ENANTIOSELECTIVE MICHAEL ADDITION OF 1-NITROPROPANE TO NITROOLEFINS WITH 2-AMINODMAP AND QUININE BASED BIFUNCTIONAL ORGANOCATALYSTS

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

ESRA KANBEROĞLU

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

FEBRUARY 2015

Approval of the thesis:

ENANTIOSELECTIVE MICHAEL ADDITION OF 1-NITROPROPANE TO NITROOLEFINS WITH 2-AMINODMAP AND QUININE BASED BIFUNCTIONAL ORGANOCATALYSTS

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I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

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ABSTRACT

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February 2015, 88 pages

1,3-dinitro compounds are key materials in the synthesis of a variety of important fine chemicals. Moreover, they are reduced to 1,3-diamines which are starting materials of biologically active compounds, agrochemicals and pharmaceuticals. In this study, ((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene was synthesized *via* the Michael addition of 1-nitropropane to *trans-β*-nitrostyrene in the presence of chiral bifunctional 2-aminoDMAP and quinine based organocatalysts. In the first part of study, reaction conditions were optimized by testing all organocatalysts and changing the solvent, temperature, catalyst loading as well as concentration. After getting the optimized condition for this reaction, derivatization studies were conducted with various nitroolefins. Excellent enantioselectivities up to 95% and high diastereoselectivities such as 96:4 were obtained in the desired 1,3-dinitro compounds.

Keywords: Michael addition, asymmetric organocatalysis, nitroolefins, bifunctional thiourea, quinine

ÖZ

2-AMİNODMAP VE KİNİN TEMELLİ BİFONKSİYONEL ORGANOKATALİZÖRLER İLE 1-NİTROPROPANIN NİTROOLEFİNLERE ENANTİYOSEÇİCİ MİCHAEL KATILMASI

Kanberoğlu, Esra

Yüksek Lisans, Kimya Bölümü

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Şubat 2015, 88 sayfa

1,3-dinitro bileşikleri, birçok önemli kimyasalın sentezlenmesinde kullanılan anahtar maddelerdir. Ayrıca, bu bileşikler biyolojik olarak aktif maddelerin, tarım kimyasallarının ve farmasötikallerin başlangıç maddesi olarak kullanılan 1,3-diaminlere indirgenebilir. Bu çalışmada, bifonksiyonel kiral 2-aminoDMAP ve kinin temelli organokatalizörler kullanılarak 1-nitropropan ve *trans*-β-nitrositirenin Michael katılma ürünü olan ((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzen sentezlenmiştir. Çalışmanın ilk kısmında, tüm katalizörler test edilerek ve çözücü, sıcaklık, katalizör miktarı aynı zamanda konsantrasyon değiştirilerek tepkime koşulları en uygun hale getirilmiştir. Optimum şartlar altında, çeşitli nitroolefinler kullanılarak türevlendirme çalışmaları yapılmıştır. Amaçlanan 1,3-dinitro maddeleri yüksek enantiyoseçicilik (95%) ve diyastereoseçicilik (96:4) ile elde edilmiştir.

Anahtar Kelimeler: Michael katılması, asimetrik organokataliz, nitroolefinler, bifonksiyonel tiyoüre, kinin

To my dear family…

ACKNOWLEDGEMENTS

I would like to thank and express my sincere appreciation to my supervisor Prof. Dr. Cihangir Tanyeli for his endless support, precious guidance and encouragement throughout this study. It was an honor and good chance for me to work with him.

I wish to express my special thanks to Devrim Özdemirhan and Serdar Sezer for their valuable advices, help and support. Also, I would like to thank Murat Işık for his help and guidance in bifunctional organocatalysis concept.

I would like to express my sincerest thanks to my long-lasting dear friends, my labmate Nurdan Sargın and my roommate Dilşad Susam for their valuable support, understanding, friendship and helping me all the time.

I also would like to express my thanks to all Tanyeli Research Group members especially İrem Bakırcı and Ayşe Ataş for their help and friendship.

I would like to extend my gratitude to TÜBİTAK and ODTÜ-BAP for the financial support for this study. Also, I would like to thank NMR specialist Betül Eymur for the NMR experiments. Besides, I would like to thank Zeynep Erdoğan at Bilkent University for HRMS analysis.

I would like to thank my dear friends Merve Kapucu, Zehra Kabasakal, Başak Öztürk, Ayşegül Hisar, Selin Ceyhan and Yağız Ünver for their well friendship and support. Furthermore, I would like to thank my long-lasting friends Ezgi San, Şefika Baltacı, Günnur Saraç, Büşra Turna Özen and Merve Şimşek for their friendship, support and encouragement.

Finally, I would like to express my deepest gratitude to my family, Meral and İbrahim Kanberoğlu, my sisters Kübra, Büşra and my brother Mahmut Can for their endless love, encouragement, support and believing in me throughout my whole life. I am the luckiest person to have this family and I love them very much.

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LIST OF ABBREVIATIONS

SOMO	Singly occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
HOMO	Highest occupied molecular orbital
***t*-BOC**	*tert*-Butyloxycarbonyl
BINAM	1,1'-Binaphthalene-2,2'-diamine
DMAP	4-Dimethylamino pyridine
DCM	Dichloromethane
THF	Tetrahydrofuran
MTBE	Methyl *tert*-butyl ether
1,2-DCE	1,2-Dichloroethane
TFMB	Trifluoromethyl benzene
GC-MS	Gas chromatography-mass spectrometry
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	InfraRed

CHAPTER 1

INTRODUCTION

1.1 Asymmetric Synthesis

Chirality plays an important role from double helix of DNA to the origins of life. Also, many of the organic compounds, like perfumes, cosmetics, flavors, pharmaceuticals, vitamins, pesticides and nutrients are chiral.[1] Although, enantiomers of these compounds have same physical properties, they have different biological activity. For example, naturally occurring enantiomers of limonene smell differently. While (*R*)-enantiomer smells like orange, (*S*)-enantiomer smells like lemon.[2]

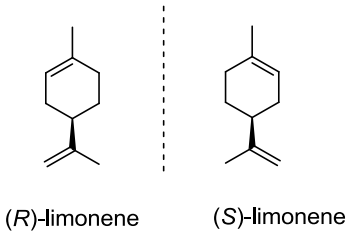


Figure 1. Enantiomers of limonene

In order to get enantiomerically enriched or pure compounds, there are several methods; chemical kinetic resolution, enzymatic resolution, chromatographic separation of enantiomers, classical optical resolution by diastereomers and asymmetric synthesis.[3]

1.1.1 Asymmetric Catalysis

Asymmetric catalysis can be seen as a major component of enantioselective synthesis. In the asymmetric catalysis, enantiomerically enriched compounds are obtained with the usage of chiral catalysts from the prochiral or racemic substances.[4]

Furthermore, asymmetric catalysis is composed of mainly three parts; biocatalysis, transition-metal catalysis and organocatalysis.

In biocatalysis, the natural products, enzymes and proteins are used as catalysts in order to get chiral compounds and to accelerate the reactions. Also, kinetic resolution of racemic mixture and using a chiral molecule for introducing chirality to substrate are two ways to enrich the substances.[5] Moreover, since the enzymes are natural compounds, the biocatalysis process is environmentally friendly and non-toxic.

The second part is transition metal-catalysis in which a transition metal complex is used to perform chemical reactions. Although transition metal catalysts are commonly used and give excellent enantioselectivity, they could have heavy-metal pollution issue.

The last type of asymmetric catalysis is the organocatalysis which is the widely used type of catalysis currently.

1.2 Organocatalysis

It is known that, organocatalysis constitutes a significant part between the enzymatic resolution and organometallic catalysis in the asymmetric synthesis. Also, in order to get chiral molecules, organocatalysis is the most basic equipment which has to be in chiral toolbox. Moreover, there is a great interest towards organocatalysis field, and the graph given in Figure 2 shows the increase in the number of publications over the years since the field emerged.[6]

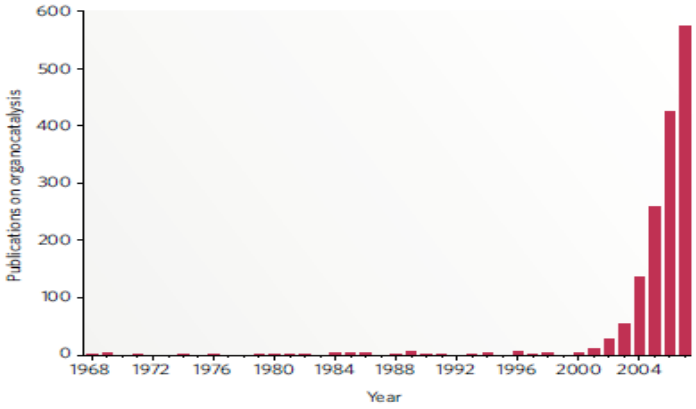


Figure 2. Increment of organocatalysis

In 2000, the organocatalysis concept is defined as the usage of small chiral organic molecules in organic reactions by David MacMillan.[7] Organocatalysis has some benefits which are very little toxicity in reactions, tolerant to water and air as well as easy to carry out.[8] In addition this, organocatalysts are small chiral organic molecules which contain elements such as carbon, hydrogen, oxygen, nitrogen, sulfur and phosphorus. Besides, they do not contain transition metals.[9] Organocatalysts generally have some advantages such as non-toxicity, easy availability, inexpensiveness and resistivity. Since they do not have any transition metal contamination, it becomes very easy to prepare some pharmaceutical compounds which do not tolerate metals. Also, there is no need for some reaction conditions such as inert atmospheres, low temperatures and absolute solvents since organocatalysts have inertness towards to oxygen and moisture.[10] In Figure 3, there are some well-known organocatalysts. The first example is *L*-Proline used to catalyze aldol and related reactions by iminium and enamine pathways. Moreover, the other examples are quinine and quinidine which are cinchona alkaloid derivatives. They are both used as a chiral base or chiral nucleophilic catalysts and also function as the basis for many highly enantioselective phase-transfer catalysts.[9]

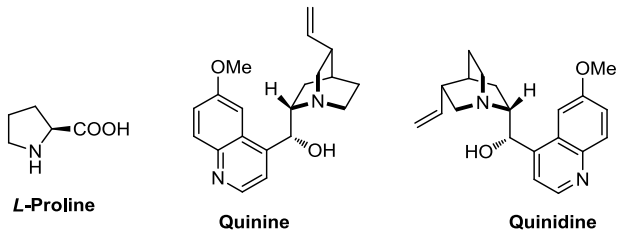
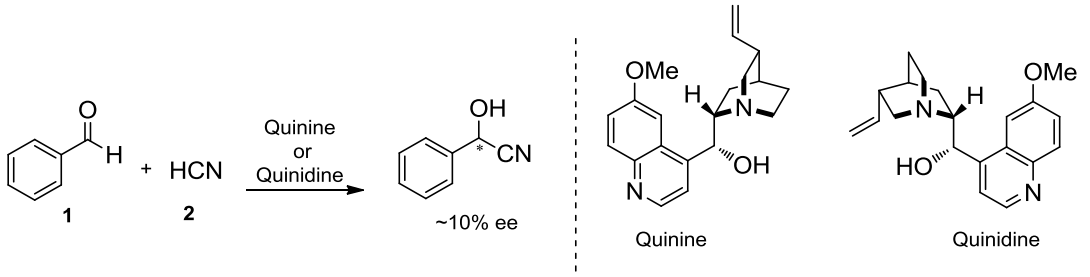


Figure 3. Examples of well-known organocatalysts

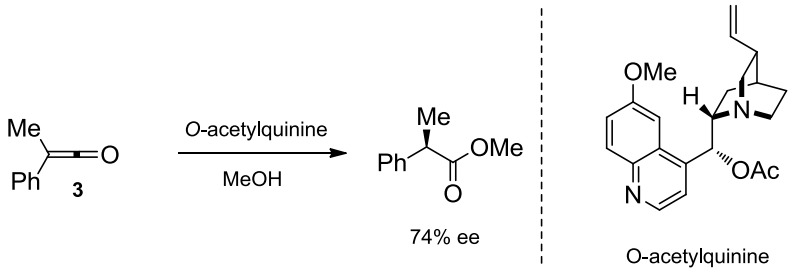
1.2.1 Historical Background

The historical development of asymmetric organocatalysis was started in 1912 with Bredig and Fiske's study which is the addition of hydrogen cyanide **(2)** to benzaldehyde **(1)** in the presence of cinchona alkaloid derivatives, quinine and quinidine in catalytic amounts. The purpose of that study was to examine the biological activity in living systems. Although, the enantiomeric excess was rather low (~10% ee), this study initiated a series of asymmetric organocatalytic reactions (Scheme 1).[11]



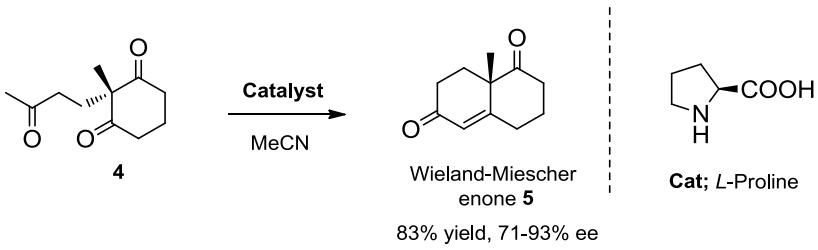
Scheme 1. First organocatalytic reaction

After Bredig and Fiske's study, in 1960, Pracejus used *O*-acetylquinine, which is also a cinchona alkaloid derivative, in the methanolysis of phenylmethylketene **(3)**. This study was significant since it was the first one getting very favorable levels of enantioselectivity (Scheme 2).[12]



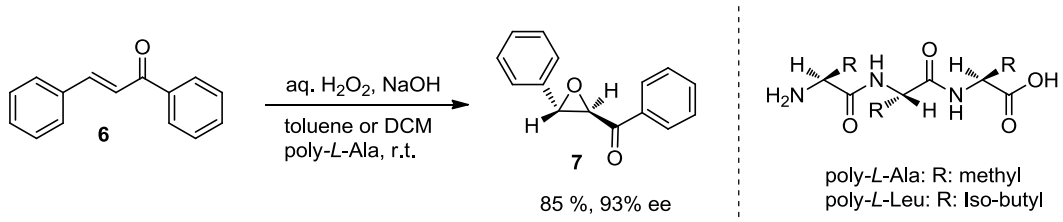
Scheme 2. Methanolysis of phenylmethylketene

In the early 1970s, there was an important study contributing the development of asymmetric organocatalysis conducted by Hajos and Parrish of Hoffman-La Roche and Eder, Sauer and Wiechert of Shering. *L*-Proline was used as an organocatalyst in the intramolecular aldol cyclization of triketone **4**. At the end of the reaction, the Wieland-Miescher enone **5** was produced and after that, this reaction was called as Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 3).[9]



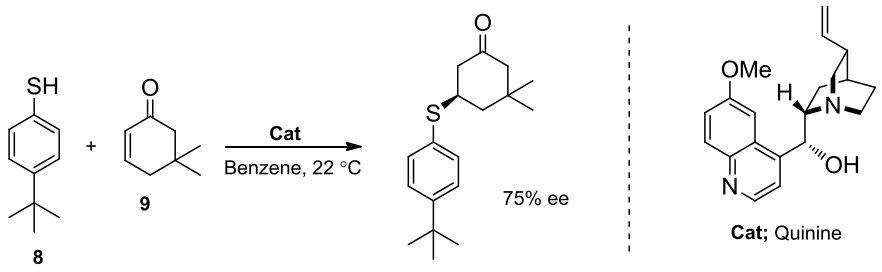
Scheme 3. Hajos-Parrish-Eder-Sauer-Wiechert reaction

After a decade, the concept of using synthetic peptides as asymmetric organocatalysts was developed by Julia and Colonna considering that concept as an alternative way to the use of enzymes. By using chiral polypeptides in the epoxidation of chalcone **(6)** to compound **7** was the first example of this kind of stereoselective reactions (Scheme 4).[13]



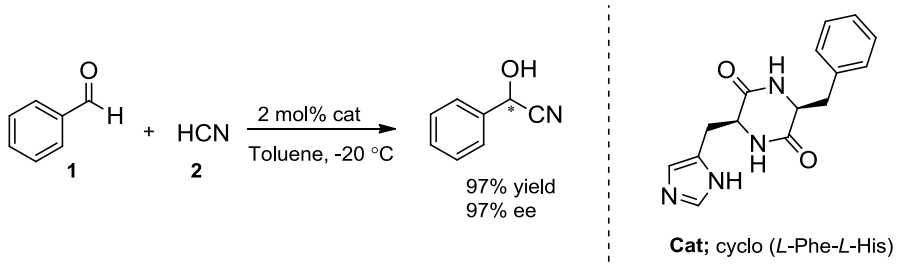
Scheme 4. Julia-Colonna epoxidation of chalcone

In 1981, Wynberg used cinchona alkaloid derivatives as chiral catalysts in the Michael addition reaction between the aromatic thiols **8** and conjugated cycloalkenones **9**. Moreover, the cinchona and ephedra alkaloids containing β-hydroxy amine moiety can be classified as bifunctional catalysts. Therefore, this study contributes not only a detailed information about mechanism of catalytic asymmetric synthesis but also benefits of bifunctional catalysis in order to get enantiomers with chiral synthetic methods (Scheme 5).[14]



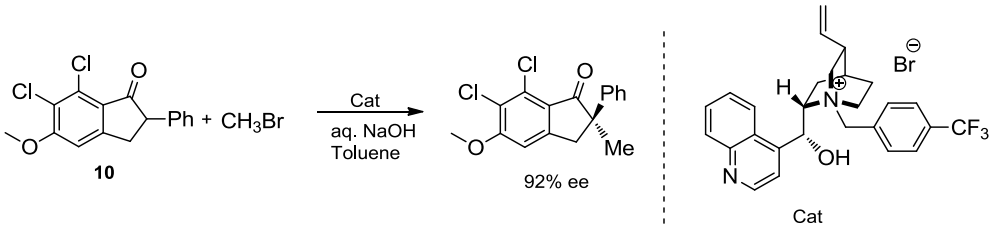
Scheme 5. Wynberg's Michael addition reaction

In the same year, 1981, a real breakthrough was the usage of a cyclic peptide which is readily available from *L*-histidine and *L*-phenylalanine in addition of HCN **(2)** to benzaldehyde **(1)**. This study was conducted by Inoue and at the end of the reaction, the enantioselectivity was up to 97% ee (Scheme 6).[15]



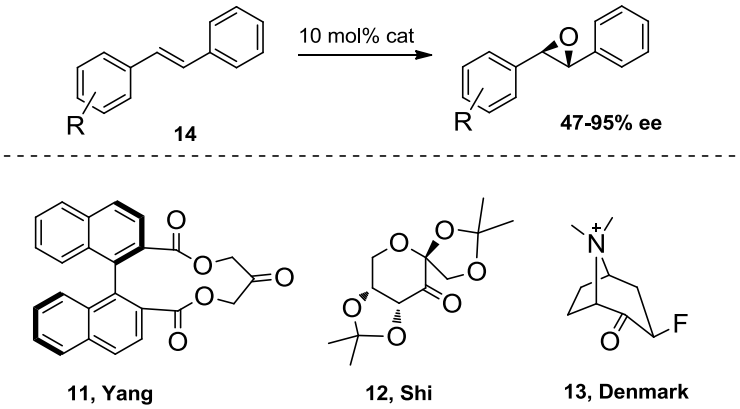
Scheme 6. Hydrocyanation by Inoue

In addition to this developments, in 1984, a group at Merck Research Laboratories conducted a study showing the first highly enantioselective organocatalytic asymmetric reaction by using phase-transfer catalysts. They used cinchona alkaloid-derived quaternary ammonium bromide in the methylation of phenylindanone **10** under biphasic conditions (Scheme 7).[16]



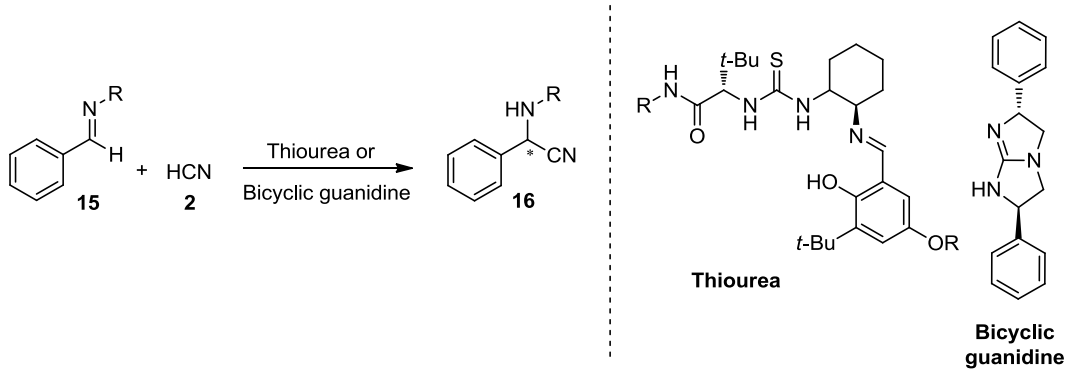
Scheme 7. Asymmetric alkylation of indanone

In 1996 and 1997, the enantioselective epoxidation reactions was the most attractive types in the field of asymmetric organocatalysis especially conducted by seminal studies of Shi, Yang and Denmark.[17] In those studies, chiral ketone catalysts, **11**, **12,** and **13** were used for asymmetric transformations of oxygen from oxone to a range of unfunctionalized olefins **14** with very high enantioselectivities (Scheme 8).[18]



Scheme 8. Epoxidation by chiral ketones

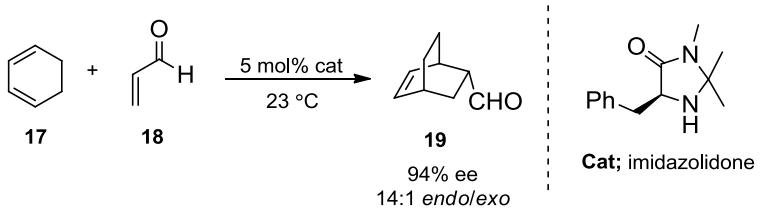
In 1998, chiral Schiff bases were used as effective catalysts for Strecker reaction in a study conducted by Jacobsen. Also, these systems were easily prepared from inexpensive materials and at the end of the reactions, enantioselectivities are very favorable both in solid state and solution.[19] After that study, Corey used bicyclic guanidine as catalyst in the same reaction. The addition of hydrogen cyanide **(2)** to imine **15** was achieved with these organocatalysts and cyanation product **16** was obtained selectively (Scheme 9).[20]



Scheme 9. Jacobsen's and Corey's organocatalysts for Strecker reaction

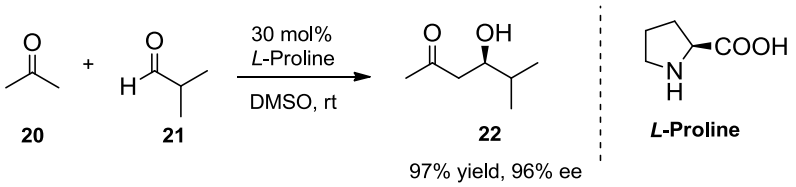
Although many studies were carried out in the field of asymmetric organocatalysis, any of them could not get much more attention as MacMillan's, List and Barbas' studies in 2000. After their works, there was a growing interest and increasing in the number of publications in this field.[21] In MacMillan's study, he defined the

organocatalyst and organocatalysis concept. Also, by using imidazolidone as organocatalyst, he succeeded the first highly enantioselective Diels-Alder reaction starting from cyclohexa-1,3-diene **(17)** and acrolein **(18)** affording bicyclic product **19** with 94% ee and 14 to 1 *endo*/*exo* isomeric ratio (Scheme 10).[7]



Scheme 10. Diels-Alder reaction by MacMillan

Moreover, in List and Barbas' study, they succeeded the direct aldol reaction between the acetone **(20)** and *iso*-butyraldehyde **(21)** catalyzed by *L*-Proline. The aldol product **22** was obtained with excellent chemical yield and enantioselectivities (Scheme 11).[22]



Scheme 11. *L*-Proline catalyzed aldol reaction

1.2.2 Classification of Organocatalysis

An effort to develop and grow field of asymmetric organocatalysis, the scientists classify organocatalysis concept in order to understand the mechanistic pathway of reactions. There are mainly three types of classifications done by Berkessel, List and MacMillan.

Firstly, Berkessel and Gröger classified the organocatalysis based on interaction between catalyst and substrate. Therefore, if there is a formation of covalent products in the catalytic cycle, this process is defined as covalent catalysis. In covalent catalysis, enamine and iminium formation are observed as multistep reactions. Moreover, the processes which are based on hydrogen bonding interactions or formation of ion pairs are named non-covalent catalysis. In addition to this, the phase transfer catalysis also falls into the non-covalent catalysis category.[9]

Secondly, the next classification was done by List and Seayad with respect to acidity or basicity of the catalytic cycle. Accordingly, organocatalysis can be divided into four major areas: Lewis base/acid, and Brønsted base/acid catalysis.[23]

Finally, in 2008, MacMillan classified the organocatalysis based on the generic activation modes of organocatalysts; enamine catalysis, hydrogen-bonding catalysis, iminium catalysis, SOMO catalysis and counter-ion catalysis.[6]

1.2.3 Bifunctional Organocatalysis

In recent years, in a diversity of asymmetric organocatalysis, acid/base catalysis has been used cooperatively in order to activate both electrophiles and nucleophiles at the same time. These kind of catalytic processes are defined as bifunctional organocatalysis including a basic part for raising the highest occupied molecular orbital of nucleophiles and acidic part for decreasing the lowest unoccupied molecular orbital of electrophiles. As a result of this, the activation energy decreases making the reaction possible.[3]

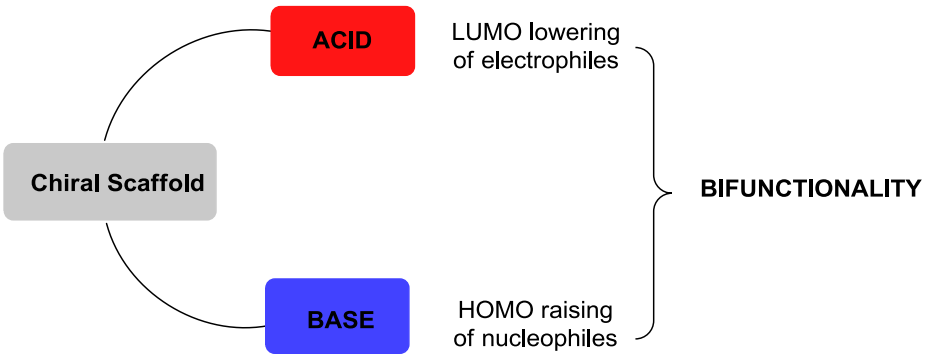
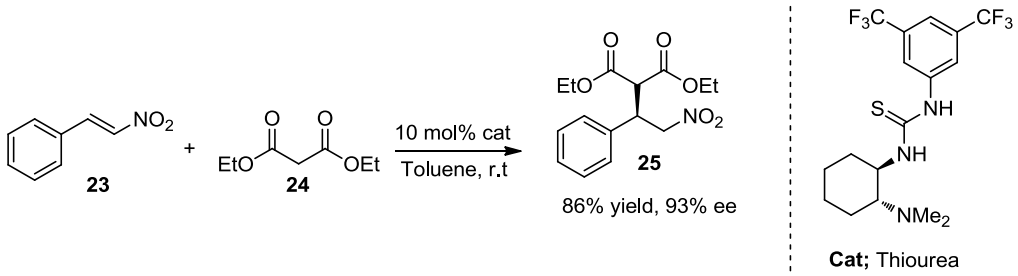


Figure 4. Bifunctionality of an organocatalyst

1.2.3.1 Thiourea as Bifunctional Organocatalysts

In bifunctional organocatalysts field, the breakthrough came with the Takemoto's bifunctional thiourea in 2003. Takemoto and his co-workers succeeded the Michael addition of diethyl malonate **(24)** to nitrostyrene **(23)** by using (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine based bifunctional organocatalyst, involving thiourea moiety as Brønsted acid and tertiary amine motif as Lewis base and the product **25** was obtained with high chemical yield and enantioselectivity. Also, this Michael addition reaction was accepted as the first truly enantioselective acid/base bifunctional organocatalysis reaction (Scheme 12).[24]



Scheme 12. First truly enantioselective bifunctional organocatalysis reaction

In Takemoto's bifunctional thiourea catalyst, (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine, was used as chiral scaffold with acidic moiety and basic site. These two different unit

functions at the same time. As a mechanistic pathway, Takemoto and co-workers proposed that the acidic thiourea unit coordinates to nitro group of the electrophile by lowering the LUMO. Besides, the basic amino part abstracts the acidic proton of the malonate by raising HOMO. The proposed transition state model was shown in Figure 5.[25]

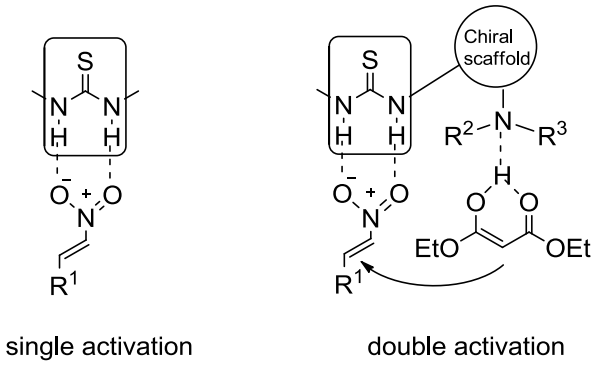
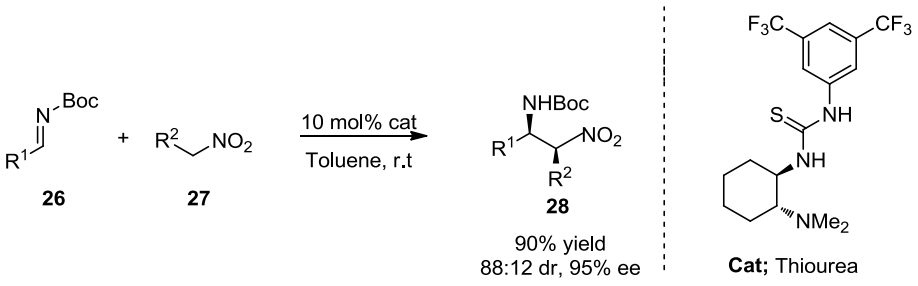


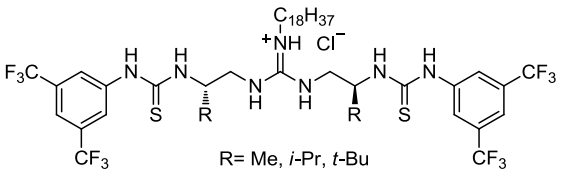
Figure 5. Multifunctional organocatalysts

In addition to this Michael addition reaction, in 2006, Takemoto used the same bifunctional thiourea organocatalyst in aza-Henry reaction using *N*-Boc imines **26** with several nucleophiles such as nitroalkanes **27**. The biologically active chiral vicinal diamine precursors **28** were showed high enantio- and diastereoselectivity (Scheme 13).[26]

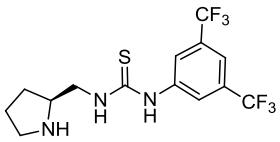


Scheme 13. Thiourea catalyzed aza-Henry reaction

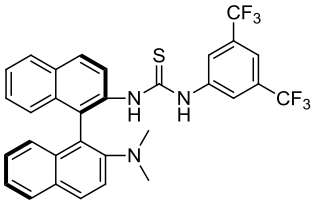
In Figure 6, examples of some bifunctional thiourea organocatalysts and their reactions are given.[27,28,29,30]



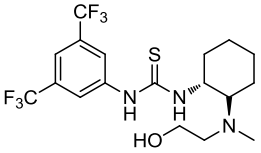
Nagasawa, 2005[27]
Guanidine functionalized bifunctional thiourea
Asymmetric catalysis of Henry reaction



Yang Tang, 2006[29]
Bifunctional pyrrolidine thiourea
Asymmetric catalysis of Michael reaction



Wei Wang, 2005[28]
Bifunctional binaphthyl-thiourea
Asymmetric catalysis of Morita-Baylis-Hillman reaction

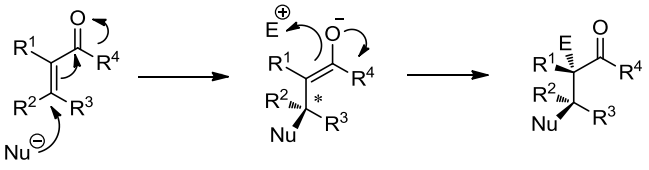


Takemoto, 2007[30]
Chelating bifunctional hydroxy-thiourea
Asymmetric catalysis of Petasis reaction

Figure 6. Bifunctional thioureas

1.3 Michael Addition Reactions

In Michael or 1,4-addition reactions, there are a nucleophile named as Michael donor and an electrophile as Michael acceptor which are generally α,β-unsaturated compounds. In the reaction mechanism, the active nucleophile is formed by deprotonation of the donor and subsequent addition to the β-carbon atom of the acceptor results in a chiral center (Scheme 14).[9]



Scheme 14. Mechanism of Michael addition reaction

That mechanism can be considered as the simplest way of asymmetric organocatalysis of Michael additions to create chiral compounds. In addition to this classical method, nowadays, two highly capable and very functional approaches have come up. One of them is the iminium ion formation by activating the Michael acceptor and the other one is the enamine pathway in which a carbonyl donor is activated by enamine formation.[9]

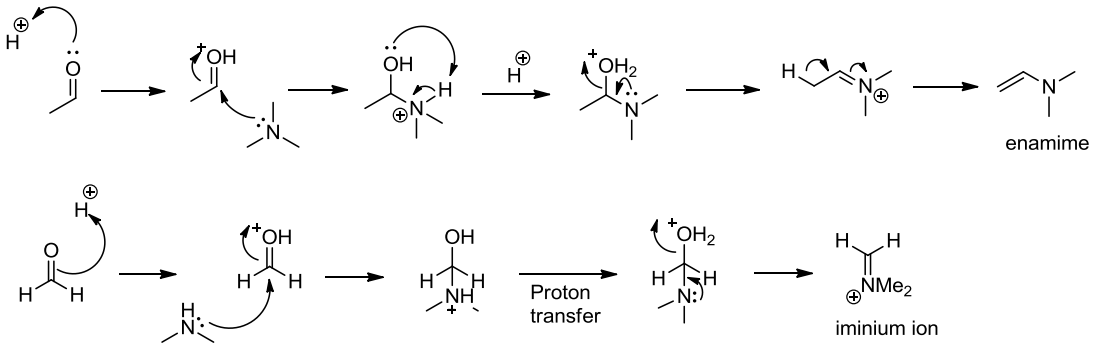
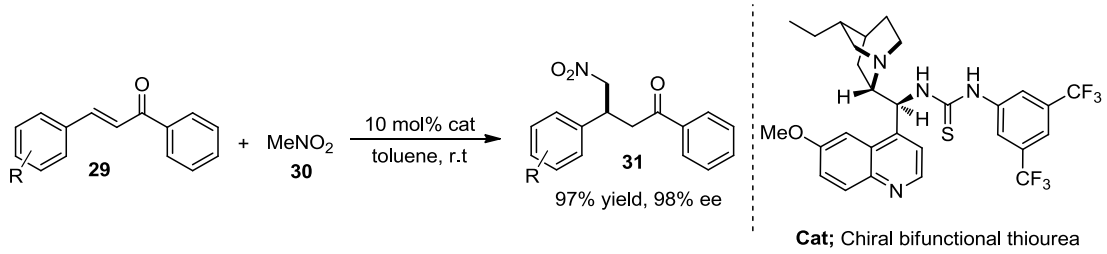


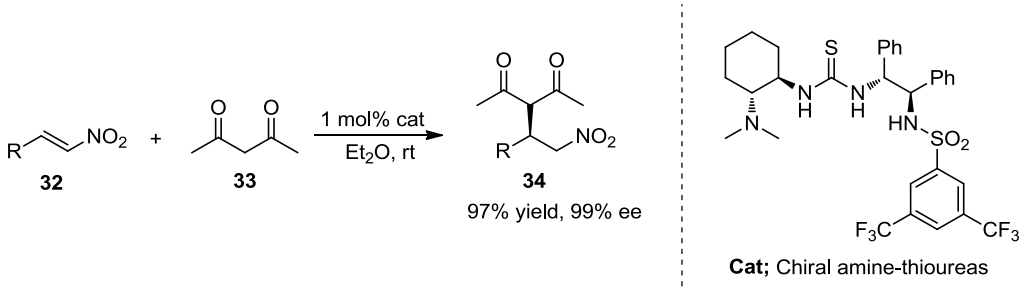
Figure 7. Enamine and iminium ion formation

Moreover, Michael addition or conjugate addition reactions are very important in carbon-carbon bond forming process. Also, these kind of reactions are one of the oldest and useful method by providing chiral compounds for asymmetric synthesis.[31] For example, in 2005, Soos and his co-workers succeeded the highly enantioselective Michael addition of nitromethane **(30)** to chalcones **29** in the presence of cinchona alkaloid derived chiral bifunctional thiourea organocatalysts.[32] The products **31** of that conjugate addition are very useful precursors of various kinds of compounds such as aminoalkanes, aminocarbonyls and pyrrolidines which were obtained with high yield (up to 97%) and high enantioselectivity (98%) in a metal-free and simple environment (Scheme 15).



Scheme 15. Michael addition of nitromethane to chalcones

In 2008, chiral amine-thioureas bearing multiple H-bonding donors were used as organocatalysts in the conjugate addition of acetylacetone **(33)** to wide range of nitroolefins **32** by Wang and his co-workers. Organocatalyst activates the nitro and carbonyl groups strongly through double hydrogen bonding interactions. In that study, the products **34** were synthesized in up to 97% chemical yield and 99% ee only using 1 mol% catalysts loading (Scheme 16).[33]

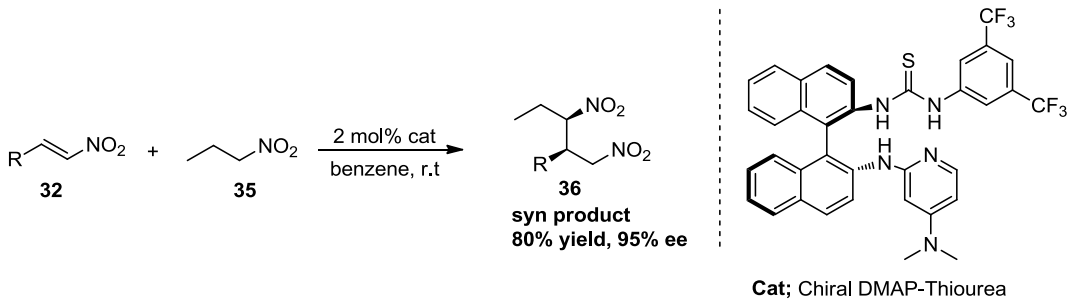


Scheme 16. Conjugate addition of acetylacetone to nitroolefins

1.3.1 Michael Additions of Nitroalkanes to Nitroolefins

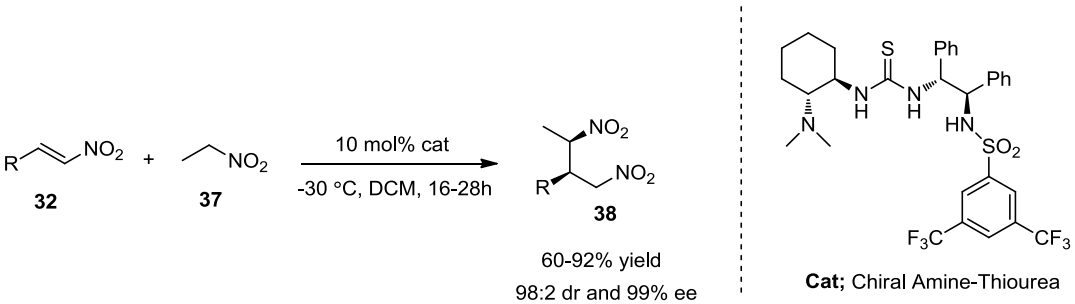
A very interesting Michael addition reaction was came up with William D. Wulff and Constantinos Rabalakos in 2008.[34] In their study, 1-nitropropane **(35)** was added to different nitroolefin derivatives **32** by using chiral BINAM based bifunctional DMAP-

thiourea organocatalysts to afford 1,3-dinitro compounds **36** (Scheme 17). Subsequent reduction yielded corresponding 1,3-diamine compounds.



Scheme 17. 1,4-addition of 1-nitropropane to nitrostyrene

The same type of Michael addition of nitroalkanes to nitroolefins was conducted by Wang and his co-workers in 2009. In that study, nitroethane **(37)** was used as a Michael donor and catalyzed by bifunctional amine-thiourea catalyst bearing multiple hydrogen-bonding donors. At the end of the reaction, 1,3-dinitro compounds **38** were obtained with excellent diastereoselectivity up to 98:2 and enantioselectivity up to 99% ee (Scheme 18).[35]



Scheme 18. Michael addition of nitroethane to nitroolefins

Additionally, in 2011, same organocatalytic Michael Addition of nitroethane to nitroolefins reaction was conducted by Du and Wang.[36] In that study, the reaction was catalyzed by low amount of chiral bifunctional squaramide organocatalyst (2 mol%)

affording 95:5 dr and up to 97% ee. The structure of that organocatalyst is depicted in Figure 8.

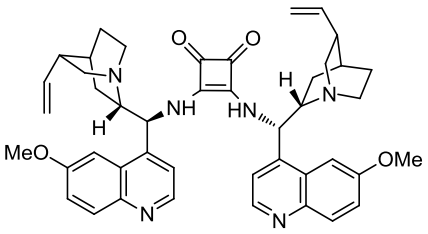
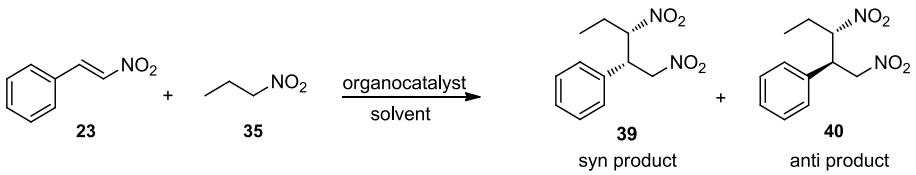


Figure 8. *C*$_2$-Symmetric quinine derived squaramide organocatalyst

1.4 The Aim of the Study

Nowadays, the concept of organocatalysis has become a very important issue in asymmetric synthesis. In Tanyeli's research group, a wide range of chiral bifunctional organocatalysts have been developed and evaluated in different type of reactions such as Michael addition, Henry or aza-Henry and aldol reactions, etc.

In this study, the main objective is to synthesize 1,3-dinitro compounds by Michael addition of 1-nitropropane to *trans*-*β*-nitroolefins in the presence of bifunctional 2-aminoDMAP and quinine based organocatalysts.



Scheme 19. Representative aim of the study

The chiral organocatalysts developed in our research group as depicted in Figure 9, will be tested to find out the proper catalyst satisfying the ideal criteria such as low

catalyst loading, short reaction duration, high chemical yield, high enantio and diastereoselectivity.

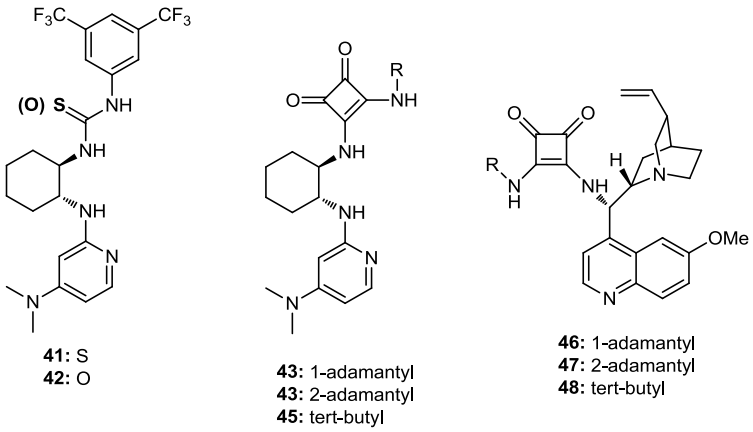
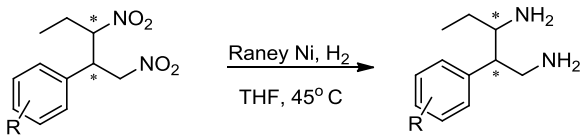


Figure 9. 2-AminoDMAP and quinine based chiral bifunctional organocatalysts

After optimization studies with the model systems shown in Scheme 19, 14 Michael acceptor nitroolefins will be tested to prove the efficacy of the organocatalyst used. Consequently, one of the synthesized 1,3-dinitro compounds will be reduced to 1,3-diamines since they are very important biologically active compounds and they are starting materials for the agrochemicals and pharmaceuticals.



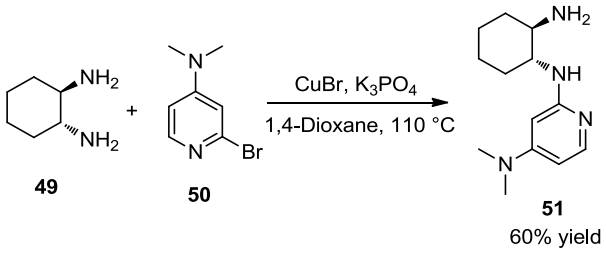
Scheme 20. Reduction of nitro groups to amines

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of 2-AminoDMAP

In Tanyeli's Research group, 2-aminoDMAP and quinine based bifunctional organocatalysts have been developed and synthesized as well as evaluated in different type of reactions. The construction of 2-aminoDMAP chiral skeleton started with anchoring Lewis basic bromo-DMAP **(50)** motif on to C_2-symmetrical (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine **(49)** *via* direct selective mono-*N*-pyrilidization in the presence of CuBr and K_3PO_4.[21]

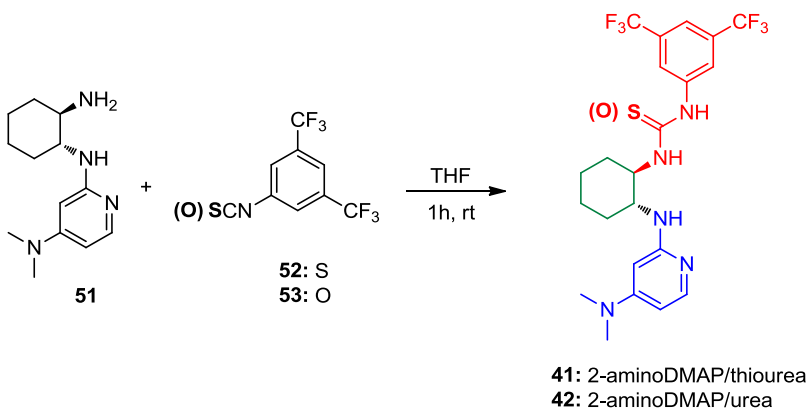


Scheme 21. Synthesis of 2-aminoDMAP

2.2 Synthesis of 2-AminoDMAP Based Bifunctional Organocatalysts

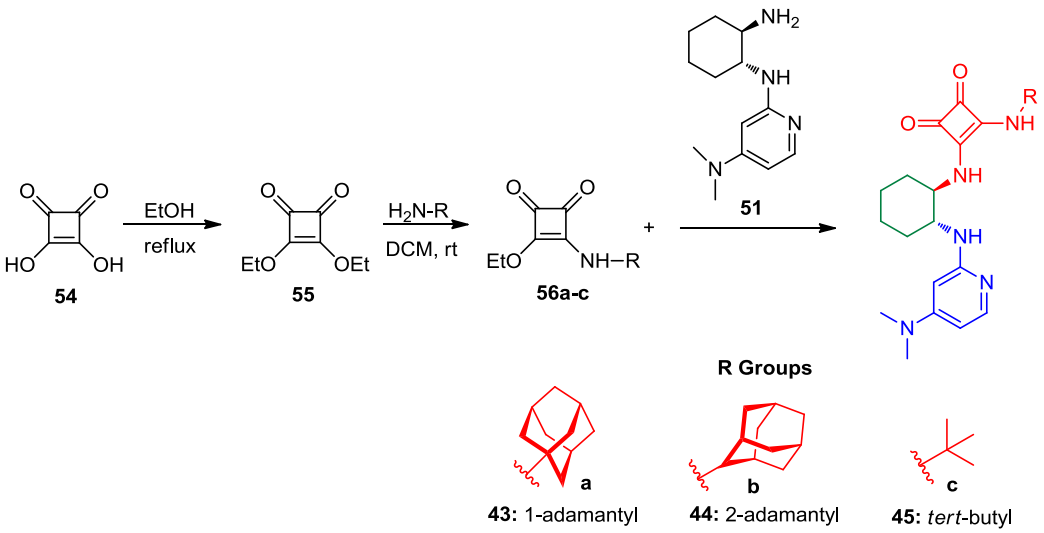
After synthesizing C_1-symmetric chiral 2-aminoDMAP **(51)**, the Brønsted acidic parts, thiourea or urea moieties were attached to free amine chiral scaffold. By using commercially available 3,5-bis(trifluoromethyl)benzene isothiocyanate **(52)** and

isocyanate **(53)**, chiral bifunctional 2-aminoDMAP/thiourea **41** and 2-aminoDMAP/urea **42** organocatalysts were synthesized in 1 hour at room temperature.



Scheme 22. Synthesis of 2-aminoDMAP/thiourea and urea organocatalysts

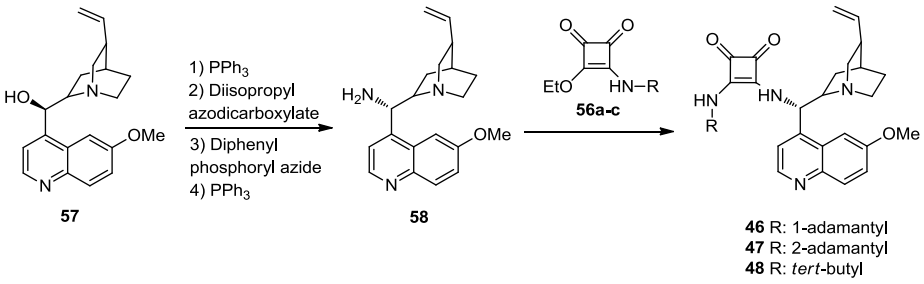
The second organocatalyst class involves various squaramides as Brønsted acidic moieties. These squaramide moieties possessing bulky adamantyl and *tert*-butyl units have two acidic hydrogens as an acidic counterpart for the target bifunctional organocatalysts. The synthetic pathway is shown in Scheme 23. By refluxing squaric acid **(54)** in absolute ethanol, diethyl squarate **(55)** was easily prepared. Subsequent addition of commercially available adamantyl and *tert*-butyl amines to diethyl squarate **(55)** in one to one ratio in DCM at room temperature afforded the corresponding mono-squaramides **56a-c**. In the last step, by the addition of chiral basic core **(51)**, organocatalysts **43**, **44** and **45** were synthesized in good yields.[21]



Scheme 23. Synthesis of 2-aminoDMAP/squaramides

2.3 Synthesis of Quinine Based Bifunctional Organocatalysts

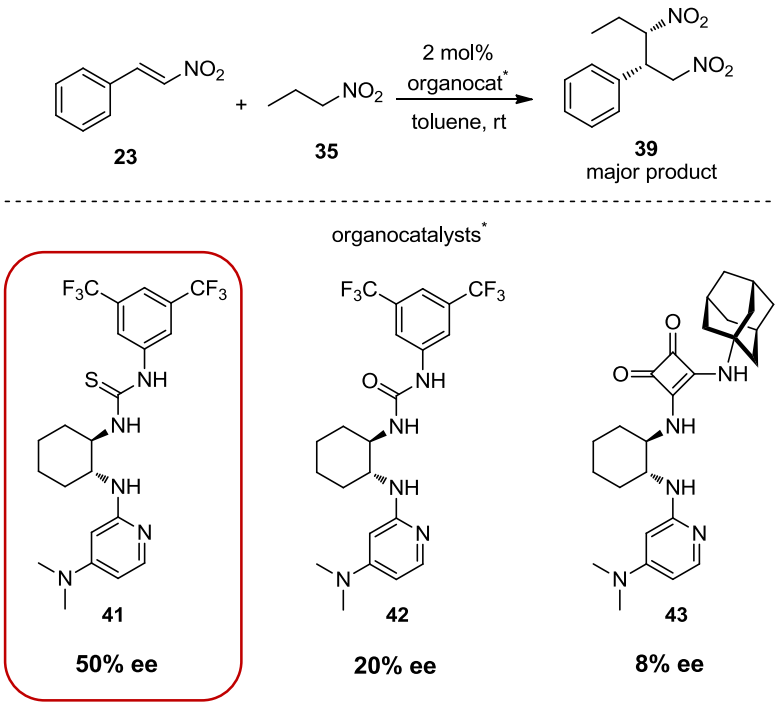
The third type of bifunctional organocatalysts in our group consists of quinine based squaramides. In the first part of the synthetic pathway, quinine was turned into quinine amine **58** with the Mitsunobu and Staudinger reactions by applying the literature procedure.[32] Similarly, as in case of 2-aminoDMAP class by the addition of monosquaramides, organocatalysts **46-48** were synthesized in high yield varied between 75 to 90%.



Scheme 24. Synthetic pathway of quinine based squaramides

2.4 Evaluation of Bifunctional Organocatalysts in the Michael Addition of 1-Nitropropane to Nitroolefins

By inspiring Wulff's study,[34] we decided to evaluate the efficiency of bifunctional organocatalysts in the Michael addition of 1-nitropropane **(35)** to *trans*-*β*-nitrostyrene **(23)**. We started with the condition given in Wulff's study just by changing the solvent as toluene. In the first part, three 2-aminoDMAP based organocatalysts **41**, **42** and **43** were tested as depicted in Scheme 25.

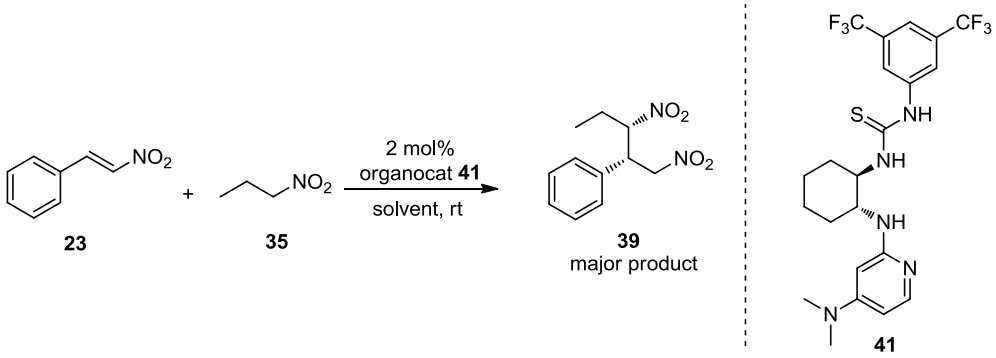


Scheme 25. Michael addition of 1-nitropropane to *trans*-*β*-nitrostyrene

As a result of preliminary tests, organocatalyst **41** was chosen as the best for further optimization studies. The solvent screening study was conducted with 15 different solvents as well as neat condition. Among the solvents, toluene, THF, xylene, benzene, dioxane, and MTBE gave acceptable results as compared to others in terms of enantioselectivity and diastereoselectivity. Methanol (Table 1, entry 15) afforded almost racemic product **39** although it yielded the highest diastereoselectivity. Because

it can make H-bonding with the catalyst and can affect the addition of 1-nitropropane **(35)** to *trans*-*β*-nitrostyrene **(23)**. Of the screened solvents, toluene proved to be the best one (Table 1, entry 1).

Table 1. Solvent screening

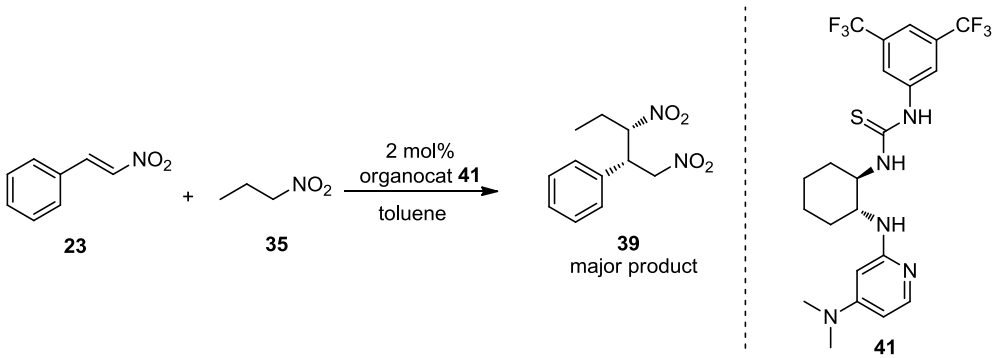


Entry	Solvent	Time (h)	Yield[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn*/*anti*)
1	Toluene	48	85	**50**	60	77:23
2	DCM	48	67	**36**	50	82:18
3	Chloroform	48	89	**34**	50	80:20
4	Cyclohexane	48	82	**44**	58	80:20
5	Hexane	48	72	**38**	58	77:23
6	THF	48	40	**56**	56	82:18
7	Xylene	48	88	**50**	62	82:18
8	Heptane	48	70	**46**	58	75:25
9	Ether	48	32	**20**	46	81:19
10	Benzene	48	85	**50**	50	77:23
11	Dioxane	48	87	**54**	60	78:22
12	1,2-DCE	48	80	**36**	54	73:27
13	MTBE	48	76	**50**	60	69:31
14	TFMB	48	80	**46**	58	72:28
15	Methanol	48	85	**8**	8	86:14
16	Neat	48	80	**38**	50	81:19

a: isolated yield *b*: Determined by HPLC

As the next optimization parameter, temperature screening was done. In general, when the temperature dropped down to room temperature, drastic decrease was observed in chemical yields (Table 2, entries 2-5). Although, at 15 ˚C and -15 ˚C, (Table 2, entries 2 and 4, respectively) both ee values of *syn* product and diastereomeric ratios were very close to each other. Surprisingly, at 0 ˚C and at -40 ˚C, (Table 2, entries 3 and 5, respectively) dr values were higher than the other conditions. Since, the best ee value (56% ee) was obtained at -15 ˚C, the reaction temperature was kept at that temperature (Table 2, entry 4).

Table 2. Temperature screening



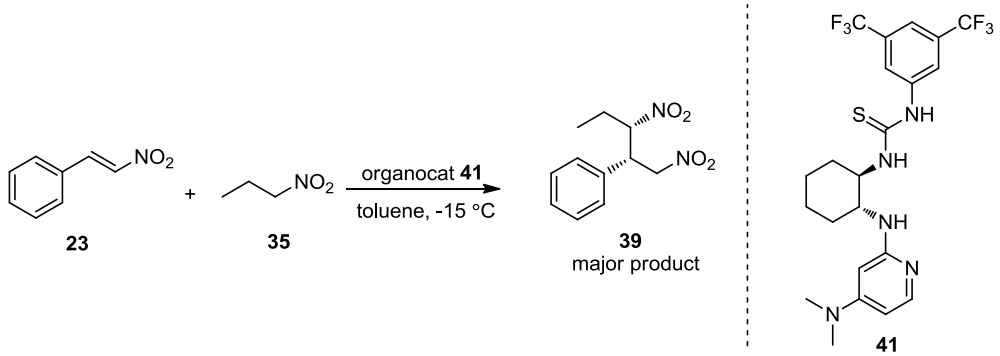
Entry	Temperature	Time (h)	Yield[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn/anti*)
1	25 ˚C	48	85	**50**	60	77:23
2	15 ˚C	48	77	**54**	64	81:19
3	0 ˚C	48	70	**50**	62	90:10
4[c]	-15 ˚C	48	65	**56**	64	85:15
5	-40 ˚C	96	25	**44**	44	92:8

a: isolated yield *b*: Determined by HPLC *c:* When the reaction is carried out for 20h, the results are in table 3, entry 2.

After determining the solvent and the temperature, as the last parameter, the catalyst loading was tested. Different catalyst loadings as 1, 2, 5, and 10 mol% were applied and all experiments were carried out for 20 h. No difference was observed with 2 and 5 mol% catalyst loading in terms of enantioselectivity and diastereoselectivity (Table 3, entries 2 and 3, respectively). Since the low catalyst loading is one of the most

important parameters, 2 mol% organocatalyst was chosen as suitable condition for further trials (Table 3, entry 2).

Table 3. Catalyst loading



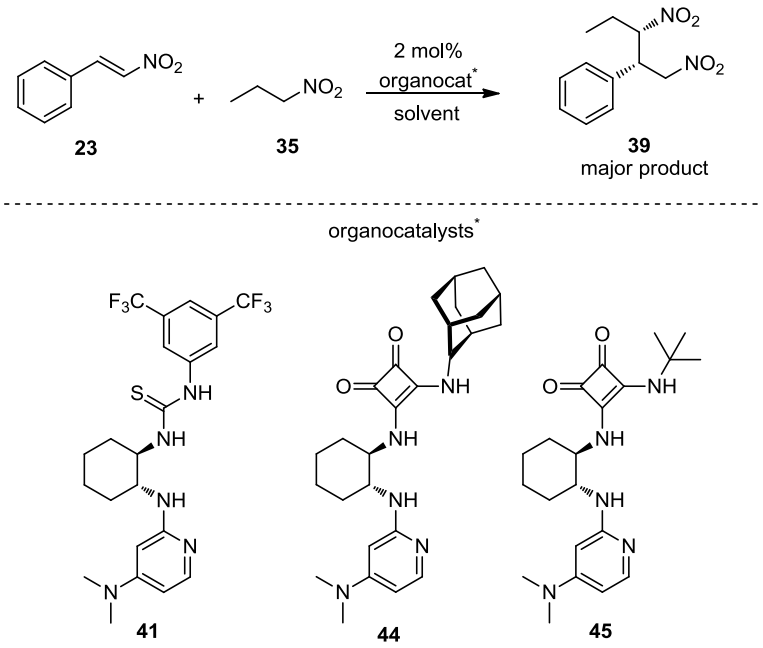
23 35 39 major product 41

Entry	Cat. Loading	Time (h)	Yield[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn/anti*)
1	1%	20	22	**46**	58	91:9
2	2%	20	50	**54**	66	88:12
3	5%	20	76	**54**	60	88:12
4	10%	20	92	**52**	54	85:15

a: isolated yield *b*: Determined by HPLC

In order to improve enantioselectivity and diastereoselectivity, we figured out that it had to be made some miscellaneous screenings. So, other organocatalysts such as 2-aminoDMAP/ 2-adamantyl squaramide **44** and 2-aminoDMAP/*tert*-butyl squaramide **45** were tested in both toluene and xylene. Though, the dr values were very high, ee values of both *syn* and *anti*-products were low (Table 4, entries 4, 5, 6, 7, respectively). As a result, it can be concluded that 2-aminoDMAP/ squaramide organocatalysts were not suitable for this Michael addition reaction. Besides, organocatalyst **41** was also tested in xylene and MTBE. Surprisingly, in xylene, the best ee value was obtained at -15 ˚C up to now in this study (Table 4, entry 2). Further lowering the temperature up to -30 ˚C caused a sharp decrease in ee and an increase in reaction duration (Table 4, entry 3).

Table 4. Additional screenings

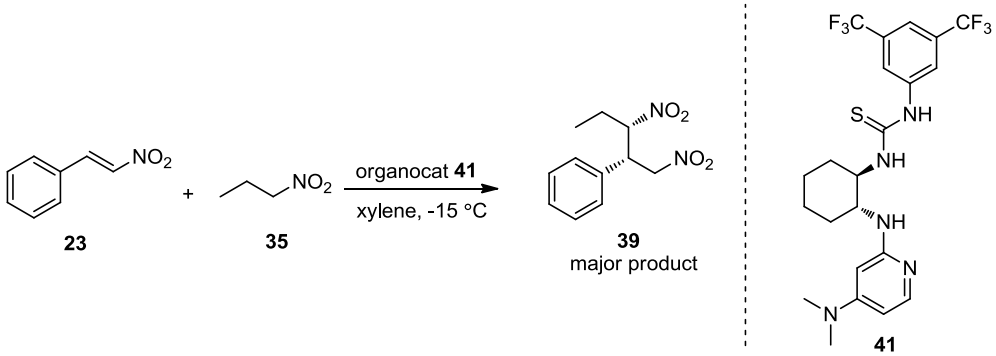


Entry	Cat.	Solvent	Temp	Time (h)	Yield[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn/anti*)
1	**41**	MTBE	-15 ˚C	48	63	**52**	64	83:17
2	**41**	Xylene	-15 ˚C	24	52	**60**	66	82:18
3	**41**	Xylene	-30 ˚C	70	35	**40**	52	92:8
4	**45**	Xylene	-15 ˚C	24	47	**8**	4	83:17
5	**45**	Toluene	-15 ˚C	24	44	**12**	Rac	83:17
6	**44**	Xylene	-15 ˚C	24	41	**8**	4	87:13
7	**44**	Toluene	-15 ˚C	24	40	**8**	10	87:13

a: isolated yield *b*: Determined by HPLC

Finally, by changing solvent to xylene at -15 ˚C, catalyst loading was repeated with organocatalyst **41**. However, there was not any increment in enantioselectivity of *syn* product and also dr values, with lower or higher than 2 mol% catalyst loading. At the end of the optimization, the best condition was set to 2 mol% organocatalyst **41** in xylene at -15 ˚C (Table 5, entry 2).

Table 5. Catalyst loading with organocatalyst **41** in xylene

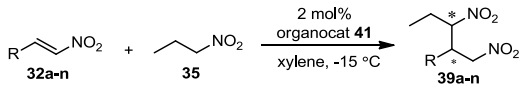


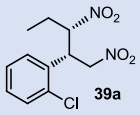
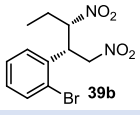
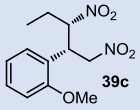
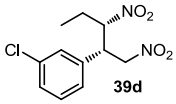
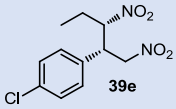
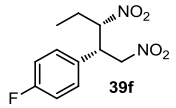
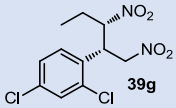
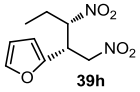
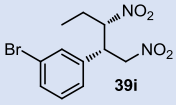
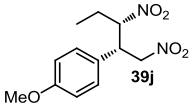
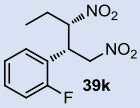
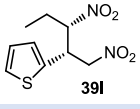
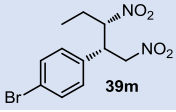
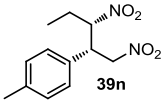
Entry	Cat. Loading	Time (h)	Yield[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn/anti*)
1	1%	46	25	**40**	56	83:17
2	2%	24	52	**60**	66	82:18
3	5%	46	71	**56**	58	84:16
4	10%	30	80	**54**	62	83:17

a: isolated yield *b*: Determined by HPLC

Having decided the best optimization condition (Table 5, entry 2), various 1,3-dinitro compounds were synthesized by using different nitroolefin derivatives possessing electron-donating and electron-withdrawing groups on *ortho*-, *meta*- and *para*-positions (Table 6). During the reactions, while chemical yield was monitored with GC-MS, diastereomeric ratios were measured by crude ^{1}H NMR and HPLC. Enantiomeric ratios of *syn* products **39a-n** varied between 52%-62% and diastereomeric ratios were around 4:1 (*syn:anti*). Moreover, when *ortho*-methoxy substituted substrate **32b** gave 9:1 dr, *para*-chloro substituted nitroolefin **32f** gave 1:1 dr. Although, the effect of electron-donating and electron-withdrawing groups was not observed clearly in both reaction time and in chemical yield, it can be concluded that electron-withdrawing substituted nitroolefins yielded higher chemical yield than electron-donating ones. Interestingly, *meta*-chloro substituted and *meta*-bromo derivatives afforded the lowest chemical yields (Table 6, entries 5 and 8).

Table 6. Derivatization with 2-aminoDMAP/thiourea

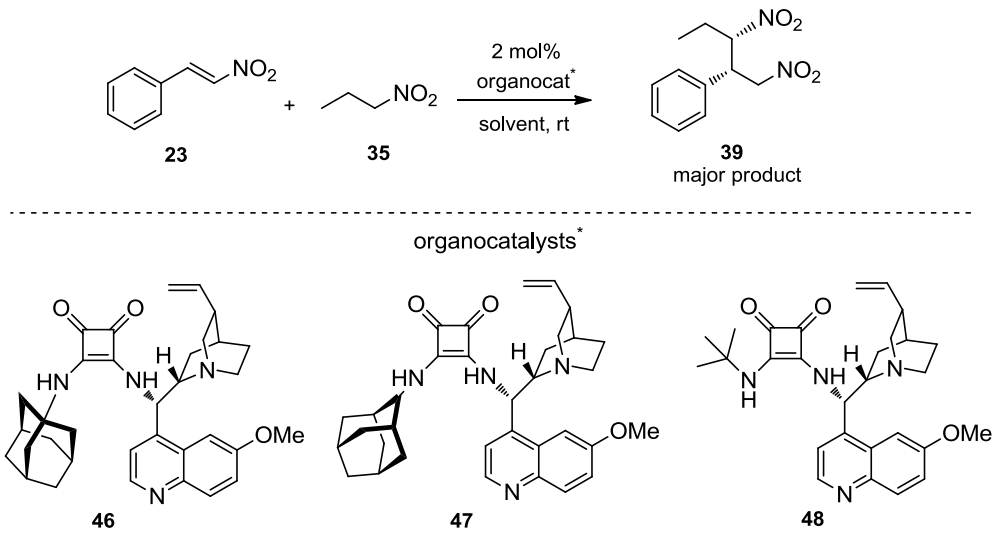


Entry	Products	Time (d)	Conversion[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn*/*anti*)
1	 **39a**	11	73	**64**	54	75:25
2	 **39b**	7	94	**62**	60	81:19
3	 **39c**	10	43	**62**	44	90:10
4	 **39d**	11	33	**60**	68	78:22
5	 **39e**	11	74	**60**	57	47:53
6	 **39f**	11	78	**58**	44	79:21
7	 **39g**	13	33	**58**	60	84:16
8	 **39h**	11	72	**58**	72	74:26
9	 **39i**	13	30	**57**	68	78:22
10	 **39j**	6	44	**56**	58	82:18
11	 **39k**	11	88	**56**	30	76:24
12	 **39l**	11	70	**56**	62	85:15
13	 **39m**	13	75	**54**	66	83:17
14	 **39n**	10	73	**52**	56	80:20

a: Determined by GC-MS *b*: Determined by crude ^{1}H NMR and HPLC

In the second part of this study, the same Michael addition reaction was tested with 2 mol% quinine based squaramide organocatalysts **46**, **47** and **48** in toluene. All three showed quite similar enantioselectivities of *syn*-product **39** and also diastereoselectivities. However, in the case of 2 mol% organocatalyst **48**, the reaction duration was shorter than adamantyl substituted organocatalysts **46** and **47** at room temperature (Table 7, entry 1). This can be attributed to steric effect of bulky adamantyl units. In the further screening with 2 mol% organocatalyst **48**, five different solvents were tested at room temperature. In all solvents, ee values were high but in dioxane and MTBE, the reaction duration was longer and also chemical yields were low (Table 7, entries 5 and 7, respectively). With the solvents xylene, DCM and hexane *trans-β*-nitrostyrene **(23)** resulted in similar enantioselectivities. In the case of hexane, we encountered some solvation problems of substrate **23** and organocatalyst **48**. Consequently, of the screened solvents, DCM proved to be the best one (Table 7, entry 6). In addition, the catalyst loading parameter was checked with 5 mol% in DCM at room temperature. We could not observe any difference in terms of enantioselectivity and diastereoselectivity (Table 7, entry 10). Finally, the effect of temperature on enantioselectivity was checked by lowering the temperature 0 ˚C. At 0 ˚C, with 2 mol% catalyst loading, substrate gave the best ee (90%) and dr (91:9) values up to now (Table 7, entry 11). Additionally, 5 mol% catalyst loading at 0 ˚C condition was tested whether there was any increase in ee and dr values, but it did not alter anything only it changed the reaction time.

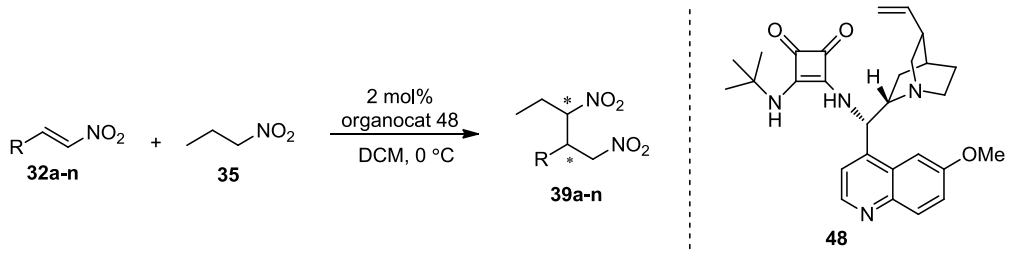
Table 7. Optimization Studies with quinine squaramides

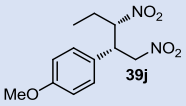
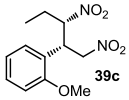
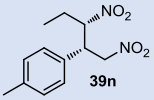
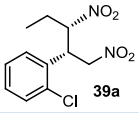
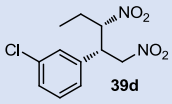
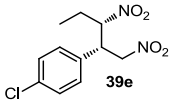
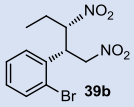
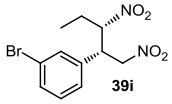
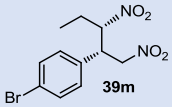
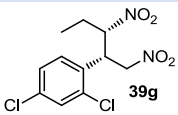
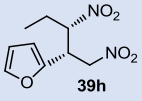
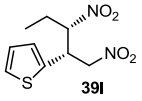


Entry	Cat.	Solvent	Time (h/d)	Yield[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn/anti*)
1	**48**	Toluene	43 h	80	**83**	55	77:23
2	**47**	Toluene	67 h	79	**80**	56	72:28
3	**46**	Toluene	70 h	84	**83**	60	75:25
4	**48**	Xylene	40 h	84	**84**	52	80:20
5	**48**	Dioxane	136 h	79	**79**	54	79:21
6	**48**	DCM	43 h	86	**86**	50	80:20
7	**48**	MTBE	7 d	65	**84**	57	81:19
8	**48**	Hexane	67 h	90	**86**	55	78:22
9[c]	**48**	DCM	44 h	76	**85**	53	81:19
10[d]	**48**	DCM	91 h	87	**90**	47	91:9
11[c,d]	**48**	DCM	67 h	78	**88**	56	87:13

a: isolated yield *b*: Determined by HPLC *c*: 5 mol% cat.loading *d*: reaction temperature is 0 ˚C

Table 8. Derivatization with quinine/*tert*-butyl squaramide **48**



Entry	R	Time (d)	Yield[a] (%)	ee (%) (*syn*)	ee (%) (*anti*)	dr[b] (*syn/anti*)
1	 **39j**	6 d	73	**95**	38	96:4
2	 **39c**	6 d	61	**90**	57	93:7
3	 **39n**	6 d	60	**90**	54	90:10
4	 **39a**	3 d	94	**90**	52	88:12
5	 **39d**	3 d	87	**92**	54	87:13
6	 **39e**	3 d	78	**92**	nd	87:13
7	 **39b**	3 d	68	**90**	58	91:9
8	 **39i**	3 d	70	**91**	52	91:9
9	 **39m**	3 d	78	**90**	54	92:8
10	 **39g**	3 d	95	**89**	56	89:11
11	 **39h**	6 d	79	**87**	58	84:16
12	 **39l**	6 d	87	**91**	64	92:8

a: isolated yield *b*: Determined by crude ^{1}H NMR and HPLC

Consequently, it was decided that the best condition of Michael addition was the use of 2 mol% organocatalyst **48** in DCM at 0˚C. In order to evaluate the efficiency of the organocatalyst **48**, a wide range of nitroolefin derivatives having electron-donating and electron-withdrawing groups on *o*-, *m*- and *p*- positions substituted was tested under aforementioned optimized condition. It was clearly seen that the effect of groups on phenyl ring directly affected the reaction duration. While electron-withdrawing group substituted substrates had shorter reaction duration (3 days) than the electron-donating ones (6 days). Furthermore, enantioselectivities varied in the range of 87%-95% ee and diastereoselectivities around 90:10 dr. Also, *p*-methoxy substituted substrate afforded both the highest enantioselectivity, 95% ee and the diastereoselectivity, 96:4 *syn/anti* (Table 8, entry 1).

The absolute configuration of *syn* product was assigned as *S,S* based on the literature comparison of HPLC analysis but those of the rest were assigned in analogy.[34]

In this thesis, the bifunctional organocatalyst was used for the activation of both electrophile and nucleophile. According to Wulff's nitro activation theory, we proposed a favorable transition state model. In the transition state, the deprotonation of nitroalkane is achieved by interaction *via* H bond while, the squaramide moiety activated the *trans-β*-nitrostyrene through double hydrogen bonding. 1-nitropropane anion attacked the activated nitroolefin from the *Si*-face.

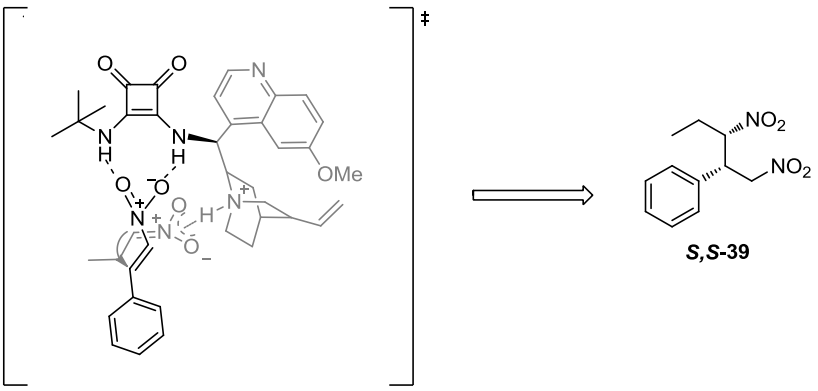


Figure 10. Proposed transition state model

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

^{1}H NMR and ^{13}C NMR spectra were recorded in Bruker Spectrospin Avance DPX 400 spectrometer with $CDCl_3$ as solvent. Chemical shifts are reported in ppm with TMS as a reference and data are specified as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dtt (doublet of triplet of triplet), t (triplet), td (triplet of doublet), m (multiplet) and coupling constants (*J*) were reported in Hertz (Hz). ^{1}H NMR and ^{13}C NMR spectra for products are given in Appendix A.

HPLC measurements were conducted on Thermo-Finnigan instrument by the usage of Daicel Chiralpak OJ-H, OD-H and AD-H columns with different hexane and isopropanol solvent systems at room temperature. HPLC chromatograms of racemic and chiral products are given in Appendix A.

Polarimetric measurements were carried out by Rudolph Scientific Autopol III polarimeter and reported as follows $[\alpha]_D^T$ (*c* in g per mL, solvent).

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

The chemical yields were controlled with Thermo Scientific DSQ II Single Quadrupole GC-MS.

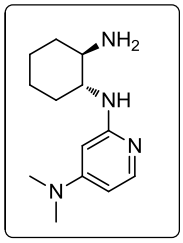
For functional groups determination, infrared radiation analysis were made on Bruker Alpha Platinum ATR. Band positions in infrared spectra were reported in cm^{-1}.

All reactions were monitored by TLC using precoated silica gel plates (Merck Silica Gel 60 F_{254}), visualized by UV-light. Column chromatography was performed on silica gel 60 with particle size of 0.063–0.200 mm.
ChemBioDraw Ultra was used for naming compounds and drawing schemes as well as MestReNova 6.0.2 was applied for interpreting NMR spectra.

3.2 Synthesis of *R, R* configurated 2-AminoDMAP (51)

For the synthesis of 2-aminoDMAP **(51)**, CuBr (0.2 mmol, 200 mg) and K_3PO_4 (2 mmol, 2.9 g) were added to an oven-dried Schlenk tube, evacuating and backfilling with argon thrice. Then, (1*R*,2*R*)-*trans*-1,2-cyclohexanediamine **(49)** (1.2 mmol, 960 mg) and 2-bromoDMAP **(50)** (1 mmol, 1.4 g) were added under the argon atmosphere.

By addition of 1,4-dioxane (dried with sodium and benzophenone) (7.8 mL), the reaction mixture was stirred at 110 ˚C for 24 hours. The resulting green-blue suspension mixture was cooled to room temperature and then 2 mL of water and 2 mL of concentrated ammonia was added. The resulting dark blue solution was extracted with DCM (3 x 25 mL). In order to dry the organic phase, brine and $MgSO_4$ was used as drying agents. The product was purified with flash column chromatography started with only saturated DCM as eluent and gradually added methanol, up to 10%. The 2-aminoDMAP **(51)** was obtained as light brown solid with 60% yield.[21]



mp: 138-140 ˚C

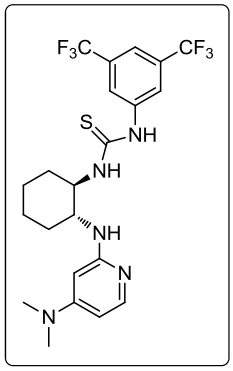
$[\alpha]_D^{25}$ = -55.0˚ (*c* 0.25, CH_2Cl_2)

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

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

3.3 Synthesis of 2-AminoDMAP/Thiourea Bifunctional Organocatalyst (41)

The Lewis basic core 2-aminoDMAP **(51)** (47 mg, 0.2 mmol) was dissolved in dry THF (1 mL). To this solution, 3,5-bis(trifluoromethyl)benzene isothiocyanate **(52)** was added dropwise at 0 ˚C. After that, this mixture was stirred for 1 hour at room temperature and then was directly loaded on the column chromatography as in the condition DCM:MeOH (90:10). Organocatalyst **41** was obtained as an off-white amorphous solid with 90% yield.[21]



mp: 115-121 ˚C

$[\alpha]_D^{25}$ = -133.0˚ (*c* 1.0, $CHCl_3$)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (bs, 1H), 8.76 (bs, 1H), 8.00 (s, 2H), 7.46 (s, 1H), 7.38 (d, J = 7.5 Hz, 1H), 6.77 (bs, 1H), 6.03 (dd, J = 2.4, 7.5Hz, 1H), 5.77 (bs, 1H), 4.47 (bs, 1H), 3.80(bs, 1H), 2.99 (s, 6H), 2.14 – 2.04 (m, 1H), 2.04 – 1.94 (m, 2H), 1.83 – 1.68 (m, 2H), 1.66 – 1.52 (m, 1H), 1.52 – 1.29 (m, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.5, 156.9, 152.1, 141.2, 135.0, 131.8, 131.4, 131.1, 130.8, 127.3, 124.6, 123.4, 121.9, 119.2, 117.5, 100.0, 87.8, 60.4, 53.8, 39.9, 30.9, 29.7, 29.3, 23.7 ppm.

IR (neat) 2930, 2857, 1609, 1525, 1471, 1377, 1274, 1168, 1126, 884, 700, 680.

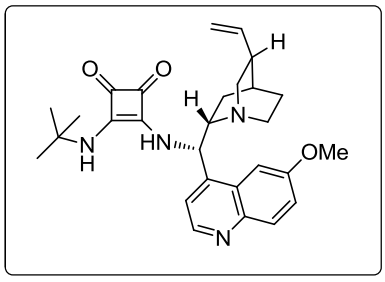
HRMS calculated for $C_{22}H_{26}F_6N_5S$ $[M + H]^+$ 506.1813, found 506.1800.

3.4 Synthesis of Quinine/*tert*-butyl Squaramide Bifunctional Organocatalyst

In order to synthesize quinine/tert-butyl squaramide bifunctional organocatalyst **48**, firstly, quinine was turned into quinine amine **58**. According to literature[32], quinine (3.24 g, 10 mmol) was dissolved in dry THF (50 mL) and after addition of triphenylphosphine (3.15 g, 12 mmol), the solution was cooled to 0 ˚C. Diisopropyl

azodicarboxylate (2.33 mL, 12 mmol) was added at all once and in another flask, the solution of diphenyl phosphoryl azide (2.58 mL, 12 mmol) in 20 mL dry THF was prepared. Then, this solution was also added to other solution dropwise at 0 ˚C. The all mixture was warmed to room temperature and after 12 hours, the reaction was heated to 50 ˚C for 2 h. After that, the second time, triphenyl phosphine (3.41 g, 13 mmol) was added and heating was maintained until the gas evolution stopped (2 h). The solution was cooled to room temperature, then the addition of 1 mL water the reaction was stirred for another 3 hours. After evaporating the solvents under the vacuum, the residue was dissolved in DCM (50 mL) and 10% HCl (50 mL). Then, aqueous phase was washed with DCM (4 x 50 mL) and made alkaline with aqueous ammonia. After, aqueous phase was washed with again DCM (4 x 50 mL). To dry organic phase, $MgSO_4$ was used as a drying agent. The residue was purified by column chromatography on silica gel EtOAc:MeOH:NEt_3 system (50:50:1). The quinine amine **58** was obtained as a yellowish viscous oil with 70% yield.

Secondly, quinine amine **58** (323 mg, 1.0 mmol) was dissolved in DCM: MeOH (2 mL:2 mL) and *tert*-butyl mono squaramide **56c** (197 mg, 1.0 mmol) was added to this solution at room temperature. Then, the solution was stirred for 48 hours, and directly loaded on column chromatography EtOAc:MeOH (75:25). The organocatalyst **48** was obtained as a white solid with 87% chemical yield.



mp: 260 ˚C (decomposed)

$[\alpha]_D^{25}$ = -180.2 ˚ (c 0.1, CH_2Cl_2)

^{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), 5.78 – 5.57 (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 (101 MHz, $CDCl_3$) δ 181.2, 180.4, 167.2, 167.0, 157.7, 146.7, 143.8, 142.8, 139.5, 130.7, 126.9, 121.4, 118.6, 114.2, 100.5, 55.0, 54.7, 52.2, 39.9, 38.0, 29.5, 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 calculated for $C_{34}H_{40}N_4O_3$ $[M + H]^+$ 475.27037, found 475.27124

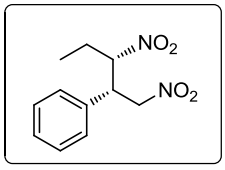
3.5 General Procedure for Asymmetric Michael Additions of 1-Nitropropane (35) to Nitroolefins

The *trans-β*-nitroolefin derivatives (0.2 mmol) were added to a solution of bifunctional organocatalyst quinine/*tert*-butyl squaramide **48** (0.004 mmol, 1.89 mg) in DCM (0.5 mL). Then, 1-nitropropane **(35)** (3 mmol, 0.5 mL) was added and the reaction was stirred for nearly 3-6 days at 0 ˚C. In this part, reactions were monitored by TLC. All reactions were purified with column chromatography using EtOAc: Hexane (1:6 or 1:8) solvent systems and expected diastereomers were obtained.

3.5.1 Synthesis of ((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39)

With the general procedure, starting from *trans-β*-nitrostyrene **(23)** (0.2 mmol, 29.8 mg) and 1-nitropropane **(35)**, compound **39** was obtained as a mixture of *syn/anti*-isomers with ratio 91:9 (*syn/anti*) and 87% yield at the end of 91 h.

***syn*-Diastereomer of 39**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 3H), 7.19-7.11 (m, 2H), 4.88 (dd, *J* =13.5 Hz, *J* = 6.2 Hz, 1H), 4.81-4.73 (m, 2H), 4.04 (m, 1H), 2.08-1.95 (m, 1H), 1.92-1.80 (m, 1H), 1.01 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.3, 126.8, 126.6, 125.4, 88.5, 73.8, 44.0, 21.8, 7.8 ppm.

HPLC (Chiralpak OJ-H, 80:20 Hexane:2-PrOH, 1.5 mL /min, 210 nm) *Syn* product retention time; t_r= 28 min, (minor) t_r= 40 min (major). *Anti*-product retention time; t_r= 17 min, (minor) t_r= 22 min (major).

IR (neat) 2974, 2927, 1547 (NO_2), 1456, 1375, 1259, 1084, 810, 770, 700 cm^{-1}.

***anti*-Diastereomer of 39**

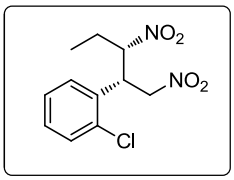
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 3H), 7.13 (dd, *J* = 7.7, 1.6 Hz, 2H), 4.73 (dd, *J* = 13.0, 10.4 Hz, 1H), 4.64 – 4.49 (m, 2H), 3.93 (td, *J* = 10.2, 4.2 Hz, 1H), 1.88 – 1.76 (m, 1H), 1.57 – 1.49 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 128.6, 128.1, 126.9, 90.5, 75.9, 45.9, 24.6, 9.0 ppm.

3.5.2 Synthesis of 1-chloro-2-((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39a)

With the general procedure, starting from (*E*)-1-chloro-2-(2-nitrovinyl)benzene (0.2 mmol, 36.7 mg) and 1-nitropropane **(35)**, compound **39a** was obtained as a mixture of *syn/anti*-isomers with ratio 88:12 (*syn/anti*) and 94% yield at the end of 3 days.

***syn*-Diastereomer of 39a**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (ddd, *J* = 7.2, 4.7, 1.7 Hz, 1H), 7.25 – 7.16 (m, 2H), 7.10 (ddd, *J* = 9.4, 7.2, 2.5 Hz, 1H), 4.94 (dd, *J* = 14.2, 7.0 Hz, 1H), 4.86 – 4.73 (m, 2H), 4.59 (m, 1H), 2.04 – 1.82 (m, 2H), 0.94 (t, *J* = 5.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.3, 131.7, 130.9, 130.7, 130.2, 127.7, 89.8, 75.1, 42.9, 24.1, 10.4 ppm.

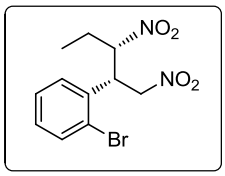
HPLC (Chiralpak OJ-H, 85:15 Hexane:2-PrOH, 1.5 mL /min, 210 nm) *Syn* product retention time; t_r= 27 min, (minor) t_r= 38 min (major). *Anti*-product retention time; t_r= 16 min, (minor) t_r= 23 min (major).

IR (neat) 2975, 2921, 1548 (NO_2), 1477, 1435, 1374, 1259, 1037, 794, 755 cm^{-1}

3.5.3 Synthesis of 1-bromo-2-((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39b)

With the general procedure, starting from (*E*)-1-bromo-2-(2-nitrovinyl)benzene (0.2 mmol, 45.6 mg) and 1-nitropropane **(35)**, compound **39b** was obtained as a mixture of *syn/anti*-isomers with ratio 91:9 (*syn/anti*) and 68% yield at the end of 3 days.

***syn*-Diastereomer of 39b**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59- 7.52 (m, 1H), 7.28 – 7.18 (m, 1H), 7.17 – 7.05 (m, 2H), 4.93 (s, 1H), 4.86 – 4.70 (m, 2H), 4.61 (s, 1H), 2.02 – 1.86 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.1, 132.3, 129.4, 127.2, 88.9, 74.2, 43.8, 22.9, 9.4 ppm.

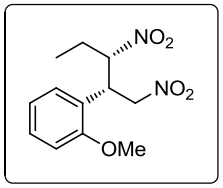
HPLC (Chiralpak OJ-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 210 nm) *Syn* product retention time; t_r= 75 min, (minor) t_r= 103 min (major). *Anti*-product retention time; t_r= 50 min, (minor) t_r= 68 min (major).

IR (neat) 2920, 2851, 1653, 1557 (NO_2), 1457, 1374, 1259, 1083, 1022, 792 cm^{-1}.

3.5.4 Synthesis of 1-((2*S*,3*S*)-1,3-dinitropentan-2-yl)-2-methoxybenzene (39c)

With the general procedure, starting from (*E*)-1-methoxy-2-(2-nitrovinyl)benzene (0.2 mmol, 35.8 mg) and 1-nitropropane **(35)**, compound **39c** was obtained as a mixture of *syn/anti*-isomers with ratio 93:7 (*syn/anti*) and 61% yield at the end of 6 days.

***anti*-Diastereomer of 39c**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 - 7.20 (m, 1H), 7.06 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.90 – 6.81 (m, 2H), 5.02 – 4.87 (m, 2H), 4.45 (dd, *J* = 12.8, 4.2 Hz, 1H), 4.10 (ddd, *J* = 15.5, 10.7, 5.7 Hz, 1H), 3.81 (s, 3H), 1.85 -1.65 (m, 1H), 1.55 -1.40 (m, 1H), 0.81 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 131.2, 130.3, 121.9, 121.4, 111.4, 89.9, 75.4, 55.5, 44.7, 25.8, 9.9 ppm.

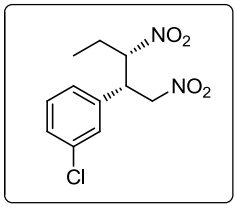
HPLC (Chiralpak OD-H, 80:20 Hexane:2-PrOH, 0.5 mL/min, 225 nm) *Syn* product retention time; t_r= 19 min, (minor) t_r= 31 min (major). *Anti*-product retention time; t_r= 15 min, (minor) t_r= 13 min (major).

IR (neat) 2921, 2851, 1551 (NO_2), 1494, 1461, 1438, 1375, 1258, 1083, 1021, 792, 737, 703 cm^{-1}.

3.5.5 Synthesis of 1-chloro-3-((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39d)

With the general procedure, starting from (*E*)-1-chloro-3-(2-nitrovinyl)benzene (0.2 mmol, 36.7 mg) and 1-nitropropane **(35)**, compound **39d** was obtained as a mixture of *syn/anti*-isomers with ratio 87:13 (*syn/anti*) and 87% yield at the end of 3 days.

***syn*-Diastereomer of 39d**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.18 (m, 2H), 7.10 (t, *J* = 1.7 Hz, 1H), 6.98 (d, *J* = 7.2, 1H), 4.79 (dd, *J* = 13.7, 6.0 Hz, 1H), 4.73 – 4.64 (m, 2H), 4.00 – 3.88 (m, 1H), 2.01 - 1.89 (m, 1H), 1.80 (dtt, *J* = 14.6, 7.4, 3.7 Hz, 1H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.2, 130.6, 129.4, 128.3, 125.9, 90.7, 75.9, 46.1, 24.4, 10.3 ppm.

HPLC (Chiralpak OJ-H, 95:5 Hexane:2-PrOH, 1.5 mL/min, 210 nm) *Syn* product retention time; t_r= 75 min, (minor) t_r= 89 min (major). *Anti*-product retention time; t_r= 47 min, (minor) t_r= 62 min (major).

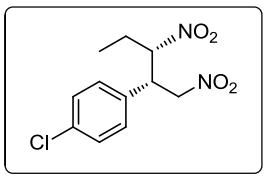
IR (neat) 2976, 2921, 1547 (NO_2), 1477, 1458, 1434, 1374, 1261, 1199, 1084, 887, 838, 809, 696 cm^{-1}.

HRMS calculated for $C_{11}H_{13}ClN_2O_4$ $[M + H]^+$ 273.0637, found 273.1663.

3.5.6 Synthesis of 1-chloro-4-((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39e)

With the general procedure, starting from (*E*)-1-chloro-4-(2-nitrovinyl)benzene (0.2 mmol, 36.7 mg) and 1-nitropropane **(35)**, compound **39e** was obtained as a mixture of *syn/anti*-isomers with ratio 87:13 (*syn/anti*) and 78% yield at the end of 3 days.

***syn*-Diastereomer of 39e**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.21 (m, 2H), 7.09 – 6.95 (m, 2H), 4.78 (dd, *J* = 13.5, 5.9 Hz, 1H), 4.72 – 4.57 (m, 2H), 3.95 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.86 – 1.69 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 135.2, 132.2, 129.6, 129.3, 90.8, 76.2, 45.9, 24.4, 10.3 ppm.

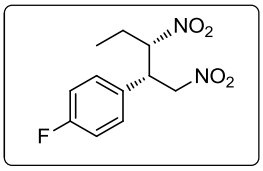
HPLC (Chiralpak OD-H, 85:15 Hexane:2-PrOH, 0.5 mL/min, 225 nm) *Syn* product retention time; t_r= 42 min, (minor) t_r= 90 min (major). *Anti*-product retention time; t_r= 28 min, (minor) t_r= 30 min (major).

IR (neat) 2979, 2922, 1542 (NO_2), 1490, 1458, 1433, 1375, 1316, 1265, 1193, 1091, 1013, 829, 804, 722, 670, 611 cm^{-1}.

3.5.7 Synthesis of 1-((2*S*,3*S*)-1,3-dinitropentan-2-yl)-4-fluorobenzene (39f)

With similar to general procedure, starting from (*E*)-1-fluoro-4-(2-nitrovinyl)benzene (0.2 mmol, 33.4 mg) and 1-nitropropane **(35)**, compound **39f** was obtained as a mixture of *syn/anti*-isomers with ratio 79:21 (*syn/anti*) and 78% yield at the end of 11 days by bifunctional 2-aminoDMAP/thiourea organocatalyst **41** (0.004 mmol, 2.02 mg) in xylene (0.5 mL).

***anti*-Diastereomer of 39f**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.08 (m, 2H), 7.05 – 6.97 (m, 2H), 4.69 (dd, *J* = 13.1, 10.4 Hz, 1H), 4.61 – 4.49 (m, 2H), 3.93 (td, *J* = 10.1, 4.3 Hz, 1H), 1.88 -1.76 (m, 1H), 1.60 -1.50 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, (d, *J* = 249.3 Hz, 1C), 128.9, (d, *J* = 3.3 Hz, 1C), 128.7 (d, *J* = 8.5 Hz, 2C), 115.7, (d, *J* = 21.7 Hz, 2C) 90.5, 75.8, 45.3, 24.5, 9.0 ppm.

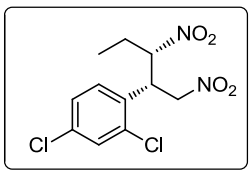
HPLC (Chiralpak OD-H, 80:20 Hexane:2-PrOH, 1.0 mL/min, 225 nm) *Syn* product retention time; t_r= 13 min, (minor) t_r= 18 min (major). *Anti*-product retention time; t_r= 11 min, (minor) t_r= 9 min (major).

IR (neat) 2977, 2923, 1605, 1547 (NO_2), 1510, 1435,1375, 1226, 1163, 836, 809, 736 cm^{-1}.

3.5.8 Synthesis of 2,4-dichloro-1-((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39g)

With the general procedure, starting from (*E*)-2,4-dichloro-1-(2-nitrovinyl)benzene (0.2 mmol, 43.6 mg) and 1-nitropropane **(35)**, compound **39g** was obtained as a mixture of *syn/anti*-isomers with ratio 89:11 (*syn/anti*) and 95% yield at the end of 3 days.

***anti*-Diastereomer of 39g**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 2.1 Hz, 1H), 7.25 – 7.18 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.89 (dd, *J* = 13.5, 10.1 Hz, 1H), 4.77 (bs, 1H), 4.64 (dd, *J* = 13.6, 4.0 Hz, 1H), 4.49 (dd, *J* = 18.1, 5.5 Hz, 1H), 2.00 – 1.87 (m, 1H), 1.68 – 1.55 (m, 1H), 0.89 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.8, 128.9, 128.8 126.5, 88.7, 72.9, 40.8, 23.6, 8.3 ppm.

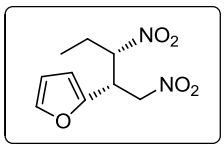
HPLC (Chiralpak OD-H, 90:10 Hexane:2-PrOH, 1.0 mL/min, 225 nm) *Syn* product retention time; t_r= 22 min, (minor) t_r= 30 min (major). *Anti*-product retention time; t_r= 15 min, (minor) t_r= 13 min (major).

IR (neat) 2975, 2939, 1589, 1548 (NO_2), 1475, 1434, 1373, 1106, 1049, 871, 822, 722, 574 cm^{-1}.

3.5.9 Synthesis of 2-((2*S*,3*S*)-1,3-dinitropentan-2-yl)furan (39h)

With the general procedure, starting from (*E*)-2-(2-nitrovinyl)furan (0.2 mmol, 27.8 mg) and 1-nitropropane **(35)**, compound **39h** was obtained as a mixture of *syn/anti*-isomers with ratio 84:16 (*syn/anti*) and 79% yield at the end of 6 days.

***anti*-Diastereomer of 39h**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 1H), 6.31 – 6.20 (m, 2H), 4.72 (ddd, *J* = 12.8, 11.6, 6.8 Hz, 2H), 4.51 (dd, *J* = 13.2, 4.0 Hz, 1H), 4.12 (td, *J* = 9.6, 4.0 Hz, 1H), 1.92 -1.76 (m, 1H), 1.69 – 1.53 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 141.4, 108.6, 108.0, 87.1, 72.5, 38.6, 23.21, 7.8 ppm.

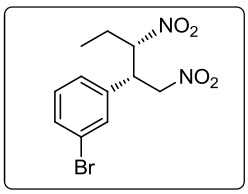
HPLC (Chiralpak OD-H, 90:10 Hexane:2-PrOH, 0.5 mL/min, 230 nm) *Syn* product retention time; t_r= 32 min, (minor) t_r= 36 min (major). *Anti*-product retention time; t_r= 26 min, (minor) t_r= 22 min (major).

IR (neat) 2921, 1548 (NO_2), 1504, 1459, 1432, 1374, 1260, 1148, 1079, 1014, 916, 811, 744, 598 cm^{-1}.

3.5.10 Synthesis of 1-bromo-3-((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39i)

With the general procedure, starting from (*E*)-1-bromo-3-(2-nitrovinyl)benzene (0.2 mmol, 45.6 mg) and 1-nitropropane **(35)**, compound **39i** was obtained as a mixture of *syn/anti*-isomers with ratio 91:9 (*syn/anti*) and 70% yield at the end of 3 days.

***syn*-Diastereomer of 39i**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4 - 7.38 (m, 1H), 7.25 (t, *J* = 1.8 Hz, 1H), 7.19 - 7.14 (m, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 4.79 (dd, *J* = 13.7, 6.0 Hz, 1H), 4.73 – 4.63 (m, 2H), 4.00 - 3.90 (m, 1H), 2.00 – 1.89 (m, 1H), 1.86 – 1.75 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 132.4, 131.2, 130.8, 126.4, 123.3, 90.7, 75.9, 46.1, 24.4, 10.3 ppm.

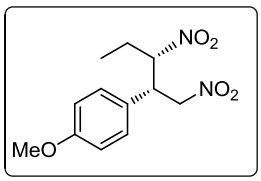
HPLC (Chiralpak OJ-H, 90:10 Hexane:2-PrOH, 1.0 mL/min, 225 nm) *Syn* product retention time; t_r= 72 min, (minor) t_r= 89 min (major). *Anti*-product retention time; t_r= 50 min, (minor) t_r= 65 min (major).

IR (neat) 2975, 2918, 1547 (NO_2), 1475, 1458, 1432, 1374, 1261, 1197, 1074, 887, 808, 790, 695 cm^{-1}.

3.5.11 Synthesis of 1-((2*S*,3*S*)-1,3-dinitropentan-2-yl)-4-methoxybenzene (39j)

With the general procedure, starting from (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (0.2 mmol, 35.8 mg) and 1-nitropropane, compound **39j** was obtained as a mixture of *syn/anti*-isomers with ratio 96:4 (*syn/anti*) and 73% yield at the end of 6 days.

***syn*-Diastereomer of 39j**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.0 (d, *J* = 8.7 Hz 2H), 6.79 (d, *J* = 8.7 Hz 2H), 4.78 (dd, *J* = 6.2 Hz, *J* = 13.4 Hz, 1H), 4.70 – 4.53 (m, 2H), 3.97 – 3.85 (m, 1H), 3.71 (s, 3H), 2.01 – 1.87 (m, 1H), 1.85 – 1.69 (m, 1H), 0.94 (t, *J* = 7.3 Hz 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 128.0, 124.4, 113.6, 90.1, 75.5, 54.2, 44.9, 23.3, 9.3 ppm.

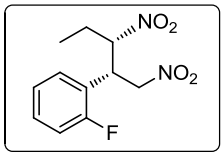
HPLC (Chiralpak OJ-H, 90:10 Hexane:2-PrOH, 1.5 mL/min, 210 nm) *Syn* product retention time; t_r= 86 min, (major) t_r= 96 min (minor). *Anti*-product retention time; t_r= 41 min, (minor) t_r= 54 min (major).

IR (neat) 2936, 2839, 1611, 1548 (NO_2), 1513, 1459, 1437, 1375, 1253, 1181, 1031, 833, 734, 566 cm^{-1}.

3.5.12 Synthesis of 1-((2*S*,3*S*)-1,3-dinitropentan-2-yl)-2-fluorobenzene (39k)

With similar to general procedure, starting from (*E*)-1-fluoro-2-(2-nitrovinyl)benzene (0.2 mmol, 33.4 mg) and 1-nitropropane **(35)**, compound **39k** was obtained as a mixture of *syn/anti*-isomers with ratio 76:24 (*syn/anti*) and 88% yield at the end of 11 days by bifunctional 2-aminoDMAP/thiourea organocatalyst **41** (0.004 mmol, 2.02 mg) in xylene (0.5 mL).

***syn*-Diastereomer of 39k**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 1H), 7.17 – 7.01 (m, 3H), 4.88 – 4.73 (m, 2H), 4.53 (dd, *J* = 13.2, 4.2 Hz, 1H), 4.19 (td, *J* = 10.2, 4.1 Hz, 1H), 1.90 – 1.75 (m, 1H), 1.61 – 1.46 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$**)** δ 160.7 (d, *J* = 247.0 Hz), 131.0 (d, *J* = 8.7 Hz), 130.6 (d, *J* = 4.2 Hz), 125.2 (d, *J* = 3.5 Hz), 121.2 (d, *J* = 13.4 Hz), 116.5 (d, *J* = 21.9 Hz), 89.9 (d, *J* = 3.3 Hz), 75.5 (d, *J* = 2.2 Hz), 42.7, 25.7, 9.9 ppm.

HPLC (Chiralpak OD-H, 80:20 Hexane:2-PrOH, 1.0 mL/min, 225 nm) *Syn* product retention time; t_r= 11 min, (minor) t_r= 23 min (major). *Anti*-product retention time; t_r= 9 min, (minor) t_r= 8 min (major).

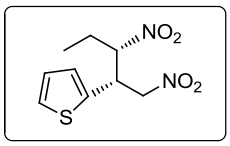
IR (neat) 2977, 2924, 1548 (NO_2), 1492, 1456, 1375, 1228, 810, 757 cm^{-1}.

HRMS calculated for $C_{11}H_{13}FN_2O_4$ $[M + Na]^+$ 279.0763, found 279.1495.

3.5.13 Synthesis of 2-((2*S*,3*S*)-1,3-dinitropentan-2-yl)thiophene (39l)

With the general procedure, starting from (E)-2-(2-nitrovinyl)thiophene (0.2 mmol, 31.0 mg) and 1-nitropropane **(35)**, compound **39l** was obtained as a mixture of *syn/anti*-isomers with ratio 92:8 (*syn/anti*) and 87% yield at the end of 6 days.

***syn*-Diastereomer of 39l**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 1H), 6.93 – 6.87 (m, 1H), 6.86 – 6.82 (m, 1H), 4.85 (dd, *J* = 13.8, 6.1 Hz, 1H), 4.74 – 4.66 (m, 2H), 4.29 (dd, *J* = 14.1, 6.3 Hz, 1H), 2.05 -1.92 (m, 1H), 1.89 – 1.77 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.3, 125.6, 125.3, 124.3, 89.0, 74.8, 39.8, 22.3, 8.4 ppm.

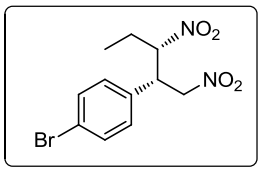
HPLC (Chiralpak OD-H, 80:20 Hexane:2-PrOH, 0.5 mL/min, 210 nm) *Syn* product retention time; t_r= 33 min, (minor) t_r= 71 min (major). *Anti*-product retention time; t_r= 28 min, (minor) t_r= 24 min (major).

IR (neat) 2976, 1546 (NO_2), 1458, 1432, 1374, 1256, 850, 810, 706, 614 cm^{-1}.

3.5.14 Synthesis of 1-bromo-4-((2*S*,3*S*)-1,3-dinitropentan-2-yl)benzene (39m)

With the general procedure, starting from (*E*)-1-bromo-4-(2-nitrovinyl)benzene (0.2 mmol, 45.6 mg) and 1-nitropropane **(35)**, compound **39m** was obtained as a mixture of *syn/anti*-isomers with ratio 92:8 (*syn/anti*) and 78% yield at the end of 3 days.

***syn*-Diastereomer of 39m**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.35 (m, 2H), 7.03 – 6.90 (m, 2H), 4.78 (dd, *J* = 13.5, 5.9 Hz, 1H), 4.72 – 4.61 (m, 2H), 3.94 (dd, *J* = 14.0, 7.8 Hz, 1H), 1.99 – 1.87 (m, 1H), 1.84 – 1.74 (m, 1H), 0.95 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8, 132.5, 129.6, 123.4, 90.7, 76.1, 46.0, 24.4, 10.3 ppm.

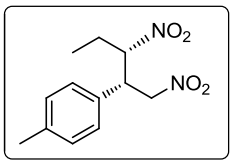
HPLC (Chiralpak AD-H, 95:5 Hexane:2-PrOH, 1.0 mL/min, 225 nm) *Syn* product retention time; t_r= 26 min, (minor) t_r= 24 min (major). *Anti*-product retention time; t_r= 33 min, (minor) t_r= 19 min (major).

IR (neat) 2975, 2919, 1547 (NO_2), 1489, 1458, 1434, 1374, 1261, 1074, 1010, 824, 810, 720, 641 cm^{-1}.

3.5.15 Synthesis of 1-((2*S*,3*S*)-1,3-dinitropentan-2-yl)-4-methylbenzene (39n)

With the general procedure, starting from (*E*)-1-methyl-4-(2-nitrovinyl)benzene (0.2 mmol, 32.6 mg) and 1-nitropropane **(35)**, compound **39n** was obtained as a mixture of *syn/anti*-isomers with ratio 90:10 (*syn/anti*) and 60% yield at the end of 6 days.

***syn*-Diastereomer of 39n**



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.1 Hz, 2H), 4.79 (dd, *J* = 13.5, 6.2 Hz, 1H), 4.73 – 4.62 (m, 2H), 3.92 (dd, *J* = 14.8, 6.7 Hz, 1H), 2.25 (s, 3H), 2.01 – 1.86 (m, 1H), 1.84 – 1.72 (m, 1H), 0.94 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9, 129.9, 127.7, 91.1, 76.4, 46.2, 24.3, 21.1, 10.3 ppm.

HPLC (Chiralpak OD-H, 80:20 Hexane:2-PrOH, 0.5 mL/min, 210 nm) *Syn* product retention time; t_r= 30 min, (minor) t_r= 108 min (major). *Anti*-product retention time; t_r= 18 min, (minor) t_r= 20 min (major).

IR (neat) 2853, 1547 (NO_2), 1516, 1457, 1435, 1374, 1317, 1262, 1078, 1043, 808, 736, 720, 616, 562 cm^{-1}.

CHAPTER 4

CONCLUSION

In this study, 1,3-dinitro compounds were synthesized *via* enantioselective Michael addition of 1-nitropropane **(35)** as Michael donor to *trans*-*β*-nitrostyrene **(23)** as Michael acceptor in the presence of 2-aminoDMAP and quinine based bifunctional organocatalysts.

Firstly, the efficacy of 2-aminoDMAP based organocatalysts were tested in that conjugate addition. Among the organocatalysts, organocatalyst **41** was chosen as the best for further studies. Optimization studies were conducted by changing the solvent, temperature, catalyst loading and concentration. The optimized condition was determined as 2 mol% organocatalyst **41** in xylene at -15 ˚C. In that condition, derivatization was done with different nitroolefins. From the results, the best enantioselectivity up to **64% ee** was obtained with *o*-chloro substrate.

Secondly, the same Michael addition reaction was used to test the efficiency of quinine based squaramides. The best suitable condition was obtained with the usage of 2 mol% organocatalyst **48** in DCM at 0 ˚C. After completing the derivatization part, the excellent enantioselectivity up to **95% ee** was obtained with *p*-methoxy substrate. In this part of study, the obtained results with quinine/*tert*-butyl squaramide **48** were higher than the results obtained with 2-aminoDMAP/thiourea **41**. Furthermore, the effect of groups on phenyl ring was clearly seen such as electron-withdrawing group substituted substrates had shorter reaction duration than the electron-donating ones.

Finally, as a future project, one of the derivative of 1,3-dinitro compounds will be reduced to corresponding 1,3-diamine.

REFERENCES

1. Gawley, R. E; Aube, J. *Principles of Asymmetric Synthesis.* 2nd ed.; Elsevier, The Netherlands, 2012.

2. Retrieved from http://www.nobelprize.org/nobel_prizes/chemistry/laureates/2001/advanced-chemistryprize2001.pdf (Last accessed on 10.10.2014)

3. Ojima, I. *Catalytic Asymmetric Synthesis.* 3rd ed.; Wiley, New Jersey, 2010.

4. Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis* University Sience Books, 2009, 2.

5. Inoue, T.; Hosomi, K.; Araki, M.; Nishide, K.; Node, M. *Tetrahedron: Asymmetry*, **1995**, *6*, 31-34.

6. MacMillan, D. W. C. *Nature* **2008**, *455*, 304-308.

7. Ahrendt, K. A; Borths C.J.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2000**, *122*, 4243–4244.

8. Gaunt, M. J; Johansson, C. C. C; McNally, A.; Vo, N. T. *Drug Discovery Today*. **2007**, *12*, 1-2.

9. Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis- From Biomimetic Concepts to Applications in Asymmetric Synthesis*. 1st ed.; Wiley-VCH, Weinheim, 2005.

10. Pellissier, H. *Tetrahedron.* **2007**, *63*, 9267-9331.

11. Bredig, G.; Fiske, W. S. *Biochem. Z.* **1912**, *46*, 7-23.

12. Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9-22.

13. Juliá, S.; Masana, J. C. *Angew. Chem. Int. Ed.* **1980**, *19*, 929-931.

14. Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417-430.

15. Oku, J.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, *183*, 229-230.

16. Waser, M. *Asymmetric Organocatalysis in Natural Product Synthesis*. Springer-Verlag, Wien, **2012**.

17. Mikami, K.; Lautens, M. *New Frontiers in Asymmetric Catalysis*. 1st ed.; Wiley-Intersicence, New Jersey, **2007**.

18. a) Yang, D.; Yip, Y. C; Tang, M. W; Wong, M. K; Zheng, J. H; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491-492.
b) Tu, Y.; Wang, Z. X; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807.
c) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288-8289.

19. Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902.

20. Corey, E. J.; Grogan, M. J. *Org. Lett*. **1999**, *1*, 157-160.

21. Işık, M. PhD. Thesis, METU, **2011**.

22. List, B.; Lerner, A. R.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

23. Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719-724.

24. Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673.

25. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X., Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *9*, 119-125.

26. Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466-476.

27. Nagasawa, K.; Hashimoto, Y.; Sohtome, Y. *Adv. Synth. Catal.* **2005**, *11-13*, 1643-1648.

28. Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005,** *7*, No. 19, 4293-4296.

29. Cao, C.; Ye, M.; Sun, X.; Tang, Y. *Org. Lett.* **2006,** *8*, No. 14, 2901-2904.

30. Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686–6687.

31. Oliva, C. G.; Silva, A. M. S.; Paz, F. A. A.; Cavaleiro, J. A. S. *Synlett*. **2010**, *7*, 1123–1127.

32. Vakulya, B.; Varga, S.; Csampai,A.; Soos, T. *Org. Lett*. **2005**, *7*, 1967-1969.

33. Wang, C.; Zhang, Z.; Dong, X.; Wu, X. *Chem. Commun.* **2008**, *12*, 1431–1433.

34. Rabalakos, C.; Wulff W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524–13525.

35. Dong, X.; Teng, H.; Wang, C. *Org. Lett.* **2009,** *11*, No. 6, 1265-1268.

36. Yang W.; Du, D. *Chem. Commun.* **2011**, *47*, 12706–12708.

APPENDIX A

SUPPORTING INFORMATION

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

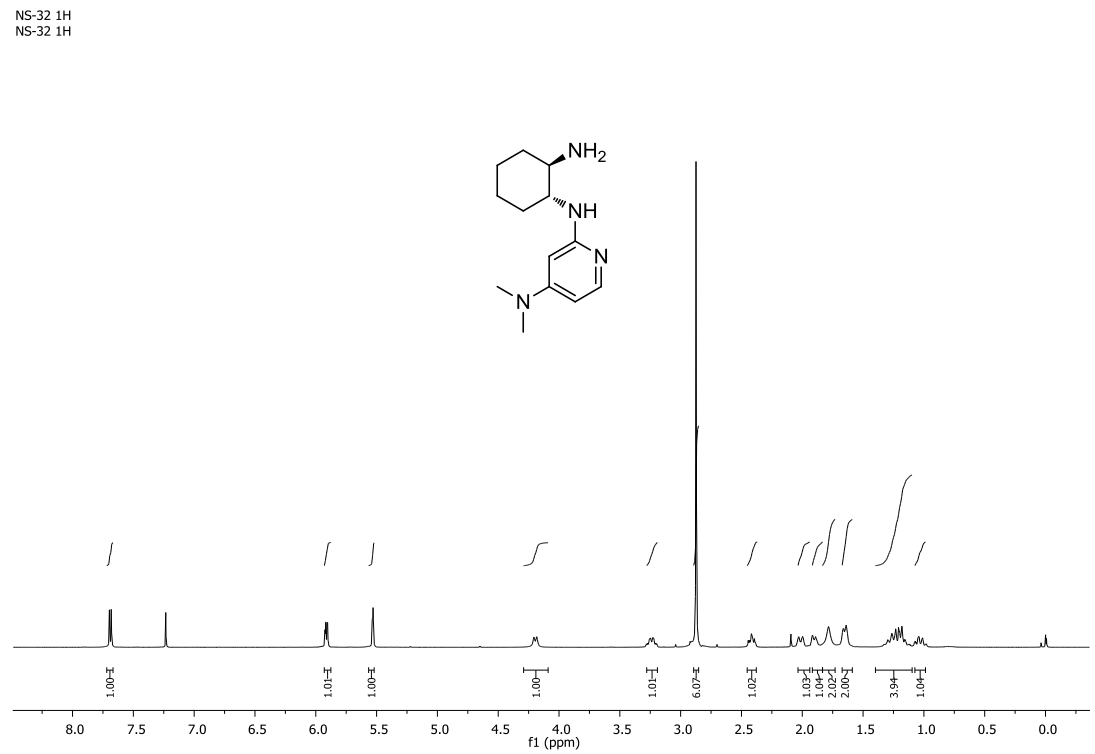


Figure A. 1. ^{1}H NMR spectrum of compound **51**

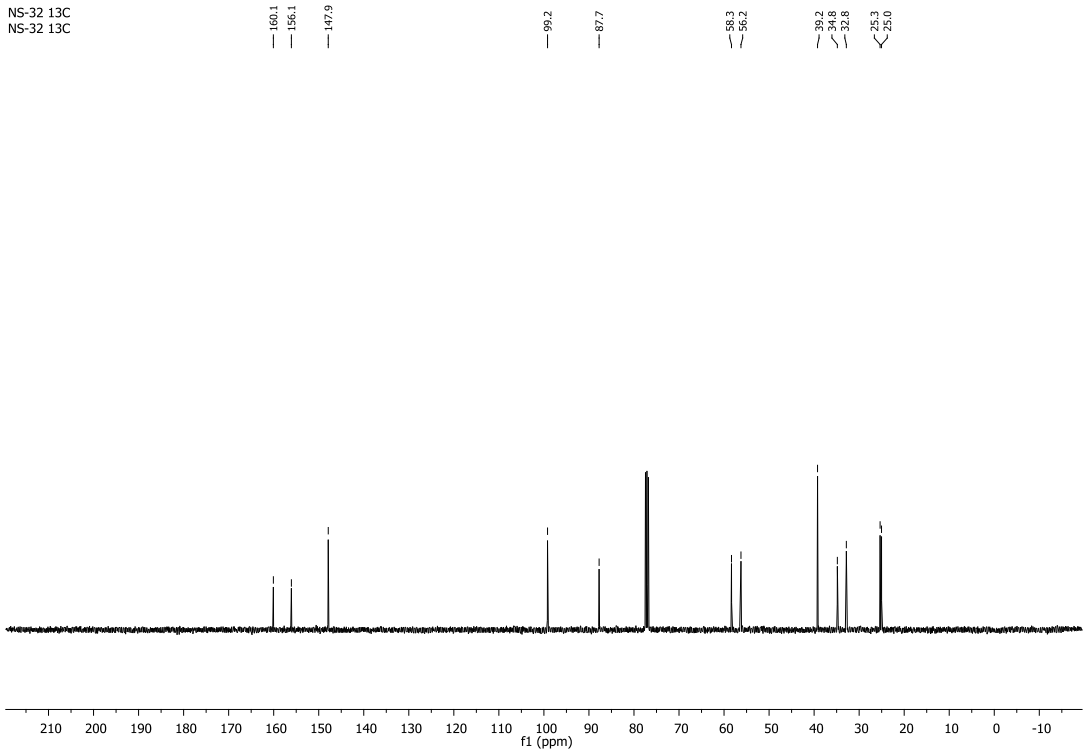


Figure A. 2. ^{13}C NMR spectrum of compound **51**

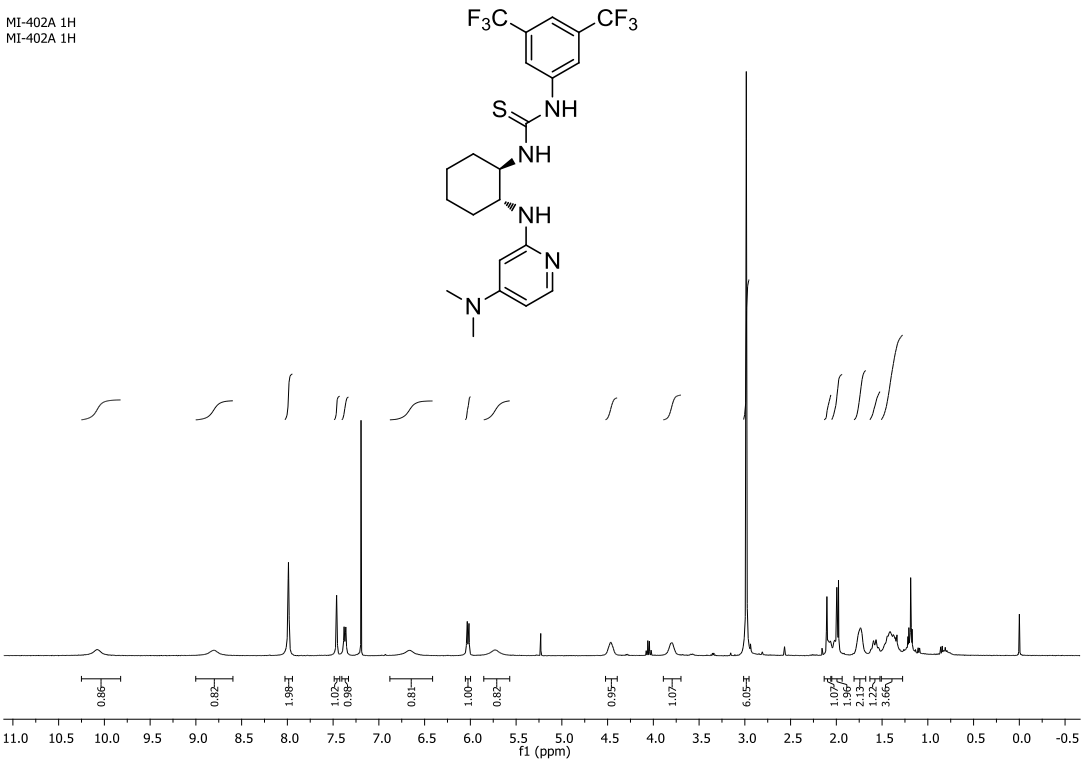


Figure A. 3. ^{1}H NMR spectrum of compound **41**

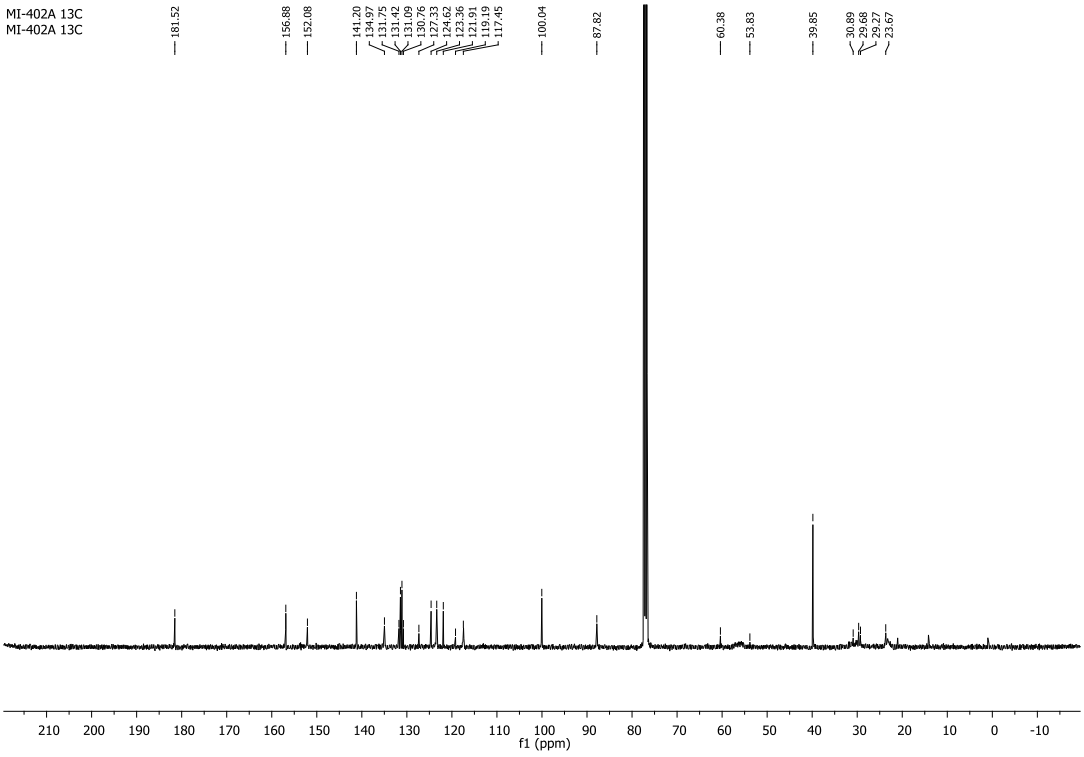


Figure A. 4. ^{13}C NMR spectrum of compound **41**

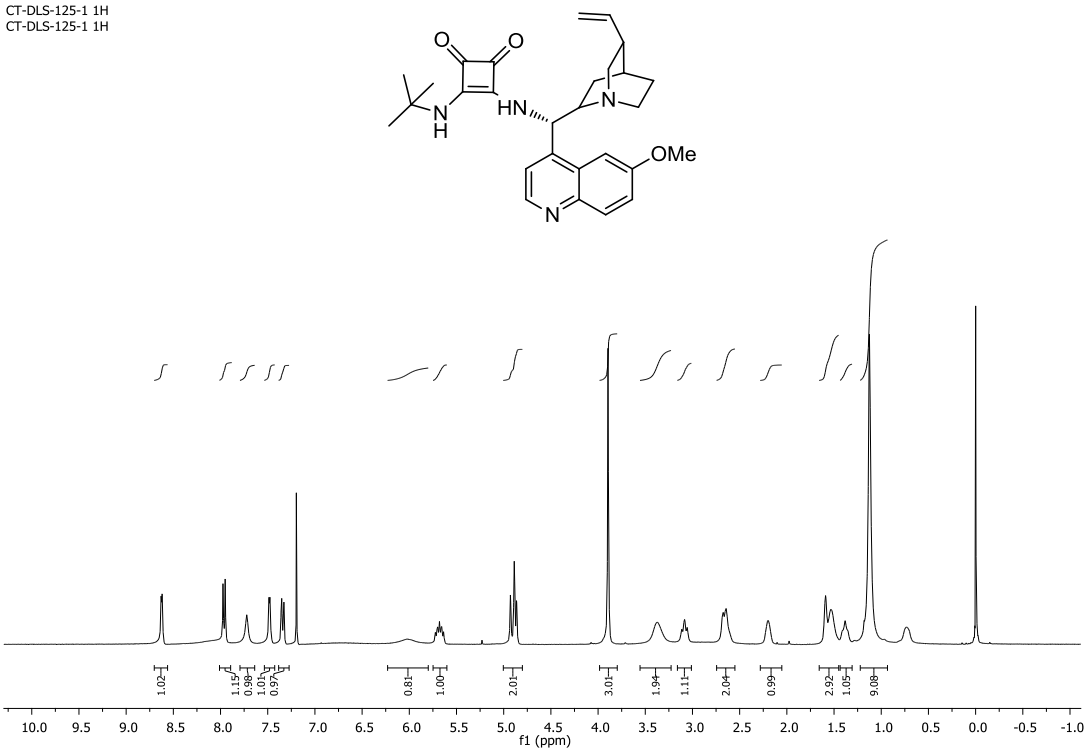


Figure A. 5. ^{1}H NMR spectrum of compound **48**

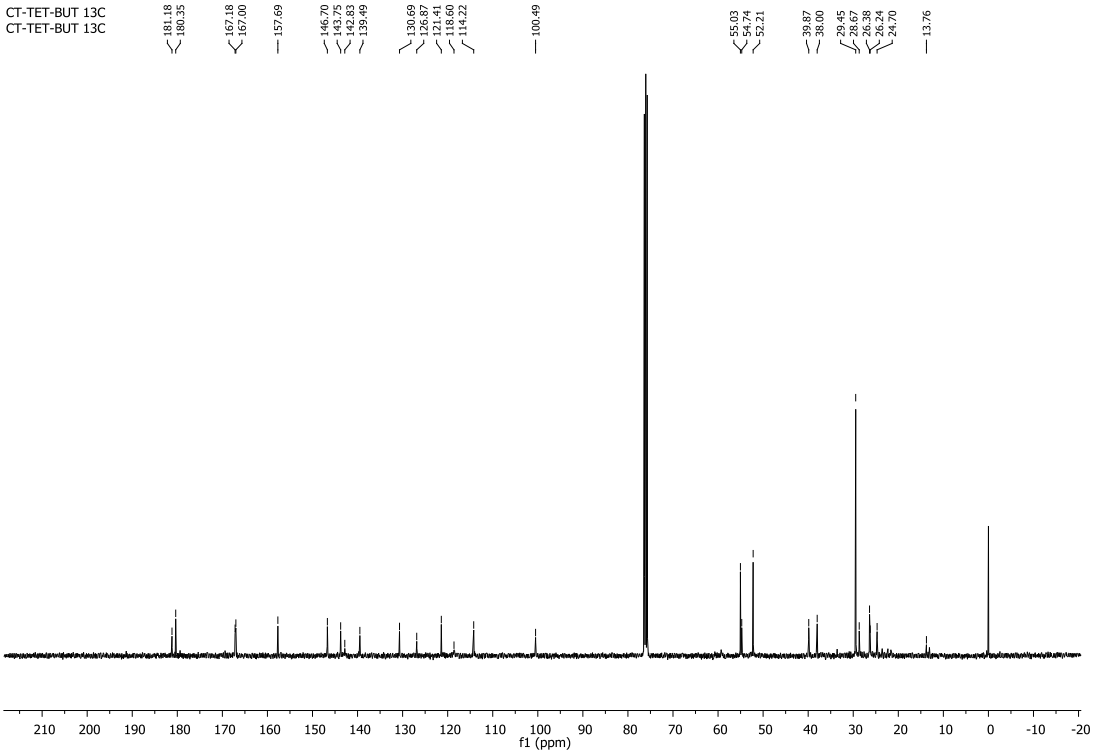


Figure A. 6. ^{13}C NMR spectrum of compound **48**

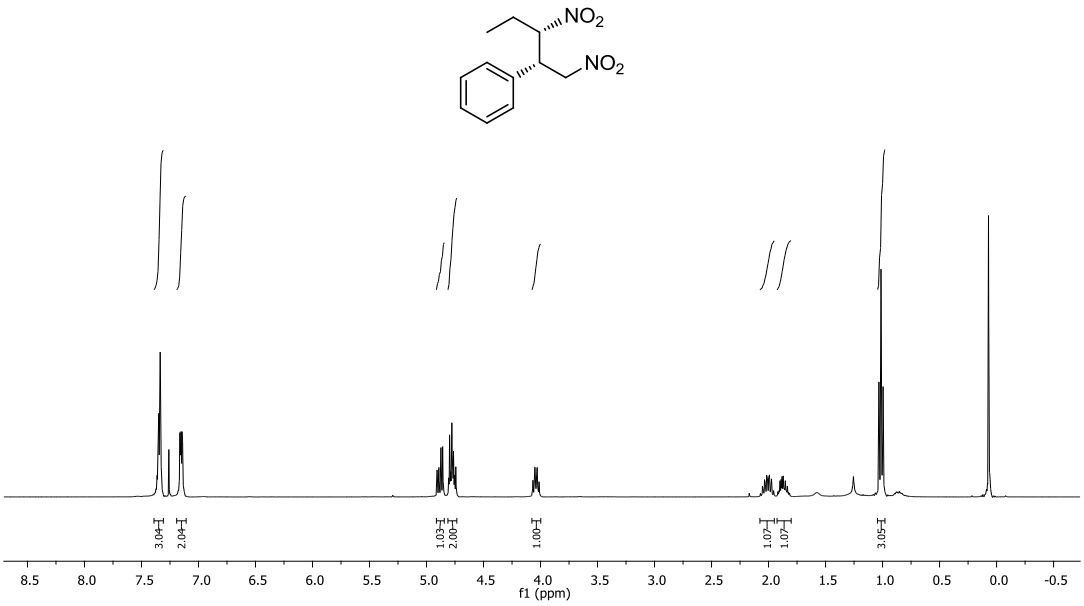


Figure A. 7. ^{1}H NMR spectrum of compound **39**

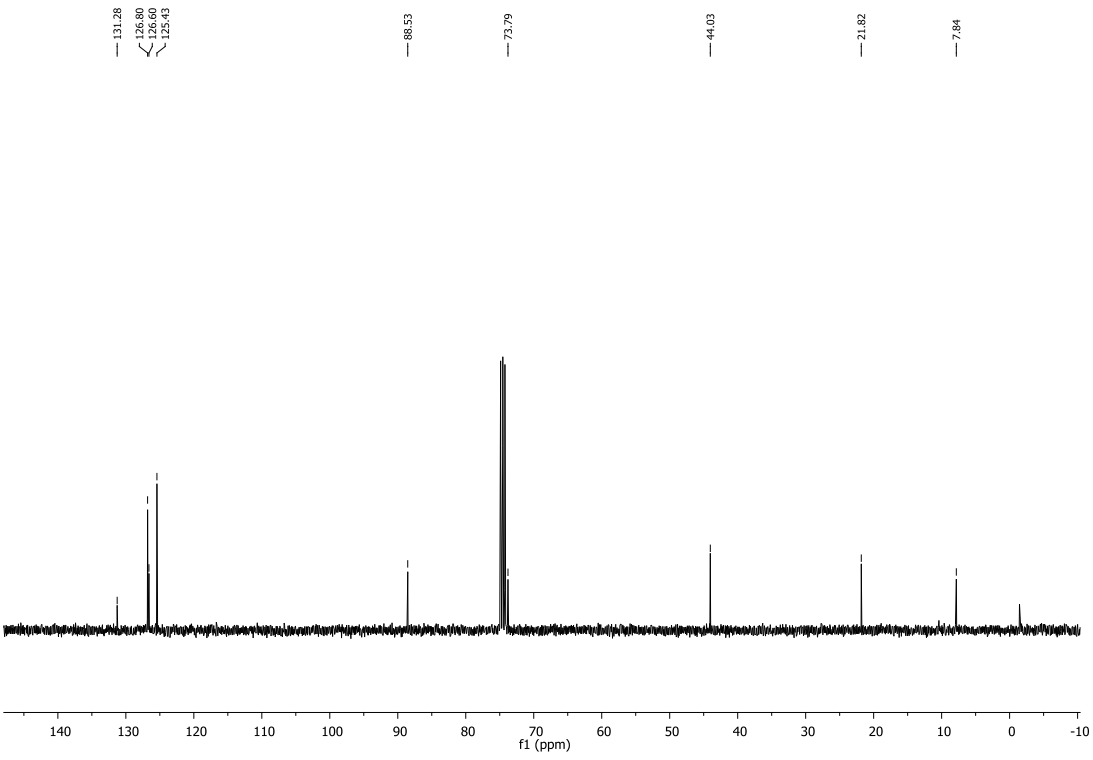


Figure A. 8. ^{13}C NMR spectrum of compound **39**

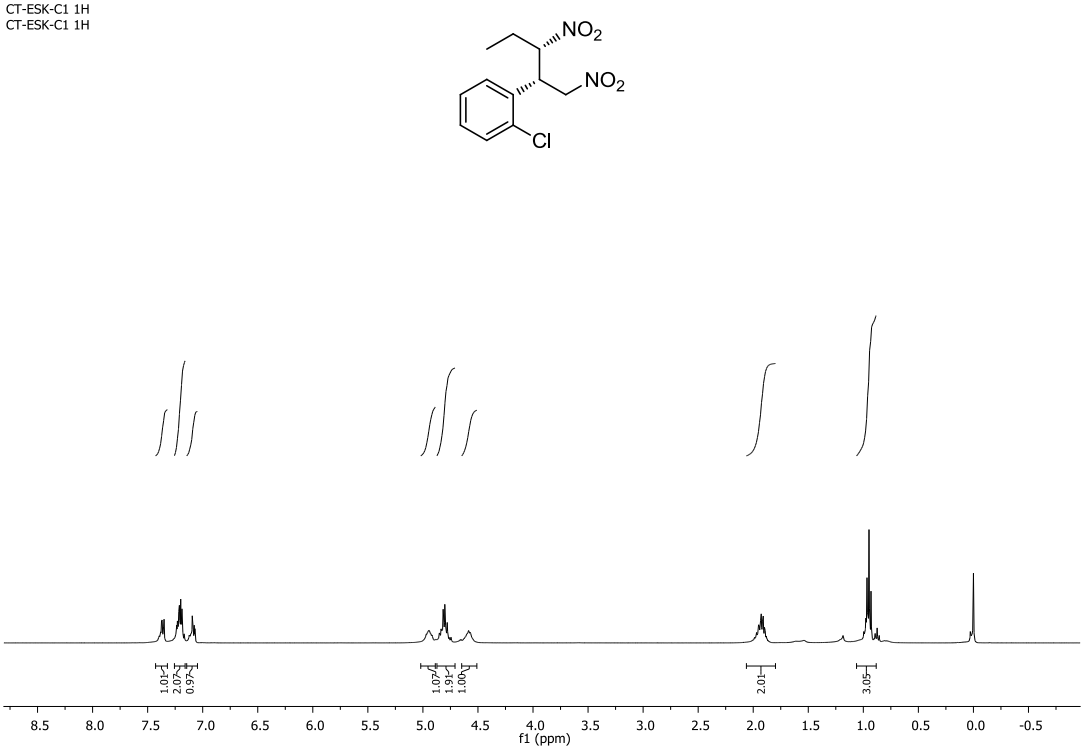


Figure A. 9. ^{1}H NMR spectrum of compound **39a**

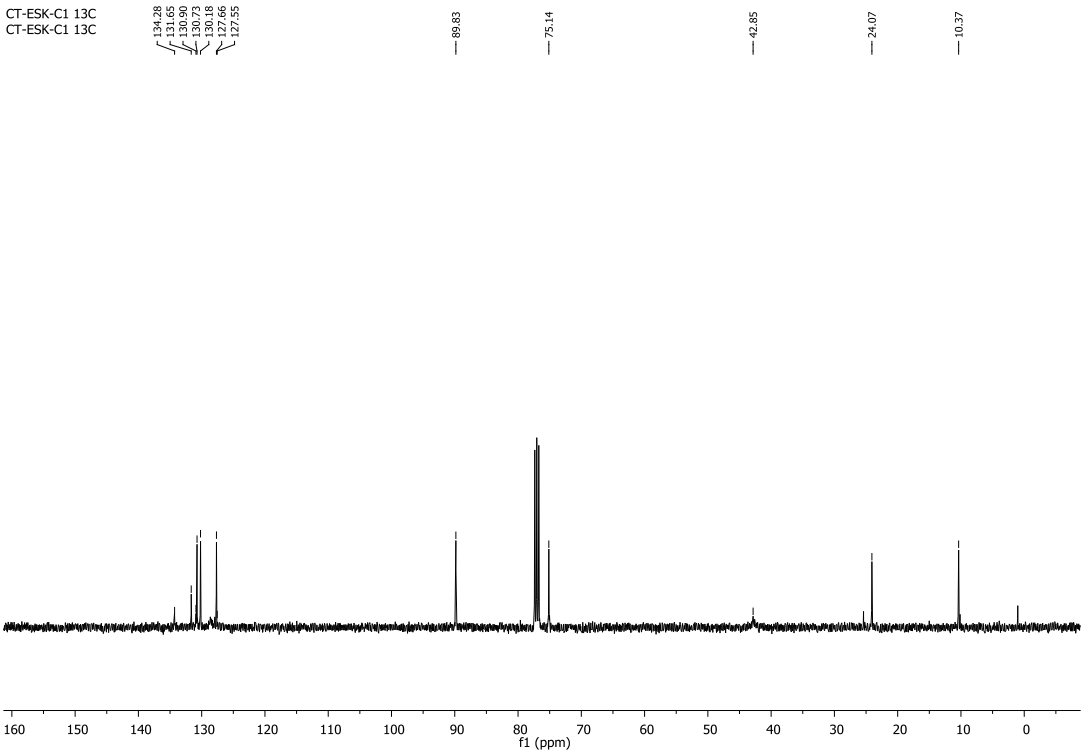


Figure A. 10. ^{13}C NMR spectrum of compound **39a**

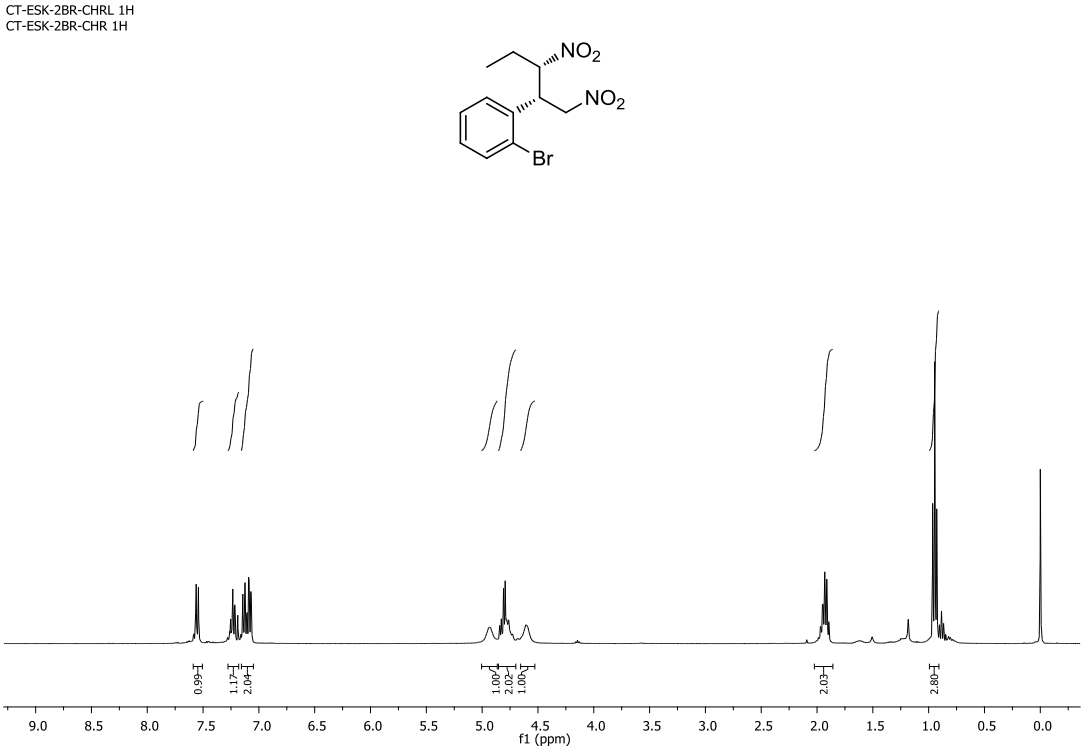


Figure A. 11. ^{1}H NMR spectrum of compound **39b**

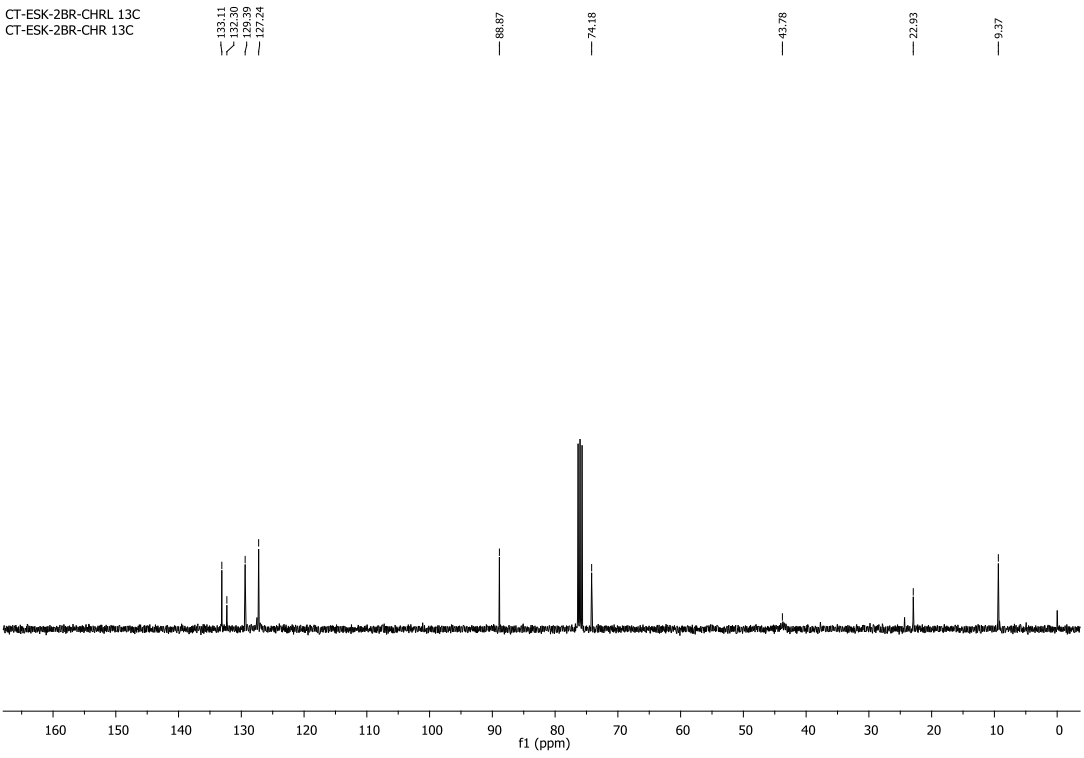


Figure A. 12. ^{13}C NMR spectrum of compound **39b**

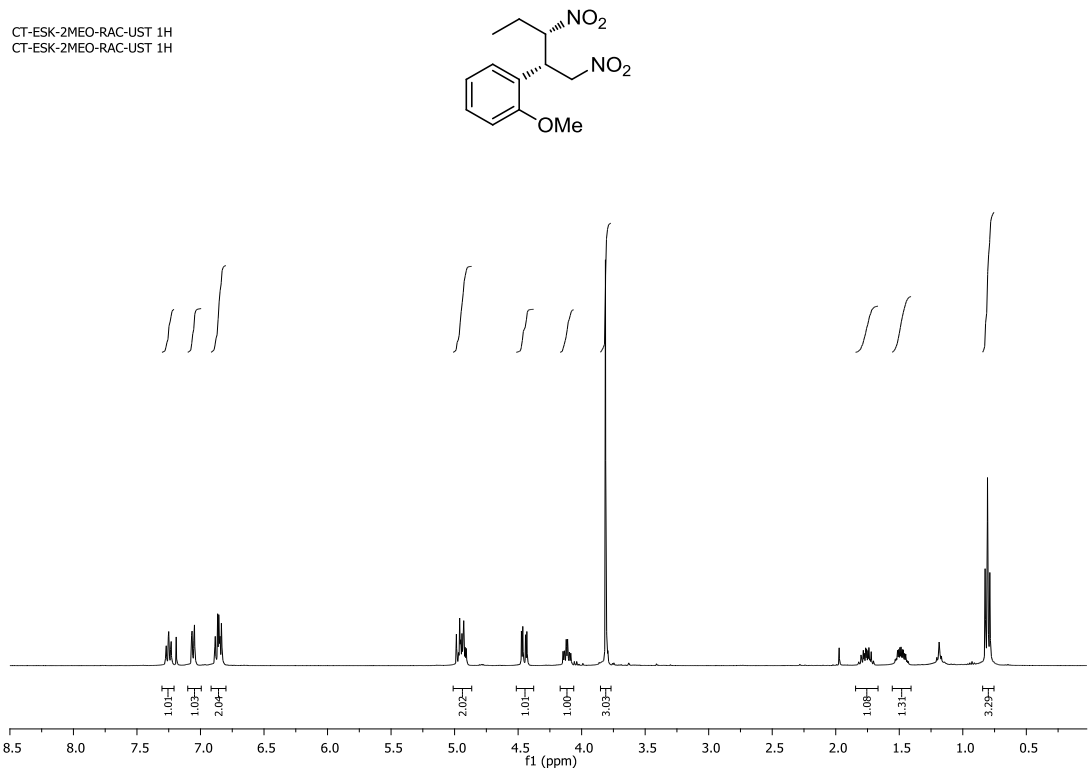


Figure A. 13. ^{1}H NMR spectrum of *anti*-diastereomer of compound **39c**

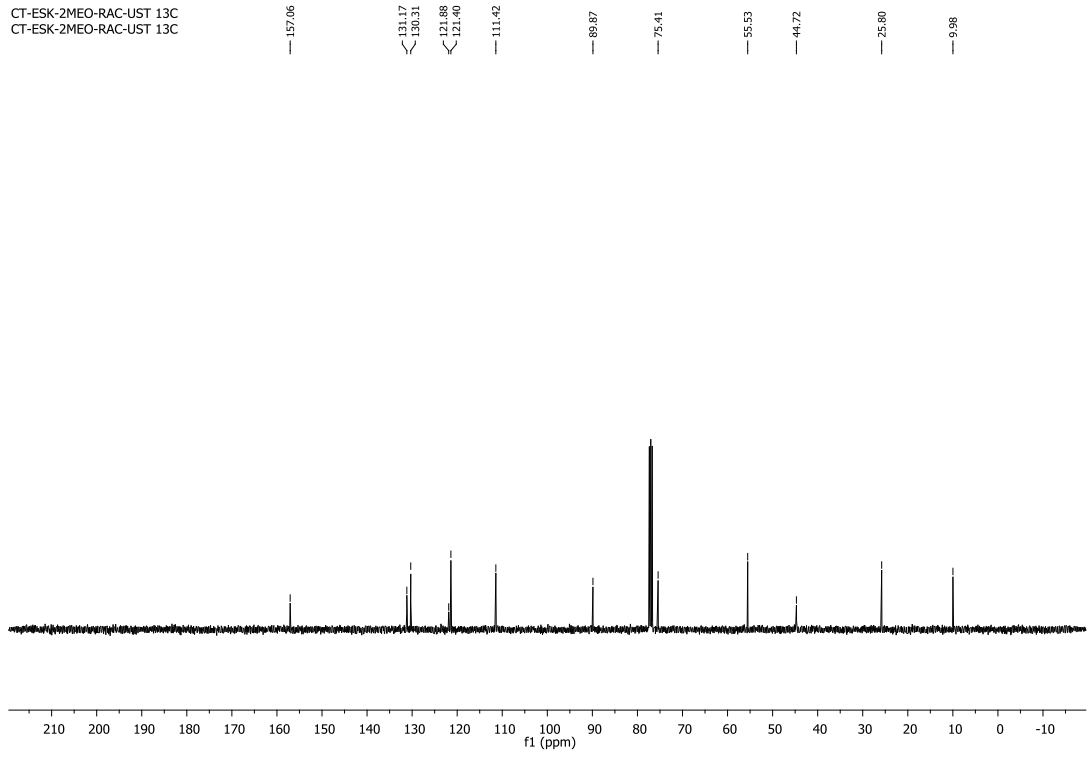


Figure A. 14. ^{13}C NMR spectrum of *anti*-diastereomer of compound **39c**

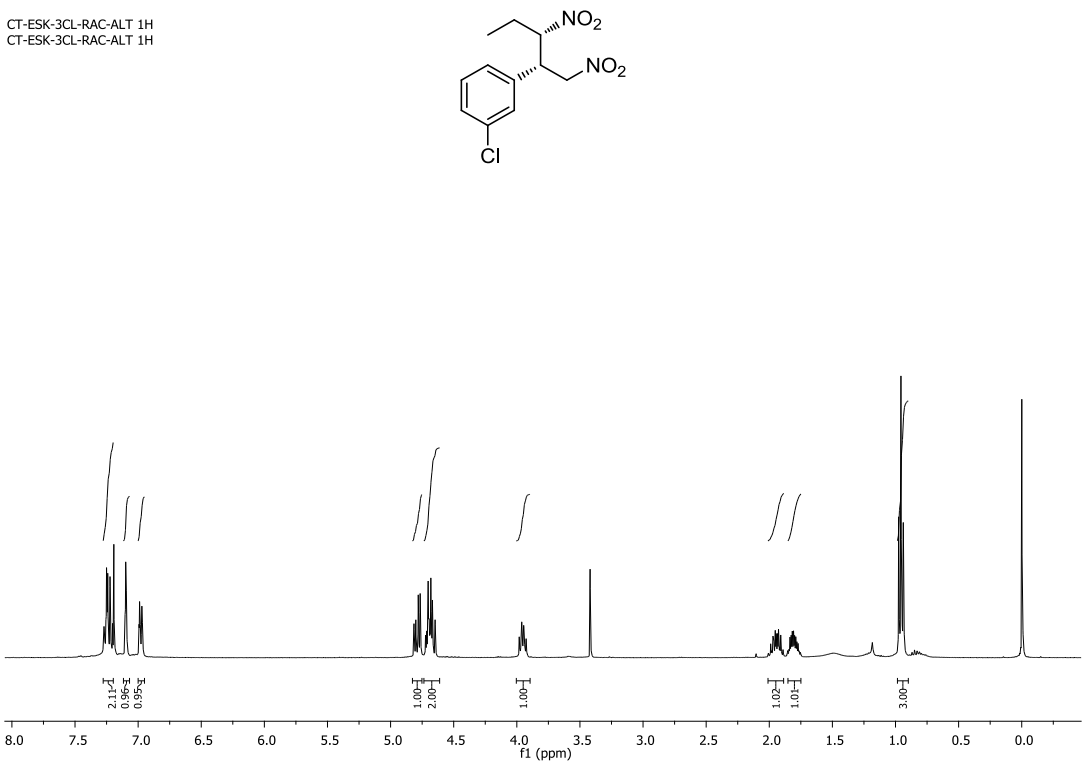


Figure A. 15. ^{1}H NMR spectrum of compound **39d**

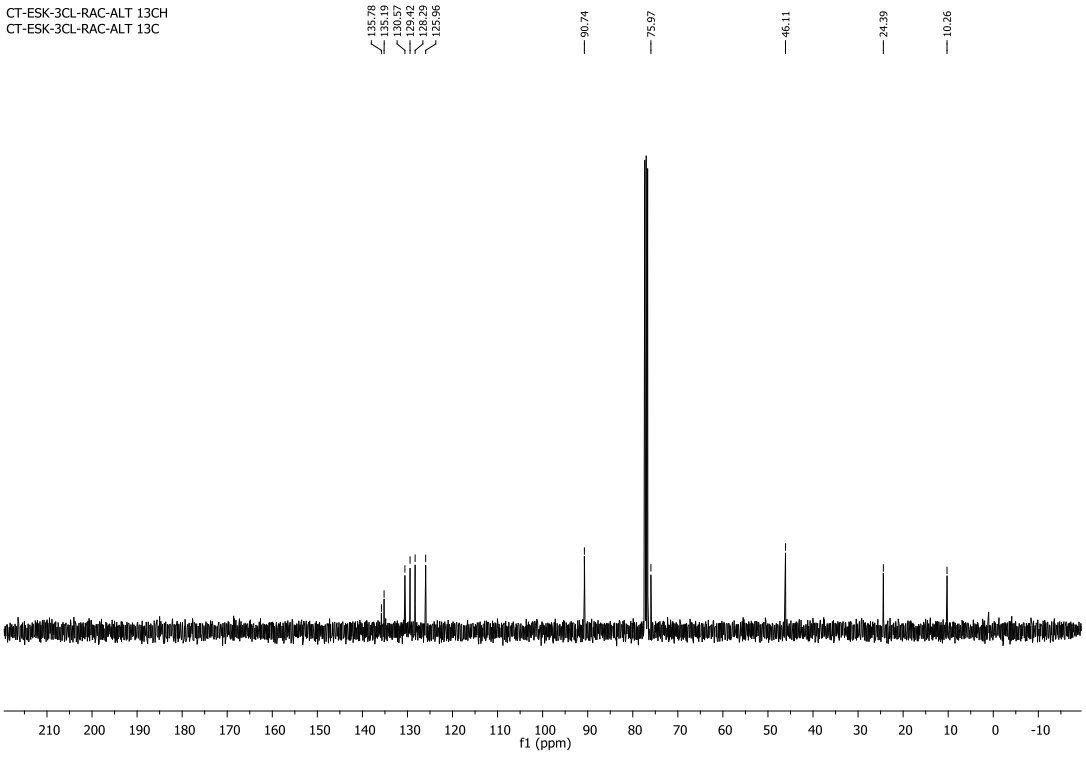


Figure A. 16. ^{13}C NMR spectrum of compound **39d**

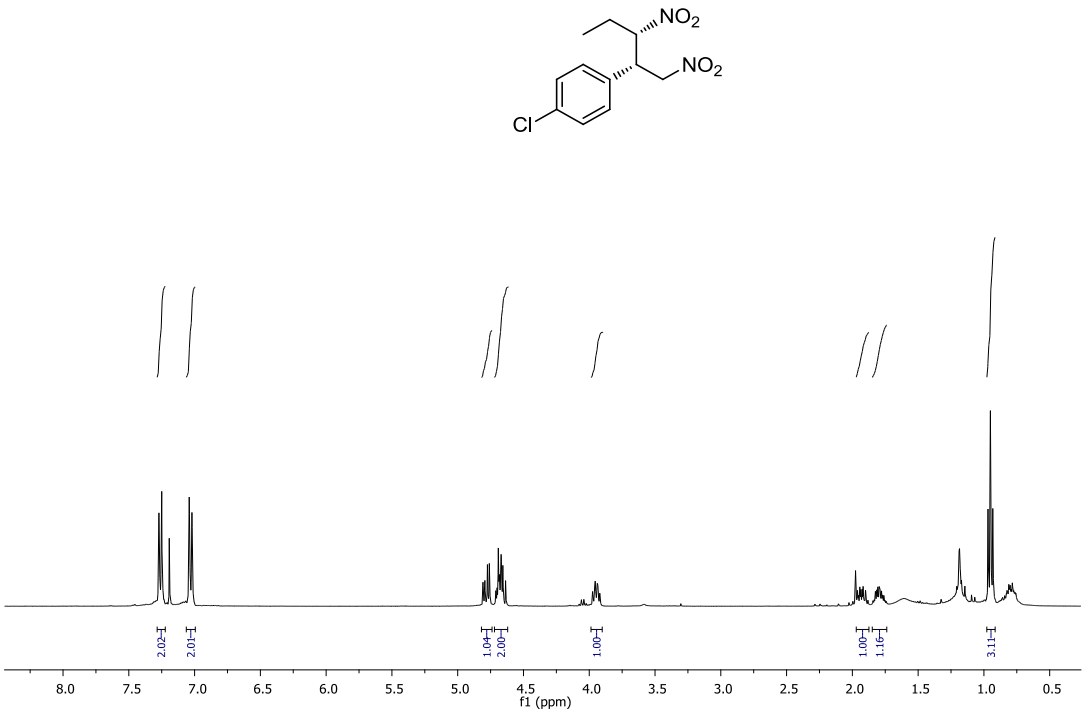


Figure A. 17. ^{1}H NMR spectrum of compound **39e**

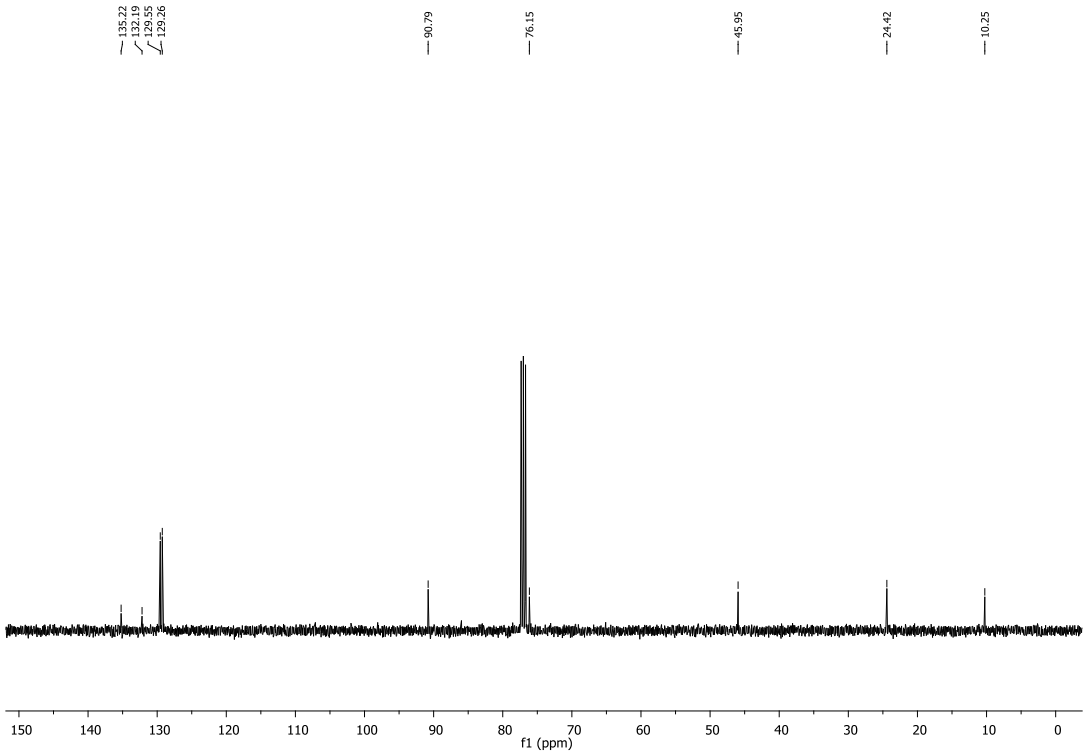


Figure A. 18. ^{13}C NMR spectrum of compound **39e**

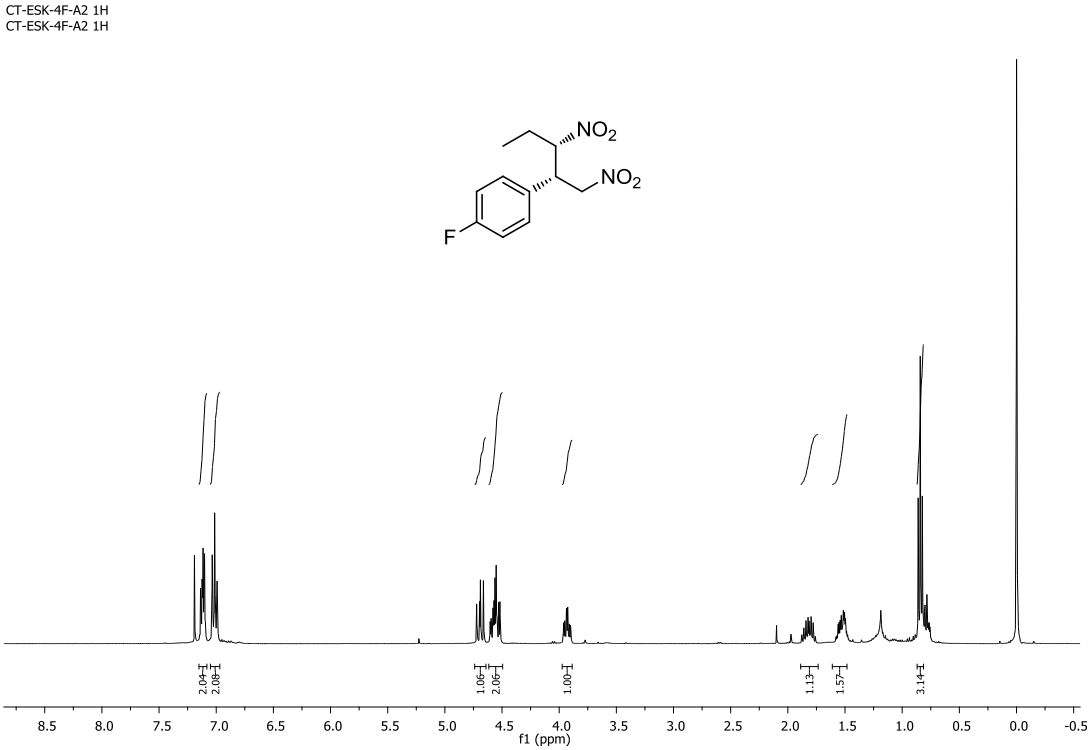


Figure A. 19. ^{1}H NMR spectrum of *anti*-diastereomer of compound **39f**

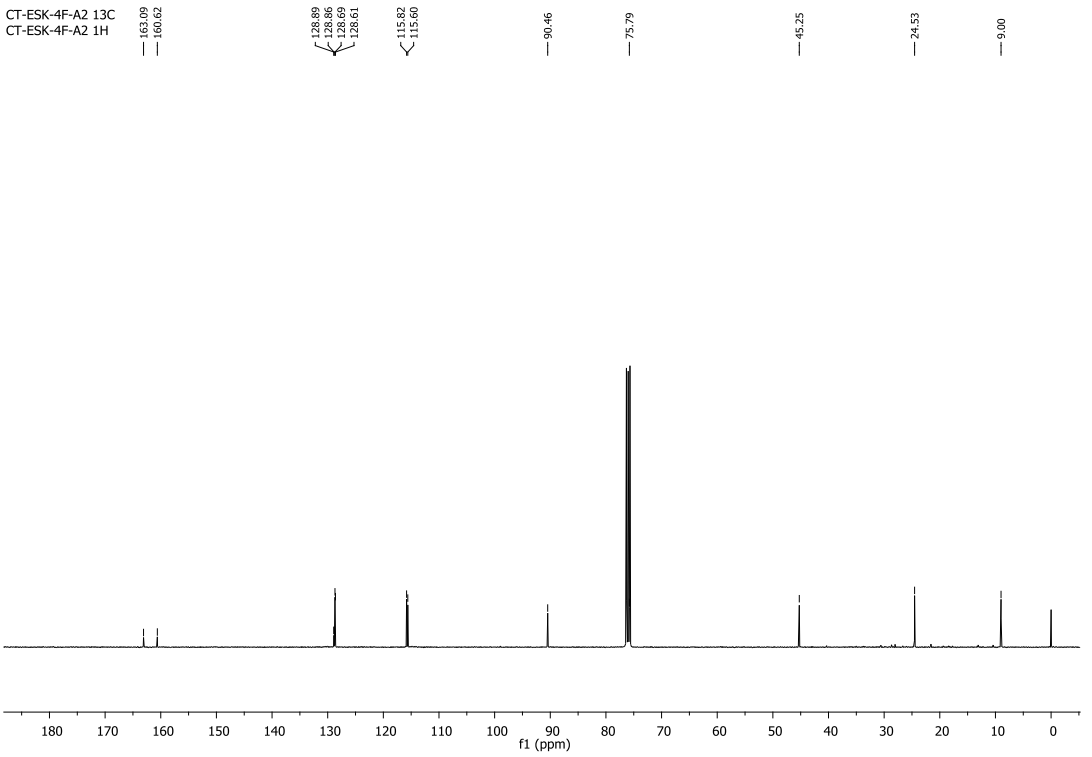


Figure A. 20. ^{13}C NMR spectrum of *anti*-diastereomer of compound **39f**

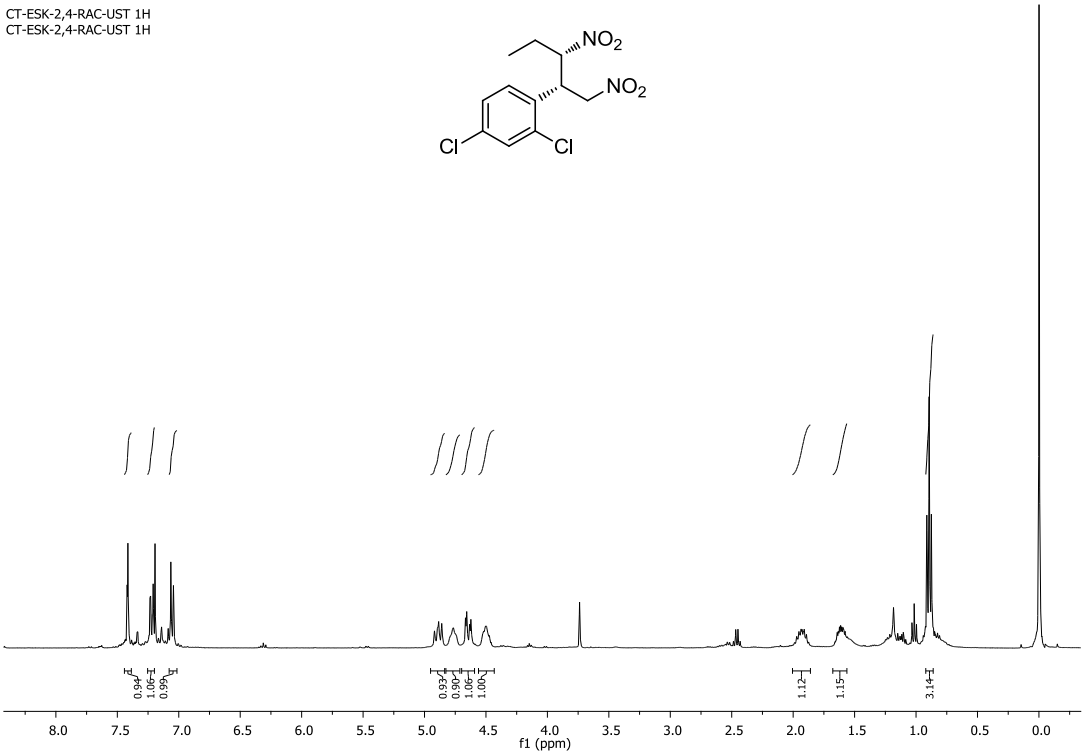


Figure A. 21. ^{1}H NMR spectrum of *anti*-diastereomer of compound **39g**

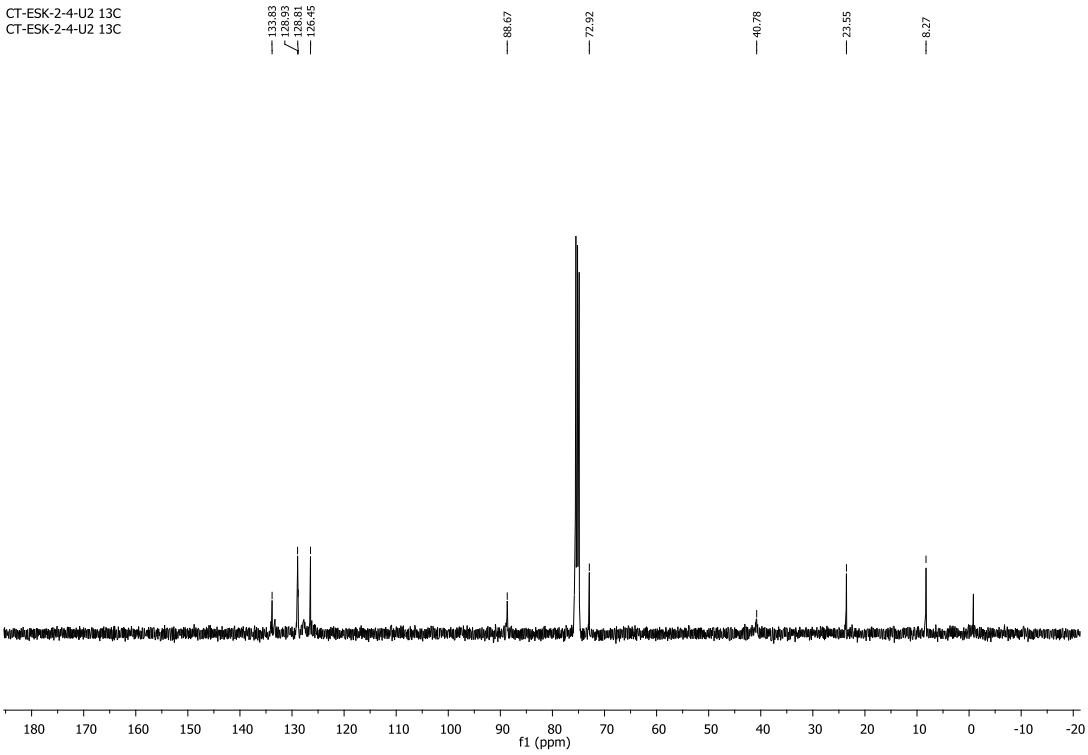


Figure A. 22. ^{13}C NMR spectrum of *anti*-diastereomer of compound **39g**

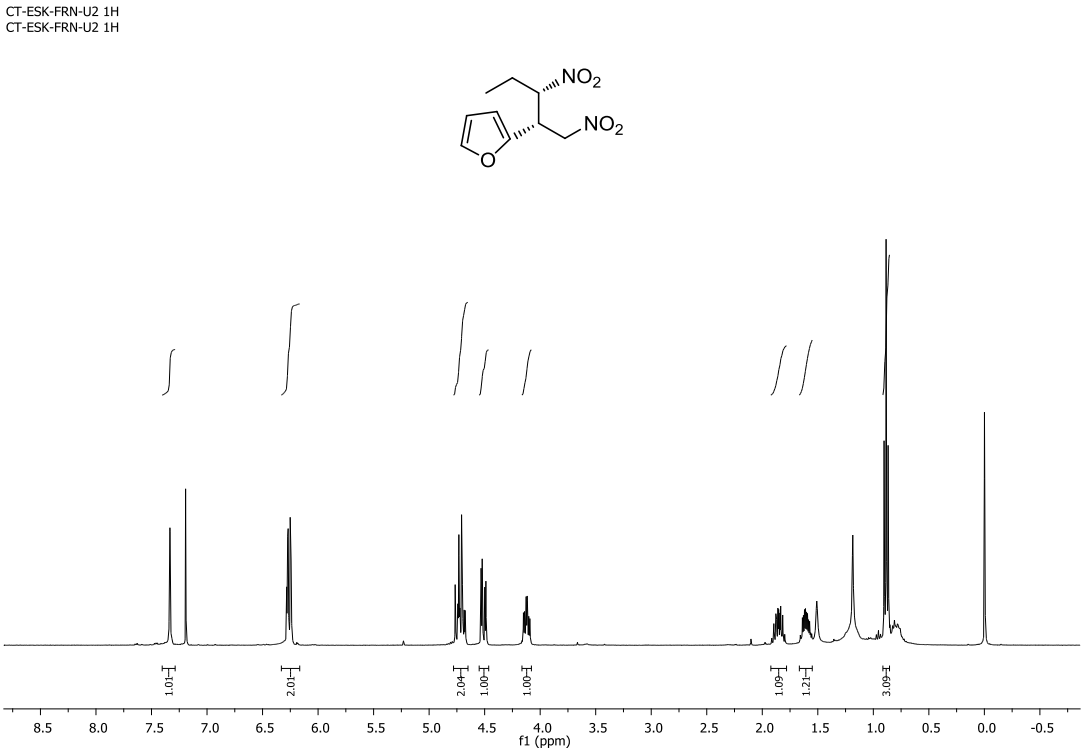


Figure A. 23. ^{1}H NMR spectrum of *anti*-diastereomer of compound **39h**

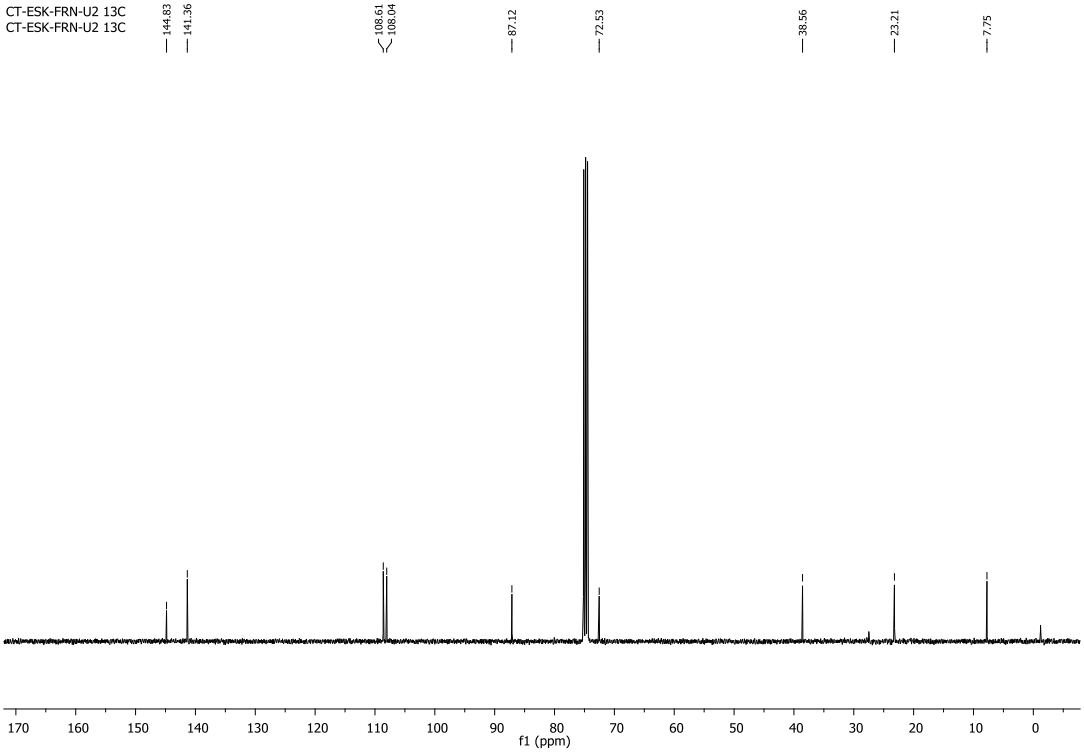


Figure A. 24. ^{13}C NMR spectrum of *anti*-diastereomer of compound **39h**

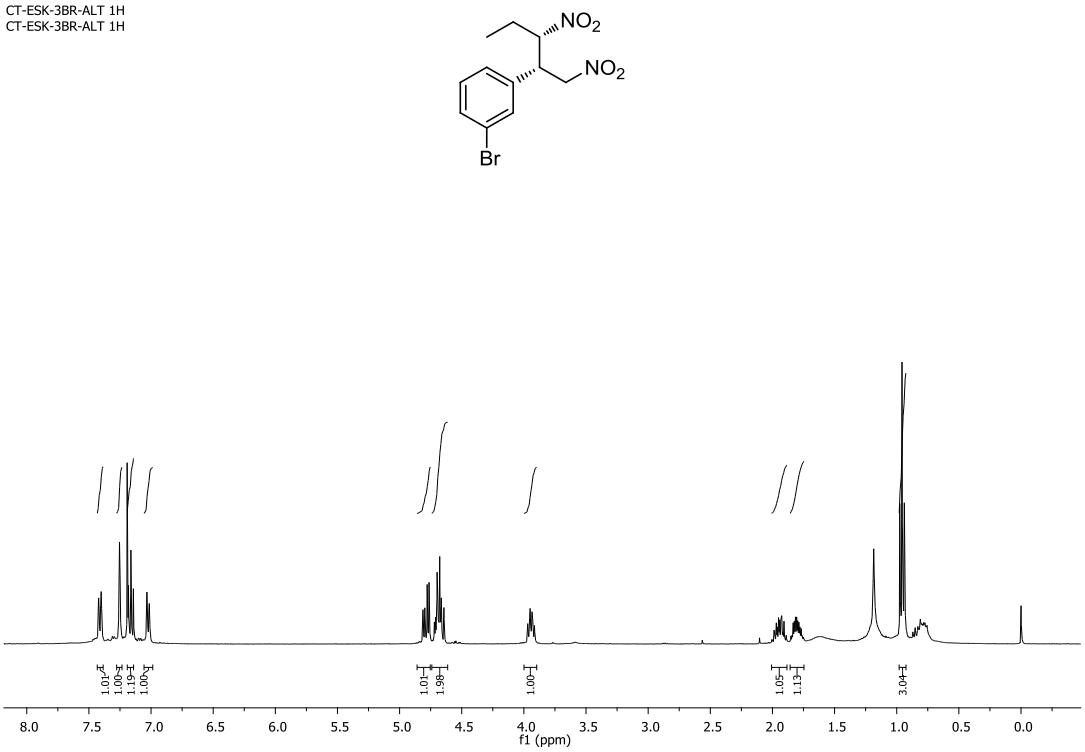


Figure A. 25. ^{1}H NMR spectrum of compound **39i**

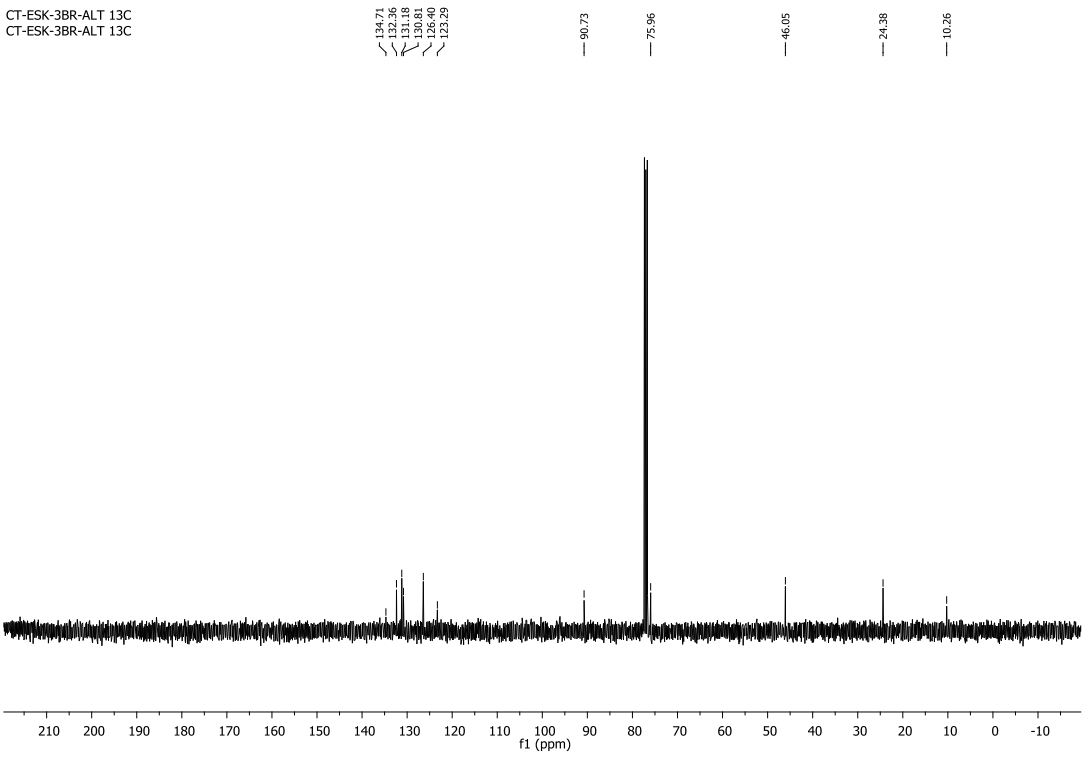


Figure A. 26. ^{13}C NMR spectrum of compound **39i**

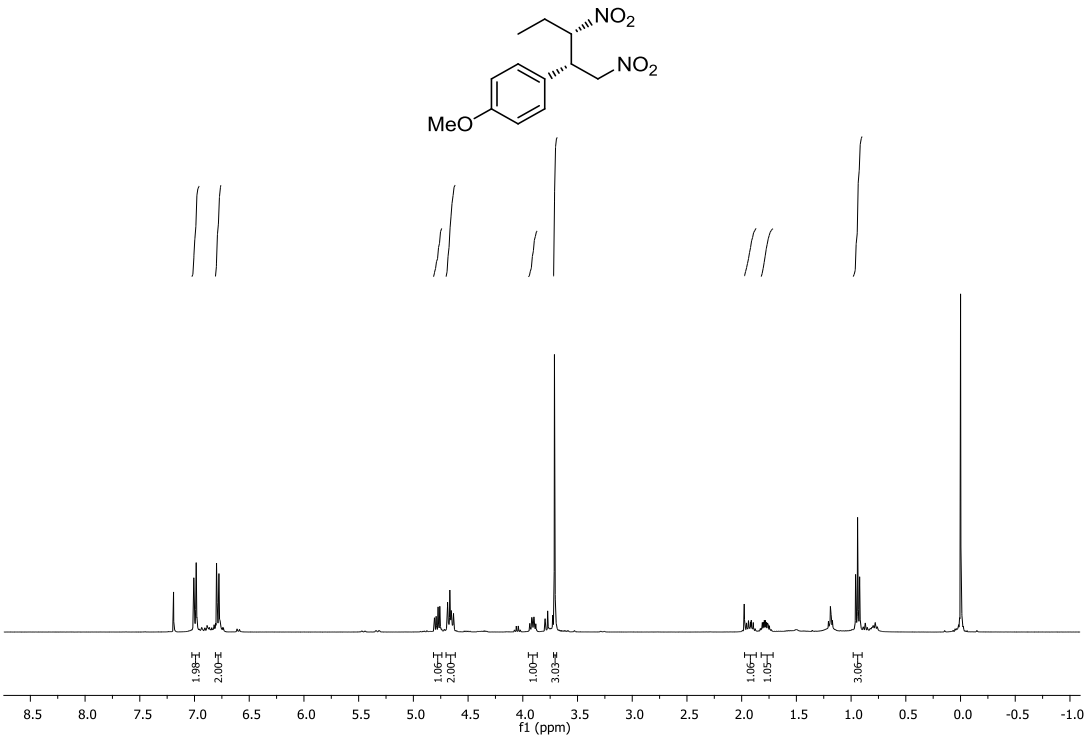


Figure A. 27. ^{1}H NMR spectrum of compound **39j**

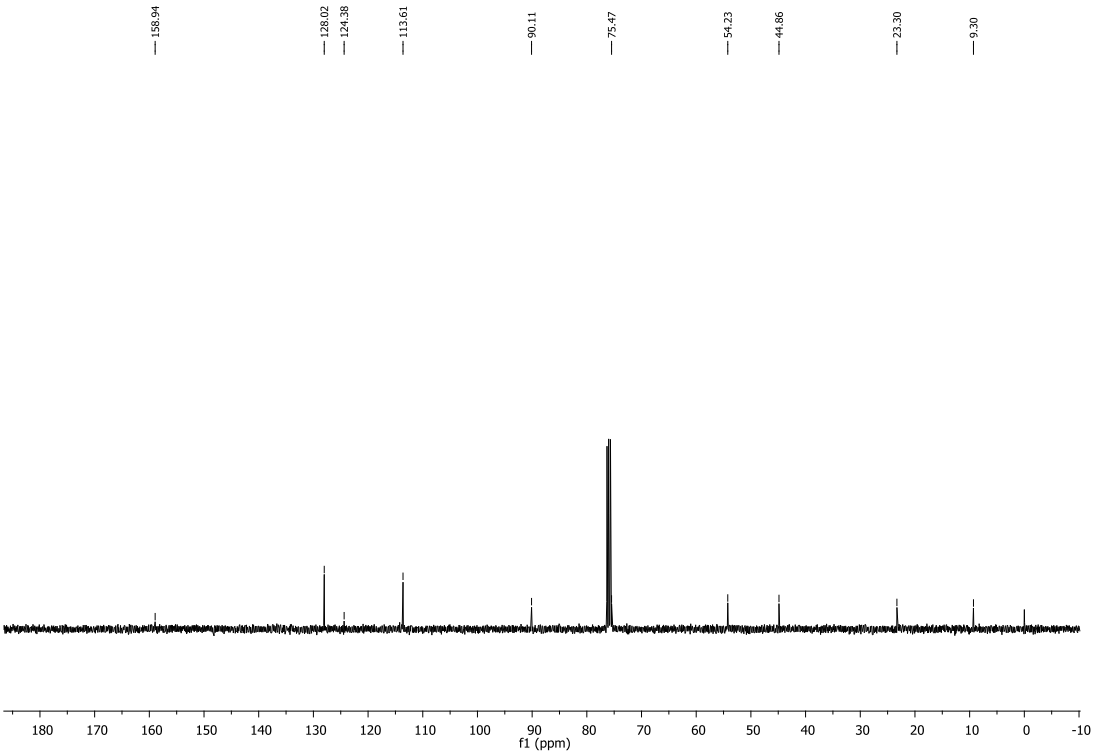


Figure A. 28. ^{13}C NMR spectrum of compound **39j**

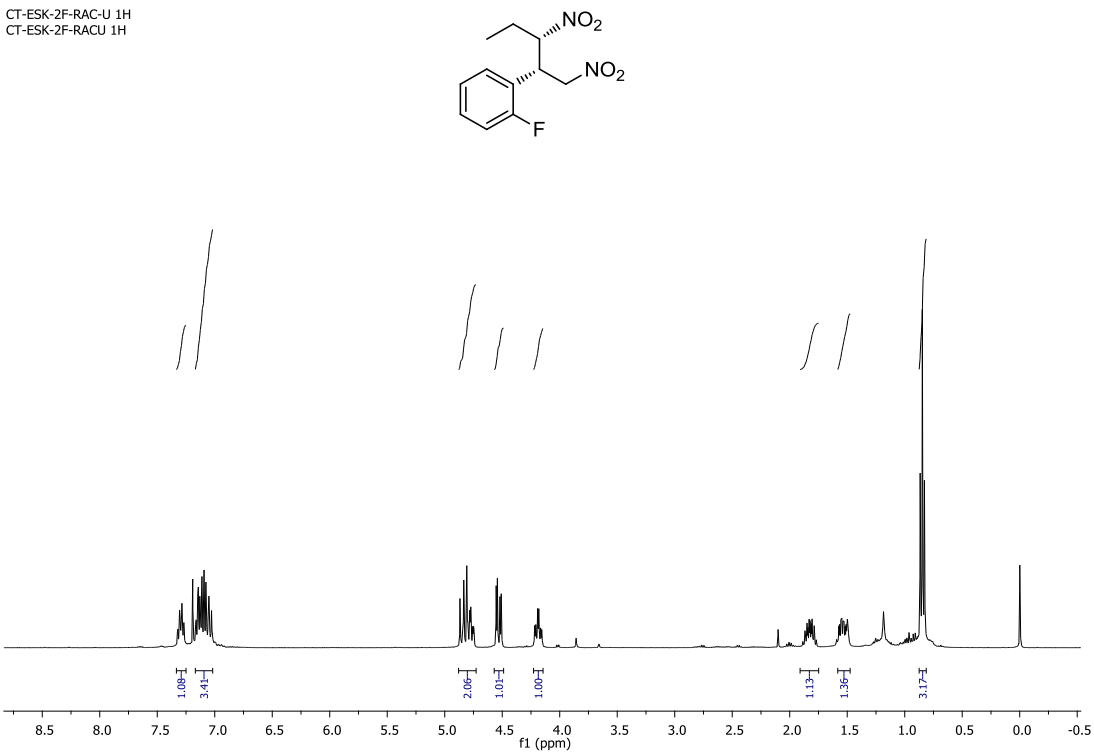


Figure A. 29. ^{1}H NMR spectrum of *anti*-diastereomer of compound **39k**

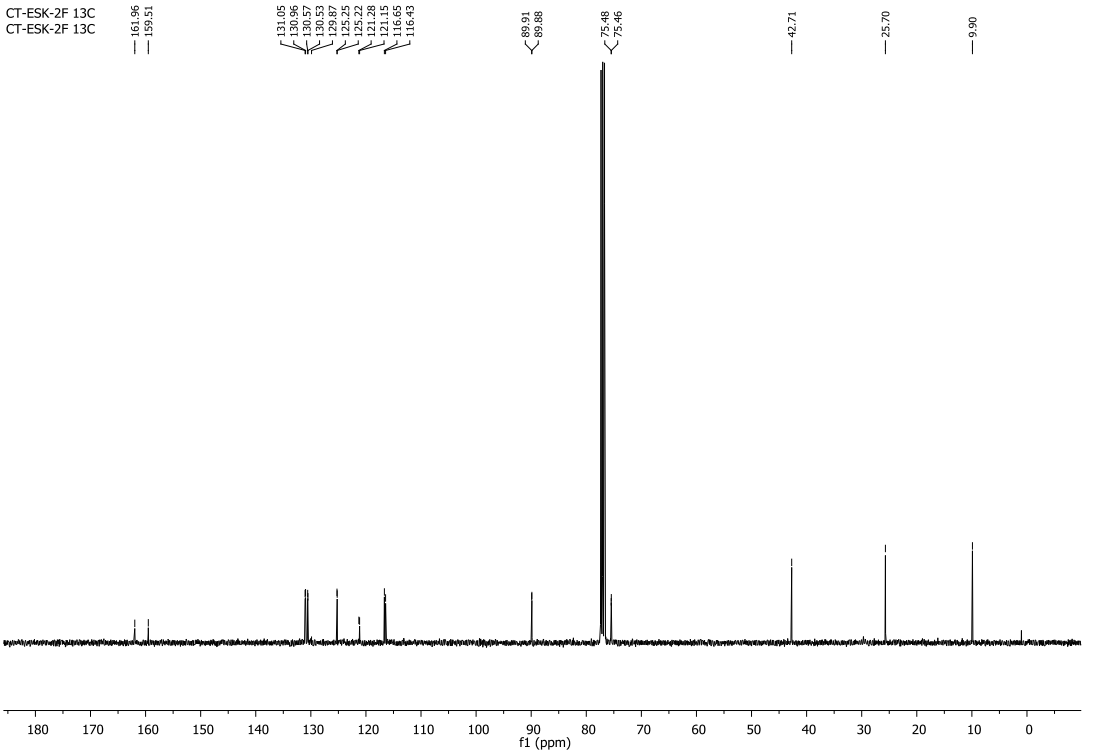


Figure A. 30. ^{13}C NMR spectrum of *anti*-diastereomer of compound **39k**

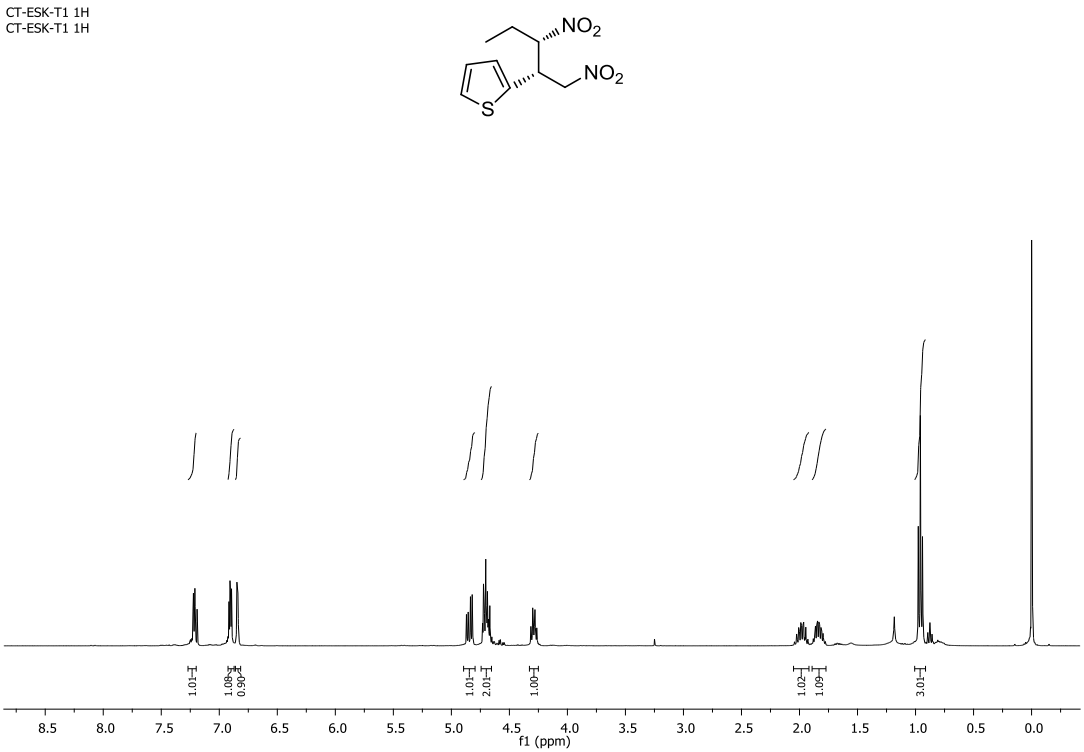


Figure A. 31. ^{1}H NMR spectrum of compound **39l**

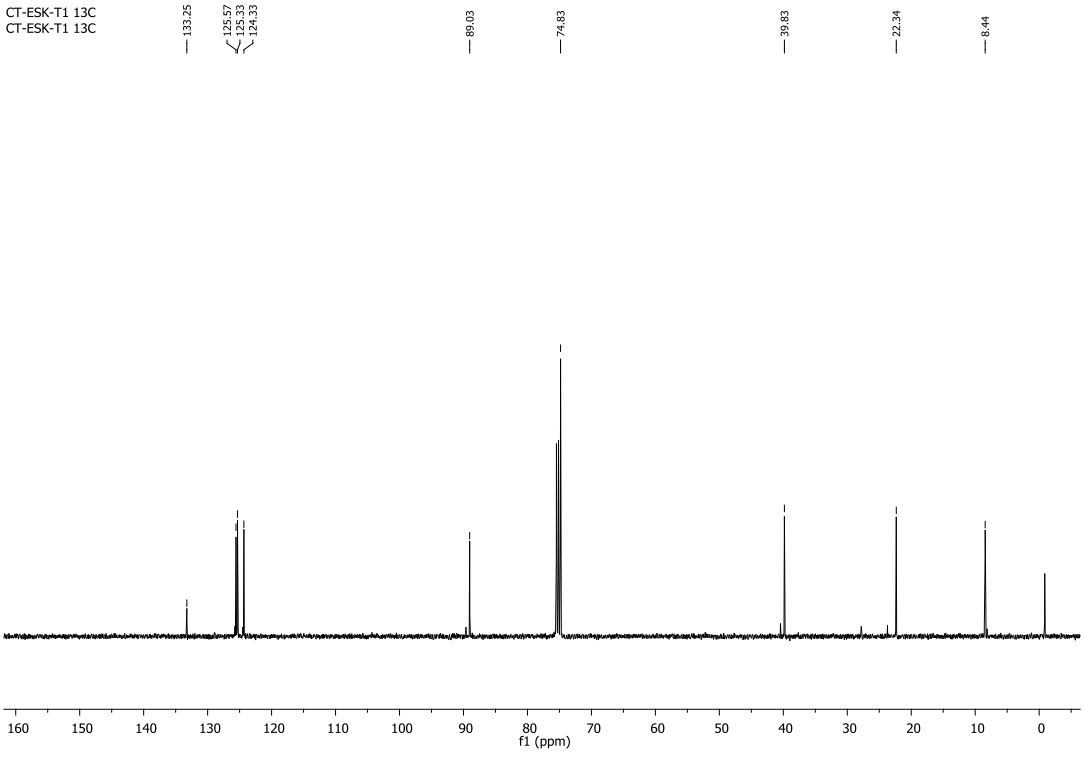


Figure A. 32. ^{13}C NMR spectrum of compound **39l**

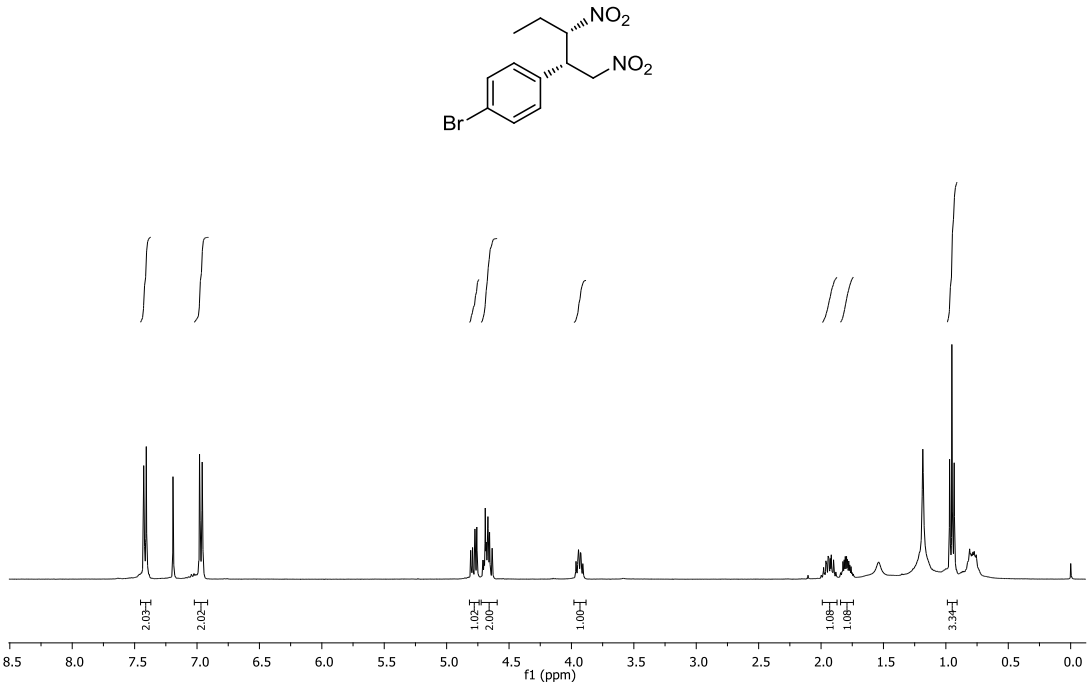


Figure A. 33. ^{1}H NMR spectrum of compound **39m**

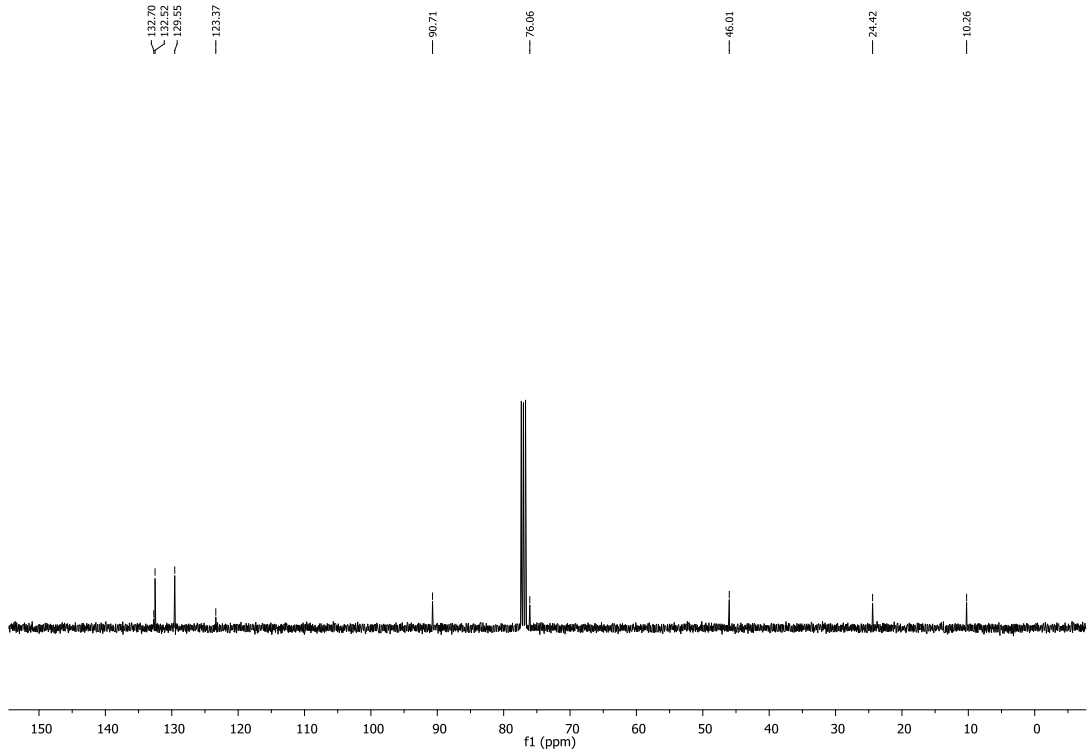


Figure A. 34. ^{13}C NMR spectrum of compound **39m**

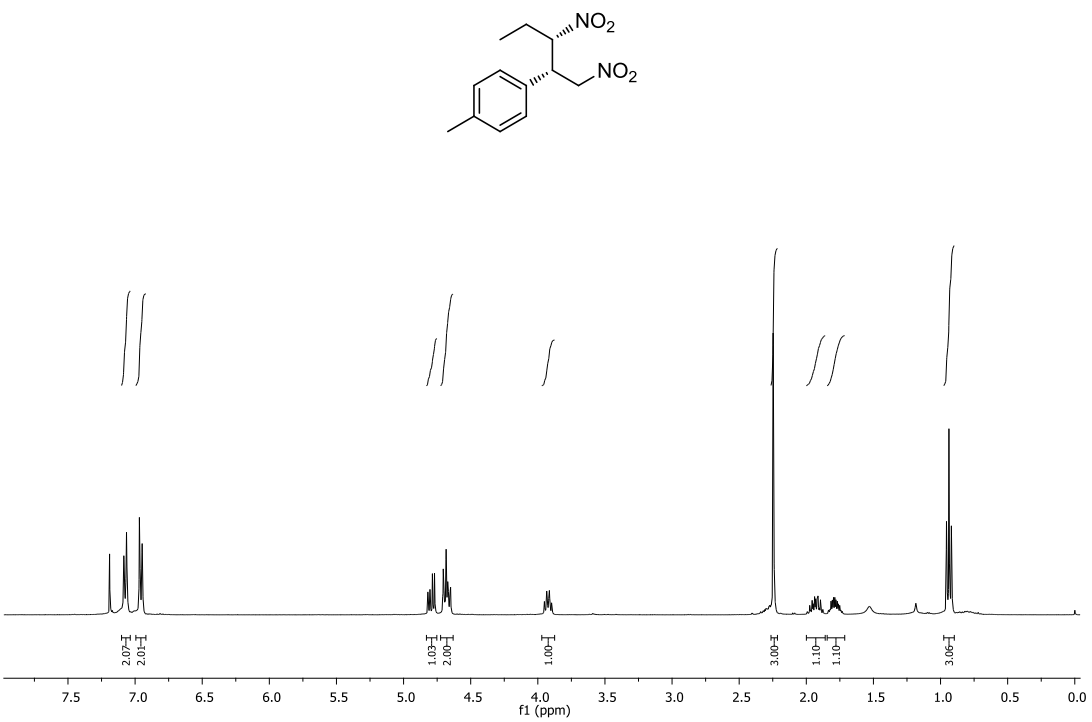


Figure A. 35. ^{1}H NMR spectrum of compound **39n**

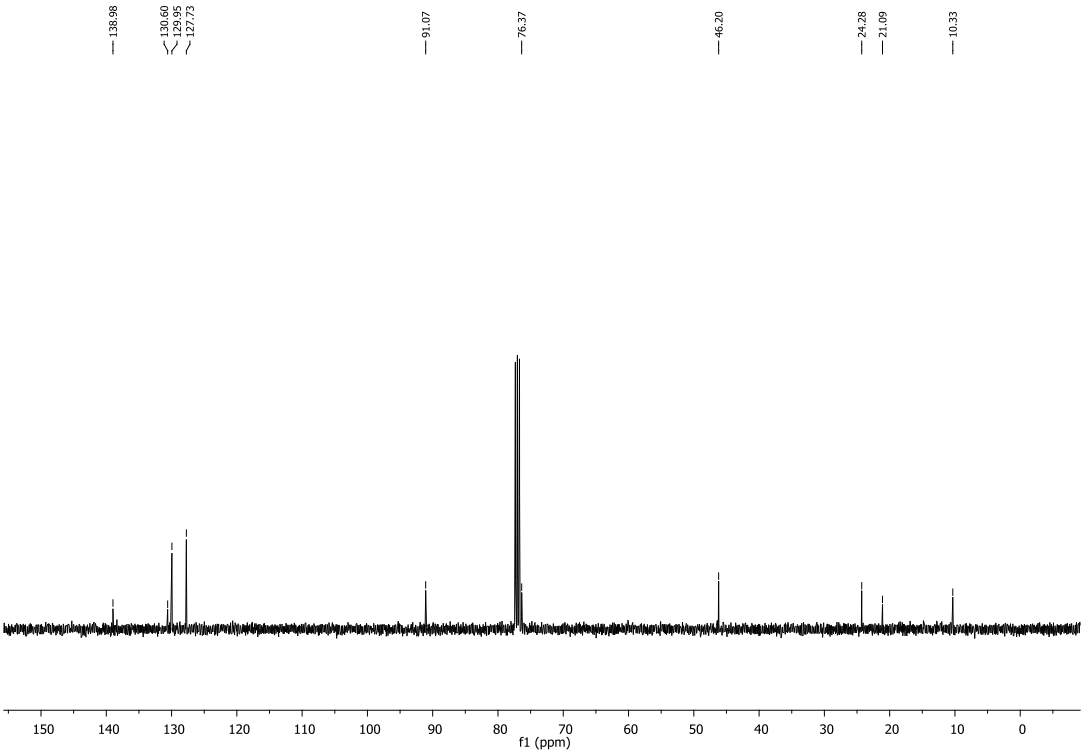
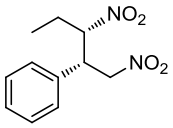


Figure A. 36. ^{13}C NMR spectrum of compound **39n**



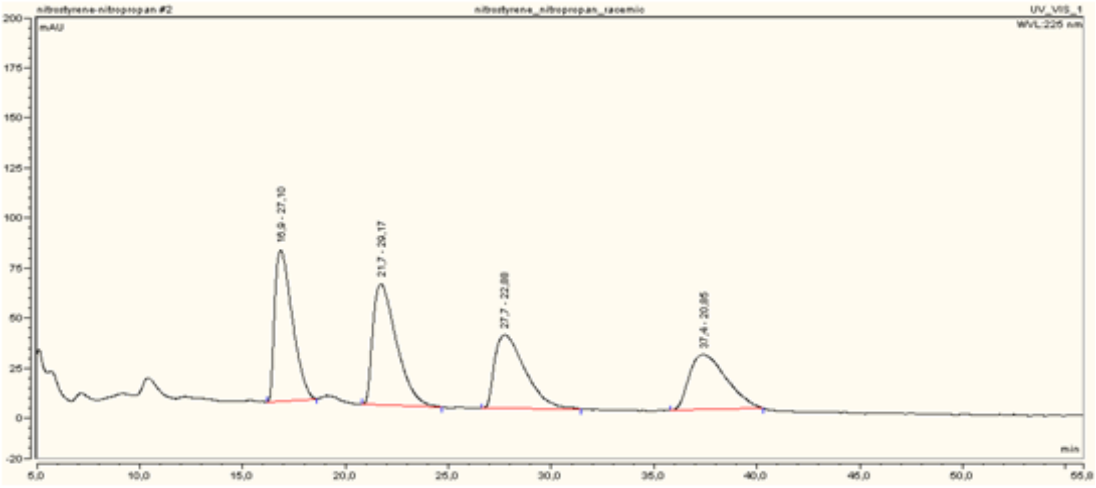


Figure A. 37. HPLC chromatogram of diastereomeric mixture of **rac-39**

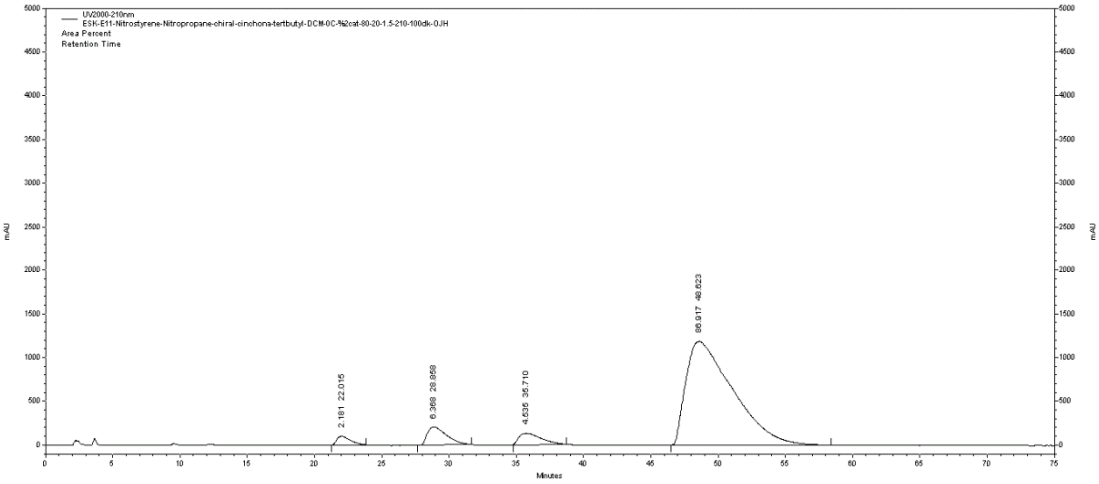
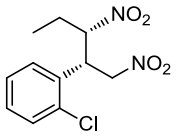


Figure A. 38. HPLC chromatogram of enantiomerically enriched product **39**



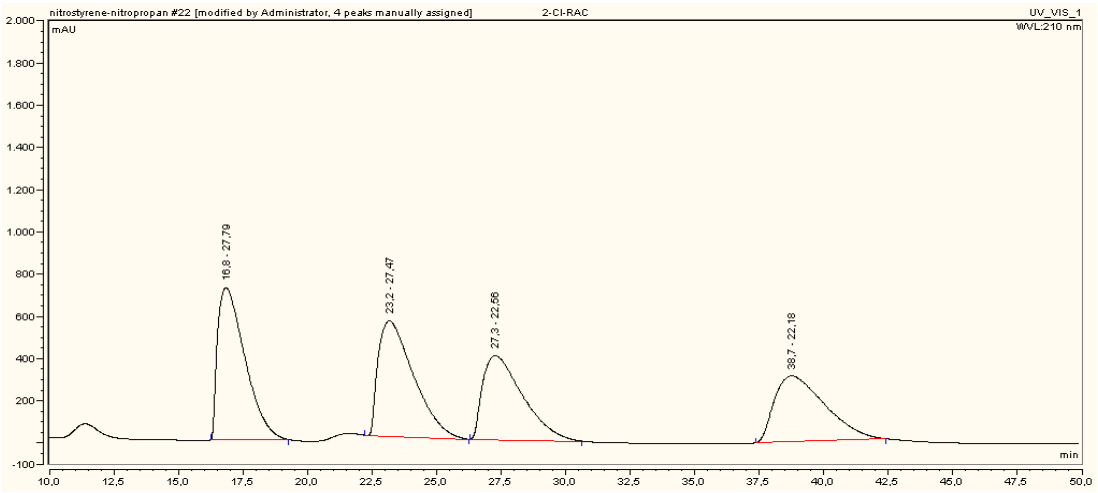


Figure A. 39. HPLC chromatogram of diastereomeric mixture of **rac-39a**

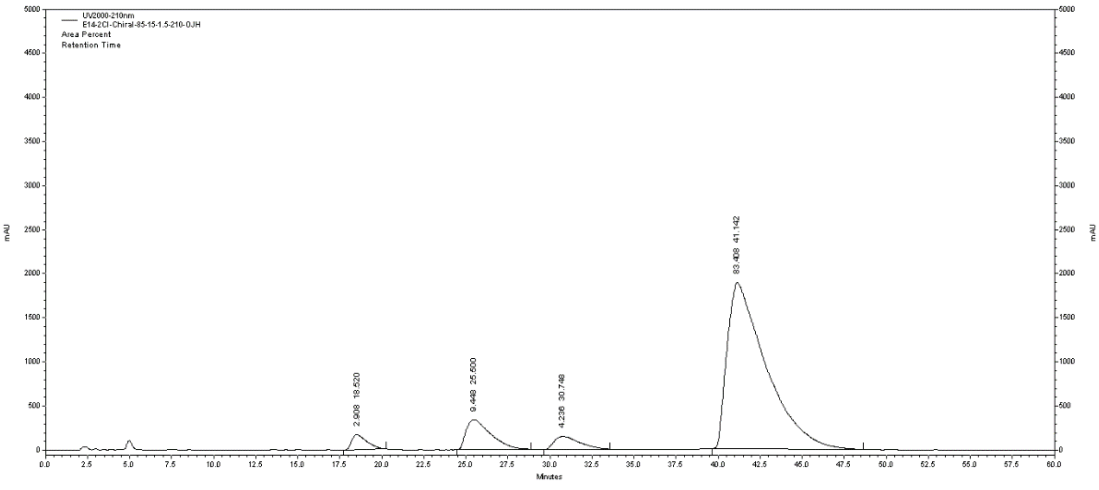
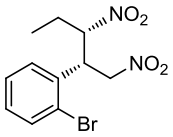


Figure A. 40. HPLC chromatogram of enantiomerically enriched **39a**



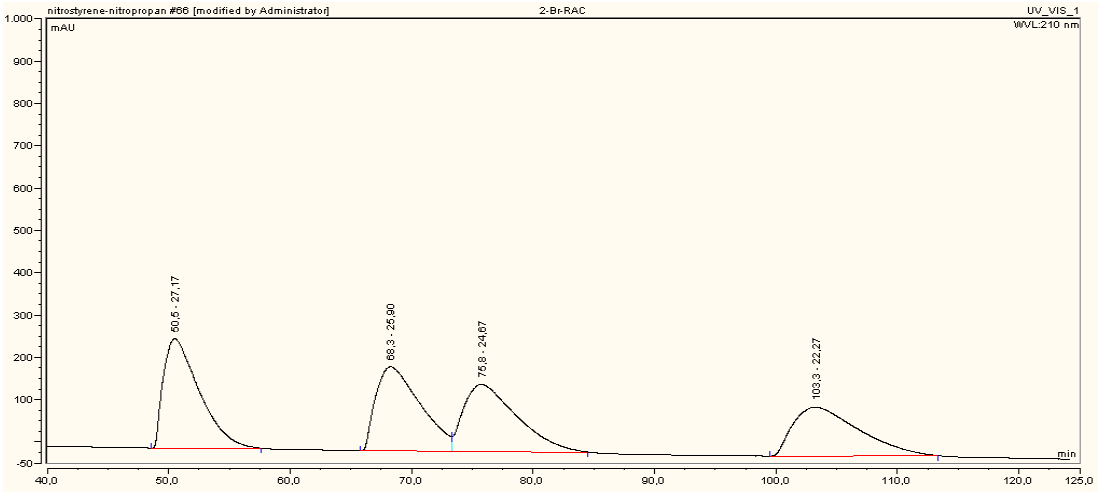


Figure A. 41. HPLC chromatogram of diastereomeric mixture of **rac-39b**

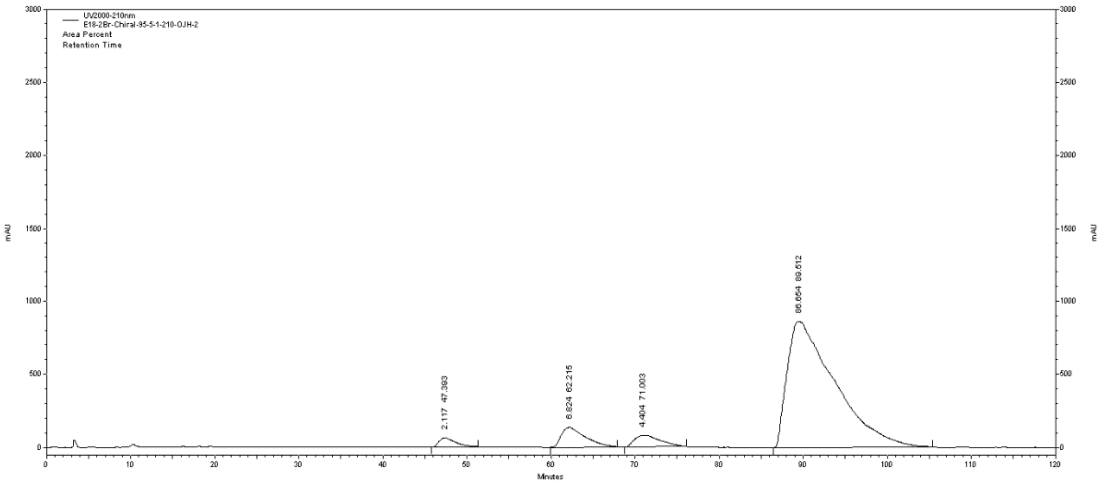
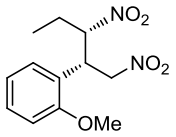


Figure A. 42. HPLC chromatogram of enantiomerically enriched product **39b**



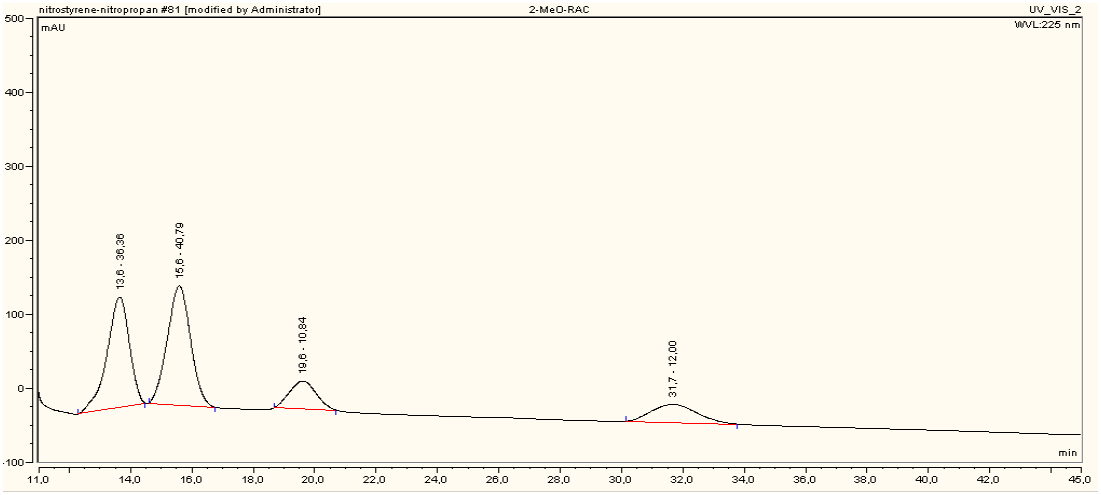


Figure A. 43. HPLC chromatogram of diastereomeric mixture of **rac-39c**

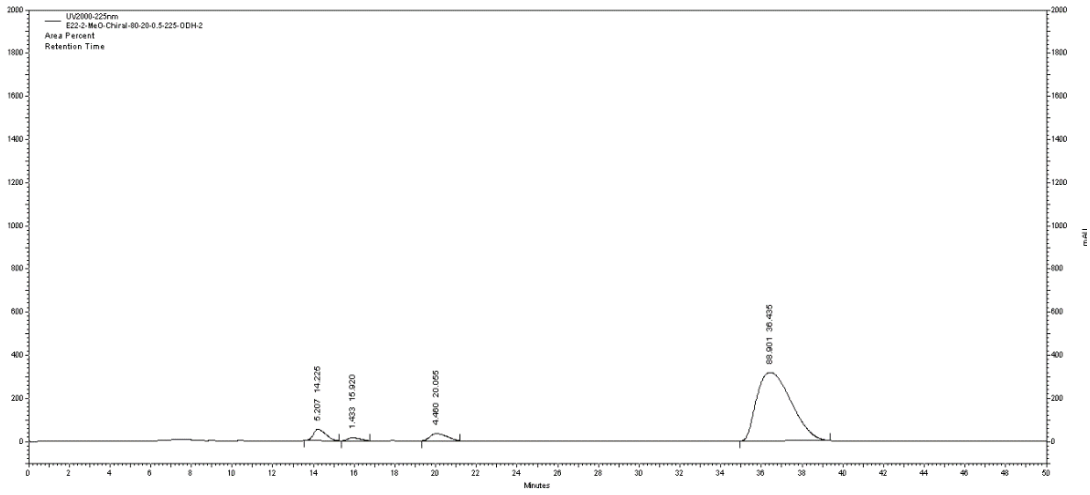
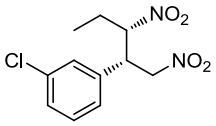


Figure A. 44. HPLC chromatogram of enantiomerically enriched product **39c**



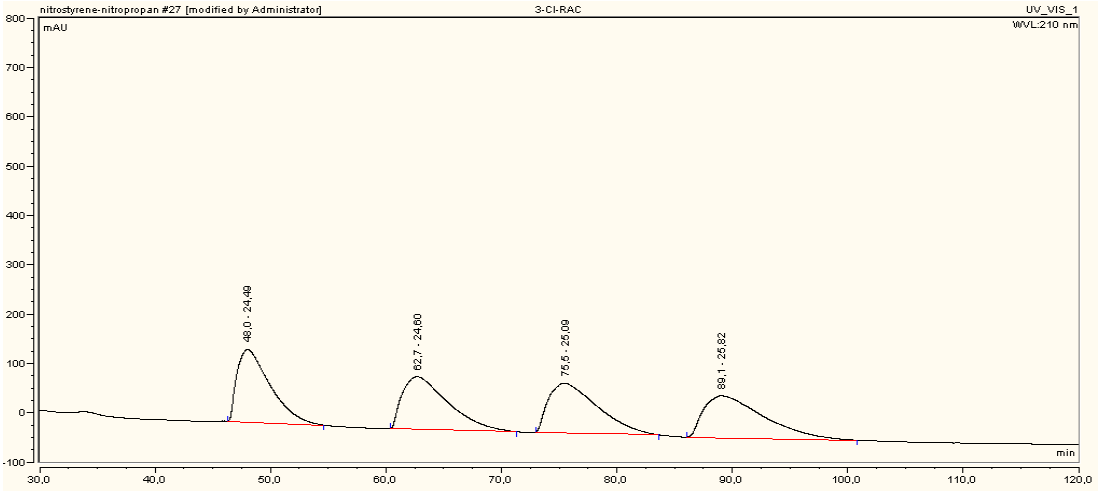


Figure A. 45. HPLC chromatogram of diastereomeric mixture of **rac-39d**

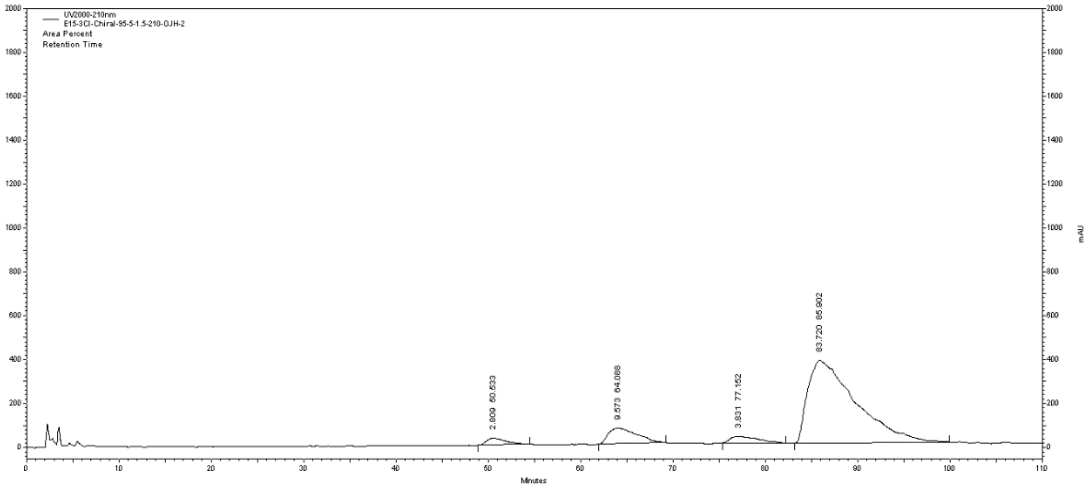
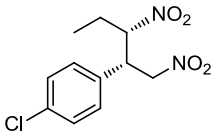


Figure A. 46. HPLC chromatogram of enantiomerically enriched product **39d**



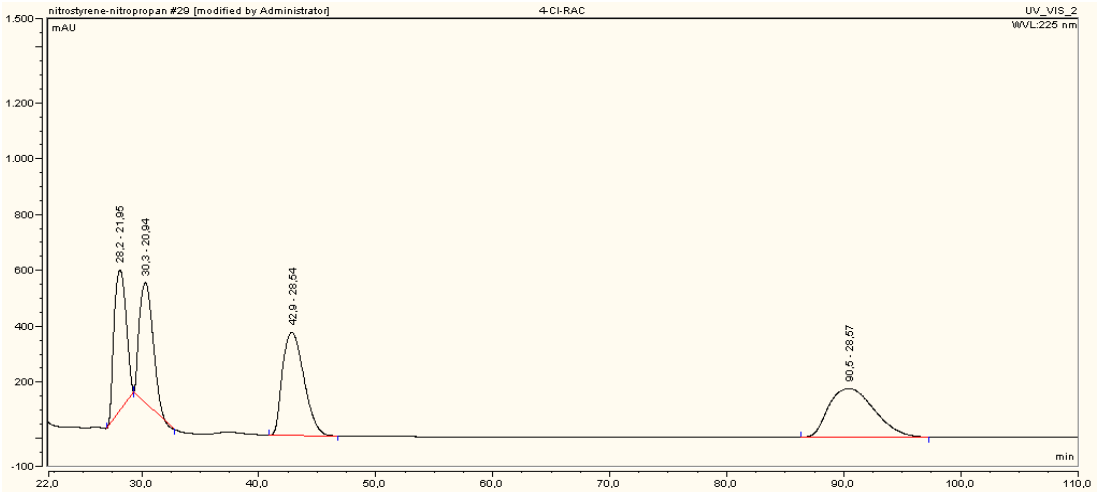


Figure A. 47. HPLC chromatogram of diastereomeric mixture of **rac-39e**

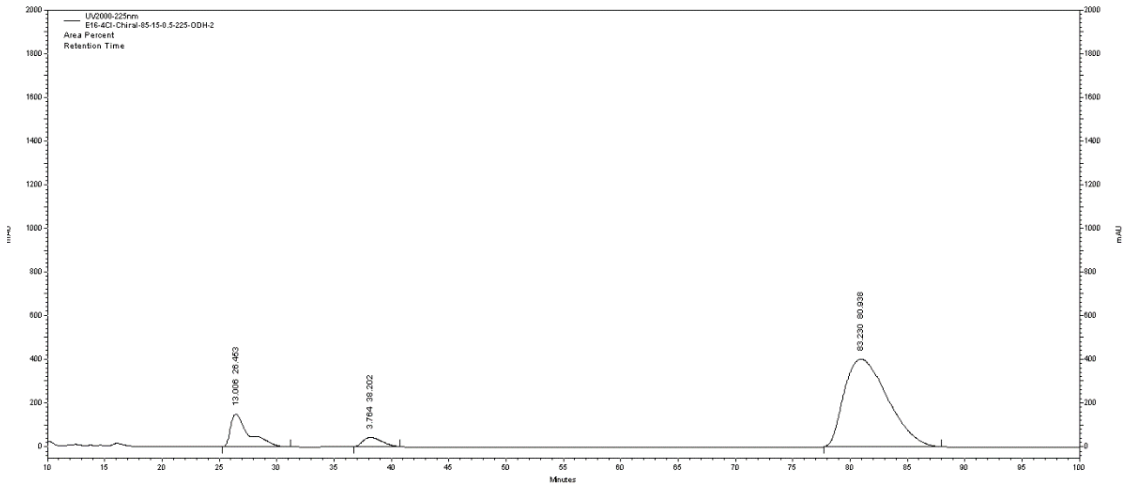
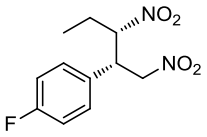


Figure A. 48. HPLC chromatogram of enantiomerically enriched product **39e**



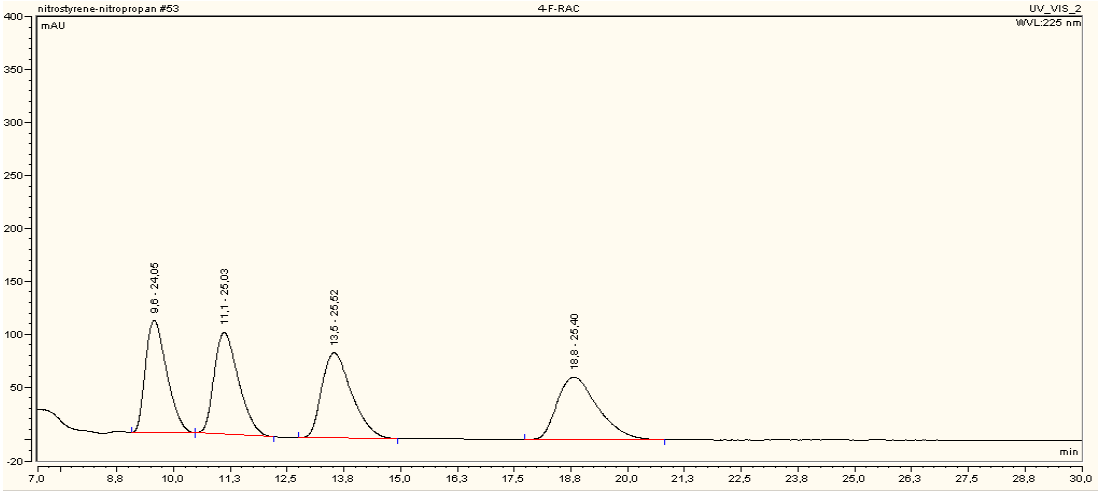


Figure A. 49. HPLC chromatogram of diastereomeric mixture of **rac-39f**

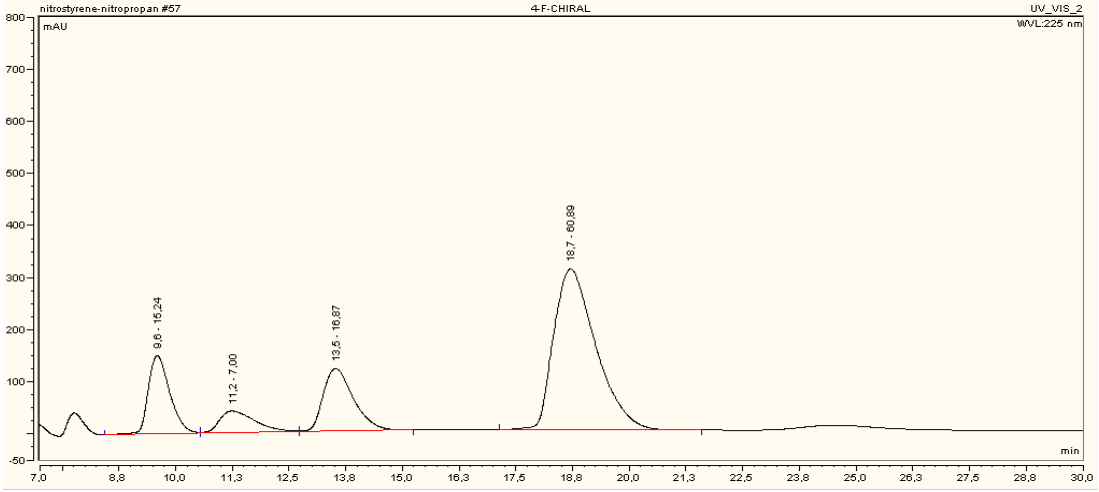
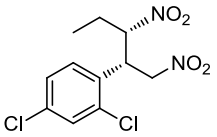


Figure A. 50. HPLC chromatogram of enantiomerically enriched product **39f**



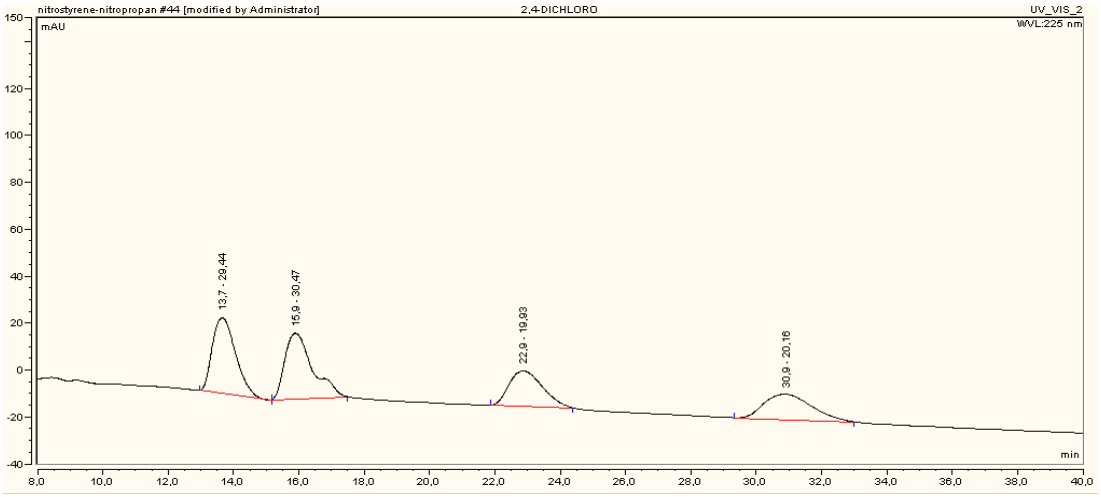


Figure A. 51. HPLC chromatogram of diastereomeric mixture of **rac-39g**

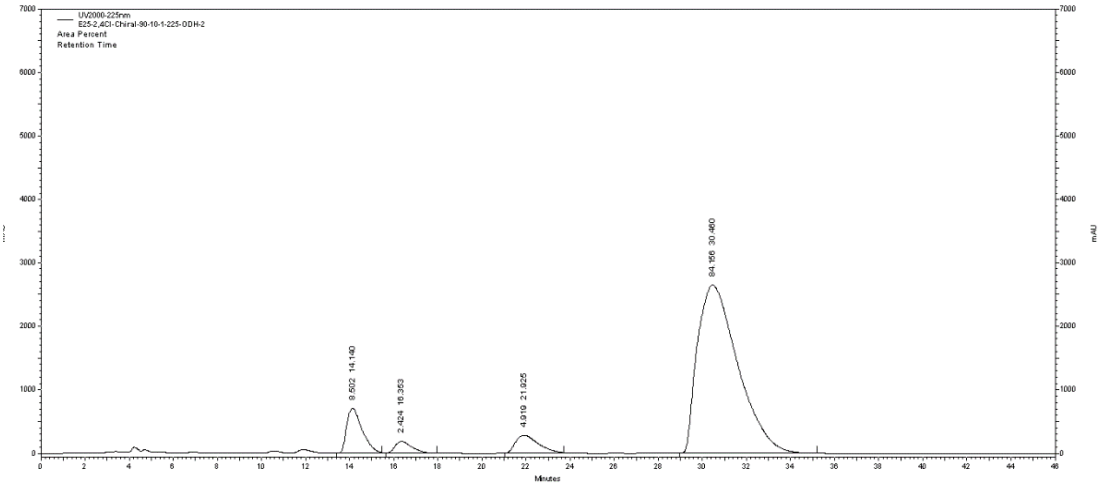
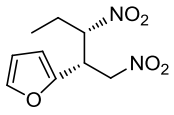


Figure A. 52. HPLC chromatogram of enantiomerically enriched product **39g**



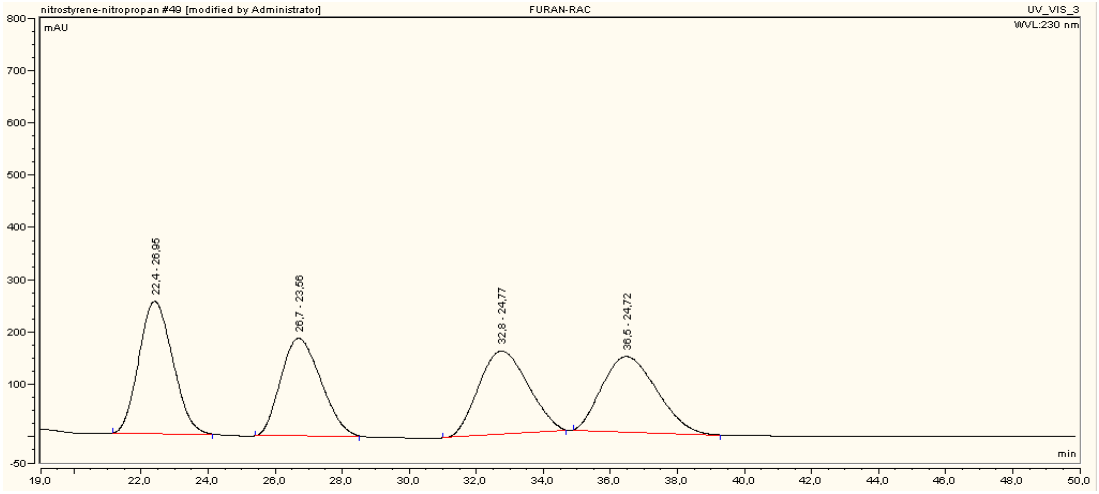


Figure A. 53. HPLC chromatogram of diastereomeric mixture of **rac-39h**

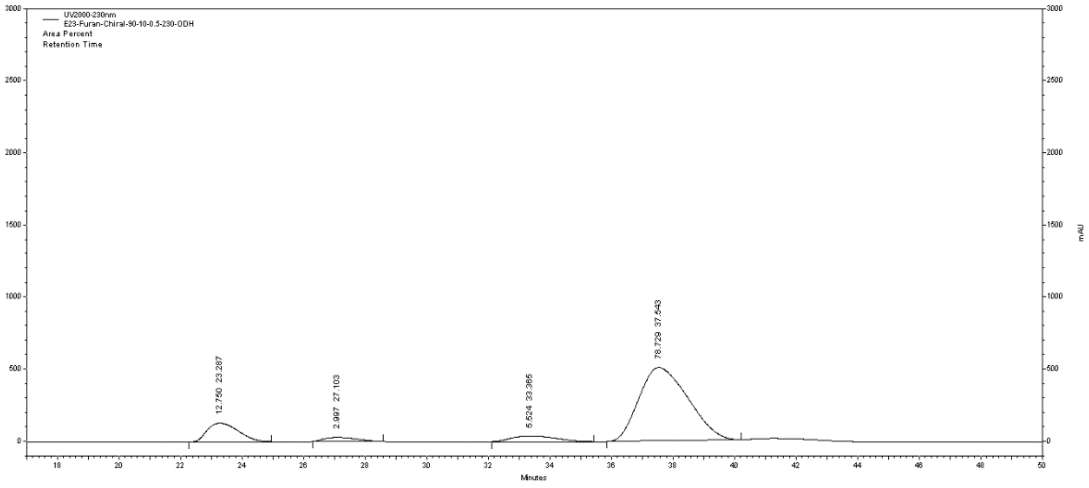
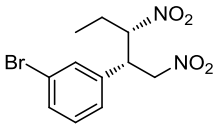


Figure A. 54. HPLC chromatogram of enantiomerically enriched product **39h**



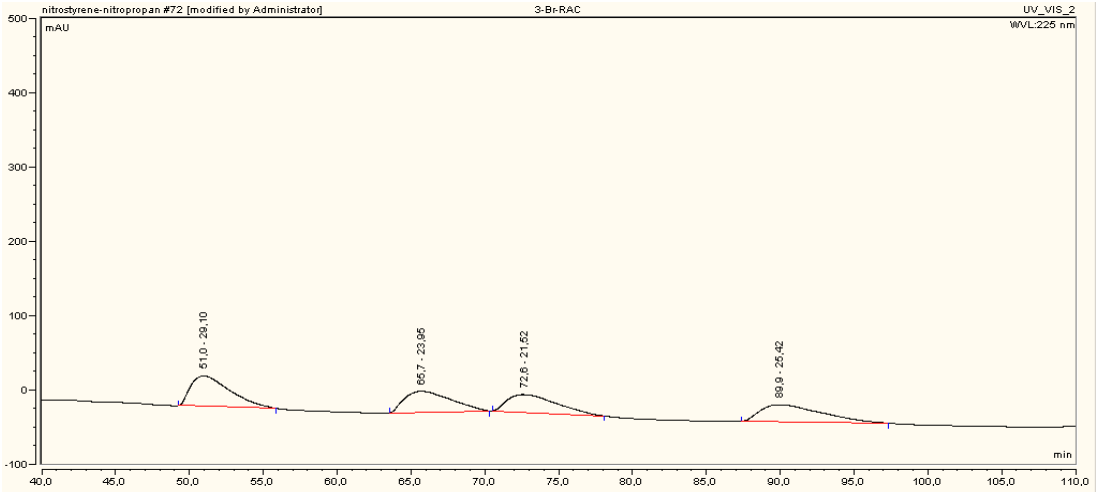


Figure A. 55. HPLC chromatogram of diastereomeric mixture of **rac-39i**

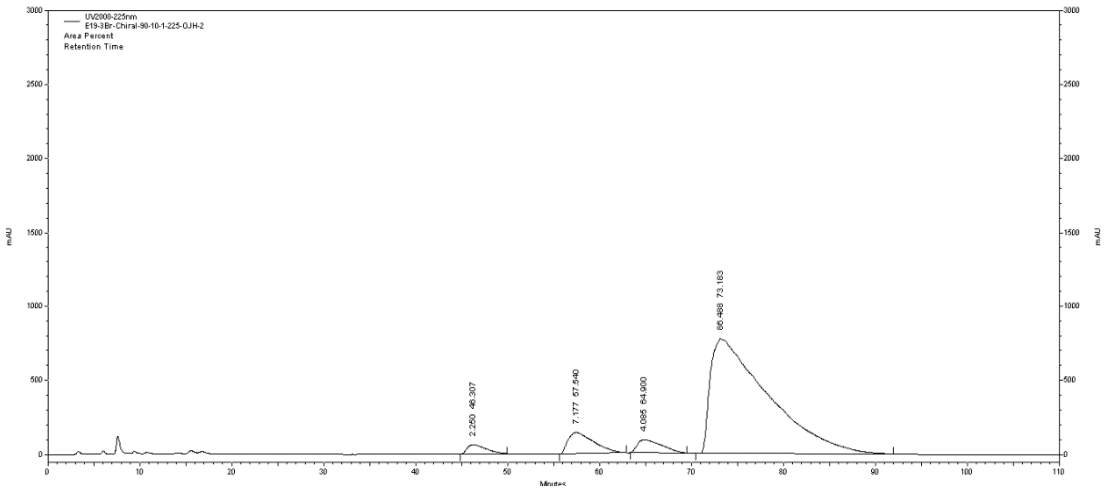
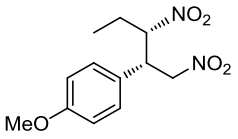


Figure A. 56. HPLC chromatogram of enantiomerically enriched product **39i**



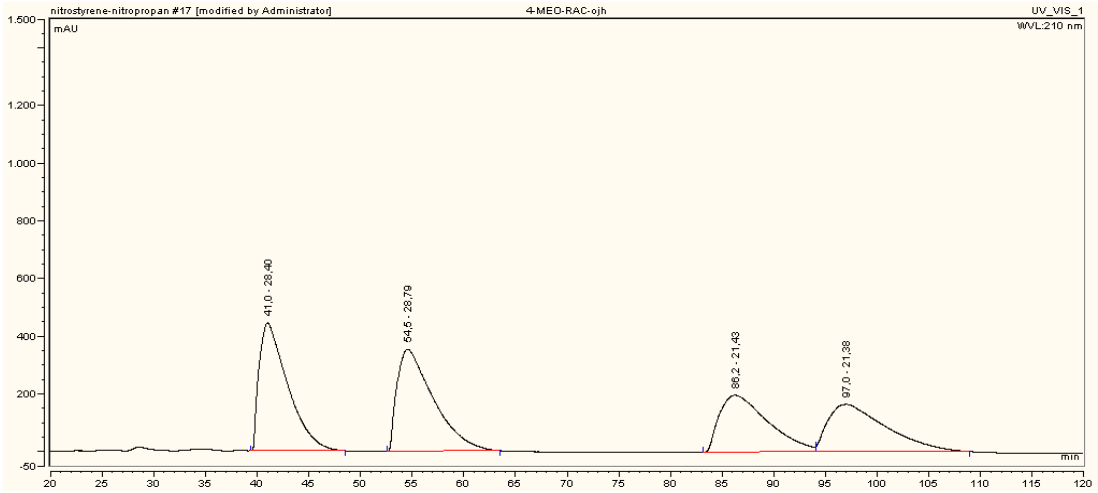


Figure A. 57. HPLC chromatogram of diastereomeric mixture of **rac-39j**

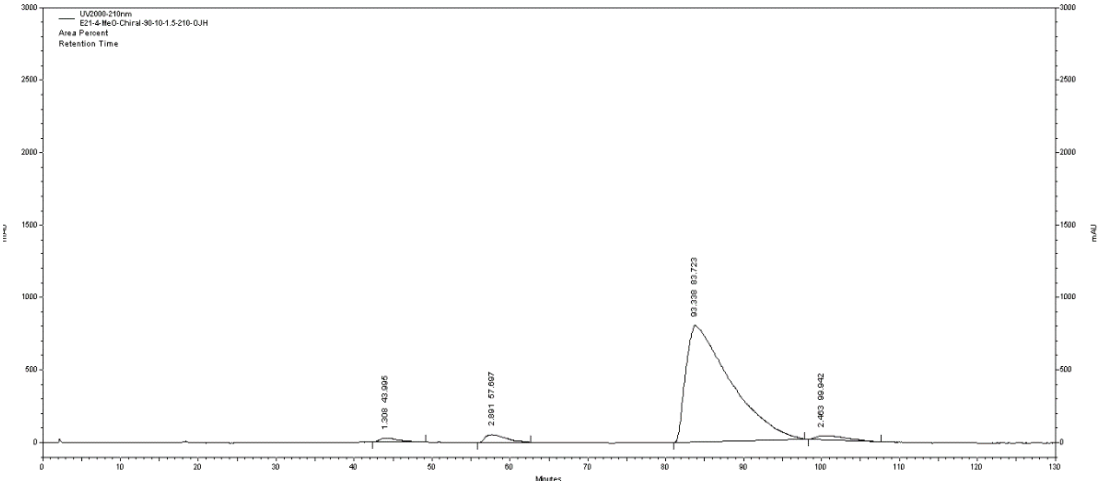
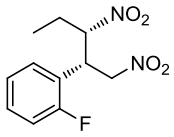


Figure A. 58. HPLC chromatogram of enantiomerically enriched product **39j**



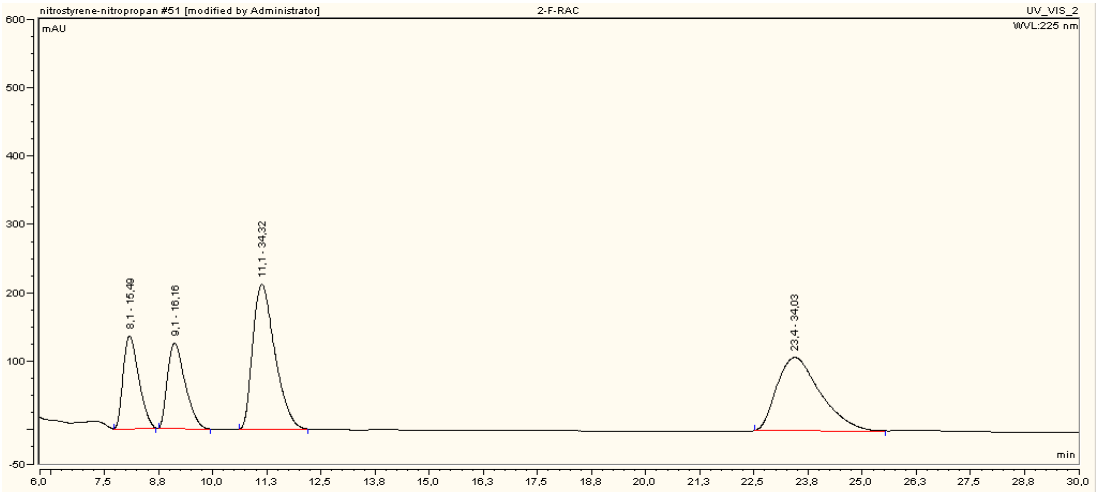


Figure A. 59. HPLC chromatogram of diastereomeric mixture of **rac-39k**

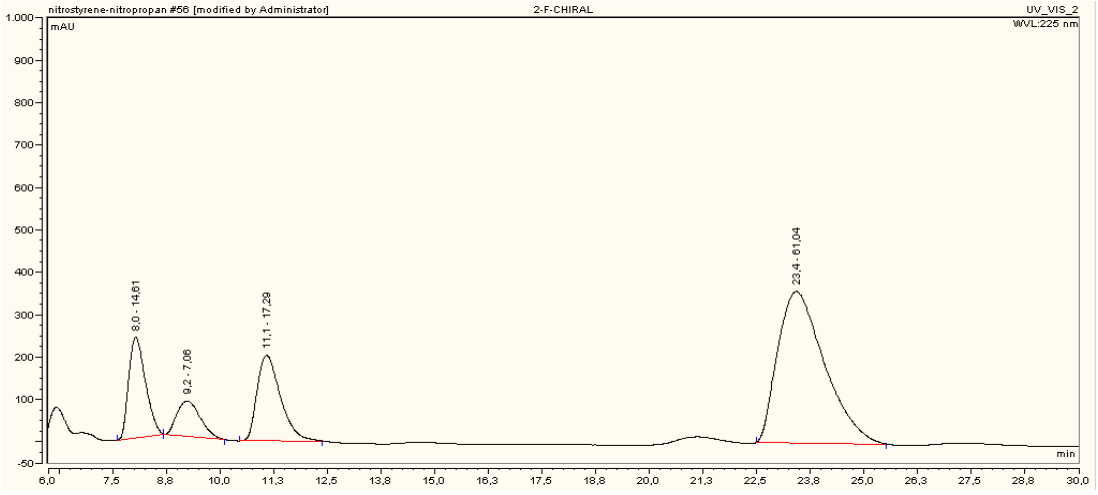
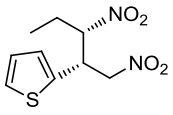


Figure A. 60. HPLC chromatogram of enantiomerically enriched product **39k**



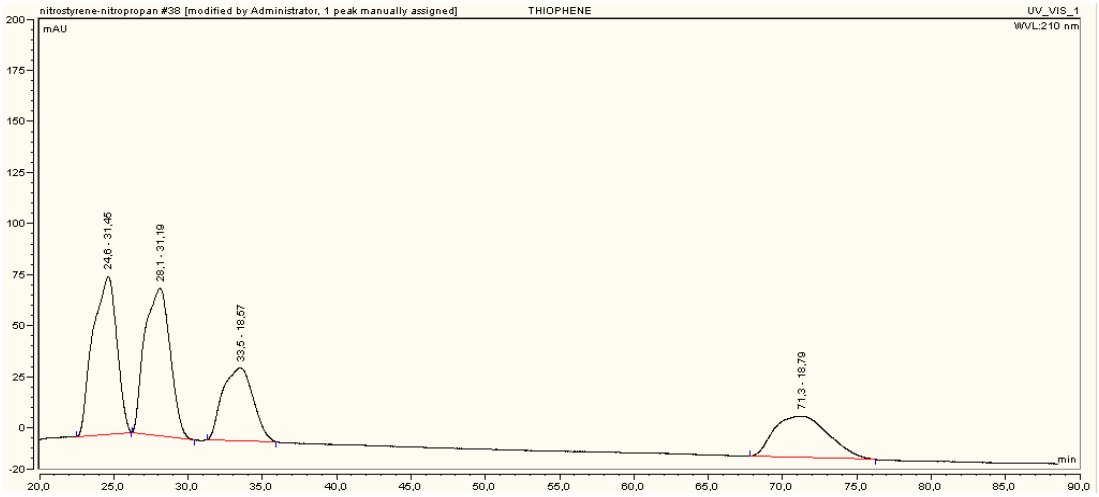


Figure A. 61. HPLC chromatogram of diastereomeric mixture of **rac-39l**

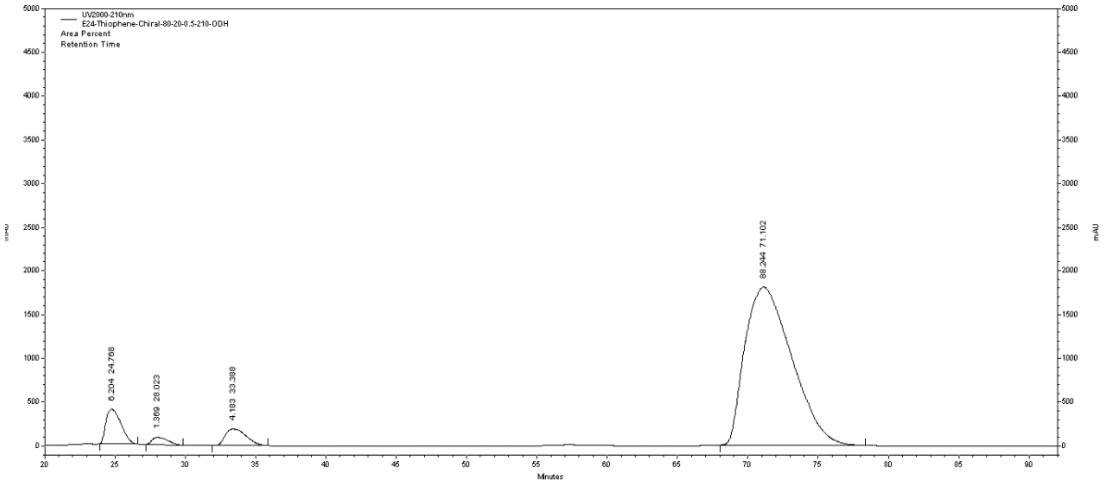
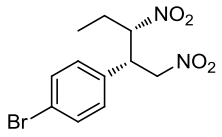


Figure A. 62. HPLC chromatogram of enantiomerically enriched product **39l**



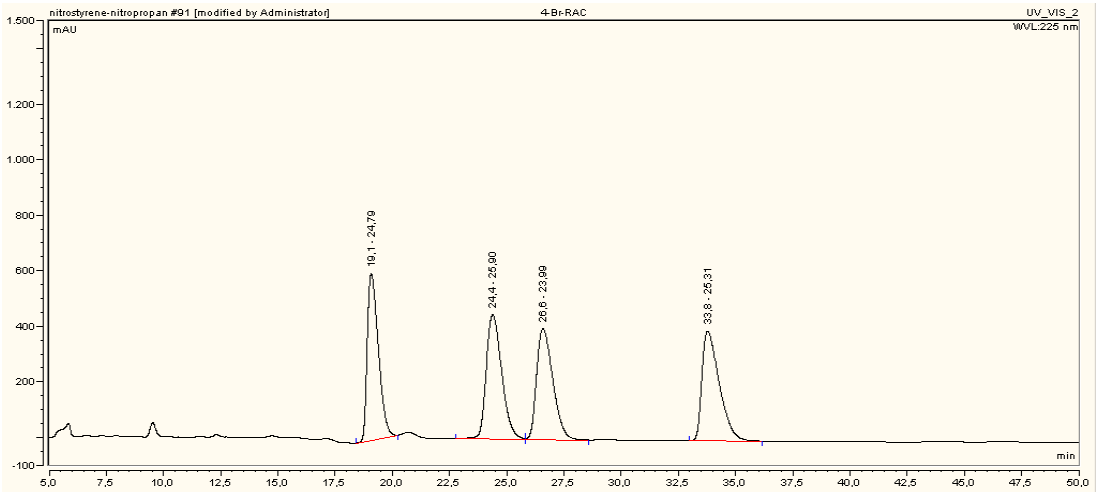


Figure A. 63. HPLC chromatogram of diastereomeric mixture of **rac-39m**

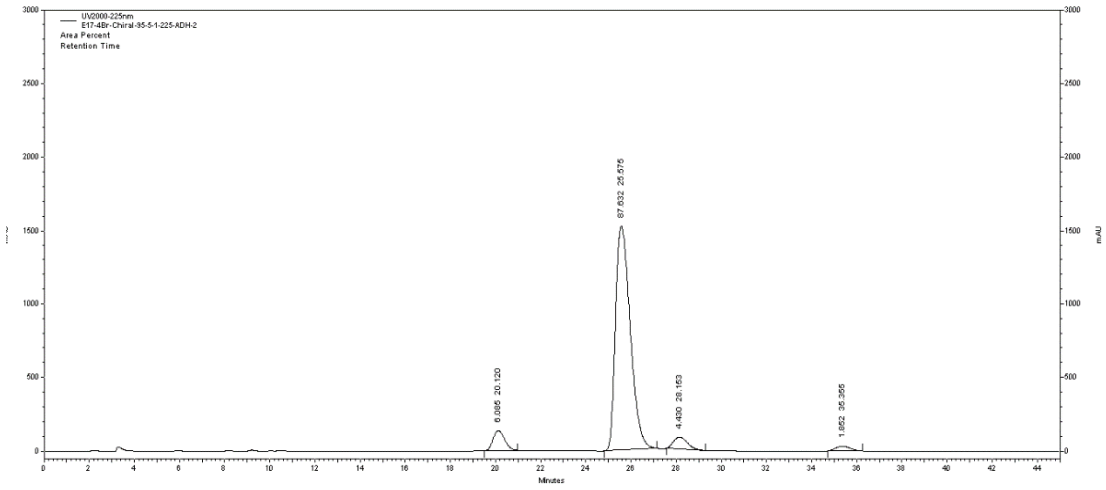
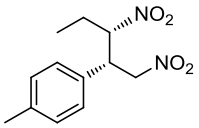


Figure A. 64. HPLC chromatogram of enantiomerically enriched product **39m**



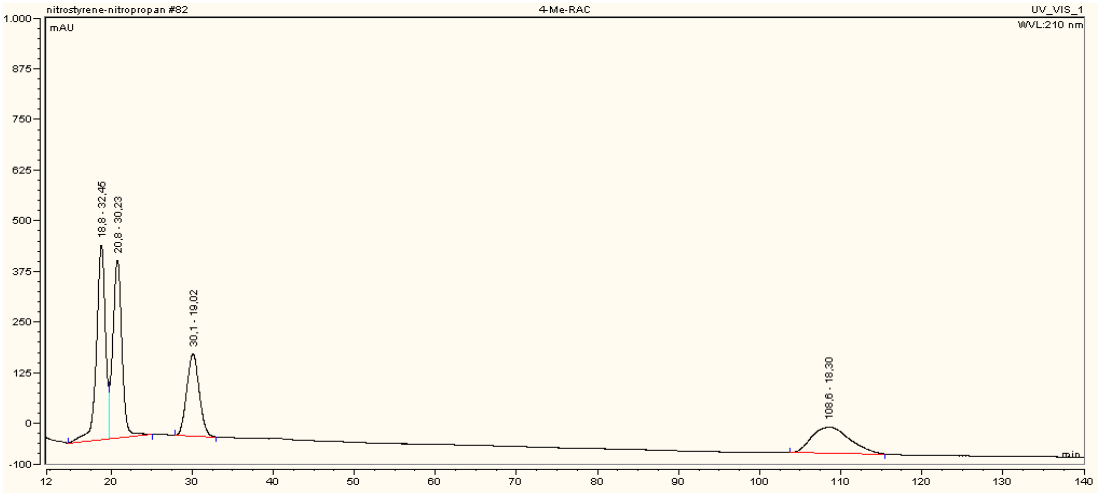


Figure A. 65. HPLC chromatogram of diastereomeric mixture of **rac-39n**

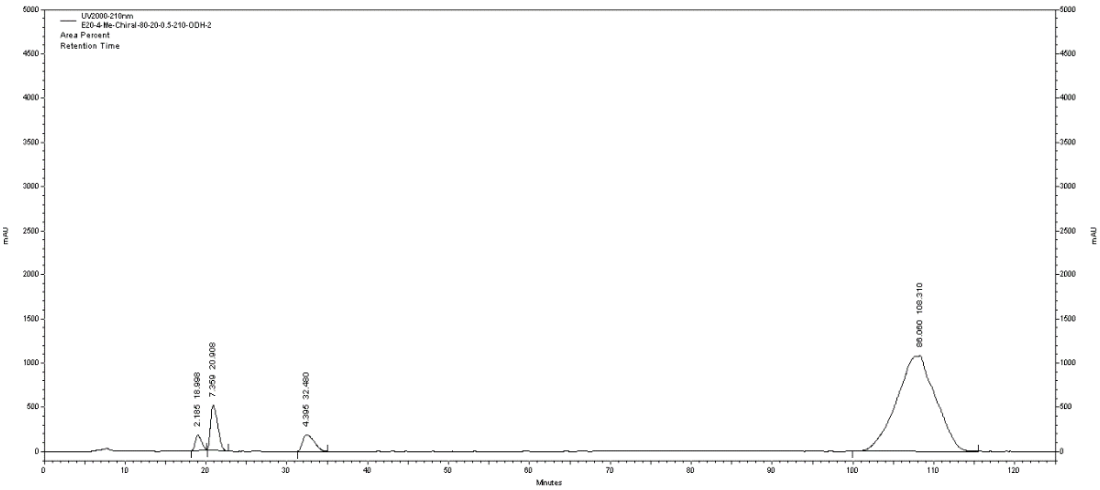


Figure A. 66. HPLC chromatogram of enantiomerically enriched product **39n**