ASYMMETRIC SYNTHESIS OF 1,4-DIAMINE BASED CHIRAL LIGAND AND ORGANOCATALYST AND THEIR APPLICATIONS

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ASYMMETRIC SYNTHESIS OF 1,4-DIAMINE BASED CHIRAL LIGAND AND ORGANOCATALYST AND THEIR APPLICATIONS

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ABSTRACT

ASYMMETRIC SYNTHESIS OF 1,4-DIAMINE BASED CHIRAL LIGAND AND ORGANOCATALYST AND THEIR APPLICATIONS

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August 2010, 77 pages

Novel 1,4-chiral diamine ligand possessing a trans-9,10-dihydro-9,10-ethanoanthracene backbone was synthesized. The synthetic plan involves first $LiAlH_4$ reduction of the Diels-Alder adduct obtained by reaction of dimenthyl fumarate and anthracene, which is followed by reacting the corresponding alcohol and subsequent attachment of mesylate and triflate units to get good leaving groups which are available substances for introducing nitrogen units *via* S_N2 type reactions. Consequently, by using dimesyl ester and ditriflate esters five catalysts **27**, **29**, **30**, **33** and **38** were synthesized. The first four catalysts **27**, **29**, **30** and **33** were used in transfer hydrogenation reactions with transition metal whereas catalyst **38** used as an organocatalyst in direct aldol reaction between acetone and *p*-nitrobenzaldehyde.

Key words: Asymmetric transfer hydrogenation, Organocatalyst, aldol, proline, thiourea

ÖZ

1,4-DİAMİN BAZLI KİRAL LİGANDLARIN VE ORGANOKATALİZÖRLERİN ASİMETRİK SENTEZİ VE UYGULAMALARI

Ortaylı, Oytun
Yüksek Lisans, Kimya Bölümü
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Ağustos 2010, 77 sayfa

Trans-9,10-dihydro-9,10-ethanoantrasen temelli özgün 1,4-kiral diamine ligandlar sentezlenmiştir. Sentez planı çeşitli basamaklardan oluşmaktadır, öncelikli olarak dimetil fumarat ve antrasen bileşiklerinin Diels-Alder tepkimesi sonucu elde edilen ürünün $LiAlH_4$ ile indirgenmesi, ardından oluşan diol yapının mesil ve triflat birimleri ile S_N2 tepkimesi sonucu daha iyi reaktivitelere sahip dimesil esteri ve ditriflat esteri elde edilmiştir. Elde edilen bu esterler ise beş tane katalizörün **27**, **29**, **30**, **33** ve **38** sentezinde kullanılmıştır. Elde edilen ilk dört katalizör **27**, **29**, **30** ve **33** geçiş metalleri kullanılarak asimetrik hidrojen transferinde kullanılmıştır, diger katalizör **38** ise aseton ve p-nitrobenzaldehit bileşiklerinin aldol tepkimelerinde organokatalizör olarak kullanılmıştır.

Anahtar kelimeler: Asimetrik hidrojen transferi, Organokatalizör, aldol, prolin, tiyoüre

To my dear family

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LIST OF ABBREVIATIONS

ATH: Asymmetric Transfer Hydrogenation

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

CAMP: Cyclic adenosine monophosphate

COD: Cyclooctadiene

DCC: Dicyclohexylcarboxydiimide

DIOP: 2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane

DIPAMP: (2-methoxyphenyl)-[2-[(2-methoxyphenyl)-phenylphosphanyl]ethyl]-phenylphosphane

DMAP: Dimethylaminopyridine

DMF: Dimethylformamide

DMSO: Dimethyl Aminosulfoxide

AcOH: Acetic Acid

HCN: Hydrogen Cyanide

HPLC: High Pressure Liquid Choromatography

HRMS: High Resolution Mass Spectroscopy

LUMO: Lowest Unoccupied Molecular Orbital

PTSA: *p*-toluenesulfonamide

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

CHAPTER 1

INTRODUCTION

1.1. Importance of asymmetric synthesis

Asymmetric synthesis is a way of organic synthesis in which enantiomeric purity is favored. Considering that the aim is to acquire an enantiomerically pure compound, there are three paths to achieve that:

i) *De novo (from the beginning)* asymmetric synthesis
ii) Asymmetric induction
iii) Chirality relay

The first way, *de novo* asymmetric synthesis, is rather rare in regard to other two ways. It is an asymmetric synthesis, starting with achiral materials that under certain circumstances can be transferred into non-racemic chiral products, and some process in this synthesis must have been responsible for the original affinity of natural products to promote enantiomeric purity. Second way is more common than others. A prochiral substrate or functional group is transferred into an enantiopure product in a reaction by using a chiral ligand, either in a stoichiometric or catalytic amount. Last option is the way which consists of direct use of optically pure starting materials in some enantiomer syntheses of target molecules. These chiral starting materials are bought-in and if they are simply taken through into the product, it does not count as a real asymmetric synthesis. The supply of these optically pure starting materials for the purpose of asymmetric synthesis is often called as chiral pool [1].

The importance of enantiomerically pure compounds comes from the known world we are living in which is chiral and it is mostly composed of organic chiral compounds. Main chemistry involved areas in industry are in need of enantiomerically pure substances. One of the biggest areas in industrial chemistry, pharmaceutical industry, higher than 50% of their drugs that were in their possession were chiral in 1990s and more or less half of those are marketed as a single enantiomer. However, nearly all of those single enantiomers were semi-synthetic or natural products. On the contrariety, almost all of the chiral synthetic drugs that are marketed were racemic [2].

As we gain more knowledge on the ways of producing enantiomerically pure compounds, we have become to be more aware of the differences in chiral compounds when it is compared to its enantiomer or its racemate. We now have enough knowledge to differentiate between the two enantiomers, such as they often have different physical properties as odors or tastes. For example; (4*R*,4a*S*,6*R*)-(+)-nootkatone smells like grapefruit however its (-)-enantiomer has more like spicy. Beside their differences in smell they also have different smell intensity, (+)-enantiomer is approximately 750 times more intense [3] (Figure 1). Consequently, it is so obvious that two enantiomers have to be considered as different compounds. The need for enantiomerically pure compounds that to be used as drugs are not seemed to be lessening in the next decades. Right example might be the drug thalidomide as both enantiomers have sedative effect however only the (-)-enantiomer can cause fetal deformities. To give another example, (-)-Propranolol was developed in the 1960s to be used as a β-blocker for the treatment of heart problems, but the (+)-enantiomer of the same compound acts as a contraceptive. As to be clearer for a lot of chiral compounds the two enantiomers have obvious differences in their biological activities [4] (Figure 1).

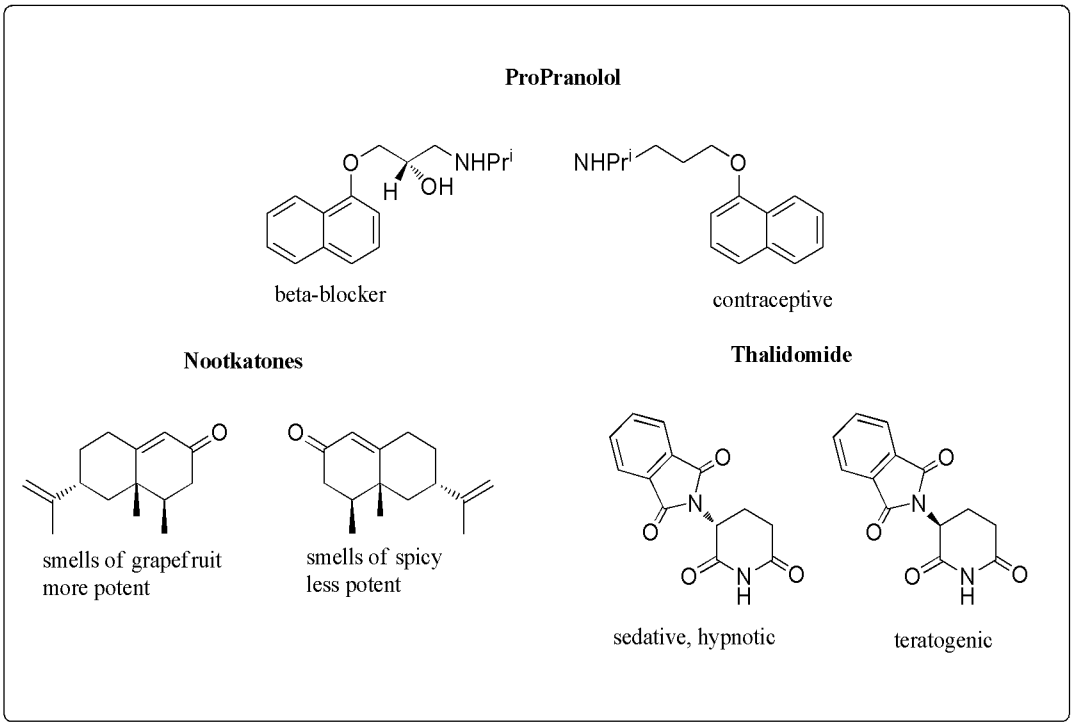
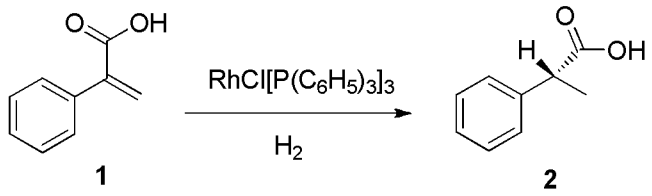


Figure 1. The structures and effects of some of the enantiomers

1.2. History of asymmetric transition-metal catalysis

First known usage of asymmetric transition-metal catalysis was done by Knowles and Horner and their co-workers in 1968. As a chiral ligand they used phosphine with a rhodium catalyst to get optical yields with 4-15% in asymmetric hydrogenation of prochiral olefins. Since today hundreds of different kinds of ligands have been developed in order to get higher optical yields (Scheme 1) [5].



Scheme 1. Knowles' and Horner's asymmetric hydrogenation of prochiral olefins

Not until synthesis of well-designed Rh complexes containing DIOP [6], CAMP [7] and DIPAMP [8] (Figure 2) higher optical yields could be obtained. After the increase in optical yields, this field started to get attraction of chemist communities [9].

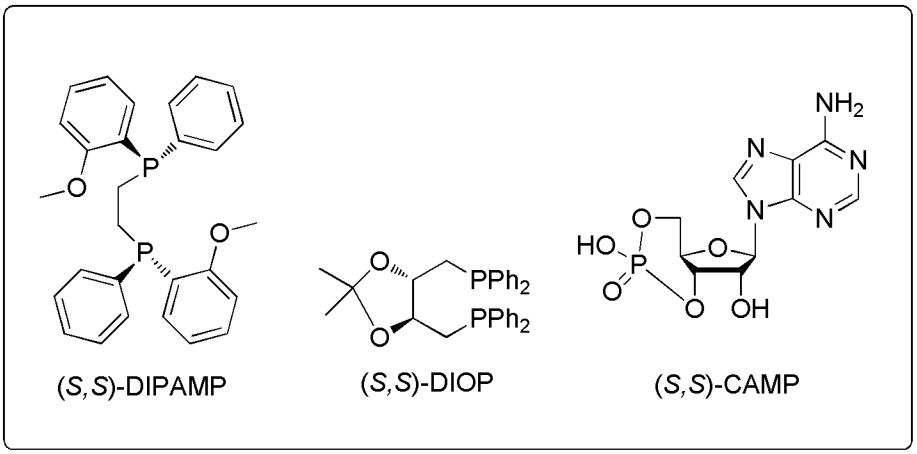
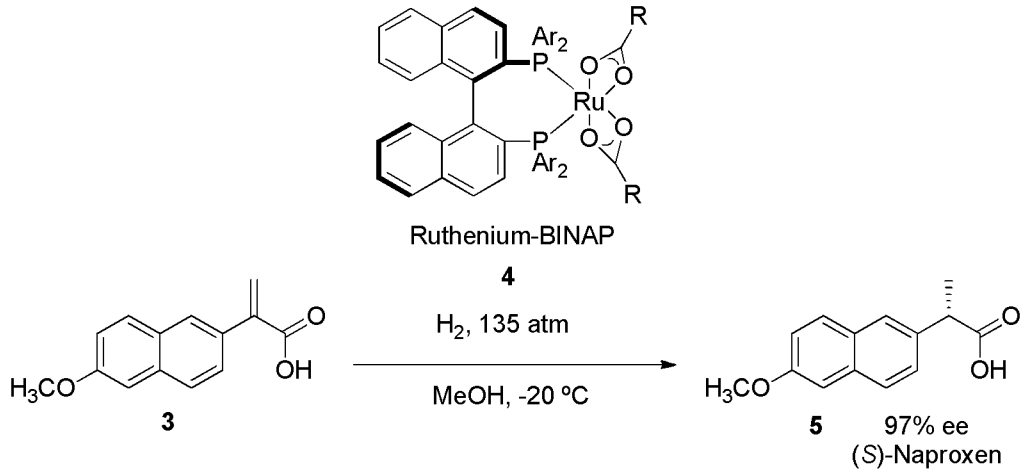


Figure 2. Some of the popular ligands in 1980s

Since invention of ligands above, chemist concentrated on designs of new biphosphine compounds as it is seen that they are much more effective in regard to monophosphine ligands to build chirality by coordinating to a metal. Synthesis of BINAP by Noyori was the next big step in transition-metal catalysis which has introduced new metal, Ruthenium. It has been used in industry in the production of (*S*)-enantiomer of Naproxen (Scheme 2).



Scheme 2. Ruthenium-BINAP complex

The extraordinary developments achieved by those scientists have improved asymmetric synthesis and used in great variety of applications which led into improvements in industry as in productions of new drugs.

Since the first asymmetric transition-metal catalysis, scientists worked on this subject to improve and apply those known and newly developed catalysts to the new area in chemistry. Today it has been applied to many areas that cover;

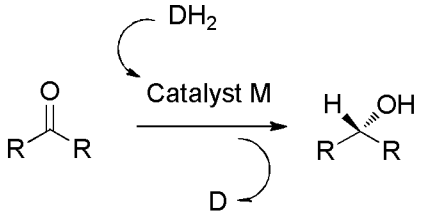
- Asymmetric hydrogenation
- Asymmetric Isomerization of Allylamines
- Asymmetric Cyclopropanation
- Asymmetric Oxidations
- Asymmetric Carbonylation
- Asymmetric Hydrosilylation
- Asymmetric Allylic Substitution and Grignard Cross-Coupling
- Asymmetric Phase Transfer Reactions

1.3. Asymmetric Transfer Hydrogenation

The synthesis of chiral non-racemic secondary alcohols by catalytic enantioselective reduction of the corresponding ketone remains a pivotal transformation in organic synthesis [10]. The three major catalytic procuderes which have emerged:

- Enantioselective hydride reduction
- Enantioselective hydrogenation
- Enantioselective transfer hydrogenation

Asymmetric transfer hydrogenation is defined as the reduction of multiple bonds with the aid of a hydrogen donor in the presence of a catalyst (Scheme 3) [11].

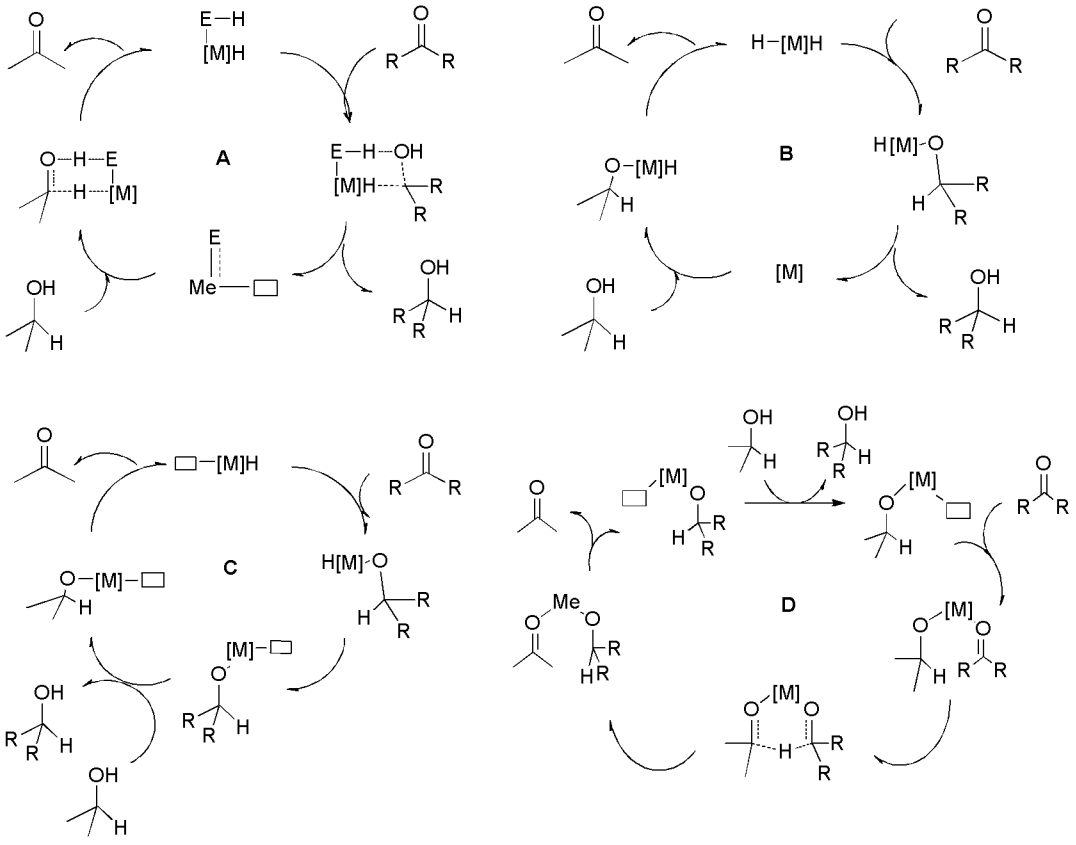


Scheme 3. Asymmetric Transfer Hydrogenation

As it is detailed by Noyori [12] and others [11], asymmetric transfer hydrogenation methodology has some distinct benefits over other methods. These includes its simplicity in procedure, absence of hazardous reagents like molecular hydrogen and borane (which also eliminates the need for specialized, expensive facilities for handling), and its explicit reactivity and enantioselectivity. Another particular advantage is requirement for the quantity of catalyst is very low, around 1 mol% [13]. Beside these advantageous properties there some drawbacks as its

unfavorable thermodynamics in regard to usage of alcohols in transfer hydrogenation as a hydrogen source, especially iso-propanol [14].

The majority of work carried out in this area has employed ruthenium-based catalyst in combination with a variety of phosphine and amine ligands. However, the interest in iridium catalysts, which has been successfully used for the asymmetric transfer hydrogenation, is rapidly growing in recent years [15]. In literature most used pre-catalysts are $[IrCl(LL')]_2$, $[IrCODl(LL')]^+$ complexes or 1:1 $[IrCl(COD)]_2$/LL′ mixtures, LL′ are chelating agents with different donor functions. According to literature studies, there are four different possible mechanisms are existing for the transfer hydrogenation of ketones catalyzed by iridium complexes (Scheme 4) [16, 17, 18, 19].



Scheme 4. Asymmetric Transfer Hydrogenation Mechanism

There are some specific applications of asymmetric transfer applications;

- Asymmetric reduction of aryl/alkyl ketones
- Asymmetric reduction of alkyl/alkyl ketones
- Asymmetric reduction of acetylenic ketones
- Asymmetric reduction of α-keto esters
- Asymmetric reduction of 1,2-diketones

1.4. History of Asymmetric Organocatalysis

In the beginning of 2000s a new catalytic approach has born between the transition-metal catalysis and enzymatic transformations, organocatalysis. They are purely organic molecules unlike organic ligands in transition-metal complexes. Their catalytic activity lies in the low-molecular weight organic molecule and does not depend on transition metals. They have many advantageous properties in contrast to transition metal catalysts. They are mostly stable, can easily be handled, less toxic, and can be easily separated from crude reaction mixture. They are readily available from natural sources or can be easily synthesized. They can also be used to prepare both enantiomers of the desired product as often both of the enantiomers of organocatalysts are available. Some of the organocatalysts are shown in figure 3 [20].

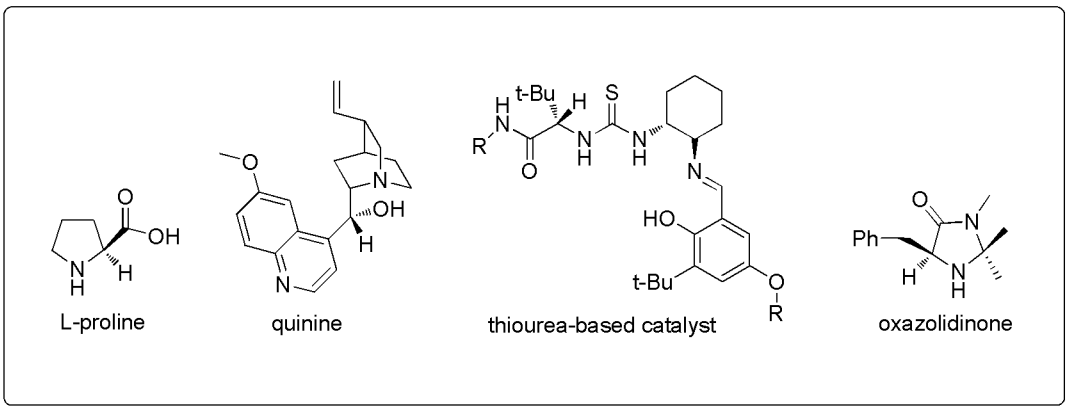
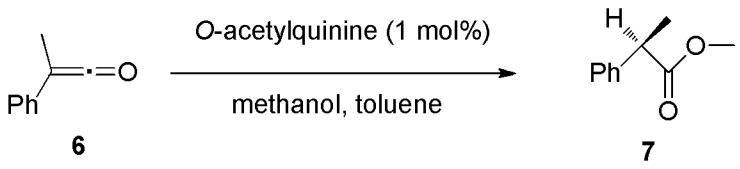


Figure 3. Some of the common organocatalysts

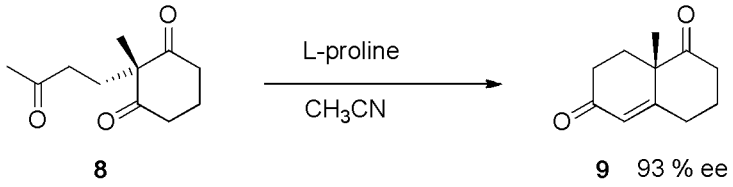
Although organic catalysts have been used since very beginning of chemistry, their usage as enantioselective catalysis has only appeared as a major concept in organic chemistry in the last decade. The first example of an asymmetric organocatalysis is reported by Bredig and Fiske in 1912, they showed that addition of HCN to benzaldehyde is accelerated by the alkaloids quinine and the resulting products are optically active and shows opposite chirality, yet their optical yields were lower than 10% [21].

In 1960s, by using alkaloids as catalysts, a remarkable enantiomeric excess was achieved in the addition of methanol to phenylmethylketene by Pracejus et al (Scheme 5) [22].



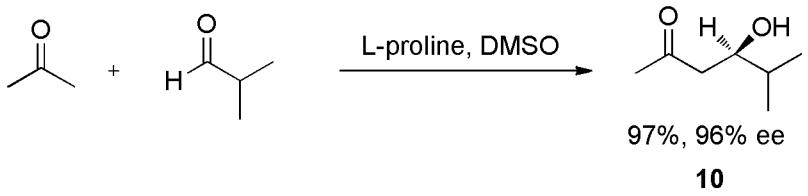
Scheme 5. Addition of methanol to phenylmethylketene

In 1971, another breakthrough was achieved that is the proline catalyzed asymmetric aldol cyclodehydration of the achiral trione to the unsaturated Wieland-Miescher ketone (Scheme 6) [23,24].



Scheme 6. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

The potential of proline in asymmetric aldol reactions was not discovered until recently. For example, recently, in the beginning of 2000s intermolecular aldol reactions were reported with quite high isolated yield and enantiomeric excess (Scheme 7) [25,26].



Scheme 7. Proline catalyzed intermolecular aldol reaction

Although asymmetric organocatalysis has begun to evolve since the 2000s, it has been growth exponentially in the field of asymmetric synthesis. Organocatalysis seems to evolve more and more in the next few decades, as it has already been into cycloadditions, Michael additions, aldol reactions, nucleophilic substitutions and many other transformations with excellent enantioselectivity.

1.5. Classification of asymmetric organocatalysis

On the basis of general mechanistic considerations, according to Gröger and Berkessel asymmetric organocatalysis can be separated into two groups; covalent catalysis and non-covalent catalysis (Figure 4).

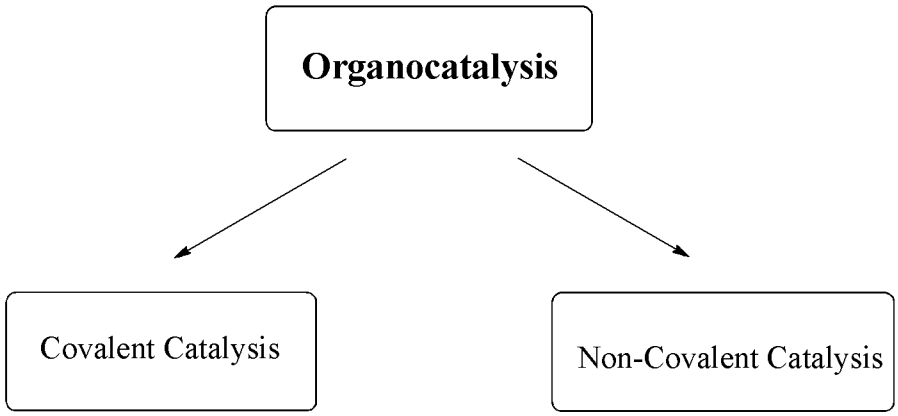
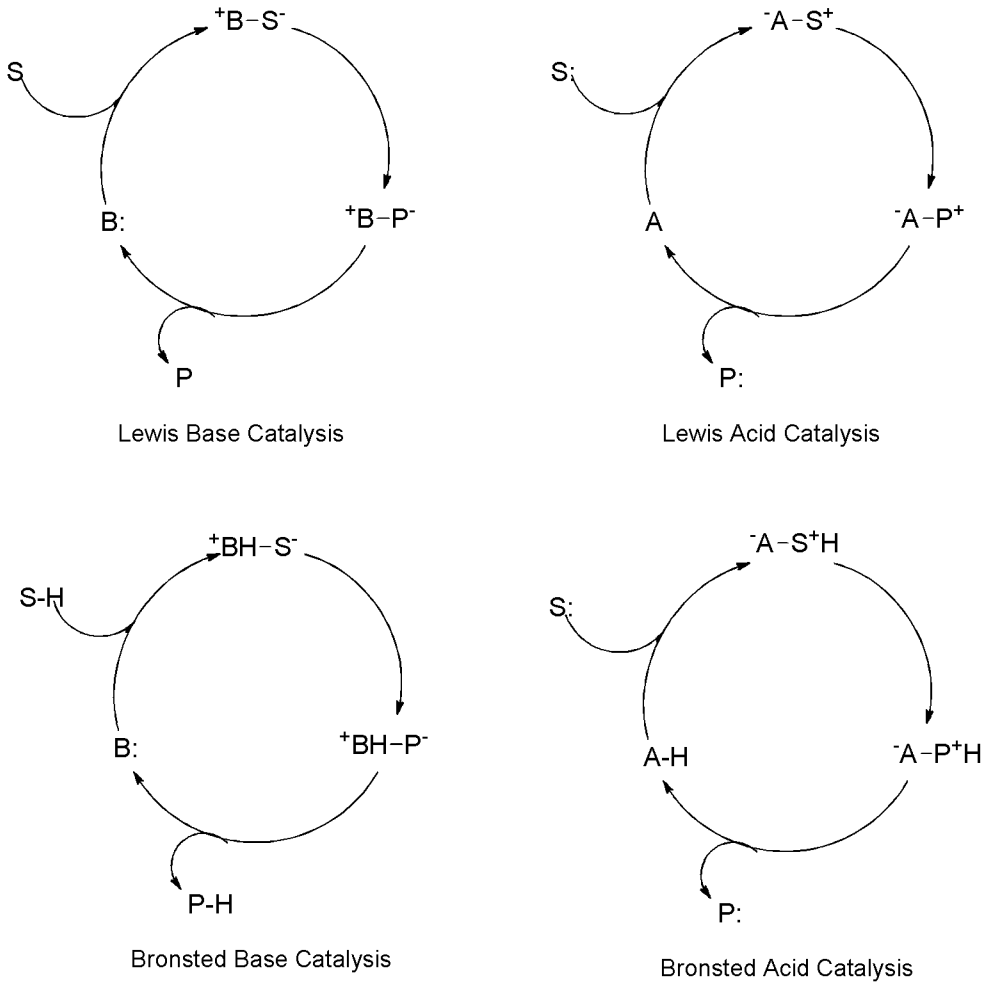


Figure 4. General mechanistic consideration

In Covalent catalysis, with the interaction between catalyst and substrate formation of covalent adducts occurs by single of multistep reactions. On the other hand, in non-covalent catalysis, it mostly relies on non-covalent interactions as hydrogen bonding or formation of ion pairs [27].

According to List and Seayad enantioselective organocatalysis can be classified as Lewis bases, Lewis acids, Bronsted bases and Bronsted acids (Scheme 8).



Scheme 8. Classification of organocatalysis by List and Seayad

According to scheme 8, Lewis base catalysts start the cycle by nucleophilic addition to the substrate. The resulted B-P complex undergoes a reaction and gives the product. Lewis acid catalysts activate the substrate and then undergo the reaction in a similar manner. On the other hand, Bronsted acid and base cycles are started by a partial protonation or deprotonation, respectively [28].

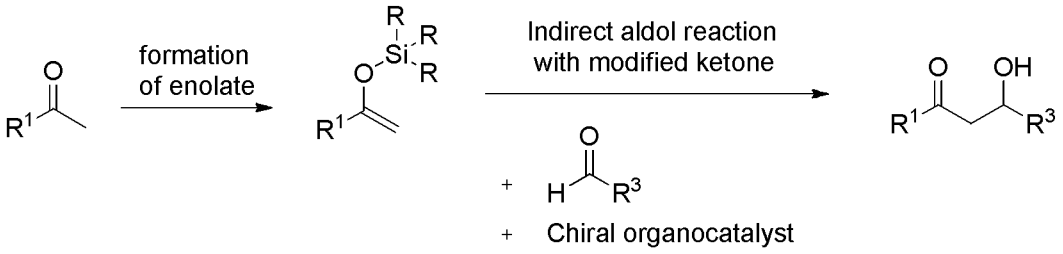
There are some specific applications of organocatalyst reactions;

- Nucleophilic substitution at aliphatic carbon
- Nucleophilic addition to electron-deficient C=C double bonds
- Nucleophilic addition to C=N double bonds
- Nucleophilic addition to C=O double bonds

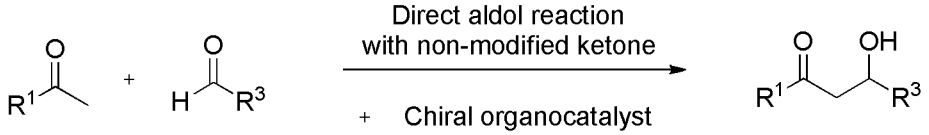
1.5.1. Asymmetric aldol reactions

Most popular topic among nucleophilic addition to C=O bonds is no doubt is aldol reactions. The product, β-hydroxy carbonyl compounds, have a very wide range of usage and high importance in production of pharmaceuticals. Shibasaki group showed that asymmetric aldol reaction can also be achieved by using ketones as organocatalysis instead of using metals [29]. In general, aldol reactions can be achieved in two ways, first one is indirect aldol reactions in which a modified ketone acts as a starting substance, second one is direct aldol reactions in which direct usage of ketone as a nucleophile happens (Scheme 9).

Pathway 1:

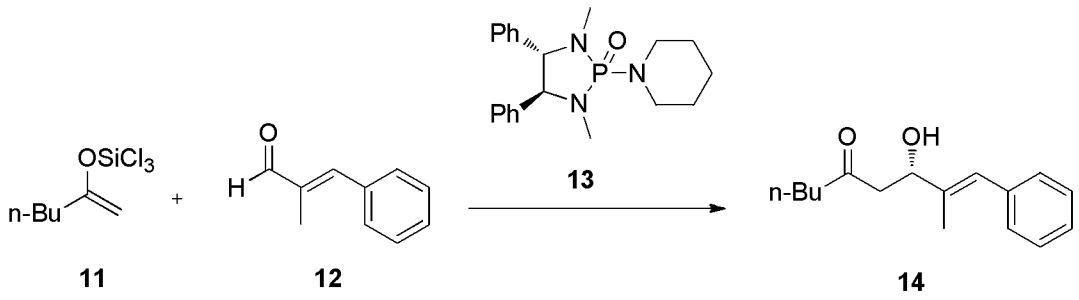


Pathway 2:



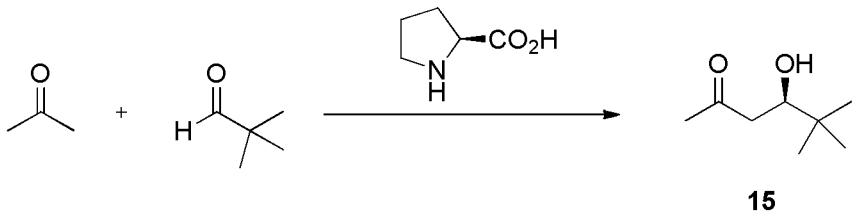
Scheme 9. Pathways of aldol reaction

For indirect aldol reactions, as wide range of aldehydes can be used Denmark's method is synthetically very valuable (Scheme 10) [30].



Scheme 10. The Denmark Method

For direct aldol reactions, with the help of organocatalyst L-Proline (S) shows great enantioselectivity with the use of tertiary aldehydes (Scheme 11) [31].

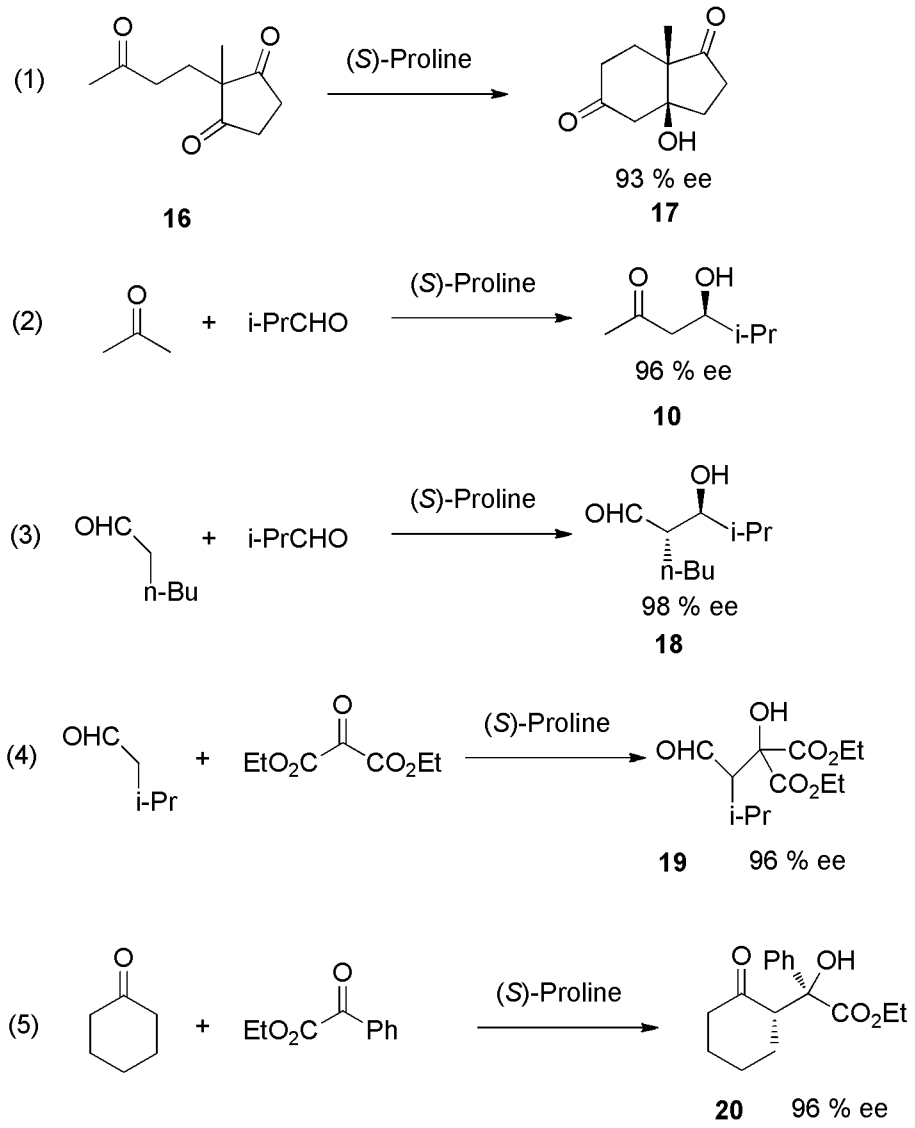


Scheme 11. Direct aldol reaction

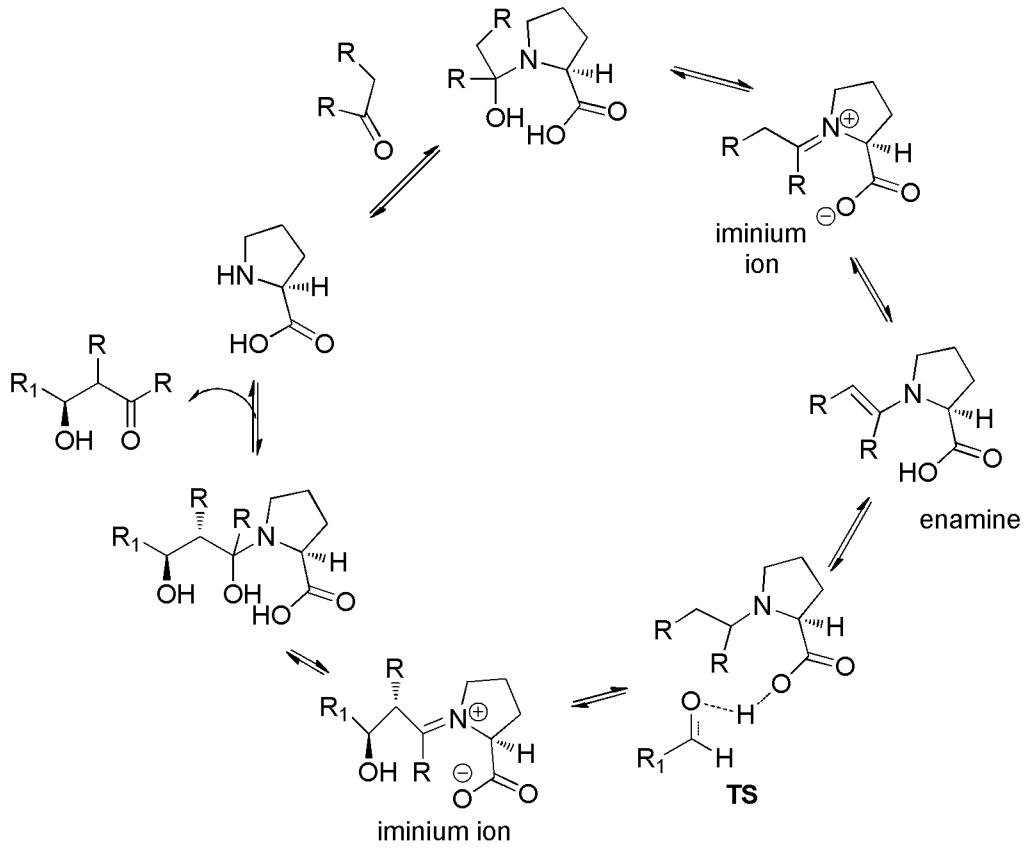
In addition to catalyzing famous Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 12; Eq 1), it was found that proline can also catalyze intermolecular aldolization (Eq 2). After that, other substrate combinations are used, aldehydes to ketone, ketone to ketone, aldehyde to aldehyde (Eq 3,4,5) [32].

According to Benjamin List, mechanism of asymmetric aldol reaction goes by formation of iminium ion and enamine (Scheme 13). As a result of the formation of iminium ion, LUMO energy of the system effectively lowers and makes it possible for the reaction to undergo by nucleophilic additions and α-

deprotonation. Afterwards deprotonation leads to enamine formation, which is the real nucleophilic carbanion equivalent. At last aldol product is synthesized by the reaction of enamine with aldehyde via transition state and hydrolysis [28].



Scheme 12. Proline catalyzed asymmetric aldol reactions



Scheme 13. The proposed mechanism proline-catalyzed aldolization

1.6. Aim of the work

The objective of this work is to synthesize novel 1,4-chiral diamine type ligands and organocatalyst possessing a *trans*-9,10-dihydro-9,10-ethanoanthracene backbone (Figure 9). Target 5 chiral compounds can be divided into two groups. First group is composed of ligands that are used to give complexes with transition metals. First group can also be divided into subgroups as secondary and tertiary amines. The second group contains a thiourea-proline type organocatalyst that is used in asymmetric aldol reactions.

Second objective of this study is to test these ligands and organocatalyst in suitable asymmetric reactions. The first group was tested in asymmetric transfer

hydrogenation reactions whereas second group is tested in aldol reactions where *p*-nitrobenzaldehyde and acetone used as reactants. Each of those reactions is discussed in more detail in results and discussion part.

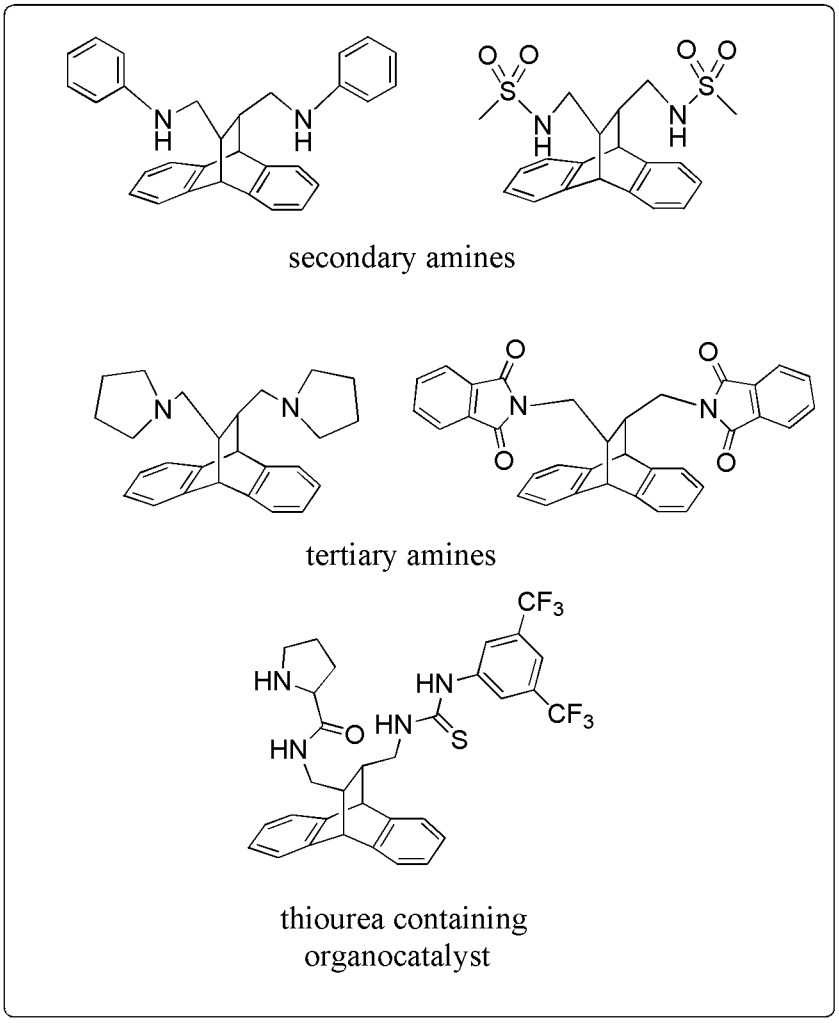


Figure 5. 1,4-Chiral diamines possessing a *trans*-9,10-dihydro-9,10-ethanoanthracene backbone

CHAPTER 2

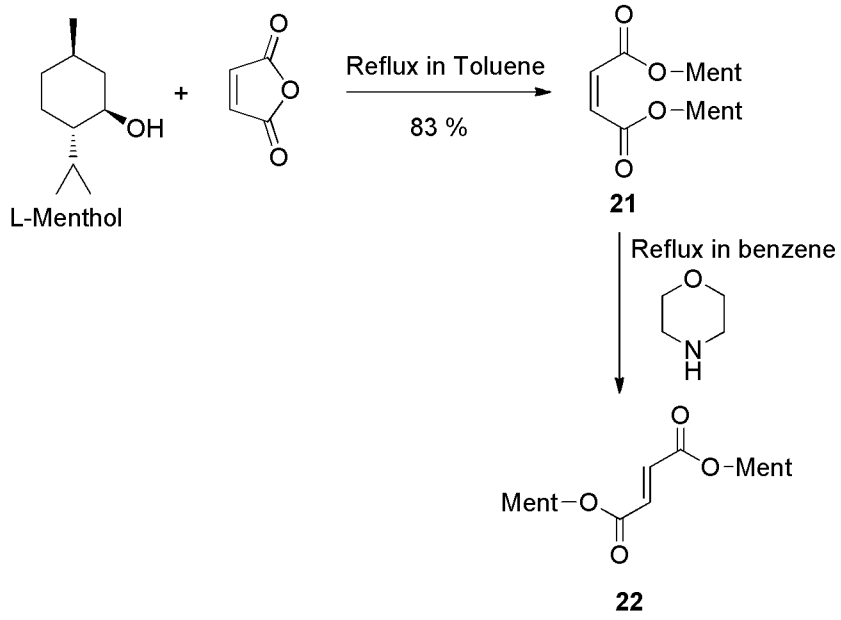
RESULTS AND DISCUSSIONS

Chiral diamines show excellent performance in regard to catalysts for the synthesis of enantiopure products, both as organocatalysts or as transition metal complexes [28, 33, 34, 35]. Effectiveness of C_2-symmetrical amine-based ligands formed transition metal complexes also prompted us to synthesize novel C_2-symmetrical 1,4-diamine type ligands. Since the first usage of proline as an organocatalyst in enantioselective intramolecular aldol reaction [22], proline has been widely used in enantioselective reactions. As proline is the only natural amino acid that contains secondary amine functionality and it is a good nucleophile that can react as a nucleophile with carbonyl groups to form enamines [36]. We also know thiourea based organocatalysts have strong activation effect on carbonyl groups as they do hydrogen bonding [37]. In the light of this knowledge we have, we decided to combine thiourea and proline in one organocatalysis classified as bifunctional organocatalyst. Here, we synthesized both anthracene based C_2-symmetrical 1,4-diamine ligands and anthracene based proline-thiourea organocatalyst.

2.1. Synthesis of enantiomerically pure 1,4-dimenthyl substituted anthracene based cycloadduct

In our synthetic strategy, first part involves the construction of enantiomerically enriched bicyclic carbon skeleton. For this purpose, we have decided to apply widely used asymmetric Diels-Alder reaction. Anthracene and dimenthyl fumarate were chosen as diene and dienophile, respectively. Menthyl unit has been considered as chiral induction source.

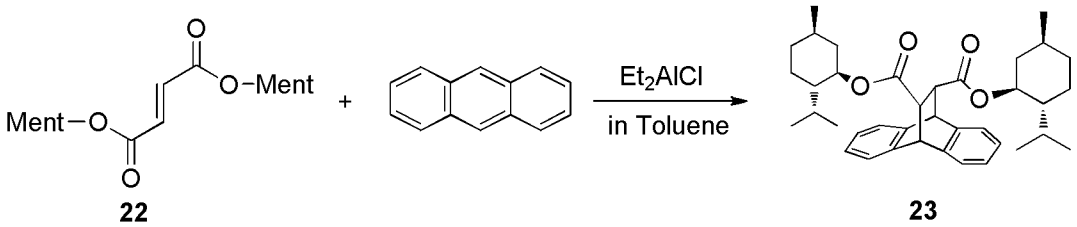
The chiral dienophile synthesis has been started with an esterification reaction. Maleic anhydride was reacted with (-)-menthol in the presence of catalytic amount of PTSA by refluxing in toluene. Subsequently, the transformation of (-)-dimenthyl maleate to (-)-dimenthyl fumarate was achieved via morpholine catalyzed isomerization reaction (Scheme 14). The spectroscopic data of both (-)-dimenthyl maleate **21** and (-)-dimenthyl fumarate **22** are in accordance with the literature results [38].



Scheme 14. Synthesis of (-)-dimenthyl fumarate

Asymmetric Diels-Alder reaction was performed between anthracene and (-)-dimenthyl fumarate. Various Lewis acids *i.e.* $AlCl_3$, $EtAlCl_2$ and Et_2AlCl were used as promoters to reduce the LUMO energy of dienophile. Among these, only Et_2AlCl promoted reaction afforded the desired chiral cycloadduct **23** in 74% chemical yields at room temperature. We obtained the product almost in enantiopure form (>99% ee) (Scheme 15) [39]. The structure elucidation of C_2-symmetrical compound **23** was done with ^1H and ^{13}C NMR. In ^1H NMR spectrum, bridgehead protons appear as singlet at 4.58 ppm. The characteristic oxygen

attached methine proton of menthyl moiety resonates at 4.47 ppm as triplet of doublet with the coupling constant values J = 10.9 and 4.3 Hz. Bridge protons appear as a singlet at 3.26 ppm. ^{13}C NMR spectrum shows the characteristic carbonyl signal at 171.7 ppm, 6 aromatic carbon signals between 142.5 and 123.5 ppm and a signal at 74.5 ppm which belongs to oxygen attached methine carbon of menthyl unit.



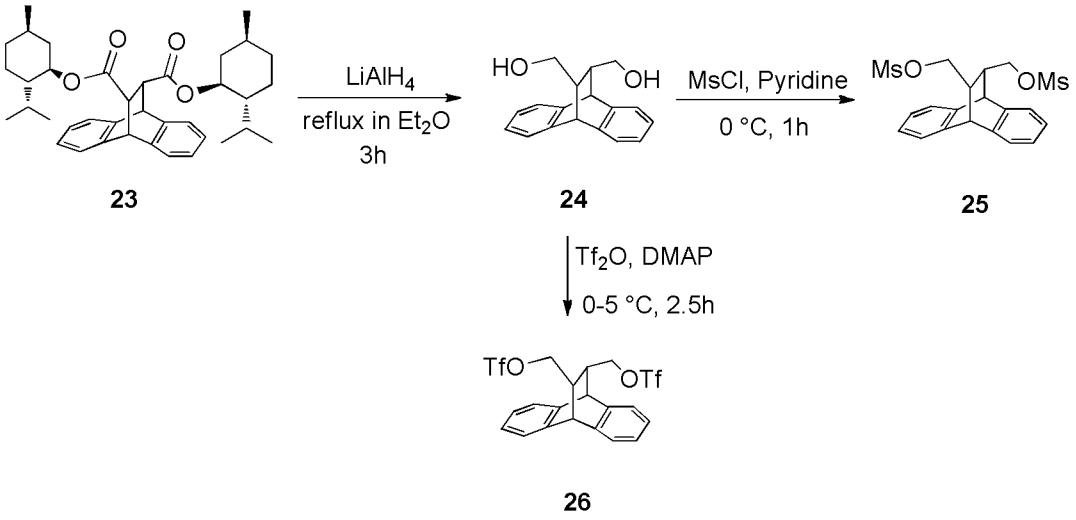
22 **23**

Scheme 15. Synthesis of cycloadduct

2.2. Synthesis of anthracene based 1,4-dimesylate and 1,4-ditriflate

This part of the study consists of the transformation of optically pure cycloadduct (-)-**23** into the corresponding 1,4-diol (+)-**24** and subsequent attachment of mesylate and triflate units to get good leaving groups which are available substances for introducing nitrogen units *via* S_N2 type reactions.

The attachment of mesylate and triflate units has been started by reduction reaction (Scheme 16). Cycloadduct (-)-**23** was reacted with $LiAlH_4$ by refluxing in diethyl ether [41]. Subsequently, methanesulfonyl and trifluoromethane sulfonyl units were successfully anchored to 1,4-diol (+)-**24** by using methanesulfonyl chloride in pyridine and trifluoromethanesulfonic anhydride in $CHCl_3$ with DMAP used as a base to afford compound (-)-**25** and compound (-)-**26**, respectively.



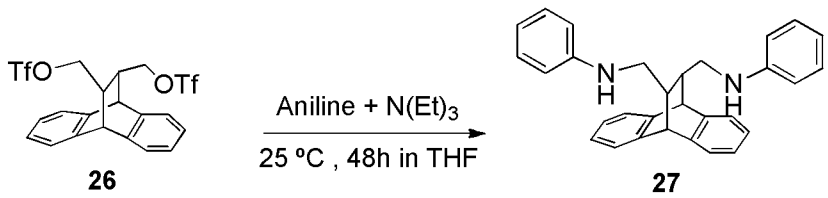
Scheme 16. Synthesis of 1,4-diol derivatives

In the ^{1}H NMR spectrum of 1,4-diol (+)-**24**, the newly generated diastereotopic methylene protons possess AB system which resonate at 3.33 and 2.88 ppm as doublet of doublets with the coupling constant values J_{AB} = 10.0, 6.0 Hz and J_{AB} = 10.0, 8.3 Hz, respectively. Hydroxyl unit protons appear at 2.50 ppm as broad singlet. In the ^{13}C NMR spectrum, the same methylene carbon is observed at 66.2 ppm. The structure elucidation of mesylated compound (-)-**25** and triflated compound (-)-**26** was also done by using ^{1}H and ^{13}C NMR spectroscopy. 1H NMR spectrum of compound (-)-**25** shows the characteristic diastereotopic methylene protons at 3.81 and 3.67 ppm as doublet of doublets and as triplets with the coupling constant values J_{AB} = 10.0, 5.8 Hz and J_{AB} = 9.2 Hz, respectively. Methyl protons of mesyl unit appear at 2.91 ppm as singlet. In the ^{13}C NMR spectrum the characteristic methylene carbon signal appeared at 71.2 and methyl carbon signal at 37.4 strongly support the structure of compound (-)-**25**. ^{1}H NMR spectrum of compound (-)-26 shows the similar diastereotopic methylene signal sets at 4.11 and 3.91 ppm as doublet of doublets and triplets with the coupling constant values J_{AB} = 10.0, 5.4 Hz and J_{AB} = 9.5 Hz, respectively. A slight shifting towards the downfield should be presumably due to the strong electron withdrawing property of triflate

unit. ^{13}C NMR signal of methylene carbon appears at 77.1 ppm overlapped with $CDCl_3$ signals.

2.3. Synthesis of anthracene based chiral 1,4-diamine ligands

As it is stated above effectiveness of diamine ligands prompted us to synthesize various 1,4-diamine ligands. In literature, there are various 1,4-*N,N*-ligands had been synthesized to used in Ir(I) catalyzed asymmetric transfer hydrogenation of ketones [44]. Here, we report four novel 1,4-*N,N*-ligands. The first one we tried to synthesize is 1,4-dianiline type ligand. In this synthesis mesylated diol (-)-**25** was reacted with aniline in the presence of $N(Et)_3$ in THF at room temperature for 48h. Unfortunately we could not get the desired product. The temperature was increased up to 80 °C and again the starting compound was isolated. In order to overcome this problem, mesylate was changed with triflate attached derivative (-)-**26** under the same conditions applied above and the desired product was isolated with low chemical yield (23%) [45] (Scheme 17).

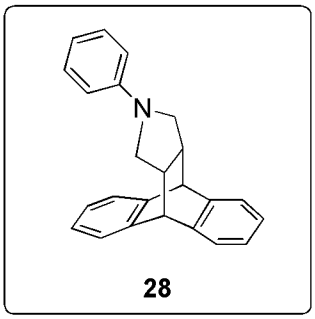


26 **27**

Scheme 17. Synthesis of 1,4-dianiline type ligand

The downside of this reaction is that the product does not favor only for the product we desired. By altering the procedure in regard to temperature and adding order and quantity of aniline, we could not increase the chemical yield. The problem in this synthesis is slightly more favored side product which is shown in figure 6, which we manage to confirm by the help of HRMS analysis (Figure 7). We proposed a reason for the problem as the low nucleophilic nature of aniline. As

soon as it is connected to one side of our reactant, reactivity of amine group increases and the reaction presumably favors the side product formation.



28

Figure 6. The resultant side product of 1,4-dianiline type ligand synthesis

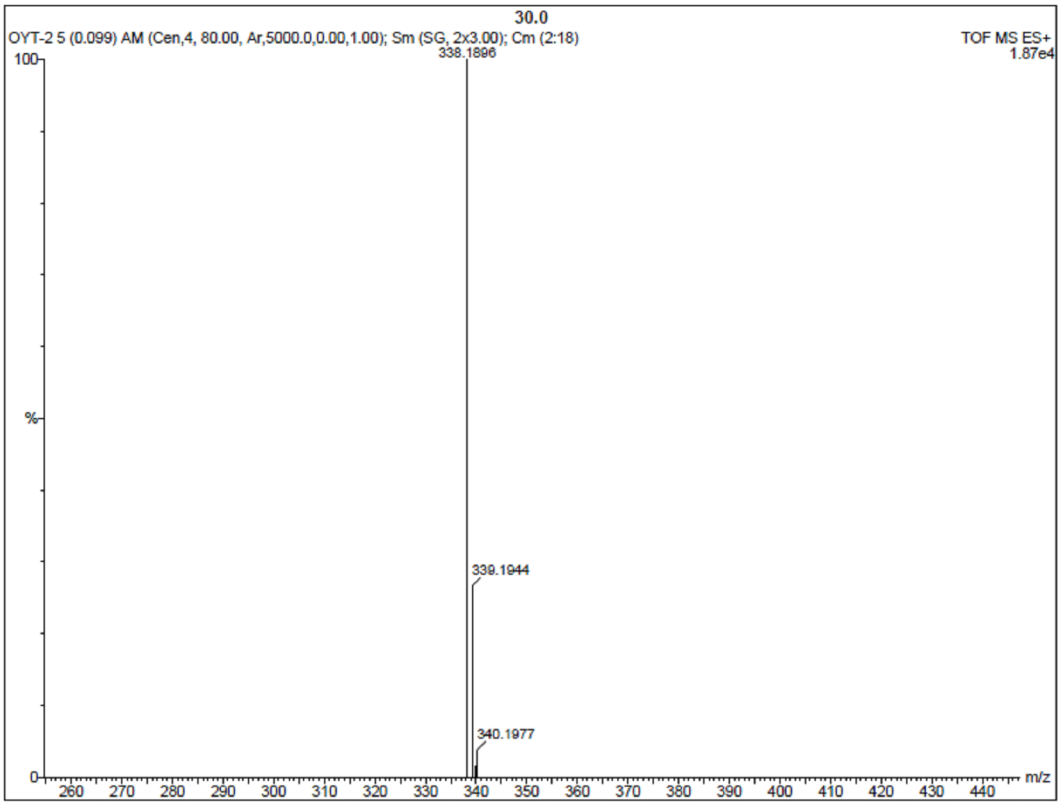
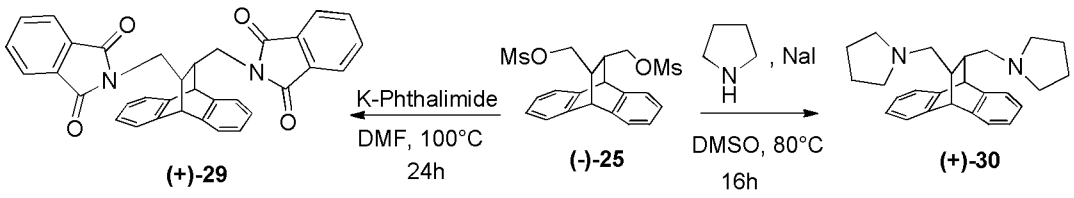


Figure 7. HRMS analysis of side product **28**

The structure characterization of aniline attached derivative was done by ^{1}H and ^{13}C NMR spectroscopy. The characteristic diastereotopic methylene protons resonate at 2.86 and 2.56 ppm as doublet of doublets with the coupling constant values J_{AB} = 12.7, 6.4 and J_{AB} = 12.7, 7.4 Hz, respectively. The characteristic amine protons are appeared at 3.81 ppm as broad singlet.

Second ligand we managed to synthesize is a tertiary amine 1,4-diphthalimide type ligand (+)-**29**. Refluxing mesylated diol (-)-**25** with K-phthalimide in DMF gave us the ligand 1,4-diphthalimide (+)-**29** in 52% chemical yield [47] (Scheme 19). In the synthesis of third ligand 1,4-dipyrrolidinyl (+)-**30** the same starting material mesylated diol (-)-**25** was heated up 80 °C in DMSO with NaI in catalytic amount [48] (Scheme 19). As a result of recrystallization target compound (+)-**30** was obtained in a chemical yield of 77%. As we could obtain pyrrolidinyl ligand easier in regard to other two ligands we mostly used pyrrolidine as screening ligand in asymmetric transfer hydrogenation reactions. By the help of HRMS analysis we managed to confirm pyrrolidine product (Figure 8). The structure characterization of 1,4-phthalimide (+)-**29** was done by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum, characteristic diastereotopic methylene protons appeared at 3.35 and 3.30 ppm as doublet of doublets with the coupling constant values J_{AB} = 13.8, 7.5 Hz and J_{AB} = 13.8, 5.5 Hz, respectively. ^{13}C NMR spectrum shows the characteristic methylene carbon next to the pthtalamide unit at 40.8 ppm and the carbonyl signal at 167.2 ppm. In ^{1}H NMR spectrum of (+)-**30**, pyrrolidine unit anchored methylene protons are observed at 2.08 and 1.94 ppm as doublet of doublets with the coupling constant values of J_{AB} = 11.8, 9.8 Hz and J_{AB} = 11.8, 4.3 Hz, respectively.



Scheme 18. Synthesis of 1,4-diphthalimide and 1,4-pyrrolidine type ligands

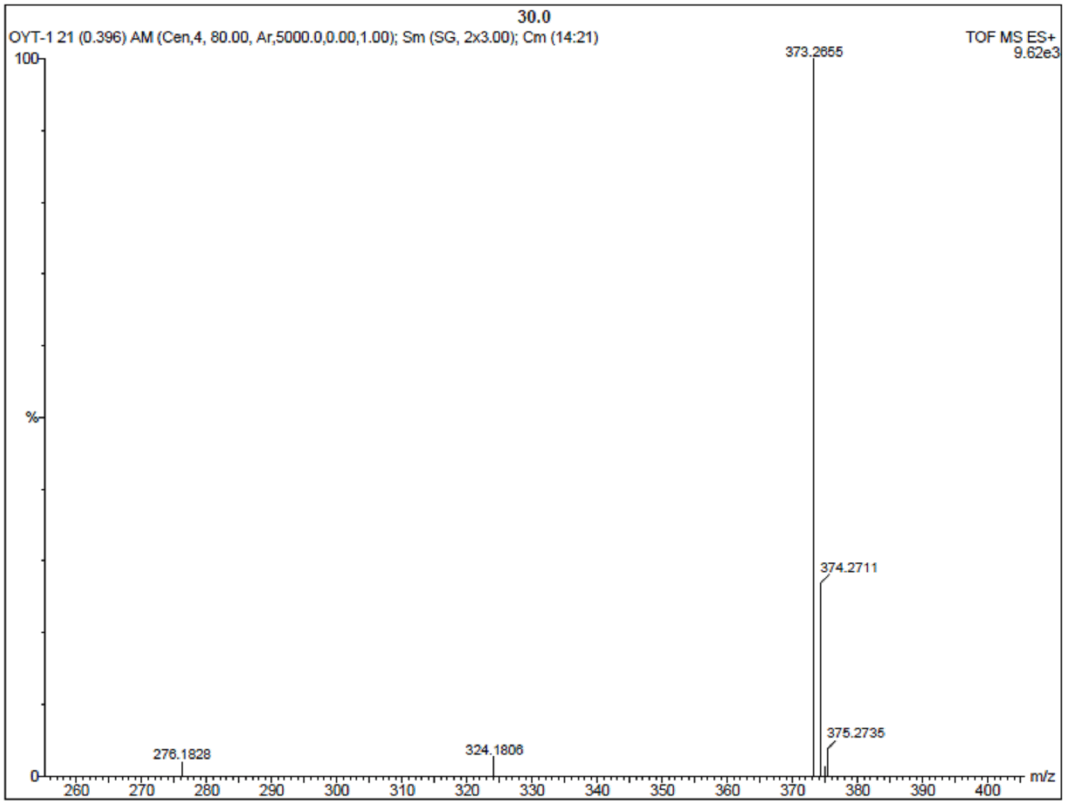
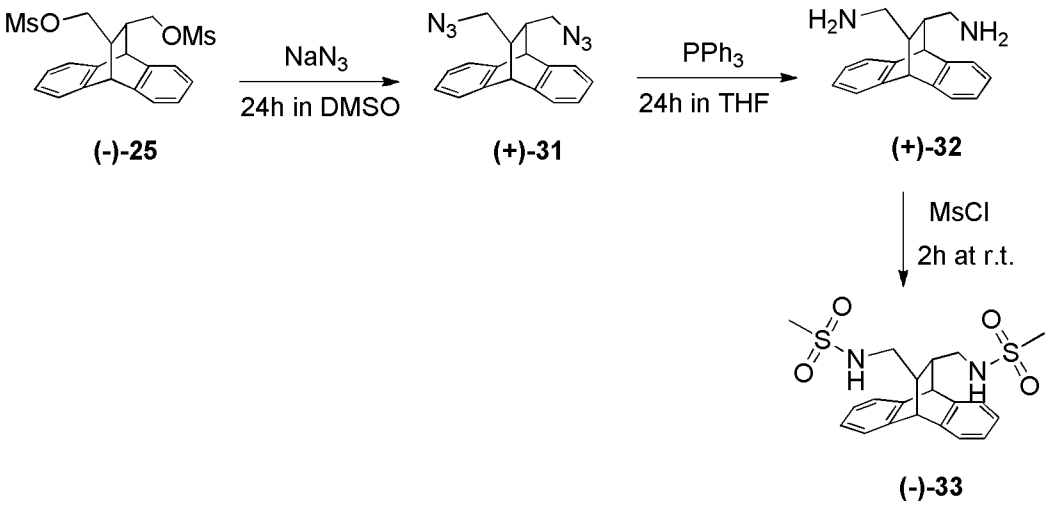


Figure 8. HRMS Analysis of pyrrolidine type ligand (+)-**30**

For the synthesis of our final 1,4-disulphonamide type ligand we followed different path than other three ligands. First step of the synthesis was the preparation of 1,4-diazide (+)-**31** through S_N2 type reaction by reacting mesylated diol (-)-**25** with sodium azide in DMSO in 82% chemical yield (Scheme 20). The spectral data of 1,4-diazide (+)-**31** are in accordance with the literature [49]. 1,4-Diazide (+)-**31** was then treated subsequently with triphenylphosphine in THF to

afford quantitatively 1,4-diamine HCl salt (+)-**32**. This procedure is known as Staudinger reaction [50].



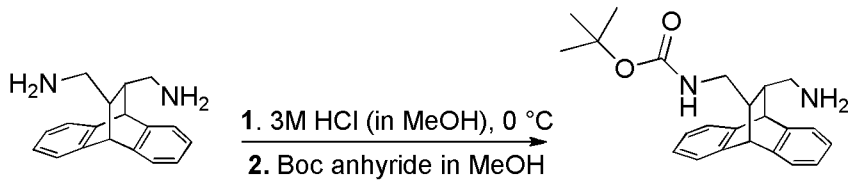
Scheme 19. Synthesis of 1,4-disulfonamide type ligand (-)-**33**

We have encountered series of problems in neutralization of (+)-**32** to isolate free 1,4-amine. It could not be isolated with a reasonable chemical yield. In order to overcome this problem, before HCl salt formation we tried to purify it by column chromatography, yet we could not efficiently isolate the product (37%). We could finally use free form of 1,4-diamine (+)-**32** to synthesize 1,4-disulphonamide (-)-**33** ligand by using methanesulfonyl chloride [51]. In ^{1}H NMR spectrum, the characteristic methyl signal of sulfonamide unit appeared at 2.81 ppm as singlet.

2.4. Synthesis of Anthracene based proline & thiourea containing organocatalyst

As stated before anthracene based 1,4-diamine backbone can be a good candidate as organocatalyst. Since the first usage of proline as an organocatalyst in enantioselective intramolecular aldol reaction [22], proline has been widely used in

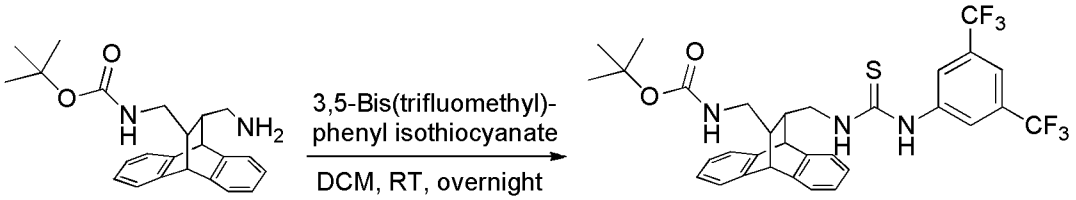
enantioselective reactions. As proline is the only natural amino acid that contains secondary amine functionality and it is a good nucleophile that can react as a nucleophile with carbonyl groups to form enamines [36]. We also know thiourea based organocatalysts have strong activation effect on carbonyl groups as they do hydrogen bonding [37]. Therefore we decided to modify this backbone with proline together with thiourea unit. In literature, there are several examples of mono-selective addition of thiourea to diamines, however it has a long reaction duration and chemical yields are very low [52]. In the first stage of the synthesis, in order to increase the yield and to lower reaction duration mono *t*-Boc protection has been done on 1,4-diamine (+)-**32** [53] (Scheme 23). ^{1}H NMR and ^{13}C NMR spectroscopy was used to do structural characterization. In the ^{1}H NMR spectrum, characteristic *t*-Boc protected amine proton resonates at 5.86 ppm as a singlet and free amines appeared at 1.25 ppm as a broad singlet. ^{13}C NMR shows the characteristic carbonyl carbon at 154.9 ppm.



32 **34**

Scheme 20. Monoprotection reaction

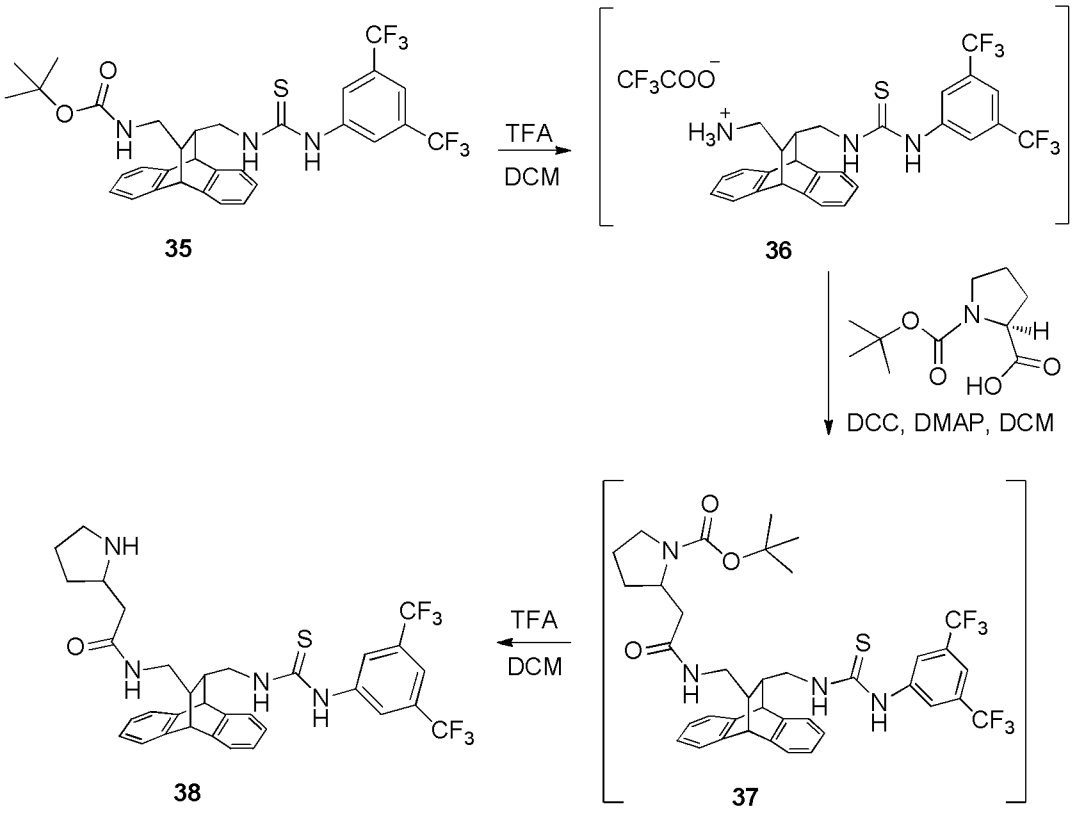
Once we managed to protect one side of compound (-)-**34** with *t*-Boc, we could introduce thiourea to un-protected primer amine by adding isothiocyanate in DCM [54] (Scheme 24). The structure of compound (-)-**35** was confirmed by ^{1}H and ^{13}C NMR. In the ^{1}H NMR, *t*-Boc attached amine proton appears at 8.68 ppm as a broad singlet and characteristic amine protons in thiourea unit show broad singlets at 5.30 and 4.35 ppm. In the ^{13}C NMR, characteristic thione carbon in thiourea unit resonates at 180.1 ppm and carbamate carbon resonates at 156.8 ppm.



34 **35**

Scheme 21. Addition of thiourea to monoprotected 1,4-diamine

Introducing thiourea unit to anthracene backbone was first part of our synthetic pathway to achieve anthracene based proline & thiourea containing organocatalyst. In the second part we managed to introduce proline to mono-thiourea compound (-)-**35** (Scheme 25). In order to accomplish that, first we deprotected *t*-Boc protected mono-thiourea with TFA in DCM [55]. Once deprotection completed, we did amidation reaction with *t*-boc protected proline by using DCC and DMAP [56]. Subsequently, *t*-Boc protected compound was deprotected again with TFA in DCM. Final product was isolated in 50% chemical yield.



Scheme 22. Synthesis of anthracene based proline & thiourea containing organocatalyst (-)-**38**

The structure characterization of anthracene based proline & thiourea containing compound (-)-**38** was done by ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum, the characteristic anthracene signals are observed and are given in experimental part. In addition to these amide protons in proline unit appeared at 8.27 ppm as a broad singlet. In the ^{13}C NMR, characteristic thione carbon in thiourea unit resonates at 180.5 ppm and carbamate carbon resonates at 176.1 ppm and quartet resonation observed at 130.5 ppm due to CF_3 units with the coupling constant value J = 33.2 Hz. HRMS analysis also supports that we managed to synthesized desired compound (-)-**38**.

2.5. Application of chiral 1,4-diamine ligands in asymmetric transfer hydrogenation reaction

Since the outstanding work of Mestroni in the transfer hydrogenation reaction of ketones [57], plenty of studying have been done on iridium-based asymmetric catalytic systems. According to literature studies, iridium(I) and diamine combination is excellent one for reduction reactions of ketones [58]. As a result, we tested synthesized 1,4-diamine ligands (+)-**27**, (+)-**29**, (+)-**30** and (-)-**33** (Figure 9) catalytic effectiveness in the asymmetric transfer hydrogenation reaction of a ketone.

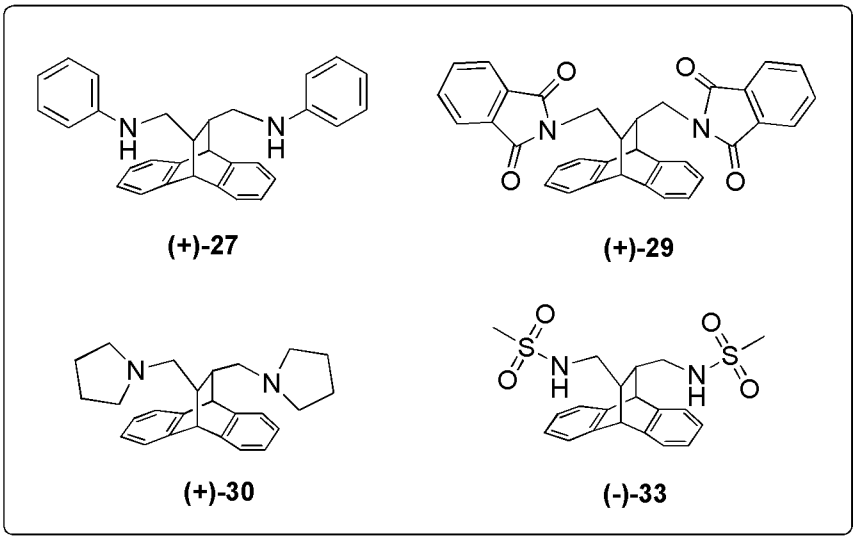
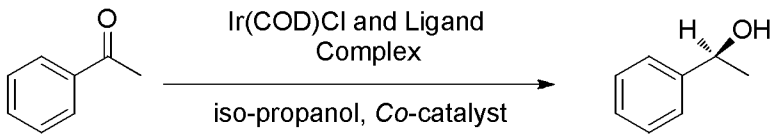


Figure 9. 1,4-diamine ligands

Acetophenone was chosen as a model substrate, a Lewis base chosen as a *co*-catalyst, and isopropyl alcohol was chosen as a hydrogen donor and solvent (Scheme 26). 2-Propanol has some favorable properties; it is easy to handle, stable, nontoxic, inexpensive and dissolves many organic substances.



Scheme 23. Asymmetric transfer hydrogenation of acetophenone

Using these stated conditions ligand (+)-**30** was used to do some screening reactions by changing temperature and different *co*-catalysts. The results are summarized in Table 1, Table 2 and Table 3. Reactions are run in a ratio of catalyst:*co*-catalyst:metal 4:8:2.

Table 1. *Co*-catalyst screening for ATH reaction at -10 °C

Entry	Catalyst	*Co*-catalyst	Temperature(°C)	Yield(%)[a]	Ee(%)[b]
1	**30**	KOH	-10	79	4
2	**30**	NaOH	-10	30	11
3	**30**	i-PrONa	-10	-	-

[a] Isolated yields were calculated after column chromatography.

[b] Enantiomeric ratios were determined by HPLC.

Table 2. *Co*-catalyst screening for ATH reaction at -20 °C

Entry	Catalyst	*co*-catalyst	Temperature(°C)	Yield(%)[a]	Ee(%)[b]
1	**30**	KOH	-20	37	7
2	**30**	NaOH	-20	-	-
3	**30**	i-PrONa	-20	-	-

[a] Isolated yields were calculated after column chromatography.

[b] Enantiomeric ratios were determined by HPLC.

Table 3. *Co*-catalyst screening for ATH reaction at -25 °C

Entry	Catalyst	*co*-catalyst	Temperature(°C)	Yield(%)[a]	Ee(%)[b]
1	**30**	KOH	-25	-	-
2	**30**	NaOH	-25	-	-
3	**30**	i-PrONa	-25	-	-

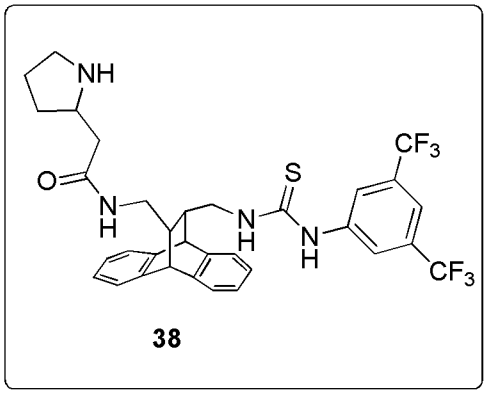
[a] Isolated yields were calculated after column chromatography.

[b] Enantiomeric ratios were determined by HPLC.

Three different co-catalysts are used in a temperature range -10°C to -25°C. Highest enantiomeric excess could be obtained at -10 °C with co-catalyst NaOH. However chemical yields were low but for KOH at -10 °C.

2.6. Application of chiral organocatalyst in asymmetric aldol reaction

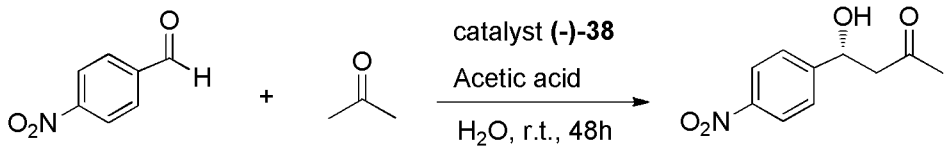
Proline and thiourea derived organocatalysts are widely used in asymmetric reactions. More detailed information regard to usage of proline and thiourea derivative organocatalyst was given in introduction part. For testing effectiveness of organocatalyst (-)-**38**, direct aldol reaction was chosen (Figure 10).



38

Figure 10. 1,4-Proline-Thiourea organocatalyst

General direct aldol reaction is shown below (Scheme 24). In this reaction 4-nitrobenzaldehyde and acetone were chosen as substrates and acetic acid was used as additive and water used as solvent. All tests were run at room temperature.



Scheme 24. Asymmetric aldol reaction using catalyst (-)-**38**

Once substrates were decided, five different additives were used for screening at room temperature with 5 mol % catalyst (-)-**38** (Table 4) using water as solvent.

Table 4. Results of asymmetric aldol reaction with different additives

Entry	Cat. (mol%)	Solvent	Additive (5 mol%)	Yield (%)[a]	Enantiomeric excess (%)[b]
1	5%	Water	HAc	53	46
2	5%	Water	Butyric Acid	81	47
3	5%	Water	Octanic Acid	73	43
4	5%	Water	Benzoic Acid	67	25
5	5%	Water	NA	65	49

[a] Isolated yields were calculated after column chromatography.

[b] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has *R* configuration.

As a result we have seen that using additives increases yield but lower enantiomeric excess. In entry 2, we see that using butyric acid as an additive increases yield up to 83% however enantiomeric excess stands at 47% in 24h. Catalyst (-)-**38** was tested without using any additive to see its catalytic activity and

effectiveness of additives. The enantiomeric excess was 49% and the isolated yield was 65% (Figure 11). Reaction goes better in means of enantiomeric excess when we didn't use any additive and yield was moderate. In order to understand the solvent effect on asymmetric aldol reaction while using catalyst (-)-**38**, we run some test experiments with 5 mol% catalyst in different solvents (Table 5). We chose not to use any additive to run those tests, as both enantiomeric excess and yield was acceptable.

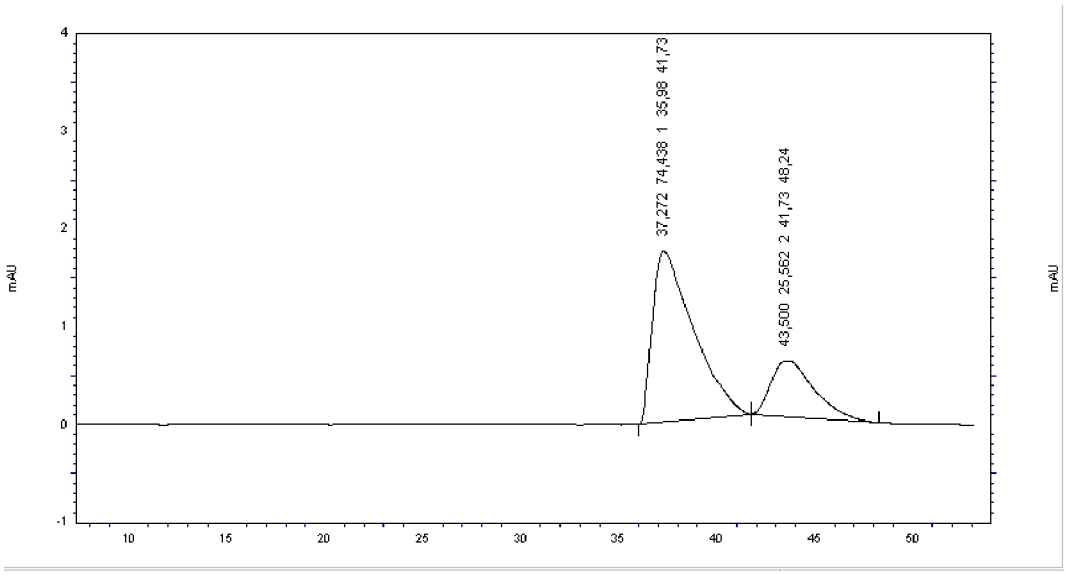


Figure 11. HPLC chromatogram of aldol product using catalyst (-)-**38**

Table 5. Results of asymmetric aldol reaction with different Solvents

Entry	Cat. (mol%)	Solvent	Additive	Yield (%)[a]	Enantiomeric excess (%)[b]
1	5%	Water	NA	65	49
2	5%	DCM	NA	53	21
3	5%	THF	NA	33	32
4	5%	MeOH	NA	19	21
5	5%	Neat	NA	38	13

[a] Isolated yields were calculated after column chromatography.

[b] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has *R* configuration.

All tests were run at room temperature, and using 5 mol% catalyst (-)-**38**. As acetone also acts as a solvent we also tested it without any solvent and as seen in entry 5, both yield and enantiomeric excess decreased. In entry 1 we have seen that water gives better results than other solvents in both enantiomeric excess and chemical yield.

And finally after we have seen the best additive and solvent that asymmetric aldol reaction ran with organocatalyst (-)-**38**, we decided to screen the reaction by using different amount of organocatalyst (-)-**38** at room temperature.

Table 6. Results of asymmetric aldol reaction with different organocatalyst (-)-**38** concentration

Entry	Cat. (mol%)	Solvent	Additive	Yield (%)[a]	Enantiomeric excess (%)[b]
1	5%	Water	NA	53	46
2	10%	Water	NA	100	29
3	20%	Water	NA	100	26

[a] Isolated yields were calculated after column chromatography.

[b] Enantiomeric ratios were determined by HPLC analysis using a chiral column. The major product has *R* configuration.

According to the results as seen in entry 2 and 3, increasing concentration gives higher yields, which is quantitative. However increasing concentration of catalyst decreases enantioselectivity of asymmetric aldol reaction decreases. From all these data we have gathered, we see that using water as a solvent and 5 mol% of organocatalyst (-)-**38** without using any additive gives the best result in asymmetric aldol reaction.

CHAPTER 3

CONCLUSION

To conclude, starting from easily available (-)-menthol, four ligands and one organocatalyst containing anthracene backbone were successfully synthesized. Those ligands can be classified into two groups, as (+)-**27** and (-)-**33** are secondary amines and (+)-**29** and (+)-**30** are tertiary amines. These ligands were tested in asymmetric transfer hydrogenation of ketones to produce secondary alcohols. The selectivity of this transfer hydrogenation reaction was low in both for enantiomeric excess and chemical yield.

As for the organocatalyst (-)-**38**, asymmetric direct aldol reaction between *p*-nitrobenzaldeyhyde and acetone was tested in various solvents. The yields were quite high and could be increased to 100% by increasing concentration of the catalyst. However enantiomeric excess could be increased to 49% at most by running the reaction without any Lewis acid additive and using water as a solvent at room temperature.

As a further work, conditions for both asymmetric transfer hydrogenation and asymmetric direct aldol reaction will be optimized to give better enantiomeric excess results. Up to now, we have just applied one ligand for asymmetric transfer hydrogenation. Catalysts (+)-**27**, (+)-**29** and (-)-**33** will also be tested and those results will give us chance for optimization for increasing both yield and enantiomeric excess for asymmetric transfer hydrogenation reaction, by adjusting substrates and hydrogen source. In order to increase enantiomeric excess value for direct asymmetric aldol reaction we will adjust temperature and using different substrates.

CHAPTER 4

EXPERIMENTAL

During the study we used following materials and instruments for characterization and purification works.

Bruker DPX 400 spectrometer was used to record NMR spectra. Chemical shifts are expressed in ppm. tetramethylsilane is used as an internal standard is the downfield. ^{1}H-NMR value of the signal, peak multiplicity (abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad) and coupling constants in Hertz integrated number of protons are represented data in same order. ^{13}C-NMR spectra measurements are done at 100 MHz and triplet at 77.0 ppm of $CDCl_3$ is used as a reference for the chemical shifts were reported.

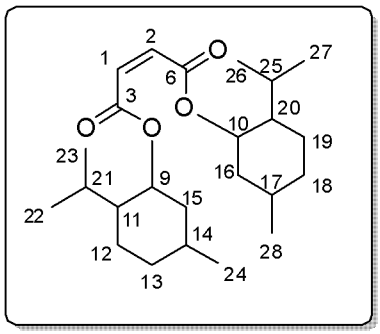
Rudolph Research Analytical Autopol III, automatic polarimeter is used for measurements of optical rotations in a 1 dm cell at specified temperatures.

ThermoFinnigan Spectra System instrument is used for HPLC measurements. To separate enantiomers Chiralcel OJ-H analytical column (250 x 4.60 mm) is used with 2-propanol/hexane as eluent.

Flash column chromatography was employed using thick-walled glass columns with a flash grade silicagel (Merck Silica Gel 60, particle size: 0.040-0.063 mm, 230-400 mesh ASTM). Pre-coated silica gel plates (Merck Silica Gel PF-254) were used to monitor reactions by thin layer chromatography. Visualization of TLC plates was done by UV-light, or anisaldehyde and ninhydrin

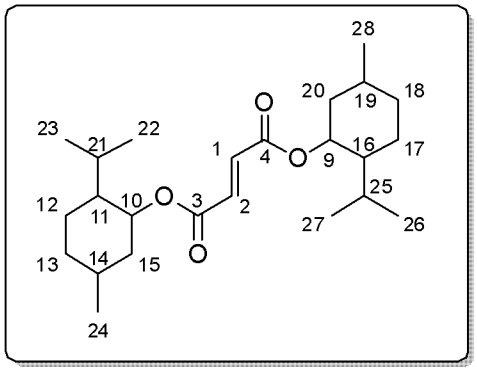
stains. Eluents for column chromatography are used in relative portions of solvents that are in volume:volume ratio.

4.1. Synthesis of dimenthyl maleate, (-)-(21)



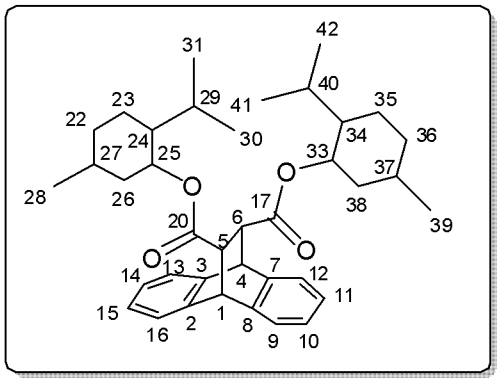
To a solution of maleic anhydride (18.8 g, 192 mmol) in 250 mL of toluene, PTSA (2.7 g, 20 mmol) was added and the mixture is stirred. After five minutes of stirring, (+)-menthol (60g, 385mmol) was added to the solution and left for refluxing with Dean-Stark water separator for 18h. After that solution was cooled down to room temperature and washed with ether. Combined organic layer was washed with saturated $NaHCO_3$ to neutralize the solution and organic layer was separated by using extraction funnel. Then organic layer was washed with 40 mL of water for twice to get rid of acid remains that might be in medium. Combined organic layer was dried over by extraction with brine and using $MgSO_4$. After filtering and evaporation of organic layer, white solid particles are recrystallized by using 50 mL methanol to yield dimenthyl maleate in 83% yield as a while solid. Mp = 98 °C [38]. $[\alpha]_D$ = -95.3 (*c* 1.76, C_6H_6) [38]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 2H, H_1-H_2), 4.71 (td, *J* = 10.9, 4.4 Hz, 2H, H_9-H_{10}), 2.03 – 1.89 (m, 2H), 1.81 (ds, *J* = 4.3, 2.6 Hz, 2H, H_{11}-H_{25}), 1.64 (dt, *J* = 4.9, 3.1 Hz, 4H), 1.52 – 1.30 (m, 4H), 1.66 – 1.60 (m, 1.09 – 0.89 (m, 4H), 0.84 (t, *J* = 7.1 Hz, 12H, H_{22}-H_{23}-H_{26}-H_{27}), 0.81 (overlapped, 2H), 0.70 (d, *J* = 6.9 Hz, 6H, H_{24}-H_{28}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 134.2, 75.5, 47.4, 41.1, 34.6, 31.8, 26.6, 23.7, 22.4, 21.1, 16.6.

4.2. Synthesis of dimenthyl fumarate, (-)-(22)



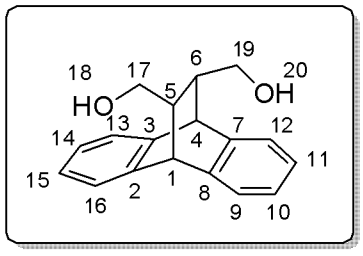
To a solution of dimenthyl maleate (60 g, 159 mmol) and 150 mL benzene morpholine (1.39 g, 16 mmol) was added. The resultant solution was refluxed for 8 h and was cooled down to room temperature. After cooling down the solution, ether 200 mL ether was added. Organic layer was washed with 2M HCl (2x 20 mL). After that organic layer was washed with saturated $NaHCO_3$ and dried over with $MgSO_4$. After evaporation of organic layer, resultant oily yellowish compound was filtered through silica gel and washed with hexane. Finally, oily product was left to crystallize under reduced pressure to get the product as yellow-white solid **2** (49.6 g, 83% yield) until it becomes solid. Product can also be used as oily though. $[\alpha]_D$ = -96 (*c* 1.20, C_6H_6) [38]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 2H, H_1-H_2), 4.71 (td, J = 10.9, 4.4 Hz, 2H, H_9-H_{10}), 2.03 – 1.89 (m, 2H), 1.81 (ds, J = 4.3, 2.6 Hz, 2H, H_{11}-H_{25}), 1.64 (dt, J = 4.9, 3.1 Hz, 4H), 1.52 – 1.30 (m, 4H), 1.66 – 1.60 (m, 4H), 1.09 – 0.89 (m, 4H), 0.84 (t, J = 7.1 Hz, 12H, H_{22}-H_{23}-H_{26}-H_{27}), 0.81 (overlapped, 2H), 0.70 (d, J = 6.9 Hz, 6H, H_{24}-H_{28}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 133.3, 74.8, 46.5, 40.2, 33.7, 30.9, 25.8, 22.9, 21.4, 20.2, 15.8.

4.3. Synthesis of *trans*-11,12-bis(dimenthyl)-9,10-dihydro-9,10-ethanoanthracene, (-)-23



To a solution of dimenthyl fumarate (5.2 g, 13 mmol) and 90 mL toluene Et_2AlCl was added slowly at 0 °C. After addition of anthracene solution was stirred it for 24 h at room temperature. After solution color becomes yellowish wash it with 2M HCl (200 mL). Add ether to organic layer and extract it with 10 % NaOH to neutralize pH of the solution. Organic layer was then dried over by using anhydrous $MgSO_4$ and evaporated. The product was purified by recrystallization in ethanol. The product was obtained as white solid in 66% chemical yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.08 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.06 – 6.95 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 4.58 (s, 2H, H_1-H_4), 4.47 (td, J = 10.9, 4.3 Hz, 2H, H_{25}-H_{33}), 3.26 (s, 2H, H_5-H_6), 1.88 (ds, J = 4.3, 2.6, 2H, H_{29}-H_{40}), 1.79 – 1.67 (m, 2H), 1.60 (m, 4H), 1.38 – 1.23 (m, 4H), 0.94 (overlapped, 4H), 0.89 (d, J = 7.0 Hz, 6H, H_{30}-H_{41}), 0.78 (d, J = 6.5 Hz, 6H, H_{31}-H_{42}), 0.72 (overlapped, 4H), 0.65 (d, J = 6.9 Hz, 6H, H_{28}-H_{39}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 142.5, 140.1, 126.3, 126.0, 124.8, 123.5, 74.9, 48.2, 47,0, 46,9, 40.7, 34.3, 31.4, 26.0, 23.1, 22.0, 21.0, 16.1.

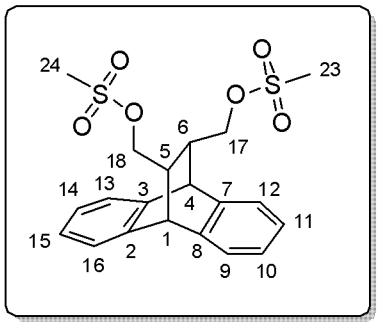
4.4. Synthesis of *trans*-11,12-bis(hydroxymethyl)-9,10-dihydro-9,10-ethano-anthracene, (+)-24



To a solution of $LiAlH_4$ (2 g, 53 mmol) in 100 mL ether, 1,4-dimenthyl (5 g, 9 mmol) in 100 mL ether was slowly added at room temperature. The resultant mixture was refluxed for 8 h. When the reaction was completed the medium is cooled down to room temperature and water was added very slowly to destroy remaining $LiAlH_4$. After

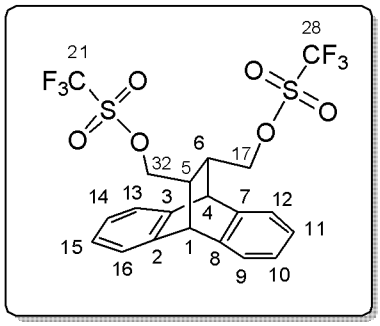
that, 10 % H_2SO_4 (100 mL) was added and stirred till the solution becomes real clear. Separated organic layer was dried over by using anhydrous MgSO4 and evaporated. The resultant menthol impurities are washed away with petroleum ether and leaving it in vacuumed medium for 2 h. After that white solid product was purified by using column filled silica gel and eluting with EtOAc:Hexane (1:1) in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.09 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.04 – 6.94 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 4.06 (d, J = 1.1 Hz, 2H, H_1-H_4), 3.33 (dd, J = 10.0, 6.0 Hz, 2H, H_{17a}-H_{19a}), 2.88 (dd, J = 10.0, 8.3 Hz, 2H, H_{17b}-H_{19b}), 2.50 (bs, 2H, H_{18}-H_{20}), 1.65 – 1.47 (m, 2H, H_5,H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 140.6, 131.7, 128.2, 126.2, 126,1, 125.8, 125.3, 125.0, 123.3, 66.2, 46.4, 46,2.

4.5. Synthesis of *trans*-11,12-bis(methanesulfonyl)-9,10-dihydro-9,10-ethano-anthracene, (-)-25



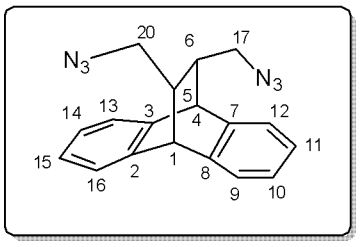
To a solution of 1,4-diol (1.4 g, 5 mmol) in dry pyridine (14 mL) methanesulfonylchloride (0.94 mL, 12 mmol) was added slowly and cooled down to 0 °C and stirred for 1 h. After reaction was completed 2M HCl (40 mL) was added and stirred for another 10 minutes. The resultant mixture was vacuum filtered and filtrate was washed with 5 mL of water twice. Filtrate then was dissolved in methanol and left for recrystallization. The purified product was then separated in 65% chemical yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.13 – 7.02 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 4.26 (s, 2H, H_1-H_4), 3.81 (dd, J = 10.0, 5.8 Hz, 2H, H_{17a}-H_{18a}), 3.67 (t, J = 9.2 Hz, 2H, H_{17b}-H_{18b}), 2.91 (s, 6H, H_{23}-H_{24}), 1.84 – 1.74 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 139.3, 126.8, 126.5, 125.6, 123.9, 71.2, 45.1, 42.7, 37.4.

4.6. Synthesis of *trans*-11,12-bis(methanetrifluorosulfonyl)-9,10-dihydro-9,10-ethano-anthracene, (-)-26



To solution of 1,4-diol (4.26 g, 16mmol) in $CHCl_3$ (65 mL) DMAP (4.73 g, 39 mmol) was added and cooled down to 0 °C and stirred for 10 mins. After 10 mins Tf_2O (10 g, 36 mmol) and $CHCl_3$ (22 mL) solution was added dropwise. The resultant mixture stirred at 0 °C for 2.5 h. After reaction completed, solution was filtered through silica gel (50 mL) by using $CHCl_3$ as eluent. Column chromatography (EtOAc:Hexane 1:6) was done to purify product (in 67% chemical yield). Mp = 128 °C. $[\alpha]^{25}_D$ = -9.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.17 – 7.10 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 4.29 (d, J = 1.5 Hz, 2H, H_1-H_4), 4.11 (dd, J = 10.0, 5.4 Hz, 2H, H_{17a}-H_{32a}), 3.91 (t, J = 9.5 Hz, 2H, H_{17b}-H_{32b}), 1.93 – 1.73 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 138.5, 127.3, 126.9, 125.7, 124.1, 77.1, 44.6, 42.4.

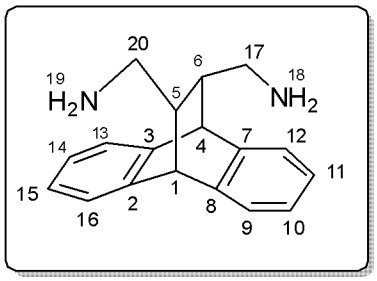
4.7. Synthesis of *trans*-11,12-bis(methanazide)-9,10-dihydro-9,10-ethano-anthracene, (+)-31



To a solution of 1,4-dimesylate (1 g, 2 mmol) in distelled DMSO (7 mL) sodium azide (489 mg, 8 mmol) was added and stirred for 24 h at 90 °C. After that solution was poured into 15 mL of water and extracted with CH_2Cl_2 (3 x 10 mL) and water (3 x 10 mL). Organic layer was dried over with $MgSO_4$ and evaporated. The white solid product was purified by using column chromatography by using hexane as an eluent. Chemical yield was 82%. ^{1}H-NMR (400 MHz,) δ 7.25 – 7.18 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.10 – 7.02 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 4.18 (d, J = 1.4 Hz, 2H, H_1-H_4), 3.00 (dd, J = 12.0, 5.7 Hz, 2H, H_{17a}-H_{20a}), 2.74 (dd, J = 12.0, 9.2 Hz, 2H, H_{17b}-

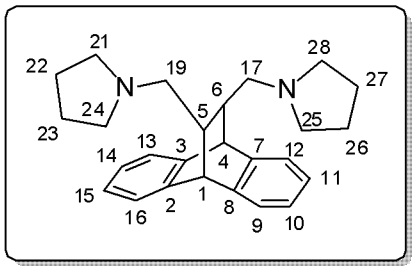
H_{20b}), 1.54 – 1.42 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 126.5, 126.2, 125.5, 123.7, 55.1, 46.3, 44.2.

4.8. Synthesis of *trans*-11,12-bis(methanamine)-9,10-dihydro-9,10-ethano-anthracene, (+)-32



To a solution of 1,4-diazide (200 mg, 0.65 mmol) and THF (10 mL) PPh_3 (550 mg, 2 mmol) solution was added (in 1 mL of water). The resultant mixture was stirred in room temperature for 18h. After 18 h, 2M HCl (5 mL) was added to complete reaction and get HCl salt of product. Product is then washed with ether to get rid of remaining PPh_3. After evaporating water from medium, white solid product was left in vacuum (100% chemical yield). ^1H NMR (400 MHz, D_2O) δ 7.41 – 7.34 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.25 – 7.06 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 4.39 (s, 2H, H_1-H_4), 2.83 (d, J = 13.2 Hz, 2H, H_{17a}-H_{19a}), 2.47 (dd, J = 12.7, 10.1 Hz, 2H, H_{17b}-H_{19b}), 1.70 – 1.68 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 139.6, 125.1, 124.7, 124.0, 122.4, 46.5, 46.0, 45.1.

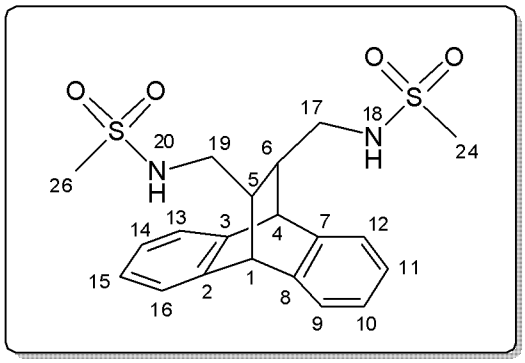
4.9. Synthesis of *trans*-11,12-bis(methanpyrrolidinyl)-9,10-dihydro-9,10-ethano-anthracene, (+)-30



To a solution of 1,4-mesylate (500 mg, 2 mmol) in distillated DMSO (2.6 mL) NaI (13 mg) was added into it. After that, pyrrolidine was added and solution was stirred for 16 h at 80 °C. The solution was washed with saturated K_2CO_3 and extracted with EtOAc (3 x 20 mL). After evaporating EtOAc, resultant solid particles are washed with 10 mL of methanol and 30 mL of water (methanol was added if the solution becomes white till it becomes clear again). Solution was left for to recrystallize at 60 °C (77% yield). Mp = 120 °C. $[\alpha]^{25}_D$ = +42.5 (*c* 1.0,

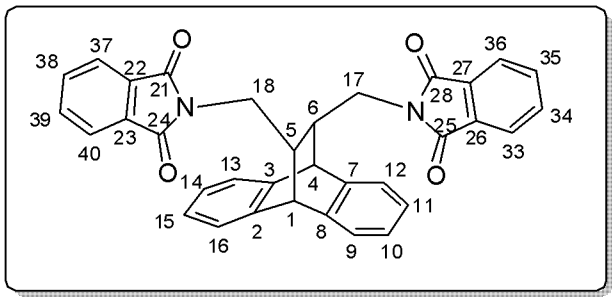
MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.02 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.10 – 7.01 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 4.35 (s, 2H, H_1-H_4), 2.49 (dd, J = 6.8, 1.9 Hz, 4H, H_{21a}-H_{24}a-H_{25a}-H_{28a}), 2.40 – 2.32 (m, 4H, H_{21b}-H_{24b}-H_{25b}-H_{28b}), 2.08 (dd, J = 11.8, 9.8 Hz, 2H, H_{17a}-H_{19a}), 1.94 (dd, J = 11.8, 4.3 Hz, 2H, H_{17b}-H_{19b}), 1.82 – 1.70 (m, 8H, H_{22}-H_{23}-H_{26}-H_{27}), 1.46 – 1.33 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 141.6, 125.6, 125.6, 125.2, 123.1, 61.0, 54.5, 46.7, 44.4, 23.7. HRMS calc. for $C_{26}H_{32}N_2$ $[M+H]^+$: 373.2565, found $[M+H]^+$: 373.2655.

4.10. Synthesis of *trans*-11,12-bis(methansulfonamide)-9,10-dihydro-9,10-ethano-anthracene, (+)-33



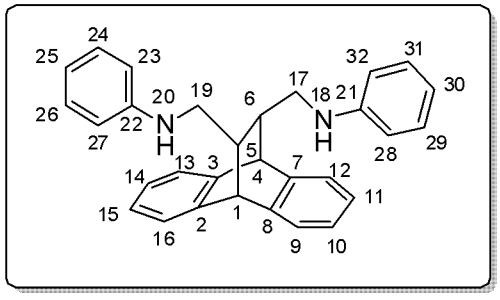
To a solution of 1,4-diamine (300 mg, 1 mmol) and THF (15 mL) add $N(Et)_3$ (0.45 mL, 3 mmol) and reflux for 2 h. After reflux was completed, add MsCl (0.19 mL, 2 mmol) and stir for 24 h at room temperature. After reaction was completed, saturated $NaHCO_3$ was added to get rid of possible acid products and solution was extracted with CH_2Cl_2 and organic layer dried over with $MgSO_4$. Evaporate organic layer and purify resultant solid by column chromatography, use EtOAc:Hexane (4:1) as an eluent. Chemical yield was 19%. Mp = decomposed at 136 °C. $[\alpha]^{25}_D$ = -4.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.12 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.08 – 6.95 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 5.21 (s, 2H, H_{18}-H_{20}), 4.14 (s, 2H, H_1-H_4), 2.86-2.80 (m, 2H, H_{17a}-H_{19a}), 2.81 (s, 6H, H_{24}-H_{26}) 2.62 – 2.51 (m, 2H, H_{17b}-H_{19b}), 1.67 – 1.62 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 139.9, 126.5, 126.1, 125.3, 123.7, 47.8, 46.8, 45.0, 40.0. HRMS calc. for $C_{20}H_{24}N_2O_4S_2$ $[M+H]^+$: 421.1177, found $[M+H]^+$: 421.1240.

4.11. Synthesis of *trans*-11,12-bis(methanphthalimide)-9,10-dihydro-9,10-ethano-anthracene, (-)-29



To a solution of 1,4-dimesylate (1.28 g, 6 mmol) and 13 mL DMF was K-Phthalimide was and stirred for 16 h at 100 °C. After 16 h medium was cooled down to room temperature and poured onto 50 mL of water. Resultant milky suspension was extracted with CH_2Cl_2 (3x25 mL). Organic layer then dried over with anhydrous $MgSO_4$ and evaporated and concentrated on *vacuo*. Purification was done with column chromatography using EtOAc:Hexane (1:2) as eluent. Chemical yield is calculated as 52%. Mp = decomposed at 258 °C. $[\alpha]^{25}_D$ = 1.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.65 – 7.58 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 7.27 (dd, *J* = 99.3, 7.0 Hz, 4H, H_{34}-H_{35}, H_{38}-H_{39}), 7.11 – 6.99 (m, 4H, H_{33}-H_{36}-H_{37}-H_{40}), 4.04 (s, 2H, H_1-H_5), 3.35 (dd, *J* = 13.8, 7.5 Hz, 2H, H_{17a}-H_{18a}), 3.30 (dd, *J* = 13.8, 5.5 Hz, 2H, H_{17b}-H_{18b}), 1.99 – 1.85 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 142.4, 138.7, 132.7, 131.1, 125.4, 125.2, 124.8, 122.2, 122.1, 45.7, 42.9, 40.8. HRMS calc. for $C_{34}H_{24}N_2O_4$ $[M+H]^+$: 525.1736, found $[M+H]^+$: 525.1836.

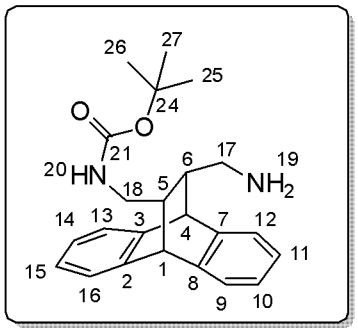
4.12. Synthesis of *trans*-11,12-bis(methananiline)-9,10-dihydro-9,10-ethano-anthracene, (-)-27



To a solution of 1,4-triflate (1 g, 2 mmol) in 40 mL THF aniline (0.34 mL, 4 mmol) was added. After solution was stirred for 10 mins, NEt_3 (0.68 mL, 5 mmol) was added to the solution and stirred for 48 h.

After reaction was completed solution was extracted with 2M HCl (2x20 mL) and organic layer was dried over with anhydrous $MgSO_4$ and evaporated. Purification was done by column choromatography with EtOAc:Hexane (1:9) as eluent (chemical yield was 23%). Mp = 129 °C. $[\alpha]^{25}_D$ = -9.5 (*c* 0.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.11 – 6.97 (m, 8H, H_{10}-H_{11}-H_{14}-H_{15}-H_{24}-H_{26}-H_{29}-H_{31}), 6.58 (t, J = 7.3 Hz, 2H, H_{25}-H_{30}), 6.36 (dd, J = 8.4, 0.8 Hz, 4H, H_{23}-H_{27}-H_{28}-H_{32}), 4.18 (d, $J_{4,1}$ = 1.4 Hz, 2H, H_1-H_4), 3.81 (s, 2H, H_{18}-H_{20}), 2.86 (dd, J = 12.7, 6.4 Hz, 2H, H_{17a}-H_{19a}), 2.56 (dd, J = 12.7, 7.4 Hz, 2H, H_{17b}-H_{19b}), 1.87 – 1.68 (m, 2H, H_5-H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 143.2, 140.9, 129.3, 126.2, 125.8, 125.2, 123.6, 117.6, 112.8, 49.2, 47.6, 44.4. HRMS calc. for $C_{30}H_{28}N_2$ $[M+H]^+$: 417.2252, found $[M+H]^+$: 417.2319

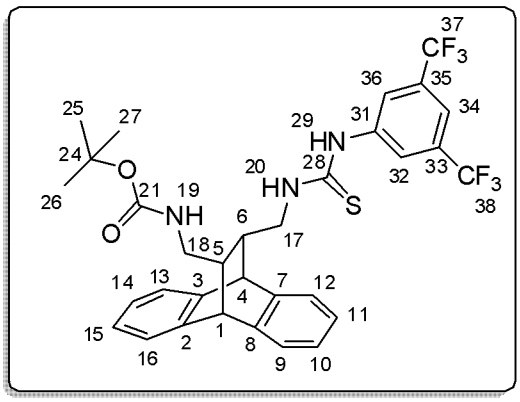
4.13. Synthesis of mono-protected 1,4-diamine, 34



1,4-diamine (530 mg, 2 mmol) was dissolved in MeOH (8 mL) and stirred for 10 mins. Solution was cooled down to 0 °C and 3N HCl (0.7 mL) was added and stirred for another 15 mins at room temperature. 0.2 mL water was added to the solution and stirred for 30 mins. At the end of 30 mins, $(BOC)_2O$ (3 mmol) dissolved in MeOH (1.3 mL) was added to the solution slowly at room temperature and stirred for another 2 h. Solution was then evaporated and extracted with ether to get rid of unreacted diamine. Residue was treated with 2N NaOH and water layer was extracted with DCM (4x15mL). Organic layer was dried over with anhydrous $MgSO_4$. Purification was done with column chromatography with eluent EtOAc:NEt_3 (95:5). Chemical yield was 16%. $[\alpha]^{33}_D$ = -6.4 (*c* 0.5, DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.08 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.05 – 6.94 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 5.86 (s, 1H, H_{20}), 4.07 (d, J = 1.7 Hz, 1H, H_1), 4.04 (d, J = 1.4 Hz, 1H, H_4), 2.84 (ddd, J = 12.2, 6.4, 5.2, 1H, H_{18a}), 2.51 (m, 2H, H_{17a}-H_{17b}), 2.03 (dd, J = 12.5, 8.7 Hz, 1H, H_{18b}), 1.60 – 1.51 (m, 1H, H_5), 1.34 (s, 9H, H_{25}-H_{26}-H_{27}), 1.25 (bs, 2H,

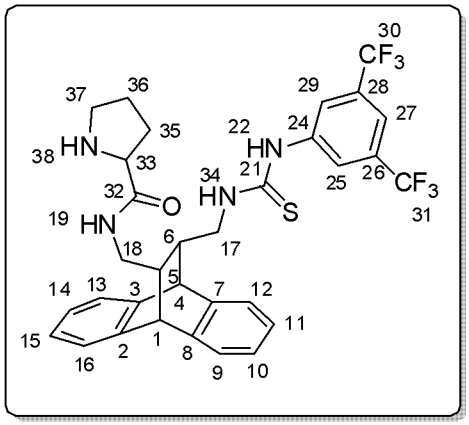
H_{19}), 1.19 (t, J = 7.1 Hz, 1H, H_6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 142.3, 142.2, 139.7, 139.6, 125.0, 124.9, 124.7, 124.5, 124.1, 123.8, 122.3, 122.2, 46.7, 46.5, 46,4, 45.8, 45.7, 43.5, 27.4 (C_{25}-C_{26}-C_{27}).

4.14. Synthesis of 1,4-*t*-boc-thiourea, 35



To a solution of mono protected 1,4-diamine (290 mg, 0.8 mmol) and DCM (10 mL) isothiocyanate (218 mg, 0.8 mmol) was slowly added. Reaction was left for overnight and solvent were evaporated. By using flush chromatography with EtOAc:Hexane (1:6) as eluent the product was purified in 56% chemical yield. $[\alpha]^{33}_D$ = -45.8 (*c* 0.5, DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (bs, 1H, H_{19}), 8.03 (s, 2H), 7.43 (s, 1H), 7.24 – 7.14 (m, 4H, H_9-H_{12}-H_{13}-H_{16}), 7.07 – 7.00 (m, 4H, H_{10}-H_{11}-H_{14}-H_{15}), 5.30 (bs, 1H, H_{29}), 4.35 (bs, 1H, H_{20}), 4.06 (d, J = 1.3 Hz, 1H, H_1), 4.03 (d, J = 1.3 Hz, 1H, H_4), 2.95 (dd, J = 13.8, 5.0 Hz, 1H, H_{17a}), 2.47 (m, 1H, H_{17b}), 2.31 (d, J = 5.7 Hz, 2H), 1.67 (dd, J = 10.5, 5.3 Hz, 1H, H_{18a}), 1.61 – 1.52 (m, 1H, H_{18b}), 1.40 (s, 9H, H_{25}-H_{26}-H_{27}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 156.8, 141.9, 140.1, 139.0, 125.5, 125.3, 125.1, 124.9, 124.5, 124.3, 122.6, 122.2, 120.4, 80.1, 47.9, 46.3, 45.7, 45.1, 44.2, 42.5, 27.3.

4.15. Synthesis of 1,4-proline-thiourea, (-)-38



To a solution of 1,4-*t*-boc-thiourea (122 mg, 0.192 mmol) and DCM (10 mL) TFA (22 mg, 2mmol) was added and stirred 12 h at room temperature. After reaction was completed, remaining acid and solvents were evaporated and remaining solid was dissolved in DCM. DMAP (0.160 mmol) was added to the solution and stirred for 10 mins at room temperature. N-boc proline (0.2 mmol) was added to the solution and stirred for another 10 mins. After 10 mins, DCC (0.2 mmol) was added to the solution and stirred for 24 h at room temperature. After completion, solution was filtered and washed with DCM (5 mL) to get rid of urea from DCC. Solid particles were dissolved in DCM and TFA was added and stirred 12 h at room temperature. After reaction was completed, remaining acid and solvents were evaporated. Crude product was dissolved in $NaHCO_3$ and extracted with DCM (4x 15 mL) and organic layer was evaporated. Purification was done with flush chromatography with eluent EtOAc:NEt_3 (95:5). (Chemical yield: 80%) $[\alpha]^{35}_D$ = -19.2 (*c* 1.0, DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (bs, 1H), 8.04 (s, 2H), 7.45 (s, 1H), 7.26 – 7.15 (m, 4H), 7.05 – 6.99 (m, 4H), 4.07 (d, J = 1.4 Hz, 1H), 4.04 (dd, J = 14.3, 7.2 Hz, 1H), 3.96 (d, J = 1.6 Hz, 1H), 3.65 (dd, J = 9.0, 5.2 Hz, 1H), 3.01 – 2.95 (m, 2H), 2.94 (s, 1H), 2.10 – 2.02 (m, 1H), 1.96 (s, 1H), 1.85 – 1.73 (m, 2H), 1.70 (dd, J = 13.5, 6.7 Hz, 2H), 1.55 – 1.48 (m, 1H), 1.18 (t, J = 7.1 Hz, 2H), 1.10 – 1.03 (m, J = 14.5, 8.1, 1.9 Hz, 1H), 0.94 – 0.73 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.5, 176.1, 130.5 (q, J = 33.2 Hz), 125.4, 125.3, 125.1, 124.9, 124.5, 124.3, 122.5, 122.0, 121.5, 121.4, 59.3, 47.9, 46.4, 46.2, 46.2, 44.7, 43.0, 42.7, 29.7, 25.1, 13.2. HRMS calc. for $C_{32}H_{30}F_6N_4OS$ $[M+H]^+$: 633.2045, found $[M+H]^+$: 633.2120.

4.16. General procedure for the asymmetric transfer hydrogenation reaction

Co-catalyst dissolved in 2-propanol was added to a 30 mins stirred solution of the catalyst and Ir(COD)Cl in 2-propanol under argon at the room temperature and stirred for another 10 mins. Acetophenone was added to the medium and reaction was stirred for desired time at desired temperature. The reaction was monitored with TLC (EtOAc:Hexane 1:8 as eluent). After completion the reaction was ended with 1M HCl and extracted with diethyl ether (3x30 mL). Solution was dried over with anhydrous MgSO4 and evaporated. Flush chromatography was used to purify with eluent EtOAc:Hexane (1:8). HPLC analysis of phenylethanol: Chiralcel OJ-H at room temperature, *n*-hexane/2-propanol = 90:10, 1.0 mL/min, 215 nm, t_R = 12.2 min, t_S = 14.2 min.

4.17. General procedure for the aldol reaction

To a solution of catalyst (0.01 mmol) in water (1.0 mL), the respective acid (0.01 or 0.02 mmol) was added. *p*-Nitrobenzaldehyde (75 mg, 0.5 mmol) and acetone (2.0 mL) were added at room temperature. The reaction was stirred at this temperature for 24 h. The reaction was monitored by TLC and quenched with saturated ammonium chloride solution (5 mL) on completion and extracted with CH_2Cl_2 (2x10 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to obtain crude product. Column chromatography of the crude on silica gel using mixture of ethyl acetate and hexane 1:2 as eluent, gave pure product. The enantiomeric excess of product was determined on HPLC using a Chiralcel OJ-H column and mixture of *n*-hexane and 2-propanol in ratio of 90:10 as eluents UV 254 nm, flow rate 1.0 mL/min. t_R = 23.3 min and t_S = 26.2 min.

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APPENDIX A

SUPPORTING INFORMATION

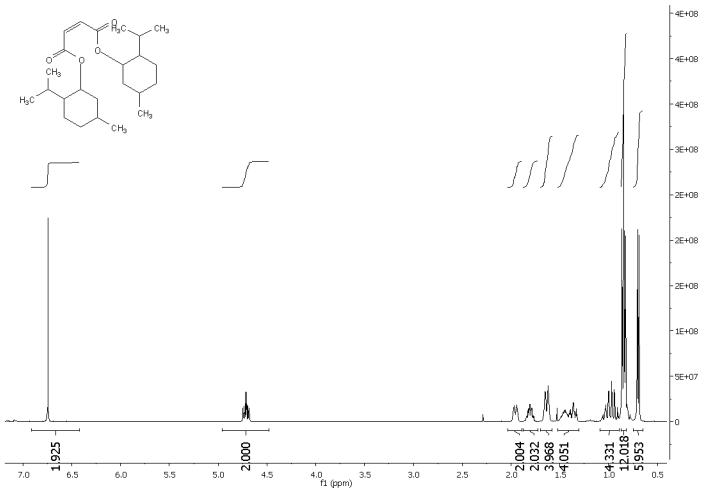

Figure A1. ^{1}H NMR Spectrum of dimenthyl maleate **21**

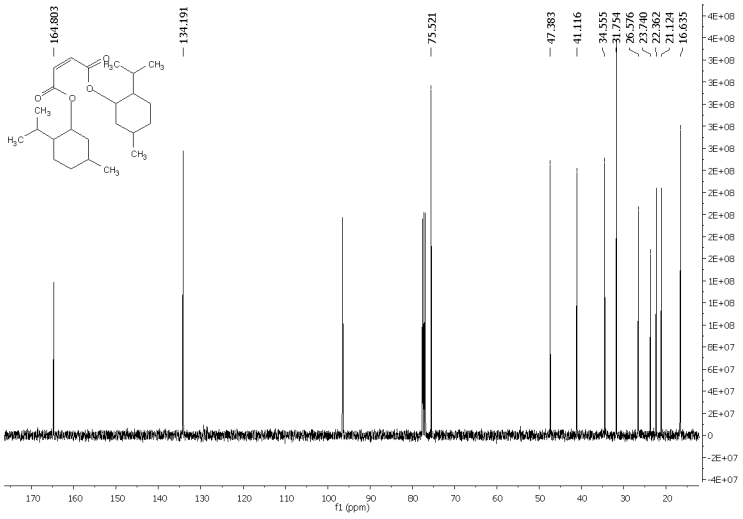

Figure A2. ^{13}C NMR spectrum of dimenthyl maleate **21**

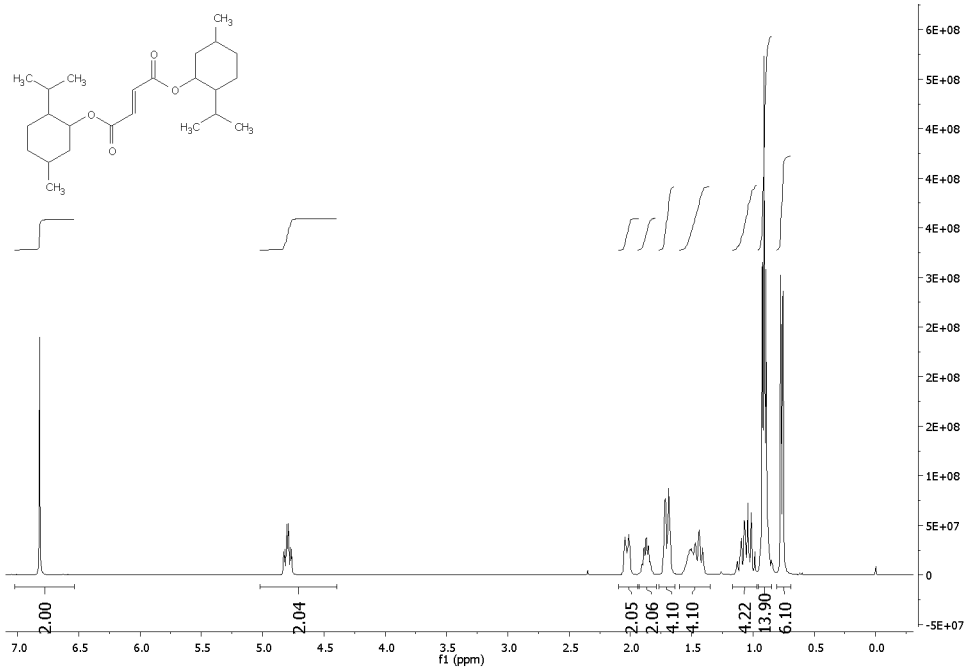

Figure A3. ^{1}H NMR spectrum of dimenthyl fumarate **22**

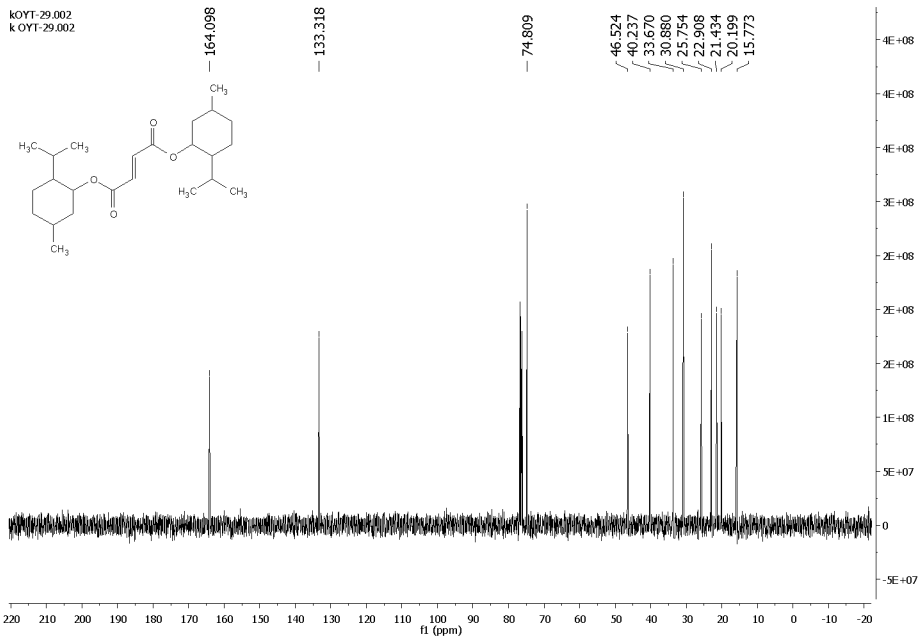

Figure A4. ^{13}C NMR spectrum of dimenthyl fumarate **22**

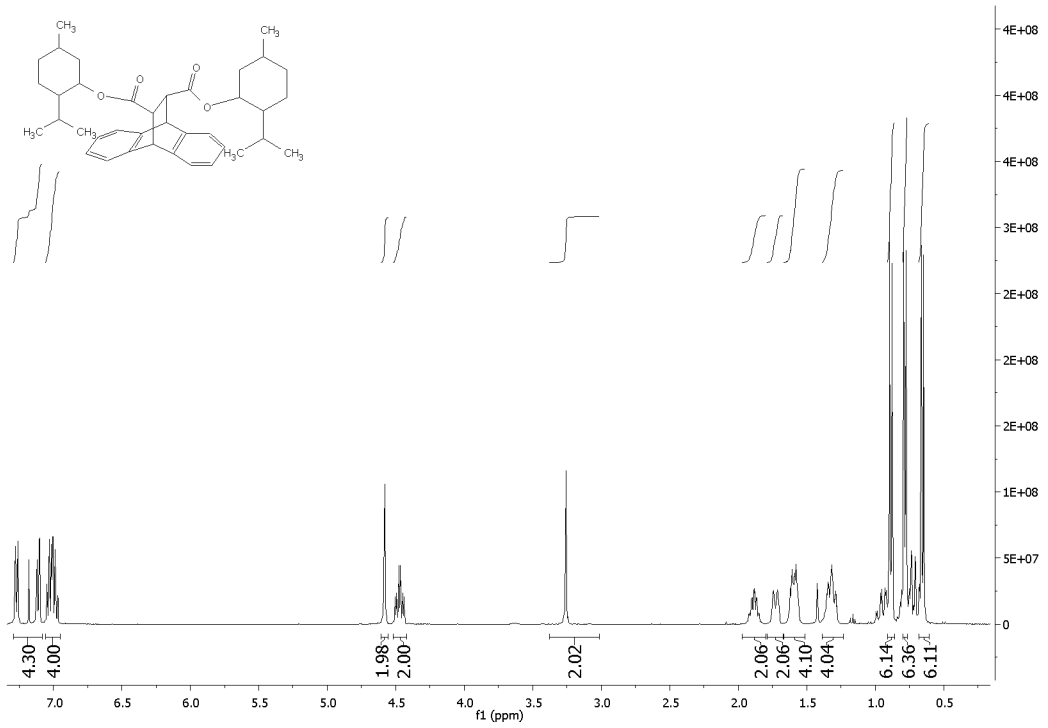

Figure A5. ^{1}H NMR spectrum of 1,4-dimenthyl **23**

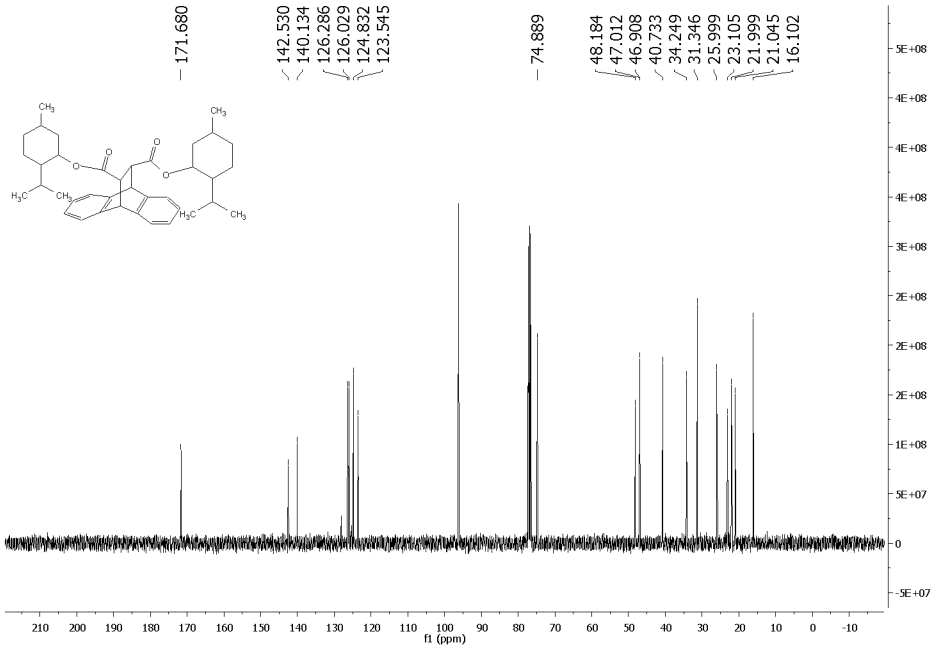

Figure A6. ^{13}C NMR spectrum of 1,4-dimenthyl **23**

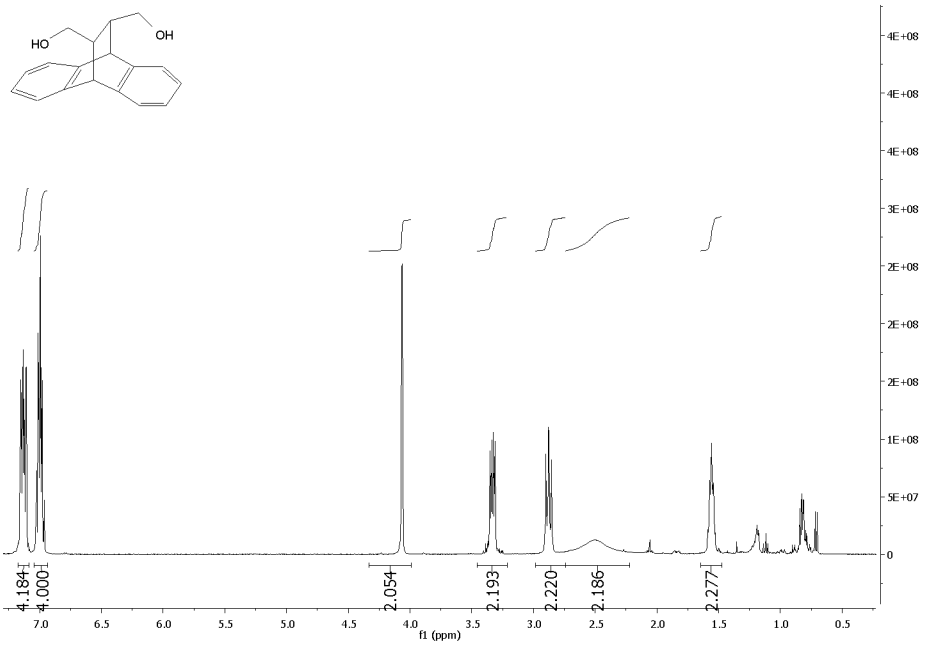

Figure A7. ^{1}H NMR spectrum of 1,4-diol **24**

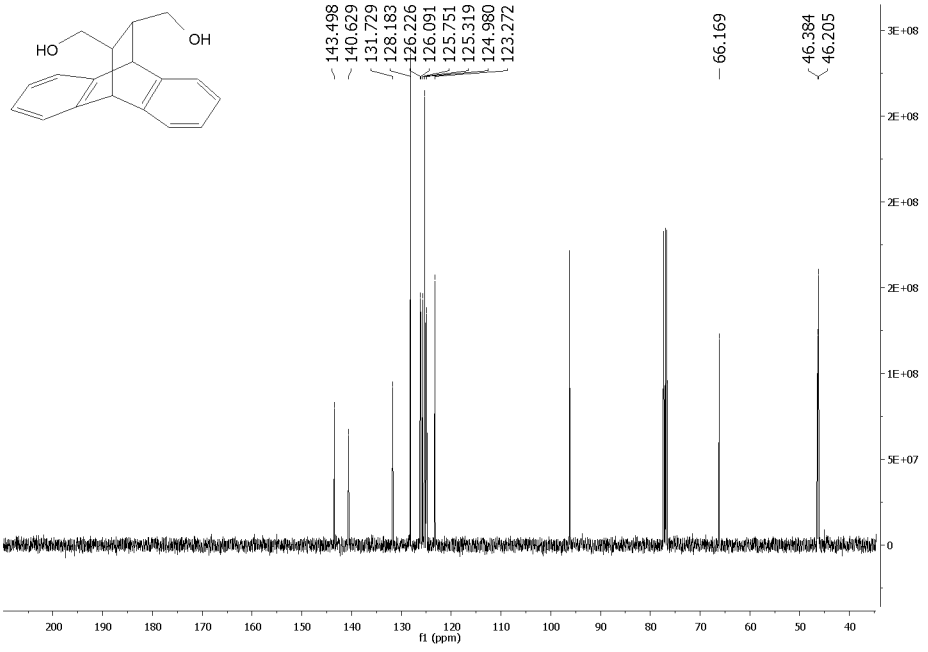

Figure A8. ^{13}C NMR spectrum of 1,4-diol **24**

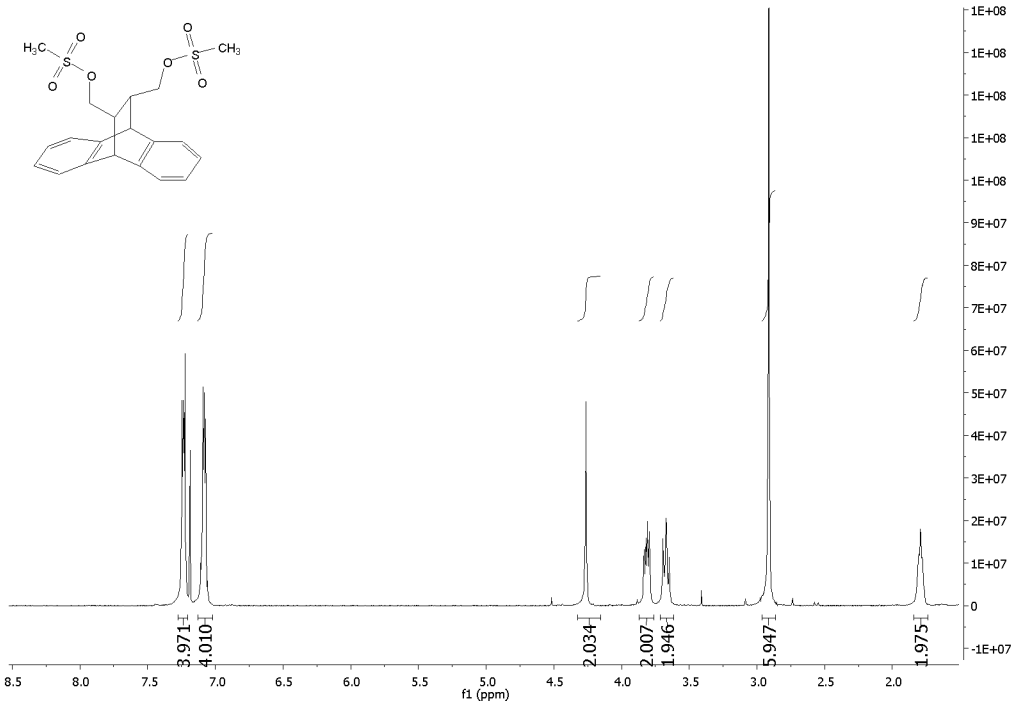

Figure A9. ^{1}H NMR spectrum of 1,4-dimesyl **25**

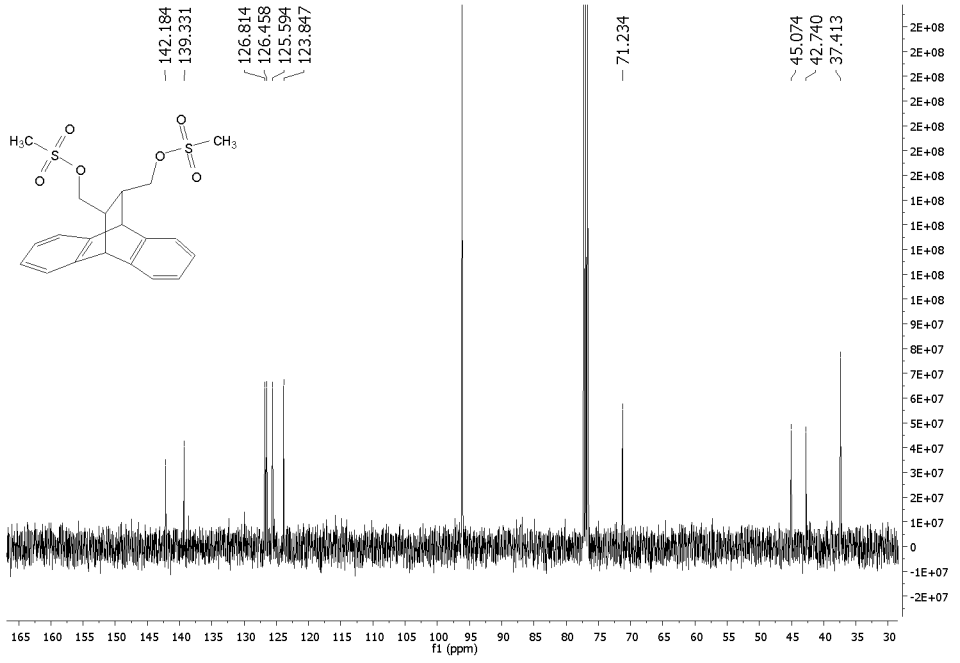

Figure A10. ^{13}C NMR spectrum of 1,4-dimesyl **25**

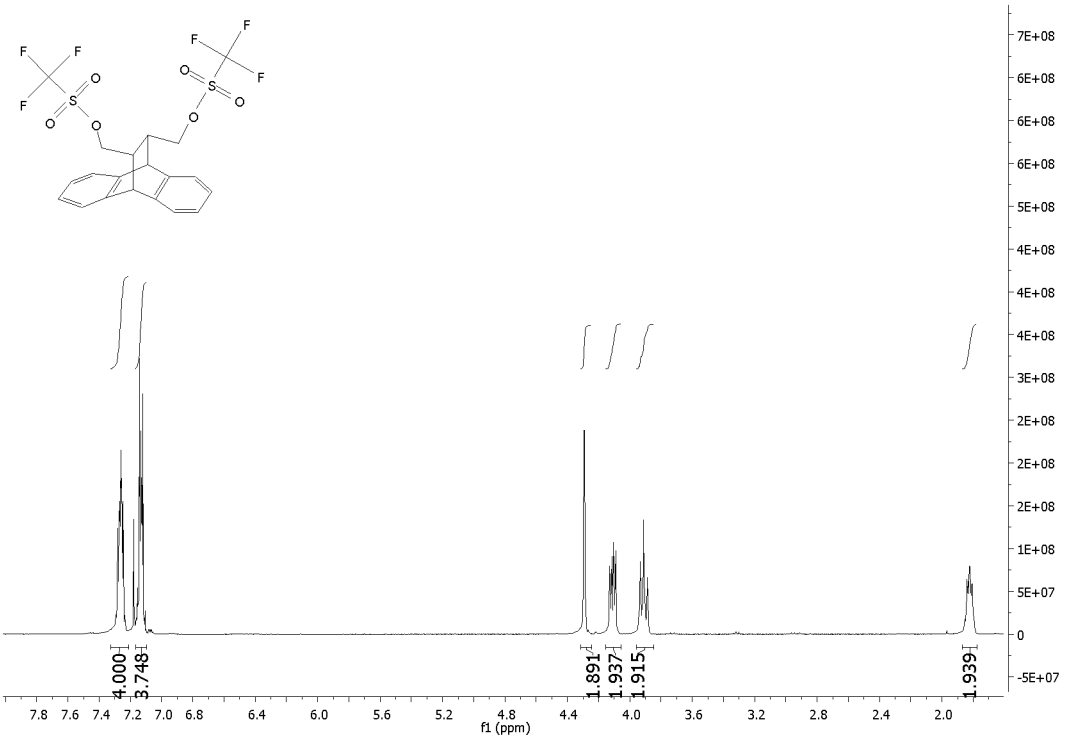

Figure A11. ^{1}H NMR spectrum of 1,4-ditriflate **26**

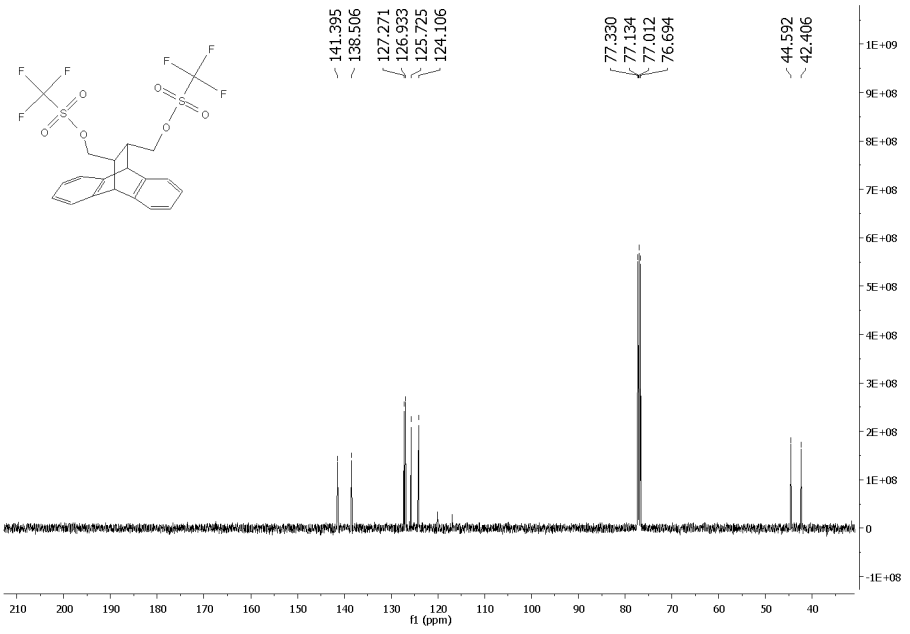

Figure A12. ^{13}C NMR spectrum of 1,4-ditriflate **26**

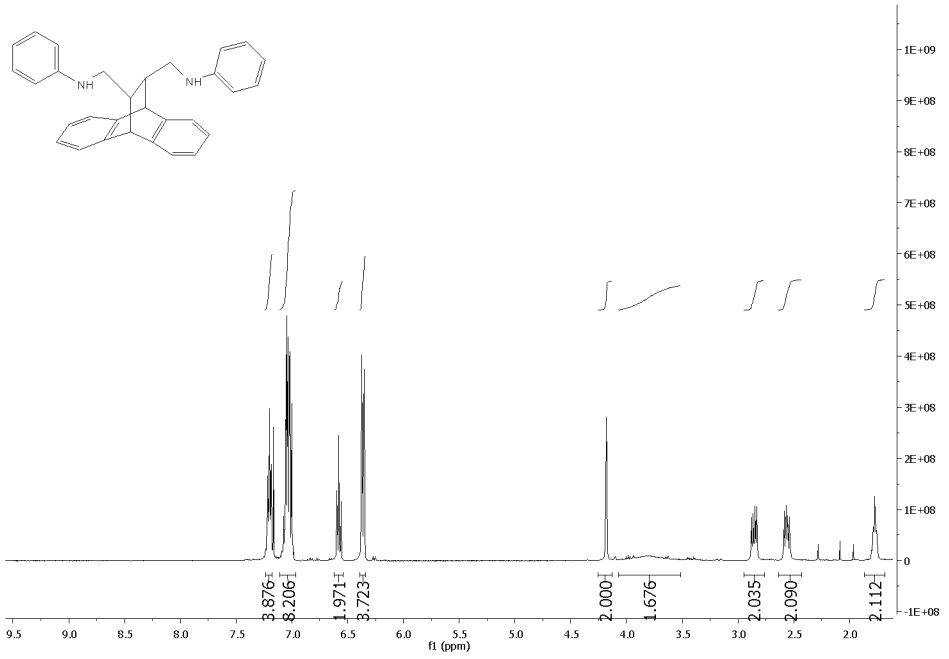

Figure A13. ^{1}H NMR spectrum of 1,4-dianiline **27**

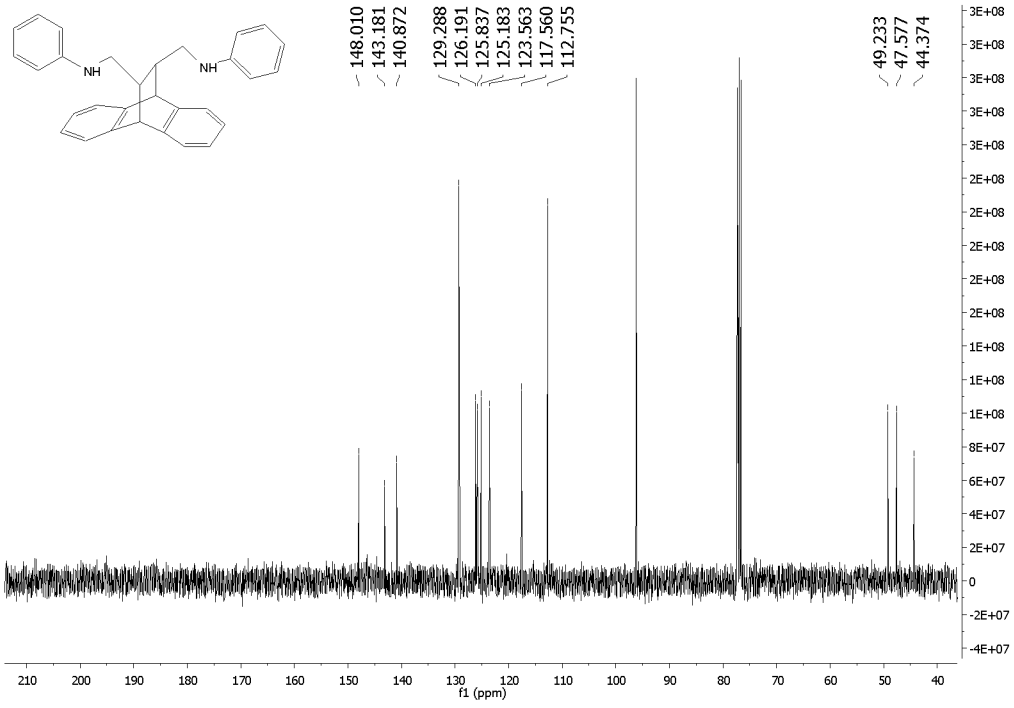

Figure A14. ^{13}C NMR spectrum of 1,4-dianiline **27**

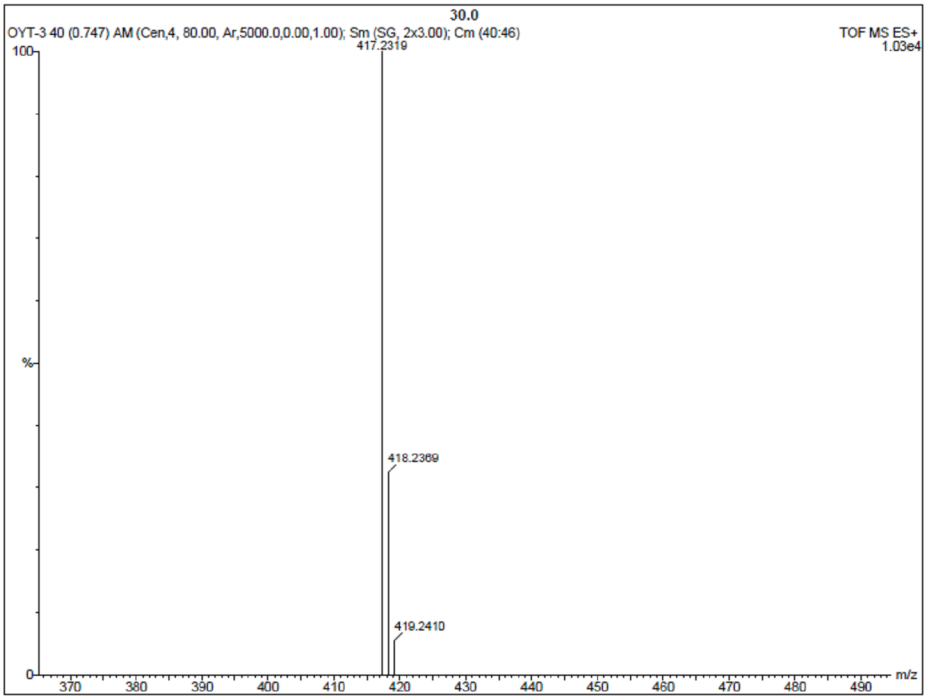

Figure A15. HRMS result of 1,4-dianiline **27**

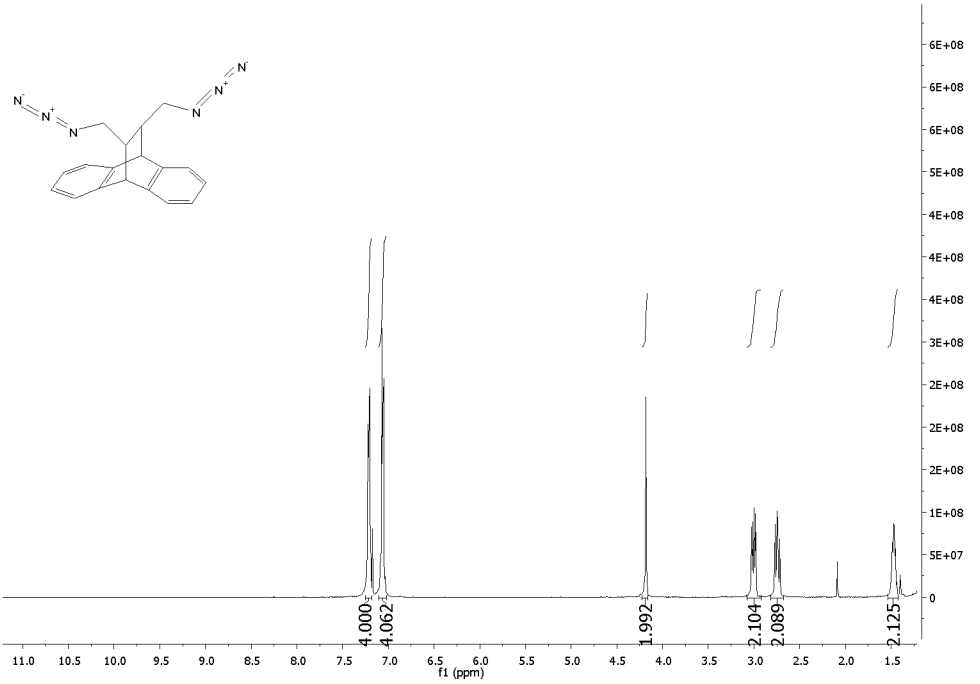

Figure A16. ^{1}H NMR Spectrum of 1,4-diazide **31**

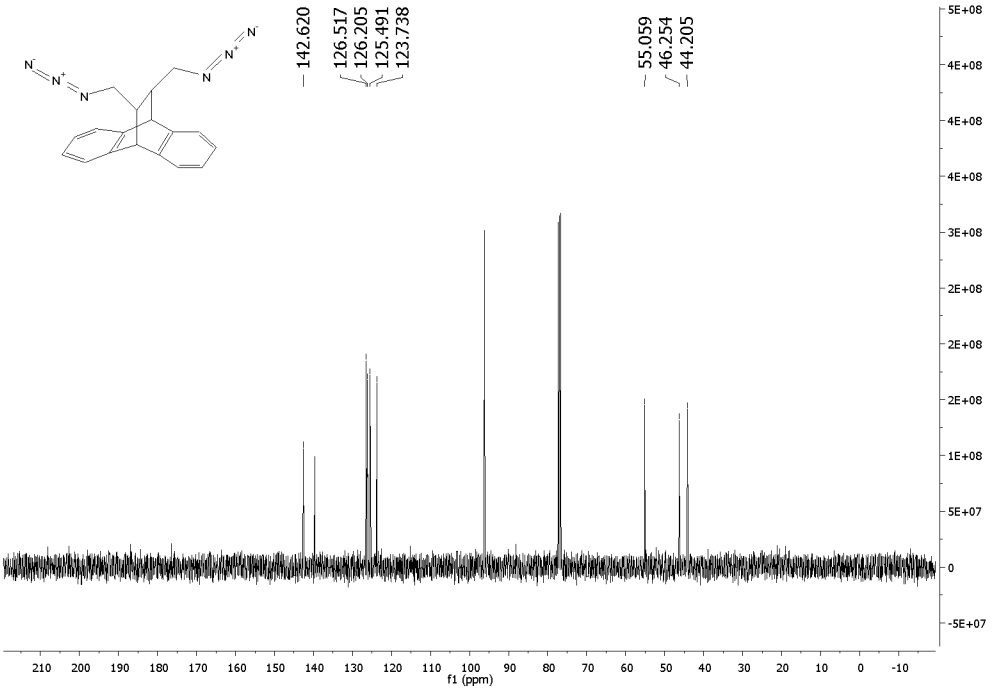

Figure A17. ^{13}C NMR spectrum of 1,4-diazide **31**

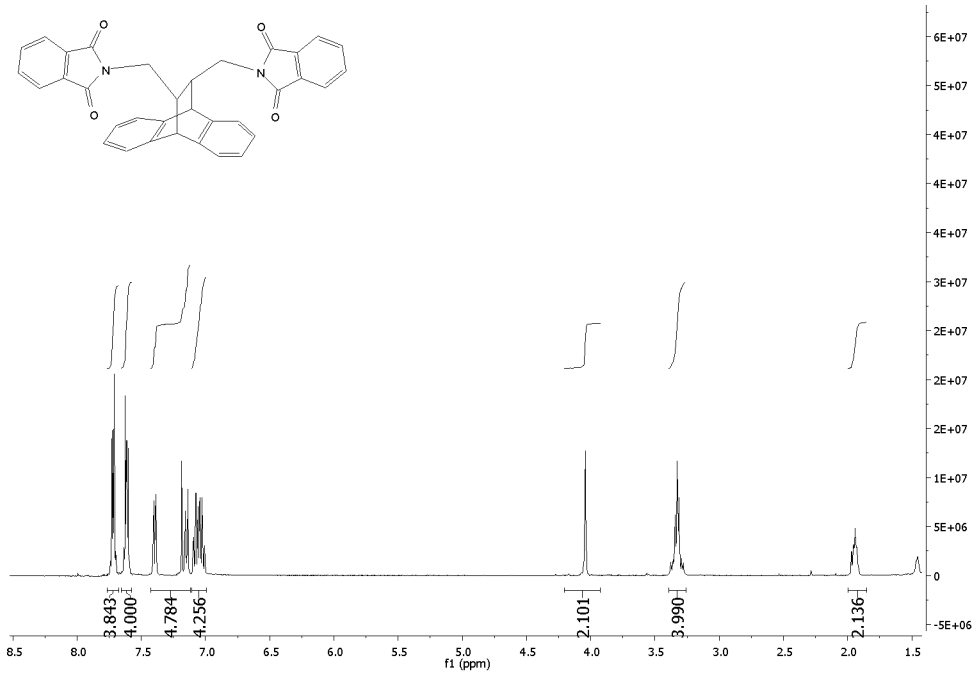

Figure A18. ^{1}H NMR Spectrum of 1,4-diphthalimide **29**

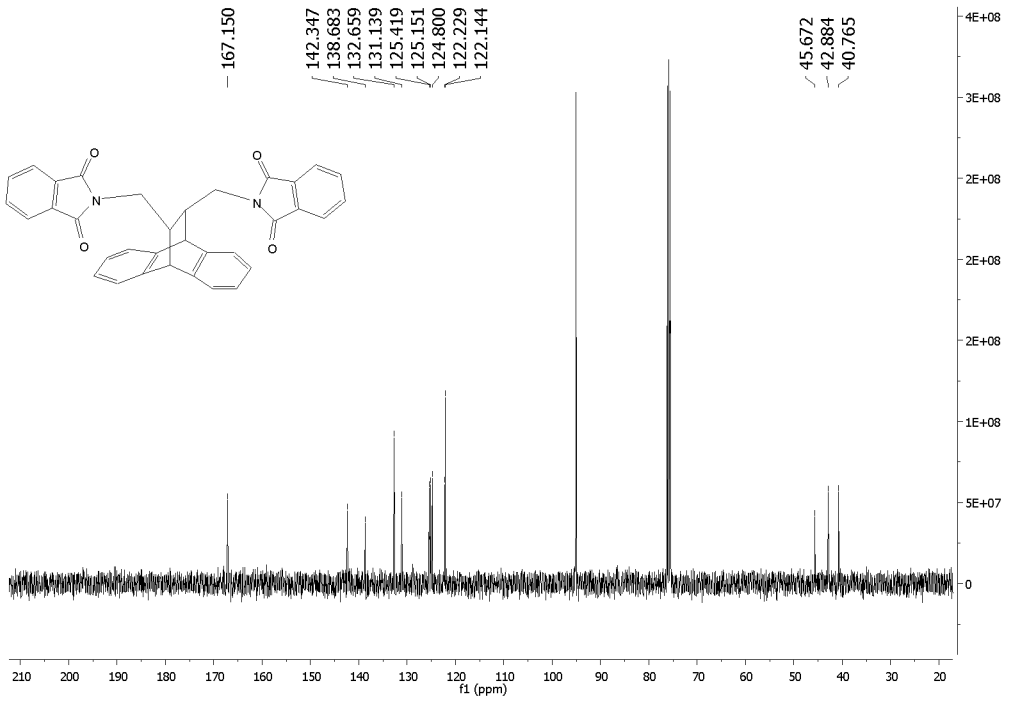

Figure A19. ^{13}C NMR Spectrum of 1,4-diphthalimide **29**

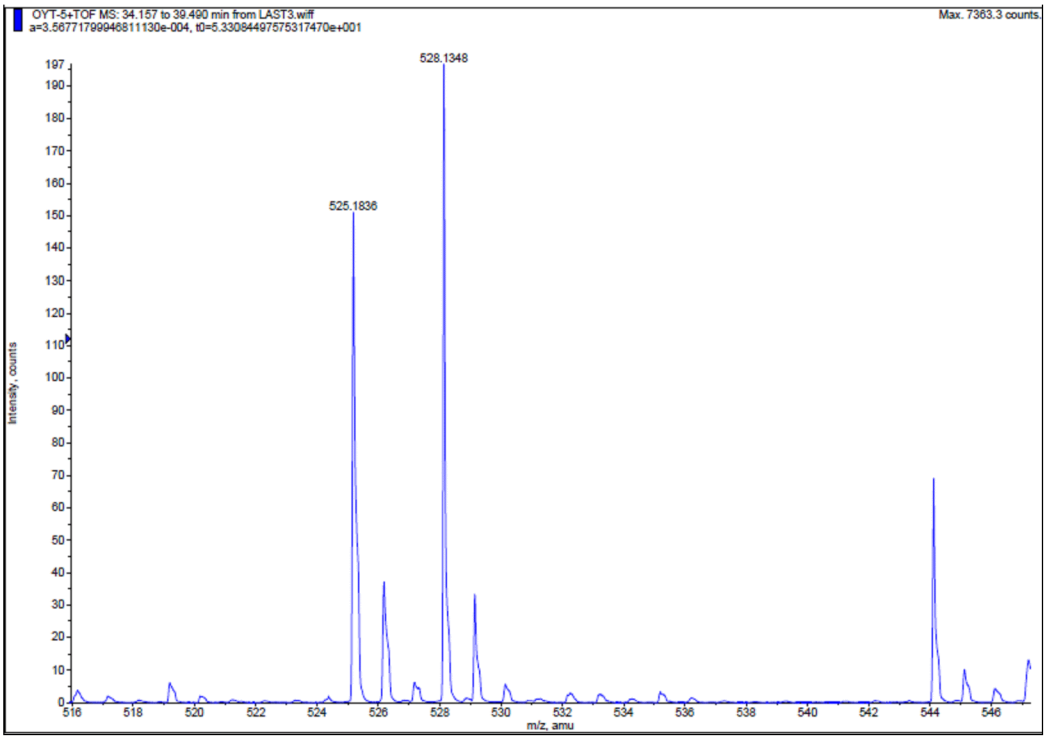

Figure A20. HRMS Result of 1,4-diphthalimide **29**

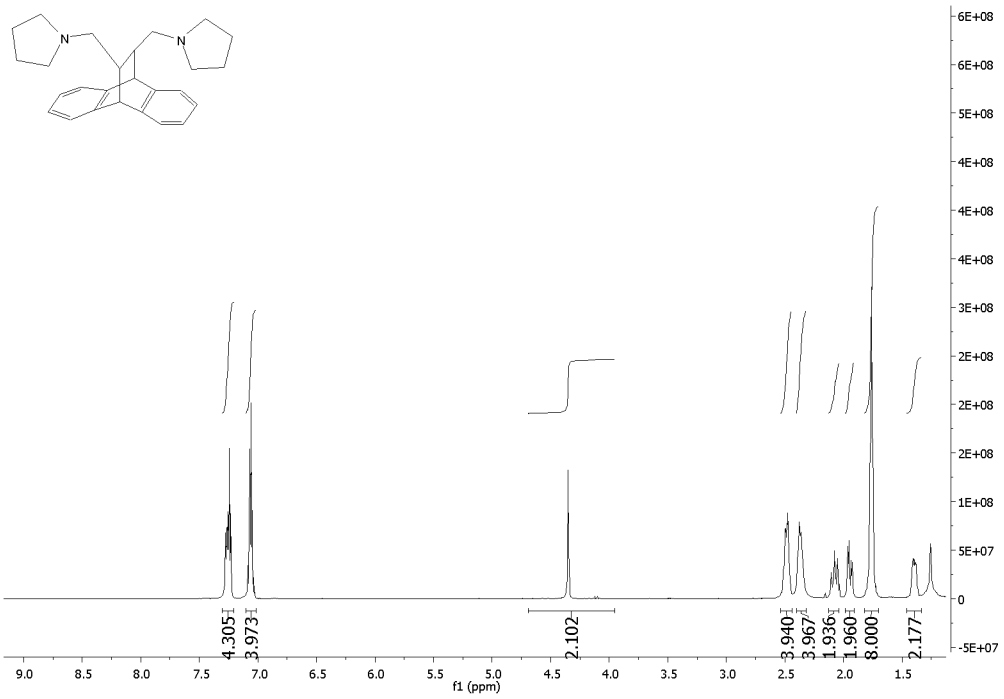

Figure A21. ^{1}H NMR Spectrum of 1,4-dipyrrolidine **30**

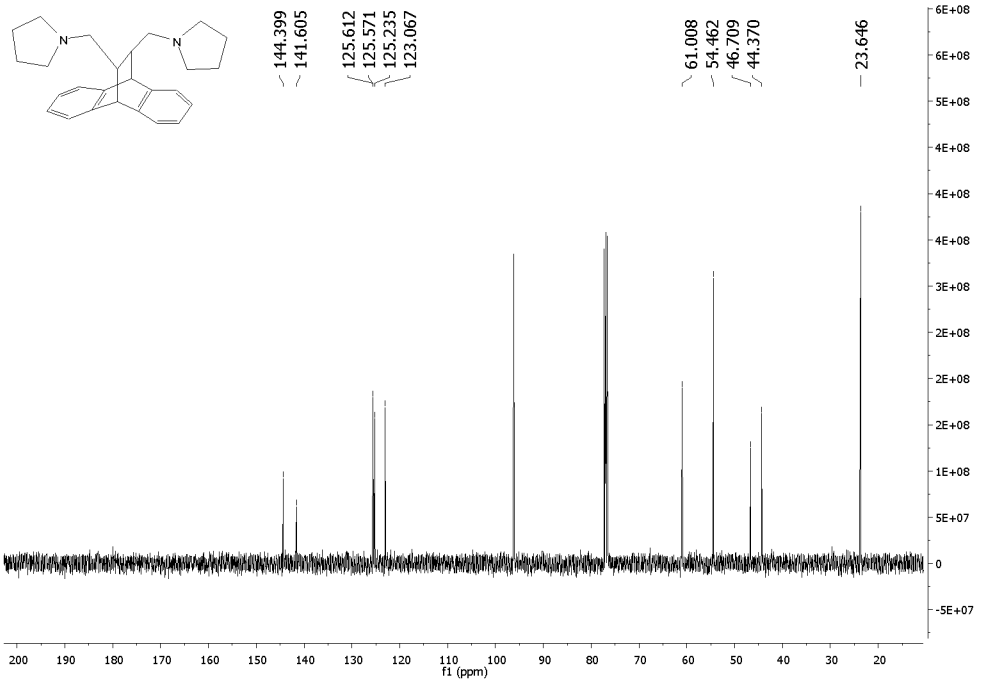

Figure A22. ^{13}C NMR Spectrum of 1,4-dipyrrolidine **30**

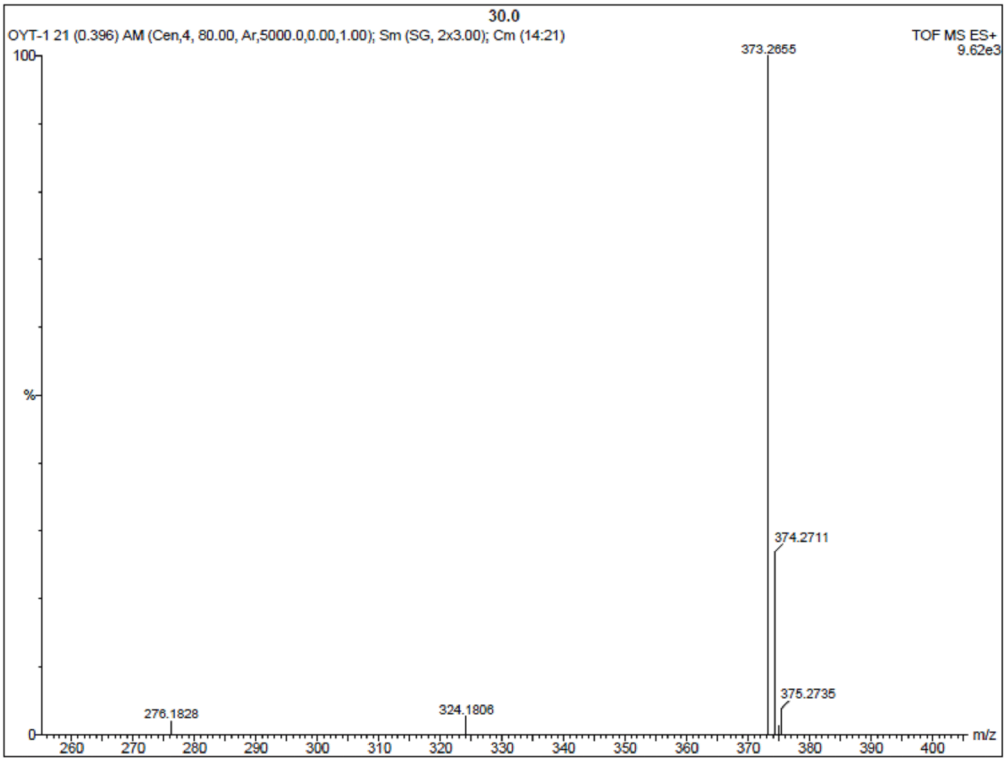

Figure A23. HRMS Result of 1,4-dipyrrolidine **30**

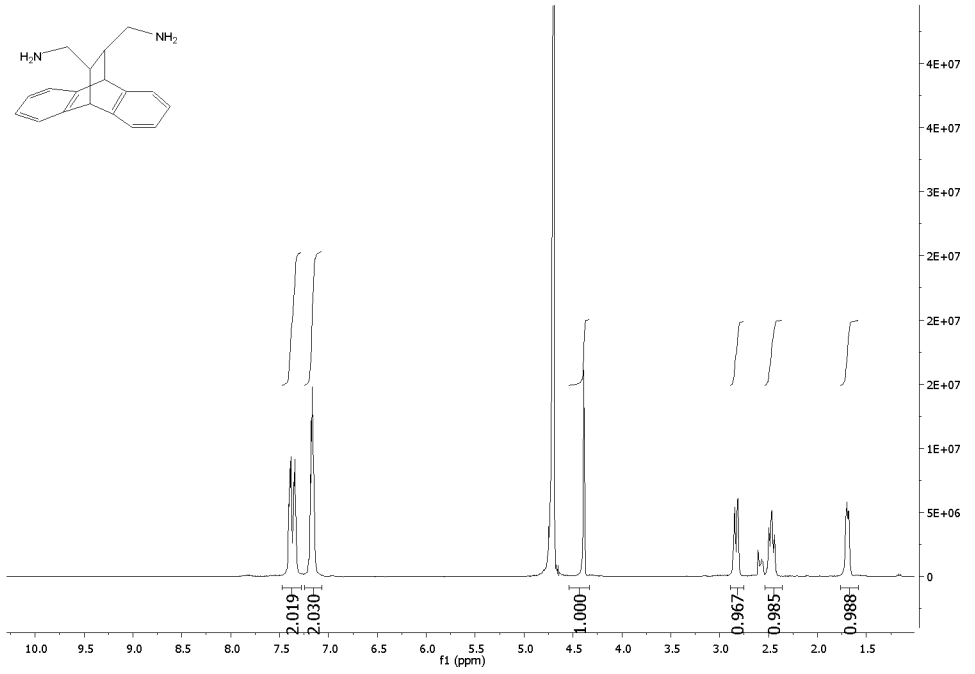

Figure A24. ^{1}H NMR Spectrum of 1,4-diamine **32**

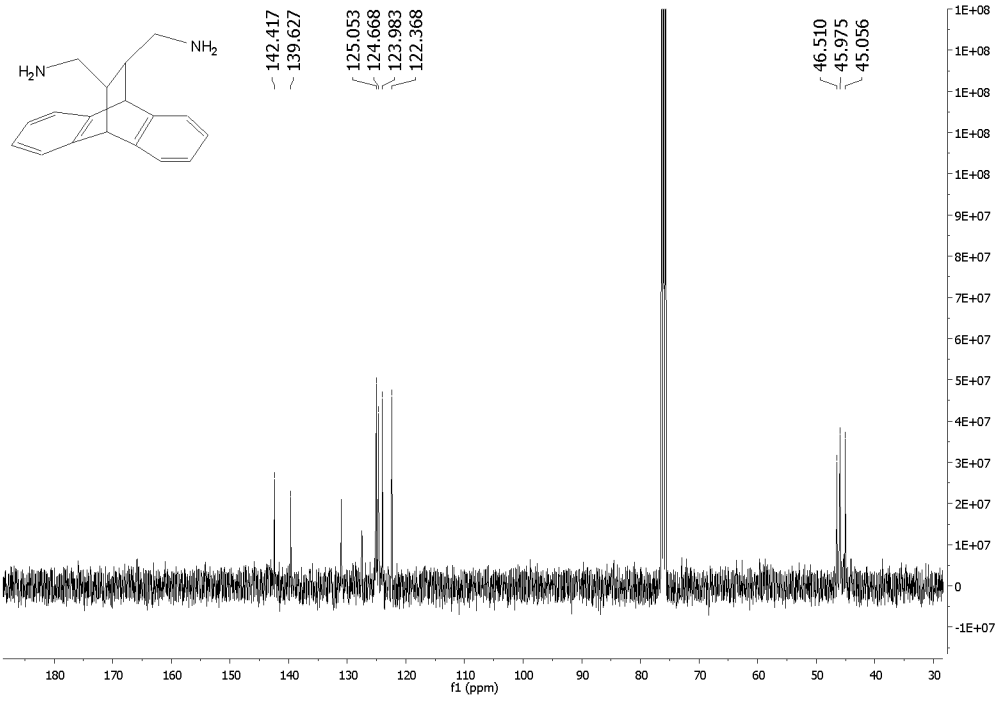

Figure A25. ^{13}C NMR Spectrum of 1,4-diamine **32**

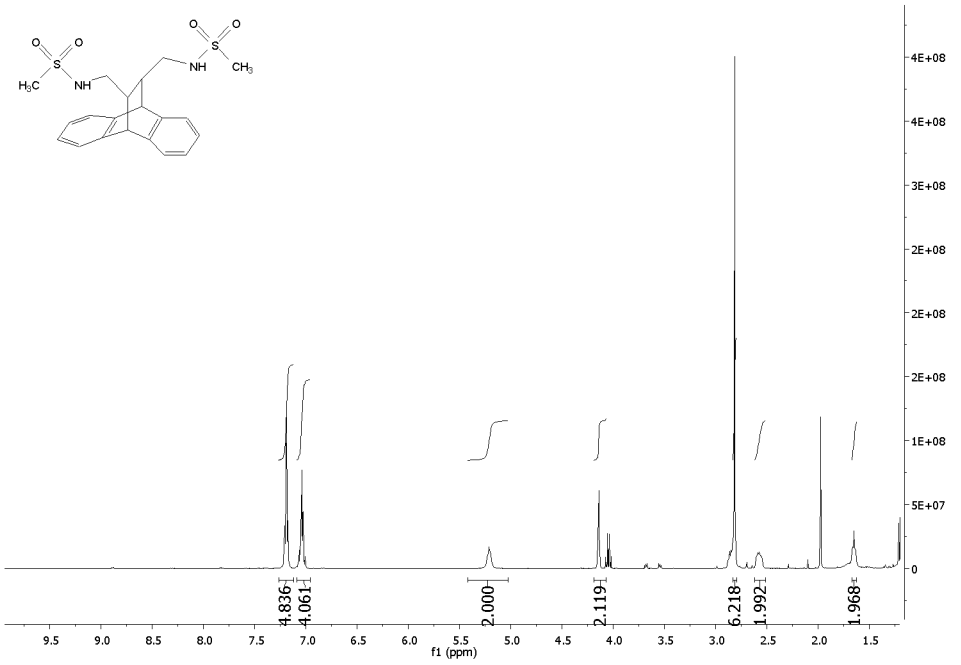

Figure A26. ^{1}H NMR Spectrum of 1,4-disulfonamide **33**

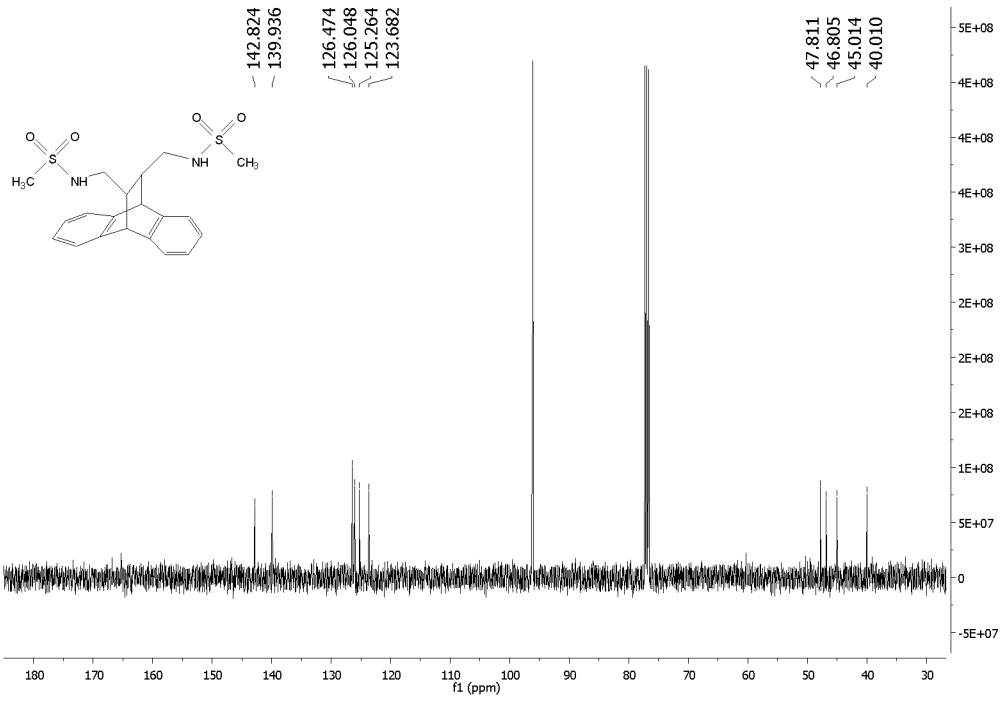

Figure A27. ^{13}C NMR Spectrum of 1,4-disulfonamide **33**

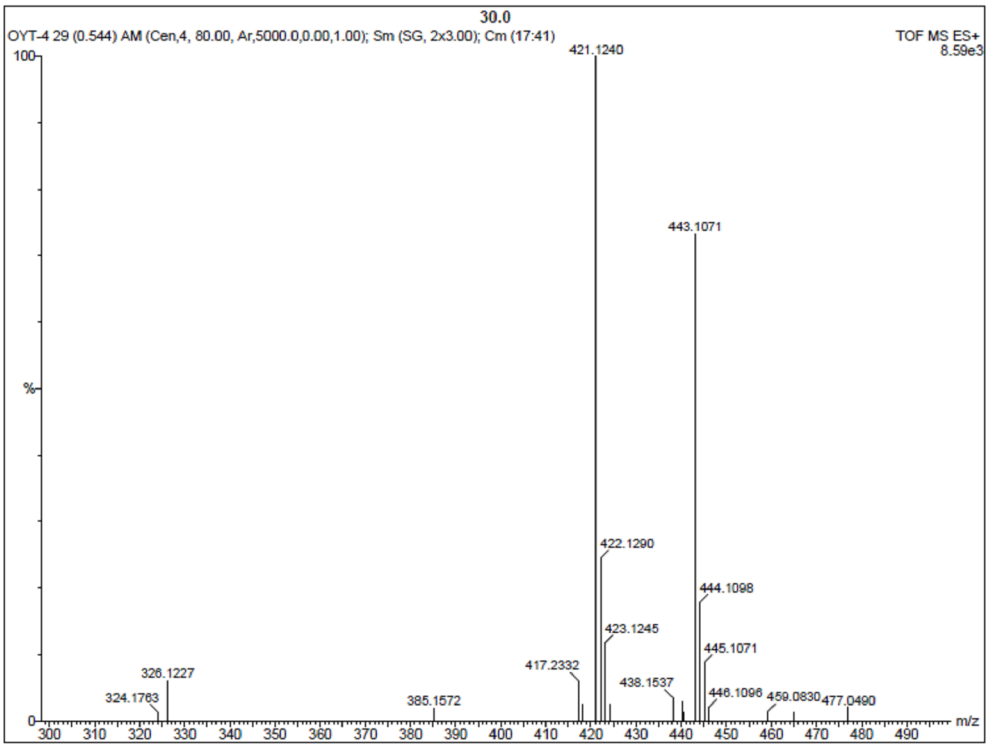

Figure A28. HRMS Result of 1,4-disulfonamide **33**

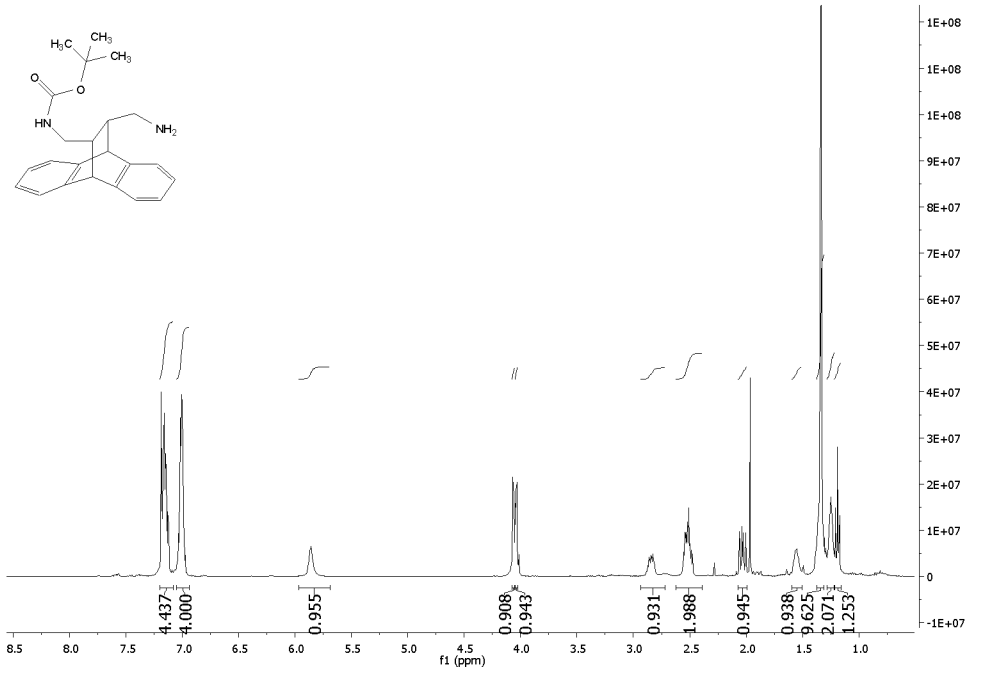

Figure A29. ^{1}H NMR Spectrum of mono-protected amine **34**

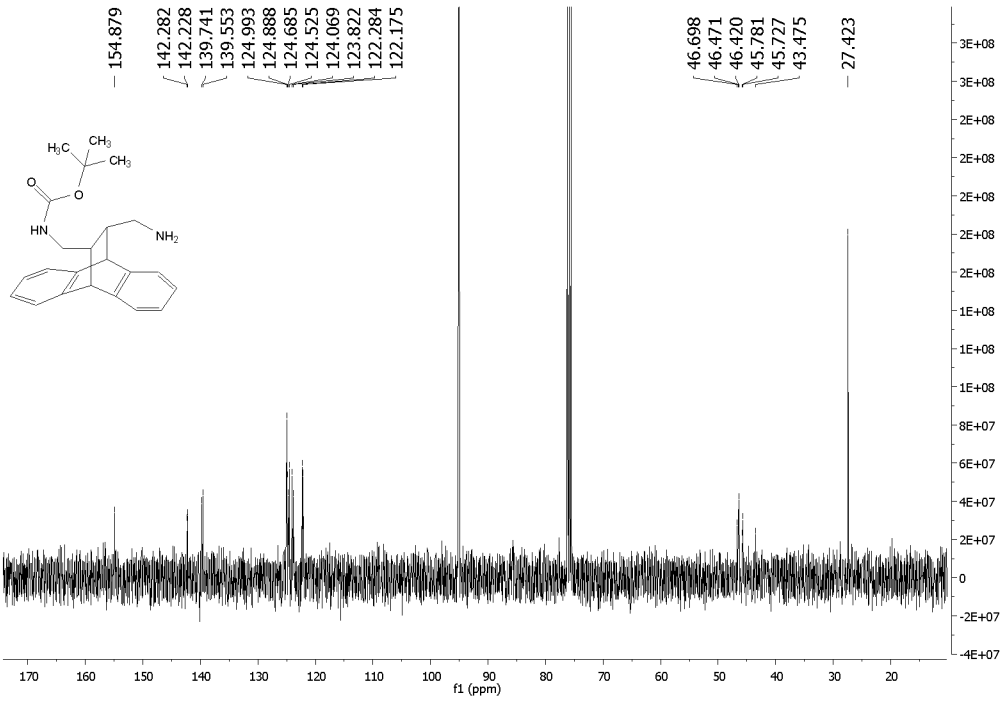

Figure A30. ^{11}C NMR Spectrum of mono-protected amine **34**

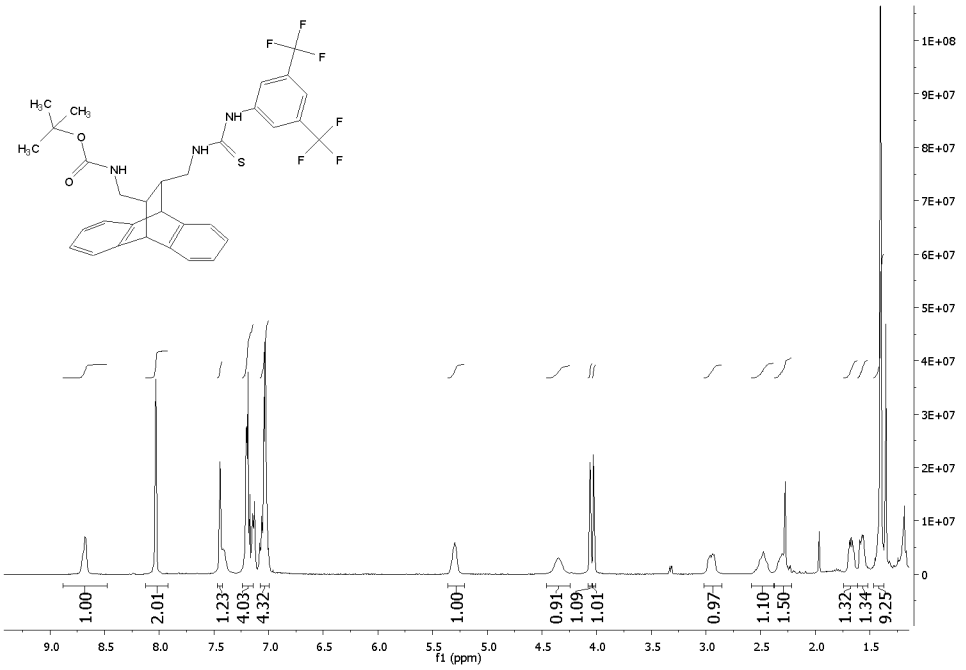

Figure A31. ^{1}H NMR Spectrum of t-boc&thiourea **35**

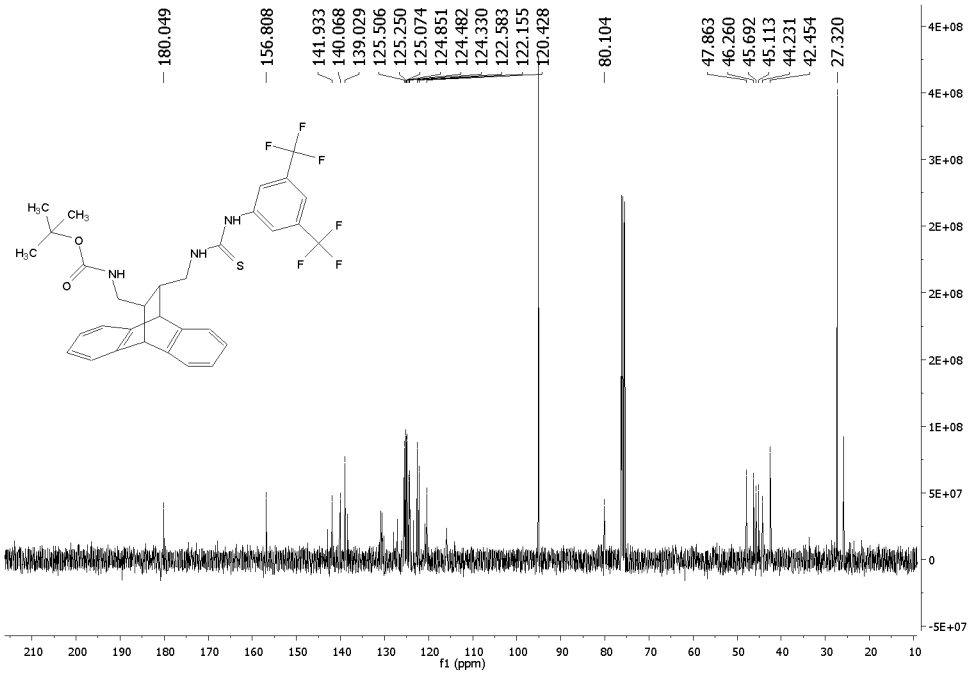

Figure A32. ^{13}C NMR Spectrum of t-boc&thiourea **35**

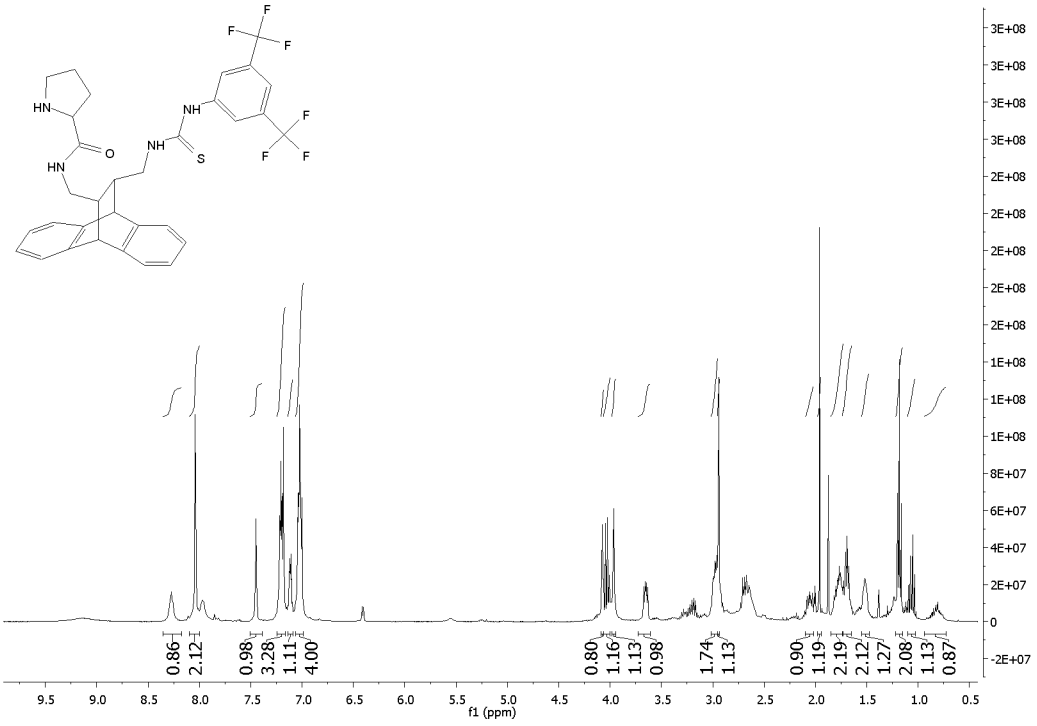

Figure A33. ^{1}H NMR Spectrum of proline&thiourea **38**

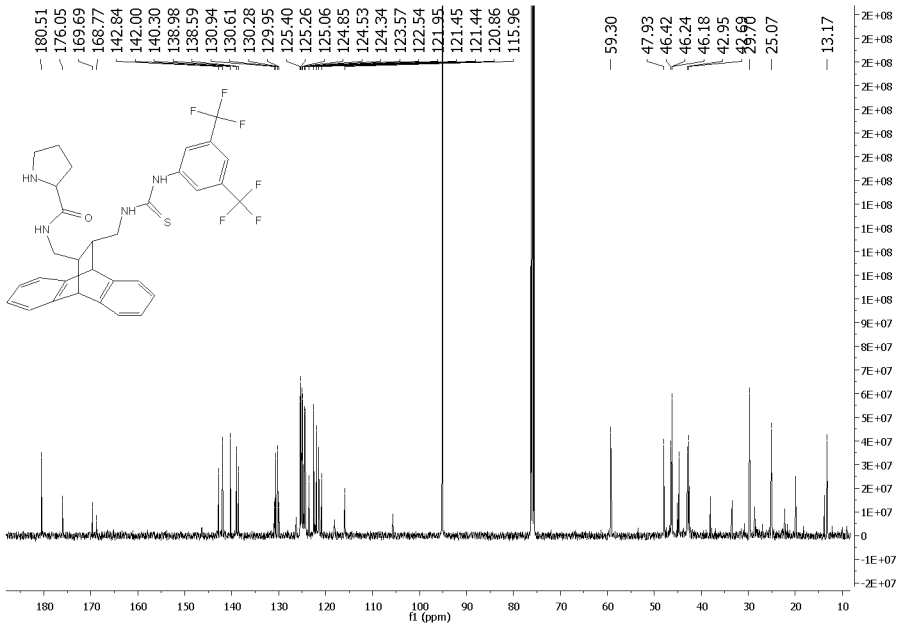

Figure A34. ^{13}C NMR Spectrum of proline&thiourea **38**

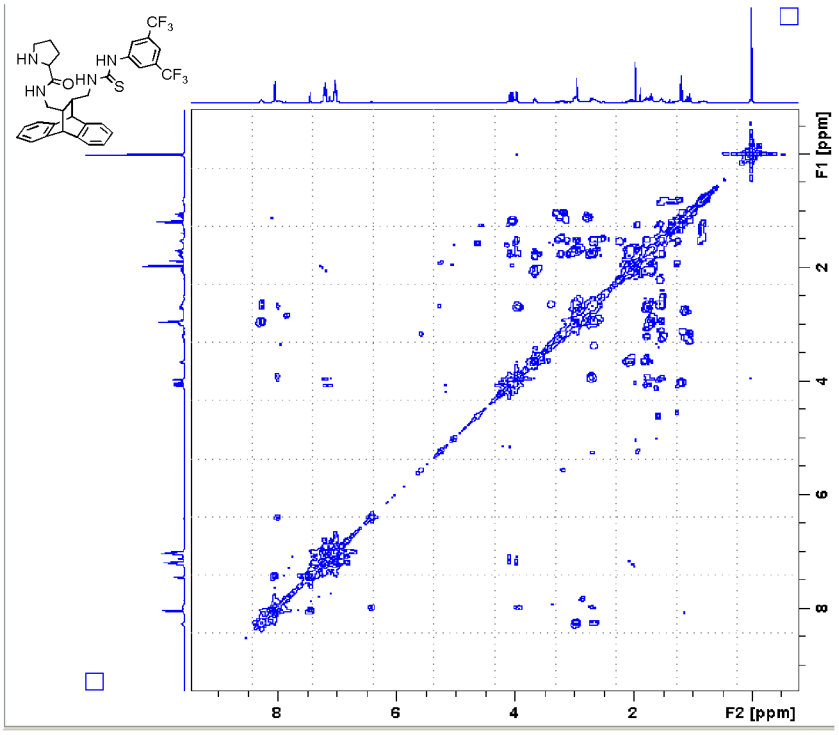

Figure A35. COSY NMR Spectrum of proline&thiourea **38**

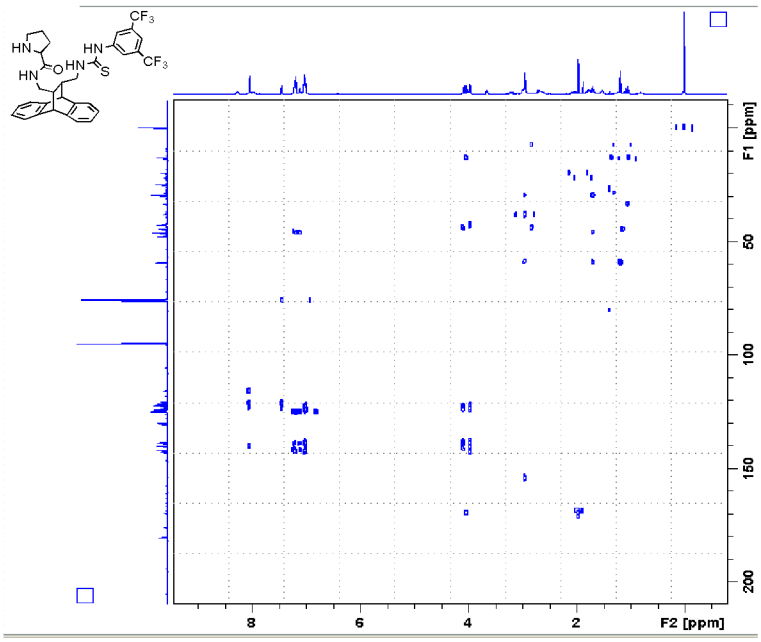

Figure A36. HMBC NMR Spectrum of proline&thiourea **38**

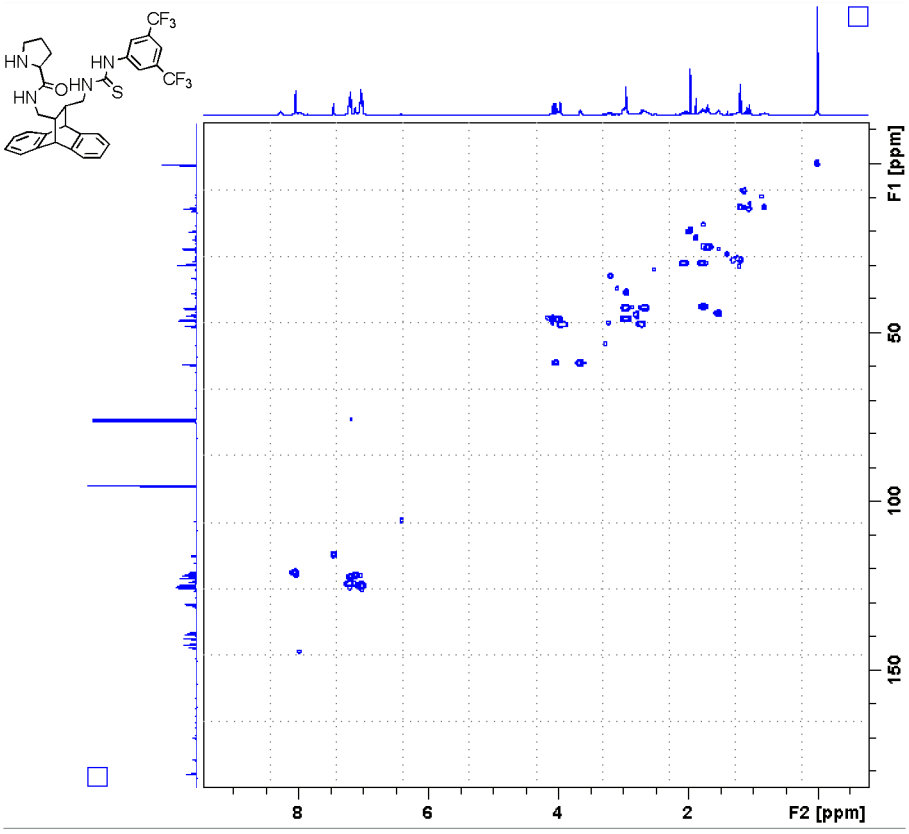

Figure A37. HSQC NMR Spectrum of proline&thiourea **38**

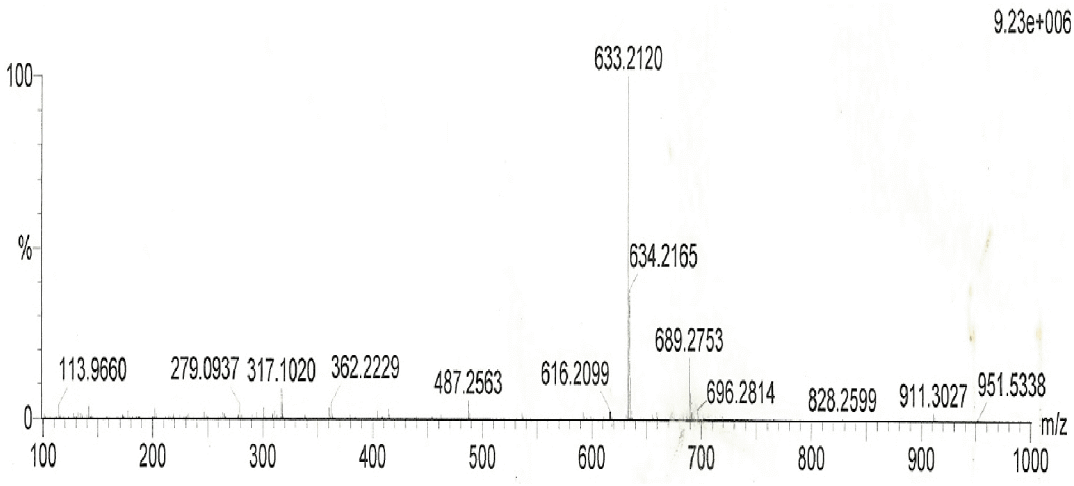

Figure A38. HRMS result of proline&thiourea **38**

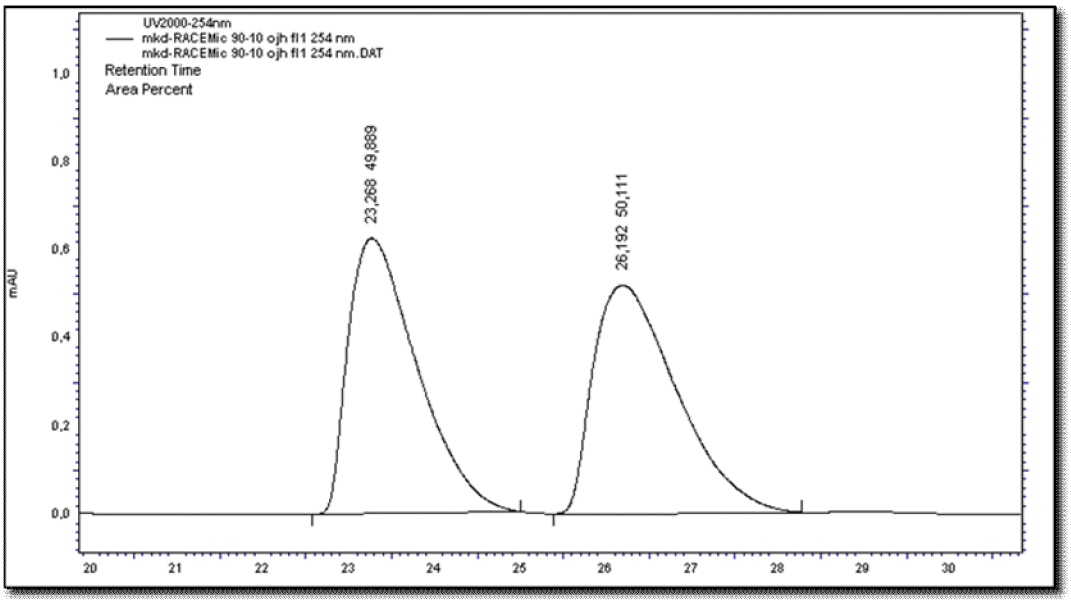

Figure A39. HPLC chromatogram of racemic 4-hydroxy-4-(4-nitrophenyl) butan-2-one

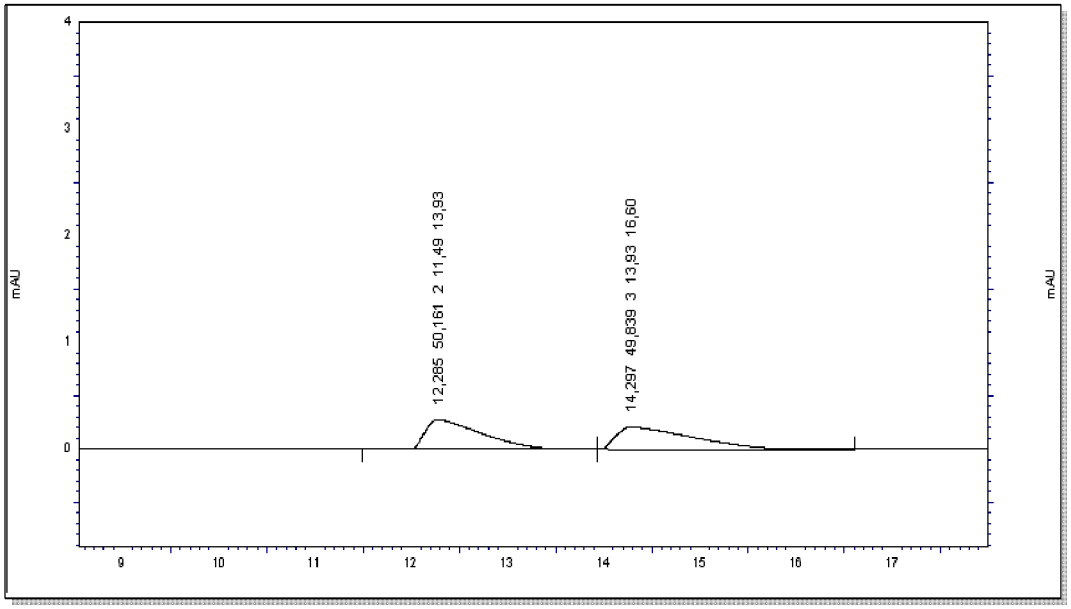

Figure A40. HPLC chromatogram of racemic phenylethanol