ASYMMETRIC SYNTHESIS OF TETRAHYDROTHIOPHENES IN THE PRESENCE OF BIFUNCTIONAL ORGANOCATALYSTS

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ASYMMETRIC SYNTHESIS OF TETRAHYDROTHIOPHENES IN THE PRESENCE OF BIFUNCTIONAL ORGANOCATALYSTS

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ABSTRACT

ASYMMETRIC SYNTHESIS OF TETRAHYDROTHIOPHENES IN THE PRESENCE OF BIFUNCTIONAL ORGANOCATALYSTS

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January 2021, 75 pages

In general, nitroolefins are convenient structures as Michael acceptors. To make it clear for this work, attack of a sulfur-containing nucleophile to a nitroolefin forms a C-S bond and opening the double bond would create a nucleophilic center on the nitroolefin which leads to the formation of a new C-C bond. In this study, asymmetric organocatalytic sulfa-Michael addition of 1,4-dithiane-2,5-diol to *trans*-β-nitrostyrene derivatives was carried out which yielded polyfunctional tetrahydrothiophenes that have the potential of biological activities, building blocks for chiral ligands and benefit in the synthesis of gold nanoparticles. In the first part, several quinine-based and 2-aminoDMAP-based bifunctional organocatalysts and different conditions were tested to find the optimized conditions for the reaction generating relatively high yield and stereoselectivity in a shorter time. Then, derivatization studies were performed by using diverse *trans*-β-nitrostyrenes in the optimized conditions determined previously. Increase in stereoselectivity was reached up to 70 % ee and 96:4 dr for the tetrahydrothiophene derivatives.

Keywords: Asymmetric synthesis, enantioselectivity, sulfa-Michael addition, bifunctional organocatalysts

ÖZ

BİFONKSİYONEL ORGANOKATALİZÖRLER VARLIĞINDA TETRAHİDROTİYOFENLERİN ASİMETRİK SENTEZİ

Tümer, Mustafa Faik
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Ocak 2021, 75 sayfa

Genel olarak nitroolefinler Michael alıcıları olarak elverişli yapılardır. Bu çalışma için açıklamak gerekirse, kükürt içeren bir nükleofilin bir nitroolefine saldırması C-S bağı oluşturur ve çift bağın açılması, nitroolefin üzerinde, yeni bir C-C bağı oluşumunu sağlayan nükleofilik bir merkez oluşturur. Bu çalışmada, biyolojik aktivite, kiral ligandlar için yapıtaşı ve altın nanopartiküllerin sentezinde fayda potansiyeline sahip olan polifonksiyonel tetrahidrotiyofenleri veren, 1,4-dithiane-2,5-diol'ün *trans*-β-nitrostiren türevlerine asimetrik organokatalitik sulfa-Michael katılması gerçekleştirilmiştir. İlk kısımda, değişik kinin temelli ve 2-aminoDMAP temelli bifonksiyonel organokatalizörler ve farklı koşullar, nispeten yüksek verim ve stereoseçiciliği daha kısa sürede sağlayan optimize koşulları bulmak için test edilmiştir. Daha sonra, belirlenen optimize koşullarda çeşitli *trans*-β-nitrostirenleri kullanarak türevlendirme çalışmaları yapılmıştır. Tetrahidrotiyofen türevleri için % 70 ee ve 96:4 dr'ye kadar stereoseçicilikte artışa ulaşılmıştır.

Anahtar Kelimeler: Asimetrik sentez, enantiyoseçicilik, sulfa-Michael katılması, bifonksiyonel organokatalizörler

To my dear family and
my beloved Nihal

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LIST OF ABBREVIATIONS

ABBREVIATIONS

DMM : Dimethoxymethane

DHQD : Dihydroquinidine

MTBE : Methyl *tert*-butyl ether

Tol. : Toluene

GC-MS : Gas Chromatography-Mass Spectrometry

HPLC : High Performance Liquid Chromatography

HRMS : High Resolution Mass Spectrometry

IR : Infrared

NMR : Nuclear Magnetic Resonance

HOMO : Highest Occupied Molecular Orbital

LUMO : Lowest Unoccupied Molecular Orbital

cat. : Catalyst

ee : Enantiomeric Excess

dr : Diastereomeric Ratio

α-Np : α-naphthyl

CHAPTER 1

INTRODUCTION

1.1 Asymmetric Synthesis

If an object is not the same as its mirror image, it is said to be chiral. Lord Kelvin, who introduced this terminology, defined it thus: "*I call any geometrical figure, or any group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself*.".[1] In connection with this, the molecules possessing non-superimposable mirror images are known as *enantiomers*. Herein, definition of the term 'optical activity' should be mentioned. A solution or solid which rotates linearly polarized light is said to be optically active. Linearly polarized light of a certain wavelength performs a rotation when it spreads through a solution or a crystal of a chiral compound. In other words, if a molecule causes linearly polarized light to rotate, it means the molecule is chiral. Relatedly, as described in IUPAC Gold Book, stereoselective synthesis of chiral compounds is called *asymmetric synthesis*.[2]

1.1.1 Significance of Enantioselectivity

It is noteworthy that at no point does nature show symmetry and chirality in biomolecules significantly affects medicinal and agricultural chemistry. Most of the time, biological systems identify a pair of enantiomers as distinct substances, and the two enantiomers may cause separate reactions. For instance, two enantiomers of phenylalanine have different flavors. The naturally occurring L-phenylalanine **1** is bitter while the mirror-image compound D-phenylalanine **2** tastes sweet (Figure 1).[3]

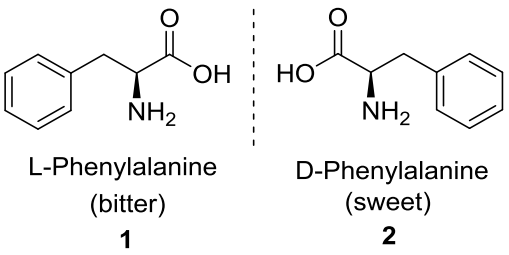


Figure 1. Enantiomers of Phenylalanine

More vitally, one enantiomer can serve as a very useful therapeutic drug whereas the other is extremely toxic. At this point, a disastrous medical event from the past had better be remembered: thalidomide tragedy. In the late 1950s and early 1960s, thalidomide was a commonly used medication for the prevention of nausea in pregnant women.[4] In the 1960s, it became clear that this medical therapy in thousands of children resulted in significant birth defects. Thalidomide has one stereogenic carbon center, and therefore (S)- **3a** and (R)- **3b** enantiomers. Twenty years after the late 1950s thalidomide calamity, Blaschke et al. discovered the enantiomers of the molecule display different biological properties and confirmed that only the (S)-enantiomer of thalidomide is teratogenic.[5]

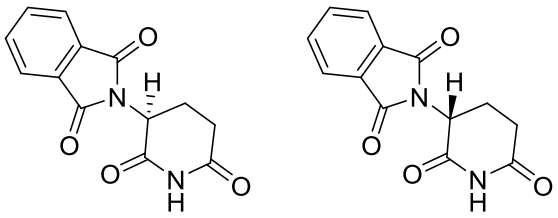


Figure 2. Enantiomers of Thalidomide

In fact, thalidomide is just one example. For lots of pharmaceutical products, it has been shown that only one enantiomer contains all the desired action, and the other is either inactive or toxic.

1.1.2 Techniques to Achieve Enantioselectivity

It is the duty of synthetic chemists to provide highly efficient and effective methods of synthesizing desired compounds in an enantiomerically pure state so that we do not repeat any tragedy. Several approaches are used for obtaining enantiomerically pure products, including classical optical resolution by diastereomers, enzymatic resolution, chemical kinetic resolution, and, last but not least, asymmetric synthesis. To date, chemists in the synthetic organic chemistry have thoroughly recognized the significance and practicality of asymmetric synthesis as a method for gaining enantiomerically pure or enantiomerically enriched compounds. This popularity is due to the explosive growth of modern and more effective methods over the last years. Among the forms of asymmetric reactions, the most desirable one is catalytic asymmetric synthesis as one chiral catalyst molecule can produce millions of chiral product molecules. Catalytic

asymmetric synthesis also has important economic advantages over the other types of asymmetric syntheses for industrial processing of enantiomerically pure compounds.[6]

A catalyst is a material that stimulates the course of a reaction without disturbing its equilibrium position. It provides reduction in the activation energy of the process and this allows it to happen under milder conditions.[7] Three types of catalytic routes are biocatalysis, transition metal catalysis and finally organocatalysis. Biocatalysis can be defined as using selectivity of enzymes for one of the enantiomers of a chiral molecule. In this method, one enantiomer of a racemate is unaffected and the other enantiomer is converted into the desired, pure chemical.[8] In transition metal catalysis, a wide range of chiral substrates are complexed with the host transition metals. Consequently, the starting compounds are attached to transition metals to afford the product by chiral induction arising from chiral substrates. Organocatalysis is the use of small chiral organic molecules to catalyze chemical transformations.[9]

1.2 Organocatalysis

Organocatalysis is a metal-free catalysis activating substrates, whether these substrates are electrophiles or nucleophiles. It provides mild conditions and thus saves energy. Generally, oxygen-stable reagents are used and there is no necessity for anhydrous conditions. That decreases the cost of the synthesis. It is compatible with several functional groups that could be sensitive to other processes. This reduces the need for protection groups, lowering the total number of reaction steps. The use of metals or organometallic compounds raises some specific environmental issues, primarily due to their toxicity and the production of polluting metal waste. Simple organocatalysts are typically cheap to prepare and readily available in a variety of amounts, ideal for small-scale reactions to

industrial reactions. Because of all these facts, organocatalysis can be considered as greener than traditional catalysis.[7] Accordingly, it has caught synthetic chemists' attention and become a thriving area for over the past 20 years. Besides the usage of organocatalytic pathway in organic synthesis, within this time period, even change in the number of publications on the topic of organocatalyzed polymerization in the Web of Science makes the situation clear (Figure 3).[10]

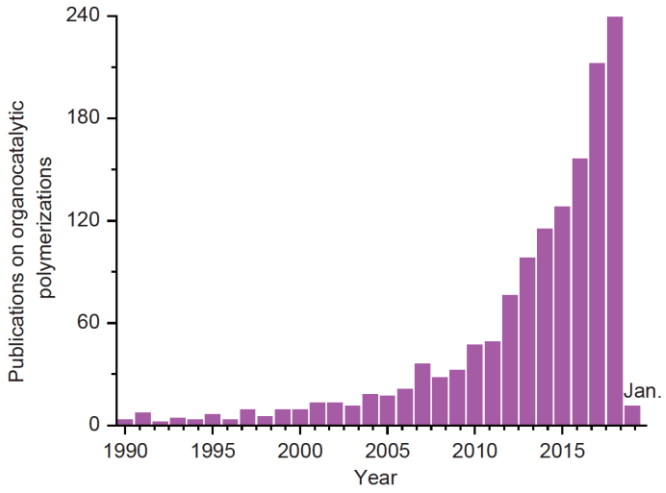


Figure 3. Interest in organocatalysis

1.2.1 Classification of Organocatalysis

Mechanistically, most of the organocatalysts can be commonly categorized as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids. Simple catalytic cycles are shown in the following figure.[11] Correspondingly, Lewis base catalysts (B:) initiate the catalytic cycle via nucleophilic addition to the substrate (S). After the resulting complex undergoes a reaction, the product (P) and the catalyst is released for further turnover. Lewis acid catalysts (A) activate nucleophilic

substrates (S:) in a similar way. Partial deprotonation and protonation are the initiative actions for Brønsted base and acid catalytic cycles respectively.[11]

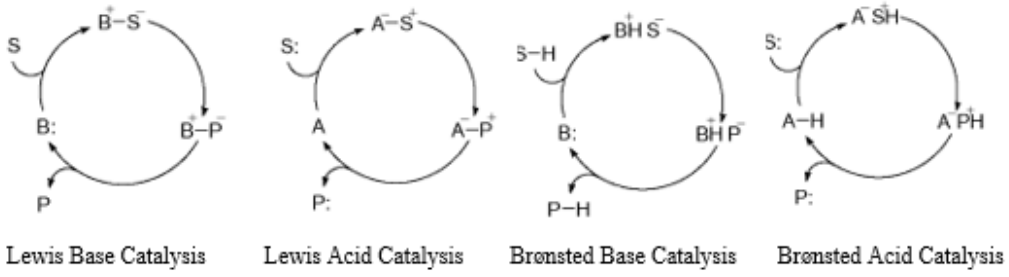
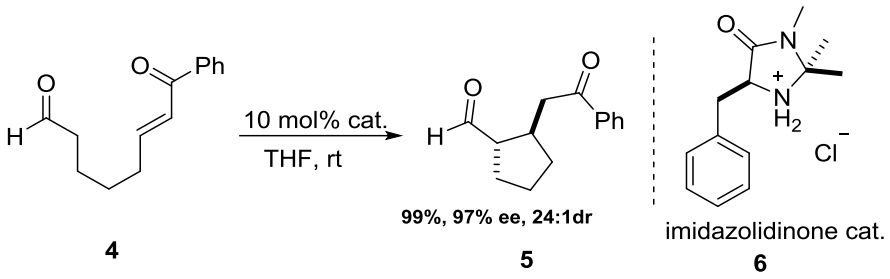


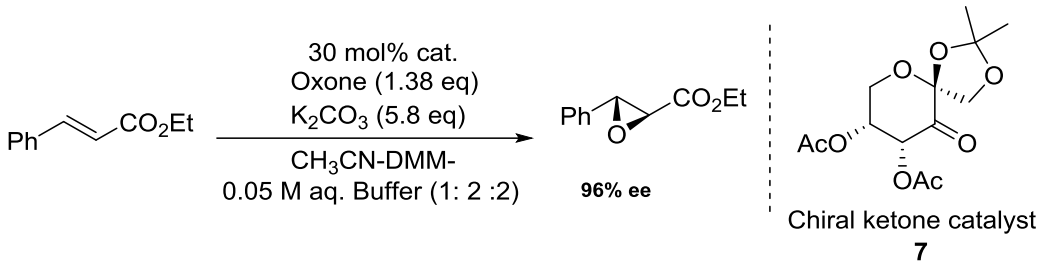
Figure 4. Classification of Organocatalysts

Enamine catalysis can be given as an example for Lewis base catalysis. It involves a catalytically generated enamine intermediate formed by deprotonation of an iminium ion and reacting with various electrophiles or undergoing pericyclic reactions. To be more precise, highly enantioselective intramolecular Michael reaction of formyl enone **4** to give ketoaldehyde **5** catalyzed by imidazolidinone catalyst **6** is shown in Scheme 1.[12]



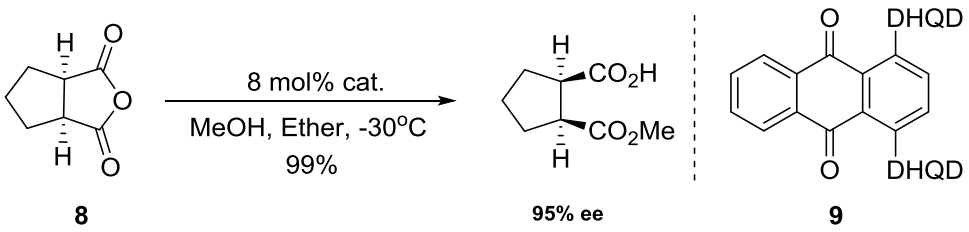
Scheme 1. Amine-catalyzed Michael cyclization

Epoxidation of olefins using chiral dioxiranes generated *in situ* from chiral ketone catalysts **7** and Oxone (potassium peroxomonosulfate) as oxidant is an important example of Lewis acid catalysis. A highly enantioselective case is seen in Scheme 2.[11]



Scheme 2. Ketone-catalyzed enantioselective epoxidation of an olefin

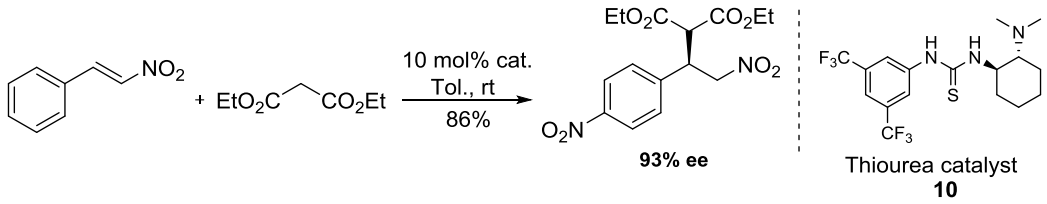
Deng and co-workers reported the desymmetrization of cyclic *meso*-anhydrides **8** by alcoholysis. Commercially available modified cinchona alkaloids (DHQD) **9** are used for this purpose. Mechanistic studies suggest that the amine catalyst acts by general base catalysis. In other words, it activates the alcohol via hydrogen bonding for nucleophilic attack on the anhydride. An example of this Brønsted basic catalysis is in Scheme 3.[11]



Scheme 3. Organic Brønsted base catalysis

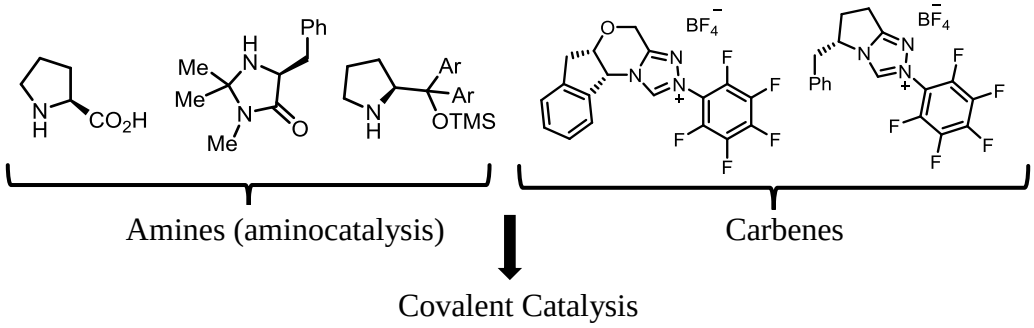
Takemoto and co-workers indicated that chiral thiourea derivatives with neighboring tertiary amino groups have the property of bifunctional organocatalyst. This provides activation of nitro compounds for enantioselective Michael reactions. The thiourea moiety interacts with the nitro group via hydrogen-bonding activation and the neighboring tertiary amino group activates the nucleophile. As shown in Scheme 4, nitroolefins react with malonates in the

presence of the thiourea catalyst **10**, forming the corresponding Michael adducts with high enantioselectivity.[11]



Scheme 4. Bifunctional organocatalysis

Organocatalysts may activate the electrophile or the nucleophile (or both in the case of bifunctional catalysts). As another function, they create an asymmetric environment which is responsible for setting the chirality of the product. They can also be classified based on their interaction with the substrate as covalent or non-covalent catalysts. A covalent bond between the organocatalyst and the substrate is formed in covalent catalysis. That increases the interaction between the substrate and the reagent in the reaction. Aminocatalysts and carbenes can be considered in this classification. In the case of non-covalent substrate-catalyst interactions, the activation of the substrate occurs through hydrogen bonding (e.g., thioureas, squaramides and phosphoric acids) or ionic interactions (e.g., chiral bases such as cinchona alkaloids and phase-transfer catalysts).[13]



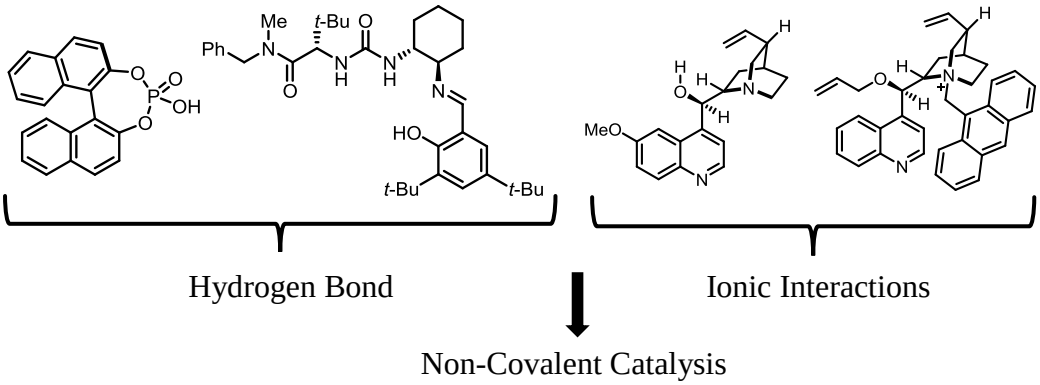


Figure 5. Classification of the activation mode in organocatalysts

1.2.2 Bifunctional Organocatalysts

In bifunctional organocatalysis, the catalysts ensure the activation of electrophile and nucleophile synchronically. These organocatalysts include both basic and acidic parts. While the basic part provides the HOMO activation of nucleophile by raising its energy level, acidic part is used for the LUMO activation of electrophile by lowering its energy level. To give an example, one of the most commonly experienced bifunctional organocatalyst structure has the *tert*-amine as the basic unit and double hydrogen-bond donor (e.g. urea or thiourea) as the acidic unit. Working principle is demonstrated in Figure 6.[14]

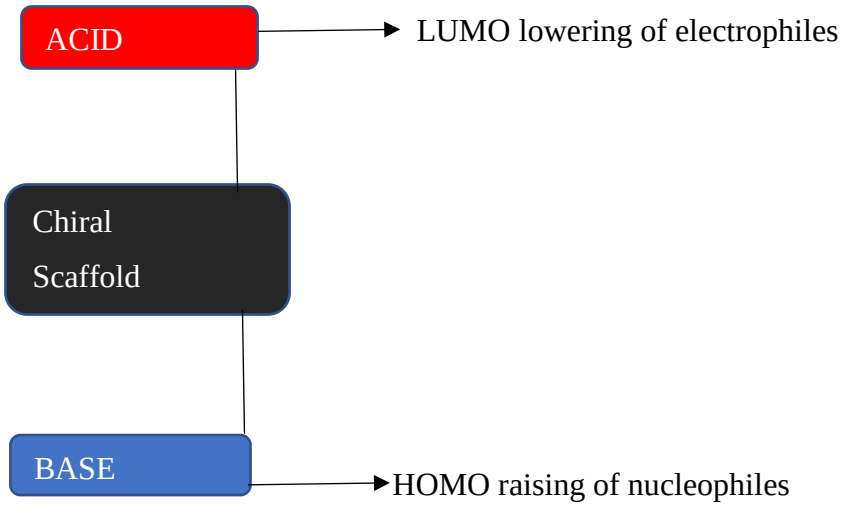
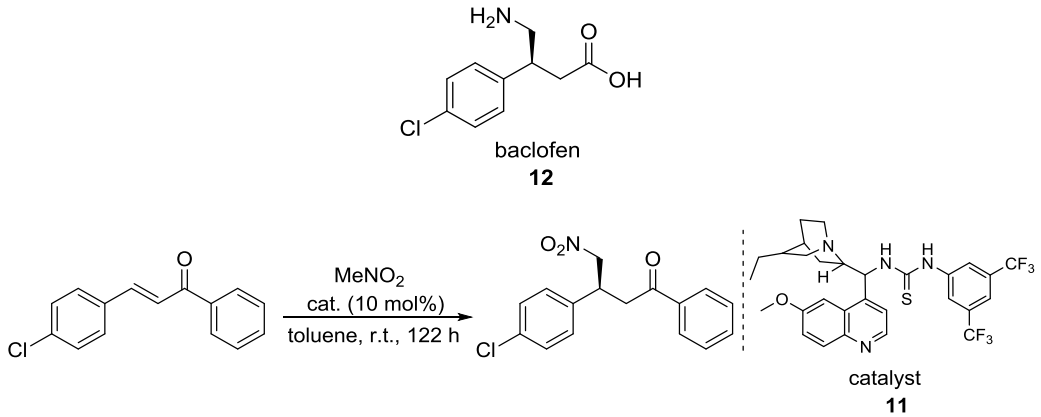


Figure 6. Working principle of acid/base type bifunctional organocatalysts

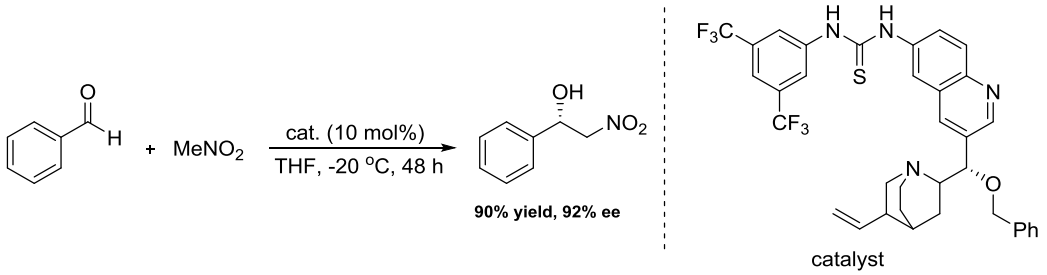
In the concept of bifunctional organocatalysts, cinchona alkaloids would occupy a noteworthy area. This versatile class of compounds is one of the most famous natural products as it has not only the broad and remarkable medicinal history but also synthetic activities in addition to its catalytic features.[15] Since the early 17th century, they have been used to treat fever and still now they are used for the treatment of malaria as well as other diseases. According to the literature, these terrific herbs have anti-obesity, anti-cancer, antioxidant, anti-microbial, anti-parasitic and anti-inflammatory effects.[16] Special molecular structure and recognition abilities of cinchona alkaloids make them and their derivatives extremely useful in almost every area of chemistry which are interested in chirality. Main components of the extract are quinine, quinidine, cinchonine and cinchonidine.[15]

As a gripping example of cinchona-based organocatalytic study, the first highly enantioselective reaction of nitromethane with chalcones is carried out by Soós and co-workers. High stereoselectivity (89-98% ee) was obtained by means of thiourea-based catalyst **11**. As a result of these conjugate additions, immensely useful molecular structures are created, namely an essential intermediate for the synthesis of baclofen **12** (Scheme 5).[15]



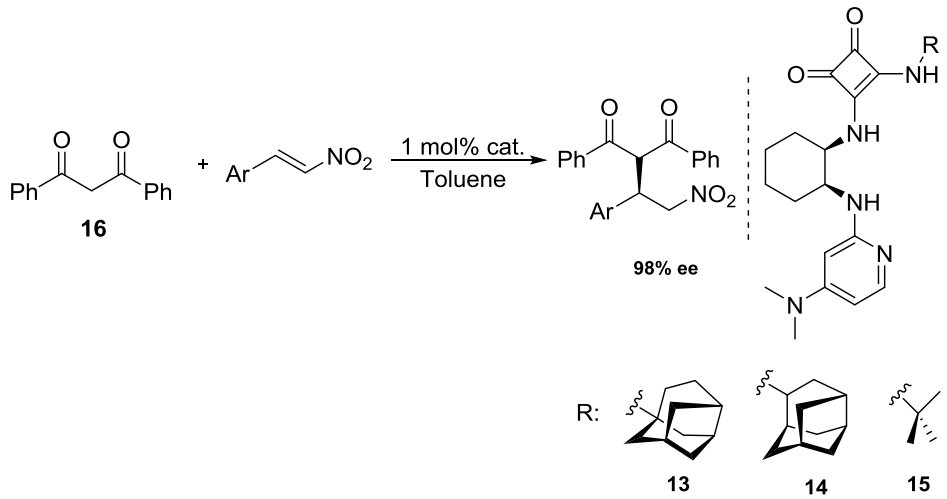
Scheme 5. The first enantioselective reaction of nitromethane with chalcones

First use of cinchona alkaloids as the catalyst in the reaction of nitromethane with inactivated aldehydes and trifluoromethyl ketones (Henry reaction) was carried out by Misumi et al. High pressure was needed for this addition and enantioselectivity was quite low (35% ee).[15] When hydroxyl group is replaced with an activated thiourea, notable enhancement in reactivity and selectivity took place (Scheme 6).[17]



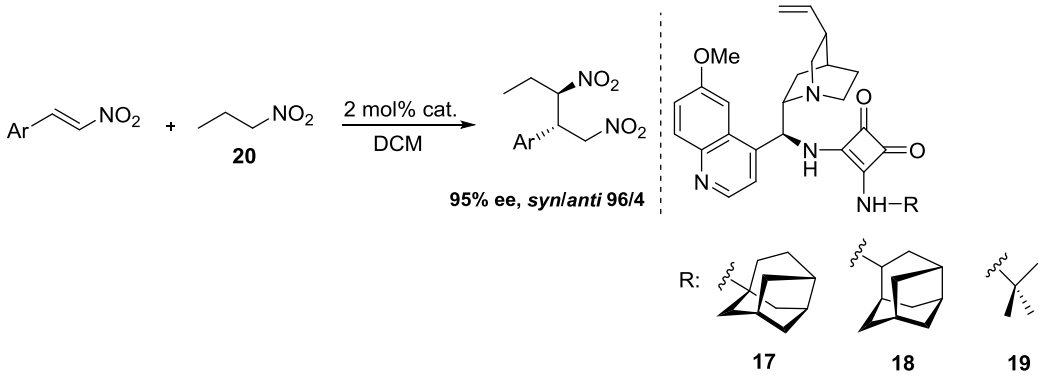
Scheme 6. Henry reaction catalyzed by thiourea derived cinchona alkaloid

A new class of chiral bifunctional organocatalysts, 2-aminoDMAP/squaramides **13**, **14** and **15**, was generated by Tanyeli and co-workers in 2014. In this work, it was shown that these catalysts are particularly active (1mol %) and encourage the conjugate addition of dibenzoylmethane **16** to diverse *trans*-β-nitroalkenes. The efficient coordination between 2-aminoDMAP and sterically hindered squaramide lead to complete conversion of several reactants into Michael adducts in a few hours with high enantioselectivities (up to 98% ee) (Scheme7).[18]



Scheme 7. 2-aminoDMAP/squaramides in Michael addition

Quinine-based squaramides **17**, **18** and **19**, another convenient group of bifunctional organocatalysts, were synthesized and used by Kanberoğlu and Tanyeli in 2016 for the first time. It was proved that these catalysts are greatly active promoters of the conjugate addition of 1-nitropropane **20** to several different *trans*-β-nitroalkenes. The catalysis occurs owing to the synergistic cooperation of quinine and sterically hampered squaramide moieties. Just 2 mol% of catalyst loading was enough to accomplish the Michael additions at 0°C, thereby acquiring the 1,3-dinitro Michael adducts with exceptional enantioselectivity and diastereoselectivity (up to 95% ee and *syn*/*anti* isomers up to 96:4) (Scheme 8).[19]



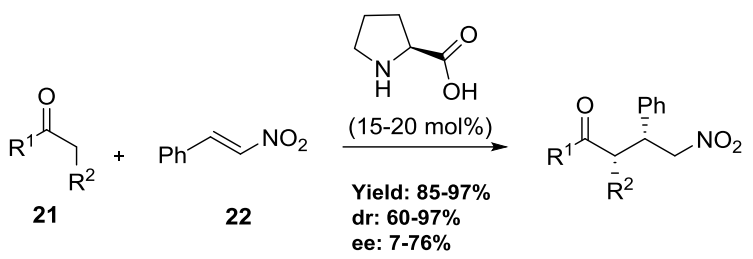
Scheme 8. Michael addition catalyzed by quinine-based squaramides

1.3 Organocatalytic Michael Reactions

The conjugate addition of a nucleophile to the β-carbon of an α, β-unsaturated structure which brings about a new carbon-carbon bond at the β-carbon is known as Michael reaction or Michael addition. Here, the nucleophile and the electrophile are named as Michael donor and Michael acceptor respectively.[20] This reaction is one of the most influential and trustworthy tools for creating carbon-carbon and carbon-heteroatom bonds that can be controlled stereochemically. Because of this usefulness, lots of organocatalytic Michael additions have been reported in which different variations of nucleophiles and conjugate acceptors are found. It has also been recognized that the functionality may be used in cascade or domino reactions. By means of this, synthesis of highly complex molecules is achieved in single step. Organocatalytic domino transformation initiated by a Michael reaction was firstly reported by Bui and Barbas in 2000[21.]

Addition of nucleophiles to nitroolefins can be thought to be one of the most crucial Michael type reactions, considering nitroolefins have multiple reactivity and synthetically valuable building blocks are produced at the end of these processes.[22] To be more precise, Michael reaction of aldehydes and ketones with nitroalkenes has the potential to produce functionalized products since the nitro

group is versatile synthetically. The proline-catalyzed Michael reaction of ketones **21** and nitrostyrene **22** was the first endeavor in this area (Scheme 9).[23]

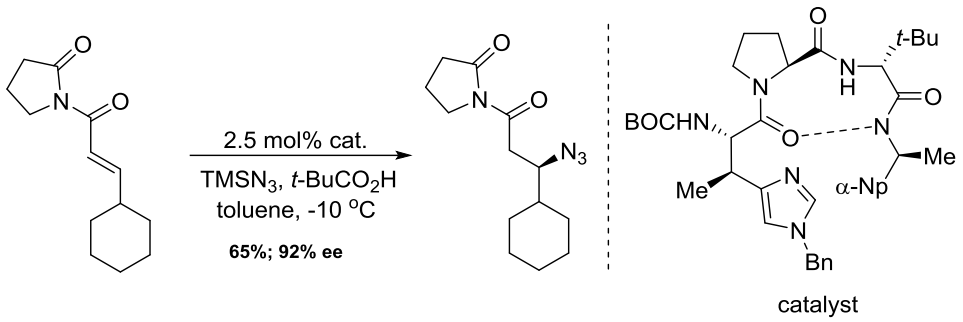


R^1	R^2
Et	Me
Me	H
Me	Ac
Ph	H
$Ph(CH_2)_2$	Me

Scheme 9. Michael reaction of ketones and nitrostyrene

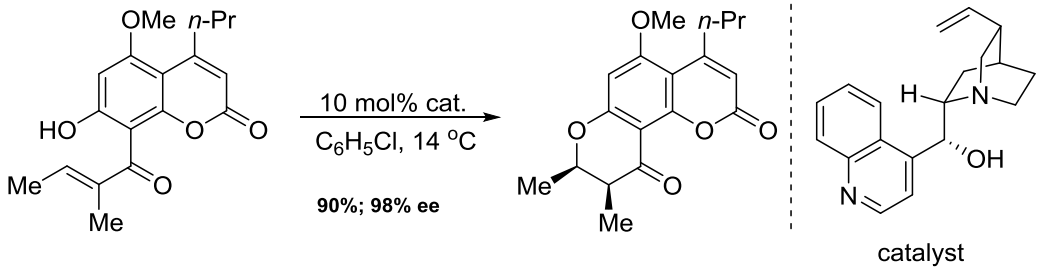
It should be pointed out for Michael reactions that there are many examples which show even slight changes in the structure of catalysts usually cause meaningful distinctions in terms of chemical yields and stereoselectivities. We, therefore, understand that a library including structurally various catalysts is necessary for proper scientific study. A lot of research on catalysts have already been conducted in order to provide practicality, increase enantioselectivity and develop more environmentally friendly methods.[24]

In some cases, heteroatom-centered nucleophiles act as Michael donors, thereby these additions are known as hetero-Michael reactions. Among these reactions, conjugate additions of sulfur, nitrogen, oxygen and phosphorous to electron-deficient olefins are called sulfa-Michael, aza-Michael, oxa-Michael and phospha-Michael reactions, respectively.[24] This 1,4-addition of heteroatoms to activated alkenes produces synthetically important β-hetero-substituted carbonyl or nitro compounds. S. Miller and co-workers reported the first organocatalytic instance of aza-Michael addition with high enantioselectivity (92% ee) (Scheme 10).[25]



Scheme 10. Organocatalytic aza-Michael addition

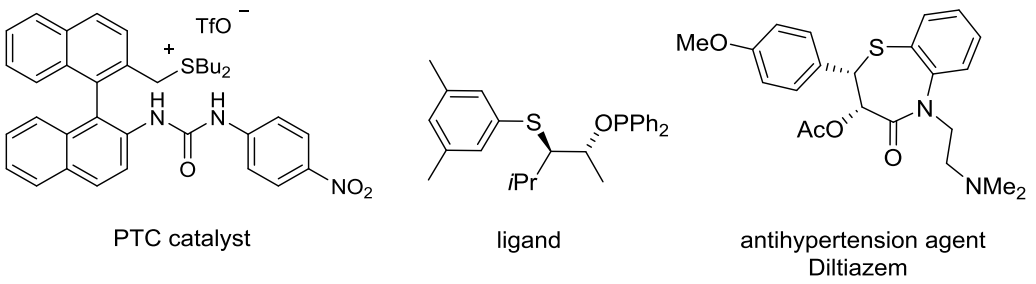
The first example of oxa-Michael addition was reported by T. Ishikawa and co-workers with high enantioselectivity as well (98% ee) (Scheme 11).[25]



Scheme 11. Organocatalytic oxa-Michael addition

1.3.1 Sulfa-Michael Reactions

Constructing carbon-sulfur bond is crucial in synthetic chemistry since it can be thought as the main part of obtaining chiral sulfides, ligands and intermediates for metal-catalyzed reactions, catalysts in enantioselective synthesis and well-known drugs in pharmaceutical field. A couple of examples related to these cases are shown in Figure 7.[26]



PTC catalyst ligand antihypertension agent Diltiazem

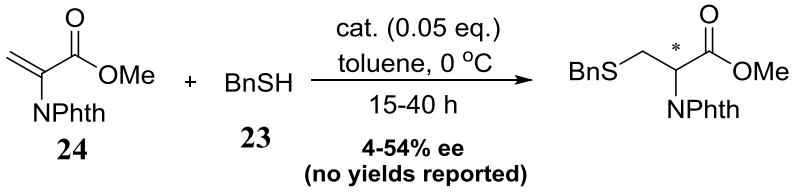
Figure 7. Some important structures containing C-S bonds

Diverse approaches such as thiocarbonylation, introducing unsaturated compounds into sulfur-sulfur bonds are used to form sulfur-carbon bonds. Among these methods, sulfa-Michael addition occupies a wide area owing to the variety and availability of nucleophilic and electrophilic constituents. Mannich and aldol reactions provide simple preparation of nitrogen- and oxygen- containing compounds, but thiocarbonyl is not an ideal electrophile for aldol reactions. They can be poor electrophiles, not stable under aldol reaction conditions and difficult to synthesize.[27]

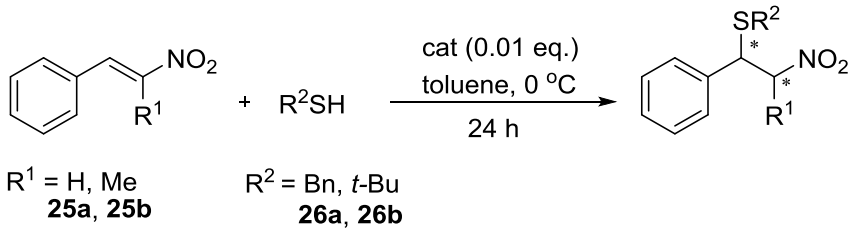
As in the case of other types of Michael additions, sulfa-Michael reactions have the possibility to get two stereogenic centers in one step if suitable acceptor is used. Sulfur functionality can be removed by oxidation or reduction. Furthermore, it may be changed to different functional groups, e.g., disulfides, sulfoxides which rises the importance of asymmetric synthesis of sulfur-containing compounds.[27]

When we glance at the literature, we see that sulfa-Michael additions can be achieved by either stoichiometric or catalytic methods. In stoichiometric methods, both Michael acceptor and sulfur donor are functionalized with a chiral supplement. In catalytic methods, on the other hand, chiral metal complexes, organocatalysts or enzymes are used as catalysts. The first catalytic asymmetric sulfa-Michael addition which has had a strong influence on later developments in this subject was reported by Pracejus and co-workers in 1977.[28] In this study, while benzyl thiol **23** was used as Michael donor, α-phthalimido methacrylate **24**

was chosen as the electrophilic reactant (Scheme 12). The reaction was catalyzed by certain optically active amines to yield cysteine derivatives. At the end of catalyst screening, it was found that cinchonas provide higher stereoselectivities compared to other alkaloids (Figure 8). On the contrary, when β-nitrostyrenes **25a** and **25b** are treated with benzyl thiol **26a** and trityl thiol **26b**, brucine **27** was the optimum catalyst (Scheme 13). Apart from the cinchona alkaloid catalysts; tertiary amino alcohol catalysts, secondary amine catalysts, (thio)urea-based catalysts have been employed for the purpose of organocatalytic asymmetric sulfa-Michael additions. It was observed that thiourea-based ones were the best in most cases and lowering catalyst loading could result in higher enantioselectivities.[27]



Scheme 12. The first catalytic asymmetric sulfa-Michael addition



Scheme 13. Sulfa-Michael addition of thiols to β-nitrostyrenes

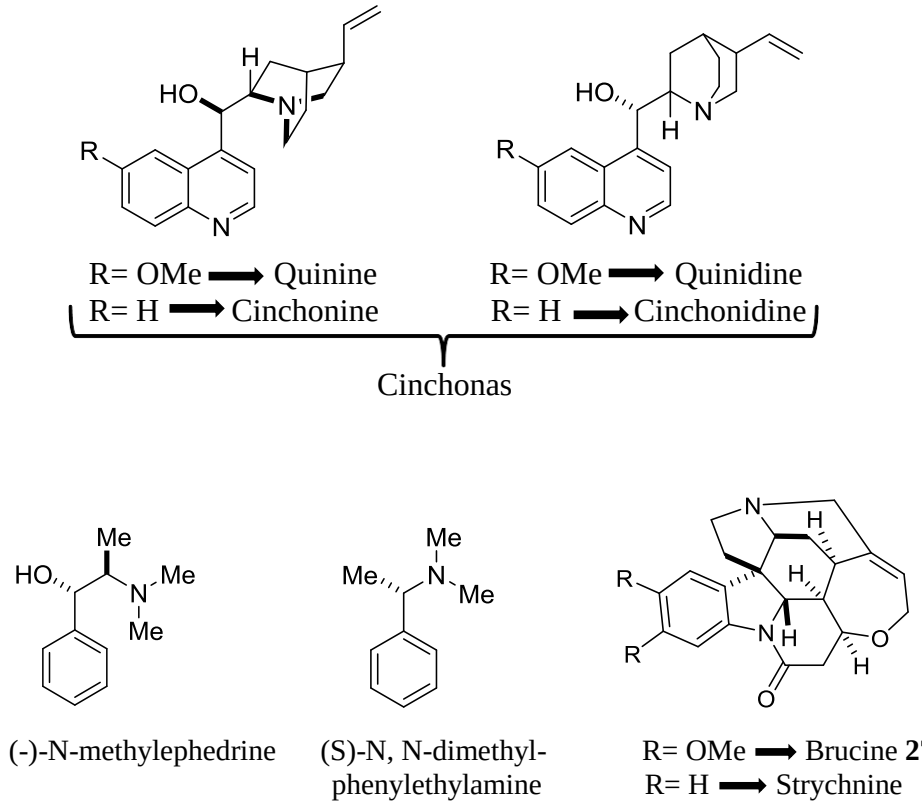
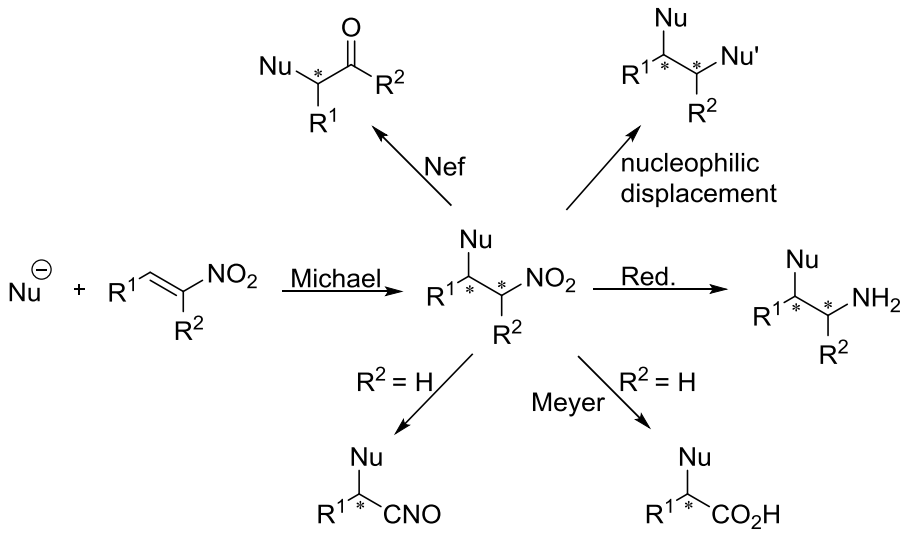


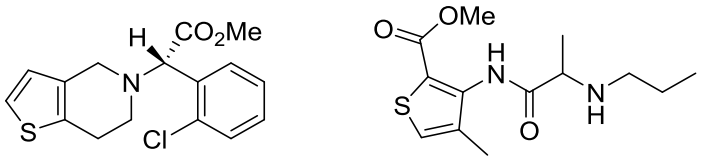
Figure 8. Catalysts screened

Strong electron withdrawing character of the nitro group makes nitroolefins open to nucleophilic attacks. For this reason, nitroolefins usually have great reactivity and they can simply be considered as proper Michael acceptors. Additionally, after Michael addition, nitro group could be transformed into various useful structures by several ways such as Nef reaction, nucleophilic displacement, reduction to an amino group, the Meyer reaction and conversion into nitrile oxide (Scheme 14).[29]



Scheme 14. Potential transformations which nitro groups may perform

On the other hand, asymmetric tetrahydrothiophene derivatives have a wide range of biological activities including coenzyme biotin, inhibitor of copper amine oxidases, antioxidant effects, leukotriene antagonism and plant growth regulations.[30] As concrete examples, Plavix **28**, a sensational drug used in the treatment of coronary artery disease[31], and Articaine **29** which is a commonly used dental anesthetic in Europe have thiophene based structures (Figure 9).[32]



Plavix®
28

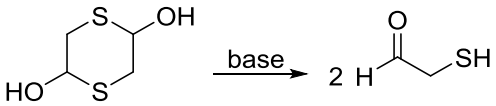
Articaine®
29

Figure 9. Thiophene-based structures used for medical purposes

In addition to the vital capabilities stated above, tetrahydrothiophenes are used as building blocks for chiral ligands in asymmetric metal catalysis, in natural product synthesis and organocatalysis. Moreover, it is known that thiophenes are beneficial for the synthesis of gold nanoparticles due to their adsorptive attributes on gold surfaces.[30]

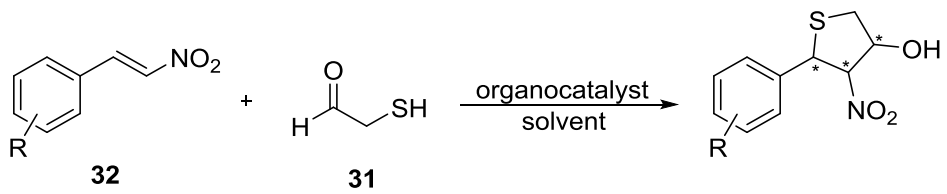
1.4 Aim of The Work

When viewed from two aspects; both versatility of nitro group and usage of thiophenes in assorted fields, constructing enantiomerically enriched tetrahydrothiophenes from 1,4-dithiane-2,5-diol (**30)** and different derivatives of *trans-β*-nitrostyrene **(32)** can be contemplated as a reasonable and promising work (Scheme 16). At this point, it should be emphasized that dithiane **(30)** is converted into two equivalents of the corresponding aldehyde **31** with the help of a base. Either an organic base or the basic unit of a bifunctional organocatalyst may enable the basicity (Scheme 15).



30 **31**

Scheme 15. Conversion of dithiane into aldehyde



32 **31**

Scheme 16. General representation of the work

We have planned to use chiral bifunctional 2-aminoDMAP and quinine based organocatalysts that are synthesized by our research group in order to accomplish satisfying stereoselectivities (Figure 10). By this way, we will have not only produced a functional compound but also tested our catalysts whether which one among them will give the best result in terms of yield, time, catalyst loading and stereoselectivity. During the study, we will try to determine the optimal conditions for the reactions as well.

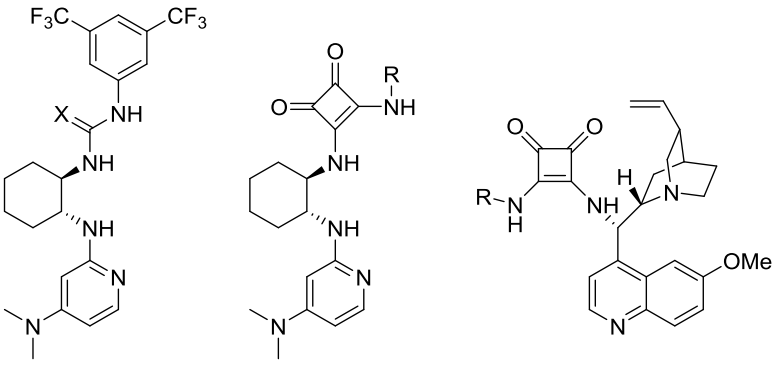


Figure 10. Chiral bifunctional organocatalysts developed by our research group

CHAPTER 2

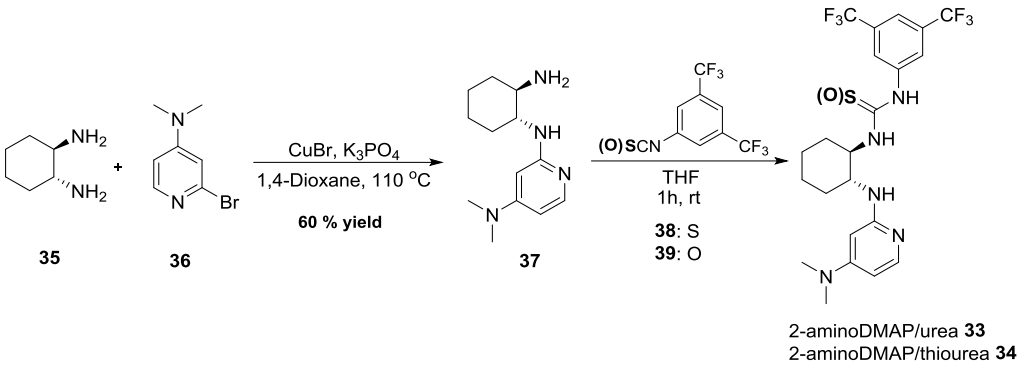
RESULTS AND DISCUSSION

2.1 Synthesis of Chiral Bifunctional Organocatalysts

Chiral bifunctional organocatalysts developed in our research group were used in reactions with the intention of getting enantiomerically enriched tetrahydrothiophene derivatives with high yields. For this purpose, in general, acidic and basic moieties are separately synthesized and then combined to get resultant bifunctional organocatalysts.

2.1.1 Synthesis of 2-aminoDMAP Based Organocatalysts

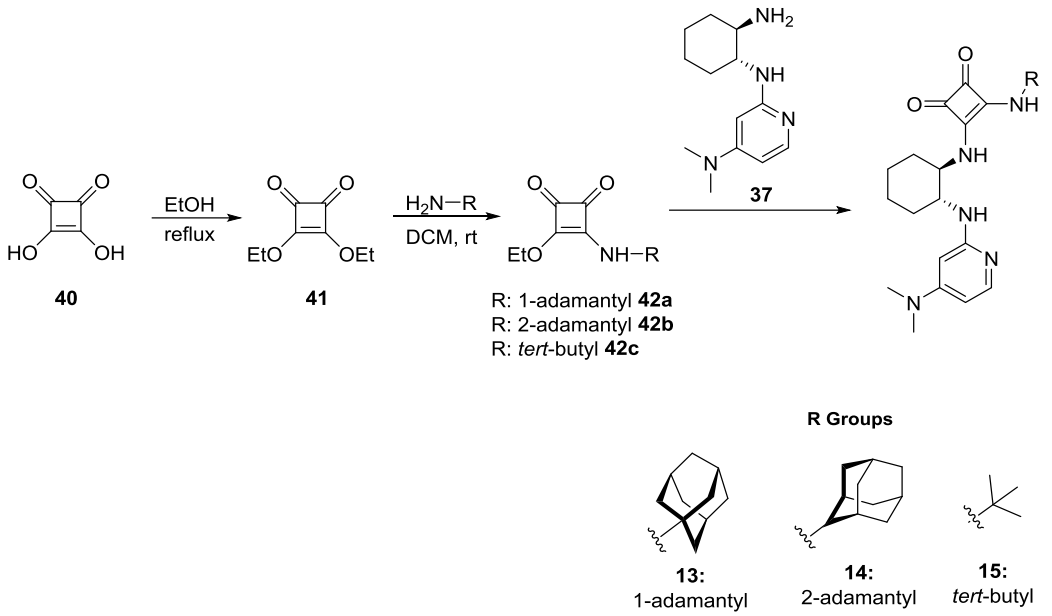
The synthesis of 2-aminoDMAP based organocatalysts was initiated with the construction of 2-aminoDMAP frame **37**. It was obtained by adding Lewis basic bromo-DMAP **36** on to (1R, 2R)-*trans*-1,2-cyclohexanediamine **(35)** by direct selective mono-N-pyrilidization in the presence of CuBr and K_3PO_4.[33]



Scheme 17. Synthesis of 2-aminoDMAP/urea and thiourea organocatalysts

The free amine part of **37** was linked to acidic moieties such as urea or thiourea. This was achieved by using commercially available 3,5-bis(trifluoromethyl)benzene isocyanate **39** or isothiocyanate **38**. As a result, chiral bifunctional 2-aminoDMAP/urea **33** or 2-aminoDMAP/thiourea **34** organocatalyst was synthesized in 1 hour at room temperature.[33]

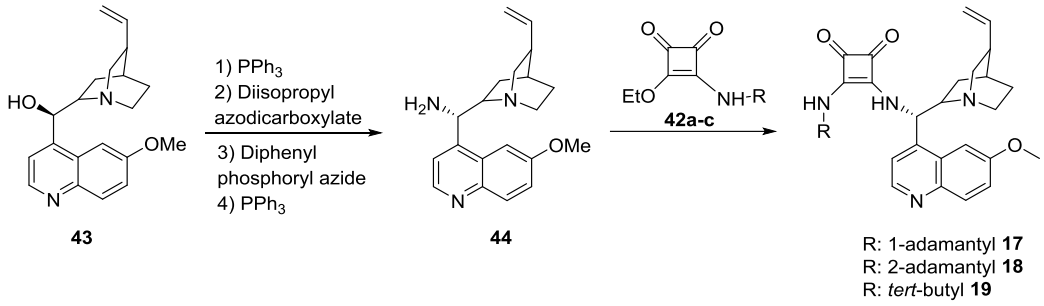
Urea and thiourea are not the only acidic moieties that could be bonded to 2-aminoDMAP. Squaramides were also used as the Brønsted acidic functional portion of the chiral 2-aminoDMAP based organocatalysts synthesized in our research group. These organocatalysts have sterically encumbered units such as 1-adamantyl, 2-adamantyl and *tert*-butyl groups and two acidic hydrogens on the squaramide moiety which are able to coordinate to electrophilic part. As shown in scheme 18, firstly, squaric acid **(40)** was left to reflux in ethanol to form diethyl squarate **41**. Then, monosquaramides **42a**, **42b** and **42c** were obtained by addition of commercially available 1-adamantyl, 2-adamantyl and tert-butyl amine to diethyl squarate **41** in DCM at room temperature. Finally, the basic 2-aminoDMAP **37** was anchored to the squaramides.



Scheme 18. Synthesis of 2-aminoDMAP/squaramide bifunctional organocatalysts

2.1.2 Synthesis of Quinine Based Organocatalysts

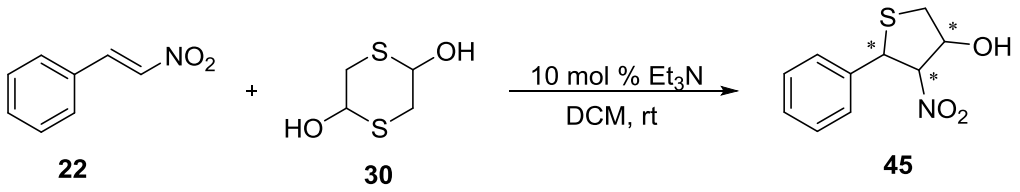
The second major class of organocatalysts developed in our group consists of backbone involving sterically encumbered squaramides as acidic moiety. During the course of quinine-based organocatalysts synthesis, first step involves the transformation of hydroxyl unit into corresponding amine functionality with the complete inversion of configuration done by Mitsunobu followed by Staudinger reactions (Scheme 19). Resultantly, already prepared amide/ester squaric acid units **42 a-c** were attached to quinine amine to afford bifunctional organocatalysts **17-19**.



Scheme 19. Synthesis of quinine based squaramides as bifunctional organocatalysts

2.2 Synthesis of 4-Nitro-5-phenyltetrahydrothiophen-3-ol by The Sulfa-Michael Addition of 1,4-Dithiane-2,5-Diol to *trans*-β-Nitrostyrene

In the beginning of the work, sulfa-Michael addition reaction was carried out by using 1,4-dithiane-2,5-diol **(30)** which is the dimeric form of 2-mercaptoacetaldehyde **31**. The base is used for in situ formation of 2-mercaptoacetaldehyde **31**. It has both strong nucleophilic and electrophilic units. The reaction with trans-β-nitrostyrene **(22)** in DCM afforded the resulting polyfunctional tetrahydrothiophene **45** with 3 stereogenic centers. Due to high reactivity of 1,4-dithiane-2.5-diol **(30)**, reaction occurred very fast. This fastness makes obtaining high stereoselectivity difficult. Hence, we tried to regulate the speed of the reaction by applying various organocatalysts in diverse conditions.



Scheme 20. Synthesis of the racemic tetrahydrothiophene **45**

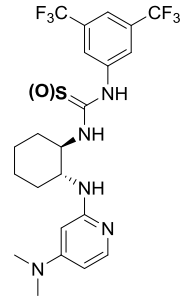
2.3 Optimization Studies on The Sulfa-Michael Addition of 1,4-Dithiane-2,5-Diol (30) to *trans*-β-Nitrostyrene (22)

We've tried to find the optimal organocatalyst and conditions (temperature, catalyst loading, concentration, solvent) which could provide the highest yield and stereoselectivity in relatively shorter times. For this purpose, we worked on each of the organocatalysts and conditions separately.

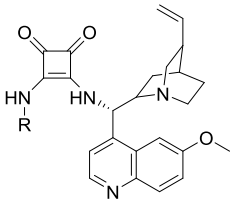
2.3.1 Studies on The Selection of The Ideal Organocatalyst

We planned to evaluate the bifunctional organocatalysts developed in our research group in terms of chemical yield and stereoselectivity in the sulfa-Michael addition of 1,4-dithiane-2,5-diol **(30)** to *trans*-β-nitrostyrene **(22)**. Additionally, commercially available quinine/urea organocatalyst **46** was also used. All the reactions were carried out in dichloromethane with 2 mol% catalyst loading at room temperature and the concentration was 0.2 M. 1,4-Dithiane-2,5-diol **(30)** and *trans*-β-nitrostyrene **(22)** were used in 1:1 equivalence. The results are summarized in Table 1.

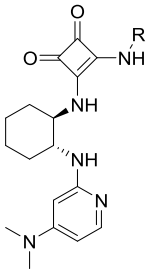
Table 1. Organocatalyst Screening



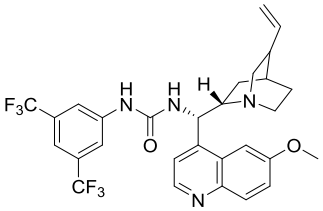
2-aminoDMAP/urea **33**
2-aminoDMAP/thiourea **34**



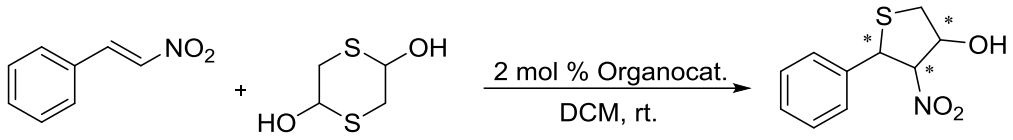
R: 1-adamantyl **17**
R: 2-adamantyl **18**
R: *tert*-butyl **19**



R: 1-adamantyl **13**
R: 2-adamantyl **14**
R: *tert*-butyl **15**



Urea Quinine **46**



22 **30** **45**

Entry[a]	Organocatalyst	Time	Yield[b] (%)	ee (%)[c] (minor)	ee (%)[c] (major)	dr[c]
1	18	1 h	78	7	10	94:6
2	19	2 h	90	21	rac	52:48
3	46	4 h	85	31	5	77:23
4	34	3 h	85	25	rac	52:48
5	33	10 min	95	21	rac	56:44
6	13	20 min	95	rac	7	56:44
7	14	0.5 h	95	rac	7	56:44
8	15	1 h	90	14	rac	50:50

a: All reactions were carried out by using 1 eq. **22**, 1 eq. **30** with 0.2 M concentration.

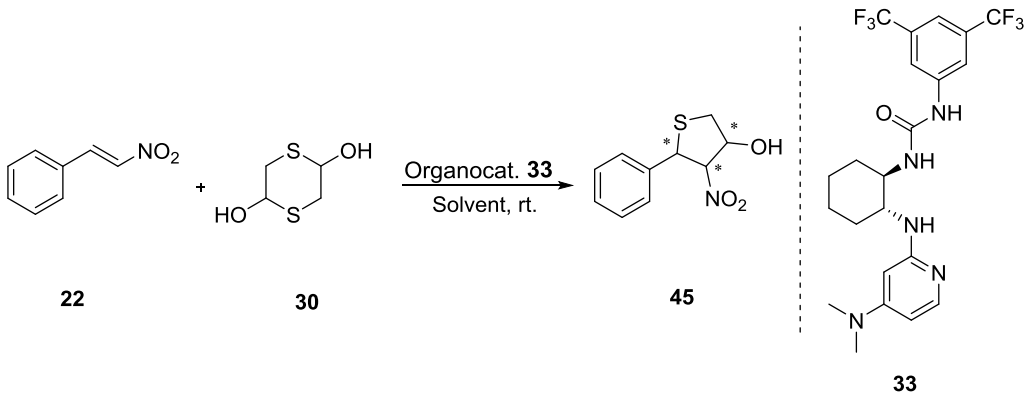
b: isolated yield *c*: determined by HPLC

None of the organocatalysts yielded acceptable level of stereoselectivity. Among them, 2-aminoDMAP/urea **33** afforded 95 % chemical yield in 10 minutes with 21 % ee value. Although the highest ee value was obtained by organocatalyst **34**, reaction duration was longer than the reaction performed with the organocatalyst **33**. Accordingly, further studies were done with the organocatalyst **33**.

2.3.2 Studies on Search for The Optimal Conditions

After choosing the organocatalyst, next attempt was done on organocatalyst loading parameter by lowering to 0.5 mol % to control the kinetic of the reaction which might increase the stereoselectivity. Slight increasing in ee value was observed as 30 %. Due to the solubility issue of 1,4-dithiane-2,5-diol in common solvents, the reaction was carried out in MTBE affording relatively high enantioselectivity as 43% ee. When the reaction was carried out in DCM, racemic major products were isolated. On the other hand, in MTBE, 31% ee value was obtained for the major product.

Table 2. Organocatalyst Loading and Solvent Screening



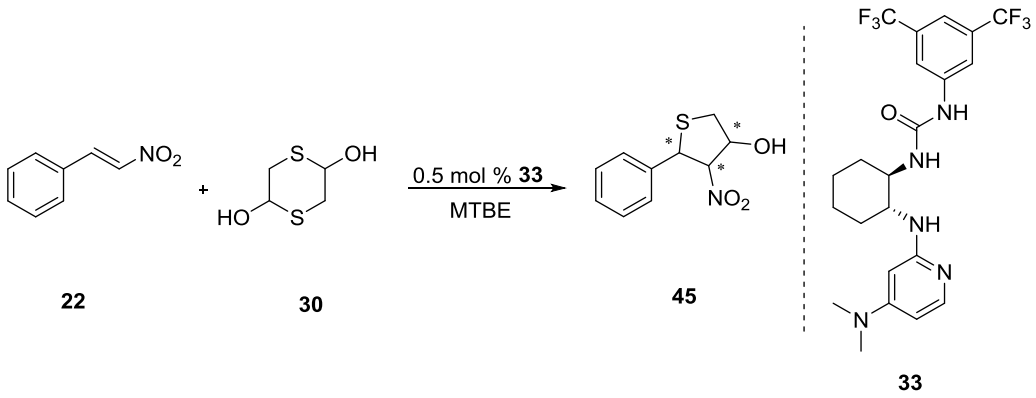
Entry[a]	Solvent	Organocat. (mol%)	Time (Min.)	Yield[b] (%)	ee (%)[c] (minor)	ee (%)[c] (major)	dr[c]
1	DCM	2	10	95	21	rac	56:44
2	DCM	0.5	10	90	30	rac	60:40
3	MTBE*	0.5	45	90	43	31	73:27

a: All reactions were carried out by using 1 eq. **22**, 1 eq. **30** with 0.2 M concentration.

b: isolated yield *c*: determined by HPLC

As the next optimization study, temperature screening was performed as shown on Table 3. We've considered that reducing temperature maintains slower reactions and this might lead to higher stereoselectivities. When the reaction was carried out at 0 ºC, the reaction got slower and ee values increased by about 10 %. Then we continued to try at -10 ºC and got 58 % ee for the minor and 39 % ee for the major products. However, at -20 ºC, both slight drop in ee and great loss in yield occurred. Therefore, -10 ºC was determined as the optimal temperature for the reaction in terms of stereoselectivity.

Table 3. Temperature Screening



22 30 45 33

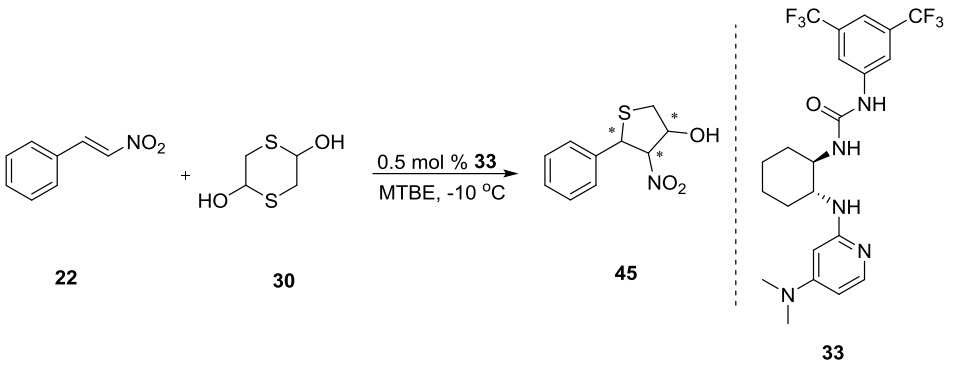
Entry[a]	Temp.	Time	Yield[b] (%)	ee (%)[c] (minor)	ee (%)[c] (major)	dr[c]
1	rt	45 min.	90	43	31	73:27
2	0 °C	4.5 h	87	52	40	75:25
3	-10 °C	9.5 h	90	58	39	80:20
4	-20 °C	13 h	52	55	39	86:14

a: All reactions were carried out by using 1 eq. **22**, 1 eq. **30** with 0.2 M concentration.

b: isolated yield *c*: determined by HPLC

As the last step of optimization studies, the effect of concentration was examined. For this purpose, the reaction was performed with the concentrations in the range of 0.1 and 0.3 M (Table 4). We had already carried out the reaction with 0.2 M. Therefore, we used 0.1 M and 0.3 M as different concentrations. Increase in the ee value of the minor product (70 % ee in 0.1 M and 66 % ee in 0.3 M) was observed for both concentrations. However, when the concentration was 0.3 M, ee value for the major product dropped from 39 % to 33 % ee. On the other hand, when the concentration was 0.1 M, higher ee value for the major product (42 % ee) was obtained and the rise in the ee value for the minor product (70 % ee) was relatively higher than the one in 0.3 M (66 % ee).

Table 4. Concentration Screening



Entry[a]	Conc. (M)	Time	Yield[b] (%)	ee (%)[c] (minor)	ee (%)[c] (major)	dr[c]
1	0.1	21 h	90	70	42	95:5
2	0.2	9.5 h	90	58	39	80:20
3	0.3	8.5 h	85	66	33	94:6

a: All reactions were carried out by using 1 eq. **22**, 1 eq. **30**.

b: isolated yield *c*: determined by HPLC

2.4 Derivatization Studies

After determining the optimal conditions for the sulfa-Michael addition reaction between *trans*-β-nitrostyrene **(22)** and 1,4-dithiane-2,5-diol **(30)**, the applicability of the reaction was extended by using various ortho, meta and para-substituted *trans*-β-nitrostyrene derivatives **22a-h** (Figure 11) under the same conditions in order to check the effect of electron-donating and electron-withdrawing substituents on the yield and stereoselectivity of the reaction. The results obtained are listed in Table 5.

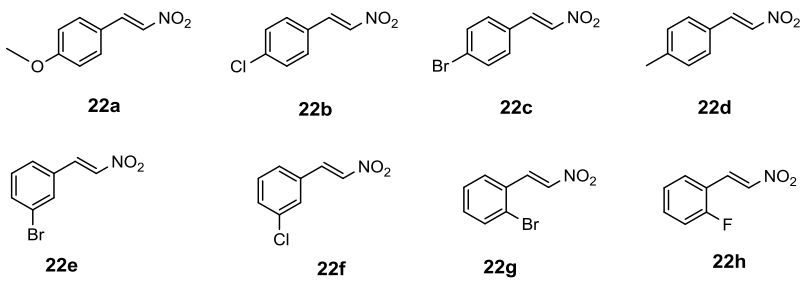
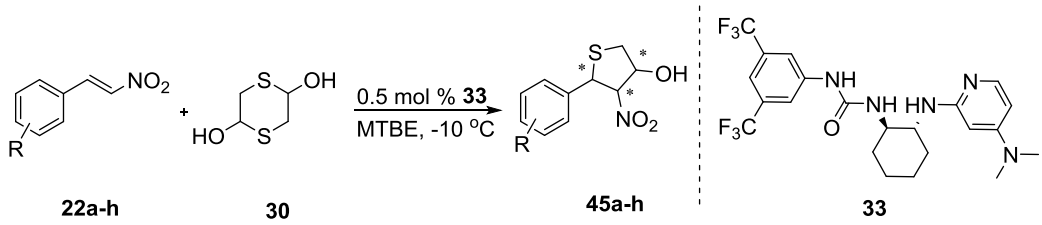
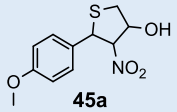
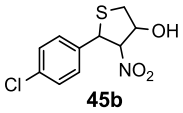
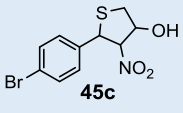
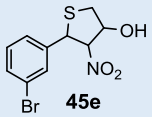
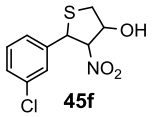
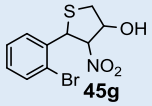
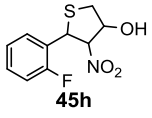


Figure 11. *trans*-β-nitrostyrene derivatives used in the work

Table 5. Derivatization Screening

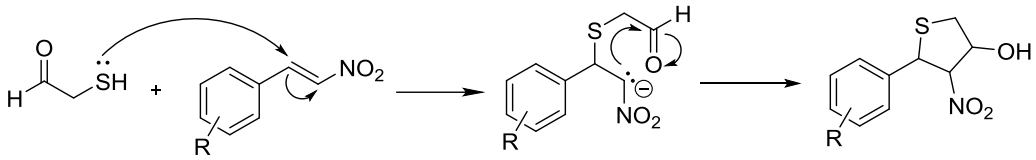


22a-h 30 45a-h 33

Entry	Product	Time (h)	Yield[a] (%)	ee (%)[b] (minor)	ee (%)[b] (major)	dr[b]
1	 45a	22	55	45	33	89:11
2	 45b	22	52	44	50	90:10
3	 45c	21	50	35	40	92:8
4	 45d	21	54	49	52	85:15
5	 45e	23	55	44	44	94:6
6	 45f	22	53	33	39	88:12
7	 45g	20	55	13	17	80:20
8	 45h	21	52	20	21	94:6

a: isolated yield *b*: determined by HPLC

Generally, it was observed that diastereomeric ratios were about 90:10 and enantiomeric excess values were about 45 % (Table 5). However, among the *trans*-β-nitrostyrene derivatives, the highest ee values for both major and minor products were reached with the 4-methyl substituted one (Table 5, entry 4). At that point, it should be emphasized that the derivative includes electron donating functional group. Because nitro group on *trans*-β-nitrostyrene has electron-withdrawing property, an electron donating unit on the phenyl may contribute to stabilization of the intermediate (Scheme 21). Due to this stability, the reaction of the derivatives containing electron donating groups may get harder compared to the ones including electron gaining substituents and this could make the selectivity easier. As a result, the enantioselectivities may have been relatively high for the products of the reactions of 4-methyl and 4-hydroxyl substituted *trans*-β-nitrostyrenes. As another interesting conclusion which can be reached from the data shown in Table 5, the lowest ee values were obtained in the reactions of *ortho*-substituted derivatives (entries 8 and 9).



Scheme 21. Proposed mechanism of the sulfa-Michael addition

In this work, both electrophiles (trans-β-nitrostyrene derivatives) and the nucleophile 1-4,dithiane-2,5-diol **(30)** were activated with the bifunctional organocatalysts. According to the transition state we proposed, while interaction through hydrogen bond provides deprotonation of thiol unit and the urea moiety activates the *trans*-β-nitrostyrene via double hydrogen bonding (Figure 12).

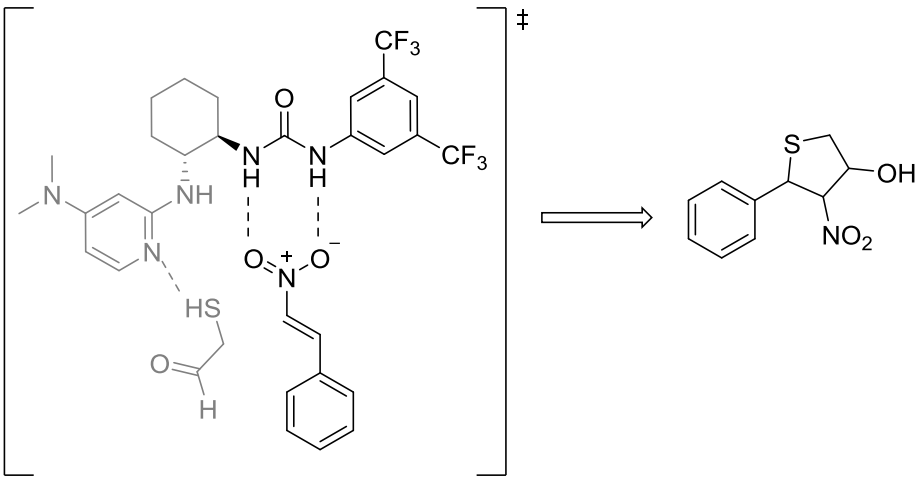


Figure 12. Proposed transition state

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

Bruker Spectrospin Avance DPX 400 spectrometer was used to record ^{1}H and ^{13}C NMR. $CDCl_3$ was used as the solvent to prepare samples for NMR. Chemical shifts are reported in parts per million and internal reference is tetramethylsilane. Spin multiplicities are symbolized as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dq (doublet of quartet), t (triplet), q (quartet), m (multiplet), sep (septet). Coupling constants (J) were reported in Hertz (Hz). ^{1}H and ^{13}C NMR spectra of the products are shown in Appendix A.

HPLC chromatograms were taken on Agilent instrument. Daicel Chiralpak AD-H, OD-H and IA columns were used with various *n*-hexane/ isopropanol eluent systems. The chromatograms are shown in Appendix B.

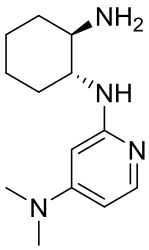
Rudolph Scientific Autopol III polarimeter was used for the measurement of optical rotations. The results were reported as $[\alpha]_D^T$ and c is the gram per 100 mL of solvent.

Agilent 6224 TOF LC/ MS was used to get the HRMS data at UNAM, Bilkent University.

Bruker Alpha Platinum ATR instrument was used to get IR analysis.Precoated silica gel plates (Merck Silica Gel 60 F_{254}) were used to monitor the reactions visualized by UV-light. Flash column chromatographies were performed on silica

gel 60 with particle size of 0.063-0.200 mm. Drying during extraction process were carried out by anhydrous magnesium sulfate and vacuum was used to remove the solvents. ChemBioDraw Ultra was used for the purpose of nomenclature and MestReNova was the tool for NMR interpretation.

3.2 Synthesis of *R, R*-Configurated 2-AminoDMAP 37



In order to synthesize 2-aminoDMAP **37**, CuBr (1.46 mmol, 0.209 g) and K_3PO_4 (14.6 mmol, 3.057 g) were added to an oven-dried Schlenk tube. Then, (1*R*, 2*R*)-*trans*-1,2-cyclohexanediamine **35** (8.65 mmol, 0.98 g) and 2-bromoDMAP **36** (7.21 mmol, 1.45 g) were added to the reaction mixture. All this work was done under argon atmosphere due to the sensitivity of the reaction to air. The reaction mixture was stirred at 110 ^oC for 24 hours after addition of 1,4-dioxane (7.3 mL) which was dried with sodium and benzophenone. After the green-blue mixture was cooled to room temperature, 2 mL of water and 2 mL of concentrated ammonia were added. The resulting dark blue solution was extracted with DCM (3×25 mL). Brine and $MgSO_4$ were used to dry the organic phase. Flash chromatography was applied to purify the product. At the beginning, only saturated DCM was used as the eluent, but methanol was added gradually up to 10 %. 2-aminoDMAP **37** was obtained as light brown solid.[14]

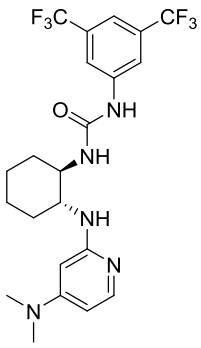
mp: 138-140 ˚C

$[\alpha]_D^{20}$ = -55.0˚ (c 0.25, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 6.1 Hz, 1H), 5.91 (dd, J = 6.1, 2.3 Hz, 1H), 5.53 (d, J = 2.1 Hz, 1H), 4.19 (d, J = 9.4 Hz, 1H), 3.31 – 3.16 (m, 1H), 2.87 (s, 6H), 2.41 (td, J = 10.4, 4.0 Hz, 1H), 2.06 – 1.94 (m, 1H), 1.93 – 1.87 (m,1H), 1.78 (bs, 2H), 1.70 – 1.57 (m, 2H), 1.29 – 1.16 (m, 4H), 1.09 – 0.94 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 156.1, 147.9, 99.2, 87.7, 58.4, 56.2, 39.2, 34.8, 32.8, 25.4, 25.0 ppm.

3.3 Synthesis of 2-AminoDMAP/Urea Bifunctional Organocatalyst 34



2-AminoDMAP **37** (0.2 mmol, 47 mg) was dissolved in 1 mL of dry THF. 1-Isocyanato-3,5-bis(trifluoromethyl)benzene **39** was added to this solution dropwise in 1 minute at room temperature. The reaction mixture was stirred for 1 hour at room temperature. Then column chromatography was applied with the eluent of DCM:MeOH (90:10). The organocatalyst **33** was obtained as a pale-yellow solid in 88% yield.[14]

mp: 110-115 ^{o}C

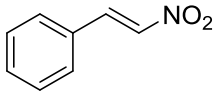
$[\alpha]_D^{20}$ = -125.0˚ (c = 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.60 (m, 3H), 7.52 – 7.16 (m, 3H), 6.94 – 5.27 (m, 2H), 4.39 (s, 1H), 3.68 (d, J = 89.6 Hz, 2H), 3.02 – 2.76 (m, 6H), 2.13 (d, J = 50.9 Hz, 4H), 1.70 (s, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.22, 155.88, 146.30, 141.34, 131.73, 131.43, 131.40, 121.81, 99.88, 89.01, 38.93, 29.58, 29.52 ppm.

IR 2923, 2855, 1695, 1379, 1273, 1165, 1128, 906, 843, 731, 702 cm^{-1}

3.4 Synthesis of trans-β-Nitrostyrene 22



According to literature, to a stirred mixture of benzaldehyde (0.1 mol, 10.46 mL) and nitromethane (0.1 mol, 5.4 mL) in

methanol (25 mL) at 0 °C, an aqueous solution of NaOH (0.1125 mol, 100 mL) was added dropwise over a period of 30 min. The stirring was continued for another half an hour in the temperature range of 0 to 5 °C. The reaction was monitored by TLC. After the reaction was completed, the mixture was diluted with 50 mL of distilled water and poured over crushed ice containing concentrated HCl (16 mL). The yellow precipitate was filtered, dried in a vacuum desiccator, and crystallized from hot EtOH.[34]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 7.88 (m, 1H), 7.67 – 7.56 (m, 2H), 7.56 – 7.49 (m, 2H), 7.49 – 7.33 (m, 2H) ppm.

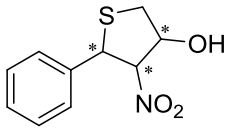
^{13}C NMR (101 MHz, $CDCl_3$) δ 139.00, 136.99, 132.06, 129.93, 129.30, 129.05 ppm.

IR 3108, 1630, 1510, 1494, 1448, 1338, 1262, 966, 766, 706, 681, 593, 534, 487 cm^{-1}

3.5 General Procedure for The Sulfa-Michael Additions of 1,4-Dithiane-2,5-Diol (30) to *Trans*-β-Nitrostyrene

For the purpose of racemic synthesis, *trans*-β-nitrostyrene derivatives (0.2 mmol), 1,4-dithiane-2,5-diol **(30)** (0.2 mmol, 30.45 mg) were dissolved in DCM (1 mL) and Et_3N (20 %) was added as the base. The reactions were carried out at room temperature and monitored by TLC. After the completion of reactions, purifications were provided with column chromatography in which the eluents were 1/7 EtOAc:Hexane. On the other hand, in asymmetric synthesis, 0.4 mmol of nitrostyrene and 0.4 mmol of 1,4-dithiane-2,5-diol **(30)** were dissolved in 4 mL of MTBE. 2×10^{-3} mmol of urea/2-aminoDMAP bifunctional organocatalyst **(34)** was added at -10 °C. After TLC monitoring, column chromatography was applied to remove the organocatalyst and impurities.[35]

3.5.1 Synthesis of 4-Nitro-5-phenyltetrahydrothiophen-3-ol (45)

The general procedure which starts from unsubstituted *trans*-β-nitrostyrene **(22)**  was carried out producing the chiral product **45** with 90 % yield by 42 % major ee, 70 % minor ee, 95:5 dr in 21 hours.

^{1}H NMR (400 MHz, CDCl3) δ 7.53 – 7.43 (m, 2H), 7.39 – 7.29 (m, 3H), 5.24 (d, J = 9.7 Hz, 1H), 5.10 – 5.04 (m, 1H), 5.00 (dd, J = 9.7, 3.8 Hz, 1H), 3.52 (dd, J = 12.0, 4.3 Hz, 1H), 3.08 (dd, J = 12.0, 2.2 Hz, 1H), 2.74 (bs, 1H) ppm.

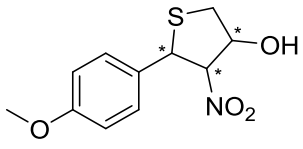
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.62, 128.97, 128.62, 128.23, 95.52, 75.47, 48.31, 36.14 ppm.

HPLC (Chiralpak AD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 210 nm) Retention time; t_r = 27 min, 44 min (major). t_r = 29 min, 63 min (minor).

IR 3318, 2923, 1562, 1478, 1347, 1203, 1067, 1034, 1002, 814, 743, 568 cm^{-1}

3.5.2 Synthesis of 5-(4-methoxyphenyl)-4-nitrotetrahydrothiophen-3-ol 45a

The general procedure which starts from *trans*-4-methoxy-β-nitrostyrene **22a** was carried out producing the chiral product **45a** with 55 % yield by 33 % major ee, 45 % minor ee, 89:11 dr in 22 hours.

 **^{1}H NMR** (400 MHz, CDCl3) δ 7.43 – 7.29 (m, 2H, both isomers), 6.87 (d, J = 8.6 Hz, 2H, both isomers), 5.21 (d, J = 9.9 Hz, 1H, min), 5.03 (bs, 1H, min), 4.99 – 4.81 (m, 2H, both isomers), 3.79 (s, 3H, both isomers), 3.48 (dd, J = 12.0, 4.4 Hz, 1H, min), 3.27 (dd, J = 10.9, 6.7 Hz, 1H, maj), 3.21 – 3.07 (m, 3H, maj), 3.03 (dd, J = 12.0, 2.0 Hz, 1H, min) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.91, 159.71, 129.41, 128.99, 128.27, 128.15, 114.44, 114.34, 98.05, 95.53, 77.29, 75.31, 55.37, 49.15, 47.91, 47.90, 36.00, 33.70 ppm.

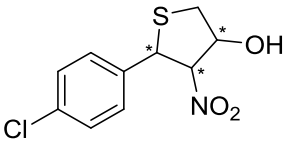
HPLC (Chiralpak AD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 210 nm) Retention time; t_r = 43 min, 45 min (major). t_r = 30 min, 38 min (minor).

$[\alpha]_D^{20}$ = -45.6˚ (c = 1.96, CH_2Cl_2)

IR 3386, 2934, 1611, 1546, 1511, 1460, 1368, 1305, 1249, 1174, 1113, 1026, 837, 790, 744, 657, 624 cm^{-1}

3.5.3 Synthesis of 5-(4-chlorophenyl)-4-nitrotetrahydrothiophen-3-ol 45b

The general procedure which starts from *trans*-4-chloro-β-nitrostyrene **22b** was carried out producing the chiral product **45b** with 52 % yield by 50 % major ee, 44 % minor ee, 90:10 dr in 22 hours.



^1H NMR (400 MHz, CDCl3) δ 7.45 – 7.27 (m, 4H, both isomers), 5.21 (d, J = 10.0 Hz, 1H, min), 5.11 – 5.04 (bs, 1H, min), 5.02 – 4.84 (m, 2H, both isomers), 3.50 (dd, J = 18.4, 7.3 Hz, 1H, min), 3.30 (dd, J = 11.0, 7.0 Hz, 1H, maj), 3.16 (dd, J = 11.0, 8.2 Hz, 1H, maj), 3.06 (dd, J = 12.0, 1.9 Hz, 1H, min), 2.98 – 2.25 (m, 2H, maj) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.28, 135.09, 134.77, 134.47, 129.66, 129.29, 129.17, 129.15, 97.74, 95.41, 76.79, 75.33, 48.83, 47.62, 36.03, 33.86 ppm.

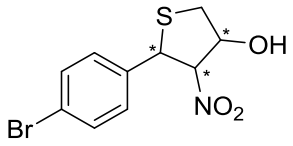
HPLC (Chiralpak OD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 220 nm) Retention time; t_r = 24 min, 34 min (major). t_r = 14 min, 15 min (minor).

$[\alpha]_D^{20}$ = -42.1° (c = 2.64, CH_2Cl_2)

IR 3417, 1545, 1490, 1368, 1169, 1089, 1040, 1013, 831, 746, 613, 510 cm^{-1}

3.5.4 Synthesis of 5-(4-bromophenyl)-4-nitrotetrahydrothiophen-3-ol 45c

The general procedure which starts from *trans*-4-bromo-β-nitrostyrene **22c** was carried out producing the chiral product **45c** with 50 % yield by 40 % major ee, 35 % minor ee, 92:8 dr in 21 hours.



^{1}H NMR (400 MHz, CDCl3) δ 7.55 – 7.05 (m, 4H, both isomers), 5.13 (d, J = 10.0 Hz, 1H, min), 5.00 (bs, 1H, min), 4.96 – 4.69 (m, 2H, both isomers), 3.44 (dd, J = 12.0, 4.3 Hz, 1H, min), 3.22 (dd, J = 10.9, 7.0 Hz, 1H, maj), 3.08 (dd, J = 10.9, 8.3 Hz, 1H, maj), 2.98 (dd, J = 12.0, 1.7 Hz, 1H, min), 2.70 (bs, 1H, maj) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.84, 135.67, 132.25, 132.10, 129.99, 129.49, 122.89, 122.56, 97.69, 95.38, 76.95, 75.35, 48.84, 47.63, 36.05, 33.80 ppm.

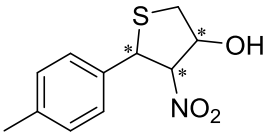
HPLC (Chiralpak OD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 220 nm) Retention time; t_r = 26 min, 36 min (major). t_r = 14 min, 16 min (minor).

$[\alpha]_D^{20}$ = -43.2° (c = 5.24, CH_2Cl_2)

IR 3332, 2914, 1545, 1486, 1369, 1170, 1071, 1042, 1009, 828, 746 cm^{-1}

3.5.5 Synthesis of 4-nitro-5-(p-tolyl)tetrahydrothiophen-3-ol 45d

The general procedure which starts from *trans*-4-methyl-β-nitrostyrene **22d** was carried out producing the chiral product **45d** with 54 % yield by 52 % major ee, 49 % minor ee, 85:15 dr in 21 hours.



^{1}H NMR (400 MHz, CDCl3) δ 7.27 (d, J = 8.0 Hz, 2H, maj), 7.21 (d, J = 8.0 Hz, 2H, min), 7.07 (d, J = 7.9 Hz, 2H, both isomers), 5.13 (d, J = 9.8 Hz, 1H, maj), 4.96 (bs, 1H, maj), 4.93 – 4.74 (m, 2H, both isomers), 3.41 (dd, J = 12.0, 4.3 Hz, 1H, maj), 3.19 (dd, J = 10.8, 6.2 Hz, 1H, min), 3.13 – 2.82 (m, 2H, both isomers; bs, 1H, min), 2.25 (s, 3H, both isomers) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.69, 138.38, 133.40, 133.32, 129.63, 129.52, 127.94, 127.50, 97.84, 95.37, 76.77, 75.28, 49.26, 48.00, 35.95, 33.75, 29.59, 21.02 ppm.

HPLC (Chiralpak OD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 220 nm) Retention time; t_r = 19 min, 25 min (major). t_r = 11 min, 13 min (minor).

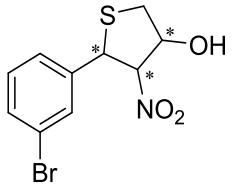
$[\alpha]_D^{20}$ = -60.5˚ (c = 0.68, CH_2Cl_2)

IR 2918, 1547, 1370, 1169, 1041, 747 cm^{-1}

HRMS for $C_{11}H_{13}NO_3S$, $[M-H]^-$ calculated: 238.0538, found: 238.1241

3.5.6 Synthesis of 5-(3-bromophenyl)-4-nitrotetrahydrothiophen-3-ol 45e

The general procedure which starts from *trans*-3-bromo-β-nitrostyrene **22e** was carried out producing the chiral product **45e** with 55 % yield by 44 % major ee, 44 % minor ee, 94:6 dr in 23 hours.



^{1}H NMR (400 MHz, CDCl3) δ 7.74 – 7.64 (m, 1H), 7.62 (m, 1H), 7.53 – 7.16 (m, 6H), 5.22 (dd, J = 9.8, 2.4 Hz, 1H), 5.10 (bs, 1H), 5.05 – 4.82 (m, 4H), 3.61 – 3.47 (m, 1H), 3.38 – 3.27 (m, 1H), 3.24 – 3.15 (m, 1H), 3.12 – 2.60 (m, 3H) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.10, 138.99, 131.93, 131.65, 131.09, 130.71, 130.46, 130.33, 127.05, 126.46, 122.94, 122.78, 97.51, 95.27, 76.74, 75.31, 48.65, 47.48, 35.97, 33.81 ppm.

HPLC (Chiralpak OD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 220 nm) Retention time; t_r = 25 min, 34 min (major). t_r = 15 min, 17 min (minor).

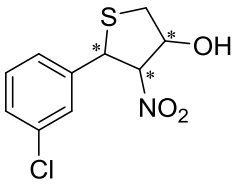
$[\alpha]_D^{20}$ = -22.0° (c = 3.12, CH_2Cl_2)

IR 3334, 2912, 1545, 1474, 1429, 1369, 1263, 1173, 1041, 996, 891, 741, 689

HRMS for $C_{10}H_{10}BrNO_3S$, $[M-H]^-$ calculated: 301.9487, found: 302.0267

3.5.7 Synthesis of 5-(3-chlorophenyl)-4-nitrotetrahydrothiophen-3-ol 45f

The general procedure which starts from *trans*-3-chloro-β-nitrostyrene **22f** was carried out producing the chiral product **45f** with 53 % yield by 39 % major ee, 33 % minor ee, 88:12 dr in 22 hours.



^{1}H NMR (400 MHz, CDCl3) δ 7.51 (d, J = 8.2 Hz, 1H, min), 7.46 (d, J = 8.3 Hz, 1H, maj), 7.40 – 7.21 (m, 3H, both isomers), 5.23 (dd, J = 9.8, 1.9 Hz, 1H, min), 5.14 – 5.06 (m, 1H, min), 5.06 – 4.82 (m, 3H maj and 1H min), 3.55 (m, 1H, min), 3.40 – 3.29 (m, 1H, maj), 3.25 – 3.16 (m, 1H, maj), 3.14 – 3.04 (m, 1H, min), 2.65 (bs, 1H min and 1H maj) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.96, 137.83, 133.94, 133.77, 129.29, 129.15, 128.08, 127.81, 127.30, 126.91, 125.63, 125.06, 96.63, 94.36, 75.85, 74.38, 47.84, 46.66, 35.07, 28.67 ppm.

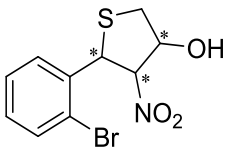
HPLC (Chiralpak OD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 220 nm) Retention time; t_r = 24 min, 33 min (major). t_r = 14 min, 16 min (minor). $[\alpha]_D^{20}$ = -27.9° (c = 2.36, CH_2Cl_2)

IR 3420, 2938, 1595, 1546, 1476, 1433, 1369, 1167, 1081, 1041, 895, 784, 745, 690 cm^{-1}

HRMS for $C_{10}H_{10}ClNO_3S$ $[M-H]^-$ calculated: 257.9992, found: 258.0710

3.5.8 Synthesis of 5-(2-bromophenyl)-4-nitrotetrahydrothiophen-3-ol 45g

The general procedure which starts from *trans*-2-bromo-β-nitrostyrene **22g** was carried out producing the chiral product **45g** with 55 % yield by 17 % major ee, 13 % minor ee, 80:20 dr in 20 hours.



^{1}H NMR (400 MHz, CDCl3) δ 7.69 (d, J = 7.7 Hz, 2H, min), 7.60 (m, 2H, maj), 7.36 (m, 2H, maj), 7.19 (m, 2H, min), 5.70 (d, J = 8.3 Hz, 1H, min), 5.51 (d, J = 8.5 Hz, 1H, maj), 5.29 – 5.17 (m, 1H, min), 5.10 (m, 2H maj and 1H min), 3.50 (dd, J = 11.7, 4.6 Hz, 1H, min), 3.40 – 3.28 (m, 1H, maj), 3.27 – 3.09 (m, 2H min and 1H maj), 2.90 (bs, 1H, maj) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.34, 136.04, 133.55, 133.30, 129.91, 129.74, 129.01, 128.82, 128.22, 127.99, 124.76, 124.39, 96.17, 93.39, 77.01, 74.83, 47.97, 47.50, 35.67, 34.23 ppm.

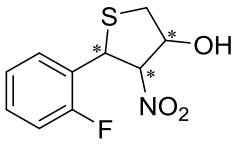
HPLC (Chiralpak OD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 220 nm) Retention time; t_r = 31 min, 37 min (major). t_r = 17 min, 25 min (minor). $[\alpha]_D^{20}$ = -6.5° (c = 3.32, CH_2Cl_2)

IR 3401, 2913, 1546, 1470, 1438, 1369, 1024, 741, 675

HRMS for $C_{10}H_{10}BrNO_3S$ $[M-H]^-$ calculated: 301.9487, found: 302.0257

3.5.9 Synthesis of 5-(2-fluorophenyl)-4-nitrotetrahydrothiophen-3-ol 45h

The general procedure which starts from *trans*-2-fluoro-β-nitrostyrene **22h** was carried out producing the chiral product **45h** with 52 % yield by 21 % major ee, 20 % minor ee, 94:6 dr in 21 hours.



^{1}H NMR (400 MHz, CDCl3) δ 7.50 (m, 2H, min), 7.41 – 7.26 (m, 2H, maj), 7.25 – 7.01 (m, 2H min and 2H maj), 5.46 (dd, J = 9.3, 3.7 Hz, 1H, min), 5.32 – 5.16 (m, 1H, both isomers), 5.16 – 4.86 (m, 2H maj and 1H min), 3.55 (m, 1H, min), 3.27 (m, 2H, maj), 3.18 – 3.07 (m, 1H, maj), 3.06 – 2.73 (m, 2H, min) ppm.

* Due to non-separable diastereomeric mixture, ^{13}C NMR signals could not be predicted well.

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.96 (d, J = 248.8 Hz), 160.68 (d, J = 248.6 Hz), 130.35 (d, J = 8.6 Hz), 130.15 (d, J = 8.8 Hz), 129.79 (d, J = 3.0 Hz), 129.15 (d, J = 3.2 Hz), 124.69 (d, J = 3.6 Hz), 124.53 (d, J = 3.3 Hz), 124.22 (d, J = 12.0 Hz), 124.03 (d, J = 11.8 Hz), 116.19 (d, J = 15.6 Hz), 115.98 (d, J = 15.7 Hz), 95.88, 93.42 (d, J = 2.5 Hz), 75.26, 42.81, 42.36, 36.07, 33.98, 29.59 ppm.

HPLC (Chiralpak OD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 220 nm) Retention time; t_r = 23 min, 28 min (major). t_r = 14 min, 16 min (minor). $[\alpha]_D^{20}$ = -20.9° (c = 1.8, CH_2Cl_2)

IR 3409, 2918, 1587, 1549, 1491, 1456, 1368, 1230, 1171, 1043, 809, 752, 473

HRMS for $C_{10}H_{10}FNO_3S$ $[M-H]^-$ calculated: 242.0287, found: 242.0980

CHAPTER 4

CONCLUSION

In this study, yield and stereoselectivity performance of quinine-based and 2-aminoDMAP-based bifunctional organocatalysts developed in our research group was tested on sulfa-Michael addition of 1,4-dithiane-2,5-diol **(30)** to *trans*-β-nitrostyrene derivatives in different conditions. The reactions afforded polyfunctional tetrahydrothiophene derivatives which have 3 stereogenic centers.

As the first step, the asymmetric reaction was tested with the bifunctional organocatalysts and 2-aminoDMAP-based urea **33** was determined as the optimal one in terms of yield, time and stereoselectivity. Therefore, further studies were done with this organocatalyst. Secondly, the work was done in diverse conditions. As a result, the optimized condition for the reaction was decided as 0.5 mol % organocatalyst **33**, at -10 ^{o}C, in MTBE. Lastly, the reaction was accomplished with 9 derivatives of *trans*-β-nitrostyrene in that condition and the best stereoselectivity was reached with the *trans*-4-methyl-β-nitrostyrene **22d** as 52 % ee for the major and 49 % ee for the minor products.

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APPENDICES

APPENDIX A – NMR DATA

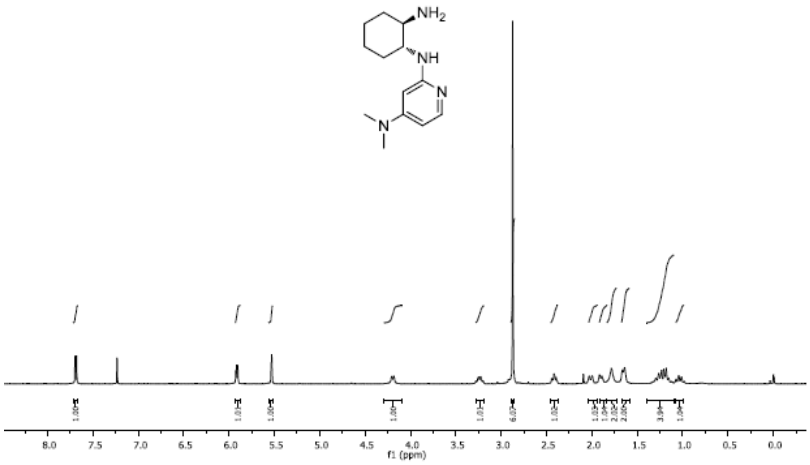


Figure A. 1. ^{1}H NMR spectrum of compound **37**

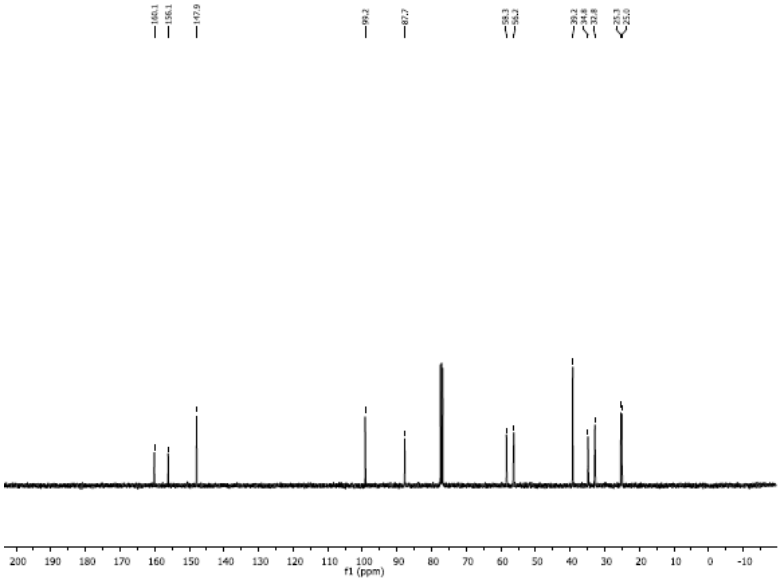


Figure A. 2. ^{13}C NMR spectrum of compound **37**

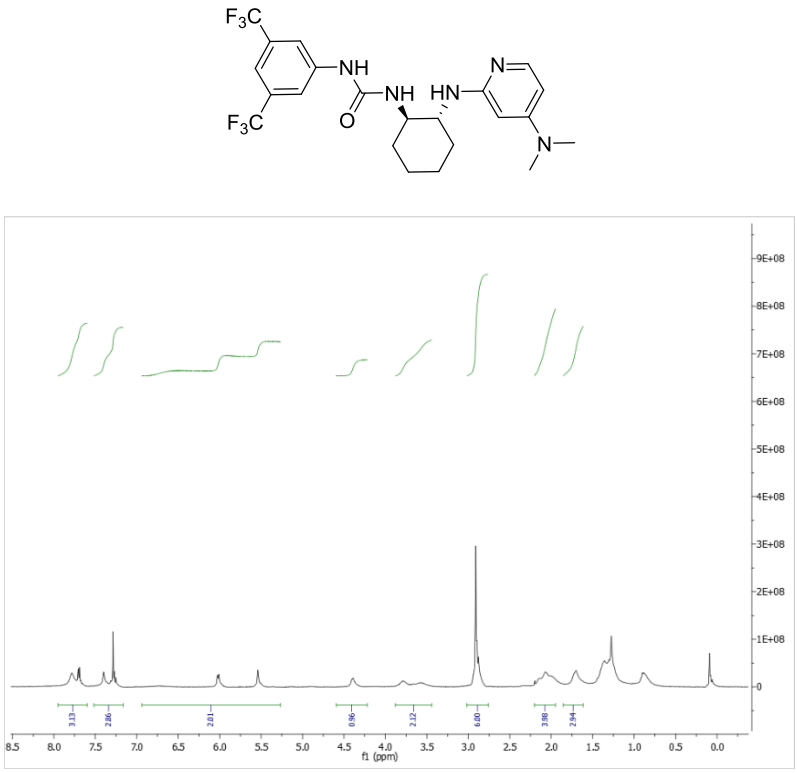


Figure A. 3. ^{1}H NMR spectrum of compound **33**

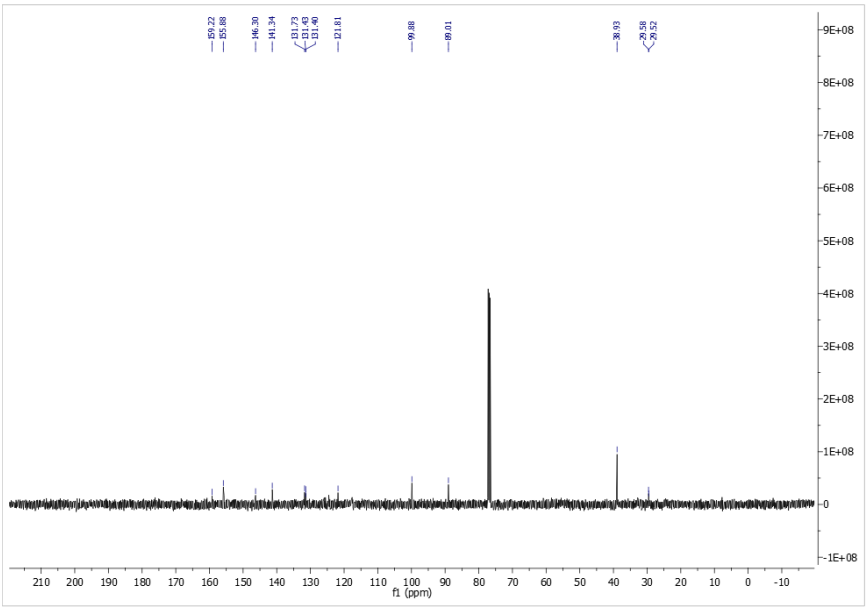


Figure A. 4. ^{13}C NMR spectrum of compound **33**

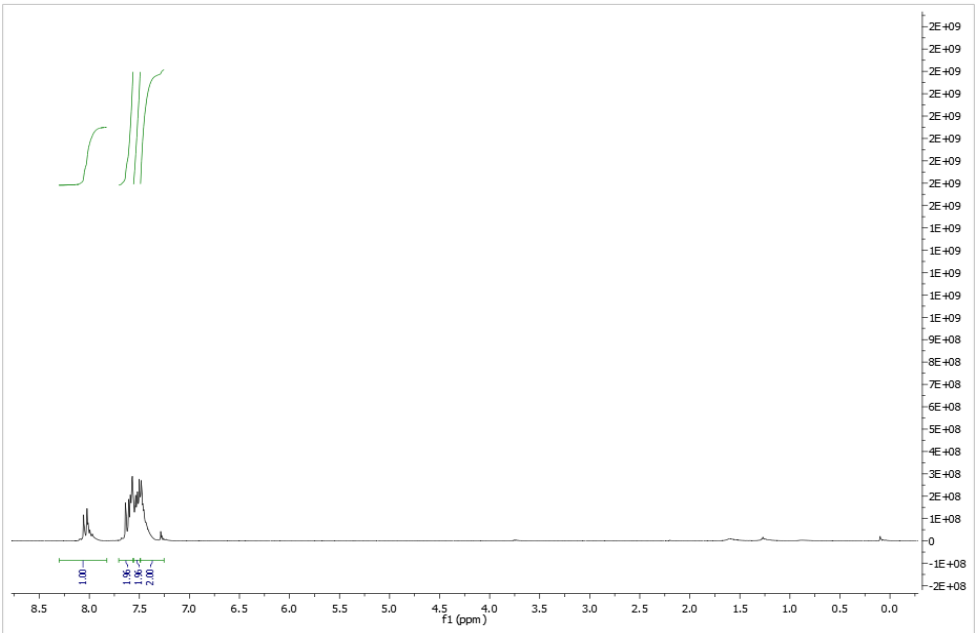


Figure A. 5. ^{1}H NMR spectrum of compound **22**

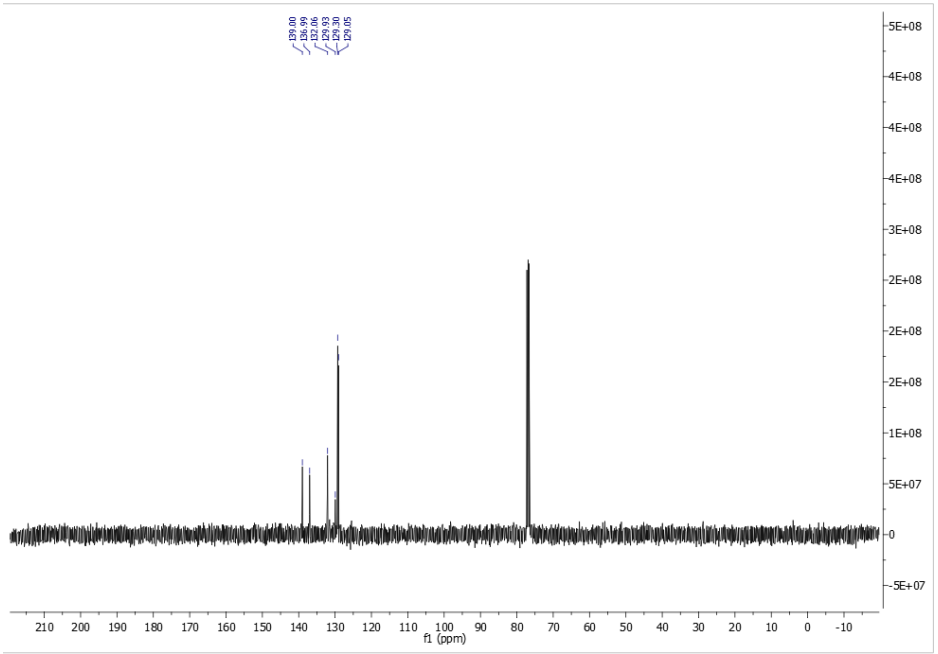


Figure A. 6. ^{13}C NMR spectrum of compound **22**

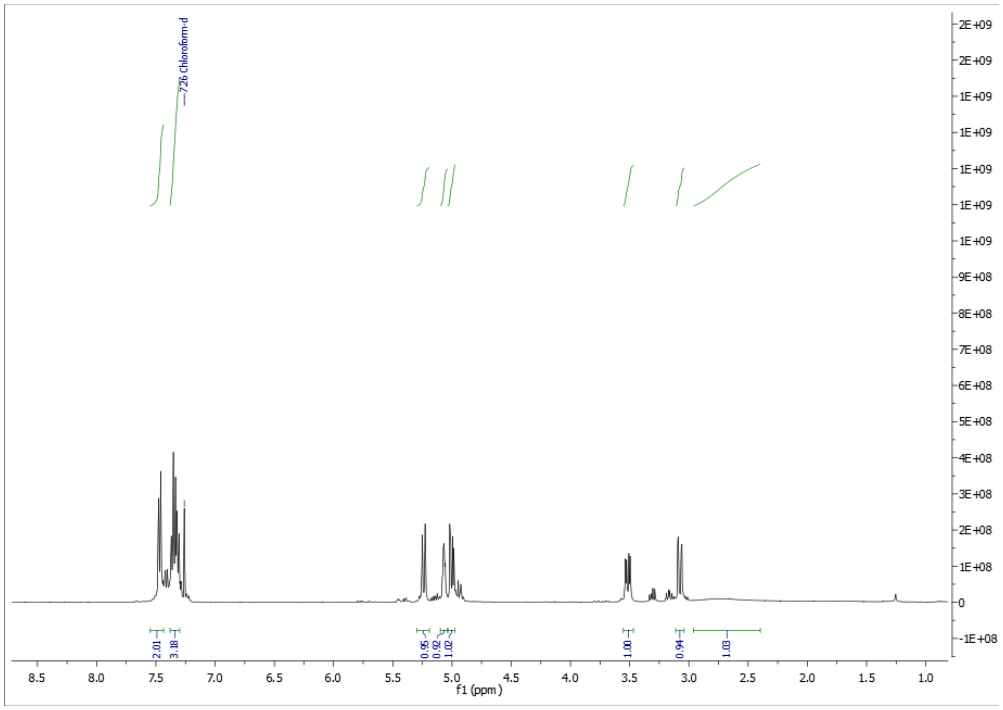


Figure A. 7. ^{1}H NMR spectrum of compound **45**

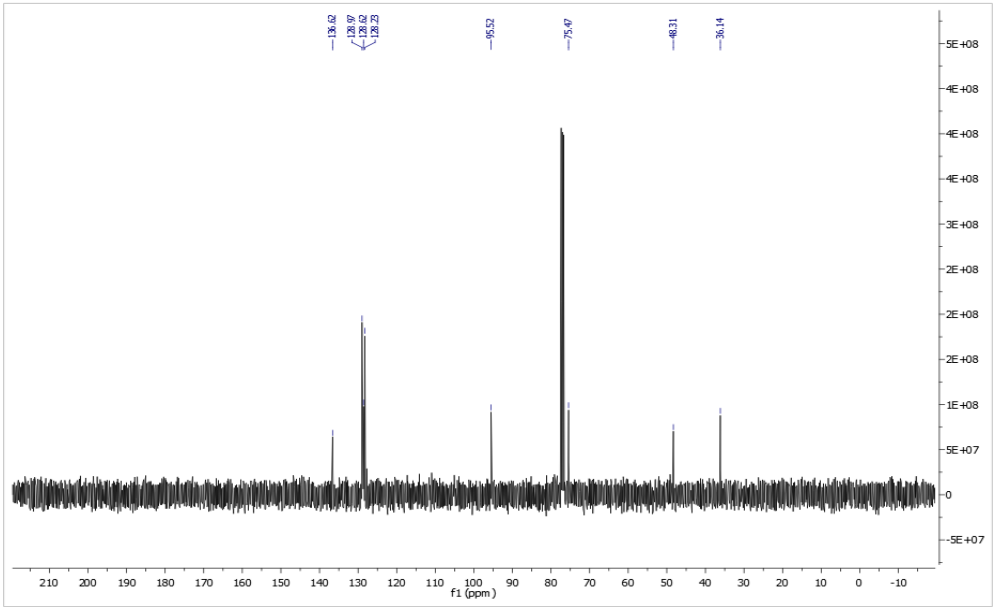
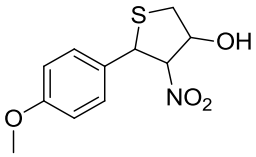


Figure A. 8. 13C NMR spectrum of compound **45**



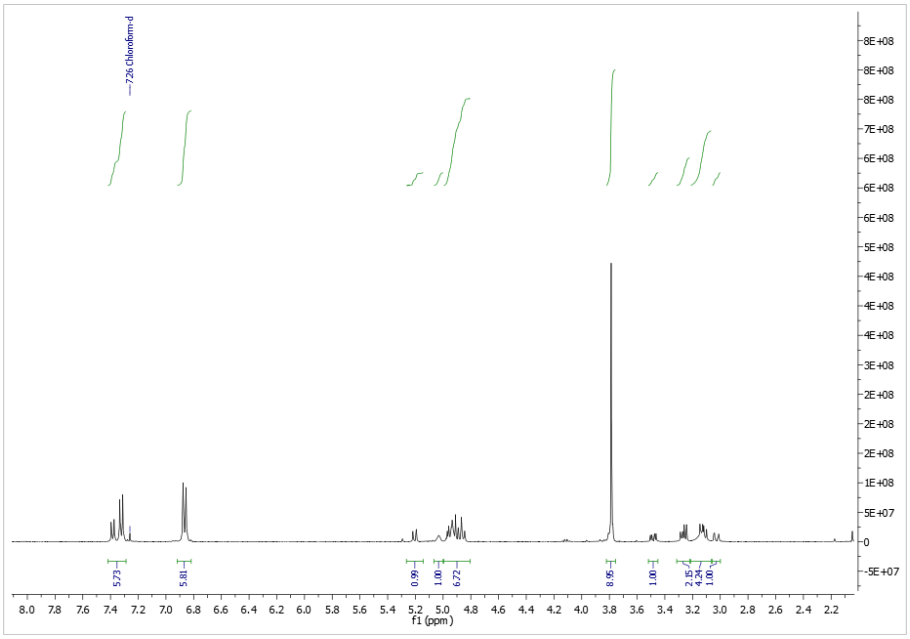


Figure A. 9. ^{1}H NMR spectrum of compound **45a**

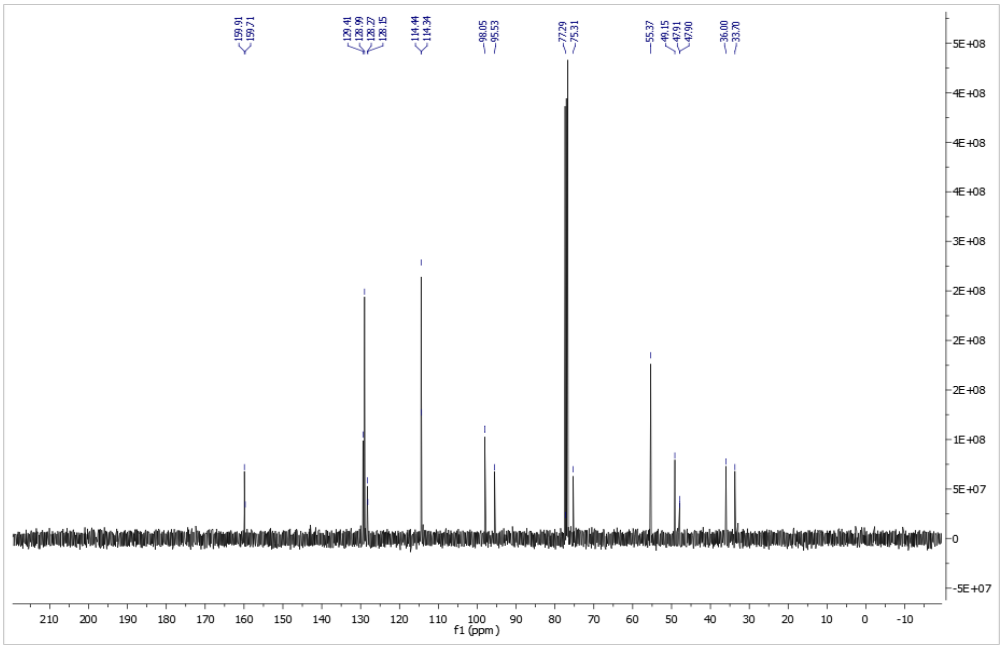
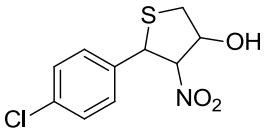


Figure A. 10. ^{13}C NMR spectrum of compound **45a**



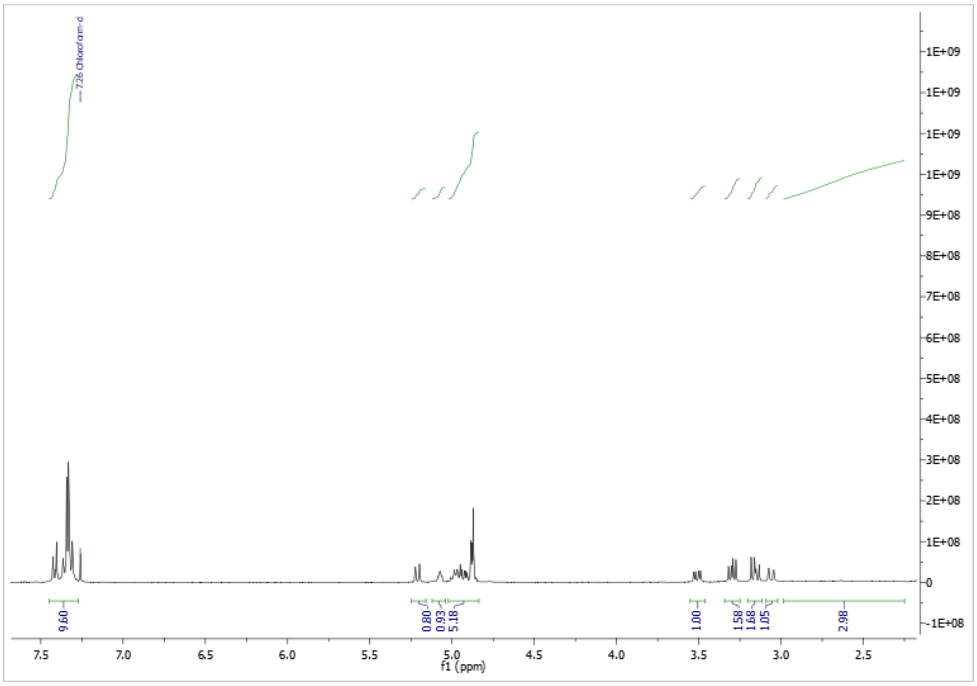


Figure A. 11. ^{1}H NMR spectrum of compound **45b**

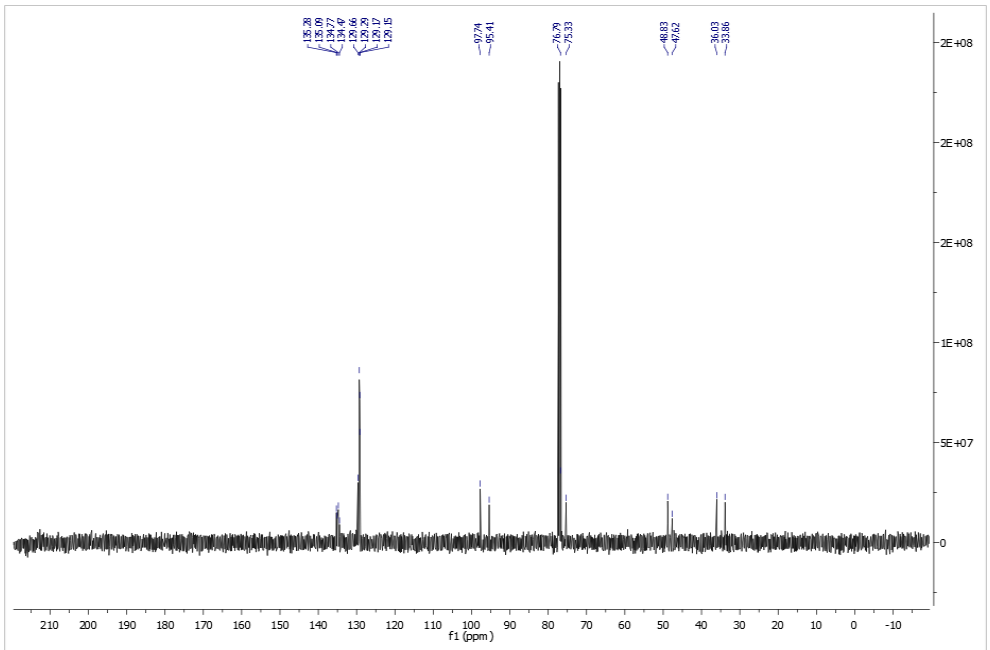
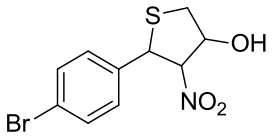


Figure A. 12. ^{13}C NMR spectrum of compound **45b**



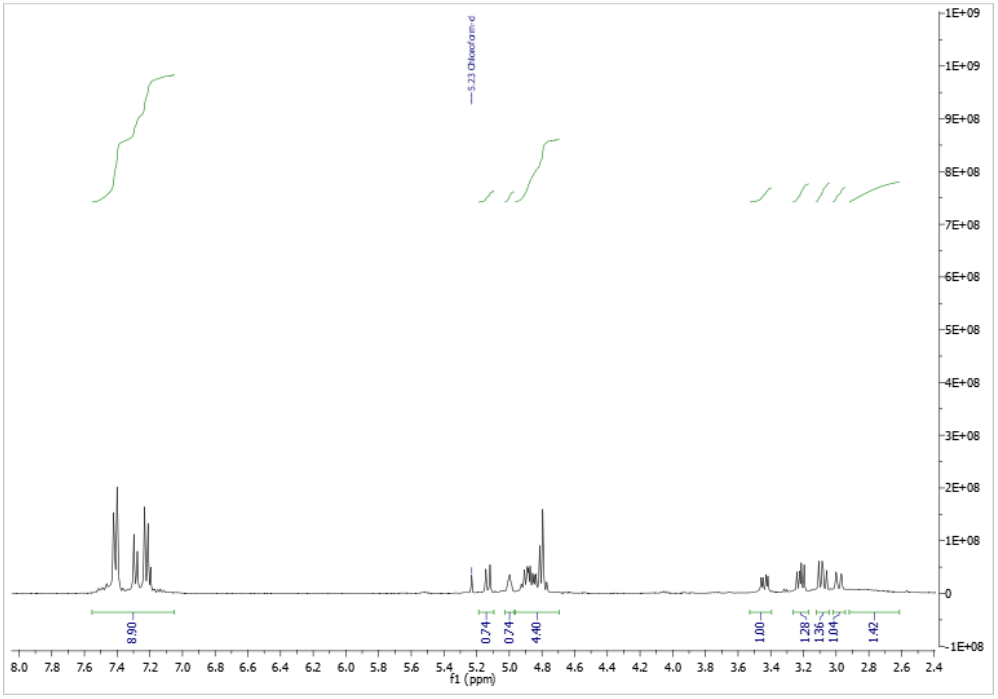


Figure A. 13. ^{1}H NMR spectrum of compound **45c**

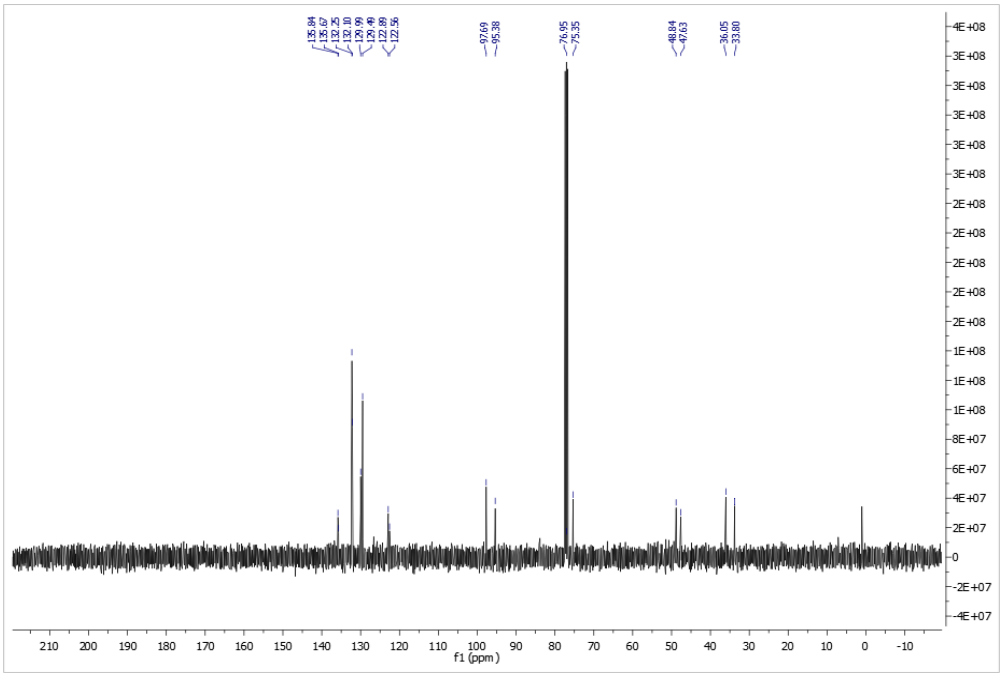
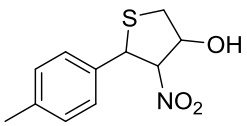


Figure A. 14. ^{13}C NMR spectrum of compound **45c**



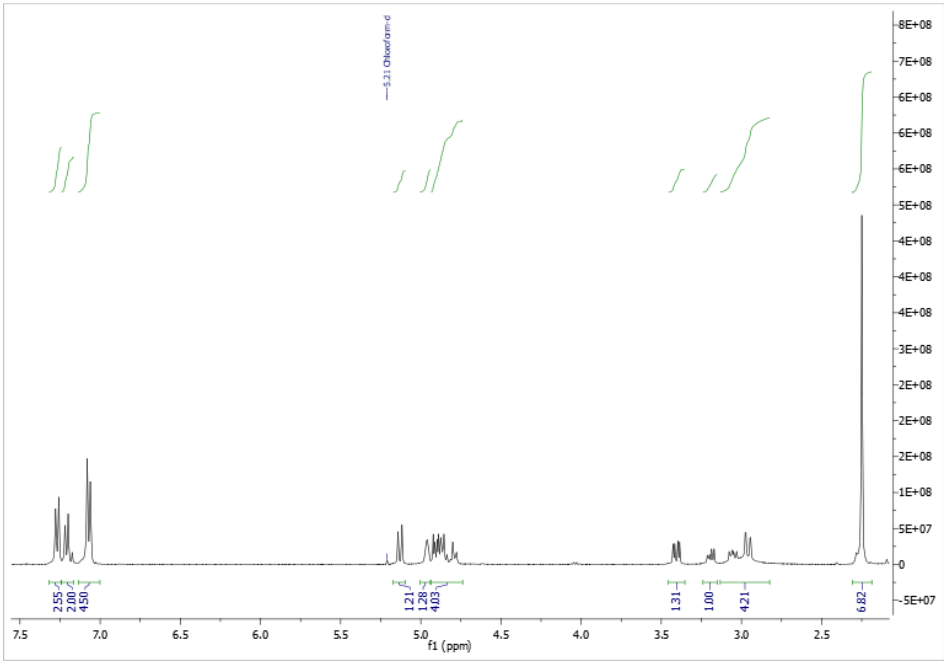


Figure A. 15. ^{1}H NMR spectrum of compound **45d**

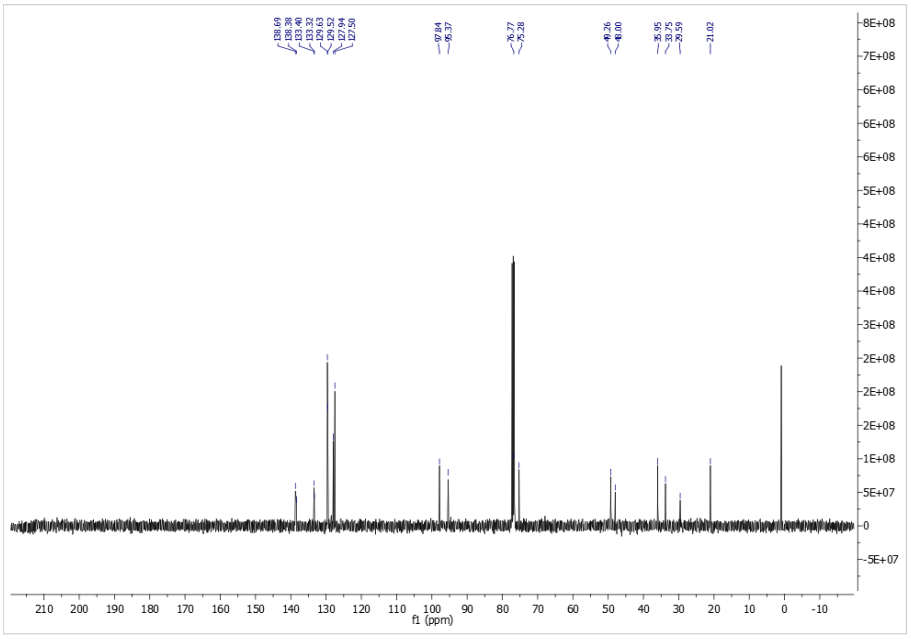
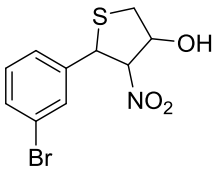


Figure A. 16. ^{13}C NMR spectrum of compound **45d**



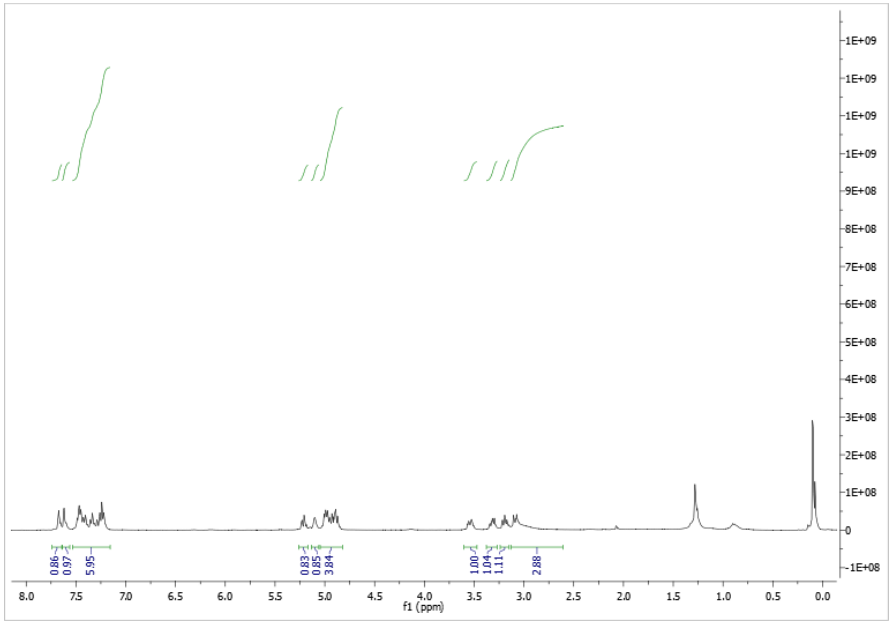


Figure A. 17. ^{1}H NMR spectrum of compound **45e**

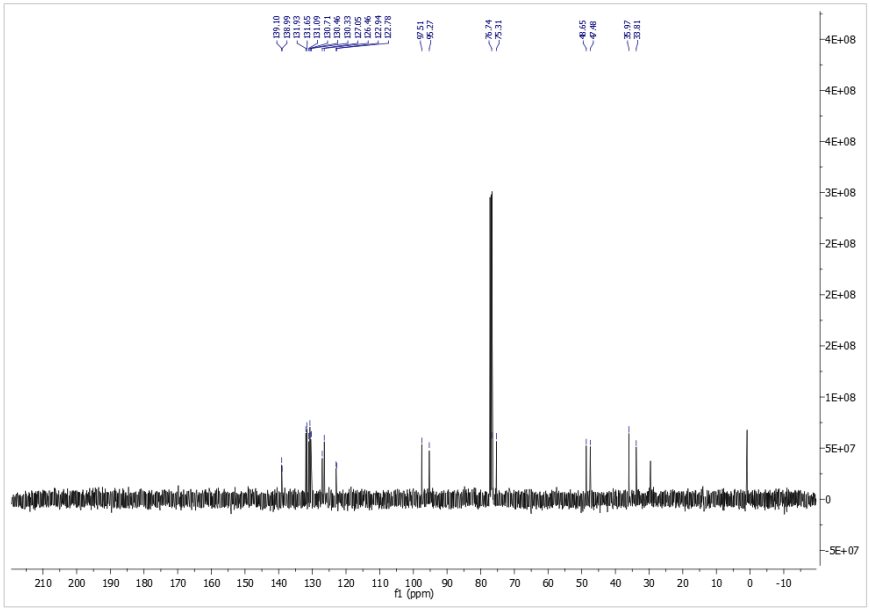
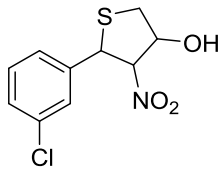


Figure A. 18. ^{13}C NMR spectrum of compound **45e**



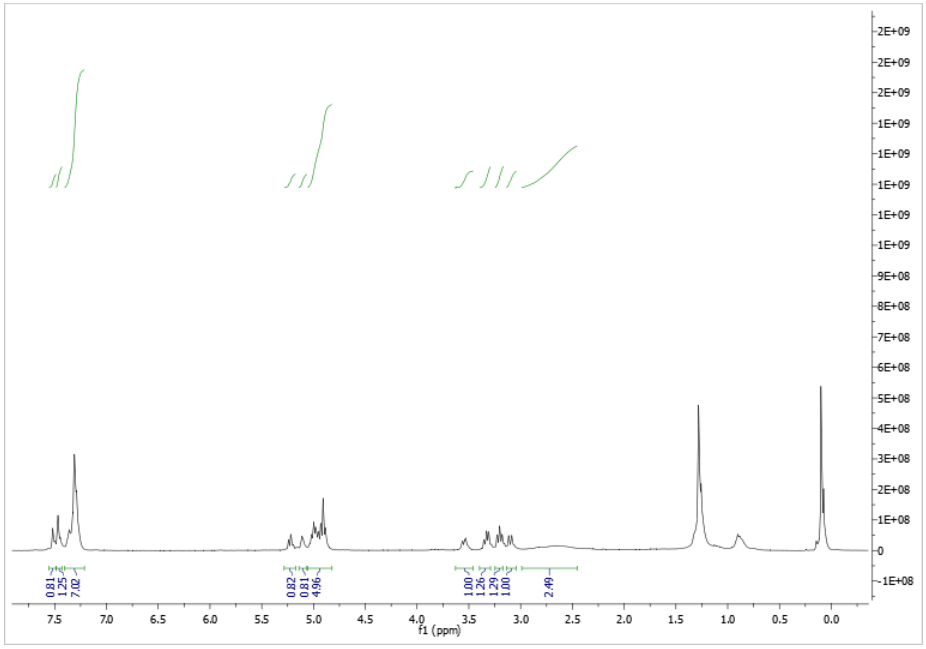


Figure A. 19. ^{1}H NMR spectrum of compound **45f**

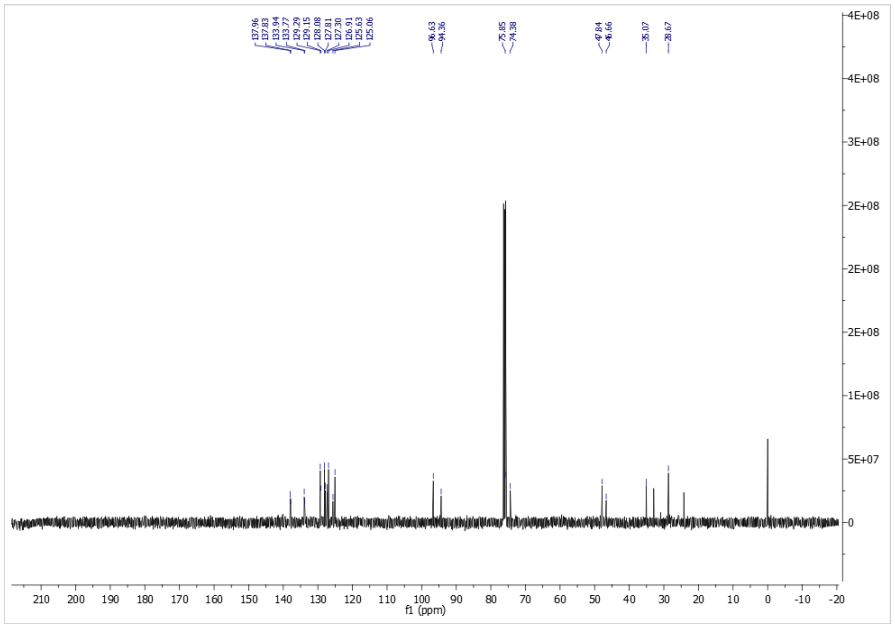
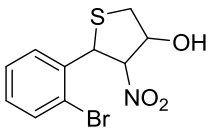


Figure A. 20. ^{13}C NMR spectrum of compound **45f**



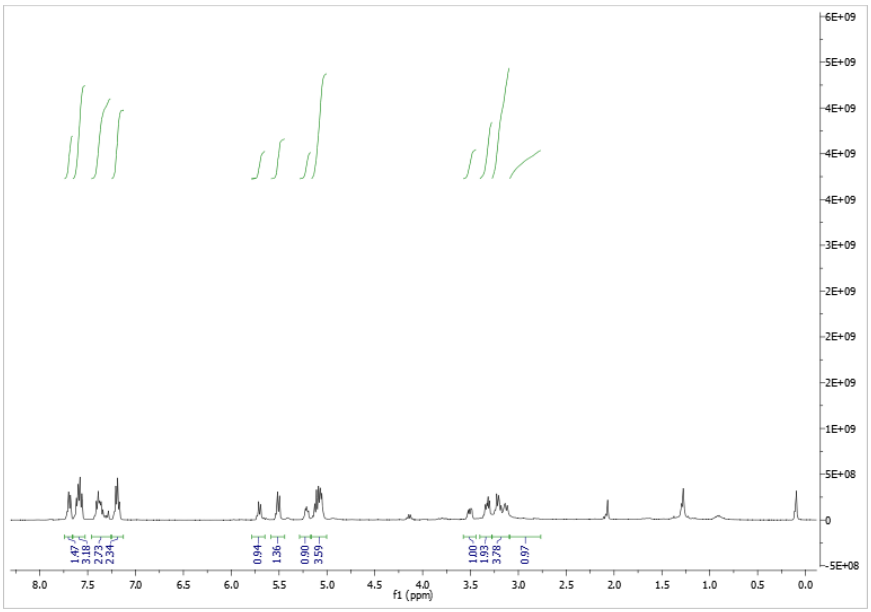


Figure A. 21. ^{1}H NMR spectrum of compound **45g**

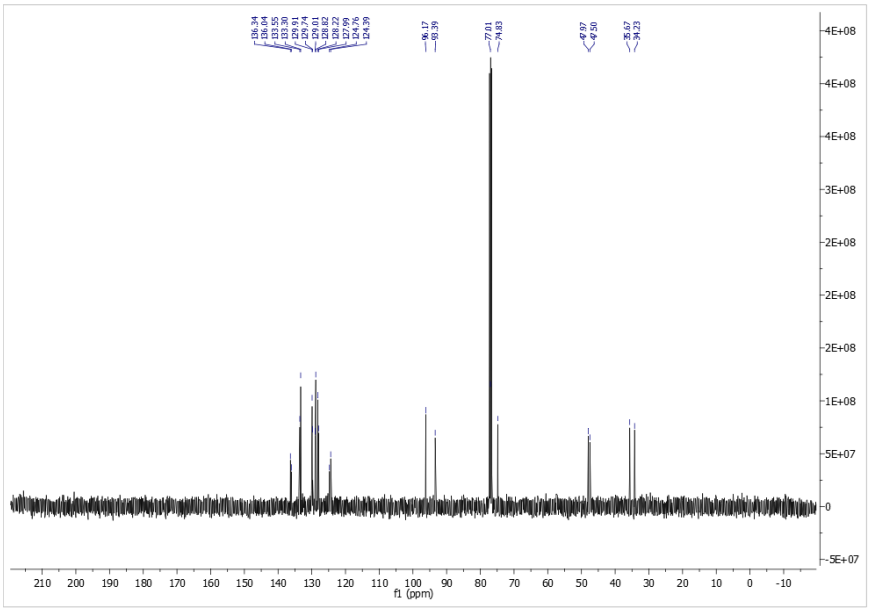
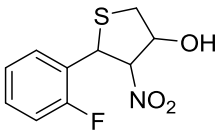


Figure A. 22. ^{13}C NMR spectrum of compound **45g**



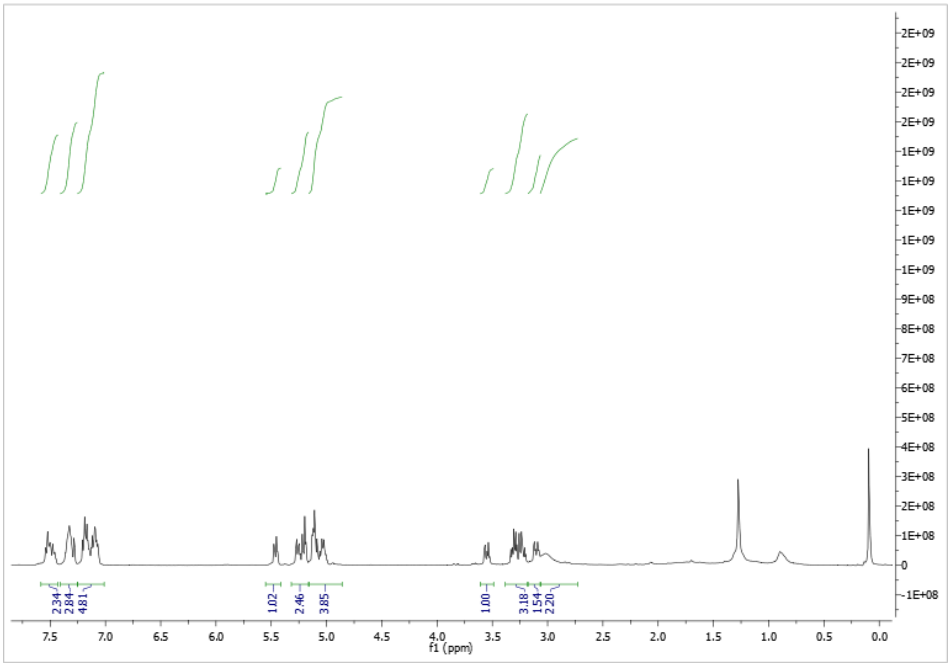


Figure A. 23. ^{1}H NMR spectrum of compound **45h**

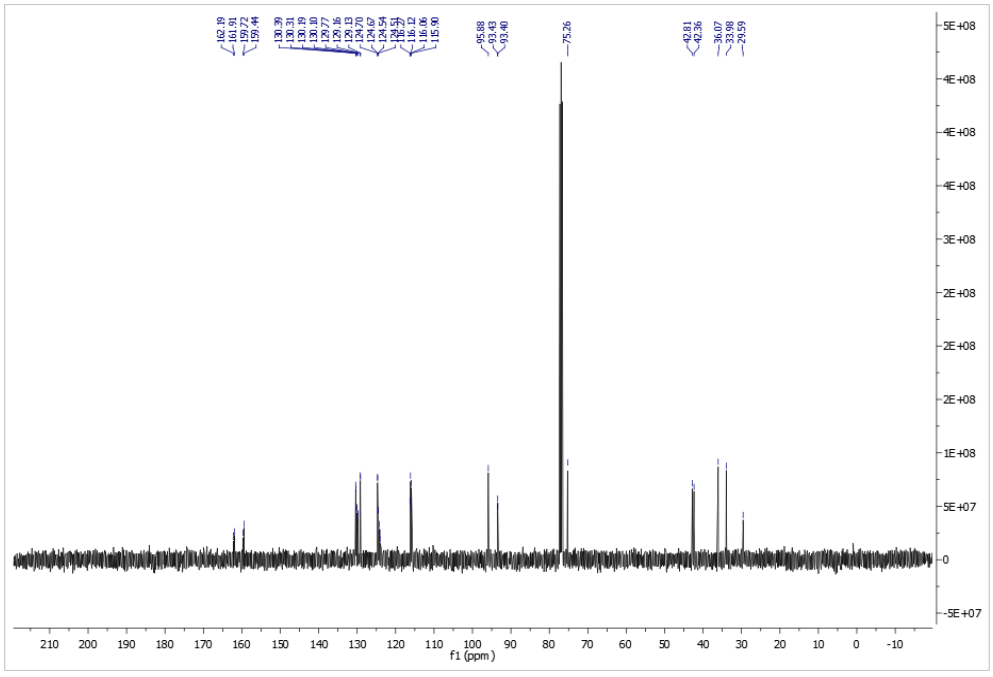
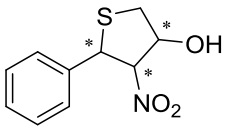


Figure A. 24. ^{13}C NMR spectrum of compound **45h**

APPENDIX B – HPLC DATA



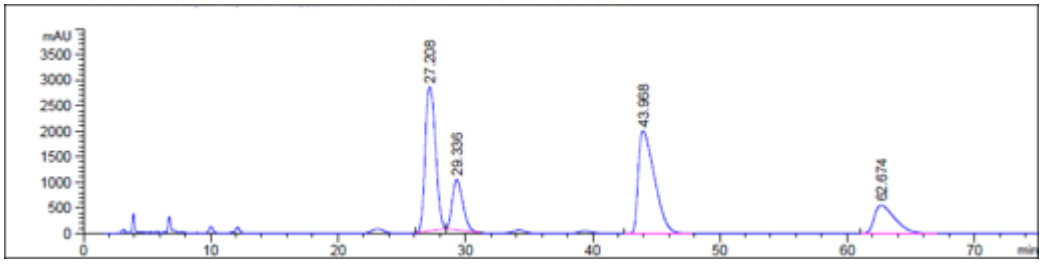


Figure B. 1. HPLC chromatogram of rac-**45**

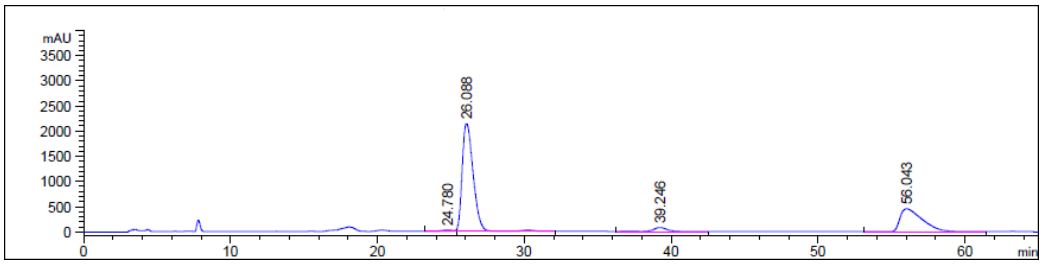
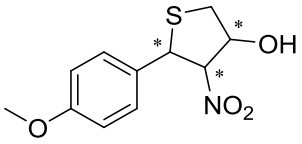


Figure B. 2. HPLC chromatogram of enantiomerically enriched **45**



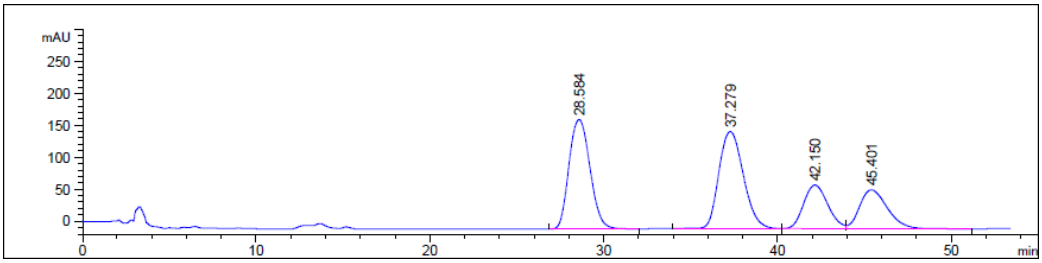


Figure B. 3. HPLC chromatogram of rac-**45a**

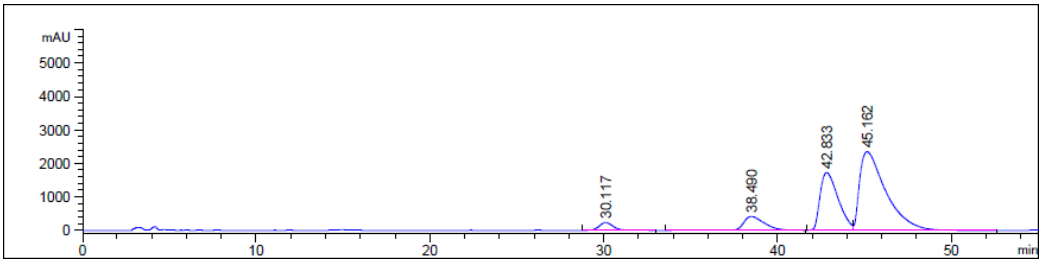
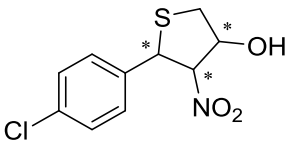


Figure B. 4. HPLC chromatogram of enantiomerically enriched **45a**



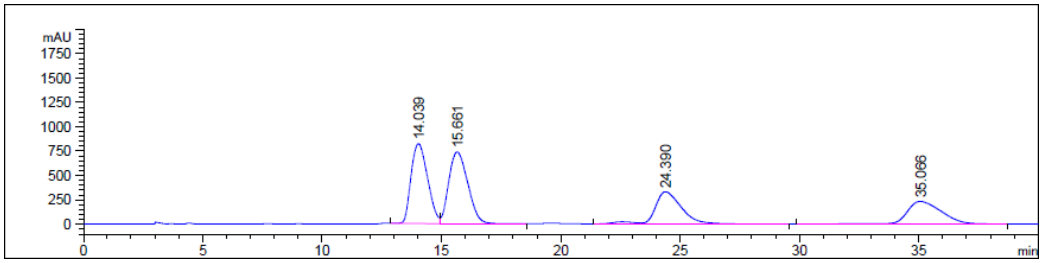


Figure B. 5. HPLC chromatogram of rac-**45b**

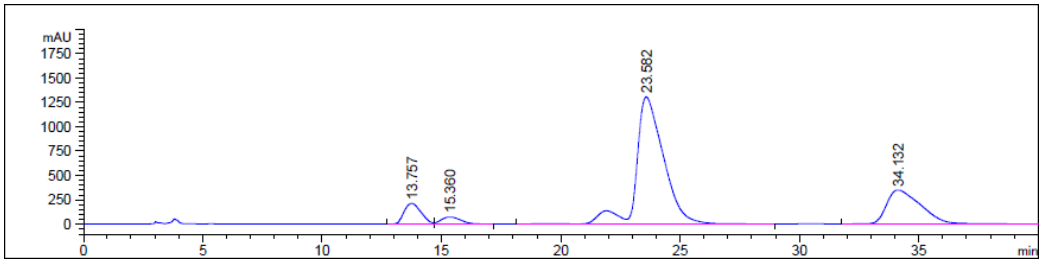
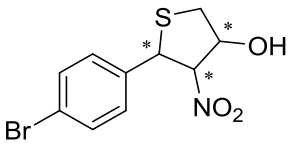


Figure B. 6. HPLC chromatogram of enantiomerically enriched **45b**



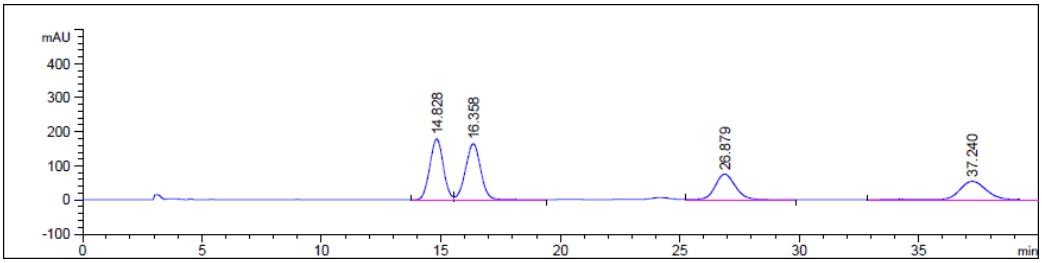


Figure B. 7. HPLC chromatogram of rac-**45c**

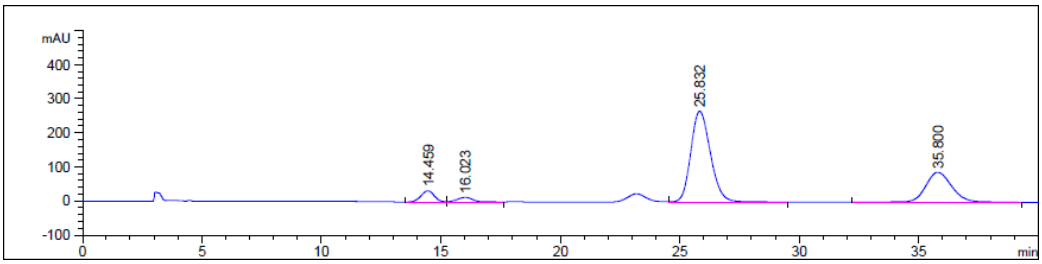


Figure B. 8. HPLC chromatogram of enantiomerically enriched **45c**

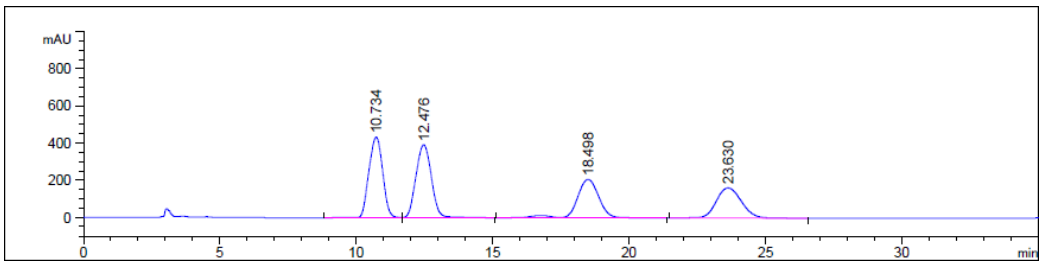


Figure B. 9. HPLC chromatogram of rac-**45d**

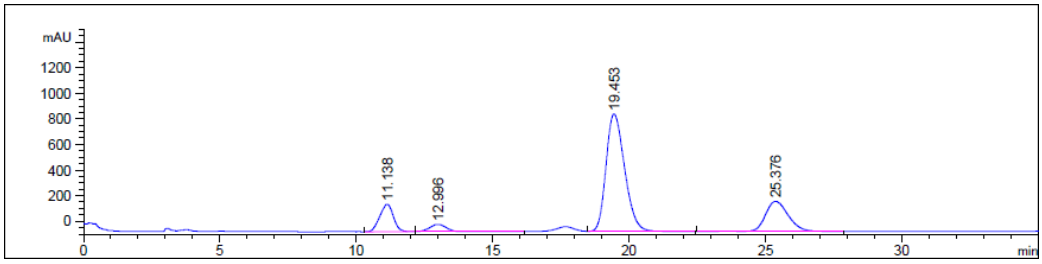
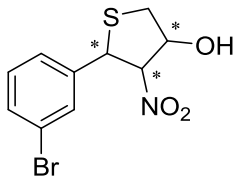


Figure B. 10. HPLC chromatogram of enantiomerically enriched **45d**



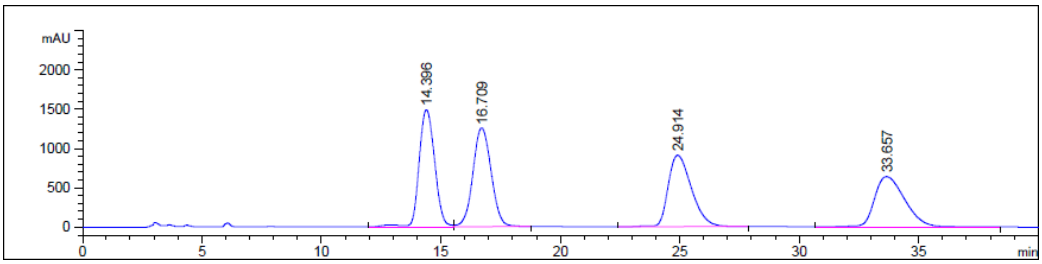


Figure B. 11. HPLC chromatogram of rac-**45e**

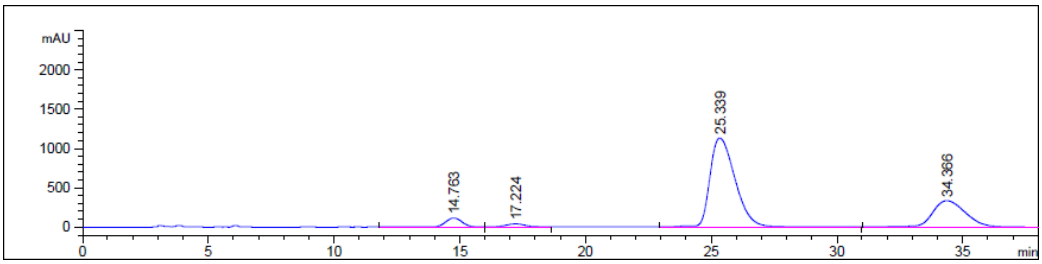
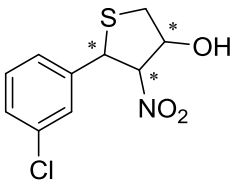


Figure B. 12. HPLC chromatogram of enantiomerically enriched **45e**



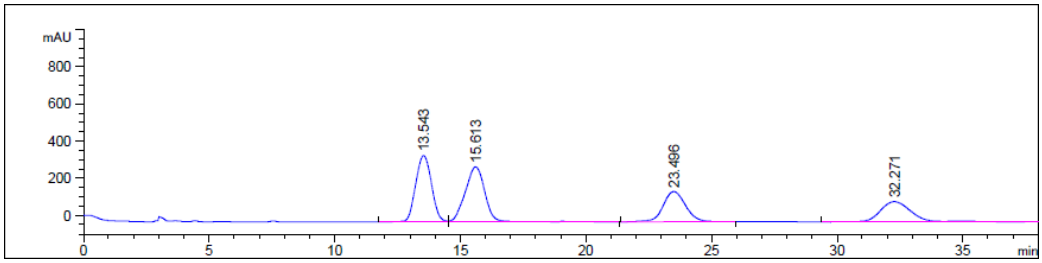


Figure B. 13. HPLC chromatogram of rac-**45f**

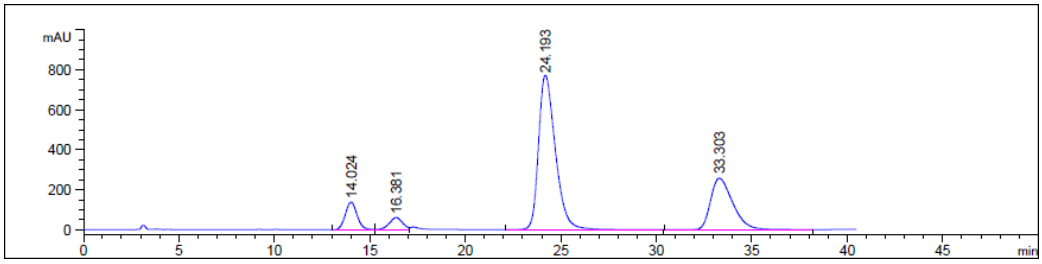
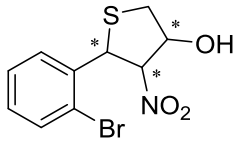


Figure B. 14. HPLC chromatogram of enantiomerically enriched **45f**



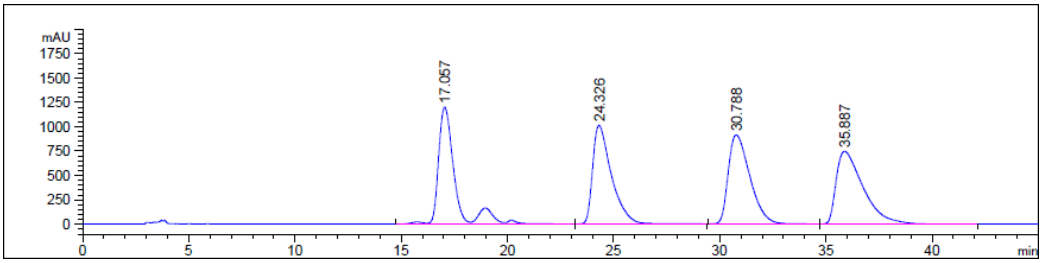


Figure B. 15. HPLC chromatogram of rac-**45g**

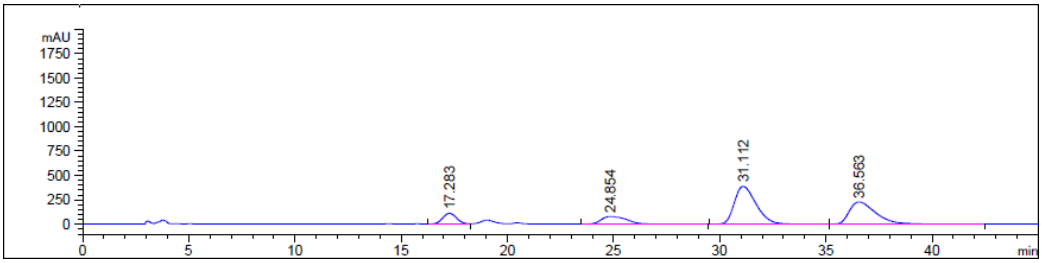
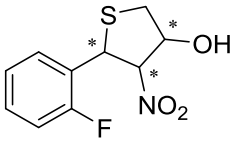


Figure B. 16. HPLC chromatogram of enantiomerically enriched **45g**



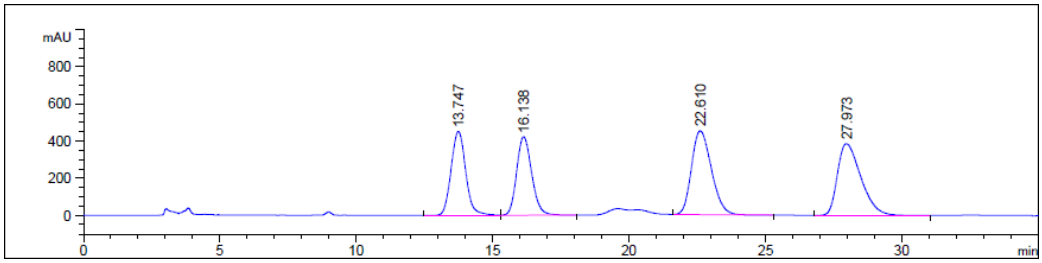


Figure B. 17. HPLC chromatogram of rac-**45h**

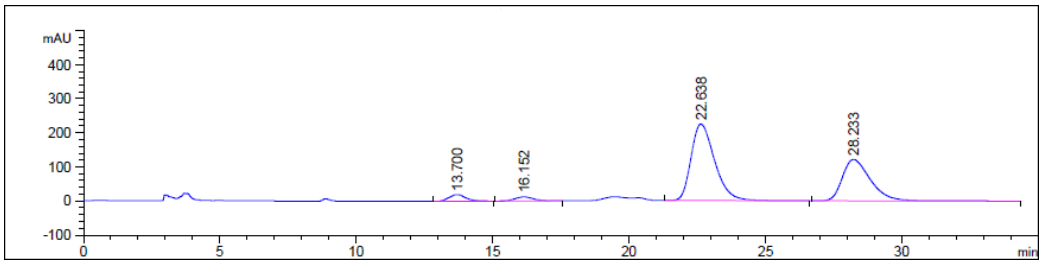


Figure B. 18. HPLC chromatogram of enantiomerically enriched **45h**