

IMPROVING ASYMMETRIC DECARBOXYLATIVE ALDOL REACTION
AND SYNTHESIS OF TPT-ACETYLENE MATRIX

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OF TPT-ACETYLENE MATRIX**

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ABSTRACT

IMPROVING ASYMMETRIC DECARBOXYLATIVE ALDOL REACTION AND SYNTHESIS OF TPT-ACETYLENE MATRIX

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In recent years, studies, and the use of organocatalysts have increased considerably. Unlike metal catalysts, non-toxic, robust organocatalysts have ensured their usability in many organic reactions. In this work, a new sulfonamide type bifunctional organocatalyst was synthesized and used in the asymmetric reaction.

First, the decarboxylative aldol reaction of α -amido hemimalonates with aldehydes was studied in the presence of a bifunctional organocatalyst. An optimization study of this reaction was performed to enhance the enantioselectivity and diastereoselectivity. Racemic and chiral products of decarboxylative aldol reaction were synthesized with α -amido hemimalonate and 4-nitrobenzaldehyde. The structure elucidation of the product was done with NMR spectroscopy, and the selectivities were determined with HPLC.

The second part of the thesis involves a different aspect of organocatalysts' usage. Because of high catalyst loading requirements or difficulties in catalyst recovery and reuse in organocatalysis, these catalysts have limited practical applicability. In this context, the immobilization of organocatalysts on solid supports has emerged as a

promising strategy to avoid these limitations. In this project, various thiophene-pyrrole-thiophene (TPT) host systems that are able to anchor proper organocatalysts were synthesized. To reach the TPT product, 1-(thiophen-2-yl)-4-(thiophen-3-yl)butane-1,4-dione (the diketone precursor) was synthesized first. Then, the TPT products were manufactured. The TPT monomer was polymerized and proved to become a reusable organocatalysts' matrix.

Keywords: Enantioselectivity, Bifunctional Organocatalyst, Decarboxylative Aldol Reaction, TPT-Acetylene Matrix, Electropolymerization



ÖZ

ASİMETRİK DEKARBOKSİLATİF ALDOL REAKSİYONUNUN GELİŞTİRİLMESİ VE TPT-ASETİLEN MATRİKS SENTEZİ

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Son yıllarda yapılan çalışmalar ve organokatalizörlerin kullanımı oldukça artmıştır. Metal katalizörlerden farklı olarak toksik özelliği bulunmaması ve iyi katalitik özellik göstermeleri organokatalizörlerin geniş bir organik reaksiyon alanında kullanılabilirliğini sağlamıştır.

Öncelikli olarak, α -amidohepimalonatların aldehitlerle olan dekarboksilatif aldol reaksiyonu, bifonksiyonel organokatalizör varlığında incelenmiştir. Hem enantiyoseçicilik hem de diastereoseçicilik anlamında en iyi değerleri sağlamak için optimizasyon çalışması yapılmıştır. α -Amidohepimalonat ve 4-nitrobenzaldehit ile yapılan dekarboksilatif aldol çalışmasında hem rasemik hem de kiral ürün sentezlenmiştir. Yapı aydınlatması NMR spektroskopisi ile yapılırken enantiyo ve diastereoseçicilik değerleri HPLC ile belirlendi.

Tezin ikinci kısmı ise organokatalizörlerin kullanımının farklı bir yönünü içermektedir. Yüksek miktarda katalizör kullanımı ya da katalizörün geri kazanımı ve tekrar kullanımındaki zorluklar nedeniyle bu tip katalizörlerin sınırlı kullanımı bulunmaktadır. Bu bağlamda, organokatalizörlerin katı destekler üzerinde immobilizasyonu, sınırlamalardan kaçınmak için umut verici bir strateji olarak

ortaya çıkmaktadır. Bu projede, uygun katalizörlerin bağlanabileceği tiyofen-pirol-tiyofen (TPT) matriks sistemleri sentezlenecektir. TPT ürününü elde etmek için önce 1-(tiyofen-2-il)-4-(tiyofen-3-il)bütan-1,4-dion (diketon öncüsü) sentezlenmektedir. Ardından TPT ürünleri üretilmiştir. Sonuç olarak, TPT monomeri elektropolimerizasyon yöntemi ile polimerleştirilerek yeniden kullanılabilir bir organokatalizör matriksi olduğu kanıtlanmıştır.

Anahtar Kelimeler: Enantioseçicilik, Bifonksiyonel Organokatalizör,
Dekarboksilatıf Aldol Reaksiyonu, TPT-Asetilen Matriksi, Elektropolimerizasyon





To My Dear Family

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LIST OF ABBREVIATIONS

CPME	: Cyclo Pentyl Methyl Ether
DMAP	: 4-Dimethylamino Pyridine
HFIP	: Hexafluoroisopropanol
HOMO	: Highest Occupied Molecular Orbital
ITO	: Indium Tin Oxide
PTSA	: p-Toluenesulfonic Acid
SNS	: dithienylpyrrole / sulfur-nitrogen-sulfur
SOMO	: Singly Occupied Molecular Orbital
TPT	: thiophene-pyrrole-thiophene

CHAPTER 1

INTRODUCTION

1.1 Importance of Chirality

Many organic compounds in different areas of our lives have a chiral character. Foods, flavors, and pharmaceuticals can be examples of it. For instance, (*R*)-(-)-linalool (**1**) is the chemical that gives lavender oil its distinctive woody-floral scent. However, (*S*)-(+)-linalool (**1**) smells like pleasant orange oil (Figure 1).¹ This is because the enantiomers of chiral molecules have different biological activities.

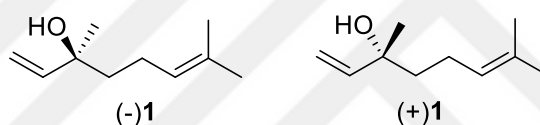


Figure 1. Structures of (*R*)-(-)-linalool & (*S*)-(+)-linalool

In 1815, Jean-Baptiste Biot established the historical root of chirality by noticing that a chiral compound used in the pharmaceutical industry rotates plane-polarized light in different directions. In 1848, Louis Pasteur discovered the concept of chirality on a molecular basis with tartaric acid. At that time, it was believed that the enantiomers of chiral molecules had the same chemical and physical properties and had the same biological effects.²

Today, scientists are working on chirality as a natural reflection and its asymmetric synthesis, which is very important for human life. To create biologically active molecules that are almost enantiopure, it is crucial to selectively synthesize one enantiomer in comparison to the other enantiomer. Once the racemate of the target molecule has been synthesized, the isolation of the desired enantiomer is quite difficult from each other.¹

When a reaction occurs as a result of the formation of a chiral center and an equal amount of enantiomer is formed, the product will be a racemic mixture. The formation of a racemic mixture as a result of a reaction can cause serious problems. The most important examples of this are in the pharmaceutical industry. In the 1950s, there was a situation with thalidomide drugs in Germany (Figure 2). Thalidomide (**2**) was synthesized to prevent morning sickness in pregnant women. Although the (*R*)-(+)-enantiomer was good for the disease, the (*S*)-(-)-enantiomer caused disability in children. Many of these and similar have been reported as drug disasters. Therefore, the detection and separation of enantiomers have gained importance.³

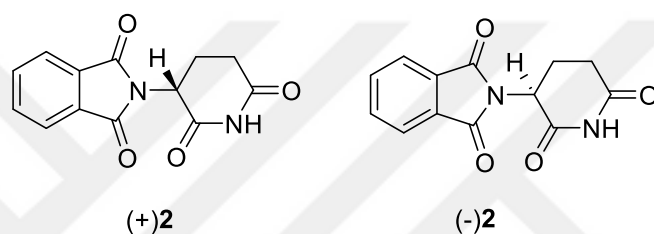


Figure 2. Molecular structures of thalidomide (**2**)

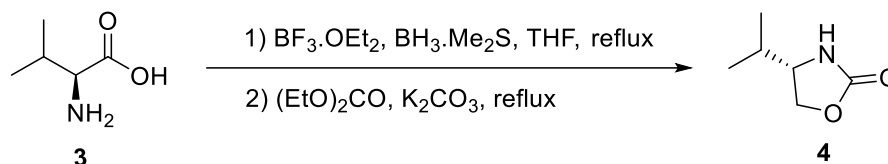
1.2 Asymmetric Synthesis

Asymmetric synthesis is a synthesis method that enables the three-dimensional structure of molecular formation to be controlled. In other words, it selectively ensures the formation of an enantiomeric form during the synthesis of a compound.⁴ Especially in recent years, this area has been given great importance by the pharmaceutical industry due to the problems arising from the difficulty of purification of enantiomers.

In chiral molecules, we can divide the methods of obtaining pure enantiomers into three main groups, which are chiral pool, kinetic resolution, and asymmetric catalysis.

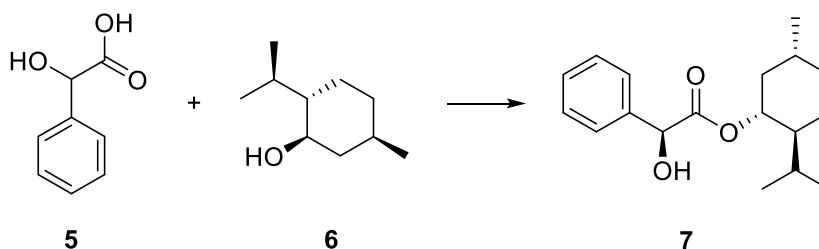
The simplest and oldest one is the chiral pool method. In this method, syntheses were made using naturally enantiopure compounds such as amino acids or carbohydrates. The use of L-valine (**3**) as a chiral pool can be seen in Scheme 1 as an example.

Although the efficiency of the method was quite good, it was inevitable to turn to another method because the products that could be created with natural substances were also limited.⁵



Scheme 1. Synthesis of (*S*)-(-)-4-isopropyl-2-oxazolidinone (**4**) by chiral pool method.

Another synthetic method to access enantiopure compounds is the kinetic resolution method. In this method, one enantiomer is made to react faster than the other by adding enzymes. In the kinetic resolution method, racemic mixtures are used. As a result of the reaction of one of the enantiomers at a faster rate, the other one will be enantioenriched in the reaction medium.⁶ This method was discovered by Marckwald and McKenzie. In this study conducted in 1899, mandelic acid (**7**) was esterified (Scheme 2). The optical activity of (-)-Menthol (**6**) was utilized. (+)-Mandelic acid (**5**) reacted faster than (-)-Mandelic acid (**5**), leaving more (-)-mandelic acid (**5**) in the medium.⁷



Scheme 2. The reaction done by Marckwald and McKenzie to produce (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-2-hydroxy-2-phenylacetate (**7**)

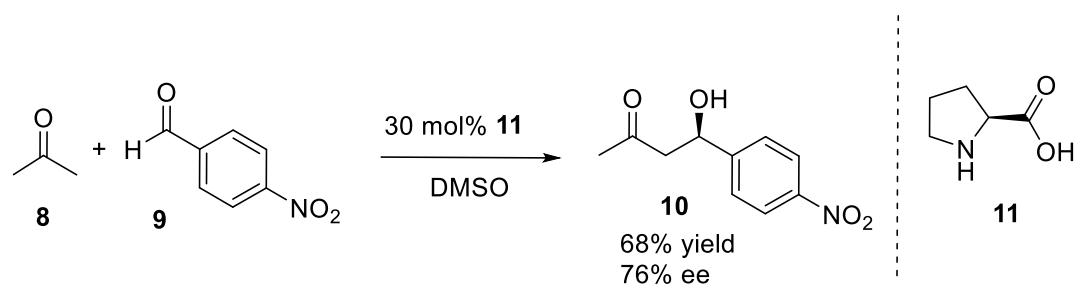
The third method is asymmetric catalysis. Catalysts with asymmetrical properties are used to control the chirality of the product. Not much catalyst is consumed in this method and so it can be used in substoichiometric amounts. Thus, waste is prevented,

and productivity increases. There can be three types of catalysts used: biocatalysts, transition metal catalysts, and organocatalysts. Among them, the most environmentally friendly, clean, inexpensive, and renewable is organocatalysis.⁸

1.3 Asymmetric Organocatalysis

Organocatalysis has many advantages over others such as being cheaper, having safer procedures, not being affected by heat or light, and less solvent usage. Small, metal-free compounds called organocatalysts are used in asymmetric synthesis to activate the electrophile or nucleophile. Because they do not create metal contamination, they make it very easy to prepare some pharmaceutical compounds that cannot tolerate metals. In the light of these advantages, the rapid growth in organocatalytic research is an expected result.⁹

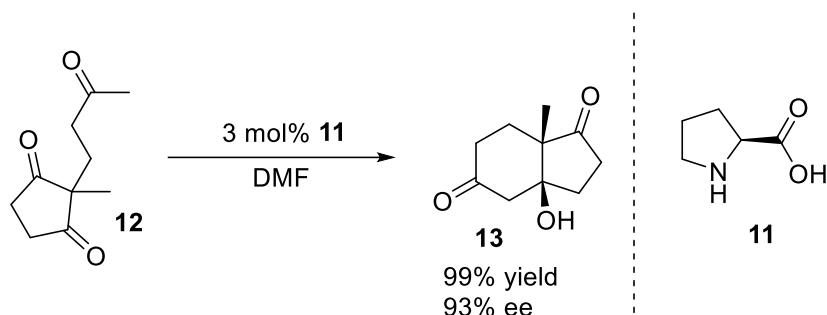
Although it is accepted that MacMillan coined the term "Organocatalysis", this definition was originally put forward as "Organic Catalysis" by Wolfgang Langenbeck in 1935. After List, Lerner, and Barbas's work was published, the development in this area started to increase.¹⁰ They use L-proline (**11**) as a catalyst as can be seen in Scheme 3.



Scheme 3. Usage of L-proline (**11**) as an organocatalyst in the reaction of acetone (**8**) and *p*-nitrobenzaldehyde (**9**) to produce the aldol product (**10**) by List, Lerner, and Barbas¹¹

Hajos–Parrish–Eder–Sauer–Wiechert reaction can be another example of the usage of L-proline (**11**) as an organocatalyst. In 1970, they use L-proline (**11**) in the

asymmetric aldol reaction with 2-methyl-2-(3-oxobutyl)cyclopentane-1,3-dione (**12**) and lead directly to the bicyclic ketol **13** shown in Scheme 4.¹²



Scheme 4. Hajos–Parrish–Eder–Sauer–Wiechert reaction

1.3.1 Classification of Organocatalysts Based on Interaction

Seayad and List state that, Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids can be used to classify the majority of organocatalysts. Figure 3 displays basic catalytic cycles.

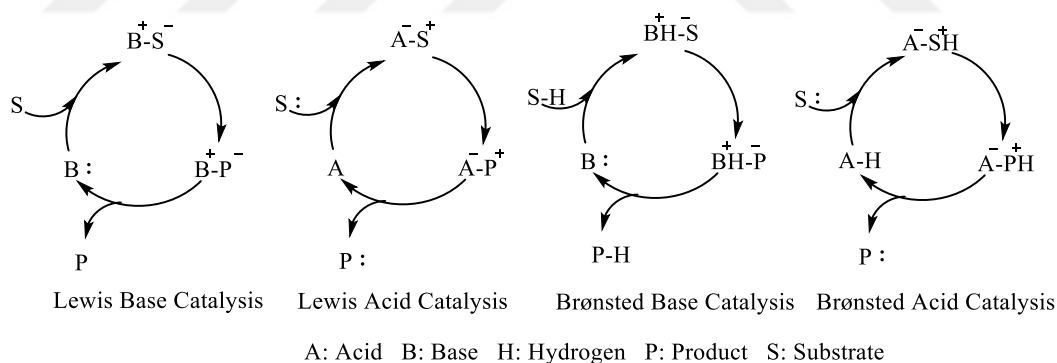
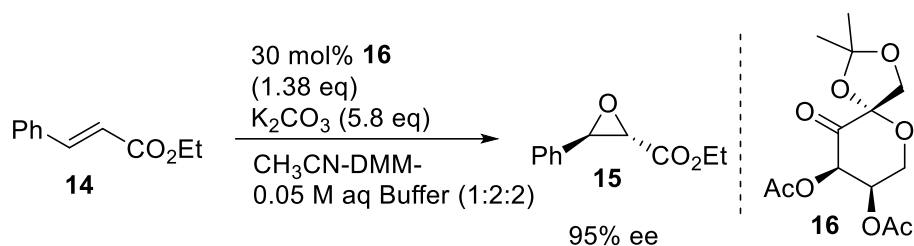


Figure 3. Classification of Organocatalysts according to Seayad and List

A noteworthy instance of Lewis acid catalysis is the epoxidation of olefin **14** employing chiral dioxirane **15** generated in situ from “chiral ketone” catalysts **16** and potassium peroxomonosulfate (oxone) as the oxidant. Scheme 5 exhibits a highly enantioselective case as 95% ee.¹³



Scheme 5. “Chiral ketone” **16** catalyzed enantioselective epoxidation of an olefin **14**

The evolution of organocatalysts was the subject of MacMillan's article published in 2008.⁹ He categorized organocatalysts into several groups based on how they are activated and induced. Enamine catalyst and hydrogen bonding catalyst are the two of them that are utilized the most commonly. For the achievement of increased enantiomeric products in such catalysts, the active form of the catalyst assumes a dominant position in the reaction's intermediate. The primary goal is to raise the HOMO level or lower the LUMO level (Figure 4).⁹

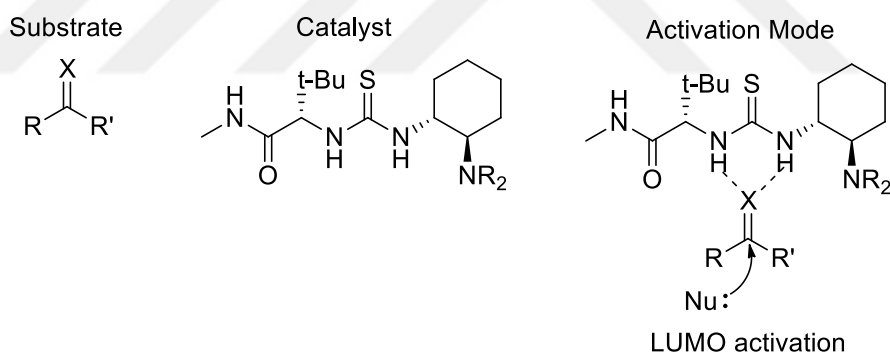


Figure 4. Hydrogen bonding as an activation mode of organocatalysts

Additionally, organocatalysts can be classified into two categories according to Berkesel and Grögel: Covalent and non-covalent catalysis as demonstrated in Figure 5. They illustrate this type of classification based on their interactions with substrates.¹⁴

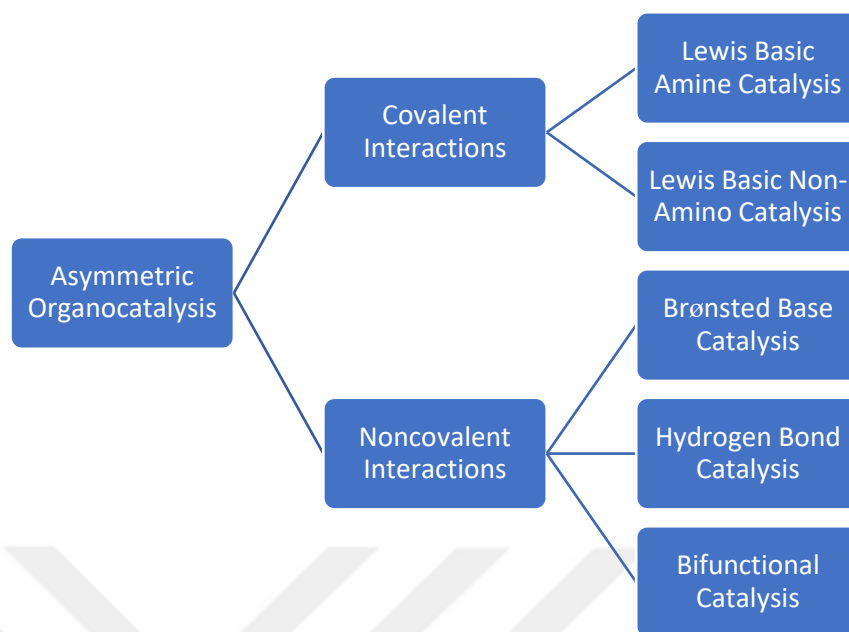
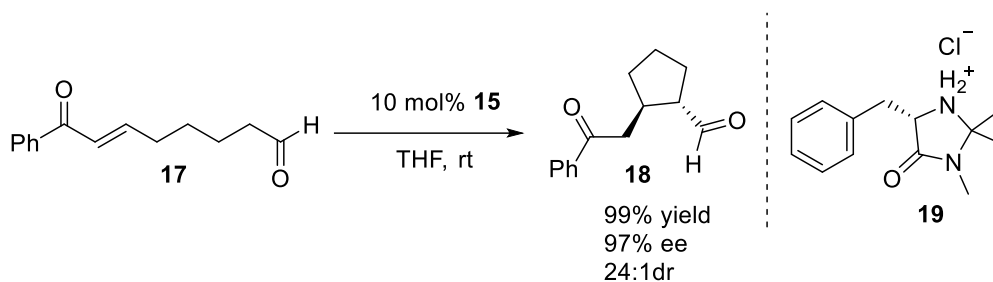


Figure 5. Classification of Asymmetric Organocatalysis

1.3.1.1 Covalent Interactions

A covalent bond is created between the substrate and the organocatalyst whenever catalysis involves covalent interactions. Covalent interactions, which can be investigated in two ways, are often catalyzed by Lewis basic catalysts. The first categories of catalysts are amines; examples include iminium catalysis, enamine catalysis, dienamine catalysis, and SOMO catalysis. Enamine catalysis serves as an example of Lewis base catalysis since it involves combining or going through pericyclic reactions with the catalytically synthesized enamine intermediate, which is created by the iminium ion's deprotonation. To be more specific, as shown in Scheme 6, the imidazolidinone catalyst **19** was utilized in the exceedingly enantioselective intramolecular Michael addition creating ketoaldehyde **18** with the usage of (E)-8-oxo-8-phenyloct-6-enal (**17**).¹⁵



Scheme 6. Amine-catalyzed Michael cyclization

Catalysts like phosphines, chalcogens, and N-heterocyclic carbenes can be used to realize non-amino catalysts, which make up the second group of catalysts.¹⁴

1.3.1.2 Noncovalent Interactions

Three different cases can be raised when investigating noncovalent catalysis. The Brønsted base interaction is the initial one. One such might be chiral amino compounds.¹⁶ The hydrogen bond interaction is the second. Commonly, a hydrogen bond motivates an electrophile toward a nucleophilic attack.¹⁷ (Thio)ureas, squaramides, sulfonamides, and Brønsted acids are a few examples of this. The remarkable noncovalent activation of thiourea systems **20** on electrophiles by H-bond was demonstrated by Schreiner and Wittkopp in 2002, as depicted in Figure 6.¹⁸

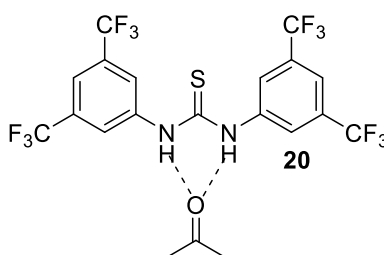


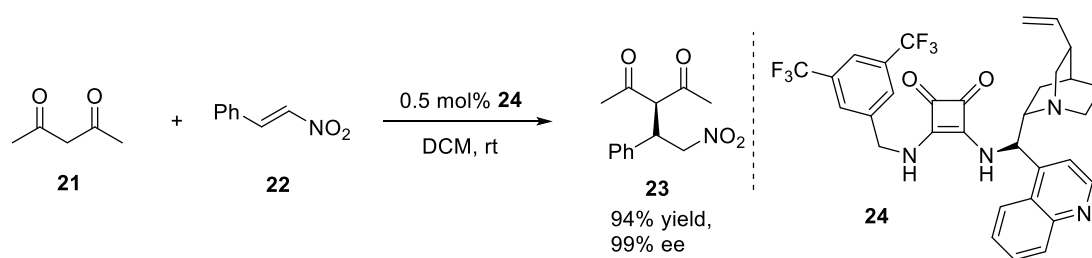
Figure 6. Schreiner thiourea complex

Bifunctional catalysts are the third and most significant ones that contain both acidic and basic sites on this type of catalyst. Some of the potent acidic components mentioned in the literature include urea, thiourea, guanidine, sulfonamide, and

squaramide moieties.¹⁹ These acidic substances may serve as H-bond suppliers, stimulating the electrophile. The Lewis/Bronsted basic units deprotonate the nucleophile whole or within a part, influencing it. DMAP, cyclohexyl diamine, and catalysts generated from cinchona alkaloids had noteworthy findings in the literature.²⁰ Enantioselectivity is produced by combining the acidic and basic units with chiral intervals.

1.3.2 Cinchona Alkaloids

In nature, there are numerous examples of organocatalysts. One of them is the Cinchona alkaloid obtained from the Cinchona tree. This was first used as a basic fraction in 2008 by Rawal et al. (Scheme 7). Bifunctionality was achieved by using squaramide as the acidic part. Rawal used this catalyst **24** in Michael reaction. The catalyst, which was used in the reaction of a nitro olefin **22** with 1,3-dicarbonyl **21** to produce 3-acetyl-5-nitro-4-phenylpentan-2-one (**23**), which was tested with a thiourea catalyst before, resulted in a better yield and enantioselectivity. It is clearly stated in this publication that more area is provided for asymmetric induction of cinchona alkaloid derivatives.²¹



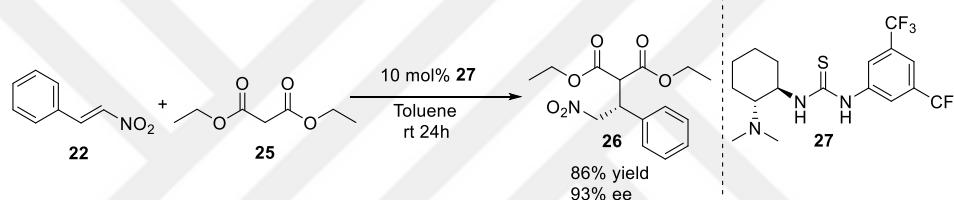
Scheme 7. First Cinchona alkaloid **24** usage in addition reaction by Rawal

1.4 Bifunctional Organocatalysis

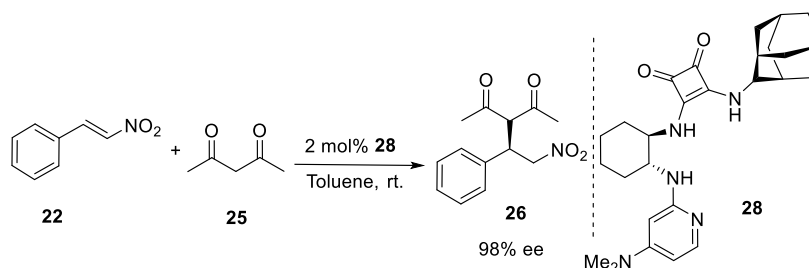
One of the catalysts that activate substrates with a non-covalent bond is "bifunctional catalysts". These catalysts have both acidic and basic units. These units are linked together to provide enantioselectivity. The acidic moieties act as H-bond donors,

activating the electrophile by decreasing the LUMO. In addition, the Lewis/Brønsted basic portions of the catalyst also lower the HOMO of the nucleophile, resulting in complete or partial deprotonation.²²

This catalyst definition was first made in 2003 by Takemoto and his team in the Michael reaction. Since the thiourea used in this study provided high enantioselectivity, it paved the way for this area. While they used thiourea as the acidic part of bifunctional organocatalysts **27**, they used trans-1,2-diamine as the basic part.²³ This catalyst **27** was used for the reaction with diethyl malonate **25** and the nitro olefin **22** to produce diethyl 2-(2-nitro-1-phenylethyl)malonate (**26**) (Scheme 8).

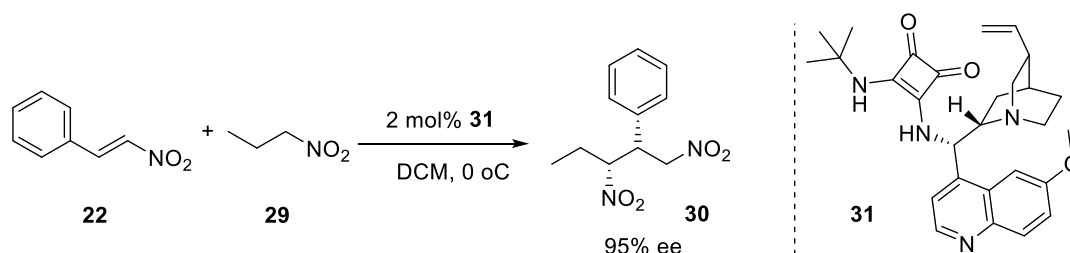


Scheme 8. The first reaction that used bifunctional organocatalyst **27** by Takemoto Tanyeli and his group published their bifunctional organocatalyst study in 2014, 2-aminoDMAP/squaramide derivative **28**. In this study, squaramide as the acidic part affects trans-β nitroalkene **22**, while the basic part, 2-aminoDMAP interacts with the β-diketonate **25** anion, in a stoichiometric ratio, applied in the Michael reaction (Scheme 9). They reached up to 98% ee with the use of the organocatalyst **28** they synthesized.²⁴



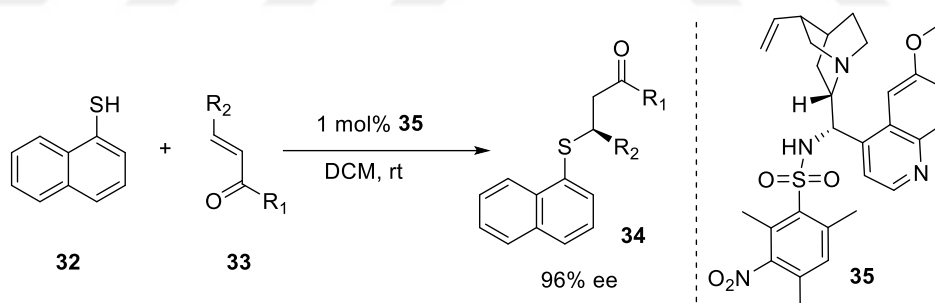
Scheme 9. Squaramide catalyst **28** promoting conjugate addition of Michael reaction

Tanyeli group examined a catalyst **31** and found that it could get 95% ee in the Michael addition reaction when quinine was used as the basic portion (Scheme 10).²⁵ The Michael addition reaction was done with the nitro olefin **22** and the nitropropane **29** to produce ((2R,3R)-1,3-dinitropentan-2-yl)benzene (**30**).



Scheme 10. Michael addition with quinine-based bifunctional organocatalyst **26**

A study on the synthesis of a bifunctional quinine-derived sulfonamide organocatalyst **35** was published in 2021 by the Tanyeli group (Scheme 11). Under user-friendly conditions and a minimal (1 mol%) catalyst loading, the desired sulfa-Michael adduct of a naphthalene-1-thiol (**32**) and a pentanone (**33**) were produced naphthalenylthiopentanone (**34**) with up to 96% ee.²⁶



Scheme 11. Quinine/ Sulfonamide cat. **35** synthesized by Tanyeli

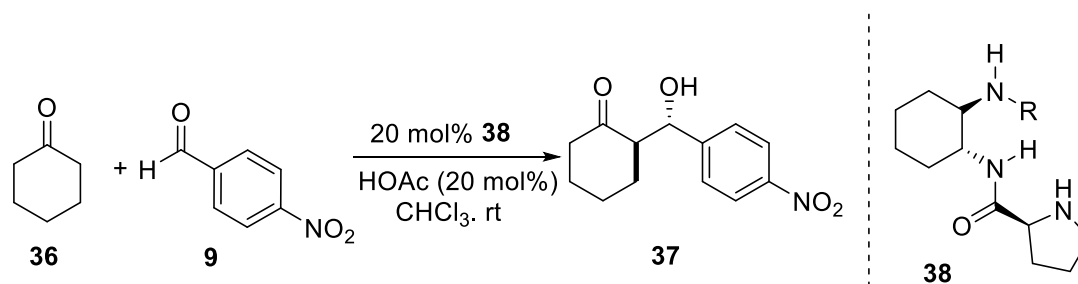
1.5 Aldol Condensation

In the synthesis of organic compounds, aldol condensation is a significant synthetic technique. An atom-economical option for these significant transformations is the development of catalytic methods that prevent the production of stoichiometric by-products while keeping the high levels of control offered by stoichiometric

processes. A wide range of catalysts for the aldol reaction, including enzymes, catalytic antibodies, transition metal catalysts, organocatalysts, and small molecules, have been identified in recent years.²⁷

When Wurtz initially produced β -hydroxy aldehyde from acetaldehyde in 1872, he gave it the name aldol (3-hydroxybutanal). This nomenclature was later adopted by other scientists. Aldol condensation comprises processes that result in β -hydroxy aldehydes or β -hydroxy ketones via self- or mixed condensations of aldehydes and ketones, as well as processes that result in α , β -unsaturated aldehydes or α , β -unsaturated ketones via dehydration of intermediate β -aldols or β -ketals. Numerous different condensations involving the reaction of an aldehyde or ketone have also been given the name "aldol condensation".²⁷

Chen et al. designed and tested sterically and electronically modified bifunctional organocatalysts **38** in the direct aldol synthesis of the product **37** with the reaction between cyclohexanone (**36**) and *p*-nitrobenzaldehyde (**9**) in 2006 (Scheme 12). It is critical to adjust the strength of the hydrogen bonding between the two NH groups because catalysts with various substituents displayed different catalytic effectiveness for comparable substrates.²⁸

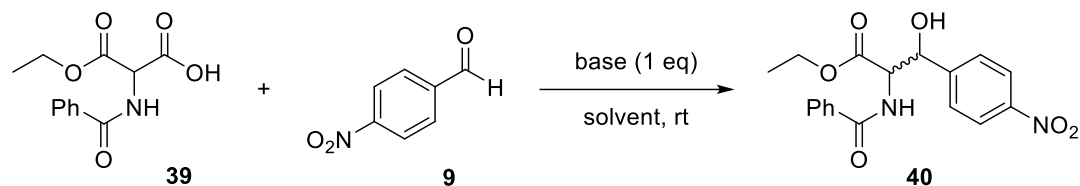


Scheme 12. Enantioselective Direct Aldol Reaction done by Chen et al.

1.5.1 Decarboxylative Aldol Reaction

Decarboxylation is a chemical process that releases carbon dioxide and removes a carboxyl group. Decarboxylation often describes a reaction between carboxylic acids that involves removing a carbon atom from a carbon chain. The reaction depicted in

Scheme 13 is noteworthy because β -hydroxy- α -amino acids **40** are crucial cornerstones for several biomolecules.²⁹



Scheme 13. The decarboxylative aldol process is used to create β -hydroxy- α -amino acids **40**

1.6 Synthesis of TPT-Acetylene Matrix as a Template for Organocatalysts

1.6.1 Electrochemical Synthesis of π -Conjugated Polymers

A substance that can be coated on the electrode surface can be used to connect a polymer film with an organocatalyst function to a solid surface. As a result, the electrode will cease to function and take on a new role as a catalyst for the processes because of the organocatalyst on its surface.

Generally, electrochemical synthesis methods are used to produce the link between the electronic and optical properties of the π -conjugated polymers. Electrochemical polymerization is a technique used to polymerize monomer structures. Since electrochemical polymerization is easily applicable even at room temperature and the polymer film thickness is controllable, it is used instead of many polymerization techniques in the literature.^{30,31}

Using the study conducted by Brillas et al. in 2000 as an example, the electrochemical performance of 2,5-di-(2-thienyl)-pyrrole (TPT) **31** on Pt was examined using cyclic voltammetry, chronopotentiometry, and chronoamperometry with a 10.0 mM monomer in 0.2 M LiClO₄ ethanol or 0.2 M LiCl ethanol. The monomer exhibits two successive oxidation reactions that are similar to one another.³²

1.6.2 TPT as π -Conjugated Polymers

After the discovery of π -conjugated systems, significant efforts have been made to design and synthesize new systems based on π -conjugated polymer systems. Polythiophenes and polypyrroles are of great interest due to their high conductivity and stability.³³

Otero et al. reported the first study on the synthesis and electrochemical polymerization of conjugated polymer systems with both heterocyclic components in the polymer structure in 1999 (Figure 7). A monomer known as 2,5-di-(2-thienyl)-pyrrole **41** structure is made up of pyrrole and thiophene units. (TPT).³⁴

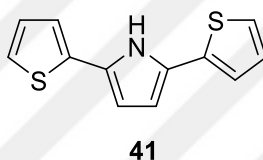
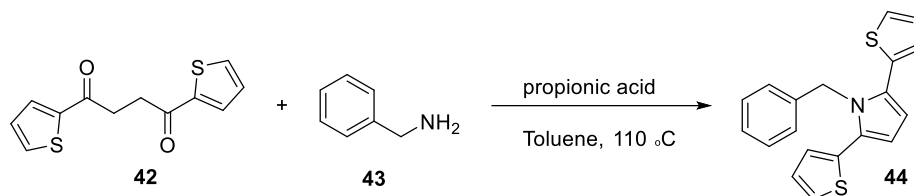


Figure 7. TPT **41** worked by Otero et al.

The TPT structure has a great advantage with the modifications that can be made in its structure by N-substitution and its electrochromic and solubility properties being adjustable. Also, the thiophene-pyrrole-thiophene unit is useful because of its ability to polymerize easily. For example, Eken et al. published a TPT project in 2014. Through the Paal-Knorr reaction mechanism of 1,4-di(2-thienyl)-1,4-butanedione **42** with related halo-substituted anilines **43**, four novel TPT type materials having meta and para-substituted benzene ring at the nitrogen atom were created. Potential cycling in an electrolytic solution of LiClO₄ and acetonitrile (ACN) was used to polymerize the monomers. The influence of the halogen group as a substituent between para- to meta-positions and various halogen atoms (F, Cl, Br) at merely meta-/para-positions in the structure were studied regarding the electrochemical and optical properties of produced monomers and polymers.³⁵

Synthesis and polymerization of N-alkyl substituted TPT derivatives by Ferraris,³⁶ with various N-substituted TPT units and N-halo-containing phenyl rings by Toppare et al.³⁷ and Cihaner et al.³⁸ have been reported. 1-Benzyl-2,5-di(thiophene-

2-yl)-1H-pyrrole (SNBS) **44**, a thiophene functionalized monomer, was synthesized in the survey performed by Tarkuç et al. in 2006 (Scheme 14). By using both chemical and electrochemical polymerization, a novel poly-thiophene derivative was created.³⁷



Scheme 14. TPT synthesis by Tarkuç et al.

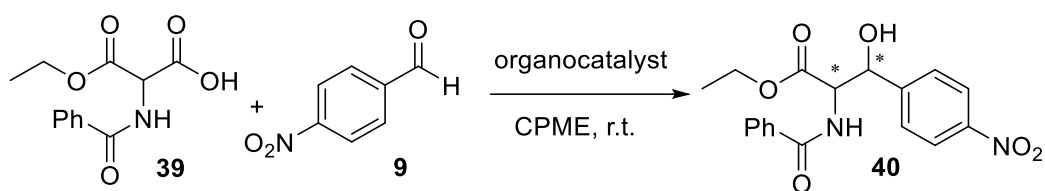
1.6.3 Paal-Knorr synthesis

The name derives from the German Chemists Carl Paal and Ludwig Knorr who first described the reaction. Although published as a method for synthesizing furans in 1884, it was found to be suitable for pyrroles and thiophenes as well.³⁹

The pyrrole ring is found in a significant part of biological compounds. It is very useful that pyrroles can be synthesized by condensing their 1,4-dicarbonyl structure with primary amines. This reaction is called Paal-Knorr condensation. Many different products can be provided by this reaction by derivatizing amines and dicarbonyls. TPT structure is one of the products of this type of reaction.⁴⁰

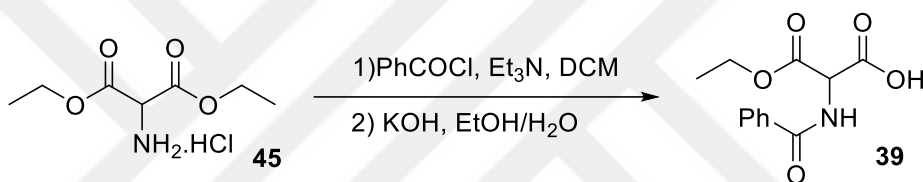
1.6.4 Aim of The Work

The scope of this thesis is aimed to find an organocatalyst that gives the highest amount of enantiomeric excess value in the decarboxylative aldol reaction depicted in Scheme 15 by searching different organocatalysts.



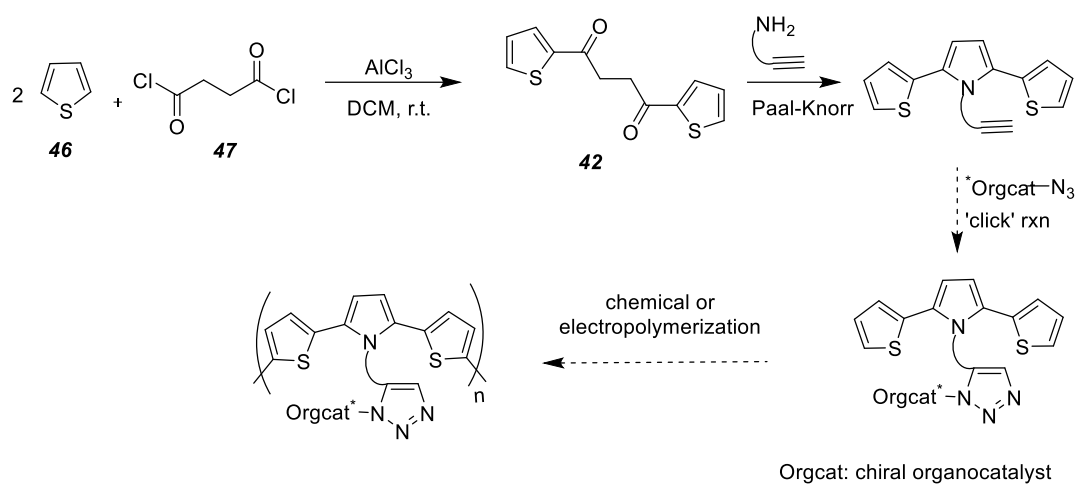
Scheme 15. Decarboxylative aldol reaction

Hemimalonate substrate **39** will be synthesized by using corresponding diethyl aminomalonate hydrochloride **45** (Scheme 16). Amine functionality is going to be protected by the benzoyl group and then will be subjected to ester hydrolysis by controlling the stoichiometry of substrate:base ratio. We will plan to use the quinine/sulfonamide organocatalyst **35** which has been recently synthesized in our group, together with quinine/tert-butylsquaramide **31**.



Scheme 16: Synthesis of monoacid

Due to the difficulties of synthesizing bifunctional organocatalysts, the limitation of their isolation from reactions, and the constraints of their subsequent reuse, the immobilization of organocatalysts is the most remarkable and unique step for the most efficient use of organocatalysts in asymmetric reaction. These reasons have made the production of new immobilization matrixes a critical need. Novel heterogeneous organocatalyst anchored thiophene-pyrrole-thiophene (TPT) host system derivatives can be a new area in organic chemistry. To this end, we will attempt to construct a pyrrole ring system possessing various acetylenic units that can be a feasible component for the [3+2] type click reactions. The synthetic strategy involves 1,4-di(thiophene-2-yl)butane-1,4-dione **42** that is available for Paal-Knorr condensation reaction (Scheme 17).



Scheme 17. Synthetic Strategy

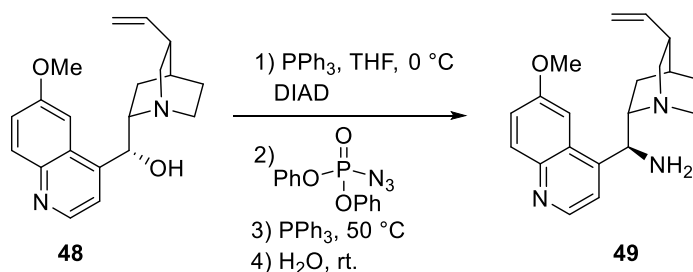
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of Bifunctional Organocatalysts

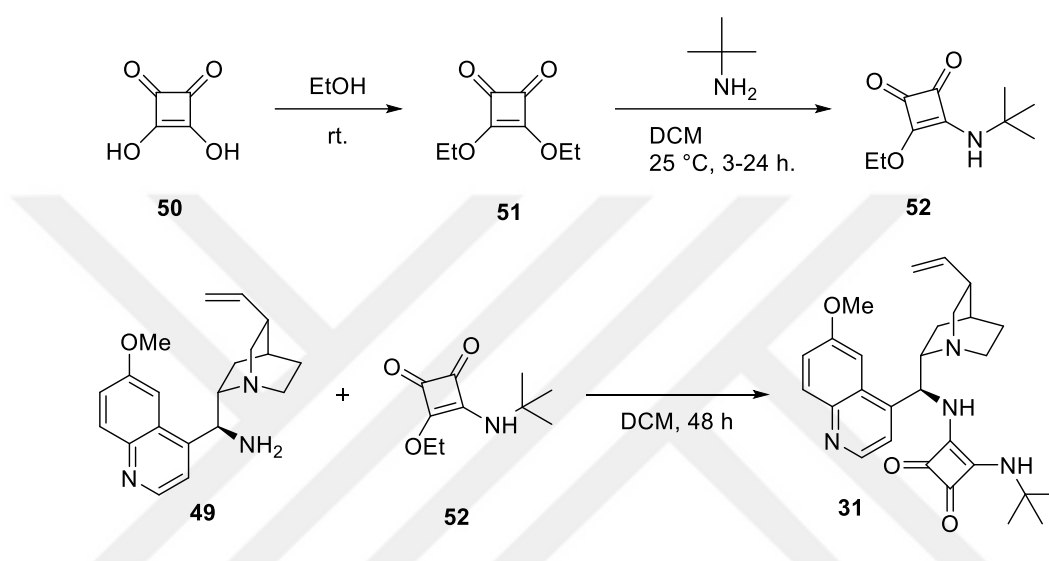
Numerous chiral synthesis reactions have been carried out with the aid of chiral bifunctional organocatalysts. Our research group has designed a series of organocatalysts to provide enantiomeric excess of one component to another. For this goal, the acidic and basic moieties are typically synthesized separately and subsequently combined to produce the resulting bifunctional organocatalysts.

The majority of the organocatalysts used in this investigation are quinine derivatives. Using the incorporation of monosquaramide **52** or nitrosulfonyl chloride **55**, the remarkable performance of quinine-derived organocatalysts of our design on the reactions of Michael, aza-Henry, and aza-Friedel-Crafts has previously been reported.²⁵ To generate quinine amine, the configuration is reversed, and the hydroxyl unit changes to the azide unit with the Mitsunobu reaction first. Then, with the Staudinger reaction, the azide unit changes to the appropriate amine functionality (Scheme 18).⁴¹



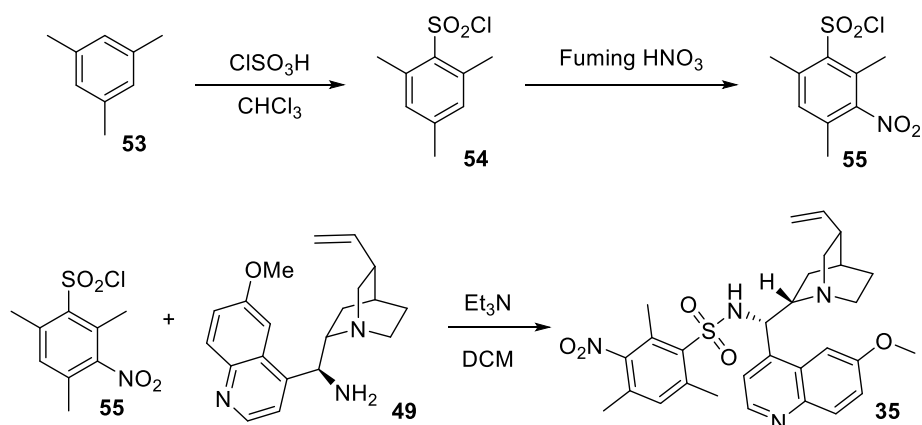
Scheme 18. Synthesis of quinine amine **49**

To complete the bifunctional organocatalyst skeleton, this unit is subsequently joined with the desired acidic unit. To synthesize the acidic part, firstly diethyl squarate (**51**) is synthesized in ethanol and at room temperature from squaric acid (**50**). Then, monosquaramide **52** is then formed with the desired amine group. The reaction between the basic quinine amine **49** moiety and the monosquaramide **52** produces squaramide/quinine organocatalysts **31** (Scheme 19).



Scheme 19. Synthesis of monosquaramide **52** as the acidic moiety and the catalyst **31**

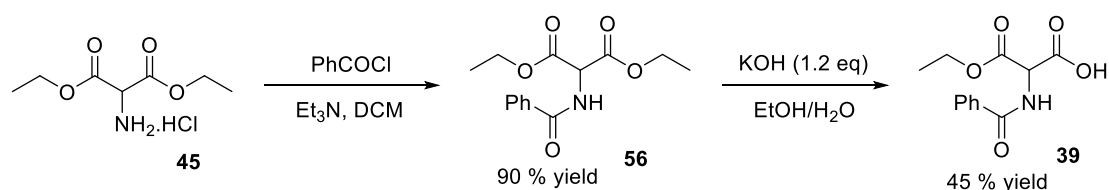
Using 2,4,6-trimethyl benzene sulfonyl chloride (**53**) as a starting point, the sulfonyl chloride unit **54** was synthesized with the presence of chlorosulfonic acid and chloroform. Then, the appropriate position is nitrated with fuming nitric acid. So, 2,4,6-trimethyl-3-nitrobenzenesulfonyl chloride (**55**) was produced.⁴² The bifunctional sulfonamide/quinine organocatalyst **35** was created next by linking nitrosulfonyl chloride **55** to the quinine amine **49** (Scheme 20).



Scheme 20. Synthesis of nitrosulfonyl chloride **55** as the acidic moiety and the organocatalyst **35**

2.2 Synthesis of Starting Material

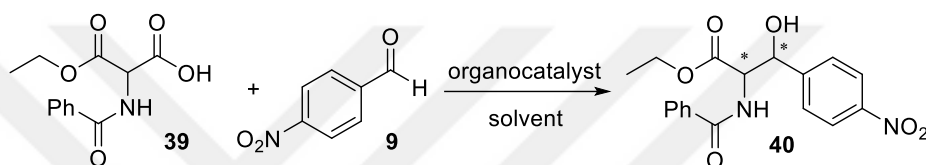
It is aimed to convert diethyl aminomalonate hydrochloride (**45**) into half ester **39** first, to increase the acidity of α -carbon, and so nucleophilic center can be created as a result of this acidity. First of all, the amine group was protected with benzoyl chloride as a white solid in 90% yield, and then, as a result of controlled hydrolysis, the diester **56** was converted to monoacid **39** as a yellowish solid in 45% yield and made ready for decarboxylation (Scheme 21).



Scheme 21. Synthesis of half ester **39**

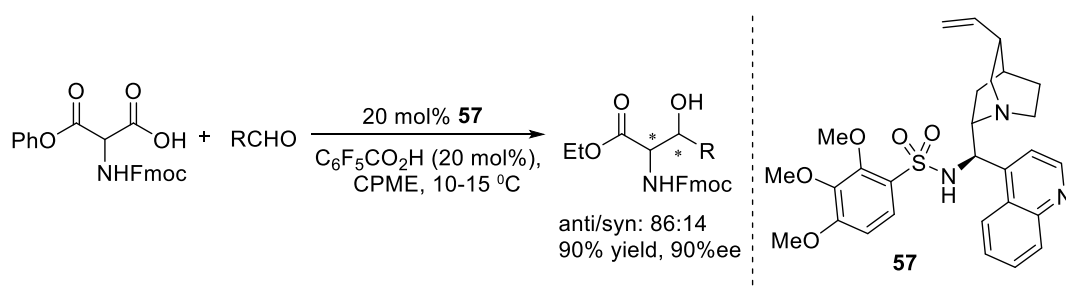
2.3 *anti*- β -Hydroxy- α -amino Acids Synthesis Through Decarboxylative Aldol Reaction

To synthesize *anti*- β -hydroxy- α -amino acids, Rouden et al. (2013) carried out a diastereoselective reaction of α -amido hemimalonates with several aldehydes utilizing numerous organic bases.⁴³ Instead of focusing on enantioselectivity, they only worked hard to create *anti*-diastereoisomeric products. We began researching this reaction using our organocatalyst library after being inspired by this Rouden's work (Scheme 22).



Scheme 22. Rouden's work

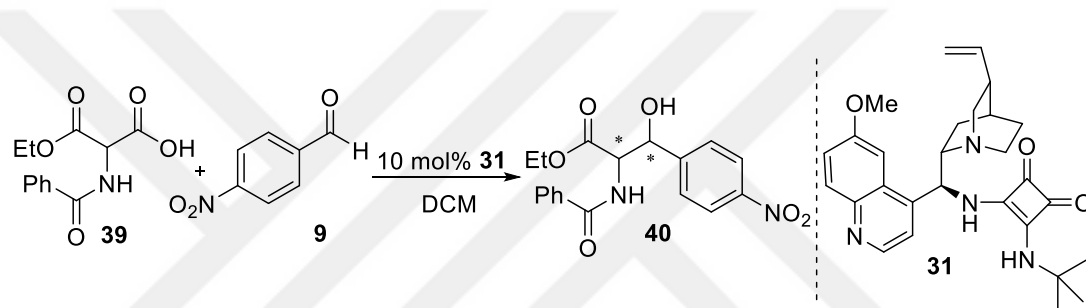
Takemoto and colleagues published the first enantioselective synthesis of *anti*- β -hydroxy- α -amino acids while we were doing our reaction (Scheme 23).²³ In this study, a 20 mol % quinine-based organocatalyst **57** and a 20 mol% doped acid produced a 90 mol% chemical yield and 90 mol% ee. Despite the high ee of the product, the approach still requires catalyst loading and additional improvements.



Scheme 23. Takemoto's work

2.4 Studies for the Asymmetric Decarboxylative Aldol Reaction

This work had previously been tried by members of the Tanyeli research group and was shelved as open for further development. At that time, the selectivity, which was brought to 55% ee for 7 days with DCM and *t*-butyl squaramide catalyst in the first stage, provided us with the information that cutting the reaction at earlier times increased the enantioselectivity in later studies. Considering that the catalyst needs an additive, basic additive addition experiments were also performed by Tanyeli group members in previous studies, but no increase in enantioselectivity was found. The results are shown in Table 1.



Entry ^a	Additive (10 mol%)	Time	Yield ^b	ee ^c (%)	Conc. (M)
1	-	7d	40	55	0.13
2	-	72 h	30	63	0.1
3	Et ₃ N	70 h	29	8	0.1
4	Cs ₂ CO ₃	70 h	27	16	0.1

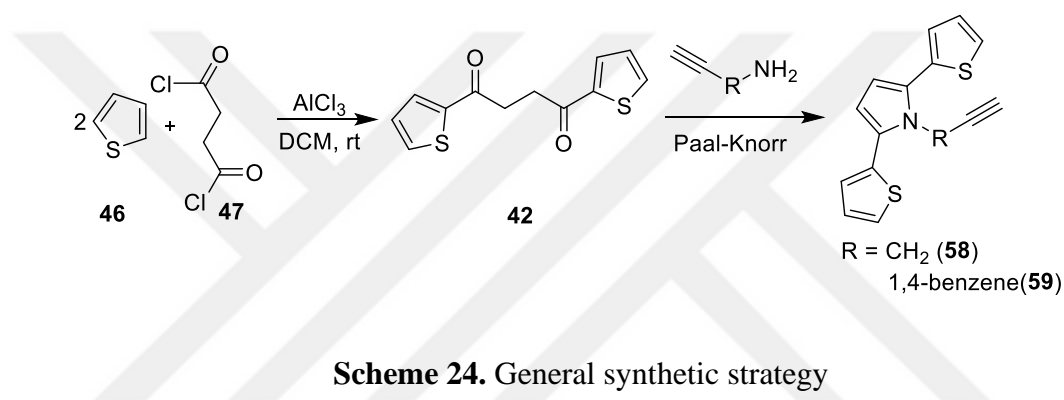
^a1.2 eq of aldehyde and 1 eq of malonic acid half ester are used in every experiment in DCM (0.1 M) at room temperature. ^bIsolated yield. ^cDetermined by HPLC.

Table 1. Tanyeli group members' previous study

In this thesis, various acidic additives combined with *tert*-butyl squaramide quinine and with quinine/sulfonamide have been tested and the results are given in Table 2.

2.5 Synthesis of TPT-Acetylene Matrix

The TPT-acetylene unit was chosen as a matrix for immobilizing a suitable bifunctional organocatalyst with a feasible azide moiety. [3+2] Cycloaddition, defined as a “click” reaction on the acetylene unit, can make a covalent anchoring of chiral organocatalyst on the TPT unit. Furthermore, this TPT monomeric unit containing an acetylene moiety is easily polymerizable via electrochemical or chemical methods and has the potential to be suitable support material for organocatalysts. Our synthetic strategy is given in Scheme 24.

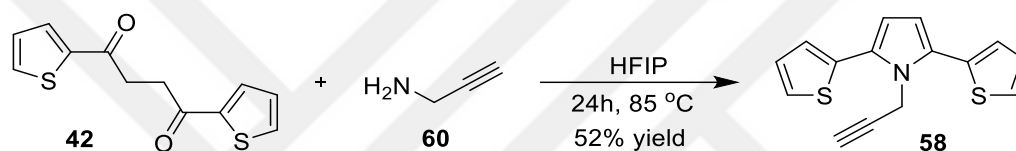


Thiophene (**46**) and succinyl chloride (**47**) underwent a Friedel-Crafts type reaction in DCM with Lewis acid AlCl_3 to afford 1,4-di(thiophene-2-yl)butane-1,4-dione **42**. Due to a well-known Paal-Knorr type reaction, the 1,4-dione **42** unit is an available starting compound to give a pyrrole ring system. This step is crucial in our synthetic strategy since inserting a wide range of primary amine-bearing acetylenic motifs is possible. Those may be potential anchoring modulus with azide units for preparing various chiral monomeric TPT compounds.

2.5.1 Synthesis of 1-(Prop-2-yn-1-yl)-2,5-di(thiophen-2-yl)-1H-pyrrole (**58**) and 1-(4-ethynylphenyl)-2,5-di(thiophen-2-yl)-1H-pyrrole (**59**)

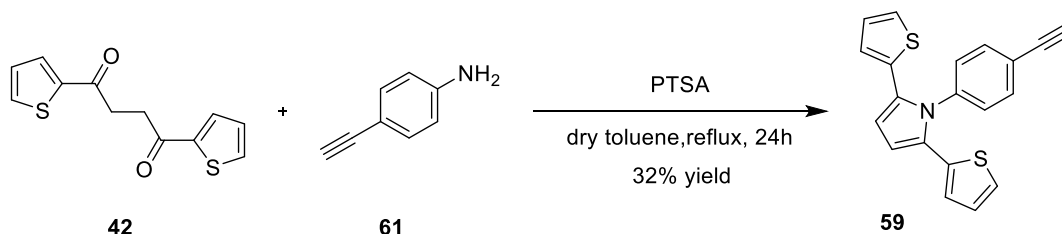
The acid-catalyzed Paal-Knorr method has been used to begin the synthesis of the TPT-acetylene derivative, 1-(prop-2-yn-1-yl)-2,5-di(thiophen-2-yl)-1H-pyrrole

(SNS-p) **58**, by refluxing in toluene with *p*-TSA and propionic acid, respectively. Since we had no success, we tried an alternative approach in which HFIP was employed as a suitable solvent with a little acidic characteristic (Scheme 25). The structure of *N*-propargyl substituted TPT derivative **58** was characterized by NMR, IR, and HRMS methods. In ¹H NMR, characteristic pyrrole protons resonate at 6.41 ppm as a singlet. The methylene protons of the propargyl unit give a signal at 4.78 ppm as a doublet with *J* = 2.5 Hz as a result of long-range coupling with acetylenic proton, whereas acetylenic proton resonates at 2.53 ppm as a triplet with *J* = 2.5 Hz. All spectroscopic data are given in the experimental part and strongly support the structure.



Scheme 25. Synthesis of 1-(prop-2-yn-1-yl)-2,5-di(thiophen-2-yl)-1H-pyrrole (**58**)

In the synthesis of 1-(4-ethynylphenyl)-2,5-di(thiophen-2-yl)-1H-pyrrole (SNS-a) **59**, the method of using propionic acid did not work. Therefore, the product was produced by refluxing in the presence of *p*-toluenesulfonic acid, and the reaction was stopped after the creation of by-products for 24 hours (Scheme 26). From a structural standpoint, in the NMR spectrum of **59**, a singlet proton signal at 6.50 ppm indicates the formation of the pyrrole ring structure. The acetylenic proton at 2.54 ppm as a singlet was another distinguishing signal. The experimental section contains all spectroscopic data, which firmly supports the structure.



Scheme 26. TPT-acetylene matrix **59** synthesis

2.5.2 Electrochemical and optical properties of TPT-based monomers.

The purpose of this research was to investigate new immobilization matrices containing organo-catalytic substituents. The thiophene-pyrrole-thiophene (TPT) host system was chosen for this purpose due to its ease of functionalization via the pyrrole ring's N-atom. Furthermore, this TPT monomeric unit can be easily polymerized using electrochemical or chemical methods and has the potential to be suitable support material for organocatalysts.

Two new TPT derivatives, **47** and **48**, were synthesized as solid state matrix candidates, and their electrochemical and optical properties were investigated before polymerization studies. The electrochemical properties of **47** and **48**, were investigated via cyclic voltammetry in an electrolyte solution containing 0.1 M tetrabutylammonium perchlorate (TBAClO₄) dissolved in DCM.

During the first anodic scan, the voltammogram of **47** exhibited an irreversible peak at 1.0 V vs. Ag/AgCl (Figure 8a), which is responsible for the initiation of the electrochemical polymerization. In the case of **48**, the irreversible oxidation peak appeared at 1.2 V vs. Ag/AgCl in the same solvent-electrolyte couple (Figure 8b). The slight anodic shift in the oxidation potential of **48** could be attributed to the substituent's electron-drawing nature, which lowers the HOMO level and raises the oxidation potential.

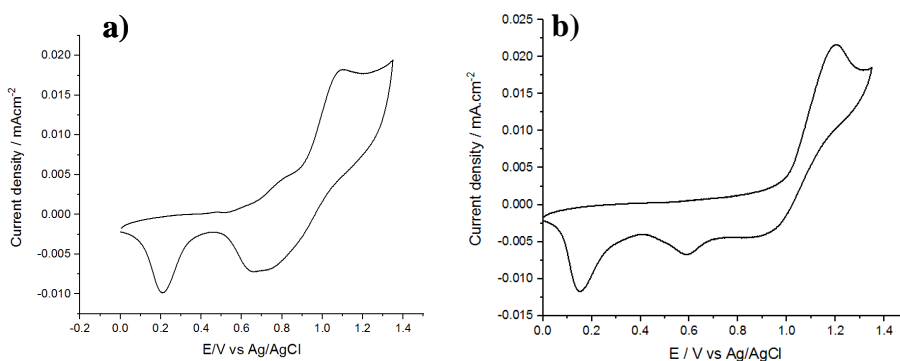


Figure 8. Cyclic voltammograms of **a) 47** and **b) 48** recorded in 0.1 MTBAClO₄/DCM electrolytic solution.

The electronic absorption spectra of the monomer solutions in DCM are shown in Figure 9. **47** exhibits an absorption band at around 320 nm due to π - π^* transition (Figure 9a). This band is shifted to 380 nm in the case of **48** (Figure 9b).

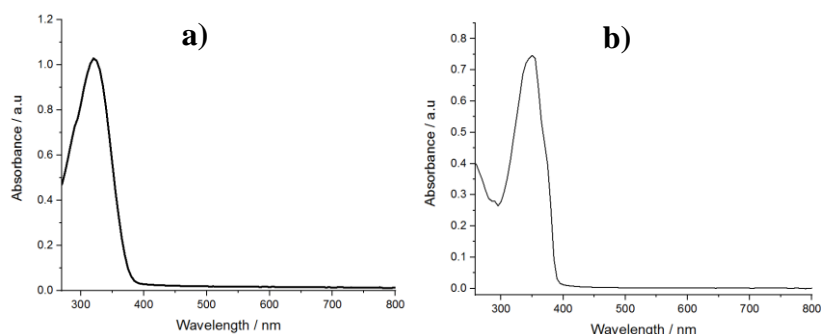


Figure 9. UV-vis spectrum of the monomers **a) 47** and **b) 48** in DCM.

2.5.3 Electrochemical Polymerization of TPT-based monomers.

After electrochemical and optical characterization of **47** and **48** were completed, their electrochemical polymerizations were studied via potentiodynamic methods in DCM-TBAClO₄ electrolytic medium. Pt-bead electrode was used as working electrode together with Pt wire counter electrode and Ag/AgCl reference electrode. Electrochemically synthesized polymers were obtained with 20 cycles (100 mV/s) via repetitive cycling within the range 0.0-1.2 V for **47** and 0.0-1.4 V for **48**, respectively. As shown in Figure 10, during the second anodic scan, new redox couples appeared at around 0.8 V for **47** (Figure 10a), and 0.9 V for **48** (Figure 10b) indicating electroactive polymer film formation on the electrode surface. After each following cycle, the current increased steadily which indicated that both the surface area and the thickness of the polymer film on the working electrode also increased.

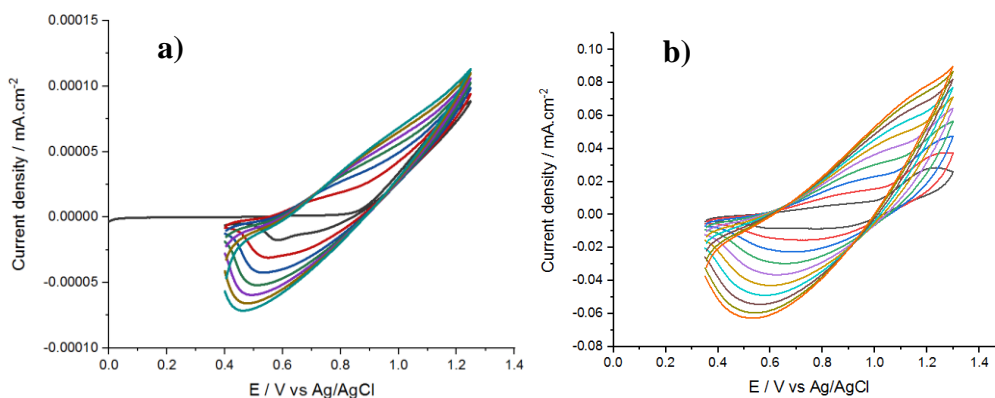


Figure 10. Cyclic voltammograms recorded during electrochemical polymerization of a) **47** and b) **48** in 0.1 M TBAClO₄ DCM electrolyte solution.

After completion of the polymer formation, the polymer film coated on WE was washed with DCM to remove any unreacted monomer and oligomeric species. Because the polymer film obtained from **47** had a dissolution problem, no further electrochemical investigation was carried out on it. However, polymer film obtained from **48** was insoluble in DCM, its electrochemical behavior was investigated by recording their CVs in a monomer-free electrolytic solution consisting of 0.1 M TBAClO₄ in DCM at different scan rates (Figure 11a).

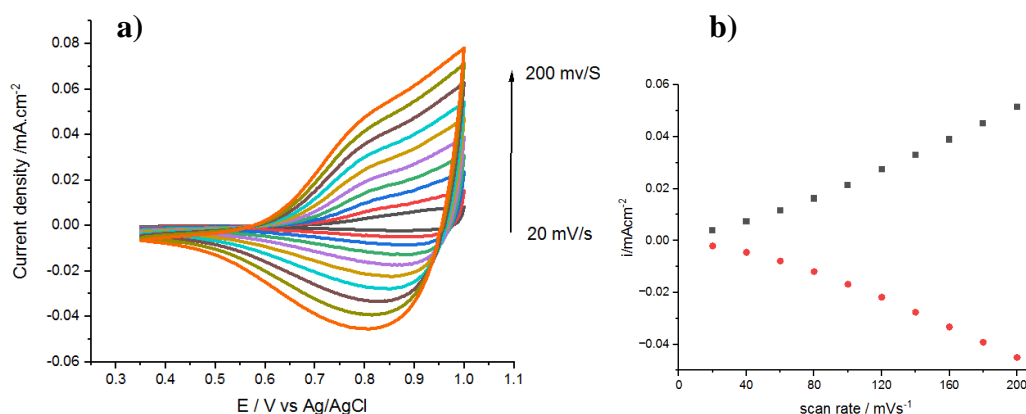


Figure 11. a) Cyclic voltammogram of polymer film obtained from **48** on Pt-bead working electrode, recorded at different scan rates between 20- 200 mV/s in DCM and 0.1 M TBAClO₄ as electrolyte **b)** Relationship of anodic and cathodic currents with respect to scan rate.

The polymer film, **P48**, was found to exhibit one reversible redox couple representing the doping and de-doping of the polymer film at about 0.80 V vs. Ag/AgCl, Figure 11a. It is found that both anodic and cathodic peak currents increase linearly with increasing scan rate, indicating that the redox process is non-diffusional and the polymer film is well-adhered to the working electrode, See Figure 11b.

2.5.4 Spectroelectrochemical Properties of the polymer, **P48**

In order to elucidate the electrochromic features of **P48**, polymer films were deposited on ITO working electrode via repetitive potential cycling. The changes in the electronic absorption spectrum were recorded during potential scanning from 0.00 V to 1.02 V with a voltage scan rate of 10 mV/s, in a monomer-free electrolytic solution, and the results are depicted in Figure 12. An inspection of the figure reveals that **P48** film exhibits a strong absorption band at about 430 nm. Upon oxidation, this band loses intensity, which is accompanied by the appearance of new intensifying bands at about 690 nm. Upon further oxidation, a new band around 1000 nm also starts intensifying. Appearance of these new bands indicates the formation of charge carriers. In the case of the polymer obtained from **47**, no spectroelectrochemical investigation was conducted due to the dissolution problem of **P47**.

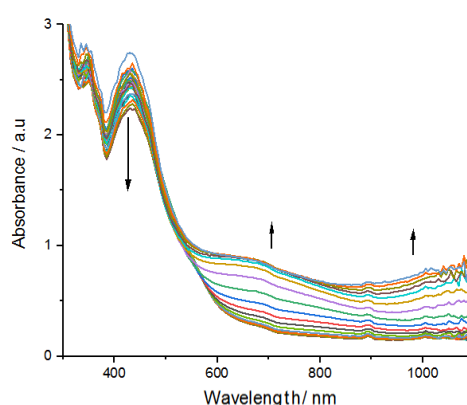


Figure 12. Electronic absorption spectra of the polymer, **P48**, on ITO recorded in DCM containing 0.1 M TBAClO₄ as the electrolyte between 0.0 and 1.2 V.

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

On a Bruker Spectrospin Avance DPX-400 spectrometer, ^1H NMR and ^{13}C NMR spectra were obtained in CDCl_3 . The chemical shifts were given in ppm with respect to CDCl_3 as the internal standard (7.26 and 77.0 for ^1H and ^{13}C NMR, respectively). Spin multiplicities were abbreviated as follows: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), dq (doublet of quartet), t (triplet), tt (triplet of triplet), q (quartet), and m (multiplet), with coupling constants (J) specified in Hertz (Hz).

Chromatograms from HPLC systems made by Dionex and Thermo-Finnigan were recorded. With various solvent solutions, Daicel ASH chiral columns are employed. The Agilent 6224 TOF LC/MS at UNAM, Bilkent University, was used to record the HRMS data. Thermo Nicolet IS10 ATR/FT-IR and Agilent 1100 Series spectrophotometers were used to record the results for infrared spectroscopy.

A MEL-TEMP 1002D device was used to measure the melting points of a solid compound that are novel to the literature.

Column chromatographies were conducted using Merck Silica Gel 60, which has particles that range from 0.04 to 0.063 mm in size. Thin layer chromatography was used to monitor reactions using precoated silica gel plates (Merck Silica Gel PF-254) and UV imaging.

pH measurements were made with pH-indicator strips pH 0 - 14 Universal indicator Merck brand.

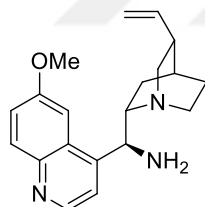
All extracts were dried over anhydrous sodium sulfate and solutions were concentrated under vacuum by using a rotary evaporator.

Compounds names were written with ChemBioDraw 14.0.

In the experimental part, only characterization information for novel compounds is provided, and relevant literature is acknowledged. Products' ^1H and ^{13}C NMR spectra are displayed in Appendix A. Appendix B contains HPLC chromatograms of chiral and racemic compounds.

Platinum (Pt) wire served as the counter electrode (CE), silver-silver chloride (Ag/AgCl) served as the reference electrode (RE), and electrochemical tests were conducted utilizing these electrodes. Using a potentiostat-galvanostat of the Gamry Reference 300 model, the cyclic voltammograms (CV) were obtained. A UV-VIS spectrometer of the Carry 60 model was used in conjunction with a Gamry Reference 300 potentiostat-galvanostat to perform the spectroelectrochemical measurements. We employed a Pt wire, an Ag wire, and indium tin oxide (ITO, Delta Tech. 8 - 12, 0.7 cm 5 cm) coated glass as WE, CE, and pseudo-RE, respectively.

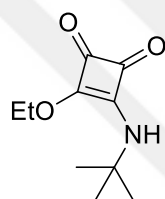
3.2 Synthesis of (8 α ,9S)-6'-Methoxycinchonan-9-Amine (Quinine Amine) (49)



Following standard procedure,⁴⁴ the solution was cooled to 0°C after being dissolved in 50 mL of dry THF with 1 eq quinine 20 (3.24 g, 10.0 mmol) and 1.2 eq triphenylphosphine (3.15 g, 12.0 mmol). The initial solution was then treated with 1.2 eq diisopropyl azodicarboxylate (2.43 g, 12.0 mmol). Diphenyl phosphoryl azide (3.30 g, 12.0 mmol) was dissolved in 20 mL of dry THF in a second flask and cooled to 0°C. After that, at 0°C, the second solution was added dropwise to the first solution. At room temperature, the mixture was stirred. The solution started heating after 12 hours and continued for 2 hours at 50°C. After adding 3.41 g, or 13.0 mmol, of triphenylphosphine in an amount equal to 1.3 eq, the solution was heated until no more gas was emitted. Approximately two hours were needed for this. 1 mL of water was added when the solution had reached room temperature, and it was stirred for 3 hours. Solvents were removed using a vacuum, and the residue was dissolved using CH_2Cl_2 and 10% hydrochloric acid. (1:1, 100 mL). Excess aqueous ammonia was

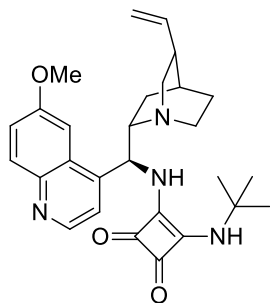
used to make the aqueous phase alkaline after the aqueous phase had been washed four times with 50 ml DCM. After that, 50 ml of DCM was used to wash the aqueous phase four times. Utilizing Na_2SO_4 , the mixed organic phases were dried and concentrated. A silica gel-coated column was used to purify the residue. As an eluent, a mixture of EtOAc, MeOH, and concentrated aqueous NH_4OH (50/50/1) was utilized. The product was synthesized as a 70 percent yield of yellowish oil. Spectroscopic information has previously been published.⁴⁴

3.3 Synthesis of Mono-Squaramide (52)



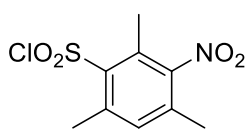
In the standard procedure,⁴⁵ squaric acid (4.3 mmol, 500 mg) was first refluxed in absolute ethanol (7 ml) under an argon environment for three hours to produce diethyl squarate. The solvent was then extracted using a vacuum. Three more times, the mixture was refluxed for 30 minutes using the same technique. Diethyl squarate was produced as a very light-yellow oil after the final evaporation. The mono-squaramide was created by mixing the diethylsquarate with the amine portion (1eq) in 4 ml DCM for 24 hours at room temperature. The amines (*t*-butyl, 1-adamantyl, and 2-adamantyl) were all obtained commercially. Using a column coated with silica gel and EtOAc: Hexane (1:3) as the eluent, pure products were produced with a 90% yield of white solid. Spectroscopic data are consistent with published data.⁴⁵

3.4 Synthesis of *t*-Butyl Squaramide/Quinine Catalyst (31)



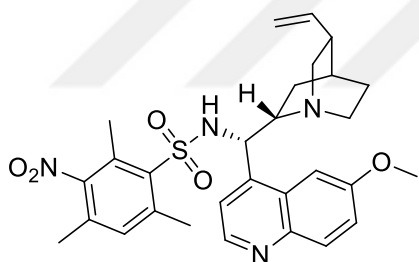
First, 0.2 mmol of quinine was dissolved in a 1:1 mixture of DCM and MeOH, and then 0.2 mmol of mono-squaramide ester was added to create squaramide/quinine catalysts. Column chromatography on silica gel was immediately applied to the mixture after stirring for 48 hours at room temperature. EtOAc: MeOH was employed as the eluent. The desired product, a quite whitish solid, was obtained with a 92% yield. Spectroscopic data are consistent with published data.²⁵

3.5 Synthesis of 2,4,6-Trimethyl-3-nitrobenzene-1-sulfonyl chloride 55



In 15 minutes, fuming nitric acid (47.6 mmol, 2 mL) was dropwise added to 2,4,6-trimethylbenzene-1-sulfonyl chloride (4 mmol, 874 mg). After 1 hour of stirring at room temperature, the reaction mixture was completed and diluted with 20 mL of ice-cold water. Using diethyl ether, the mixture was extracted (2 x 25 mL). Combining and washing the organic phases repeatedly in 25 mL of cold water, 25 mL of 1 percent Na_2CO_3 , and brine (2 x 25 mL). The combined organic phases were concentrated in a vacuum and dried over Na_2SO_4 . With a yield of 43%, the residue was recrystallized from n-pentane to produce the product as white crystals. Analytical results were consistent with published values in the literature.⁴²

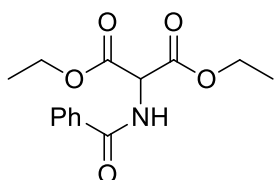
3.5 Synthesis of Bifunctional Catalyst 35



A mixture of quinine amine (1.0 mmol, 323.4 mg), triethylamine (1.1 mmol, 140 μL in DCM (2.5 mL), and 2,4,6-trimethyl-3-nitrobenzene-1-sulfonyl chloride was added at 0 °C. Stirring the mixture for 48 hours after bringing it to room temperature. After that, the mixture was immediately put into a silica gel column. An off-white solid with a 35 % yield was produced by elution with $\text{EtOAc/MeOH/TEA} = 90:10:1$. Spectroscopic data are consistent with published data.⁴⁶

3.6 Synthesis of α -Amidohemimalonates

3.6.1 Protection of amine group of Diethyl 2-Aminomalonate Hydrochloride 56

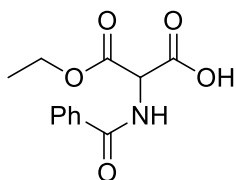


1 eq diethyl aminomalonate hydrochloride (500 g, 2.36 mmol) was dissolved in 3 eq triethylamine (1 mL, 7.087 mmol) and 35 mL DCM and stirred for 15 min at 0 °C. 1 eq benzoyl chloride (0.275 mL, 2.36 mmol) was added dropwise at 0 °C as the stirring continuous. The reaction was stirred for 15 hours at room temperature. Then, the reaction was diluted with DCM, for about 35 mL, and the solution was made acidic by adding 1N HCl until pH=1. Extraction was applied with DCM and organic layers were obtained and dried. After the organic phase was concentrated under pressure recrystallization was applied in EtOH: Heptane (1:10) condition. A white solid of benzoyl-protected aminomalonate was produced with 90% yield.

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.89 – 7.81 (m, 2H), 7.57 – 7.51 (m, 1H), 7.46 (dd, $J = 6.5, 1.6$ Hz, 2H), 7.14 (d, $J = 6.8$ Hz, 1H), 5.34 (d, $J = 6.9$ Hz, 1H), 4.37 – 4.24 (q, 4H), 1.32 (t, $J = 7.1$ Hz, 6H).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.7, 166.3, 132.9, 132.0, 128.5, 127.2, 62.5, 56.7, 13.9.

3.6.2 Synthesis of Hemimalonates 39



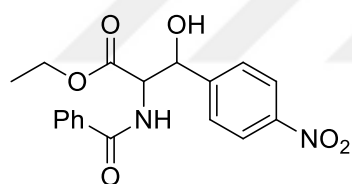
1 eq. diethyl 2-benzamidomalonate and 1.2 eq. KOH was dissolved in 1:10 $\text{H}_2\text{O}:\text{EtOH}$ solution, 11 mL for each, separately. KOH solution was added dropwise at 0 °C. After 1 day of stirring at room temperature, the solution was made acidic with 1N HCl added until pH=1 and then saturated with solid NaCl. Extraction was applied with EtOAc and organic layers were collected and dried. After

concentrating the solution under reduced pressure, the crude product was washed with saturated NaHCO₃. Then, extraction was done with ether and the aqueous phase was collected. Acidic work-up was applied with 1N HCl until pH=1. Extraction was performed one more with ether and the organic layer was collected and dried. After concentrating the reaction under pressure, the intended product was produced at a yield of 45% as a yellowish solid.

¹H NMR (400 MHz, CDCl₃): δ 9.93 (bs, 1H), 7.82-7.79 (m, 2H), 7.50 (tt, *J*= 7.41, 1.86 Hz, 1H), 7.45-7.41 (m, 2H), 5.36 (d, *J*= 6.70 Hz, 1H), 4.33-4.28 (m, 2H), 1.31 (t, *J*= 7.12 Hz, 3H).

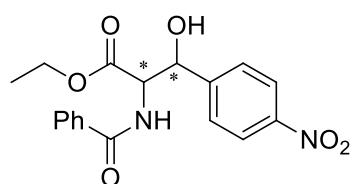
¹³C NMR (100 MHz, CDCl₃): δ 168.4, 168.2, 166.6, 132.7, 132.4, 128.7, 127.6, 63.1, 57.1, 14.1.

3.7 Decarboxylative Aldol Reaction: 4-Nitrobenzaldehyde addition to α -Amidohemimalonates 40



Racemic synthesis: In THF with 1M in concentration, 1 eq. of malonic acid half ester, 1.2 eq. aldehyde, and 1 eq. Et₃N were dissolved and mixed at room temp for 15 hours. TLC was used to observe the reaction

duration. Column chromatography on silica gel was used to purify the desired product. As an eluent, a 3:7 mixture of EtOAc and hexane was utilized.



Asymmetric synthesis; In solvent, 1.2 eq. of aldehyde, 1 eq. of malonic acid half ester, and different mol % of organocatalysts were dissolved. The reaction was then stirred at room temperature. TLC was used to

monitor the reaction, and after that, the reaction was immediately loaded into column chromatography. As an eluent, a 3:7 mixture of EtOAc and hexane was utilized.

¹H NMR (400 MHz, CDCl₃): δ 8.20 (d, *J*= 8.9 Hz, 2H) 7.71-7.67 (m, 2H), 7.62 (d, *J*= 8.6 Hz, 2H), 7.53 (tt, *J*=7.5, 1.21 Hz, 1H), 7.45-7.41 (m, 3H), 6.88 (d, *J*= 8.9

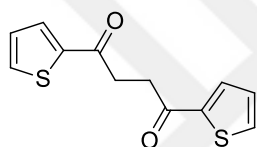
Hz, 1H), 5.51 (d, $J= 2.9$ Hz, 1H), 5.16 (dd, $J=8.8, 3.1$ Hz, 1H), 4.31-4.20 (m, 2H), 1.30 (t, $J= 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 169.0, 168.8, 147.7, 147.3, 132.8, 132.1, 129.1, 127.5, 127.2, 123.4, 75.2, 62.9, 60.2, 14.3.

HPLC Chiralpak ASH column, 80:20 (n-hexane/*i*-PrOH), flow rate 1.0 mL/min, 210 nm, temp=25°C, $t_{\text{minor}}= 11.6$ min, $t_{\text{major}}= 18.1$ min.

IR 3307, 2917, 1727, 1467, 1177, 1107, 667 cm^{-1}

3.8 Synthesis of Diketone Product 42

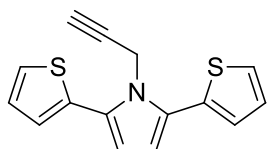


A suspension of 2 eq of AlCl_3 (16.0 g) in 15 mL of dry CH_2Cl_2 was prepared and stirred in a round-bottom flask. Then, in another flask, 1 eq. of thiophene (9.61 ml) and 1 eq. of succinyl chloride (6.60 mL) were mixed in 30 mL of dry CH_2Cl_2 . The second mixture was then dropped slowly into the first reaction flask. The reaction was stirred overnight at room temperature in an inert atmosphere. The next day, the reaction was put into ice (around 90 g), and 10 ml of concentrated HCl was added to the ice mixture. The mixture was then stirred for a further two hours. Ice began to melt during this process, and phase separation could be seen clearly. The residue was extracted with CH_2Cl_2 , the organic phase was washed with 10% NaHCO_3 , (5 x 30 mL) and lastly, 10% NaCl solution. The desired product was recrystallized with ethanol and was produced at a yield of 25 % as a silver solid.

^1H NMR (400 MHz, CDCl_3) δ 7.82 (dd, $J = 3.8, 1.1$ Hz, 2H), 7.65 (dd, $J = 5.0, 1.1$ Hz, 2H), 7.15 (dd, $J = 5.0, 3.8$ Hz, 2H), 3.40 (s, 4H).

^{13}C NMR (101 MHz, CDCl_3) δ 191.4, 143.8, 133.7, 132.1, 128.5, 33.2.

3.9 Synthesis of 1-(prop-2-yn-1-yl)-2,5-di(thiophen-2-yl)-1H-pyrrole 58



1 eq. of 1,4-di(thiophen-2-yl) butane-1,4-dione and 15 eq. of propargylamine was mixed in HFIP in 0.5 concentration. Then the reaction was stirred under the inert atmosphere at 85 °C for 1 day. It was controlled with TLC. Column chromatography was used to purify the product. As an eluent, a 25:1 Hex: EtOAc mixture was used. The desired product was synthesized as a white solid with 52 % yield.

¹H NMR (400 MHz, CDCl₃) δ 7.41 (dd, *J* = 3.5, 0.9 Hz, 2H), 7.34 (dd, *J* = 5.1, 1.0 Hz, 2H), 7.14 (dd, *J* = 5.1, 3.6 Hz, 2H), 6.41 (s, 2H), 4.78 (d, *J* = 2.5 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H).

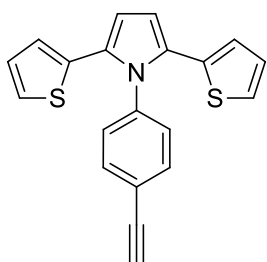
¹³C NMR (101 MHz, CDCl₃) δ 134.2, 128.8, 127.6, 125.4, 125.2, 110.6, 80.3, 73.5, 35.56.

Mp: 135-136 °C

IR (neat): 3261, 3101, 2922, 2851, 1729, 1492, 1332, 1259, 1193, 1086, 917, 831, 771, 693, 649, 500

HRMS calculated for C₁₅H₁₀NS₂ (M-H)⁺ 268.0255, found 268.0260

3.10 Synthesis of 1-(4-ethynylphenyl)-2,5-di(thiophen-2-yl)-1H-pyrrole 59



1 eq. of 1,4-di(thiophen-2-yl)butane-1,4-dione was mixed with 5 eq. of 4-ethynylaniline in a round-bottom flask. After, 20 mol% of *p*-TSA was added to the reaction flask. Then, 5 mL dry toluene was introduced as the reaction solvent. The reaction was refluxed under the inert atmosphere for 1 day. Column chromatography on silica gel was immediately applied to the mixture, As an eluent 25:1 Hex: EtOAc mixture was used. The target product was synthesized in 32 % yield green solid.

¹H NMR (400 MHz, CDCl₃) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 5.1 Hz, 2H), 6.78 – 6.73 (m, 2H), 6.50 – 6.40 (m, 4H), 2.54 (s, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 148.58, 139.19, 133.47, 128.07, 127.72, 127.62, 124.31, 124.25, 122.73, 107.18, 77.37, 76.73.

Mp: 59-61 °C





CONCLUSION

Bifunctional organocatalysts that had already been synthesized in Tanyeli's research group were used in the first part of this thesis to evaluate the decarboxylative aldol reactions of anti- β -hydroxy- α -amino acid with *p*-nitrobenzaldehyde. Decarboxylative aldol reactions of 4-nitrobenzaldehyde to α -amidohemimalonates were carried out. Excitingly, 83% ee was produced with a 10 mol% sulfonamide catalyst **27** and 20 mol % 3,5 dinitrobenzoic acid as an acidic additive, while avoiding the previously reported high reaction time and low yield.

Although our first study was better compared to the literature study, in terms of the catalyst loading, due to the increase in the number of publications of this issue in the literature, there was a need for a more innovative study, and the second part was started to be studied. We obtained better results in terms of catalyst loading when comparing the results to Takemoto's literature study. At that point, we decided to end the study because we thought that if it were presented, no one would notice the difference.

In the second part of this thesis, we attempted to synthesize two different TPT-attached acetylenic matrix systems since they can be available in monomeric systems for further polymerizations, and additionally, the acetylenic core can easily couple with azide-bearing organocatalyst systems. We have synthesized acetylenic units anchored via the saturated carbon and aromatic carbons to the pyrrole component of the TPT system. We prove that those possessive propargyl and phenylacetylene units can be available for electropolymerization.

This study led to the formation of new, easily polymerizable TPT-Acetylene matrixes, which will be a pioneer work in the synthesis of heterogeneous polymers in the future.

In future work, after the application [3+2] cycloaddition reaction of organized bifunctional organocatalysts with TPT-acetylene, these derivatives will be

polymerized and heterogeneous, reusable organocatalysts will be synthesized and finally, they will be tested in a variety of asymmetric reactions.



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APPENDICES

A. NMR SPECTRA

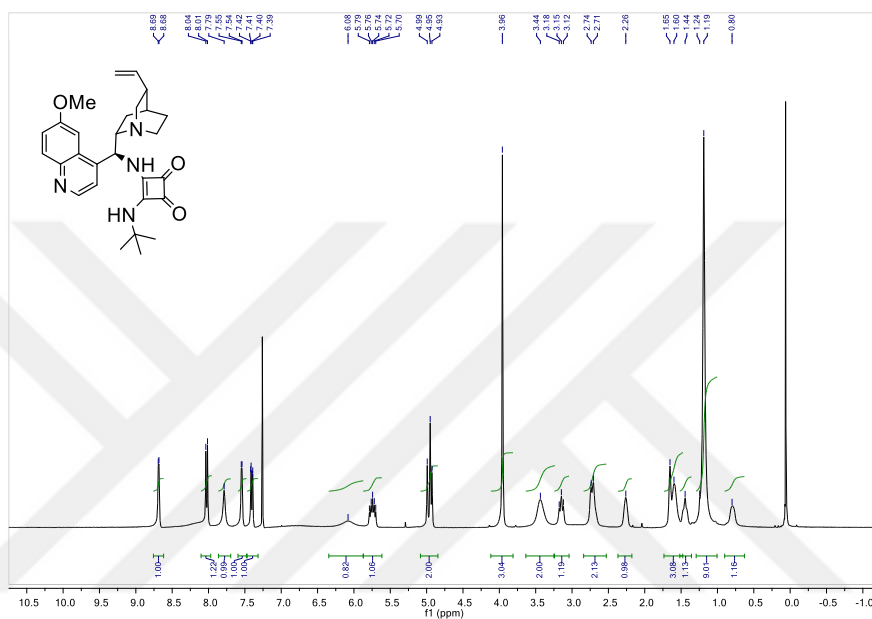


Figure A. 1. The ¹H-NMR spectrum of compound 31

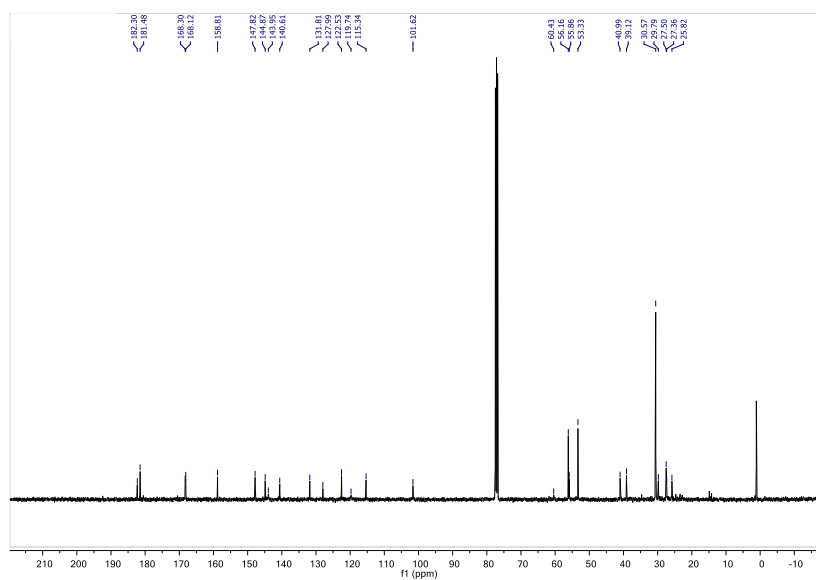


Figure A. 2. The ¹³C-NMR spectrum of compound 31

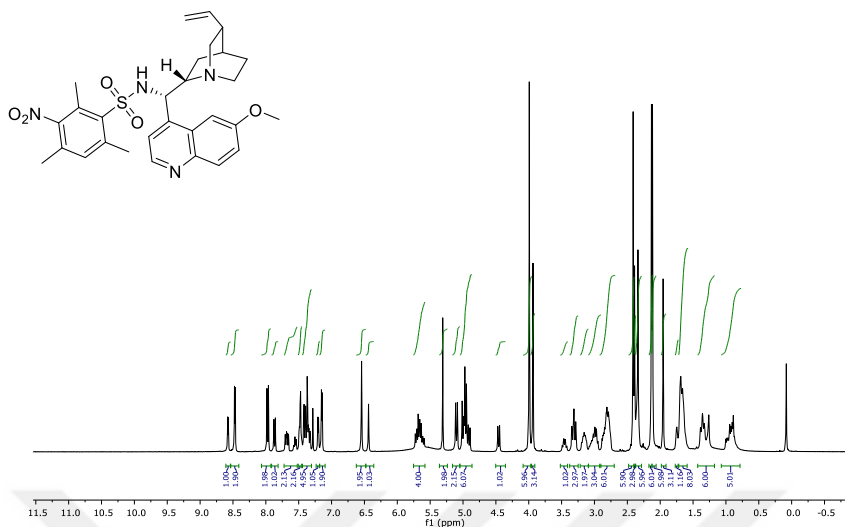


Figure A. 3. The $^1\text{H-NMR}$ spectrum of compound 35

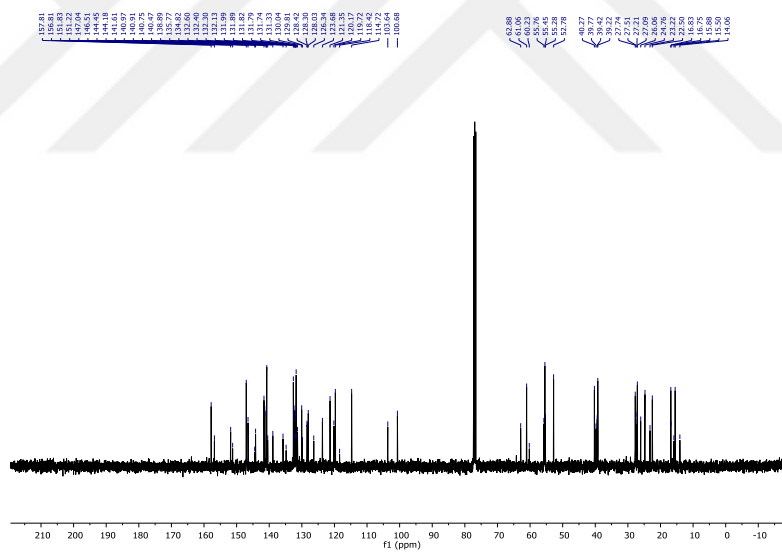


Figure A. 4. The $^{13}\text{C-NMR}$ spectrum of compound 35

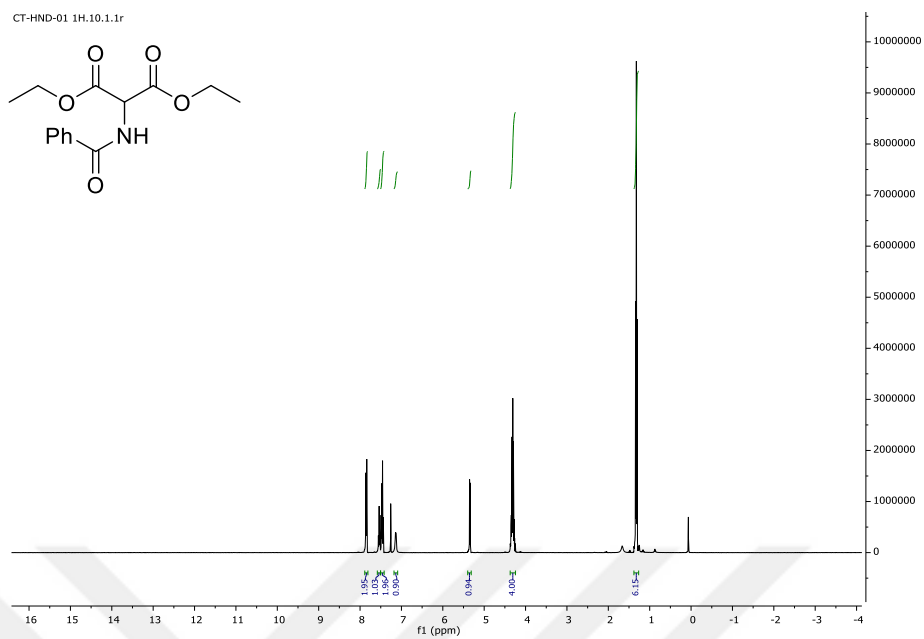


Figure A. 5. The $^1\text{H-NMR}$ spectrum of compound 56

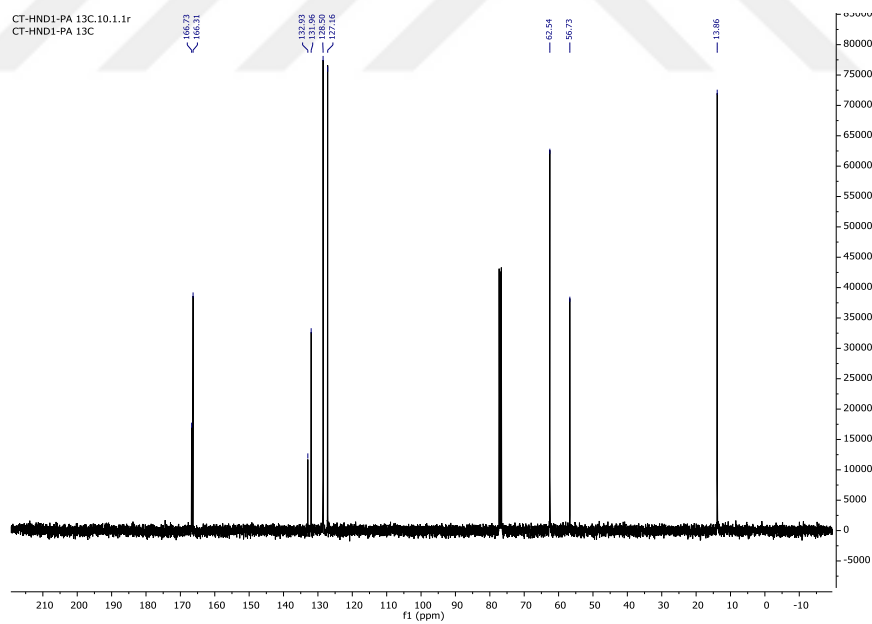


Figure A. 6. The $^{13}\text{C-NMR}$ spectrum of compound 56

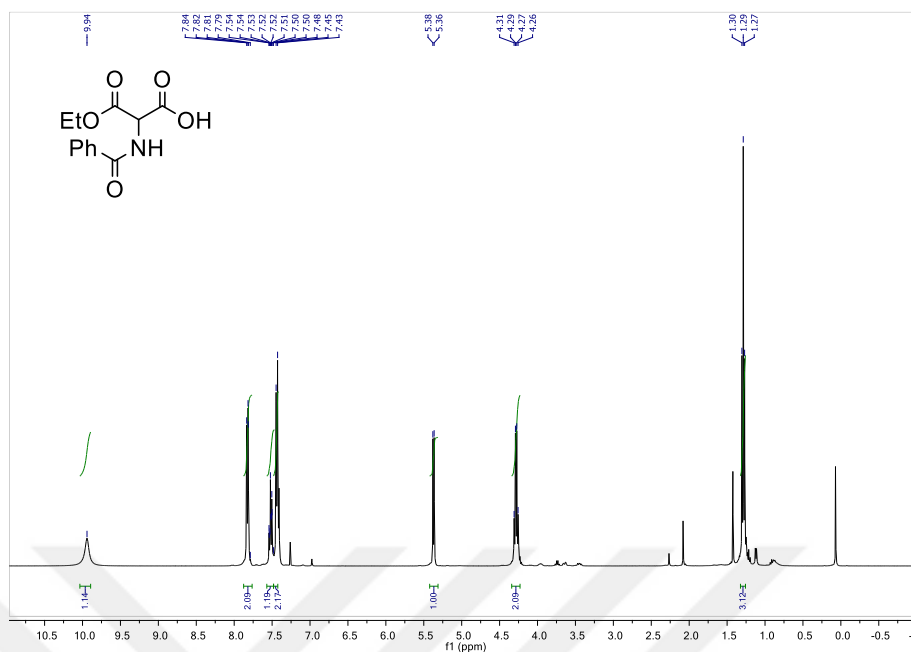


Figure A. 7. The ¹H-NMR spectrum of compound 39

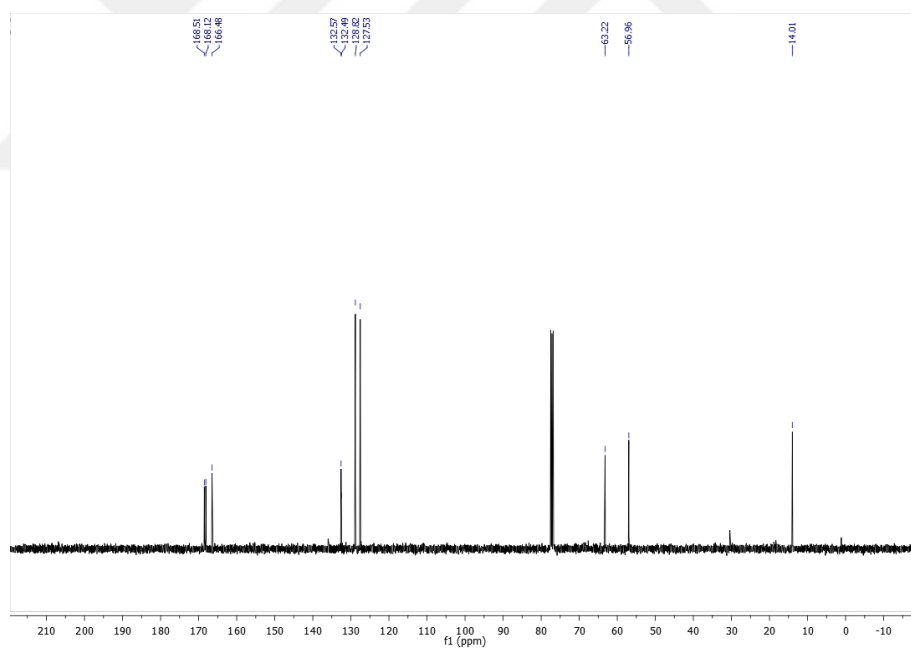


Figure A. 8. The ¹³C-NMR spectrum of compound 39

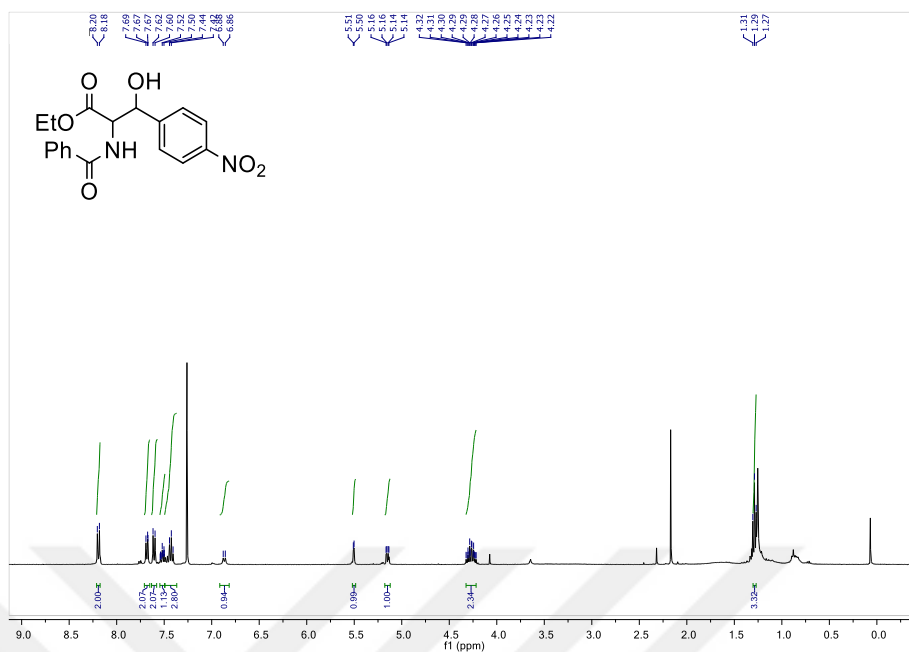


Figure A. 9. The ¹H-NMR spectrum of compound 40

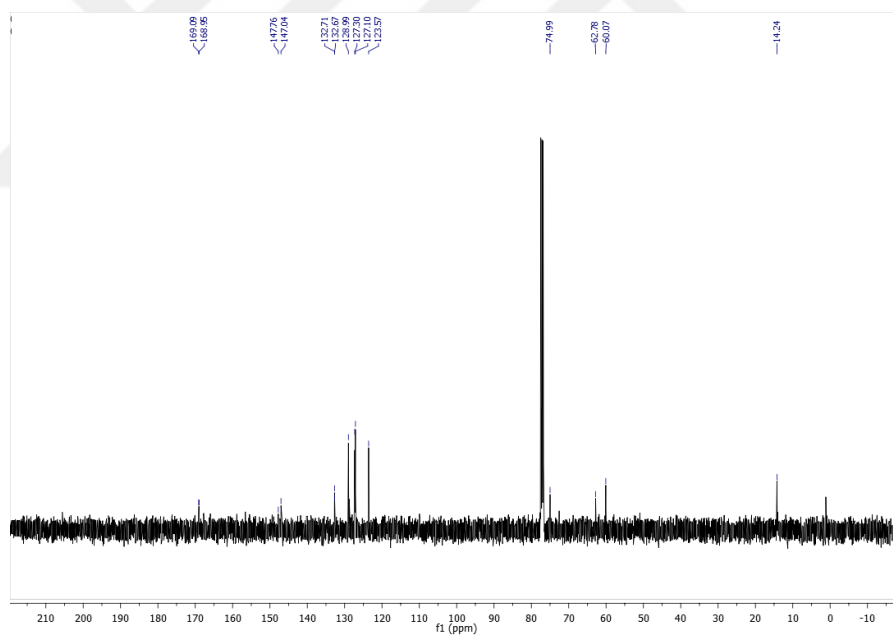


Figure A. 10. The ¹³C-NMR spectrum of compound 40

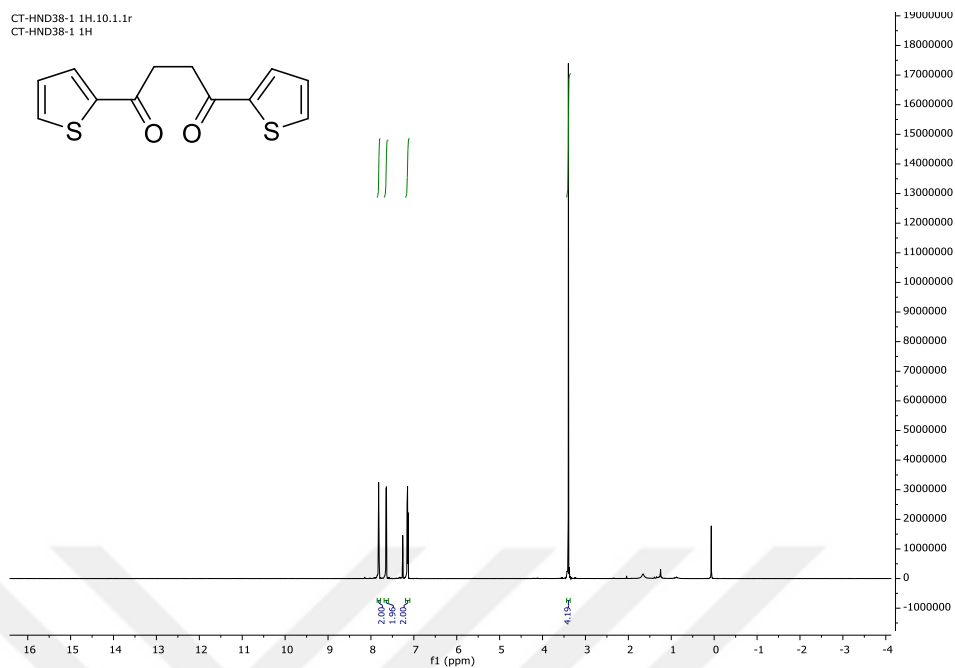


Figure A. 11. The ^1H -NMR spectrum of compound 42

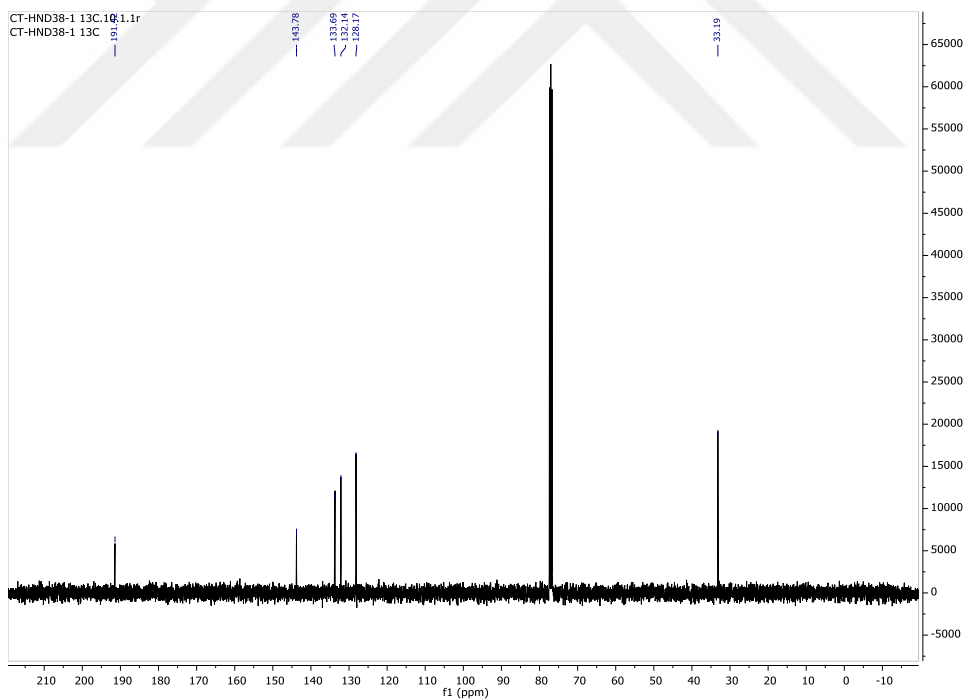


Figure A. 12. The ^{13}C -NMR spectrum of compound 42

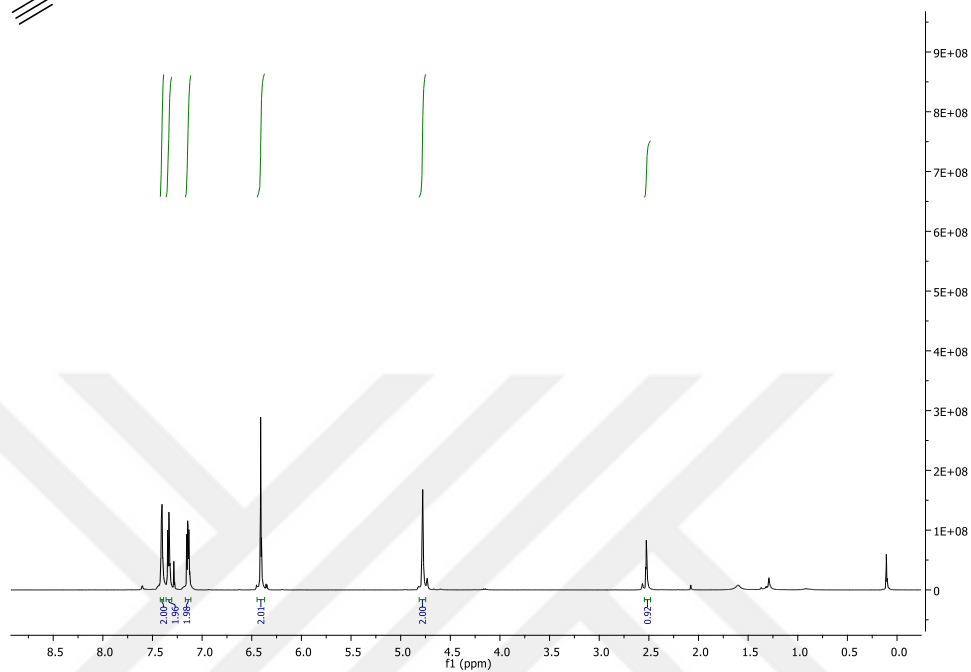
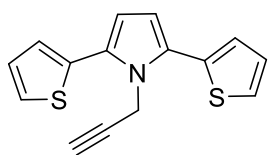


Figure A. 13. The $^1\text{H-NMR}$ spectrum of compound 58

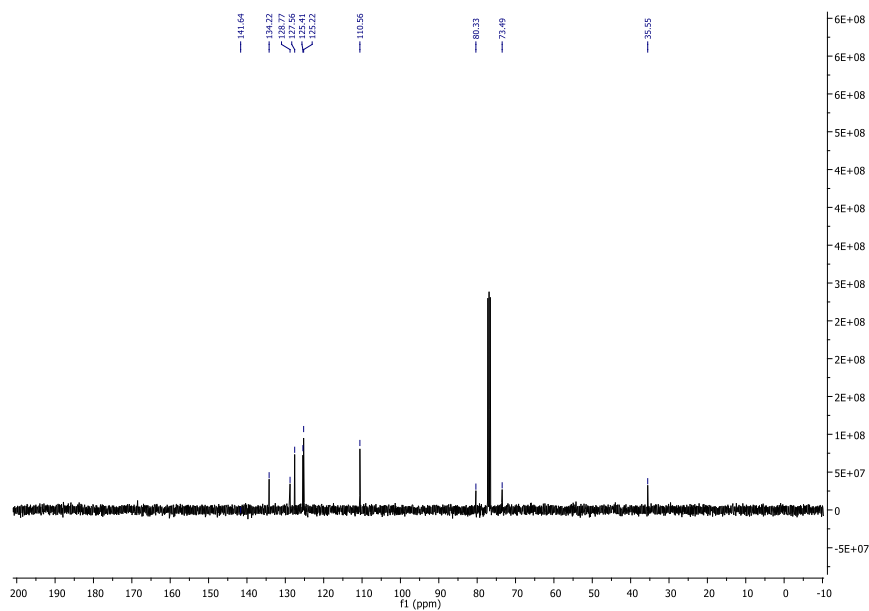


Figure A. 14. The $^{13}\text{C-NMR}$ spectrum of compound 58

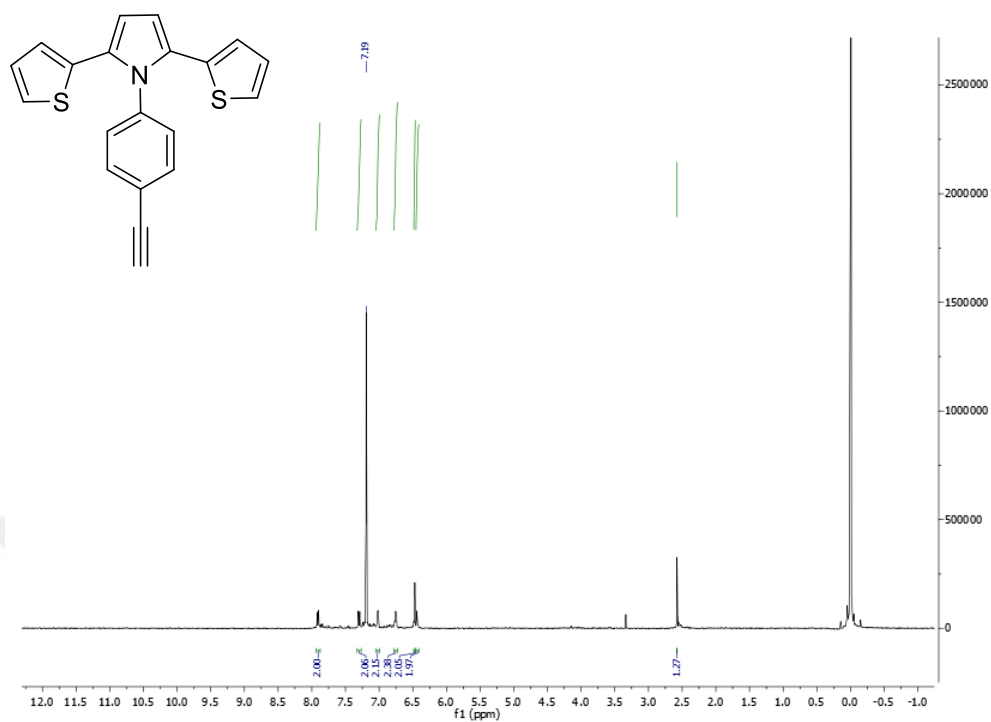


Figure A. 15. The ¹H-NMR spectrum of compound **59**

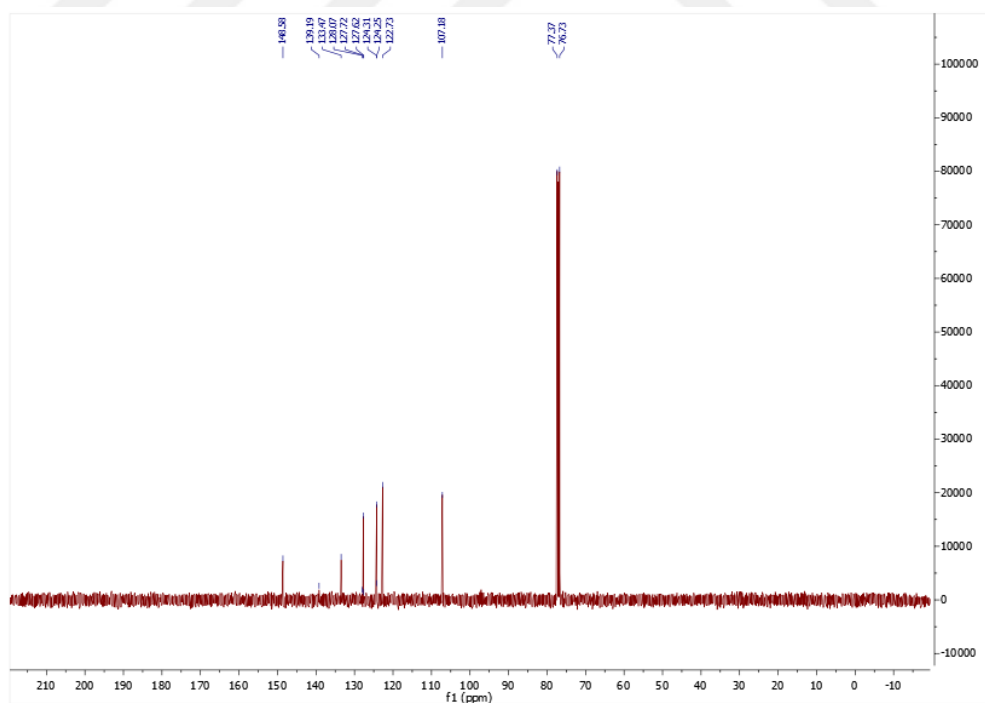


Figure A. 16. The ¹³C-NMR spectrum of compound **59**

B. HPLC CHROMATOGRAMS

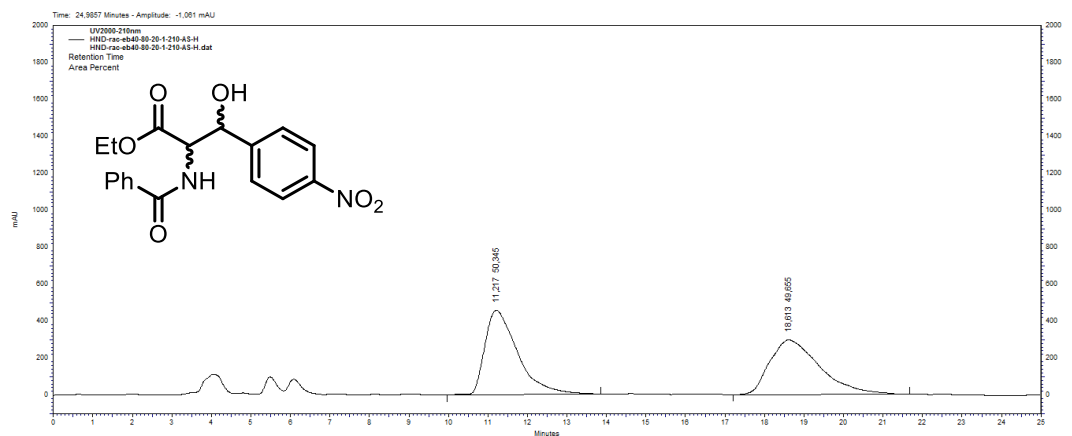


Figure B. 1. HPLC chromatogram of *rac*-40

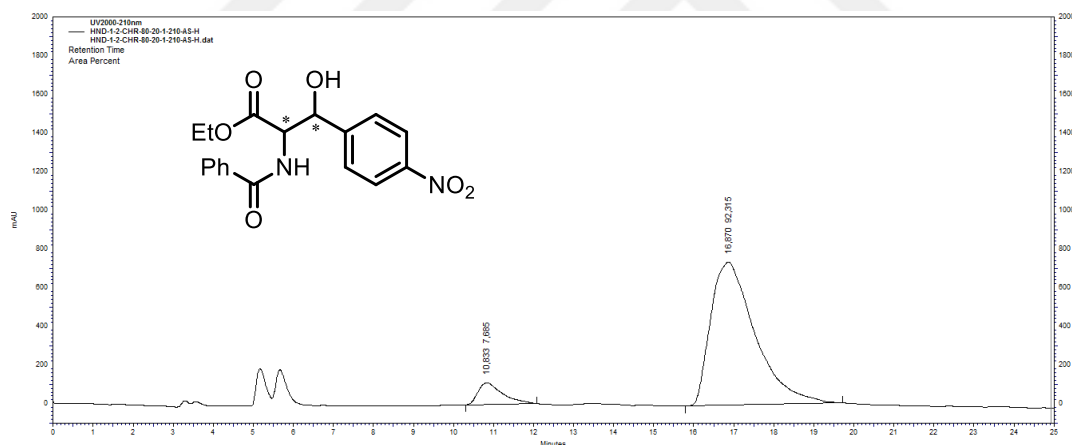


Figure B. 2. HPLC chromatogram of enantiomerically enriched