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The Hong Kong Polytechnic University

Department of Applied Biology and Chemical Technology

Synthesis of Chiral Diphosphine Ligands Derived from Diols and Tartaric Acid Derivative via Diastereomeric Coupling

Chan Shu Sun

A Thesis Submitted

In

Partial Fulfillment of the Requirements for

the Degree of Doctor of Philosophy

November, 2007

Declaration

I hereby declare that this thesis summarizes my own research work carried out since my registration for the degree of Doctor of Philosophy in September, 2003 and that it has not been previously been included in a thesis, dissertation or report presented to this or any other institution for a degree, diploma, or other qualifications.

Mr Chan Shu Sun

November, 2007

Abstract

Asymmetric hydrogenation utilizing molecular hydrogen is one of the most efficient methods for constructing chiral compounds as this method is the simplest, cleanest, efficient, environmentally friendly and economical. It is most widely applied in both industry and academia. This thesis focused on the development of novel C_2-symmetric biphenyl diphosphine ligands with chiral linkers and their applications in asymmetric hydrogenations.

A C_2-symmetric biphenyl diphosphine ligand (*R*)-[6,6'-(*2S,3S*-butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **117** with a chiral linker was synthesized. Complete atropdiastereoselectivity was observed in asymmetric intramolecular Ullmann coupling. (*S*)-[6,6'-(*2S,3S*-butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **124**, (*S*)-[6,6'-(*2R,4R*-pentadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **128** and (*S*)-[6,6'-(*2R,5R*-hexadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **132** were synthesized via ring closure process. The enantioselectivities of the corresponding Ir and Ru complexes compared well with MeO-BIPHEP **5a**. The configuration of the product was controlled by the axial chirality rather than the additional central chirality.

Another novel C_2-symmetric biphenyl diphosphine ligand, [6,6'-(*4S,5S*-2,2-dimethyl-1, 3-dioxolane-4,5-dimethoxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **141** and **142** were synthesized via asymmetric Ullmann coupling. However, no atropdiastereoselectivity was observed. The enantioselectivities of the corresponding Ru complexes compared favorably with MeO-BIPHEP **5**a. The corresponding Rh complexes showed better enantioselectivities than MeO-BIPHEP **5a**. The configuration of product was also controlled by the axial chirality rather than the additional central chirality.

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Abbreviations

acac	acetylacetonate
Ar	aryl group
BDPAB	2,2’-bis(diphenylphosphinoamino)-1,1’-binaphthyl
BDPMI	4,5-bis(diphenylphosphinomethyl)imidazolidin-2-ones
BDPP or SKEWPHOS	(*S*,*S*)-2,4-bis(diphenylphosphino)pentane
BICHEP	2,2’-bis(dicyclohexylphosphino)-6,6’-dimethyl-1,1’-biphenyl
BICP	bis(diphenylphosphino)-dicyclopentane
BIFAP	2,2’-bis(diphenylphosphanyl)-1,1’-bidibenzofuranyl
BIBFUP	2,2’-bis(diphenylphosphino)-3,3’-bibenzo[*b*]furan
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
o-BINAPO	3,3’-disubstituted 2,2’-bis(diphenylphosphinyl)-1,1’-binaphthyl
BIPHEMP	2,2’-bis(diphenylphosphino)- 6,6’-dimethyl-1,1’-biphenyl
BITIANP	2,2’-bis(diphenylphosphino)-3,3’-bibenzo[*b*]thiophene
BITIOP	4,4’-bis(diphenylphosphino)-3,3’-bithiophene
Bn	benzyl
BoPhoz	*R*-*N*-methyl-*N*-diphenylphosphino-1-[*S*-2-(diphenylphosphino)ferrocenyl]ethylamine
BPE	1,2-bis(2,5-dimethylphospholanyl)ethane
BPPM	N-(tertbutoxycarbonyl)-4-(diphenylphosphino)-2-[(diphenylphosphino)methyl]pyrrolidine
CHIRAPHOS	2,3-bis(diphenylphosphino)butane
COD	1,5-cyclooctadiene
config.	configuration
DAIPEN	1,1’-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine
de	diastereomeric excess
Degphos	1-substituted 3,4-bis(diphenylphosphino)pyrrolidine
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DIPAMP	1,2-bis[*o*-methoxyphenyl]phenylphosphino]ethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DuPHOS	substituted 1,2-bis(phospholano)benzene
L-DOPA	*L*-3-(3,4-dihydroxyphenyl)aniline
DPEN	1,2-diphenyl ethylenediamine
EA	ethyl acetate
ee	enantiomeric excess
EI	electron impact (in mass spectrometry)
ESI	electron spray ionization (in mass spectrometry)
Et-DuPHOS	1,2-bis(2,5-diethylphospholano)benzene
GC	gas chromatography
H_8-BDPAB	2,2'-bis(diphenylphosphino-amino)-5,5',6,6',7,7',8',8'-octahydro-1,1'-binaphthyl
H_8-BINAP	2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl
HPLC	high-performance liquid chromatography
J	coupling constant (in NMR)
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
MeO-BIPHEP	2,2'-bis(diphenylphosphino)- 6,6'-dimethoxy-1,1'-biphenyl
Me-PennPhos	*P*,*P*'-1,2-phenylene-bis(2,5-dimethyl-7-phosphabicyclo[2.2.1]heptane)
MOM	methoxymethyl
MonoPhos	2,2'-*O*,*O*'-(1,1'-binaphthyl)-*O*,*O*'-dioxo-*N*,*N*-dimethylphospholidine
Ms	methanesulfonyl, mesyl group
MS	mass spectrometry
o-NAPHOS	*o*-disubstituted 2,2'-bis(diphenylphosphinomethyl)-1,1'-binaphthyl
naproxen	2-(6'-methoxy-2'-naphthyl)propenoic acid
NMR	nuclear magnetic resonance

NORPHOS	5,6-bis(diphenylphosphino)-2-norborene
OAc	acetate
PhanePhos	4,12-bis(diphenylphosphino)-[2,2]-paracyclophane
P-Phos	2,2’,6,6’-tetramethoxy-4,4’-bis(diphenylphosphino)-3,3’-bipyridine
Pyrphos	3,4-bis(diphenylphosphino)pyrrolidine
rt	room temperature
S/C	substrate-to-catalyst ratio
SEGPHOS	4,4’-bi-1,3-benzodioxole-5,5’-diyl-bis(diphenylphosphine)
spiroP	1,6-bis(diphenylphosphinoxy)spiro-[4,4]-norane
TangPhos	1,1’-di-*tert*-butyl-[2,2’]-diphospholanyl
THF	tetrahydrofuran
Tol-BINAP	2,2’-bis[(di-*p*-tolyl)phosphino]-1,1’-binaphthyl
TRAP	2,2’’-bis[1-(diarylphosphino)ethyl]-1,1’’-biferrocene or 2,2’’-bis[1-(dialkylphosphino)ethyl]-1,1’’-biferrocene
Ts	*p*-toluenesulfonyl, tosyl group
Xyl-BINAP	2,2’-bis[(3,5-dimethylphenyl)phosphino]-1,1’-binaphthyl
[α]	special optical rotation

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CHAPTER ONE

INTRODUCTION

1.1 Importance of Asymmetric Catalysis

Chirality (handedness: left and right) is an intrinsic feature and as old as life. The world is made up of chirality. The 19 naturally occurring proteogenic amino acids are *L*-form. The carbohydrates, starch and proteins we survived are also chiral. Inside organisms, DNA, enzymes, antibodies and hormones are chiral too. Therefore, enantiomers of compounds will interact with the receptor sites in biological systems differently and different effects will be resulted.

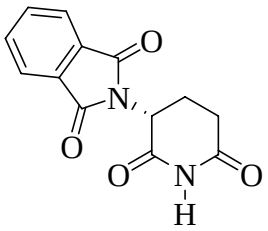
The enantiomers of naturally occurring limonene smell differently as our olfactory receptors are also made of chiral molecules. The (*R*)-enantiomer smells of oranges while the (*S*)-enantiomer smells of lemons.

(*R*)-limonene
orange odor

(*S*)-limonene
lemon odor

Figure 1-1 The different odors of enantiomers of limonene

In the early 1960s, the drug thalidomide was used therapeutically as a sedative and a hypnotic to alleviate morning sickness in pregnant women. The molecule contains a chiral center but this drug was used clinically as a racemate. However, a high incidence of fetal deaths, neonatal deaths and deformities in the limbs of the children born was resulted [1]. Only the (*S*)-enantiomer is teratogenic and causes fetal deformities [2]. Even if the pure (*R*)-enantiomer is used, problems will still arise as the two enantiomers interconvert under physiological conditions.


(*R*)-thalidomide

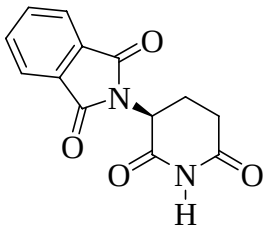
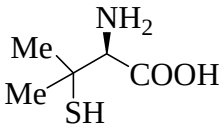

(*S*)-thalidomide

Figure 1-2 Structure of drug, thalidomide

The *D*-enantiomer of amino acid, penicillamine is used to treat Wilson's disease and biliary cirrhosis [3] while the *L*-enantiomer causes optic atrophy, leading to blindess [4].


D-penicillamine

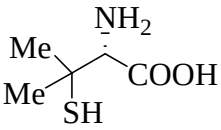
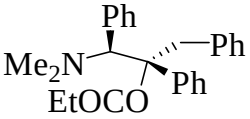

L-penicillamine

Figure 1-3 Structure of amino acid, penicillamine

The enantiomers of drug propoxyphene have different biological activities [5]. The *D*-enantiomer is an analgesic while the *L*-enantiomer possesses antitussive properties. The trade names Darvon® and Novrad® showed their mirror image relationship.


Darvon

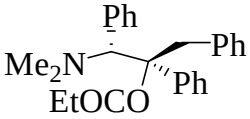

Novrad

Figure 1-4 Structure of drug, propoxyphene

Nature provides an enormous range and diversity of chiral compounds, e.g. amino acids and amino alcohols, hydroxy acids, alkaloids and other amines, terpenes and carbohydrates. Traditionally, chiral compounds can be obtained by using an appropriate chiral precursor from the natural source. The desired compound can be obtained through modification of the chiral precursor in a series of chemical steps. These chemical steps

will generally not involve the chiral centers and avoid racemisation. The chiral centers of the product are all derived from the chiral starting material as no new chiral centers are formed.

On the other hand, resolution is another classical method to obtain chiral compounds. The racemic compound reacts with a resolving agent to form diastereomers. The diastereomers may be separated by crystallization or chromatography and then are separately treated to liberate the two enantiomers. The resolving agent is recovered unchanged and can be reused. The most commonly used resolving agent for amines are camphorsulphonic acid and tartaric acid. Organic acids are resolved by cinchonine, quinine, brucine and strychnine. Development of resolution procedures is a matter of trial and error and resolution requires numerous recycle loops and fractional crystallizations. As a result, resolution method is very time-consuming and expensive.

Asymmetric synthesis is defined as an achiral unit in a substrate molecule is converted to a chiral unit in a reaction. In principle, the use of a chiral substrate, reagent, solvent, or catalyst should lead to asymmetric synthesis. Asymmetric catalysis is the most attractive method as a small amount of the chiral catalyst can produce a large amount of the desired chiral product [6].

1.2 History of Asymmetric Hydrogenation

In 1965 Wilkinson reported the hydrogenation of alkenes catalyzed by $Rh(PPh_3)_3Cl$ [7]. Asymmetric hydrogenation could be carried out by replacing the triphenylphosphine of Wilkinson's catalyst with a chiral phosphine. This concept was realized by two groups. In 1968 Knowles [8] and Horner [9] reported independently the first homogenous asymmetric hydrogenation of phenylacrylic acid and 2-phenyl-1-

propene with chiral monodentate tertiary phosphine-Rh complexes. The enantioselectivities were very low (3-15% ee) but these results led to the future development of asymmetric hydrogenation.

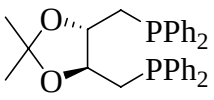
A major breakthrough was introduced by Kagan when he synthesized DIOP **1**, a C_2-symmetrical chiral diphosphine derived from tartaric acid [10]. The Rh complex catalyzed asymmetric hydrogenation of dehydroamino acids led to phenylalanine with 80% ee. The introduction of DIOP **1** led to the rapid development of C_2-symmetrical chiral diphosphine while the chiral monodentate phosphines live under the shadow until very recently.

Knowles introduced a C_2-symmetrical chiral diphosphine, DIPAMP **2** later and its Rh complex catalyzed asymmetric hydrogenation of dehydroamino acids [11].

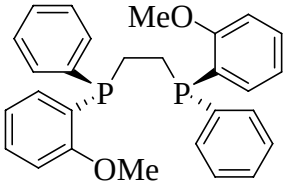
Noyori firstly reported a well known C_2-symmetrical chiral biaryl diphosphine ligand BINAP **3a** in 1980 and its Rh complex showed high enantioselectivities in the asymmetric hydrogenation of dehydroamino acids [12].

1.3 Development of Diphosphine Ligands

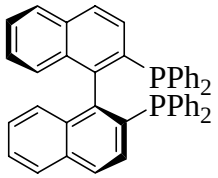
Following the chemistry of BINAP **3a**, other C_2-symmetrical chiral biaryl diphosphine ligands were introduced such as Schmid's BIPHEMP **4a** [13] and MeO-BIPHEP **5a** [14]. In 1990 Burk introduced two efficient C_2-symmetrical chiral diphospholane ligands, BPE **6** and DuPhos **7** and excellent results were obtained in the asymmetric hydrogenation of a range of substances [15]. A large number of chiral diphosphine ligands have been prepared [16] and some reported ligands are shown in Figure 1-5.



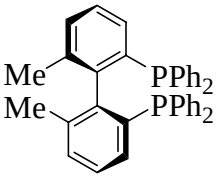
1 [10]
(*S*,*S*)-DIOP



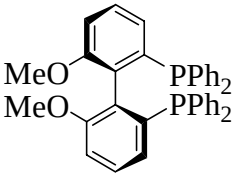
2 [11]
(*S*,*S*)-DIPAMP



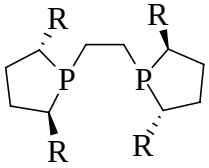
3a [12]
(*S*)-BINAP



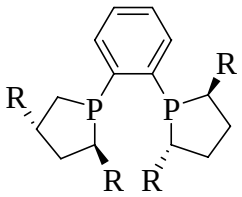
4a [13]
(*S*)-BIPHEMP



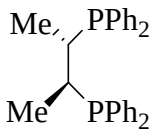
5a [14]
(*S*)-MeO-BIPHEP



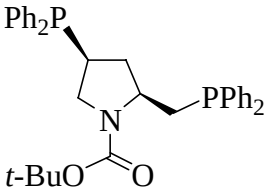
6 [15]
a R = Me, Me-BPE
b R = Et, Et-BPE
c R = *i*-Pr, *i*-Pr-BPE



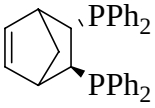
7 [15]
a R = Me, Me-DuPHOS
b R = Et, Et-DuPHOS
c R = *i*-Pr, *i*-Pr-DuPHOS



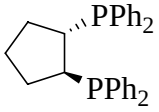
8 [17]
(*S*,*S*)-CHIRAPHOS



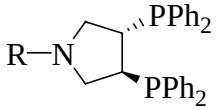
9 [18]
(*S*,*S*)-BPPM



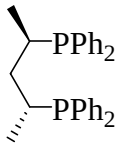
10 [19]
(*S*,*S*)-NORPHOS



11 [20]
(*S*,*S*)-DPCP



12 [21]
a R = H, (*S*,*S*)-Pyrphos
b R = CH_2Ph, Degphos

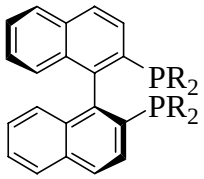


13 [22]
(*S*,*S*)-BDPP
(SKEWPHOS)

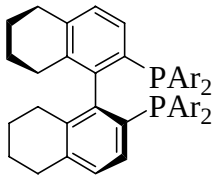
Figure 1-5 Structures of some diphosphine ligands

1.3.1 BINAP Analogues

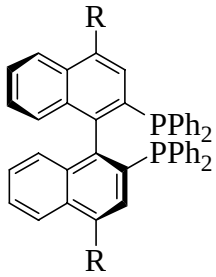
After the first synthesis of BINAP **3a**, many analogues were prepared [23] and some are shown in Figure 1-6.



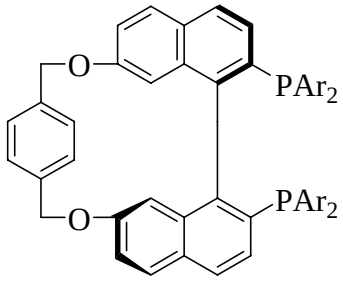
3 [12]
a R = Ph, (*S*)-BINAP
b R = 4-MeC_6H_4, (*S*)-Tol-BINAP
c R = 3,5-$Me_2C_6H_3$, (*S*)-Xyl-BINAP
d R = Cy, (*S*)-Cy-BINAP



14 [24]
a Ar = Ph, (*S*)-H_8-BINAP
b Ar = 3,5-$Me_2C_6H_3$, (*S*)-Xyl-H_8-BINAP



15 [25]
a R = $SiMe_3$,
b R = $P(O)(OH)_2$ etc



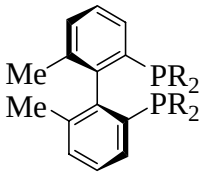
16 [26]
a Ar = Ph, (*R*)-DANP
b Ar = 3,5-$Me_2C_6H_3$, (*R*)-DMDANP

Figure 1-6 Structures of some BINAP analogues

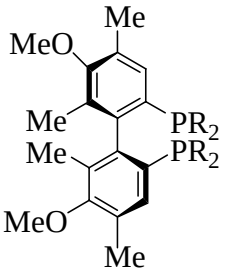
H_8-BINAP **14** was found to give higher catalytic activity and enantioselectivity in Ru-catalyzed asymmetric hydrogenation of unsaturated carboxylic acids [24]. Lin *et al.* recently synthesized some 4,4-disubstituted BINAP derivatives **15** and enhanced enantioselectivities were obtained in the asymmetric hydrogenation of β–ketoesters [25a], aromatic ketones [25b], α-phthalimide ketones [25c] and 1,3-diaryl diketones [25c]. Takasago introduced a 7,7-disubstituted BINAP derivative **16** and higher activity and enantioselectivity were obtained in the asymmetric hydrogenation of dehydronaproxen [26].

1.3.2 BIPHEMP Analogues

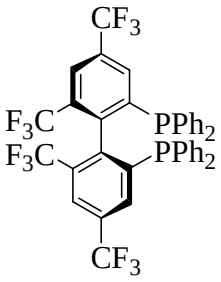
In the mid-1980's Schmid [13a, b] and Frejd [13c, d] synthesized BIPHEMP **4a** independently and this ligand performed very well in asymmetric hydrogenation [27]. Some derivatives have been synthesized by introduction of additional chloro, methoxy, methyl or trifluoromethyl groups. These will change the catalytic activity and enantioselectivity in asymmetric hydrogenation. They are shown in Figure 1-7.



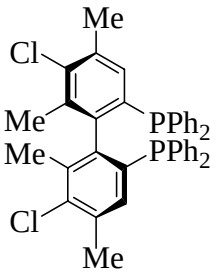
4 [13]
a R = Ph, (*S*)-BIPHEMP [13]
b R = Cy, (*S*)-BICHEP [28]



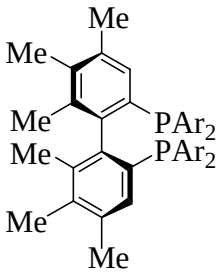
17 [29]
a R = Ph, (*S*)-BIMOP
b R = 4-$MeOC_6H_4$, (*S*)-*p*-MeO-BIMOP
c R = Cy, (*S*)-Cy-BIMOP



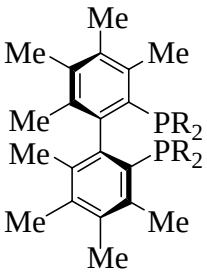
18 [29b, 30]
(*S*)-BIFUP



19 [31]
(*S*)-CM-BIPHEMP



20 [32]
a Ar = Ph, (*S*)-HexaPHEMP
b Ar = 3,5-$Me_2C_6H_3$,
(*S*)-Xyl-HexaPHEMP

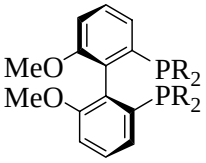


(*S*)-**21** [33]
a R = Ph
b R = Cy
c R = Et

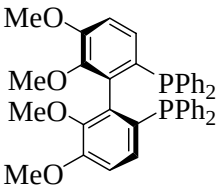
Figure 1-7 Structures of some BIPHEMP analogues

1.3.3 MeO-BIPHEP Analogues

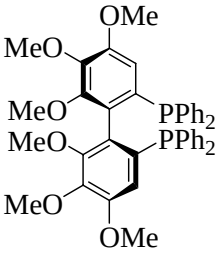
Schmid of Hoffman-La-Roche developed MeO-BIPHEP **5a** [14a, b] and more than 60 analogues had been developed [14c]. Due to the easy preparation, a large number of this ligand type has been reported (Figure 1-8) such as Bayer's Cl-MeO-BIPHEP **24**, PPG-Sipsy's Soniphos **25**, Zhang's *o*-Ph-hexaMeO-BIPHEP **26**, *o*-Ph-MeO-BIPHEP **27** and TunaPhos **28**, Takasago's SEGPHOS **29**, Chan's BisbenzodioxanPhos **30** , Solvia's Solphos **31** and Genet's Difluorophos **32**.



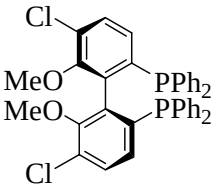
5 [14]
a R = Ph, (*S*)-MeO-BIPHEP
b R = 4-MeC_6H_4
c R = 3,5-$Me_2C_6H_3$
d R = Cy
> 60 analogues



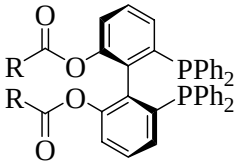
(*S*)-**22** [14]



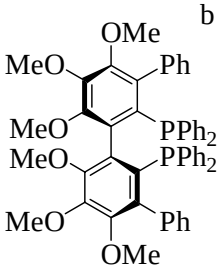
(*S*)-**23** [14]



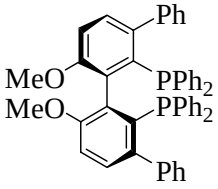
24 [34]
a R = Ph, (*S*)-Cl-MeO-BIPHEP
b R = 3,5-$Me_2C_6H_3$



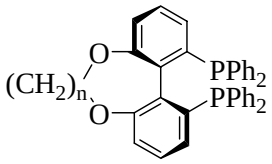
25 [35]
a R = Me, (*S*)-Methyl Soniphos
b R = *c*-Cy, (*S*)-Cyclohexyl Soniphos



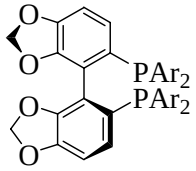
26 [36]
(*S*)-*o*-Ph-hexaMeO-BIPHEP



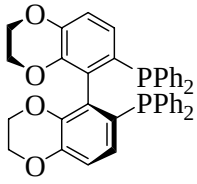
27 [37]
(*S*)-*o*-Ph-MeO-BIPHEP



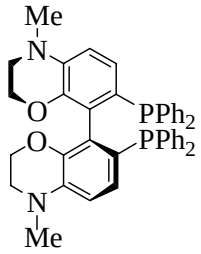
28 [38]
n = 1-6, (*S*)-C_n-TunaPhos



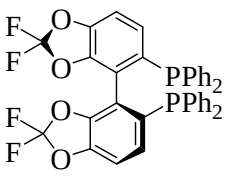
29 [39]
a R = Ph, (*S*)-SEGPHOS
b R = 4-MeC_6H_4, (*S*)-T-SEGPHOS
c R = 3,5-$Me_2C_6H_3$, (*S*)-DM-SEGPHOS
d R = 4-MeO-3,5-$Me_2C_6H_2$, (*S*)-DMM-SEGPHOS
e R = 4-MeO-3,5-(*t*-Bu)$_2C_6H_2$, (*S*)-DTBM-SEGPHOS



30 [40]
(*S*)-BisbenzodioxanPhos



31 [41]
(*S*)-Solphos

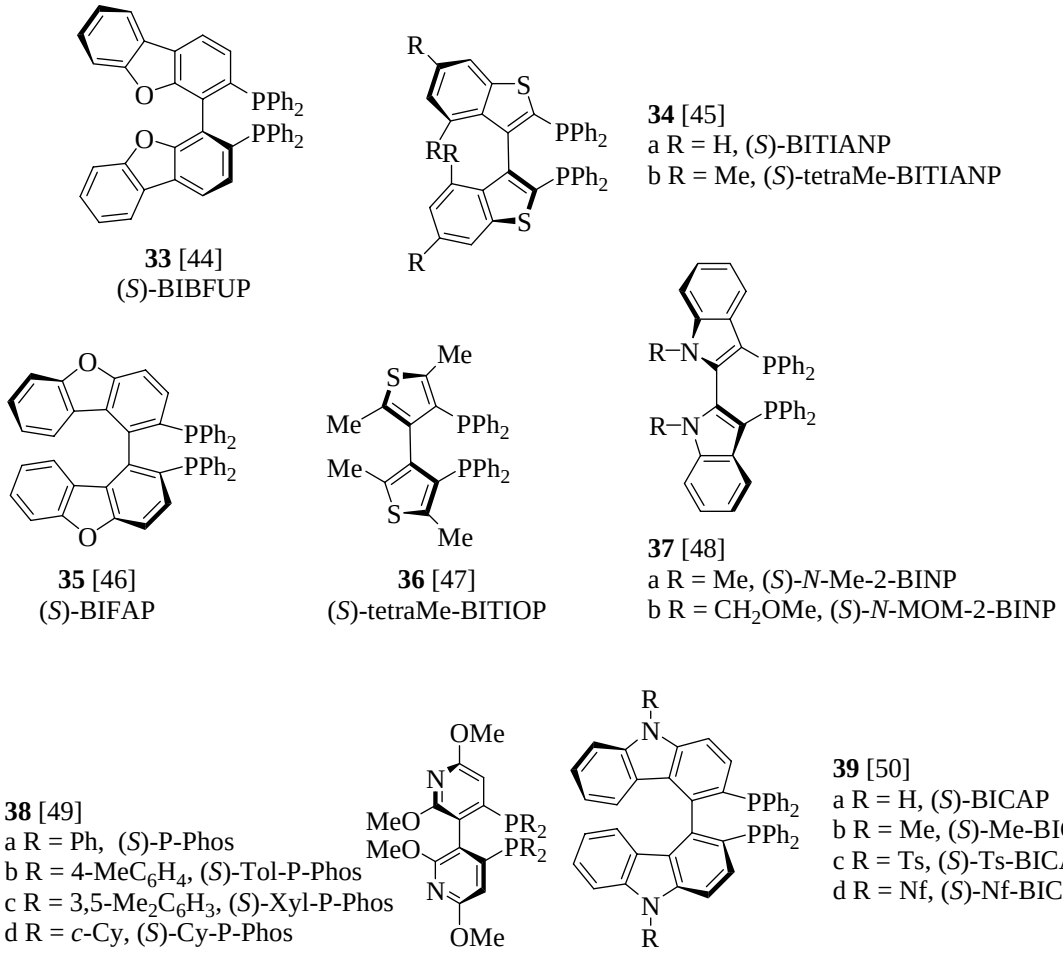


32 [40h-j, 42]
(*S*)-Difluorophos

Figure 1-8 Structures of some MeO-BIPHEP analogues

1.3.4 Biheteroaryl Analogues

A new ligand type based on biheteroaryl backbones has been introduced over the past few years (Figure 1-9) [43]. Laue firstly synthesized a dibenzofuran-based diphosphine BIBFUP **33**. Then Sannicol developed a series of different biheteroaryl diphosphines such as BITIANP **34a**, TetraMe-BITIANP **34b**, tetraMe-BITIOP **36** and 2-BINP **37**. These ligands showed similiar or higher enantioselectivity in asymmetric hydrogenation. Chan and co-workers have also developed P-Phos **38** using 2, 6-dimethoxypyridine as the ligand scaffolds for the phosphine groups.



33 [44]
(*S*)-BIBFUP

34 [45]
a R = H, (*S*)-BITIANP
b R = Me, (*S*)-tetraMe-BITIANP

35 [46]
(*S*)-BIFAP

36 [47]
(*S*)-tetraMe-BITIOP

37 [48]
a R = Me, (*S*)-*N*-Me-2-BINP
b R = CH_2OMe, (*S*)-*N*-MOM-2-BINP

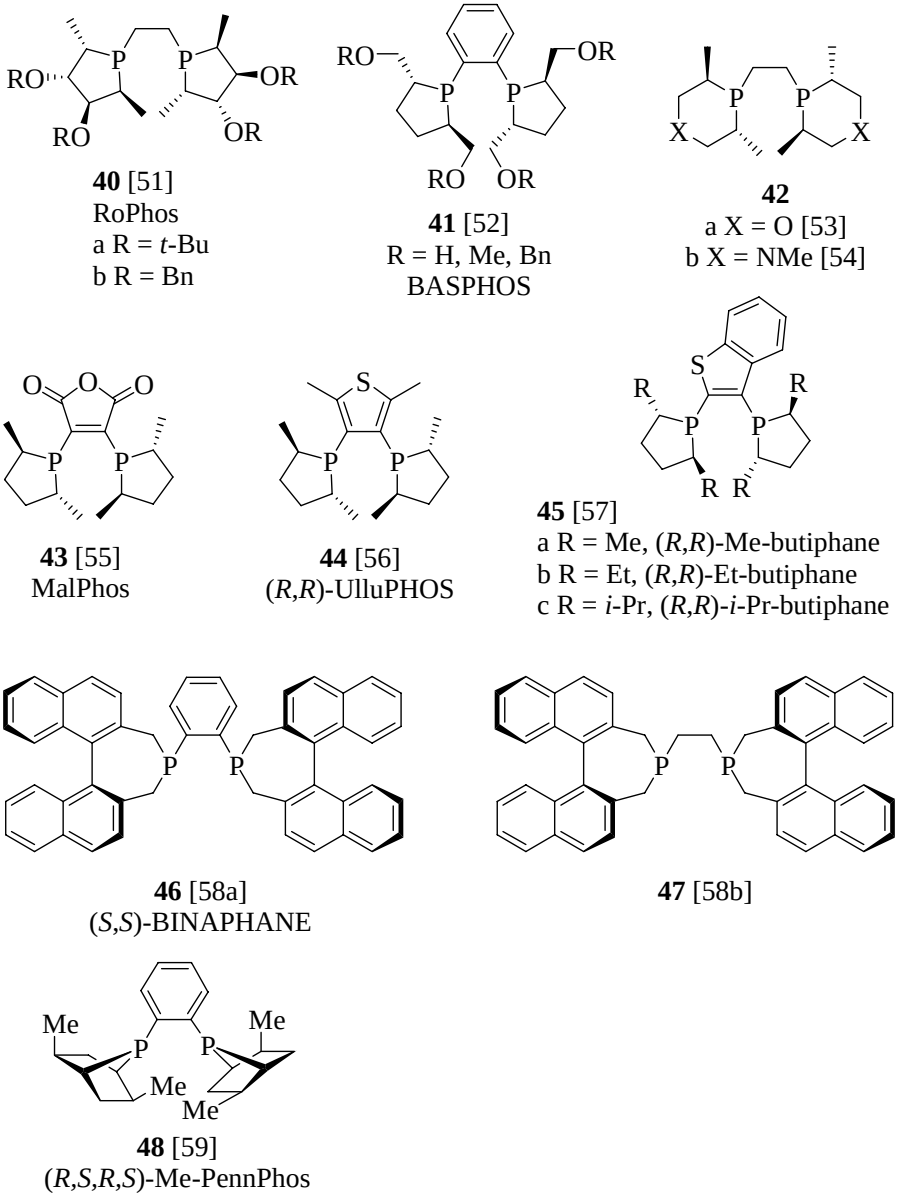
38 [49]
a R = Ph, (*S*)-P-Phos
b R = 4-MeC_6H_4, (*S*)-Tol-P-Phos
c R = 3,5-$Me_2C_6H_3$, (*S*)-Xyl-P-Phos
d R = *c*-Cy, (*S*)-Cy-P-Phos

39 [50]
a R = H, (*S*)-BICAP
b R = Me, (*S*)-Me-BICAP
c R = Ts, (*S*)-Ts-BICAP
d R = Nf, (*S*)-Nf-BICAP

Figure 1-9 Structures of some biheteroaryl diphosphine ligands

1.3.5 BPE and DuPhos Analogues

The excellent results of BPE and DuPhos in the asymmetric hydrogenation led to the development of other bisphospholanes such as Borner's RoPhos **40**, BASPHOS **41**. Some hetero-DuPhos ligands were reported by replacing the benzene backbone with maleic anhydride, 2,5-dimethylthiophene and benzothiophene. Zhang introduced two bisdinaphthophospheines, **46**, **47** and PennPhos **48**.



40 [51]
RoPhos
a R = *t*-Bu
b R = Bn

41 [52]
R = H, Me, Bn
BASPHOS

42
a X = O [53]
b X = NMe [54]

43 [55]
MalPhos

44 [56]
(*R*,*R*)-UlluPHOS

45 [57]
a R = Me, (*R*,*R*)-Me-butiphane
b R = Et, (*R*,*R*)-Et-butiphane
c R = *i*-Pr, (*R*,*R*)-*i*-Pr-butiphane

46 [58a]
(*S*,*S*)-BINAPHANE

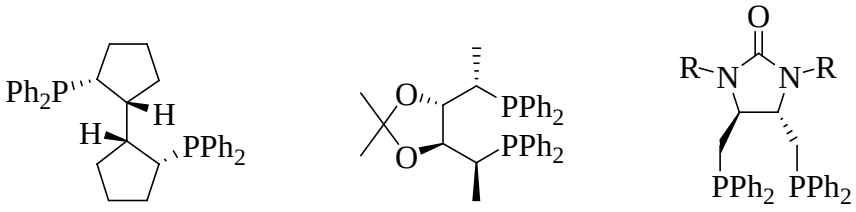
47 [58b]

48 [59]
(*R*,*S*,*R*,*S*)-Me-PennPhos

Figure 1-10 Structures of some BPE and DuPhos analogues

1.3.6 DIOP Analogues

The introduction of DIOP led to the rapid development of C_2-symmetrical chiral diphosphines. The applications of DIOP in asymmetric hydrogenation have rarely been disclosed as only moderate to good enantioselectivities were obtained in asymmetric hydrogenation of dehydroamino acid derivatives. Several DIOP derivatives have been synthesized with five-membered ring on the backbone **49**, additional methyl groups at the α positions of the diphenylphosphine groups **50** and with an imidazoline-2-one as backbone **51** rigidified the conformational flexibility of DIOP.



49 [60]
(*R*,*R*)-BICP

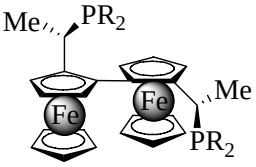
50 [61]
(*S*,*R*,*R*,*S*)-DIOP*

51 [62]
a R = H, (*S*,*S*)-H-BDPMI
b R = Me, (*S*,*S*)-Me-BDPMI
c R = Et, (*S*,*S*)-Et-BDPMI
d R = Ph, (*S*,*S*)-Ph-BDPMI
e R = Bn, (*S*,*S*)-Bn-BDPMI

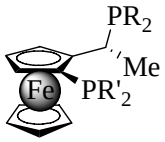
Figure 1-11 Structures of some DIOP analogues

1.3.7 Ferrocene-Based Diphosphine Ligands

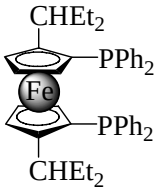
Many chiral ferrocene-based diphosphine ligands have been developed [63]. (Figure 1-12) Ito and co-workers developed a family of TRAP **52** and they showed great capabilities in asymmetric hydrogenation [64]. Togni and Spindler had reported Josiphos-type ligands **53**. Josiphos **53a** was shown to be very effective for asymmetric hydrogenation of α-acetamidocinnamate, dimethyl itaconate, β–ketoesters [65]. Knochel developed MandyPhos **55** [67] and TaniaPhos **56** [68] and these two ligands were found to be very effective for Rh or Ru-catalyzed asymmetric hydrogenation. Weissensteiner and Spindler reported Walphos **57** and good results were obtained in some Ru-catalyzed asymmetric hydrogenations [69]. Zhang devised *f*-binaphane **59** and high enantioselectivities were achieved in the Ir-catalyzed asymmetric hydrogenation of acyclic arylimines [71].



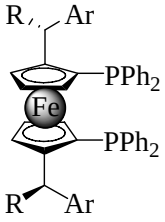
52 [64]
(*R*,*R*)-(*S*,*S*)-TRAP
R = Et, Bu, *i*-Bu



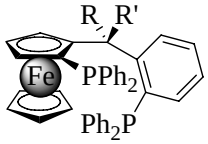
53 [65]
a R = Cy, R' = Ph, (*R*)-(*S*)-JosiPhos
b R = *t*-Bu, R' = Ph, (*R*)-(*S*)-PPF-*t*-Bu_2
c R = 3,5-Me_2-C_6H_3, R' = Ph, (*R*)-(*S*)-XyliPhos
d R = Cy, R' = Cy, (*R*)-(*S*)-cy_2PF-Pcy_2



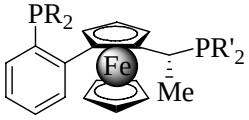
54 [66]
(*S*,*S*)-FerroTANE



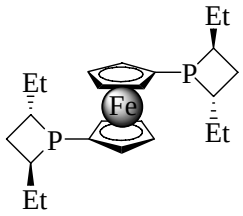
55 [67]
MandyPhos
a R = Me, Ar = Ph,
b R = M*e*, Ar = *o*-Tolyl,
c R = Me, Ar = 2-Np
d R = *i*-Pr, Ar = Ph,
e R = NMe_2, Ar = Ph



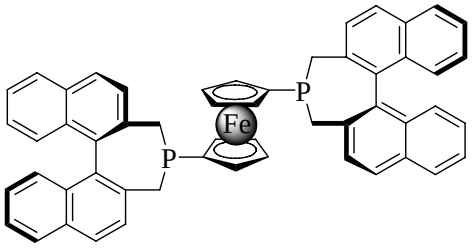
56 [67d, 68]
TaniaPhos
a R = Me_2N, R' = H
b R = *i*-Bu_2N, R' = H
c R = *N*-Pyrrolidyl, R' = H
d R = *i*-Pr, R' = H
e R = H, R' = OMe



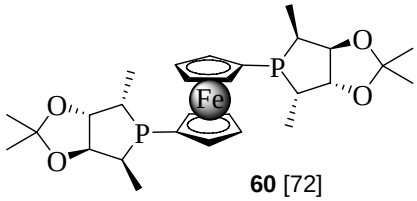
57 [69]
Walphos
a R = Ph, R' = 3,5-$(CF_3)_2$-C_6H_3
b R = 3,5-Me_2-4-MeO-C_6H_2, R' = 3,5-$(CF_3)_2$-C_6H_3



58 [70]
(*S*,*S*)-Et-ferroTANE



59 [71]
(*R*,*R*)-*f*-binaphane

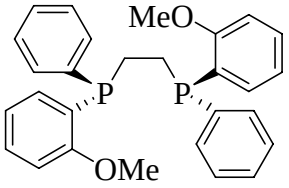


60 [72]

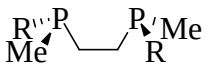
Figure 1-12 Structures of some ferrocene-based diphosphine ligands

1.3.8 P-Chiral Diphosphine Ligands

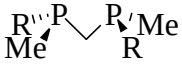
After the introduction of DIPAMP **2** by Knowles, the development of P-chiral diphosphine ligands was very slow due to the difficulty in ligand synthesis. Imamoto introduced a series of P-chiral ligands such as BisP* **61**, MiniPhos **62**, **63** and QuinoxP* **64**. A rigid P-chiral ligand, TangPhos **65** and DuanPhos **66** were developed by Zhang and they were found to be very efficient in Rh-catalyzed asymmetric hydrogenation of a variety of substrates.



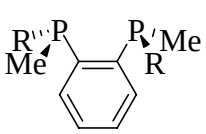
2 [11]
(*S*,*S*)-DIPAMP



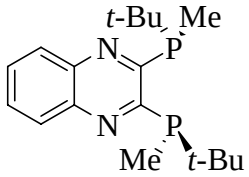
61 [73]
a R = *t*-Bu, (*S*,*S*)-*t*-Bu-BisP*
b R = 1-adamantyl, (*S*,*S*)-Ad-BisP*
c R = Cy, (*S*,*S*)-Cy-BisP*



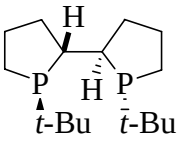
62 [73b-d, 74]
a R = *t*-Bu, (*S*,*S*)-*t*-Bu-MiniPhos
b R = Cy, (*S*,*S*)-Cy-MiniPhos
c R = *i*-Pr, (*S*,*S*)-*i*-Pr-MiniPhos



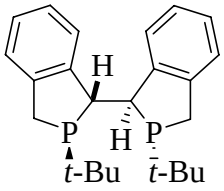
63 [75]



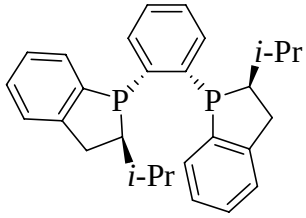
64 [76]
(*R*,*R*)-QuinoxP*



65 [77]
(*S*,*S*,*R*,*R*)-TangPhos



66 [78]
DuanPhos

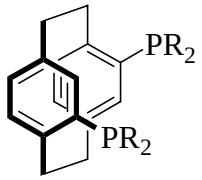


67 [79]
i-Pr-BeePHOS

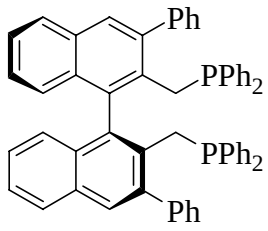
Figure 1-13 Structures of some P-chiral diphosphine ligands

1.3.9 Other Diphosphine Ligands

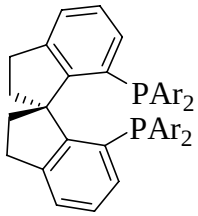
A planar chiral diphosphine ligand, PhanePhos **68**, based on a paracyclophane backbone was reported and this ligand gave excellent results in asymmetric hydrogenation [80]. Zhou synthesized a spiro diphosphine SDP **70** [82] and a spirobifluorene diphosphine SFDP **71** [83] and high activities and excellent enantioselectivities were obtained in the asymmetric hydrogenation of simple ketones and α, β–unsaturated carboxylic acids respectively.



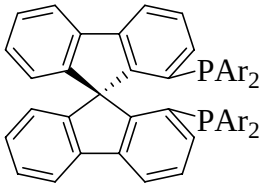
68 [80]
a Ar = Ph, (*S*)-PhanePhos
b Ar = 3,5-$Me_2C_6H_3$, (*S*)-Xyl-PhanePhos



69 [81]
(*S*)-Ph-*o*-NAPHOS



70 [82]
a Ar = Ph, (*S*)-SDP
b Ar = 4-MeC_6H_4, (*S*)-Tol-SDP
c Ar = 4-$MeOC_6H_4$, (*S*)-An-SDP
d Ar = 3,5-$Me_2C_6H_3$, (*S*)-Xyl-SDP

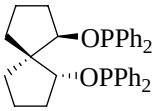


71 [83]
a Ar = Ph, (*R*)-SFDP
b Ar = 4-MeC_6H_4, (*R*)-Tol-SFDP
c Ar = 4-$MeOC_6H_4$, (*R*)-An-SFDP
d Ar = 3,5-$Me_2C_6H_3$, (*R*)-Xyl-SFDP
e Ar = 3,4,5-$Me_3C_6H_2$

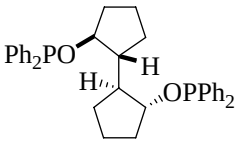
Figure 1-14 Structures of some other diphosphine ligands

1.3.10 Bisphosphinite, Bisphosphonite, Bisphosphite and Bisphosphoramidite Ligands

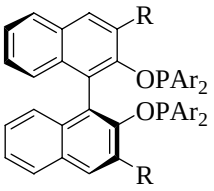
Greater conformational flexibility and instability account for the slow development of highly enantioselective bisphosphinite, bisphosphonite and bisphosphite ligands. Chan introduced a novel rigid spiro bisphosphinite **72** and excellent enantioselectivies were obtained in the asymmetric hydrogenation of α-dehydroamino derivatives [84]. Zhang reported a rigid bis-cyclopentyl ring ligand **73** [85]. Chan found that the H_8-BINAPO **75** gave higher enantioselectivities than BINAPO **74a** in the asymmetric hydrogenation of α-dehydroamino derivatives [87]. A series of 3,3-disubstituted BINAPO, *o*-BINAPO **74b-e** was introduced by Zhang and they were applied in the asymmetric hydrogenation of enamides, α-dehydroamino acid derivatives and β–aryl-substituted β–(acylamino)acrylates [81, 86]. Reetz reported excellent activities and enantioselectivities in the asymmetric hydrogenation of itaconates and α-dehydroamino acid derivatives with a binaphthol-derived ferrocene-based bisphosphonite ligand, **76** [88]. A chiral paracyclophane backbone bisphosphonite ligand, **77** was developed by Zanotti-gerosa [89] and was utilized in the asymmetric hydrogenation of α-dehydroamino acid derivatives. Reetz reported BINOL-derived diphosphonite **78** and diphosphoramidites **80** and they are effective for asymmetric hydrogenation of β–ketoesters [90a], quinolines [90b], dimethyl itaconate [92] respectively. Several efficient bisphosphite ligands have been developed for asymmetric hydrogenation. Reetz has devised a series of bisphosphite ligands such as **79** based on C_2-symmetric 1,4;3,6-dianhydro-*D*-mannitol and excellent results were obtained in the asymmetric hydrogenation of itaconates [91].



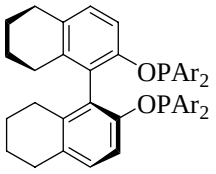
72 [84]
(*R*,*R*,*R*)-spirOP



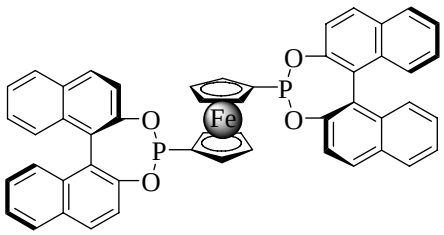
73 [85]
(*R*,*S*)-BICPO



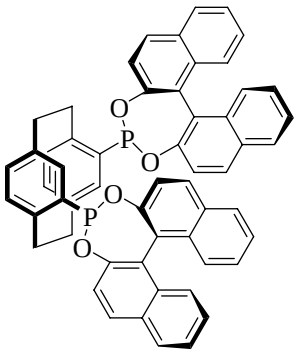
74 [81, 86]
a R = H, Ar = Ph, (*S*)-BINAPO
b R = Me, Ar = Ph, (*S*)-Me-*o*-BINAPO
c R = Ph, Ar = Ph, (*S*)-Ph-*o*-BINAPO
d R = 3,5-$Me_2C_6H_3$, Ar = Ph, (*S*)-Xylyl-*o*-BINAPO
e R = Ph, Ar = 3,5-$Me_2C_6H_3$, (*S*)-Ph-*o*-Xylyl-BINAPO



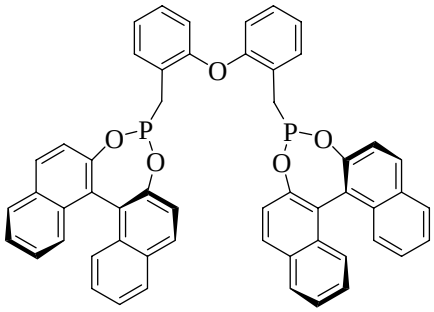
75 [87]
a Ar = Ph, (*S*)-H_8-BINAPO
b Ar = 3,5-$Me_2C_6H_3$, (*S*)-H_8-Xylyl-BINAPO



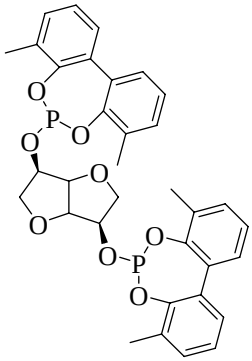
(*R*,*R*)-**76** [88]



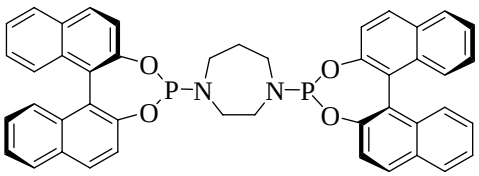
(*S*)-(*R*)-**77** [89]



(*S*,*S*)-**78** [90]



79 [91]

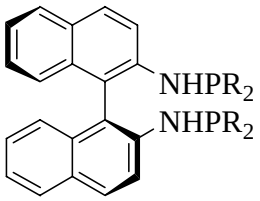


(*S*,*S*)-**80** [92]

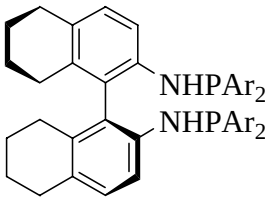
Figure 1-15 Structures of some bisphosphinite, bisphosphonite and bisphosphite ligands

1.3.11 Chelating Aminophosphines

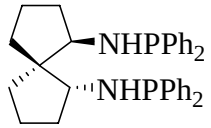
In 1998, Chan reported two bisaminophosphine ligands, BDPAB **81** and H_8-BDPAB **82** and they were successfully applied in the asymmetric hydrogenation of enamides and α-dehydroamino acid derivatives [87a, 93]. Recently, a rigid spiro bisaminophosphine spiroNP **83** was also reported by Chan and high enantioselectivies were obtained in the asymmetric hydrogenation of α-dehydroamino acid derivatives [94]. Boaz has introduced a series of ferrocene-based phosphine-aminophosphine ligands, BoPhoz **84**. They showed excellent activities and enantioselectvities in the asymmetric hydrogenation of α-dehydroamino acid derivatives, itaconic acids and α–ketoesters with outstanding air stability [95]. A phosphine-phosphoramidite ligand based on the 1,2-dihydroquinoline backbone, QUINAPHOS **85** was introduced by Leitner and very high enantioselectivities were obtained in rhodium-catalyzed hydrogenation of dimethyl itaconate [96a] and ruthenium-catalyzed hydrogenation of aromatic ketones [96b].



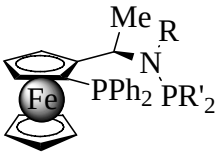
81 [87a, 93]
a R = Ph, (*S*)-BDPAB
b R = 3,5-$Me_2C_6H_3$, (*S*)-Xylyl-BDPAB
c R = *c*-Cy, (*S*)-Cy-BDPAB



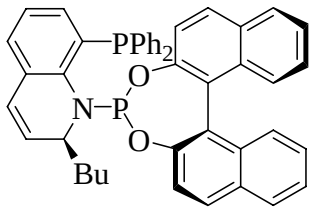
82 [87a, 93]
a R = Ph, (*S*)-H_8-BDPAB
b R = 3,5-$Me_2C_6H_3$, (*S*)-H_8-Xylyl-BDPAB



83 [94]
(*R*,*R*,*R*)-spiroNP



84 [95]
BoPhoz
a R = H, R' = Ph
b R = Me, R' = Ph
c R = Et, R' =Ph
d R = *i*-Pr, R' = Ph
e R = Me, R' = Cy

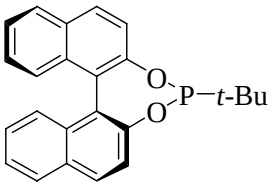


85 [96]
(*Ra*,*Sc*)-QUINAPHOS

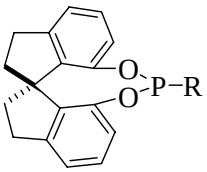
Figure 1-16 Structures of some aminophosphine ligands

1.3.12 Monophosphorus Ligands

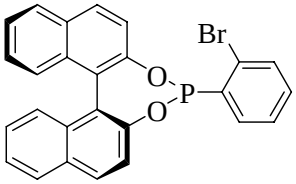
After the introduction of DIOP by Kagan, the development of chiral phosphorus ligands has been focused in the synthesis of bidentate ligands. The use of monophosphorus ligands for asymmetric hydrogenation has rarely been diclosed but some efficient monophosphorus ligands have been developed recently [97]. Orpen and Pringle have reported a monophosphonite **86** and up to 92% ee was obtained in the asymmetric hydrogenation of methyl (2-acetamido)acrylate [98]. Zhou devised a spiro monophosponite **87** and excellent results were obtained in the hydrogenation of *N*, *N*-dialkylenamines [99]. Wills reported a family of monophosphonites such as **88** and excellent results were achieved in the asymmetric hydrogenation of ketones [100]. De Vries and Feringa developed a series of monophosphoramidites, MonoPhos **90** [102], PipPhos **92a** [104] and MorfPhos **92b** [104] and they were very effective in Rh-catalyzed hydrogenation. Zhou reported SIPHOS **93** and excellent results were obtained in the asymmetric hydrogenation of α-dehydroamino acids, arylenamides and dimethy itaconates [105]. Zhang devised **94** and excellent results were obtained in asymmetric hydrogenation of α-dehydroamino acid derivatives [106]. Ding introduced DpenPhos **95** [107] and CydamPhos **96** [108] and excellent enantioselectivities were achieved in asymmetric hydrogenation of α-dehydroamino acid derivatives and arylenamides. Beller has developed monophosphine **97** [109].



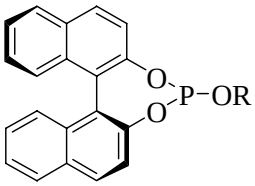
(*S*)-**86** [98]



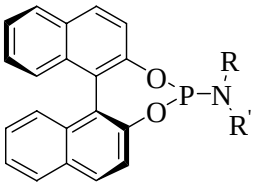
87 [99]
Spiro Phosphonite
R = *t*-Bu
R = Ar



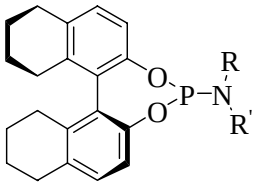
(*S*)-**88** [100]
BrXuPHOS



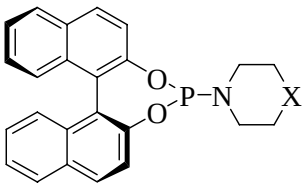
(*S*)-**89** [101]
a R = *i*-Pr
b R = Ph
c R = (*R*)-CH(Me)Ph



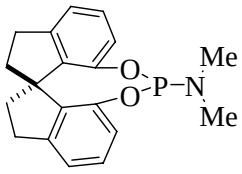
90 [102]
a R = R' = Me, (*S*)-MonoPhos
b R = Bn, R' = Me
c R = (*R*)-CH(Me)Ph, R' = H



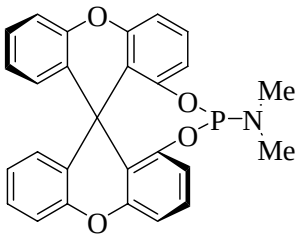
91 [103]
a R = R' = Me, (*S*)-H_8-MonoPhos
b R = R' = Et, (*S*)-Et-H_8-MonoPhos



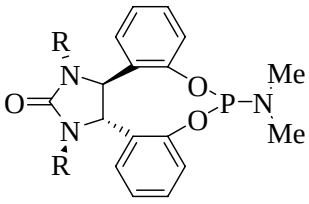
92 [104]
a X = CH_2, (*S*)-PipPhos
b X = O, (*S*)-MorfPhos



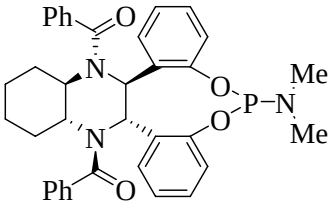
93 [105]
SIPHOS



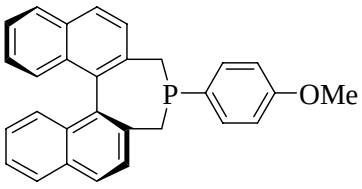
94 [106]



95 [107]
DpenPhos



96 [108]
CydamPhos



97 [109]

Figure 1-17 Structures of some monophosphorus ligands

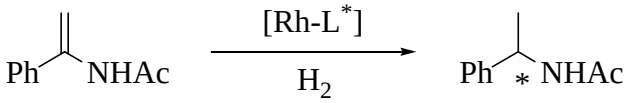
1.4 Rhodium-Catalyzed Asymmetric Hydrogenation of Olefins

Rhodium-catalyzed asymmetric hydrogenations have been performed with α-dehydroamino acids and their derivatives, β-dehydroamino acids and their derivatives, enamides, itaconic acids and their derivatives.

1.4.1 Asymmetric Hydrogenation of Enamides with Rh Complexes

Optically active amines and their derivatives are valuable compounds as they have been used as chiral auxiliaries, resolving agents and intermediates in the synthesis of many biologically active compounds. Asymmetric hydrogenation of enamides is a very efficient and convenient method for producing many chiral amine derivatives. Some reported results for the hydrogenation of α-phenylenamide are summarized in Table 1-1.

Table 1-1 Rhodium-catalyzed asymmetric hydrogenation of α-phenylenamide

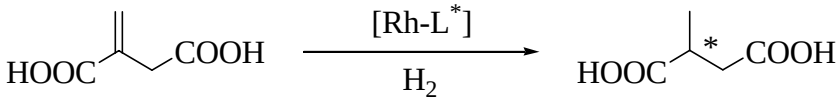


Ligand	S/C	Reaction Conditions	% ee (config.)	Ref
(*S*,*S*)-DIOP **1**	100	CH_2Cl_2, rt, 30 psig H_2, 12 h	60.2 (*R*)	61a
(*R*,*R*)-Me-BPE **6a**	500	MeOH, 22°C, 75 psig H_2, 15 h	95.2 (*R*)	15h
(*S*,*S*)-Me-DuPHOS **7a**	500	MeOH, 22°C, 75 psig H_2, 15 h	94.7 (*S*)	15h
42b	100	CH_2Cl_2, rt, 30 psig H_2, 24 h	96 (*R*)	54
(*S*,*R*,*R*,*S*)-DIOP* **50**	50	MeOH, rt, 160 psig H_2, 48-60 h	98.3 (*R*)	61c
(*S*,*S*)-Me-BDPMI **51b**	100	CH_2Cl_2, rt, 30 psig H_2, 12 h	98.5 (*R*)	62a
TaniaPhos **56e**	100	MeOH/toluene (1:1), rt, 30 psig H_2, 15 h	96 (*S*)	68c
(*S*,*S*)-*t*-Bu-BisP* **61a**	100	MeOH, rt, 60 psig H_2, 24-36 h	99 (*R*)	73c
(*R*,*R*)-QuinoxP* **64**	100	MeOH, rt, 60 psig H_2, 6 h	99.9 (*R*)	76
(*S*,*S*,*R*,*R*)-TangPhos **65**	10000	MeOH, rt, 35 psig H_2, 12 h	99.3 (*R*)	77a
(*R*,*R*,*S*,*S*)-DuanPhos **66**	100	MeOH, rt, 35 psig H_2	>99 (*R*)	78
(*S*)-Ph-*o*-BINAPO **74c**	100	THF, rt, 60 psig H_2, 12 h	94.3 (*S*)	81
(*R*)-BDPAB **81a**	200	THF, 5°C, 30 psig H_2, 0.5 h	92.9 (*R*)	93a
(*R*)-H_8-BDPAB **82a**	200	THF, 5°C, 30 psig H_2, 0.5 h	96.8 (*R*)	93a
(*S*)-MonoPhos **90a**	100	CH_2Cl_2, -20°C, 315 psig H_2, 8 h	95 (*S*)	102b
(*S*)-SIPHOS **93**	200	Toluene, 5°C, 750 psig H_2, 12 h	98.8 (*S*)	105b
(*R*,*R*)-DpenPhos **95**	100	CH_2Cl_2, rt, 605 psig H_2, 2 h	97.6 (*S*)	107
(*S*,*S*,*R*,*R*)-CydamPhos **96**	100	CH_2Cl_2, rt, 165 psig H_2, 5 h	98.1 (*R*)	108

1.4.2 Asymmetric Hydrogenation of Itaconic Acids and their Derivatives with Rh Complexes

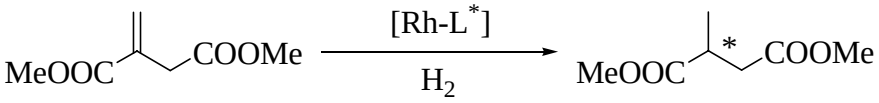
Optically active carboxylic acids and their derivatives are very important compounds for agrochemicals, flavors, fragrances and pharmaceuticals. There are many examples of asymmetric hydrogenation of itaconic acid and its dimethyl ester. High catalytic activity was observed with electron-rich diphosphine ligands and electron-deficient phosphonite or phosphite ligands. Some reported results for the hydrogenation of itaconic acid and dimethyl itaconate are summarized in Table 1-2 and Table 1-3.

Table 1-2 Rhodium-catalyzed asymmetric hydrogenation of itaconic acid



Ligand	S/C	Reaction Conditions	% ee (config.)	Ref
(*R*)-BICHEP **4b**	1000	EtOH, 25°C, 30 psig H_2, 10 h	96 (*R*)	28b
RoPhos **40b**	100	MeOH, rt, 30 psig H_2	98 (*R*)	51
BASPHOS **41b**	100	MeOH, 25°C, 30 psig H_2	96.9 (*R*)	52b
(*S*,*S*)-**61**	100	MeOH, rt, 95 psig H_2, 12 h	99.5 (*R*)	7
(*S*,*S*,*R*,*R*)-TangPhos **65**	200	THF, rt, 35 psig H_2, 24 h	99 (*S*)	77c
BoPhoz **84b**	100	MeOH, rt, 315 psig H_2, 6 h	97.4 (*R*)	95
89c	1000	CH_2Cl_2, 20°C, 35 psig H_2, 20 h	99.6 (S)	101a
(*S*)-MonoPhos **90a**	20	CH_2Cl_2, rt, 30 psig H_2, 20 h	96.6 (*S*)	102a
(*S*)-SIPHOS **93**	20	EA, rt, 30 psig H_2, <24 h	94.7 (*R*)	105a
(*R*)-**94**	100	CH_2Cl_2, rt, 40 psig H_2, 12 h	97.9 (*S*)	106

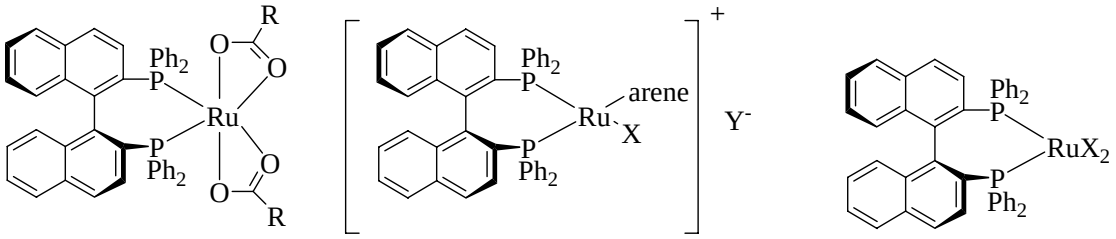
Table 1-3 Rhodium-catalyzed asymmetric hydrogenation of dimethyl itaconate



Ligand	S/C	Reaction Conditions	% ee (config.)	Ref
(*R*)-BICHEP **4b**	100	EtOH, 25°C, 90 psig H_2, 5 mins	>99 (*R*)	28b
(*R*,*R*)-Et-DuPhos **7b**	1000	MeOH, rt, 95 psig H_2, 1 h	97 (*R*)	15j
RoPhos **40a**	100	MeOH, rt, 30 psig H_2	99.1 (*R*)	51
BASPHOS **41b**	100	MeOH, 25°C, 30 psig H_2	97.9 (*R*)	52b
(*R*,*R*)-UlluPHOS **44**	1000	MeOH, 27°C, 45 psig H_2, 170 h	>99.5 (*S*)	56
(*R*,*R*)-(*S*,*S*)-Et-TRAP **52**	200	CH_2Cl_2, reflux, 30 psig H_2, 6 h	96 (*S*)	64c
(*R*)-(*S*)-Josiphos **53a**	100	MeOH, rt, 30 psig H_2, 0.5 h	98-99 (*S*)	65
TaniaPhos **56d**	100	MeOH, rt, 30 psig H_2, 14 h	98 (*S*)	68a
(*S*,*S*)-Et-FerroTANE **58**	200	MeOH, 20°C, 95 psig H_2, 1 h	98 (*R*)	70b
(*S*,*S*)-Ad-BisP* **61b**	500	MeOH, rt, 40 psig H_2, 1 h	99.6	73b
(*S*,*S*,*R*,*R*)-TangPhos **65**	5000	THF, rt, 35 psig H_2, 24 h	99 (*S*)	77c
(*R*,*R*,*S*,*S*)-DuanPhos **66**	100	THF, rt, 35 psig H_2	>99 (*S*)	78
(*R*,*R*)-**76**	5380	CH_2Cl_2, rt, 35 psig H_2, 20 h	>99.5 (*R*)	88
79	1000	CH_2Cl_2, -10°C, 20 psig H_2, 20 h	98.2 (*R*)	91
(*S*,*S*)-**80**	1000	CH_2Cl_2, 22°C, 35 psig H_2, 20 h	99 (*S*)	92
84b	100	MeOH, rt, 315 psig H_2, 6 h	94 (*R*)	95
(*Ra*,*Rc*)-**85**	1000	CH_2Cl_2, rt, 450 psig H_2, 24 h	98.8 (*R*)	96a
89c	1000	CH_2Cl_2, 20°C, 35 psig H_2, 20 h	99.6 (*S*)	101a
(*S*)-**92a**	500	CH_2Cl_2, rt, 90 psig H_2, 4 h	>99 (*S*)	104
(*S*)-**92b**	500	CH_2Cl_2, rt, 90 psig H_2, 4 h	98 (*S*)	104
(*S*)-SIPHOS **93**	100	CH_2Cl_2, rt, 30 psig H_2, <24 h	94 (*R*)	105a

1.5 Ruthenium Catalyzed Asymmetric Hydrogenation

In 1975 James reported the first ruthenium-catalyzed asymmetric hydrogenation and the chiral carboxylic acid was obtained with 60% ee [110]. After the introduction of BINAP, the ruthenium-catalyzed asymmetric hydrogenation undertook a quantum leap. By comparing to rhodium-catalyzed asymmetric hydrogenation, ruthenium-catalyzed asymmetric hydrogenation has wider applications [111]. The ruthenium-based catalysts can hydrogenate a broad range of substances e.g. allylic and homoallylic alcohols, α-, β-, γ-keto esters, functionalized ketones and olefins, α, β-unsaturated carboxylic acids and enamides with excellent results [111a]. Different Ru-BINAP catalyst systems were developed with different (anionic) ligands such as halogens, acetates, acetoacetonato and cyclopentadienyls.



98 [112]
a R = Me
b R = *t*-Bu
c R = CMe=CHMe

99 [113]
arene = C_6H_5
(i) X = Cl, Br, I
(ii) X = Cl; Y = ClO_4, BF_4, BPh_4
arene = *p*-$MeC_6H_4CHMe_2$
X = Y = Cl, Br, I

100 [114]

$[NH_2Et_2]^+[\{RuCl(BINAP)\}_2(\mu\text{-}Cl)_3]^-$

101 [115]

$RuCl_2(BINAP)(DMF)_n$

102 [116]

Figure 1-18 Structures of some Ru-BINAP catalysts

1.5.1 Asymmetric Hydrogenation of Functionalized Olefins

The Ru-BINAP dicarboxylate catalyst **98** showed excellent enantioselectivities in the asymmetric hydrogenation of various functionalized olefins [112].

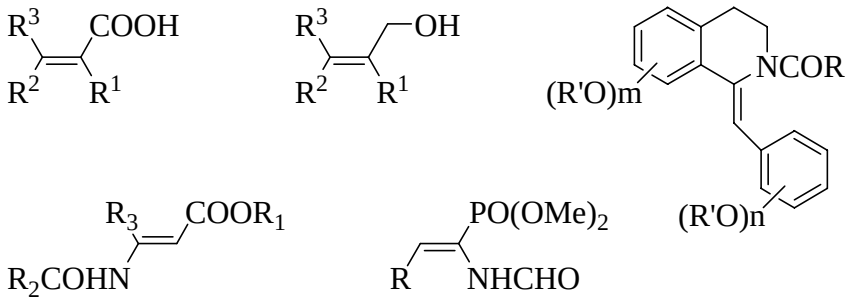
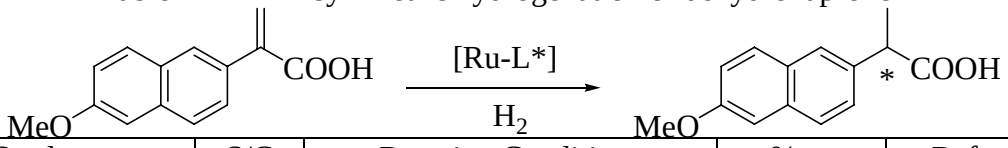


Figure 1-19 Structures of some functionalized olefins hydrogenated by Ru-(*S*)-BINAP dicarboxylate

Asymmetric hydrogenation of α, β-unsaturated carboxylic acids is the most promising method for producing optically active carboxylic acids such as a non-steroidal anti-inflammatory (NSAI) drug, (*S*)-naproxen [117].

Table 1-4 Asymmetric hydrogenation of dehydronaproxen



Catalyst	S/C	Reaction Conditions	% ee (config.)	Ref
Ru[(*S*)-BINAP **3a**](OAc)$_2$	215	MeOH, 2000 psig H_2, 12 h	97 (*S*)	110d
Ru[(-)-DMDANP **16b**](OAc)$_2$	500	MeOH, 15°C, 740 psig H_2, 7 h	92.3	26
Ru[(*R*)-BisbenzodioxanPhos **30**]Cl_2(*p*-cymene)	-	MeOH, 20-25°C, 1715 psig H_2	92.2	40a
Ru[(*R*)-P-Phos **38a**](acac)$_2$	200	MeOH, 0°C, 1015 psig H_2, 0.6 equiv of H_3PO_4, 18 h	96.2 (*R*)	49a, b

The chiral Ru-BINAP complexes also catalyzed the asymmetric hydrogenation of prochiral allylic and homoallylic alcohols [112c], (*Z*)-2-acyl-1-benzylidene-1,2,3,4-tetrahydroisoquinoline alkaloids [112a, 118], β-dehydroamino esters [119] and α-amino phosphonic acids [120] in a highly enantioselective manner.

1.5.2 Asymmetric Hydrogenation of Functionalized Ketones

The Ru-BINAP complexes hydrogenate a broad range of functionalized ketones with different coordinating groups. The coordinating groups include alkoxyl, alkoxycarbonyl, alkylthiocarbonyl, carbonyl, dialkylamino, (dialkylamino)carbonyl, hydroxyl, keto and silyloxyl groups. The corresponding alcohols are obtained with high enantioselectivities in a predictable manner [114b]. Halogen-containing Ru complexes are the best choice of catalysts for these kinds of substances [113, 116]. Some examples are shown in Figure 1-20 [114a].

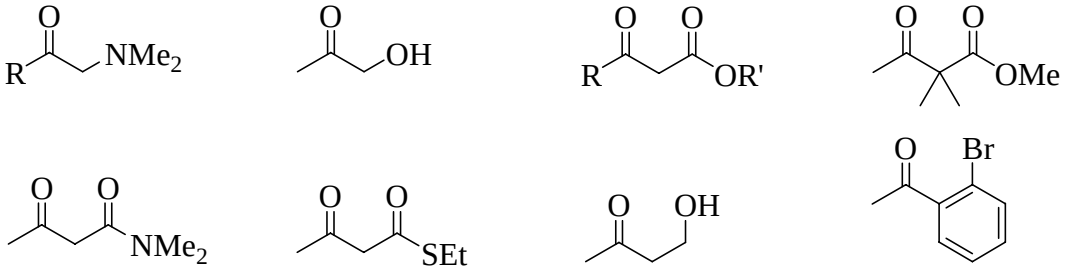
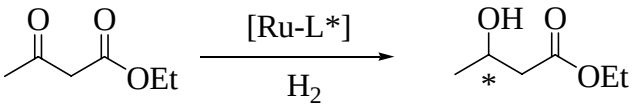


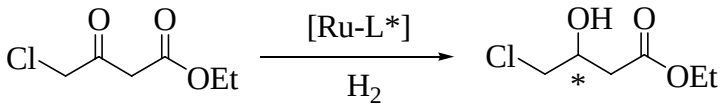
Figure 1-20 **S**ome functionalized ketones hydrogenated by Ru-BINAP

Table 1-5 Asymmetric hydrogenation of ethyl acetoacetate



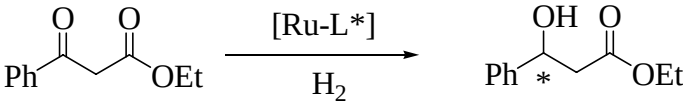
Ligand	S/C	Reaction Conditions	% ee (config.)	Ref
Ru[(*R*)-BINAP **3a**]Cl_2	1000	EtOH, 23-30°C, 1530 psig H_2, 58 h	99 (*R*)	112a
Ru[(*R*)-BisbenzodioxanPhos **30**] $Cl_2(DMF)_n$	-	EtOH, 80-90°C, 65 psig H_2, 12-24 h	99.5 (*R*)	40a
Ru[(*S*)-Solphos **31**]I_2(*p*-cymene)	75000	EtOH, 80°C, 1175 psig H_2, 19 h	97.1 (*R*)	41
Ru[(+)-tetraMe-BITIANP **34b**]$Cl_2(DMF)_n$	1000	MeOH, 70°C, 1485 psig H_2, 2h	99 (*R*)	45b
Ru[(+)-tetraMe-BITIOP **36**]$Cl_2(DMF)_n$	1000	EtOH, 70°C, 1485 psig H_2, 1 h	98 (*S*)	47
Ru[(-)-*N*-Me-2-BINP **37a**]I_2 (*p*-cymene)	1000	MeOH/H_2O (20:1), 10°C, 725 psig H_2,30 h	95 (*S*)	48
Ru[(*S*)-P-Phos **38a**]$Cl_2(DMF)_n$	400	EtOH/CH_2Cl_2 (1:1), 70°C, 65 psig H_2, 12-36h	98.6	49b
Ru[BASPHOS **41b**]Br_2	300	MeOH, 35°C, 450 psig H_2, 24 h	97.2 (*S*)	52b
Ru[TaniaPhos **56b**]Br_2	125	EtOH, 50°C, 740 psig H_2, 19 h	98.6 (*S*)	68b
Ru[(*S*,*S*,*R*,*R*)-TangPhos **65]**$Cl_2(DMF)_n$	1000	MeOH/H_2O (10:1), 50°C, 90 psig H_2, 10 h	98.9 (*R*)	77f
Ru[(*S*)-PhanePhos **68**]$(OCOCF_3)_2$ + Bu_4NI	125-250	MeOH/H_2O (10:1), -5°C, 65 psig H_2, 18 h	96 (*R*)	80b
Ru[(*S*)-Ph-*o*-Xylyl-BINAPO **74e**] Cl_2(*p*-cymene)	100	EtOH/CH_2Cl_2 (3:1), 50°C, 95 psig H_2, 20 h	96 (*S*)	86
Ru[(*S*,*S*)-**78**]$Cl_2(DMF)_n$	100	EtOH/CH_2Cl_2 (3:1), 60°C, 1175 psig H_2, 20 h	95 (*S*)	90a

Table 1-6 Asymmetric hydrogenation of ethyl chloroacetoacetate



Ligand	S/C	Reaction Conditions	% ee (config.)	Ref
Ru[(*S*)-BINAP **3a]**OAc_2	2000	EtOH, 100°C, 1485 psig H_2, < 5mins	97 (*R*)	110f
Ru[(*R*)-Methyl Soniphos **25a**]OAc_2	2000	EtOH, 95°C, 131 psig H_2, 22 h	94	35
(NH_2Me_2)[{RuCl[(*R*)-SEGPHOS **29**]}$_2$(μ-Cl)$_3$]	2500	EtOH, 90°C, 445 psig H_2, 2 h	98.5	39b
Ru[(*R*)-BisbenzodioxanPhos **30**] $Cl_2(DMF)_n$	-	EtOH, 80-90°C, 65 psig H_2, 12-24 h	97 (*R*)	40a
Ru[(*S*)-DifluoroPhos **32**]Br_2	100	EtOH, 110°C, 160 psig H_2, 3 h	97 (*R*)	42a
Ru[(*S*)-P-Phos **38a**]$Cl_2(DMF)_n$	2800	EtOH/CH_2Cl_2, 80°C, 65 psig H_2, 12-36 h	98	49b
Ru[(*S*,*S*,*R*,*R*)-TangPhos **65]**$Cl_2(DMF)_n$	1000	EtOH, 100°C, 750 psig H_2, 10 h	98.2 (*S*)	77f
Ru[(*S*)-Ph-*o*-Xylyl-BINAPO **74e**] Cl_2(*p*-cymene)	100	EtOH/CH_2Cl_2 (3:1), 50°C, 950 psig H_2, 20 h	98 (*R*)	86

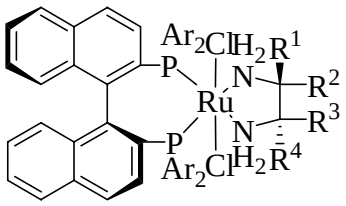
Table 1-7 Asymmetric hydrogenation of ethyl benzoylacetate



Ligand	S/C	Reaction Conditions	% ee (config.)	Ref
Ru[(*R*)-BINAP **3a**]Br_2	760	EtOH, 23-30°C, 1355 psig H_2, 106 h	85 (*S*)	112a
Ru[(*R*)-MeO-BIPHEP **5a**]Br_2	50	EtOH, 50°C, 30 psig H_2, 44 h	96 (*S*)	119
Ru[(*R*)- 4,4'-BINAP **15a**] $Cl_2(DMF)_n$	100	MeOH, rt, 1415 psig H_2, 20 h	99.5 (*R*)	25a
Ru[(*R*)-Methyl Soniphos **25a**]Br_2	100	EtOH, 50°C, 305 psig H_2, 22 h	97.8	35
Ru[(*S*)-Solphos **31**]I_2(*p*-cymene)	200	EtOH, 80°C, 1175 psig H_2, 21 h	98 (*S*)	41
Ru[(*R*)-DifluoroPhos **32**]Br_2	100	EtOH, 80°C, 160 psig H_2, 24 h	92 (*S*)	40h, 42a
Ru[(-)-tetraMe-BITIANP **34b**]$Cl_2(DMF)_n$	1000	MeOH, 25°C, 1485 psig H_2, 100h	90 (*R*)	45b
Ru[(-)-tetraMe-BITIOP **36**]$Cl_2(DMF)_n$	257	MeOH/H_2O, 45°C, 1485 psig H_2, 2 h	93 (*S*)	47
Ru[(-)-*N*-Me-2-BINP **37a**]$Cl_2(DMF)_n$	251	MeOH/H_2O, 45°C, 1440 psig H_2, 0.8 h	93 (*R*)	48
Ru[(*R*)-Xyl-P-Phos **38c**] $Cl_2(C_6H_6)$	800	EtOH/CH_2Cl_2, 90°C, 315 psig H_2, 2 h	96.2 (*S*)	49d
Ru[TaniaPhos **56e**]Br_2	200	EtOH, 50°C, 740 psig H_2, 19 h	98 (*R*)	68c
Ru[(*S*,*S*,*R*,*R*)-TangPhos **65]**$Cl_2(DMF)_n$	200	EtOH, 80°C, 750 psig H_2, 20 h	96.2 (*S*)	77f
Ru[(*S*)-xylyl-*o*-BINAPO **74d**] Cl_2(*p*-cymene)	100	EtOH/CH_2Cl_2 (3:1), 50°C, 95 psig H_2, 20 h	99 (*R*)	86
Ru[(*S*,*S*)-**78**]$Cl_2(DMF)_n$	100	EtOH/CH_2Cl_2 (3:1), 85°C, 740 psig H_2, 20 h	97	90a

1.5.3 Asymmetric Hydrogenation of Unfunctionalized Simple Ketones

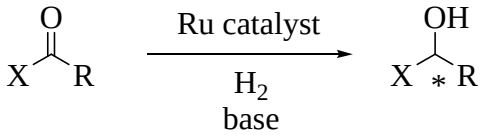
Asymmetric hydrogenation of functionalized ketones is very successful. However, asymmetric hydrogenation of simple ketones is very difficult due to the absence of anchoring groups. Some chiral ruthenium and rhodium catalysts have been attempted. A breakthrough was introduced by Noyori and coworkers with a new chiral Ru catalyst system [122]. The complexation of Ru-BINAP with a chiral 1,2-diamine with an alkaline base such as *t*-BuOK, KOH or K_2CO_3 in isopropanol catalyzed asymmetric hydrogenation of simple, unfunctionalized aromatic, heteroaromatic, olefinic and certain aliphatic ketones quantitatively with excellent enantioselectivity [123]. *Trans*-[$RuCl_2$(Xyl-BINAP)-DAIPEN] is the most effective. Some reported results for the hydrogenation of acetophenone are summarized in Table 1-8.



103

Ar = Ph, (*S*)-BINAP
Ar = 4-MeC_6H_4, (*S*)-Tol-BINAP
Ar = 3,5-$Me_2C_6H_3$, (*S*)-Xyl-BINAP

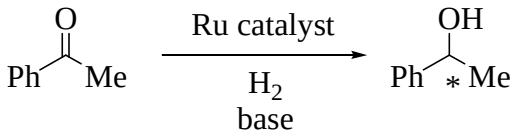
(*S*,*S*)-DPEN: $R^1 = R^4$ = Ph; $R^2 = R^3$ = H
(*S*)-DAIPEN: $R^1 = R^2$ = 4-$MeOC_6H_4$; R^3 = H; $R^4 = Me_2CH$



X = aryl, heteroaryl, alkenyl

Scheme 1-1 General asymmetric hydrogenation of simple ketone and its catalyst

Table 1-8 Asymmetric hydrogenation of acetophenone

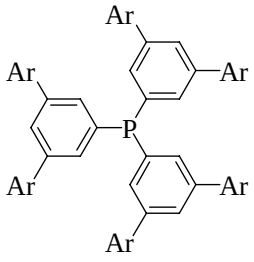


Catalyst	S/C	Reaction Conditions	% ee (config.)	Ref
Ru[(*S*)-Xyl-BINAP **3c**][(S)-DAIPEN]Cl_2 + *t*-BuOK	100000	*i*-PrOH, 26-30 °C, 135 psig H_2, 60 h	99 (*R*)	121d
Ru[(*R*)-4,4'-BINAP **15a**][(*R*)-DAIPEN]Cl_2 + *t*-BuOK	1000000	*i*-PrOH, rt, 715 psig H_2, 50 h	98.6 (*S*)	25b
Ru[(*S*)-Xyl-HexaPHEMP **20b**][(*S*)-DAIPEN]Cl_2 + *t*-BuOK	3000	*i*-PrOH, rt, 135 psig H_2, 0.5 h	99 (*R*)	32b
Ru[(*R*)-Xyl-P-Phos **38c**][(*R*,*R*)-DPEN]Cl_2 + *t*-BuOK	100000	*i*-PrOH, 25-28 °C, 515 psig H_2, 36 h	99.1 (*S*)	49e
Ru[(*R*)-Xyl-PhanePhos **68b**][(*S*,*S*)-DPEN]Cl_2 + *t*-BuOK	20000	*i*-PrOH, 18-20 °C, 135 psig H_2, 1.5 h	99 (*R*)	80c
Ru[(*S*)-Xyl-SDP **70d**][(*R*,*R*)-DPEN]Cl_2 + *t*-BuOK	100000	*i*-PrOH, 40°C, 750 psig H_2, 72 h	98 (*S*)	82
Ru[(R_a,S_c)-QUINAPhos **85**] [(*S*,*S*)-DPEN]Cl_2 + *t*-BuONa	500	MeOH, rt, 450 psig H_2, 16 h	94 (*R*)	96b
Ru[(*S*)-BrXuPHOS **88**]$_2$[(*S*,*S*)-DPEN]Cl_2 + *t*-BuOK	2000	*i*-PrOH, 0°C, 740 psig H_2, 4 h	93 (*R*)	100
Ru[(**104**)$_2$(*R*,*R*)-DPEN]Cl_2 + *t*-BuOK	1000	*n*-PrOH, 25°C, 315 psig H_2, 10 h	95.5 (*S*)	124
Ru(DPBP **105**)[(*S*,*S*)-DPEN]Cl_2+ KOH	250	*i*-PrOH, rt, 235 psig H_2, 4 h	90 (*R*)	125

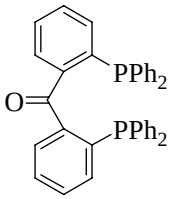
The Ru catalysts with other bidentate diphosphine ligands, such as Xyl-HexaPHEMP **20b** [32b], Xyl-P-Phos **38c** [49e, f, k, m], Xyl-SDP **70d** [82] and Xyl-PhanePhos **68b** [80c] gave similar excellent results. By introducing bulky substitutens on the 4,4'-positions of BINAP, excellent results were obtained by Ru catalyst with 4,4'-BINAP **15a** without

resorting to the bis(xylyl)phosphino group [25b]. High enantioselectivities were obtained using a phosphine-phosphoramidite ligand, QUINAPHOS **85** [96]. Replacing Xyl-BINAP **3c** with two monophosphonites BrXuPHOS **88** also gave excellent results [100].

A ruthenium complex composed of a cheap nonchiral monodentate phosphine ligand **104** and (*R*,*R*)-DPEN was developed by Ding and this catalyst system afforded the alcohols with high enantioselectivity [124]. Mikami [125a] and Ding [125b] independently reported the use of achiral benzophenone ligand, DPBP **105** instead of the chiral BINAP of Ru-BINAP-1,2-diamine catalyst systems **103** in the asymmetric hydrogenation of simple ketones, and up to 99% yield and 99% ee were obtained for hydrogenation of 1-acetylnaphthalene.



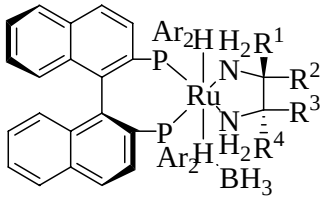
104
Ar = 3,5-$Me_2C_6H_3$



105
DPBP

Figure 1-21 Structures of two achiral phosphines

A robust (pre)catalyst RuH(η^1-BH_4)(BINAP)(1,2-diamine) complex **106** was developed for asymmetric hydrogenation of simple ketones under a base-free condition with high activity (S/C up to 100000) and high enantioselectivity (up to 99% ee) [126].

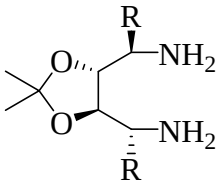


106

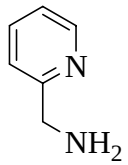
(*S*,*S*,*S*): Ar = 3,5-$Me_2C_6H_3$, R^1 = R^4 = Ph; R^2 = R^3 = H
(*S*,*R*,*R*): Ar = 3,5-$Me_2C_6H_3$, R^1 = R^4 = H; R^2 = R^3 = Ph

Figure 1-22 *Trans*-RuH(η^1-BH_4)(BINAP)(1,2-diamine) complex **106**

However, the asymmetric hydrogenation of tetralones and *tert*-alkyl ketones has not been successful using the Ru-BINAP-1,2-diamine catalyst systems **103**. These two problems were overcome by replacement of the symmetrical 1,2-diamine with other diamines.



107
a R = H, (*R*)-IPBAN
b R = Me, (*R*)-IPHAN



108
PICA

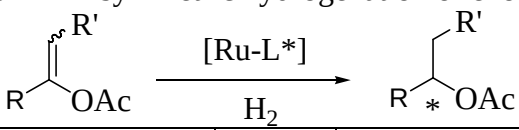
Figure 1-23 Structures of chiral symmetrical 1,4-diamine **107** and non-chiral unsymmetrical amine **108**

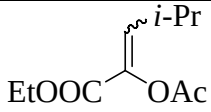
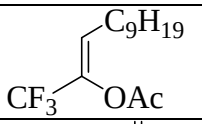
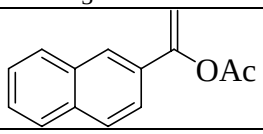
Using chiral symmetrical 1,4-diamine **107**, tetralones were hydrogenated with S/C ratio of 1000-55000 to the corresponding alcohols with 92-98% ee [127]. On the other hand, the problem of *tert*-alkyl ketones was solved by using a non-chiral unsymmetrical NH_2/pyridine hybrid ligand, α-picolylamine (PICA) **108** and the use of ethanol as solvent. With this new Ru-BINAP-PICA catalyst system, a wide range of sterically congested *tert*-alkyl ketones was hydrogenated to chiral *tert*-alkyl alcohols with high enantioselectivities under mild conditions with or without a strong base depending on the anionic ligand [128].

1.5.4 Asymmetric Hydrogenation of Enol Acetates

The structures of enol acetates are similar to enamides but with weaker coordinating ability of the acyl group to the metal. There are only a few examples for the ruthenium-catalyzed asymmetric hydrogenation involving enol acetates as substrate.

Table 1-9 Asymmetric hydrogenation of enol acetates

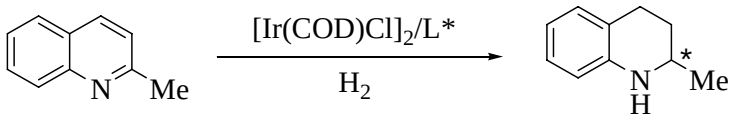


Catalyst	Enol acetate	S/C	Reaction Conditions	% ee (config.)	Ref
Ru[(*R*)-BINAP **3a**] Cl_2(*p*-cumene)		-	MeOH, 50°C, 740 psig H_2, 4 days	98 (*S*)	129
Ru[(*R*)-BINAP **3a**] Cl_2(*p*-cymene)		2500	MeOH, 50°C, 310 psig H_2, 90 h	>99 (*R*)	130
(NH_2Me_2)[{RuCl[(*S*)-C_2-TunaPhos **28**]}$_2$(μ-Cl)$_3$]		100	EtOH/CH_2Cl_2 (4:1), rt, 60 psig H_2, 12 h	97.7(*S*)	38c

1.6 Iridium-Catalyzed Asymmetric Hydrogenation of Quinolines

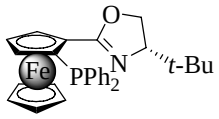
Optically active tetrahydroquinoline and their derivatives are very important synthetic intermediate and building blocks for the synthesis of alkaloids and other biologically active compounds. However, methods for the asymmetric synthesis of optically active tetrahydroquinoline derivatives are limited. Asymmetric hydrogenation is the most attractive and convenient method for producing optically active tetrahydroquinoline derivatives in which case synthesis by direct cyclization is often difficult. Chiral Rh, Ru and Ir complexes have been showed to be very efficient and enantioselective for the asymmetric hydrogenation of prochiral olefins, ketones and imines. However, these complexes often gave poor results. Quinolines have a resonance stability that prevents hydrogenation. The nitrogen of quinolines may poison the catalyst. These may account for the low activity of quinolines towards hydrogenation. There are only six ligand systems known to give ee values greater than 90%.

Table 1-10 Asymmetric hydrogenation of 2-methylquinoline



Ligand	S/C	Reaction Conditions	% ee (config.)	Ref
(*R*)-MeO-BIPHEP **5a**	100	Toluene, rt, 715 psig H_2, 18 h + I_2	94 (*R*)	131
(*R*)-P-Phos **38a**	100	THF, rt, 715 psig H_2, 20 h + I_2	91(*R*)	49j
(*S*)-H_8-BINAPO **74a**	100	THF, rt, 715 psig H_2, 20 h + I_2	95 (*R*)	86c
(*S*,*S*)-**78**	50	Toluene, 0°C, 885 psig H_2, 20 h + I_2	96 (*S*)	90b
(*S*,*Sp*)-**109**	100	Toluene, rt, 615 psig H_2, 12 h + I_2	90 (*R*)	132
(*S*)-SEGPHOS **29a**	100	THF, rt, 615 psig H_2, 15 h	90 (*S*)	133

Zhou and co-workers reported that the iridium complexes generated in situ from $[Ir(COD)Cl]_2$ and (*R*)-MeO-BIPHEP **5a** [131] or a ferrocene-oxazoline derived P, N ligand **109** [132] catalyzed the asymmetric hydrogenation of 2-substituted quinolines, i.e. maximum ee = 96 and 92 % resepectively.



(S, S*p*)-**109**

Chan reported similar results by using (*R*)-P-Phos **38a** [49j] and (*S*)-H_8-BINAPO **74a** **[**86c**]**. The iridium-P-Phos complex was found to be air-stable and the catalyst immobilized in DMPEG was recycled for eight times without loss of activity and enantioselectivity. Reetz used a chiral diphosphonite (*S*,*S*)-**78** derived from BINOL and up to 96% ee was obtained [90b]. The above five ligand systems also required the presence of iodine as additive to speed up the reaction rate and enhance the

enantioselectivity. Recently, Zhou reported the iridium-SEGPHOS **29a** system to catalyze asymmetric hydrogenation of quinolines in the presence of chloroformates and lithium carbonate instead of iodine [133]. This ligand system also worked well for isoquinolines with enantioselectivity up to 83%.

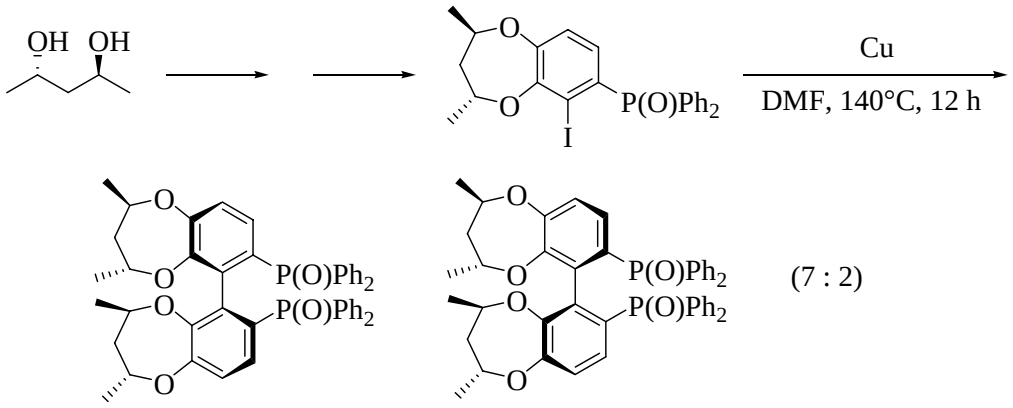
1.7 Synthesis of Axially Chiral C_2-Symmetrical Biaryl Diphosphine Ligands

Axially chiral C_2-symmetrical biaryl diphosphine ligands are very important for asymmetric hydrogenation as mentioned [6, 134]. The traditional synthesis of novel axially chiral C_2-symmetrical biaryl diphosphine ligands involves aryl-aryl coupling (Ullmann coupling) of different kinds of aryl backbones such as naphthyl, phenyl, heteroaryl. Enantiomerically pure biaryl diphosphine ligands are obtained after classical resolution followed by reduction. Development of resolution procedures is a matter of trial and error and resolution requires numerous recycle loops and fractional crystallizations. As a result, resolution method is very time-consuming and expensive. Various methods have been developed for the direct, atroposelective synthesis of axially chiral biaryl compounds mainly biphenols and binaphthols [135]. However, the atroposelective synthesis of biaryl diphosphine oxides have rarely been disclosed. There are only five reports in the literature concerning the direct, atroposelective synthesis of biaryl diphosphine oxides via asymmetric coupling of aryl phosphine oxide either with extra chiral center on the backbone or with chiral linker.

1.7.1 Asymmetric Intermolecular Ullmann Coupling

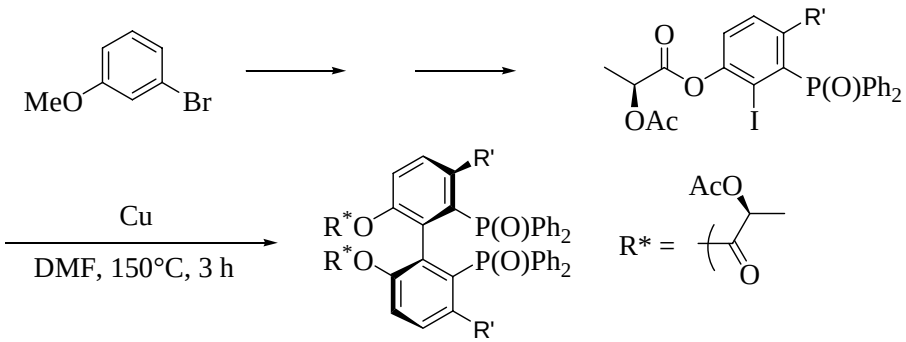
Chan reported the first example of asymmetric intermolecular Ullmann coupling of chiral phosphine oxide [136] with moderate atropdiastereoselectivity (7:2). The reduced ligands

were found to give higher enantioselectivities in the Ru-catalyzed asymmetric hydrogenation of dehydronaproxen and β–keto esters than BINAP.



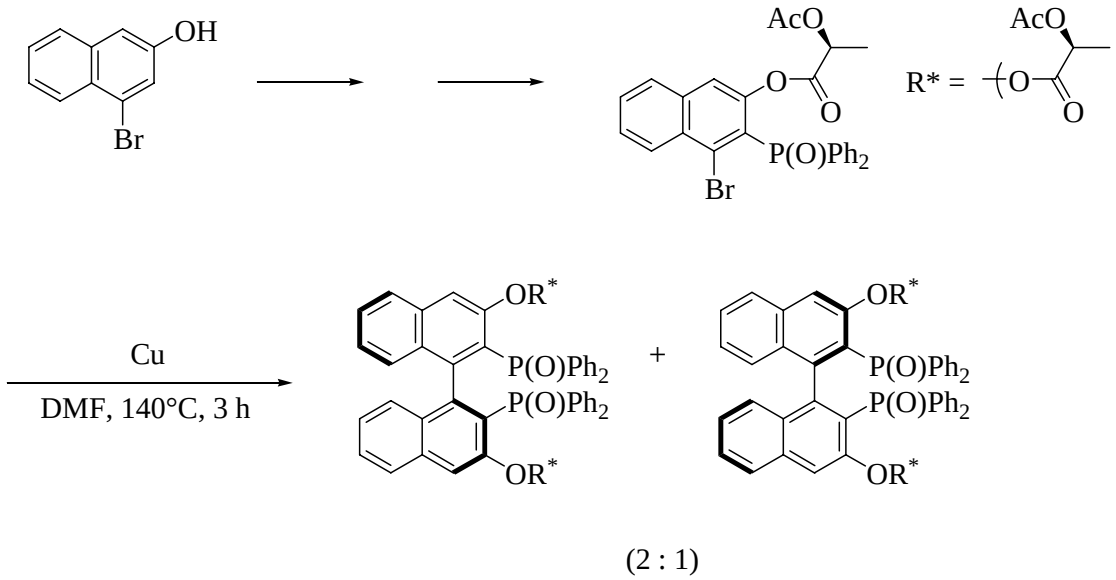
Scheme 1-2 Synthesis of diastereomeric diphosphine oxide derived from chiral diol

Keay employed a chiral auxillary, (*S*)-2-acetoxypropanoyl chloride in the synthesis of 3,3'-disubstituted MeO-BIPHEP derivatives [137] and 3,3'-disubstituted BINAP derivatives [138] via asymmetric intermolecular Ullmann coupling with moderate atropdiastereoselectivity. The 3,3'-disubstituted MeO-BIPHEP derivatives gave good enantioselectivities while the 3,3'-disubstituted BINAP derivatives gave excellent enantioselectivities in the rhodium-catalyzed asymmetric hydrogenation of α-dehydroamino acids and their derivatives.



R' = H, 33% de
R' = O-*t*-Bu, 24% de
R' = *i*-Pr, 20% de
R' = Ph, 13% de

Scheme 1-3 Synthesis of 3,3'-disubstituted MeO-BIPHEP derivatives

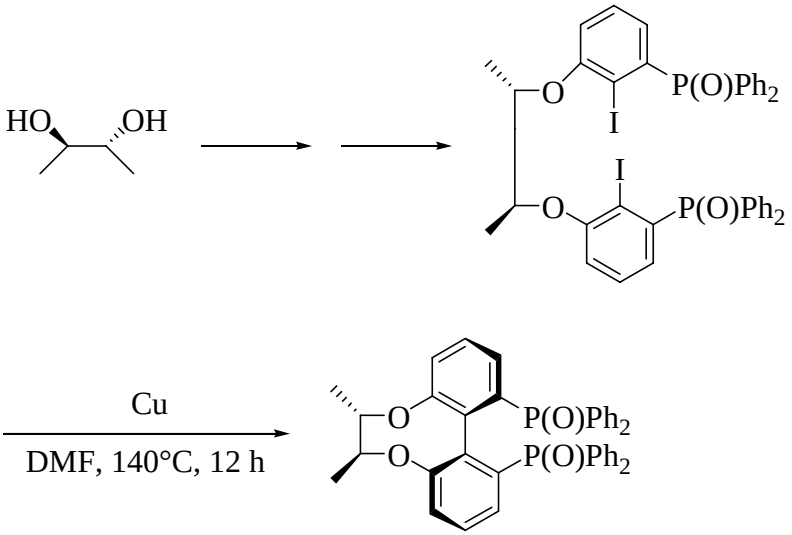


(2 : 1)

Scheme 1-4 Synthesis of 3,3'-disubstituted BINAP derivatives

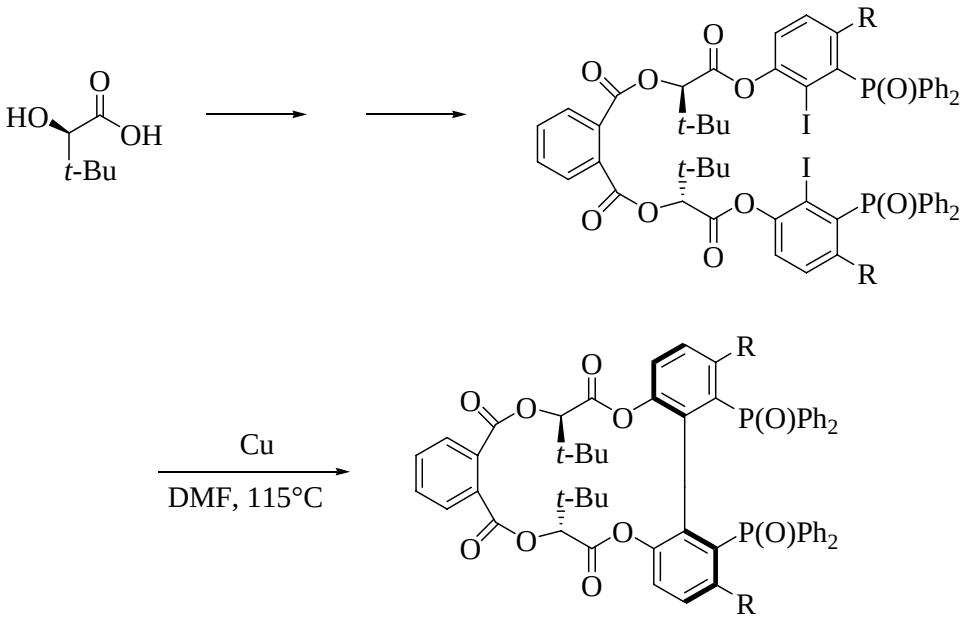
1.7.2 Asymmetric Intramolecular Ullmann Coupling

Chan reported the first example of essentially complete atropdiastereoselectivity in the synthesis of MeO-BIPHEP derivatives and excellent results were obtained in the asymmetric hydrogenation of α- and β-ketoesters, dehydronaproxen, β-dehydroamino esters and enol acetates [139].



Scheme 1-5 Synthesis of atropdiastereomeric diphosphine oxide derived from chiral diol

Keay reported the second example of essentially complete atropdiastereoselectivity in the synthesis of 3,3'-disubstituted MeO-BIPHEP derivatives [140]. However, no asymmetric catalysis was carried out with these ligands.



R = H, OMe, Otolyl, Ph, mesityl

Scheme 1-6 Synthesis of atropdiastereomeric diphosphine oxide derived from chiral hydroxyl acid

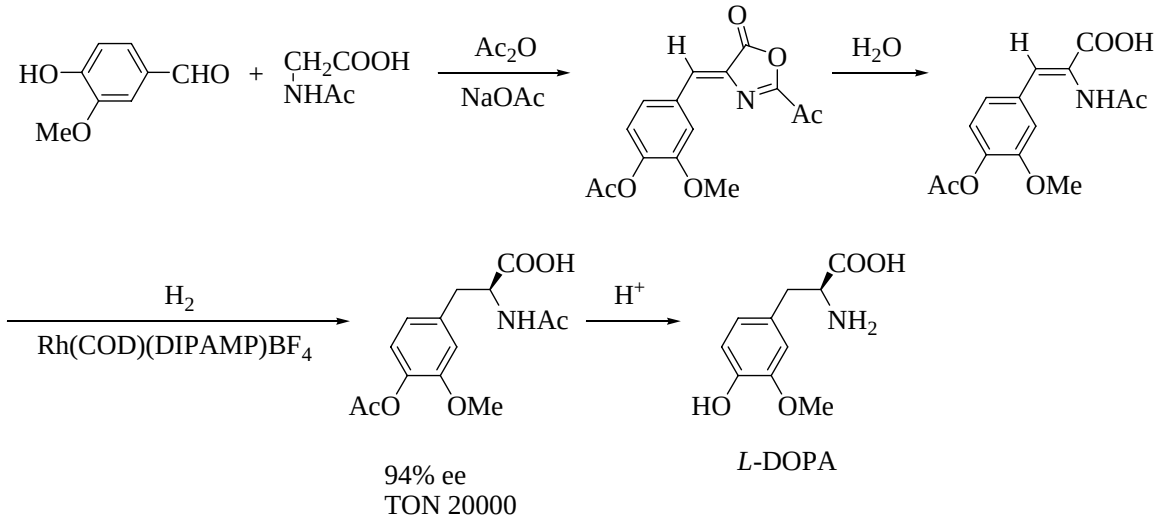
1.8 Industrial Application of Asymmetric Hydrogenation

Asymmetric hydrogenation is very important for agrochemicals, flavors, fragrances, and pharmaceuticals [141].

1.8.1 *L*-DOPA

Parkinson's disease is related to the low level of dopamine in certain parts of brain. *L*-Dopa is a prodrug for the treatment of Parkinson's disease by increasing dopamine levels. *L*-dopa can cross the blood brain barrier while dopamine cannot. After crossing the blood brain barrier, *L*-dopa is converted to dopamine by the enzyme, aromatic-*L*-amino acid

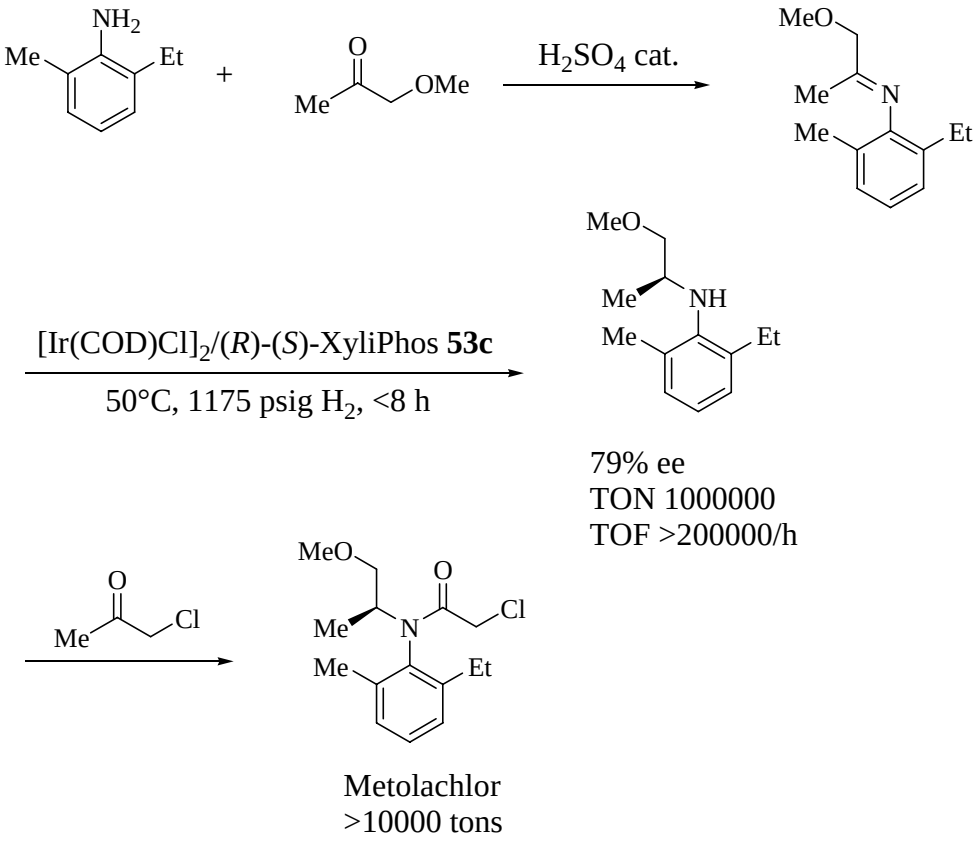
decarboxylase. The increase in brain dopamine levels improve nerve conduction and alleviate the movement disorders in Parkinson's disease. Knowles *et al.* developed DIPAMP **2** and the Rh-complex catalyzed asymmetric hydrogenation of the dehydroamino acid for production of *L*-DOPA [142]. (Scheme 1-7) This was the first successful industrial catalytic asymmetric process and made asymmetric hydrogenation a popular subject of research.



Scheme 1-7 Monsanto *L*-DOPA Process

1.8.2 Metolachlor

Metolachlor (trade name Dual Magnum®) is an important grass herbicide. It has a chiral center and a chiral axis, leading to four stereoisomers. It was sold as a mixture of all four stereoisomers since 1976. The two (1'*S*)-diastereomers were found to retain about 95% of the herbicidal activity in 1982. After years of research, the asymmetric hydrogenation of an imine catalyzed by Ir-XyliPhos complex was developed. Dual Magnum® with about 90% (1'*S*)-diastereomers content and with the same herbicidal activity was introduced in 1997 [143]. More than 10000 tons of metolachlor is producing every year and this is the largest-scale asymmetric catalytic industrial process. (Scheme 1-8)



Scheme 1-8 Metolachlor Process

1.9 Aims and Objectives of this project

Chiral diphosphines are very important ligands in asymmetric catalysis as they are widely used in many asymmetric catalytic reactions such as hydrogenation, hydrocyanation, hydrosilylation, isomerization, etc. Very little attentions was focused on the synthesis of chiral diphosphine ligand with chiral linkers. This project is aimed at developing novel chiral C_2-symmetrical biaryl diphosphine ligands with chiral linkers by means of asymmetric Ullmann coupling with central-to-axial chirality transfer. The corresponding metal catalysts are expected to give better activity and enantioselectvitiy in asymmetric hydrogenation.

CHAPTER TWO

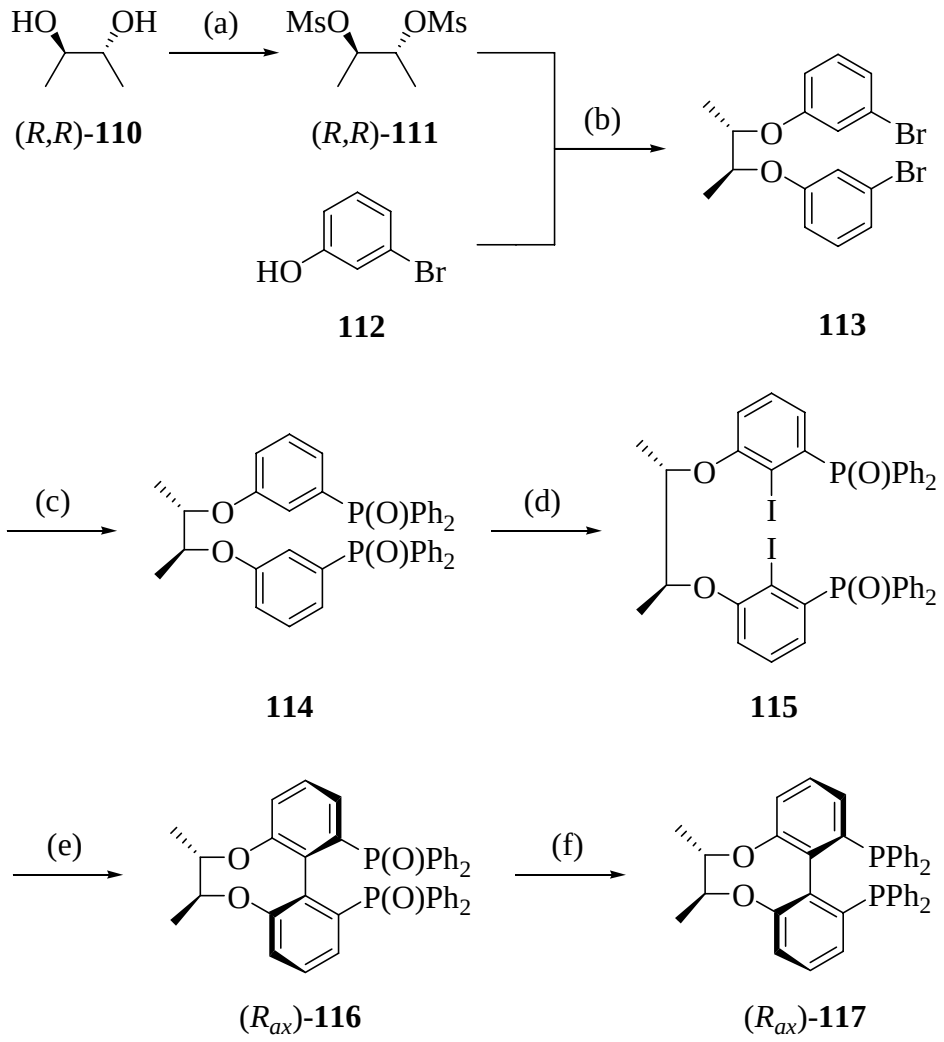
RESULTS AND DISCUSSIONS

2.1 Synthesis of (*R*) or (*S*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl

The ligands were synthesized either via asymmetric intramolecular Ullmann coupling or ring closure process.

2.1.1 Synthesis of (*R*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 117 via Asymmetric Intramolecular Ullmann Coupling

(2*R*,3*R*)-Butanediol **110** reacted with methanesulfonyl chloride in pyridine to give (2*R*,3*R*)-butanediol dimesylate **111** with 92% yield. Dimesylate **111** reacted with 3-bromophenol **112** in DMSO in the presence of Cs_2CO_3 to give chiral bromoether (2*S*,3*S*)-2,3-bis(3-bromophenoxy) butane **113** with 53% yield. Lithiation of chiral bromoether **113** with *n*-butyllithium and quenching with chlorodiphenylphosphine gave phosphine, which was oxidized with H_2O_2 to give phosphine oxide **114** with 85% yield for the two steps. Then *ortho*-lithiation with lithium diisopropylamide followed by quenching with iodine gave diioide **115** with 85% yield. Finally an intramolecular Ullmann coupling of diioide **115** gave compound diphosphine dioxides **116** with 91% yield.



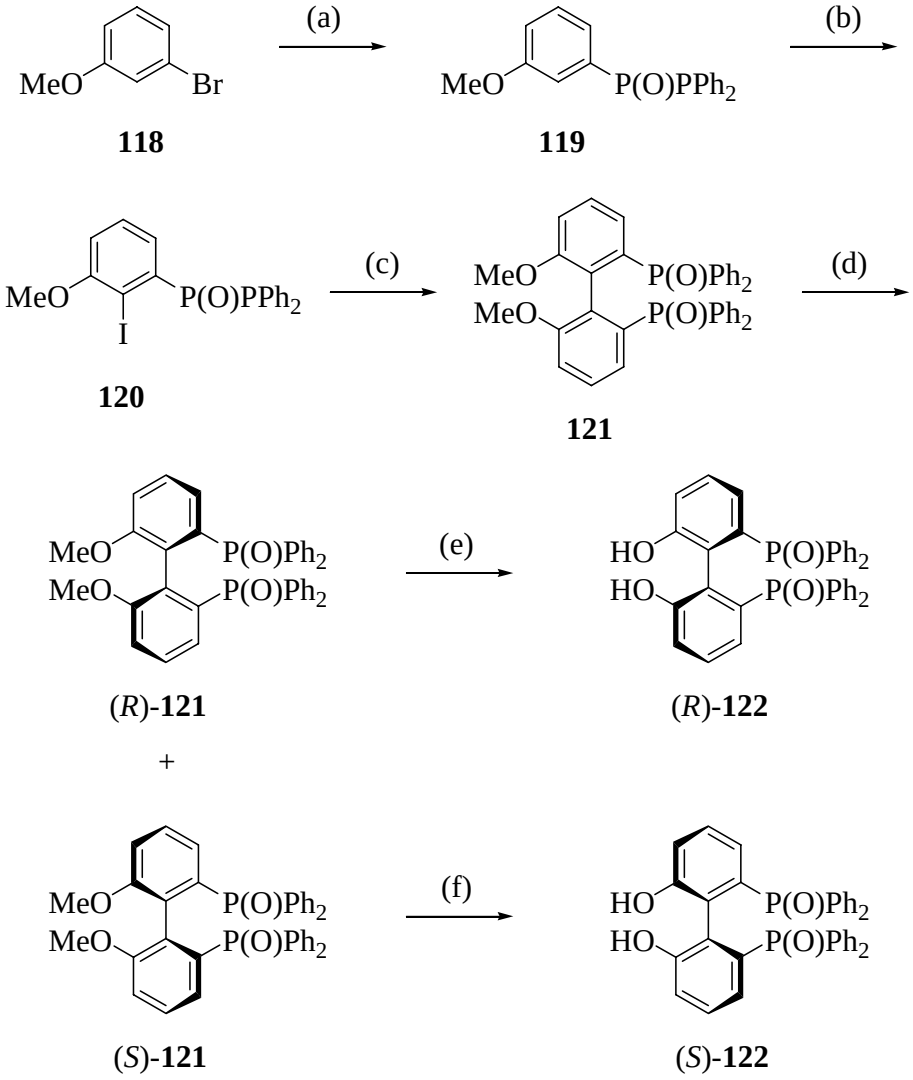
Scheme 2-1 Asymmetric Ullmann coupling route of (*R*)-[6,6'-(2*S*,3*S*-butadioxy)]-(2,2')- bis(diphenylphosphino)-(1,1')-biphenyl **117**

(a) MsCl, pyridine, 0°C – rt, 92%; (b) Cs_2CO_3, DMSO, 55°C, 8h, 53%; (c) i. *n*-BuLi, THF, -78°C; ii. Ph_2PCl, -78°C – rt; iii. H_2O_2, acetone, 0°C, 85% from **113**; (d) i. LDA, THF, -78°C; ii. I_2, -78°C – rt, 85%; (e) Cu, DMF, 140°C, 12 h, 91%; (f) $HSiCl_3$, *n*-Bu_3N, toluene, reflux, 96%.

Only one atropdiastereomer was obtained. (R_{ax})-**116** was reduced with trichlorosilane in toluene in the presence of tributylamine to give diphosphine **117** with 96% yield.

2.1.2 Synthesis of (*S*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 124 via Ring Closure Process

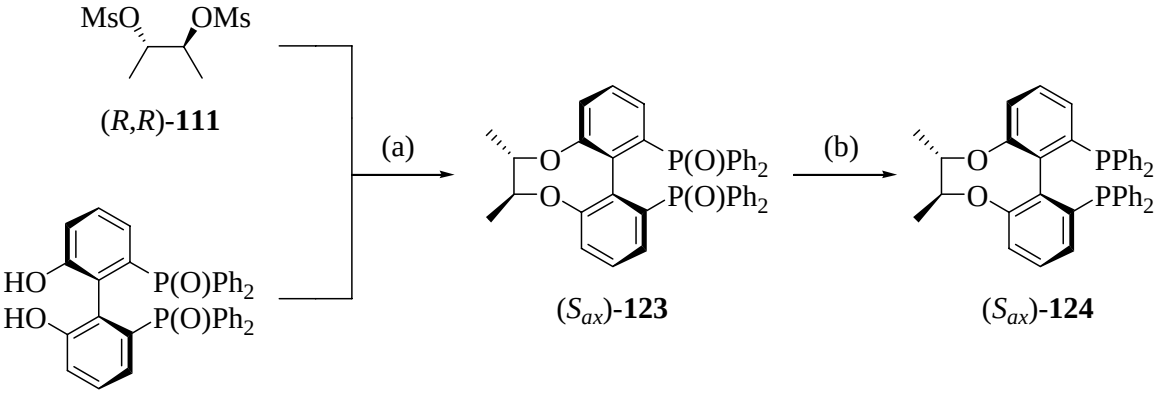
(*R*)- and (*S*)-MeO-BIPHEPO **121** as the starting materials were prepared according to the procedures in literature [14b] and shown in Scheme 2-2. (*R*)- or (*S*)-MeO-BIPHEPO **121** reacted with BBr_3 followed by hydrolysis to give (*R*)- or (*S*)-HO-BIPHEPO **122**.



Scheme 2-2 Synthetic route of HO-BIPHEPO **122**

(a) i. *n*-BuLi, THF, -78°C; ii. Ph_2PCl, -78°C – rt; iii. H_2O_2, acetone, 0°C; (b) i. LDA, THF, -78°C; ii. I_2, -78°C – rt; (c) Cu, DMF, 140°C; (d) resolution, (-)-DBTA, (+)-DBTA, CH_2Cl_2/EA = 1.2; (e) BBr_3, CH_2Cl_2, -78°C - rt, 78%; (f) BBr_3, CH_2Cl_2, -78°C - rt, 75%.

The ring closure reaction of (*S*)-HO-BIPHEPO **122** and dimesylate **111** produced the (S_{ax})-form **123** with 58% yield. (S_{ax})-**123** was reduced with trichlorosilane in toluene in the presence of tributylamine to give diphosphine **124** with 95% yield.

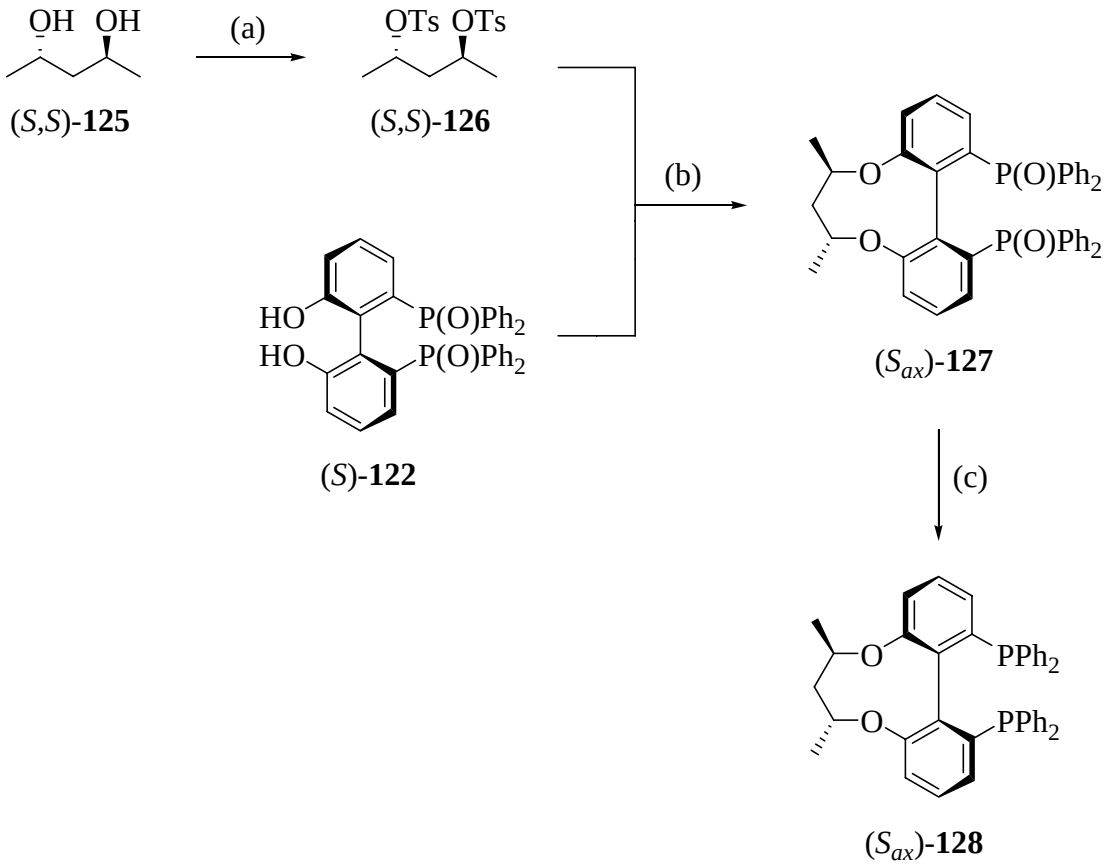


Scheme 2-3 Ring closure route of (*S*)-[6,6'-(2*S*,3*S*-butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **124**

(a) Cs_2CO_3, DMF, 60°C, 48 h, 58%; (b) $HSiCl_3$, *n*-Bu_3N, toluene, reflux, 95%.

2.2 Synthesis of (*S*)-[6,6'-(2*R*,4*R*-Pentadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 128 via Ring Closure Route

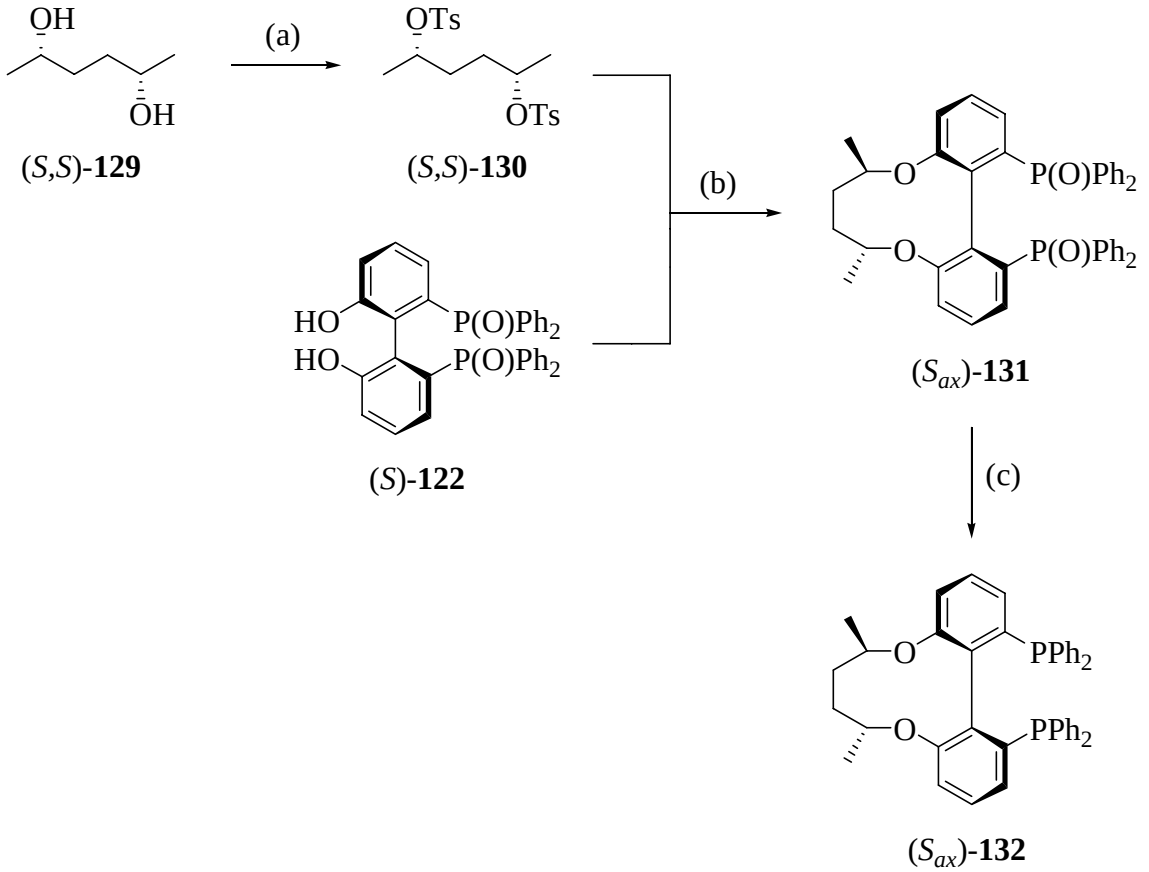
(2*S*,4*S*)-Pentanediol **125** reacted with *p*-toluenesulfonyl chloride in the presence of triethylamine in dichloromethane yielded (2*S*,4*S*)-pentanediol ditosylate **126** with 80% yield. The ring closure reaction of (*S*)-HO-BIPHEPO **122** and ditosylate **126** produced the (S_{ax})-form **127** with 72% yield. (S_{ax})-**127** was reduced with trichlorosilane in toluene in the presence of tributylamine to give diphosphine **128** with 93% yield.



Scheme 2-4 Ring closure route of (*S*)-[6,6'-(2*R*,4*R*-pentadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **128**

(a) TsCl, Et_3N, CH_2Cl_2, 0°C – rt, 80%; (b) K_2CO_3, DMF, 55°C, 72 h, 72%; (c) $HSiCl_3$, *n*-Bu_3N, toluene, reflux, 93%.

2.3 Synthesis of (*S*)-[6,6'-(2*R*,5*R*-Hexadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl via Ring Closure Route



Scheme 2-5 Ring closure route of (*S*)-[6,6'-(2*R*,5*R*-hexadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **132**

(a) TsCl, pyridine, 0°C – rt, 72%; (b) K_2CO_3, DMF, 55°C, 72 h, 68%; (c) $HSiCl_3$, *n*-Bu_3N, toluene, reflux, 97%.

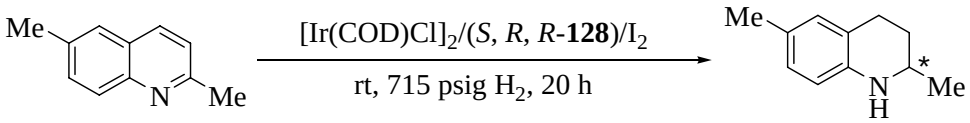
(2*S*,5*S*)-Hexanediol **129** reacted with *p*-toluenesulfonyl chloride in pyridine and yielded (2*S*,5*S*)-hexanediol ditosylate **130** with 72% yield. The ring closure reaction of (*S*)-HO-BIPHEPO **122** and ditosylate **130** produced the (S_{ax})-form **131** with 68% yield. (S_{ax})-**131** was reduced with trichlorosilane in toluene in the presence of tributylamine gave diphosphine **132** with 97% yield.

2.4 Applications of the Ligands in Asymmetric Hydrogenation

2.4.1 Iridium-Catalyzed Asymmetric Hydrogenation of Quinolines

The developed ligands, (*R*,*S*,*S*)-**117**, (*S*,*S*,*S*)-**124**, (*S*,*R*,*R*)-**128** and (*S*,*R*,*R*)-**132** were examined in the Ir-catalyzed asymmetric hydrogenation of quinolines using $[Ir(COD)Cl]_2$/L/I_2 catalyst system. 2,6-dimethylquinoline was chosen as the model substrate and the ligand (*S*,*R*,*R*)-**128** was chosen as the model ligand. The catalyst was generated in situ from $[Ir(COD)Cl]_2$ and (*S*,*R*,*R*)-**128** with I_2 as additive and the hydrogenation was carried out under the reaction conditions previously developed by Zhou [129] as mentioned in Chapter 1. Some solvents were screened and the results were listed in Table 2-1. Toluene was found to the best choice of solvent.

Table 2-1 Effect of solvent on the asymmetric hydrogenation of 2,6-dimethylquinoline catalyzed by $[Ir(COD)Cl]_2$/(*S*,*R*,*R*)-**128**



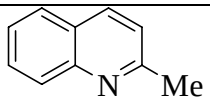
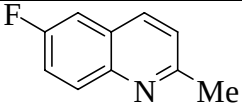
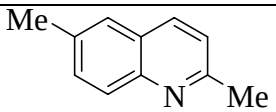
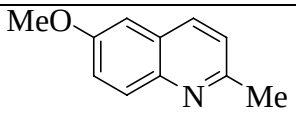
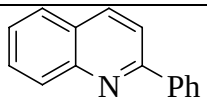
Entry	Solvent	% ee (config.)
1	Toluene	92 (*S*)
2	CH_2Cl_2	80 (*S*)
3	THF	84 (*S*)
4	*i*-PrOH	58 (*S*)

Reaction conditions: 0.2 mmol substrate, S/C = 100 (mol/mol), substrate concentration = 0.2 mmol/ml, P = 715 psig H_2, reaction time = 20 h and the conversions were greater than 99% in all cases. The ee values were determined by chiral HPLC.

A series of substituted quinoline derivatives were hydrogenated using Ir/L/I_2 catalyst in toluene and the results were listed in Table 2-2. The enantioselectivities of the

corresponding tetrahydroquinolines with ligands (*R*,*S*,*S*)-**117**, (*S*,*S*,*S*)-**124**, (*S*,*R*,*R*)-**128** and (*S*,*R*,*R*)-**132** for all studied substrates compared favorably with those obtained using (*S*)-MeO-BIPHEP **5a** under otherwise identical conditions. It is of high interest to note that the enantioselectivities were related to the dihedral angles. For the asymmetric hydrogenation of 2-phenylquinoline (entry 5 of Table 2-2), ligand (*S*,*R*,*R*)-**128** gave the best result, 70% ee which was similar to that of MeO-BIPHEP **5a**. Further increasing or decreasing the dihedral angle decreased the enantioselectivities. As a result, ligand (*S*,*R*,*R*)-**128** was found to be the best choice of ligands for the asymmetric hydrogenation of substituted quinoline derivatives.

Table 2-2 Asymmetric hydrogenation of substituted quinolines

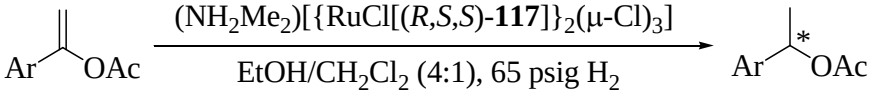
		% ee (config.)				
Entry	Substrate	(*R*,*S*,*S*)-**117**	(*S*,*S*,*S*)-**124**	(*S*,*R*,*R*)-**128**	(*S*,*R*,*R*)-**132**	(*S*)-MeO-BIPHEP **5a**
1		82 (*R*)	88 (*S*)	89 (*S*)	79 (*S*)	83 (*S*)
2		89 (*R*)	92 (*S*)	93 (*S*)	92 (*S*)	94 (*S*)
3		85 (*R*)	88 (*S*)	92 (*S*)	91 (*S*)	90 (*S*)
4		77 (*R*)	81 (*S*)	89 (*S*)	84 (*S*)	88 (*S*)
5		53 (*S*)	61 (*R*)	70 (*R*)	64 (*R*)	72 (*R*)
Calculated Dihedral Angles		-66.5°	64.8°	80°	88.8°	83.2°

Reaction conditions: 0.2 mmol substrate, S/C = 100 (mol/mol), substrate concentration = 0.2 mmol/ml, toluene, P = 715 psig H_2, reaction time = 20 h and the conversions were greater than 99.9% in all cases. The ee values were determined by chiral HPLC.

2.4.2 Ruthenium-Catalyzed Asymmetric Hydrogenation of Enol Acetates

Asymmetric hydrogenation of enol acetates is an alternative method for obtaining chiral alcohols other than asymmetric hydrogenation of unfunctionalized, simple ketones. These researches are mainly focused on the rhodium-catalyzed asymmetric hydrogenation. There are only a few reports utilizing Ru-phosphine catalyst system as mentioned in Chapter 1. Ligand (*R*,*S*,*S*)-**117** was also examined in the ruthenium-catalyzed asymmetric hydrogenation of enol acetates using $(NH_2Me_2)[\{RuCl[(R,S,S)\text{-}\mathbf{117}]\}_2(\mu\text{-}Cl)_3]$. Ligand (*R*,*S*,*S*)-**117** gave similar enantioselectivities to TunaPhos **28** for electron deficient substances such as Ar = *p*-F-C_6H_4, *p*-Cl-C_6H_4 and 2-naphthyl. (Entry 2, 3 and 5) However, Ru-(*R*,*S*,*S*)-**117** could catalyze the hydrogenation of relatively electron-rich substrates, Ar = Ph and *p*-MeO-C_6H_4 (entry 1 and 4) while Ru-TunaPhos gave no reaction.

Table 2-3 Asymmetric hydrogenation of enol acetates catalyzed by $((NH_2Me_2)[\{RuCl[(R,S,S\text{-}\mathbf{117})]\}_2(\mu\text{-}Cl)_3]$



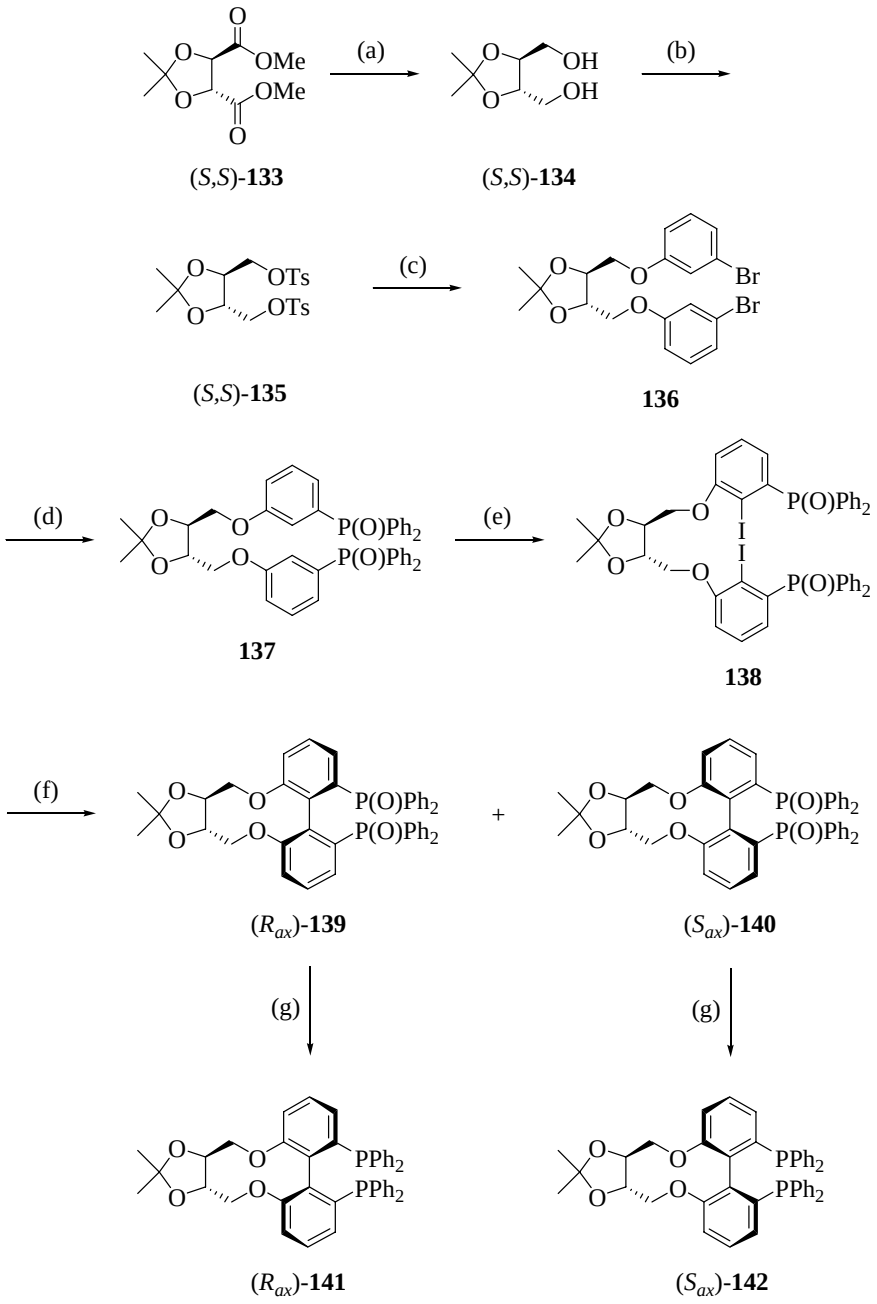
Entry	Ar	Temp / °C	Time / h	Conversion / %	% ee (config.)
1	Ph	50	96	75	94.9 (*R*)
2	*p*-F-C_6H_4	rt	12	>99	97.1 (*R*)
3	*p*-Cl-C_6H_4	rt	14	>99	96.5 (*R*)
4	*p*-MeO-C_6H_4	50	48	>99	92.6 (*R*)
5	Naphthyl	rt	12	>99	96.7 (*R*)

Reaction conditions: 0.1 mmol substrate, S/C = 100 (mol/mol), substrate concentration = 0.08 mmol/ml, $EtOH/CH_2Cl_2$ (4:1), P = 65 psig H_2. Conversions of the substrates and

enantiomeric excesses of the products were determined by chiral GC with a Varian 25 m × 0.25 mm CPCYCLODEX B 236M column.

2.5 Synthesis of (*R*) or (*S*)-[6,6'-(4*S*,5*S*-2,2-Dimethyl-1,3-dioxolane-4,5-dimethoxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl via Asymmetric Ullmann Coupling

Dimethyl-2,3-isopropylidene-*L*-tartrate **133** was reduced with LAH in ether to give crude diol **134** with 45% yield. Crude diol **134** reacted with *p*-toluene sulfonyl chloride in pyridine to give ditosylate **135** with 50% yield. Ditosylate **135** reacted with 3-bromophenol **112** in DMSO in the presence of potassium carbonate to yield chiral bromoether **136** with 83% yield. Lithiation of chiral bromoether **136** with *n*-butyllithium and quenching with chlorodiphenylphosphine gave phosphine, which was oxidized with H_2O_2 to give phosphine oxide **137** with 64% yield for the two steps. Then *ortho*-lithiation with lithium diisopropylamide followed by quenching with iodine gave diioide **138** with 34% yield. Finally an intramolecular Ullmann coupling of diioide **138** gave two atropdiastereomers **139** and **140** with ratio of about 1 to 1 and they were separated by chiral HPLC column, Daicel AD-H. The molecular structure of **140** in (S_{ax})-form was confirmed by single-crystal X-ray diffraction (Appendix II). They were reduced with trichlorosilane in toluene in the presence of tributylamine to give diphosphine **141** and **142** respectively. Triethylamine was also tried for the reduction under the same condition but only one phosphine oxide group was reduced.



Scheme 2-6 Asymmetric Ullmann coupling route of (*R*) or (*S*)-[6,6'-(4*S*,5*S*-2,2-Dimethyl-1,3-dioxolane-4,5-dimethoxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl

(a) LAH, ether, 0°C – rt, 45% yield; (b) TsCl, pyridine, 0°C – rt, 50%; (c) K_2CO_3, DMSO, 55°C, 90%; (d) i. *n*-BuLi, THF, -78°C; ii. Ph_2PCl, -78°C – rt; iii. H_2O_2, acetone, 0°C, 83% from **136**; (e) i. LDA, THF, -78°C; ii. I_2, -78°C – rt, 57%; (f) Cu, DMF, 140°C, 12 h, **139**:**140** = 1:1, 65% yield; (h) $HSiCl_3$, *n*-Bu_3N, toluene, reflux.

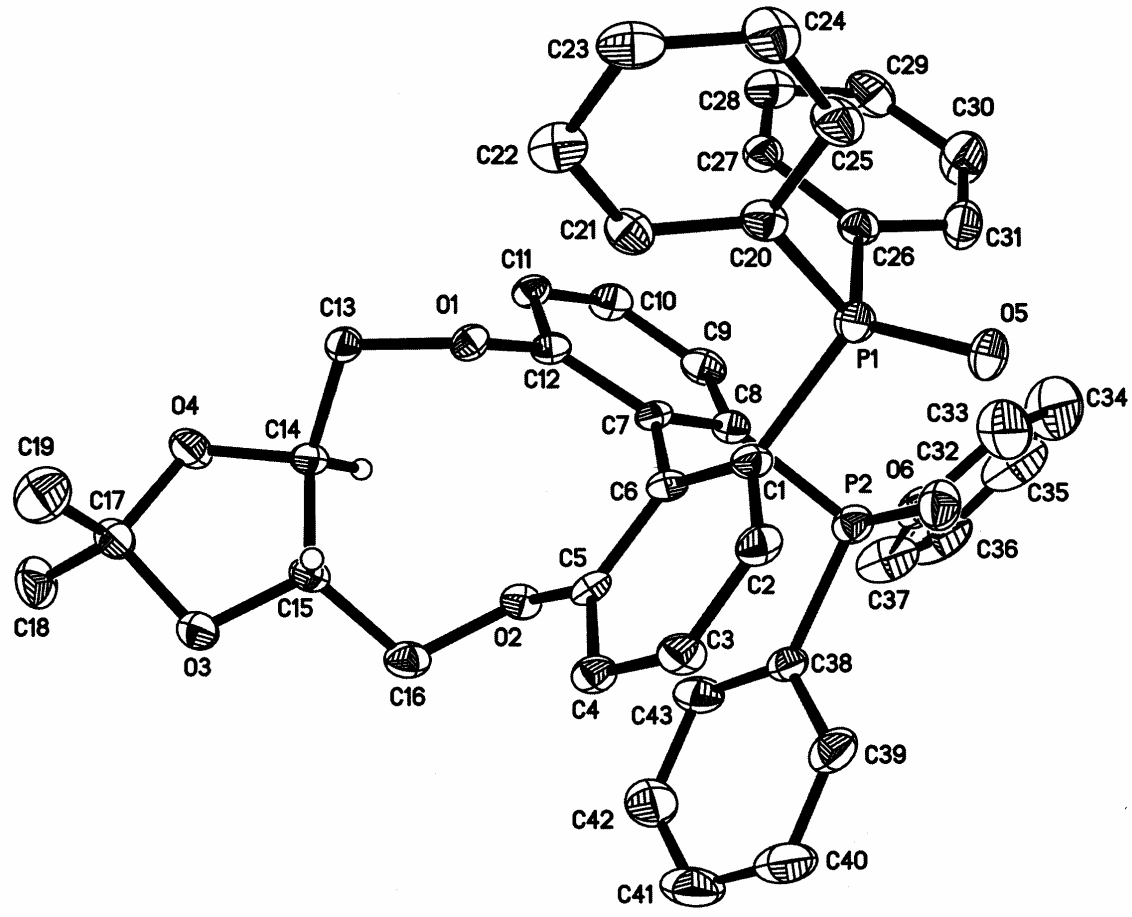


Figure 2-1 The ORTEP drawing of (S_{ax})-**140**

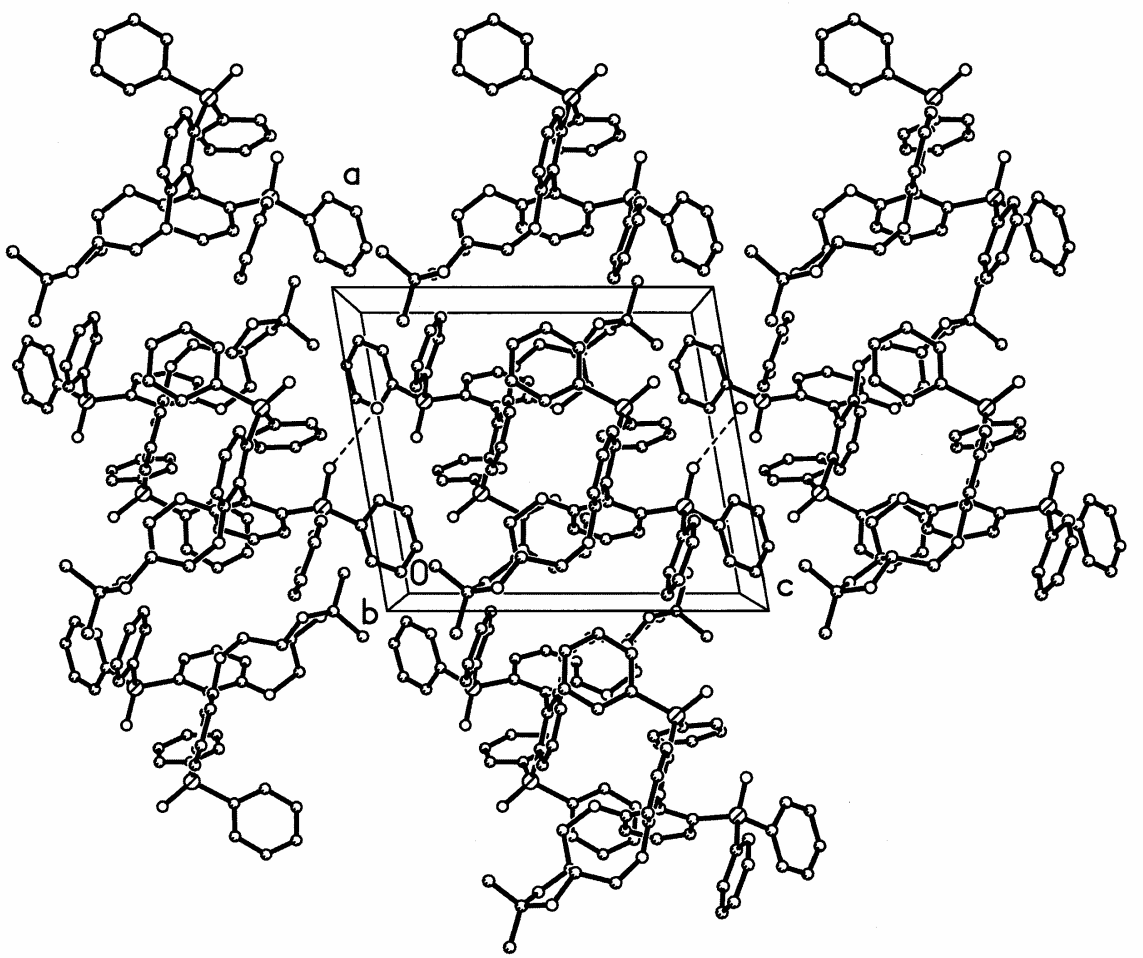


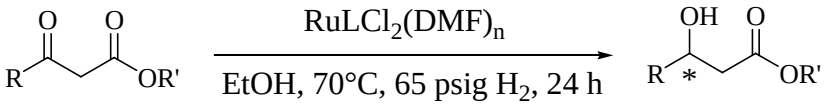
Figure 2-2 The packing of (S_{ax})-**140**, C_{43} H_{40} O_7 P_2 in the crystal along the *a* direction

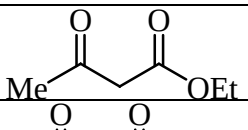
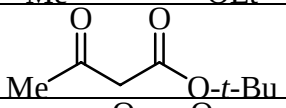
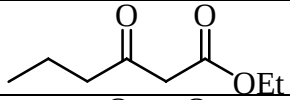
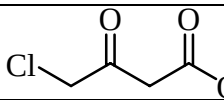
2.6 Applications of the Ligands in Asymmetric Hydrogenation

2.6.1 Ruthenium-Catalyzed Asymmetric Hydrogenation of β-Ketoesters

The asymmetric hydrogenation of β-ketoesters with diphosphine ligands has been used for the synthesis of a wide variety of natural chiral compounds. The asymmetric hydrogenation of β-ketoesters was chosen for the first model reaction. The $RuLCl_2(DMF)_n$ catalysts [L= (R_{ax})-**141** or (S_{ax})-**142**] were prepared *in situ* according to literature procedure [114]. The results of asymmetric hydrogenation of β-ketoesters were listed in Table 2-4. The enantioselectivities of the products, hydroxylesters were also very high and compared favorably with the Ru[(*S*)-BINAP]$Cl_2(DMF)_n$ and Ru[(*S*)-MeO-BIPHEP]$Cl_2(DMF)_n$ system. However, (R_{ax})-**141** and (S_{ax})-**142** gave the same ee with opposite configurations. The configurations of the corresponding products, hydroxylesters were controlled by the axial chirality of the ligands.

Table 2-4 Asymmetric hydrogenation of β-ketoesters catalyzed by $RuLCl_2(DMF)_n$



Entry	Substrate	(R_{ax})-**141**	(S_{ax})-**142**	(*S*)-BINAP **3a**	(*S*)-MeO-BIPHEP **5a**
1		97 (*R*)	98 (*S*)	98 (*S*)	98 (*S*)
2		>99	>99		
3		>99	>99		
4		91 (*S*)	91 (*R*)	94 (*R*)	92 (*R*)

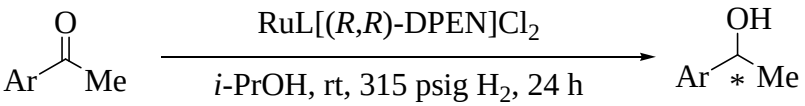
Reaction conditions: 0.25 mmol substrate, S/C = 667 (mol/mol), solvents = 6.3 μl CH_2Cl_2 + 493.7 μl EtOH, 70°C, P = 65 psig H_2, reaction time = 24 h, and the conversions were greater than 99% in all cases. The ee values were determined by chiral GC with a WCOT fused silica CP Chirasil-DEX CB column (25 m × 0.25 mm) after converting the products to the corresponding acetyl derivatives.

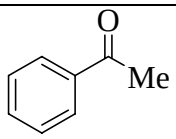
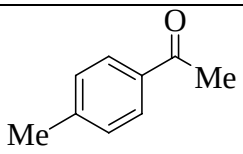
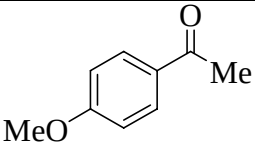
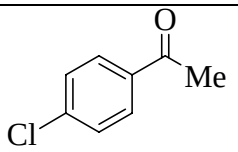
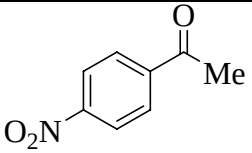
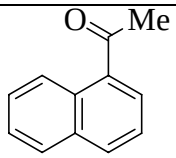
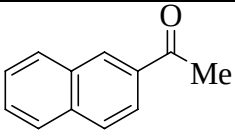
2.6.2 Ruthenium-Catalyzed Asymmetric Hydrogenation of Unfunctionalized, Simple Ketones

The asymmetric hydrogenation of unfunctionalized, simple ketones was chosen for the second model reaction. The $RuLCl_2(DMF)_n$ catalyst solution [L= (R_{ax})-**141** or (S_{ax})-**142**] was prepared *in situ* according to literature procedure [114] and treatment of the resulting catalyst solution with 1 equivalent of (*R*,*R*)-DPEN at rt gave Ru[(*R*,*R*)-DPEN]Cl_2. The results of asymmetric hydrogenation of ketones were listed in Table 2-5. (R_{ax})-**141** and (S_{ax})-**142** were found to give the same activity and enantioselectivity in the asymmetric hydrogenation of β-ketoesters as mentioned in the previous section. However, they behaved differently in the asymmetric hydrogenation of ketones as different conversion and enantioselectivity were obtained by the corresponding Ru[(*R*,*R*)-DPEN]Cl_2 catalysts. The hydrogenation of acetophenone with S/C = 2000 under 300 psi hydrogen pressure at rt in 2-propanol containing Ru[(R_{ax})-**141**][(*R*,*R*)-DPEN]Cl_2 and *t*-BuOK gave 97% conversion and 75% ee. Ru[(S_{ax})-**142**][(*R*,*R*)-DPEN]Cl_2 gave >99% conversion with only 24% ee under otherwise identical conditions (entry 1 of Table 2-5). The enantioselectivities of the alcohols obtained by Ru[(R_{ax})-**141**][(*R*,*R*)-DPEN]Cl_2 were also higher than those of Ru[(S_{ax})-**142**][(*R*,*R*)-DPEN]Cl_2 for other ketones (entry 2-4, 7 of Table 2-5). The selectivity of the Ru-catalyzed asymmetric hydrogenation of ketones replied on the synergistic effects of the chiral diphosphine and diamine ligands. As a result, (R_{ax})-**141**/(*R*,*R*)-DPEN was the match pair while (S_{ax})-**142**/(*R*,*R*)-DPEN was the mismatch pair. However, both Ru[(R_{ax})-**141**][(*R*,*R*)-DPEN]Cl_2 and Ru[(S_{ax})-**142**][(*R*,*R*)-DPEN]Cl_2 gave no conversion for *p*-nitroacetophenone (entry 5) while Ru[(*S*)-BINAP)][(*S*)-DAIPEN]Cl_2 gave 83% ee [122b]. Similarly, both Ru[(R_{ax})-**141**][(*R*,*R*)-

DPEN]Cl_2 and Ru[(S_{ax})-**142**][(*R*,*R*)-DPEN]Cl_2 gave no conversion for 1'-acetonaphthone (entry 6) while Ru[(*S*)-BINAP][(*S*,*S*)-DPEN]Cl_2 gave >99% conversion and 97% ee [123a]. The configurations of the corresponding products, alcohols were controlled by the chirality of the diamine. Products with same configuration were obtained with Ru[(R_{ax})-**141**][(*R*,*R*)-DPEN]Cl_2 and Ru[(S_{ax})-**142**][(*R*,*R*)-DPEN]Cl_2 respectively.

Table 2-5 Asymmetric hydrogenation of ketones catalyzed by Ru(L)(DPEN)Cl_2

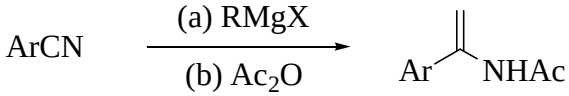


Entry	Substrate	(R_{ax})-**141**/(*R*,*R*)-DPEN		(S_{ax})-**142**/(*R*,*R*)-DPEN	
		Conversion / %	% ee (config.)	Conversion / %	% ee (config.)
1		97	75 (*S*)	>99	24 (*S*)
2		36	76 (*S*)	70	17 (*S*)
3		62	79 (*S*)	>99	11 (*S*)
4		87	59 (*S*)	60	27 (*S*)
5		No conversion	-	No conversion	-
6		No conversion	-	No conversion	-
7		97	77 (*S*)	87	18 (*S*)

Reaction conditions: 0.25 mmol of ketone, S/C = 2000, S/ *t*-BuOK = 800, *i*-PrOH, P = 315 psig H_2, reaction time = 24 h. The conversion and the ee values were determined by chiral GC with a WCOT fused silica CP Chirasil-DEX CB column (25m x 0.25 mm).

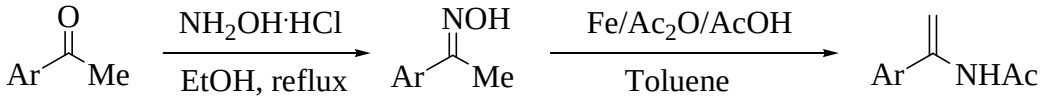
2.6.3 Rhodium-Catalyzed Asymmetric Hydrogenation of Enimide

Rhodium-catalyzed asymmetric hydrogenation of enamides has been investigated extensively as mentioned in Chapter 1. There are two methods for preparing enamides. The first one is the addition of a Grignard reagent to an aryl nitrile followed by quenching with acetic anhydride [10c, 15h, 101b]. Complex reaction mixtures were obtained with irreproducible results and low yields.



Scheme 2-7 Synthesis of enamide via the addition of Grignard reagent to nitrile

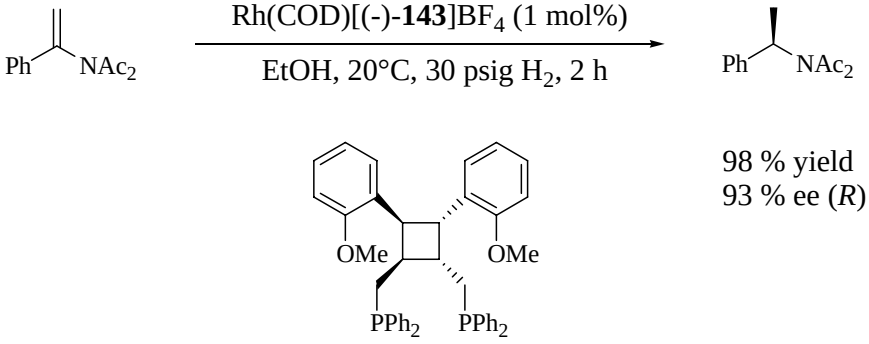
The reaction of an oxime with acetic anhydride in the presence of iron powder was the second approach for the synthesis of enamides [15m, 59b]. However, the yields of this method were low.



Scheme 2-8 Synthesis of enamide via oxime with iron and acetic anhydride

The first method gave a complex reaction mixture including enamide and enimide. The enimide can be converted to enamide by alkaline washing. After hydrogenation followed by hydrolysis, the enimides give the same amines. The enimides are other choices of substrates for the synthesis of chiral amines. In contrast to the hydrogenation of enamides, the asymmetric hydrogenation of enimide is relatively unexplored. There is only one report in the literature concerning the asymmetric hydrogenation of enimide. Hashimoto and Saigo reported the synthesis of a C_2-symmetric cyclobutane ring-diphosphine ligand, (-)-CDP **143**. Its rhodium complex catalyzed the asymmetric

hydrogenation of enimide and the corresponding diacetylamine was obtained with 93% ee [144].



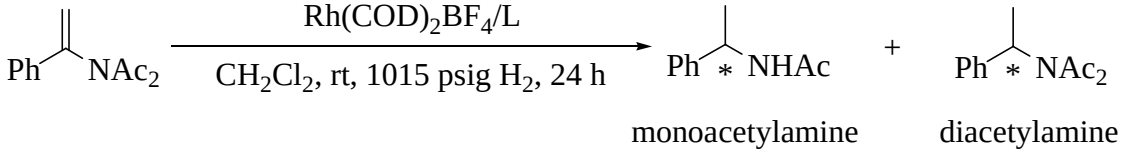
(-)-CDP **143**

Scheme 2-9 Asymmetric hydrogenation of enimide catalyzed by Rh/(-)-CDP complex

The asymmetric hydrogenation of enimide was chosen for the third model reaction. The catalyst was generated in situ from $Rh(COD)_2BF_4$ and a selected ligand and the hydrogenation was carried out in CH_2Cl_2 under 1015 psig of H_2 for 24 h. Some ligands were screened and the results were listed in Table 2-6. The asymmetric hydrogenation of enimide gave two products, monoacetylamine and diacetylamine. These ligands gave greater than 99% conversion except for P-Phos **38a**, MeO-BIPHEP **5a**, difluorophos **32** and MonoPhos **90a**. The enantioselectivities of monacetylamine and diacetylamine products were low. (*R*)-Xyl-P-Phos **38c** gave the best result: 99.8% conversion and 69% ee. Both (R_{ax})-**141** and (S_{ax})-**142** gave higher enantioselectivity than MeO-BIPHEP. (R_{ax})-**141** gave 89% conversion and 27% ee while (S_{ax})-**142** gave >99.9 conversion and 37% ee.

By using (S_{ax})-**142**, the effect of pressure was investigated. The e.e.'s of monoacetylamine increased slightly as the pressure decreased from 1815 psig to 515 psig. Further decrease in pressure reduced the conversion and ee. 515 psig was found to be the optimal pressure.

Table 2-6 Asymmetric hydrogenation of enimide catalyzed by different ligands



Ligand	Conversion / %	monoacetylamine (% ee)	diacetylamine (% ee)	Ratio of monoacetylamine: diacetylamine
(*R*)-BINAP **3a**	99.5	39	-	98:2
(*R*)-Tol-BINAP **3b**	99.8	42	-	97:3
(*S*)-MeO-BIPHEP **5a**	95.3	0	-	96:4
(*R*)-Cl-MeO-BIPHEP **24**	99.3	2	-	98:2
(*R*)-BisbenzodioxanePhos **30**	99.7	17	-	98:2
(*R*)-Difluorophos **32**	47	61	-	94:6
(*R*)-P-Phos **38a**	88	54	-	97.5:2.5
(*R*)-Xyl-P-Phos **38c**	99.8	69	-	97.5:2.5
(R_{ax})-**141**	89	27	-	91:9
(S_{ax})-**142**	>99.9	37	-	97:3
(*R*)-(*S*)-JosiPhos **53a**	>99.9	21	-	94:6
Et-FerroTANE **58**	>99.9	48	65	50:50
(*R*,*R*)-DIOP **1**	>99.9	17	20	33:67
(*R*)-MonoPhos **90a**	55	69	36	25:75

Reaction conditions: 0.05 mmol substrate, S/C = 100 (mol/mol), CH_2Cl_2, P = 1015 psig H_2, reaction time = 24 h; the conversion and the ee values were determined by chiral GC with a WCOT fused silica CP Chirasil-DEX CB column (25 m × 0.25 mm)

Table 2-7 Effect of pressure on asymmetric hydrogenation of enimide catalyzed by (S_{ax})-**142**

Pressure / psig	Conversion / %	monoacetylamine (% ee)	diacetylamine (% ee)	Ratio of monoacetylamine: diacetylamine
1815	99.7	36	-	95:5
1515	99.9	37	-	96:4
1015	99.9	37	-	96.5:3.5
515	99.9	38	-	96.5:3.5
215	92	34	-	94:6
115	96	35	-	97:3

Reaction conditions: 0.025 mmol substrate, S/C = 100 (mol/mol), CH_2Cl_2, reaction time = 24 h; the conversion and the ee values were determined by chiral GC with a WCOT fused silica CP Chirasil-DEX CB column (25 m × 0.25 mm)

Different solvents were screened under 515 psig of H_2. These solvents gave low conversion and a mixture of monoacetylamine and diacetylamine products. Dichloromethane and TFE gave 99.9 % conversion with very high ratio of monoacetylamine to diacetylamine.

However, both the conversion and the ee decreased with the addition of triethylamine for the four solvents screened. The enantioselectivity decreased while the ratio of monoacetylamine to diacetylamine increased for TFE.

Table 2-8 Effect of solvent on asymmetric hydrogenation of enimide catalyzed by (S_{ax})-**142**

Solvent	Conversion / %	monoacetylamine (% ee)	diacetylamine (% ee)	Ratio of monoacetylamine: diacetylamine
MeOH	56	30	5	57:43
EtOH	72	34	12	70:30
i-PrOH	42	35	2	71:29
CH_2Cl_2	99.9	38	-	96.5:3.5
Toluene	22	33	11	54:46
THF	67	46	2	66:34
Ether	22	43	6	42:58
TFE	>99.9	17	-	97:3
EA	22	28	5	37:63
Dioxane	20	18	8	31:69
n-Hexane	28	44	8	40:60

Reaction conditions: 0.025 mmol substrate, S/C = 100 (mol/mol), P = 515 psig H_2, reaction time = 24 h; the conversion and the ee values were determined by chiral GC with a WCOT fused silica CP Chirasil-DEX CB column (25 m × 0.25 mm)

Table 2-9 Effect of addition of triethylamine on asymmetric hydrogenation of enimide catalyzed by (S_{ax})-**142**

Solvent	Conversion / %	monoacetylamine (% ee)	diacetylamine (% ee)	Ratio of monoacetylamine: diacetylamine
EtOH	17	3	13	35:65
CH_2Cl_2	13	2	7	27:73
Toluene	11	6	15	25:75
TFE	99.8	11	-	99.7:0.3

Reaction conditions: 0.025 mmol substrate, S/C = 100 (mol/mol), triethylamine (5μl), P = 515 psig H_2, reaction time = 24 h; the conversion and the ee values were determined by chiral GC with a WCOT fused silica CP Chirasil-DEX CB column (25 m × 0.25 mm)

2.7 Conclusion

A C_2-symmetric biphenyl diphosphine ligand (*R*)-[6,6'-(*2S*,*3S*-butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **117** was synthesized via asymmetric intramolecular Ullmann coupling with complete atropdiastereoselectivity. Its diastereoisomer, (*S*)-[6,6'-(*2S*,*3S*-butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **124** could only be synthesized via ring closure process. Another two diphosphine ligands (*S*)-[6,6'-(*2R*,*4R*-pentadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **128** and (*S*)-[6,6'-(*2R*,*5R*-hexadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **132** were also synthesized via ring closure process. These four ligands were found to be highly efficient in the asymmetric hydrogenation of quinolines and compared well with MeO-BIPHEP **5a**. The configuration of the product was controlled by the axial chirality rather than the additional central chirality.

Another kind of novel C_2-symmetric biphenyl diphosphine ligand, [6,6'-(*4S*,*5S*-2,2-dimethyl-1,3-dioxolane-4,5-dimethoxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **141** and **142** were synthesized via asymmetric Ullmann coupling without atropdiastereoselectivity. Rhodium catalysts containing these ligands were more effective than MeO-BIPHEP **5a** catalytic systems in the asymmetric hydrogenation of enimide under otherwise identical conditions. Ruthenium catalysts containing these ligands showed similiar results to BINAP **3a** and MeO-BIPHEP **5a**. The configuration of product was also controlled by the axial chirality rather than the additional central chirality.

CHAPTER THREE

EXPERIMENTAL SECTION

3.1 General Information

All reactions were carried out under an atmosphere of nitrogen. Glassware was oven dried before use. THF and toluene were freshly distilled from sodium/benzophenone ketyl. CH_2Cl_2, hexane and DMF were distilled from CaH_2 under nitrogen. DMSO was dried over CaH_2 and was used directly without distillation. MeOH and EtOH were distilled from magnesium under nitrogen. Reaction products were purified by column chromatography using NA silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on silica gel 60-F plates and the plates were visualized under UV light. Analytical gas chromatography (GC) of the crude reaction products was performed on a HP 5890 series II GC with an FID detector. All chemicals were purchased from Aldrich, Acros, Strem or Fluka and were used as received without further purification. Optical rotations were measured on a Perkin-Elmer 341 polarimeter with a sodium lamp in 10 cm cell. ^{1}H NMR spectra were recorded on a Varian 500 (500 MHz) spectrometer and the chemicals shifts are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Proton-decoupled ^{13}C NMR spectra were recorded on a Varian 500 (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77 ppm). ^{31}P NMR spectra were recorded on a Varian 500 (202 MHz) spectrometer and the chemicals shifts are reported in ppm using 85% H_3PO_4 as an external standard (H_3PO_4 at 0 ppm).

3.2 Synthesis of (*R*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 117 via Asymmetric Intramolecular Ullmann Coupling

3.2.1 Synthesis of (2*R*,3*R*)-butanediol dimesylate 111

To an ice-cooled solution of (2*R*,3*R*)-butanediol **110** (3.0 g, 33.3 mmol) in 30 ml pyridine under N_2 was added a solution of methanesulfonyl chloride (14.20 g, 74.5 mmol) in 30 ml of pyridine over an hour and the reaction mixture was stirred at 0 °C for 2 hours. After stirring at room temperature for overnight, the reaction mixture was poured into ice-water (500 ml) with vigorous stirring. The solid was filtered and washed with 500 ml of cold water. Colorless crystals **111** (7.53 g, 31 mmol, 92% yield) were obtained after recrystallization from acetone.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45-1.46 (d, J = 6.5 Hz, 6H), 3.07 (s, 6H), 4.74- 4.80 (m, 2H);

^{13}C NMR (125 MHz, $CDCl_3$): δ 17.25, 38.79, 78.66;

MS (ESI): calcd for $C_6H_{14}S_2O_6$ $[M]^+$ 246.3, found 247; HRMS (ESI): calcd for $C_6H_{14}S_2O_6$ $[M+Na]^+$ 269.0129, found 269.0187; calcd for $C_6H_{14}S_2O_6$ $[M+H]^+$ 247.0310, found 247.0372;

$[\alpha]^{20}_D$ = 1.3 ° (c = 1, $CHCl_3$).

3.2.2 Synthesis of (2*S*,3*S*)-2, 3-bis(3-bromophenoxy) butane 113

A suspenson of 3-bromophenol **112** (0.75g, 4.3 mmol) and Cs_2CO_3 (2.8 g 8.6 mmol) in 5 ml of DMSO was stirred at room temperature for an hour. Then a solution of (2*R*,3*R*)-butanediol dimesylate **111** in 10 ml of DMSO was added dropwise into the reaction mixture over 4 hours. The reaction mixture was stirred at 55°C for 8 hours. Water (100

ml) was then added and the reaction mixture was extracted with CH_2Cl_2. The combined extract was washed with 2 N HCl solution (10 ml), water and brine. The extract was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a colorless oil **113** (0.461 g, 1.15 mmol, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.0 Hz, 6H), 4.47–4.53 (m, 2H), 6.83-6.86 (m, 2H) and 7.08–7.16 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.27, 76.34, 115.11, 119.62, 123.07, 124.46, 130.88 and 159.00.

HRMS (EI + VE + LMR): calcd for $C_{16}H_{16}Br_2O_2$ $[M]^+$ 397.9517, found 397.9529.

$[\alpha]^{20}_D$ = –22.6 ° (c = 1, $CHCl_3$).

3.2.3 Synthesis of (2*S*,3*S*)-2, 3-bis[3-(diphenylphosphoryl)phenoxy]butane 114

To a solution of (2*S*,3*S*)-2,3-bis(3-bromophenoxy) butane **113** (1.8g, 4.5 mmol) in 100 ml THF at -78°C was added *n*-BuLi (9.45 mmol, 1.6 M solution in hexane) dropwise within 30 min. The reaction mixture was stirred at -78°C for an hour and then chlorodiphenylphosphine (1.8 ml, 9.45 mmol) in 5 ml THF was added dropwise to the reaction mixture. The reaction mixture was stirred at -78°C for an hour. After stirring at room temperature for overnight, water was added and the reaction mixture was extracted with CH_2Cl_2. The combined extract was washed with water and brine, then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a colorless oily solid. The solid was dissolved in 20 ml acetone and an aqueous H_2O_2 solution (30%, 6 ml) was added at 0°C. The reaction mixture was stirred at room temperature for overnight. The reaction mixture extracted with CH_2Cl_2

and the combined extract was washed with $Na_2S_2O_3$ solution, water and brine. The extract was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a colorless solid **114** (2.46 g, 3.83 mmol, 85% yield based on **113**).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 5.5 Hz, 6H), 4.45-4.51 (m, 2H), 6.97–7.00 (m, 2H), 7.06–7.11 (dd, *J* = 11.8 Hz, 7.8 Hz, 2H), 7.25–7.29 (m, 4H), 7.39–7.44 (m, 8H), 7.48-7.52 (m, 4H) and 7.61–7.65 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.06, 76.03, 118.78, 118.87, 119.83, 119.85, 124.44, 124.52, 128.34, 128.44, 129.56, 129.68, 131.85, 131.88, 131.96, 132.66, 133.30, 134.12, 157.87 and 157.99.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.39.

HRMS (ESI): calcd for $C_{40}H_{37}P_2O_4$ $[M + H]^+$ 643.2169, found 643.2119.

$[\alpha]^{20}_D$ = –19.6 ° (c = 1, $CHCl_3$).

3.2.4 Synthesis of (2*S*,3*S*)-2,3-bis[2-iodo-3-(diphenylphosphoryl)phenoxy]butane 115

To a solution of (2*S*,3*S*)-2,3-bis[3-(diphenylphosphoryl)phenoxy]butane **114** (1 g, 1.56 mmol) in 40 ml THF at -78°C was added a solution of LDA (1.7 ml, 2 M) dropwise over 30 minutes and the reaction mixture was stirred at -78°C for 3 hours. Then the reaction mixture was cannulated into a flask containing iodine (1.584 g, 6.24 mmol) in 40 ml THF at -78°C over 30 minutes. After stirring at room temperature overnight, the reaction mixture was concentrated in vacuo and the residue was dissolved in 50 ml of CH_2Cl_2. The CH_2Cl_2 extract was washed with NH_4Cl solution, water, saturated $Na_2S_2O_3$ solution. The extract was then dried over Na_2SO_4 and concentrated in vacuo. The crude product

was purified by chromatography on silica gel to afford a solid **115** (1.185 g, 1.33 mmol, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 6.0 Hz, 6H), 4.67–4.73 (m, 2H), 6.68–6.73 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.19–7.23 (m, 2H), 7.43–7.49 (m, 8H), 7.52–7.57 (m, 4H) and 7.65–7.71 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.70, 77.49, 94.47, 94.53, 117.21, 117.23, 128.49, 128.59, 128.77, 128.88, 128.97, 131.13, 131.15, 131.83, 131.85, 131.98, 132.00, 132.13, 132.16, 132.20, 132.24, 137.37, 138.21, 157.29 and 157.39.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 35.09.

HRMS (ESI): calcd for $C_{40}H_{35}I_2P_2O_4$ $[M + H]^+$ 895.0101, found 895.0002.

$[\alpha]^{20}_D$ = +54.8 ° (c = 1, $CHCl_3$).

3.2.5 Synthesis of (*R*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl 116

A suspenson of (2*S*,3*S*)-2,3-bis[2-iodo-3-(diphenylphosphoryl)phenoxy]butane **115** and copper (0.62 g, 0.693 mmol) in 5 ml of DMF was stirred at 140 °C for 12 hours. The reaction mixture was concentrated in vacuo. The residue was washed with hot chloroform (10ml x 3) and filtered. The combined filtrate was washed with NH_4Cl solution and brine. The filtrate was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a white solid **116** (406 mg, 0.634 mmol, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.0 Hz, 6H), 3.65–3.71 (m, 2H), 6.85 (d, *J* = 7.5 Hz, 2H), 6.93–6.97 (m, 2H), 7.08–7.13 (m, 6H), 7.21–7.24 (m, 2H), 7.27–7.34 (m, 8H), 7.37–7.40 (m, 2H) and 7.63–7.67 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.97, 86.33, 123.80, 123.82, 127.16, 127.26, 127.66, 127.76, 127.79, 127.87, 129.34, 129.46, 130.20, 130.22, 130.74, 130.76, 131.97, 132.04, 132.33, 132.40, 132.92, 133.65, 133.76, 134.49, 134.72, 135.56, 158.97 and 159.08.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 28.46.

HRMS (ESI): calcd for $C_{40}H_{35}P_2O_4$ $[M + H]^+$ 641.2011, found 641.1991.

$[\alpha]^{20}_D$ = -197.4 ° (c = 1, $CHCl_3$).

3.2.6 Synthesis of (*R*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 117

A solution of (*R*)-[6,6'-(2*S*,3*S*-butadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl **116** (480 mg, 0.75 mmol), tributylamine (3.7 ml, 15.5 mmol) and trichlorosilane (1.6 ml, 15.5 mmol) in 10 ml toluene was refluxed overnight. After cooling the reaction mixture to 0°C, a 30% aqueous NaOH solution (23 ml) was added dropwise. The mixture was stirred at 60°C until the separation of organic and aqueous layer and the aqueous layer was extracted with toluene (10 ml x 3). The combined extract was washed with water and brine and dried over Na_2SO_4. After filtration, the extract was concentrated under reduced pressure to afford a light yellow solid. The light yellow solid was washed with hexane to give a white solid **117** (439 mg, 0.72 mmol, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.28 (d, *J* = 6.0 Hz, 6H), 3.71–3.78 (m, 2H), 6.80 (d, *J* = 7.5 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H) 7.01–7.04 (m, 4H), 7.13–7.19 (m, 8H), 7.35–7.38 (m, 6H) and 7.58–7.61 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.09, 86.33,122.20, 127.74, 127.76, 127.78, 128.24, 128.26, 128.96, 129.50, 133.21, 133.29, 133.38, 133.87, 133.96, 134.05, 135.08, 135.20,

135.32, 137.39, 137.42, 137.46, 138.33, 138.40, 138.46, 138.57, 138.60, 138.63, 159.69, 159.72 and 159.75.

^{31}P NMR (202 MHz, $CDCl_3$): δ = -8.42.

HRMS (ESI): calcd for $C_{40}H_{35}P_2O_2$ $[M + H]^+$ 609.2113, found 609.2089.

$[\alpha]^{20}_D$ = -341.6 ° (c = 1, toluene).

3.3 Synthesis of (*S*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 124 via Ring Closure Process

3.3.1 Synthesis of (*S*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl 123 via Ring Closure Process

A suspension of (*S*)-(6,6'-dihydroxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) **122** (0.55 g, 0.94 mmol) and Cs_2CO_3 (2.445 g, 7.51 mmol) in 50 ml of DMF was stirred at room temperature for an hour. To this reaction mixture was added a solution of (2*R*, 3*R*)-butanediol dimesylate **111** (0.925 g, 3.75 mmol) in 25 ml of DMF dropwise over 3 hours at room temperature. After stirring at 60°C for 48 hours, the reaction mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 extract was washed with water and brine. The extract was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a white solid **123** (0.346 g, 0.54 mmol, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 5.0 Hz, 6H), 3.95-4.03 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.94 (dd, *J* = 13.5 Hz, 7.0 Hz, 2H), 7.06 (dt, *J* = 7.8 Hz, 3.3 Hz, 2H), 7.19-7.22 (m, 4H), 7.29-7.44 (m, 12H) and 7.70-7.75 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.43, 78.30, 125.37, 127.44, 127.53, 127.86, 127.89, 127.95, 127.98, 128.52, 128.64, 130.58, 130.60, 130.98, 131.00, 131.86, 131.93, 132.41, 132.49, 133.31, 134.15, 135.27, 136.10, 154.98 and 155.08.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 28.69.

HRMS (ESI): calcd for $C_{40}H_{35}P_2O_4$ $[M + H]^+$ 641.2011, found 641.1973.

$[\alpha]^{20}_D$ = +134.5 ° (c = 1, $CHCl_3$).

3.3.2 Synthesis of (*S*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 124

A solution of (*S*)-[6,6'-(2*S*,3*S*-butadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl **123** (515 mg, 0.80 mmol), tributylamine (3.8 ml, 16.1 mmol) and trichlorosilane (1.7 ml, 16.1 mmol) in 10 ml toluene was refluxed overnight. After cooling the reaction mixture to 0°C, a 30% aqueous NaOH solution (24 ml) was added dropwise. The mixture was stirred at 60°C until the separation of organic and aqueous layers and the aqueous layer was extracted with toluene (10 ml x 3). The combined organic solutions was washed with water and brine and dried over Na_2SO_4. After filtration, the extract was concentrated under reduced pressure to afford a light yellow solid. The light yellow solid was washed with hexane to give a white solid **124** (489 mg, 0.72 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.5 Hz, 6H), 3.92-3.99 (m, 2H), 6.28 (d, *J* = 8.5 Hz, 2H), 6.73-6.76 (m, 2H) 7.05-7.09 (m, 6H), 7.16-7.26 (m, 6H), 7.32-7.37 (m, 6H) and 7.49-7.53 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.75, 76.93, 122.68, 127.74, 127.77, 127.80, 127.84, 128.10, 128.26, 128.29, 128.31, 128.36, 128.59, 133.07, 133.19, 133.31, 133.55, 133.63,

133.72, 134.17, 134.26, 134.35, 136.51, 136.54, 136.58, 138.17, 138.23, 138.30, 140.80, 140.82, 140.84, 154.80, 154.83 and 154.86.

^{31}P NMR (202 MHz, $CDCl_3$): δ = -6.58.

HRMS (ESI): calcd for $C_{40}H_{35}P_2O_2$ $[M + H]^+$ 609.2113, found 609.2087.

$[\alpha]^{20}_D$ = +351.5 ° (c = 1, toluene).

3.4 Synthesis of (*S*)-[6,6'-(2*R*,4*R*-Pentadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 128 via Ring Closure Route

3.4.1 Synthesis of (2*S*,4*S*)-pentanediol ditosylate 126

To an ice-cooled solution of (2*S*,4*S*)-pentanediol **125** and triethylamine(14 ml, 101 mmol) in 50 ml of CH_2Cl_2 was added a solution of *p*-toluenesulfonyl chloride (19.3 g, 101.0 mmol) in 50 mL of CH_2Cl_2 over 4 hours and the reaction mixture was stirred at 0 °C for 2 hours. After stirring at room temperature for overnight, the reaction mixture was concentrated in vacuo. Colorless crystals **126** (15.88 g, 39 mmol, 80% yield) were obtained after recrystallization from methanol.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.5 Hz, 6H), 2.01 (t, J = 7.3 Hz, 2H), 4.49-4.56 (m, 2H) and 6.84-6.90 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.49, 45.31, 75.48, 120.62, 122.32, 149.40.

MS (EI): $[M]^+$ 178.1; HRMS (EI+VE+LMR): calcd for $C_{17}H_{18}Br_2O_2$ $[M]^+$ 178.0994, found 178.1030.

calcd for $C_{17}H_{18}Br_2O_2$: C, 74.13; H, 7.92; found: C, 74.06; H, 8.04;

$[\alpha]^{20}_D$ = +38.4 ° (c = 1, hexane).

3.4.2 Synthesis of (*S*)-[6,6'-(2*R*,4*R*-pentadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl 127

A suspension of (*S*)-(6,6'-dihydroxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) **122** (0.40 g, 0.68 mmol) and K_2CO_3 (0.51 g, 3.70 mmol) in 50 ml of DMF was stirred at room temperature for an hour. To this reaction mixture was added a solution of (2*S*, 4*S*)-pentanediol di-*p*-tosylate **126** (1.135 g, 2.75 mmol) in 30 ml of DMF dropwise over 3 hours at room temperature. After stirring at room temperature for 12 hours and then at 55°C for 72 hours, the reaction mixture was concentrated in vacuo and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 extract was washed with water and brine. The extract was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a white solid **127** (0.323 g, 0.49 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19-1.21 (d, *J* = 6 Hz, 6H), 1.64 (t, *J* = 4.0 Hz, 2H), 4.31-4.36 (m, 2H), 6.82 (d, *J* = 7.5 Hz, 2H), 6.86-6.90 (dd, *J* = 13.3 Hz, 7.8 Hz, 2H), 7.04-7.14 (m, 6H), 7.24 (t, *J* = 7.3 Hz, 2H), 7.31-7.35 (m, 8H), 7.41 (t, *J* = 7.5 Hz, 2H) and 7.65-7.69 (dd, *J* = 11.5 Hz, 7.0 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.84, 40.57, 75.52, 120.52, 120.54, 126.77, 126.86, 127.19, 127.29, 127.80, 127.89, 128.44, 128.55, 130.43, 130.45, 131.00, 132.36, 132.44, 132.54, 133.01, 133.25, 133.69, 134.11, 134.51, 134.94, 156.99 and 157.10.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 29.29.

MS (EI): $[M]^+$ 178.1; HRMS (ESI): calcd for $C_{41}H_{37}P_2O_4$ $[M+H]^+$ 655.2168, found 655.2181.

$[\alpha]^{20}_D$ = +170 ° (c = 1, $CHCl_3$).

3.4.3 Synthesis of (*S*)-[6,6'-(2*R*,4*R*-pentadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 128

A solution of (*S*)-[6,6'-(2*R*,4*R*-pentadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl **127** (mg, mmol), tributylamine (3.8 ml, 16.1 mmol) and trichlorosilane (1.7 ml, 16.1 mmol) in 10 ml toluene was refluxed overnight. After cooling the reaction mixture to 0°C, a 30% aqueous NaOH solution (24 ml) was added dropwise. The mixture was stirred at 60°C until the separation of organic and aqueous layer and the aqueous layer was extracted with toluene (10 ml x 3). The combined extract was washed with water and brine and dried over Na_2SO_4. After filtration, the extract was concentrated under reduced pressure to afford a light yellow solid. The light yellow solid was washed with hexane to give a white solid **128** (489 mg, 0.72 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.5 Hz, 6H), 1.72 (t, *J* = 4.0 Hz, 2H), 4.36-4.42 (m, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 7.5 Hz, 2H), 7.05-7.20 (m, 12H), 7.30-7.40 (m, 6H) and 7.56-7.60 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.03, 40.72, 74.97, 118.03, 127.40, 127.56, 127.58, 128.16, 128.19, 128.22, 128.25, 128.63, 133.47, 133.55, 133.62, 133.81, 133.90, 133.98, 135.43, 135.56, 135.69, 137.38, 137.42, 137.45, 138.51, 138.57, 138.63, 138.70, 157.61, 157.65 and 157.70.

^{31}P NMR (202 MHz, $CDCl_3$): δ = -9.88.

HRMS (ESI): calcd for $C_{41}H_{37}P_2O_2$ $[M+H]^+$ 623.2269, found 623.2250.

$[\alpha]^{20}_D$ = +313.8 ° (c = 1, toluene).

3.5 Synthesis of (*S*)-[6,6'-(2*R*,5*R*-Hexadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 134 via Ring Closure Route

3.5.1 Synthesis of (2*S*,5*S*)-hexanediol ditosylate 130

To an ice-cooled solution of (2*S*,5*S*)-hexanediol **129** (4.0 g, 33.8 mmol) in 20 mL pyridine under N_2 was added a solution of *p*-toluenesulfonyl chloride (14.20 g, 74.5 mmol) in 30 mL of pyridine over 4 hours and the reaction mixture was stirred at 0 °C for 2 hours. After stirring at room temperature overnight, the reaction mixture was poured into ice-water (500 ml) with vigorous stirring. The solid was filtered and washed with 500 ml of cold water. White crystals **130** (10.33 g, 24 mmol, 72% yield) were obtained after recrystallization from acetone.

^{1}H NMR (500 MHz, $CDCl_3$): δ =1.12-1.14 (d, J = 6.5 Hz, 6H), 1.48-1.51 (m, 2H), 1.56-1.61 (m, 2H), 2.45 (s, 6H), 4.50-4.53 (m, 2H), 7.33-7.35 (d, J = 8 Hz, 4H), 7.76-7.78 (d, J = 8.5 Hz, 4H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.77, 21.58, 31.55, 79.01, 127.65, 129.79, 134.23, 144.65;

HRMS (ESI): calcd for $C_{20}H_{26}S_2O_6$ $[M+Na]^+$ 449.1068, found 449.1109; calcd for $C_{20}H_{26}S_2O_6$ $[M+H]^+$ 427.1249, found 427.1295;

$[\alpha]^{20}_D$ = -14.7 ° (c = 1, $CHCl_3$).

3.5.2 Synthesis of (*S*)-[6,6'-(2*R*, 5*R*-hexadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl 131

(*S*)-[6,6'-(2*R*,5*R*-hexadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl **131** was prepared from (*S*)-(6,6'-dihydroxybiphenyl-2,2'-diyl)bis(diphenylphosphine oxide) **122** and (2*S*,5*S*)-hexanediol ditosylate **130** by following the same procedure described above

for (*S*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl **123** (68% yield)**.**

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6 Hz, 6H), 1.16 (d, 10.0 Hz, 2H), 1.72 (d, *J* = 9.0 Hz, 2H), 4.42-4.49 (m, 2H), 6.82 (dd, *J* = 13.5Hz, 7.5 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 7.11-7.15 (m, 2H), 7.20-7.23 (m, 4H), 7.32-7.38 (m, 6H), 7.41-7.45 (m, 6H), 7.74 (dd, *J* = 11.8 Hz, 7.2 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.65, 25.63, 75.61, 118.90, 125.88, 125.98, 127.31, 127.40, 127.80, 127.89, 128.05, 130.49, 130.51, 130.94, 132.27, 132.35, 132.55, 132.63, 132.78, 133.36, 133.65, 133.88, 134.19, 134.71, 155.82, 155.93.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.03.

HRMS (ESI): calcd for $C_{42}H_{39}P_2O_4$ $[M+H]^+$ 669.2324, found 669.2251.

$[\alpha]^{20}_D$ = +76 ° (c = 1, $CHCl_3$).

3.5.3 Synthesis of (*S*)-[6,6'-(2*R*,5*R*-hexadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl 132

(*S*)-[6,6'-(2*R*,5*R*-hexadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl **131** was reduced with trichlorosilane to (*S*)-[6,6'-(2*R*,5*R*-hexadioxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl **132** by following the same procedure described above for (*S*)-[6,6'-(2*S*,3*S*-Butadioxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl **128**. (97% yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.5 Hz, 6H), 1.17-1.20 (m, 2H), 1.71-1.78 (m, 2H), 4.36-4.44 (m, 2H), 6.62 (d, *J* = 7.5 Hz, 2H), 6.75 (d, 8.5 Hz, 2H), 7.08-7.17 (m, 12H), 7.24-7.26 (m, 6H) and 7.38-7.41 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.28, 27.17, 75.82, 115.75, 126.42, 127.50, 127.52, 127.55, 127.60, 127.92, 128.10, 128.12, 128.14, 128.45, 133.60, 133.69, 133.77, 133.82, 133.91, 133.99, 134.88, 135.02, 135.16, 137.46, 137.50, 137.55, 138.62, 138.67,138.74, 139.23, 139.25, 139.27, 156.41, 156.46 and 156.50.

^{31}P NMR (202 MHz, $CDCl_3$): δ = -10.75.

HRMS (ESI): calcd for $C_{42}H_{39}P_2O_2$ $[M+H]^+$ 637.2425, found 637.2402.

$[\alpha]^{20}_D$ = +243.5 ° (c = 1, toluene).

3.6 Synthesis of (*R*) or (*S*)-[6,6'-(4*S*,5*S*-2,2-Dimethyl-1,3-dioxolane-4,5-dimethoxy)]-(2,2')-bis(diphenylphosphino)-(1,1')-biphenyl via Asymmetric Ullmann Coupling

3.6.1 Synthesis of (-)-1,4-Di-*O*-tosyl-2,3-*O*-isopropylidene-*L*-threitol 135

To a suspension of LAH (4 g, 105 mmol) in 200 ml of ether at 0°C was added a solution of dimethyl-2,3-isopropylidene-*L*-tartrate **133** (11.9 g, 54.5 mmol) in 50 ml ether dropwise. The reaction mixture was stirred at room temperature for overnight. To the reaction mixture at 0°C was added water (3 ml), 5% NaOH solution (3 ml) and water (10 ml) respectively and the reaction mixture was stirred for an hour. The reaction mixture was then filtered and the filter cake was washed with acetone. The combined filtrate was dried over Na_2SO_4 and concentrated in vacuo to give a crude diol **134** which was used in the next step without further purification. To a solution of crude diol **134** (4 g) in 30 ml of pyridine at 0°C was added *p*-toluenesulfonyl chloride (10 g, 52 mmol) in one portion. The reaction mixture was stirred at room temperature overnight and then 100 ml of water was added. The reaction mixture was extracted with CH_2Cl_2. The combined extract was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a white solid **135**.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 6H), 2.46 (s, 6H), 4.01 (s, 2H), 4.09 (s, 4 H), 7.36 (d, *J* = 7.5 Hz, 4 H) and 7.78 (d, *J* = 8 Hz, 4H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.65, 26.70, 68.38, 75.02, 110.81, 127.984, 129.97, 132.41 and 145.22.

$[\alpha]^{20}_D$ = -16° (c = 0.0033, $CHCl_3$).

3.6.2 Synthesis of (-)-1,4-Di-*O*-3-bromophenoxy-2,3-*O*-isopropylidene-*L*-threitol 136

A suspension of ditosylate **135** (9.3 g, 19.8 mmol), 3-bromophenol (10.7 g, 62 mmol) and K_2CO_3 (10 g, 72 mmol) in 200 ml of DMSO was stirred at 70°C. The reaction mixture was monitored by TLC. Water (200ml) was added and the reaction mixture was extracted with CH_2Cl_2. The combined extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a coloress oil **136**. (8.4 g 17.8 mmol, 90 % yield)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 6H), 4.18 (q, *J* = 13.5 Hz, 4H), 4.34 (s, 2 H), 6.86 (d, *J* = 7.5 Hz, 2H) and 7.09-7.16 (m, 6H).

^{13}C NMR (125 MHz, C_6D_6): δ = 27.84, 69.16, 77.30, 110.953, 114.89, 118.58, 123.93, 125.22, 131.55, 160.43.

HRMS (ESI): calcd for $C_{19}H_{20}Br_2O_4$ $[M+Na]^+$ 492.9626, found 492.9603

$[\alpha]^{20}_D$ = -12.2 ° (c = 0.0152, toluene).

3.6.3 Synthesis of (-)-1,4-Di-*O*-3-(diphenylphosphoryl)phenoxy-2,3-*O*-isopropylidene-*L*-threitol 137

To a solution of bromoether **136** (4.2 g, 8.90 mmol) in 100 ml THF at -78°C was added *n*-BuLi (13.5 ml, 9.45 mmol, 1.6 M solution in hexane) dropwise within 30 min. The reaction mixture was stirred at -78°C for 2 hours and then chlorodiphenylphosphine (3.8 ml, 20 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at -78°C for an hour. After stirring at room temperature for overnight, water was added and the reaction mixture was extracted with CH_2Cl_2. The combined extract was washed with water and brine, then dried over Na_2SO_4 and concentrated in vacuo. The

residue was dissolved in 100 ml acetone and an aqueous H_2O_2 solution (30%, 13 ml) was added at 0°C. The reaction mixture was stirred at room temperature for overnight. The reaction mixture extracted with CH_2Cl_2 and the combined extract was washed with $Na_2S_2O_3$ solution, water and brine. The extract was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a white solid **137** (5.3 g, 7.4 mmol, 83 % yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 6H), 4.14 (q, *J* = 13.5 Hz, 4H), 4.30 (m, 2 H), 7.07–7.09 (m, 2H), 7.13–7.17 (dd, *J* = Hz, Hz, 2H), 7.30–7.37 (m, 4H), 7.44–7.47 (m, 8H), 7.528-7.56 (m, 4H) and 7.63–7.67 (m, 8H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.92, 68.50, 76.48, 110.60, 117.23, 117.31, 118.72, 124.84, 124.92, 128.46, 128.56, 129.66, 129.78, 131.75, 131.97, 132.05, 132.58, 133.46, 134.27, 158.39 and 158.51.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.27

HRMS (ESI): calcd for $C_{43}H_{40}O_6P_2$ $[M+H]^+$ 715.2378, found 715.2374

$[\alpha]^{20}_D$ = -9.4° (c = 0.0064, toluene).

3.6.4 Synthesis of (*R*) or (*S*)-[6,6'-(4*S*,5*S*)-2,2-Dimethyl-1,3-dioxolane-4,5-dimethoxy)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl 139 and 140

To a solution of **137** (5.3 g, 7.4 mmol) in 120 ml THF at -78°C was added a solution of LDA (9.5 ml, 2 M in hexane) dropwise and the reaction mixture was stirred at -78°C for 3 hours. Then the reaction mixture was cannulated into a flask containing iodine (8 g, mmol) in 120 ml THF at -78°C. After stirring at room temperature overnight, the reaction mixture was concentrated in vacuo and the residue was dissolved in 50 ml of CH_2Cl_2. The CH_2Cl_2 extract was washed with NH_4Cl solution, water, saturated $Na_2S_2O_3$ solution.

The extract was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a light yellow solid **138** (4.2 g, 4.3 mmol, 57% yield). A suspenson of **138** (4.2 g, 4.3 mmol) and copper (4.2 g, mmol) in 50 ml of DMF was stirred at 140 °C for 24 hours. The reaction mixture was concentrated in vacuo. The residue was washed with hot chloroform (10ml x 3) and filtered. The combined filtrate was washed with NH_4Cl solution and brine. The filtrate was then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography on silica gel to afford a white solid **139** and **140** (2 g, 2.8 mmol, 65 % yield).

139

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31 (s, 3H), 3.70-3.72 (m, 1H), 3.93-3.97 (m, 1H), 4.21-4.24 (m, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.83-6.88 (dd, *J* = 7.5 Hz, 1H), 7.14-7.18 (m, 1H), 7.20-7.24 (m, 2H), 7.30-7.35 (m, 3H), 7.38-7.42 (m, 3H), 7.64-7.68 (m, 2H), 7.64-7.68 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.58, 73.53, 80.08, 108.56, 117.93, 126.25, 126.34, 127.33, 127.42, 127.84, 127.94, 128.51, 128.63, 130.69, 131.07, 132.21, 132.28, 132.53, 132.61, 132.93, 133.23, 133.75, 134.01, 134.06, 134.84, 157.30, 157.41

^{31}P NMR (202 MHz, $CDCl_3$): δ = 29.21

HRMS (ESI): calcd for $C_{43}H_{38}O_6P_2$ $[M+H]^+$ 713.2222, found 713.2208

$[\alpha]^{20}_D$ = -25° (c = 0.0046, $CHCl_3$).

140

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 3H), 3.56 (t, *J* = 11 Hz, 1H), 3.98-4.00 (m, 1H), 4.49-4.52 (m, 1H), 6.83-6.87 (dd, 1H), 7.01 (d, *J* = 8 Hz, 1H), 7.16-7.20 (m, 1H), 7.25-

7.30 (m, 2H), 7.30-7.36 (m, 2H), 7.35-7.40 (m, 2H), 7.42-7.46 (m, 2H), 7.67-7.71 (m, 2H)

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.12, 69.67, 76.51, 110.14, 116.19, 126.40, 126.49, 127.41, 127.51, 127.85, 127.95, 128.16, 128.28, 130.82, 131.11, 132.02, 132.30, 132.37, 132.66, 132.75, 133.06, 133.19, 133.91, 134.02, 134.73, 154.60, 154.71.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 29.63

HRMS (ESI): calcd for $C_{43}H_{38}O_6P_2$ $[M+H]^+$ 713.2222, found 713.2208

$[\alpha]^{20}_D$ = 52° (c = 0.0050, $CHCl_3$).

3.7 Asymmetric Hydrogenation Reactions

3.7.1 General Procedure for the Asymmetric Hydrogenation of Quinolines

A solution of quinoline (0.2 mmol), Ir(COD)LCl (2.2 x 10^{-3} mmol), iodine (1 x 10^{-2} mmol) and toluene (1 mL) was added to a glasslined stainless steel autoclave under a nitrogen atmosphere. Hydrogen was introduced into the autoclave at a pressure of 715 psig. The reaction mixture was stirred at rt for 20 h before releasing the unreacted H_2. The reaction mixture was diluted with dichloromethane (4 ml) and then stirred with saturated Na_2CO_3 solution (1 ml) for 15 min. The organic layer was separated and the aqueous layer was extracted with dichloromethane (5 ml x 3). The combined organic layers were dried over Na_2SO_4 and concentrated to afford the crude product. The conversion of substrate was determined by NMR. After purified by column chromatography, the enantiomeric excess was determined by chiral HPLC.

3.7.2 General Procedure for the Asymmetric Hydrogenation of Enol Acetates

A solution of $(NMe_2H_2)[(Ru\mathbf{116}Cl)_2(\mu\text{-}Cl)_3]$ (5×10^{-4} mmol) in CH_2Cl_2 (0.25 ml), enol acetate (0.1 mmol) and ethanol (1.0 ml) was added to a glasslined stainless steel autoclave under a nitrogen atmosphere. Hydrogen was introduced into the autoclave at a pressure of 65 psig. The reaction mixture was stirred at room temperature to 50°C before releasing the unreacted H_2. The conversion of the substrate and the enantiomeric excess of the corresponding product were determined by chiral GC with a Varian 25 m × 0.25 mm CPCYCLODEX B 236M column.

3.7.3 General Procedure for the Asymmetric Hydrogenation of β-Ketoesters

A solution of β-ketoester (0.25 mmol), $RuLCl_2(DMF)_n$ (3.75×10^{-4} mmol), CH_2Cl_2 (6.25 μL) and ethanol (493.75 μL) was added to a glasslined stainless steel autoclave under a

nitrogen atmosphere. Hydrogen was introduced into the autoclave at a pressure of 65 psig. The reaction mixture was stirred at 50°C before releasing the unreacted H_2. The conversion of the substrate and the enantiomeric excess of the corresponding product were determined by chiral GC with a CHROMPACK 25 m × 0.25 mm Chirasil-DEX CB column after converting the product to the corresponding acetyl derivative.

3.7.4 General Procedure for the Asymmetric Hydrogenation of Ketones

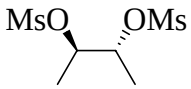
A solution of Ru(L)[(*R*, *R*)-DPEN]Cl_2 (1.25×10^{-4} mmol), $(CH_3)_3COK$ (3.125×10^{-4} mmol), isopropanol (220 μL) was added to a glasslined stainless steel autoclave which was charged with ketone (0.25 mmol) under a nitrogen atmosphere. Hydrogen was introduced into the autoclave at a pressure of 315 psig. The reaction mixture was stirred at room temperature for 24 h before releasing the unreacted H_2. The conversion of the substrate and the enantiomeric excess of the corresponding product were determined by chiral GC with a CHROMPACK 25 m × 0.25 mm Chirasil-DEX CB column.

3.7.5 General Procedure for the Asymmetric Hydrogenation of Enimide

A solution of Rh(COD)LBF_4 (5×10^{-4} mmol), enimide (0.05 mmol) and CH_2Cl_2 (250 μl) was added to a glasslined stainless steel autoclave under a nitrogen atmosphere. Hydrogen was introduced into the autoclave at a pressure of 1015 psig. The reaction mixture was stirred at room temperature for 24 h before releasing the unreacted H_2. The conversion of the substrate and the enantiomeric excess of the corresponding product were determined by chiral GC with a CHROMPACK 25 m × 0.25 mm Chirasil-DEX CB column.

APPENDIX I

^{1}H, ^{31}P and ^{13}C-NMR SPECTRA



(*R*,*R*)-**111**

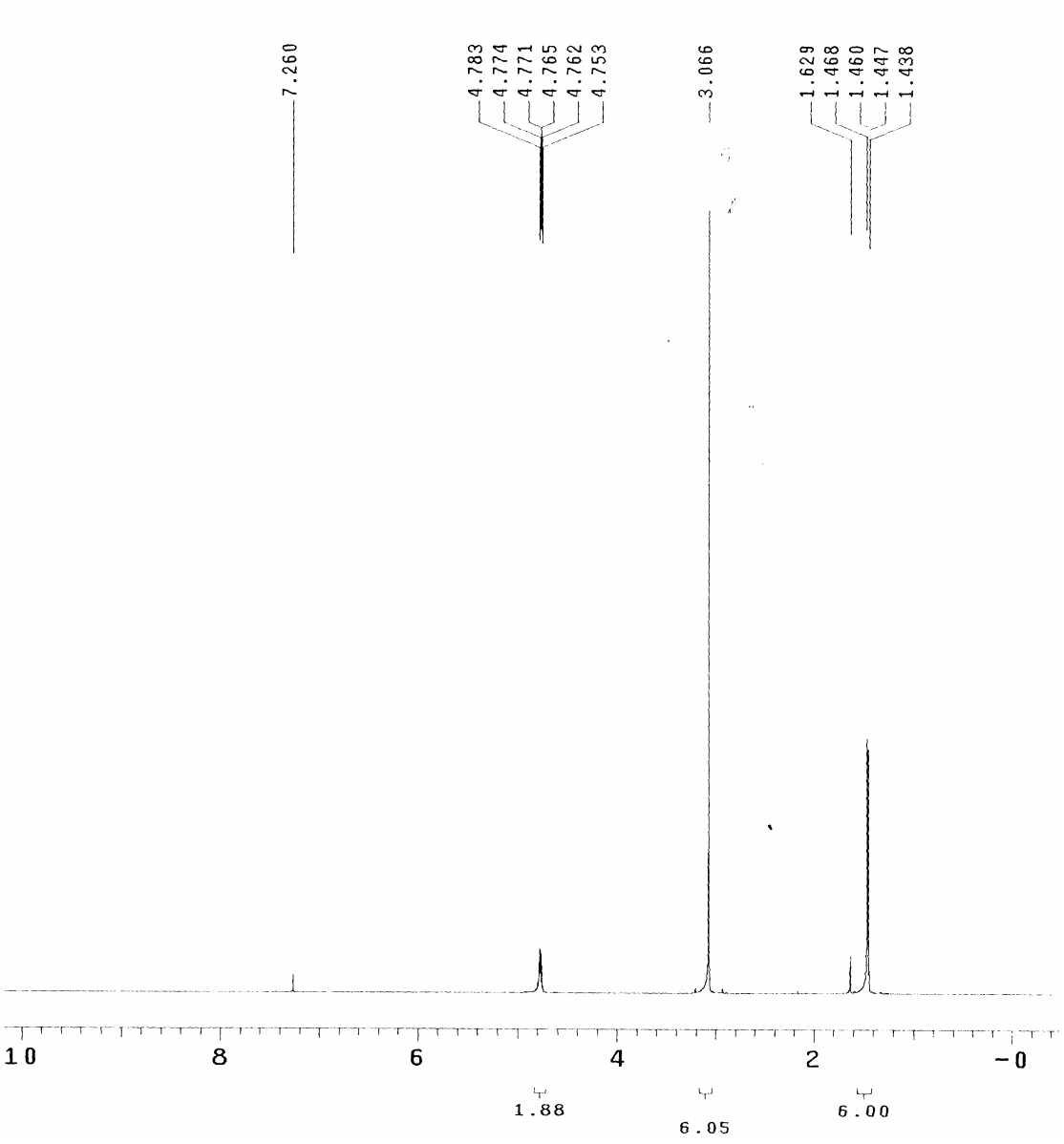
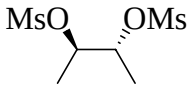


Figure 4.1-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*R*,*R*)-**111**



(*R*,*R*)-**111**

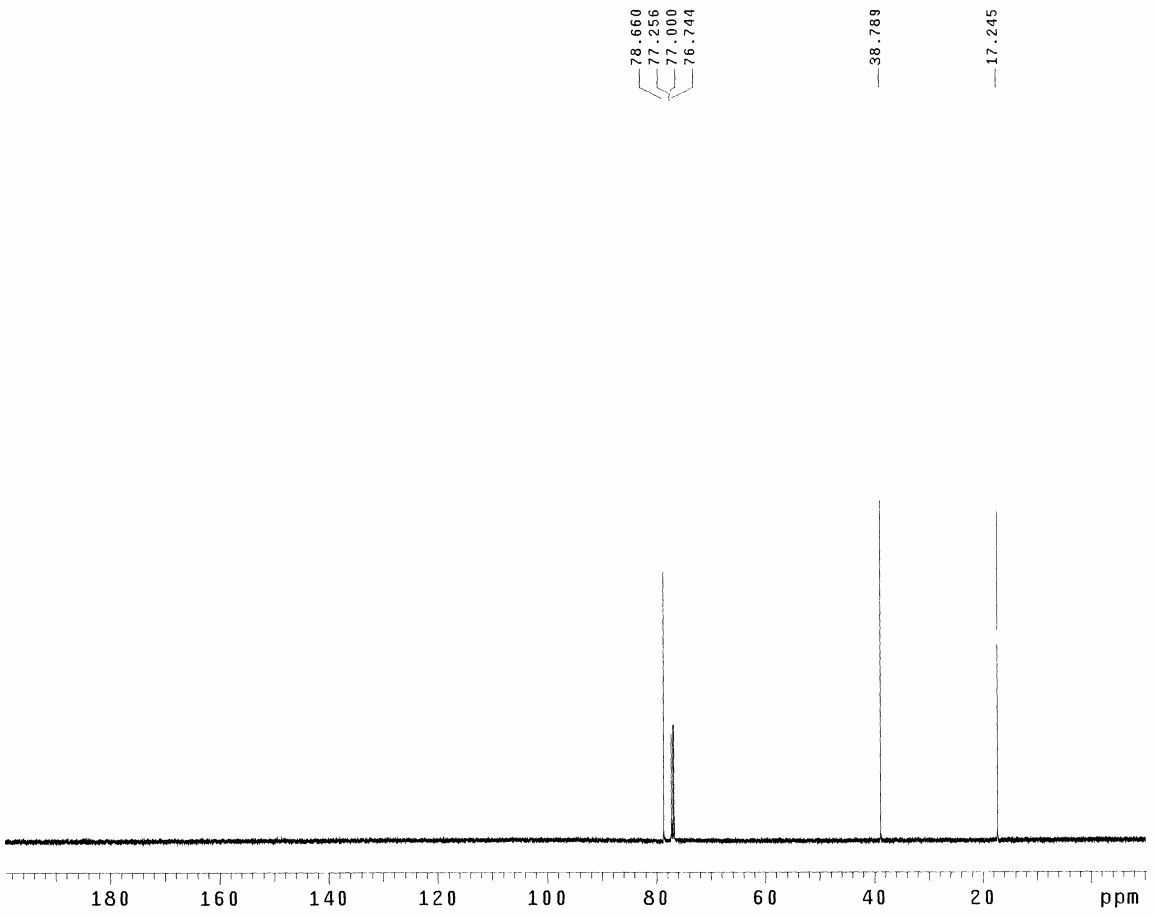
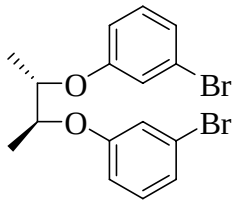


Figure 4.1-2 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (*R*,*R*)-**111**



(*S*,*S*)-**113**

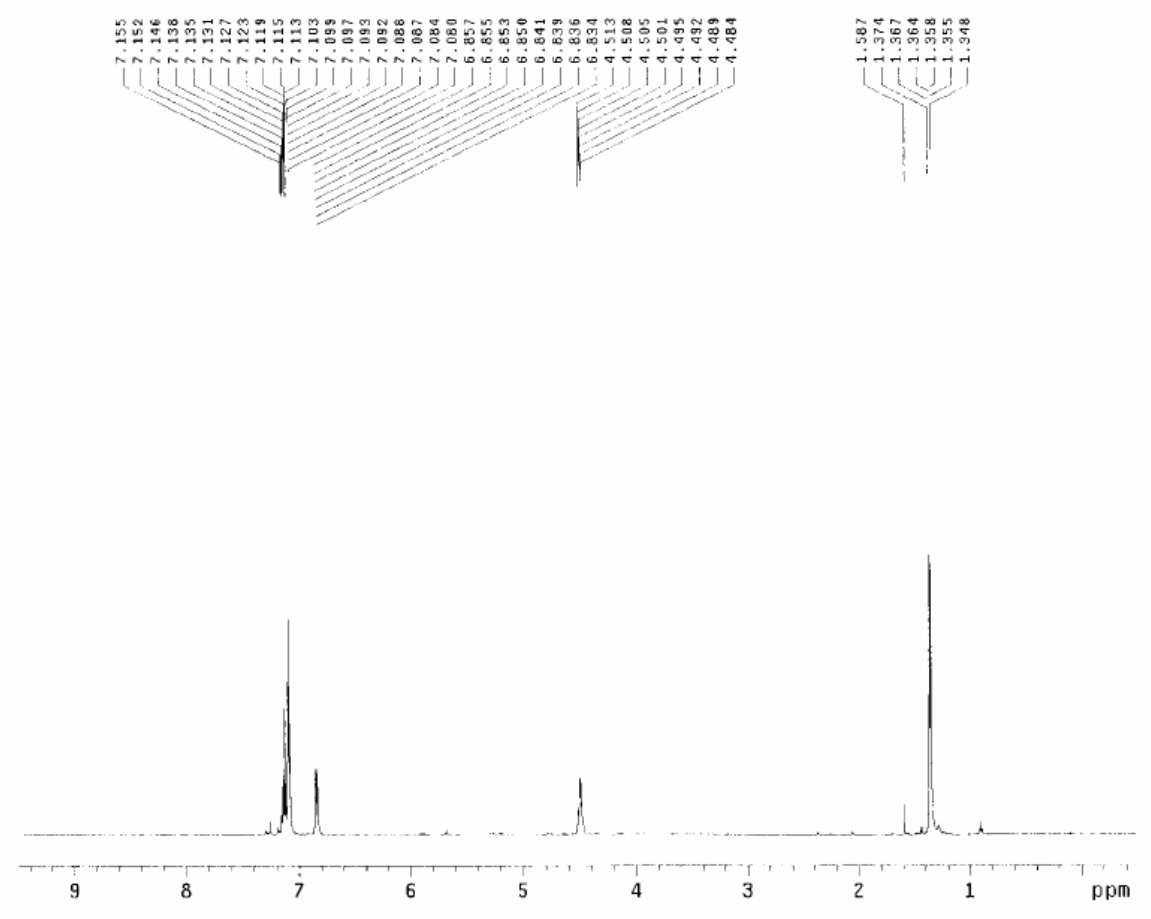
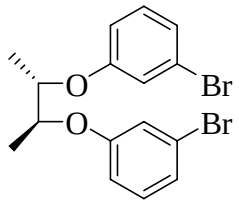


Figure 4.2-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**113**



(*S*,*S*)-**113**

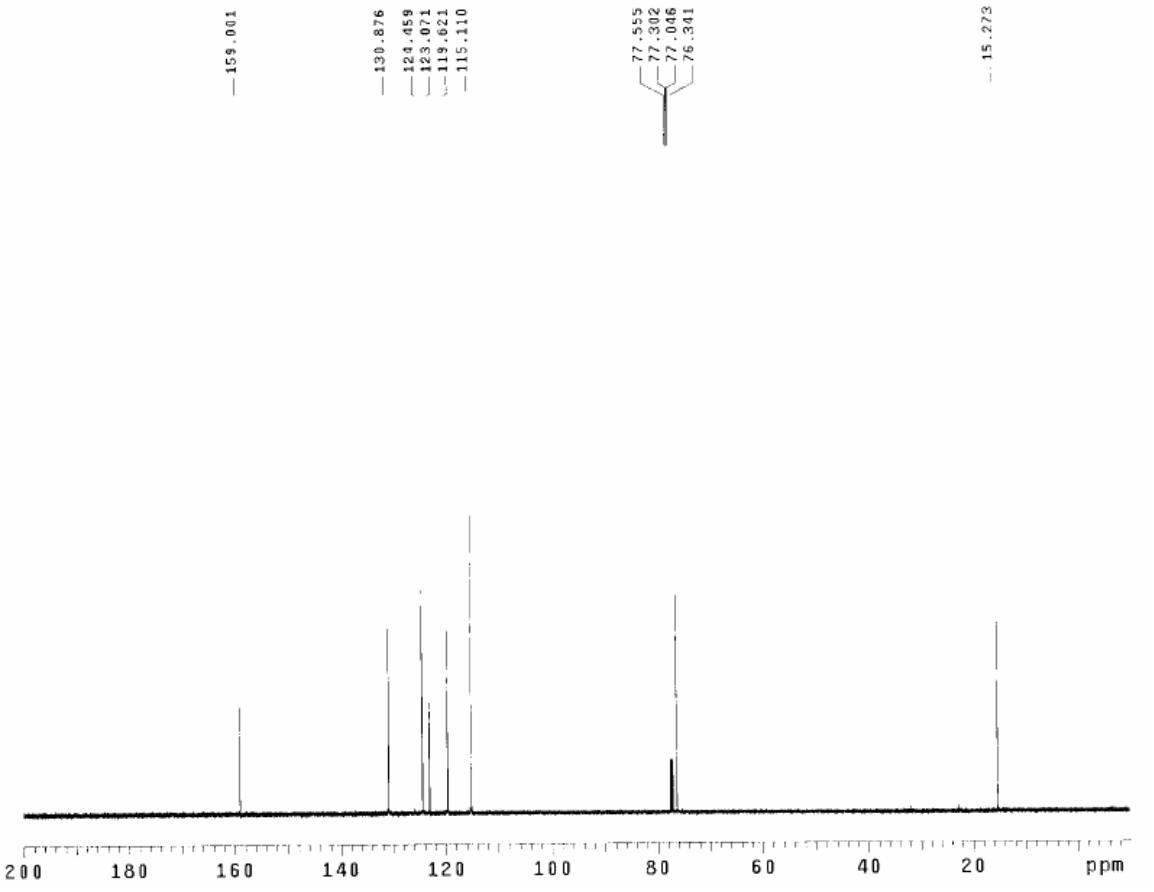
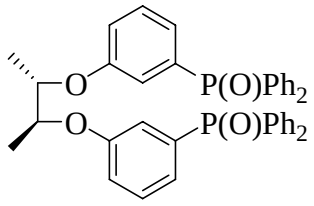


Figure 4.2-2 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**113**



(*S*,*S*)-**114**

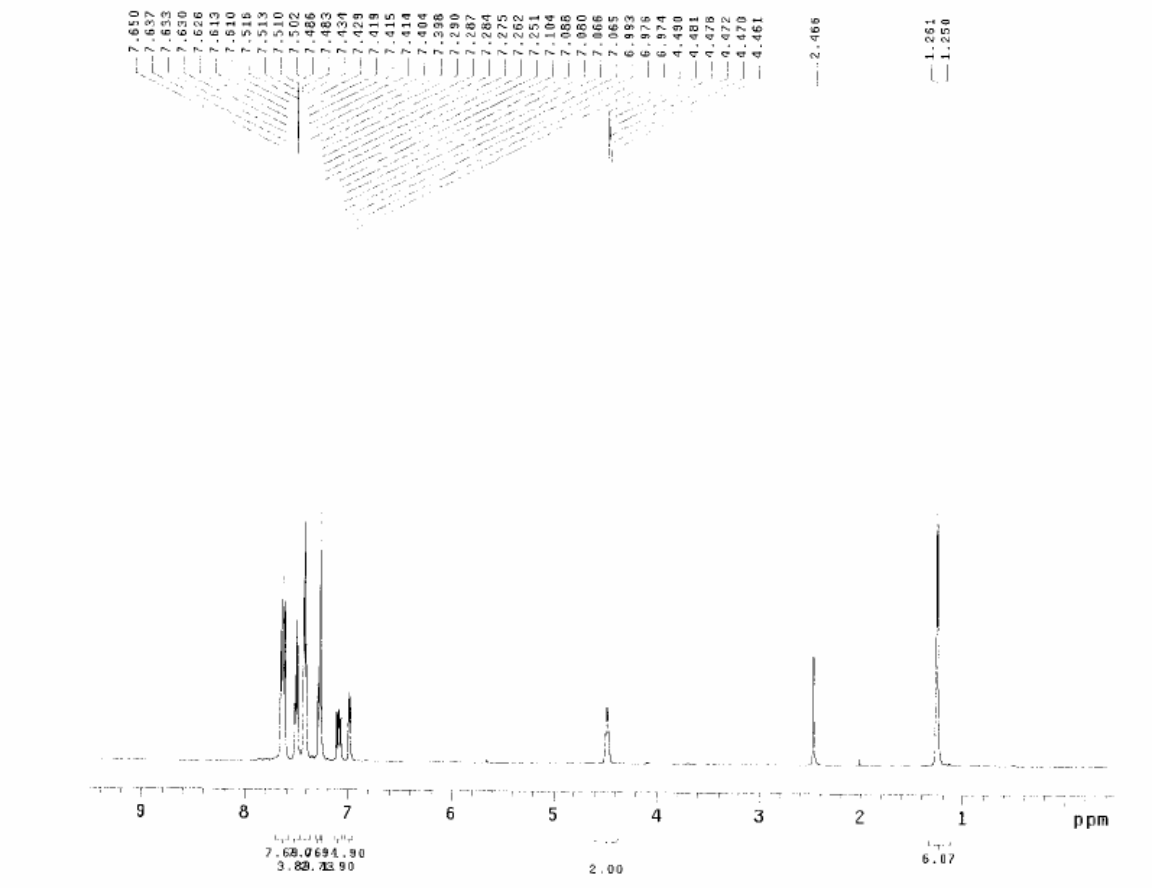
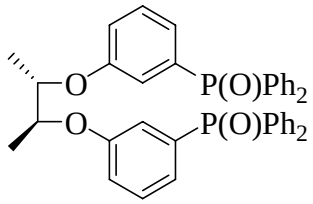


Figure 4.3-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**114**



(*S*,*S*)-**114**

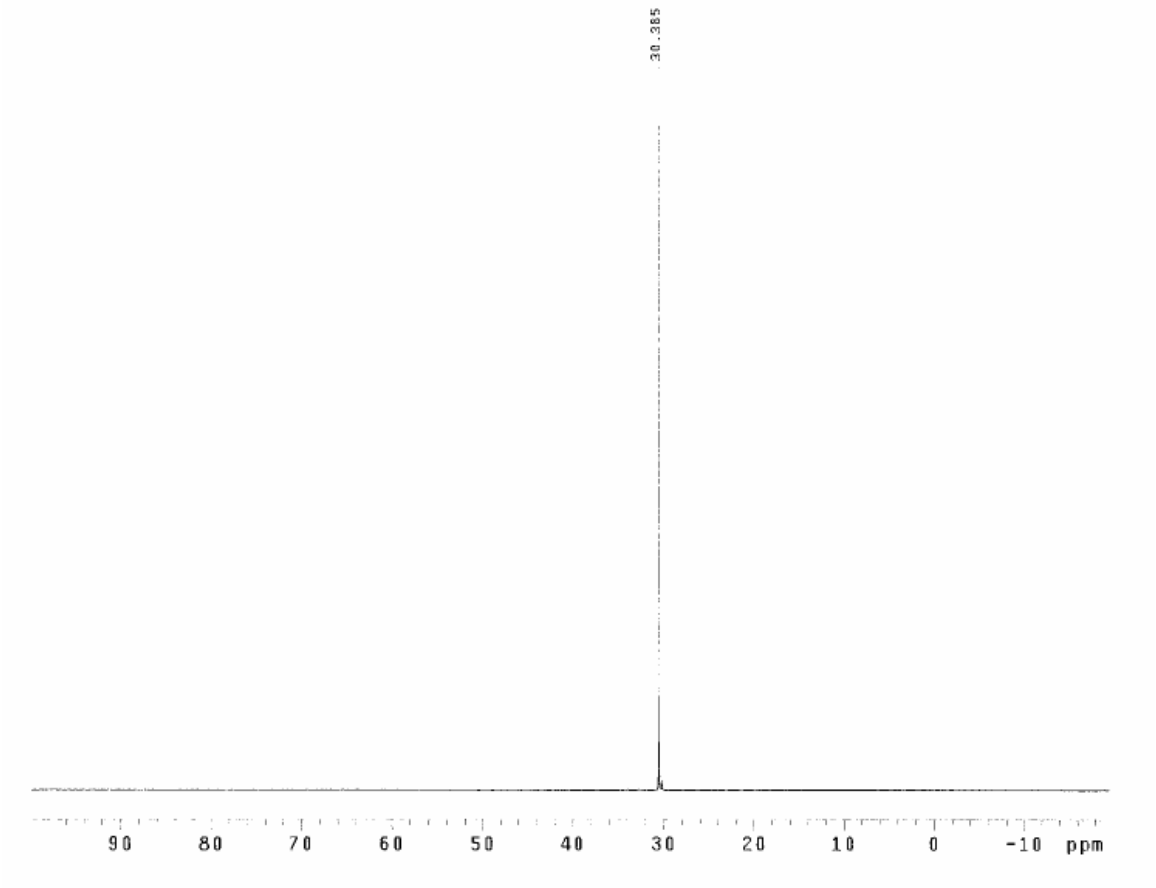
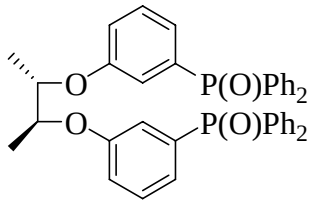


Figure 4.3-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**114**



(*S*,*S*)-**114**

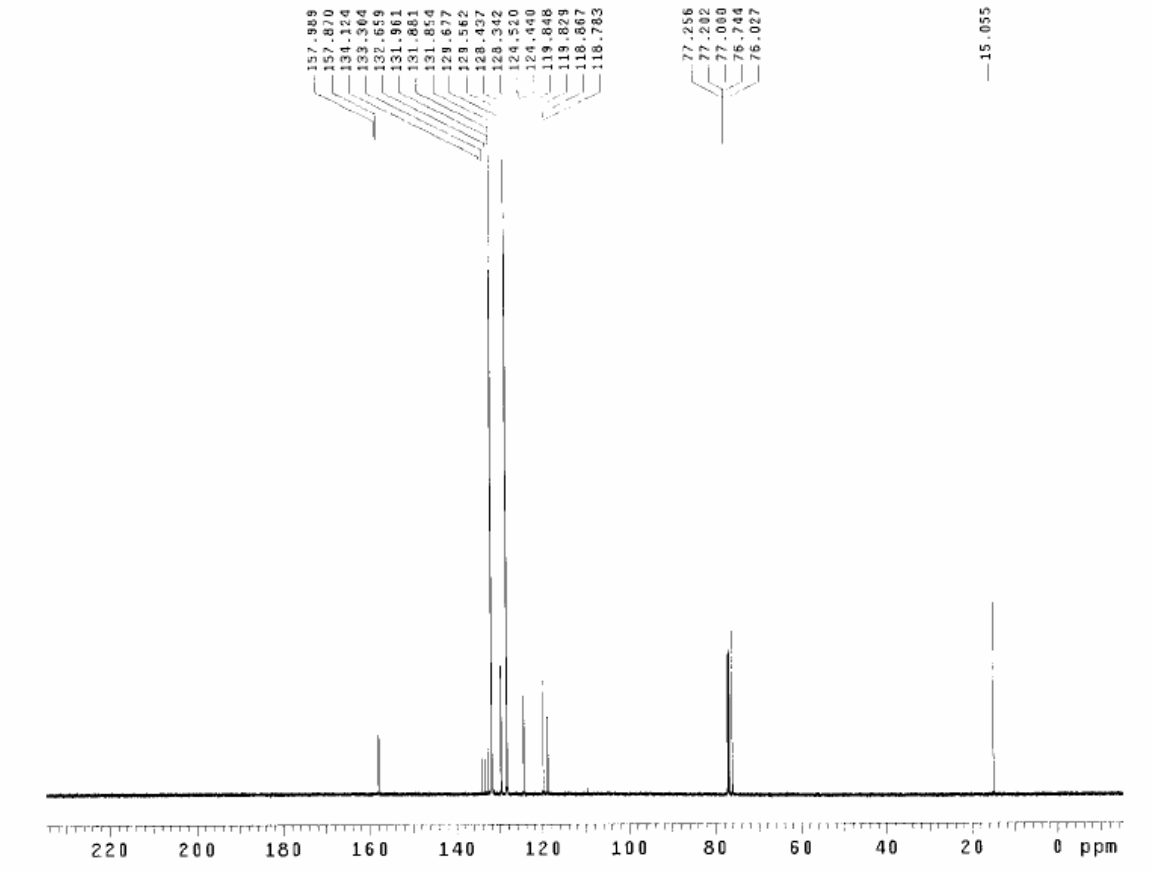
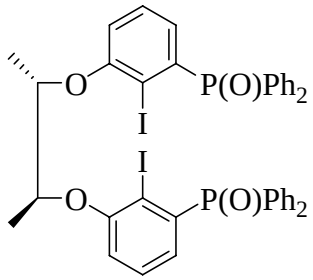


Figure 4.3-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**114**



(*S*,*S*)-**115**

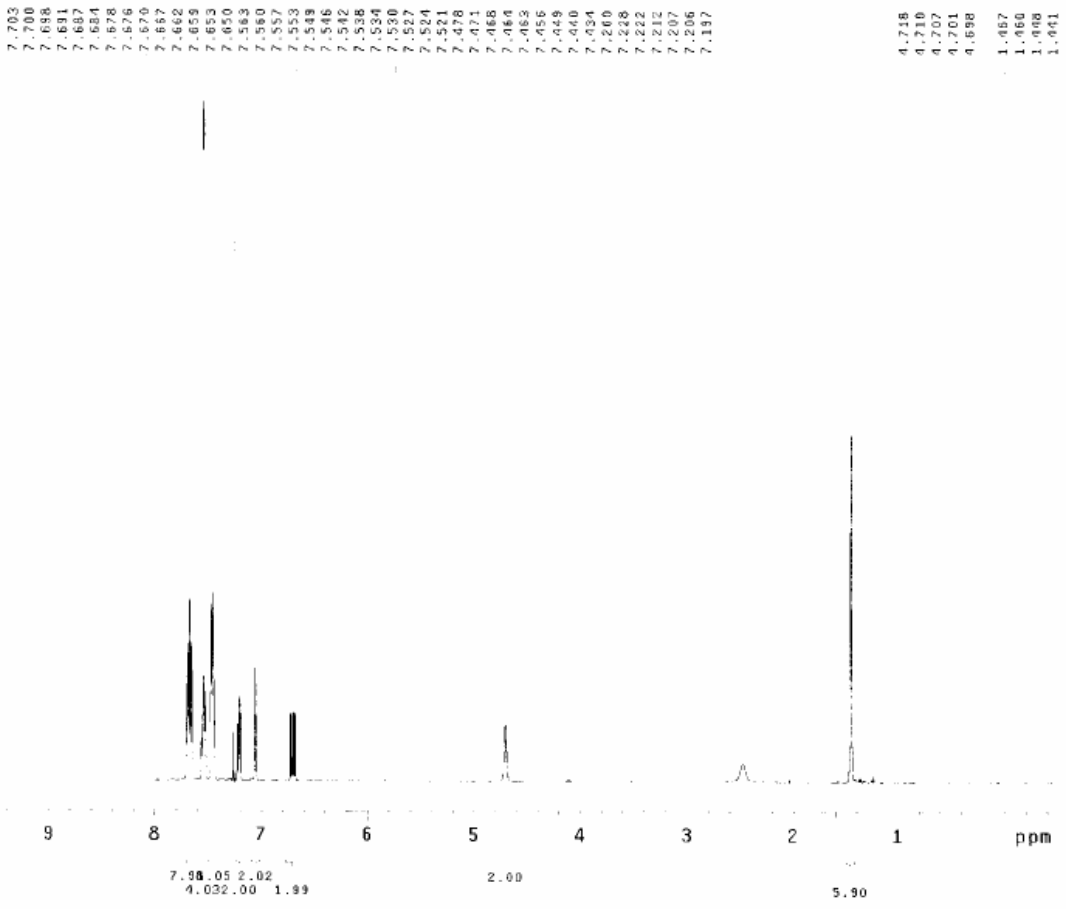
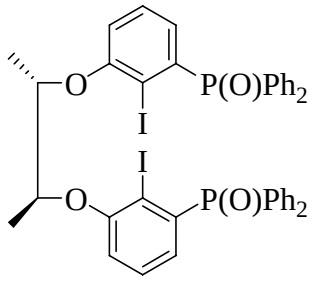


Figure 4.4-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**115**



(*S*,*S*)-**115**

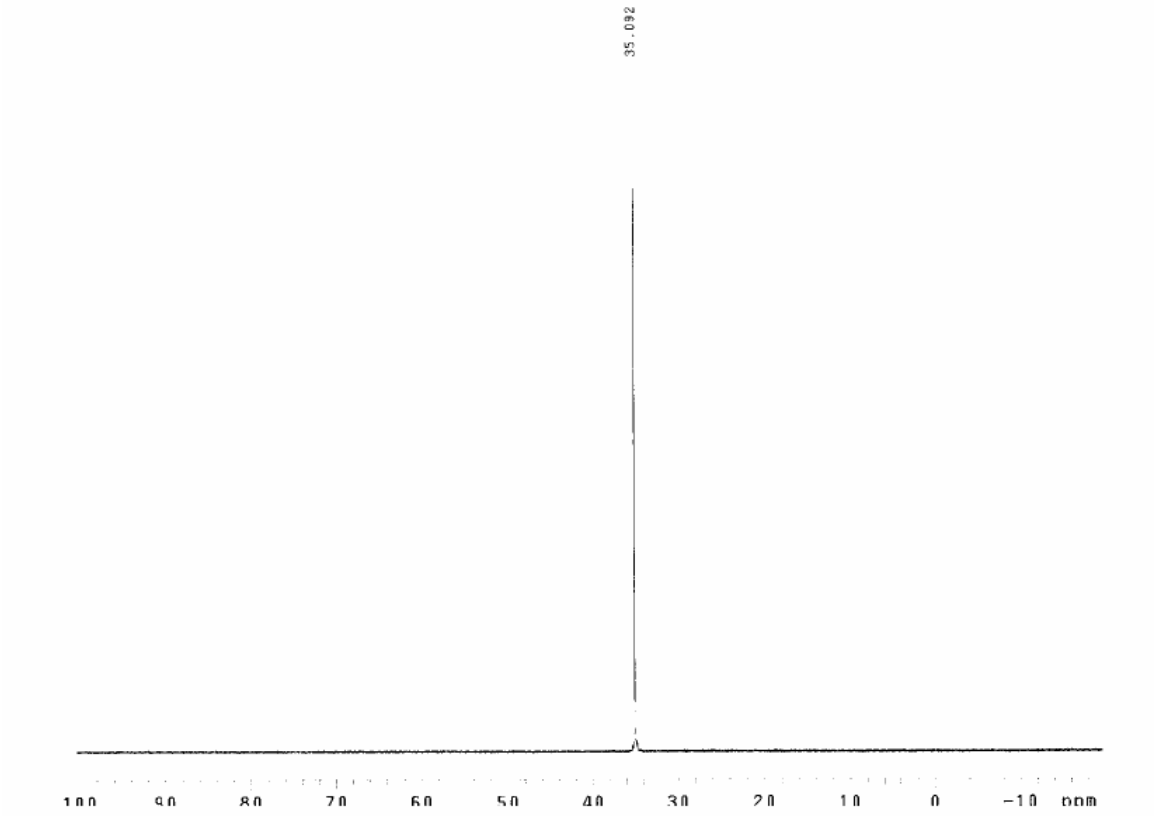
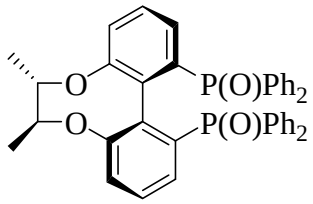


Figure 4.4-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**115**



(R_{ax})-**116**

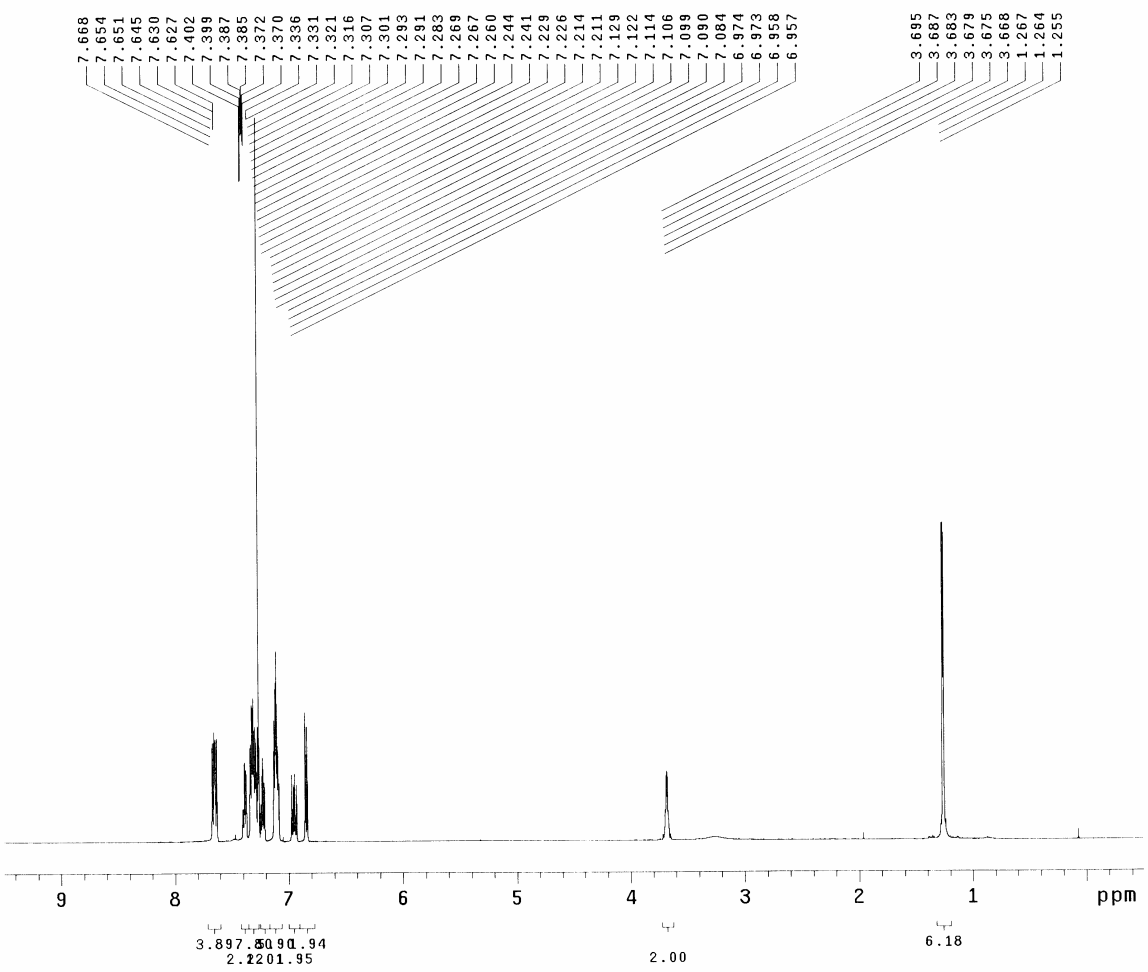
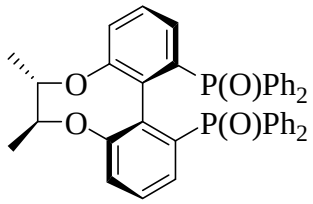


Figure 4.5-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (R_{ax})-**116**



(R_{ax})-**116**

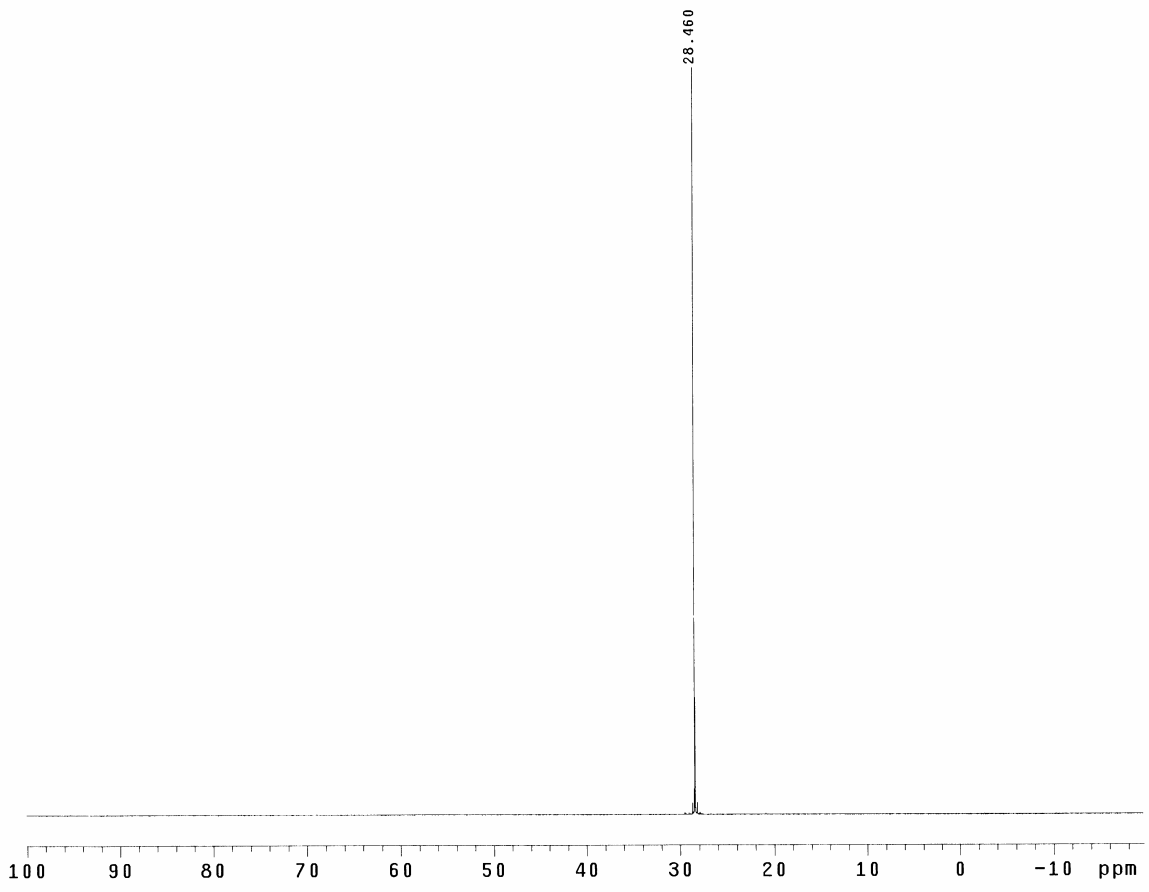
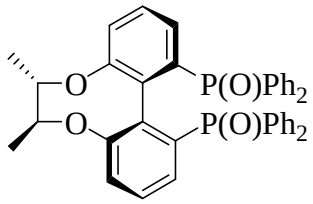


Figure 4.5-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (R_{ax})-**116**



(R_{ax})-**116**

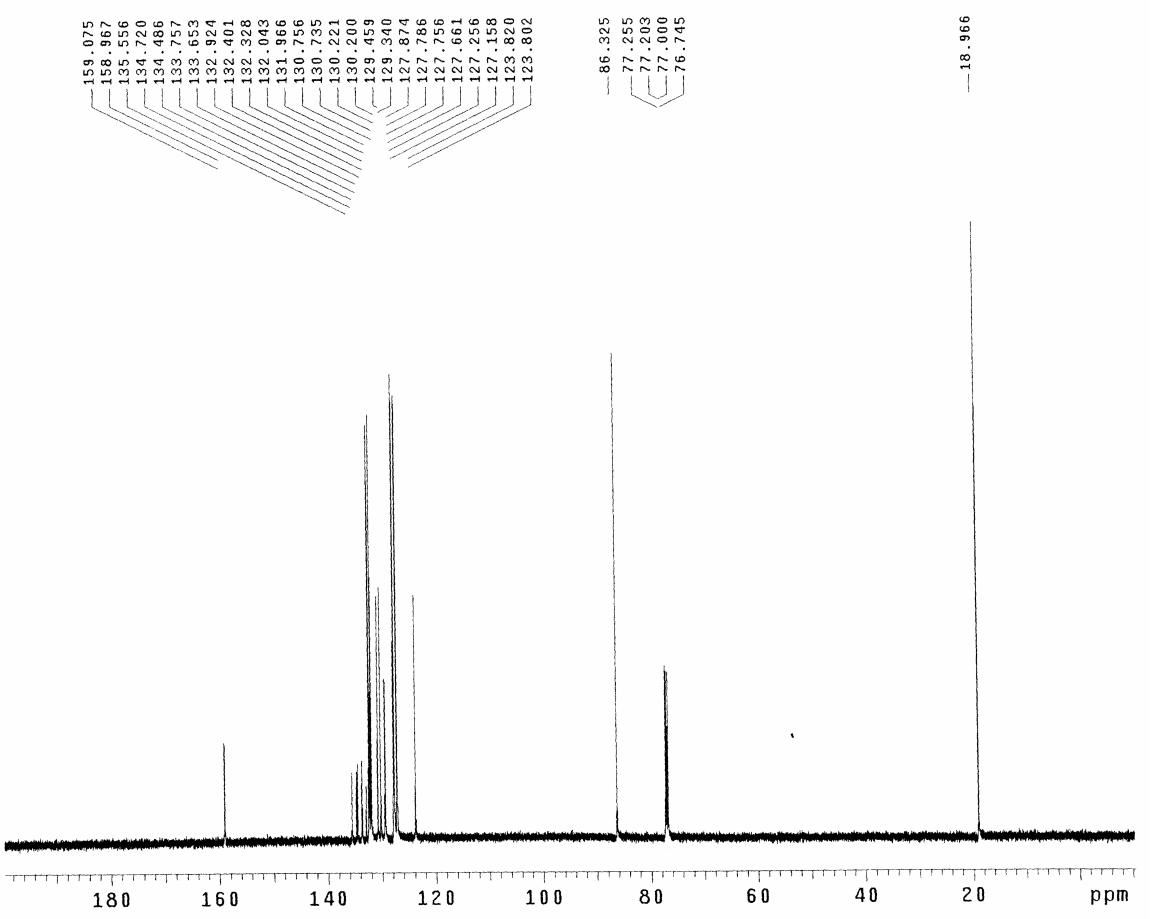
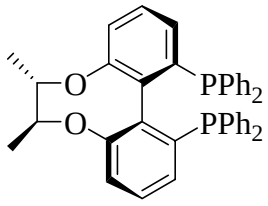


Figure 4.5-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (R_{ax})-**116**



(R_{ax})-**117**

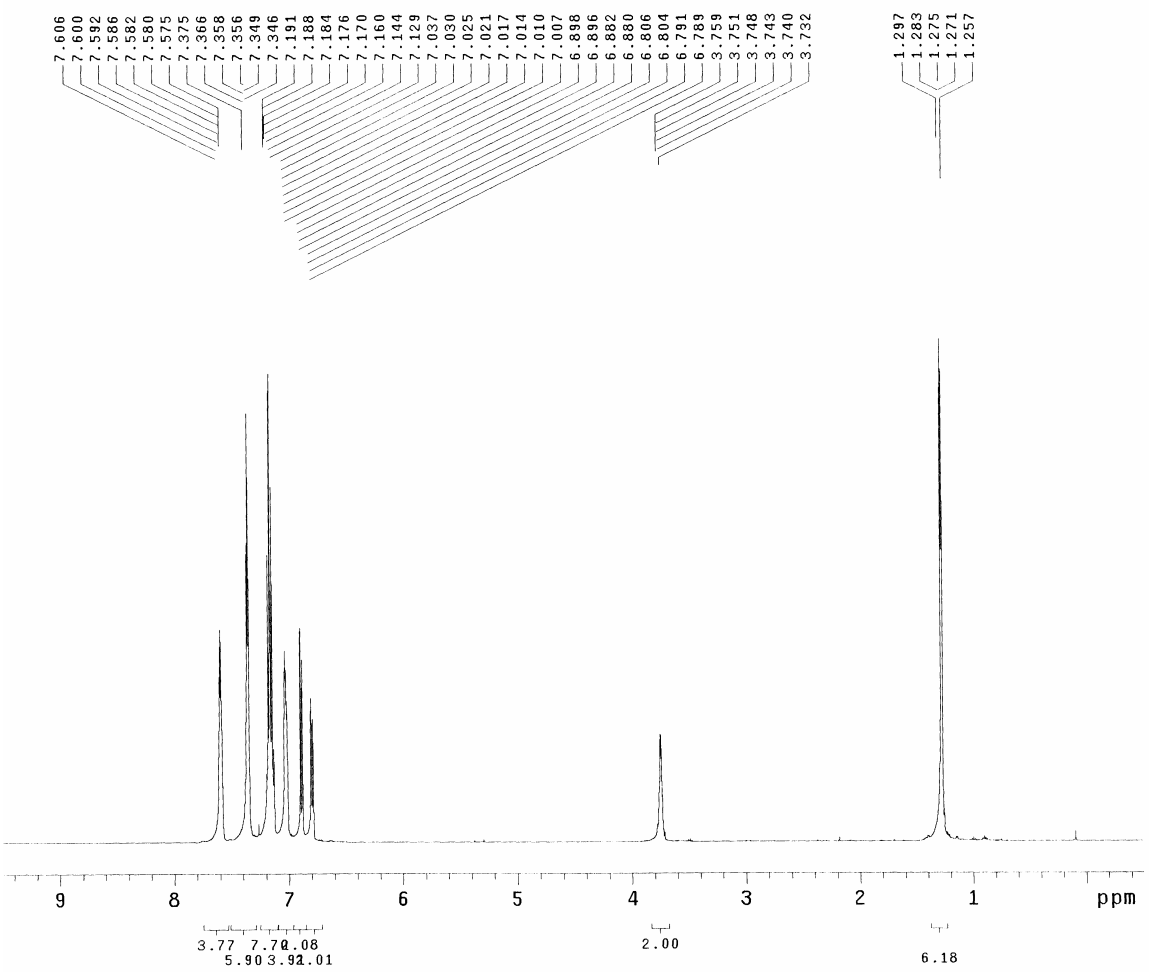
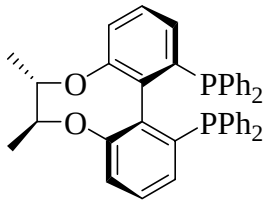


Figure 4.6-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (R_{ax})-**117**



(R_{ax})-**117**

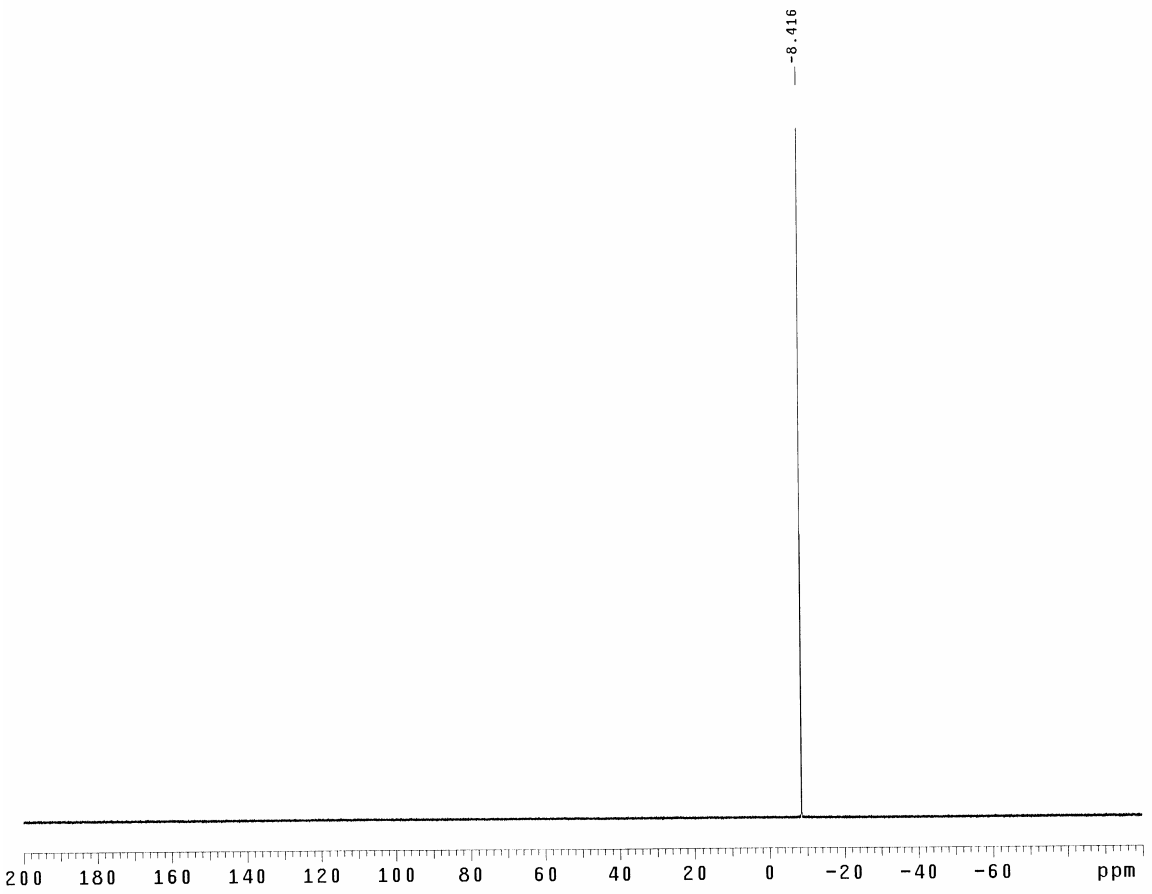
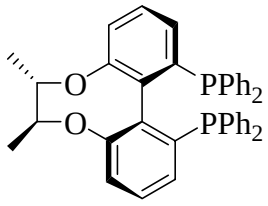


Figure 4.6-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (R_{ax})-**117**



(R_{ax})-**117**

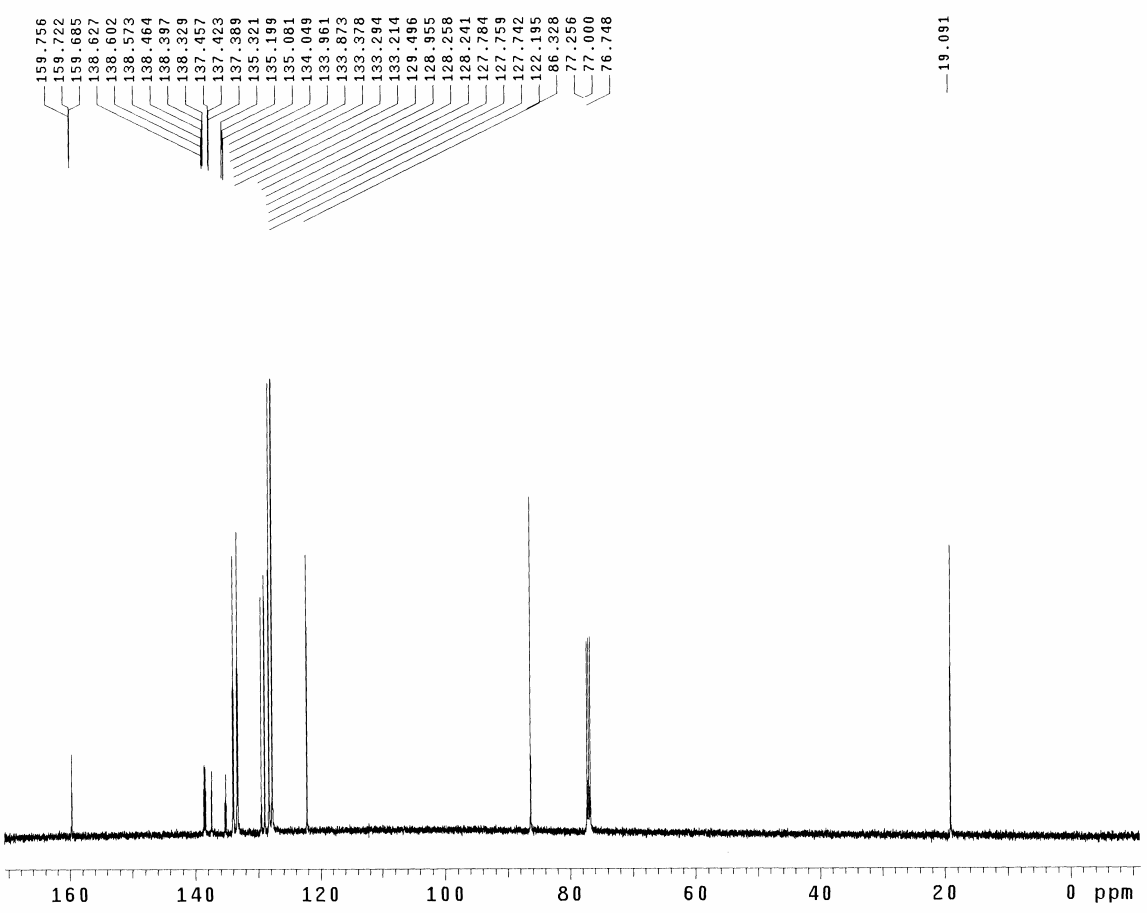
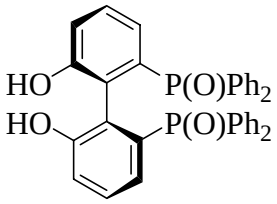


Figure 4.6-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (R_{ax})-**117**



(*S*)-**122**

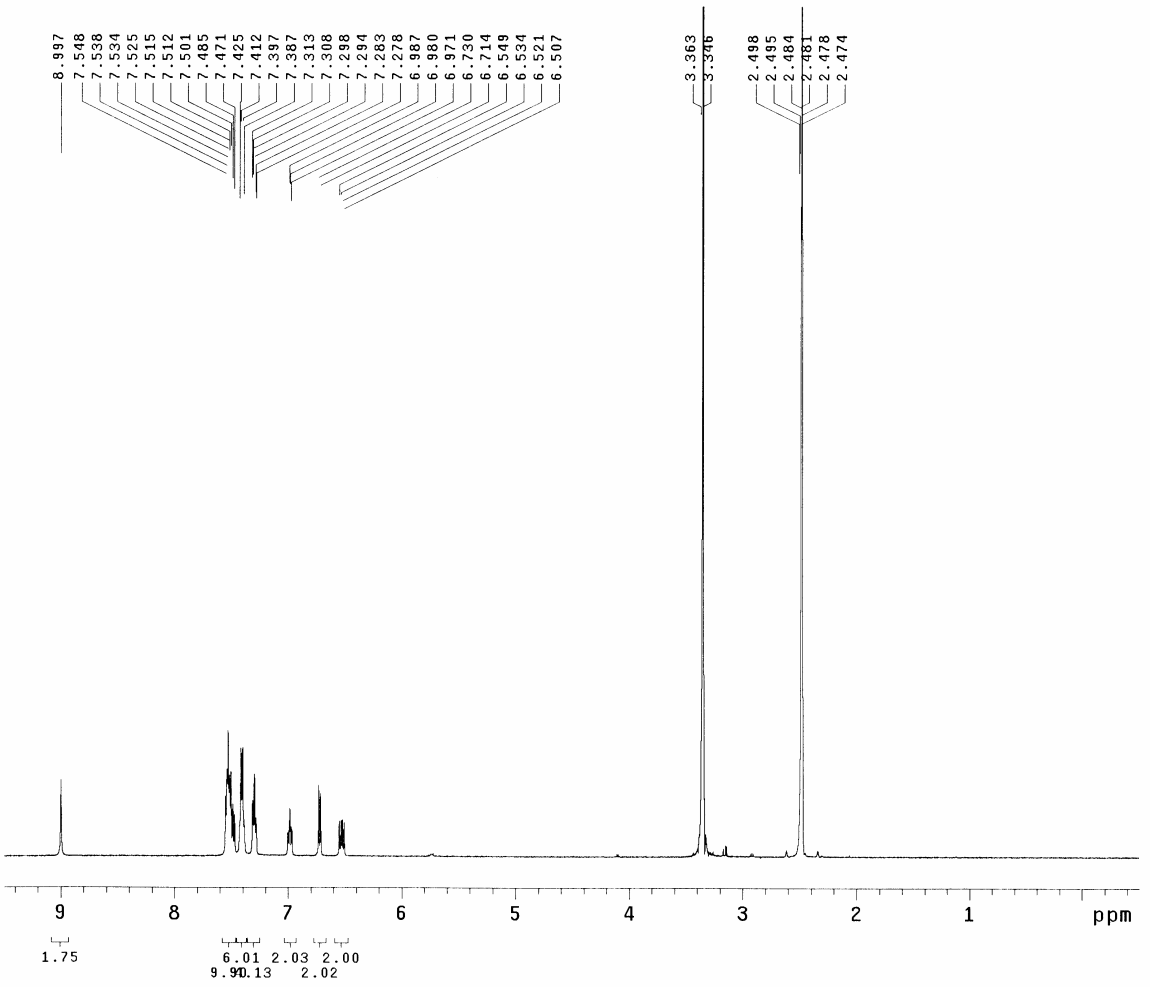
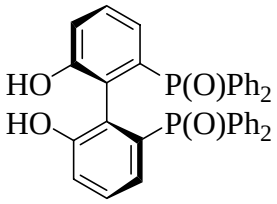


Figure 4.7-1 ^{1}H NMR (500 MHz, *d*-DMSO) Spectrum of (*S*)-**122**



(*S*)-**122**

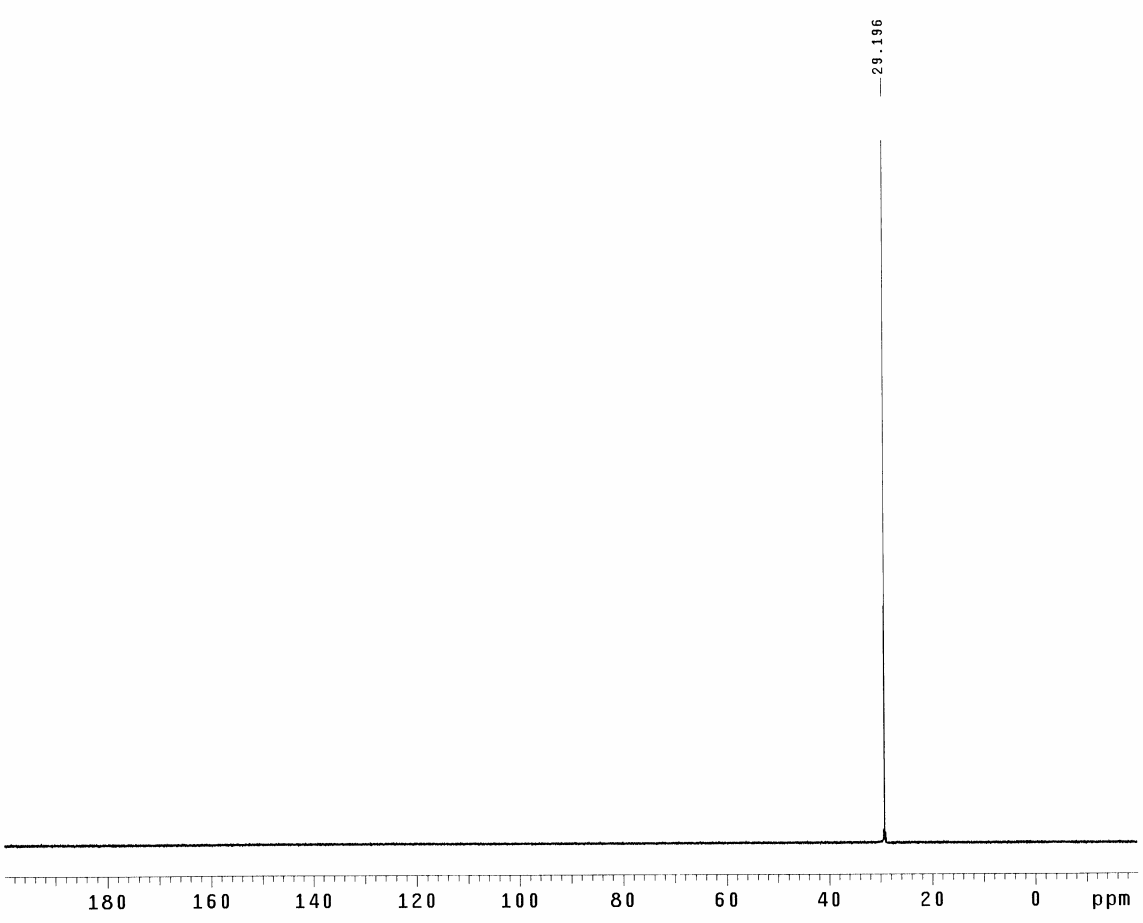
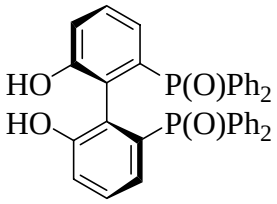


Figure 4.7-2 ^{31}P NMR (202 MHz, *d*-DMSO) Spectrum of (*S*)-**122**



(*S*)-**122**

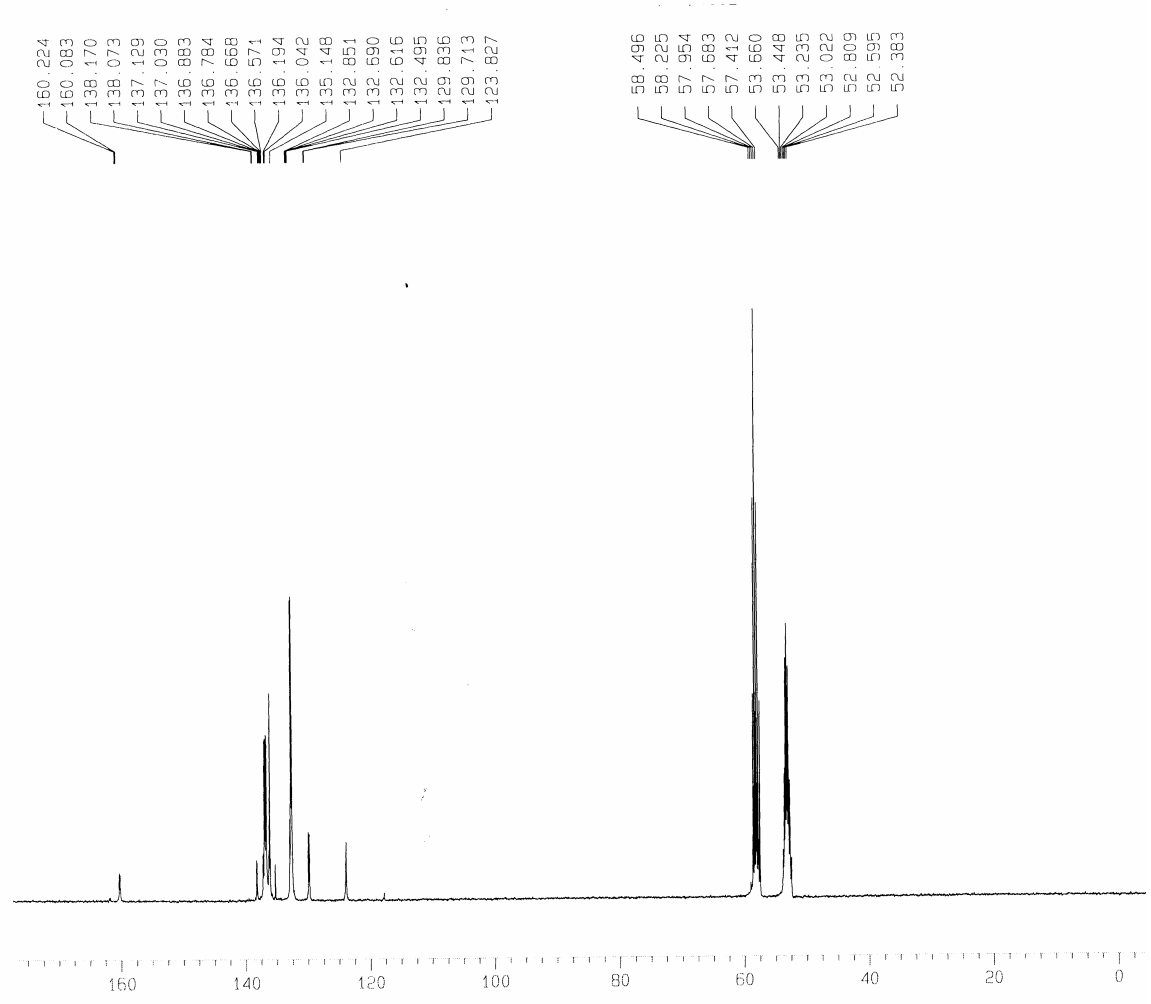
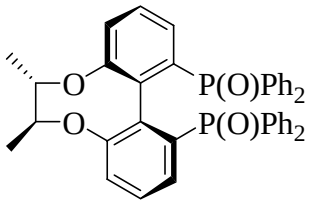


Figure 4.7-3 ^{13}C NMR (125 MHz, CD_2Cl_2+CD_3OD) Spectrum of (*S*)-**122**



(S_{ax})-**123**

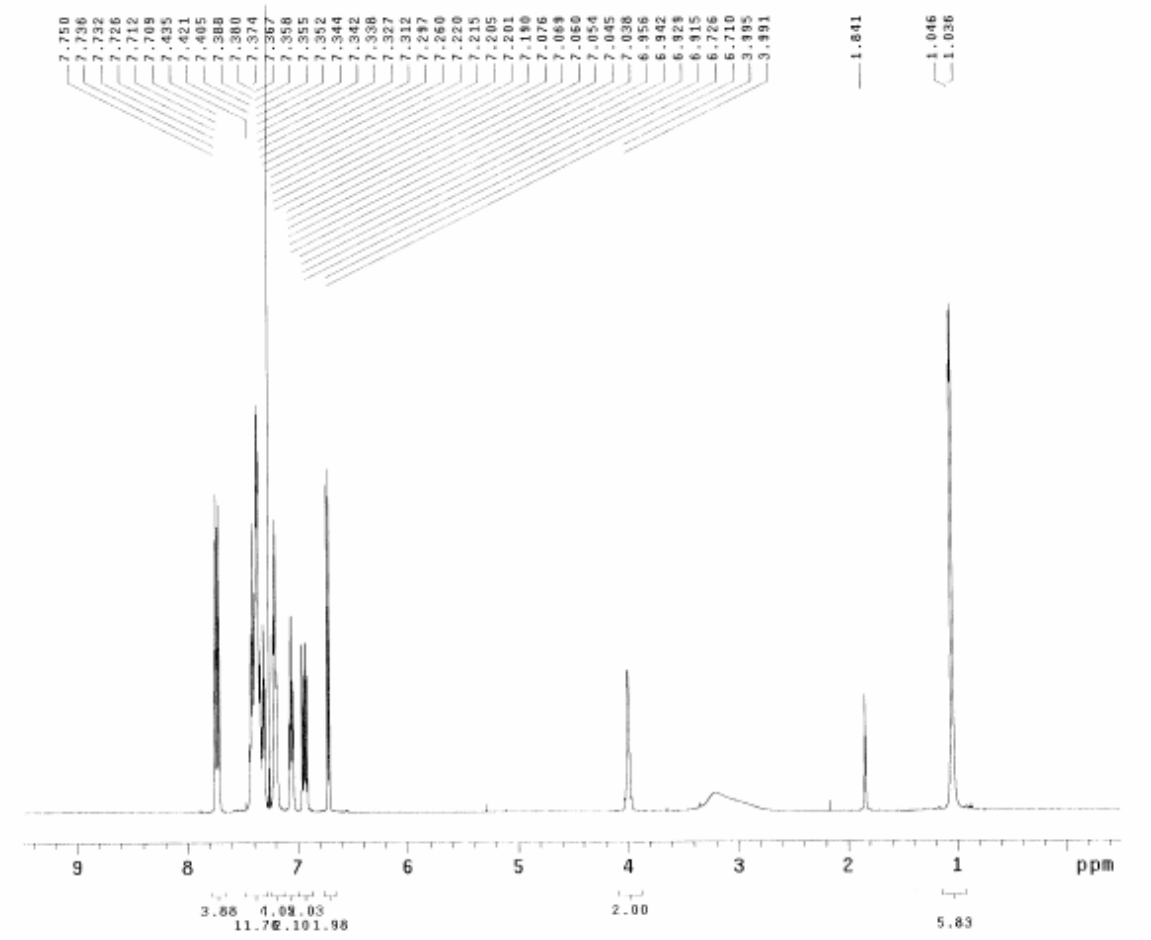
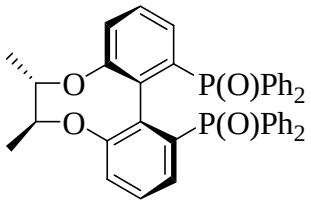


Figure 4.8-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (S_{ax})-**123**



(S_{ax})-**123**

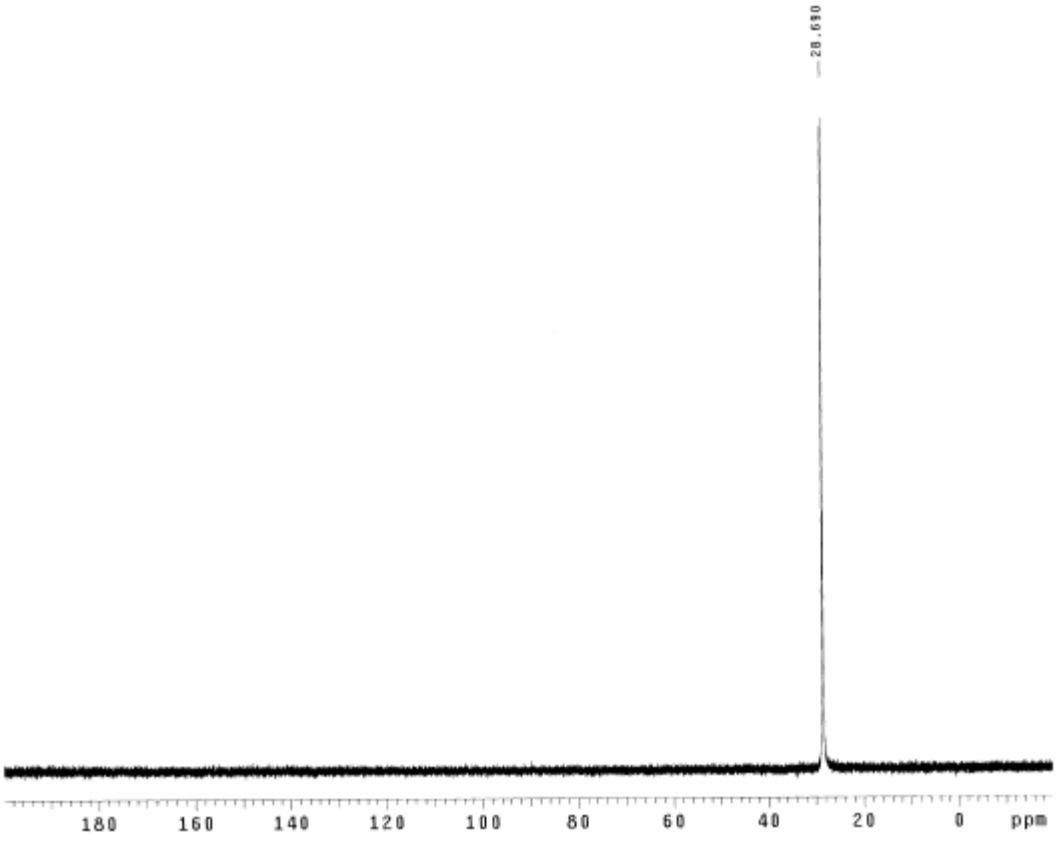
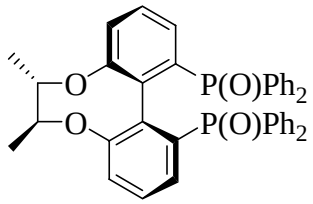


Figure 4.8-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (S_{ax})-**123**



(S_{ax})-**123**

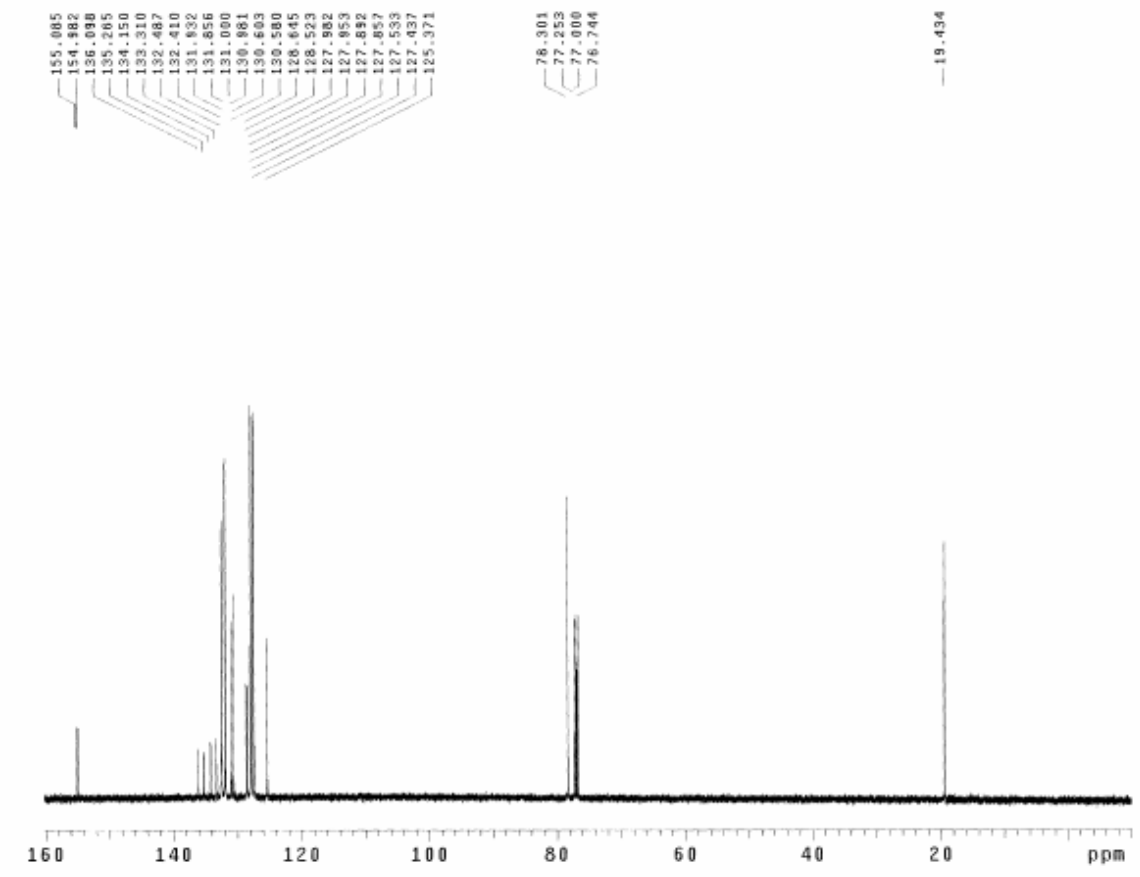
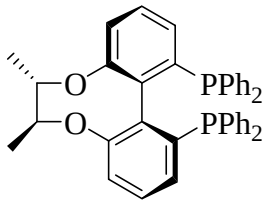


Figure 4.8-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (S_{ax})-**123**



(S_{ax})-**124**

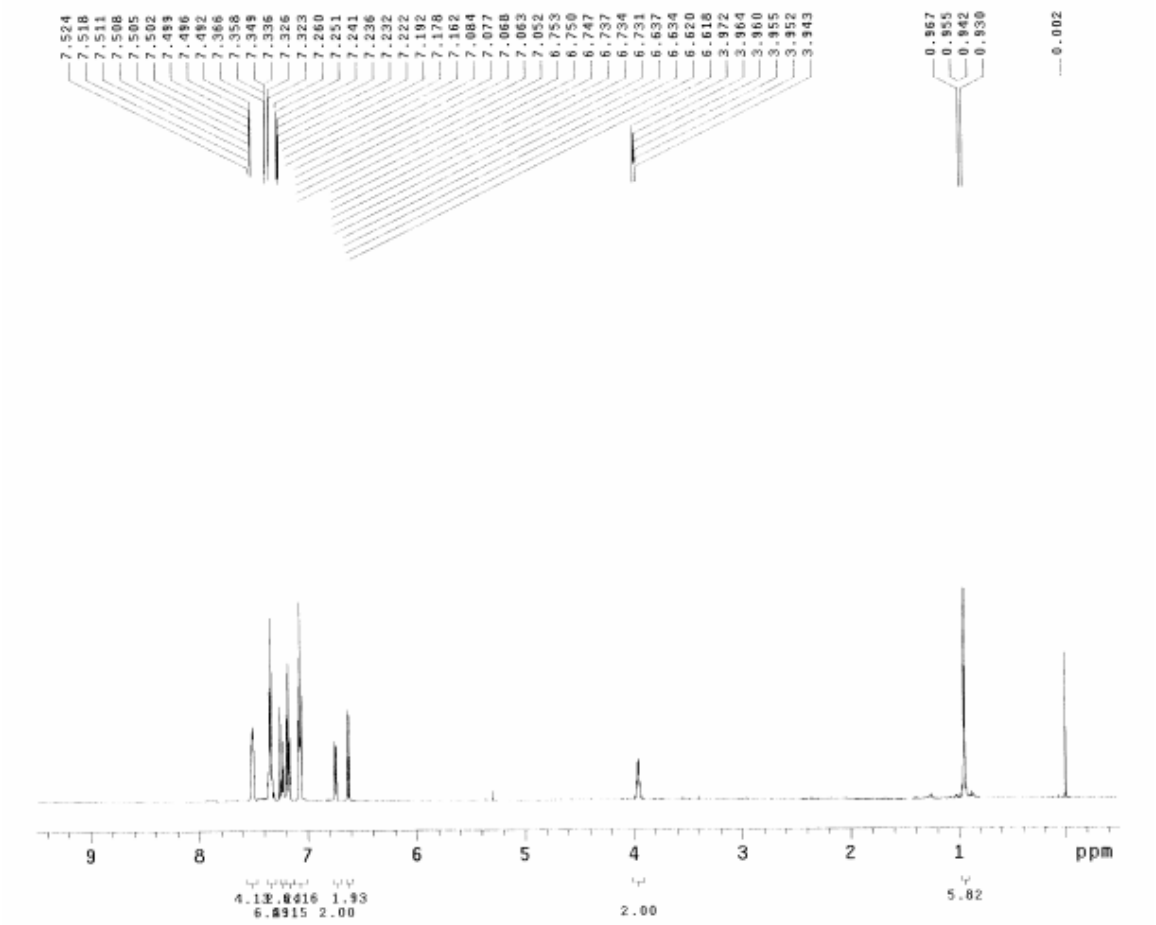
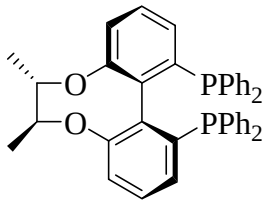


Figure 4.9-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (S_{ax})-**124**



(S_{ax})-**124**

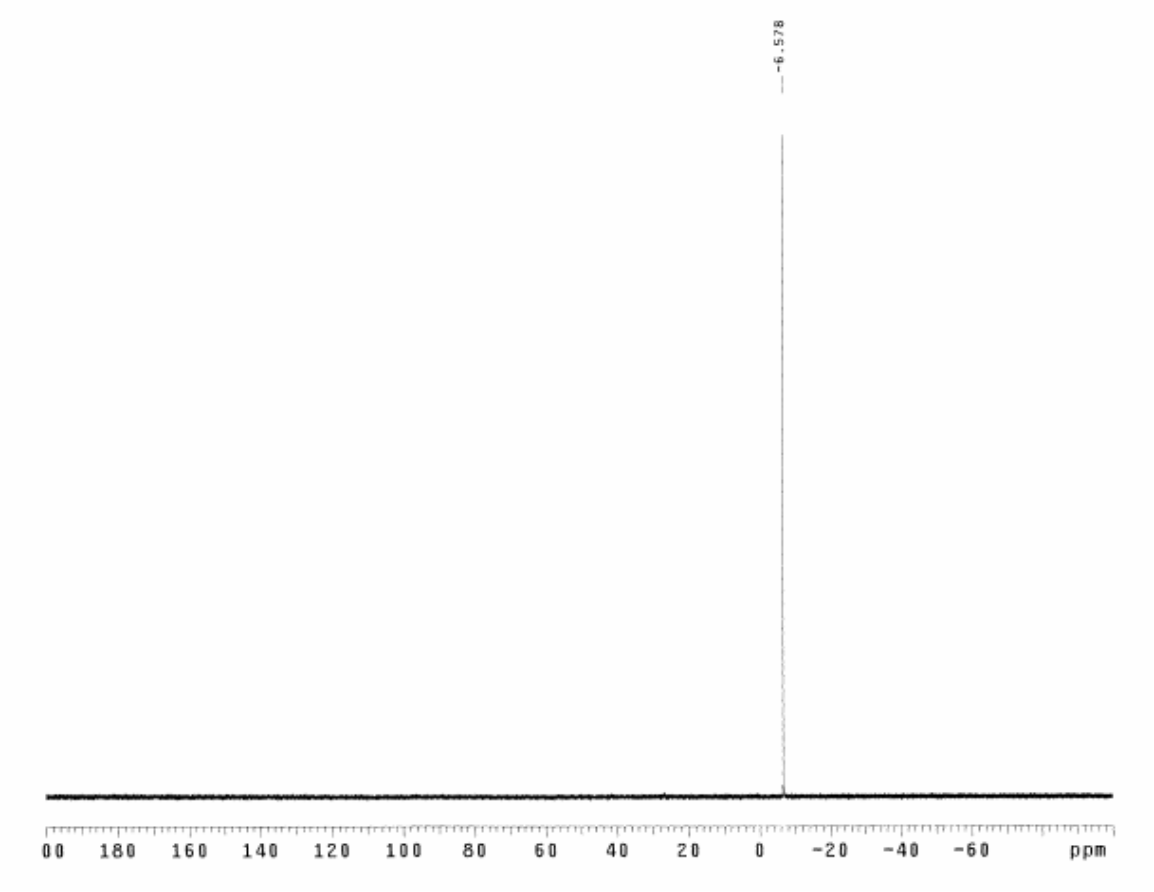
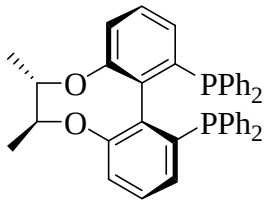


Figure 4.9-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (S_{ax})-**124**



(S_{ax})-**124**

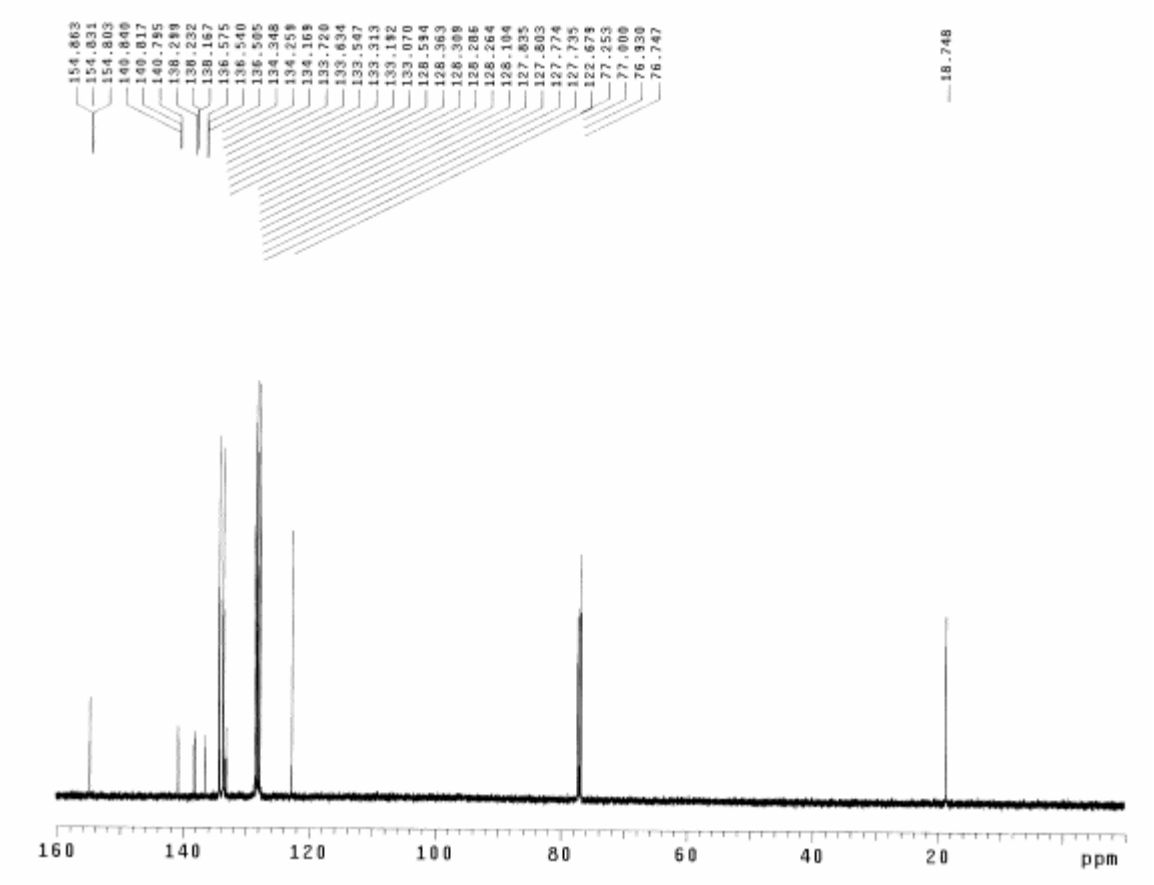
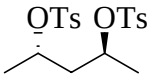


Figure 4.9-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (S_{ax})-**124**



(*S*,*S*)-**126**

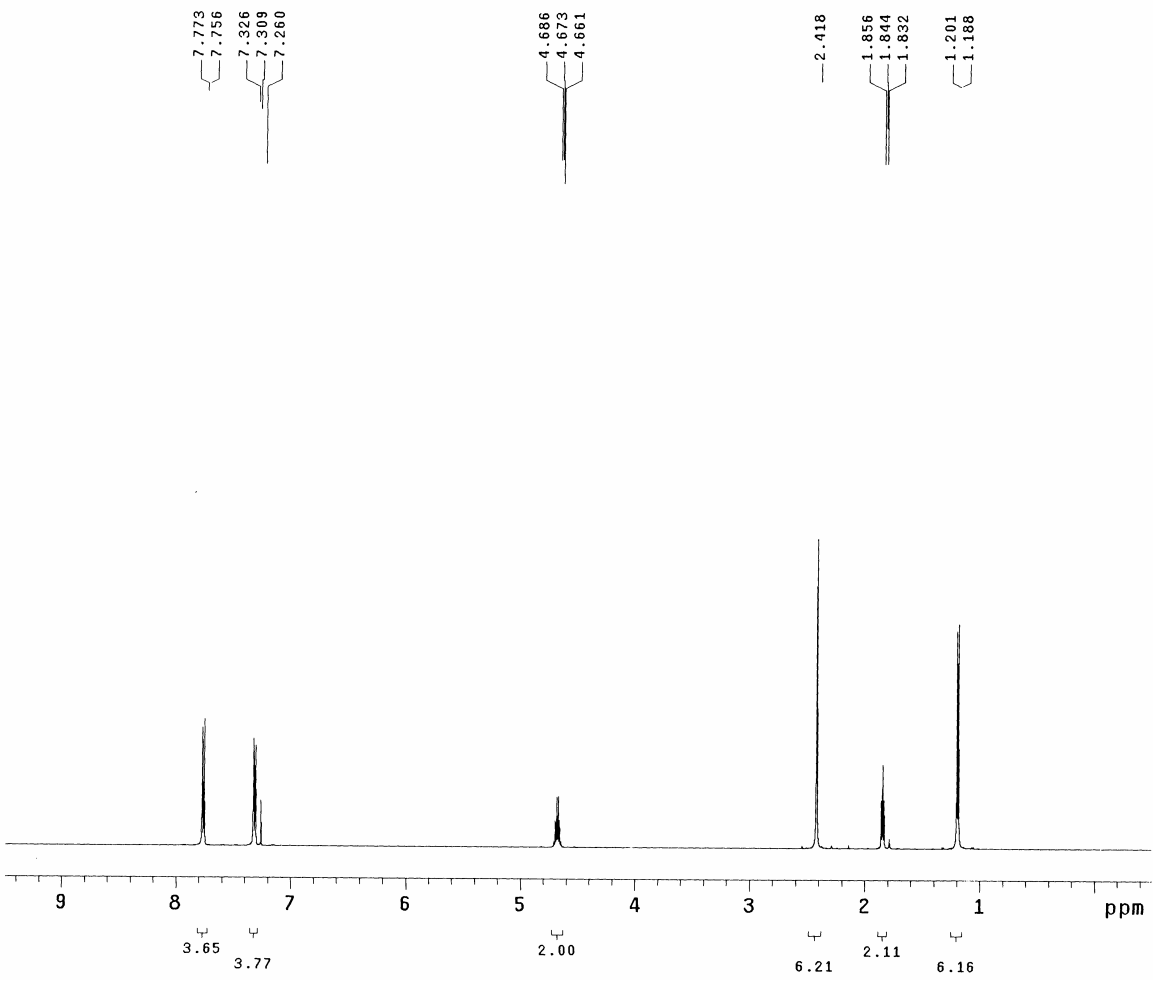
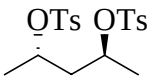


Figure 4.10-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**126**



(*S*,*S*)-**126**

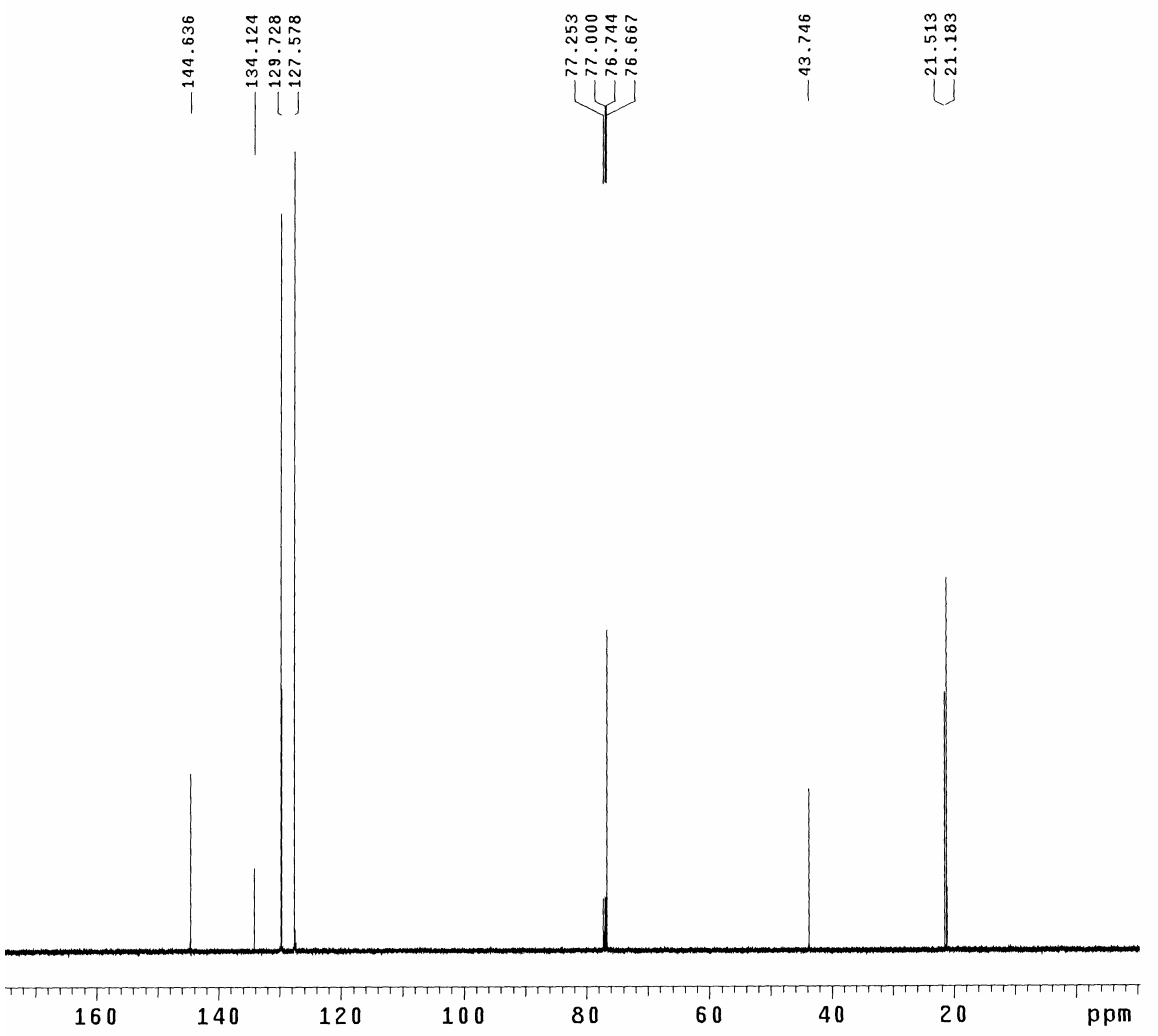
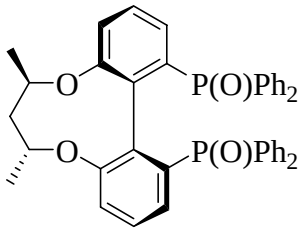


Figure 4.10-2 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**126**



(S_{ax})-**127**

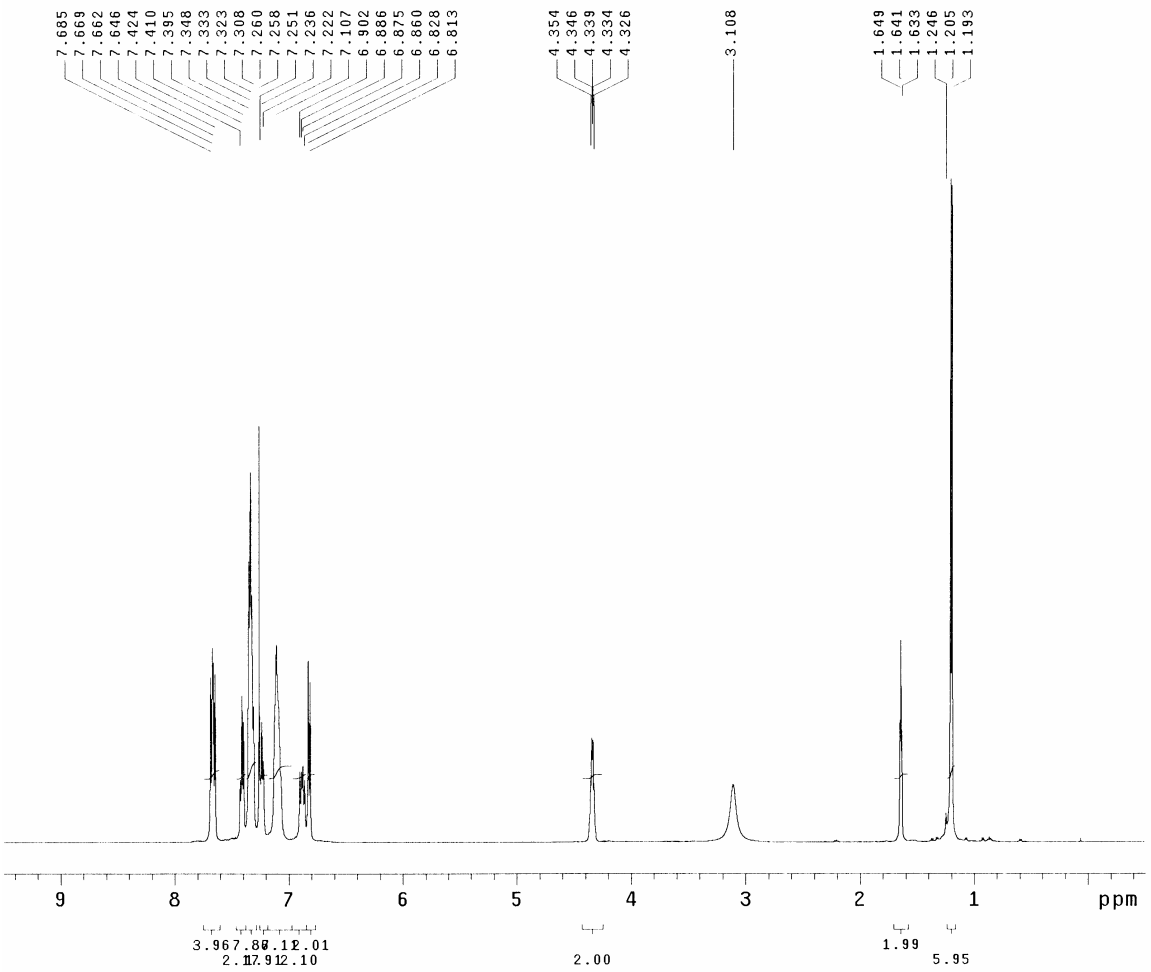
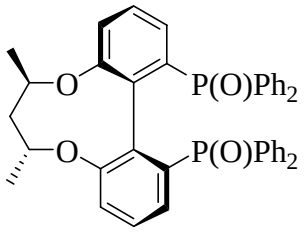


Figure 4.11-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (S_{ax})-**127**



(S_{ax})-**127**

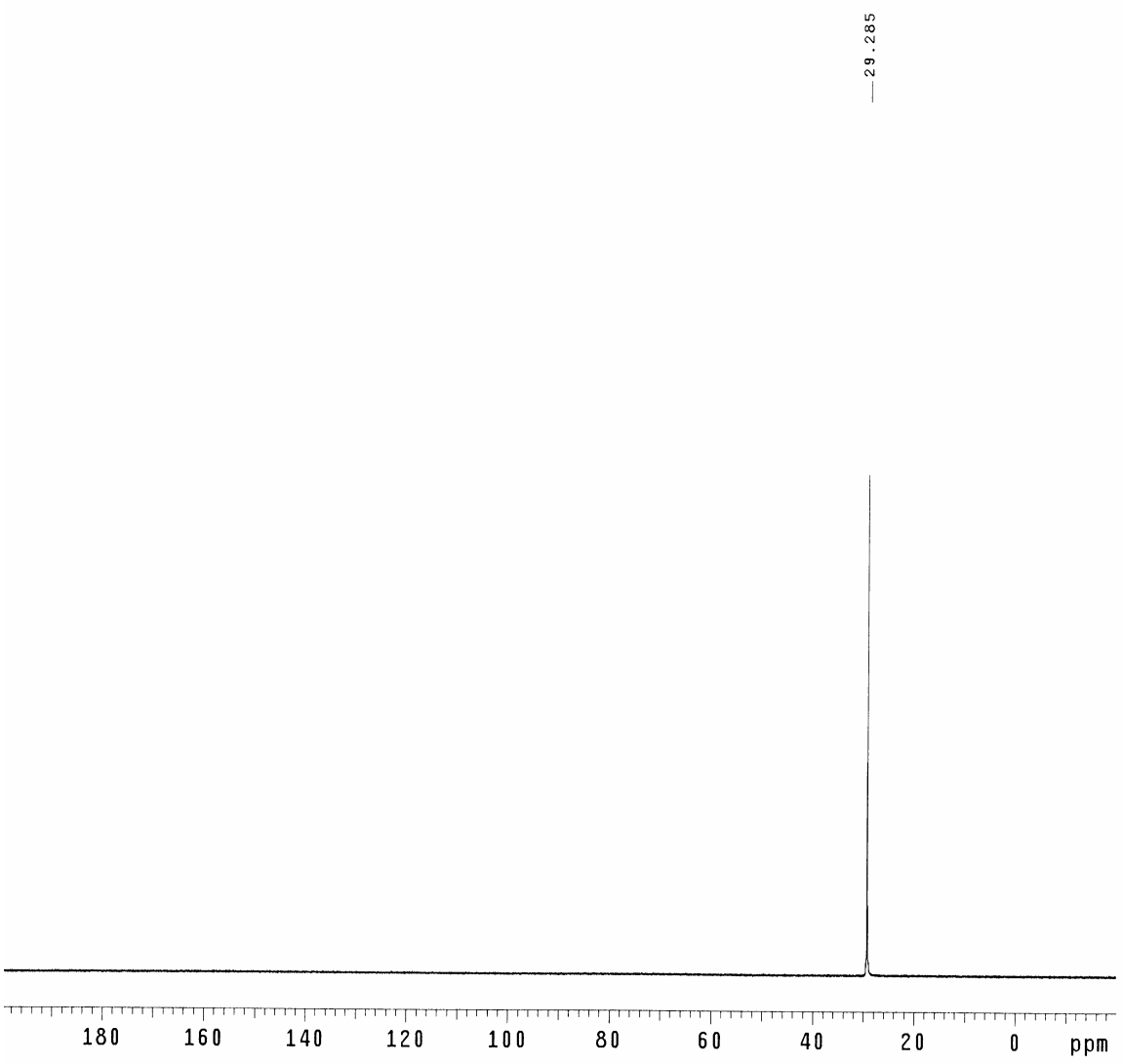
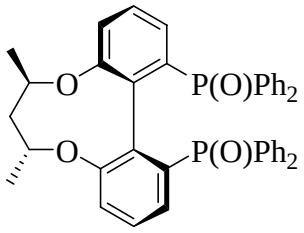


Figure 4.11-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (S_{ax})-**127**



(S_{ax})-**127**

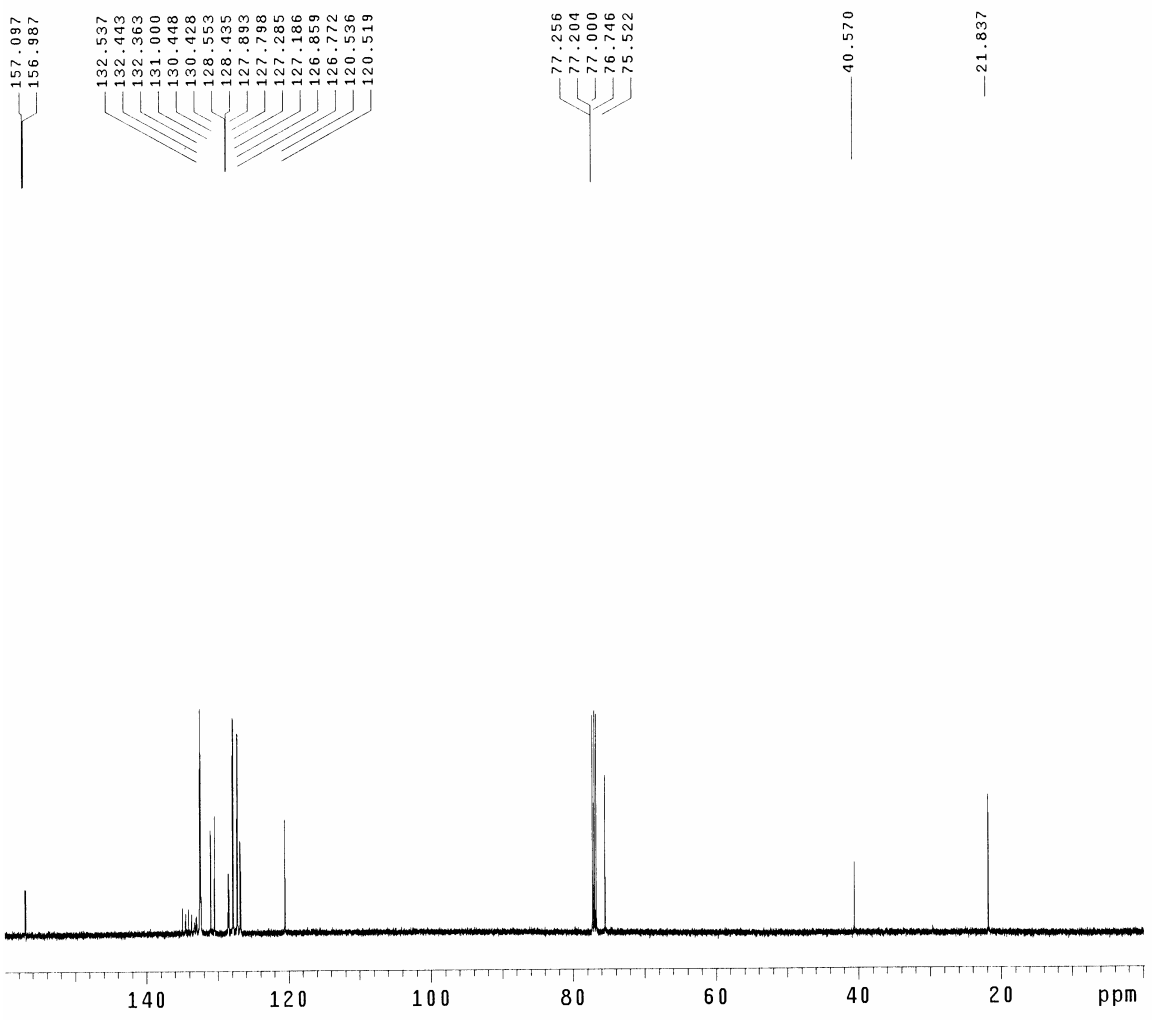
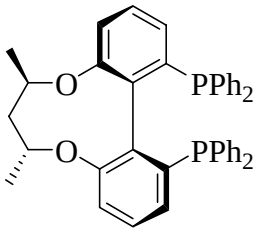


Figure 4.11-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (S_{ax})-**127**



(S_{ax})-**128**

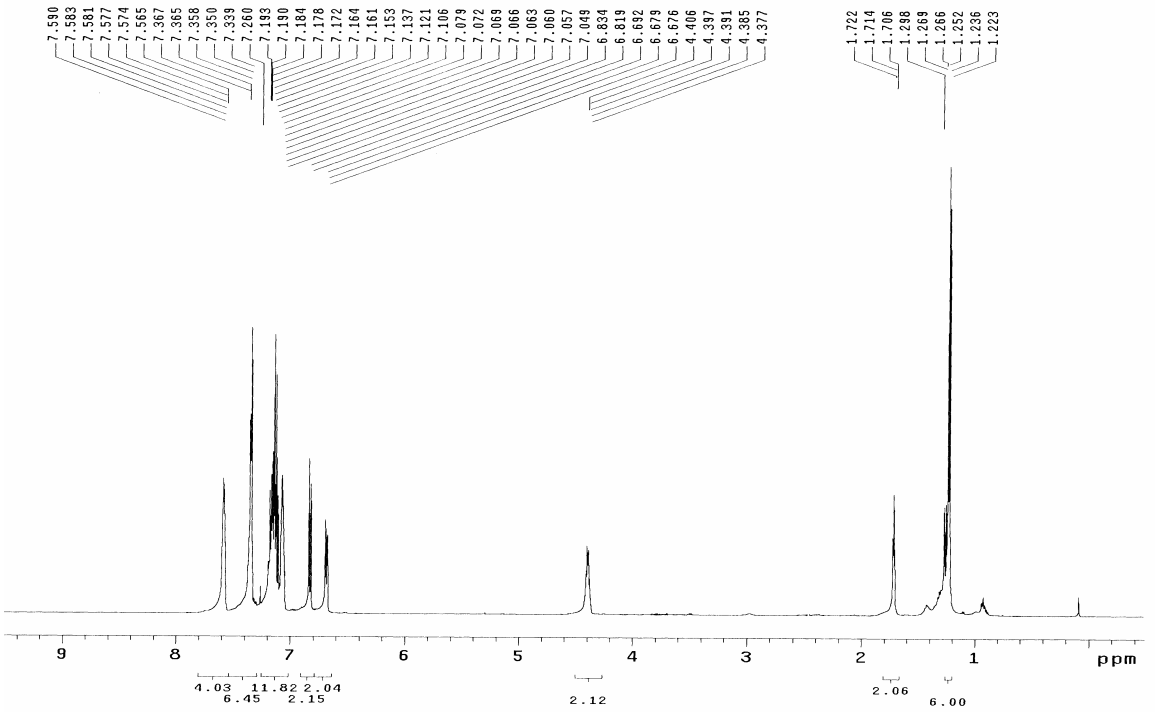
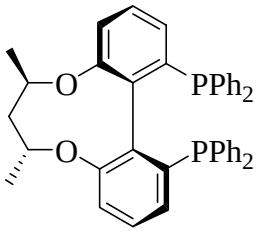


Figure .4.12-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (S_{ax})-**128**



(S_{ax})-**128**

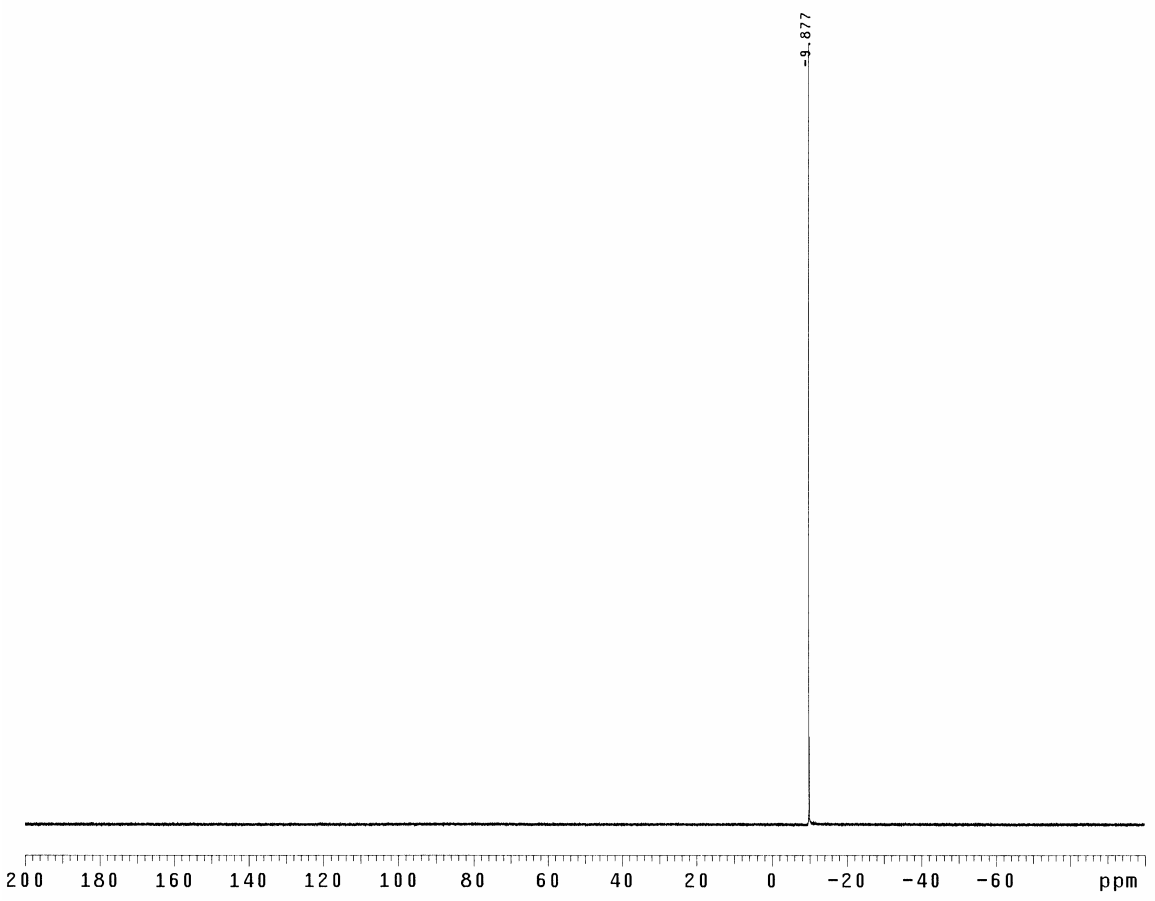
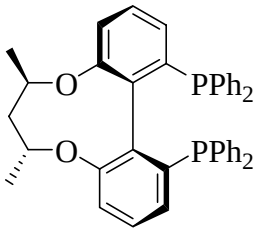


Figure 4.12-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (S_{ax})-**128**



(S_{ax})-**128**

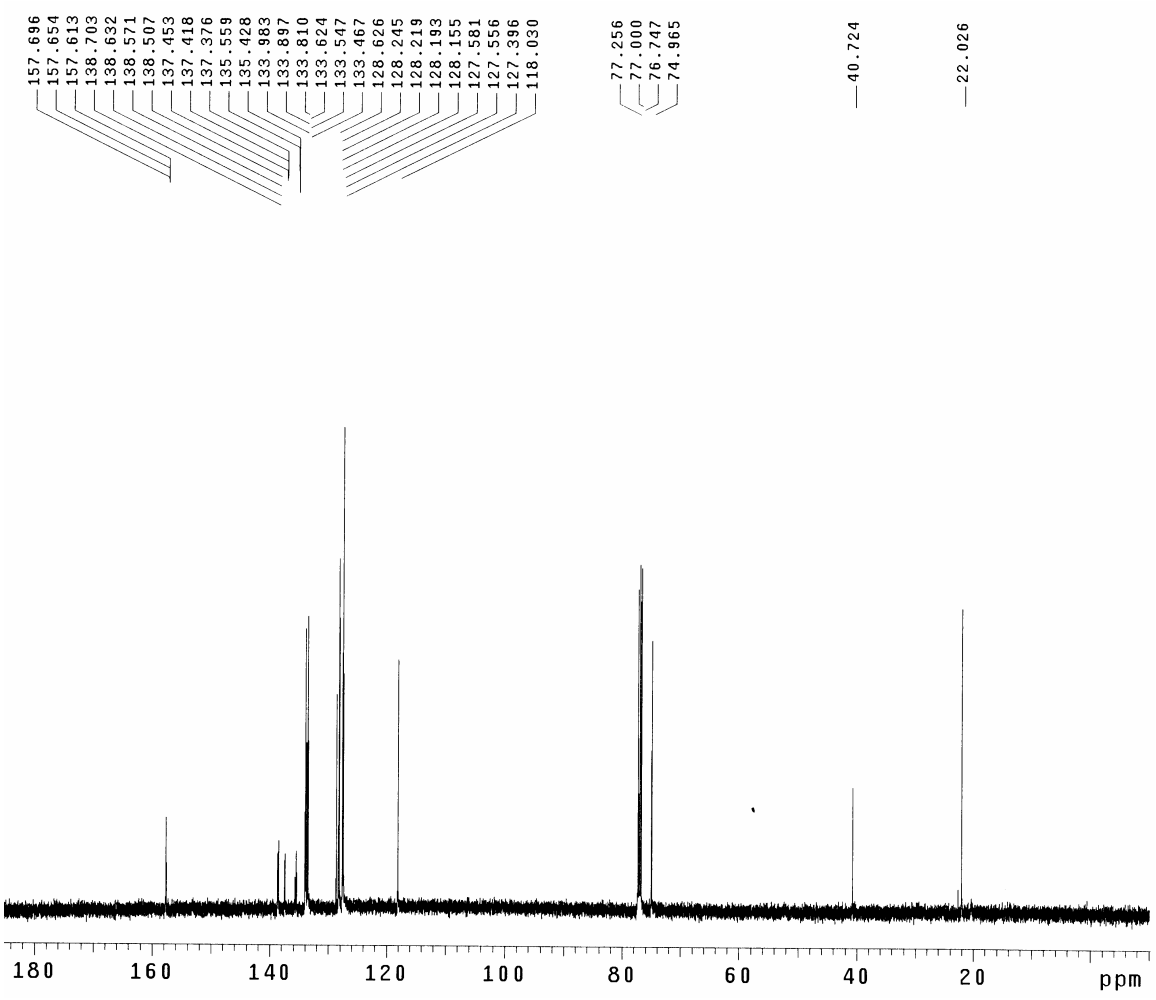
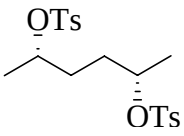


Figure 4.12-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (S_{ax})-**128**



(*S*,*S*)-**130**

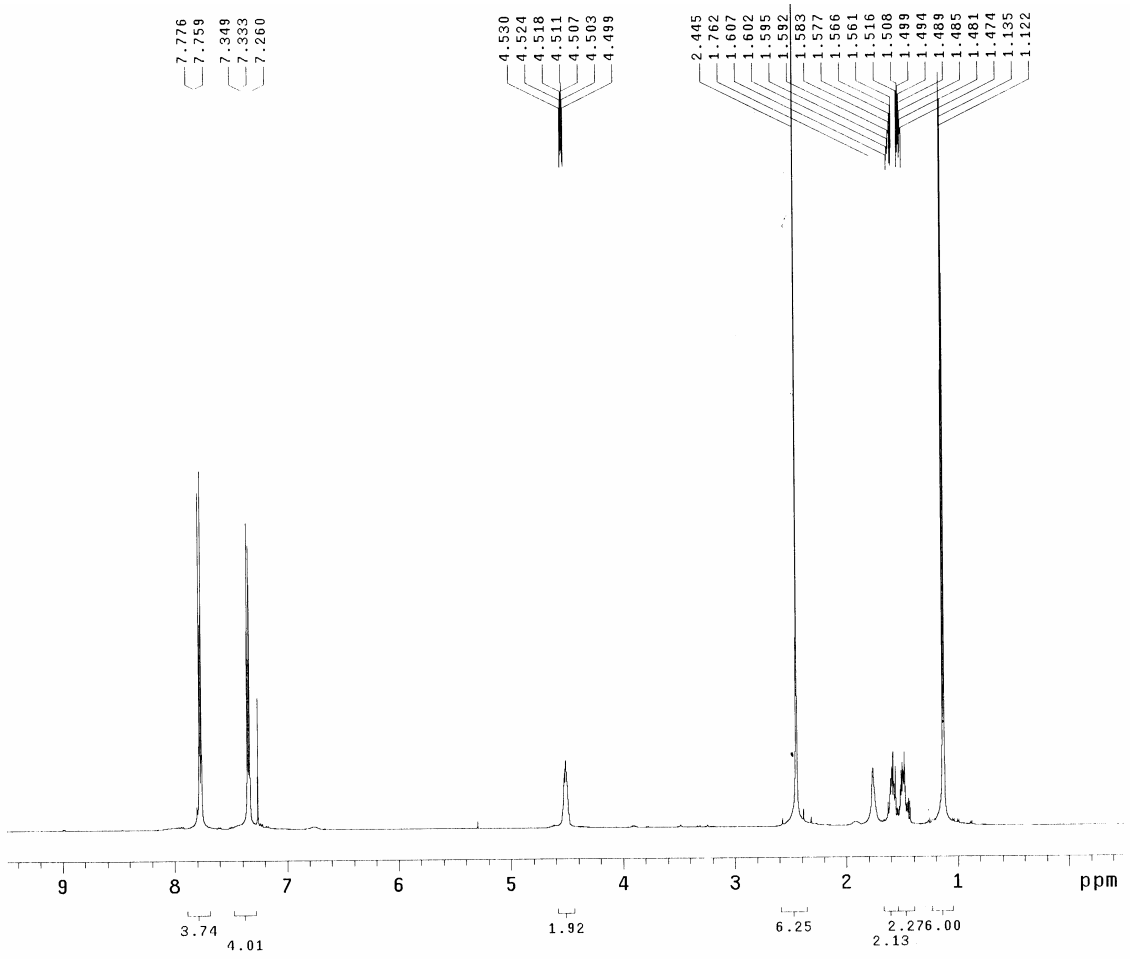
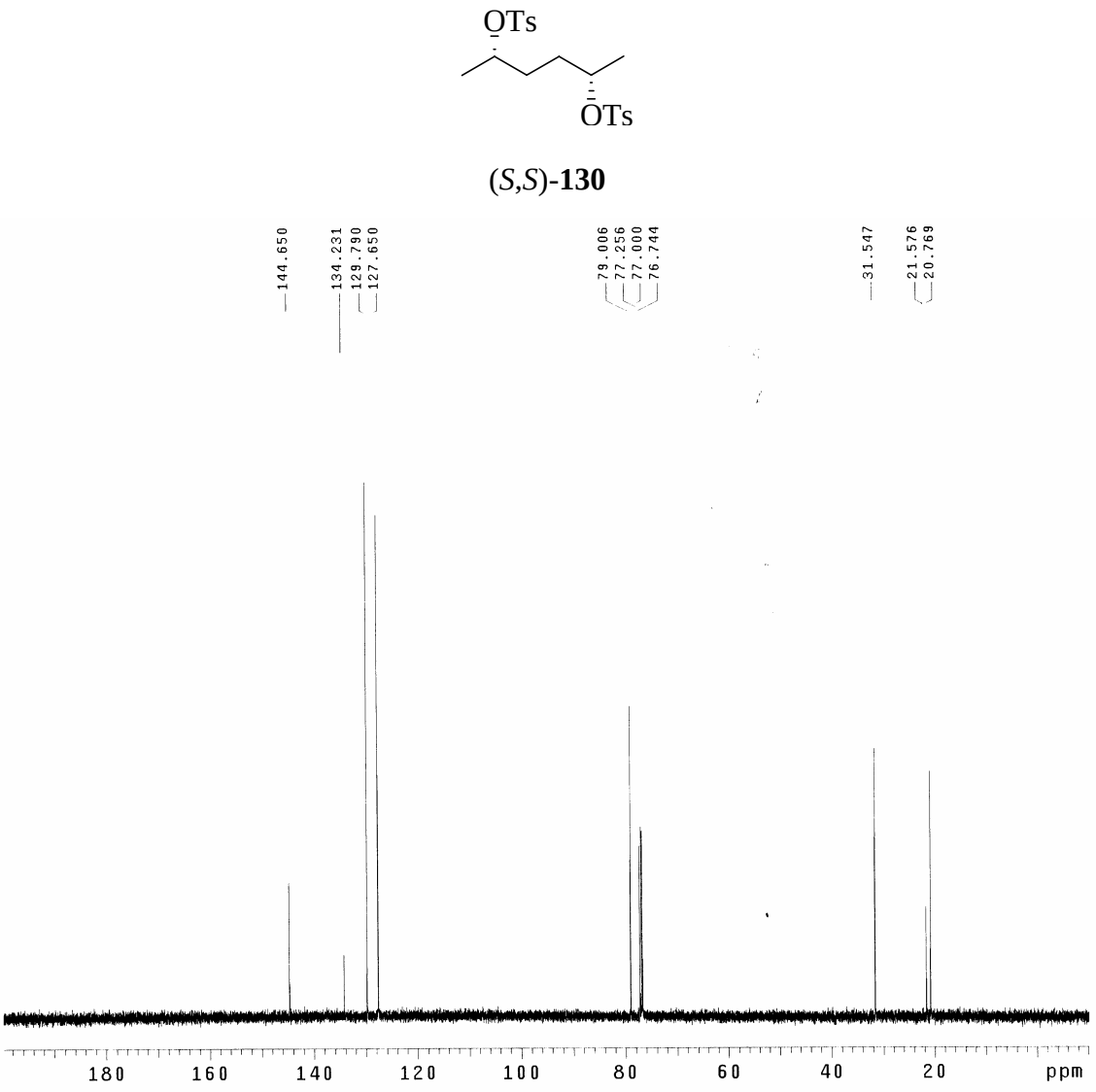
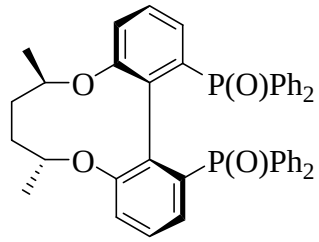


Figure 4.13-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**130**



(*S*,*S*)-**130**

Figure 4.13-2 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**130**



(S_{ax})-**131**

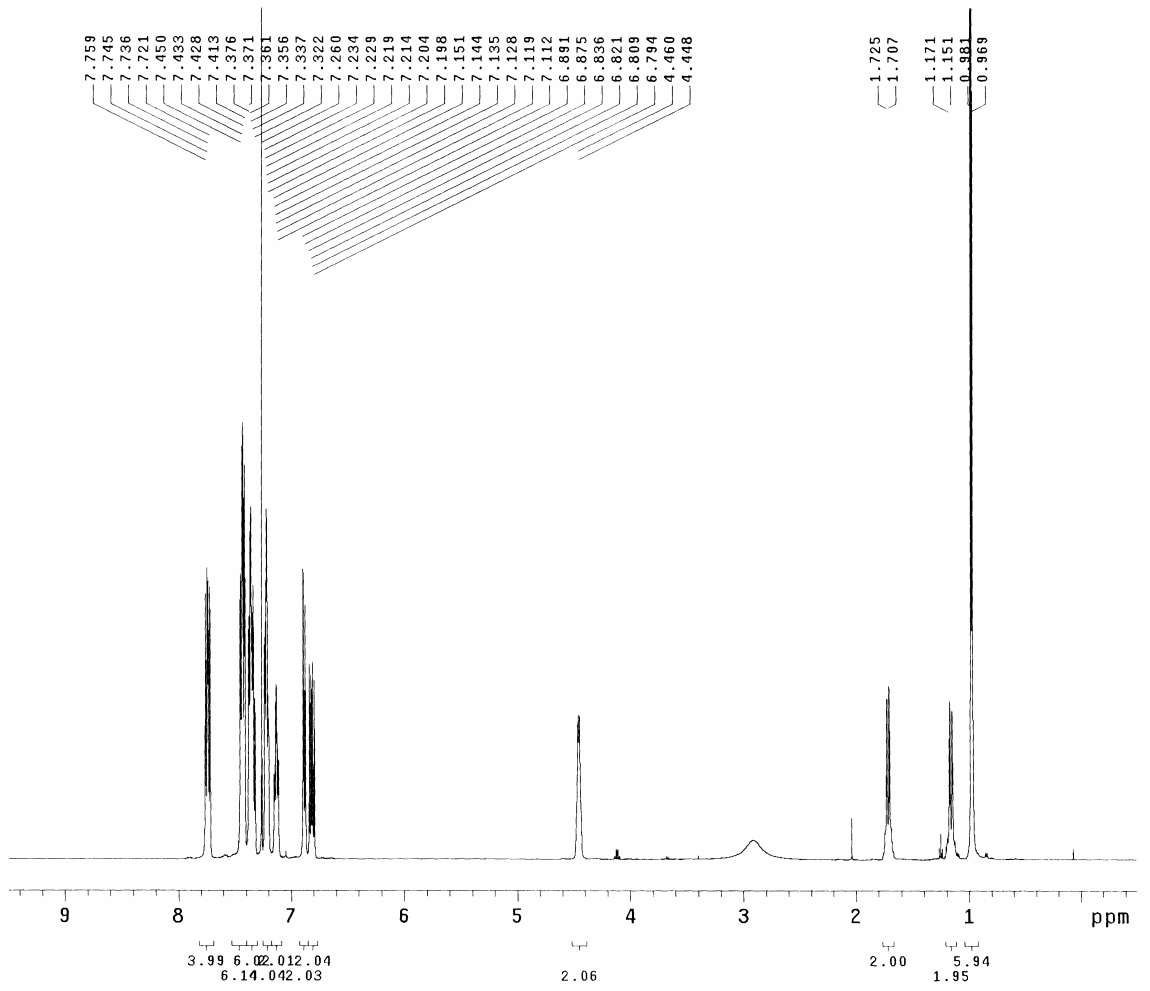
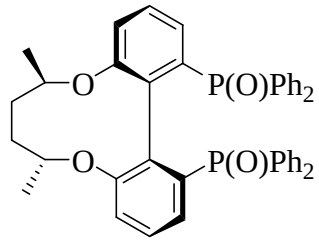


Figure 4.14-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (S_{ax})-**131**



(S_{ax})-**131**

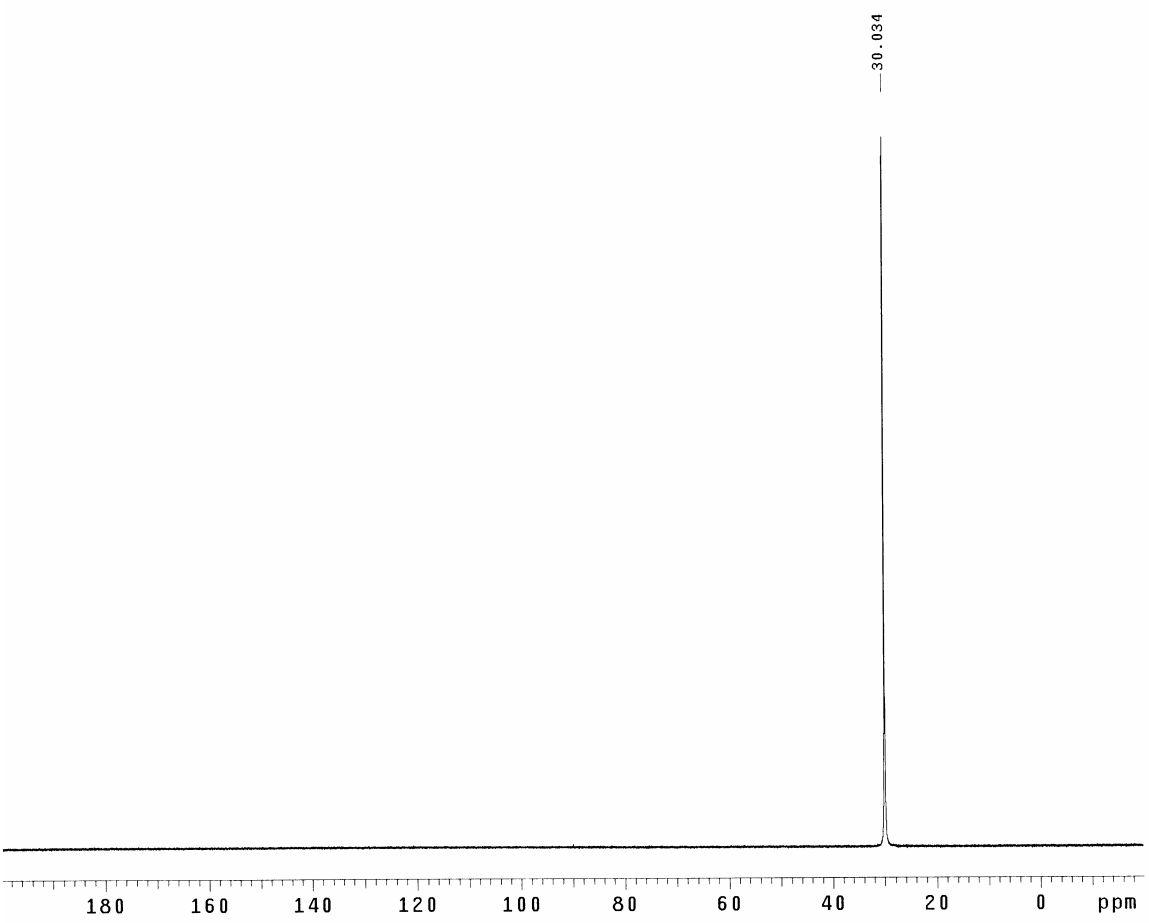
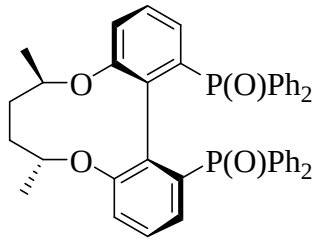


Figure 4.14-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (S_{ax})-**131**



(S_{ax})-**131**

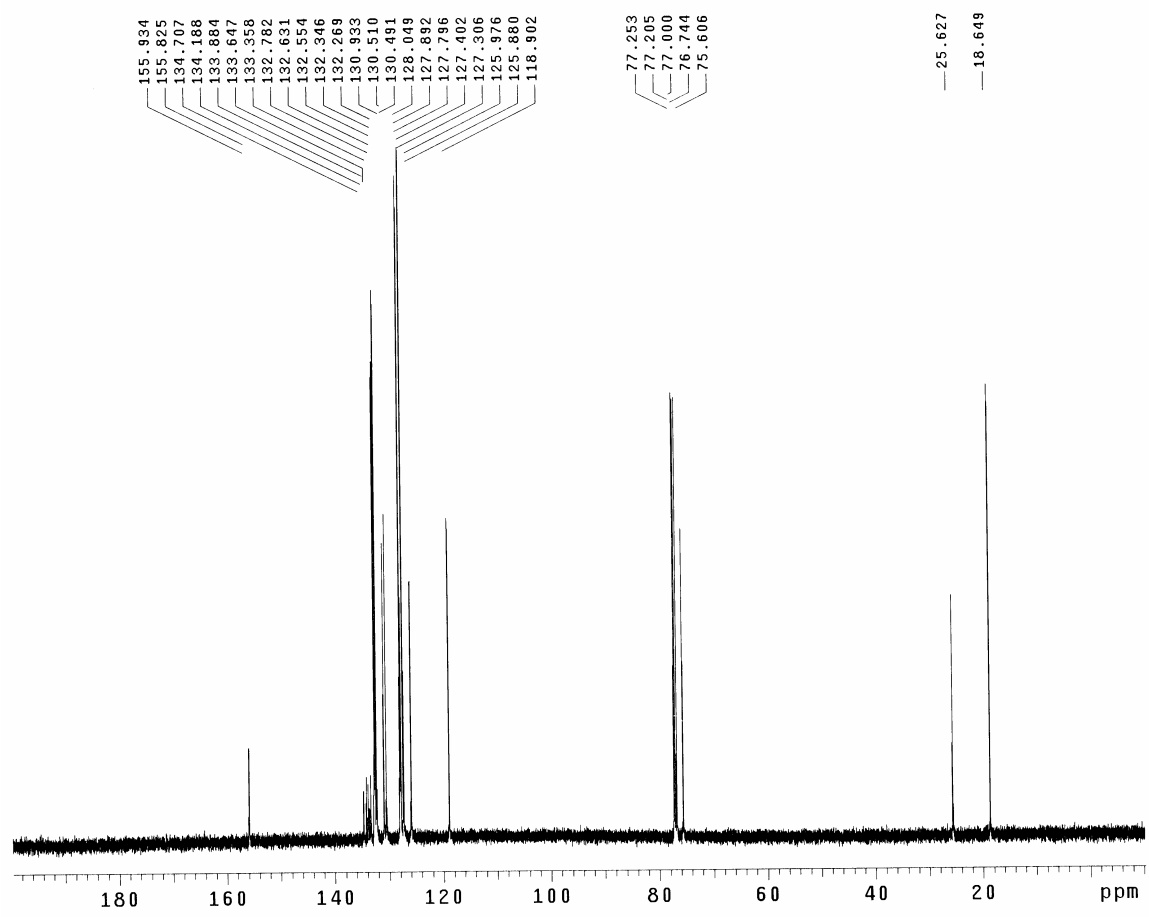
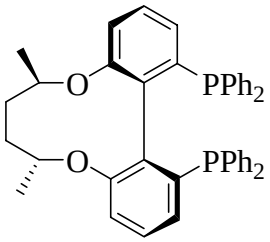


Figure 4.14-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (S_{ax})-**131**



(S_{ax})-**132**

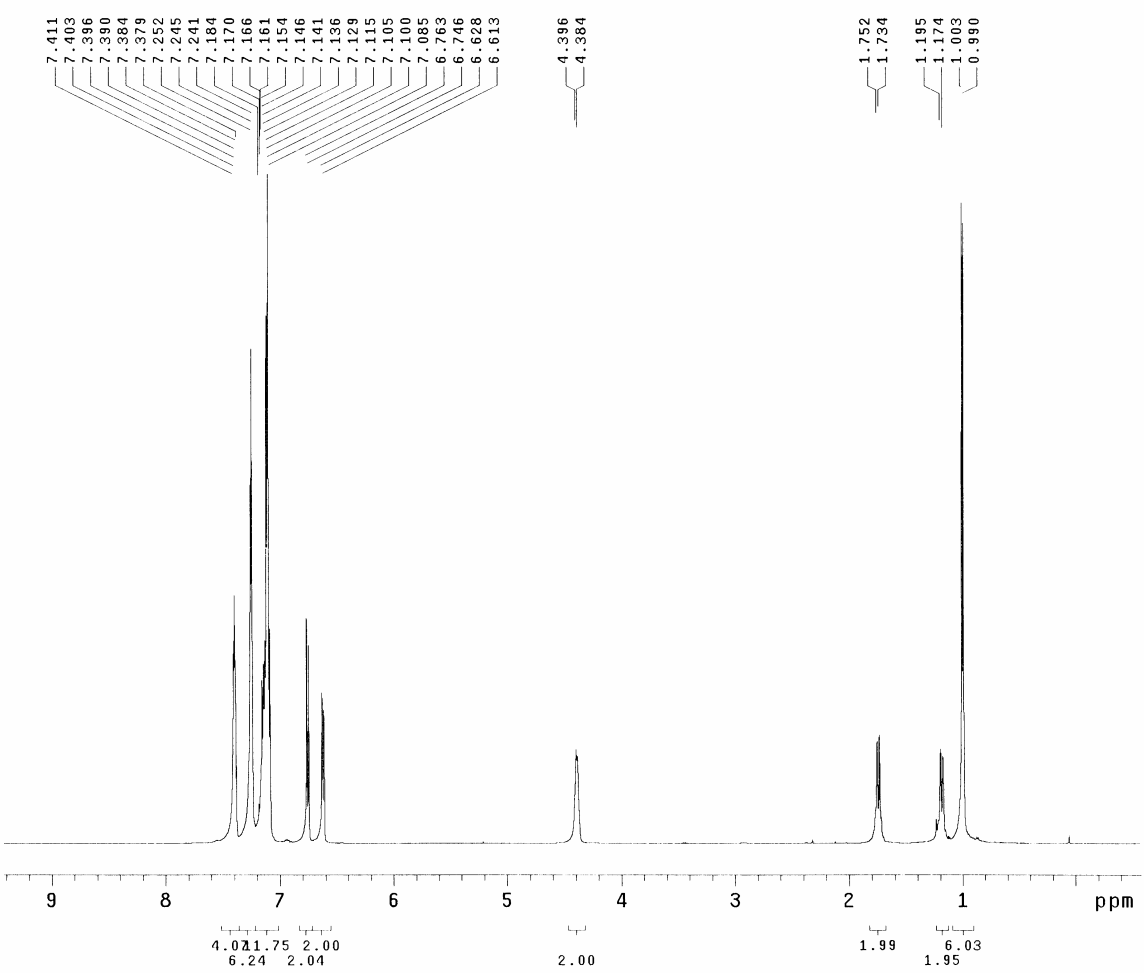
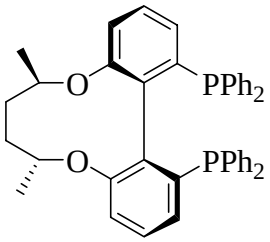


Figure 4.15-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (S_{ax})-**132**



(S_{ax})-**132**

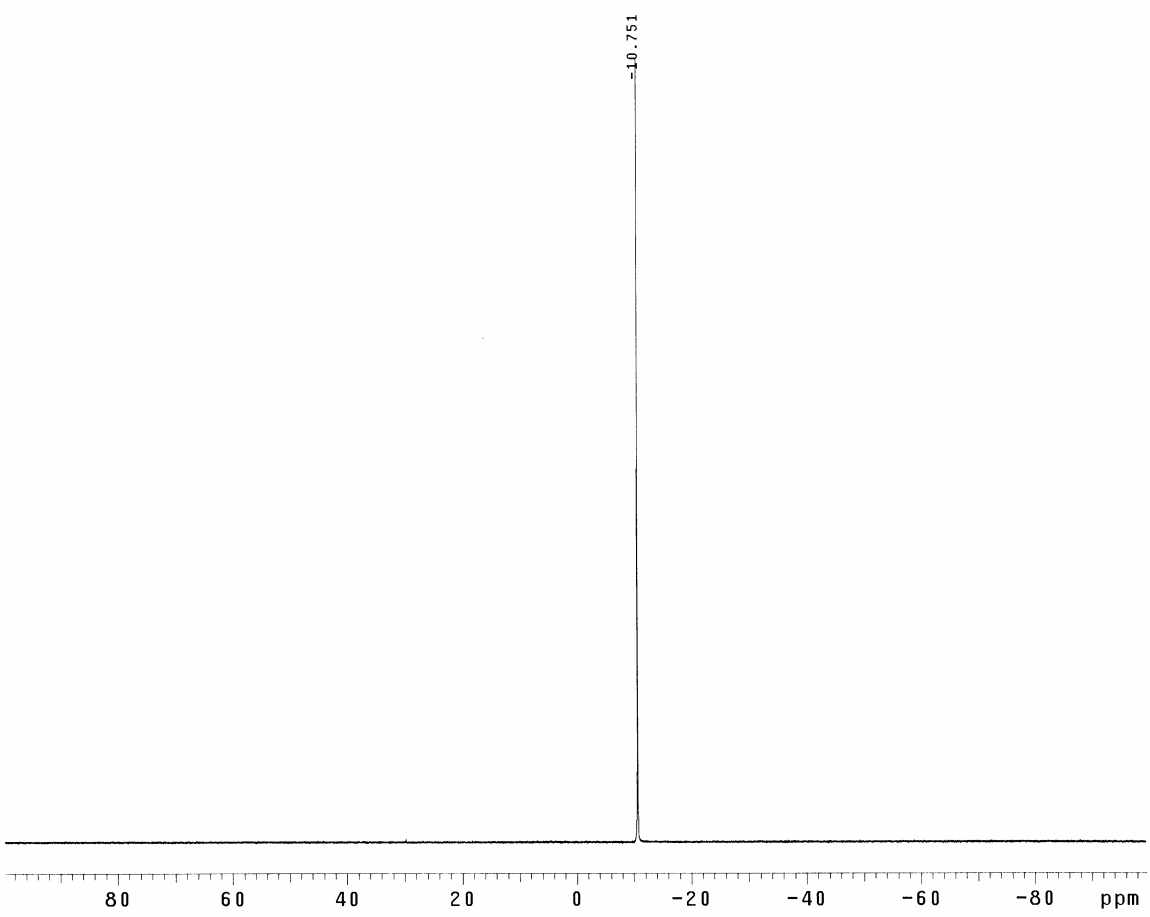
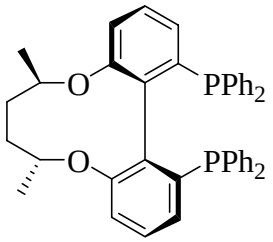


Figure 4.15-2 ^{31}P NMR (202 MHz, $CDCl_3$) Spectrum of (S_{ax})-**132**



(S_{ax})-**132**

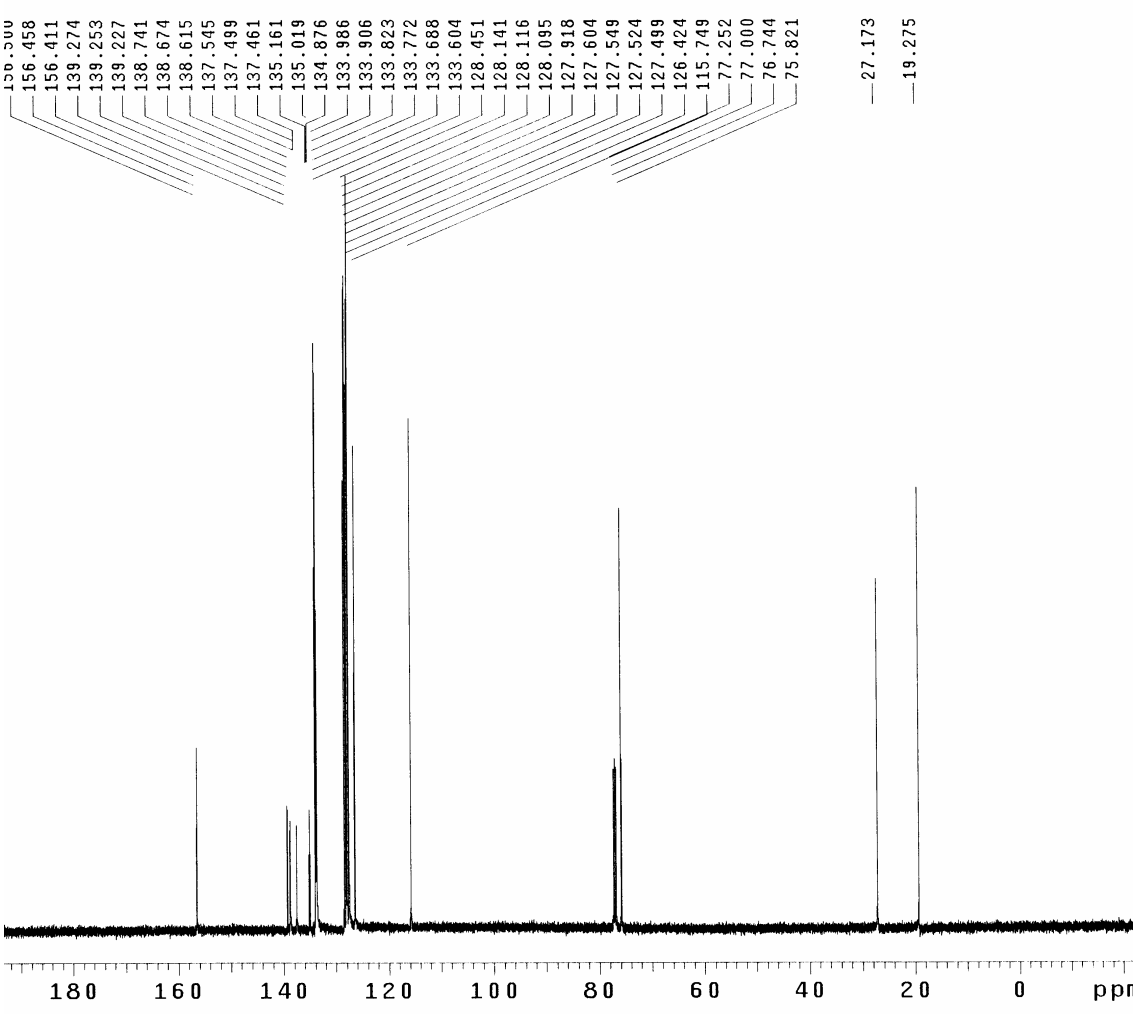
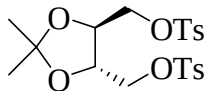


Figure 4.15-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (S_{ax})-**132**



(*S*,*S*)-**135**

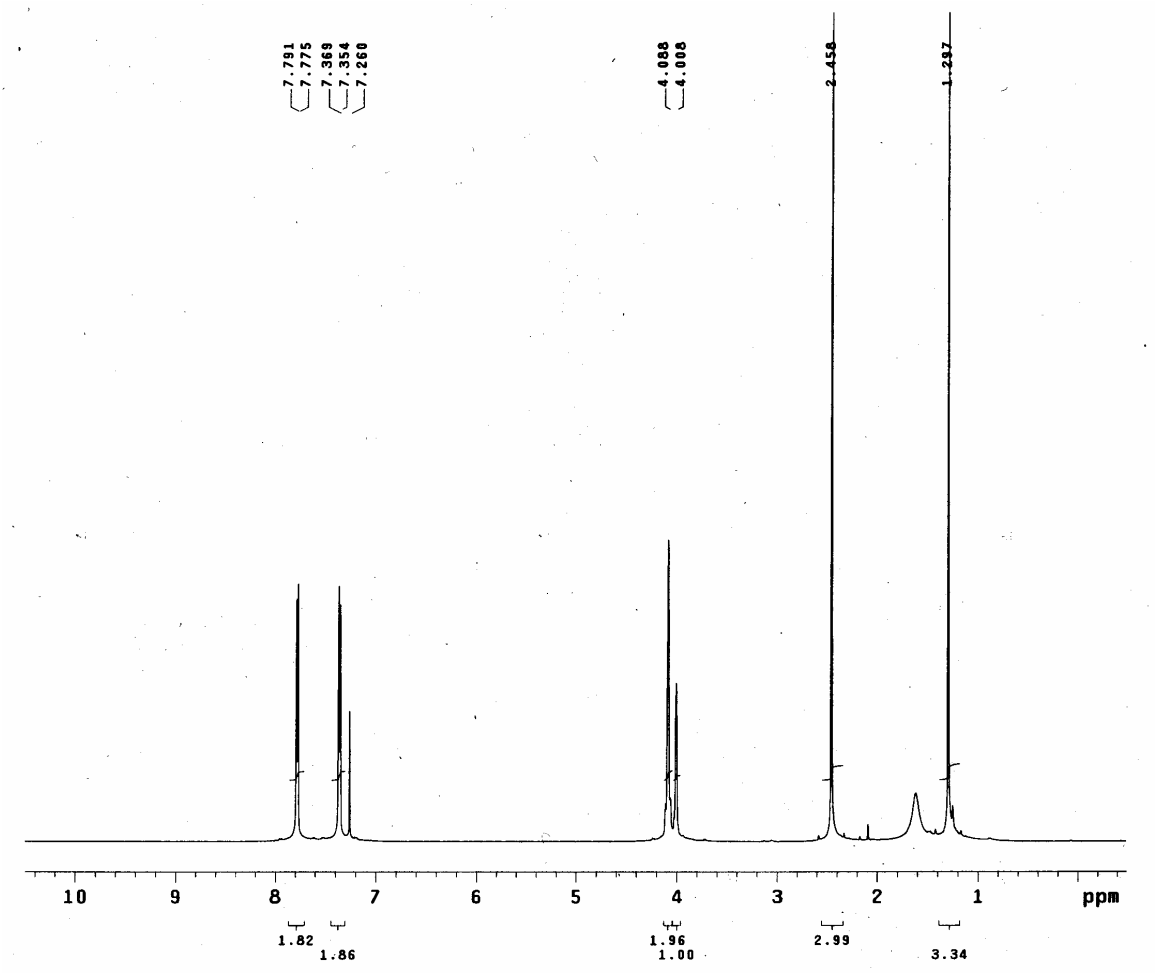
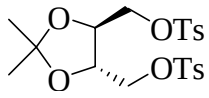


Figure 4.16-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**135**



(*S*,*S*)-**135**

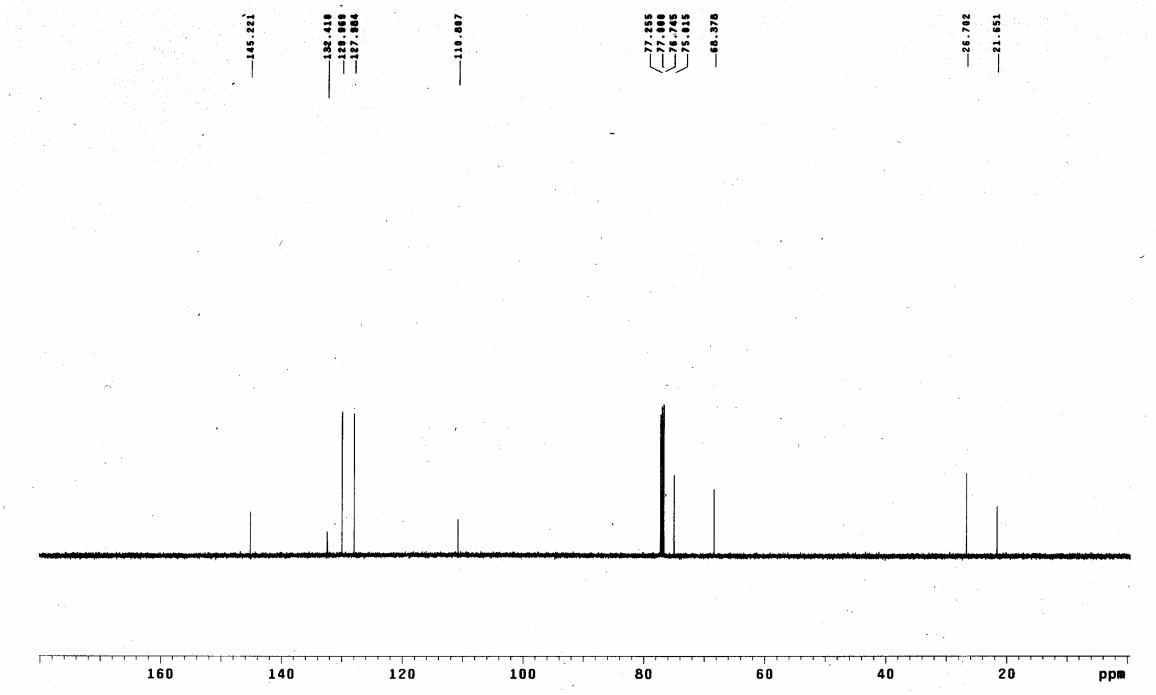
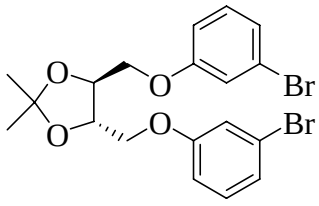


Figure 4.16-2 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**135**



(*R*,*R*)-**136**

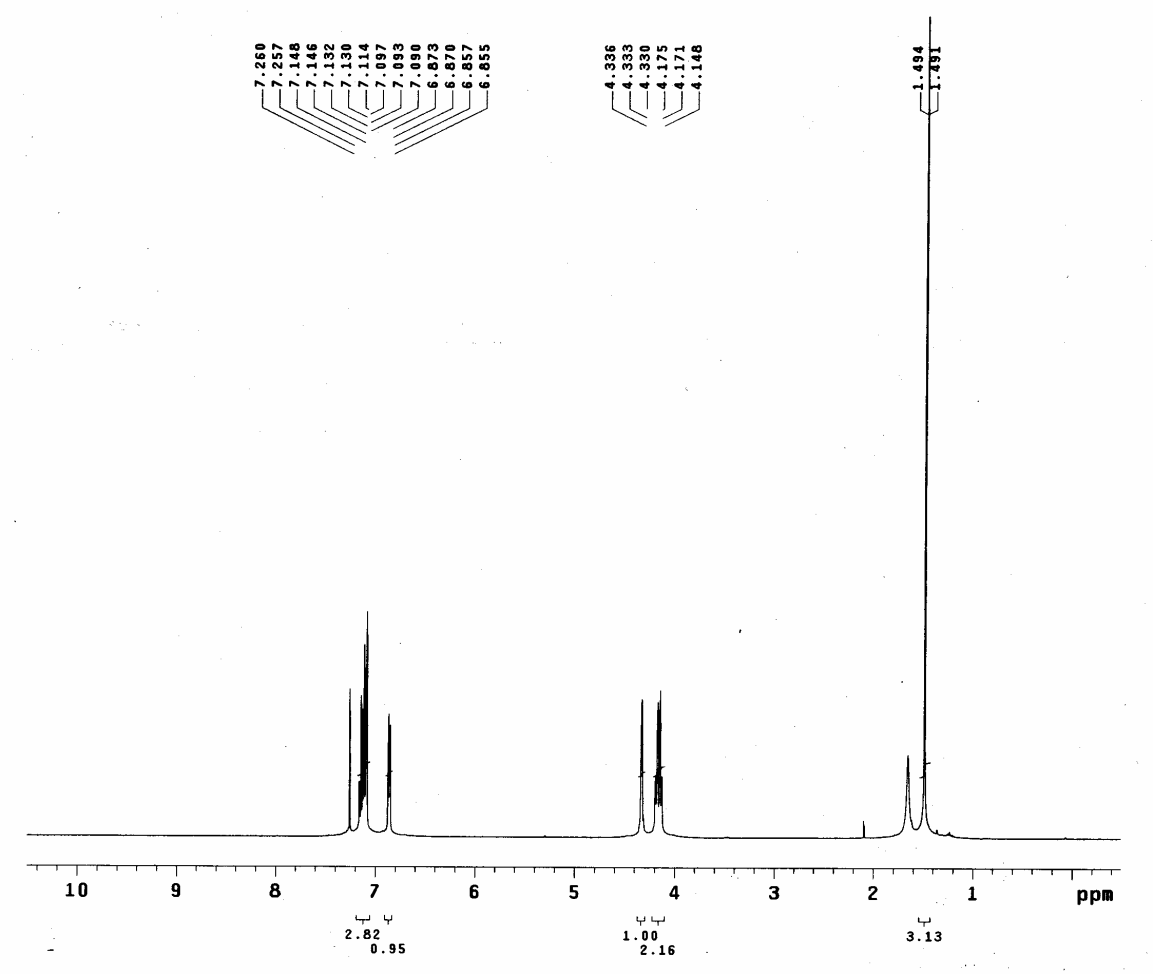
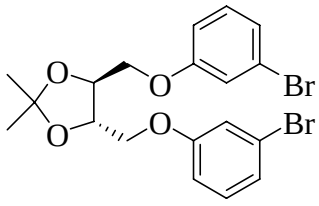


Figure 4.17-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (*S*,*S*)-**136**



(*R*,*R*)-**136**

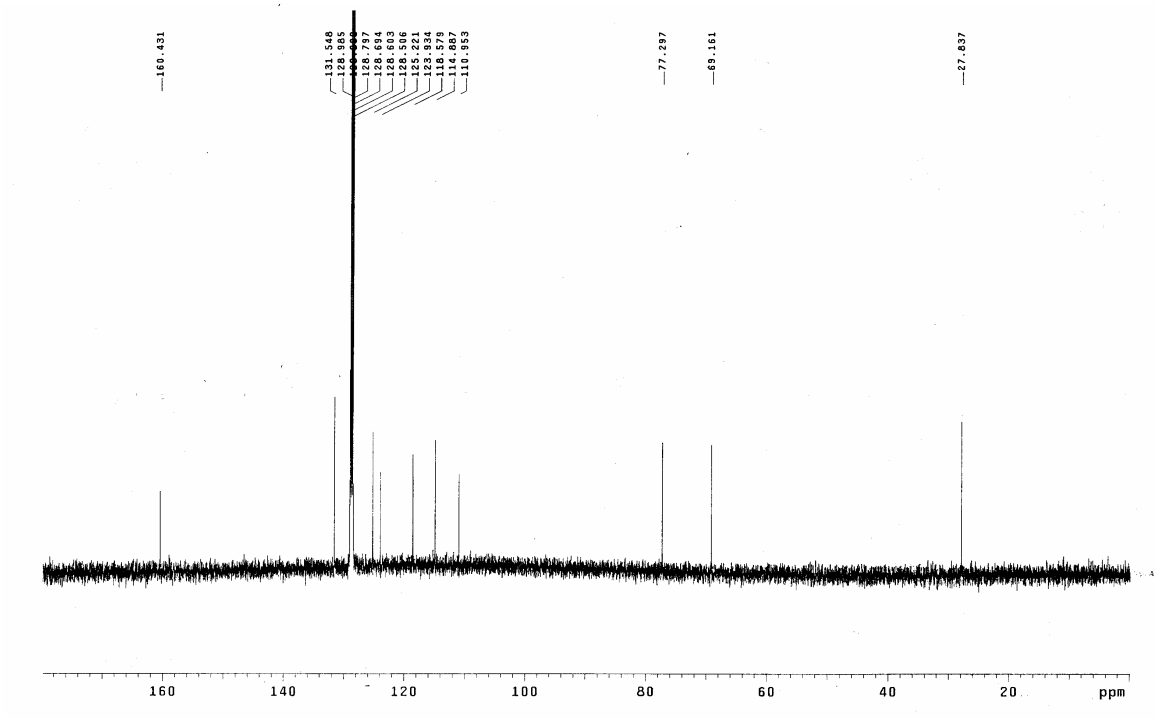
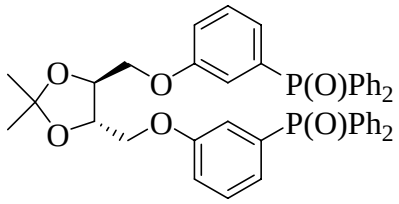


Figure 4.17-2 ^{13}C NMR (125 MHz, C_6D_6) Spectrum of (*S*,*S*)-**136**



137

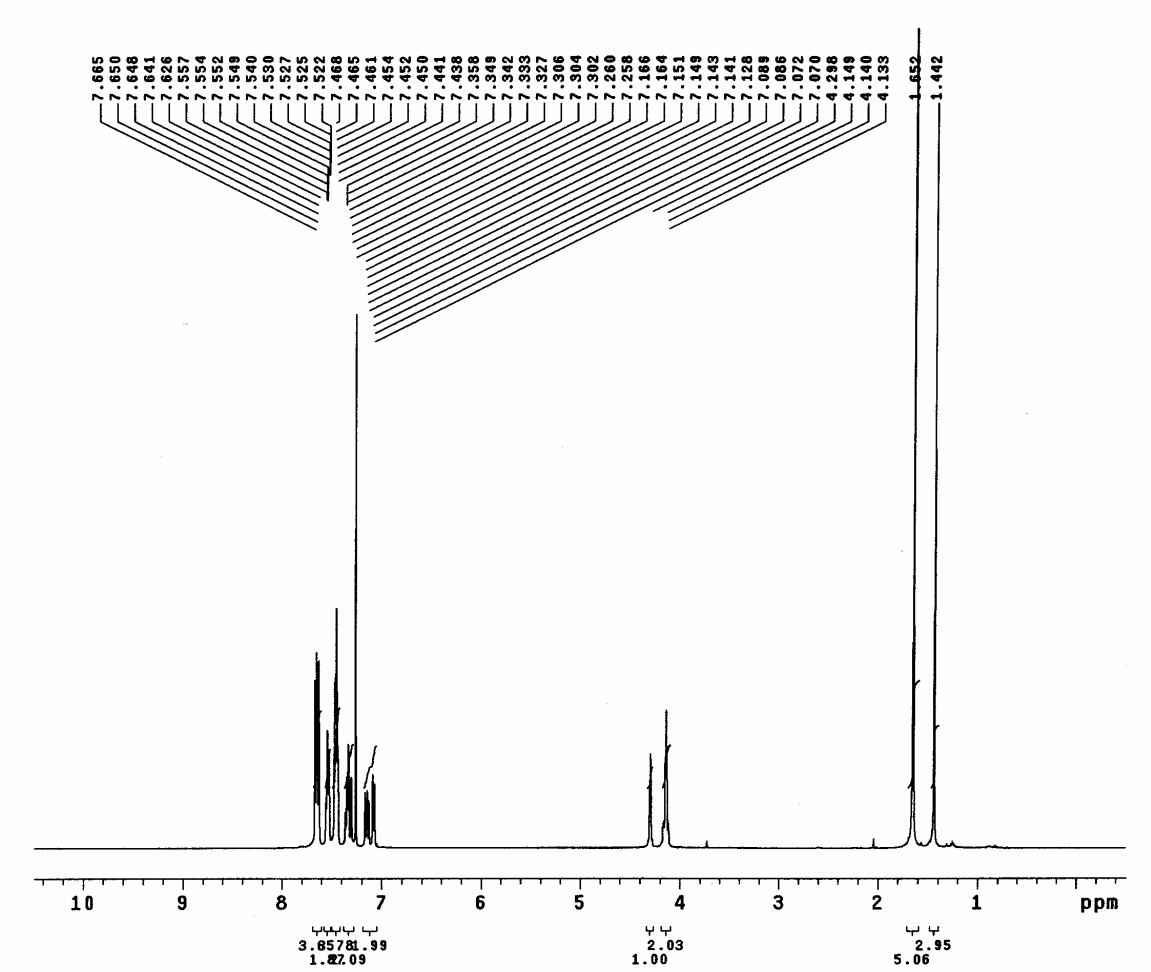
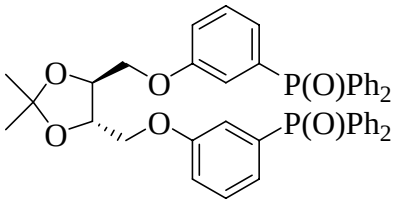


Figure 4.18-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of **137**



137

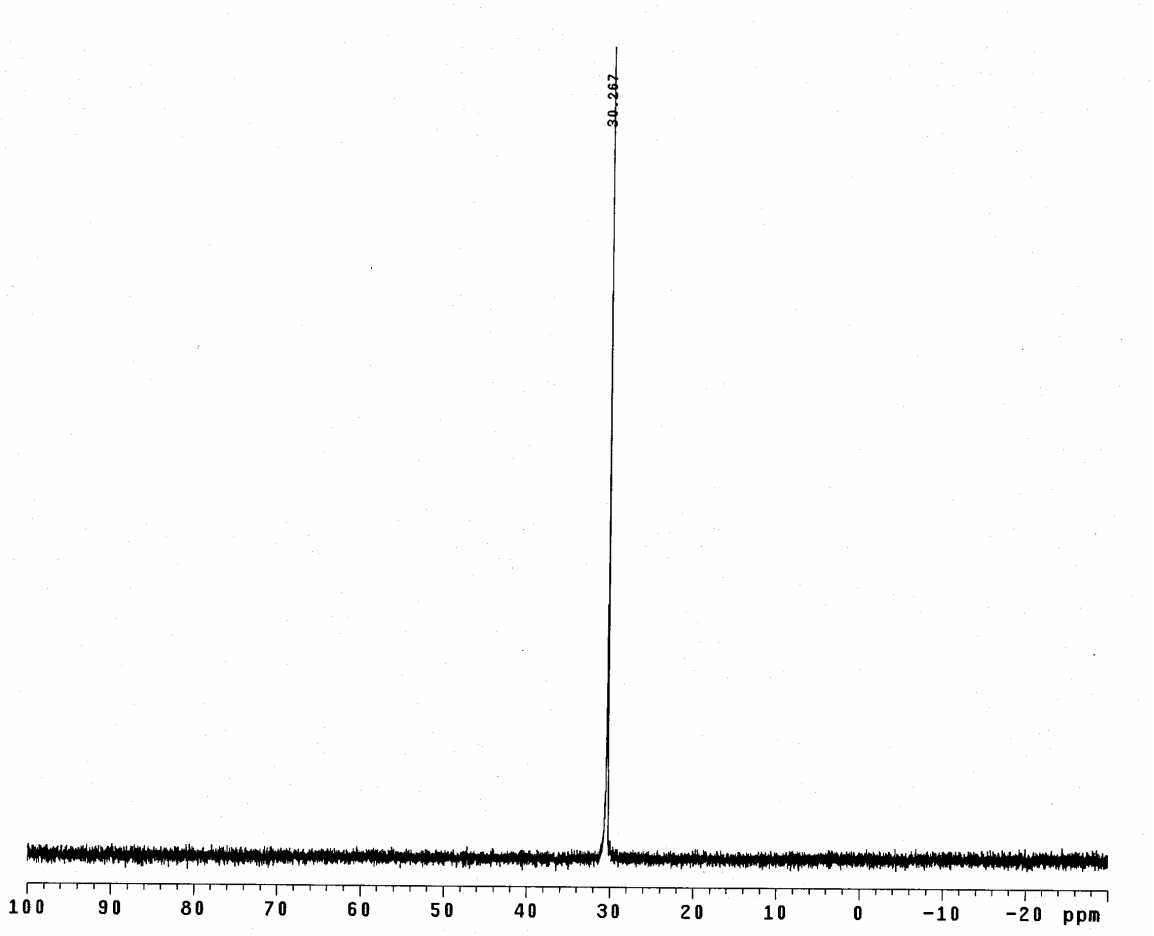
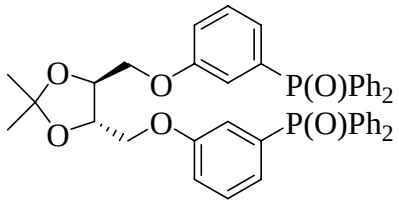


Figure 4.18-2 ^{31}P NMR (162 MHz, $CDCl_3$) Spectrum of **137**



137

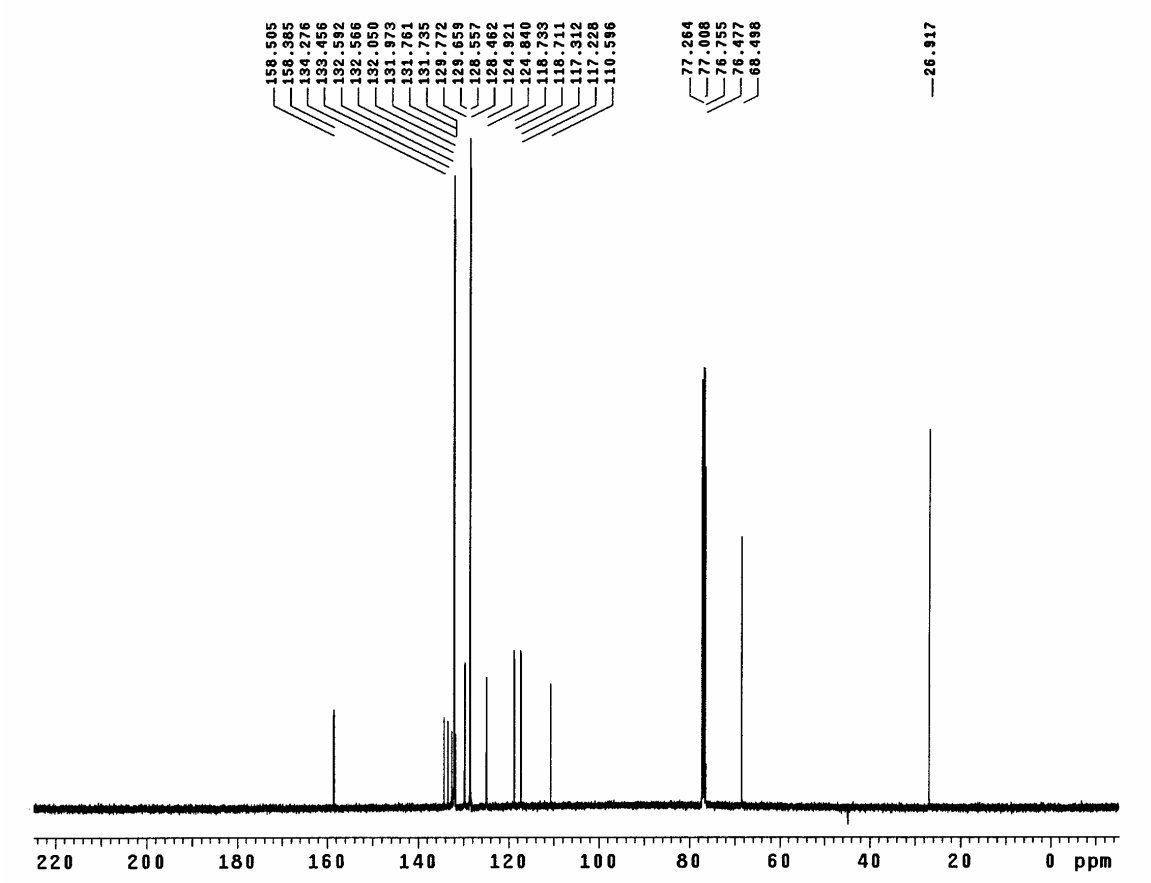
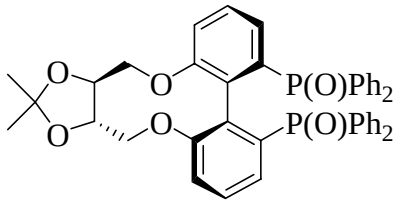


Figure 4.18-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of **137**



(R_{ax})-**139**

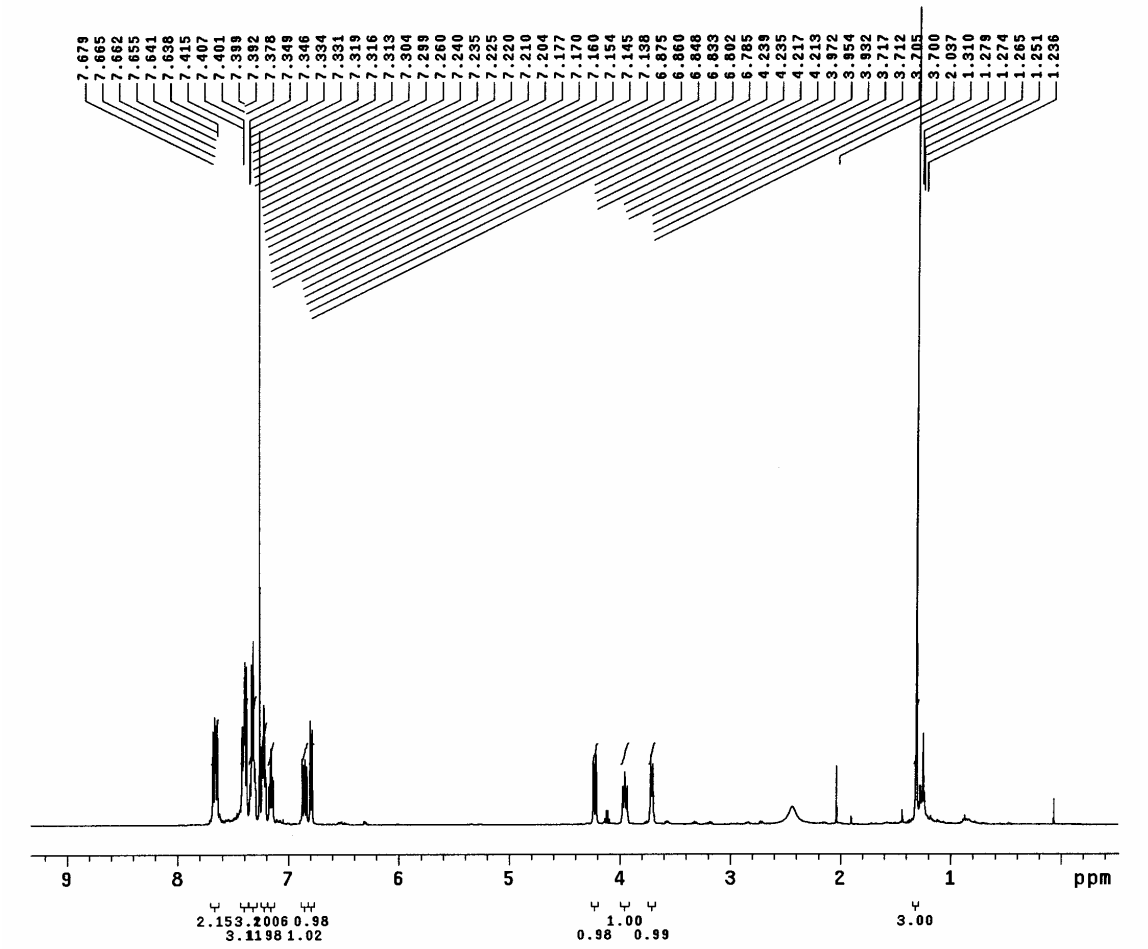
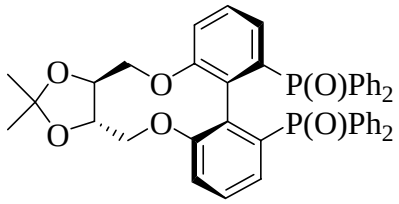


Figure 4.19-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (R_{ax})-**139**



(R_{ax})-**139**

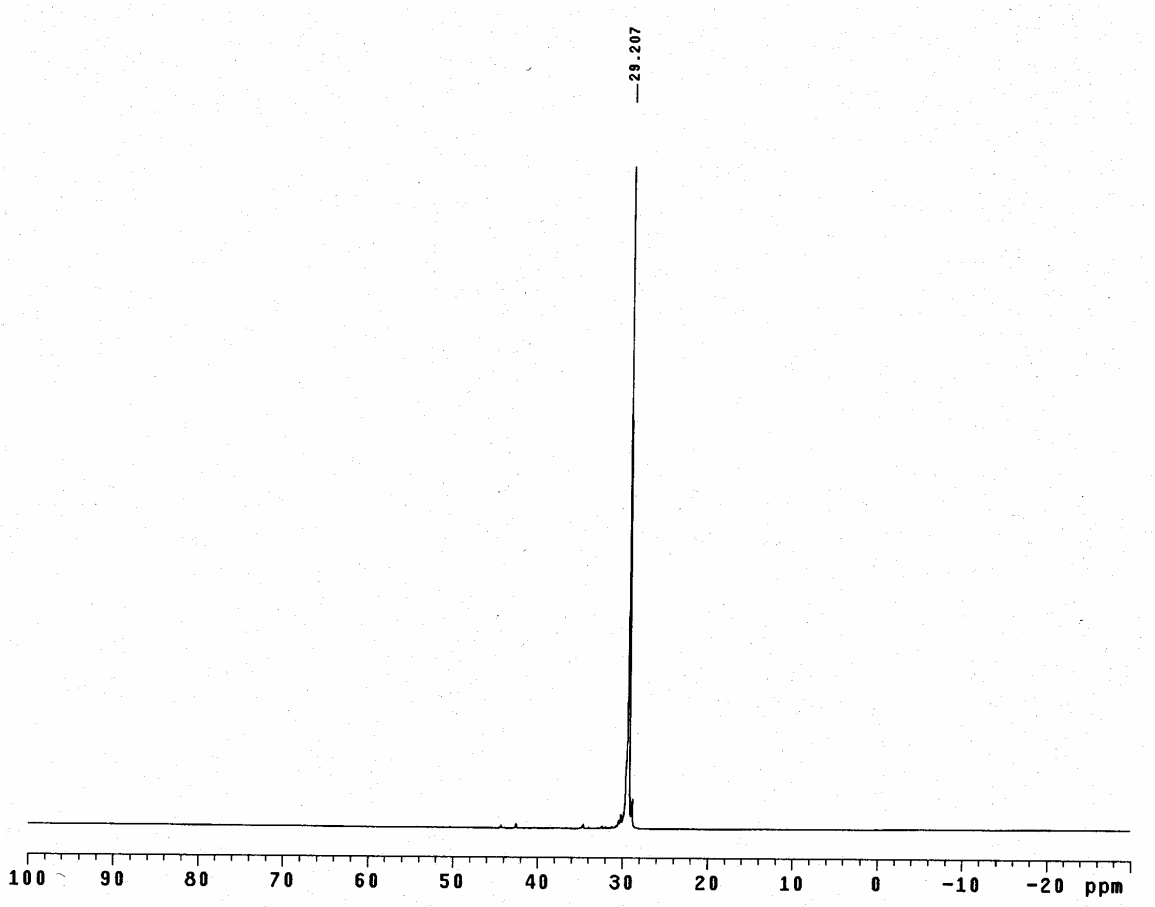
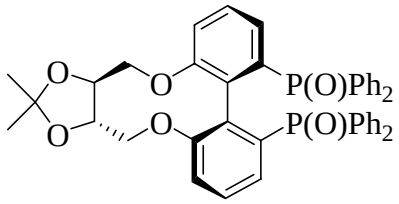


Figure 4.19-2 ^{31}P NMR (162 MHz, $CDCl_3$) Spectrum of (R_{ax})-**139**



(R_{ax})-**139**

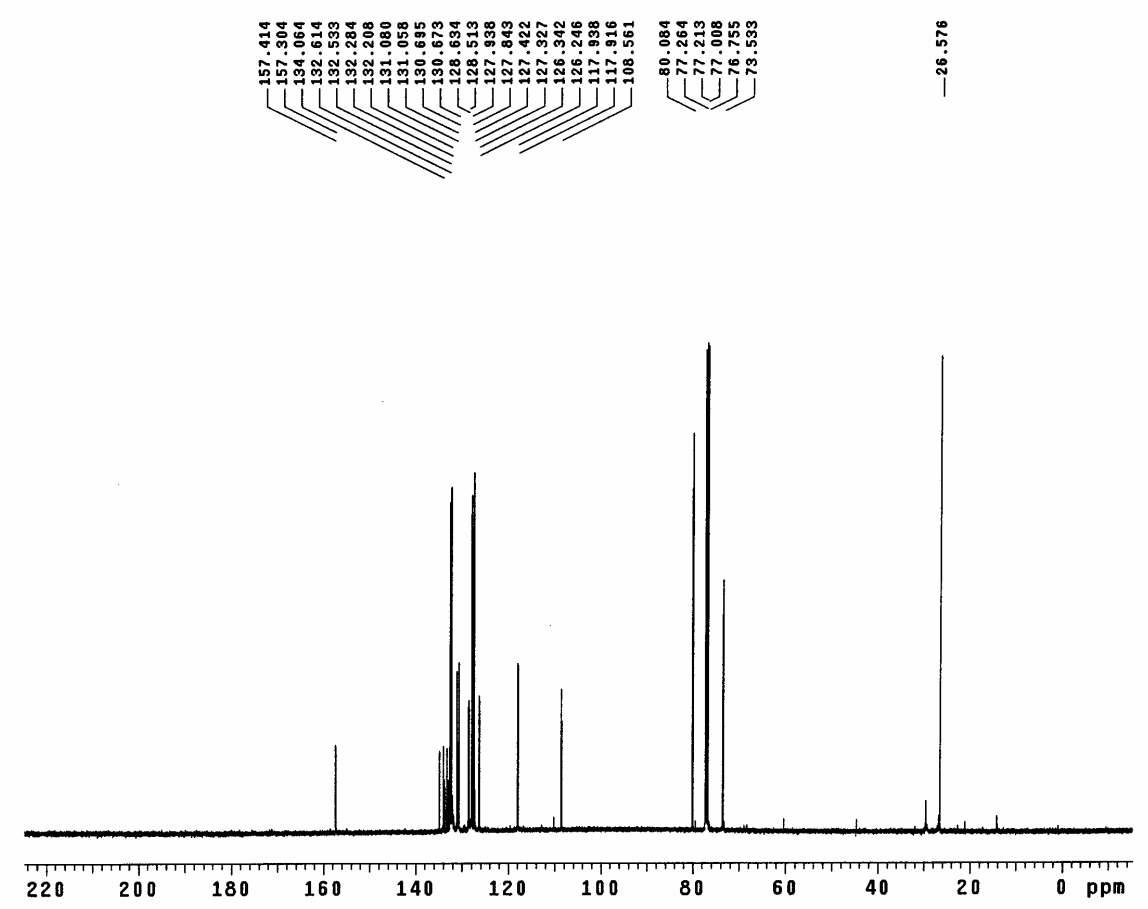
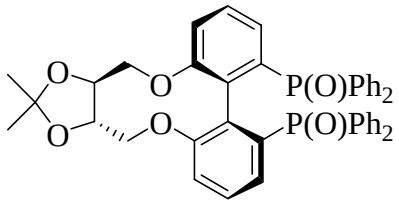


Figure 4.19-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (R_{ax})-**139**



(S_{ax})-**140**

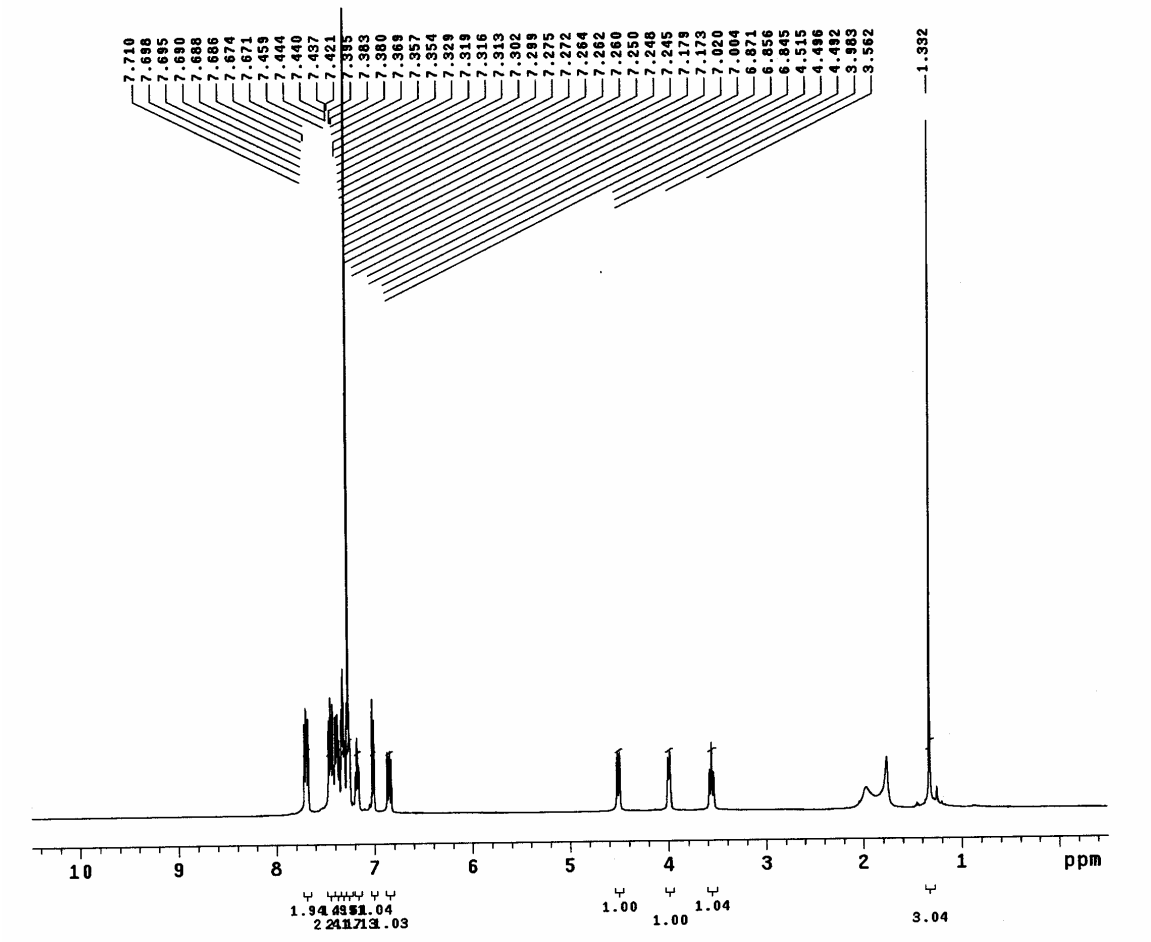
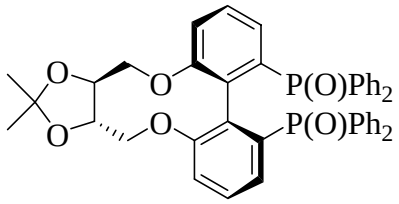


Figure 4.20-1 ^{1}H NMR (500 MHz, $CDCl_3$) Spectrum of (S_{ax})-**140**



(S_{ax})-**140**

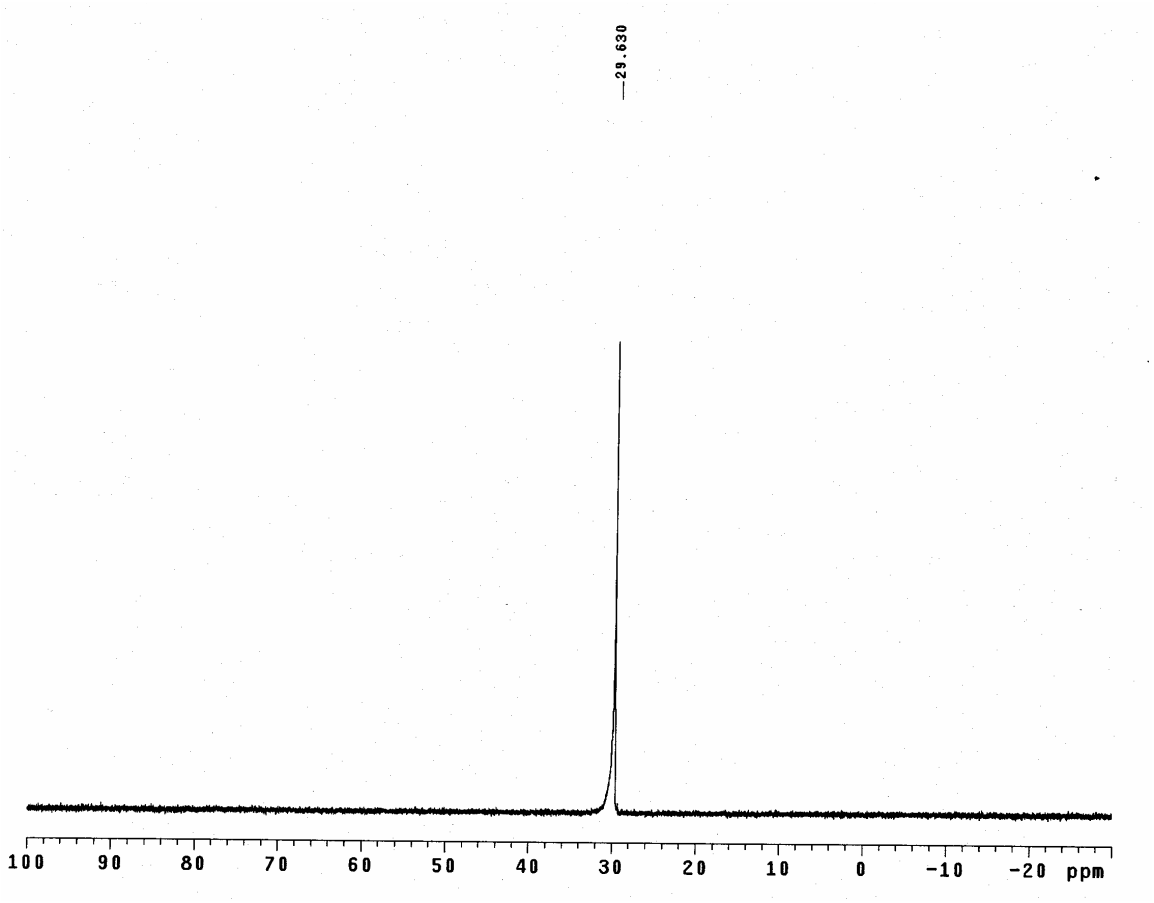
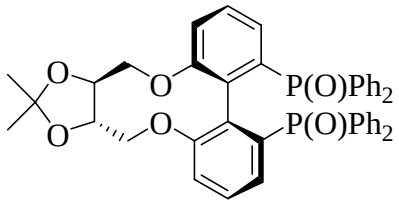


Figure 4.20-2 ^{31}P NMR (162 MHz, $CDCl_3$) Spectrum of (S_{ax})-**140**



(S_{ax})-**140**

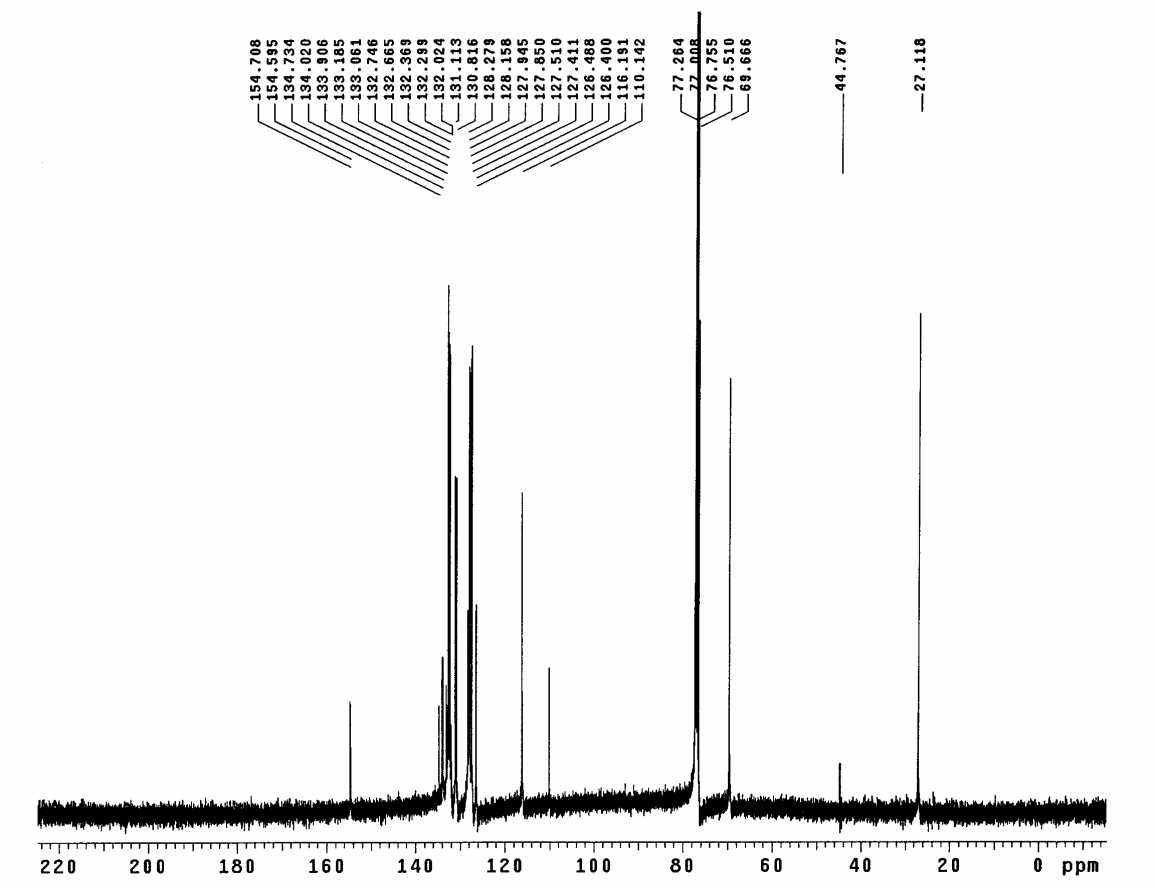
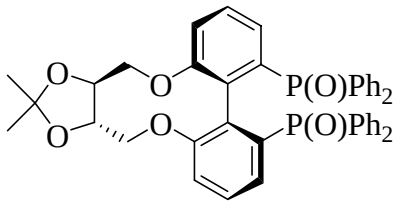


Figure 4.20-3 ^{13}C NMR (125 MHz, $CDCl_3$) Spectrum of (S_{ax})-**140**

APPENDIX II

X-RAY STRUCTURE AND CRYSTALLOGRAPHIC

DATA



S_{ax} **-140**

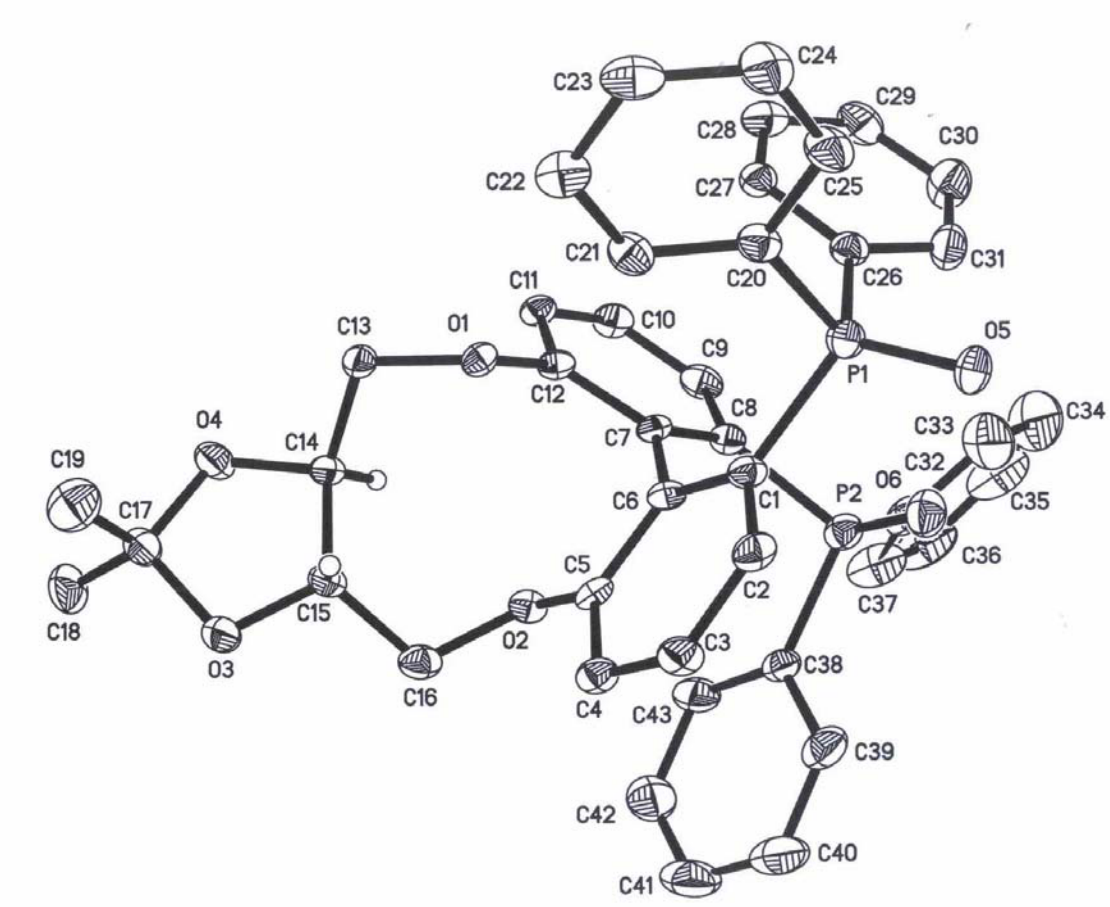


Figure 4.21 ORTEP drawing of S_{ax}**-140**

Table 1. Crystal data and structure refinement for S_{ax}-**140**.

Identification code	css3	
Empirical formula	C_{43} H_{40} O_7 P_2	
Formula weight	730.69	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.232(2) Å	α = 90°.
	b = 13.259(3) Å	β = 99.746(3)°.
	c = 12.957(3) Å	γ = 90°.
Volume	1901.8(7) Å^3	
Z	2	
Density (calculated)	1.276 Mg/m^3	
Absorption coefficient	0.165 mm^{-1}	
F(000)	768	
Crystal size	0.32 x 0.20 x 0.12 mm^3	
Theta range for data collection	2.21 to 27.57°.	
Index ranges	-14<=h<=14, -17<=k<=17, -16<=l<=16	
Reflections collected	17825	
Independent reflections	8689 [R(int) = 0.1010]	
Completeness to theta = 27.57°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.734	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8689 / 13 / 472	
Goodness-of-fit on F^2	0.995	
Final R indices [I>2sigma(I)]	R1 = 0.0627, wR2 = 0.1128	
R indices (all data)	R1 = 0.2150, wR2 = 0.1542	
Absolute structure parameter	-0.22(13)	
Extinction coefficient	0.0094(7)	
Largest diff. peak and hole	0.343 and -0.223 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for CSS3. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	3591(1)	6811(1)	2774(1)	56(1)
P(2)	6821(1)	6758(1)	1545(1)	61(1)
O(1)	6559(2)	6483(1)	5463(1)	46(1)
O(2)	7953(2)	8013(2)	4391(2)	53(1)
O(3)	9363(2)	8571(2)	7037(2)	69(1)
O(4)	9278(2)	6909(2)	7399(2)	71(1)
O(5)	2766(2)	7198(2)	1839(2)	75(1)
O(6)	5549(2)	7022(2)	1150(2)	81(1)
C(1)	4825(3)	7692(2)	3233(2)	48(1)
C(2)	4406(3)	8676(2)	3242(3)	57(1)
C(3)	5154(3)	9455(3)	3622(3)	60(1)
C(4)	6353(3)	9270(3)	4047(2)	55(1)
C(5)	6775(3)	8285(2)	4048(2)	44(1)
C(6)	6048(3)	7479(2)	3629(2)	43(1)
C(7)	6637(3)	6493(2)	3653(2)	43(1)
C(8)	7039(3)	6079(2)	2774(2)	49(1)
C(9)	7686(3)	5156(3)	2907(3)	65(1)
C(10)	7930(3)	4684(2)	3848(3)	59(1)
C(11)	7587(3)	5105(2)	4724(3)	49(1)
C(12)	6956(3)	6004(2)	4621(2)	44(1)
C(13)	7343(3)	6473(3)	6454(2)	52(1)
C(14)	8505(3)	7033(2)	6416(2)	47(1)
C(15)	8400(3)	8188(2)	6267(2)	53(1)
C(16)	8664(3)	8549(3)	5225(3)	63(1)
C(17)	9542(3)	7879(3)	7893(3)	72(1)
C(18)	10853(3)	7900(4)	8390(3)	94(2)
C(19)	8712(4)	8106(4)	8650(3)	106(2)

C(20)	2820(3)	6734(3)	3907(3)	57(1)
C(21)	3364(3)	6942(3)	4909(3)	62(1)
C(22)	2724(3)	6881(3)	5736(3)	72(1)
C(23)	1512(3)	6589(3)	5525(3)	80(1)
C(24)	989(3)	6382(3)	4532(3)	82(2)
C(25)	1629(3)	6427(3)	3714(3)	73(1)
C(26)	4083(3)	5538(3)	2613(3)	53(1)
C(27)	4481(3)	4899(3)	3449(3)	53(1)
C(28)	4844(3)	3930(3)	3312(3)	75(1)
C(29)	4799(3)	3572(3)	2322(3)	82(1)
C(30)	4405(4)	4156(3)	1486(3)	93(2)
C(31)	4042(3)	5127(3)	1615(3)	75(1)
C(32)	7434(3)	5970(3)	636(3)	80(1)
C(33)	6632(5)	5302(4)	56(3)	134(2)
C(34)	6993(5)	4623(5)	-647(4)	165(3)
C(35)	8205(4)	4627(4)	-724(4)	141(2)
C(36)	9022(5)	5281(4)	-205(4)	143(2)
C(37)	8616(4)	5946(3)	507(3)	113(2)
C(38)	7745(3)	7858(2)	1805(3)	58(1)
C(39)	7248(4)	8793(3)	1467(3)	85(2)
C(40)	7898(4)	9667(3)	1647(4)	116(2)
C(41)	9071(4)	9629(3)	2175(4)	129(2)
C(42)	9585(4)	8722(3)	2507(3)	113(2)
C(43)	8917(3)	7844(3)	2315(3)	84(1)
O(1W)	3560(4)	7112(3)	-401(3)	177(2)

Table 3. Bond lengths [Å] and angles [°] for CSS3.

P(1)-O(5)	1.486(2)
P(1)-C(26)	1.799(4)
P(1)-C(20)	1.829(3)
P(1)-C(1)	1.833(3)
P(2)-O(6)	1.475(2)
P(2)-C(38)	1.788(3)
P(2)-C(32)	1.797(4)
P(2)-C(8)	1.809(3)
O(1)-C(12)	1.399(4)
O(1)-C(13)	1.428(3)
O(2)-C(5)	1.372(3)
O(2)-C(16)	1.421(4)
O(3)-C(17)	1.427(4)
O(3)-C(15)	1.433(4)
O(4)-C(14)	1.425(4)
O(4)-C(17)	1.445(4)
C(1)-C(2)	1.387(4)
C(1)-C(6)	1.411(4)
C(2)-C(3)	1.369(5)
C(2)-H(2A)	0.9300
C(3)-C(4)	1.388(4)
C(3)-H(3A)	0.9300
C(4)-C(5)	1.389(4)
C(4)-H(4A)	0.9300
C(5)-C(6)	1.398(4)
C(6)-C(7)	1.463(4)
C(7)-C(8)	1.406(4)
C(7)-C(12)	1.404(4)
C(8)-C(9)	1.420(5)
C(9)-C(10)	1.356(5)
C(9)-H(9A)	0.9300
C(10)-C(11)	1.377(5)
C(10)-H(10A)	0.9300
C(11)-C(12)	1.382(4)

C(11)-H(11A)	0.9300
C(13)-C(14)	1.510(4)
C(13)-H(13A)	0.9700
C(13)-H(13B)	0.9700
C(14)-C(15)	1.546(4)
C(14)-H(14A)	0.9800
C(15)-C(16)	1.508(4)
C(15)-H(15A)	0.9800
C(16)-H(16A)	0.9700
C(16)-H(16B)	0.9700
C(17)-C(19)	1.493(6)
C(17)-C(18)	1.505(5)
C(18)-H(18A)	0.9600
C(18)-H(18B)	0.9600
C(18)-H(18C)	0.9600
C(19)-H(19A)	0.9600
C(19)-H(19B)	0.9600
C(19)-H(19C)	0.9600
C(20)-C(21)	1.366(4)
C(20)-C(25)	1.380(4)
C(21)-C(22)	1.390(5)
C(21)-H(21A)	0.9300
C(22)-C(23)	1.397(5)
C(22)-H(22A)	0.9300
C(23)-C(24)	1.349(5)
C(23)-H(23A)	0.9300
C(24)-C(25)	1.380(5)
C(24)-H(24A)	0.9300
C(25)-H(25A)	0.9300
C(26)-C(27)	1.388(4)
C(26)-C(31)	1.397(5)
C(27)-C(28)	1.369(5)
C(27)-H(27A)	0.9300
C(28)-C(29)	1.360(5)
C(28)-H(28A)	0.9300
C(29)-C(30)	1.343(5)

C(29)-H(29A)	0.9300
C(30)-C(31)	1.369(6)
C(30)-H(30A)	0.9300
C(31)-H(31A)	0.9300
C(32)-C(37)	1.366(5)
C(32)-C(33)	1.390(5)
C(33)-C(34)	1.388(6)
C(33)-H(33A)	0.9300
C(34)-C(35)	1.381(6)
C(34)-H(34A)	0.9300
C(35)-C(36)	1.356(6)
C(35)-H(35A)	0.9300
C(36)-C(37)	1.406(5)
C(36)-H(36A)	0.9300
C(37)-H(37A)	0.9300
C(38)-C(43)	1.369(4)
C(38)-C(39)	1.399(4)
C(39)-C(40)	1.368(5)
C(39)-H(39A)	0.9300
C(40)-C(41)	1.379(5)
C(40)-H(40A)	0.9300
C(41)-C(42)	1.371(5)
C(41)-H(41A)	0.9300
C(42)-C(43)	1.385(5)
C(42)-H(42A)	0.9300
C(43)-H(43A)	0.9300
O(1W)-H(1WA)	0.8918
O(1W)-H(1WB)	0.8588

O(5)-P(1)-C(26)	113.03(15)
O(5)-P(1)-C(20)	111.04(15)
C(26)-P(1)-C(20)	103.72(16)
O(5)-P(1)-C(1)	112.12(15)
C(26)-P(1)-C(1)	113.92(15)
C(20)-P(1)-C(1)	102.11(15)
O(6)-P(2)-C(38)	111.69(16)

O(6)-P(2)-C(32)	111.52(16)
C(38)-P(2)-C(32)	108.85(17)
O(6)-P(2)-C(8)	113.68(15)
C(38)-P(2)-C(8)	104.59(15)
C(32)-P(2)-C(8)	106.09(17)
C(12)-O(1)-C(13)	117.8(2)
C(5)-O(2)-C(16)	120.1(2)
C(17)-O(3)-C(15)	107.7(2)
C(14)-O(4)-C(17)	110.0(2)
C(2)-C(1)-C(6)	119.7(3)
C(2)-C(1)-P(1)	111.3(2)
C(6)-C(1)-P(1)	128.8(2)
C(3)-C(2)-C(1)	121.6(3)
C(3)-C(2)-H(2A)	119.2
C(1)-C(2)-H(2A)	119.2
C(2)-C(3)-C(4)	120.3(3)
C(2)-C(3)-H(3A)	119.8
C(4)-C(3)-H(3A)	119.8
C(5)-C(4)-C(3)	118.3(3)
C(5)-C(4)-H(4A)	120.8
C(3)-C(4)-H(4A)	120.8
O(2)-C(5)-C(4)	123.9(3)
O(2)-C(5)-C(6)	113.1(3)
C(4)-C(5)-C(6)	122.8(3)
C(5)-C(6)-C(1)	117.2(3)
C(5)-C(6)-C(7)	116.3(3)
C(1)-C(6)-C(7)	126.6(3)
C(8)-C(7)-C(12)	118.4(3)
C(8)-C(7)-C(6)	122.5(3)
C(12)-C(7)-C(6)	118.5(3)
C(7)-C(8)-C(9)	117.8(3)
C(7)-C(8)-P(2)	120.3(2)
C(9)-C(8)-P(2)	121.8(3)
C(10)-C(9)-C(8)	121.9(3)
C(10)-C(9)-H(9A)	119.1
C(8)-C(9)-H(9A)	119.1

C(9)-C(10)-C(11)	120.8(3)
C(9)-C(10)-H(10A)	119.6
C(11)-C(10)-H(10A)	119.6
C(10)-C(11)-C(12)	118.7(3)
C(10)-C(11)-H(11A)	120.6
C(12)-C(11)-H(11A)	120.6
C(11)-C(12)-O(1)	122.9(3)
C(11)-C(12)-C(7)	122.2(3)
O(1)-C(12)-C(7)	114.9(3)
O(1)-C(13)-C(14)	111.8(2)
O(1)-C(13)-H(13A)	109.3
C(14)-C(13)-H(13A)	109.3
O(1)-C(13)-H(13B)	109.3
C(14)-C(13)-H(13B)	109.3
H(13A)-C(13)-H(13B)	107.9
O(4)-C(14)-C(13)	108.3(2)
O(4)-C(14)-C(15)	104.3(2)
C(13)-C(14)-C(15)	116.3(3)
O(4)-C(14)-H(14A)	109.2
C(13)-C(14)-H(14A)	109.2
C(15)-C(14)-H(14A)	109.2
O(3)-C(15)-C(16)	105.7(3)
O(3)-C(15)-C(14)	103.4(2)
C(16)-C(15)-C(14)	113.8(3)
O(3)-C(15)-H(15A)	111.2
C(16)-C(15)-H(15A)	111.2
C(14)-C(15)-H(15A)	111.2
O(2)-C(16)-C(15)	110.6(3)
O(2)-C(16)-H(16A)	109.5
C(15)-C(16)-H(16A)	109.5
O(2)-C(16)-H(16B)	109.5
C(15)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	108.1
O(3)-C(17)-O(4)	103.7(3)
O(3)-C(17)-C(19)	111.1(3)
O(4)-C(17)-C(19)	111.5(3)

O(3)-C(17)-C(18)	108.7(3)
O(4)-C(17)-C(18)	108.5(3)
C(19)-C(17)-C(18)	113.0(3)
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(17)-C(19)-H(19A)	109.5
C(17)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(17)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(21)-C(20)-C(25)	119.7(3)
C(21)-C(20)-P(1)	123.8(2)
C(25)-C(20)-P(1)	116.6(3)
C(20)-C(21)-C(22)	121.0(3)
C(20)-C(21)-H(21A)	119.5
C(22)-C(21)-H(21A)	119.5
C(21)-C(22)-C(23)	118.7(3)
C(21)-C(22)-H(22A)	120.7
C(23)-C(22)-H(22A)	120.7
C(24)-C(23)-C(22)	119.7(4)
C(24)-C(23)-H(23A)	120.2
C(22)-C(23)-H(23A)	120.2
C(23)-C(24)-C(25)	121.6(4)
C(23)-C(24)-H(24A)	119.2
C(25)-C(24)-H(24A)	119.2
C(24)-C(25)-C(20)	119.3(3)
C(24)-C(25)-H(25A)	120.4
C(20)-C(25)-H(25A)	120.4
C(27)-C(26)-C(31)	116.1(3)
C(27)-C(26)-P(1)	123.1(3)
C(31)-C(26)-P(1)	120.7(3)

C(28)-C(27)-C(26)	122.4(4)
C(28)-C(27)-H(27A)	118.8
C(26)-C(27)-H(27A)	118.8
C(29)-C(28)-C(27)	119.0(4)
C(29)-C(28)-H(28A)	120.5
C(27)-C(28)-H(28A)	120.5
C(30)-C(29)-C(28)	120.9(4)
C(30)-C(29)-H(29A)	119.5
C(28)-C(29)-H(29A)	119.5
C(29)-C(30)-C(31)	120.5(4)
C(29)-C(30)-H(30A)	119.7
C(31)-C(30)-H(30A)	119.7
C(30)-C(31)-C(26)	121.0(4)
C(30)-C(31)-H(31A)	119.5
C(26)-C(31)-H(31A)	119.5
C(37)-C(32)-C(33)	118.2(4)
C(37)-C(32)-P(2)	125.6(3)
C(33)-C(32)-P(2)	116.1(3)
C(32)-C(33)-C(34)	122.2(5)
C(32)-C(33)-H(33A)	118.9
C(34)-C(33)-H(33A)	118.9
C(35)-C(34)-C(33)	116.5(5)
C(35)-C(34)-H(34A)	121.8
C(33)-C(34)-H(34A)	121.8
C(36)-C(35)-C(34)	124.0(5)
C(36)-C(35)-H(35A)	118.0
C(34)-C(35)-H(35A)	118.0
C(35)-C(36)-C(37)	117.3(5)
C(35)-C(36)-H(36A)	121.4
C(37)-C(36)-H(36A)	121.4
C(32)-C(37)-C(36)	121.7(4)
C(32)-C(37)-H(37A)	119.2
C(36)-C(37)-H(37A)	119.2
C(43)-C(38)-C(39)	117.6(3)
C(43)-C(38)-P(2)	124.0(3)
C(39)-C(38)-P(2)	118.4(3)

C(40)-C(39)-C(38)	121.6(4)
C(40)-C(39)-H(39A)	119.2
C(38)-C(39)-H(39A)	119.2
C(39)-C(40)-C(41)	119.4(4)
C(39)-C(40)-H(40A)	120.3
C(41)-C(40)-H(40A)	120.3
C(42)-C(41)-C(40)	120.2(4)
C(42)-C(41)-H(41A)	119.9
C(40)-C(41)-H(41A)	119.9
C(41)-C(42)-C(43)	119.7(4)
C(41)-C(42)-H(42A)	120.2
C(43)-C(42)-H(42A)	120.2
C(38)-C(43)-C(42)	121.5(4)
C(38)-C(43)-H(43A)	119.2
C(42)-C(43)-H(43A)	119.2
H(1WA)-O(1W)-H(1WB)	103.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for CSS3. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	50(1)	55(1)	59(1)	6(1)	2(1)	2(1)
P(2)	74(1)	58(1)	55(1)	1(1)	19(1)	1(1)
O(1)	45(1)	47(1)	48(1)	8(1)	12(1)	6(1)
O(2)	52(1)	45(1)	62(1)	0(1)	11(1)	-2(1)
O(3)	80(2)	53(2)	69(2)	4(1)	-6(1)	-12(1)
O(4)	68(2)	52(2)	82(2)	2(2)	-18(1)	-6(1)
O(5)	64(2)	81(2)	69(2)	22(1)	-19(1)	10(1)
O(6)	68(2)	104(2)	68(2)	6(2)	4(1)	2(2)
C(1)	46(2)	40(2)	58(2)	9(2)	9(2)	1(2)
C(2)	53(2)	48(2)	68(2)	16(2)	8(2)	15(2)
C(3)	63(2)	34(2)	80(3)	4(2)	6(2)	12(2)
C(4)	69(2)	36(2)	61(2)	3(2)	17(2)	8(2)
C(5)	52(2)	41(2)	44(2)	15(2)	21(2)	11(2)
C(6)	46(2)	33(2)	53(2)	6(2)	19(2)	3(2)
C(7)	43(2)	40(2)	49(2)	11(2)	12(2)	-3(2)
C(8)	47(2)	47(2)	56(2)	-1(2)	14(2)	-4(2)
C(9)	65(2)	48(2)	84(3)	-14(2)	20(2)	-4(2)
C(10)	56(2)	39(2)	81(3)	4(2)	13(2)	13(2)
C(11)	60(2)	33(2)	55(2)	7(2)	12(2)	6(2)
C(12)	42(2)	36(2)	57(2)	4(2)	17(2)	3(2)
C(13)	43(2)	63(2)	48(2)	9(2)	5(2)	-10(2)
C(14)	47(2)	40(2)	55(2)	3(2)	8(2)	-4(2)
C(15)	50(2)	42(2)	64(2)	1(2)	2(2)	-6(2)
C(16)	47(2)	60(2)	82(3)	11(2)	9(2)	-8(2)
C(17)	83(3)	57(2)	68(3)	-2(2)	-7(2)	-12(2)
C(18)	87(3)	102(3)	78(3)	0(3)	-26(2)	-3(3)
C(19)	106(3)	121(4)	100(3)	2(3)	41(3)	3(3)
C(20)	44(2)	50(2)	74(2)	6(2)	6(2)	1(2)
C(21)	41(2)	72(3)	75(2)	-5(2)	14(2)	-4(2)

C(22)	73(2)	65(2)	86(2)	-3(2)	36(2)	8(2)
C(23)	61(2)	68(3)	119(3)	9(3)	41(2)	5(2)
C(24)	43(2)	98(3)	103(3)	8(3)	7(2)	5(2)
C(25)	46(2)	89(3)	85(3)	-5(3)	13(2)	-9(2)
C(26)	45(2)	54(2)	61(2)	2(2)	11(2)	-6(2)
C(27)	47(2)	53(2)	58(2)	7(2)	6(2)	-2(2)
C(28)	69(3)	61(3)	97(3)	12(2)	20(2)	-2(2)
C(29)	85(3)	59(3)	100(3)	-23(3)	10(3)	-3(2)
C(30)	134(4)	72(3)	71(3)	-12(3)	12(3)	12(3)
C(31)	87(3)	75(3)	57(3)	3(2)	-5(2)	5(2)
C(32)	120(3)	74(3)	53(2)	6(2)	34(2)	6(3)
C(33)	188(5)	130(4)	91(3)	-54(3)	44(3)	-14(4)
C(34)	250(7)	161(6)	91(4)	-48(4)	54(4)	-15(5)
C(35)	235(5)	91(4)	122(4)	13(3)	101(4)	55(4)
C(36)	237(5)	93(4)	127(4)	21(3)	111(4)	44(4)
C(37)	167(4)	77(3)	116(3)	0(3)	89(3)	23(3)
C(38)	68(2)	52(2)	57(2)	9(2)	19(2)	-5(2)
C(39)	116(3)	80(3)	64(3)	14(2)	29(2)	2(3)
C(40)	181(5)	65(3)	114(4)	8(3)	59(3)	-18(3)
C(41)	182(5)	97(4)	126(4)	-11(3)	74(4)	-66(4)
C(42)	103(3)	143(4)	100(3)	2(3)	37(3)	-52(3)
C(43)	73(3)	84(3)	100(3)	12(3)	27(2)	-28(2)
O(1W)	177(3)	188(4)	136(3)	41(3)	-55(3)	20(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for CSS3.

	x	y	z	U(eq)
H(2A)	3597	8809	2984	68
H(3A)	4857	10111	3596	72
H(4A)	6862	9792	4324	66
H(9A)	7951	4866	2332	78
H(10A)	8334	4069	3902	70
H(11A)	7776	4790	5372	59
H(13A)	7527	5780	6662	62
H(13B)	6934	6780	6976	62
H(14A)	8896	6745	5862	57
H(15A)	7615	8435	6392	64
H(16A)	8490	9264	5149	76
H(16B)	9514	8451	5197	76
H(18A)	11344	7749	7871	141
H(18B)	10996	7407	8939	141
H(18C)	11056	8558	8677	141
H(19A)	7898	8156	8280	160
H(19B)	8943	8733	8998	160
H(19C)	8761	7574	9158	160
H(21A)	4174	7127	5040	75
H(22A)	3095	7032	6415	86
H(23A)	1068	6538	6067	96
H(24A)	176	6205	4396	99
H(25A)	1262	6253	3039	88
H(27A)	4502	5138	4126	64
H(28A)	5117	3521	3887	90
H(29A)	5044	2915	2222	99
H(30A)	4380	3899	815	112
H(31A)	3762	5519	1028	90
H(33A)	5827	5310	141	161

H(34A)	6448	4189	-1044	198
H(35A)	8476	4152	-1158	169
H(36A)	9819	5290	-316	172
H(37A)	9166	6380	899	135
H(39A)	6457	8821	1111	102
H(40A)	7552	10281	1415	139
H(41A)	9516	10221	2307	155
H(42A)	10378	8696	2859	136
H(43A)	9272	7230	2537	101
H(1WA)	4015	6972	-884	212
H(1WB)	4006	6936	175	212

Table 6. Torsion angles [°] for CSS3.

O(5)-P(1)-C(1)-C(2)	44.1(3)
C(26)-P(1)-C(1)-C(2)	174.0(2)
C(20)-P(1)-C(1)-C(2)	-74.8(3)
O(5)-P(1)-C(1)-C(6)	-141.3(3)
C(26)-P(1)-C(1)-C(6)	-11.4(4)
C(20)-P(1)-C(1)-C(6)	99.8(3)
C(6)-C(1)-C(2)-C(3)	0.4(5)
P(1)-C(1)-C(2)-C(3)	175.6(3)
C(1)-C(2)-C(3)-C(4)	-2.4(6)
C(2)-C(3)-C(4)-C(5)	1.7(5)
C(16)-O(2)-C(5)-C(4)	33.0(4)
C(16)-O(2)-C(5)-C(6)	-151.3(3)
C(3)-C(4)-C(5)-O(2)	176.2(3)
C(3)-C(4)-C(5)-C(6)	0.9(5)
O(2)-C(5)-C(6)-C(1)	-178.5(3)
C(4)-C(5)-C(6)-C(1)	-2.7(5)
O(2)-C(5)-C(6)-C(7)	1.9(4)
C(4)-C(5)-C(6)-C(7)	177.7(3)
C(2)-C(1)-C(6)-C(5)	2.0(5)
P(1)-C(1)-C(6)-C(5)	-172.2(2)
C(2)-C(1)-C(6)-C(7)	-178.4(3)
P(1)-C(1)-C(6)-C(7)	7.4(5)
C(5)-C(6)-C(7)-C(8)	-99.9(3)
C(1)-C(6)-C(7)-C(8)	80.6(4)
C(5)-C(6)-C(7)-C(12)	71.5(4)
C(1)-C(6)-C(7)-C(12)	-108.0(4)
C(12)-C(7)-C(8)-C(9)	3.6(4)
C(6)-C(7)-C(8)-C(9)	175.0(3)
C(12)-C(7)-C(8)-P(2)	-172.2(2)
C(6)-C(7)-C(8)-P(2)	-0.8(4)
O(6)-P(2)-C(8)-C(7)	-56.3(3)
C(38)-P(2)-C(8)-C(7)	65.8(3)
C(32)-P(2)-C(8)-C(7)	-179.2(3)
O(6)-P(2)-C(8)-C(9)	128.1(3)

C(38)-P(2)-C(8)-C(9)	-109.8(3)
C(32)-P(2)-C(8)-C(9)	5.2(3)
C(7)-C(8)-C(9)-C(10)	-0.8(5)
P(2)-C(8)-C(9)-C(10)	174.9(3)
C(8)-C(9)-C(10)-C(11)	-2.0(5)
C(9)-C(10)-C(11)-C(12)	1.9(5)
C(10)-C(11)-C(12)-O(1)	179.4(3)
C(10)-C(11)-C(12)-C(7)	1.0(5)
C(13)-O(1)-C(12)-C(11)	39.1(4)
C(13)-O(1)-C(12)-C(7)	-142.5(3)
C(8)-C(7)-C(12)-C(11)	-3.8(4)
C(6)-C(7)-C(12)-C(11)	-175.5(3)
C(8)-C(7)-C(12)-O(1)	177.7(3)
C(6)-C(7)-C(12)-O(1)	6.0(4)
C(12)-O(1)-C(13)-C(14)	63.5(3)
C(17)-O(4)-C(14)-C(13)	-118.8(3)
C(17)-O(4)-C(14)-C(15)	5.8(3)
O(1)-C(13)-C(14)-O(4)	-174.7(2)
O(1)-C(13)-C(14)-C(15)	68.2(4)
C(17)-O(3)-C(15)-C(16)	-150.0(3)
C(17)-O(3)-C(15)-C(14)	-30.1(3)
O(4)-C(14)-C(15)-O(3)	14.5(3)
C(13)-C(14)-C(15)-O(3)	133.8(3)
O(4)-C(14)-C(15)-C(16)	128.7(3)
C(13)-C(14)-C(15)-C(16)	-112.1(3)
C(5)-O(2)-C(16)-C(15)	80.9(3)
O(3)-C(15)-C(16)-O(2)	165.2(3)
C(14)-C(15)-C(16)-O(2)	52.4(4)
C(15)-O(3)-C(17)-O(4)	33.9(3)
C(15)-O(3)-C(17)-C(19)	-86.0(4)
C(15)-O(3)-C(17)-C(18)	149.2(3)
C(14)-O(4)-C(17)-O(3)	-24.0(4)
C(14)-O(4)-C(17)-C(19)	95.6(3)
C(14)-O(4)-C(17)-C(18)	-139.4(3)
O(5)-P(1)-C(20)-C(21)	-143.2(3)
C(26)-P(1)-C(20)-C(21)	95.1(3)

C(1)-P(1)-C(20)-C(21)	-23.6(4)
O(5)-P(1)-C(20)-C(25)	38.0(3)
C(26)-P(1)-C(20)-C(25)	-83.7(3)
C(1)-P(1)-C(20)-C(25)	157.7(3)
C(25)-C(20)-C(21)-C(22)	-2.1(6)
P(1)-C(20)-C(21)-C(22)	179.2(3)
C(20)-C(21)-C(22)-C(23)	0.8(6)
C(21)-C(22)-C(23)-C(24)	-0.5(6)
C(22)-C(23)-C(24)-C(25)	1.6(6)
C(23)-C(24)-C(25)-C(20)	-2.9(6)
C(21)-C(20)-C(25)-C(24)	3.1(6)
P(1)-C(20)-C(25)-C(24)	-178.1(3)
O(5)-P(1)-C(26)-C(27)	-156.6(3)
C(20)-P(1)-C(26)-C(27)	-36.2(3)
C(1)-P(1)-C(26)-C(27)	73.9(3)
O(5)-P(1)-C(26)-C(31)	21.2(3)
C(20)-P(1)-C(26)-C(31)	141.6(3)
C(1)-P(1)-C(26)-C(31)	-108.3(3)
C(31)-C(26)-C(27)-C(28)	1.6(5)
P(1)-C(26)-C(27)-C(28)	179.5(3)
C(26)-C(27)-C(28)-C(29)	-0.9(5)
C(27)-C(28)-C(29)-C(30)	0.0(6)
C(28)-C(29)-C(30)-C(31)	0.1(7)
C(29)-C(30)-C(31)-C(26)	0.8(7)
C(27)-C(26)-C(31)-C(30)	-1.6(5)
P(1)-C(26)-C(31)-C(30)	-179.5(3)
O(6)-P(2)-C(32)-C(37)	149.8(4)
C(38)-P(2)-C(32)-C(37)	26.1(4)
C(8)-P(2)-C(32)-C(37)	-86.0(4)
O(6)-P(2)-C(32)-C(33)	-33.2(4)
C(38)-P(2)-C(32)-C(33)	-156.9(3)
C(8)-P(2)-C(32)-C(33)	91.0(3)
C(37)-C(32)-C(33)-C(34)	-0.3(7)
P(2)-C(32)-C(33)-C(34)	-177.6(4)
C(32)-C(33)-C(34)-C(35)	1.5(8)
C(33)-C(34)-C(35)-C(36)	-3.7(8)

C(34)-C(35)-C(36)-C(37)	4.6(8)
C(33)-C(32)-C(37)-C(36)	1.2(7)
P(2)-C(32)-C(37)-C(36)	178.1(3)
C(35)-C(36)-C(37)-C(32)	-3.2(7)
O(6)-P(2)-C(38)-C(43)	170.3(3)
C(32)-P(2)-C(38)-C(43)	-66.2(4)
C(8)-P(2)-C(38)-C(43)	46.9(4)
O(6)-P(2)-C(38)-C(39)	-9.9(3)
C(32)-P(2)-C(38)-C(39)	113.6(3)
C(8)-P(2)-C(38)-C(39)	-133.3(3)
C(43)-C(38)-C(39)-C(40)	-0.8(6)
P(2)-C(38)-C(39)-C(40)	179.4(3)
C(38)-C(39)-C(40)-C(41)	-0.1(7)
C(39)-C(40)-C(41)-C(42)	0.7(8)
C(40)-C(41)-C(42)-C(43)	-0.5(8)
C(39)-C(38)-C(43)-C(42)	1.1(6)
P(2)-C(38)-C(43)-C(42)	-179.2(3)
C(41)-C(42)-C(43)-C(38)	-0.4(7)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for CSS3 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1W)-H(1WB)...O(6)	0.86	1.97	2.744(4)	149.8

Symmetry transformations used to generate equivalent atoms:

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