BIFUNCTIONAL 2-AMINODMAP/THIOUREA CATALYZED ENANTIOSELECTIVE MICHAEL ADDITION OF THIOACETIC ACID TO *TRANS*-BETA-NITROSTYRENES

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BIFUNCTIONAL 2-AMINODMAP/THIOUREA CATALYZED ENANTIOSELECTIVE MICHAEL ADDITION OF THIOACETIC ACID TO TRANS-BETA-NITROSTYRENES

submitted by **ZEHRA KABASAKAL** in partial fulfillment of the requirements for the degree of **Master of Science in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Canan Özgen
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. İlker Özkan
Head of Department, **Chemistry** _____

Prof. Dr. Cihangir Tanyeli
Supervisor, **Chemistry Dept., METU** _____

Examining Committee Members:

Prof. Dr. Metin Zora
Chemistry Dept., METU _____

Prof. Dr. Cihangir Tanyeli
Chemistry Dept., METU _____

Prof. Dr. Özdemir Doğan
Chemistry Dept., METU _____

Assoc. Prof. Dr. Adnan Bulut
Chemistry Dept., Kırıkkale University _____

Assist. Prof. Dr. Salih Özçubukçu
Chemistry Dept., METU _____

Date: 20.11.2013

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Name, Last name: Zehra KABASAKAL

Signature:

ABSTRACT

BIFUNCTIONAL 2-AMINODMAP/THIOUREA CATALYZED ENANTIOSELECTIVE MICHAEL ADDITION OF THIOACETIC ACID TO *TRANS*-BETA-NITROSTYRENES

Kabasakal, Zehra
M.Sc. Department of Chemistry
Supervisor: Prof. Dr. Cihangir Tanyeli

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Michael addition reactions as an efficient method for carbon-carbon bond formations have been intensively explored in the context of enantioselective organocatalysis using aldehydes, ketones, 1,3-dicarbonyl compounds and nitroalkenes as donors. However, there are very few studies using thiol derivative as a nucleophile. In this thesis, enantioselective Michael addition reaction of thioacetic acid as Michael donor and 10 trans-*β*-nitrostyrene derivatives as Michael acceptors have been studied. The products of this reaction are very important candidates for the synthesis of chiral 1,2-aminothiols. Bifunctional acid/base type organocatalyst named as 2-aminoDMAP/thiourea was found as the best organocatalyst. In the first part of the study, optimization studies were done by screening different parameters such as temperature, solvent and catalyst loading. By applying the optimized reaction conditions, thioacetic acid underwent Michael addition reactions with 10 *trans*-β-nitrostyrene derivatives to afford enantiomerically enriched thioester type addition products up to 96% ee.

Keywords: Michael addition, asymmetric organocatalysis, trans-*β*-nitrostyrenes, bifunctional thiourea.

ÖZ

BİFONKSİYONEL 2-AMİNODMAP/TiYOÜRE KATALİZÖRLÜĞÜNDE TiYOASETİK ASİDİN TRANS-*BETA*-NİTROSTİREN TÜREVLERİNE ENANTİOSEÇİCİ MICHAEL KATILMASI

Kabasakal, Zehra
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

November 2013, 62 sayfa

Michael tipi katılma tepkimeleri karbon-karbon bağı oluşturmak için kullanılan etkili bir yöntemdir. Aldehit, keton, 1,3-dikarbonil türevleri ve nitroalkenlerin donör olarak kullanıldığı enantiyoseçici organokataliz tepkimeleri yoğun olarak araştırılmıştır. Fakat, tiyo türevlerinin nükleofil olarak kullanıldığı çok az çalışma bulunmaktadır. Bu tezde, tiyoasetik asitin Michael donörü, 10 *trans*-β-nitrostiren türevinin Michael alıcısı olarak kullanılacağı Michael tipi katılma reaksiyonları hedeflenmiştir. Bu tepkime sonucu ortaya çıkan ürünler, kiral 1,2-aminotiyol türevlerinin hazırlanması için gerekli önemli aday ürünlerdir. 2-AminoDMAP/tiyoüre olarak adlandırılan asit/baz bifonksiyonel organakatalizörün bu çalışma için en uygun olduğu saptanmıştır. Çalışmanın ilk kısmında sıcaklık, çözücü ve katalizör miktarı gibi parametreler değiştirilerek optimizasyon çalışmaları yapılmıştır. Optimum tepkime koşulları altında, tiyoasetik asit ve 10 farklı *trans*-β-nitrostiren türevi ile Michael tipi katılma tepkimesi gerçekleştirilmiş ve tiyoester tipi katılma ürünleri %96'ya varan enentiyoseçiciliklerle elde edilmiştir.

Anahtar kelimeler: Michael katılma, organokatalizör, *trans*-β-nitrostirenler, bifonksiyonel tiyoüre.

To my dear family..

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LIST OF ABBREVIATIONS

DMAP: 4-Dimethylaminopyridine

SOMO: Singly Occupied Molecular Orbital

HOMO: Highest Occupied Molecular Orbital

LUMO: Lowest Unoccupied Molecular Orbital

THF: Tetrahydrofuran

DCM: Dichloromethane

MCPE: Cyclopentyl methyl ether

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CHAPTER 1

INTRODUCTION

1.1 Asymmetric Synthesis

Enantiomerically pure substances play very important role in variety of areas such as biochemistry, organic chemistry, pharmaceuticals, agrochemicals etc. In order to get enantiomerically pure substances there are mainly two different processes. The first one is the separation of enantiomers from the racemic mixture. This method is called chiral resolution which is widely used; however, only 50% of the desired enantiomer can be obtained.[1] The second method is asymmetric synthesis, also called enantioselective synthesis, chiral synthesis or stereoselective synthesis. It is the synthesis of enantiomerically pure substances begining from a molecule that contains a prochiral center. Chirality can be obtained by using a chiral auxiliary, internal induction of asymmetry by nearby chiral center or using a chiral catalyst. The latter has more advantages since very low amounts of chiral catalyst is sufficient to get desired enantiomerically pure substance with high yields.[2]

"The world is chiral and clinal; enjoy the symmetry wherever you find it."

-Vladimir Prelog

These words are written almost a fifty years ago by Vladimir Prelog and they underlies the development of asymmetric studies which are very attractive and challenging topic of today's researches. Since the resulting enantiomerically pure products are very important keystones, there is a growing demand for asymmetric synthesis not only by academics but also by chemical companies and pharmaceutical industry.

Enantiomers are nonsuperimposible mirror images and are known to show same physical properties. The key property making them so attractive is that their different physiologic effects. The biological activity of many compounds are associated with their molecular configuration.[3] According to the stereochemistry of the molecule, they interact with different receptors in human body so that they have different therapeutic actions. For example, two enantiomers of Carvone molecule have different smells (Figure 1). While the *R*-(–)-carvone smells like spearmint, *S*-(+)-carvone, smells like caraway.[4]

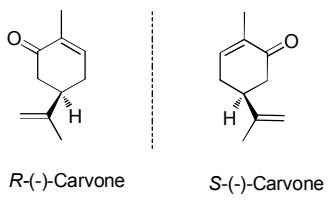


Figure 1. The structure of enantiomers of carvone molecule

By looking from the pharmaceutical industry, asymmetric synthesis plays an indispensable role. Since human body also contains chiral molecules such as enzymes, receptors, DNA and RNA, their interactions with chiral drugs show different responses such as rate of metabolism, excretion, potency and selectivity for receptors and enzymes. Pharmaceutical companies are aware of the superiority of using single-enantiomer form over the racemic mixture and hence there are intense researches on asymmetric synthesis.[5] Today, most of the marketted drugs contain single-enantiomer form and albuterol[6], thalidomide[7], propranolol[8] and DOPA[9] are known examples for chiral drugs whose enantiomers show different pharmacological effects (Figure 2).

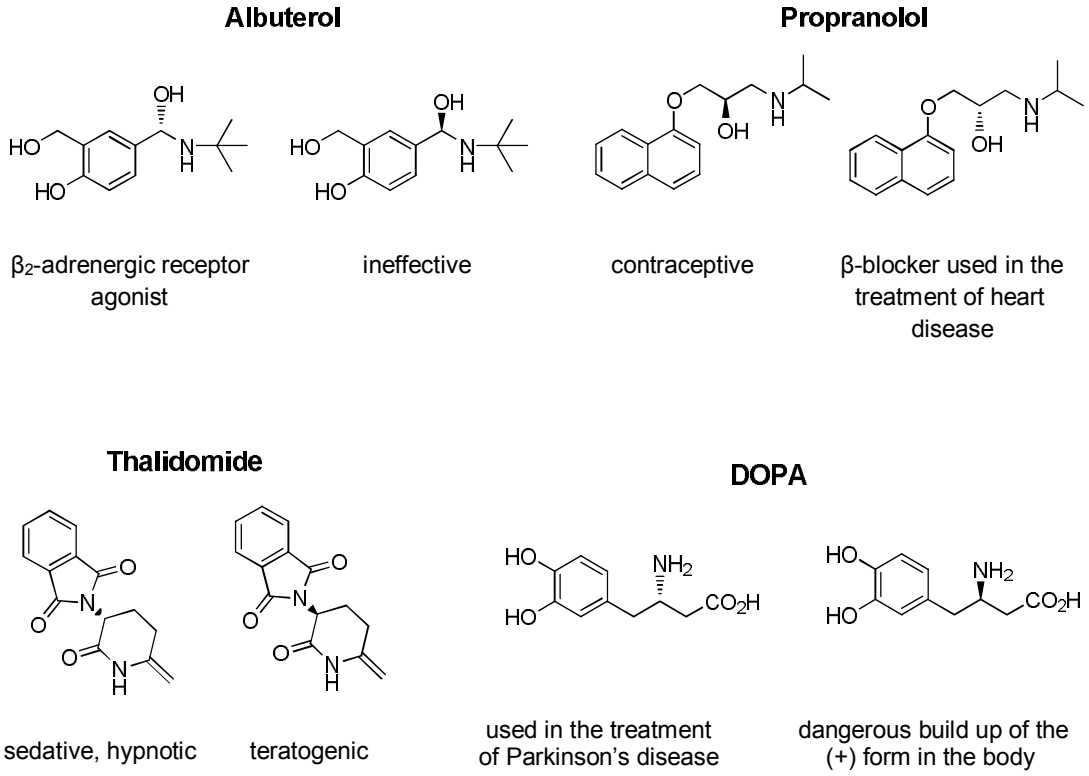


Figure 2. The structures and biologic effects of some chiral drugs

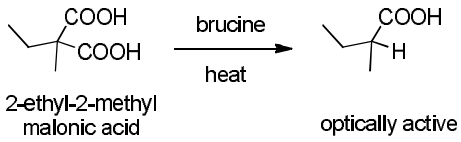
1.2 The History of Asymmetric Synthesis

The first experiment for separation of enantiomers from racemic mixture conducted by Louiss Pasteur in 1858. He performed decarboxylated kinetic resolution of ammonium tartarate solution. He observed that the existence of a microorganism called *penicillium glauca* destroys *d*-enantiomer more rapidly.[10] It was the first time to consider enzymes as catalyst in living systems.[11]

In 1874, Le Bel and van't Hoff published articles separately investigating the stereochemistry of tetrahedral carbon atom. Both of them concluded the same result which is the presence of polarized light provides optically active compounds.[12]

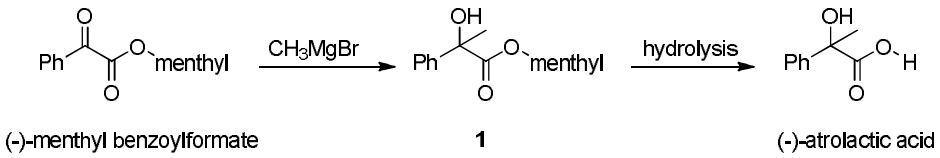
In 1890, Fischer recognized sugar family tree and served new methodology for the writing configurations by using Le Bel-van't Hoff approach for the stereochemistry. By this work, he was deemed to deserve Nobel Prize in 1902.[13]

In 1904, Marckwald studied monodecarboxylation of the monobrucine salt of methylethyl malonic acid and the resultant product was optically active (Scheme 1). It was the first time for the definition of asymmetric synthesis and he described as follow: "Asymmetric syntheses are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes".[14]



Scheme 1. Marckwald's reaction for the asymmetric synthesis of methylethylacetic acid

McKenzie was a postdoctoral student in Marckwald laboratory and he was interested in Fischer's contributions to asymmetric synthesis. In 1906, he synthesized optically active atrolactic acid starting from menthyl benzoylformate by using newly discovered Grignard reagent (Scheme 2).[15]



Scheme 2. Asymmetric synthesis of (-)-atrolactic acid

As time goes, optically active compounds gained importance and more intense researches were done. It become popular using compounds for the acceleration of reaction rather than resolution of racemic mixture. Several enzymes and synthetic, soluble transition-metal complexes were used as catalyst for this aim since they were considered as providing optical activity. Later, small organic molecules were used for the same aim and they started a new challeging area for the asymmetric synthesis.

When the history of asymmetric synthesis is investigated, there are mainly 3 type of catalysis which are transition-metal catalysis, biocatalysis and organocatalysis (Figure 3).

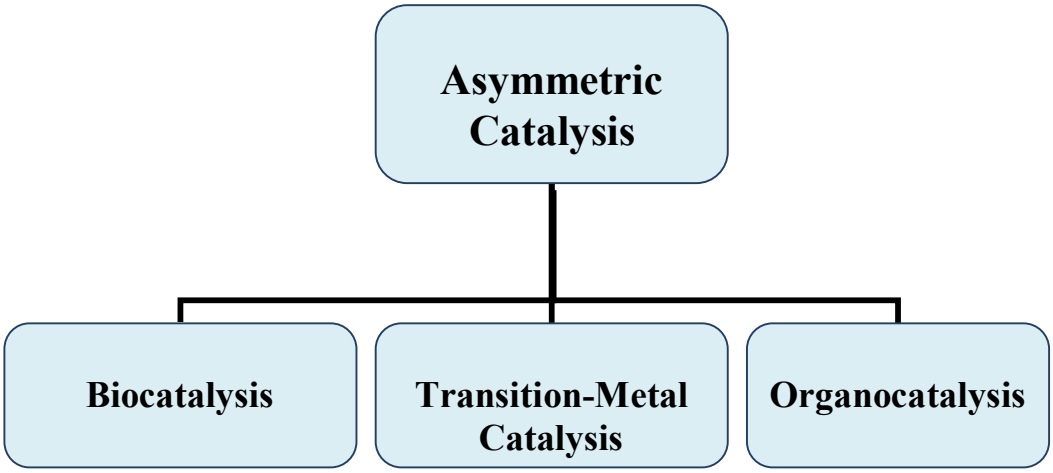


Figure 3. Classification of asymmetric catalysis

Biocatalysis is defined as the using natural molecules such as enzymes, proteins etc. for the accelaration of organic reactions. Biocatalysts can produce enantiopure compounds by two ways. The first one is kinetic resolution of the racemic mixture. The presence of enzyme or microorganism like in the case of Pasteur, causes the formation or destruction of one enantiomer more rapidly. The second one is directly introducing chirality to substrate by using a chiral molecule. For example, baker's yeast is a commonly used biocatalyst for the reduction of ketones enantioselectively.[16] Biocatalysts are very commonly used in organic reactions and there are many advantages of them.[17] For example, they have high enantioselectivity. Since they are natural, they are enviromentally friendly and non-toxic. However, they have limited substrate scope which is an disadvantage.

Transition-metal catalysis is also called organometallic catalysis and it is defined as using a chiral ligand bonded to a transition metal. Palladium, lithium, zinc and copper are very common metals used for this aim.[18] For example, organomagnesium compounds such diethylmagnesium (Et_2Mg), and all Grignard reagents provides high yield and enantioselectivity.[19] Transition metal catalysts are also widely used and provides high enantioselectivity. However, they may have tedious application processes and also heavy-metal pollution.

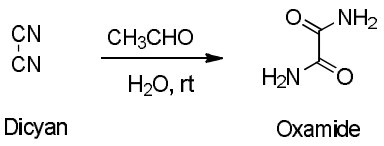
Organocatalysis is the most attractive and challenging asymmetric catalysis among the other ones for the last years. It also covers this master thesis's application area and explained more intensely in the following topic.

1.3 Asymmetric Organocatalysis

MacMillan was the first scientist who used the term "organocatalyst" in the literature and described the process as "organocatalysis".[20] He defined organocatalysis as using catalytic amount of small organic molecules consisting of carbon, oxygen, hydrogen, sulphur and nitrogen for the accelaration of reactions enantioselectively. Moreover these molecules are absence of trantion metals.

Organocatalysis generates the majority of today's asymmetric synthesis studies. When compared with the biocatalysis and transition metal catalysis, there are so many advantages of organocatalysis. For example, they are inexpensive, robust and non-toxic. They are inert to moisture and oxygen so they serve wide application area. They can also work at very low temperatures which is required for the increasing enantioselectivity in most of the asymmetric reactions. When compared with the transition-metal catalysis, organocatalysts are enviromentally friendly. For this reason they are preferred for the preparation of some pharmaceuticals which can not tolerate metal contamination. When compared with the biocatalysis, organocatalysis has wider application area.[18] When all these advantages are considered, it is not suprising that scientist are attracked in this area.

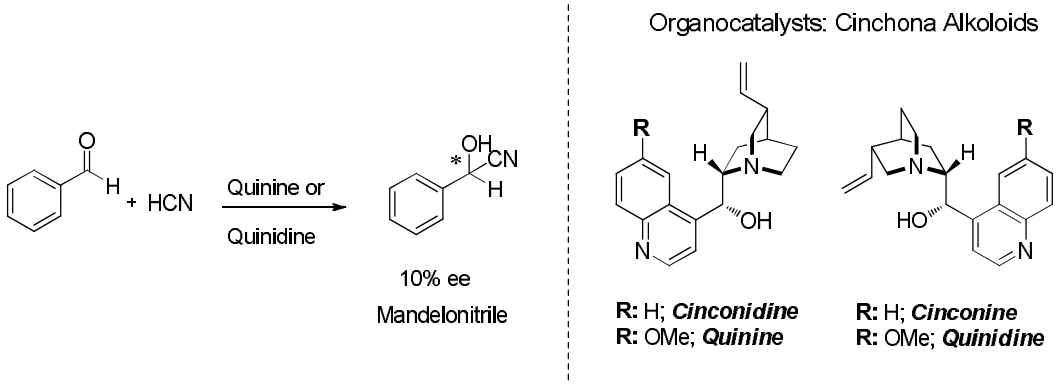
In the historical development, the first organocatalysis reaction is known the synthesis of oxamide molecule from dicyan and water. This reaction is conducted by Justus von Liebig in 1871 and he used acetaldehyde which is an achiral molecule for the acceleration of the reaction (Scheme 3).[21]



Scheme 3. von Liebeg's oxamide synthesis

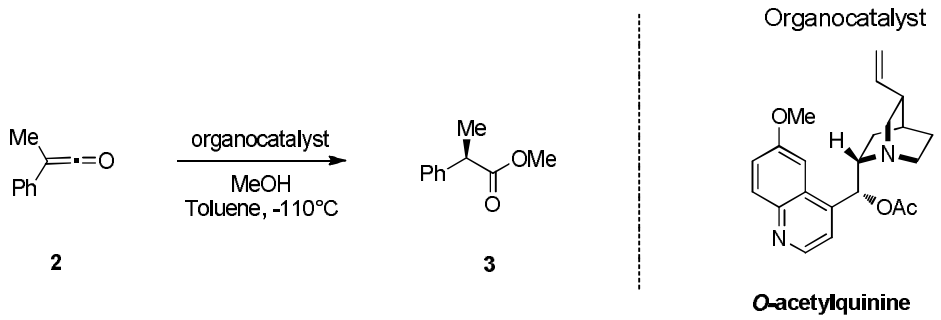
von Liebeg's experiment was the pioneer for the organocatalysis. Although this kind of organic molecules used for the accelaration of the reaction since very early times of the chemistry, it took almost two centuries to utilize them in enantioselective reactions as an organocatalysts.

Long after than Liebeg's work, in 1912, Bredig and Fiske reported enantioselective mandelonitrile synthesis by using benzaldehyde and hydrogen cyanide. They have used cinchona alkoloids as catalyst which are natural organic molecules (Scheme 4).[22] Although they have only 10% enantioselectivity, this study is very valuable for increasing the awareness toward organocatalysis.



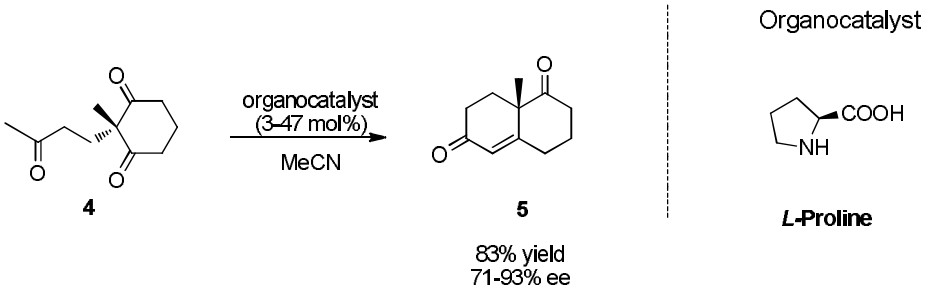
Scheme 4. Asymmetric synthesis of Mandelonitrile - Bredig and Fiske's work

In 1960, Pracejus et al. performed enantioselective methanolysis of phenylmethylketene **(2)** at -110°C. They have used only 1% mol *O*-acetyl-quinine as catalyst and got product **3** in 74% enantioselectivity. By this work, they have proved the wide applicability of cinchona alkoloids as organocatalyst (Scheme 5).[23]



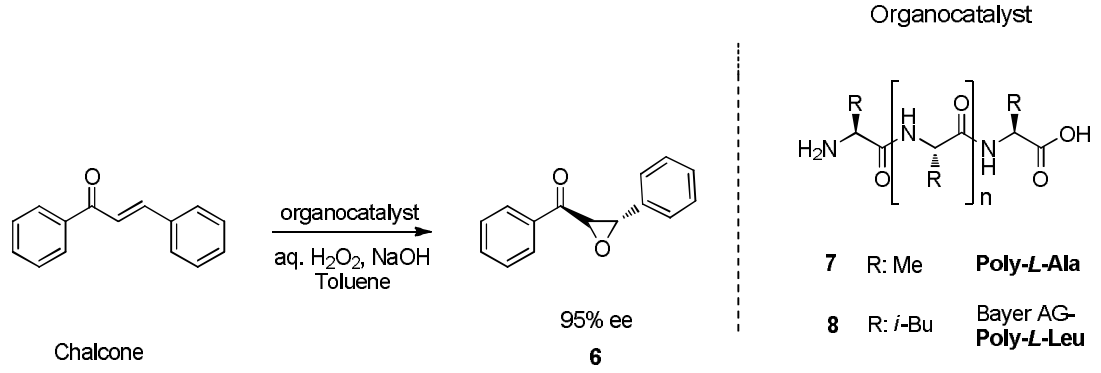
Scheme 5. Pracejus's work

In 1971, there had been a breakthrough in organocatalysis by employees of a pharmaceutical company. They have achieved intramolecular asymmetric aldol reaction by using very simple amino acid, *L*-proline. This reaction was very important because the resultant product was an important intermediate for the synthesis of steroids. Later, this reaction is named by the chemist's names. (Scheme 6).[24]



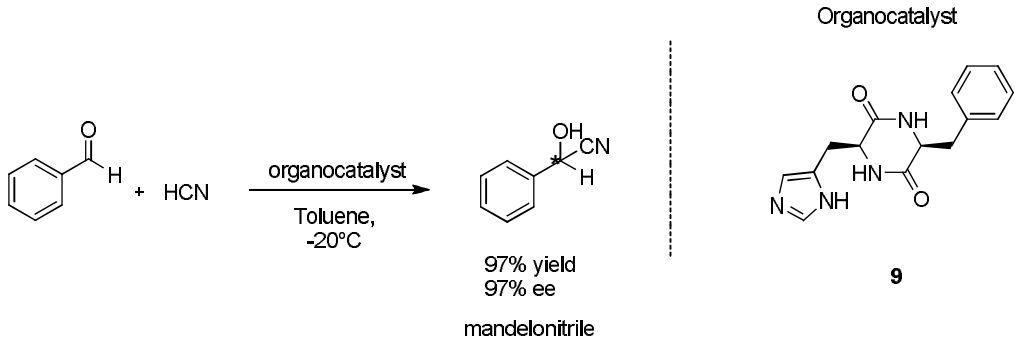
Scheme 6. Asymmetric aldol reaction

Another milestone of the asymmetric organocatalysis was come from Juliá and Colonna *et al.* in 1980. They have achieved asymmetric chalcone epoxidation up to 95% enantioselectivity by using poly amino acid which is derived from alanine. This reaction was very attractive for some industrial groups because very cheap oxidant (H_2O_2) and base (NaOH) were used. However, it has some drawbacks such as very long reaction time (5 days) and high catalyst loading. Fortunately, Bayer AG workers searched for decreasing reaction time and found that Poly-*L*-Leu was also gave the same product **6** in 3 h. (Scheme 7).[25]



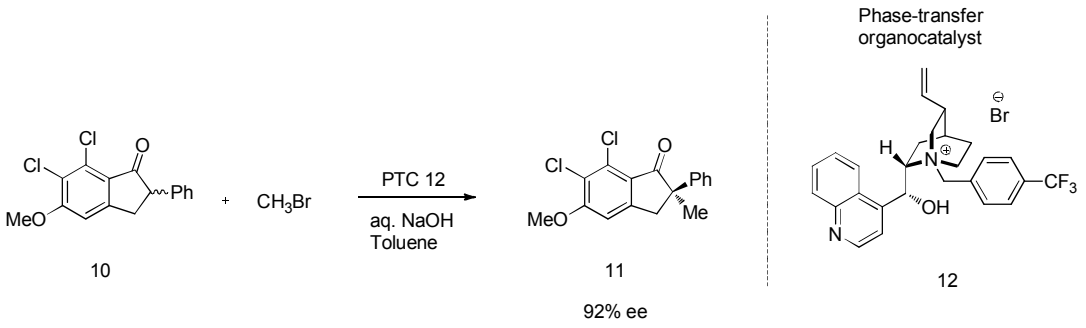
Scheme 7. Asymmetric chalcone epoxidation

In 1981, Inoue and co-workers studied asymmetric synthesis of mandelonitrile by the addition reaction of HCN to benzaldehyde. As mentioned before, this reaction was the first example of enantioselective reaction conducted by Bredig and Fiske.[22] Inoue and coworkers had designed a cyclic dipeptide catalyst **9** which is derived from *L*-histidine and *L*-phenylalanine. This catalyst showed very high catalytic activity and the resulted mandelonitrile was obtained in 97% enantiomerically pure form (Scheme 8).[26]



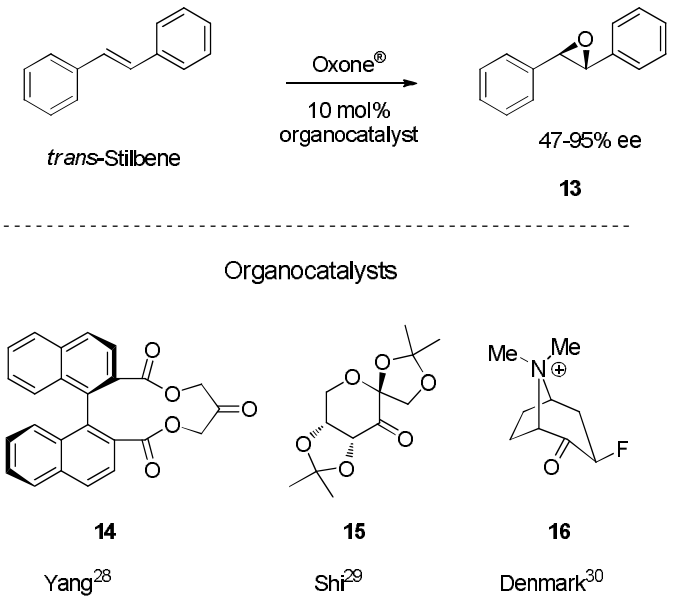
Scheme 8. Asymmetric synthesis of mandelonitrile by Inoue and coworkers

Another striking experiment in asymmetric organocatalysis conducted by Merck's researchers in 1984. They have achieved asymmetric α-alkylation of a racemic ketone **10** by the help of quaternary ammonium salt of cinchonidine. This molecule was the first example of chiral phase-transfer-catalyst (PTC) in the litarature and gave very high yield and enantioselectivity (Scheme 9).[27]



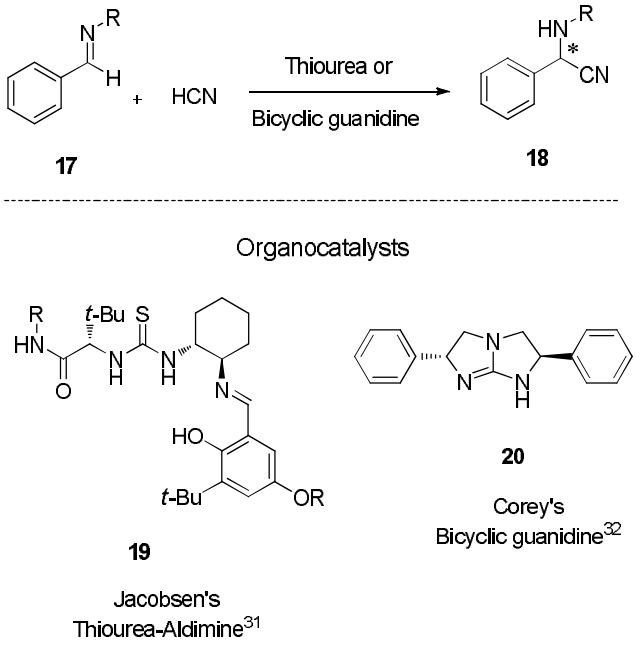
Scheme 9. Asymmetric α-alkylation of ketones by PTC

In year 1960, the epoxidation of trans-stilbene was investigated by Yang[28] and Shi[29], separately. Oxone® was used to get corresponding epoxide. They have developed chiral ketones for this asymmetric epoxidation as shown in Scheme 10. One year later, Denmark[30] also conducted same experiment by designing another catalyst system (Scheme 10).



Scheme 10. Yang's, Shi's and Denmark's chiral ketone organocatalysts

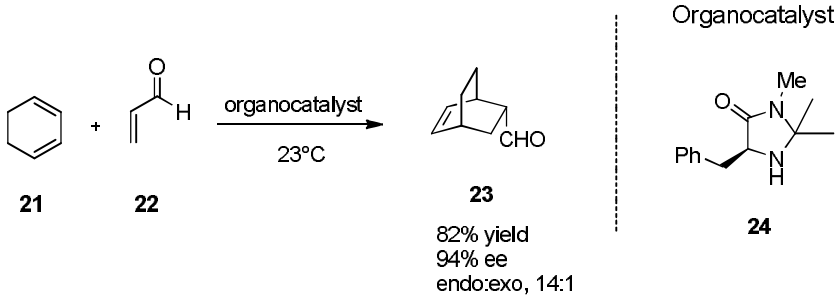
20th century has witnessed very intense research on organocatalysis. The last examples of this decade came from Jacobsen[31] and Corey[32] in 1998 and 1999, respectively. Jacobsen has introduced thioureas-Schiff base hybrid for the activation of imine electrophiles while Corey described using bicyclic guanidines for the same aim. These two catalysts were used in asymmetric Strecker reaction and high enantioselectivity and yields are obtained (Scheme 11).[29]



Scheme 11. Jacobsen's and Corey's organocatalyst

There had been several impressive studies in asymmetric synthesis at 20th century. Hovewer, none of them was striking as much of MacMillan[20] and List &Barbas's[33] studies published successively in 2000. Their studies were like seeds for later development of asymmetric organocatalysis. Moreover after their work, the research on small organic molecules got intenser and the number of publications on organocatalysis had exponentially increased.

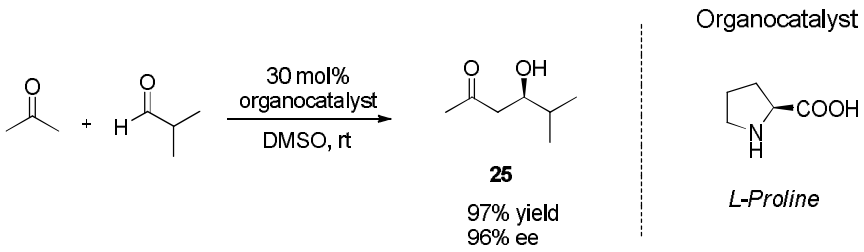
MacMillan reported asymmetric Diels-Alder reaction of α,β-unsaturated aldehydes by using phenylalanine-derived imidazolidone as catalyst. By this work, he got 94% enantioselectivity. The importance of this work was not only obtaining high enantioselectivity but also the introduction of the term "organocatalysis" for the first time.[20]



Scheme 12. MacMillan's work and organocatalyst

Other important article published in 2000 belongs to List and Barbas.[33] They have used natural amino acid *L*-Proline as catalyst for the first intermolecular asymmetric aldol reaction

of acetone and isobutyraldehyde. This was a pioneering work and later a lot of reactions are tested catalyzed by proline (Scheme 13).[27]



Scheme 13. List and Barbas's study

1.3.1 Classification of Asymmetric Organocatalysis

In order to organize getting wider and growing concept of organocatalysis, scientist have proposed several classification systems. According to Berkessel and Gröger, there are two types of organocatalysis namely covalent catalysis and non-covalent catalysis (Figure 4).[34]

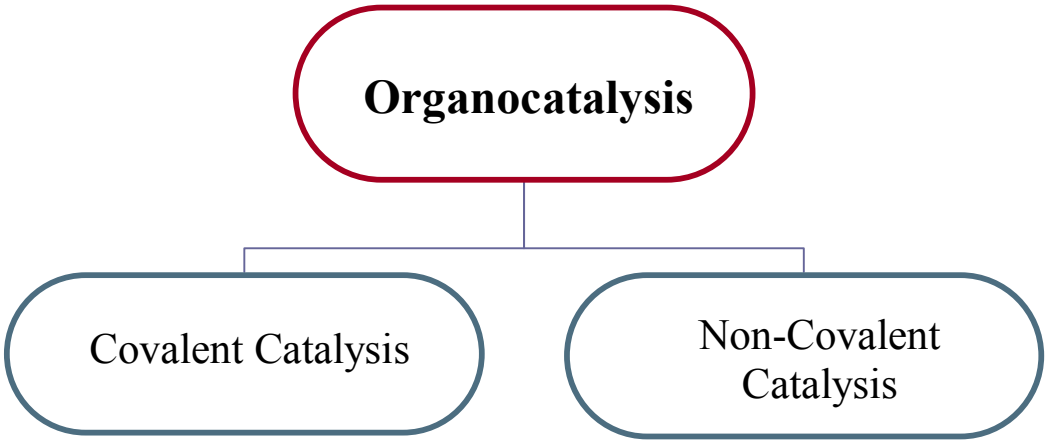


Figure 4. Classification of Asymmetric Organocatalysis

In the first group, a covalent bond formation between organocatalyst and substrate occurs. The most common examples for the covalent bond catalysis includes proline-catalyzed aldol and Michael-reactions. Covalent bond formation occurs mostly by Lewis acid and Lewis base interactions.

In the second group, non-covalent interactions such as hydrogen bonding or ion pairs included in the mechanism in place of covalent bond formation. This mostly occurs by protonation or deprotonation process between catalyst and substrate. Phase-transfer catalysis aldo belongs to non-covalent catalysis however they have different mechanism than protonation and deprotanation such transport phenomenon.

Other classification system has introduced by List and Seayad in 2000.[35] It was the mechanism based classification and divided into four major groups. (Figure 5).

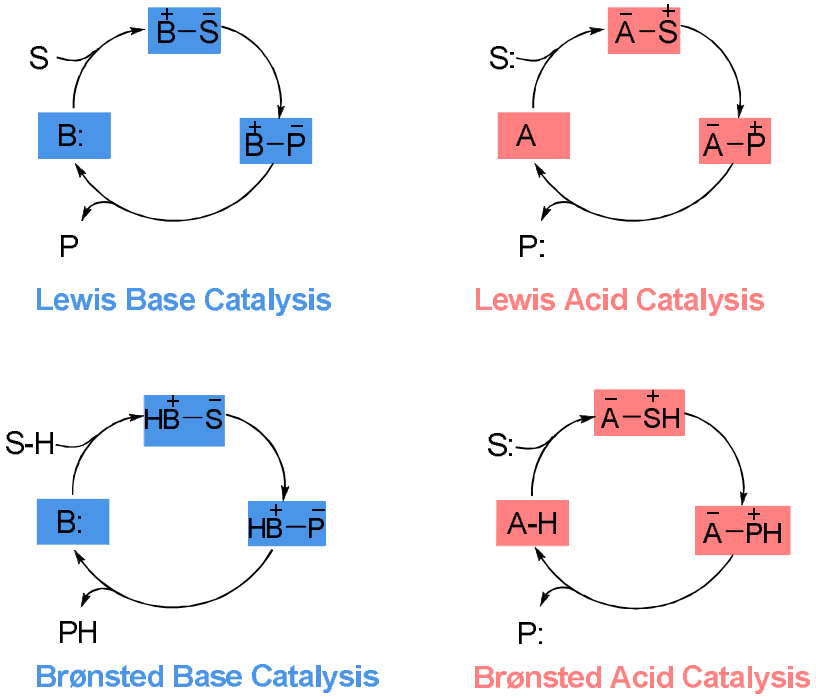


Figure 5. The classification of organocatalysis by List and Seayad

Lewis base catalysis is described as the reversibly activation of substrate (S) by the donation of a pair of electrons by the Lewis base (B:). The resulting transition state undergoes a reaction and then leaves the product (P) and catalyst in order to the cycle to go on. This classification is described in the articles of List[35] and MacMillan[36].

Lewis acid catalysis is described as substrates activated by accepting a pair of electrons from the Lewis acid (A). Similarly, The resulting transition state undergoes a reaction and then leaves the product (P) and catalyst in order to cycle to go on.

In the case of Bronsted base and acid catalytic cycles are started via a (partial) deprotonation or protonation for the activation of substrate, respectively.

Another classification system is reported by MacMillan and it is based on the generic modes that describes the transition state.[36] According to the article, there are mainly five generic modes that describes the whole organocatalytic reactions up to 2008:

- Enamine catalysis
- Hydrogen-bonding catalysis
- Iminium catalysis
- Somo catalysis
- Counterion catalysis

In terms of mechanism, enamine catalysis can be defined as the reactions that contains an amine catalyst interacting with a ketone substrate. The resulting enamine intermediate goes a further electrophilic reaction either hydrogen bonding or electrostatic interaction.

In the case of hydrogen-bonding catalysis, the activation of the substarate is achieved by hydrogen-bonding during the transition state. As mentioned before, Jacobsen and Corey has reported succesful results by using hydrogen-bonding organocatalysts for the activation of imine electrophiles.

Iminium catalysis is the formation of iminium ions from α,β-unsaturated aldehydes and chiral amines so that lowering the LUMO energy of the system. Decreasing the energy of LUMO enables the activation of carbonyl carbon by increasing the acidity of α-hydrogen.

SOMO catalysis is fistly introduced by MacMillan in 2006 and he described the activation mode by increasing the electrophilicity of the singly occupied molecular orbital (SOMO). This is achieved by the oxidation of electron-rich enamine generating a reactive radical cation.

Counterion system is based on the thiourea catalysts which is developed by Jacobsen. It is defined as the activation by the N-acyl-iminium ions and oxocarbenium ions. Thiourea catalyst forms strong complexes with halide ions..

1.3.2 Bifunctional Organocatalysis

Recently, there has been an explosively emerging interest toward dual activation of both nucleophile and electrophile by the combination of acid and base units. This process is called bifunctional organocatalysis. This new concept has become the most popular research area of asymmetric catalysis for the last 10 years because it allows high reaction rates and excellent stereoselectivities.

Bifunctional organocatalysts consist of two major parts which are basic unit and an acidic moiety. Basic unit provides the activation of nucleophile by increasing the energy of highest-occupied molecular orbital (HOMO). On the other hand, acidic moiety provides the activation of electrophile by decreasing the energy of lowest-unoccupied molecular orbital (LUMO). This process causes a decrease in activation energy which renders reactions possible.

In asymmetric reactions, variety of bifunctional organocatalyst are used. Among them, the most common ones are proline and its analogues[37], ammonium salts of diamine[38], cinchona

alkaloids and derivatives[39] and hydrogen bonding phase-transfer catalysts[40]. Also, *tert*-amines are very common examples used as base and double hydrogen-bond donor unit as the acidifying moiety (Figure 6).

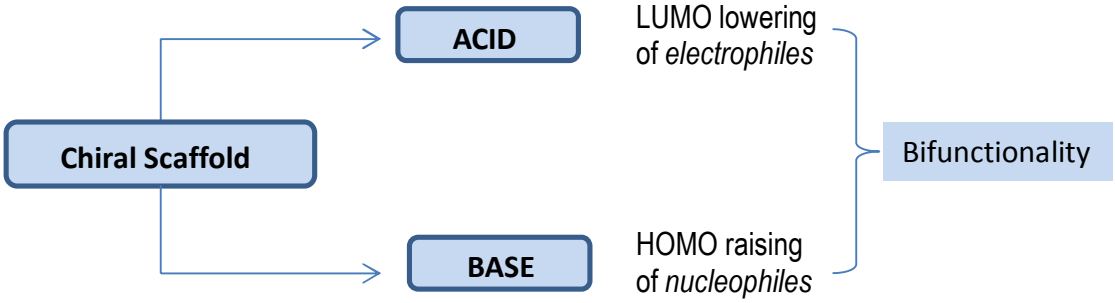
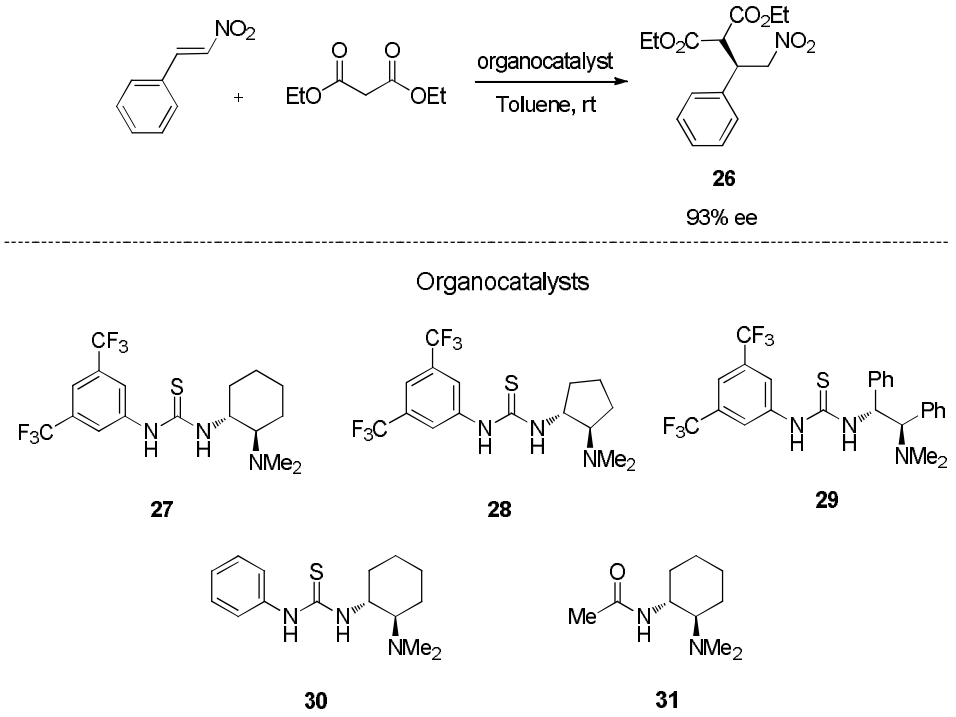


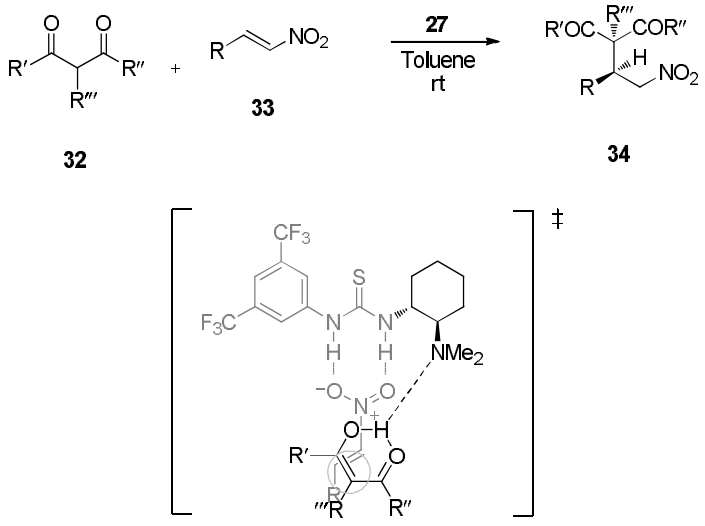
Figure 6. Bifunctionality of a chiral tert-amine/thiourea organocatalyst

The first study in bifunctional organocatalysis has become from Takemoto[41] and coworkers in 2003. They have designed several tertiary amine/thiourea catalysts and tested them in the reaction of conjugate addition of malonates to nitroolefins and got up to 93% stereoselectivity (Scheme 14).



Scheme 14. Takemoto and coworker's study by using bifunctional organocatalyst

In 2005, they have published another study extending the scope of substrates to *β*-ketoesters and *β*-diketones with various nitrostyrenes. By this work, they not only showed the wide applicability of the thiourea catalyst but also presented a transition state model to describe stereoselectivity (Scheme 15).[42]



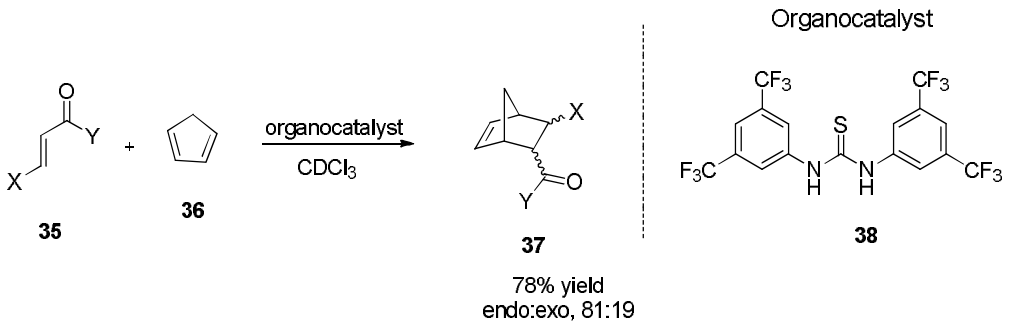
Scheme 15. General reaction scheme and TS model of Takemoto

1.4 Some Selected Thiourea Organocatalytic Reactions in Literature

By the evolution of the asymmetrical organocatalysis, today chemists can control the direction of asymmetric reactions. Cinchona alkoliods and enzymes were used and the mechanism for these reactions are well investigated. Lately, the interesting and attractive area for the organocatalysis is small organic molecules based on urea or thiourea units. Thiourea and urea catalysts have become popular over the past 10 years because these molecules can form double hydrogen bonds with the substrate. This allows the activation or coordination with the substrate which provides stereoselectivity. Sometimes these both functions act in a synergetic manner.[43]

The known oldest research on this area was done by Jacobsen et al. in 1998 as shown in Scheme 11 before. He reported Strecker reaction of HCN with imines by using thiourea organocatalyst and obtained 91% enantioselectivity. This reaction was one of the precious method to synthesize α-aminoacids.[31]

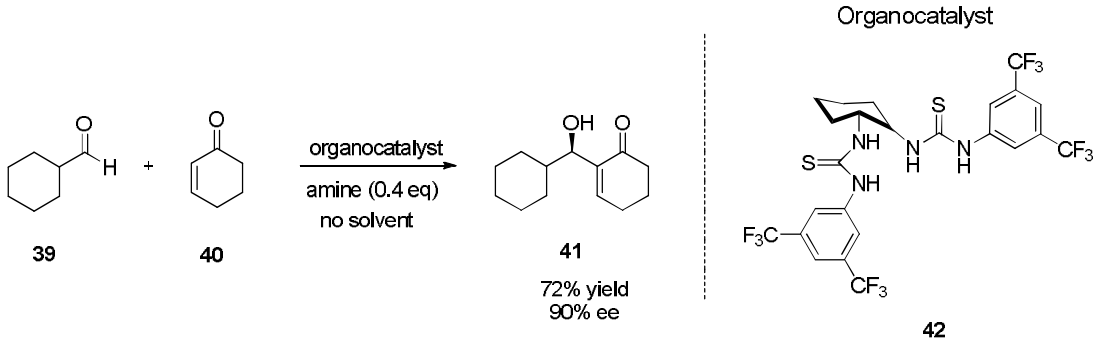
In 2001, Schreiner and Wittkopp has developed *N,N*-disubstituted thiourea derivatives and tested these organocatalysts on Diels-Alder reaction of α,β-unsaturated carbonyl compounds with cyclopentadiene. The results showed that thiourea organocatalyst accelerates and provides stereoselectivity in Diels-Alder reactions (Scheme 16).[44]



Scheme 16. Schreiner and Wittkopp's research and thiourea organocatalyst

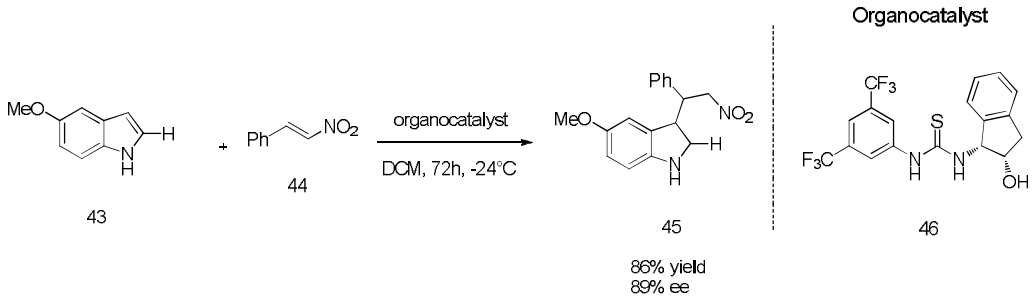
By the breakthrough research of Takemoto et al. in 2003, researches on "bifunctional organocatalysis" has been exploded. As shown before in Scheme 14, their organacatalyst was also based on thiourea.[41]

One year later, another thiourea based asymmetric organocatalysis reaction was reported by Nagasawa *et al*. They tested bis-thiourea-type organocatalyst on the Baylis–Hillman reaction of cyclohexenone with aldehydes (Scheme 17).[45]



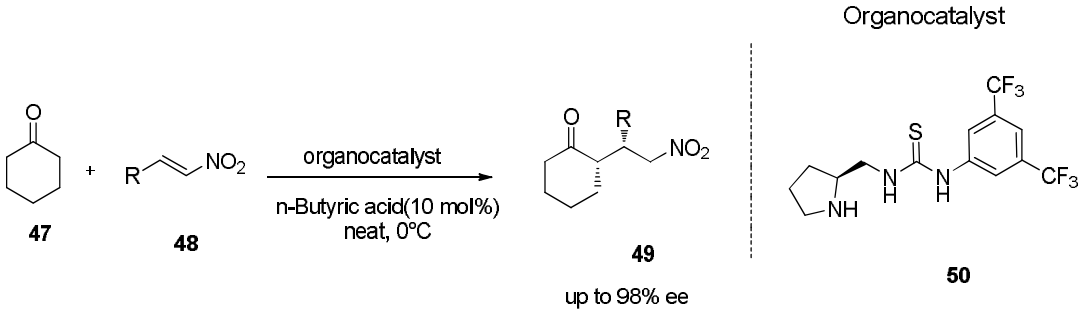
Scheme 17. Nagasawa and coworker's research and bis-thiourea based organocatalyst

In 2005, Ricci and coworkers have used bis[3,5-bis(trifluoromethyl)phenyl]thiourea organocatalyst **(42)** which was developed previously by Schreiner and used for Diels-Alder reaction.[46] This time, they have tested the availability of thiourea organocatalyst for Friedel–Crafts alkylation of aromatic and heteroaromatic compounds with nitroalkenes. This study was the first asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes, which provides high yield and enantioselectivity (Scheme 18).



Scheme 18. First Asmmetric Friedel-Crafts alkylation reaction by using thiourea organocatalyst

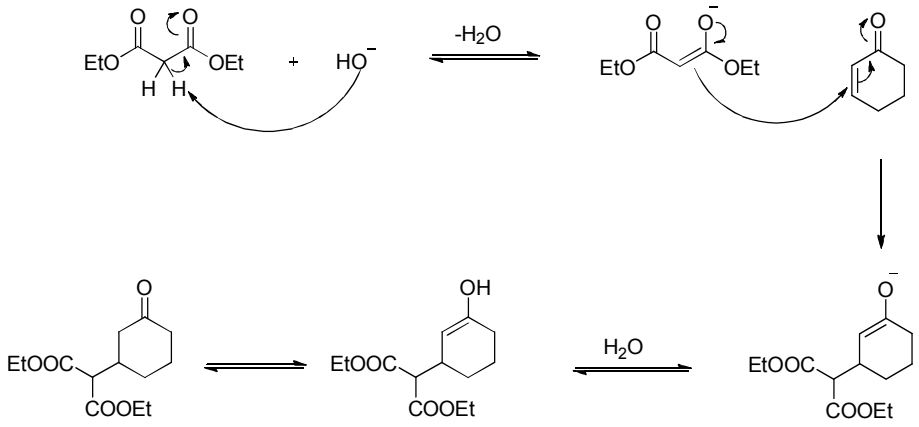
Another striking study was reported in 2006 by Yong Tang and coworkers and it includes asymmetric Michael additions of cyclohexanone to both aryl and alkyl nitroolefins.[47] They have designed a bifunctional pyrolidine-thiourea based organocatalyst and obtained high enantioselectivity up to 98% (Scheme 19).



Scheme 19. Yong Tang and coworker's study and pyrolidine-thiourea based organocatalyst

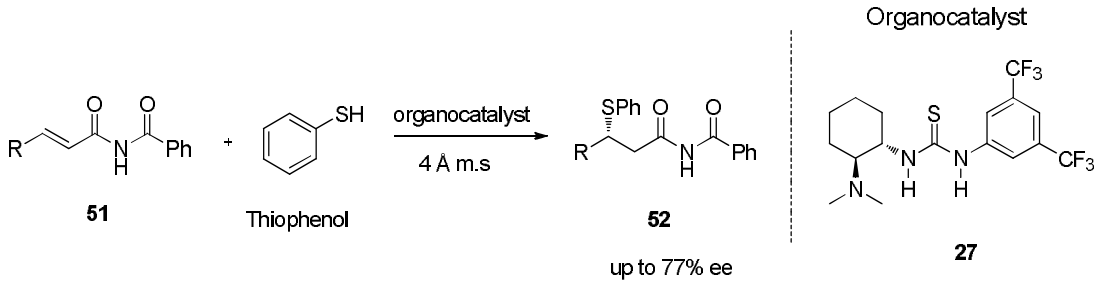
1.5 Asymmetric Michael Addition Reaction

Michael addition reaction is described as the addition of nucleophile to the β-position of an α,β-unsaturated compound which is a Michael acceptor. The reaction starts with the activation of Michael donor by strong base and goes on with the nucleophilic addition to Michael acceptor. Further hydrolytic work up gives the final product as shown in Sheme 20. Michael donors contain active $–CH_2$ or –CH groups and the acidity of methylene group can be increased by electron withdrawing groups. Common malonates are β-keto esters are common Michael donors. On the other hand, Michael acceptors are compounds with activated double bonds such as α,β-unsaturated ketones, esters, nitriles and sulfones.



Scheme 20. Michael addition reaction

One of the inspiring study for asymmetric Michael addition reaction is done by Chen *et al*. in 2005.[48] They have used Takemoto's organocatalyst which is comprising thiourea and tertiary amine groups. This catalyst have been tested on asymmetric Michael addition of arylthiols to α,β-unsaturated carbonyl compounds and enantioselectivity up to 77% has been achieved (Scheme 21). Chen's study carries special weight with sulphur-containing Michael donor and similar Michael acceptor as in this thesis study.

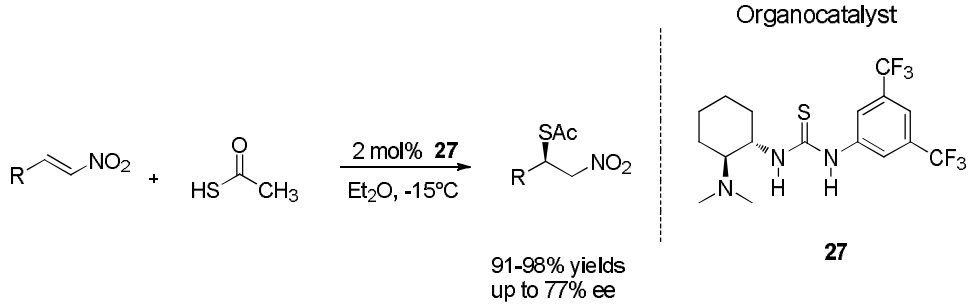


Scheme 21. Asymmetric Michael addition reaction by Chen *et al.*

1.5.1 Some Selected Asymmetric Michael Addition Reactions in the Literature

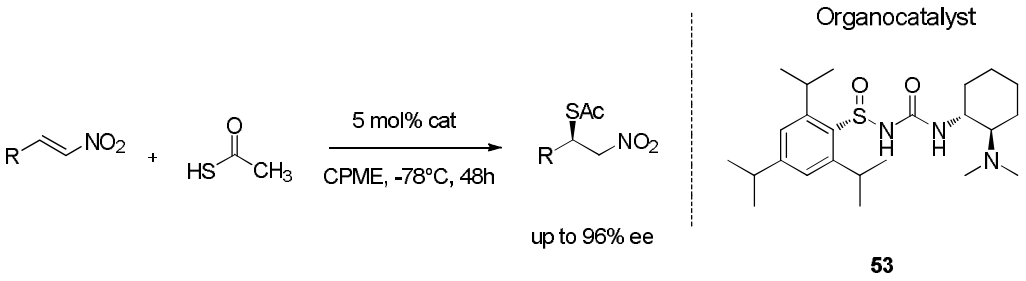
Michael addition reaction is very common and efffective way for the construction of new C-C bond in asymmetric synthesis. Various type of Michael donors and acceptors can be used for the derivation of desired products. Altough it has a wide applicability, there are limited processes including thiol containing nucleophiles in literature. The following representative studies are not only an example for the asymmetric Michael addition reaction, but also starting point of this thesis study employing thioacetic acid as nucleophile.

The first sulfa-Michael addition reaction was reported by Wang[49] in 2006. They have used Takemoto's organocatalyst **27** for the addition of thioacetic acid to trans-*β*-nitrostyrene derivatives. Although they obtained products in high yields, the enantioselectivities were unsatisfactory (Scheme 22).



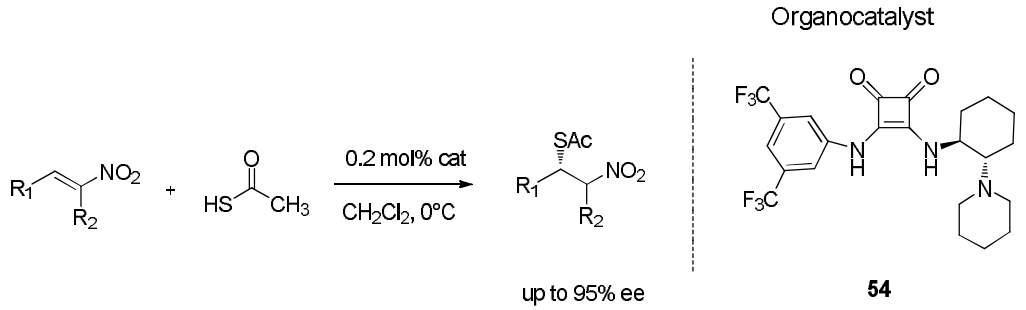
Scheme 22. Asymmetric sulfa-Michael addition reaction by Wang

Another research in this area was conducted in 2009 by Ellman and coworkers.[50] They have designed a bifunctional organocatalyst to test following reaction and obtained good enantioselectivities up to 96% (Scheme 23).



Scheme 23. Asymmetric sulfa-Michael addition reaction by Ellman

In 2012, another research in asymmetric sulfa-Michael addition was reported by Yang and coworkers.[51] They have employed chiral squaramide organocatalyst for enantioselective addition of following reaction. They have synthesized desired products in good diastereoselectivities up to 94 : 6 and high enantioselectivities up to 95% (Scheme 24).



Scheme 24. Asymmetric sulfa-Michael addition reaction by Yang

1.6 Aim of the Work

Today, it is obvious that the advantages of asymmetric organocatalysis creates a challenging research area. Hence, the importance of using chiral catalysts that contains both acidic and basic units has been growing. The increased possibility of the synthesis of enantiopure intermediates for the production of pharmaceuticals keeps the eyes on bifunctional organocatalysis. There are also so many advantages such as shorter reaction duration, lower impurity and inexpensive processes.

In this master thesis, the aim was to develop a convenient bifunctional organocatalyst in our catalyst library and synthesize the corresponding products by Michael addition of thioacetic acid to *trans*-β-nitrostyrene derivatives. The reason why we interested in this topic is that the products of these reactions are important for the synthesis of 1,2-aminothiols which are common in biologically acitive compounds.

In our research group, the chiral scaffold is determined as *(1R,2R)*-2-aminoDMAP which was derived via selective mono-N-pyridilization of (*1R,2R*)-cyclohexane-1,2-diamine (**53**) as shown in Figure 5. DMAP unit shows Lewis base character. By introducing thiourea, urea, squareamide or sulfonamide groups showing Bronsted acid character to the remaining primary amine, we have constructed our Lewis base-Bronsted acid bifunctional organocatalyst systems.

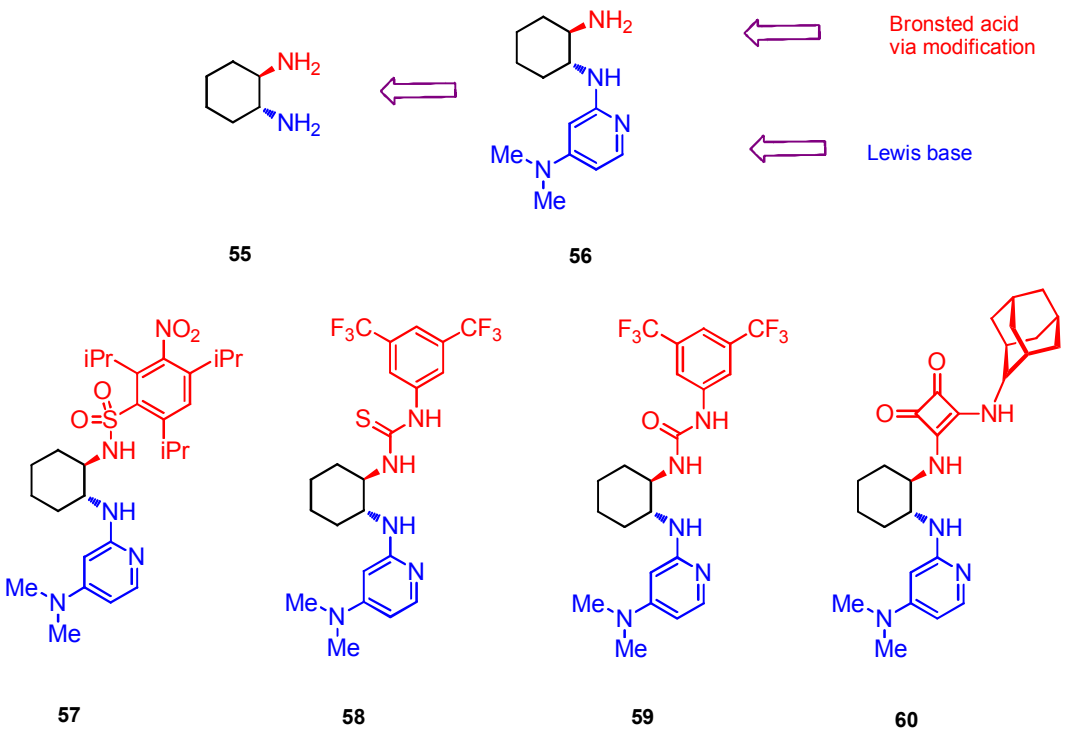
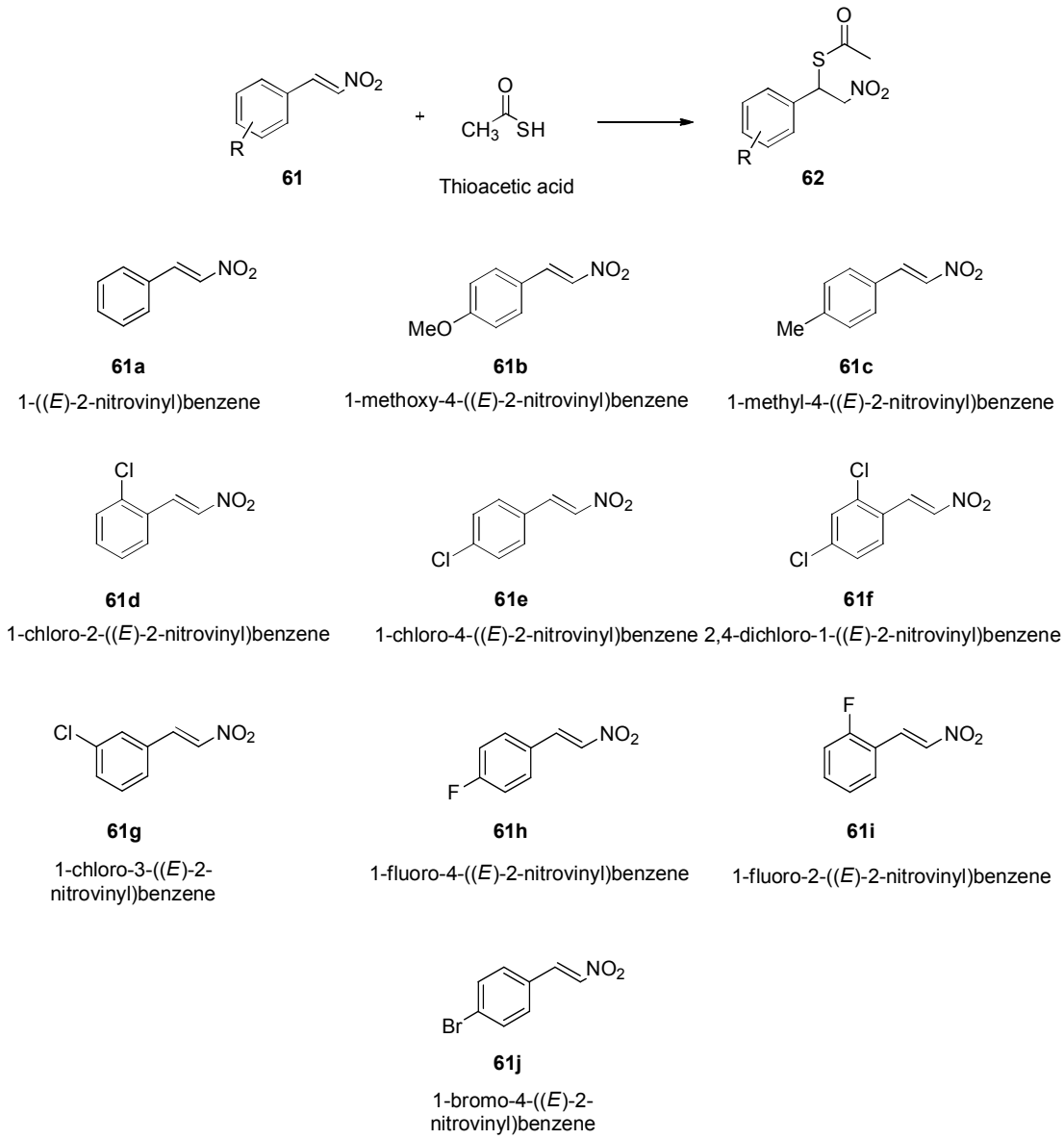


Figure 7. Synthetic strategy for our catalyst library

After the synthesis of bifunctional organocatalysts, their catalytic activity for the Michael addition of thioacetic acid to *trans*-β-nitrostyrene derivatives will be tested. For this aim, thioacetic acid is going to be used as Michael donor and *trans*-β-nitrostyrene as Michael acceptor. In order to optimize reaction conditions, many parameters will be tested such as;

- Catalyst screening
- Solvent screening
- Organocatalyst concentration
- Temperature

After the optimization of reaction conditions, various Michael acceptors shown in Scheme 25 were chosen to prove wide applicability of the organocatalysts.



Scheme 25. The target reaction and Michael acceptors

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Enantioselctive Michael Addition of Thioacetic Acid to trans-β-Nitrostyrene Derivatives via bifunctional organocatalyst

Recently, bifunctional organocatalysis constitutes very big portion of the asymmetric studies. Although there is a intense research on this area, there are still uncovered parts and sulfa-Michael addition reactions are one of them. In the literature, there are some researchs focusing on alkyl or aryl thiols as Michael donors. However, thioacetic acid addition reaction is less explored. As given in the introduction part of this thesis, Wang[49] was the pioneering on this area reporting the first asymmetric Michael addition reaction employing thioacetic acid. The reaction is catalyzed by Takemoto's thiourea catalyst **27**[41], however low enantioselectivities are obtained. Another valuble research on this area was done by the Ellman research group[50]. They have designed *N*-sulfinyl urea organocatalyst and achieved high enantioselectivies. One other research was done by Yang[51] and coworkers by using chiral squaramide organocatalyst. They have also studied thioacetic acid addition but their electophiles were α,β-disubstituted nitroalkenes and obtained diastereomerically enriched products.

In this thesis study, it was aimed to obtain high enantioselectivities with low catalyst amount and in shorter reaction times. The fact that the existence of limited works on this area encouraged us to add new results to literature.

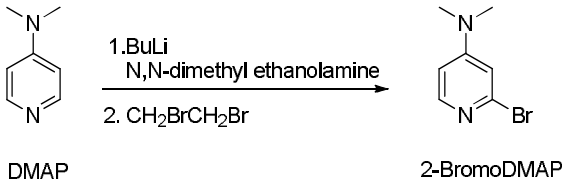
Investigation has started with *trans*-β-nitrostyrene and thioacetic acid as a role model reaction. The first aim was to determine which bifunctional organocatalyst will be employed. We have chosen most promising catalysts from Tanyeli's research group catalyst library. 2-AminoDMAP derived sulfonamide **57**, thiourea **58** and urea **59** and squaramide **60** are tested. All of them gaved racemic products at room temperature except 2-aminoDMAP/thiourea (11% ee). So, we have decided to use this organocatalyst for further applications.

2.2 Synthesis of 2-AminoDMAP/Thiourea Bifunctional Organocatalyst

In literature, there are several bifunctional organocatalyst skeletons. Among them, Chiral 4-(*N,N*-dimethylamino)pyridine (DMAP) analogues are the most common Lewis basic catalaphore. Not only the highly catalytic role by its nucleophilic character but also the easy introduction of the chiral units by its symmetrical nature, DMAP-containing designs are very common and numerous chiral analogues are reported.

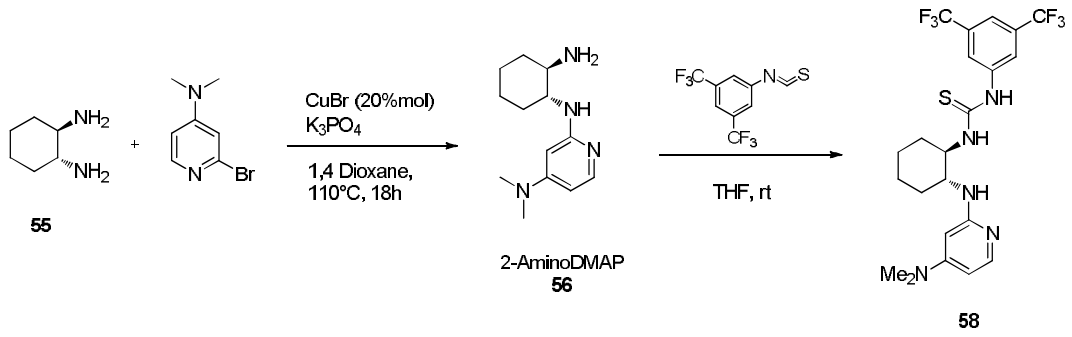
For the chiral unit, *trans*-cyclohexane-1,2-diamine is chosen and the product of Ullman coupling reaction, which is 2-aminoDMAP, comprises the main skeleton of the bifunctional organocatalysts synthesized in our research group.[43]

For the first step, 2-bromo-*N,N*-dimethylpyridin-4-amine which is known as 2-BromoDMAP was synthesized by using ligand *N,N*-dimethyl ethanolamine, BuLi as a base and dibromoethane as an electrophile at -78˚C according to literature procedure (Scheme 23).[53]



Scheme 26. 2-BromoDMAP Synthesis

After that, direct and selective mono-*N*-heteroarylation of the vicinal diamine was carried out. Copper-catalyzed modified Ullmann coupling reaction was achieved between diamine **55** and 2-BromoDMAP so that 2-AminoDMAP is synthesized in 60% yield as shown in Scheme 24.



Scheme 27. (*1R,2R*)-2-aminoDMAP Synthesis

By this coupling reaction, we got our general skeleton for bifunctional organocatalyst. For the final step, the remaining primary amine unit is functionalized by introducing the

Bronsted acid moiety which is thiourea unit for this study and finally we got our acid-base bifunctional organocatalyst (Figure 8).

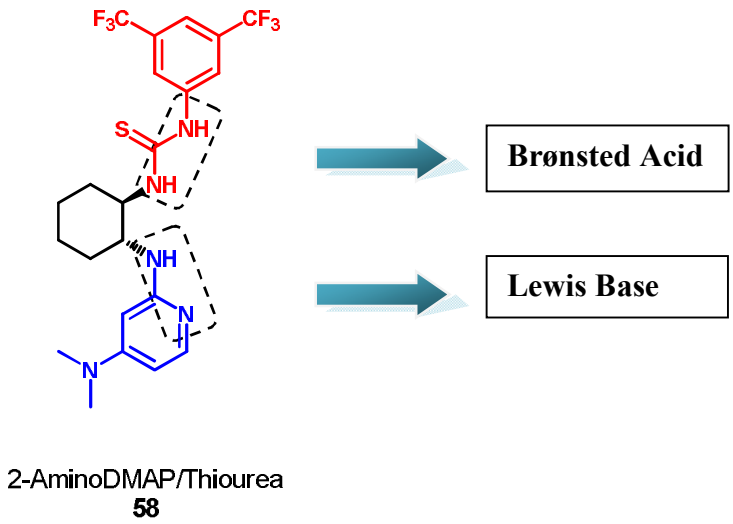


Figure 8. 2-AminoDMAP/Thiourea bifunctional ogranocatalyst

This bifunctional organocatalyst **58** contains two acidic hydrogens on thiourea unit that enables the activation of electrophile via LUMO lowering. On the other hand, the basic unit, DMAP, activates the nucleophile by HOMO raising. Hence, there occurs a decrease in the energy gap between HOMO and LUMO levels so that the reaction favors. The structure of 2-aminoDMAP/thiourea organocatalyst **(58)** was characterized by ^{1}H NMR, ^{13}C NMR, HRMS and IR.

2.3 Optimization Studies

Optimization studies were started first by screening the temperature. By using 0.2 mmol *trans*-β-nitrostyrene, 0.4 mmol thioacetic acid and 5 mol% of 2-aminoDMAP/thiourea catalyst 58, different temperatures were tested in the range of room temperature to -70 ˚C (Table 1). As expected, drastic increase was observed in terms of enantioselectivity as the temperature decreased. As shown in Table 1, it is seen that the highest enantioselectivity (75% ee) was obtained at -70 ˚C (Table1, entry 5), so we continued our optimization studies at this temperature.

Table 1. Temperature screening results

entry	temperature	yield (%)	ee (%)
1	RT	95	11
2	-15˚C	90	17
3	-30 ˚C	84	59
4	-50 ˚C	81	67
5	-70 ˚C	80	75

As second parameter, the effect of solvent was screened as shown in Table 2. Although there is a little difference compared to diethyl ether and toluene (entries 4 and 5, respectively) we decided to use toluene as solvent for further experiments.

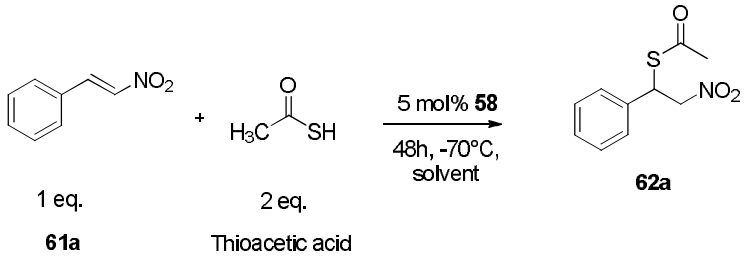
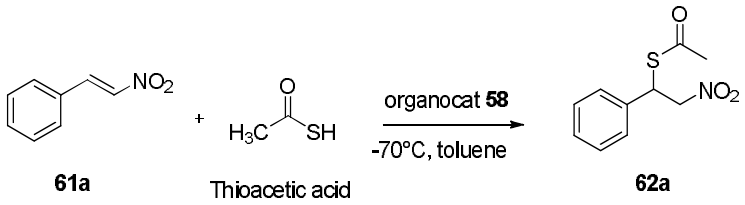


Table 2. Solvent Screening Results

entry	solvent	yield (%)	ee (%)
1	Hexane	78	63
2	CPME	60	61
3	*t*-BME	55	59
4	Et_2O	80	75
5	Toluene	83	77
6	Acetone	70	61
7	Ethanol	75	67

The last part of the optimization studies involves the screening of catalyst amount which is the most demanding parameter in the asymmetric synthesis context. It was observed that there was a decrease in terms of enantioselectivity from 77% to 73% when the amount of organocatalyst was increased two-fold (Table 3, entries 2 and 1). Suprisingly, when the amount of organocatalyst was decreased from 5 mol% to 2 mol%, there was a drastic increase in enantioselectivity up to 96% ee as shown in Table 3 (entry 3). Therefore, we determined catalyst loading as 2 mol%. This decrease in catalyst loading not only means lower cost, but also a good aproach in terms of green chemistry.



61a Thioacetic acid 62a

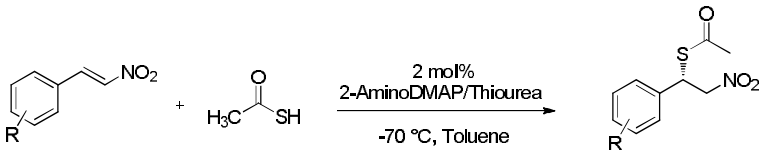
Table 3. Different Catalyst Loadings and Results

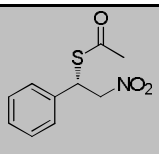
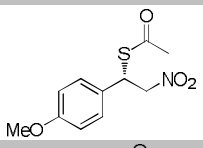
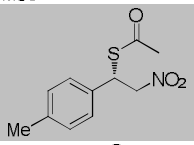
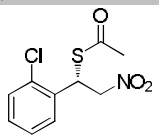
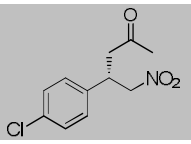
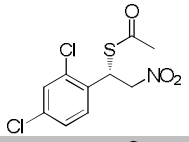
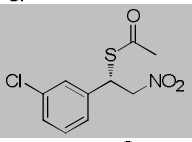
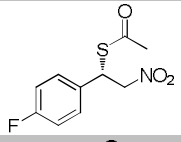
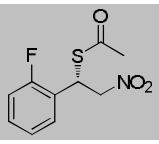
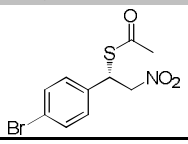
entry	organocat loading (%)	temperature	time (h)	yield (%)	ee (%)
1	10	-70˚C	20	65	73
2	5	-70˚C	22	83	77
3	2	-70˚C	25	80	96
4	1	-70˚C	28	75	83

2.4 Evaluation of 2-AminoDMAP/Thiourea Bifunctional Organocatalyst in Asymmetric Michael Addition of Thioacetic Acid to *trans*-β-Nitrostyrene Derivatives

As a result of all test reactions, the best condition for the sulfa-Michael addition reaction was determined as -70˚C, toluene as solvent and 2 mol% of 2-aminoDMAP/thiourea as organocatalyst loading. Having established the reaction conditions, different *ortho*-, *meta*-, and *para*- substituted nitroolefins were tested for their ability to undergo sulfa-Michael reaction.

Table 4. The products and enantioselectivities of the different *trans*-β-nitrostyrene derivatives.



entry	Product	Time (h)	yield (%)	ee (%)
1		25	80	96
2		25	82	91
3		25	80	88
4		20	85	*rac*
5		23	85	85
6		20	88	*rac*
7		23	85	*rac*
8		23	84	77
9		23	80	*rac*
10		23	78	55

According to our results, it can be concluded that 2-aminoDMAP/thiourea bifunctional organocatalyst **58** enables high enantioselectivities under certain circumstances. Although our system has some drawbacks such as very low reaction temperature, it has also many advantages in terms of low catalyst loading and short reaction times. For example, when we compare our results with the Ellman's work[50], they used 5 mol% catalyst loading and 48 h to complete the reaction, whereas we obtain almost the same enantioselectivity with 2 mol% catalyst loading in 25 h. Low catalyst loading is very important in asymmetric studies and it can satisfy the requirements in the context of green chemistry. On the other hand, when we compare our results with the Wang[49], it can easily seen that our work is quite more valuble in terms of enantioselectivity.

When we consider our results, except the racemic ones, we have enantioselectivities from 55% for **62j** to 96% for **62a**. Among them, we observed that phenyl rings substituted by electron-donating groups provided higher enantioselectivities (Table 4, entries 2, 3 and 4) when compared those sustituted by electron withdrawing groups (entries 5-10).

We observed that, *ortho* substituted derivatives (Table 4, entries 4, 6, 7 and 9) gave racemic products. It is seen that, these derivatives are electron withdrawing substituted ones which are closer to the double bond. Here, the inductive effect of the substituent is felt more strongly so that double bond is more electron-deficient. This enables the addition of thioacetic acid directly to the β-carbon without any interaction with the organocatalyst. Therefore, the desired products are obtained in racemic forms. Similarly, we got racemic product from the *meta* substituted derivative (Table 4, entry 7).

When we consider *para* substituted derivatives, the results are quite satisfactory except the *p*-bromo substituted one. (Table 4, entry 10). We got 55% enantioselectivity which is unexpected for para-substituted derivatives. We concluded that, the reason for this low enantioselectivity may be again loss of interaction with the organocatalyst; however, this time the reason is steric hinderance.

When the results given in Table 4 are inspected, the enantioselectivities are varied in the range of 55-96% ee, except the racemic products. The best result was obtained with unsubsituted phenyl ring moiety as 96% ee (Table 4, entry 1). When the phenyl ring is substituted in the *para* position, there is a slight decrease in enantioselectivities but still satisfactory results are obtained. On the other hand, when the phenyl ring is substituted in the *ortho* and *para* position, the products are obtained in racemic form (Table 4, entries 4 and 9). In these circumtances, inductive effect promotes the background reaction which means the loss of interaction with organocatalyst. Hence, racemic products are obtained.

The absolute configuration of enantiomerically enriched products were found to be *S* for all addition products according to the specific rotations reported in literature previously.[49,50]

The structure elucidation of *S*-(2-nitro-1-phenylethyl) ethanethioate **(62a)** was done by ^{1}H and ^{13}C NMR are shown below. In ^{1}H NMR spectrum, it is seen the stereogenic proton's peak at 5.22 ppm as doublet of doublet, and diastereotopic protons at 4.76 as doublet of

doublet, the aromatic protons between at 7.19-7.28 ppm as multiplet and methyl protons at 2.29 ppm as singlet.

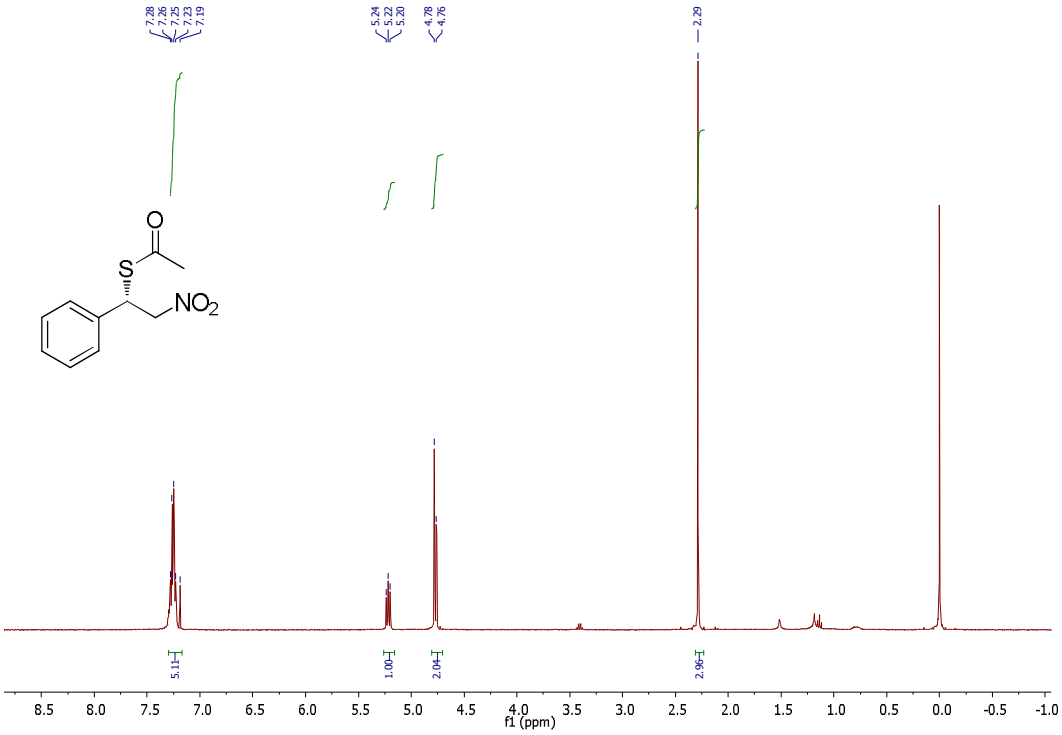


Figure 9. ^{1}H NMR spectrum of product **62a**

^{13}C NMR spectrum shows eight signals as expected. Six of them resonates at low field and the one at 192.2 ppm belongs to carbonyl carbon.

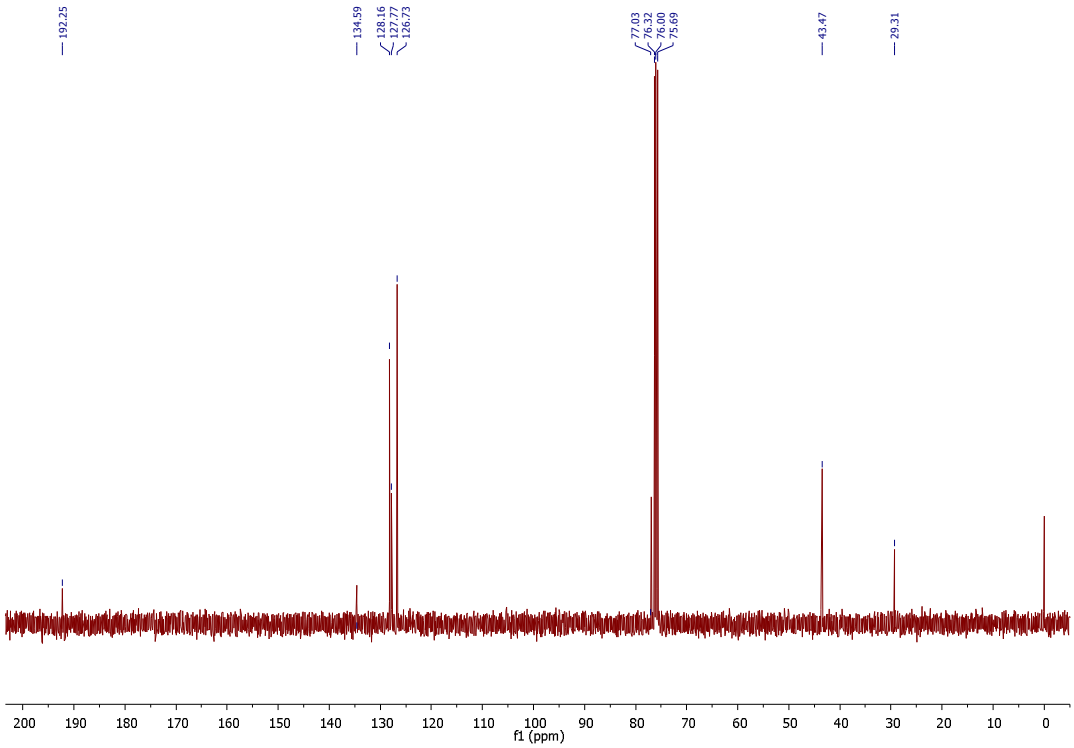
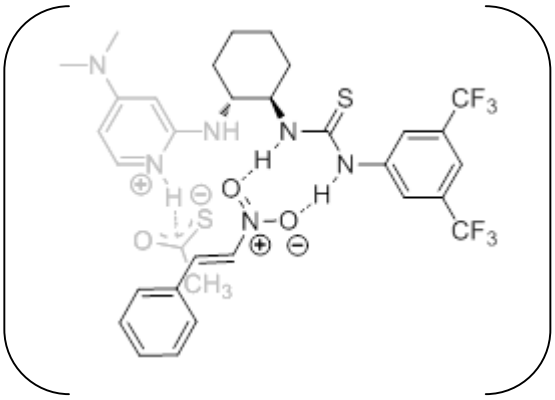


Figure 10. ^{13}C NMR spectrum of product **62a**

As mentioned through this thesis, bifunctional organocatalyst is employed for the activation of both electrophile and nucleophile. According to the Takemoto's dual activation theory, we proposed a transition state in order to illuminate activation modes of nucleophile and electrophile by our catalyst system **(58)**.



In the transition state, thiiourea moiety activates nitroolefin through double hydrogen bonding, and thioacetic acid is deprotanated by the basic nitrogen atoms of the DMAP unit. Thioacetic acid anion attacks the activated nitroolefin from the Si-face

Figure 11. Favorable Transition State

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

In this study, for the purification and characterization of the products following instruments and materials are used.

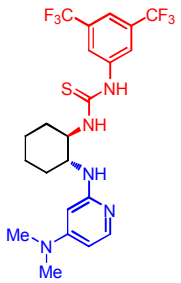
Bruker Spectrospin Advance DPX 400 spectrometer was used to record ^{1}H-NMR and ^{13}C-NMR spectra. Chemical shifts are reported in ppm downfield from tetramethylsilane, which is used as internal standard. $CDCl_3$ was used as solvent (triplet centered at 77.0 ppm at 100 MHz). Spin multiplicities are expressed as; s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad).

Rudolph Scientific Autopol III was used for the measurement of optical rotations by using 1 dm cell. HPLC chromatograms were recorded by using Dionex HPLC system. Daicel AD-H,AS-H and IA chiral columns were used with different solvent systems. HPLC chromatograms of chiral products and racemic forms were given in Appendix B.

HRMS data were detected on a Agilent 6224 TOF LC/ MS at UNAM, Bilkent University. Infrared Spectra were recorded on Bruker Alpha Platinum ATR. Band positions were reported in reciprocal centimeters (cm^{-1}).

Flash column chromatography was employed using thick-walled glass columns with a flash grade silicagel (Merck Silica Gel 60, particle size: 0.040- 0.063 mm, 230-400 mesh ASTM). Reactions were monitored by thin layer chromatography using pre-coated silica gel plates (Merck Silica Gel PF-254), and visualized with UV-light. The solvent systems for flash column chromatography were generally EtOAc/Hexane and DCM/MeOH.

3.2 Synthesis of Bifunctional Organocatalyst 58



58

(*R*,*R*)-Configurated compound 2aminoDMAP **56** (47 mg, 0.2 mmol) was dissolved in 1 mL THF (dried on Na wire) in a screw capped vial. To this vial, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (54 mg, 36 µL, 0.2 mmol) was added dropwise in 1 min. at room temperature. This mixture was stirred for 1 hour at rt then directly loaded on to column. Applied flash column chromatography using 90:10 MeOH: CH_2Cl_2 yielded 2-aminoDMAP/thiourea catalyst **58** as an off-white amorphous solid (0.89 mg, 88% yield). Spectroscopic data have been reported previously.

mp: 115-121 °C.

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

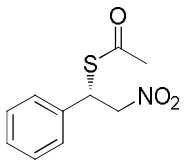
IR (neat) 2930, 2857, 1609, 1525, 1471, 1377, 1274, 1168, 1126, 884, 700, 680.
HRMS (ESI) calcd for $C_{22}H_{26}F_6N_5S$ $[M + H]^+$ 506.1813, found 506.1800.

3.3 General Procedure for Addition of Thioacetic Acid to *trans*-β-Nitrostyrene Derivatives

A mixture of *trans*-β-nitrostyrene (0.20 mmol) and 2-aminoDMAP/thiourea catalyst **58** (0.010 mmol) in toluene (2.0 mL) was cooled to -70 ˚C. Thioacetic acid (0.40 mmol) was added. The reaction mixture was stirred at -70 ˚C until the limiting agent is consumed. Then, quenched at that temperature by addition of saturated $NaHCO_3$(aq) (1 mL). The mixture was then diluted with diethyl ether (1 mL) and allowed to warm with shaking. The layers were separated and the organic layer was washed quickly with saturated $NaHCO_3$ (aq) (3 x 1 mL). The resulting solution was concentrated in vacuo. The crude product was purified by silica gel chromatography (90:9:1 Hexanes:EtOAc:AcOH). Enantiomeric excess was determined by chiral HPLC analysis.

3.3.1 Synthesis of (S)-(2-nitro-1-phenylethyl) ethanethioate 62a

The general procedure was followed using *trans*-β-nitrostyrene (30 mg, 0.20 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62a with %80 yield and 96% ee as a white solid.



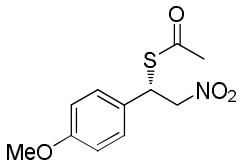
HPLC (IA, 98:2 n-Hexane:Isopropanol, 1 mL / min, 230 nm): t_{minor}=15.3 min, t_{major}=17.2 min, $[\alpha]_D^{20}$= 61.3° (*c* = 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, CDCl3): δ 7.41-7.35 (m, 5H), 5.35-5.31 (t, 1H, *J* = 7.6 Hz), 4.90-4.88 (d, 2H, *J* = 7.6 Hz), 2.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 135.7, 129.2, 128.8, 127.8, 78.0,44.5, 30.4.
IR (neat): 3032, 2964, 2919, 2855, 1683, 1548, 1494, 1453, 1377, 1138, 1109, 953, 638cm^{-1}

3.3.2 Synthesis of (S)-(1-(4-methoxyphenyl)-2-nitroethyl) ethanethioate 62b

The general procedure was followed using 4-methoxy-*trans*-β-nitrostyrene (36 mg, 0.20 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62b with %82 yield and 91% ee as a light yellow solid.



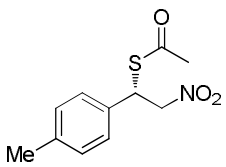
HPLC (IA, 98:2 n-Hexane:Isopropanol, 1 ml / min, 230 nm): t_{minor}=13.21 min, t_{major}=17.10 min, $[\alpha]_D^{20}$= 57.2° (*c* = 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, CDCl3): δ 7.28-7.26 (d, 2H, *J* = 8.4 Hz), 6.92-6.89 (d, 2H, *J* =8.4 Hz), 5.29-5.26 (m, 1H), 4.90-4.80 (m, 2H), 3.83 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, CDCl3): δ 193.6, 159.8, 129.0, 127.4, 114.6, 78.2, 55.3, 44.1, 30.4.
IR (neat): 3040, 2924, 2856, 1697, 1551, 1449, 1453, 1377, 1114, 970, 617 cm-1

3.3.3 Synthesis of (S)-(2-nitro-1-(p-tolyl)ethyl) ethanethioate 62c

The general procedure was followed using 4-methyl-*trans*-β-nitrostyrene (33 mg, 0.20 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 59c with %85 yield and 88% ee as a white solid.



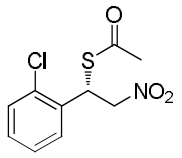
HPLC (IA, 98:2 n-Hexane:Isopropanol, 1 mL / min, 210 nm): t_{minor}=11.26 min, t_{major}= 13.56 min. $[\alpha]_D^{20}$= 37.2° (*c* = 0.25, $CHCl_3$).

^{1}H NMR(400 MHz, CDCl3): □□7.25-7.23 (d, 2H, *J* = 8.4 Hz), 7.20-7.18 (d, 2H, *J* = 8.4 Hz), 5.32-5.28 (t, 1H, *J* = 8.0 Hz), 4.88-4.85 (d, 2H, *J* = 8.0 Hz), 2.39 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (400 MHz, CDCl3): δ 193.5, 138.8, 132.5, 129.9, 127.6, 78.1, 44.3, 30.4, 21.2.
IR (neat): 3034, 2922, 2853, 1687, 1553, 1514, 1441, 1377, 1131, 949, 632 cm^{-1}

3.3.4 Synthesis of (S)-(1-(2-chlorophenyl)-2-nitroethyl) ethanethioate 62d

The general procedure was followed using 2-chloro-*trans*-β-nitrostyrene (38 mg, 0.20 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62d with %85 yield as a colorless oil.



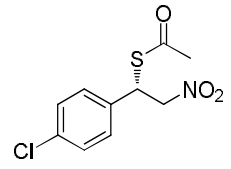
HPLC (AS-H, 98:2 n-Hexane:Isopropanol, 1 mL / min, 210 nm): t_{minor}=22.63 min, t_{major}= 31.00 min.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.14 (m, 4H), 5.62 (dd, *J* = 8.8, 6.4 Hz, 1H), 4.97 – 4.68 (m, 2H), 2.26 (d, *J* = 5.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 130.6 (d, *J* = 8.7 Hz), 130.0, 124.7, 116.3, 116.1, 76.8, 39.5, 30.2.
IR (neat): 3026, 2956, 1694, 1552, 1475, 1428, 1373, 1128, 852, 753, 622 cm^{-1}

3.3.5 Synthesis of (S)-(1-(4-chlorophenyl)-2-nitroethyl) ethanethioate 62e

The general procedure was followed using 4-chloro-*trans*-β-nitrostyrene (38 mg, 0.20 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62e with %85 yield and 85% ee as a colorless oil.



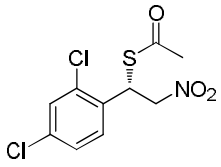
HPLC (AD-H, 99:1 n-Hexane:Isopropanol, 0.7 mL / min, 230nm): t_{minor}=22.95 min, t_{major}=26.27 min, $[\alpha]_D^{20}$= 40.4° (*c* = 0.25, $CHCl_3$).

^{1} H NMR(400 MHz, CDCl3): δ 7.27 – 7.16 (m, 4H), 5.18 (dd, *J* =9.1, 6.5 Hz, 1H), 4.78 – 4.69 (m, 2H), 2.29 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$): δ 191.9, 133.7, 133.3, 128.3, 128.1, 76.7, 42.7, 29.3.
IR (neat): 3022, 2950, 1698, 1544, 1470, 1428, 1364, 1126, 860, 724, 624 cm^{-1}

3.3.6 Synthesis of (S)-(1-(2,4-dichlorophenyl)-2-nitroethyl) ethanethioate 62f

The general procedure was followed using 2,4-dichloro-*trans*-β-nitrostyrene (38 mg, 2.0 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62e with %88 yield as a colorless viscous oil.



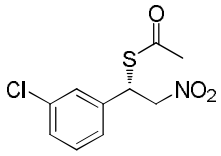
HPLC (AS-H, 98:2 n-Hexane:Isopropanol, 1 mL / min, 210 nm): t_{minor}=23.95 min, t_{major}=37.76 min.

^{1}H NMR(400 MHz, CDCl3): d 7.44 (d, 1H, *J* = 2.0 Hz), 7.34-7.32 (d, 1H, *J* = 8.4 Hz), 7.27-7.24 (dd, 1H, *J* = 2.0 Hz, 8.4 Hz), 5.67-5.63 (dd, 1H, *J* = 6.0 Hz, 4.8 Hz), 5.01-4.95 (dd, 1H, *J* = 9.2 Hz, 4.8 Hz), 4.88-4.83 (dd, 1H, *J* = 6.0 Hz, 9.2 Hz), 2.38 (s, 3H).

^{13}C NMR (400 MHz, CDCl3): δ 192.2, 135.3, 134.5, 131.9, 130.4, 130.3, 127.7, 77.3, 41.4, 30.2.
IR (neat): 3091, 3025, 2919, 1698, 1554, 1475, 1427, 1374, 1129, 1103, 953, 828, 619 cm^{-1}

3.3.7 Synthesis of (S)-(1-(3-chlorophenyl)-2-nitroethyl) ethanethioatee 62g

The general procedure was followed using 3-dichloro-*trans*-β-nitrostyrene (38 mg, 2.0 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62e with %88 yield as a colorless viscous oil.



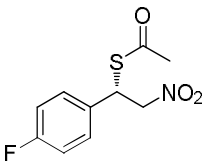
HPLC (AD-H, 99:1 n-Hexane:Isopropanol, 0,5 mL / min, 210 t_{minor}=14.45 min, t_{major}=15.56 min.

^{1}H NMR(400 MHz, CDCl3): δ 7.30 – 7.14 (m, 4H), 5.18 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.86 – 4.64 (m, 2H), 2.29 (d, *J* = 10.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 135.0, 130.4, 129.0, 128.0, 125.9, 121.3, 77.6, 43.8, 30.3.
IR (neat): 3030, 2982, 1686, 1551, 1467, 1429, 1356, 1127, 932, 744, 630 cm^{-1}

3.3.8 Synthesis of (S)-(1-(4-fluorophenyl)-2-nitroethyl) ethanethioate 62h

The general procedure was followed using 4-fluoro-*trans*-β-nitrostyrene (33 mg, 2.0 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62h with %84 yield and 77% ee as a white solid.



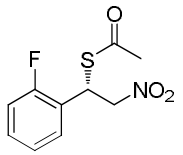
HPLC (AS-H, 99:1 n-Hexane:Isopropanol, 0.5 mL / min, 210 nm): t_{minor}=110.20 min, t_{major}=120.16 min, $[\alpha]_D^{20}$= 33.8° (*c* = 0.25, $CHCl_3$).

^{1}H NMR(400 MHz, CDCl3): δ 7.25 – 7.18 (m, 2H), 6.99 – 6.94 (m, 2H), 5.19 (dd, *J* = 9.3, 6.4 Hz, 1H), 4.80 – 4.67 (m, 2H), 2.29 (s, 3H).

^{13}C NMR (400 MHz, CDCl3): δ 193.1, 163.9, 161.4, 156.5, 131.5, 129.6 (d, *J* = 8.3 Hz), 116.3, 116.1, 77.9, 43.7, 30.3.
IR (neat): 3028, 2958, 1688, 1548, 1488, 1380, 1131, 1073, 1009, 954, 686, 592 cm^{-1}.

3.3.9 Synthesis of (S)-(1-(2-fluorophenyl)-2-nitroethyl) ethanethioate 62i

The general procedure was followed using 2-fluoro-*trans*-β-nitrostyrene (33 mg, 2.0 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62i with %79 yield as a colorless viscous oil.



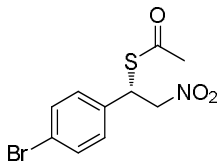
HPLC (AS-H, 99:1 n-Hexane:Isopropanol, 0,5 mL / min, 210 t_{minor}=55.23 min, t_{major}=63.33 min**.**

^{1}H NMR(400 MHz, CDCl3): δ 7.31 – 7.19 (m, 2H), 7.09 – 6.96 (m, 2H), 5.41 (dd, *J* = 9.0, 6.5 Hz, 1H), 4.81 (ddd, *J* = 19.9, 13.4, 7.8 Hz, 2H), 2.29 (s, 3H).

^{13}C NMR (400 MHz, CDCl3): δ 192.9, 130.6 (d, *J* = 8.7 Hz), 130.0, 124.7, 116.3, 116.1, 76.8, 39.5, 30.2.
IR (neat): 3027, 2982, 1681, 1550, 1490, 1374, 1102, 950, 833, 755, 683 cm^{-1}.

3.3.10 Synthesis of (S)-(1-(4-bromophenyl)-2-nitroethyl) ethanethioate 62j

The general procedure was followed using 4-bromo-*trans*-β-nitrostyrene (45 mg, 2.0 mmol), catalyst **58** (2.2 mg, 0.010 mmol) and thioacetic acid (29 μL, 0.40 mmol) to afford product 62i with %79 yield as a yellowish viscous oil.



HPLC (AD-H, 99:1 n-Hexane:Isopropanol, 0,7 mL / min, 230 t_{minor}=59.04 min, t_{major}=70.05 min, $[\alpha]_D^{20}$= 27.8° (*c* = 0.25, $CHCl_3$).

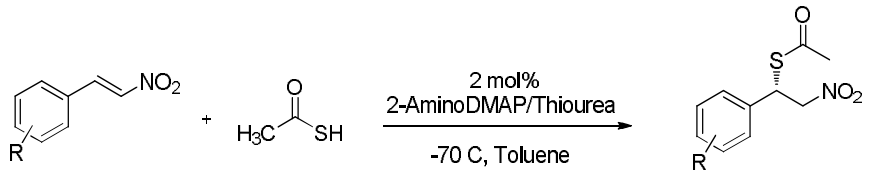
^{1}H NMR(400 MHz, CDCl3): δ 7.31 – 7.20 (m, 5H), 5.26 – 5.16 (m, 1H), 4.80 – 4.73 (m, 2H), 2.29 (s, 3H).

^{13}C NMR (400 MHz, CDCl3): δ 191.1, 133.1, 130.1, 127.6, 121.1, 75.8, 42.1, 28.5.
IR (neat): 3031, 2984, 1688, 1548, 1488, 1380, 1131, 1009, 954, 794, 710, 686 cm^{-1}.

CHAPTER 4

CONCLUSION

In this thesis, we have demonstrated that a 2-aminoDMAP/thiourea bifunctional organocatalyst promotes the enantioselective Michael addition of thioacetic acid to aromatic nitroalkene derivatives. The resulting thioester products can be readily transformed into 1,2-aminothiol derivatives which are pharmaceutically more useful intermediates.



Scheme 28. Enantioselective sulfa-Michael addition reaction

As a result of optimization studies, we have found that temperature is the critical factor to discriminate the background reaction occured very fast. Unfortunatelly, we could not control the background reaction when the strong electron withdrawing group is subsituted on *ortho* and *meta* positions presumably due to the high activation of β-carbon of nitrostyrene derivatives. The enantioselectivities are varied in the range of 55-96% ee, except the racemic products. Consequently, we obtained satisfactory results under certain circumtances and when compared with the literature this method provides shorter reaction duration and lower catalyst loading which are the most demanding criteria in the context of asymmetric synthesis.

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APPENDIX A

NMR DATA

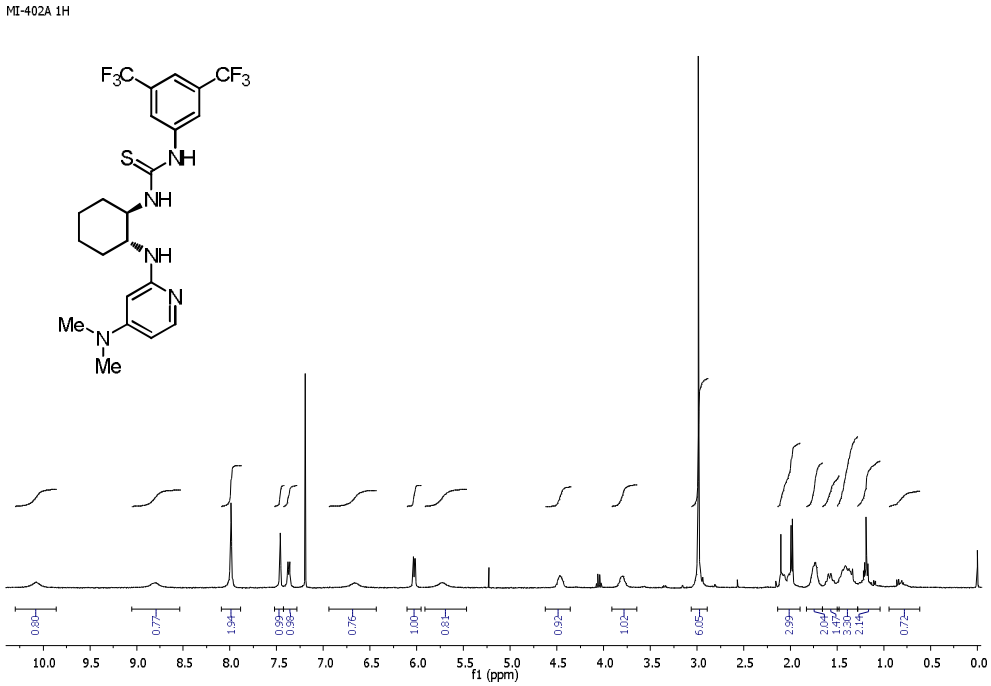


Figure A 1. ^{1}H NMR spectrum of compound **58**

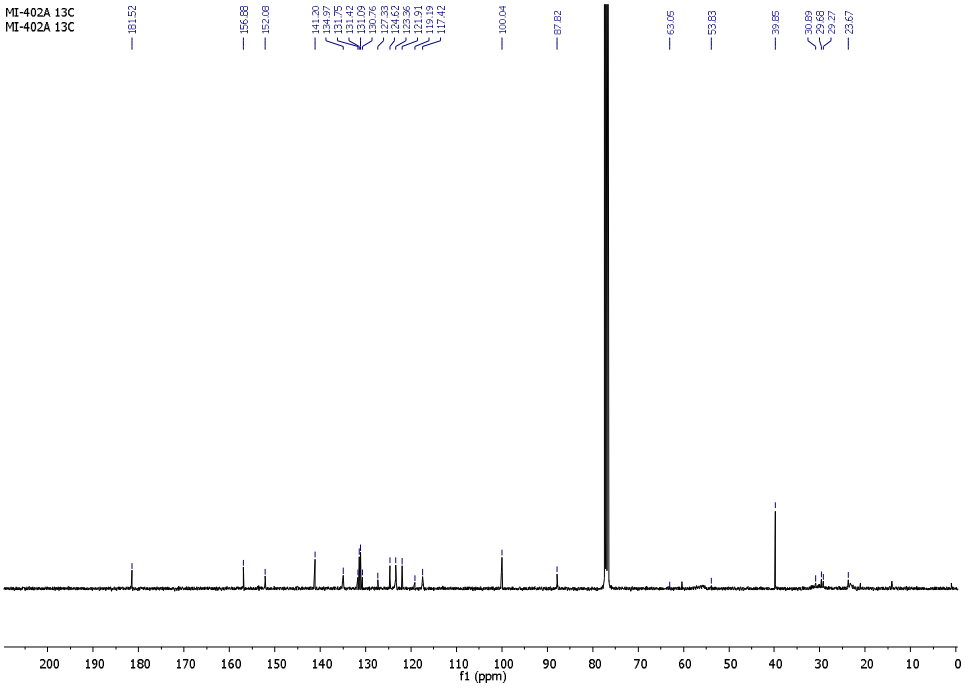


Figure A 2. ^{13}C NMR spectrum of compound **58**

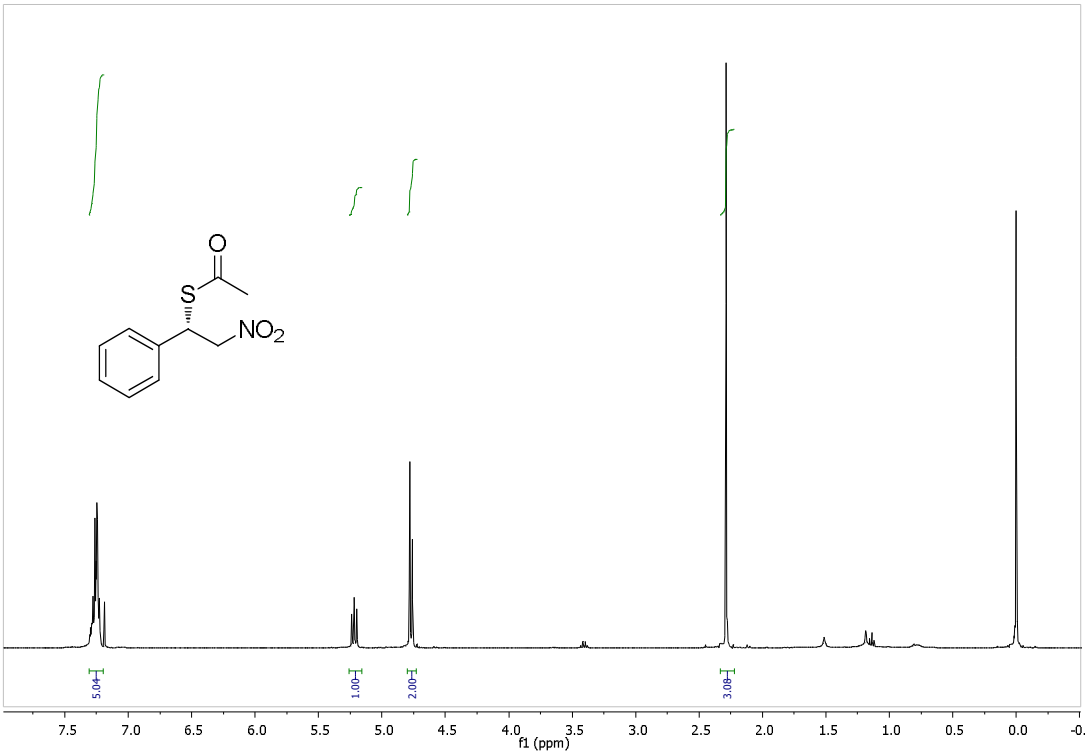


Figure A 3. ^{1}H NMR spectrum of product **62a**

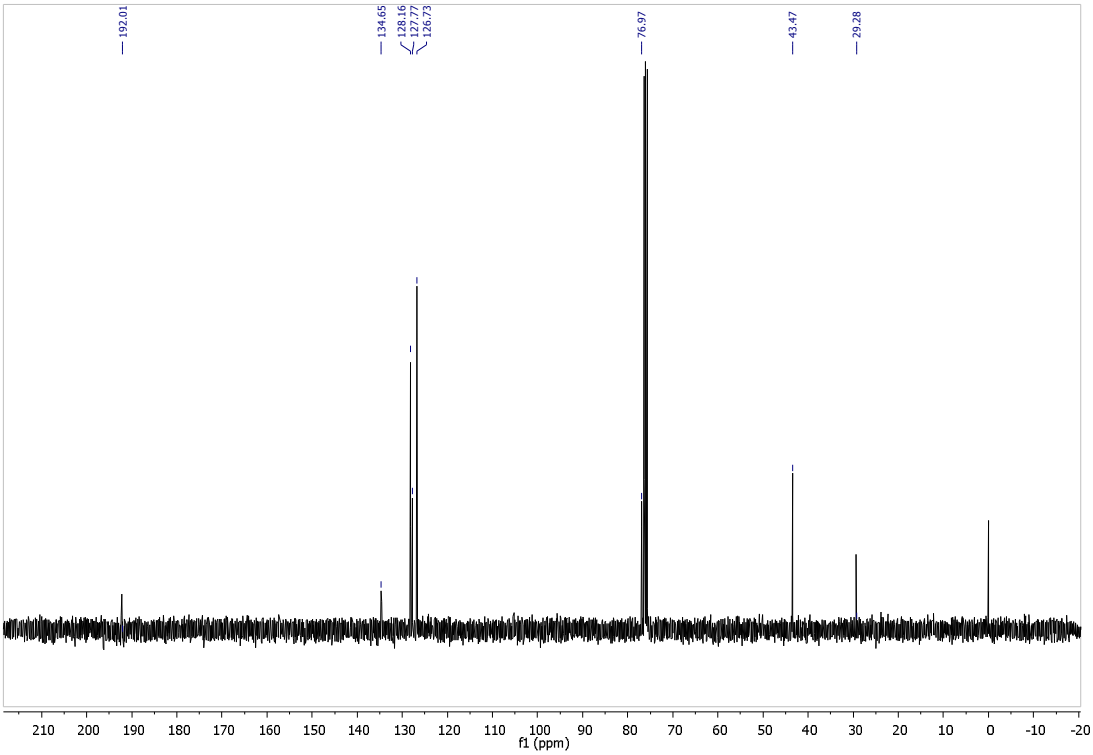


Figure A 4. ^{13}C NMR spectrum of product **62a**

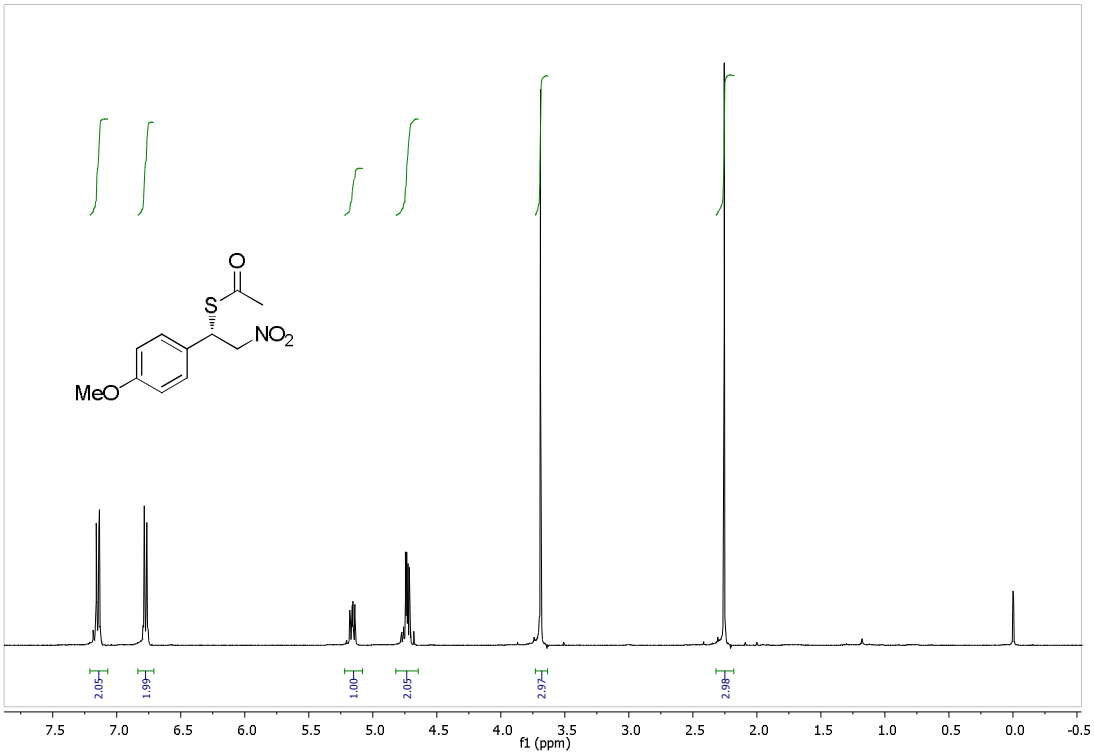


Figure A 5. ^{1}H NMR spectrum of product **62b**

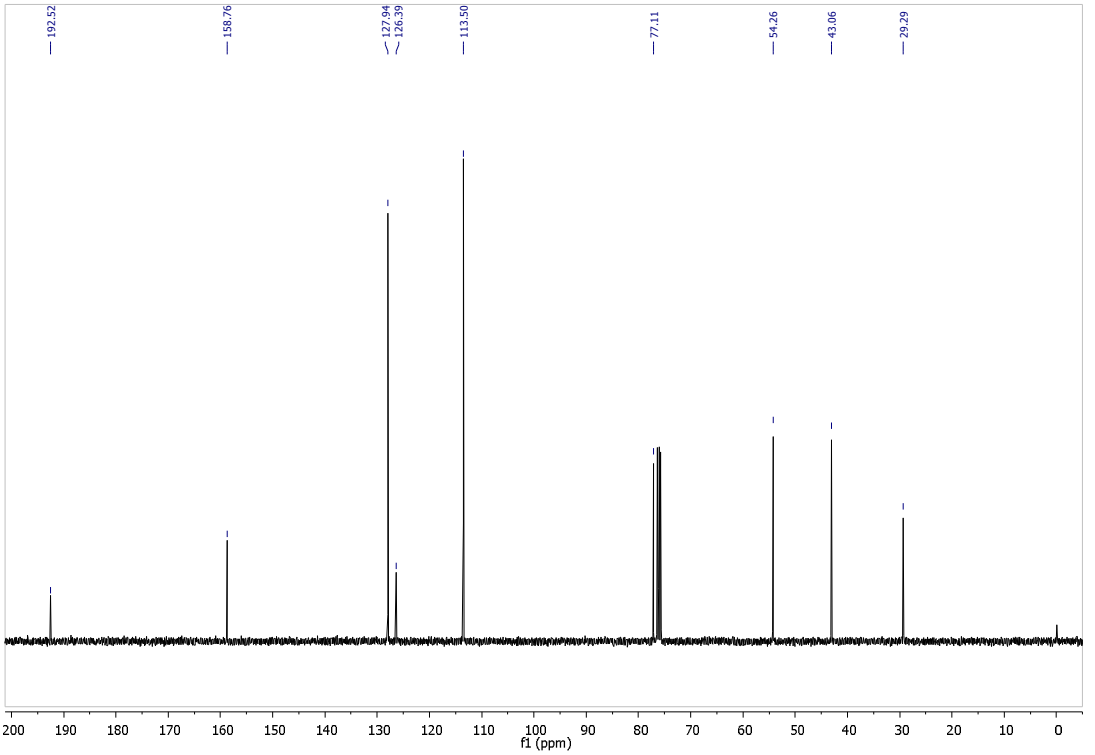


Figure A 6. ^{13}C NMR spectrum of product **62b**

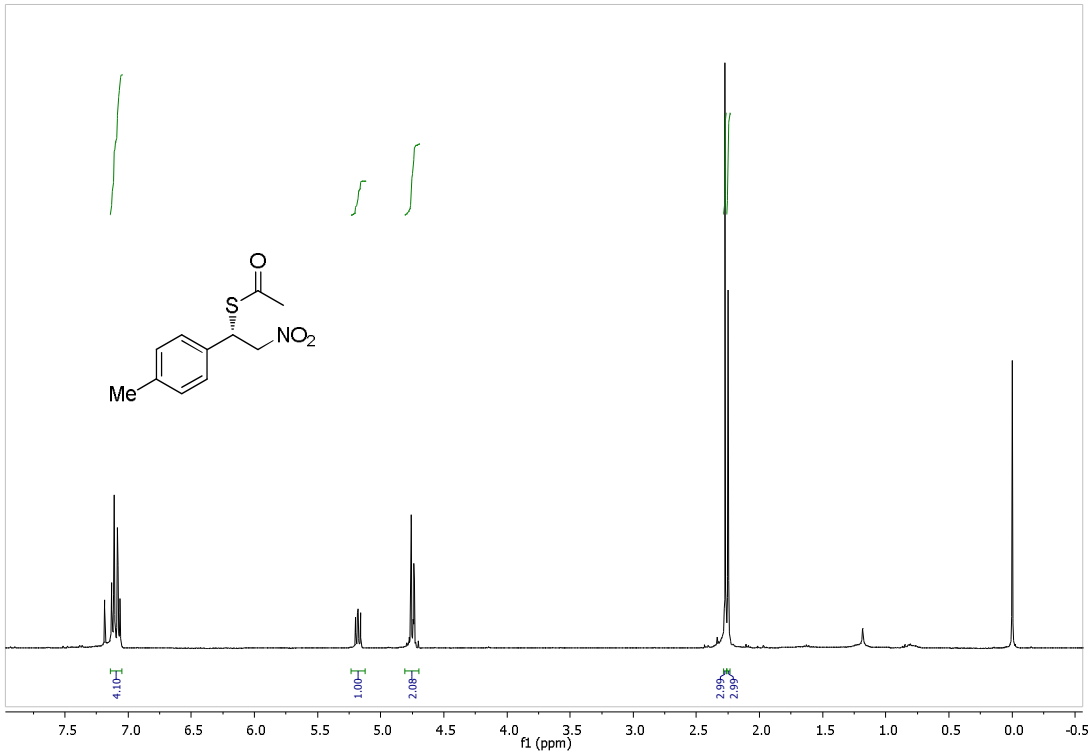


Figure A 7. [1]H NMR spectrum of product **62c**

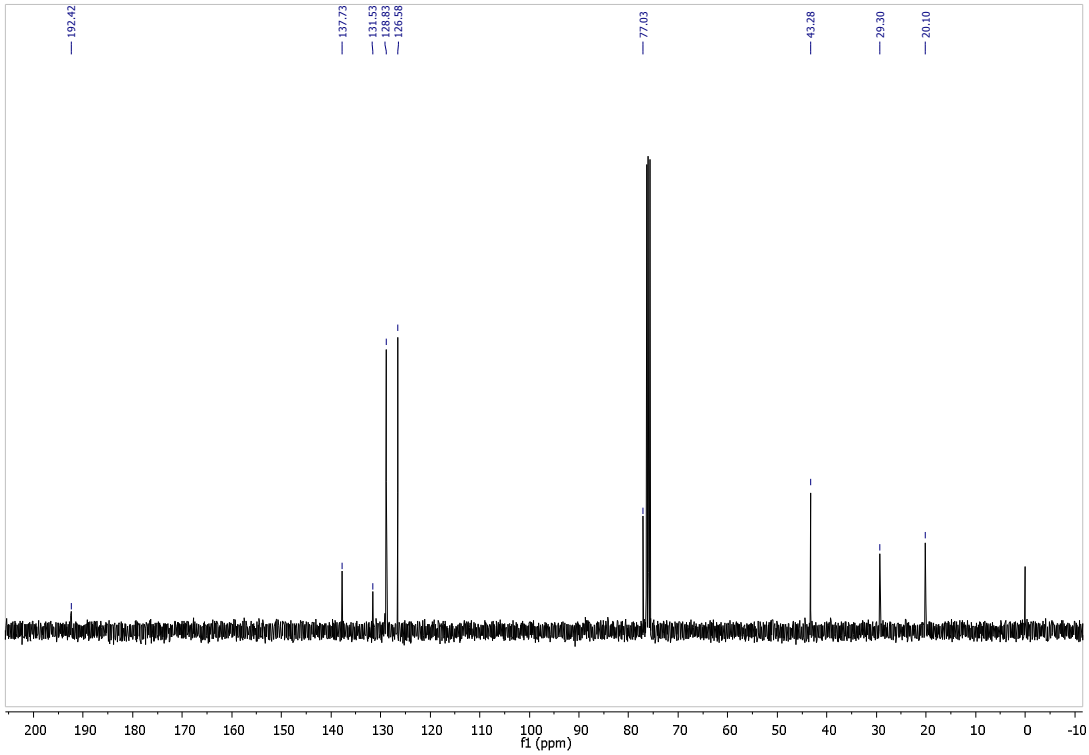


Figure A 8. [13]C NMR spectrum of product **62c**

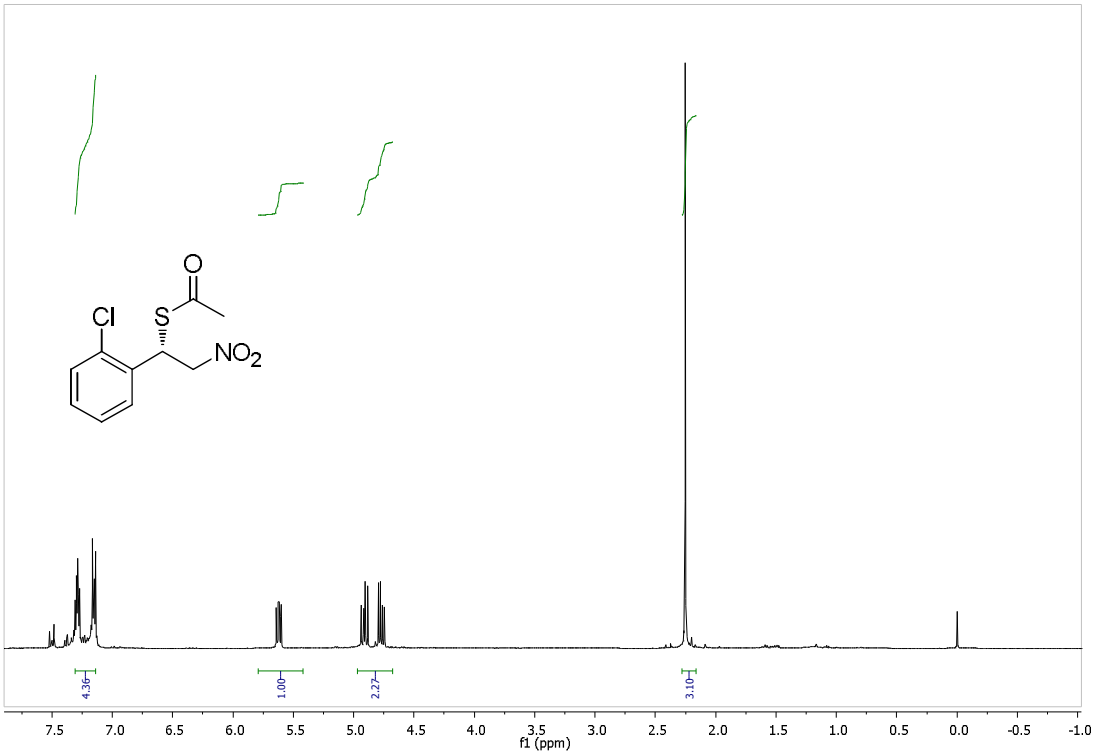


Figure A 9. ^{1}H NMR spectrum of product **62d**

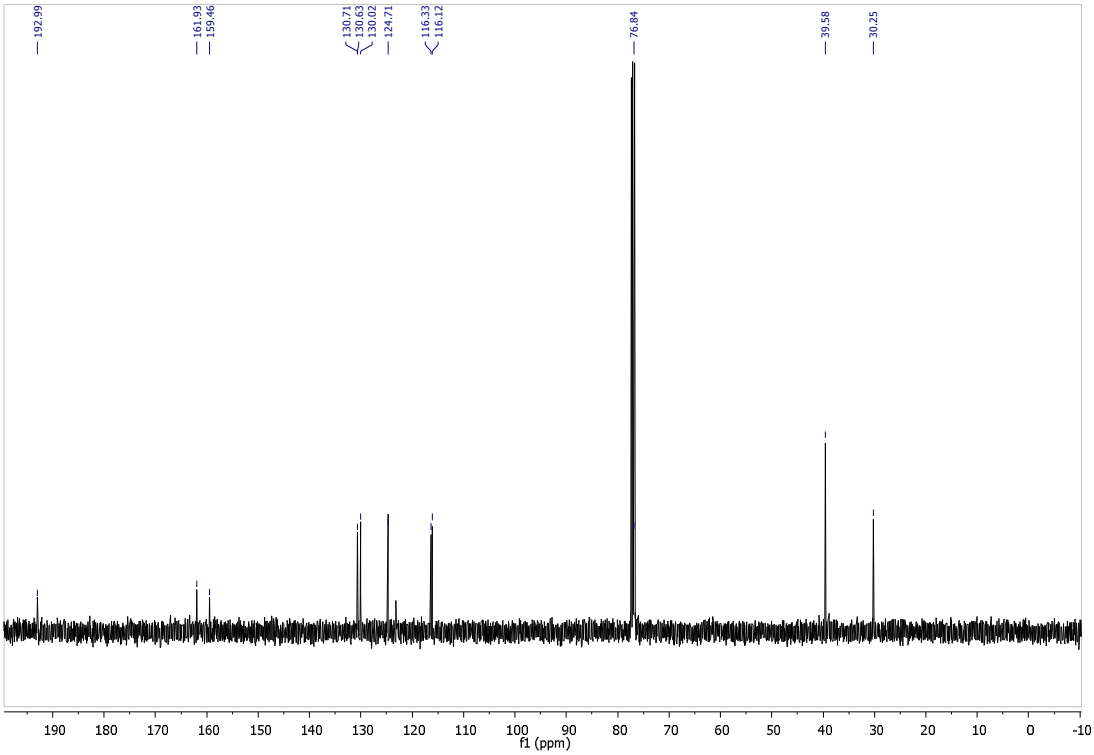


Figure A 10. ^{13}C NMR spectrum of product **62d**

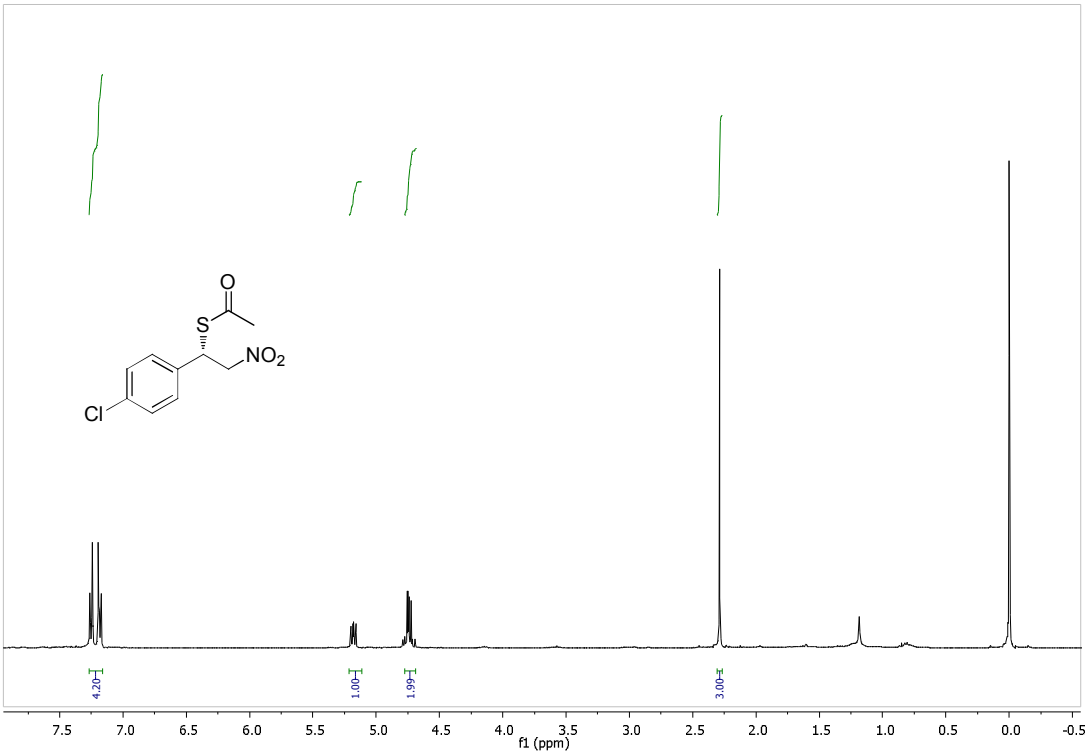


Figure A 11. ^{1}H NMR spectrum of product **62e**

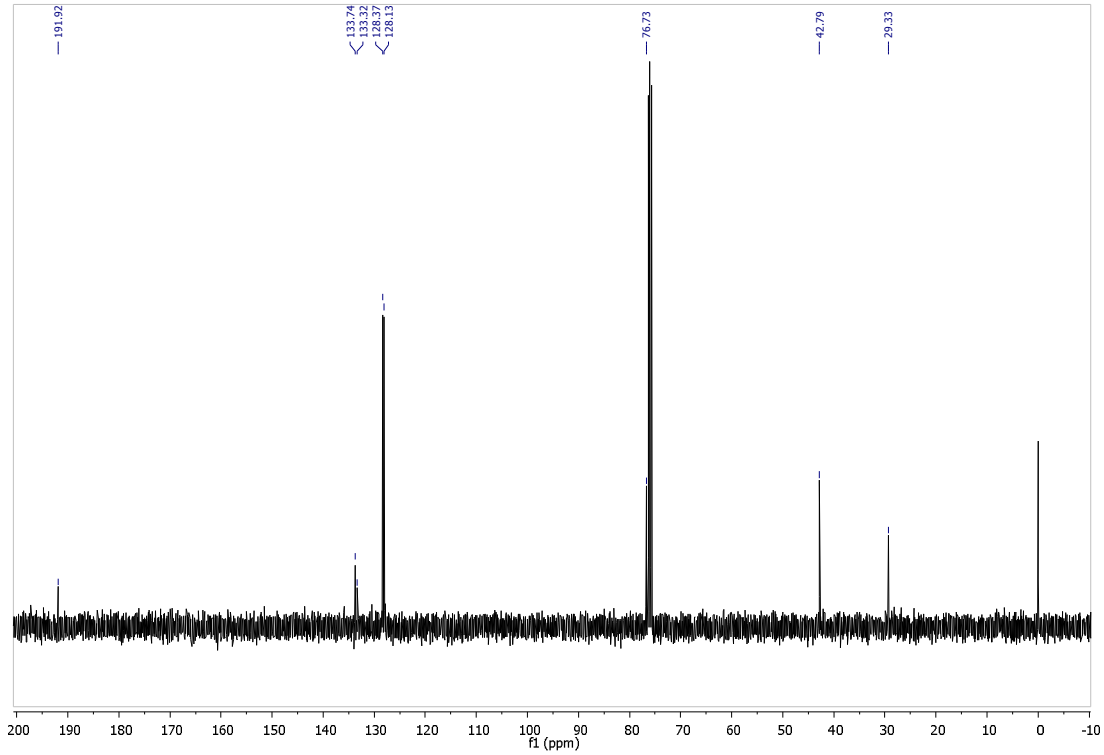


Figure A 12. ^{13}C NMR spectrum of product **62e**

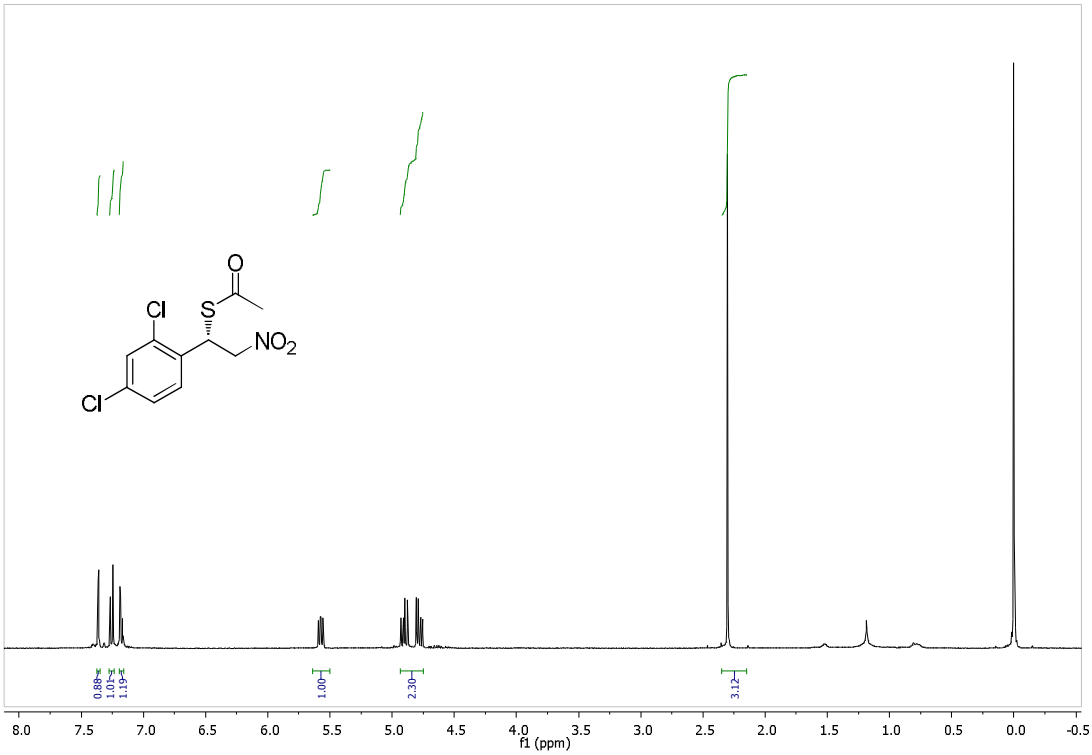


Figure A 13. ^{1}H NMR spectrum of product **62f**

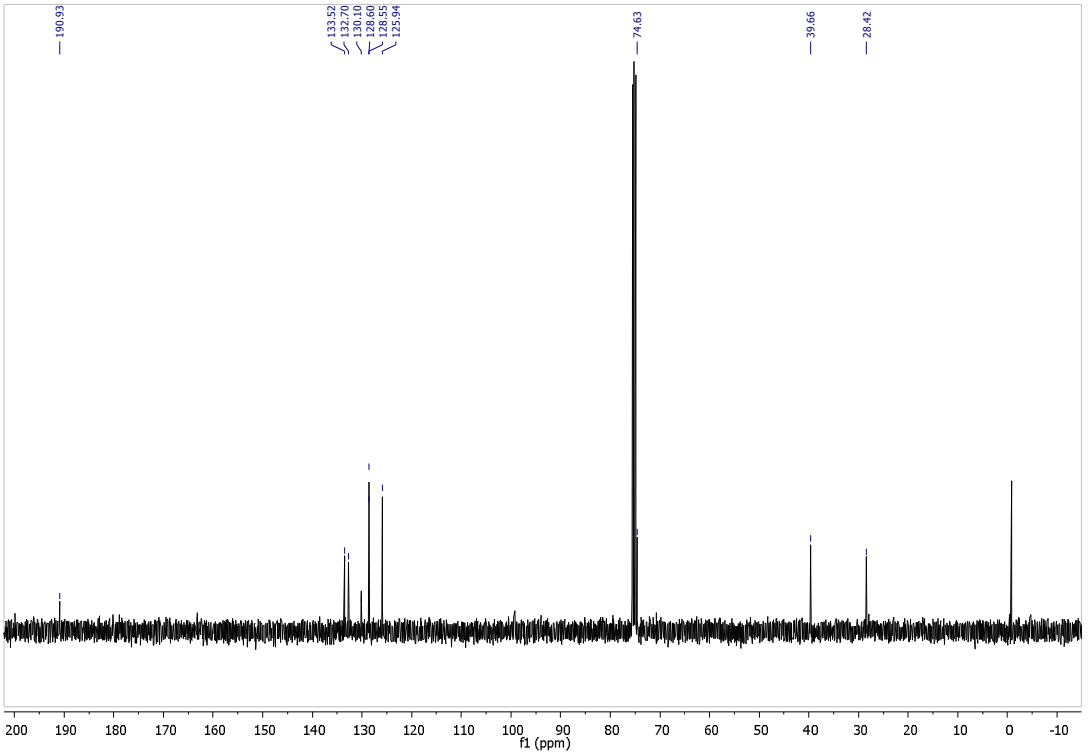


Figure A 14. ^{13}C NMR spectrum of product **62f**

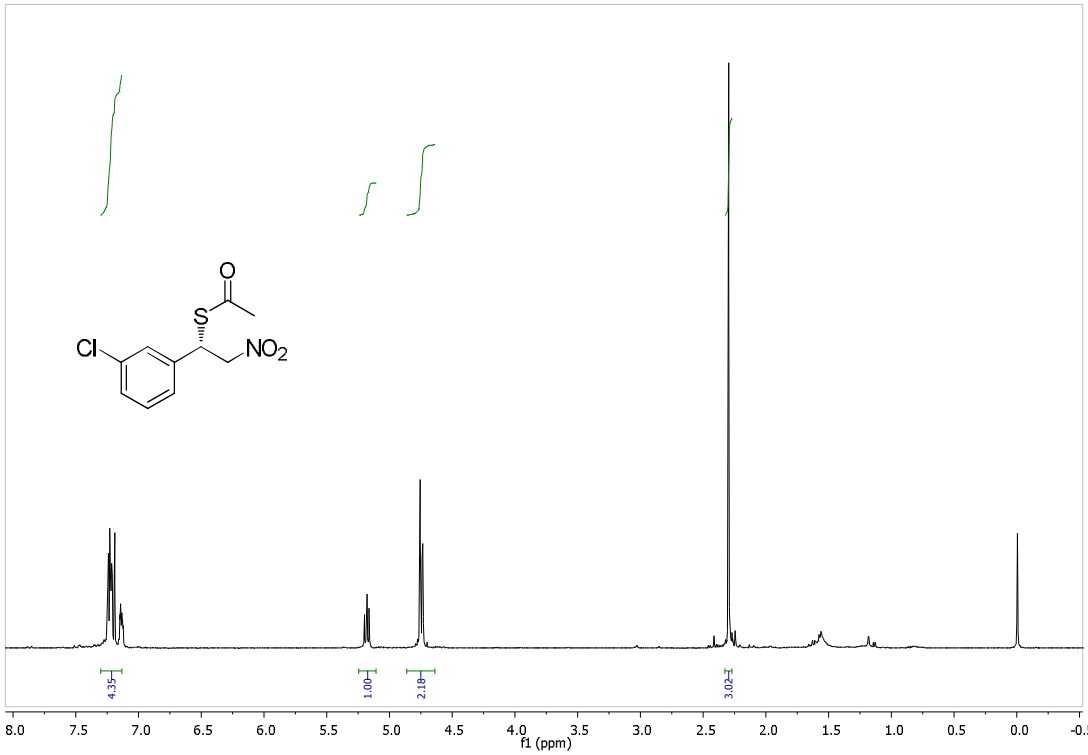


Figure A 15. ^{1}H NMR spectrum of product **62g**

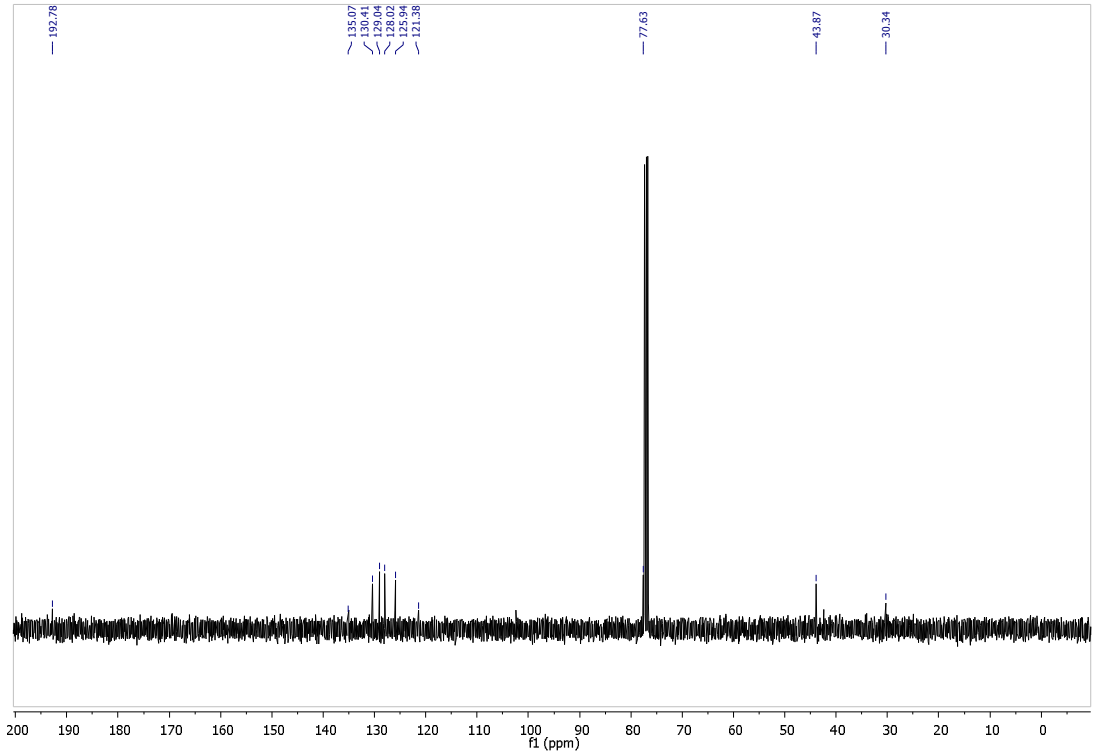


Figure A 16. ^{13}C NMR spectrum of product **62g**

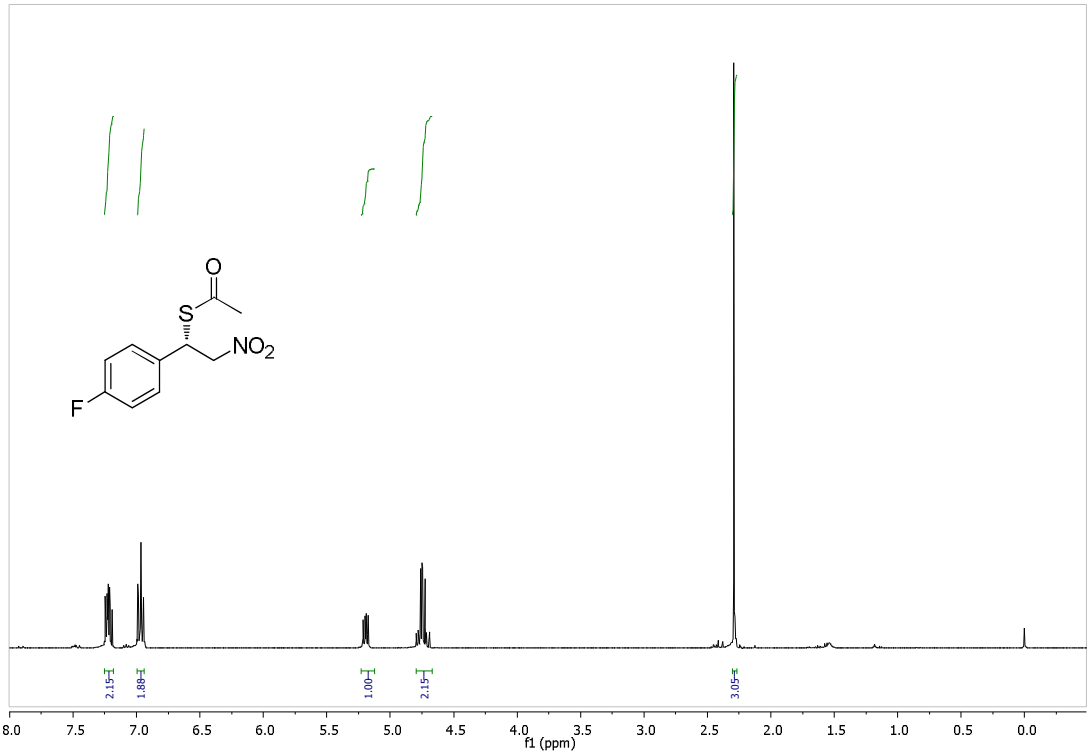


Figure A 17. ^{1}H NMR spectrum of product of **62h**

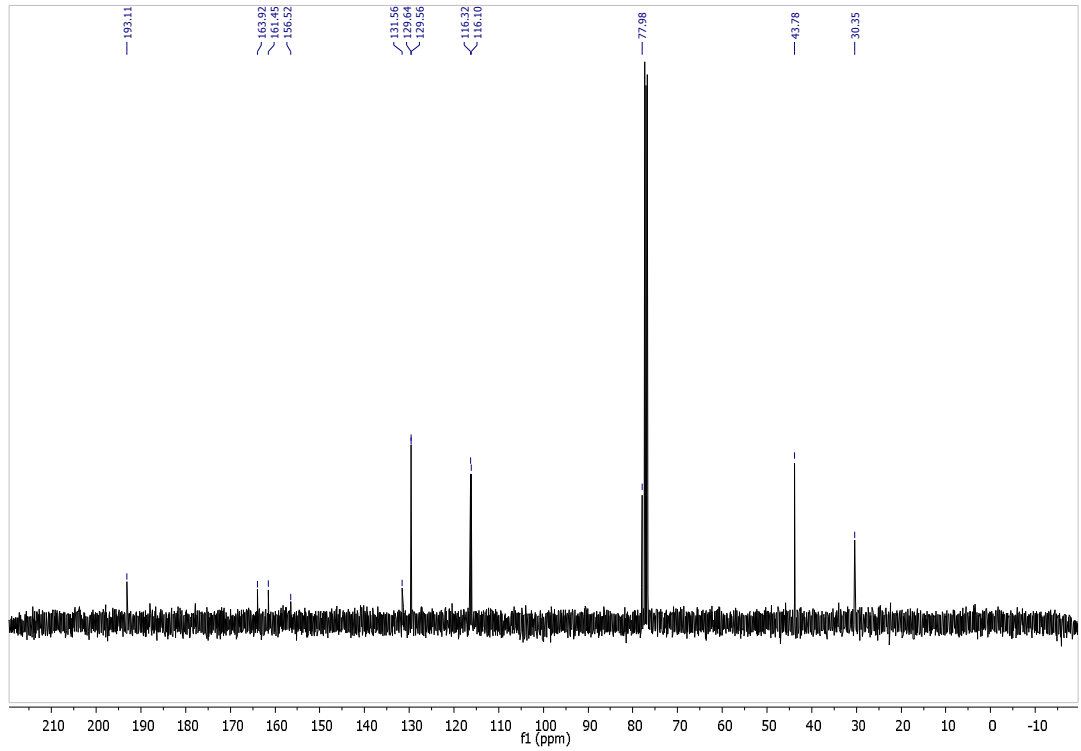


Figure A 18. ^{13}C NMR spectrum of product **62h**

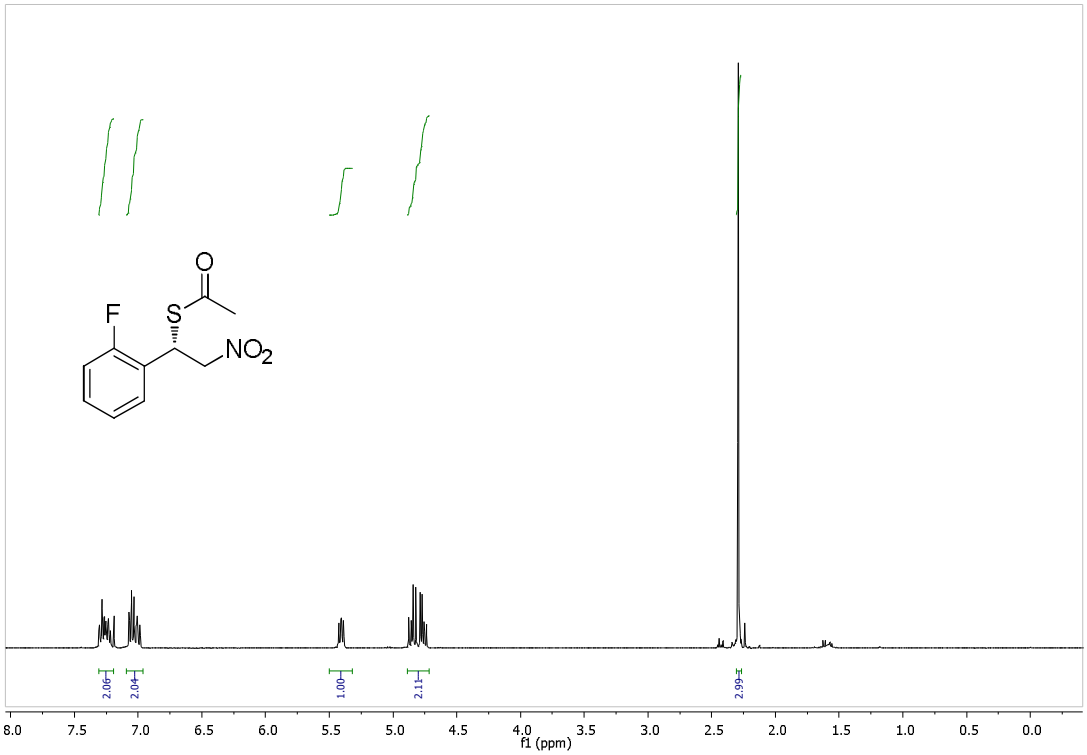


Figure A 19. ^{1}H NMR spectrum of product **62i**

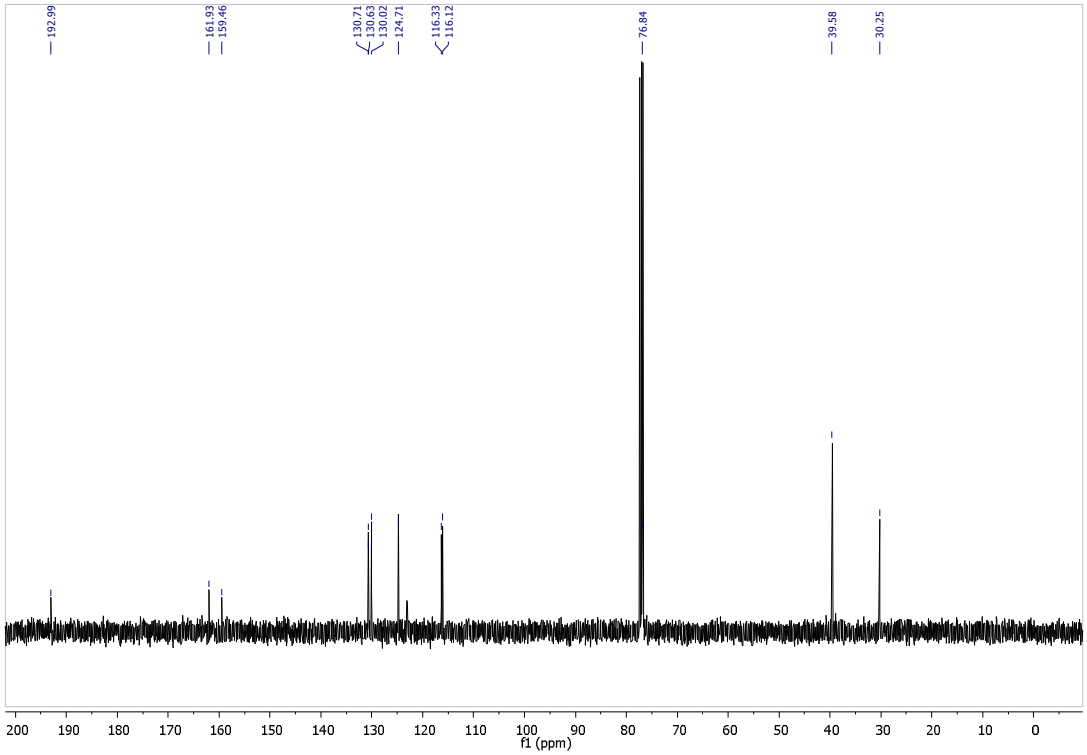


Figure A 20. ^{13}C NMR spectrum of product **62i**

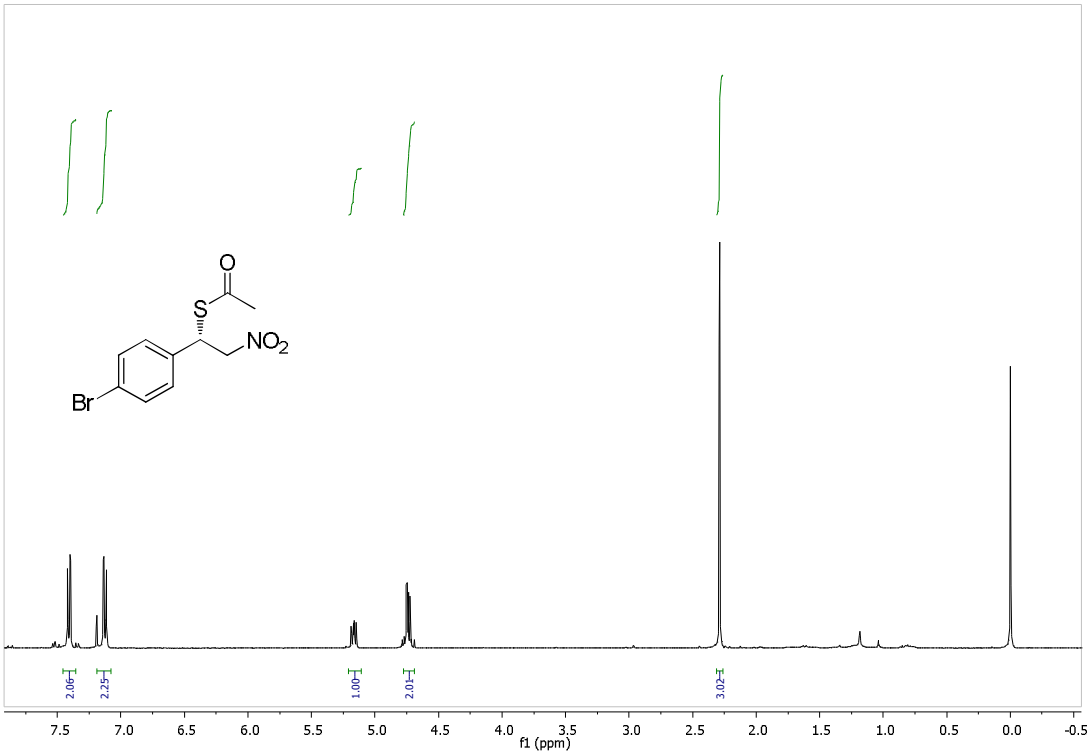


Figure A 21. ^{1}H NMR spectrum of product **62j**

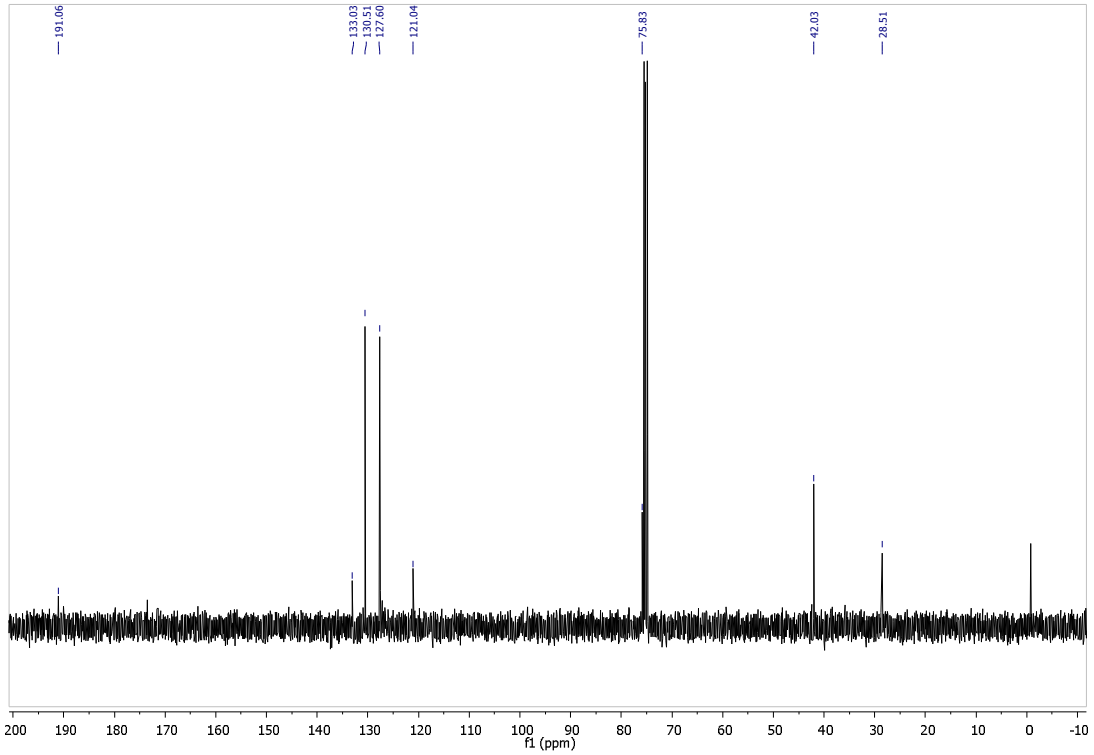


Figure A 22. ^{13}C NMR spectrum of product **62j**

APPENDIX B

HPLC DATA

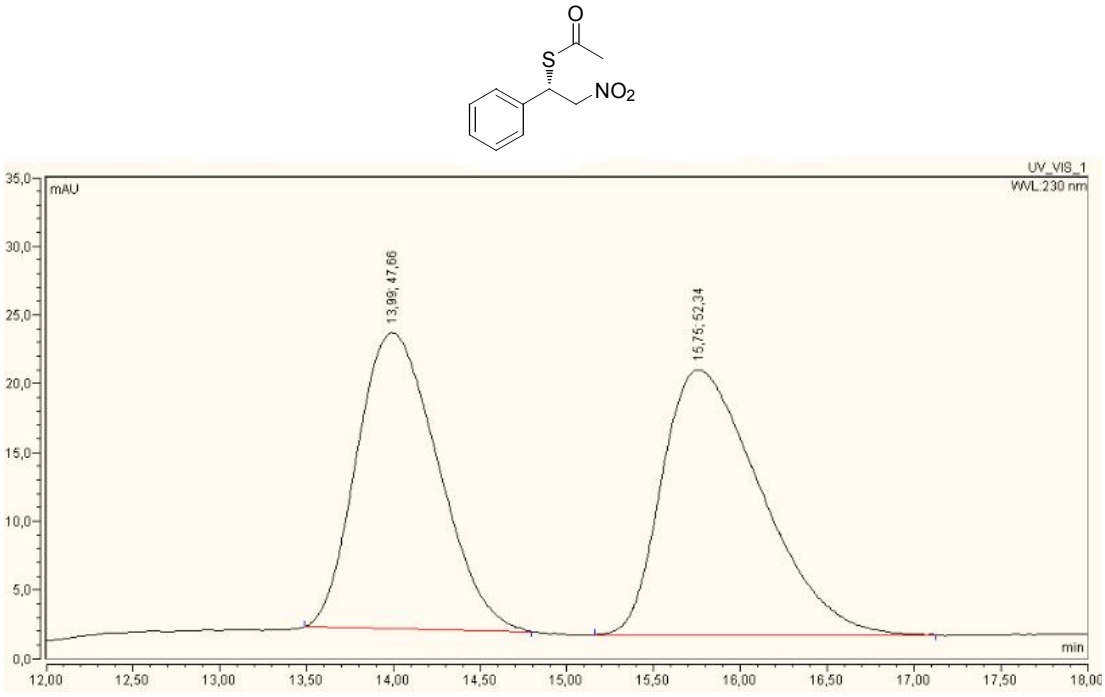


Figure B 1. HPLC chromatogram of ***rac*-62a**

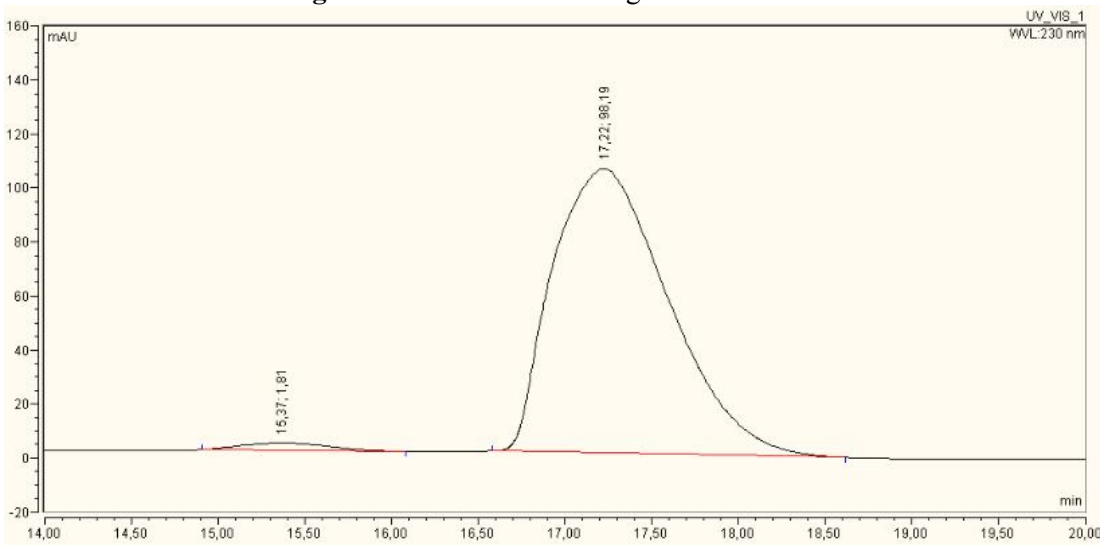


Figure B 2. HPLC chromatogram of **62a**

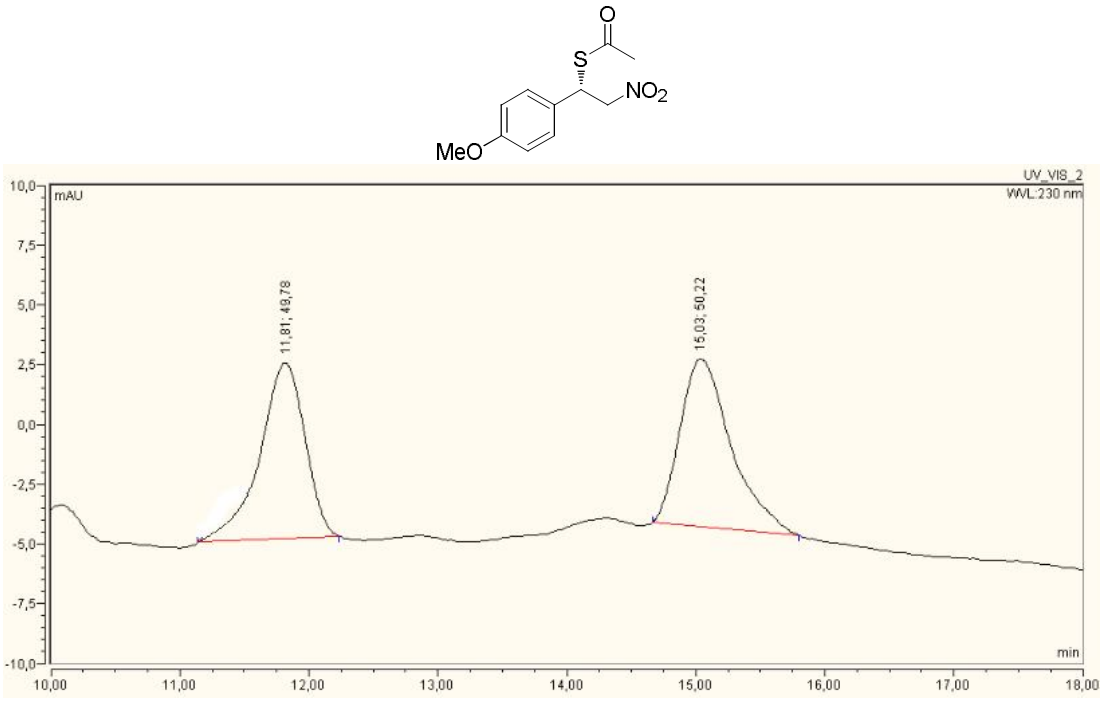


Figure B 3. HPLC chromatogram of ***rac*-62b**

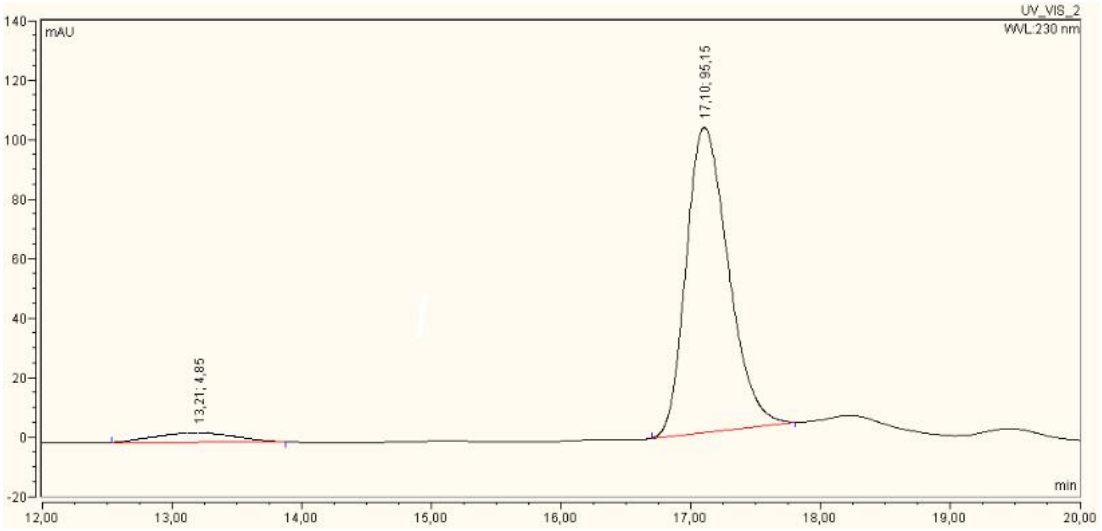


Figure B 4. HPLC chromatogram of **62b**

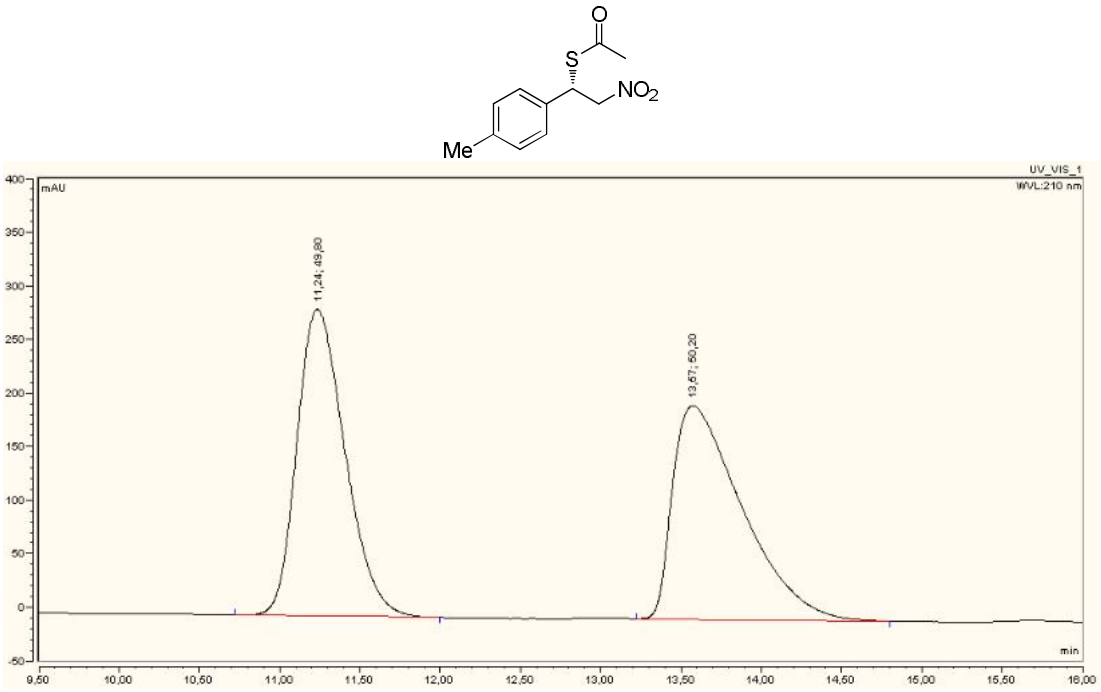


Figure B 5. HPLC chromatogram of ***rac*-62c**

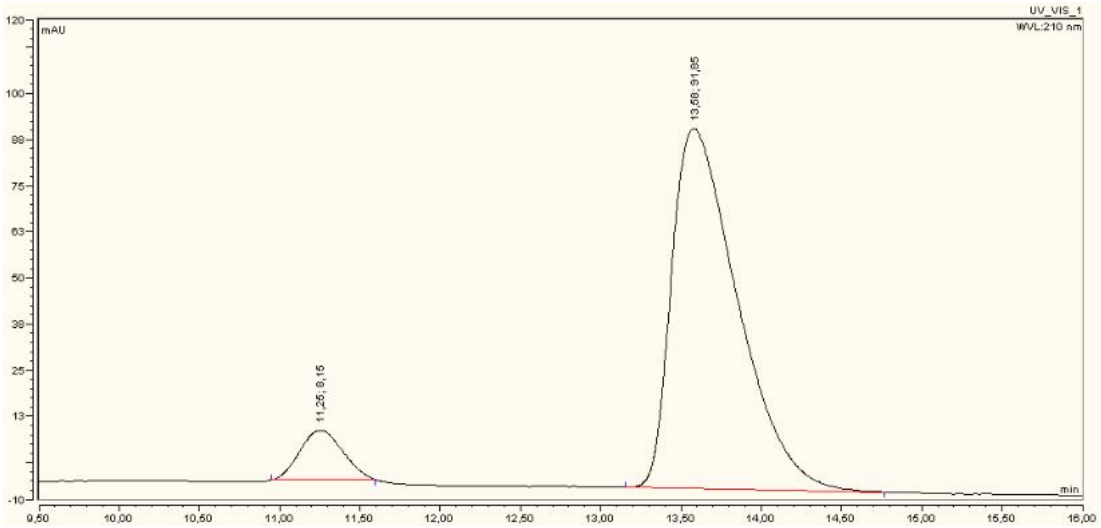


Figure B 6. HPLC chromatogram of **62c**

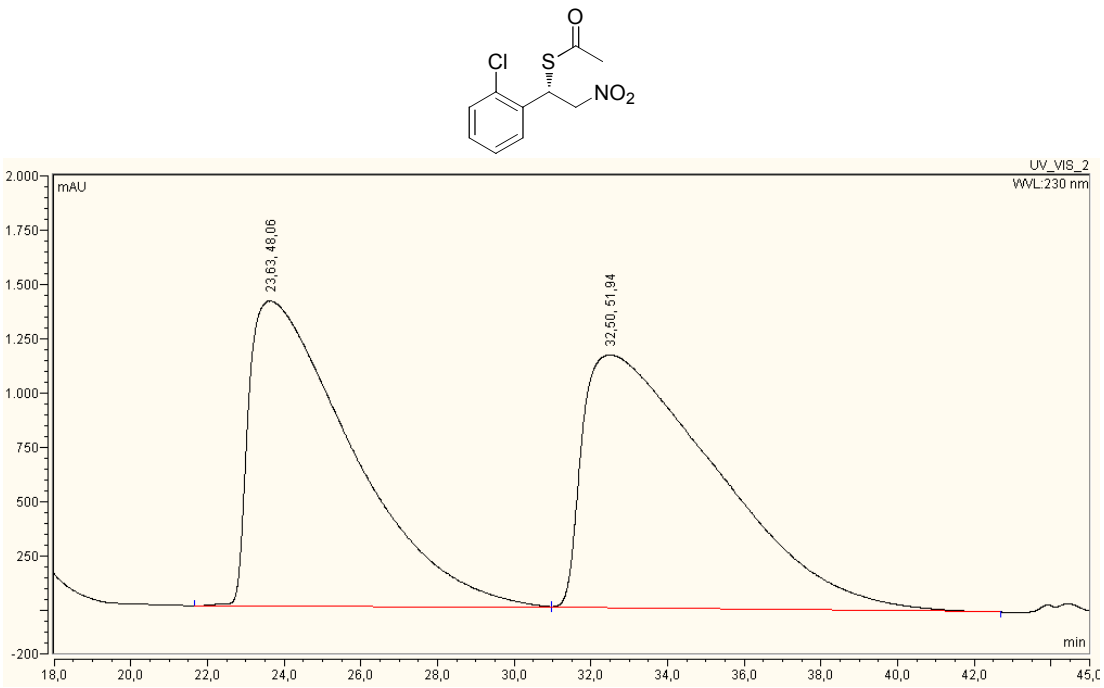


Figure B 7. HPLC chromatogram of ***rac*-62d**

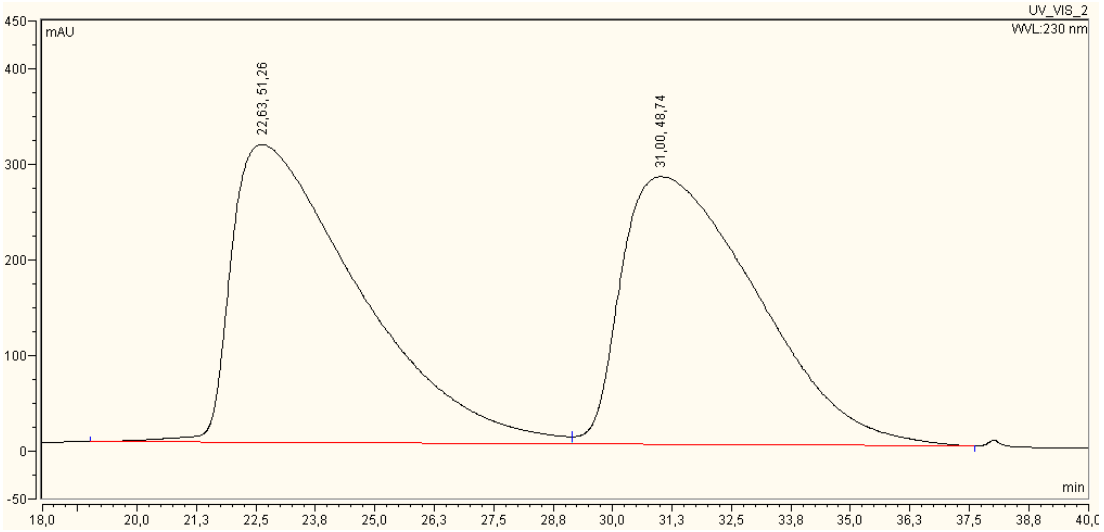


Figure B 8. HPLC chromatogram **of 62d**

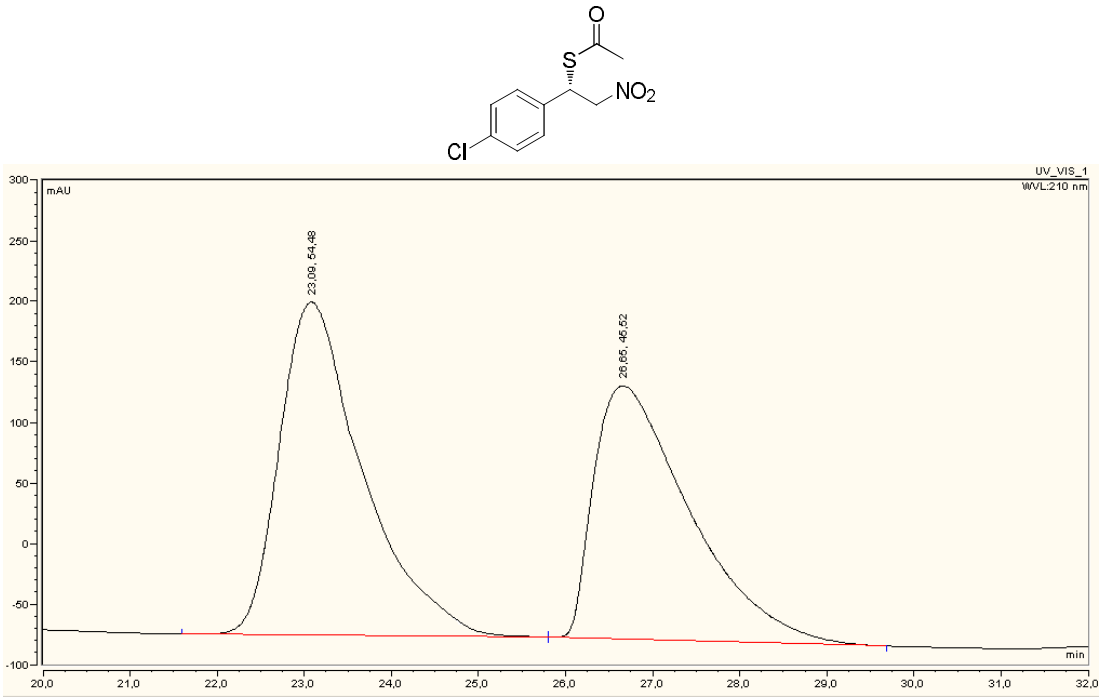


Figure B 9. HPLC chromatogram of ***rac*-62e**

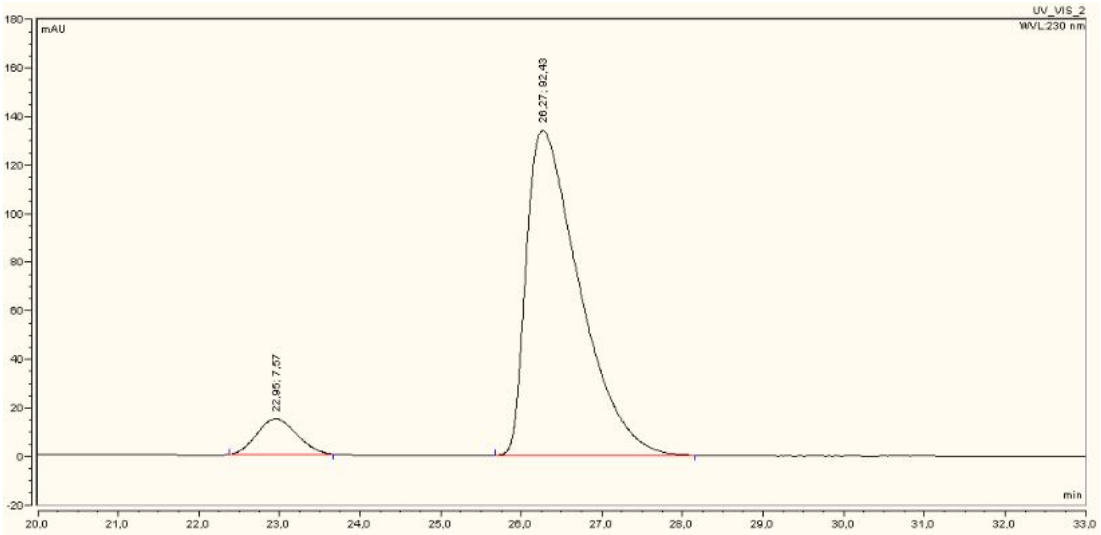


Figure B 10. HPLC chromatogram of **62e**

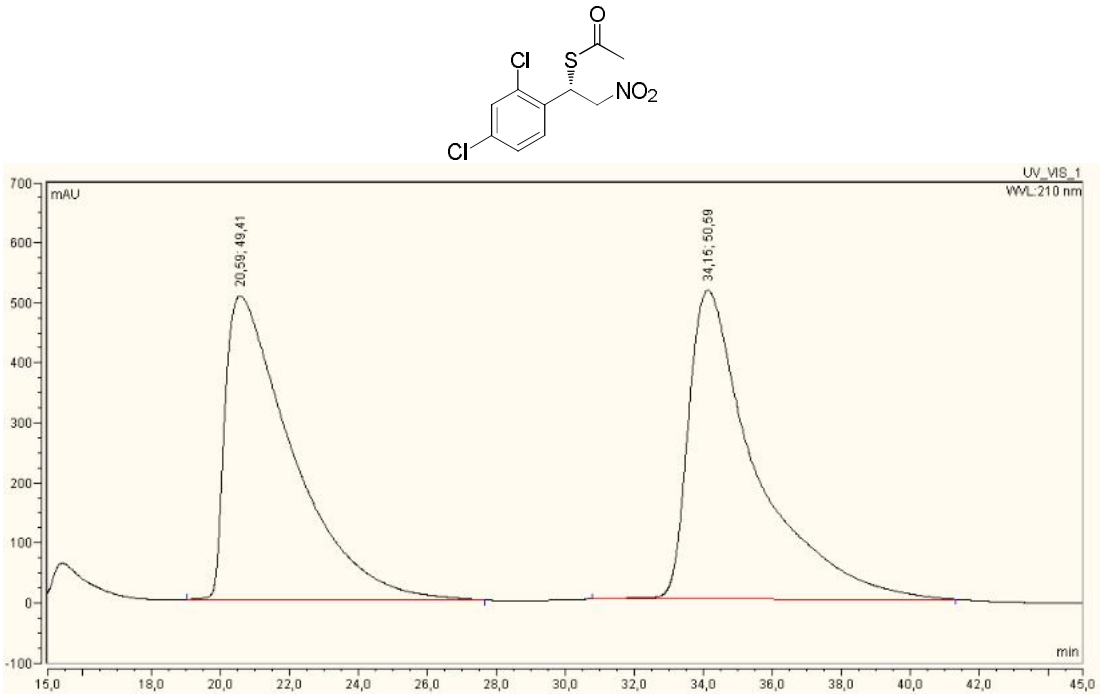


Figure B 11. HPLC chromatogram of ***rac*-62f**

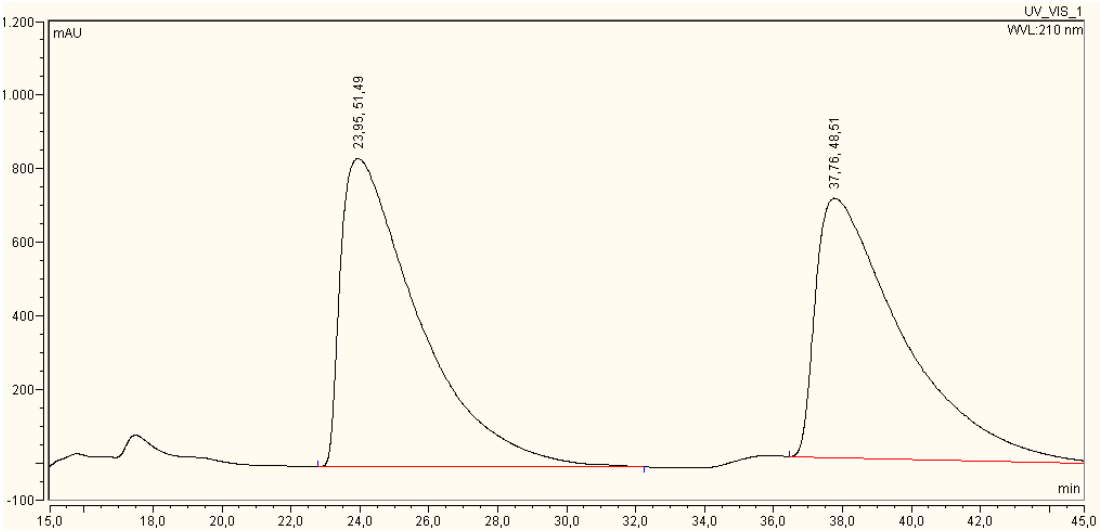


Figure B 12. HPLC chromatogram of **59f**

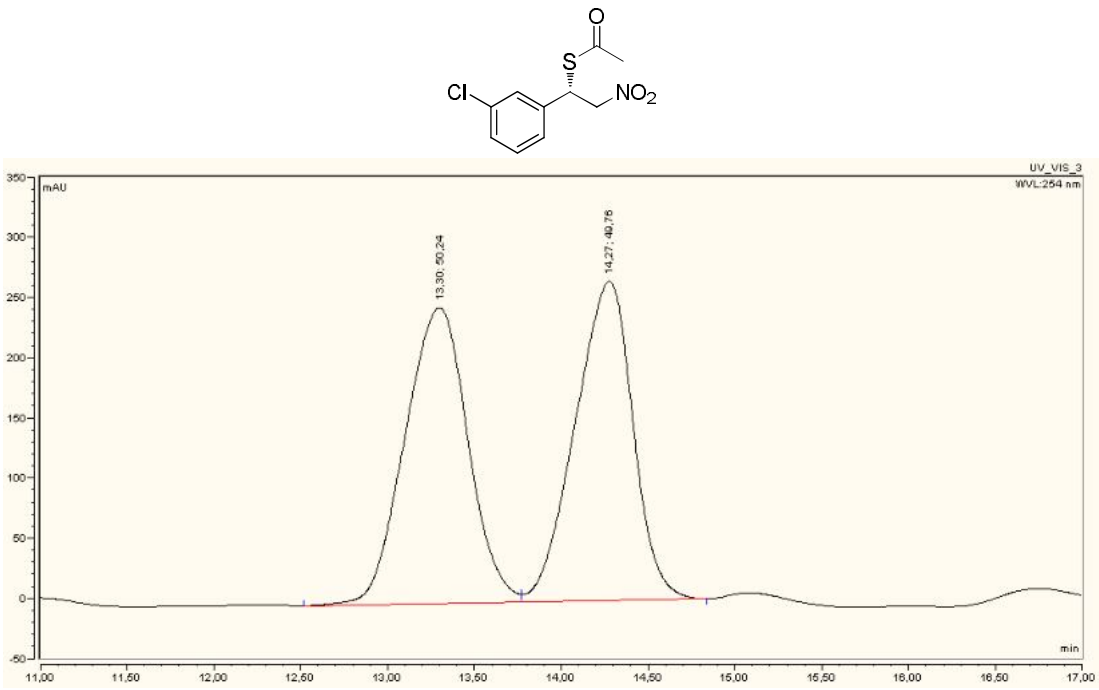


Figure B 13. HPLC chromatogram of ***rac*-62g**

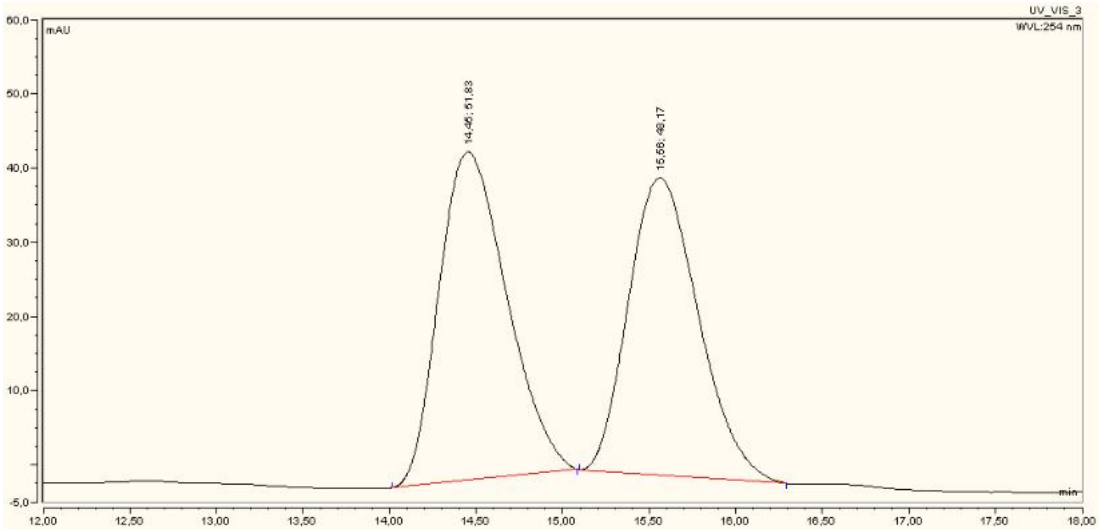


Figure B 14. HPLC chromatogram of **62g**

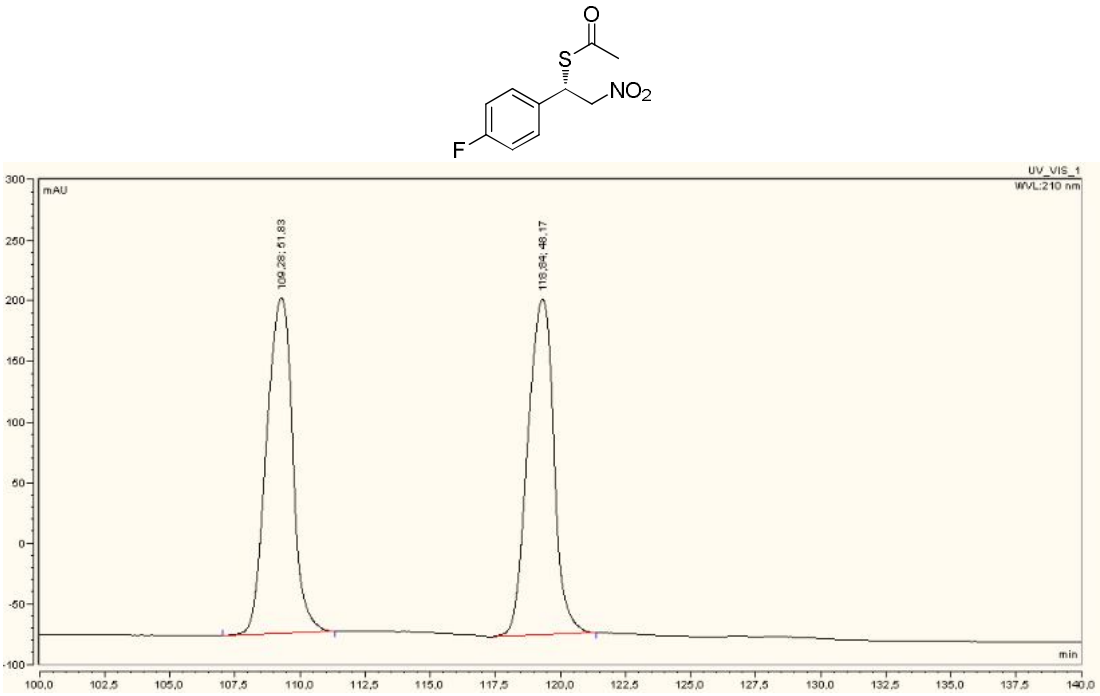


Figure B 15. HPLC chromatogram of ***rac*-62h**

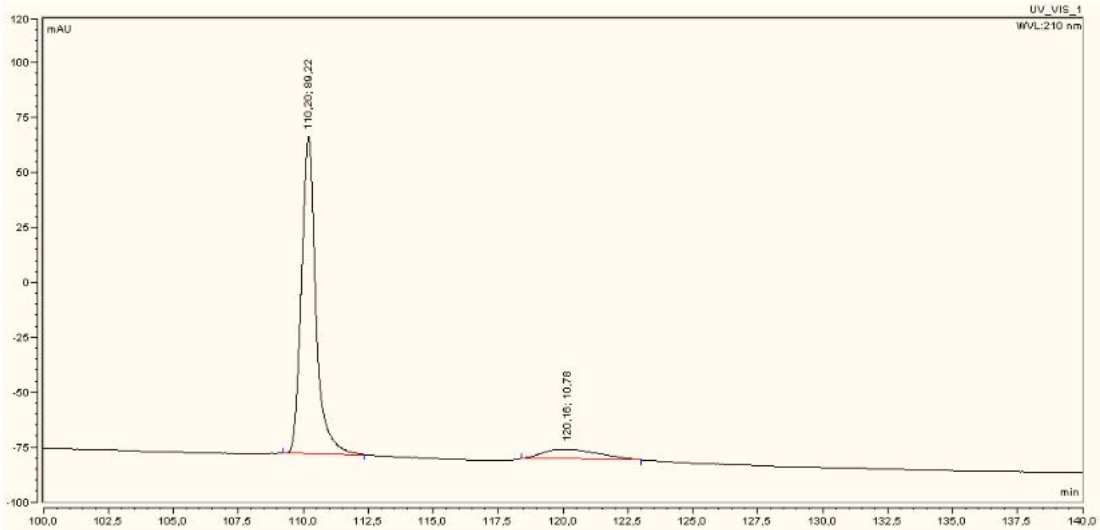
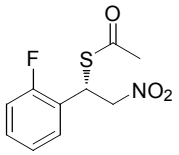


Figure B 16. HPLC chromatogram of **62h**



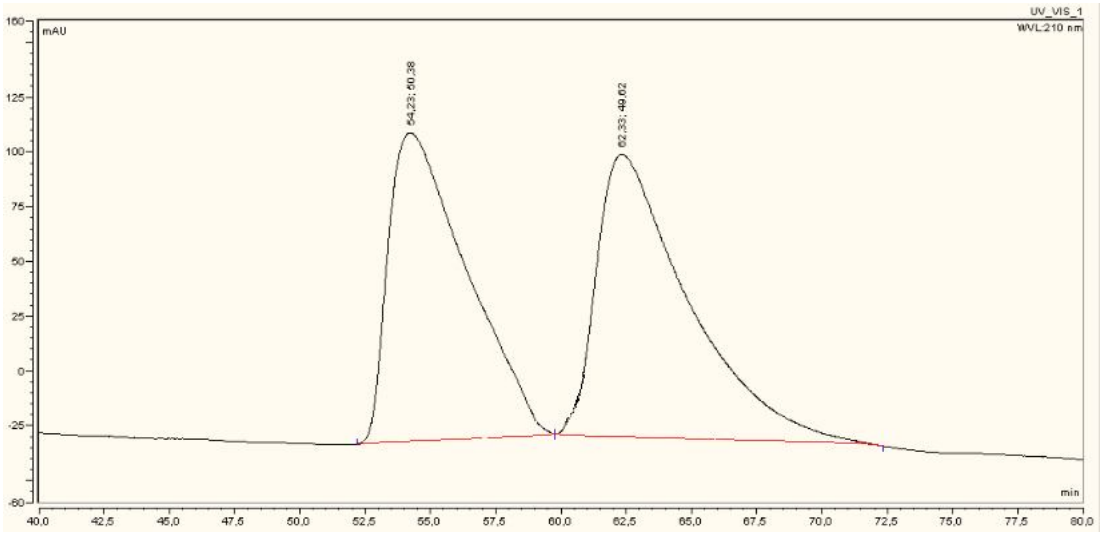


Figure B 17. HPLC chromatogram of ***rac*-62i**

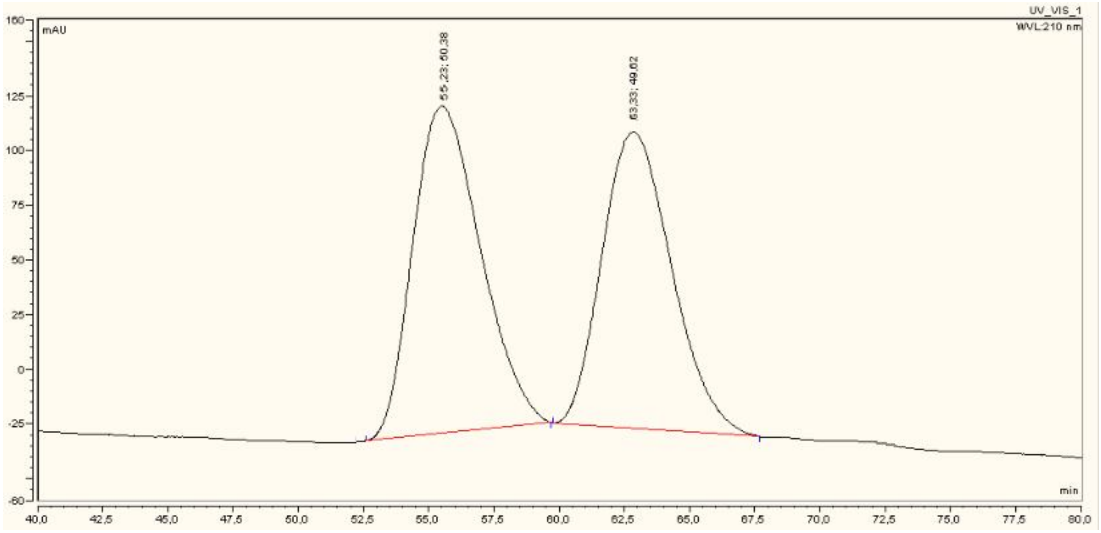


Figure B 18. HPLC chromatogram of **62i**

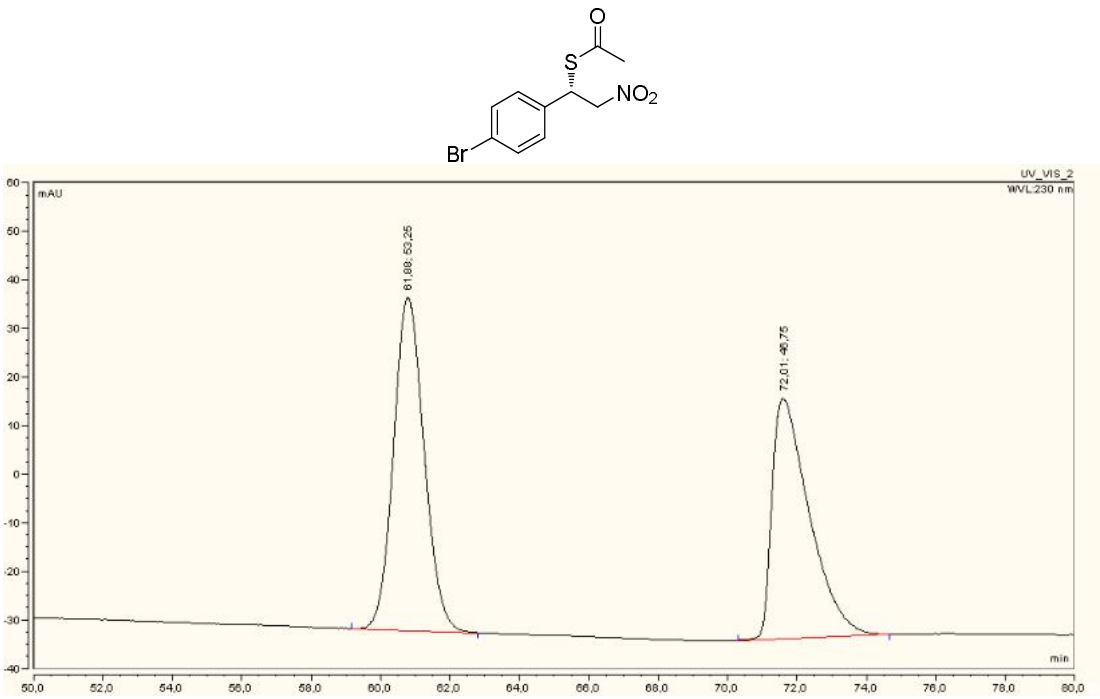


Figure B 19. HPLC chromatogram of ***rac*-62j**

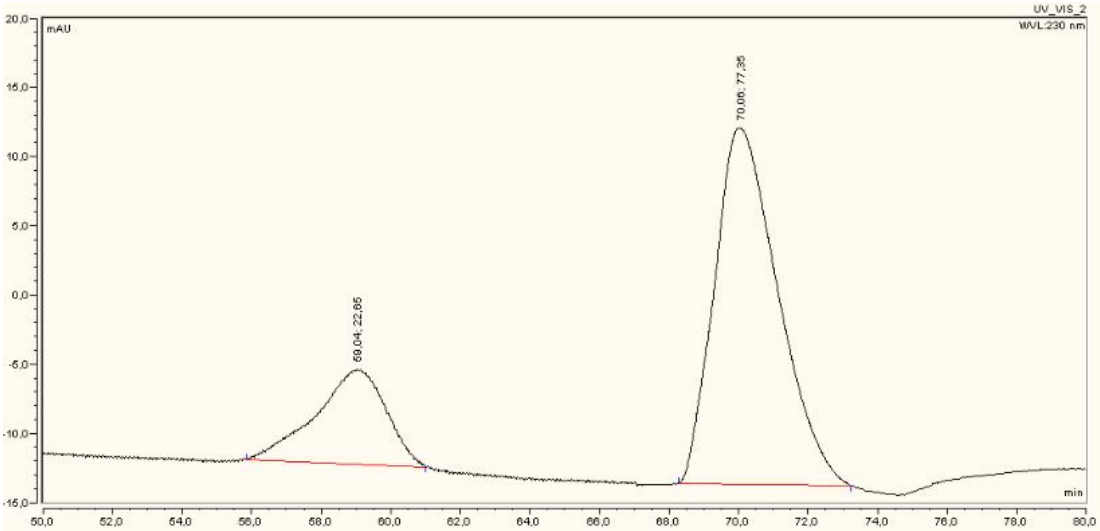


Figure B 20. HPLC chromatogram of **62j**