of **IV-IAA-5a-1** with *Z* olefin geometry (**Entry 1**). The results indicate that the sense of enantioface selection by the chiral catalyst is the same in these two cases, leading to the formation of the two enantiomers of **IV-IAA-7a**. In contrast to the **IV-IAA-5a** series, the reactions of the **IV-IAA-5b** series are highly sensitive to the carbonate substituent R' (**Entries 5-7**). The introduction of a vinyl- or a phenyl-carbonate to the **IV-IAA-5b** series

substantially increased the enantioselectivity of the reaction, and tetrahydroisoquoline **IV-IAA-7b** with 95% ee (*S*) was obtained with the phenyl-carbonate substrate **IV-IAA-5b-3** (**Entry 7**). It is also noteworthy that a marked difference was observed between **IV-IAA-5a-2** (46% ee) and **IV-IAA-5b-2** (89% ee), which have the same vinyl-carbonate moiety but differs in the amide moiety, i.e., *N*-Ts vs. *N*-CF_3CO (**Entries 2 and 6**).

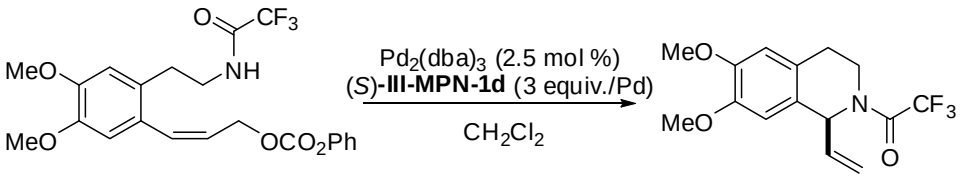
Table IV-3 Reactions of **IV-IAA-5a** and **5b** using (*S*)**-III-MPN-1d** as the chiral ligand

Entry	Substrate (**IV-IAA**)	R	R'	Olefin geometry	Time (h)	Conv. (%)[a,b]	% ee[b]
1	**5a-1**	Ts	Me	*Z*	10	100	74(*S*)
2	**5a-2**	Ts	vinyl	*Z*	5	100	46(*S*)
3	**5a-3**	Ts	*t*-Bu	*Z*	18	100	77(*S*)
4	**5a-1-t**	Ts	Me	*E*	10	100	71(*R*)
5	**5b-1**	CF_3CO	Me	*Z*	10	100	79(*S*)
6	**5b-2**	CF_3CO	vinyl	*Z*	7	100	89(*S*)
7	**5b-3**	CF_3CO	Ph	*Z*	7	100	95(*S*)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC; for *N*-Ts products **7a**: Chiralpak AD-RH, CH_3CN/H_2O; for *N*-TFA products **7b**: Chiralcel OD-H, hexanes/*i*-PrOH.

Finally, the effects of the reaction variables, i.e., reaction temperature and concentration, on the reaction rate and enantioselectivity were examined with the optimized ligand and substrate combination using (*S*)**-III-MPN-1d** as the chiral ligand and **IV-IAA-5b-3** as the substrate (**Scheme IV-12**). As **Table IV-4** shows, the substrate concentration only affects reaction rate, as anticipated. The enantioselectivity increases slightly when the reaction is run at a lower temperature (-25 ºC) (**Entry 5**, 96% ee). However, the enantioselectivity clearly drops when the reaction is carried out at 50 ºC

(**Entry 6**, 84% ee). Thus, the reaction at room temperature (25 ºC) and 0.5 M concentration appears to be near optimal, which is synthetically very convenient.



IV-IAA-5b-3 **IV-IAA-7b** (*S*)

Scheme IV-12 Highly efficient catalytic asymmetric synthesis of **IV-IAA-7b**

Table IV-4 Effects of reaction temperature and concentration

Entry	Conc. (M)	Temp. (°C)	Time (h)	Conv. (%)[a, b]	% ee[b]
1	0.01	25	14	100	95(*S*)
2	0.05	25	7	100	95(*S*)
3	0.5	25	6	100[c]	94(*S*)
4	0.05	0	10	100	95(*S*)
5	0.05	-25	14	100	96(*S*)
6[d]	0.05	50	5	100	84(*S*)

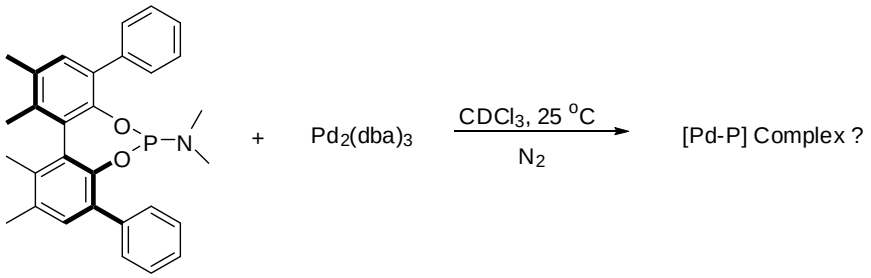
[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralcel OD-H, hexanes/*i*-PrOH.
[c] 87% isolated yield (100% product selectivity) in the 1.0 mmol scale reaction.
[d] Reaction was performed in a sealed tube.

§4.2.2.4 Mechanistic Study on the Catalytic System

Despite the successful applications of monodentate phosphorus ligands in Pd-catalyzed asymmetric alllylic substitutions, the mechanistic studies aimed at the identification of the catalytic species and illustration of the enantiomeric discrimination are still very limited. Only recently, several crystal structures of the Pd-phosphoramidite and Pd-Bis(phosphoramidite) complexes were reported in the literature. Yet the identification of the catalytic species is still ambiguous.[86-89] In the case of bulky

monodentate ligands, it has been hypothesized that there is 1:1 ratio between transition metal and ligand in a catalytic palladium complex.[86,87] A working model has also been proposed to explain the regio- and enantioselectivity based on a palladium complex with the 1:1 ratio of palladium to phosphoramidite ligand.[87] However, when small or even medium-sized ligands are used in the reactions, it may not be the case that the ratio between palladium and phosphoramidite ligands remains 1:1.

Therefore, we conducted ^{31}P NMR studies to investigate the stoichiometry of palladium metal to monodentate phosphoramidite ligand (*S*)-**III-MPN-1d**. Mixtures of tris(dibenzylideneacetone)dipalladium (0) and (*S*)-**III-MPN-1d** with different Pd:P molar ratios (i.e. 1:1, 1:2 and 1:2.5) were dissolved in degassed $CDCl_3$ under nitrogen atmosphere. The solutions were incubated for 10 min before being subjected to ^{31}P NMR study. From **Figure IV-4**, it is clear that the chemical shift that corresponded to the free ligand is not observed until Pd:P molar ratio turn is to 1:2.5. In all cases, the major signals are two distinctive doublets (*J*= 7.3 Hz). From these observations, we have hypothesized that the active palladium catalyst species bears two phosphoramidite ligands on the same palladium (i.e., ratio of Pd:P= 1:2) with pseudo-C_2 symmetry, which may be caused by one equivalent of dibenzylideneacetone still associated with the complex.



(S)-**III-MPN-1d**
^{31}P NMR (162 Hz, $CDCl_3$): 141.1 ppm

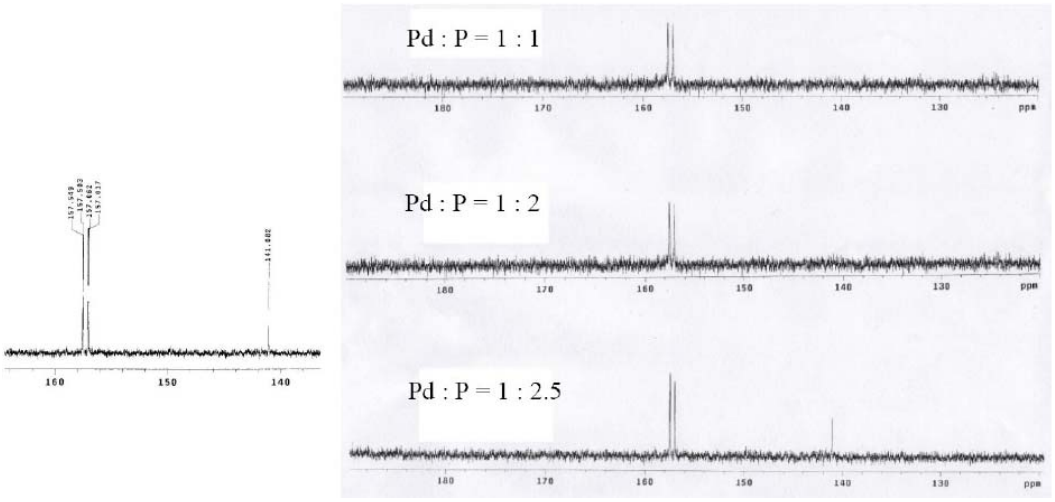
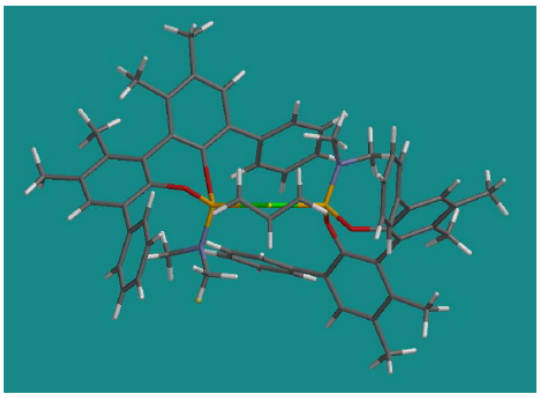
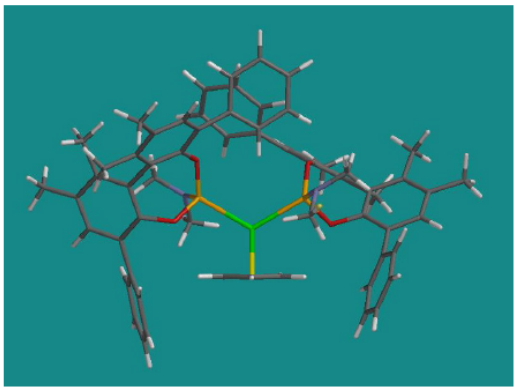


Figure IV-4 ^{31}P NMR of palladium complexes with ligand (*S*)-**III-MPN-1d**

With the information obtained from the ^{31}P NMR studies, we proceeded to perform a molecular modeling study on the simplified active-catalyst complex [Pd(II)L*$_2$ (Allyl)]$^+$(L*= (*S*)-**III-MPN-1d**). The result after energy minimization (Spartan program; MM2/PM3) clearly indicates a pseudo-C_2 symmetrical structure, in which the two phosphoramidite ligands created a C_2 symmetrical environment surrounding the allyl moiety(**Figure IV-5**). The measured bite angle (P*-Pd-P*) is 114^o which can help to extend the chiral influence beyond the π-allyl moiety, thus leading to high enantio-selectivity. The proposed structure was also supported by a recent publication where the crystal structure of a similar palladium (II) complex bearing two phosphoramidite ligands on the same palladium was reported.[89]



$[Pd(II)L^*_2(Allyl)]^+$ equatorial view
L*= (*S*)-**III-MPN-1d**



$[Pd(II)L^*_2(Allyl)]^+$ apical view
L*= (*S*)-**III-MPN-1d**

Figure IV-5 Proposed structure of $[Pd(II)L^*_2(Allyl)]^+$ (L*= (*S*)-**III-MPN-1d**)

In conclusion, a highly efficient Pd-phosphoramidite catalyst system has been developed for an intramolecular allylic amination reaction that leads to the formation of 1-vinyltetrahydroisoquinoline derivatives with excellent enantioselectivity. ^{31}P NMR studies and molecular modeling revealed that the active catalyst species is very likely to bear two phosphoramidite ligands coordinating to the same palladium with pseudo-C_2 symmetry. Further studies on obtaining crystal structure of the $[Pd(II)L^*_2(Allyl)]^+$ complex are in progress.

§4.3 Experimental Section

General Method. ^1H and ^{13}C NMR spectra were measured on a Varian Inova-400 NMR (400 MHz ^1H and 100 MHz ^{13}C) or a Varian Gemini-2300 (300 MHz ^1H and 75 MHz ^{13}C) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^1H, 7.26 ppm; ^{13}C, 77.0 ppm. C_6H_6: ^1H, 7.15 ppm) as the internal standard. . The enantiomeric excess

was determined by HPLC: Waters M45 system with Waters 484 detector using Chiralcel OD-H column (hexanes/*i*-PrOH = 98/2, 0.5 mL/min) or a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH column (CH_3CN/H_2O = 50/50, 0.5 mL/min).Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and flash chromatography was carried out on silica gel 60 (Silicyle; 40–63 μm particle size). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL.

Materials. All solvents were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. All chemicals were purchased from Aldrich and Acros Chemical Co. unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) was purchased from Strem Chemicals Inc. All reactions were carried out under nitrogen or argon atmosphere.

Synthesis of substrates IV-IAA-5a-1 ~ 5a-3 and 5b-1 ~ 5b-3

1-Iodo-4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl)]benzene (IV-IAA-2b). To a stirred solution of homoveratrylamine (**IV-IAA-1**) (1 g, 5.5 mmol) and NEt_3 (1.2 g, 11 mmol) in CH_2Cl_2 (8 mL) was added slowly trifluoroacetic anhydride (1.4 g, 6.6 mmol) at 0 ^oC. The mixture was stirred at 0 ^oC for 1 h. Reaction was quenched by addition of water at the same temperature, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 three times, and combined organic layer was washed with brine,

dried over $MgSO_4$, filtered, and concentrated to afford *N*-trifluoroacetyl-**IV-IAA-1** as a pale yellow solid: mp 82.0-83.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (t, J = 6.7 Hz, 2H), 3.60 (q, J = 6.7 Hz, 2H), 3.87 (s, 6H),. 6.27 (br, 1H), 6.69 (d, J = 1.7 Hz, 1 H), 6.73 (dd, J = 1.7, 8.1 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1 H). The product was used in the next step without further purification.

To a well-stirred solution of *N*-trifluoroacetyl- **IV-IAA-1** in CH_2Cl_2 (10 mL), 1*M* ICl in CH_2Cl_2 (6.1 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature until TLC had indicated the complete conversion of the starting material. The reaction was quenched by addition of saturated Na_2SO_3 solution. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with water, brine and dried over $MgSO_4$. The crude product was obtained after filtration and evaporation of the solvent. Recrystallization of the crude product from MeOH afforded **IV-IAA-2b** as a white solid (2.1g, 95% yield): mp 124.5-125.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (t, J = 7.2 Hz, 2H), 3.61 (q, J = 6.6 Hz, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 6.37 (br s, 1H), 6.69 (s, 1H), 7.24 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.9, 40.0, 55.8, 56.1, 87.9, 112.6, 115.7 (q, J = 286 Hz), 121.8, 132.6, 148.5, 149.6, 157.3 (q, J = 36 Hz); HRMS (ESI) calcd for $C_{12}H_{14}NO_3F_3I$ $[M+H]^+$ 403.9971, found 403.9981 (Δ= 2.5 ppm).

1-Iodo-4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]benzene (IV-IAA-2a). This compound was synthesized in the same manner as that described for **IV-IAA-2b**: White solid; 93% isolated yield; mp 125-127 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.84 (t, J = 6.9Hz, 2H), 3.18 (q, J = 4.8 Hz, 2H), 3.80 (s, 3H),

3.81(s, 3H), 4.70 (br s, 1H), 6.67 (s, 1H), 7.13 (s, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.70 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 40.2, 43.0, 55.9, 56.1, 87.9, 112.9, 121.7, 127.0, 129.6, 132.8, 136.9, 143.4, 148.3, 149.4; HRMS (ESI) calcd for $C_{17}H_{21}INO_4S$ $[M+H]^+$ 462.0236, found 462.0245 (Δ= 1.9 ppm).

3-{4,5-Dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-ynol (IV-IAA-3b). A mixture of **IV-IAA-2b** (403 mg, 1 mmol), $Pd(PPh_3)_2Cl_2$ (14 mg, 0.02 mmol), and CuI (1.9 mg, 0.01 mmol) was placed in a 50 mL round-bottomed flask. After purging the flask with nitrogen, diethylamine (5 mL) was added to the mixture, and the solution was stirred for 20 min. Propargyl alcohol (68 mg, 1.2 mmol) was added to the reaction mixture via a syringe. The reaction mixture was stirred at room temperature until TLC indicated the completion of the reaction. Then, saturated ammonium chloride solution was added to quench the reaction. The aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 5/1~1/1) afforded **IV-IAA-3b** as a white solid (311mg, 94% yield): mp 117.5-119 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (t, J = 7.2 Hz, 2H), 3.02 (br s, 1H), 3.59 (q, J = 7.2 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.49 (s,2H), 6.56 (br s, 1H), 6.89 (s, 1H), 6.98 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 33.5, 40.7, 51.4, 55.9, 55.9, 83.6, 90.3, 112.1, 114.4, 114.6, 115.9 (q, J = 280 Hz), 133.0, 147.6, 149.6, 157.5 (q, J = 36 Hz); HRMS (ESI) calcd for $C_{15}H_{17}NO_4F_3$ $[M+H]^+$ 332.1110, found 332.1116 (Δ= 1.8 ppm).

3-{4,5-Dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-ynol (IV-IAA-3a). This compound was synthesized in the same manner as that described for **IV-IAA-3b**: White solid; 91% isolated yield; mp 126-128 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.95 (t, J = 6.9Hz, 2H), 3.23 (q, J = 6.1Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.50 (d, J = 6.0Hz, 2H), 4.63 (t, J = 6.1Hz, 1H), 6.56 (s, 1H), 6.89 (s, 1H), 7.25 (d, J = 8.4Hz, 2H). 7.68 (d, J = 8.4Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 34.8, 43.9, 51.4, 55.8, 55.9, 83.7, 90.5, 112.1, 114.2, 114.6, 126.9, 129.6, 133.5, 136.9, 143.3, 147.4, 149.5; MS (ES) cacld for $C_{20}H_{22}NO_4S$ $[M\text{-}OH]^+$ 372.1, found 372.1; HRMS (ESI) calcd for $C_{20}H_{22}NO_4S$ $[M\text{-}OH]^+$ 372.1270, found 372.1268 (Δ= -0.5 ppm).

(*Z*)-3-{4,5-Dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enol (IV-IAA-4b). P2-Ni catalyst was generated in *situ* following the standard procedure by adding $NaBH_4$ (1.0 mg, 0.02 mmol) to a suspension of $Ni(OAc)_2$ (3.0 mg, 0.01 mmol) in EtOH (2 mL) at room temperature under an nitrogen atmosphere with stirring. After 30 min, neat ethylenediamine (1.64 μL, 0.024 mmol) was introduced to the reaction mixture. After stirring the catalyst solution for 10 min, **3b** (165 mg, 0.5 mmol) in ethanol (5 mL) was added. The nitrogen atmosphere was then replaced by hydrogen. The reaction mixture was stirred until TLC indicated the completion of the reaction. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine. After dried over $MgSO_4$, crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 3/1~1/1) afforded **4b** as a colorless oil (161mg, 97% yield): ^{1}H NMR

(300 MHz, $CDCl_3$) δ2.19 (br s, 1H), 2.83 (t, J = 6.9 Hz, 2H), 3.52 (q, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.84 (s, 3H), 4.23 (dd, J = 1.5 Hz, 6.9 Hz, 2H), 5.90 (dt, J = 6.9 Hz, 11.4 Hz, 1H), 6.62 (d, J = 11.4 Hz, 1H), 6.64(s, 1H), 6.66 (s, 1H), 6.81 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ32.2, 40.2, 55.9, 56.0, 59.2, 112.8, 113.1, 115.8 (q, J = 286 Hz), 127.8, 128.1, 129.6, 131.3, 147.4, 148.4, 157.3 (q, J = 37 Hz); HRMS (ESI) calcd for $C_{15}H_{18}NO_4F_3Na$ $[M+Na]^+$ 356.1086, found 356.1088 (Δ= 0.6 ppm).

3-{4,5-Dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}prop-2-enol (IV-IAA-4a). This compound was synthesized in the same manner as that described for **IV-IAA-4b**: White solid; 95% isolated yield; mp 104-106 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (s, 1H), 2.41 (s, 3H), 2.73 (t, J = 6.2Hz, 2H), 3.14 (q, J = 6.0Hz, 2H), 3.82 (s, 3H), 3.84 (s, 3H), 4.23 (dd, J = 1.2Hz, 6.9Hz, 2H), 4.64 (t, J = 6.0Hz, 1H), 5.90 (dt, J = 6.9Hz, 8.9Hz, 1H) 6.53 (d, J = 8.9Hz, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 7.25 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ21.8, 33.1, 44.1, 56.2, 56.3, 59.6, 112.9, 113.4, 127.3, 128.3, 128.7, 129.9, 130.1, 132.1, 137.1, 143.7, 147.6, 148.8; HRMS (ESI) calcd for $C_{20}H_{24}NO_4S$ $[M-OH]^+$ 374.1426, found 374.1425 (Δ= -0.3 ppm).

(*E*)-3-{4,5-Dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}-prop-2-enol (IV-IAA-4a-t). Compound **IV-IAA-2a** (461 mg, 1.0 mmol) was added to a solution of $Pd(OAc)_2$ (5.6 mg, 0.0025 mmol) and P(*o*-tol)$_3$ (15.2 mg, 0.0050 mmol) and NEt_3 (202 mg, 2.0 mmol) in toluene (10 mL). Then, methyl acrylate (95 mg, 1.1 mmol) was added to this mixture via a syringe. The reaction mixture was heated to reflux until

TLC indicated the disappearance of the starting material, and was cooled to room temperature. After filtration through a pad of celite, the filtrate was concentrated *in vacuo* and redissolved in CH_2Cl_2, washed with 2*N* HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexane/EtOAc = 8/1~3/1) afforded methyl (*E*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl]phenyl}propenoate (**IV-IAA-6a**) as a white solid (388 mg, 93% isolated yield): mp 149-150 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.92 (t, *J* = 6.9Hz, 2H), 3.14 (q, *J* = 6.6Hz, 2H), 3.80 (s, 3H), 3.88 (s, 6H), 4.41 (t, *J* = 6.0 Hz, 1H), 6.23 (d, *J* = 15.9Hz, 1H), 6.64 (s, 1H), 7.00 (s,1H), 7.27 (d, *J* = 5.1Hz, 2H), 7.68 (d, *J* = 5.1Hz, 2H), 7.79 (d, *J* = 15.9Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 33.0, 44.2, 51.7, 55.9, 56.0, 108.9, 113.1, 117.1, 125.2, 127.0, 129.6, 131.3, 136.9, 140.9, 143.4, 148.1, 150.9, 167.4; HRMS (ESI) calcd for $C_{21}H_{26}NO_6S$ $[M+H]^+$ 420.1481, found 420.1477 (Δ = -1.0 ppm).

To a solution of **IV-IAA-6a** (210 mg, 0.5 mmol) in toluene at -78 ^oC, was added dropwise 1*M* DIBAL-H (2.0 mL) in hexanes. The mixture was kept at -78 ^oC for 1h, warmed up to room temperature and kept for 3h. The reaction was quenched by MeOH (0.5 mL), followed by the addition of saturated Rochelle's salt solution. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$.Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 95/5) afforded **IV-IAA-4a-t** as a colorless oil (172 mg, 88% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.83 (t, *J* = 7.2 Hz, 2H), 3.11 (q, *J* = 6.9 Hz,

2H), 3.82 (s, 3H), 3.86 (s, 3H), 4.30 (dd, J = 1.2 Hz, 5.6 Hz, 2H), 4.81 (t, J = 6.3 Hz, 1H), 6.13 (dt, J = 5.6 Hz, 15.6Hz, 1H), 6.53 (s, 1H), 6.76 (dt, J = 1.2 Hz, 15.6 Hz, 1H). 6.93 (s, 1H), 7.24 (d, J = 6.6 Hz, 2H), 7.67 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 33.2, 44.1, 55.9, 63.6, 109.2, 112.8, 126.9, 127.9, 128.0, 128.4, 129.5, 129.6, 137.0, 143.4, 148.0, 148.7; HRMS (ESI) calcd for $C_{20}H_{25}NO_5SNa$ $[M+Na]^+$ 414.1351, found 414.1342 (Δ = -2.2 ppm).

Methyl (*Z*)-3-{4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (IV-IAA-5b-1). To a solution of **IV-IAA-4b** (166 mg, 0.5 mmol) and pyridine (1.0 mL) in CH_2Cl_2 (10 mL) was added slowly methyl chloroformate (52 mg, 0.55 mmol) in 3 mL CH_2Cl_2 (3 mL) at 0 ºC. After stirring the mixture at 0 ^{o}C for 3 h, the reaction was quenched by saturated $CuSO_4$, and aqueous phase was extracted with diethyl ether four times. Combined organic layer was washed with water, brine and dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 3/1) afforded **IV-IAA-5b-1** as a white solid (185 mg, 95% yield): mp 76.5-77.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ2.93 (t, J = 6.6 Hz, 2H), 3.58 (q, J = 6.6 Hz, 2H), 3.78 (s, 3H), 3.92 (s, 6H), 4.83 (dd, J = 1.2 Hz, 6.6 Hz, 2H), 5.91 (dt, J = 6.6 Hz, 11.4 Hz, 1H), 6.69 (s, 1H), 6.71 (s, 1H), 6.84 (d, J = 11.4 Hz, 1H),), 6.85 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ32.0, 39.8, 54.8, 55.8, 56.0, 64.4, 113.1, 115.8 (q, J = 286 Hz), 125.7, 126.9, 128.4, 132.7, 147.3, 148.7, 155.8, 157.3 (q, J = 37 Hz); HRMS (ESI) calcd for $C_{17}H_{20}NO_6F_3Na$ $[M+Na]^+$ 414.1140, found 414.1156 (Δ= 3.9 ppm).

Other carbonates, **IV-IAA-5a-1-2**, **5b-2-3**, and **5a-1-t** were synthesized in the same manner as that described for **IV-IAA-5b-1**.

Methyl (*Z*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl] phenyl}prop-2-enyl carbonate (**IV-IAA-5a-1**): White solid; 95% isolated yield; mp 49-50 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.75 (t, J = 6.2 Hz, 2H), 3.17 (q, J = 6.0 Hz, 2H), 3.76 (s, 3H), 3.84 (s, 6H), 4.26 (dd, J = 1.2 Hz, 6.9 Hz, 2H), 4.61 (t, J = 6.0 Hz, 1H), 5.93 (dt, J = 6.9 Hz, 8.9 Hz, 1H) 6.55 (d, J = 8.9 Hz, 1H), 6.57 (s, 1H), 6.64 (s, 1H), 7.27 (d, J = 8.1 Hz, 2H), 7.64 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ21.8, 33.6, 43.8, 55.2, 56.2, 56.3, 64.8, 113.1, 113.2, 125.8, 127.3, 127.4, 128.9, 129.9, 132.9, 137.4, 143.6, 147.6, 149.0, 156.0; HRMS (ESI) calcd for $C_{22}H_{27}NO_7SNa$ $[M+Na]^+$ 472.1406, found 472.1395 (Δ= -2.3 ppm).

Ethenyl (*Z*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl] phenyl}prop -2-enyl carbonate (**IV-IAA-5a-2**): White solid; 94% isolated yield; mp 68-70 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.72 (t, J = 7.2 Hz, 2H), 3.10 (q, J = 7.2 Hz, 2H), 3.83 (s, 6H), 4.57 (dd, J = 1.2 Hz, 6.0 Hz, 1H), 4.64 (t, J = 5.7 Hz, 2H), 4.71 (dd, J = 1.2 Hz, 6.6 Hz, 2H), 4.91 (dd, J = 1.2 Hz, 11.1 Hz, 1H), 5.81 (dt, J = 6.9 Hz, 14.4 Hz, 1H), 6.62 (s, 2H), 6.69 (d, J = 14.4 Hz, 1H), 7.04 (dd, J = 6.0 Hz, 11.1 Hz, 1H), 7.27 (d, J = 6.3 Hz, 2H), 7.68 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ21.4, 33.3, 43.4, 55.9, 64.9, 97.9, 112.7, 112.9, 124.9, 126.9, 127.0, 128.6, 129.6, 133.2, 137.0, 142.6, 143.3, 147.4, 148.7, 152.6; HRMS (ESI) calcd for $C_{23}H_{28}NO_7S$ $[M+H]^+$ 462.1586, found 462.1583 (Δ= -0.6 ppm).

Methyl (*E*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl] phenyl}prop-2-enyl carbonate (IV-IAA-5a-1-t): Colorless oil; 96% isolated yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ2.41 (s, 3H), 2.82 (t, J = 6.9 Hz, 2H), 3.12 (q, J = 6.9 Hz, 2H), 3.80 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.58 (t, J = 6.3 Hz, 1H), 4.75 (dd, J = 1.2 Hz, 6.6 Hz, 2H), 6.03 (dt, J = 6.6 Hz, 15.3 Hz, 1H), 6.55 (s, 1H), 6.78 (d, J = 15.3 Hz, 1H), 6.90 (s, 1H), 7.26 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ21.5, 33.1, 43.9, 54.8, 55.9, 68.6, 109.1, 112.8, 122.8, 127.0, 127.4, 128.3, 129.6, 132.0, 137.0, 143.3, 148.0, 149.2, 155.6. HRMS (ESI) calcd for $C_{22}H_{27}NO_7SNa$ $[M+Na]^+$ 472.1406, found 472.1397 (Δ= -1.9 ppm).

Ethenyl (*Z*)-3-{4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (IV-IAA-5b-2): White solid; 93% isolated yield; mp 59-60.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ2.86 (t, J = 6.9 Hz, 2H), 3.51 (q, J = 6.3 Hz, 2H), 3.85 (s, 6H), 4.57 (dd, J = 2.1 Hz, 6.0 Hz, 1H), 4.84 (dd, J = 1.2 Hz, 6.9 Hz, 2H), 4.90 (dd, J = 2.1 Hz, 13.8 Hz, 1H), 5.87 (dt, J = 6.9 Hz, 11.4 Hz, 1H), 6.64 (s, 1H), 6.65 (s, 1H), 6.65 (br s, 1H), 6.81 (d, J = 11.4 Hz, 1H), 6.98 (dd, J = 6.0 Hz, 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ32.0, 39.9, 55.9, 56.0, 64.9, 98.2, 113.1, 115.9 (q, J = 286 Hz), 125.1, 126.8, 128.4, 133.2, 142.4, 147.4, 148.8, 152.8, 157.3 (q, J = 37 Hz); HRMS (ESI) calcd for $C_{18}H_{20}NO_6F_3Na$ $[M+Na]^+$ 426.1140, found 426.1148 (Δ= 1.9 ppm).

Phenyl (*Z*)-3-{4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (IV-IAA-5b-3): Colorless oil; 97% isolated yield; ^{1}H NMR (300 MHz,

$CDCl_3$) δ2.92 (t, J = 6.6 Hz, 2H), 3.54 (q, J = 6.6 Hz, 2H), 3.90 (s, 3H), 3.92 (s, 3H), 4.94 (dd, J = 1.2 Hz, 6.9 Hz, 2H), 5.99 (dd, J = 6.9 Hz, 11.4 Hz, 1H), 6.70 (s, 1H), 6.72 (s, 1H), 6.80 (br s, 1H), 6.90 (d, J = 11.4 Hz, 1H), 7.14 (m, 2H), 7.30 (m, 1H), 7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ31.9, 39.8, 55.8, 55.9, 65.0, 113.0, 115.6 (q, J = 286 Hz), 120.8, 125.0, 126.1, 126.7, 128.5, 129.4, 133.3, 147.2, 148.6, 150.8, 153.8, 157.2 (q, J = 37 Hz); HRMS (ESI) calcd for $C_{22}H_{22}NO_6F_3Na$ $[M+Na]^+$ 476.1297, found 476.1313 (Δ= 3.4 ppm).

***tert*-Butyl (*Z*)-3-{4,5-dimethoxy-2-[2-(4-methylbenzenesulfonylamino)ethyl] phenyl}-prop-2-enyl carbonate (IV-IAA-5a-3).** To a solution of **IV-IAA-4a** (195 mg, 0.5 mmol), (t-Boc)$_2$O (133 mg, 1mmol) and Bu_4NI (18 mg, 0.05 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise 1mL 2*M* NaOH aqueous solution (1.0 mL) at 0 ^{o}C. After addition, the mixture was stirred overnight. The reaction was quenched by addition of water. The aqueous layer was separated and extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine and dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 2/1) afforded **IV-IAA-5a-3** as a colorless oil (225 mg, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.41 (s, 3H), 2.72 (t, J = 7.2 Hz, 2H), 3.15 (q, J = 7.2 Hz, 2H), 3.83 (s, 6H), 4.53 (t, J = 6.0 Hz, 1H), 4.59 (dd, J = 1.5Hz, 6.9Hz, 2H), 5.79 (dt, J = 6.9 Hz, 11.4 Hz, 1H), 6.60 (s, 1H), 6.64 (s, 1H), 7.27 (d, J = 6.3 Hz, 2H), 7.68 (d, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ21.5, 27.7, 33.3, 43.4, 55.9, 63.5, 83.3, 112.7, 112.9, 125.9, 127.0, 127.2,128.5, 129.6,

132.0, 137.1, 143.3, 147.3, 148.5, 153.3; HRMS (ESI) calcd for $C_{25}H_{33}NO_7SNa$ $[M+H]^+$ 514.1875, found 514.1878 (Δ= 0.6 ppm).

General procedure for intramolecular asymmetric allylic amination

1-Ethenyl-2-trifluroacetyl-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline (IV-IAA-7b). A solution of ligand (*S*)**-III-MPN-1e** (3.5 mg, 0.0075 mmol) and $Pd_2(dba)_3$ (1.2 mg, 0.00125 mmol) in CH_2Cl_2 (0.5 mL) was added to a 5 mL round-bottomed flask with a stirring bar under N_2. The solution was stirred at room temperature until the color of the solution turned to light yellow from purple. Then, **IV-IAA-5b-3** (23 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added to the catalyst solution via a syringe. The mixture was stirred at room temperature until TLC indicated completion of the reaction. The reaction mixture was passed through a short pad of silica gel using hexanes/EtOAc (10/1~6/1) as the eluent. The filtrate was then concentrated and subject to HPLC analysis, using a Chiralcel OD-H column (hexanes/*i*-PrOH = 98/2, 0.5 mL/min), which indicated that the enantiopurity of the product **IV-IAA-7b** was 95% ee with 100% conversion and product selectivity. The product **IV-IAA-7b** was isolated as colorless oil as a mixture of two rotamers in 75:25 ratio (determined by ^{1}H NMR at 25 ^{o}C): $[\alpha]_D^{23}$ 169.7 (*c* 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68-2.78 (m, 1H), 2.91-3.01 (m, 1H), 3.01-3.28 (m, 0.25H), 3.50-3.58 (m, 0.75H), 3.83 (s, 2.25H), 2.854 (s, 2.25H), 3.85(s, 0.75H), 3.86 (s, 0.75H), 3.99-4.04 (m, 0.75H), 4.47-4.52 (m, 0.25H), 5.01-5.17 (m, 1H), 5.29-5.33 (m, 1H), 5.43-5.45 (m, 0.25H), 5.91-6.07 (m, 1.75H), 6.59 (s, 0.75H), 6.61 (s, 0.75H), 6.55 (s, 0.25H), 6.63 (s, 0.25H); ^{13}C NMR (100 MHz, $CDCl_3$) Major: δ 28.9, 40.2, 55.8, 56.1, 56.2, 110.9, 111.3, 116.8 (q, *J* = 287 Hz), 118.9, 125.0, 125.5, 135.9, 148.1, 148.6, 155.9

(q, J = 26 Hz); Minor: δ 27.5, 38.0, 56.2, 56.3, 58.1, 110.5, 111.7, 116.8 (q, J = 287 Hz), 118.7, 124.7, 126.3, 136.8, 148.0, 148.9, 156.0 (q, J = 26 Hz); HRMS (ESI) calcd for $C_{15}H_{17}NO_3F_3$ $[M+H]^+$ 316.1161, found 316.1164 (Δ= 0.9 ppm).

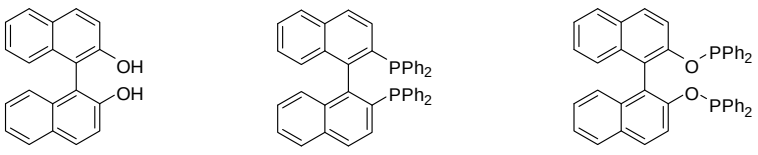
1-Ethenyl-2-(4-methylbenzenesulfonyl)-6,7-dimethoxy-3,4-dihydro-1*H*-isoquinoline (IV-IAA-7a). This compound was obtained in the same manner as that described for **IV-IAA-7b**: White solid; 87% isolated yield; 74% ee (Chiralpak AD-RH; CH_3CN/H_2O = 50/50, 0.5 mL/min); mp 137-138 ^oC; $[\alpha]_D^{23}$ 67 (*c* 0.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.47-2.52 (m, 1H), 2.63-2.75 (m, 1H), 3.25-3.35 (m, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.87-3.88 (m, 1H), 5.05 (dt, J = 1.5 Hz, 17.1 Hz, 1H), 5.17 (dt, J = 1.5 Hz, 10.2 Hz, 1H), 5.46 (d, J = 5.4 Hz, 1H), 5.90 (ddd, J = 1.5 Hz, 5.4 Hz, 10.2 Hz, 17.1 Hz, 1H), 6.64 (s, 1H), 6.52 (s, 1H), 7.19 (d, J = 6.3 Hz, 2H), 7.66 (d, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 27.2, 39.1, 55.8, 55.9, 57.7, 110.4, 111.3, 117.6, 125.4, 125.6, 127.1, 129.4, 137.3, 137.9, 143.0, 147.4, 148.0; HRMS (ESI) calcd for $C_{20}H_{24}NO_4S$ $[M+H]^+$ 374.1426, found 374.1436 (Δ= 2.7 ppm).

Chapter V

Palladium(0)-Catalyzed Asymmetric Allylic Substitutions with Bidentate Diphosphonite Ligands

§4.1 Introduction

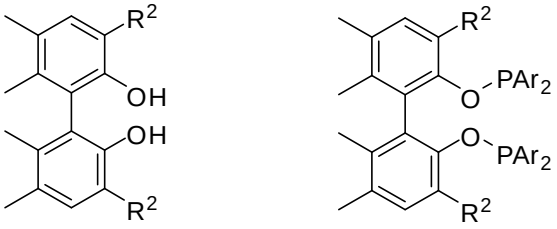
Biaryl atropisomeric ligands have been explored as effective scaffolds for many transition-catalyzed asymmetric transformations.[90] Among them, the most frequently used chiral chelating ligands are BINAP[91] and BINOL[92], which form 7-membered ring with transition metals (**Figure V-1**). Yet the simple analogues BINAPO,[43] which forms 9-membered ring with transition metals, are not as effective as BINAP for asymmetric hydrogenation due to their conformational flexibility (**Figure V-1**). On the other hand, taking advantage of the large bite angle (P-M-P) in the 9-membered chelating ring with transition metals,[42] BINAPO has proven to be an effective ligand in asymmetric allylic substitutions.[44] Mori et al. have demonstrated its utility in several asymmetric allylic substitutions as the key steps in the total synthesis of natural products.[45-47] However, no ees greater than 90% were reported.



BINOL BINAP BINAPO

Figure V-1 Biaryl atropisomeric ligands

In our lab, a series of chiral biphenols bearing various substituents on the 3, 3' positions were designed and synthesized (Chapter II).[53] Based on these chiral skeletons, we designed and synthesized a library of BINAPO-type diphosphonite ligands (BOP) bearing substituents of the 3,3' positions of the biphenol moiety (**Figure V-2**). We hypothesized that with the proper substituents, conformational rigidity could be potentially improved by controlling the orientation of the phenyl ring adjacent to phosphorus atoms of their metal complexes. In this chapter, the application of the newly designed diphosphonite ligands to a Pd-catalyzed intermolecular allylic amination which is the key step in the total synthesis of *Strychnos* indole alkaloids[47] will be discussed. The initial study on a Pd-catalyzed intramolecular allylic amination which leads to the enantioselective synthesis of the tricylic core of Schulzeines A-C[73] will also be presented.



R^2= H, Me, Br, Ph, t-Bu, CH_2Ar, etc.
Ar= Ph, p-Tolyl, 3,5-m-Xylyl, etc.

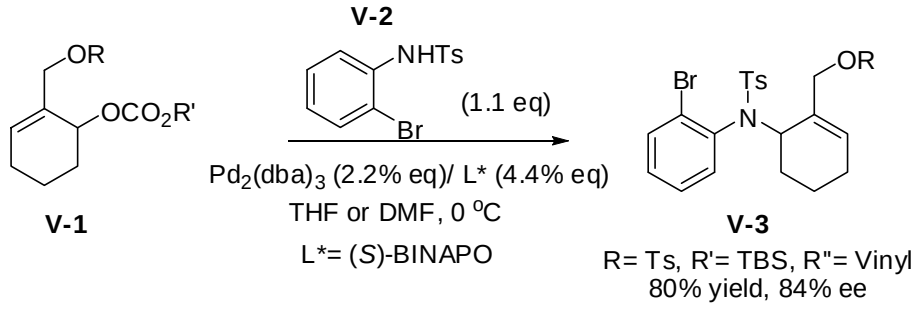
Figure V-2 Design of diphosphonite ligands based on chiral biphenols

§5.2 Application of Chiral Biphenol-Based Diphosphonite Ligands to Pd-Catalyzed Intermolecular Allylic Amination

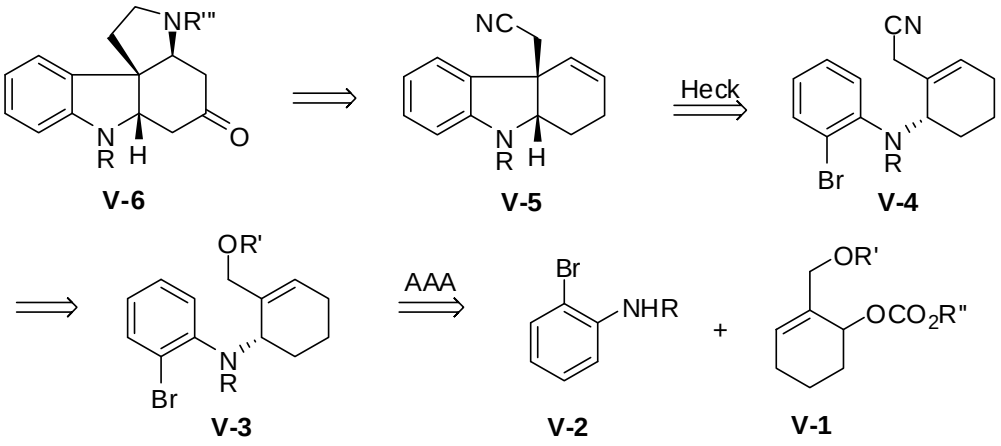
§5.2.1 Total Synthesis of *Strychnos* Indole Alkaloids

In 2003, Mori et al. reported the total synthesis of *Strychnos* indole alkaloids using a Pd-BINAPO complex-catalyzed intermolecular allylic amination as the key

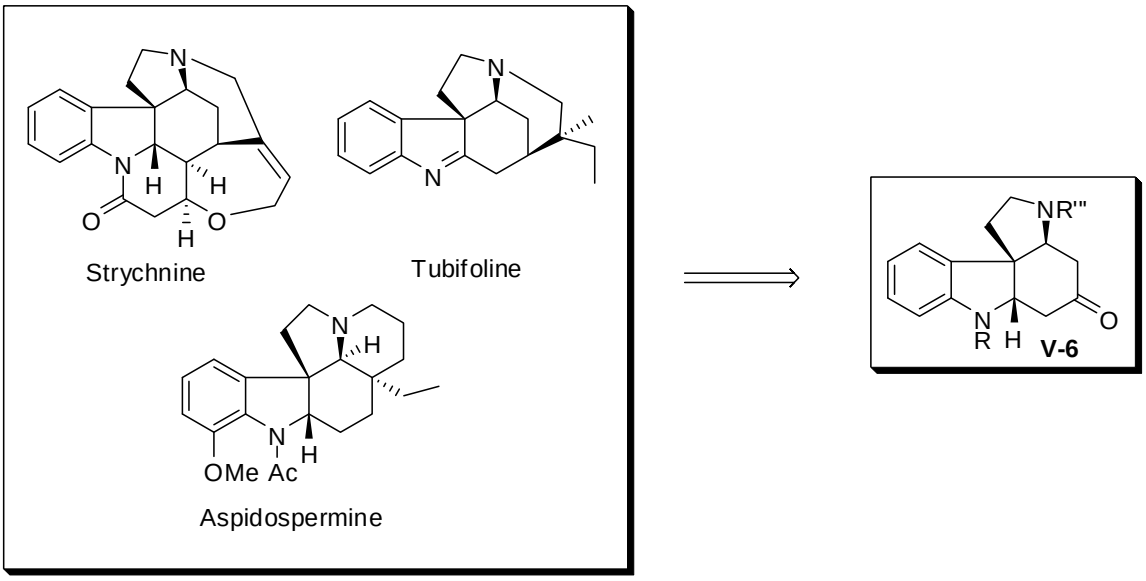
reaction to construct chiral centers in the structures (**Scheme V-1**).[47] The product from the key reaction then underwent a series of modifications, including intramolecular Heck reaction to construct the quaternary chiral center, allylic oxidation and intramolecular aza-Michael addition to form compound **V-6** (**Scheme V-2**), which is a very versatile intermediate and can be easily transformed into various *Strychnos* indole alkaloids (**Scheme V-3**).[47]



Scheme V-1 Intermolecular allylic amination catalyzed by Pd-BINAPO complex [47]



Scheme V-2 Retrosynthesis of intermediate **V-6** [47]



Scheme V-3 Total synthesis of *Strychnos* Indole Alkaloids [47]

As shown in **Scheme V-1**, the best result for the key step reaction is 84% ee and 80% isolated yield, which also required the reaction to be performed at 0 ^{o}C. An additional recrystalization was required in the following step to obtain enantiomerically pure intermediate.[47] Thus there is a need to improve the reaction in terms of the yield and the enantioselectivity. Here we present our structure-efficacy relationship study on this reaction using our fine-tunable diphosphonite ligands.

§5.2.2 Results and Discussion

§5.2.2.1 Bidentate Diphosphonite Ligand Library (BOPs)

A library of enantiopure bidentate diphosphonite ligands (**BOP**s) consisting of various biphenol and phosphine moieties were prepared according to the procedures described in Chapter III (**Figure V-3**) and used for the intermolecular allylic amination reactions.

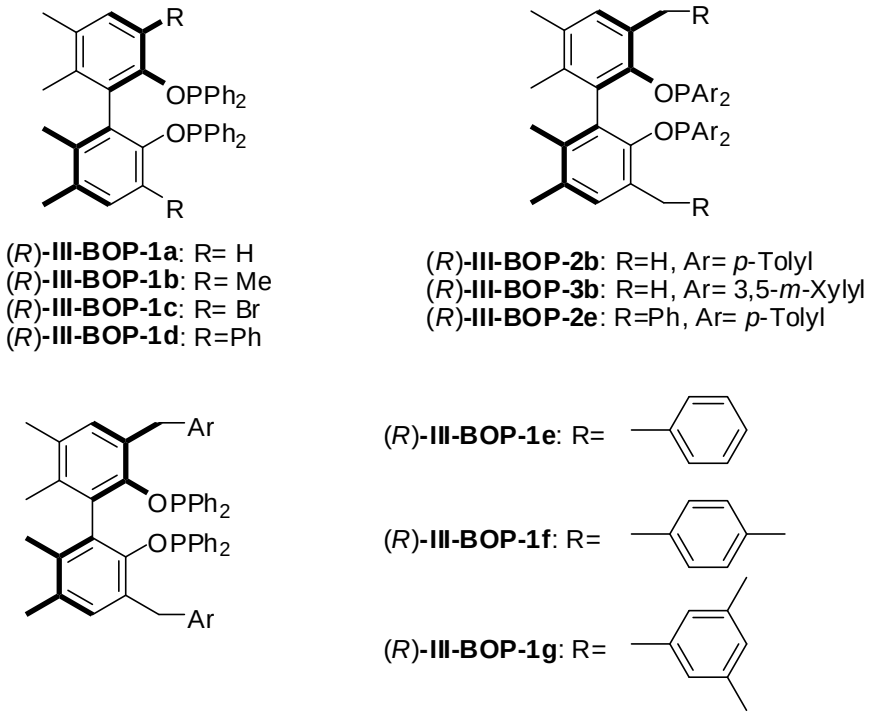
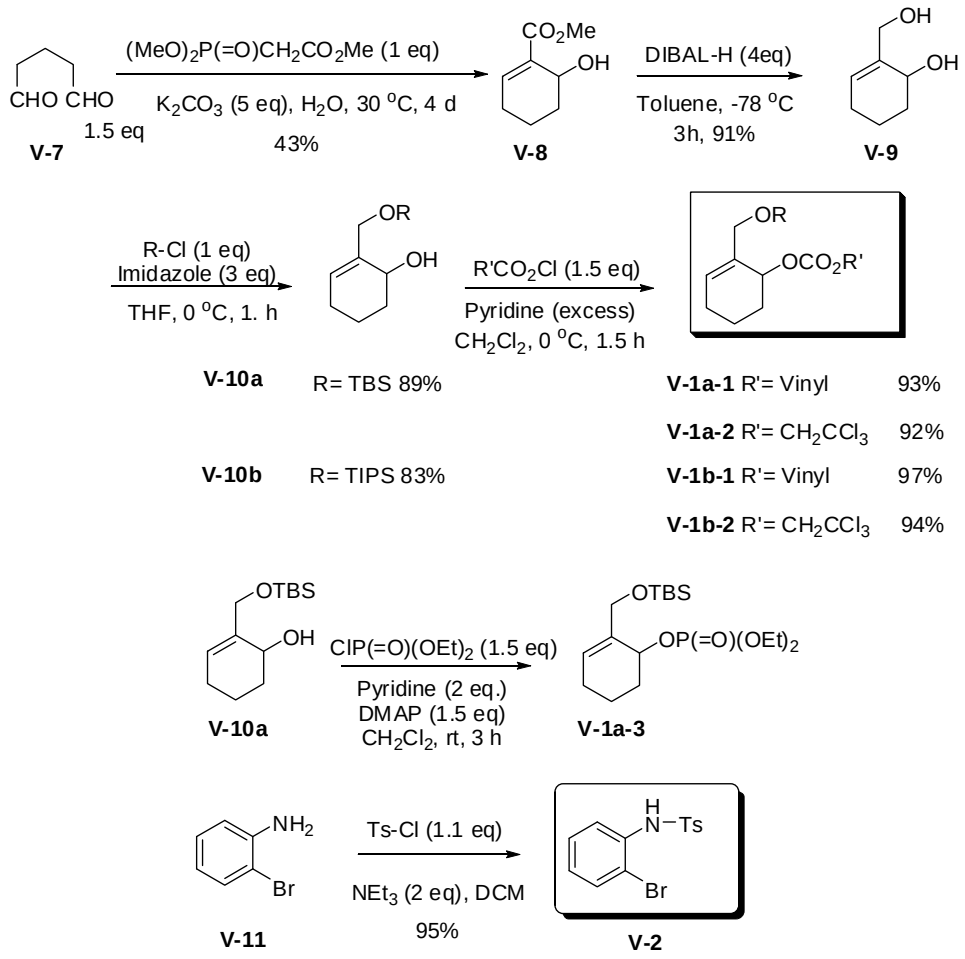


Figure V-3 Bidentate diphosphonite ligand library (**BOP**s)

§5.2.2.2 Preparations of Substrates

The synthesis of the 2-silyloxymethylcyclohexenol substrates **V-1a-1-3** and **V-1b-1/2** was carried out according to the reported procedure (**Scheme V-4**).[47] First, glutaraldehyde (**V-7**) was reacted with trimethyl phosphonoacetate under basic conditions to afford the cyclic allyic alcohol intermediate **V-8**. Then intermediate **V-8** was subjected to reduction conditions using DIBAL-H, and was converted into diol intermediate **V-9**. The primary alcohol moiety of intermediate **V-9** was then protected by either TBS or TIPS to give intermediate **V-10a** or **V-10b,** respectively, in excellent yields. Once the silyl protected intermediates were obtained, two types of chloroformates were coupled with them to afford the desired substrates **V-1a-1/2** and **V-1b-1/2** with high yields. The TBS-protected intermediate **V-10a** was also coupled with diethyl chlorophosphate to

afford subtrate **V-1a-3**. The nucleophile **V-2** was obtained in one step by reaction of *ortho*-bromo- aniline (**V-11**) with tosyl chloride.

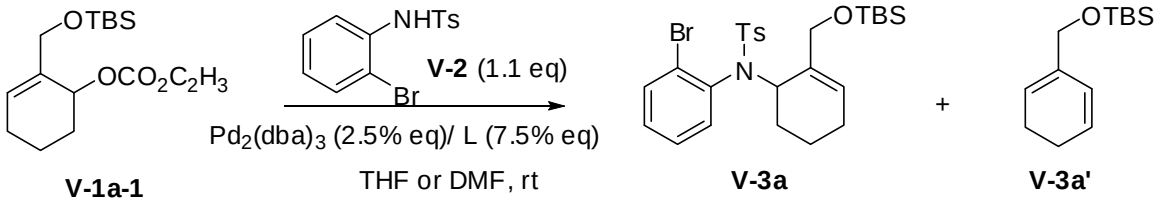


Scheme V-4 Synthesis of substrates for intermolecular allylic amination [47]

§5.2.2.3 Pd-Catalyzed Intermolecular Asymmetric Allylic Amination

For initial ligand screening, we decided to start with slightly modified reaction conditions from the optimal conditions for Pd-BINAPO catalyst system reported by Mori et al..[47] Substrate **V-1a-1** was chosen as the primary choice of substrate since it was the best substrate in the original conditions, and nucleophile **V-2** was kept in slight excess. The choice of solvent at this point was THF or DMF and the concentration of substrate

V-1a-1 was kept at 0.05 M. The Pd / L ratio was increased from the original 1:1 to 1: 1.5, to ensure the formation of (BOP)Pd(0) as the major catalyst species. Ligands (*R*)-**III-BOP-1a-d** are first tested and the results were summarized in **Table V-1**.



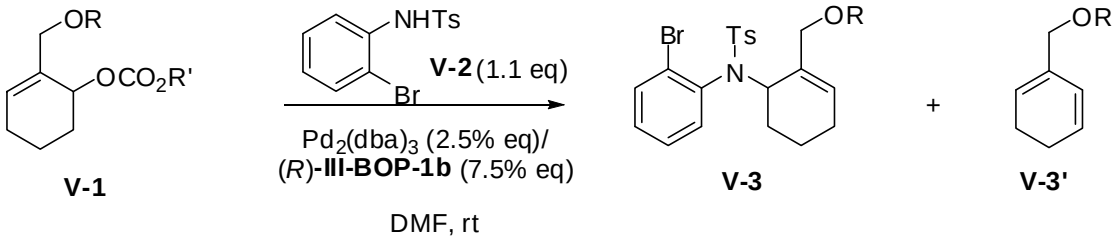
Entry	Ligand(**III-BOP**)	Solvent	Time (h)	Conv.%[a,b]	Ee% (**3a:3a'**)[a,b]
1	(*R*)-**1a**	THF	48	100	65 (70:30)
2	(*R*)-**1b**	THF	60	100	89 (65:35)
3	(*R*)-**1c**	THF	72	~30	74 (50:50)
4	(*R*)-**1d**	THF	72	<5	/
5	(*R*)-**1a**	DMF	12	100	67 (95:5)
6	(*R*)-**1b**	DMF	20	100	88 (95:5)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC using Chiralpak AD-RH, CH_3CN/H_2O

Table V-1 Initial ligand screening and condition optimization

As **Table V-1** shows, all reactions give formation of the desired product **3a** but with different reactivity and enantioselectivity as R^2 groups of the ligands were varied. We also observed the formation of **V-3a'**, which was not reported previously. The ratio of **V-3a** and **V-3a'** was estimated based on NMR integration. From the initial results in THF, it was found that the reactions were generally slowed down, as the size of the substituents groups increased (**Entry 1-4**). When (*R*)-**BOP-1a** (R= H) and (*R*)-**BOP-1b** (R= Me) were used, the reactions were completed in 48 h (Entry 1) and 60 h (Entry 2) respectively. In the case of (*R*)-**BOP-1c** (R= Br) (Entry 3) and (*R*)-**BOP-1d** (R= Ph)

(Entry 4), the reactions gave little conversion after 72 h. As R^2 groups were changed from H to Me, the ee increased from 65% to 89% (**Entry 1 and 2**). Increasing the size of the substituents led to reduced ee and poor reactivity (**Entry 3 and 4**). When the solvent was switched to DMF, acceleration of the reaction rate was observed. When (*R*)-**BOP-1a** (R= H) and (*R*)-**BOP-1b** (R= Me) were tested in DMF, the reactions were completed in 12 h and 20 h, respectively, with the ee unaffected and improved ratio of **V-3a** and **V-3a'.** At this point, DMF became the solvent of choice and (*R*)-**BOP-1b** (R= Me) was considered as the lead ligand.



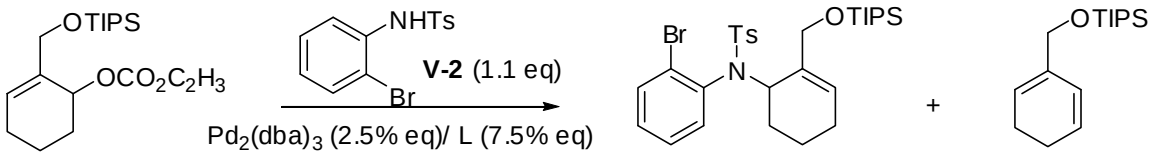
Entry	Substrate (**V-1**)	Time (h)	Conv.%[a,b]	Ee% (**3:3'**)[a,b]
1	**a-1** (R= TBS, R'= Vinyl)	20	100	89(95:5)
2	**a-2** (R= TBS, R'= CH_2CCl_3)	24	100	85(90:10)
3	**a-3** (R= TBS, P(=O)$(OEt)_2$)	16	100	83(97:3)
4	**b-1** (R= TIPS, R'= Vinyl)	24	100	91(95:5)
5	**b-2** (R= TIPS, R'= CH_2CCl_3)	30	100	88(90:10)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC; for *O*-TBS products **3a**: Chiralpak AD-RH, CH_3CN/H_2O;
for *O*-TIPS products **3b**: ee was determined after desilylation, Chiralcel OD-H, hexanes/*i*-PrOH.

Table V-2 Substrate structure optimization

The substrate screening was conducted in the next step with the lead BOP ligand (*R*)-**III-BOP-1b**. The results are summarized in **Table V-2**. For the substrates **V-1a-1-3** bearing TBS on the alcohol moiety, changes on the leaving groups from vinyl carbonate

to 2,2,2-trichloroethyl carbonate (**Entry 2**) or diethyl phosphate (**Entry 3**) did not lead to better enantioselectivity. For the substrates **V-1b-1/2** series, a slight boost of ee was observed from 89% (**Entry 1**) to 91%(**Entry 4**), when the silyl group was changed from TBS to TIPS. Substrate **V-1b-2** with variation on both R and R' groups (R= TIPS, R'= CH_2CCl_3) didn't give better enantioselectivity (**Entry 5**). Thus, substrate **V-1b-1** (R= TIPS, R'= Vinyl) was considered to be the lead substrate at this stage.



V-1b-1 **V-3b** **V-3b'**

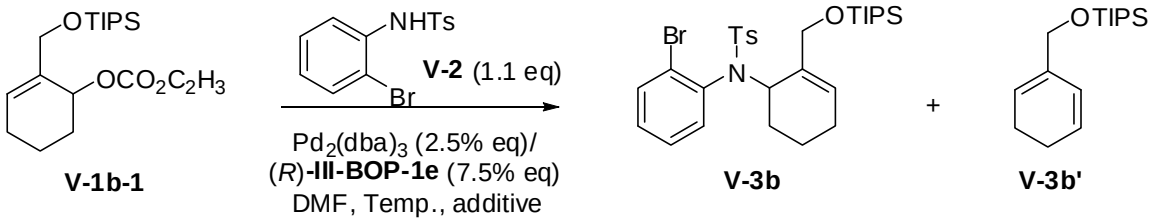
Entry	Ligand (**III-BOP**)	Time (h)	Conv.%[a,b]	Ee% (**3b:3b'**)[a,b]
1	(*R*)-**2b**	50	100	89 (85:15)
2	(*R*)-**3b**	50	100	43 (65:35)
3	(*R*)-**1e**	24	100	96 (93:7)
4	(*R*)-**1f**	24	100	94 (89:11)
5	(*R*)-**1g**	24	100	91 (90:10)
6	(*R*)-**2e**	50	100	89 (80:20)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC; for *O*-TIPS products **3b**: ee was determined after desilylation, Chiralcel OD-H, hexanes/*i*-PrOH.

Table V-3 Continuation of ligand screening

The BOP ligands with slight modification from ligand (*R*)-**BOP-1b** were tested in the optimized reaction conditions to further improve the enantioselectivity (**Table V-3**). Increase in the steric hindrance on the PAr_2, using (*R*)-**III-BOP-2b** (Ar= *p*-tolyl (**Entry 1**)) and (*R*)-**III-BOP-3b** (Ar= 3,5-*m*-xylyl (**Entry 2**)), did not lead to better ees.

Reactions were slowed down and product selectivities were lowered. Next, ligands with benzyl ((*R*)-**III-BOP-1e**) or substituted benzyl groups ((*R*)-**III-BOP-1f** and (*R*)-**III-BOP-1g**) at the 3, 3' positions of the biphenol moiety were tested (**Entry3-5**). The use of (*R*)-**III-BOP-1e** gave 100% conversion of the substrate and the desired product with 96% ee and 93:7 (**V-3b:V-3b'**) product selectivity (**Entry 3**), which is the best results so far. The introduction of substituted benzyl groups did not help to improve the ee further (94% ee in Entry 4 and 91% ee in Entry 5). Keeping the Bn groups on the 3, 3' positions of the biphenol moiety, increasing the steric effect on the PAr_2 (Ar= *p*-tolyl) did not improve the ee, but decrease in the ee and product selectivity was observed. Thus, (*R*)-**III-BOP-1e** (R= Bn, Ar= Ph) became the lead ligand.



Entry	Additive	Temp.	Time (h)	Conv.%[a,b]	Ee%(3b:3b')[a,b]
1	/	RT	24	100	96 (93:7)
2	/	0 °C	48	100	96 (90:10)
3	AcOH (1 eq)	RT	24	<5	/
4	NEt_3 (1.1 eq)	RT	8	100	88 (92:8)
5	NEt_3 (1.1 eq)	0 °C	17	100	91 (80:20)
6	NEt_3 (1.1 eq)	-25 °C	48	~80	77(80:20)

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC; for *O*-TIPS products **3b**: ee was determined after desilylation, Chiralcel OD-H, hexanes/*i*-PrOH.

Table V-4 Continuation of condition optimization

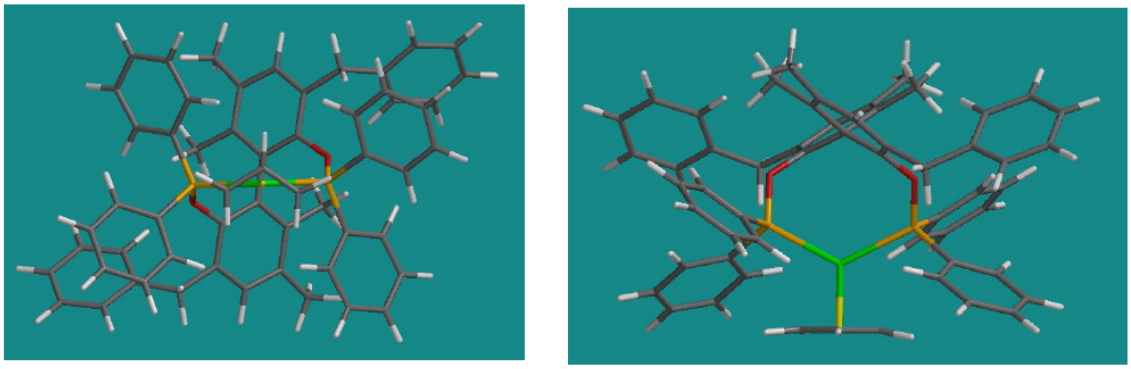
The reaction conditions were again optimized using the lead substrate **V-1b-1** and the lead ligand (*R*)-**III-BOP-1e** (**Table V-4**). When the temperature was lowered to 0 ^{o}C, the reaction required longer time to finish and gave the same enantioselecivity with slightly lower product selectivity (90:10 vs 93:7) (**Entry 2**). Additives were tested in the reaction system (**Entry 3-6**). The addition of 1 equivalent of AcOH to **V-1b-1** nearly shut down the reaction completely, resulted in less than 4% conversion. The addition of 1.1 equivalent of NEt_3 to **V-1b-1** accelerated the reaction drastically, but the ee was lowered to 88% with the product selectivity unchanged. Lowering the temperature in the presence of NEt_3 didn't lead to better ee, i.e., with 91% ee at 0 ^{o}C (**Entry 5**) and 77% ee at -25 ^{o}C (**Entry 6**). Therefore, the original condition in Entry 1 remain the optimal conditions for the reaction.

In conclusion, a highly effective Pd-BOP catalytic system has been presented for the intermolecular asymmetric allylic amination reaction, giving 96% ee and 93:7 product selectivity (favoring the desired product). The results strongly support our hypothesis that introduction of substituents on the 3 and 3' positions of the biphenol moiety may improve the rigidity of the ligand structure thus improving enantioselectivity. Mechanistic study on the effect of the substiuents to the ligand structure is in progress.

§5.2.2.4 Preliminary Mechanistic Study on the Pd-BOP Catalytic System

In order to gain insight into the active catalyst species, we conducted molecular modeling to construct a simplified active catalyst complex $[Pd(II)L^*_2(Allyl)]^+$. (L*= (*R*)-**III-BOP-1g,** R^2=Bn), assuming that the complex with 1:1 ratio of Pd to BOP is the major catalyst species. The result after energy minimization (Spartan program; MM2/PM3)

clearly indicates a pseudo C_2-symmetrical structure, in which the Ph groups of the PPh_2 moieties create a C_2-symmetrical environment surrounding the π-allyl moiety (**Figure V-4**). The measured bite angle (P*-Pd-P*) is 125° which is beneficial in extending the chiral influence beyond the π-allyl moiety, thus leading to high enantioselectivity. The 3D structure of $[Pd(II)L^*_2(Allyl)]^+$. (L*= (*R*)-**III-BOP-1a**, R^2= Me) was also constructed using molecular modeling. The measured bite angle (P*-Pd-P*) is 119°. The difference on the bite angle (119° (R^2= Me) vs 125° (R^2= Bn)) may also help to explain the improved enantioselectivity when substituents at the 3,3' positions of the biphenol moiety were changed from Me (Entry 4 in **Table V-2**) to Bn (Entry 3 in **Table V-3**).



$[Pd(II)L^*_2(Allyl)]^+$. (L*= (*R*)-**III-BOP-1e**) Equatorial view

$[Pd(II)L^*_2(Allyl)]^+$. (L*= (*R*)-**III-BOP-1e**) Apical view

Figure V-4 Proposed structure of $[Pd(II)L^*_2(Allyl)]^+$ (L*= (*R*)-**III-BOP-1e**)

§5.3 Enantioselective Synthesis of the Tricyclic Core of Schulzeines A-C via Pd-Catalyzed Intramolecular Allylic Amination

§5.3.1 Asymmetric Synthesis of Schulzeines (A-C)

Schulzeines (A-C), isolated from a marine sponge, *Penares Schulzei*, have been identified as a new class of marine natural products (**Figure V-5**).[73] They have been found to exhibit potent α-glucosidase inhibitory activity making them promising leads for

drug development for diseases such as cancer, diabetes and viral infections.[93-95] Therefore, it is of great importance to develop efficient synthetic strategies for those natural products to conduct structure-activity relationship study.

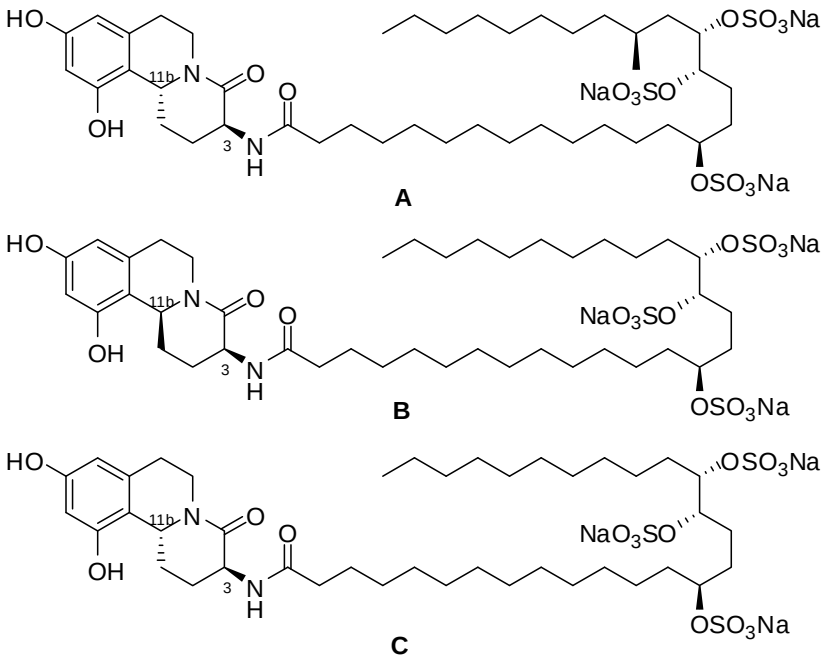
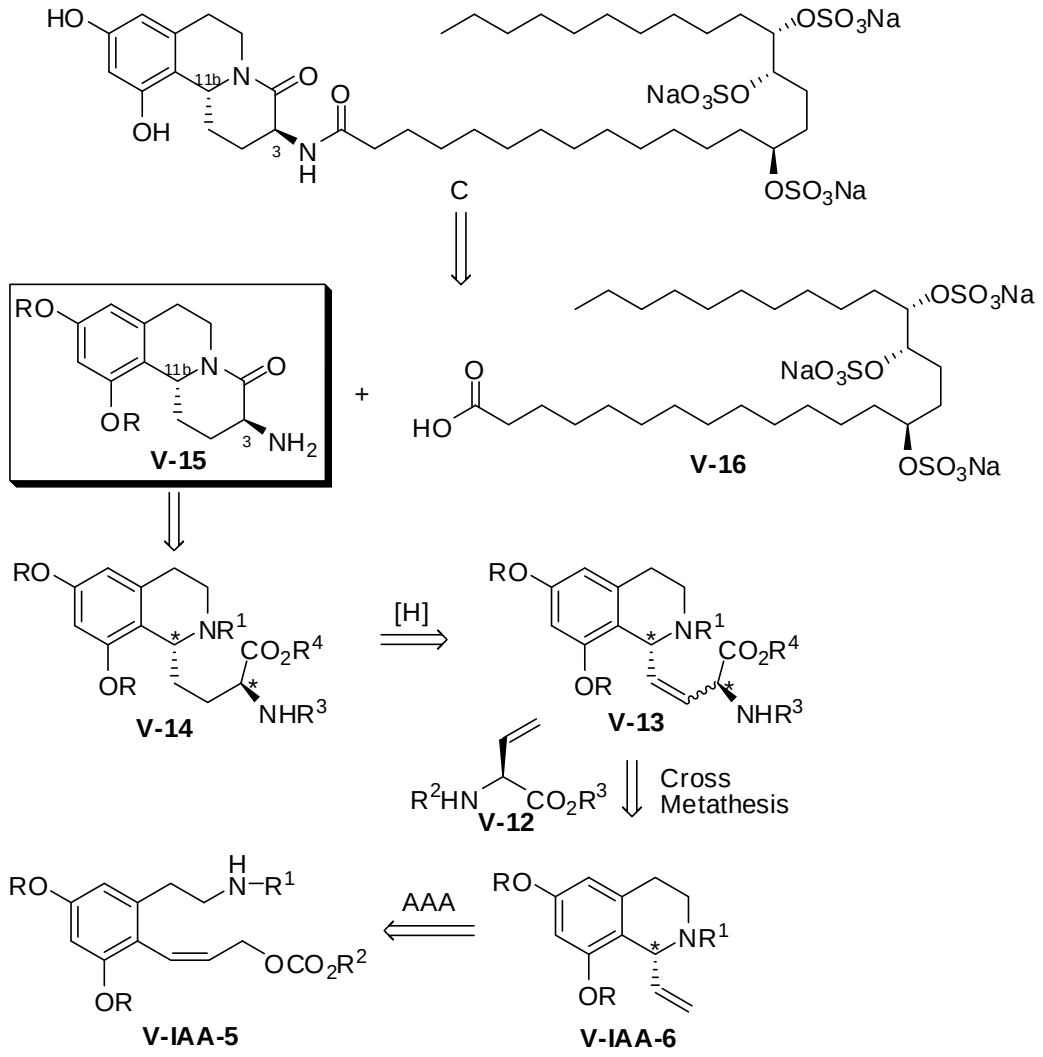


Figure V-5 Schulzeines A-C

The structure of Schulzeines can be divided into two major components, i.e., the tricyclic core containing tetrahydroisoquinoline fused with *δ*-lactam and the 28-carbon fatty acid side chain (**Figure V-5**) . The tricyclic core bears two chiral centers at C-3 and C-11b. The stereocenters at C-3 were assigned as *S* in all members of this family whereas the stereocenters at C-11b were assigned as *R* in Schulzeines A and C, and *S* in Schulzeine B. The 28-carbon fatty acid side chain of schulzeines bear three stereo-centers at C-14, C-17, and C-18 as sodium sulfate salts with the configurations assigned as *S,S,S* respectively. Schulzeine A has an extra stereo-center at C-20 bearing a methyl substituent.

Thus far, only Kuntiyong et al. reported the synthesis of the tricyclic core of Schulzeines A-C, using *N*-acyliminium ion cyclization in the key step.[96] However, the synthesis suffered from low diastereoselectivity and difficulties of separating the two diastereomers.[96] Thus, more efficient synthetic routes are needed for the construction of the tricyclic core.



Scheme V-5 Proposed retrosynthesis of the tricyclic core of Schulzeine C

Therefore, we proposed an enantioselective synthesis of the tricyclic core of Schulzeines A-C using an intramolecular allylic amination in the key step (**Scheme V-5**).

Retrosynthetically, the stereocenters at C-11b can be controlled by a Pd-catalyzed allylic amination reaction with the formation of 1-vinyltetrahydronisoquinoline intermediate **V-IAA-6**. The additional stereocenters at C-3 can be introduced through cross-metathesis reactions with (*S*)-vinylglycine derivatives (**V-12**). After reduction and lactamization, intermediate **V-13** can be converted into the desired tricyclic core (**V-15**) with the designed stereochemistry at both C-3 and C-11b positions. (**Scheme V-5**)

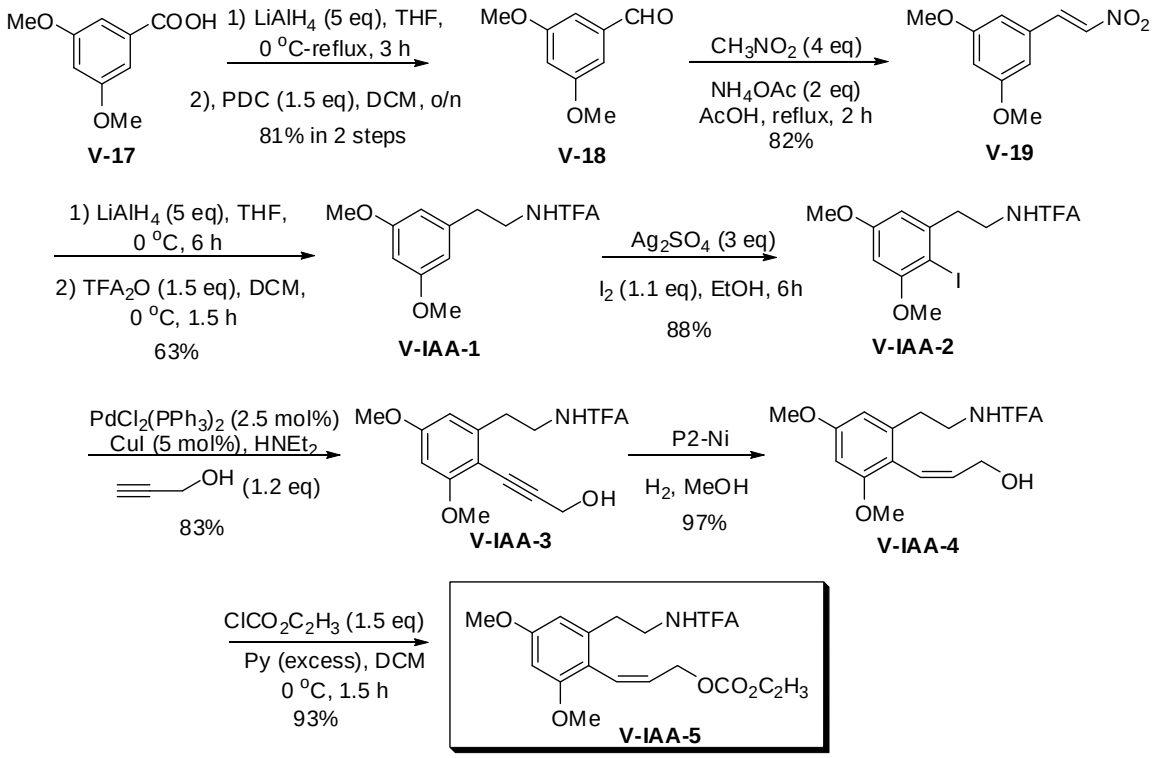
Since both our monodentate phosphoramidite ligands and bidentate diphosphonite ligands have been applied to the Pd-catalyzed allylic aminations successfully, we want to examine the efficacy of our ligands (both monodentate and bidentate) in this proposed intramolecular allylic amination, with the hope of achieving high reactivity and enantioselectivity and completing the whole synthesis.

§5.3.2 Results and Discussion

§5.3.2.1 Synthesis of Substrate V-IAA-5

The synthesis of the desired substrate **V-IAA-5** is outlined below (**Scheme V-6**). The intermediate **V-IAA-1** was synthesized according to the reported procedure.[97,98] The rest of the synthetic procedures were very similar to the ones used for substrates **IV-IAA-5** in Chapter IV**.** In the iodination step, the combination of iodine and silver sulfate was found to be more efficient system in this case to introduce iodo group with decent isolated yield, although the formation of bis-iodinated product was always observed. In the next step, the Sonogashira coupling reaction proceeded slowly even at elevated temperature, giving desired product **V-IAA-3** in 81% isolated yield. After controlled

hydrogenation of **V-IAA-3,** followed by coupling with vinyl chloroformate, **V-IAA-4** was converted into **V-IAA-5** in excellent yield.

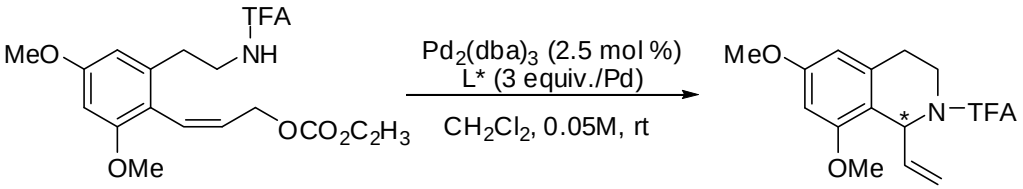


Scheme V-6 Synthesis of 3,5-disubstituted substrate **V-IAA-5**

§5.3.2.2 Pd-Catalyzed Intramolecular Asymmetric Allylic Amination

With substrate **V-IAA-5** in hand, we proceeded to test the reaction first using monodentate phosphoramidite ligands under the conditions that worked well for the 3,4-disubstituted substrates previously discussed in Chapter IV. The reaction did proceed smoothly, giving the desired product in excellent conversion and yields (**Table V-5**). Not surprisingly, our initial screening of chiral ligands using (*S*)-**III-MPN-1a-d** indicated a different trend as the substitution pattern was changed on the phenyl ring of the subtrates. From (*S*)-**III-MPN-1a** to (*S*)-**III-MPN-1d**, Me groups were kept on the amine moiety. As the size of the substituents on the 3,3'-position of biphenol moiety kept increasing, the

same trend of changing the enantiomeric preference was observed as the substituents were changed from H to Me.(**Entry 1** and **2**). Increasing the size of the substituents did lead to better enantioselectivity. However, (*S*)-**III-MPN-1d** (R= Ph) (**Entry 4**), which was the superior ligand for 3,4-disubstituted substrates**,** was not the best ligand in the case of 3,5-disubstituted substrate **V-IAA-5**. Again, the results proved the importance and practicality in finding the most suitable ligand rather than a universally powerfully ligand. So far, 47% was the best ee obtained using monodentate ligand (*S*)-**III-MPN-1c** (R= Br) (**Entry 3**).



V-IAA-5 **V-IAA-6**

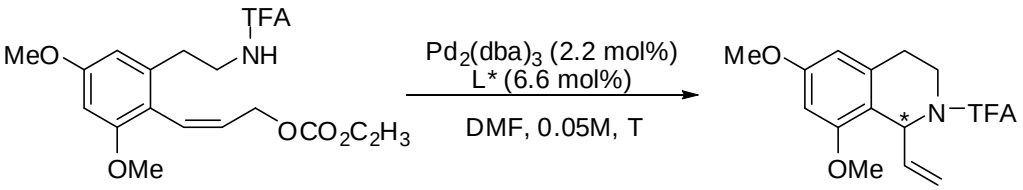
Entry	Ligand (**III-MPN**)	Time (h)	Conv.[a, b] (%)	% ee[b]
1	(*S*)-**1a** (R^2 = H)	10	100	26(+)
2	(*S*)-**1b** (R^2 = Me)	16	100	19(-)
3	(*S*)-**1c** (R^2 = Br)	22	100	47(-)
4	(*S*)-**1d** (R^2 = Ph)	48	100	23(-)

[a] Determined by ^{1}H NMR and HPLC.
[b] Determined by HPLC using Chiralcel OD-H Hex:iPrOH=99.5:0.5, 0.5 mL/min.

Table V-5 Intramolecular asymmetric allylic amination using monodentate ligands

A series of bidentate diphosphonite ligands ((*R*)-**III-BOP-1a-g, 2-3b**) were then tested in this reaction under the conditions described in **Section 5.2**, and the results are summarized in **Table V-6**. As the substituents varied on the 3, 3' of the biphenol moieties,

the ee changed drastically (**Entry 1-5**). **Entry 2** (R^2= Me), Entry 3 (R^2=Br) and **Entry 4** (R^2=Bn) show very promising results, giving 68% ee, 72% ee and 79% ee, respectively. Further modifications of the Bn moieties of ligand **(*R*)-III-BOP-1e** led to better enantioselectivity, giving 84% ee (**Entry 6,** R^2= CH_2-*p*-tolyl**)** and 88% ee (**Entry 9,** R^2= CH_2-3,5-*m*-xylyl). Lowering the temperature also helped to improve the ee. At 0 ^oC, ees were improved to 88% (**Entry 7**, (*R*)-**III-BOP-1f**) and 90% (**Entry 10**, (*R*)-**III-BOP-1g**). Lowering the temperature further to -25 ^oC basically shut down the reaction, and little conversion was observed (**Entry 8** and **Entry 11**). Increasing the steric bulk on the PAr_2 also helped to improve the ee compared to the results in **Entry 2** (R^2= Me, Ar= Ph) , giving 72% (**Entry 12**, R^2= Me, Ar= *p*-tolyl) and 80% (**Entry 13**, R^2= Me, Ar= 3,5-*m*-xylyl).



V-IAA-5 **V-IAA-6**

Entry	Ligand (**III-BOP**)	Temp.(°C)	Time (h)	Conv. (%)[a]	Ee%[b]
1	(*R*)-**1a**	RT	1.5	100	35
2	(*R*)-**1b**	RT	4	100	68
3	(*R*)-**1c**	RT	8	100	72
4	(*R*)-**1d**	RT	8	100	68
5	(*R*)-**1e**	RT	6	100	79
6	(*R*)-**1f**	RT	8	100	84
7	(*R*)-**1f**	0	24	100	88
8	(*R*)-**1f**	-25	48	<5	/
9	(*R*)-**1g**	RT	8	100	88
10	(*R*)-**1g**	0	24	100	90
11	(*R*)-**1g**	-25	48	<5	/
12	(*R*)-**2b**	RT	8	100	72
13	(*R*)-**3b**	RT	12	100	80

[a] Determined by ^{1}H NMR and HPLC.
[b] Determined by HPLC using Chiralcel OD-H Hex:iPrOH=99.5:0.5, 0.5 mL/min

Table V-6 Intramolecular asymmetric allylic amination using bidentate ligands (**BOP**s)

So far, the best ee achieved is 90% using (*R*)-**III-BOP-1g** as chiral ligand at 0 °C. Further optimization on the structure of both the ligands and the substrates is still in progress. Once targeted enantioselectivity (>95% ee) for the asymmetric allylic

amination is achieved, attempts to complete the synthesis of the tricyclic core of Schulzeins A-C will be performed.

§5.3 Experimental Section

General Method. ^{1}H and ^{13}C NMR spectra were measured on a Varian Inova-400 NMR (400 MHz ^{1}H and 100 MHz ^{13}C) or a Varian Gemini-2300 (300 MHz ^{1}H and 75 MHz ^{13}C) spectrometer in a deuterated solvent using residual protons ($CHCl_3$: ^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm.) as the internal standard. . The enantiomeric excess was determined by HPLC: Waters M45 system with Waters 484 detector using Chiralcel OD-H column (hexanes/*i*-PrOH = 98/2, 0.5 mL/min) or a Shimadzu LC-2010A HPLC system using a Chiralpak AD-RH column (CH_3CN/H_2O = 80/20, 0.5 mL/min).Melting points were measured on a Thomas Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. TLC was performed on Merck DC-alufolien with Kieselgel 60F-254 and flash chromatography was carried out on silica gel 60 (Silicyle; 40–63 μm particle size). High-resolution mass spectrometric analyses were carried out at the Mass Spectrometry Laboratory, University of Illinois Urbana-Champaign, Urbana, IL.

Materials. All solvents were purified using the Solvent Purification System 400-4 from Innovative Technology, Inc. All chemicals were purchased from Aldrich and Acros Chemical Co. unless otherwise noted. Tris(dibenzylideneacetone)dipalladium (0) was purchased from Strem Chemicals Inc. All reactions were carried out under nitrogen or

argon atmosphere. Compound **V-2**,[47] **V-8**[99] and **V-IAA-1**[97,98] were synthesized according to the literature procedures.

Synthesis of substrates **V-1a-1-3** and **V-1b-1-2**

2-(Hydroxymethyl)cyclohex-2-enol (**V-9**) A toluene solution of DIBALH (1.01 M, 15 mL, 15.2 mmol) was added to a solution of **V-8** (520 mg, 3.05 mmol) in toluene (25 mL) at -78 °C and the solution was stirred at room temperature for 3 h. To this solution was added MeOH (0.25 mL) and saturated Rochelle's salt. Then AcOEt was added and the organic layer was washed with water, dried over Na2SO4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexanes/AcOEt (1:2) gave 356 mg of 2-hydroxymethyl-2-cyclohexenol as a colorless oil in 91% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55-2.17 (m, 7H), 2.32 (br s, 1H), 4.21 (br s, 2H), 4.33 (br s, 1H), 5.83 (t, J= 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 25.0, 31.4, 65.5, 65.8, 127.7; All data are consistent with literature results.[47]

2-*tert*-Butyldimethylsilanyloxymethyl-2-cyclohexenol (**V-10a**). A solution of 2-hydroxymethyl-2-cyclohexenol (**V-9**) (7.8 g, 60.9 mmol), TBDMSCl (9.1 g, 60.9 mmol) and imidazole (12.4 g, 182.1 mmol) in THF (100mL) was stirred at 0 °C for 1.5 h. Then AcOEt was added and the organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel. Elution with hexane/AcOEt (6:1) gave 13.3 g of 2-*tert*-butyldimethylsilanyloxymethyl-2-cyclohexenol (**V-10a**) as colorless oil in 89% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$)

δ 0.03 (s, 6H), 0.85 (s, 9H), 1.45 (m, 1H), 1.67 (m, 3H), 2.01 (m, 1H), 3.06 (s, 1H), 4.16 (m, 3H), 5.69 (br t, *J*= 3.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6, 17.7; 25.1, 35.8, 30.9, 55.9, 57.4, 126.5, 137.5; All data are consistent with literature results.[47]

2-((Triisopropylsilyloxy)methyl)cyclohex-2-enol (V-10b). The titled compound was prepared following the same procedure as for (**V-10a**). Colorless oil; 83% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (m, 21H), 1.53 (m, 1H), 1.80 (m, 3H), 1.95 (m, 1H), 2.01 (m, 1H), 2.92 (br s, 1H), 4.25 (m, 3H), 5.72 (br t, *J*= 4.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.9, 25.1, 30.9, 66.3, 68.2, 126.5, 137.5; HRMS (EI) calcd. for $C_{13}H_{25}O_2Si$ [M-*i*Pr]$^+$ 241.1624, found 241.1622 (Δ = +0.2 ppm).

1-*tert*-Butyldimethylsilanyloxymethyl-6-vinyloxycarbonyloxy-1-cyclohexene (V-1a-1). To a solution of 2-*tert*butyldimethylsilanyloxymethyl-2-cyclohexenol (**V-10a**) (822 mg, 3.39 mmol) and pyridine (3 mL) in CH_2Cl_2 (10 mL) was added vinyl chloroformate (0.29 mL, 3.41 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h. After removal of the solvent, the residue was purified by column chromatography on silica gel. Elution with hexane gave 1.0 g of desired product in 93% isolated yield as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 9H), 1.71(m, 3H), 2.15 (m, 3H), 4.04 (d, *J*= 12.8 Hz, 1H), 4.15 (d, *J*= 12.8 Hz, 1H), 4.54 (dd, *J*= 2, 6.4 Hz, 1H), 4.87 (dd, J= 2, 14 Hz, 1H). 5.27 (br t, *J*= 4 Hz, 1H), 5.98 (br s, 1H), 7.09 (dd, J= 6, 14 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5, 17.7, 24.7, 25.9, 28.3, 64.3, 71.2, 97.3, 129.2, 134.0, 142.7, 152.4; IR (neat) 2930, 2858, 1757, 1649 cm^{-1}; LR MS *m/z* 255 (M$^+$-*t*Bu), 225 (M$^+$-CH_2=$CHOCO_2$), 167, 145; All data are consistent with literature results.[47]

2-((*tert*-Butyldimethylsilyloxy)methyl)cyclohex-2-enyl 2,2,2-trichloroethyl car bonate (V-1a-2). The titled compound was prepared following the same procedure as for (**V-1a-1**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 6H), 0.88 (s, 9H), 1.71 (m, 3H), 2.03 (m, 3H), 4.03 (d, *J*= 12.8 Hz, 1H); 4.16 (d, *J*= 12.8 Hz, 1H); 4.75 (s, 2H), 4.30 (t, *J*= 4 Hz, 1H), 5.99 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 17.7, 24.7, 25.9, 28.3, 64.2, 72.4, 77.2, 77.3, 129.3, 133.9, 153.7.

2-((Triisopropylsilyloxy)methyl)cyclohex-2-enyl ethenyl carbonate (V-1b-1). The titled compound was prepared following the same procedure as for (**V-1a-1**).). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (m, 21H), 1.69 (m, 3H), 2.04 (m, 3H), 4.12 (d, *J*= 12.6 Hz, 1H), 4.23 (d, *J*= 12.6 Hz, 1H), 4.53 (dd, *J*= 2, 6.4 Hz, 1H), 4.88 (dd, *J*= 2, 14 Hz, 1H), 5.29 (br s, 1H), 6.01 (br s, 1H), 7.09 (dd, J= 6.4, 14 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 17.9, 24.7, 28.3, 64.4, 71.9, 97.3, 128.5, 134.2, 142.7, 152.4.

2,2,2-Trichloroethyl 2-((triisopropylsilyloxy)methyl)cyclohex-2-enyl carbon-ate (V-1b-2). The titled compound was prepared following the same procedure as for (**V-1a-1**).). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (m, 21H), 1.69 (m, 3H), 2.04 (m, 3H), 4.10 (d, *J*= 12.6 Hz, 1H), 4.21 (d, *J*= 12.6 Hz, 1H), 4.77 (s, 2H), 5.31 (br s, 1H), 6.01 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.2, 24.9, 28.6, 64.5, 65.4, 72.8, 76.8, 77.6, 128.8, 134.3, 154.1.

2-(Silyloxymethyl)-2-cyclohexenyl diethylphosphate (V-1a-3). To a solution of 2-*tert*butyldimethylsilyloxymethyl-2-cyclohexenol (**V-10a**) (250 mg, 1.0 mmol), pyridine

(0.17mL,2.0 mmol) and DMAP (187 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was added diethyl chlorophosphate (0.22 mL, 1.5 mmol). The resulting mixture was stirred at room temperature for 3 h. Then AcOEt was added, and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification on a silica gel column using hexane/AcOEt (2:1) as eluant gave 342.6 mg of the desired product **V-1a-3** in 88% isolated yield as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.29 (tt, *J*= 1.2, 7.2 Hz, 6H), 1.70 (m, 3H), 2.04 (m, 3H), 4.08 (m, 6H), 4.80 (br s, 1H), 5.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4, 16.0, 17.5, 18.2, 24.6, 25.8, 29.8, 63.4, 71.7, 127.2, 135.2; IR (neat) 2930, 2857, 1264, 1037, 988, 53 cm^{-1}; LR MS m/z 321 (M^+-*t*Bu), 224; All data are consistent with literature results.[47]

General procedure for asymmetric allylic substitution. A 1 mL solution of subtrate **V-1a/b** (0.1 mmol) in THF or DMF was added to a solution of Pd_2dba_3 (2.2 mol %) and (*R*)-**III-BOP** (6.6 mol %) in 0.6 mL THF or DMF which was pre-incubated for 15 mins before the addition. To this solution was added tosylamide **V-2** (18 mg, 0.055 mmol) in 0.4 mL THF or DMF and the solution was stirred at appropriate temperature. Then AcOEt was added and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was passed through a short pad of silica gel using hexanes/EtOAc (10/1~5/1) as the eluent. The filtrate was then concentrated and subjected to HPLC analysis.

(*R*)-*N*-(2-Bromophenyl)-*N*-(2-[(2-*tert*-butyldimethylsilanyloxymethyl-2-cyclohexenyl)-4-methylbenzenesulfonamide (V-3a). 89% ee; $[\alpha]_D^{23}$ -1.9 (*c* 0.5, $CHCl_3$);

^{1}H NMR (400 MHz, $CDCl_3$) δ -0.04 (d, *J*=4.5 Hz, 4.8H), 0.06 (d, *J*=4.5 Hz, 1.2 H), 0.60-0.70 (m, 0.2H), 0.90 (s, 7.2H), 0.94(s, 1.8H), 1.05-1.10 (m, 0.8H), 1.21-1.31(m, 0.2H), 1.44-1.50 (m, 0.8H), 1.75-1.87 (m, 3H), 2.04-2.09 (m, 0.2H), 2.42 (s, 3H), 2.55-2.62 (m, 0.8H), 3.55 (br d, *J*= 14.5 Hz, 0.8H), 3.62 (br d, *J*= 14.5 Hz, 0.8H), 4.16 (br d, *J*= 15.2 Hz, 0.2H), 4.49 (br d, *J*= 15.2 Hz, 0.2H), 4.55 (br s, 0.8H), 4.65 (br s, 0.2H), 7.65-7.70 (m, 2.8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4 (major), -5.1 (minor), 17.8 (major), 18.2 (minor), 21.6, 24.1 (minor), 24.3 (major), 25.8 (minor), 26.0 (major), 27.9 (minor), 30.1 (major), 55.4, 64.0 (major), 65.2 (minor), 127.2 (m), 129.4 (m), 133.5 (m), 137.4, 138.4, 143.3; IR (neat) 3072, 1598, 1470, 1350, 1160 cm^{-1}; LR MS *m/z* 535 (M^+-Me), 493 (M^+-tBu); All data are consistent with literature results.[47]

***N*-(2-Bromophenyl)-4-methyl-*N*-(2-((triisopropylsilyloxy)methyl)cyclohex-2-enyl)benzenesulfonamide (V-3b).** 96% ee, $[\alpha]_D^{23}$ -2.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (m, 0.2H), 1.11 (m, 21H), 1.72 (m, 4.3H), 2.22 (m, 1.5H), 3.12 (s, 0.75H), 3.21 (s, 2.25H), 4.62 (m, 2H), 5.92 (br s, 0.2H), 6.07 (br s, 0.8H), 7.17 (m, 4H), 7.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0 (major), 12.6 (minor), 18.0 (major), 18.8 (minor), 24.3, 28.6 (minor), 29.4 (major), 41.1 (major), 41.9 (minor), 55.2 (major), 57.1 (minor), 65.1 (major), 65.7 (minor), 127.8 (m), 129.7 (m), 134.3 (m), 135.6 (minor), 136.9 (major); HRMS (EI) calcd. for $C_{26}H_{35}O_3NBrSSi$ $[M\text{-}i\text{Pr}]^+$ 548.1290, found 548.1288 (Δ = -0.2 ppm).

***N*-(3,5-Dimethoxyphenethyl)-2,2,2-trifluoroacetamide (V-IAA-1).** White solid; mp 84.0-85.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81 (t, *J*=6.9 Hz, 2H), 3.59 (q, *J*=6.9 Hz,

2H), 3.77 (s, 6H), 6.35 (m, 3H), 6.55 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.1, 40.8, 55.2, 98.8, 106.6, 115.8 (q, *J*= 286 Hz), 139.9, 157.0 (q, *J*= 36 Hz); 161.1; HRMS (EI) calcd. for $C_{12}H_{14}F_3NO_3$ $[M]^+$ 277.0926, found 277.0926 (Δ = 0.0 ppm).

1-Iodo-4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl)]benzene (V-IAA-2). To a suspension of **V-IAA-1** (277 mg, 1mmol) and Ag_2SO_4 (936 mg, 3 mmol) in 10 mL EtOH at 0 ^{o}C, was added a solution of I_2 (280 mg, 1.1 mmol) in 30 mL EtOH dropwise over 30 mins. The mixture was kept stirred at the same temperature for another 6 h after completion of the addition. TLC indicated full conversion of the starting material and formation of both mono-iodinated product (**V-IAA-2**) and bis-indinated product. The mixture was then filtrated through a pad of celite and the filtrate was concentrated to afford the crude mixture. The pure mono-iodinated product was isolated in 88% isolated yield as white solid through flash column chromagraphy (Hexanes:EtOAc= 10:1-5:1): mp 126-128 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.07 (t, *J*=6.9 Hz, 2H), 3.62 (q, *J*=6.9 Hz, 2H), 3.78 (s, 3H), 3.80 (s, 3H), 6.33 (d, *J*= 2.7 Hz, 1H), 6.41 (d, *J*= 2.7 Hz, 1H), 6.47 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.6, 39.7, 55.4, 56.5, 81.5, 97.6, 106.8, 115.8 (q, *J*= 286 Hz), 142.3, 157.0 (q, *J*= 36 Hz); 161.1; HRMS (EI) calcd. for $C_{12}H_{13}O_3NIF_3$ $[M]^+$ 402.9893, found 402.9892 (Δ = -0.1 ppm).

3-{4,6-Dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-ynol (V-IAA-3). A mixture of **V-IAA-2** (403 mg, 1 mmol), $Pd(PPh_3)_2Cl_2$ (21 mg, 0.025 mmol), and CuI (9.5 mg, 0.05 mmol) was placed in a 50 mL round-bottomed flask. After purging the flask with nitrogen, diethylamine (5 mL) was added to the mixture, and the solution

was stirred for 20 min. Propargyl alcohol (68 mg, 1.2 mmol) was added to the reaction mixture via a syringe. The reaction mixture was stirred at room temperature until TLC indicated the completion of the reaction (48 h). Then, saturated ammonium chloride solution was added to quench the reaction. The aqueous layer was extracted with EtOAc three times. The combined organic layer was dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 5/1-1/1) afforded **V-IAA-3** as a white solid (275 mg, 83% yield): mp 121.5-123 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (t, J = 6.9 Hz, 2H), 3.15 (br s, 1H), 3.59 (q, J = 6.9 Hz, 2H), 3.79 (s, 3H), 3.83 (s, 3H), 4.54(s,2H), 6.33 (br s, 2H), 7.09 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.3, 40.4, 51.7, 55.4, 79.8, 94.7, 96.9, 104.3, 106.1, 115.9 (q, J = 286 Hz), 142.9, 157.5 (q, J = 36 Hz), 160.9, 161.6; HRMS (EI) calcd for $C_{15}H_{16}NO_4F_3$ $[M]^+$ 331.1031, found 331.1034 (Δ= +0.3 ppm).

(*Z*)-3-{4,6-Dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enol (V-IAA-4). P2-Ni catalyst was generated in *situ* following the standard procedure by adding $NaBH_4$ (1.0 mg, 0.02 mmol) to a suspension of $Ni(OAc)_2$ (3.0 mg, 0.01 mmol) in EtOH (2 mL) at room temperature under an nitrogen atmosphere with stirring. After 30 min, neat ethylenediamine (1.64 μL, 0.024 mmol) was introduced to the reaction mixture. After stirring the catalyst solution for 10 min, **V-IAA-3** (165 mg, 0.5 mmol) in ethanol (5 mL) was added. The nitrogen atmosphere was then replaced by hydrogen. The reaction mixture was stirred until TLC indicated the completion of the reaction. The reaction was quenched by addition of water. The aqueous layer was extracted with EtOAc three times.

The combined organic layer was washed with saturated $NaHCO_3$ solution and brine. After dried over $MgSO_4$, crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 3/1~1/1) afforded **V-IAA-4** as a colorless oil (161mg, 97% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (br s, 1H), 2.83 (t, *J* = 6.9 Hz, 2H), 3.52 (q, *J* = 6.6 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.95 (d, *J* = 6.6 Hz, 2H), 6.03 (dt, *J* = 6.9, 11.1 Hz, 1H), 6.31 (d, *J* = 11.1 Hz, 1H), 6.33(d, *J* = 2.4 Hz, 1H), 6.39 (d, *J* = 2.4 Hz, 1H), 6.80 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 39.7, 55.3, 55.7, 60.1, 97.3, 105.9, 115.8 (q, *J* = 286 Hz), 117.2, 124.5, 133.1, 137.9, 157.3 (q, *J* = 37 Hz), 157.7, 160.0 ; HRMS (ESI) calcd for $C_{15}H_{17}NO_3F_3$ $[M\text{-}OH]^+$ 316.1161, found 316.1172 (Δ = +3.5 ppm).

Ethenyl (*Z*)-3-{4,5-dimethoxy-2-[2-(trifluoroacetylamino)ethyl]phenyl}prop-2-enyl carbonate (V-IAA-5). To a solution of **V-IAA-4** (166 mg, 0.5 mmol) and pyridine (1.0 mL) in CH_2Cl_2 (10 mL) was added slowly vinyl chloroformate (52 mg, 0.55 mmol) in 3 mL CH_2Cl_2 (3 mL) at 0 ºC. After stirring the mixture at 0 ^{o}C for 3 h, the reaction was quenched by saturated $CuSO_4$, and aqueous phase was extracted with diethyl ether four times. Combined organic layer was washed with water, brine and dried over $MgSO_4$. Crude product was obtained after filtration and evaporation of the solvent. Further purification by flash column chromatography on silica gel (hexanes/EtOAc = 3/1) afforded **V-IAA-5** as a white solid (187 mg, 93% yield): mp 65-67 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.87 (t, *J*= 6.9 Hz, 2H), 3.53(q, J= 6.9 Hz, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.56 (m, 3H), 4.88 (dd, *J*= 2.1, 13.8 Hz, 1H), 5.91 (dt, *J*= 6.3, 11.1 Hz, 1H), 6.30 (d, *J*= 2.1 Hz, 1H), 6.39 (d, *J*= 2.7 Hz, 1H); 6.45 (d, J= 11.4 Hz, 1H), 6.71 (br s, 1H), 6.95 (dd,

J= 6.3, 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.6, 39.3, 55.3, 55.5, 66.4, 97.3, 98.0, 106.2, 115.8 (q, *J* = 286 Hz), 116.0, 126.7, 127.2, 138.2, 142.3, 152.9, 157.3 (q, *J*= 37 Hz), 157.8, 160.3; HRMS (ESI) calcd for $C_{15}H_{17}NO_3F_3$ $[M\text{-}OCO_2C_2H_3]^+$ 316.1161, found 316.1157 (Δ= -1.3 ppm).

1-Ethenyl-2-trifluroacetyl-6,7-dimethoxy-3,5-dihydro-1*H*-isoquinoline (V-IAA-6). A solution of ligand (*R)*-**III-BOP-1g** (2.8 mg, 0.0033 mmol) and $Pd_2(dba)_3$ (1.0 mg, 0.0011mmol) in DMF (0.5 mL) was added to a 5 mL round-bottomed flask with a stirring bar under N_2. The solution was stirred at room temperature until the color of the solution turned to light yellow from purple and cooled down to 0 ^oC. Then, **V-IAA-5** (20 mg, 0.05 mmol) in DMF (0.5 mL) was added to the catalyst solution via a syringe. The mixture was stirred at 0 ^oC until TLC indicated completion of the reaction. The reaction mixture was then concentrated and passed through a short pad of silica gel using hexanes/EtOAc (12/1-8/1) as the eluent. The filtrate was then concentrated and subject to HPLC analysis, using a Chiralcel OD-H column (hexanes/*i*-PrOH = 99.5/0.5, 0.5 mL/min). The product **V-IAA-5** was isolated as colorless oil, a mixture of two rotamers in 80:20 ratio (determined by ^{1}H NMR at 25 ^oC): 90% ee, $[\alpha]_D^{23}$ 159.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63-2.75 (m, 1H), 2.87-3.01 (m, 1H), 3.01-3.33 (m, 0.2H), 3.50-3.58 (m, 0.6H), 3.85 (s,2.4H), 3.86(s, 2.4H), 3.87 (s, 0.6H), 4.00-4.07 (m, 0.6H), 4.47-4.52 (m, 0.2H), 5.01-5.17 (m, 1H), 5.29-5.33 (m, 1H), 5.43-5.45 (m, 0.2H), 5.91-6.07 (m, 1.6H), 6.59 (s, 0.6H), 6.61 (s, 0.6H), 6.55 (s, 0.2H), 6.63 (s, 0.2H).

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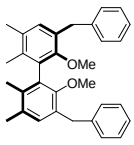
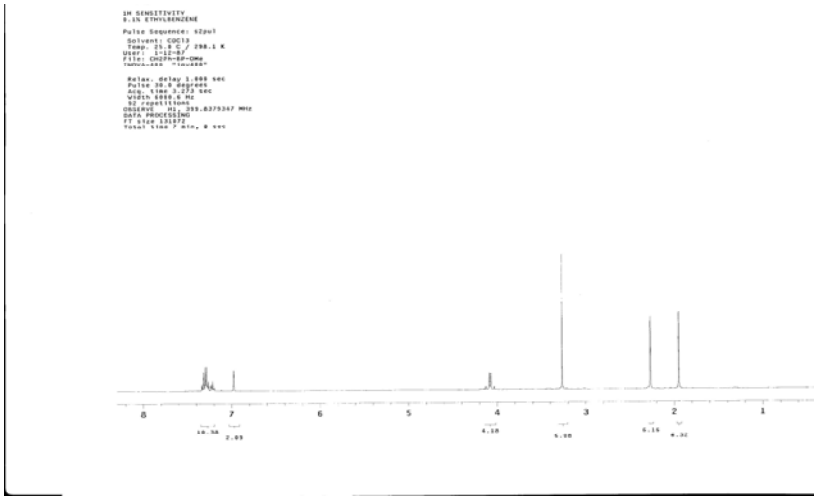
Appendix

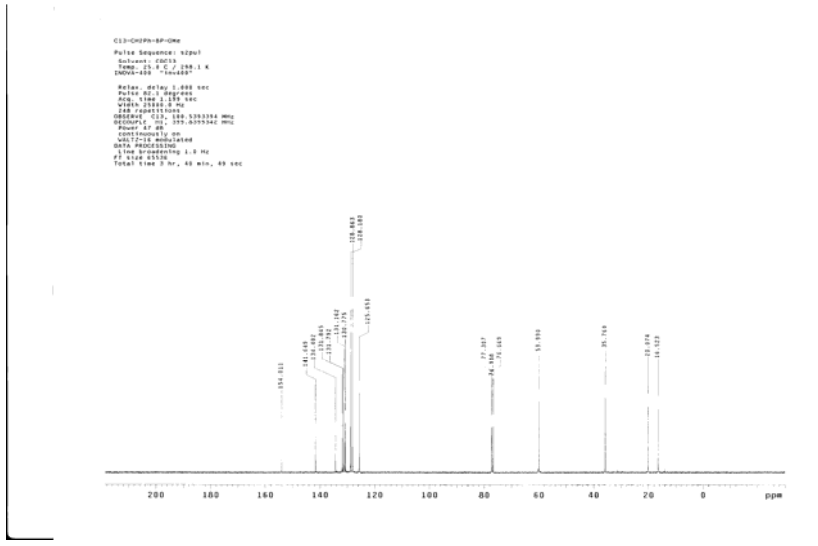
^{1}H, ^{13}C, ^{31}P NMR Spectra

^{1}H and ^{13}C NMR spectra of **(*R*)-II-12a**

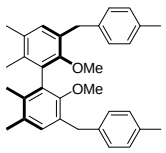


(*R*)-II-12a

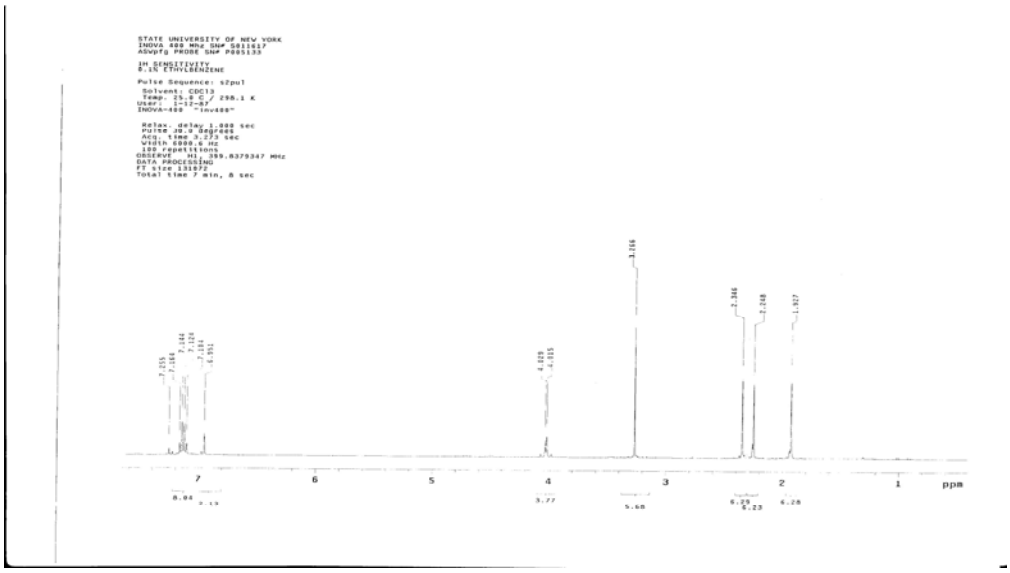


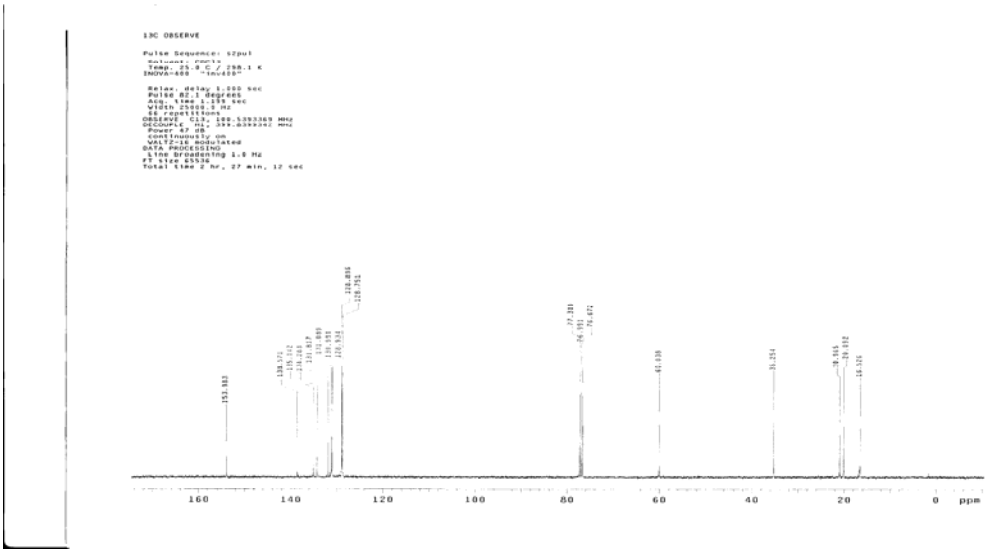


^{1}H and ^{13}C NMR spectra of **(*R*)-II-12b**

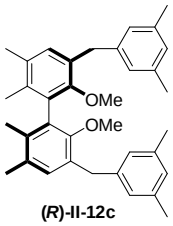


(*R*)-II-12b

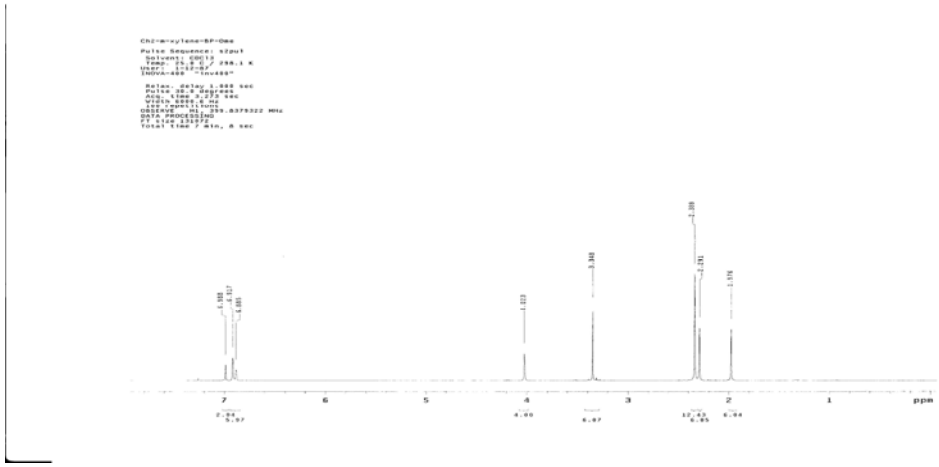


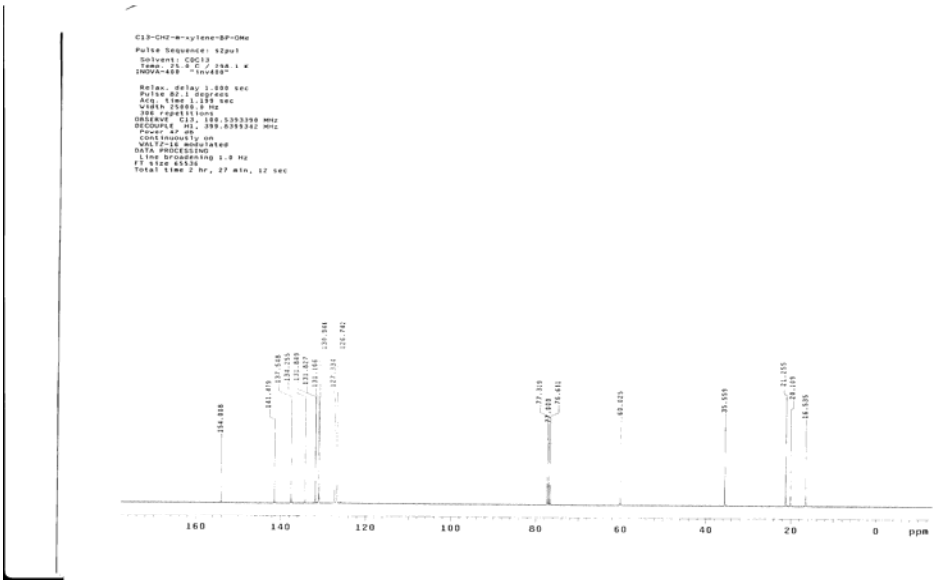


^{1}H and ^{13}C NMR spectra of **(*R*)-II-12c**

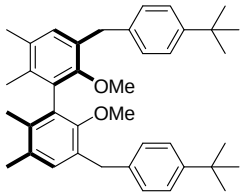


(*R*)-II-12c

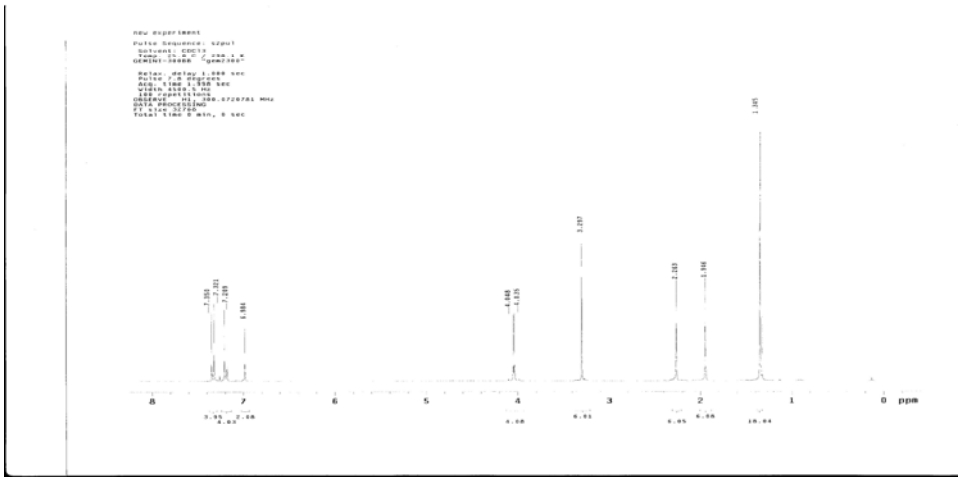


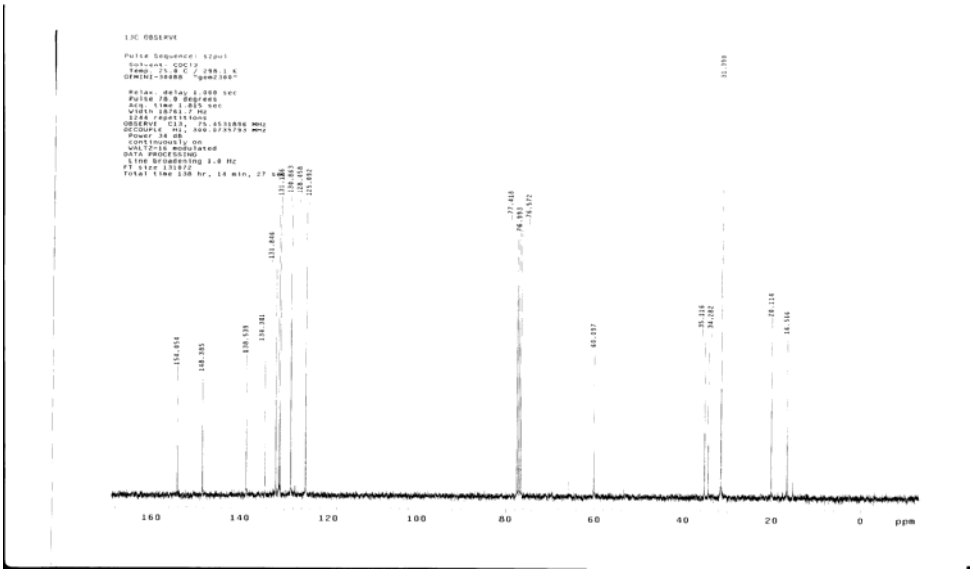


^{1}H and ^{13}C NMR spectra of **(*R*)-II-12d**

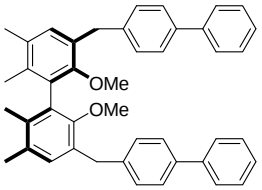


(*R*)-II-12d

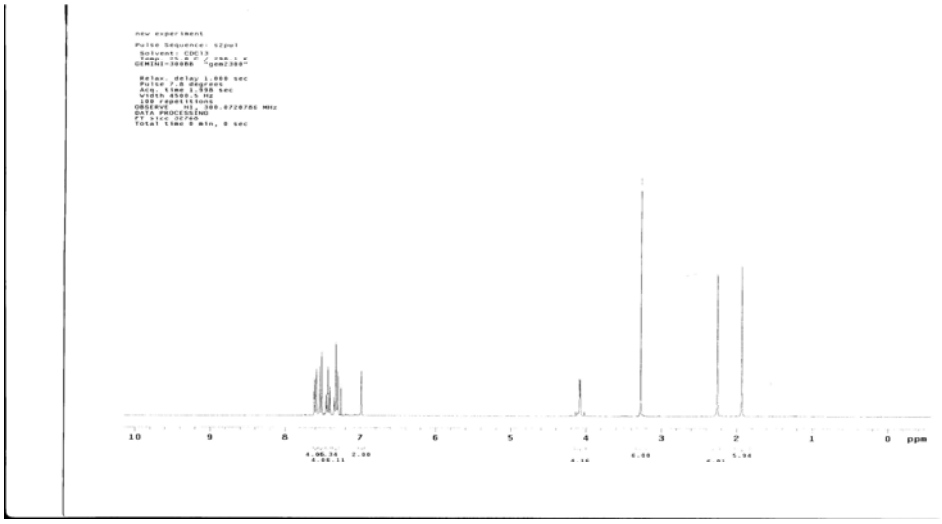


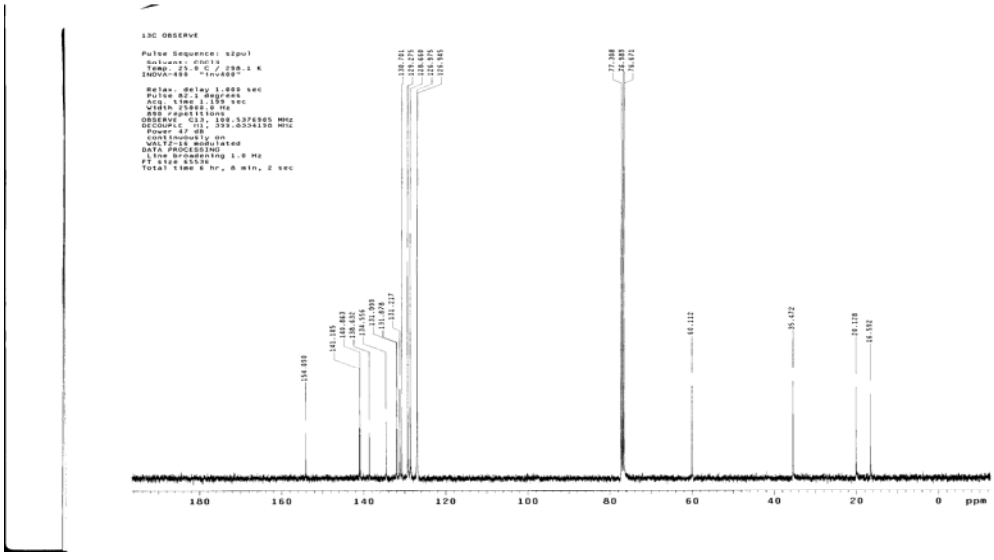


^{1}H and ^{13}C NMR spectra of **(*R*)-II-12e**

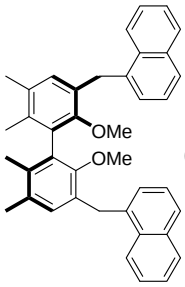


(*R*)-II-12e

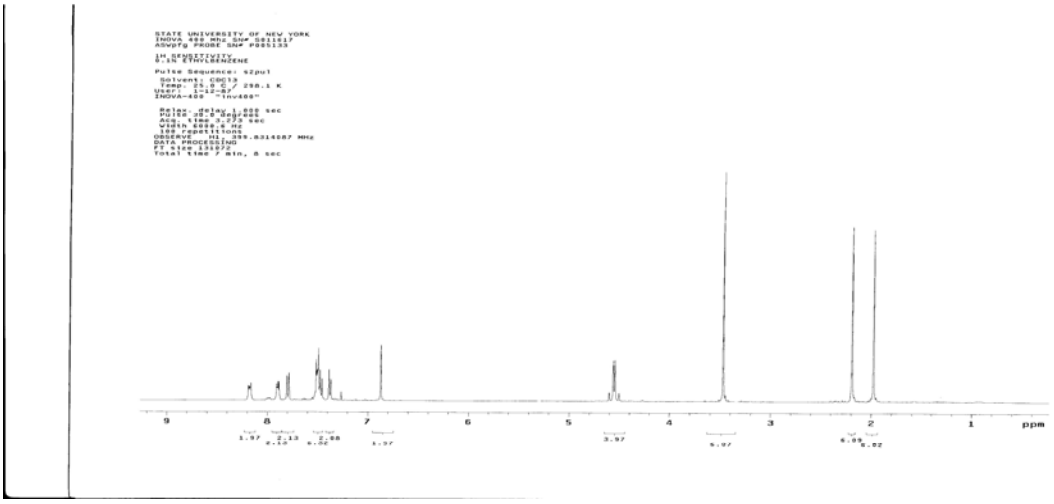


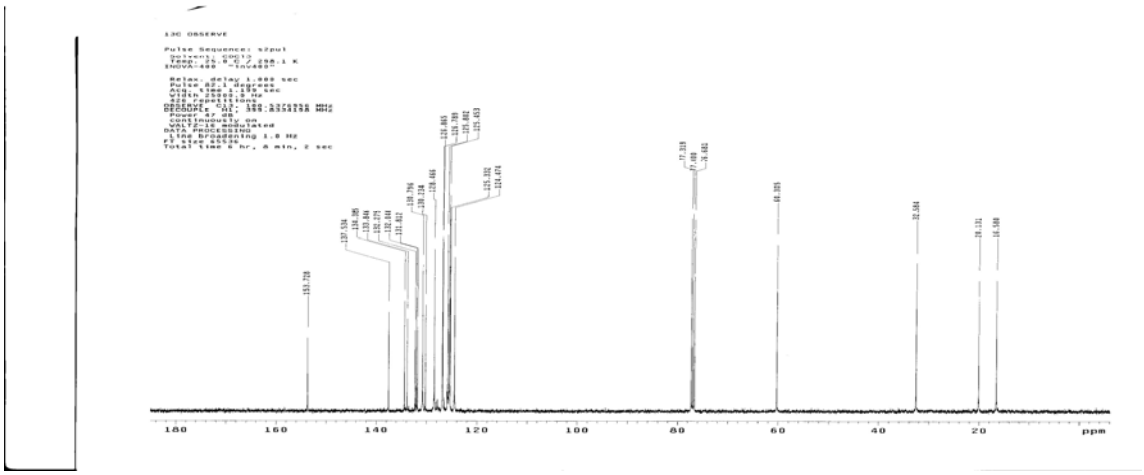


^{1}H and ^{13}C NMR spectra of **(*R*)-II-12f**

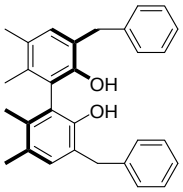


(*R*)-II-12f

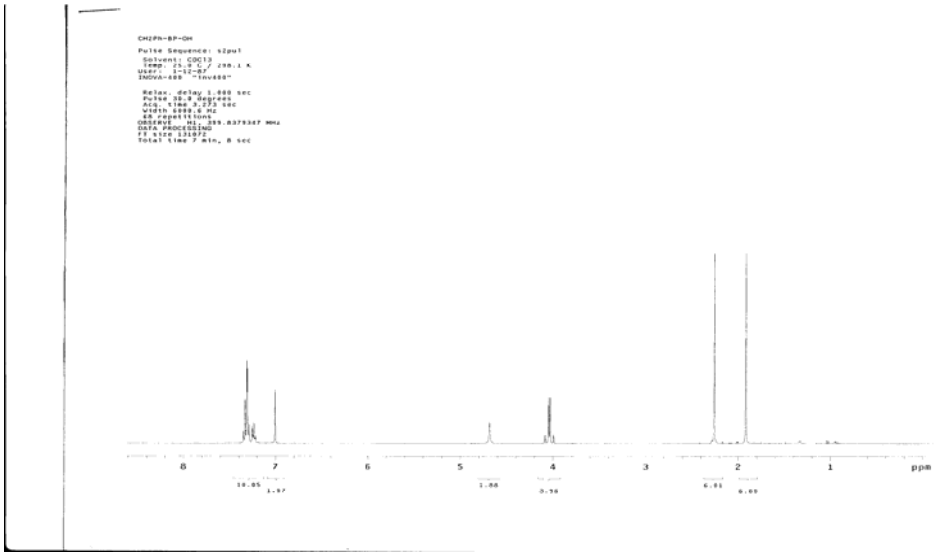


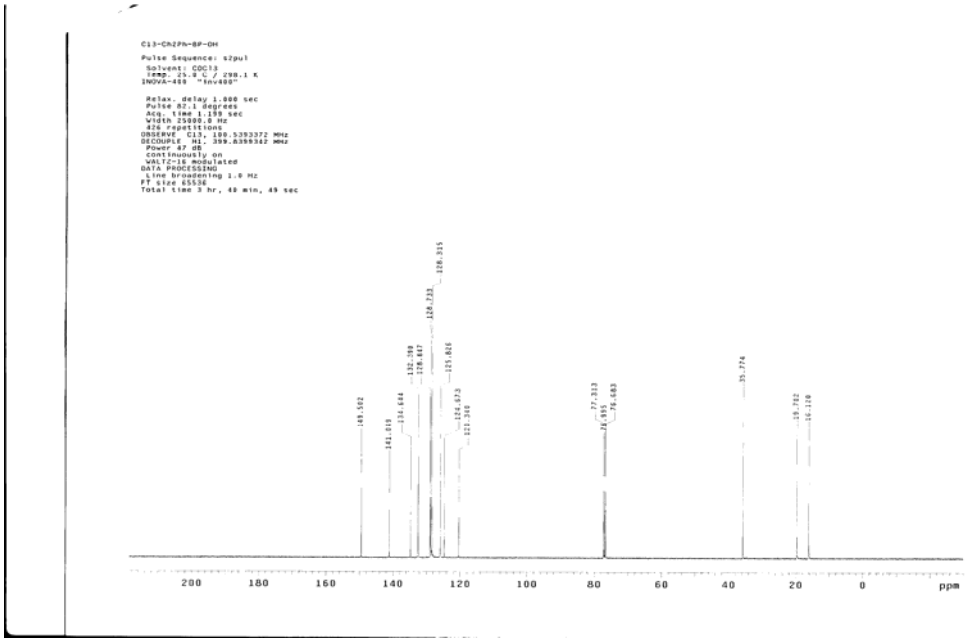


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1f**

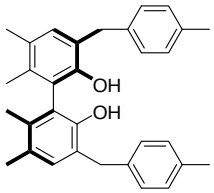


(*R*)-II-1f

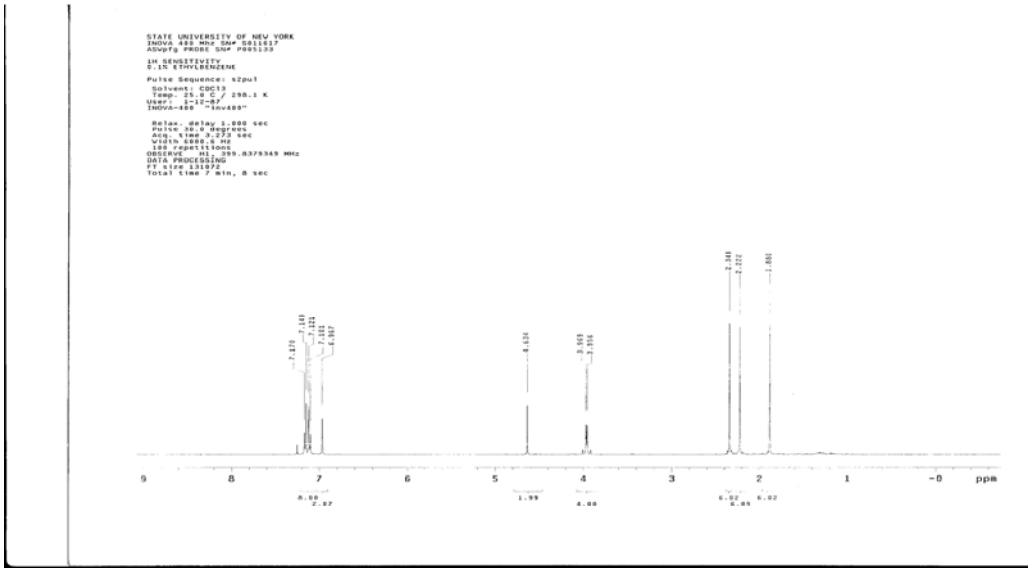


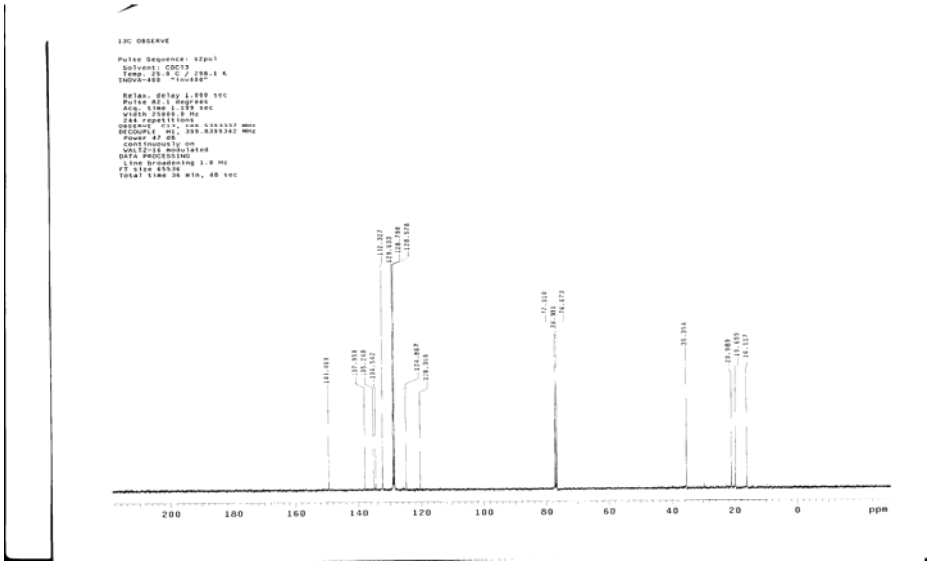


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1g**

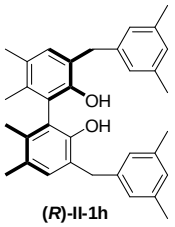


(*R*)-II-1g

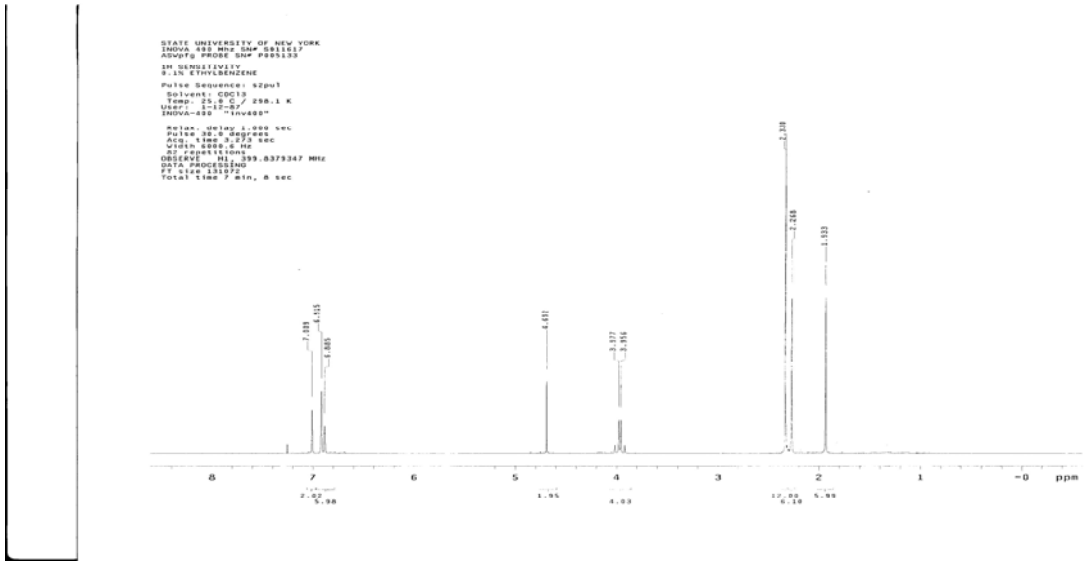


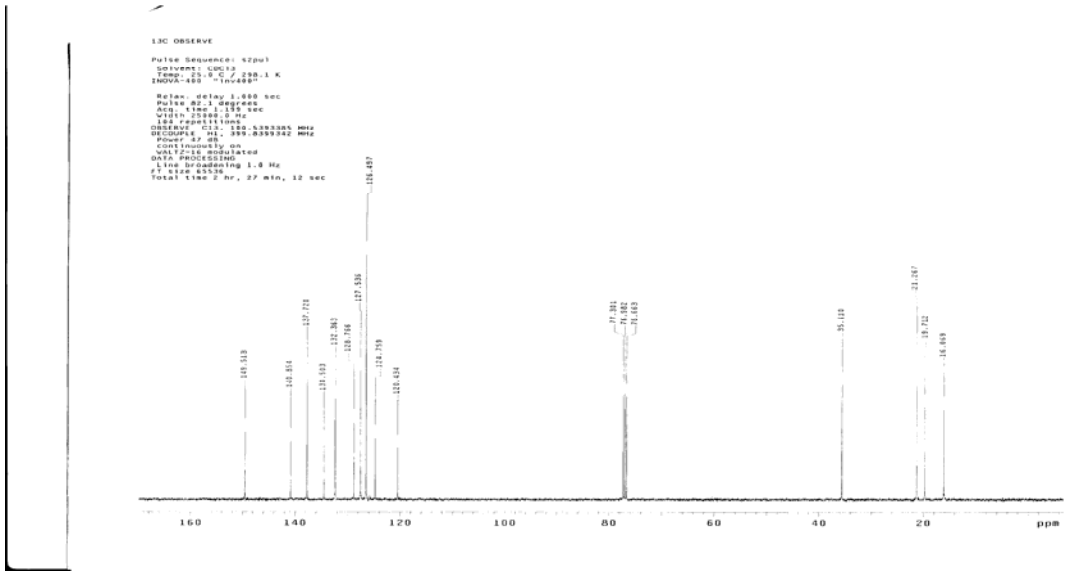


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1h**

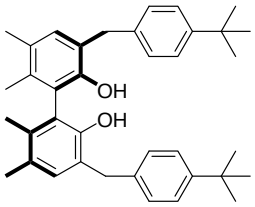


(*R*)-II-1h

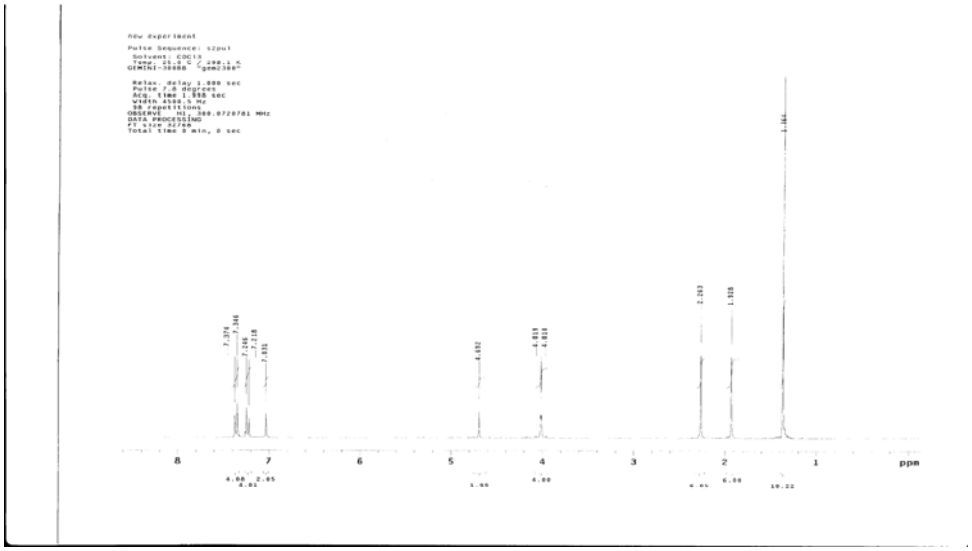


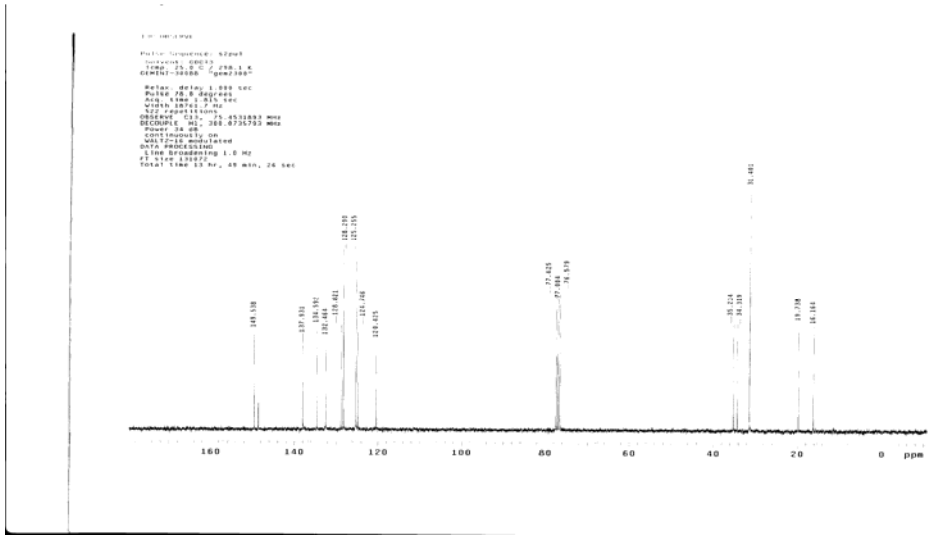


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1i**

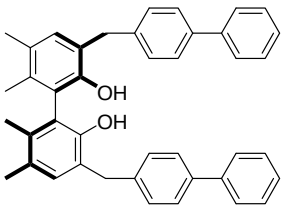


(*R*)-II-1i

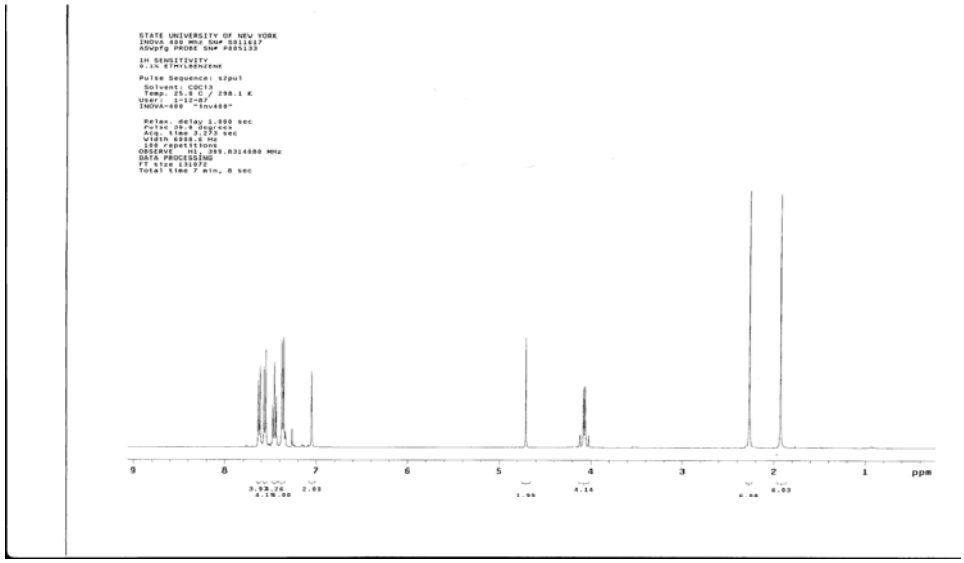


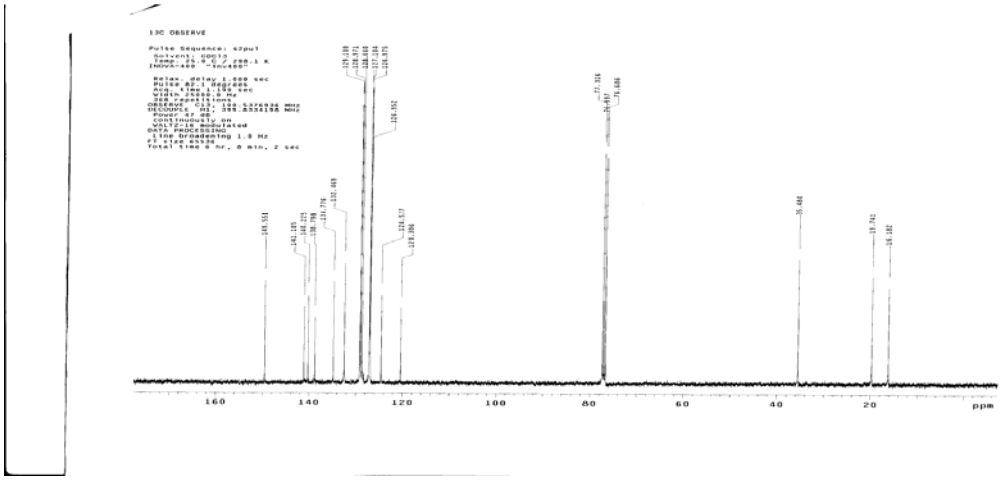


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1j**

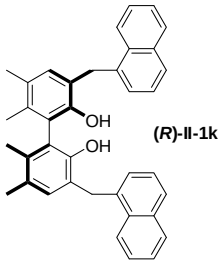


(*R*)-II-1j

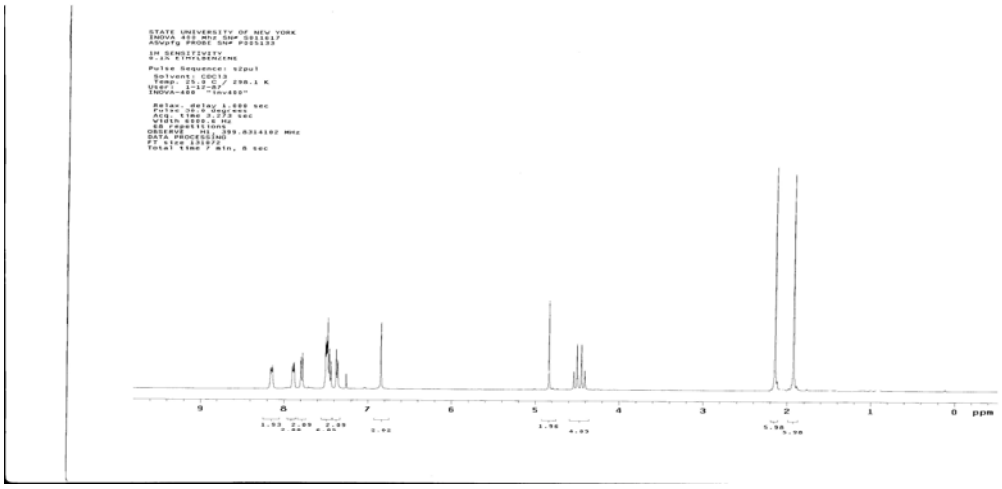


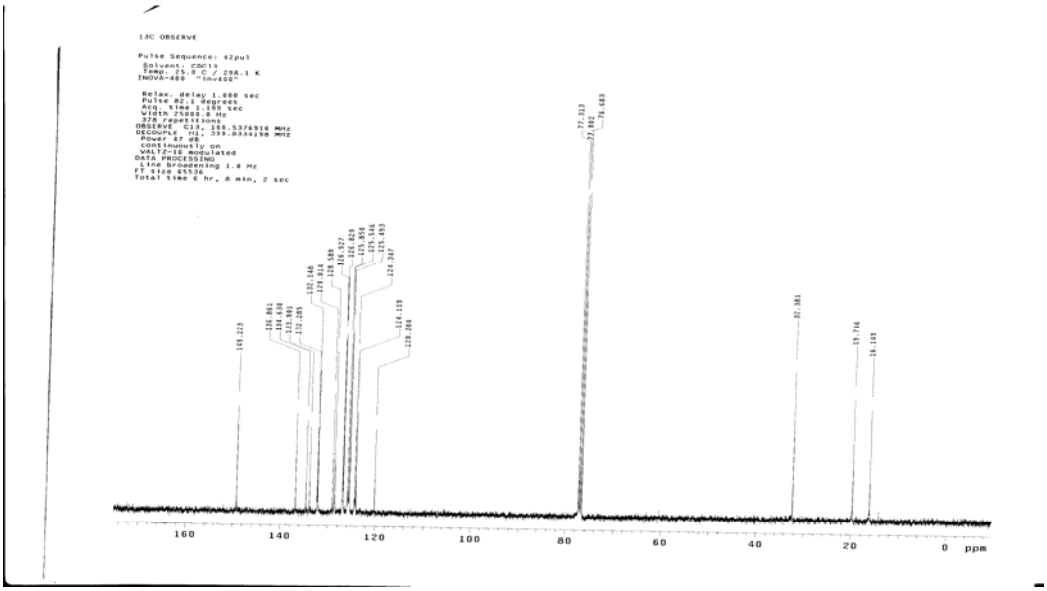


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1k**

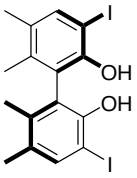


(*R*)-II-1k

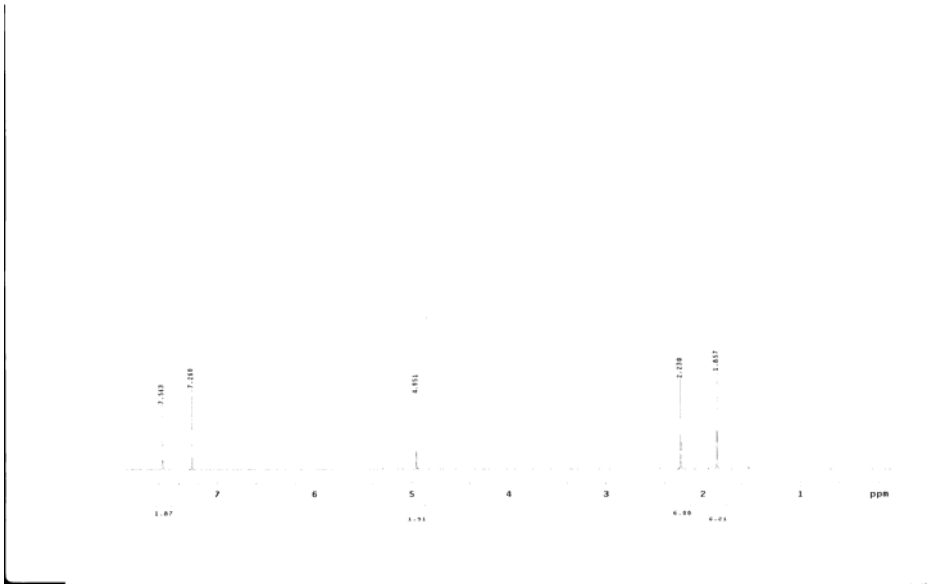


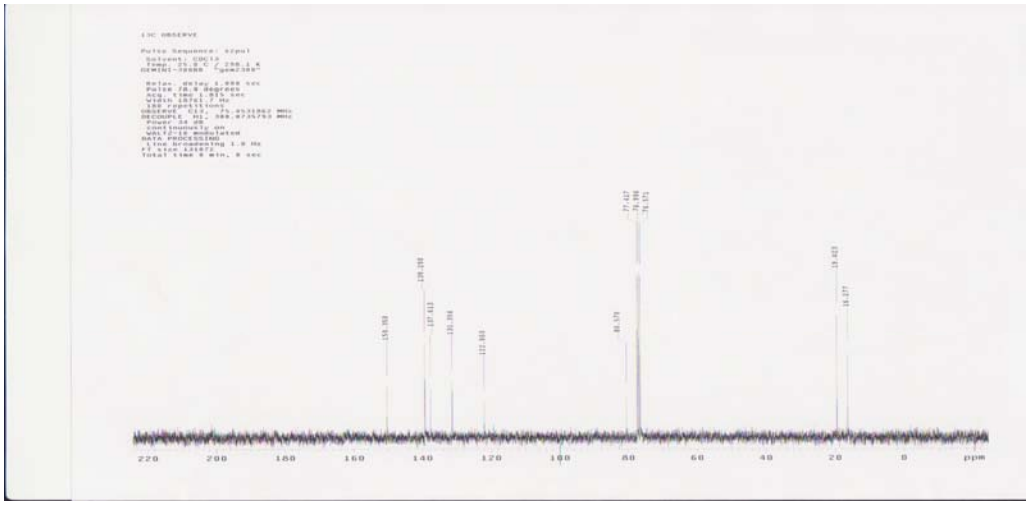


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1l**

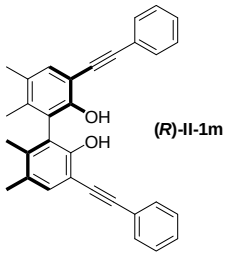


(*R*)-II-1l

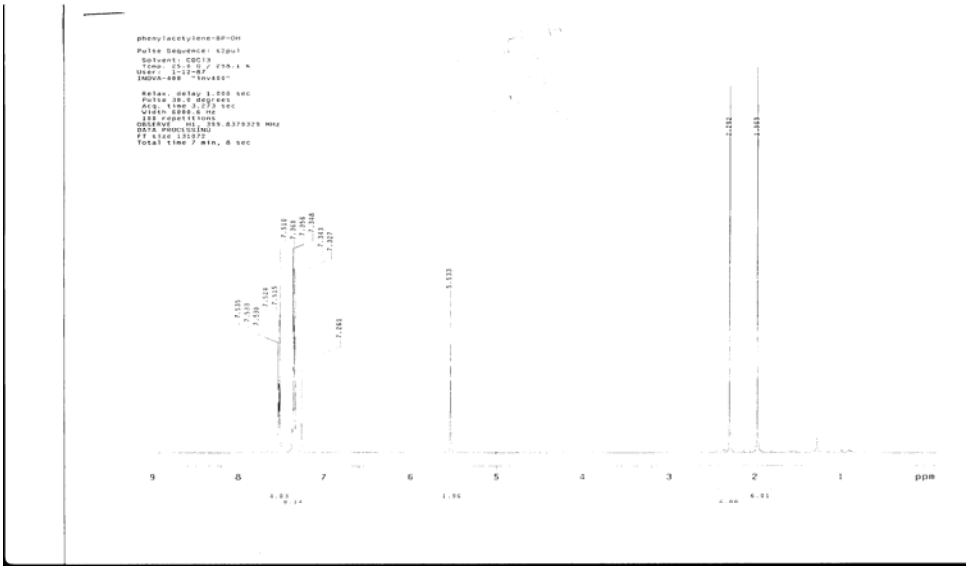


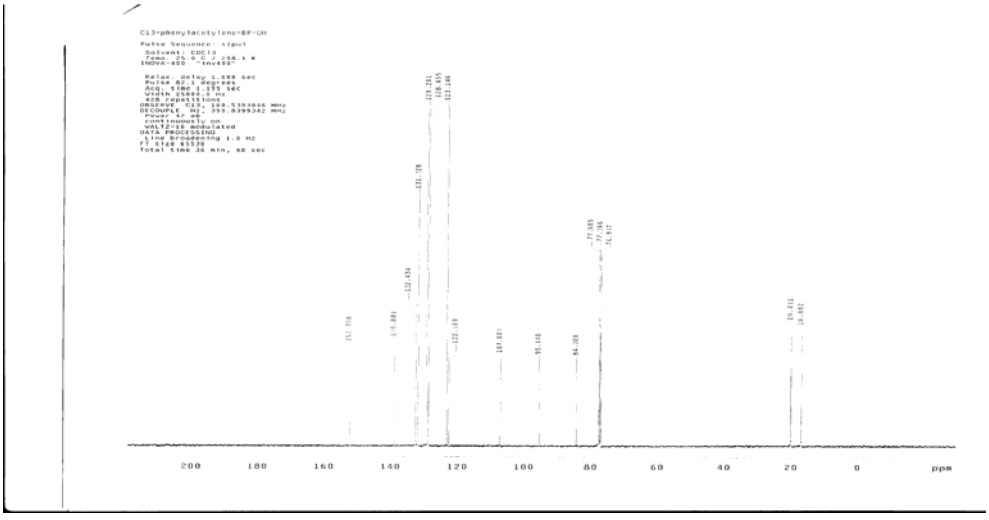


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1m**

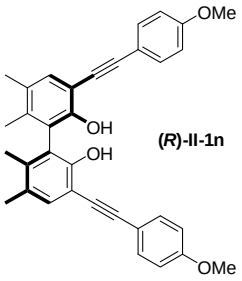


(*R*)-II-1m

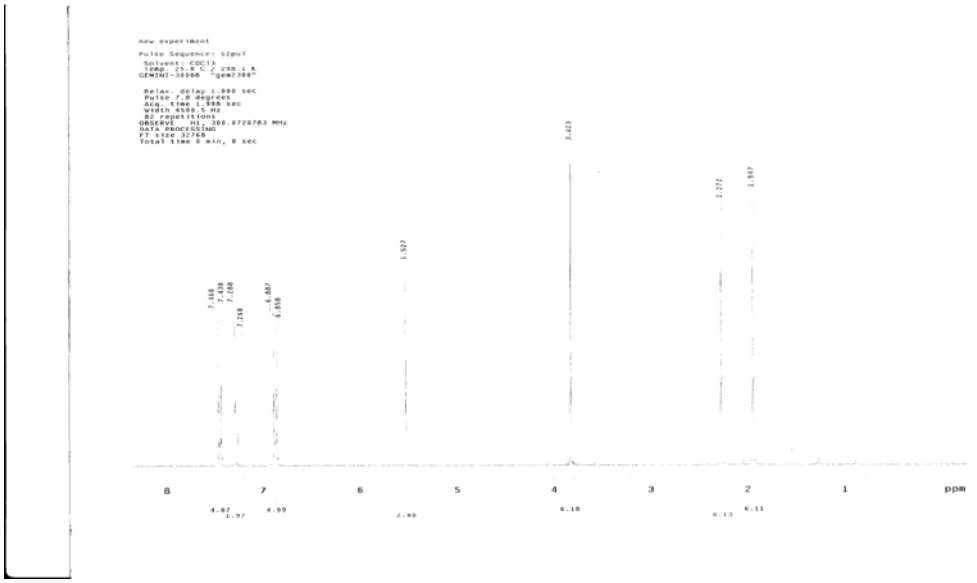


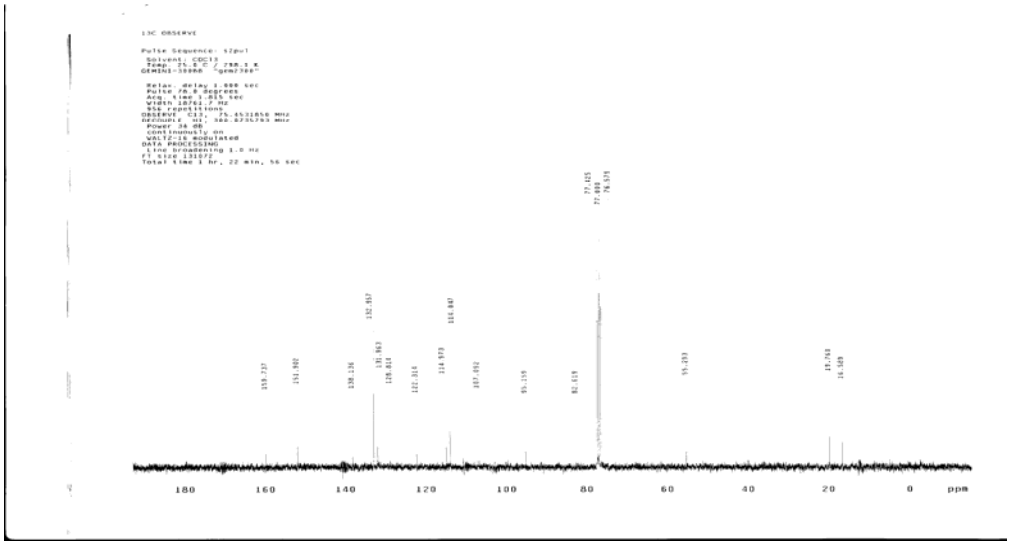


^{1}H and ^{13}C NMR spectra of **(*R*)-II-1n**

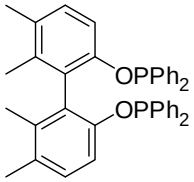


(*R*)-II-1n

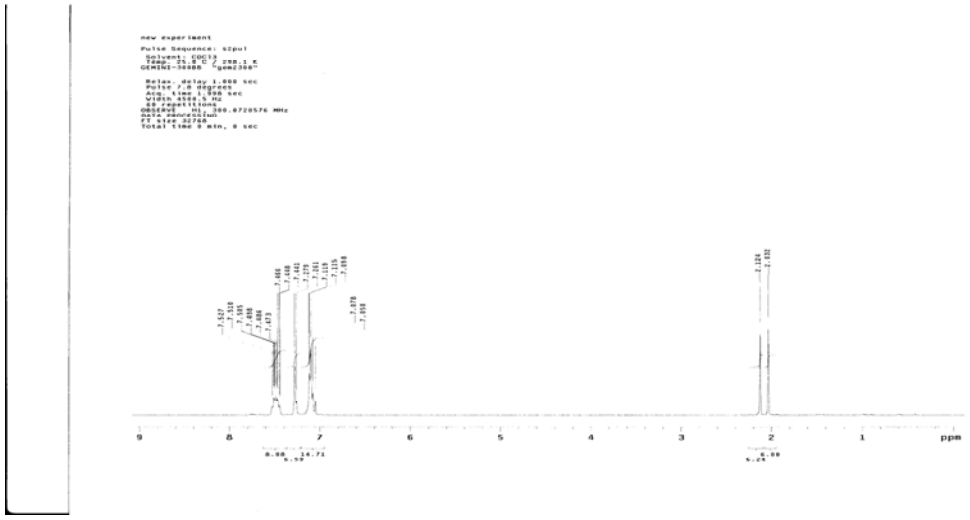


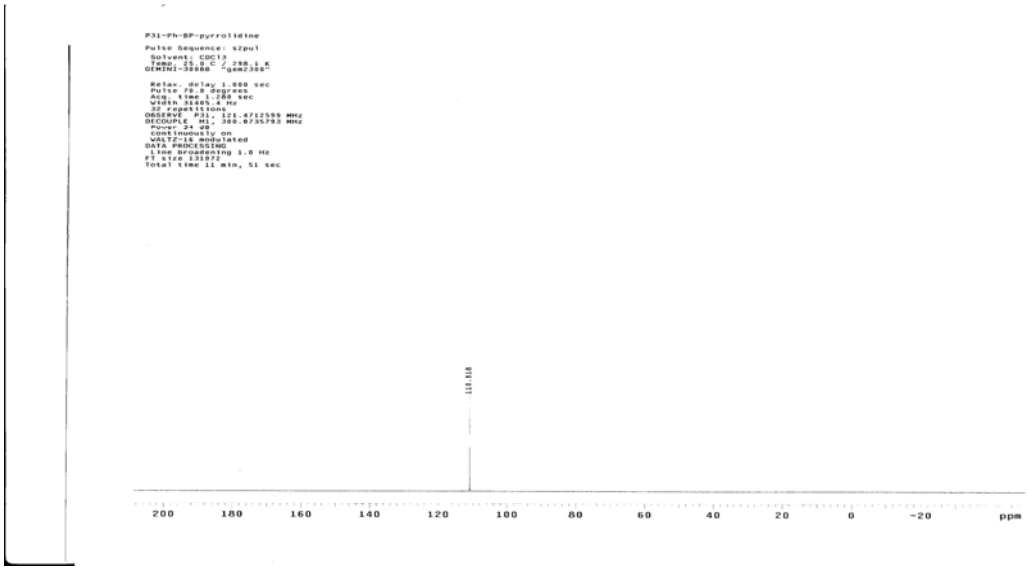


^{1}H and ^{31}P NMR spectra of **III-BOP-1a**

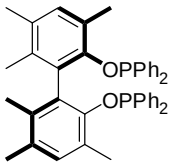


III-BOP-1a

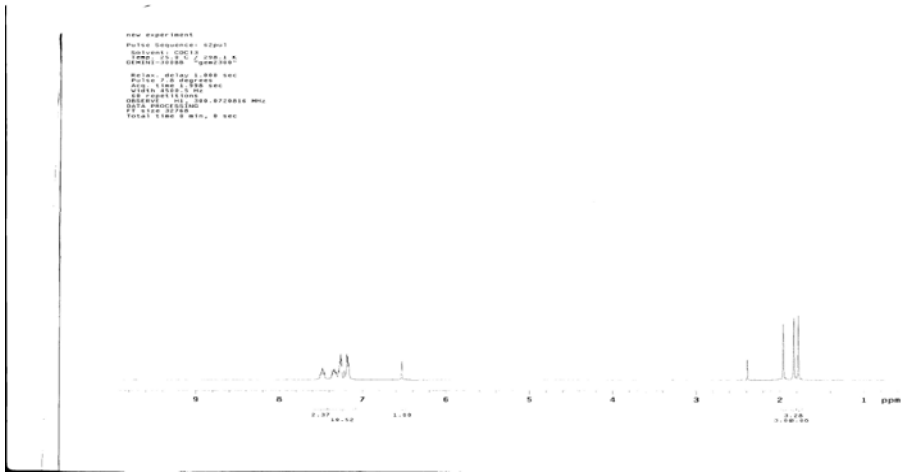


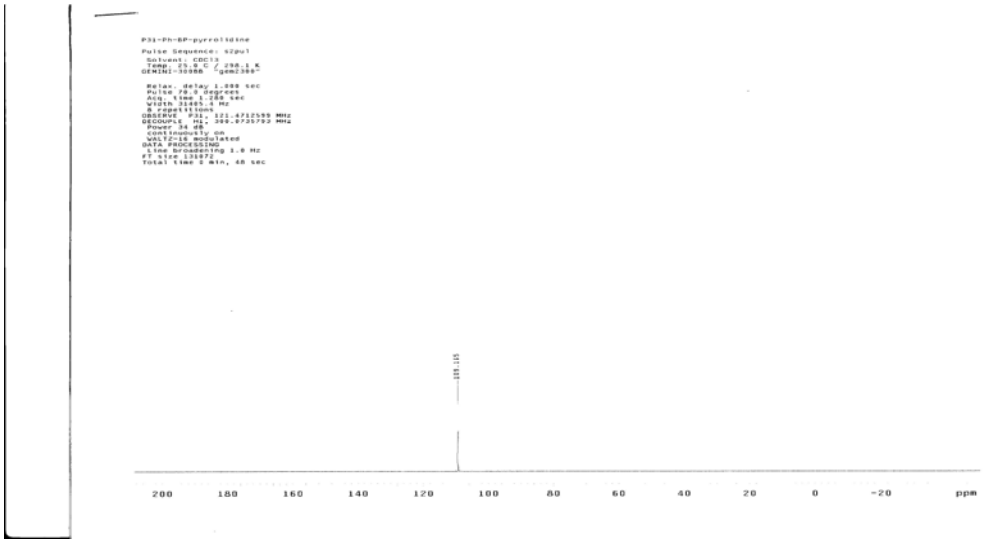


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-1b**

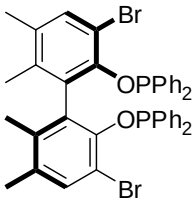


(*R*)-III-BOP-1b

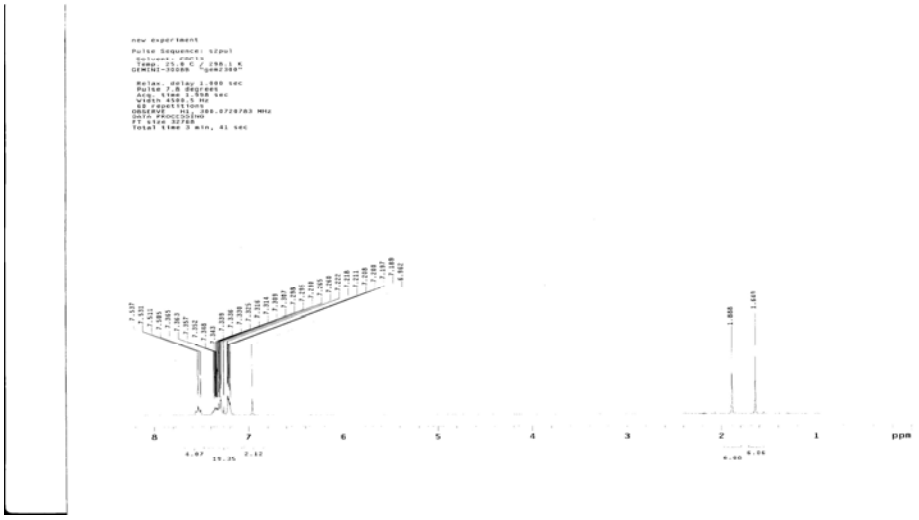


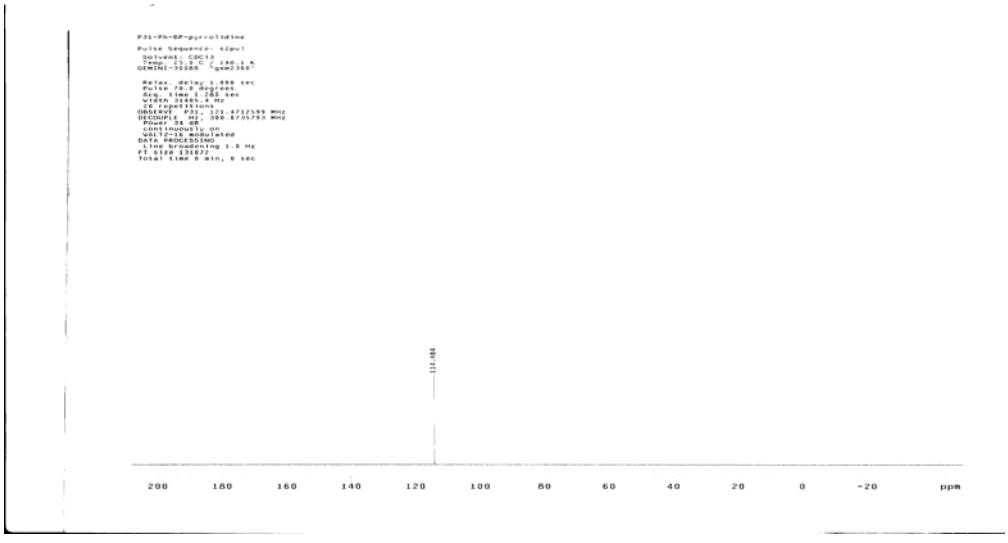


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-1c**

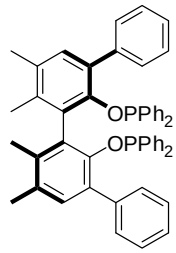


(*R*)-III-BOP-1c

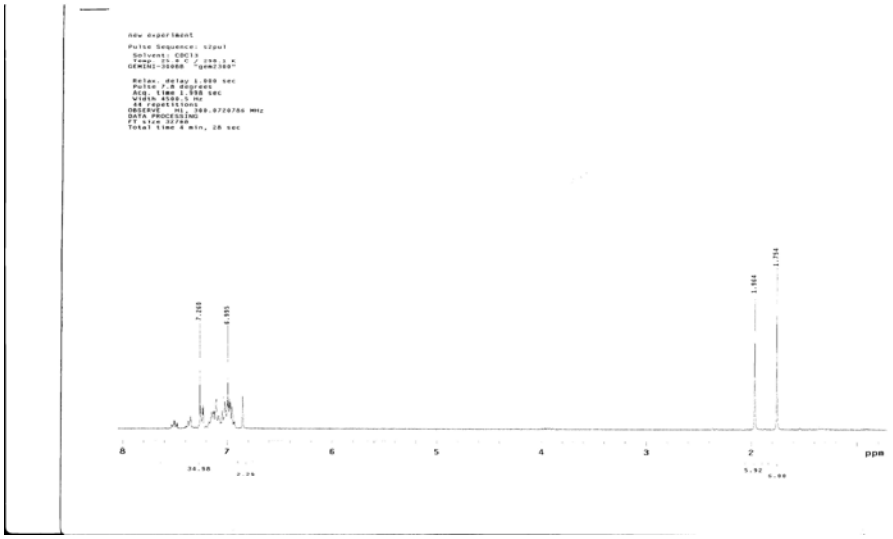


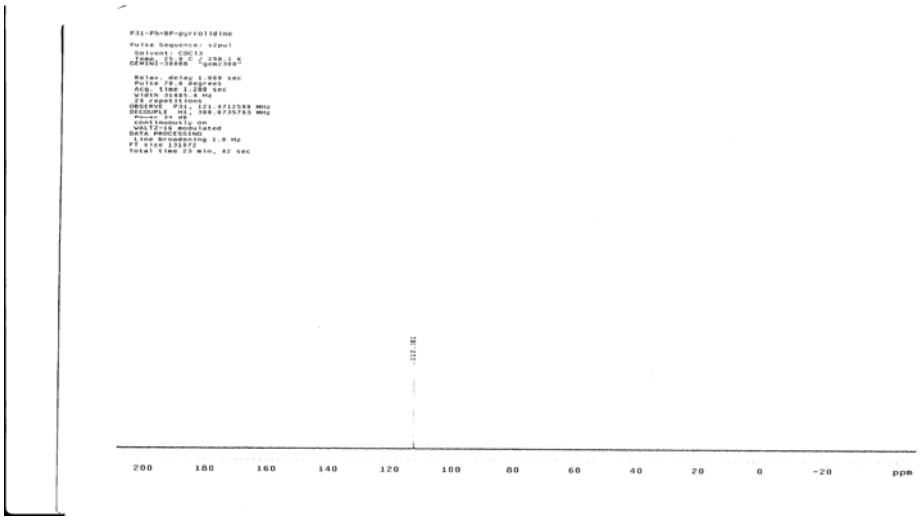


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-1d**

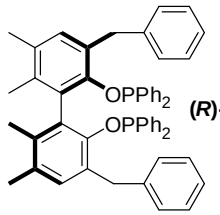


(*R*)-III-BOP-1d

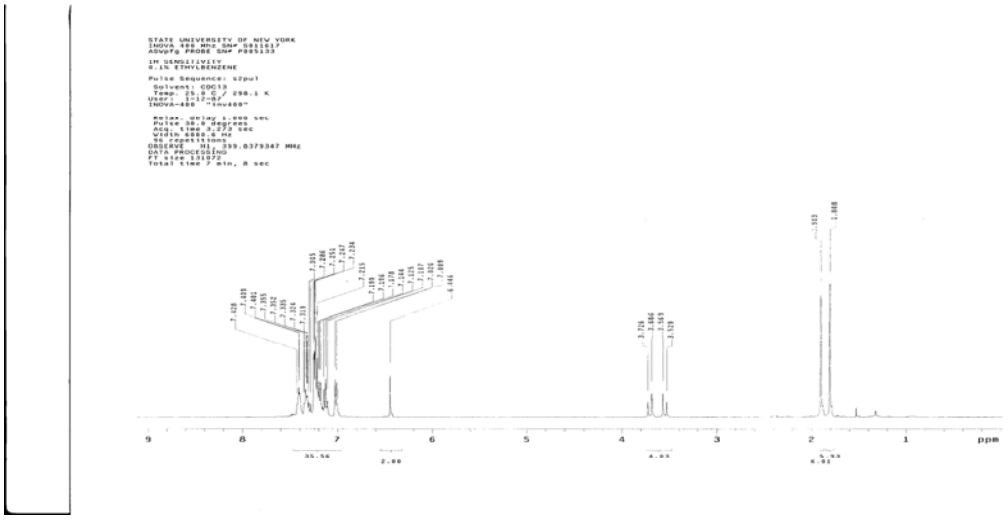


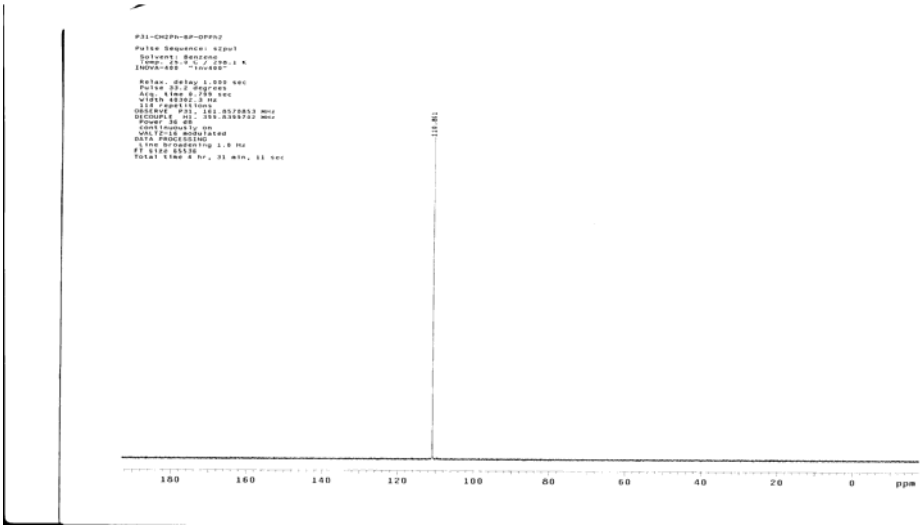


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-1e**

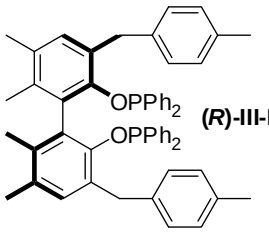


(*R*)-III-BOP-1e

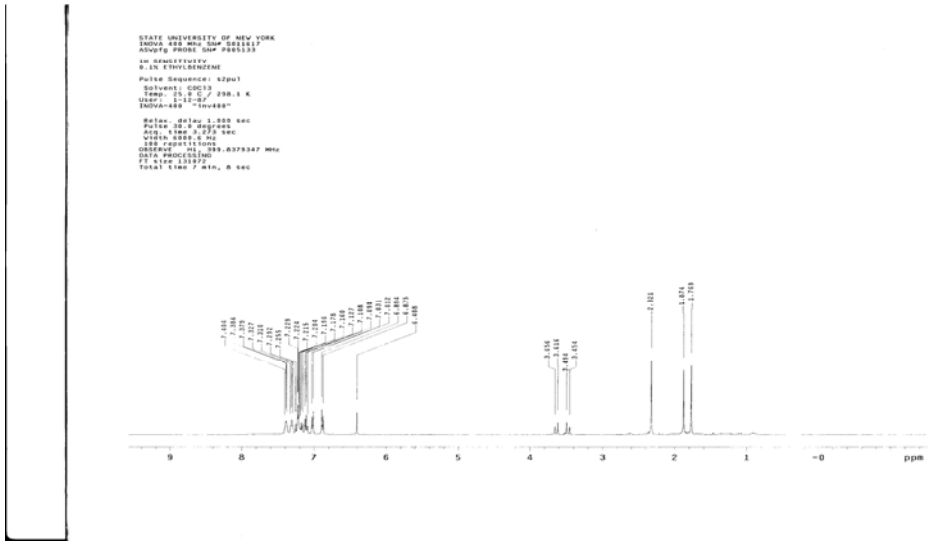


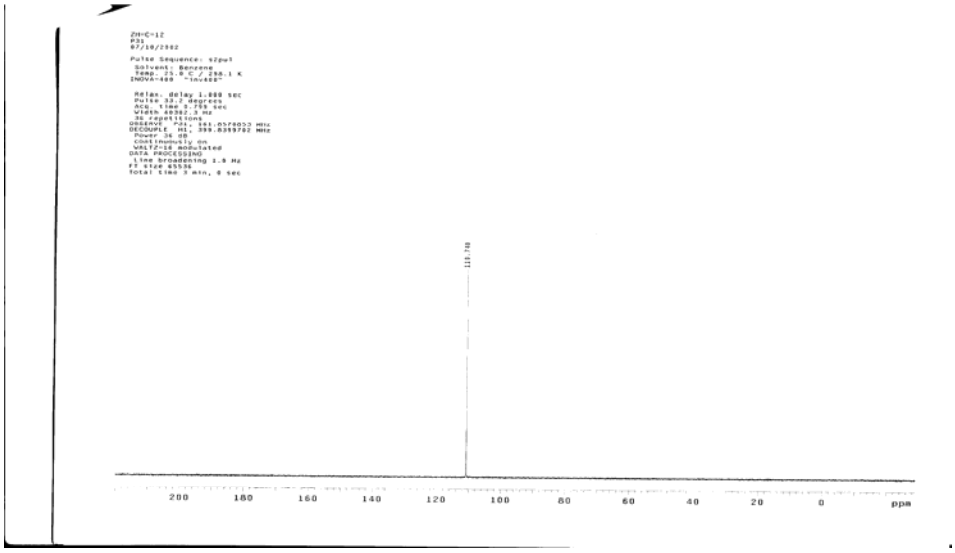


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-1f**

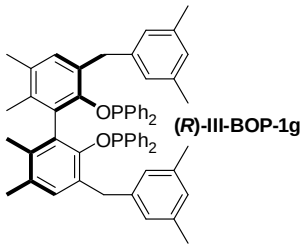


(*R*)-III-BOP-1f





^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-1g**



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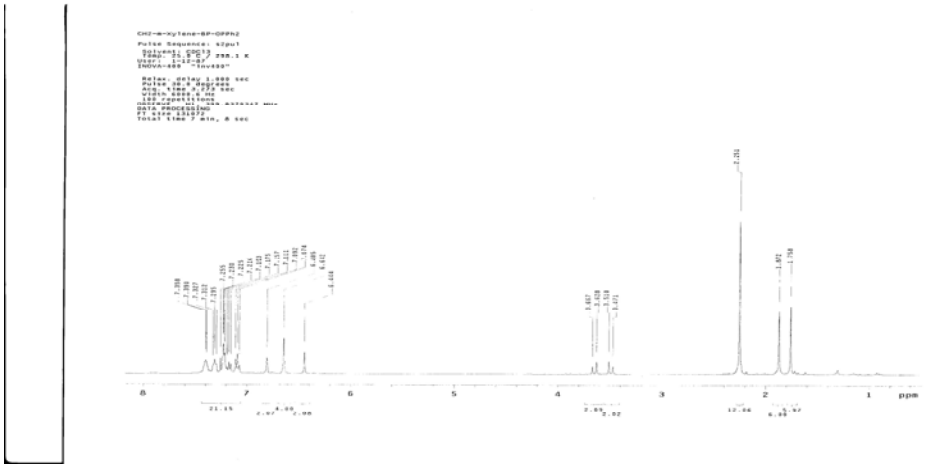
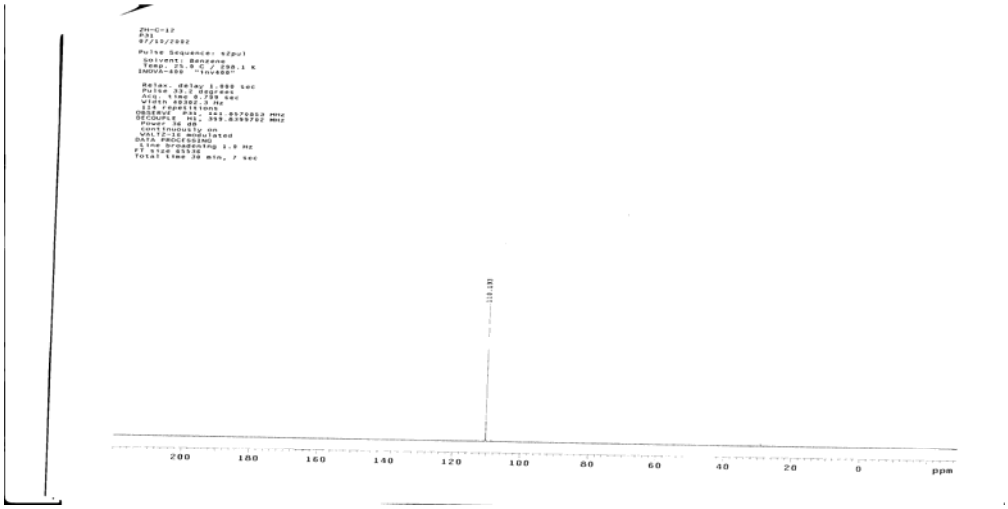
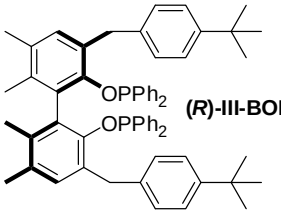
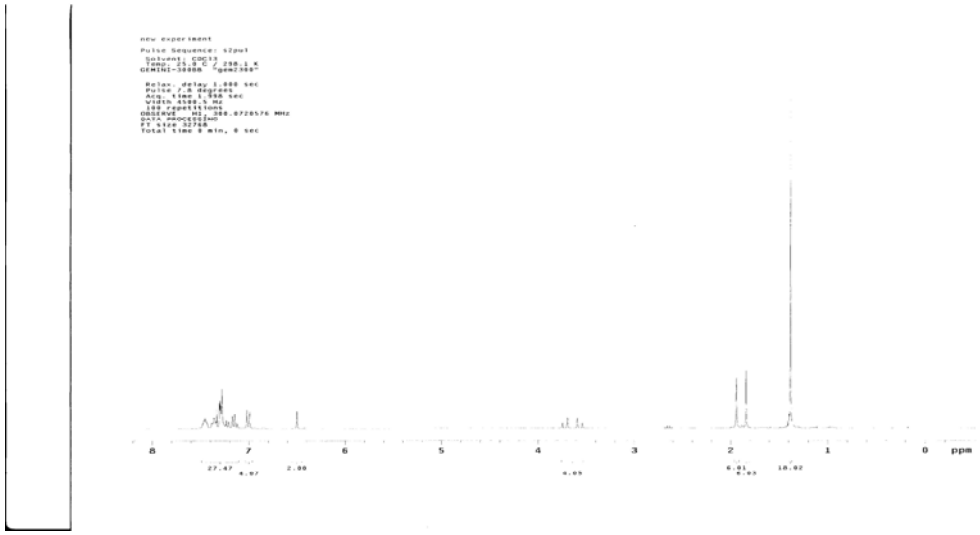


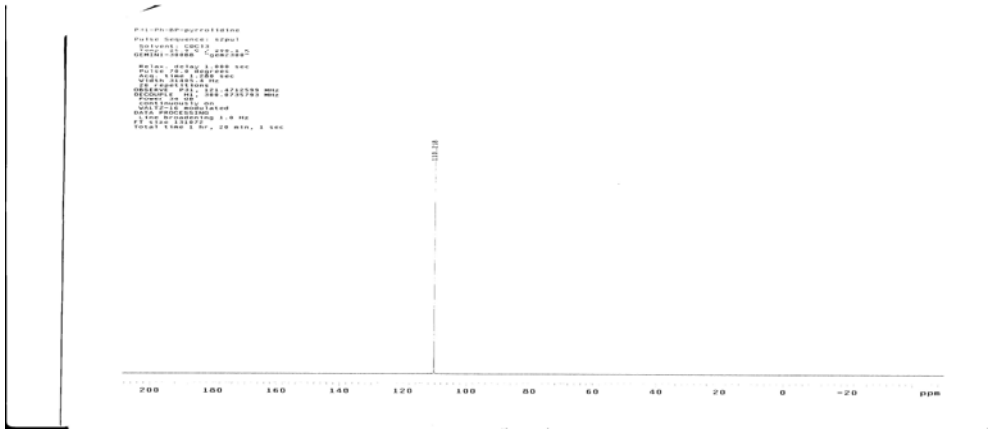


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-1h**

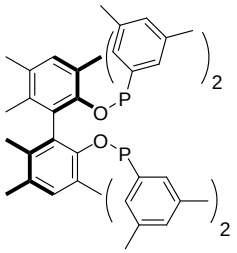


(*R*)-III-BOP-1h

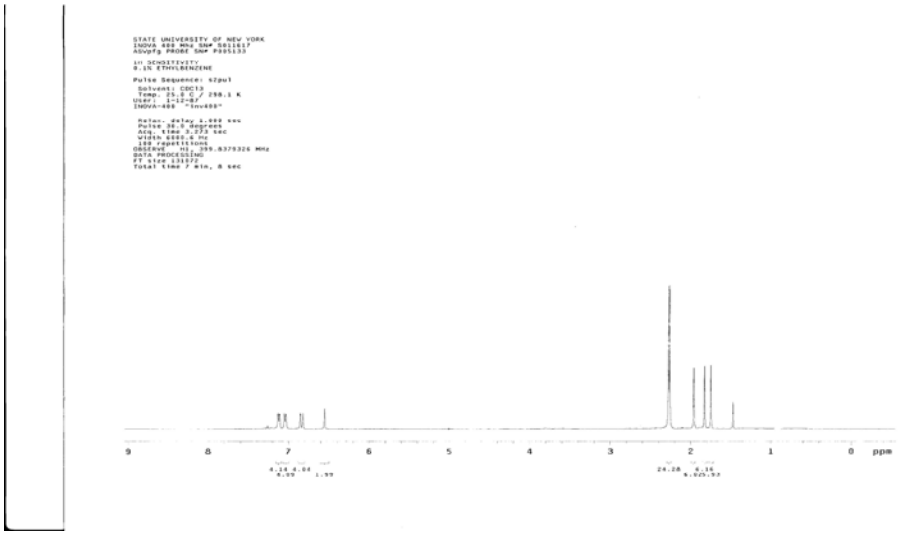


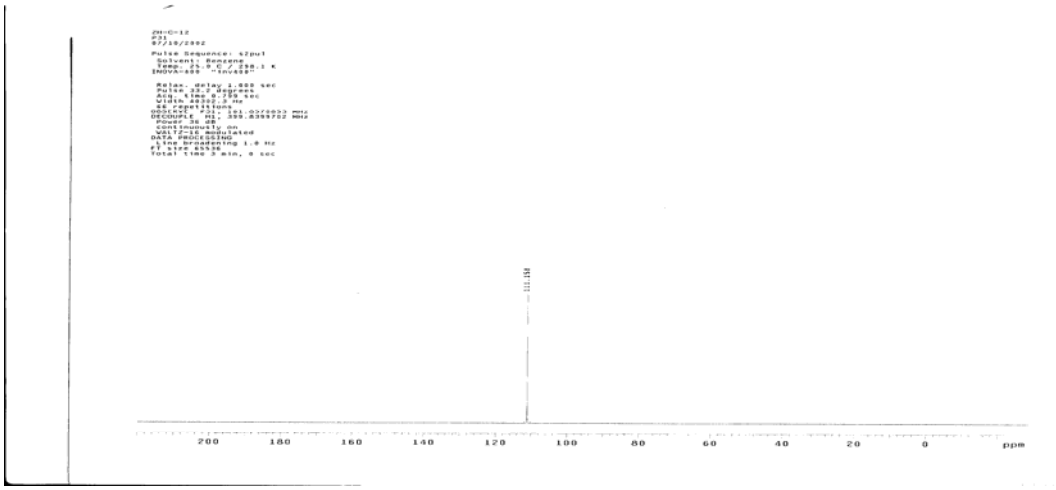


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-3b**

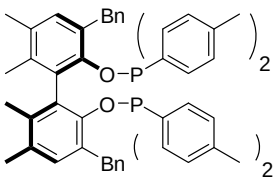


(*R*)-III-BOP-3b

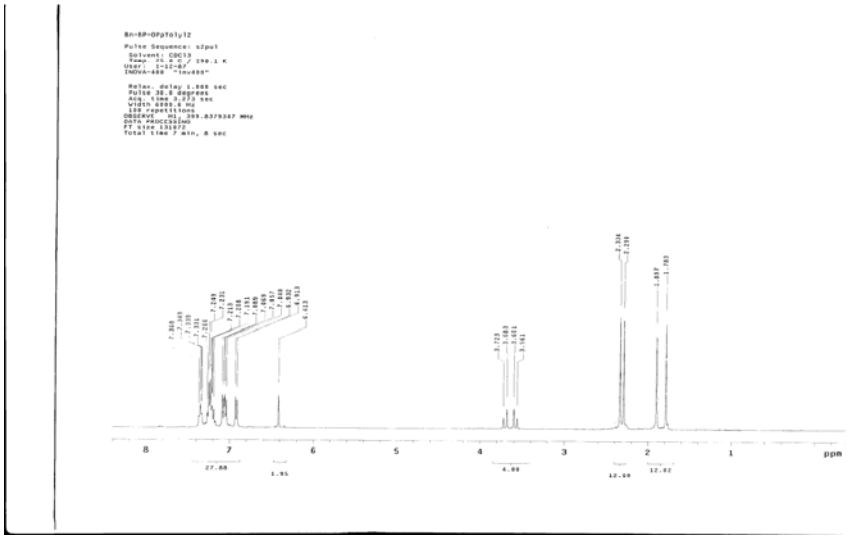


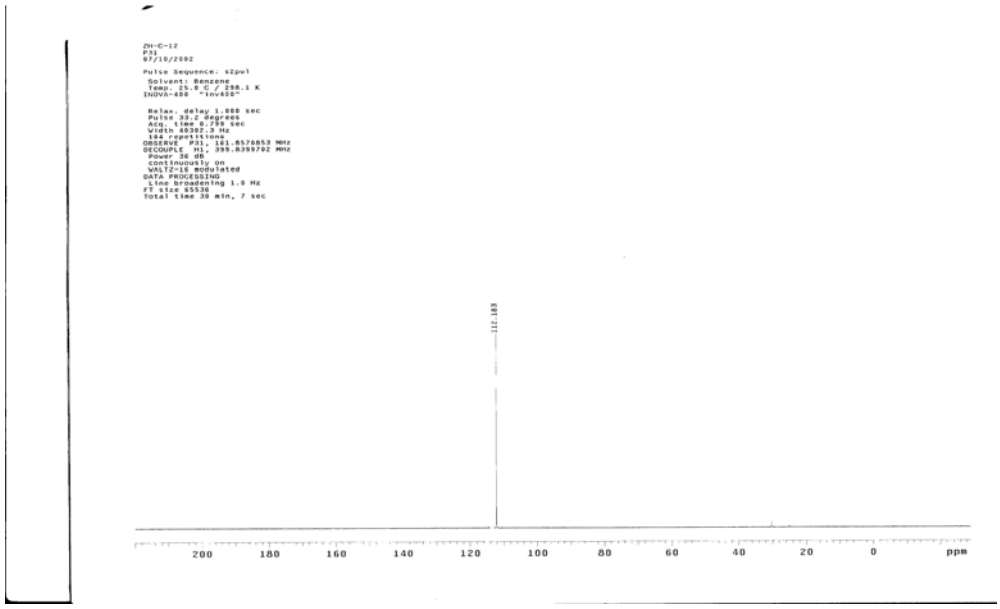


^{1}H and ^{31}P NMR spectra of (***R***)-**III-BOP-2e**

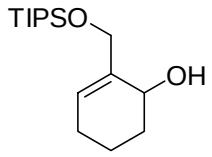


(*R*)-III-BOP-2e

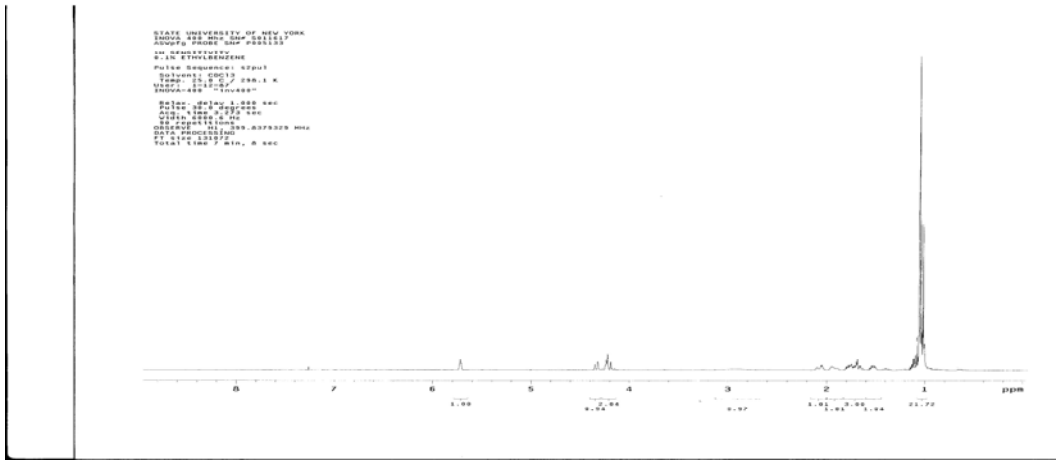


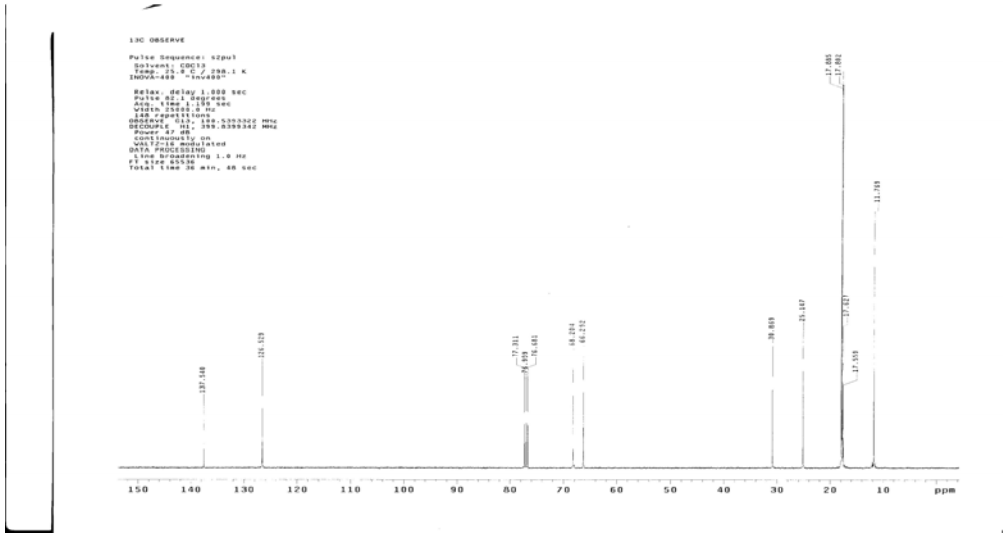


^{1}H and ^{13}C NMR spectra of **V-10b**

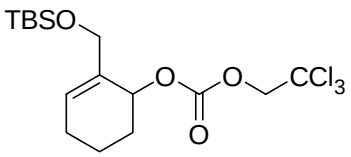


V-10b

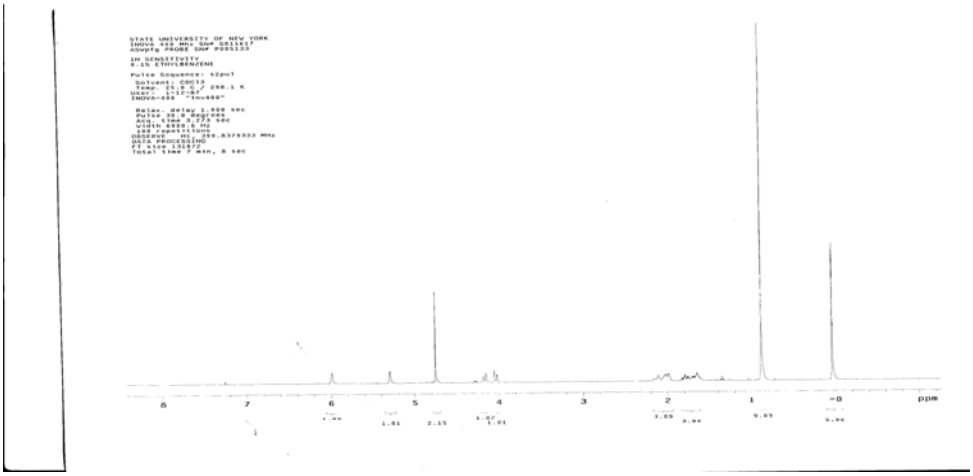


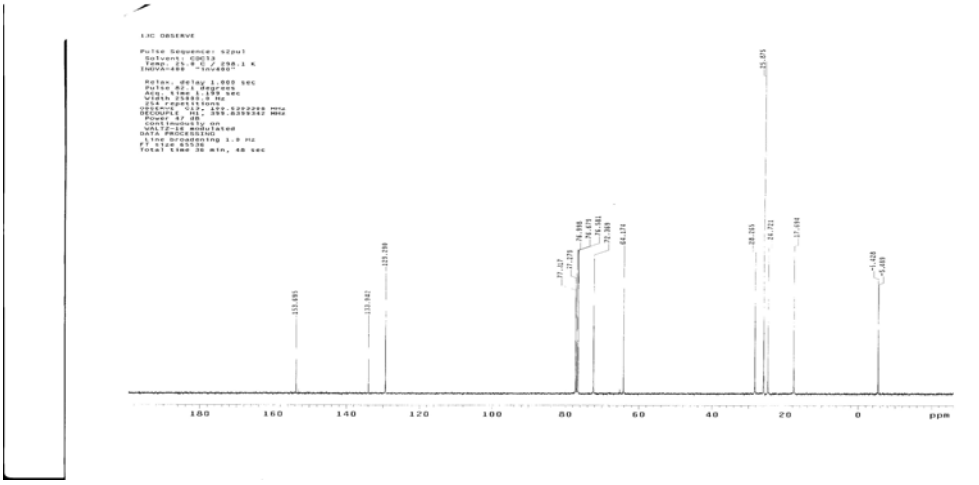


^{1}H and ^{13}C NMR spectra of **V-1a-2**

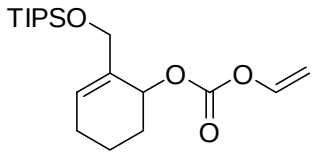


V-1a-2

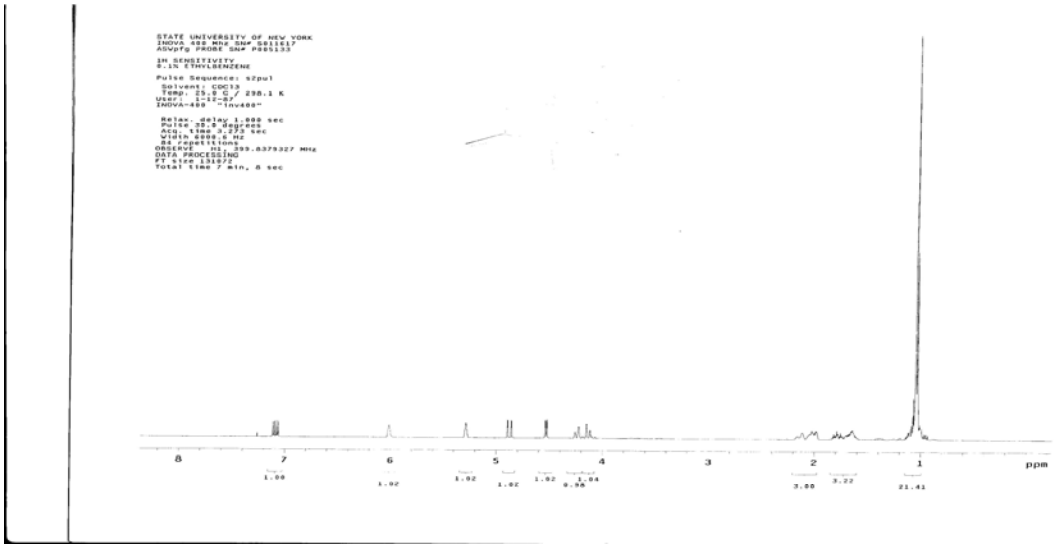


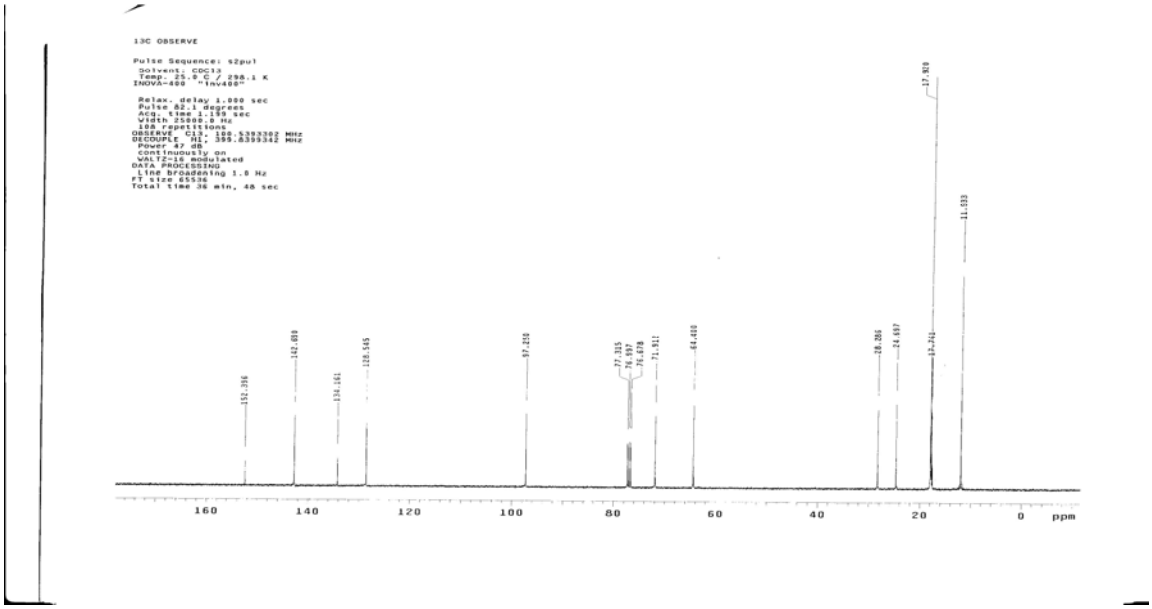


^{1}H and ^{13}C NMR spectra of **V-1b-1**

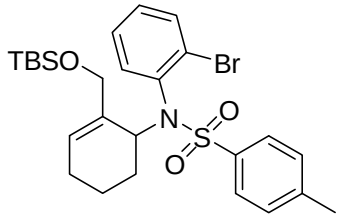


V-1b-1

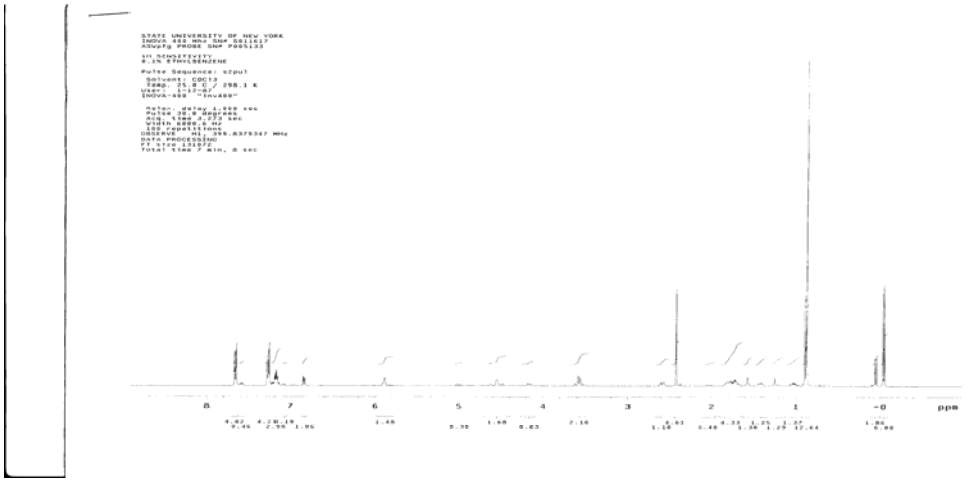


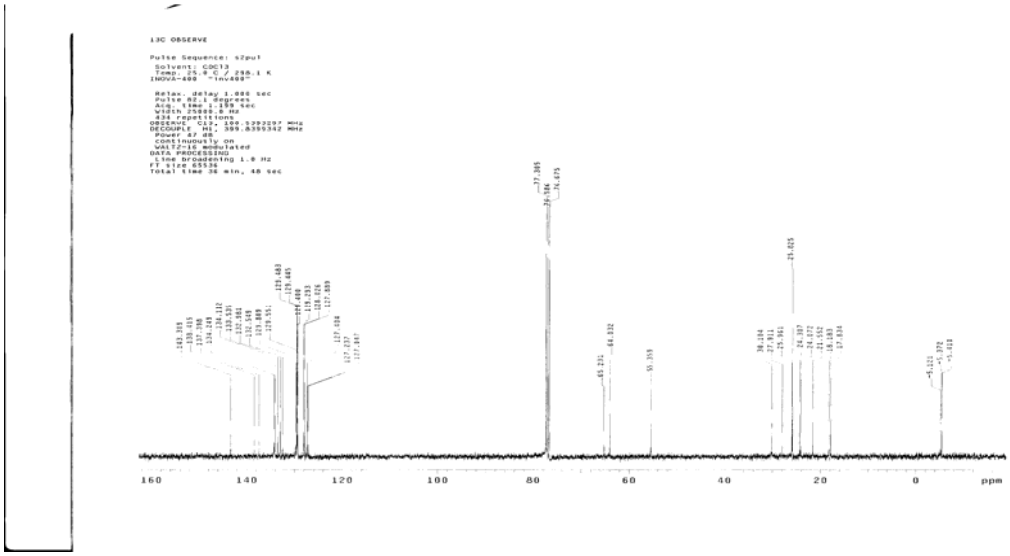


^{1}H and ^{13}C NMR spectra of **V-3a**

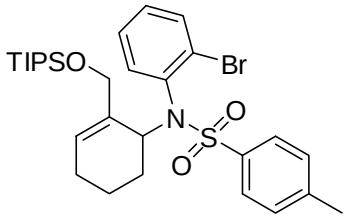


V-3a

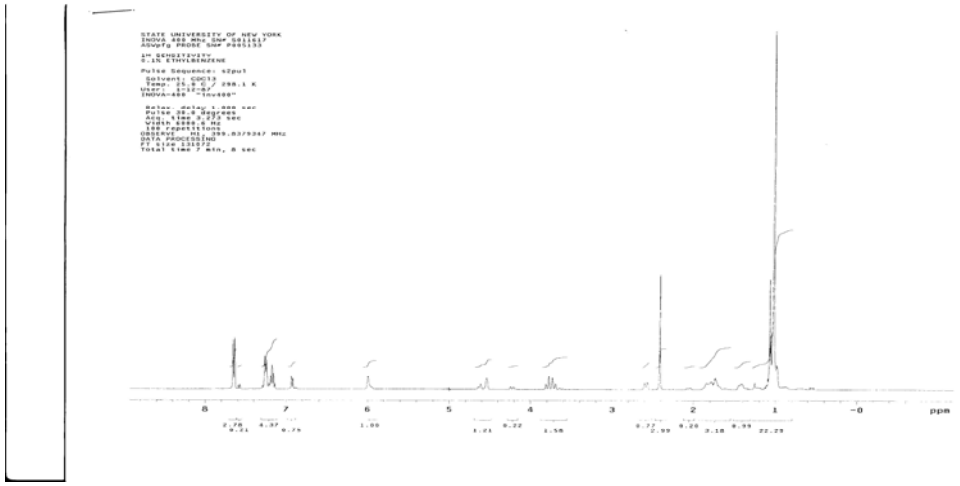


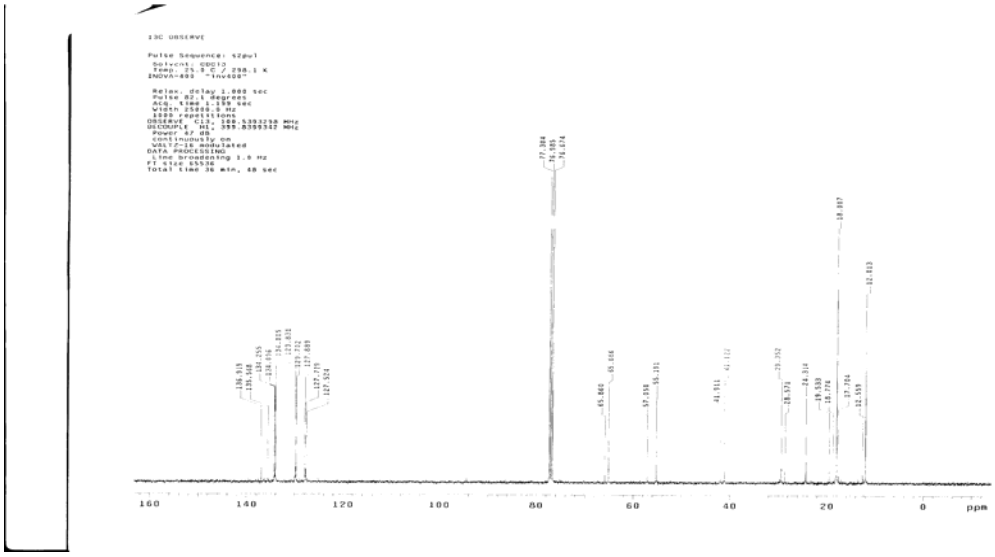


^{1}H and ^{13}C NMR spectra of **V-3b**

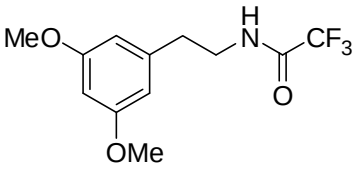


V-3b

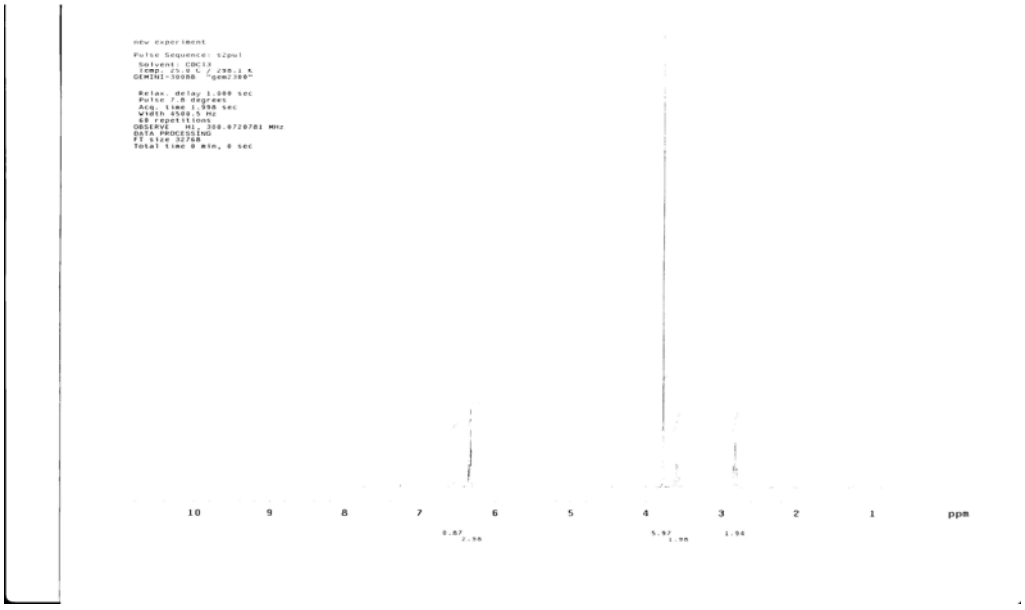


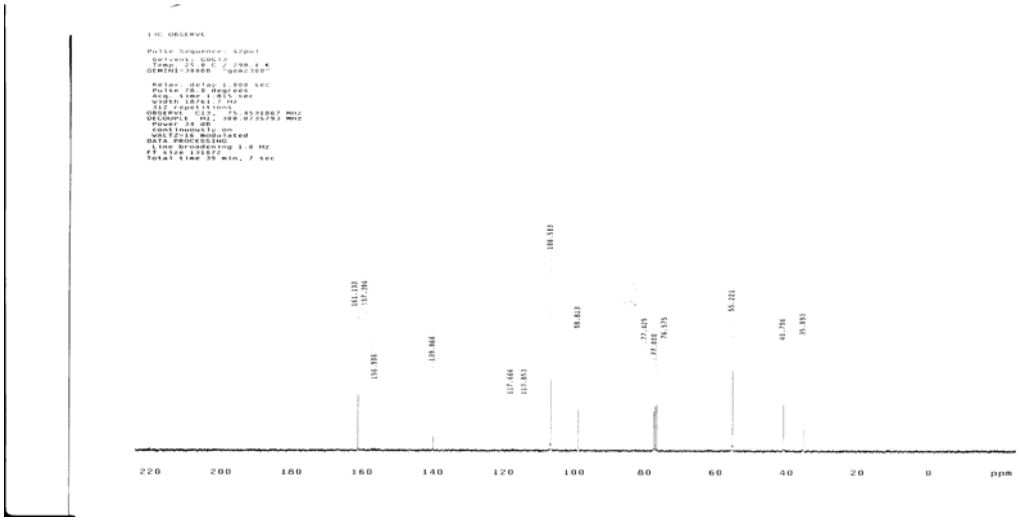


^{1}H and ^{13}C NMR spectra of **V-IAA-1**

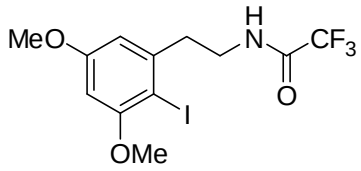


V-IAA-1

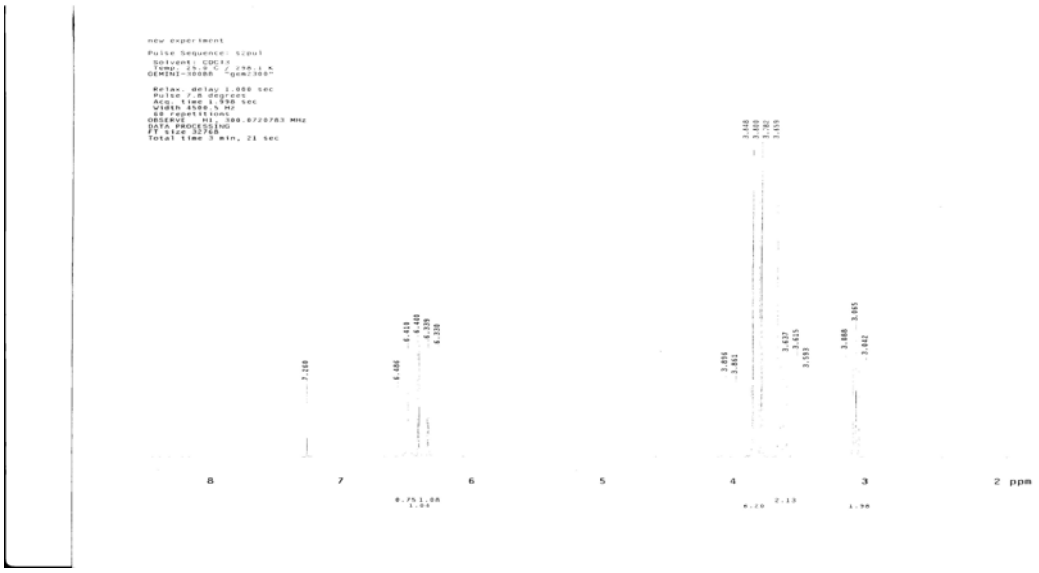


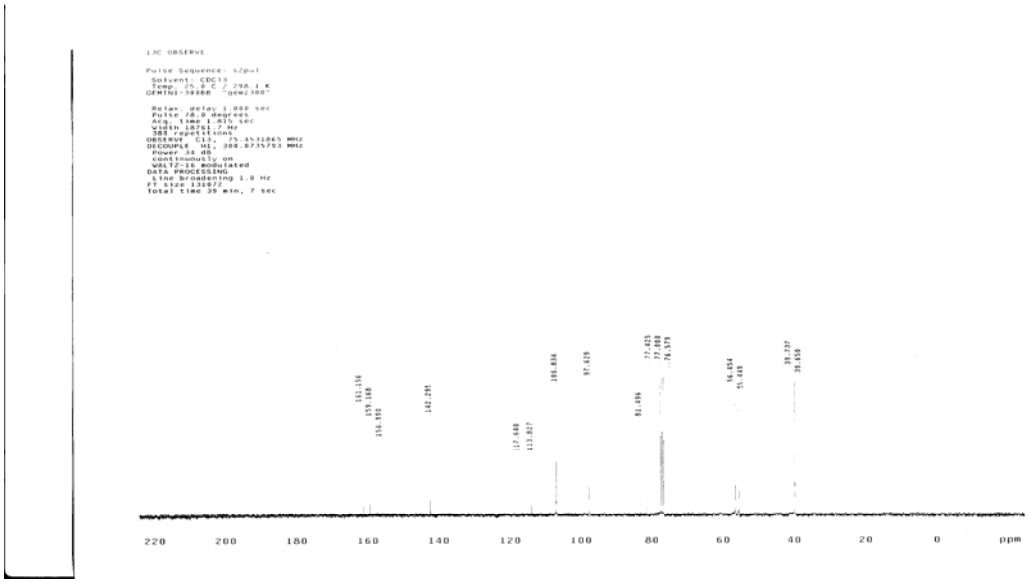


^{1}H and ^{13}C NMR spectra of **V-IAA-2**

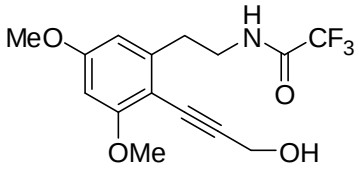


V-IAA-2

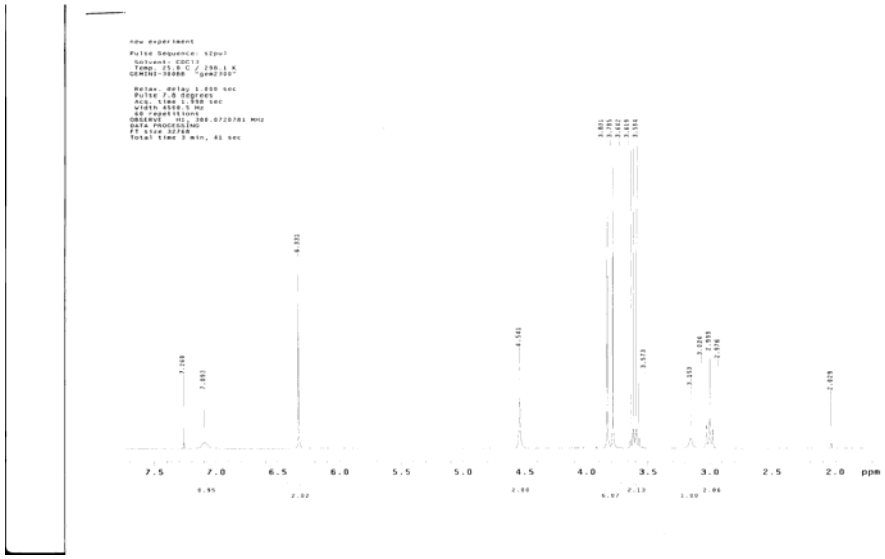


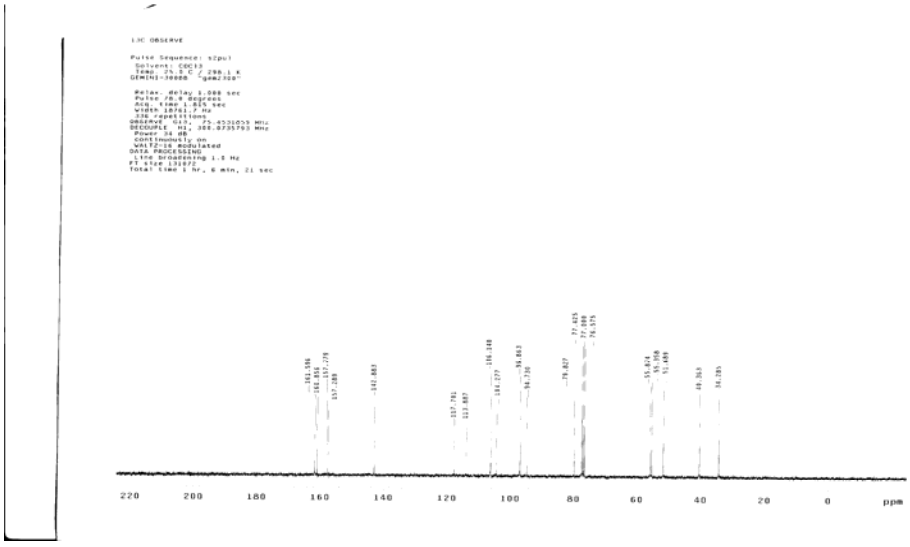


^{1}H and ^{13}C NMR spectra of **V-IAA-3**

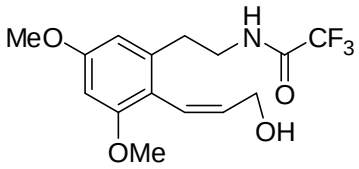


V-IAA-3

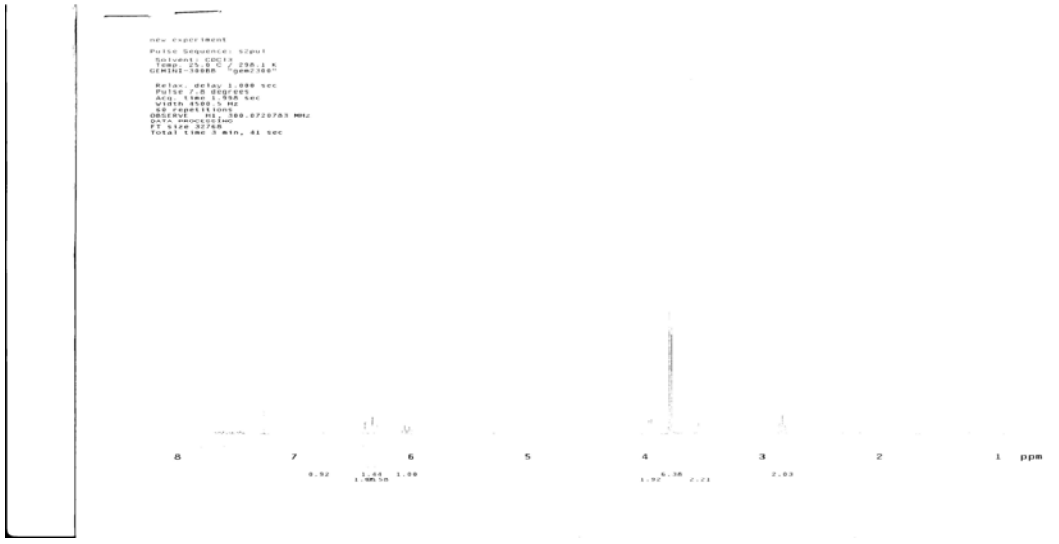


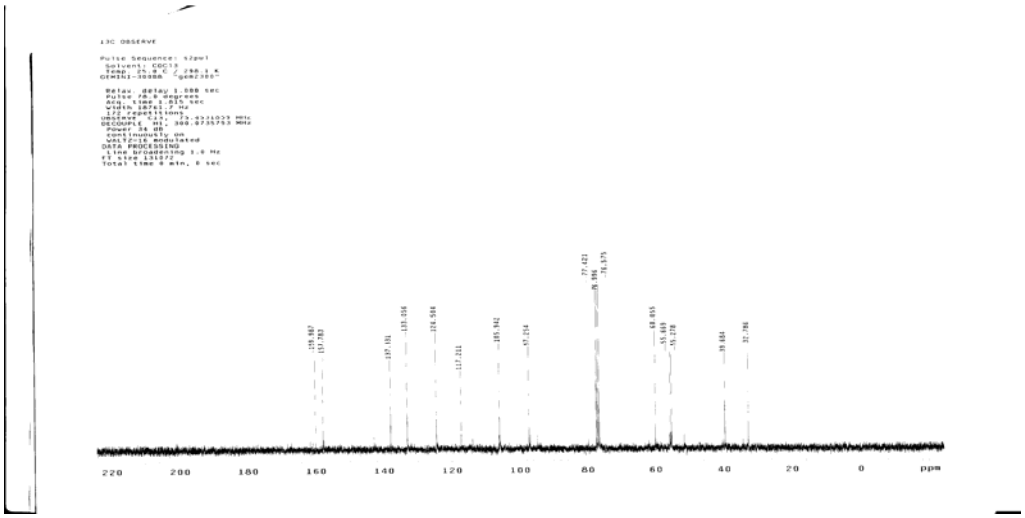


^{1}H and ^{13}C NMR spectra of **V-IAA-4**

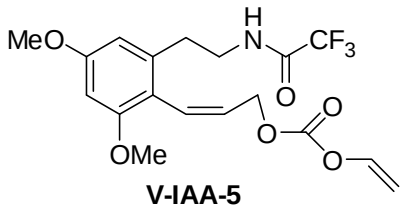


V-IAA-4





^{1}H and ^{13}C NMR spectra of **V-IAA-5**



V-IAA-5