ENANTIOSELECTIVE DECARBOXYLATIVE MICHAEL AND ALDOL REACTIONS WITH BIFUNCTIONAL SQUARAMIDE ORGANOCATALYSTS

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ABSTRACT

ENANTIOSELECTIVE DECARBOXYLATIVE MICHAEL AND ALDOL REACTIONS WITH BIFUNCTIONAL SQUARAMIDE ORGANOCATALYSTS

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June 2018, 85 pages

The decarboxylative Michael and aldol reactions are quite new in the asymmetric studies and are used for forming new C-C bonds by nucleophilic attack. In the first part of this thesis, decarboxylative Michael reaction of isatylidene malononitriles with ethyl benzoyl acetate was accomplished in the presence of chiral 2-aminoDMAP and quinine derived bifunctional acid/base organocatalysts, which are developed in our research group. In this part, 12 derivatives were synthesized with quinine based 1-adamantyl squaramide bifunctional organocatalyst up to 46% ee under the optimized condition with 10 mol% catalysts loading at -20 °C.

In the second part, the enantioselective decarboxylative aldol reactions of α-amidohemimalonates with various aldehydes were accomplished in the presence of the organocatalysts developed in our research group. In this part, the best result was achieved with 10 mol% *t*-butyl squaramide quinine organocatalyst as 63% ee.

Keywords: asymmetric synthesis, organocatalysis, enantioselectivity, decarboxylative, Michael, aldol

ÖZ

BİFONKSİYONEL SKUARAMİT ORGANOKATALİZÖRLER İLE ENANTİYOSEÇİCİ DEKARBOKSİLATİF MICHAEL VE ALDOL REAKSİYONLARI

Bayer, Ezgi
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli
Temmuz 2018, 85 sayfa

Dekarboksilatif Michael ve aldol tepkimeleri, asimetrik çalışmalarda oldukça yenidir ve nükleofilik saldırı ile yeni C-C bağları oluşturmak için kullanılır. Bu tezin ilk kısmında, araştırma grubumuzda geliştirilen çeşitli kiral 2-aminoDMAP ve kinin temelli bifonksiyonel asit/baz organokatalizörler eşliğinde isatiliden malononitrillerin etil benzoil asetatlar ile enantiyoseçici dekarboksilatif Michael tepkimeleri çalışılmıştır. Bu kısımda, grubumuzda sentezlenen kinin temelli 1-adamantil skuaramit bifonksiyonel organokatalizör yardımıyla, %10 mol miktarında ve –20 °C de optimize edilmiş koşul ile %46 enantiyoseçiciliklere kadar 12 türev sentezlenmiştir.

İkinci kısımda, araştırma grubumuzda geliştirilen organokatalizörler eşliğinde α-amidohemimalonatların çeşitli aldehitlerle enantiyoseçici dekarboksilatif aldol tepkimeleri çalışılmıştır. Bu kısımda en iyi sonuç *t*-bütil skuaramit kinin organokatalizörü ile %63 enantiyoseçicilikle elde edilmiştir.

Anahtar Kelimeler: asimetrik sentez, organokataliz, enantiyoseçicilik, dekarboksilatif, Michael, aldol

To My Dear Family

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LIST OF ABBREVIATIONS

BINOL : 1,1'-Bi-2-Naphtol

Cs_2CO_3 : Cesium Carbonate

DBU : 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCE : 1,2-Dichloroethane

DCM : Dichloromethane

DMAP : 4-Dimethylaminopyridine

dr : Diastereomeric Ratio

ee : Enantiomeric Excess

Et_2O : Diethyl Ether

Et_3N : Triethylamine

HPLC : High Performance Liquid Chromatography

HRMS : High Resolution Mass Spectroscopy

IR : Infrared Spectroscopy

LUMO : Lowest Unoccupied Molecular Orbital

MAHO : Malonic Acid Half Oxyester

MeOH : Methanol

NMR : Nuclear Magnetic Resonance

THF : Tetrahydrofuran

CHAPTER 1

INTRODUCTION

1.1 Asymmetric Synthesis

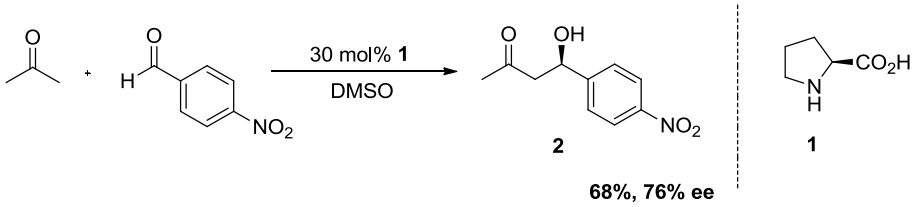
In 1848, Louis Pasteur discovered chirality by examining tartaric acid, which is produced from grapes. He obtained two types of crystals and they rotate polarized light in different directions.[1] In 1857, he explored that the sample containing equal number of right and left handed molecules does not rotate light and it is optically inactive. After all observation, Pasteur stated that 'The universe is chiral'.[2] Chirality which is widespread from spinal galaxies to DNA helix is found in natural and bioactive products. Chirality plays a significant role in chemical synthesis. Chiral molecules have their mirror images non-superimposable and those molecules are named as enantiomers, which are different substances. Although their physical properties are the same, their chemical properties and biological activities are absolutely different. While one of them can be used to treat a disease, the other one can be toxic. For example, in 1957, thalidomide was produced as sedative drug to treat morning sickness in pregnant women. However, after few years, many infants died and most of them were born with some genetic disorder. It turned out that the (*R*)-enantiomer is sedative but the (*S*)-isomer has teratogenic effects. So, enantiomers must be regarded as different compounds due to their different pharmacological activities.[3] Asymmetric synthesis is one of the most important methods to eliminate the unwanted consequences which are emphasized above. Research on this topic has been increasing day by day. In asymmetric synthesis, prochiral units are intended to be transformed into chiral units in enantiomerically pure form.[4] The methods to do so are summarized below.

1.2 Organocatalysis

There are three independent synthetic tools used to form enantiomerically pure substances, namely metal catalysis, biocatalysis and organocatalysis.[5] Organocatalysts are small pure metal-free molecules and used to activate the electrophile or nucleophile for asymmetric transformations.[6] Organocatalysis has several advantages compared to others. They are less expensive, the procedures are relatively non-toxic and the waste is reduced by avoiding the use of large amount of solvents. In addition, they can be used under mild conditions and it is not necessary to use inert atmosphere due to their air and moisture stability.[7] Considering these advantages, the rapid growth in the organocatalytic research is already expected.

1.2.1 Classification of Organocatalysts

Organocatalysts are divided into two categories according to their interaction with the substrate as covalent and noncovalent organocatalysis by Berkesel and Gröger.[8] A new covalent bond is created between catalyst and substrate in covalent organocatalysis. As a good example of covalent organocatalysis, proline **1** catalyzed direct asymmetric intermolecular aldol reaction of acetone with β-nitrobenzaldehyde afforded β-hydroxyketo aldol product **2** with 68% yield and 76% ee. The work was published by List in 2000 (Scheme 1).[9]



Scheme 1. Proline **1** catalyzed direct asymmetric aldol reactions by List *et al.*

Initially, the acetone reacts with proline's nitrogen atom and forms iminium ion **3** via dehydration. Then the iminium ion loses a proton and is converted to the enamine **4** which subsequently reacts with aldehyde (Figure 1). According to proposed mechanism, initially enamine **4**, which is a more reactive nucleophile than the

acetone reacts with aldehyde. Finally, the proline organocatalyst is removed from the aldol intermediate by hydrolysis.

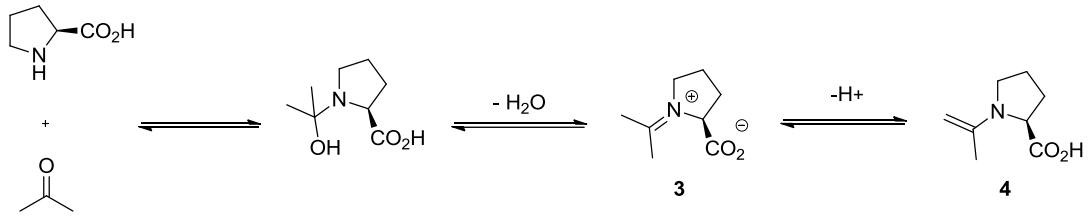


Figure 1. Formation of enamine intermediate

In the noncovalent interaction, hydrogen bonds are formed between an organocatalyst and a substrate. In general, hydrogen bonding activates the electrophile towards a nucleophilic attack.[10]

The coordination of Lewis base part of substrate via *H*-bonds should lower the substrate's LUMO energy level and consequently, can stabilize the transition state complex.[11] Schreiner and Witkopp in 2002 showed the excellent noncovalent effect of thiourea **5** systems via *H*-bonds to activate electrophiles as shown in Figure 2.[12]

In 2008, Rawal and his co-workers have introduced the squaramide motif **6** as a new *H*-donor source in the field of organocatalysis.[13] Rawal *et al*. found that the position of *H*-bond directly influences the stabilization of transition state. They also claimed that the squaric acid moiety **6** provides a larger space than thiourea. The angle of the hydrogens in the squaric acid makes the *H*-bonding more effective in the transition state (Figure 2).[13]

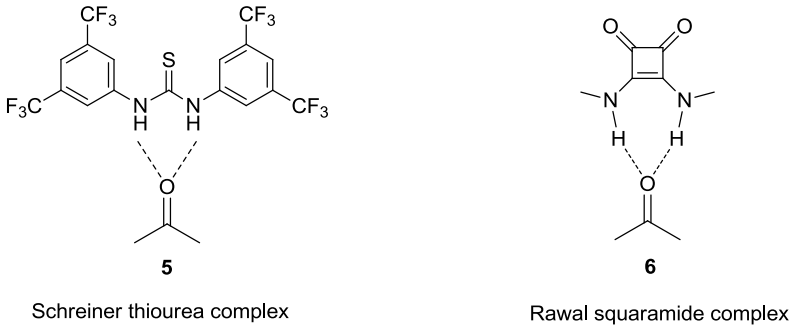


Figure 2. Schreiner thiourea and *N*,*N*'-dimethylsquaramide

Another classification for organocatalysts has been done by List in 2005 based upon the characterization of catalophoric units as Lewis acids, Lewis bases, Brønsted acids or Brønsted bases. The mechanistic classification is restricted due to the lack of knowledge of the activation of the substrates. Nevertheless, the classification assists to organize reaction condition.[14]

The Lewis acid catalyst activates nucleophile via addition of nucleophilic substrate **(S:)**. After the formation of catalyst-substrate complex **(A-S)**, it undergoes reaction with electrophile (**E)**. Product **(P:)** is formed and the catalyst is released for further reaction (Figure 3).[14]

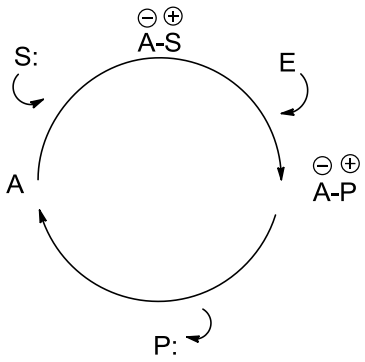
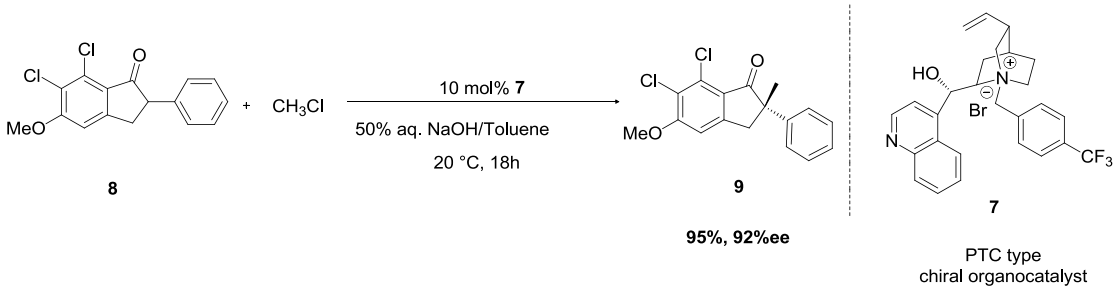


Figure 3. Lewis acid organocatalytic cycle

Phase transfer catalysts, PTC, are considered as Lewis acid type organocatalyst. One of the groups of Merck company performed the first catalytic enantioselective alkylation reaction by a chiral phase transfer catalyst **7**. They carried out α-methylation of indanone derivative with methylchloride **8** catalyzed by 10 mol% *N*-benzyl cinchoninium salt **7** to get compound **9** in 95% yield and 92% ee (Scheme 2).[15]



Scheme 2. The First chiral phase-transfer catalysis by Merck group

Lewis basic organocatalyst activates electrophile via nucleophilic addition to substrate **(S)**. Product **(P)** is formed by nucleophilic attack to activated catalyst-substrate complex. Then catalyst is released in a similar way as in the case of Lewis acid catalyst Lewis base type organocatalysts form iminium ions as intermediates. Due to better reactivity of iminium ion compared to carbonyl substrate, it provides convenience for reaction (Figure 4).[14]

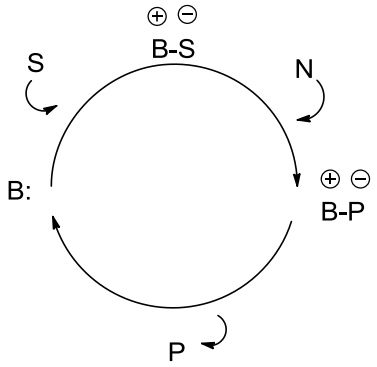
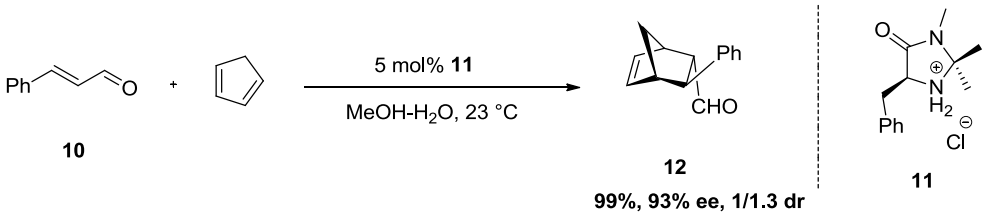


Figure 4. Lewis base organocatalytic cycle

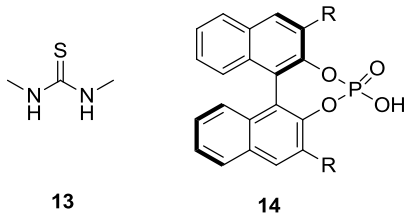
Macmillan submitted the first iminium catalysis example in the literature. In this work, enantioselective Diels-Alder reaction of cinnamaldehyde **10** as dienophile with cyclopentadienes by using 5 mol% chiral imidazolidinone organocatalyst **11** afforded cycloadduct **12** in 99% yield with 93% ee and 1/ 1.3 dr (Scheme 3).[16]



Scheme 3. Organocatalyzed Diels-Alder reaction

Brønsted acid catalysts can be classified as general acid catalysts and specific acid catalysts. In general acid catalyst, *H*-bond formation activates substrate to react with nucleophile. Thiourea derivative **13** is an example to general acid catalysts. In specific acid catalyst, catalyst partially protonates substrate and activates it for the

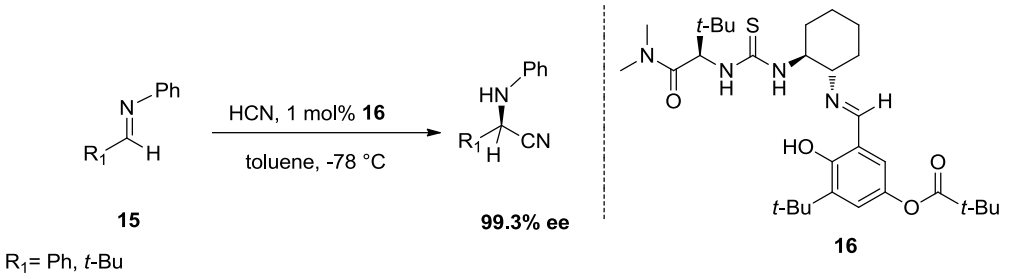
reaction. BINOL phosphate **14**, a phosphoric acid derivative, is an example for specific acid catalysts (Figure 5).[17]



13 **14**

Figure 5. Thiourea and BINOL phosphate

As an example to general acid catalysis, Jacobsen and his co-workers reported enantioselective Strecker reactions in 2002. In Strecker reaction of *N*-benzylideneaniline **15** with HCN by using thiourea organocatalyst derivative **16**, they obtained 99% ee (Scheme 4).[18]

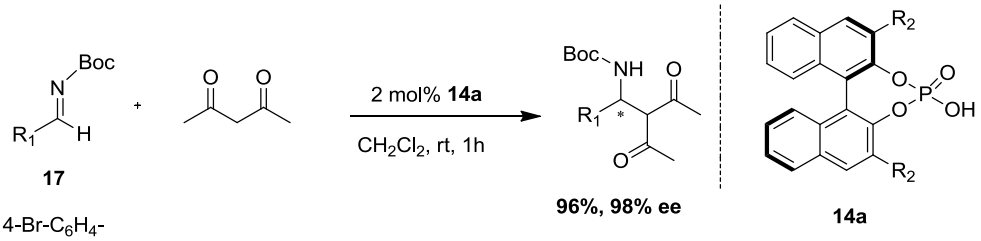


15 **99.3% ee** **16**

R_1= Ph, *t*-Bu

Scheme 4. General Brønsted acid catalysis

Terada and Uraguchi performed direct Mannich reaction with *N*-Boc-protected aldimines **17** and acetyl acetone using phosphoric acid derivatives **14** (Scheme 5).[19] They obtained quite good results as 96% yield and 98% ee in optimized condition.

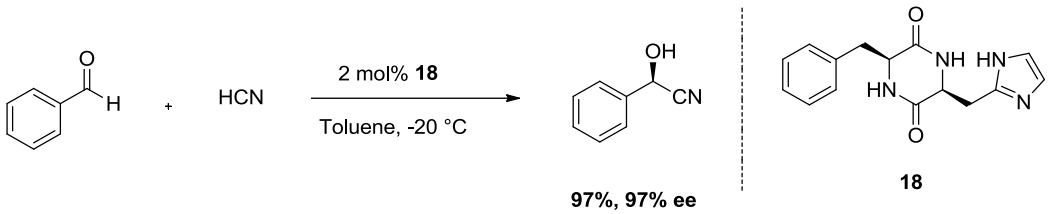


17 **96%, 98% ee** **14a**

R_1= 4-Br-C_6H_4-
R_2= 4-(b-Napth)-C_6H_4- **14a**
R_2= H **14b**

Scheme 5. Specific Brønsted acid catalysis

Brønsted base catalyst partially deprotonates nucleophile to trigger the reaction.[17] For instance, in 1990, HCN addition to various aldehyde by cyclopeptide **18** as a Brønsted base catalyst was carried out by Inoue and his co-workers (Scheme 6).[20]



Scheme 6. Brønsted base catalysis

Nitrogen on the cyclopeptide activates electrophile by hydrogen bonding and nitrogen atom on imidazole group deprotonates the hydrogen atom on HCN to form cyanide ion. Then the cyanide ion reacts with carbonyl carbon of the electrophile (Figure 6). In other words, using Brønsted base catalyst not only speeds up the reaction, but it also provides improvement in the yield and high enantioselectivity.

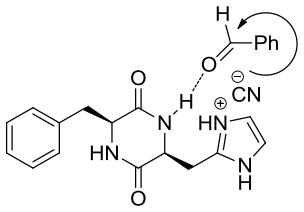


Figure 6. Possible transition state of Brønsted base catalyst and substrates

1.2.2 Cinchona Alkaloids as Asymmetric Catalysts

Cinchona alkaloids are extracted from cinchona genus trees. The main components of the extract are quinine (QN) **19**, quinidine (QD) **20**, cinchonine (CN) **21**, and cinchonidine (CD) **22** which have broad biological activities. To mention the structural characteristics of cinchona alkaloids, they have low molecular weight and contain 5 stereogenic centers. Moreover, they have a quinuclidine unit, a vinyl group, a secondary alcohol and a quinoline ring. While quinine (QN) **19** and quinidine (QD) **20** are substituted by methoxy group at C_6 position, cinchonine (CN) **21**, and

cinchonidine (CD) **22** are unsubstituted (Figure 7).[21] The cinchona alkaloids are used as diagnostic and therapeutic agents and food additives. In addition, they have a major role in the field of asymmetric organocatalysis. The richness of the reactive group contributes to adjusting them as proper catalyst for desired reactions.[21]

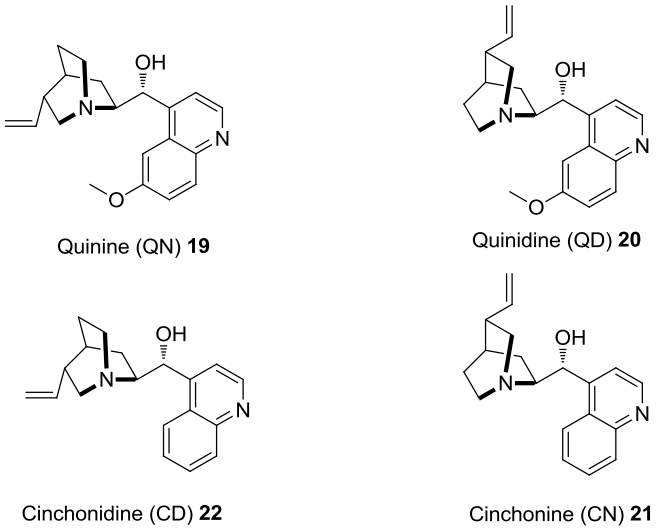
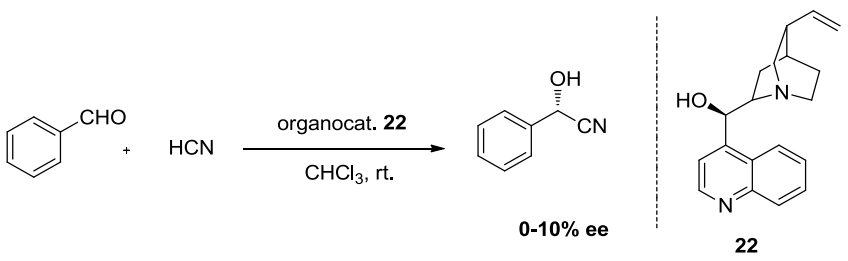


Figure 7. The structure of cinchona alkaloids

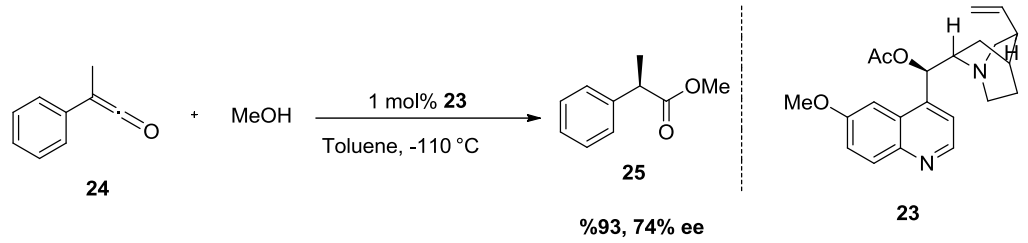
Cinchona alkaloids can easily be considered as Lewis or Brønsted base due to the deprotonation ability of nitrogen on the quinuclidine ring. Also, C_9-hydroxyl group and C_6-methoxy group of quinine **19** and quinidine **20** have hydrogen bonding capabilities.[22]

Bredig and Fiske published the first asymmetric reaction accomplished by cinchona alkaloids in 1912. Natural cinchona alkaloid (-)-cinchonidine **22** was tested in the addition reaction of HCN to benzaldehyde resulting 0-10% ee (Scheme 7).[23]



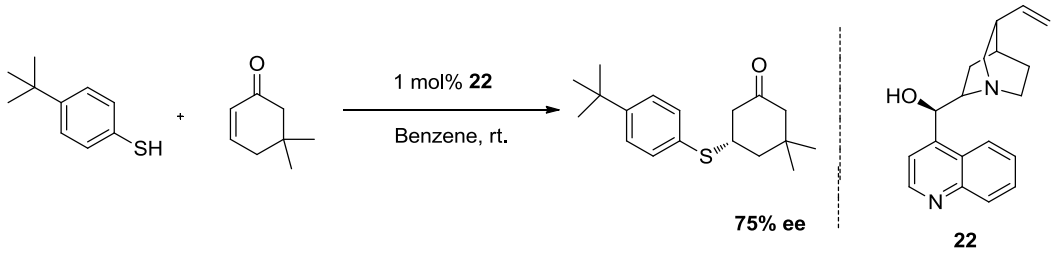
Scheme 7. Cinchonidine catalyzed addition reaction of HCN to benzaldehyde

Then in 1960, Pracejus developed addition reaction of methanol to phenyl methyl ketene **24** by using 1 mol% *O*-acetylquinine **23** affording methyl phenylpropionate **25** with a high enantioselectivity of 74% ee (Scheme 8).[24]



Scheme 8. *O*-acetylquinine catalyzed addition reaction of methanol with phenyl methyl ketene

In 1981, Wynberg and his co-workers investigated the detailed mechanism of asymmetric Michael addition of aromatic thiols with conjugated cycloalkenones by using quinine **19**, quinidine **20**, cinchonine **21** and cinchonidine **22**. They found that cinchonidine **22** gave nearly quantitative yield and 75% ee (Scheme 9).[25]

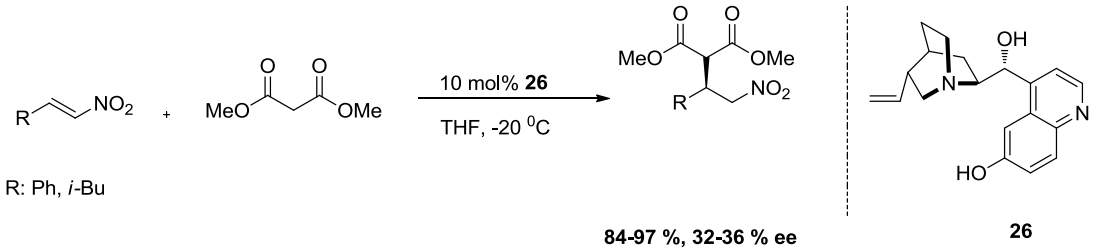


Scheme 9. Michael addition by using cinchonidine

Cinchona alkaloids have become a very popular class of organocatalysts in asymmetric synthesis with the studies of Pracejus[24]and Wynberg[25]. The rate of growth of cinchona alkaloid catalyzed asymmetric reaction was boosted especially after 1990.

In 2004, Deng and co-workers used quinine **19** and quinidine **20** derivatives in catalytic asymmetric Michael addition of malonates to nitroolefins. Methylmalonate was added to aromatic or aliphatic nitrolefins with high enantioselectivity and yield. In this research, 6′-hydroxyquinoline derived cinchona alkaloid catalyst **26** gave

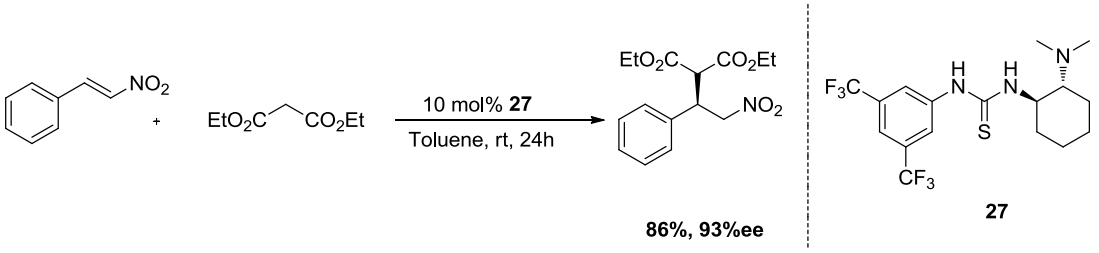
higher enantioselectivity and faster reaction than 6′-methoxyquinoline derived one with 92-96% ee versus 6-24% ee, respectively. The authors concluded that phenolic hydroxy group made the transition state more stable compared to methoxy group since hydroxy group was a hydrogen bond donor (Scheme 10).[26]



Scheme 10. Cinchona alkaloid catalyzed Michael reaction

1.2.3 Chiral Bifunctional Organocatalysts

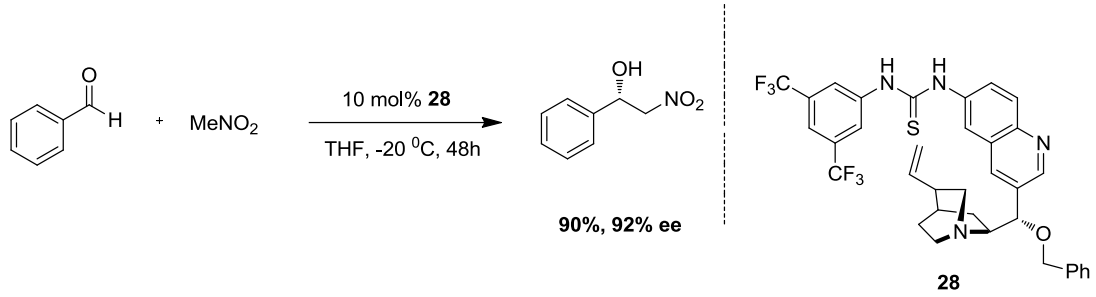
Bifunctional organocatalyst which contains both acidic and basic part all in one unit was firstly introduced in literature by Takemoto and his co-workers in 2003. Michael reaction of malonates with various nitroolefins was investigated by using chiral thiourea catalyst **27** as a bifunctional organocatalyst with high enantioselectivities (Scheme 11).[27] They have chosen cyclohexane *trans*-1,2-diamine as a chiral unit bearing dimethyl functionalize as a basic motif and bis(trifluoromethyl) aniline containing thiourea as the acidic motif. The nucleophile and the electrophile are both activated simultaneously by this new type of bifunctional organocatalyst.



Scheme 11. First bifunctional organocatalytic Michael reaction

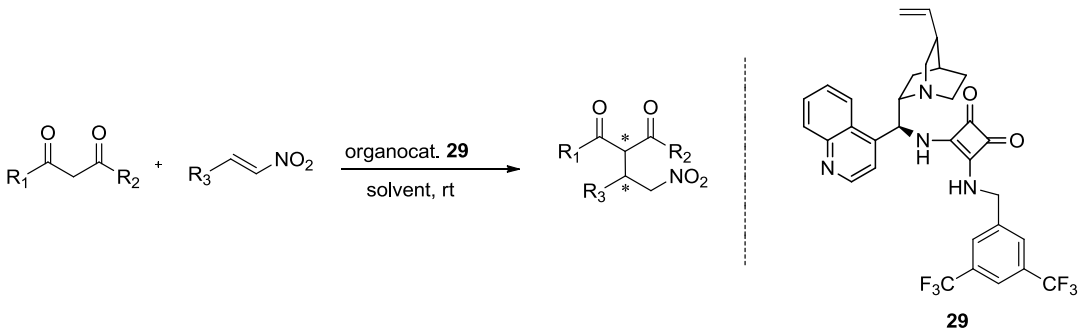
Considering the advantages of bifunctional organocatalyst, many groups begun to work with cinchona alkaloids derived (thio)urea organocatalysts. In 2005, the first

Henry reaction of nitromethane with aldehydes was done by using unmodified cinchona alkaloid catalyst. However, enantioselectivity was 35%, which was not satisfying. After modification of C_6-hydroxyl on cinchona alkaloid to an activated thiourea moiety **28**, the chemical yield and enantioselectivity was enhanced to 90-99% and 85-92% respectively (Scheme 12).[28]



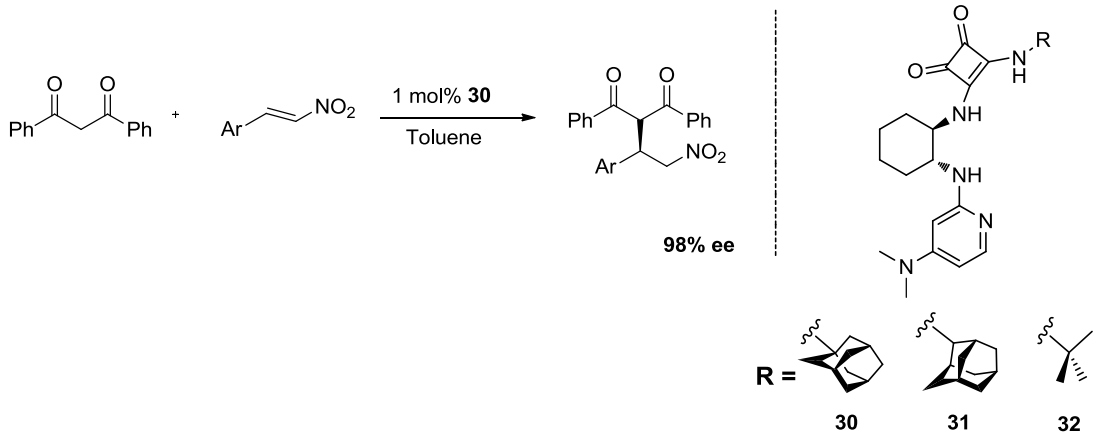
Scheme 12. Henry reaction done with cinchona alkaloids derived thio(urea)

Rawal and his co-workers brought the first cinchona alkaloids derived squaramide catalyst in the literature in 2008.[13] They studied on addition reactions of 1,3-dicarbonyl compounds to nitroolefins by using cinchona alkaloids derived squaramide **29** in high yields and enantioselectivities. The reaction was previously performed by using simple thiourea based organocatalyst. Rawal stated out that squaramide having more effective *H*-bond donor property is able to activate electrophile and also provides larger space for asymmetric induction compared to thiourea (Scheme 13).[13]



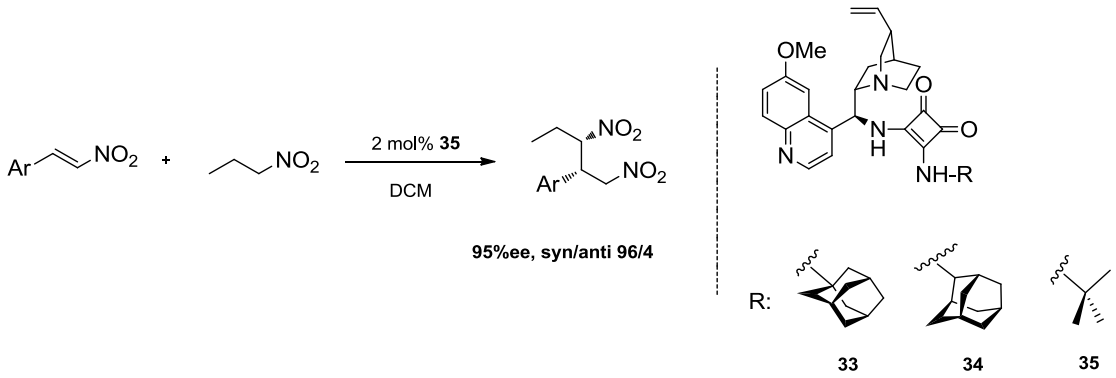
Scheme 13. Cinchona alkaloid derived squaramide catalyzed Michael reaction

In 2014, Tanyeli and his co-workers reported a new chiral bifunctional acid/base organocatalysts, 2-aminoDMAP/squaramides **30**, **31**, and **32**. The new organocatalysts were tested in the conjugate addition of dibenzoylmethane to various *trans*-β-nitroalkenes, in which the squaramide part activates *trans*-β-nitroalkenes and 2-aminoDMAP part stabilizes β-diketonate anion. By using 1 mol% organocatalyst **30**, highly enantiomerically enriched Michael products (up to 98% ee) were obtained in acceptable yield and short reaction duration. The sterically bulked (1-adamantyl) group on the squaramide unit can be considered as a reason for the high enantioselectivity. The results prove that the new chiral bifunctional acid base organocatalysts are highly active as promoters in Michael reaction (Scheme 14).[29]



Scheme 14. 2-aminoDMAP/squaramides in Michael addition

In 2016, the enantioselective Michael addition reactions of 1-nitropropane to various *trans*-β-nitroalkenes were catalyzed by new chiral bifunctional acid/base quinine-based squaramide organocatalysts **33**, **34** and **35**, which were brought to the literature by Kanberoğlu and Tanyeli.[30] In this study, only 2 mol% *t*-butyl squaramide quinine organocatalyst **35** was used to afford the product with excellent enantioselectivity (up to 95% ee) and diastereoselectivity (*syn*/*anti* isomers up to 96:4). The combination of the quinine and sterically bulky squaramide moieties is the reason for being immensely active in the promotion of the conjugate additions of nitroalkanes to nitroalkenes (Scheme 15).[30]

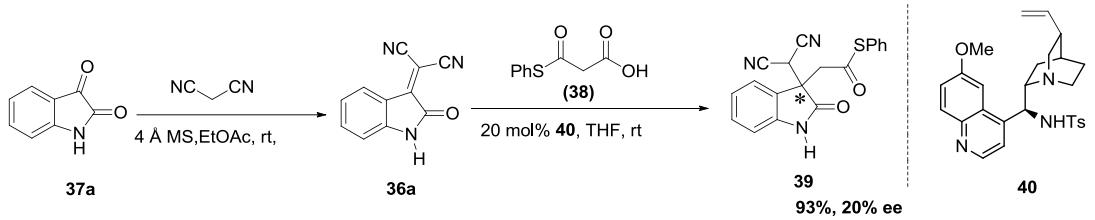


Scheme 15. Bifunctional quinine based squaramides in Michael addition

1.3 Decarboxylative Michael Reactions

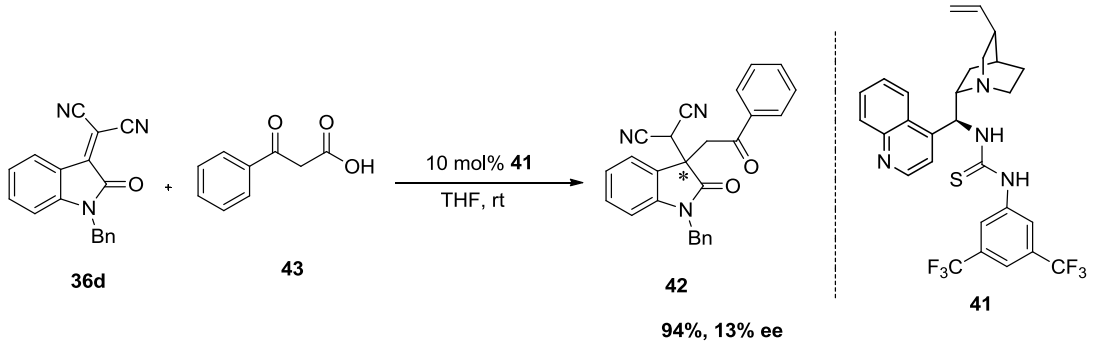
In 1904, Marckward reported the first enantioselective decarboxylative protonation of α-ethyl-α-methylmalonic acid using brucine.[31] However, this reaction failed to be reproduced by Kenyon and his co-workers.[32] This result forced other researchers to study on enantioselective decarboxylative reactions. Decarboxylative Michael reaction is one of the most powerful organic methods used for the formation of C-C bonds, which provide valuable multifunctional molecules in organic chemistry.

In 2016, Yi-Lin Guo reported molecular sieve mediated sequential Knoevenagel condensation/decarboxylative Michael addition reaction. *N-H*-isatylidine malononitrile **36a** obtained by using Knoeveganel condensation of isatin **37a** and malononitrile. Then, subsequent decarboxylative Michael reaction of 3-oxo-3-(phenylthio) propanoic acid **(38)** resulted in compound **39** (Scheme 17).[33] Molecular sieve was used to promote the Knoevenagel condensation and decarboxylative process. They performed the reaction with various cinchona alkaloid organocatalysts. However, they got low enantioselectivities (0-20% ee). They claimed that the chirality of the substance was demanding to control.



Scheme 16. Asymmetric version of decarboxylative addition of 3-oxo-3-(phenylthio) propanoic acid **(38)** to *N*-*H*-isatylidene malononitrile **36a**

In the same year, Chimni and his co-workers performed grinding assisted free decarboxylative C-C bond formation of 3, 3-disubstituted oxindoles. They carried out the solvent-free decarboxylative addition of β-ketoacid to isatylidene malononitrile derivative **36d** catalyzed by DBU in 5 min and 98% yield. They also investigated enantioselectivity by using 10 mol% thiourea and squaramide derived cinchona alkaloids. Their enantiomeric excess results were in the range of 4-13% ee. Thiourea derived cinchonidine **41** gave the best result as 13% ee and 94% yield in this study (Scheme 17).[34]

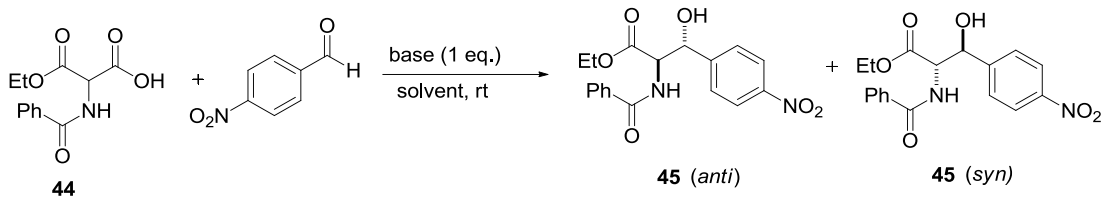


Scheme 17. Asymmetric version of decarboxylative addition of β-ketoacid to *N*-Bn-isatylidene malononitrile **36d**

1.4 Decarboxylative Aldol Reactions

Rouden and his co-workers performed on organic base mediated diastereoselective decarboxylative aldol reaction of benzoamido-MAHO **44** and various aldehydes to synthesize β-hydroxy-α-amino **45** acid. The reaction is significant because β-hydroxy-α-amino acid **45** is a very important building block for many active biological compounds. DMAP showed the best result in THF affording the aldol

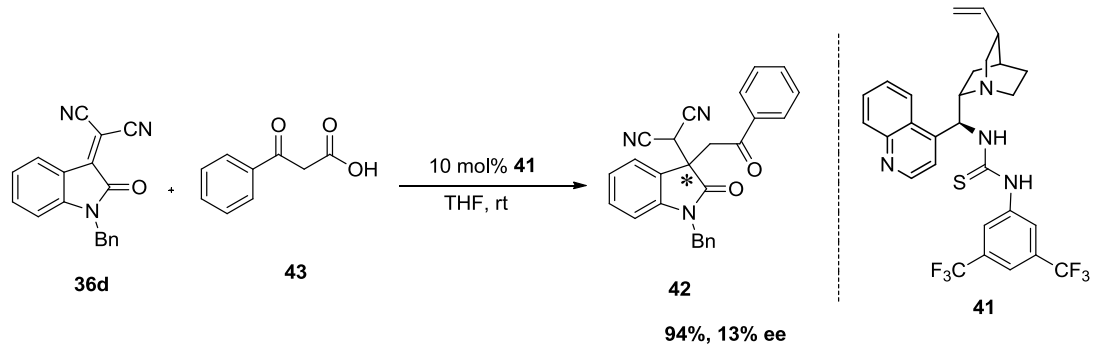
product in 99% yield and 100/0 diastereomeric ratio. The enantioselective version of this reaction was not performed in this article (Scheme 18).[35]



44 **45** (*anti*) **45** (*syn*)

Scheme 18. Synthesis of β-hydroxy-α-amino acids via decarboxylative aldol reaction

We were inspired by Rouden's report and started to work on enantioselective decarboxylative aldol reaction to synthesize β-hydroxy-α-amino acids. While we were working on this reaction, Takemato published the first enantioselective synthesis of *anti*-β-hydroxy-α-amino esters by using organocatalysts. The quinine based organocatalyst **46** and acid additive facilitated the reaction to obtain high yield and high ee. (Scheme 19).[36]



36d **43** **42** **41**

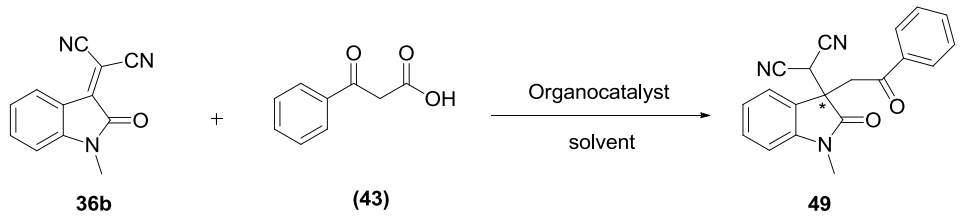
94%, 13% ee

Scheme 19. Enantioselective decarboxylative aldol reaction to synthesize β-hydroxy-α-amino acids

1.5 Aim of the Work

In this thesis, the main goal is to test our research group's novel bifunctional organocatalysts in decarboxylative Michael and aldol reactions and to obtain products with high enantiomeric excess after optimizing the reaction conditions.

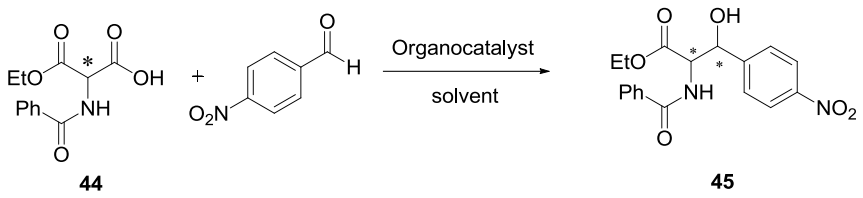
The first part involves the decarboxylative Michael reaction of *N*-Me isatylidine malononitrile **36b** and 3-oxo-3-phenylpropanoic acid **(43)** to get desired product by using quinine and 2-aminoDMAP based squaramide type bifunctional organocatalysts (Scheme 20). 3,3 disubsituted oxindole framework was chosen because it is found in natural products and pharmaceuticals.



Scheme 20. Enantioselective decarboxylative Michael reaction

In this part, we planned to synthesize *N*-Me isatylidene malononitrile **36b** by Knoevenagel condensation. Then, by using chiral organocatalysts, enantioselective decarboxylative Michael reactions of *N*-Me-isatylidine malononitrile **36b** and 3-oxo-3-phenylpropanoic acid **(43)** were aimed to be performed. After determination of optimized condition for this reaction, various *N*-substituted and aromatic core derivatives of isatylidene malononitriles were designed. Then, derivatization studies were intended to improve enantiomerically pure compounds.

The second part of this thesis involves the enantioselective decarboxylative aldol reaction of benzoamido-MAHO **44** and 4-nitrobenzaldehyde to synthesize β-hydroxy-α-amino acid **45**. The target molecule was chosen because it is a significant building block for many biologically active compounds (Scheme 21).



Scheme 21. Enantioselective decarboxylative aldol reaction reaction

Our research group has a wide range of bifunctional organocatalysts. They include two main chiral frameworks as 2-aminoDMAP and quinine type cinchona alkaloid as shown in Figure 8. These organocatalysts will be used in the mentioned reaction.

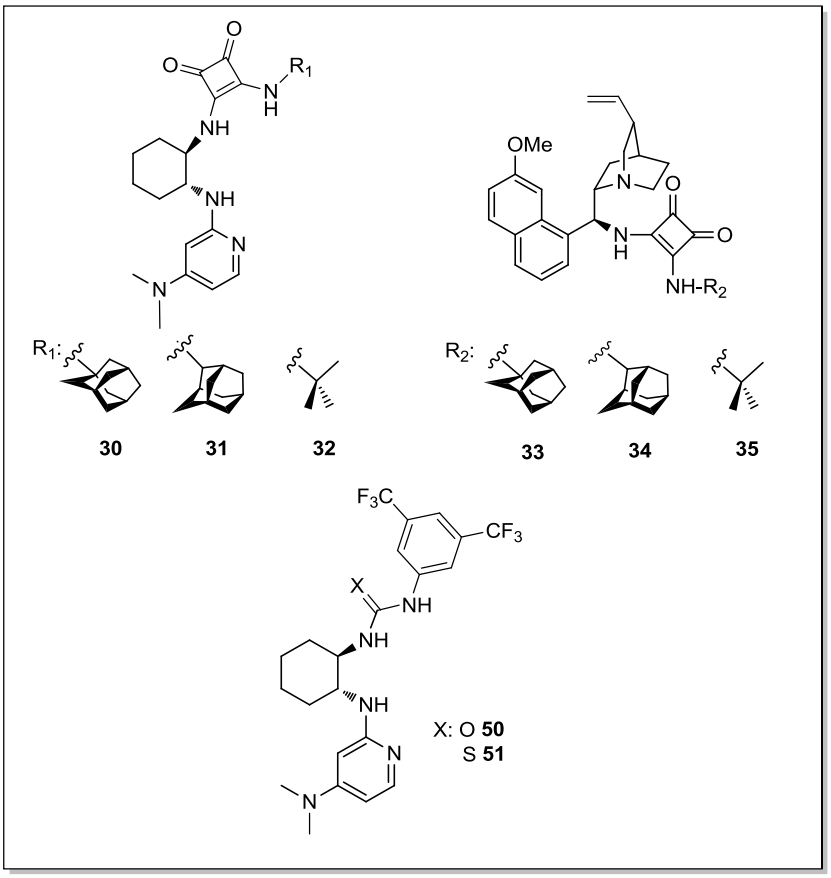


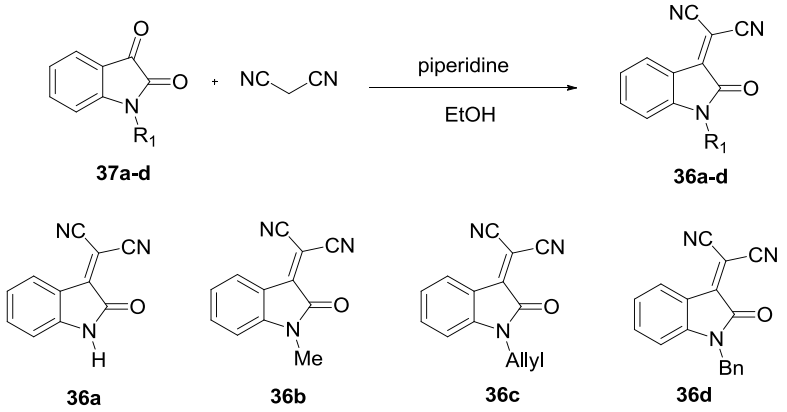
Figure 8. Our research group's bifunctional organocatalysts

CHAPTER 2

RESULTS AND DISCUSSION

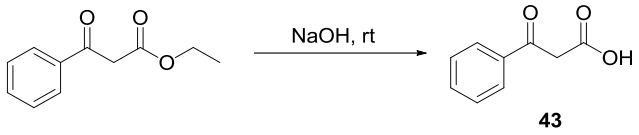
2.1 Synthesis of Isatylidene Malononitrile and Benzoyl Acetic Acid

In the first part of this study, isatylidene malononitrile was synthesized by the Knoevenagel condensation of commercially available isatin **37a** and malononitrile according to literature procedure.[4] 1*H*-indole-2,3-dione, which is commonly known as isatin, is a well-known natural product found in the plant genus isatis. Isatin was first obtained by Erdman and Lourent in 1841 by oxidation of indigo using nitric acid. It has also been isolated as a metabolic derivative of adrenaline in humans. Isatin derivatives also have various important biological activities such as being an antibacterial and antitubercular agent.[37] Considering all the advantages of isatin **37a**, it was chosen as the scaffold of the target products. Isatylidene malononitrile was synthesized according to the procedure given in the experimental part. In the beginning of the reaction, piperidine was chosen to deprotonate the activated methylene and subsequently form an enolate intermediate which attacks to the C_3-carbonyl of the isatin. After dehydration, the isatylidene malononitrile **36a** was obtained with high yield (93% up to full conversion). Spectroscopic data of isatylidene malononitrile **36a** is in accordance with the literature data (Scheme 22).[4]



Scheme 22. Knoevenagel condensation of isatin with malononitrile

The nucleophilic benzoylacetic acid **(43)** was synthesized by simple ester hydrolysis procedure starting with ethyl benzoylacetate. (Scheme 23).[2]



43

Scheme 23. Synthesis of benzoylacetic acid

2.2 Synthesis of 2-(1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl) Malononitrile via Decarboxylative Michael Reaction

As reported by Guo[33] in 2017 and Chimni[34] in 2017, the decarboxylative Michael reactions of isatylidene malononitriles and β-ketoacids in the presence of base catalyst were known in literature. In those studies, although they also investigated the asymmetric version of decarboxylative Michael reaction, they found very low ee values as 13% and 20%, respectively. Because of demanding enantioselectivities in this field, we intended to get highly enantiomerically enriched product. The racemic form of compound **49** used as reference was synthesized under basic conditions using Et_3N at rt in just 5 min with excellent chemical yield (>99%) as depicted in Scheme 24.

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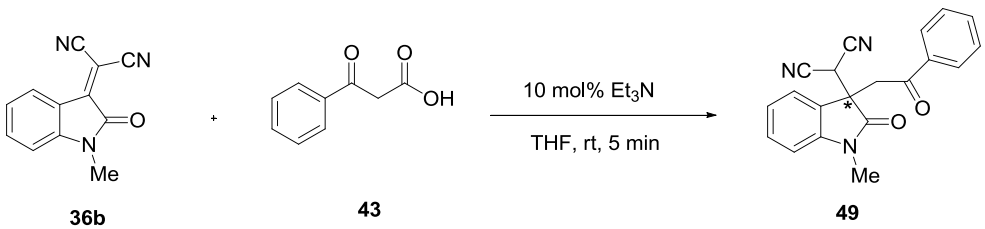


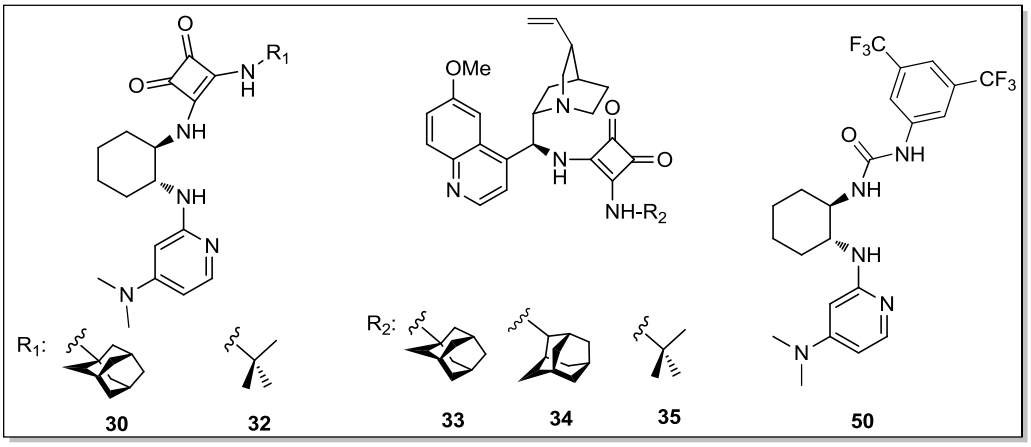
36b **43** **49**

Scheme 24. Synthesis of racemic compound **49**

2.2.1 Optimization Studies for the Asymmetric Decarboxylative Michael Reaction

The decarboxylative Michael reaction has been initiated with the bifunctional organocatalysts, which are developed in our research group. The bifunctional organocatalysts involve 2-aminoDMAP **30**, **32** and three different chiral quinine based **33**, **34** squaramide and 2-aminoDMAP based (thio)urea **50**. 3-oxo-3-phenylpropanoic acid **43** was reacted with *N*-Me-isatylidene malononitrile **36b** in the presence of bifunctional organocatalysts. Parameters which affect the yield and ee were checked and the optimized condition was investigated for the reaction. In order to specify the best bifunctional organocatalyst, all organocatalysts were screened. Initially, 10 mol% catalyst loading were tested with 2.0 M concentration in THF at rt and, 1 eq. *N*-Me isatylidine malononitrile **36b** and 1.2 eq. 3-oxo-3-phenylpropanoic acid **43** were used (Scheme 24).

Table 1. Catalyst screening results

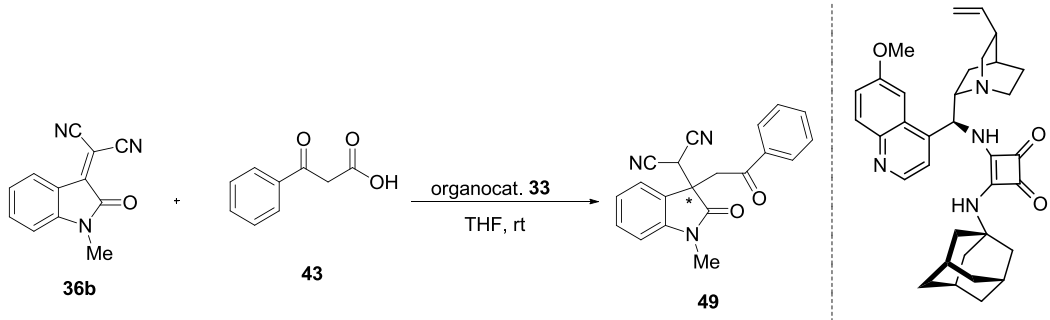


Entry[a]	Catalyst	Time (min)	Yield[b] (%)	ee[c] (%)
1	35	90	94	29
2	**33**	**55**	**>99**	**40**
3	34	85	93	27
4	50	60	>99	2
5	32	70	92	2
6	30	70	95	4

[a]All reactions were carried out by using 1 eq. **36b**, 1.2 eq. **43**. [b]isolated yield. [c]Determined by HPLC

According to the obtained data in Table 1, bifunctional 1-adamantyl quinine derived organocatalyst **33** was defined as the best one in terms of enantioselectivity. Therefore, further studies were performed with organocatalyst **33** (Table 1).

Table 2. Catalyst loading and concentration screening results



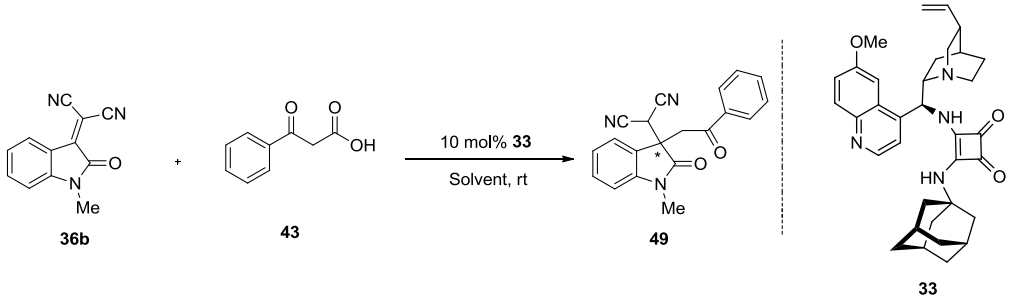
Entry[a]	Cat. (mol%)	Conc. (M)	Time (min)	Yield[b] (%)	ee[c] (%)
1	2	0.2	120	94	31
2	5	0.2	60	93	40
3	**10**	**0.2**	**55**	**>99**	**40**
4	20	0.2	120	95	27
5	10	0.1	90	>99	21
6	10	0.3	90	81	15

[a]All reactions were carried out by using 1 eq. **36b**, 1.2 eq. **43** and organocatalyst **33**. [b]isolated yield. [c]Determined by HPLC

In the next optimization step, catalyst loading and concentration were both studied. Catalyst loading optimization was done in the range of 2 to 20 mol%, as given in Table 2. Unfortunately, increasing or decreasing the amount of catalyst percentage did not show any enhancement in the enantioselectivity compared to 10 mol%. Although 5 mol% catalyst loading afforded the same ee result with 10 mol% catalyst loading, we decided to continue with 10 mol% catalyst ratio due to relatively less chemical yield (entry 2, 93% yield). Afterwards, concentration effect was tested in the range of 0.1 to 0.3 M in THF (Table 2). Although, decreasing the concentration from 0.2 to 0.1 M caused lower reaction duration as expected, drastic decrease in

enantioselectivity was observed as 21% ee (entry 5). Increasing the concentration to 0.3 M resulted in much more decrease in enantioselectivity (15% ee) and chemical yield (81%) due to low solubility of starting compounds and organocatalyst (entry 6).

Table 3. Solvent screening results

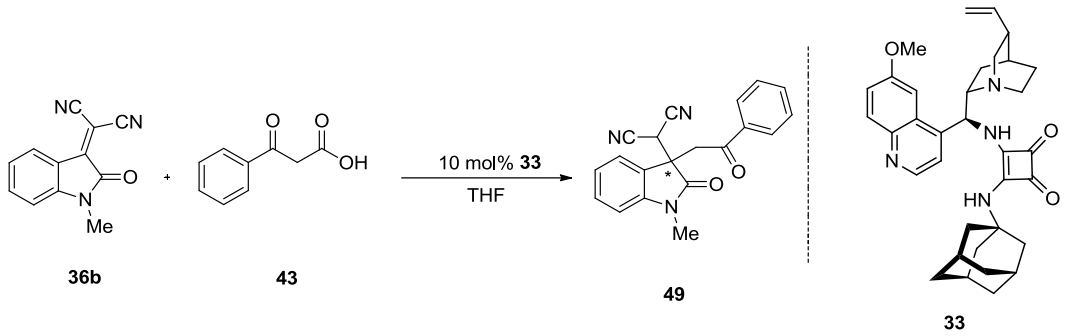


Entry[a]	Solvent	Time (min)	Yield[b] (%)	ee[c] (%)
1	Toluene	120	87	7
2	**THF**	**55**	**>99**	**40**
3	Chloroform	120	92	rac
4	DCM	120	81	20
5	1,4-Dioxane	60	>99	33
6	Acetonitrile	15	87	14
7	Et_2O	60	93	19
8	Xylene	120	54	6
9	DCE	120	78	26
10	Hexane	-	-	-

[a]All reactions were carried out by using 1 eq. **36b**, 1.2 eq. **43** and with 0.2 M concentration. [b]isolated yield. [c]Determined by HPLC

Of the screened solvents, THF proved to be the best one (Table 3, entry 2). Nonpolar solvents as xylene and toluene gave lower enantioselectivities (entries 8 and 1, respectively). Surprisingly, chloroform afforded racemic product. Due to low solubility of the components in hexane, no conversation was observed (entry 10).

Table 4. Temperature screening results.

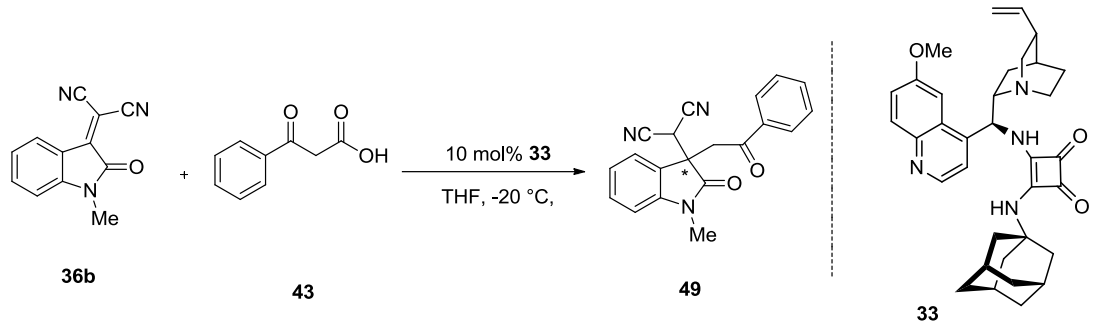


Entry[a]	T (°C)	Time	Yield[b] (%)	ee[c] (%)
1	rt	55 min	>99	40
2	0	20 h	>99	43
3	-10	23 h	78	33
4	**-20**	**22 h**	**78**	**46**
5	-40	48 h	49	17

[a]All reactions were carried out by using 1 eq. **36b**, 1.2 eq. **43** with 0.2 M concentration. [b]isolated yield. [c]Determined by HPLC.

Temperature effect was also examined and summarized in Table 4. In general, since enantioselectivity can be enhanced by decreasing the reaction rate, temperature was decreased. When the reaction was carried out at 0 °C, enantioselectivity was slightly enhanced to 43% ee from 40% ee. However, at -10 °C and -40 °C, slight decrease in enantioselectivity was observed (entries 3 and 5, respectively). The best result was acquired at -20 °C as 46% ee (entries 4), and then we continued with further trials.

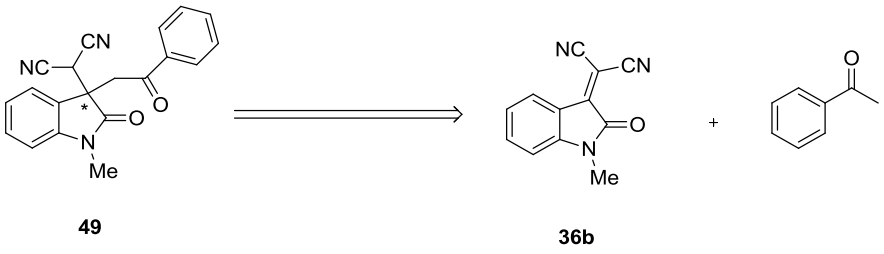
Table 5. Time screening results.



Entry[a]	Time (h)	ee[b] (%)
1	2	8
2	4	25
3	6	20
4	8	1
5	10	31
6	12	39
7	20	27
8	**22**	**46**
9	24	29

[a]All reactions were carried out by using 1 eq. **36b**, 1.2 eq. **43** with 0.2 M concentration. [b]Determined by HPLC.

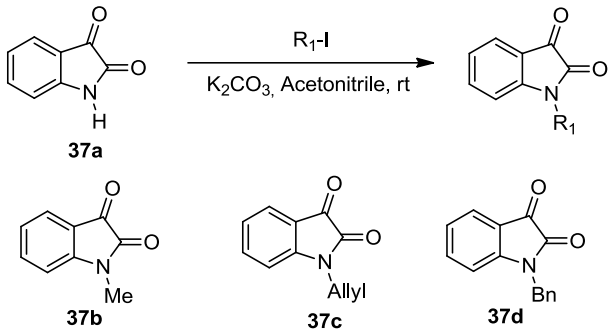
Detailed inspection of reaction duration has been done to get more information regarding the course of the decarboxylative Michael addition reaction. For this purpose, at two hours time intervals, a sample was withdrawn from the mixture, and checked by HPLC. The results are given in Table 5. Drastic fluctuations were observed in terms of enantioselectivity. This is due to retro Michael reaction of the product **49.**



Scheme 25. Retro Michael reaction of the product **49**

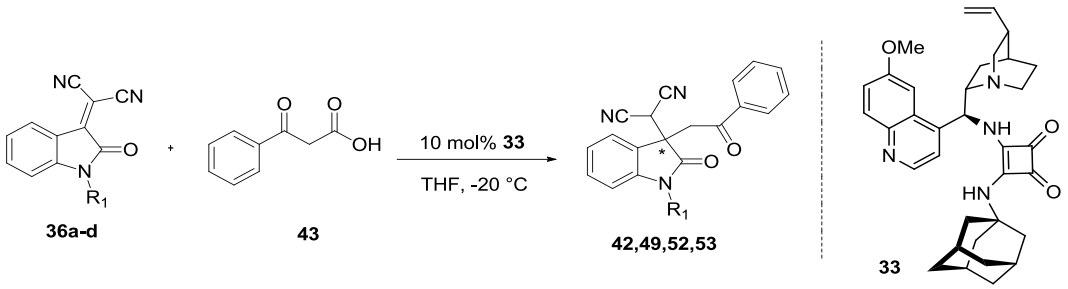
2.2.2 Derivatization of *N*-units on Isatin

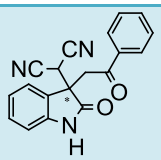
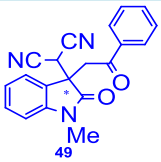
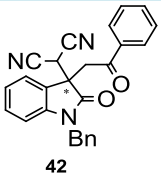
In order to see effect on nitrogen functionality on enantioselectivity under optimized reaction condition, various *N*-substituted isatin derivatives were synthesized (Scheme 26). Then, they were used in Knoevenagel condensation with malononitrile. After formation of desired isatylidine malononitrile derivatives **36a-d**, the decarboxylative Michael reaction was performed under optimized conditions. The results are summarized in Table 6. By using standard literature procedure, three isatin derivatives **37b-d** were synthesized in good yields (Scheme 26).



Scheme 26. *N*-substitution of isatin

Table 6. Derivatization screening on *N*-unit.



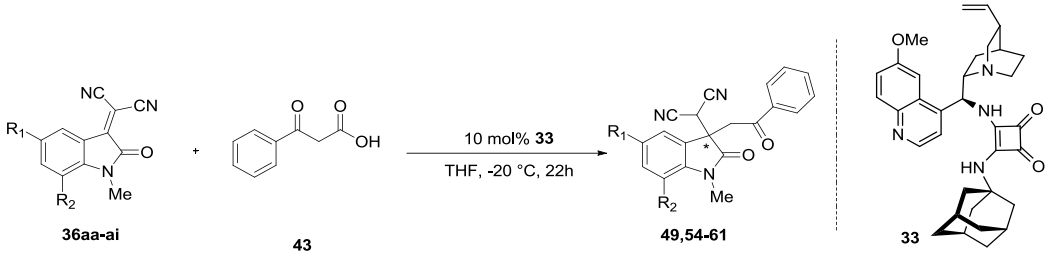
Entry[a]	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	 52	22	34	21
2	 49	**22**	**78**	**46**
3	 53	22	88	32
4	 42	22	79	33

[a]All reactions were carried out by using 1 eq. **36b**, 1.2 eq. **43** with 0.2 M concentration.

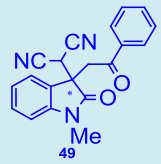
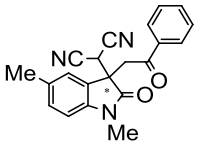
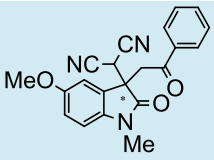
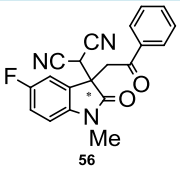
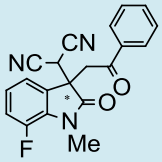
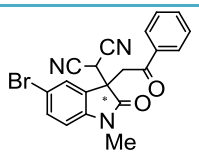
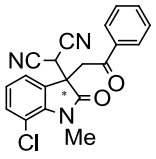
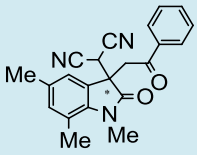
[b]isolated yield. [c]Determined by HPLC

The best result was obtained with N-Me isatylidene malononitrile **36b** as 46% ee (Table 6, entry 2). Based on this result, further studies were continued with *N*-methyl substituted isatin derivatives.

Table 7. Derivatization screening studies with aromatic core derivatives of isatin system.



36aa-ai 43 49,54-61 33

Entry[a]	Product	Yield[b] (%)	ee[c](%)
1	 49	78	46
2	 54	82	29
3	 55	95	26
4	 56	35	30
5		35	30
6	 58	44	32
7	 59	30	25
8	 60	44	23
9	 61	45	25

[a]All reactions were carried out by using 1 eq. **36b**, 1.2 eq. **43** with 0.2 M concentration. [b]isolated yield. [c]Determined by HPLC.

Results of derivatization screening studies are shown in Table 7 indicating the products, conversion and ee values. The best enantioselectivity (46% ee) among other derivatives was obtained for unsubstituted one (entry 1).

All of the derivatives were analyzed by ^{1}H and ^{13}C NMR spectroscopy, and the spectra are given in Appendix A. Also, IR and HRMS data are given in experimental part.

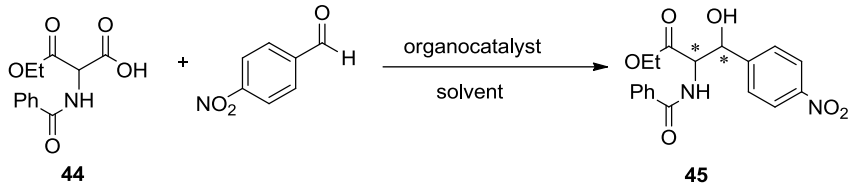
2.3 Synthesis of *anti*-β-hydroxy-α-amino Acids via Decarboxylative Aldol Reaction

Rouden and his co-workers performed diastereoselective reaction of α-amidohemimalonates with various aldehydes by using different organic bases to synthesize *anti*-β-hydroxy-α-amino acids **45**.[35] They obtained only *anti*-diastereoisomeric product and they did not work on enantioselectivity. Inspired by this valuable work, we started to study this reaction with our organocatalyst library. While we performed our reaction, Takemato and his co-workers published first enantioselective synthesis of *anti*-β-hydroxy-α-amino acids.[36] In this study, 20 mol% quinine based organocatalyst and 20 mol% additive acid resulted 90% chemical yield, 86/14 dr and 90% ee. Although the product has high ee value, the protocol still demands improvements in terms of catalyst loading and additives.

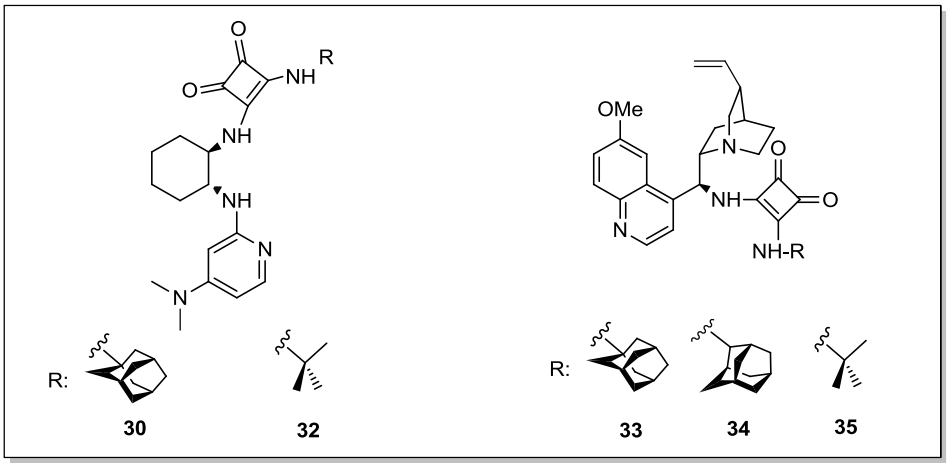
2.4 Optimization Studies for the Asymmetric Decarboxylative Aldol Reaction

The enantioselective decarboxylative aldol reaction of *anti*-β-hydroxy-α-aminoacid **45** has been performed with our bifunctional organocatalyst library and the results are given in Table 8.

Table 8. Catalyst screening results.



44 45



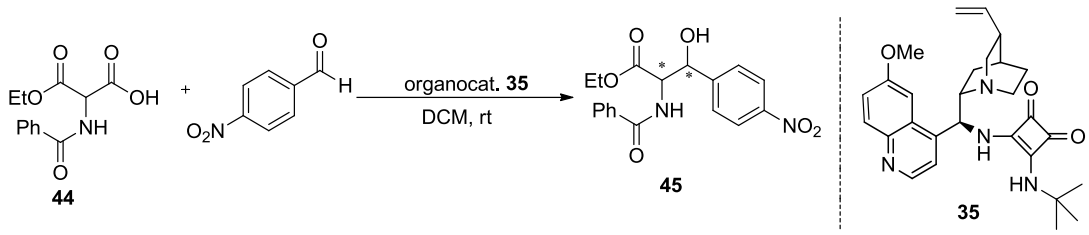
30 32 33 34 35

Entry[a]	Organocatalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	32	72	27	35
2	30	72	18	20
3	2-AminoDMAP	26	21	11
4	33	72	29	37
5	34	72	19	22
6	**35**	**72**	**30**	**63**

[a]All reactions were carried out by using 1 eq. **44**, 1.2 eq. 4-nitrobenzaldehyde and 10 mol% organocatalyst with 0.1 M concentration in DCM at rt. [b]isolated yield. [c]Determined by HPLC .

In the first part, catalyst screening was performed with 10 mol% catalyst loading, with 0.1 M concentration in DCM at rt (Table 8). All reactions were very slow and chemical yields were not good. The best result was found with *t*-butyl squaramide quinine organocatalyst **35** in terms of both chemical yield and enantioselectivity (entry 6).

Table 9. Catalyst loading results

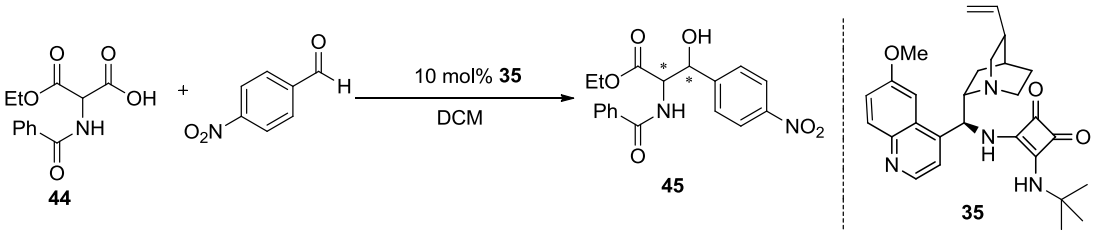


Entry[a]	Cat (mol%)	Time	Yield[b] (%)	ee[c] (%)
1	**10**	**72 h**	**30**	**63**
2	20	60 h	34	31
3	5	120 h	13	16
4	2	120 h	9	rac

[a]All reactions were carried out by using 1 eq. **44**, 1.2 eq. 4-nitrobenzaldehyde with 0.1 M concentration. [b]isolated yield. [c]Determined by HPLC

After deciding *t*-butyl squaramide quinine **35** as the suitable organocatalyst, catalyst loading experiments were performed with four different catalyst ratios in the range of 20 to 2 mol% (Table 9). When the catalyst loading was 20 mol%, conversion slightly increased (34%) but enantioselectivity drastically decreased (31% ee). In the 2 mol% catalyst loading, racemic product was obtained. Consequently, we chose optimum catalyst loading as 10 mol% (entry 1).

Table 10. Temperature screening and additive screening results



Entry[a]	Temperature (°C)	Time (h)	Base Additive	Yield[b] (%)	ee[c] (%)
1	50	72	-	21	18
2	rt	70	10% Et_3N	29	8
3	rt	70	10% Cs_2CO_3	27	16

[a]All reactions were carried out by using 1 eq. **44**, 1.2 eq. 4-nitrobenzaldehyde with 0.1 M concentration. [b]isolated yield. [c]Determined by HPLC.

Afterwards, temperature and additive screening were done and results are given in Table 10. First, to increase conversion and reaction rate, we decided to increase temperature to 50 °C (entry 1). Unfortunately, no enhancement in terms of chemical yield and enantioselectivity was observed. Due to slow reaction rate at rt, we did not further decrease the temperature below rt. Then we continued the experiments with base additives such as 10 mol% Et_3N as an organic base and 10 mol% Cs_2CO_3 as an inorganic base to accelerate the reaction (entry 2 and 3, respectively) However, the additives caused the loss of enantioselectivity.

Consequently, for the decarboxylative aldol reaction, the best condition was determined as 10 mol% of *t*-butyl squaramide quinine **35** with 0.1 M concentration in DCM at room temperature.

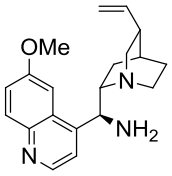
CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

Bruker Spectrospin Avance DPX 400 spectrometer were used to record ^{1}H NMR and ^{13}C NMR spectra. $CDCl_3$ were used as solvent. The chemical shifts are reported in parts per million. TMS was used as an internal standard. Spin multiplicities were shortened as s (singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dq (doublet of quartet), t (triplet), tt (triplet of triplet), q (quartet), m (multiplet) and coupling constants (*J*) are indicated in Hertz (Hz). In Appendix A, ^{1}H and ^{13}C NMR spectra of new products were given. HPLC chromatograms were obtained on Dionex & Thermo-Finnigan HPLC system by using Daicel ADH, ODH and ASH chiral column with different solvent systems. In Appendix B, HPLC chromatograms of chiral and racemic products are shown. HRMS data were recorded on a Agilent 6224 TOF LC/MS at UNAM, Bilkent University. Infrared results were obtained by using Thermo Nicolet IS10 ATR/ FT-IR and Agilent 1100 Series spectrophotometer. Rudolph Scientific Autopol III polarimeter were used to measure optical rotations and reported as follows $[\alpha]_D^T$ (c is in gram per 100 mL solvent). Reactions were monitored by TLC using Merck Silica Gel 60 F254 and were visualized by UV-light. Chromatographic separations were performed on silica gel 60 with particle size of 0.04–0.063 mm purchased from Macherey-Nagel. All extracts were dried by anhydrous magnesium sulphate and then solutions were concentrated by using vacuum. ChemDraw Ultra 12.0 were used to determine the name of the compounds.

3.2 Synthesis of (8α,9S)-6′-Methoxycinchonan-9-Amine



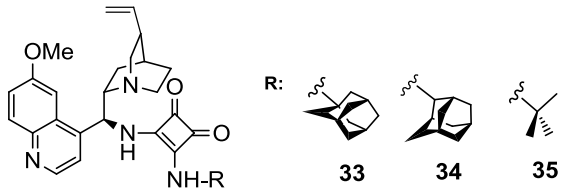
According to literature procedure[38], after dissolving 1 eq quinine **20** (1.62 g, 5.00 mmol) and 1.2 eq. triphenylphosphine (1.58 g, 6.00 mmol) in 25 mL of dry THF, the solution was cooled to 0 °C. Then 1.2 eq. diisopropyl azodicarboxylate (1.22 g, 6.00 mmol) was added to the first solution all at once. In another flask, diphenyl phosphoryl azide (1.65 g, 6.00 mmol) was dissolved in 10 mL of dry THF and was cooled to 0 °C. After that, the second solution was added dropwise to the first solution at 0 °C. The mixture was stirred at room temperature. After 12 h, the solution was heated to 50 °C for 2 h. Then 1.3 eq. triphenylphosphine (1.71 g, 6.50 mmol) was added to the solution and heating was continued until the gas evolution stopped. This took about 2 h. After the solution was cooled to rt, 0.5 mL of water was added and the solution was stirred for 3 h. Vacuum was used to remove solvents and CH_2Cl_2 and 10% hydrochloric acid were used to dissolve the residue(1:1, 50 mL). After the aqueous phase was washed four times with 25 ml DCM, excess aqueous ammonia was used to make the aqueous phase alkaline. Then the aqueous phase was washed with four times with 25 mL DCM. The combined organic phases were dried by using Na_2SO_4 and concentrated. The residue was purified by using a column packed with silica. EtOAc/MeOH/NH_4OH (50/50/1) mixture was used as eluent. The product was afforded as a yellowish oil with 70% yield. Spectroscopic data have been reported previously.[38]

3.3 Synthesis of Mono-Squaramides

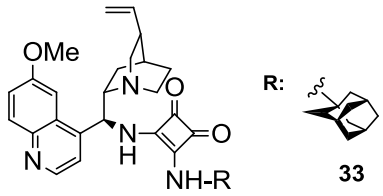
According to literature procedure[13], firstly, to form diethyl squarate, squaric acid (4.3 mmol, 500 mg) was refluxed in absolute ethanol (7 mL) under argon atmosphere for 3h After that, the solvent was removed under vacuum. The mixture was refluxed for 30 minutes with 7 mL of ethanol three more times by applying same procedure. After last evaporation, diethyl squarate were obtained as very light yellow oil. Then, the diethyl squarate was added to 1 eq. amine part in 4 mL DCM and stirred for 24 h at rt

to obtain the mono-squaramide. All amine parts (*t*-butyl, 1-adamantyl, 2-adamantyl) were commercially supplied. Pure product was obtained by using a column filled silica and EtOAc/Hexane (1:3) as eluent, in 90% yield as a white solid. Spectroscopic data are in accordance with the literature.[13]

3.4 Synthesis of *t*-butyl, 1-adamantyl, 2-adamantyl Squaramide/Quinine Catalyst



In order to form squaramide/quinine catalysts, firstly, 1 eq. quinine was disolved in DCM/MeOH (1:1) and then 1 eq. mono-squaramide ester was added. After stirring 48 h at rt, column chromatography with silica was directly applied to the mixture, in which EtOAc/MeOH was used as eluent. Desired product was obtained with 92% yield as a white solid. Spectroscopic data are in accordance with the literature.[30]

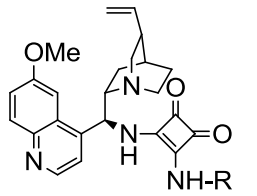


^{1}H NMR (400 MHz, $CDCl_3$): δ=8.73 (d, *J* = 4.4 Hz, 1H), 7.94 (t, *J* = 16.8 Hz, 1H), 7.78–7.62 (m, 2H), 7.34 (dd, *J* = 9.2, 2.3 Hz, 1H), 5.81 – 5.60 (m, 1H), 5.21 – 5.00 (m, 2H), 4.18 (s, 1H), 3.95 (s, 3H), 3.50 (t, *J* = 11.8 Hz, 1H), 3.02 (q, *J* = 7.3 Hz, 6H), 1.75 (d, *J* = 41.1 Hz, 7H), 1.51 (s, 6H), 1.31 (t, *J* = 7.3 Hz, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ=180.2, 179.6, 167.9, 164.7, 157.2, 145.5, 142.9, 134.2, 130.0, 125.4, 121.0, 116.1, 98.6, 58.6, 54.4, 52.3, 51.8, 43.8, 41.3, 41.0, 39.9, 34.5, 33.7, 27.5, 24.6, 22.3, 22.1 ppm.

HRMS for $C_{34}H_{40}N_4O_3$ (MH^+), calcd 553.31732, found: 553.31684

Mp. 196–210 °C (decomposed) $[\alpha]_D^{20}$ -27.2 (c = 0.1 in CH_2Cl_2)

IR (neat) 3198, 3140, 2907, 2603, 2496, 1786, 1669, 1620, 1584, 1518, 1474, 1446, 1397, 1360, 1226, 1033, 852, 719, 681, 623 cm^{-1}



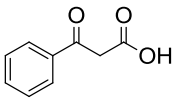
35

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.53 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H),7.79 (bs, 1H), 7.54 (d, *J* = 4.6 Hz, 1H), 7.41 (dd, *J* = 9.1, 2.56 Hz, 1H), 6.08 (bs, 1H), 5.74 (ddd, *J* = 17.4, 10.1, 7.3 Hz, 1H), 4.95 (dd, *J* = 16.3, 9.7 Hz, 2H), 3.96 (s, 3H), 3.44 (bs, 2H), 3.21 – 3.10 (m, 1H), 2.72 (bd, *J* = 11.4 Hz, 2H), 2.26 (bs, 1H), 1.71 – 1.51 (m, 3H), 1.48 – 1.42 (m, 1H), 1.19 (s, 9H), 0.8 (bs, 1H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 182.3, 181.5, 168.3, 168.1, 158.8, 147.8, 144.9, 144.0, 140.6, 131.8, 128.0, 122.5, 119.7, 115.3, 101.6, 60.4, 56.2, 55.9, 53.3, 41.0, 39.1, 30.6, 29.8, 27.5, 27.4, 25.8 ppm.

HRMS for $C_{28}H_{34}N_4O_3$ (MH^+), calcd 475.2709, found 475.2712 $[\alpha]_D^{20}$ = -180.2° (c = 0.1, CH_2Cl_2)

IR (neat) 3362, 3226, 2979, 1793, 1653, 1624, 1585, 1526, 1474, 1367, 1223 cm^{-1}.

3.5 Synthesis of Benzoyl Acetic Acid 43



The following literature procedure was performed to synthesize benzoylacetic acid.[39] 1 eq. 1N NaOH (20 mL) was added to 1 eq. ethyl benzoylacetate (3.84 g, 20 mmol). After the reaction was stirred for overnight at room temperature, the reaction mixture was washed with Et_2O (3 x 50 mL). 3N HCl is used to acidify the obtained aqueous layer to pH = 1, and a precipitated white solid was filtered and dried under vacuum to give benzoylacetic acid (72%, 2.37 g, 14.4 mmol) as a pure product. Spectroscopic data are in accordance with the literature.[39]

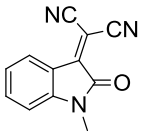
3.6 Synthesis of N-substituted Isatin

Literature procedure for *N*-allylation and *N*-methylation of isatin was performed.[40] After 1 eq. isatin (30 mmol, 4.4 g) was dissolved in 100 mL of acetonitrile, 2 eq. potassium carbonate (60 mmol, 8.3 g) and 1.1 eq. appropriately substituted alkyl iodide (allyl bromide, methyl iodide) (33 mmol) were added to the solution. After the solution was stirred at room temperature overnight, the reaction was monitored by

TLC. After observing the consumption of starting material, the reaction was quenched by using deionized water. Then, ethyl acetate was used for extraction of the aqueous phase. The organic layer was washed three times with 5% (w/v) sodium bicarbonate solution, then deionised water and brine consecutively. The product was dried over anhydrous sodium sulphate and then concentrated in vacuo to obtain pure product. The residue was recrystallized from ethyl acetate and hexane. For the synthesis of *N*-benzylation of isatin, the following literature procedure was done.[40] After dissolving 1 eq isatin (30 mmol, 4.4 g) in 100 mL of acetonitrile, 2 eq potassium carbonate (60 mmol, 8.3 g), 0.1 eq potassium iodide (3 mmol, 0.5 g), and 1.1 eq. substituted benzyl bromide (33 mmol) was added to the solution. After reaction was stirred at room temperature overnight, the reaction was washed with deionized water. The workup procedure was performed in the same way with the synthetic procedure of *N*-allylation and *N*-methylation. Spectroscopic data are in accordance with the literature.[40]

3.7 Synthesis of Isatylidene Malononitrile

According to the literature procedure[41], 1 eq. isatin (5 mmol) and 1 eq. malononitrile (5 mmol) was dissolved in absolute ethanol (5 mL) in the presence of piperidine (0.1 mL). The reaction was stirred overnight at room temperature. After monitoring the reaction by TLC, if the reaction was not complete, the reaction mixture was heated under reflux for about 1 h in oil bath. The product was purified with a column packed with silica. EtOAc/Hexane (1:3) was used as eluent. Chromatography afforded deep red compound.



^{1}H NMR (400 MHz, DMSO) δ 7.90 (d, *J* = 7.7 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.28 – 7.10 (m, 2H), 3.15 (s, 3H) ppm. **^{13}C NMR** (100 MHz, DMSO) δ 162.36, 149.75, 147.13, 137.65, 125.42, 123.39, 117.95, 112.89, 111.37, 110.49, 81.14, 26.22 ppm.

IR 2927, 2838, 2228, 1718, 1483, 1286, 1071, 755, 492 cm^{-1}

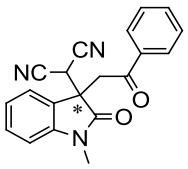
3.8 General Procedure for Decarboxylative Michael Reaction: Benzoyl Acetic Acid Addtion to Isatylidine Malononitrile

Racemic synthesis; 0.2 mmol of isatylidene malononitrile derivatives, 0.24 mmol benzoylacetic acid and 0.02 mmol of Et_3N were dissolved in THF (1 mL) and stirred at room temperature. The reaction was monitored with TLC. Column chromatography with silica (EtOAc/Hexane, 1:3 as eluent) was applied for the purification of products.

Asymmetric synthesis; 0.1 mmol isatylidene malononitrile derivatives and 0.01 mmol of 1-adamantyl/quinine was dissolved in THF (0.5 mL) and the solution was stirred for half an hour at -20 °C . Then 0.12 mmol benzoylacetic acid was added to solution and stirred at -20 °C for 22 h. Then reaction mixture was directly loaded into column chromatography.

3.8.1 Synthesis of 2-(1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 49:

The general procedure starting from *N*-methyl isatylidene malononitrile afforded the desired chiral product **49** in 78% yield and 46% ee in 22 hours.

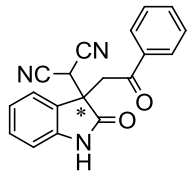


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.39 (m, 4H), 7.10 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 4.66 (s, 1H), 4.11 (d, *J* = 17.8 Hz, 1H), 3.74 (d, *J* = 17.8 Hz, 1H), 3.35 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.2, 173.9, 144.5, 135.4, 134.2, 130.8, 128.9, 128.1, 125.3, 123.6, 123.5, 110.74, 109.7, 109.4, 49.3, 42.2, 30.6, 27.0 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 9.8, t_{minor} = 22.8. $[\alpha]_D^{32}$ = -16.2° (c = 0.8, CH_2Cl_2). **IR** 2962, 2914, 1711, 1693, 1615, 1470, 1259, 1092, 1000, 731, 690 cm^{-1}

3.8.2 Synthesis of 2-(2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 52:

The general procedure starting from *N-H* isatylidene malononitrile afforded the desired chiral product **52** in 34% yield and 21% ee in 22 hours.

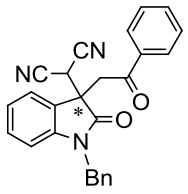


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.77 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.34 (dd, *J* = 16.4, 8.2 Hz, 3H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.01 – 6.86 (m, 2H), 4.66 (s, 1H), 4.03 (d, *J* = 17.5 Hz, 1H), 3.70 (d, *J* = 17.5 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.7, 176.0, 141.7, 135.4, 134.2, 130.8, 128.9, 128.2, 125.8, 123.8, 123.5, 111.3, 110.7, 109.8, 49.7, 42.2, 30.4.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 12.3, t_{minor} = 23.7. $[\alpha]_D^{31}$ = -5.6° (c = 0.7, CH_2Cl_2). **IR** 3271, 2896, 1719, 1619, 1472, 1218, 750, 687, 573 cm^{-1}

3.8.3 Synthesis of 2-(1-benzyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 42:

General procedure starting from *N*-benzyl isatylidene malononitrile afforded the desired chiral product **42** in 79% yield and 33% ee in 22 hours.

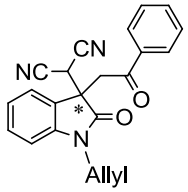


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.9 Hz, 2H), 7.48 (t, *J* = 6.9 Hz, 1H), 7.36 (dt, *J* = 15.5, 7.1 Hz, 5H), 7.26 (dd, *J* = 14.3, 6.6 Hz, 2H), 7.23 – 7.09 (m, 2H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 4.96 (s, 2H), 4.60 (s, 1H), 4.05 (d, *J* = 17.7 Hz, 1H), 3.66 (d, *J* = 17.7 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.0, 173.1, 142.7, 134.4, 133.8, 133.1, 129.6, 127.9, 127.8, 127.1, 126.8, 126.4, 124.2, 122.6, 122.7, 109.7, 109.5, 108.7, 48.3, 43.9, 41.4, 29.6 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 20.5, t_{minor} = 35.3. $[\alpha]_D^{32}$ = -5.2° (c = 1.1, CH_2Cl_2). **IR** 3062, 2918, 1712, 1687, 1611, 1355, 1216, 1001, 749, 687 cm^{-1}

3.8.4 Synthesis of 2-(1-allyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 53:

The general procedure starting from *N*-allyl isatylidene malononitrile afforded the desired chiral product **53** in 88% yield and 32% ee in 22 hours.

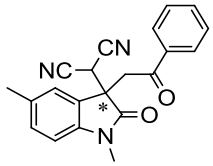


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.24 (m, 3H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 5.99 – 5.66 (m, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.56 (s, 1H), 4.48 – 4.24 (m, 2H), 4.03 (d, *J* = 17.7 Hz, 1H), 3.64 (d, *J* = 17.7 Hz, 1H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.0, 173.7, 143.8, 135.5, 134.1, 130.7, 130.7, 128.8, 128.2, 125.3, 123.5, 123.5, 118.6, 110.7, 110.4, 109.6, 49.2, 43.3, 42.4, 30.7 ppm.

HPLC Chiralpak ADH column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, $t_{majo\ r}$= 16.4, t_{minor} = 34.2. $[\alpha]_D^{32}$ = -9.0° (c = 1.0, CH_2Cl_2). **IR** 2922, 2361, 1712, 1611, 1488, 1359, 1216, 1002, 750, 687 cm^{-1}

3.8.5 Synthesis of 2-(1,5-dimethyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 54:

The general procedure starting from *N*-methyl 5-methyl isatylidene malononitrile afforded the desired chiral product **54** in 82% yield and 29% ee in 22 hours.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 6.9 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.28 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 4.60 (s, 1H), 4.08 (d, *J* = 17.8 Hz, 1H), 3.68 (d, *J* = 17.8 Hz, 1H), 3.35 (s, 3H), 2.32 (s, 3H) ppm.

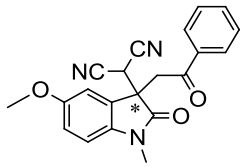
^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 173.8, 142.1, 135.5, 134.1, 133.4, 131.1, 128.8, 128.1, 125.2, 124.2, 110.7, 109.5, 109.1, 49.3, 42.2, 30.7, 27.0, 21.2 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25°C, t_{major} = 11.0, t_{minor} = 21.3. $[\alpha]_D^{32}$ = -6.5° (c = 1.0, CH_2Cl_2). **IR** 2921, 1700, 1501, 1355, 1259, 1016, 799, 684 cm^{-1}

HRMS for $C_{21}H_{17}N_3O_2$ (MH^+), calcd 344.1399, found 344.1408

3.8.6 Synthesis of 2-(5-methoxy-1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 55:

The general procedure starting from *N*-methyl 5-methoxy isatylidene malononitrile afforded the desired chiral product **55** in 95% yield and 26% ee in 22 hours.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.10 (dd, *J* = 2.0, 0.7 Hz, 1H), 6.95 – 6.93 (m, 2H), 4.61 (s, 1H), 4.07 (d, J= 17.8 Hz, 1H), 3.77 (s, 3H), 3.67 (d, *J* = 17.8 Hz, 1H), 3.35 (s, 3H) ppm.

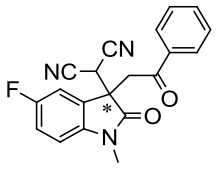
^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 173.5, 156.5, 137.8, 135.4, 134.2, 128.9, 128.1, 126.4, 114.7, 111.2, 110.7, 109.9, 109.6, 55.8, 49.6, 42.2, 30.6, 27.0 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 15.6, t_{minor} = 29.1. $[\alpha]_D^{32}$ = -6.0° (c = 1.1, CH_2Cl_2). **IR** 2893, 1710, 1499, 1364, 1224, 1031, 758, 687 cm^{-1}

HRMS for $C_{21}H_{17}N_3O_3$(MH+), calcd 360.1348, found 360.1354

3.8.7 Synthesis of 2-(5-fluoro-1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 56:

The general procedure starting from *N*-methyl 5-fluoro isatylidene malononitrile afforded the desired chiral product **56** in 35% yield and 30% ee in 22 hours.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 6.9 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.24 – 7.14 (m, 1H), 7.08 (td, *J* = 8.8, 2.6 Hz, 1H), 6.89 (dd, *J* = 8.6, 4.1 Hz, 1H), 4.54 (s, 1H), 4.01 (d, *J* = 17.9 Hz, 1H), 3.63 (d, *J* = 17.9 Hz, 1H), 3.29 (s, 3H) ppm.

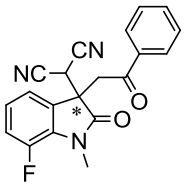
^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 172.1, 158.0 (d, *J* = 243.5 Hz), 139.2, 133.8, 132.9, 127.5, 126.7, 125.2 (d, *J* = 8.3 Hz), 115.8 (d, *J* = 23.5 Hz), 110.7 (d, *J* = 25.8 Hz), 108.9, 108.7 (d, *J* = 8.3 Hz), 107.8, 48.15, 40.9, 29.0, 25.7 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25°C, t_{major} = 9.2, t_{minor} = 22.3. $[\alpha]_D^{32}$ = -3.9° (c = 0.5, CH_2Cl_2). **IR** 2923, 1712, 1496, 1355, 1208, 1002, 795, 684 cm^{-1}

HRMS for $C_{20}H_{14}FN_3O_2$ (MH^+), calcd 348.1148, found 348.1153

3.8.8 Synthesis of 2-(7-fluoro-1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 57:

The general procedure starting from *N*-methyl 7-fluoro isatylidene malononitrile afforded the desired chiral product **57** in 35% yield and 30% ee in 22 hours.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 5.3 Hz, 2H), 7.53 (d, *J* = 7.1 Hz, 1H), 7.39 (d, *J* = 7.0 Hz, 2H), 7.20 (t, *J* = 5.6 Hz, 1H), 7.16 – 7.03 (m, 1H), 7.05 – 6.91 (m, 1H), 4.47 (s, 1H), 3.99 (d, *J* = 17.7 Hz, 1H), 3.63 (d, *J* = 17.7 Hz, 1H)., 3.51 (s, 3H) ppm.

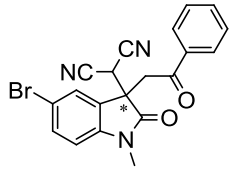
^{13}CNMR (100 MHz,$CDCl_3$) δ 192.8, 172.6, 147.1 (d, *J* = 245.7 Hz), 134.2, 133.2, 130.4 (d, *J* = 8.9 Hz), 127.9, 127.1, 125.9, 123.2 (d, *J* = 6.7 Hz), 118.1 (d, *J* = 3.3 Hz), 118.0, 117.8, 108.4, 48.4, 41.6, 29.8, 28.7 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major}= 12.5, t_{minor} = 33.0. $[\alpha]_D^{32}$ = -4.3° (c = 0.5, CH_2Cl_2). **IR** 2918, 1714, 1483, 1370, 1243, 1004, 783, 687 cm^{-1}

HRMS for $C_{20}H_{14}FN_3O_2$ (MH^+), calcd 348.1148, found 348.1146

3.8.9 Synthesis of 2-(5-bromo-1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 58:

The general procedure starting from *N*-methyl 5-bromo isatylidene malononitrile afforded the desired chiral product **58** in 44% yield and 32% ee in 22 hours.



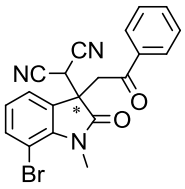
^{1}H NMR (400 MHz,) δ 7.78 (d, *J* = 7.2 Hz, 2H), 7.51 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 3H),6.83 (d, *J* = 8.3 Hz, 1H), 4.54 (s, 1H), 4.00 (d, *J* = 18.0 Hz, 1H), 3.66 (d, *J* = 18.0 Hz, 1H), 3.27 (s, 3H) ppm. **^{13}C NMR** (100 MHz,) δ 193.9, 173.4, 143.7, 135.1, 134.4, 133.8, 128.9, 128.2, 127.3, 126.8, 116.2, 110.9, 110.4, 109.3, 49.3, 42.4, 39.0, 30.5, 27.1 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 9.4, t_{minor} = 24.6. $[\alpha]_D^{32}$ = -6.34° (c = 0.5, CH_2Cl_2). **IR** 2899, 1717, 1489, 1359, 1219, 1002, 754, 687 cm^{-1}

HRMS for $C_{20}H_{14}BrN_3O_2$ (MH^+), calcd 408.0348, found 408.0353

3.8.10 Synthesis of 2-(7-bromo-1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 59:

The general procedure starting from *N*-methyl 7-bromo isatylidene malononitrile afforded the desired chiral product **59** in 30% yield and 25% ee in 22 hours.



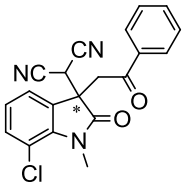
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.41 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.01 – 6.92 (m, 1H), 4.49 (s, 1H), 4.08 (d, *J* = 17.7 Hz, 1H), 3.67 (d, *J* = 17.7 Hz, 1H).3.75 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.7, 174.5, 142.0, 136.5, 135.2, 135.2, 134.3, 128.9, 128.1, 124.6, 122.3, 110.4, 109.3, 103.7, 48.8, 42.7, 30.9, 30.8 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 15.6, t_{minor} = 32.3. $[\alpha]_D^{32}$ = -27.7° (c = 0.3, CH_2Cl_2). **IR** 2895, 1715, 1460, 1365, 1219, 1002, 733, 687 cm^{-1}

HRMS for $C_{20}H_{14}BrN_3O_2$ (MH^+), calcd 408.0348, found 408.0361

3.8.11 Synthesis of 2-(7-chloro-1-methyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 60:

The general procedure starting from *N*-methyl 7-chloro isatylidene malononitrile afforded the desired chiral product **60** in 44% yield and 23% ee in 22 hours.



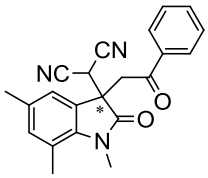
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.31 – 7.23 (m, 2H), 6.94 (t, *J* = 7.8 Hz, 1H), 4.45 (s, 1H), 4.01 (d, *J* = 17.8 Hz, 1H), 3.66 (d, *J* = 17.8 Hz, 1H), 3.65 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.7, 174.3, 140.6, 135.2, 134.3, 133.2, 128.9, 128.1, 127.9, 124.3, 121.8, 117.0, 110.4, 109.2, 48.9, 42.6, 30.9, 30.5 ppm.

HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 13.5, t_{minor} = 31.5. $[\alpha]_D^{32}$ = -11.2° (c = 0.7, CH_2Cl_2). **IR** 2893, 1716, 1464, 1370, 1224, 1016, 734, 687 cm^{-1}

HRMS for $C_{20}H_{14}ClN_3O_2$ (MH^+), calcd 364.0853, found 364.0860

3.8.12 Synthesis of 2-(1,5,7-trimethyl-2-oxo-3-(2-oxo-2-phenylethyl)indolin-3-yl)malononitrile 61:

The general procedure starting from *N*-methyl 5,7-dimethyl isatylidene malononitrile afforded the desired chiral product **61** in 45% yield and 25% ee in 22 hours.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.09 (s, 1H), 6.95 (s, 1H), 4.56 (s, 1H), 3.96 (d, *J* = 17.7 Hz, 1H), 3.60 (d, *J* = 17.7 Hz, 1H), 3.60 (s, 3H), 2.59 (s, 3H), 2.25 (s, 3H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.1, 174.6, 139.8, 135.5, 135.1, 134.1, 133.1, 128.8, 128.1, 125.9, 121.7, 120.8, 110.8, 109.6, 48.8, 42.4, 30.3, 24.5, 20.8, 19.0 ppm.

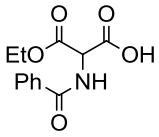
HPLC Chiralpak AD-H column, 90:10 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 254 nm, T = 25 °C, t_{major} = 12.56, t_{minor} = 25.1. $[\alpha]_D^{32}$ = +7.9° (c = 0.3, CH_2Cl_2). **IR** 2921, 1687, 1401, 1354, 1222, 1100, 759, 687, 551, 458 cm^{-1}

HRMS for $C_{22}H_{19}N_3O_2$ (MH^+), calcd 358.1556, found 358.1560

3.9 Synthesis of α-amidohemimalonate 43

According to literature procedures,[35,42] 1 eq diethylmalonate amine hydrochloride (2.36 mmol, 500 mg), 3 eq. triethylamine (7.078 mmol, 1 ml) in 35 mL dichloromethane were stirred for 15 minutes. After that, 1 eq benzoyl chloride (2.36 mmol, 0.275 mL) was added to the mixture at 0 °C dropwise and the mixture was allowed to stir at rt for 15 h. After 15 hours, the mixture was diluted with DCM, washed with 1N HCl and then extraction was done with DCM. The organic layers were dried over $MgSO_4$ and concentrated. After recrystallization from EtOAc/Heptane (1:10), benzoyl protected aminomalonate was afforded as white solid with 90% yield. Then 1 eq. benzoyl protected aminomalonate was dissolved in H_2O/EtOH (1:10) solution. In another flask, 1 eq. KOH dissolved in H_2O/EtOH (1:10) solution and then the KOH solution was added dropwise to the solution containing benzoyl protected aminomalonate at 0°C. After the reaction was stirred for 24 hours at rt, 1N HCl was added dropwise until pH = 1. Then NaCl is added to

saturate the mixture and the mixture was extracted with EtOAc twice. The organic layers were combined and dried over $MgSO_4$ and concentrated. Saturated $NaHCO_3$ is used to wash the crude product then the crude product was extracted with ether. After adding 1N HCl to acidify the water phase until pH = 1, extraction was done with ether. And finally, desired product was obtained as yellowish solid in 45% yield.



^{1}H-NMR (400 MHz, $CDCl_3$): δ9.94 (bs, 1H), 7.84 – 7.80 (m, 2H), 7.52 (tt, *J* = 7.40, 1.87 Hz, 1H), 7.45 – 7.40 (m, 2H), 5.37 (d, *J* = 6.71 Hz, 1H), 4.30 – 4.25 (m, 2H), 1.29 (t, *J* = 7.14 Hz, 3H) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.5, 168.1, 166.5, 132.6, 132.5, 128.8, 127.5, 63.2, 57.0, 14.0 ppm.

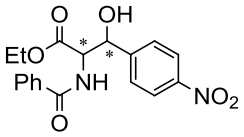
3.10 General Procedure for Decarboxylative Aldol Reaction: 4-Nitrobenzaldehyde Addition to α-Amidohemimalonates

Racemic synthesis; 0.2 mmol of malonic acid half ester and 0.24 mmol aldehyde and 0.2 mmol Et_3N were dissolved in THF and was stirred at rt for 15 h. The reaction was monitored with TLC. Purification of the desired product was done by column chromatography with silica. EtOAc/Cyclohexane (3:7) mixture was used as a eluent.

Asymmetric synthesis; 0.1 mmol of aldehyde, 0.12 mmol of malonic acid half ester and 0.01 mmol of *t*-butyl 2-aminoDMAP was dissolved in DCM (1.0 mL) and then reaction was stirred at rt. The reaction was monitored with TLC, and then the reaction directly loaded into the column.

3.10.1 Synthesis of ethyl 2-benzamido-3-hydroxy-3-(4-nitrophenyl) propanoate 45:

The general procedure starting from malonic acid half ester **43** afforded to desired chiral product **45** in 30% yield and 63% ee in 72 hours.



^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.8 Hz, 2H) 7.70 – 7.66 (m, 2H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.52 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.44 – 7.40 (m, 3H), 6.87 (d, *J* = 8.8 Hz, 1H), 5.50 (d, *J* = 3.0 Hz, 1H), 5.15 (dd, *J* = 8.7, 3.1 Hz, 1H), 4.32 – 4.21 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H) ppm. **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 169.1, 169.0, 147.8, 147.0, 132.7, 132.0, 129.0, 127.3, 127.1, 123.6, 75.0, 62.8, 60.1, 14.2 ppm.

HPLC Chiralpak AS-H column, 80:20 (*n*-hexane/*i*-PrOH), flow rate 1.0 mL/min, 210 nm, T = 25 °C, t_{minor} = 11.6, t_{major} = 18.1. **IR** 3305, 2915, 1729, 1464, 1178, 1106, 660 cm^{-1}

CHAPTER 4

CONCLUSION

In this thesis, bifunctional organocatalysts already developed in our research group library were tested on decarboxylative Michael and aldol reactions.

In the first part, decarboxylative Michael reactions of isatylidene malononitrile and ethyl benzoyl acetate were tested with 2-aminoDMAP and quinine based bifunctional organocatalysts. The best result was obtained with 10 mol% of 1-adamantyl squaramide quinine **33**, 0.2 M concentration in THF at -20°C at 22h. Under this optimized condition, derivatization studies were performed with different *N*-substituted and aromatic core substituted isatin. The enantioselectivity was found as 46% ee with 78% chemical yield for *N*-methyl and unsubstituted isatylidene malononitrile **49**.

In the second part of the thesis, decarboxylative aldol reactions of 4-nitrobenzaldehyde to α-amidohemimalonates were performed. Unfortunately, the reaction was very slow and the chemical yield was 30%. Maximum enantioselectivity (63% ee) was achieved with *t*-butyl squaramide quinine **35**. Although there is a parallel study where enantioselective decarboxylative aldol reaction is applied in the literature, our results indicate that it can be improved with additional screenings. For the decarboxylative aldol reaction, optimization studies will continue with acid addition screening and then derivatization of the starting materials will be performed in the near future.

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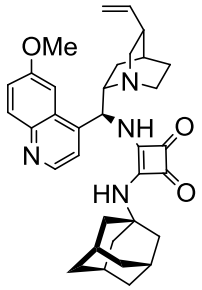
APPENDIX A

NMR DATA



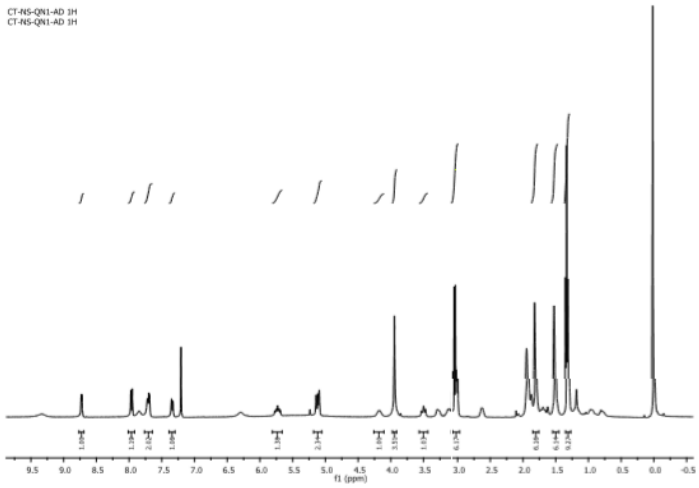


Figure A. 1. ^{1}H NMR spectrum of compound **33**

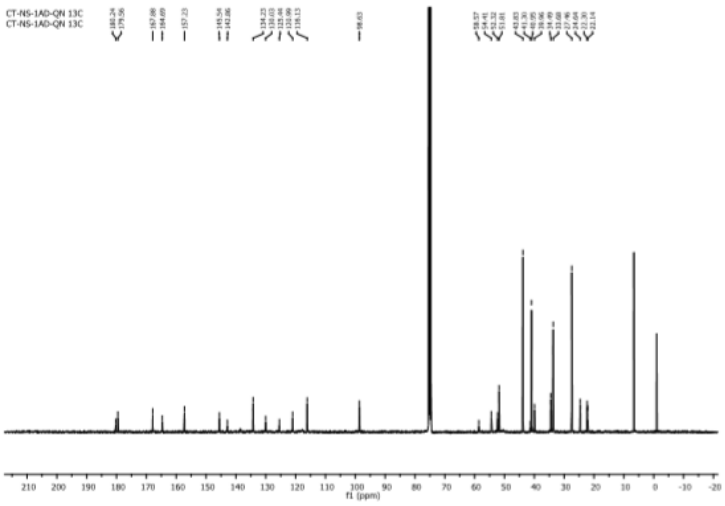


Figure A. 2. ^{13}C NMR spectrum of compound **33**

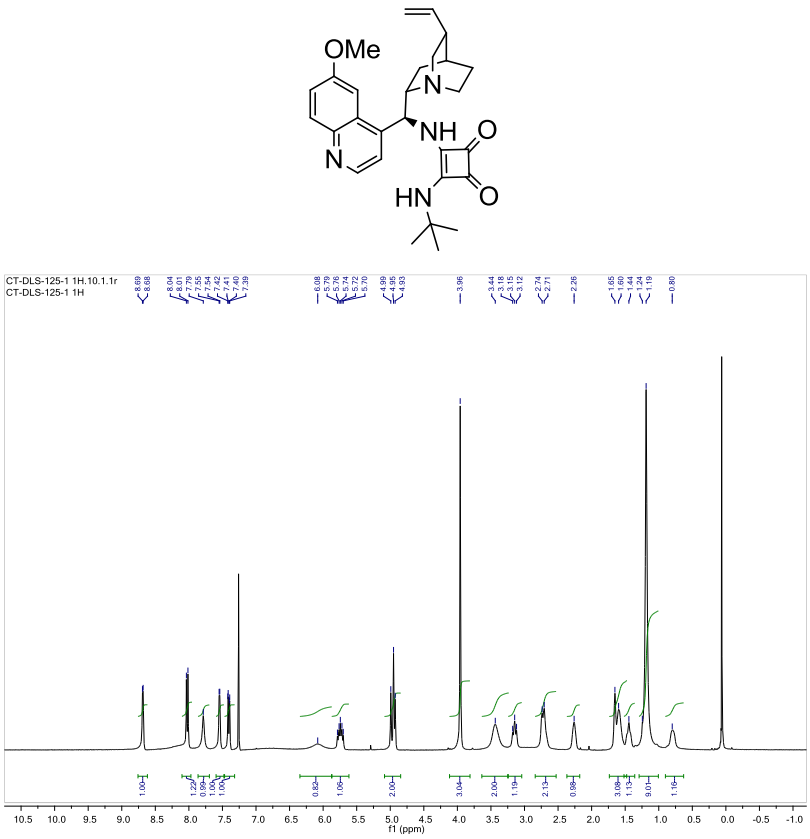


Figure A. 3. ^{1}H NMR spectrum of compound **35**

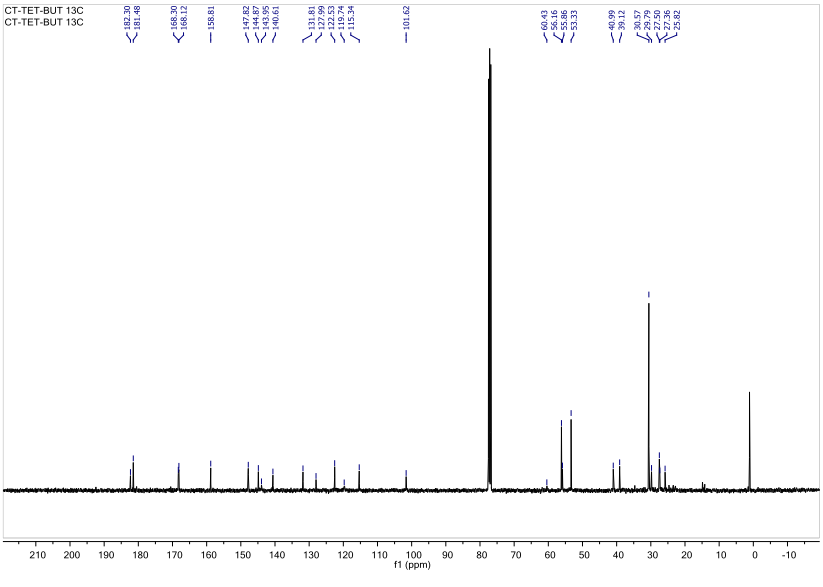


Figure A. 4. ^{13}C NMR spectrum of compound **35**

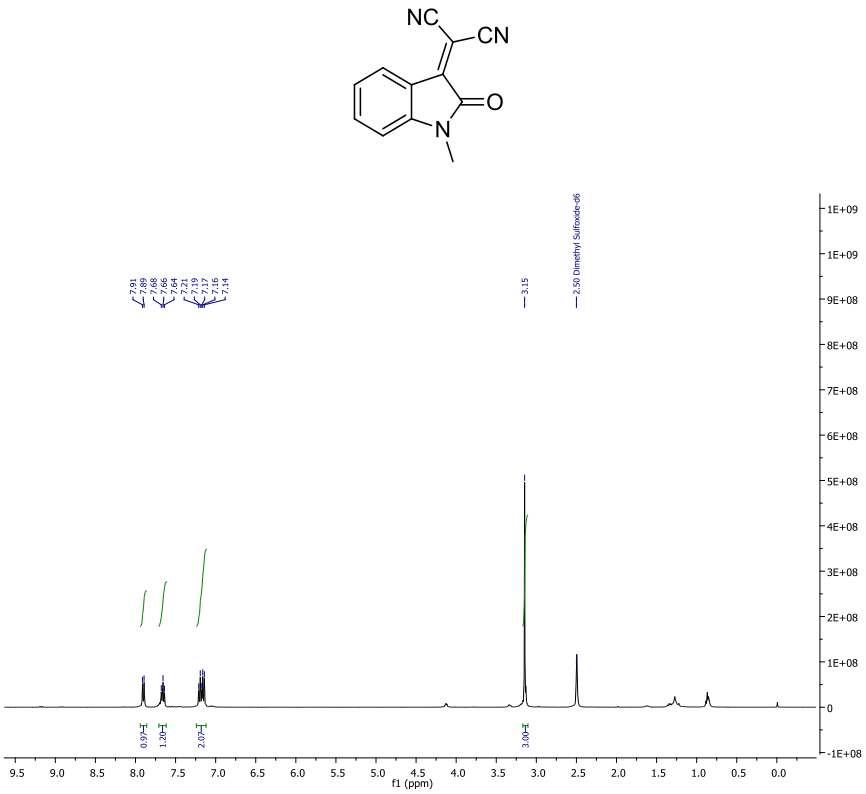


Figure A. 5. ^{1}H NMR spectrum of compound **36b**

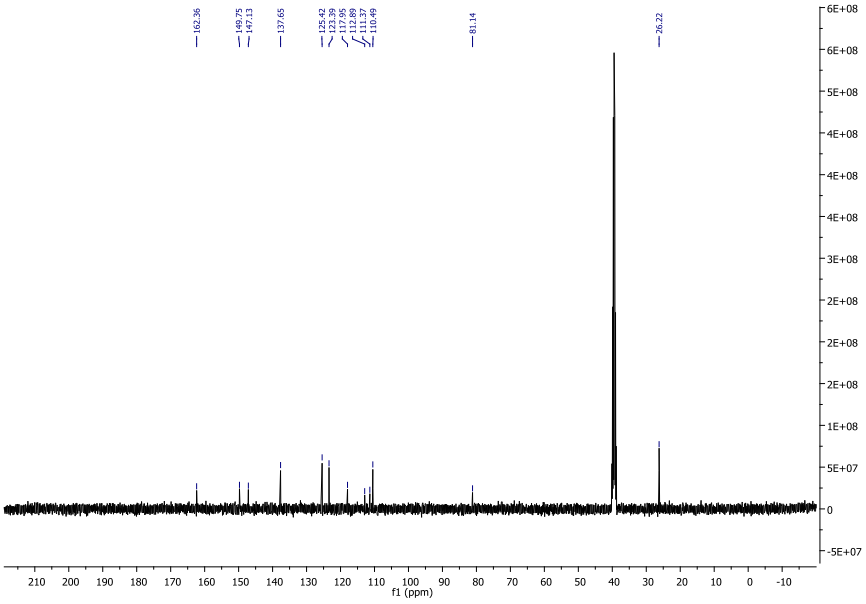


Figure A. 6. ^{13}C NMR spectrum of compound **36b**

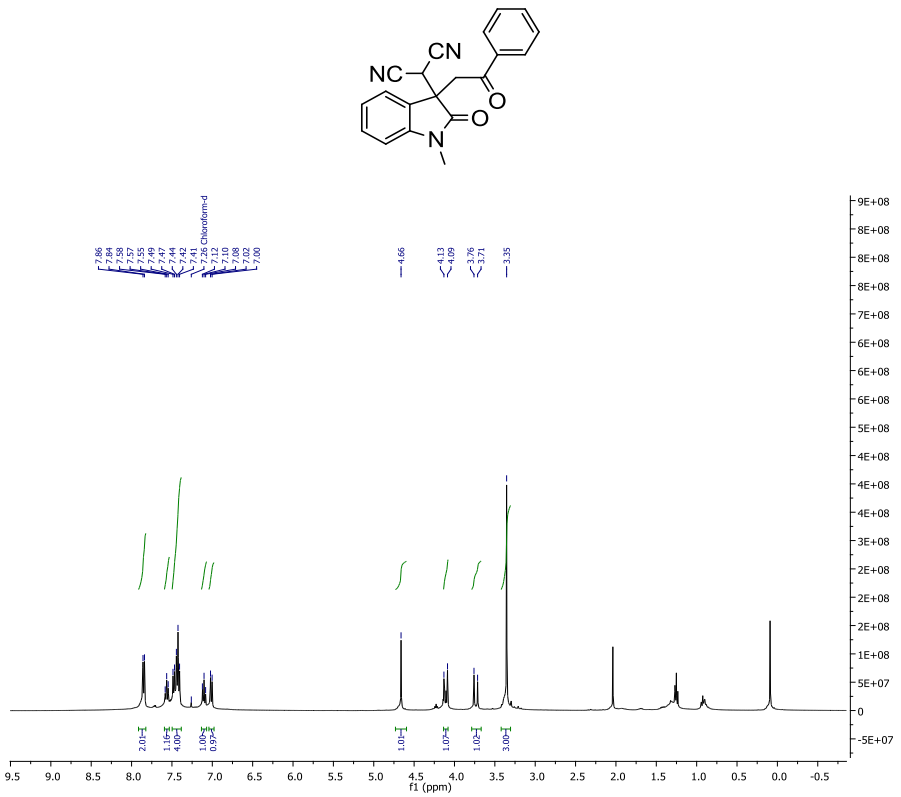


Figure A. 7. ^{1}H NMR spectrum of compound **49**

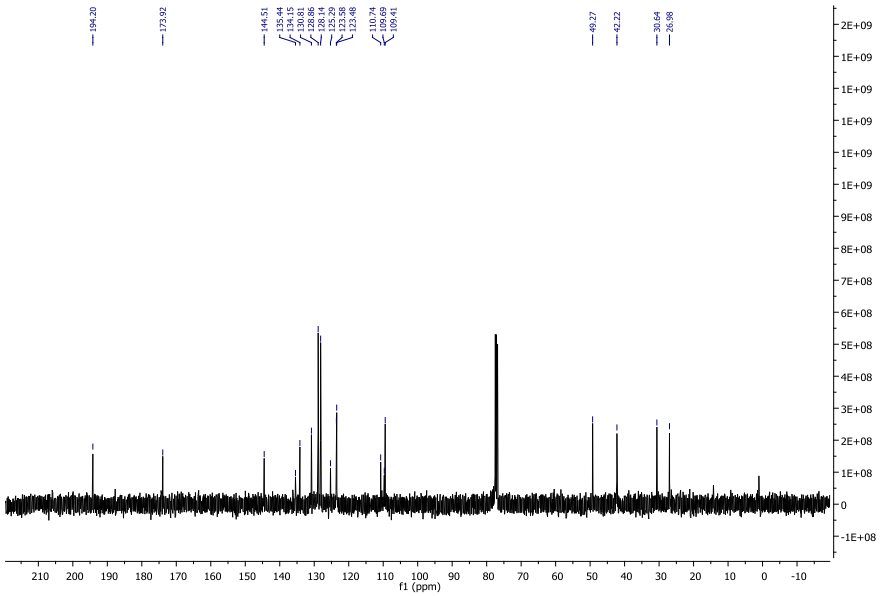


Figure A. 8. ^{13}C NMR spectrum of compound **49**

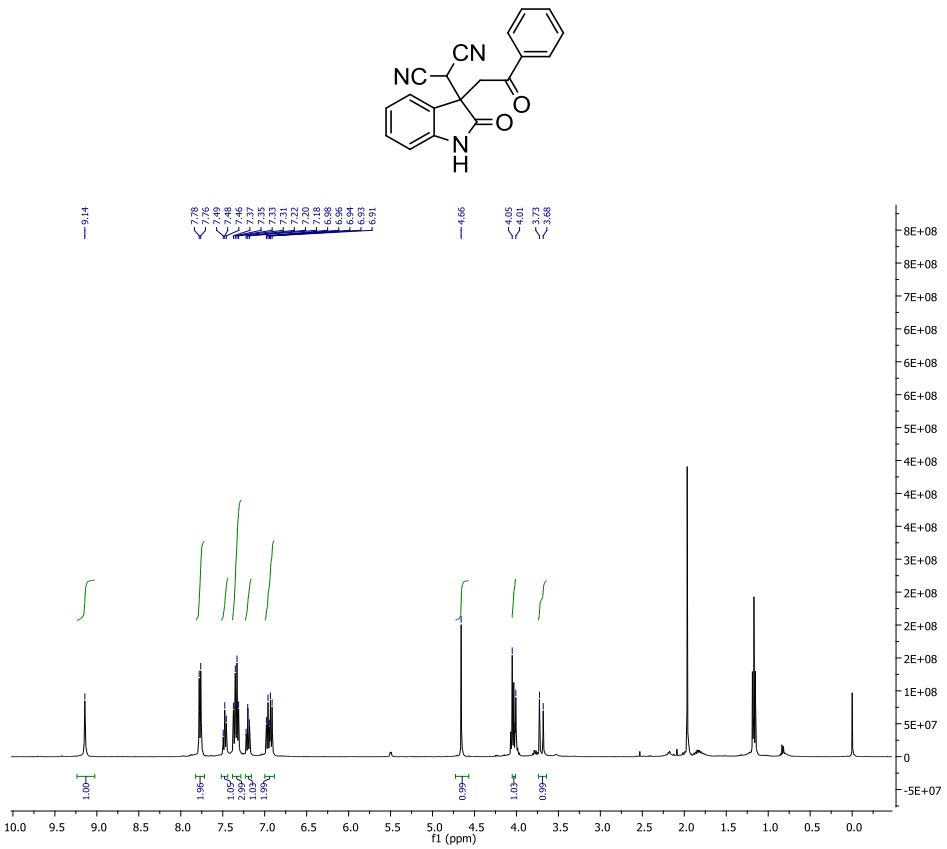


Figure A. 9. ^{1}H NMR spectrum of compound **52**

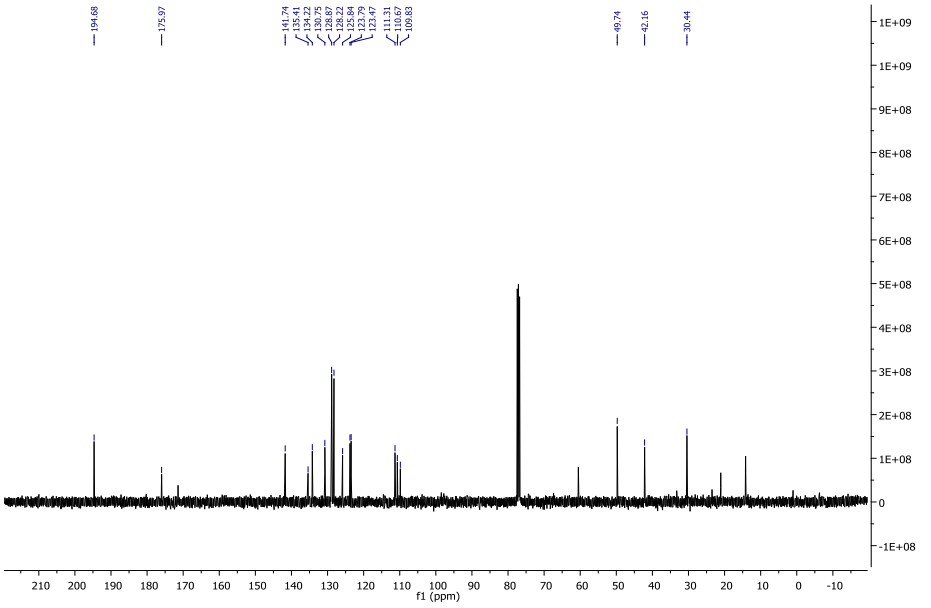


Figure A. 10. ^{13}C NMR spectrum of compound **52**

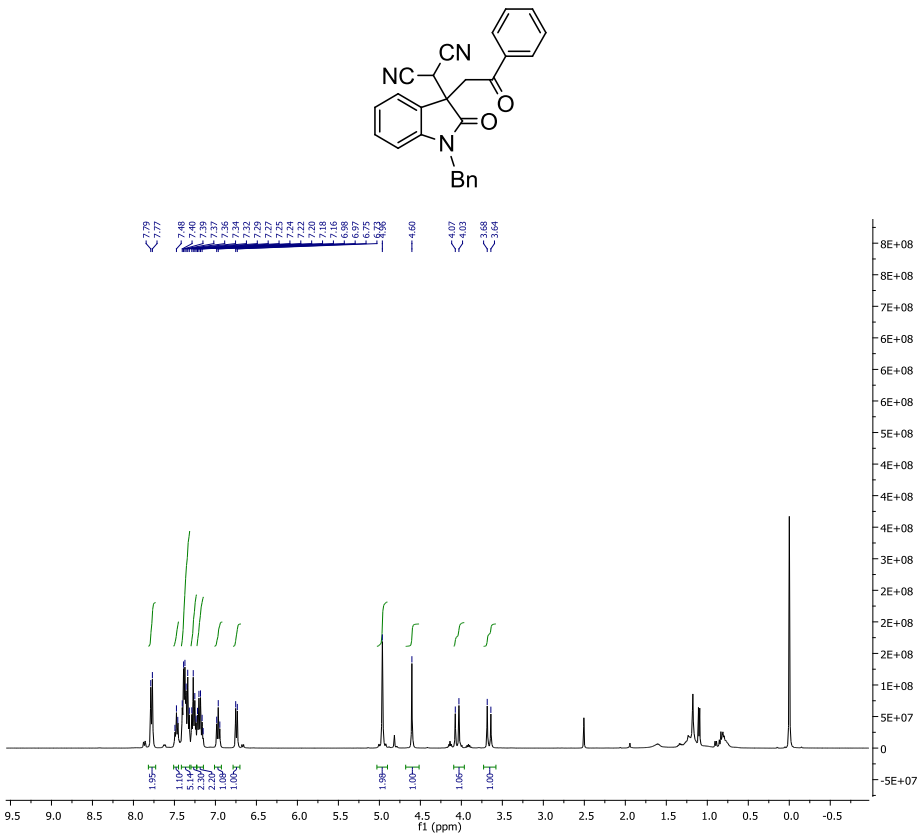


Figure A. 11. ^{1}H NMR spectrum of compound **42**

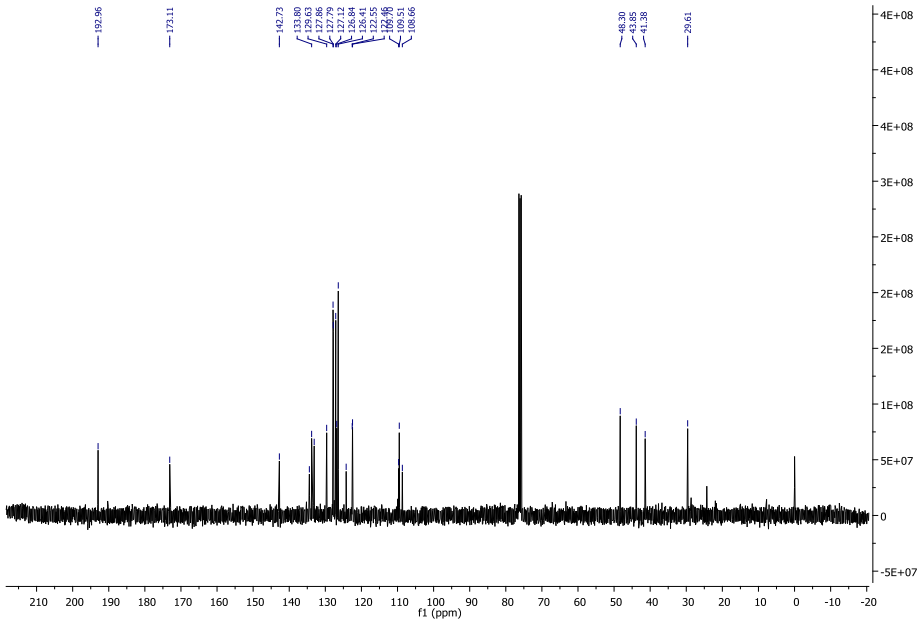


Figure A. 12. ^{13}C NMR spectrum of compound **42**

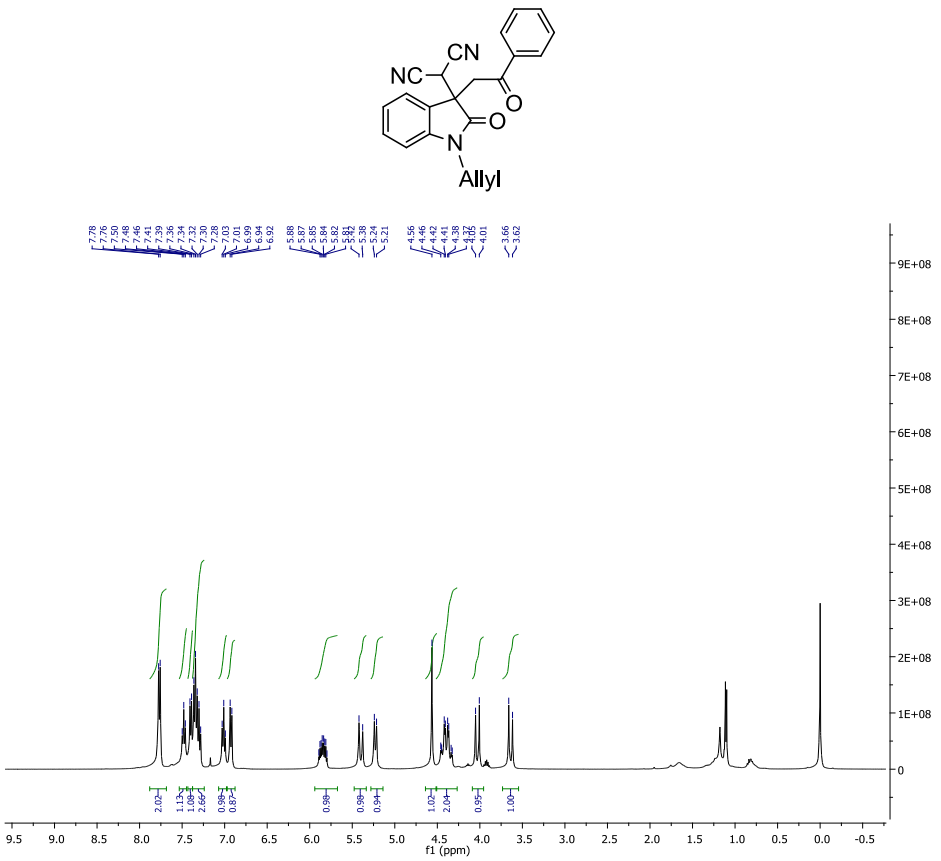


Figure A. 13. ^{1}H NMR spectrum of compound**53**

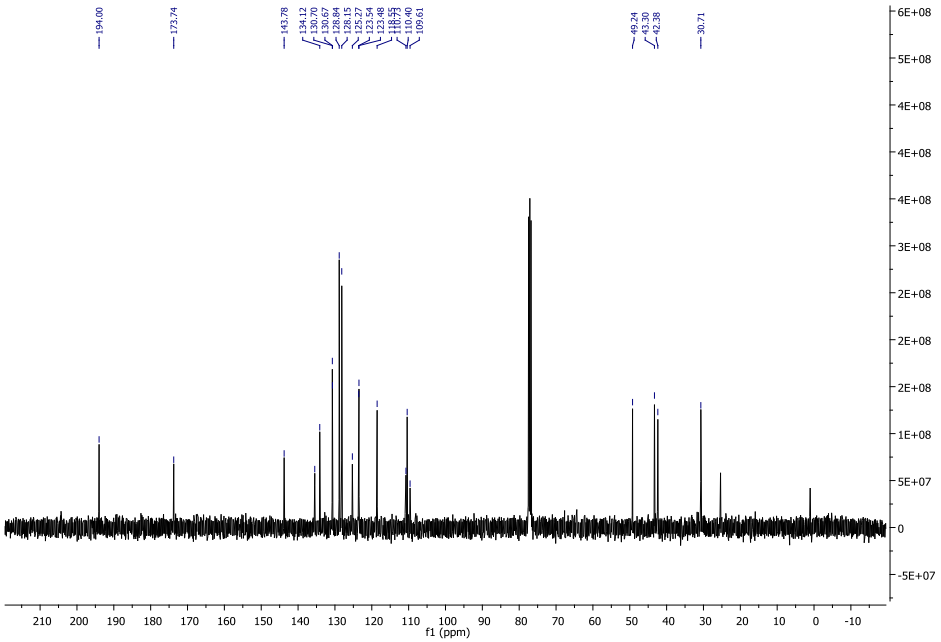


Figure A. 14. ^{13}C NMR spectrum of compound **53**

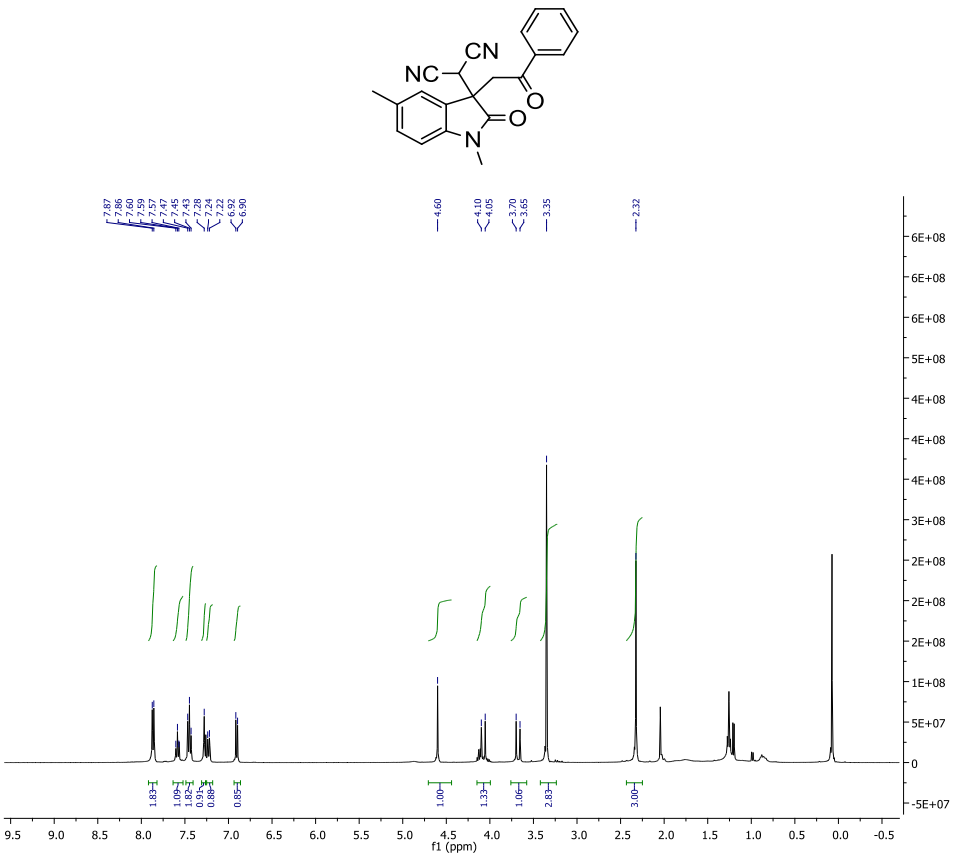


Figure A. 15. ^{1}H NMR spectrum of compound **54**

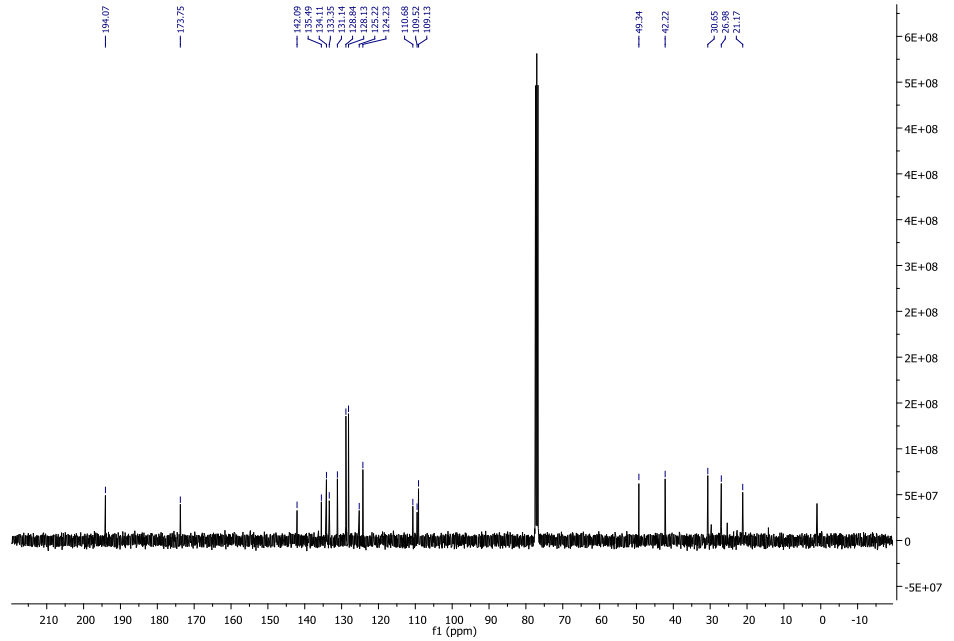


Figure A. 16. ^{13}C NMR spectrum of compound **54**

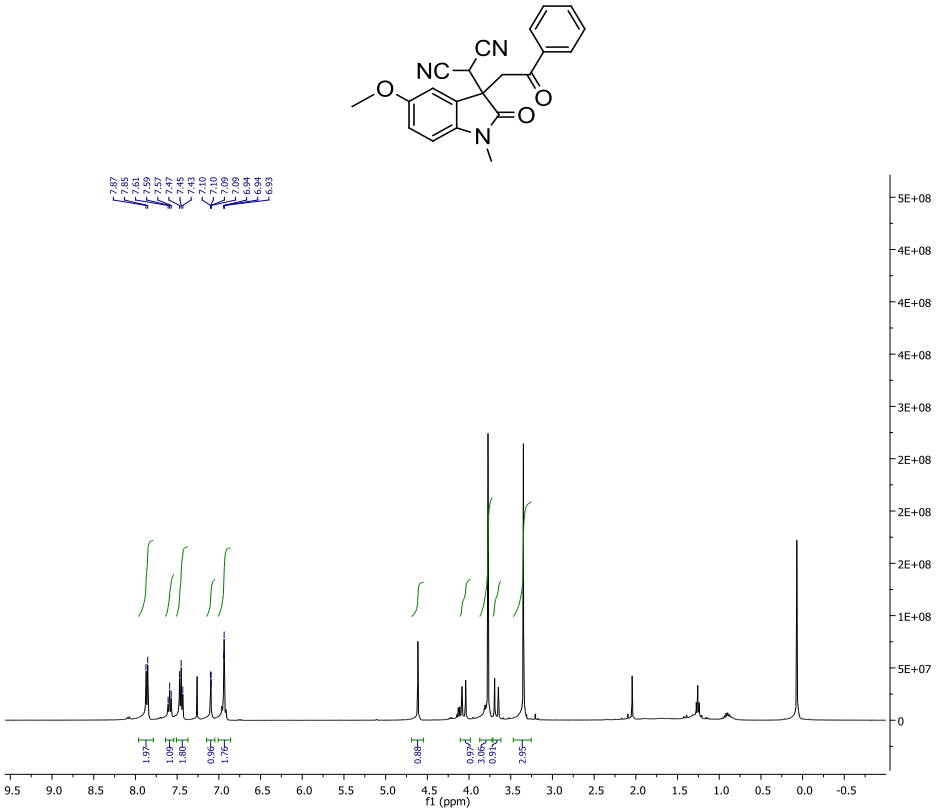


Figure A. 17. ^{1}H NMR spectrum of compound **55**

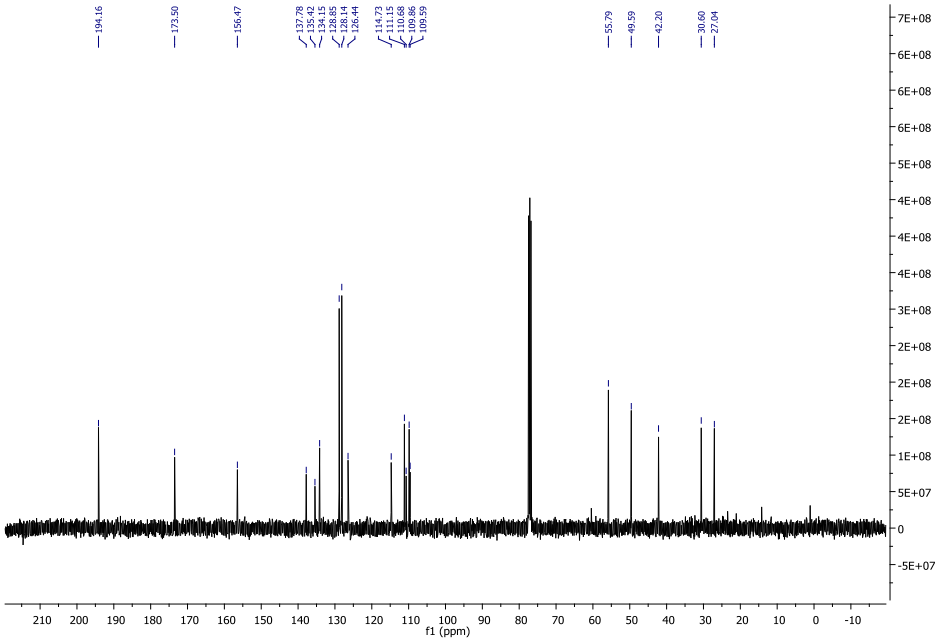


Figure A. 18. ^{13}C NMR spectrum of compound **55**

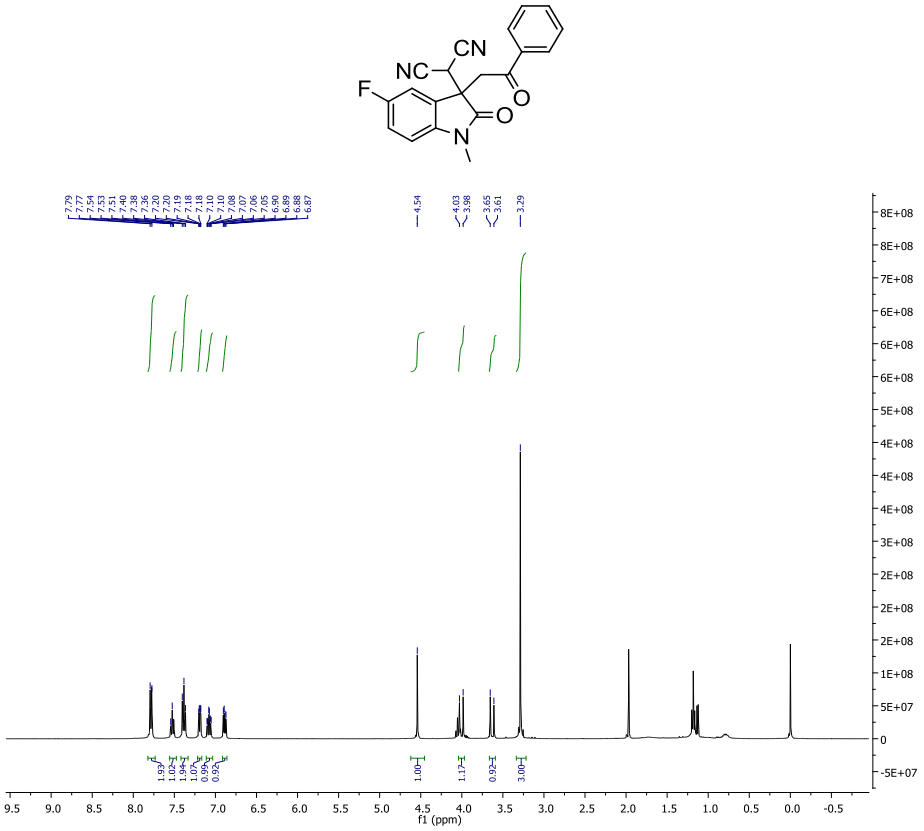


Figure A. 19. ^{1}H NMR spectrum of compound **56**

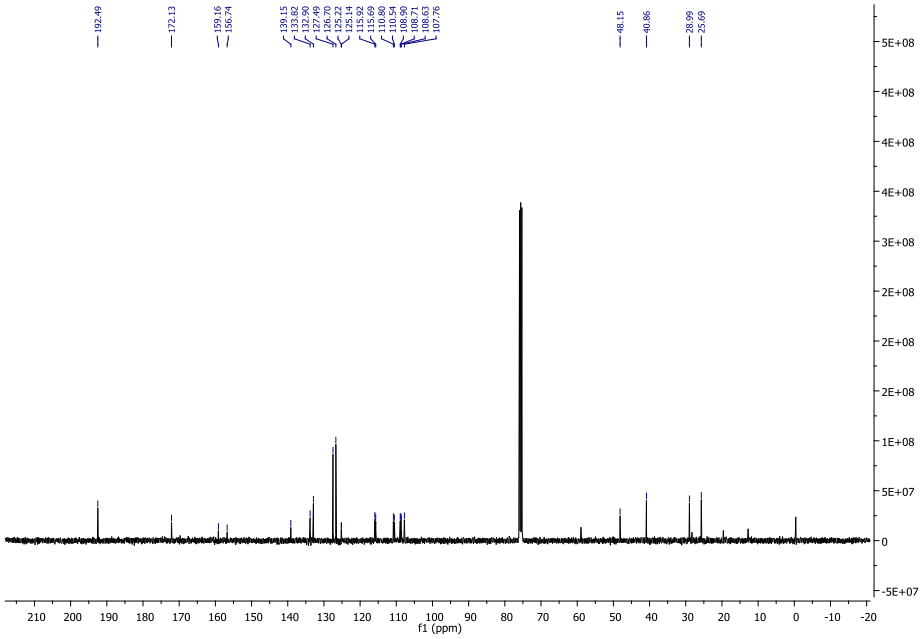


Figure A. 20. ^{13}C NMR spectrum of compound **56**

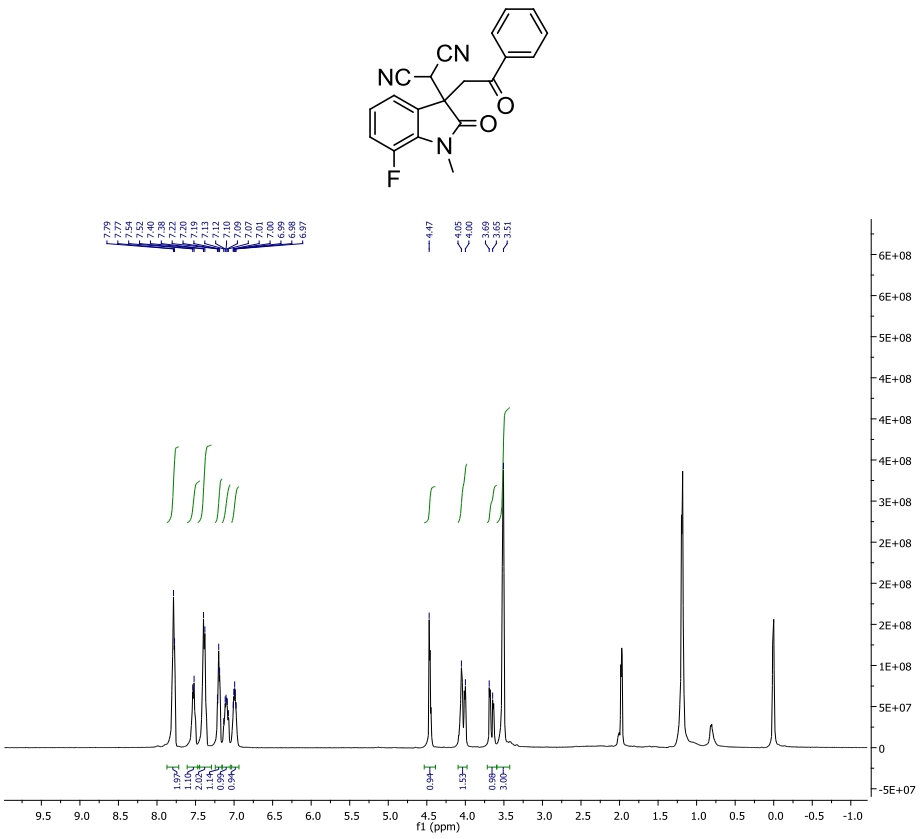


Figure A. 21. ^{1}H NMR spectrum of compound **57**

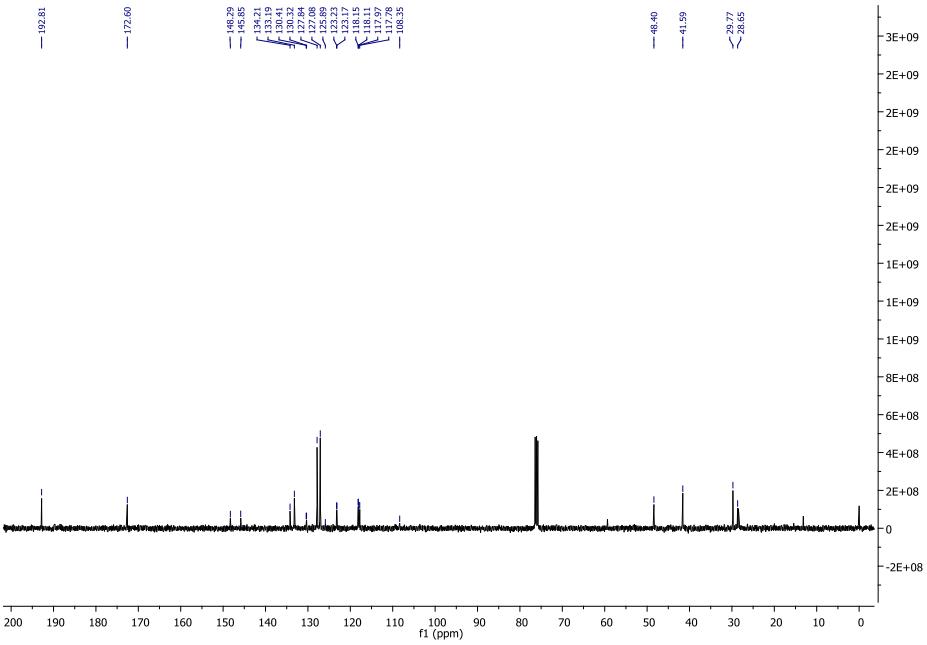


Figure A. 22. ^{13}C NMR spectrum of compound **57**

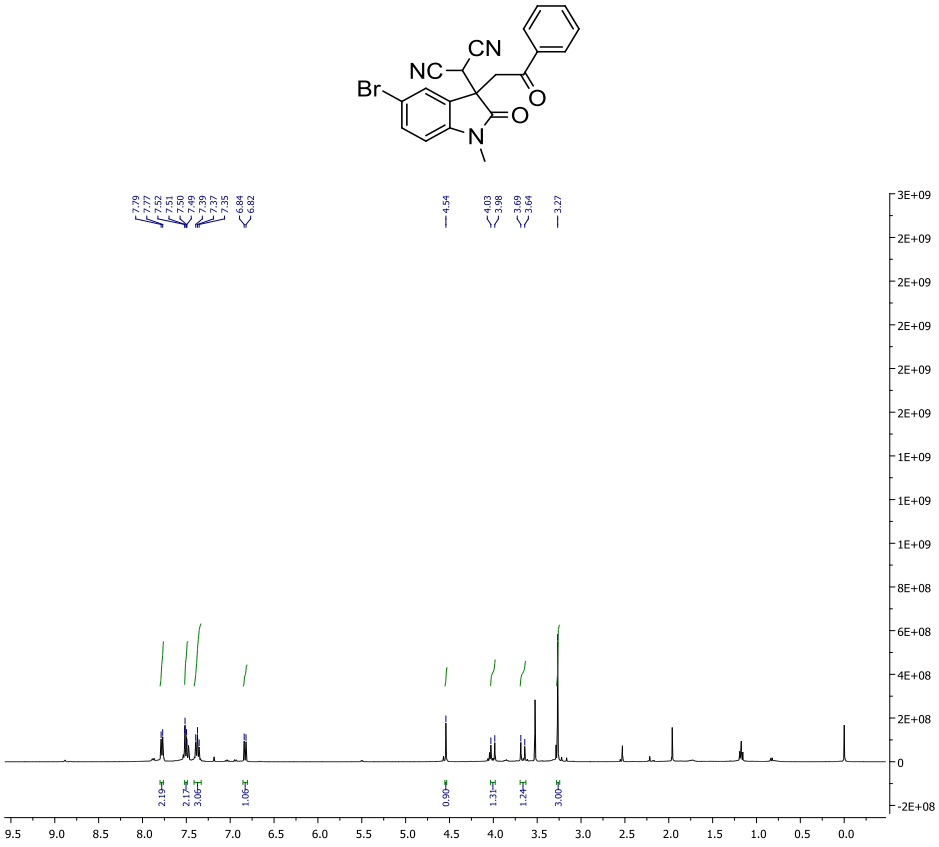


Figure A. 23. ^{1}H NMR spectrum of compound **58**

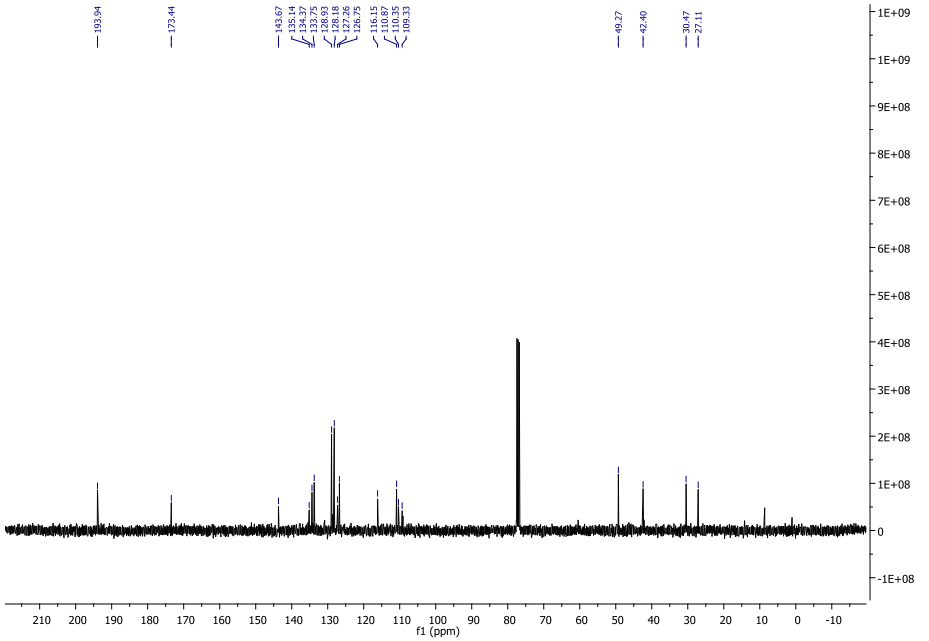


Figure A. 24. ^{13}C NMR spectrum of compound **58**

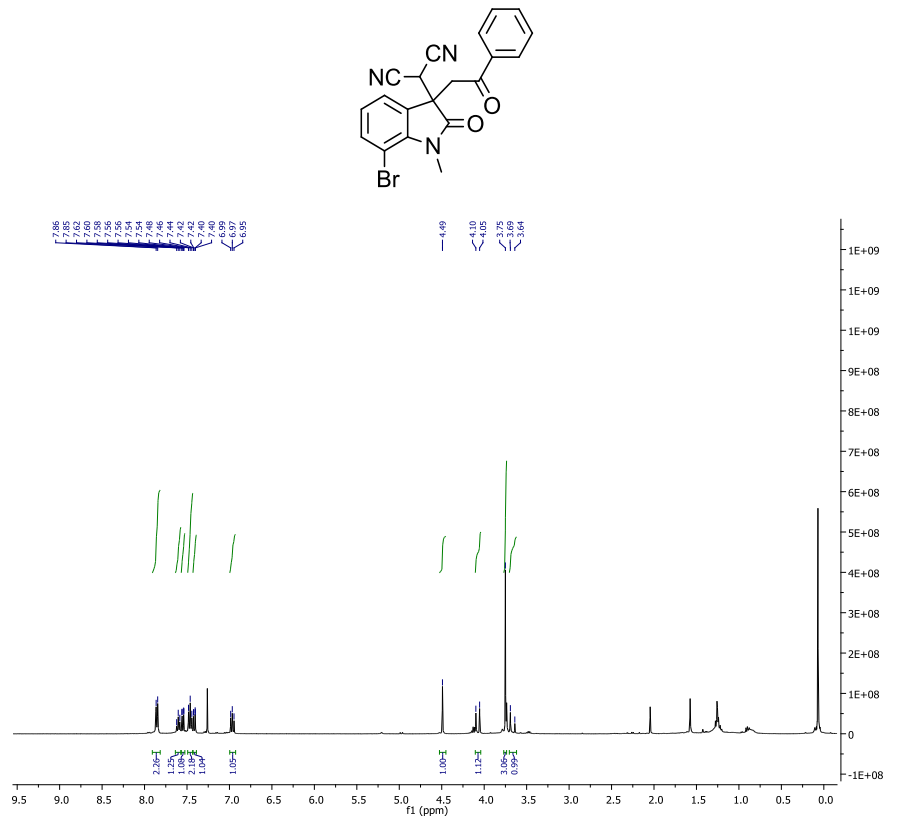


Figure A. 25. ^{1}H NMR spectrum of compound **59**

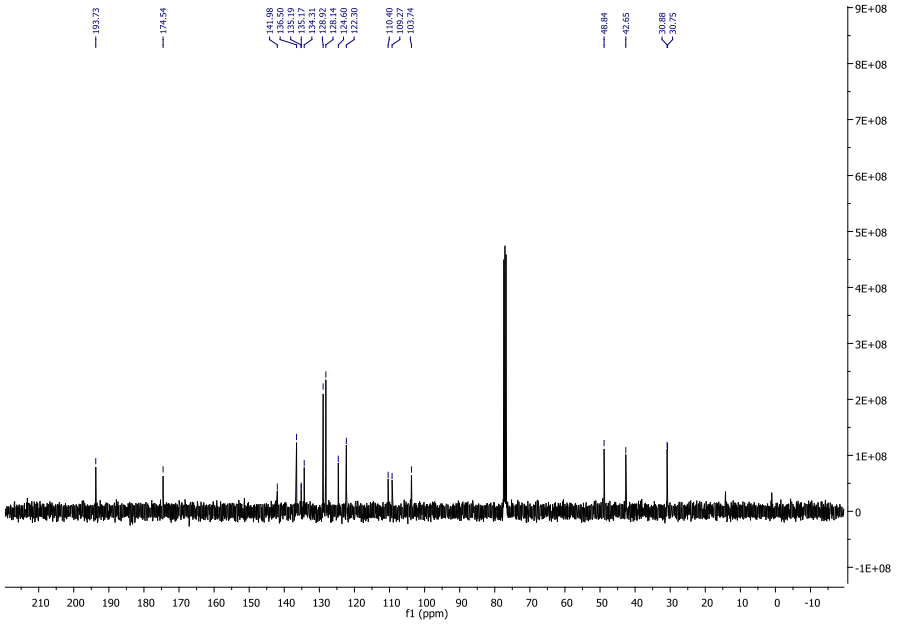


Figure A. 26. ^{13}C NMR spectrum of compound **59**

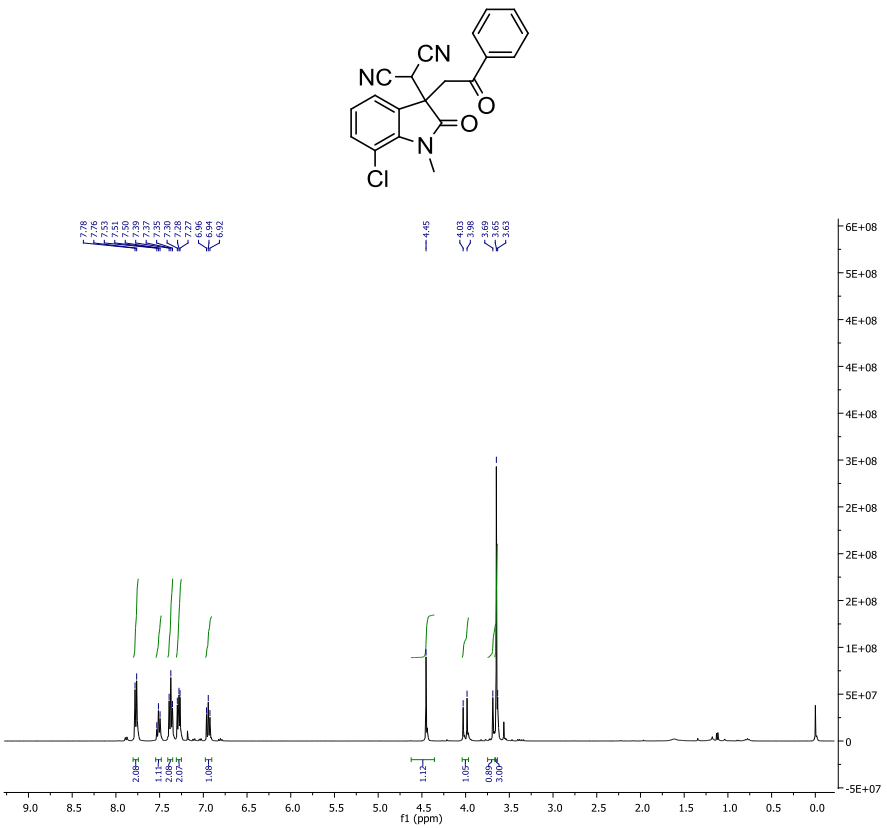


Figure A. 27. ^{1}H NMR spectrum of compound **60**

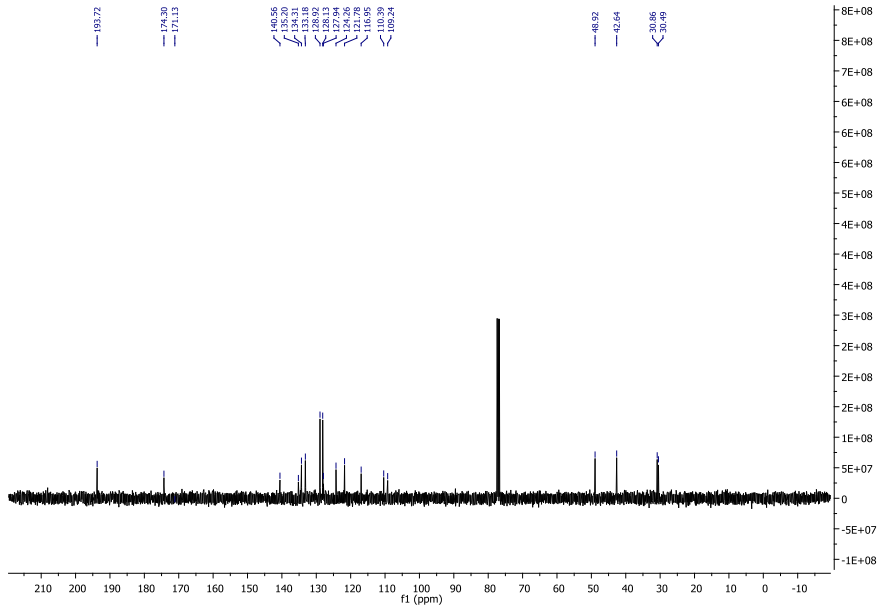


Figure A. 28. ^{13}C NMR spectrum of compound **60**

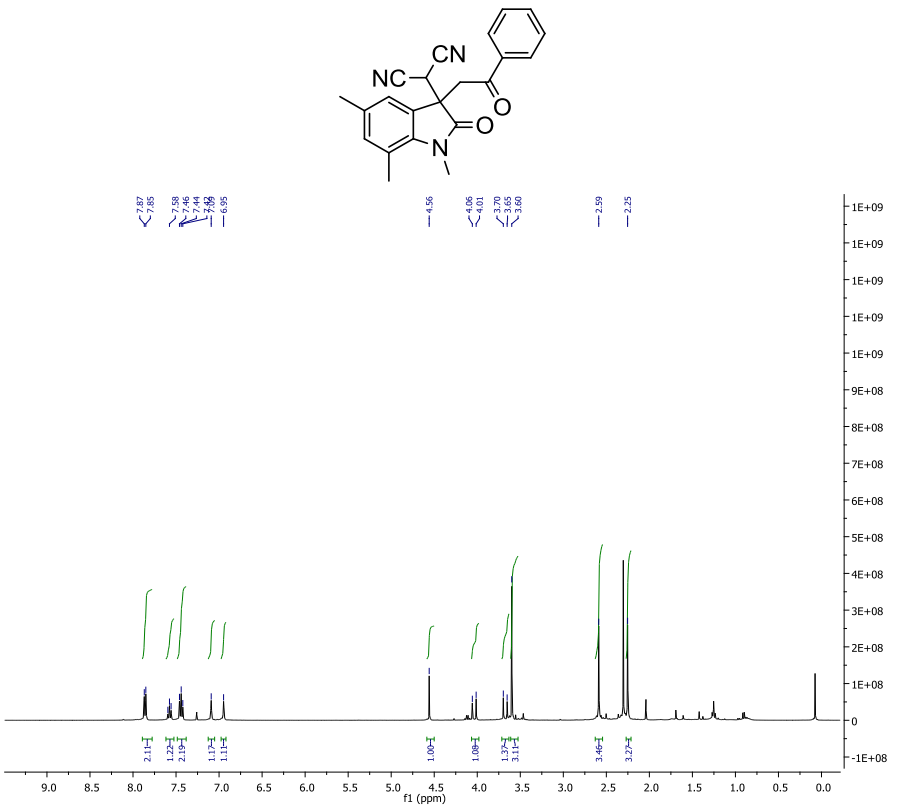


Figure A. 29. ^{1}H NMR spectrum of compound **61**

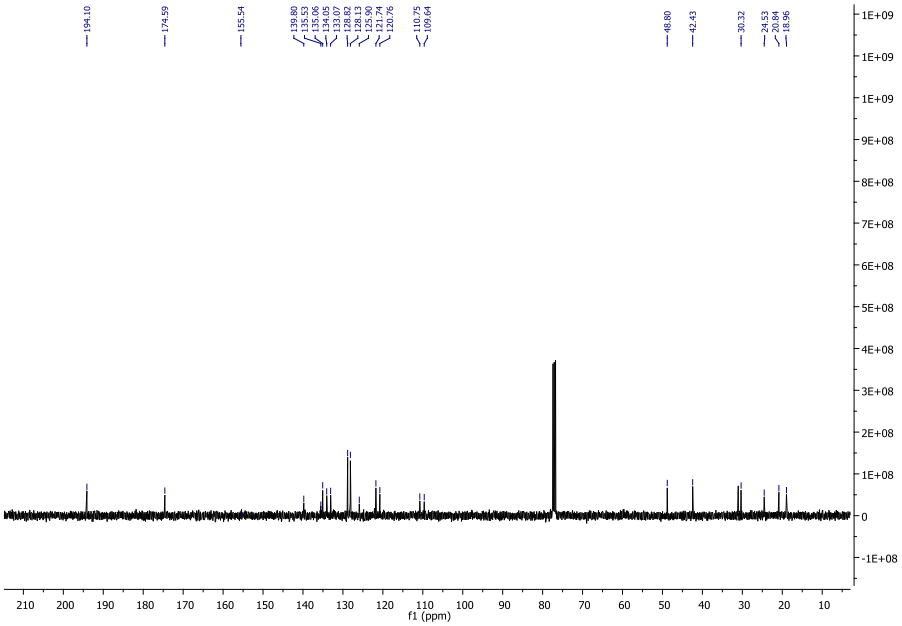


Figure A. 30. ^{13}C NMR spectrum of compound **61**

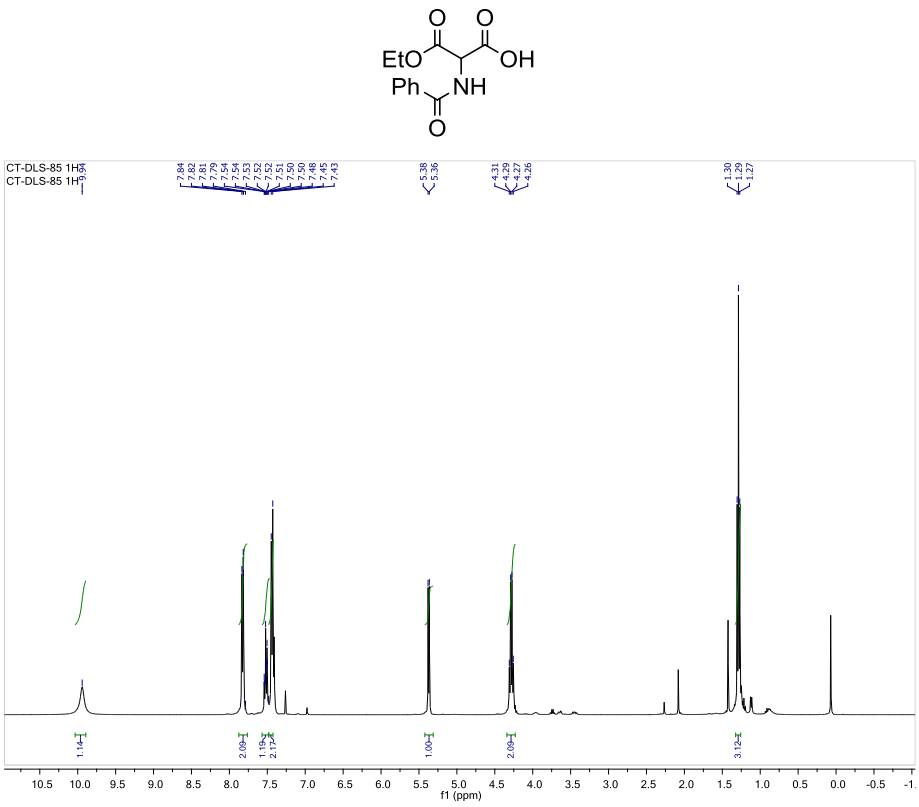


Figure A. 31. ^{1}H NMR spectrum of compound **43**

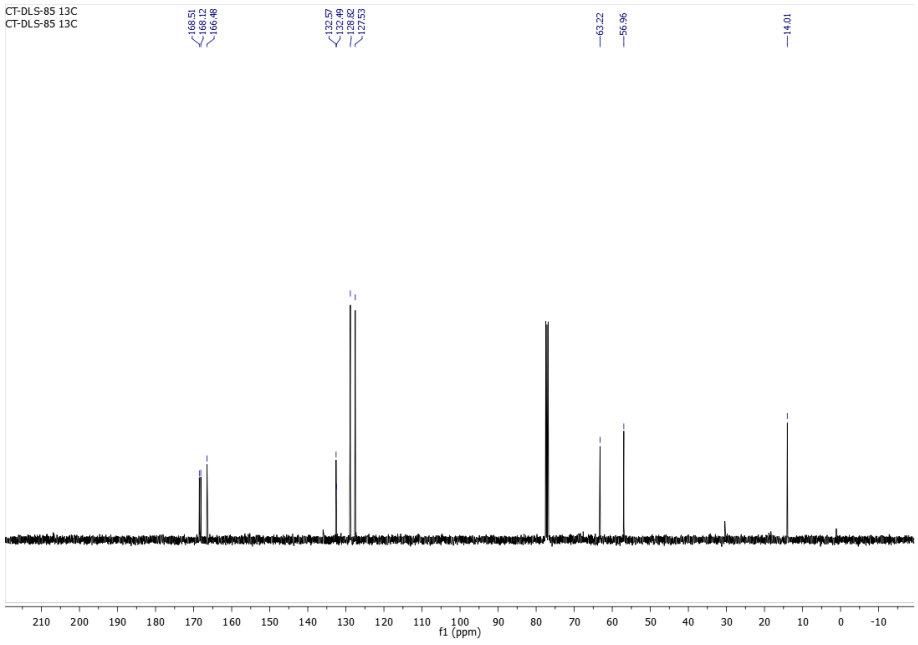
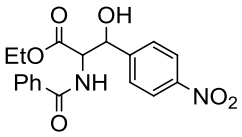


Figure A. 32. ^{13}C NMR spectrum of compound **43**



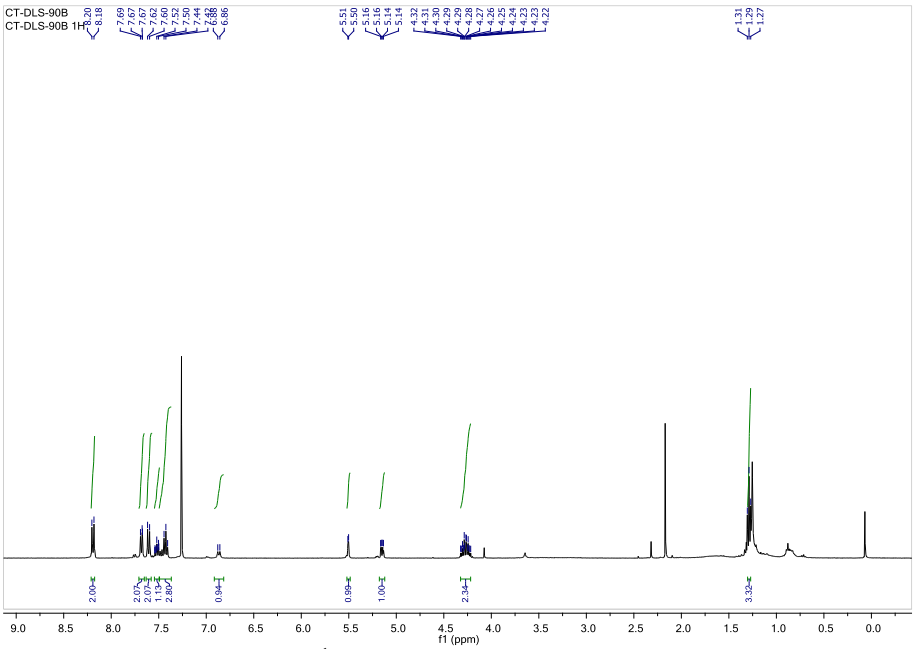


Figure A. 33. ^{1}H NMR spectrum of compound **45**

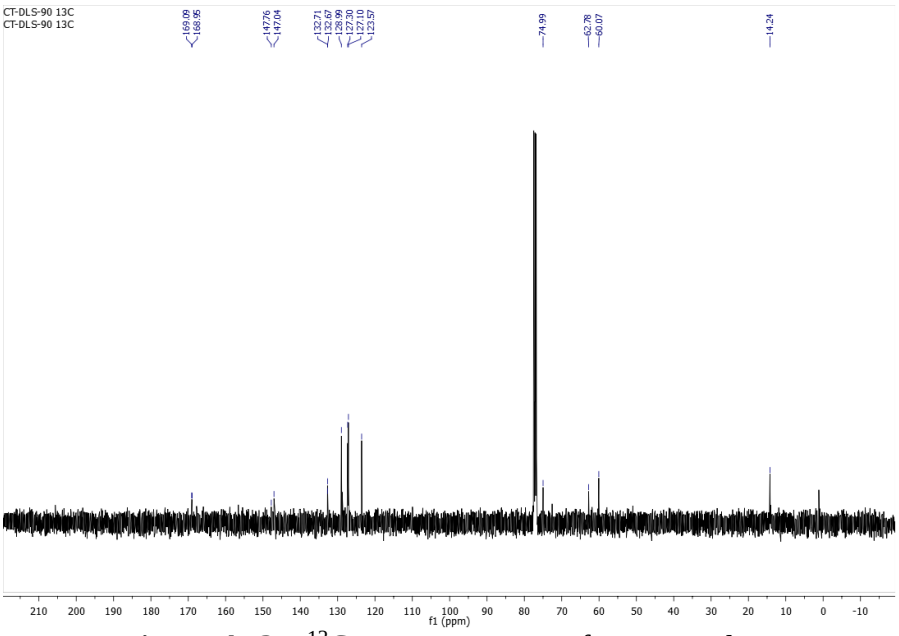
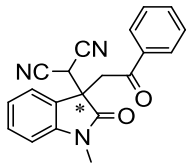


Figure A. 34. ^{13}C NMR spectrum of compound **45**

APPENDIX B

HPLC DATA



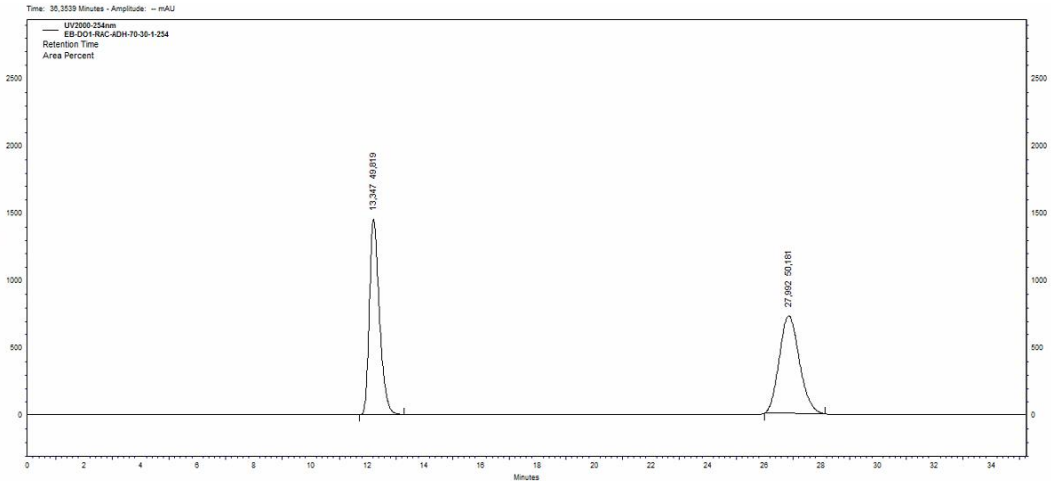


Figure B. 1. HPLC chromatogram of *rac*-**49**

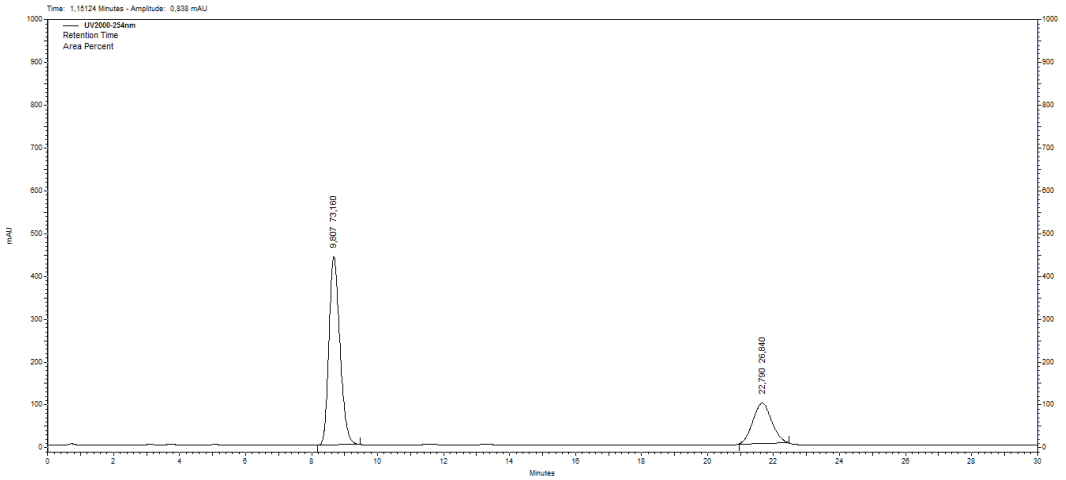
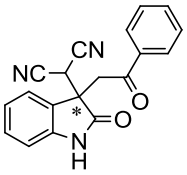


Figure B. 2. HPLC chromatogram of enantiomerically enriched **49**



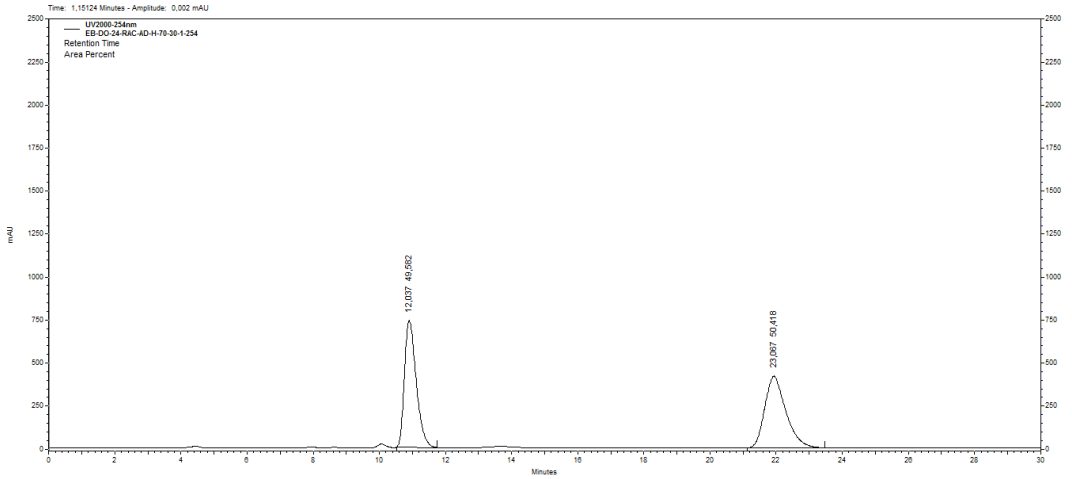


Figure B. 3. HPLC chromatogram of *rac*-**52**

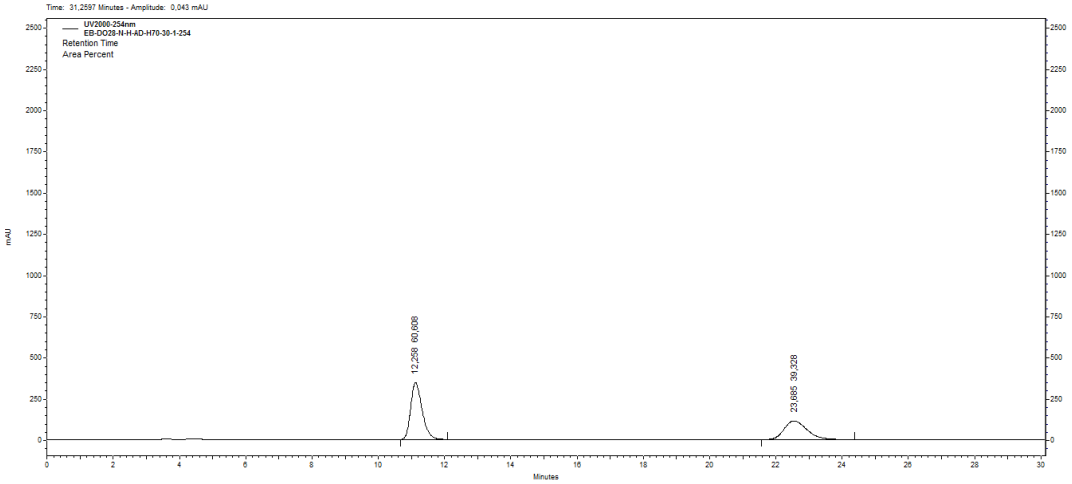


Figure B. 4. HPLC chromatogram of enantiomerically enriched **52**

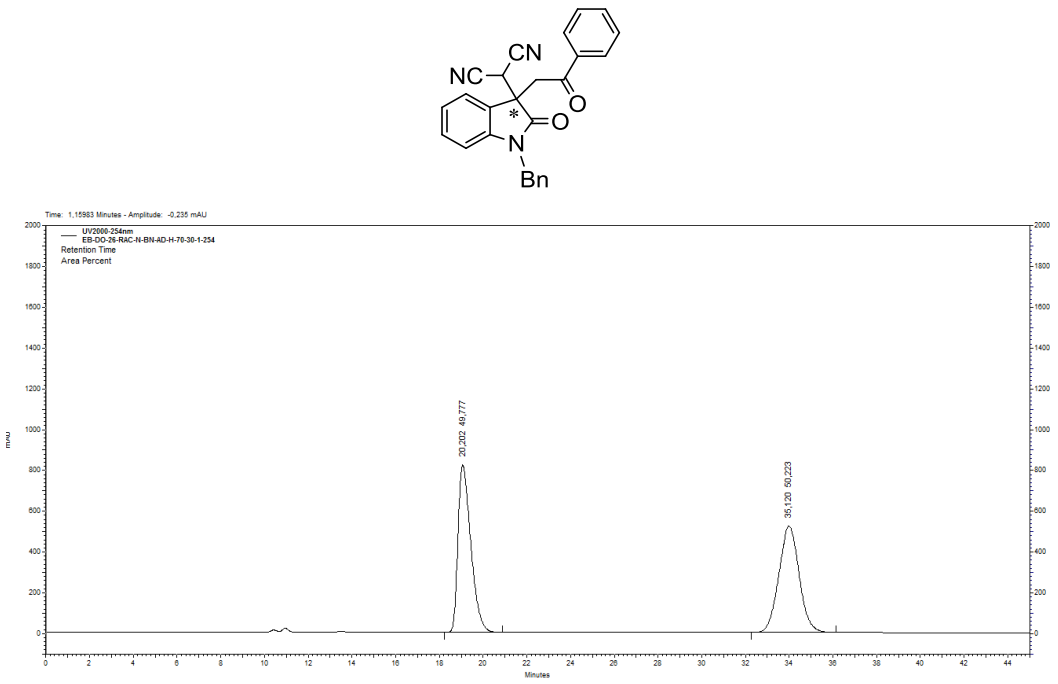


Figure B. 5. HPLC chromatogram of *rac*-**42**

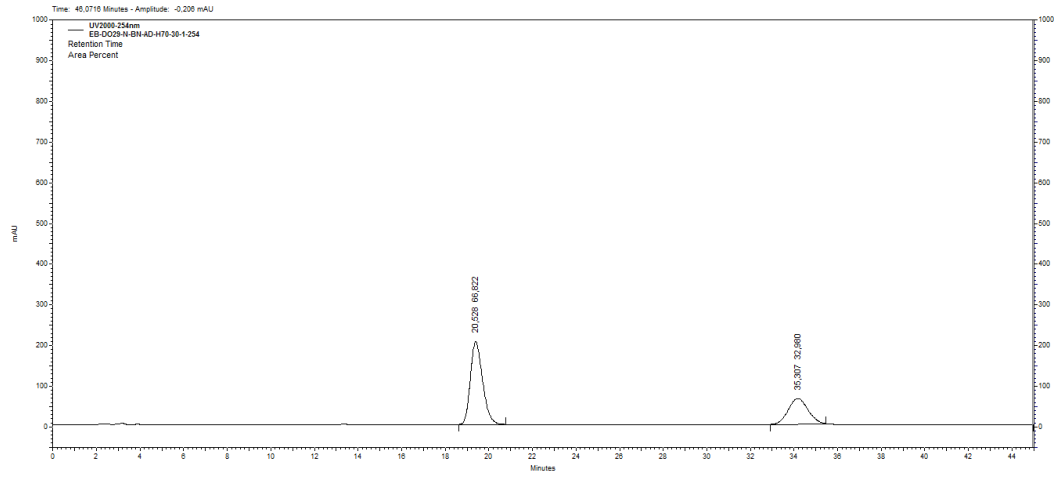
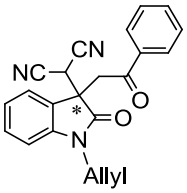


Figure B. 6. HPLC chromatogram of enantiomerically enriched **42**



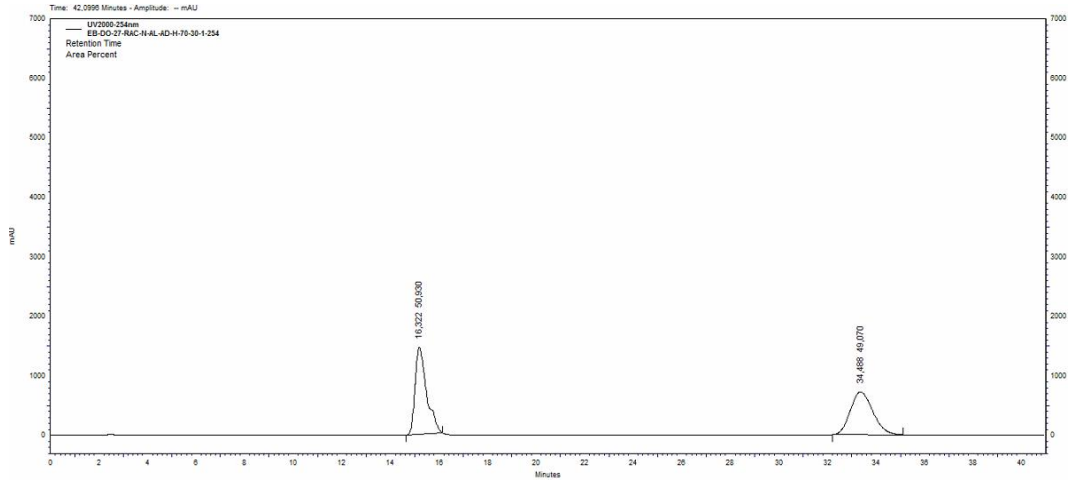


Figure B. 7. HPLC chromatogram of *rac*-**53**

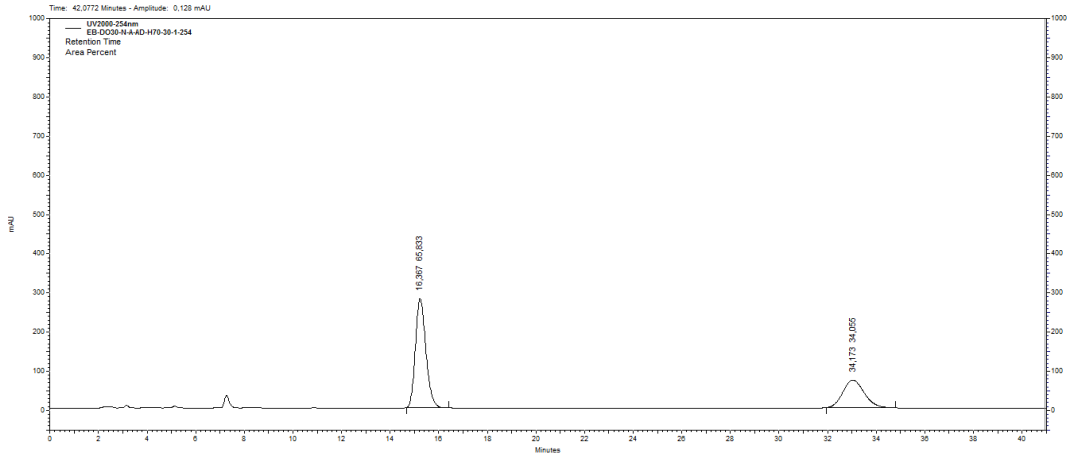


Figure B. 8. HPLC chromatogram of enantiomerically enriched **53**

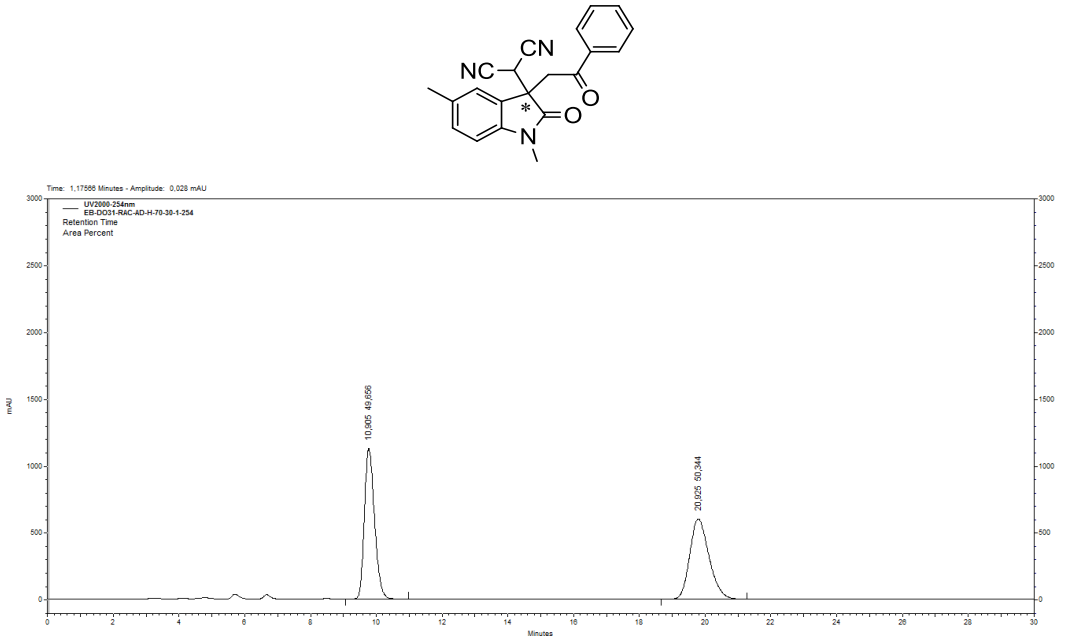


Figure B. 9. HPLC chromatogram of *rac*-**54**

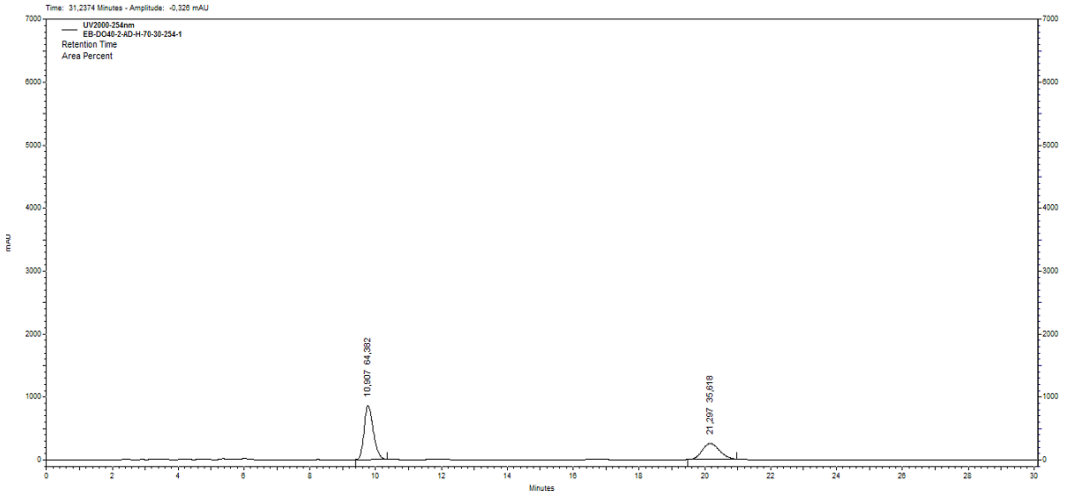
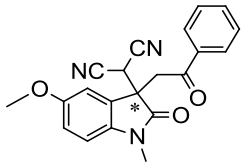


Figure B. 10. HPLC chromatogram of enantiomerically enriched **54**



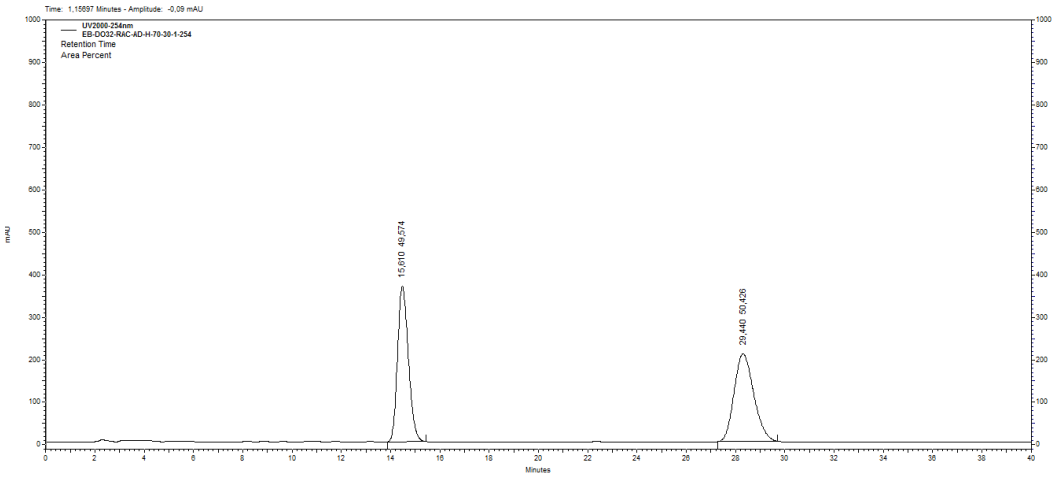


Figure B. 11. HPLC chromatogram of *rac*-**55**

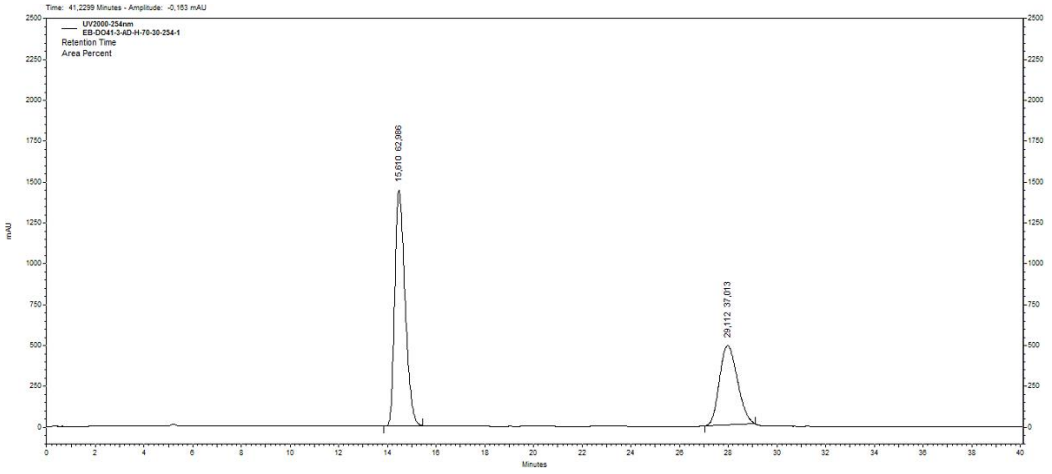
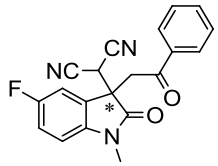


Figure B. 12. HPLC chromatogram of enantiomerically enriched **55**



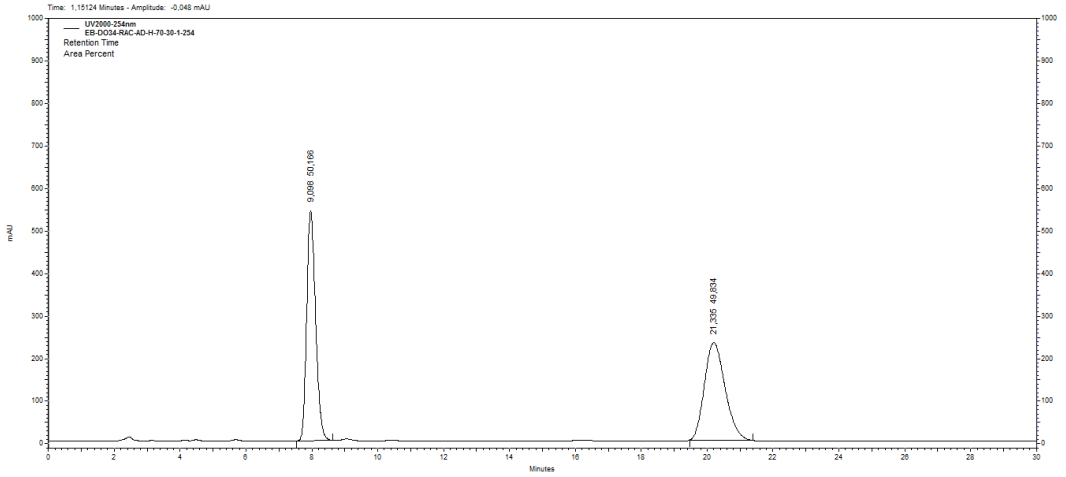


Figure B. 13. HPLC chromatogram of *rac*-**56**

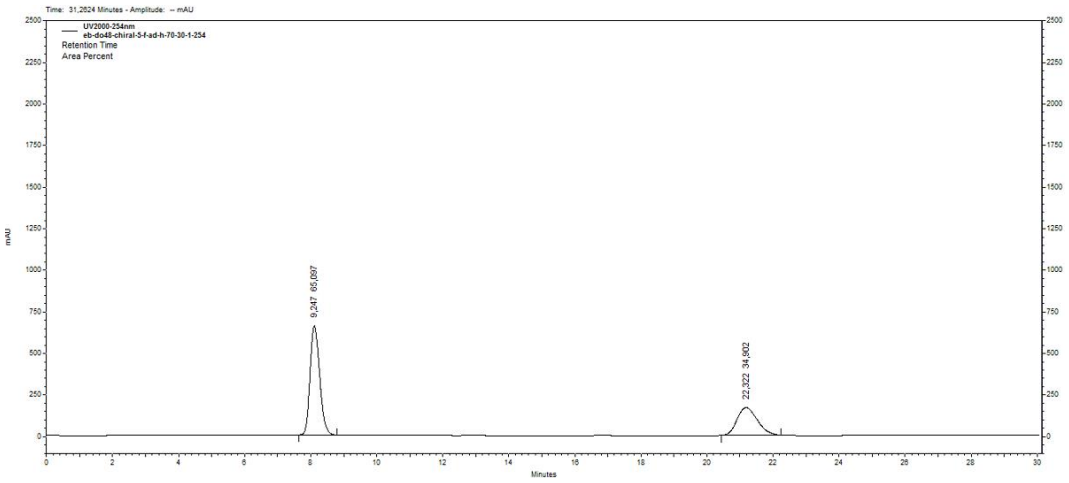
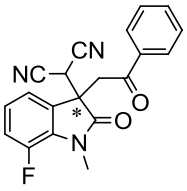


Figure B. 14. HPLC chromatogram of enantiomerically enriched **56**



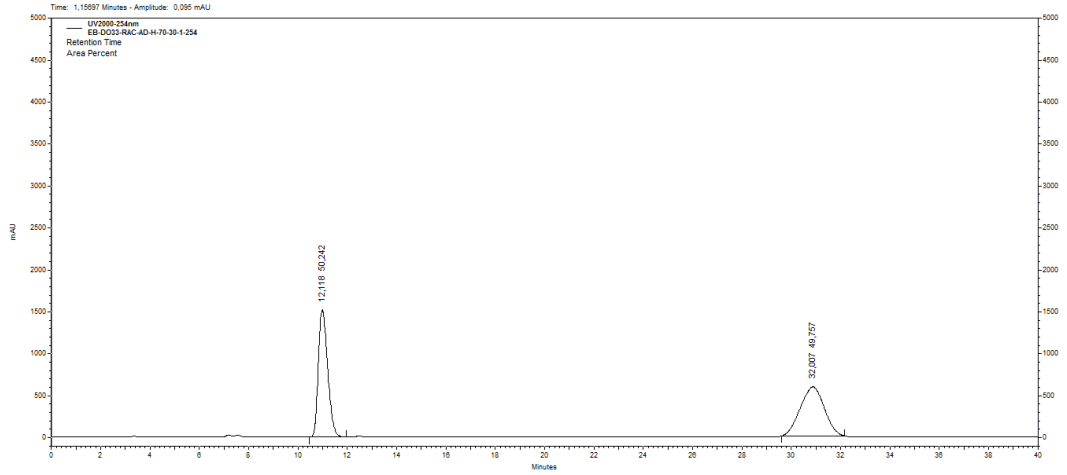


Figure B. 15. HPLC chromatogram of *rac*-**57**

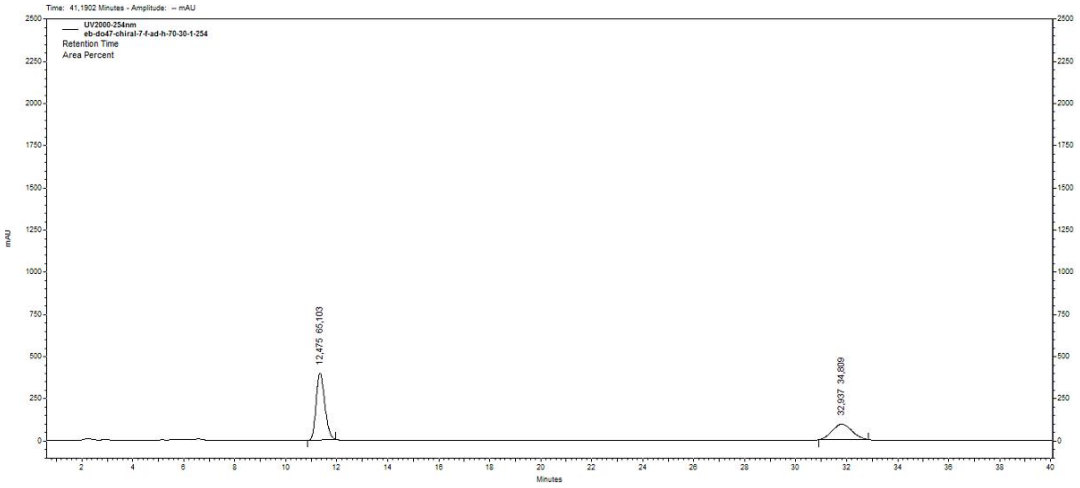
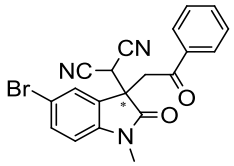


Figure B. 16. HPLC chromatogram of enantiomerically enriched **57**



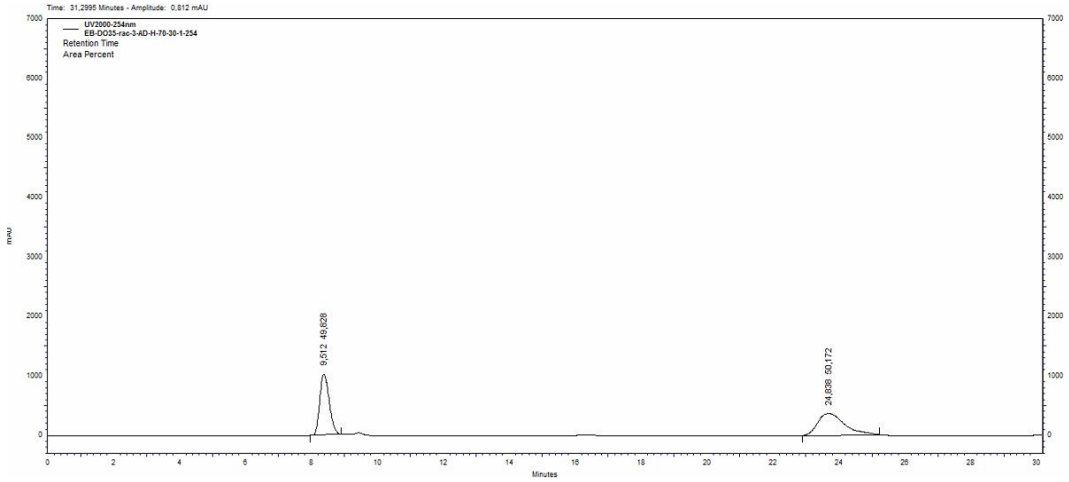


Figure B. 17. HPLC chromatogram of *rac*-**58**

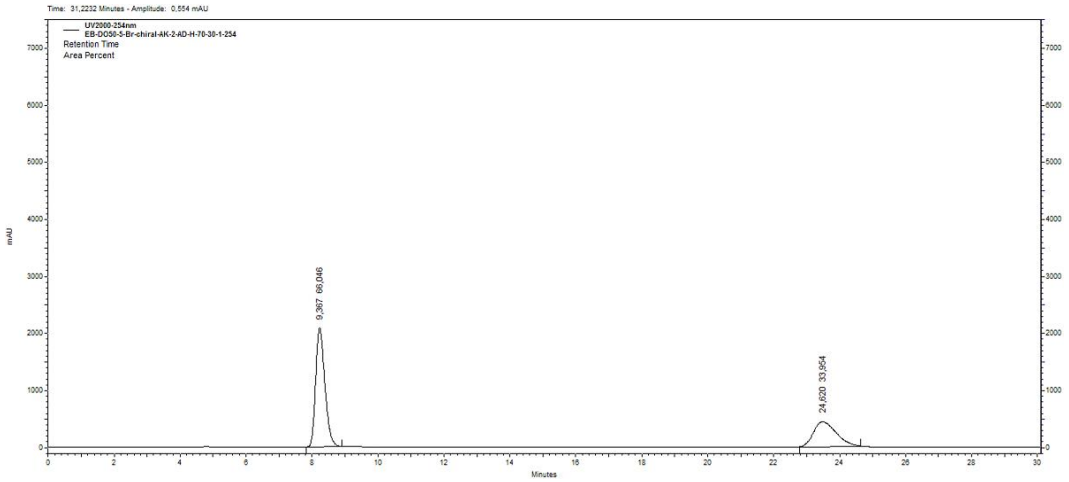
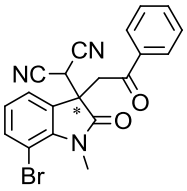


Figure B. 18. HPLC chromatogram of enantiomerically enriched **58**



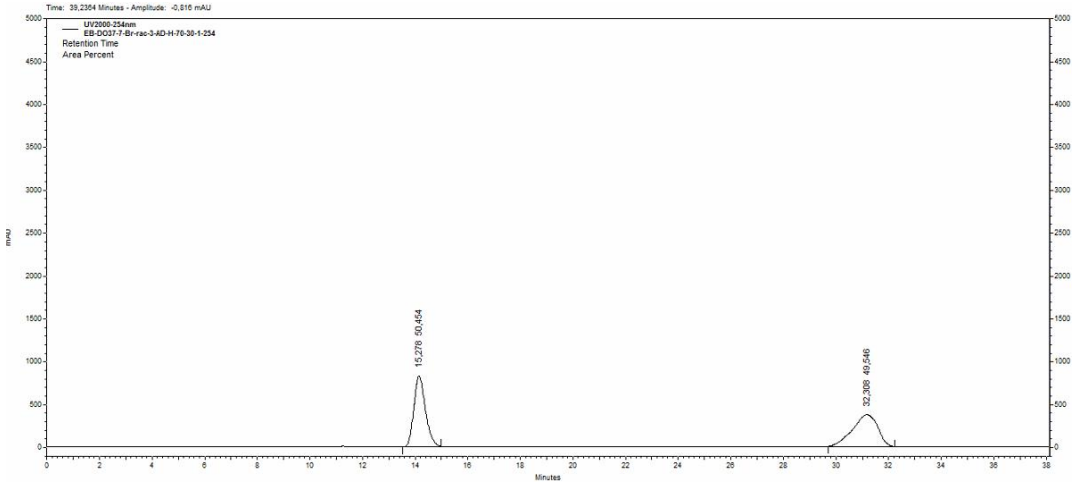


Figure B. 19. HPLC chromatogram of *rac*-**59**

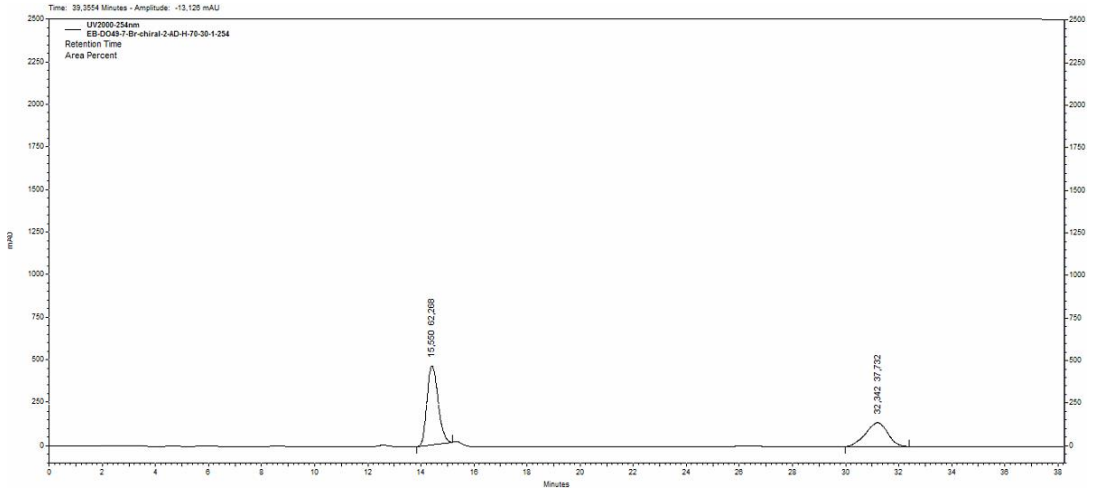


Figure B. 20. HPLC chromatogram of enantiomerically enriched **59**

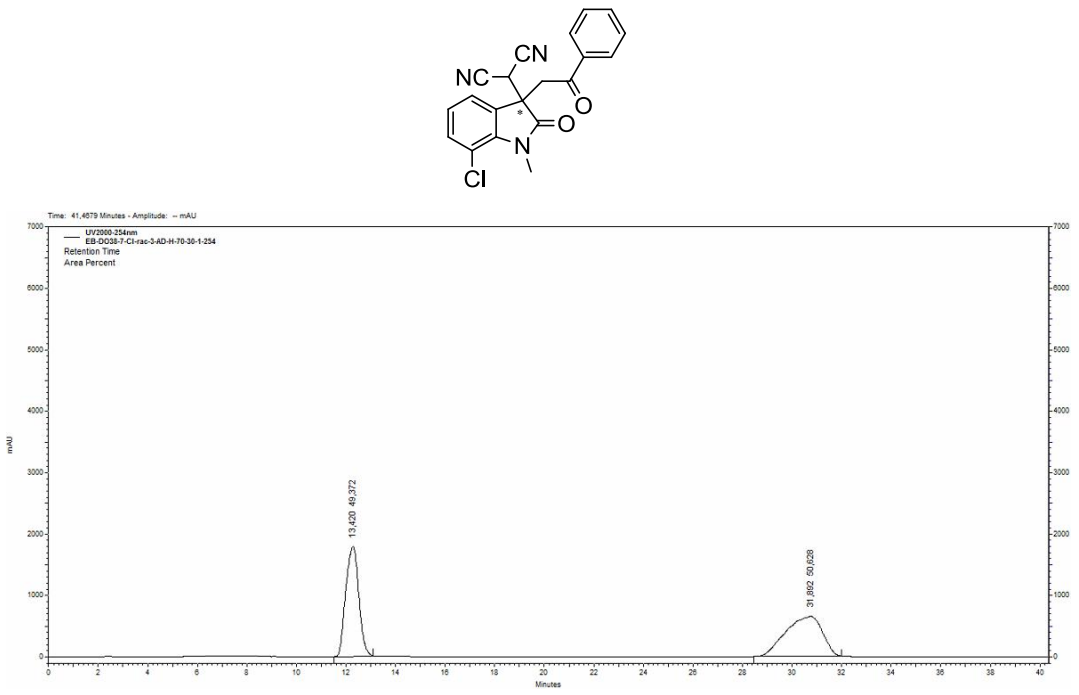


Figure B. 21. HPLC chromatogram of *rac*-**60**

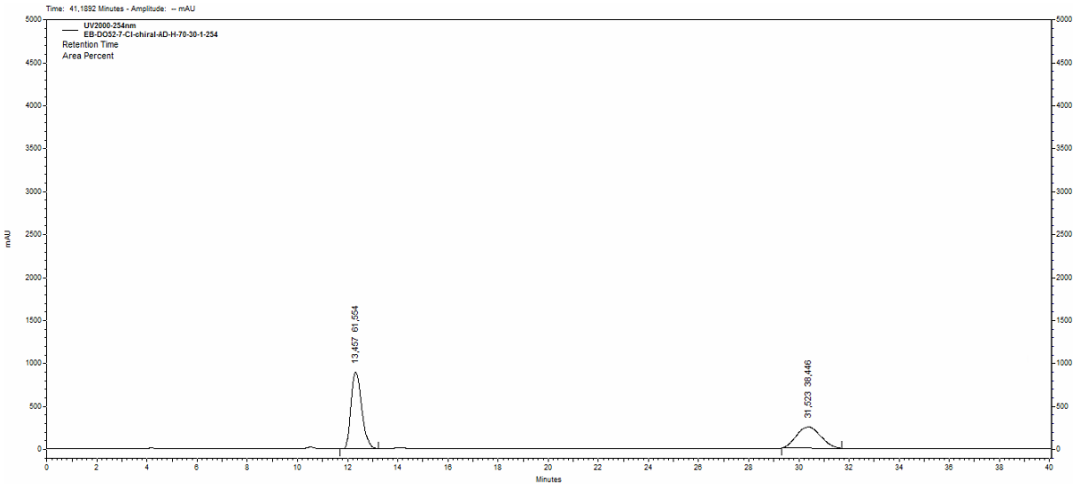


Figure B. 22. HPLC chromatogram of enantiomerically enriched **60**

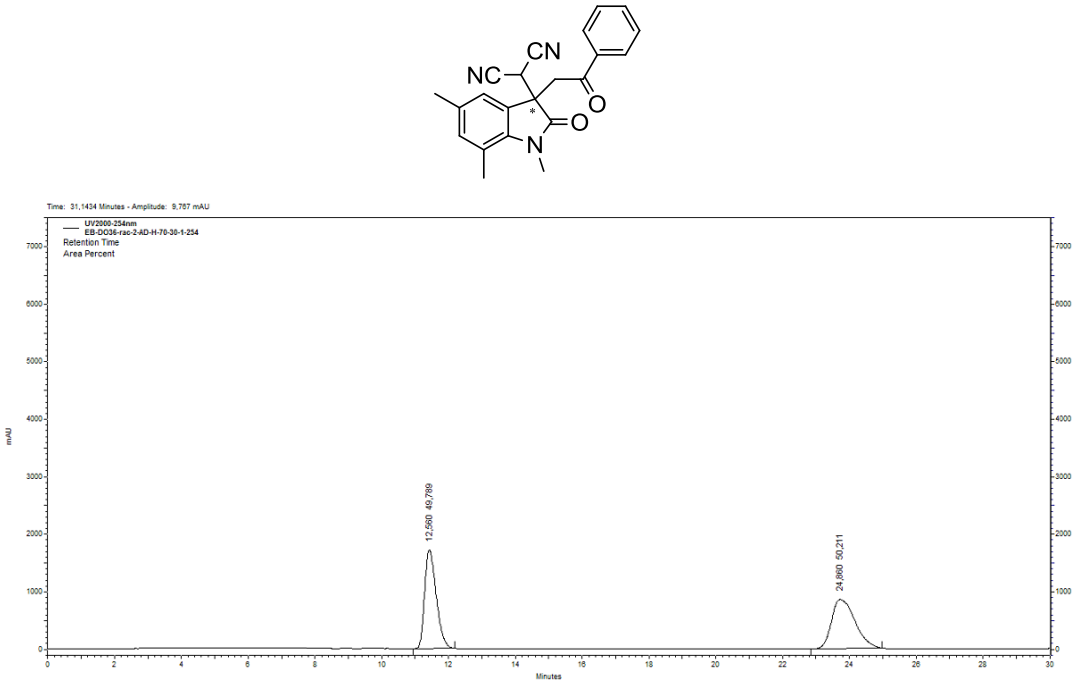


Figure B. 23. HPLC chromatogram of *rac*-**61**

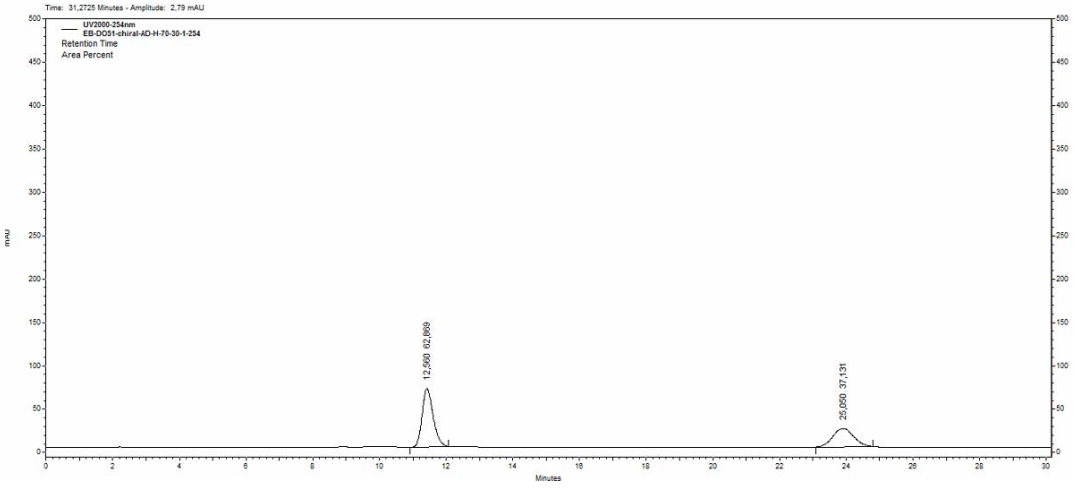
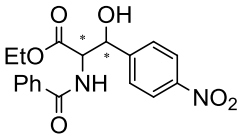
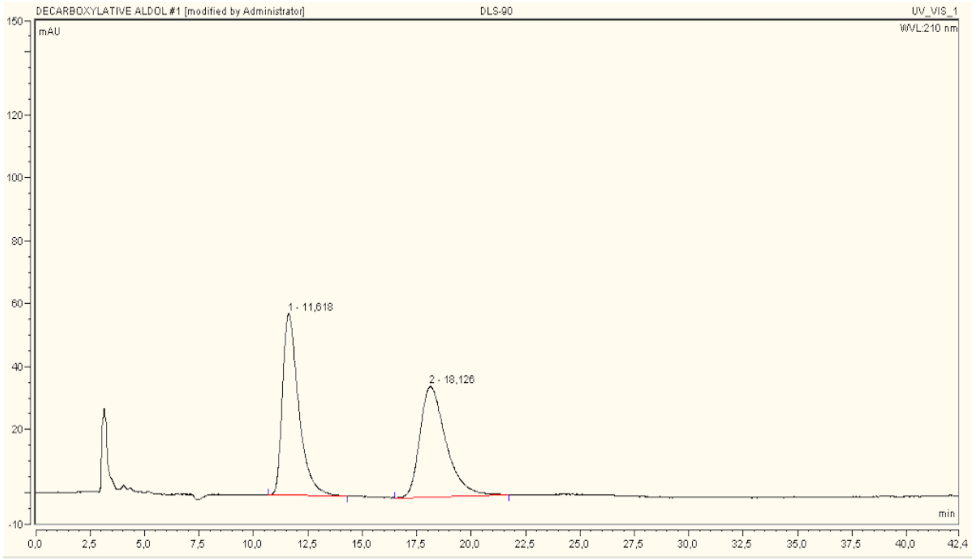


Figure B. 24. HPLC chromatogram of enantiomerically enriched **61**





No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	11,618	49,8690	n.a.	BMB*	57,664	50,561	3,83
2	n.a.	18,126	48,7529	n.a.	BMB*	35,051	49,439	n.a.
Total:			98,6120	0,0000		92,715	100,00	

Figure B. 25. HPLC chromatogram of *rac*-**45**

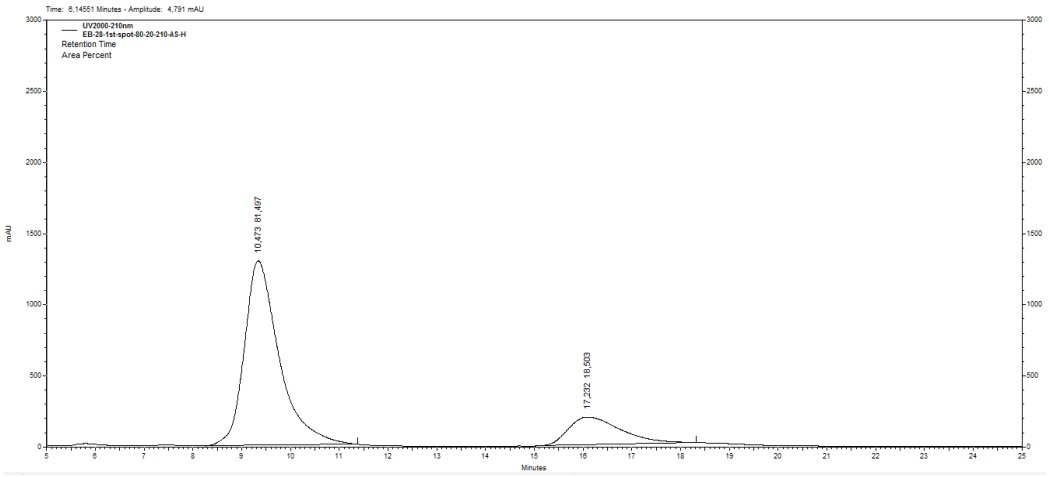


Figure B. 26. HPLC chromatogram of enantiomerically enriched **45**