ENANTIOSELECTIVE MICHAEL ADDITION OF MALONONITRILE TO CHALCONE WITH BIFUNCTIONAL SQUARAMIDE ORGANOCATALYSTS

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ABSTRACT

ENANTIOSELECTIVE MICHAEL ADDITION OF MALONONITRILE TO CHALCONE
WITH
BIFUNCTIONAL SQUARAMIDE ORGANOCATALYSTS

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M.S., Department of Chemistry

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4*H*-pyran derivatives show diverse biological activity such as antimicrobial, antibacterial, antiviral and antifungal. 4*H*-pyran derivatives can be synthesized easily from 2-(3-oxo-1,3-diphenylpropyl)malononitrile which is the Michael addition product of malononitrile to *trans*-chalcone. Synthesizing chiral biologically active compounds with metal free approach (organocatalysis) is a significant topic. In this thesis, chiral 2-(3-oxo-1,3-diphenylpropyl)malononitrile was synthesized with quinine or 2-aminoDMAP based novel bifunctional organocatalysts which were developed in our group. In the asymmetric Michael addition reaction, 2-adamantyl anchored quinine-squaramide organocatalyst was found the best among the other tested organocatalysts in the optimization reactions. Consequently, 10 different derivatives of Michael product were synthesized up to 86% ee under the optimized condition with very low catalyst loading (0.5 mol%).

Keywords: asymmetric synthesis, organocatalysis, enantioselectivity, Michael addition

ÖZ

BİFONKSİYONEL SKUARAMİT ORGANOKATALİZÖRLER
İLE
MALONONİTRİLİN ÇALKONA ENANTİYOSEÇİCİ MICHAEL KATILMASI

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Yüksek Lisans, Kimya Bölümü

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4*H*-Piran türevleri antimikrobiyel, antibakteriyel, antiviral ve antifungal gibi birçok değişik biyolojik aktivitelere sahiptir. Bu türevler malononitril ve çalkonun Michael katılma ürünü olan 2-(3-okzo-1,3-difenilpropil)malononitril'den kolayca sentezlenebilir. Biyolojik olarak aktif kiral maddelerin metal kullanılmayarak, (organokataliz) sentezlenmesi önemli bir konudur. Bu tezde, grubumuzda geliştirilen özgün 2-aminoDMAP ve kinin temelli kiral bifonksiyonel organokatalizörler kullanılarak kiral 2-(3-okzo-1,3-difenilpropil)malononitril sentezlenmiştir. Asimetrik Michael katılma tepkimesinde 2-adamantil gurubu bağlı kinin-skuaramit organokatalizörü diğer test edilen organokatalizörler içinde en iyi sonucu vermiştir. Sonuç olarak, bulunan optimum koşullar altında, 10 farklı asimetrik Michael katılma ürünü çok düşük katalizör kullanılarak (0.5 mol%) maksimum %86 enantiyoseçicilik ile sentezlenmiştir.

Anahtar Kelimeler: asimetrik sentez, organokataliz, enantiyoseçicilik, Michael katılma

To my dear family…

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LIST OF ABBREVIATIONS

PTA : Paratartaric acid

DMAP : 4-Dimethylamino pyridine

HOMO : Highest occupied molecular orbital

LUMO : Lowest unoccupied molecular orbital

NBO : Natural bond orbital

DCM : Dichloromethane

THF : Tetrahydrofuran

MS : Molecular Sieves

ee : Enantiomeric excess

HRMS : High Resolution Mass Spectroscopy

NMR : Nuclear Magnetic Resonance

IR : InfraRed

CHAPTER 1

INTRODUCTION

1.1. Importance of Chirality

The term of the *Chiral* or *Chirality* was used firstly in 1894 by Lord Kelvin (1824-1907).[1] It is derived from *cheir* in Greek, means hand. Nowadays hands are still being used as a metaphor to understand chirality more easily. He defined this concept by the following comment:

> "*I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself*".

However, Kelvin was not the first scientist working on this phenomena. In 1848, Louis Pasteur (1822-1895) discovered molecular chirality.[2,3] Pasteur worked on many salts of two acids, natural (+)-tartaric acid (TA) and paratartaric acid (PTA, old name of racemic tartaric acid). He recognized that sodium ammonium salt of PTA have two different crystals which were hemihedral. After manually separation of two enantiomorphous crystals, he analyzed their optical rotation and realized that two of them rotate polarized light with same degree but opposite direction.[3]

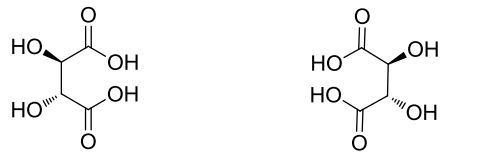


Figure 1. Enantiomers of optically active tartaric acid

Pasteur's this discovery could be stated as a milestone in stereochemistry. Nowadays, chirality is a significant property especially in drug industry. Enantiomers have the same chemical and physical properties but they show different biological activities in most cases. Since human body is chiral, generally it needs chiral therapy. Enantiomers have different appearance in space so enantiomers of drug interact with receptors by different ways. For this reason one enantiomer can be potent compound called eutomer to cure while the other can be less, none or anti effective compound called distomer.[4]

Because of different behavior of enantiomers on metabolism, it is needed to be obtained or synthesized with high purity of one isomer. Chirality or asymmetric synthesis possesses an important place in life sciences.

1.2. Asymmetric Synthesis

Asymmetric organic reactions have acquired a crucial place in both industry and academic world. Especially pharmaceutical industry has indicated substantially scaled up interest in asymmetric organic reactions.

In general, to describe asymmetric synthesis it can be said that it is a reaction in chiral environment and in this reaction achiral reagent turns into chiral product.[5]

There are so many ways to obtain enantiopure products. It can be divided into three categories. The first and oldest method is the isolation from natural sources. Most of the alkaloids, terpenes and carbohydrates naturally occur as enantiomerically pure compounds. Second method is the racemic resolutions done by preferential crystallization (separating optically inactive isomer), crystallization of diastereomeric salts and kinetic (enzymatic or chemical) resolution.[6] The last one is the asymmetric induction: (a) Internal asymmetric induction. In this method chiral product is synthesized by starting with chiral compound. (b) Relayed asymmetric induction or chiral auxiliaries. Substrate must have enantiotopic groups or faces and chiral auxiliary is covalently added and consequently separated from the substrate. (c) External asymmetric induction. In this method catalytic amount of chiral moiety is used. After

experiment it is reacquired in its original form and so it can be used for other experiments.[7]

1.2.1. Catalytic Asymmetric Synthesis

Among the all asymmetric synthetic methods, the most popular and assertive one is the catalytic asymmetric synthesis. It is more convenient than stoichiometric asymmetric synthesis for industrial production since having apparent economic advantages.

Catalytic asymmetric synthesis can be divided into three groups in terms of types of catalyst. These are biocatalysis, transition metal catalysis and organocatalysis.

Biocatalysis is a significant way to obtain chiral product in which enzymes could be placed in chief part in this type of reactions. Enzymes having diverse functionalities are used for kinetic resolution of racemates and used as a catalyst in asymmetric synthesis (Figure 2).

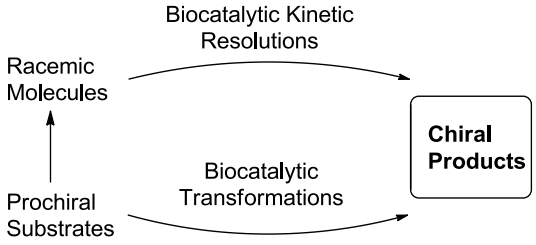
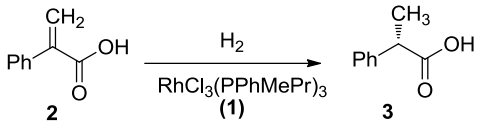


Figure 2. Types of biocatalysis

Transition-metal catalysis is a wide range topic. In 1968, Knowles *et al*.[8] showed the first time, chiral transition metal based catalyst can transfer chiral information to the product. He worked with chiral rhodium catalyst **1** (69% ee) for hydrogenation of α-phenylacrylic acid **(2)**, and obtained (+)-hydratropic acid **(3)** with 15% ee (Scheme 1).



Scheme 1. The first asymmetric work with transition-metal based catalyst

Then he discovered a cationic rhodium catalyst for synthesizing of rare amino acid *L*-DOPA[9] (Figure 3). In 2001, he was awarded the Nobel Prize shares with Noyori[10] worked on asymmetric hydrogenation and Sharpless[11] worked on asymmetric epoxidation by transition-metal based catalyst.

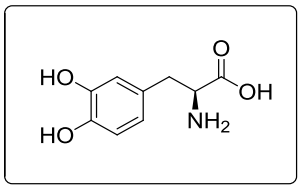
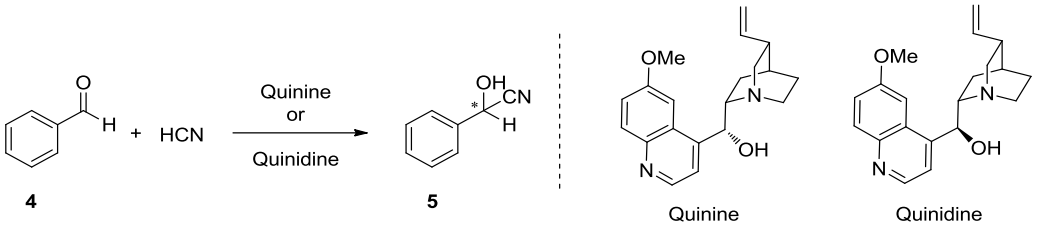


Figure 3. Structure of L-DOPA

The last and third catalytic asymmetric synthesis way is the organocatalysis. Organocatalysts are metal-free, pure organic molecules mostly comprising carbon, hydrogen, oxygen, nitrogen, sulphur and phosphorus. The first asymmetric organocatalytic reaction is the hydrocyanation. In 1912, Bredig and Fiske[12] synthesized chiral cyanohydrins **5** by addition of HCN to benzaldehyde **(4)** in the presence of quinine and quinidine alkaloids (Scheme 2).



Scheme 2. The first asymmetric work with organocatalyst

1.3. Asymmetric Organocatalysis

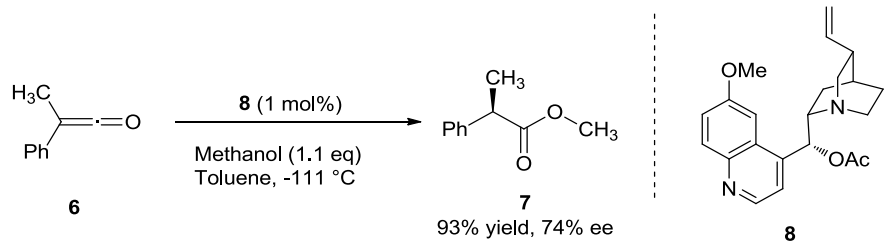
Organocatalysts have an important position in pharmaceutical industry because of the absence of transition metals and their toxicity. Moreover, organocatalysts are resistive, inexpensive, easily available and most importantly environmentally friendly.[13] Generally they are inert to moisture and oxygen so no need to hard experimental conditions.

Organocatalysis is relatively new area among the other methods, enzyme- and metal-catalysis, to synthesize enantiomerically enriched molecules. Organocatalysts have been used in asymmetric synthesis for a century but after 2000 there is a sharp increase in the number of organocatalysis publications.[14]

1.3.1. History of Asymmetric Organocatalysis Advent

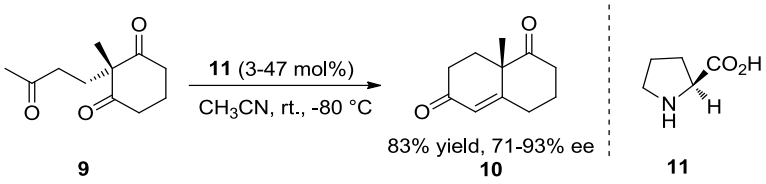
Before asymmetric case, in 1860 first organocatalytic reaction was reported by Justus von Liebig.[15] He used acetaldehyde as organocatalyst to synthesize oxamide from dicyan. After 50 years later from this work, organocatalysts were used firstly in asymmetric synthesis by Bredig and Fiske.[12] Unfortunately they could not exceeded 10 percent enantioselectivity (Scheme 2).

Until 1960's, chemists were not attracted by this field. In 1960, Pracejus *et al*.[16] used alkaloids as a catalyst by adding acetyl group to the quinine alkaloid. They obtained quite remarkable enantioselectivity in the addition of methanol to phenylmethylketene **(6)**. In this reaction using 1 mol% *o*-acetyl-quinine **8** catalyst they got the product **7** with 74% enantioselectivity (Scheme 3).



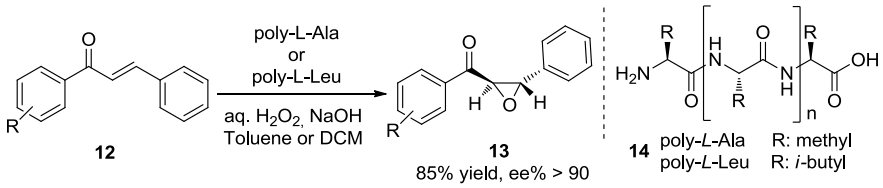
Scheme 3. The first spectacular organocatalytic asymmetric work

The other progress in the asymmetric synthesis was achieved in 1971 by the finding of the Hajos-Parrish-Eder-Saurer-Wiechert reaction.[17] *L*-proline **(11)** was used as a catalyst to synthesize Wieland-Miescher ketone **(10)** which is an important precursor of steroids from trione **9** by intramolecular aldol cyclodehydration, up to 93% ee (Scheme 4).



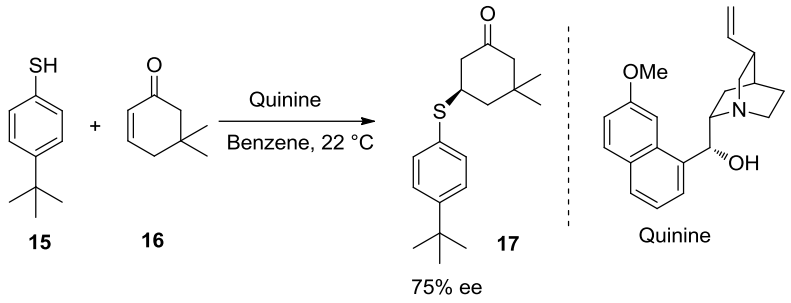
Scheme 4. The Hajos-Parrish-Eder-Saurer-Wiechert reaction

Almost ten years later, in 1980 Juliá *et. al*.[18] reported that poly-amino acids **14** catalyze asymmetric epoxidation of *trans*-chalcones **12** with hydrogen peroxide. This reaction was known as Juliá-Colonna epoxidation and by this method corresponding products **13** were obtained with the grater than 90% enantiomeric excesses (Scheme 5).



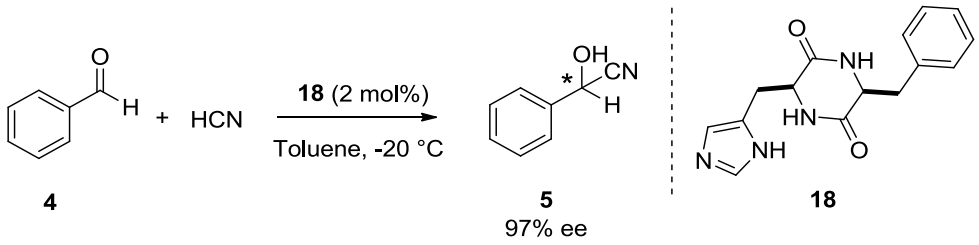
Scheme 5. The Juliá-Colonna epoxidation reaction

In 1980 another striking event, reported by Wynberg and his co-workers,[19] emerged by the discovery of bifunctional organocatalysis in the asymmetric synthesis. They worked on cinchona alkaloid catalyzed asymmetric Michael addition of thiophenol **15** to cyclohexenone **16**. They achieved up to 75% enantioselectivity in the presence of quinine (Scheme 6). By this study Wynberg proposed the bifunctional activation property of the quinine which activates both nucleophile and electrophile.



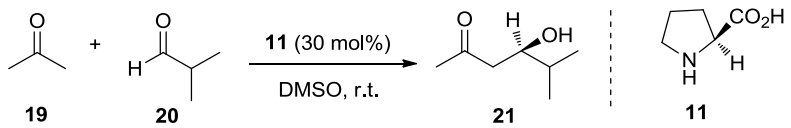
Scheme 6. Asymmetric Michael addition reaction by Wynberg *et al.*

In 1981 Inoue *et. al*.[20] repeated the work of Bredig and Fiske[12] using 2 mol% cyclic dipeptide catalyst **18,** to obtain mandelonitrile **(5)** with 97% ee (Scheme 7).



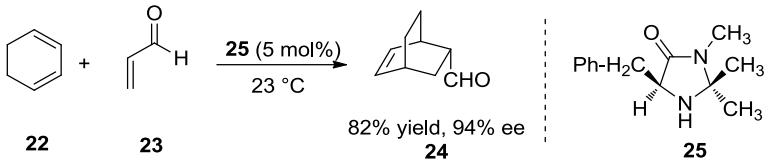
Scheme 7. Enantioselective addition reaction by Inoue *et al*.

When it comes to the 2000's, organocatalysis field withdrawn the more attention. In the past, *L*-proline was used as a catalyst in some asymmetric synthesis but no one realized the catalytic potential of it in the aldol reaction.[13] In 2000, List and Barbas[21] used *L*-proline **(11)** the first time in the intermolecular aldol reaction which involves the addition of acetone **(19)** to isobutyraldehyde **(20)** to afford corresponding aldol product **21** in 97% yield and 93% ee (Scheme 8).



Scheme 8. Enantioselective intermolecular aldol reaction by List and Barbas

In 2000 MacMillan[22] conceptualized the term *organocatalysis* and *organocatalyst* in his work as the first time.[23] MacMillan reported asymmetric Diels-Alder reaction catalyzed by secondary amine organocatalyst **25** to synthesize bicyclic adduct **24** in 82% yield and 94% ee using cyclohexa-1,3-diene **(22)** and acrolein **(23)** (Scheme 9).



Scheme 9. Enantioselective Diels-Alder reaction by MacMillan *et al*.

1.3.2. Classification of Asymmetric Organocatalysis

Organocatalysis is a swiftly developing field and attracts the attention of lots of organic chemists around the world. There is no distinct classification of organocatalysts and can be classified with different perspectives.

Berkessel and Gröger[13] divided organocatalysis into two groups in terms of catalyst-substrate interaction in the transition state, these are *covalent catalysis* and *non-covalent catalysis*. In the first case reaction mechanism depends on formation of the covalent interaction between substrate and catalyst. In the non-covalent catalysis instead of covalent interaction there could be hydrogen bonding or ion pair formation.

On the other hand, List[24] classified the organocatalysis on the basis of mechanistic property. According to List, most of the organocatalysts are generally categorized as Lewis acids, Lewis bases, Brønsted acids and Brønsted bases depending upon their functions. Lewis acid and Lewis base catalytic cycle are initiated by nucleophilic addition to the substrate. In the Brønsted acid and base the manner is a little bit different, initiation is started by the partial protonation and deprotonation. All of the cases are illustrated in the Figure 4.[24]

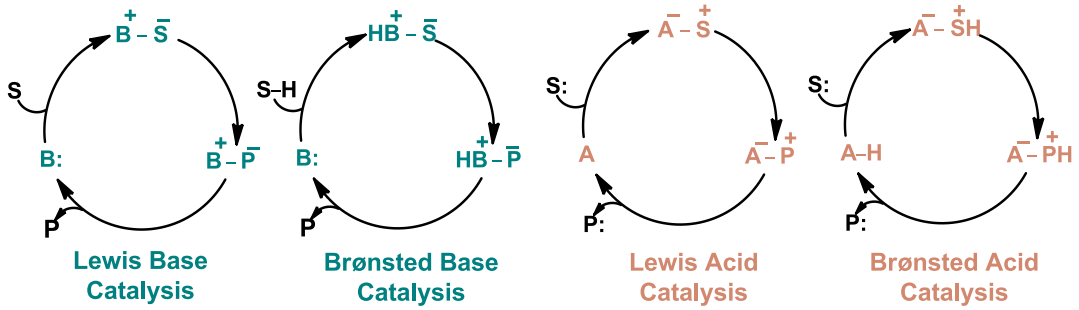


Figure 4. Classification of organocatalysis by List

In 2008, MacMillan[25] also reported a work about the classification of organocatalysis in terms of generic activation modes. According to his report, between the years 1998-2008, 130 organocatalytic reaction was established but they are based on just five or six activation modes. Knowing the activation modes of catalysts is the crucial information for chemists because it leads to improvement of organocatalysts. These are the modes of catalysis: iminium catalysis, enamine catalysis, hydrogen bonding catalysis, SOMO catalysis and counterion catalysis. In 2000, MacMillan group design organocatalytic activation mode for the first time which is iminium catalysis.[22,25]

1.3.3. Bifunctional Organocatalysis

Bifunctional catalysis sometimes called dual activation differs from traditional or classical catalysis. Traditional catalyst has only single active site and activate one substrate while bifunctional catalyst has two (or more) active sites and makes simultaneous activation of two substrates (Figure 5).[26]

Figure 5. Traditional catalysis versus bifunctional catalysis

Nowadays, most of the organocatalysts are bifunctional since they activate both the electrophile and the nucleophile thus this makes a respectable acceleration in the reaction rate.[27] Also commonly used bifunctional organocatalysts are composed of Brønsted acid and Lewis base.[27] In a bifunctional organocatalyst, basic part activate nucleophile by increasing highest occupied molecular orbital (HOMO) and acidic moiety activates electrophile by decreasing lowest unoccupied molecular orbital (LUMO) (Figure 6).

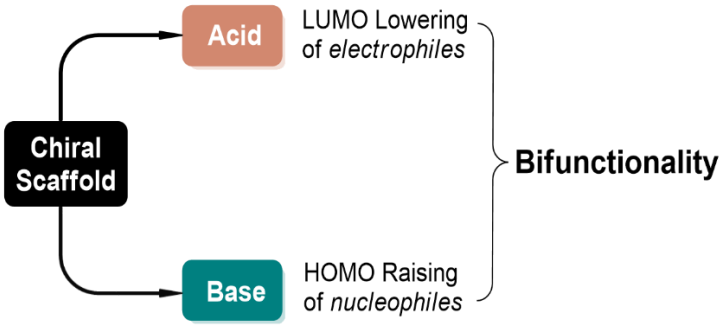


Figure 6. Bifunctionality of organocatalysts

Presumably, it can be said that natural amino acids are the simplest bifunctional organocatalyst. List[21] and co-workers used *L*-Proline as an organocatalyst in direct asymmetric aldol reaction of acetone **(19)** with isobutyraldehyde **(20)** and proposed a transition state structure.[28] Figure 7 demonstrates this reaction and proposed TS structure. Carboxylate proton of proline has an acidic property and interacts with

isobutyraldehyde **(20)**. Secondary amine in proline acts as a base and forms enamine intermediate. Six membered cyclic structure would occur in this TS model.

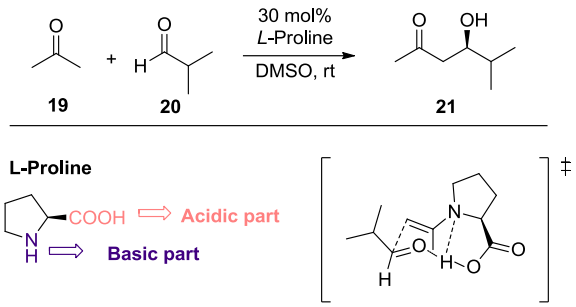


Figure 7. Bifunctionality of *L*-proline in direct aldol reaction

In this field first significant work was done by Takemoto *et. al.*[29] in 2003. Takemoto group designed many thiourea based bifunctional organocatalysts, shown in Figure 8 as **26-29.** They inspired the work of Schreiner's while designing these catalysts.

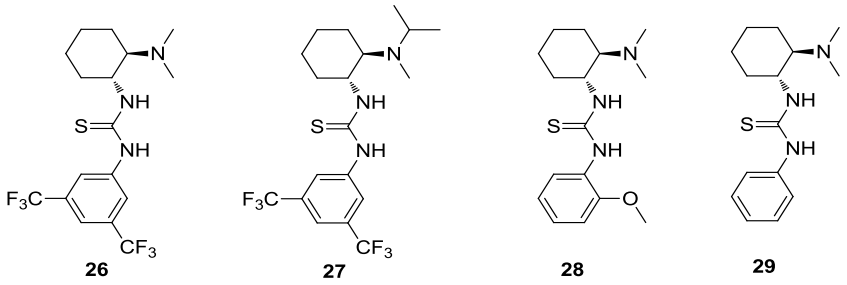
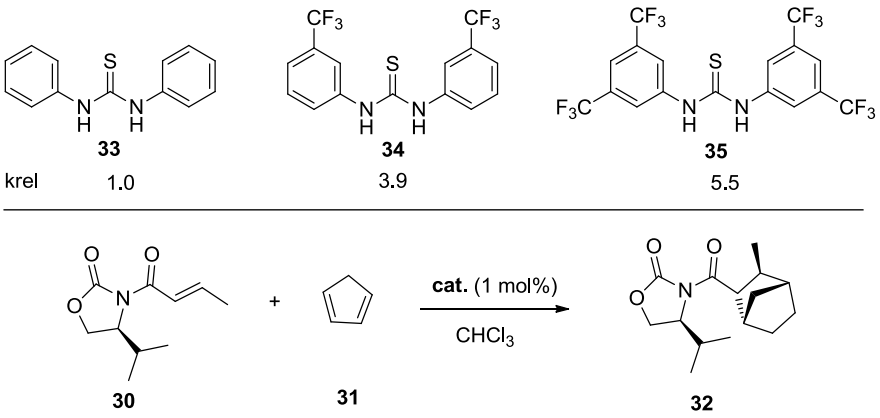


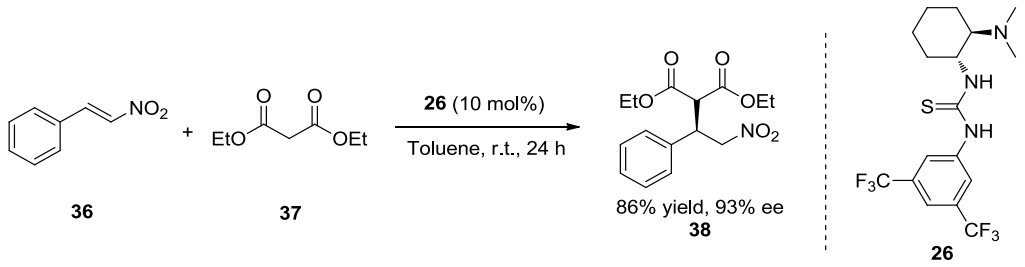
Figure 8. Takemoto's organocatalysts

Schreiner *et. al.*[30] showed that the Diels-Alder reactions of **30** and cyclopentadiene **(31)** catalyzed by symmetric thiourea catalysts **33**, **34, 35** to obtain concerned product **32** (Scheme 10). They observed the increasing reaction rate by the increasing acidity of thiourea.



Scheme 10. Schreiner's thiourea catalyzed Diels-Alder reaction

Takemoto group selected nitroolefins as an electrophile have two oxygen atom, which can be activated effectively by acidic hydrogens of thiourea moiety in the Michael reaction. Basic part of the catalysts also activates the nucleophiles synergistically. In this work all of the catalysts were examined in the addition of diethyl malonate (**37)** to *trans-β*-nitrostyrene (**36)** to synthesize enantiomerically enriched Michael product **38,** and the best result was achieved after optimization experiments by the catalyst **26** with 86% yield and 93% ee.[29]



Scheme 11. Takemoto's bifunctional thiourea catalyst in the asymmetric Michael reaction

Hydrogen bonding has very effective feature for the activation of reactants and has also stereoselective role in the reaction by the position of the bonds. Since hydrogen

bond length and angle are flexible, there could be charge separation more easily along the reaction pathway, especially in the transition state.[31]

In 2005 Takemoto and co-workers[32] proposed the possible transition state of their work with hydrogen bonding activation using bifunctional organocatalyst (Figure 9). On the chiral scaffold there are both thiourea moiety and an amine group that activate the electrophile and nucleophile respectively.

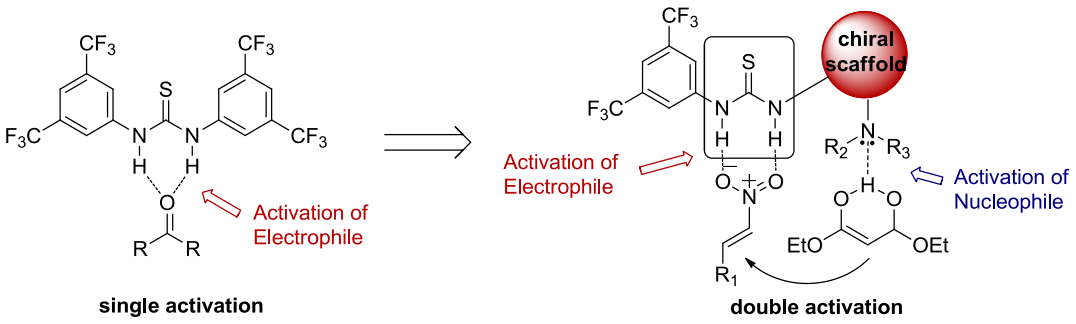
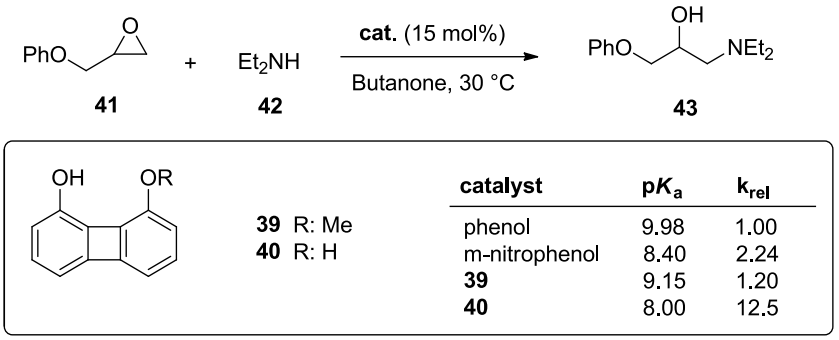


Figure 9. Possible transition state of thiourea based organocatalyst by Takemoto

1.3.4. Squaramides as Bifunctional Organocatalyst

In asymmetric synthesis, hydrogen bonding based catalysis has grown substantially within the last 12 years.[33] However, Hine *et. al.*[34] reported the first H-bond donor catalyzed organic transformation in 1985. Biphenylenediols **39, 40** and phenols are used as catalyst in the reaction of phenyl glycidyl ether **(41)** with diethylamine **(42)**. Hine and co-workers supposed that two hydroxyl groups participate in catalysis on the same oxygen atom by comparing the relative conversion of related product **43**.[35]



Scheme 12. Biphenylenediol catalyzed epoxide-opening reaction

In the beginning stages, thiourea based H-bond donor organocatalysts predominated in this field.[36,37] First work belongs to Curran *et. al.*[38] who designed diarylthiourea catalyst **44.** Then Jacobsen *et. al.*[39] reported thiourea catalyst **45** and used in the Strecker reaction. After the Schneiner's[30] and Takemoto's[29] catalysts mentioned above H-bond donor catalysts those based on thiourea core made striking improvement in that area (Figure 10).

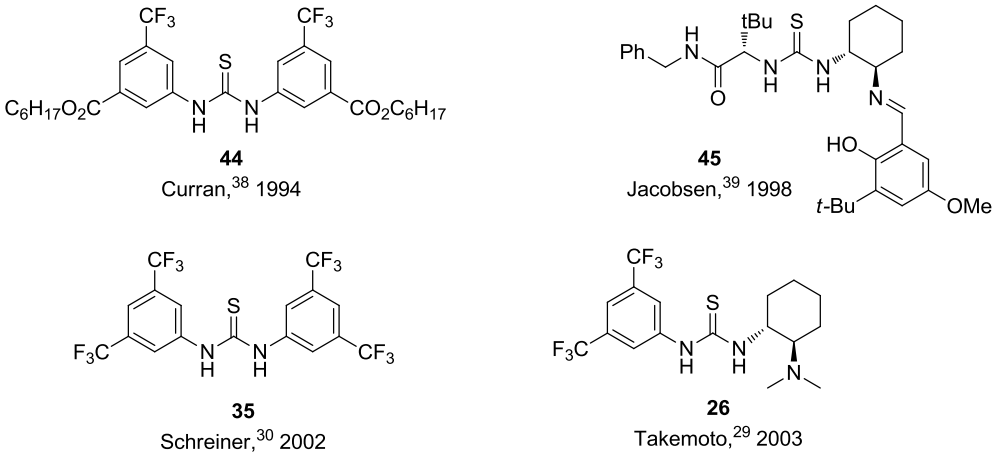


Figure 10. Some examples of thiourea based organocatalysts

In 2008, Rawal *et al.*[36] demonstrated novel chiral H-bonding bifunctional organocatalysts based on the squaramide core. Squaramides are spectacular 4-membered ring systems. They could be easily obtained from squaric acid and have

high tendency for hydrogen bonding.[40] According to Rawal[36] urea/thiourea-based organocatalysts showed important success because of their ability to create two hydrogen bonds to a substrate. Second H-bonding not only activates the substrate but also restricts the orientation of it, essential for asymmetric synthesis. This is the similarity between urea/thiourea and squaramide, but there are also many differences. The Takemoto[32] and Rawal[36] groups calculated the distances between two N-H groups by the help of crystallographic results. In *N,N*-dimethylthiourea **(46)** two hydrogens are positioned approximately 2.1 Å apart and in *N,N*-dimethylsquaramide **(47)** hydrogens are positioned more distant points, 2.7 Å (Figure 11).

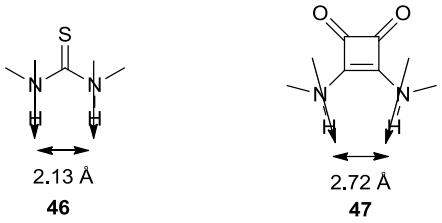


Figure 11. Orientation of hydrogen bonds and calculated H-bond distances in thiourea and squaramide

In addition to this, squaric structure of cyclobutenedione ring conduces to a convergent orientation of H-bonds, bending each by nearly 6°. This property could not be observed in urea/thiourea compounds. This feature of squaramido unit may generate excellent linearity in hydrogen bonding ability and supply different transition state in the way of binding property.[41]

Another main difference is the duality in ion and hydrogen bonding. Ureas and thioureas show great anion-binding but they could not recognize cations easily. On the other hand, squaramide unit can be made ditopic binding[42] (Figure 12). Two N-H groups provide the H-bond donor property, whereas two carbonyl groups provide the H-bond acceptor ability.

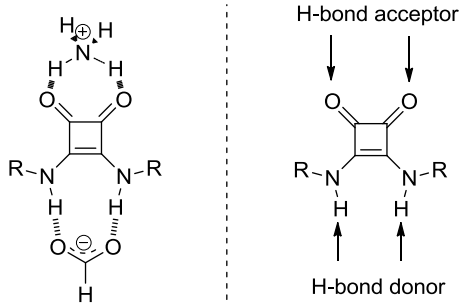


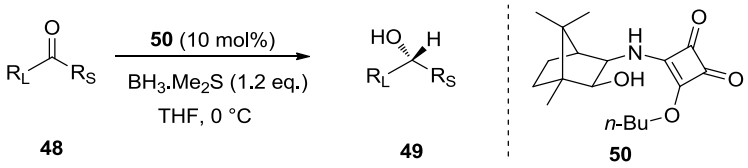
Figure 12. Duality in binding of squaramides

The third important property of squaramides is being structurally rigid like ureas and thioureas. Whereas, urea/thiourea based compounds are normal (thio)amides, squaramides can be called as vinylogous amides.[41] In both cases delocalization starts from nitrogen lone pair and continues to carbon-oxygen (C=O) double bond, restriction of the carbon-nitrogen bond rotation is provided by this way. Nevertheless, just squaramide case delocalization takes place over the partially aromatic cyclobutenedione ring structure. As a result, high restriction in the structure makes the squaramides more rigid than counterparts and let this molecule to be coplanar.[41]

Lastly, acidity of N-H protons in squaramides and ureas/thioureas could be different values. In 2010, the first study about pK_a values (varied between 8.5-21.1) of thiourea based organocatalysts in DMSO was done by Luo and Cheng.[43] In 2014, Li and Cheng worked on the acidity of squaramide based bifunctional hydrogen bonding organocatalysts. The pK_a range of those catalysts was found as 8.4-16.5.[44]

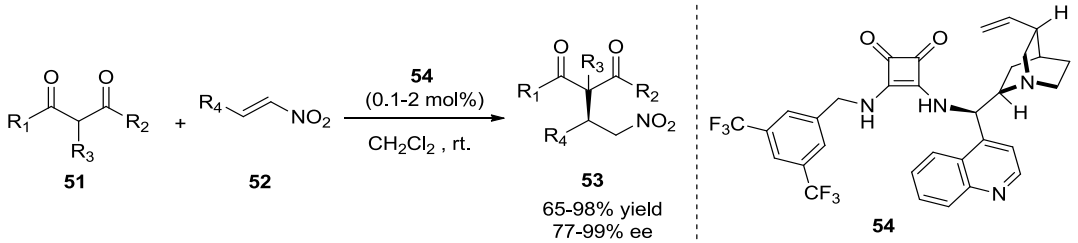
1.3.4.1. Asymmetric Reactions with Squaramide Organocatalysts

The first example using squaramide skeleton was reported by Xie *et al.*[45] in 2005. Xie group made an asymmetric reduction on ketone **48** by using borane dimethyl sulfide and chiral squaric amido alcohol **50** (Scheme 13). Desired product **49** was obtained with high enantioselectivity. In that work chiral squaramide compound used as a ligand not the bifunctional catalyst, but this study opened a new area in asymmetric organocatalysis.



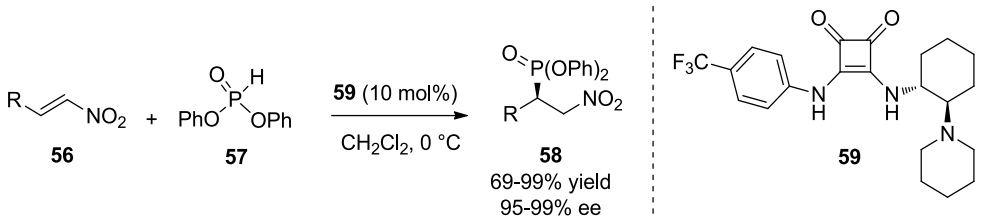
Scheme 13. The first asymmetric reaction *via* chiral squaramide ligand

In 2008, as it was mentioned above, Rawal[36] reported the first bifunctional squaramide based organocatalyst. He used cinchonine unit as a chiral scaffold and synthesized desired bifunctional organocatalyst **54**. Then this catalyst was tested in the asymmetric conjugate addition of the dicarbonyl compounds **51** to nitroolefins **52 (**Scheme 14).



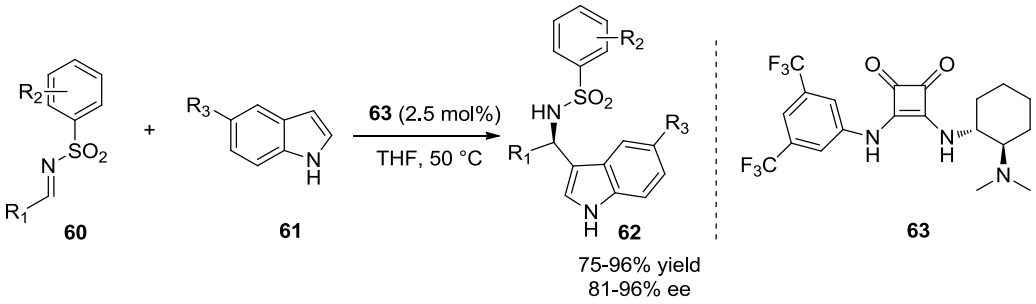
Scheme 14. Asymmetric addition of dicarbonyl compounds to nitroalkenes *via* bifunctional organocatalyst

In 2010, Rawal *et. al*.[46] published new squaramide bifunctional organocatalyst structurally looks like Takemoto[29,32] group's bifunctional thioureas. They changed the chiral moiety with the 1,2-diaminocyclohexane unit. After the reaction of diphenyl phosphite **(57)** and nitroalkene **56** in the presence of bifunctional organocatalyst **59**, the desired product **58** was obtained up to 99% enantiomeric purity (Scheme 15).



Scheme 15. Enantioselective Michael addition of diphenyl phosphite to nitroalkene

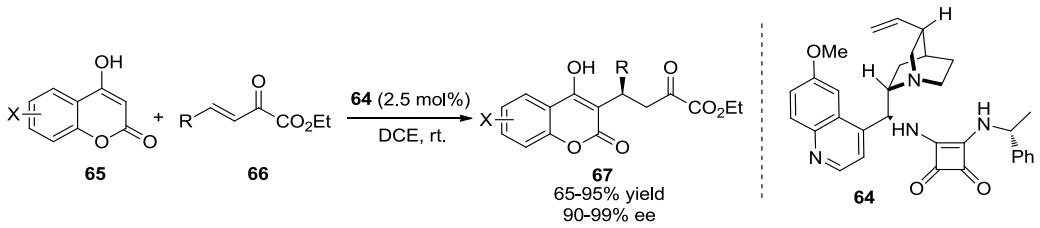
In the same year Rawal and co-workers[47] also published the enantioselective Friedel-Crafts reaction of arylsulfonylimines **60** with indoles **61** (Scheme 16). They found out that the most convenient squaramide organocatalyst was the cyclohexyldiamine-derived **63**. End of the reaction the Friedel-Crafts product **62** was synthesized with good yield and enantioselectivities. Chiral squaramide **63** was also tested over many imine and indole derivatives. The results were good with diverse range of imines and just only unsubstituted or electron rich indoles.



Scheme 16. Squaramide **63** catalyzed enantioselective Friedel-Crafts reaction

In 2010, Xu *et al.*[48] reported a study by using chiral squaramide derived **64** organocatalyst in the enantioselective Michael addition reaction of 4-hydroxycoumarins **65** to β,γ-unsaturated α-ketoesters **66** (Scheme 17). In this study, they also made the natural bond orbital (NBO) analysis to see the nature of the activation of γ-carbon of **66** while both interacting with squaramide and thiourea. Calculations show that squaramide activation (q = -0.073 *e*) makes the γ-carbon more

electrophilic than thiourea activation (q = -0.082 *e*), which is consistent with the experimental results.



Scheme 17. Asymmetric Michael addition of hydroxycoumarins to *β,γ*-unsaturated α-ketoesters

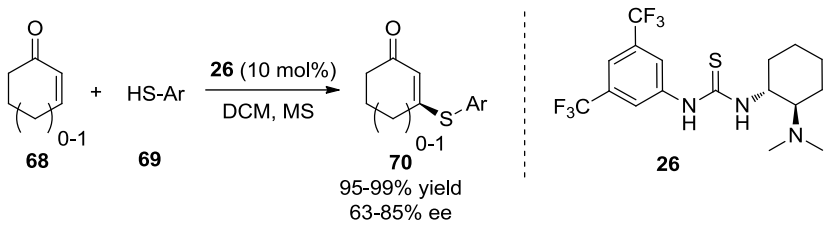
1.4. Enantioselective Michael Addition Reaction

Michael reaction has been widely investigated and used in organic chemistry since it's discovery, 1880's.[49] Moreover, asymmetric Michael reaction is one of the most proper method for the carbon-carbon bond formation.

Various organocatalysts have been developed for diverse asymmetric reactions in the last decade. Thereby, organocatalytic asymmetric Michael reaction took precious attention, many reviews were published about former progress in this topic.[50]

Takemoto's catalyst **26** which is bifunctional amine-thiourea organocatalysts was used in highly enantioselective Michael reactions. It is a logical enlargement of previous study on thiourea hydrogen bonding organocatalysts by Schreiner,[30] Curran,[38] and Jacobsen.[39]

In 2005, Li *et. al*.[51] used Takemoto's catalyst **26** for Michael reaction of aryl thiols **69** with cyclic enones **68** (Scheme 18). They got the related products **70** with high enantiomeric excess.

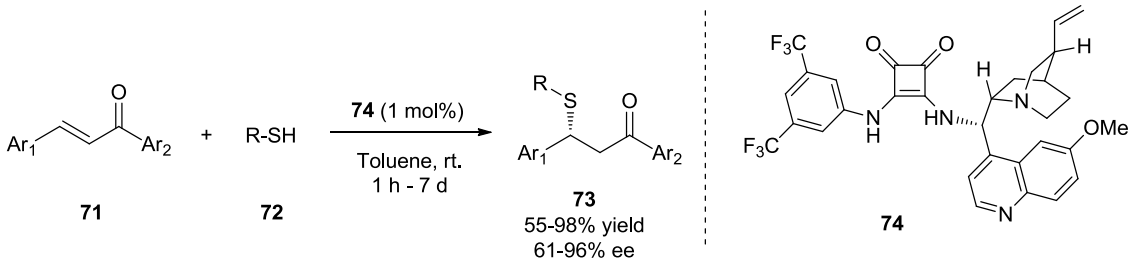


Scheme 18. Michael reaction of thiols to cyclic enones *via* Takemoto's catalyst

1.5. Asymmetric Michael Addition Reactions of *trans*-Chalcones

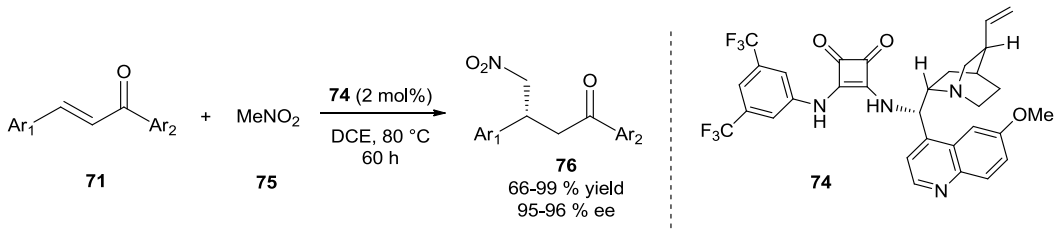
The two major components of the asymmetric Michael addition reaction are Michael donor and Michael acceptor. Chalcone is one of the widely used reagent in this reaction as Michael acceptor. Chalcones are the member of flavonoid family which is a class of natural products and found in fruits, vegetables, chocolate and tea.[52] It was published that chalcones and their structural analogues show different bioactivities such as cytotoxic, anticancer, antimicrobial, antitumor, antifungal, and chemo preventative activities.[53] As a result, there have been so many works of asymmetric Michael additions of *trans*-chalcones with various nucleophiles including malonates,[54] nitroalkanes,[55] cyanoacetates,[56] malononitrile,[57] thiols,[58] and hydroxylamines[59] etc.

Asymmetric Michael addition of thiols provide wide range of chiral thiol compounds.[60] Chen and co-workers[58] have reported that chiral squaramide catalyzed enantioselective sulfa-Michael reaction of thiols to diverse *trans*-chalcones (Scheme 19).



Scheme 19. Asymmetric sulfa-Michael addition of thiols to *trans*-chalcones

Asymmetric Michael addition of nitroalkane to enone provide a convenient route for the synthesis of optically active γ-lactams, γ-aminoacids and pyrrolidines.[60] Du *et. al*. published the squaramide catalyzed enantioselective Michael reaction of nitroalkanes to *trans*-chalcones in 2010.[55a] In this work reactions were performed at 80 ºC since both enantioselectivity and yield increase when temperature is increased. Related Michael adducts were obtained with very high yield and enantioselectivity (Scheme 20).



Scheme 20. Enantioselective Michael addition of nitroalkane to *trans*-chalcone

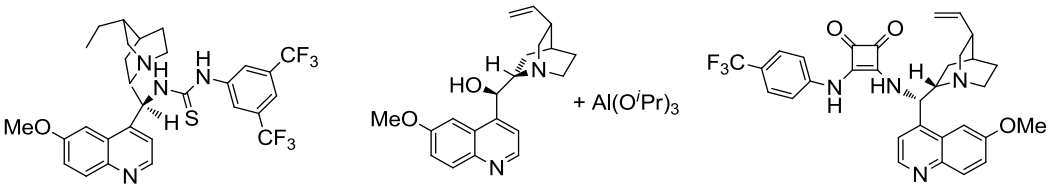
1.5.1. Asymmetric Michael Addition Reactions of Malononitrile to *trans*-Chalcone

The first organocatalytic asymmetric Michael addition reaction of malononitrile **77** to *trans*-chalcone **71** was done by Wang *et. al*. in 2006.[57b] In this work cinchona thiourea derived organocatalyst **78** was used for the addition of various nucleophile to *trans*-chalcone. In malononitrile case it was obtained the related product **79** with 88% ee and 77% yield (Scheme 21).

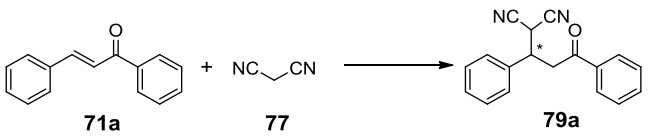
In 2009, Feng *et.al.*[57d] applied different catalyst system for that asymmetric reaction. In this work alkaloid-Al(III) complex was used as catalyst. Desired product of malononitrile and *trans*-chalcone was obtained with 90% ee and 92% yield by using $Al(O^iPr)_3$ complex of quinine **80** (Scheme 21).

Lastly, in 2012, Du and co-workers[57f] demonstrated enantioselective Michael addition reaction of malononitrile to *trans*-chalcone catalyzed by squaramide organocatalyst **81**. The highest enantioselective Michael product was obtained when decreasing

catalyst loading to 0.5 mmol% in this study. Wide range of *trans*-chalcone derivatives were examined and related products were obtained in good to high enantioselectivity (Scheme 21).



78 Wang *et. al*. 2006 | **80** Feng *et. al*. 2009 | **81** Du *et. al*. 2012

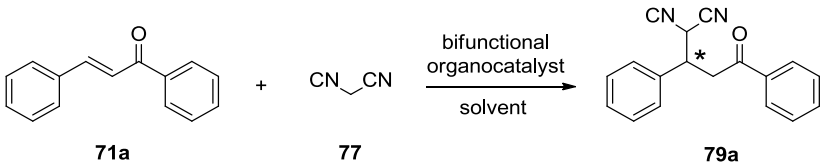


catalyst	cat. (mol %)	temp.(°C)	time (h)	yield %	ee %
78	10	rt	120	77	88
80	10	0	80	92	90
81	0.5	rt	24	82	90

Scheme 21. Enantioselective Michael addition reactions of malononitrile to *trans*-chalcone

1.6. Aim of the Work

In this thesis study, our aim was to synthesize Michael products **79a-k** of malononitrile **(77)** and *trans*-chalcones **71a-k** in asymmetric manner by using novel bifunctional organocatalysts already developed in our group (Scheme 22). Although that reaction is well known in literature and has so many applications since 2006 (Scheme 22),[57] we planned to test our organocatalyst library to prove their availability in asymmetric Michael reactions.



Scheme 22. Michael addition reaction of malononitrile to *trans*-chalcone

In our group, we have synthesized a wide range of (1*R*,2*R*)-*trans*-cyclohexadiamine based organocatalysts abbreviated as 2-AminoDMAP/urea **85,** thiourea **86,** squaramides **82-86**. Additionally, we have synthesized quinine based squaramide organocatalysts that is different from literature **87-89** (Figure 13).

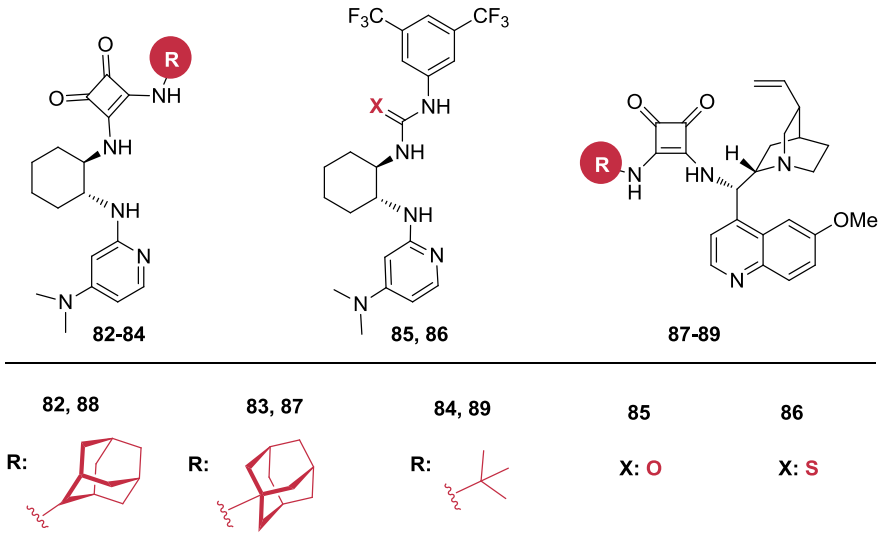


Figure 13. 2-AminoDMAP and quinine based bifunctional organocatalysts

Malononitrile was chosen as Michael donor having active methylene unit with the p*K*a value of 11, and *trans*-chalcone was used as Michael acceptor.

The compound **79a,** the simplest target product**,** has multiple functionalities and can be easily converted into 2-amino-3-nitrile-4,6-diphenyl-4*H*-pyran **(90)** by reaction with piperidine in ethanol (Figure 14).[61] 4*H*-pyran derivatives show diverse biological activity such as antimicrobial, antiviral, mutagenic, antitumor.[62] Moreover, further derivatives can be synthesized by different synthetic route (Figure 14, **91a-c**).[61]

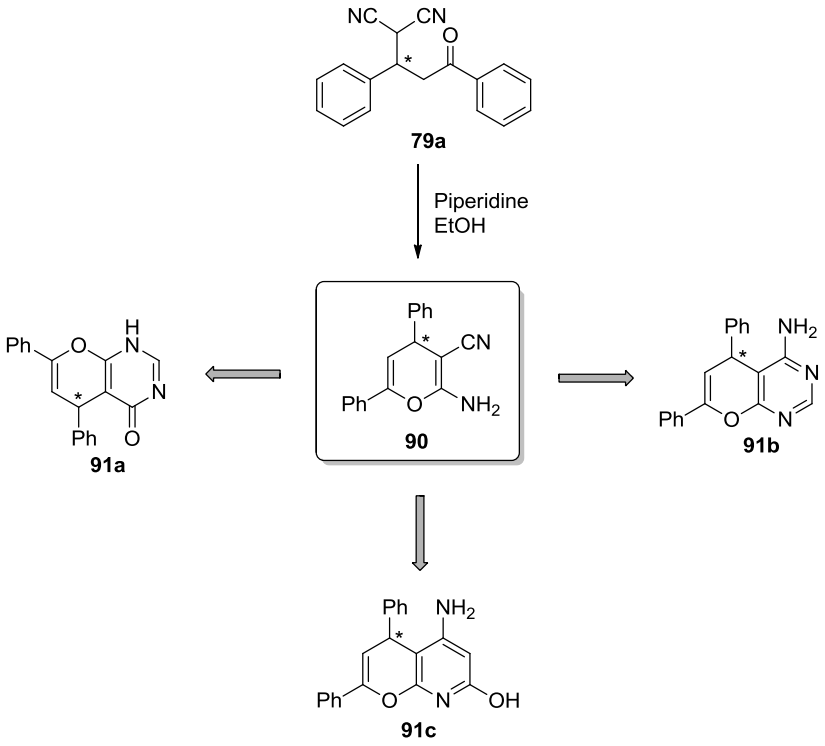


Figure 14. Potent application area of the Michael adduct

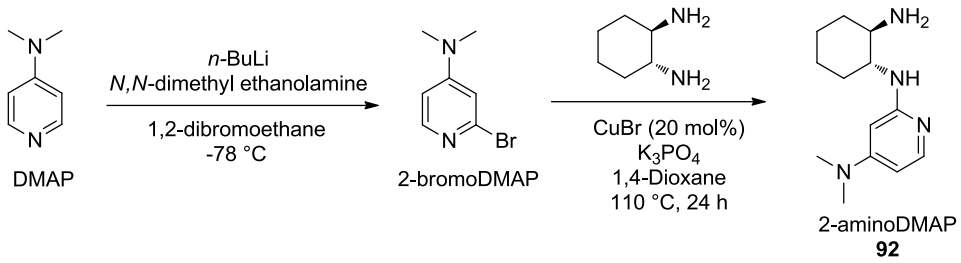
CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of 2-aminoDMAP Based Bifunctional Organocatalysts

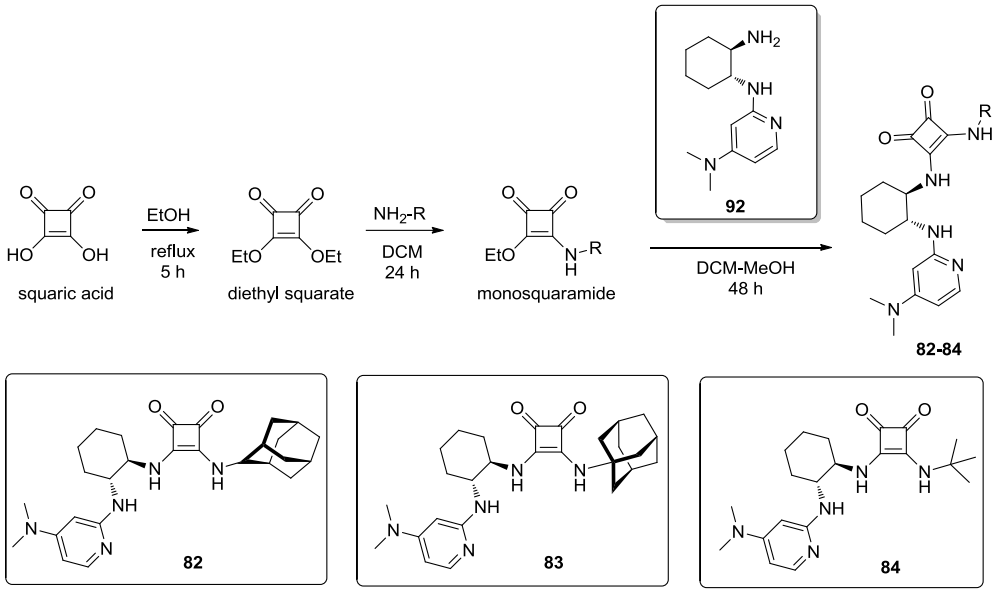
Different types of bifunctional organocatalysts were used in this work. First set has 2-aminoDMAP unit as basic part composed of (1*R*,2*R*)-cyclohexadiamine as a chiral scaffold and DMAP unit. The synthesis of 2-aminoDMAP has already accomplished in our group following the route as shown in Scheme 23.

DMAP was brominated by using *N*,*N*-dimethyl ethanolamine as a chelating ligand, *n*-BuLi as a base and dibromoethane as an electrophile. The desired product 2-bromo-*N*,*N*-dimethylpyridin-4-amine (2-bromoDMAP) was synthesized according to literature (Scheme 23).[63] Subsequently, 2-aminoDMAP **92** was synthesized in one step *via* mono-*N*-heteroarylation of C_2-symmetric cyclohexadiamine. Modified Ullman coupling reaction was accomplished by using CuBr as a catalysts and K_3PO_4 as a base. End of the reaction, 2-aminoDMAP **92** was obtained with 60% yield.[64] After synthesizing of 2-aminoDMAP skeleton, different acidic motifs were anchored and consequently various bifunctional organocatalysts were synthesized.



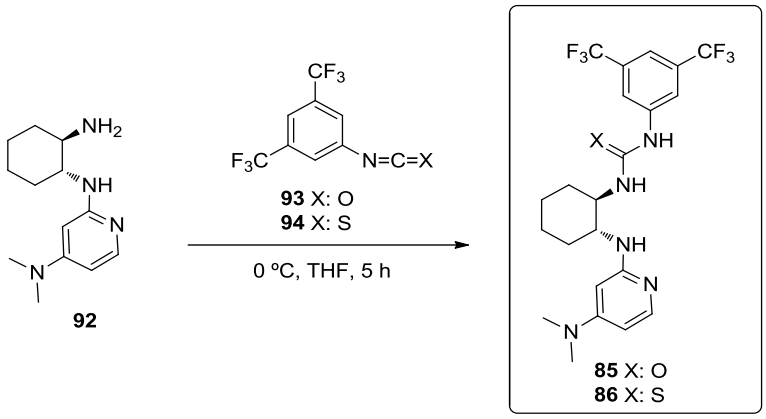
Scheme 23. Synthesis of 2-aminoDMAP

The general route for the synthesis of squaramide based organocatalysts is shown in Scheme 24. Diethyl squarate was synthesized from squaric acid by refluxing in ethanol for 5 hours. Then diethyl squarate was reacted with commercially available amines to afford corresponding mono-squaramides by literature procedure.[36] In the last step, mono-squaramides and 2-aminoDMAP **92** were coupled with one to one ratio in DCM-MeOH to yield squaramide type organocatalysts **82-84**. Only three of them were shown here since they were used in this work. Nearly 10 different 2-aminoDMAP based squaramide organocatalysts were synthesized in Tanyeli research group.[23]



Scheme 24. General synthetic route for squaramide based organocatalysts

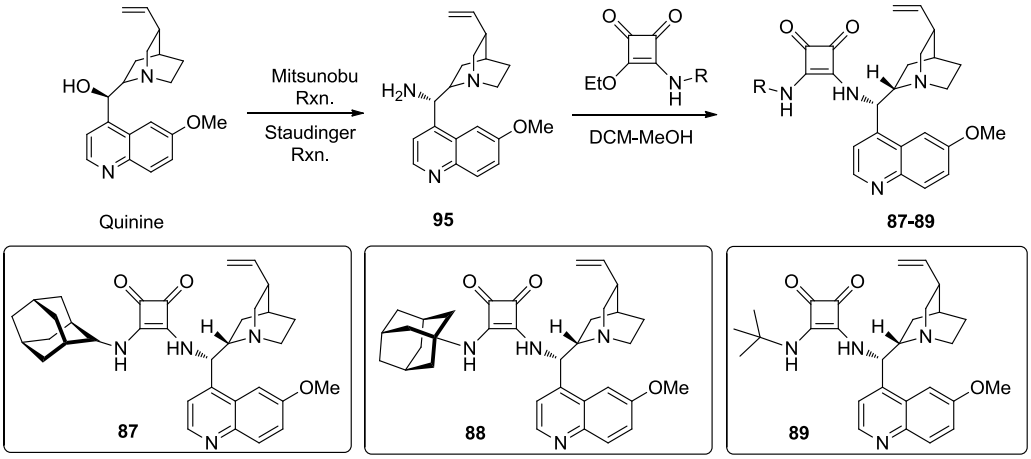
As the second set of 2-aminoDMAP based organocatalysts, urea and thiourea **85, 86** derivatives were synthesized by the reaction of 2-aminoDMAP **92** with 3,5-(bistrifluoromethyl) phenyl isocyanate **(93)** and 3,5-(bistrifluoromethyl) phenyl thioisocyanate **(94)**, respectively (Scheme 25).



Scheme 25. Synthetic route for the urea and thiourea organocatalysts

2.2. Synthesis of Quinine/Squaramide Bifunctional Organocatalysts

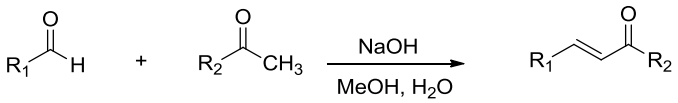
In addition to 2-aminoDMAP based organocatalysts, quinine based squaramide type organocatalysts were designed and synthesized by following the literature procedures. First part involved the transformation of hydroxyl to amine unit in quinine structure by Mitsunobu reaction.[65] The resultant amine functionalized quinine derivatives **95** was subjected to reaction with 3 mono-squaramides to afford novel quinine/squaramide type organocatalysts **87-89**.



Scheme 26. Synthetic route for the Quinine/Squaramide organocatalysts

2.3. Synthesis of the *trans*-Chalcone Derivatives as a Starting Compounds

As Michael acceptor, 11 different *trans*-chalcone derivatives were synthesized by applying aldol condensation procedure.[66] Aldol reaction was performed with the different derivatives of benzaldehyde **96** and acetophenone **97** (Scheme 26).



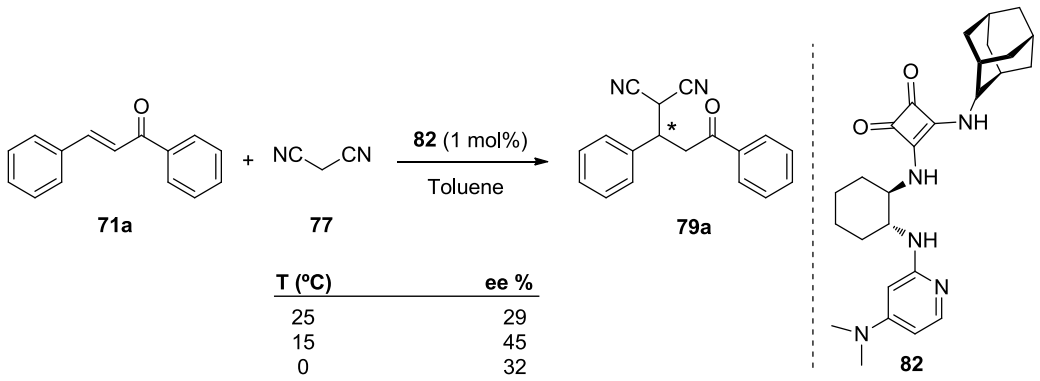
96 **97** **71 a-k**

comp.	R_1	R_2	comp.	R_1	R_2
71a	C_6H_5	C_6H_5	71g	2-Thienyl	C_6H_5
71b	4-$MeOC_6H_4$	C_6H_5	71h	C_6H_5	4-$NO_2C_6H_4$
71c	3-ClC_6H_4	C_6H_5	71i	3,4,5-$OMeC_6H_2$	C_6H_5
71d	2-$CF_3C_6H_4$	C_6H_5	71j	4-MeC_6H_4	C_6H_5
71e	4-$NO_2C_6H_4$	C_6H_5	71k	4-$CF_3C_6H_4$	C_6H_5
71f	2-Furyl	C_6H_5			

Scheme 27. General synthetic route for the *trans*-Chalcone

2.4. Evaluation of the Bifunctional Organocatalysts in Asymmetric Michael Addition Reaction

Evaluation studies were started with 2-aminoDMAP/squaramide organocatalyst **82** (Scheme 28). The model reaction was prepared with 1 mol% of organocatalyst **82** at room temperature in toluene. Unfortunately, the ee value was too low (29%). The same reaction was carried out at relatively low temperatures 15 ºC and 0 ºC, respectively. Slight increase was observed in terms of enantioselectivity as 45% and 32% ee, respectively. We decided to carry out the further screening studies at 15 ºC.

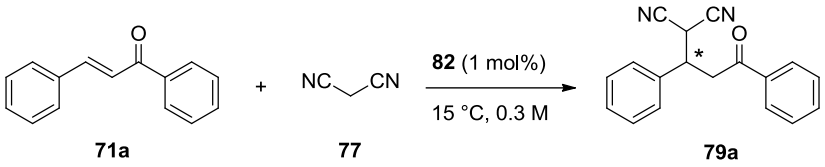


T (ºC)	ee %
25	29
15	45
0	32

Scheme 28. Temperature screening with catalyst **82**

The next optimization studies were done by screening different solvents by keeping temperature 15 ºC, using 0.2 mmol *trans*-chalcone **(71a)** and 0.24 mmol malononitrile **(77)**. The results are given in Table 1. All the solvents gave moderate enantioselectivity varied between 14-66% ee, except methanol (racemic product with 96% chemical yield). Methanol is a polar protic solvent and can make hydrogen bonding with organocatalyst, so it could deactivate it. As a result of solvent screening, chloroform was chosen as the best solvent (66% ee).

Table 1. Solvent screening results of catalyst **82**



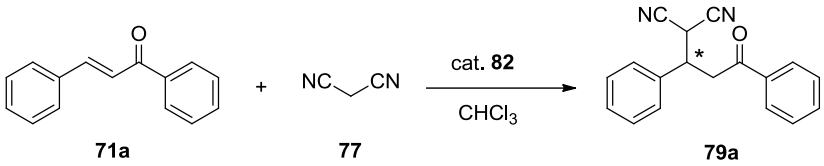
71a 77 79a

entry	solvent	time (h)	yield (%) [a]	ee (%)
1	toluene	6	91	46
2	xylene	6	87	50
3	cyclohexane	12	92	28
4	THF	12	47	38
5	heptane	12	90	14
6	chloroform	6	82	66
7	DCM	6	87	34
8	1,4-dioxane	18	20	50
9	methanol	6	96	rac

[a] Isolated yields

After choosing chloroform as the solvent, the other parameters were screened including temperature (Table 2). In the former temperature screening (Scheme 28), 15 ºC was found as the best value with toluene. In order to be sure, temperature screening repeated with chloroform too. By lowering temperature to 0 ºC and 5 ºC (entries 1 and 2), the system afforded sluggish reactions (24 h) with a significant loss of enantioselectivities (56% and 58% ee respectively). In the solvent screening study 66% ee have been found at 15 °C (entry 4). When the reaction was stopped at 2h (entry 5), 68% ee was obtained with low chemical yield (65%). When the reaction was performed at 25 °C, 40% ee was obtained (entry 6) with 0.5 mol % catalyst loading, 56% ee was observed. As the last parameter, the reactions were performed with 0.4 and 0.2 M concentrations (entries 8, and 9), no increase in ee values was observed. Consequently, it was decided that the best condition for asymmetric Michael addition of malononitrile to *trans*-chalcone with organocatalyst **82** is 0.3 M concentration, 1 mol% catalyst loading at 15 ºC in chloroform.

Table 2. Screening of the parameters with chloroform and catalyst **82**



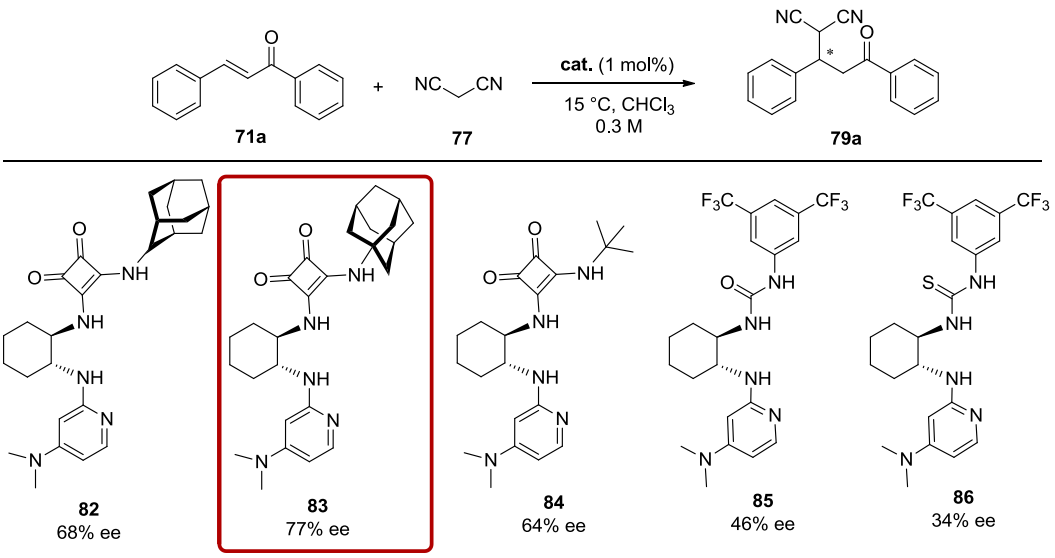
71a 77 79a

entry	conc.	time (h)	temp. (°C)	cat. (mol%)	yield (%)[a]	ee (%)
1	0.3	24	0	1	85	56
2	0.3	24	5	1	88	58
3	0.3	3	5	1	67	60
4	0.3	6	15	1	82	66
5	0.3	2	15	1	65	68
6	0.3	2	25	1	73	40
7	0.3	4	15	0.5	75	56
8	0.4	2	15	1	75	50
9	0.2	2	15	1	71	55

[a] Isolated yields

The other 2-aminoDMAP/squaramide **83**, and **84** and (thio)urea **85**, and **86** were also tried under the condition decided for organocatalyst **82**. Interestingly 1-adamantyl anchored squaramide organocatalyst **83** gave the higher enantioselectivity (77% ee) than 2-adamantyl substituted organocatalyst **82** (68% ee) under the same condition. The main difference between on two adamantyl units is bulkiness. In **82** amine attached corban is secondary, in **83** amine attached carbon is tertiary.

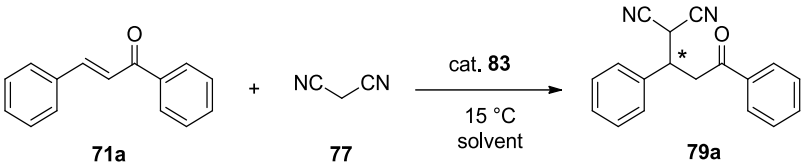
According to organocatalyst screening results, it can be generalized that the squaramides work more effective than urea and thiourea type organocatalysts in this Michael reaction (Scheme 29). As a result, the next experiments were performed with organocatalyst **83.**



Scheme 29. Screening of the 2-aminoDMAP based organocatalysts

Reaction condition was again screened with **83**. Toluene and xylene were tested as solvent and catalyst loading was screened (Table 3). The resulting enantioselectivities were parallel to former experiments performed with **82.** As a result, optimized reaction condition of Michael reaction was found as 0.3 M concentration in chloroform with 1 mol% catalyst **83** at 15 °C.

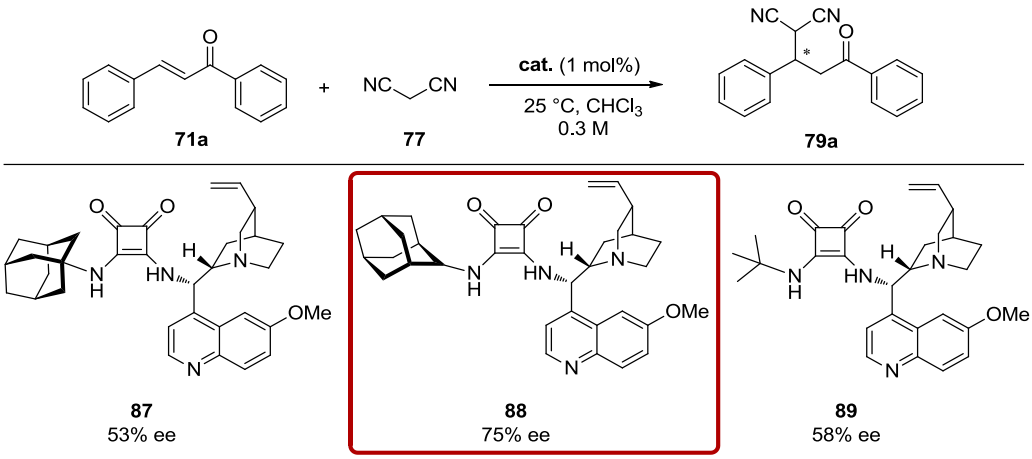
Table 3. Screening of the parameters with catalyst **83**



entry	solvent	cat. (mol%)	time (h)	yield (%)[a]	ee (%)
1	chloroform	1	2	75	77
2	toluene	1	2	85	54
3	xylene	1	2	74	68
4	chloroform	2	2	79	66
5	chloroform	0.5	3	80	52

[a] Isolated yields

After finishing the optimization reactions with 2-aminoDMAP based organocatalysts **82-86,** quinine based squaramide organocatalysts **87-89** were also tested in this reaction. In literature, different type quinine-squaramide based organocatalysts were used for many reactions. In our group, three different new types of quinine-squaramide organocatalysts were synthesized. The difference is the adamantyl amines and *t*-butyl amine parts as we used in 2-aminoDMAP based squaramide organocatalysts. These three novel quinine organocatalysts were tested at room temperature with chloroform, 1 mol% catalyst loading and 0.3 M concentration.



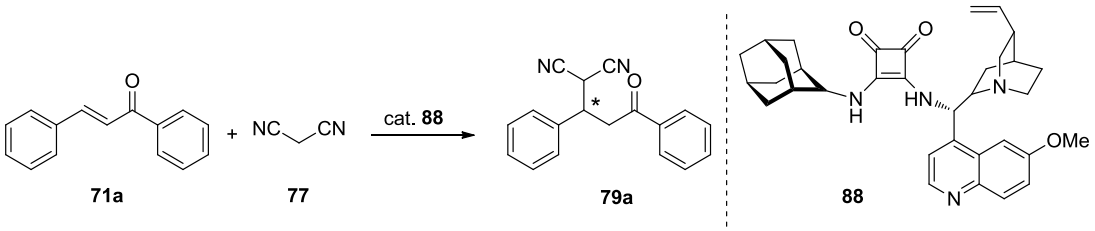
Scheme 30. Screening of the quinine/squaramide organocatalysts

According to results, organocatalyst **88** gave clearly higher enantioselectivity (75%) than organocatalysts **87** and **89** as 53% and 58%, respectively. In the 2-aminoDMAP organocatalysts optimization reactions, 1-adamantyl added organocatalysts worked more efficient than 2-adamantyl one, but in quinine based organocatalysts, results reversed. In addition to this, in the first case *R* enantiomer was excess, in the second case *S* enantiomer was excess.

After choosing the best quinine organocatalyst **88**, many reaction parameters were screened to find optimized condition. The best condition, found for 2-aminoDMAP/squaramide organocatalyst, was tested, interestingly the same enantioselectivity was found as 77% ee with longer reaction time (Table 4, entry 1). After temperature decreasing and solvent screening reactions, enantioselectivity increased up to 82% (Table 4, entry 5). Then catalyst loading and concentration were

screened. Lowering catalyst loading made positive effect on enantioselectivity. In entry 9, 11 and 13, the best enantioselectivities were obtained and it was very hard to decide the best condition for further reactions. As a result, the condition, in entry 9, was chosen as the optimized parameters with 0.5 mol% catalyst loading (85% ee).

Table 4. Screening of the parameters with catalyst **88**



71a 77 79a 88

entry	solvent	cat. (mol%)	temp. (°C)	time (h)	yield (%)[a]	ee (%)
1	chloroform	1	15	24	57	77
2	chloroform	1	0	48	55	80
3	toluene	1	0	48	53	74
4	cyclohexane	1	25	43	88	53
5	DCM	1	0	48	54	82
6	xylene	1	0	48	55	75
7	DCM	5	-30	90	56	67
8	DCM	2	0	48	65	80
9	DCM	0.5	0	72	52	85
10	DCM	0.5	25	72	62	83
11	DCM	0.25	0	72	48	86
12[b]	DCM	1	0	72	53	83
13[c]	DCM	1	0	72	45	85
14[c]	DCM	5	0	24	47	82
15[b]	DCM	1	25	72	68	82
16	DCM	1	25	48	65	81

[a] Isolated yields, [b] concentration 0.2 M, [c] concentration 0.1 M

In the last part of this thesis, different derivatives of *trans*-chalcone **71 b-k** were reacted with malononitrile **(77)** under the optimized reaction condition to obtain wide range of 2-(3-oxo-1,3-diphenylpropyl)malononitrile **79 a-k**. It was synthesized *ortho*-, *meta*-, *para*- substituted electron donating and withdrawing groups chalcone derivatives for this reason. The results are given in Table 5.

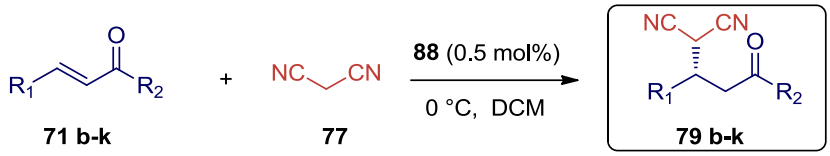
All of the derivatives were obtained with similar enantioselectivity varied between 76-86 % ee, except the *o*-CF_3 derivative **79d** having 53% ee (entry 3).

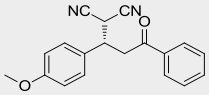
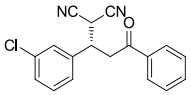
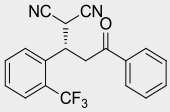
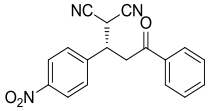
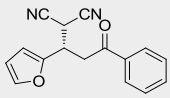
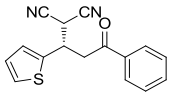
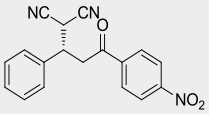
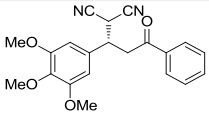
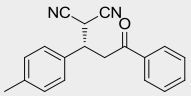
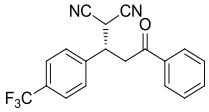
Furyl substituted derivative **79f** was obtained with 76% ee, which is the second lowest enantioselectivity. In the thienyl substituted case **79g**, result was higher (84% ee) but speed of the reaction nearly same.

The highest enantioselectivity among the other derivatives was found as 86% with the products of **79e** and **79h**. These two compounds **79e** and **79h** have same electron withdrawing group *p*-NO_2 on left and right phenyl group, respectively. On the other hand, reaction durations were shorter than the other derivatives.

There is no sharp discrimination between electron donating or withdrawing group effect, but it can be said electron withdrawing groups have slightly better effect on yield and enantioselectivity.

Table 5. Results of various derivatives of 2-(3-oxo-1,3-diphenylpropyl)malononitrile with **88**



entry	compound		time (d)	yield (%)[a]	ee (%)
1		79b	4	56	83
2		79c	3	59	80
3		79d	4	47	53
4		79e	2	63	86
5		79f	4	48	76
6		79g	4	45	84
7		79h	2	66	86
8		79i	4	48	83
9		79j	4	55	79
10		79k	3	51	84

The absolute configuration was found as *S*, which was determined by comparison with the optical rotation values in the literature.[57]

In order to understand the selectivity of the Michael addition of malononitrile **(77)** to *trans*-chalcone **(71a)** catalyzed by bifunctional quinine derived squaramide organocatalyst **88** we proposed a transition-state model which is similar to that literature by Du *et al*.[57f] Based on the proposed activation modes of nucleophile and electrophile, a plausible transition state model was designed to show the origin of the enantioselectivity.

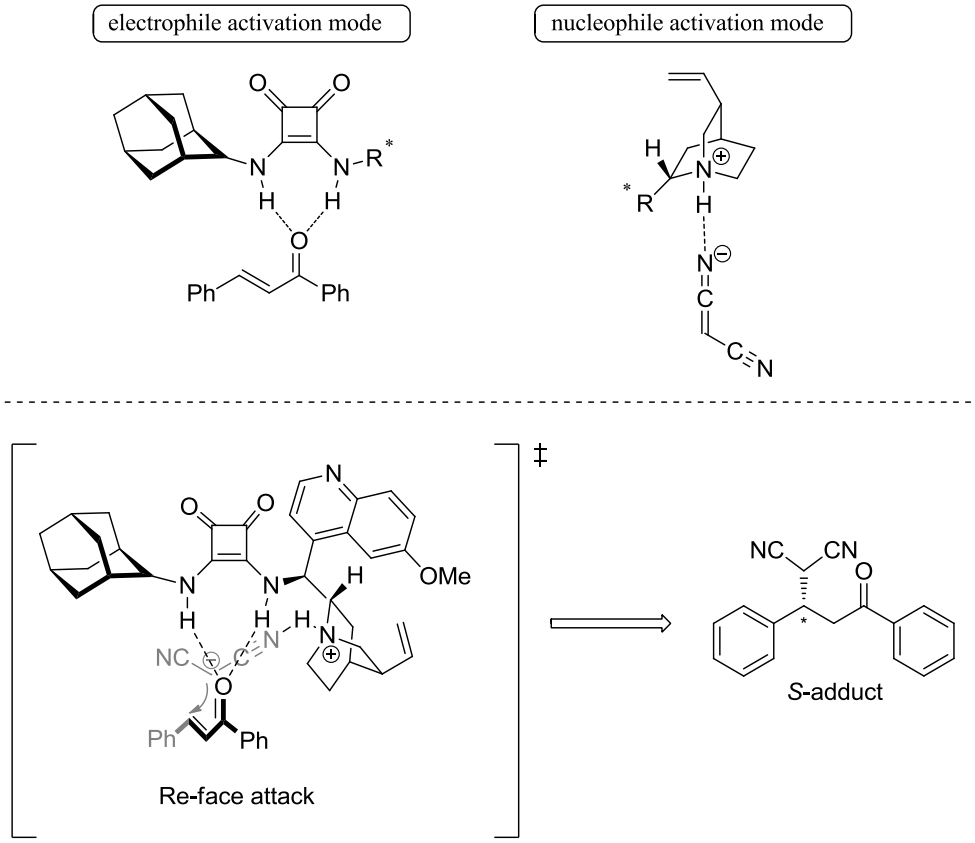


Figure 15. Proposed Transition State model explaining enantioselectivity

CHAPTER 3

EXPERIMENTAL

3.1. Materials and Methods

In this study, structural elucidations of products were done with the following instruments and materials.

Nuclear magnetic (^{1}H-NMR and ^{13}C-NMR) spectra were recorded in $CDCl_3$ or d_6-DMSO on Bruker Spectrospin Avance DPX 400 spectrometer. Chemical shifts are expressed in parts per million (ppm) with tetramethylsilane as internal standard. ^{1}H-NMR data are given in the order; signal value, spin multiplicity and coupling constant. These are some abbreviations of spin multiplicities: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dq, doublet of quarted; m, multiplet. Coupling constants (*J*) were reported in Hertz (Hz). ^{13}C-NMR spectra were measured at 100 MHz. Chemical shifts were reported from low field to highly field and $CDCl_3$ signal was seen as triplet at 77.0 ppm on spectrum.

Optical rotation values of chiral products were measured in 1 dm cell using Rudolph Scientific Autopol III polarimeter and reported as $[\alpha]_D^T$ (c is in gram per 100 mL solvent). HPLC measurements were performed on Thermo-Finnigan systems with the using Daicel Chiralpak IA and Chiralpak AD columns.

HRMS results were obtained from Agilent 6224 TOF LC/MS at UNAM, Bilkent University. Melting point determinations were done using Melt-Temp 1002D.

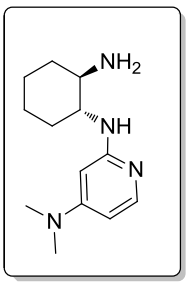
All reactions were monitored TLC using precoated silica gel plates (Merck Silica Gel 60 F_{254}), visualized by UV-light and some TLC stains. Flash column chromatograph

were done using thick-walled glass column with silica gel (Merck Silica Gel 60, particle size: 0,063-0.200 mm).

Compounds were named by using ChemDraw Ultra 12.0.

3.2. Synthesis of 2-AminoDMAP 92

CuBr (0.2 mmol, 200.8 mg) and K_3PO_4 (2.0 mmol, 2.9 g) were added to an oven-dried Schlenk tube. Then, tube was evacuated and backfilled with argon thrice. *R,R*-cyclohexadiamine (1.2 mmol, 960 mg) and 2-bromoDMAP **65** (1 mmol, 1.4 g) were added and same procedure was applied. 1,4-dioxane (7.8 mL) that was dried with sodium and benzophenone was added under argon atmosphere and the reaction mixture was stirred at 110 °C for 24 hours. The resulting green-blue suspension mixture was left at room temperature for cooling. Then 2 mL of water and 2 mL of concentrated ammonia solution was added. The resulting dark blue solution was extracted with dichloromethane (3 x 25 mL). Then organic phase was dried with brine and $MgSO_4$ consecutively. Product was purified by flash column chromatograph on silica gel using dichloromethane which was saturated with aqueous ammonia and methanol. Flash column chromatograph procedure was started with only saturated dichloromethane as eluent and gradually added the methanol, up to 10%. Desired product **92** was obtained as light brown solid with 60% yield.



mp: 138-140 °C.

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

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 6.1 Hz, 1H), 5.91 (dd, *J* = 6.1, 2.3 Hz, 1H), 5.53 (d, *J* = 2.1 Hz, 1H), 4.19 (d, *J* = 9.4 Hz, 1H), 3.28 – 3.15 (m, 1H), 2.87 (s, 6H), 2.41 (td, *J* = 10.4, 4.0 Hz, 1H), 2.03-1.93 (m, 1H), 1.94 – 1.87 (m, 1H), 1.78 (bs, 2H), 1.70 – 1.60 (m, 2H), 1.29 – 1.16 (m, 4H), 1.08 – 0.98 (m, 1H) ppm.

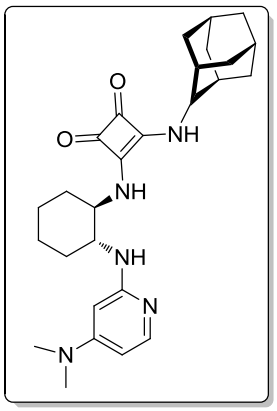
^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 156.1, 147.9, 99.2, 87.7, 58.4, 56.2, 39.2, 34.8, 32.8, 25.4, 25.0 ppm.

3.3. General Procedure for the Synthesis of 2-AminoDMAP/Squaramide Bifunctional Organocatalysts

To a solution of 2-aminoDMAP **92** (47 mg, 0.2 mmol) in DCM : MeOH (0.5 mL:0.5 mL) mixture was added mono-squaramide (55 mg, 0.2 mmol) at rt. The solution was stirred 48 hours at this temperature and directly loaded on to silica gel column which was eluted saturated DCM : MeOH (90:10).

3.3.1. Synthesis of 2-AminoDMAP/Squaramide organocatalyst 82

Starting from 3-(adamantan-2-ylamino)-4-ethoxycyclobut-3-ene-1,2-dione (55 mg, 0,2 mmol) compound **82** was obtained as a pale yellow solid with 69% yield. Spectroscopic data have been reported previously.[23]



$[\alpha]_D^{25}$ = -59.0° (*c* 0.25, $CHCl_3$)

Mp: 160-174 °C

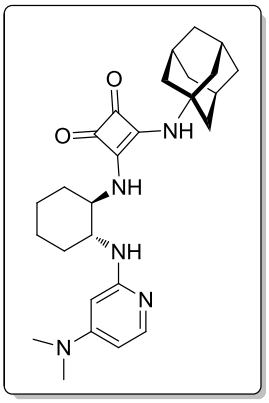
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=2.4, 1H), 7.42-7.63 (m, 2H), 6.02 (bs, 1H), 5.75 (bs, 1H), 5.58 (bs, 1H), 4.13 (bs, 1H), 3.94 (bs, 1H), 3.79 (s, 1H), 2.02-2.22 (m, 2H), 2.91 (s, 6H), 1.68-2.01 (m, 14H), 1.08-1.68 (m, 8H) ppm. Two protons extra located.

^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 180.2, 166.3, 165.5, 157.9, 153.8, 145.6, 97.4, 87.3, 60.6, 56.3, 55.6, 52.4, 37.2, 35.4, 34.9, 32.3, 31.4, 31.3, 30.9, 28.9, 25.2, 24.9, 24.0, 23.1, 23.0 ppm.

HRMS (ESI) calcd for $C_{27}H_{37}N_5O_2$ $[M + H]^+$ 464.30203, found 464.30230

3.3.2. Synthesis of 2-AminoDMAP/Squaramide organocatalyst 83

Starting from 3-(adamantan-1-ylamino)-4-ethoxycyclobut-3-ene-1,2-dione (55 mg, 0.2 mmol) compound **83** was obtained as a pale yellow solid with 66% yield. Spectroscopic data have been reported previously.[23]



$[\alpha]_D^{25}$ = -38.0º (*c* 0.25, DMSO)

Mp: 254-259 °C

^{1}H NMR (400 MHz, DMSO) δ δ7.58 (d, *J* = 6.2 Hz, 1H), 7.40 (bs, 2H), 5.98 (dd, *J* = 2.0, 6.2 Hz, 1H), 5.84 (d, *J* = 7.6 Hz, 1H), 5.51 (s, 1H), 3.58 – 3.86 (m, 4H), 2.84 (s, 6H), 1.91 – 2.11 (m, 2H), 1.56 –1.86 (m, 6H), 1.45 – 1.55 (m, 1H), 1.02 – 1.46 (m, 10H) ppm. Two protons could not be located.

^{13}C NMR (100 MHz, DMSO) δ 182.2, 181.6, 167.5, 167.0, 158.7, 155.4, 146.0, 98.9, 88.4, 57.6, 54.8, 53.8, 51.8, 38.8, 33.7, 33.5, 32.2, 24.8, 24.3, 23.8 ppm.

HRMS (ESI) calcd for $C_{27}H_{37}N_5O_2$ $[M + H]^+$ 464.30255, found 464.30230

3.4. Synthesis of 9-amino(9-deoxy)quinidine 95

According to literature procedure,[65] to a solution of quinine (3.24g, 10 mmol) in dry THF (50 mL) mixture was added triphenylphosphine (3.15 g, 12 mmol) and the solution was cooled to 0 °C. Then diisopropyl azodicarboxylate (2.33 mL, 12 mmol) was added. In another flask, diphenyl phosphoryl azide (2.58 mL, 12 mmol) was dissolved in 20 mL dry THF and cooled to 0 °C. Diphenyl phosphoryl azide solution was added drop wise to the original flask at 0 °C. Completing the addition, reaction mixture was allowed to warm room temperature and was stirred 12 h. After 12 h, reaction was heated to 50 °C for 2 h. Then, triphenylphosphine (3.41 g, 13 mmol) was added, and it was stirred at 50 °C until the gas evolution has stopped (nearly 2 h). The solution was allowed to cool at room temperature, and was added 1 mL of water and was stirred for 3 h. then solvents was evaporated under the vacuum and residue was dissolved in DCM (50 mL) and 10% HCl (50 mL). Then aqueous phase was washed

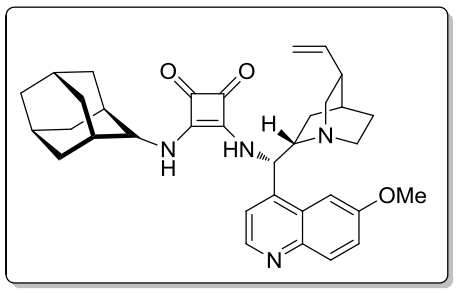
with DCM (4 x 50 mL). Aqueous phase was made alkaline with aqueous ammonia and washed with DCM (4 x 50 mL). Then all organic phases was dried with $MgSO_4$, and concentrated. Purification was done by column chromatograph on silica gel (EtOAc/MeOH/NEt_3 50/50/1 as eluent). 9-amino(9-deoxy)quinidine **95** was obtained as yellowish viscous oil with 70% yield. Spectroscopic data are in accordance with the literature.[65]

3.5. General Procedure for the Synthesis of Quinine/Squaramide Bifunctional Organocatalysts

To a solution of 9-amino(9-deoxy)quinidine **95** (323 mg, 1.0 mmol) in DCM : MeOH (2.0 mL : 2.0 mL) mixture was added mono-squaramide (1.0 mmol) at rt. The solution was stirred 48 hours at this temperature and directly loaded on to silica gel column chromatograph (EtOAc - MeOH = 75 - 25 as eluent). Squaramide catalysts **87-89** were obtained with high yield varied between 75-87% yield.

3.5.2. Synthesis of Quinine/Squaramide Bifunctional Organocatalyst 88

General procedure was followed using 3-(adamantan-1-ylamino)-4-ethoxycyclobut-3-ene-1,2-dione (275 mg, 1.0 mmol) to afford the product compound **88** as a pale yellow solid with 79% yield.



$[\alpha]_D^{20}$ = -376° (*c* 0.25, CH_2Cl_2)

Mp: 200-220 °C (decomposed)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.76 (bs, 1H), 7.35 (dd, *J* = 23.3, 6.3 Hz, 2H), 6.13 (bs, 1H), 5.74 – 5.57 (m, 1H), 5.01 – 4.85 (m, 2H), 4.00 (bs, 1H), 3.91 (s, 3H), 3.45 (bs, 2H), 3.18 – 3.13 (m, 1H), 2.72 (bs, 2H), 2.30 (bs, 1H), 1.95 (d, *J* = 10.7 Hz, 1H), 1.83 – 1.11 (m, 19H), 0.77 (bs, 1H) ppm.

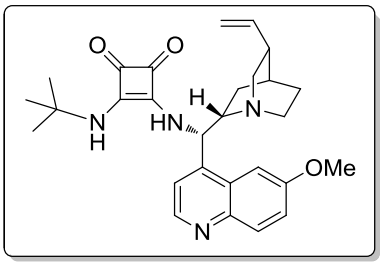
^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 181.0, 166.9, 166.2, 157.6, 146.5, 143.7, 140.2, 136.7, 130.5, 128.9, 125.0, 121.5, 113.7, 100.5, 59.4, 57.4, 55.0, 39.7, 38.4, 36.2, 35.8, 35.7, 32.3, 32.1, 29.6, 26.7, 26.5, 26.0, 25.7, 25.1, 20.3, 20.0, 18.7, 13.2 ppm.

IR (neat) 3226, 2905, 2853, 2359, 1792, 1660, 1620, 1574, 1506, 1455, 1363, 1339, 1228, 1100, 1026, 977, 909, 847, 727, 691 cm^{-1}

HRMS (ESI) calcd for $C_{34}H_{40}N_4O_3$ $[M + H]^+$ 553.31732, found 553.31730

3.5.3. Synthesis of Quinine/Squaramide Bifunctional Organocatalyst 89

General procedure was followed using 3-(tert-butylamino)-4-ethoxycyclobut-3-ene-1,2-dione (197 mg, 1.0 mmol) to afford the product compound **89** as a white solid with 87% yield.



$[\alpha]_D^{20}$ = -180.2° (*c* 0.1, CH_2Cl_2)

Mp: 260 °C (decomposed)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.0 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.72 (s, 1H), 7.59 – 7.26 (m, 2H), 6.01 (bs, 1H), 5.76 – 5.58 (m, 1H), 4.89 (m, 2H), 3.90 (s, 3H), 3.37 (bs, 2H), 3.08 (t, *J* = 11.5 Hz, 1H), 2.66 (d, *J* = 12.3 Hz, 2H), 2.15 (s, 1H), 1.68 – 1.30 (m, 4H), 1.15 (d, *J* = 22.4 Hz, 9H), 0.74 (s, 1H) ppm. Two protons could not be located.

^{13}C NMR (100 MHz, $CDCl_3$) δ 181.2, 180.4, 167.2, 167.0, 157.7, 146.7, 143.8, 142.8, 139.49, 130.7, 126.9, 121.4, 118.6, 114.2, 100.5, 55.0, 54.7, 52.2, 39.9, 38.0, 29.4, 28.7, 26.4, 26.2, 24.7, 13.8 ppm.

IR (neat) 3305, 3228, 2943, 2858, 1793, 1654, 1618, 1561, 1524, 1471, 1432, 1367, 1243, 1196, 1029, 990, 914, 848, 815, 710, 669, 646, 624, 609 cm^{-1}

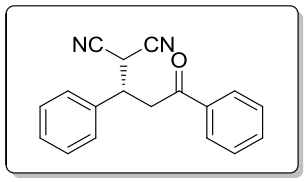
HRMS (ESI) calcd for $C_{34}H_{40}N_4O_3$ $[M + H]^+$ 475.27037, found 475.27124

3.6. General Procedure for Asymmetric Addition of Malononitrile to *trans*-Chalcone Derivatives

To a solution of organocatalyst **88** (0.002 mmol, 1.1 mg) in DCM (1.3 mL) was added *trans*-chalcone derivative (0.4 mmol). Then malononitrile (0.48 mmol) was added to mixture at 0 °C. Reaction was ended by with TLC monitoring. Then reaction mixture was purified with flash column chromatograph using 1:8 EtOAc:*n*-hexane as eluent and desired product was obtained.

3.6.1. Synthesis of (*S*)-2-(3-oxo-1,3-diphenylpropyl)malononitrile (79a)

General procedure starting from (*E*)-chalcone (83.2 mg, 0.4 mmol) was followed to afford the product **79a** with 51% yield and 85% ee as a white solid. Spectroscopic data have been reported previously.[57f]



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 15.4 min, t_{major}: 29.5 min

$[\alpha]_D^{24}$ = -6.9° (*c* 0.2, CH_2Cl_2), mp: 107-109 ºC, Lit.[57f] $[\alpha]_D^{20}$ = -11.6° (*c* 0.5, CH_2Cl_2), 90% ee.

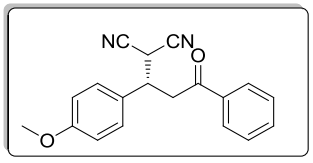
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 - 7.30 (m, 7H), 4.58 (d, *J* = 5.1 Hz, 1H), 3.95 - 3.80 (m, 1H), 3.75 - 3.48 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 136.5, 135.8, 134.2, 129.4, 129.2, 128.9, 128.1, 128.0, 111.9, 111.7, 41.2, 40.1, 28.8 ppm.

IR (neat) 2910, 2231, 1679, 1596, 1579, 1497, 1448, 1370, 1262, 1210, 1077, 999, 754, 700,688, 574 cm^{-1}

3.6.2. Synthesis of (*S*)-2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl) malononitrile (79b)

General procedure starting from (*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (95.2 mg, 0.4 mmol) was followed to afford the product **79b** with 56% yield and 83% ee as a colorless viscous oil. Spectroscopic data have been reported previously.[57f]



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 23.0 min, t_{major}: 34.7 min

$[\alpha]_D^{20}$ = -11.5° (*c* 1.5, CH_2Cl_2); Lit.[57f] $[\alpha]_D^{20}$ = -5.6° (*c* 1.15, CH_2Cl_2), 90% ee.

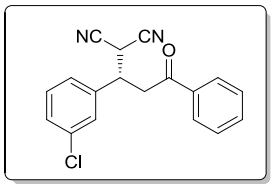
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.86 (m, 2H), 7.59 - 7.52 (m, 1H), 7.47 - 7.39 (m, 1H), 7.35 - 7.28 (m, 2H), 6.91 - 6.85 (m, 2H), 4.54 (d, *J* = 5.0 Hz, 1H), 3.85 (dt, *J* = 8.6, 5.1 Hz, 1H), 3.75 (s, 3H), 3.66 - 3.49 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 158.9, 134.6, 132.9, 127.9, 127.7, 127.2, 126.9, 113.4, 110.7, 110.5, 54.1, 39.4, 39.0, 27.8 ppm.

IR (neat) 2908, 2231, 1681, 1607, 1581, 1514, 1448, 1433, 1372, 1552, 1210, 1180, 1117, 1029, 1000, 834, 690, 537 cm^{-1}

3.6.3. Synthesis of (*S*)-2-(1-(3-chlorophenyl)-3-oxo-3-phenylpropyl) malononitrile (79c)

General procedure starting from (*E*)-3-(3-chlorophenyl)-1-phenylprop-2-en-1-one (91.6 mg, 0.4 mmol) was followed to afford the product **79c** with 59% yield and 80% ee as a pale yellow viscous oil. Spectroscopic data have been reported previously.[57d]



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 17.3 min, t_{major}: 20.8 min

$[\alpha]_D^{20}$ = -8.5° (*c* 1.0, CH_2Cl_2), Lit.[57d] $[\alpha]_D^{20}$ = -13.5° (*c* 0.178, CH_2Cl_2), 87% ee.

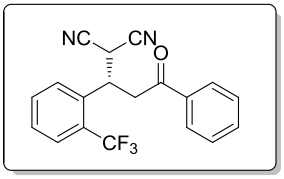
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 - 7.84 (m, 2H), 7.59 - 7.52 (m, 1H), 7.44 - 7.40 (m, 2H), 7.37 (d, *J* = 1.3 Hz, 1H), 7.32 - 7.25 (m, 3H), 4.56 (d, *J* = 5.5 Hz, 1H), 3.86 (dt, *J* = 8.3, 5.3 Hz, 1H), 3.67 - 3.49 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 137.4, 134.6, 134.2, 133.3, 129.6, 128.5, 127.9, 127.2, 127.1, 125.3, 110.6, 110.4, 76.3, 76.0, 75.7, 39.8, 38.9, 27.5 ppm.

IR (neat) 2910, 2358, 2231, 1683, 1597, 1576, 1477, 1448, 1434, 1368, 1212, 1183, 1085, 1000, 978, 792, 757, 689 cm^{-1}

3.6.4. Synthesis of (*S*)-2-(3-oxo-3-phenyl-1-(2-(trifluoromethyl)phenyl)propyl) malononitrile (79d)

General procedure starting from (*E*)-1-phenyl-3-(2-(trifluoromethyl)phenyl)prop-2-en-1-one (110.6 mg, 0.4 mmol) was followed to afford the product **79d** with 47% yield and 54% ee as colorless viscous oil. Absolute configuration was assigned by analogy.



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{major}: 10.4 min, t_{minor}: 11.5 min

$[\alpha]_D^{20}$ = -22.4° (*c* 1.0, CH_2Cl_2)

^{1}H NMR (400 MHz, CDCl3) δ 7.90 - 7.87 (m, 2H), 7.76 - 7.69 (m, 2H), 7.61 - 7.52 (m, 2H), 7.47 - 7.39 (m, 3H), 4.73 (d, *J* = 5.6 Hz, 1H), 4.37 (dt, *J* = 8.0, 5.7 Hz, 1H), 3.72 - 3.58 (m, 2H) ppm.

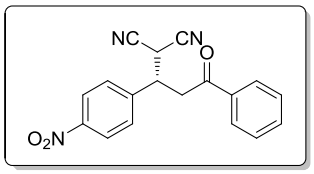
^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 135.0, 134.5, 133.2, 131.9, 128.0, 127.9, 127.1, 126.6, 126.1, 126.0, 110.1, 39.7, 34.9, 26.6 ppm.

IR (neat) 2909, 2231, 1683, 1606, 1581, 1448, 1434, 1375, 1311, 1212, 1159, 1114, 1064, 1037, 999, 690, 647 cm^{-1}

HRMS (ESI) calcd for $C_{19}H_{13}F_3N_2O$ $[M - H]^+$ 341.08999 found 341.08693

3.6.5. Synthesis of (*S*)-2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malononitrile (79e)

General procedure starting from (*E*)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (101.2 mg, 0.4 mmol) was followed to afford the product **79e** with 63% yield and 86% ee as a pale yellow solid. Spectroscopic data have been reported previously.[57d]



HPLC (IA, 80:20 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 17.6 min, t_{major}: 24.2 min

$[\alpha]_D^{24}$ = -6.3° (*c* 1.0, CH_2Cl_2), mp:156-158 ºC, Lit.[57d] $[\alpha]_D^{20}$ = -7.1° (*c* 0.042, CH_2Cl_2), 89% ee.

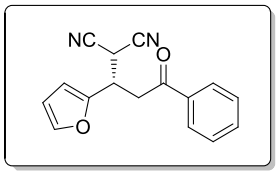
^{1}H NMR (400 MHz, CDCl3) δ 8.26 - 8.22 (m, 2H), 7.92 - 7.87 (m, 2H), 7.63 - 7.55 (m, 3H), 7.44 (m, 2H), 4.62 (d, *J* = 5.2 Hz, 1H), 4.04 (dt, *J* = 8.3, 5.3 Hz, 1H), 3.65 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7, 147.4, 142.3, 134.4, 133.5, 128.3, 128.1, 127.1, 123.5, 110.2, 110.1, 40.0, 38.8, 27.3 ppm.

IR (neat) 2961, 2921, 1680, 1596, 1521, 1446, 1406, 1351, 1258, 1086, 1013, 839, 790, 748, 701, 659, 586, 561 cm^{-1}

3.6.6. Synthesis of (*S*)-2-(1-(furan-2-yl)-3-oxo-3-phenylpropyl) malononitrile (79f)

General procedure starting from (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-one (79.2 mg, 0.4 mmol) was followed to afford the product **79f** with 48% yield and 76% ee as a pale brown viscous oil. Spectroscopic data have been reported previously.[57f]



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 19.9 min, t_{major}: 22.6 min

$[\alpha]_D^{24}$ = +13.0° (*c* 0.3, CH_2Cl_2), Lit.[57f] $[\alpha]_D^{20}$ = +13.5° (*c* 1.45, CH_2Cl_2), 83% ee.

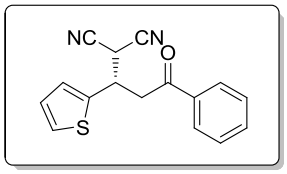
^{1}HNMR (400MHz, $CDCl_3$) δ7.94 - 7.88 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 1.3 Hz, 1H), 6.37 (d, *J* = 3.3 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H), 4.53 (d, *J* = 5.1 Hz, 1H), 4.09 (dt, *J* = 7.9, 5.4 Hz, 1H), 3.67 - 3.51 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 148.5, 142.4, 134.6, 133.2, 127.9, 127.1, 110.5, 110.2, 109.8, 108.1, 37.6, 34.7, 26.1 ppm.

IR (neat) 2915, 2231, 1683, 1596, 1580, 1503, 1448, 1414, 1259, 1214, 1013, 798, 759, 688 cm^{-1}

3.6.7. Synthesis of (*S*)-2-(3-oxo-3-phenyl-1-(thiophen-2-yl)propyl) malononitrile (79g)

General procedure starting from (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-one (85.8 mg, 0.4 mmol) was followed to afford the product **79g** with 45% yield and 84% ee as a pale brown viscous oil. Spectroscopic data have been reported previously.[57d]



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 21.9 min, t_{major}: 25.9 min

$[\alpha]_D^{20}$ = -2.4° (*c* 0.75, CH_2Cl_2), Lit.[57d] $[\alpha]_D^{24}$ = -1.47° (*c* 0.068, CH_2Cl_2), 86% ee.

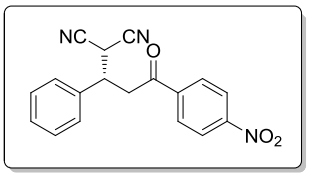
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 - 7.87 (m, 2H), 7.59 - 7.55 (m, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 5.1 Hz, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.99 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.62 (d, *J* = 4.9 Hz, 1H), 4.25 - 4.20 (m, 1H), 3.63 (d, *J* = 7.0 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 137.5, 133.3, 129.5, 128.0, 127.1, 126.5, 126.2, 125.1, 110.7, 110.4, 40.4, 36.2, 28.5 ppm.

IR (neat) 2909, 2232, 1682, 1637, 1597, 1580, 1448, 1434, 1374, 1357, 1259, 1214, 1182, 1000, 759, 707, 688, 556 cm^{-1}

3.6.8. Synthesis of (*S*)-2-(3-(4-nitrophenyl)-3-oxo-1-phenylpropyl) malononitrile (79h)

General procedure starting from (*E*)-1-(4-nitrophenyl)-3-phenylprop-2-en-1-one (101.2 mg, 0.4 mmol) was followed to afford the product **79h** with 65% yield and 86% ee as a pale yellow viscous oil. Spectroscopic data have been reported previously.[57c]



HPLC (AD, 80:20 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{major}: 29.1 min, t_{minor}: 33.3 min.

$[\alpha]_D^{25}$= +45.6° (*c* 1.0, CH_2Cl_2), Lit.[57c] $[\alpha]_D^{20}$= +24.4° (*c* 0.504, EtOAc), 72% ee.

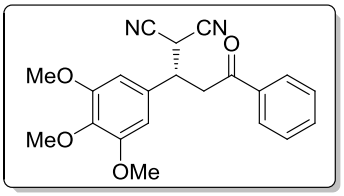
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 - 8.24 (m, 2H), 8.08 - 8.03 (m, 2H), 7.40 - 7.32 (m, 5H), 4.49 (d, *J* = 5.3 Hz, 1H), 3.95 - 3.89 (m, 1H), 3.66 (d, *J* = 6.7 Hz, 2H) ppm.

^{13}C NMR (100 MHz, CDCl3) δ 194.1, 149.9, 139.0, 135.1, 128.5, 128.4, 128.2, 126.8, 123.1, 110.6, 110.5, 76.3, 76.0, 75.7, 40.1, 39.8, 27.8 ppm.

IR (neat) 2915, 2231, 1692, 1603, 1524, 1454, 1407, 1346, 1319, 1260, 1207, 1088, 999, 858, 798, 744, 701 cm^{-1}

3.6.9. Synthesis of (*S*)-2-(3-oxo-3-phenyl-1-(3,4,5-trimethoxyphenyl)propyl) malononitrile (79i)

General procedure starting from (*E*)-1-phenyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (119.4 mg, 0.4 mmol) was followed to afford the product **79i** with 48% yield and 83% ee as a white solid. Absolute configuration was assigned by analogy.



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 32.2 min, t_{major}: 36.1 min.

$[\alpha]_D^{20}$= -21.0° (*c* 0.2, CH_2Cl_2), mp: 84-87 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.88 (m, 2H), 7.58 - 7.54 (m, 1H), 7.45 - 7.41 (m, 2H), 6.57 (s, 2H), 4.59 (d, *J* = 4.9 Hz, 1H), 3.81 (s, 6H), 3.78 (s, 3H), 3.58 (d, *J* = 6.9 Hz, 2H) ppm.

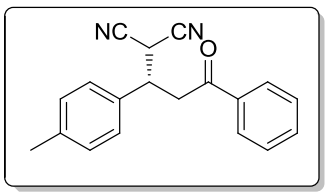
^{13}C NMR (100 MHz, $CDCl_3$**)** δ 196.9, 153.9, 138.5, 135.8, 134.2, 132.1, 129.0, 128.1, 111.9, 105.1, 60.9, 56.3, 41.6, 40.2, 28.8 ppm.

IR (neat) 2897, 1673, 1590, 1509, 1463, 1449, 1449, 1349, 1325, 1249, 1124, 1001, 760, 690 cm^{-1}

HRMS (ESI) calcd for $[M - H]^+$ 363.1349 found 363.1332

3.6.10. Synthesis of (*S*)-2-(3-oxo-3-phenyl-1-(p-tolyl)propyl)malononitrile (79j)

General procedure starting from (*E*)-1-phenyl-3-(p-tolyl)prop-2-en-1-one (91.3 mg, 0.4 mmol) was followed to afford the product **79j** with 55% yield and 79% ee as a pale yellow viscous oil. Spectroscopic data have been reported previously.[57f]



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 15.6 min, t_{major}: 21.4 min.

$[\alpha]_D^{20}$ = -5.2° (*c* 1.0, CH_2Cl_2), Lit.[57f] $[\alpha]_D^{20}$ = -7.3° (*c* 1.0, CH_2Cl_2), 90% ee.

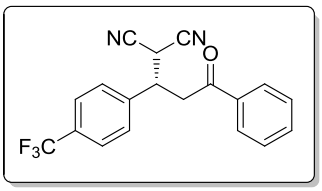
^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 6.9 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.54 (d, *J* = 5.1 Hz, 1H), 3.85 (dt, *J* = 8.4, 5.3 Hz, 1H), 3.58 (m, 2H), 2.29 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$**)** δ 195.7, 138.1, 134.9, 133.1, 132.5, 129.0, 127.9, 127.1, 126.8, 110.9, 110.7, 39.9, 39.2, 27.9, 20.1 ppm.

IR (neat) 2958, 2919, 2851, 1680, 1595, 1515, 1448, 1367, 1258, 1208, 1073, 1013, 793, 759, 688 cm^{-1}

3.6.11. Synthesis of (*S*)-2-(3-oxo-3-phenyl-1-(4-(trifluoromethyl)phenyl)propyl) malononitrile (79k)

General procedure starting from (*E*)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (110.5 mg, 0.4 mmol) was followed to afford the product **79k** with 51% yield and 84% ee as a white solid. Spectroscopic data have been reported previously.[57g]



HPLC (IA, 90:10 *n*-Hexane:Isopropanol, 1 mL/min, 254 nm) t_{minor}: 17.90min, t_{major}: 24.1 min.

$[\alpha]_D^{20}$ = +5.6° (*c* 0.5, CH_2Cl_2), mp: 106-108 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.2 Hz, 2H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 6.3 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.44 (t, *J* = 6.9 Hz, 2H), 4.60 (d, *J* = 5.1 Hz, 1H), 3.97 (dt, *J* = 8.5, 5.2 Hz, 1H), 3.62 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 139.3, 134.5, 133.4, 128.0, 127.6, 127.1, 125.4, 125.3, 110.5, 39.9, 38.8, 28.7, 27.4 ppm.

IR (neat) 2913,1681, 1602, 1597, 1449, 1422, 1323, 1212, 1165, 1114, 1068, 1016, 1000, 844, 762, 687, 607 cm^{-1}

CHAPTER 4

CONCLUSION

In this work, asymmetric synthesis of 2-(3-oxo-1,3-diphenylpropyl)malononitrile and its derivatives were studied in the presence of novel chiral bifunctional organocatalysts developed in our research group.

In the first part this work, 2-aminoDMAP based urea, thiourea and squaramide types organocatalysts were screened and 1-adamantyl anchored squaramide organocatalyst **83** showed good result with 75% yield and 77% ee at 2 h. Subsequently, quinine based three different squaramide organocatalysts were tested and 2-adamantyl anchored catalyst **88** was found to be the best among them. In this case, reaction duration was longer than before with the increasing enantioselectivity. After searching many kinds of parameters, optimum conditions were determined as 0 °C and 0.5% catalyst loading and the addition product was obtained in 55% yield and 85% ee at 3 days.

In the last part, 10 different 2-(3-oxo-1,3-diphenylpropyl)malononitrile derivatives were synthesized under the optimized condition. Except one derivative having 54% ee, 9 derivatives were obtained with good enantioselectivity varied between 76-86% ee and 45-66% yield.

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APPENDIX A

SUPPORTING INFORMATION

^{1}H NMR and ^{13}C NMR spectrums and HPLC chromatograms of compounds are shown in the following pages.

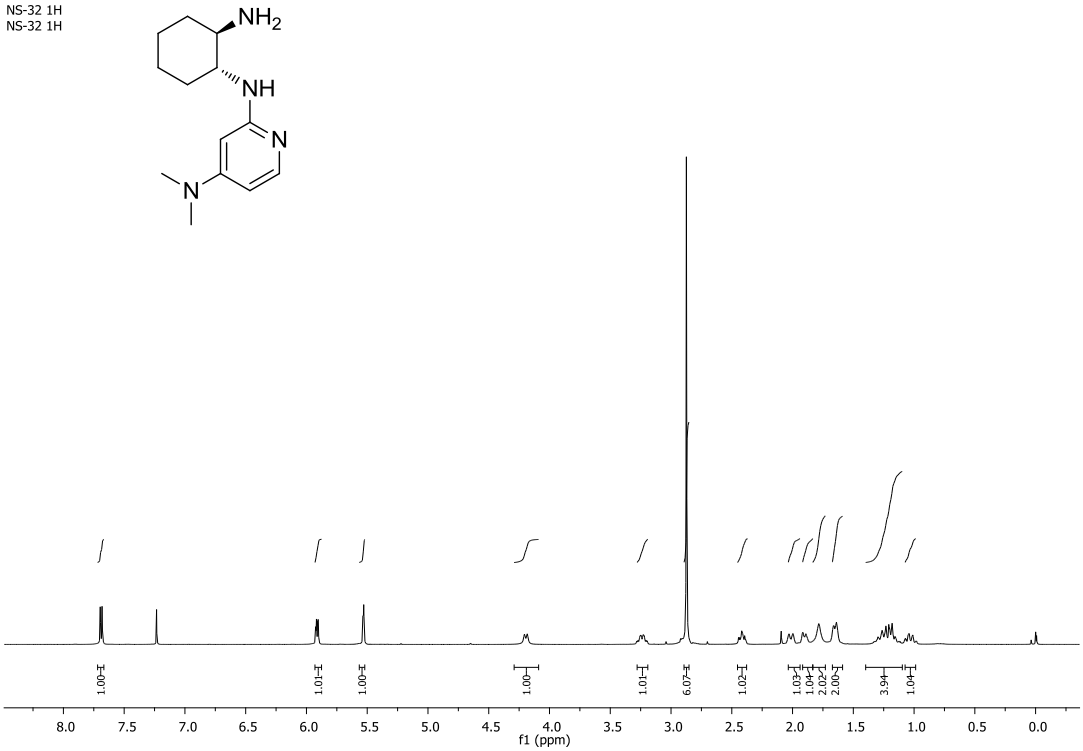


Figure A. 1. [1]H NMR spectrum of compound **2-amino DMAP**

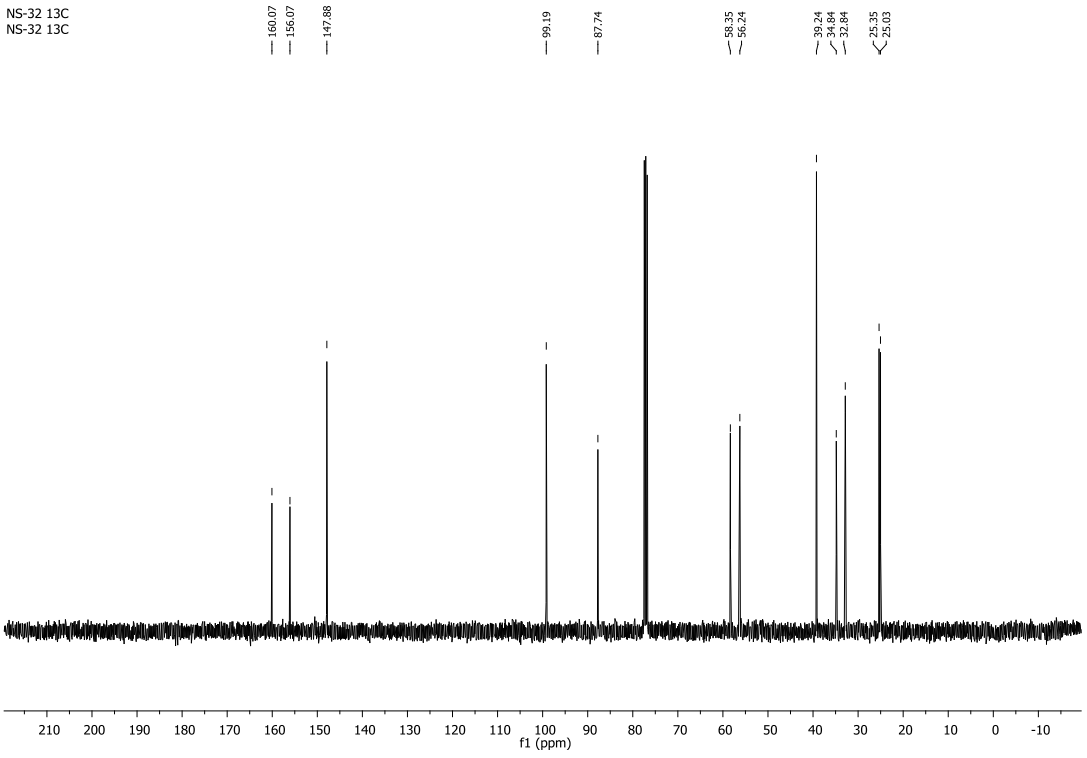


Figure A. 2. [13]C NMR spectrum of compound **2-amino DMAP 92**

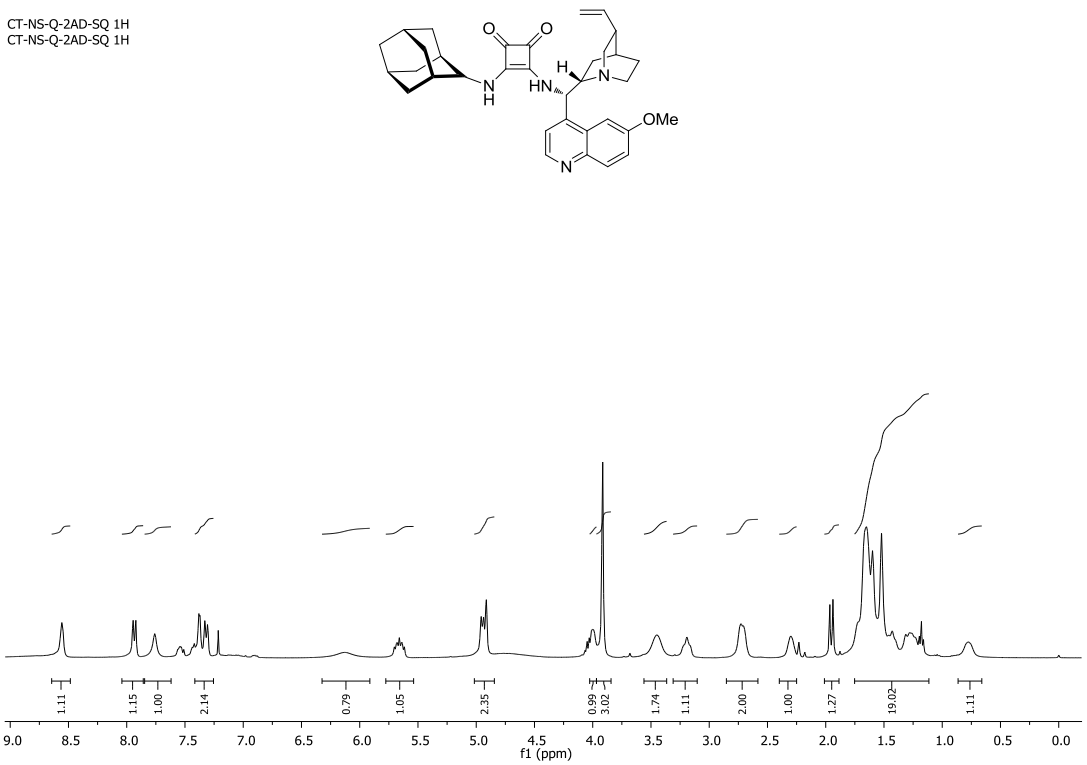


Figure A. 3. ^{1}H NMR spectrum of compound **88**

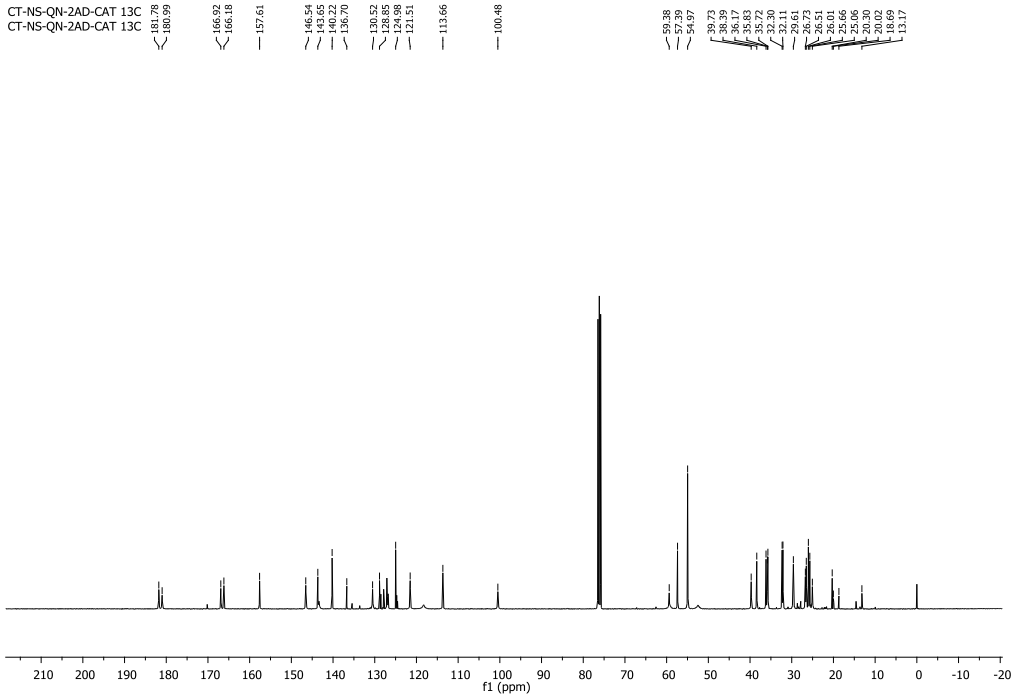


Figure A. 4. ^{13}C NMR spectrum of compound **88**

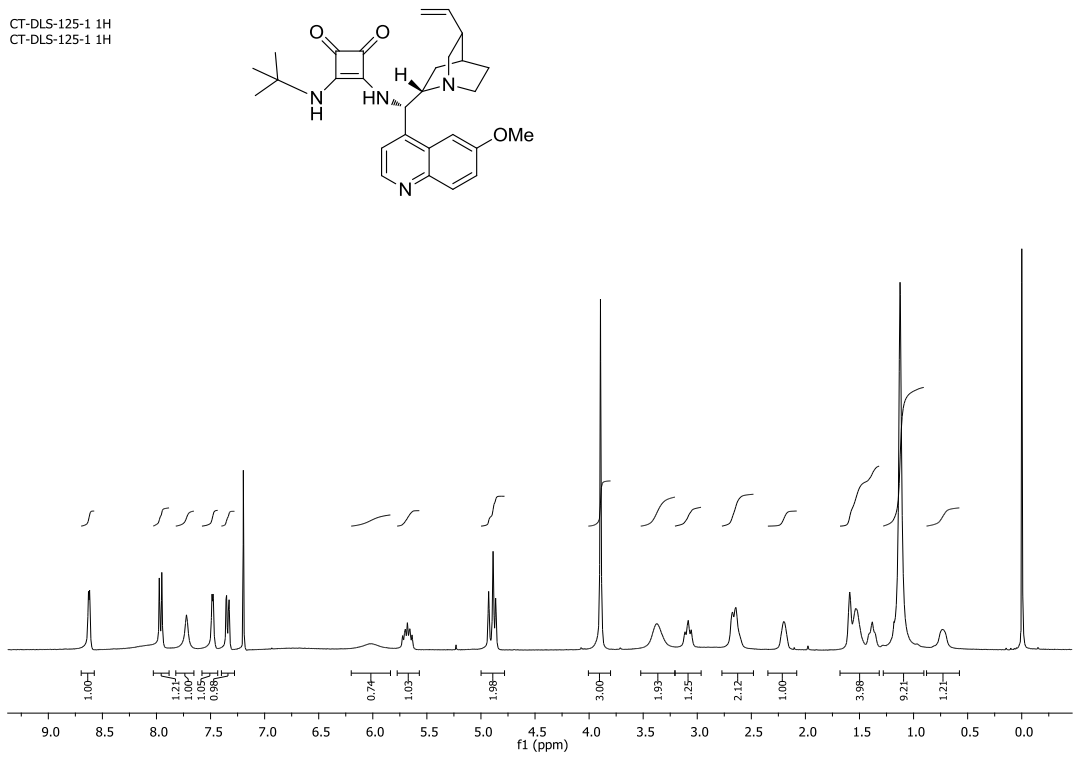


Figure A. 5. ^{1}H NMR spectrum of compound **89**

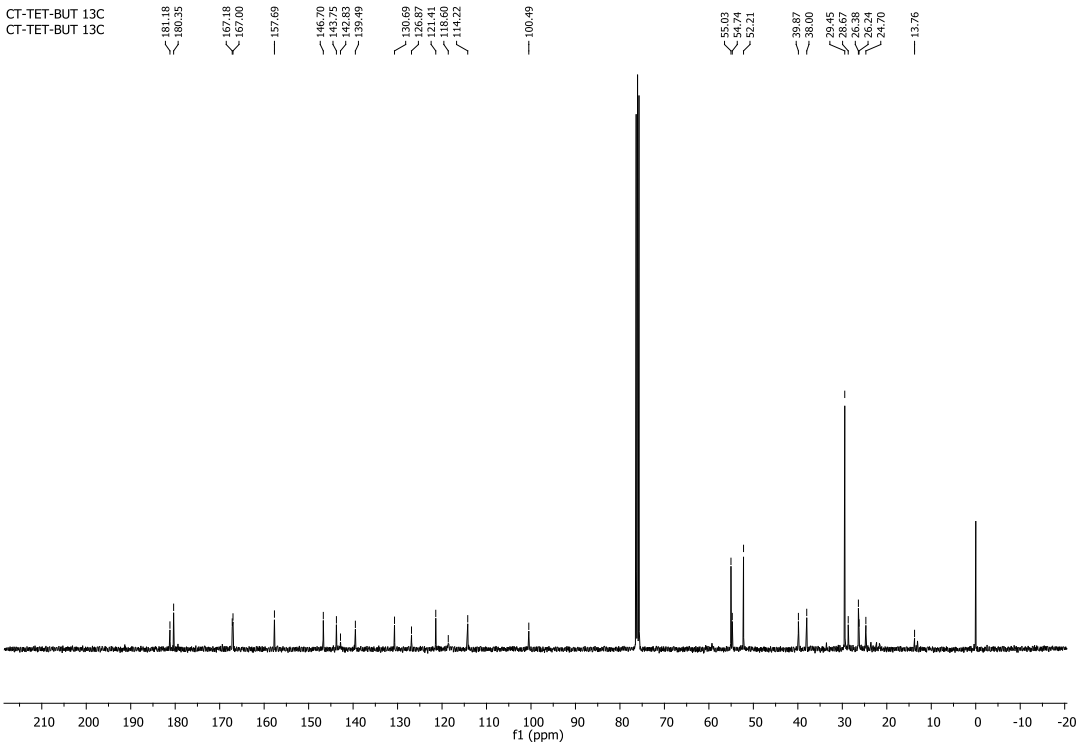


Figure A. 6. ^{13}C NMR spectrum of compound **89**

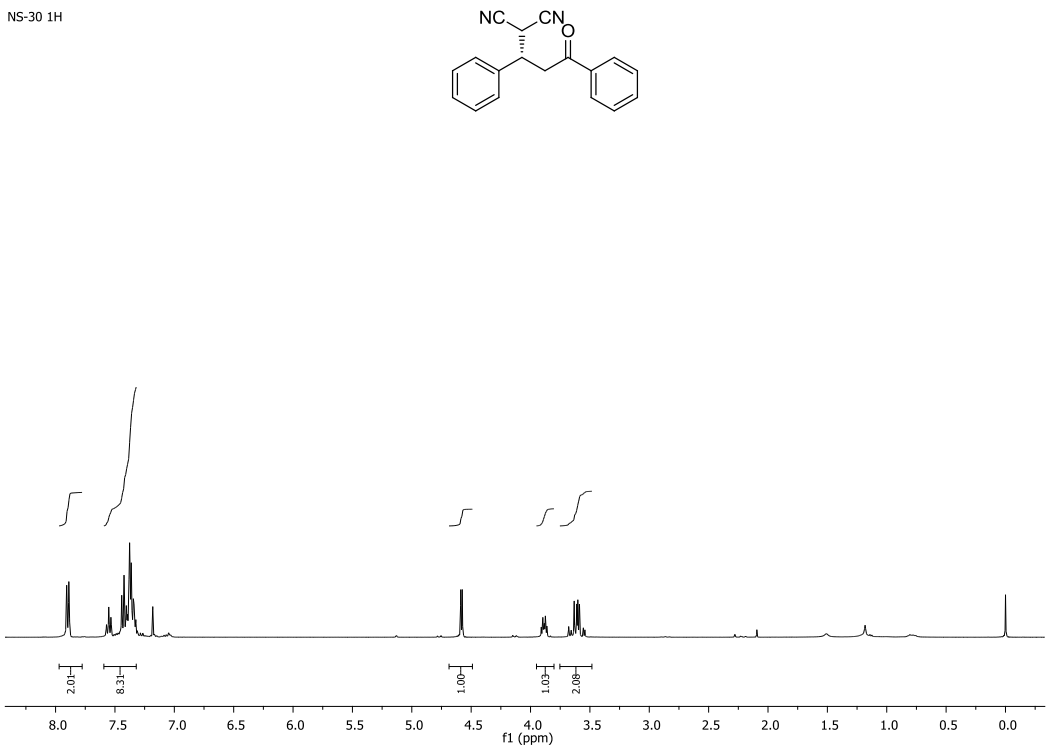


Figure A. 7. ^{1}H NMR spectrum of compound **79a**

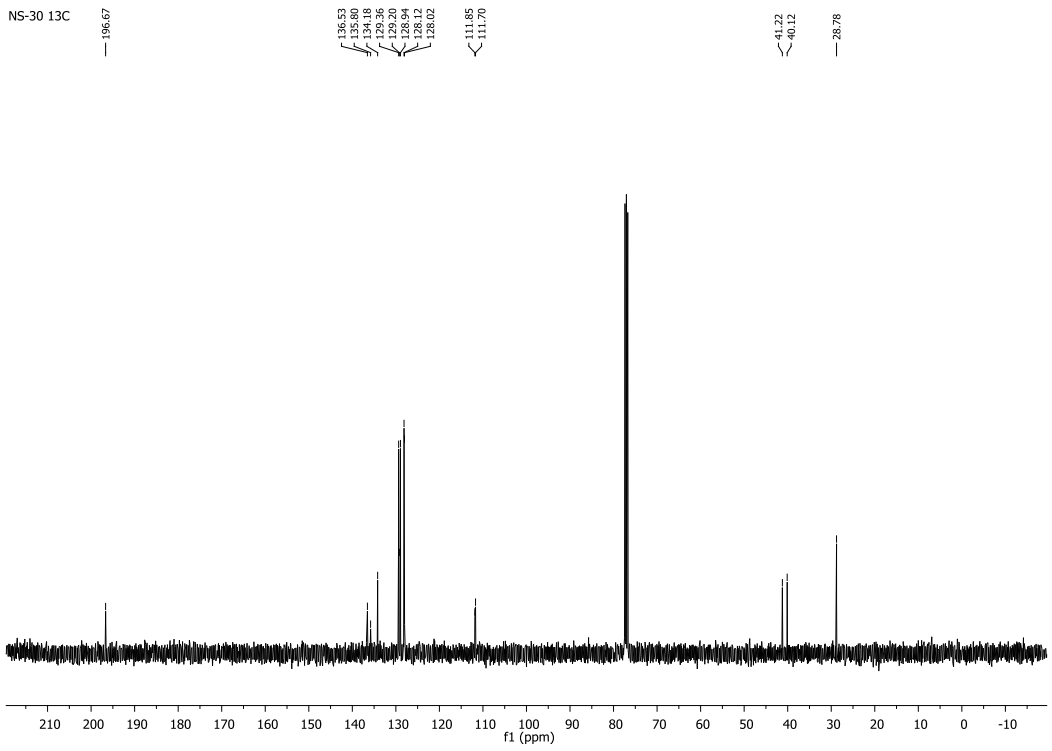


Figure A. 8. ^{13}C NMR spectrum of compound **79a**

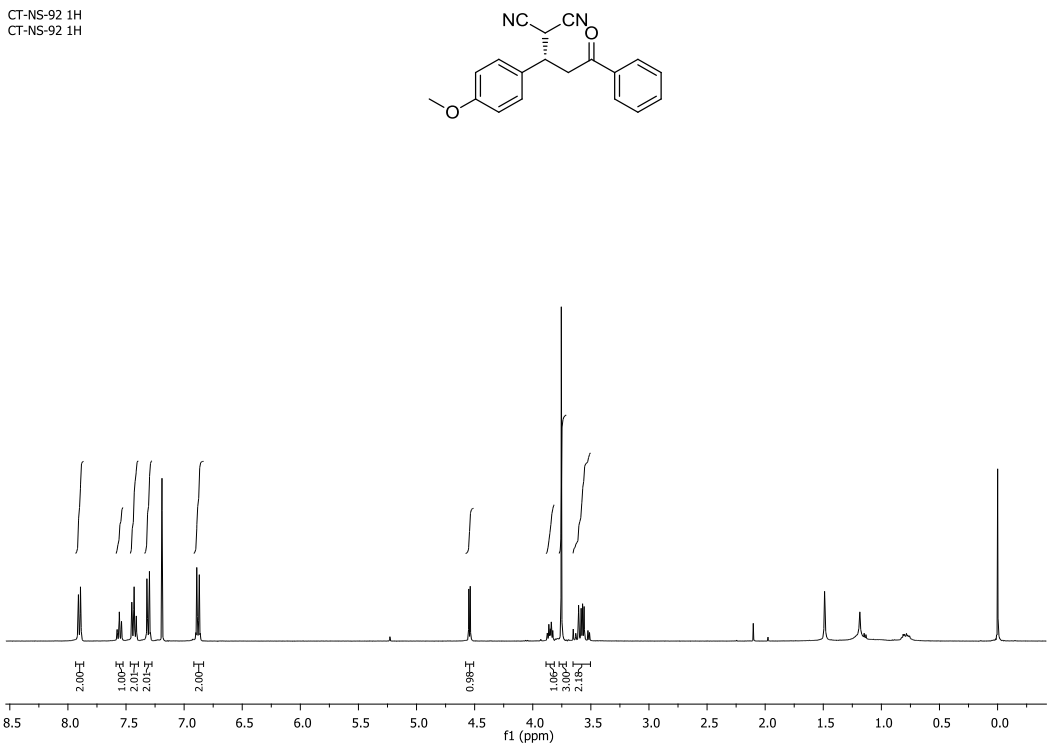


Figure A. 9. ^{1}H NMR spectrum of compound **79b**

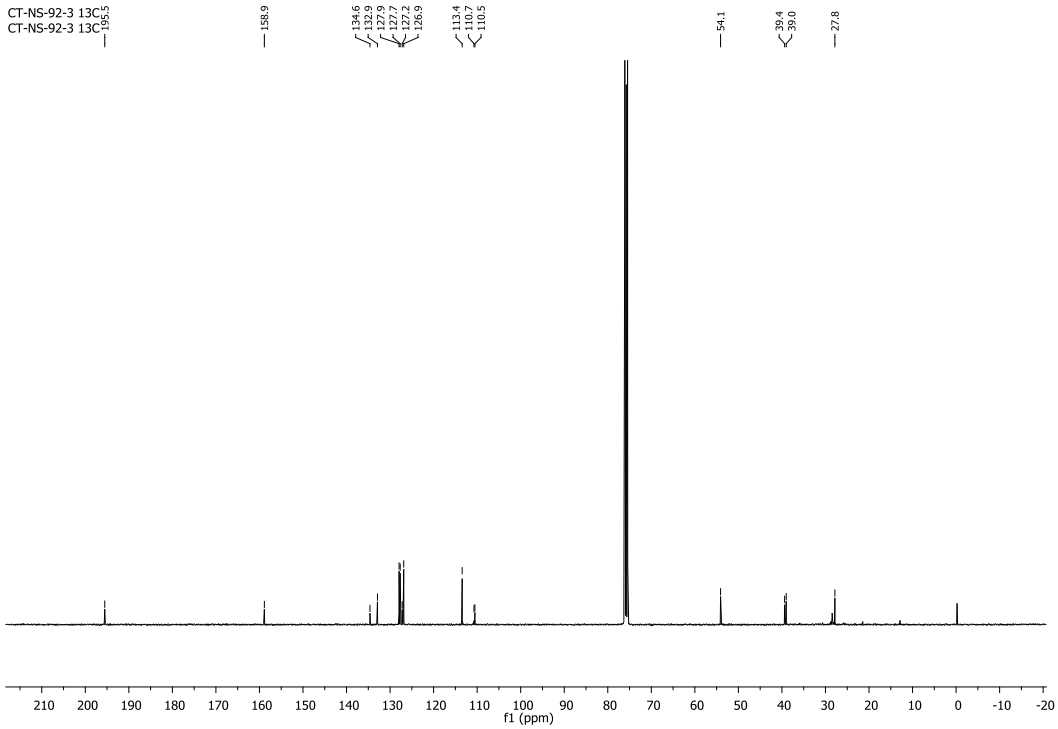


Figure A. 10. ^{13}C NMR spectrum of compound **79b**

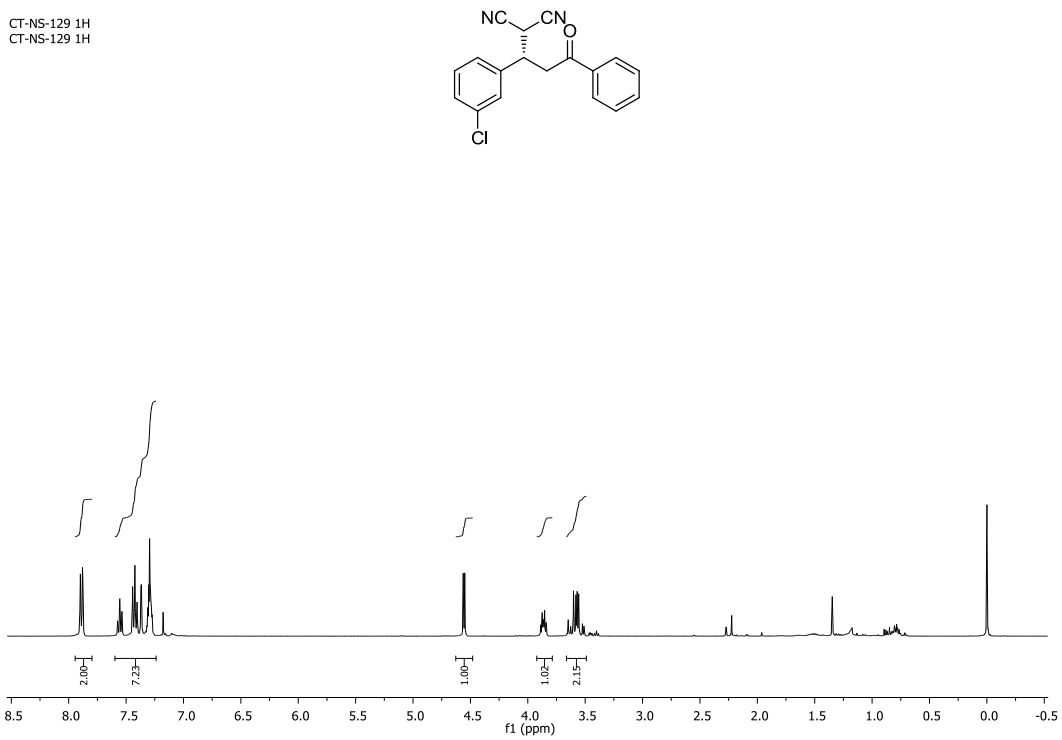


Figure A. 11. ^{1}H NMR spectrum of compound **79c**

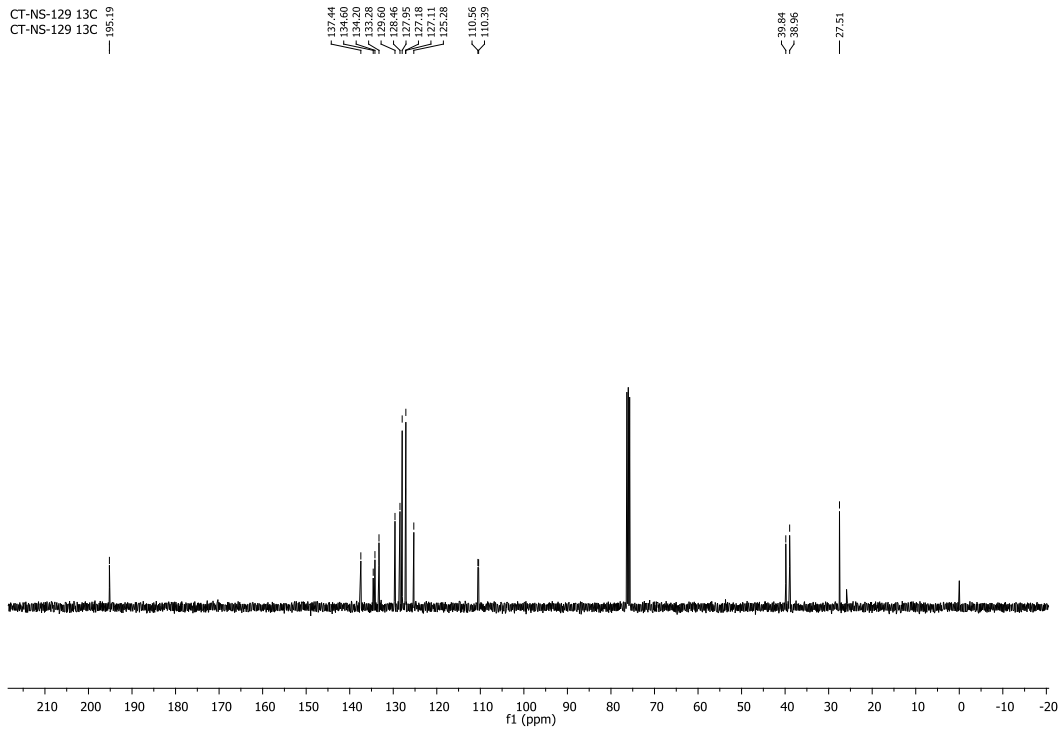


Figure A. 12. ^{13}C NMR spectrum of compound **79c**

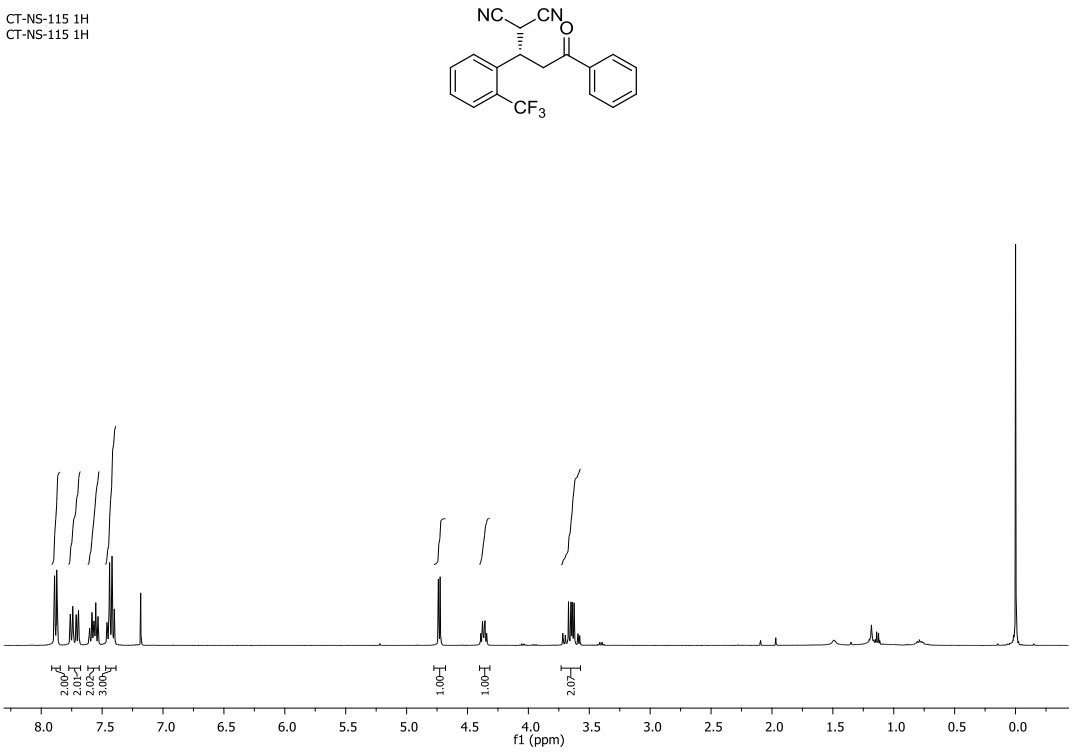


Figure A. 13. ^{1}H NMR spectrum of compound **79d**

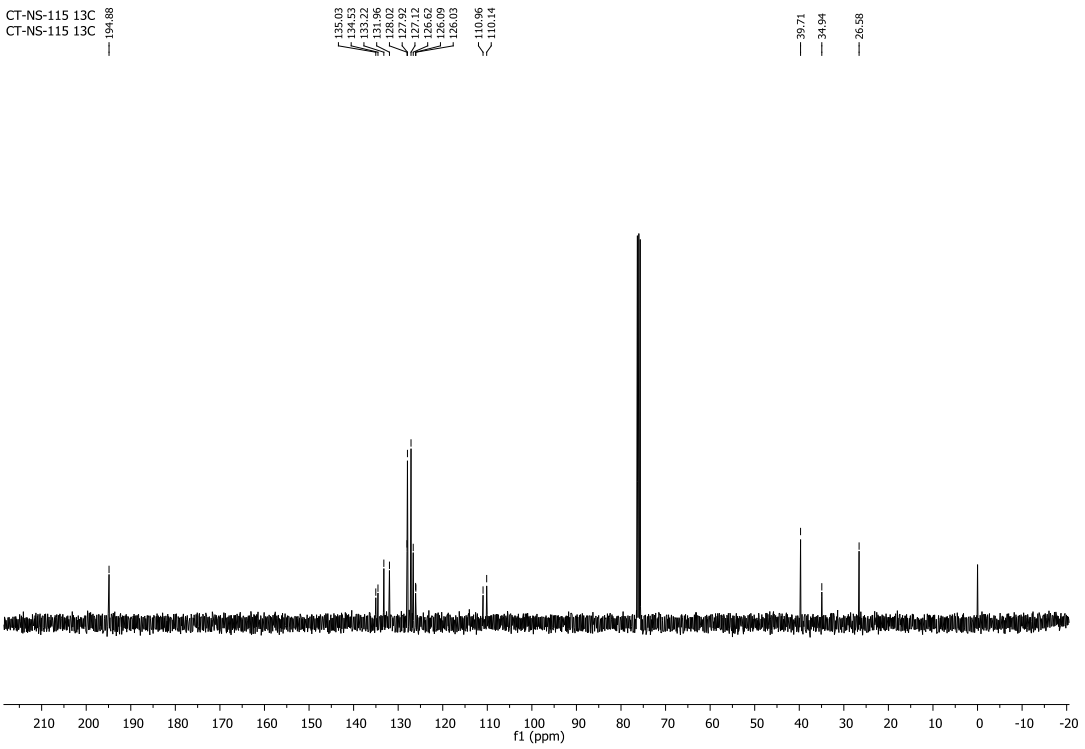


Figure A. 14. ^{13}C NMR spectrum of compound **79d**

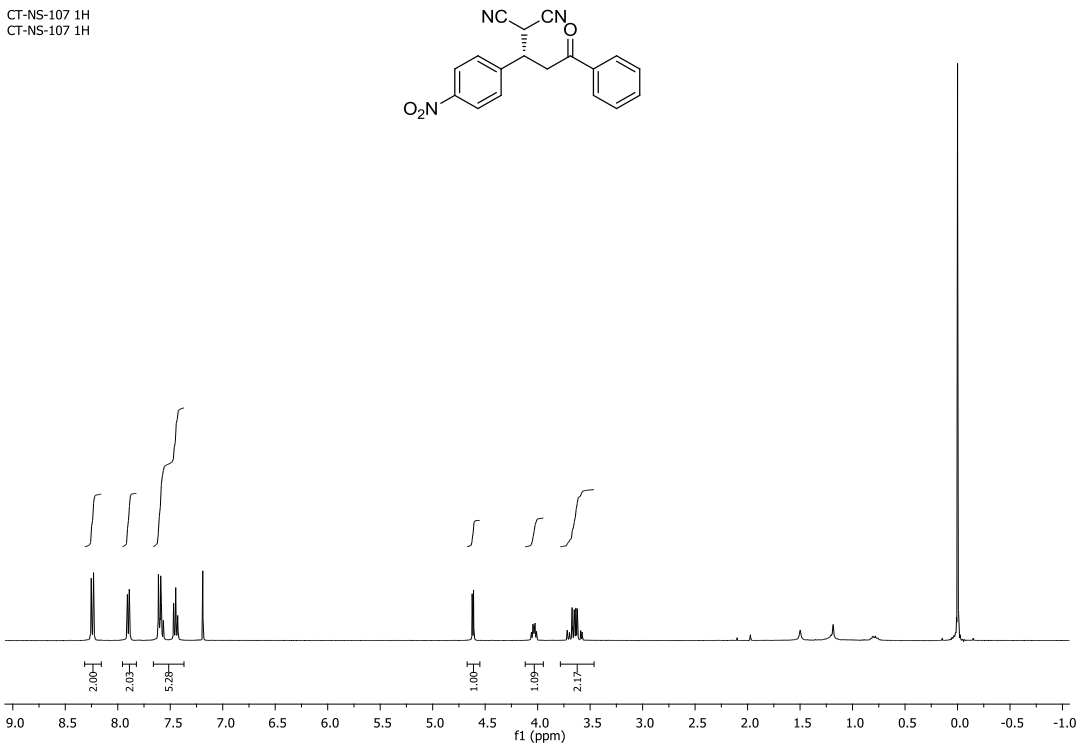


Figure A. 15. ^{1}H NMR spectrum of compound **79e**

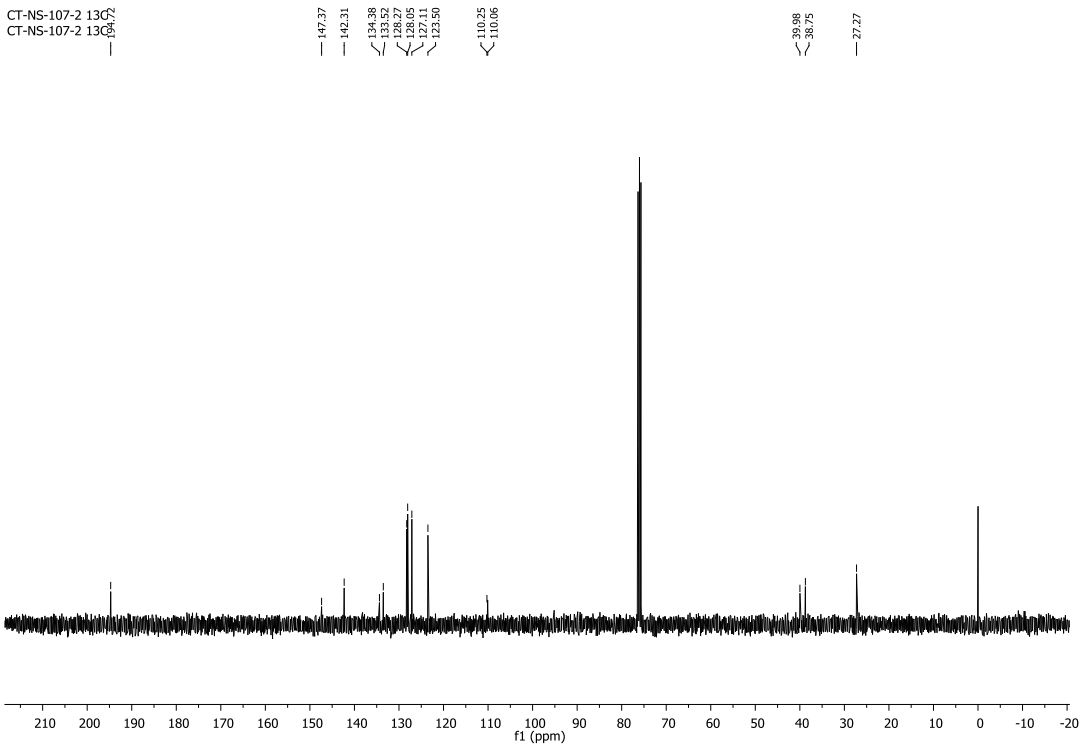


Figure A. 16. ^{13}C NMR spectrum of compound **79e**

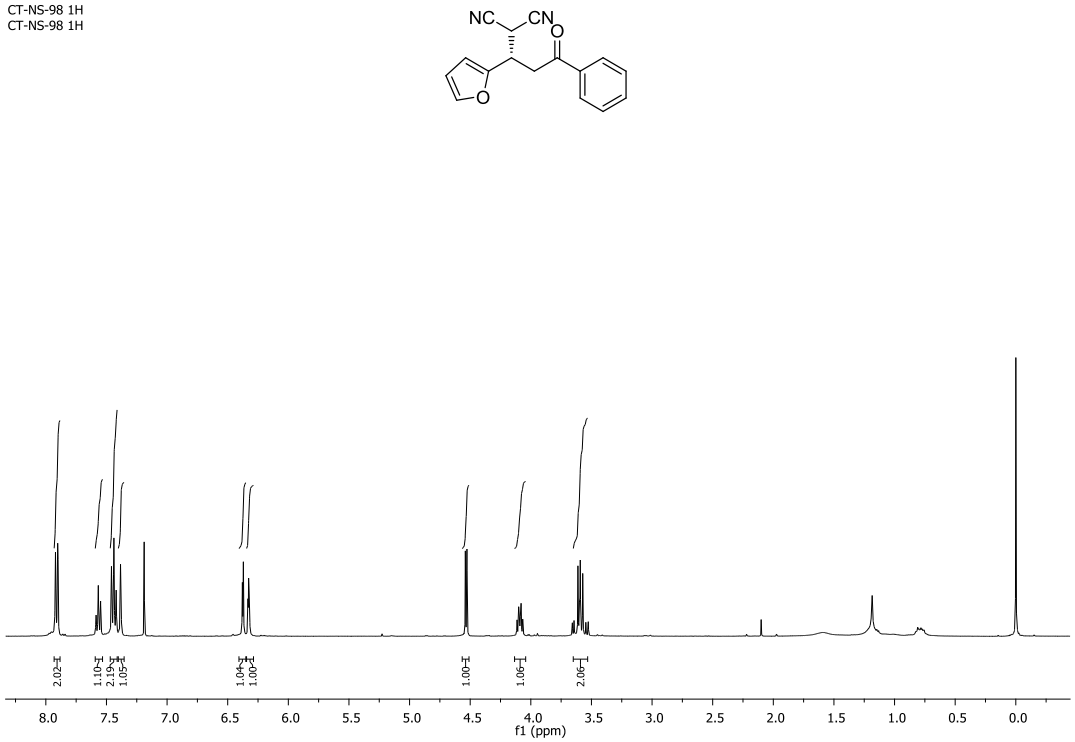


Figure A. 17. ^{1}H NMR spectrum of compound **79f**

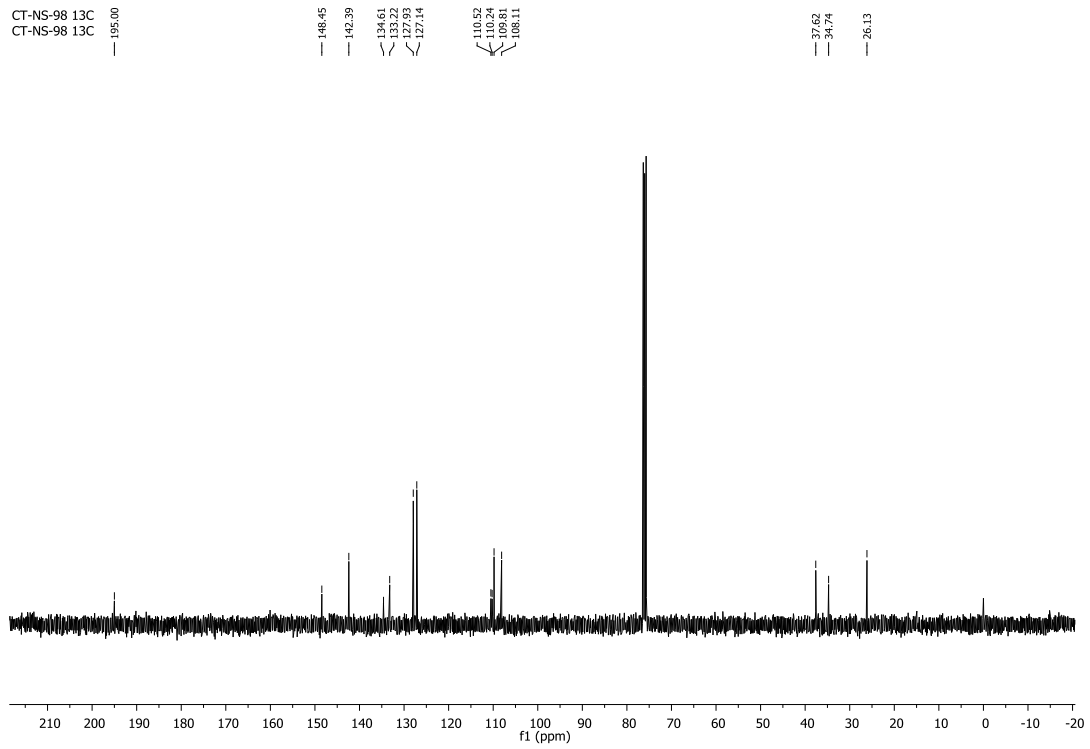


Figure A. 18. ^{13}C NMR spectrum of compound **79f**

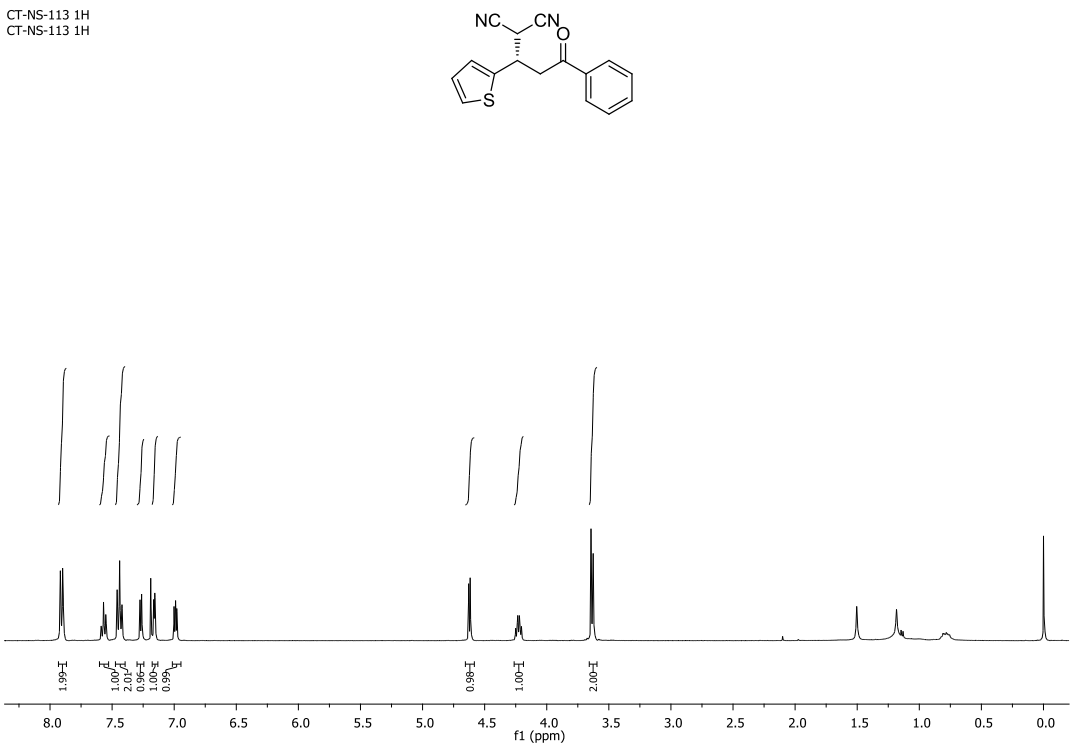


Figure A. 19. ^{1}H NMR spectrum of compound **79g**

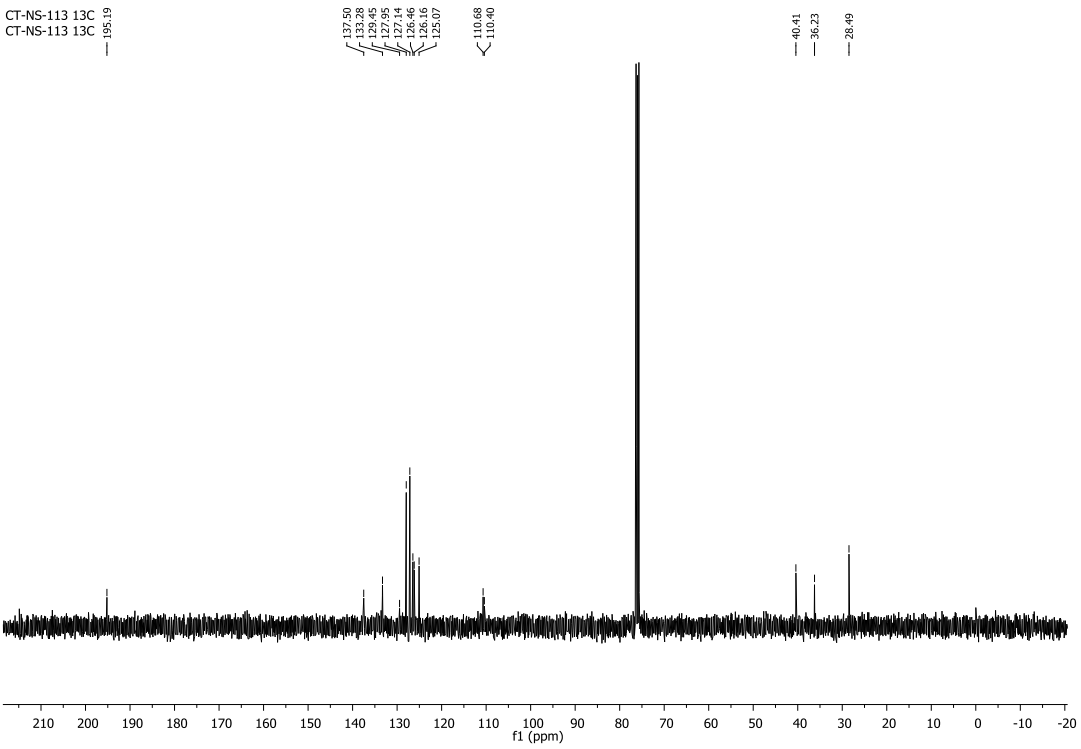


Figure A. 20. ^{13}C NMR spectrum of compound **79g**

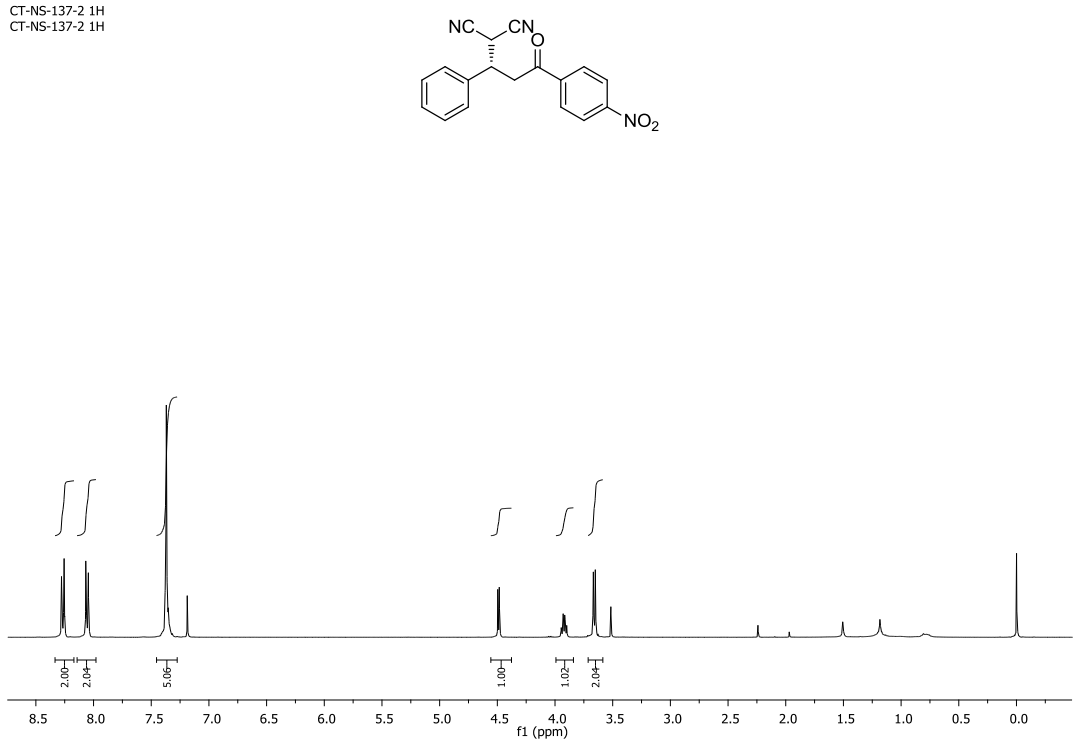


Figure A. 21. ^{1}H NMR spectrum of compound **79h**

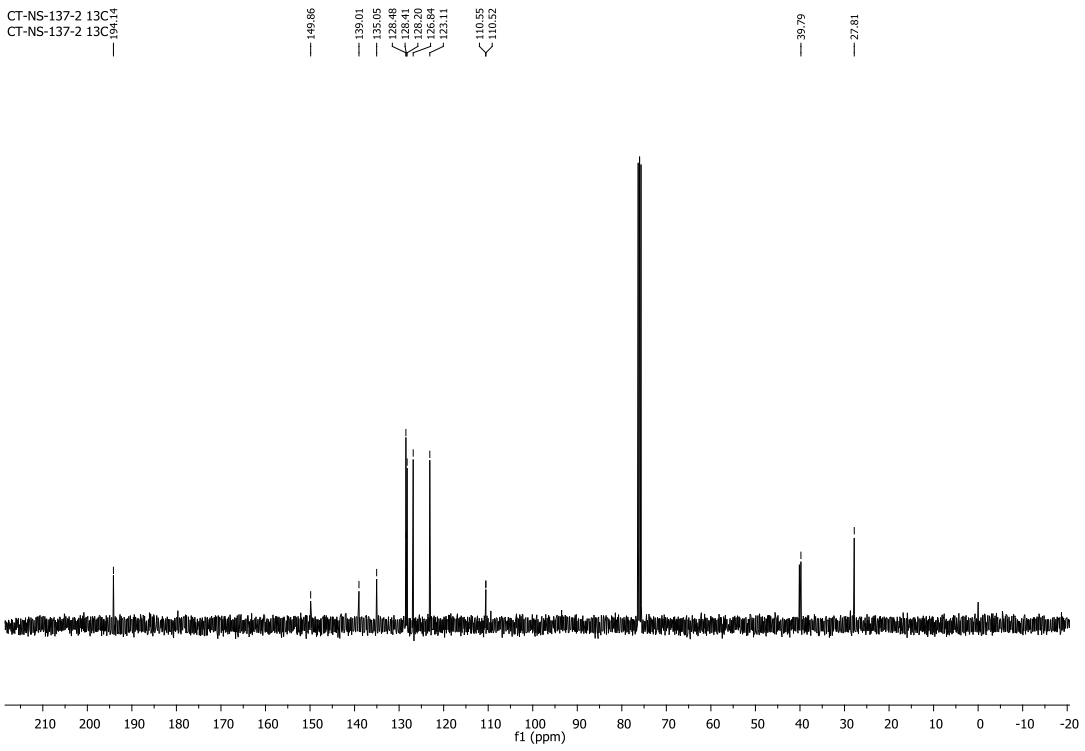


Figure A. 22. ^{13}C NMR spectrum of compound **79h**

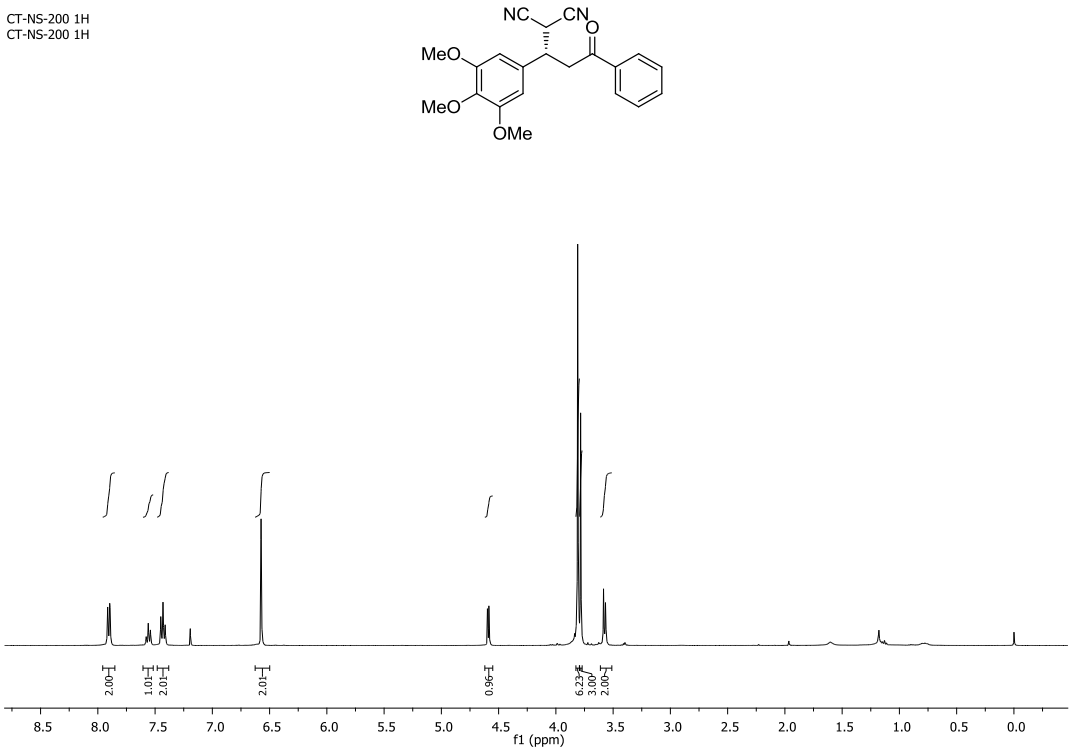


Figure A. 23. ^{1}H NMR spectrum of compound **79i**

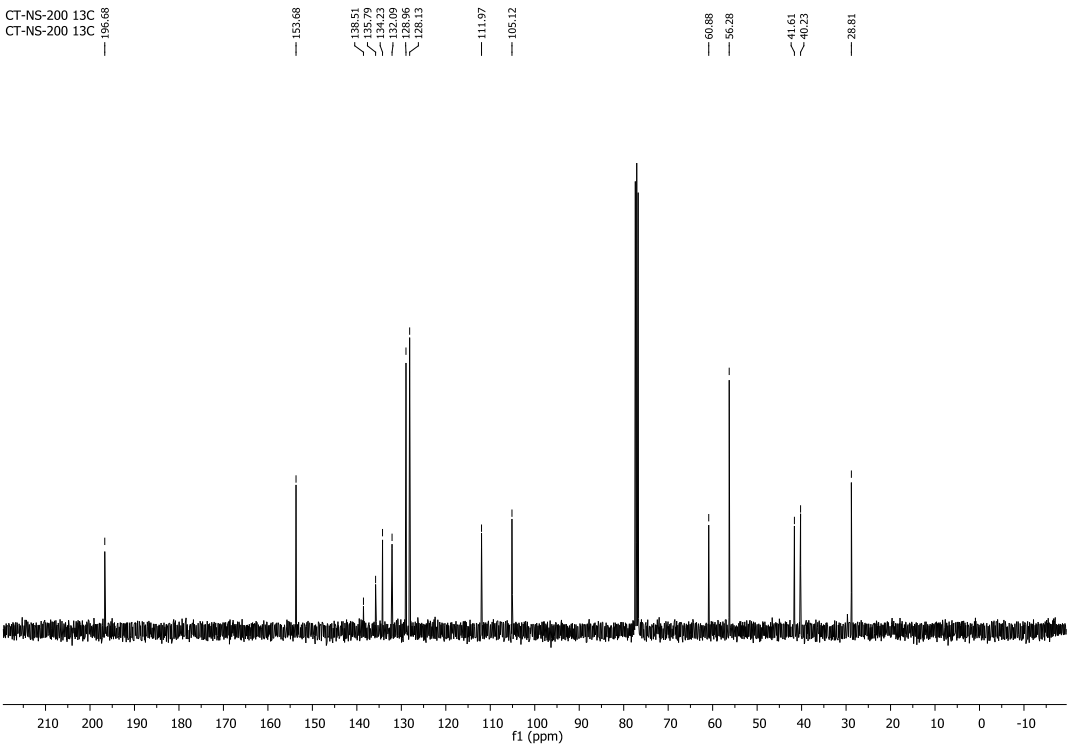


Figure A. 24. ^{13}C NMR spectrum of compound **79i**

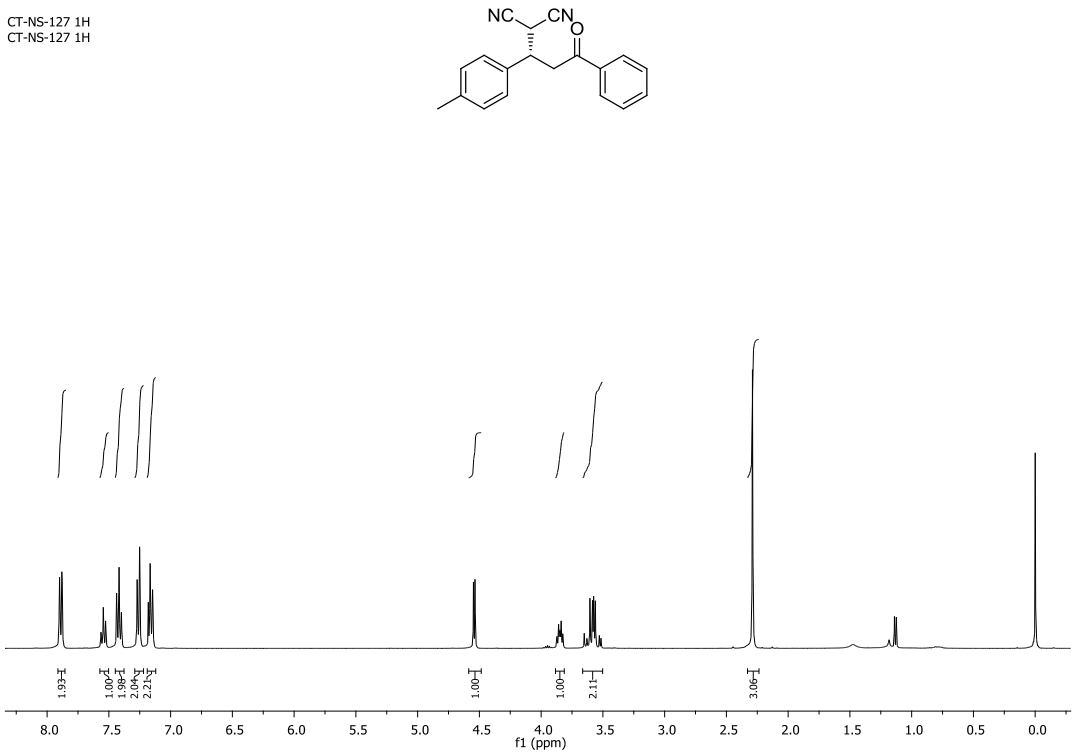


Figure A. 25. ^{1}H NMR spectrum of compound **79j**

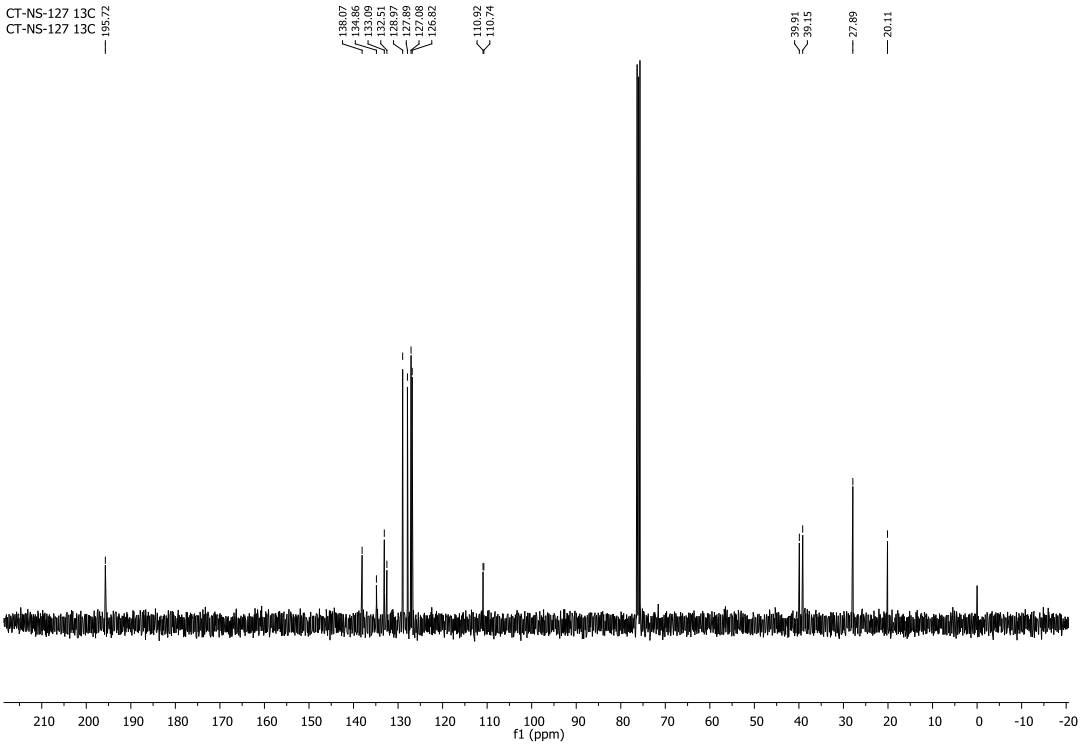


Figure A. 26. ^{13}C NMR spectrum of compound **79j**

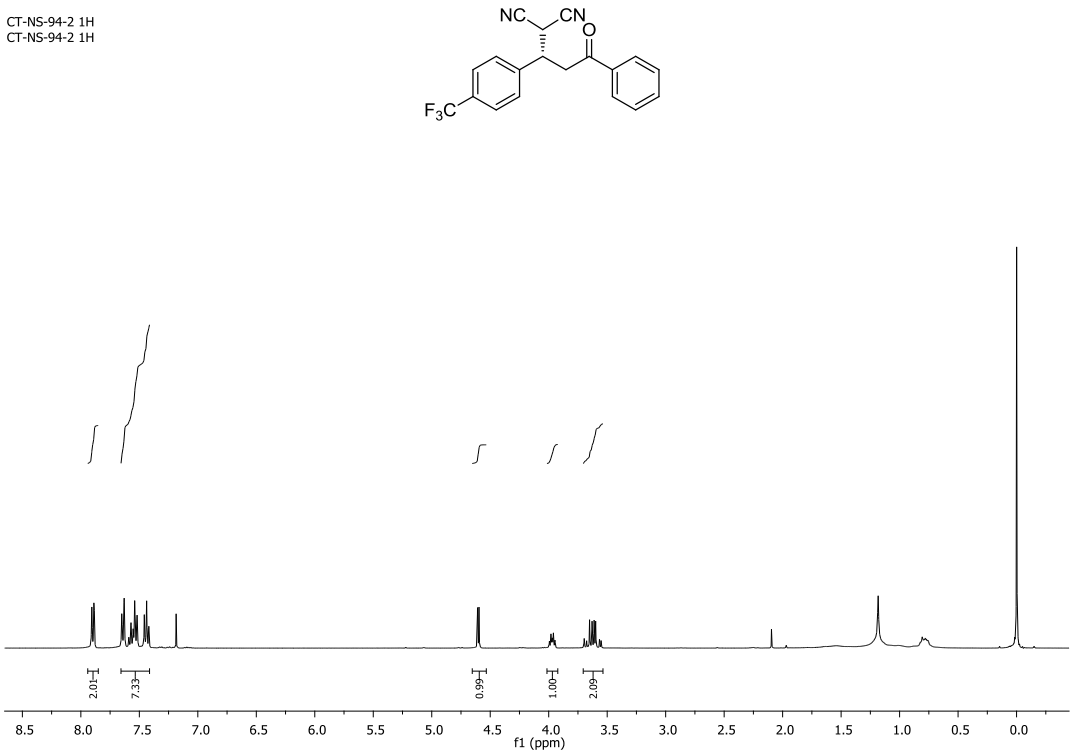


Figure A. 27. ^{1}H NMR spectrum of compound **79k**

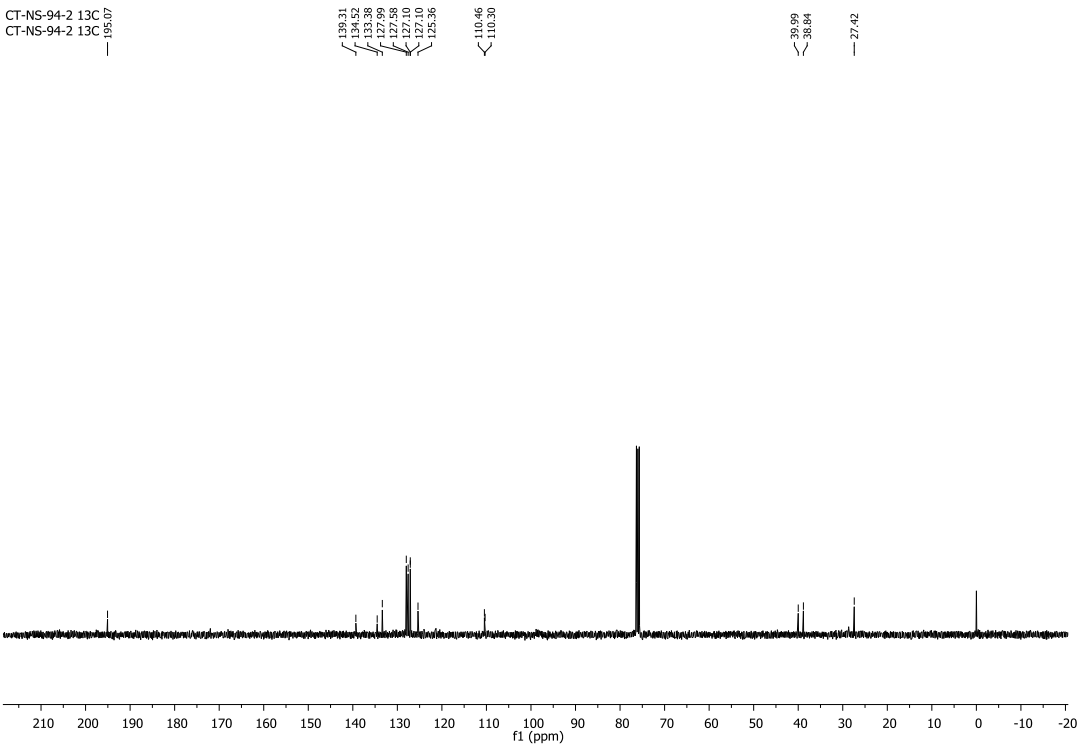
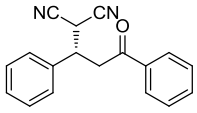


Figure A. 28. ^{13}C NMR spectrum of compound **79k**



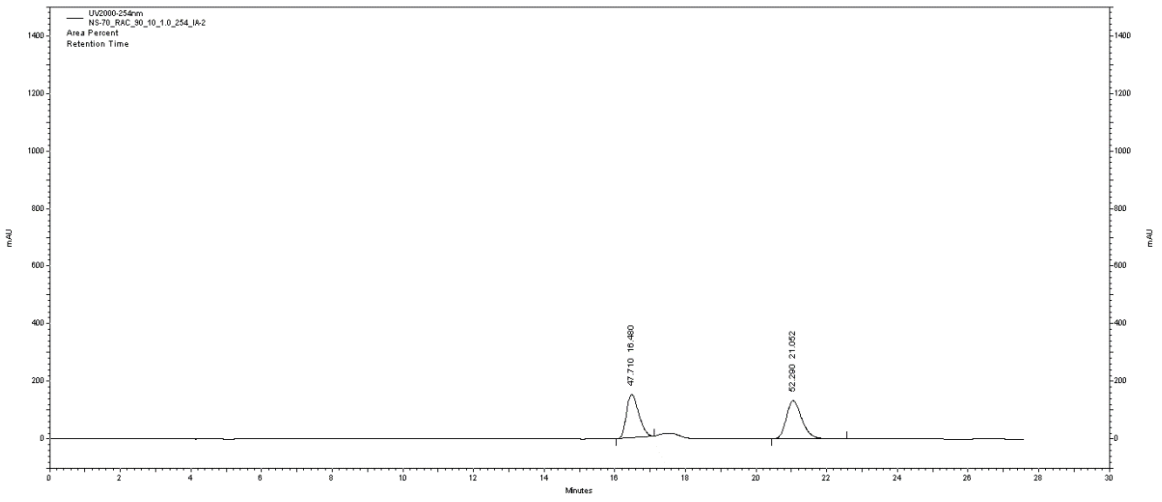


Figure A. 29. HPLC chromatogram of rac-79a

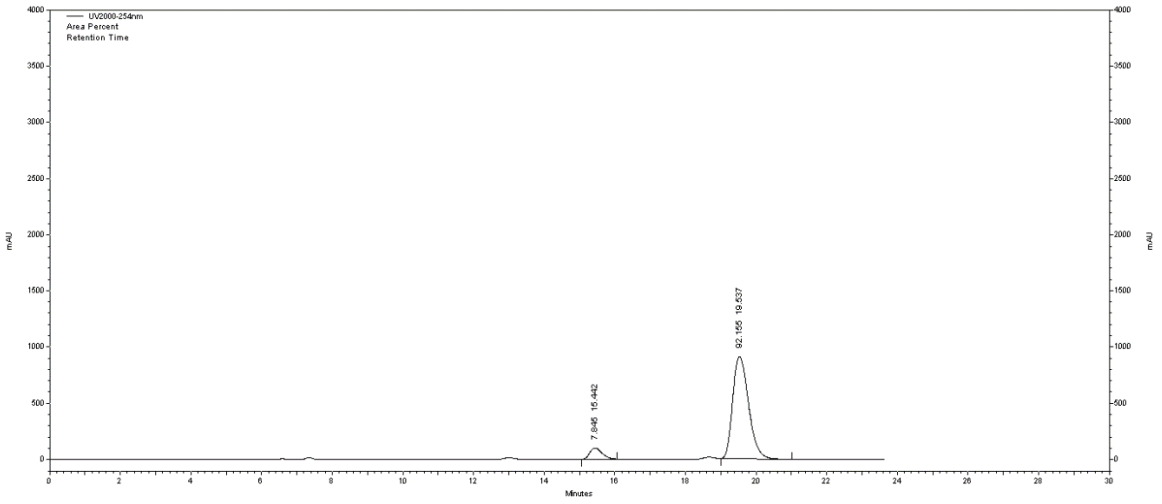
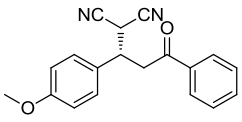


Figure A. 30. HPLC chromatogram of enantiomerically enriched product **79a**



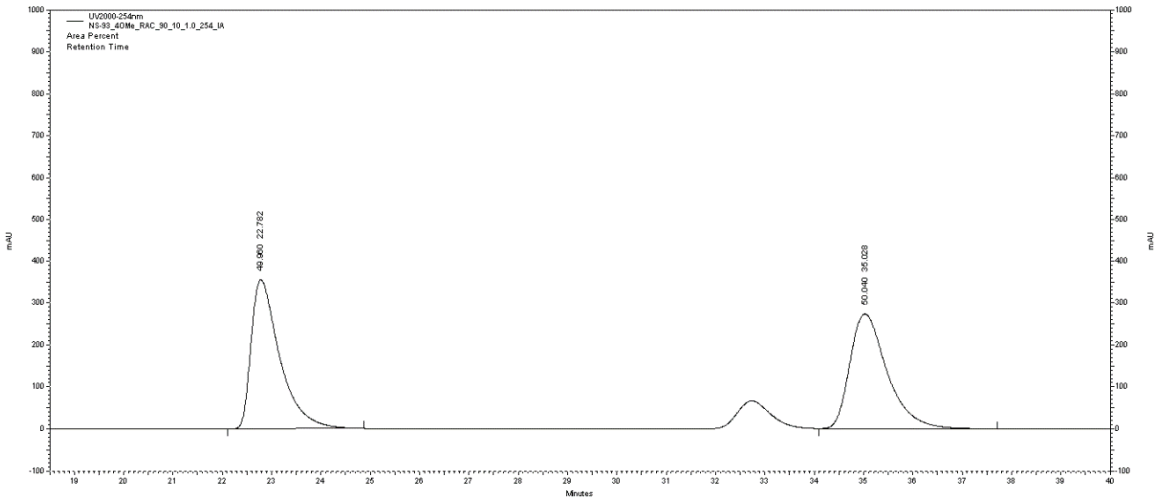


Figure A. 31. HPLC chromatogram of *rac*-**79b**

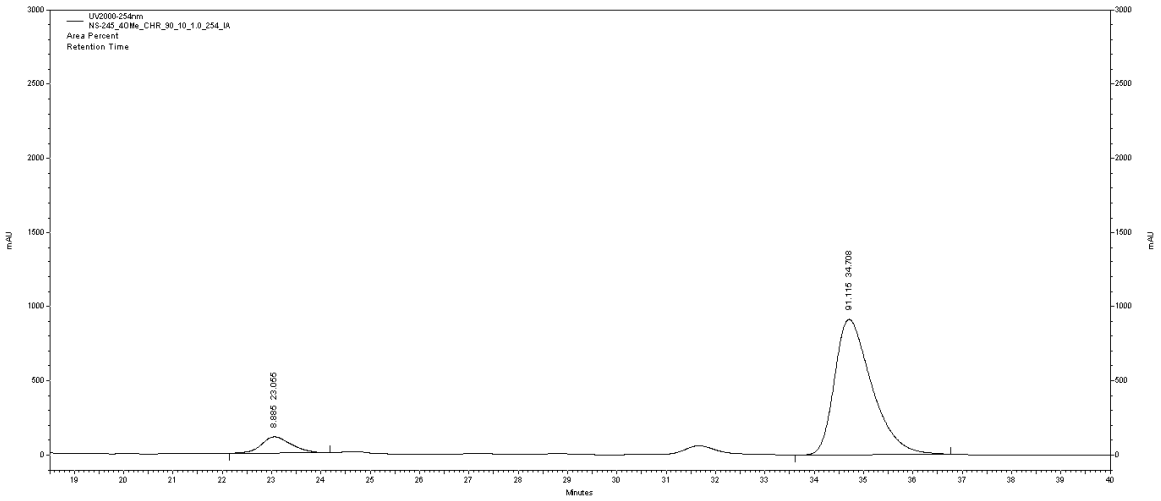


Figure A. 32. HPLC chromatogram of enantiomerically enriched product **79b**

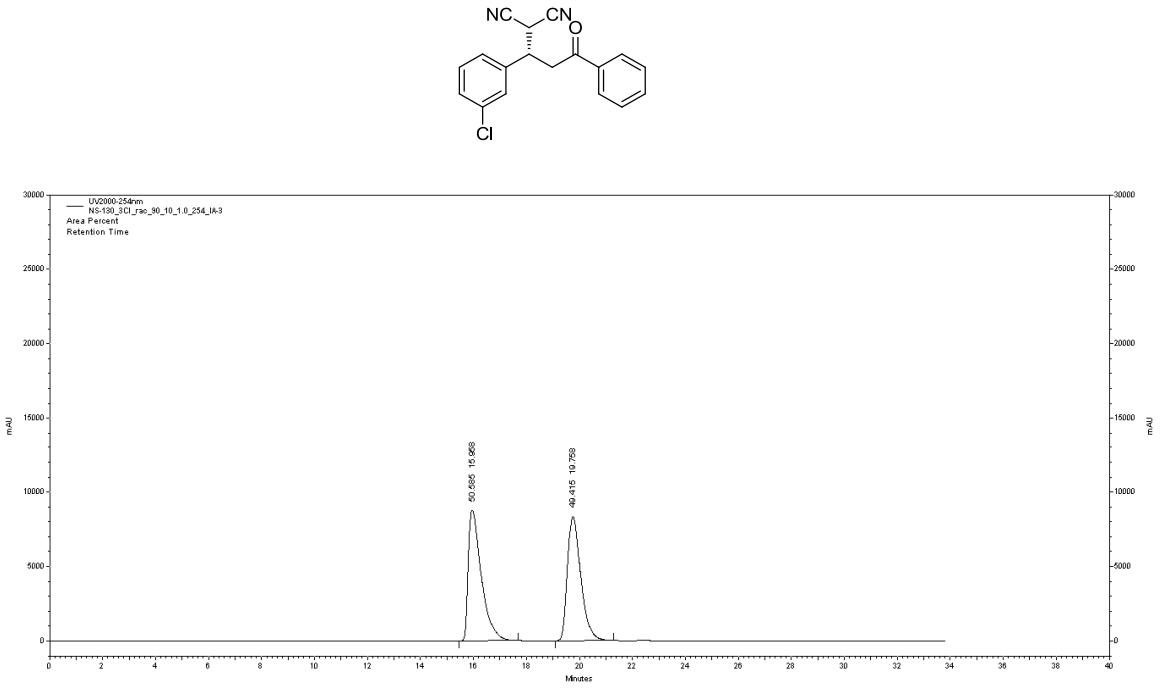


Figure A. 33. HPLC chromatogram of *rac*-**79c**

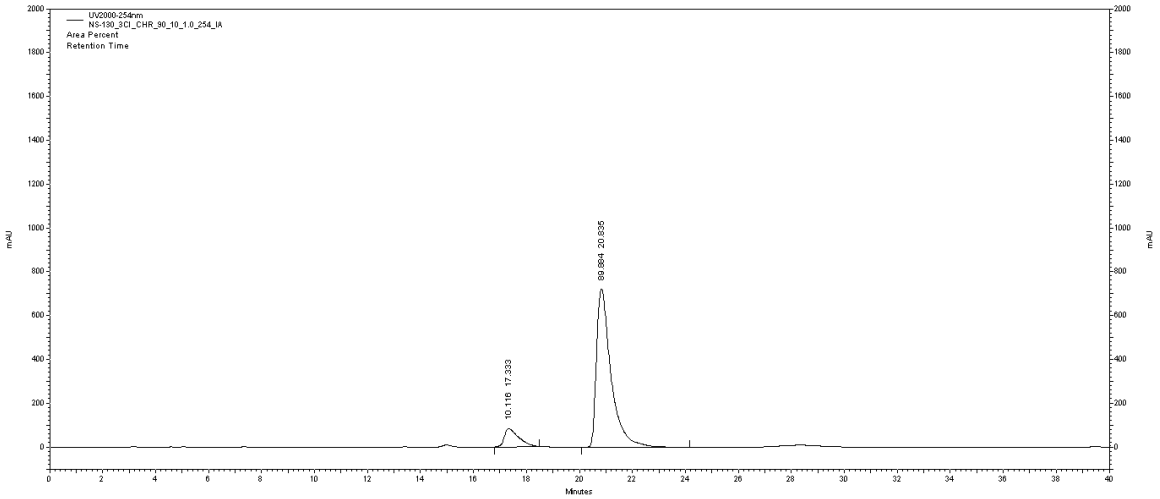
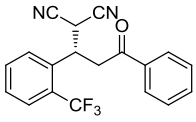


Figure A. 34. HPLC chromatogram of enantiomerically enriched product **79c**



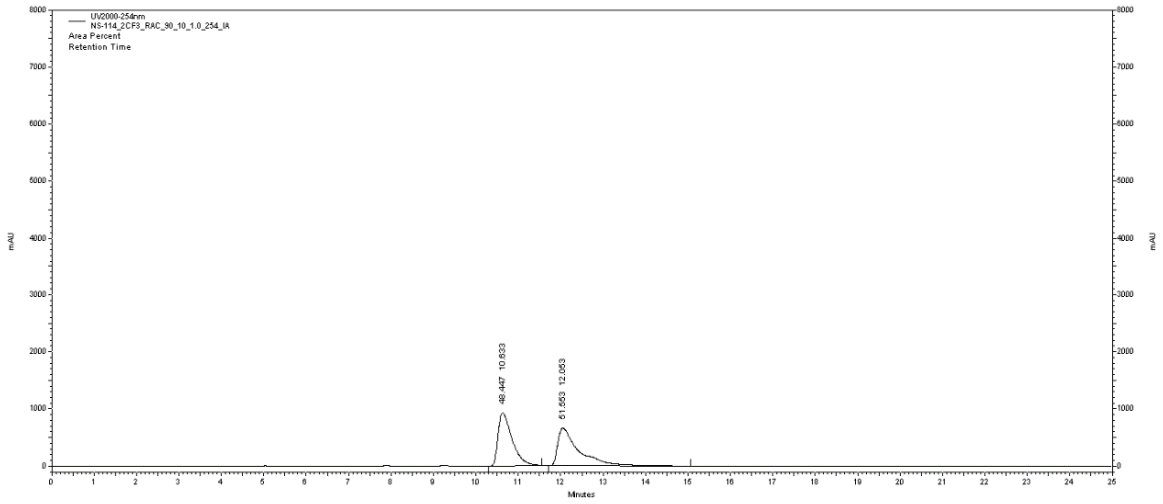


Figure A. 35. HPLC chromatogram of *rac*-**79d**

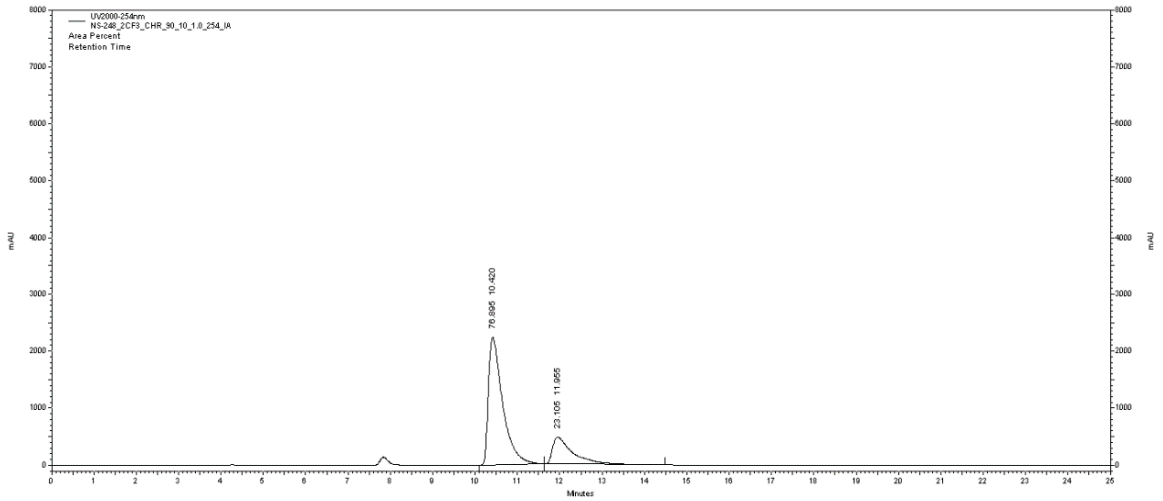
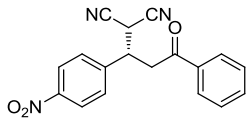


Figure A. 36. HPLC chromatogram of enantiomerically enriched product **79d**



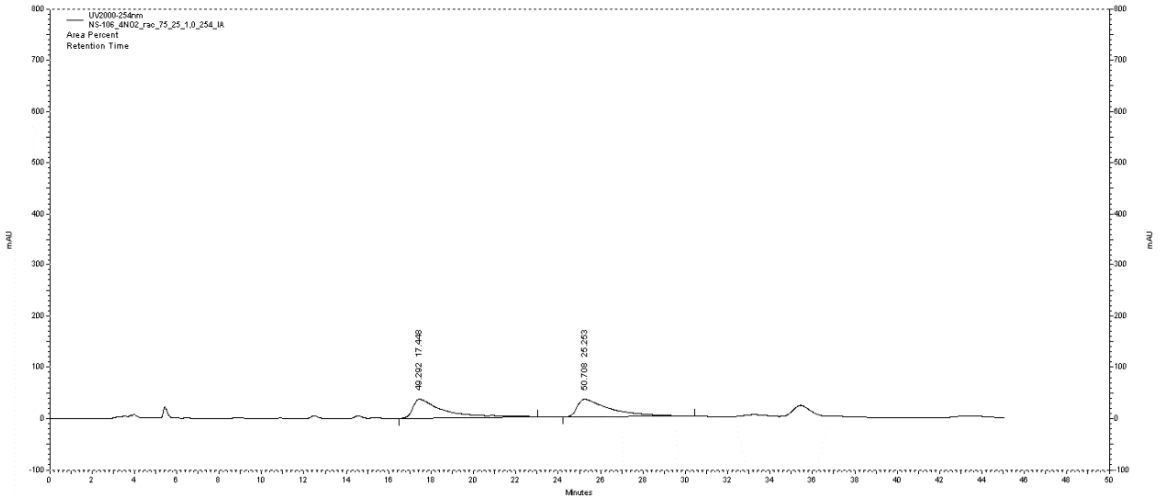


Figure A. 37. HPLC chromatogram of *rac*-**79e**

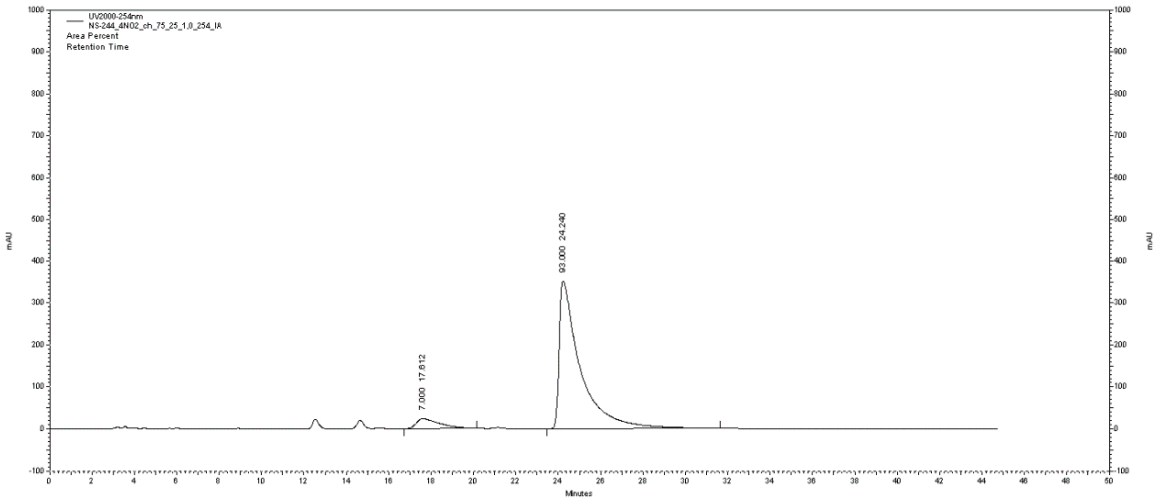
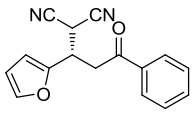


Figure A. 38. HPLC chromatogram of enantiomerically enriched product **79e**



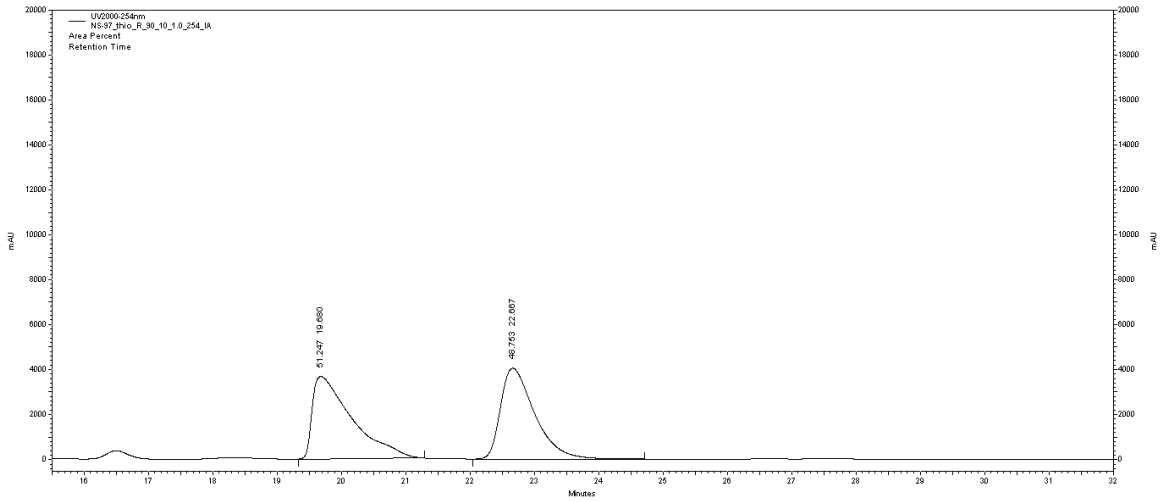


Figure A. 39. HPLC chromatogram of *rac*-**79f**

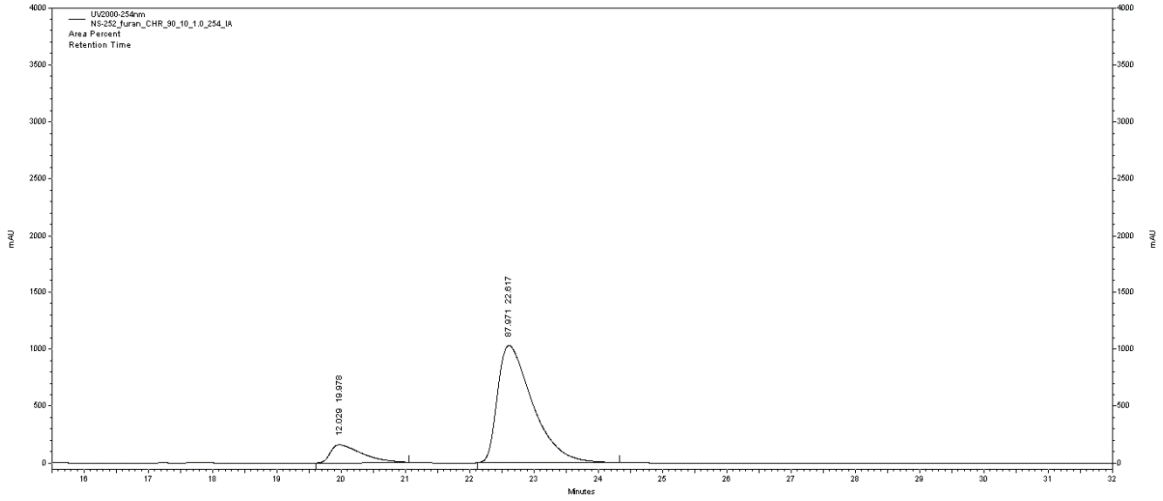
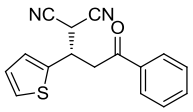


Figure A. 40. HPLC chromatogram of enantiomerically enriched product **79f**



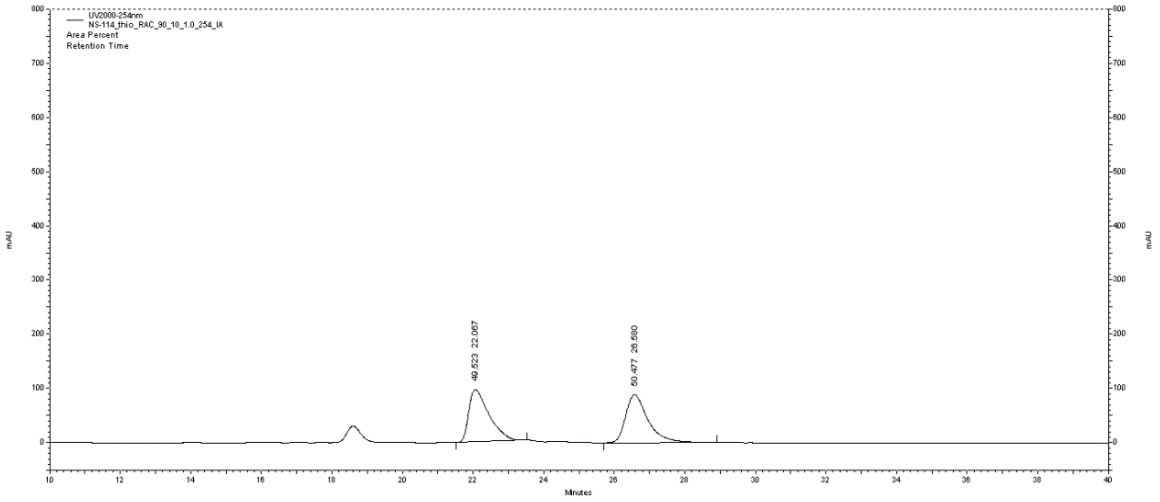


Figure A. 41. HPLC chromatogram of *rac*-**79g**

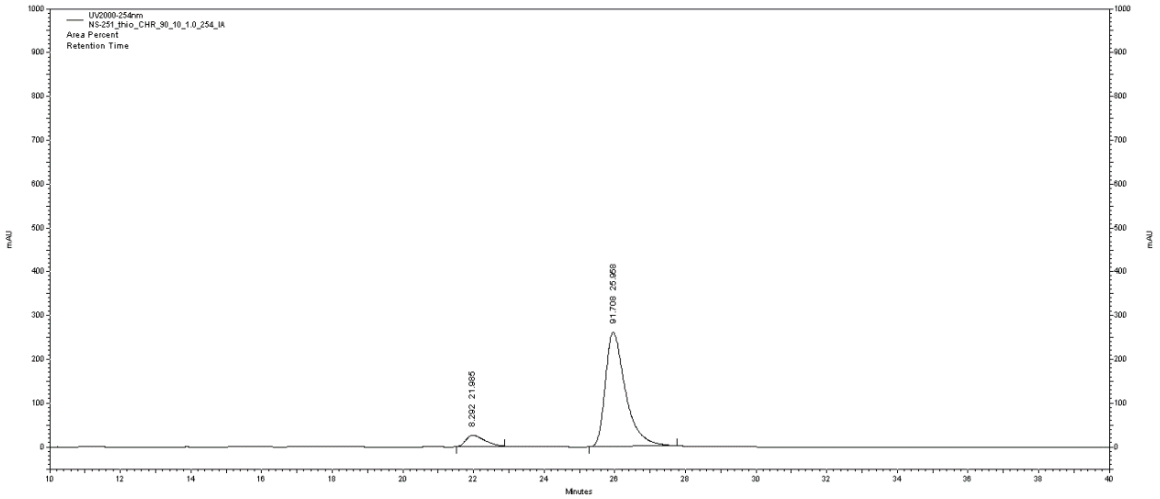
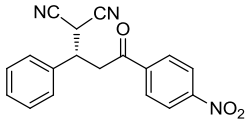


Figure A. 42. HPLC chromatogram of enantiomerically enriched product **79g**



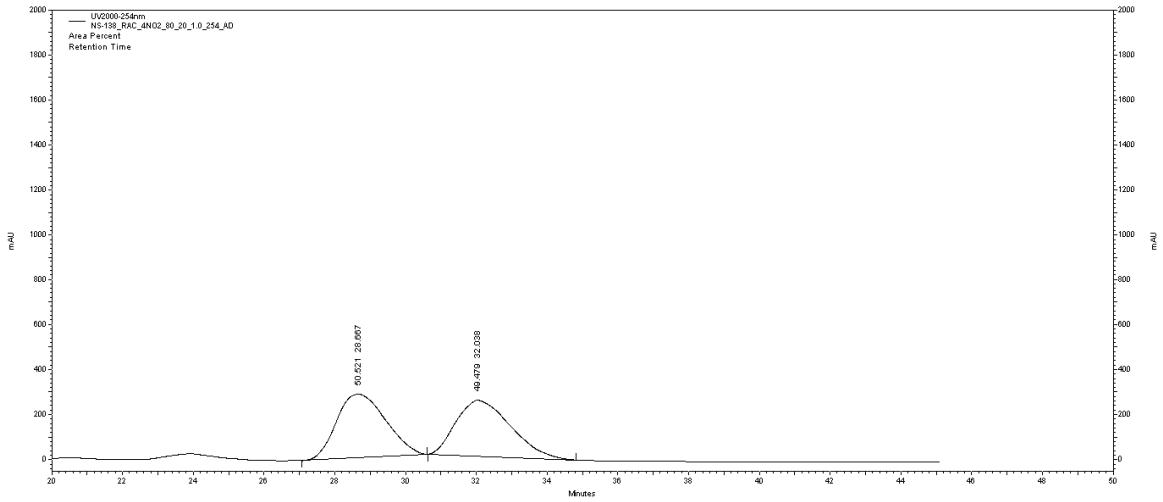


Figure A. 43. HPLC chromatogram of *rac*-**79h**

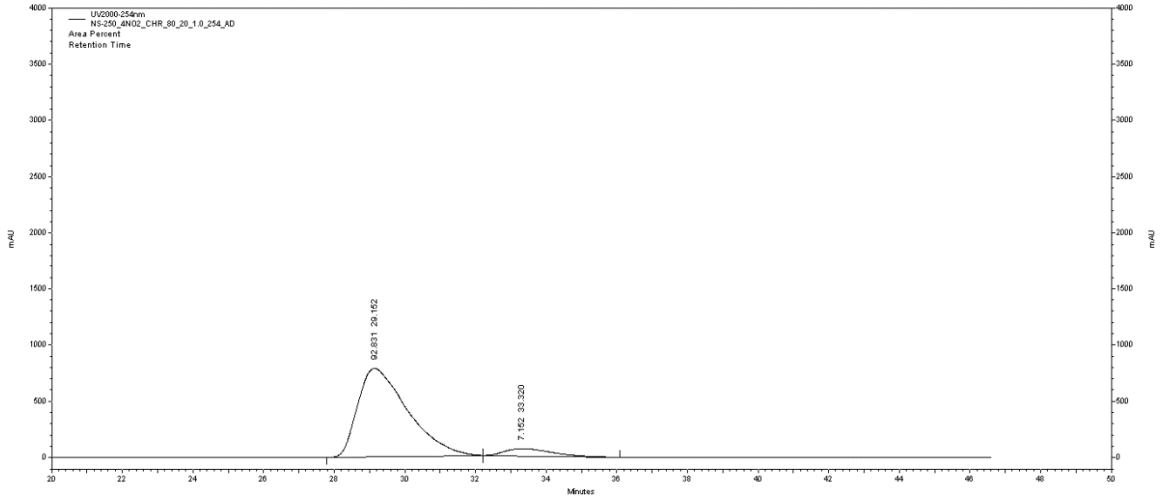
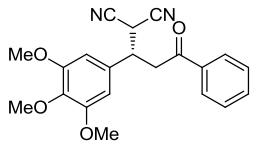


Figure A. 44. HPLC chromatogram of enantiomerically enriched product **79h**



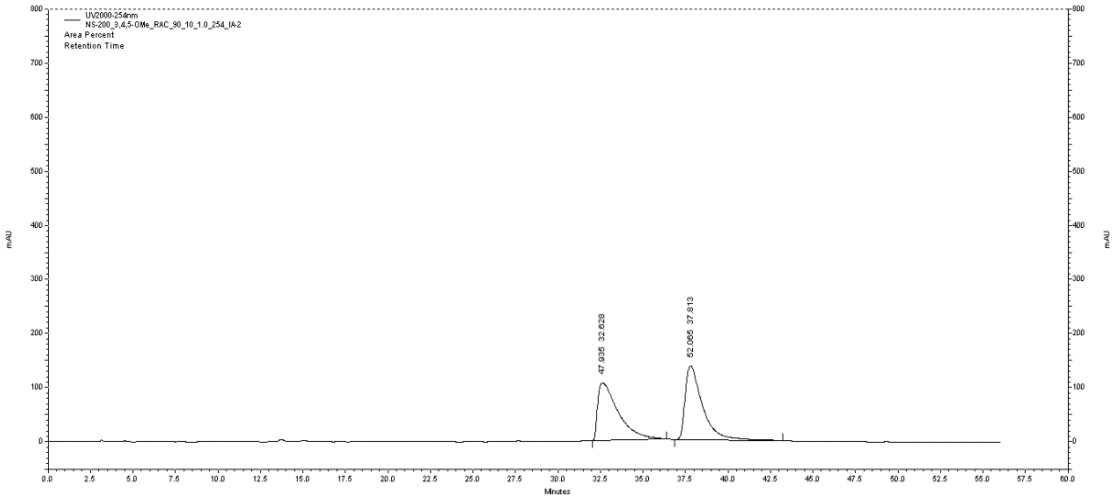


Figure A. 45. HPLC chromatogram of *rac*-**79i**

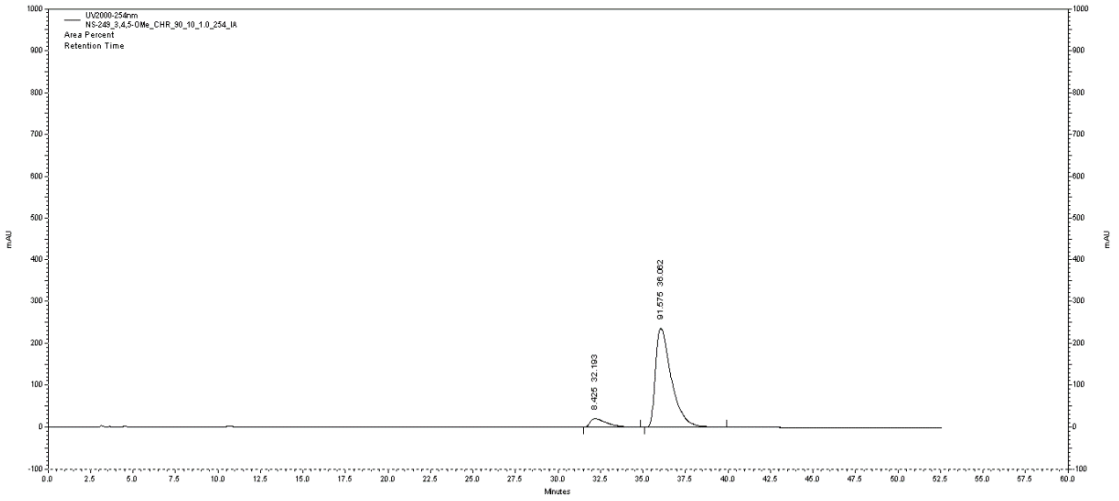
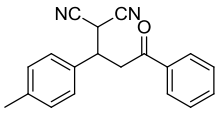


Figure A. 46. HPLC chromatogram of enantiomerically enriched product **79i**



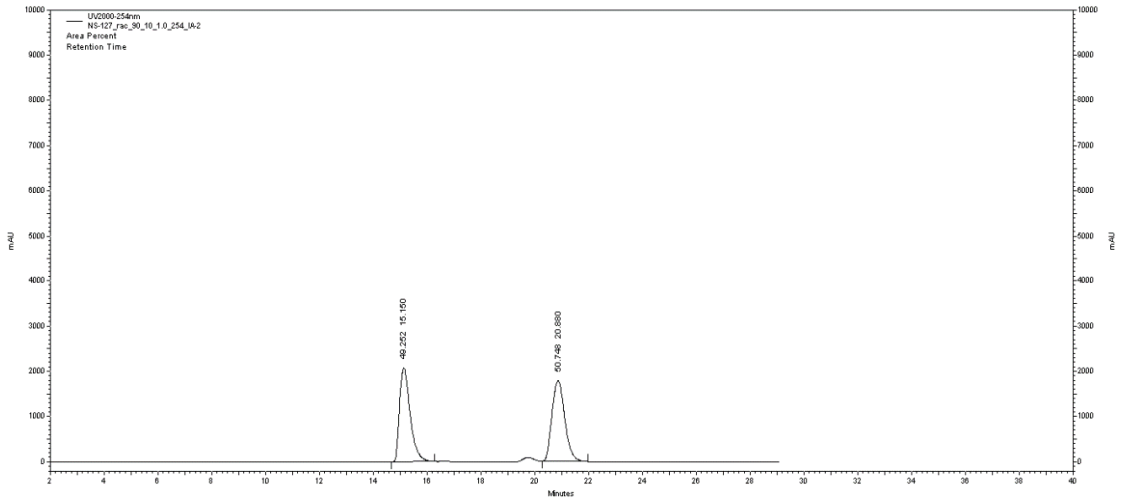


Figure A. 47. HPLC chromatogram of *rac*-**79j**

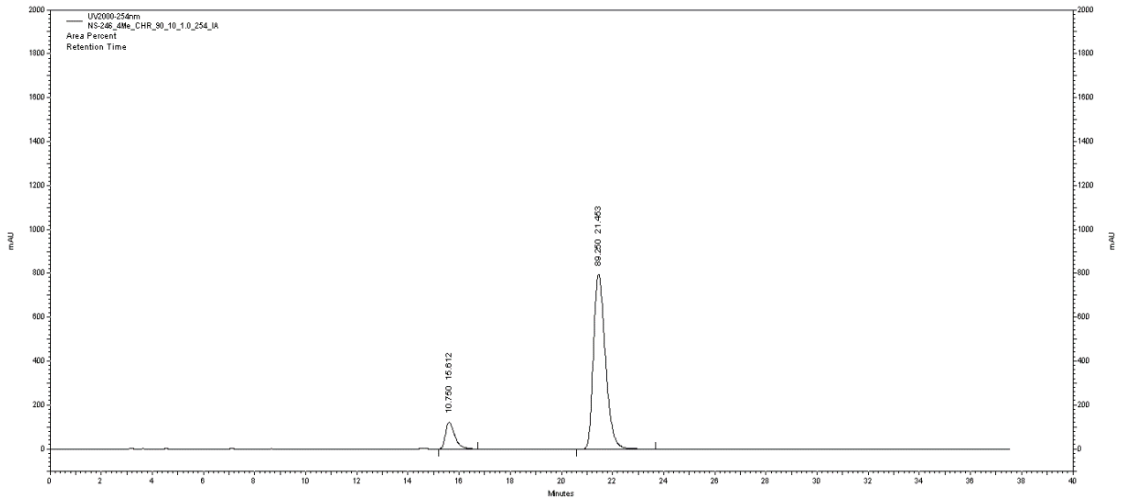
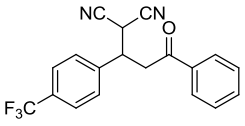


Figure A. 48. HPLC chromatogram of enantiomerically enriched product **79j**



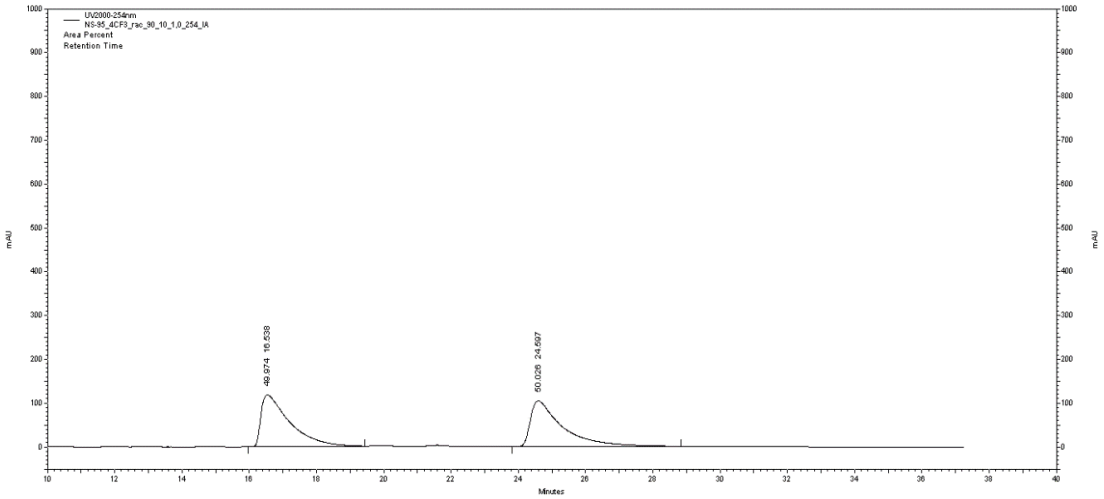


Figure A. 49. HPLC chromatogram of *rac*-**79k**

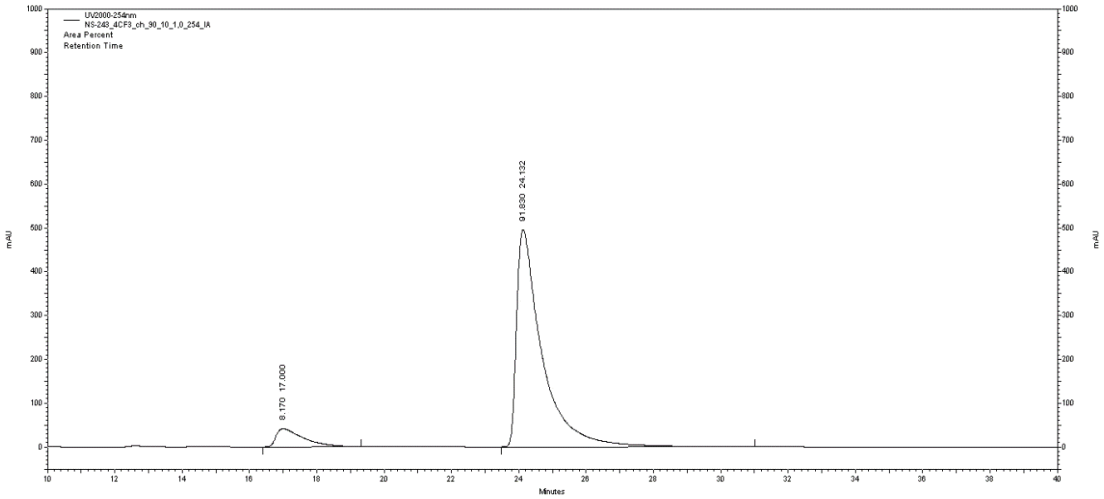


Figure A. 50. HPLC chromatogram of enantiomerically enriched product **79k**