NANYANG
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NOVEL 1,1'-BISISOQUINOLINES:
SYNTHESIS, RESOLUTION AND APPLICATION IN ASYMMETRIC CATALYSIS

GAO QI

SCHOOL OF CHEMICAL AND BIOMEDICAL ENGINEERING

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ABSTRACT

This thesis deals with the chemistry of novel 1,1'-bisisoquinolines and derivatives. Application of enantiopure 1,1'-bisisoquinolines as ligands for various asymmetric C-C bond forming reactions has been examined.

Condition for the preparation of the anticipated 1,1'-bisisoquinolines has been established. *Racemic* C_2-symmetric 1,1'-bisisoquinolines and pseudo symmetric 1,1'-bisisoquinolines were synthesized through classical double Bischler-Napieralski reaction followed by reduction with borohydrides. *Racemic* pseudo symmetric 1,1'-bisisoquinoline could also be synthesized directly through double Bischler-Napieralski reaction using polyphosphoric acid at elevated temperatures. Resolution of the *racemic* 1,1'-bisisoquinolines *via* diastereomeric salt and covalent bond formation was explored thoroughly. Diasteromeric salts failed to separate to give individual enantiomers. Covalent bond formation using chiral isocyanates such as α-methylbenzyl isocyanate gave diastereomeric urea derivatives that were separated by a combination of column chromatography and recrystallization techniques. Acid and base catalyzed alcoholysis approaches were explored to obtain the free enantiopure 1,1'-bisisoquinolines. Difficulties were met during the alcoholysis mainly due to racemization of the enantiomers. However, after optimization of the reaction conditions, base alcoholysis followed by recrystallization gave the required 1,1'-bisisoquinoline in enantiopure form. The reactivity and structural features of (+)-1,2,3,4-tetrahydro--1,1'-bisisoquinoline were explored in details through formation of various *N*-alkyl, amide, urea and thiourea derivatives and by studying the X-ray structures of some of these derivatives.

The scope of the chiral 1,1'-bisisoquinolines was examined in the enantioselective C-C bond forming reactions. Therefore, chiral 1,1'-bisisoquinoline ligands were tested in the enantioselective addition of diethylzinc to various aldehydes. The ligands were found to be very efficient as they generated the expected chiral secondary alcohols in excellent yield and ee (up to 91%). The scope of these novel ligands were also examined in the enantioselective conjugate addition of Grignard reagents to cyclic enones. The present ligands gave the desired 1,4 adducts in good yield and moderate ee (up to 35%). Insight into the mechanism by which these catalysts operate was presented. This piece of work represented a major contribution to the use of 1,1'-bisisoquinolines as ligands in asymmetric catalysis. Excellent results have been reported in this thesis.

LIST OF ABBREVIATIONS

AH	Asymmetric hydrogenation
^{13}C NMR	Carbon-13 nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
BINOL	1,1'-Binaphthol
BIQ	Bisisoquinoline
$CDCl_3$	Deuterated chloroform
COSY	^{1}H-^{1}H Correlation Spectroscopy
D-BCSA	*D*-(+)-α-Bromocamphor-π-sulfonic acid
D-CSA	*D*-(+)-Camphor-10-sulfonic acid
de	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutyl aluminium hydride
DMAP	*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DPEN	1,2-Diphenylethylenediamine
EA	Ethyl acetate
ee	Enantiomeric excess
equiv	Equivalent
ESI	Electrospray impact ionisation
Et_2O	Diethyl ether
Et_2Zn	Diethylzinc
Et_3N, TEA	Triethylamine
EtOH	Ethanol
FTIR	Fourier transform infrared

GC	Gas Chromatography
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Coherence
HPLC	High Performance Liquid Chromatography
HRMS	High resolution mass spectroscopy
Hz	Hertz
IPA	Isopropyl alcohol
i-Pr_2O	Diisopropyl ether
m.p.	Melting point
m/z	Mass/Charge
MeOH	Methanol
NaOBu	Sodium butoxide
n-BuOH	*n*-Butanol
NHC	*N*-Heterocyclic carbene
Pd/C	Palladium on charcoal
PPA	Polyphosphoric acid
ppm	Parts per million
r.t.	Room temperature
S/C	Substrate/Catalyst
t-BuOH	*tert*-Butanol
t-BuOK	Potassium *tert*-butoxide
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
THF	Tetrohydrofuran
$Ti(O^iPr)_4$	Titanium(IV) isopropoxide
TLC	Thin layer chromatography

TMS	Tetramethylsilane
TS	Transition state
UV	Ultraviolet

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Chapter 1. Introduction

1.1. The significance of chirality

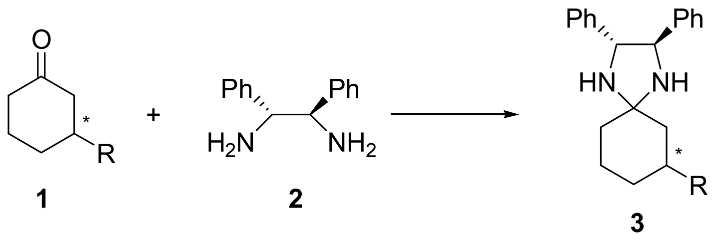
Chirality is a fundamental property of many three-dimensional objects. An object is chiral if it can not be superimposed on its mirror image. In such a case, there are two possible forms of the same object, called enantiomers. Chirality is of prime significance since most of the biological molecules of living systems occur in nature in only one enantiomeric form. A biologically active chiral compound interacts with its receptor site in a chiral manner. Thus, it is not surprising that the two enantiomers of a drug may interact differently with a receptor leading to different effects. For example, one enantiomer may be therapeutically effective, while the other may be ineffective or even toxic. This importance of chirality can be realized from the fact that approximately four out of every five drugs currently in the development phases are single isomers.[1] New FDA rules require both enantiomers of chiral drugs to be fully investigated and their therapeutic and toxicity effects well studied and evaluated.

1.2. Importance of vicinal *N/N*-ligands in asymmetric synthesis

Many chiral compounds have potential to be ligands and form metal complexes that can be used in asymmetric catalysis. Among those compounds, several kinds of chiral vicinal *N*/*N*-ligand have been used in various asymmetric reactions. In the context of this thesis, we will focus on vicinal chiral diamines and chiral amine-imine (amine-pyridine) type compounds and mention their application in various asymmetric transformations.

1.2.1. Vicinal chiral diamines

Vicinal chiral diamines have been used as resolving agents for *racemic* primary alcohols[2] and aldehydes[3]. They have also been used to determine the enantiomer composition of cyclic ketones and aldehydes. For example, reaction between 3-substituted cyclohexanone **1** and (*R,R*)-1,2-diphenylethylenediamine (DPEN, **2)** gave diastereomeric aminal **3** (Scheme 1). By comparing the integrations of certain peaks in the ^{13}C NMR spectrum of the products, the enantiomeric excess (ee) of ketone **1** can be deduced.[4,5]

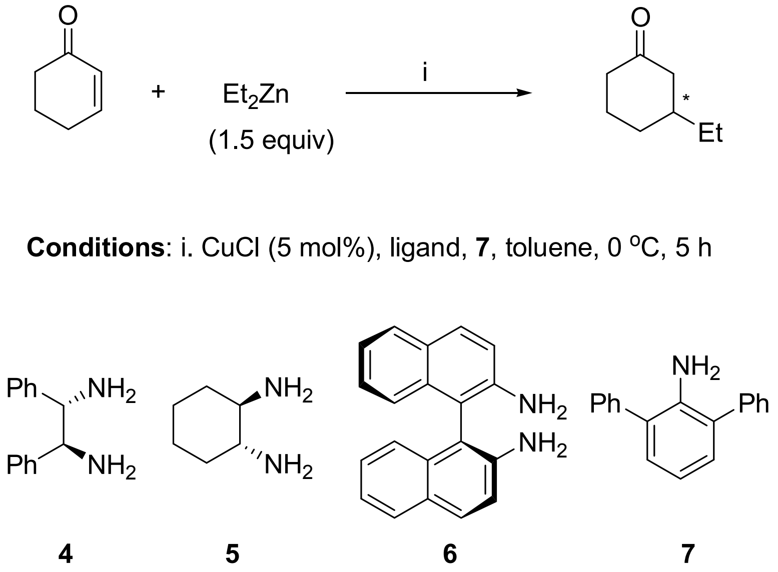


Scheme 1

Besides this, vicinal acyclic and cyclic chiral diamines are widely used as ligands in various asymmetric reactions.

1.2.1.1. Acyclic vicinal chiral diamine ligands

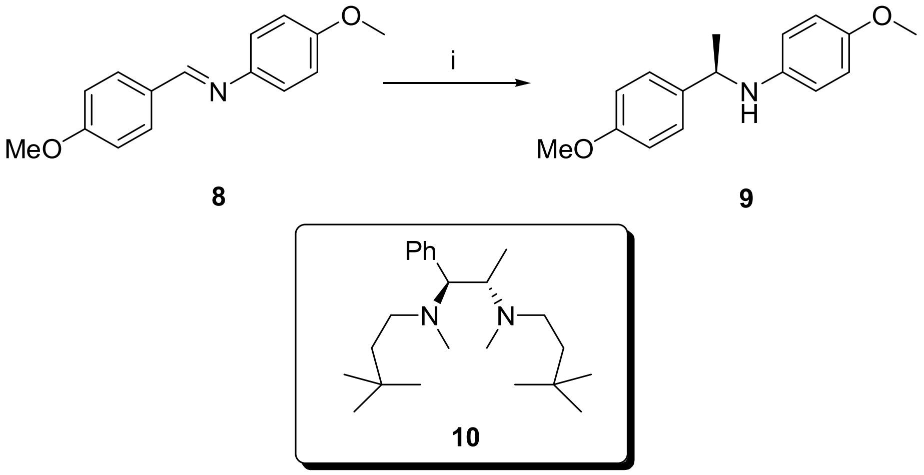
Hatano *et al.* studied the enantioselective conjugate addition of diethylzinc (Et_2Zn) to 2-cyclohexenone using Cu(I) complexes of (*S,S*)-DPEN **4**, (*R,R*)-1,2-cyclohexanediamine **5** and (*S*)-binaphthyldiamine **6** (Scheme 2). In the presence of 2,6-diphenylaniline **7,** the reaction catalyzed by Cu(I)-**6** complex gave the desired 1,4-adduct in 74% ee.[6]



Conditions: i. CuCl (5 mol%), ligand, **7**, toluene, 0 °C, 5 h

Scheme 2

Pseudo C_2-symmetric tertiary diamine **10** reported by Perron *et al.* catalyzed the enantioselective addition of methyllithium to aromatic imine **8** to gave product **9** in 91% ee.[7-11]

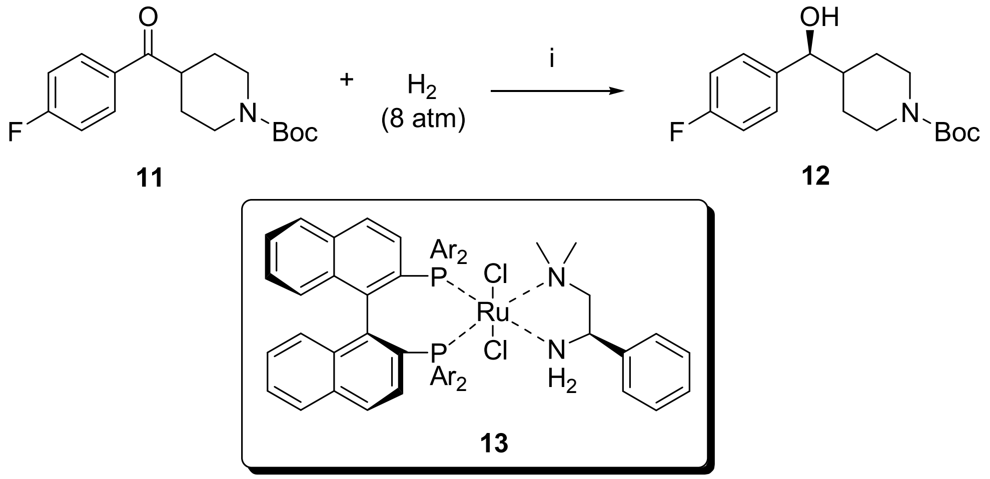


Conditions: i. MeLi (3.0 equiv), **10** (1.0 equiv), toluene, -78 °C, 38 h

Scheme 3

Asymmetric hydrogenation (AH) of unfunctionalised ketones can be achieved in high enantiomeric excess using diphosphine-Ru-diamine complexes. This class of catalysts was first reported by Noyori in 1995,[12] and has since been developed by many research groups.[13–20]

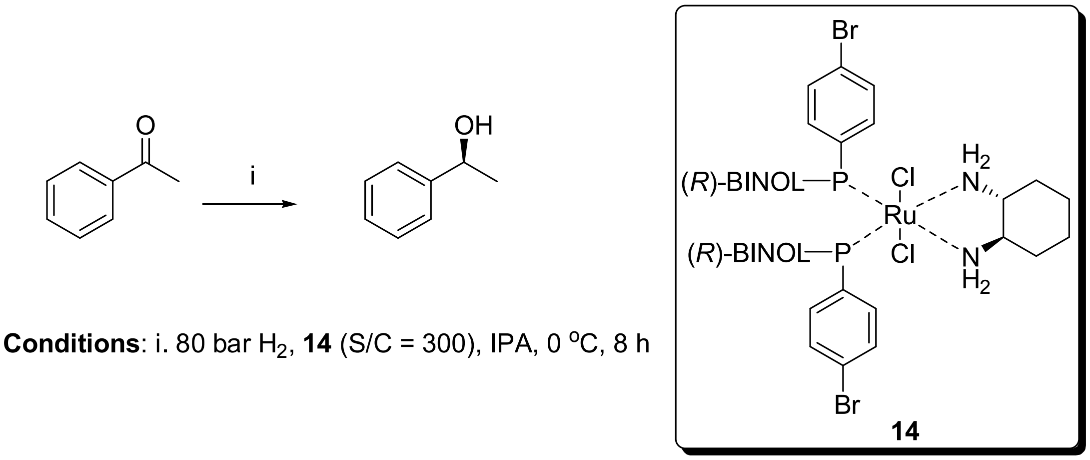
Recently, two research groups independently reported asymmetric hydrogenation of aromatic ketones in the presence of diphosphine-Ru-diamine complex. Using (*S*)-2,2'--bis(di-4-tolylphosphino)-1,1'-binaphthyl-Ru(II)-(*R*)-2-dimethyl-amino-1-phenylethylamine complex **13**, Ooka *et al.* achieved complete stereo control (>99% ee) for asymmetric hydrogenation of alkyl aryl ketone **11** (Scheme 4).[21]



Conditions: i. *t*-BuOK, **13** (S/C=400), IPA, r.t., 7 h

Scheme 4

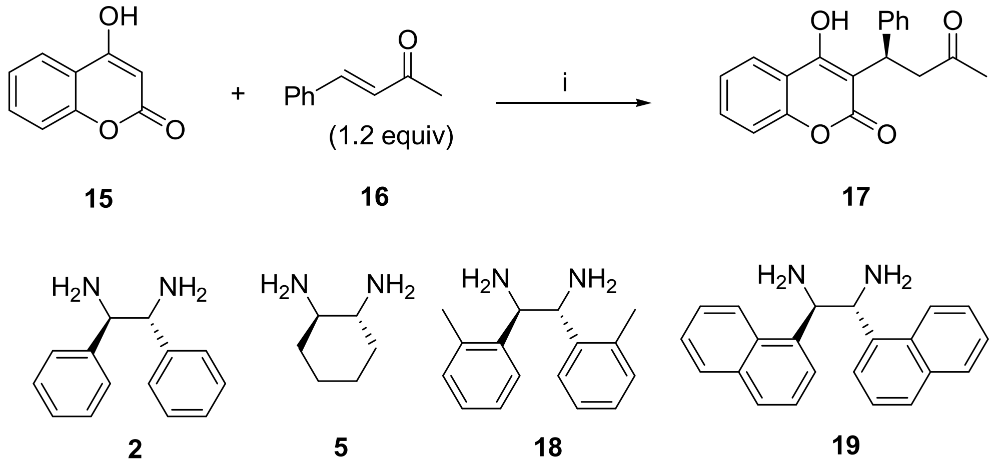
Another diphosphine-Ru-diamine catalyst **14** derived from (*R*)-1,1'-2-Binaphthol (BINOL) and (*R*,*R*)-1,2-cyclohexanediamine **5** has been applied in asymmetric hydrogenation of acetophenone to yield the expected alcohol in 90% ee (Scheme 5).[22]



Conditions: i. 80 bar H_2, **14** (S/C = 300), IPA, 0 °C, 8 h

Scheme 5

Apart from serving as classical ligands, vicinal diamines in recent years have been used increasingly as organocatalysts.[23-29] Kim used vicinal diamines such as **2**, **5**, **18** and **19** to catalyze the synthesis of warfarin **17** (Scheme 6). The best result was rendered by diamine **18** which gave 92% ee.[30]



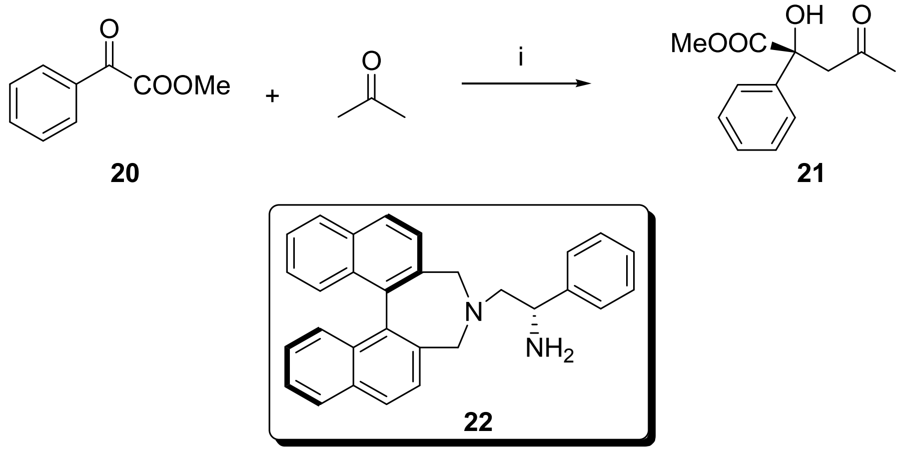
15 **16** **17**

2 **5** **18** **19**

Conditions: i. diamine (10 mol%), AcOH (10 equiv), THF, r.t., 48 h

Scheme 6

Qin and co-workers have synthesized a new family of chiral diamines having a highly tunable tertiary-primary amine motif. When methyl 2-oxo-2-phenylacetate **20** was reacted with acetone in the presence of 10 mol% of catalyst **22**, the desired chiral tertiary alcohol **21** was obtained in 99% yield and 96% ee (Scheme 7).[31]



20 **21**

22

Conditions: i. **22** (10 mol%), TFA (20 mol%), 0 °C

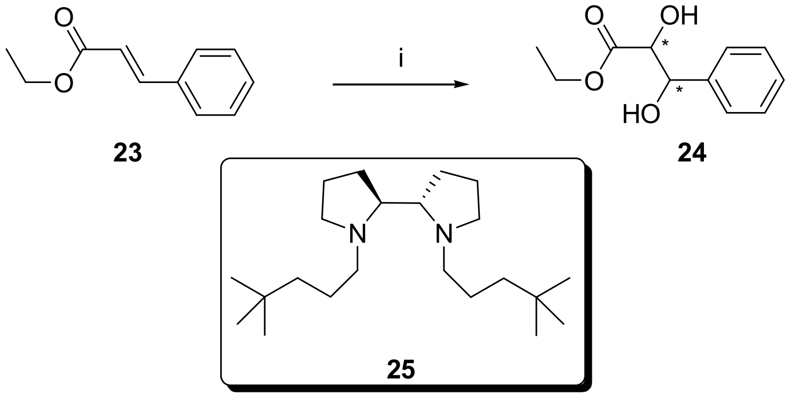
Scheme 7

1.2.1.2. Cyclic vicinal chiral diamine ligands

Cyclic vicinal diamines are much less explored compared to the acyclic ones due difficulties in their synthesis. One striking feature of these diamines is the rigidity of their structures.

L-Proline is the most commonly used starting material for preparation of various chiral cyclic diamines.

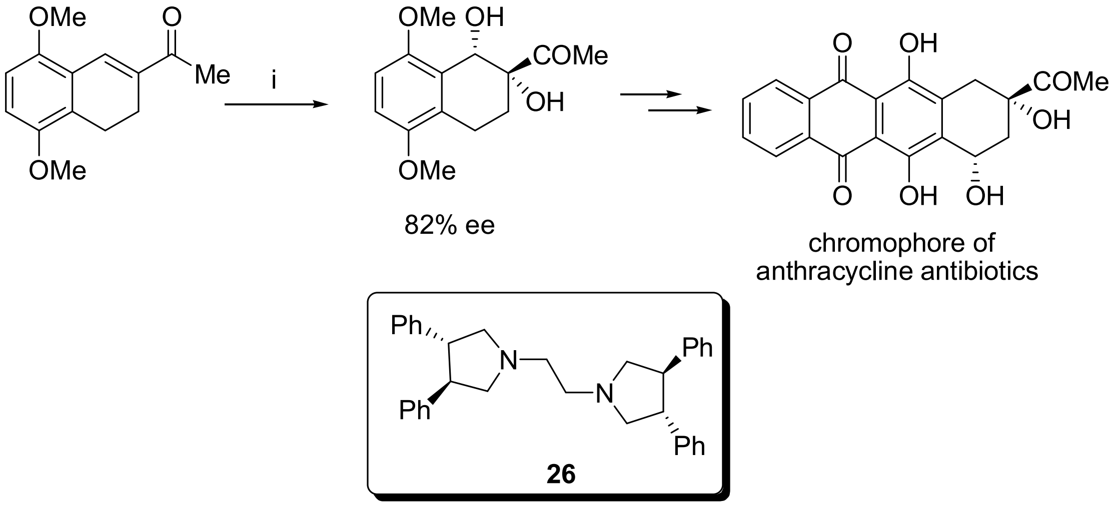
Hirama *et al.* developed a series of cyclic chiral bidentate diamine ligands for OsO_4-mediated dihydroxylation of *trans*-disubstituted and monosubstituted olefins. Thus, asymmetric dihydroxylation of ethyl (*E*)-3-phenylacrylate **23** using chiral ligand **25** provided 97% yield and 99% ee of the desired dihydroxylated product **24** (Scheme 8).[32,33]



Conditions: i. OsO_4, **25**, toluene, -78 °C

Scheme 8

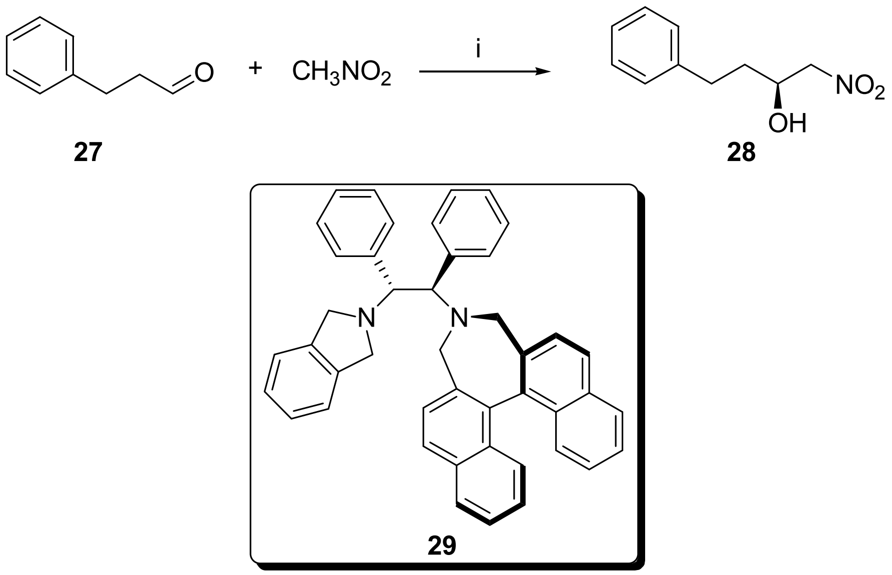
The outstanding results obtained using cyclic chiral diamine ligands in asymmetric dihydroxylation attracted application in drug sysnthesis.[34-37] Tomioka *et al.* reported the synthesis of the chromophore part of anthracycline antibiotic by applying chiral diamine catalyzed dihydroxylation procedure as a key step (Scheme 9).[38]



Conditions: i. OsO_4, **26**, THF

Scheme 9

Yanagisawa and co-workers reported the synthesis of a novel cyclic chiral diamine **29** and its application in enantioselective Henry reactions. For example, hydrocinnamaldehyde **27** was converted to the expected product **28** in >99.5% ee under the catalysis of **29**-Cu(II) complex (Scheme 10).[39]

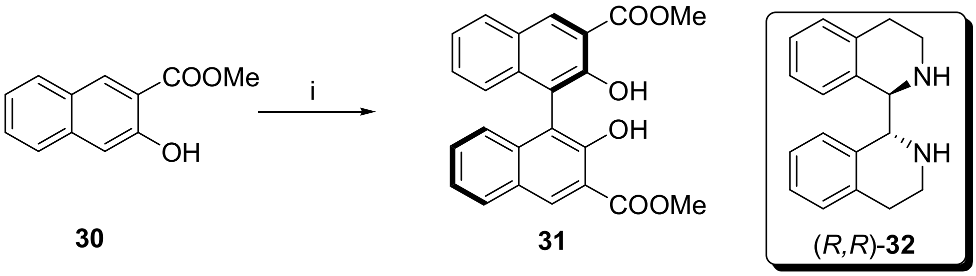


Conditions: i. **29**-$Cu(OAc)_2$ (5 mol%), *n*-PrOH, r.t., 48 h

Scheme 10

1.2.1.3. Chiral 1,1'-bis-tetrahydroisoquinoline based ligands

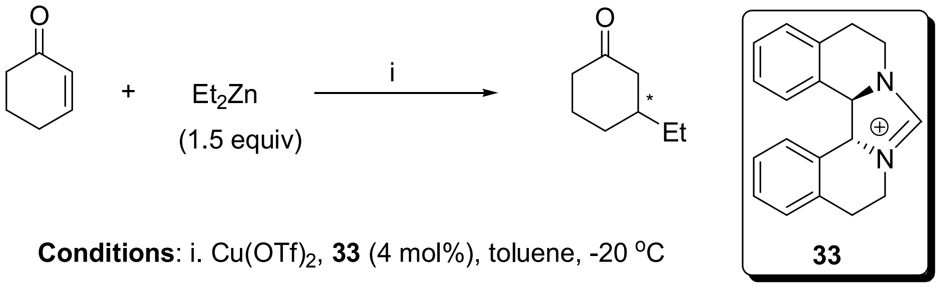
Although chiral 1,1'-bisisoquinolines (BIQs) were thought as potential asymmetric catalysts for a long time, only limited examples have been reported till now. Arai used chiral BIQ (*R,R*)-**32** in combination with CuCl to catalyze the asymmetric oxidative coupling of ester **30** to give 3,3'-substituted BINOL **31** in moderate yield (60%) and up to 48% ee (Scheme 11).[40]



Conditions: i. **32** (10 mol%), CuCl (10 mol%), CH_3CN, 0 °C, 48 h

Scheme 11

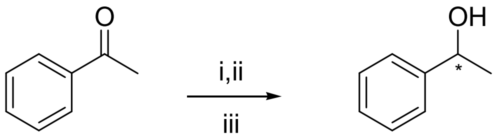
The chiral *N*-heterocyclic carbene (NHC) **33** which is based upon BIQ (*R,R*)-**32** was used by Cavell *et al.* in the stereoselective conjugate addition of Et_2Zn to cyclohexanone to give the alkylated ketone in only 10% ee (Scheme 12).[41]



Conditions: i. $Cu(OTf)_2$, **33** (4 mol%), toluene, -20 °C

Scheme 12

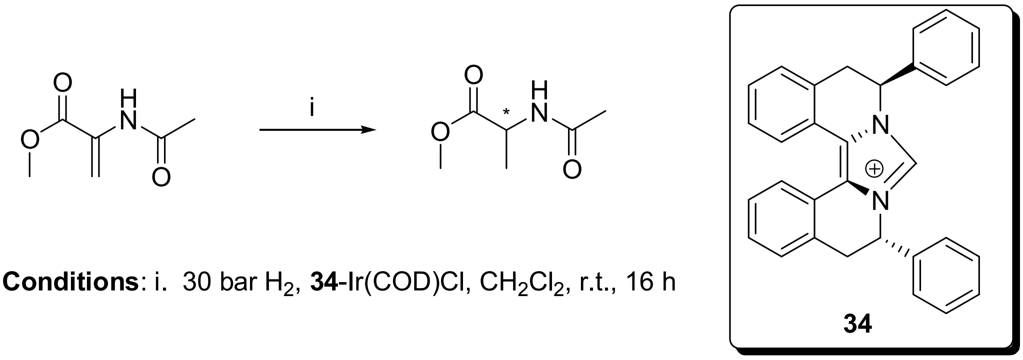
Further application of NHC **33** in asymmetric hydrosilylation and transfer hydrogenation to acetophenone by Herrmann *et al.* gave the products in unsatisfactory low 28% ee and 24% ee respectively (Scheme 13).[42]



Conditions:i. SiH_2Ph_2, **33**-Rh(COD)Cl, THF, -20 °C, 16 h
ii. *p*-TsOH, MeOH
iii. *t*-BuOK, **33**-Ir(COD)Cl, IPA, 60 °C, 72 h

Scheme 13

Nevertheless, Hoffmann and co-workers reported good enantioselectivity (67% ee) through the use of NHC **34** complex in asymmetric hydrogenation of methyl 2-acetamidoacrylate (Scheme 14).[43]

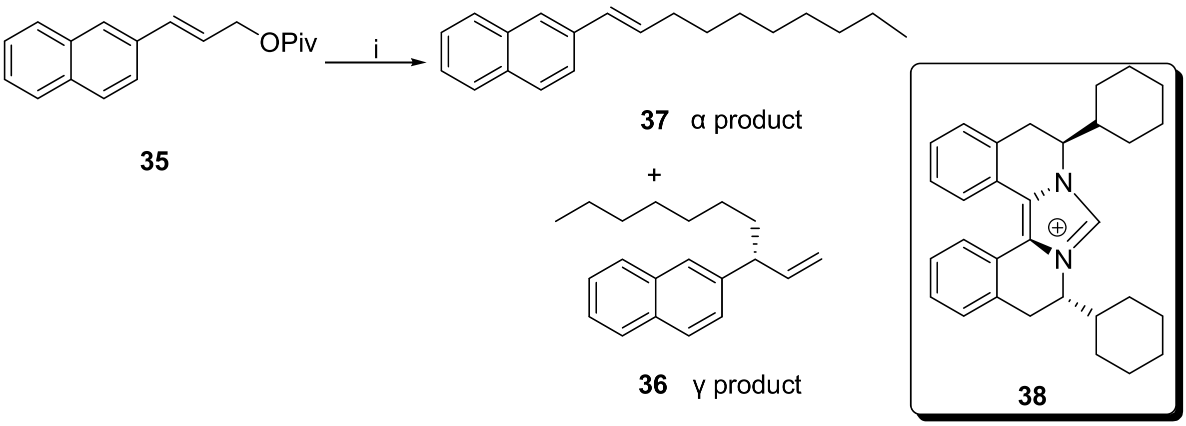


Conditions: i. 30 bar H_2, **34**-Ir(COD)Cl, CH_2Cl_2, r.t., 16 h

34

Scheme 14

The latest example reported by Seo *et al.* used Cu(I) complex of NHC **38** in asymmetric allylic alkylations of **35** to generate the desired γ product **36** in moderate conversion (70%) and good ee (77%) (Scheme 15).[44]



35

37 α product

36 γ product

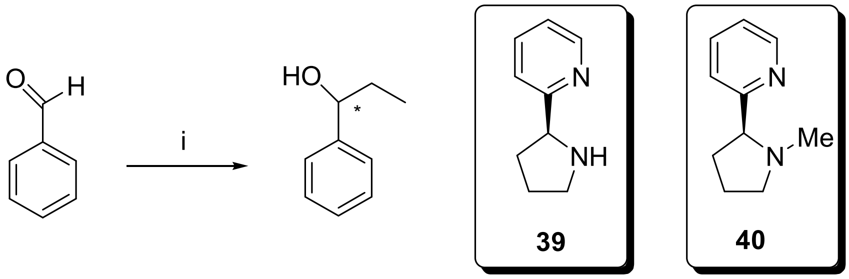
38

Conditions: i. **38** (3 mol%), CuCl (3 mol%), *n*-HexMgBr (1.5 equiv), Et_2O, 0 °C, 1 h

Scheme 15

1.2.2. Chiral vicinal amine-pyridine ligands

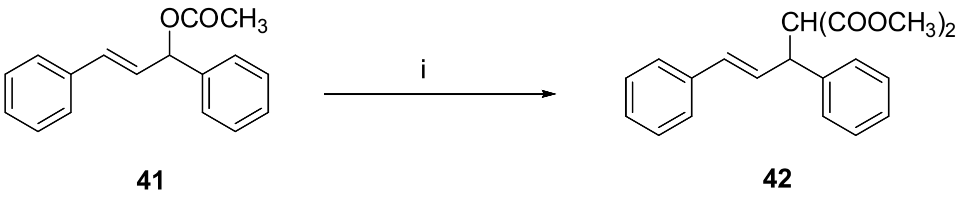
The use of chiral vicinal amine-imine (amine-pyridine) type ligands for asymmetric synthesis is very limited. For example, ligand **39** and **40** were synthesized by Chelucci from natural (*S*)-proline[45] and were tested in the enantioselective addition of Et_2Zn to aldehydes (Scheme 16).[46,47] Addition of Et_2Zn to benzaldehyde in the presence of 6 mol% of **39** yielded the expected secondary (*S*)-alcohol in up to 93% ee. However, under same conditions, ligand **40** gave the (*R*)-alcohol in only 6% ee. Thus, it was concluded that the hydrogen on the pyrrolidine nitrogen was essential for good enantioselectivity.



Conditions: i. **39** or **40** (6 mol%), Et_2Zn (2.0 equiv), Et_2O/hexane, r.t., 20 h

Scheme 16

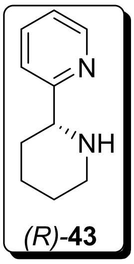
When the same ligands were used, together with palladium salt, for the allylic substitution of 1,3-diphenylprop-2-enyl acetate **41** with dimethyl malonate, ligand **39** yielded (*R*)-**42** in 64% ee, while ligand **40** gave (*S*)-**42** in only 8% ee (Scheme 17).[48]



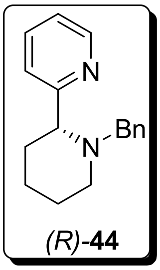
Conditions: i. **39** or **40** (10 mol%), dimethyl malonate (3 equiv),
N,O-bis(trimethylsilyl)acetamide (BSA) (3 equiv),
$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2.5 mol%), KOAc (3 mol%),
CH_2Cl_2, r.t., 24 h

Scheme 17

Recently, Gao and co-workers reported the synthesis and resolution of ligands *rac*-**43** and *rac*-**44**, and examined them in the enantioselective addition of Et_2Zn to benzaldehyde. Ligands (*R*)-**43** and (*R*)-**44** were found to give the tertiary alcohols with (*R*)-configuration in 93% ee and 12% ee, respectively.[49] Again here, the NH hydrogen on (*R*)-**43** was essential for good enantioselectivity.



(*R*)-**43**



(*R*)-**44**

1.3. Strategies to enantiomerically pure compounds

There are three main broad strategies (Figure 1) to obtain compounds in enantiopure forms: (1) synthesis from naturally occurring chiral compounds (chiral pool synthesis), (2) resolution of racemates and (3) asymmetric synthesis or biological transformation using prochiral substrates.

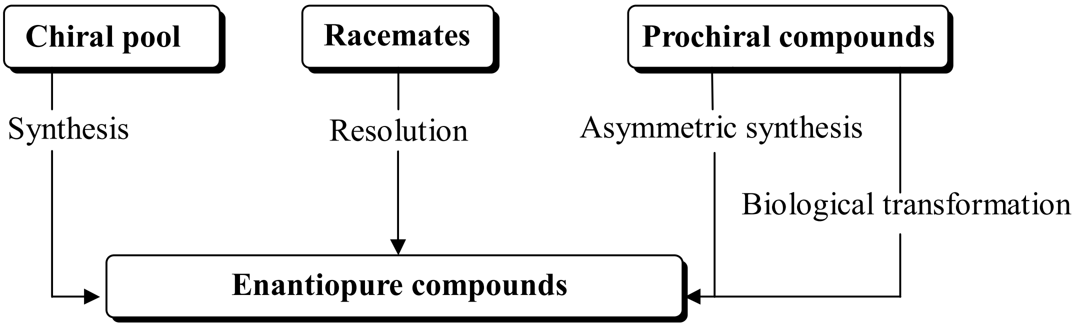


Figure 1

The conversion or derivatization of readily available naturally occurring chiral compounds is a very convenient way to obtain desired chiral products. However, the limited number of chiral pool compounds and lack of availability of both enantiomeric forms puts constrains on the scope of this method. On the other hand, resolution of racemates is a classical route which is frequently used in various industries to obtain bulk amounts of enantiopure products through resolution of the corresponding *racemic* species. In the pharmaceutical industry, because generally only one enantiomer is useful, half of the synthetic product is often discarded since it possesses the opposite chirality of the required enantiomer. Obviously, this is economically and environmentally depleting and is taken as a major disadvantage of this route. Asymmetric synthesis refers to the conversion of a prochiral starting material to a chiral product under chiral environment conditions. It is presently the most powerful method for chiral molecule preparation. So far, most of the successful asymmetric syntheses are catalyzed by enzymes, i.e. biological transformation. Unfortunately, the scope of enzymatic reactions is limited due to high specificity of enzymes towards substrates. Therefore, the main challenge is to develop chemical routes that are as efficient as enzymatic ones.

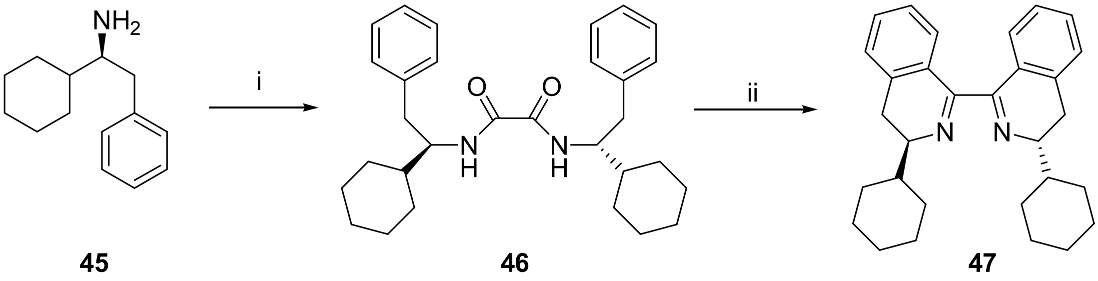
The most significant advancement in asymmetric synthesis in the past three decades has been the application of chiral catalysts to induce conversion of achiral substrates to chiral products. The obvious benefit of catalytic asymmetric synthesis is that only small amounts of chiral catalysts are needed to generate large quantities of chiral products. The enormous economic potential of asymmetric catalysis has made it one of the most extensively explored areas of research in recent years.

1.4. Strategies to obtain chiral BIQs

As described in section 1.3, there are normally three routes to enantiomerically pure compound, namely, chiral pool synthesis, resolution of racemates and asymmetric synthesis. Consequently, chiral BIQs in principle can be sought from all of the three routes.

1.4.1. Preparation of chiral BIQs through chiral pool synthesis

This strategy always starts with the homochiral pure compounds obtained either from natural sources or from commercial sources. For example, Seo *et al.* developed a route to synthesize chiral BIQ **47** using available chiral phenethylamine **45** as starting material. As shown in Scheme 18, **45** was converted to bisamide **46** which then was subjected to modified Bischler-Napieralski cyclization conditions to afford 3,3'-disubstituted tetrahydrobisisoquinoline **47** in moderate yield (61%).[44]



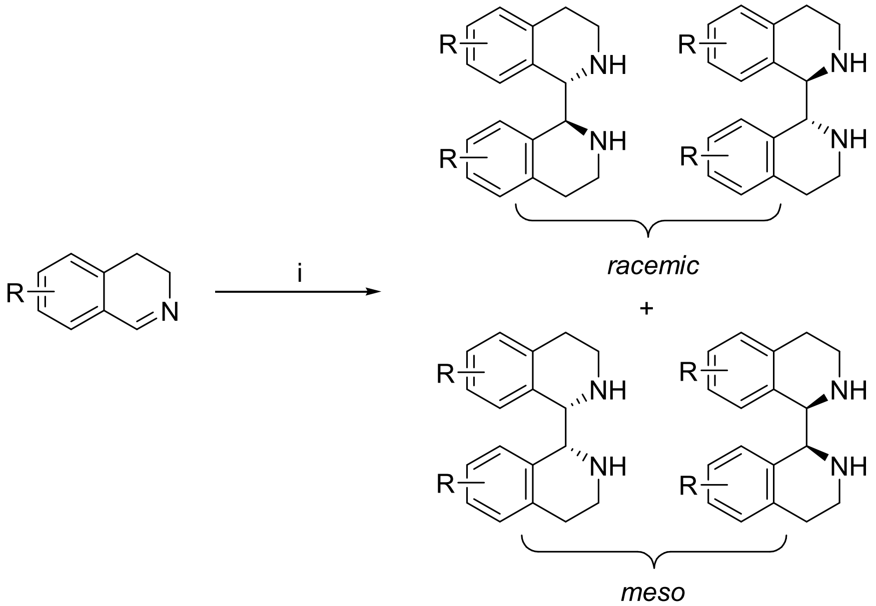
Conditions: i. Oxalyl chloride, Et_3N, THF, 0 °C to r.t., 12 h
ii. PCl_5, $Zn(OTf)_2$, toluene, 85 °C, 12 h

Scheme 18

1.4.2. Preparation of chiral BIQs through resolution of racemates

1.4.2.1. Preparation of *racemic* 1,1'-bis-tetrahydroisoquinolines

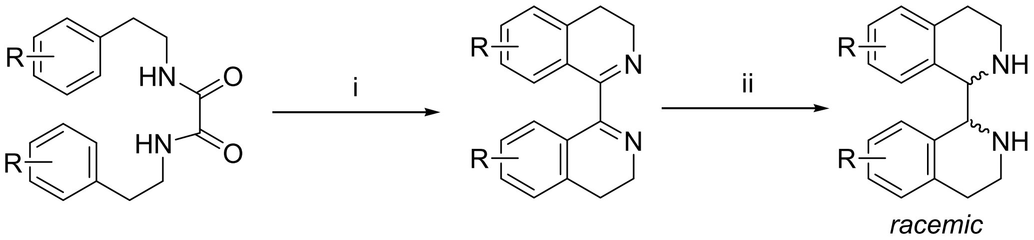
Coupling and cyclization are two general methods used to synthesize *racemic* bis-tetrahydroisoquinolines. The first method involves either oxidative coupling[50-52] of tetrahydroisoquinolines or reductive coupling[40,43,53-60] of dihydroisoquinolines. A typical reductive coupling process is shown in Scheme 19. The biggest disadvantage of this approach is the production of a diastereomeric mixture of *racemic* and *meso* products in 1:1 ratio. Although the separation of the diastereomers was normally feasible, the production of undesired *meso* isomers is considered a waste.



Conditions : i. Zn, Lewis acid

Scheme 19

The second method involves dehydration of bisoxamides through double Bischler-Napieralski reaction to yield 1,1'-bis-dihydroisoquinolines followed by stereoselective reductions to give *racemic* 1,1'-bis-tetrahydroisoquinolines (Scheme 20).[50,61-63] This method was confirmed to be efficient for synthesis of such compounds.[64,65]



Conditions: i. Dehydration reagents
ii. $NaCNBH_3$

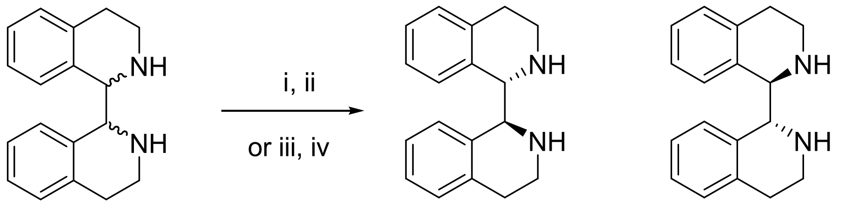
Scheme 20

A wide range of dehydrating agents can be used to promote Bischler-Napieralski reactions including phosphrous oxychloride,[66] phosphorus pentoxide,[67] phosphorus pentachloride,[68,69] polyphosphoric acid,[70] aluminium chloride,[71] pyrophosphoryl chloride,[62] zinc chloride[72] and a combination of trifluoromethanesulfonic anhydride (Tf_2O) and *N*,*N*-dimethylaminopyridine (DMAP).[61]

The stereoselective reductions of 1,1'-bis-dihydroisoquinolines had been thoroughly studied and a clear understanding has been established. Stereoselective reduction of 1,1'-bis-dihydroisoquinolines using $NaCNBH_3$[50,61-63] afforded *racemic* 1,1'-bis-tetrahydroisoquinolines while reduction using $NaBH_4$[50], diisobutylaluminium hydride (DIBAL-H)[65] or catalytic hydrogenation over PtO_2[73] all yielded *meso* products exclusively.

1.4.2.2. Resolution of *racemic* 1,1'-bis-tetrahydroisoquinolines

Resolution of *racemic* compounds normally involves screening various resolving agents. BIQs have been resolved earlier through diasteromeric salt formation. Elliott *et al.* reported the resolution of BIQ *rac*-**32** employing chiral α-bromocamphor-π-sulfonic acid (BCSA) ammonium salt. In this case, when *rac*-**32** was recrystallised with *D*-BCSA in EtOH, crystals of (*S,S*)-**32**•BCSA salt were obtained. Crystals of (*R,R*)-**32**•BCSA salt could be obtained similarly when *L*-BCSA was used. Consequently, enantiopure BIQs (*S,S*)-**32** and (*R,R*)-**32** were obtained after treatment of the salts (*S,S*)-**32**•BCSA and (*R,R*)-**32**•BCSA separately with NaOH solution followed by extraction.[59] BIQ *rac*-**32** was also resolved by Arai *et al.* in a similar fashion using chiral camphorsulfonic acid (CSA) as resolving agent (Scheme 21).[40]



rac-**32**

(*S,S*)-**32** >99% ee

crystaline
if *D*-BCSA
or *D*-CSA
used

(*R,R*)-**32** >99% ee

crystaline
if *L*-BCSA
or *L*-CSA
used

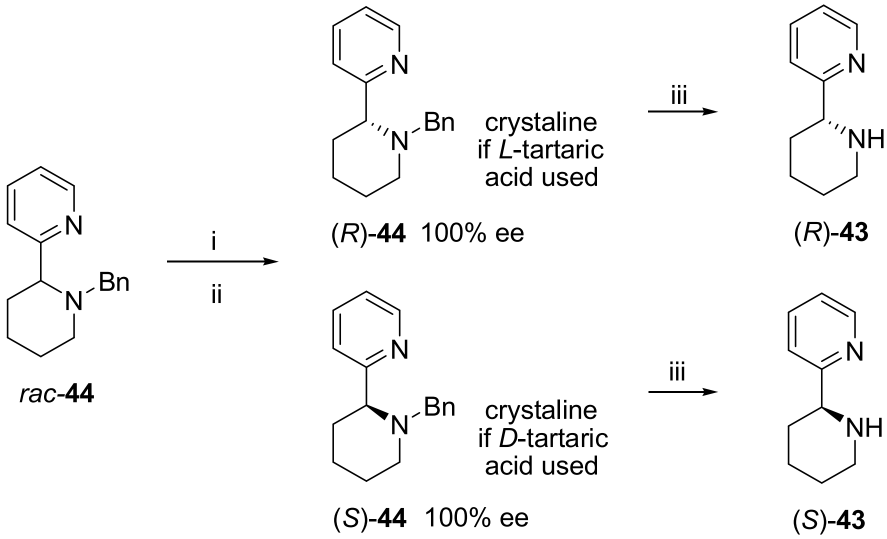
Reagents : i. *D*-CSA or *L*-CSA (2.0 equiv), recrystallization from *i*-Pr_2O/EtOH
ii. 10% NaOH
iii. *D*-BCSA or *L*-BCSA ammonium salt (1.0 equiv), recrystallization from EtOH
iv. 5 M $NaOH/CH_2Cl_2$

Scheme 21

1.4.2.3. Resolution of compounds having similar structure as BIQs

Literature precedents revealed that compounds having similar structures usually could be resolved using the same resolving agent. Thus, resolution procedures for compounds having similar structure as BIQs are reviewed and summarized here.

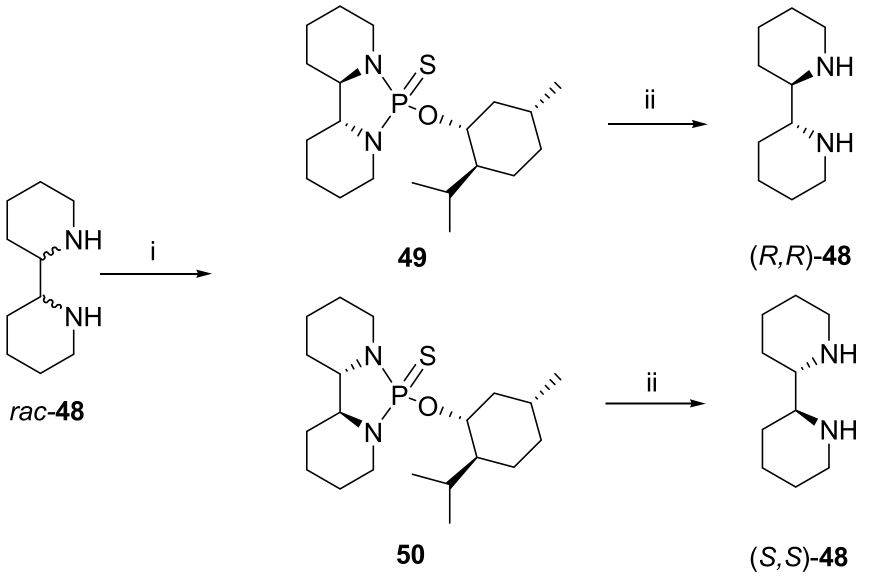
Gao and co-workers reported the resolution of compound *rac*-**44** by using *L*- and *D*-tartaric acid as resolving agent. The resulting enantiomers (*R*)-**44** and (*S*)-**44** could be further hydrogenated to afford enantiomers (*R*)-**43** and (*S*)-**43** (Scheme 22).[49]



Conditions: i. *D*- or *L*-tartaric acid, recrystallization from CH_3CN/THF (5:1)
ii. 15% NaOH
iii. $Pd(OH)_2/C$, H_2, 1 atm, EtOH, 2 d

Scheme 22

Herrmann *et al.* reported the resolution of compound *rac*-**48** using l-menthol as a resolving agent (Scheme 23). The resulting diastereomeric mixture **49** and **50** was hydrolysed in concentrated HBr to give compounds (*R,R*)-**48** and(*S,S*)-**48**.[42]



Conditions: i. PCl_3, 1-Menthol, S_8, recrystallization from MeOH
ii. HBr

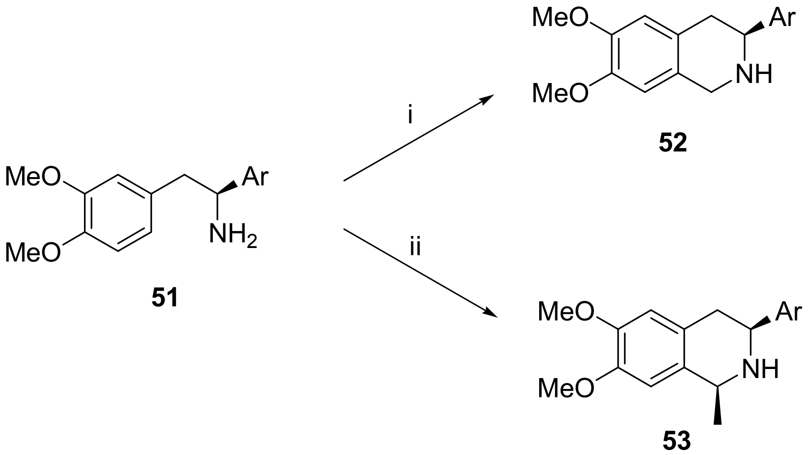
Scheme 23

1.5. Strategies to obtain chiral isoquinolines

Methods that are used to obtain enantiopure isoquinolines could potentially be applied to obtain chiral BIQs. We will mention some of the routes here as we see important in the context of this thesis.

1.5.1. Preparation of chiral isoquinolines through chiral pool synthesis

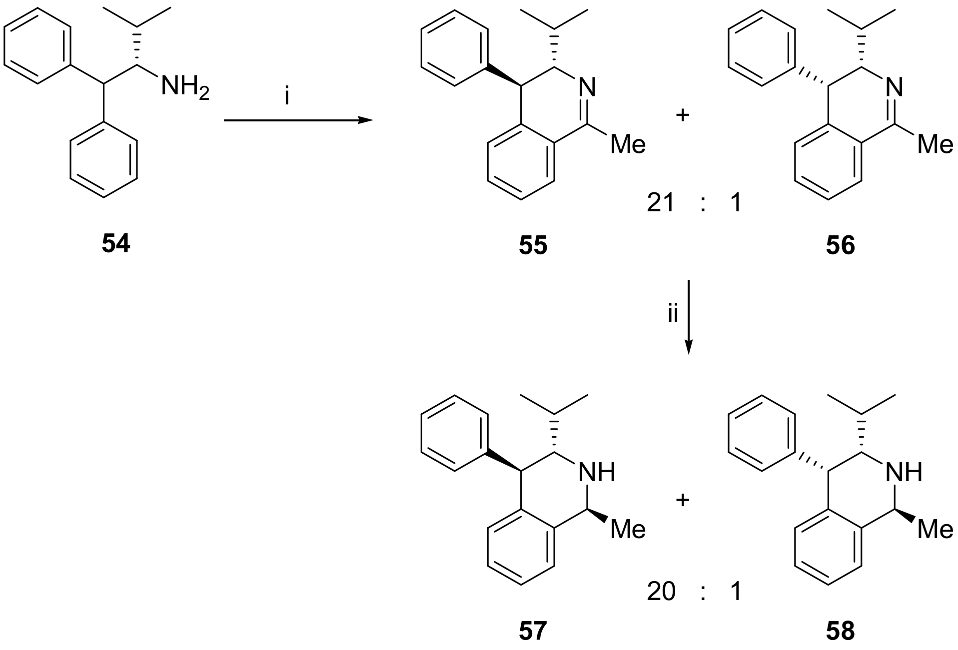
Carrillo *et al.* reported an efficient stereo-controlled synthetic approach to (3*S*)-3-aryl-tetrahydroisoquinoline **52** and (1*S*,3*S*)-3-aryl-1-methyl-tetrahydro-isoquinoline **53** using a Pictet-Spengler heterocyclization reaction of optically active (*S*)-1,2-diarylethylamines **51** (Scheme 24).[74]



Conditions: i. HCHO, HCl
ii. MeCHO, H_2SO_4

Scheme 24

Bischler-Napieralski cyclization of (*S*)-1-isopropyl-1,2-diphenylethylamide **54** gave a mixture of diastereomers **55** and **56** (21:1) which upon reduction gave diastereoisomeric products **57** and **58** (20:1) (Scheme 25).[75,76]



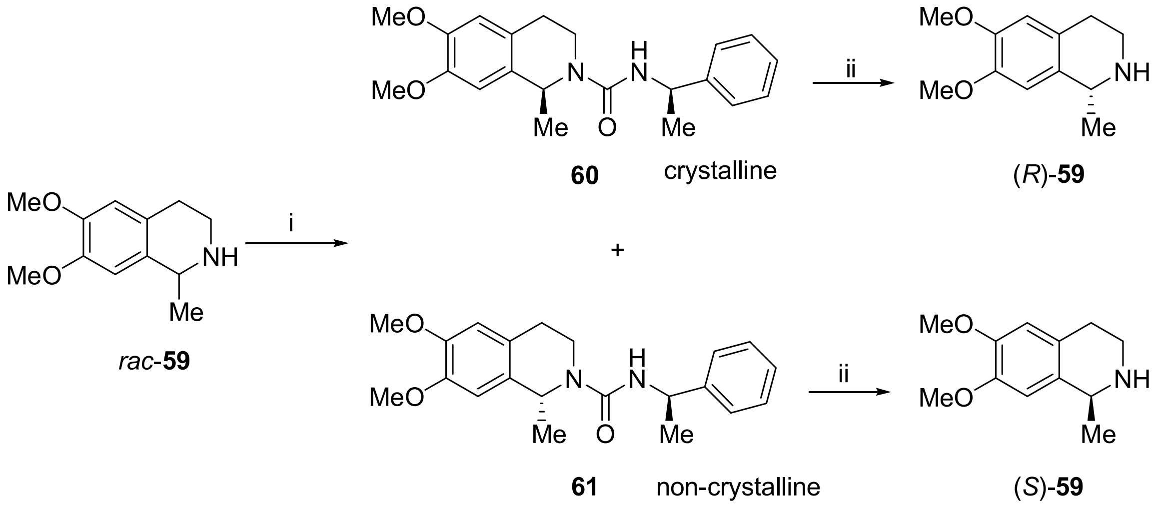
Conditions : i. AcCl, Et_3N, CH_2Cl_2, 25 °C, 12 h
ii. $LiAlH_4$, THF, reflux

Scheme 25

Brossi,[77] and Yamada[78] also reported the synthesis of chiral tetrahydroisoquinolines following similar synthetic sequences.

1.5.2. Preparation of chiral isoquinolines through resolution of racemates

Racemic 1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **59** was resolved successfully by Brossi *et al.* using (*R*)-(+)-α-methylbenzyl isocyanate.[79] After complete separation by recrystallization, the two diastereomers **60** and **61** were alcoholysed in *n*-butanol (*n*-BuOH) in the presence of sodium butoxide (NaOBu) to yield the pure enantiomers (*R*)-**59** and (*S*)-**59** (Scheme 26).

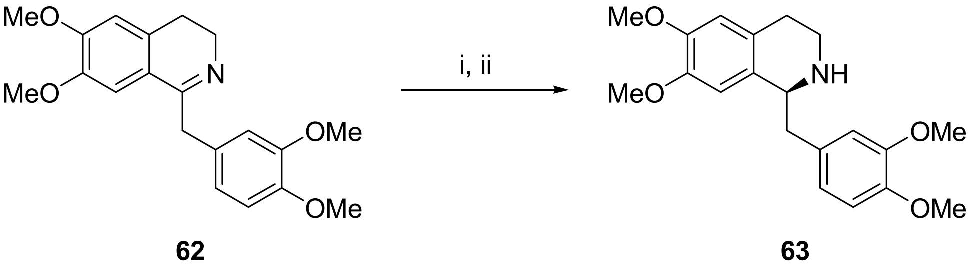


Conditions: i. (*R*)-(+)-α-methylbenzyl isocyanate, CH_2Cl_2, 1 h
ii. NaOBu, *n*-BuOH, reflux

Scheme 26

1.5.3. Preparation of chiral isoquinolines through asymmetric synthesis

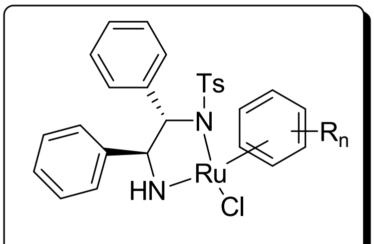
Iwakuma and co-workers reported the asymmetric reduction of prochiral isoquinoline **62** using chiral acyloxyborohydrides with $NaBH_4$. BIQ **63** was produced in moderate 70% ee (Scheme 27).[80]



Conditions: i. (*S*)-*N*-benzyloxycarbonylproline, $NaBH_4$, CH_2Cl_2, -30 °C, 12 h
ii. HCl, 60-70 °C, 0.5 h

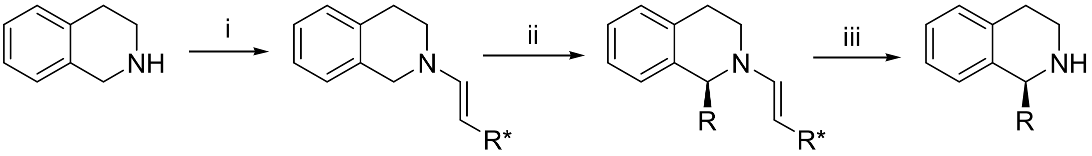
Scheme 27

An efficient ruthenium catalyst **64** was reported by Noyori to provide excellent ees (84-95%) in the asymmetric reduction of a variety of 1-substituted 6,7-dimethoxy-3,4-dihydroisoquinolines.[81]



64

Meyers developed a diastereoselective alkylation route for 1-lithiated tetrahydroisoquinolines having chiral *N*-amidine auxiliary. The isoquinolines were obtained with high ees after cleavage of the chiral auxiliary (Scheme 28).[82-84]



R* = chiral auxiliary

Conditions: i. Et_3OBF_4, R^*NH_2
ii. Lithium diisopropylamide, RX, -78 °C, THF
iii. NH_2NH_2, AcOH

Scheme 28

Besides the examples listed above, there are other feasible routes to obtain enantiopure isoquinolines such as asymmetric hydrogenation of ketimines[85-103] and asymmetric addition of nucleophiles to aldimines.[104-106]

As mentioned earlier, the above protocols can be potentially applied to obtain enantiopure BIQs.

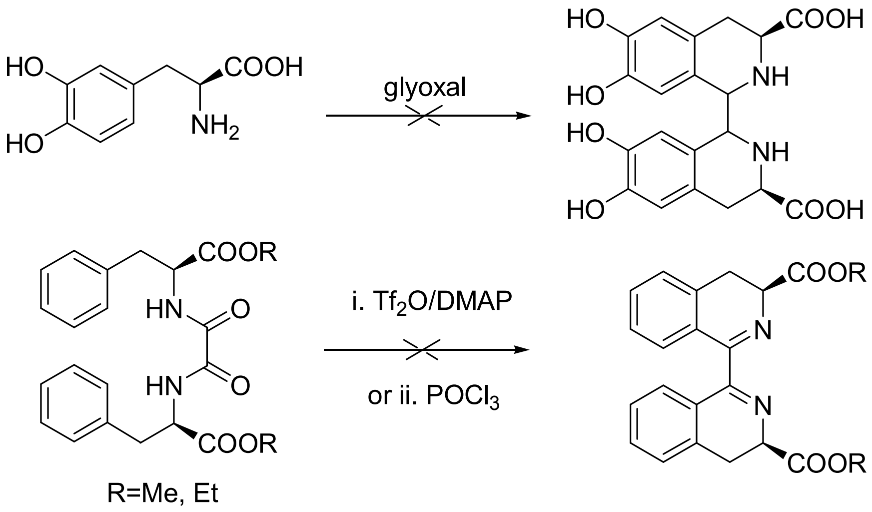
1.6. Objectives

Design, synthesis and utilization of a number of cyclic, structurally novel enantiopure vicinal *N*/*N* containing compounds are desired. We are interested in BIQ-based *N*/*N* ligands since they offer structurally constrained motifs that are similar to the well-used and explored chiral 1,1'-binaphthyls. BIQs are rarely used in asymmetric transformation since their chemistry is still being developed. Consequently, we aim to:

1. Develop the chemistry of novel BIQs.
2. Develop efficient resolution protocols for BIQs.
3. Design various chiral BIQ-based ligands and use them in C-C bond forming reactions.
4. Understand the structural features that control the efficiency/selectivity of these ligands by preparing several ligands having different functional moieties.

Chapter 2. Synthesis and resolution of BIQ ligands

As mentioned in Chapter 1, there are three possible strategies to prepare chiral BIQs. Among those routes, asymmetric synthesis was thought not suitable since the chiral catalysts to be used are normally very expensive and highly substrate-depended, thus making the synthesis of new chiral ligands in large amounts really difficult. Between the other two strategies, resolution route of *racemic* BIQs attracted us more because:1) Unlike the synthesis using the chiral pool where the chirality of products is determined by the starting materials, resolution of racemates could provide both enantiomers. 2) Our initial attempts at the synthesis of chiral BIQs from relatively cheap starting materials such as natural chiral amino acids have been proved unsuccessful (Scheme 29).[65]



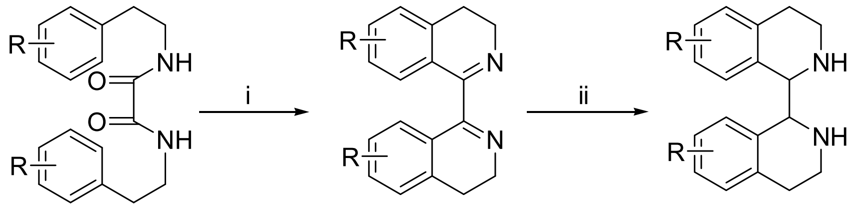
Scheme 29

Therefore, synthesis and resolution of BIQs was adapted as the most suitable route to obtain the required chiral compounds in this project.

2.1. Synthesis of *racemic* BIQs

Out of the many methods used for isoquinoline synthesis, the Bischler-Napieralski[72] and Pictet-Spengler[107-110] approaches are most widely used. The latter reaction gives 1,2,3,4-tetrahydroisoquinolines while the former one provides 3,4-dihydroisoquinolines. Accordingly, double Bischler-Napieralski (Scheme 30) reaction will provide

3,3',4,4'-tetrahydro-1,1'-bisisoquinolines which could be further reduced to give *racemic* BIQs. Because double Bischler-Napieralski reaction normally involves the use of less expensive reagents and does not require strictly controlled reaction conditions, it was employed for the preparation of the desired BIQs. The *racemic* BIQs can then be subjected to chiral resolution to obtain the desired enantiomerically pure BIQs. These could further be modified structurally according to our interest.



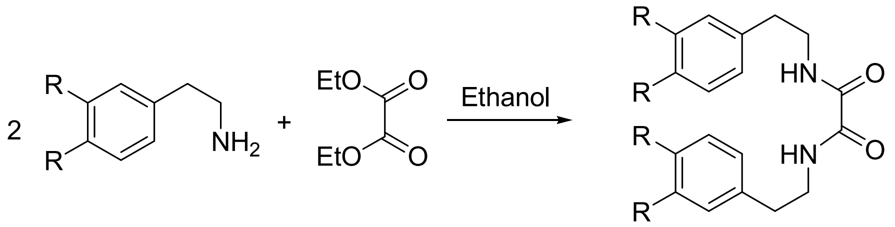
Conditions: i. dehydration; ii. reduction

Scheme 30

To realize this synthesis, bisoxamides were first synthesized as starting materials for double Bischler-Napieralski reaction.

2.1.1. Preparation of bisoxamides

The precursors for double Bischler-Napieralski reaction, namely bisoxamides **65** and **66**, were synthesized successfully as fluffy white solids in quantitative yield by treating diethyl oxalate with the corresponding arylamines in ethanol (Scheme 31). The FTIR, ^{1}H and ^{13}C NMR spectra of the products were identical to those reported in the literature.[65,111]



65: R = H

66: R = MeO

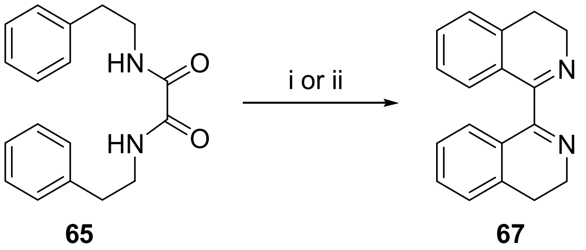
Scheme 31

2.1.2. Cyclisation of bisoxamides 65 and 66

A number of dehydrating reagents have been used to promote Bischler-Napieralski reaction. In this project, classical and widely used reagents namely phosphorus oxychloride ($POCl_3$) or a combination of phosphorus oxychloride and diphosphorus pentoxide (P_2O_5) were employed to cyclise bisoxamides **65** and **66**. For comparison and in order to enhance the yield of the products, polyphosphoric acid (PPA) and trifluoromethanesulfonic anhydride (Tf_2O)/*N,N*-dimethylaminopyridine (DMAP) were also used to cyclise bisoxamide **65** and **66**.

2.1.2.1. Cyclisation of bisoxamide 65

Following the procedures developed by Chan *et al.*,[111] bisoxamide **65** was cyclised using $POCl_3$/P_2O_5 in toluene or Tf_2O/DMAP in CH_2Cl_2 (Scheme 32) to give the expected 3,3',4,4'--tetrahydro-1,1'-bisisoquinoline **67** in 59% and 77% yield, respectively. The FTIR, ^1H and ^{13}C NMR spectra of the product were identical to those reported in the literature.[40,111]

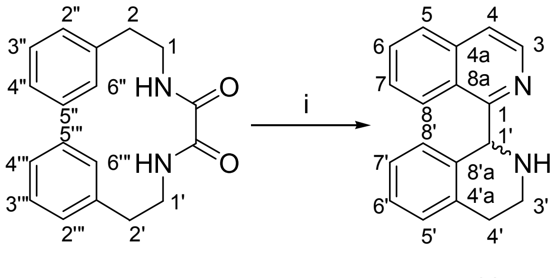


Conditions: i. $POCl_3$, P_2O_5, toluene reflux, 24 h
ii. Tf_2O, DMAP, CH_2Cl_2, 24 h

Scheme 32

Interestingly, when neat PPA was used to cyclise bisoxamide **65** at 190 °C, TLC analysis (EA/MeOH = 8/2) of the reaction mixture, after 12 h, revealed the presence of a new component that has a different R_f value compared to BIQ **67.** After the product was extracted, the off-white solid obtained was purified by recrystallization from EtOH to give needle shape crystals. FTIR of the new compound revealed the disappearance of the bisoxamide carbonyl absorption peak at 1654 cm^{-1} indicating the successful cyclisation. The high resolution mass spectrum (HRMS) of the new product showed a base peak at *m/z* 261.1178 (M+1), indicating a molecular formula of $C_{18}H_{16}N_2$. Interestingly, BIQ **67** has the same base peak value. Unlike BIQ **67**, the ^{1}H and ^{13}C NMR spectra of the new product showed a large number of splitted signals (clearly splitted sixteen proton signals and eighteen carbon signals). Such a splitting pattern could only result from an unsymmetrical structure indicating the loss of C_2-axis symmetry across the C1-C1' bond of BIQ **67**.

Detailed analysis of ^{1}H and ^{13}C NMR spectra were carried out to deduce the structure of the new product. In the ^{1}H NMR, the broad one-proton singlet at δ 2.44 ppm disappeared after proton exchange with D_2O, thus an NH proton could be confirmed. Two one-proton multiplets at δ 2.86-2.96 ppm and δ 3.47-3.57 ppm together with one two-proton mutiplet at δ 3.20-3.34 ppm representing two methylene groups, instead of two triplets in spectra of BIQ **67**, are assigned to the protons at C3' and C4', respectively. Therefore, a tetrahydro-isoquinoline structure could be deduced. In the ^{1}H NMR spectra, characteristic peaks for an isoquinoline moiety can also be seen at δ 7.62 and 8.50 ppm (two mutually coupled doublets with J = 5.7 Hz representing protons at C3 and C4). Considering all the data, the structure of the new product can be deduced to have two different isoquinoline units (compound *rac*-**68** in Scheme **33**).



65 *rac*-**68**

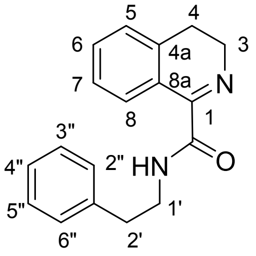
Conditions: i. PPA, 190 °C, 12 h

Scheme 33

To provide further evidence, a series of advanced NMR spectral analysis were performed including DEPT, HMQC, HMBC and COSY. In HMQC, the four protons giving rise to three multiplets at δ 2.86-2.96 ppm, δ 3.47-3.57 ppm and δ 3.20-3.34 ppm showed cross peaks with the two carbons whose nucleus resonated at δ 29.6 and 43.4 ppm respectively, thus confirming the presence of two adjacent methylene groups at C3' and C4'. In addition, an one-proton singlet at δ 6.01 ppm correlation with a carbon signal at δ 61.1 ppm corresponding to the methine group at C1'. Moreover, ten aromatic signals with chemical shift from δ 6.60 ppm to δ 8.50 ppm were assigned with the help of HMBC and COSY experiments. All the conclusions were consistent with the structure of unsymmetrical BIQ *rac*-**68**.

The formation of unexpected product *rac*-**68** in high yield (86%) prompted us to explore the mechanism of its formation. The reaction was traced under a lower temperature (140 ^{o}C) for 26 days and aliquots were taken during the reaction at specified time intervals. The ^{1}H NMR spectra of these aliquots were recorded and then the samples were purified by column chromatography on silica gel (EA/CH_2Cl_2 = 1/9). The structure of each separated compound was confirmed by comparing its spectroscopic data with those of authentic samples. Thus, the composition of reaction mixture at various reaction times could be followed. This provided us with information regarding the reaction progress.

After progressing for 3 h, TLC analysis of a crude sample from the reaction mixture showed three spots. After separation using column chromatography, the fractions with highest and lowest R_f value were confirmed to be compounds **65** and **67,** respectively. The spectroscopic data of the fraction with the moderate R_f value were analysed. In its ^{1}H NMR spectrum, three two-proton triplets at δ 2.65, 2.87 and 3.68 ppm and one two-proton quartet at δ 3.60 ppm indicated two pairs of methylene groups (eight protons at C3, C4, C1' and C2'). A one-proton broad singlet at δ 7.47 ppm indicated an amido NH proton. Moreover, a carbonyl carbon signal at δ 164.4 ppm could be found in its ^{13}C NMR spectrum, further confirmed the presence of the amide group. The above information suggested that bisoxamide **65** was only half cyclised. Thus the structure of this compound was assigned to be partially cyclised compound **69**.



69

The discovery of compound **69** in this reaction mixture revealed that cyclisation of bisoxamide **65** went through stepwise cyclisation: first cyclisation of one of the oxamide groups of **65** gave compound **69**, followed by the second oxamide cyclisation to give BIQ **67**. No BIQ *rac*-**68** was observed at this stage of the reaction.

The ratio of the compounds at different reaction time intervals was calculated based on the integrations values of representative signals arising from each compound in the ^{1}H NMR spectrum of a crude reaction sample. For example, in Figure 2, the triplet at δ 2.65 ppm represented two protons at C4 in compound **69**, while the doublet of triplet at δ 3.50 ppm represented four protons at C1 and C1' in bisoxamide **65** and the triplet at δ 3.94 ppm represented four protons at C3 and C3' in BIQ **67**. Thus, the molar ratio of **65**:**67**:**69** = 0.15:0.35:1.0 observed indicated that 90% of the starting material **65** had already been consumed after reacting for 3 h to form compound **69**, and 26% of **69** had been converted to **67** as well.

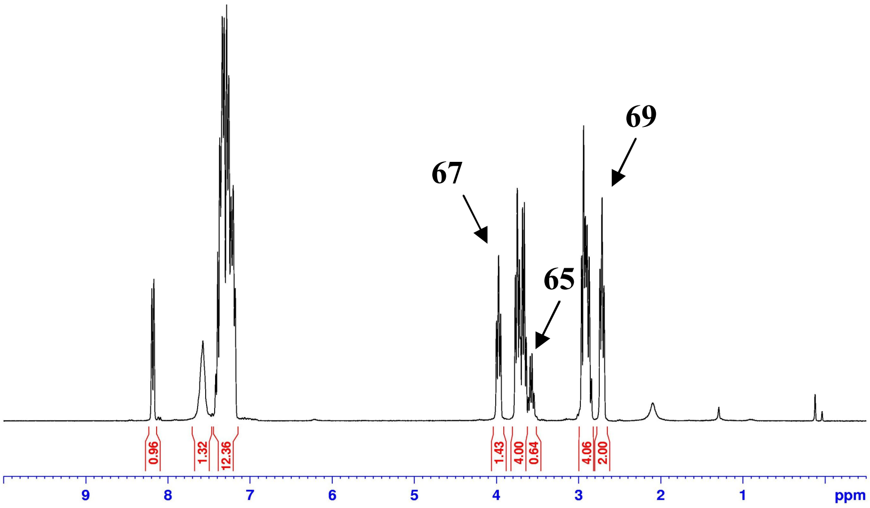
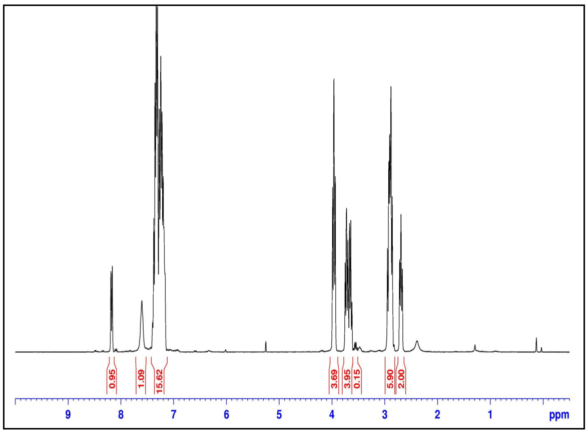
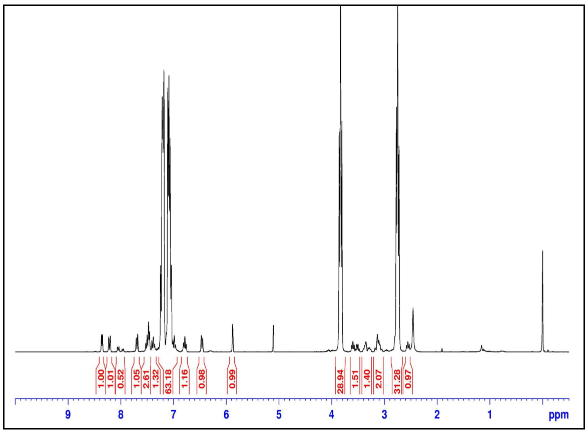


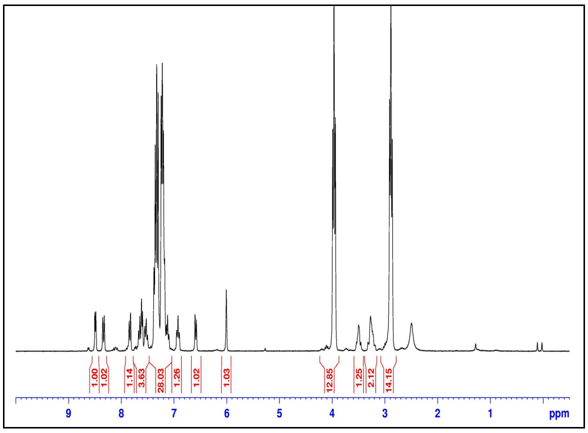
Figure 2

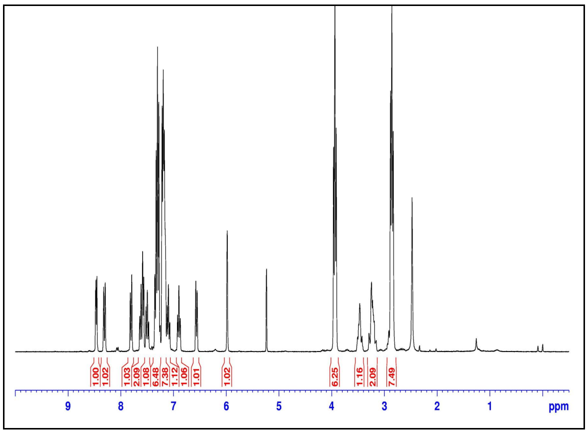
The aliquots taken at 7.5, 28.5 h and 2, 3, 5, 11, 16, 26 d were analysed in the same manner as described for the first sample above. The ^{1}H NMR spectra of the crude products (Figure 3) showed that all bisoxamide **65** was consumed within 7.5 h and compound **69** was converted completely to BIQ **67** within 28.5 h. It was also noticed that BIQ *rac*-**68** appeared in the sample taken at 28.5 h. Therefore, the formation of BIQ **68** actually started after complete conversion of the compound **69** to BIQ **67**. The aliquots taken at time intervals 2 to 26 d showed a trend of decreasing in BIQ **67** with a corresponding increase in BIQ *rac*-**68** (^{1}H NMR integration). These results indicated a very slow conversion of **67** to *rac*-**68**.



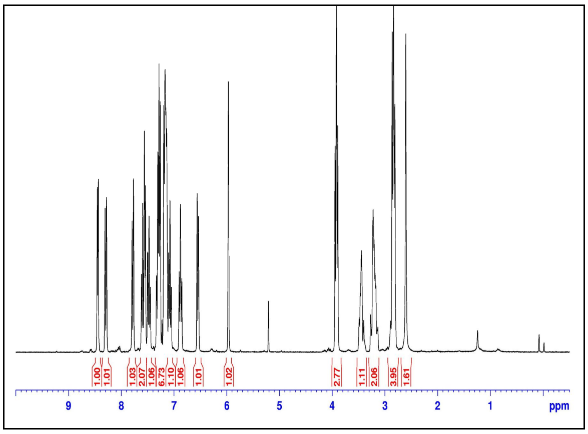


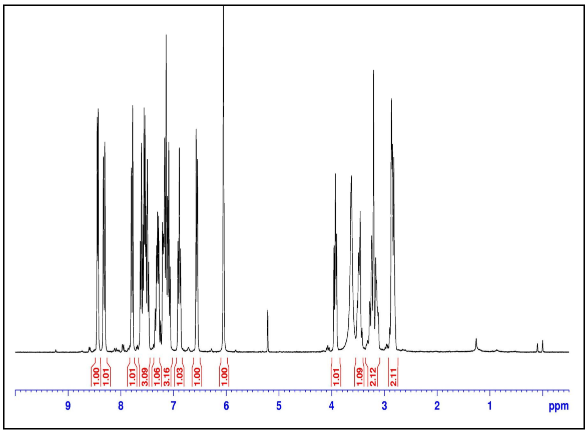
140 °C 7.5 h **140 °C 28.5 h**



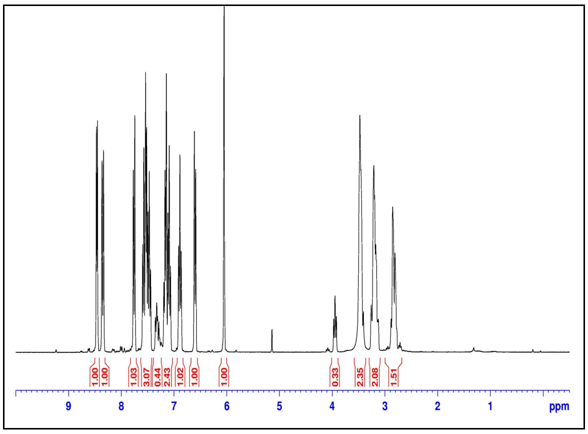


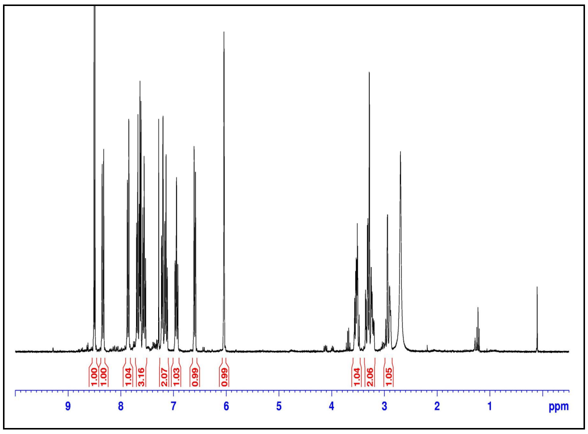
140 ^{o}C 2 d **140 ^{o}C 3 d**





140 ^{o}C 5 d **140 ^{o}C 11 d**

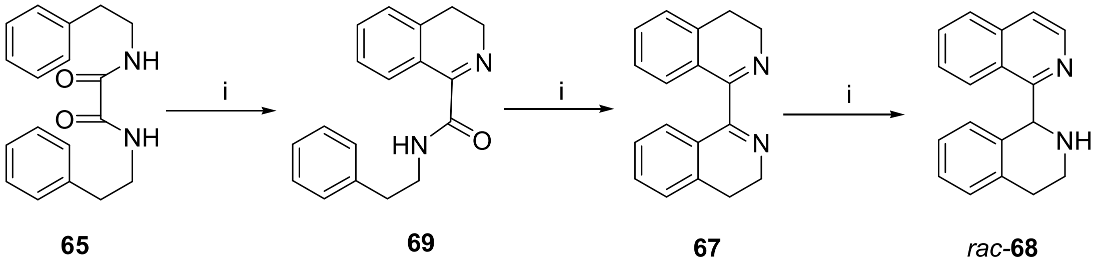




140 ^{o}C 16 d **140 ^{o}C 26 d**

Figure 3

Combining all the information together, the whole process of PPA mediated cyclisation of bisoxamide **65** can be shown as Scheme 34. Initially, bisoxamide **65** undergoes a two-step cyclisation sequence to form BIQ **67**. After complete conversion of **65** (through **69**) to **67**, BIQ **67** undergoes a disproportionation reaction to give BIQ *rac*-**68** as the final reaction product.

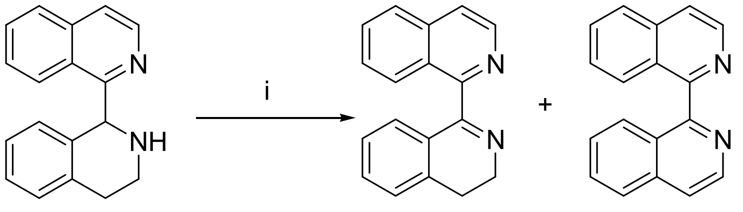


Reagents: i. neat PPA

Scheme 34

The reaction was repeated several times, often on large scale (> 30 g), and was found to be highly reproducible, providing unsymmetrical BIQ *rac*-**68** in high Yield (>80%). BIQ *rac*-**68** was proved to be air stable in solid form. Nevertheless, it could be easily aromatized in a warm alcohol solution under basic conditions. Therefore, when *rac*-**68** was allowed to stir in an EtOH solution with NaOBu at 60 ^{o}C overnight, TLC analysis revealed the presence of two new compounds besides *rac*-**68**. The components were separated by column chromatography and then analysed by various spectroscopic methods.

The ESI mass spectrum of the new compound with the lower R_f value showed a molecular ion peak at *m/z* 259.40 (M+1), indicating a formula of $C_{18}H_{14}N_2$ which was two hydrogen less than that of BIQ *rac*-**68**. The NMR spectra of this compound showed similar unsymmetrical structural features as BIQ *rac*-**68**. Comparing its ^{1}H and ^{13}C NMR spectra with those of BIQ *rac*-**68**, the disappearance of one-proton singlet at δ 6.01 ppm and corresponding carbon signal at δ 61.1 ppm revealed the loss of methine group. Moreover, this new compound showed sixteen aromatic carbons, one more than that of BIQ *rac*-**68**. Therefore, it was assigned the partially oxidised structure BIQ **70** (Scheme 35).



rac-**68** **70** **71**

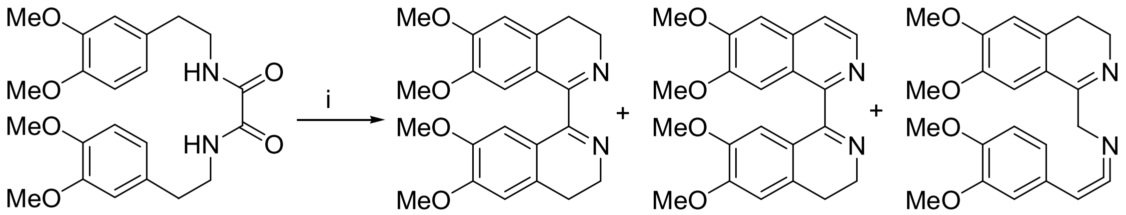
Conditions: i. NaOBu, EtOH, 60 °C, overnight

Scheme 35

Assignment of the structure to the compound with the higher R_f value was accomplished easily. Its ESI mass spectrum showed a molecular ion at 257.47 (M+1), indicating a formula of $C_{18}H_{12}N_2$, two hydrogen less than BIQ **70** and four hydrogen less than BIQ *rac*-**68**. The simple ^1H and ^{13}C NMR spectra of this compound indicated a symmetrical structure. In addition, all proton and carbon signals appeared in the aromatic region indicating a fully aromatic structure. Therefore, it was assigned the fully oxidised structure BIQ **71** (Scheme 35).

2.1.2.2. Cyclisation of bisoxamide 66

Bisoxamide **66** was cyclised in the presence of Tf_2O/ DMAP in CH_2Cl_2[65] to provide the expected BIQ **72** in 72% yield. The FTIR, ^1H and ^{13}C NMR spectra of the product were identical to those reported in the literature.[50,65] When bisoxamide **66** was cyclised using $POCl_3$ in toluene, a black gum was obtained after refluxing for 5 h (Scheme 36). TLC analysis showed the presence of two new spots in addition to a spot corresponding to BIQ **72**. The components were separated by column chromatography and then identified using mass spectroscopy, FTIR, ^1H, ^{13}C NMR and 2-D NMR experiments (HMQC, HMBC and COSY).



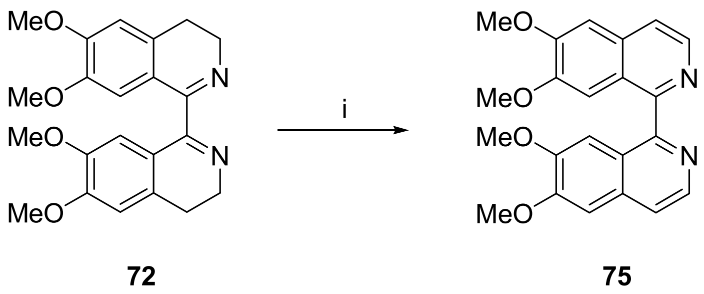
66 **72** **73** **74**

Conditions: i. $POCl_3$, toluene, reflux

Scheme 36

The compound that had R_f value just above that of BIQ **72** was assigned the partially oxidised structure **73**. Its ^{1}H and ^{13}C NMR spectra resembled those of compound **70**. The compound that had the highest R_f value was assigned structure **74**. It is reasonable that the reaction under high temperature underwent aerial oxidation of product BIQ **72** to give BIQ **73**, but the mechanism for the formation of compound **74** was not clear. However, no attempts were made to study the reaction progress in detail. BIQ **73** is a potential precursor for substituted pseudo-symmetric tetrahydro-bisisoquinoline such like BIQ *rac*-**68**. Therefore, the optimum reaction conditions for its formation were sought. After few experiments, reaction time was found to be decisive for enhancing the yield of compound **73**. When the reaction time was prolonged from 6 h to 24 h, a dramatic increase in the yield of compound **73** from 6% to 39% was observed. Thus, a simple route by which large quantities of BIQ **73** were prepared without any difficulty was established.

Under the above conditions, although partially aromatic BIQ **73** could be obtained with moderate yield, no sign of the fully aromatic BIQ **75** was detected. Instead, BIQ **75** was synthesized *via* a typical oxidation route where a toluene solution of BIQ **72** was heated at reflux in air, in the presence of palladium on charcoal (Pd/C) to give BIQ **75** in 65% yield (Scheme 37). The assignment of structure **75** was also done by analysing its spectroscopic data and in comparison to those of BIQ **71**.



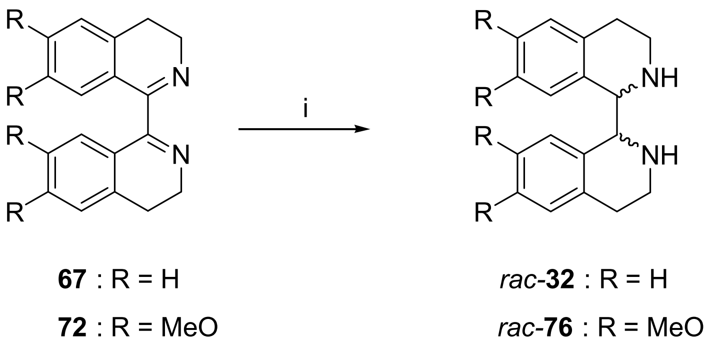
Conditions: i. Pd/C, toluene, reflux, 3 d

Scheme 37

2.1.3. Reduction of BIQs 67, 72 and 73

With bis-dihydroisoquinoline **67**, **72** and unsymmetrical dihydrobisisoquinoline **73** in hand, we turned our attention to conversion of these compounds to their reduced counterparts.

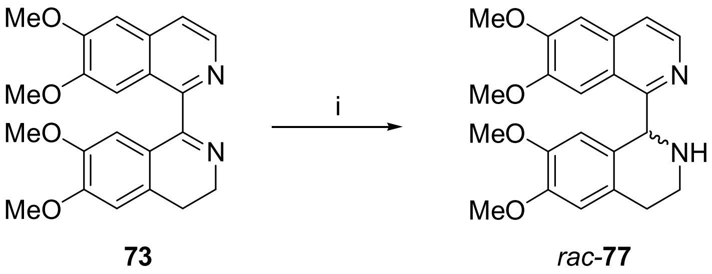
Dreiding *et al.*[50] reported the stereoselective reduction of BIQ **72** using sodium cyanoborohydride in acidic methanol to give exclusively the *racemic* isomer **76**. This method was applied successfully to the reduction of various other bis-dihydroisoquinolines by Judeh[65] and Chan[111], and was adapted in this project. Following the procedures described in the literature,[50,65,111] BIQ *rac*-**32** and *rac*-**76** were prepared successfully in 89% and 73% yield, respectively (Scheme 38). The FTIR, ^{1}H and ^{13}C NMR spectra of the products were all identical to those reported in the literature.[65,111]



Conditions: i. $NaCNBH_3$, MeOH, HCl

Scheme 38

Reduction of BIQ **73** was relatively simple because, potentially, only one chiral centre could be formed. Therefore, treating compound **73** with sodium borohydride ($NaBH_4$) in MeOH furnished the expected product *rac*-**77** in 91% yield (Scheme 39). The HRMS of the product showed molecular ion at *m/z* of 381.1392 (M+1) confirming the molecular formula $C_{22}H_{24}N_2O_4$. A large number of signals were observed in the NMR spectra revealing the unsymmetrical nature of this structure. In addition, its ^1H NMR spectrum showed a broad singlet at δ 2.10 ppm indicating the presence of a NH proton. Two one-proton multiplets at δ 2.10, 3.43-3.52 ppm and one two-proton multiplet at δ 3.13-3.29 ppm corresponding to the methylene protons at C3' and C4' were also observed. Four three-proton singlets were observed at δ 3.46, 3.81, 3.87 and 4.02 ppm corresponded to the four methoxy groups. A singlet at δ 5.79 ppm corresponded to the methine proton at C1' indicating successful reduction of the imine bond. In the aromatic region of the ^1H NMR spectrum, four one-proton singlets at δ 6.13, 6.69, 7.06 and 7.59 ppm corresponded to the aromatic protons in benzene ring, and two mutually coupled doublets (J = 5.7 Hz) at δ 7.48 and 8.37 ppm corresponded to the aromatic protons in the heterocyclic ring. Moreover, the ^{13}C NMR spectrum showed seven signals in the aliphatic region and fifteen signals in the aromatic region which were consistent with the number of carbons in structure *rac*-**77**. Hence the newly generated product was assigned structure *rac*-**77**.



Conditions: i. $NaBH_4$, MeOH

Scheme 39

In summary, two octahydro-bisisoquinoline *rac*-**32** and *rac*-**76**, and two unsymmetrical tetrahydro-bisisoquinoline *rac*-**68** and *rac*-**77** have been synthesized successfully utilizing Bischler-Napieralski reaction.

2.2. Resolutions of *racemic* BIQs

As mentioned in Chapter 1 section 1.6, one of the goals of this project is to find a feasible route to obtain tetrahydro-bisisoquinolines and octahydro-bisisoquinolines in enantiomerically pure form. Hence, various methods were investigated to resolve BIQs *rac*--**32**, *rac*-**76**, *rac*-**68** and *rac*-**77**.

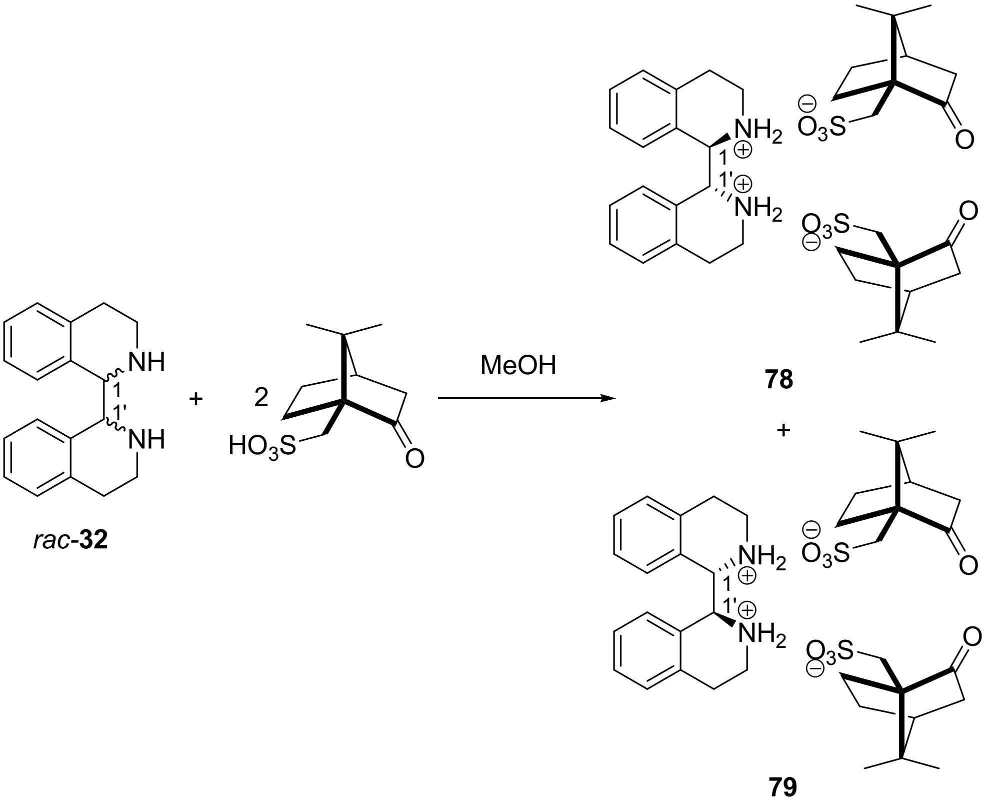
Diastereomeric salt formation using chiral acids is an attractive approach to resolve *racemic* amines (Chapter 1 section 1.4.2.2 and 1.4.2.3). Therefore, chiral camphorsulfonic acid and other naturally occurring chiral carboxylic acids such as malic acid, lactic acid and tartaric acid had been used extensively for this purpose. Another method involved the formation of diastereomeric derivatives by condensing *racemic* amines with chiral aldehydes, ketones, carboxylic acids and derivatives. The initial works reported by Brossi,[112] Kametani,[113,114] Yamada,[115,116] Meyers[117-119], Gawley[120] and Comins[121] had opened a wide range of routes to obtain enantiomerically pure tetrahydro-isoquinolines and their derivatives using the formation of diastereomeric derivatives method.

2.2.1. Resolution by formation of diastereomeric salts

D-(+)-camphor-10-sulfonic acid (*D*-CSA) and *D*-(+)-α-bromocamphor-π-sulfonic acid (*D*-BCSA) had been used to resolve BIQ *rac*-**32**.[40,59] Therefore**,** these two chiral acids were believed to be suitable resolving agents for other BIQs such as *rac*-**76**, *rac*-**68** and *rac*-**77,** having similar structural features to *rac*-**32**.

2.2.1.1. Resolution of BIQ *rac*-32

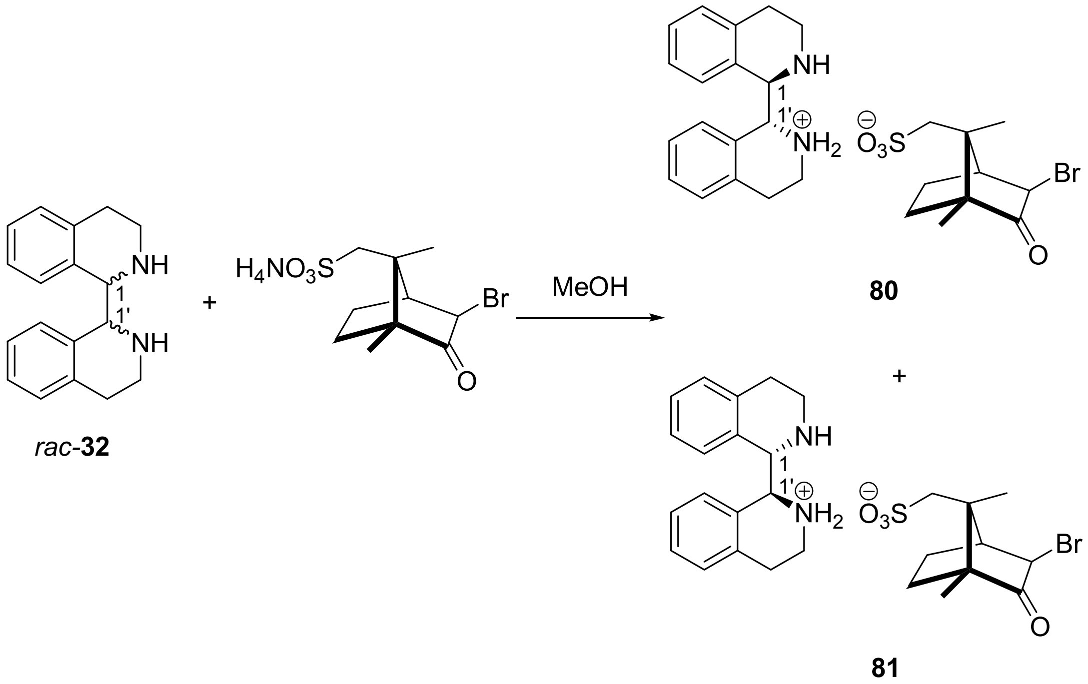
The procedure of Arai[40] was followed to resolve BIQ *rac*-**32** with *D*-CSA (Scheme 40). The diastereomeric salt mixture was prepared in MeOH and its ^{1}H NMR spectrum showed the expected pattern. The singlets at δ 5.42 and 5.49 ppm represented the methine protons (protons at C1 and C1') of diastereomeric salts **78** and **79**, respectively. Other spectral features were similar to those reported in the literature.[40] Although a yield of 29% was reported[40], repetitive recrystallization of the diastereomeric salts mixture **78** and **79** under reported conditions gave no successful separation. Attempts at recrystallization from other solvents failed to give any crystals.



Scheme 40

As the attempt at resolution of BIQ *rac*-**32** failed using Arai's procedure, we then switched to the procedure reported by Elliott[59]. BIQ *rac*-**32** was treated with equimolar *D*-BCSA in MeOH (Scheme 41). The ^{1}H NMR spectrum of the resulting diastereomeric salt mixture **80** and **81** showed only one set of signals. The signal representing the methine proton at C1 and

C1' of diastereomeric salts **80** and **81** showed only one singlet at δ 4.86 ppm which was identical with the reported data[59]. Recrystallization of the mixture **80** and **81** from EtOH gave off-white needle crystals. After liberation of BIQ **32** from the crystals using NaOH solution, an ee of 98% was achieved (HPLC analysis, Figure 4) and the configuration of the major enantiomer was confirmed to be (*S*,*S*) by comparing the sign of optical rotation value with literature[59]. Accordingly, the crystals were confirmed to be salt **81**.



Scheme 41

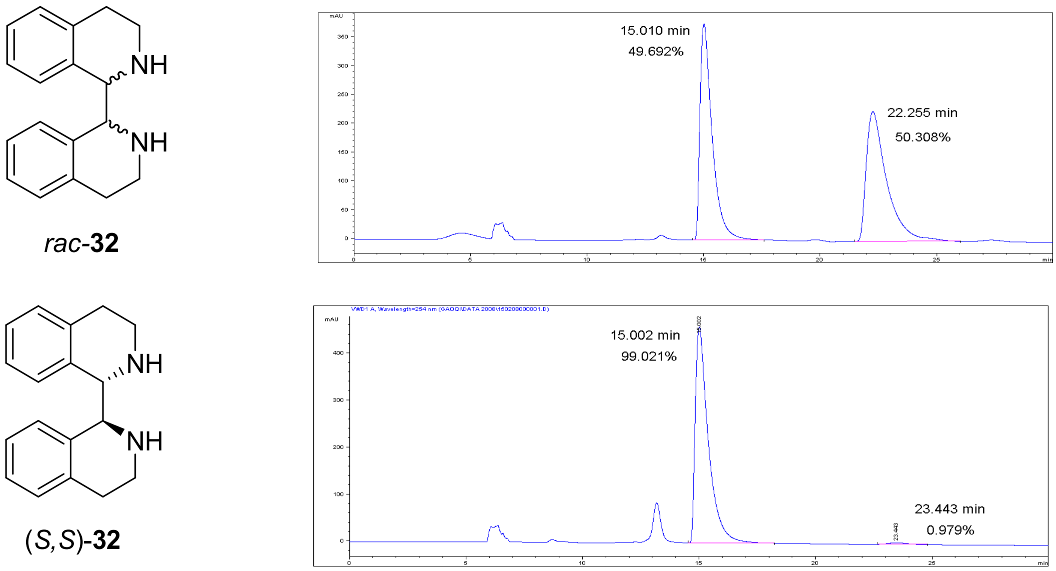


Figure 4

The purity of the BIQ (*S*,*S*)-**32** obtained from the crystals was also confirmed by formation of *D*-CSA salt followed by ^{1}H NMR analysis (Figure 5 (b)). An ee of >95% was confirmed by comparing the integrations of singlets at δ 5.42 and 5.49 ppm.

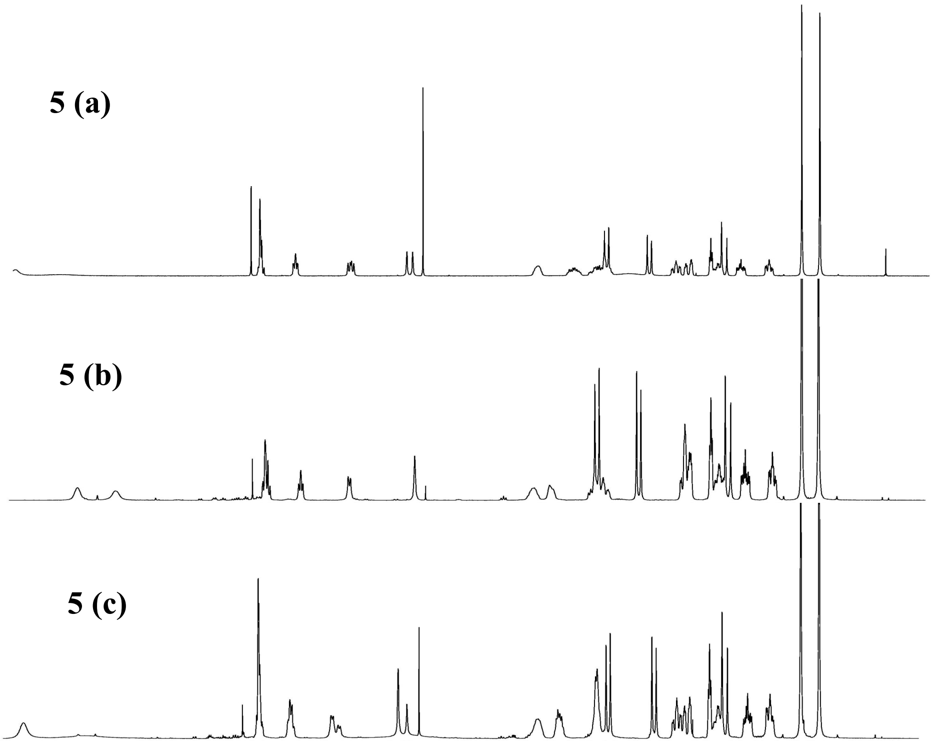
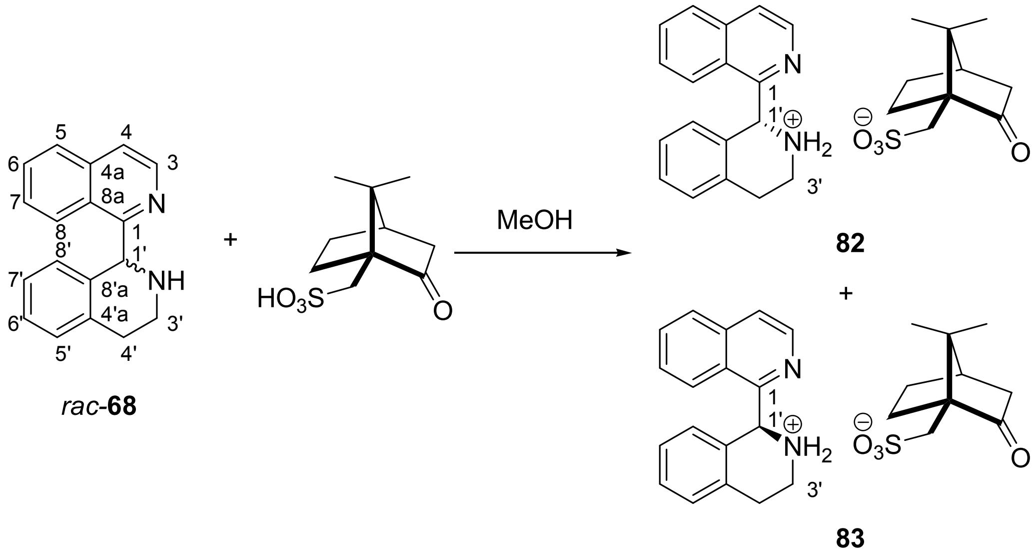


Figure 5 *D*-CSA salt of (a) BIQ *rac*-32 (b) BIQ 32 from crystal (c) BIQ 32 from mother liquor

The mother liquor was evaporated till dryness under vacuum. The ee of the resulting off-white powder was checked using *D*-CSA (Figure 5 (c)) in the same way as performed in the case of the crystals. Although only 30% ee of the (*R*,*R*)-enantiomer of BIQ **32** was achieved from the residue, no attempts were made to get it in purer form. Therefore, only BIQ (*S*,*S*)-**32** was prepared and used as a ligand in this project.

2.2.1.2. Attempts at resolution of BIQ *rac*-68

BIQ *rac*-**68** was treated with equimolar *D*-CSA in MeOH to give a mixture of diastereomeric salts **82** and **83** as an off-white powder in quantitative yield (Scheme 42). Comparing the ^{1}H NMR spectrum of this mixture with that of BIQ *rac*-**68**, the most striking difference was that the singlet at δ 6.01 ppm, representing the methine proton (proton at C1') of BIQ *rac*-**68**, splitted into two singlets and shifted to δ 6.84 and 6.86 ppm indicating the formation of the expected diastereomeric salts **82** and **83**. Moreover, the broad singlet at δ 2.44 ppm representing the proton on the nitrogen of BIQ *rac*-**68** disappeared. The signals of proton at C3' shifted to the downfield while the signals of proton at C4' and the signals of aromatic protons only changed slightly. As the distinction between the two diastereomeric salts was observed in ^1H NMR spectrum, it could be used as a simple method to check the ee of enantiomerically pure BIQ **68**. To try to separate diastereomeric salts **82** and **83**, their mixture was recrystallized from various solvents such as MeOH, EtOH and IPA. Colourless needle-shape crystals were obtained in all cases. However, the ^1H NMR spectrum of the crystals obtained revealed a 1:1 mixture of salts **82** and **83** through the integration of signals at δ 6.84 and 6.86 ppm. After liberation of BIQ **68** from the salt by treating the crystals with NaOH solution, HPLC analysis of the sample confirmed its *racemic* nature.

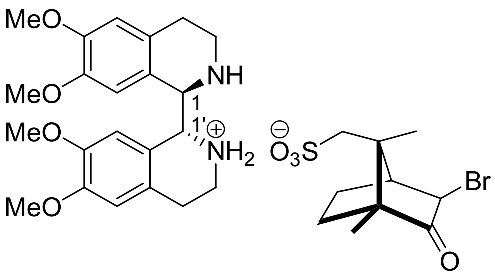


Scheme 42

Another diastereomeric salt mixture was synthesized by reacting BIQ *rac*-**68** with *D*-(+)-α-bromocamphor-π-sulfonic acid ammonia salt in MeOH. All attempts to recrystallize one of the diastereomeric salts from MeOH, EtOH, IPA, CH_3CN, THF or EA were unsuccessful. Hence, both chiral acids *D*-CSA and *D*-BCSA were not suitable for resolution of BIQ *rac*-**68**.

2.2.1.3. Attempts at resolution of BIQs *rac*-76 and *rac*-77

Resolution of BIQs *rac*-**76** and *rac*-**77** by formation of diastereomeric salt again met with difficulties. BIQ *rac*-**76**·*D*-CSA, BIQ *rac*-**77**·*D*-CSA and BIQ *rac*-**77**·*D*-BCSA salt mixtures all failed to give crystals from various solvents examined. BIQ *rac*-**76**·*D*-BCSA salt mixture (**84** and **85**) was found to yield needle like crystals when recrystallized from EtOH or IPA. Disappointedly, the crystals obtained from EtOH were confirmed to be BIQ *rac*-**76** while the crystals obtained from IPA were confirmed to be a 1:1 mixture of **84** and **85** by checking ^{1}H NMR (The ^{1}H NMR spectrum of the mixture of **84** and **85** showed two methine proton singlets at δ 4.71 and 4.73 ppm).



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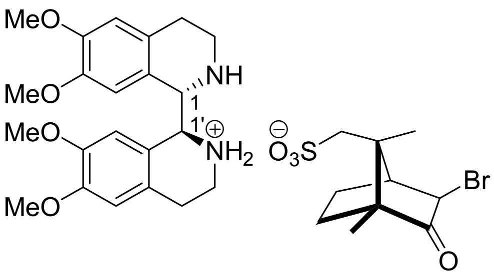


85

In summary, besides BIQ *rac*-**32** which was resolved successfully using *D*-BCSA, BIQs *rac*-**68**, *rac*-**76** and *rac*-**77** all showed resistance to resolution through diastereomeric salts formation with *D*-CSA and *D*-BCSA.

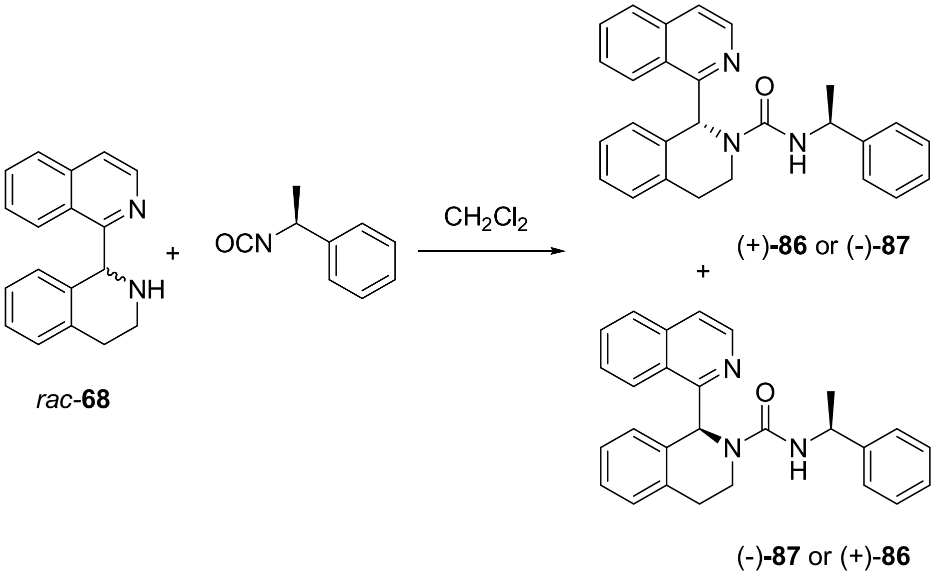
2.2.2. Resolution by formation of diastereomeric derivatives

Due to the limited success achieved by using *D*-CSA and *D*-BCSA as resolving agents, the method involving formation of covalent bond derivatives was investigated.

Brossi *et al.*[79] used chiral α-methylbenzyl isocyanate to resolve *racemic* isoquinolines successfully. Although preliminary studies by our group revealed this method to be unsuitable for resolving BIQ *rac*-**76**,[65] it was still adapted to resolve BIQs *rac*-**68** and *rac*-**77**.

2.2.2.1. Preparation and separation of diastereomeric urea derivatives of *rac*-68

BIQ *rac*-**68** was treated with stoichiometric amount of (*S*)-(-)-α-methylbenzyl isocyanate in CH_2Cl_2 to give the diastereomeric urea mixture (+)-**86** and (-)-**87** in quantitative yield (Scheme 43).



Scheme 43

The ^{1}H NMR spectrum of this mixture showed the expected two set of signals corresponding to the two diastereomers (+)-**86** and (-)-**87**. Due to the unsymmetrical nature of (+)-**86** and (-)-**87**, a large number of overlapped signals appeared in the ^{1}H NMR spectrum. This made the discrimination of the signals very difficult. However, two well resolved broad doublets, integrated for one proton each, were observed at δ 6.30 ppm and δ 6.39 ppm and were assigned to the NH proton of (-)-**87** and (+)-**86**, respectively. Moreover, two three-proton doublets were found at δ 1.36 ppm and δ 1.45 ppm corresponding to the methyl groups in (+)-**86** and (-)-**87,** respectively (Figure 6). Therefore, the ratio of (+)-**86** and (-)-**87** can be calculated from the integration of signals at δ 1.36 and 1.45 ppm as well as the integration of signals at δ 6.30 and 6.39 ppm.

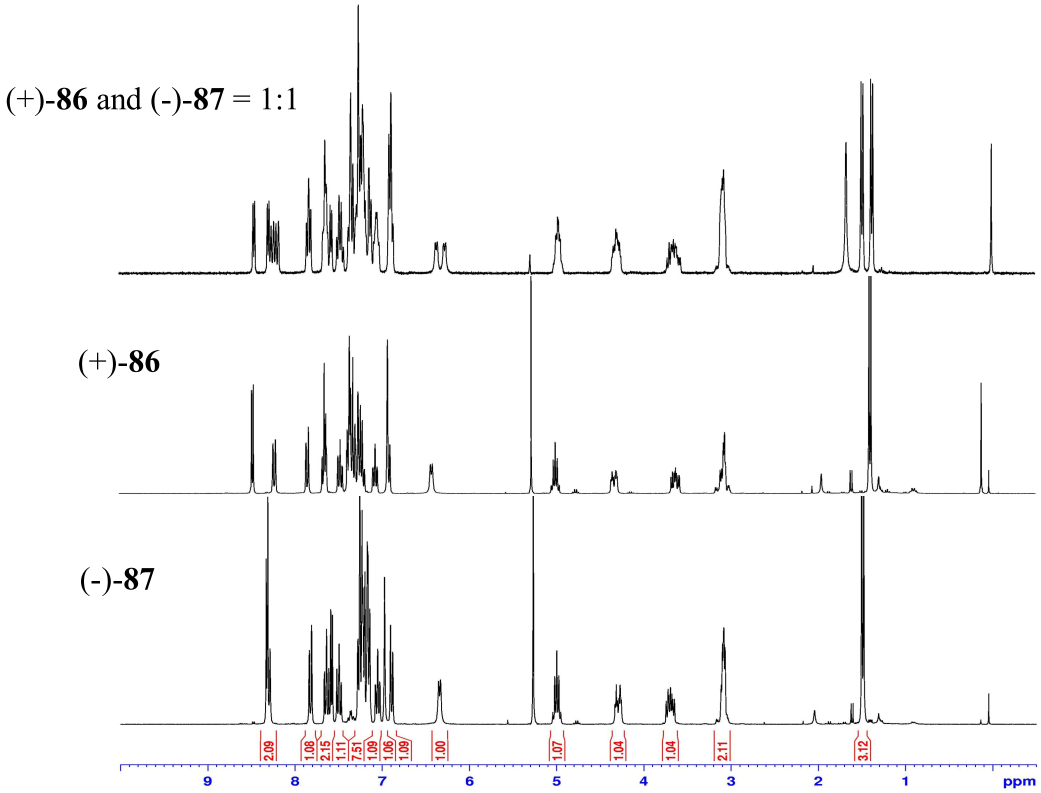


Figure 6 ^{1}H NMR of ureas (+)-86, (-)-87 and 1:1 mixture of (+)-86 and (-)-87

To separate diastereomeric ureas (+)-**86** and (-)-**87**, recrystallization of the mixture was firstly attempted in various solvents such as EtOH, IPA and EA. Disappointedly, the crystals obtained from all the solvents were found to be a mixture with a 1:1 ratio of (+)-**86** and (-)-**87**. Thus, we tried separation using column chromatography. Although TLC analysis showed elongated spot instead of two clear ones, we decided to pass a mixture of (+)-**86** and (-)-**87** through a silica gel column. Gratifyingly, the ratio between (+)-**86** and (-)-**87** was disturbed after passing through the column as indicated from the fractions collected. After screening several solvent systems, the combination of EA and CH_2Cl_2 (gradient from 1:4 to 1:1) was found to be most suitable. Despite the fact that the pure diastereomers were accessible by repetitive column chromatography, other routes of separation were sought to avoid that tedious procedure. During this course, an interesting property of diastereomers (+)-**86** and (-)-**87** was discovered. When an enriched mixture of (+)-**86** and (-)-**87** was allowed to recrystallize from EA/hexane, the crystals formed were found to contain the two diastereomers (+)-**86** and (-)-**87** in a ratio of 1:1 while the mother liquor contained a highly enriched mixture with the diastereomer that was in excess in the original sample. By repeating the recrystallization several times, the diastereomer in excess could be obtained in enantiopure form. It was thought that the conformation of the diastereomers might bring some influences on how the molecules pack in the crystal unit, making urea derivatives (+)-**86** and (-)-**87** prone to crystallize together in 1:1 ratio. As a consequence, the separation process was simplified as shown in Figure 7. Both diastereomers could be obtained in enantiopure form through one time column chromatography followed by several times of recrystallization.

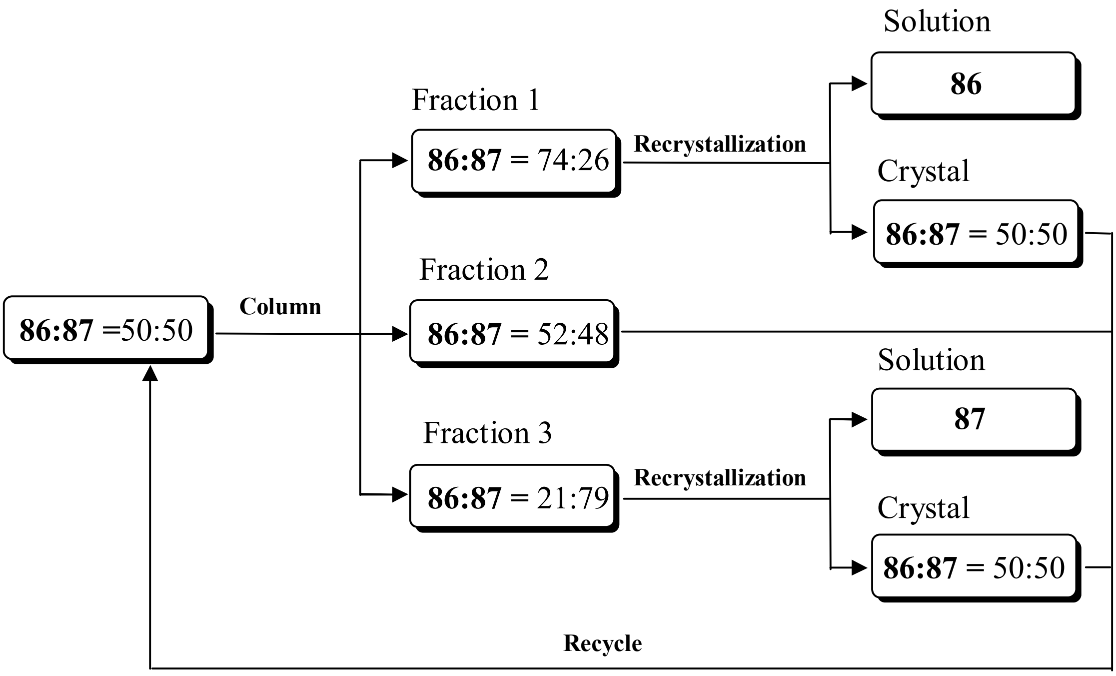


Figure 7

A large amount (> 20 g) of diastereomeric ureas (+)-**86** and (-)-**87** were separated *via* this route without any complication. The diastereomeric excesses (des) were examined and confirmed by ^{1}H NMR (Figure 6) and HPLC analysis (Figure 8). Complete separation has been achieved where des of > 95% were obtained for both diastereomers.

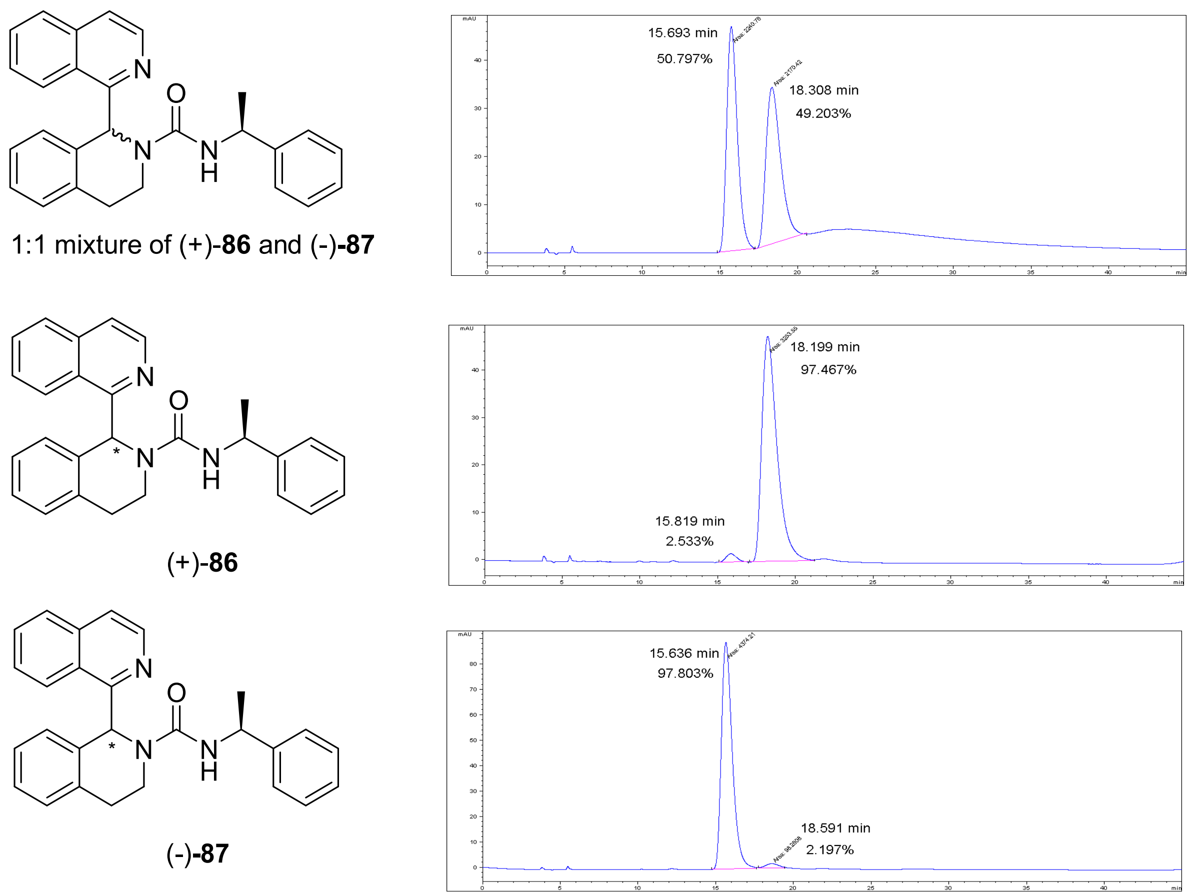
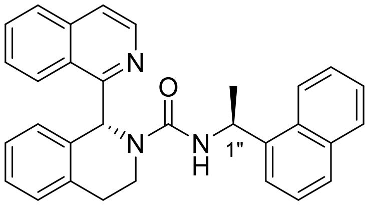


Figure 8 HPLC results of ureas (+)-86, (-)-87 and 1:1 mixture of (+)-86 and (-)-87

The unusual crystalline property of (+)-**86** and (-)-**87** in EA/hexane prompted us to carry out a thorough investigation using similar resolving agents. For this purpose, two new diastereomeric mixtures were prepared by treating BIQ *rac*-**68** with (*S*)-(-)-1-naphthylethyl isocyanate and (*S*)-(-)-α-methylbenzyl isothiocyanate. The expected diasteromeric ureas (+)-**88** and (-)-**89** as well as (+)-**90** and (-)-**91** were obtained in quantitative yields.



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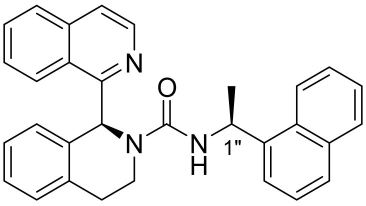

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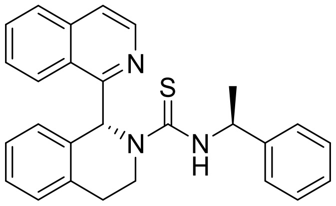

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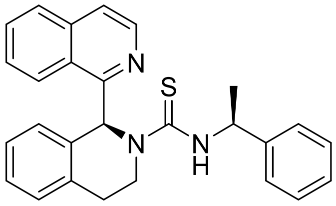

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The reason for preparing mixture of (+)-**88** and (-)-**89** was to understand whether the bulkiness of substituents (e.g. Ph in **86**/**87** *vs* naphthyl in **88**/**89**) could affect the crystallization behaviour of related diastereomeric salt mixtures of BIQ *rac*-**68**.

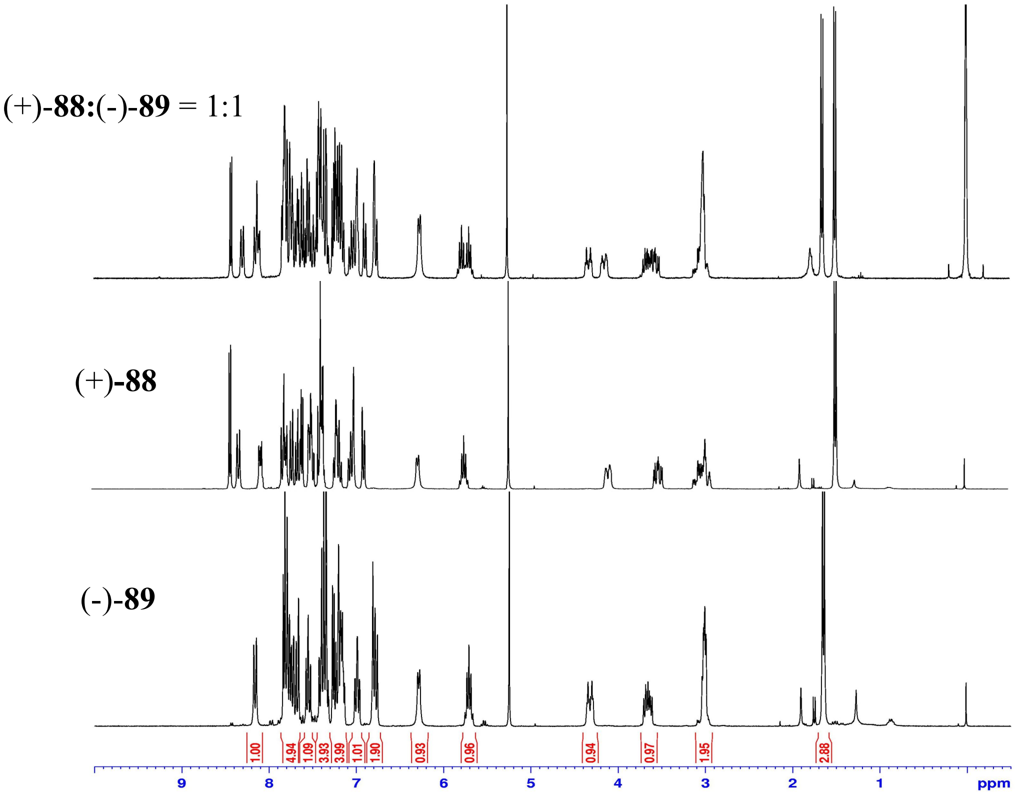


Figure 9 ^{1}H NMR of ureas (+)-88, (-)-89 and 1:1 mixture of (+)-88 and (-)-89

The ^{1}H NMR spectrum of mixture (+)-**88** and (-)-**89** showed clearly two set of signals. Unlike mixture (+)-**86** and (-)-**87**, the broad doublets assigned to the NH protons of (+)-**88** and (-)-**89** did not separate well, while the methyl doublets splitted clearly and were found at δ 1.48 and 1.65 ppm. Remarkably, well separated signals of proton at C1" of (-)-**89** and (+)-**88** were observed at δ 5.71 and 5.74 ppm, respectively (Figure 9).

When a diastereomeric mixture of (+)-**88** and (-)-**89** (ratio = 1:1) was subjected to recystallization from various solvents (MeOH, EtOH, IPA, CH_3CN, THF, EA, $CHCl_3$ or combination of these solvents), no separation of the diastereomers could be achieved. However, when a sample of (+)-**88** and (-)-**89** (ratio = 1:1) was passed through column chromatography, the fractions collected were found to be enriched with either of the diastereomers (+)-**88** and (-)-**89**. Therefore, several fractions with different ratio of (+)-**88** and (-)-**89** were obtained. Further recrystallization of these fractions from EA/hexane and analysis of the crystals and the mother liquor indicated almost negligible change in the ratio of (+)-**88** and (-)-**89**. From this result, we can conclude that the bulkiness of the substituent has a major role in the way the diastereomers crystallize. Therefore, compounds (+)-**88** and (-)-**89** could not be separated using the route described in Figure 7. However, complete separation of (+)-**88** and (-)-**89** was achieved by repetitive column chromatography. The des of > 95% were obtained for both diastereomers as depicted by ^{1}H NMR analysis (Figure 9) as well as chiral HPLC analysis (Figure 10).

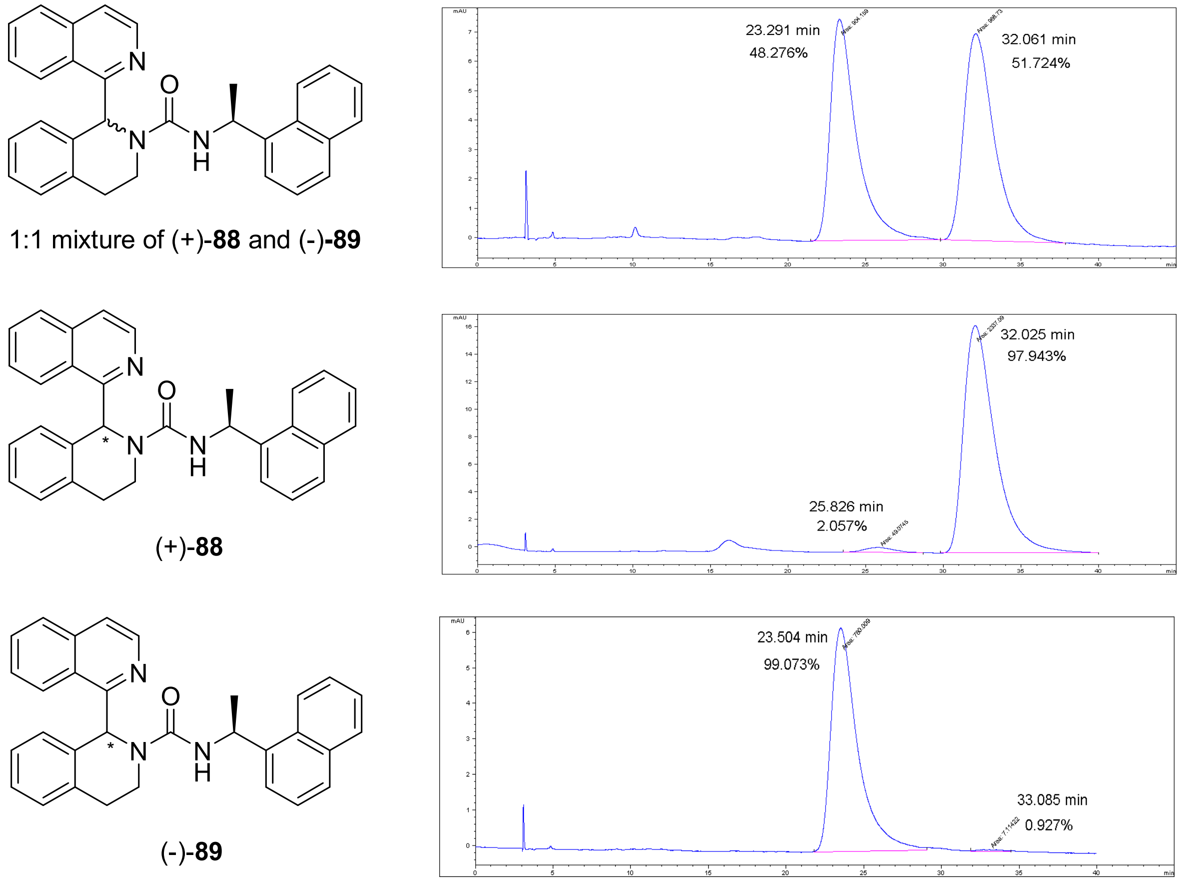


Figure 10 HPLC results of ureas (+)-88, (-)-89 and 1:1 mixture of (+)-88 and (-)-89

The electronegativity was also considered probable factor that might affect the crystalline property of diastereomeric mixture. To examine this idea, a mixture of thiourea derivatives (+)-**90** and (-)-**91** was prepared. Again the ^{1}H NMR spectrum of the mixture showed two set of signals. Clearly separated signals were found at δ 1.53 and 1.66 ppm as well as at δ 8.08 and 8.47 ppm (Figure 11).

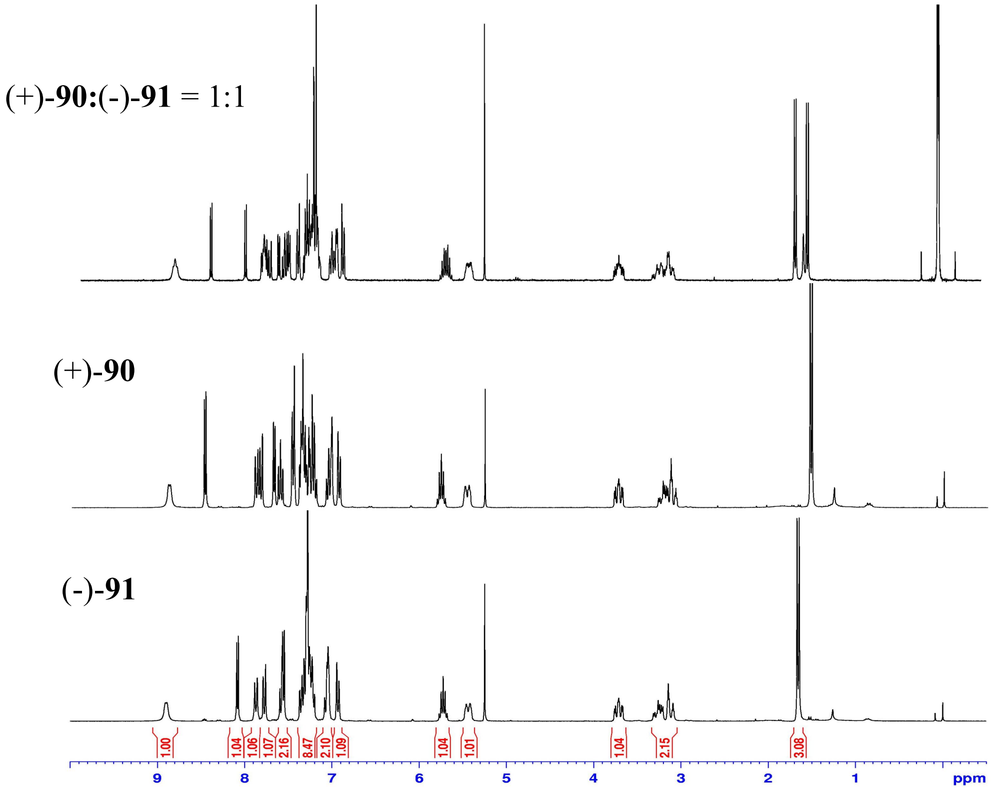


Figure 11 ^{1}H NMR of ureas (+)-90, (-)-91 and 1:1 mixture of (+)-90 and (-)-91

All attempts to separate diastereomers (+)-**90** and (-)-**91** by recrystallization from various solvents failed. However, the ratio of two diastereomers (+)-**90** and (-)-**91** varied after passing the mixture through a silica gel column chromatography and eluting with a gradient of EA/CH_2Cl_2. When the fractions containing different ratio of compounds (+)-**90** and (-)-**91** were recrystallized from EA/hexane, the same phenomena as for compounds (+)-**86** and (-)-**87** were observed. Thus, the route in Figure 7 was adapted where diastereomers (+)-**90** and (-)-**91** were separated with des > 95% (Figure 11). The des were double confirmed by chiral HPLC analysis (Figure 12). This finding revealed that the electronegativity of the chiral auxiliary did not affect the crystalline property of diastereomeric mixture (+)-**90** and (-)-**91**.

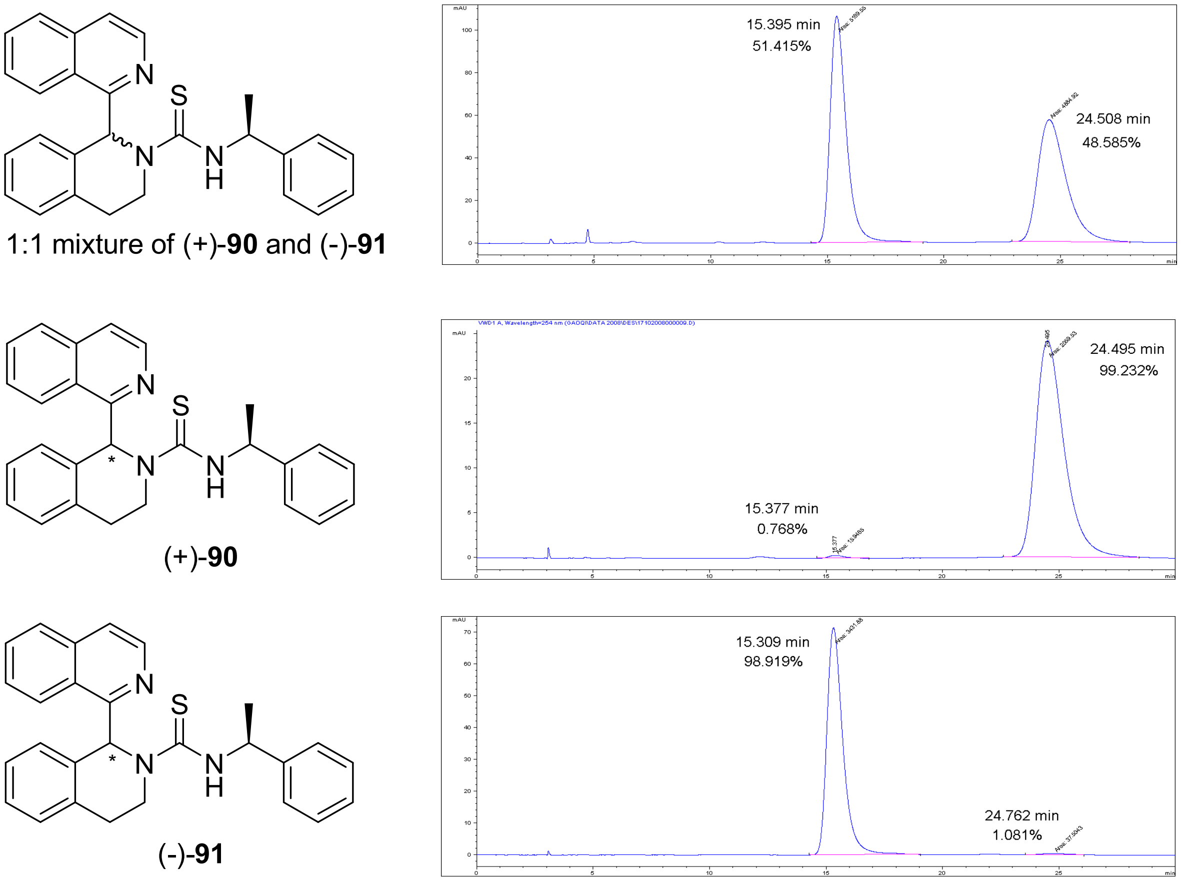


Figure 12 HPLC results of ureas (+)-90, (-)-91 and 1:1 mixture of (+)-90 and (-)-91

2.2.2.2. Alcoholysis of urea derivatives (+)-86 and (-)-87

Although both diastereomeric mixtures (+)-**86** and (-)-**87** as well as (+)-**90** and (-)-**91** could be prepared in excellent yields and separated easily, but due to differences in the cost of the resolving agents, preparation and separation of diastereomers (+)-**86** and (-)-**87** was used to obtain enantiopure BIQ **68**.

With a large amount of pure diastereomers (+)-**86** and (-)-**87** in hand, the next aim was to achieve cleavage of the urea substituents to obtain the desired enantiomerically pure BIQ **68**. Simple acidic or basic alcoholysis route can be used to achieve this aim. Acidic alcoholysis of diastereomeric ureas (+)-**86** and (-)-**87** was investigated firstly. Compound (+)-**86** and (-)-**87** were heated at reflux separately in EtOH in the presence of 1 M HCl to provide the cleaved products (+)-**68** and (-)-**68**, respectively. During this process, an interesting phenomenon was discovered: the rates of alcoholysis of compounds (+)-**86** and

(-)-**87** were quite different under the same conditions. Complete alcoholysis of urea derivative (+)-**86** took 12 h, whereas, compound (-)-**87** required 24 h. To further verify the observed result, alcoholysis of a 1:1 mixture of compound (+)-**86** and (-)-**87** was attempted. Several aliquots were taken during the reaction and the ^{1}H NMR spectra of those crude reaction samples were recorded (Figure 13). From those spectra, we can see clearly that the molar ration between (+)-**86** and (-)-**87** (calculated by integration of doublets at δ 6.30 and 6.39 ppm) kept changing during reaction process indicating that urea (+)-**86** had been consumed much faster than urea (-)-**87**. Thus, the difference in reaction rates of acidic alcoholysis between two diastereomers (+)-**86** and (-)-**87** was confirmed.

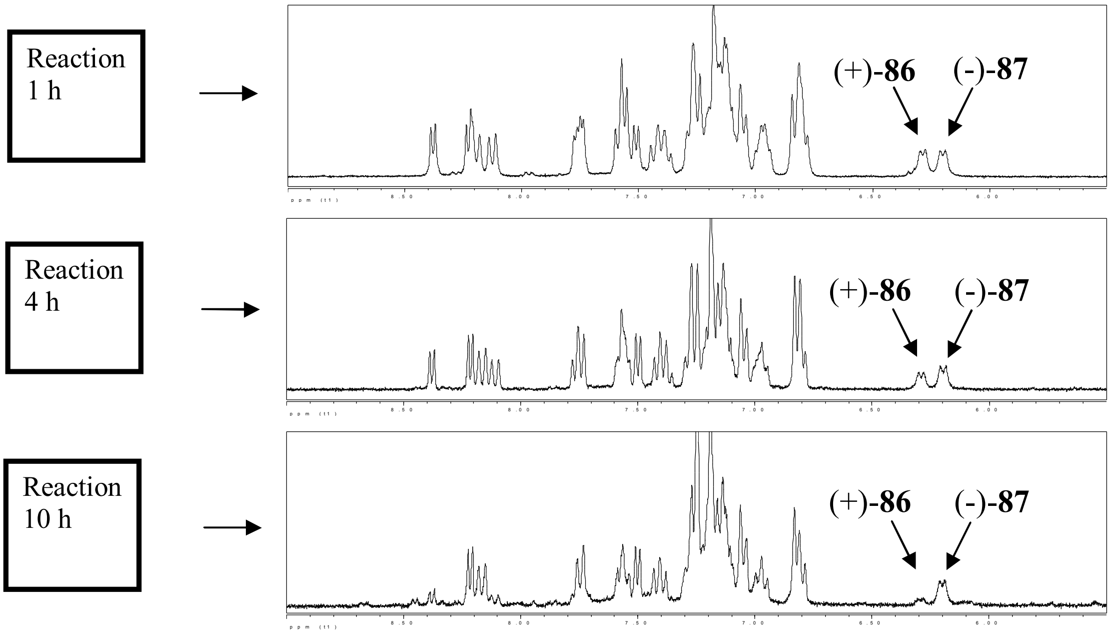
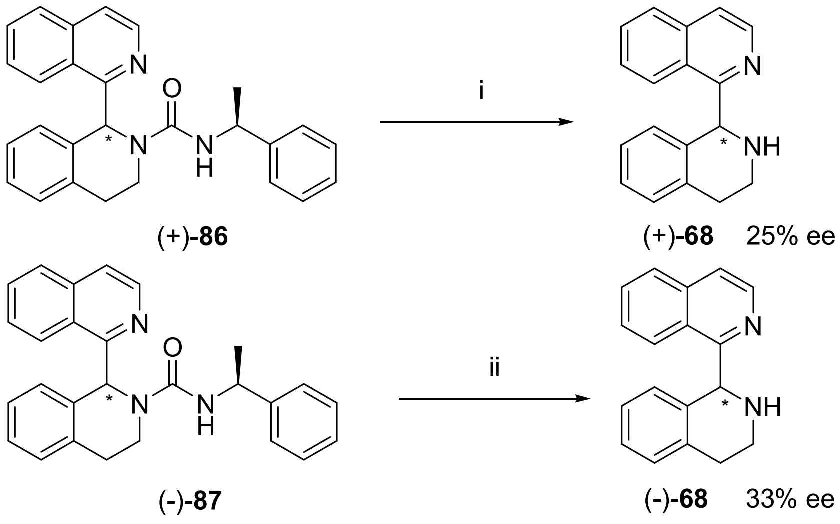


Figure 13

The ees of the products from acidic alcoholysis were examined by chiral HPLC. To our surprise, only 25% ee of (+)-**68** and 33% ee of (-)-**68** were obtained despite the fact that all reactions were carried out with pure diastereomers (Scheme 44).



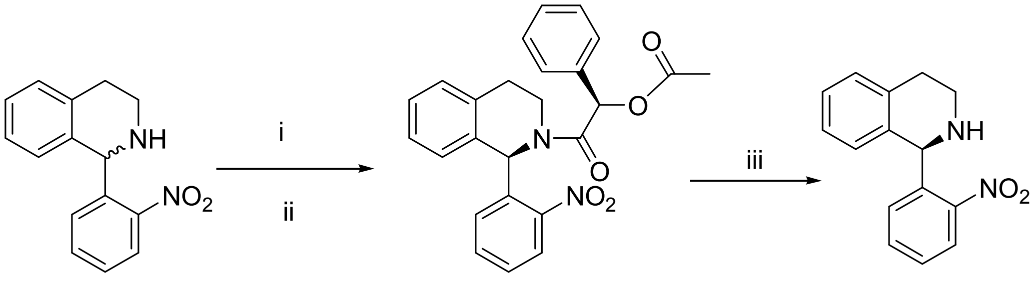
(+)-**86** (+)-**68** 25% ee

(-)-**87** (-)-**68** 33% ee

Conditions: i. 1 M HCl, EtOH, reflux, 12 h
ii. 1 M HCl, EtOH, reflux, 24 h

Scheme 44

Repeated reactions using various amounts of HCl showed similar results. The low ee can only be explained by racemization during the acidic alcoholysis. In fact, similar phenomenon was observed by Edgars[122] during the resolution of nitro-isoquinoline **92** (Scheme 45). The mechanism for this racemization might involve an isoquinoline ring opening and closure sequence in strongly acidic media. However, no attempts were made to understand the mechanism in detail. Thus, alcoholysis under acidic condition was thought not suitable because of the low ee of the products.

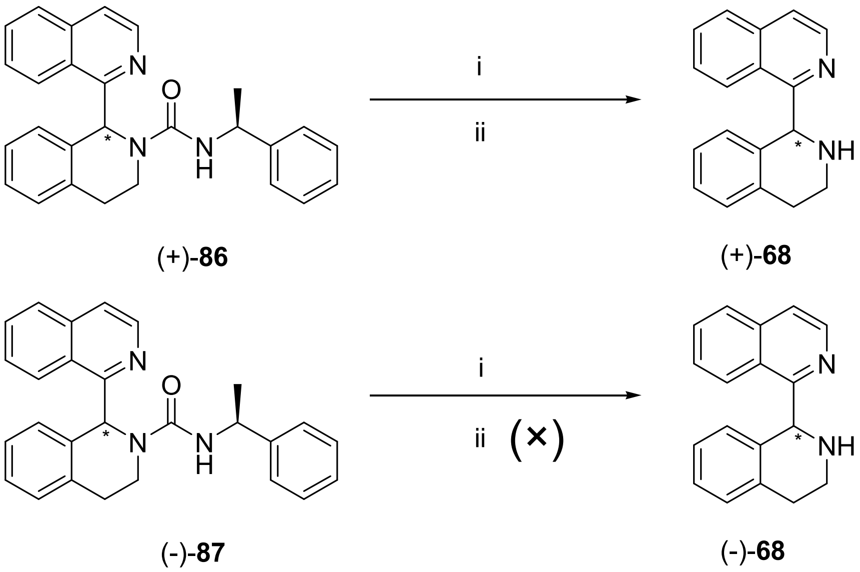


92 **93** (*R*)-**92**
46% yield, 54% ee

Conditions: i. (*R*)-(-)-o-acetylmandelic acid, DCC/DMAP, CH_2Cl_2
ii. Recrysatllization from EA/hexane
iii. 6 M HCl, Dioxane

Scheme 45[122]

Alcoholysis of diastereomeric ureas (+)-**86** and (-)-**87** under basic conditions were examined. When ureas (+)-**86** and (-)-**87** were treated separately with sodium *n*-butoxide (NaOBu) in hot *n*-BuOH, both reactions gave cleaved products at same reaction rate. However, if sodium *n*-butoxide was replaced with sodium *tert*-butoxide, alcoholysis of compound (-)-**87** did not take place at all while alcoholysis of (+)-**86** proceeded smoothly but at a slower reaction rate compared to the reaction with sodium *n*-butoxide (Scheme 46).

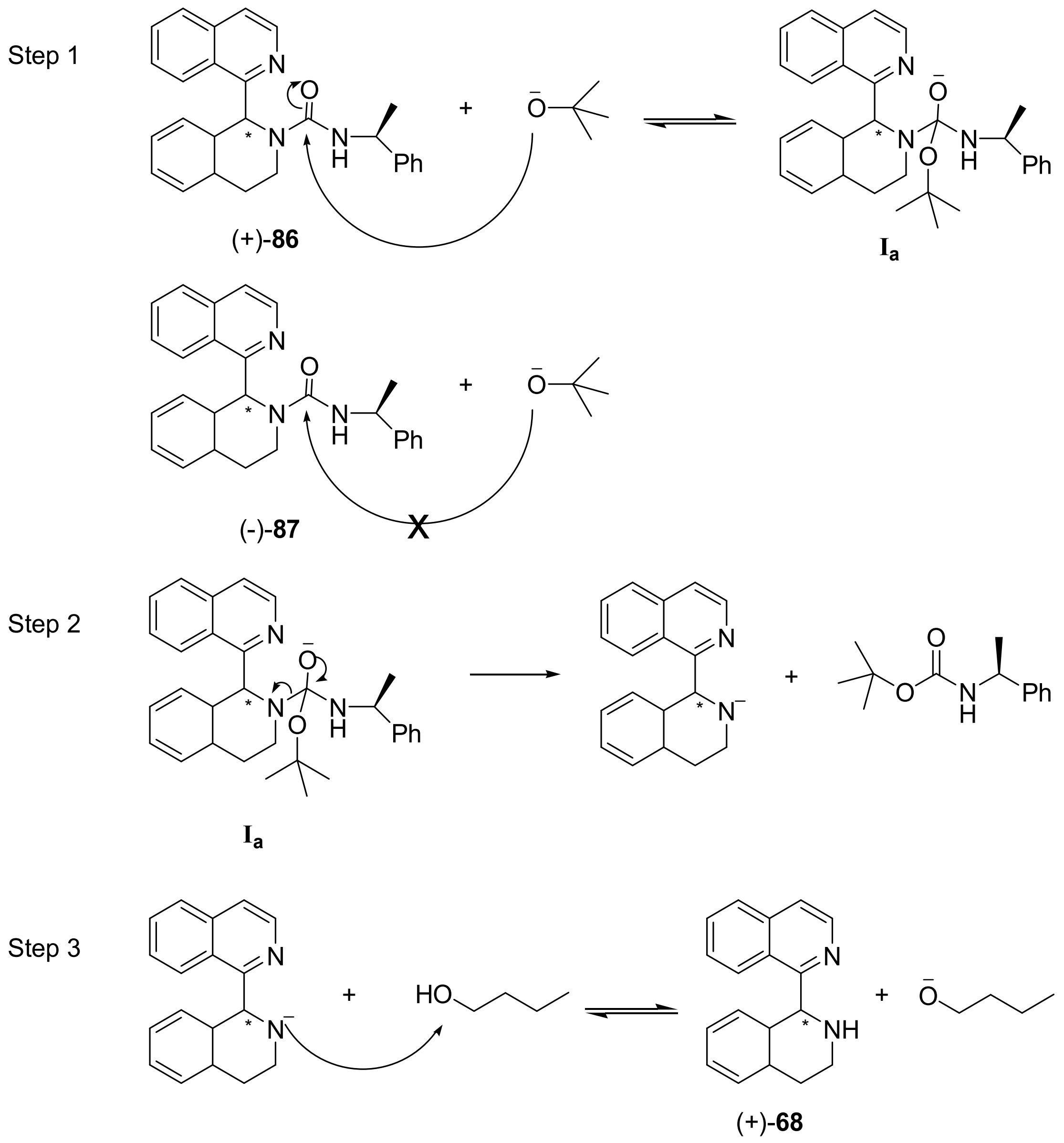


Conditions: i. 2.0 equiv Sodium butoxide, *n*-Butanol, 120 °C, 45 min
ii. 2.0 equiv Sodium *tert*-butoxide, n-Butanol, 120 °C, 6 h

Scheme 46

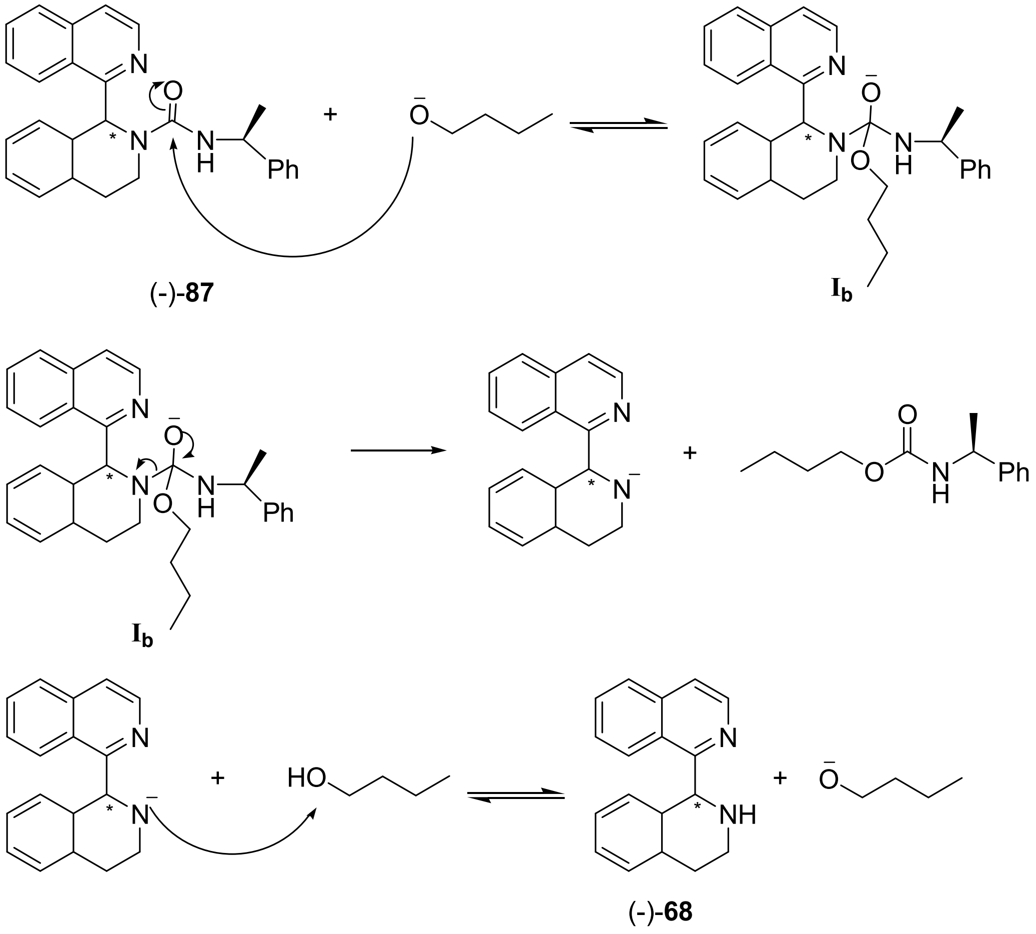
Based on these results, an attempt to simplify the resolution procedure was carried out. An original mixture of urea derivatives (+)-**86** and (-)-**87** (ratio = 1:1) was treated with sodium *tert*-butoxide in hot *n*-BuOH for eight hours. It was predicted that only (+)-**86** could be cleaved to the corresponding product and (-)-**87** will be recovered unchanged. Surprisingly, the ^{1}H NMR spectrum of crude product revealed that both urea derivatives (+)-**86** and (-)-**87** were completely converted to the cleaved products. To find a reasonable explanation for this apparently contradictory result, a possible mechanism of alcoholysis of the original mixture under basic condition was proposed.

As illustrated in Scheme 47, nucleophilic attack by *tert*-butoxide anion on the carbonyl carbon of urea (+)-**86** gave a tetrahedral intermediate **Ia**. In the mean time, urea (-)-**87** was unchanged due to its conformation where attack by the bulky anion was not feasible. Rearrangement of intermediate **I$_a$** gave an ammonium anion. Finally, the ammonium anion was protonated by the solvent to yield the cleaved product (+)-**68** and a *n*-butoxide anion as well.



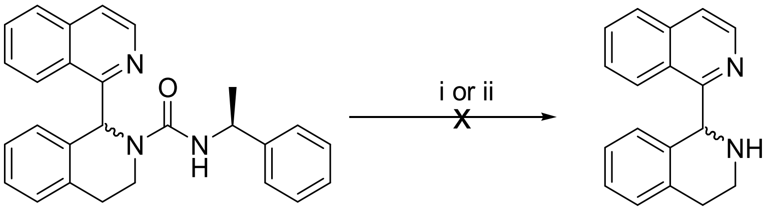
Scheme 47

It is important to note that the last step of reaction gave out a *n*-butoxide anion which was proven to attack both compounds (+)-**86** and (-)-**87** to give the cleaved products. Therefore, the previously unreacted urea (-)-**87** could possibly be attacked by the *n*-butoxide anion to form another tetrahedral intermediate **I$_b$** (Scheme 48). A similar rearrangement of electrons and deprotonation of solvent might have taken place to furnish compound (-)-**68** and also a *n*-butoxide anion. Thus, both the diastereomers were consumed to yield the *racemic* product. To verify our assumption, the solvent of reaction was changed to *t*-BuOH to avoid generating the *n*-butoxide anions. Unfortunately, no cleaved product was formed even after refluxing the mixture for 3 d. It was observed that the diastereomeric mixture (+)-**86** and (-)-**87** has very low solubility in *t*-BuOH which may have prevented their reactions. Consequently, the attempt to simplify the resolution process in this fashion was not successful.



Scheme 48

The ees of products achieved by alcoholysis of ureas (+)-**86** and (-)-**87** with NaOBu in *n*-BuOH (Scheme 46) were checked by chiral HPLC. Disappointingly, only 38% ee for compound (+)-**68** and 41% ee for compound (-)-**68** were obtained. These ees, although higher than those of acid-cleaved products, were still thought to be unacceptable. Therefore, another method, namely the reductive cleavage of amide bond was sought. Despite this method's success with many amides,[123,124] this method was found not suitable in our case. Treating urea mixture (+)-**86** and (-)-**87** with lithium aluminium hydride ($LiAlH_4$) or diisobutyl aluminium hydride (DIBAL-H) for 3-5 d gave no sign of cleaved products (Scheme 49).



1:1 mixture of (+)-**86** and (-)-**87**

Conditions: i. $LiAlH_4$, THF, reflux, 3 d
ii. DIBAL-H, CH_2Cl_2, r.t., 5 d

Scheme 49

We then turned our attention to optimization of the alcoholysis under basic conditions to achieve better ees. Reaction temperature was the first factor examined. Reactions were examined with compound (+)-**86** and 2 equivalent of sodium *n*-butoxide in *n*-BuOH at different temperatures (Table 1). The reactions were quenched when all of the starting materials were completely consumed, as indicated by TLC analysis.

As shown in Table 1, there was no clear trend revealing the effect of temperature on the ees of (+)-**68**. However, the temperature affected the yields of the reactions greatly. Higher temperature led to the shorter reaction time and provided higher yield. It was reasonable because the cleaved product was found to be easily oxidized under basic alcoholic conditions to form BIQs **70** and **71**. Therefore, longer reaction led to oxidation and thus lower yield of (+)-**68** thus giving. Hence 120 °C was chosen as the best temperature for this reaction.

Table 1 Effect of temperature on basic alcoholysis of compound (+)-86

Entry	Temperature (°C)	Time	Yield[a] %	ee[b] of (+)-**68** %
1	120	45 min	98	38
2	110	2 h	90	30
3	95	10 h	46	35

[a] Isolated yield.

[b] Determined by HPLC using Daicel OD-H column.

The effect of loading of NaOBu was another factor investigated. Here compound (-)-**87** was utilized as starting material. All the reactions were carried out at 120 °C using different amounts of NaOBu. The results are shown in Table 2. Interestingly, the ees of the products increased dramatically with the decrease in the amount of NaOBu. To verify this finding, another two reactions were conducted with compound (+)-**86** as starting material. Comparing with the former reactions, the results using (+)-**86** showed the same trend. The strong base NaOBu might take a role in the racemization process through some unclear ways. It was also noticeable that less amount of NaOBu led to longer reaction time thus providing lower yield of the desired product. Making a compromise between the ee and the yield, 0.5 equivalent of NaOBu was taken as the best scenario (Table 2, entry 2). Although only 84% ee was obtained from this reaction, gratifyingly, one recrystallization could bring the ee to up to 99%. Hence, the best conditions for the base induced alcoholysis of compound (+)-**86** and (-)-**87** were confirmed (Scheme 50).

Table 2 Effect of amount of NaOBu on basic alcoholysis of compound (-)-87

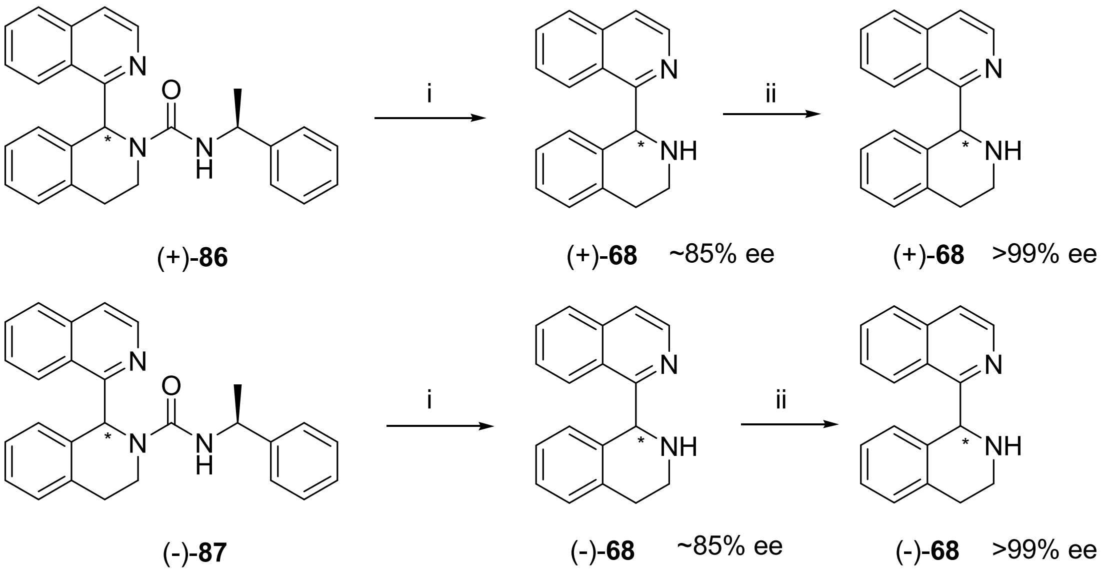
Entry	NaOBu	Time	Yield[a] %	ee[b] % (Configuration)
1	0.25 equiv	6 h	62	86 (+)
2	0.5 equiv	2 h	93	84 (-)
3	1.0 equiv	1 h	98[c]	56[c] (+)

4			98	51 (-)
5	2.0 equiv	45 min	98[c]	38[c] (+)
6			98	41 (-)

[a] Isolated yield.

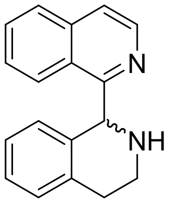
[b] Determined by HPLC using Daicel OD-H column.

[c] Using urea (+)-**86** as the starting material.

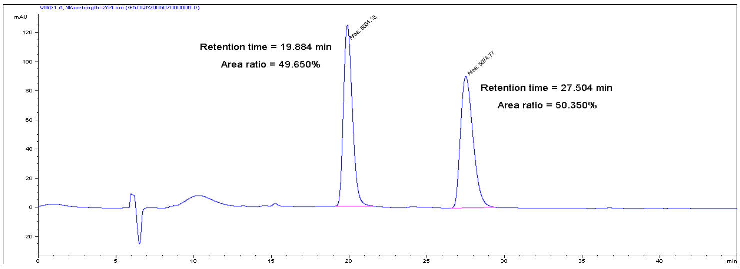


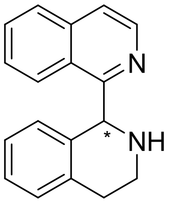
Conditions: i. 0.5 equiv NaOBu, *n*-BuOH, 120 °C, 2 h
ii. Recrystallization from EtOH

Scheme 50

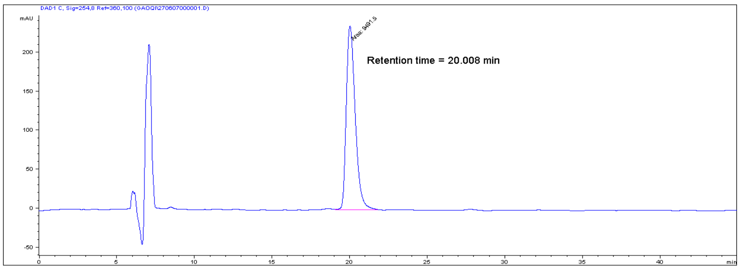


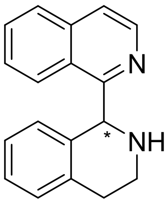
rac-**68**





(+)-**68**





(-)-**68**

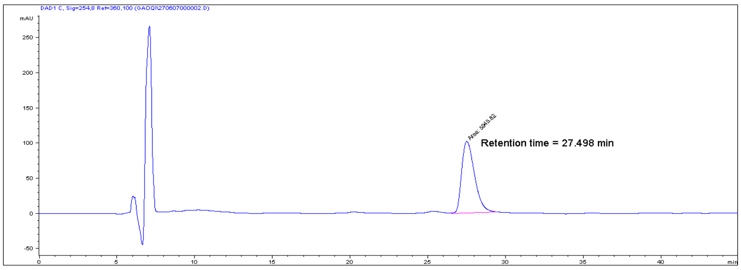


Figure 14

The ees of crystals were confirmed to be >99% by chiral HPLC analysis (Figure 14). The crystals obtained from cleavage of urea (-)-**87** were found suitable for X-ray crystallographic analysis. As shown in Figure 15, the piperidine ring appeared as a twisted chair conformation with the benzylic proton projecting into an equatorial-like position and the bridging bond resident into an axial position. It was also observed that isoquinoline ring and hydrogenated isoquinoline ring connected by the bridging bond were perpendicular to each other.

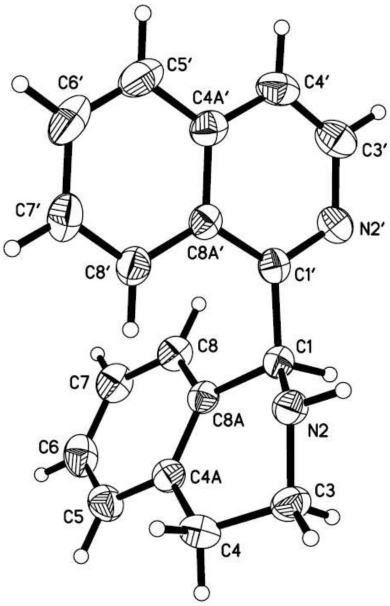
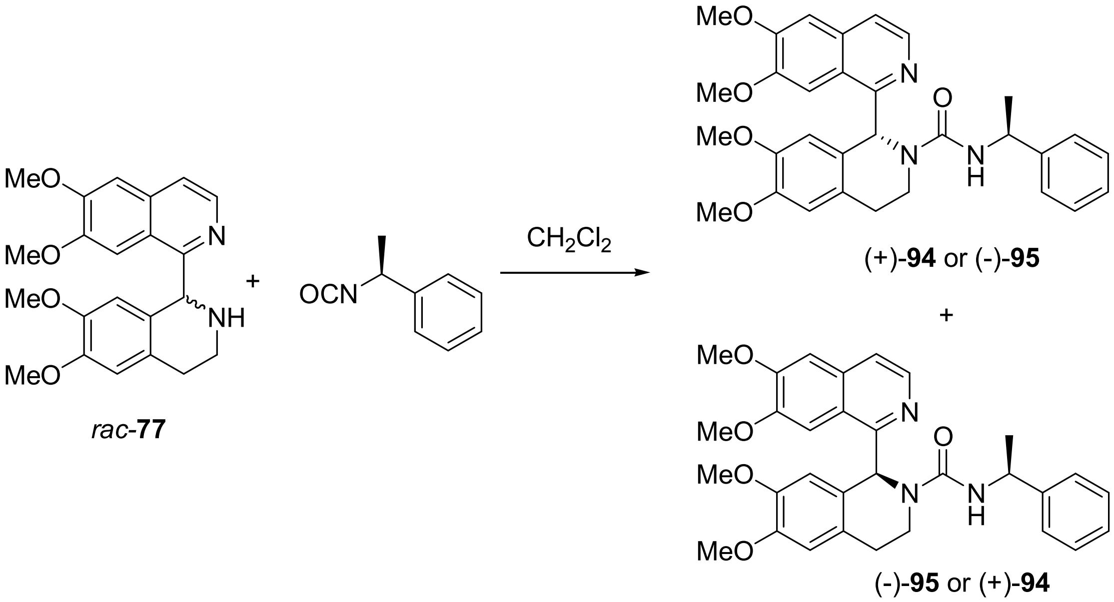


Figure 15

At this stage, the whole resolution process of BIQ *rac*-**68** was established successfully and a large amount of enantiomerically pure (+)-**68** and (-)-**68** were prepared *via* this route.

2.2.2.3. Preparation and separation of diastereomeric urea derivatives of *rac*-77

Successful resolution of BIQ *rac*-**68** using chiral isocyanate stimulated us to adapt the same method to resolve BIQ *rac*-**77**. Treating *rac*-**77** with stoichiometric amount of (*S*)-(-)-α-methylbenzyl isocyanate in CH_2Cl_2 gave the expected diastereomeric urea mixture (+)-**94** and (-)-**95** (due to the difficulties met in preparing crystals suitable for X-ray crystallographic analysis, the configuration of diastereomers were not confirmed in this project) in quantitative yield (Scheme 51).



Scheme 51

Again, ^{1}H NMR spectrum showed two sets of signals for the mixture of (-)-**95** and (+)-**94**. Clearly separated signals were found at δ 1.43, 1.52 ppm and δ 8.15, 8.32 ppm (Figure 16). Following the routine procedure, the diastereomeric mixture (-)-**95** and (+)-**94** was recrystallised from various solvents. Surprisingly, the ^{1}H NMR spectrum of the crystals collected from EtOH showed only one set of signals indicating successful separation of compound (+)-**94** by simple recrystallization. In comparison to the analogues (+)-**86** and (-)-**87**, which could not be separated by recrystallization, diastereomers (+)-**94** and (-)-**95** could be separated with ease. Therefore, the four methoxy groups on the aromatic rings in compounds (+)-**94** and (-)-**95** were believed to induce a remarkable difference by which these compounds crystalise. However, not all of (+)-**94** in the mixture crystalized out, thus, the mother liquor after filtration of crystals could only give a mixture with enriched ratio of diastereomer (-)-**95**.

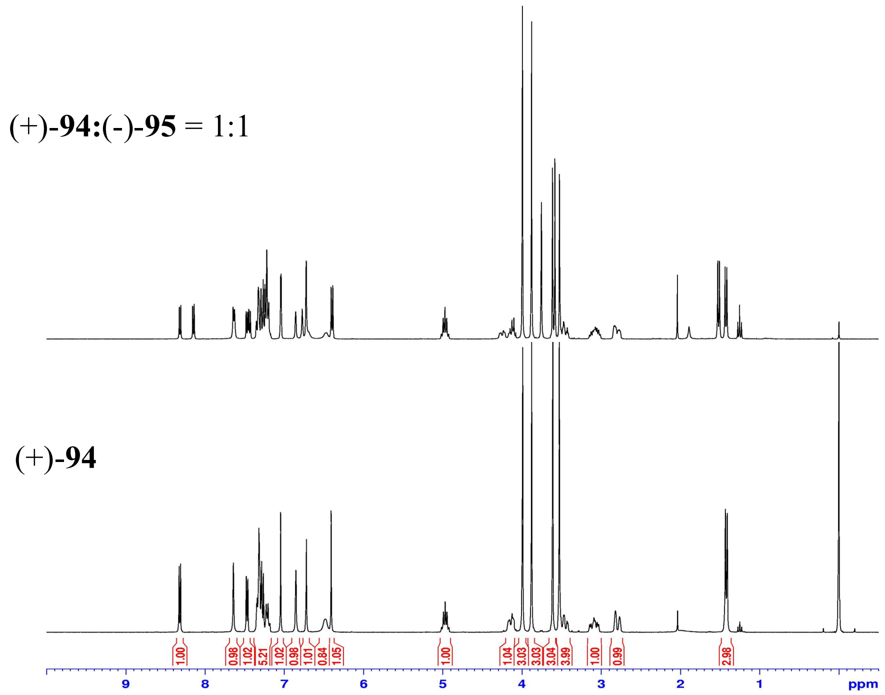
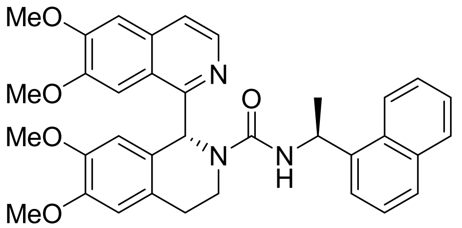
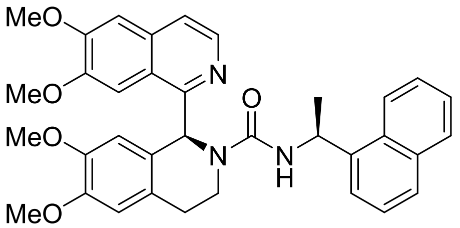


Figure 16

Again, the scope of this study was expanded to the other diastereomeric urea derivatives of BIQ *rac*-77. Mixture of urea derivatives **96** and **97** was prepared by treating BIQ *rac*-77 with (*S*)-(-)-1-naphthylethyl isocyanate as usual. Not surprisingly, recrystallization of mixture **96** and **97** from EtOH gave only partially enriched diastereomeric mixture. Thus, the steric effect of the bulky naphthyl group was thought responsible for this behaviour.

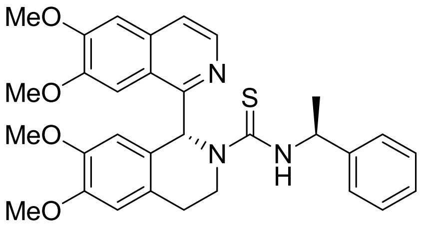


96

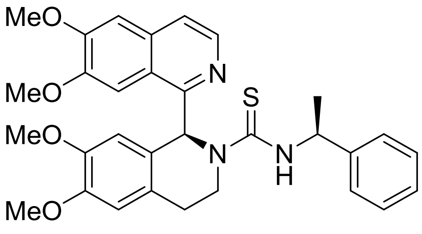


97

Similarly, diastereomeric mixture of (+)-**98** and (-)-**99** (the configuration of diastereomers were also not confirmed in this project) was prepared by treating BIQ *rac*-**77** with (*S*)-(-)-α-methylbenzyl isothiocyanate. As envisioned, recrystallization of this mixture from EtOH gave complete separation of diastereomer (+)-**98** (Figure 17). This finding confirmed that replacing oxygen atom with more electronegative sulphur atom did not affect the crystalline properties of (+)-**98** and (-)-**99**.



(+)-**98** or (-)-**99**



(-)-**99** or (+)-**98**

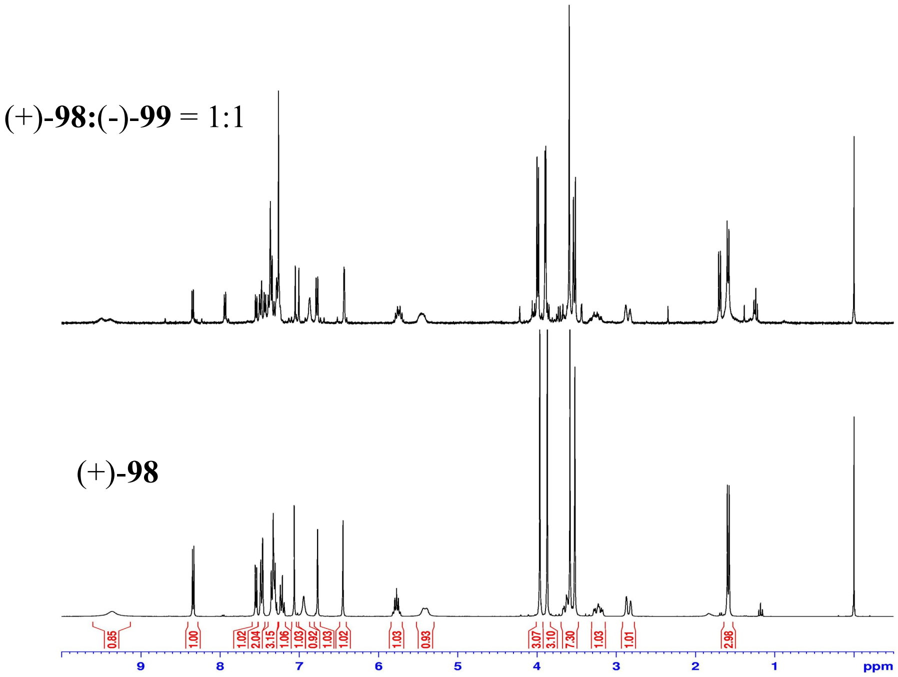


Figure 17

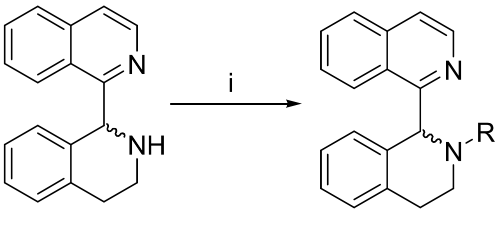
Although a large amount of enantiomerically pure diastereomers (+)-**94** and (+)-**98** could be obtained easily via recrystallization, further cleavage of these diastereomers to give expected (+)-**77** met difficulties. Applying the conditions for acidic or basic alcoholysis of analogues (+)-**86** and (-)-**87** to (+)-**94** or (+)-**98** gave recovered starting materials even at prolonged reaction time. The reductive cleavage of amide bond also failed to give enantiomerically pure BIQ **77**. However, the enantiomerically pure diastereomers (+)-**94** and (+)-**98** were utilized as chiral ligands in asymmetric catalysis and will be discussed in later chapters.

2.3. Derivatization of BIQ *rac*-68 and (+)-68

In the early part of this chapter, procedures were developed for synthesis of a series of 1,1'-tetrahydrobisisoquinolines. Unsymmetrical BIQ *rac*-**68** was resolved to give enantiomerically pure BIQs (+)-**68** and (-)-**68**. With these chiral compounds in hand, attention was now turned to their chemistry. Initially, the derivation reaction was carried out on BIQ *rac*-**68** and then the successful protocols were applied to BIQ (+)-**68**. BIQ (-)-**68** is expected to behave similar to (+)-**68** and its chemistry was not explored in details. Several types of substituents will be introduced on BIQ scaffold to examine the reactivity of BIQ *rac*-**68** and its structural properties. All chiral derivatives of BIQ (+)-**68** can act as potential ligands in various catalytic asymmetric reactions.

2.3.1. Derivatization of BIQ *rac*-68

To introduce geometrical variations and examine their effects on enantioinduction, we carefully prepared ligands **100-118**. We rationalized that since there are no substitutents at or near the chelating nitrogens of compound **68** (i.e. at both nitrogens or at carbons 3 and 3'), the active chiral space at the metal center is relatively ill-defined considering the free rotation around the C1-C1' bond. We envisioned that introduction of substituents of variable sizes at the nitrogen of reduced heterocyclic ring should lead to more rigid and well-defined chiral motifs. We expected that the greater rigidity afforded by those ligands will result in higher enantioinduction. Therefore, we prepared *N*-alkyl derivatives **100-104**, amides **105** & **106**, ureas **107-111** and thioureas **112-118** by various condensation and addition reactions (Scheme 52).



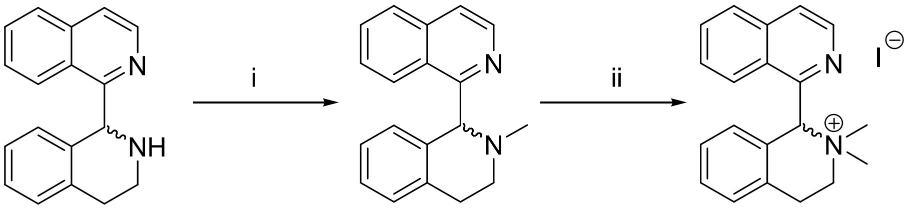
rac-**68**

Reactions: i. Condensation or addition

Scheme 52

2.3.1.1. *N*-alkyl derivatives of BIQ *rac*-68

At the outset, nucleophilic substitution with alkyl halides was attempted. By this method, various alkyl groups could be introduced on BIQ *rac*-**68**. When BIQ *rac*-**68** was treated with 1.1 equivalent of methyl iodide in CH_3CN in the presence of potassium carbonate, it gave, after workup and column chromatography purification, a compound in 66% yield (Scheme 53). Its mass spectrum showed a molecular ion at *m/z* value of 275.13 indicating the expected molecular formula $C_{19}H_{18}N_2$. Moreover, its ^{1}H NMR spectrum showed a new singlet integrating for three protons at δ 2.19 ppm which was assigned to a methyl group attached to nitrogen. Hence the structure of the product was assigned compound *rac*-**100**.



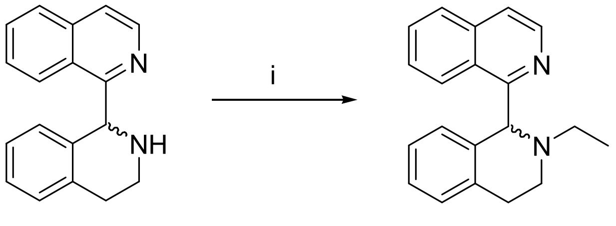
rac-**68** *rac*-**100** *rac*-**101**

Conditions: i. 1.1 equiv CH_3I, K_2CO_3, CH_3CN, 50 °C, overnight
ii. 4.0 equiv CH_3I, K_2CO_3, CH_3CN, 50 °C, overnight

Scheme 53

Further methylation of *rac*-**100** could be achieved using 4 equiv of methyl iodide under the same conditions to give, after recrystrallization from EtOH, the expected reaction product *rac*-**101** in 54% yield (Scheme 53). The ^{1}H NMR spectrum of *rac*-**101** showed two three-proton singlets at δ 3.24 and 3.81 ppm and its ^{13}C NMR spectrum showed two new signals at δ 51.1 and 52.5 ppm indicating two methyl groups attached to nitrogen. Hence the product was confirmed to be compound *rac*-**101**.

Treatment of *rac*-**68** with bromoethane under standard reaction conditions developed for methyl iodide gave expected product *rac*-**102** in 74% yield (Scheme 54). Its mass spectrum showed molecular ion at *m/z* value of 289.13 indicating a molecular formula of $C_{20}H_{20}N_2$. In the ^1H NMR spectrum, one new three-proton triplet at δ 0.93 ppm and two new one-proton hexets at δ 2.32 and 2.55 ppm confirmed the presence of the ethyl group attached to nitrogen. Two new signals were observed in ^{13}C NMR spectrum at δ 11.3 and 48.2 ppm which were assigned to the ethyl carbons. Thus, the assignment of product *rac*-**102** was assured.

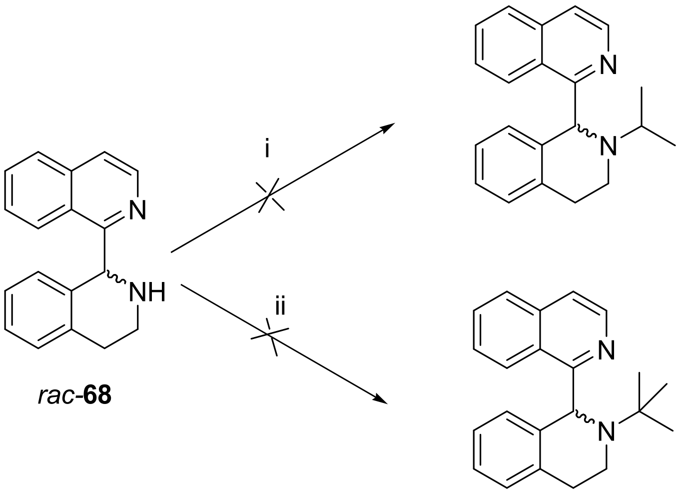


rac-**68** *rac*-**102**

Conditions: i. 1.1 equiv CH_3CH_2Br, K_2CO_3, CH_3CN, 50 °C, overnight

Scheme 54

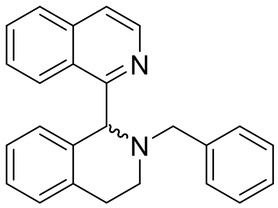
However, under the same alkylation conditions, isopropyl bromide and *t*-butyl bromide could not be introduced on BIQ *rac*-**68** (Scheme 55). Elongated reaction time (up to 3 d) and use of more equivalents of alkyl halides only resulted in oxidized products **70** and **71**. In these cases, steric effect was believed to be the main force to prevent the formation of the products. Therefore, introduction of bulky groups such as isopropyl or *t*-butyl were unsuccessful while relatively small groups such as methyl or ethyl could be introduced without any problem.



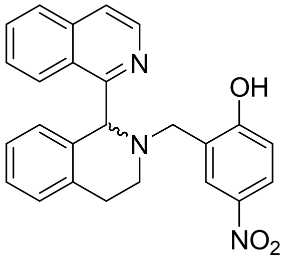
Conditions: i. 1.1 eq. $(CH_3)_2CH_2Br$, K_2CO_3, CH_3CN, 50 °C, overnight
ii. 1.1 eq. $(CH_3)_3CH_2Br$, K_2CO_3, CH_3CN, 50 °C, overnight

Scheme 55

Attention was then turned to the preparation of *N*-benzyl derivative. Treatment of compound *rac*-**68** with benzyl bromide in the presence of K_2CO_3 in CH_3CN followed by recrystallization from EtOH gave the expected product *rac*-**103** in 62% yield. The mass spectrum of the product showed molecular ion at *m/z* 351.13 indicating a molecular formula of $C_{25}H_{22}N_2$. Its ^1H NMR spectrum showed new multiplets at δ 3.21-3.40 ppm (2H) and at δ 7.06-7.20 ppm (5H). In the mean time, the ^{13}C NMR spectrum showed new signals at δ 58.4 ppm and another four signals in the aromatic region. All of these evidences confirmed the presence of a benzyl substituent on the nitrogen, thus the product was assigned structure *rac*-**103**.



rac-**103**

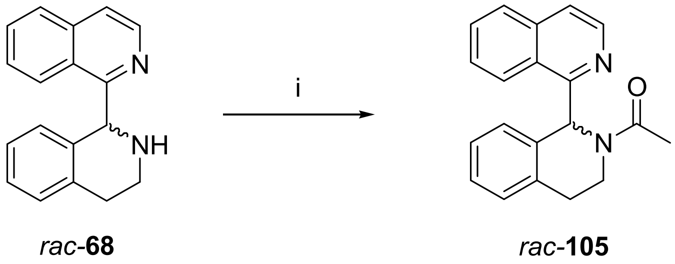


rac-**104**

Similarly, treatment of BIQ *rac*-**68** with 2-hydroxy-5-nitro-benzylbromide gave *rac*-**104** in 88% yield. This di-substituted *N*-benzyl derivative was synthesised because the hydroxyl group is expected to act as a good coordinating site to metal ions in asymmetric catalysis. The mass spectrum of the product showed the expected molecular ion at *m/z* 412.07. Moreover, its ^{1}H NMR spectrum showed two new benzylic methylene doublets at δ 3.52 and 3.91 ppm (*J* = 14.4 Hz) and another three signals in aromatic region which were assigned to the benzyl aromatic protons. Its ^{13}C NMR spectrum showed new signal at δ 58.0 ppm and another six signals in the aromatic region. Hence, the product was assigned structure *rac*-**104**.

2.3.1.2. Amide derivatives

Acylation is another approach to provide *N*-substituted derivatives. Only two representative amide derivatives were synthesised in this project. First, the simplest example, *N*-acetyl derivative *rac*-**105** was prepared by treatment of *rac*-**68** with acetyl chloride in THF in the presence of K_2CO_3 (Scheme 56). After workup and recrystallization from EtOH, the product was obtained in 69% yield. Its mass spectrum showed molecular ion at *m/z* 303.73 corresponding to formula $C_{20}H_{18}N_2O$. The appearance of a three-proton singlet at δ 2.16 ppm in its ^{1}H spectrum indicated a methyl group. Its ^{13}C spectrum showed two new signals, namely a methyl signal at δ 21.8 ppm and a carbonyl signal at δ 169.2 ppm. In addition, the chemical shift of the methine proton moved downfield to δ 7.67 ppm in comparison to δ 6.01 ppm in BIQ *rac*-**68** indicating that the acetyl group was attached to the nitrogen atom. Hence the product was assigned structure *rac*-**105**.



Conditions: i. 1.2 equiv CH_3COCl, K_2CO_3, THF, 50 °C, overnight

Scheme 56

The crystals of amide *rac*-**105** were found suitable for crystallographic analysis and the solid state structure of the molecule was determined as shown in Figure 18. Unlike BIQ (-)-**68**, the piperidine ring in *rac*-**105** appeared as a twisted boat conformation. The isoquinoline ring and the hydrogenated isoquinoline ring were found almost perpendicular to each other and the acetyl group introduced projected away from the isoquinoline part, presumably to minimise any steric interactions.

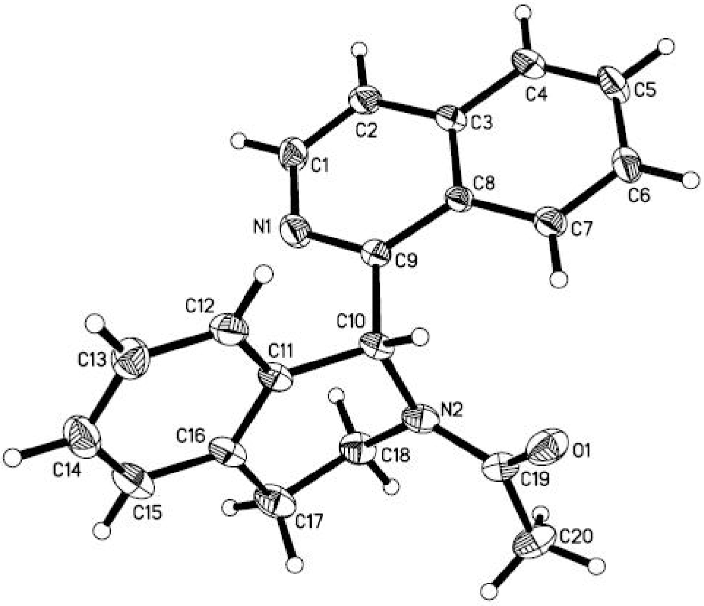
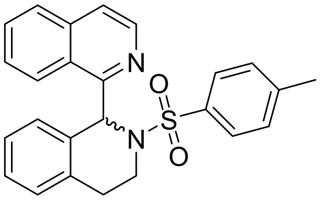


Figure 18

Sulfamide derivative *rac*-**106** was prepared by treating *rac*-**68** with *p*-toluene sulfonyl chloride in the same manner as described for acetyl chloride (Scheme 56). The resulting solid was recrystallised from EtOH to give product *rac*-**106** in 71% yield. All spectroscopic data of the product were consistent with structure *rac*-**106**. The mass spectrum showed molecular ion at *m/z* 415.20; the ^{1}H NMR spectrum showed new three-proton singlet at δ 2.24 ppm and another four signals in the aromatic region. ^{13}C NMR spectrum showed a new signal at δ 21.3 ppm (methyl group) and another four new signals in aromatic region. Hence the product was assigned structure *rac*-**106**.



rac-**106**

The crystals of amide *rac*-**106** were subjected X-ray crystallographic analysis which revealed the structure shown in Figure 19. Analogous to amide *rac*-**105**, the piperidine ring of *rac*-**106** adopted the twisted boat conformation and the isoquinoline ring was perpendicular to the hydrogenated isoquinoline ring.

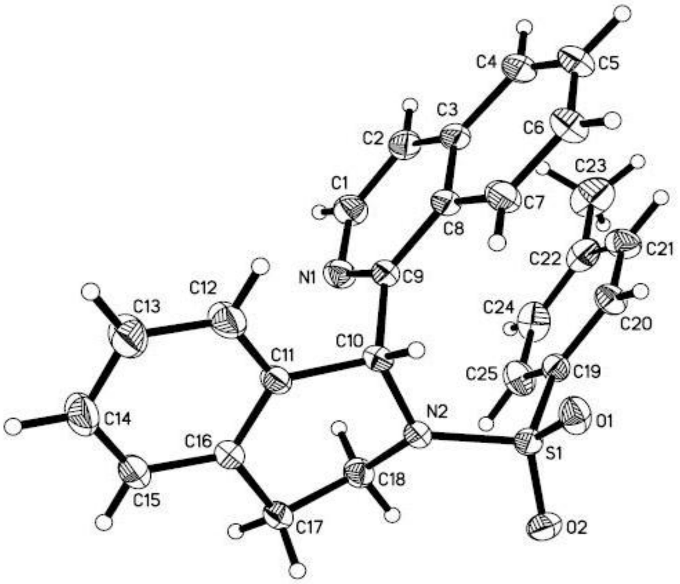
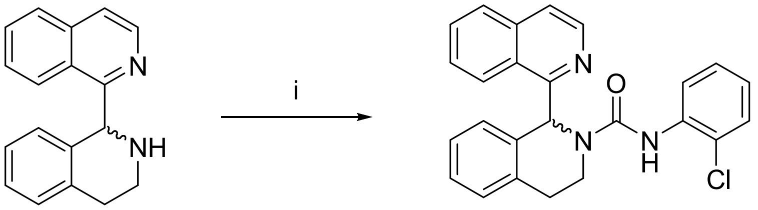


Figure 19

2.3.1.3. Urea derivatives

In the early part of this chapter, chiral isocyanates were reacted with BIQ *rac*-**68** to form urea diastereomers in excellent yield. Thus, another efficient way to obtain *N*-substituted derivatives was at hand. BIQ *rac*-**68** was treated with equimolar amount of 2-chlorophenyl isocyanate in CH_2Cl_2 to give the expected urea *rac*-**107** in 96% yield (Scheme 57). The mass spectrum of the product showed molecular ion at *m/z* 414.13 indicating molecular formula $C_{25}H_{20}ClN_3O$. The ^{1}H NMR spectrum showed four new signals in the aromatic region and a broad singlet at δ 8.15 ppm consistent with the incorporation of the

2-chloro-substituted phenylamide group. The chemical shift of the methine singlet moved downfield thus confirming that substitution had taken place on the nitrogen. In addition, the ^{13}C NMR spectrum showed a new signal at δ 160.9 ppm corresponding to the carbonyl carbon. Six other new signals in the aromatic region were observed consistent with the di-substituted phenyl group. Hence the reaction was confirmed to have proceeded successfully to yield urea *rac*-**107**.

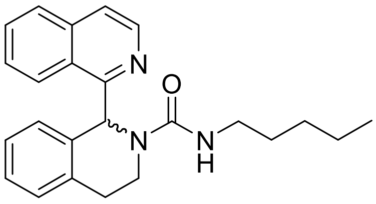


rac-**68** *rac*-**107**

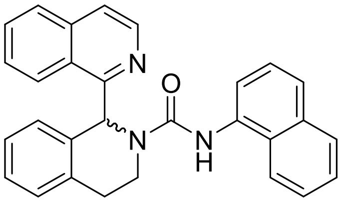
Conditions: i. 1.0 equiv 2-chlorophenyl isocyanate, CH_2Cl_2, r.t., overnight

Scheme 57

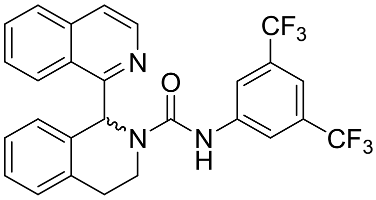
Based on the successful preparation of urea *rac*-**107**, a series of other urea derivatives *rac*-**108** ~ *rac*-**111** were synthesised by treating BIQ *rac*-**68** with various isocyanates employing the same reaction condition mentioned in Scheme 57. The mass spectra of ureas *rac*-**108** ~ *rac*-**111** all gave molecular ions at the expected *m/z* values and the FTIR spectra revealed characteristic amide carbonyl absorptions at 1610-1654cm^{-1}. The NMR spectra also showed clear evidences confirming the attachment of new substituents to the original BIQ *rac*-**68**. For example, in the case of urea *rac*-**108**, ^{1}H NMR spectrum showed four new signals at δ 0.86, 1.16-1.35, 1.45 and 3.11-3.30 ppm representing the eleven protons of the pentyl group as well as a broad singlet at δ 5.72 ppm representing the NH proton. ^{13}C NMR spectrum showed five new signals at δ 14.0, 22.4, 28.9, 29.1 and 38.9 ppm corresponding to the five carbons of the pentyl group, and also a new signal at δ 161.6 ppm corresponding to the carbonyl carbon. In the case of urea *rac*-**109**, seven new aromatic signals in the ^{1}H NMR spectrum and ten new aromatic signals in the ^{13}C NMR spectrum confirmed the presence of naphthyl group while a broad one-proton singlet at δ 9.03 ppm indicated the presence of NH proton. For urea *rac*-**110,** in addition to the broad singlet assigned to the NH proton at δ 9.78 ppm and the carbon signal assigned to the carbonyl carbon at δ 160.5 ppm, two obscured multiplets at δ 115.6 and 119.2 ppm were observed in the ^{13}C NMR spectrum which were consistent with two trifluromethyl substituents on the newly introduced aromatic ring. In the case of urea *rac*-**111**, the broad singlet of the NH proton was found at δ 7.38 ppm while carbon signal of the carbonyl group was found at δ 161.5 ppm. In addition, one six-proton singlet was observed at δ 2.01 ppm and one three-proton singlet was observed at δ 2.23 ppm revealed the presence of three methyl substituents on the newly attached aromatic ring. Hence the structure assignments of ureas *rac*-**108** ~ *rac*-**111** were confirmed.



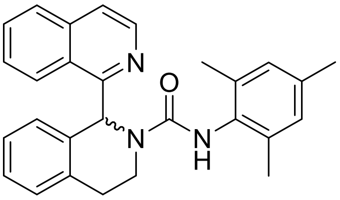
rac-**108**



rac-**109**



rac-**110**

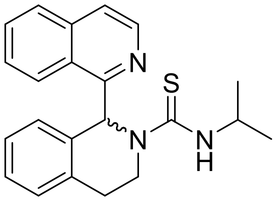


rac-**111**

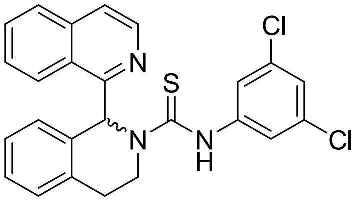
2.3.1.4. Thiourea derivatives

The successful protocol for preparing urea derivatives *rac*-**108** ~ *rac*-**111** was expanded to the preparation of a similar kind of compounds namely thioureas. Seven different isothiocyanates were chosen to react with BIQ *rac*-**68** to yield the corresponding thioureas. All the reactions gave the expected products in excellent yields without any problem. However, when BIQ *rac*-**68** was treated with *tert*-butyl isothiocyanate to give thiourea *rac*-**115**, the reaction rate was found much slower than other isothiocyanates. After reacting for 18 h, TLC analysis of the crude product revealed incomplete conversion. Thus the reaction time was extended to 4 d to achieve complete conversion of all the starting material. This phenomenon was again attributed to the steric effect caused by the bulky *t*-butyl group.

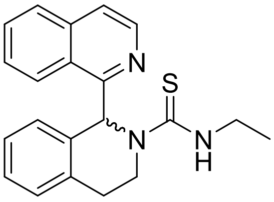
The mass spectra of thiourea *rac*-**112** ~ *rac*-**118** all gave molecular ions at the expected *m/z* value and the infrared spectra revealed characteristic thioamide carbonyl absorptions at 1474-1588cm^{-1}. The most striking feature of their ^{13}C NMR spectra was the presence of a new signal with high chemical shift at δ 181.6 to 182.8 ppm which corresponded to the thioamide carbon. It was also noticed from the ^{1}H NMR spectra that the NH proton gave rise to a broad singlet at relatively high chemical shift in comparison to those of the urea derivatives. For example, the ^{1}H NMR spectrum of compound *rac*-**117** showed the broad singlet at δ 10.43 ppm, while in case of the thioureas with more electronegative groups such as compounds *rac*-**113** and *rac*-**118**, the broad singlet appeared at even higher chemical shift of δ 11.00 and 11.55 ppm, respectively.



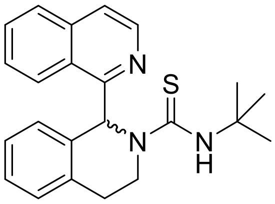
rac-**112**



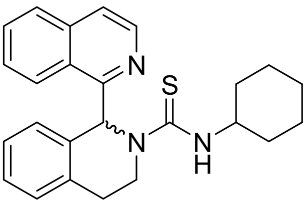
rac-**113**



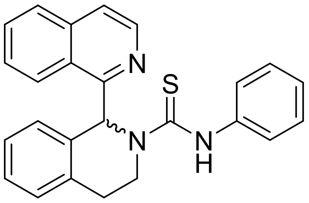
rac-**114**



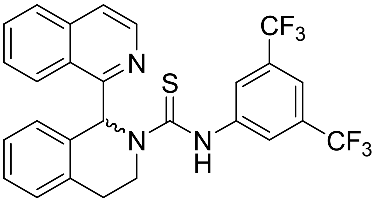
rac-**115**



rac-**116**



rac-**117**



rac-**118**

The single crystal X-ray crystallographic analysis of thiourea *rac*-**112** confirmed its structure and revealed features that were similar to those of the compound *rac*-**105**. The representation of the molecular structure (Figure 20) indicated an axial bridging bond joining the two isoquinoline rings and the two rings projected in an almost perpendicular fashion to each other. The piperidine ring of thiourea *rac*-**112** also adopted the twisted boat conformation which was similar to those shown by the piperidine rings of amides *rac*-**105** and *rac*-**106**. The thioamide substituent introduced in thiourea *rac*-**112** projected well away from the isoquinoline ring system to minimise any steric interactions.

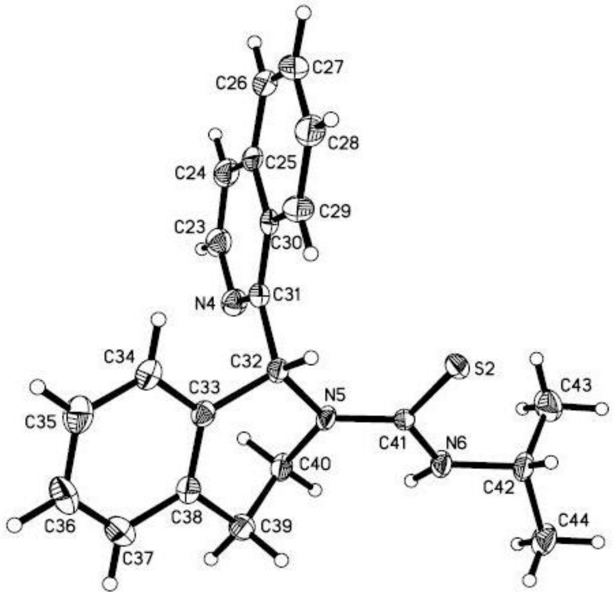
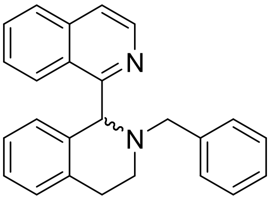


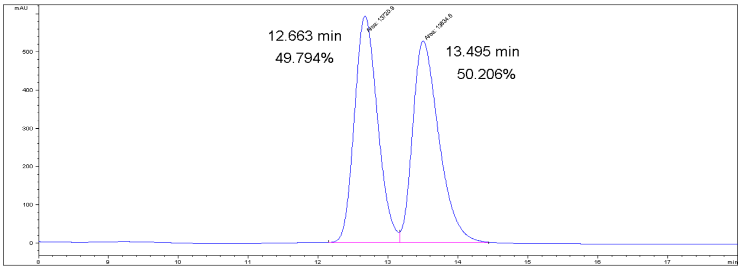
Figure 20

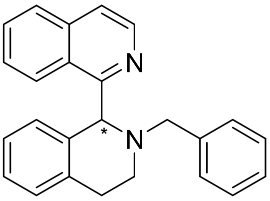
2.3.2. Derivatization of BIQ (+)-68

After establishing the reaction conditions for preparation of *racemic* *N*-substituted derivatives, we turned our attention to the preparation of chiral derivatives as well. As the chiral BIQ (+)-**68** possessed exactly same chemical properties as *racemic* BIQ **68**, we simply adapted all the reaction conditions described for BIQ *rac*-**68** to prepare derivatives of BIQ (+)-**68.** The desired enantiomerically pure derivatives (+)-**100** ~ (+)-**118** were obtained and their structures were confirmed. The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of the chiral derivatives (+)-**100** ~ (+)-**118** were identical to those of *racemic* counterparts. In order to confirm that no racemization took place during the derivatization process, the chiral derivatives were subjected to chiral HPLC, and the results were compared with those of the corresponding *racemic* derivatives. Figure 21 illustrates a pair of typical HPLC results of *racemic* and chiral *N*-benzyl derivatives. An ee of 95% could be obtained which proved no racemization had taken place during the process of alkylation (the starting BIQ (+)-**68** was 95% ee).



rac-**103**





(+)-**103**

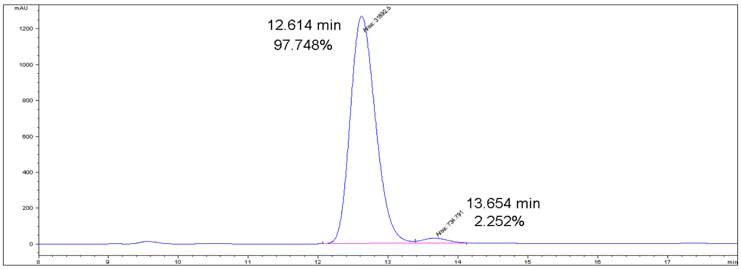
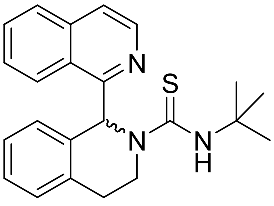
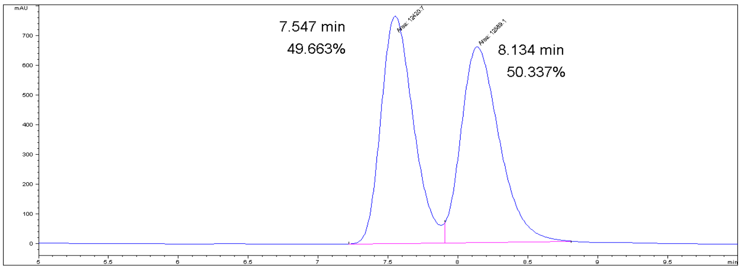


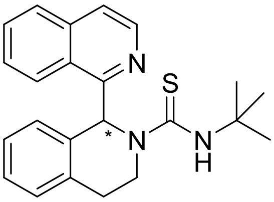
Figure 21

Same conclusion could be drawn from the HPLC results in Figure 22. Condensation between BIQ (+)-**68** and isothiocyanates did not cause any racemization either. Besides these two examples, the ees of other ten chiral derivatives were also determined by chiral HPLC. None of these derivatives showed any sign of racemization (see Appendix). Thus, all chiral derivatives were assured to be enantiomerically pure compounds and could be used as ligands in catalytic reactions without any doubt.



rac-**115**





(+)-**115**

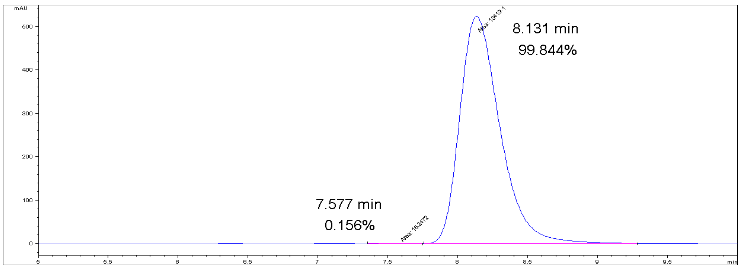


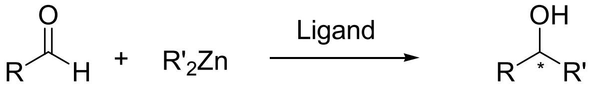
Figure 22

In conclusion, we have prepared a number of BIQs and explored their chemistry and reactivity. BIQ *rac*-**68** was successfully resolved into both enantiomers. Various derivatives of this BIQ were prepared in both *racemic* and enantiopure form. The Chiral BIQs and derivatives will be used is subsequent chapters (Chapters 3 and 4) as ligands for C-C bond forming reactions. The results will be discussed in details.

Chapter 3. Catalytic enantioselective addition of diethylzinc to aldehydes using chiral BIQ ligands

3.1. Introduction

The nucleophilic addition of organozinc reagents to aldehydes (Scheme 58) with total facial discrimination is a very significant reaction.[123] It is a simple method and frequently used to prepare chiral secondary alcohols which are very important in the pharmaceutical and fine chemical industries.[124]



Scheme 58

Numerous chiral catalysts have been applied successfully for the asymmetric addition of dialkylzincs to aldehydes. The most successful catalysts include amino alcohols, diols, diamines and disulfides.[125-127] Among those reactions, asymmetric diethylzinc (Et_2Zn) addition to aldehydes has attracted a lot of attentions since ogunis' first work.[128] Nowadays, this reaction is commonly used to test the potential of new chiral ligands through the addition of Et_2Zn to benzaldehyde to optimize the reaction conditions. Some of the most successful ligands introduced within the last three years for the addition of Et_2Zn to benzaldehyde are mentioned here.

Chiral amino alcohols are probably the most successful and widely used ligands for enantioselective diethylzinc addition to benzaldehyde. The most successful ligands introduced in 2006 are shown in Figure 23. Scarpi used chiral 1,4-aminoalcohol **119** to achieve up to 97% ee.[129] Similar bicyclic 1,2-aminoalcohol **120** was reported by Huang to give ees up to 97%.[130] A variety of chiral C/N functionalized morpholine alcohols were synthesized from serine, among them, ligand **121** gave up to 76% ee.[131] The simple and efficient ligand **122** reported by Roudeau gave up to 98% ee even with a 2 mol% loading.[132] Ahern reported a series of planar chiral *N*,*O*-ferrocenyl pyrrolidine ligands such as ligand **123** which gave ees up to 95%.[133] A 91% ee was reported by Sugiyama when ligand **124** was employed for addition of Et_2Zn to benzaldehyde.[134] Other ligands such as **125**, **126**, **127** and **128** were reported (for the same reaction) to give 62%, 75%, 56% and 95% ee, respectively.[135-138]

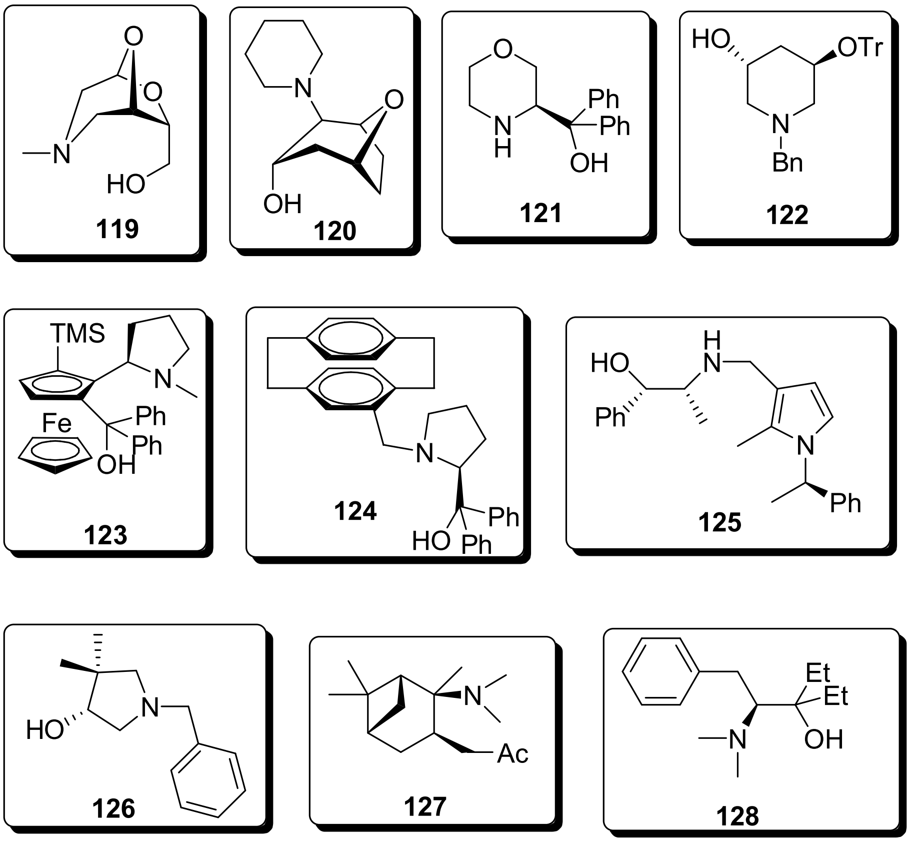


Figure 23

Two efficient and recyclable polymer supported heterogeneous catalysts **129** and **130** were reported by Wang[139] and Kelsen[140] respectively in 2007 and were found to give 63% and 93% ee, respectively. Ferrocenyl substituted aziridinylmethanol **131** and azetidinylmethanol **132** gave the desired product in up to 96% ee and 98% ee.[141,142] Other chiral amino alcohol ligands reported in 2007 including: Zhang's **133**,[143] Paolucci's **134**,[144] Parrott's **135**,[145] Zhang's **136**[146] and Yang's **137**[147]. These ligands gave ees ranging from 59% to 96%.

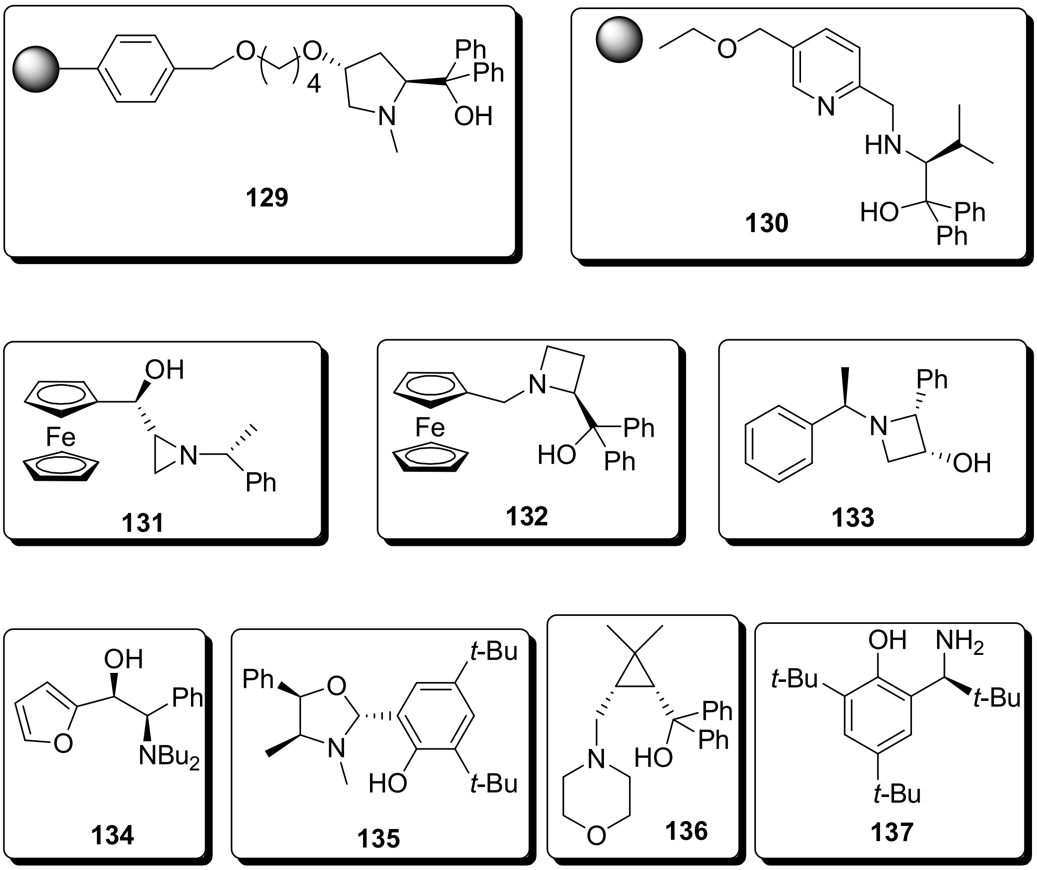


Figure 24

Several amino alcohol ligands were introduced in 2008 (Figure 25). The 3-substituted BINOL ligand **138** gave 87% ee in the addition reaction of Et_2Zn to benzaldehyde.[148] When morphine alkaloid **139** was employed, the alcohol was obtained in up to 89% ee.[149] The monoterpene-based chiral aminodiol **140** reported by Szakonyi[150] gave up to 84% ee while the tridentate aminophenol ligand **141** reported by Yang[151] gave up to 96% ee. In the same year, four bidentate ligands **142**,[152] **143**,[153] **144**[154] and **145**[155] were reported to furnish 80%, 89%, 97% and 98% ee, respectively.

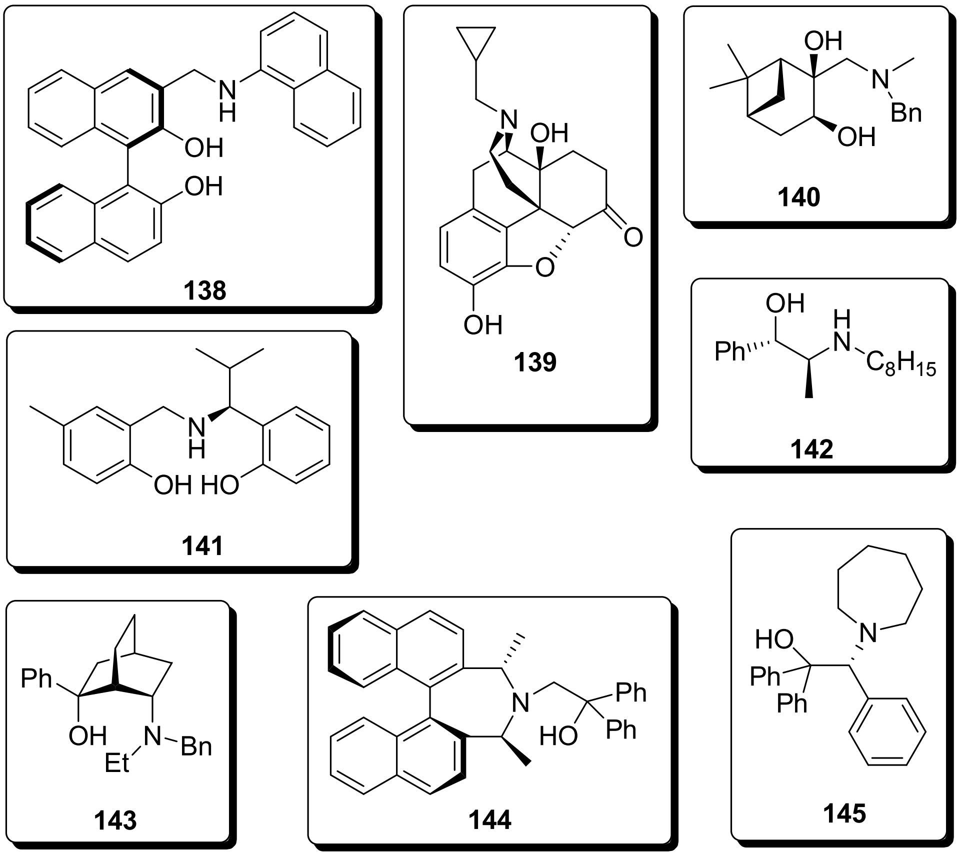


Figure 25

Chiral hydroxy-amides were also used as chiral ligands for the enantiomeric addition of Et_2Zn to benzaldehyde (Figure 26). Tomás reported the synthesis of a camphor-based tertiary-amido isoborneol **146** and found this ligand to give 90% ee of the alcohol.[156] An 86% ee of the alcohol was obtained by Blay when mandelic acid derived amide **147** was used for the same reaction.[157] Ligand **148** synthesized by Hsieh gave 93% ee of the alcohol.[158] Synthesis and application of novel 1,4-aminoalcohols having norbornane backbone was reported by Tanyeli. Among these ligands, ligand **149** gave up to 97% ee.[159] Hatano's ligand **150**, having a 3,3'-substituted BINOL , also gave excellent catalytic results of up to 97% ee.[160]

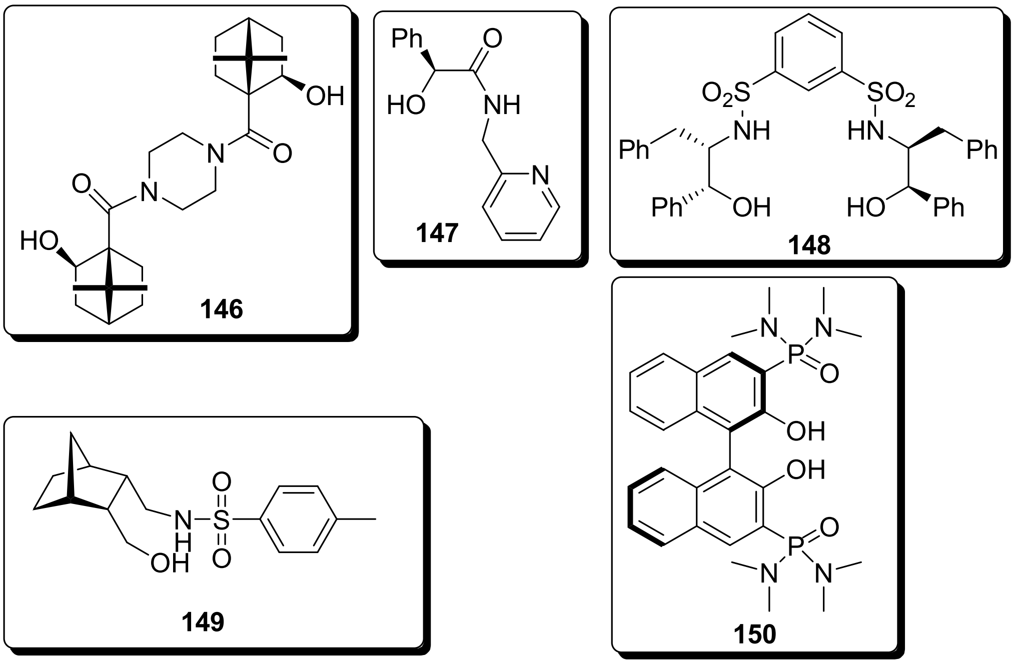


Figure 26

Chiral amino amides were also found to be efficient ligands for the asymmetric addition of diethylzinc to benzaldehyde (Figure 27). Ligand **151** was reported by Javier to give up to 68% ee.[161] José reported ligand **152**, which produced the chiral alcohol in up to 79% ee.[162] Burguete reported ligand **153** which gave the alcohol in up to 99% ee.[163]

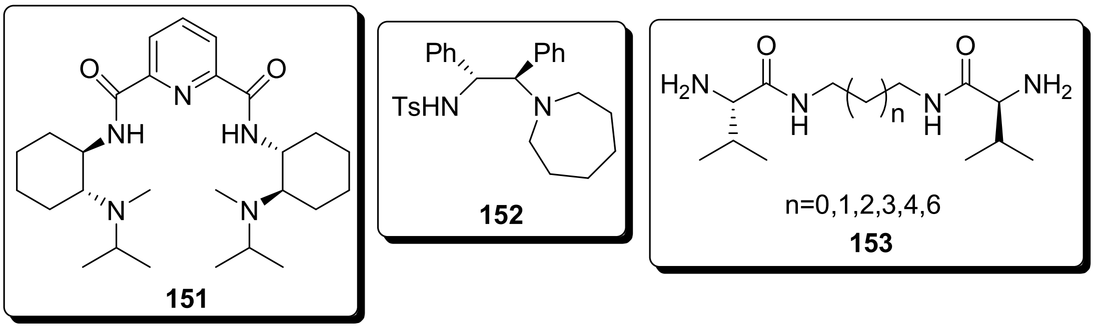
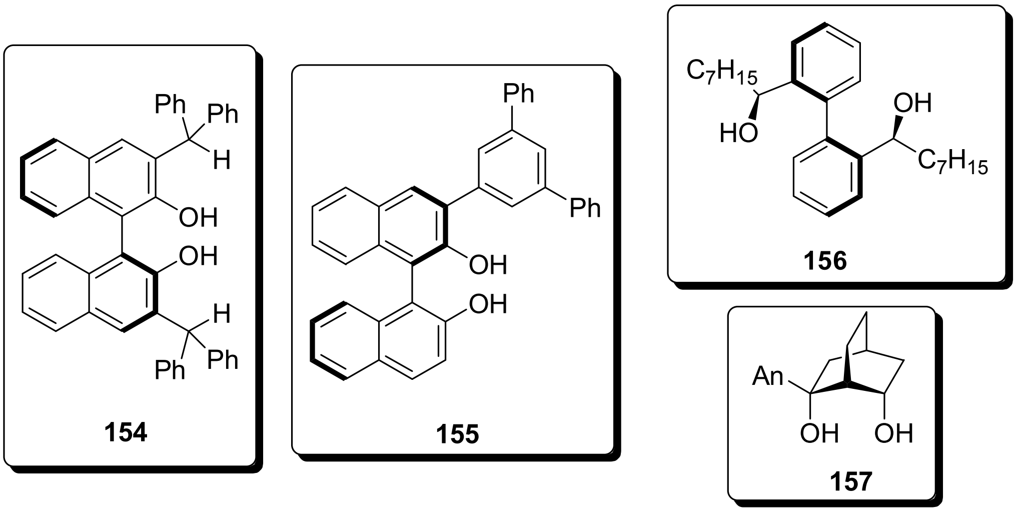


Figure 27

Diols were also frequently used as ligands in the enantiomeric addition of Et_2Zn to benzaldehyde. Some structures of diol ligands are illustrated in Figure 28. A symmetric 3,3'-substituted BINOL ligand **154** and the unsymmetric 3-substituted BINOL ligand **155** were reported by Zhang[164] and Harada,[165] respectively, to give the alcohol in 95% ee. Later, ligand **156** was reported by Omote and was found to give up to 97% ee.[166] Diol **157** reported by Olsson was found to give up to 90% ee.[167]



154 **155** **156** **157**

Figure 28

Other kinds of ligands also showed good enantioselectivity in the addition reaction of Et_2Zn to benzaldehyde (Figure 29). For example, the unsymmetrical chiral bis-sulfonamide **158** gave desired alcohol in 96% ee.[168] The H_4-BINOL ligand **159** reported by Lu gave the alcohol in 82.5% ee.[169] Mastranzo reported a 76% ee using ligand **160**.[170] Moreover, sulfur containing ligands **161** reported by Huang,[171] **162** reported by Grach,[172] **163** reported by Dong,[173] and **164** reported by Braga[174] were found to provide 96%, 90%, 81% and 95% ee, respectively. Notably, ligand (*R*)-**43** reported by Cheng[49] possessed a structure similar to our chiral BIQ ligands (+)-**68** and (-)-**68**. Excellent ee of 93% was obtained when ligand (*R*)-**43** was used.

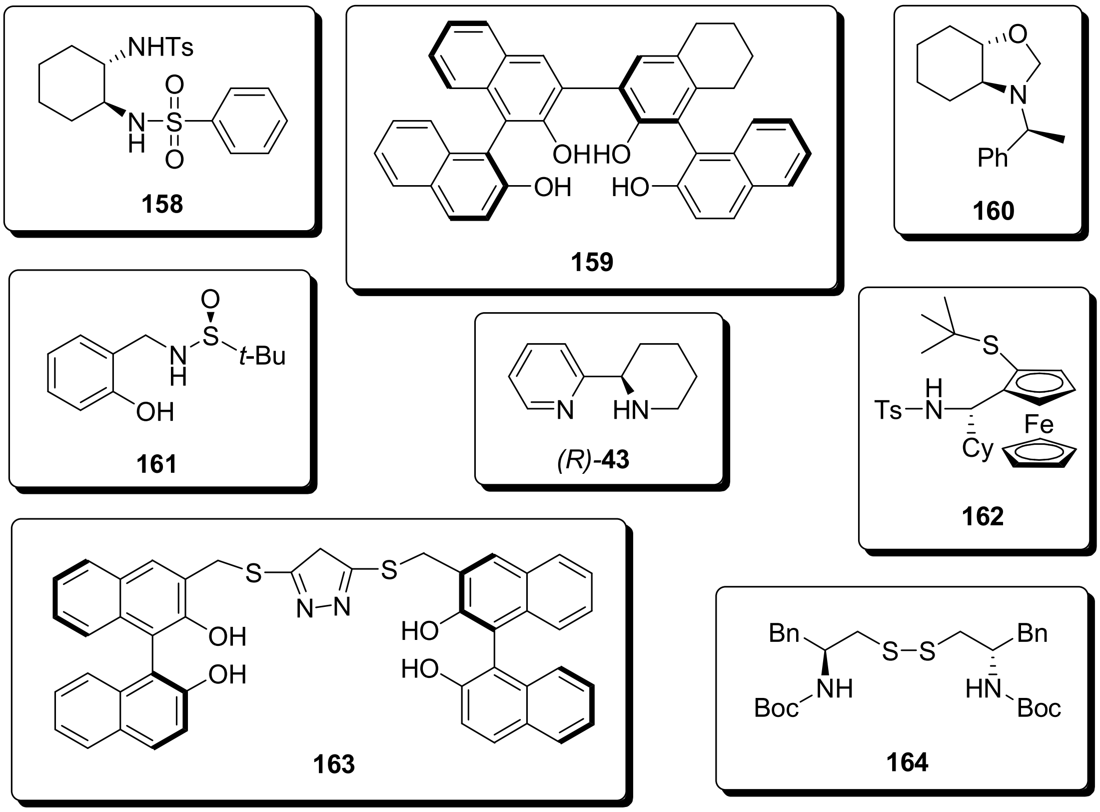


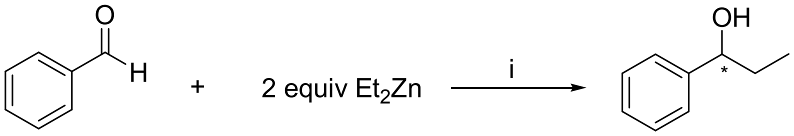
Figure 29

In summary, most of the successful ligands applied in the enantioselective addition of Et_2Zn to benzaldehyde are amino alcohols, hydroxyl-amides, diols and amino amides. Application of chiral BIQ (+)-**68** and (-)-**68** as rare examples of amine-imine type ligands to investigate the catalytic efficiency of this type of ligands in the enantioselective addition of Et_2Zn to aldehydes was thought to be interesting and challenging. Therefore, we set ourselves to fully investigate this reaction in order to develop an efficient alkylation protocol.

3.2. Results and discussion

Initially, several reactions were performed using a general literature procedure[46] to test the feasibility and enantioselectivity of diethylzinc addition to benzaldehyde in presence of chiral ligands (+)-**68** and (-)-**68**. As shown in Table 3, reactions of benzaldehyde **165** with Et_2Zn using (+)-**68** and (-)-**68** gave secondary alcohol **166** in moderate ees of 63% and 61% and moderate yields of 72% and 70% (Table 3, entries 1 and 2). At the same time, (+)-**68** gave the (*R*)-**166** while (-)-**68** gave the complimentary (*S*)-**166** in approximately the same ee indicating no preferential stereoselection and that the transition states are equivalent except for the chirality at the stereocenter i.e. at C1' of chiral BIQ **68**.

Table 3 Diethylzinc addition to benzaldehyde catalyzed by (+)-68 and (-)-68



165 **166**

Conditions: i. Ligand (0.1 equiv), THF:hexane = 1:2, r.t, 20 h

Entry	Ligand	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	(+)-**68**	72	63 (*R*)
2	(-)-**68**	70	61 (*S*)

[a] The yield was determined by GC using HP-5 column.

[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

Based on these promising catalytic results, a series of reactions were conducted to optimize the reaction condition to improve both the ee and yield of the product.

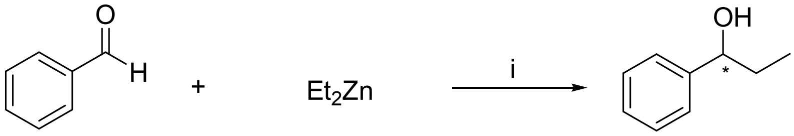
3.2.1. Optimization of reaction conditions

Benzaldehyde was taken as a standard substrate and BIQ (+)-**68** was taken as standard ligand for optimization of the reaction conditions.

3.2.1.1. Effect of amount of diethylzinc

The effect of the amount of diethylzinc was examined first and the catalytic results are listed in Table 4.

Table 4 Effect of amount of Et_2Zn on the addition reaction catalyzed by (+)-68



165 **166**

Conditions: i. (+)-**68** (0.1 equiv), THF:hexane*, r.t, 20 h

Entry	Diethylzinc	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	1 equiv	trace	NA
2	2 equiv	72	63 (*R*)
3	3 equiv	95	73 (*R*)
4	5 equiv	97	64 (*R*)

* 1.0 M Et_2Zn solution in hexane was used, therefore, the solvent ratio of THF:hexane were 1:2, 1:3 and 1:5 accordingly.

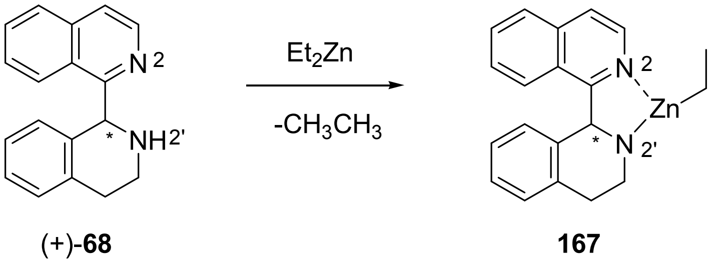
[a] The yield was determined by GC using HP-5 column.

[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

Before discussing the results listed in Table 4, the mechanism of the catalytic reaction was proposed by following the methods reported in literatures[46,49,175,176].

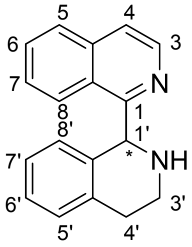
Upon addition of Et_2Zn to (+)-**68**, formation of complex **167** was expected in which Zn covalently bonded to N2' to form Zn-N2' covalent bond and coordinated with N2 to form Zn-N2 coordination bond (Scheme 59).



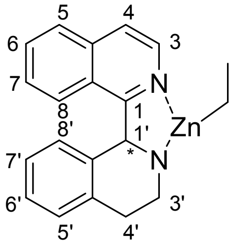
Scheme 59

The formation of complex **167** could be followed by *in situ* ^1H NMR (Table 5). Upon addition of Et_2Zn to an NMR tube containing a sample of (+)-**68** in $CDCl_3$, the NH proton signal at δ 2.44 ppm disappeared immediately, indicating the formation of a Zn-N2' bond. Moreover, a downfield shift of the proton at C1' from δ 6.01 to 6.26 ppm was observed. This shifting was thought due to the formation of Zn-N2' and Zn-N2 bonds as a result of metal complexation with Zn.

Table 5. ^{1}**H NMR data of ligand (+)-68 and complex 167**



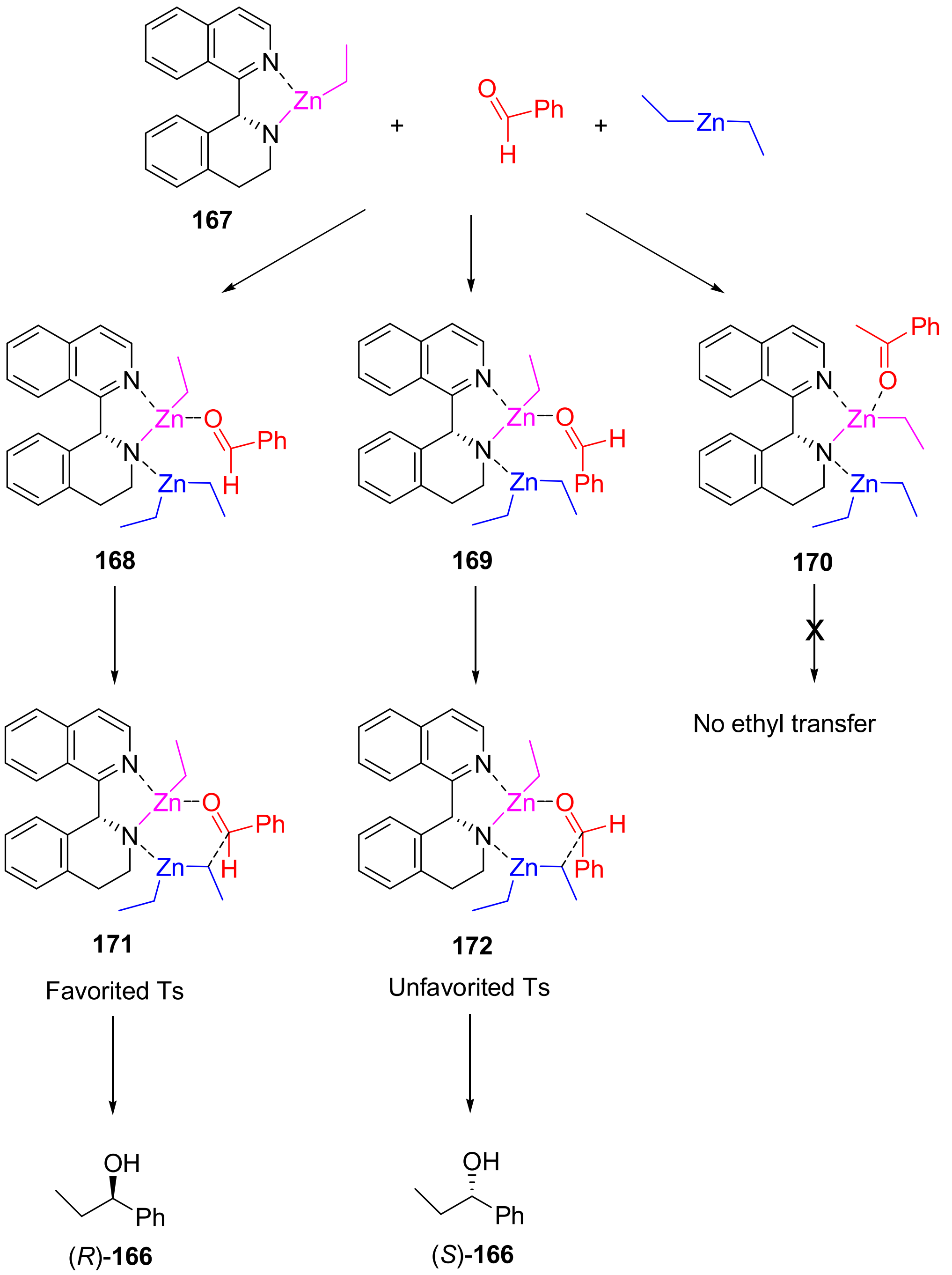
(+)-**68**



167

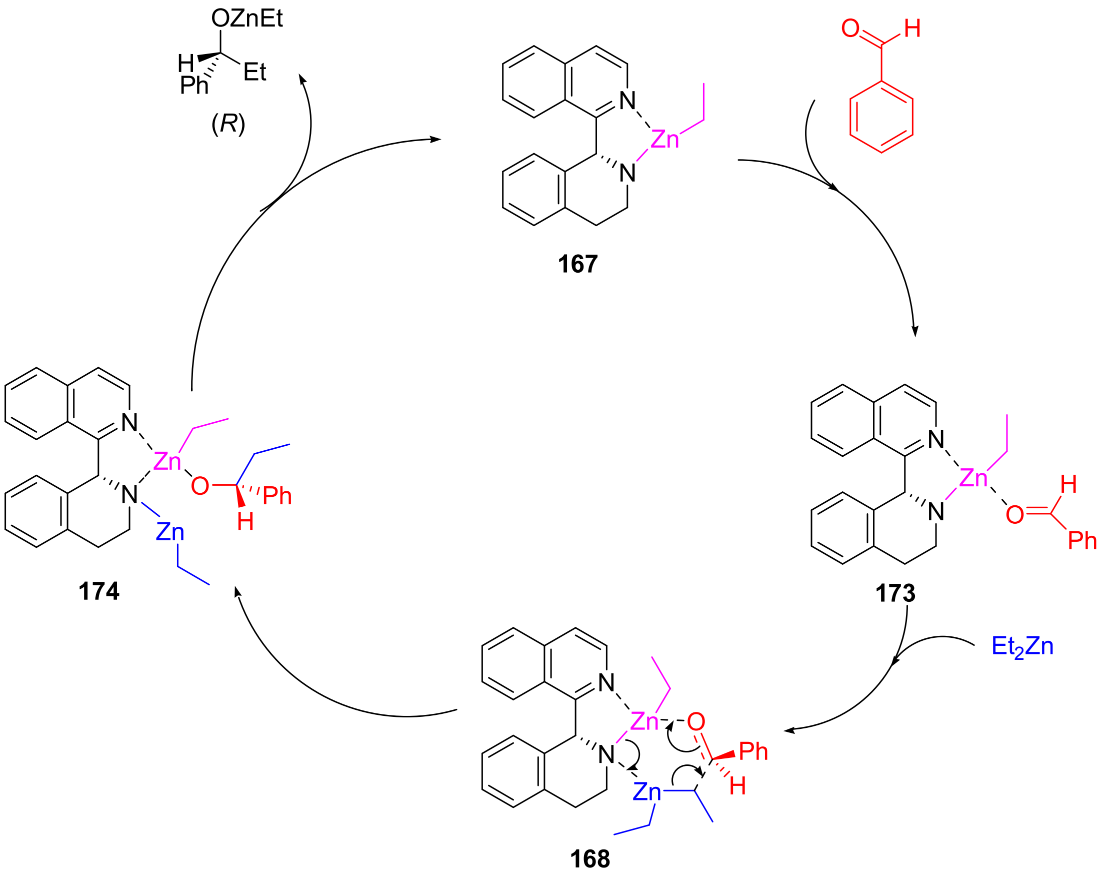
Proton	(+)-**68** δ (ppm)	**167** δ (ppm)
H3	8.50	8.35
H4	7.62	7.82
H5	7.86	7.97
H6	7.54	7.71
H7	7.67	7.89
H8	8.34	8.30
H5'	6.60	6.44
H6'	7.14	7.14
H7'	6.94	6.86
H8'	7.22	7.20
H1'	6.01	6.26

Complex **167** was the actual catalyst which promoted the reactions to proceed. After the formation of the covalent bond with N2', Zn could act as a Lewis acid to activate the carbonyl functionality in benzaldehyde, in the mean time N2' could act as a Lewis base to activate the Et_2Zn. One benzaldehyde molecule approaching Zn as well as one Et_2Zn molecule approaching N2' resulted in three possible intermediates **168**, **169** and **170** (Scheme 60). One of these intermediates, **170** could not undergo the ethyl transformation because of the long distance between activated carbonyl and Et_2Zn (Blue). The other two intermediates could yield the secondary alcohol with opposite configuration through transition state (TS) **171** and **172**. TS **171** was thought to be the favored transition state because the bulky phenyl group located at the *trans* position (here (+)-**68** was assumed to be (*R*) configuration) to Zn could minimize the steric effect to make **171** more stable. TS **172**, on the contrary, was disfavored. Therefore, the product with (*R*) configuration generated from TS **171** was predominant.



Scheme 60

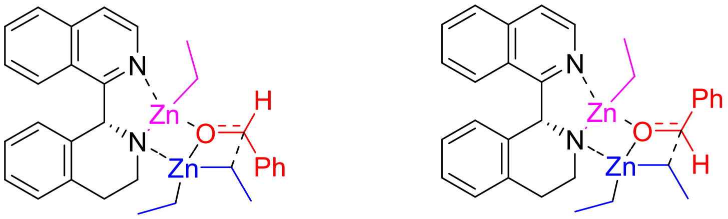
An entire catalytic cycle via favored TS is proposed as shown in Scheme 61. Initially, the carbonyl oxygen atom coordinated with the zinc atom of **167** to form adduct **173**. Then another diethylzinc molecule took part into the reaction to yield intermediate **168** which was responsible for the alkylation reaction. After that, an ethyl group was transferred to the carbonyl carbon through a six- member transition state to yield the intermediate **174**. Finally, **174** regenerated the catalytic chiral complex **167** through elimination of the optically active zinc alkoxide which could further release the corresponding enantiomerically pure alcohol (*R*)-**166** by quenching with weak acid.



Scheme 61

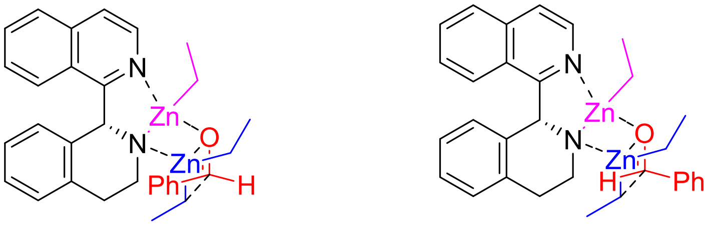
The mechanism of the reaction could also be proposed by adapting the method described by Yamakawa and Noyori.[175,176] Following this mechanism, the first step was still the formation of complex **167**. The reaction then proceeded through two 5/4/4-fused tricyclic transition states (the numbers referred to the size of the rings involved in the process), namely the *anti* tricyclic TS and *syn* tricyclic TS. The terms *anti* and *syn* were used to define the relative disposition of the two terminal rings in the tricyclic TSs. Due to the two different projections of phenyl group in TSs, each of TS could be further differentiated into two TSs, which were *anti-trans* TS **175**, *anti-cis* TS **176**, *syn-cis* TS **177** and *syn-trans* TS

178 as shown in Scheme 62. Comparing with the 5/6 bicyclic transition states discussed before, these tricyclic TSs possessed lower energy which rendered them more stabilities. In this sense, the tricyclic TSs might be closer to the real situation.



175
anti-trans TS

176
anti-cis TS



177
syn-cis TS

178
syn-trans TS

Scheme 62

It was clear that ethyl transfer through **175** or **177** would provide the access to (*S*)-1-Phenyl-1-propanol while ethyl transfer through **176** or **178** would form the (*R*) enantiomer. Among those TSs, the *syn-cis* TS **177** was highly disfavored due to the steric effect between the bulky phenyl and isoquinoline groups. According to the experimental results which showed (*R*) as the dominant configuration, and also considering that the *anti* TSs normally possessed a lower energy than *syn* TSs, the *anti-cis* TS **176** was predicted as the most favored transition state.

As the mechanism of the catalytic reaction was well understood, the discussion of results listed in Table 4 was carried out based on it. It is noteworthy that excess amount of diethylzinc affected the catalytic reaction greatly; comparing the loading of three equivalent of diethylzinc, use of two equivalent of diethylzinc led to lower yield and ee while five equivalent of diethylzinc led to higher yield but lower ee (Table 4, entries 2-4). One possible explanation for this behavior is that more diethylzinc could accelerate the step from **173** to **168** (Scheme 61), thus increasing the reaction rate of the whole cycle to give higher yield under the same reaction time. In the mean time, shortening of the reaction time of the catalytic cycle made efficient use of complex **167** thus higher ee was obtained. Nevertheless, too much excess of diethylzinc could also increase the possibility of uncatalyzed reaction between benzaldehyde and diethylzinc. Consequently, five equivalent of diethylzinc gave higher yield but lower ee. In conclusion, three equivalent of diethylzinc was the best choice to give optimal result.

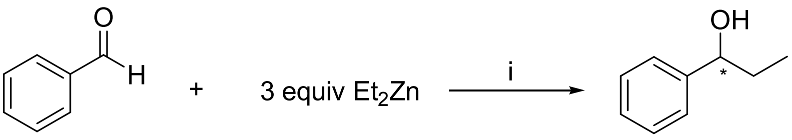
3.2.1.2. Effect of solvent, temperature and reaction time

Optimization of the reaction temperature was carried out in various solvents at different reaction times. The time factor is particularly important since BIQ (+)-**68** was found to be easily oxidized under basic conditions (see Chapter 2, section 2.1.2.1). Therefore, the possibility of ligand (+)-**68** losing its chirality during the course of the reaction due to its oxidation to BIQs **70** and **71** must be considered. If this were the case, a dramatic drop in the ee of the product along with time could be expected. In this project, four solvents: toluene, diethyl ether, THF and EA were chosen. Samples were taken at different reaction time intervals and analyzed to study how solvents and temperature affect the reaction progress.

The addition reactions were performed first in a mixture of toluene/hexane and the results are summarized in Table 6. The effect of reaction temperature with and without using ligand (+)-**68** on the addition of Et_2Zn to benzaldehyde **165** was examined at 50 ^{o}C, r.t., 0 ^{o}C and -40 ^{o}C. The rationale behind finding the reactivity without using ligand (+)-**68** is to probe its activation role at different temperatures. Therefore, aliquots of the reaction mixtures run at different temperatures were taken at different time intervals and both the yield and ee were calculated. When the reaction was performed with ligand (+)-**68** at 50 ^{o}C and aliquots were taken at 0.5 h and 1.5 h and analyzed, alcohol **166** was obtained in almost quantitative yield in 66% ee in both cases (Table 6, entries 1 and 2). When the reaction was performed with (+)-**68** at r.t. and aliquots taken at 12 and 20 h, quantitative yields were also obtained in both cases but a slight decrease (from 66% to 59%, Table 6, entries 5 and 6) in the ee of **166** was observed for the sample collected at 20 h. In the case where the addition reaction was performed at 0 ^{o}C, all samples taken at different reaction time intervals of 1.5, 20 and 30 h gave the same ee of 64% (Table 6, entries 9-11). While the 97% yield of **166** was obtained at 20 and 30 h (Table 6, entries 10 and 11), the sample collected at 1.5 h gave only 58% yield (Table 6, entry 9) indicating a slower reaction rate at 0 ^{o}C that has no effect on the ee of **166**. When the reaction was performed at -40 ^{o}C, a dramatic reduction in both the yields and ees of **166** were observed (Table 6, entries 15-18). Trace amount of **166** was obtained after reaction for 5 or 10 h (Table 6, entries 15 and 16). The best yield of 31% (Table 6, entry 18) was obtained when the reaction was allowed to stir for 40 h where **166** was obtained in 15% ee. If we compared the yields and ees of **166** obtained from reactions carried out at different temperatures, we could conclude (i) the ee of **166** remained almost unchanged at 50 ^{o}C, r.t., and 0 ^{o}C (Table 6, entries 1, 2, 5, 6, 9, 10 and 11) indicating that the temperature change in this range had no effect on the ee of **166**. (ii) the reaction time also had no major effect on the ee of **166**. (iii) at -40 ^{o}C, the yield and ee of compound **166** reduced dramatically which might be due to the low solubility of (+)-**68**/Et_2Zn complex in toluene/hexane solvent at such a low temperature. In fact, when the toluene/hexane solution containing (+)-**68**/Et_2Zn complex was cooled to -40 ^{o}C, white precipitates were observed. This observation suggested that the addition reaction may have proceeded under heterogeneous condition instead of homogeneous condition, thus reducing the yield and ee of **166**.

To understand if (+)-**68** has an activation role; reactions were conducted in its absence at various temperatures and the results (Table 6, entries 3, 4, 7, 8, 12-14, 19 and 20) were compared to those obtained from reactions conducted in its presence (Table 6, entries 1, 2, 5, 6, 9-11 and 15-18). The comparison confirmed the acceleration effect that ligand (+)-**68** had on the conversion of **165** to **166**. For example, if we compared the yields of **166** in Table 6, entries 1 and 3, we found that the yield of **166** obtained using ligand (+)-**68** was about 13 times higher than the yield without the ligand. At 0 °C, the difference was even more pronounced; the yield of **166** in Table 6, entry 9 (using ligand (+)-**68**) was about 57 times higher than that in Table 6, entry 12 (without ligand (+)-**68**). It was also noticed that the reactions at -40 °C (after 20 h, Table 6, entries 17 and 19), showed similar yields with or without the use of ligand (+)-**68**. This observation supported the conclusion that precipitation of (+)-**68**/Et_2Zn complex decreased the efficiency of the catalyst remarkably.

Table 6 Diethylzinc addition to benzaldehyde in toluene/hexane (1:3) at different temperatures



165 **166**

Conditions: i. (+)-**68** (0.1 equiv), toluene:hexane = 1:3

Entry	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	50	0.5	98	66 (*R*)
2		1.5	>99	66 (*R*)
3		0.5[d]	7	-
4		1.5[d]	16	-
5	r.t	12	>99	66 (*R*)
6		20	>99	59 (*R*)
7		12[d]	32	-
8		20[d]	84	-
9	0	1.5	58	64 (*R*)
10		20	97	64 (*R*)
11		30	97	64 (*R*)
12		1.5[d]	1	-
13		20[d]	16	-

14		30[d]	24	-
15	-40	5	trace	NA
16		10	trace	NA
17		20	12	18 (*R*)
18		40	31	15 (*R*)
19		20[d]	12	-
20		40[d]	24	-

[a] The yield was determined by GC using HP-5 column.

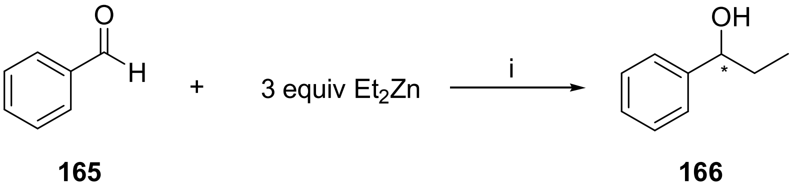
[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

[d] Without ligand.

The reactions performed in a mixture of diethyl ether and hexane at different temperatures with ligand (+)-**68** showed similar trends to those performed in the mixture of toluene and hexane. When the reaction was performed at 50 ^{o}C and aliquots were taken at 0.5 h and 1.5 h, results of analysis showed that alcohol **166** was obtained in quantitative yield and in 56% ee in both cases (Table 7, entries 1 and 2). When the reaction was performed at r.t. and aliquots taken at 3, 20 and 30 h, **166** was obtained in quantitative yield in all cases with 65% ee (Table 7, entry 3-5). When the reaction was performed at 0 ^{o}C, the sample collected after 1.5 h gave **166** in 57% yield and 62% ee only (Table 7, entry 6), however, excellent yields (97% and 98%) and moderate ee of 62% of **166** were obtained at 20 and 30 h intervals (Table 7, entries 7 and 8). The precipitation of the Zn-complex was again observed when the reaction was carried out at -40 ^{o}C, and the expected decreases of the ee and yield (Table 7, entries 9-12) were observed. If the yields and ees of **166** obtained from reactions carried out at different temperatures were compared, a conclusion could be drawn that (i) similar ees were obtained for **166** when the reactions were conducted at temperatures ranging from 0 ^{o}C to r.t.. (ii) a slight decrease of ee of **166** was observed at 50^{o}C and a dramatic decrease of ee and yield of **166** were observed at -40 ^{o}C. (iii) the reactions performed in toluene/hexane or diethyl ether/hexane had similar reaction rates at same temperature. For example, in different solvent systems, the samples at 1.5 h and 0 ^{o}C gave similar yields of 57% (Table 6, entry 9 and Table 7, entry 6) while the samples at 20 h and 0 °C also gave similar yields of 97% (Table 6, entry 10 and Table 7, entry 7).

Table 7 Diethylzinc addition to benzaldehyde in diethyl ether/hexane (1:3) at different temperatures



Conditions: i. (+)-**68** (0.1 equiv), diethyl ether:hexane = 1:3

Entry	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	50	0.5	98	56 (*R*)
2		1.5	>99	56 (*R*)
3	r.t	3	98	65 (*R*)
4		20	>99	65 (*R*)
5		30	>99	66 (*R*)
6	0	1.5	57	64 (*R*)
7		20	97	62 (*R*)
8		30	98	62 (*R*)
9	-40	5	trace	NA
10		10	14	26 (*R*)
11		20	16	24 (*R*)
12		40	25	25 (*R*)

[a] The yield was determined by GC using HP-5 column.

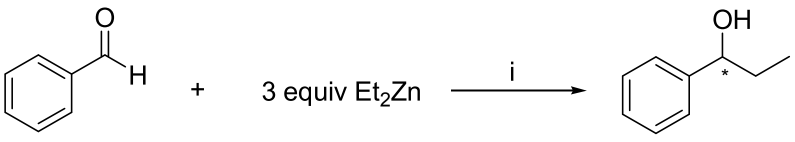
[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

The reactions were then carried out in a mixture of THF and hexane at different temperatures. When the reaction was performed at 50 °C and aliquots were taken at 3 h and 20 h, analysis of results showed that alcohol **166** were obtained in quantitative yield and 61% ee in both cases (Table 8, entries 1 and 2). When the reaction was performed at r.t. and aliquots taken at 3 and 20 h, excellent yields (91% and 98%, respectively) and 73% ee of **166** were obtained in both cases (Table 8, entries 3 and 4). When the reaction was performed at 0 °C, the sample collected after 1.5 h gave **166** in only 26% yield but in a higher ee of 84% (Table 8, entry 5). The samples taken at 20 and 30 h gave **166** in better yields of 81% and 83%, respectively, and in slightly lower ee of 80% in both cases (Table 8, entries 6 and 7). The complex precipitated out again at -40 °C and **166** were obtained in trace amounts and low ees (Table 8, entries 11-14). When comparing the ees of **166** obtained from reactions carried out at different temperatures (except -40 °C), a trend was observed in such a way that when the reaction temperature decreased from 50 °C to r.t to 0°C, the ee of **166** increased from 61% to 73% to 80% irrespective of the time at which the samples are taken (Table, 8 entries 1-7). However, the increase in the ee was accompanied with the decrease in the yield of **166** (Table 8, entries 1-7). To find out an optimum temperature, the reaction was conducted at -10 °C. In this case, product **166** were obtained in similar ees of 82% (compared to reaction at 0 °C) while the drop in the yields of **166** were observed (Table 8, entries 8-10). In order to have a compromise between the yield and ee, reaction should be conducted at 0 °C.

Unlike the solvent systems discussed before (toluene/hexane and diethyl ether/hexane), here the temperature was proved to be an important factor affecting the ee and yield of reaction conducted in a mixture of THF and hexane.

Table 8 Diethylzinc addition to benzaldehyde in THF/hexane (1:3) at different temperatures



165 **166**

Conditions: i. (+)-**68** (0.1 equiv), THF:hexane = 1:3

Entry	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	50	3	>99	61 (*R*)
2		20	>99	61 (*R*)

3	r.t.	3	91	73 (*R*)
4	r.t.	20	98	73 (*R*)
5	0	1.5	26	84 (*R*)
6		20	81	80 (*R*)
7		30	83	80 (*R*)
8	-10	3	23	84 (*R*)
9		20	62	82 (*R*)
10		40	67	81 (*R*)
11	-40	5	trace	NA
12		10	trace	NA
13		20	trace	NA
14		40	9	26 (*R*)

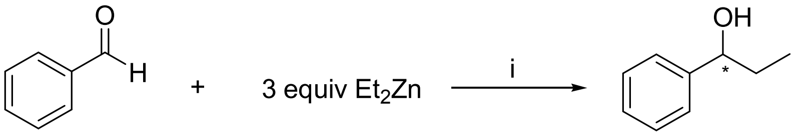
[a] The yield was determined by GC using HP-5 column.

[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

Generally, reactions conducted in a mixture of EA and hexane gave poor yields and ees of **166** (Table 9, entries 1-4). Obviously, EA/hexane was not a suitable solvent system and further investigations were abandoned.

Table 9 Diethylzinc addition to benzaldehyde in EA/hexane (1:3) at different temperatures



165 **166**

Conditions: i. (+)-**68** (0.1 equiv), EA:hexane = 1:3

Entry	Temperature (°C)	Time (h)	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	50	20	99	32 (*R*)
2	-10	3	trace	NA
3		20	20	39 (*R*)
4		40	23	41 (*R*)

[a] The yield was determined by GC using HP-5 column.

[b] The ee was determined by GC using Chiraldex G-TA column.

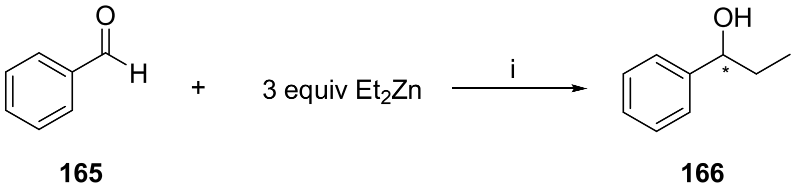
[c] The configuration was determined by comparing the sign of optical rotation value with literature.

In summary, THF/hexane solvent system at 0 °C proved to be the best combination from the viewpoint of yield and ee of product **166**.

3.2.1.3. Loading of ligand

The last but very important factor that needed to be optimized was the ligand loading. To achieve that objective, ligand loadings of 0.01, 0.05, 0.10, 0.15, 0.20, 0.50 and 1.0 equiv (with respect to benzaldehyde **165**) were examined at different time intervals. As the results in Table 10 illustrated, when the loading of ligand (+)-**68** increased from 0.01 to 0.15 equiv, an increase in both the yield and ee of **166** was observed (Table 10, entries 1-11). However, a slight decrease in the ee was observed in some cases when the reaction time was extended (for example Table 10, entries 3-5). A further increase in the loading of (+)-**68** from 0.2 to 0.5 to 1.0 equiv was beneficial for the ee of **166**. However, the increase in ee was accompanied with a decrease in the yield of **166** (Table 10 entries 12-17). Therefore, the loading of ligand was thought to affect the reaction in two ways: previous studies revealed that ligand (+)-**68** could accelerate the reaction rate (pages 94-95), on the other hand, more ligand would consume more Et_2Zn to form the complex thus slowing the reaction rate. At a lower ligand loading (0.01-0.15 equiv), it was believed that acceleration effect was dominant while at a higher ligand loading (0.2-1.0 equiv), deacceleration effect took place. As a consequence, the reaction rate reached a maximum value when 0.15 equiv of ligand (+)-**68** was used. In conclusion, 0.15 equiv was chosen as the best loading amount of ligand (+)-**68** for this reaction.

Table 10 Diethylzinc addition to benzaldehyde with different loading of (+)-68



Conditions: i. (+)-**68**, THF:hexane = 1:3, 0 °C

Entry	Loading of (+)-**68**	Time (h)	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	0.01 equiv	3	6	49 (*R*)
2		30	28	49 (*R*)
3	0.05 equiv	3	33	81 (*R*)
4		10	49	75 (*R*)
5		30	62	72 (*R*)
6	0.10 equiv	1.5	26	84 (*R*)
7		20	81	80 (*R*)
8		30	83	80 (*R*)
9	0.15 equiv	3	74	85 (*R*)
10		10	93	85 (*R*)
11		30	96	84 (*R*)
12	0.20 equiv	3	47	84 (*R*)
13		30	57	82 (*R*)
14	0.50 equiv	3	21	88 (*R*)
15		30	23	89 (*R*)
16	1.00 equiv	3	7	90 (*R*)
17		30	9	90 (*R*)

[a] The yield was determined by GC using HP-5 column.

[b] The ee was determined by GC using Chiraldex G-TA column.

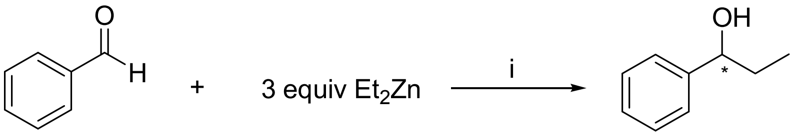
[c] The configuration was determined by comparing the sign of optical rotation value with literature.

3.2.2. Different ligands

After establishing the optimum reaction conditions, BIQ (+)-**68**-based chiral ligands (**86-91** and (+)-**100**~(+)-**118)** along with chiral ligands ((*S,S*)-**32**, (+)-**94** and (+)-**98**) were used in the Et_2Zn addition to benzaldehyde to examine their efficiency. All the reactions were conducted under the optimum conditions obtained above (Table 10, entry 11) and the results were shown in Table 11.

To our surprise, when the reactions were conducted using (+)-**68**-based chiral ligands or other chiral ligands, the yields and ees of **166** dropped dramatically. Most striking is the fact that ligands **86-91**, (+)-**104**~(+)-**106**, (*S,S*)-**32**, (+)-**94** and (+)-**98** gave product **166** in *racemic* form (Table 11, entries 1-6, 11-13 and 26-28). Notably, although all of the derivatives ((+)-**100**~(+)-**118**) had the same configuration as (+)-**68**, but the reactions catalyzed by these derivatives gave (*S*)-**166** as major enantiomer (Table 11, entries 7-25), instead of the (*R*)-**166** obtained using (+)-**68** as ligand.

Table 11 Diethylzinc addition to benzaldehyde in the presence of different ligands



165 **166**

Conditions: i. Ligand (0.15 equiv), THF:hexane = 1:3, 0 °C, 30 h

Entry	Ligand	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	(+)-**86**	25	0
2	(-)-**87**	19	0
3	(+)-**88**	23	0
4	(-)-**89**	21	0
5	(+)-**90**	18	0
6	(-)-**91**	16	0
7	(+)-**100**	26	15 (*S*)
8	(+)-**101**	trace	NA
9	(+)-**102**	35	12 (*S*)
10	(+)-**103**	23	13 (*S*)
11	(+)-**104**	22	0
12	(+)-**105**	15	0
13	(+)-**106**	13	0
14	(+)-**107**	trace	NA
15	(+)-**108**	17	3 (*S*)
16	(+)-**109**	21	6 (*S*)
17	(+)-**110**	22	9 (*S*)
18	(+)-**111**	11	3 (*S*)
19	(+)-**112**	trace	NA
20	(+)-**113**	17	9 (*S*)
21	(+)-**114**	13	10 (*S*)
22	(+)-**115**	trace	NA

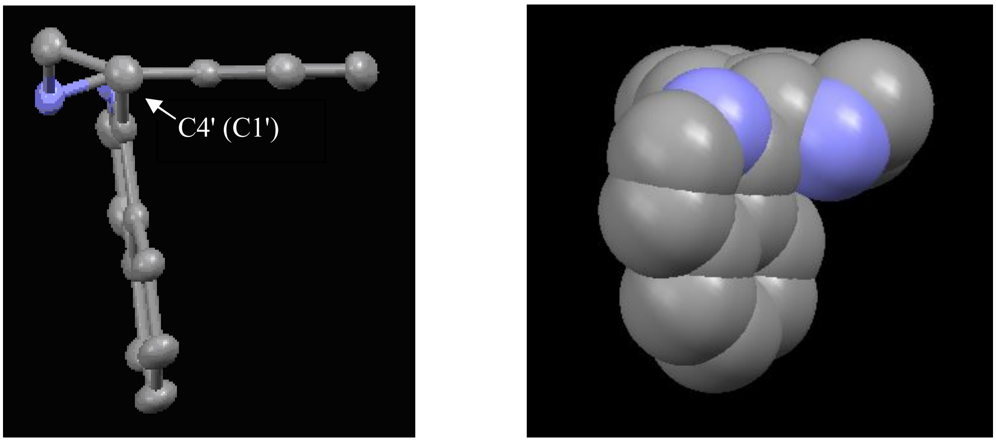
23	(+)-**116**	13	6 (*S*)
24	(+)-**117**	12	7 (*S*)
25	(+)-**118**	16	2 (*S*)
26	(*S*,*S*)-**32**	46	0
27	(+)-**94**	18	0
28	(+)-**98**	15	0

[a] The yield was determined by GC using HP-5 column.

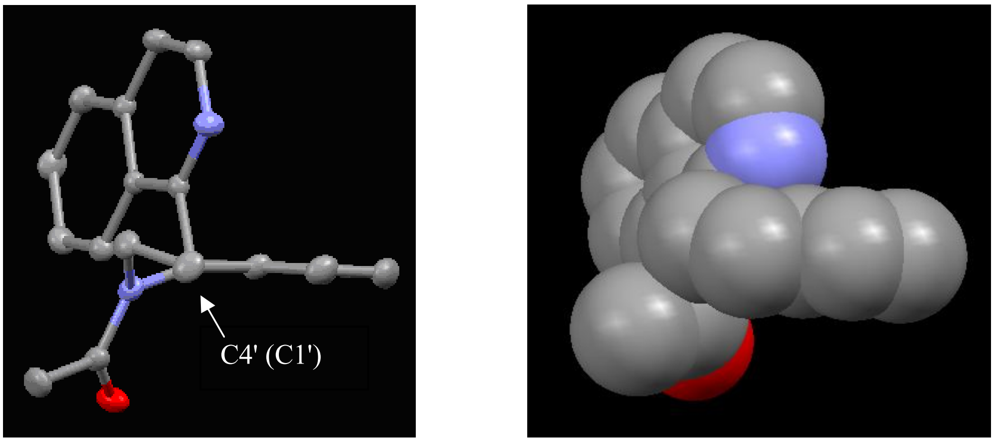
[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

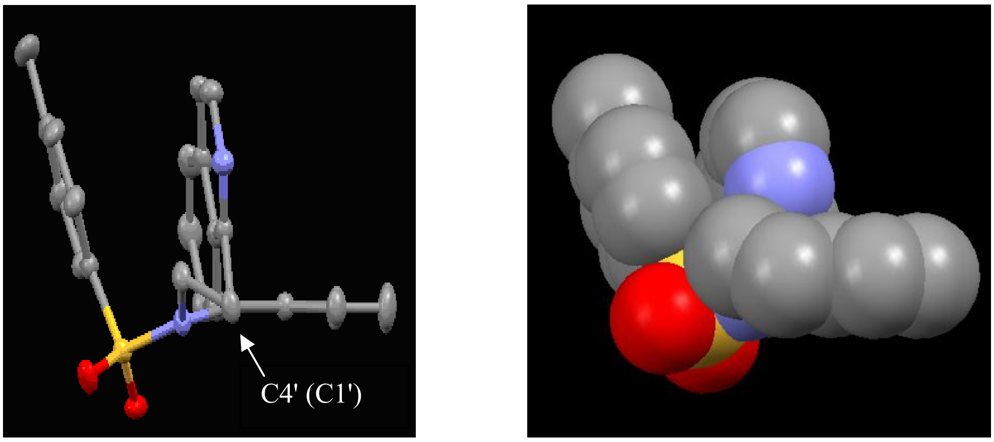
In order to understand the results in table 11, we resided to the structural features of some derivatives and tried to rationalize the results obtained. The ball-stick and space-fill models of the x-ray structures of BIQs **68**, **105** and **106** are shown in Figure 30. For easy visualization, the structures were oriented in such a way that the benzene ring in the tetrahydroisoquinoline part was projecting flat along the viewer's vision while C4' and C1' were in an eclipsed orientation. The consequence of having the isoquinoline ring of BIQs **105** and **106** in an axial orientation resulted in sever crowd at the chiral core area, therefore the coordination of Et_2Zn to the nitrogens was not feasible. It could also be seen from Figures 30 (b) and 30 (c) that N2 and N2' were projecting in such a way that the two nitrogens were not sharing a common space, thus the coordination to both of them was less likely. Consequently, when the ligands (+)-**105** and (+)-**106** were used in enantioselective addition of Et_2Zn to benzaldehyde, they could not form the desired complexes with Et_2Zn to go through the catalytic cycle, hence gave only the *racemic* product **166**. Similar thing could be said about the other ligands **86-91**, (+)-**104**, (*S*,*S*)-**32**, (+)-**94** and (+)-**98** where the extent of Et_2Zn coordination is negligible. Other ligands (+)-**100**, (+)-**102**, (+)-**103**, (+)-**108**~(+)-**111**, (+)-**113**, (+)-**114** and (+)-**116**~(+)-**118** gave very low ees of **166**. In these cases, inefficient coordination of Et_2Zn to the ligands might have resulted in such outcome. This explanation was supported by the fact that in all cases much lower yields of **166** were obtained in comparison to the yields (80%-99%) obtained when (+)-**68** was used. If we recollected from Table 6, uncatalyzed addition reactions proceeded with low yields, thus providing further evidence that the reactions using the ligands mentioned above were probably inefficiently catalyzed.



(a) Ball-stick model and space-fill model of structure BIQ **68**



(b) Ball-stick model and space-fill model of structure BIQ **105**



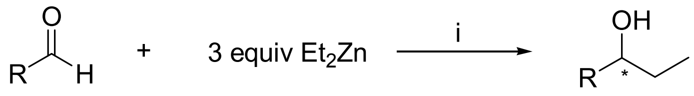
(c) Ball-stick model and space-fill model of structure BIQ **106**

Figure 30

3.2.3. Different substrates

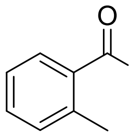
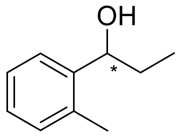
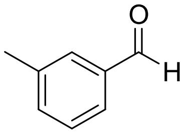
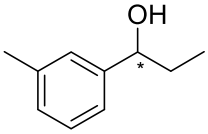
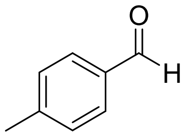
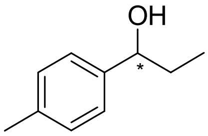
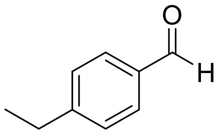
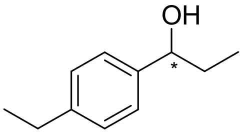
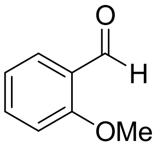
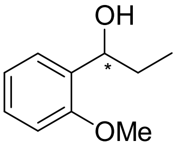
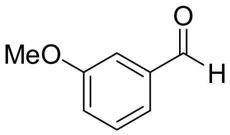
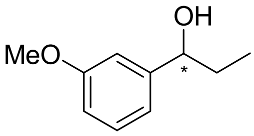
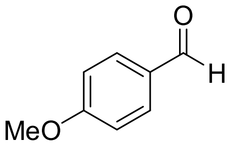
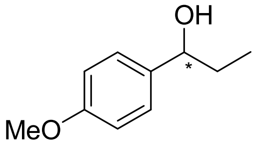
To study the scope and limitation of ligand (+)-**68**, a number of aldehydes (compounds **179-197**) having electron-donating and electron-withdrawing substituents were examined under the optimum conditions (Table 10, entry 11). In general, good yields and enantioselectivities of the secondary alcohols (compounds **198-216**) were obtained (Table 12). The following observation can be made from the results: (i) electron withdrawing substituents (Table 12, entries 8-16) gave better yields and enantioselectivities compared to poor (Table 12, entries 1-4) and strong (Table 12, entries 5-7) electron-donating substituents. (ii) electron-donating and withdrawing substituents at the *ortho*- positions gave better yields and enantioselectivities compared to the same substituents at the *para*- and *meta*- positions while substituents at the *meta*- positions gave better results compared to those at the *para*- positions (see for example Table 12, entries 5-7). (iii) substituents effect was more pronounced at the *ortho*- position due to steric bulkiness that these groups present compared to same *meta*- or *para*- substituents. In support of this fact, doubly substituted aldehyde **194** gave product **213** in the highest yield of >99% and second highest ee of 87% (Table 12, entries 16). Notably, among those *para*-substituted benzaldehydes, 1-pyrrolidinal substituted benzaldehyde **193** gave product **212** in the best ee of 91% and moderate yield of 75% (Table 12, entries 15). Alkylation of 2-naphthaldehydes **195** and cyclohexanecarbaldehyde **197** resulted in 81% and 68% ee, respectively (Table 12, entries 17 and 19, respectively). However, 3-pyridinaldehyde **196** gave product **215** in the lowest ee of 9%. In this case, the pyridine nitrogen might be the cause of this low ee through complexation with Et_2Zn.

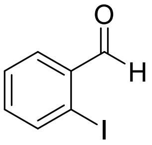
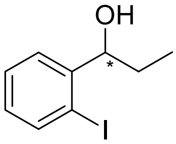
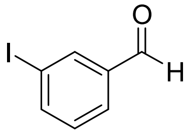
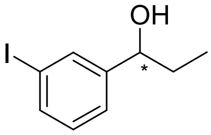
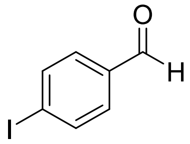
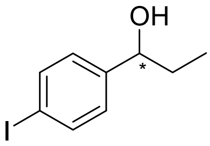
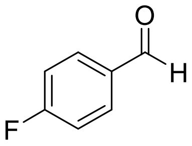
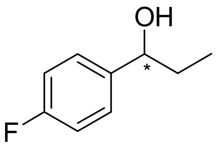
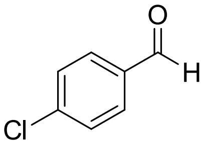
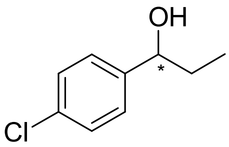
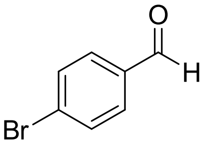
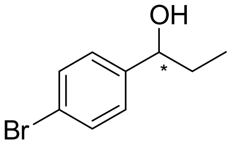
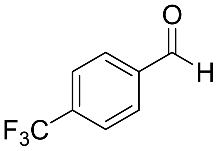
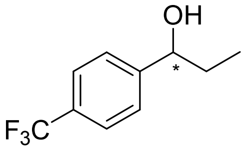
Table 12 Diethylzinc addition to various aldehydes in the presence of (+)-68

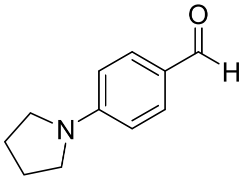
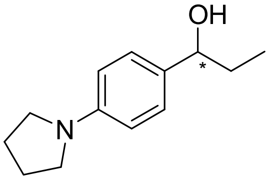
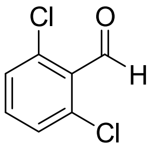
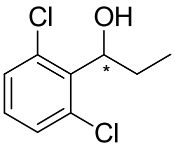
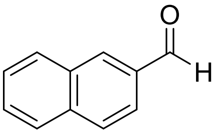
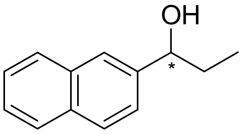
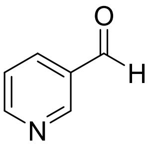
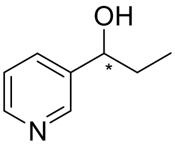
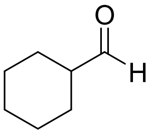
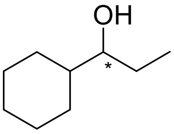


179-197 **198-216**

Conditions: i. (+)-**68** (0.15 equiv), THF:hexane = 1:3, 0 °C, 30 h

Entry	Substrate	Product	Yield[a] (%)	ee[b] (%) (Configuration)[c]
1	 **179**	 **198**	51	70 (*R*)
2	 **180**	 **199**	69	65 (*R*)
3	 **181**	 **200**	17	40 (*R*)
4	 **182**	 **201**	38	71 (NA)
5	 **183**	 **202**	83	74 (*R*)
6	 **184**	 **203**	82	73 (*R*)
7	 **185**	 **204**	51	52 (*R*)

8	 **186**	 **205**	95	73 (NA)
9	 **187**	 **206**	89	80 (NA)
10	 **188**	 **207**	59	66 (NA)
11	 **189**	 **208**	33	61 (*R*)
12	 **190**	 **209**	90	72 (*R*)
13	 **191**	 **210**	52	71 (*R*)
14	 **192**	 **211**	88	72 (*R*)

15	 **193**	 **212**	75[e]	91[f] (NA)
16	 **194**	 **213**	>99	87 (NA)
17	 **195**	 **214**	73[e]	81[f] (*R*)
18	 **196**	 **215**	63[e]	9[f] (*R*)
19	 **197**	 **216**	55	68 (*R*)

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[a] The yield was determined by GC using Chiraldex G-TA column.

[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

[e] Isolated yield.

[f] The ee was determined by HPLC using OD-H column.

In conclusion, chiral compound **68** showed great efficiency in enantioselective addition of diethylzinc to various aldehydes to give desired secondary alcohols in generally excellent yield and good ee (up to 91%) which compared well with the best reported in the literatures. However, the chiral derivatives of **68** were found not efficient for this reaction. Those results were rationalized in terms of solid state structures of several ligands that the conformations of derivatives have prevented the formation of proper complexes to catalyze the reactions.

Chapter 4. Catalytic enantioselective conjugate addition of Grignard reagents to cyclic enones using chiral BIQ ligands

4.1. Introduction

The conjugate addition (1,4-addition) of carbon nucleophiles to *α,β*-unsaturated carbonyl compounds is one of the most widely used methods for the formation of C-C bonds. A tremendous effort was devoted over the last three decades on this reaction because of its importance in synthetic area which has been used as key steps in the synthesis of numerous chiral compounds. This reaction also showed a broad scope because of the large number of donor and acceptor compounds that can be employed.[177]

In catalyzed asymmetric conjugate addition, an *α,β*-unsaturated substrate is attacked by a carbon nucleophile resulting in the formation of a new stereogenic carbon centre. In order to apply this reaction to the synthesis of more complex chiral organic compounds, remarkable efforts have been made to expand the scope of substrates and nucleophiles.[178]

4.1.1. Substrates of asymmetric conjugate addition reactions

4.1.1.1. Cyclic enones

The most widely studied substrate of choice for testing ligands in copper promoted asymmetric conjugate addition reactions is the 6-membered cyclohexenone **218**. There are two main reasons for this selection: 1) Its cyclic structure: avoid the occurrences of the interconversion of *s-cis* and *s-trans* conformations which is a major problem when using acyclic substrates; 2) High reactivity: arising from the conjugated system between the carbonyl group and the double bond in the molecule. In many studies published, this may be the only substrate screened against several ligands. It is also noteworthy to point out that the use of cycloheptenone **219** and cyclooctenone **220** would generally provide higher ee compared to cyclohexenone with same ligands[179].

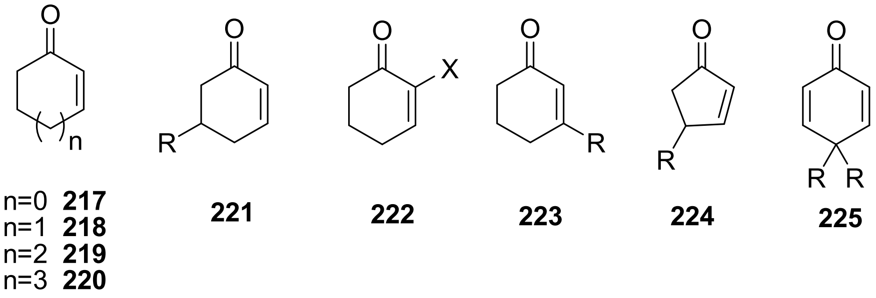


Figure 31

Cyclopentenone **217** has also been studied. However, it generally provide lower ee[180] due to the low steric hindrance since the molecule is almost flat. Moreover, its high reactivity would mean that the resulting enolate intermediate produced in the reaction might react with unreacted cyclopentenone to form more side products, lowering the reaction yield. To overcome this problem, several specialized ligands have been specifically synthesized for the conjugate addition to compound **217**[181].

Other cyclic enones studied include substituted cyclohexenones **221**, **222**, and **223**, substituted cyclopentenones **224** and cyclodienones **225**.

4.1.1.2. Acyclic enones

Not like the cyclic enones, the acyclic enones normally need special ligands to achieve good enantioselectivity in conjugate addition reactions because of the *s*-cis and *s*-trans conformational interconversion of them. The most widely studied substrates include chalcone **226** and related structures bearing two aryl groups. There are a large amount of alkyl-substituted acyclic enones (**227** and **228**), however, those substrates were less studied.

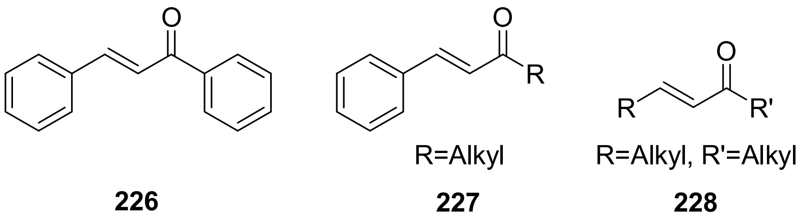


Figure 32

4.1.2. Nucleophiles of asymmetric conjugate addition reactions

4.1.2.1. Diorganozinc as nucleophiles

Diorganozinc reagents have been studied by Alexakis and co-workers in the early 1990s. They showed a viable approach where diorganozinc reagents can be easily undergo conjugate addition reactions in the presence of copper salts.[182] Consequently, considerable progress has been made in this area with the main focus on the design of more effective catalysts.

Phosphorus-containing ligands were found to be most effective for the copper catalyzed conjugate addition reactions with diorganozinc reagents. For diphosphine ligands, the best ee values have been obtained with NORPHOS **229**, CHIRAPHOS **230** and particularly MINIPHOS **231** (Figure 33). The former two ligands both gave 44% ee with enone **218**,[183] whereas ligand **231** afforded up to 97% ee with enone **219**[184].

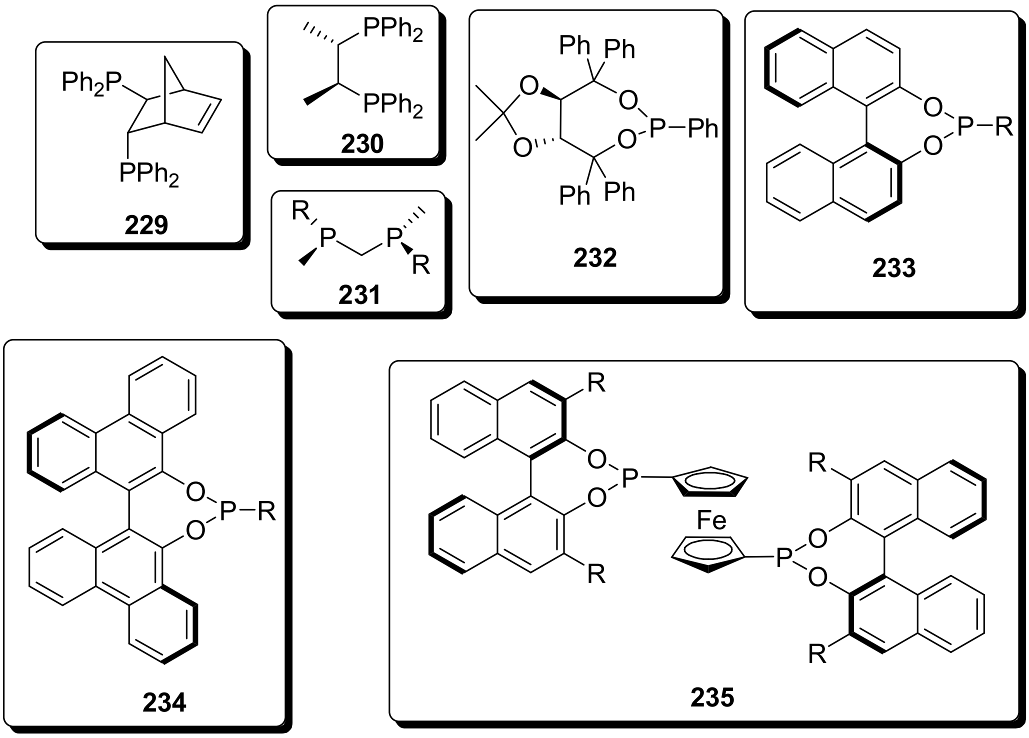
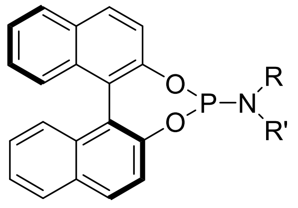


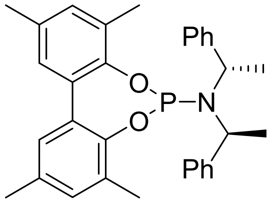
Figure 33

Phosphinite and phosphonite type ligands are scarce and most of them are derived from TADDOL or BINOL. The TADDOL-based ligand **232** gave poor to moderate ees with cyclic or acyclic enones.[185] The BINOL-based monophosphonites **233** and **234** also gave moderate results with cyclic enones (ees up to 41%) but good ee values (up to 82%) with chalcone **226**.[186] It was notable that the bidentate diphosphonites **235**, which combine two BINOL units on a ferrocene backbone, provided excellent enantioselectivities (ees up to 96%) for cyclic enones.[187]

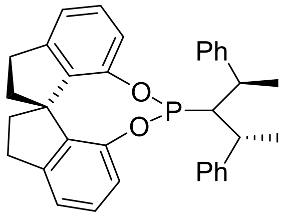
By far the most studied phosphorus ligands are phosphites and phosphoramidites. Among these ligands, BINOL-based phosphites and phosphoramidites ligands **236** are intensely studied. These ligands have provided excellent enantioselectivities with a wide range of substrates.[182,188-196] Recently, the biphenol-type ligands were more frequently used in catalytic conjugate additions than those BINOL-based ones. For example, ligand **237** has provided excellent enantioselectivities with cyclic enones (ees up to >99%).[197] Besides the above ligands, the spiro phosphoroamidite ligands **238**[198] and **239**[199] have been successfully applied to the diethyl zinc addition to cyclic enones (ees up to 98% and 99%, respectively).



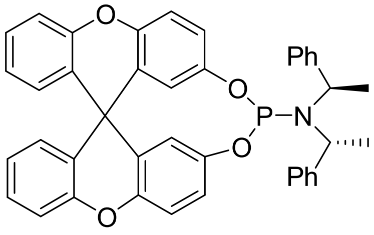
236



237



238



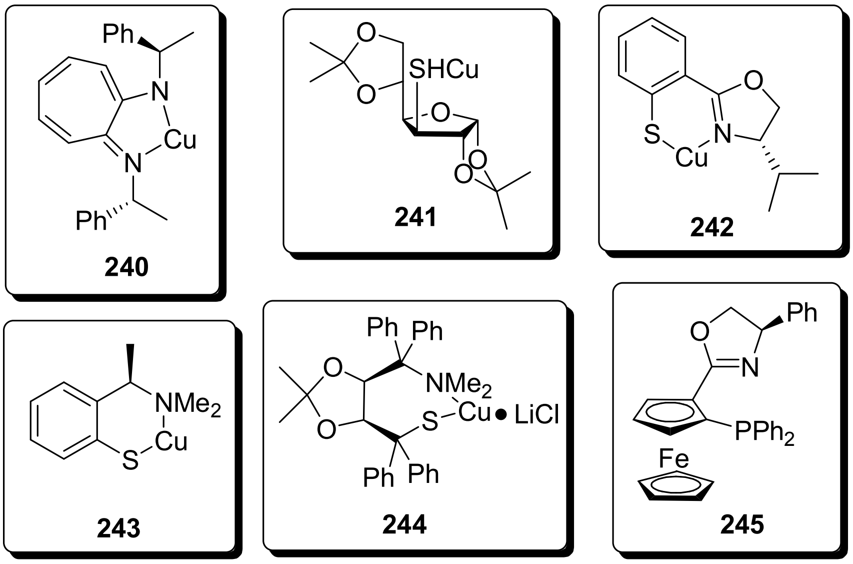
239

Figure 34

Despite the successful examples mentioned above, the main disadvantage of using diorganozinc reagents is that most of these reagents are not readily available commercially and require a separate reaction to synthesize the desired diorganozinc reagent.[200]

4.1.2.2. Grignard Reagents as Nucleophiles

The Grignard compounds is another very important source of alkylating reagent. Because of the very high reactivity of Grignard reagents, conjugate addition of them to *α ,β*-unsaturated carbonyl systems normally lead to the uncatalyzed 1,2- and 1,4-additions. For this reason, the application of Grignard compounds in the copper-catalyzed asymmetric conjugate addition reactions has received less attention comparing with those organozinc reagents. However, due to their obvious advantages, such as ready availability and cheap price, considerable effort has been made to apply Grignard reagents in the copper-catalyzed asymmetric conjugated addition. In many cases, it was noted that the ligands favorable for organozinc reagents additions are not effective for Grignard compounds.[178]



240 **241** **242** **243** **244** **245**

Figure 35

Lippard and co-workers reported the first successful case of conjugate addition of a Grignard reagent to an enone, using a catalytic amount of Cu-amide complex **240**.[201] Subsequently, a variety of catalytic systems, mainly based on Cu-thiolates **241-244**[202-205] and phosphine-oxazoline ligand **245**[206,207], were introduced for the conjugate addition of Grignard reagents. At this stage, the scope of the ligands remained limited and ees infrequently reached the 90% level.

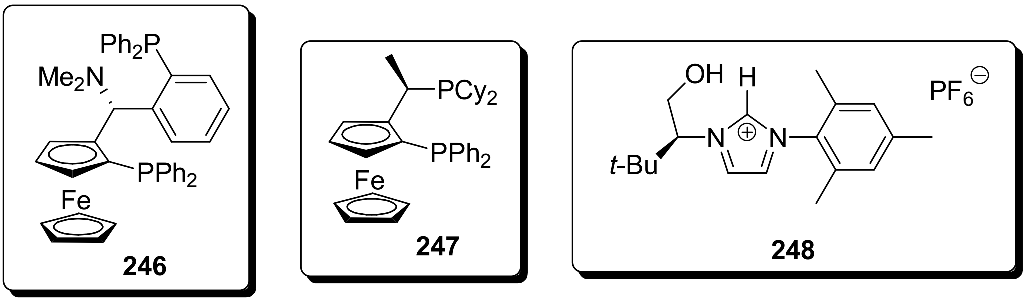


Figure 36

There was a breakthrough in 2004 that Feringa and coworkers applied the chiral diphosphines Taniaphos **246** and Josiphos **247** in conjugate addition of Grignard reagents to enones. These ferrocene-based ligands provided high ees with cyclic enones (ees up to 96%)[208] and acyclic enones (ees up to 98%)[209]. Recently, Alexakis and co-workers reported a successful example of Cu-catalyzed asymmetric conjugate addition of Grignard reagents to *β,β′*-disubstituted enones **223** by using diaminocarbene **248** (ees up to 96%).[210] These catalytic results led the way to the use of Grignard reagents for a highly active and selective copper-catalyzed conjugate addition of a wide range of substrates. In this thesis, the efficiencies of our novel bisisoquinolines ligands were examined on the copper prompted asymmetric conjugate addition of Grignard reagents to cyclic enones.

4.2. Results and discussion

4.2.1. Enantioselective conjugate addition of Grignard reagents to enone 218

4.2.1.1. Optimization of reaction conditions

Ethyl magnesium chloride was taken as the standard Grignard reagent for addition to enone **218** and BIQ (-)-**68** was taken as the standard ligand to perform the optimization.

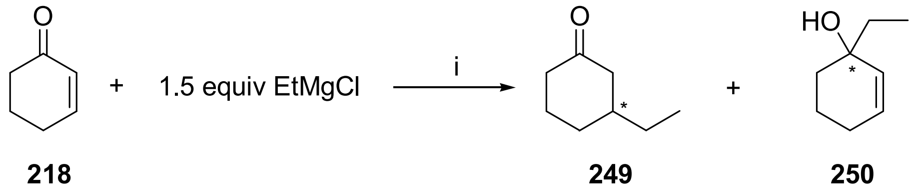
4.2.1.1.1. Effect of metal ions

In conjugate addition of Grignard reagents to cyclic enones, Zn and Cu were most frequently used metal ions. Thus, our optimization was initiated with both metal ions (using $ZnCl_2$ and $Cu(OTf)_2$ as representative salts respectively) to find the best coordinating metal ion. As shown in Table 13, reaction with both $ZnCl_2$/(-)-**68** and $Cu(OTf)_2$/(-)-**68** was completed within 15 min at -90 °C to give a mixture of 1,4-adduct **249** and 1,2-adduct **250** (Table 13, entries 2 and 4). Compared to the reaction using $ZnCl_2$/(-)-**68,** the reaction with $Cu(OTf)_2$/(-)-**68** provided better regioselectivity (ratio of **249**/**250**: 87/13 *vs* 84/16) and enantioselectivity (22% ee *vs* 2% ee) of desired product **249**.

Two benchmark reactions were performed without ligand (-)-**68** to investigate the influence of the ligands on the regioselectivity of the products (Table 13, entries 1 and 3). The results showed that ligand (-)-**68** could favor the formation of the desired 1,4-adduct **249**. For example, the reaction with $Cu(OTf)_2$ gave the mixture of **249**/**250** in ratio of 74/26; while when $Cu(OTf)_2$/(-)-**68** was used, the ratio of **249**/**250** increased to 87/13 (Table 13, entries 3 and 4).

In conclusion, copper ion was favored metal ion to coordinate with ligand (-)-**68** to catalyze the enantioselective conjugate addition of EtMgCl to enone **218**.

Table 13 Effect of metal ions on the conjugate addition of EtMgCl to enone 218



Conditions: i. Salt (0.1 equiv) with or without (-)-**68** (0.1 equiv), THF, -90 °C, 15min

Entry	Catalyst	Conversion[a] %	**249/250**[b]	ee[c] (%) (Configuration)[d]
1	$ZnCl_2$	>99	69/31	-
2	$ZnCl_2$/(-)-**68**	>99	84/16	2 (*S*)

3	$Cu(OTf)_2$	>99	74/26	-
4	$Cu(OTf)_2$/(-)-**68**	>99	87/13	22 (*S*)

[a] The conversion was determined by GC using HP-5 column.

[b] The ratio of **249**/**250** was determined by GC using HP-5 column.

[c] The ee was determined by GC using Chiraldex G-TA column.

[d] The configuration was determined by comparing the sign of optical rotation value with literature.

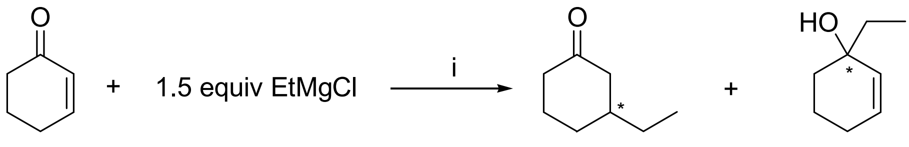
4.2.1.1.2. Effect of different Cu salts

Having confirmed that copper ion was the preferred metal ion for enantioselective conjugate addition of EtMgCl to enone **218**, the effects of various copper sources such as CuI, $CuCl_2$, and $Cu(AcAc)_2$ were investigated (Table14). All reactions were completed within 15 min at -90 ^{o}C. Moreover, the reactions using CuI and $Cu(AcAc)_2$ (Table 14, entries 1 and 3) gave products with similar moderate regioselectivity (with the ratio of **249**/**250** as 81/19 and 82/18, respectively) and poor enantioselectivity (4% and 7% ee of **249**, respectively). In comparison, the reaction performed with $CuCl_2$ (Table 14, entry 2) gave an enhanced regioselectivity (with the ratio of **249**/**250** as 89/11) with an ee of 35%.

Great difference in copper(I) and copper(II) in terms of the ee values can be observed with the reaction preferring Cu(II) (35% ee) rather than Cu(I) (4% ee). Comparing the differences between $Cu(OTf)_2$, $CuCl_2$ and $Cu(AcAc)_2$ (Table 13, entry 4 and Table 14, entries 2, 3), it is reasonable to infer that bulkiness of the counter anion might have an effect on the efficiency of the metal salt used.

In conclusion, $CuCl_2$ was chosen as the most suitable copper salt for catalyzing the enantioselective conjugate addition of EtMgCl to enone **218**.

Table 14 Effect of different Cu salts on the conjugate addition of EtMgCl to enone 218



218 **249** **250**

Conditions: i. Cu salt (0.1 equiv), (-)-**68** (0.1 equiv), THF, -90 ^{o}C, 15 min

Entry	Cu source	Conversion[a]	**249/250**[b]	ee[c] (%) (Configuration)[d]
1	CuI	>99	81/19	4 (*S*)
2	$CuCl_2$	>99	89/11	35 (*S*)
3	$Cu(AcAc)_2$	>99	82/18	7 (*S*)

[a] The conversion was determined by GC using HP-5 column.

[b] The ratio of **249**/**250** was determined by GC using HP-5 column.

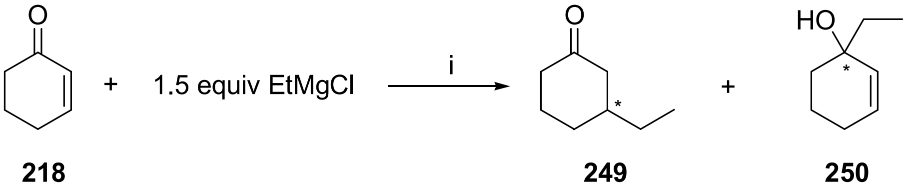
[c] The ee was determined by GC using Chiraldex G-TA column.

[d] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.1.1.3. Effect of temperature and solvent

Optimization of the reaction temperature was carried out in typical coordinating solvents (THF and Et_2O) and non-coordinating solvents (toluene and CH_2Cl_2) (Table 15)., Surprisingly, reactions using Et_2O or toluene gave *racemic* product **249** (Table 15, entries 4-7). In comparison, reactions in THF and CH_2Cl_2, gave product **249** in moderate ees at -90 °C (35% and 28% respectively, Table 15, entries 3 and 9) but in *racemic* form (Table 15, entry 1 and 8) or very low ee (3%, Table 15, entry 2) at higher temperature. Moreover, the reaction in THF showed much better regioselectivity than the reaction in CH_2Cl_2 (the ratio of **249**/**250**: 89/11 *vs* 68/32), Thus, the best solvent was inferred to be THF and the reaction temperature is -90 °C.

Table 15 Effect of solvent and temperature on the conjugate addition of EtMgCl to enone 218



Conditions: i. $CuCl_2$ (0.1 equiv), (-)-**68** (0.1 equiv), 15 min

Entry	Solvent	Temperature (°C)	**249/250**[a]	ee[b] (%) (Configuration)[c]
1	THF	r.t	100/0	0
2	THF	-30	100/0	3 (*S*)

3	THF	-90	89/11	35 (*S*)
4	Et_2O	-30	99/1	0
5	Et_2O	-90	95/5	0
6	toluene	-30	98/2	0
7	toluene	-90	91/9	0
8	CH_2Cl_2	-30	76/24	0
9	CH_2Cl_2	-90	68/32	28 (*S*)

[a] The ratio of **249**/**250** was determined by GC using HP-5 column.

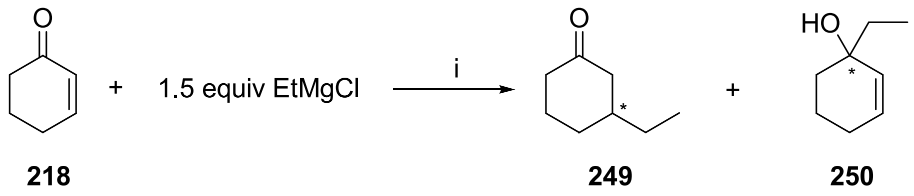
[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.1.1.4. Loading of catalyst

Loading of catalyst was another factor to be optimized. Reactions with different loading of $CuCl_2$/(-)-**68** as 0.05, 0.10, 0.15, 0.20 and 1.0 equiv (with respect to enone **218**) were carried out in THF at -90 °C (Table 17). An increase of $CuCl_2$/(-)-**68** from 0.05 to 1.0 equiv, resulted in an increase of the ratio of **249/250** from 89/11 to 100/0. This observation agreed with the conclusion that ligand (-)-**68** had positive influence on the regioselectivity of 1,4-adduct **249**. However, the highest ee of **249** (35%, Table 17, entry 2) was observed when 0.10 equiv of $CuCl_2$/(-)-**68** was used; higher or lower catalyst loading afforded inferior ees (13-24%, Table 17, entries 1 and 3-5). Thus 0.10 equiv was chosen as the best loading amount of $CuCl_2$/(-)-**68** for this reaction.

Table 17 EtMgCl conjugate addition to enone 218 with different loading of $CuCl_2$/(-)-68



Conditions: i. $CuCl_2$/(-)-**68** (1:1), THF, -90 °C, 15 min

Entry	$CuCl_2$/(-)-**68** (1:1) (equiv)	**249/250**[a]	ee[b] (%) (Configuration)[c]
1	0.05	89/11	24 (*S*)

2	0.10	89/11	35 (*S*)
3	0.15	97/3	14 (*S*)
4	0.20	97/3	13 (*S*)
5	1.00	100/0	13 (*S*)

[a] The ratio of **249**/**250** was determined by GC using HP-5 column.

[b] The ee was determined by GC using Chiraldex G-TA column.

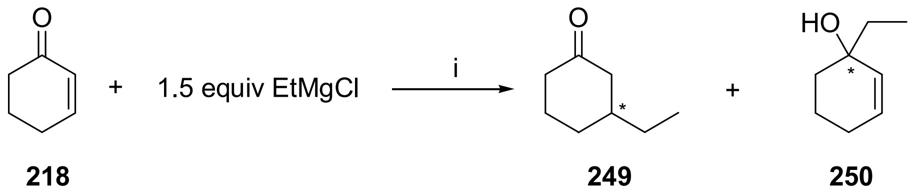
[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.1.2. The use of different ligands

After the optimum reaction conditions were established, other chiral ligands in hands were examined in conjugate addition of EtMgCl to enone **218** (Table 18). The reaction using ligand (+)-**68** gave 1,4-adduct **249** in 24% ee with the major enantiomer as (*R*) (Table 18, entry 1). Interestingly, the reactions using ligand (+)-**100** and (+)-**102** gave product **249** in 10% and 8% ee respectively but with the major enantiomer having the (*S*) configuration (Table 18, entries 2 and 3). The same phenomenon was observed when those ligands were used in enantioselective addition of diethylzinc to benzaldehyde (Chapter 3, Table 11).

Disappointedly, when using *N*-benzyl derivative (+)-**103**, amides (+)-**105** and (+)-**106**, ureas (+)-**107**~(+)-**111**, thioureas (+)-**112**~(+)-**111** and (*S,S*)-**32** as ligands, only *racemic* products were obtained (Table 18, entries 4-19). Those results might have arisen due to inefficient coordination of $CuCl_2$ and Grignard reagent to the ligands which had been discussed in Chapter 3 (Chapter 3, page 105 and 106).

Table 18 EtMgCl conjugate addition to enone 218 in the presence of different ligands



Conditions: i. $CuCl_2$ (0.1 equiv), ligand (0.1 equiv), THF, -90 °C, 15 min

Entry	Ligand	**249/250**[a]	ee[b] (%) (Configuration)[c]
1	(+)-**68**	93/7	24 (*R*)

2	(+)-**100**	98/2	10 (*S*)
3	(+)-**102**	94/6	8 (*S*)
4	(+)-**103**	82/18	0
5	(+)-**105**	80/20	0
6	(+)-**106**	77/23	0
7	(+)-**107**	84/16	0
8	(+)-**108**	85/15	0
9	(+)-**109**	78/22	0
10	(+)-**110**	68/32	0
11	(+)-**111**	79/21	0
12	(+)-**112**	85/15	0
13	(+)-**113**	83/17	0
14	(+)-**114**	87/13	0
15	(+)-**115**	87/13	0
16	(+)-**116**	89/11	0
17	(+)-**117**	78/22	0
18	(+)-**118**	85/15	0
19	(*S*,*S*)-**32**	87/13	0

[a] The ratio of **249**/**250** was determined by GC using HP-5 column.

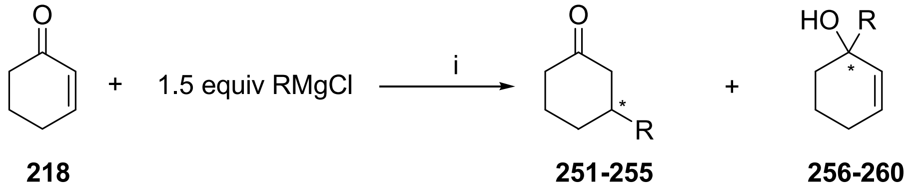
[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

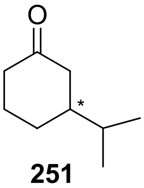
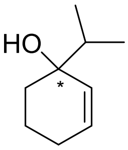
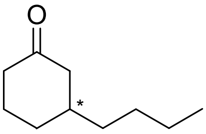
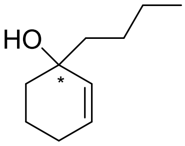
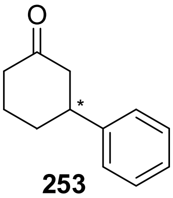
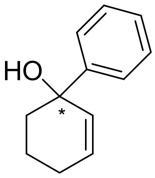
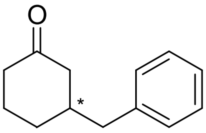
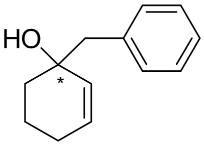
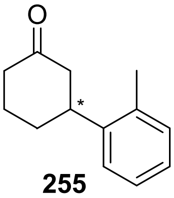
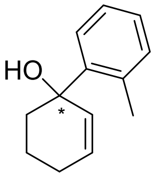
4.2.1.3. Use of different Grignard reagents

Several Grignard reagents besides EtMgCl were added to enone **218** under optimum conditions to study the scope and limitation of ligand (-)-**68**. In general, good regioselectivities of the desired 1,4-adducts (compounds **251**-**255**) were obtained in all cases. Out of all the Grignard reagents tested, only BuMgCl gave 1,4-adduct **252** in significant ee (35%, Table 19, entry 2) while *i*-PrMgCl gave 1,4-adduct **251** in a low ee (8%, Table 19, entry 1) and the rest of the Grignard reagents such as PhMgCl, BnMgCl and *o*-tolylMgCl provided only *racemic* products (Table 19, entries 3-5). Those results indicated that the bulkiness of alkyl substituents in the Grignard reagents affected the ees of products significantly. The Grignard reagents with small groups such as Et and Bu gave the products in highest ee, while bulkier groups (*i*-Pr, Ph, Bn and *o*-tolyl) gave negligible ee or racemic products.

Table 19 Conjugate addition to enone 218 catalyzed by $CuCl_2$/(-)-68 using different Grignard reagents



Conditions: i. $CuCl_2$ (0.1 equiv), (-)-**68** (0.1 equiv), THF, -90 °C, 15 min

Entry	1,4-adduct	1,2-adduct	1,4-adduct /1,2-adduct[a]	ee[b] (%) (Configuration)[c]
1	 **251**	 **256**	90/10	8 (*S*)
2	 **252**	 **257**	100/0	35 (*S*)
3	 **253**	 **258**	91/9	0
4	 **254**	 **259**	100/0	0
5	 **255**	 **260**	100/0	0

[a] The ratio of 1,2-adduct/1,4-adduct was determined by GC-Mass using HP-5 column.

[b] The ee was determined by GC using TBDAc column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.1.4. Proposed mechanism

The mechanism of catalytic reaction was proposed by following the methods reported in the literature[177,180] and the catalytic cycle *via* favored TS was depicted as shown in Figure 37.

Firstly, ligand (-)-**68** was coordinated with $CuCl_2$ to form the chiral Cu complex **261** (here (-)-**68** was assumed to be (*S*) configuration). The next step should be the alkyl transfer from the Grignard reagent to complex **261** to generate the Cu complex **262**. Then, a molecule of enone **218** which was activated by another molecule of Grignard reagent approaches complex **262** to yield intermediate **263** (Cu-olefin π-complex). Finally, TS **263** regenerated the catalytic chiral complex **261** through elimination of the optically active magnesium alkoxide which could further release the corresponding enantiomerically pure 1,4-adduct by quenching with weak acid.

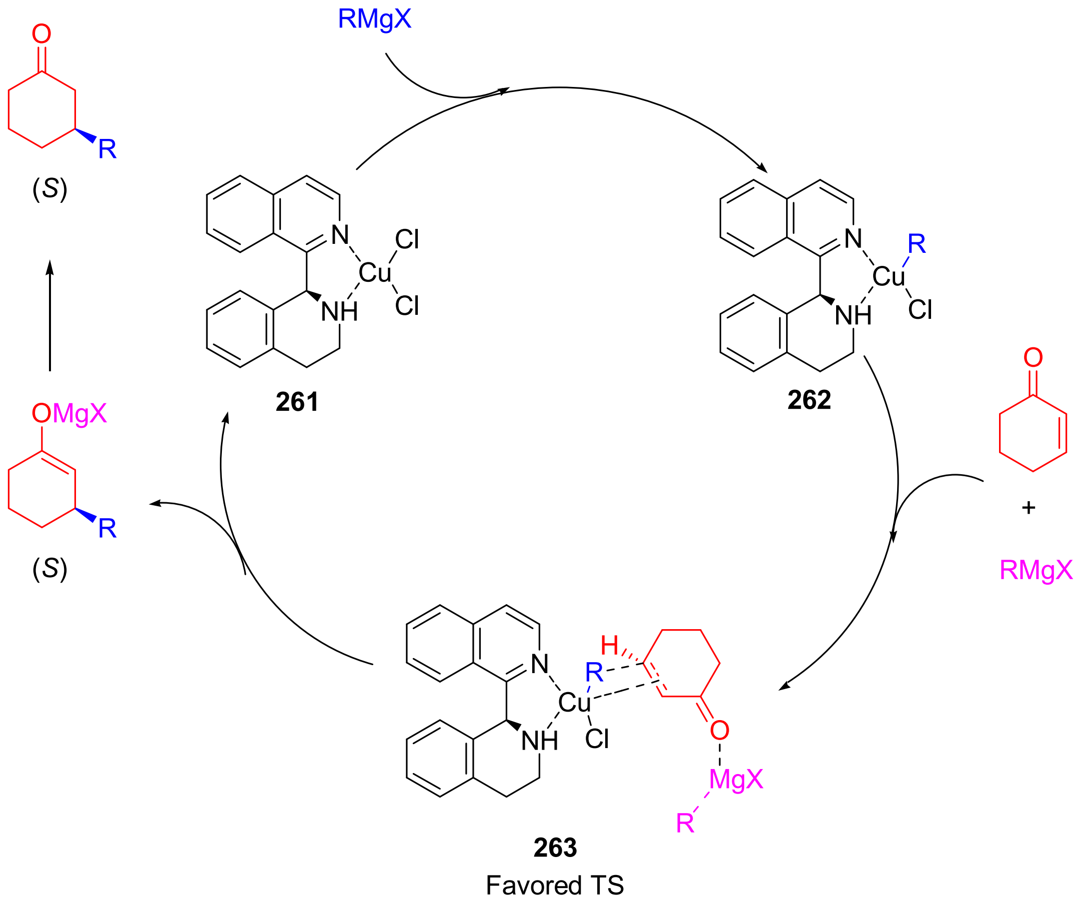


Figure 37

4.2.2. Enantioselective conjugate addition of Grignard reagents to enone 217

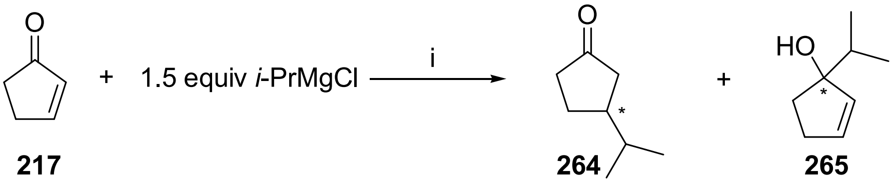
4.2.2.1. Optimization of reaction conditions

Isopropyl magnesium chloride was taken as the standard Grignard reagent for addition to enone **217** and BIQ (-)-**68** was taken as the standard ligand to perform the optimization.

4.2.2.1.1. Effect of solvent

The effect of solvent on the enantioselective conjugate addition of *i*-PrMgCl to enone **217** was examined using four different solvents: CH_2Cl_2, toluene, Et_2O and THF (Table 20). The results showed that reactions in CH_2Cl_2 and THF gave the desired 1,4-adduct **264** in much better ees (17% and 23% respectively, Table 20, entries 1 and 4) than those of reactions in toluene and Et_2O (2% and 5% respectively, Table 20, entries 2 and 3). Reaction using THF showed the highest regioselectivity of product **264** (ratio of **264**/**265**: 90/10) followed by reactions in toluene and CH_2Cl_2 (ratio of **264**/**265**: 85/15 and 86/14 respectively) while Et_2O gave the lowest regioselectivity of **264** (ratio of **264**/**265**: 65/35). Those observations indicated that the reaction was not affected by the coordination effects of the solvent as THF and Et_2O are strongly coordinating solvents while toluene and CH_2Cl_2 are non-coordinating solvents. THF was selected as the solvent of choice since it provided the highest ee and regioselectivity of desired product **264**.

Table 20 Effect of solvent on the conjugate addition of *i*-PrMgCl to enone 217



Conditions: i. $Cu(OTf)_2$ (0.1 equiv), (-)-**68** (0.1 equiv), -90 °C, 15 min

Entry	Solvent	**264/265**[a]	ee[b] (%) (Configuration)[c]
1	CH_2Cl_2	86/14	17 (*S*)
2	Toluene	85/15	2 (*S*)

3	Et_2O	65/35	5 (*S*)
4	THF	90/10	23 (*S*)

[a] The ratio of **264**/**265** was determined by GC using Chiraldex G-TA column.

[b] The ee was determined by GC using Chiraldex G-TA column.

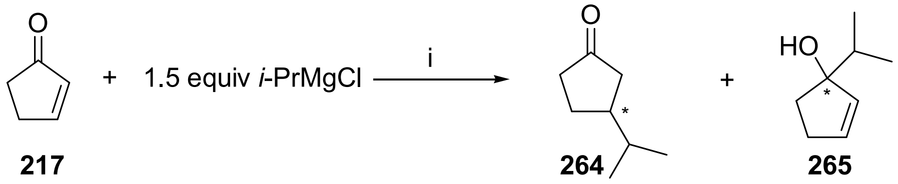
[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.2.1.2. Effect of metal salts

The effect of various copper salts such as CuI, $CuCl_2$, and $Cu(AcAc)_2$ on the reaction were investigated (Table21). It was observed that the reaction using CuI gave *racemic* product **264** *albeit* in good regioselectivity (ratio of **264**/**265**: 93/7, Table 21, entries 1); the reaction using $Cu(AcAc)_2$ gave product **264** in 6% ee and moderate regioselectivity (ratio of **264**/**265**: 88/12, Table 21, entries 3); while the reaction performed using $CuCl_2$ gave product **264** in 22% ee and good regioselectivity (ratio of **264**/**265**: 92/8, Table 21, entries 2) which was comparable with that of $Cu(OTf)_2$ (Table 20, entry 4).

Hence, the most practical choices for metal salts would be $CuCl_2$ and $Cu(OTf)_2$; either metal salt could be chosen to continue the optimization process. In this project, $Cu(OTf)_2$ was chosen because it was foreseen that $CuCl_2$'s lower solubility might affect subsequent investigations.

Table 21 Effect of metal salts on the conjugate addition of *i*-PrMgCl to enone 217



Conditions: i. Salt (0.1 equiv), (-)-**68** (0.1 equiv), THF, -90 °C, 15 min

Entry	Metal salt	**264/265**[a]	ee[b] (%) (Configuration)[c]
1	CuI	93/7	0
2	$CuCl_2$	92/8	22 (*S*)
3	$Cu(AcAc)_2$	88/12	6 (*S*)

[a] The ratio of **264**/**265** was determined by GC using Chiraldex G-TA column.

[b] The ee was determined by GC using Chiraldex G-TA column.

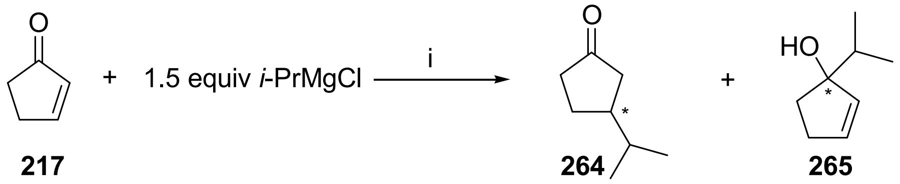
[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.2.1.3. Effect of reaction temperature

The reaction temperature was the next factor to be optimized and the results are shown in Table 22. The effect of varying temperature on the ee of product **264** showed an obvious trend: at -90°C, the ee of product **264** was relatively higher at 23%. It quickly dropped to 6% as temperature was increased to -30°C, upon further increase to r.t., the product **264** was almost *racemic*, with an ee of only 2%. It was obvious that low temperature favored high enantioselectivity, possibly due to lower reaction rate that would allow the reactants to get into their stereo-specific orientation before a reaction took place. The Grignard reagents were highly reactive and this slowdown in rate of reaction could be critical in obtaining high enantioselectivity. It was also notable that the regioselectivity of product **264** increased along with the increasing of reaction temperature: the ratio of **264**/**265** increased from 90/10 to 96/4 to 97/3 when reaction temperature increased from -90 °C to -30 °C to r.t..

As a result, -90 °C was chosen as the optimum reaction temperature for conjugate addition of *i*-PrMgCl to enone **217**.

Table 22 Effect of reaction temperature on the conjugate addition of *i*-PrMgCl to enone 217



Conditions: i. $Cu(OTf)_2$ (0.1 equiv), (-)-**68** (0.1 equiv), THF, 15 min

Entry	Temperature (°C)	**264/265**[a]	ee[b] (%) (Configuration)[c]
1	r.t.	97/3	2 (*S*)
2	-30	96/4	6 (*S*)
3	-90	90/10	23 (*S*)

[a] The ratio of **264**/**265** was determined by GC using Chiraldex G-TA column.

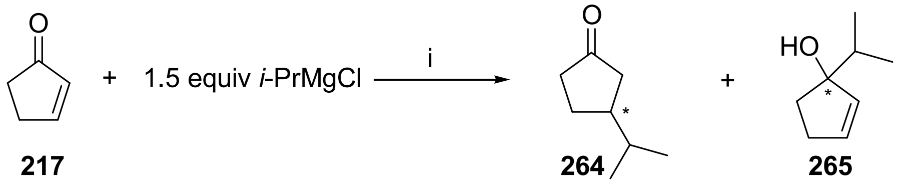
[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.2.1.4. Loading of catalyst

The last factor need to be optimized was catalyst loading. A series of reactions were carried out with different loading of Cu(OTf)$_2$/(-)-**68** as 0.05, 0.10, 0.15, 0.20, 0.50 and 1.0 equiv (with respect to enone **217**) in THF at -90 °C. A similar trend as conjugate addition EtMgCl to enone **218** was observed: increasing amount of catalyst led to a better regioselectivity of 1,4-adduct. When the loading of Cu(OTf)$_2$/(-)-**68** increased from 0.05 equiv to 1.0 equiv, the ratio of **264/265** increased from 83/17 to 97/3 accordingly (Table 23). On the other hand, the ee of product **264** increased sharply from 3% to 23% when the loading of Cu(OTf)$_2$/(-)-**68** increased from 0.05 equiv to 0.10 equiv. However, further increase in the catalyst's loading to 0.15 equiv only slightly enhanced the ee of **264** to 27% and subsequent increase in the catalyst's loading to 0.20, 0.50 equiv and then to 1.0 equiv revealed a plateau with the ee of **264** reaching a maximum of 27%. Therefore, 0.15 equiv was chosen as the optimum loading of catalyst which could provide product **264** in good regioselectivity and maximum ee.

Table 23 *i*-PrMgCl conjugate addition to enone 217 with different loading of Cu(OTf)$_2$/(-)-68



Conditions: i. Cu(OTf)$_2$/(-)-**68** (1:1), THF, -90 °C, 15 min

Entry	Cu(OTf)$_2$/(-)-**68** (1:1)	**264/265**[a]	ee[b] (%) (Configuration)[c]
1	0.05 equiv	83/17	3 (*S*)
2	0.10 equiv	90/10	23 (*S*)
3	0.15 equiv	89/11	27 (*S*)
4	0.20 equiv	90/10	27 (*S*)
5	0.50 equiv	97/3	27 (*S*)
6	1.00 equiv	97/3	27 (*S*)

[a] The ratio of **264/265** was determined by GC using Chiraldex G-TA column.

[b] The ee was determined by GC using Chiraldex G-TA column.

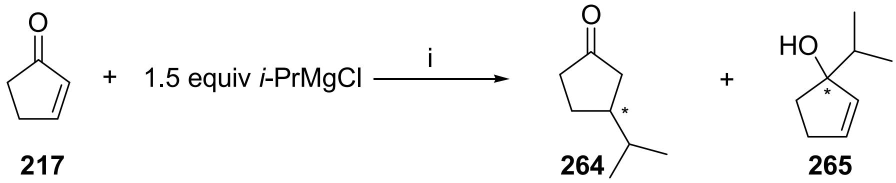
[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.2.2. The use of different ligands

The efficiency of other chiral ligands was investigated under the optimum reaction conditions established before and the results are shown in Table 24. Compared to the reaction catalyzed by $Cu(OTf)_2$/(-)-**68** which gave (*S*)-**264** in 27% ee (Table 23, entry 3), reaction catalyzed by $Cu(OTf)_2$/(+)-**68** gave the complimentary (*R*)-**264** in a similar ee of 30% (Table 24, entry 1). This observation indicated that there was no preferential stereoselection between the two enantiomers of BIQ **68** in catalyzing the conjugate addition of *i*-PrMgCl to enone **217**.

Not surprisingly, *N*-benzyl derivative (+)-**103**, amide derivative (+)-**106** and urea derivative (+)-**107** gave *racemic* product **264** with moderate to good regioselectivity (Table 24, entries 3-5). However, it was interesting that the *N*-ethyl derivative (+)-**102** gave product **264** in similar ee as that of (+)-**68** but with inverse configuration (25% ee of (*S*)-**264**, Table 24, entry 2).

Table 24 *i*-PrMgCl conjugate addition to enone 217 in the presence of different ligands



Conditions: i. $Cu(OTf)_2$ (0.15 equiv), ligand (0.15 equiv), THF, -90 °C, 15 min

Entry	Ligand	**264/265**[a]	ee[b] (%) (Configuration)[c]
1	(+)-**68**	97/3	30 (*R*)
2	(+)-**102**	96/4	25 (*S*)
3	(+)-**103**	95/5	0
4	(+)-**106**	89/11	0
5	(+)-**107**	83/17	0

[a] The ratio of **264/265** was determined by GC using Chiraldex G-TA column.

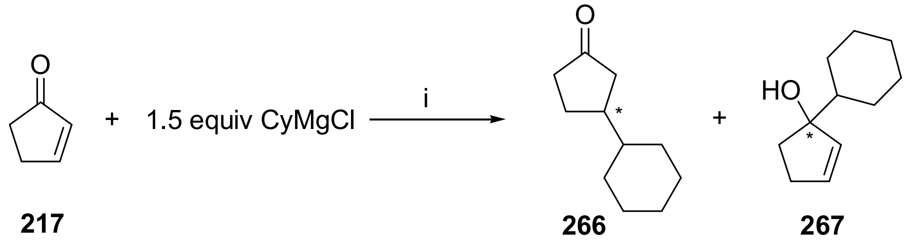
[b] The ee was determined by GC using Chiraldex G-TA column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

4.2.2.3. Use of different Grignard reagents

Only CyMgCl was attempted besides *i*-PrMgCl in the addition to enone **217** under the optimized reaction conditions (Table 25). The addition proceeded to give exclusively the 1,4-adduct **266** in 18% ee.

Table 25 CyMgCl conjugate addition to enone 217 catalyzed by Cu(OTf)$_2$/(-)-68



Conditions: i. Cu(OTf)$_2$ (0.15 equiv), (-)-**68** (0.15 equiv), THF, -90 °C, 15 min

Entry	Grignard reagent	**266**/**267**[a]	ee[b] (%) (Configuration)[c]
1	CyMgCl	100/0	18 (*S*)

[a] The ratio of **266**/**267** was determined by GC-Mass using HP-5 column.

[b] The ee was determined by GC using TBDAc column.

[c] The configuration was determined by comparing the sign of optical rotation value with literature.

In conclusion, chiral compound **68** showed moderate efficiency in enantioselective conjugate addition of Grignard reagents to cyclohexenone or cyclopentenone to give desired 1,4-adducts in generally excellent yield and moderate ee (up to 35%). Again, the chiral derivatives of **68** were found not efficient which might be due to the difficulties in formation of proper complexes between the derivatives and copper ion to catalyze the reactions.

Chapter 5. Experimental

General

All commercial materials used in this project were used as received unless indicated.

Melting points were determined on Bamstead Electrothermal 9100 melting point tester. FTIR were recorded on Perkin Elmer FTIR system Spectrum BX. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Advanced DPX 300. Unless stated, data refer to solutions in $CDCl_3$ with the TMS as internal reference. ^{1}H NMR multiplicities were designated as singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), triplet (t), triplet of doublet (td), quartet (q), pentet (p), multiplet (m) and broad (br). ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker Advanced DPX 300. DEPT, C-H (HMBC, HMQC) and H-H (COSY) correlations were all measured on the same instrument using Bruker automation programs. Routine mass spectra were recorded on ABI QSTAR Elite mass spectrometer. High resolution mass spectra were recorded on Qstar XL MS/MS system. X-ray single crystal diffraction data were obtained on Bruker-AXS Smart Apex CCD single-crystal diffractometer.

Analytical thin layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plate (0.2 mm thickness) and visualized using UV radiation (254 nm). Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Anhydrous solvents including toluene, THF and diethyl ether were freshly taken from PURE SOLV PS-400-5-MD system. Anhydrous dichloromethane was distilled from calcium hydride.

HPLC was performed on Agilent 1100 using Diacel chiralcel OD-H chiral column. GC was conducted on Agilent 6890 using Agilent HP-5, Astec Chiraldex G-TA or MN Hydrodex-β-TBDAc column. GC-Mass spectra were recorded on Agilent 6890 GC system with Agilent 5973 Mass selective detector. Optical rotation values were measured on JASCO P-1020 polarimeter.

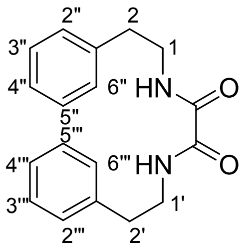
5.1. Synthesis of *racemic* BIQs

5.1.1. Preparation of bisoxamides

***General Procedure*:** A solution of diethyl oxalate in absolute ethanol (300 mL per 1.0 mol) was added dropwise over a period of 5-15 minutes to a solution of phenethylamine or substituted phenethylamine in absolute ethanol (500 mL per 1.0 mol). During the addition a fine white solid precipitated. After complete addition, the mixture was vigorously stirred at room temperature. After reaction completion (TLC analysis), the solvent was evaporated under vacuum, and the solid was washed with hexane.

The general procedure was used to prepare bisoxamide **65** and **66.**

5.1.1.1. Preparation of N,N'-bisphenethyloxamide 65

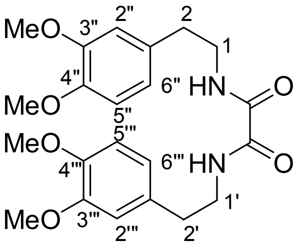


65

Diethyl oxalate (11.2 mL, 0.083 mol) and phenethylamine (20.0 g, 0.165 mol) gave *N*,*N'*-bisphenethyloxamide **65** as white powder (22.63 g, 92%). m.p. 186-188 °C. FTIR (Nujol) ν_{max}: 3307, 1654, 1522, 1280, 1226, 1190, 742, 698 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.79 (4H, t, *J* = 7.2 Hz, H2 and H2'), 3.50 (4H, q, *J* = 6.9 Hz, H1 and H1'), 7.12-7.27 (10H, m, H2", H3", H4", H5", H6" and H2'", H3'", H4'", H5'", H6'"), 7.53 (2H, br s, N*H*). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 35.5 (C2 and C2'), 40.9 (C1 and C1'), 126.7 (C4" and C4'"), 128.7 (C2", C6" and C2'", C6'"), 128.8 (C3", C5" and C3'", C5'"), 138.1 (C1" and C1'"), 159.7 (2×*C*O). HRMS (ESI) calcd for $C_{18}H_{20}N_2O_2$: 296.1525, found 319.1078 (M+Na).

5.1.1.2 Preparation of *N*,*N'*-bis-(3,4-dimethoxyphenethyl)oxamide 66

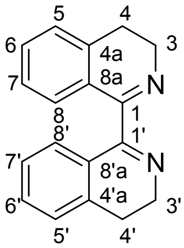
Diethyl oxalate (37.31 mL, 0.276 mol) and 3,4-dimethoxy-phenethylamine (100.0 g, 0.552 mol) gave *N*,*N'*-bis-(3,4-dimethoxyphenethyl)-oxamide **66** as white powder (102 g, 89%). m.p. 173-175 °C. FTIR (Nujol) ν_{max}: 3299, 1654, 1516, 1460, 1258, 1238, 1226, 1157, 1140, 1027, 767 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.81 (4H, t, *J* = 7.2 Hz, H2 and H2'), 3.55 (4H, q, *J* = 6.9 Hz, H1 and H1'), 3.87 (6H, s, 3''-OC*H*$_3$ and 3'''-OC*H*$_3$), 3.88 (6H, s, 4''-OC*H*$_3$ and 4'''-OC*H*$_3$), 6.72-6.84 (6H, m, H6'', H6''', H2'', H2''', H5'' and H5'''), 7.55 (2H, br s, N*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 35.0 (C2 and C2'), 41.0 (C1 and C1'), 55.8 (4''-O*C*H$_3$ and 4'''-O*C*H$_3$), 55.9 (3''-O*C*H$_3$ and 3'''-O*C*H$_3$), 111.5 (C2'' and C2'''), 111.8 (C5'' and C5'''), 120.6 (C6'' and C6'''), 130.6 (C1'' and C1'''), 147.8 (C4'' and C4'''), 149.1 (C3'' and C3'''), 159.7, (2×*C*O). HRMS (ESI) calcd for $C_{22}H_{28}N_2O_6$: 416.1947, found 439.1298 (M+Na).



66

5.1.2. Cyclisation of bisoxamides

5.1.2.1. Preparation of 3,3',4,4'-tetrahydro-1,1'-bisisoquinoline 67

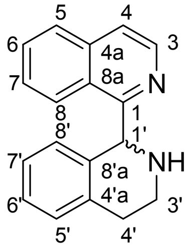


67

$POCl_3$ (110 mL, 1.2 mol) was added dropwise over 30 min to a suspension of bisoxamide **65** (35.5 g, 0.12 mol) and P_2O_5 (171 g, 1.2 mol) in toluene (200 mL) in an ice bath. After complete addition, the mixture was heated under reflux overnight with stirring. The reaction mixture was cooled to room temperature, hexane (200 mL) was added and the mixture was left undisturbed for 2 h. The solvent was then decanted and the remaining black solid was dissolved in water. Solid Na_2CO_3 was added until no bubbling was observed followed by addition of 1.0 M NaOH solution to adjust PH to 10. The alkaline solution was extracted with CH_2Cl_2 (4 × 150 mL) and the combined extracts were washed with brine and then dried over $MgSO_4$. The solvent was removed under vacuum, and the obtained dark purple solid was dissolved in EtOH (250 mL) and heated at reflux with charcoal (60 g) for 3 h to remove the color. Charcoal was filtered and the solution was concentrated to 1/10 volume and left to stand overnight where 3,3',4,4'-tetrahydro-1,1'-bisisoquinoline **67** was obtained as dark yellow powder (18.5 g, 59%). m.p. 104-106 ^{o}C. FTIR (Nujol) ν_{max}: 1607, 1231, 1215, 1010, 913, 740 cm^{-1}. ^{1}H

NMR (300 MHz, $CDCl_3$) δ: 2.86 (4H, t, *J* = 7.7 Hz, H4 and H4'), 3.94 (4H, t, *J* = 7.5 Hz, H3 and H3'), 7.15-7.36 (8H, m, H5, H6, H7, H8 and H5', H6', H7', H8'). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 25.8 (C4 and C4'), 47.4 (C3 and C3'), 126.9 (C8 and C8'), 127.0 (C5 and C5'), 127.6 (C7 and C7'), 128.2 (C8a and C8'a), 131.2 (C6 and C6'), 137.5 (C4a and C4'a), 165.4 (C1 and C1'). Mass (ESI) calcd for $C_{18}H_{16}N_2$: 260.13, found 261.27 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

5.1.2.2. Preparation of *rac*-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline 68

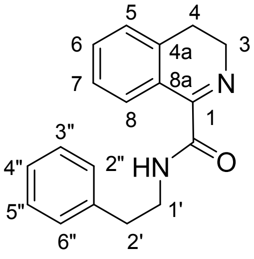


rac-**68**

Bisoxamide **65** (5.0 g, 16.9 mmol) was mixed with polyphosphoric acid (70.0 g), under N_2 atmosphere and stirred at 190 °C for 12 h. The mixture was then cooled, diluted with water (30 mL) and NaOH (10% in water) was added to obtain PH11. The alkaline solution was then extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were washed with brine and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was recrystallized from ethanol to give *rac*-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-**68** as light-yellow needles (3.76 g, 86%). m.p. 125-129 °C. FTIR (Nujol) ν_{max}: 3301, 2805, 1494, 1452, 1345, 1121, 826, 751, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.44 (1H, br s, N*H*), 2.86-2.96 (1H, m, H_β4'), 3.20-3.34 (2H, m, H_α4' and H_β3'), 3.47-3.57 (1H, m, H_α3'), 6.01 (1H, s, H1'), 6.60 (1H, d, *J* = 7.8 Hz, H5'), 6.94 (1H, t, *J* = 7.5 Hz, H7'), 7.14 (1H, t, *J* = 7.2 Hz, H6'), 7.22 (1H, d, *J* = 7.8 Hz, H8'), 7.54 (1H, t, *J* = 7.8 Hz, H6), 7.62 (1H, d, *J* = 5.7 Hz, H4), 7.67 (1H, t, *J* = 7.7 Hz, H7), 7.86 (1H, d, *J* = 8.4 Hz, H5), 8.34 (1H, d, *J* = 8.7 Hz, H8), 8.50 (1H, d, *J* = 5.7 Hz, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.6 (C4'), 43.4 (C3'), 61.1 (C1'), 120.7 (C4), 126.0 (C8), 126.1 (C7'), 126.5 (C7), 126.8 (C6'), 127.0 (C5), 127.3 (C8a), 127.4 (C5'), 129.4 (C8'), 129.9 (C6), 134.9 (C4'a), 137.0 (C4a), 137.8 (C8'a), 141.8 (C3), 161.8 (C1). HRMS (ESI) calcd for $C_{18}H_{16}N_2$: 260.1313, found 261.1157 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

5.1.2.3. Preparation of *N*-phenethyl-3,4-dihydroisoquinoline-1-carboxamide 69

Bisoxamide **65** (1.0 g, 3.4 mmol) was mixed with polyphosphoric acid (14.0 g) and stirred at 140°C for 3 h. The mixture was cooled, diluted with water (10 mL) and NaOH (10% in water) was added till PH 11. The alkaline solution was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine and then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography (pure EA) to give *N*-phenethyl-3,4-dihydroisoquinoline-1-carboxamide **69** as yellow gum (0.36 g, 38%). FTIR (Nujol) ν_{max}: 3368, 3027, 2940, 1670, 1610, 1522, 1236, 751, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.65 (2H, t, *J* = 7.4 Hz, H4), 2.87 (2H, t, *J* = 7.2 Hz, H2'), 3.60 (2H, apparent q, *J* = 6.9 Hz, H1'), 3.68 (2H, t, *J* = 7.5 Hz, H3), 7.13 (1H, d, *J* = 7.2 Hz, H5), 7.19-7.35 (7H, m, H6, H7, H2", H3", H4", H5" and H6"), 7.47 (1H, br s, N*H*), 8.10 (1H, d, *J* = 7.5 Hz, H8). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 25.8 (C4), 35.8 (C2'), 40.7 (C1'), 47.2 (C3), 126.3 (C8a), 126.5 (C5), 127.0 (C4"), 127.1 (C6), 128.4 (C8), 128.6 (C3" and C5"), 128.8 (C2" and C6"), 131.3 (C7), 137.9 (C4a), 138.9 (C1"), 159.9 (C1), 164.4 (*C*O). Mass (ESI) calcd for $C_{18}H_{18}N_2O$: 278.14, found 279.79 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

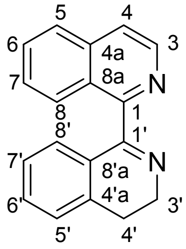


69

5.1.2.4. Oxidization of *rac*-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline 68

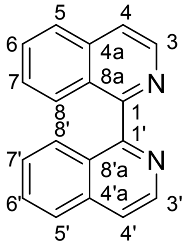
A solution of BIQ *rac*-**68** (1.30 g, 5 mmol) and NaOBu (2.5 mmol, 1.46 mL of 1.71 M solution in *n*-BuOH) in EtOH (20 mL) was stirred overnight at 60 °C. The reaction solvent was removed under vacuum and the residue was stirred in a mixture of CH_2Cl_2 and water (30 mL/30 mL) for 2 h. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to give a brown gum that was subjected to column chromatography

(EA/CH_2Cl_2 = 4/6) to give two fractions other than starting material. The fraction with the lower R_f value obtained as yellow gum (0.3 g, 23%) was confirmed to be 3',4'-dihydro-1,1'-bisisoquinoline **70.** FTIR (Nujol) ν_{max}: 3054, 2941, 1621, 1285, 1253, 1018, 829, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.99 (2H, t, *J* = 7.5 Hz, H4'), 4.10 (2H, t, *J* = 7.5 Hz, H3'), 6.90 (1H, d, *J* = 7.5 Hz, aromatic H), 7.13 (1H, t, *J* = 7.3 Hz, aromatic H), 7.28 (1H, d, *J* = 7.5 Hz, aromatic H), 7.37 (1H, apparent t, *J* = 7.4 Hz, aromatic H), 7.53 (1H, t, *J* = 7.7 Hz, aromatic H), 7.66-7.74 (2H, m, 2 × aromatic H), 7.88 (1H, d, *J* = 8.4 Hz, aromatic H), 8.10 (1H, d, *J* = 8.4 Hz, aromatic H), 8.61 (1H, d, *J* = 5.7 Hz, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 25.9 (C4'), 47.8 (C3'), 121.1, 126.8, 126.96, 126.97, 127.1, 127.5, 127.57, 127.59, 129.3, 130.4, 131.2, 136.8, 137.6, 141.9 (C3, C4, C5, C6, C7, C8, C4a, C8a and C5', C6', C7', C8', C4'a, C8'a), 157.7, 165.8 (C1 and C1'). Mass (ESI) calcd for $C_{18}H_{14}N_2$: 258.12, found 259.40 (M+1). ^1H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.



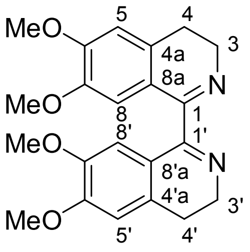
70

The fraction with the higher R_f value obtained as light yellow solid (0.58 g, 45%) was confirmed to be 1,1'-bisisoquinoline **71** m.p. 161-165 °C. FTIR (Nujol) ν_{max}: 3050, 1619, 1682, 1558, 1318, 829, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.48 (2H, t, *J* = 7.7 Hz, H7 and H7'), 7.71 (2H, t, *J* = 7.8 Hz, H6 and H6'), 7.75 (2H, d, *J* = 8.4 Hz, H5 and H5'), 7.82 (2H, d, *J* = 5.7 Hz, H4 and H4'), 7.95 (2H, d, *J* = 8.4 Hz, H8 and H8'), 8.71 (2H, d, *J* = 5.7 Hz, H3 and H3'). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 121.1 (C4 and C4'), 127.0 (C8 and C8'), 127.2 (C5 and C5'), 127.6 (C7 and C7'), 127.8 (C8a and C8'a), 130.4 (C6 and C6'), 136.9 (C4a and C4'a), 141.9 (C3 and C3'), 158.1 (C1 and C1'). Mass (ESI) calcd for $C_{18}H_{12}N_2$: 256.10, found 257.47 (M+1). ^1H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.



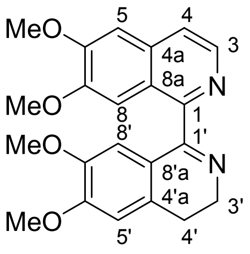
71

5.1.2.5. Preparation of 6,6',7,7'-tetramethoxy-3,3',4,4'-tetrahydro-1,1'-bisisoquinoline 72 and 6,6',7,7'-tetramethoxy-3',4'-dihydro-1,1'-bis-isoquinoline 73



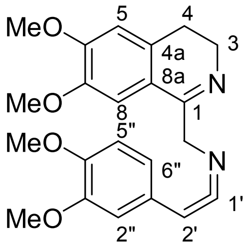
72

$POCl_3$ (75 mL, 0.82 mol) was added dropwise over 15 min to a stirred suspension of bisoxamide **66** (40.0 g, 96 mmol) in toluene (200 mL) in an ice bath. After complete addition, the mixture was heated under reflux for 6 h. The reaction mixture was cooled to room temperature, water (500 mL) was added slowly with vigorous stirring till the black solid dissolved completely. The mixture was then left undisturbed untill two clear layers were formed. The organic layer was separated and extracted with water (3 × 150 mL). The aqueous extracts were combined, solid Na_2CO_3 was added until no bubbling was observed and the PH was adjusted to 10 using 1.0 M NaOH solution. The alkaline solution was then extracted with CH_2Cl_2 (4 × 200 mL) and the combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum and the black solid obtained was heated at reflux with charcoal (100 g) in EtOH (600 mL) for 3 h. Charcoal was filtered and the solvent was removed under vacuum to yield a yellow powder which contained three major fractions (TLC analysis). The fractions were separated using silica gel column chromatography (gradient from pure EA to EA/MeOH = 2/8) to give, in the order of increasing R_f value: 6,6',7,7'-tetramethoxy-3,3',4,4'-tetrahydro-1,1'-bisisoquinoline **72** as an off-white powder (17.7 g, 49%). m.p. 201-203 ^{o}C. FTIR (Nujol) ν_{max}: 2930, 2834, 1603, 1568, 1515, 1460, 1351, 1321, 1281, 1266, 1241, 1219, 1127, 921, 864, 808, 782 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.80 (4H, t, *J* = 7.7 Hz, H4 and H4'), 3.73 (6H, s, 7-OCH_3 and 7'-OCH_3), 3.91 (4H, apparent t, *J* = 7.7 Hz, H3 and H3'), 3.92 (6H, s, 6-OCH_3 and 6'-OCH_3), 6.73 (2H, s, H8 and H8'), 6.88 (2H, s, H5 and H5'). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 25.6 (C4 and C4'), 47.1 (C3 and C3'), 56.0 (6-OCH_3, 6'-OCH_3, 7-OCH_3 and 7'-OCH_3), 110.4 (C5 and C5'), 110.7 (C8 and C8'), 120.8 (C8a and C8'a), 131.6 (C4a and C4'a), 147.5 (C7 and C7'), 151.7 (C6 and C6'), 164.7 (C1 and C1'). HRMS (ESI) calcd for $C_{22}H_{24}N_2O_4$: 380.1736, found 381.1370 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed by comparing with the literature precedent.[65]



73

And 6,6',7,7'-tetramethoxy-3',4'-dihydro-1,1'-bisisoquinoline **73** as white needles (2.3 g, 6%). m.p. 186-189 °C. FTIR (Nujol) ν_{max}: 2933, 2835, 1564, 1508, 1482, 1267, 1232, 1137, 851 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.90 (2H, t, *J* = 7.7 Hz, H4'), 3.58 (3H, s, 6'-OCH_3), 3.89 (3H, s, 6-OCH_3), 3.94 (3H, s, 7'-OCH_3), 4.04 (5H, t and s, *J* = 7.5 Hz, H3' and 7-OCH_3), 6.52 (1H, s, H8'), 6.79 (1H, s, H5'), 7.12 (1H, s, H5), 7.46 (1H, s, H8), 7.57 (1H, d, *J* = 5.7 Hz, H4), 8.47 (1H, d, *J* = 5.4 Hz, H3). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 25.7 (C4'), 47.8 (C3'), 55.76 (6-O*C*H$_3$), 55.97 (6'-O*C*H$_3$), 56.03 (7'-O*C*H$_3$), 56.07 (7-O*C*H$_3$), 104.77 (C8), 104.83 (C5), 110.3 (C5'), 111.0 (C8'), 119.9 (C4), 122.1 (C8'a), 123.1 (C8a), 131.7 (C4'a), 134.0 (C4a), 140.8 (C3), 147.4 (C6'), 150.2 (C6), 151.3 (C7'), 152.9 (C7), 155.0 (C1), 165.4 (C1'). HRMS (ESI) calcd for $C_{22}H_{22}N_2O_4$: 378.1580, found 379.1052 (M+1) and 401.0982 (M+Na). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

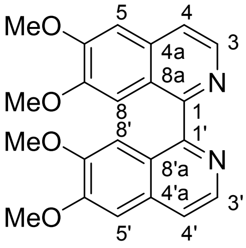


74

And (6,7-dimethoxy-3,4-dihydroisoquinolin-1-yl)-*N*-(2-(3,4--dimethoxyphenyl)vinylidene)-methanamine **74** as dark yellow powder (6.4 g, 18%). m.p. 93-99 °C. FTIR (Nujol) ν_{max}: 3199, 2961, 2836, 1509, 1467, 1342, 1266, 1231, 1140, 1026, 797 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.89 (2H, t, *J* = 6.6 Hz, H4), 3.82 (3H, s, 6-OCH_3), 3.84 (3H, s, 4"-OCH_3), 3.86 (2H, obscure t, H3), 3.88 (3H, s, 7-OCH_3), 3.92 (3H, s, 3"-OCH_3), 4.10 (2H, s, NCH_2), 6.70-6.80 (4H, m, H2', H2", H5" and H6"), 7.02 (1H, s, H8), 7.24 (1H, s, H5). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 28.6 (C4), 41.0 (C3), 55.9, 55.9, 56.0, 56.1 (6-O*C*H$_3$, 7-O*C*H$_3$, 3"-O*C*H$_3$ and 4"-O*C*H$_3$), 58.0 (N*C*H$_2$), 106.1 (C5), 111.2 (C2"), 111.3 (C8), 111.5 (C5"), 120.2 (C1" and C6"), 121.3 (C8a), 122.7 (C4a), 129.5 (C4"), 129.6 (C3"), 145.7 (C7) 147.8 (C6), 148.1 (C2'), 148.5 (C1), 149.2 (C1'). Mass (ESI) calcd for $C_{22}H_{24}N_2O_4$: 380.1736, found 381.27 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

During the scale up of compound **73**, the reaction time had to be prolonged to 24 h. Bisoxamide **66** (5.0 g, 12 mmol) under the same reaction conditions as metioned before (for compound **72**) provided BIQ **73** (1.76 g, 39%) as the main product while BIQ **72** as the minor one (0.91 g, 20%).

5.1.2.6. Oxidization of 6,6',7,7'-tetramethoxy-3,3',4,4'-tetrahydro-1,1'-bisisoquinoline 72

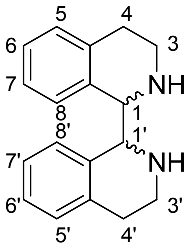


75

A mixture of BIQ **72** (3.80 g, 10 mmol) and Pd/C (2.65 g, 2.5 mmol) in toluene (100 mL) heated under reflux for 3 days. After filtration, the solvent in mother liquor was removed under vacuum and the resulting black solid was recrystallized from EtOH to give 6,6',7,7'-tetramethoxy-1,1'-bisisoquinoline **75** as yellow needles (2.45 g, 65%). m.p. 218-222 °C. FTIR (Nujol) ν_{max}: 2960, 2940, 2835, 1621, 1557, 1508, 1479, 1436, 1254, 1230, 1149, 851, 837 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.74 (6H, s, 6-OCH_3 and 6'-OCH_3), 4.06 (6H, s, 7-OCH_3 and 7'-OCH_3), 7.14 (2H, s, H8 and H8'), 7.18 (2H, s, H5 and H5'), 7.65 (2H, d, J = 5.4 Hz, H4 and H4'), 8.57 (2H, d, J = 5.7 Hz, H3 and H3'). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 55.8 (6-OCH_3 and 6'-OCH_3), 56.1 (7-OCH_3 and 7'-OCH_3), 104.8 (C5 and C5'), 105.2 (C8 and C8'), 119.8 (C4 and C4'), 123.7 (C4a and C4'a), 134.1 (C8a and C8'a), 140.9 (C3 and C3'), 150.2 (C6 and C6'), 152.9 (C7 and C7'), 155.8 (C1 and C1'). Mass (ESI) calcd for $C_{22}H_{20}N_2O_4$: 376.14, found 377.33 (M+1). ^{1}H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

5.1.3. Reduction of BIQs 67, 72 and 73

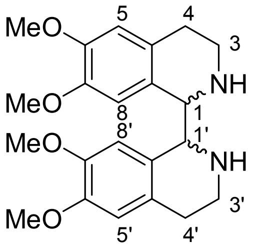
5.1.3.1. Reduction of bis-imine 67



rac-**32**

$NaCNBH_3$ (0.6 g, 9.5 mmol) was added portionwise to a solution of bis-imine **67** (1.12 g, 4.31 mmol) in 0.5 M HCl/MeOH (14 mL) at 0 °C. The resulting dark brown solution was stirred at room temperature for 2 h. 0.5 M HCl/MeOH solution was added to adjust the PH to 3-4 and the mixture was stirred for another 1 h. The precipitates were filtered off and the mother liquor was concentrated to give a second batch of solid. The combined solids were washed with cold MeOH (3 × 5 mL) and then dissolved in a mixture of H_2O (15 mL) and CH_2Cl_2 (20 mL). 1.0 M NaOH was added to the above mixture under vigorous stirring until the aqueous solution reached PH 10. The stirring was continued for another 1 h. The aqueous phase was separated and extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic phases were washed with brine (25 mL) and then dried over $MgSO_4$. The solvent was evaporated under vacuum and the product was recrystallized from EtOH to give *rac*-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline *rac*-**32** as light-yellow crystals (0.63 g, 89%). m.p. 129-130 °C. FTIR (Nujol) ν_{max}: 2917, 2853, 2801, 1489, 1453, 1126, 853, 766, 752, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.81 (2H, br s, 2×N*H*), 2.61 (2H, apparent d, *J* = 18 Hz, $H_{\alpha}4$ and $H_{\beta}4'$), 2.77-2.99 (4H, m, $H_{\alpha}3'$, $H_{\beta}3$, $H_{\alpha}4'$ and $H_{\beta}4$), 3.16-3.22 (2H, m, $H_{\alpha}3$ and $H_{\beta}3'$), 4.69 (2H, s, H1 and H1'), 7.11 (2H, apparent d, *J* = 7.2 Hz, H5 and H5'), 7.16 (2H, td, *J* = 7.2, 1.2 Hz, H7 and H7'), 7.23 (2H, td, *J* = 6.3, 1.8 Hz, H6 and H6'), 7.38 (2H, d, *J* = 7.5 Hz, H8 and H8'). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 30.6 (C4 and C4'), 43.0 (C3 and C3'), 60.2 (C1 and C1'), 125.2 (C8 and C8'), 126.2 (C7 and C7'), 126.4 (C6 and C6'), 129.5 (C5 and C5'), 136.8 (C4a and C4'a), 137.5 (C8a and C8'a). Mass (ESI) calcd for $C_{18}H_{20}N_2$: 264.16, found 265.20 (M+1). ^1H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

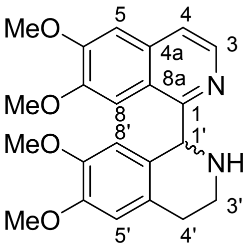
5.1.3.2. Reduction of bis-imine 72



rac-**76**

Bis-imine **72** (4.0 g, 10.5 mmol) was dissolved in 0.5 M HCl/MeOH (50 mL) and the resulting brown solution was evaporated to give a gummy brown residue. The residue was redissolved in MeOH (30 mL) and the solution added over 15 minutes to a stirred suspension of $NaCNBH_3$ (1.74 g, 27.6 mmol) in a mixture of MeOH (40 mL) and 3% HCl/MeOH (2 mL) at room temperature. A brown precipitate was formed as the addition was continued. When addition was completed, 3% HCl/MeOH was added to bring the mixture to PH 3-4 and stirring was continued for another 10 min. The solvent was evaporated till almost dry and NaOH (10% solution) was added to adjust the PH of the aqueous solution to 10. The solution was extracted with CH_2Cl_2 (4 × 25 mL) and the combined organic layers were washed with brine then dried over $MgSO_4$. The solvent was evaporated to dryness under vacuum and the product recrystallized from ethanol to give *rac*-6,6',7,7'-tetramethoxy-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline *rac*-**76** as grey needles (2.95 g, 73%). m.p. 179-183 °C. FTIR (Nujol) ν_{max}: 2925, 2835, 1608, 1518, 1468, 1439, 1241, 1220, 1118, 1108, 831, 786 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.80 (2H, br s, 2×N*H*), 2.53-2.60 (2H, m, $H_\alpha4$ and $H_\beta4'$), 2.78-2.92 (4H, m, $H_\alpha3'$, $H_\beta3$, $H_\alpha4'$ and $H_\beta4$), 3.18-3.28 (2H, m, $H_\alpha3$ and $H_\beta3'$), 3.89 (12H, s, 6-OC*H*$_3$, 6'-OC*H*$_3$, 7-OC*H*$_3$ and 7'-OC*H*$_3$), 4.54 (2H, s, H1 and H1'), 6.62 (2H, s, H5 and H5'), 6.82 (2H, s, H8 and H8'). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.6 (C4 and C4'), 42.5 (C3 and C3'), 55.8 (7-O*C*H$_3$ and 7'-O*C*H$_3$), 56.0 (6-O*C*H$_3$ and 6'-O*C*H$_3$), 59.6 (C1 and C1'), 108.6 (C8 and C8'), 111.9 (C5 and C5'), 127.4 (C8a and C8'a), 129.5 (C4a and C4'a), 147.5 (C6 and C6'), 147.6 (C7 and C7'). HRMS (ESI) calcd for $C_{22}H_{28}N_2O_4$: 384.2049, found 385.1659 (M+1). ^1H NMR and ^{13}C NMR assignments were consistant with the literature precedent.[65]

5.1.3.3. Reduction of BIQ 73



rac-**77**

$NaBH_4$ (4.3 g, 113.2 mmol) was added portionwise to a stirred solution of bisisoquinoline **73** (5.4 g, 14.1 mmol) in MeOH (80 mL) at room temperature. After complete addition, the mixture was kept stirring for 2 h. 0.5 M HCl/MeOH was added to bring the PH to 3-4 and the mixture was stirred for another 30 min. The solvent was removed under vacuum and the resulting white solid was dissolved in a mixture of 1.0 M NaOH solution (50 mL) and CH_2Cl_2 (50 mL). The mixture was stirred for 1 h and the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 25 mL). The organic phase and extracts were combined, washed with brine (3 × 30 mL), dried over $MgSO_4$ and the solvent was evaporated to dryness under vacuum. The product was subjected to silica gel column chromatography (gradient from pure EA to EA/MeOH = 2/8) to give *rac*-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-**77** as pink powder (4.85 g, 91%)**.** m.p. 124-129 °C. FTIR (Nujol) ν_{max}: 2935, 2832, 1508, 1467, 1251, 1233, 1114, 853 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.10 (2H, br s, N*H*), 2.82 (1H, apparent d, *J* = 13.5 Hz, $H_\beta4'$), 3.13-3.29 (2H, m, $H_\alpha4'$ and $H_\beta3'$), 3.43-3.52 (1H, obscure m, $H_\alpha3'$), 3.46 (3H, s, 6'-OCH_3), 3.81 (3H, s, 6-OCH_3), 3.87 (3H, s, 7'-OCH_3), 4.02 (3H, s, 7-OCH_3), 5.79 (1H, s, H1'), 6.13 (1H, s, H8'), 6.69 (1H, s, H5'), 7.06 (1H, s, H5), 7.48 (1H, d, *J* = 5.4 Hz, H4), 7.59 (1H, s, H8), 8.37 (1H, d, *J* = 5.7 Hz, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.5 (C4'), 43.6 (C3'), 55.65 (6-OCH_3), 55.73 (6'-OCH_3), 55.88 (7'-OCH_3), 55.93 (7-OCH_3), 62.9 (C1'), 104.95 (C5), 105.0 (C8), 109.8 (C8'), 111.6 (C5'), 119.6 (C4), 122.6 (C4a), 126.9 (C8'a), 130.0 (C4'a), 134.1 (C8a), 140.6 (C3), 147.4 (C6'), 147.6 (C7'), 149.3 (C6), 152.3 (C7), 159.7 (C1). HRMS (ESI) calcd for $C_{22}H_{24}N_2O_4$: 380.1736, found 381.1392 (M+1). ^1H NMR and ^{13}C NMR assignments were confirmed through H-H COSY, HMQC, HMBC, and DEPT experiments at 300 MHz.

5.2. Resolution of BIQs *rac*-32, *rac*-68, *rac*-76 and *rac*-77

5.2.1. Resolution through diastereomeric salt formation

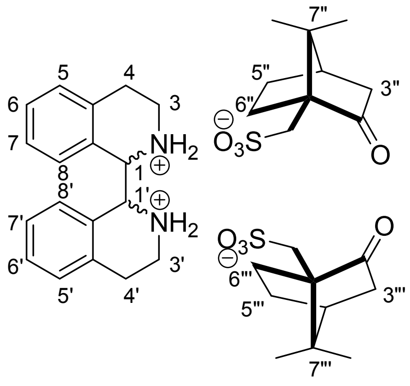
***General Procedure*:** A solution of *rac*-BIQ in MeOH was added dropwise to a hot solution (50 °C) of chiral acid in MeOH. After complete addition, the mixture was stirred for 4 h, allowed to cool to room temperature and the solvent was evaporated under vacuum to give the diastereomeric salt mixture. The resulting mixture was dissolved by heating (50-70 °C) in various solvents, allowed to cool slowly to room temperature and kept undisturbed overnight for crystallization. The crystals obtained were filtered, washed with cold MeOH and redissolved in a mixture of 1.0 M NaOH and CH_2Cl_2. After stirring for 2 h, the two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer and extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give the BIQ. The ee of the BIQ was examined by HPLC analysis.

This general procedure was adapted to resolve BIQs *rac*-**32**, *rac*-**68**, *rac*-**76** and *rac*-**77**.

5.2.1.1. Resolution of BIQ *rac*-32

i. With (*D*)-(+)-camphorsulfonic acid

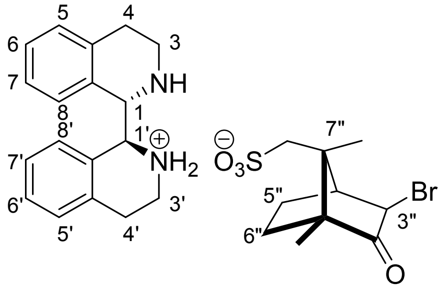
BIQ *rac*-**32** (264 mg, 1.0 mmol) was treated with (*D*)-(+)-camphorsulfonic acid (464 mg, 2.0 mmol) in MeOH to give a mixture of (*R,R*)-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline·(*D*)-CSA salt **78** and (*S,S*)-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline·(*D*)-CSA salt **79** as off-white powder (725 mg, > 99%). The mixture (200 mg) was recrystallized from *i*-Pr_2O/EtOH to give small off-white cubes (110 mg, 55%). FTIR (Nujol) ν_{max}: 3446, 2961, 1740, 1458, 1416, 1197, 1149, 1026, 769, 612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.75 (12H, s, 7''-CH_3 , 7'''-CH_3 of **78** and **79**), 0.96 (12H, s, 7''-CH_3 and



mixture of **78** and **79**

7'''-C*H*$_3$ of **78** and **79**), 1.34 (4H, ddd, *J* = 12.6 Hz, 9.0 Hz, 3.3 Hz, 1×H5'', 1×H5''' of **78** and **79**), 1.66 (4H, ddd, *J* = 14.1 Hz, 9.2 Hz, 4.5 Hz, 1×H6'', 1×H6''' of **78** and **79**), 1.85 (4H, d, *J* = 18.3 Hz, 1×H3'', 1×H3''' of **78** and **79**), 1.88-1.94 (4H, m, 1×H5'', 1×H5''' of **78** and **79**), 2.00 (4H, t, *J* = 4.2 Hz, H4'', 1×H4''' of **78** and **79**), 2.27 (4H, dt, *J* = 14.4 Hz, 3.6 Hz, 1×H3'', 1×H3''' of **78** and **79**), 2.40 (4H, ddd, *J* = 14.1 Hz, 11.9 Hz, 3.6 Hz, 1×H6'', 1×H6''' of **78** and **79**), 2.71 (4H, d, *J* = 14.7 Hz, 1''-SO$_3$C*H*H, 1'''-SO$_3$C*H*H of **78** and **79**), 3.20 (4H, d, *J* = 14.4 Hz, 1''-SO$_3$CH*H*, 1'''-SO$_3$CH*H* of **78** and **79**), 3.18-3.40 (8H, m, 1×H4, 1×H3, 1×H4', 1×H3' of **78** and **79**), 3.50-3.65 (4H, m, 1×H4, 1×H4' of **78** and **79**), 3.99 (4H, apparent d, *J* = 6.0 Hz, 1×H3, 1×H3' of **78** and **79**), 5.42 (2H, s, H1 and H1' of **78**), 5.49 (2H, s, H1 and H1' of **79**), 6.10-6.16 (4H, m, H5, H5' of **78** and **79**), 6.74-6.79 (4H, m, H7, H7' of **78** and **79**), 7.12-7.17 (8H, m, H6, H6', H8, H8' of **78** and **79**).

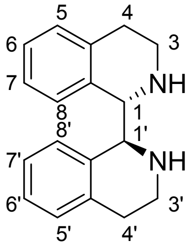
ii. With *D*-(+)-α-bromocamphor-π-sulfonic acid



81

BIQ *rac*-**32** (1.0 g, 3.8 mmol) was treated with *D*-(+)-α-bromocamphor-π-sulfonic acid ammonia salt (1.24 g, 3.8 mmol) in MeOH (30 mL) to give the mixture of (*R,R*)-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline·(*D*)-BCSA salt **80** and (*S,S*)-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline·(*D*)-BCSA salt **81** as yellow powder (2.11 g, 98%). The salt mixture (1.0 g) was then recrystallized from EtOH to give chiral pure **81** as light yellow needle clusters (96 mg, 19%). m.p. 182-184 °C. FTIR (Nujol) ν_{max}: 3424, 2967, 1765, 1640, 1210, 1143, 784 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.91 (3H, s, 7''-C*H*$_3$), 1.05 (3H, s, 1''-C*H*$_3$), 1.34-1.44 (1H, m, 1×H5''), 1.52-1.62 (1H, m, 1×H5''), 2.00 (2H, t, *J* = 7.2 Hz, H6''), 2.53 (1H, d, *J* = 14.4 Hz, SO$_3$C*H*H), 2.86-2.95 (4H, m, SO$_3$CH*H*, H4'', 1×H4 and 1×H4'), 3.10-3.22 (4H, m, 1×H4, 1×H4', 1×H3 and 1×H3'), 3.52-3.60 (2H, m, 1×H3 and 1×H3'), 4.46 (1H, d, *J* = 4.8 Hz, H3''), 4.86 (2H, s, H1 and H1'), 7.08 (2H, d, *J* = 7.8 Hz, H5 and H5'), 7.21-7.33 (6H, m, H6, H7, H8, H6', H7' and H8'). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 9.9 (7"-CH_3), 17.6 (1"-CH_3), 22.1 (C5"), 27.6 (C4 and C4'), 30.2 (C6"), 40.9 (C3 and C3'), 46.8 (C4"), 47.1 (C7"), 47.2 (C1"), 53.5 (C3"), 53.8 (O_3SCH_2), 58.9 (C1 and C1'), 59.6 (C2"), 127.2 (2×aromatic C), 127.3 (2×aromatic C), 128.3 (2×aromatic C), 129.6 (2×aromatic C), 130.0 (2×aromatic C), 135.2 (2×aromatic C), 212.3 (*C*O). ^{1}H NMR and ^{13}C NMR assignments were confirmed by comparing with literature precedent.[59]

The acid part of crystal salt **81** (96 mg, 0.17 mmol) was librated following the general procedure to give (*S,S*)-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline (*S,S*)-**32** as yellow powder (42 mg, 94%). Melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass spectra of (*S,S*)-**32** were same as those of *rac*-**32**. The ee of 98% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 90/10, 0.5 mL/min, 25 °C, 254 nm, t_1 = 15.01 min for (*S,S*) and t_2 = 22.26 min for (*R,R*). $[\alpha]_D^{25}$ = +243.6 (c = 1.04, CH_2Cl_2) {lit.[40] $[\alpha]_D^{22}$ = +254.8 (c = 1.07, $CHCl_3$) for > 99% ee (*S,S*)}.

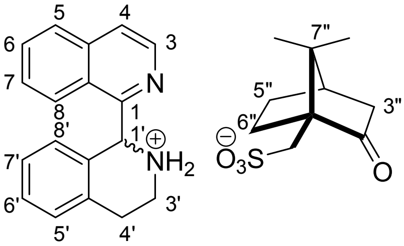


(*S,S*)-**32**

5.2.1.2. Attempts at resolution of BIQ *rac*-68

i. With (*D*)-(+)-camphorsulfonic acid

BIQ *rac*-**68** (260 mg, 1.0 mmol) was treated with (*D*)-(+)-camphorsulfonic acid (232 mg, 1.0 mmol) in MeOH (8 mL) to give a mixture of (*R*)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline·(*D*)-CSA salt **82** and (*S*)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline·(*D*)-CSA salt **83** as pale yellow powder (490 mg, > 99%). Recrystallization of the mixture from MeOH, EtOH or IPA gave colourless needle clusters in all cases (Yield: 26% from MeOH, 24% from EtOH, 43% from IPA). FTIR (Nujol) ν_{max}: 2957, 1743, 1390, 1239, 1149, 1026, 748 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.60 (6H, s, 7"-CH_3 of **82** and **83**), 0.85 (6H, s, 7"-CH_3



mixture of **82** and **83**

of **82** and **83**), 1.09 (2H, ddd, *J* = 12.3 Hz, 9.3 Hz, 3.9 Hz, 1×H5" of **82** and **83**), 1.33 (2H, ddd, *J* = 14.1 Hz, 9.6 Hz, 4.8 Hz, 1×H6" of **82** and **83**), 1.66 (2H, d, *J* = 18.3 Hz, 1×H3" of **82** and **83**), 1.68-1.80 (2H, m, 1×H5" of **82** and **83**), 1.89 (2H, t, *J* = 4.4 Hz, H4" of **82** and **83**), 2.11-2.17 (2H, m, 1×H3" of **82** and **83**), 2.32 (2H, ddd, *J* = 13.8 Hz, 12.0 Hz, 3.9 Hz, 1×H6" of **82** and **83**), 2.48 (2H, d, *J* = 14.4 Hz, $SO_3C\mathit{H}H$ of **82** and **83**), 2.96 (2H, d, *J* = 14.7 Hz, $SO_3CH\mathit{H}$ of **82** and **83**), 3.14 (2H, dt, *J* = 16.8 Hz, 4.8 Hz, 1×H4' of **82** and **83**), 3.34-3.45 (2H, m, 1×H4' of **82** and **83**), 3.76-3.85 (2H, m, 1×H3' of **82** and **83**), 3.90-3.99 (2H, m, 1×H3' of **82** and **83**), 6.61 (2H, d, *J* = 7.8 Hz, H5' of **82** and **83**), 6.84 (1H, s, H1' of **82** or **83**), 6.86 (1H, s, H1' of **82** or **83**), 6.96 (2H, t, *J* = 7.2 Hz, H7' of **82** and **83**), 7.15-7.22 (4H, m, H6', H8' of **82** and **83**), 7.65-7.80 (6H, m, H6, H4, H7 of **82** and **83**), 7.90 (2H, d, *J* = 7.8 Hz, H5 of **82** and **83**), 8.39-8.46 (4H, m, H8, H3 of **82** and **83**).

ii. With *D*-(+)-α-bromocamphor-π-sulfonic acid

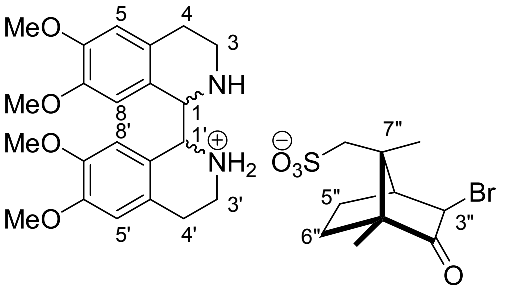
BIQ *rac*-**68** (130 mg, 0.5 mmol) was treated with *D*-(+)-α-bromocamphor-π-sulfonic acid ammonia salt (164 mg, 0.5 mmol) in MeOH (3 mL) to give a mixture of (*R*)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline·(*D*)-BCSA salt and (*S*)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline·(*D*)-BCSA salt as light yellow powder (280 mg, 98%). All attempts to recrystallize the pure diastereomeric salt from the mixture using various solvent: MeOH, EtOH, IPA, CH_3CN, THF or EA were unsuccessful.

5.2.1.3. Attempts at resolution of BIQ *rac*-76

i. With (*D*)-(+)-Camphorsulfonic acid

BIQ *rac*-**76** (384 mg, 1.0 mmol) reacted with *D*-(+)-CSA (464 mg, 2.0 mmol) in MeOH (10 mL) to give the mixture of (*R,R*)-6,6',7,7'-tetramethoxy-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline·(*D*)-CSA salt and (*S,S*)-6,6',7,7'-tetramethoxy-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline·(*D*)-CSA salt as white powder (840 mg, 99%). All attempts to recrystallize a pure diastereomeric salt from the mixture using various solvent: MeOH, EtOH, IPA, CH_3CN, THF or EA were unsuccessful.

ii. With *D*-(+)-α-bromocamphor-π-sulfonic acid



mixture of **84** and **85**

BIQ *rac*-**76** (192 mg, 0.5 mmol) was reacted with *D*-(+)-α-bromocamphor-π-sulfonic acid ammonia salt (164 mg, 0.5 mmol) in MeOH (5 mL) to give the mixture of (*R,R*)-6,6',7,7'-tetramethoxy-1,1',2,2',3,3',4,4'-octahydro-1,1'-bisisoquinoline··(*D*)-BCSA salt **84** and (*S,S*)-6,6',7,7'-tetramethoxy-1,1',2,2',3,3',4,4'-octahydro-1,1'- -bisisoquinoline·(*D*)-BCSA salt **85** as white powder (342 mg, 99%). The mixture (100 mg) was recrystallized from EtOH to give colourless needle clusters (30 mg, 30%) which were confirmed to be compound *rac*-**76** by checking ^{1}H NMR. Nevertheless, recrystallization from IPA gave the crystals of salt as colourless flakes (23 mg, 23%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (6H, s, 7"-C*H*$_3$ of **84** and **85**), 1.04 (6H, s, 7"-C*H*$_3$ of **84** and **85**), 1.32-1.42 (2H, m, 1×H5" of **84** and **85**), 1.51-1.61 (2H, m, 1×H5" of **84** and **85**), 1.95-2.00 (4H, m, H6" of **84** and **85**), 2.53 (2H, d, *J* = 14.4 Hz, SO$_3$C*H*H of **84** and **85**), 2.80-3.08 (12H, m, SO$_3$CH*H*, H4", 1×H4, 1×H3, 1×H4', 1×H3' of **84** and **85**), 3.18-3.26 (4H, m, 1×H4, 1×H4' of **84** and **85**), 3.47-3.55 (4H, m, 1×H3, 1×H3' of **84** and **85**), 3.73 (12H, s, 7-OC*H*$_3$, 7'-OC*H*$_3$ of **84** and **85**), 3.87 (12H, s, 6-OC*H*$_3$, 6'-OC*H*$_3$ of **84** and **85**), 4.46 (2H, d, *J* = 4.8 Hz, H3" of **84** and **85**), 4.71 (2H, s, H1 and H1' of **84** and **85**), 4.73 (2H, s, H1 and H1' of **84** or **85**), 6.37 (2H, s, H5 and H5' of **84** or **85**), 6.40 (2H, s, H5 and H5' of **84** or **85**), 6.66 (4H, s, H8, H8' of **84** or **85**).

5.2.1.4. Attempts at resolution of BIQ *rac*-77

BIQ *rac*-**77** (190 mg, 0.5 mmol) was reacted with *D*-(+)-camphorsulfonic acid (116 mg, 0.5 mmol) in MeOH (5 mL) to give a mixture of (*R*)-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline·(*D*)-CSA salt and (*S*)-6,6',7,7'-tetramethoxy-1',2',3',4'-

-tetrahydro-1,1'-bisisoquinoline·(*D*)-CSA salt as white powder (305 mg, > 99%). BIQ *rac*-**77** (190 mg, 0.5 mmol) was also treated with *D*-(+)-α-bromocamphor-π-sulfonic acid ammonia salt (164 mg, 0.5 mmol) in MeOH (5 mL) to give the mixture of (*R*)-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline·(*D*)-BCSA salt and (*S*)-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline·(*D*)-BCSA salt as white powder (348 mg, > 99%). Both diastereomeric salts mixtures could not give any crystals when recrystallized from MeOH, EtOH, IPA, CH_3CN, THF, EA or combination of these solvents.

5.2.2. Resolution of BIQ *rac*-68 and BIQ *rac*-77 through diastereomeric covalent bond formation

***General Procedure*:** A solution of chiral isocyanate in dry CH_2Cl_2 was added dropwisely under nitrogen atmosphere to an ice-cold stirred solution of BIQ in dry CH_2Cl_2. After complete addition, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was washed with brine and then dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give the diastereomeric urea mixture.

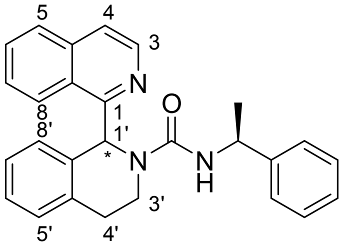
The general procedure was adapted to prepare the diastereomeric urea mixture of BIQ *rac*-**68** and BIQ *rac*-**77.**

5.2.2.1. Resolution of BIQ *rac*-68

5.2.2.1.1. Preparation and separation of diastereomeric urea derivatives

i. With (*S*)-(-)-α-methylbenzyl isocyanate

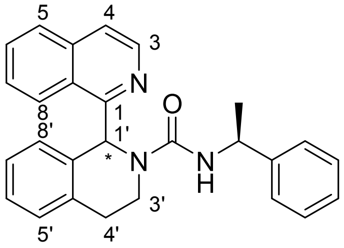
BIQ *rac*-**68** (13.0 g, 50 mmol) was treated with (*S*)-(-)-α-methylbenzyl isocyanate (7.4 g, 50 mmol) in CH_2Cl_2 (80 mL) according to the general procedure to give the mixture (+)-2'-((*S*)-1'-phenylethylcarbamoyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**86** and (-)-2'-((*S*)-1'-phenylethylcarbamoyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (-)-**87** as white powder (20.4 g, > 99%). All attempts to separate ureas (+)-**86** and (-)-**87** by recrystallizing the mixture from various solvents (MeOH, EtOH, IPA, CH_3CN, THF, EA, $CHCl_3$ or combination of these solvents) were not successful. Therefore, the mixture was subjected to column chromatography on silica gel (EA/CH_2Cl_2 gradient from 1:4 to 1:1). 10.0 g of the mixture ((+)-**86**:(-)-**87** = 50:50) was passed through a long column containing 800 g silica gel and eluted with the solvent mixture to give three fractions with the ratio of (+)-**86**:(-)-**87** as 74:26 (first fraction, 2.93 g, 29%), 52:48 (second fraction, 4.34 g, 43%) and 21:79 (third fraction, 2.73 g 27%). The first fraction (2.93 g) was dissolved into minimum amount of EA at 60 °C. Hexane was added to the hot solution dropwisely till it was just turned to cloudy. The solution was then kept at room temperature undisturbed overnight. It produced the white crystals (1.21 g, 41 %) in which the ratio of (+)-**86**:(-)-**87** was exactly 50:50. After filtering off the crystals, the filtrate was evaporated to dryness to give a white powder (1.72 g, 59%) with the ratio of (+)-**86**:(-)-**87** as 91:9. The procedure was repeated again to give urea (+)-**86** as white powder (1.40 g, 28% of total amount of urea (+)-**86** in starting mixture). m.p. 83-88 °C. FTIR (Nujol) ν_{max}: 3337, 1624, 1527, 1376, 1235, 747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36 (3H, d, *J* = 6.9 Hz, C*H*$_3$), 2.98-3.13 (2H, m, 1×H4' and 1×H3'), 3.59 (1H, ddd, *J* = 13.2 Hz, 10.4 Hz, 4.8 Hz, 1×H4'), 4.29 (1H, dt, *J* = 13.5 Hz, 4.1 Hz, 1×H3'), 4.97 (1H, p, *J* = 6.8 Hz, PhC*H*CH_3), 6.39 (1H, br d, *J* = 6.6 Hz, CON*H*), 6.88 (1H, d, *J* = 8.7 Hz, aromatic H), 6.89 (1H, s, H1'), 7.03 (1H, t, *J* = 7.4 Hz, aromatic H), 7.15-7.36 (7H, m, 7×aromatic H), 7.43 (1H, ddd, *J* = 8.7 Hz, 6.9 Hz, 1.2 Hz, aromatic H), 7.59-7.64 (2H, m, 2×aromatic H), 7.81 (1H, d, *J* = 8.1 Hz, aromatic H), 8.19 (1H, d, *J* = 8.7 Hz, aromatic H), 8.44 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.9 (*C*H_3), 29.1 (C4'), 38.7 (C3') 50.3 (Ph*C*HCH_3), 59.4 (C1'), 121.3, 126.1, 126.2, 126.4, 126.6, 126.9, 127.0, 127.47, 127.51, 127.52, 128.5, 129.3, 130.1, 134.7, 135.3, 137.5, 140.9, 144.9, 157.2



(+)-**86**

(21×aromatic C), 161.4 (N*C*ON). HRMS (ESI) calcd for $C_{27}H_{25}N_3O$: 407.1998, found 408.1524 (M+1), 430.1329 (M+Na). The de of > 95% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 90/10, 0.8 mL/min, 25 °C, 280 nm, t = 18.31 min for (+). $[\alpha]_D^{25}$ = +235.7 (c = 0.71, CH_2Cl_2).

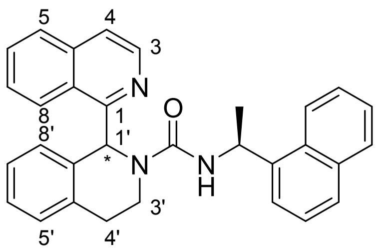
The third fraction (2.73 g) was treated in a similar manner to the first fraction to give urea (-)-**87** as white powder (1.56 g, 31% of total amount of urea (-)-**87** in starting mixture). m.p. 85-88 °C. FTIR (Nujol) ν_{max}: 3337, 1623, 1528, 1377, 1235, 828, 747, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.45 (3H, d, *J* = 6.9 Hz, C*H*$_3$), 3.02-3.07 (2H, m, 1×H4' and 1×H3'), 3.60-3.70 (1H, m, 1×H4'), 4.25 (1H, dt, *J* = 13.2 Hz, 4.1 Hz, 1×H3'), 4.95 (1H, p, *J* = 6.9 Hz, PhC*H*CH$_3$), 6.30 (1H, br d, *J* = 6.6 Hz, CON*H*), 6.85 (1H, d, *J* = 7.8 Hz, aromatic H), 6.93 (1H, s, H1'), 7.01 (1H, t, *J* = 7.5 Hz, aromatic H), 7.09-7.21 (7H, m, 7×aromatic H), 7.45 (1H, ddd, *J* = 8.4 Hz, 6.9 Hz, 1.2 Hz, aromatic H), 7.54 (1H, d, *J* = 5.7 Hz, aromatic H), 7.59 (1H, ddd, *J* = 8.1 Hz, 7.1 Hz, 1.2 Hz, aromatic H), 7.78 (1H, d, *J* = 8.1 Hz, aromatic H), 8.25 (1H, d, *J* = 7.5 Hz, aromatic H), 8.28 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 23.2 (*C*H$_3$), 29.2 (C4'), 38.9 (C3') 50.5 (Ph*C*HCH$_3$), 59.0 (C1'), 121.0, 126.0, 126.1, 126.4, 126.6, 126.8, 126.9, 127.44, 127.49, 127.53, 128.4, 129.2, 130.1, 134.8, 135.4, 137.4, 141.1, 144.7, 157.1 (21×aromatic C), 161.5 (N*C*ON). HRMS (ESI) calcd for $C_{27}H_{25}N_3O$: 407.1998, found 408.1614 (M+1), 430.1395 (M+Na). The de of > 95% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 90/10, 0.8 mL/min, 25 °C, 280 nm, t = 15.69 min for (-). $[\alpha]_D^{25}$ = -297.5 (c = 1.15, CH_2Cl_2).



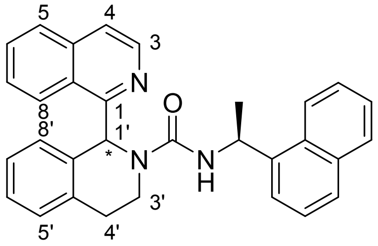
(-)-**87**

ii. With (*S*)-(-)-1-naphthylethyl isocyanate

BIQ *rac*-**68** (1.3 g, 5.0 mmol) was treated with (*S*)-(-)-1-naphthylethyl isocyanate (0.99 g, 5.0 mmol) in CH_2Cl_2 (30 mL) following the general procedure to give the mixture of (+)-2'-((*S*)-1'-(1-naphthyl)ethylcarbamoyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**88** and (-)-2'-((*S*)-1'-(1-naphthyl)ethylcarbamoyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (-)-**89** as white powder (2.3 g, > 99%). All attempts to separate ureas (+)-**88** and (-)-**89** by recrystallizing the mixture from various solvents (MeOH, EtOH, IPA, CH_3CN, THF, EA, $CHCl_3$ or combination of these solvents) were unsuccessful. The mixture was then separated by repetitive column chromatography to give urea (+)-**88** as white powder (0.38 g, 33%). m.p. 98-102 ^oC. FTIR (Nujol) ν_{max}: 3338, 1624, 1526, 1376, 1232, 778, 748 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.48 (3H, d, *J* = 6.9 Hz, C*H*$_3$), 2.91-3.11 (2H, m, 1×H4' and 1×H3'), 3.51 (1H, ddd, *J* = 13.2 Hz, 11.0 Hz, 4.5 Hz, 1×H4'), 4.08 (1H, dt, *J* = 13.2 Hz, 3.5 Hz, 1×H3'), 5.74 (1H, p, *J* = 6.8 Hz, PhC*H*CH$_3$), 6.27 (1H, br d, *J* = 6.6 Hz, CON*H*), 6.89 (1H, d, *J* = 7.8 Hz, aromatic H), 7.00 (1H, s, H1'), 7.03 (1H, t, *J* = 7.8 Hz, aromatic H), 7.14-7.22 (2H, m, 2×aromatic H), 7.33-7.41 (3H, m, 3×aromatic H), 7.45-7.50 (2H, m, 2×aromatic H), 7.59 (1H, d, *J* = 5.4 Hz, aromatic H), 7.63 (1H, ddd, *J* = 9.0 Hz, 6.9 Hz, 1.2 Hz, aromatic H), 7.71 (1H, d, *J* = 8.1 Hz, aromatic H), 7.76-7.82 (2H, m, 2×aromatic H), 8.05-8.08 (1H, m, 1×aromatic H), 8.32 (1H, d, *J* = 8.4 Hz, aromatic H), 8.41 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.0 (*C*H$_3$), 28.9 (C4'), 38.8 (C3') 46.3 (Ph*C*HCH$_3$), 58.8 (C1'), 121.1, 122.3, 123.7, 125.3, 125.6, 126.1, 126.2, 126.3, 126.8 126.9, 127.5, 127.55, 127.65, 127.8, 128.7, 129.2, 130.1, 131.0, 134.0, 134.8, 135.4, 137.3, 140.2, 141.0, 157.0 (25×aromatic C), 161.5 (N*C*ON). Mass (ESI) calcd for $C_{31}H_{27}N_3O$: 457.22, found 458.13 (M+1). The de of 96% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 ^oC, 254 nm, t = 32.06 min for (+). $[\alpha]_D^{25}$ = +272.2 (c = 0.83, CH_2Cl_2).



(+)-**88**

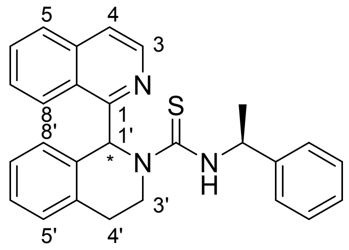


(-)-**89**

And urea (-)-**89** as white powder (0.41 g, 36%). m.p. 96-99 °C. FTIR (Nujol) ν_{max}: 3338, 1623, 1525, 1376, 1235, 778, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (3H, d, J = 6.6 Hz, CH_3), 2.99-3.04 (2H, m, 1×H4' and 1×H3'), 3.61-3.71 (1H, m, 1×H4'), 4.32 (1H, dt, J = 13.2 Hz, 3.9 Hz, 1×H3'), 5.71 (1H, p, J = 6.9 Hz, $PhCHCH_3$), 6.29 (1H, br d, J = 6.9 Hz, CON*H*), 6.77 (1H, d, J = 7.8 Hz, aromatic H), 6.81 (1H, s, H1'), 6.99 (1H, t, J = 7.4 Hz, aromatic H), 7.13-7.27 (4H, m, 4×aromatic H), 7.32-7.43 (4H, m, 4×aromatic H), 7.55 (1H, t, J = 7.7 Hz, aromatic H), 7.66-7.84 (5H, m, 5×aromatic H), 8.16 (1H, d, J = 8.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 21.6 (CH_3), 29.3 (C4'), 38.9 (C3') 46.3 ($PhCHCH_3$), 59.5 (C1'), 120.9, 122.4, 123.5, 125.2, 125.6, 125.9, 126.1, 126.2, 126.4 126.9, 127.30, 127.33, 127.5, 127.8, 128.5, 129.1, 129.9, 131.1, 133.9, 134.8, 135.3, 137.2, 139.4, 140.6, 157.1 (25×aromatic C), 161.1 (N*C*ON). Mass (ESI) calcd for $C_{31}H_{27}N_3O$: 457.22, found 458.27 (M+1). The de of 98% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t = 23.29 min for (-). $[\alpha]_D^{25}$ = -100.1 (c = 1.07, CH_2Cl_2).

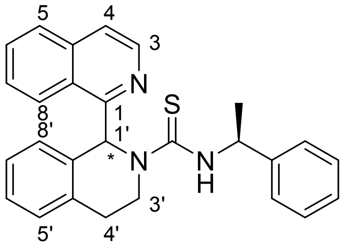
iii. With (*S*)-(-)-α-methylbenzyl isothiocyanate

BIQ *rac*-**68** (1.3 g, 5.0 mmol) was treated with (*S*)-(-)-α-methylbenzyl isothiocyanate (0.82 g, 5.0 mmol) in CH_2Cl_2 (30 mL) following the general procedure to give the mixture (+)-2'-((*S*)-1'-phenylethylcarbathiomoyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**90** and (-)-2'-((*S*)-1'-phenylethylcarbathiomoyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (-)-**91** as white powder (2.11 g, > 99%). All attempts to separate ureas (+)-**90** and (-)-**91** by recrystallizing the mixture from various solvents (MeOH, EtOH, IPA, CH_3CN, THF, EA, $CHCl_3$ or combination of these solvents) were unsuccessful. The mixture was then separated in the same fashion as separation of ureas (+)-**86** and (-)-**87** to give urea (+)-**90** as white powder (0.48 g, 45%). m.p. 85-91 °C. FTIR (Nujol) ν_{max}: 3028, 2926, 1518, 1350, 1222, 1180, 829, 748, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.53 (3H, d, J = 6.9 Hz, CH_3), 3.10 (1H, dt, J = 16.2 Hz, 3.3 Hz, 1×H4'), 3.23 (1H, ddd, J = 16.2 Hz, 11.0 Hz, 5.1 Hz, 1×H3'), 3.73 (1H, ddd, J = 13.2 Hz, 11.1 Hz, 3.6 Hz, 1×H4'), 5.47 (1H, dt, J = 12.9 Hz, 3.6 Hz, 1×H3'), 5.77 (1H, p, J = 6.9 Hz, PhC*H*CH$_3$), 6.94 (1H, d, J = 7.5 Hz, aromatic H), 7.02 (1H, s, H1'), 7.06 (1H, t, J = 7.5 Hz, aromatic H), 7.20-7.39 (6H, m, 6×aromatic H), 7.46 (2H, apparent d, J = 7.5 Hz, 2×aromatic H), 7.61 (1H, t, J = 7.5 Hz, aromatic H), 7.68 (1H, d, J = 5.4 Hz, aromatic H), 7.83 (1H, d, J = 8.1 Hz, aromatic H), 7.88 (1H, d, J = 8.7 Hz, aromatic H), 8.47 (1H, d, J = 5.4 Hz, aromatic H), 8.88 (1H, br d, J = 6.6 Hz, CSN*H*). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 22.4 (*C*H$_3$), 28.8 (C4'), 43.9 (C3') 55.3 (Ph*C*HCH$_3$), 64.5 (C1'), 122.0, 126.1, 126.5, 126.6, 126.7, 127.0, 127.1, 127.4, 127.6, 127.8, 128.6, 129.5, 130.2, 134.4, 134.7, 138.0, 140.3, 144.0, 159.5 (21×aromatic C), 182.2 (N*C*SN). Mass (ESI) calcd for $C_{27}H_{25}N_3S$: 423.18, found 424.13 (M+1). The de of 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t = 24.51 min for (+). $[\alpha]_D^{25}$ = +405.4 (c = 0.56, CH$_2$Cl$_2$).



(+)-**90**

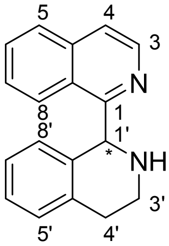
And urea (-)-**91** as white powder (0.43 g, 41%). m.p. 89-92 °C. FTIR (Nujol) ν_{max}: 3027, 2926, 1519, 1454, 1350, 1221, 1180, 829, 748, 699 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.66 (3H, d, J = 6.9 Hz, C*H*$_3$), 3.12 (1H, dt, J = 15.9 Hz, 3.3 Hz, 1×H4'), 3.26 (1H, ddd, J = 15.9 Hz, 11.4 Hz, 5.1 Hz, 1×H3'), 3.72 (1H, ddd, J = 12.9 Hz, 11.4 Hz, 3.6 Hz, 1×H4'), 5.44 (1H, dt, J = 12.3 Hz, 3.5 Hz, 1×H3'), 5.73 (1H, p, J = 6.9 Hz, PhC*H*CH$_3$), 6.93 (1H, d, J = 7.8 Hz, aromatic H), 7.04-7.08 (2H, m, H1' and aromatic H), 7.20-7.37 (8H, m, 8×aromatic H), 7.54-7.59 (2H, m, 2×aromatic H), 7.77 (1H, d, J = 8.1 Hz, aromatic H), 7.87 (1H, d, J = 8.7 Hz, aromatic H), 8.08 (1H, d, J = 5.7 Hz, aromatic H), 8.90 (1H, br d, J = 5.7 Hz, CSN*H*). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 22.4 (*C*H$_3$), 28.8 (C4'), 43.8 (C3') 55.4 (Ph*C*HCH$_3$), 64.6 (C1'), 121.8, 126.1, 126.5, 126.66,



(-)-**91**

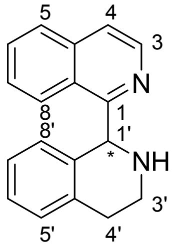
126.73, 127.0, 127.1, 127.4, 127.5, 127.7, 128.5, 129.5, 130.2, 134.4, 134.7, 137.9, 140.4, 143.4, 159.4 (21×aromatic C), 182.1 (N*C*SN). Mass (ESI) calcd for $C_{27}H_{25}N_3S$: 423.18, found 424.27 (M+1). The de of 98% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t = 15.40 min for (-). $[\alpha]_D^{25}$ = -200.5 (c = 0.5, CH_2Cl_2).

.5.2.1.2. Alcoholysis of urea derivatives (+)-86 and (-)-87



(+)-**68**

Sodium butoxide (3.07 mmol, 1.8 mL of 1.71 M solution in *n*-BuOH) was added to a solution of urea (+)-**86** (2.5 g, 6.14 mmol) in *n*-BuOH (50 mL) under nitrogen atmosphere. The mixture was heated up to 120 °C and stirred for 1 h and 40 min. The mixture was then cooled to room temperature and 1.0 M HCl solution (10 mL) was added to quench the reaction. The solvent was evaporated under vacuum and the resulting yellow solid was dissolved into a mixture of Et_2O (30 mL) and H_2O (50 mL). The organic layer was separated and extracted with H_2O (3 × 25 mL). The aqueous layer and extracts were combined and 1.0 M NaOH solution was added to bring the PH to 11. The alkaline solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (3 × 30 mL) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was recrystallized from EtOH to give (+)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**68** as off-white needles (0.97 g, 61%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**68** were identical to those of BIQ *rac*-**68**. The ee of > 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA/TEA = 90/10/0.1, 0.5 mL/min, 25 °C, 254 nm, t = 19.88 min for (+). $[\alpha]_D^{25}$ = +202.0 (c = 0.9, CH_2Cl_2).



(-)-**68**

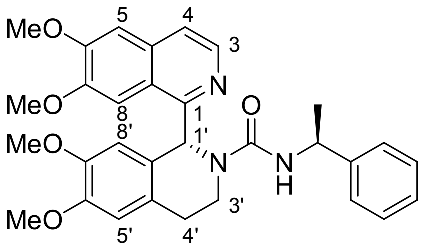
Urea (-)-**87** (2.5 g, 6.14 mmol) was treated with sodium butoxide (3.07 mmol, 1.8 mL of 1.71 M solution in *n*-BuOH) in *n*-BuOH (50 mL) in a similar fashion used for urea (+)-**86** to give a yellow gum which was recrysatllized from EtOH to give (-)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (-)-**68** as an off-white needles (0.86 g, 54%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (-)-**68** were identical to those of BIQ *rac*-**68**. The ee of > 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA/TEA = 90/10/0.1, 0.5 mL/min, 25 °C, 254 nm, t = 27.40 min for (-). $[\alpha]_D^{25}$ = -195.8 (c = 1.2, CH_2Cl_2).

5.2.2.2. Resolution of BIQ *rac*-77

5.2.2.2.1. Preparation and separation of diastereomeric urea derivatives

i. With (*S*)-(-)-α-methylbenzyl isocyanate

BIQ *rac*-**77** (3.8 g, 10.0 mmol) was treated with (*S*)-(-)-α-methylbenzyl isocyanate (1.47 g, 10.0 mmol) in CH_2Cl_2 (30 mL) following the general procedure to give the mixture of (+)-2'-((*S*)-1'-phenylethylcarbamoyl)-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**94** and (-)-2'-((*S*)-1'-phenylethylcarbamoyl)-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (-)-**95** as white powder (5.25 g, > 99%). The mixture was recrystallized from EtOH to give urea (+)-**94** as white needles (0.54 g, 21%). m.p. 223-227 °C. FTIR (Nujol) ν_{max}: 3437, 2925, 1627, 1512, 1478, 1256, 1240, 1159, 1117, 1032, 861, 747, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.42 (3H, d, *J* = 6.9 Hz, C*H*$_3$), 2.80 (1H, apparent d, *J* = 16.5 Hz, 1×H4'), 3.09 (1H, ddd, *J* = 15.6 Hz, 12.2 Hz, 5.7 Hz, 1×H3'), 3.42-3.53 (1H, m, 1×H4'), 3.53 (3H, s, 1×OC*H*$_3$), 3.61 (3H, s, 1×OC*H*$_3$), 3.88 (3H, s, 1×OC*H*$_3$), 3.99 (3H, s, 1×OC*H*$_3$), 4.11-4.17 (1H, m, 1×H3'), 4.97 (1H, p, *J* = 6.9 Hz, PhC*H*CH$_3$), 6.41 (1H, s, H1'), 6.48 (1H, br s, CON*H*), 6.72 (1H, s, aromatic H), 6.86 (1H, s, aromatic H), 7.05 (1H, s, aromatic H), 7.18-7.34 (5H, m, 5×aromatic H), 7.47 (1H, d, *J* = 5.7 Hz, H4), 7.64 (1H, s, aromatic H), 8.32 (1H, d, *J* = 5.7 Hz, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 23.2 (*C*H$_3$), 28.0 (C4'), 38.6 (C3') 50.5 (Ph*C*HCH$_3$), 55.88, 55.91, 55.93, 55.97



(+)-**94** or (-)-**95**

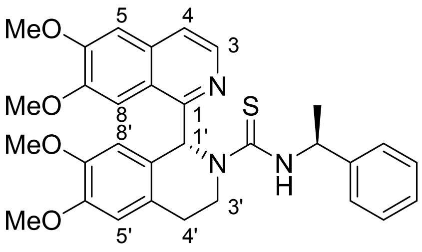
(4×OCH_3), 59.0 (C1'), 105.0, 105.1, 110.7, 111.6, 119.9, 123.0, 126.0, 126.6, 126.9, 127.3, 128.5, 134.2, 139.9, 145.1, 147.9, 148.1, 149.9, 152.5, 157.1 (21×aromatic C), 158.3 (N*C*ON). HRMS (ESI) calcd for $C_{31}H_{33}N_3O_5$: 527.2420, found 528.2784 (M+1). $[\alpha]_D^{25}$ = +268.9 (c = 1.15, CH_2Cl_2).

ii. With (*S*)-(-)-1-naphthylethyl isocyanate

BIQ *rac*-**77** (1.9 g, 5.0 mmol) was treated with (*S*)-(-)-1-naphthylethyl isocyanate (0.99 g, 5.0 mmol) in CH_2Cl_2 (20 mL) following the general procedure to give the mixture of (*1'R*)-2'-((*S*)-1'-(1-naphthyl)ethylcarbamoyl)-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro--1,1'-bisisoquinoline **96** and (*1'S*)-2'-((*S*)-1'-(1-naphthyl)ethylcarbamoyl)-6,6',7,7'--tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline **97** as white powder (2.85 g, 99%). Repetitive recrystallization of the mixture from EtOH only gave partial separation of the two diastereomers.

iii. With (*S*)-(-)-α-methylbenzyl isothiocyanate

BIQ *rac*-**77** (1.9 g, 5.0 mmol) was treated with (*S*)-(-)-α-methylbenzyl isothiocyanate (0.82 g, 5.0 mmol) in CH_2Cl_2 (20 mL) following the general procedure to give the mixture of (+)-2'-((*S*)-1'-phenylethylcarbathiomoyl)-6,6',7,7'-tetramethoxy-1',2',3',4'-tetrahydro-1,1'--bisisoquinoline (+)-**98** and (-)-2'-((S)-1'-phenylethylcarbathiomoyl)-6,6',7,7'--tetramethoxy-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (-)-**99** as white powder (2.7 g, > 99%). The mixture was recrystallized from EtOH to give (+)-**98** as white needles (0.32 g, 12%). m.p. 195-198 °C. FTIR (Nujol) ν_{max}: 3349, 2932, 1512, 1479, 1273, 1239, 1108, 704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.59 (3H, d, *J* = 6.9 Hz, CH_3), 2.85 (1H, apparent d, *J* = 15.6 Hz, 1×H4'), 3.23 (1H, ddd, *J* = 15.9 Hz, 12.5 Hz, 5.1 Hz, 1×H3'), 3.52 (3H, s, 1×OCH_3), 3.55-3.67 (1H, m, 1×H4'), 3.59 (3H, s, 1×OCH_3),



(+)-**98** or (-)-**99**

3.87 (3H, s, 1×OCH_3), 3.97 (3H, s, 1×OCH_3), 5.41 (1H, apparent d, *J* = 10.8 Hz, 1×H3'), 5.77 (1H, p, *J* = 6.8 Hz, PhC*H*CH_3), 6.45 (1H, s, aromatic H), 6.77 (1H, s, aromatic H), 6.95 (1H, br s, H1'), 7.06 (1H, s, aromatic H), 7.22 (1H, apparent t, *J* = 7.4 Hz, aromatic H), 7.31-7.36 (3H, m, 3×aromatic H), 7.48 (2H, apparent d, *J* = 7.5 Hz, 2×aromatic H), 7.55 (1H, d, *J* = 5.7 Hz, H4), 8.34 (1H, d, *J* = 5.4 Hz, H3), 9.37 (1H, br s, CSN*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.5 (*C*H_3), 27.9 (C4'), 43.5 (C3') 55.3 (Ph*C*HCH_3), 55.86, 55.97, 56.02, 55.05 (4×O*C*H_3), 64.5 (C1'), 104.9, 105.3, 110.1, 111.7, 120.7, 122.9, 126.4, 126.5, 126.6, 126.9, 128.5, 135.1, 139.3, 144.2, 148.3, 148.5, 149.8, 152.6, 156.5 (21×aromatic C), 182.3 (N*C*SN). Mass (ESI) calcd for $C_{31}H_{33}N_3O_4S$: 543.22, found 544.13 (M+1). $[\alpha]_D^{25}$ = +448.6 (c = 0.83, CH_2Cl_2).

5.3. Synthesis of *racemic* derivatives based on BIQ *rac*-68 and chiral derivatives based on BIQ (+)-68

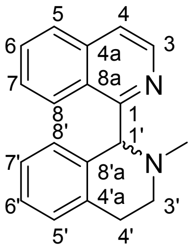
5.3.1. Preparation of *racemic* derivatives based on BIQ *rac*-68

N-Alkyl derivatives

***General Procedure*:** Alkyl bromides or alkyl iodides were added to a mixture of BIQ *rac*-**68** and K_2CO_3 in dry CH_3CN under nitrogen atmosphere. The mixture was heated up to 50 ^{o}C and stirred overnight. The reaction mixture was cooled to room temperature, filtered and the solid was washed with CH_2Cl_2. The combined organic phases were evaporated under vacuum to dryness. The residue was recrystallized from EtOH or subjected to column chromatography to give pure *N*-alkyl derivatives of BIQ *rac*-**68**.

This general procedure was used to prepare derivatives *rac*-**100** ~ *rac*-**104.**

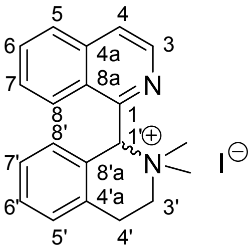
5.3.1.1. Preparation of *rac-N'*-methyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-100



rac-**100**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with iodomethane (78.1 mg, 34.3 µl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give an off-white solid which was purified by column chromatography (EA) to give *rac-N'*-methyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-**100** as light yellow foam (90.4 mg, 66%). m.p. 89-93 °C. FTIR (Nujol) ν_{max}: 2786, 1717, 1621, 1344, 1140, 822, 754, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.19 (3H, s, NCH_3), 2.74 (1H, td, *J* = 11.7 Hz, 3.6 Hz, H_β4'), 2.93 (1H, apparent d, *J* = 16.5 Hz, H_α4'), 3.25 (1H, ddd, *J* = 11.3 Hz, 5.7 Hz, 1.8 Hz, H_β3'), 3.50 (1H, ddd, *J* = 16.2 Hz, 11.7 Hz, 5.7 Hz, H_α3'), 4.98 (1H, s, H1'), 6.53 (1H, d, *J* = 7.8 Hz, H5'), 6.85 (1H, t, *J* = 7.5 Hz, H7'), 7.08 (1H, t, *J* = 7.4 Hz, H6'), 7.19 (1H, d, *J* = 7.5 Hz, H8'), 7.33 (1H, t, *J* = 7.2 Hz, H6), 7.54 (1H, t, *J* = 7.5 Hz, H7), 7.61 (1H, d, *J* = 5.7 Hz, H4), 7.76 (1H, d, *J* = 8.1 Hz, H5), 8.42 (1H, d, *J* = 8.7 Hz, H8), 8.52 (1H, d, *J* = 5.7 Hz, H3). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.8 (C4'), 44.7 (NCH_3), 53.5 (C3'), 75.1 (C1'), 121.0 (C4), 125.9 (C8), 126.2 (C7'), 126.4 (C7), 126.5 (C6'), 126.9 (C5), 127.0 (C8a), 127.3 (C5'), 128.6 (C8'), 129.7 (C6), 133.5 (C4'a), 137.3 (C4a), 137.6 (C8'a), 141.1 (C3), 162.1 (C1). Mass (ESI) calcd for $C_{19}H_{18}N_2$: 274.15, found 275.13 (M+1). ^1H NMR and ^{13}C NMR assignments were accomplished according to those of *rac*-**68**.

5.3.1.2. Preparation of *rac-N',N'*-dimethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline iodide *rac*-101

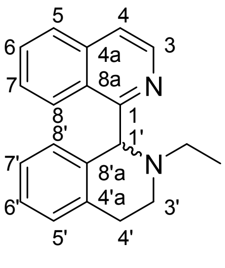


rac-**101**

BIQ *rac*-**100** (137 mg, 0.5 mmol) was reacted with iodomethane (284 mg, 2.0 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (5 mL) to give a light yellow solid which was recrystallized from EtOH to give *rac-N',N'*-dimethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline iodide *rac*-**101** as pale yellow needles (113.0 mg, 54%). m.p. 72-74 °C. FTIR (Nujol) ν_{max}: 3004, 1623, 1583, 1458, 996, 836, 750 cm^{-1}. ^1H

NMR (300 MHz, $CDCl_3$) δ: 3.24 (3H, s, NCH_3), 3.42-3.47 (2H, m, H4'), 3.81 (3H, s, NCH_3), 4.33-4.41 (1H, m, $H_β$3'), 4.90-4.99 (1H, m , $H_α$3'), 6.69 (1H, d, J = 7.8 Hz, aromatic H), 7.00 (1H, t, J = 7.2 Hz, aromatic H), 7.07 (1H, s, H1'), 7.22 (1H, t, J = 7.1 Hz, aromatic H), 7.29 (1H, d, J = 7.5 Hz, aromatic H), 7.70 (1H, d, J = 5.7 Hz, aromatic H), 7.81 (1H, t, J = 7.2 Hz, aromatic H), 7.88-7.95 (2H, m, 2×aromatic H), 8.45 (1H, d, J = 5.4 Hz, aromatic H), 9.42 (1H, d, J = 8.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 24.3 (C4'), 51.1 (NCH_3), 52.5 (NCH_3), 57.4 (C3'), 68.5 (C1'), 122.6, 125.8, 127.3, 127.6, 128.0, 128.6, 128.7, 128.9, 129.1, 130.1, 130.4, 131.4, 136.9, 141.6, 153.3 (15×aromatic C). Mass (ESI) calcd for $C_{20}H_{21}N_2^+$: 289.17, found 289.20.

5.3.1.3. Preparation of *rac-N'*-ethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-102

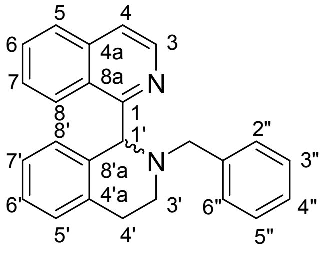


rac-**102**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with bromoethane (66 mg, 45 μl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give a light yellow solid which was purified by column chromatography (EA) to give *rac-N'*-ethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-**102** as an off-white foam (105.8 mg, 74%). m.p. 59-63 °C. FTIR (Nujol) $ν_{max}$: 3400, 2968, 2797, 1586, 1459, 1376, 1342, 1298, 1139, 826, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.93 (3H, t, J = 7.1 Hz, CH_3), 2.32 (1H, hex, J = 6.7 Hz, $CHHCH_3$), 2.55 (1H, hex, J = 6.8 Hz, $CHHCH_3$), 2.62-2.71 (1H, m, $H_β$4'), 2.90-2.98 (1H, m, $H_α$4'), 3.36-3.48 (2H, m, H3'), 5.27 (1H, s, H1'), 6.55 (1H, d, J = 7.8 Hz, H5'), 6.84 (1H, t, J = 7.7 Hz, H7'), 7.06 (1H, t, J = 7.5 Hz, H6'), 7.18 (1H, d, J = 7.5 Hz, H8'), 7.32 (1H, t, J = 7.1 Hz, H6), 7.53 (1H, t, J = 7.5 Hz, H7), 7.59 (1H, d, J = 5.7 Hz, H4), 7.75 (1H, d, J = 8.1 Hz, H5), 8.51 (1H, d, J = 5.7 Hz, H3), 8.59 (1H, d, J = 8.7 Hz, H8). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 11.3 (CH_3), 29.7 (C4'), 48.2 (NCH_2CH_3), 49.0 (C3'), 72.5 (C1'), 120.9 (C4), 125.8 (C8), 126.1 (C7'), 126.2 (C7), 126.7 (C6'), 126.9 (C5), 127.1 (C8a), 127.6 (C5'), 128.6 (C8'), 129.7 (C6), 134.0 (C4'a), 137.3 (C4a), 138.0 (C8'a), 141.0

(C3), 162.5 (C1). Mass (ESI) calcd for $C_{20}H_{20}N_2$: 288.16, found 289.13 (M+1). ^{1}H NMR and ^{13}C NMR assignments were accomplished according to those of *rac*-**68**.

5.3.1.4. Preparation of *rac-N'*-benzyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-103

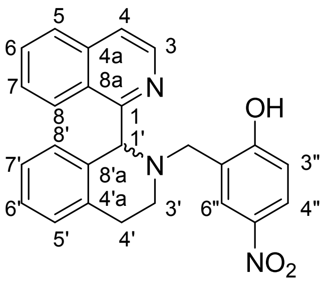


rac-**103**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with benzylbromide (171 mg, 65.4 µl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give a white solid which was recrystallized from EtOH to give *rac-N'*-benzyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-**103** as colorless hexgon crystals (108.5 mg, 62%). m.p. 92-95 °C. FTIR (Nujol) ν_{max}: 3048, 3022, 2927, 2788, 1585, 1493, 1451, 1344, 1138, 1125, 823, 746, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.55 (1H, td, *J* = 11.3 Hz, 3.3 Hz, H_β4'), 2.86 (1H, apparent d, *J* = 16.5 Hz, H_α4'), 3.21-3.40 (3H, m, H_β3' and PhC*H*$_2$), 3.69 (1H, d, *J* = 9.6 Hz, H_α3'), 5.31 (1H, s, H1'), 6.62 (1H, d, *J* = 7.8 Hz, H5'), 6.88 (1H, t, *J* = 7.5 Hz, H7'), 7.06-7.20 (7H, m, H6', H8', H2", H3", H4", H5" and H6"), 7.39 (1H, t, *J* = 7.8 Hz, H6), 7.56 (1H, t, *J* = 7.5 Hz, H7), 7.60 (1H, d, *J* = 5.7 Hz, H4), 7.76 (1H, d, *J* = 8.1 Hz, H5), 8.52 (1H, d, *J* = 5.7 Hz, H3), 8.67 (1H, d, *J* = 8.4 Hz, H8). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.6 (C4'), 48.8 (C3'), 58.4 (NCH_2Ph), 73.7 (C1'), 121.1, 125.9, 126.2, 126.3, 126.5, 126.7, 127.0, 127.2, 127.8, 128.1, 128.7, 128.8, 129.8, 134.0, 137.5, 137.6, 139.1, 141.0, 162.3 (21×aromatic C). Mass (ESI) calcd for $C_{25}H_{22}N_2$: 350.18, found 351.13 (M+1). ^{1}H NMR assignment was accomplished according to that of BIQ *rac*-**68**.

5.3.1.5. Preparation of *rac-N'*-(2-hydro-5-nitro-benzyl)-1',2',3',4'-tetrahydro-1,1'--bisisoquinoline *rac*-104

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with 2-hydro-5-nitro-benzylbromide (116 mg, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give an off-white solid which was purified by column chromatography (EA) to give *rac*-*N'*-(2-hydro-5-nitro-benzyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-**104** as light yellow foam (180 mg, 88%). m.p. 98-101 °C. FTIR (Nujol) ν_{max}: 3058, 2832, 1588, 1491, 1337, 1288, 1091, 829, 750 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.73-2.82 (1H, m, 1×H4'), 2.92 (1H, d, *J* = Hz, 1×H4'), 3.32-3.43 (2H, m, H3'), 3.52 (1H, d, *J* = 14.4 Hz, NC*H*H), 3.91 (1H, d, *J* = 14.1 Hz, NCH*H*), 5.60 (1H, s, H1'), 6.61 (1H, d, *J* = 7.8 Hz, aromatic H), 6.72 (1H, d, *J* = 9.0 Hz, aromatic H), 6.91 (1H, t, *J* = 7.5 Hz, aromatic H), 7.11 (1H, t, *J* = 7.4 Hz, aromatic H), 7.19 (1H, d, *J* = 6.9 Hz, aromatic H), 7.56-7.69 (3H, m, 3×aromatic H), 7.83-7.86 (2H, m, 2×aromatic H), 7.97 (1H, dd, *J* = 9.0 Hz, 2.7 Hz, aromatic H), 8.16 (1H, d, *J* = 8.4 Hz, aromatic H), 8.54 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 29.0 (C4'), 48.9 (C3'), 58.0 (N*C*H$_2$Ph), 69.0 (C1'), 116.5, 121.5, 122.1, 125.1, 125.2, 125.3, 126.5, 126.9, 127.2, 127.3, 127.91, 127.94, 129.0, 130.4, 133.5, 136.1, 137.3, 140.0, 142.0, 160.2, 163.7 (21×aromatic C). Mass (ESI) calcd for C$_{25}$H$_{21}$N$_3$O$_3$: 411.16, found 412.07 (M+1).



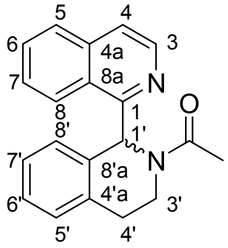
rac-**104**

Amide derivatives

General Procedure**:** Carbonyl chloride or sulfonyl chloride was added to a mixture of BIQ *rac*-**68** and K$_2$CO$_3$ in dry THF under nitrogen atmosphere. The mixture was heated up to 50 °C and stirred overnight. The solvent was removed under vacuum and the solid formed was redissolved in a mixture of H$_2$O and CH$_2$Cl$_2$. The aqueous layer was separated and extracted with CH$_2$Cl$_2$. The combined organic layer and extracts were washed with brine, dried over MgSO$_4$ and evaporated till dryness under vacuum. The residue was recrystallized from EtOH to give pure product.

This general procedure was used to prepare derivatives *rac*-**105** and *rac*-**106.**

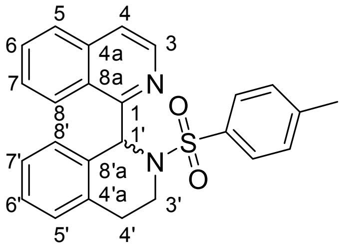
5.3.1.6. Preparation of *rac-N'*-ethanoyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-105



rac-**105**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with acetyl chloride (78.5 mg, 39.1 µl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in THF (5 mL) to give a white solid that was recrystallized from EtOH to give *rac-N'*-ethanoyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-**105** as colorless needles (104.3 mg, 69%). m.p. 97-99 °C. FTIR (Nujol) ν_{max}: 3430, 1585, 1333, 1161, 1091, 971, 735, 667 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.16 (3H, s, C*H*$_3$), 3.07-3.11 (2H, m, H4'), 3.81 (1H, dt, *J* = 13.5 Hz, 3.9 Hz, 1×H3'), 4.15-4.25 (1H, m, 1×H3'), 6.88 (1H, d, *J* = 7.8 Hz, aromatic H), 7.07 (1H, td, *J* = 7.4 Hz, 1.5 Hz, aromatic H), 7.17 (1H, t, *J* = 7.2 Hz, aromatic H), 7.22 (1H, apparent d, *J* = 6.9 Hz, aromatic H), 7.53 (1H, d, *J* = 5.4 Hz, aromatic H), 7.67 (1H, s, H1'), 7.69-7.75 (2H, m, 2×aromatic H), 7.80-7.83 (1H, m, aromatic H), 8.37 (1H, d, *J* = 5.4 Hz, aromatic H), 8.96 (1H, apparent d, *J* = 9.3 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 21.8 (CO*C*H$_3$), 29.3 (C4'), 41.3 (C3'), 52.9 (C1'), 120.4, 126.0, 126.2, 126.7, 127.1, 127.3, 127.9, 128.0, 129.0, 130.1, 134.2, 136.1, 136.6, 141.7, 161.2 (15×aromatic C), 169.2 (N*C*OCH$_3$). Mass (ESI) calcd for $C_{20}H_{18}N_2O$: 302.14, found 303.73 (M+1).

5.3.1.7. Preparation of *rac-N'*-tosyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline *rac*-106



rac-**106**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with *p*-toluene sulfonyl chloride (95 mg, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in THF (5 mL) to give a white solid that was recrystallized from EtOH to give *rac-N'*-tosyl-1',2',3',4'--tetrahydro-1,1'-bisisoquinoline *rac*-**106** as colorless cubes (147.0 mg, 71%). m.p. 122-125 °C. FTIR (Nujol) ν_{max}: 2912, 1643, 1430, 835, 769, 747, 635 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.24 (3H, s, PhC*H*$_3$), 2.89-3.02 (2H, m, H4'), 3.91 (1H, dt, *J* = 14.4 Hz, 4.4 Hz, 1×H3'), 4.11-4.21 (1H, m, 1×H3'), 6.81 (1H, d, *J* = 7.8 Hz, aromatic H), 6.88 (2H, apparent d, *J* = 7.8 Hz, 2×aromatic H), 6.99 (1H, td, *J* = 6.9 Hz, 2.4 Hz, aromatic H), 7.07 (1H, s, H1'), 7.06-7.13 (2H, m, 2×aromatic H), 7.28 (1H, apparent d, *J* = 8.1 Hz, 2×aromatic H), 7.44 (1H, d, *J* = 5.4 Hz, aromatic H), 7.68-7.79 (3H, m, 3×aromatic H), 8.21 (1H, d, *J* = 5.7 Hz, aromatic H), 8.80 (1H, apparent d, *J* = 9.3 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 21.3 (PhCH_3), 27.8 (C4'), 40.5 (C3'), 55.7 (C1'), 120.3, 125.3, 126.1, 126.8, 126.9, 127.0, 127.17, 127.19, 128.0, 128.9, 129.2, 130.1, 133.8, 134.9, 136.6, 136.8, 141.8, 142.7, 160.1 (21×aromatic C). Mass (ESI) calcd for $C_{25}H_{22}N_2O_2S$: 414.14, found 415.20 (M+1).

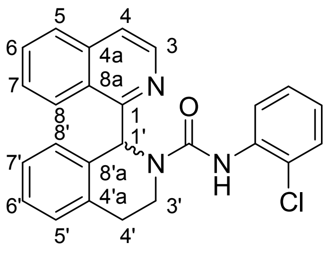
Urea derivatives

***General Procedure*:** Isocyanate was added to a solution of BIQ *rac*-**68** in dry CH_2Cl_2 under nitrogen atmosphere. The reaction mixture was stirred overnight and then washed with brine. The organic phase was separated, dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was recrystallized from EtOH or subjected to column chromatography to give the pure urea derivative.

This general procedure was used to prepare derivatives *rac*-**107** ~ *rac*-**111**.

5.3.1.8. Preparation of *rac-N'*-(2-chlorophenyl)-1,1'-bisisoquinoline-2'-carboxamide *rac*-107

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with 2-chlorophenyl isocyanate (76.8 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 1/9) to give *rac-N'*-(2--chlorophenyl)-1,1'-bisisoquinoline-2-carboxamide *rac*-**107** as light grey foam (199.0 mg, 96%). m.p. 170-173 °C. FTIR (Nujol) ν_{max}: 3231, 1656, 1591, 1502, 1438, 1383, 1288, 1220, 821, 746 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.21-3.25 (2H, m, H4'), 3.90-3.99 (1H, m, 1×H3'), 4.15-4.22 (1H, m, 1×H3'), 6.93 (1H, td, *J* = 7.7 Hz, 1.5

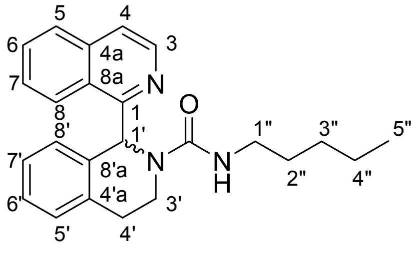


rac-**107**

Hz, aromatic H), 7.02 (1H, d, *J* = 7.5 Hz, aromatic H), 7.10 (1H, td, *J* = 7.4 Hz, 1.5 Hz, aromatic H), 7.18-7.33 (5H, m, H1' and 4×aromatic H), 7.57 (1H, td, *J* = 8.4 Hz, 1.2 Hz, aromatic H), 7.60 (1H, d, *J* = 5.4 Hz, aromatic H), 7.67 (1H, td, *J* = 7.5 Hz, 0.9 Hz, aromatic H), 7.84 (1H, d, *J* = 8.1 Hz, aromatic H), 8.09 (1H, dd, *J* = 8.4 Hz, 1.5 Hz, aromatic H), 8.15 (1H, br s, CON*H*), 8.43 (1H, d, *J* = 8.7 Hz, aromatic H), 8.47 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.8 (C4'), 39.9 (C3'), 57.8 (C1'), 121.0, 122.0, 123.0, 123.3, 125.8, 126.5, 126.7, 127.1, 127.46, 127.53, 127.6, 127.7, 128.9, 129.3, 130.1, 134.6, 135.3, 136.3, 137.3, 141.5, 154.8 (21×aromatic C), 160.9 (N*C*ON). Mass (ESI) calcd for $C_{25}H_{20}ClN_3O$: 413.13, found 414.13 (M+1).

5.3.1.9. Preparation of *rac-N'*-pentyl-1,1'-bisisoquinoline-2'-carboxamide *rac*-108

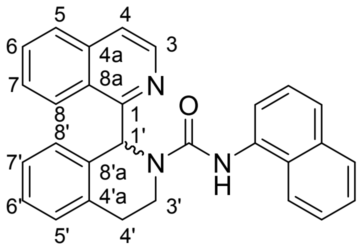
BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with pentyl isocyanate (57 mg, 65 µl, 0.5 mmol) in CH_2Cl_2 (5 mL) to give an off-white solid that was recrystallized from EtOH to give *rac-N'*-pentyl-1,1'-bisisoquinoline-2'--carboxamide *rac*-**108** as white needles (119.2 mg, 64%).



rac-**108**

m.p. 139-142 °C. FTIR (Nujol) ν_{max}: 3282, 3057, 2953, 2926, 2859, 1610, 1543, 1250, 826, 740 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (3H, t, *J* = 6.9 Hz, H5"), 1.16-1.35 (4H, m, H4" and H3"), 1.45 (2H, p, *J* = 7.1 Hz, H2"), 3.05-3.08 (2H, m, H4'), 3.11-3.30 (2H, m, H1"), 3.66-3.75 (1H, m, 1×H3'), 4.14 (1H, dt, *J* = 13.5 Hz, 3.9 Hz, 1×H3'), 5.72 (1H, br s, CON*H*), 6.88 (1H, d, *J* = 7.8 Hz, aromatic H), 6.99 (1H, s, H1'), 7.04 (1H, t, *J* = 7.5 Hz, aromatic H), 7.17 (1H, t, *J* = 7.4 Hz, aromatic H), 7.23 (1H, d, *J* = 7.5 Hz, aromatic H), 7.52 (1H, apparent t, *J* = 7.2 Hz, aromatic H), 7.57 (1H, d, *J* = 5.4 Hz, aromatic H), 7.63 (1H, t, *J* = 7.5 Hz, aromatic H), 7.81 (1H, d, *J* = 8.1 Hz, aromatic H), 8.39 (1H, d, *J* = 7.5 Hz, aromatic H), 8.41 (1H, d, *J* = 5.4 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 14.0 (C5"), 22.4 (C4"), 28.9 (C3"), 29.1 (C2"), 29.8 (C4'), 38.9 (C1"), 41.0 (C3'), 58.4 (C1'), 120.9, 126.1, 126.3, 126.7, 126.8, 127.4, 127.50, 127.55, 129.1, 130.0, 134.8, 135.6, 137.2, 141.2, 157.9 (15×aromatic C), 161.6 (NCON). Mass (ESI) calcd for $C_{24}H_{27}N_3O$: 373.22, found 374.13 (M+1).

5.3.1.10. Preparation of *rac*-*N'*-naphthyl-1,1'-bisisoquinoline-2'-carboxamide *rac*-109

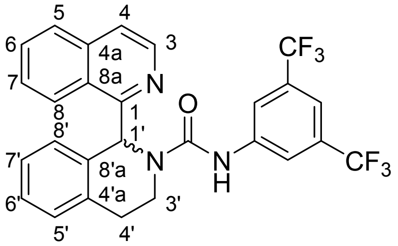


rac-**109**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with 1-naphthyl isocyanate (84.5 mg, 72 µl, 0.5 mmol) in CH_2Cl_2 (5 mL) to give a white solid that was recrystallized from EtOH to give *rac*-*N'*-naphthyl-1,1'-bisisoquinoline-2'-carboxamide *rac*-**109** as white needles (189.2 mg, 88%). m.p. 153-157 °C. FTIR (Nujol) ν_{max}: 3276, 3053, 1619, 1525, 1502, 1389, 1248, 1224, 824, 790, 773, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.13 (1H, apparent d, *J* = 16.2 Hz, 1×H4'), 3.29 (1H, ddd, *J* = 16.5 Hz, 16.2 Hz, 5.4 Hz, 1×H4'), 3.67 (1H, td, *J* = 12.6 Hz, 3.3 Hz, 1×H3'), 4.62 (1H, apparent dd, *J* = 10.5 Hz, 3.0 Hz, 1×H3'), 6.98 (1H, d, *J* = 7.8 Hz, aromatic H), 7.10 (1H, s, H1'), 7.11 (1H, t, *J* = 7.2 Hz, aromatic H), 7.27 (1H, t, *J* = 7.5 Hz, aromatic H), 7.36 (1H, d, *J* = 7.8 Hz, aromatic H), 7.40-7.54 (4H, m, 4×aromatic H), 7.61 (1H, d, *J* = 8.1 Hz, aromatic H), 7.65 (1H, t, *J* = 7.2 Hz, aromatic H), 7.71 (1H, d, *J* = 5.7 Hz, aromatic H), 7.81-7.89 (3H, m, 3×aromatic H), 8.07(1H, d, *J* = 8.7 Hz, aromatic H), 8.12 (1H, d, *J* = 8.1 Hz, aromatic H), 8.55 (1H, d, *J* = 5.7 Hz, aromatic H), 9.03 (1H, br s, CON*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 29.2 (C4'), 38.8 (C3'), 60.8 (C1'), 119.9, 121.7, 121.8, 124.2, 125.6, 125.7, 125.9, 126.3, 126.62, 126.63, 127.2, 127.5, 127.56, 127.64, 127.7, 128.5, 129.5, 130.2, 134.3, 134.6, 134.8, 134.9, 137.9, 141.0, 156.4 (25×aromatic C), 161.0 (NCON). Mass (ESI) calcd for $C_{29}H_{23}N_3O$: 429.18, found 430.27 (M+1).

5.3.1.11. Preparation of *rac*-*N'*-(3,5-di-trifluoromethylphenyl)-1,1'-bisisoquinoline-2'--carboxamide *rac*-110

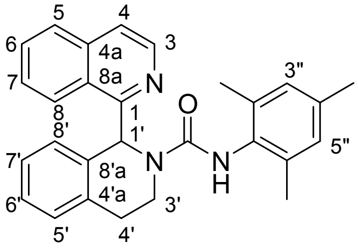
BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with 3,5-ditrifluoromethylphenyl isocyanate (128 mg, 87 µl, 0.5 mmol) in CH_2Cl_2 (5 mL) to give a white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give *rac*-*N'*-(3,5-di-trifluoromethylphenyl)-1,1'-bisisoquinoline-2'-carboxamide *rac*-**110** as white foam (245.3 mg, 95%). m.p. 103-107 °C. FTIR (Nujol) ν_{max}: 3328, 3058, 1654, 1560, 1474, 1444, 1376, 1278, 1179, 1131, 934, 883, 829, 747 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.98-3.17 (2H, m, H4'), 3.55 (1H, apparent t, *J* = 14.0 Hz, 1×H3'), 4.51 (1H, apparent d, *J* = 12.3 Hz, 1×H3'), 6.90 (1H, d, *J* = 7.8 Hz, aromatic H), 6.92 (1H, d, *J* = 4.5 Hz, aromatic H), 7.04 (1H, t, *J* = 7.4 Hz, aromatic H), 7.18-7.27 (2H, m, 2×aromatic H), 7.37 (1H, t, *J* = 7.8 Hz, aromatic H), 7.45 (1H, s, H1'), 7.57 (1H, t, *J* = 6.9 Hz, aromatic H), 7.63 (1H, d, *J* = 5.7 Hz, aromatic H), 7.78 (1H, d, *J* = 8.1 Hz, aromatic H), 7.98 (3H, s, 3×aromatic H), 8.49 (1H, d, *J* = 5.7 Hz, aromatic H), 9.78 (1H, br s, CON*H*). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 29.0 (C4'), 38.6 (C3'), 60.5 (C1'), 115.6 (1×*C*F$_3$), 119.2 (1×*C*F$_3$), 121.6, 122.1, 125.2, 126.0, 126.5, 126.8, 127.3, 127.4, 127.8, 129.5, 130.4, 131.7, 132.1, 134.16, 134.20, 137.9, 140.6, 141.6, 155.2 (21×aromatic C), 160.5 (N*C*ON). Mass (ESI) calcd for $C_{27}H_{19}F_6N_3O$: 515.14, found 516.07 (M+1).



rac-**110**

5.3.1.12. Preparation of *rac*-*N'*-(2,4,6-trimethylphenyl)-1,1'-bisisoquinoline-2'-carboxamide *rac*-111

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with 2,4,6-trimethylphenyl isocyanate (80.5 mg, 0.5 mmol) in CH$_2$Cl$_2$ (5 mL) to give a white solid that was recrystallized from EtOH to give *rac*-*N'*-(2,4,6-trimethylphenyl)-1,1'-bisisoquinoline-2'-carboxamide *rac*-**111** as colourless long needles (147.5 mg, 70%). m.p. 223-227 °C. FTIR (Nujol) ν_{max}: 3260, 3024, 2942, 1625, 1509, 1396, 1292, 1238, 842, 831, 740 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.01 (6H, s, 2''-C*H*$_3$ and 6''-C*H*$_3$), 2.23 (3H, s, 4''-C*H*$_3$), 3.03 (1H, dt, *J* = 16.2 Hz, 3.0 Hz, 1×H4'), 3.17 (1H, ddd, *J* = 16.2 Hz, 13.8 Hz, 5.1 Hz, 1×H4'), 3.66 (1H, td, *J* = 12.6 Hz, 3.9 Hz, 1×H3'),



rac-**111**

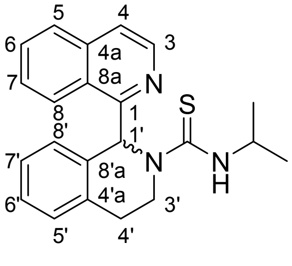
4.36 (1H, dd, *J* = 13.2 Hz, 2.7 Hz, 1×H3'), 6.82 (2H, s, H3" and H5"), 6.91 (1H, d, *J* = 7.8 Hz, aromatic H), 7.07 (1H, s, H1'), 7.07 (1H, t, *J* = 6.9 Hz, aromatic H), 7.22 (1H, t, *J* = 7.4 Hz, aromatic H), 7.29 (1H, d, *J* = 7.2 Hz, aromatic H), 7.38 (1H, br s, CON*H*), 7.45 (1H, t, *J* = 7.8 Hz, aromatic H), 7.61-7.66 (2H, m, 2 × aromatic H), 7.83 (1H, d, *J* = 8.4 Hz, aromatic H), 8.26 (1H, d, *J* = 8.4 Hz, aromatic H), 8.43 (1H, d, *J* = 5.4 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 18.3 (2"-CH_3 and 6"-CH_3), 20.9 (4"-CH_3), 29.3 (C4'), 39.0 (C3'), 59.7 (C1'), 121.2, 126.2, 126.4, 126.7, 127.0, 127.48, 127.54, 127.7, 128.8, 129.4, 130.1, 133.1, 134.8, 135.2, 135.3, 135.7, 137.5, 141.2, 156.1 (21×aromatic C), 161.5 (N*C*ON). Mass (ESI) calcd for $C_{28}H_{27}N_3O$: 421.22, found 422.53 (M+1).

Thiourea derivatives

***General Procedure*:** Isothiocyanate was added to a solution of BIQ *rac*-**68** in dry CH_2Cl_2 under nitrogen atmosphere and the reaction mixture was stirred overnight. The mixture was washed with brine. The organic phase was separated, dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was recrystallized from EtOH or subjected to column chromatography to give the pure thiourea derivative.

This general procedure was used to prepare derivatives *rac*-**112** ~ *rac*-**118**.

5.3.1.13. Preparation of *rac-N'*-isopropyl-1,1'-bisisoquinoline-2'-carbothioamide *rac*-112

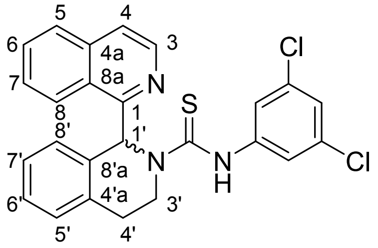


rac-**112**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with isoprpyl isothiocyanate (50.5 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) to give a white solid that was recrystallized from EtOH to give *rac-N'*-isopropyl-1,1'-bisisoquinoline-2'-carbothioamide *rac*-**112** as colourless cubes (153.0 mg, 85%). m.p. 102-105 °C. FTIR (Nujol) ν_{max}: 3331, 2970, 1522, 1491, 1346, 1306, 1234, 1192, 1166, 830, 735 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (3H, d, *J* = 6.6 Hz, C*H*$_3$CHCH$_3$), 1.33 (3H, d, *J* = 6.3 Hz,

CH_3CHCH_3), 3.12-3.30 (2H, m, H4'), 3.78 (1H, ddd, *J* = 10.5 Hz, 13.2 Hz, 4.5 Hz, 1×H3'), 4.62 (1H, oct, *J* = 6.6 Hz, CH_3CHCH_3), 5.36 (1H, dt, *J* = 13.2 Hz, 4.2 Hz, 1×H3'), 6.96 (1H, d, *J* = 7.8 Hz, aromatic H), 7.07 (1H, s, H1'), 7.08 (1H, t, *J* = 7.4 Hz, aromatic H), 7.23 (1H, t, *J* = 7.1 Hz, aromatic H), 7.31 (1H, d, *J* = 7.2 Hz, aromatic H), 7.41 (1H, apparent t, *J* = 7.8 Hz, aromatic H), 7.62 (1H, apparent t, *J* = 7.2 Hz, aromatic H), 7.65 (1H, d, *J* = 6.0 Hz, aromatic H), 7.82 (1H, d, *J* = 8.1 Hz, aromatic H), 7.99 (1H, d, *J* = 8.4 Hz, aromatic H), 8.16 (1H, br d, *J* = 6.0 Hz, CSN*H*), 8.44 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 22.4 (CH_3CHCH_3), 23.1 (CH_3CHCH_3), 28.7 (C4'), 43.6 (C3'), 47.8 (CH_3CHCH_3), 64.3 (C1'), 121.8, 126.1, 126.5, 126.7, 127.0, 127.4, 127.5, 127.7, 129.4, 130.2, 134.6, 134.7, 137.9, 140.4, 159.7 (15×aromatic C), 181.6 (N*C*SN). Mass (ESI) calcd for $C_{22}H_{23}N_3S$: 361.16, found 362.00 (M+1).

5.3.1.14. Preparation of *rac*-*N'*-(3,5-dichlorophenyl)-1,1'-bisisoquinoline-2'-carbothioamide *rac*-113

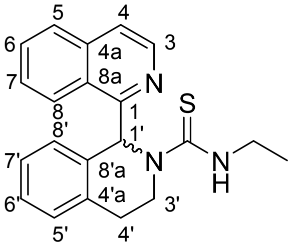


rac-**113**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with 3,5-dichlorophenyl isothiocyanate (102 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) to give an off-white solid that was recrystallized from EtOH to give *rac*-*N'*-(3,5-dichloro-phenyl)-1,1'-bisisoquinoline-2'-carbothioamide *rac*-**113** as light yellow cubes (215.1 mg, 94%). m.p. 108-110 °C. FTIR (Nujol) ν_{max}: 3449, 2962, 2884, 1588, 1543, 1444, 1421, 1371, 1318, 1192, 1048, 834, 804, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.11 (1H, apparent d, *J* = 16.8 Hz, 1×H4'), 3.36 (1H, td, *J* = 14.4 Hz, 5.1 Hz, 1×H4'), 3.65 (1H, td, *J* = 12.0 Hz, 3.3 Hz, 1×H3'), 5.47 (1H, apparent d, *J* = 11.7 Hz, 1×H3'), 6.98 (1H, d, *J* = 7.5 Hz, aromatic H), 7.10-7.15 (2H, m, 2 × aromatic H), 7.22 (1H, s, H1'), 7.27-7.39 (3H, m, 3×aromatic H), 7.45 (1H, s, aromatic H), 7.46 (1H, s, aromatic H), 7.65 (1H, apparent t, *J* = 7.5 Hz, aromatic H), 7.74 (1H, d, *J* = 8.4 Hz, aromatic H), 7.77 (1H, d, *J* = 5.7 Hz, aromatic H), 7.88 (1H, d, *J* = 8.1 Hz, aromatic H), 8.58 (1H, d, *J* = 5.7

Hz, aromatic H), 11.00 (1H, br s, CSN*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.5 (C4'), 44.1 (C3'), 64.7 (C1'), 122.3, 122.4, 124.4, 126.0, 126.8, 127.0, 127.2, 127.8, 127.89, 127.91, 129.7, 130.5, 133.9, 134.3, 134.5, 138.1, 140.5, 142.6, 159.3 (21×aromatic C), 182.2 (N*C*SN). Mass (ESI) calcd for $C_{25}H_{19}Cl_2N_3S$: 463.07, found 463.93 (M+1).

5.3.1.15. Preparation of *rac*-*N'*-ethyl-1,1'-bisisoquinoline-2'-carbothioamide *rac*-114

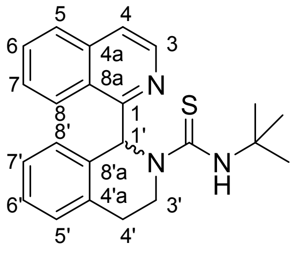


rac-**114**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with ethyl isothiocyanate (43.5 mg, 43.7 µl, 0.5 mmol) in CH_2Cl_2 (5 mL) to give an off-white solid that was recrystallized from EtOH to give *rac*-*N'*-ethyl-1,1'-bisisoquinoline-2'-carbothioamide *rac*-**114** as small yellow cubes (53.4 mg, 31%). m.p. 93-96 °C. FTIR (Nujol) ν_{max}: 3310, 2971, 2930, 1685, 1523, 1450, 1388, 1307, 1230, 829, 748 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 3.15-3.28 (2H, m, H4'), 3.60-3.74 (2H, m, C*H*$_2$CH$_3$), 3.75-3.83 (1H, m, 1×H3'), 5.25 (1H, dt, *J* = 12.9 Hz, 4.1 Hz, 1×H3'), 6.97 (1H, d, *J* = 7.5 Hz, aromatic H), 7.07 (1H, t, *J* = 7.5 Hz, aromatic H), 7.17 (1H, s, H1'), 7.21 (1H, t, *J* = 7.5 Hz, aromatic H), 7.29 (1H, d, *J* = 7.5 Hz, aromatic H), 7.42 (1H, t, *J* = 7.8 Hz, aromatic H), 7.59-7.64 (2H, m, 2×aromatic H), 7.81 (1H, d, *J* = 8.1 Hz, aromatic H), 8.03 (1H, br s, CSN*H*), 8.05 (1H, d, *J* = 8.4 Hz, aromatic H), 8.43 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 14.4 (CH$_2$*C*H$_3$), 28.6 (C4'), 41.3 (*C*H$_2$CH$_3$), 43.5 (C3'), 63.7 (C1'), 121.6, 126.1, 126.5, 126.6, 127.1, 127.3, 127.5, 127.7, 129.2, 130.2, 134.7, 134.8, 137.6, 140.6, 159.9 (15×aromatic C), 182.4 (N*C*SN). Mass (ESI) calcd for $C_{21}H_{21}N_3S$: 347.15, found 348.07 (M+1).

5.3.1.16. Preparation of *rac*-*N'*-(*t*-butyl)-1,1'-bisisoquinoline-2'-carbothioamide *rac*-115

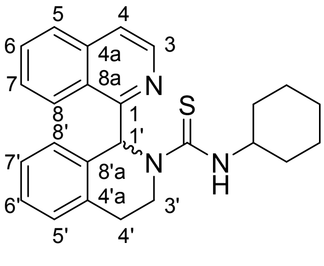
BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with *tert*-butyl isothiocyanate (57.6 mg, 63.4 µl, 0.5 mmol) in CH_2Cl_2 (5 mL) for 4 d to give a white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give *rac*-*N'*-(*t*-butyl)-



rac-**115**

-1,1'-bisisoquinoline-2'-carbothioamide *rac*-**115** as white foam (179.9 mg, 96%). m.p. 97-101 °C. FTIR (Nujol) ν_{max}: 3407, 3052, 2961, 1527, 1394, 1350, 1196, 1162, 829, 747 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.58 (9H, s, 3×C*H*$_3$), 3.09-3.29 (2H, m, H4'), 3.72 (1H, ddd, *J* = 14.4 Hz, 10.7 Hz, 4.2 Hz, 1×H3'), 5.25 (1H, dt, *J* = 13.2 Hz, 4.1 Hz, 1×H3'), 6.97 (1H, d, *J* = 7.5 Hz, aromatic H), 7.04 (1H, t, *J* = 7.4 Hz, aromatic H), 7.12 (1H, s, H1'), 7.19 (1H, t, *J* = 7.4 Hz, aromatic H), 7.27 (1H, d, *J* = 7.5 Hz, aromatic H), 7.37 (1H, t, *J* = 7.5 Hz, aromatic H), 7.57 (1H, t, *J* = 7.7 Hz, aromatic H), 7.61 (1H, d, *J* = 5.4 Hz, aromatic H), 7.78 (1H, d, *J* = 8.1 Hz, aromatic H), 7.98 (1H, d, *J* = 8.4 Hz, aromatic H), 8.24 (1H, br s, CSN*H*), 8.42 (1H, d, *J* = 5.7 Hz, aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 29.3 (3×*C*H$_3$), 30.7 (C4'), 43.1 (C3'), 54.4 (*C*(CH$_3$)$_3$), 64.3 (C1'), 121.7, 126.1, 126.5, 126.6, 127.0, 127.3, 127.5, 127.7, 129.4, 130.1, 134.9, 135.0, 137.8, 140.5, 159.9 (15×aromatic C), 181.6 (N*C*SN). Mass (ESI) calcd for $C_{23}H_{25}N_3S$: 375.18, found 376.00 (M+1).

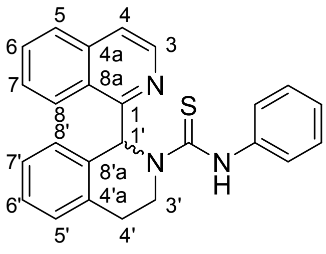
5.3.1.17. Preparation of *rac-N'*-cyclohexyl-1,1'-bisisoquinoline-2'-carbothioamide *rac*-116



rac-**116**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with cyclohexyl isothiocyanate (70.6 mg, 0.5 mmol) in CH$_2$Cl$_2$ (5 mL) to give a white solid that was recrystallized from EtOH to give *rac-N'*-cyclohexyl-1,1'-bisisoquinoline-2'-carbothioamide *rac*-**116** as white needles (116.4 mg, 58%). m.p. 176-179 °C. FTIR (Nujol) ν_{max}: 3233, 3015, 2929, 2847, 1585, 1450, 1399, 1362, 1174, 1143, 754 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.20-2.13 (10H, m, 5×C*H*$_2$), 3.12 (1H, dt, *J* = 16.2 Hz, 3.3 Hz, 1×H4'), 3.26 (1H, ddd, *J* = 16.5 Hz, 11.1 Hz, 5.1 Hz, 1×H4'), 3.74 (1H, ddd, *J* = 12.9 Hz, 11.3 Hz, 3.9 Hz, 1×H3'), 4.31-4.40 (1H, m, CH$_2$C*H*CH$_2$), 5.41 (1H, dt, *J* = 13.2 Hz, 3.6 Hz, 1×H3'), 6.94 (1H, d, *J* = 7.5 Hz, aromatic H), 7.01 (1H, s, H1'), 7.06 (1H, t, *J* = 7.2 Hz, aromatic H), 7.22 (1H, t, *J* = 7.4 Hz, aromatic H), 7.30 (1H, d, *J* = 7.5 Hz, aromatic H), 7.38 (1H, t, *J* = 7.2 Hz, aromatic H), 7.60 (1H, t, *J* = 7.7 Hz, aromatic H), 7.65 (1H, d, *J* = 5.4 Hz, aromatic H), 7.82 (1H, d, *J* = 8.1 Hz, aromatic H), 7.93 (1H, d, *J* = 8.7 Hz, aromatic H), 8.34 (1H, br d, *J* = 6.3 Hz, CSN*H*), 8.44 (1H, d, *J* = 5.4 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 24.6, 24.7, 25.8 (3×CH_2), 28.7 (C4'), 32.4, 33.1 (2×CH_2), 43.6 (C3'), 54.4 (CH_2CHCH_2), 64.6 (C1'), 121.9, 126.2, 126.6, 126.7, 127.0, 127.4, 127.5, 127.7, 129.4, 130.2, 134.6, 134.7, 137.9, 140.4, 159.6 (15×aromatic C), 181.6 (N*C*SN). Mass (ESI) calcd for $C_{25}H_{27}N_3S$: 401.19, found 402.13 (M+1).

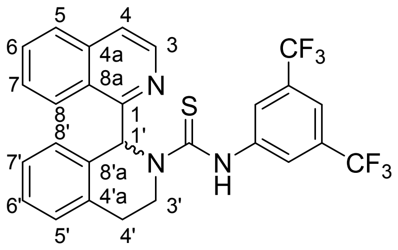
5.3.1.18. Preparation of *rac-N'*-phenyl-1,1'-bisisoquinoline-2'-carbothioamide *rac*-117



rac-**117**

BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with phenyl isothiocyanate (67.6 mg, 95.2 µl, 0.5 mmol) in CH_2Cl_2 (5 mL) to give a white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give *rac-N'*-phenyl--1,1'-bisisoquinoline-2'-carbothioamide *rac*-**117** as white foam (180.6 mg, 91%). m.p. 102-104 °C. FTIR (Nujol) ν_{max}: 3246, 3026, 2928, 1498, 1329, 1228, 934, 827, 748, 694 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.08 (1H, dt, *J* = 16.2 Hz, 3.0 Hz, 1×H4'), 3.28 (1H, ddd, *J* = 15.9 Hz, 12.2 Hz, 5.1 Hz, 1×H4'), 3.72 (1H, td, *J* = 12.5 Hz, 3.6 Hz, 1×H3'), 5.28 (1H, apparent d, *J* = 12.3 Hz, 1×H3'), 6.95 (1H, d, *J* = 7.5 Hz, aromatic H), 7.06-7.11 (2H, m, 2×aromatic H), 7.19-7.40 (8H, m, H1' and 7×aromatic H), 7.57 (1H, t, *J* = 7.7 Hz, aromatic H), 7.65 (1H, d, *J* = 5.4 Hz, aromatic H), 7.79 (1H, d, *J* = 8.1 Hz, aromatic H), 7.94 (1H, d, *J* = 8.4 Hz, aromatic H), 8.48 (1H, d, *J* = 5.7 Hz, aromatic H), 10.43 (1H, br s, CSN*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.6 (C4'), 43.9 (C3'), 64.5 (C1'), 122.1, 124.8, 125.1, 126.1, 126.8, 126.9, 127.2, 127.6, 127.7, 127.8, 128.6, 129.6, 130.4, 134.4, 134.6, 138.0, 140.57, 140.62, 159.6 (21×aromatic C), 182.8 (N*C*SN). Mass (ESI) calcd for $C_{25}H_{21}N_3S$: 395.15, found 396.07 (M+1).

5.3.1.19. Preparation of *rac-N'*-(3,5-di-trifluromethylphenyl)-1,1'-bisisoquinoline-2'--carbothioamide *rac*-118



rac-**118**

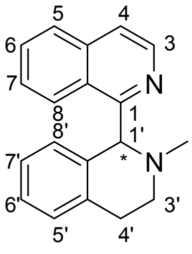
BIQ *rac*-**68** (130 mg, 0.5 mmol) was reacted with 3,5-di-trifluromethylphenyl isothiocyanate (135.6 mg, 91.3 µl, 0.5 mmol) in CH_2Cl_2 (5 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give *rac-N'*-(3,5-di-trifluromethylphenyl)--1,1'-bisisoquinoline-2'-carbothioamide *rac*-**118** as light yellow foam (247.4 mg, 93%). m.p. 102-105 °C. FTIR (Nujol) ν_{max}: 2935, 1474, 1380, 1278, 1180, 1133, 884, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.13 (1H, apparent d, *J* = 16.5 Hz, 1×H4'), 3.36 (1H, ddd, *J* = 16.2 Hz, 12.5 Hz, 5.1 Hz, 1×H4'), 3.66 (1H, t, *J* = 11.6 Hz, 1×H3'), 5.50 (1H, apparent d, *J* = 9.3 Hz, 1×H3'), 6.98 (1H, d, *J* = 7.5 Hz, aromatic H), 7.12 (1H, t, *J* = 7.5 Hz, aromatic H), 7.23-7.38 (4H, m, 3×aromatic H and H1'), 7.60-7.74 (3H, m, 3×aromatic H), 7.77 (1H, d, *J* = 5.7 Hz, aromatic H), 7.86 (1H, d, *J* = 8.4 Hz, aromatic H), 8.06 (2H, s, 2×aromatic H), 8.56 (1H, d, *J* = 5.7 Hz, aromatic H), 11.55 (1H, br s, CSN*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 28.4 (C4'), 43.9 (C3'), 65.1 (C1'), 117.7 (1×*C*F_3), 122.8 (aromatic C), 123.8 (1×*C*F_3), 125.1, 125.9, 126.8, 127.1, 127.9, 128.0, 128.7, 129.8, 130.6, 131.4, 131.8, 132.3, 133.5, 134.2, 138.3, 140.2, 142.2, 159.0 (20×aromatic C), 182.4 (N*C*SN). Mass (ESI) calcd for $C_{27}H_{19}F_6N_3S$: 531.12, found 531.93 (M+1).

5.3.2. Preparation of chiral derivatives based on BIQ (+)-68

The reaction conditions described for preparation of *racemic* derivatives *rac*-**100** ~ *rac*-**118** were adapted accordingly to prepare chiral derivatives (+)-**100** ~ (+)-**118**.

5.3.2.1. Preparation of (+)-*N'*-methyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-100

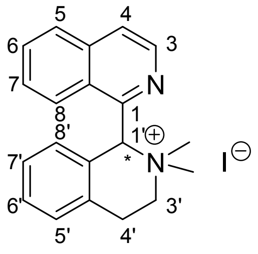
BIQ (+)-**68** (130 mg, 0.5 mmol) was reacted with iodomethane (35 µl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give an off-white solid that was purified by column chromatography (EA) to give (+)-*N'*-methyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**100** as yellow foam (104.1 mg, 76%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**100** were identical to those of *rac*-**100**. $[\alpha]_D^{25}$ = +159.7 (c = 1.13, CH_2Cl_2).



(+)-**100**

5.3.2.2. Preparation of (+)-*N',N'*-dimethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline iodide (+)-101

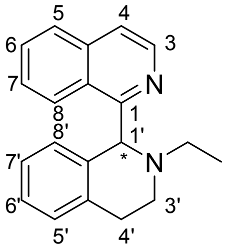
BIQ (+)-**100** (137 mg, 0.5 mmol) was reacted with iodomethane (130 µl, 2.0 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give a light yellow solid that was recrystallized from EtOH to give (+)-*N',N'*-dimethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline iodide (+)-**101** as light yellow needles (116.5 mg, 56%). The melting point, FTIR, ^{1}H NMR and ^{13}C NMR of (+)-**101** were identical to those of *rac*-**101**. $[\alpha]_D^{25}$ = +377.9 (c = 1.21, CH_2Cl_2).



(+)-**101**

5.3.2.3. Preparation of (+)-*N'*-ethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-102

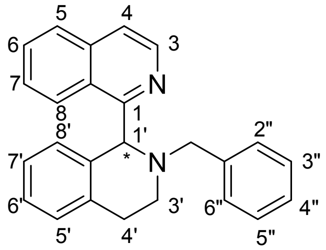
BIQ (+)-**68** (130 mg, 0.5 mmol) was reacted with bromoethane (45 µl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give an off-white solid that was purified by column chromatography (EA) to give (+)-*N'*-ethyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**102** as an off-white foam (132.5 mg, 92%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**102** were identical to those of *rac*-**102**. The ee of > 95% was determined by HPLC (Chiralcel OD-H column):



(+)-**102**

hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 9.92 min for (-) and t_2 = 10.34 min for (+). $[\alpha]_D^{25}$ = +158.2 (c = 1.0, CH_2Cl_2).

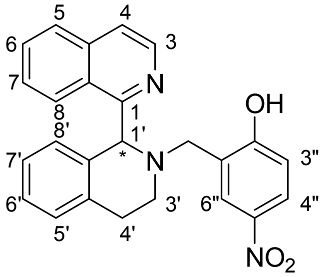
5.3.2.4. Preparation of (+)-*N'*-benzyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-103



(+)-103

BIQ (+)-**68** (130 mg, 0.5 mmol) was reacted with benzylbromide (65 μl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (4 mL) to give an off-white solid that was purified by column chromatography (EA) to give (+)-*N'*-benzyl-1',2',3',4'--tetrahydro-1,1'-bisisoquinoline (+)-**103** as light yellow foam (166.5 mg, 95%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**103** were identical to those of *rac*-**103**. The ee of 96% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 12.66 min for (+) and t_2 = 13.50 min for (-). $[\alpha]_D^{25}$ = +147.5 (c = 0.83, CH_2Cl_2).

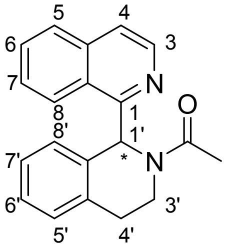
5.3.2.5. Preparation of (+)-*N'*-(2-hydro-5-nitro-benzyl)-1',2',3',4'-tetrahydro-1,1'--bisisoquinoline (+)-104



(+)-104

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with 2-hydro-5-nitro-benzylbromide (58 mg, 0.28 mmol) in presence of K_2CO_3 (69 mg, 0.5 mmol) in CH_3CN (3 mL) to give an off-white solid that was purified by column chromatography (EA) to give (+)-*N'*-(2-hydro-5-nitro-benzyl)-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**104** as an off-white foam (93.5 mg, 91%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**104** were identical to those of *rac*-**104**. The ee of 97% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 26.17 min for (-) and t_2 = 29.72 min for (+). $[\alpha]_D^{25}$ = +62.5 (c = 0.77, CH_2Cl_2).

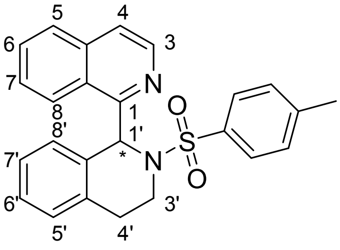
5.3.2.6. Preparation of (+)-*N'*-ethanoyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-105



(+)-105

BIQ (+)-**68** (130 mg, 0.5 mmol) was reacted with acetyl chloride (39 µl, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in THF (5 mL) to give a white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N'*-ethanoyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**105** as white foam (134.0 mg, 89%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**105** were identical to those of *rac*-**105**. $[\alpha]_D^{25}$ = +399.4 (c = 0.65, CH_2Cl_2).

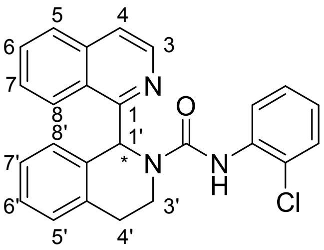
5.3.2.7. Preparation of (+)-*N'*-tosyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-106



(+)-106

BIQ (+)-**68** (130 mg, 0.5 mmol) was reacted with *p*-toluene sulfonic chloride (95 mg, 0.55 mmol) in presence of K_2CO_3 (138 mg, 1.0 mmol) in THF (5 mL) to give a white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N'*-tosyl-1',2',3',4'-tetrahydro-1,1'-bisisoquinoline (+)-**106** as white foam (204.5 mg, 99%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**106** were identical to those of *rac*-**106**. $[\alpha]_D^{25}$ = +243.5 (c = 1.0, CH_2Cl_2).

5.3.2.8. Preparation of (+)-*N'*-(2-chlorophenyl)-1,1'-bisisoquinoline-2'-carboxamide (+)-107

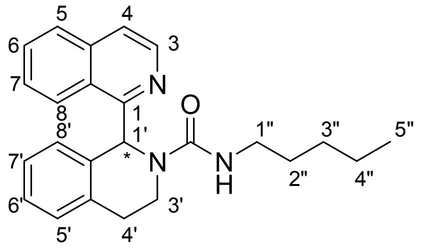


(+)-107

BIQ (+)-**68** (130 mg, 0.5 mmol) was reacted with 2-chlorophenyl isocyanate (76.8 mg, 0.5 mmol) in CH_2Cl_2 (4 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N'*-(2-chloro--phenyl)-1,1'-bisisoquinoline-2-carboxamide (+)-**107** as light grey foam (205.0 mg, 99%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of

(+)-**107** were identical to those of *rac*-**107**. The ee of 95% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 14.16 min for (+) and t_2 = 15.64 min for (-). $[\alpha]_D^{25}$ = +310.4 (c = 0.91, CH_2Cl_2).

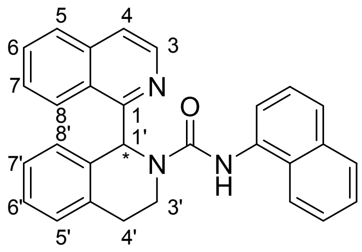
5.3.2.9. Preparation of (+)-*N'*-pentyl-1,1'-bisisoquinoline-2'-carboxamide (+)-108



(+)-108

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with pentyl isocyanate (32.5 µl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N'*--pentyl-1,1'-bisisoquinoline-2'-carboxamide (+)-**108** as white foam (88.9 mg, 96%). The melting point, FTIR, ^1H NMR, ^{13}C NMR and ESI-Mass of (+)-**108** were identical to those of *rac*-**108**. The ee of 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 17.51 min for (+) and t_2 = 26.26 min for (-). $[\alpha]_D^{25}$ = +298.7 (c = 0.91, CH_2Cl_2).

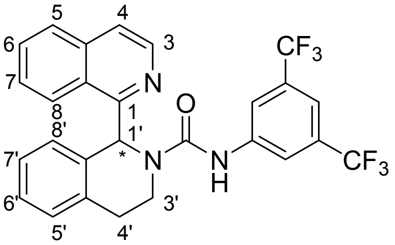
5.3.2.10. Preparation of (+)-*N'*-naphthyl-1,1'-bisisoquinoline-2'-carboxamide (+)-109



(+)-109

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with 1-naphthyl isocyanate (36 µl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N'*-naphthyl-1,1'-bisisoquinoline-2'-carboxamide (+)-**109** as white powder (100.9 mg, 94%). The melting point, FTIR, ^1H NMR, ^{13}C NMR and ESI-Mass of (+)-**109** were identical to those of *rac*-**109**. $[\alpha]_D^{25}$ = +342.4 (c = 1.04, CH_2Cl_2).

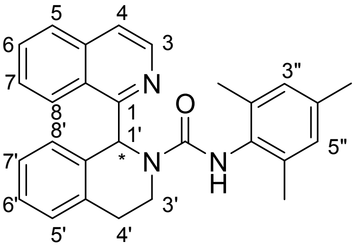
5.3.2.11. Preparation of (+)-*N′*-(3,5-di-trifluoromethylphenyl)-1,1'-bisisoquinoline-2'-carboxamide (+)-110



(+)-**110**

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with 3,5-di-trifluoromethylphenyl isocyanate (43.5 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give (+)-*N′*-(3,5-di-trifluoromethylphenyl)-1,1'-bisisoquinoline-2'-carboxamide (+)-**110** as white foam (115.5 mg, 90%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**110** were identical to those of *rac*-**110**. The ee of > 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 9.18 min for (-) and t_2 = 9.79 min for (+). $[\alpha]_D^{25}$ = +375.7 (c = 1.05, CH_2Cl_2).

5.3.2.12. Preparation of (+)-*N′*-(2,4,6-trimethylphenyl)-1,1'-bisisoquinoline-2'-carboxamide (+)-111



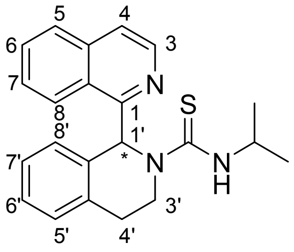
(+)-**111**

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with 2,4,6-trimethylphenyl isocyanate (40.3 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N′*-(2,4,6-trimethylphenyl)-1,1'-bisisoquinoline-2'-carboxamide (+)-**111** as white powder (97.1 mg, 92%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**111** were identical to those of *rac*-**111**. $[\alpha]_D^{25}$ = +213.8 (c = 0.95, CH_2Cl_2).

5.3.2.13. Preparation of (+)-*N′*-isopropyl-1,1'-bisisoquinoline-2'-carbothioamide (+)-112

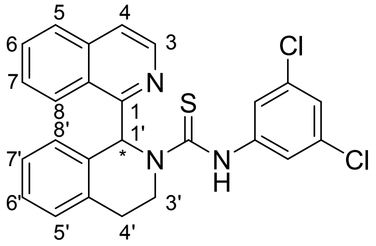
BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with isoprpyl isothiocyanate (26.7 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give a white solid that was purified by column chromatography

(EA/Hexane = 1/9) to give (+)-*N'*-isopropyl-1,1'-bisisoquinoline-2'-carbothioamide (+)-**112** as white foam (86.8 mg, 96%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**112** were identical to those of *rac*-**112**. $[\alpha]_D^{25}$ = +268.0 (c = 0.88, CH_2Cl_2).



(+)-**112**

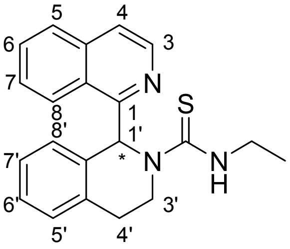
5.3.2.14. Preparation of (+)-*N'*-(3,5-dichlorophenyl)-1,1'-bisisoquinoline-2'-carbothioamide (+)-113



(+)-**113**

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with 3,5-dichlorophenyl isothiocyanate (51 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N'*-(3,5-dichlorophenyl)-1,1'-bisisoquinoline-2'-carbothioamide (+)-**113** as light yellow foam (98.8 mg, 85%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**113** were identical to those of *rac*-**113**. The ee of 98% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 24.56 min for (-) and t_2 = 42.08 min for (+). $[\alpha]_D^{25}$ = +381.6 (c = 0.94, CH_2Cl_2).

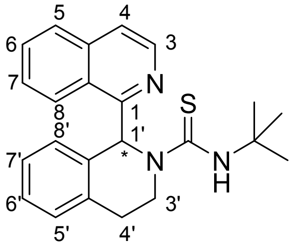
5.3.2.15. Preparation of (+)-*N'*-ethyl-1,1'-bisisoquinoline-2'-carbothioamide (+)-114



(+)-**114**

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with ethyl isothiocyanate (22 µl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 1/9) to give (+)-*N'*-ethyl-1,1'-bisisoquinoline-2'-carbothioamide (+)-**114** as yellow foam (78.6 mg, 90%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**114** were identical to those of *rac*-**114**. $[\alpha]_D^{25}$ = +43.7 (c = 0.83, CH_2Cl_2).

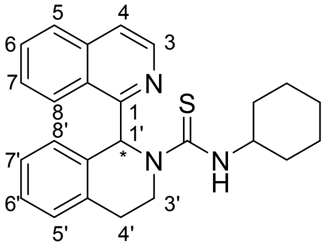
5.3.2.16. Preparation of (+)-*N'*-(*t*-butyl)-1,1'-bisisoquinoline-2'-carbothioamide (+)-115



(+)-**115**

BIQ (+)-**68** (65 mg, 0.25 mmol) was reacted with *tert*-butyl isothiocyanate (31.7 μl, 0.25 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give (+)-*N'*-(*t*-butyl)-1,1'-bisisoquinoline-2'-carbothioamide (+)-**115** as white foam (74.6 mg, 80%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**115** were identical to those of *rac*-**115**. The ee of > 99% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 7.55 min for (-) and t_2 = 8.13 min for (+). $[\alpha]_D^{25}$ = +228.2 (c = 0.83, CH_2Cl_2).

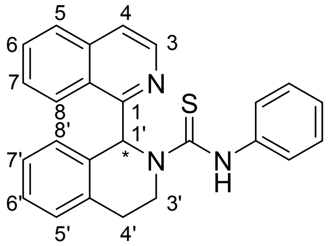
5.3.2.17. Preparation of (+)-*N'*-cyclohexyl-1,1'-bisisoquinoline-2'-carbothioamide (+)-116



(+)-**116**

BIQ (+)-**68** (52 mg, 0.2 mmol) was reacted with cyclohexyl isothiocyanate (27.3 μl, 0.2 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give (+)-*N'*-cyclohexyl-1,1'-bisisoquinoline-2'-carbothioamide (+)-**116** as white foam (73.4 mg, 92%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**116** were identical to those of *rac*-**116**. The ee of > 95% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 13.31 min for (+) and t_2 = 14.45 min for (-). $[\alpha]_D^{25}$ = +195.6 (c = 1.2, CH_2Cl_2).

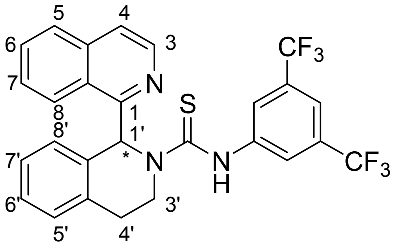
5.3.2.18. Preparation of (+)-*N'*-phenyl-1,1'-bisisoquinoline-2'-carbothioamide (+)-117



(+)-117

BIQ (+)-**68** (52 mg, 0.2 mmol) was reacted with phenyl isothiocyanate (38.1 µl, 0.2 mmol) in CH_2Cl_2 (3 mL) to give a white solid which was purified by column chromatography (EA/Hexane = 0.5/9.5) to give (+)-*N'*-phenyl-1,1'--bisisoquinoline-2'-carbothioamide (+)-**117** as white foam (70.2 mg, 89%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**117** were identical to those of *rac*-**117**. $[\alpha]_D^{25}$ = +159.9 (c = 1.0, CH_2Cl_2).

5.3.2.19. Preparation of (+)-*N'*-(3,5-di-trifluromethylphenyl)-1,1'-bisisoquinoline-2'--carbothioamide (+)-118



(+)-118

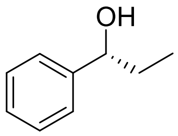
BIQ (+)-**68** (52 mg, 0.2 mmol) was reacted with 3,5-di-trifluromethylphenyl isothiocyanate (36.5 µl, 0.2 mmol) in CH_2Cl_2 (3 mL) to give an off-white solid that was purified by column chromatography (EA/Hexane = 0.5/9.5) to give (+)-*N'*-(3,5-di-trifluromethylphenyl)-1,1'--bisisoquinoline-2'-carbothioamide (+)-**118** as an off-white foam (92.1 mg, 87%). The melting point, FTIR, ^{1}H NMR, ^{13}C NMR and ESI-Mass of (+)-**118** were identical to those of *rac*-**118**. The ee of 97% was determined by HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 10.44 min for (-) and t_2 = 15.88 min for (+). $[\alpha]_D^{25}$ = +199.2 (c = 1.89, CH_2Cl_2).

5.4. Catalytic enantioselective addition of diethylzinc to aldehydes using chiral BIQ ligands

5.4.1. Catalytic enantioselective addition of diethylzinc to benzaldehyde using ligand (+)-68 or (-)-68

General procedure: Ligand (+)-**68** or (-)-**68** (26 mg, 0.1 mmol) was dissolved in THF (1 mL) and diethylzinc (2 mL of 1.0 M in hexane, 2 mmol) was added dropwise at room temperature. The mixture was stirred for 10 min and benzaldehyde **165** (106 mg, 0.1 mL, 1.0 mmol) was injected dropwise *via* a syringe needle. The mixture was stirred for 20 h at room temperature under N_2 atmosphere. The reaction was then quenched with saturated NH_4Cl solution (5 mL). The organic phase was separated and washed with HCl solution (3 × 5 mL), saturated Na_2CO_3 solution (3 × 5 mL) and dried over $MgSO_4$. The resulting organic solution was diluted with diethyl ether (5 mL) and subjected to GC directly for analysis. The yield of product was determined by GC using HP-5 column. The ee value was determined by GC using Chiraldex G-TA column. The absolute configuration of the major enantiomer of product was assigned by comparing the sign of optical rotation value with literature precedents.

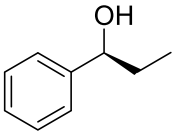
5.4.1.1. (*1R*)-1-phenyl-1-propanol (*R*)-166


(*R*)-**166**

Benzaldehyde **165** (106 mg, 0.1 mL, 1.0 mmol) was treated with diethylzinc (2 mL of 1.0 M in hexane, 2.0 mmol) in the presence of (+)-**68** (26 mg, 0.1 mmol) following the general procedure to give (*1R*)-1-phenyl-1-propanol (*R*)-**166** (72%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.92 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.71-1.88 (2H, m, C*H*$_2$), 4.60 (1H, td, *J* = 6.5 Hz, 2.7 Hz, C*H*), 7.26-7.36 (5H, m, 5×aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 10.1 (*C*H$_3$), 31.9 (*C*H$_2$), 76.1 (*C*H), 126.0 (2×aromatic C), 127.1 (aromatic C), 127.5 (aromatic C), 128.4 (2×aromatic C). The ee of 63% was determined by GC. GC (Chiraldex G-TA column):

Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 8.98 min for (*R*) and t_2 = 9.23 min for (*S*). $[\alpha]_D^{25}$ = +30.7 (c = 0.55, $CHCl_3$) {lit.[146] $[\alpha]_D^{26}$ = +40.3 (c = 1.21, $CHCl_3$) for 96% ee (*R*)}.

5.4.1.2. (*1S*)-1-phenyl-1-propanol (*S*)-166



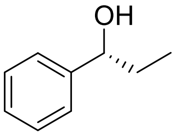
(*S*)-**166**

Benzaldehyde **165** (106 mg, 0.1 mL, 1.0 mmol) was treated with diethylzinc (2 mL of 1.0 M in hexane, 2.0 mmol) in the presence of (-)-**68** (26 mg, 0.1 mmol) following the general procedure to give (*1S*)-1-phenyl-1-propanol (*S*)-**166** (70%, GC yield). The ^1H NMR and ^{13}C NMR spectra of (*S*)-**166** were identiacal to those of (*R*)-**166**. The ee of 61% was determined by GC. $[\alpha]_D^{25}$ = -31.5 (c = 0.62, $CHCl_3$) {lit.[146] $[\alpha]_D^{26}$ = +40.3 (c = 1.21, $CHCl_3$) for 96% ee (*R*)}.

5.4.2. Catalytic enantioselective addition of diethylzinc to various aldehydes using ligand (+)-68

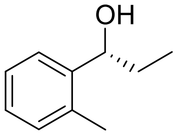
General procedure: Ligand (+)-**68** (39 mg, 0.15 mmol) was dissolved in THF (1 mL) and diethylzinc (3 mL of 1.0 M in hexane, 3 mmol) was added dropwise at room temperature. After complete addition, the color of solution turned orange-red. The mixture was cooled down to 0 °C and stirred for 10 min whereby the aldehyde (1.0 mmol) was injected dropwise *via* a syringe needle. The mixture was stirred for 30 h at 0 °C under N_2 atmosphere. The reaction was then quenched with saturated NH_4Cl solution (5 mL). The organic phase was separated and washed with diluted HCl solution (3 × 5 mL), saturated Na_2CO_3 solution (3 × 5 mL) and dried over $MgSO_4$. The resulting organic solution was diluted with diethyl ether (5 mL) and subjected to GC directly or purified by column chromatography and subjected to HPLC for analysis. The yield of product was determined by GC using HP-5 or Chiraldex G-TA column. The ee value was determined by GC using Chiraldex G-TA column or HPLC using Chiralcel OD-H column. The absolute configuration of the major enantiomer of product was assigned by comparing the sign of optical rotation value with literature precedents.

5.4.2.1. (*1R*)-1-phenyl-1-propanol (*R*)-166


(*R*)-**166**

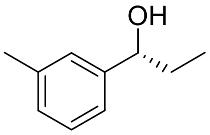
Benzaldehyde **165** (106 mg, 0.1 mL, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-phenyl-1-propanol (*R*)-**166** (96%, GC yield). The ee of 85% was determined by GC. $[\alpha]_D^{25}$ = +43.8 (c = 1.30, $CHCl_3$) {lit.[146] $[\alpha]_D^{26}$ = +40.3 (c = 1.21, $CHCl_3$) for 96% ee (*R*)}.

5.4.2.2. (*1R*)-1-(2-methylphenyl)-1-propanol (*R*)-198


(*R*)-**198**

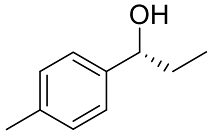
2-methylbenzaldehyde **179** (120 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(2-methylphenyl)-1-propanol (*R*)-**198** (51%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.01 (3H, t, *J* = 7.5 Hz, CH_2CH_3), 1.78 (2H, p, *J* = 7.1 Hz, CH_2), 2.37 (3H, s, CH_3), 2.44 (1H, br s, O*H*), 4.86 (1H, t, *J* = 6.5 Hz, C*H*), 7.16-7.29 (3H, m, 3×aromatic H), 7.48 (1H, d, *J* = 7.2 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 10.4 (CH_2CH_3), 19.1 (CH_3), 30.9 (CH_2), 72.0 (*C*H), 125.3, 126.2, 127.1, 130.3, 134.6, 142.8 (6×aromatic C). The ee of 70% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 16.44 min for (*R*) and t_2 = 18.82 min for (*S*). $[\alpha]_D^{25}$ = +40.5 (c = 0.45, $CHCl_3$) {lit.[211] $[\alpha]_D^{18}$ = -43.0 (c = 0.97, CH_2Cl_2) for 78% ee (*S*)}.

5.4.2.3. (*1R*)-1-(3-methylphenyl)-1-propanol (*R*)-199


(*R*)-**199**

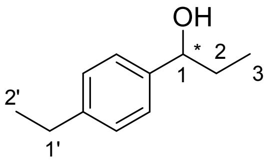
3-methylbenzaldehyde **180** (120 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(3-methylphenyl)-1-propanol (*R*)-**199** (69%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.71-1.88 (2H, m, CH_2), 2.40 (3H, s, CH_3), 2.64 (1H, br s, O*H*), 4.55 (1H, t, *J* = 6.6 Hz, C*H*), 7.11-7.18 (3H, m, 3×aromatic H), 7.28 (1H, apparent t, *J* = 7.5 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 10.2 (CH_2CH_3), 21.5 (CH_3), 31.8 (CH_2), 76.0 (*C*H), 123.1, 126.7, 128.2, 128.3, 138.0, 144.6 (6×aromatic C). The ee of 65% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 14.18 min for (*R*) and t_2 = 14.56 min for (*S*). $[\alpha]_D^{25}$ = +38.7 (c = 0.68, $CHCl_3$) {lit.[168] $[\alpha]_D^{25}$ = +37.9 (c = 1.76, $CHCl_3$) for 95% ee (*R*)}.

5.4.2.4. (*1R*)-1-(4-methylphenyl)-1-propanol (*R*)-200


(*R*)-**200**

4-methylbenzaldehyde **181** (120 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(4-methylphenyl)-1-propanol (*R*)-**200** (17%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J* = 7.4 Hz, CH_2CH_3), 1.68-1.91 (2H, m, CH_2), 2.39 (3H, s, CH_3), 2.66 (1H, br s, O*H*), 4.55 (1H, t, *J* = 6.6 Hz, C*H*), 7.18 (2H, apparent d, *J* = 8.1 Hz, 2 × aromatic H), 7.25 (2H, apparent d, *J* = 8.1 Hz, 2×aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 10.2 (CH_2CH_3), 21.1 (CH_3), 31.8 (CH_2), 75.8 (*C*H), 126.0 (2×aromatic C), 129.0 (2×aromatic C), 137.0 (aromatic C), 141.7 (aromatic C). The ee of 40% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 13.37 min for (*R*) and t_2 = 13.63 min for (*S*). $[\alpha]_D^{25}$ = +18.3 (c = 0.21, $CHCl_3$) {lit.[211] $[\alpha]_D^{18}$ = -27.7 (c = 1.24, CH_2Cl_2) for 65% ee (*S*)}.

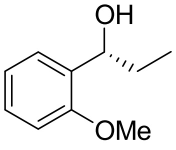
5.4.2.5. (+)-1-(4-ethylphenyl)-1-propanol (+)-201



(+)-**201**

4-ethylbenzaldehyde **182** (134 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (+)-1-(4-ethylphenyl)-1-propanol (+)-**201** (38%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.96 (3H, t, *J* = 7.5 Hz, H3), 1.29 (3H, t, *J* = 7.7 Hz, H2'), 1.71-1.89 (2H, m, H2), 2.61 (1H, br s, O*H*), 2.69 (2H, q, *J* = 7.6 Hz, H1'), 4.55 (1H, t, *J* = 6.8 Hz, H1), 7.21 (2H, appearent d, *J* = 8.1 Hz, 2×aromatic H), 7.28 (2H, appearent d, *J* = 8.1 Hz, 2×aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 10.3 (C3), 15.6 (C2'), 28.6 (C2), 31.8 (C1'), 75.8 (C1), 126.1 (2×aromatic C), 127.8 (2×aromatic C), 142.0 (aromatic C), 143.4 (aromatic C). The ee of 71% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 ^{o}C, t_1 = 6.50 min for (+) and t_2 = 6.57 min for (-). $[\alpha]_D^{25}$ = +21.3 (c = 1.22, $CHCl_3$).

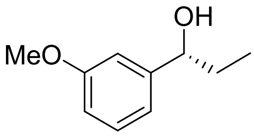
5.4.2.6. (*1R*)-1-(2-methoxyphenyl)-1-propanol (*R*)-202



(*R*)-**202**

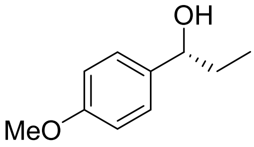
2-methoxybenzaldehyde **183** (136 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(2-methoxyphenyl)-1-propanol (*R*)-**202** (83%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.98 (3H, t, *J* = 7.5 Hz, C*H*$_3$), 1.83 (2H, p, *J* = 7.4 Hz, C*H*$_2$), 2.98 (1H, br s, O*H*), 3.84 (3H, s, OC*H*$_3$), 4.84 (1H, t, *J* = 6.6 Hz, C*H*), 6.89 (1H, d, *J* = 8.1 Hz, aromatic H), 6.98 (1H, td, *J* = 7.5 Hz, 1.2 Hz, aromatic H), 7.26 (1H, td, *J* = 7.8 Hz, 1.8 Hz, aromatic H), 7.34 (1H, dd, *J* = 7.5 Hz, 1.8 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 10.4 (*C*H$_3$), 30.3 (*C*H$_2$), 55.2 (OC*H*$_3$), 71.9 (*C*H), 110.5, 120.7, 127.0, 128.1, 132.6, 156.6 (6×aromatic C). The ee of 74% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 ^{o}C, t_1 = 31.22 min for (*R*) and t_2 = 33.57 min for (*S*). $[\alpha]_D^{25}$ = +19.6 (c = 0.85, $CHCl_3$) {lit.[146] $[\alpha]_D^{26}$ = +23.7 (c = 1.40, $CHCl_3$) for 95% ee (*R*)}.

5.4.2.7. (*1R*)-1-(3-methoxyphenyl)-1-propanol (*R*)-203


(*R*)-**203**

3-methoxybenzaldehyde **184** (136 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(3-methoxyphenyl)-1-propanol (*R*)-**203** (82%, GC yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.92 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.69-1.86 (2H, m, C*H*$_2$), 2.44 (1H, br s, O*H*), 3.81 (3H, s, OC*H*$_3$), 4.55 (1H, t, *J* = 6.5 Hz, C*H*), 6.82 (1H, dd, *J* = 8.4 Hz, 2.4 Hz, aromatic H), 6.91-6.93 (2H, m, 2×aromatic H), 7.26 (1H, t, *J* = 8.1 Hz, aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 10.1 (*C*H$_3$), 31.8 (*C*H$_2$), 55.2 (OC*H*$_3$), 75.9 (*C*H), 111.5, 112.9, 118.4, 129.4, 146.4, 159.7 (6×aromatic C). The ee of 73% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 42.94 min for (*R*) and t_2 = 45.08 min for (*S*). $[\alpha]_D^{25}$ = +22.8 (c = 0.43, CHCl$_3$) {lit.[146] $[\alpha]_D^{26}$ = +40.3 (c = 1.21, CHCl$_3$) for 95% ee (*R*)}.

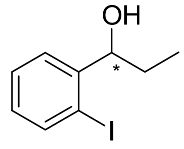
5.4.2.8. (*1R*)-1-(4-methoxyphenyl)-1-propanol (*R*)-204


(*R*)-**204**

4-methoxybenzaldehyde **185** (136 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(4-Methoxyphenyl)-1-propanol (*R*)-**204** (51%, GC yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.89 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.63-1.88 (2H, m, C*H*$_2$), 2.53 (1H, br s, O*H*), 3.79 (3H, s, OC*H*$_3$), 4.50 (1H, t, *J* = 6.8 Hz, C*H*), 6.87 (2H, apparent d, *J* = 8.7 Hz, 2×aromatic H), 7.25 (2H, apparent d, *J* = 8.7 Hz, 2×aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 10.2 (*C*H$_3$), 31.8 (*C*H$_2$), 55.2 (OC*H*$_3$), 75.5 (*C*H), 113.7 (2×aromatic C), 127.2 (2×aromatic C), 136.9 (aromatic C), 158.9 (aromatic C). The ee of 52% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 39.71 min for (*R*) and t_2 = 40.98 min for (*S*). $[\alpha]_D^{25}$ = +20.3 (c = 0.76, CHCl$_3$) {lit.[146] $[\alpha]_D^{26}$ = +38.9 (c = 1.23,

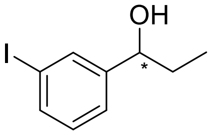
$CHCl_3$) for 96% ee (*R*)}.

5.4.2.9. (+)-1-(2-iodophenyl)-1-propanol (+)-205


(+)-205

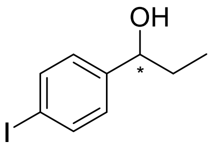
2-iodobenzaldehyde **186** (232 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (+)-1-(2-iodophenyl)-1-propanol (+)-**205** (95%, GC yield). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.03 (3H, t, *J* = 7.4 Hz, CH_3), 1.62-1.86 (2H, m, CH_2), 2.01 (1H, br s, O*H*), 4.83 (1H, t, *J* = 7.5 Hz, C*H*), 6.96 (1H, td, *J* = 7.8 Hz, 1.8 Hz, aromatic H), 7.37 (1H, t, *J* = 8.1 Hz, aromatic H), 7.50 (1H, dd, *J* = 7.8 Hz, 1.5 Hz, aromatic H), 7.80 (1H, dd, *J* = 8.1 Hz, 1.2 Hz, aromatic H). The ee of 73% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 °C, t_1 = 21.10 min for (-) and t_2 = 24.12 min for (+). $[\alpha]_D^{25}$ = +17.8 (c = 1.71, $CHCl_3$).

5.4.2.10. (+)-1-(3-iodophenyl)-1-propanol (+)-206


(+)-206

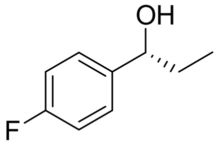
3-iodobenzaldehyde **187** (232 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (+)-1-(3-iodophenyl)-1-propanol (+)-**206** (89%, GC yield). ^1H NMR (300 MHz, $CDCl_3$) δ: 0.93 (3H, t, *J* = 7.4 Hz, CH_3), 1.71-1.83 (2H, m, CH_2), 2.01 (1H, br s, O*H*), 4.55 (1H, t, *J* = 6.5 Hz, C*H*), 7.09 (1H, t, *J* = 7.8 Hz, aromatic H), 7.31 (1H, d, *J* = 7.8 Hz, aromatic H), 7.62 (1H, apparent d, *J* = 7.5 Hz, aromatic H), 7.72 (1H, s, aromatic H). The ee of 80% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 °C, t_1 = 27.27 min for (+) and t_2 = 29.26 min for (-). $[\alpha]_D^{25}$ = +15.3 (c = 1.70, $CHCl_3$).

5.4.2.11. (+)-1-(4-iodophenyl)-1-propanol (+)-207


(+)-**207**

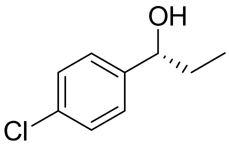
4-iodobenzaldehyde **188** (232 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (+)-1-(4-iodophenyl)-1-propanol (+)-**207** (59%, GC yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.90 (3H, t, *J* = 7.5 Hz, CH_3), 1.63-1.83 (2H, m, CH_2), 1.96 (1H, br s, O*H*), 4.55 (1H, t, *J* = 6.6 Hz, C*H*), 7.08 (1H, apparent d, *J* = 8.4 Hz, 2×aromatic H), 7.66 (1H, apparent d, *J* = 8.4 Hz, 2×aromatic H). The ee of 66% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 ^{o}C, t$_1$ = 28.16 min for (+) and t$_2$ = 29.45 min for (-). $[\alpha]_D^{25}$ = +16.8 (c = 0.85, CHCl$_3$).

5.4.2.12. (*1R*)-1-(4-fluorophenyl)-1-propanol (*R*)-208


(*R*)-**208**

4-fluorobenzaldehyde **189** (124 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(4-fluorophenyl)-1-propanol (*R*)-**208** (33%, GC yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.87 (3H, t, *J* = 7.4 Hz, CH_3), 1.61-1.85 (2H, m, CH_2), 2.86 (1H, br s, O*H*), 4.53 (1H, t, *J* = 6.6 Hz, C*H*), 6.98-7.04 (2H, m, 2×aromatic H), 7.25-7.30 (2H, m, 2×aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 10.0 (*C*H$_3$), 31.9 (*C*H$_2$), 75.3 (*C*H), 114.9, 115.2, 127.6, 127.7, 140.25, 140.30, 160.5, 163.7 (6×aromatic C). The ee of 61% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 ^{o}C, t$_1$ = 3.50 min for (*R*) and t$_2$ = 3.64 min for (*S*). $[\alpha]_D^{25}$ = +23.5 (c = 0.30, CHCl$_3$) {lit.[212] $[\alpha]_D$ = +29.7 (c = 3.0, CHCl$_3$) for 79% ee (*R*)}.

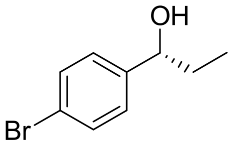
5.4.2.13. (*1R*)-1-(4-chlorophenyl)-1-propanol (*R*)-209



(*R*)-**209**

4-chlorobenzaldehyde **190** (141 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(4-chlorophenyl)-1-propanol (*R*)-**209** (90%, GC yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.86 (3H, t, *J* = 7.5 Hz, C*H*$_3$), 1.61-1.79 (2H, m, C*H*$_2$), 2.66 (1H, br s, O*H*), 4.50 (1H, t, *J* = 6.6 Hz, C*H*), 7.21 (2H, appearent d, *J* = 8.4 Hz, 2×aromatic H), 7.28 (2H, appearent d, *J* = 8.4 Hz, 2×aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 10.0 (*C*H$_3$), 31.9 (*C*H$_2$), 75.2 (*C*H), 127.4 (2×aromatic C), 128.5 (2×aromatic C), 133.0 (aromatic C), 143.0 (aromatic C). The ee of 72% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 °C, t_1 = 9.19 min for (*R*) and t_2 = 9.58 min for (*S*). $[\alpha]_D^{25}$ = +21.7 (c = 2.31, CHCl$_3$) {lit.^{146} $[\alpha]_D^{26}$ = +30.6 (c = 2.08, CHCl$_3$) for 96% ee (*R*)}.

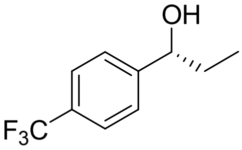
5.4.2.14. (*1R*)-1-(4-bromophenyl)-1-propanol (*R*)-210



(*R*)-**210**

4-bromobenzaldehyde **191** (185 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(4-bromophenyl)-1-propanol (*R*)-**210** (52%, GC yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.85 (3H, t, *J* = 7.5 Hz, C*H*$_3$), 1.58-1.80 (2H, m, C*H*$_2$), 2.83 (1H, br s, O*H*), 4.47 (1H, t, *J* = 6.6 Hz, C*H*), 7.15 (2H, appearent d, *J* = 8.4 Hz, 2×aromatic H), 7.42 (2H, appearent d, *J* = 8.1 Hz, 2×aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 10.0 (*C*H$_3$), 31.8 (*C*H$_2$), 75.2 (*C*H), 121.1 (aromatic C), 127.8 (2×aromatic C), 131.4 (2×aromatic C), 143.5 (aromatic C). The ee of 71% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 °C, t_1 = 15.14 min for (*R*) and t_2 = 15.88 min for (*S*). $[\alpha]_D^{25}$ = +23.4 (c = 0.61, CHCl$_3$) {lit.^{141} $[\alpha]_D^{20}$ = +26.7 (c = 1.50, CHCl$_3$) for 98% ee (*R*)}.

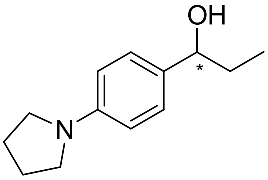
5.4.2.15. (*1R*)-1-(4-trifluoromethylphenyl)-1-propanol (*R*)-211



(*R*)-**211**

4-trifluoromethylbenzaldehyde **192** (174 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(4-trifluoromethylphenyl)-1--propanol (*R*)-**211** (88%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.4 Hz, CH_3), 1.65-1.81 (2H, m, CH_2), 2.84 (1H, br s, O*H*), 4.59 (1H, t, *J* = 6.6 Hz, C*H*), 7.39 (2H, appearent d, *J* = 8.4 Hz, 2×aromatic H), 7.57 (2H, appearent d, *J* = 8.1 Hz, 2×aromatic H). The ee of 72% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 12.34 min for (*R*) and t_2 = 13.18 min for (*S*). $[\alpha]_D^{25}$ = +15.8 (c = 1.30, $CHCl_3$) {lit.[141] $[\alpha]_D^{20}$ = +18.6 (c = 3.40, $CHCl_3$) for 98% ee (*R*)}.

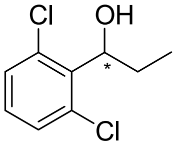
5.4.2.16. (+)-1-(4-(1-pyrrolidinal)-phenyl)-1-propanol (+)-212



(+)-**212**

4-(1-pyrrolidinal)-benzaldehyde **193** (175 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (+)-1-(4-(1-pyrrolidinal)--phenyl)-1-propanol (+)-**212** (153 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (3H, t, *J* = 7.2 Hz, CH_3), 1.63-1.84 (2H, m, CH_2CH_3), 1.96 (4H, apparent t, *J* = 6.6 Hz, NCH_2CH_2), 2.14 (1H, br s, O*H*), 3.24 (4H, apparent t, *J* = 6.6 Hz, NCH_2CH_2), 4.40 (1H, t, *J* = 6.8 Hz, C*H*), 6.51 (2H, d, *J* = 8.7 Hz, 2×aromatic H), 7.15 (2H, d, *J* = 8.7 Hz, 2×aromatic H). The ee of 91% was determined by HPLC. HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 11.88 min for (-) and t_2 = 14.20 min for (+). $[\alpha]_D^{25}$ = +46.3 (c = 1.55, $CHCl_3$).

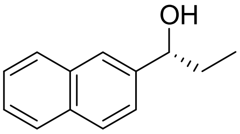
5.4.2.17. (-)-1-(2,6-dichlorophenyl)-1-propanol (-)-213



(-)-**213**

2,6-dichlorobenzaldehyde **194** (175 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (-)-1-(2,6-dichlorophenyl)-1-propanol (-)-**213** (>99%, GC yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.01 (3H, t, *J* = 7.5 Hz, C*H*$_3$), 1.91-2.18 (2H, m, C*H*$_2$), 2.84 (1H, br s, O*H*), 5.36 (1H, t, *J* = 7.5 Hz, C*H*), 7.15 (1H, t, *J* = 8.0 Hz, aromatic H), 7.31 (2H, apparent d, *J* = 8.1 Hz, 2×aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 10.5 (*C*H$_3$), 28.7 (*C*H$_2$), 73.6 (*C*H), 128.7 (2×aromatic C), 129.4 (2×aromatic C), 134.3 (aromatic C), 137.9 (aromatic C). The ee of 87% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 3.0 mL/min, oven = 130 °C, t$_1$ = 13.29 min for (+) and t$_2$ = 13.74 min for (-). $[\alpha]_D^{25}$ = -16.4 (c = 1.82, CHCl$_3$).

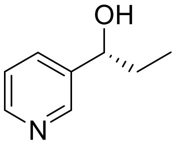
5.4.2.18. (*1R*)-1-(2-naphthyl)-1-propanol (*R*)-214



(*R*)-**214**

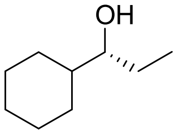
2-naphthaldehyde **195** (156 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(2-naphthyl)-1-propanol (*R*)-**214** (136 mg, 73%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.98 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.81-1.98 (2H, m, C*H*$_2$), 3.07 (1H, br s, O*H*), 4.72 (1H, t, *J* = 6.6 Hz, C*H*), 7.48-7.56 (3H, m, 3×aromatic H), 7.77 (1H, s, aromatic H), 7.83-7.90 (3H, m, 3×aromatic H). ^{13}C NMR (75.6 MHz, CDCl$_3$) δ: 10.2 (*C*H$_3$), 31.8 (*C*H$_2$), 76.0 (*C*H), 124.3, 124.8, 125.8, 126.1, 127.8, 128.0, 128.2, 133.0, 133.3, 142.1 (10×aromatic C). The ee of 81% was determined by HPLC. HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t$_1$ = 14.93 min for (*S*) and t$_2$ = 17.09 min for (*R*). $[\alpha]_D^{25}$ = +28.6 (c = 0.77, CHCl$_3$) {lit.[141] $[\alpha]_D^{20}$ = +35.1 (c = 2.40, CHCl$_3$) for 92% ee (*R*)}.

5.4.2.19. (*1R*)-1-(pyridin-3-yl)-propan-1-ol (*R*)-215


(*R*)-**215**

3-pyridinaldehyde **196** (107 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-(pyridin-3-yl)-propan-1-ol (*R*)-**215** (86 mg, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.65-1.59 (2H, m, C*H*$_2$), 4.69 (1H, dd, *J* = 6.9 Hz, 4.8 Hz, C*H*), 7.19 (1H, t, *J* = 5.7 Hz, aromatic H), 7.28 (1H, d, *J* = 7.8 Hz, aromatic H), 7.68 (1H, td, *J* = 7.7 Hz, 1.8 Hz, aromatic H), 8.52 (1H, d, *J* = 4.8 Hz, aromatic H). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 9.4 (*C*H$_3$), 31.2 (*C*H$_2$), 73.9 (*C*H), 120.4, 122.2, 136.6, 148.1, 162.2 (5×aromatic C). The ee of 9% was determined by HPLC. HPLC (Chiralcel OD-H column): hexane/IPA = 95/5, 1.0 mL/min, 25 °C, 254 nm, t_1 = 7.61 min for (*S*) and t_2 = 8.09 min for (*R*). $[\alpha]_D^{25}$ = +16.3 (c = 1.25, $CHCl_3$) {lit.[213] $[\alpha]_D^{20}$ = -41.4 (c = 2.10, MeOH) for 88% ee (*S*)}.

5.4.2.20. (*1R*)-1-cyclohexylpropanol (*R*)-216


(*R*)-**216**

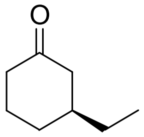
Cyclohexaldehyde **197** (112 mg, 1.0 mmol) was treated with diethylzinc (3 mL of 1.0 M in hexane, 3.0 mmol) following the general procedure to give (*1R*)-1-cyclohexylpropanol (*R*)-**216** (55%, GC yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.94 (3H, t, *J* = 7.4 Hz, C*H*$_3$), 1.00-1.78 (13H, m, C*H*$_2$CH$_3$ and 11 H on cyclohexyl), 3.26 (1H, p, *J* = 4.4 Hz, HOC*H*). ^{13}C NMR (75.6 MHz, $CDCl_3$) δ: 10.2 (*C*H$_3$), 26.2, 26.4, 26.6, 26.8, 27.7, 29.3 (*C*H$_2$CH$_3$ and 5 C on cyclohexyl), 43.1 (CH$_2$*C*HCH$_2$), 77.6 (HO*C*H). The ee of 68% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 1.0 mL/min, oven = Gradient 65-95 °C, t_1 = 52.50 min for (*R*) and t_2 = 53.33 min for (*S*). $[\alpha]_D^{25}$ = +6.6 (c = 0.65, $CHCl_3$) {lit.[146] $[\alpha]_D^{26}$ = +5.4 (c = 0.61, $CHCl_3$) for 93% ee (*R*)}.

5.5. Catalytic enantioselective conjugated addition of Grignard reagents to cyclic enones using chiral BIQ ligands

5.5.1. Enantioselective conjugate addition of Grignard reagents to enone 218

General procedure: Ligand (-)-**68** or (+)-**68** (26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) were dissolved in THF (4 mL) to form a green solution. The mixture was stirred at room temeperature for 1 h and 2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was injected *via* a syringe needle. The mixture was stirred for another 1 h at room temperature and then cooled to -90 ^{o}C (MeOH mixed with liquid nitrogen). The Grignard reagent (1.5 mmol) was injected dropwisely over a period of 5 min and the mixture was stirred for another 15 min. The reaction was then quenched with saturated NH_4Cl solution (5 mL) and the resulting mixture was allowed to warm up to r.t.. The organic phase was separated and washed with HCl solution (3 × 5 mL), saturated Na_2CO_3 solution (3 × 5 mL) and dried over $MgSO_4$. The resulting organic solution was diluted with THF (5 mL) and subjected to GC-Mass and GC directly for analysis. The yield of product was determined by GC using HP-5 column. The ee value was determined by GC using Chiraldex G-TA column or Hydrodex-β-TBDAc column. The absolute configuration of the major enantiomer of product was assigned by comparing the sign of optical rotation value with literature.

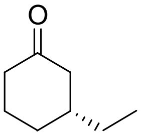
5.5.1.1. (*S*)-3-ethylcyclohexanone (*S*)-249


(S)-**249**

2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was treated with EtMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68** (26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) following the general procedure to give (*S*)-3-ethylcyclohexanone (*S*)-**249** (89%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 110 ^{o}C, t_r = 2.31 min, Mass calcd for $C_8H_{14}O$: 126, found 126 (M). The ee of 35% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 ^{o}C, t_1 = 5.48 min for (*R*) and t_2 = 5.64

min for (*S*). $[\alpha]_D^{25}$ = -13.3 (c = 0.66, $CHCl_3$) {lit.[214] $[\alpha]_D$ = +119.7 (c = 1.0, $CHCl_3$) for 76% ee (*R*)}.

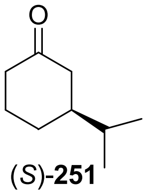
5.5.1.2. (*R*)-3-ethylcyclohexanone (*R*)-249



(*R*)-**249**

2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was treated with EtMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (+)-**68** (26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) following the general procedure to give (*R*)-3-ethylcyclohexanone (*R*)-**249** (93%, GC yield). The ee of 24% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 2.0 mL/min, oven = 110 °C, t_1 = 5.48 min for (*R*) and t_2 = 5.64 min for (*S*). $[\alpha]_D^{25}$ = +11.5 (c = 0.45, $CHCl_3$) {lit.[214] $[\alpha]_D$ = +119.7 (c = 1.0, $CHCl_3$) for 76% ee (*R*)}.

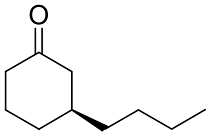
5.5.1.3. (*S*)-3-isopropylcyclohexanone (*S*)-251



(*S*)-**251**

2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was treated with *i*-PrMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68** (26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) following the general procedure to give (*S*)-3-isopropylcyclohexanone (*S*)-**251** (90%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 120 °C, t_r = 2.58 min, Mass calcd for $C_9H_{16}O$: 140, found 140 (M). The ee of 8% was determined by GC. GC (Hydrodex-β-TBDAc column): Helium flowrate = 2.0 mL/min, oven = 130 °C, t_1 = 8.73 min for (*R*) and t_2 = 9.22 min for (*S*). $[\alpha]_D^{25}$ = -5.3 (c = 0.70, $CHCl_3$) {lit.[203] $[\alpha]_D$ = +13.6 (c = 1.92, $CHCl_3$) for 72% ee (*R*)}.

5.5.1.4. (*S*)-3-butylcyclohexanone (*S*)-252

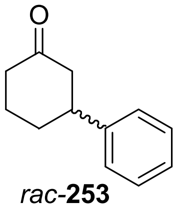


(*S*)-**252**

2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was treated with BuMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68**

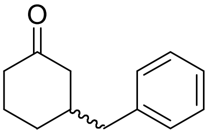
(26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) following the general procedure to give (*S*)-3-butylcyclohexanone (*S*)-**252** (> 99%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 120 °C, t_r = 3.97 min, Mass calcd for $C_{10}H_{18}O$: 154, found 154 (M). The ee of 35% was determined by GC. GC (Hydrodex-β-TBDAc column): Helium flowrate = 2.0 mL/min, oven = 130 °C, t_1 = 14.78 min for (*R*) and t_2 = 15.31 min for (*S*). $[\alpha]_D^{25}$ = -10.5 (c = 1.24, $CHCl_3$) {lit.[215] $[\alpha]_D^{22}$ = +12.2 (c = 1.0, $CHCl_3$) for 90% ee (*R*)}.

5.5.1.5. *rac*-3-phenylcyclohexanone *rac*-253


rac-**253**

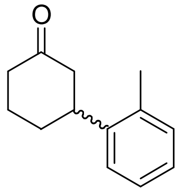
2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was treated with PhMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68** (26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) following the general procedure to give *rac*-3-phenylcyclohexanone *rac*-**253** (88%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 150 °C, t_r = 5.11 min, Mass calcd for $C_{12}H_{14}O$: 174, found 174 (M). The product was confirmed to be *racemic* by GC. GC (Hydrodex-β-TBDAc column): Helium flowrate = 2.0 mL/min, oven = 150 °C, t_1 = 31.64 min and t_2 = 32.69 min.

5.5.1.6. *rac*-3-benzylcyclohexanone *rac*-254


rac-**254**

2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was treated with BnMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68** (26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) following the general procedure to give *rac*-3-benzylcyclohexanone *rac*-**254** (> 99%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 150 °C, t_r = 5.47 min, Mass calcd for $C_{13}H_{16}O$: 188, found 188 (M). The product was confirmed to be *racemic* by GC. GC (Hydrodex-β-TBDAc column): Helium flowrate = 2.0 mL/min, oven = 160 °C, t_1 = 28.55 min and t_2 = 29.48 min.

5.5.1.7. *rac*-3-*o*-tolylcyclohexanone *rac*-255



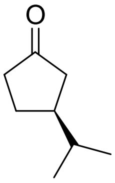
rac-**255**

2-cyclohexenone **218** (96mg, 0.1 mL, 1.0 mmol) was treated with *o*-TolylMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68** (26 mg, 0.1 mmol) and $CuCl_2$ (13.5 mg, 0.1 mmol) following the general procedure to give *rac*-3-*o*-tolylcyclohexanone *rac*-**255** (> 99%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 150 ^{o}C, t_r = 5.42 min, Mass calcd for $C_{13}H_{16}O$: 188, found 188 (M). The product was confirmed to be *racemic* by GC. GC (Hydrodex-β-TBDAc column): Helium flowrate = 2.0 mL/min, oven = 160 ^{o}C, t_1 = 24.88 min and t_2 = 25.63 min.

5.5.2. Enantioselective conjugate addition of Grignard reagents to enone 217

General procedure: Ligand (-)-**68** or (+)-**68** (39 mg, 0.15 mmol) and $Cu(OTf)_2$ (54 mg, 0.15 mmol) were dissolved in THF (4 mL) to form a blue solution. The mixture was stirred at room temeperature for 1 h and 2-cyclopentenone **217** (82 mg, 84 μL, 1.0 mmol) was injected *via* a syringe needle. The mixture was stirred for another 1 h at room temperature and then cooled to -90 ^{o}C (MeOH mixed with liquid nitrogen). The Grignard reagent (1.5 mmol) was injected dropwisely over a period of 5 min and the mixture was stirred for another 15 min. The reaction was then quenched with saturated NH_4Cl solution (5 mL) and the resulting mixture was allowed to warm up to r.t.. The organic phase was separated and washed with HCl solution (3 × 5 mL), saturated Na_2CO_3 solution (3 × 5 mL) and dried over $MgSO_4$. The resulting organic solution was diluted with THF (5 mL) and subjected to GC-Mass and GC directly for analysis. The yield and ee value of product were determined by GC using Chiraldex G-TA or Hydrodex-β-TBDAc column. The absolute configuration of the major enantiomer of product was assigned by comparing the sign of optical rotation value with literature precedents.

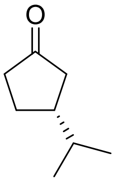
5.5.2.1. (*S*)-3-isopropylcyclopentanone (*S*)-264



(*S*)-**264**

2-cyclopentenone **217** (82 mg, 84 µL, 1.0 mmol) was treated with *i*-PrMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68** (39 mg, 0.15 mmol) and Cu(OTf)$_2$ (54 mg, 0.15 mmol) following the general procedure to give (*S*)-3-isopropylcyclopentanone (*S*)-**264** (97%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 100 °C, t_r = 2.58 min, Mass calcd for $C_8H_{14}O$: 126, found 126 (M). The ee of 26% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 0.8 mL/min, oven = 77 °C, t_1 = 40.70 min for (*S*) and t_2 = 41.93 min for (*R*). $[\alpha]_D^{25}$ = -13.8 (c = 0.30, CHCl$_3$) {lit.[216] $[\alpha]_D^{23}$ = -87.5 (c = 0.28, CHCl$_3$) for (*S*)}.

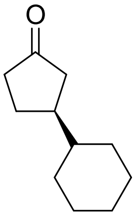
5.5.2.2. (*R*)-3-isopropylcyclopentanone (*R*)-264



(*R*)-**264**

2-cyclopentenone **217** (82 mg, 84 µL, 1.0 mmol) was treated with *i*-PrMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (+)-**68** (39 mg, 0.15 mmol) and Cu(OTf)$_2$ (54 mg, 0.15 mmol) following the general procedure to give (*R*)-3-isopropylcyclopentanone (*R*)-**264** (97%, GC yield). The ee of 30% was determined by GC. GC (Chiraldex G-TA column): Helium flowrate = 0.8 mL/min, oven = 77 °C, t_1 = 40.70 min for (*S*) and t_2 = 41.93 min for (*R*). $[\alpha]_D^{25}$ = +17.9 (c = 1.20, CHCl$_3$) {lit.[216] $[\alpha]_D^{23}$ = -87.5 (c = 0.28, CHCl$_3$) for (*S*)}.

5.5.2.3. (*S*)-3-cyclohexylcyclopentanone (*S*)-266



(*S*)-**266**

2-cyclopentenone **217** (82 mg, 84 µL, 1.0 mmol) was treated with CyMgCl (0.75 mL of 2.0 M inTHF, 1.5 mmol) in the presence of (-)-**68** (39 mg, 0.15 mmol) and Cu(OTf)$_2$ (54 mg, 0.15 mmol) following the general procedure to give (*S*)-3-cyclohexylcyclopentanone (*S*)-**266** (95%, GC yield). GC-Mass (HP-5 column): Helium flowrate = 2.0 mL/min, oven = 130 °C, t_r = 6.08 min, Mass calcd for $C_{11}H_{18}O$: 166, found 166 (M). The ee of 18% was determined by GC. GC (Hydrodex-β-TBDAc column): Helium flowrate = 2.0 mL/min, oven = 160 ^{o}C, t_1 = 11.83 min for (*S*) and t_2 = 12.10 min for (*R*). $[\alpha]_D^{25}$ = -6.3 (c = 0.75, $CHCl_3$) {lit.[215] $[\alpha]_D^{22}$ = +8.6 (c = 1.0, $CHCl_3$) for 93% ee (*R*)}.

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APPENDIX

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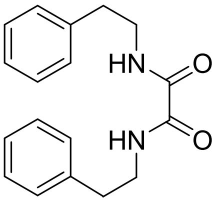

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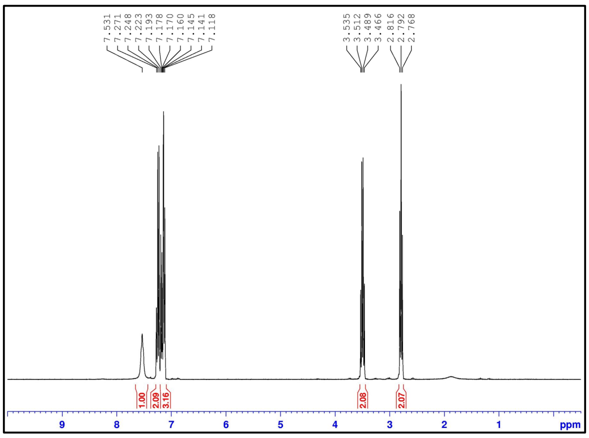

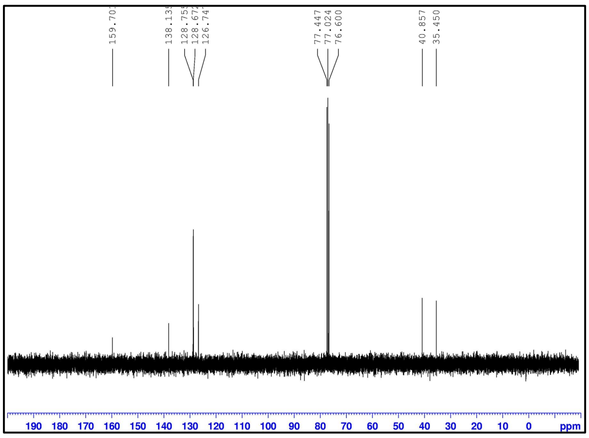

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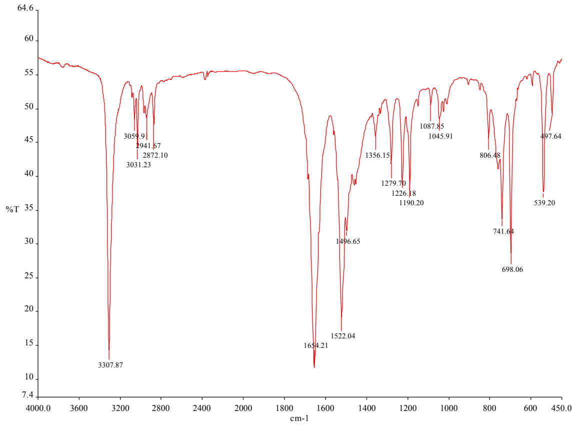

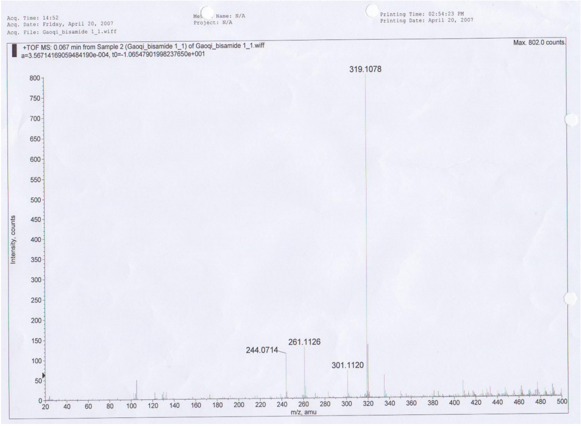

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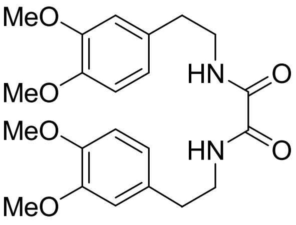

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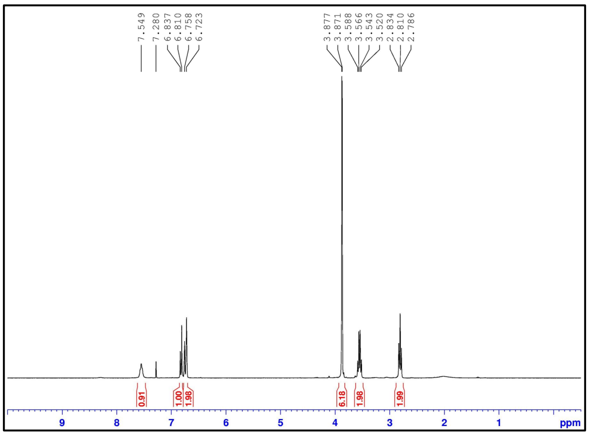

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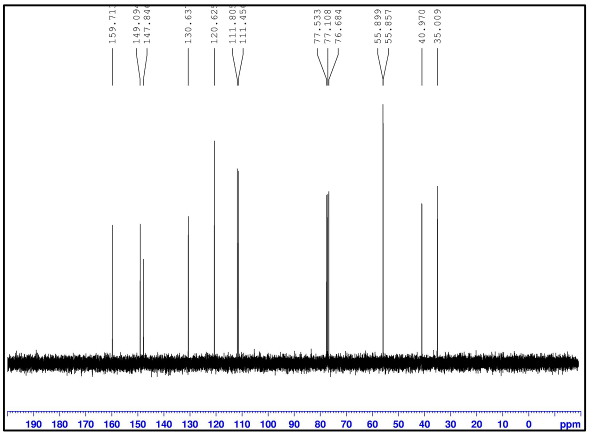

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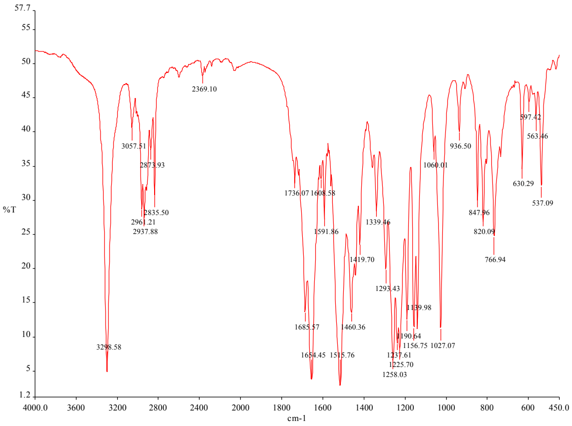

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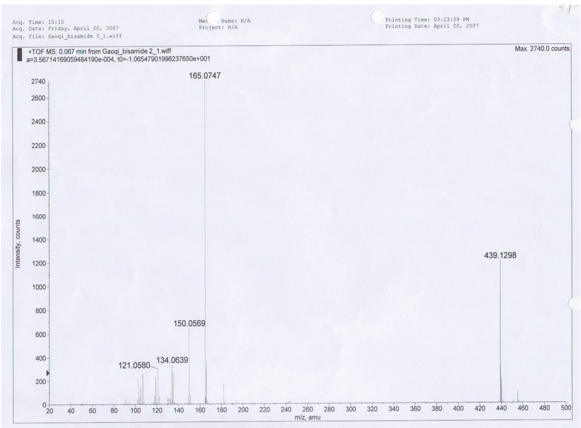

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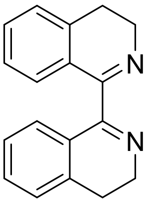

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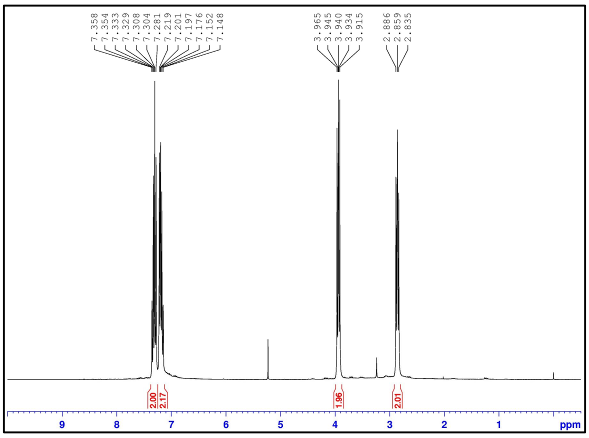

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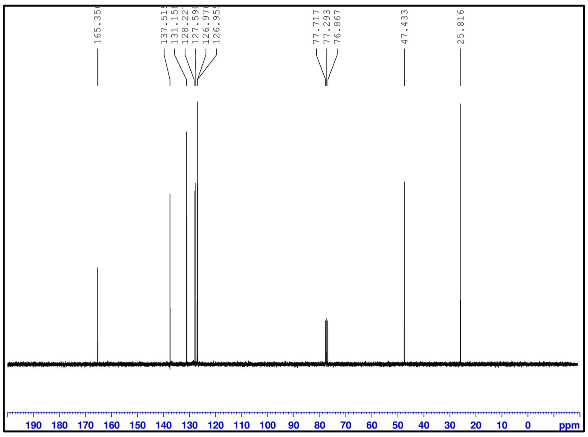

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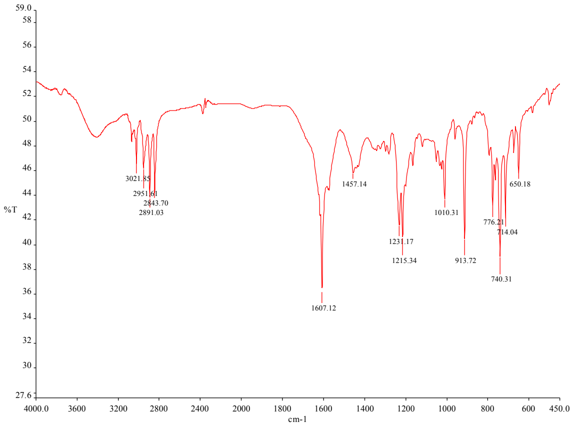

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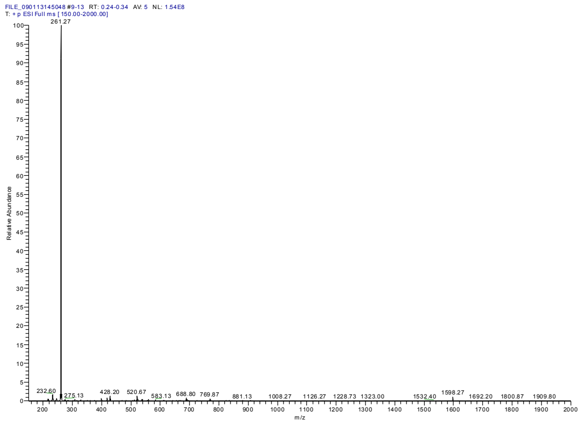

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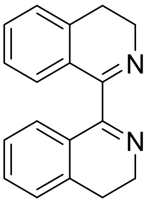

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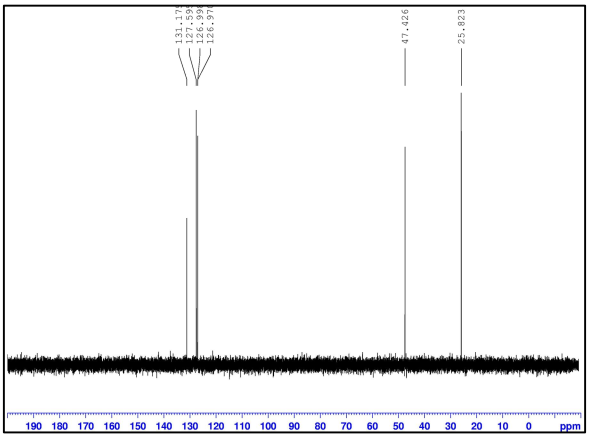

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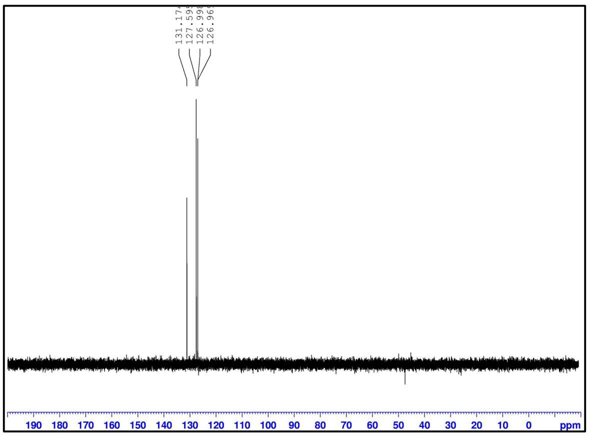

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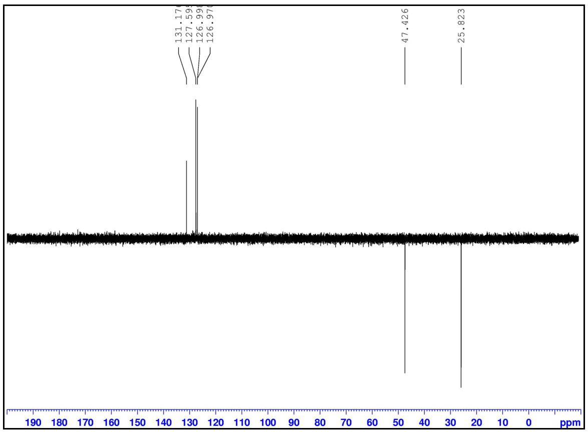

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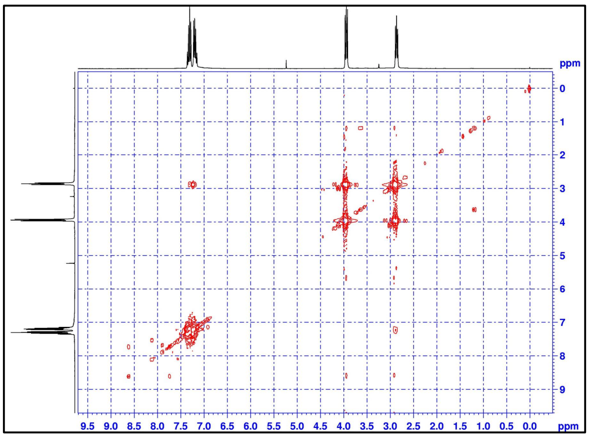

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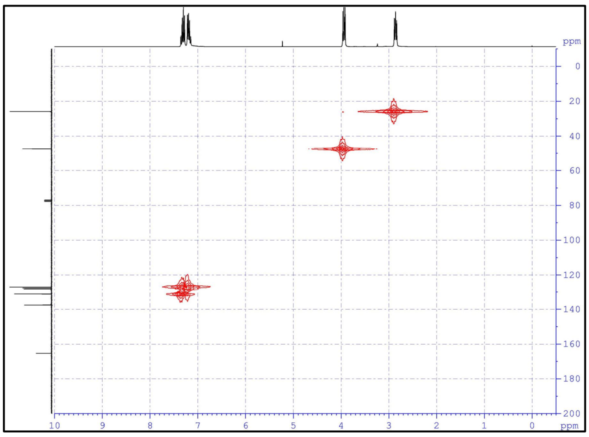

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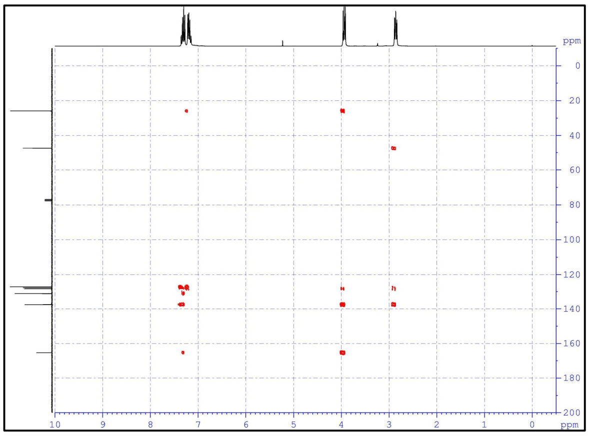

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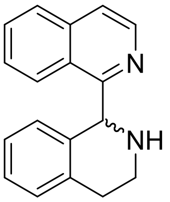

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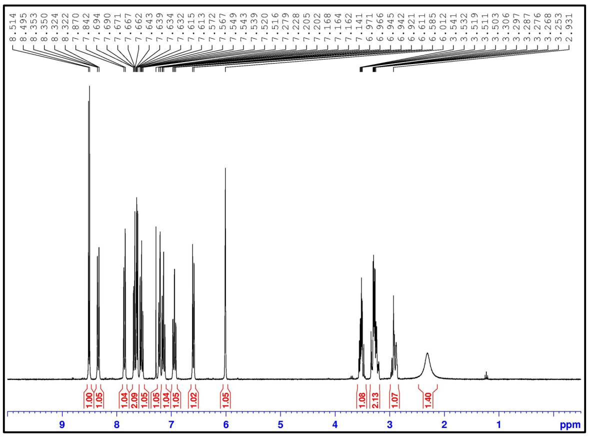

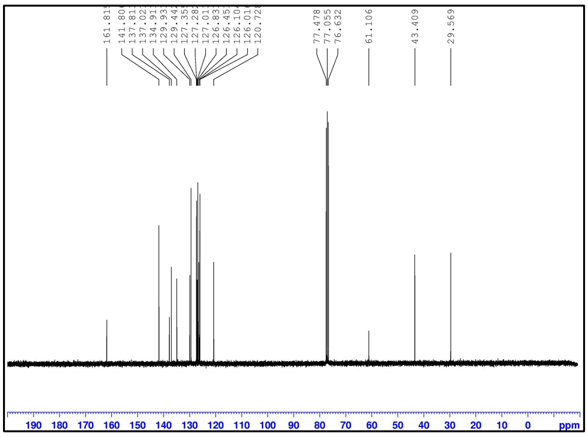

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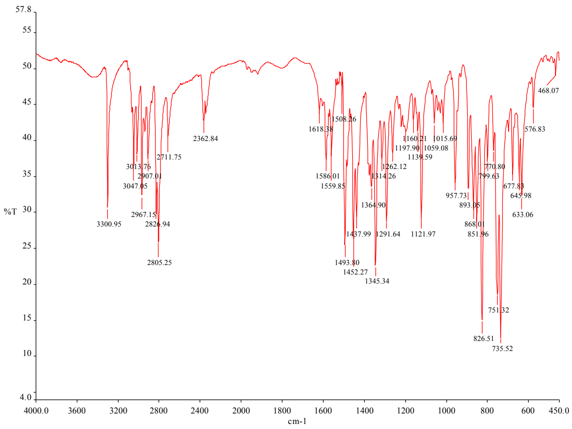

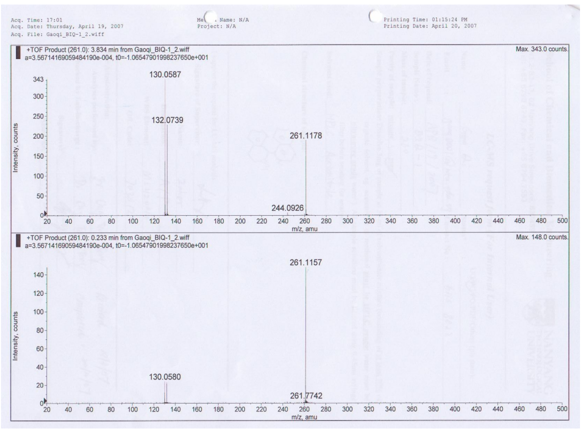

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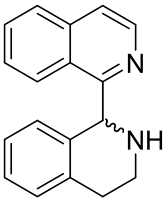

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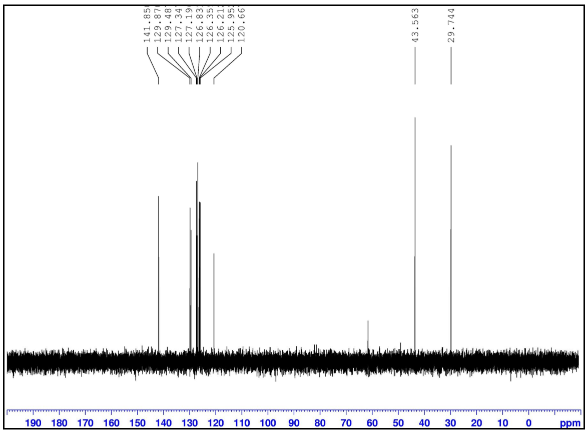

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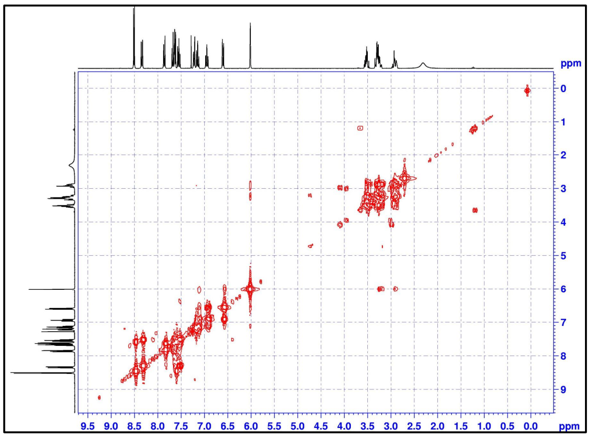

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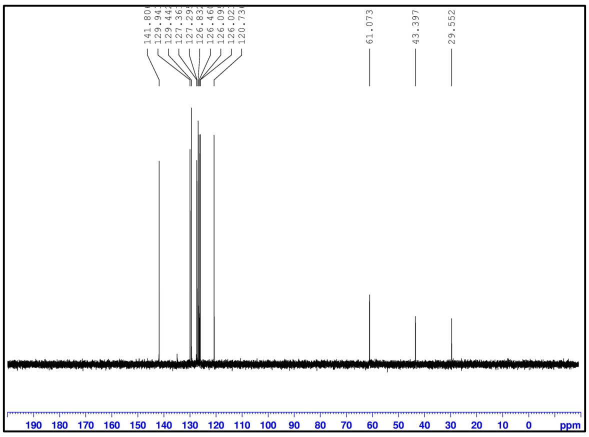

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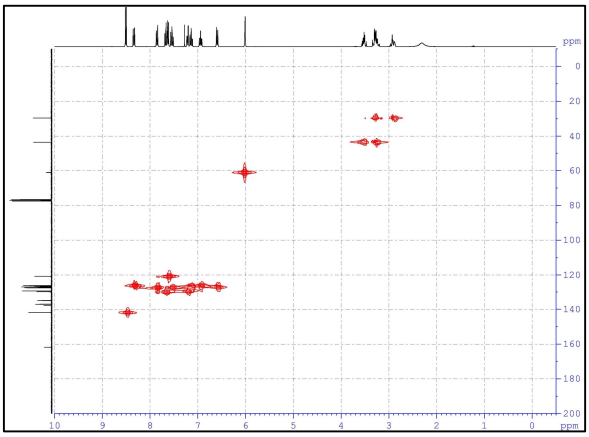

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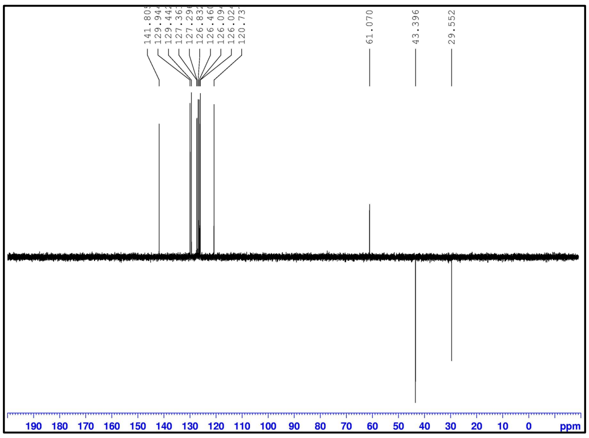

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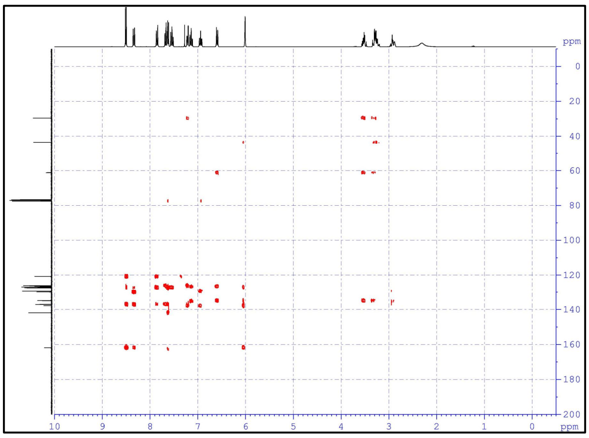

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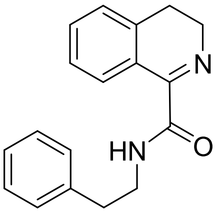

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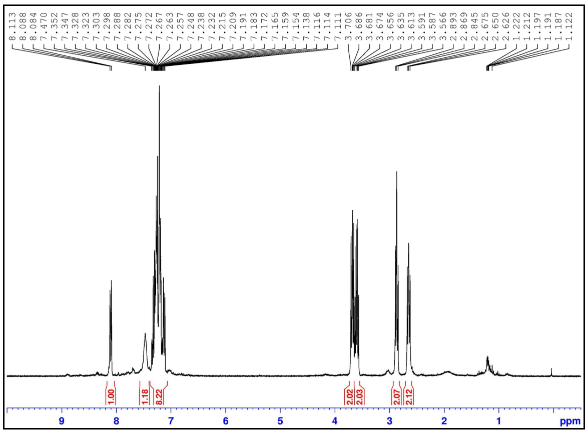

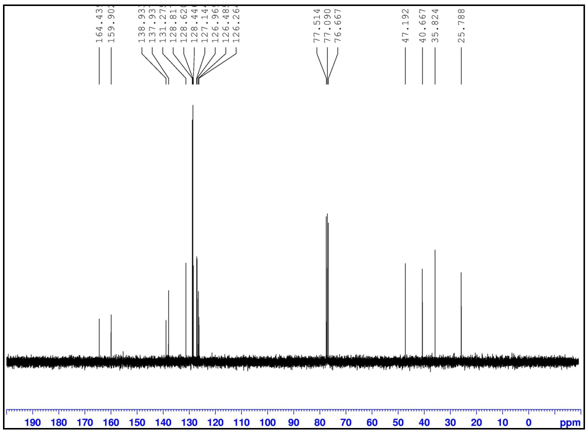

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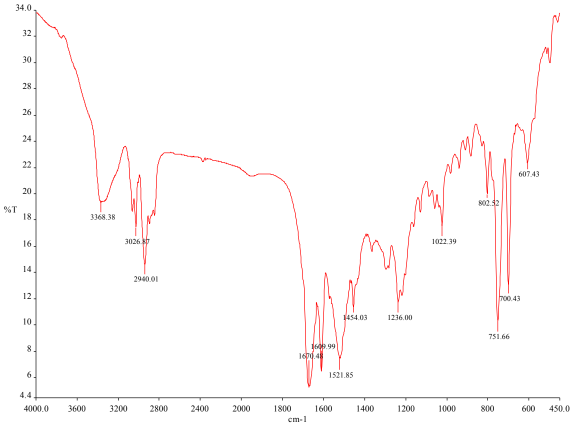

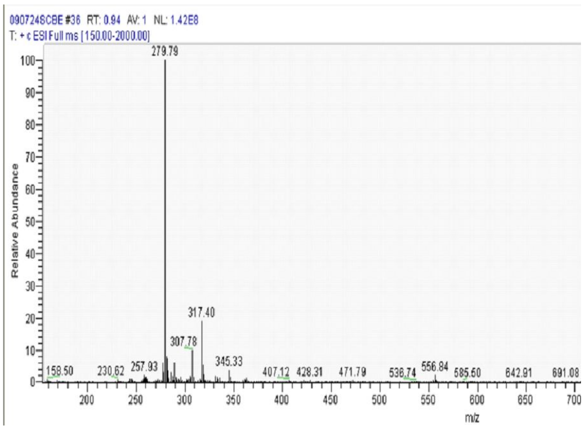

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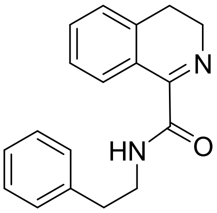

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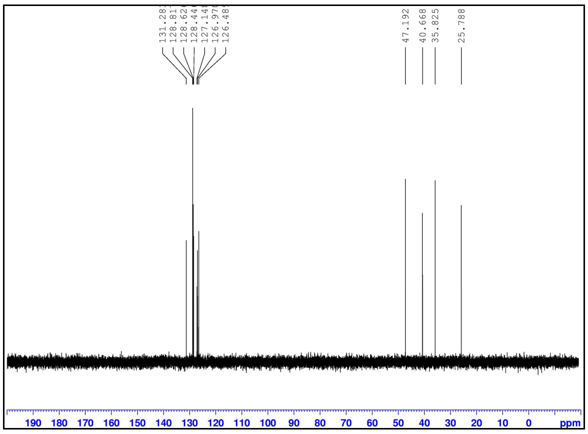

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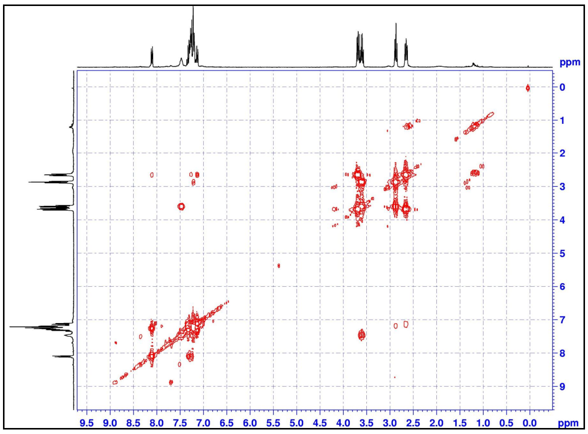

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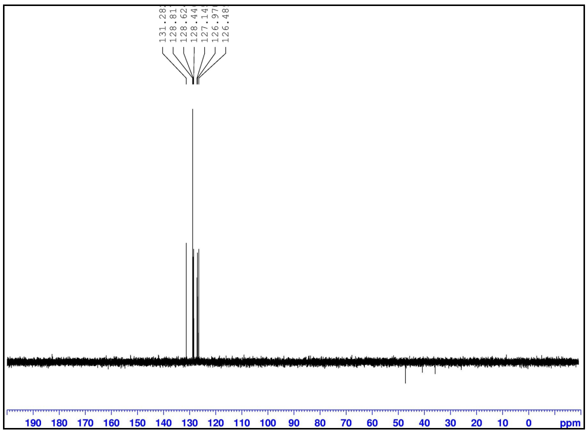

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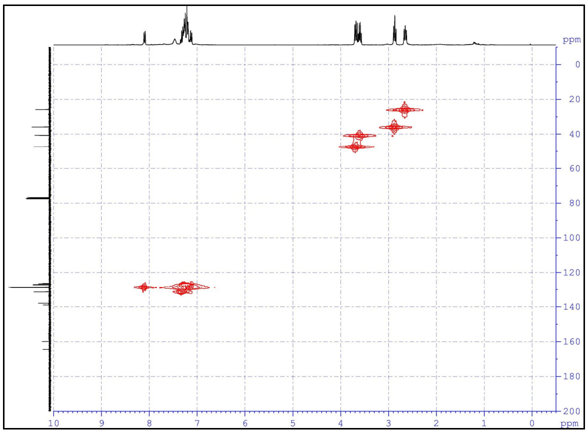

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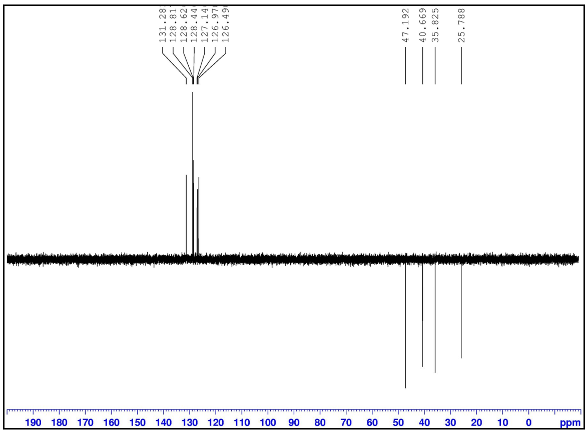
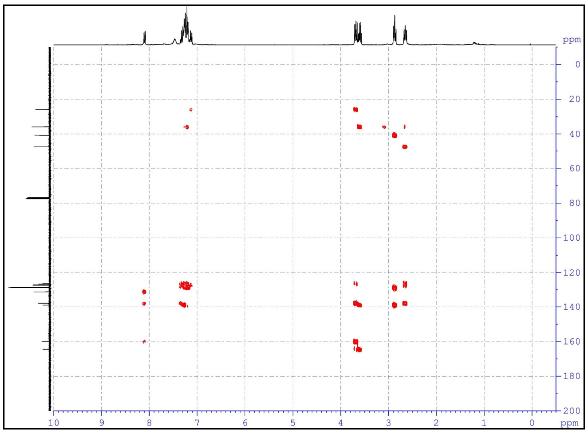


DEPT 135



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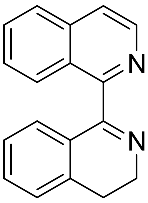

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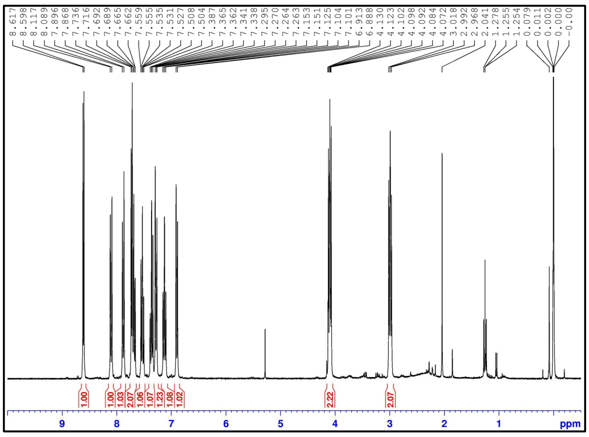

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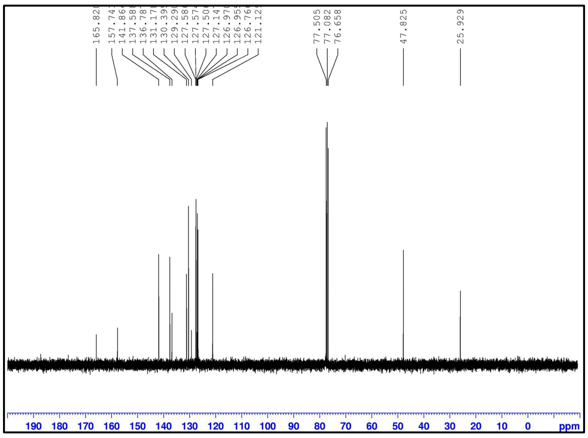
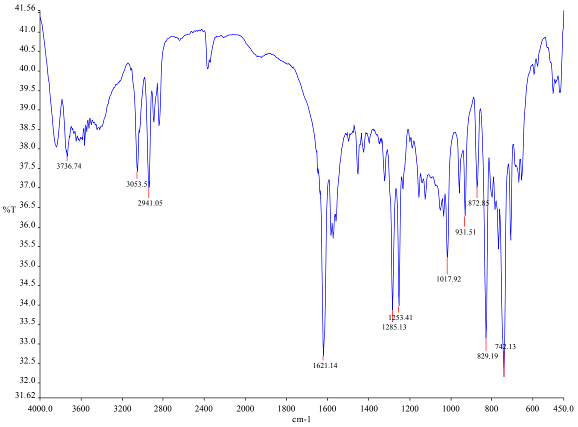


^{13}C NMR



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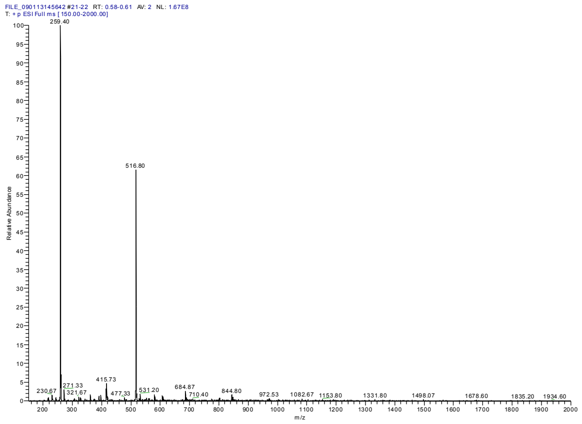

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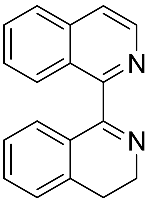

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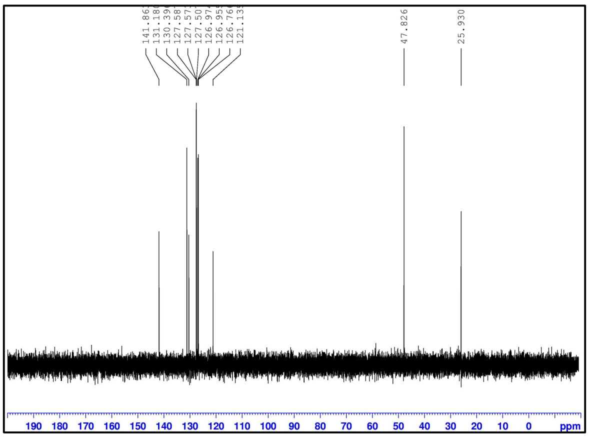
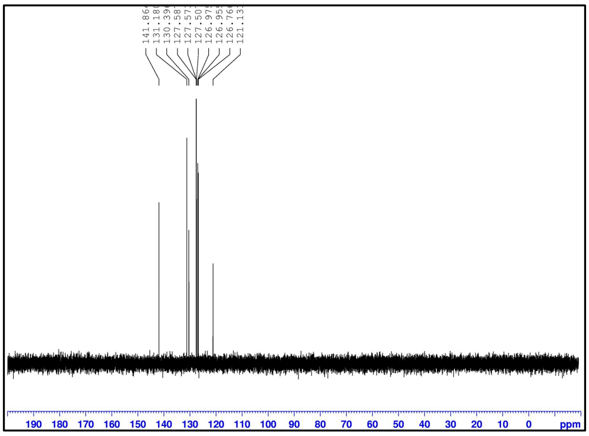
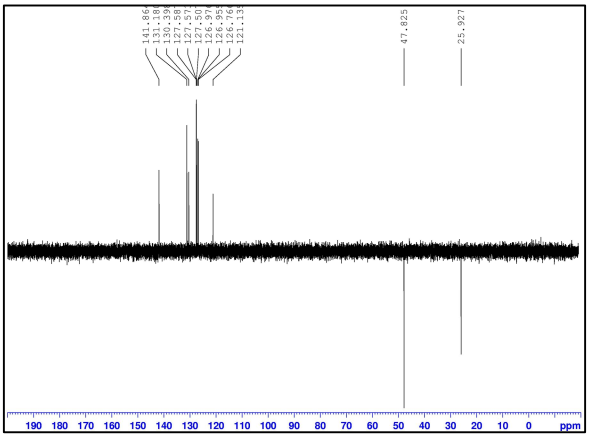


DEPT 45

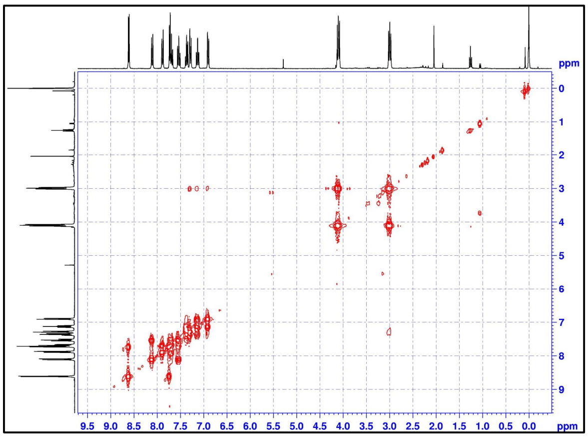


DEPT 90

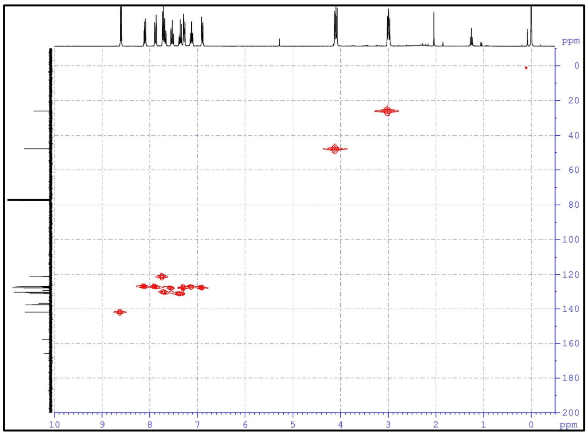


DEPT 135

2D NMR spectra:



COSY



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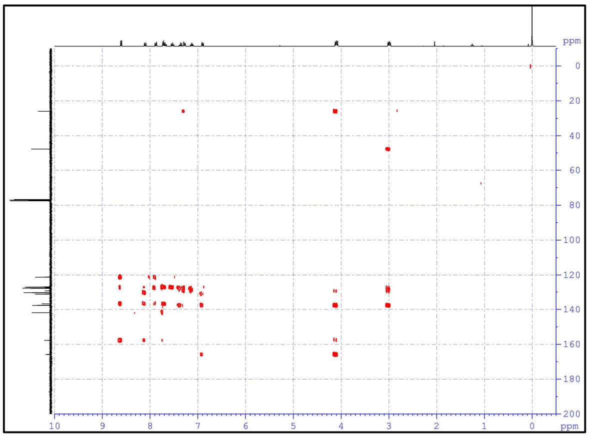

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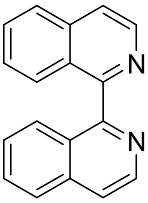

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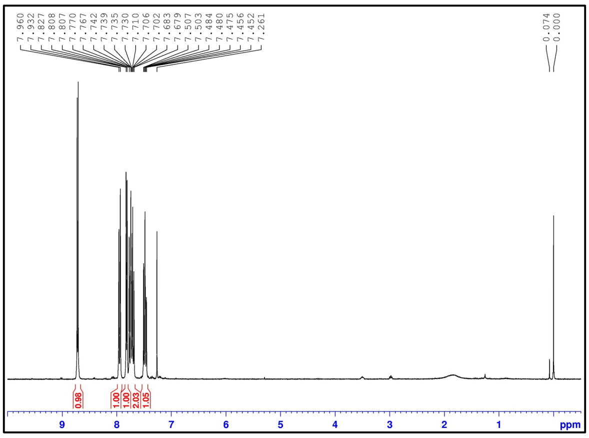
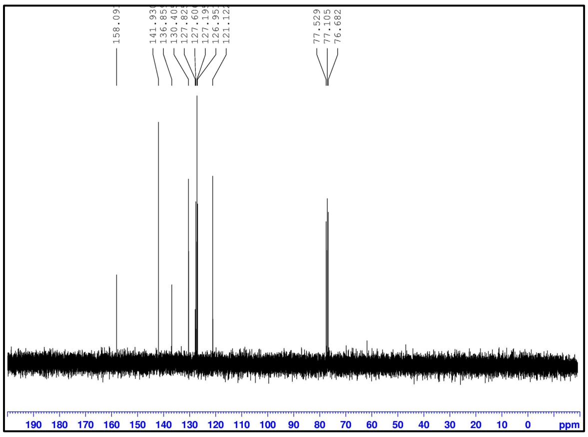
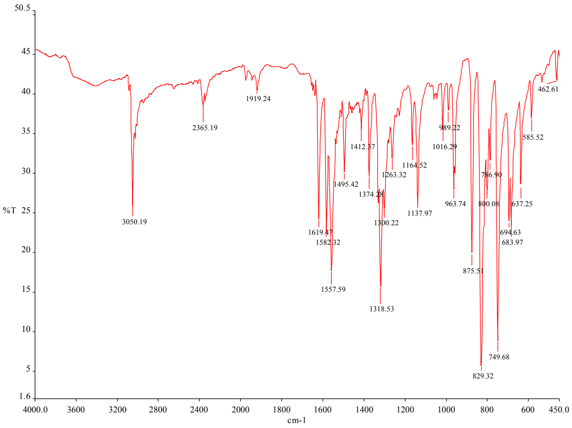
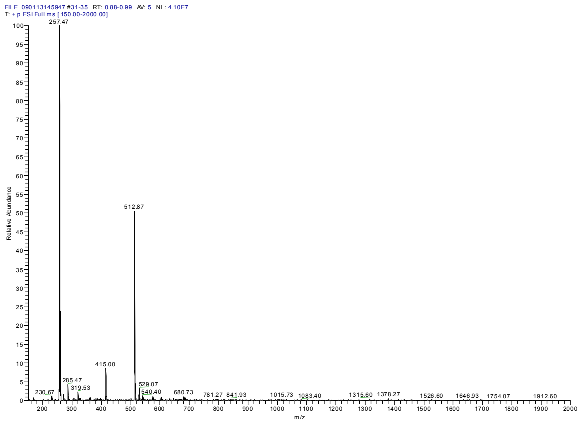




^{1}H NMR

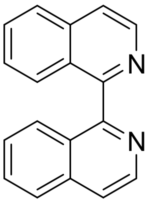
^{13}C NMR





FTIR

Mass



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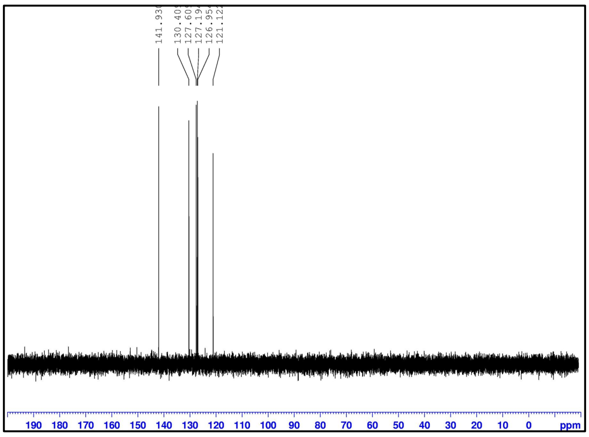
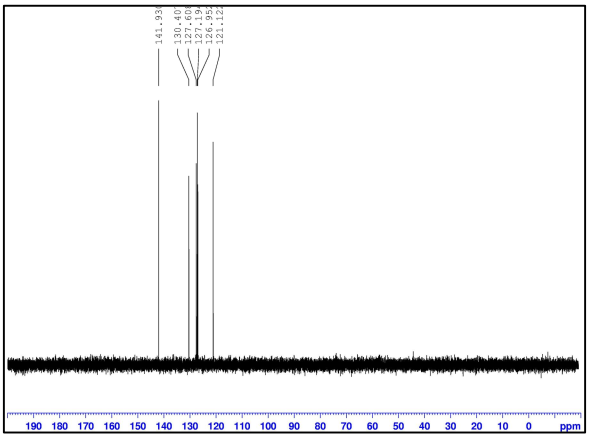
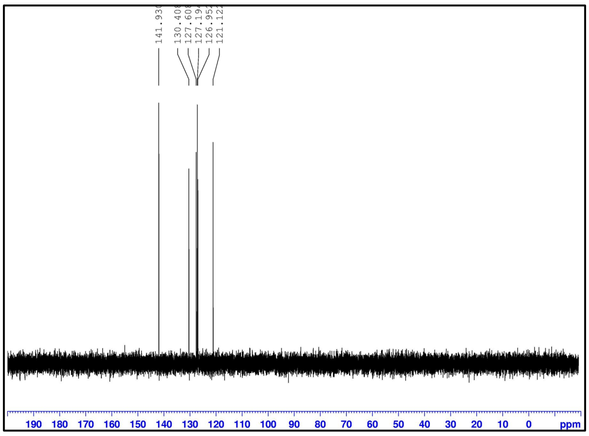
DEPT:



DEPT 45



DEPT 90



DEPT 135

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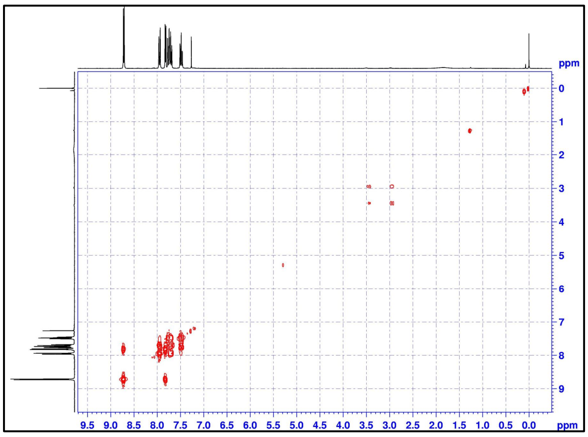
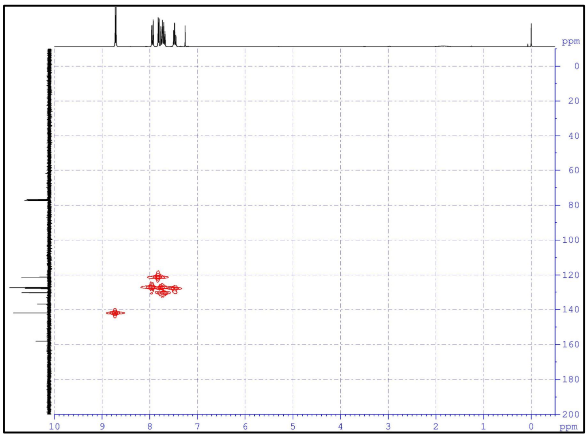


COSY



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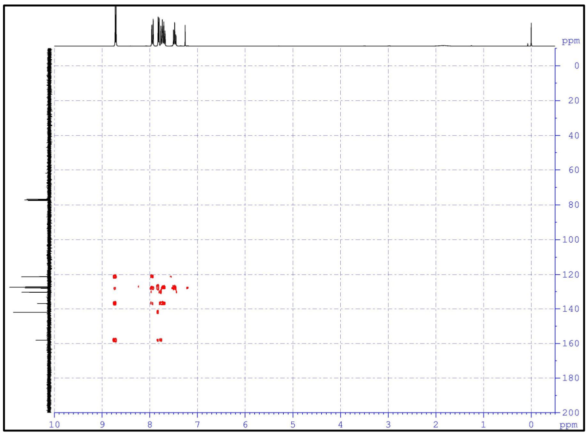

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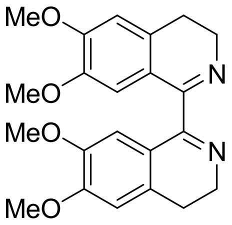

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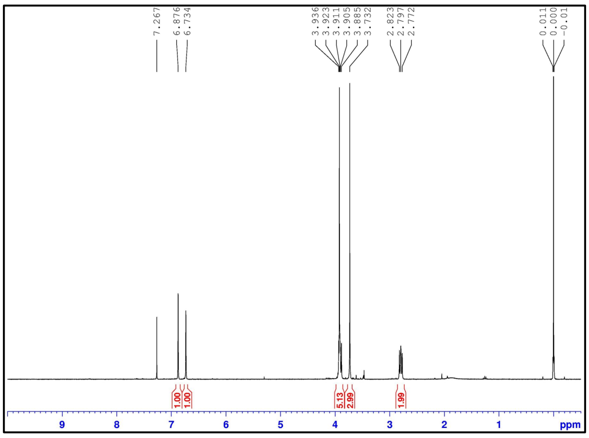
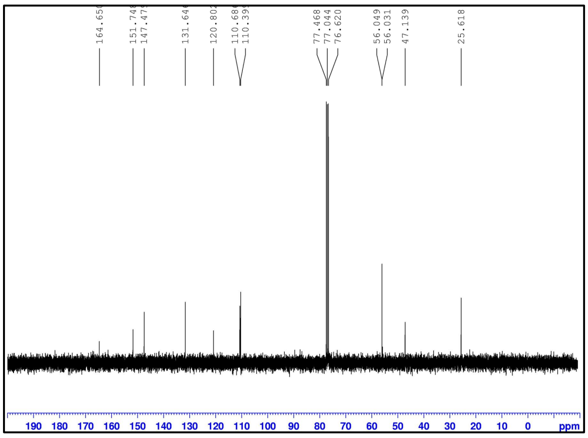
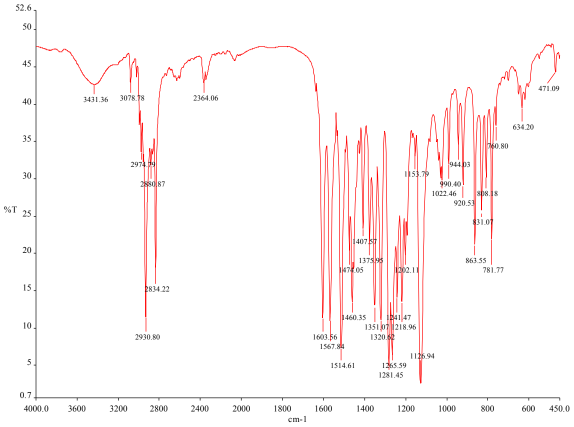


^{1}H NMR



^{13}C NMR



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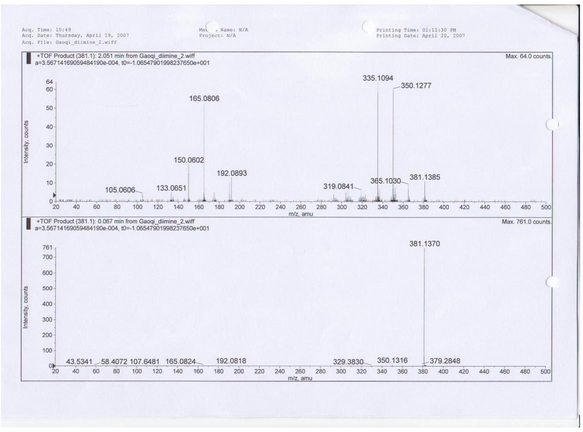

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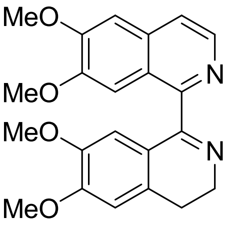

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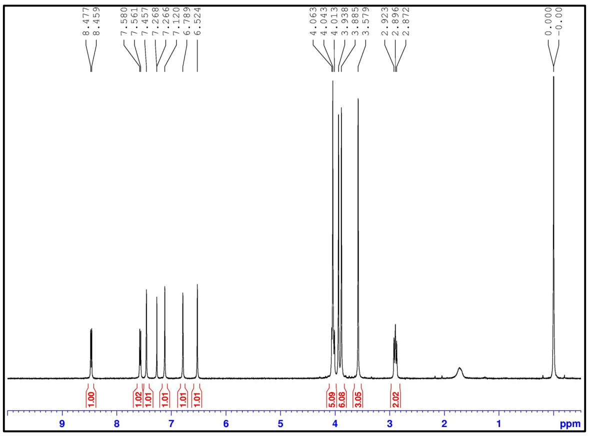

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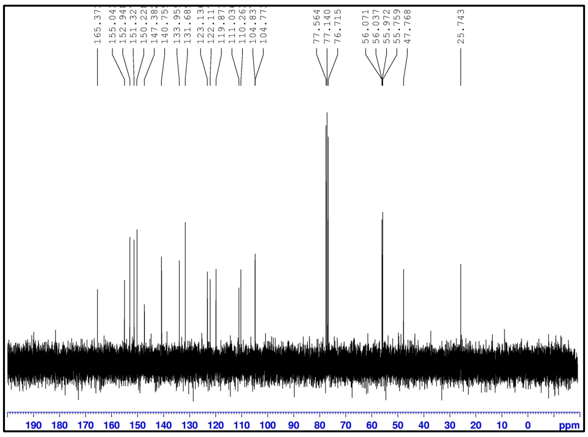

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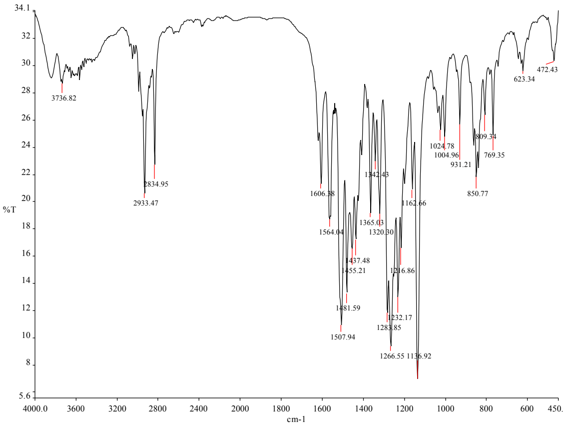

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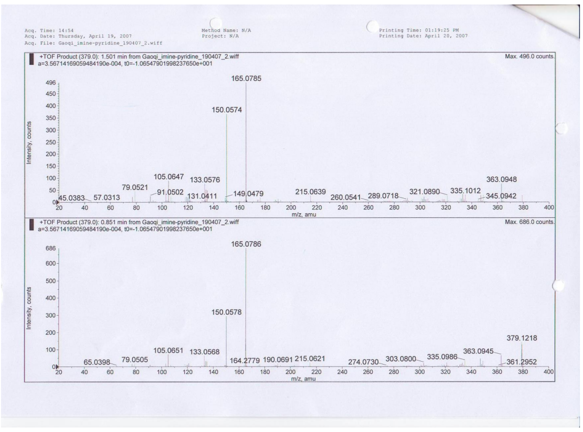
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Acq. Date: Thursday, April 19, 2007
Acq. File: Gaoqi_imine-pyridine_190407_2.wiff

Method Name: N/A
Project: N/A

Printing Time: 01:19:25 PM
Printing Date: April 20, 2007

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Max. 496.0 counts.

+TOF Product (379.0): 0.851 min from Gaoqi_imine-pyridine_190407_2.wiff
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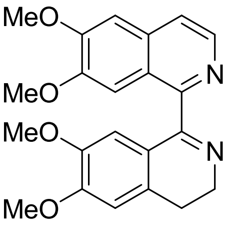
Max. 686.0 counts.

Mass



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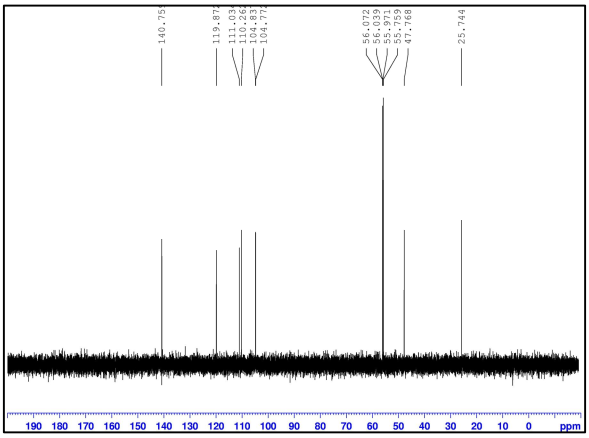
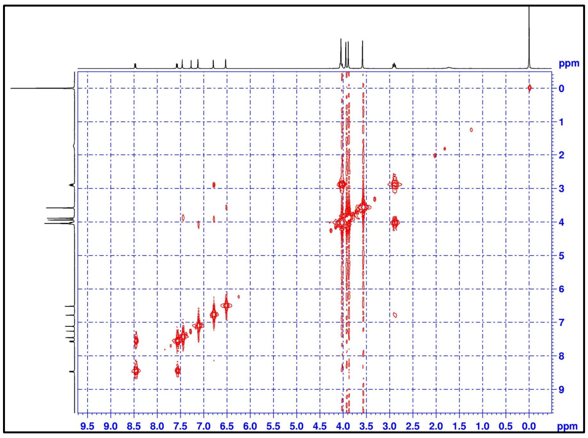
DEPT:

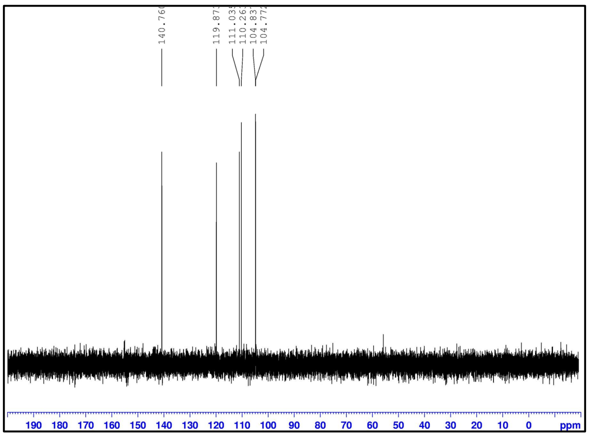
2D NMR spectra:



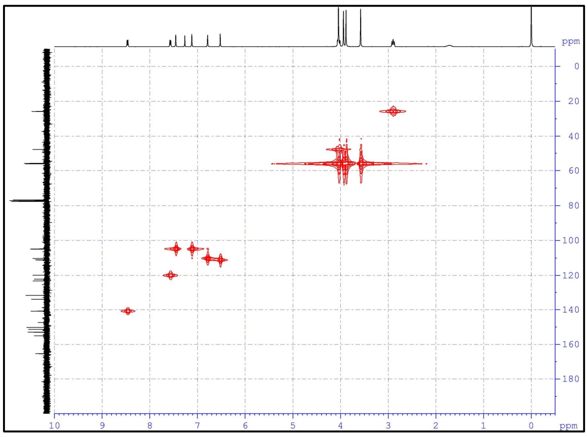
DEPT 45



COSY



DEPT 90



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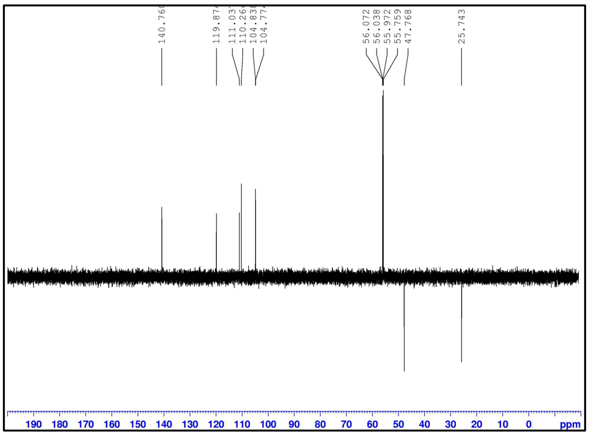
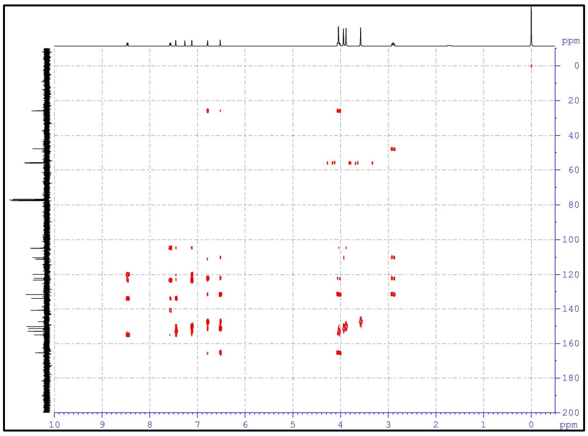
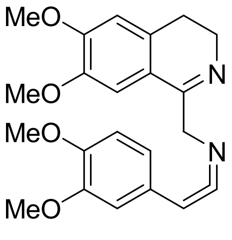


DEPT 135



HMBC



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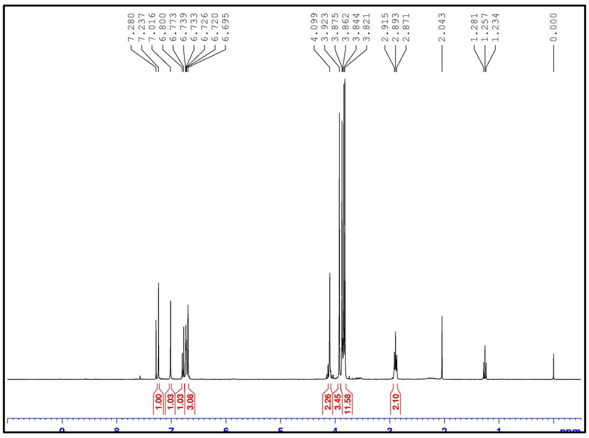
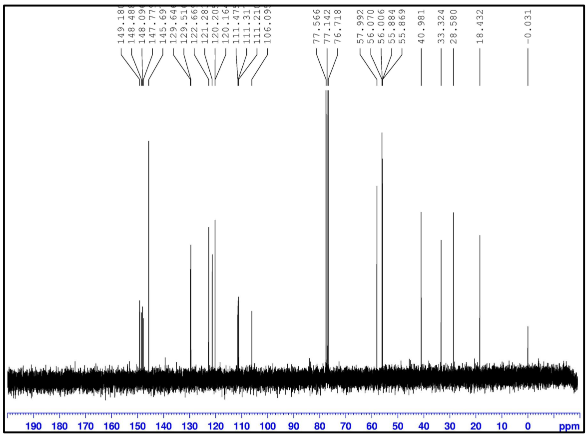
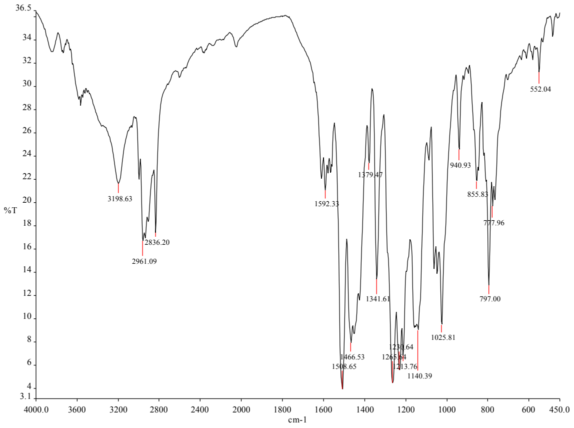


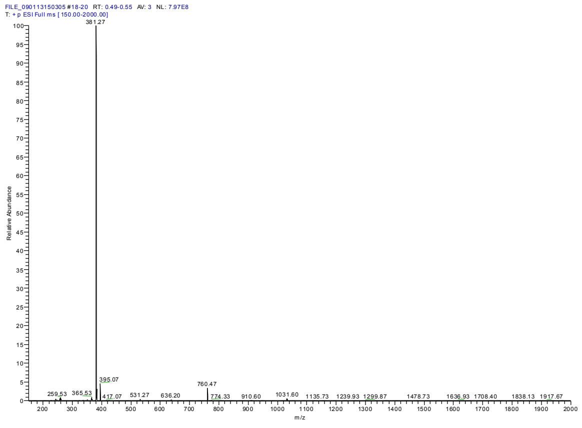
^{1}H NMR



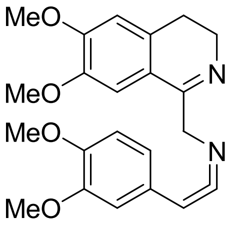
^{13}C NMR



FTIR



Mass



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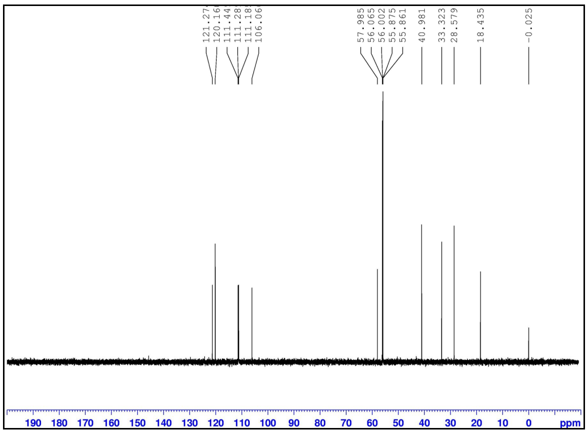
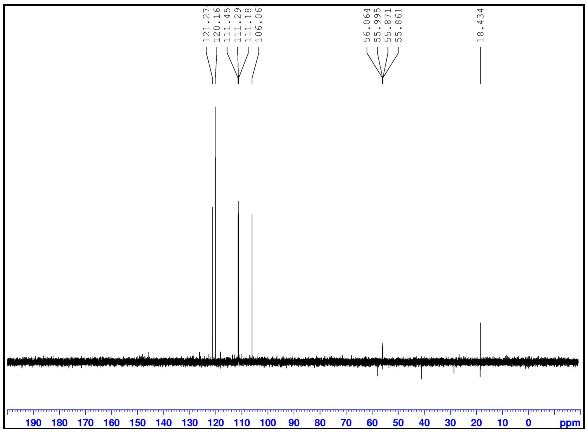
DEPT:



DEPT 45



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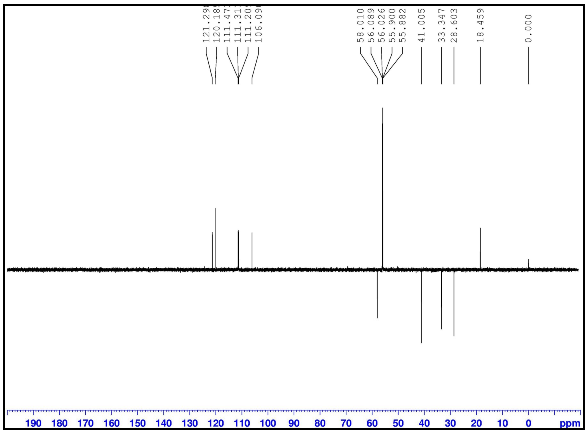

DEPT 135

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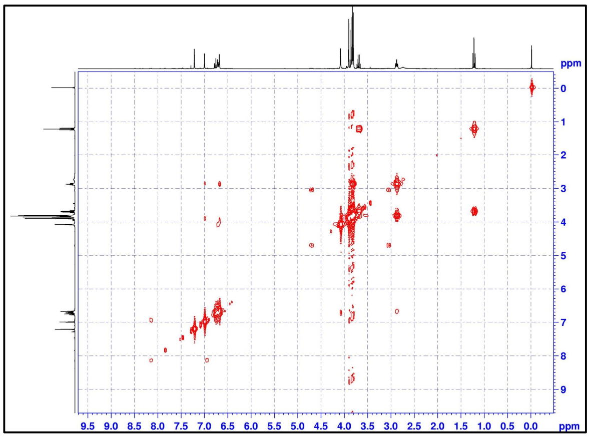
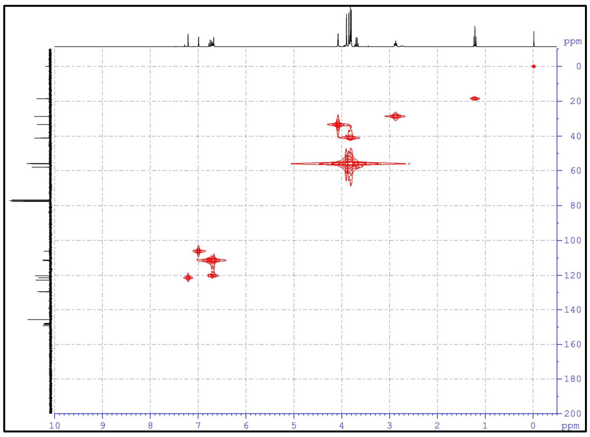
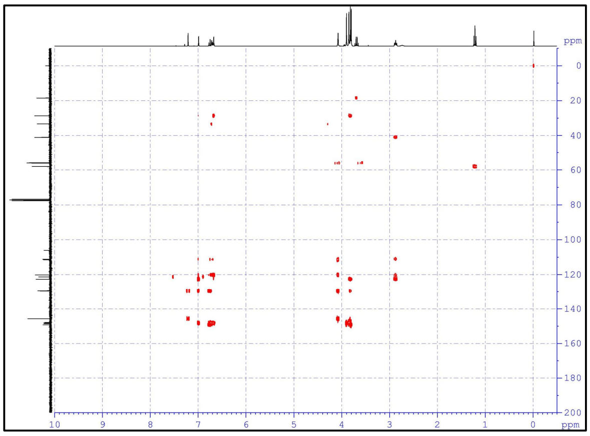


COSY



HMQC



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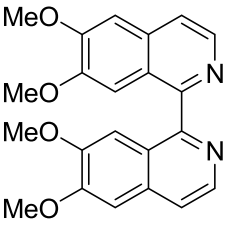

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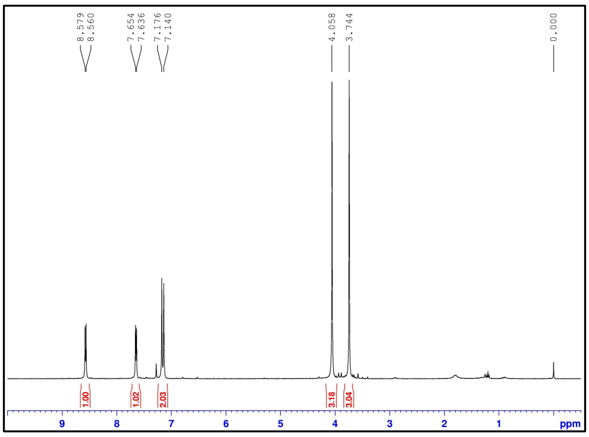
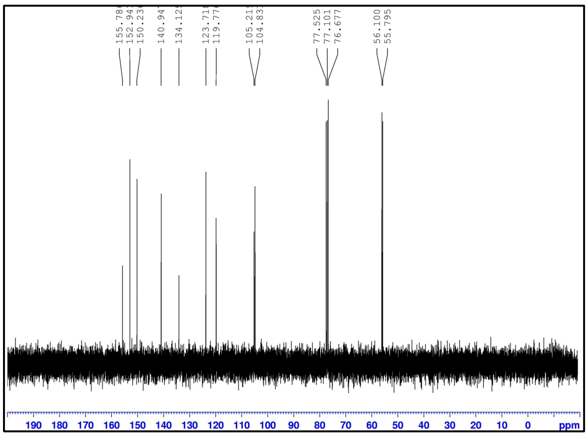
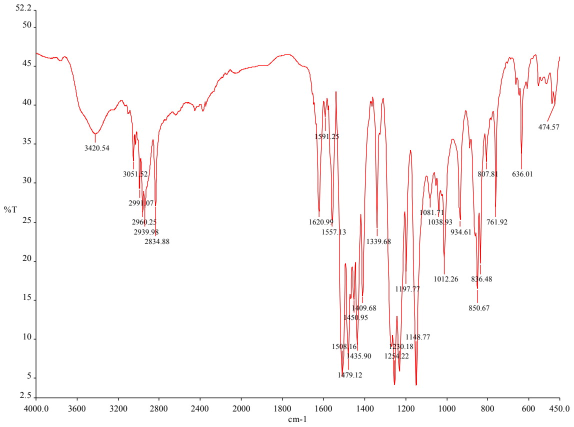
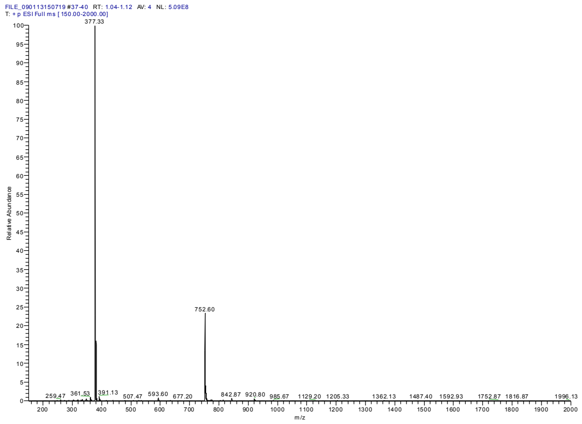




^{1}H NMR

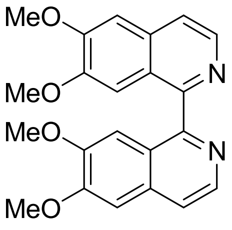
^{13}C NMR





FTIR

Mass



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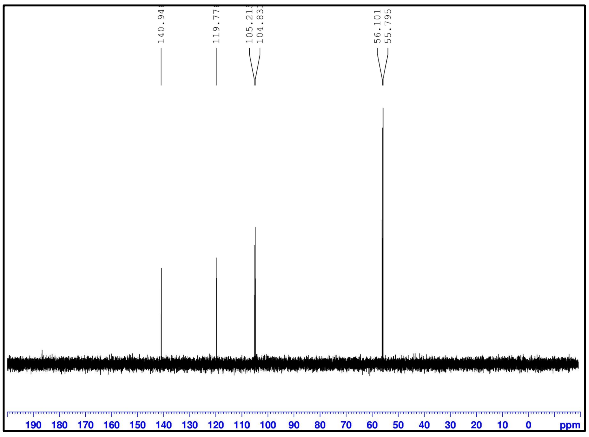
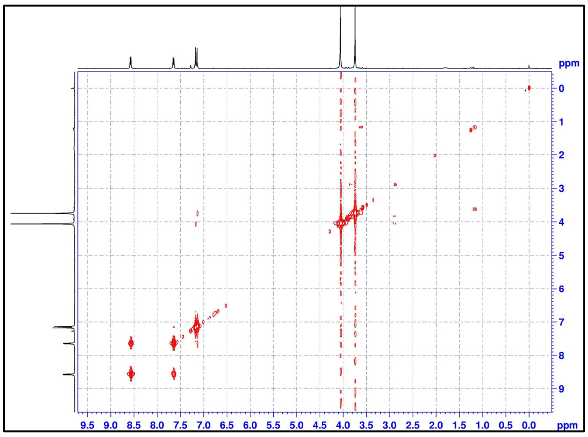
DEPT:

2D NMR spectra:



DEPT 45



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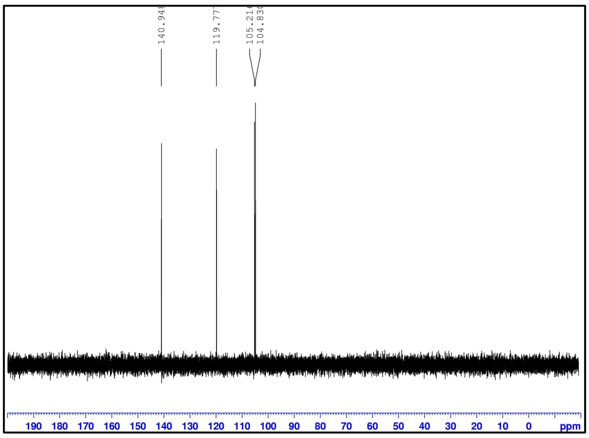
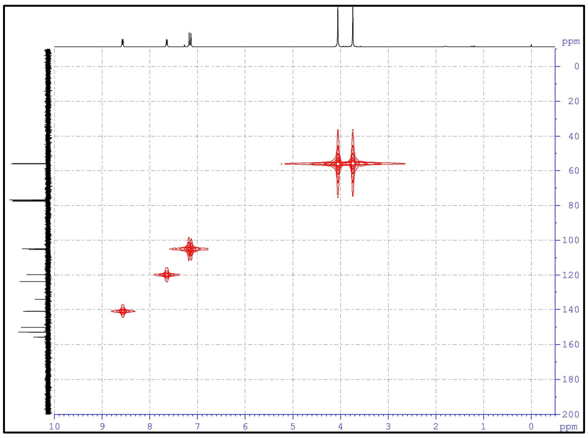


DEPT 90



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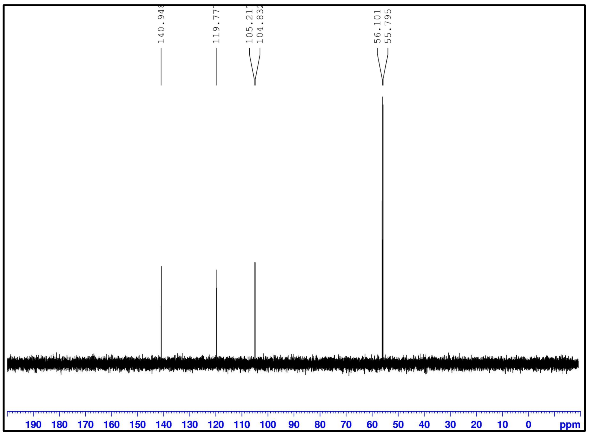
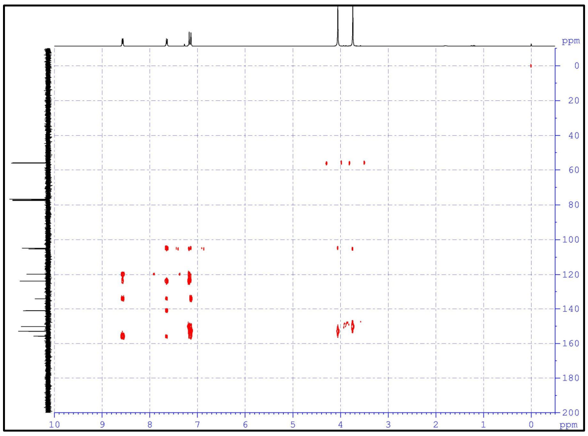


DEPT 135



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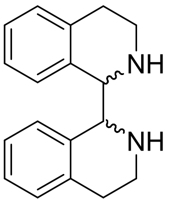

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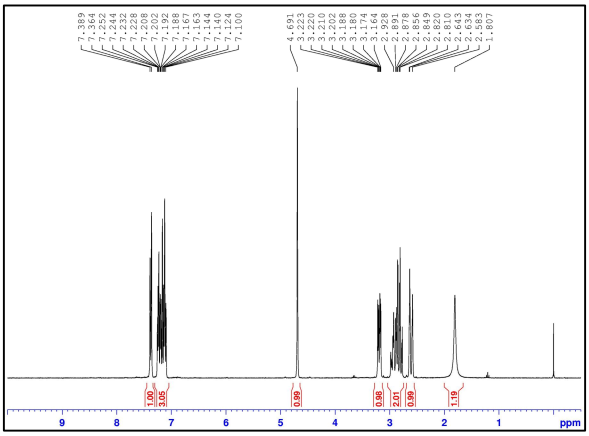
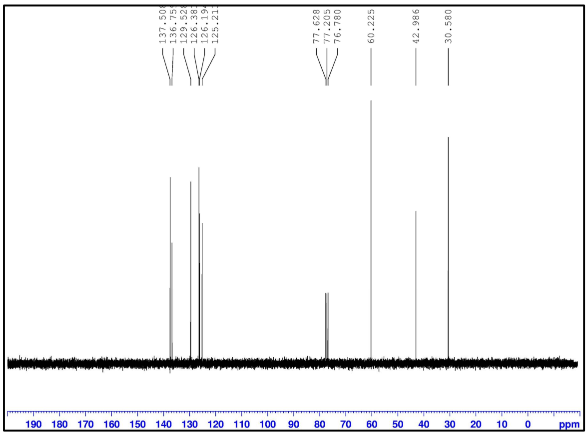
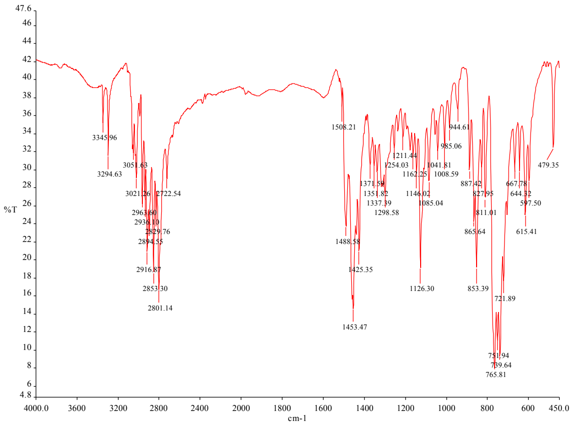
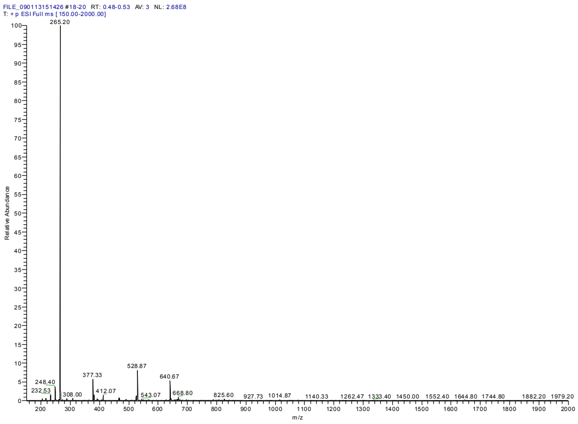




^{1}H NMR

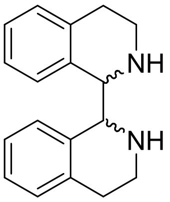
^{13}C NMR





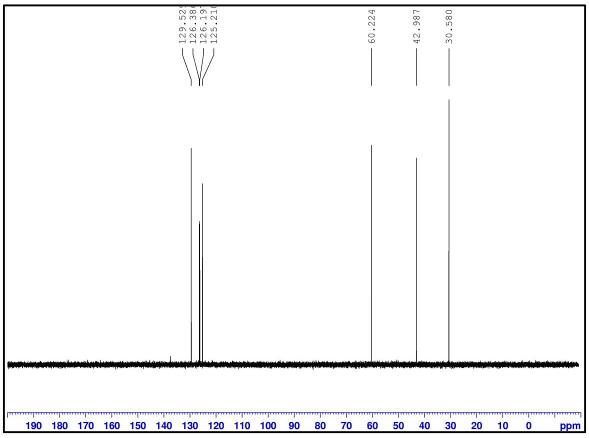
FTIR

Mass

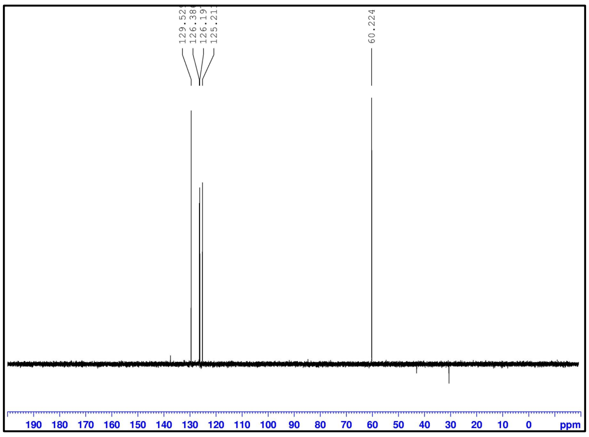


rac-**32**

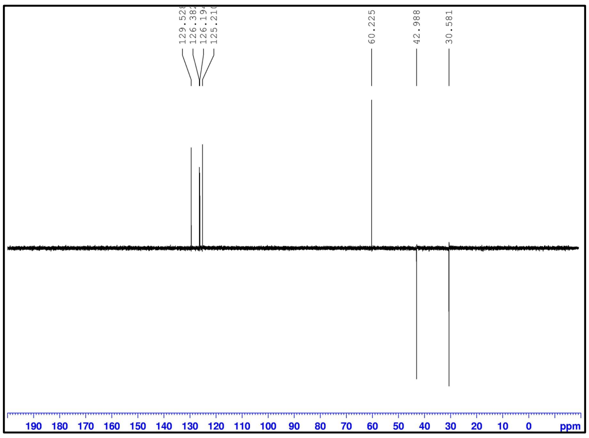
DEPT:



DEPT 45

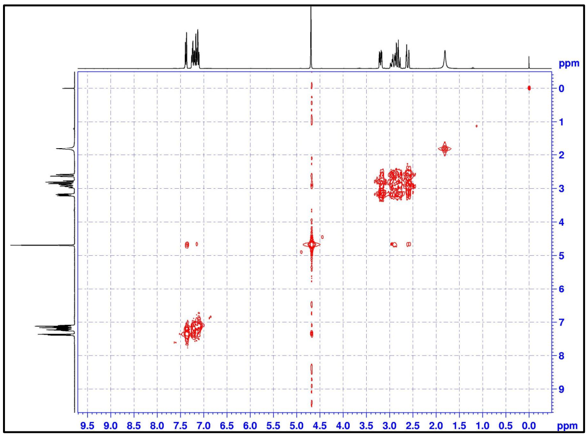


DEPT 90

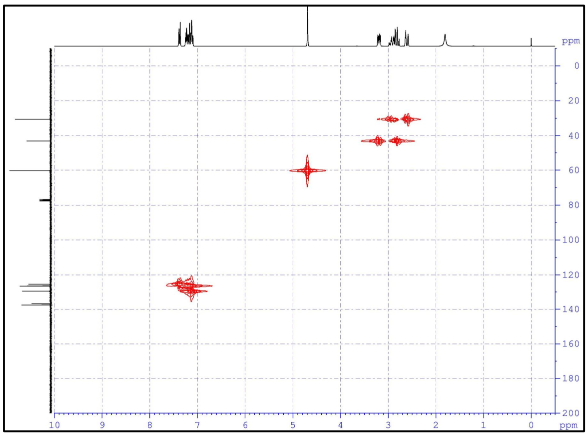


DEPT 135

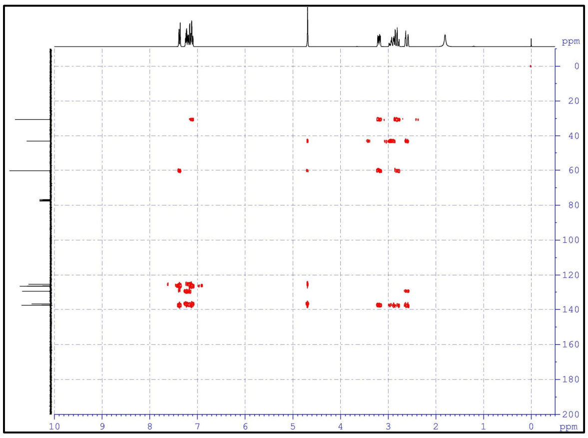
2D NMR spectra:



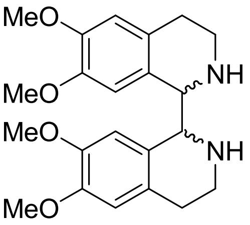
COSY



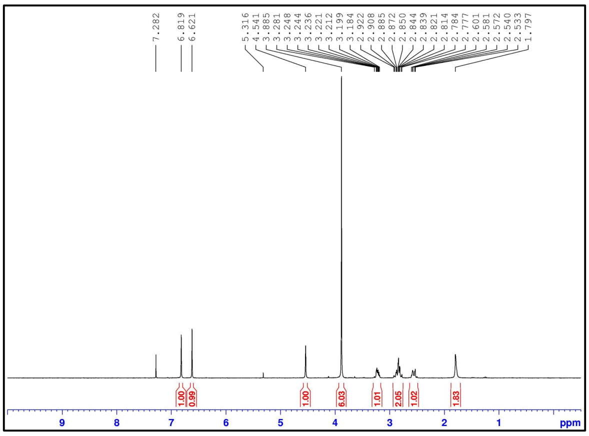
HMQC



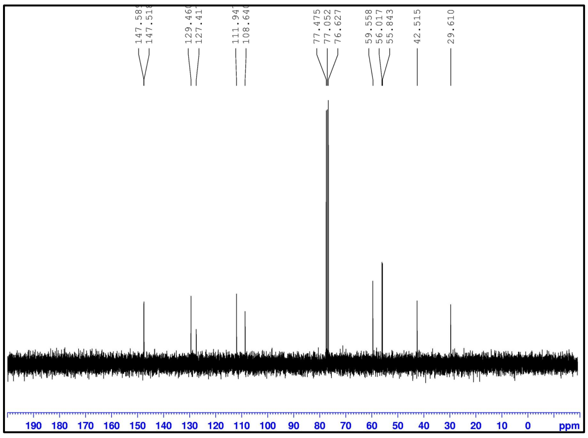
HMBC



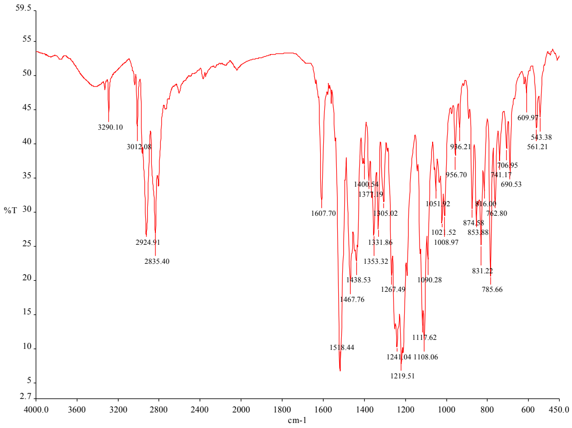
rac-**76**



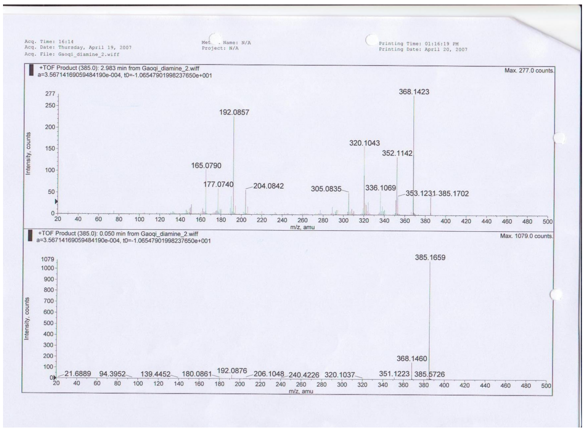
^{1}H NMR



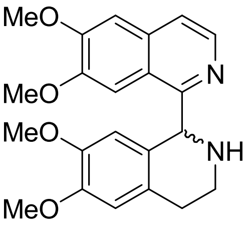
^{13}C NMR



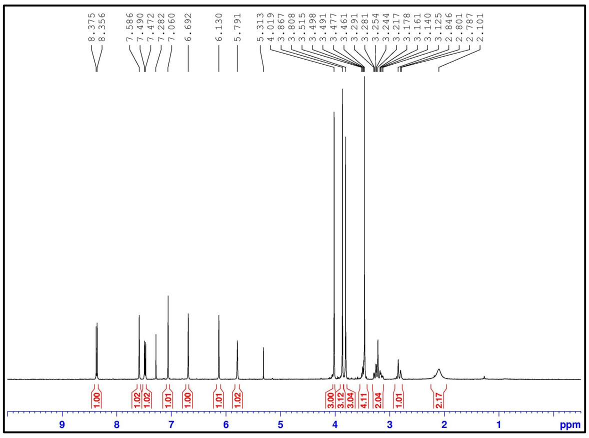
FTIR

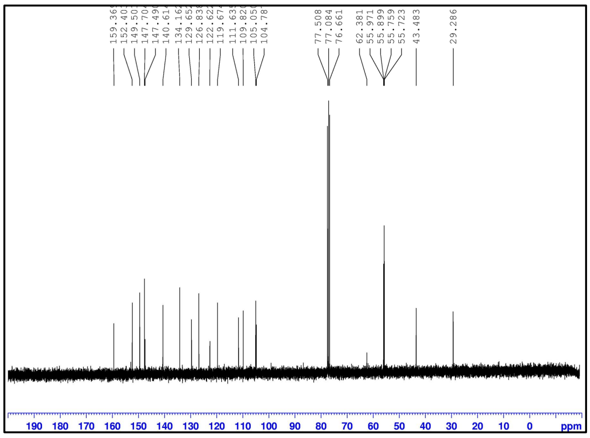


Mass



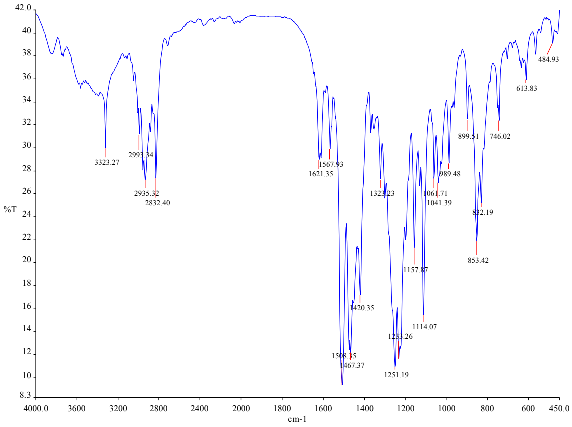
rac-**77**

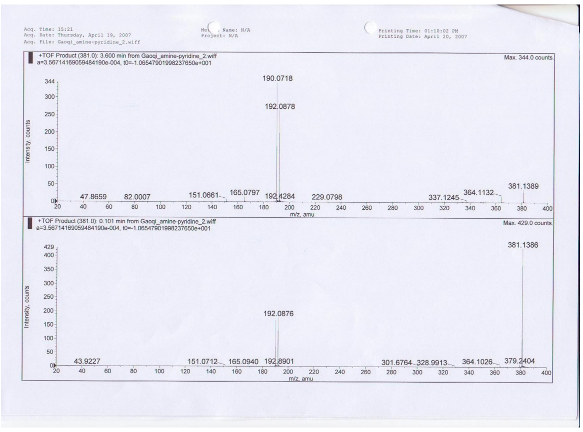




^{1}H NMR

^{13}C NMR




Acq. Time: 15:21
Acq. Date: Thursday, April 19, 2007
Acq. File: Gaoqi_amine-pyridine_2.wiff

Me[illegible] Name: N/A
Project: N/A

Printing Time: 01:10:02 PM
Printing Date: April 20, 2007

+TOF Product (381.0): 3.600 min from Gaoqi_amine-pyridine_2.wiff
a=3.56714169059484190e-004, t0=-1.06547901998237650e+001

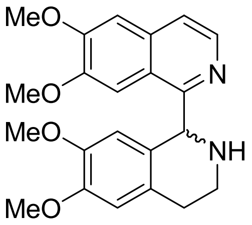
Max. 344.0 counts.

+TOF Product (381.0): 0.101 min from Gaoqi_amine-pyridine_2.wiff
a=3.56714169059484190e-004, t0=-1.06547901998237650e+001

Max. 429.0 counts.

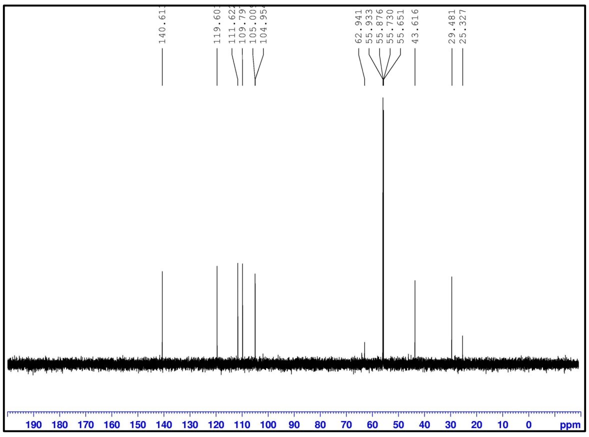
FTIR

Mass

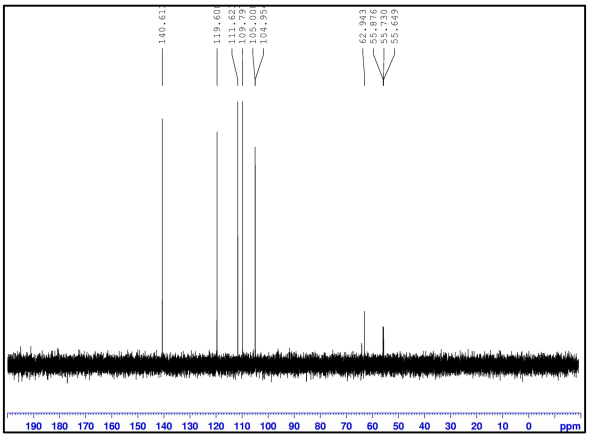


rac-**77**

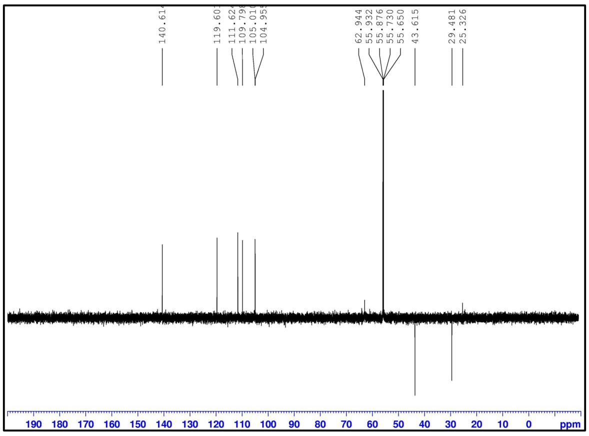
DEPT:



DEPT 45

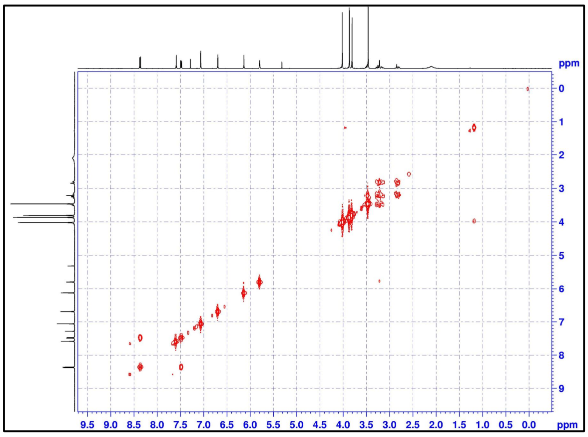


DEPT 90

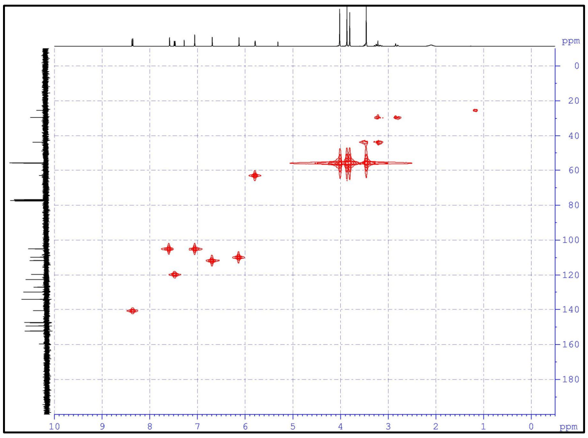


DEPT 135

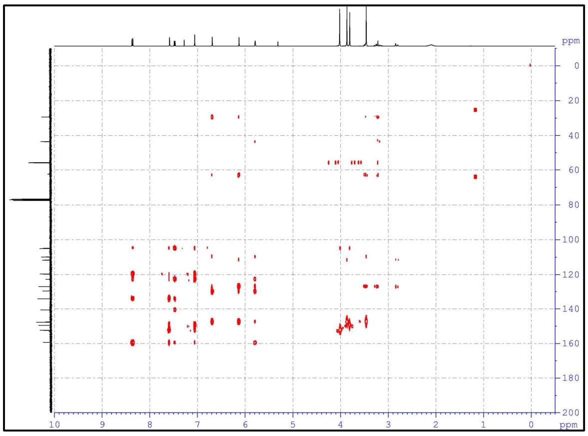
2D NMR spectra:



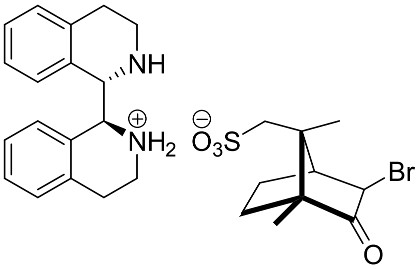
COSY



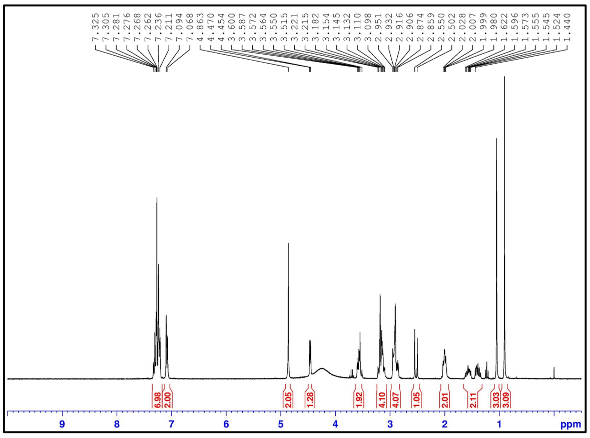
HMQC

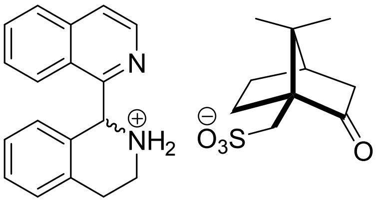


HMBC

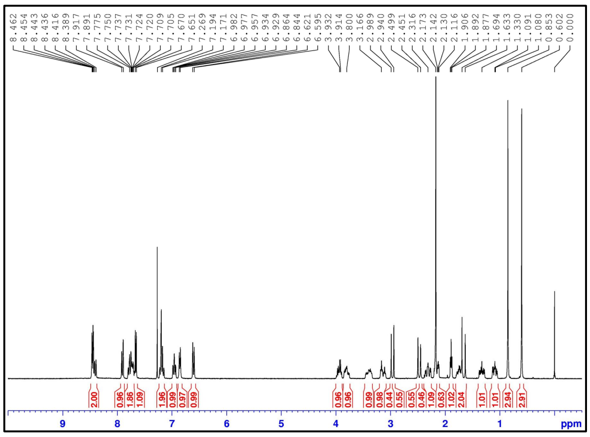


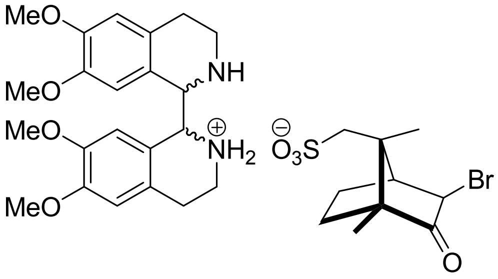
81



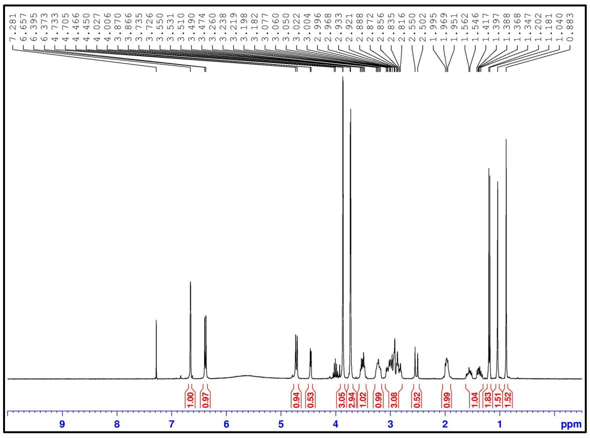


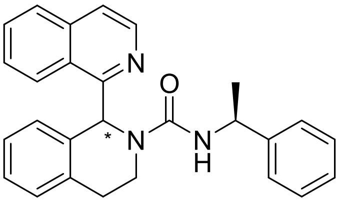
1:1 mixture of **82** and **83**



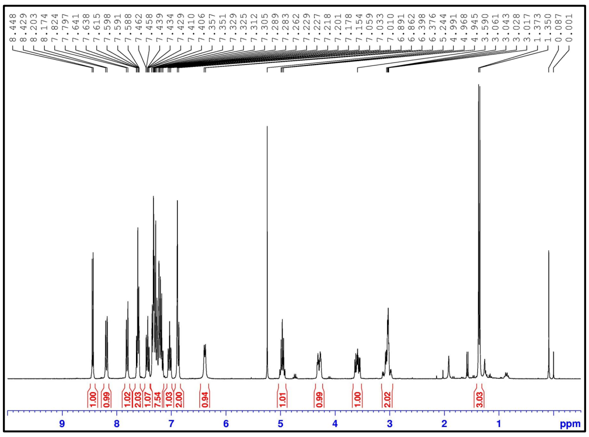


1:1 mixture of **84** and **85**

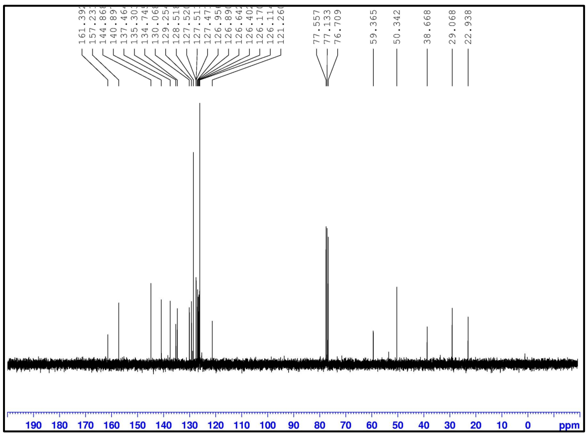




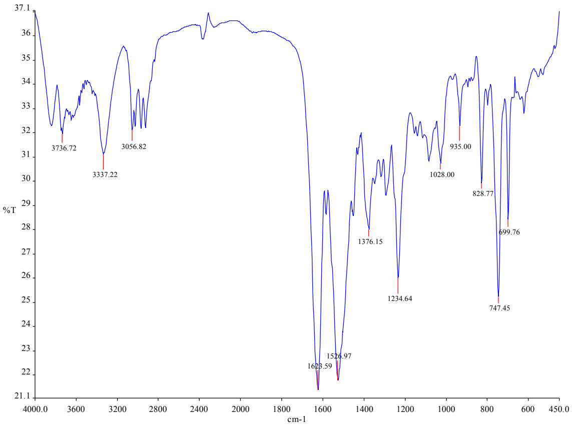
(+)-**86**



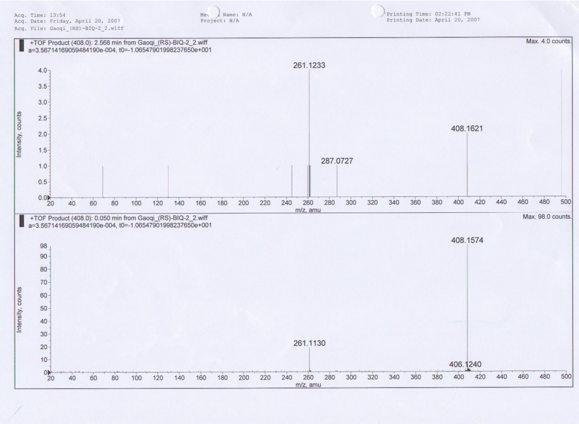
^{1}H NMR



^{13}C NMR



FTIR



Acq. Time: 13:54
Acq. Date: Friday, April 20, 2007
Acq. File: Gaoqi_(RS)-BIQ-2_2.wiff

Me[illegible] Name: N/A
Project: N/A

Printing Time: 02:22:41 PM
Printing Date: April 20, 2007

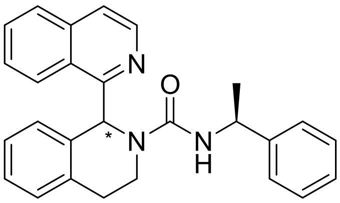
+TOF Product (408.0): 2.568 min from Gaoqi_(RS)-BIQ-2_2.wiff
a=3.56714169059484190e-004, t0=-1.06547901998237650e+001

Max. 4.0 counts.

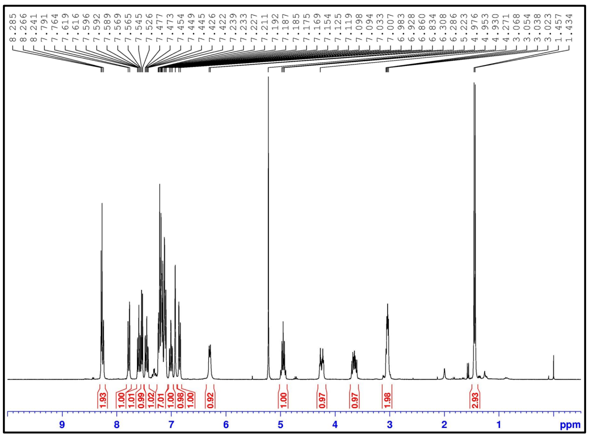
+TOF Product (408.0): 0.050 min from Gaoqi_(RS)-BIQ-2_2.wiff
a=3.56714169059484190e-004, t0=-1.06547901998237650e+001

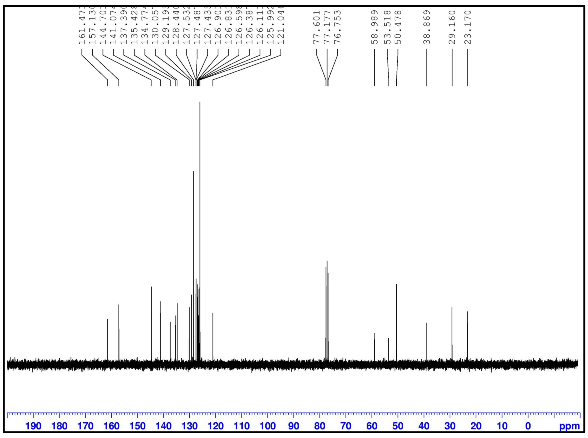
Max. 98.0 counts.

Mass



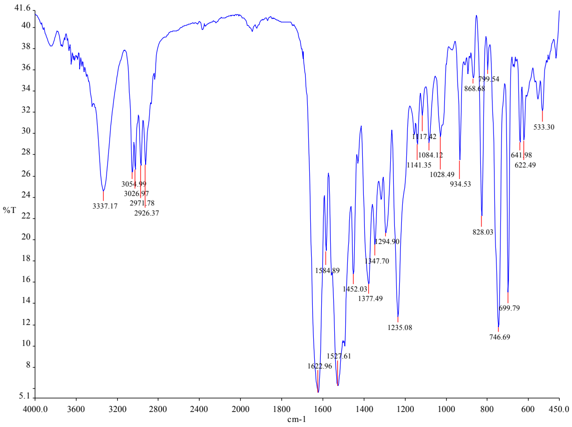
(-)-**87**

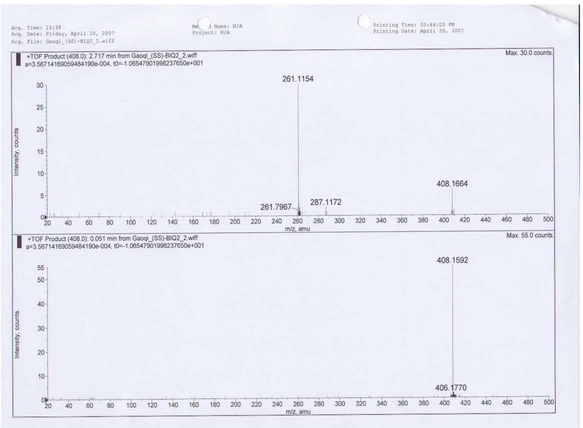




^{1}H NMR

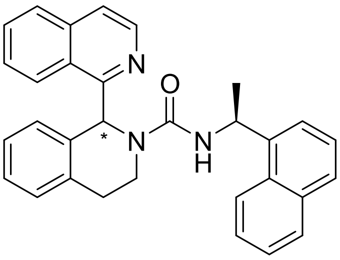
^{13}C NMR



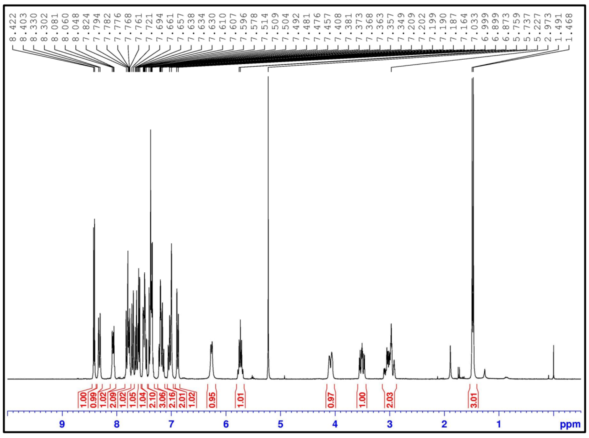


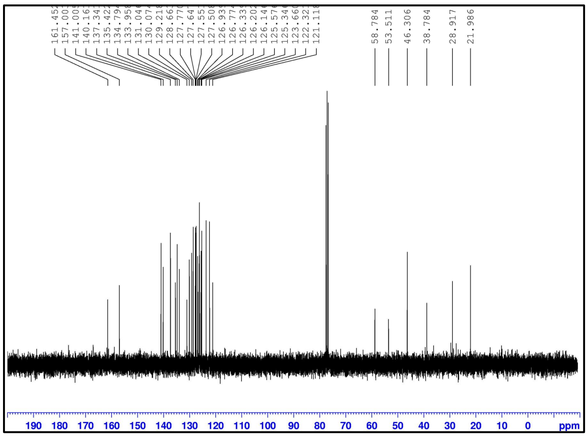
FTIR

Mass



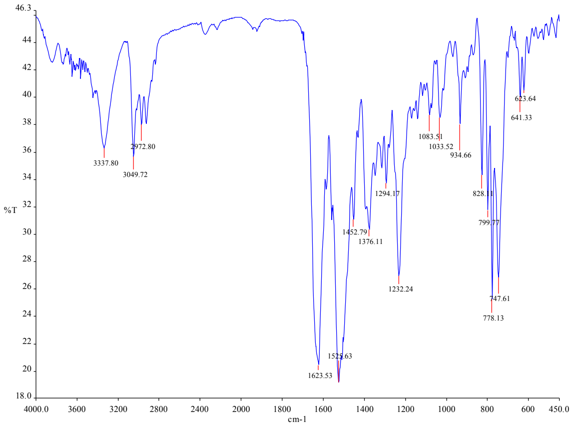
(+)-**88**

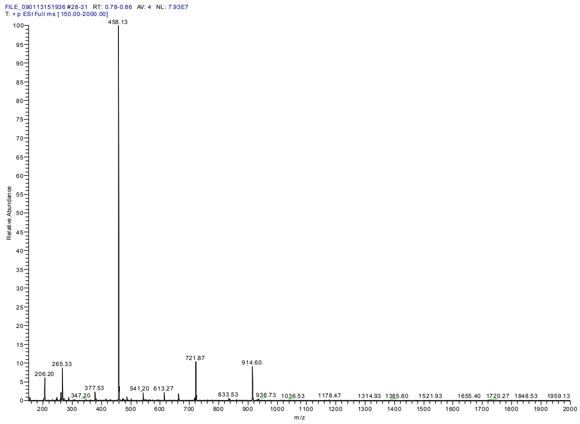




^{1}H NMR

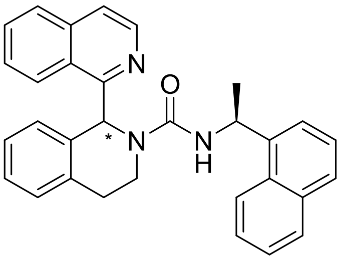
^{13}C NMR



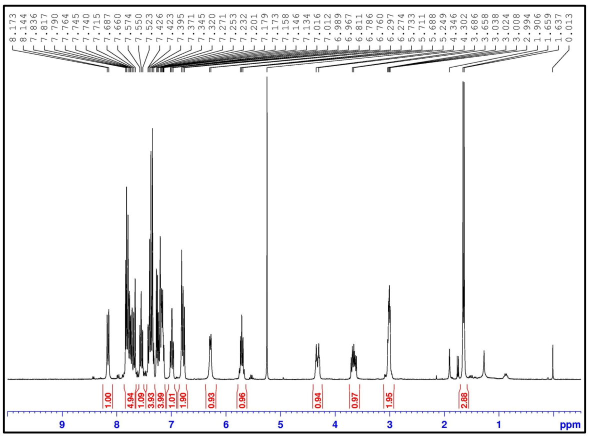


FTIR

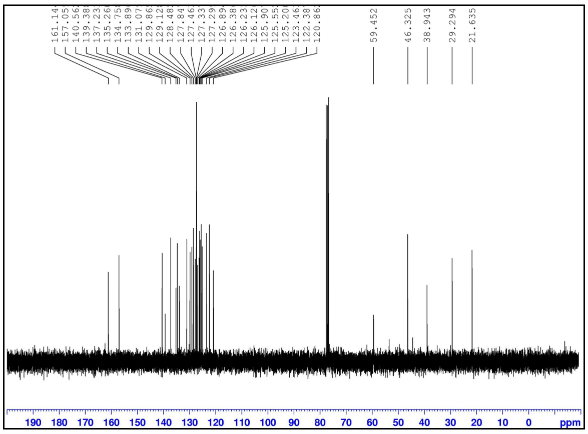
Mass



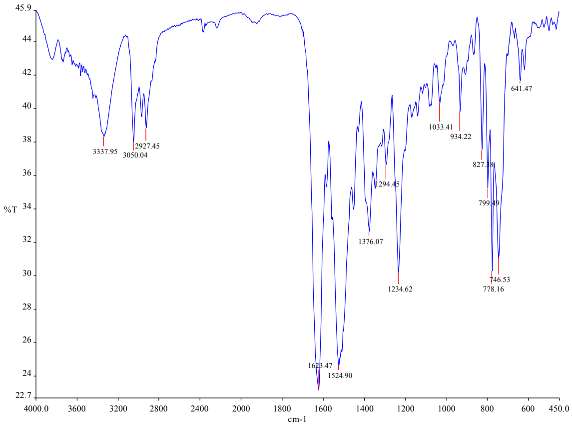
(-)-**89**



^{1}H NMR



^{13}C NMR



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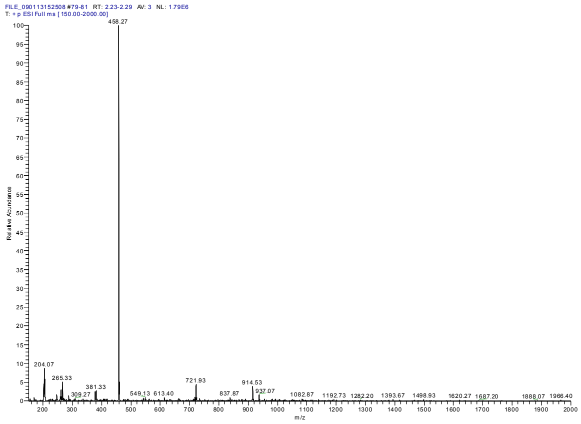

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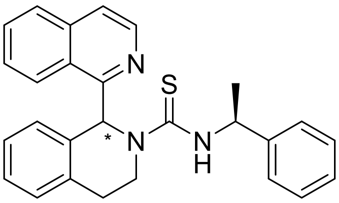
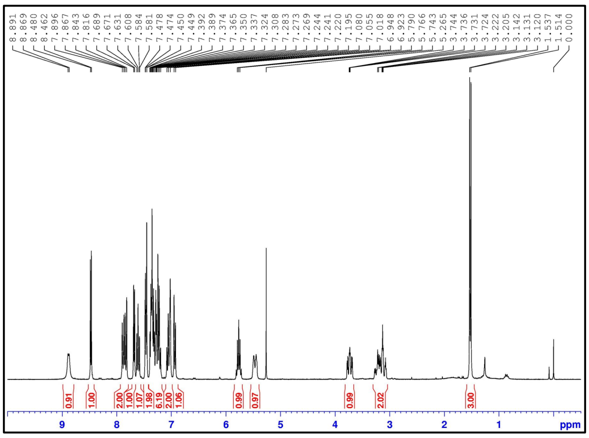
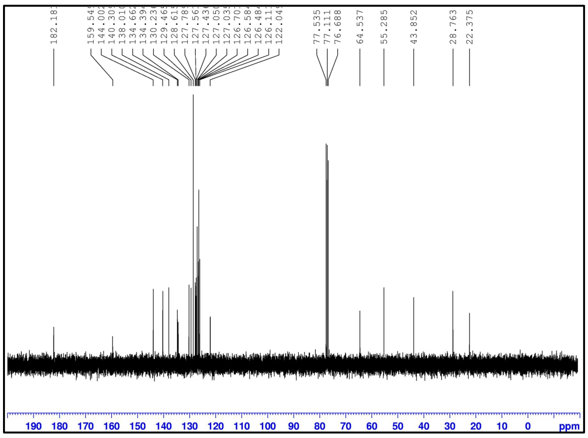


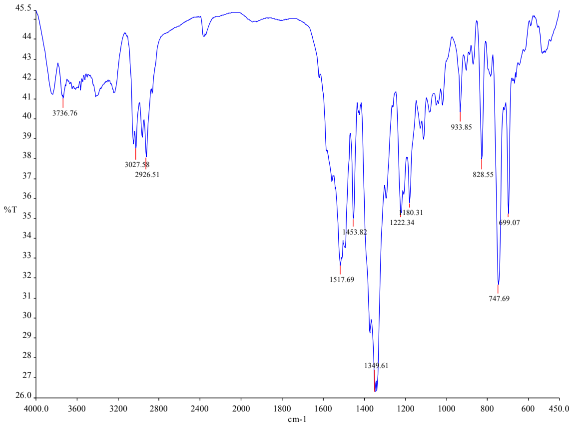
(+)-90

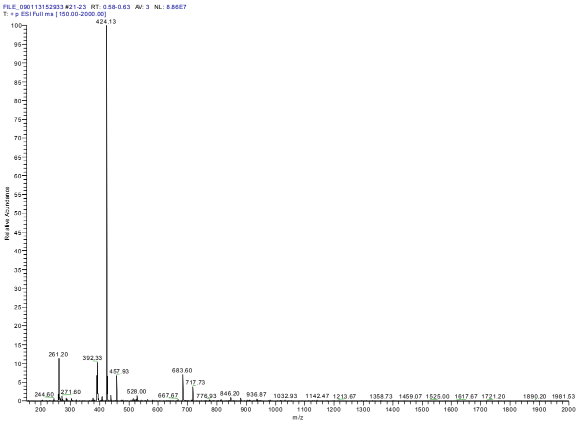




^{1}H NMR

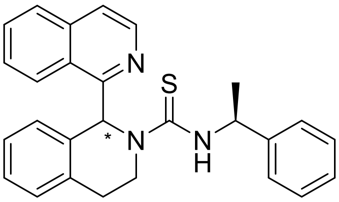
^{13}C NMR



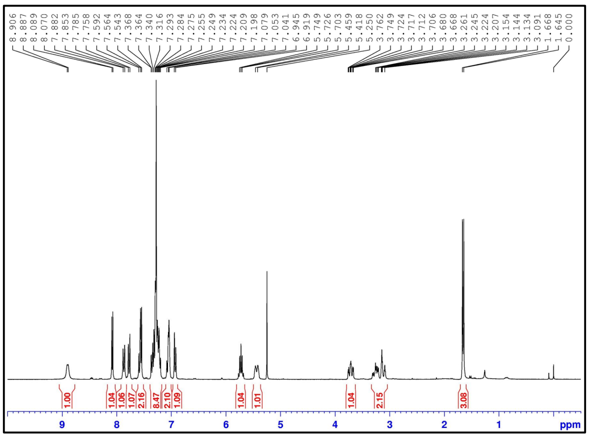


FTIR

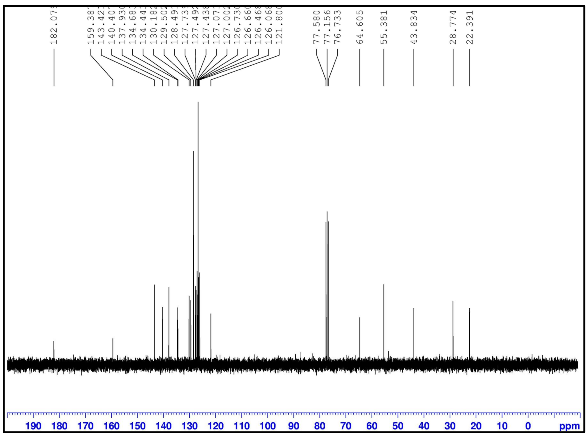
Mass



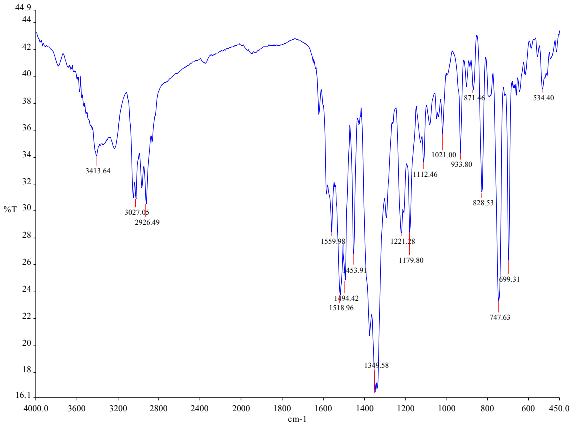
(-)-**91**



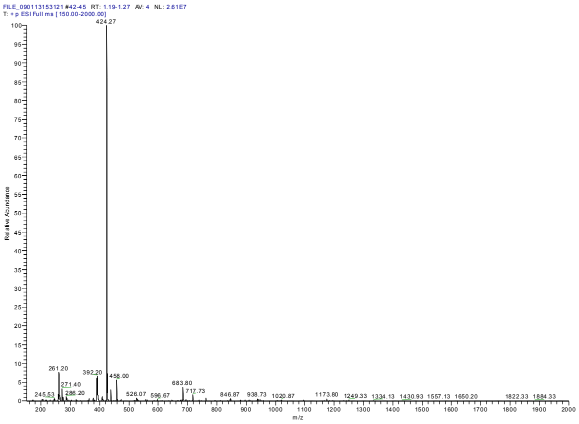
^{1}H NMR



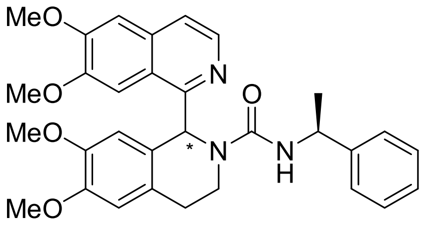
^{13}C NMR



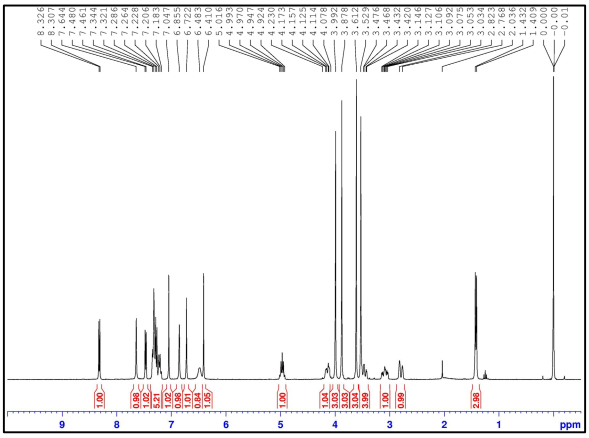
FTIR

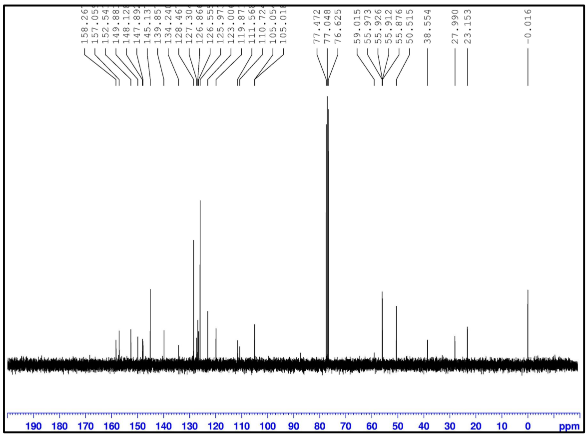


Mass



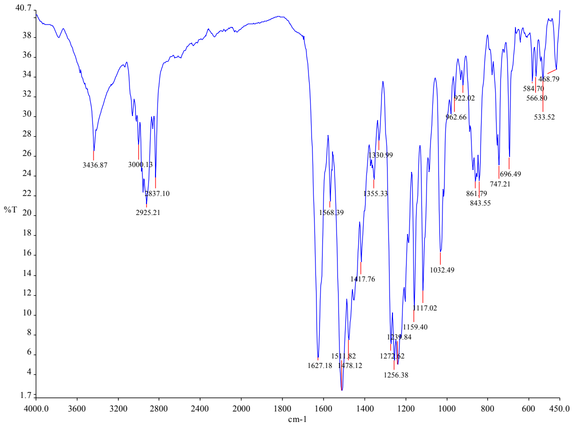
(+)-**94**

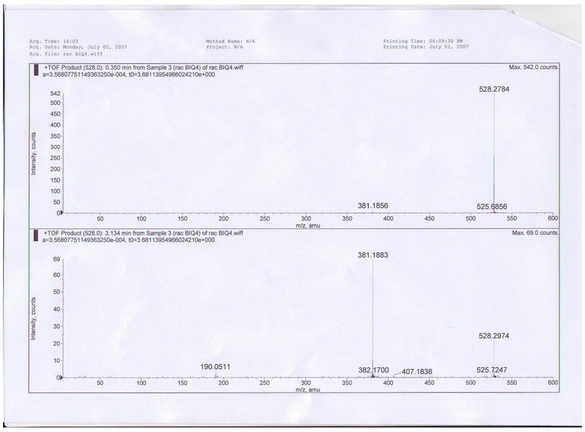




^{1}H NMR

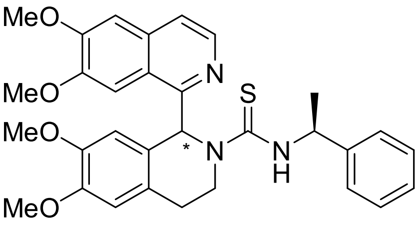
^{13}C NMR



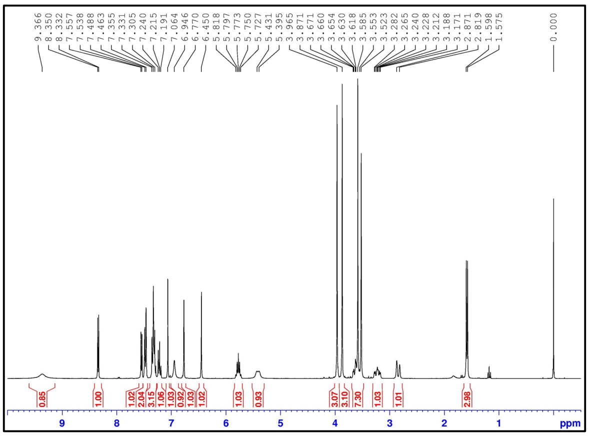


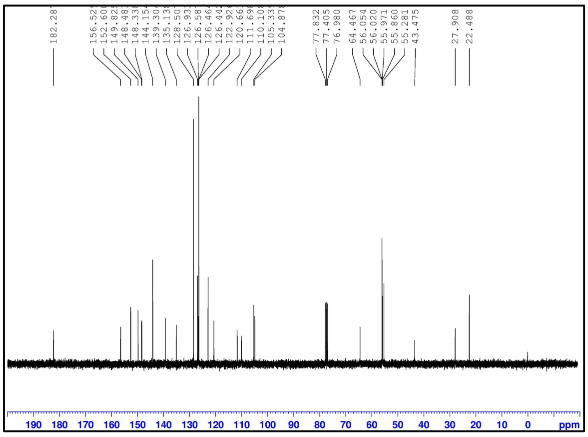
FTIR

Mass



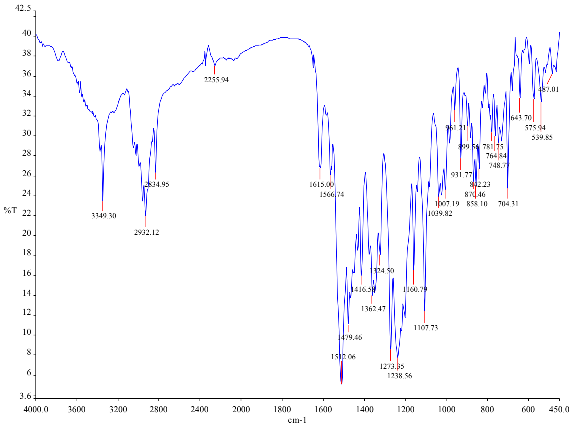
(+)-98

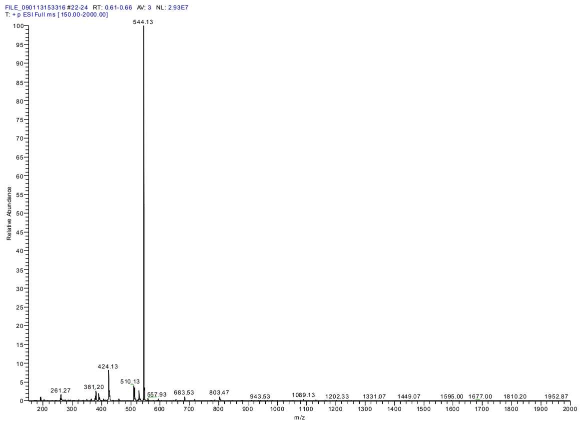




^{1}H NMR

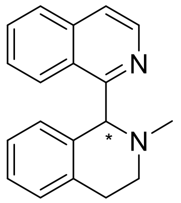
^{13}C NMR



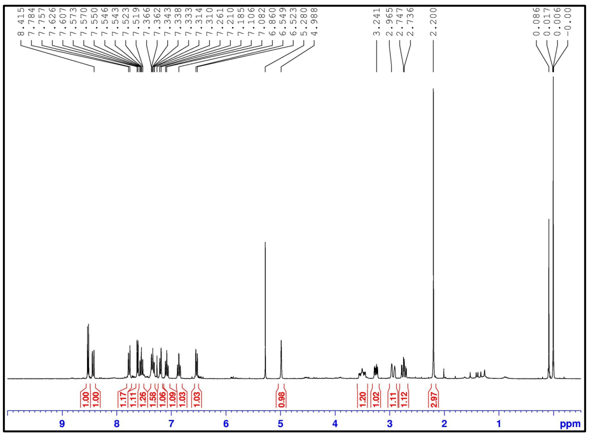


FTIR

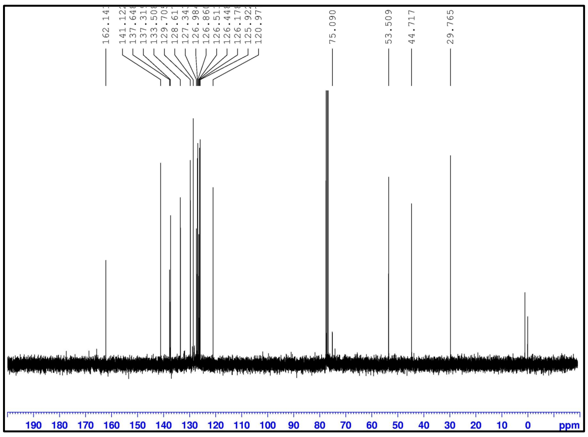
Mass



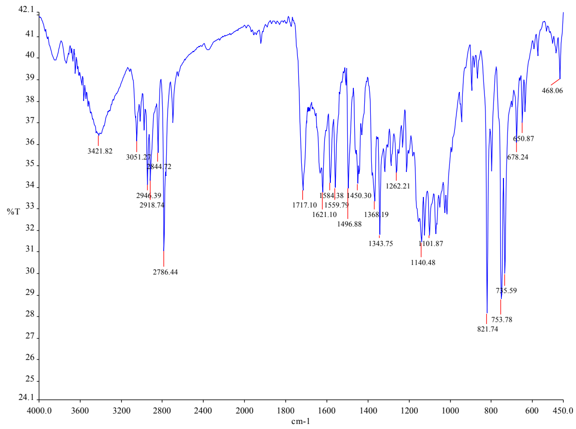
(+)-**100**



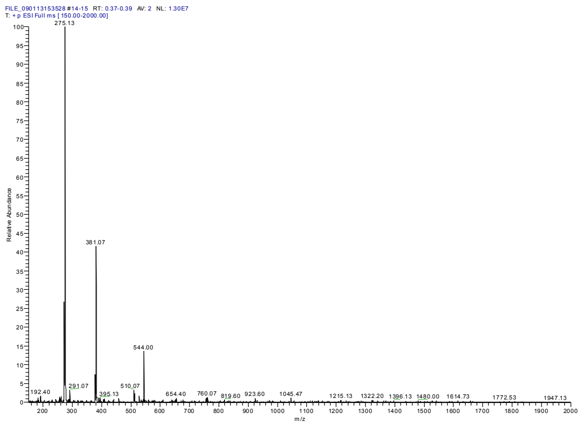
^{1}H NMR



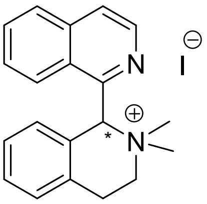
^{13}C NMR



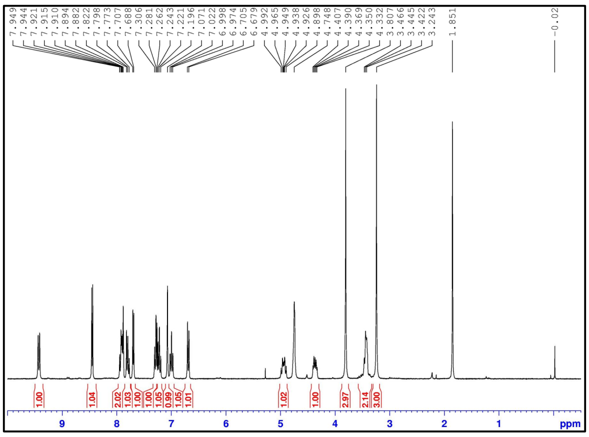
FTIR

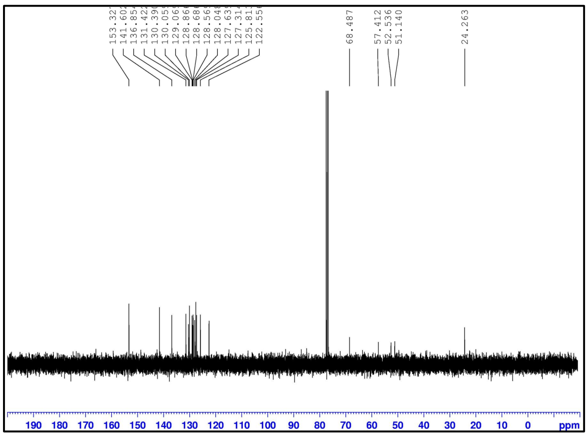


Mass



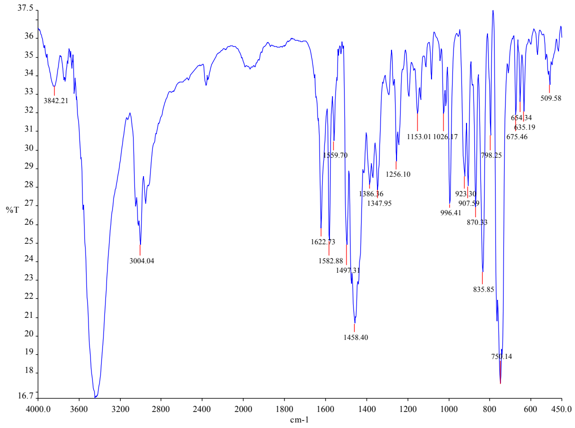
(+)-**101**

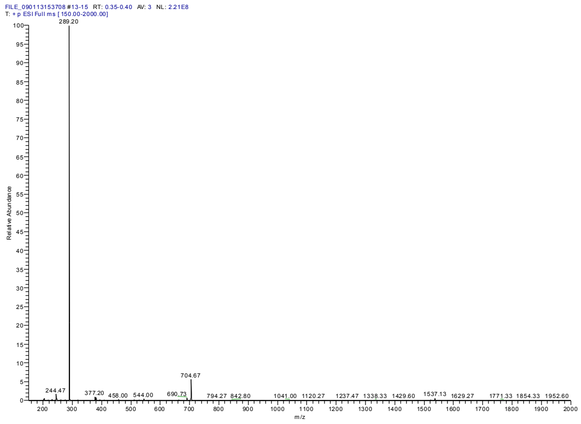




^{1}H NMR

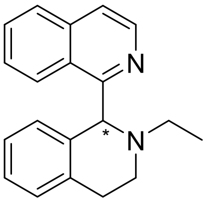
^{13}C NMR



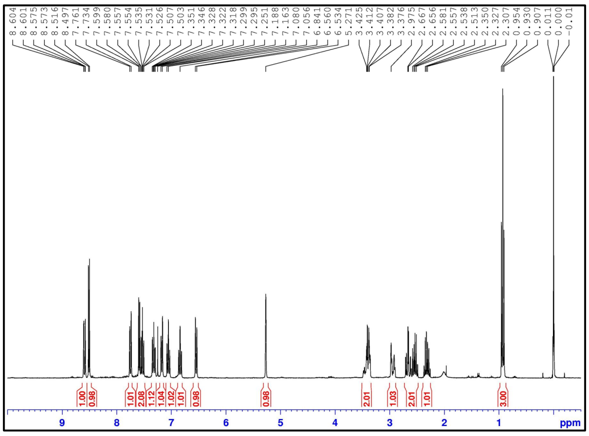


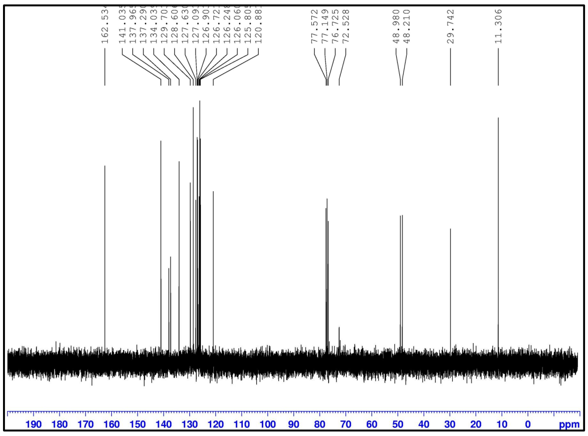
FTIR

Mass

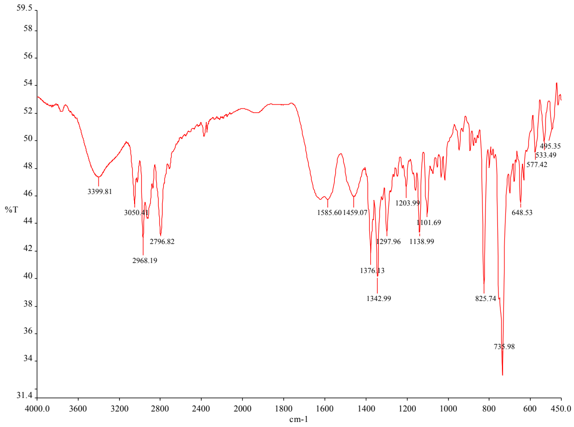


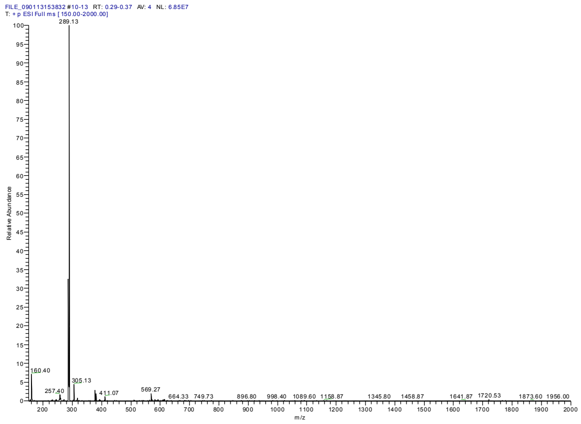
(+)-102





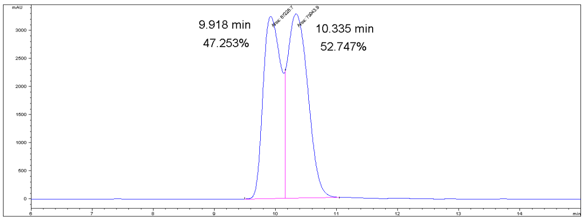
^{1}H NMR **^{13}C NMR**



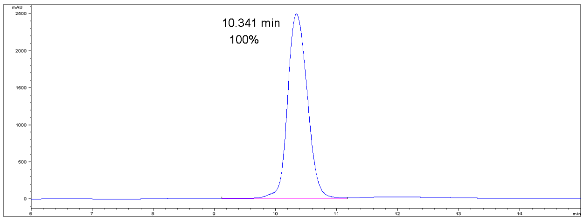


FTIR **Mass**

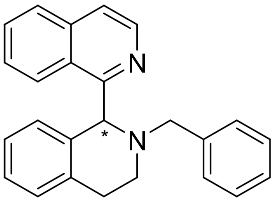
***rac*-102**



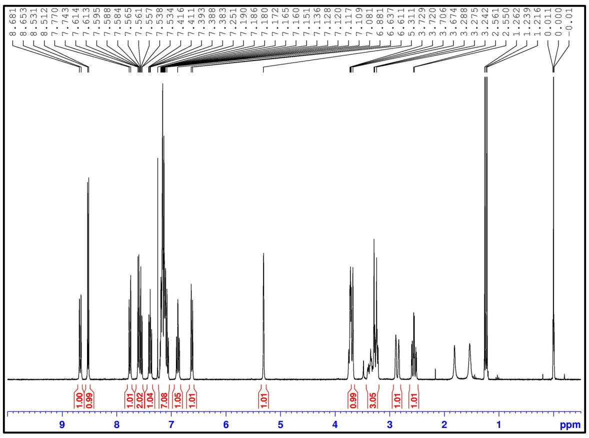
(+)-102

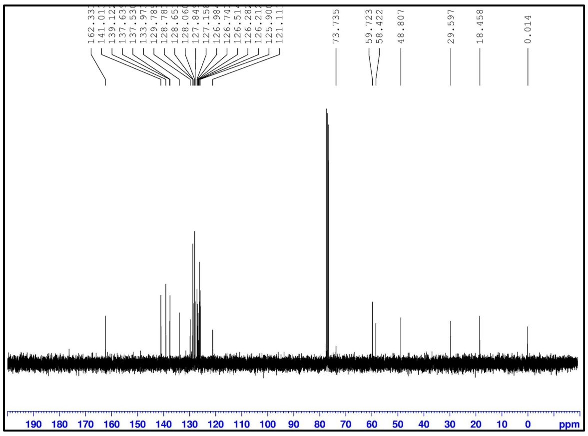


HPLC



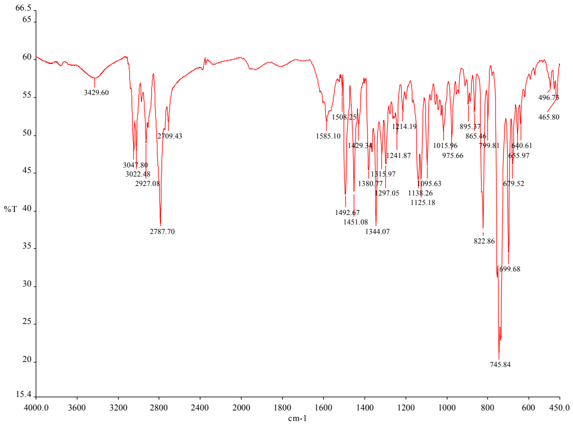
(+)-**103**

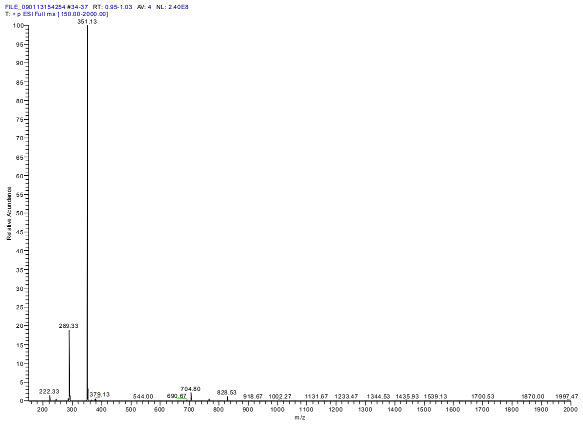




^{1}H NMR

^{13}C NMR

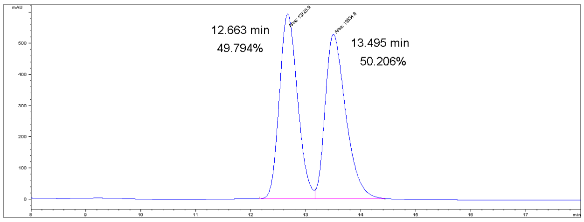




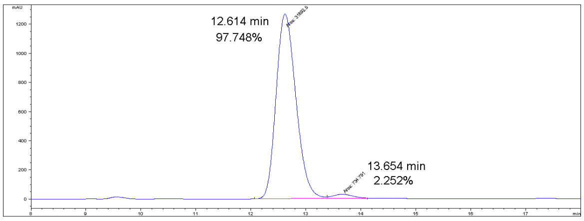
FTIR

Mass

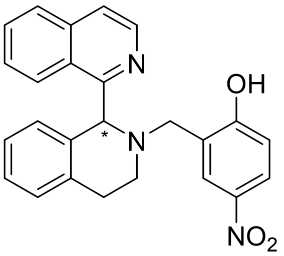
rac-**103**



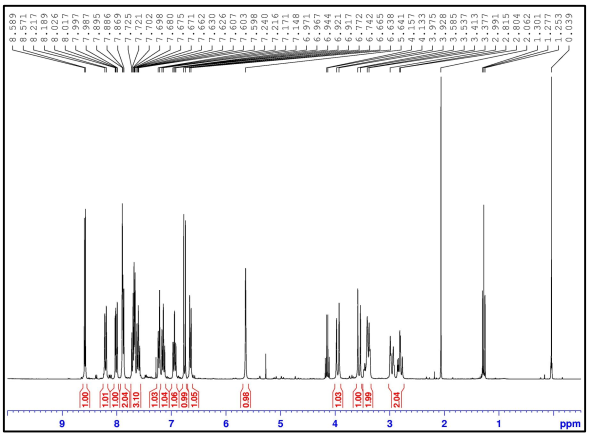
(+)-**103**

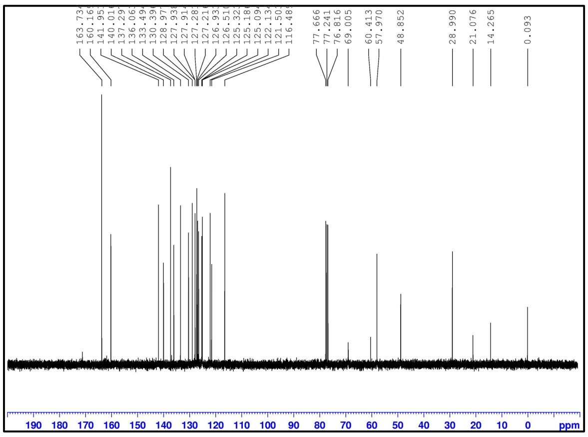


HPLC



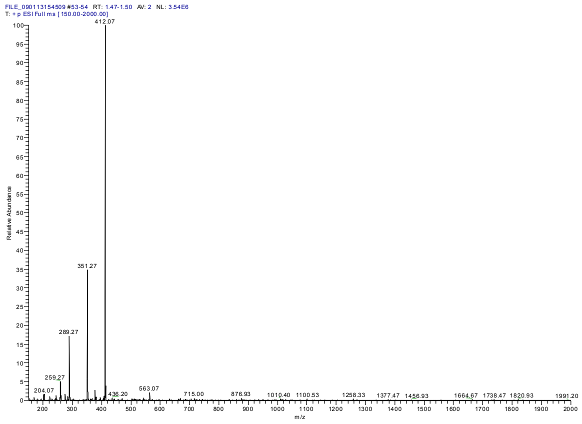
(+)-**104**





^{1}H NMR

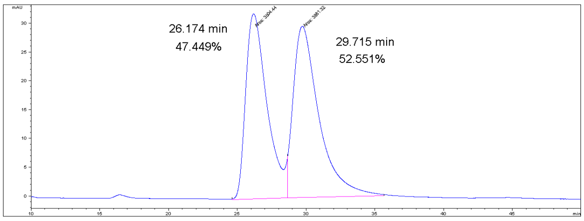
^{13}C NMR



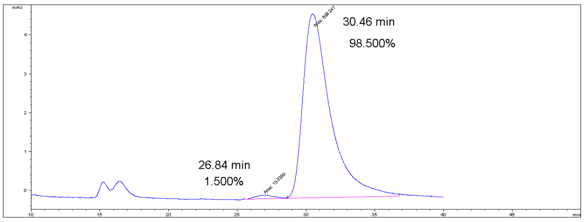
FTIR

Mass

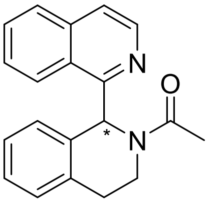
rac-**104**



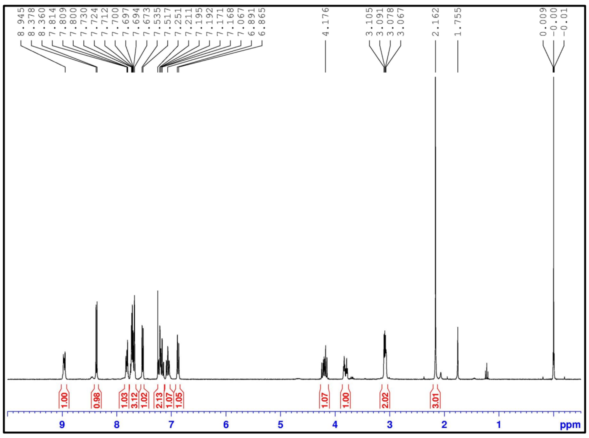
(+)-**104**



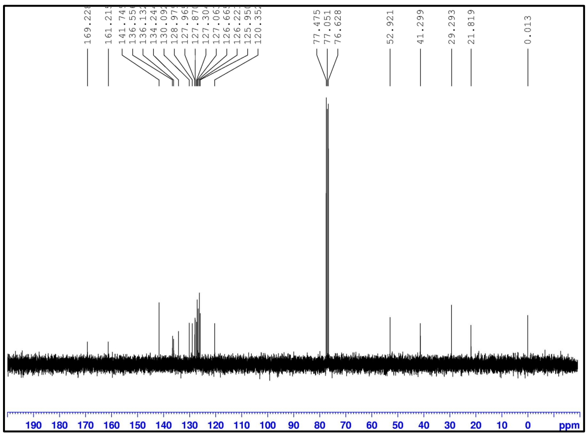
HPLC



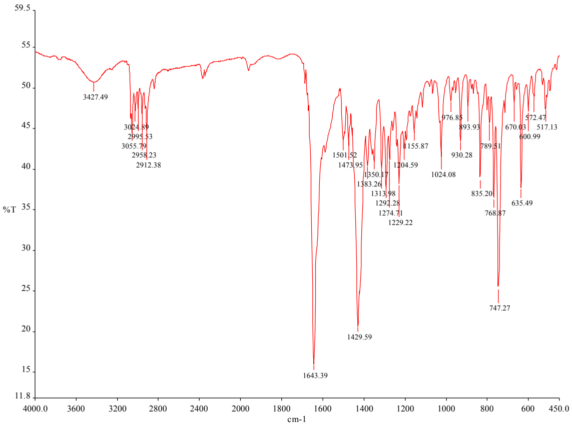
(+)-**105**



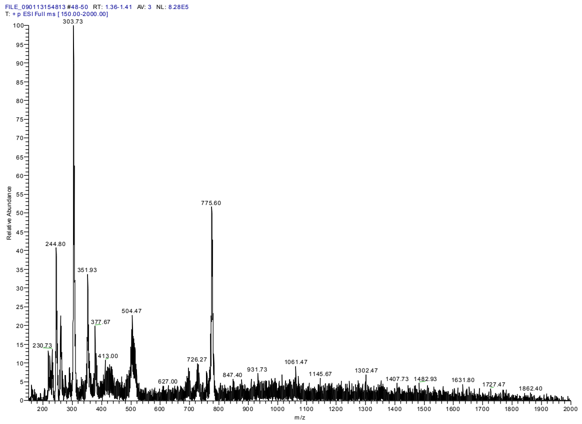
^{1}H NMR



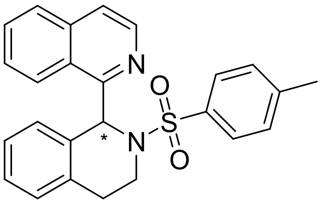
^{13}C NMR



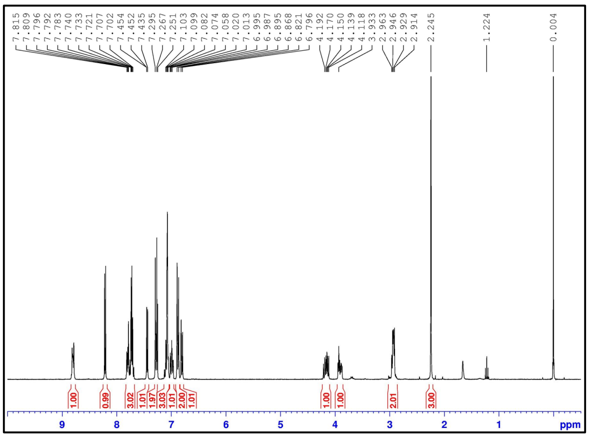
FTIR



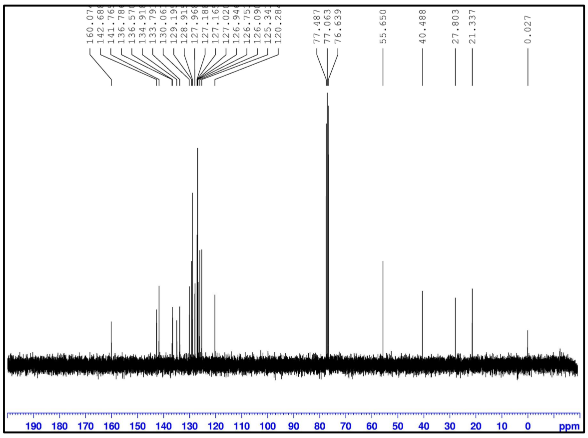
Mass



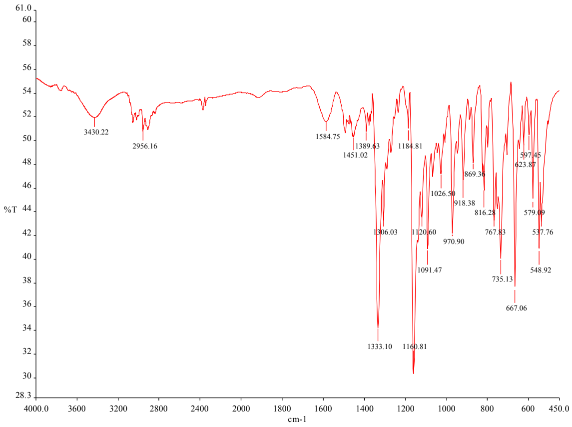
(+)-**106**



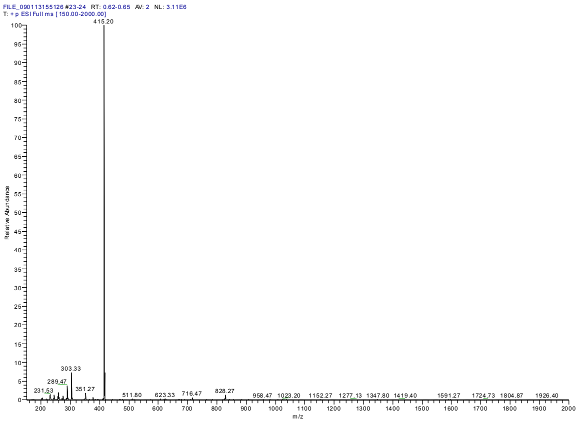
^{1}H NMR



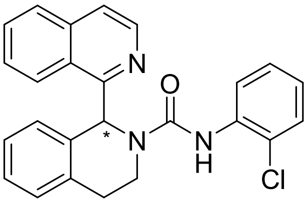
^{13}C NMR



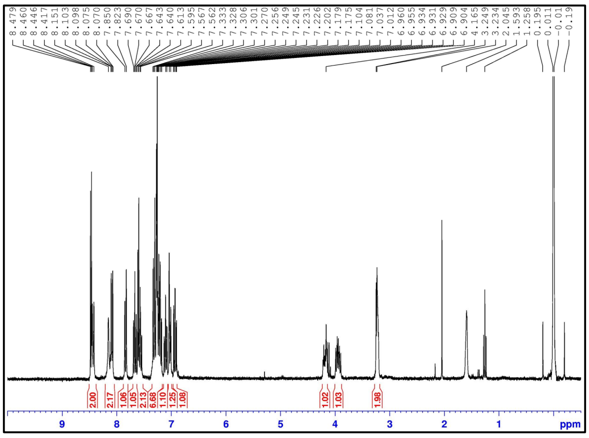
FTIR

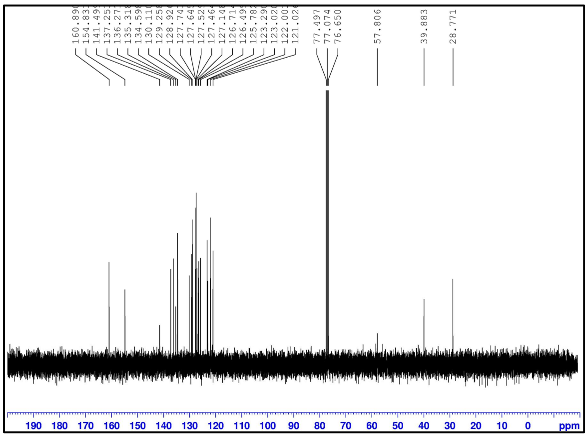


Mass



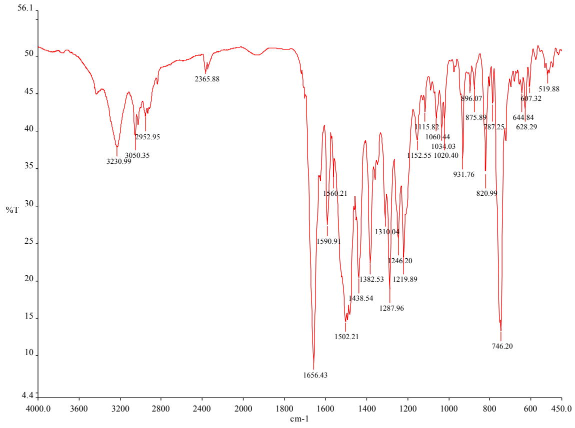
(+)-**107**

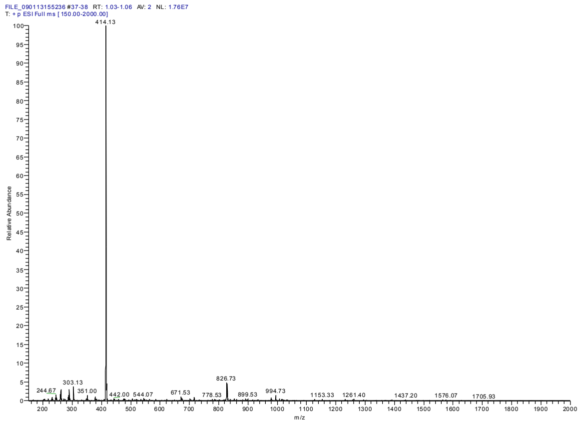




^{1}H NMR

^{13}C NMR

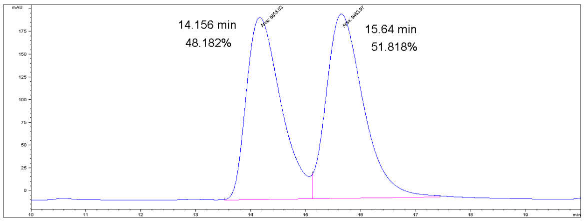




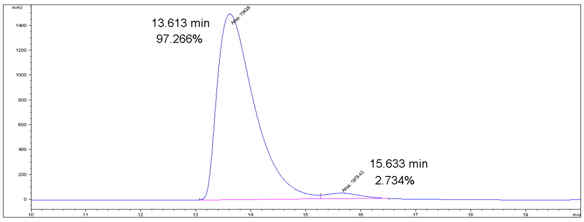
FTIR

Mass

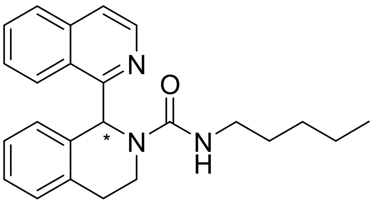
rac-**107**



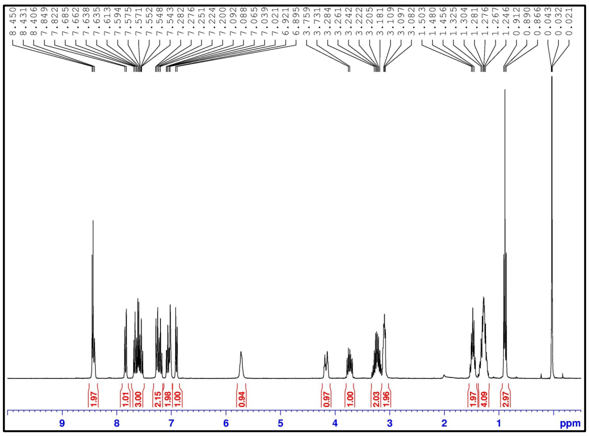
(+)-**107**

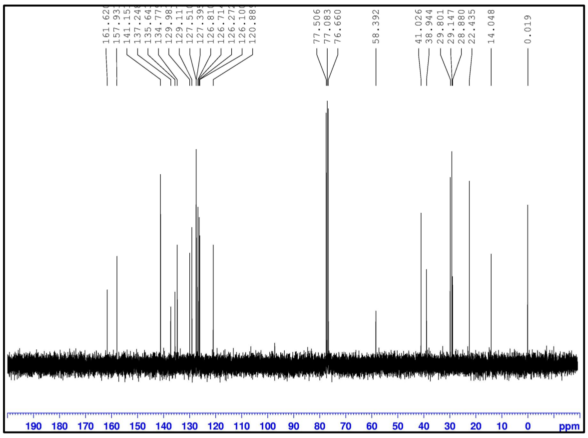


HPLC

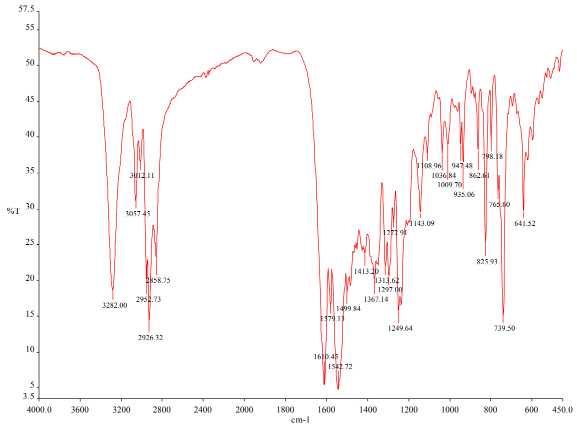


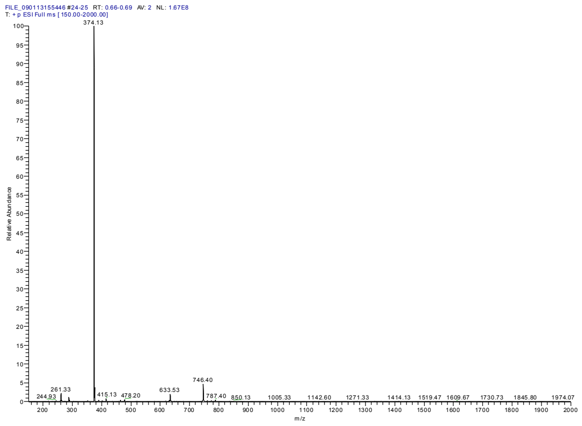
(+)-**108**





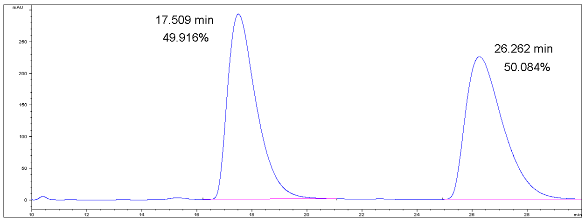
^{1}H NMR **^{13}C NMR**



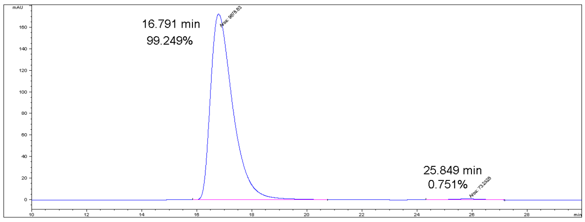


FTIR **Mass**

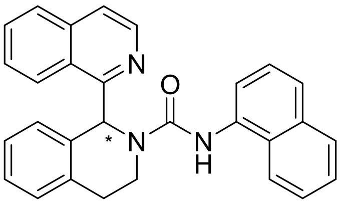
rac-**108**



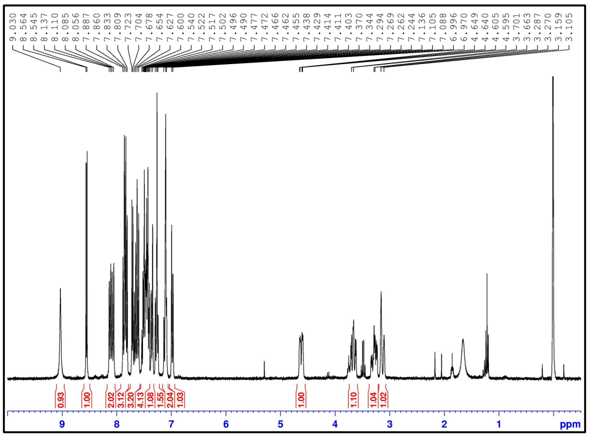
(+)-**108**

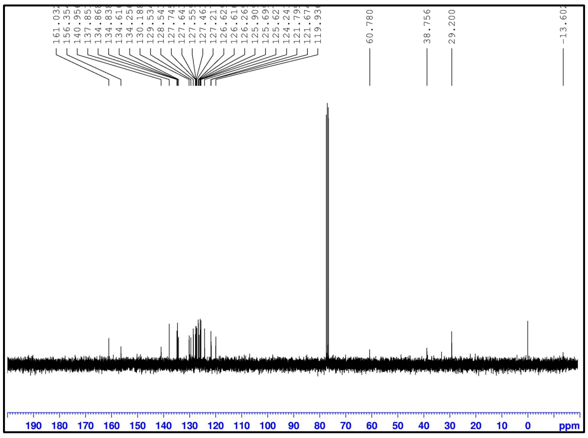


HPLC

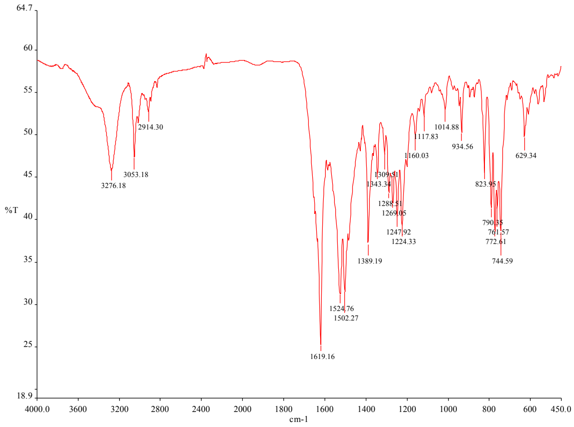


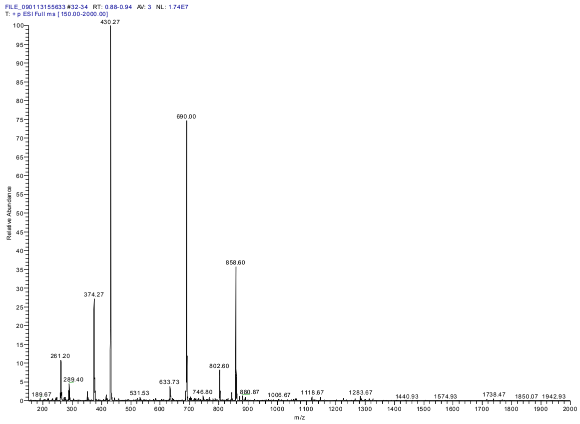
(+)-109



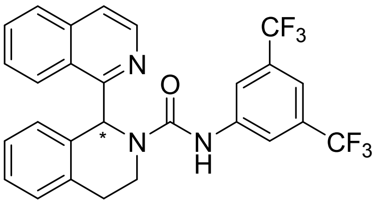


^{1}H NMR **^{13}C NMR**

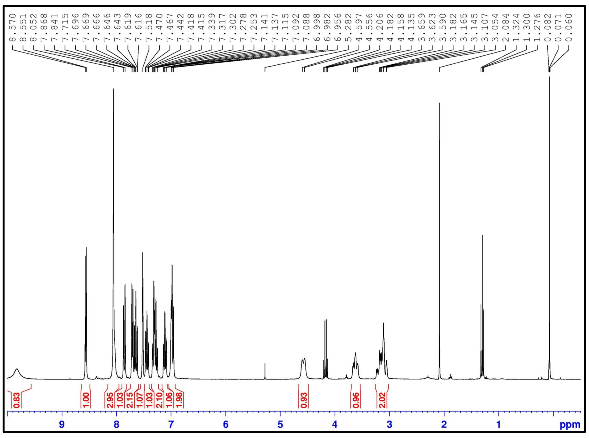


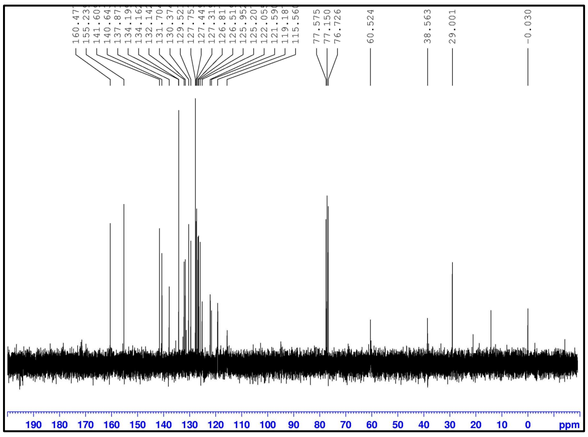


FTIR **Mass**



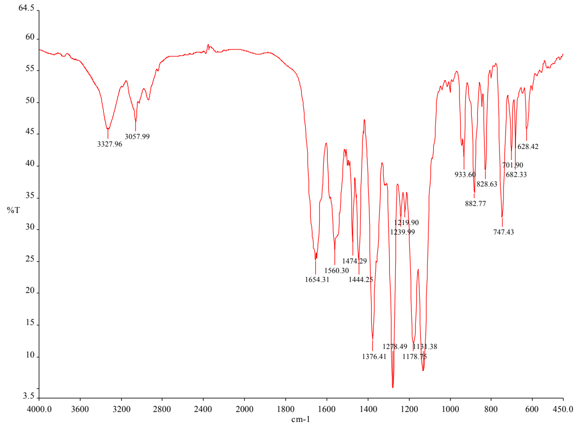
(+)-110

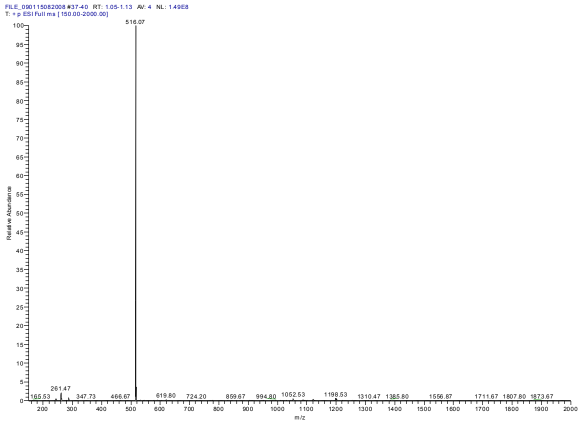




^{1}H NMR

^{13}C NMR

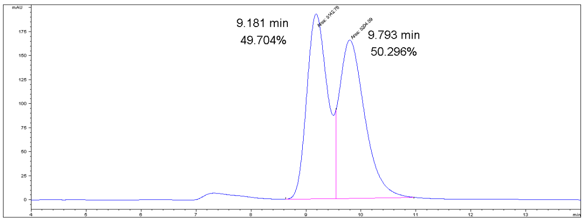




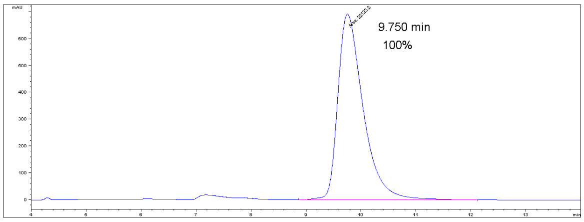
FTIR

Mass

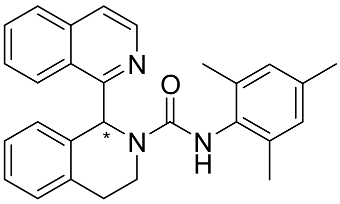
rac-**110**



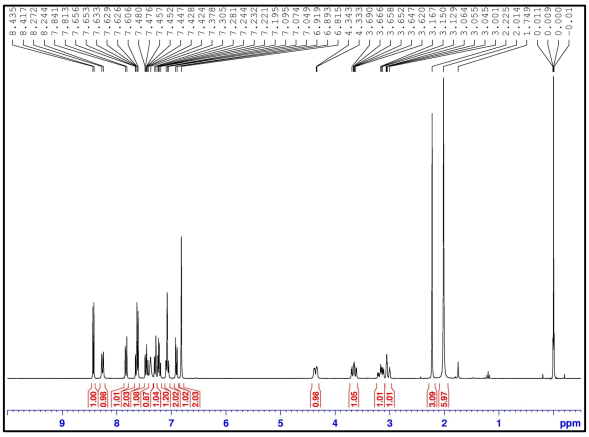
(+)-**110**



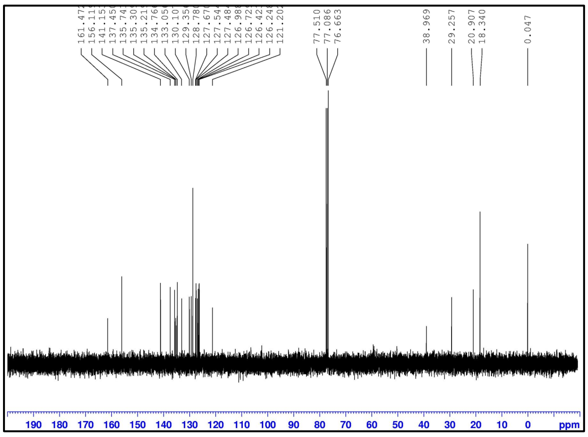
HPLC



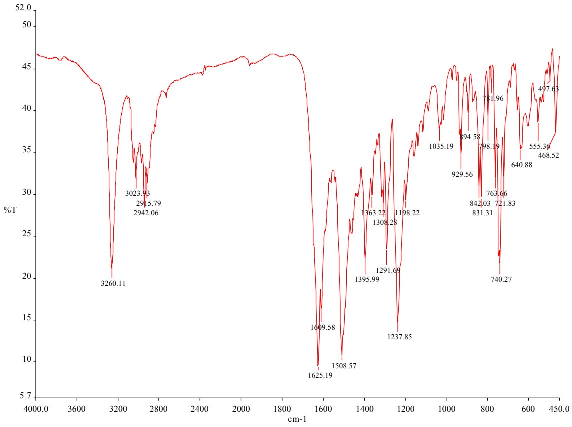
(+)-**111**



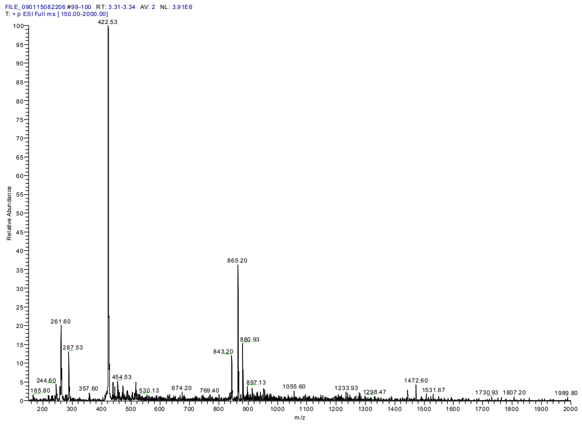
^{1}H NMR



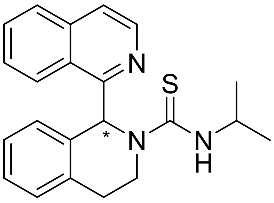
^{13}C NMR



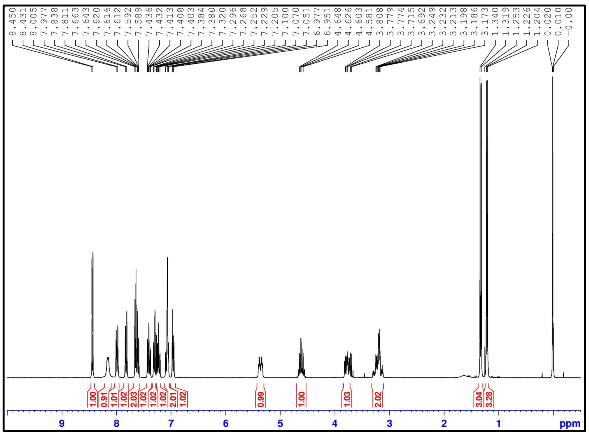
FTIR

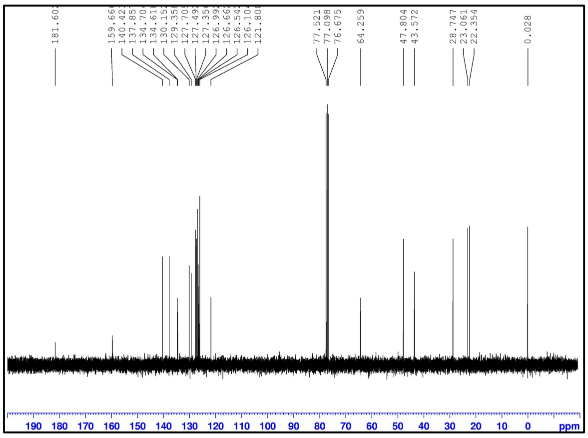


Mass



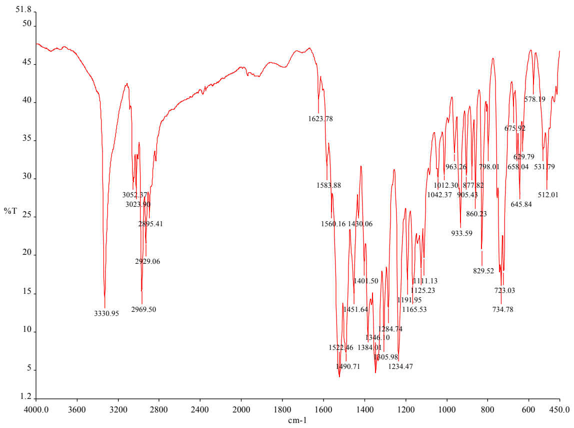
(+)-**112**

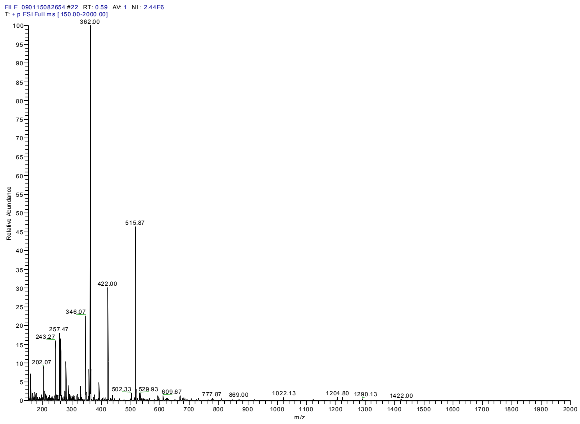




^{1}H NMR

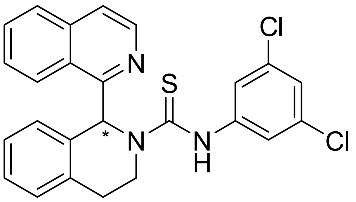
^{13}C NMR



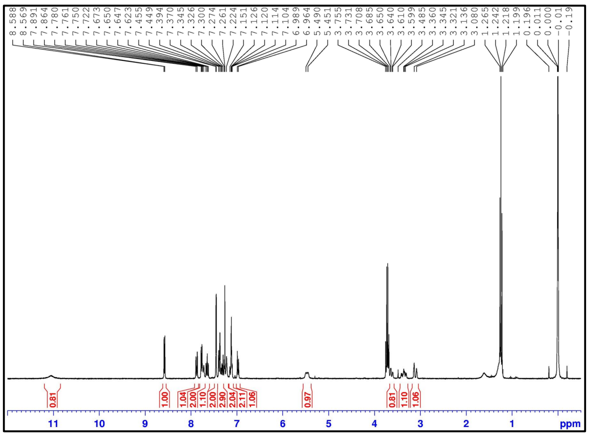


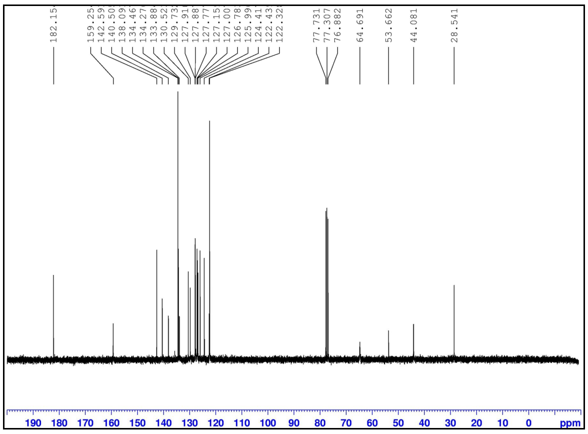
FTIR

Mass



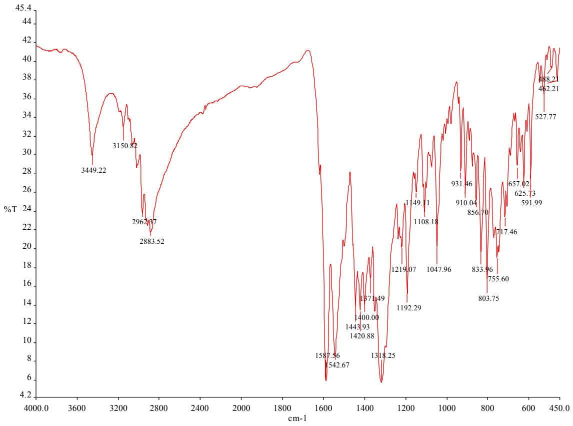
(+)-113

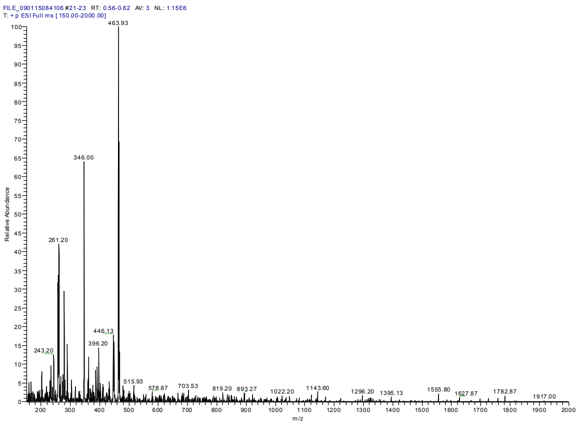




^{1}H NMR

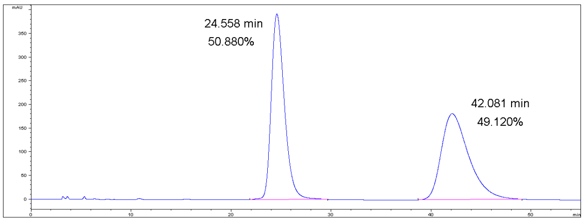
^{13}C NMR



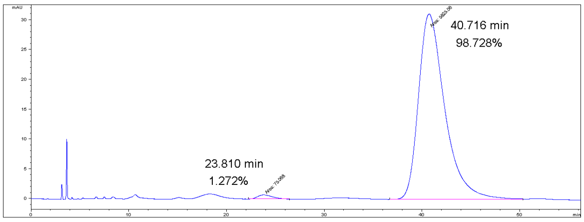


FTIR

Mass

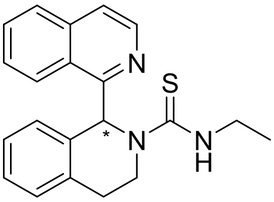


rac-**113**

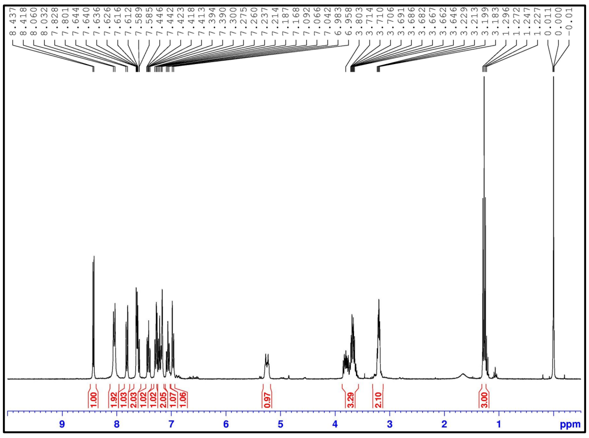


(+)-**113**

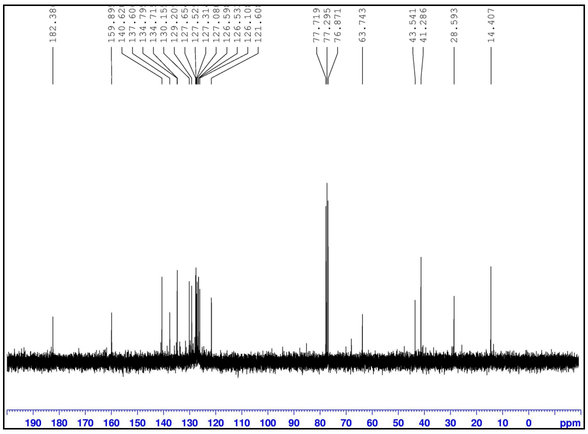
HPLC



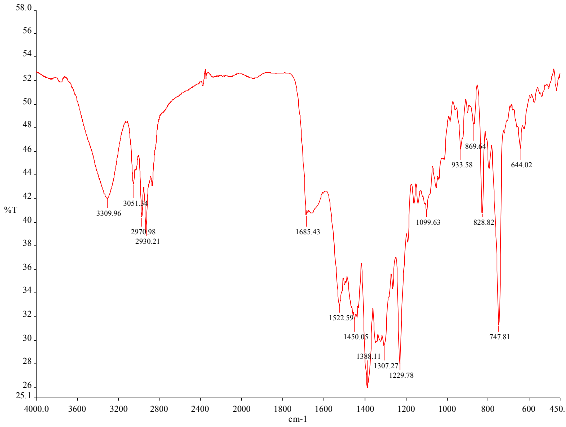
(+)-**114**



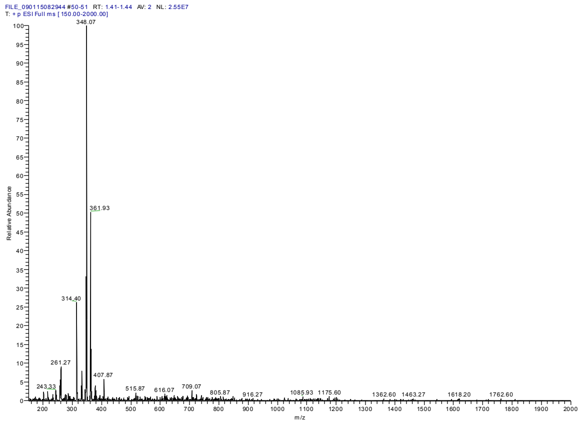
^{1}H NMR



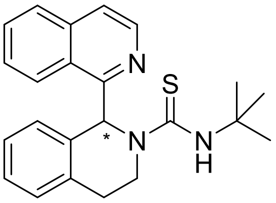
^{13}C NMR



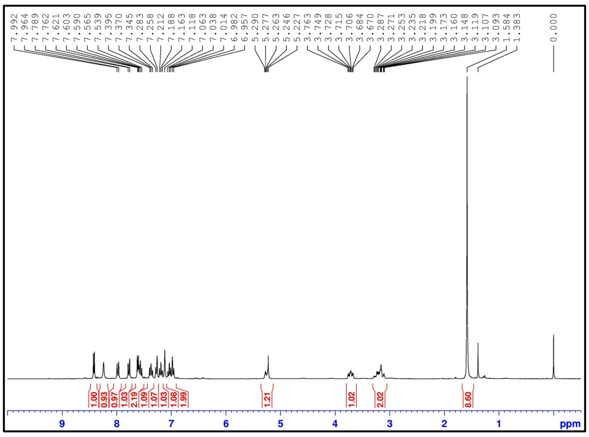
FTIR

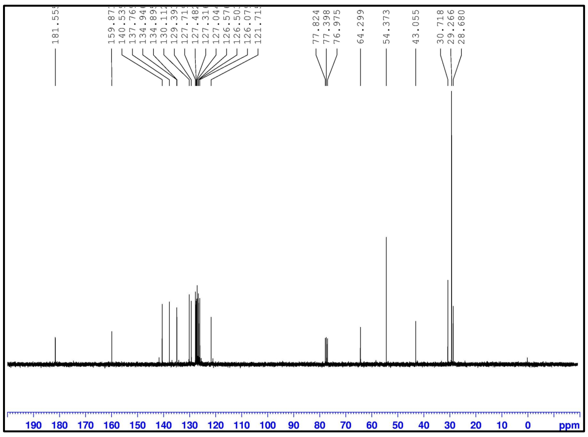


Mass



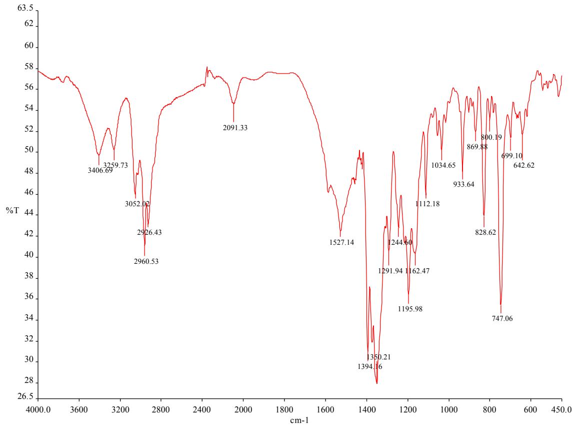
(+)-115

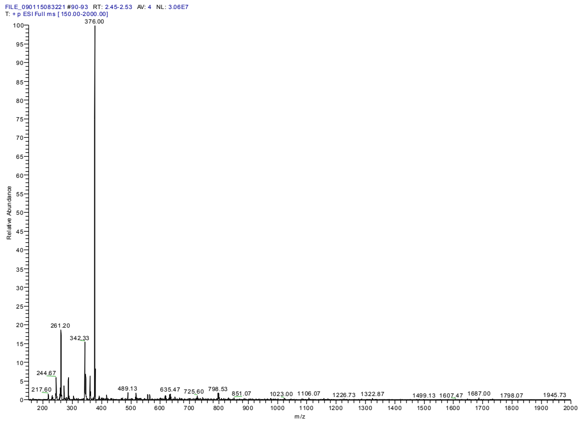




^{1}H NMR

^{13}C NMR

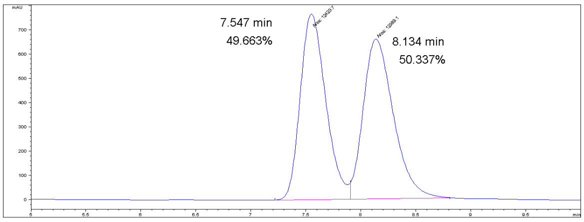




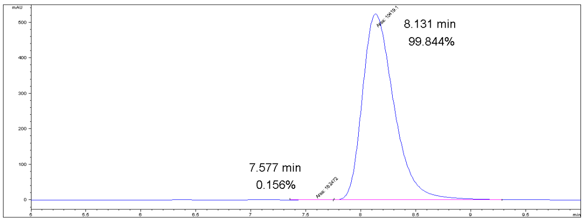
FTIR

Mass

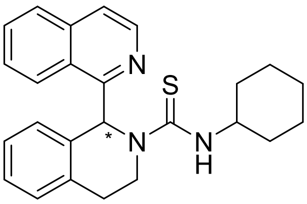
rac-**115**



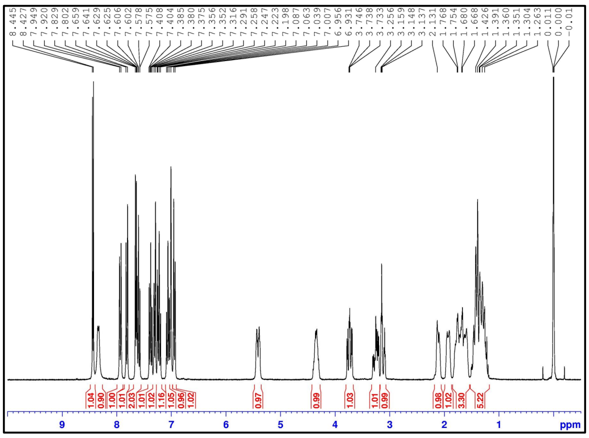
(+)-**115**

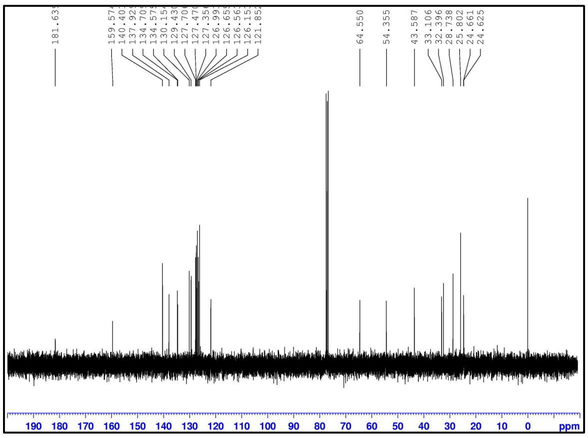


HPLC



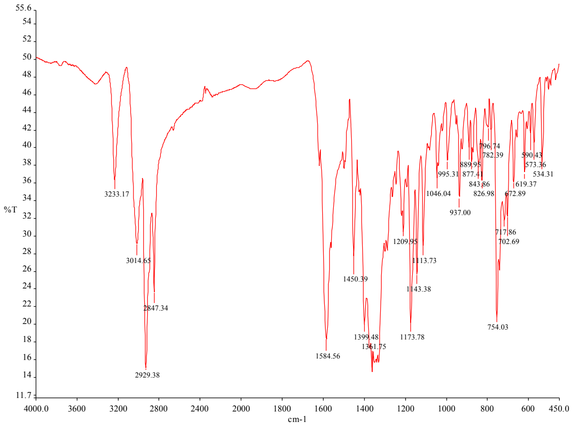
(+)-116

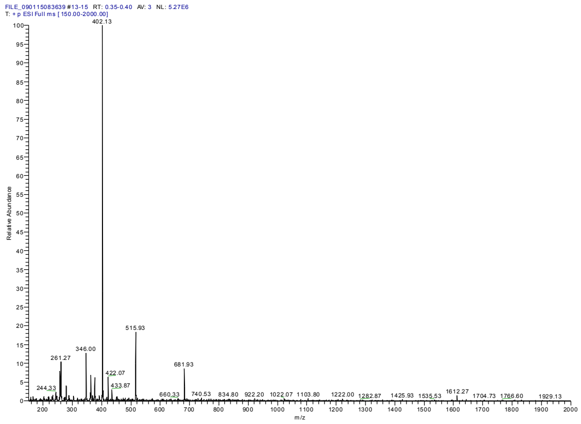




^{1}H NMR

^{13}C NMR

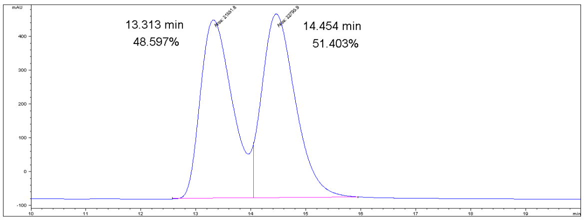




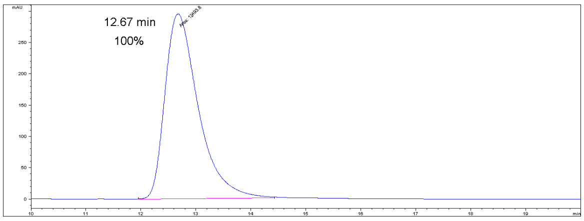
FTIR

Mass

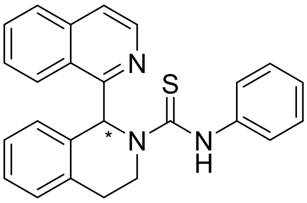
rac-**116**



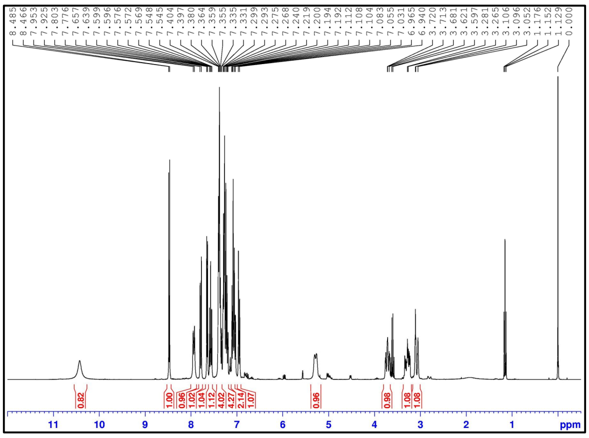
(+)-116

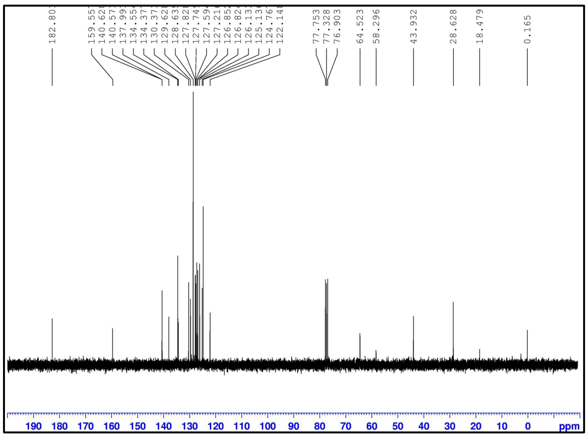


HPLC



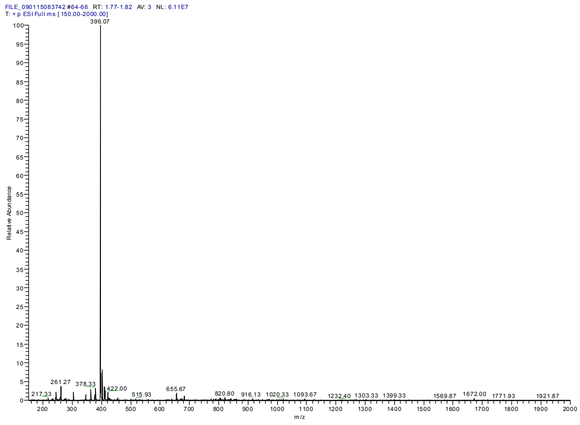
(+)-**117**





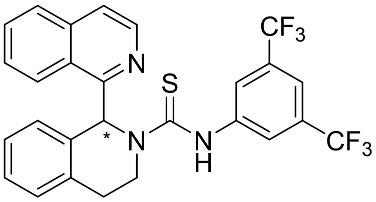
^{1}H NMR

^{13}C NMR

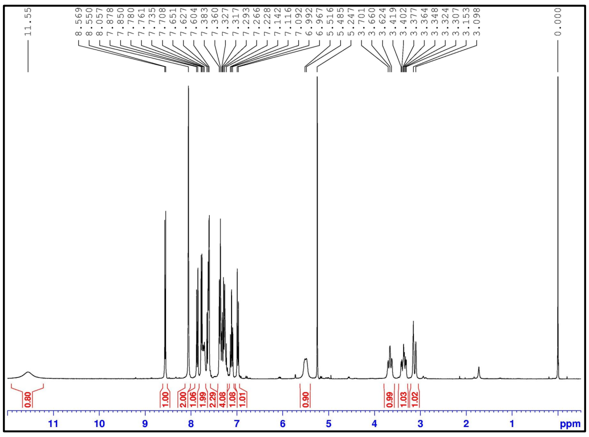


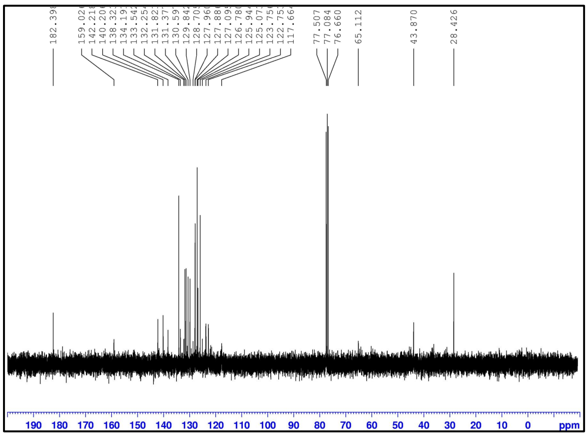
FTIR

Mass



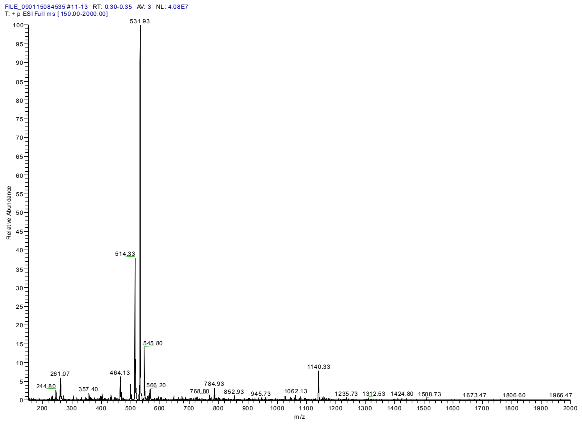
(+)-**118**





^{1}H NMR

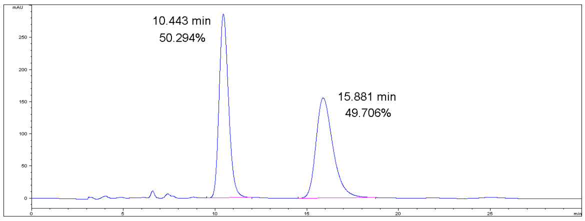
^{13}C NMR



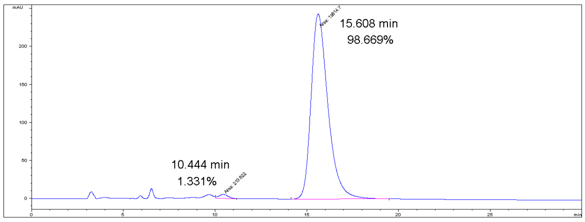
FTIR

Mass

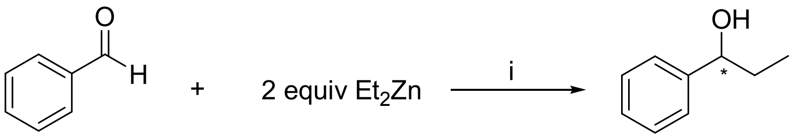
rac-**118**



(+)-**118**



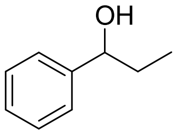
HPLC



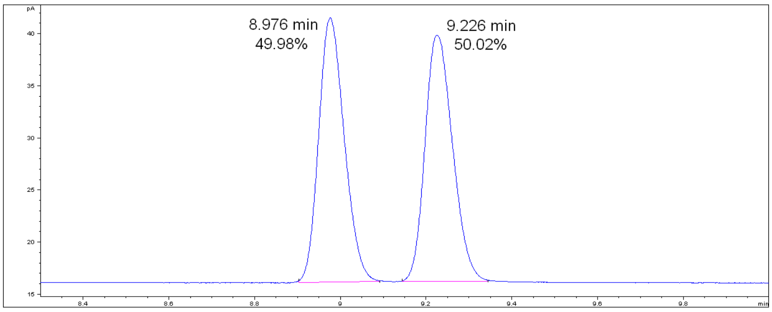
165 **166**

Conditions: i. Ligand (0.1 equiv), THF:hexane = 1:2, r.t, 20 h

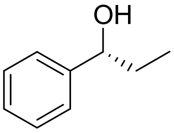
GC results:



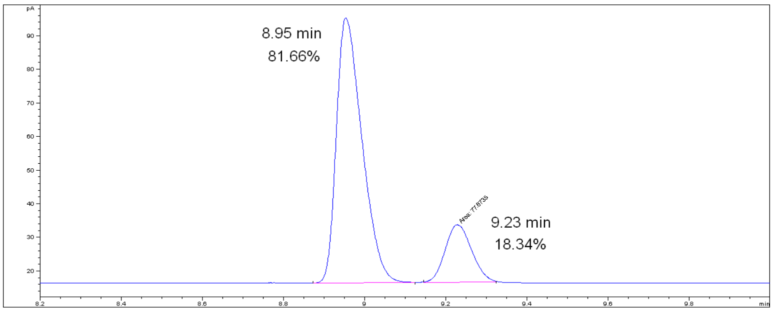
rac-**166**



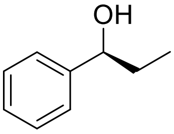
Catalyzed by (*R*)-68:



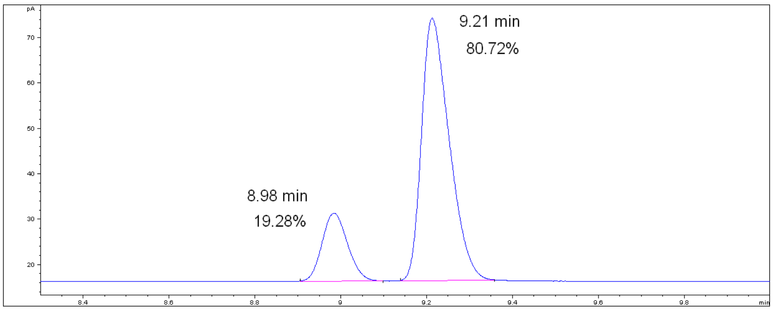
(*R*)-**166**



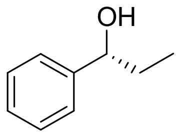
Catalyzed by (*S*)-68:



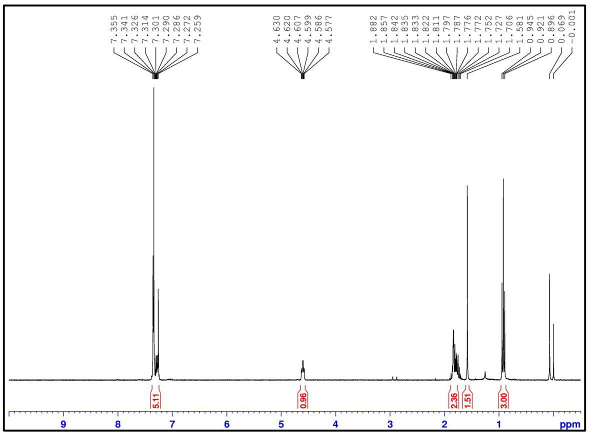
(*S*)-**166**

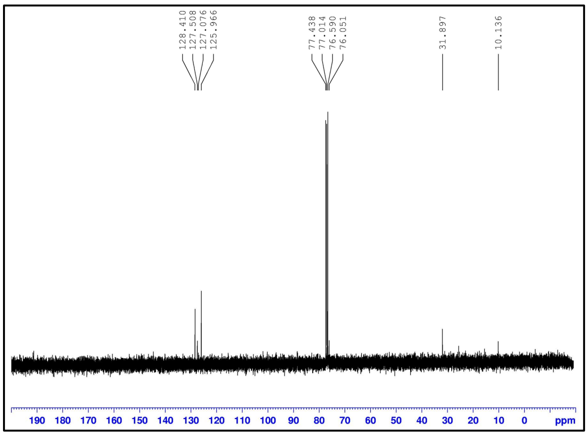


Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 ^{o}C
Column: Chiraldex G-TA



(*R*)-**166**

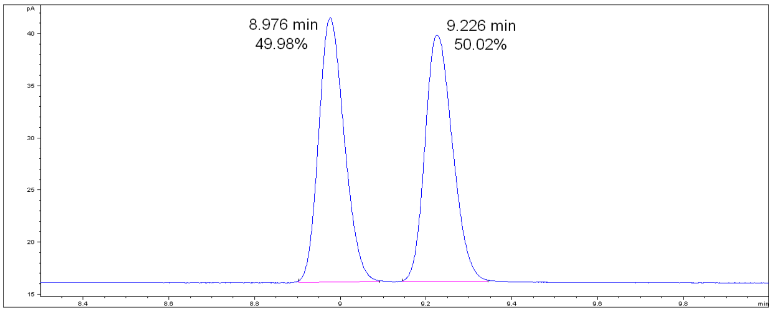




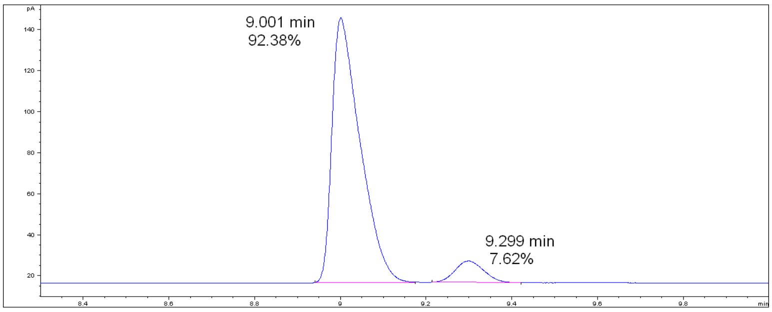
^{1}H NMR **^{13}C NMR**

GC results:

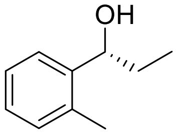
rac-**166**



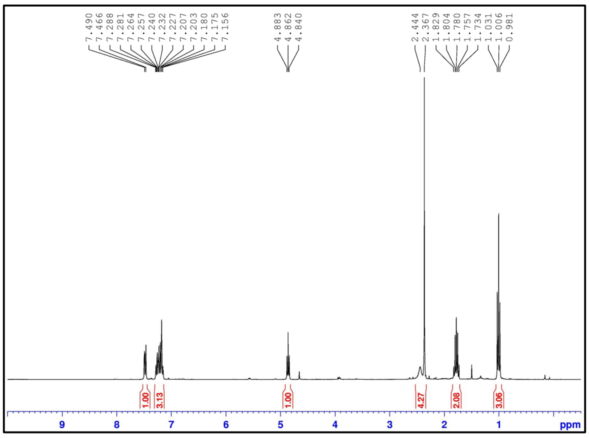
(*R*)-**166**



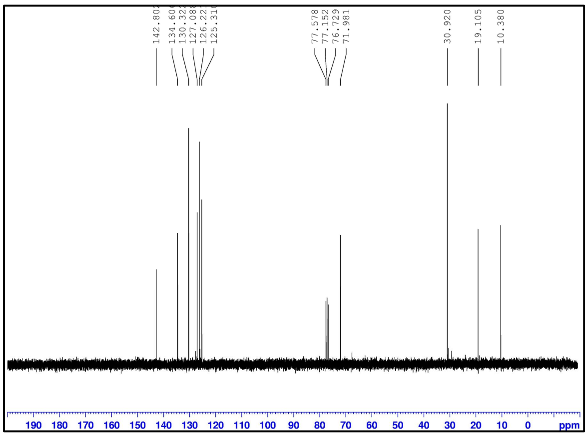
Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 °C
Column: Chiraldex G-TA



(*R*)-**198**



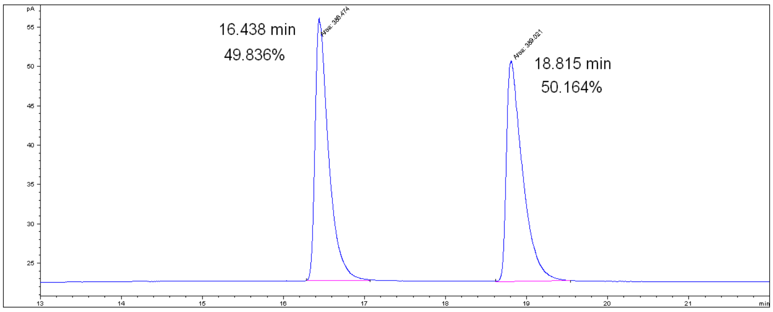
^{1}H NMR



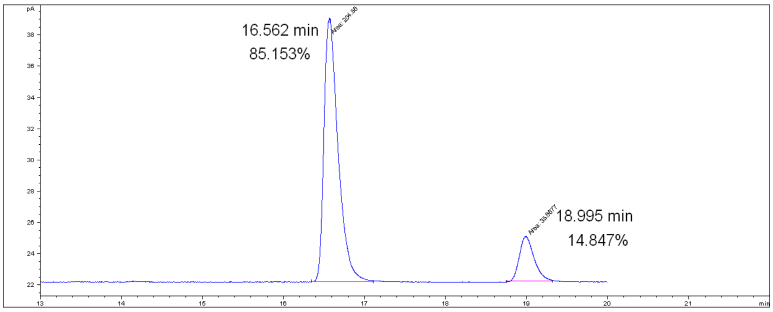
^{13}C NMR

GC results:

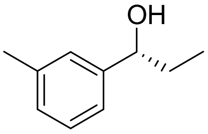
rac-**198**



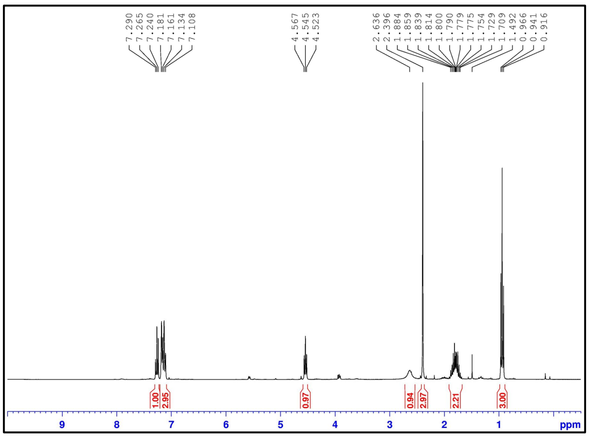
(*R*)-**198**



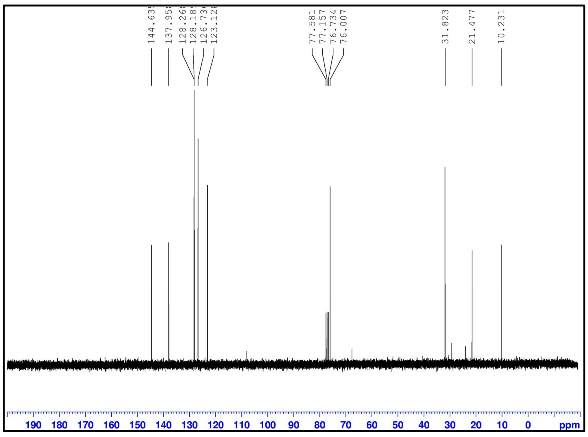
Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 °C
Column: Chiraldex G-TA



(*R*)-**199**



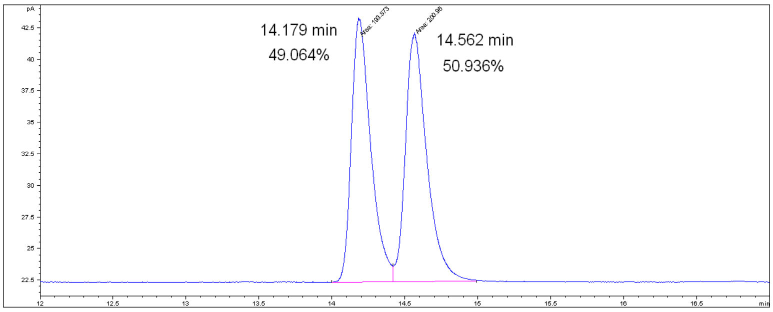
^{1}H NMR



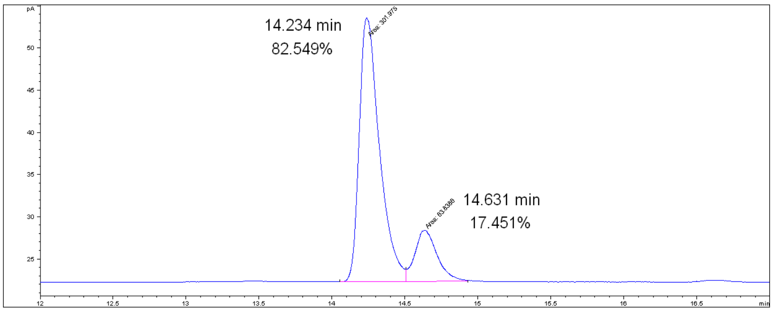
^{13}C NMR

GC results:

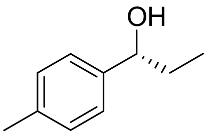
rac-**199**



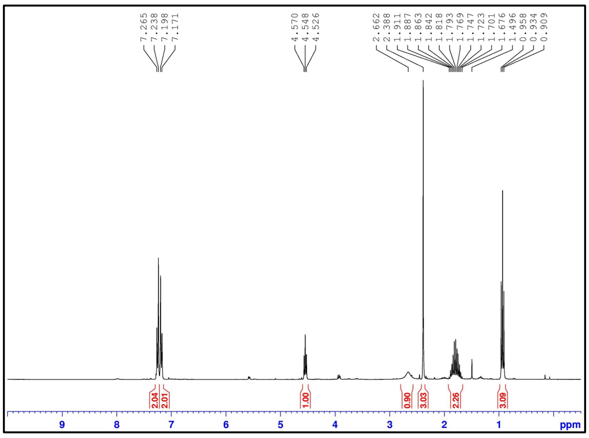
(*R*)-**199**

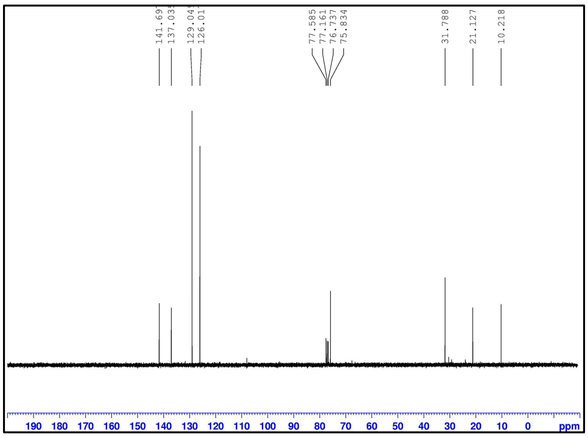


Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 °C
Column: Chiraldex G-TA



(*R*)-**200**



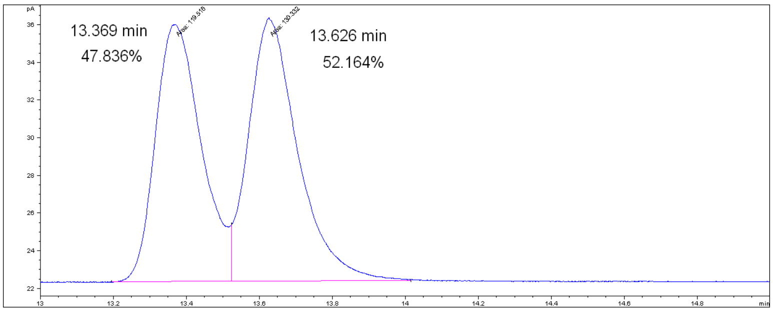


^{1}H NMR

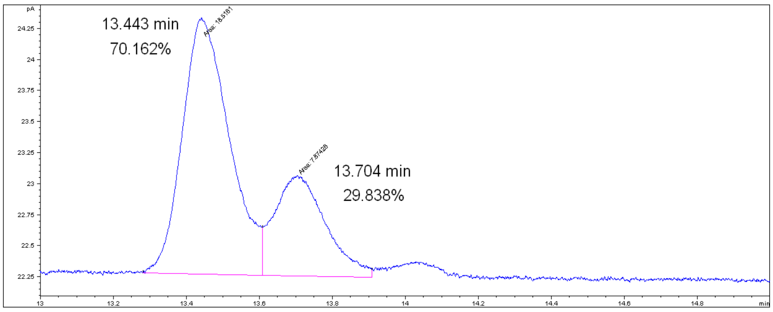
^{13}C NMR

GC results:

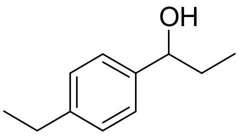
rac-**200**



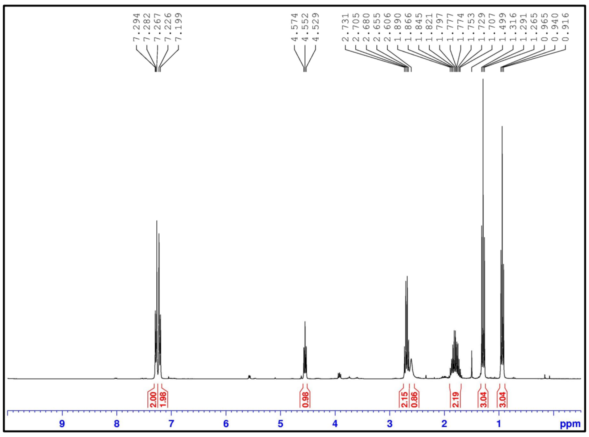
(*R*)-**200**



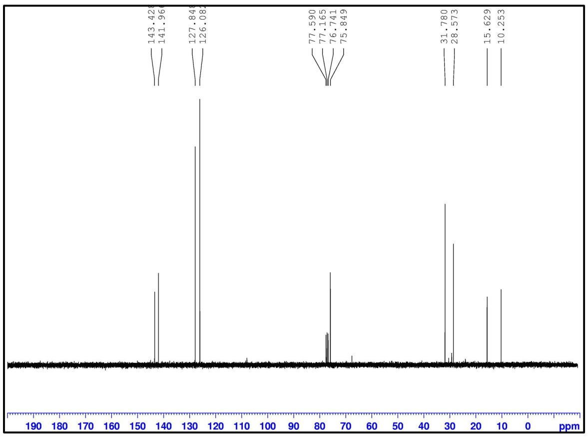
Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 ^{o}C
Column: Chiraldex G-TA



(+)-**201**



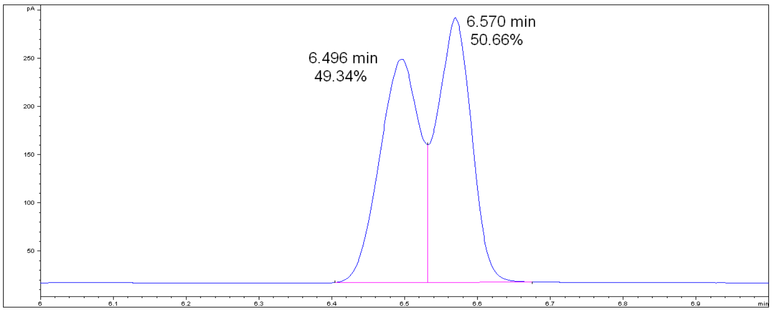
^{1}H NMR



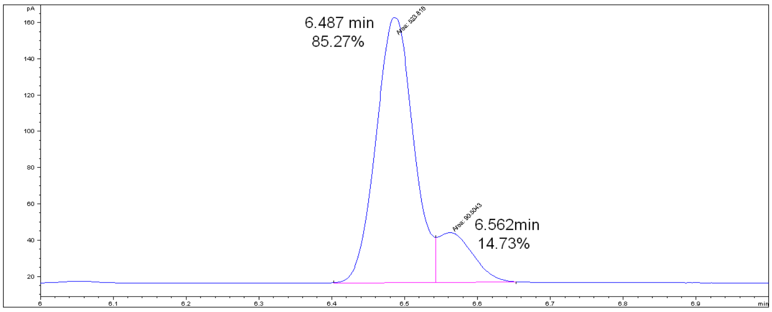
^{13}C NMR

GC results:

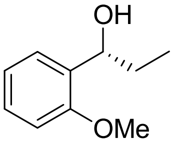
rac-**201**



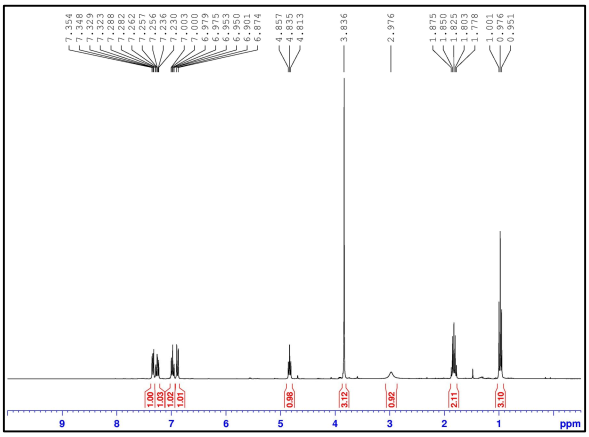
(+)-**201**



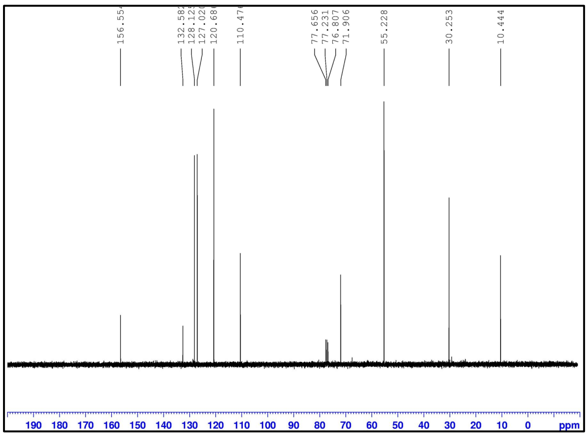
Separation conditions: Flow rate = 3.0 mL/min (constant flow)
Temperature = 130 °C
Column: Chiraldex G-TA



(*R*)-**202**



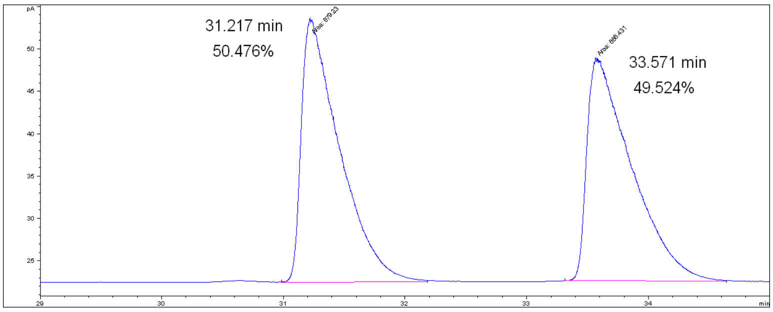
^{1}H NMR



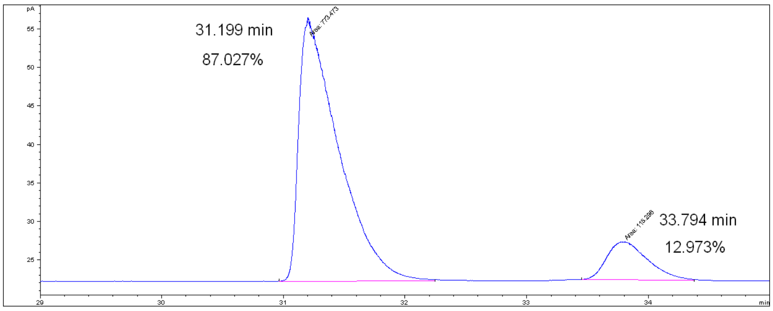
^{13}C NMR

GC results:

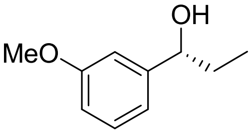
rac-**202**



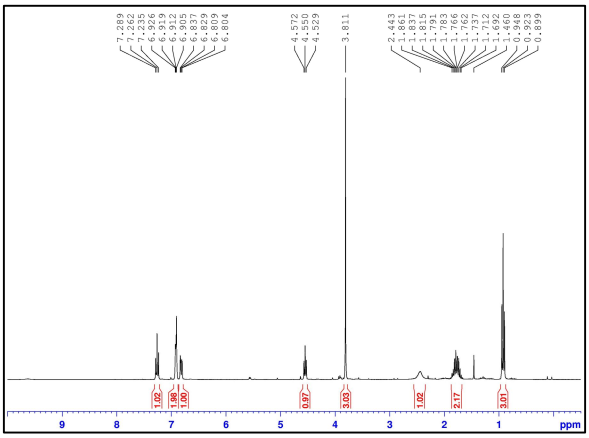
(*R*)-**202**

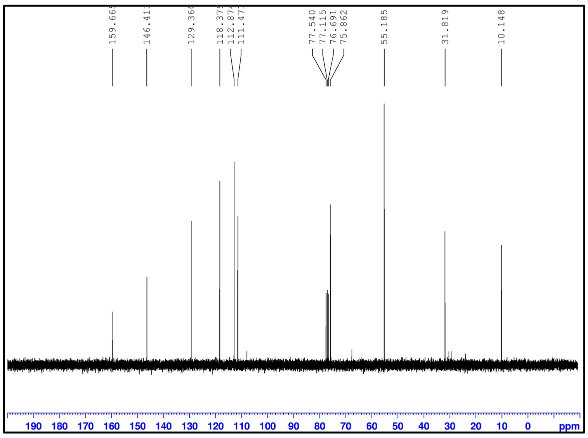


Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 °C
Column: Chiraldex G-TA



(*R*)-**203**



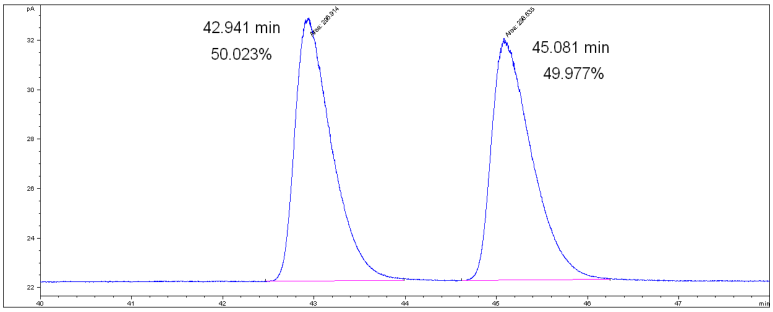


^{1}H NMR

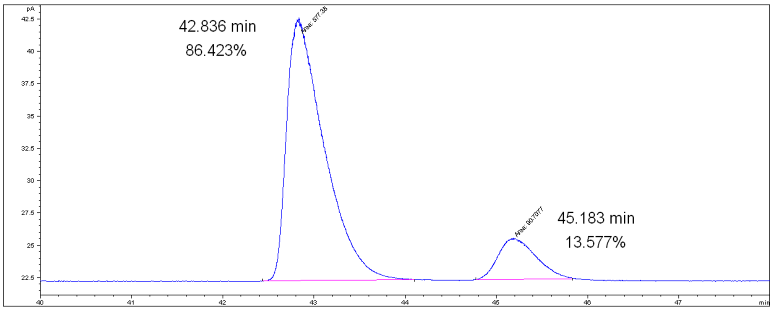
^{13}C NMR

GC results:

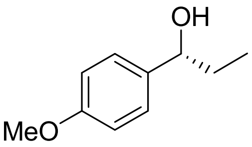
rac-**203**



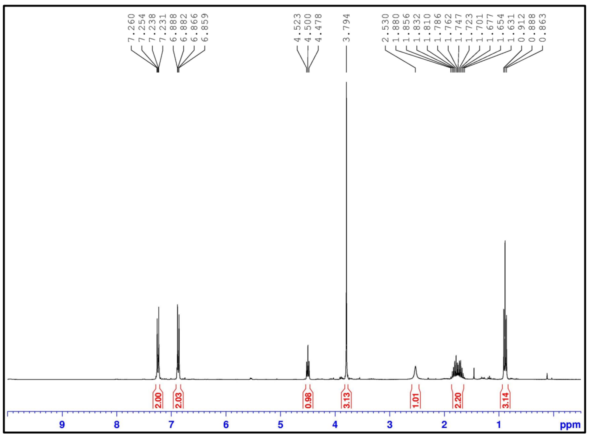
(*R*)-**203**



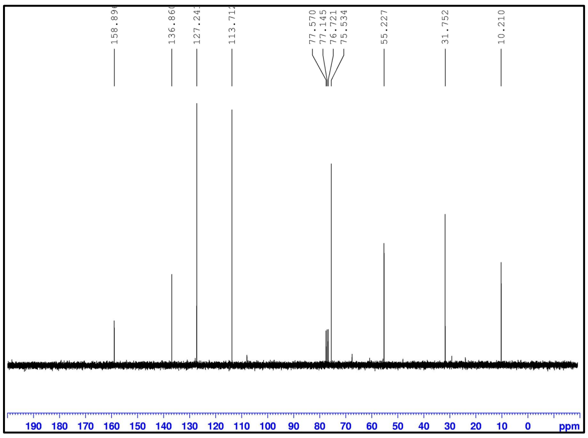
Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 °C
Column: Chiraldex G-TA



(*R*)-**204**



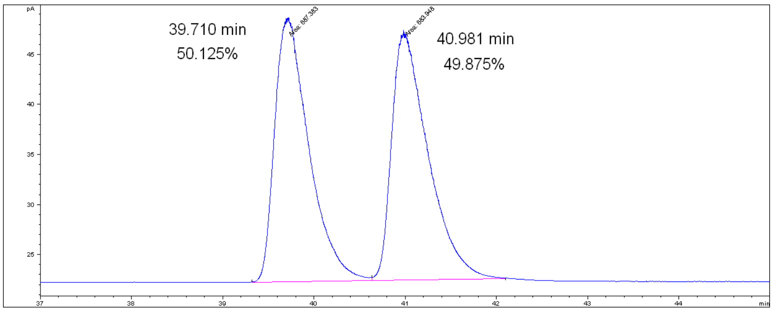
^{1}H NMR



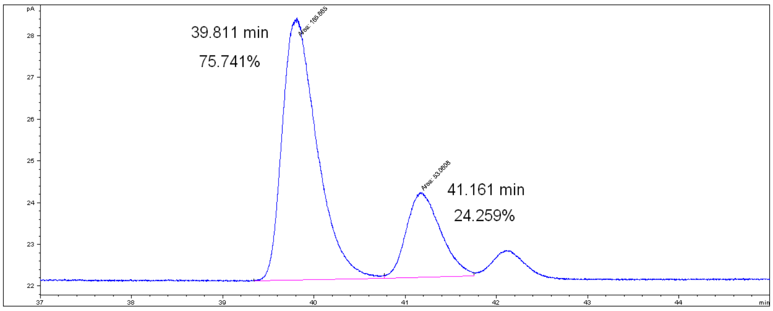
^{13}C NMR

GC results:

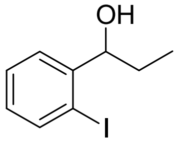
rac-**204**



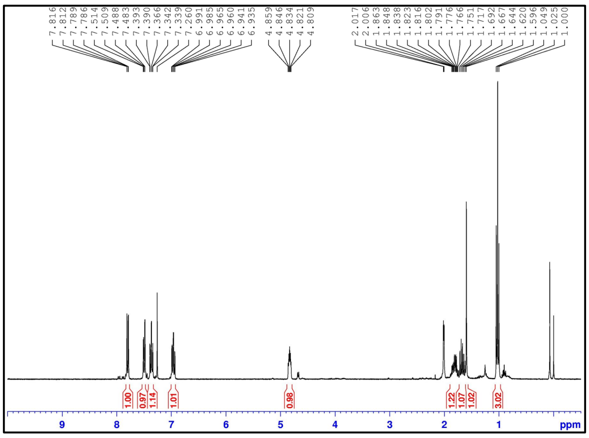
(*R*)-**204**



Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 ^{o}C
Column: Chiraldex G-TA



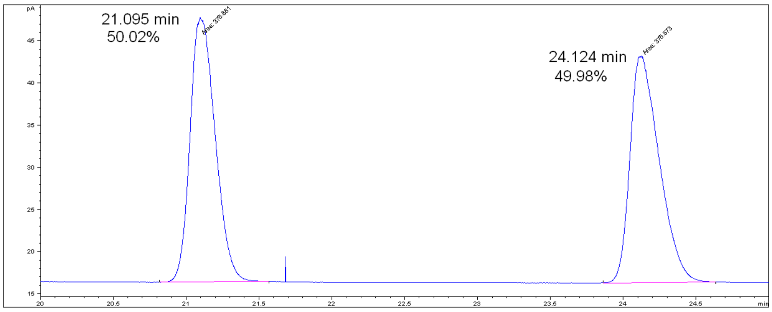
(+)-**205**



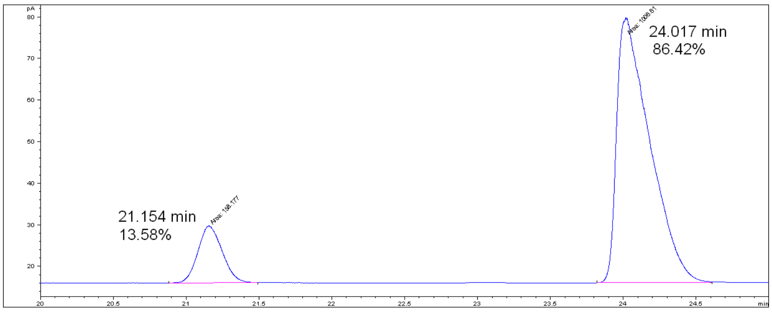
^{1}H NMR

GC results:

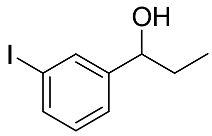
rac-**205**



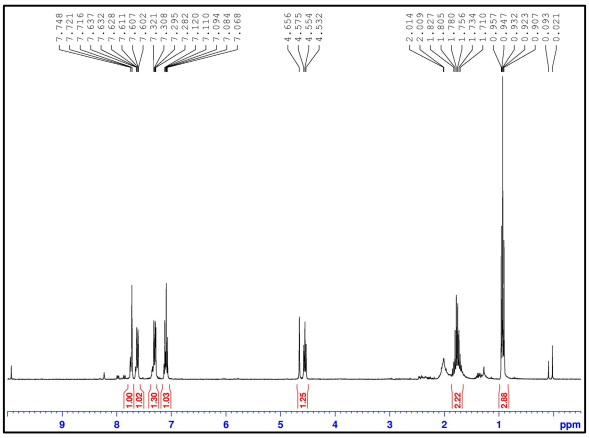
(+)-**205**



Separation conditions: Flow rate = 3.0 mL/min (constant flow)
Temperature = 130 °C
Column: Chiraldex G-TA



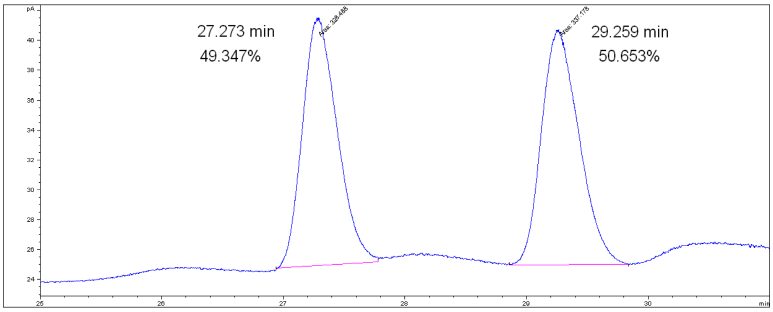
(+)-**206**



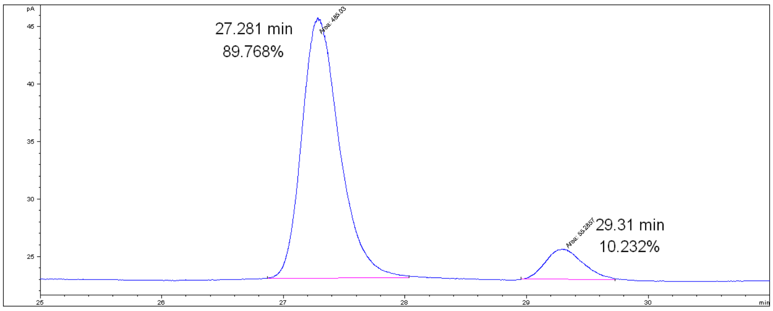
^{1}H NMR

GC results:

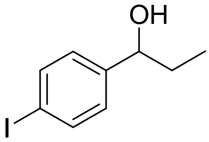
rac-**206**



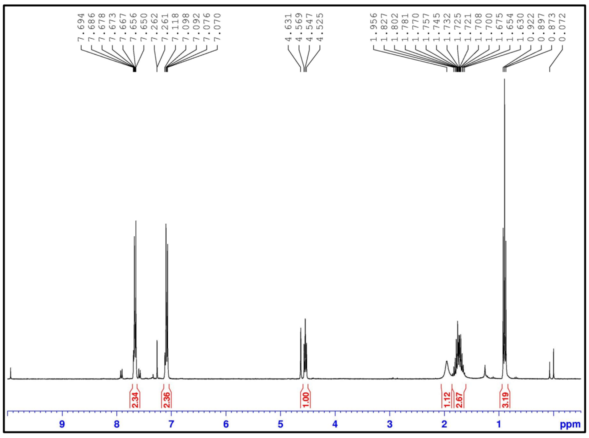
(+)-**206**



Separation conditions: Flow rate = 3.0 mL/min (constant flow)
Temperature = 130 °C
Column: Chiraldex G-TA



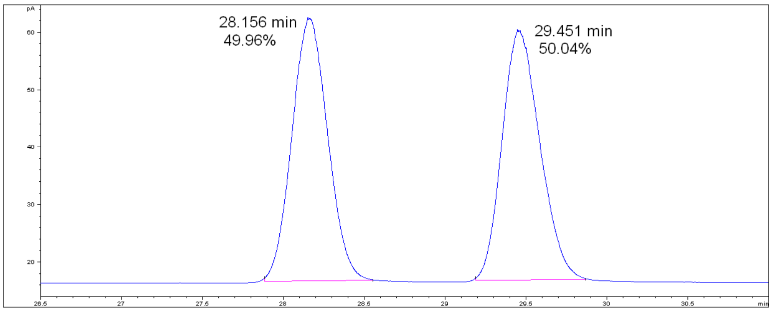
(+)-**207**



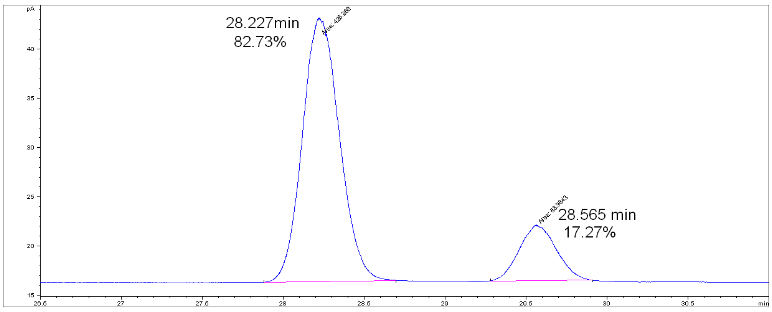
^{1}H NMR

GC results:

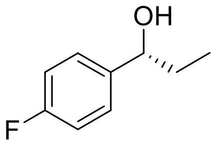
rac-**207**



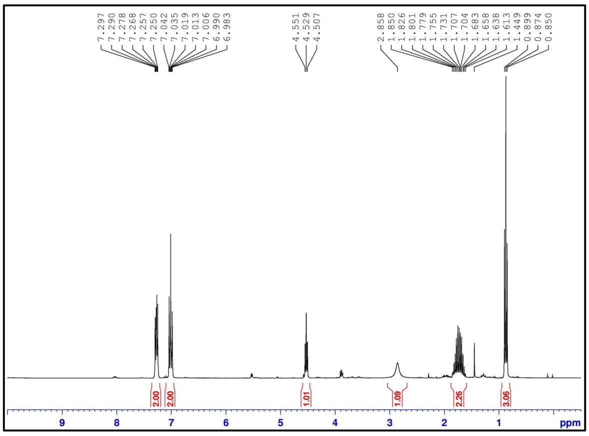
(+)-**207**



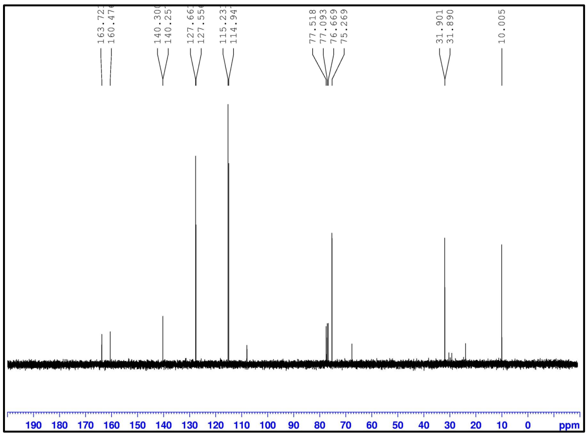
Separation conditions: Flow rate = 3.0 mL/min (constant flow)
Temperature = 130 ^{o}C
Column: Chiraldex G-TA



(*R*)-**208**



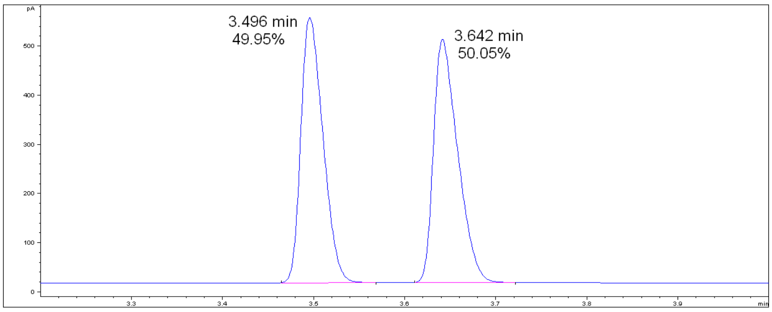
^{1}H NMR



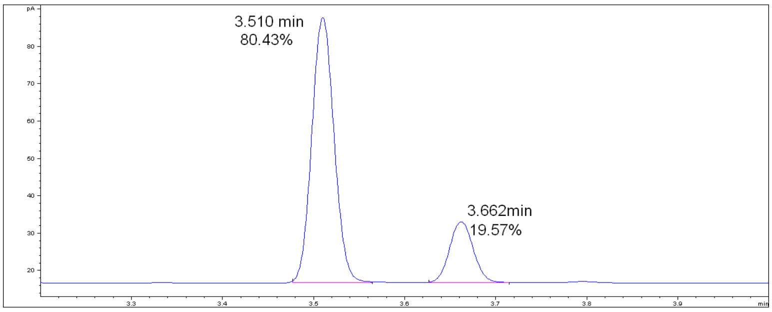
^{13}C NMR

GC results:

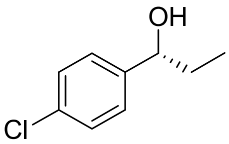
rac-**208**



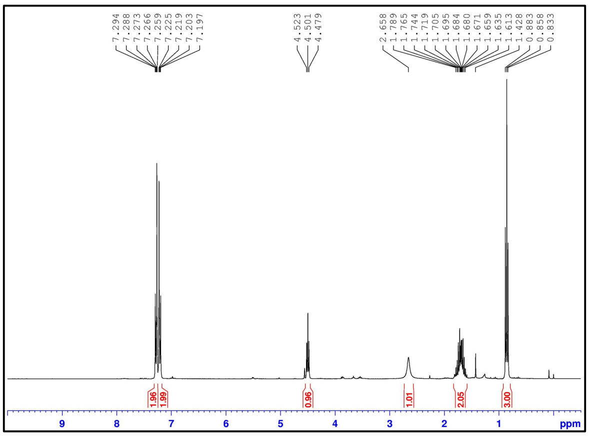
(*R*)-**209**



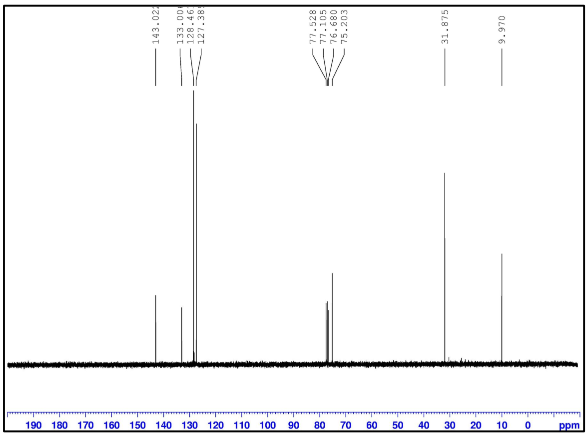
Separation conditions: Flow rate = 3.0 mL/min (constant flow)
Temperature = 130 °C
Column: Chiraldex G-TA



(*R*)-**209**



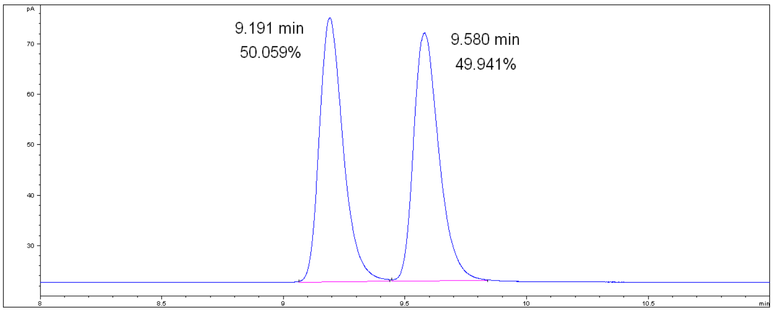
^{1}H NMR



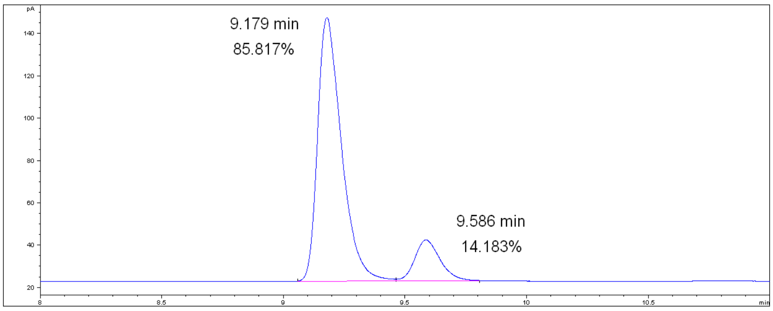
^{13}C NMR

GC results:

rac-**209**



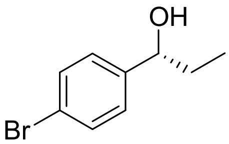
(*R*)-**209**



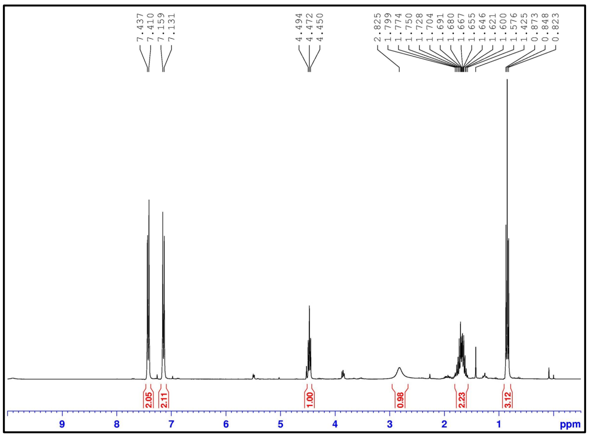
Separation conditions: Flow rate = 3.0 mL/min (constant flow)

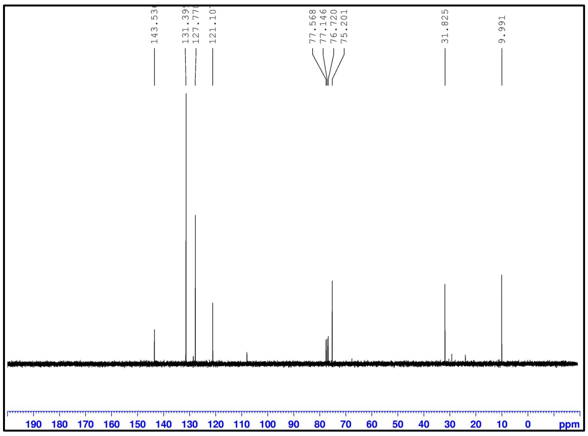
Temperature = 130 ^{o}C

Column: Chiraldex G-TA



(*R*)-**210**



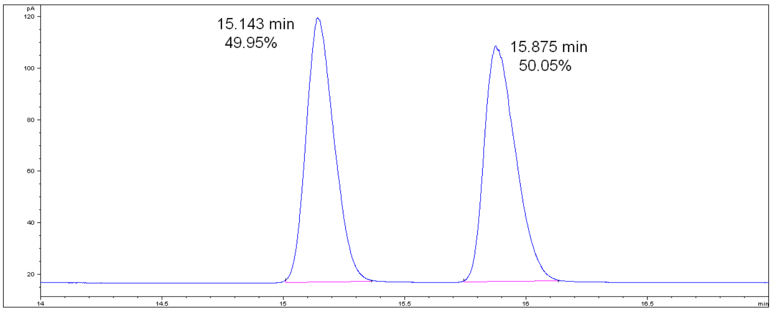


^{1}H NMR

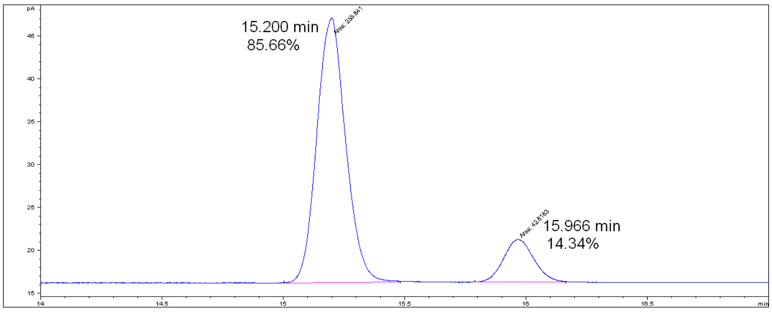
^{13}C NMR

GC results:

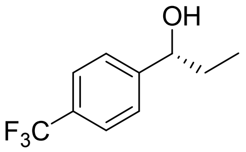
rac-**210**



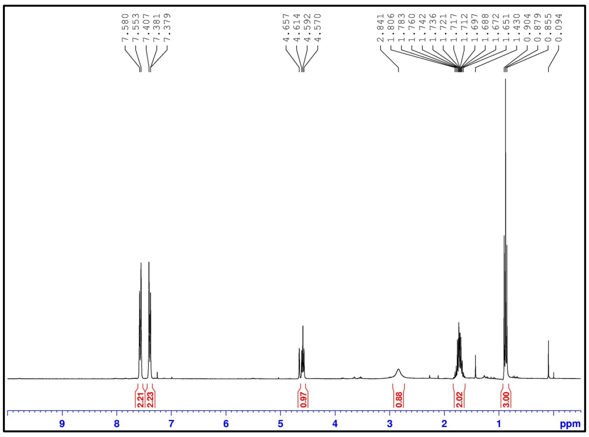
(*R*)-**210**



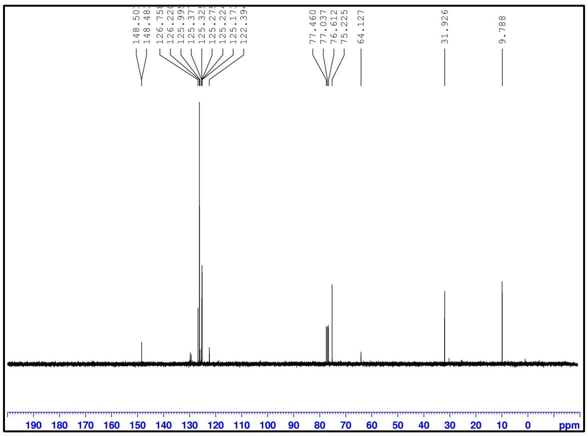
Separation conditions: Flow rate = 3.0 mL/min (constant flow)
Temperature = 130 °C
Column: Chiraldex G-TA



(*R*)-**211**



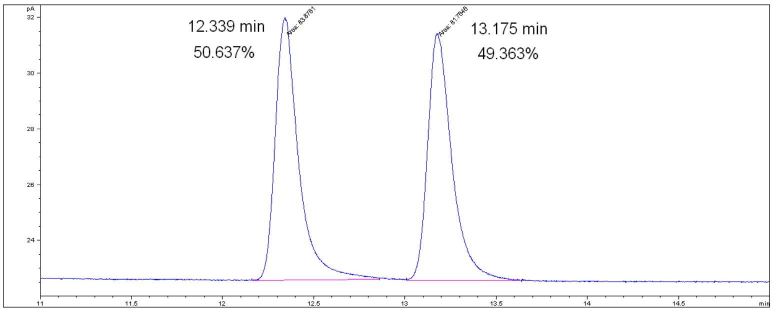
^{1}H NMR



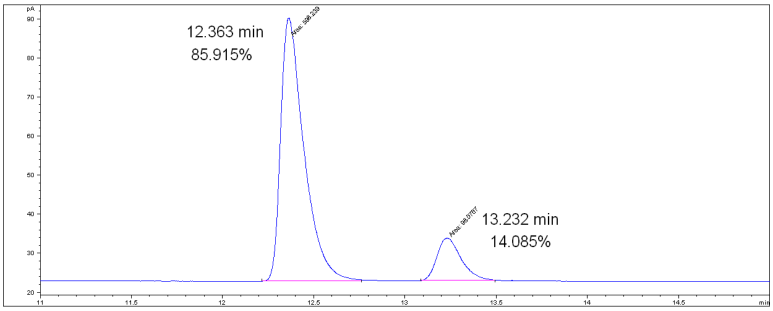
^{13}C NMR

GC results:

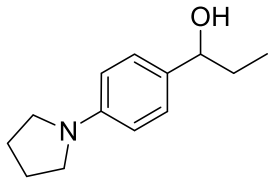
rac-**211**



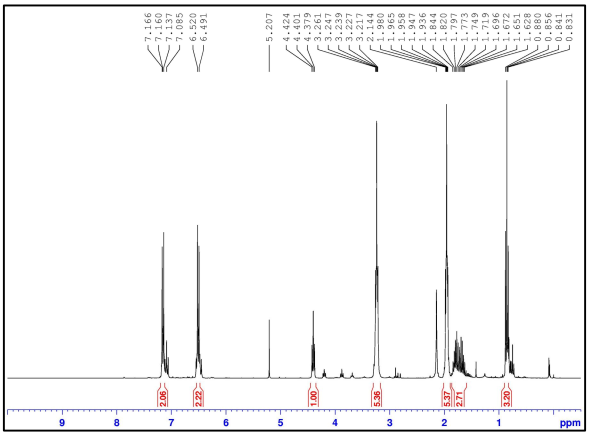
(*R*)-**211**



Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 °C
Column: Chiraldex G-TA



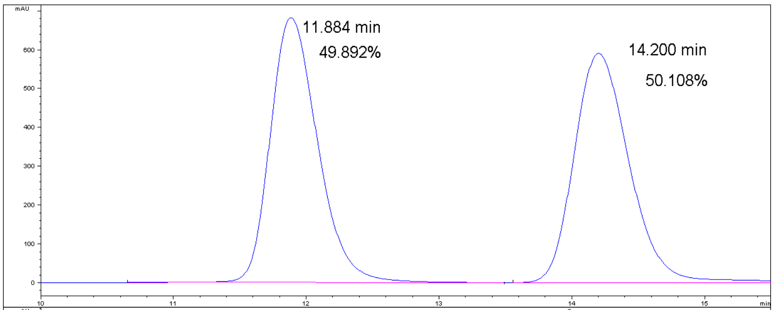
(+)-**212**



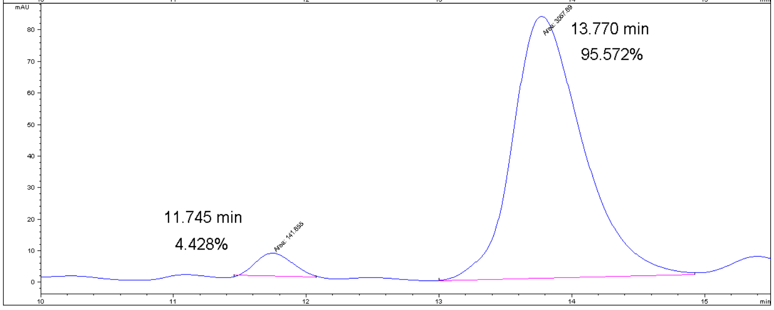
^{1}H NMR

HPLC results:

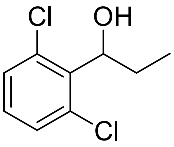
rac-**212**



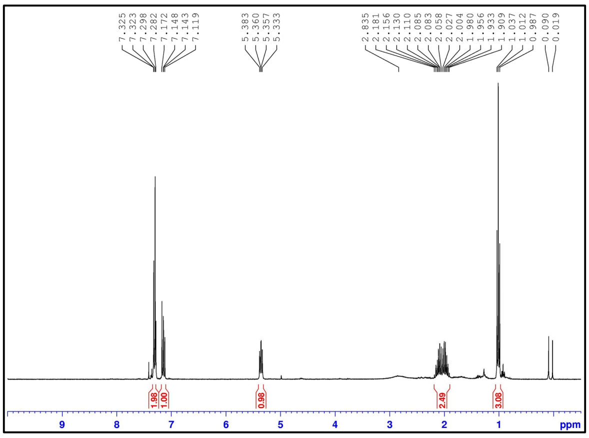
(+)-**212**



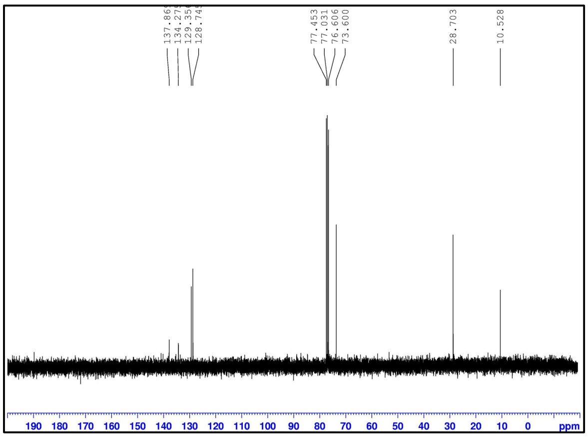
Separation conditions: Flow rate = 1.0 mL/min
Hexane/IPA = 95/5
Column: Daicel OD-H



(-)-**213**



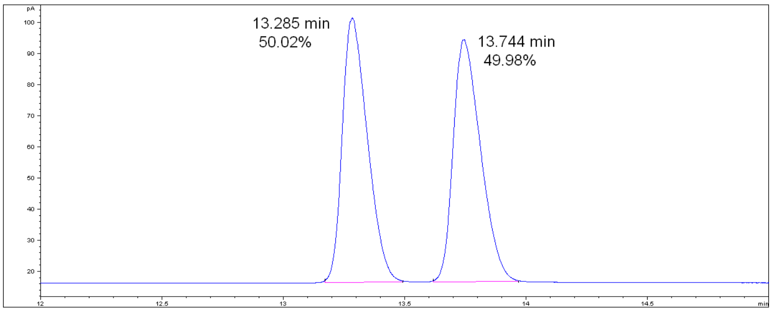
^{1}H NMR



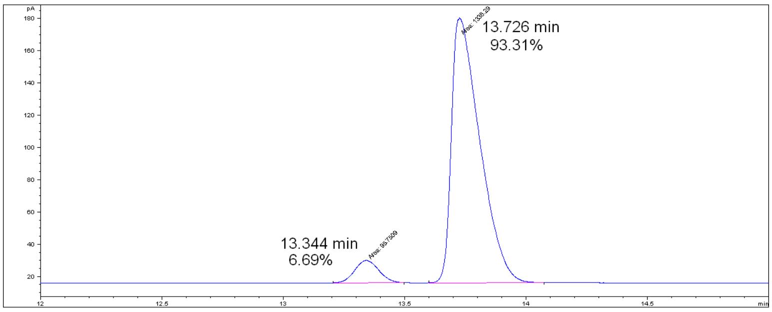
^{13}C NMR

GC results:

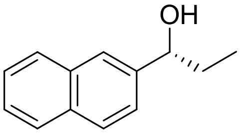
rac-**213**



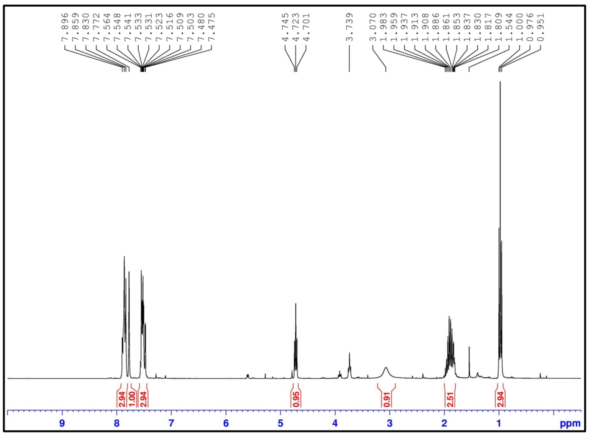
(-)-**213**

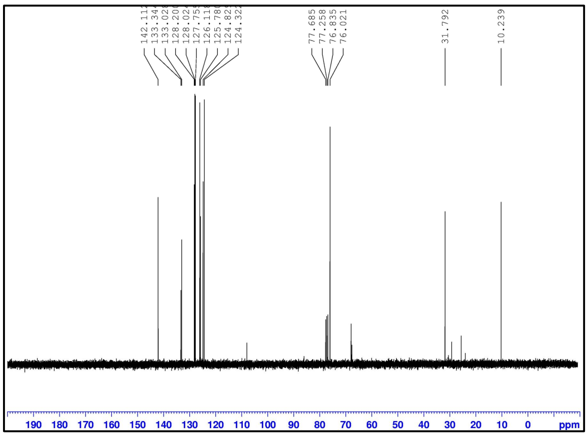


Separation conditions: Flow rate = 3.0 mL/min (constant flow)
Temperature = 130 °C
Column: Chiraldex G-TA



(*R*)-**214**



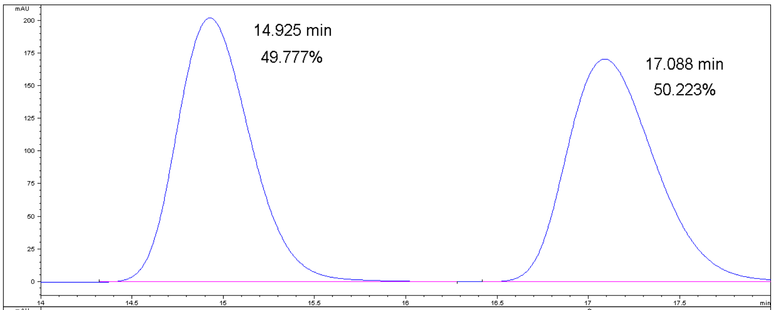


^{1}H NMR

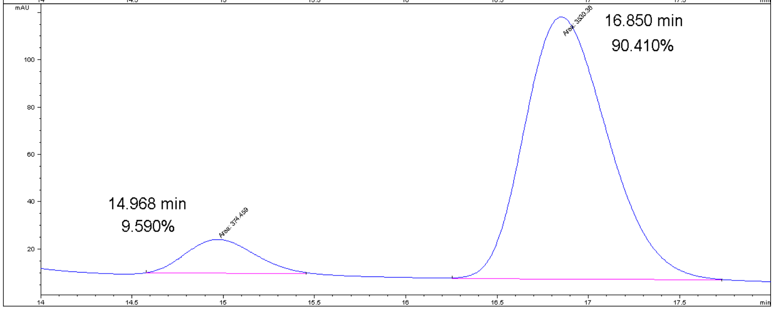
^{13}C NMR

HPLC results:

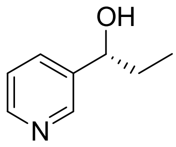
rac-**214**



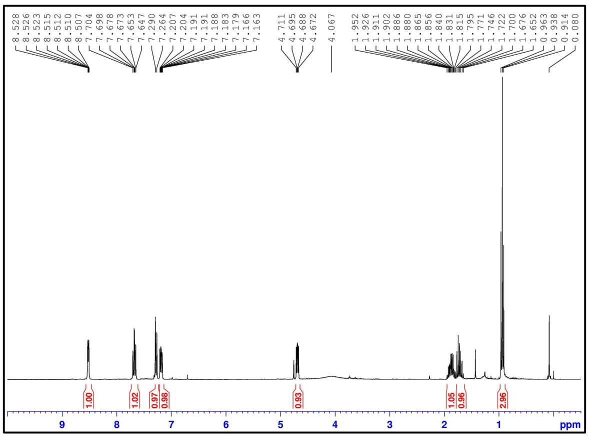
(*R*)-**214**



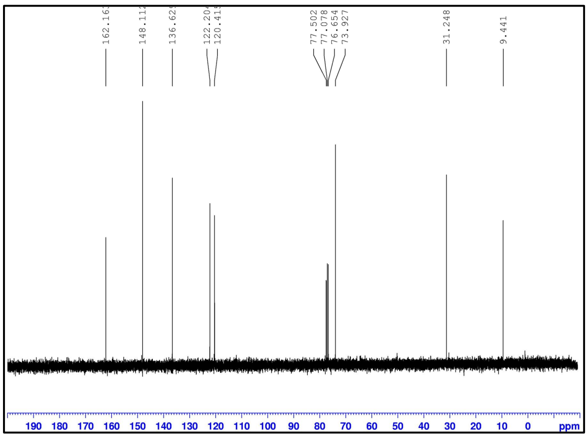
Separation conditions: Flow rate = 1.0 mL/min
Hexane/IPA = 95/5
Column: Daicel OD-H



(*R*)-**215**



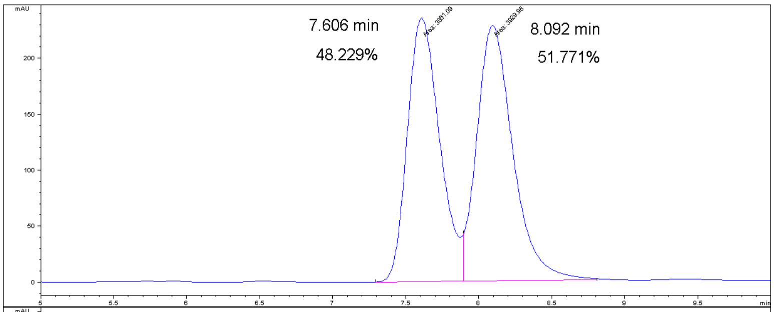
^{1}H NMR



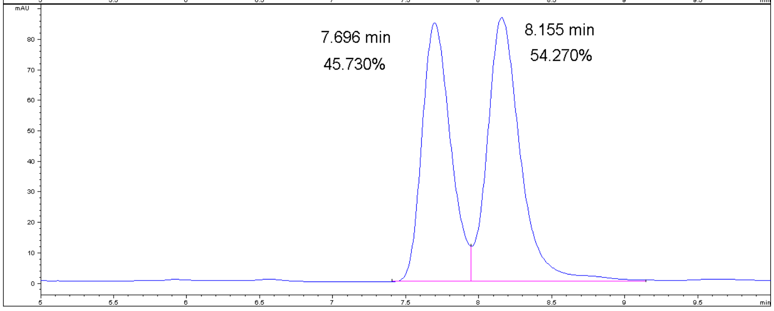
^{13}C NMR

HPLC results:

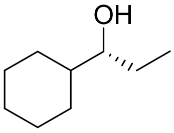
rac-**215**



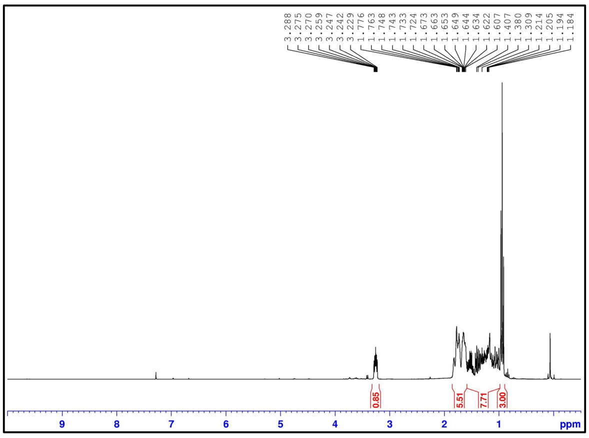
(*R*)-**215**



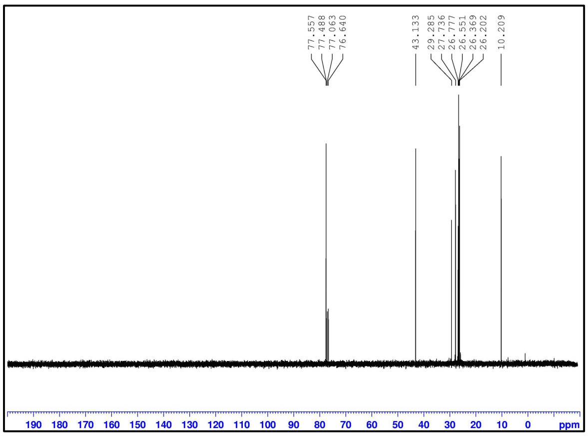
Separation conditions: Flow rate = 1.0 mL/min
Hexane/IPA = 95/5
Column: Daicel OD-H



(*R*)-**216**



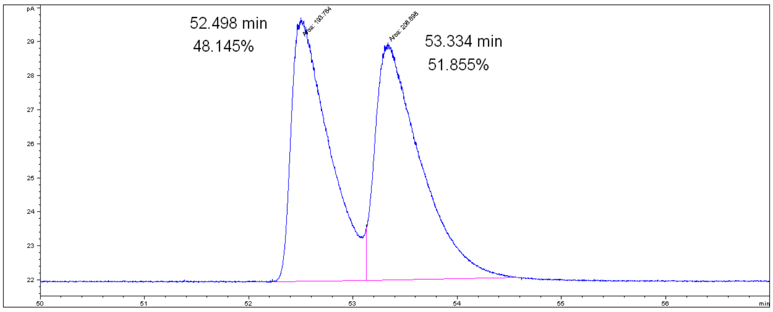
^{1}H NMR



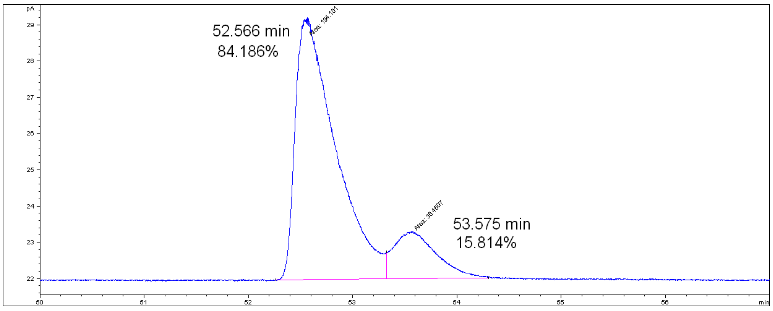
^{13}C NMR

GC results:

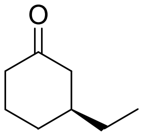
rac-**216**

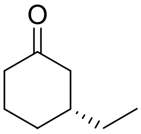


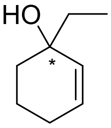
(*R*)-**216**



Separation conditions: Flow rate = 1.0 mL/min (constant flow)
Temperature = 65-96 °C (Gradient)
Column: Chiraldex G-TA

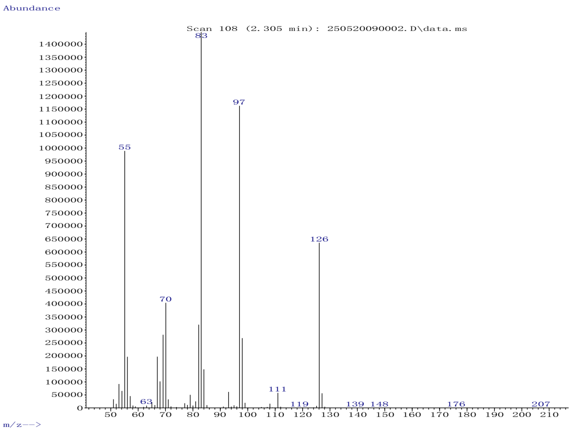

(*S*)-**249**

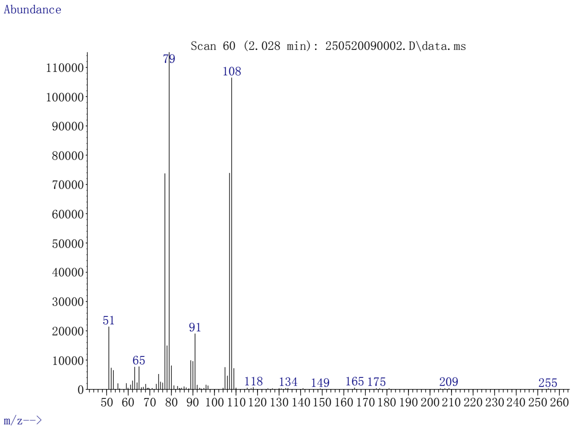

(*R*)-**249**



250

GC-Mass results:

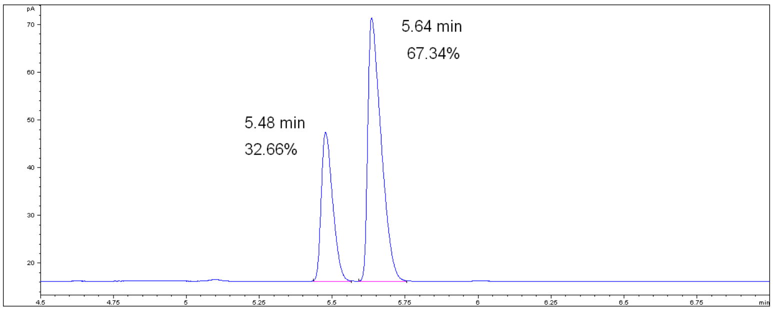




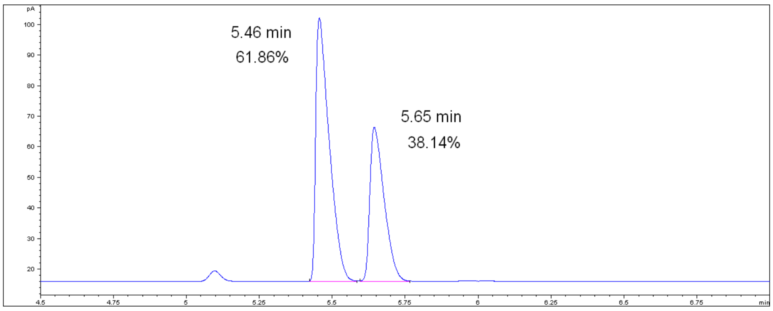
GC-Mass of (*S*)-249 **GC-Mass of 250**

GC results:

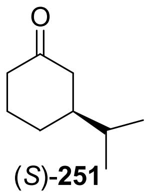
(*S*)-249



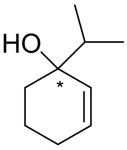
(*R*)-249



Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 110 ^{o}C
Column: Chiraldex G-TA

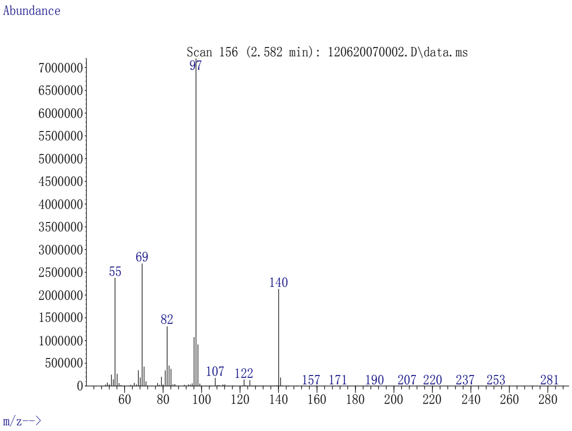


(*S*)-**251**

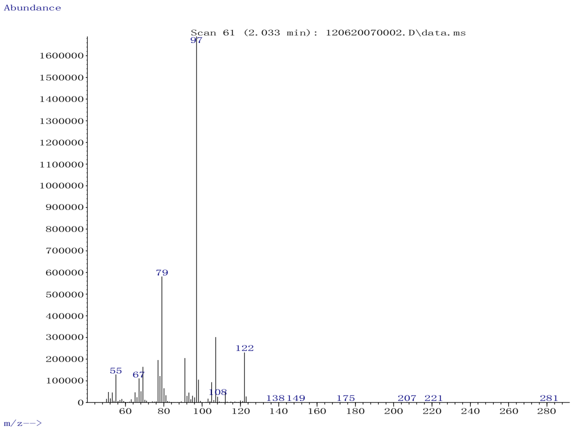


256

GC-Mass results:



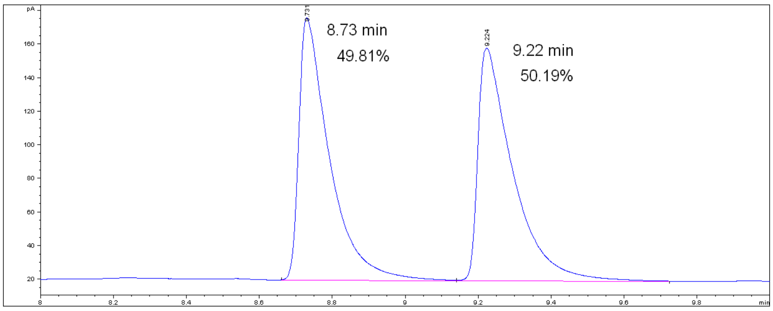
GC-Mass of (*S*)-251



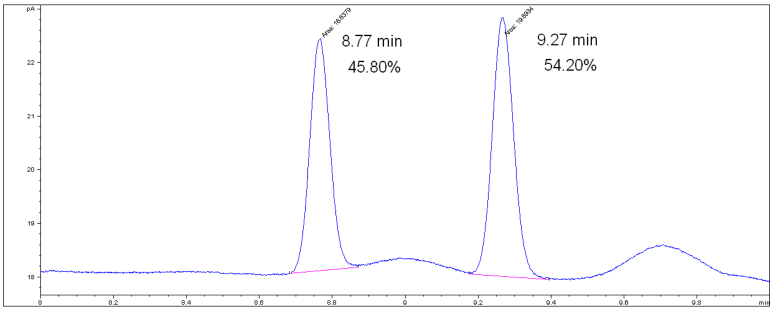
GC-Mass of 256

GC results:

rac-**251**



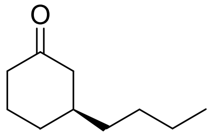
(*S*)-**251**



Separation conditions: Flow rate = 2.0 mL/min (constant flow)

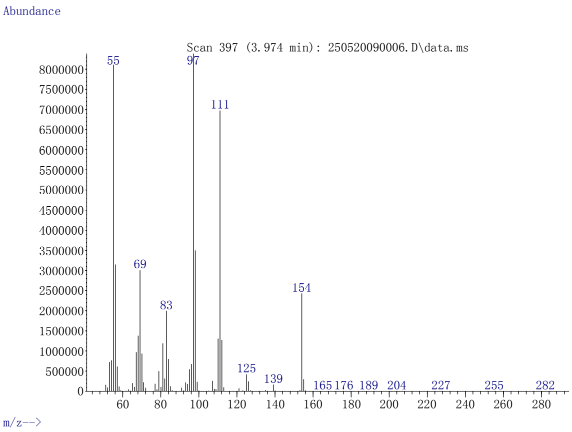
Temperature = 130 ^{o}C

Column: Hydrodex-β-TBDAc



(*S*)-**252**

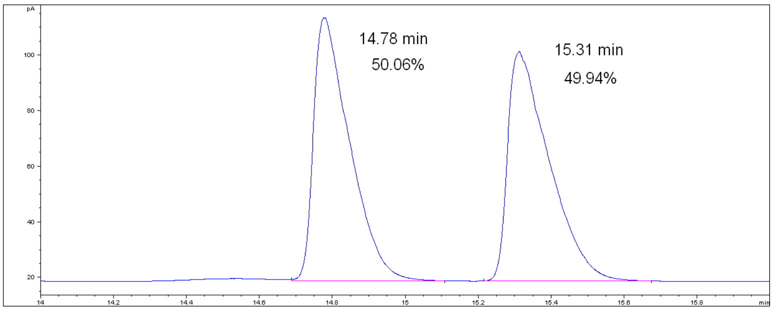
GC-Mass results:



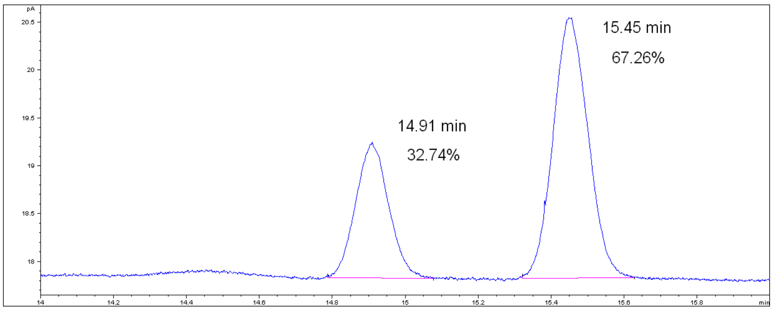
GC-Mass of (*S*)-252

GC results:

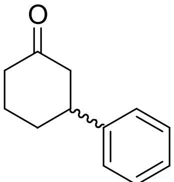
rac-**252**



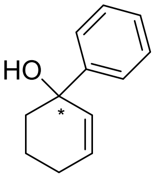
(*S*)-**252**



Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 130 ^{o}C
Column: Hydrodex-β-TBDAc

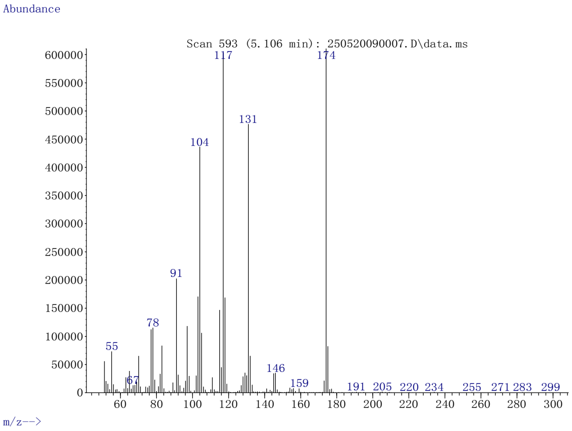


rac-**253**

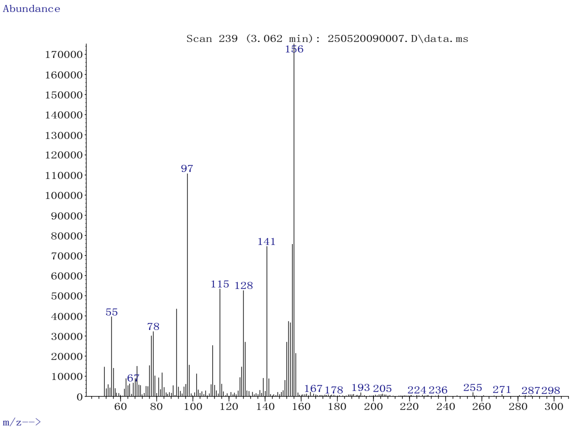


258

GC-Mass results:



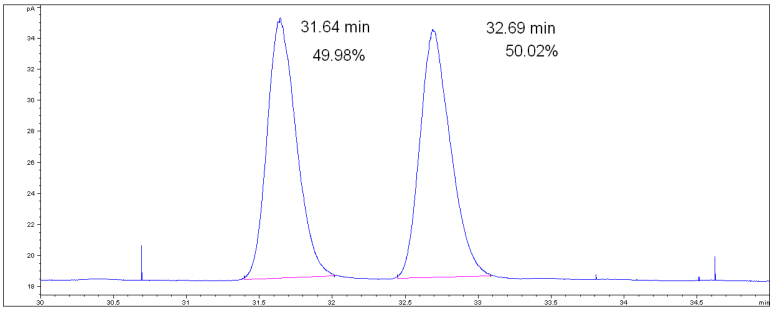
GC-Mass of *rac*-253



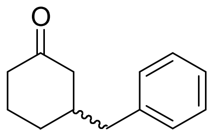
GC-Mass of 258

GC results:

rac-**253**

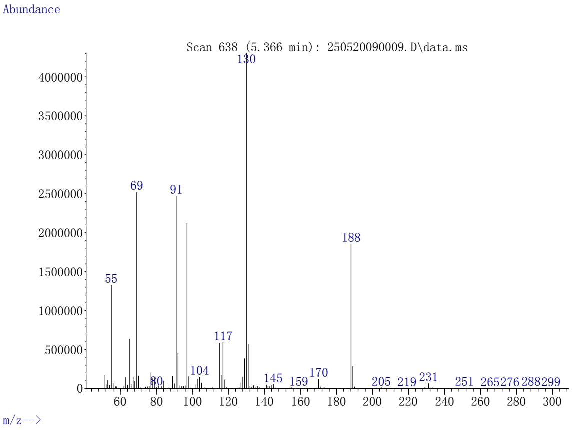


Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 150 ^{o}C
Column: Hydrodex-β-TBDAc



rac-**254**

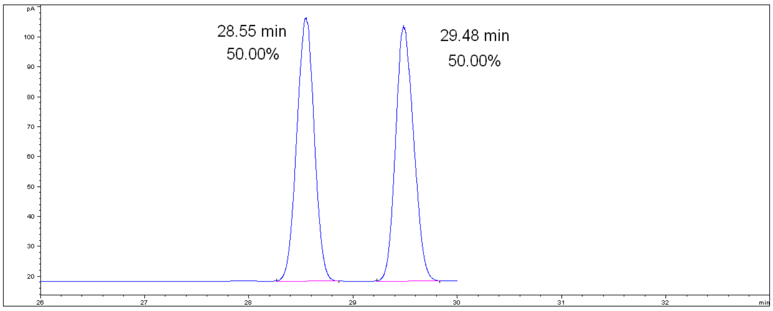
GC-Mass results:



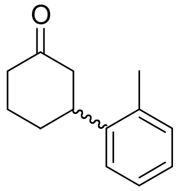
GC-Mass of *rac*-254

GC results:

rac-**254**

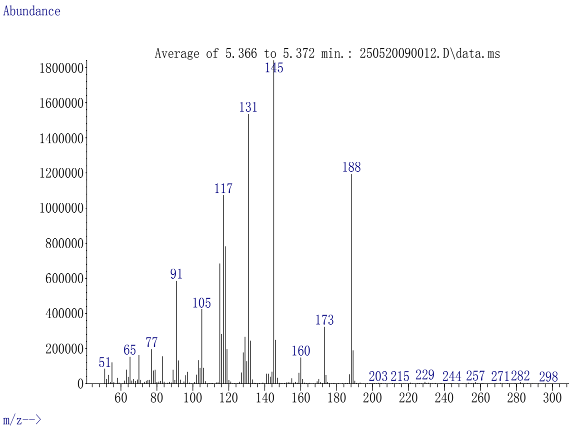


Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 160 ^{o}C
Column: Hydrodex-β-TBDAc



rac-**255**

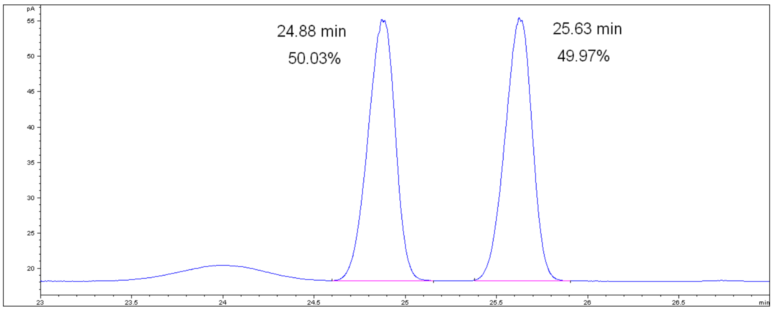
GC-Mass results:



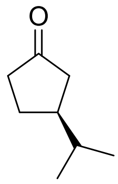
GC-Mass of *rac*-255

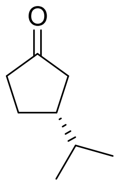
GC results:

rac-**255**

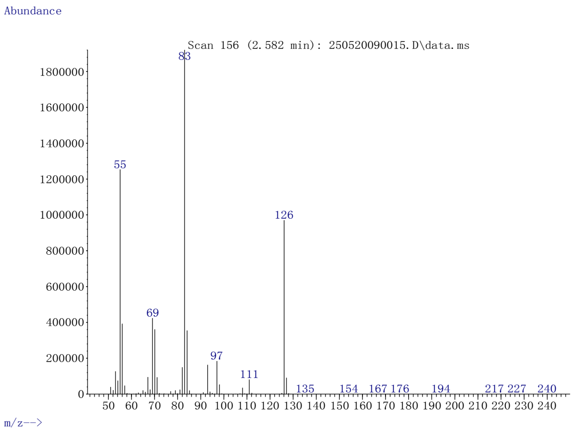


Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 160 ^{o}C
Column: Hydrodex-β-TBDAc


(*S*)-**264**


(*R*)-**264**

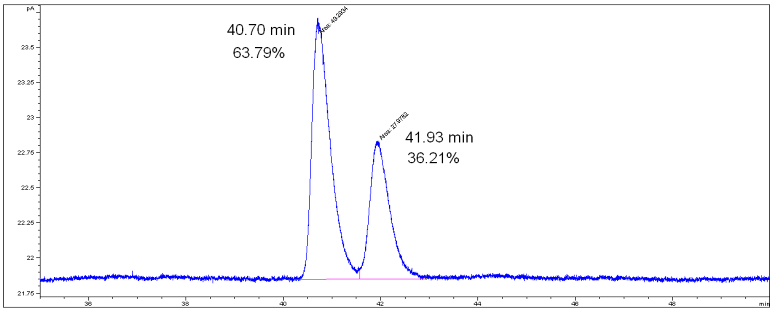
GC-Mass results:



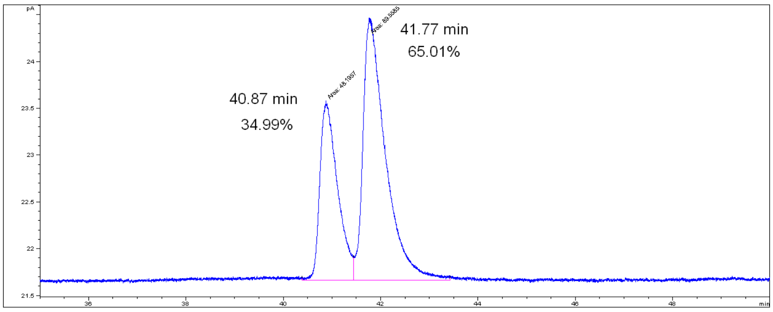
GC-Mass of (*S*)-264

GC results:

(*S*)-**264**



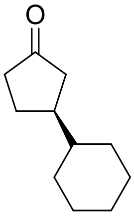
(*R*)-**264**



Separation conditions: Flow rate = 0.8 mL/min (constant flow)

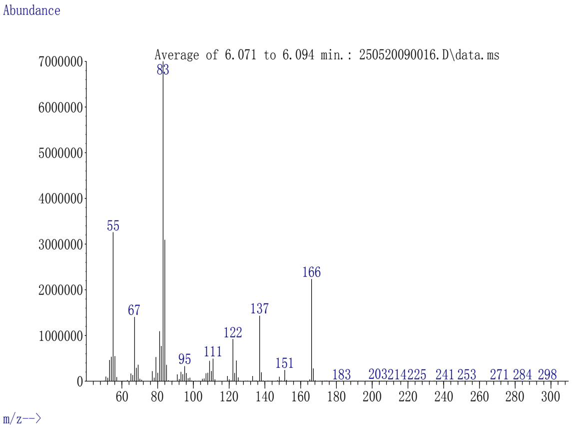
Temperature = 77 °C

Column: Chiraldex G-TA



(*S*)-**266**

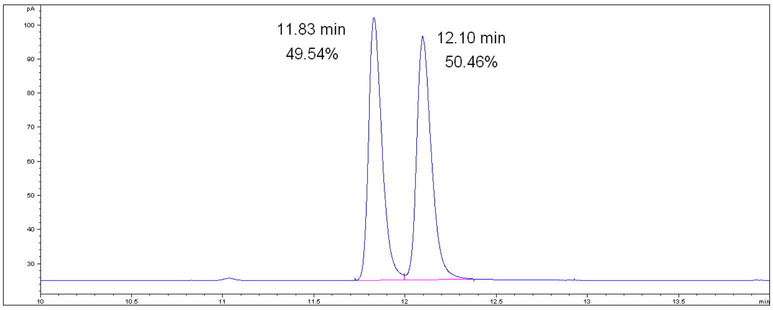
GC-Mass results:



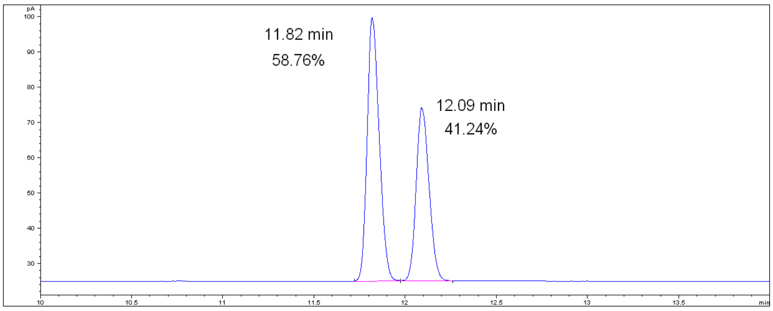
GC-Mass of (*S*)-266

GC results:

rac-**266**



(*S*)-**266**



Separation conditions: Flow rate = 2.0 mL/min (constant flow)
Temperature = 160 ^{o}C
Column: Hydrodex-β-TBDAc