# ASYMMETRIC SYNTHESIS OF 2,3-DIHYDROFURANS WITH BIFUNCTIONAL QUININE / SQUARAMIDE ORGANOCATALYSTS

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**ASYMMETRIC SYNTHESIS OF 2,3-DIHYDROFURANS WITH BIFUNCTIONAL QUININE / SQUARAMIDE ORGANOCATALYSTS**

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# ABSTRACT

## ASYMMETRIC SYNTHESIS OF 2,3-DIHYDROFURANS WITH BIFUNCTIONAL QUININE / SQUARAMIDE ORGANOCATALYSTS

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Organocatalytic asymmetric reactions are efficient and environmentally friendly methods to synthesize products with higher enantioselectivities. Asymmetric domino Michael-$S_N2$ reactions are one of the type of organocatalytic reaction frequently used to form carbon-carbon bonds in the synthesis of the derivatives of dihydrofurans, which are intermediates mainly utilized as precessor materials in the pharmaceutical fields. In this thesis, the reaction occuring between acetylacetone and *(Z)*-(2-bromo-2-nitrovinyl)benzene was chosen as a model reaction. As a first step, bifunctional 2-aminoDMAP and quinine-anchored squaramide organocatalysts were tested. Then, quinine / *t*-butyl squaramide organocatalyst was identified as the most suitable organocatalyst for our reaction. Subsequently, optimization studies were done and using different α-bromonitroalkenes and 1,3-dicarbonyl compounds, 14 different derivatives were synthesized. In optimized conditions with 10 mol% organocatalyst loading, the best result gave 97 % enantiomeric excess.

Keywords: Asymmetric Synthesis, Enantioselectivity, Organocatalyst, Domino Reactions, Michael Addition, Nitroolefin, Dihydrofuran

# ÖZ

## 2,3-DİHİDROFURANLARIN BİFONKSİYONEL KİNİN / SKUARAMİT ORGANOKATALİZÖRLER İLE ASİMETRİK SENTEZİ

Bozdemir, Merve
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Ağustos 2019, 78 sayfa

Organokatalitik asimetrik reaksiyonlar yüksek enantiyosaflıkta ürün sentezinde kullanılan etkili ve çevre dostu bir yöntemdir. Karbon-Karbon bağı oluşturmada sıklıkla kullanılan organokatalitik reaksiyon çeşitlerinden asimetrik domino Michael-$S_N2$ reaksiyonları ise farmasötik alanda öncül olarak kullanılan dihidrofuran türevlerinin sentezlenmesinde tercih edilen önemli tepkimelerdir. Bu tezde model reaksiyon olarak asetil aseton ve *(Z)*-(2-bromo-2-nitrovinil) benzen kullanılmıştır. İlk aşama olarak bifonksiyonel 2-aminoDMAP ve kinin temelli skuaramit organokatalizörler denenmiş olup, reaksiyon için en uygun organokatalizörün kinin / *t*-bütil skuaramit olduğu belirlenmiştir. Ardından, optimizasyon çalışmaları yapılmış, farklı α-bromonitroalkenler ve 1,3-dikarbonil bileşikleri kullanılarak 14 farklı türev sentezlenmiştir. %10 mol organokatalizör oranı kullanılarak optimize edilmiş koşulda, en yüksek enantiyoseçicilik %97 olarak elde edilmiştir.

Anahtar Kelimeler: Asimetrik Sentez, Enantiyoseçicilik, Organokatalizör, Domino Reaksiyonu, Michael Katılma, Nitroolefin, Dihidrofuran

To My Precious Mother and Brother

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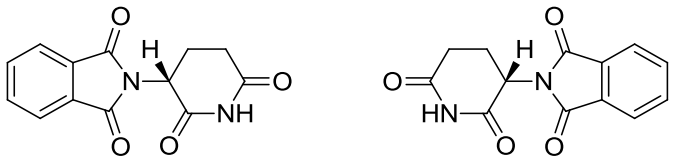
# CHAPTER 1

# INTRODUCTION

## 1.1. The Importance of Asymmetric Synthesis

Many biologically relevant organic compounds, such as nutrients, flavors and pharmaceuticals have chiral characters. In the historical origin of chirality, in 1815, Jean-Baptiste Biot investigated the difference in rotation of plane polarized light by enantiomers of a chiral compound used especially in nutrition and pharmaceutical industries.[1] After his investigation, in 1848, Louis Pasteur also revealed the chirality concept in molecular basis of tartaric acid.[2] Thus far, it has been known that the enantiomers of a chiral molecule had the same chemical and physical properties; however, their biological activities and effects on human body were in the darkness.

In 1957, Chemie Grünenthal, a German drug company, launched Thalidomide as a drug to heal the morning sickness of the pregnant women to the market; however, use of this drug has resulted in unexpected birth defects. Also, nearly 90,000 miscarriages and more than 10,000 disabled and dead birth were reported.[3] Studies done after this disaster showed that while *(R)*-(+) thalidomide has healing effect, *(S)*-(-) thalidomide leads to birth defects (Figure 1.1).[4]




*(R)*-Thalidomide — **healer**

*(S)*-Thalidomide — **teratogenic**

*Figure 1.1.* Enantiomers of Thalidomide

After this incident, the pharmaceutical industry has starting paying more attention to the production of enantiopure molecules in one specific enantiomeric form.

### 1.2. Chiral Induction Methods

Asymmetric synthesis[5] is the method used to gain chiral molecules from achiral (or prochiral) precursors. Asymmetric synthesis can be done using three approaches; chiral pool, kinetic resolution, and asymmetric catalysis.

Among the methods mentioned above, the least expensive and easiest way is utilization of the chiral pool in which the chiral natural compounds are chosen as chiral induction host molecules or precuresors. Amino acids, alkaloids, and carbohydrates are some examples utilized as starting materials to produce enantiopure compounds. Due to the source limitation drawbacks, scientists developed alternative methods.[6] One of these approaches involves the kinetic resolution method using mainly enzymes and chiral compounds.[7] In addition to these, the most widely used and efficient method is asymmetric catalysis to produce enantio-enriched compounds from racemic or prochiral molecules.[8] In this method, small molecules called chiral catalysts are used to decrease the activation energy of the transition states of the reaction and also speed up the rate of the reaction with the same end product.

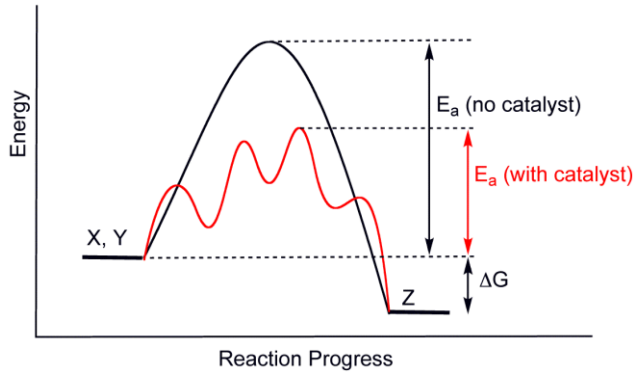



*Figure 1.2.* Reaction Progress with Catalyst

Asymmetric catalysis has emerged over three major pillars, namely biocatalysis, transition metal catalysis, and organocatalysis. In the biocatalysis case, enzymes and some natural products are utilized as catalysts. Being non-toxic and environmentally friendly make the biocatalyst preferable to synthesize asymmetric molecules. Transition metal catalysis would attain efficiently a great amount of enantiomerically-enriched chiral molecules by using transition metals bearing chiral ligands in pharmaceutical industry. However, in the last two decades, due to the high level of heavy-metal waste production, studies turned toward different type of asymmetric catalysis method named as organocatalysis.

Organocatalysts consist of carbon, hydrogen, nitrogen, oxygen, phosphorus, and sulphur atoms without any transition metals.[9] Being wieldy, insensitive to the humidity and air and showing lower toxicity are some advantages of employing organocatalysts to synthesize asymmetric molecules.[10] For this reason, reactions can be performed in the ambient conditions and easily accesible temperatures. Figure 1.3 shows some well-known chiral organocatalysts.[11]

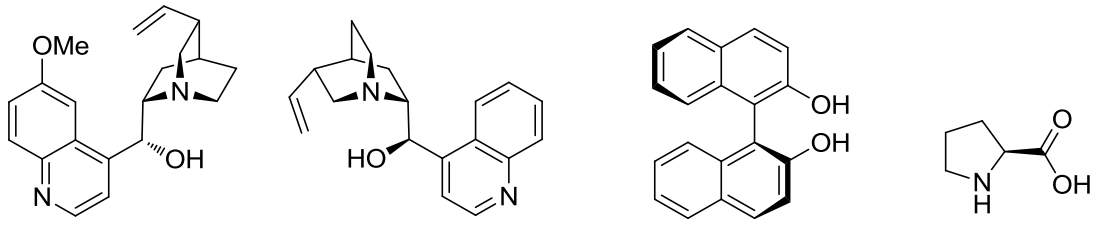



*Figure 1.3.* Seleceted Examples of Organocatalysts

### 1.3. Organocatalysis in Asymmetric Synthesis

There have been three main mechanisms to explain the organocatalysis, which were proposed by Seayad, Berkessel, and MacMillan. In the case followed by Seayad and List, Brønsted acids / bases or Lewis acids / bases were used as catalysts.[12] For the Lewis acids and bases case, nucleophilic addition to the substrate was triggered by

catalysts; whereas, in the other case, Brønsted acids or bases initiated the reaction by protonation and deprotonation of the substrates.

In 2005, Berkessel and Gröger reported their study in two main concepts, namely covalent and non-covalent interactions. New chemical bonding took place between substrate and catalyst in covalent interaction; on the other hand, for the non-covalent interaction case, weak binding occurred.[9] Examples belonging covalent and non-covalent catalysis are shown in Figure 1.4.

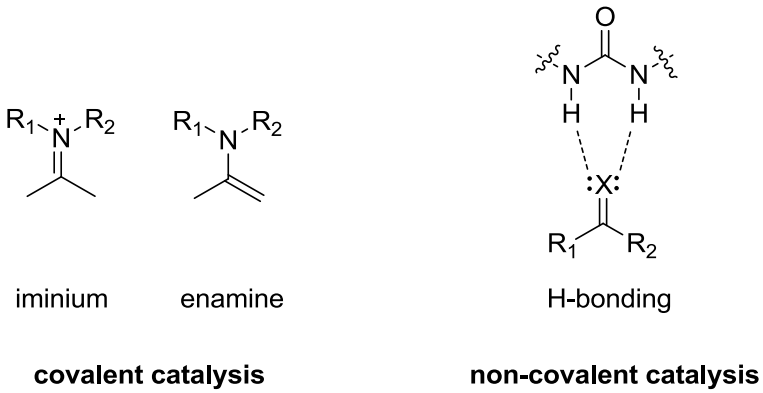



*Figure 1.4.* Covalent and Non-covalent Catalysis

For the third pathway, MacMillan utilizes hydrogen-bonding, iminium, enamine, and counter ion catalysis.[13]

### 1.3.1. Cinchona Alkaloids

From 1800s, cinchona alkaloids have been isolated from the Cinchona trees; however, utilizing them as catalyst in organic synthesis started after 1912.[14] Their biological activities, low molecular weights, and many functionalized units make these cinchona alkaloid derivatives desirable catalysts.

The first isolated derivative of cinchona alkaloid was quinine[15] obtained by Pierre-Joseph Pelletier and Joseph Bienaime Caventou in 1812. In Figure 1.5, there are some examples of cinchona alkaloids used mainly in catalytic studies.

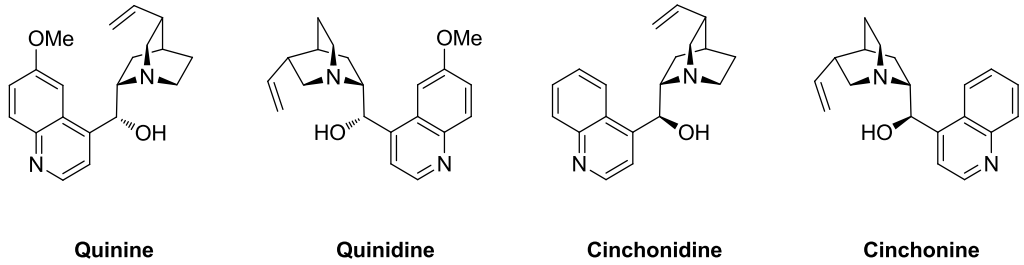



*Figure 1.5.* Some Derivatives of Cinchona Alkaloids

### 1.3.2. Bifunctional Organocatalysis

In last few decades, studies were focused on bifunctional organocatalysis due to the demand of the activation of nucleophilic and electrophilic substances at the same time. Mechanism proposed via bifunctional organocatalyst takes place by increasing the HOMO level of the nucleophilic substance and decreasing the LUMO level of the electrophilic substance, as shown in Figure 1.6; thus, the activation energy of the reaction decreases more easily[16] and the rate of the reaction rises remarkably[17].

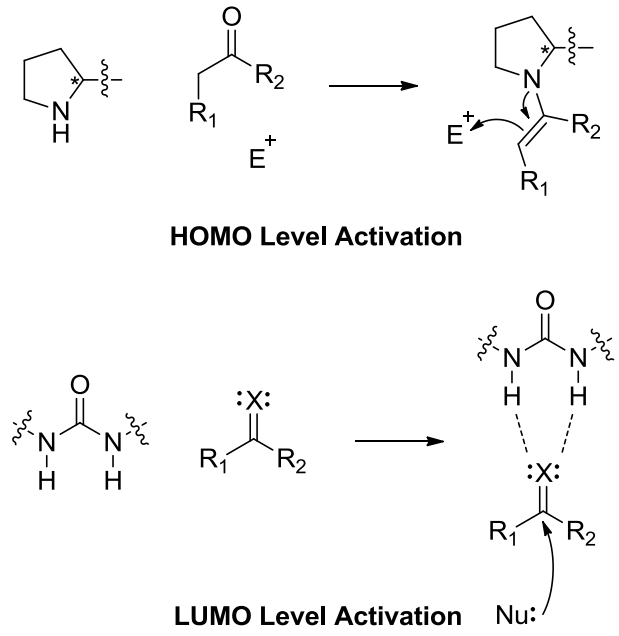



*Figure 1.6.* Activation Modes of HOMO and LUMO Levels

The basic interactions of this type of bifunctional organocatalyst are demonstrated in Figure 1.7.

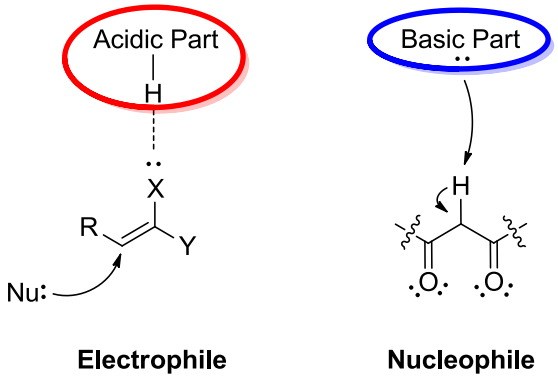



*Figure 1.7.* Interaction of Bifunctional Organocatalyst and Substrates

In the light of these findings, the most important work reported by Takemoto et al.[18] has included bifunctional organocatalyst derived from Schreiner thiourea catalyst **(1)** (Figure 1.8) with the hydrogen-bond interaction pathway.[19]

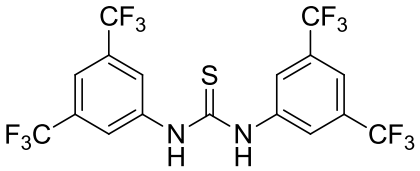



*Figure 1.8.* Schreiner Thiourea Catalyst

They carried out Michael addition reaction between *trans*-β-nitrostyrene **(2)** and diethyl malonate **(3)** (Figure 1.9). The thiourea moiety as the acidic side of the bifunctional organocatalyst lowered the LUMO level of **(2)** when the cyclohexanamine part as the basic side increased the HOMO level of **(3)** to obtain the product **(4)**.

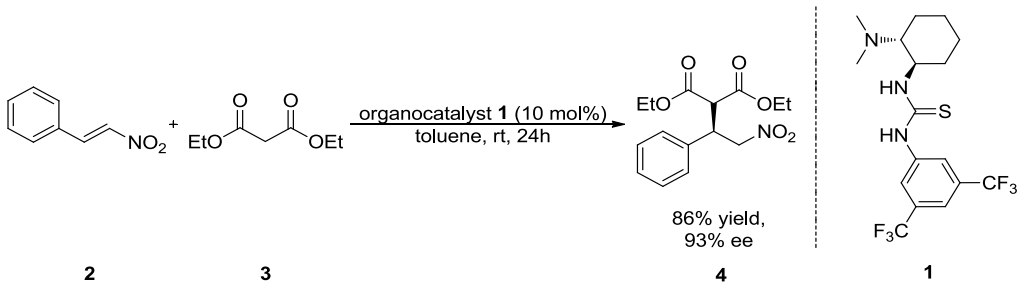



*Figure 1.9.* Michael Addition Reaction with Takemoto's Bifunctional Organocatalyst

Another alternative used as acidic moiety in bifunctional organocatalyst is derivatives of squaramide, revealed by Rawal et al. in 2008.[20] The important stage in the process of activation of LUMO level is H-bonding taking place in between acidic part of the organocatalyst and the electrophilic substance in the reaction and to gain more effective H-bonding, the acidic part should have proper angle. Thus, it is seen in Figure 1.10, the angle between N-H's, calculated by Takemoto[18] and Rawal[20], in squaramide is more suitable than in the case of urea/thiourea.

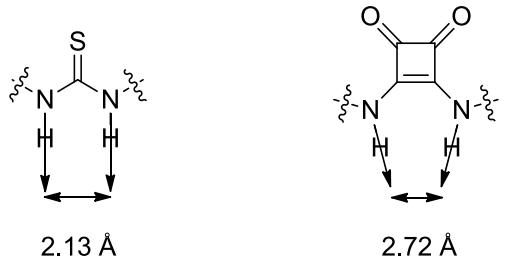



*Figure 1.10.* Calculated H-bond Distance in Thiourea and Squaramide

In addition to the angle and distance properties, the convergent positioned hydrogens in squaramide-type catalysts cause linearity of bonding[21] and ensure the determined configuration of the product.[20,22,23]

## 1.4. Hydrofuran Motifs in Bioactive Compounds

Owing to the impactful properties of hydrofuran skeleton included in many biologically active natural products like phyllaemblic acid methyl ester[24] and precursor material for pharmacologically very important furanoid lignans like

nymphone[25,26] (Figure 1.11), many research groups have focused on the synthesis of hydrofuran derivatives.

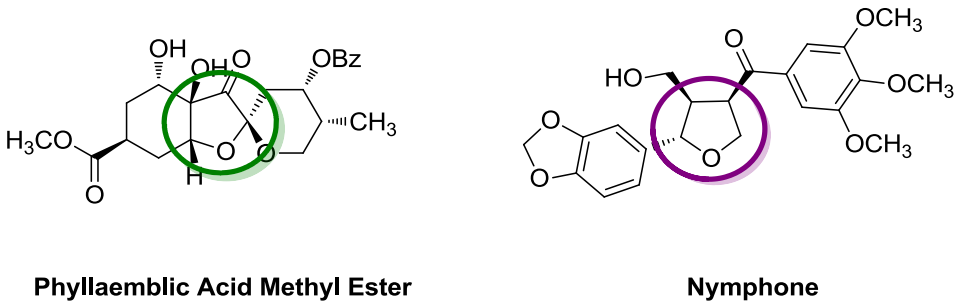



*Figure 1.11.* Hydrofuran Skeleton Containing Natural Compund and Pharmacological Lignan Example

In 2010, Fan and co-workers generated monocyclic enantioselective 2,3-dihydrofurans **8** by the domino Michael-$S_N2$ type addition in between acyclic 1,3-dicarbonyl compounds **7** and *(E)*-α-bromonitroolefines **6** through quinine derived bifunctional thiourea organocatalyst **(5)** in 96 h at -50°C (Figure 1.12).[27]

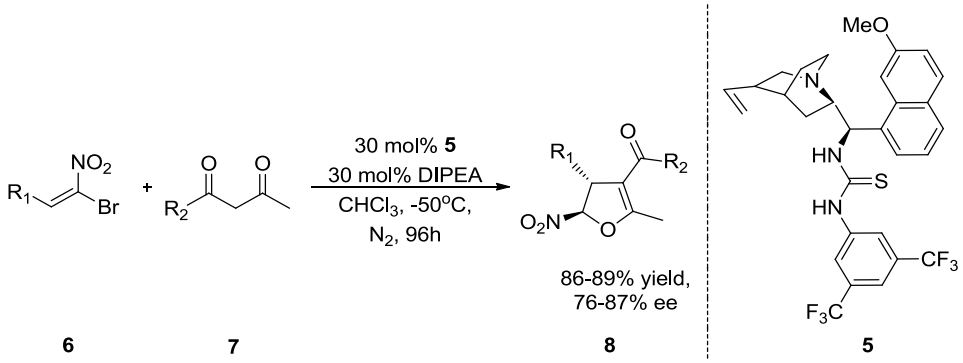



*Figure 1.12.* Michael-$S_N2$ Type Addition Reaction via Quinine-Bonded Thiuorea

The second example performed by Rueping et al. was a Brønsted acid catalyzed Mannich-ketalization reaction to synthesize tetrasubstituted dihydrofurans.[28] Then, they recognized that Michael-$S_N2$ type addition reactions enable more suitable mechanism to gain more enantiopure multisubstituted dihydrofuran derivatives **12** in the presence of cinchona alkaloid thiourea organocatalysts **(9)** at -20°C (Figure 1.13).[29]

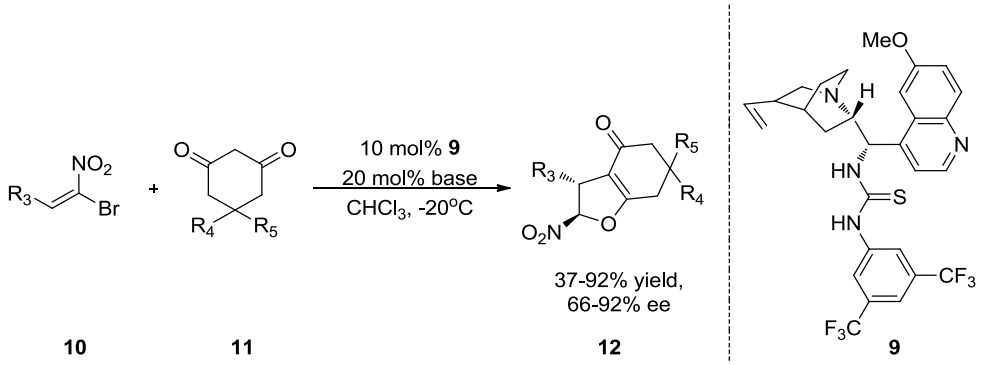



*Figure 1.13.* Michael-$S_N2$ Type Addition Reaction via Cinchona Alkaloid Bonded Thiourea

The third example was about the work done by Feng et al. and included *N,N*'-dioxides[30a] organocatalyst **(13)** Michael-$S_N2$ type alkylation reaction. The results of the reactions of cyclic 1,3-dicarbonyl compound **15** using different solvents in known ratio of them at -50°C were reported (Figure 1.14).[30b]

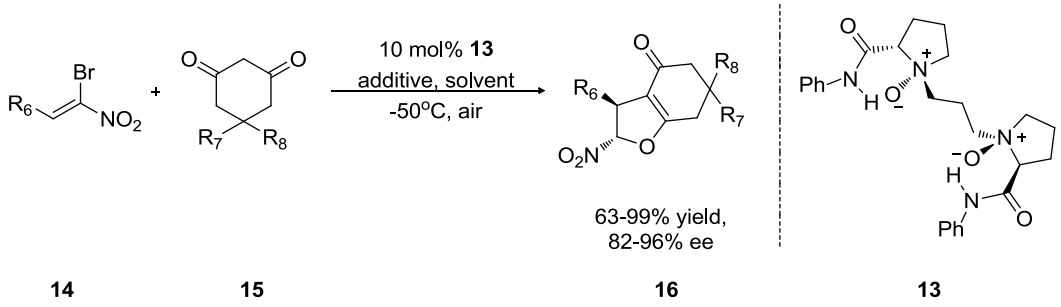



*Figure 1.14.* Michael-$S_N2$ Type Alkylation Reaction via *N,N'*-dioxide Derivated Bifunctional Organocatalyst

As it can be seen from the examples, the most proper method to form carbon-carbon bond[31] is Michael-$S_N2$ type addition reactions. In this type of reactions, nucleophilic substance is called as Michael donor, such as malonates[32], malononitriles[33] and 1,3-dicarbonyl compounds; on the other hand, Michael acceptors such as acrylates[34] and nitroolefines[35] act as electrophile. The basic mechanism for Michael addition is demonstrated in Figure 1.15.[9]

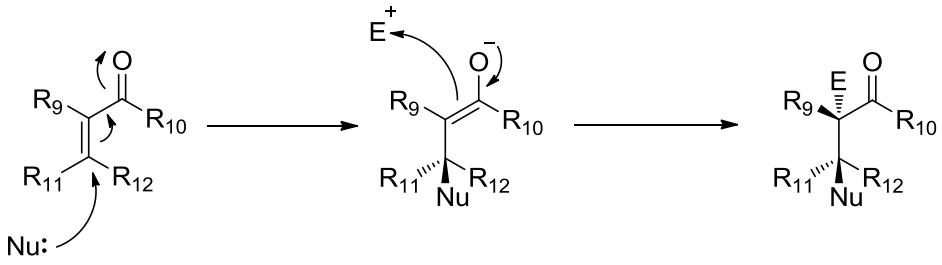



*Figure 1.15.* Michael Addition Mechanism

## 1.5. Aim of the Study

We get inspired by the properties of hydrofurans especially in the pharmaceutical field. Based on the published studies to obtain enantiomerically-enriched 2,3-dihydrofurans, our concentration has been focused on the asymmetric domino Michael-$S_N2$ type organocatalytic addition reaction.[36]

There are many methods for this synthesis; however, most of them required harsh conditions, such as higher amount of catalyst loading or very low reaction temperatures. For this reason, in this study, we mainly made an effort on facilitating to obtain good yields and enhanced enantiomeric excess by changing the reaction conditions, such as temperature and bifunctional organocatalysts. Thereby, *(Z)*-α-bromonitroolefins **17** and β-dicarbonyl compounds **18** substituted with different electron donating-withdrawing units were used at room temperature in the presence of a quinine amine and squaramide based organocatalysts mostly synthesized in our research group to obtain derivatives of 2,3-dihydrofurans **19** (Figure 1.16).

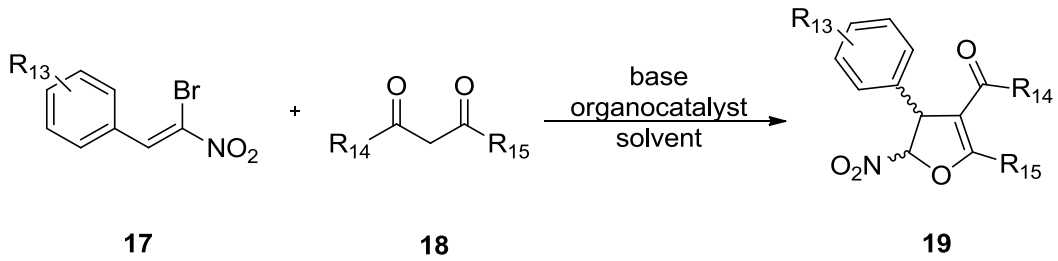
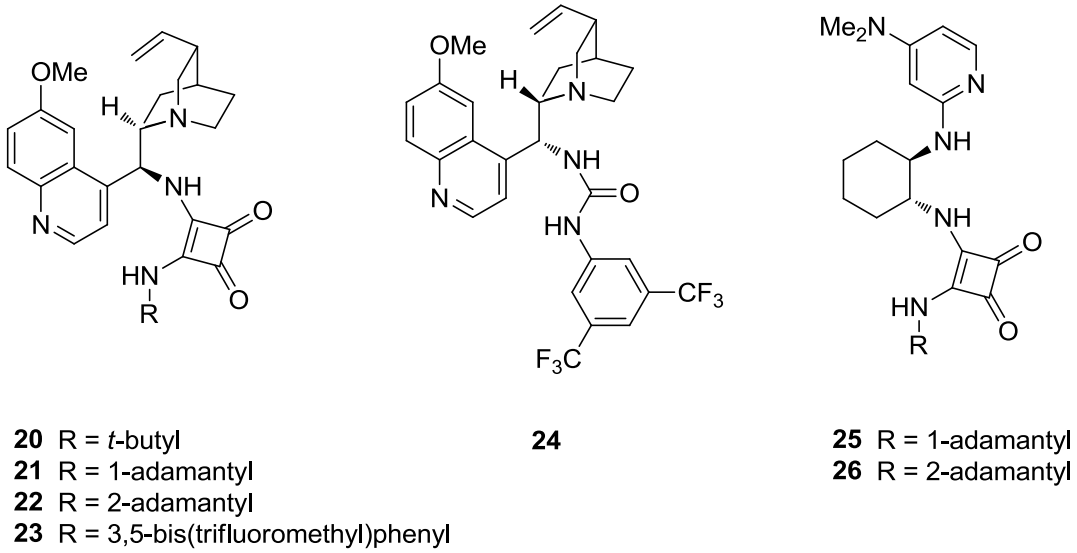



*Figure 1.16.* The Representative Model of the Study

Based on the literature, quinine amine-based ureas and thioureas[27,28,29] were typically used in the asymmetric synthesis; however, a wide application of the quinine amine-based squaramide organocatalysts has also been reported in recent studies[20].

At this juncture, bifunctional organocatalysts **20 - 26** (Figure 1.17) have been selected to be used in the synthesis of asymmetric 2,3-dihydrofurans with α-bromonitroolefins as electrophiles and 1,3-dicarbonyl compounds as nucleophiles.




**20** R = *t*-butyl
**21** R = 1-adamantyl
**22** R = 2-adamantyl
**23** R = 3,5-bis(trifluoromethyl)phenyl

**24**

**25** R = 1-adamantyl
**26** R = 2-adamantyl

*Figure 1.17.* Bifunctional Organocatalysts **20** – **26**

In our model reaction, bifunctional organocatalysts mainly derived from quinine-based squaramides gave very good results when combining with additive bases used to prevent the protonation of the basic side of the organocatalysts due to released hydrobromic acid produced during the reaction. Also the α-bromonitroolefins having bromo as a good leaving group to facilitate to production of our desired enantiopure products.

# CHAPTER 2

# RESULTS AND DISCUSSIONS

## 2.1. Synthesis of Squaramide-Type Acidic Motifs

In our research group, we synthesized a series of bifunctional organocatalysts possessing acidic and basic motifs. Quinine amine[37,38] and 2-aminoDMAP[39] have been used as basic catalaphoric site. The rest of the molecule posseses acidic moiety and different kinds of squaramides were synthesized for this purpose. Among the acidic moieties, together with squaramides, urea and sulfonamides are expected to give interactions with a wide range of electrophilic substrates based on the existence of double H-bond forming ability with the proper angular position.

As a representative example, herein, general procedure for the synthesis of different types of squaramides is demostrated in Figure 2.1. Firstly, squaric acid was transformed to diethylsquarate by refluxing squaric acid in absolute ethanol. Subsequent addition of sterically encumbered primary amines, *i.e. t*-butyl, 1-adamantyl, and 2-adamantyl, to diethylsquarates in DCM at room temperature afforded corresponding monosquaramides **29 – 31** in 24 h.[20,40]

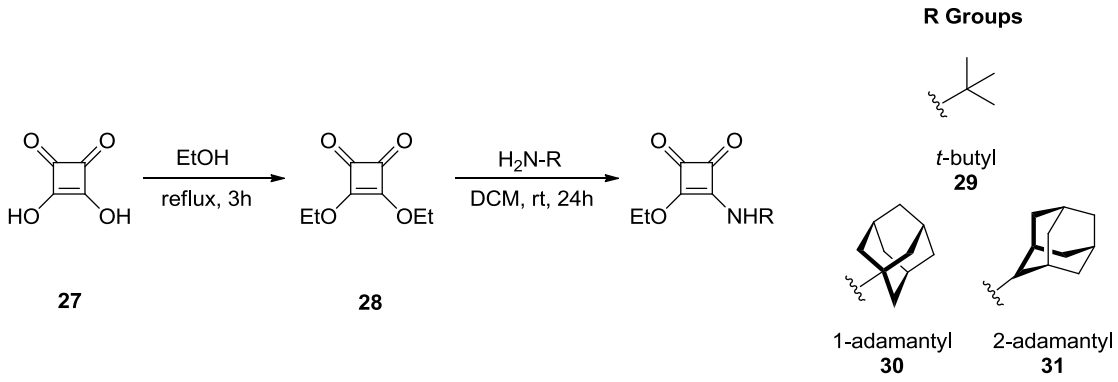



*Figure 2.1.* The Synthesis of Types of Squaramides

## 2.2. Synthesis of Quinine-Based Bifunctional Organocatalysts

General way to synthesize quinine anchored squaramide-type bifunctional organocatalyts in our study is depicted in Figure 2.2. By using Mitsunobu reaction followed by Staudinger reactions,[37] quinine **(32)** was converted into quinine amine **(33)** possesing inverted configuration of the amine attached stereogenic center. At the end, the resultant quinine amine and monosquaramide derivative reacted in DCM:MeOH solvent mixture at room temperature for 48 h to afford **20 - 22**.[41,42]

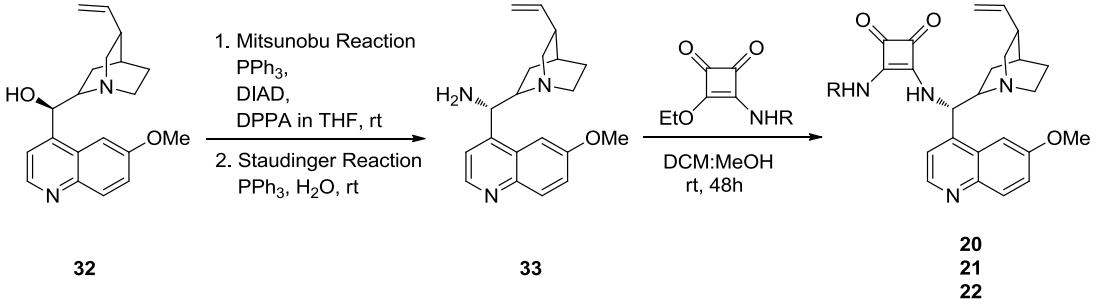



*Figure 2.2*. The Synthetic Pathway of Quinine-Anchored Squaramides

## 2.3. Evaluation of Bifunctional Organocatalysts in the Facile Domino Michael-$S_N2$ Addition of 1,3-Dicarbonyl Compounds to Nitroolefines

Our model reaction as given in the literature comes from the Fan's study[27] about the facile domino Michael-$S_N2$ addition reaction between 1,3-dicarbonyl compounds and α-bromonitroalkenes. First of all, we modified the reaction conditions of the Fan's study to generate the desired products in an easily accessible condition. Fortunately, our reactions took place in a very short period of time when compared to the literature results. To improve %ee and %yield, optimization processes were started with screening different reaction conditions.

### 2.3.1. Organocatalyst Screening

In this thesis, the organocatalysts, developed in Tanyeli's research group, involving quinine-based three sorts of squaramide and 2-aminoDMAP-based two different squaramide were utilized. Additionally, other types of quinine based bifunctional organocatalysts, produced previously in others work, *i.e.* urea and a kind of squaramide were used. The molecular structures of the selected bifunctional organocatalysts are shown in Figure 2.3.

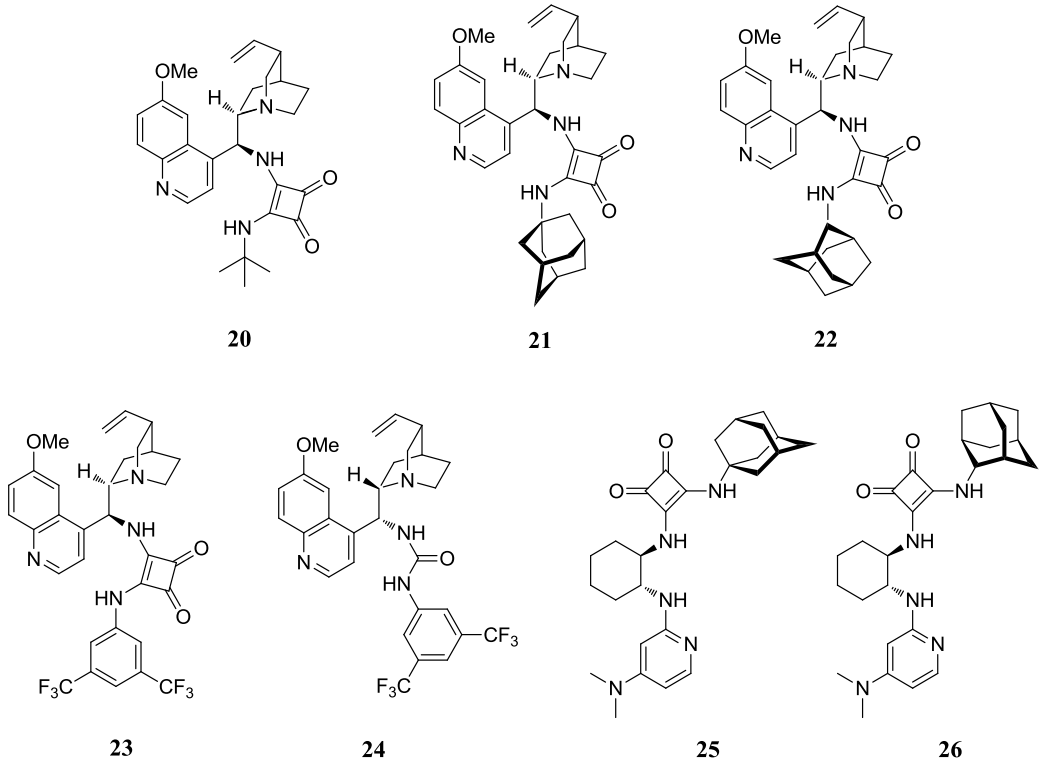
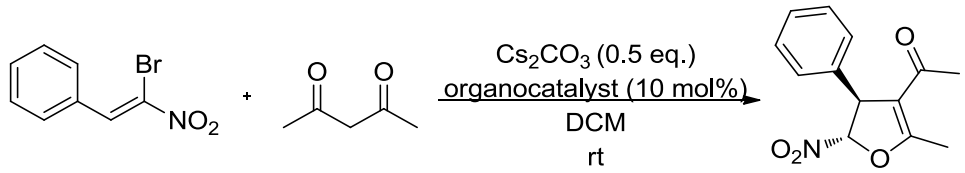



*Figure 2.3.* Quinine and 2-AminoDMAP-Anchored Bifunctional Organocatalysts

First of all, acetylacetone **(35)** as a 1,3-dicarbonyl source was reacted with unsubstitued α-bromonitroalkene **(34)** in the presence of 10 mol% organocatalyst, 0.5 equivalent of $Cs_2CO_3$ as an additive base and DCM as a solvent at room temperature. The results were given in Table 2.1 and the best results obtained from the reaction belong to organocatalyst **(20)** (Table 2.1, entry 1). Although, the %ee value was a bit lower, the time required to finish the reaction, the temperature provided for reaction

and obtained %yield gave us to continue this study. Thus, by using the chosen organocatalyst, further optimization studies on reaction conditions were proceeded.

Table 2.1. *Organocatalyst Screening*




**34** **35** **36**

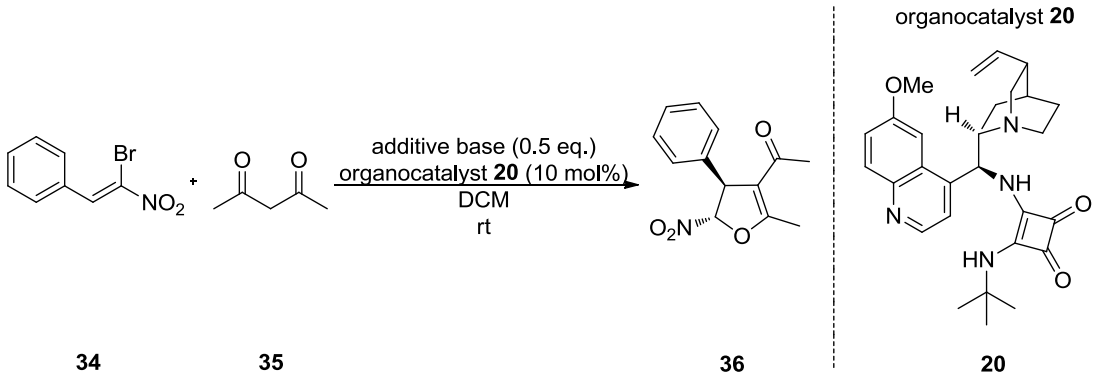
| Entry | Organocatalysts | Time (h) | Conversion (%) | ee (%) |
|---|---|---|---|---|
| **1** | 20 | 1 | 83 | 37 |
| **2** | 21 | 1 | 32 | 13 |
| **3** | 25 | 1 | 50 | 14 |
| **4** | 26 | 1 | 69 | 17 |

All of the studies were carried out with 10 mol% organocatalyst, 0.5 eq. $Cs_2CO_3$, and DCM at rt with 0.5 M concentrated solution.

### 2.3.2. Base Screening

There was an acidic by-product, HBr, deactivating the basic part of the organocatalyst, of the main reaction and it should be removed from the reaction medium. To do this issue, both organic and inorganic bases were tested as additives. In the first trial, organocatalyst **(20)** gave better results compared to others, to further improvements of the enantioselectivity and conversion, we screened additives. For this purpose, in the second optimization step, nine different organic and inorganic bases were tested and Table 2.2 demonstrated the obtained results. Among these bases, inorganic ones provided superior results compared to the organic ones. $Na_2CO_3$ (Table 2.2, entry 8) gave the best enantioselectivity with 95 %ee and full conversion.

Table 2.2. *Base Screening*




| Entry | Base | Time (h) | Conversion (%) | ee (%) |
|---|---|---|---|---|
| **1** | $Cs_2CO_3$** | 1 | 83 | 37 |
| **2** | DBU* | 5 | 17 | 13 |
| **3** | DIPEA* | 5 | 78 | 39 |
| **4** | DMAP* | 5 | 35 | 9 |
| **5** | DABCO* | 5 | 70 | 30 |
| **6** | NaOAc* | 7 | 76 | 84 |
| **7** | $NaHCO_3$* | 7 | 81 | 85 |
| **8** | $Na_2CO_3$** | 1 | quantitative | 95 |
| **9** | $K_2CO_3$** | 6 | 82 | 32 |

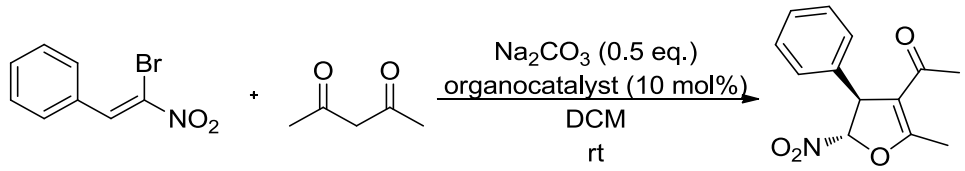
All of the studies were carried out with 10 mol% organocatalyst **20**, *1 eq. and **0.5 eq. additive base and DCM at rt with 0.5 M concentrated solution.

### 2.3.3. Organocatalyst Screening II

When we changed the additive base, we observed good %ee values and to be sure that we chose the best organocatalyst, the organocatalyst screening part was repeated. In this part, five different organocatalysts were tested (Table 2.3) and the conversion of the reaction was monitored by of GC-MS instrument. The results coming from the 2-aminoDMAP-based organocatalysts were not good; however, quinine-based organocatalysts, except for organocatalyst **(24)**, provided better results. The best result

was obtained from the reaction with organocatalyst **(20)** with 95 %ee and full conversion (entry 1).

Table 2.3. *Organocatalyst Screening II*




**34** **35** **36**

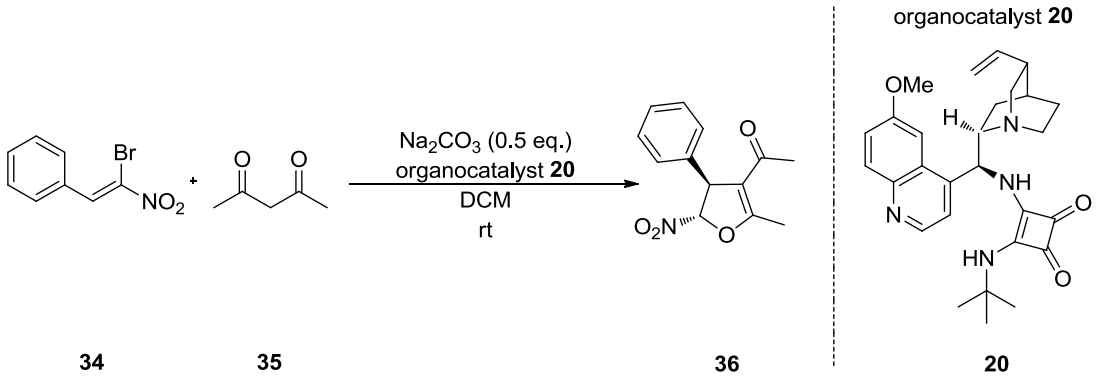
| Entry | Organocatalysts | Time (h) | ee (%) |
|---|---|---|---|
| **1** | 20 | 1 | 95 |
| **2** | 22 | 4 | 81 |
| **3** | 24 | 2.5 | 73 |
| **4** | 23 | 3 | 84 |
| **5** | 26 | 23 | 5 |

All of the studies were carried out with 10 mol% organocatalyst, 0.5 eq. $Na_2CO_3$ and DCM at rt with 0.5 M concentrated solution. All conversions were quantitative.

### 2.3.4. Organocatalyst Loading

After selecting the organocatalyst and base, we turned our attention to another optimization parameter, catalyst loading. In this part, to monitor the conversion, again we used GC-MS. In addition, 5 mol% and 2 mol% catalyst loading were studied (Table 2.4). Along with the higher conversions obtained in a short period of time, the highest %ee value was obtained only when the catalyst loading was 10 mol% (Table 2.4, entry 1).

Table 2.4. *Organocatalyst Loading*



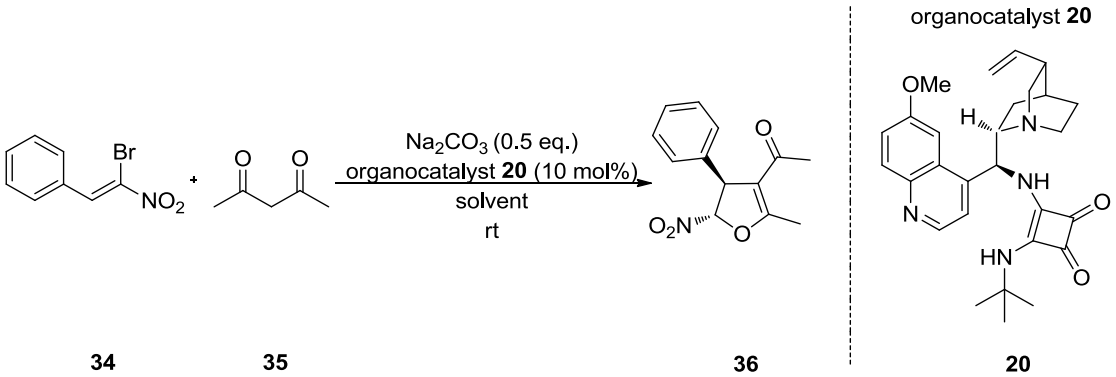

| Entry | Catalysts Loading (%) | Time (h) | ee (%) |
|---|---|---|---|
| **1** | 10 | 1 | 95 |
| **2** | 5 | 2 | 73 |
| **3** | 2 | 5 | 64 |

All of the studies were carried out with organocatalyst **20**, 0.5 eq. $Na_2CO_3$ and DCM at rt with 0.5 M concentrated solution. All conversions were quantitative.

### 2.3.5. Solvent Screening

Next optimization step was done with different solvents namely, chloroform, acetonitrile, hexane, tetrahydrofuran, xylene, toluene, 1,2-dichloroethane and *p*-trifluoromethyl toluene (Table 2.5). Although conversions monitored by GC-MS were increased in a short time, the %ee values were decreased due to the solubility of our organocatalysts is low. Therefore, we kept dichloromethane as the solvent for further optimization studies.

Table 2.5. *Solvent Screening*



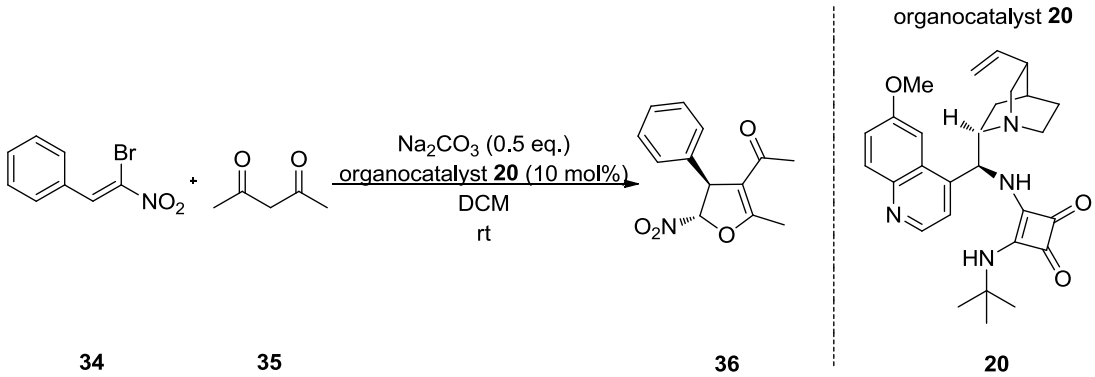

| Entry | Solvent | Time (h) | Conversion (%) | ee (%) |
|---|---|---|---|---|
| **1** | DCM | 1 | quantitative | 95 |
| **2** | $CHCl_3$ | 2 | quantitative | 79 |
| **3** | Acetonitrile | 2 | quantitative | 14 |
| **4** | Hexane | 5 | 97 | 42 |
| **5** | THF | 1 | quantitative | 17 |
| **6** | Xylene | 7 | 98 | 46 |
| **7** | Toluene | 2.5 | 97 | 23 |
| **8** | 1,2-DCE | 3 | 98 | 69 |
| **9** | $CF_3$-Toluene | 3 | 97 | 33 |

All of the studies were carried out with 10 mol% organocatalyst **20**, 0.5 eq. $Na_2CO_3$ at rt with 0.5 M concentrated solution.

### 2.3.6. Concentration Screening

For further optimization, concentration screening was performed (Table 2.6). Since the initial optimization were done with 0.5 M concentrated solution medium by using DCM, we next worked with 0.25 M and 0.1 M concentrations to see the results with lower concentrations. Conversion data were obtained from GC-MS. There was no direct connetion between the concentration and the %ee values but again we obtained the highest ee value as 95 %ee with 0.5 M concentration.

Table 2.6. *Concentration Screening*



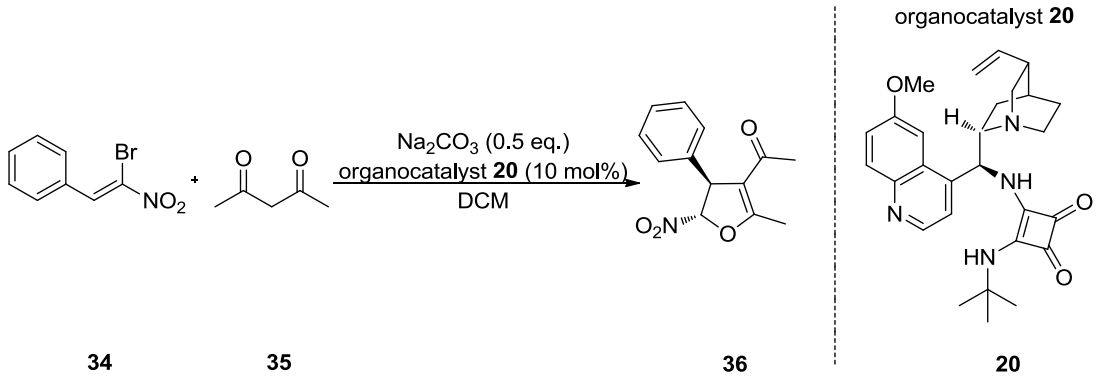

| Entry | Concentration (M) | Time (h) | Conversion (%) | ee (%) |
|---|---|---|---|---|
| **1** | 0.50 | 1 | quantitative | 95 |
| **2** | 0.25 | 3 | 98 | 64 |
| **3** | 0.10 | 6 | 67 | 80 |

All of the studies were carried out with 10 mol% organocatalyst **20**, 0.5 eq. $Na_2CO_3$ and DCM at rt.

### 2.3.7. Temperature Screening

Last optimization step was temperature screening (Table 2.7). In the literature data, lower temperatures have been worked to obtain higher %ee results. Thus, we provided lower temperature conditions and when we decreased the temperature of the reaction medium, both the time required to higher conversions and the %ee values were dropped. This result was a good outcome since this reaction occurs at room temperature which we can easily procure without using any device.

Table 2.7. *Temperature Screening*




34 35 36 20

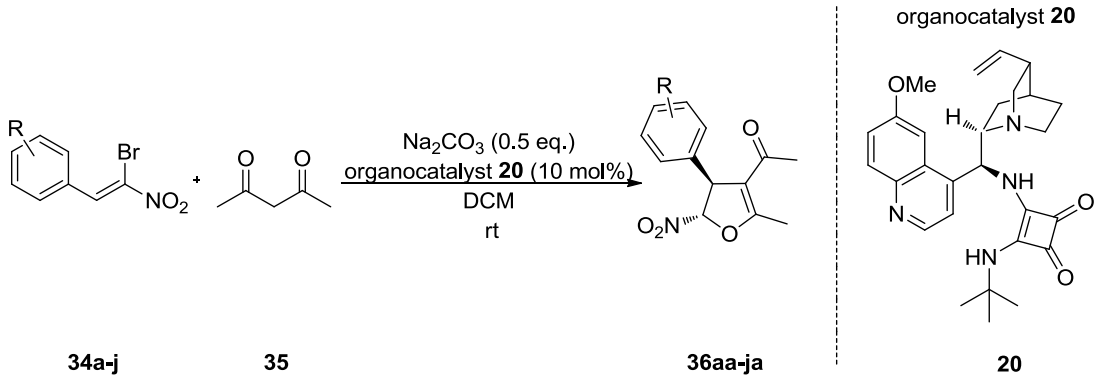
| Entry | Temperature (°C) | Time (h) | Conversion (%) | ee (%) |
|---|---|---|---|---|
| **1** | rt | 1 | quantitative | 95 |
| **2** | 0 | 5 | 95 | 69 |
| **3** | -40 | 23 | 97 | 76 |

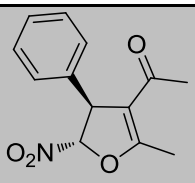
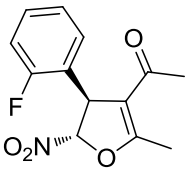
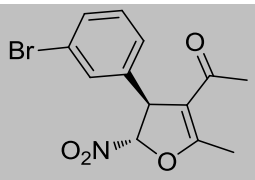
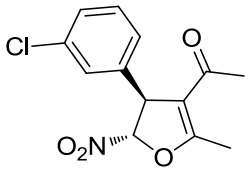
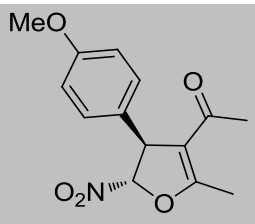
All of the studies were carried out with 10 mol% organocatalyst **20**, 0.5 eq. $Na_2CO_3$ and DCM with 0.5 M concentrated solution.

After determining the optimized conditions, other α-bromonitroalkene derivatives were tested to see the alteration of the %ee values and the summary of the results were shown in Table 2.8. Morever, to observe the effect of different 1,3-dicarbonyl compounds on enantiomeric excess, additionally four kinds of them were studied and their results were demonstrated in Table 2.9.

While comparing our results with the literature; although, the amount of organocatalyst was less and the applied temperature was room temperature, gained ee values and conversions are very high, which shows the organocatalyst used in this study to carry out asymmetric domino Michael-$S_N2$ type addition reaction is preferable one.

Table 2.8. *Results of α-bromonitroalkene Derivatives*




| Entry | Derivative | Time (h) | ee (%) | dr (%) |
|---|---|---|---|---|
| **1 (36aa)** |  | 1 | 95 | >99:1 |
| **2 (36ba)** |  | 1.5 | 97 | >99:1 |
| **3 (36ca)** |  | 1.5 | 76 | >99:1 |
| **4 (36da)** |  | 4.5 | 83 | >99:1 |
| **5 (36ea)** |  | 4.5 | 92 | >99:1 |

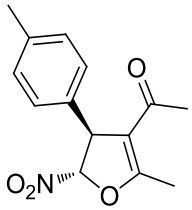
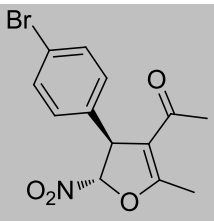
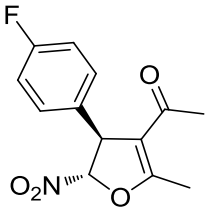
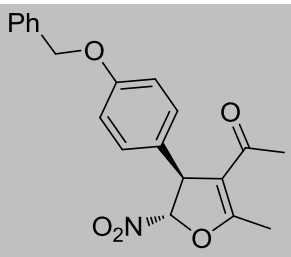
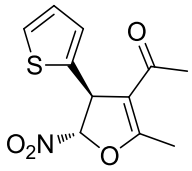
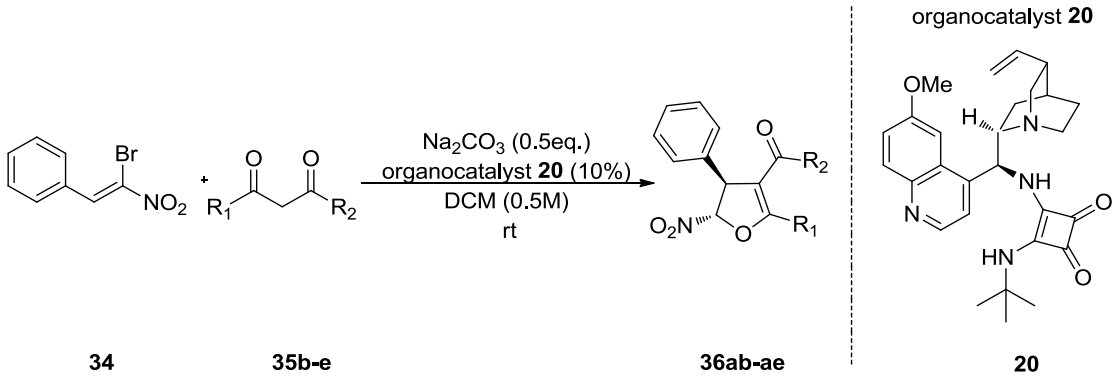
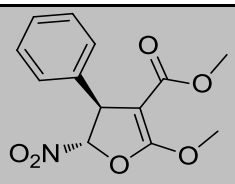
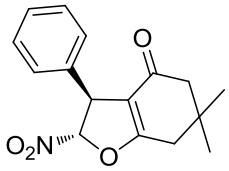
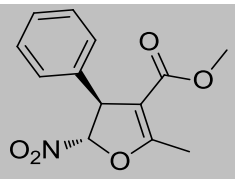
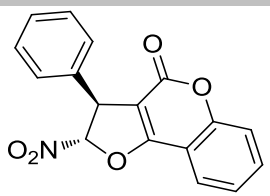
| | | | | |
|---|---|---|---|---|
| **6 (36fa)** |  | 6 | 78 | >99:1 |
| **7 (36ga)** |  | 5.5 | 76 | >99:1 |
| **8 (36ha)** |  | 6 | 82 | >99:1 |
| **9 (36ia)** |  | 4.5 | 79 | >99:1 |
| **10 (36ja)** |  | 5 | 86:90 | 68:32 |

Table 2.9. *Results of 1,3-dicarbonyl Compound Derivatives*




| Entry | Derivative | Time (h) | ee (%) | dr (%) |
|---|---|---|---|---|
| **1 (36ab)** |  | 6 | 4 | >99:1 |
| **2 (36ac)** |  | 4 | 70 | >99:1 |
| **3 (36ad)** |  | 5 | 80 | >99:1 |
| **4 (36ae)** |  | 6 | 33 | >99:1 |

# CHAPTER 3

# EXPERIMENTAL

## 3.1. Materials and Methods

In this study, nuclear magnetic spectra for $^{1}H$ and $^{13}C$ were recorded in $CDCl_3$ solvent on Bruker Spectrospin Avance DPX-400 spectrometer. Reported chemical shifts were in ppm comparative to $CDCl_3$ ($\delta$ 7.26 for $^{1}H$ and and 77.0 for $^{13}C$) as internal standard. Signals expressed in NMR spectra designated as s (singlet), bs (broad singlet), d (doublet), t (triplet), dt (doublet of triplet), tt (triplet of triplet), q(quarted), m (multiplet) and coupling constants (*J*) in Hertz (Hz).

The mass spectra were taken on Thermo Scientific DSQ II Single Quadropole GC/MS.

HRMS data were recorded on an Agilent 6224 TOF LC/MS at UNAM, Bilkent University.

HPLC chromatograms were obtained from Thermo-Finnigan by the usage of Daicel Chiralpak ODH, ASH, OJH and IA chiral columns with different n-hexane and *i*-propanol solvent systems.

The values of optical rotations of our chiral products were measured with the help of Rudolph Scientific Autopol III polarimeter and reported as $[\alpha]_D^{25}$ (c is in gram per 100 mL solvent).

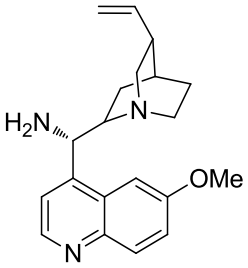
Melting points were measured by using Thomas Hoover capillary melting point apparatus (temperature is in °C).

IR data were recorded on Thermo Nicolet IS10 ATR/FT-IR spectrophotometer (the band position is in $cm^{-1}$).

By using TLC (precoated silica gel plates by Merck Silica Gel 60 $F_{254}$) and UV-light, all reactions were monitored. Also, by using thick-walled glass column with silica gel (Merck Silica Gel 60, particle size; 0.063-0.200 nm) and different solvent systems, flash column chromatography were done.

Naming of products was done via ChemBioDraw Ultra 12.0.

### 3.2. Synthesis of *(S)*-(6-methoxyquinolin-4-yl)((1S,2S,4S,5R)-5-vinylquinuclidin-2-yl)methanamine (33)

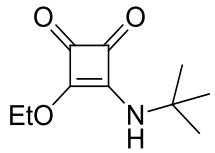



In order to synthesize the quinine amine from quinine, the literature procedure was performed[37,38] as follows: Hydroquinine (12.0 g, 40 mmol) and triphenylphosphine (12.6 g, 48 mmol) were dissolved in 200 mL dry THF and after that addition, mixture was cooled to 0°C. Then, diisopropyl azodicarboxylate (9.8 g, 48 mmol) was added in a lump to this mixture. In another flask, the solution of diphenyl phosphoryl azide (13.2 g, 48 mmol) and 80 mL of dry THF was prepared; then, this solution was added dropwise at 0°C to the original mixture flask. When dropwise addition finished, the mixture was heated to the room temperature and was allowed to stir for 12 hours. After 12 h stirring, the solution was warmed up 50°C for 2 h and then triphenylphosphine (13.6 g, 52 mmol) was put. Until the gas evolution ended up, heating of the solution was continued (2 h). Then the solution was cooled to the room temperature. Sequent step was addition of 4 mL of water and after this addition; reaction was stirred for 3 h. After all stirring was finished, solvent was oved away from the solution via vacuum. Then, all residues were solved in $CH_2Cl_2$ and 10% HCl (1:1, 400 mL) solution. The aqueous phase was washed with $CH_2Cl_2$ (4x200 mL) and then to make the aqueous

phase alkaline, excess aqueous ammonia was used. Then the aqueous phase washed with $CH_2Cl_2$ (4x200 mL) again. All organic phases were come together and dried over $MgSO_4$. Obtained residue was purified by flash column chromatography on silica gel (EtOAc:MeOH:$NEt_3$ (49.5:49.5:1) as eluent) and obtained as yellowish viscous oil.

Spectroscopic data are confirmed with the literature.[37]

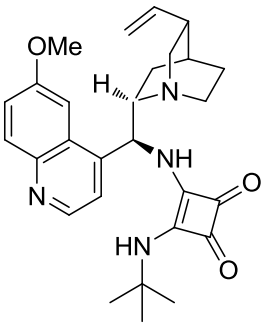
### 3.3. Synthesis of 3-(*t*-butylamino)-4-ethoxycyclobut-3-ene-1,2-dione (29)




To synthesize *t*-butyl Mono-Squaramide from squaric acid, the literature procedure was performed[20,40] as follows: Squaric acid (1.0 g, 8.8 mmol) in absolute ethanol (10 mL) was refluxed under argon atmosphere for 3 h and then ethanol was evaporated under vacuo. Addition of ethanol (10 mL), reflux for 30 minutes under argon atmosphere and evaporation of solvent were repeated for 3 times. Final evaporation product was diethyl squarate as light-yellow oil (decayed quickly). To produce mono-squaramide, the diethyl squarate was added fastly to the solution of *t*-butylamine (1 eq.) in $CH_2Cl_2$ (8 mL). The solution was allowed to stir for 24 h at room temperature. For purification of product, flash column chromatography with silica gel and EtOAc:Hexane (1:3) as eluent was used. Desired product was gained 88 %yield as white solid.

Spectroscopic data are confirmed with the literature.[40]

### 3.4. Synthesis of Quinine / *t*-butyl Squaramide Catalyst (20)




In order to synthesize quinine based *t*-butyl squaramide bifunctional organocatalyst from quinine amine and *t*-butyl mono-squaramide, the procedure[41,42] was performed as follows: *t*-butyl mono-squaramide (197 mg, 1.0 mmol) was added to a mixture of quinine amine (323 mg, 1.0 mmol) in DCM:MeOH (1:1, 4 mL) solution. After stirring of the reaction for 48 h at room temperature, product was planted to the silica gel column filled with EtOAc:MeOH (3:1) as eluent. Product was obtained with 85 % chemical yield as a white solid.

**MP:** 259°C (decomposed).

$[\alpha]_D^{25}$ = -179.9° (*c* = 0.1, $CH_2Cl_2$).

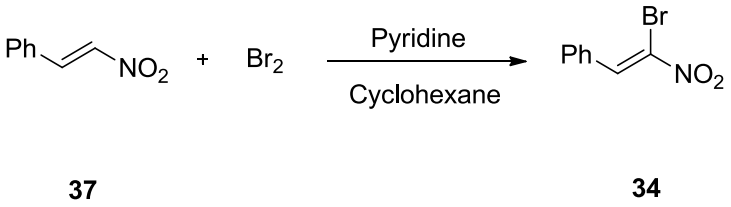
**$^1$H-NMR** (400 MHz, $CDCl_3$): δ 8.63 (d, *J*= 4 Hz, 1H), 7.93 (d, *J*= 9.2 Hz, 1H), 7.73 (s, 1H), 7.49 - 7.30 (m, 2H), 6.01 (bs, 1H), 5.72 – 5.64 (m, 1H), 4.91 (m, 2H), 3.87 (s, 3H), 3.34 (bs, 2H), 3.05 (t, *J* = 11.5 Hz., 1H), 2.67 (d, *J*= 12.3 Hz, 2H), 2.20 (s, 1H), 1.98-1.38 (m, 4H), 1.18 (d, *J*= 22.4, 9H), 0.71 (s, 1H) ppm.

**$^{13}$C-NMR** (101 MHz, DMSO): δ 182.0, 180.2, 177.4, 167.5, 167.1, 157.9, 147.8, 144.3, 143.6, 142.2, 131.4, 127.4, 121.9, 114.3, 101.4, 96.1, 58.7, 58.7, 58.7, 55.7, 52.3, 30.1, 27.3, 27.3, 26.3, 26.3.

**IR (neat):** 3360, 3223, 2971, 1789, 1650, 1623, 1581, 1525, 1473, 1366, 1222 $cm^{-1}$.

**HRMS:** Exact mass calculated for $C_{28}H_{34}N_4O_3$+H]$^+$ : 475.2709; found as 475.2712.

### 3.5. Synthesis of *(Z)*-(2-bromo-2-nitrovinyl)benzene (34)




**37** **34**

*Figure 3.1.* Synthesis of *(Z)*-(2-bromo-2-nitrovinyl)benzene

To synthesize our starting material, the literature procedure was pursued as follows;[43,44]

First of all, to the solution of β-nitrostyrene **37**[44] (12.5 mmol) and cyclohexane (48 mL), pyridine (16.6 mmol) was added. Then, addition of neat $Br_2$ (15.3 mmol) was done over 5 min. After addition of $Br_2$ finished, solution was heated to reflux approximately 85°C for 6-12 h and the reaction process was followed by TLC. The mixture, then, taken and put in another round-bottom flask by using small amount of ethyl acetate. Before starting the extraction process, the solvent was removed. For the extraction, ethyl acetate (150 mL) was used to taken on the residue. Then the organic phase was washed with $Na_2S_2O_3$ (1.0 M, 2x48 mL), distilled $H_2O$ (48 mL) and brine (48 mL), respectively. After washing process was finished, then $Na_2SO_4$ was used to dry. After filtration and taking the resulting product, the solvent was removed via vacuum. At the end, the crude solid product was purified with column chromatography ($CH_2Cl_2$:Petroleum Ether).

Spectroscopic data are conformed with the literature.[43]

### 3.6. General Procedure for Asymmetric Domino Michael-$S_N2$ Addition Reaction: 1,3-Dicarbonyl Compounds Addition to α-Bromonitroalkenes

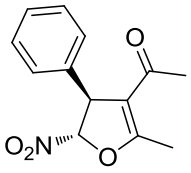
Synthesis of Racemic Product:

In DCM (0.5 M), $Na_2CO_3$ (0.05 mmol) as a base and α-bromonitroalkenes derivative (0.10 mmol) were dissolved. Then, 1,3-dicarbonyl compound derivative (0.18 mmol) was added to this mixture stirred at room temperature. For the optimization process, the time for finishing the reaction was monitered by following the limiting reactant via GC-MS. To purify the product, the reaction mixture was directly loaded into the flash column chromatography and Hexane:EtOAc system was used as eluent.

Synthesis of Chiral Product:

In DCM (0.5 M), *t*-butyl/quinine (0.01 mmol), $Na_2CO_3$ (0.05 mmol) as a base and α-bromonitroalkenes derivative (0.10 mmol) were dissolved. Then, 1,3-dicarbonyl compound derivative (0.18 mmol) was added to this mixture stirred at room temperature. For the optimization process, the reaction was monitored by GC-MS. To purify the product, the reaction mixture was directly loaded into the flash column chromatography and Hexane:EtOAc system was used as eluent.

#### 3.6.1. Synthesis of 1-(2-methyl-5-nitro-4-phenyl-4,5-dihydrofuran-3-yl)ethanone (36aa)




To synthesize our first chiral target product, *(Z)*-(2-bromo-2-nitrovinyl)benzene and acetyl acetone were used and full conversion was obtained with 95 %ee in 3 h as a white solid.

**MP:** 95°C

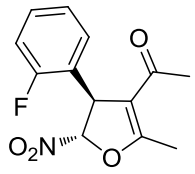
$[\alpha]_D^{25}$ = -0.91° (*c* = 0.5, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.36 – 7.25 (m, 3H), 7.19 – 7.14 (m, 2H), 5.67 (d, *J* = 1.8 Hz, 1H), 4.58 (d, *J* = 2.7 Hz, 1H), 2.48 (d, *J* = 1.4 Hz, 3H), 1.97 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 192.1, 165.9, 136.4, 128.5, 127.7, 126.1, 114.6, 108.4, 55.3, 28.8, 13.5.

**IR (neat):** 2919, 1678, 1608, 1561, 1420, 1365, 1216, 1186 $cm^{-1}$.

### 3.6.2. Synthesis of 1-(4-(2-fluorophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl)ethanone (36ba)




To synthesize our second chiral target product, *(Z)*-1-(2-bromo-2-nitrovinyl)-2-fluorobenzene and acetyl acetone were used and full conversion was obtained with 97 %ee in 3 h as a white solid.

**MP:** 76°C

$[\alpha]_D^{25}$ = -2.68° (*c* = 1.0, $CH_2Cl_2$).

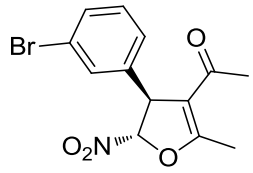
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.43 – 7.20 (m, 1H), 7.14 – 6.82 (m, 3H), 5.73 (s, 1H), 4.91 (s, 1H), 2.47 (s, 3H), 2.01 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 190.2, 164.8, 128.1, 128.1 - 128.0 (d, *J* = 8.3 Hz), 126.1, 126.1, 122.5 - 122.5 (d, *J* = 3.7 Hz), 122.5, 114.0 - 113.9 (d, *J* = 21.4 Hz), 113.7, 112.3, 106.3, 47.0, 27.1, 12.1.

**IR (neat):** 2920, 1733, 1631, 1572, 1489, 1375, 1204, 1170 $cm^{-1}$.

**HRMS:** Exact mass calculated for $[C_{13}H_{12}FNO_4+H]^+$ : 266.0829; found as 266.0823.

### 3.6.3. Synthesis of 1-(4-(3-bromophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl)ethanone (36ca)




To synthesize our third chiral target product, *(Z)*-1-bromo-3-(2-bromo-2-nitrovinyl)benzene and acetyl acetone were used and full conversion was obtained with 76 %ee in 3 h as a yellowish viscous compound.

$[\alpha]_D^{25}$ = -1.47° (*c* = 1.0, $CH_2Cl_2$).

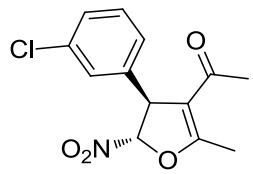
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 1H), 7.31 – 7.26 (m, 1H), 7.22 – 7.16 (m, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 5.65 (d, *J* = 1.7 Hz, 1H), 4.56 (s, 1H), 2.49 (d, *J* = 1.3 Hz, 3H), 2.03 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 190.5, 165.2, 137.8, 129.9, 129.0, 128.1, 124.0, 121.6, 113.7, 107.0, 53.9, 27.7, 12.6.

**IR (neat):** 3005, 1685, 1640, 1619, 1564, 1364, 1210, 1181 $cm^{-1}$.

**HRMS:** Exact mass calculated for $[C_{13}H_{12}BrNO_4+H]^+$: 326.0029; found as 326.0023.

### 3.6.4. Synthesis of 1-(4-(3-chlorophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl)ethanone (36da)



To synthesize our 4th chiral target product, *(Z)*-1-(2-bromo-2-nitrovinyl)-3-chlorobenzene and acetyl acetone were used and full conversion was obtained with 83 %ee in 4.5 h as a white solid.

**MP:** 79°C

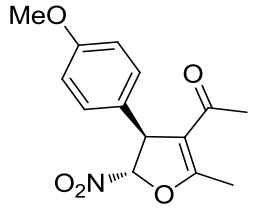
$[\alpha]_D^{25}$ = -1.37° (*c* = 1.0, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 3.6, 1.5 Hz, 2H), 7.13 (s, 1H), 7.11 – 7.05 (m, 1H), 5.65 (d, *J* = 1.7 Hz, 1H), 4.57 (d, *J* = 1.1 Hz, 1H), 2.49 (d, *J* = 1.3 Hz, 3H), 2.03 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 192.5, 167.1, 139.5, 135.5, 130.8, 129.0, 127.2, 125.5, 115.7, 108.9, 55.9, 29.7, 14.6.

**IR (neat):** 2920, 1734, 1682, 1613, 1561, 1363, 1215, 1182 $cm^{-1}$.

### 3.6.5. Synthesis of 1-(4-(4-methoxyphenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl)ethanone (36ea)




To synthesize our 5th chiral target product, *(Z)*-1-(2-bromo-2-nitrovinyl)-4-methoxybenzene and acetyl acetone were used and full conversion was obtained with 92 %ee in 4.5 h as a dark yellowish viscous compound.

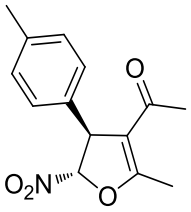
$[\alpha]_D^{25}$ = -1.78° (*c* = 1.0, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.14 – 7.01 (m, 2H), 6.92 – 6.77 (m, 2H), 5.63 (d, *J* = 1.7 Hz, 1H), 4.53 (s, 1H), 3.74 (s, 3H), 2.46 (d, *J* = 1.4 Hz, 3H), 1.95 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 192.2, 165.7, 158.8, 128.4, 127.3, 114.7, 113.9, 108.7, 54.7, 54.3, 28.7, 13.4.

**IR (neat):** 2933, 1686, 1620, 1562, 1510,1366, 1255, 1179 $cm^{-1}$.

### 3.6.6. Synthesis of 1-(2-methyl-5-nitro-4-(*p*-tolyl)-4,5-dihydrofuran-3-yl)ethanone (36fa)




To synthesize our 6$^{th}$ chiral target product, *(Z)*-1-(2-bromo-2-nitrovinyl)-4-methylbenzene and acetyl acetone were used and full conversion was obtained with 78 %ee in 6 h as a white solid.

**MP:** 95°C (decomposed)

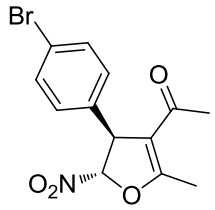
$[\alpha]_D^{25}$ = -1.40° (*c* = 1.0, $CH_2Cl_2$).

**$^{1}$H NMR** (400 MHz, $CDCl_3$): δ 7.16 – 7.09 (m, 2H), 7.07 – 7.03 (m, 2H), 5.65 (d, *J* = 1.8 Hz, 1H), 4.54 (s, 1H), 2.47 (d, *J* = 1.4 Hz, 3H), 2.29 (s, 3H), 1.95 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 193.3, 166.9, 138.6, 134.5, 130.2, 128.8, 127.0, 115.6, 109.7, 55.9, 29.9, 21.1, 14.5.

**IR (neat):** 2918, 1734, 1680, 1613, 1565, 1369, 1215, 1185 $cm^{-1}$.

### 3.6.7. Synthesis of 1-(4-(4-bromophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl)ethanone (36ga)




To synthesize our 7th chiral target product, *(Z)*-1-bromo-4-(2-bromo-2-nitrovinyl)benzene and acetyl acetone were used and full conversion was obtained with 76 %ee in 6 h as a dark yellow.

**MP:** 131°C (decomposed)

$[\alpha]_D^{25}$ = 0.01° (*c* = 0.5, $CH_2Cl_2$).

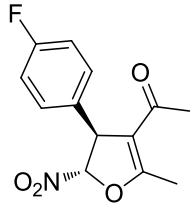
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.66 – 7.60 (m, 2H), 7.48 – 7.44 (m, 2H), 5.63 (d, *J* = 1.8 Hz, 1H), 4.55 (d, *J* = 5.7 Hz, 1H), 2.48 (d, *J* = 1.4 Hz, 3H), 2.01 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 191.6, 166.0, 135.5, 131.7, 129.9, 127.8, 107.9, 67.1, 54.8, 13.1.

**IR (neat):** 2992, 1734, 1677, 1609, 1562, 1362, 1210, 1180 $cm^{-1}$.

**HRMS:** Exact mass calculated for $[C_{13}H_{12}BrNO_4+H]^+$: 326.0029; found as 326.0023.

### 3.6.8. Synthesis of 1-(4-(4-fluorophenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl)ethanone (36ha)



To synthesize our 8th chiral target product, *(Z)*-1-(2-bromo-2-nitrovinyl)-4-fluorobenzeneand acetyl acetone were used and full conversion was obtained with 82 %ee in 6 h as a yellow solid.

**MP:** 66°C

$[\alpha]_D^{25}$ = -1.45° (*c* = 1.0, $CH_2Cl_2$).

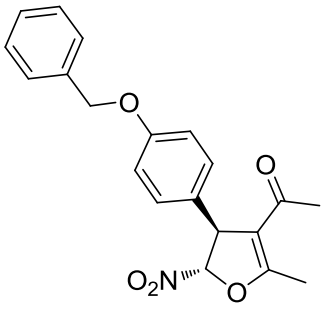
**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.18 – 7.11 (m, 2H), 7.07 – 6.97 (m, 2H), 5.64 (d, *J* = 1.8 Hz, 1H), 4.58 (s, 1H), 2.48 (d, *J* = 1.4 Hz, 3H), 2.00 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 192.8, 166.9, 163.9, 133.3 - 133.3 (d, *J* = 3.2 Hz), 133.3, 128.9, 128.9, 116.6, 116.4, 115.9, 109.2, 55.6, 29.7, 14.6.

**IR (neat):** 2821, 1685, 1617, 1569, 1509, 1363, 1217, 1188 $cm^{-1}$.

**HRMS:** Exact mass calculated for $[C_{13}H_{12}FNO_4+H]^+$: 266.0829; found as 266.0823.

### 3.6.9. Synthesis of 1-(4-(4-(benzyloxy)phenyl)-2-methyl-5-nitro-4,5-dihydrofuran-3-yl)ethanone (36ia)




To synthesize our 9th chiral target product, *(Z)*-1-(benzyloxy)-4-(2-bromo-2-nitrovinyl)benzene and acetyl acetone were used and full conversion was obtained with 97 %ee in 3 h as a light yellow solid.

**MP:** 137°C (decomposed)

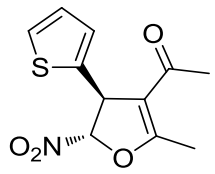
$[\alpha]_D^{25}$ = -0.22° (*c* = 0.25, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 6H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.92 (t, *J* = 5.6 Hz, 2H), 5.63 (d, *J* = 1.7 Hz, 1H), 4.99 (s, 2H), 4.53 (s, 1H), 2.46 (d, *J* = 1.2 Hz, 3H), 1.95 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 192.3, 165.7, 158.0, 135.6, 128.6, 127.6, 127.3, 127.1, 126.4, 114.8, 114.6, 108.6, 69.1, 54.7, 28.8 13.5.

**IR (neat):** 2919, 1680, 1610, 1564, 1511, 1369, 1215, 1182 $cm^{-1}$.

### 3.6.10. Synthesis of 1-(2-methyl-5-nitro-4-(thiophen-2-yl)-4,5-dihydrofuran-3-yl)ethanone (36ja)




To synthesize our 10$^{th}$ chiral target product, *(Z)*-2-(2-bromo-2-nitrovinyl)thiophene and acetyl acetone were used and full conversion was obtained anti/syn-isomers with 68:32 %dr and 86:90 %ee in 5 h as a yellowish viscous compound.

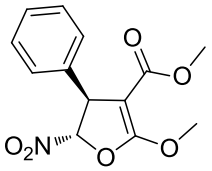
$[\alpha]_D^{25}$ = -1.47° (*c* = 1.0, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.65 – 7.21 (m, 1H), 7.02 – 6.70 (m, 2H), 5.71 (dd, *J* = 5.7, 1.6 Hz, 1H), 4.85 (d, *J* = 34.8 Hz, 1H), 2.44 (dd, *J* = 3.8, 1.4 Hz, 3H), 2.06 (d, *J* = 19.8 Hz, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 192.8, 167.2, 130.6, 127.8, 126.2, 126.0, 109.0, 51.3, 29.5, 14.5.

**IR (neat):** 2929, 1685, 1641, 1617, 1565, 1364, 1312, 1188 $cm^{-1}$.

### 3.6.11. Synthesis of methyl 2-methoxy-5-nitro-4-phenyl-4,5-dihydrofuran-3-carboxylate (36ab)



To synthesize our 11th chiral target product, *(Z)*-(2-bromo-2-nitrovinyl)benzene and dimethyl malonate were used and full conversion was obtained with 4 %ee in 6 h as a yellowish viscous compound.

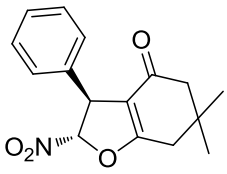
$[\alpha]_D^{25}$ = 0.05° (*c* = 1.0, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.6 Hz, 2H), 7.23 – 7.13 (m, 3H), 5.34 (d, *J* = 5.9 Hz, 1H), 4.13 (d, *J* = 5.9 Hz, 1H), 3.78 (s, 3H), 3.47 (s, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 162.8, 162.5, 129.1, 127.9, 127.8, 127.6, 127.2, 65.2, 52.9, 52.4, 45.0, 36.7.

**IR (neat):** 2957, 1737, 1555, 1501, 1436, 1366, 1288, 1118 $cm^{-1}$.

### 3.6.12. Synthesis of 6,6-dimethyl-2-nitro-3-phenyl-2,3,6,7-tetrahydrobenzofuran-4(5*H*)-one (36ac)



To synthesize our 12th chiral target product, *(Z)*-(2-bromo-2-nitrovinyl)benzene and dimedone were used and full conversion was obtained with 72 %ee in 4 h as a white solid.

**MP:** 139°C

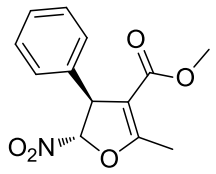
$[\alpha]_D^{25}$ = -1.08° (*c* = 1.0, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.20 (m, 3H), 7.17 – 7.08 (m, 2H), 5.89 (d, *J* = 2.0 Hz, 1H), 4.54 (s, 1H), 2.67 – 2.47 (m, 2H), 2.24 (d, *J* = 2.8 Hz, 2H), 1.13 (d, *J* = 2.5 Hz, 6H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 192.0, 174.0, 135.9, 128.3, 127.4, 125.9, 114.0, 110.3, 52.1, 50.2, 36.2, 33.6, 27.7, 27.5.

**IR (neat):** 2934, 1666, 1651, 1563, 1392, 1369, 1256, 1188 $cm^{-1}$.

### 3.6.13. Synthesis of 1-(2-methoxy-5-nitro-4-phenyl-4,5-dihydrofuran-3-yl)ethanone (36ad)




To synthesize our 13$^{th}$ chiral target product, *(Z)*-(2-bromo-2-nitrovinyl)benzene and methyl acetoacetate were used and full conversion was obtained with 80 %ee in 5 h as a white solid.

**MP:** 75°C

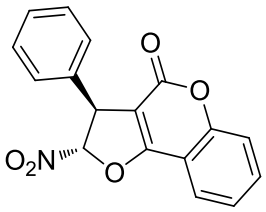
$[\alpha]_D^{25}$ = -1.69° (*c* = 1.0, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.36 – 7.28 (m, 2H), 7.27 – 7.22 (m, 1H), 7.22 – 7.09 (m, 2H), 5.70 (d, *J* = 1.7 Hz, 1H), 4.53 (s, 1H), 3.56 (d, *J* = 19.8 Hz, 3H), 2.44 (d, *J* = 1.4 Hz, 3H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 167.5, 163.9, 137.8, 129.2, 128.4, 127.0, 109.6, 107.4, 55.7, 51.5, 13.8.

**IR (neat):** 2956, 1707, 1671, 1604, 1562, 1431, 1319, 1226, 1184 $cm^{-1}$.

### 3.6.14. 2-nitro-3-phenyl-2*H*-furo[3,2-*c*]chromen-4(3*H*)-one (36ae)




To synthesize our last chiral target product, *(Z)*-(2-bromo-2-nitrovinyl)benzene and 4-OH Coumarine were used and full conversion was obtained with 33 %ee in 6 h as a white solid.

**MP:** 147°C (decomposed)

$[\alpha]_D^{25}$ = -0.25° (*c* = 1.0, $CH_2Cl_2$).

**$^1$H NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.45 – 7.28 (m, 5H), 7.20 (dd, *J* = 5.6, 4.3 Hz, 1H), 6.19 (d, *J* = 2.1 Hz, 1H), 4.89 (d, *J* = 1.9 Hz, 1H).

**$^{13}$C NMR** (101 MHz, $CDCl_3$): δ 164.6, 157.0, 154.6, 134.5, 132.8, 128.6, 128.0, 126.1, 123.7, 122.1, 116.3, 110.4, 110.1, 103.9, 52.7.

**IR (neat):** 3030, 1717, 1657, 1608, 1569, 1497, 1453, 1408 $cm^{-1}$.

# CHAPTER 4

# CONCLUSIONS

In this study, quinine amine anchored squaramide type bifunctional organocatalysts synthesized in Tanyeli's research group were utilized to attain asymmetric 2,3-dihydrofuran derivatives via domino Michael-$S_N2$ type addition reaction in an optimal contidions.

First of all, optimization studies were started with organocatalyst screening. Then all reaction conditions have been changed and their effects on the %ee and %yield values have been evaluated. Compound **(34)** used as an electrophile and compound **(35)** acted as a nucleophile for Michael addition reaction. At the end of the screening part, the highest result as 95 %ee was gained by conditions 10 mol% organocatalyst **(20)**, 0.05 mmol $Na_2CO_3$ as an inorganic additive base, DCM as a solvent at room temperature in 0.5 M concentrated solution.

After optimizing the reaction conditions, ten different derivatives of α-bromonitroolefins **(34a-j)** and five different 1,3-dicarbonyl compounds **(35a-e)** were examined. Finally, highest %ee value was obtained as 97 % by *o*-F-Ph substituted **(36ba)** derivative.

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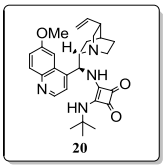
# APPENDICES

## A. NMR DATA




**20**

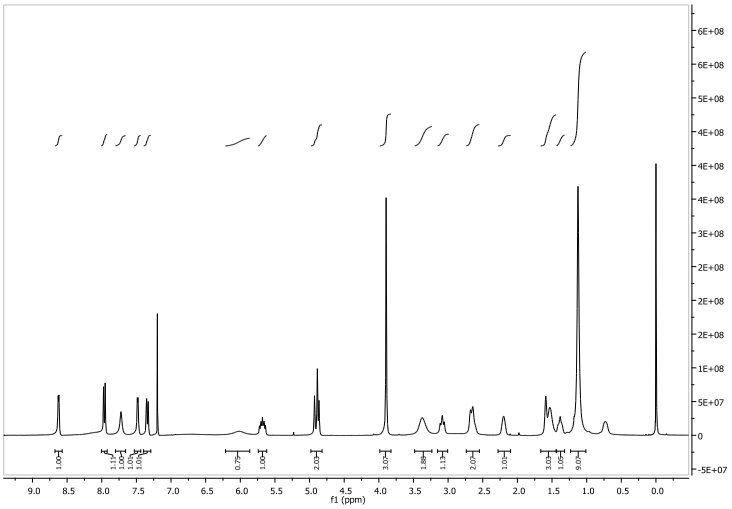



*Figure 0.1.* $^{1}$H NMR Spectrum of Quinine / *t*-butyl Squaramide (20)

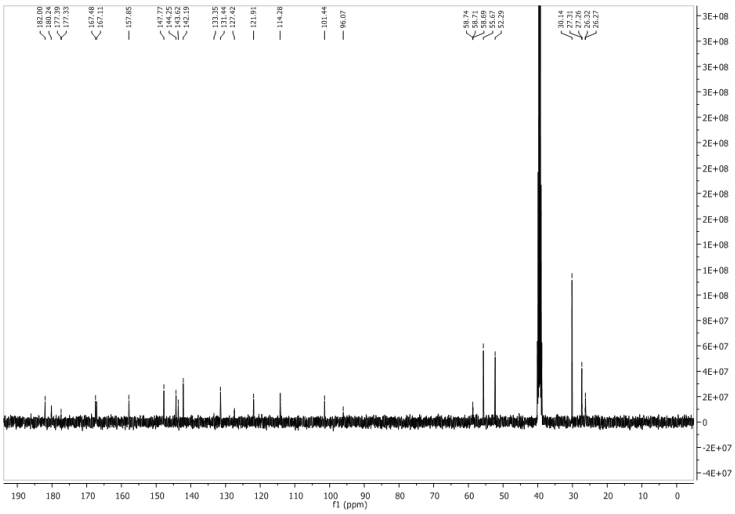
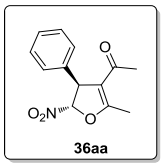



*Figure 0.2.* $^{13}$C NMR Spectrum of Quinine / *t*-butyl Squaramide (20)



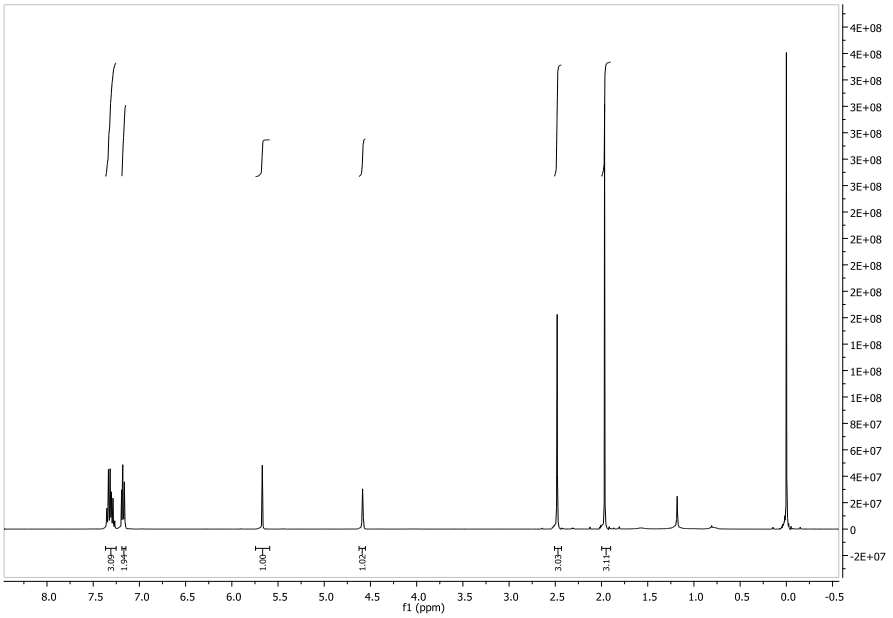




*Figure 0.3.* $^{1}$H NMR Spectrum of (36aa)

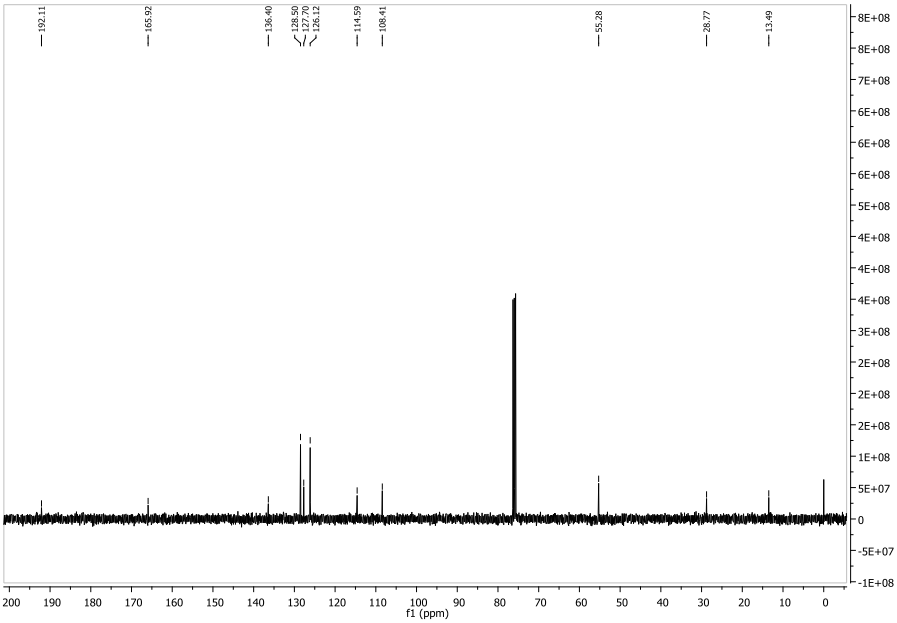
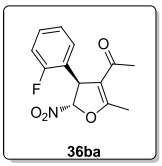



*Figure 0.4.* $^{13}$C NMR Spectrum of (36aa)



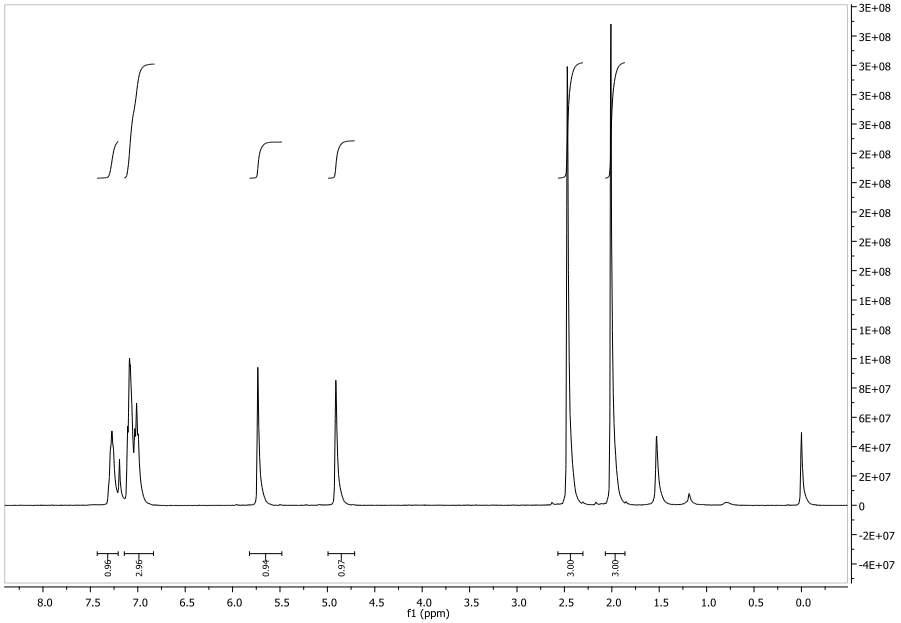




*Figure 0.5.* $^{1}$H NMR Spectrum of (36ba)

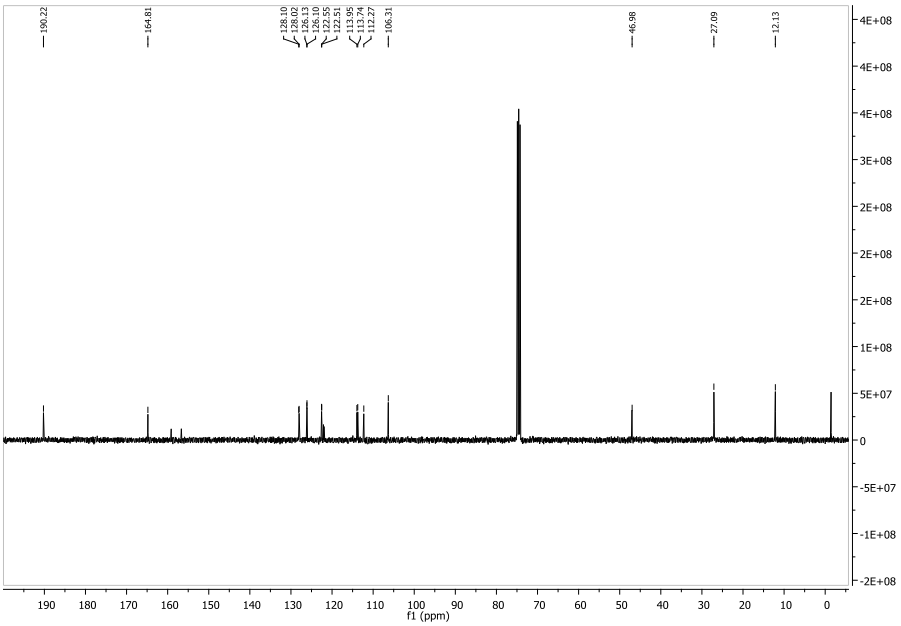
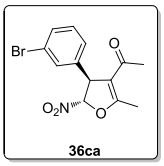



*Figure 0.6.* $^{13}$C NMR Spectrum of (36ba)



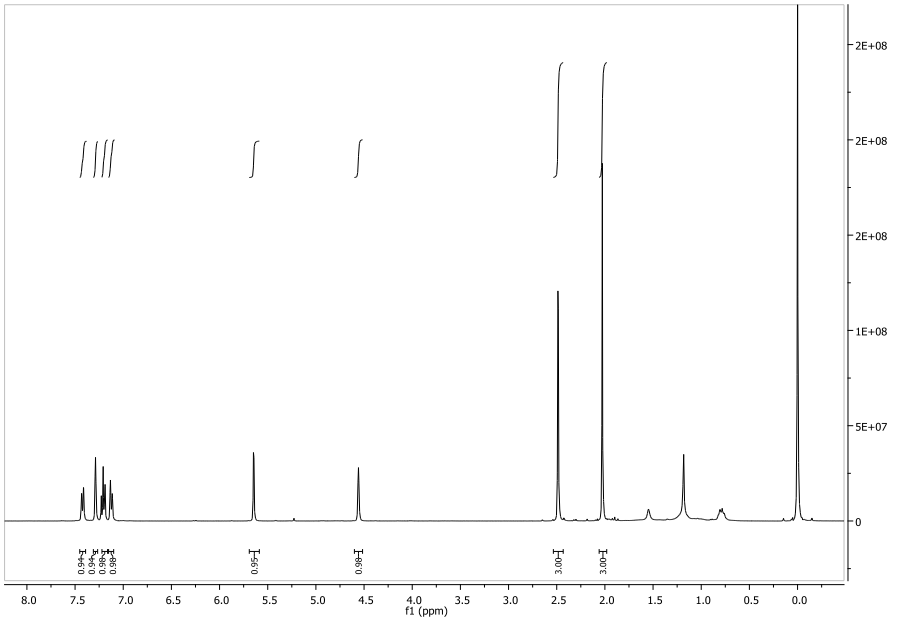




*Figure 0.7.* $^{1}$H NMR Spectrum of (36ca)

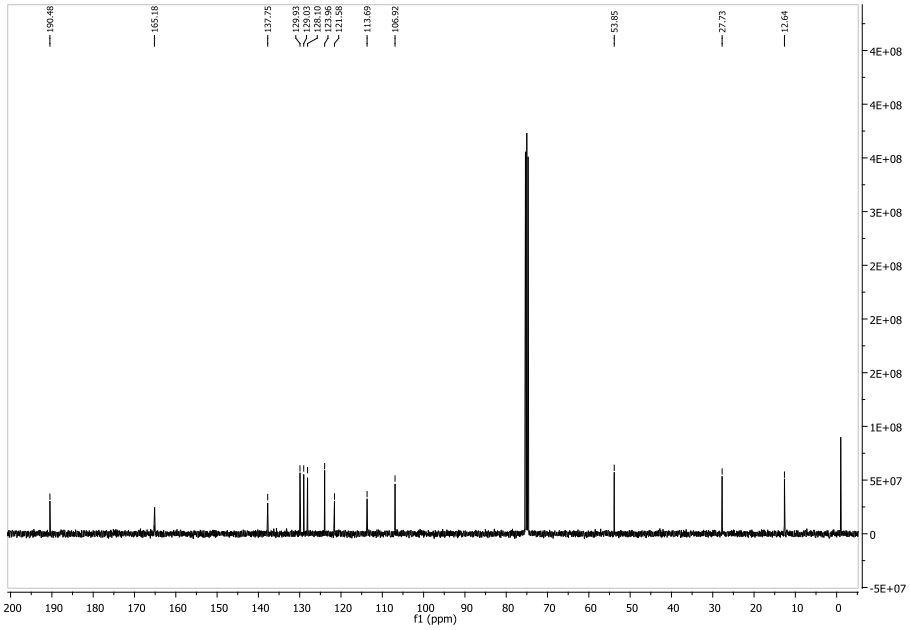
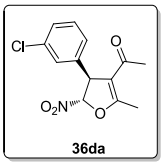



*Figure 0.8.* $^{13}$C NMR Spectrum of (36ca)



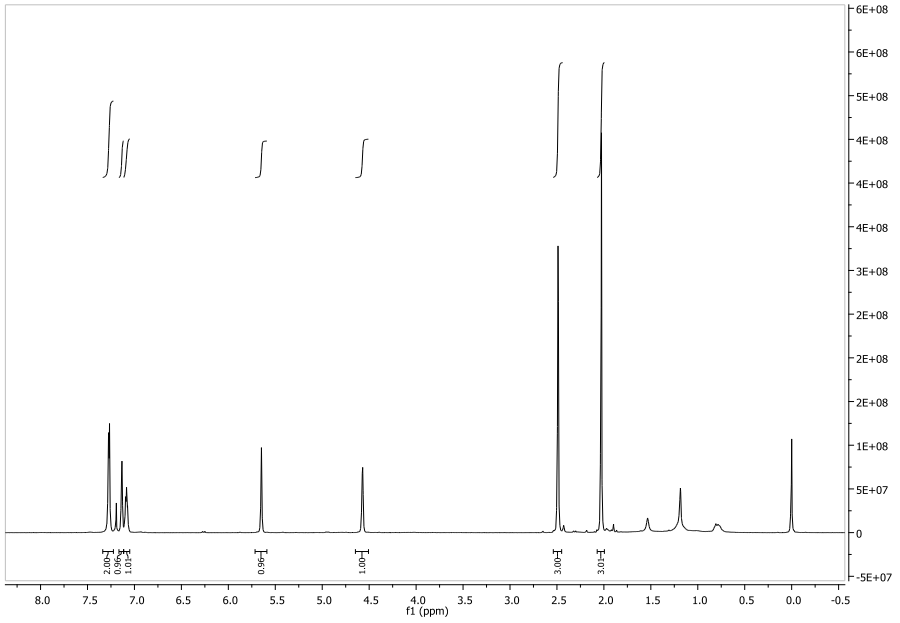




*Figure 0.9.* $^{1}$H NMR Spectrum of (36da)

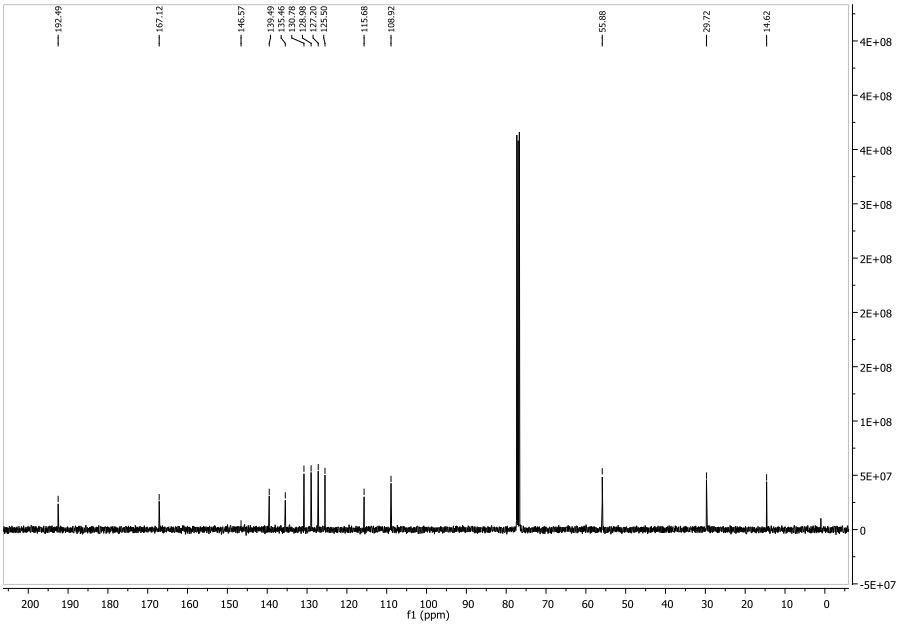
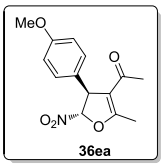



*Figure 0.10.* $^{13}$C NMR Spectrum of (36da)



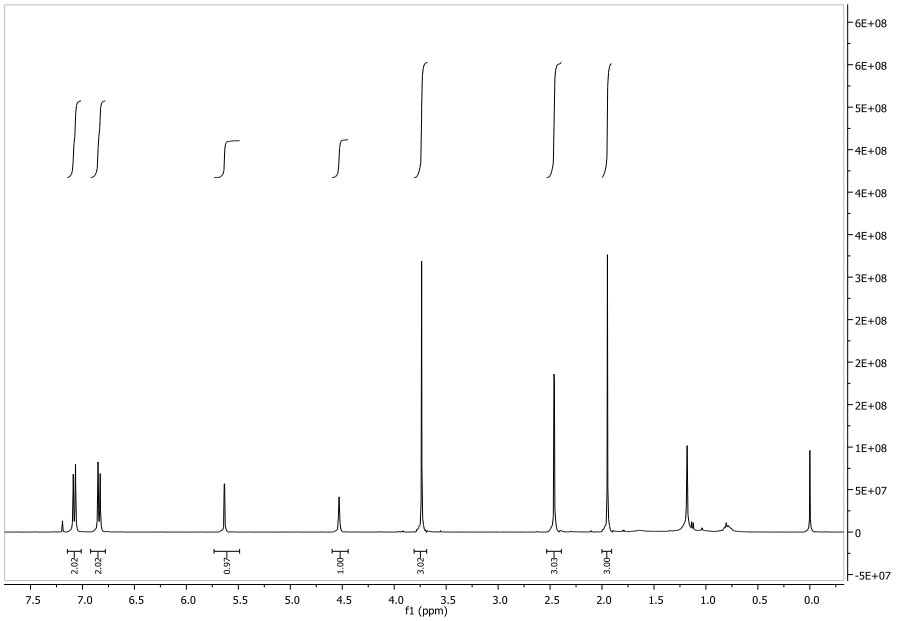




*Figure 0.11.* $^{1}$H NMR Spectrum of (36ea)

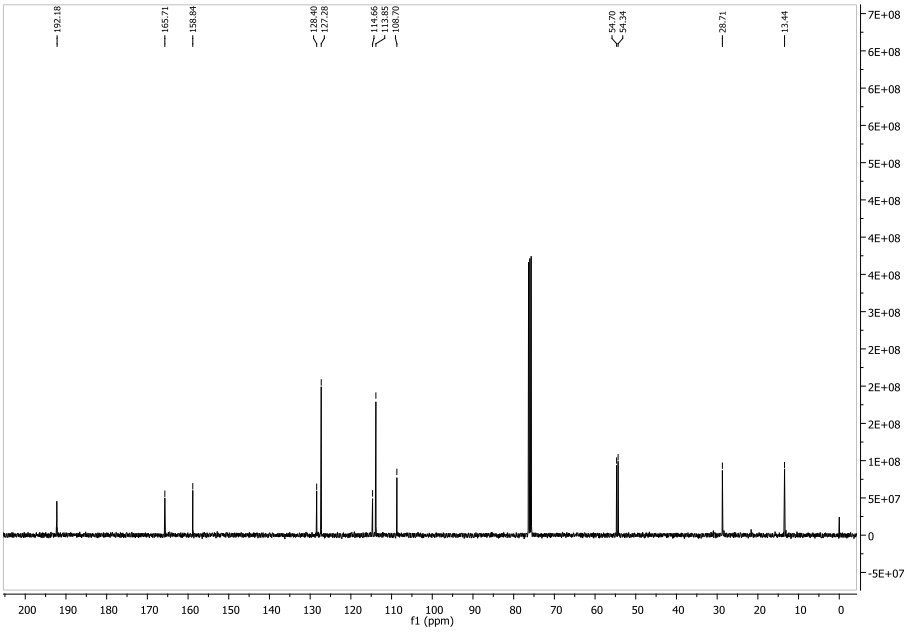
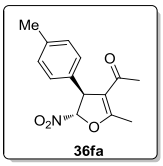



*Figure 0.12.* $^{13}$C NMR Spectrum of (36ea)



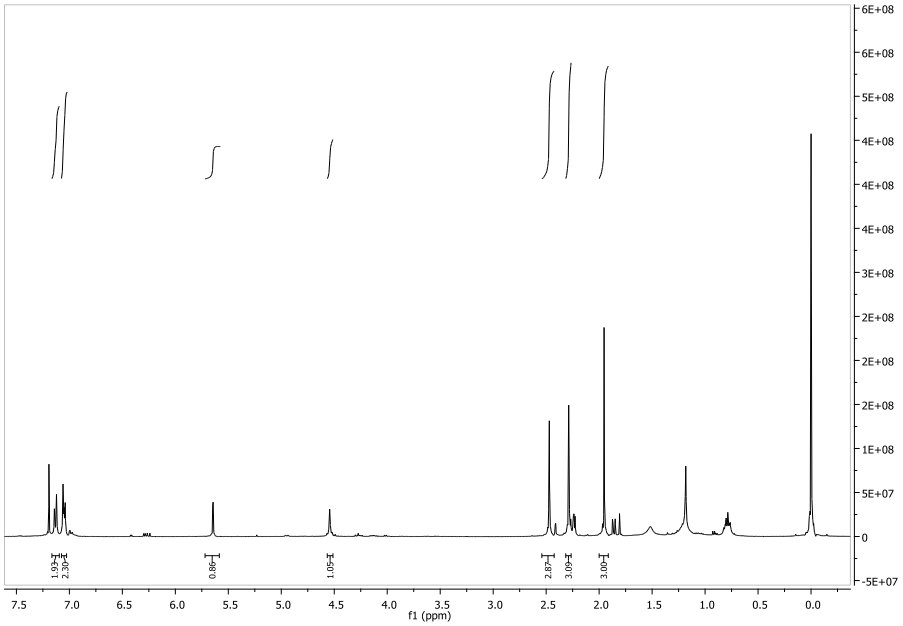
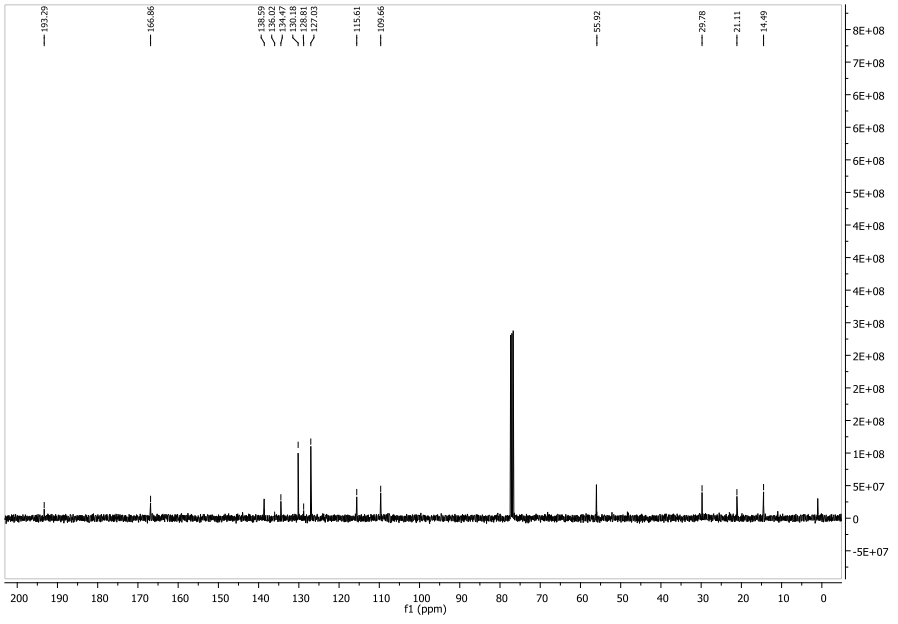




*Figure 0.13.* $^{1}$H NMR Spectrum of (36fa)

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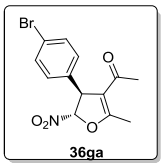


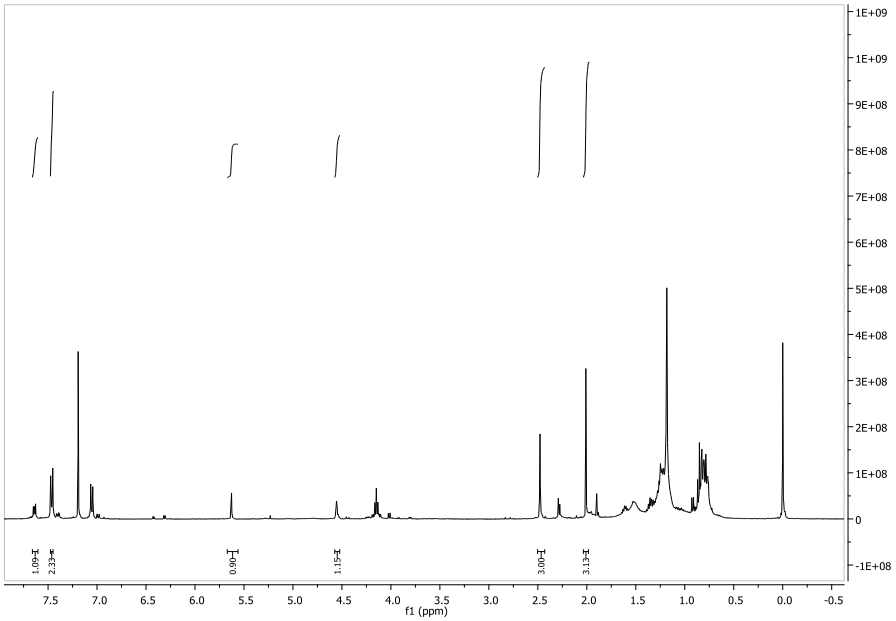




*Figure 0.15.* $^{1}$H NMR Spectrum of (36ga)

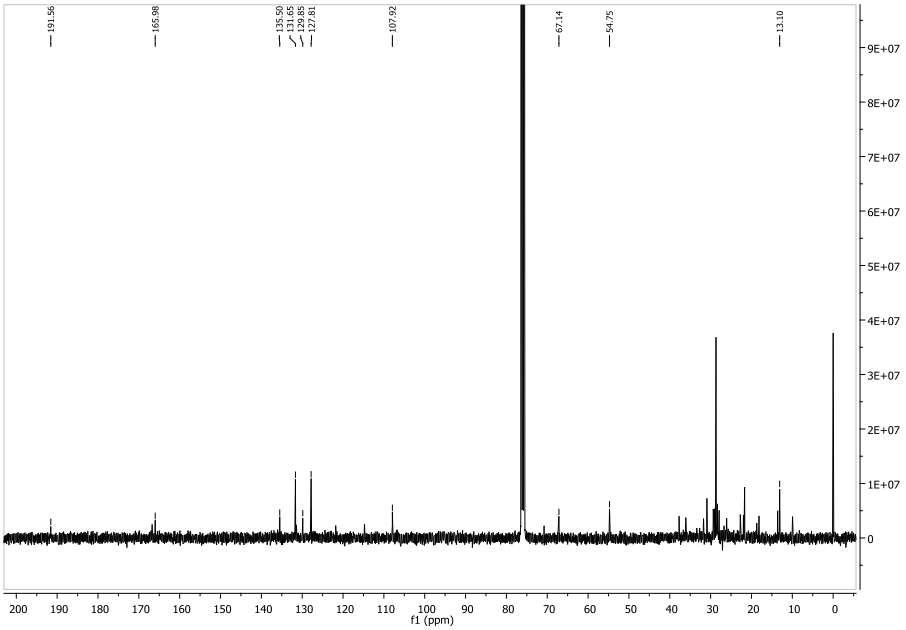
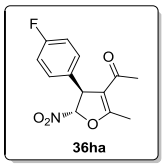



*Figure 0.16.* $^{13}$C NMR Spectrum of (36ga)



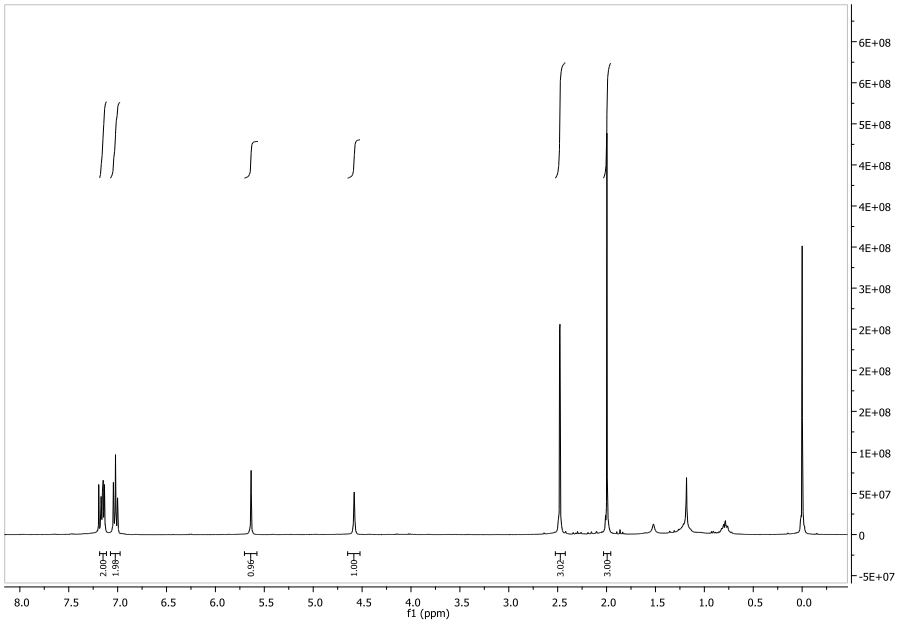




*Figure 0.17.* $^{1}$H NMR Spectrum of (36ha)

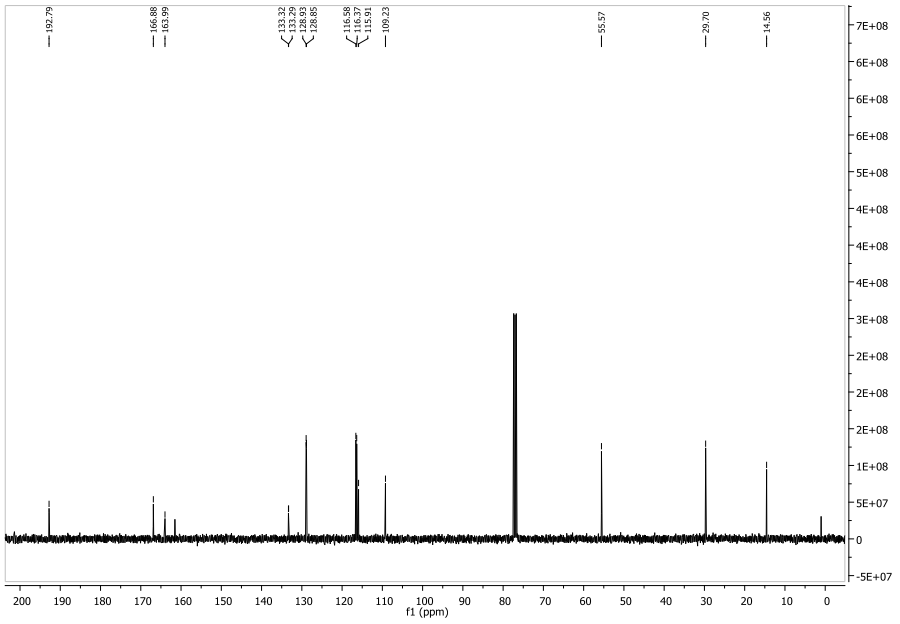
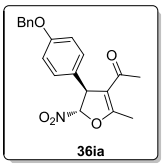



*Figure 0.18.* $^{13}$C NMR Spectrum of (36ha)



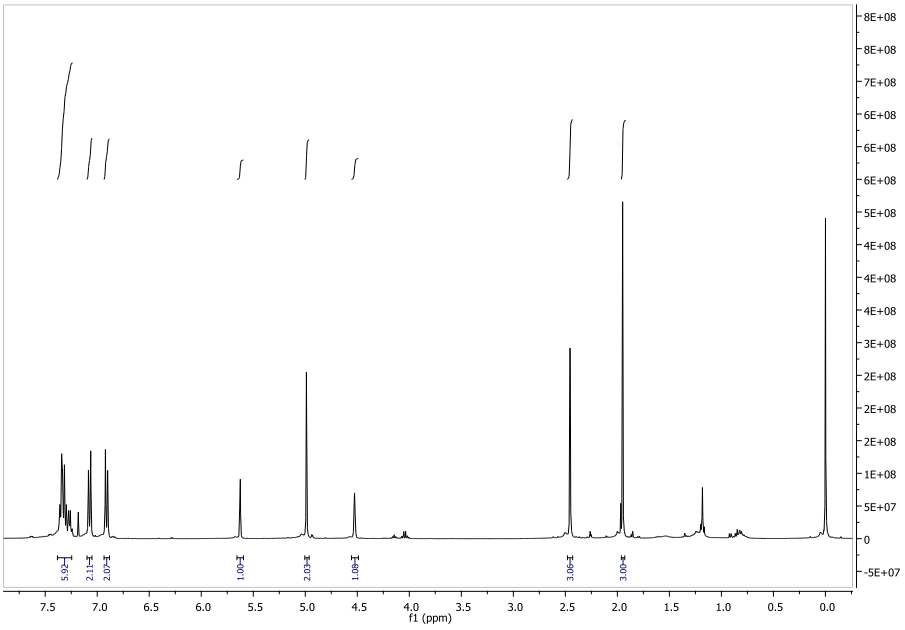




*Figure 0.19.* $^{1}$H NMR Spectrum of (36ia)

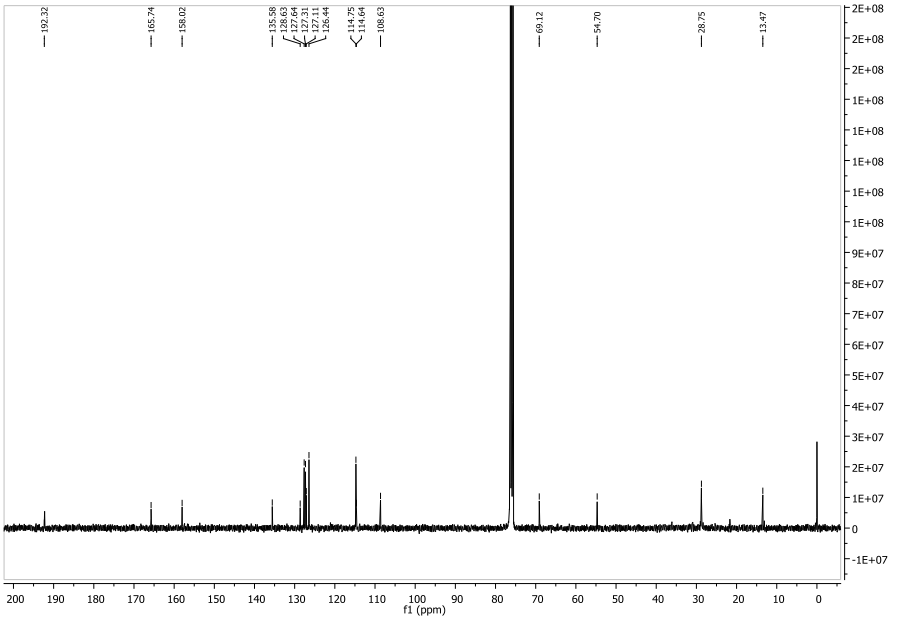
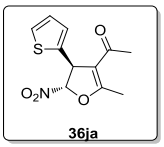



*Figure 0.20.* $^{13}$C NMR Spectrum of (36ia)



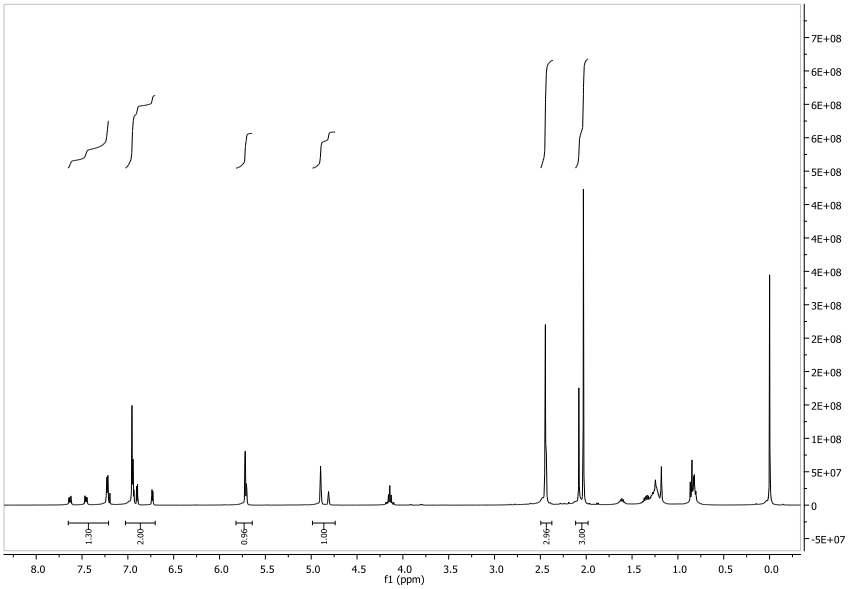




*Figure 0.21.* $^{1}$H NMR Spectrum of (36ja)

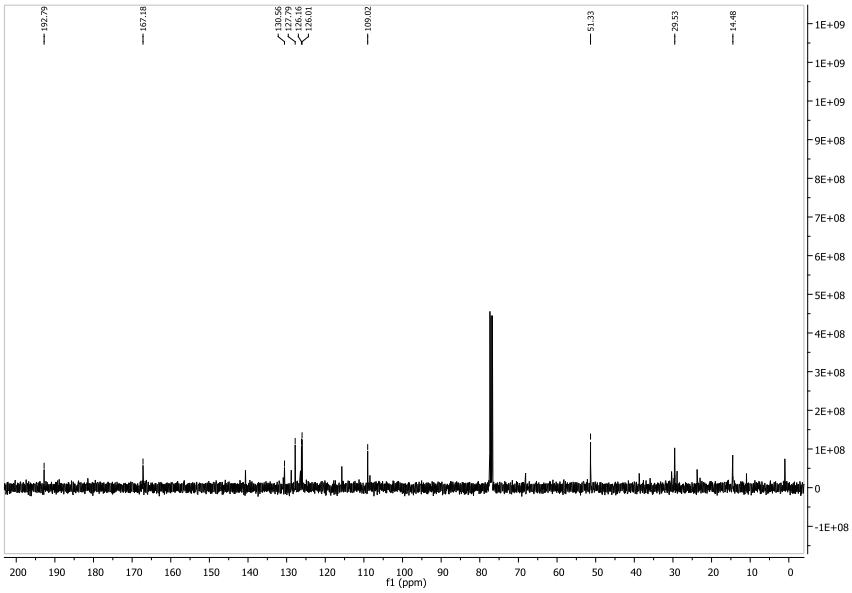
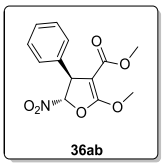



*Figure 0.22.* $^{13}$C NMR Spectrum of (36ja)



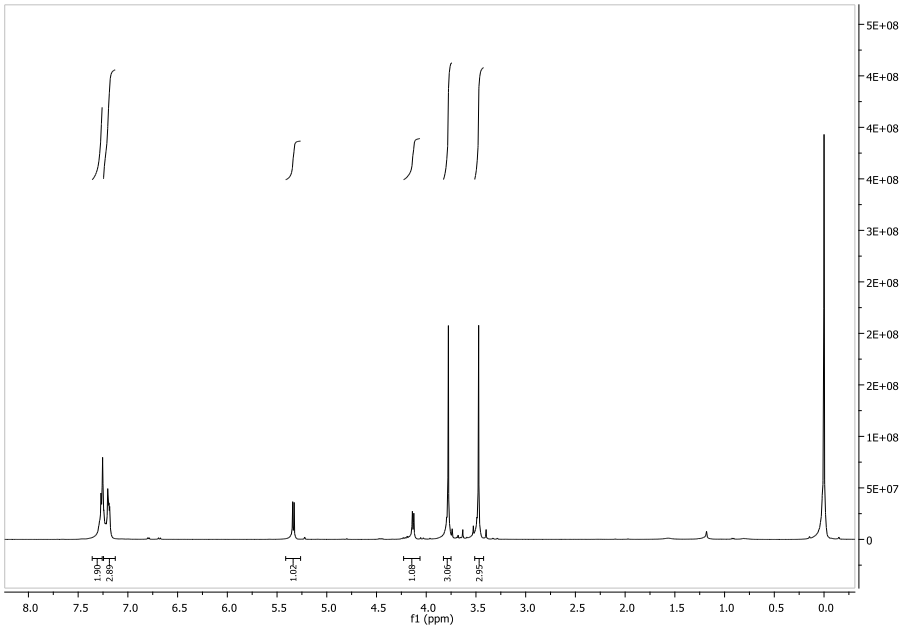




*Figure 0.23.* $^{1}$H NMR Spectrum of (36ab)

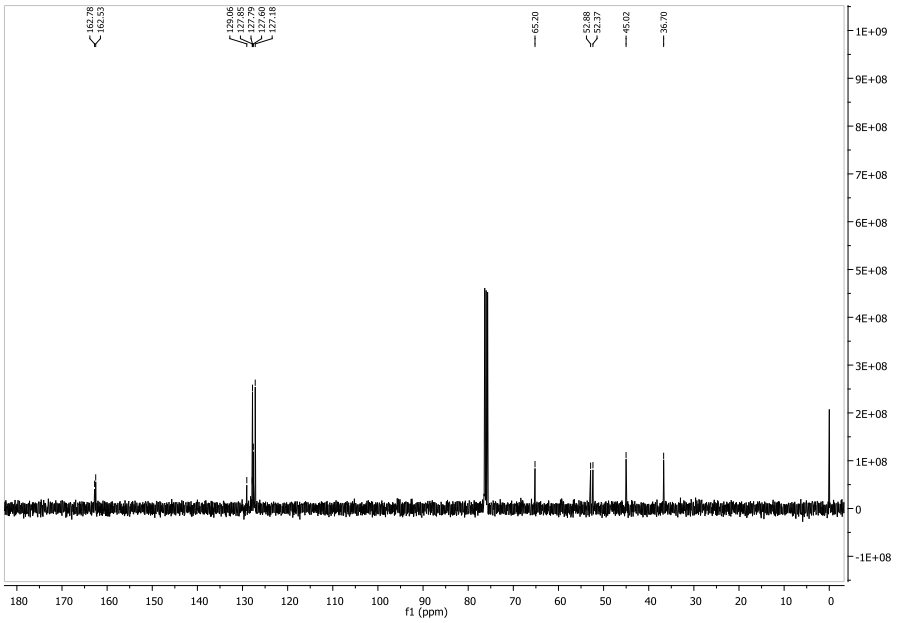
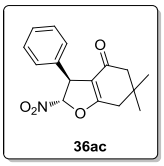



*Figure 0.24.* $^{13}$C NMR Spectrum of (36ab)



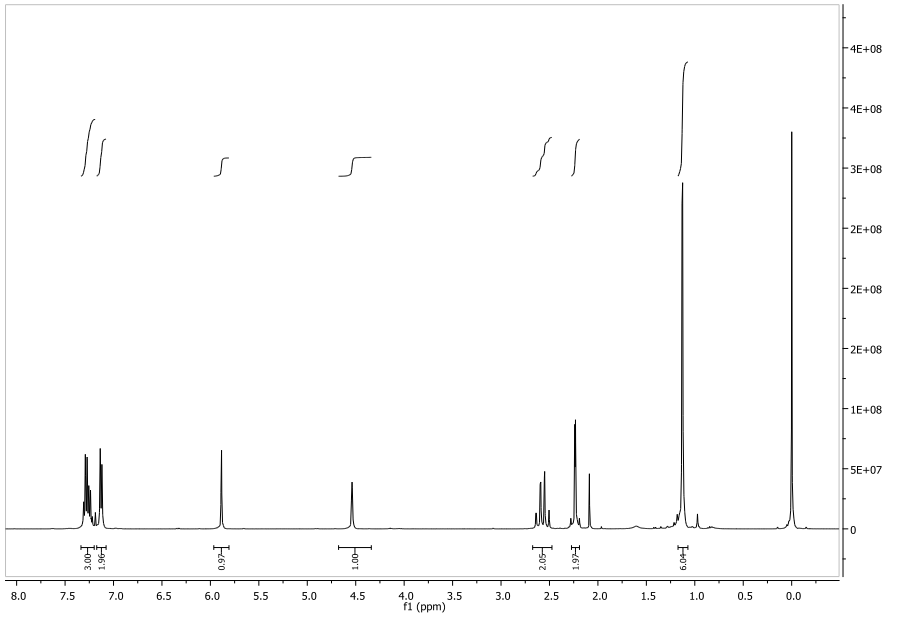




*Figure 0.25.* $^{1}$H NMR Spectrum of (36ac)

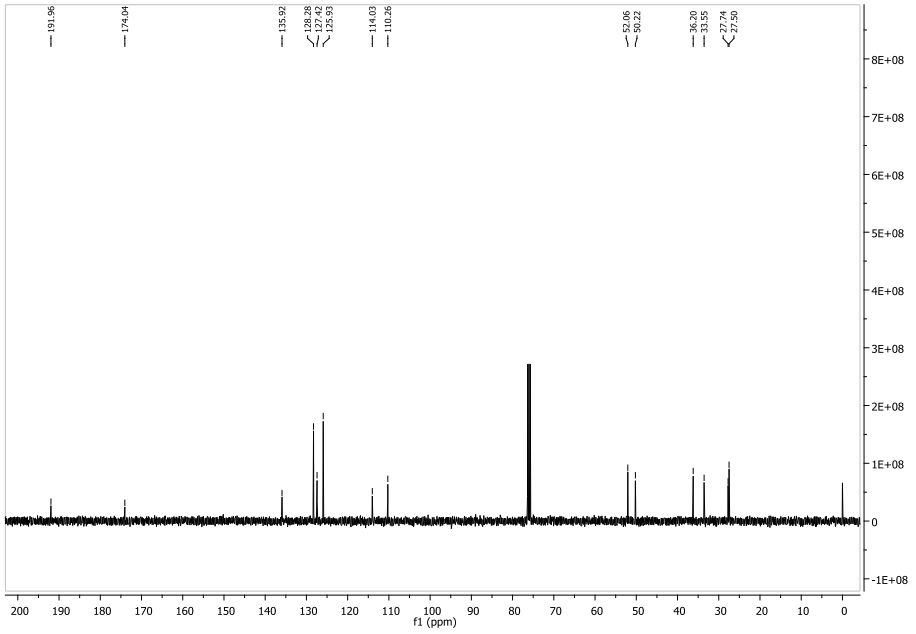
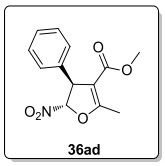



*Figure 0.26.* $^{13}$C NMR Spectrum of (36ac)



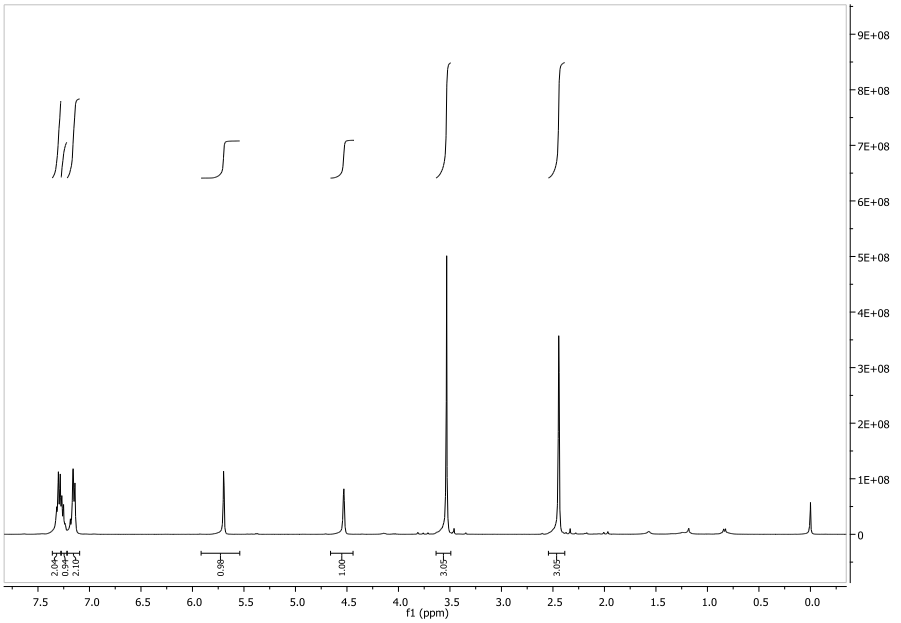




*Figure 0.27.* $^{1}$H NMR Spectrum of (36ad)

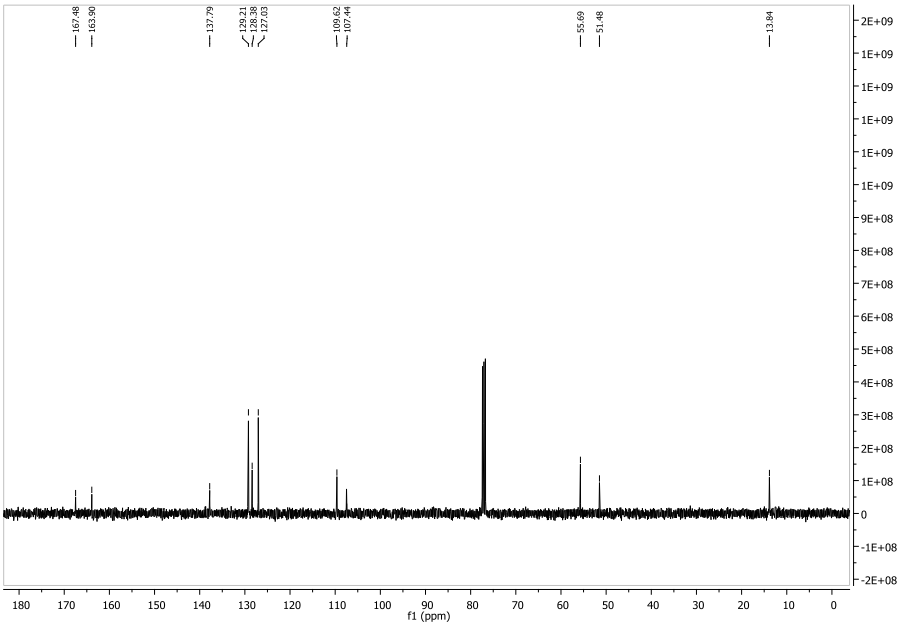
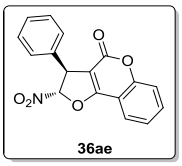



*Figure 0.28.* $^{13}$C NMR Spectrum of (36ad)



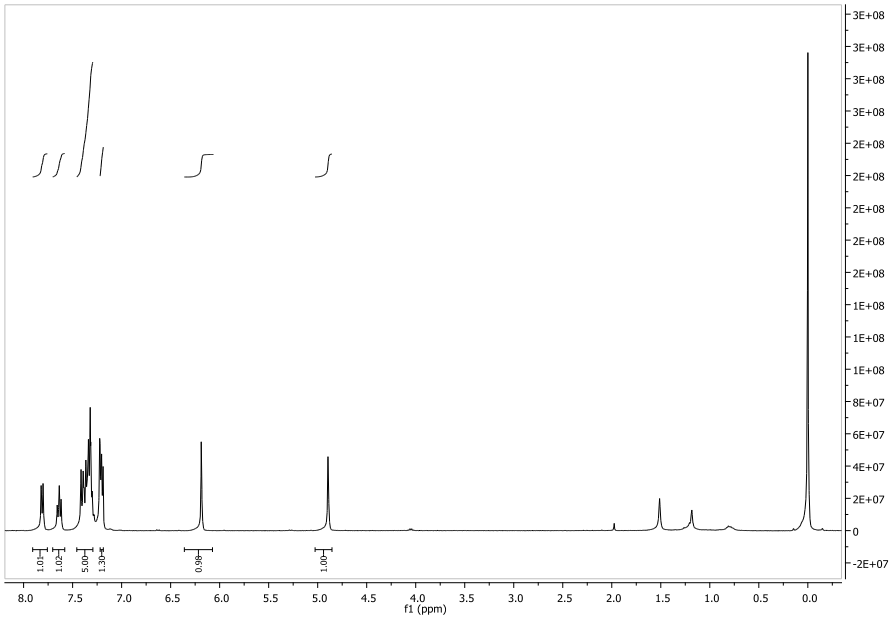




*Figure 0.29.* $^{1}$H NMR Spectrum of (36ae)

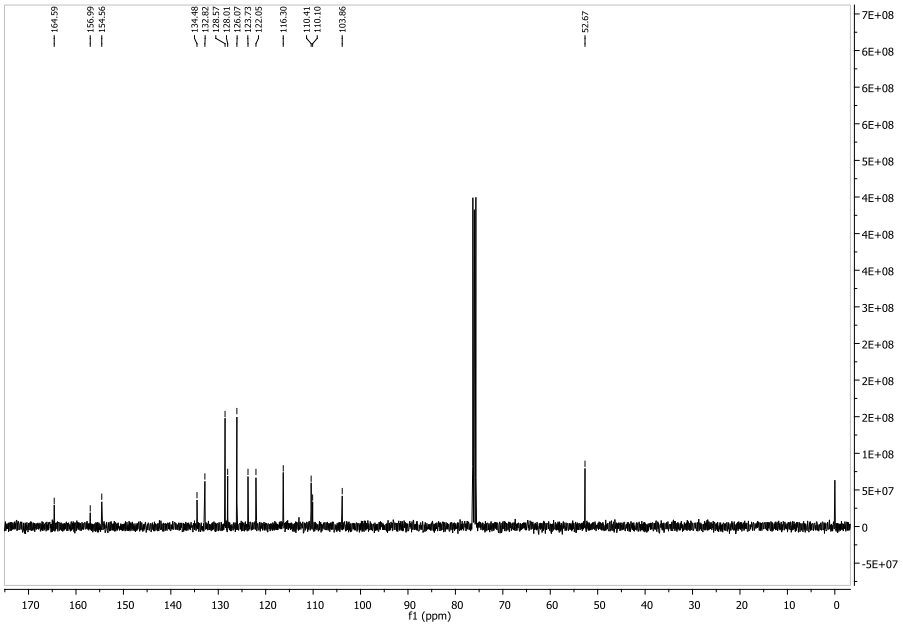
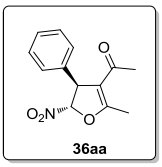



*Figure 0.30.* $^{13}$C NMR Spectrum of (36ae)

## B. HPLC DATA



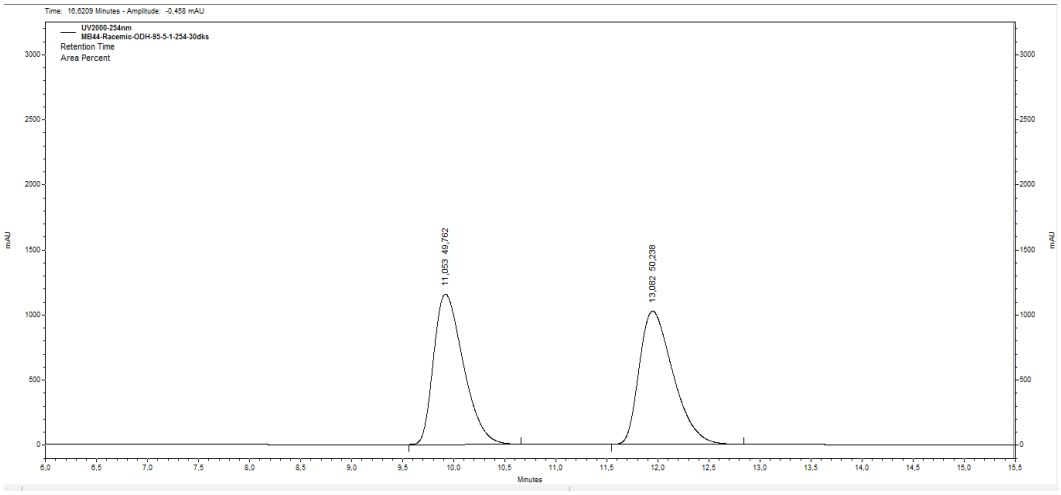




*Figure 0.31.* HPLC Chromatogram of *racemic* (36aa)

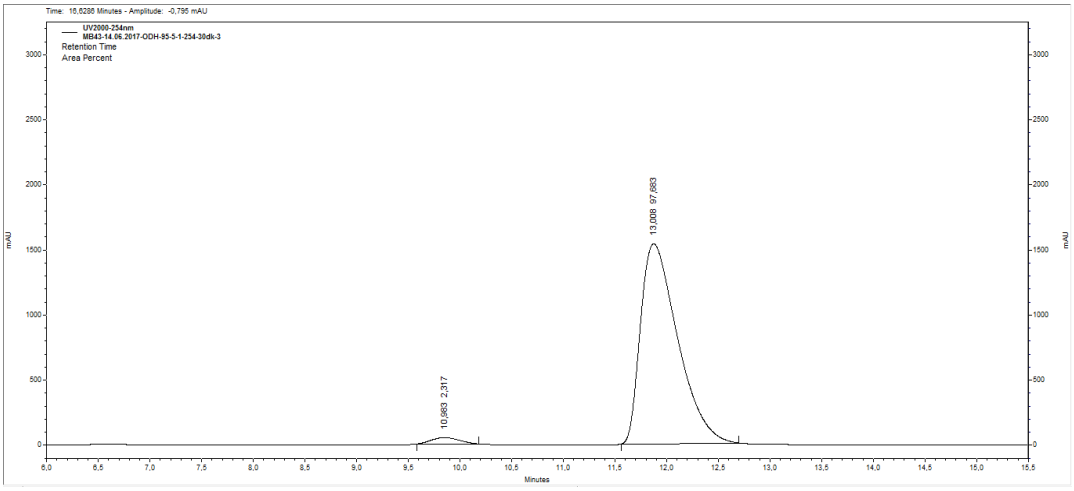
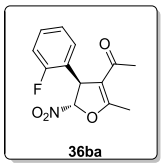



*Figure 0.32.* HPLC Chromatogram of *chiral* (36aa)




**36ba**

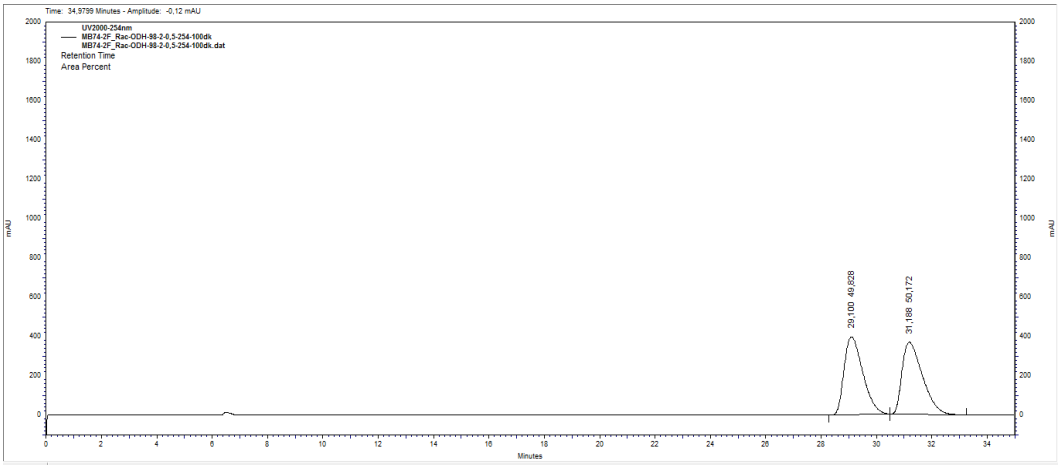



*Figure 0.33.* HPLC Chromatogram of *racemic* (36ba)

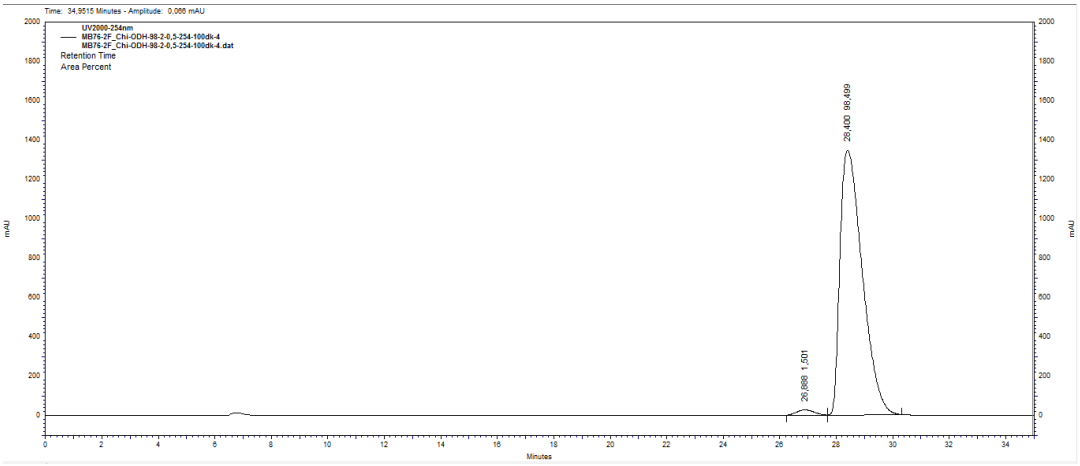
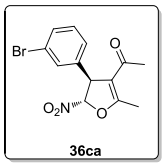



*Figure 0.34.* HPLC Chromatogram of *chiral* (36ba)



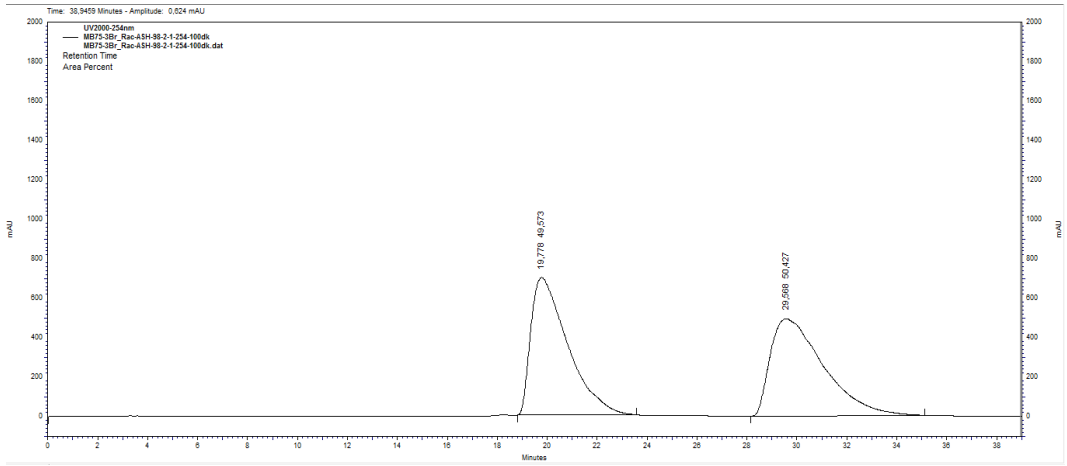




*Figure 0.35.* HPLC Chromatogram of *racemic* (36ca)

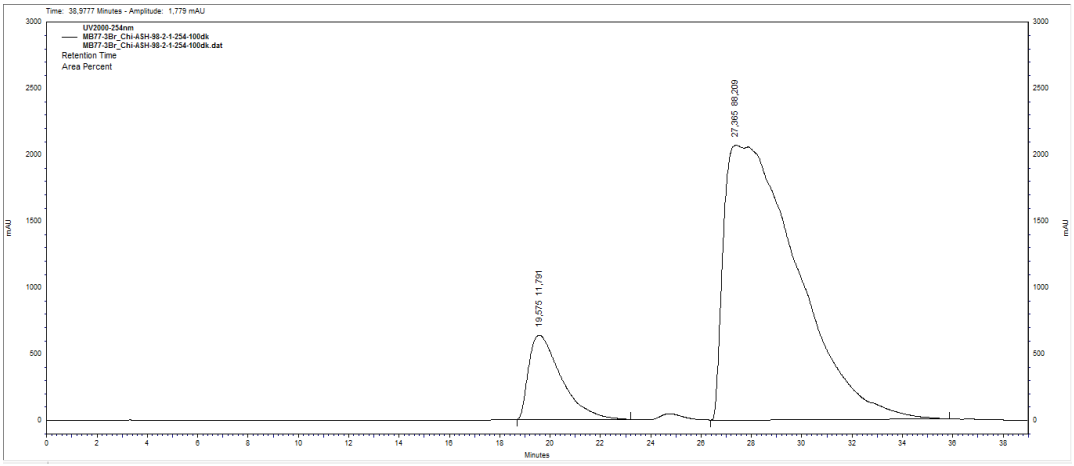
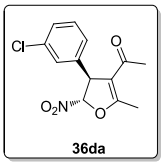



*Figure 0.36.* HPLC Chromatogram of *chiral* (36ca)




**36da**

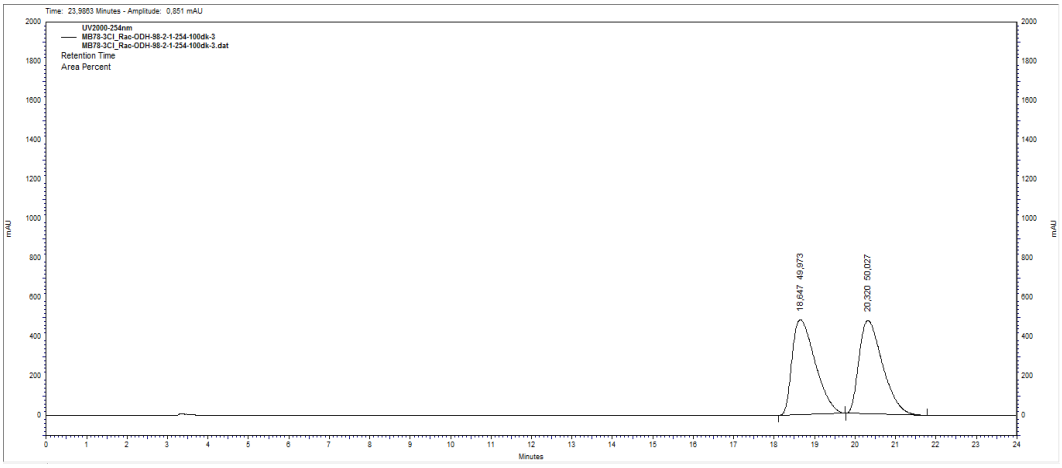



*Figure 0.37.* HPLC Chromatogram of *racemic* (36da)

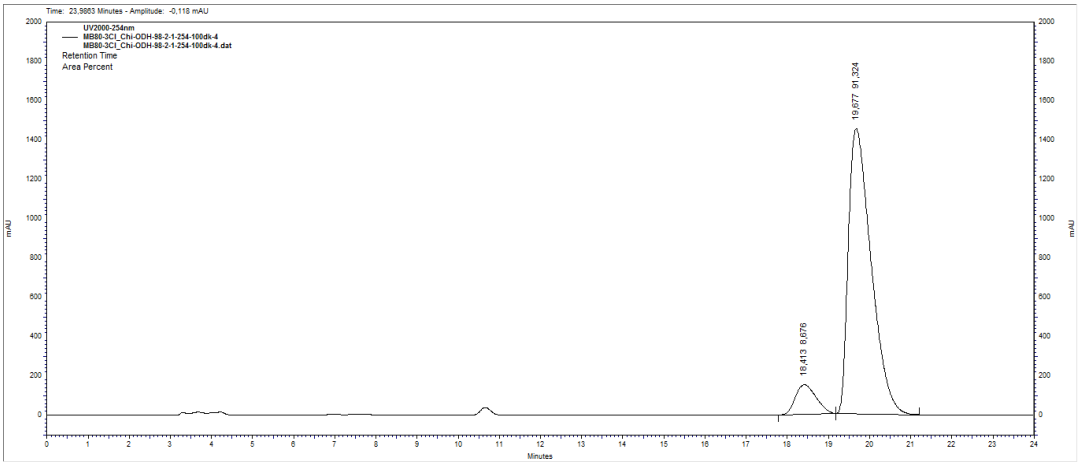
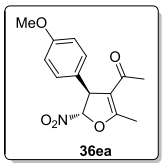



*Figure 0.38.* HPLC Chromatogram of *chiral* (36da)



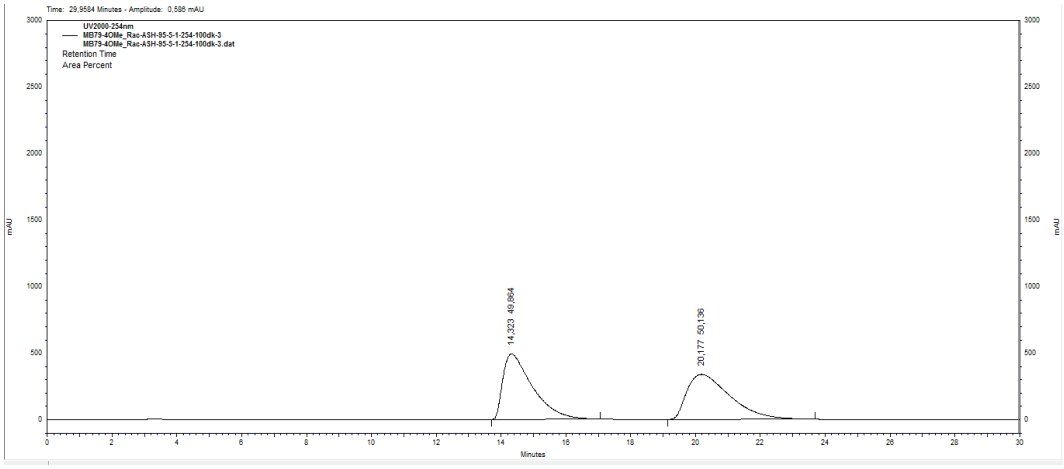




*Figure 0.39.* HPLC Chromatogram of *racemic* (36ea)

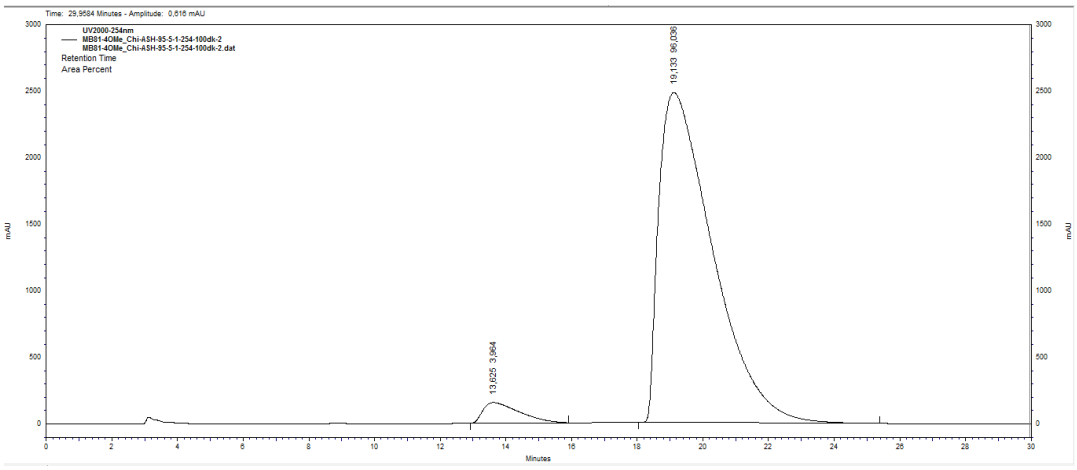
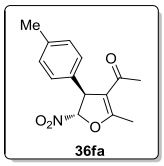



*Figure 0.40.* HPLC Chromatogram of *chiral* (36ea)



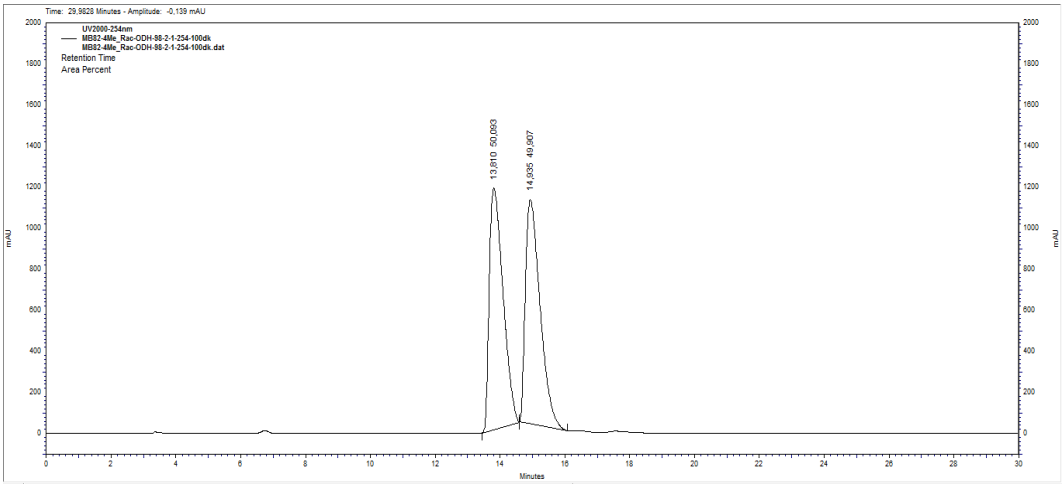




*Figure 0.41.* HPLC Chromatogram of *racemic* (36fa)

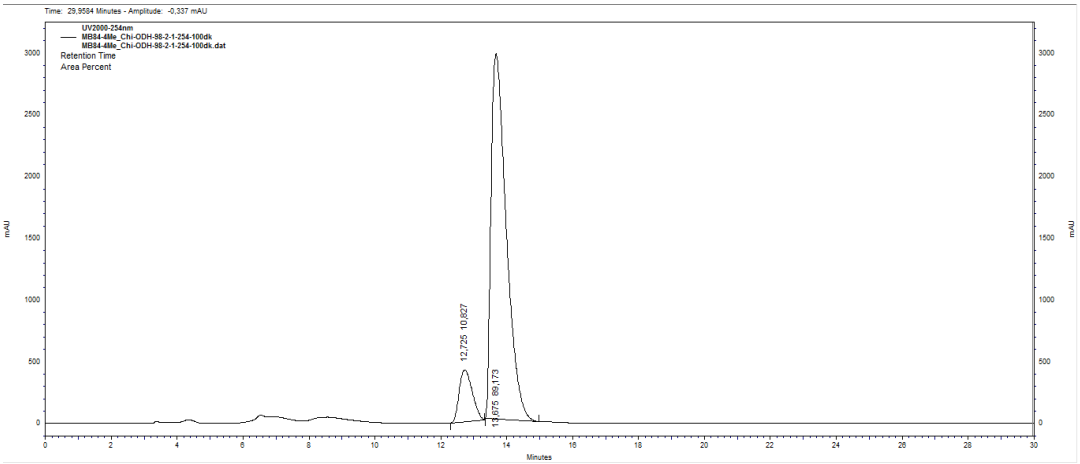
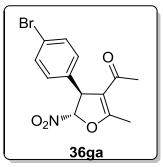



*Figure 0.42.* HPLC Chromatogram of *chiral* (36fa)



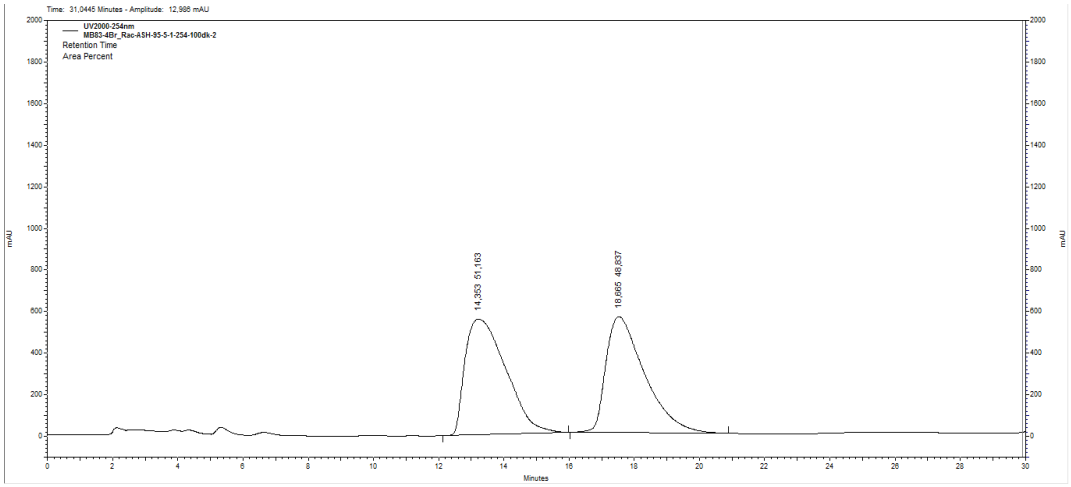




*Figure 0.43.* HPLC Chromatogram of *racemic* (36ga)

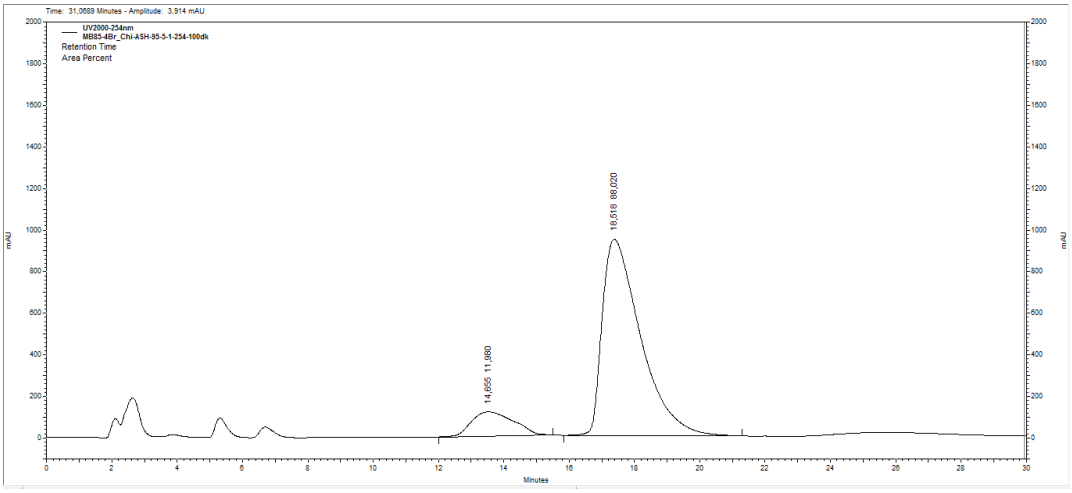
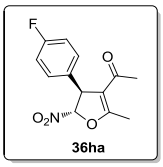



*Figure 0.44.* HPLC Chromatogram of *chiral* (36ga)



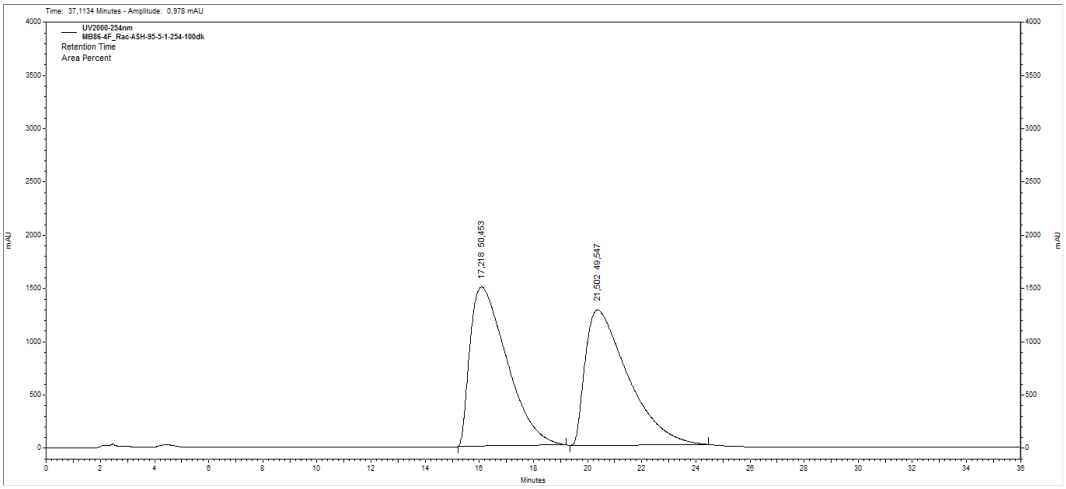




*Figure 0.45.* HPLC Chromatogram of *racemic* (36ha)

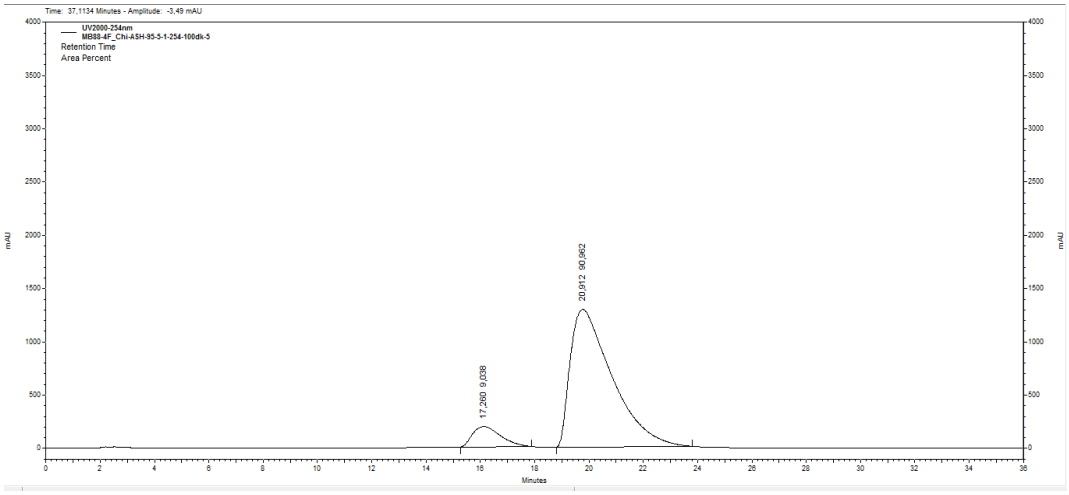
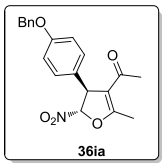



*Figure 0.46.* HPLC Chromatogram of *chiral* (36ha)




**36ia**

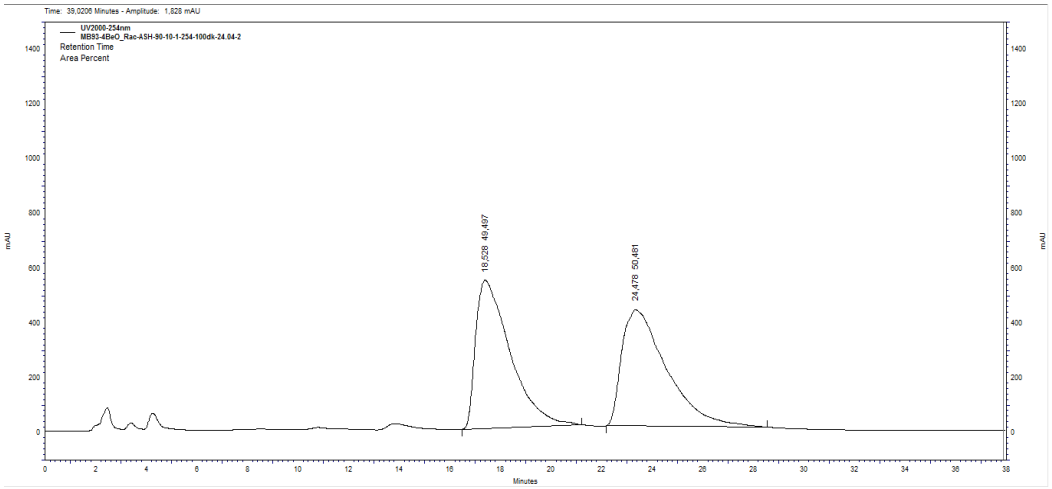



*Figure 0.47.* HPLC Chromatogram of *racemic* (36ia)

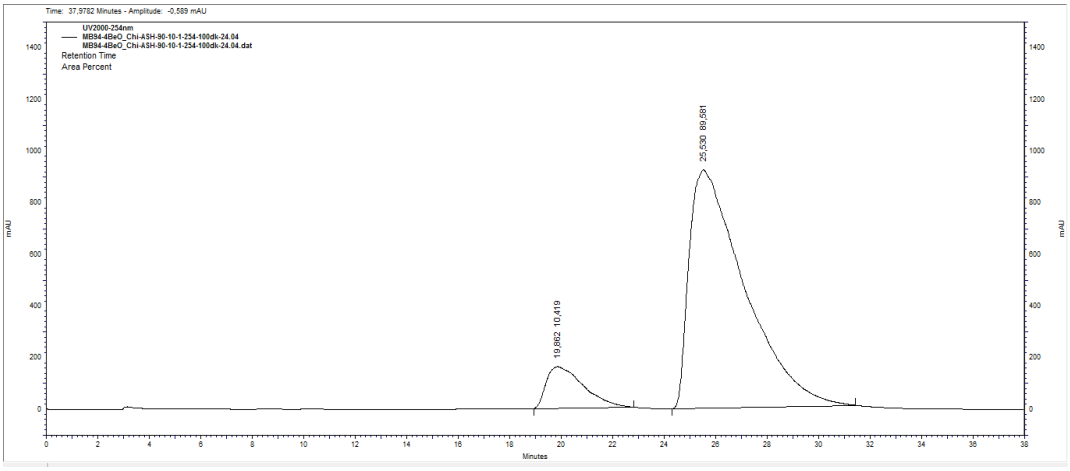
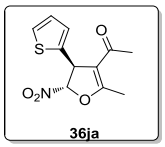



*Figure 0.48.* HPLC Chromatogram of *chiral* (36ia)




**36ja**

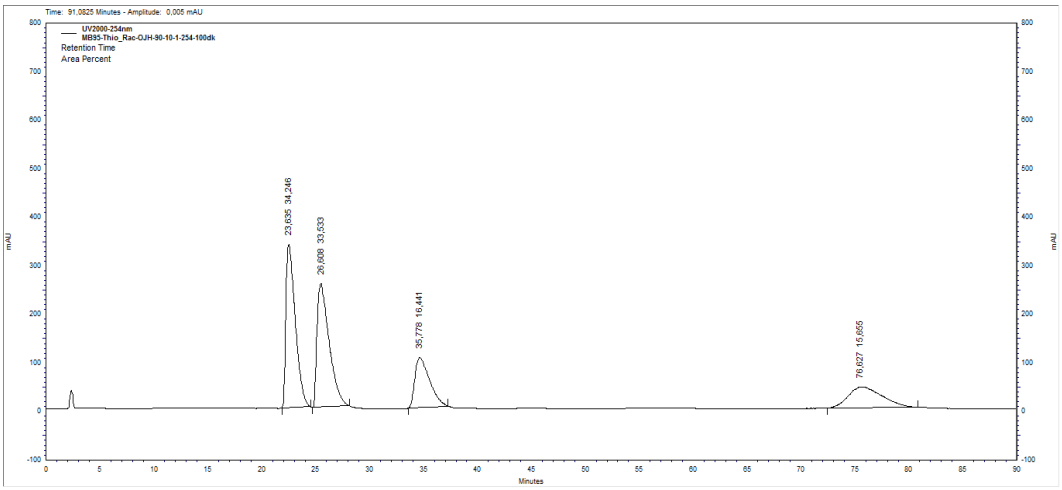



*Figure 0.49.* HPLC Chromatogram of *racemic* (36ja)

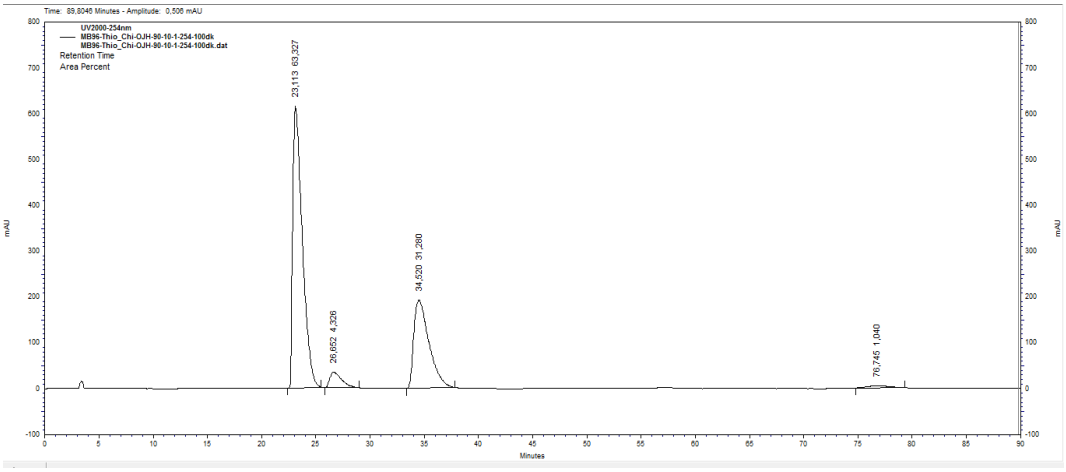
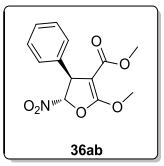



*Figure 0.50.* HPLC Chromatogram of *chiral* (36ja)



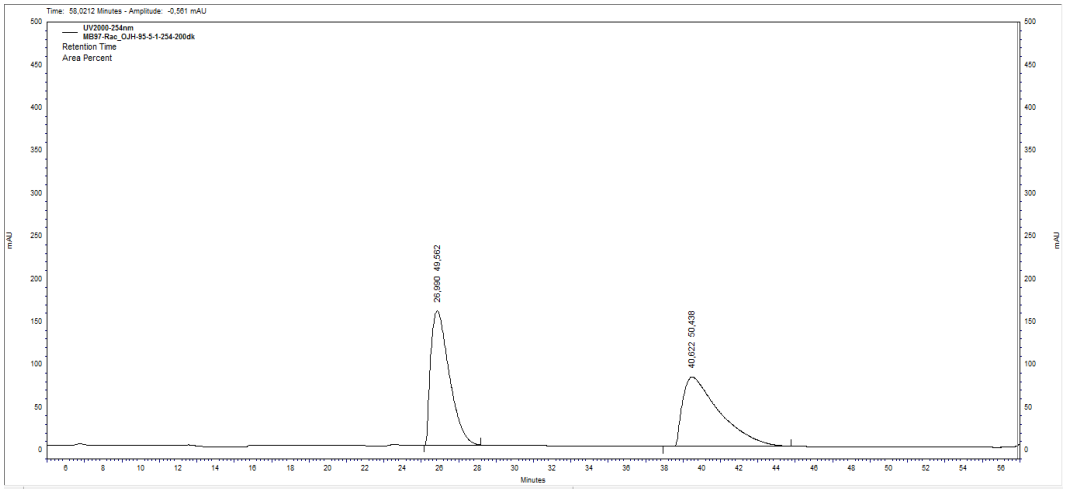




*Figure 0.51.* HPLC Chromatogram of *racemic* (36ab)

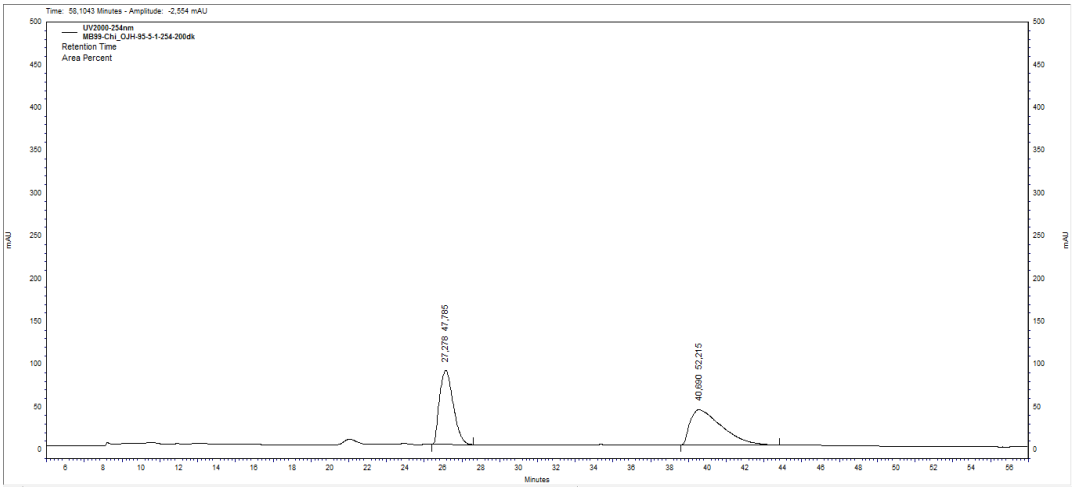
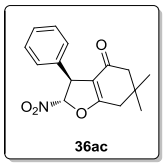



*Figure 0.52.* HPLC Chromatogram of *chiral* (36ab)



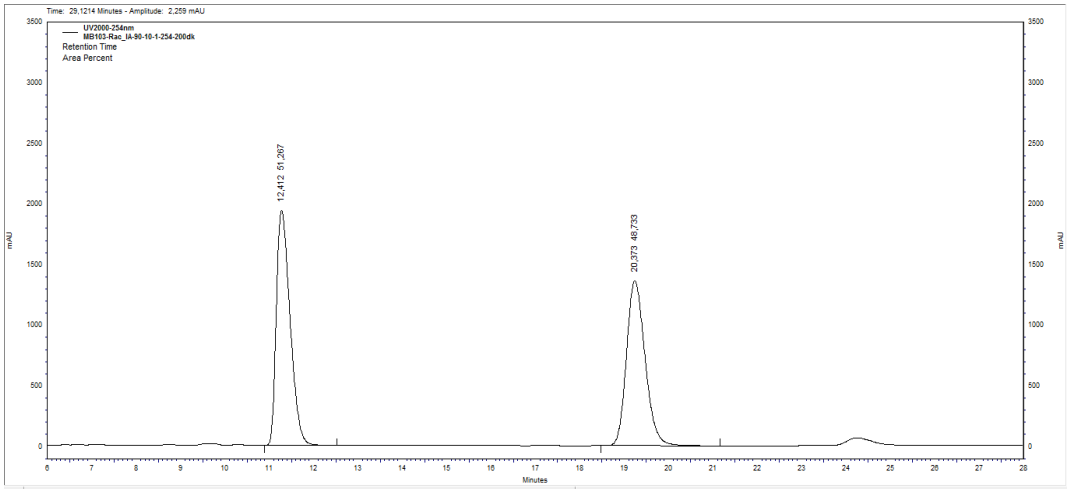




*Figure 0.53.* HPLC Chromatogram of *racemic* (36ac)

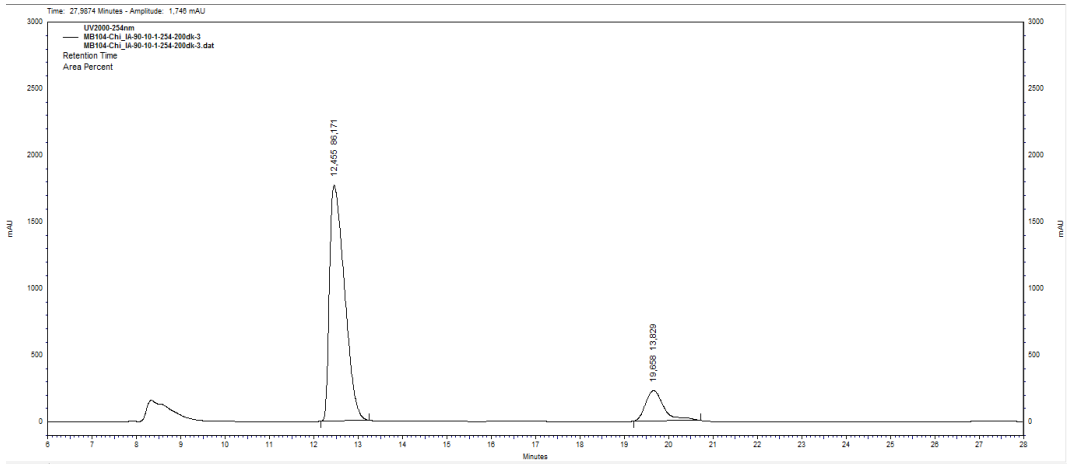
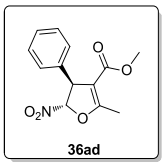



*Figure 0.54.* HPLC Chromatogram of *chiral* (36ac)




36ad

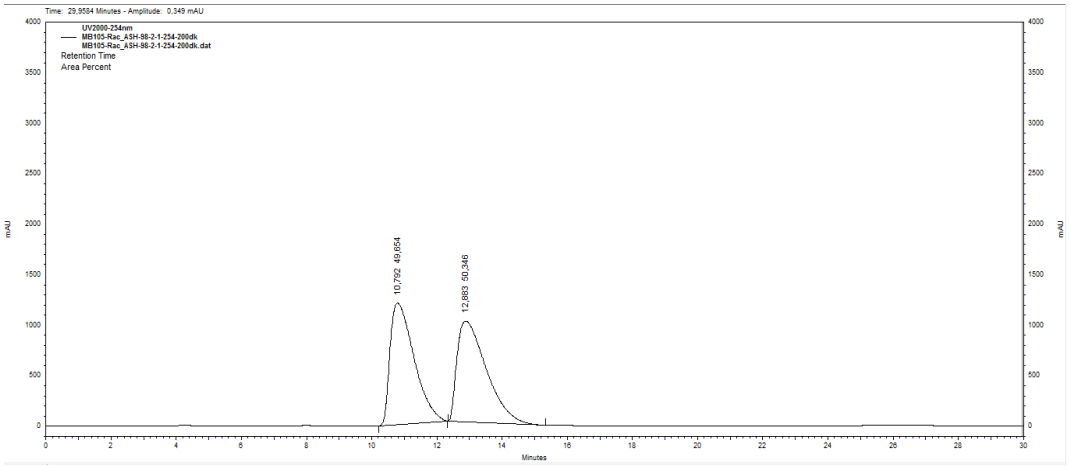



*Figure 0.55.* HPLC Chromatogram of *racemic* (36ad)

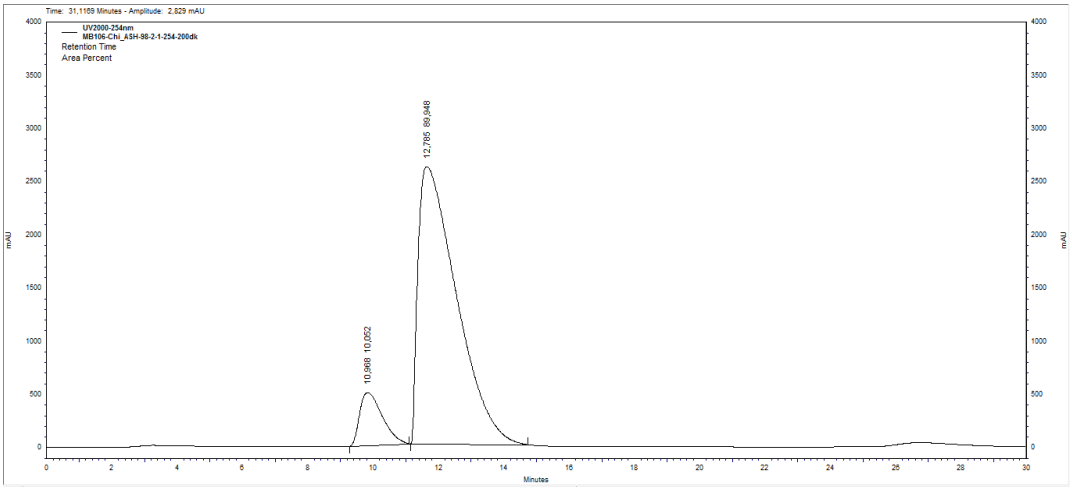
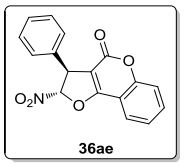



*Figure 0.56.* HPLC Chromatogram of *chiral* (36ad)



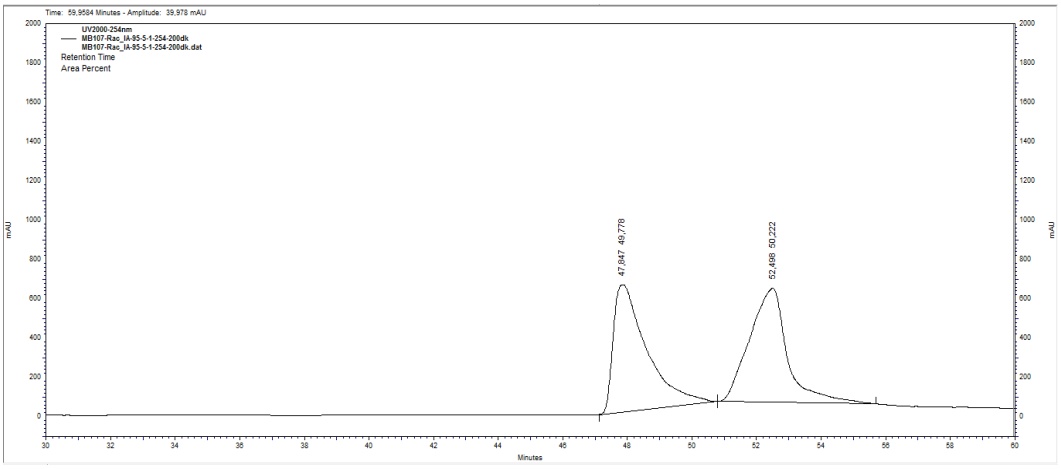




*Figure 0.57.* HPLC Chromatogram of *racemic* (36ae)

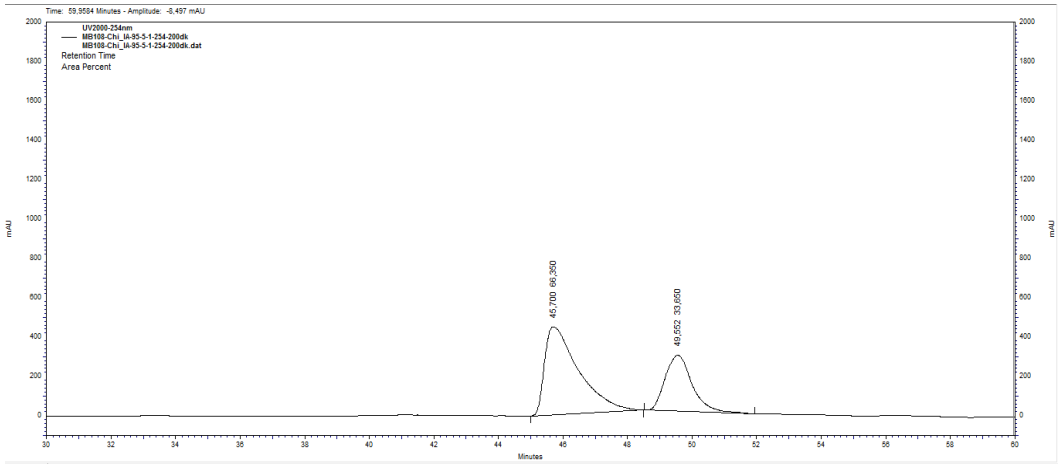



*Figure 0.58.* HPLC Chromatogram of *chiral* (36ae)