ASYMMETRIC MICHAEL ADDITION OF ALDEHYDES TO NITROOLEFINS WITH L-PROLINE AND BIFUNCTIONAL ORGANOCATALYST COMBINATION

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ASYMMETRIC MICHAEL ADDITION OF ALDEHYDES TO NITROOLEFINS WITH L-PROLINE AND BIFUNCTIONAL ORGANOCATALYST COMBINATION

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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

ASYMMETRIC MICHAEL ADDITION OF ALDEHYDES TO NITROOLEFINS WITH L-PROLINE AND BIFUNCTIONAL ORGANOCATALYST COMBINATION

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Organocatalysis describes the acceleration of chemical reactions through the addition of a substoichiometric quantity of an organic compound. Enantioselective Michael addition reaction catalyzed by organocatalysts has been highly progressing and gained importance in recent years due to its functions in organic synthesis. Asymmetric conjugate addition reactions are one of the most important carbon-carbon and carbon-heteroatom bond forming reactions in which active methylenes are used as donors and α,β-unsaturated compounds used as acceptors. This thesis comprises the asymmetric Michael addition reaction of aldehydes having active methylene to nitroolefins catalyzed by *L*-proline and 2-aminoDMAP/Urea bifunctional organocatalyst combination. Aldehydes are gained nucleophilic property by deprotonation of methylene protons and readily react with electrophilic nitroolefins. Furthermore, *L*-proline plays a role in activation of aldehydes by forming enamine and 2-aminoDMAP/Urea bifunctional organocatalyst plays a role in activation of nitroolefin and in forming an assembly with carboxylate moiety of *L*-proline. In the first part, optimization studies were conducted by screening several parameters such as solvent, catalyst loading, concentration and temperature for Michael addition reaction. In the second part, derivatization studies were performed according to optimized conditions. Consequently, high enantioselectivities up to 89% and high conversions up to 100% were achieved in the desired products.

Keywords: conjugate addition, Michael addition reaction, asymmetric organocatalysis, bifunctional organocatalysis, *L*-proline, 2-AminoDMAP/urea

ÖZ

L-PROLİN VE BİFONKSİYONEL ORGANOKATALİZÖR KOMBİNASYONU İLE ALDEHİTLERİN NİTROOLEFİNLERE ASİMETRİK MICHAEL KATILMASI

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Eylül 2013, 72 sayfa

Organokatalizörler kimyasal tepkimeleri hızlandıran substökiometrik miktarlarda kullanılan organik bileşiklerdir. Organik sentezlerdeki fonksiyonlarından dolayı, organokatalizörlerle katalizlenen enantioseçici Michael katılma tepkimeleri son zamanlarda büyük ölçüde ilerlemekte ve önem kazanmaktadır. Aktif metilenlerin donör ve α,β-doymamış bileşiklerin akseptör olarak kullanıldığı asimetrik konjuge katılma tepkimeleri karbon-karbon ve karbon-heteroatom bağı yapım tepkimelerinin en önemlilerinden biridir. Bu tez, *L*-prolin ve 2-aminoDMAP/ üre bifonksiyonel organokatalizör kombinasyonu ile katalizlenen aktif metilene sahip aldehitlerin nitroolefinlere asimetrik Michael katılma reaksiyonlarını kapsamaktadır. Metilen protonlarının deprotonasyonu ile aldehitler nükleofilik özellik kazanır ve elektrofilik nitroolefinlerle kolayca tepkimeye girer. *L*-prolin enamin oluşturarak aldehitin aktifleştirilmesinde rol oynarken, 2-aminoDMAP/ üre nitroolefinin aktivasyonunda ve prolinin karboksil kısmı ile birliktelik oluşturmasında rol oynar. İlk kısımda Michael katılma reaksiyonu için çözücü, katalizör miktarı, konsantrasyon ve sıcaklık gibi parametreler taranarak optimizasyon çalışmaları yapıldı. İkinci kısımda ise ilk aşamada belirlenen optimum tepkime şartları kullanılarak ürünler türevlendirildi. Sonuç olarak, istenilen ürünlerin sentezi %100'ü bulan yüksek dönüşüm ve %89'u bulan yüksek düzeyde enantioseçicilikle başarıyla gerçekleştirilmiştir.

Anahtar Kelimeler: konjuge katılma, Michael katılma tepkimesi, asimetrik organokataliz, bifonksiyonel organokataliz, L-prolin, 2-aminoDMAP/üre

To my family and Prof. Dr. Ayhan Sıtkı Demir

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LIST OF ABBREVIATIONS

DMAP: 4-Dimethylaminopyridine

HOMO: Highest Occupied Molecular Orbital

LUMO: Lowest Unoccupied Molecular Orbital

SOMO: Singly Occupied Molecular Orbital

***i*PBM:** Isopropylbimorpholine

DABCO: 1,4-diazabicyclo[2.2.2]octane

DIPEA: *N*,*N*-Diisopropylethylamine

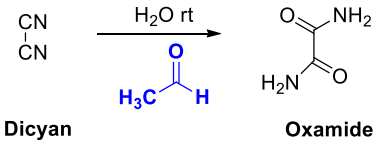
CHAPTER 1

INTRODUCTION

1.1 Organocatalysis

‘‘*Organocatalysis*’’ is a term that describes the acceleration of chemical reactions with a substoichiometric amount of a non-metal containing organic molecule.[1] These purely organic molecules are introduced as ‘‘*organocatalysts*’’ and composed of C (carbon), H (hydrogen), N (nitrogen), S (sulfur) and P (phosphorous). Transition metals or other metals are not required for the catalytic activity of organocatalysts.[2]

The use of small pure organic molecules as a catalyst in reactions has been known for centuries. In this field, the first organocatalytic reaction without any metal was reported by German chemist Justus von Leibig in 1860 for the synthesis of oxamide from dicyan in water and acetaldehyde was used as an accelerator for this chemical transformation (Scheme1).[3]



Scheme 1. Justus von Leibig’s Oxamide synthesis

Justus von Leibig’s work can be recognized as the beginning of the new era of organocatalysis. Furthermore, organocatalysis has developed spectacularly and became a thriving area in asymmetric reactions in the last 15 years. The interest in this field has been increasing tremendously and a new publication on organocatalyic reactions has come up almost every passing day which was demonstrated in Figure 1. The data were obtained based on the research conducted by ISI Web of Knowledge in May 2008. The word organocatalysis or its derivatives has been used as a title in more than 600 articles and as a subject in more than 40,000 web pages.[2]

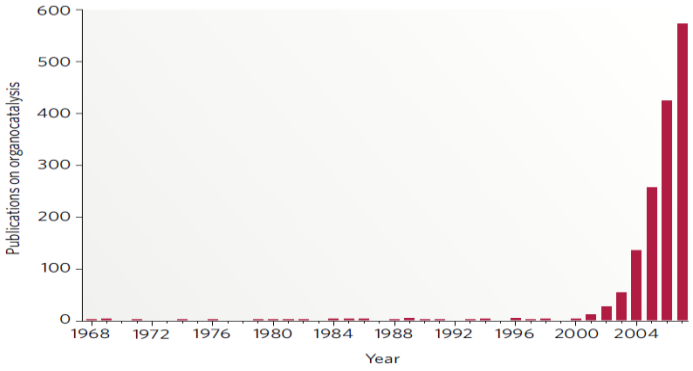


Figure 1. The number of publications on the topic of organocatalysis from 1968 to 2004

An increase in this area might show that organocatalysis filled the gap between enzyme-catalysis and metal catalysis by offering highly efficient and stereoselective transformations.[4] As such, organocatalysts have several advantages. They are inexpensive, non-toxic, robust and easy to prepare. Thus, this reveals the reduction in chemical waste, savings in cost, time and energy. Moreover, they offer simple storage, handling, and non-inert reaction conditions toward moisture and oxygen in the atmosphere. They are available from biological materials and also many of them are commercially available which will hopefully stimulate the use of organocatalysts in asymmetric synthesis.[5]

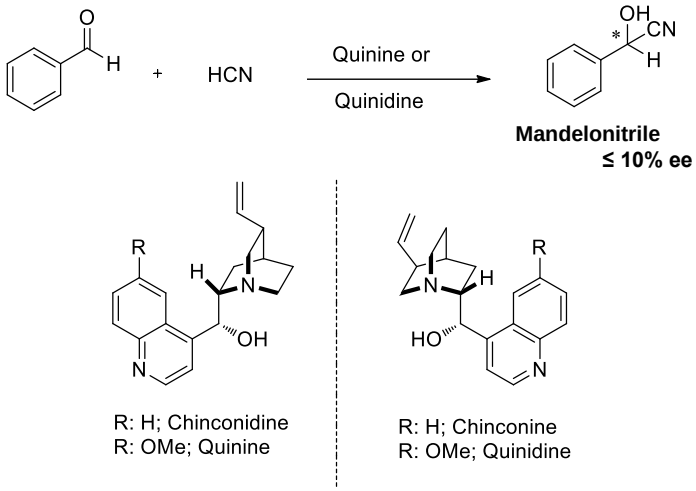
1.1.1 Asymmetric Organocatalysis

Chiral organic molecules have been used for promoting transformations from the early days of chemistry. Since the spatial arrangement or selectivity in molecules became important, the interest in enantioselective synthesis has increased.[6] In history, the first asymmetric reaction was performed by Louis Pasteur in 1858 for decarboxylative kinetic resolution of ammonium tartarate by using the microorganism *Penicilium glauca*. L. Pasteur realized that *(d)* - enantiomer of a racemic solution of ammonium tartarate was destroyed more rapidly than *(l)* - enantiomer in the presence of this organism.[7] That is why enzymes were considered as a highly efficient and selective first catalyst for organic reactions.

In asymmetric reactions, the main goal is to get enriched and enantiomerically pure compound in the most practical and efficient manner. In fact, transition-metal complexes and enzymes were accepted as main classes for asymmetric synthesis to get enantiomerically enriched compounds for many years. However, the simple fact about organocatalysis that they are organic molecules made the organocatalysts attractive for chemists and the use of pure organic catalysis for asymmetric reactions turned out to be an efficient tool for the synthesis of chiral building blocks.[8] These chiral building blocks are generally used as drug intermediates, agrochemicals and are important for biological activity of molecules. Because almost all of the molecules in organism such as nucleic acids (DNA, RNA), enzymes, receptors and cell membranes are asymmetric and contain only one chiral form.

1.1.2 Historical Development of Asymmetric Organocatalysis

In literature, the first example of an asymmetric organocatalytic reaction was reported in 1912, by Bredig and Fiske for the enantioselective cyanohydrin synthesis, mandelonitrile, from benzaldehyde and HCN in the presence of quinine and quinidine alkaloids as chiral catalyst. Unfortunately, in this pioneering work the optical yields achieved in most up to 10% ee and thus it was insufficient for preparative purposes (Scheme 2).[9]



Scheme 2. The first example of asymmetric organocatalysis, Bredig and Fiske's work

The milestones in historical development of asymmetric organocatalysis are summarized in Figure 2.

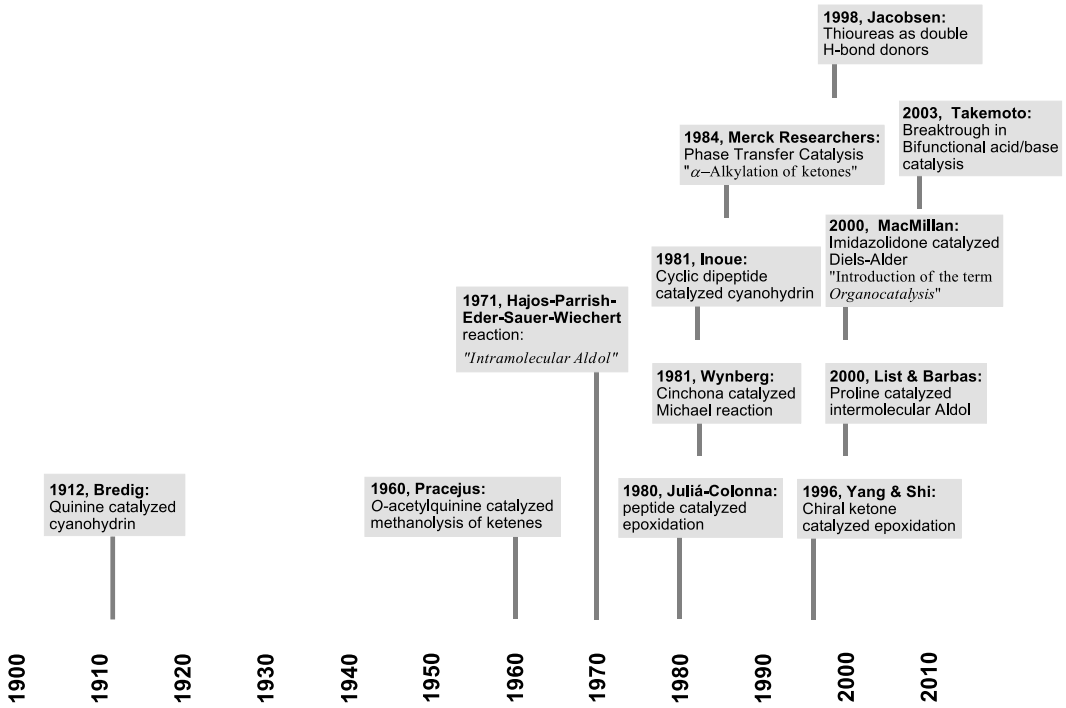
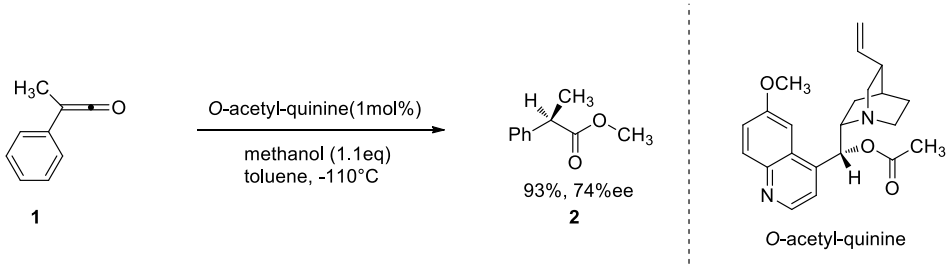


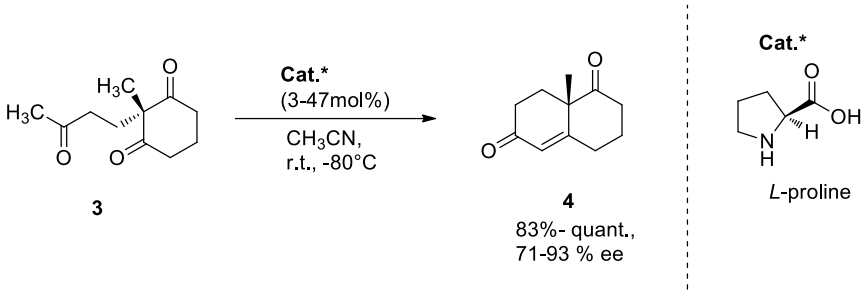
Figure 2. Milestones in historical development in asymmetric organocatalysis

After Bredig's work, the pioneering work was reported in 1960's by Pracejus *et al* and showed that significant enantioselectivities could be obtained by using cinchona type organocatalysts. In the reaction of methanol to phenylmethylketene (**1)** they obtained addition product **2** with remarkable selectivity as 74% at -110 °C using only 1 mol% of *O*-acetyl-quinine (hydroxyl-acetylated quinine derivative) as shown in Scheme 3.[2]



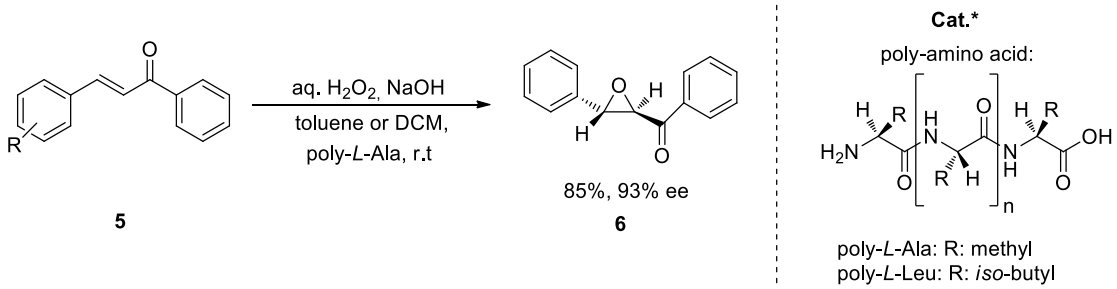
Scheme 3. Methanolysis of phenylmethylketene, Pracejus' work

Further breakthrough in the area of asymmetric organocatalysis came in 1970s by two industrial groups employees whose are Hajos and Parrish of Hoffman- La Roche and Eder, Sauer and Wiechert of Shering. They published the first and highly selective intramolecular asymmetric aldol cyclodehydration of achiral trione **3** to the Wieland-Miescher ketone **4**, which is an important intermediate in steroid synthesis, using the proline, simple amino acid, as a catalyst. This reaction is known later as Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 4).[2]



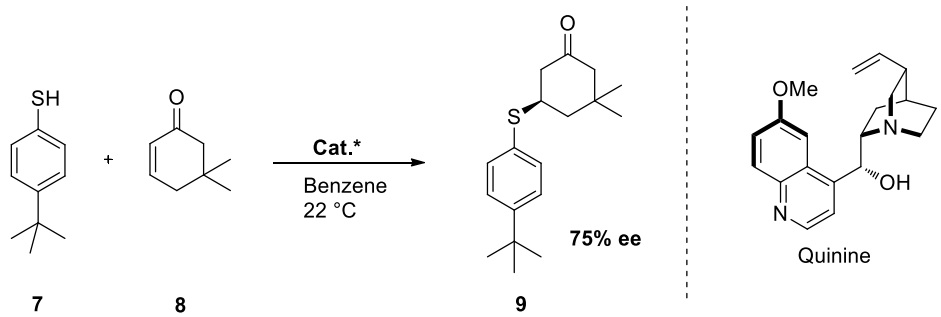
Scheme 4. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

Another striking discovery came up in 1980s by Juliá and Colonna *et al*. They discovered that asymmetric epoxidation of enones such as chalcones **5** by alkaline hydrogen peroxide which is catalyzed by leucine and alanine-derived poly-amino acid catalyst. They readily achieved enantiomeric excess up to 95% (Scheme 5).[2, 10]



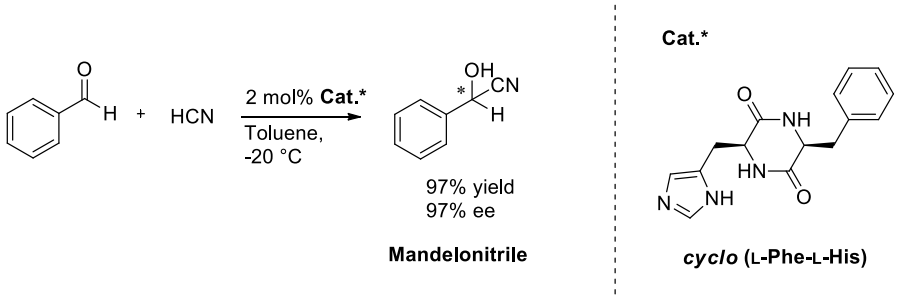
Scheme 5. The Juliá- Colonna asymmetric epoxidation of chalcones

Another study by using cinchona alkaloids was reported again by Wynberg *et al*. in 1981. They investigated that the employment of cinchona alkaloid-based catalysts in Michael addition reactions between aromatic thiols **7** and conjugated cycloalkenones **8** afforded optically active 3-arylthiocycloalkanones **9** (Scheme 6). They demonstrated that cinchona and ephedra alkaloids could serve as bifunctional catalysts in Michael reactions by activating both nucleophile and electrophile respectively. As a result of this study, they get higher reaction rates and higher enantiomeric excesses up to 75% with catalysts containing β-hydroxy amine moiety without a hydroxyl function.[11]



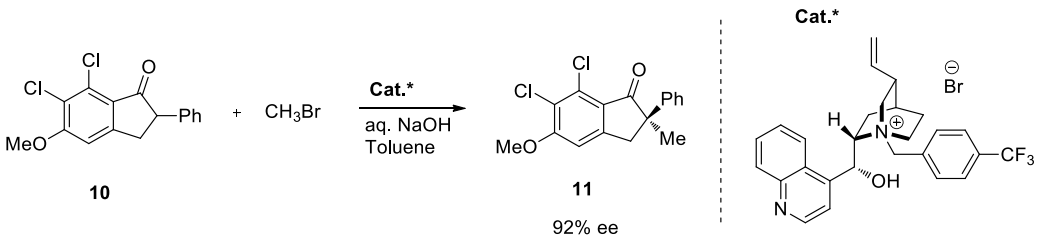
Scheme 6. Wynberg's Cinchona-based catalyzed Michael Addition Reaction

Moreover, again in 1981, Inoue and coworkers reported asymmetric cyanohydrin synthesis catalyzed by a synthetic cyclic dipeptide organic catalyst derived from *L*-phenylalanine and *L*-histidine in which the imidazole group of histidine is catalytically active as base (Scheme 7). Mandelonitrile was obtained with excellent ee value up to 97% as opposed to the first attempt done by Bredig & Fiske.[12]



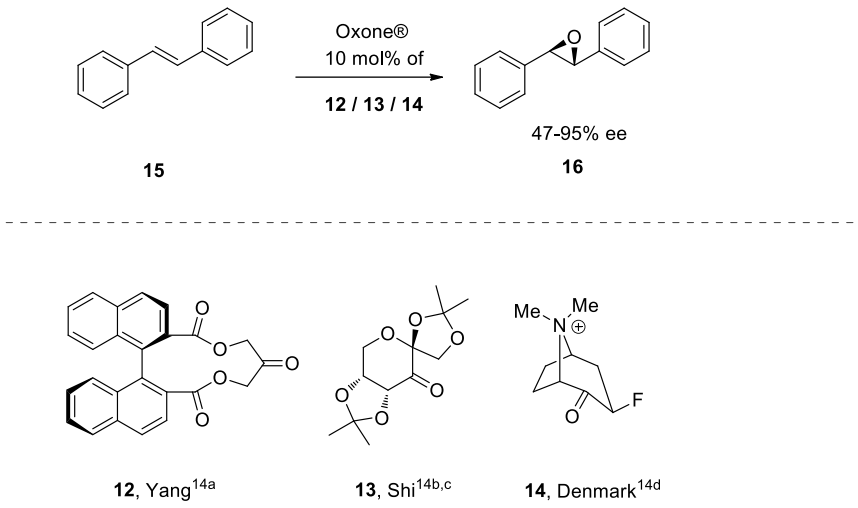
Scheme 7. Cyclic dipeptide catalyzed cyanohydrin formation by Inoue *et al*.

Furthermore, the first efficient catalytic asymmetric α-alkylation reaction in asymmetric organocatalysis was reported by Merck Researchers in 1984. They applied a chiral phase transfer catalyst (PTC) to catalyze the reaction of racemic ketone. By applying a quaternary ammonium salt of cinchonidine as PTC, they got high yield and high enantioselectivity in the formation of α-methylated ketone **11** from racemic ketone **10** as depicted in Scheme 8.[13]



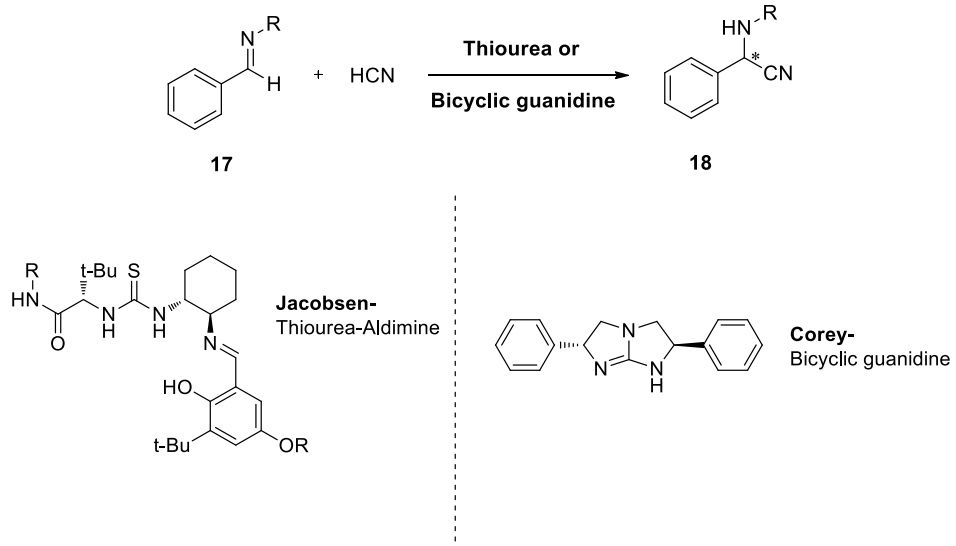
Scheme 8. Asymmetric α-alkylation of ketones by Researchers at Merck

In 1996, two remarkable studies in catalytic epoxidations mediated by a chiral ketone were reported by Yang[14a] and Shi,[14b,c] respectively. They utilizied chiral ketones **12** and **13** for the formation of epoxide **16** from *trans*-stilbene **15** and employed oxone® as an oxidant for this transformation. After a year, Denmark[14d] reported another chiral ketone **14** for epoxidation from *trans*-stilbene. The enantioselectivities obtained in all these reactions were between 47% and 95% (Scheme 9).[14]



Scheme 9. Chiral ketones as an organocatalyst used in epoxidations-Yang, Shi and Denmark

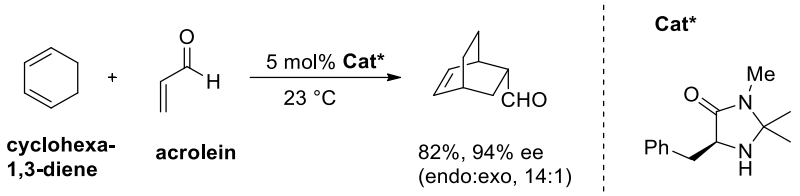
Following these studies, Jacobsen[15a] and Corey[15b] published two intriguing papers in 1998 and 1999 respectively. They described novel catalytic enantioselective Strecker reaction by the utility of chiral thiourea-Schiff base (Jacobsen) and bicyclic guanidine (Corey) as a bifunctional catalyst for the addition of HCN to *N*-arylimines **17**. They achieved enantioselectivity of product **18** up to 91% and 86%, respectively (Scheme 10).[15]



Scheme 10. Jacobsen's thiourea-aldimine and Corey's guanidine catalysts for Strecker reaction

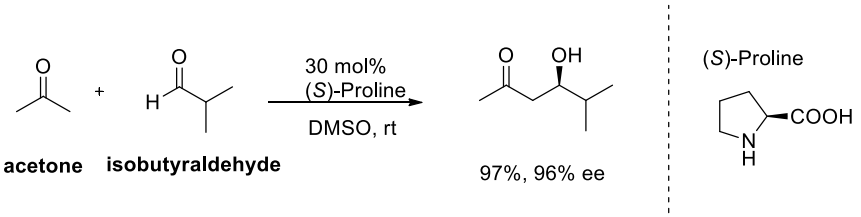
Although some studies were reported in asymmetric small purely organic molecule catalyzed reactions up to 20th century, they were not effective and have not drawn attention at all. The breakthrough work that caused an increase in the interest of using organocatalyst in asymmetric reactions was reported by MacMillan in 2000.[16] Following this work, List & Barbas[17] also published an important work in this field at the same year. Their highly

influential works have drawn attention by chemists that work on asymmetric synthesis to go for organocatalysis rush and as a result of this attention, publications on the topic of organocatalysis has been increasing spectacularly for the last decade. In their work, MacMillan reported the first highly enantioselective phenylalanine derived imidazolidone catalyzed Diels-Alder reaction between α,β-unsaturated aldehydes and various dienes. They achieved 94% enantioselectivity and quite good 14:1 isomeric ratio of bicyclic adduct in Diels-Alder reaction of cyclohexa-1,3-diene and acrolein (Scheme 11). Besides that by this transformation they not only introduced the term 'organocatalysis' but also showed that secondary amines can catalyze asymmetric reactions effectively and successfully.[16]



Scheme 11. MacMillan's imidazolidone catalyzed Diels-Alder reaction

Following MacMillan's work, other innovative work was published by List & Barbas.[17] They described the first example of (*S*)-Proline catalyzed direct asymmetric aldol reaction between unmodified acetone and a variety of aldehydes (Scheme 12). They presented that amino acid (*S*)-Proline is an effective asymmetric catalyst in mimicking the aldolase enzyme. They proposed that this novel aldol reaction proceeds via an enamine mechanism in which proline functions as a 'micro-aldolase' that provides both nucleophilic amino group and an acid/base cocatalyst in the form of carboxylate.[34] After this pioneering work, the catalytic potential of proline in asymmetric reactions has been investigated by many chemists worldwide.[17]



Scheme 12. (*S*)-Proline catalyzed direct intermolecular aldol reaction by List

1.1.3 Classification of Organocatalysis

Over the past decade, the field of asymmetric organocatalysis was tremendously progressing and has become a growing area for research groups around the world.[18] As mentioned before, organocatalysts are small, pure organic molecules that accelerate the chemical reactions. This acceleration can be achieved by activation of nucleophile or electrophile and also depends on typical interactions between organic molecules. However, it is not easy to classify organocatalysis in mechanistic way due to the variety of mechanisms in organocatalytic

reactions. The best conceptualizations in the mechanistic classification of asymmetric organocatalysis were done by Berkessel[2], List[18] and MacMillan[5].

Berkessel made a general distinction according to typical interactions and bonding between organic molecules and substrate and also classified them as covalent catalysis and non-covalent catalysis as shown in Figure 3. In covalent catalysis, the interactions between substrate and catalyst leads to formation of covalent adducts in catalytic cycle. The formation of catalytic adducts can be observed by iminium and enamine formations from aldehyde or secondary amines such as proline. Moreover, non-covalent catalysis is based on hydrogen-bonding interactions between substrate and catalyst or on protonation and deprotonation processes. Besides, phase-transfer catalysis (PTC) takes part in non-covalent catalysis by involving a transport phenomenon.[2]

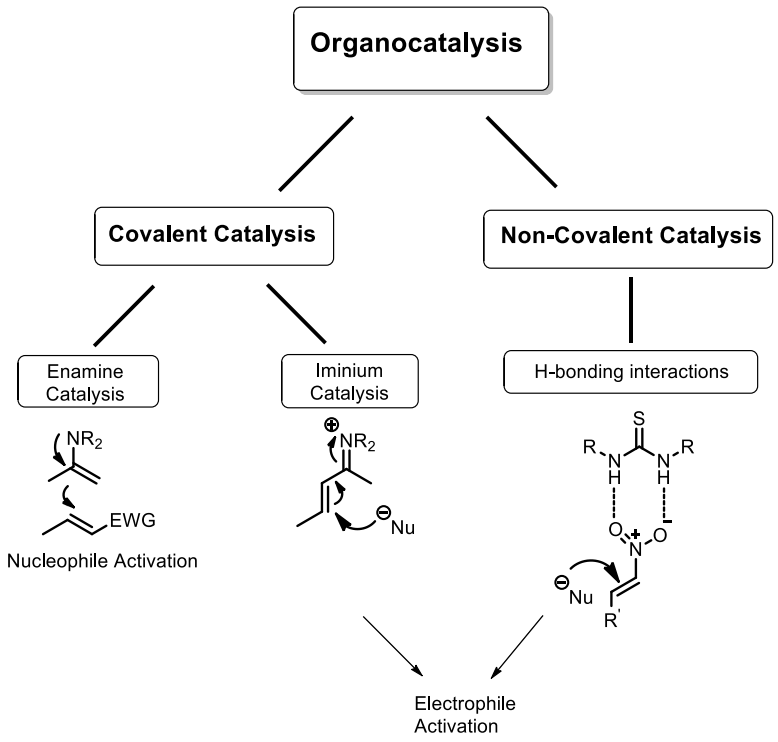


Figure 3. The classification of an organocatalyst according to Berkessel

Furthermore, the second classification was done by List & Seayad.[18] According to their functions in reactions, most but not all organocatalysts have categorized into four types such as Lewis acid, Lewis Base, Brønsted acid and Brønsted base catalysis as shown in Figure 4.[18] The catalytic cycle in Lewis Base catalysts **B:** starts with the nucleophilic addition of base to the substrate **S** which forms the complex **B-S.** The resulting complex then undergoes a reaction to form **B-P** and then releases the product **P** and the catalyst for further turnover. Lewis acid catalysts **A** initiate the catalytic cycle by activating nucleophilic species **S:** in a similar way. Brønsted base and Brønsted acid catalytic cycles are started by deprotonation and protonation processes, respectively.

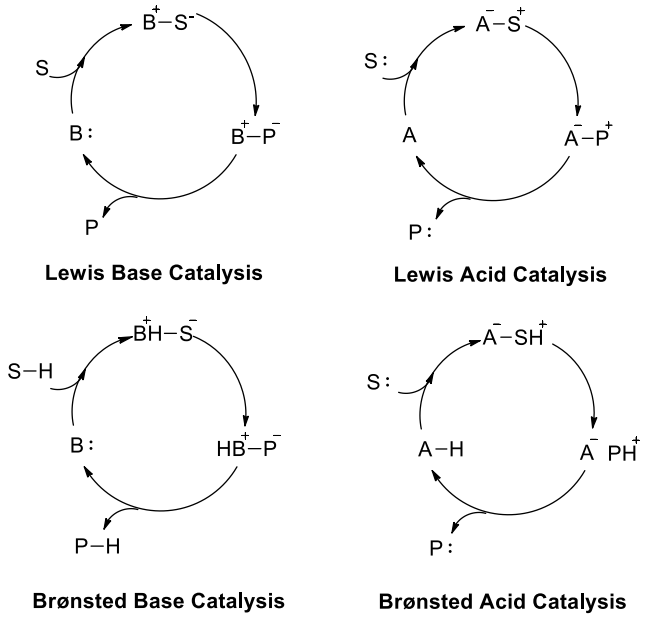


Figure 4. Classification of organocatalysts according to List & Seayad

The third classification was reported by MacMillan.[5] He focused on generic modes of activation that commonly used in organocatalysis while classification of organocatalysts as shown in Figure 5.[5] A generic mode is associated with reactive species which can take part in many reactions with consistently high levels of enantioselectivity. Such reactive species can be obtained by the interaction of a single chiral catalyst with a basic functional group (such as aldehyde, ketone, imine or alkene) in a highly organized and predictable manner. The significance of generic activation modes arise from the fact that after they have been established, it becomes relatively straightforward using them as a platform for the design of new enantioselective transformations.

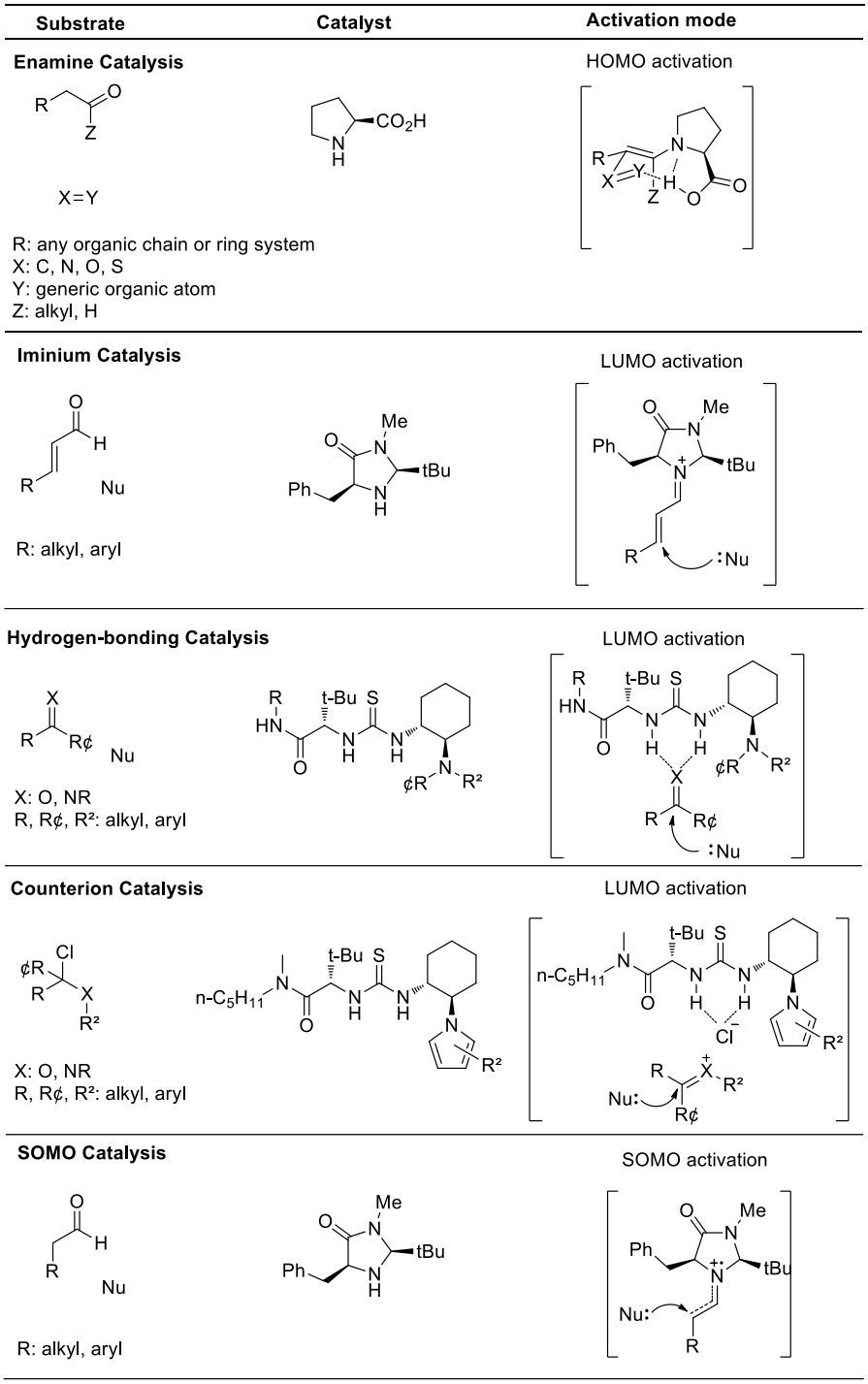


Figure 5. Classification of organocatalysts according to generic activation modes by MacMillan

The ‘‘enamine’’ and ‘‘iminium’’ catalysis are the most frequently encountered generic modes of activation in asymmetric organocatalysis. Furthermore, hydrogen-bonding catalysis is being next in frequent. The enamine catalysis concept is based upon the condensation of an aldehyde or ketone **19** with a chiral amine **21** to form nucleophilic enamine unit **22** that leads to an overall increase in HOMO (Highest Occupied Molecular Orbital) energy which is similar to

HOMO-raising ability of Lewis acids (Figure 6). Up to now, by utilizing enamine catalysis, various enantioselective α-functionalizations of aldehydes or ketones with electrophilic reagents have been carried out.[19]

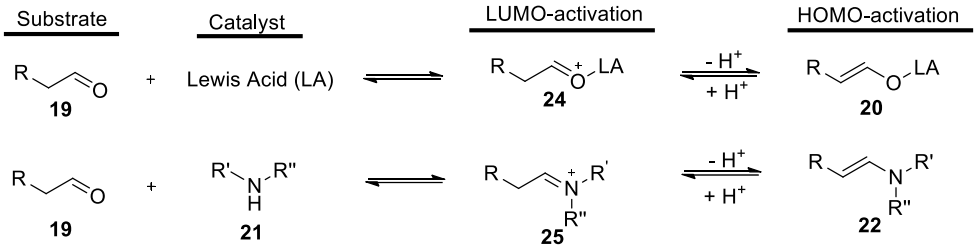


Figure 6. Enamine catalysis concepts

The iminium catalysis concept is based on the reversible reaction of a chiral amine **21** with aldehyde or ketone **23** to form the active iminium ion species **25** as a reactive intermediate (Figure 7). This transformation leads to a decrease in LUMO (Lowest Unoccupied Molecular Orbital) energy of substrate. The iminium catalysis or LUMO lowering approach which is in contrast with enamine catalysis (HOMO-activation) can promote several enantioselective organocatalytic trasnformations with unsaturated aldehydes or ketones.[18]

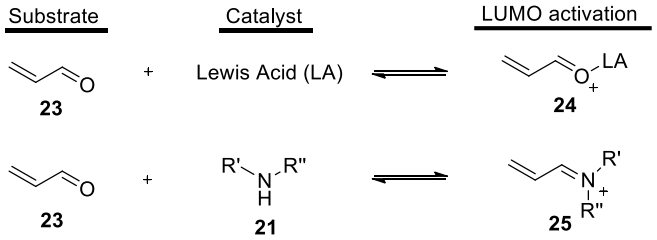


Figure 7. Iminium catalysis concepts

1.1.4 Enamine Catalysis

The reversible and catalytic generation of enamine from primary and secondary amines and carbonyl compounds (aldehydes or ketones) is called ‘‘enamine catalysis’’. Enamine catalysis is commonly used in electrophilic α-functionalization reactions of ketones and aldehydes.[20] The concept of enamine catalysis was originally introduced by Stork and it can be regarded as a catalytic verison of the classical enamine chemistry.[21]

As shown in Figure 8, in enamine catalysis, the catalytic cycle begins with the reaction of aldehyde or ketone **26** with the amine catalyst **21** to form the nucleophilic enamine species **28** under dehydration conditions. The catalytically activated enamine **28** can attack an electrophile **29** (X=Y or X-Y) to afford corresponding iminium ion **30** as an intermediate. Subsequent hydrolysis of the iminium ion intermediate **30** with in situ generated water gives

the corresponding addition product **31** which then allowing the catalytic cycle to be completed. In enamine catalysis, aldehydes or ketones **26** are converted to more activated nucleophiles with a HOMO of higher energy compared to respective carbonyl compound.

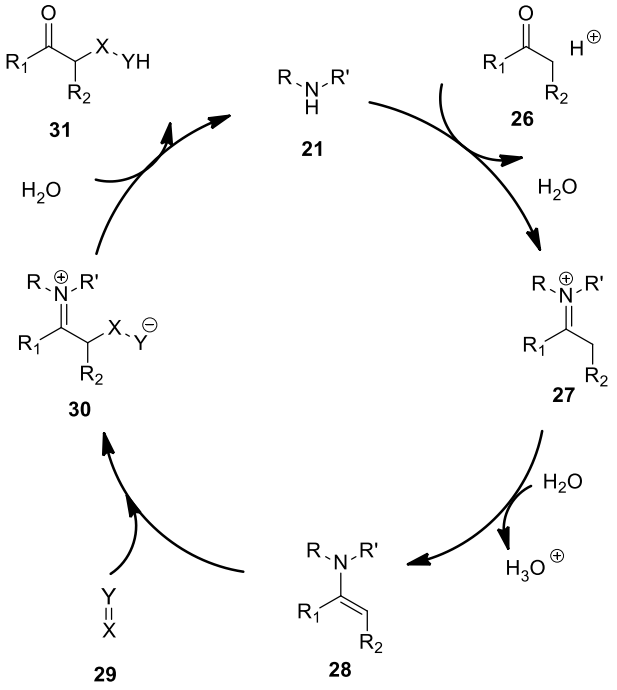
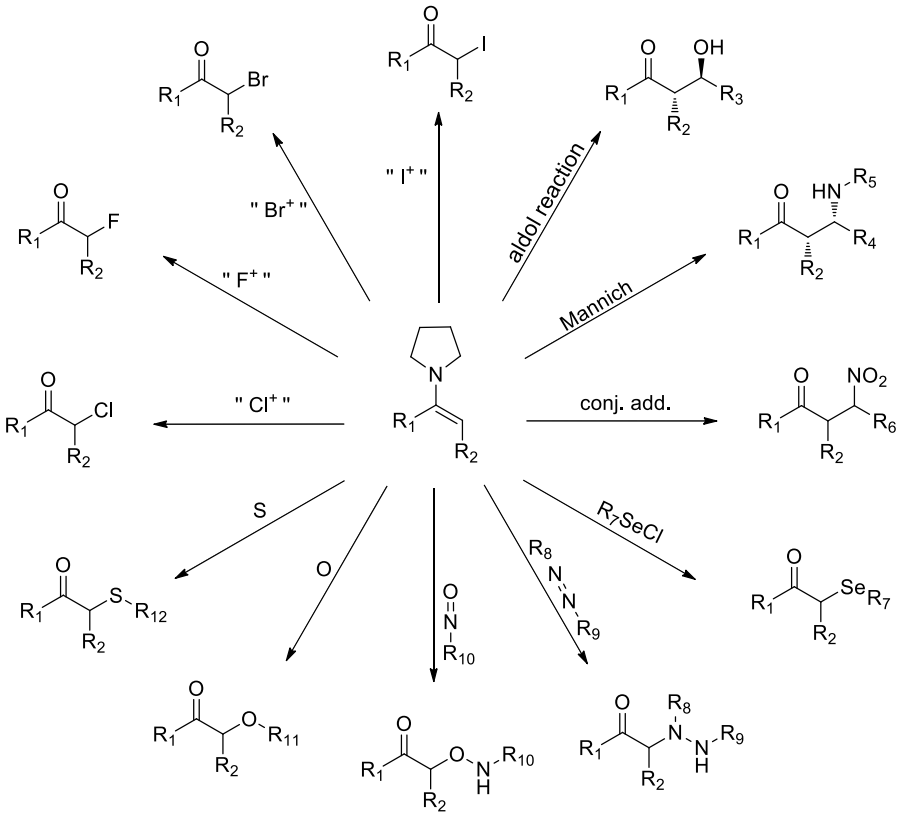


Figure 8. General mechanism of enamine catalysis

The first example of enantioselective enamine catalysis was the intramoleculaer aldol reaction catalyzed by proline which known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction.[22] Then about 30 years later, the key discovery in this field was introduced by List and coworkers as the proline-catalyzed enantioselective intermolecular aldol reactions.[17] Since then, there have been extensive efforts to develop new asymmetric reactions catalyzed by enamine catalysis. Up to now, a wide variety of examples have been reported for the organocatalytic reactions proceeding via enamine activation and the range of reactions that can be catalyzed by enamine catalysis is summarized in Scheme 13.[18]



Scheme 13. A range of reactions promoted by enamine catalysis

1.1.5 Hydrogen Bonding Interactions and Bifunctional Organocatalysis

Non-covalent catalysis, in which small organic molecules used as organocatalysts to form non-covalent adducts for chemical transformations employing essentially hydrogen-bonding, has arisen a powerful method for organic synthesis.[23] Among other interactions, hydrogen-bonding which can be regarded a slightly old interaction is an efficient way to activate Lewis basic substrates as general acid catalyst. Therefore, there have been extensive efforts to develop new Brønsted acid catalysts which have stimulated the discovery of various hydrogen-bonding catalysts such as ureas/ thioureas, and phosphoric acids. Those catalysts play a role in activation of carbonyl compounds electrophilically and decreases the LUMO level. Furthermore, these new hydrogen-bonding donors have several advantages over metal-centered Lewis acid catalysis. They are modularly nature and flexible in design. They are water and air stable and also potentially recoverable and reusable.

Among the hydrogen-bonding catalysts, urea and thiourea derivatives are more popular and can be used successfully in a wide variety of enantioselective transformations. They can partially develop negatively charged atoms in the substrates and have stronger hydrogen-bonding activity than the other ones. Many urea or thiourea catalysts exhibit the 3,5-bis(trifluoromethyl)phenyl group which was reported as a key structural motif in urea catalysis in 2002.[24] It showed that 3,5-bis (trifluoromethyl)phenyl moiety generally has advantages on

organocatalysts. Those advantages include the increase in catalyst polarity, acidity, polarizability and π-π interactions through the highly polarized aryl groups.[25]

Furthermore, up to 2003 thiourea and urea derivatives have been utilized for several organocatalytic transformations and the functions or mobility of these urea derivatives as general acids have been investigated and reported by several groups. However, the application of the urea or thiourea catalysts to asymmetric reactions is somewhat limited, because ureas are weaker acids than metallic Lewis acids. To come up with this limitation, a bifunctional organocatalysts which involves an acidic and basic unit in the chiral scaffold has been first designed and reported by Takemoto in 2003. He proved that dual-activation of bifunctional thioureas can be as effective and useful as monofuntional thiourea for use in catalytic asymmetric reactions (Figure 9).

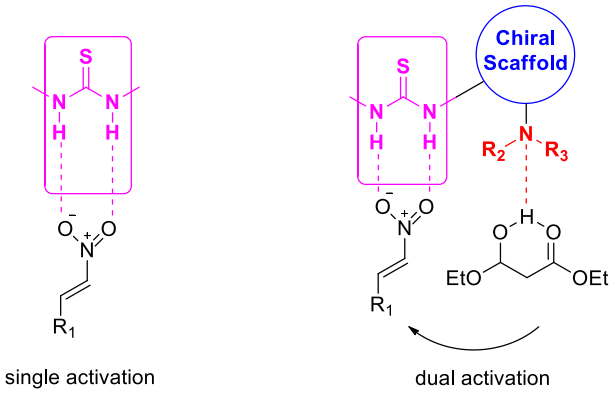


Figure 9. Dual activation concept using bifunctional thiourea organocatalyst

In bifunctional organocatalysts, the basic unit is for the HOMO activation (increase) of nucleophiles and acidic part is for the LUMO activation (decrease) of electrophiles which stimulates a decrease in activation energy to make reaction possible. The first bifunctional thiourea catalyst discovered by Takemoto **32**, bears a tertiarty amine group as a basic unit and this basic and thiourea moiety (acidic) are important for the acceleration of reaction rate and high enantioselectivity. Because of this importance, the bifunctional organocatalyst can be considered to activate both electrophiles and nucleophiles at the same time and to control the selective approach of substrates.[26]

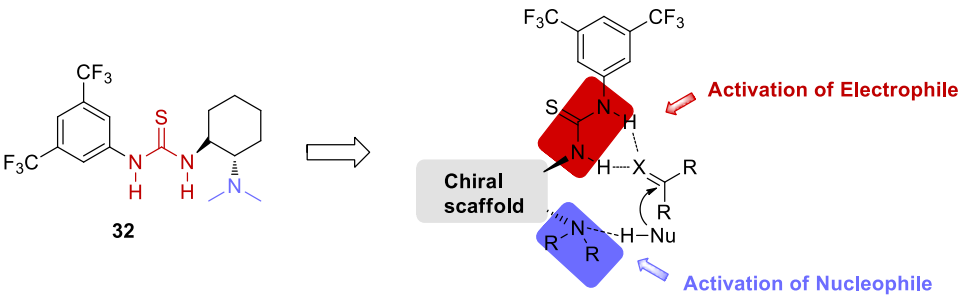
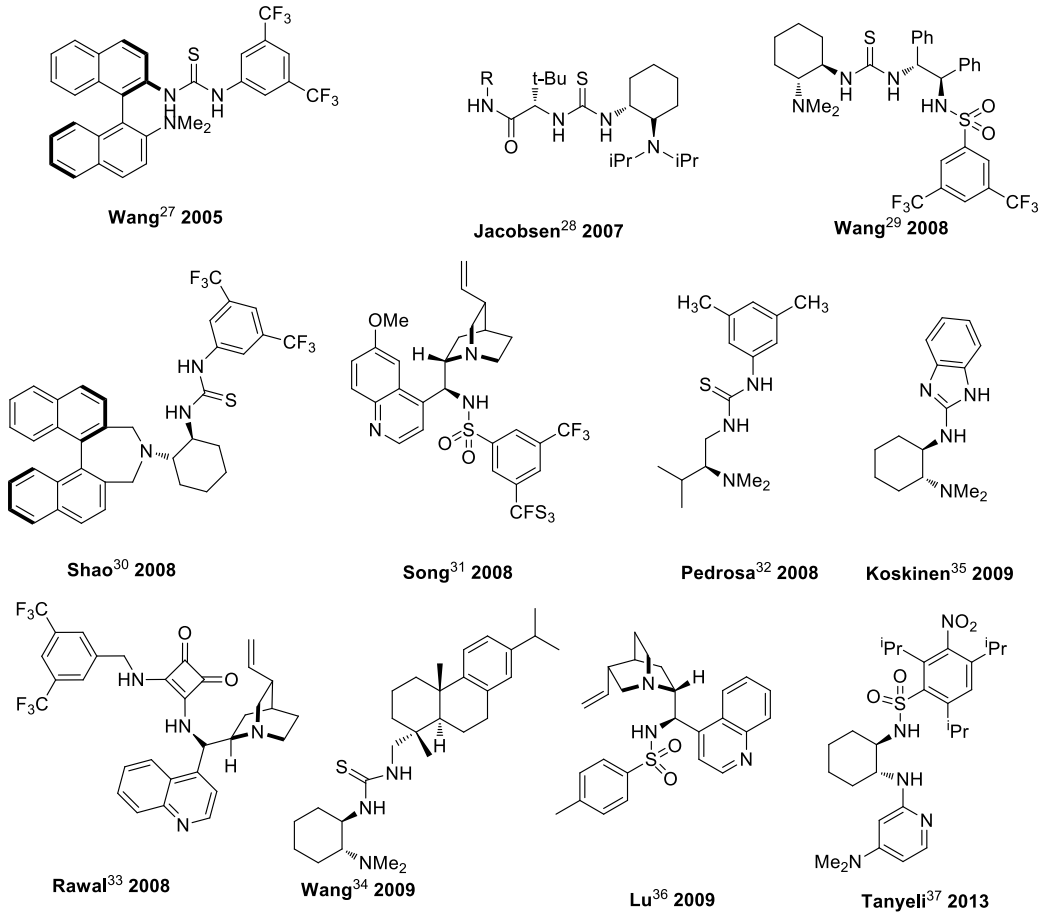


Figure 10. Takemoto's design of bifunctional *tert*-amine/thiourea catalysts

After Takemoto's pioneering work, the concept of bifuctionality has been increasing impressively for asymmetric tarsnformations in recent years. Several groups have designed various novel acid/base organocatalyst for enantioselective reactions and some selected literature examples concerning bifunctional organocatalyst are shown in the Scheme 14.



Scheme 14. Literature examples concerning bifunctional organocatalysts

1.1.6 Proline and Its Applications

Proline is a naturally occurring cyclic α-amino acid which efficiently mimicks the enzymatic catalysis and because of its successive results it has been considered as simplest enzyme in the nature.[19] Proline is also the simplest chiral bifunctional organocatalyst which has both a basic amine part and an acidic carboxyl moiety that gives importance to proline's role in catalysis and it can be used extensively and effectively in many ways in several asymmetric reactions such as the aldol, Mannich and Michael reactions. Furthermore, proline can be used as a chiral modifier in heterogeneous catalyzed hydrogenations and it can play a role as a bidentate ligand in asymmetric transition-metal catalysis. Due to the fact that it can also be considered as a universal asymmetric catalyst (Figure 11).[38]

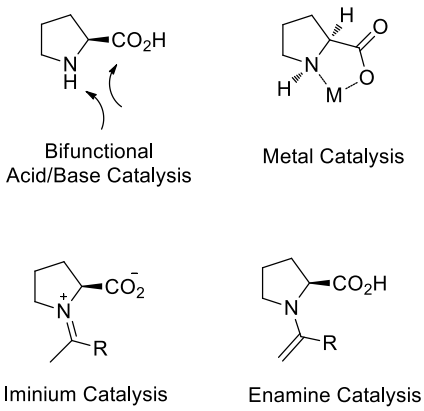
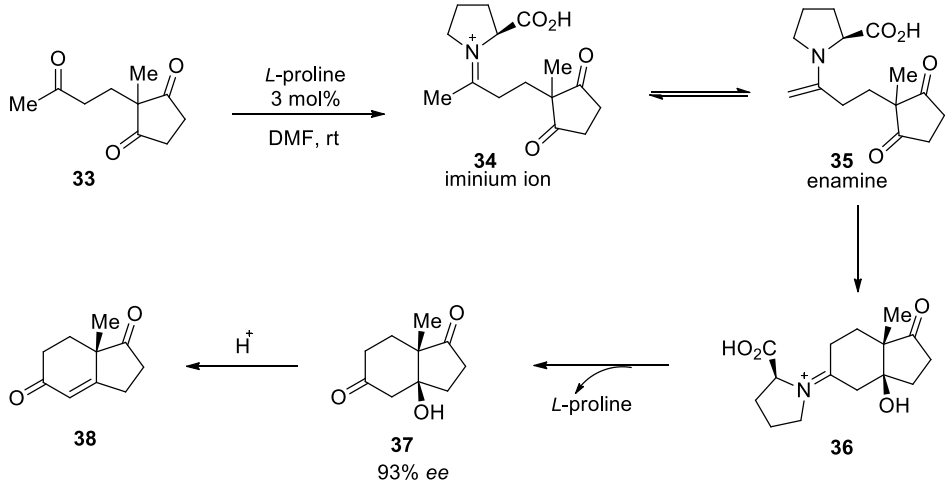


Figure 11. Modes of action in Proline catalysis

Additionally, there are several advantages of using proline such as being an abundant chiral molecule, inexpensive and to be found in both enantiomeric forms (*D*- and *L*-Proline). It is also non-toxic and soluble in water. Although proline is a good catalyst for enantioselective trasnformations with its benefits such as versatility and wide availability, it has some potential drawbacks. It can be listed as;

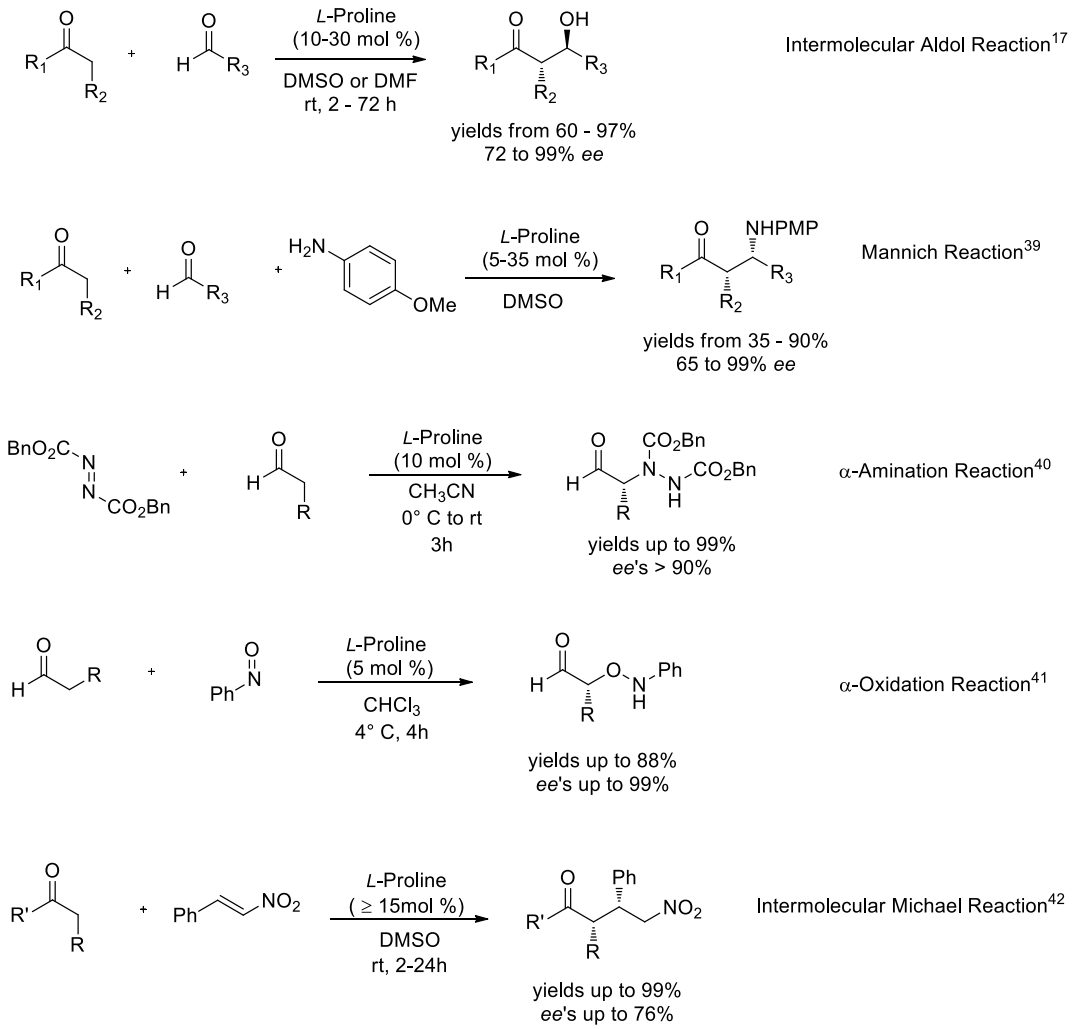
- Proline has a low solubility in non-polar solvents which limits its reactivity
- It can give possible side reactions
- It has low selectivities with planar aromatic aldehydes.

Over the last ten years, several useful methodologies have been developed by using the secondary amino acid proline as a catalyst. In 1970s, the use of proline as a chiral organocatalyst was discovered independently by Hajos and Parrish at Hoffman-La-Roche and Eder, Sauer, Wiechert at Schering AG for the intermolecular aldol cyclization of triketone **33** to get the bicyclic enones **38** which can be used as starting material for steroid synthesis as mentioned before (Scheme 15).[22]



Scheme 15. Mechanism of Hajos-Parrish-Eder-Sauer-Wiechert aldol reaction

This first reaction in which *L*-proline was used as an organocatalyst was the pioneering work in the area of organocatalysis and enamine catalysis. This pioneering work has not only been used in steroid synthesis but also in several other natural product synthesis and also it is not only the beginning of organocatalysis but also asymmetric catalysis. In addition, *L*-proline has been used in various type of reactions such as aldol, Michael, Mannich, α-oxidation, α-alkylation and etc. Those reactions that proline used as an organocatalyst are summarized in Scheme 16.



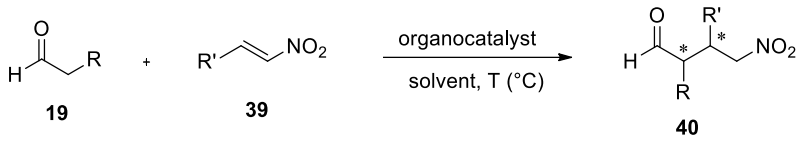
Scheme 16. Representative examples of Proline-catalyzed asymmetric reactions

1.1.7 Enantioselective Organocatalytic Michael Addition Reactions

Carbon-carbon bond formation is the most important process in the organic synthesis and attractive side of C-C bond forming reactions is the possibility to synthesize chiral molecules. Asymmetric conjugate addition or Michael addition reaction is one of the most important and effective methods for enantioselective C-C bond formation and it is used as an important step

in the synthesis of many biologically active compounds and natural products. In this part enantioselective Michael addition reaction will be explained in detail since it is related to our work.

The enantioselective organocatalytic Michael addition reaction is one of the most versatile and important carbon-carbon and carbon-heteroatom bond-forming reactions in organic synthesis as mentioned before.[43] The importance of Michael reaction also comes from the generation of up to three stereogenic centers in the reactions and the resulting molecules can be valuable synthetic intermediates and have many functionalities. For instance, the conjugate addition of an aldehyde with a nitroalkene is the most studied and investigated reaction which is catalyzed by organocatalysts for recent years as shown in the Scheme 17.



19 39 40

Scheme 17. Asymmetric Michael addition of aldehydes to nitroalkenes

In enantioselective Michael addition reactions, a chiral environment can be created by organocatalysts to the process for the activation of electrophile, nucleophile or both reagents through H-bonding, ion pairing or much stronger interactions such as covalent bonding. The possible organocatalytic activations in Michael addition reactions are shown in Figure 12. Enamine catalysis is the most attractive one of these organocatalysis for Michael reactions in which nucleophile activation occurs by a chiral enamine intermediate and then nucleophile can react with various electrophiles.[44]

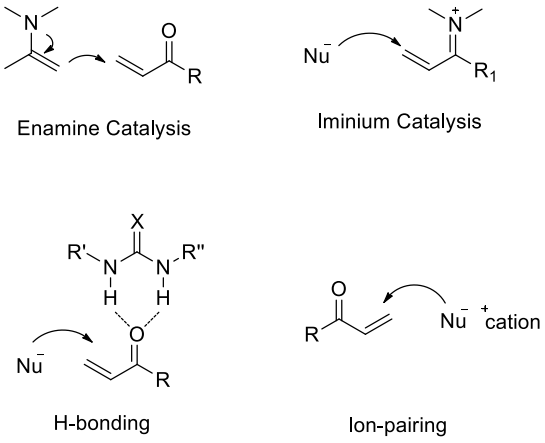
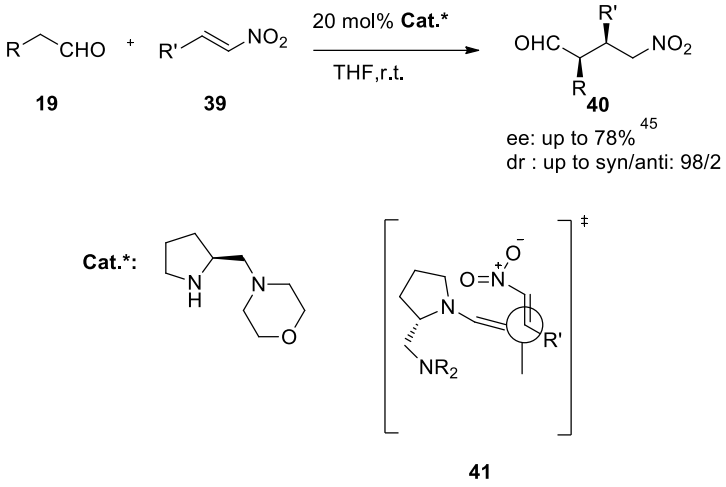


Figure 12. Organocatalytic activation modes in Michael Addition Reactions

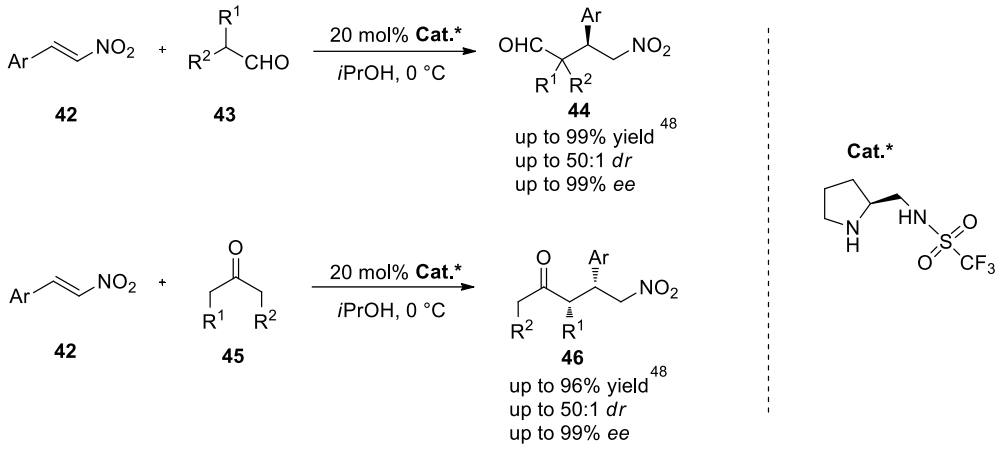
In Michael addition reactions, carbon nucleophiles which have an active methylene center such as carbonyl compounds have been generally studied and used as donors which then converted to more activated and reactive enamine or enol species.[45] In addition, various

Michael acceptors such as nitroolefins, α,β-unsaturated carbonyl compounds and alkylidene malonates have been successfully used in the organocatalytic Michael addition reactions.[46] Among a broad range of these reactions, Michael addition of aldehydes to nitroolefins has received great importance and interest, since the resulting γ-nitroaldehydes are valuable synthetic intermediates which can be readily converted into γ-amino acids, γ-butyrolactones, chiral pyrrolidines and tetrahydropyrans.[47] The first study in this field for conjugate addition of unmodified aldehydes to nitroolefins was reported by Betancort and Barbas in 2001 as shown in Scheme 18. They used (*S*)-2-(morpholinomethyl)-pyrrolidine as a catalyst and they synthesized various γ-formyl nitro compounds from different starting materials in high yields up to 96% with moderate enantioselectivities. All γ-formyl nitro products had *syn*-stereoselectivity and they proposed a transition state based on an acyclic synclinal model to explain the high *syn*-selectivity. In this model, there are favorable electrostatic interactions between the partially negative nitro group and the partially positive nitrogen of the enamine in the transition state **41** as depicted in Scheme 18.[45]



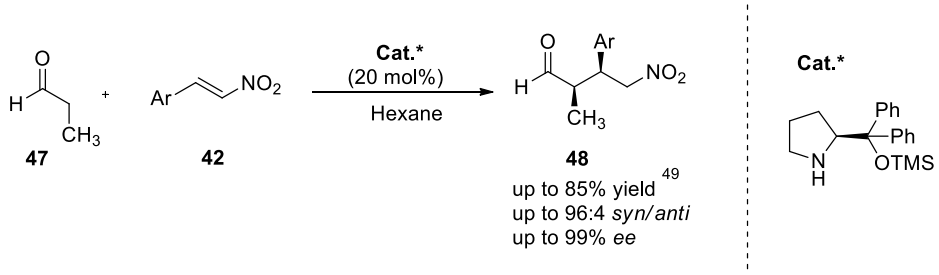
Scheme 18. The first organocatalytic asymmetric Michael addition of unmodified aldehydes to nitroolefins and proposed transition state

Furthermore, with the development of highly enantioselective Michael addition reactions of unmodified aldehydes to nitroolefins, Wang *et al.* introduced that chiral (*S*)-pyrrolidine trifluoromethane sulfonamide as an efficient catalyst for Michael addition of aldehydes or ketones to *trans*-β-nitrostyrenes as shown in Scheme 19. They examined both nitrostyrene, aldehyde and ketone derivatives and they achieved excellent levels of enantioselectivities (99% ee) and diastereoselectivity (up to 50:1 dr).[48]



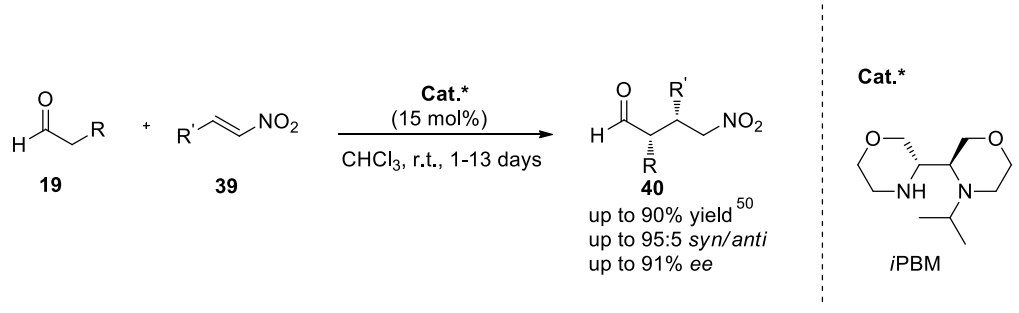
Scheme 19. Wang's Asymmetric Michael addition of aldehydes or ketones to *trans*-β-nitrostyrenes

Later, Hayashi and coworkers showed that introduction of a siloxy group to the prolinol leads to a dramatic increase in the catalytic activity. They used diphenylprolinol trimethylsilyl ether which can be easily synthesized from commercially avaliable diphenylprolinol to serve as a catalyst. The reaction has a wide range applicability with respect both to the Michael acceptor and donor and in almost all cases, Michael adducts were obtained in nearly optically pure form with 99% *ee* and excellent *syn* diastereoselectivities (Scheme 20).[49]



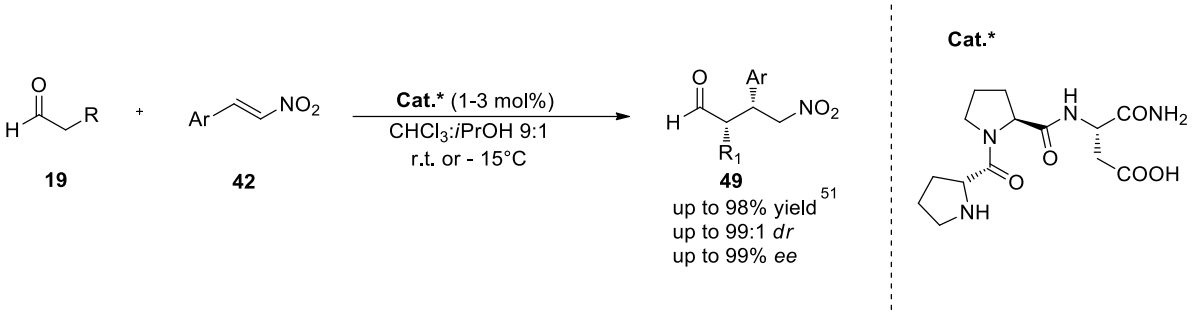
Scheme 20. Hayashi's asymmetric Michael addition of aldehydes to nitroolefins

Further, Alexakis and co-workers have developed new *N*-alkyl-3,3'-bimorpholine derivatives (*i*PBM) for asymmetric Michael addition of various aldehydes to different *trans*-β-nitrostyrenes. The Michael adducts were afforded in high yields up to 90% with high levels of enantioselectivities up to 90% as shown in Scheme 21.[50]



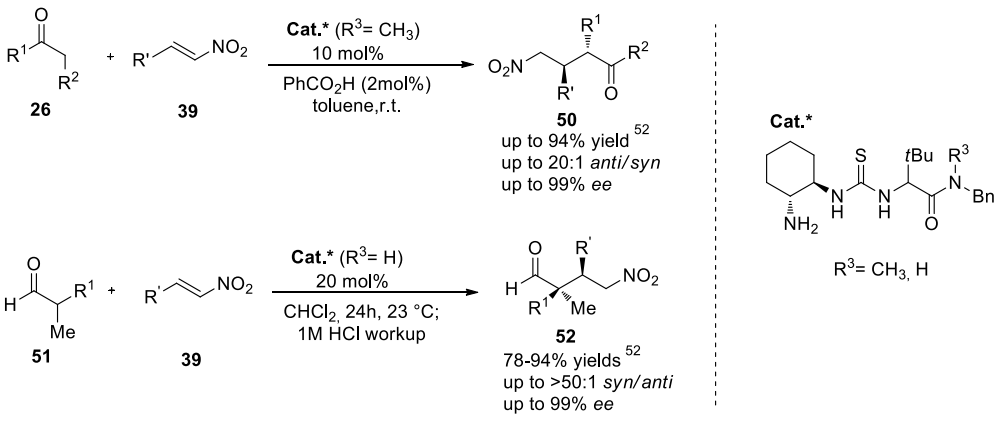
Scheme 21. Alexakis' Michael addition with *N*-alkyl-3,3'-bimorpholine catalyst

Then, Wennemers used tripeptides as efficient catalyst for conjugate addition of aldehydes to nitroolefins as shown in Scheme 22. They introduced that peptide catalyst was an excellent catalyst for Michael addition reactions between aldehydes and nitroolefins due to its much lower catalyst loading. In previous studies, other chiral amines which have been used as catalysts require the use of 10 or 20 mol% of catalyst. However, using 1 or 3 mol% of the peptide catalyst is sufficient to provide Michael adducts in high yields and streoselectivities unlike other amines.[51]



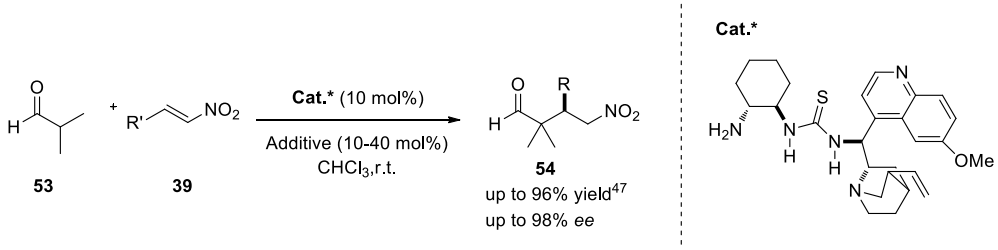
Scheme 22. Wennemers study in conjugate addition of aldehydes to nitrostyrenes with tripeptide catalyst

In addition to the use of proline-based amine catalysts, a different concept has been opened up by several research groups. They introduced that chiral thio(urea)-based bifunctional compounds can be used as an efficient organocatalysts for asymmetric Michael reactions between aldehydes/ ketones and nitroolefins. To illustrate, Jacobsen *et al.* have shown that chiral primary amine/thiourea catalyst is highly effective organocatalyst for conjugate addition of both ketone **26** and α,α-disubstituted aldehydes **51** to nitroalkenes **39** very recently (Scheme 23). Employing chiral primary amine/thiourea catalyst to the system can lead the simultaneous activation of both electrophile and nucleophile and thus allows this compelling reaction to occur under mild reaction conditions with a wide range of substrate scope.[52]



Scheme 23. Jacobsen's asymmetric Michael addition with chiral primary amine/thiourea organocatalyst

Furthermore, Chen and coworkers have reported that chiral amine catalysts based on rational combination of *L*-proline and cinchonidine backbones are efficient catalysts for enantioselective nitro-Michael addition of aldehydes and nitroolefins. They developed and examined several primary amine thiourea organocatalysts for conjugate addition of isobutyraldehyde **53** to nitroolefins **39** and get the best result with the catalyst as shown in Scheme 24 and also they used some additives such as DABCO, $PhCO_2H$, DIPEA, pyridine, Et_3N to increase the selectivity. As a result of this study, they have developed a highly enantioselective Michael addition of aldehydes to nitrostyrenes by the use of cinchona alkaloid-based bifunctional thiourea catalysts and achieved in most up to 96% yield and 98% enantioselectivity.[47]



Scheme 24. Chen's enantioselective Michael addition by Cinchona alkaloid-based bifunctional thiourea

Besides these studies, there are several examples of organocatalysts which are used in asymmetric conjugate addition of aldehydes and ketones to nitroalkenes in the literature. Some selected examples are shown in the Figure 13. Therefore, there are still considerable efforts to develop and improve the catalytic system for Michael addition reactions.[44]

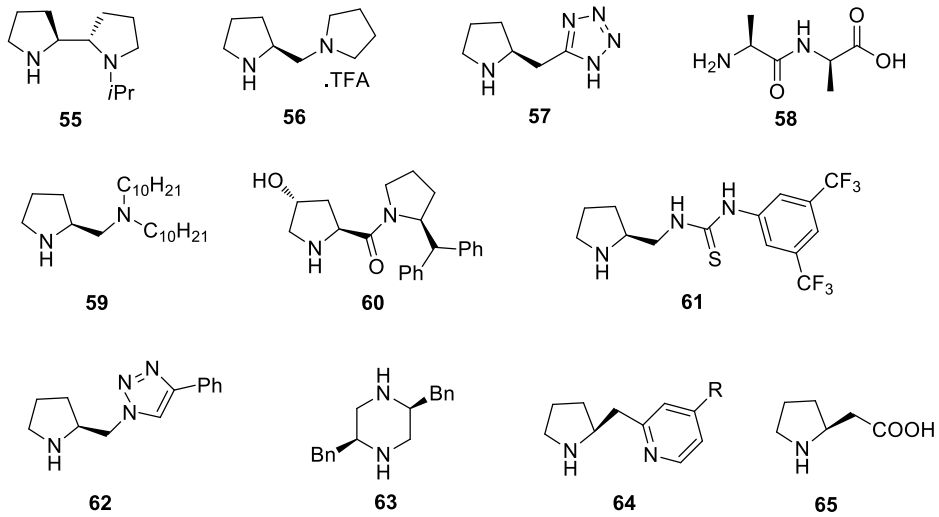
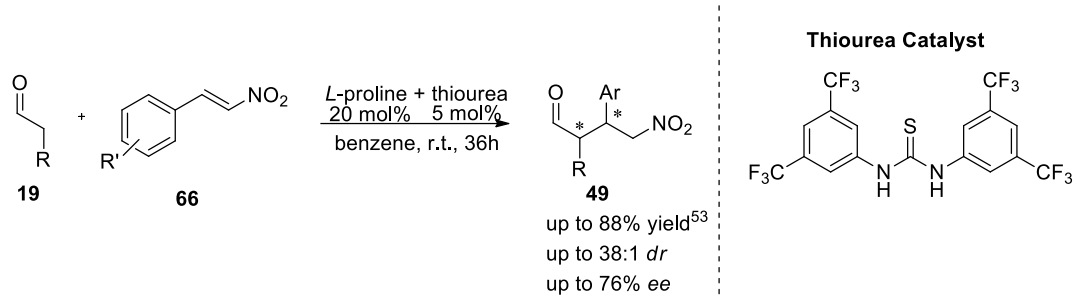


Figure 13. Selected literature examples of organocatalysts for asymmetric Michael addition of aldehydes to nitroolefins

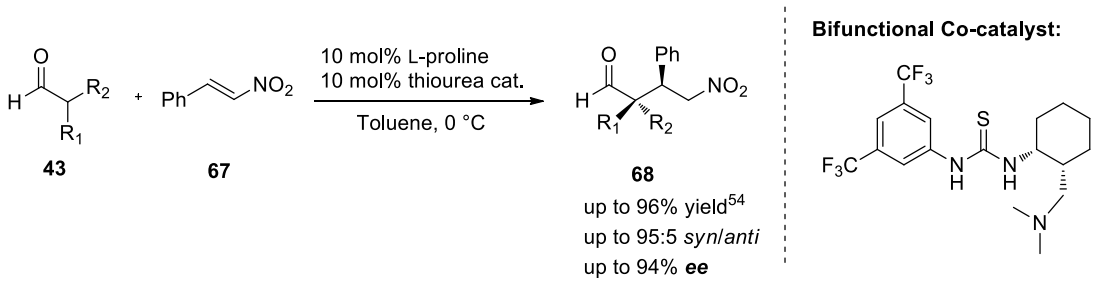
Moreover, all these newly designed catalysts which mimics the structure of proline or derived from proline have developed to improve the selectivity and activity of Michael addition

reactions of aldehydes to nitroolefins and also some studies showed that using co-catalyst or additives could enhance the reactivity and selectivity of the catalytic system. To illustrate, there have been some examples in which they used *L*-proline and co-catalyst combination for conjugate addition of aldehydes to nitoalkenes. Recently, Demir and Eymur reported that 1,3-bis[3,5-bis (trifluoromethyl)phenyl] thiourea (Schreiner's thiourea) can form an assembly with *L*-proline via hydrogen bonding and using thiourea as a co-catalyst for Michael addition can improve the reactivity of proline and selectivity in this transformation (Scheme 25).[53]



Scheme 25. Demir and Eymur's Michael addition reaction catalyzed by self-assembly of proline with thiourea

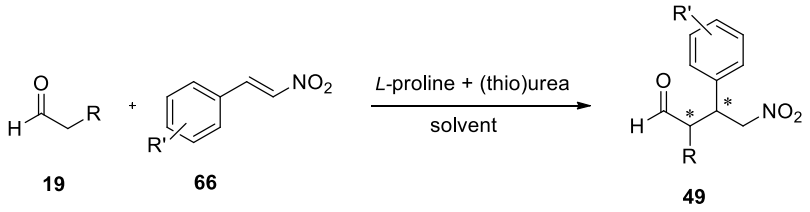
Following Demir and Eymur's work, Wang and coworkers have introduced that self-assembly of *L*-proline and chiral bifunctional thiourea is highly effective for the asymmetric Michael addition of aldehydes to nitrostyrenes. The bifunctional co-catalyst has been synthesized from chiral 1,3 diamines and it can form assembly with carboxylate moiety of proline and catalyzes the reaction cooperatively. In this transformation, proline plays a role in the formation of enamine species and bifunctional thiourea plays an important role in hydrogen bond formation to facilitate the enamine generation, activation of the nitroolefin with the ammonium group and subsequent hydrolysis of the enamine. Consequently, they showed that *L*-proline and bifunctional organocatalyst combination can be used as efficient catalyst for this transformation and also bifunctional thiourea can improve the solubility problem of proline in less polar solvents (Scheme 26).[54]



Scheme 26. Wang's enantioselective Michael addition reaction with *L*-proline and bifunctional thiourea combination

1.2 Aim of the work

The main objective of this thesis is to develop an efficient organocatalytic system for the asymmetric Michael addition of aldehydes to nitroolefins. It is well known that the highly active α-methylene protons of aliphatic aldehydes are the source to originate a feasible carbon nucleophile which can undergo Michael type additions with proper electrophiles, i.e. nitroalkenes chosen in our case. The resulting conjugate addition products, γ-nitrocarbonyl compounds, can be easily converted into γ-aminoacids, γ-buyrolactones, aminoalcohols and tetrahydropyrans and etc. Although, there have been great efforts to develop organocatalysts that can exhibit high enantioselectivities and activities for asymmetric Michael addition reactions, there were some problems encountered in these organocatalytic systems. These problems were high catalyst loading (up to 30-40%) and large excess amounts of aldehyde donors (up to 10 equivalent) which are required for reactions to be completed with high enantioselectivities, and using the organic solvents which have high polarity and volatility such as DMSO, DMF and CH_2Cl_2. Therefore, Michael addition of aldehydes to nitroolefins with efficient organocatalytic system and high selectivity in non-polar medium was aimed for this study. For this purpose, we devised two different organocatalytic system in both *L*-proline used to create enamine for activation of nucleophile and these organocatalytic systems based on the *L*-proline-(thio)urea host guest complex. One of the organocatalytic system designed with calix[4]arene based thiourea and the other one designed with chiral bifunctional organocatalyst which are both used as cocatalyst to *L*-proline. The reaction to be conducted is depicted in Scheme 27.



19 66 49

Scheme 27. Representative reaction scheme of this study

CHAPTER 2

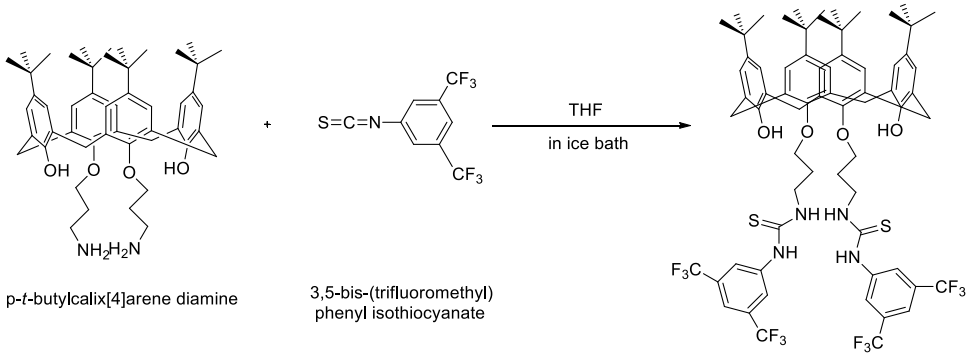
RESULTS AND DISCUSSION

2.1 Synthesis of Calix[4]arene based thiourea organocatalyst and application in Michael addition reaction of aldehydes to nitroolefins

Since L-proline was not effective catalyst in terms of enantioselectivity for asymmetric Michael addition reaction of aldehydes to nitroalkenes, there have been extraordinary efforts to improve its selectivity and reactivity. To illustrate, Demir and Eymur reported the first example of the self-assembly of organocatalysts with an achiral additive in Michael addition reaction wherein aldehydes are utilized as donors recently. They used Schreiner's thiourea as an achiral additive and investigated the use of proline- thiourea host- guest complex as a catalyst in nitro-Michael addition of aldehydes to nitroalkenes. In this study, they indicated that the addition of achiral thiourea to the catalytic system improved the reactivity and selectivity of *L*-proline and eliminated the use of low temperatures. The self-assembled organocatalyst was also a good catalyst for direct asymmetric Michael addition reaction of aldehydes to nitroolefins with moderate enantioselectivities.[53]

Inspired from Demir and Eymur's work, our initial investigation for this study was to test the catalytic activity of self-assembly of Calix[4]arene based thiourea catalyst with *L*-proline in asymmetric Michael addition reaction of isovaleraldehyde to *trans*-β-nitrostyrene.

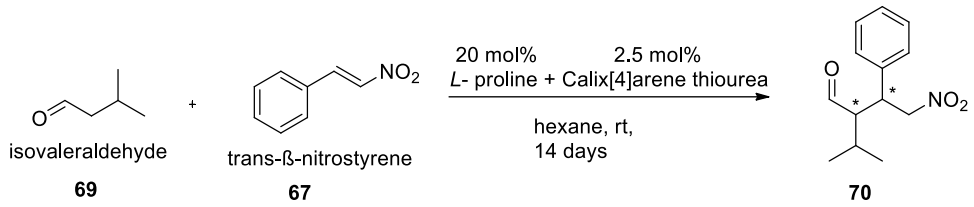
Calix[4]arene based thiourea catalyst was synthesized according to the literature[56] by the reaction of commercially available 3,5-bis(trifluoromethyl)phenyl isothiocyanate with p-*t*-butylcalix[4]arene diamine in THF (Scheme 28).



Scheme 28. Synthesis of Calix[4]arene based thiourea organocatalyst

Characterization of Calix[4]arene based thiourea organocatalyst was done by ^{1}H and ^{13}C NMR spectroscopy which is depicted in Appendix A. In addition to NMR data, the catalyst verified by HRMS analysis that reveals the molecular formula of the compound as $C_{68}H_{76}F_{12}N_4O_4S_2$.

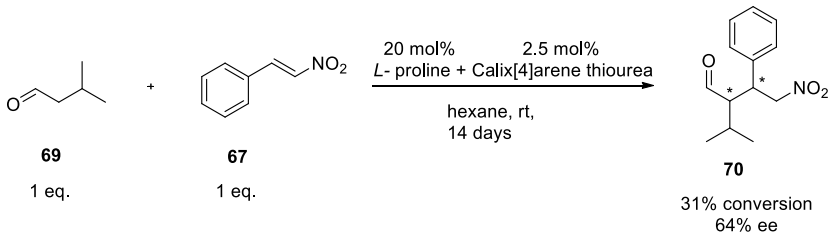
According to previous work done in our group by Eymur, optimization studies started up with the use of isovaleraldehyde as a donor and *trans*-β-nitrostyrene as an acceptor (Scheme 30).



Scheme 29. Michael addition reaction with *L*-proline and Calix[4]arene based thiourea catalyst system

At the first part, the effect of solvent on selectivity and conversion was screened. Although conversions were too low for all solvents, hexane solvent was the best choice for the conjugate addition of isovaleraldehyde to *trans*-β-nitrostyrene that exhibited the higher conversion than the other ones. Secondly, effect of amount of aldehyde donor on the reactivity and selectivity was examined. For this purpose, two different isovaleraldehyde amounts, 3 eq. and 1 eq., were checked in the same reaction catalyzed by *L*-proline and Calix[4]arene based thiourea. Changing the amount of aldehyde equivalencies caused an increase in enantioselectivity from 25% to 64% with a slight increase in conversion. Since there is an improvement in enantioselectivity, 1 eq. was chosen as the best amount for aldehyde donor.

As the third parameter, the effect of catalyst loading on selectivity was monitored. To detect the best amount of catalyst system for the reaction, four different catalyst loading ratios of *L*-proline and Calix[4]arene based thiourea such as 20% to 10%, 15% to 7.5%, 10% to 5%, 5% to 2.5% were examined in addition to 20% *L*-proline and 2.5% Calix[4]arene based thiourea. As a result of these experiments, 20 mol% *L*-proline and 2.5 mol% Calix[4]arene based thiourea gave the best result in terms of enantioselectivity and conversion. The efforts expended to increase the enantioselectivity and conversion in optimization studies did not give any improvements for the conjugate addition of isovaleraldehyde to trans-β-nitrostyrene. After all, the best result was found as 20% *L*-proline and 2.5% Calix[4]arene based thiourea in hexane at room temperature in 64% ee.



Scheme 30. Optimized conditions for direct asymmetric Michael addition catalyzed by *L*-Proline-thiourea host-guest complex

2.2 Michael addition reactions of aldehydes to nitroolefins with L-proline and bifunctional organocatalyst combination

Unsuccessive results obtained in the preliminary work done with Calix[4]arene based thiourea as achiral additive directed us towards to the use of chiral acid/base type bifunctional organocatalyst together with *L*-proline. Bifunctional organocatalysts already synthesized in Tanyeli's research group were examined in Michael addition of isovaleraldehyde and *trans*-β-nitrostyrene. 2-AminoDMAP/urea **71,** 2-AminoDMAP/thiourea **72** and 2-AminoDMAP/squaramid **73** were chosen as organocatalysts (Figure 14).

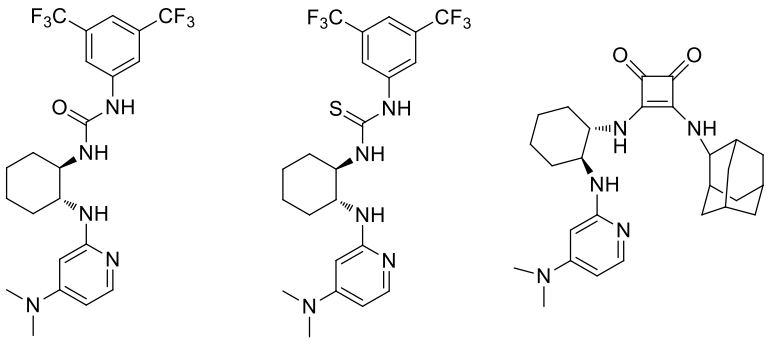


Figure 14. Bifunctional organocatalysts screened in Michael addition reaction

In the first part, *L*-proline and bifunctional organocatalyst loading was kept constant at 5 mol% of each and 3 eq. of isovaleraldehyde (**69**) was used. Reactions were carried out in hexane at room temperature and monitored each hour. The preliminary results are summarized in Table 1.

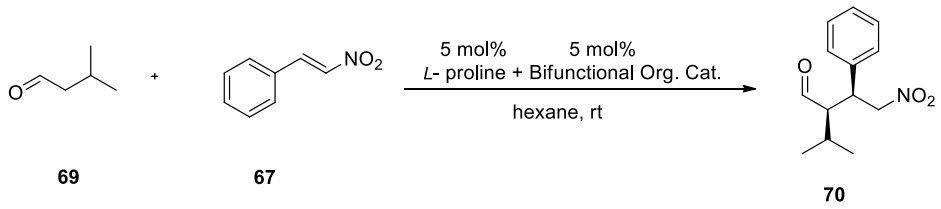
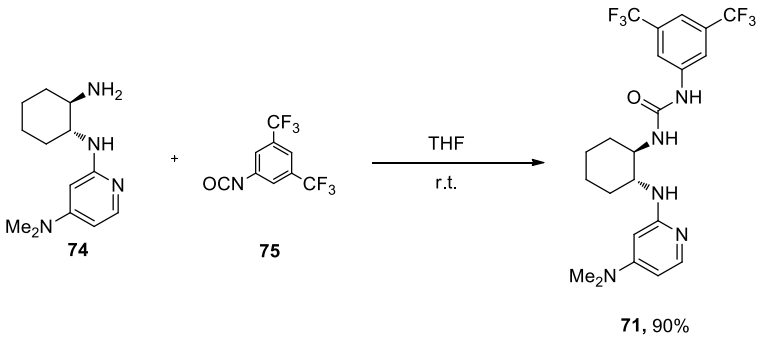


Table 1. Catalyst screening results

Catalyst	eq. of **69**	Solvent	Catalyst Loading	*L*-Proline Loading	T (°C)	time	conversion[a]	dr[a] (*syn/anti*)	ee %
71	3	Hexane	5 mol%	5 mol%	r.t	24h	80	19 : 1	75
72	3	Hexane	5 mol%	5 mol%	r.t.	24h	79	28 : 1	68
73	3	Hexane	5 mol%	5 mol%	r.t	24h	99	23 : 1	41

a: Determined by crude ^{1}H NMR

According to obtained data shown in Table 1, bifunctional 2-aminoDMAP/urea **71** catalyst was determined as the best one in terms of enantioselectivity. Eventhough, the enantiomeric excesses obtained with bifunctional thiourea **72** and squaramid catalyst **73** were not very low compared to urea catalyst, optimization studies were continued by using 2-aminoDMAP/urea bifunctional organocatalyst **71** and *L*-proline combination. 2-AminoDMAP/urea bifunctional catalyst was synthesized from (1*R*,2R) 2-aminoDMAP and commercially available 3,5 bis(trifluoromethyl)phenyl isocyanate (**75**) in THF at room temperature (Scheme 31).



Scheme 31. Synthesis of 2-AminoDMAP/urea catalyst

Characterization of 2-aminoDMAP/urea catalyst **71** was done by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.

As the second parameter, the effect of *L*-proline amount in the catalytic system was checked. To determine how it affects the selectivity and conversion, three different amounts of *L*-proline were examined. Although, there is a slight increase in enantioselectivity from 80% ee up to 82%ee in the case of 5 mol% and 2.5 mol% respectively, the dramatic decrease in conversions can prove the *L*-proline dependence of reaction rate and conversion. Besides, the reaction did not take place when *L*-proline was not used in the catalytic system as shown in Table 2 and it can prove that this reaction proceeds via enamine mechanism. Since, the biggest increase in enantioselectivity (82%) achieved by using 2.5 mol% *L*-proline, optimization studies continued with 2.5 mol% *L*-proline and 2.5 mol% 2-aminoDMAP/urea catalyst (Table 2).

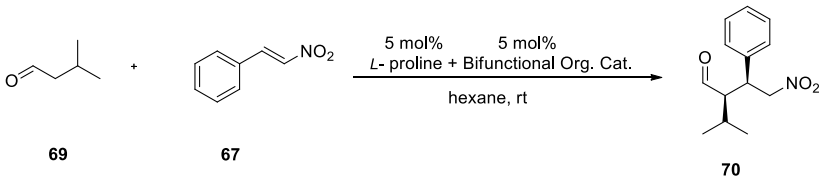


Table 2. *L*-Proline Loading results

Catalyst	eq. of **69**	Solvent	Catalyst Loading	*L*-Proline Loading	T (°C)	time	conversion[a]	dr[a] (*syn/anti*)	ee %
71	3	Hexane	2.5 mol%	5 mol%	r.t	24h	25	17 : 1	80.4
71	3	Hexane	2.5 mol%	2.5 mol%	r.t.	24h	23	19 : 1	82
71	3	Hexane	5 mol%	---	r.t	24h	No conversion	---	---

a: Determined by crude ^{1}H NMR

As the third parameter, the effect of temperature which is the crucial part of optimization was screened. For this purpose three different temperature conditions were applied. Generally, at low temperatures, selectivity increases while reactivity decreases. As in our reaction, reducing temperature from 25 °C to 15 °C, increases the both enantioselectivity and diastereoselectivity and decreases the conversion as expected. However, our major aim for this reaction is to get high conversion with high selectivity. For this reason, 25°C was accepted as an optimum temperature for this reaction (Table 3).

Table 3. Temperature Screening

Catalyst	eq. of **69**	Solvent	Catalyst Loading	*L*-Proline Loading	T (°C)	time	conversion[a]	dr[a] (*syn/anti*)	ee %
71	3	Hexane	2.5 mol%	2.5 mol%	25	24h	82	16 : 1	71
71	3	Hexane	2.5 mol%	2.5 mol%	20	24h	35	19 : 1	79.2
71	3	Hexane	2.5 mol%	2.5 mol%	15	24h	42	19 : 1	77.2

a: Determined by crude ^{1}H NMR

Afterward, to determine the possible reaction mechanism and the existence of matching or mismatching problem in the catalyst system, *L*-proline was replaced with *D*-proline, *rac*-proline and pyrrolidine. It is realized that in *D*-proline case, there was a small decrease in enantioselectivity compared to *L*-proline case (from 71% to 60%) and it could be from slight but not in considerable amount of mismatching problem of *D*-proline with bifunctional urea catalyst. Besides, in pyrrolidine case which has not carboxylate moiety as proline, there was a sharp decrease in both enantioselectivity and diastereoselectivity compared to *L*-proline. It was also proved that 2-aminoDMAP/urea catalyst was effective and could induce selectivity without forming an assembly. As a result of these trials, it is shown that *L*-proline is dominant for this reaction and carboxylate moiety of proline forms a host-guest complex with bifunctional urea catalyst in the transition state (Table 4).

Table 4. Catalyst system screening results

Catalyst*	eq. of **69**	Solvent	Catalyst **71** Loading	Cat.* Loading	T (°C)	time	conversion[a]	dr[a] (*syn/anti*)	ee %
***L*-proline**	3	Hexane	2.5 mol%	2.5 mol%	25	24h	82	16 : 1	71
***D*-proline**[b]	3	Hexane	2.5 mol%	2.5 mol%	25	24h	17	20 : 1	60
***rac*-proline**	3	Hexane	2.5 mol%	2.5 mol%	25	24h	70	12 : 1	65
Pyrrolidine	3	Hexane	2.5 mol%	2.5 mol%	25	24h	91	3 : 1	11

a: Determined by crude ^{1}H NMR
b: Absolute configuration of enantiomerically enriched product is opposed to product **70**

The effect of catalyst loading on selectivity was also checked by using 5 different amounts of catalysts. Eventhough, all trials gave moderately good enantioselectivities, full conversion with the highest enantioselectivity only achieved in 10 mol% *L*-proline and 5 mol% bifunctional urea catalyst combination case. Since, our aim is to get high conversion with high enantioselectivity, 10 mol% *L*-proline and 5 mol% 2-aminoDMAP/urea catalyst was decided as an optimum catalyst loading for this reaction (Table 5).

Table 5. Catalyst Loading Results

Catalyst	eq. of **69**	Solvent	Catalyst Loading	*L*-Proline Loading	T (°C)	time	conversion[a]	dr[a] (*syn/anti*)	ee %
71	3	Hexane	2.5 mol%	2.5 mol%	25	24h	82	16 : 1	71
71	3	Hexane	5 mol%	2.5 mol%	25	24h	91	14 : 1	73
71	3	Hexane	5 mol%	5 mol%	25	24h	98	17 : 1	67
71	3	Hexane	5 mol%	10 mol%	25	24h	100	14 : 1	75
71	3	Hexane	5 mol%	20 mol%	25	24h	98	15 : 1	71

a: Determined by crude ^{1}H NMR

As the sixth parameter, concentration of the reaction medium was screened to determine how it affects the selectivity and conversion, as the amount of aldehyde and solvent were changed. At the beginning of this study, optimization screening started with 3 eq. aldehyde with 3.2 mL hexane solvent according to literature.[53] To observe the effect of concentration, both higher and lower amounts of aldehyde (5 eq. and 1 eq.) were used and the amount of hexane solvent was decreased to 1 mL. Consequently, we realized that increasing concentration of reaction medium decreases the enantioselectivity and the presence of over than 3 eq. aldehyde could cause the formation of self- aldol product as a side product in the reaction (Table 6).

Table 6. Screening results of concentration

Catalyst	eq. of **69**	Solvent	Concentration	Catalyst Loading	*L*-Proline Loading	T (°C)	time	conversion[a]	dr[a] (*syn/anti*)	ee %
71	5	Hexane	0.25M	5 mol%	10 mol%	25	24h	100	16 : 1	57
71	1	Hexane	0.08M	5 mol%	10mol%	25	24h	100	13 : 1	67

a: Determined by crude ^{1}H NMR

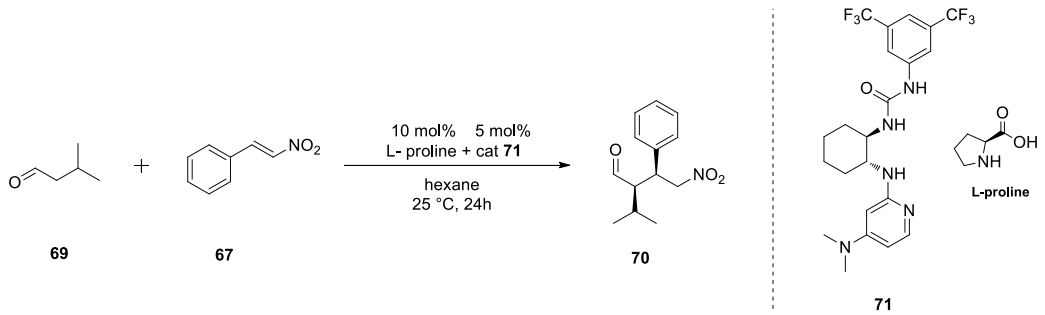
As a completion of the optimization studies, we examined the effect of solvents on selectivity and conversion. For this reason, the reaction was conducted in 9 different solvents other than hexane. In polar solvents (DCM, $CHCl_3$, THF, dioxane), although conversion were not very low, both enantioselectivities and diastereoselectivities decreased dramatically compared to hexane solvent as seen in Table 7. In non-polar solvents, both enantioselectivities and diastereoselectivities are moderately high and the best result in selectivity was obtained with hexane solvent as 75% ee. Additionally, water was checked as a solvent for our reaction. However, the reaction did not take place due to the solubility problems of both nitrostyrene and catalyst. After all, due to the high selectivity and high conversion, hexane was accepted as the best solvent of choice for our reaction (Table 7).

Table 7. Solvent Screening Results

Catalyst	eq. of **69**	Solvent	Catalyst Loading	*L*-Proline Loading	T (°C)	time	conversion[a]	dr[a] (*syn/anti*)	ee %
71	3	Hexane	5 mol%	10 mol%	25	24h	100	14 : 1	**75**
71	3	Toluene	5 mol%	10 mol%	25	24h	78	7 : 1	71
71	3	DCM	5 mol%	10 mol%	25	24h	82	13 : 1	38
71	3	Heptane	5 mol%	10 mol%	25	24h	98	14 : 1	68
71	3	$CHCl_3$	5 mol%	10 mol%	25	24h	80	9 : 1	44
71	3	THF	5 mol%	10 mol%	25	24h	73	8 : 1	46
71	3	*t*-butyl-methyl ether	5 mol%	10 mol%	25	24h	96	6 : 1	64
71	3	Dioxane	5 mol%	10 mol%	25	24h	85	6 : 1	41
71	3	Benzene	5 mol%	10 mol%	25	24h	80	7 : 1	70
71	3	Water	5 mol%	10 mol%	25	24h	n.d	n.d	n.d

a: Determined by crude ^1H NMR

As a result of screening studies, the optimum condition for Michael addition reaction of aldehydes to nitroolefins was decided to be 5 mol% 2-aminoDMAP/urea and 10 mol% *L*-proline loading, hexane as solvent at 25 °C and for 24 hours.

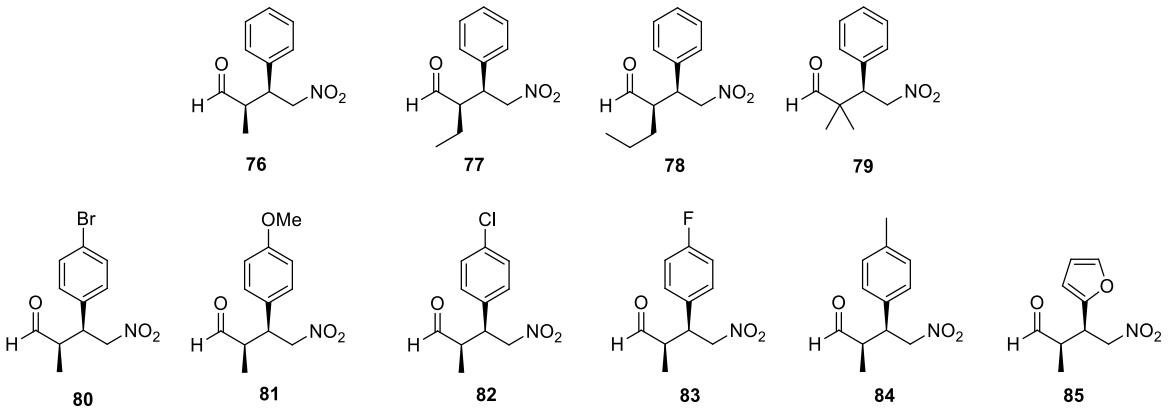


69 67 70 71

Scheme 32. Optimized conditions of direct asymmetric Michael reaction catalyzed by *L*-proline and 2-aminoDMAP/Urea catalyst combination

2.2.1 Derivatization of γ-nitroaldehydes

In this part, various derivatives of γ-nitroaldehydes were synthesized under the optimized conditions (Figure 15). Conversions and diastereomeric ratios were determined by ^{1}H NMR and enantiomeric excess value by chiral HPLC.



76 77 78 79 80 81 82 83 84 85

Figure 15. Derivatives of γ-nitroaldehydes

Results of derivatization studies are summarized in Table 8. As seen in Table 8, firstly branched and unbranched aldehyde derivatives were examined and the highest enantioselectivity (80% ee) and conversion (100%) were obtained with unbranched aldehyde, propionaldehyde. Addition to propionaldehyde, other unbranched aldehydes such as butyraldehyde and valeraldehyde were also tested and they gave high conversions with moderate enantioselectivities. Additionally, isobutyraldehyde was used as Michael donor in our reaction. However, conversion was very low and it caused a difficulty in purification. Due

to the fact that, the enantiomeric excess of this trial was determined by crude product such as 73% ee. According to data obtained from these experiments, derivatization studies continued with propionaldehyde which gave the best enantioselectivity and conversion.

Secondly, the reaction of propionaldehyde with nitrostyrene derivatives were studied. For this purpose, nitroolefins with both electron-donating and electron-withdrawing groups were tested. However, an unexpected problem was encountered in these trials. The issue for the reaction of propionaldehyde with *trans*-β-nitrostyrenes was the solubility problems of nitroolefins in hexane. To come up with this problem, another non-polar solvent, toluene, which exbihited the second best result in optimization studies, was used. To detect the amount of toluene solvent for the reaction, two reactions were tested. One of them was carried out with only toluene as a solvent and the other one was carried out with hexane and toluene mixture as solvent. In the case of hexane and toluene mixture, the enantiomeric excess value was higher than the case of toluene solvent. As a result of these trials, it is determined that the addition of toluene to hexane with minimum amount, in which nitrostyrene derivatives dissolved, was not affected enantioselectivity in a considerable amount. After all, the reactions carried out in hexane and toluene mixture. The best result (89% ee) among other derivatives was obtained when inductively electron donating methyl group is on para position of *trans*-β-nitrostyrene. Moreover, other electron-donating and withdrawing groups were examined and it is realized that electron-donating groups increases both enantioselectivitiy and conversion compared to electron-withdrawing groups. Electron-withdrawing groups (*p*-Br, *p*-Cl, *p*-F) gave high conversions but low enantioselectivities in constrast to *p*-methyl group. Additionally, nitroolefins with electron-donating groups (*p*-OMe-C_6H_4 and furan) were also tested and they exhibited high enantioselectivities (81%, 87%) with good conversions as *p*-methyl group (Table 8).

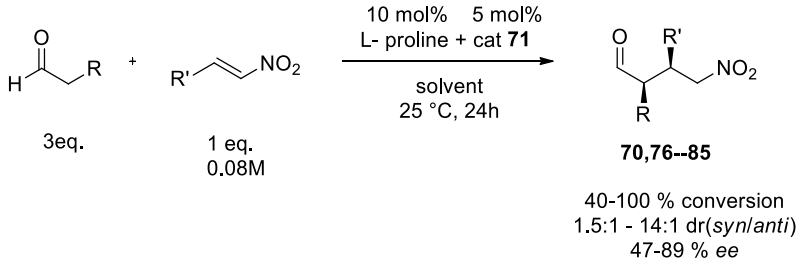


Table 8. Results for derivatization studies

Product	R	R'	Solvent	conversion[a]	dr[a] (*syn/anti*)	ee %
70	-$CH(CH_3)_2$	-C_6H_5	Hexane	100	14 : 1	75
76	-CH_3	-C_6H	Hexane	99	2 : 1	80
77	-CH_2CH_3	-C_6H_5	Hexane	99	4 : 1	41
78	-$CH_2CH_2CH_3$	-C_6H_5	Hexane	99	5 : 1	58
79	-CH_3, -CH_3	-C_6H_5	Hexane	10	--	73

80	-CH_3	*p*-Br-C_6H_4	Hexane + Toluene[b]	97	2 : 1	52
81	-CH_3	*p*-OMe-C_6H_4	Hexane + Toluene[b]	40	4.4 : 1	81
82	-CH_3	*p*-Cl-C_6H_4	Hexane + Toluene[b]	98	3.4 : 1	60
83	-CH_3	*p*-F-C_6H_4	Hexane + Toluene[b]	93	3.8 : 1	47
84	-CH_3	*p*-Me-C_6H_4	Hexane + Toluene[b]	98	3 : 1	**89**
85	-CH_3	furanyl	Hexane	96	1.5 : 1	87

a: Determined by crude ^{1}H NMR
b: 1.5 mL Toluene

CHAPTER 3

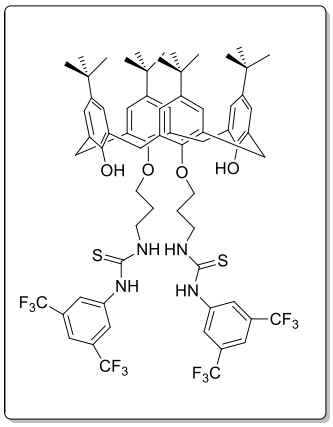
EXPERIMENTAL

3.1 Materials and Methods

NMR (Nuclear Magnetic Resonance) spectra were recorded on Bruker Spectrospin Avance DPX 400 spectrometer in $CDCl_3$. Chemical shifts are reported in ppm and data are specified as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), t (triplet), td (triplet of doublet), q (quartet), m (multiplet) and coupling constants (*J*) in Hertz (Hz). Chromatographic seperations was conducted by glass precoated silica gel-200 purchased from Macherey-Nagel and TLC was carried out using precoated silica gel aluminum plates (Merck Silica Gel 60 F_{254}). Infrared Spectra were recorded on Bruker Alpha Platinum ATR and data were reported in cm^{-1}. HRMS were recorded on Agilent 6224 TOF LC/MS. HPLC analysis were carried out on Agilent 1100 Series and Daicell AD-H, AS-H, OD-H, OC and IA chiral columns were used. Polarimetric measurements were carried out by Rudolph Scientific Autopol III polarimeter. Diastereomeric ratio was determined by crude ^1H NMR.

3.2 Synthesis of Calix[4]arene based thiourea catalyst

p-t-Butylcalix[4]arene diamine (1.0 mmol, 0.762 mg) was dissolved in 30 mL dried THF. Then, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (2.2 mmol, 400 µL) was added via syringe in ice bath and the mixture was stirred at room temperature until the completion of the reaction. The completion of reaction was monitored by TLC. After completion of the reaction, volatile material was removed and remaining solid dissolved in minimum amount of EtOAc. The residue was purified by column chromatography over silica gel using hexane:ethyl acetate (4:1) as an eluent to afford a pure product.



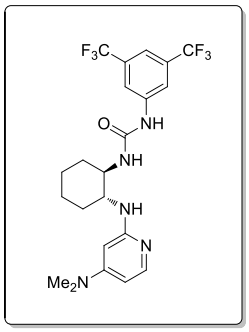
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17-9.07 (m, 2H), 7.87-7.85 (m, 4H), 7.81-7.74 (m, 2H), 7.61-7.57 (m, 2H), 7.57-7.53 (m, 2H), 7.18-7.16 (m, 4H), 6.86-6.81 (m, 4H), 4.10-3.97 (m, 12H), 3.51-3.39 (m, 4H), 2.24-2.03 (m, 4H), 1.31(s, 18H), 0.99 (s, 18H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.6, 148.6, 148.5, 148.0, 144.7, 140.4, 132.0, 131.7, 126.1, 126.2, 124.4, 122.7, 117.9, 44.7, 34.1, 31.9, 30.9, 28.3.

HRMS: calculated for $C_{68}H_{76}F_{12}N_4O_4S_2$ [M + H] 1304.2003, found 1305.5212

3.3 Synthesis of 2-AminoDMAP/urea bifunctional catalyst

(*R*,*R*)-Configurated compound 2-aminoDMAP **74** (47 mg, 0.2 mmol) was dissolved in 1 mL THF in a screw capped vial. To this vial, 1-isocyanato-3,5-bis(trifluoromethyl)benzene **75** (51 mg, 34.5 μL, 0.2 mmol) was added dropwise in 1 min. At 0 °C. This mixture was stirred for 1 day at room temperature then directly loaded on to column. The compound was purified by column chromatography using saturated CH_2Cl_2 as eluent affording 2-aminoDMAP/urea catalyst **71** as an off-white amorphous solid (88 mg, 90% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (bs, 2H), 7.52 (d, *J* = 13.8 Hz, 1H), 7.27 (s, 1H), 6.52 (bs, 1H), 5.88 (d, *J* = 6.1 Hz, 1H), 5.45 (s, 1H), 5.23 (s, 1H), 4.55 (bs, 1H), 3.59 (bs,1H), 3.53 – 3.35 (bs, 1H), 2.81 (s, 6H), 1.99 (d, *J* = 14.2 Hz, 2H), 1.60 (bs, 2H), 1.15 (dd, *J* = 17.1, 10.0 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 155.1, 154.8, 144.4, 140.5, 131.2, 130.8, 130.5, 130.2, 123.6, 120.9, 118.2, 117.0, 113.7, 98.9, 88.0, 54.4, 38.0, 31.5, 29.8, 28.7, 23.5.

IR (neat): 2922, 2853, 1610, 1527, 1473, 1389, 1275, 1169, 1125, 878, 702, 681

HRMS: calculated for $C_{22}H_{26}F_6N_5O$ [M + H] 490.20413, found 490.13713

Optical rotation was determined as $[\alpha]_D^{23}$ = -35.3° (*c* = 1, $CHCl_3$)

Melting point: 180-200 °C

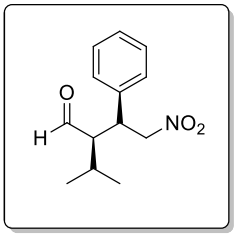
3.4 General procedure for enantioselective Michael addition of aldehydes to nitroolefins

L-Proline (0.025 mmol, 2.88 mg), 2-AminoDMAP/urea **71** (0.0125 mmol, 6.12 mg) and 3.2 mL of hexane were placed in a screw-capped vial. After 30 min, aldehyde (0.75 mmol) was added and stirred for 30 min at 25 °C. Then, nitroalkene (0.25 mmol) was added and stirred

for 24 hours. The reaction was monitored by TLC and after completion of the reaction, the reaction mixture was treated with saturated ammonium chloride solution and extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Then, the crude product was purified by column chromatography over silica gel using hexane:ethyl acetate (7:1) as an eluent to afford a pure product.

3.4.1 Synthesis of 2-Isopropyl-4-nitro-3-phenylbutanal (70)

Using general procedure starting from isovaleraldehyde (0.75 mmol, 80.4 μL) and *trans*-β-nitrostyrene (0.25 mmol, 37.25 mg), compound **70** was obtained as yellow oil with 14:1 dr (*syn*/*anti*) and 100% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (d, *J* = 2.4 Hz, 1H), 7.32 – 7.20 (m, 3H), 7.11 (m, 2H), 4.60 (dd, *J* = 12.8, 4.7 Hz, 1H), 4.51 (dd, *J* = 12.5, 9.9 Hz, 1H), 3.83 (td, *J* = 10.3, 4.4 Hz, 1H), 2.70 (ddd, *J* = 10.7, 4.1, 2.4 Hz, 1H), 1.72 – 1.58 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H).

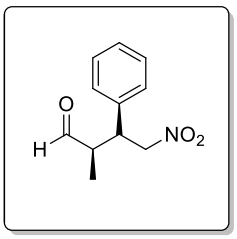
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 136.3, 128.4, 127.3, 127.2, 58.2, 40.9, 28.9, 27.1, 20.8, 16.2.

Enantiomerically enriched product was obtained in a maximum 75% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak AD/H column (hexane/*i*-PrOH 98:2); flow rate 0.5 ml/min, syn: t_{major} = 32.1 min and t_{minor} = 40.6 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +19.68° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.2 Synthesis of 2-Methyl-4-nitro-3-phenylbutanal (76)

Using general procedure starting from propionaldehyde (0.75 mmol, 54.1 μL) and *trans*-β-nitrostyrene (0.25 mmol, 37.25 mg), compound **76** was obtained as yellow oil with 2:1 dr (*syn*/*anti*) and 99% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, *J* = 1.7 Hz, 1H), 4.61 (dd, *J* = 12.7, 9.3 Hz, 1H), 3.82 – 3.65 (m, 1H), 2.79 – 2.63 (m, 1H), 0.97 – 0.89 (d, *J* = 7.3 Hz, 3H). Inseparable signals both *syn*-76 and *anti*-76: 7.31 – 7.20 (m, 5H), 7.16 – 7.07 (m, 3H), 4.76 – 4.68 (m, 2H)

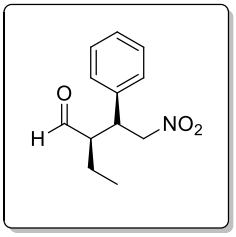
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 135.7, 128.1, 127.1, 127.1, 47.5, 43.8, 43.1, 11.1.

Enantiomerically enriched product was obtained in a maximum 80% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak OD/H column (hexane/*i*-PrOH 80:20); flow rate 0.5 ml/min, syn: t_{minor} = 33.5 min and t_{major} = 41.2 min, anti: t_{major} = 27.1 min and t_{minor} = 43.3 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +20.99° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.3 Synthesis of 2-Ethyl-4-nitro-3-phenylbutanal (77)

Using general procedure starting from butyraldehyde (0.75 mmol, 67.6 μL) and *trans*-β-nitrostyrene (0.25 mmol, 37.25 mg), compound **77** was obtained as yellow oil with 4:1 dr (*syn*/*anti*) and 99% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 2.6 Hz, 1H), 4.69 – 4.62 (dd, *J* = 12.8, 4.9 Hz, 1H), 4.60 – 4.50 (dd, *J* = 12.8, 9.7 Hz, 1H), 3.73 (ddd, *J* = 14.8, 9.6, 5.9 Hz, 1H), 2.61 (ddd, *J* = 10.1, 7.5, 4.9, 2.6 Hz, 1H). Inseparable signals both *syn*-77 and *anti*-77: 7.31 – 7.20 (m, 4H), 7.13 – 7.08 (m, 2H),1.51 – 1.35 (m, 3H), 0.76 (t, *J* = 7.5 Hz, 3H).

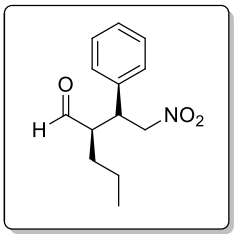
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 135.2, 127.9, 126.9, 126.7, 53.8, 41.5, 35.6, 19.3, 9.6.

Enantiomerically enriched product was obtained in a maximum 41% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak OD/H column (hexane/*i*-PrOH 80:20); flow rate 0.8 ml/min, syn: t_{minor} = 16.7 min and t_{major} = 19.6 min, anti: t_{minor} = 17.4 min and t_{major} = 29.3 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +15.48° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.4 Synthesis of 2-(2-nitro-1-phenylethyl) pentanal (78)

Using general procedure starting from valeraldehyde (0.75 mmol, 79.7 μL) and *trans*-β-nitrostyrene (0.25 mmol, 37.25 mg), compound **78** was obtained as yellow oil with 5:1 dr (*syn*/*anti*) and 99% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 2.8 Hz, 1H), 4.60 (m, 2H), 3.77 – 3.64 (td, *J* = 5.3, 1H), 2.62 (tt, *J* =3.2, 9.5, 1H), 0.74 (t, *J*=7.1, 3H). Inseparable signals both *syn*-78 and *anti*-78: 7.31 – 7.20 (m, 5H), 7.15 – 7.04 (m, 4H), 1.41 (m, 2H), 1.34 – 1.20 (m, 5H).

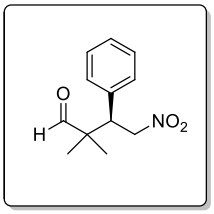
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 136.9, 129.1, 128.2, 128.0, 53.8, 43.2, 29.4, 19.7, 14.2, 13.9.

Enantiomerically enriched product was obtained in a maximum 58% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak OD/H column (hexane/*i*-PrOH 90:10); flow rate 0.5 ml/min, syn: t_{minor} = 38.7 min and t_{major} = 48.9 min, anti: t_{minor} = 43.0 min and t_{major} = 70.7 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +15.22° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.5 Synthesis of 2,2-dimethyl-4-nitro-3-phenylbutanal (79)

Using general procedure starting from isobutyraldehyde (0.75 mmol, 68.5 μL) and *trans*-β-nitrostyrene (0.25 mmol, 37.25 mg), compound **79** was obtained as yellow oil with 99% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.29 – 7.21 (m, 3H), 7.15 – 7.09 (m, 2H), 4.79 (dd, *J* = 13.0, 11.3 Hz, 1H), 4.62 (dd, *J* = 13.1, 4.2 Hz, 1H), 3.71 (dd, *J* = 11.3, 4.2 Hz, 1H), 1.07 (s, 3H), 0.95 (s, 3H).

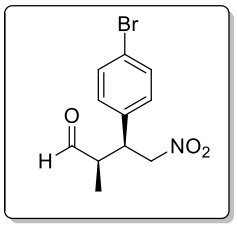
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 133.8, 127.5, 127.2, 126.6, 46.9, 46.6, 20.2, 17.4.

Enantiomerically enriched product was obtained in a maximum 73% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak OD/H column (hexane/*i*-PrOH 80:20); flow rate 0.8 ml/min, t_{major} = 17.0 min and t_{minor} = 24.9 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +19.15° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.6 Synthesis of 3-(4-Bromophenyl)-2-methyl-4-nitrobutanal (80)

Using general procedure starting from propionaldehyde (0.75 mmol, 54.1 μL) and trans-4-Bromo-β-nitrostyrene (0.25 mmol, 57.01 mg), compound **80** was obtained as yellow oil with 2:1 dr (syn/anti) and 97% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, *J* = 1.5 Hz, 1H), 4.57 (dd, *J* = 12.8, 9.6 Hz, 1H), 0.90 (d, *J* = 7.3 Hz, 3H). Inseparable signals both *syn*-80 and *anti*-80: 7.49 – 7.25 (m, 3H), 7.10 – 6.86 (m, 3H), 4.79 – 4.64 (m, 2H), 3.78 – 3.60 (m, 2H), 2.80 – 2.52 (m, 2H).

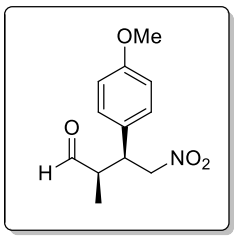
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 133.7, 130.2, 127.6, 120.1, 46.5, 46.0, 41.4, 10.1.

Enantiomerically enriched product was obtained in a maximum 52% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak OD/H column (hexane/*i*-PrOH 90:10); flow rate 1.0 ml/min, syn: t_{major} = 33.3 min and t_{minor} = 38.7 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +13.64° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.7 Synthesis of 2-Methyl-4-nitro-3-(4-methoxyphenyl)butanal (81)

Using general procedure starting from propionaldehyde (0.75 mmol, 54.1 μL) and *trans*-4-Methoxy-β-nitrostyrene (0.25 mmol, 44.79 mg), compound **81** was obtained as yellow oil with 4.4:1 dr (*syn*/*anti*) and 40.4% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.7 Hz, 1H), 4.56 (dd, *J* = 12.5, 9.4 Hz, 1H), 3.71 (s, 3H), 2.76 – 2.57 (m, 1H), 0.94 (t, *J* = 9.0 Hz, 3H). Inseparable signals both *syn*-81 and *anti*-81: 7.08 – 6.96 (m, 3H), 6.83 – 6.74 (m, 3H), 4.72 – 4.64 (m, 2H).

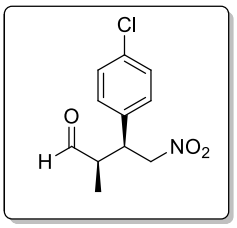
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 159.5, 129.0, 128.1, 114.3, 55.4, 48.5, 44.5, 43.4, 11.9.

Enantiomerically enriched product was obtained in a maximum 81% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak AS/H column (hexane/*i*-PrOH 85:15); flow rate 0.8 ml/min, syn: t_{minor} = 25.8 min and t_{major} = 33.9 min, anti: t_{minor} = 30.1 min and t_{major} = 42.4 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +21.25° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.8 Synthesis of 3-(4-Chlorophenyl)-2-methyl-4-nitrobutanal (82)

Using general procedure starting from propionaldehyde (0.75 mmol, 54.1 μL) and *trans*-4-Chloro-β-nitrostyrene (0.25 mmol, 45.89 mg), compound **82** was obtained as yellow oil with 2:1 dr (*syn*/*anti*) and 98% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 1.4 Hz, 1H), 4.71 (dd, 1H), 4.57 (dd, *J* = 12.8, 9.6 Hz, 1H), 3.81 – 3.64 (m, 1H), 2.78 – 2.61 (m, 1H), 0.93 (d, *J* = 7.3 Hz, 3H). Inseparable signals both *syn*-82 and *anti*-82: 7.30 – 7.20 (m, 3H), 7.12 – 7.01 (m, 3H)

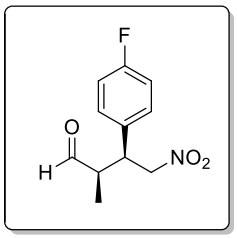
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 135.2, 134.1, 129.4, 129.3, 48.3, 43.4, 12.2, 11.7.

Enantiomerically enriched product was obtained in a maximum 60% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak AD/H column (hexane/*i*-PrOH 97:3); flow rate 0.7 ml/min, syn: t_{major} = 30.0 min and t_{minor} = 38.7 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +15.74° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.9 Synthesis of 3-(4-Fluorophenyl)-2-methyl-4-nitrobutanal (83)

Using general procedure starting from propionaldehyde (0.75 mmol, 54.1 μL) and *trans*-4-Fluoro-β-nitrostyrene (0.25 mmol, 41.78 mg), compound **83** was obtained as yellow oil with 3.8:1 dr (*syn*/*anti*) and 93% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.4 Hz, 1H), 4.71 (dd, *J* = 13.4, 6.7 Hz, 1H), 4.57 (dd, *J* = 12.7, 9.6 Hz, 1H), 3.79 – 3.68 (m, 1H), 2.78 – 2.63 (m, 1H), 0.93 (d, *J* = 7.3 Hz, 3H). Inseparable signals both *syn*-83 and *anti*-83: 7.15 – 7.04 (m, 3H), 7.00 – 6.94 (m, 3H).

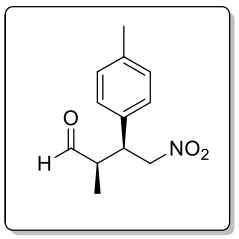
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.8, 161.1, 129.9, 129.8, 116.2, 48.5, 44.1, 43.4, 12.2.

Enantiomerically enriched product was obtained in a maximum 47% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak AD/H column (hexane/*i*-PrOH 97:3); flow rate 0.7 ml/min, syn: t_{major} = 26.0 min and t_{minor} = 42.1 min, anti: t_{major} = 31.1 min and t_{minor} = 38.3 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +12.33° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.10 Synthesis of 2-Methyl-3-(4-methylphenyl)-4-nitrobutanal (84)

Using general procedure starting from propionaldehyde (0.75 mmol, 54.1 μL) and *trans*-4-Methyl-β-nitrostyrene (0.25 mmol, 40.79 mg), compound **84** was obtained as yellow oil with 3:1 dr (*syn*/*anti*) and 98% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.7 Hz, 1H), 4.58 (dd, *J* = 12.6, 9.3 Hz, 1H), 3.76 – 3.64 (m, 1H), 2.74 – 2.63 (m, 1H), 2.25 (s, 3H), 0.92 (d, *J* = 7.2 Hz, 3H). Inseparable signals both *syn*-84 and *anti*-84: 7.10 – 6.94 (m, 6H), 4.69 (ddd, *J* = 12.5, 5.9, 2.9 Hz, 2H).

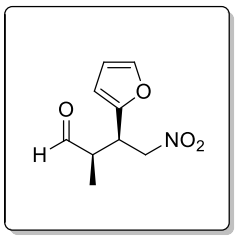
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 136.8, 132.4, 128.7, 126.9, 47.5, 42.8, 28.7, 20.0, 11.2.

Enantiomerically enriched product was obtained in a maximum 89% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak OC column (hexane/*i*-PrOH 90:10); flow rate 1.0 ml/min, syn: t_{minor} = 26.7 min and t_{major} = 29.1 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +23.35° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.4.11 Synthesis of 3-furyl-2-methyl-4-nitrobutanal (85)

Using general procedure starting from propionaldehyde (0.75 mmol, 54.1 μL) and 2-(2-nitrovinyl) furan (0.25 mmol, 34.77 mg), compound **85** was obtained as yellow oil with 1.5:1 dr (*syn*/*anti*) and 96% conversion at the end of 24h.



^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (d, J=1.7 Hz, 1H), 4.08 – 3.96 (m, 1H), 1.00 (d, *J* = 7.3 Hz, 3H). Inseparable signals both *syn*-85 and *anti*-85: 7.29 (d, J=3.2 Hz, 2H), 6.28 – 6.21 (m, 2H), 6.15 – 6.10 (m, 2H), 4.76 – 4.56 (m, 4H), 2.83 – 2.66 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 149.8, 142.7, 110.4, 108.7, 47.0, 38.5, 37.7, 10.9.

Enantiomerically enriched product was obtained in a maximum 87% ee. Enantiomeric purity was determined by chiral HPLC analysis on chiralpak IA column (hexane/*i*-PrOH 80:20); flow rate 1.0 ml/min, syn: t_{minor} = 11.2 min and t_{major} = 13.8 min.

Optical rotation was determined as $[\alpha]_D^{30}$ = +22.82° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

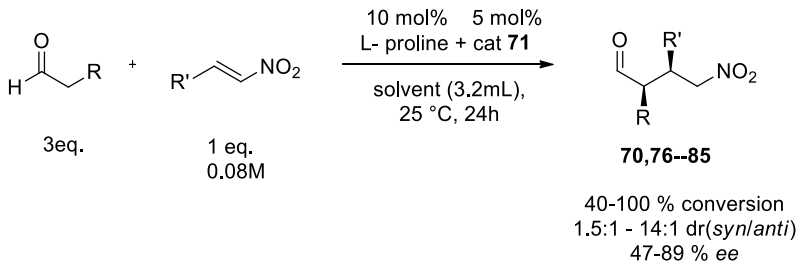
CHAPTER 4

CONCLUSION

In this study, we developed an efficient catalyst combination with *L*-proline and 2-aminoDMAP/urea bifunctional organocatalyst for the asymmetric Michael addition of aliphatic aldehydes to nitroolefins. The resulting γ-nitro carbonyl compounds have a versatile functionality due to their easy transformation into γ-amino acids, tetrahydropyrans and γ-butyrolactones.

In the first part of this study, in order to determine how a chiral additive affects the enamine catalyzed conjugate addition of aldehydes to nitroalkenes, some bifunctional organocatalysts were tested and then to improve the selectivity and conversion, screening studies were performed. By screening solvent, temperature, catalyst loading, concentration and catalyst system, optimum conditions were determined. In the second part of this work, derivatization studies were done with the best condition in which enantioselectivity and conversion exhibited the highest value.

To conclude, 2-aminoDMAP/urea bifunctional organocatalyst was an effective additive to L-proline in terms of selectivity and conversion. Moreover, since proline has solubility problems in non-polar solvents, the results of our trials showed that the addition of bifunctional urea to an L-proline have an incredible effect on solubility, reactivity and selectivity even in non-polar reaction medium. As compared to literature, considerable improvement was achieved in enantioselectivity most up to 89% ee and conversion up to 100% with 10 mol% *L*-proline and 5 mol% 2-aminoDMAP/urea.



Scheme 33. Michael addition reaction of aldehydes to nitroolefins with *L*-proline and 2-aminoDMAP/urea combination

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APPENDIX A

NMR DATA

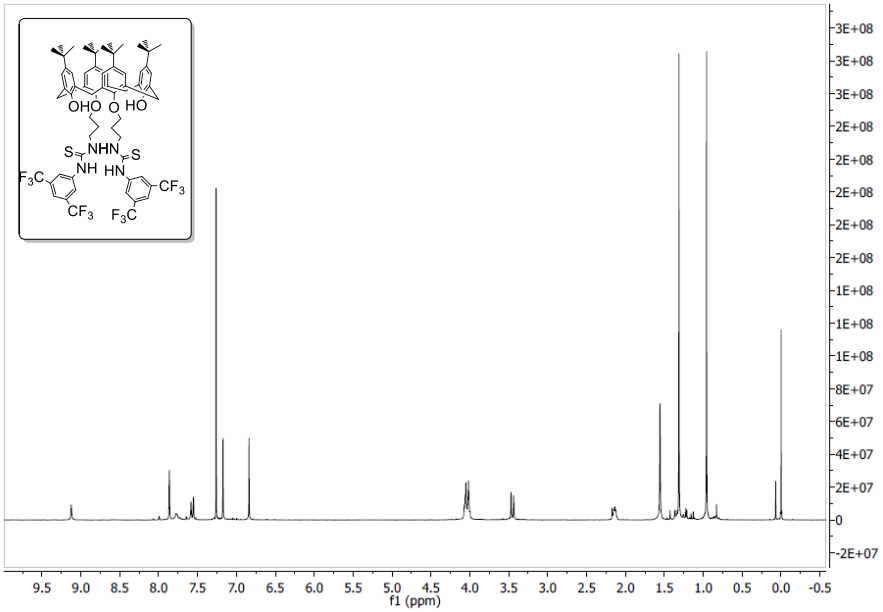

Figure A. 1 ^{1}H NMR spectrum of Calix[4]arene based thiourea

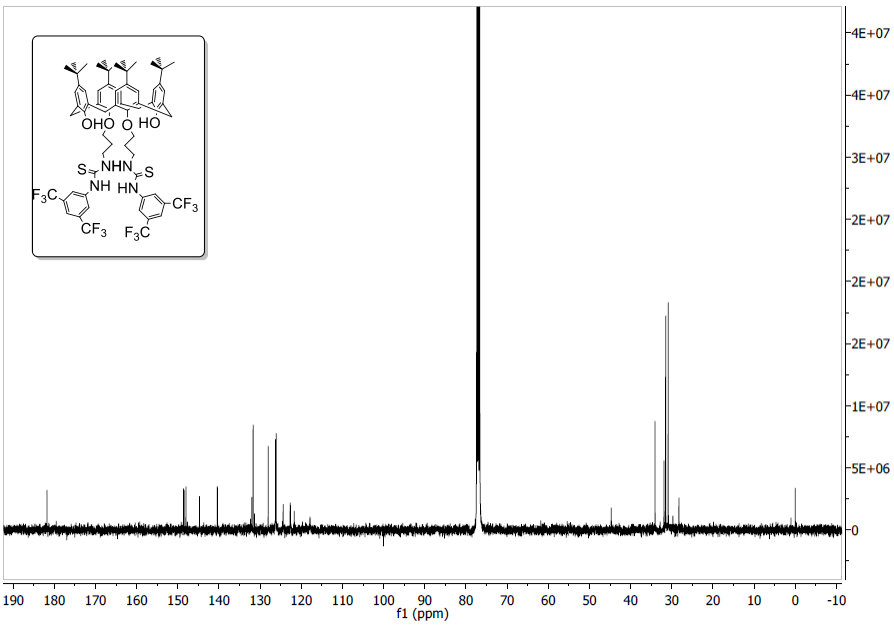

Figure A. 2 ^{13}C NMR spectrum of Calix[4]arene based thiourea

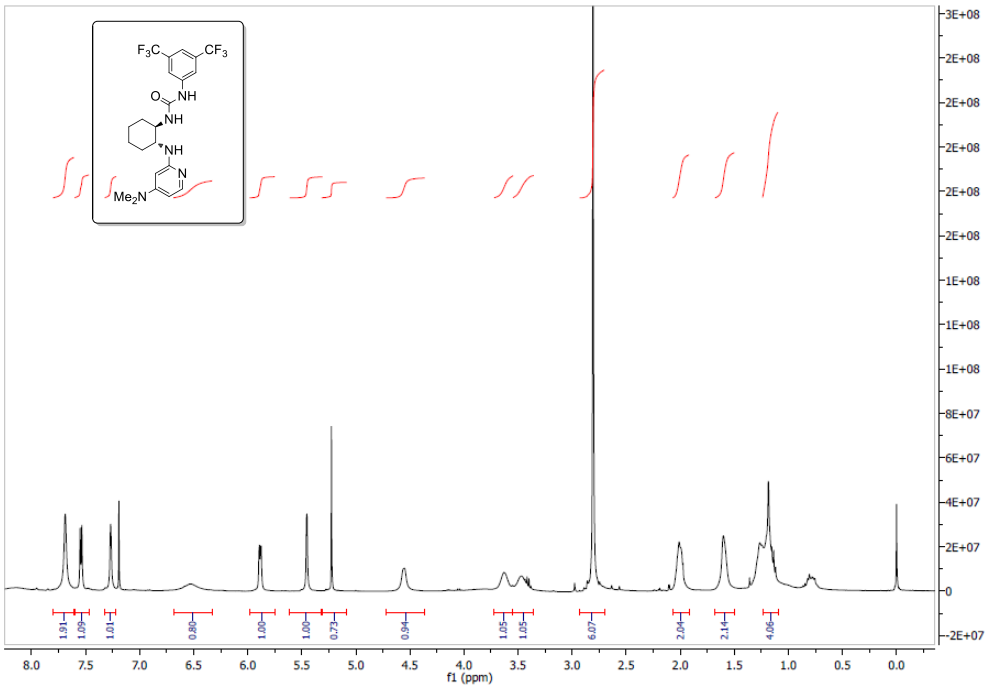

Figure A.3 ^{1}H NMR spectrum of catalyst **71**

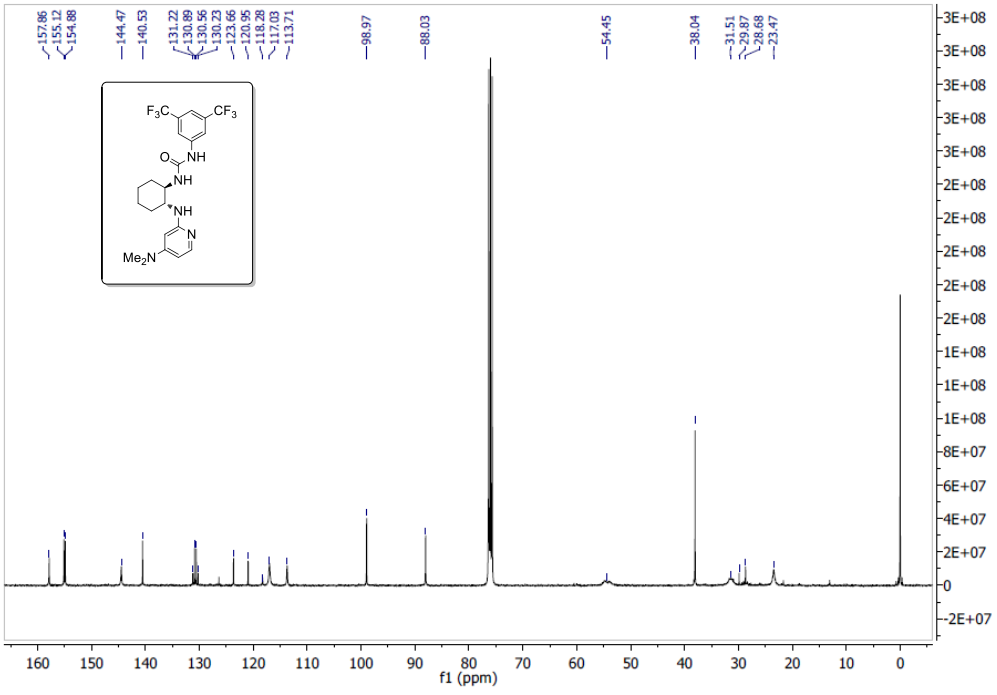

Figure A. 4 ^{13}C NMR spectrum of catalyst **71**

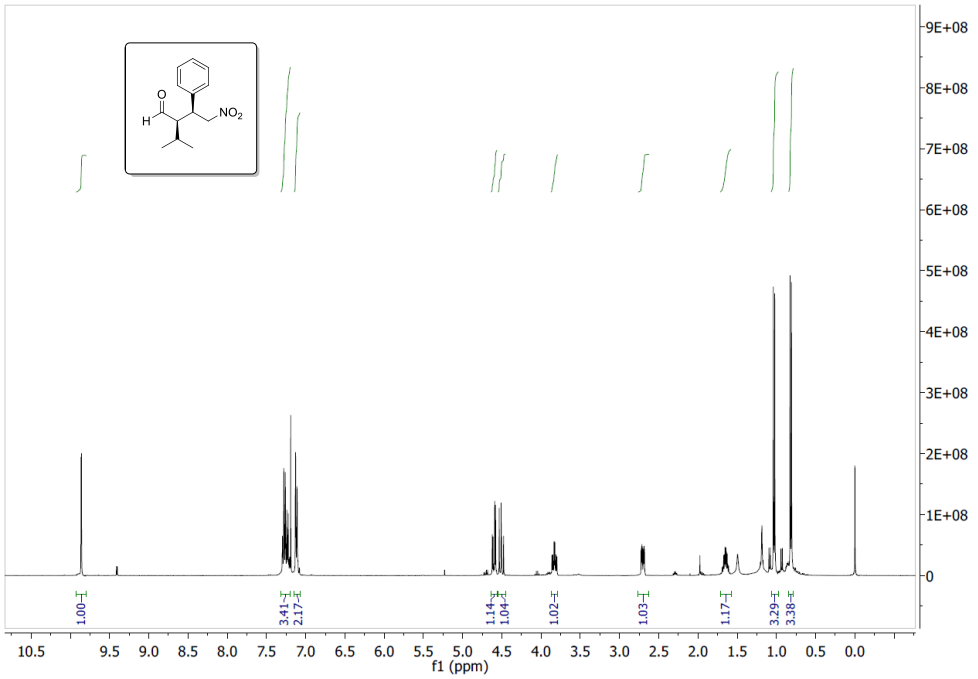

Figure A. 5 ^{1}H NMR spectrum of **70**

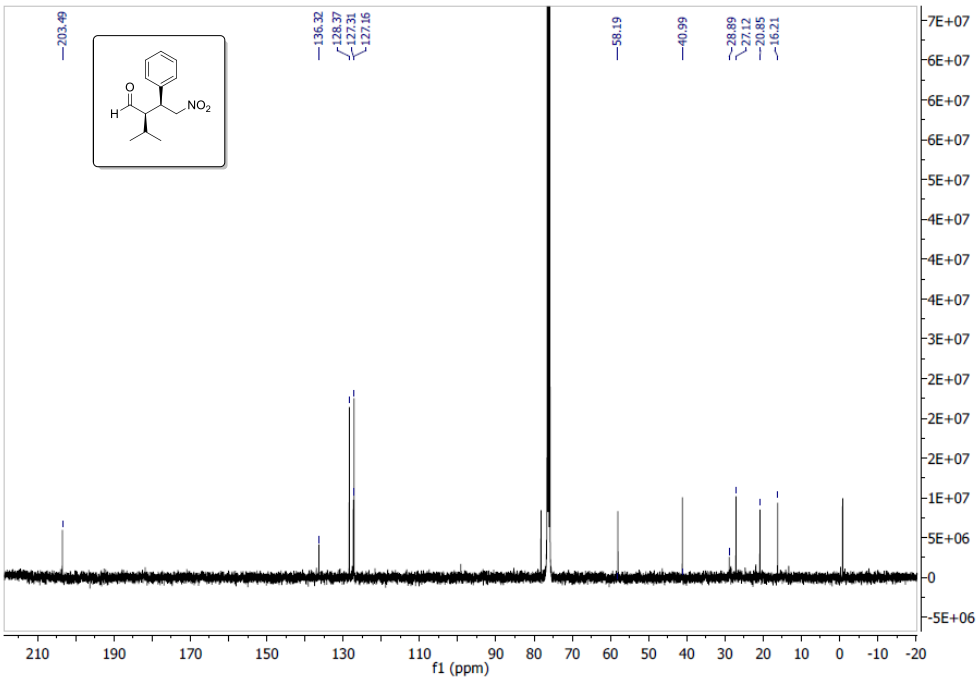

Figure A. 6 ^{13}C NMR spectrum of **70**

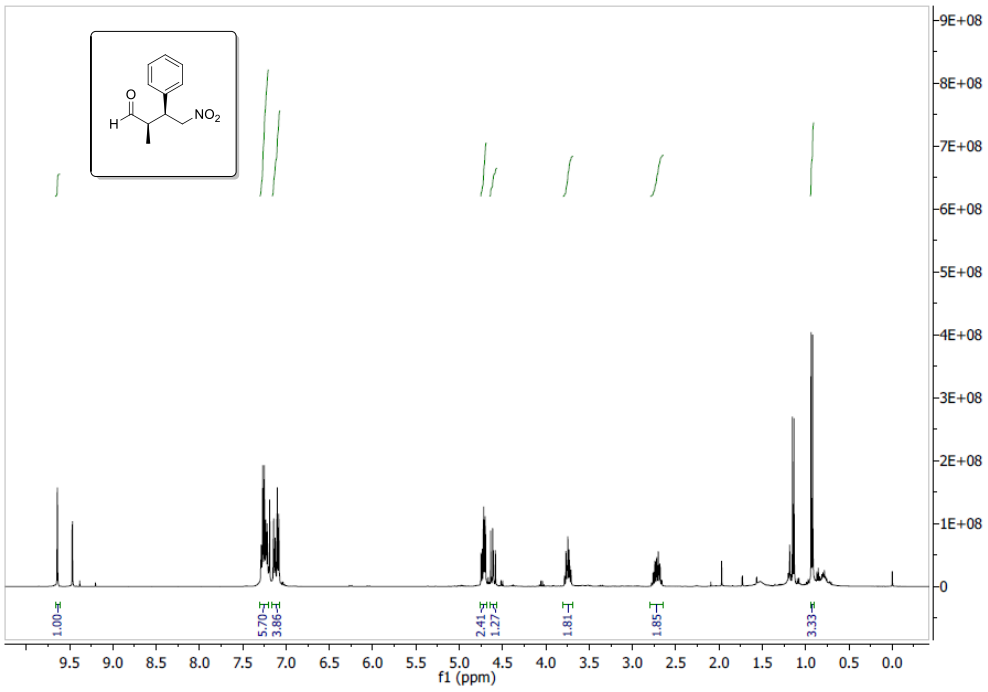

Figure A. 7 ^{1}H NMR spectrum of **76**

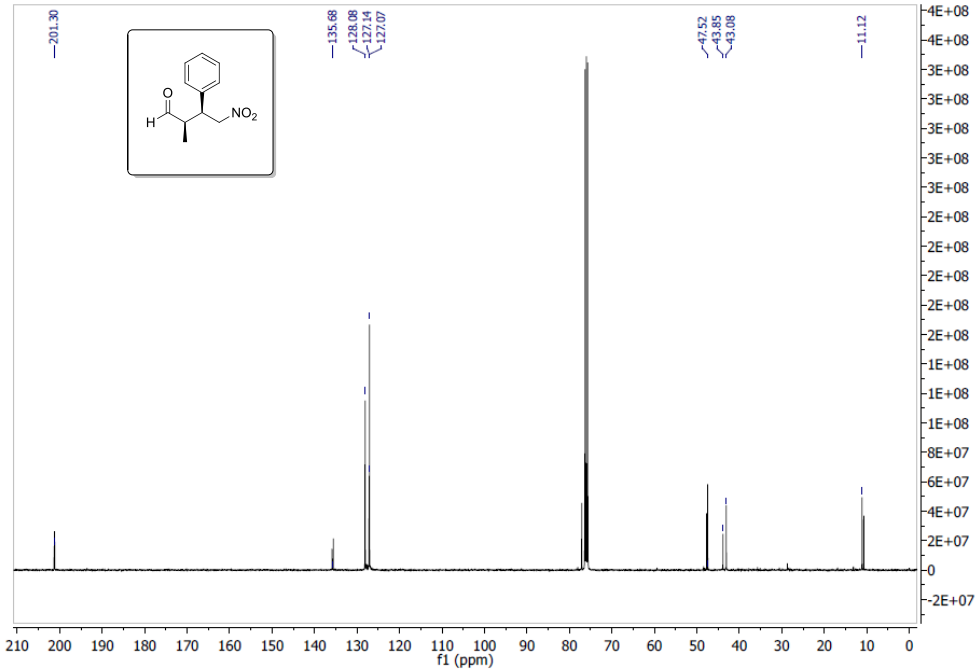

Figure A. 8 ^{13}C NMR spectrum of **76**

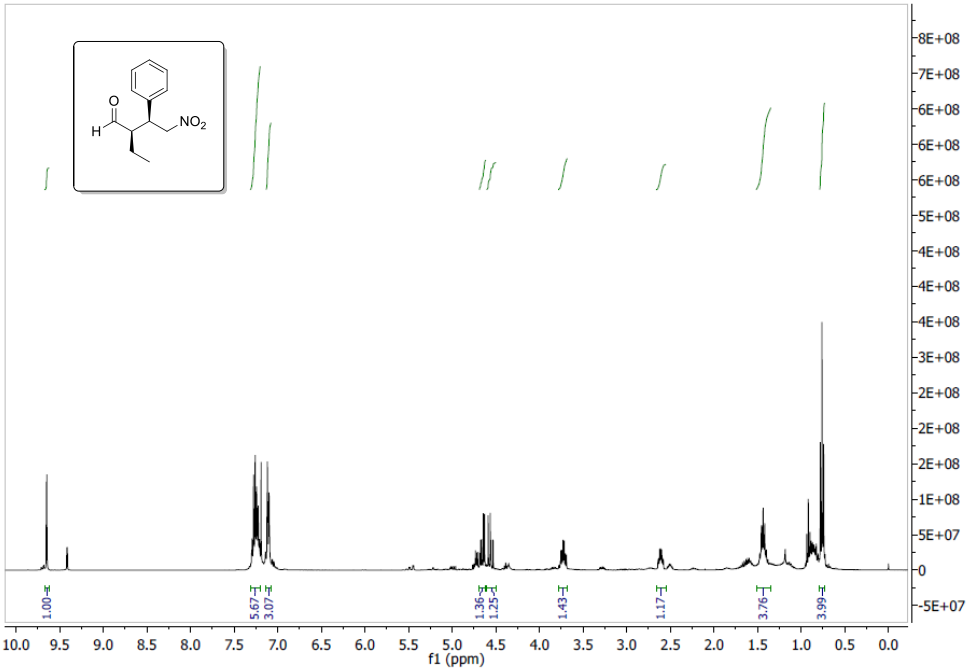

Figure A. 9 ^{1}H NMR spectrum of **77**

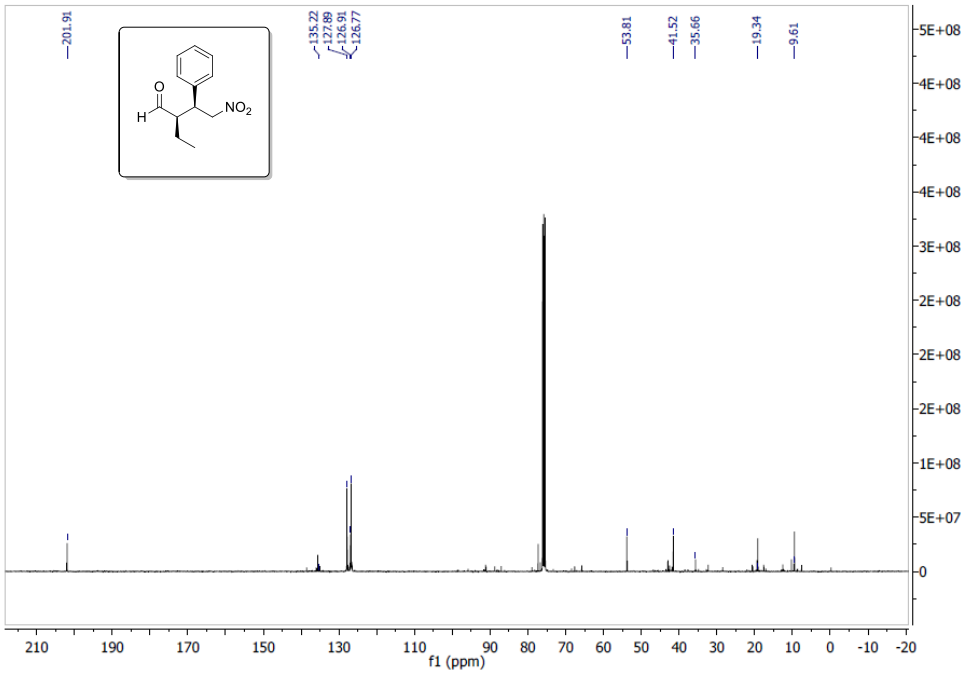

Figure A. 10 ^{13}C NMR spectrum of **77**

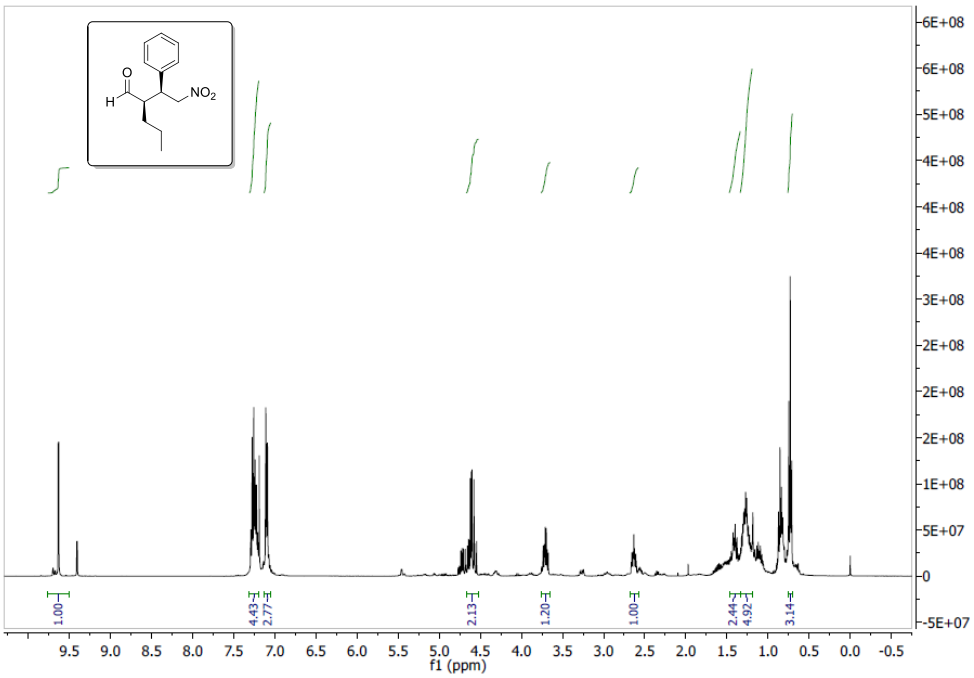

Figure A. 11 ^{1}H NMR spectrum of **78**

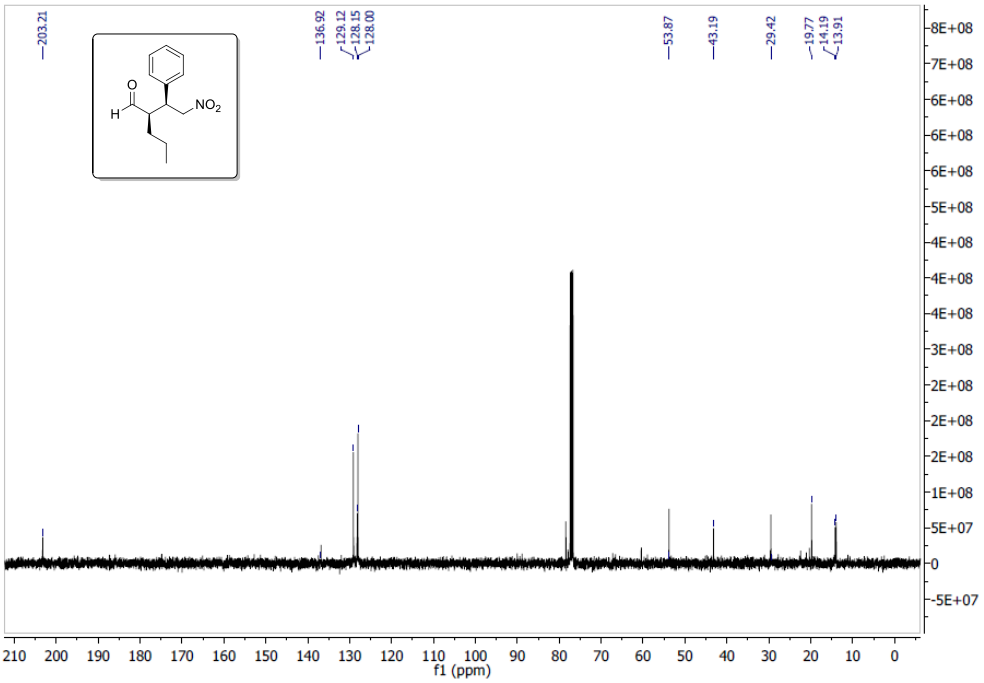

Figure A. 12 ^{13}C NMR spectrum of **78**

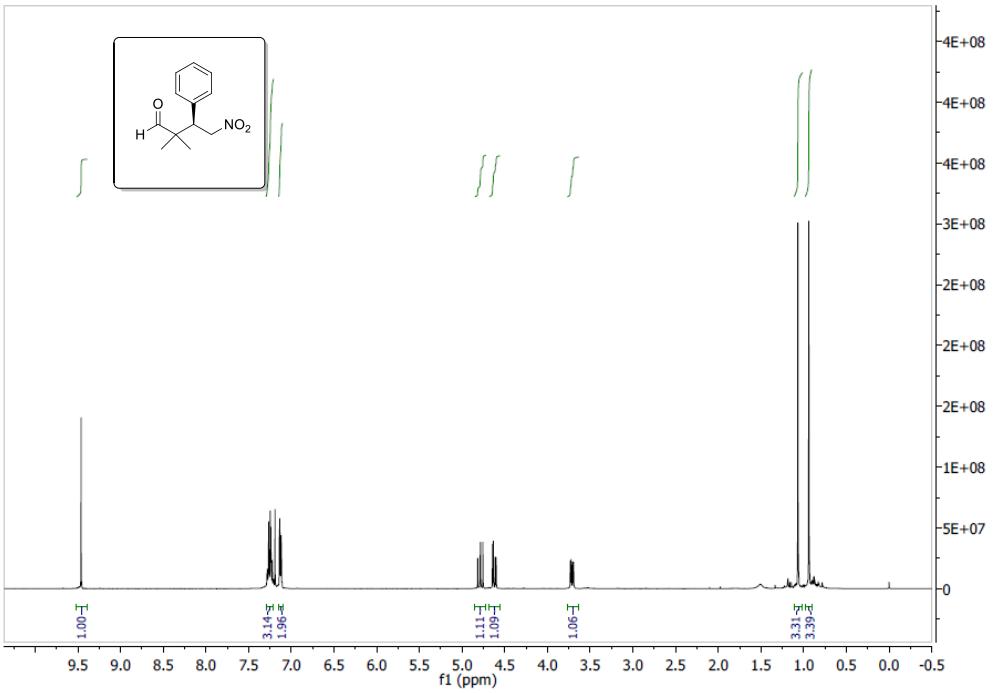

Figure A. 13 ^{1}H NMR spectrum of **79**

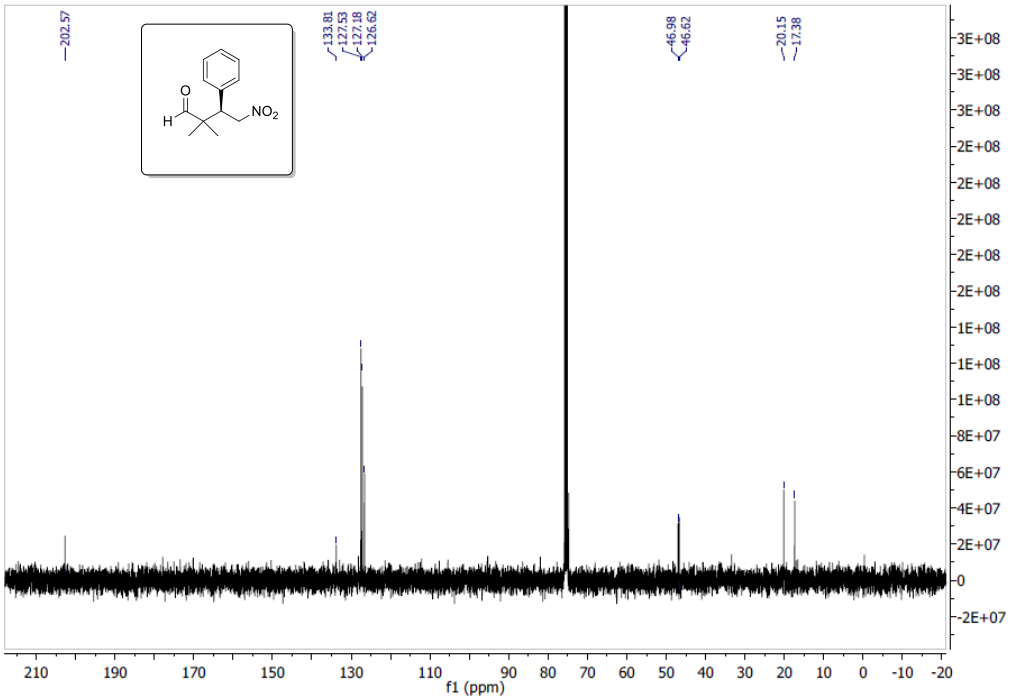

Figure A. 14 ^{13}C NMR spectrum of **79**

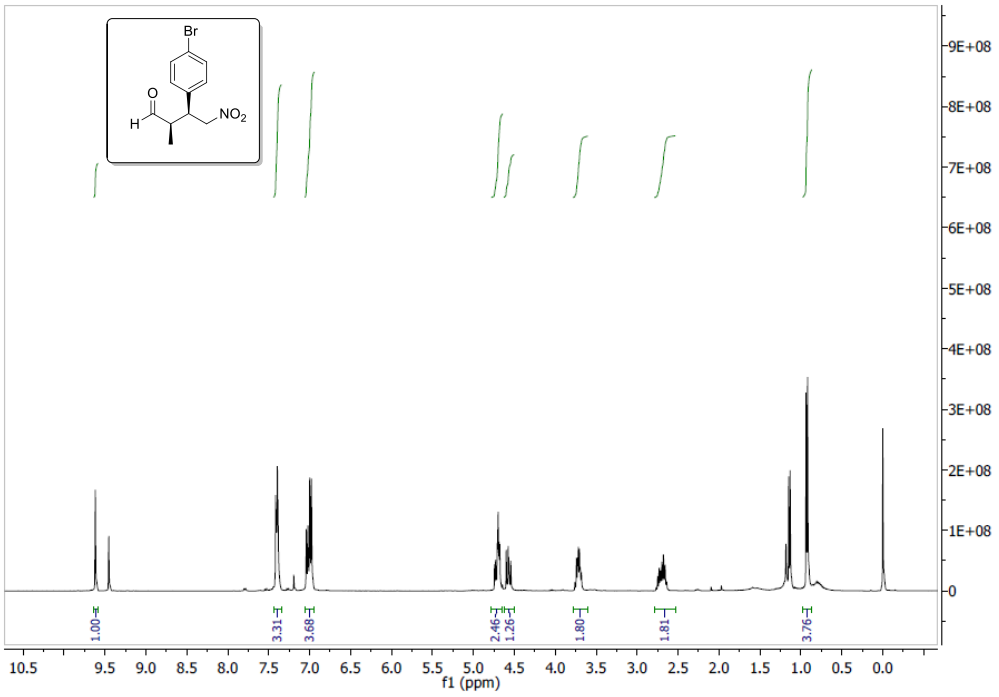

Figure A. 15 ^{1}H NMR spectrum of **80**

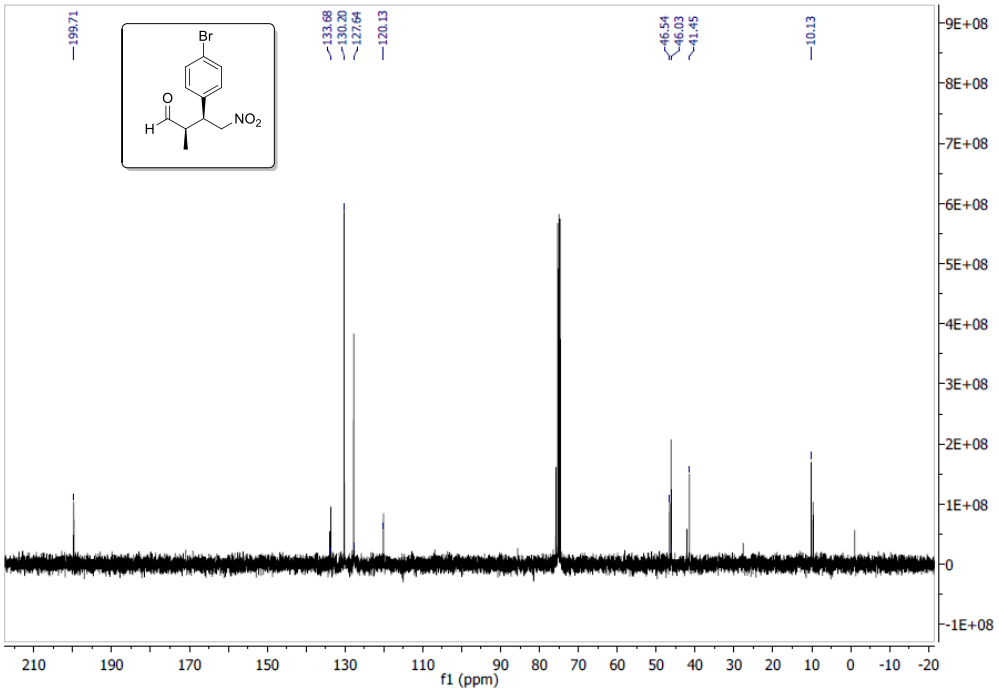

Figure A. 16 ^{13}C NMR spectrum of **80**

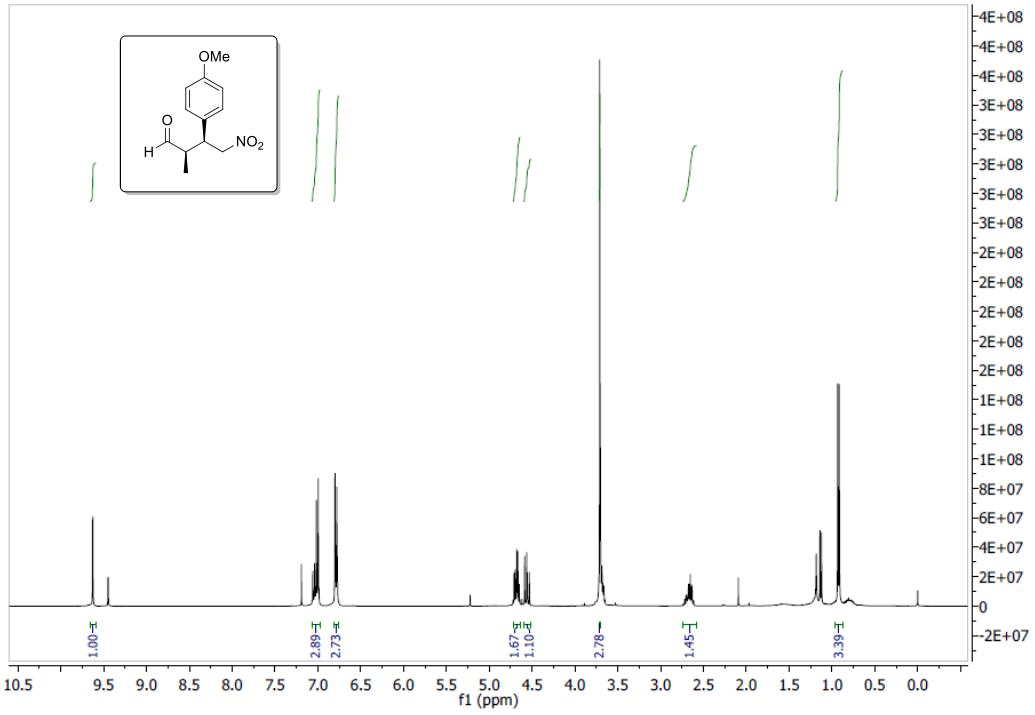

Figure A. 17 ^{1}H NMR spectrum of **81**

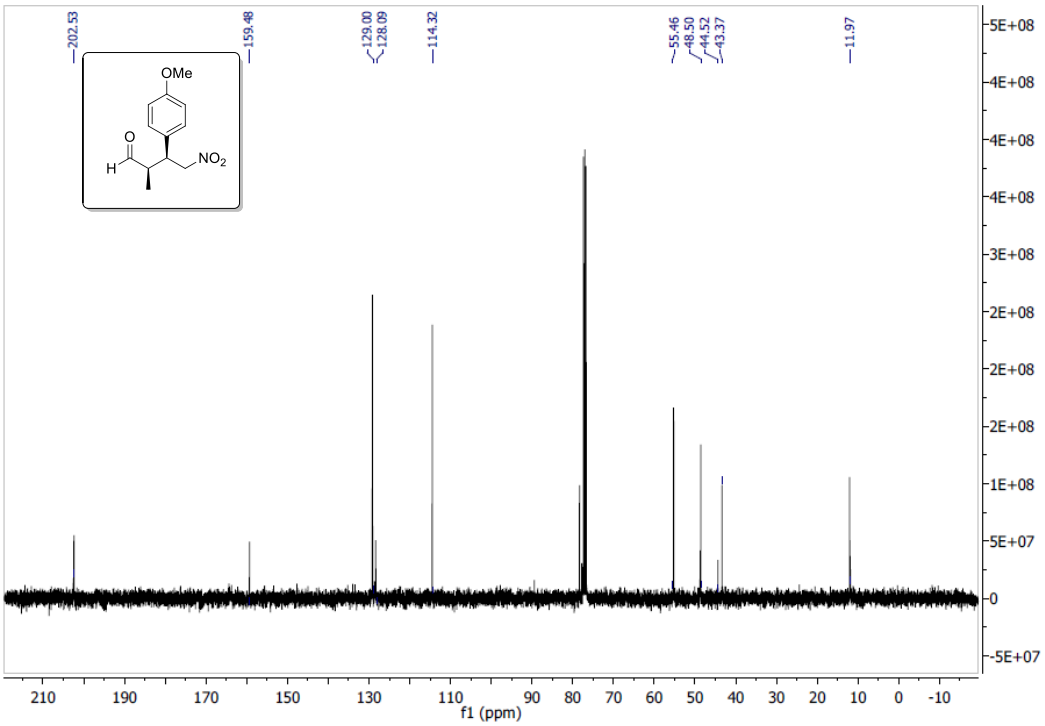

Figure A. 18 ^{13}C NMR spectrum of **81**

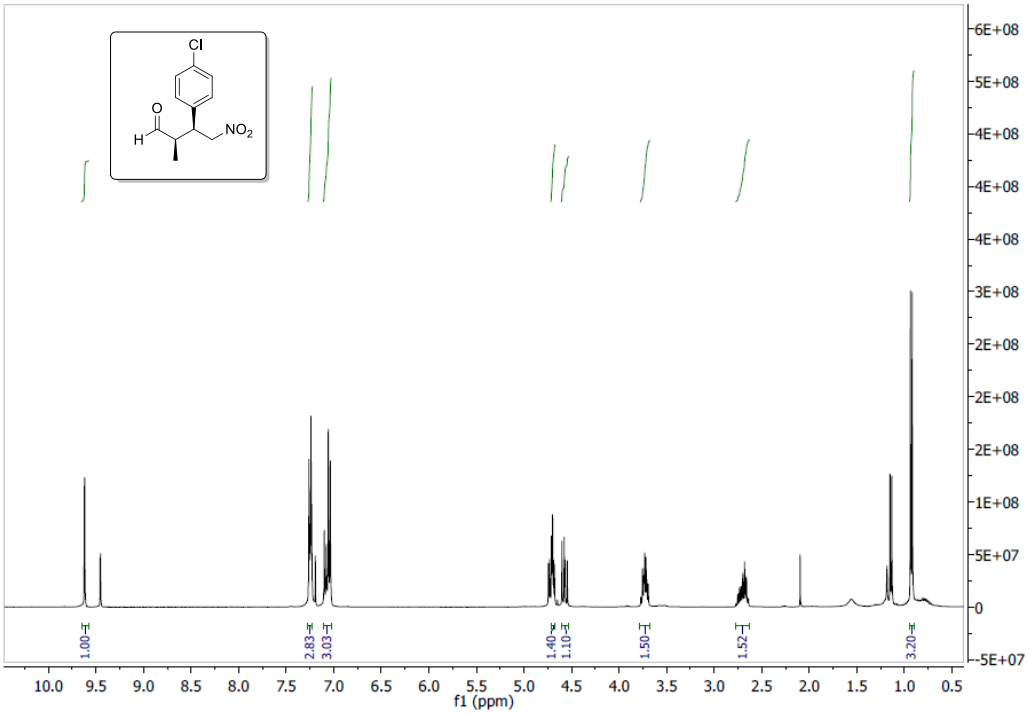

Figure A. 19 ^{1}H NMR spectrum of **82**

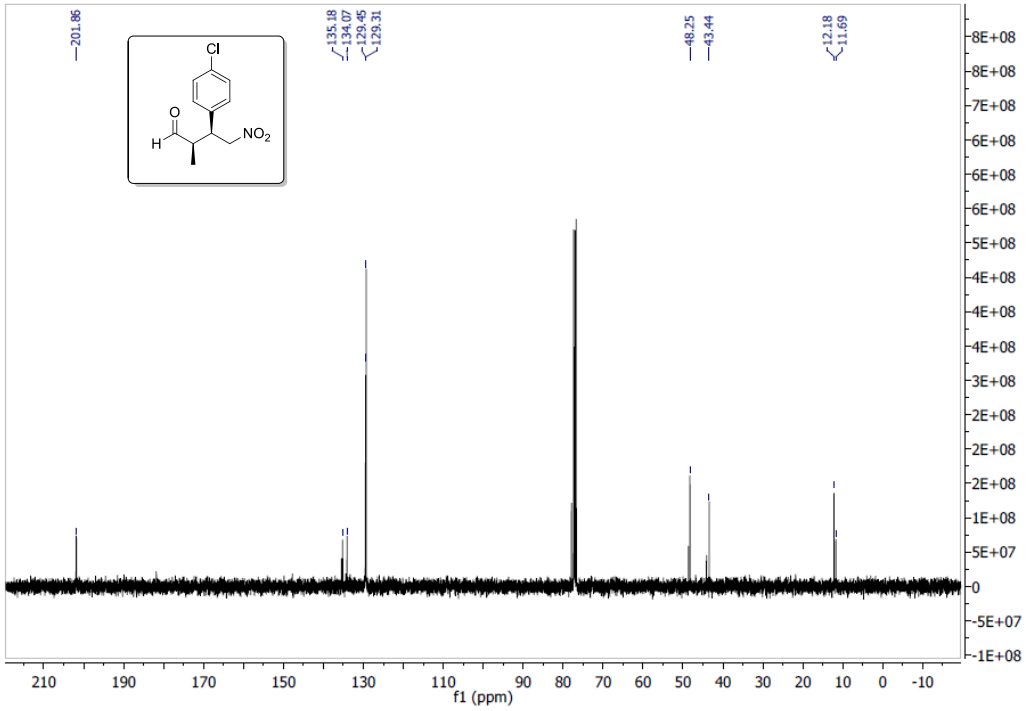

Figure A. 20 ^{13}C NMR spectrum of **82**

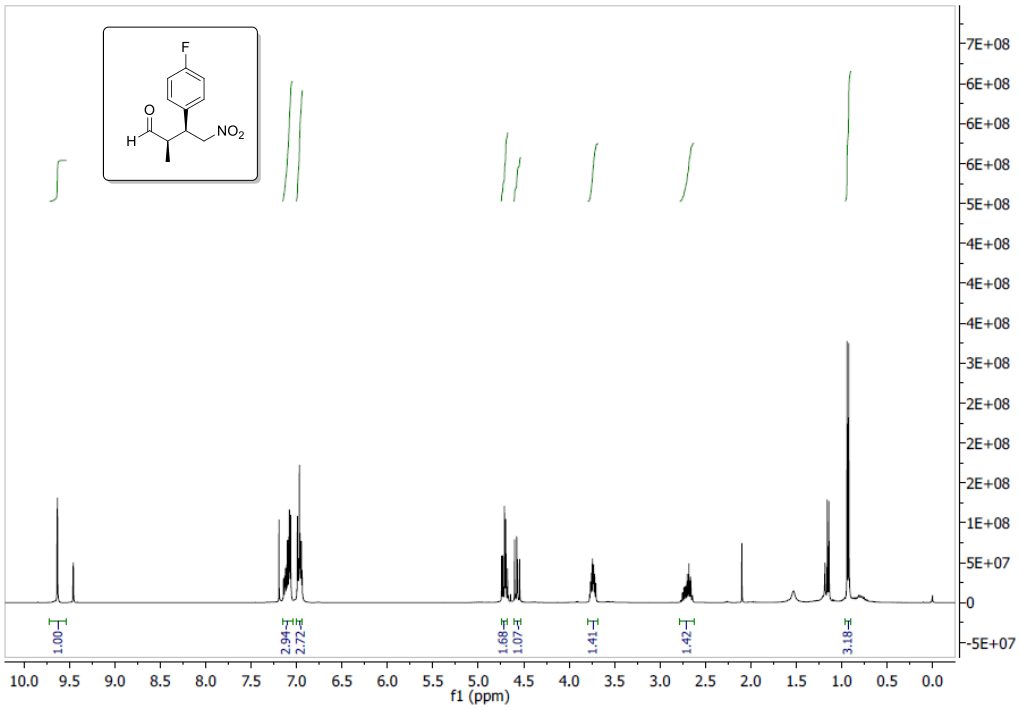

Figure A. 21 ^{1}H NMR spectrum of **83**

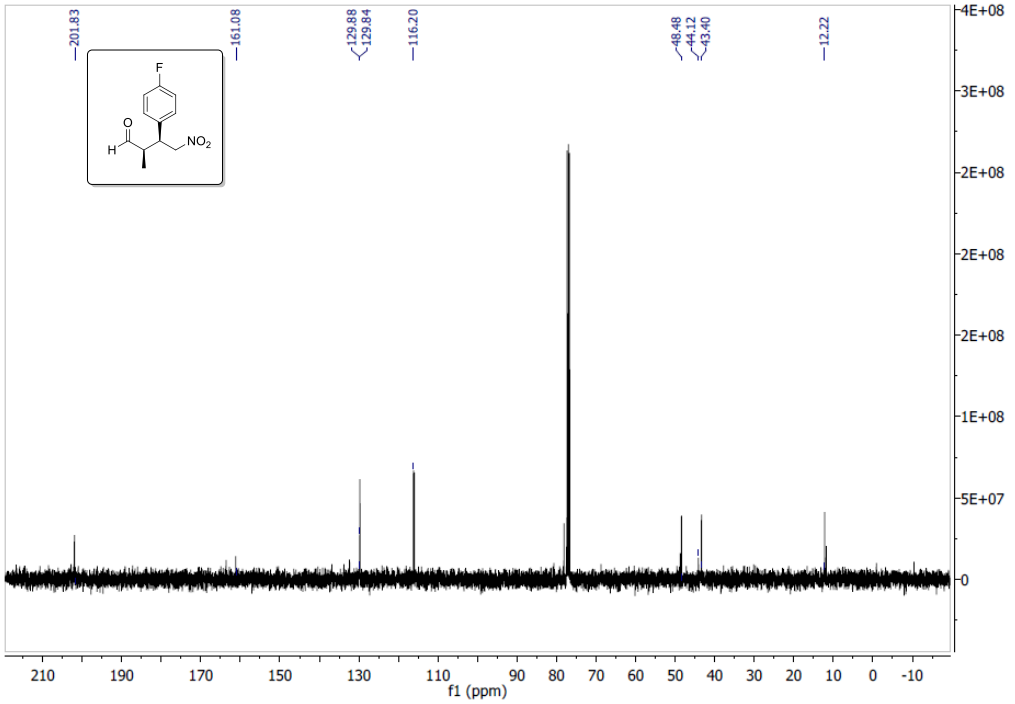

Figure A. 22 ^{13}C NMR spectrum of **83**

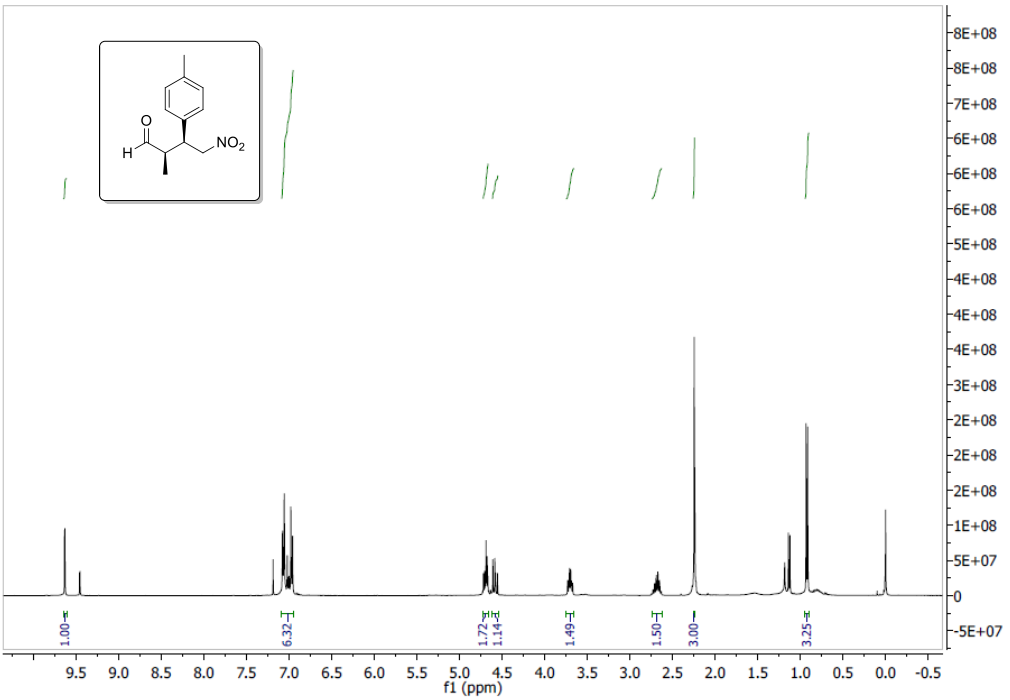

Figure A. 23 ^{1}H NMR spectrum of **84**

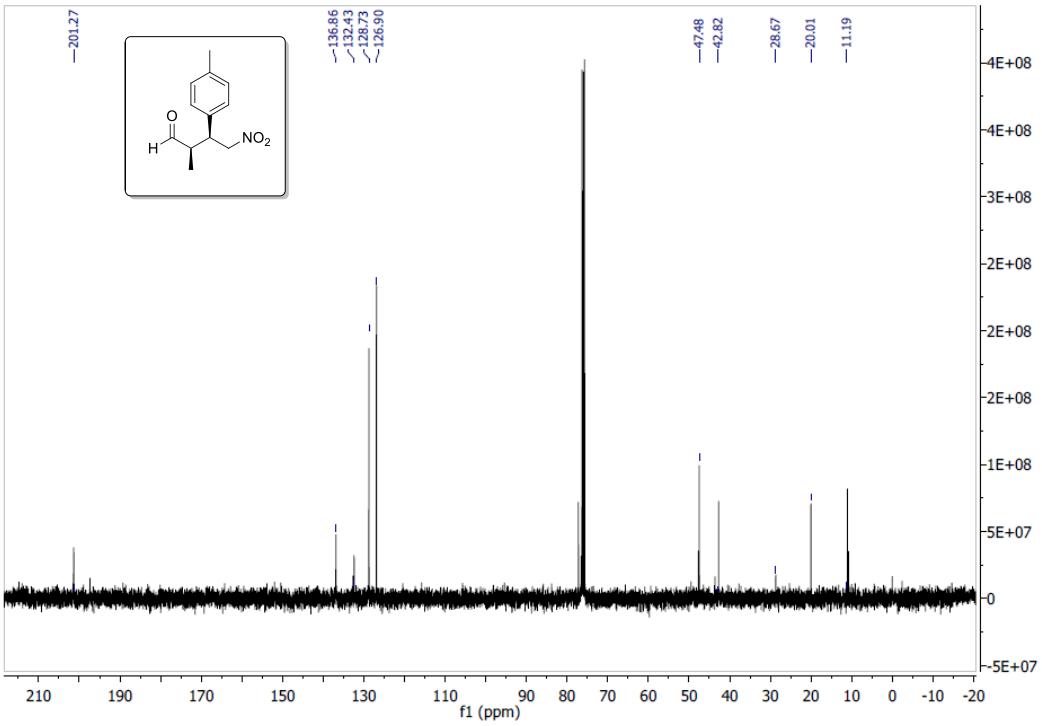

Figure A. 24 ^{13}C NMR spectrum of **84**

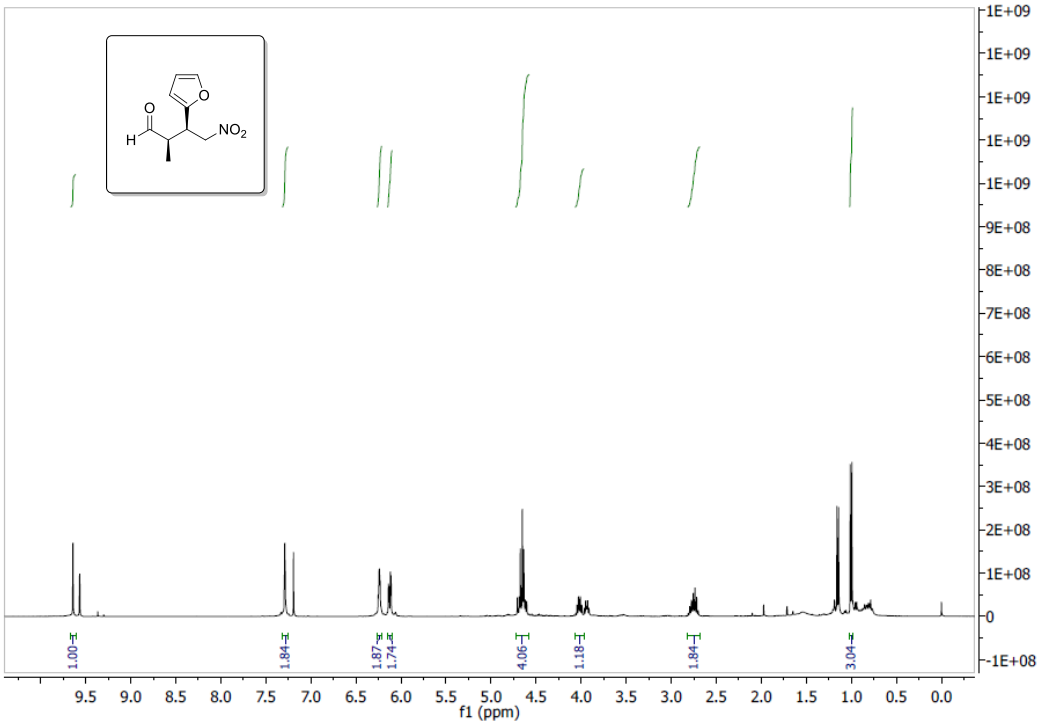

Figure A. 25 ^{1}H NMR spectrum of **85**

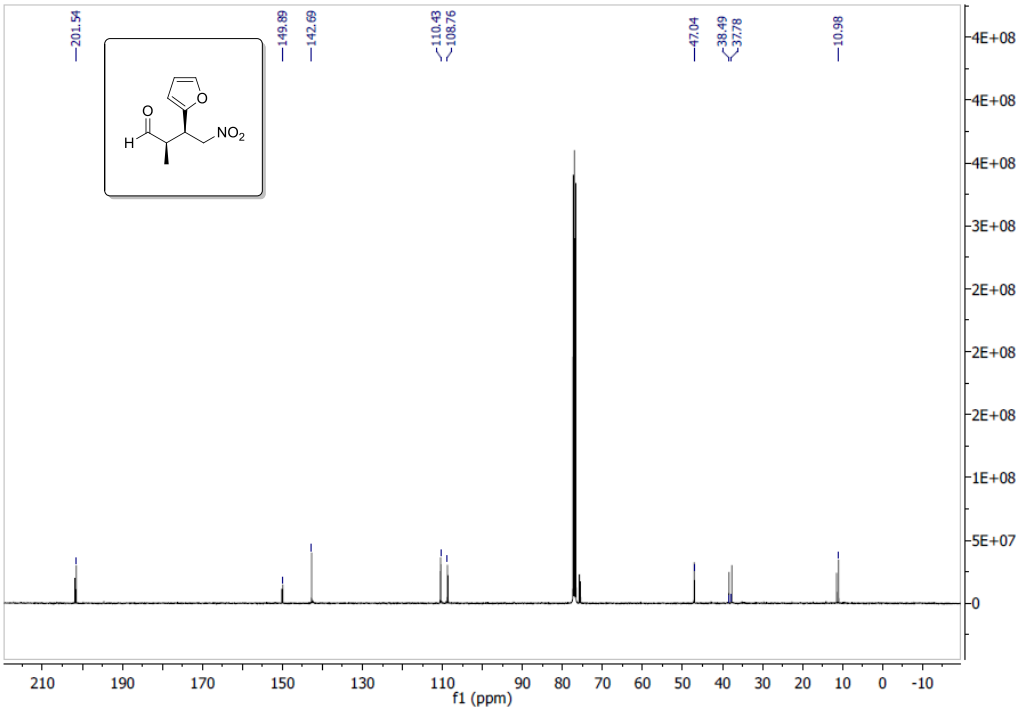

Figure A. 26 ^{13}C NMR spectrum of **85**

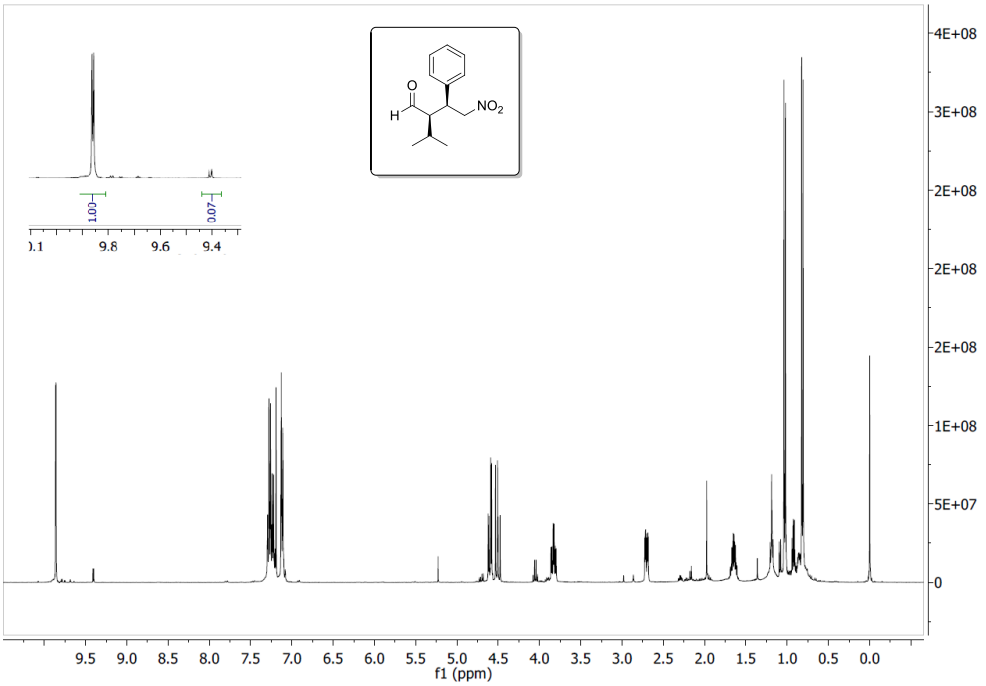

Figure A. 27 Crude ^{1}H NMR spectrum of **70**

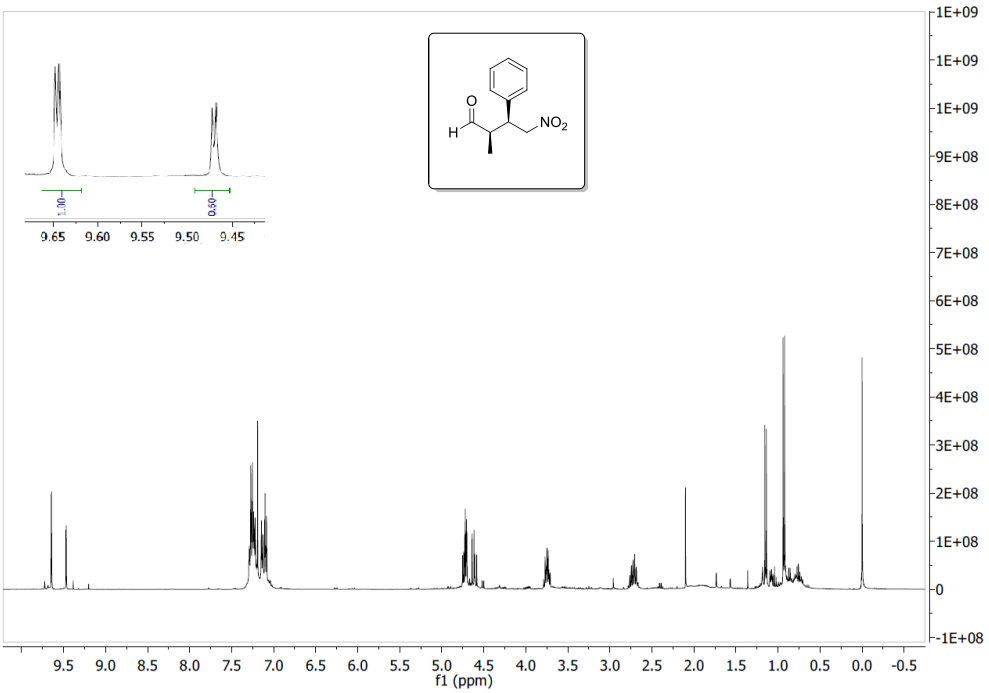

Figure A. 28 Crude ^{1}H NMR spectrum of **76**

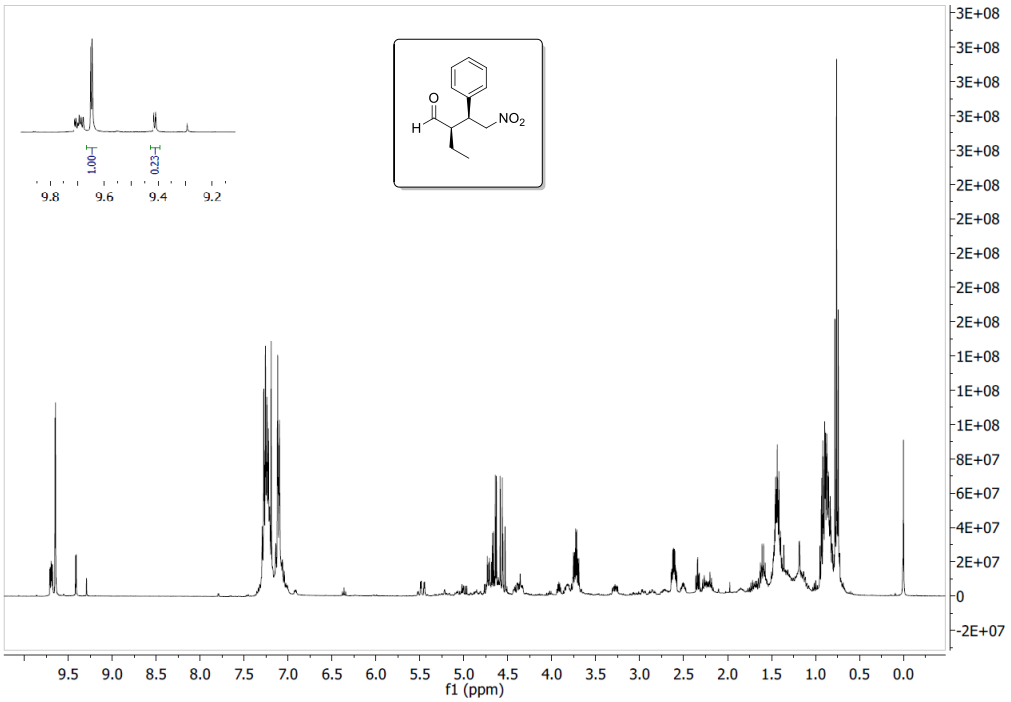

Figure A. 29 Crude ^{1}H NMR spectrum of **77**

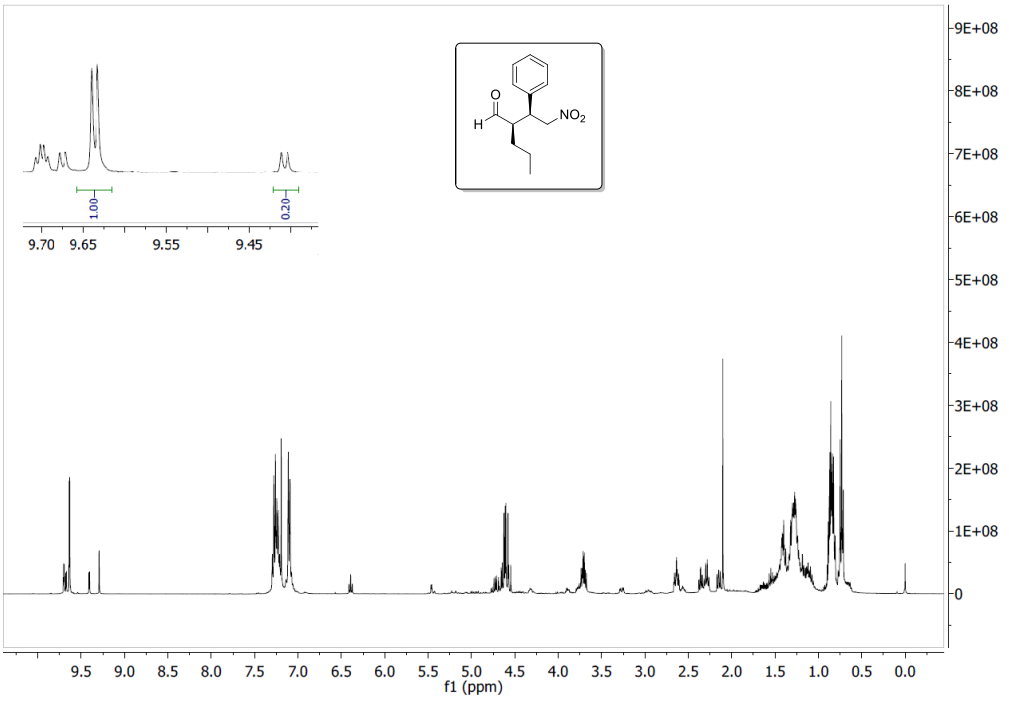

Figure A. 30 Crude ^{1}H NMR spectrum of **78**

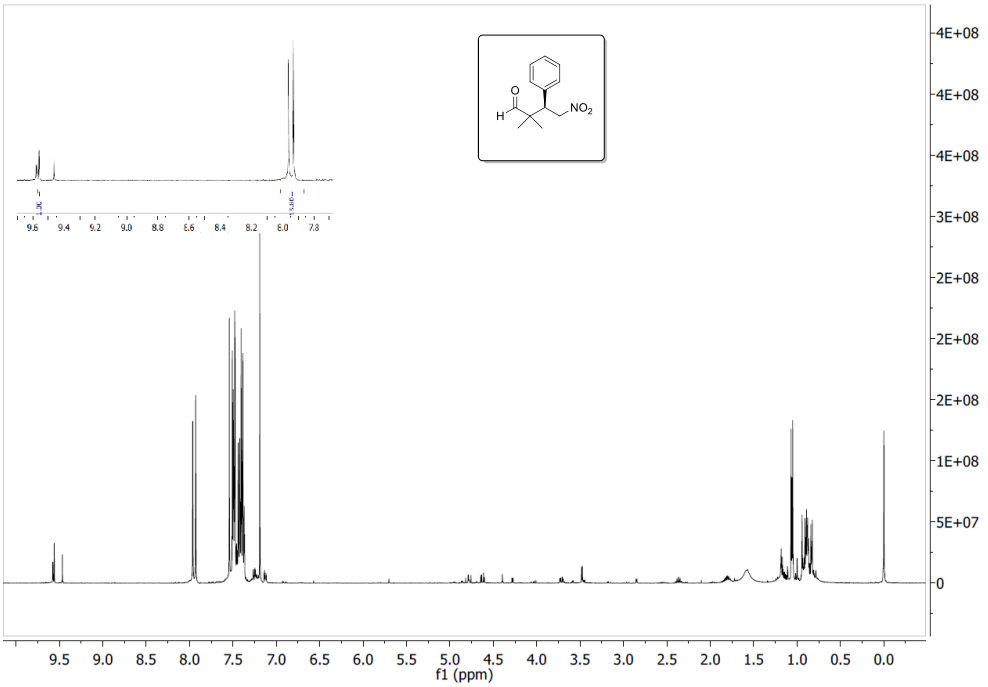

Figure A. 31 Crude ^{1}H NMR spectrum of **79**

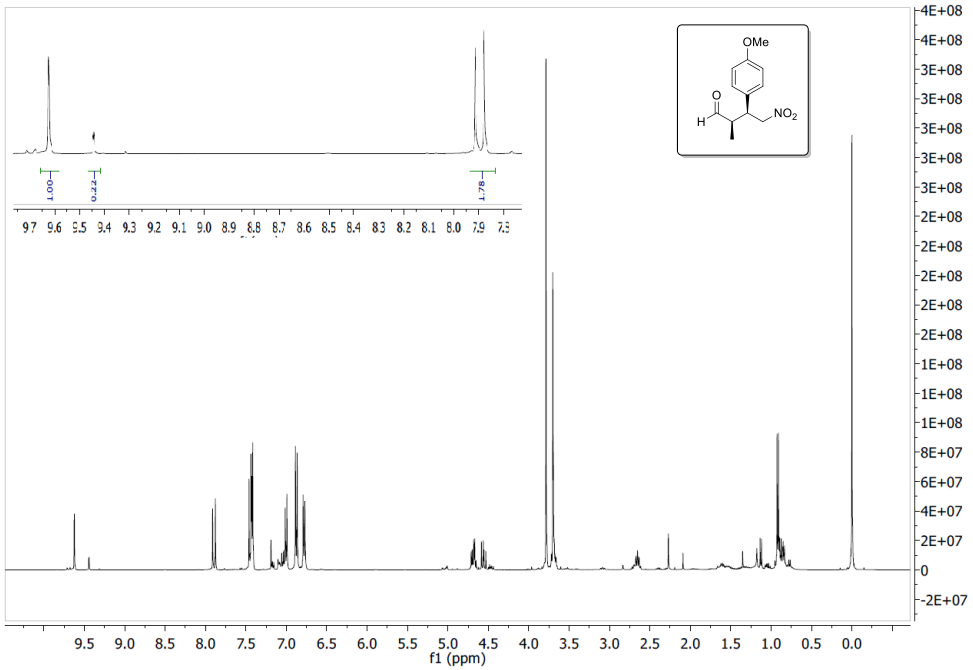

Figure A. 32 Crude ^{1}H NMR spectrum of **81**

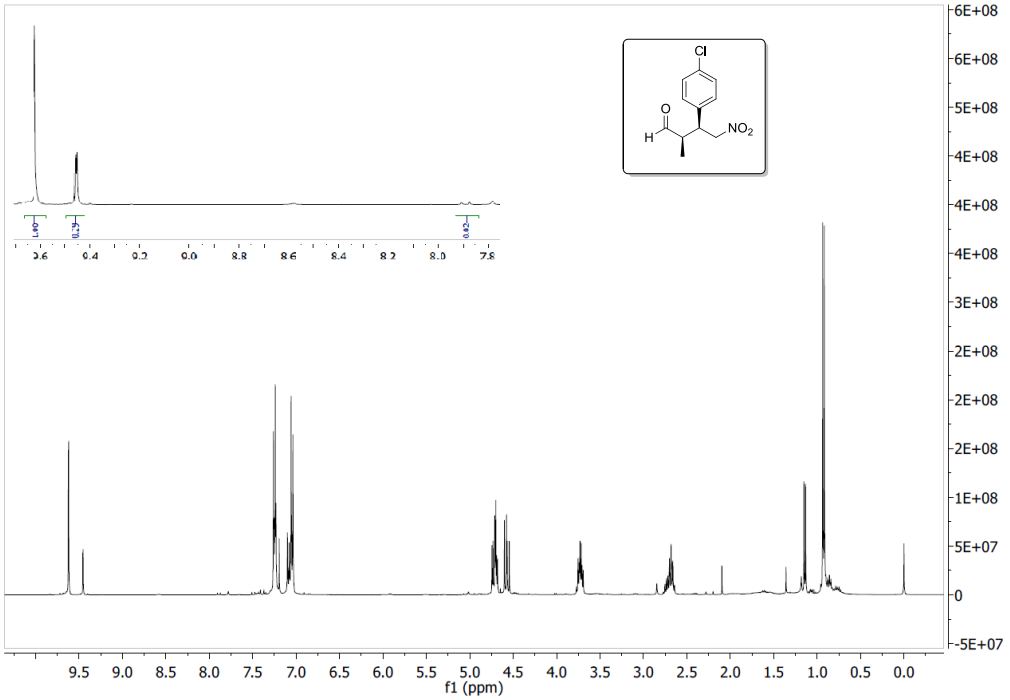

Figure A. 33 Crude ^{1}H NMR spectrum of **82**

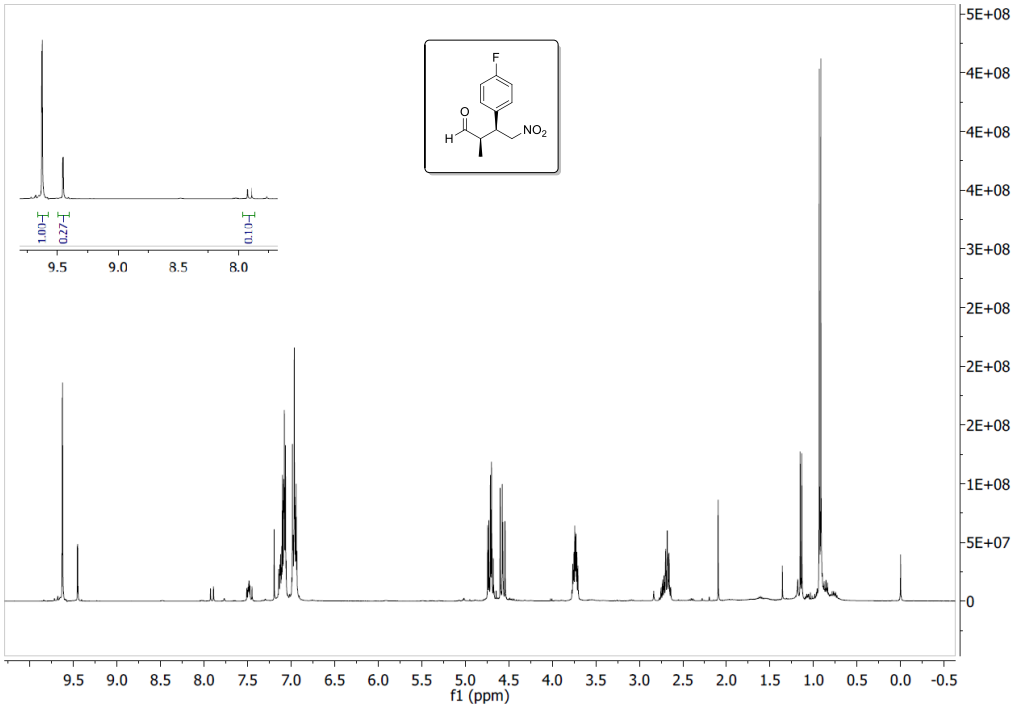

Figure A. 34 Crude ^{1}H NMR spectrum of **83**

APPENDIX B

HPLC DATA

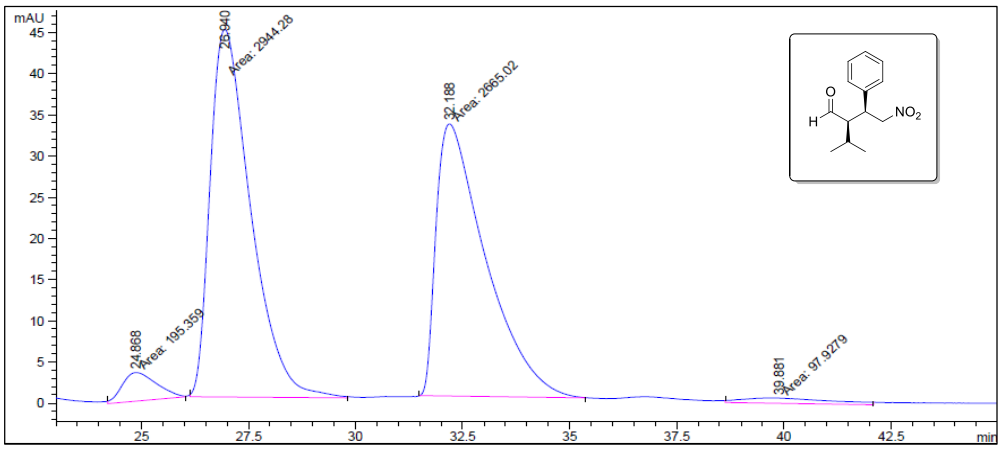

Figure B. 1 HPLC chromatogram of ***rac*- 70**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.868	MM	0.9297	195.35866	3.50216	3.3097
2	26.940	MM	1.0993	2944.28125	44.63713	49.8812
3	32.188	MM	1.3444	2665.01685	33.03812	45.1500
4	39.881	MM	2.4727	97.92787	6.60071e-1	1.6591

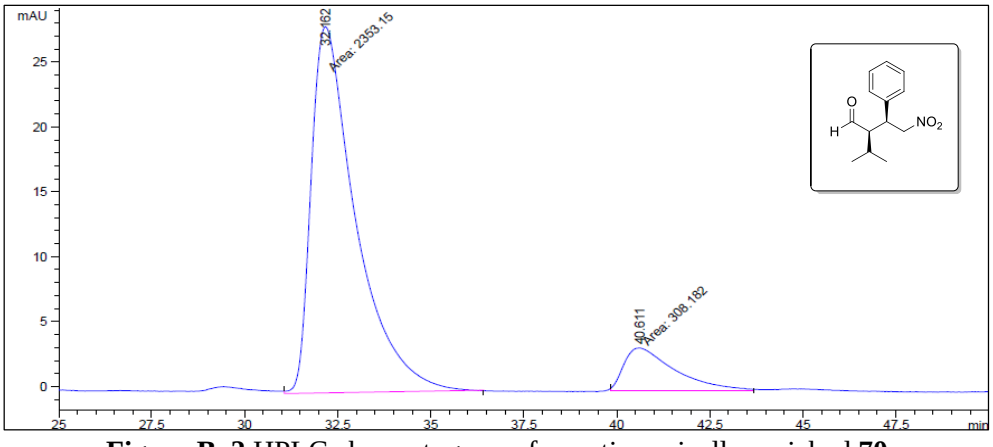

Figure B. 2 HPLC chromatogram of enantiomerically enriched **70**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.162	MM	1.3890	2353.14746	28.23453	88.4200
2	40.611	MM	1.5712	308.18243	3.26912	11.5800

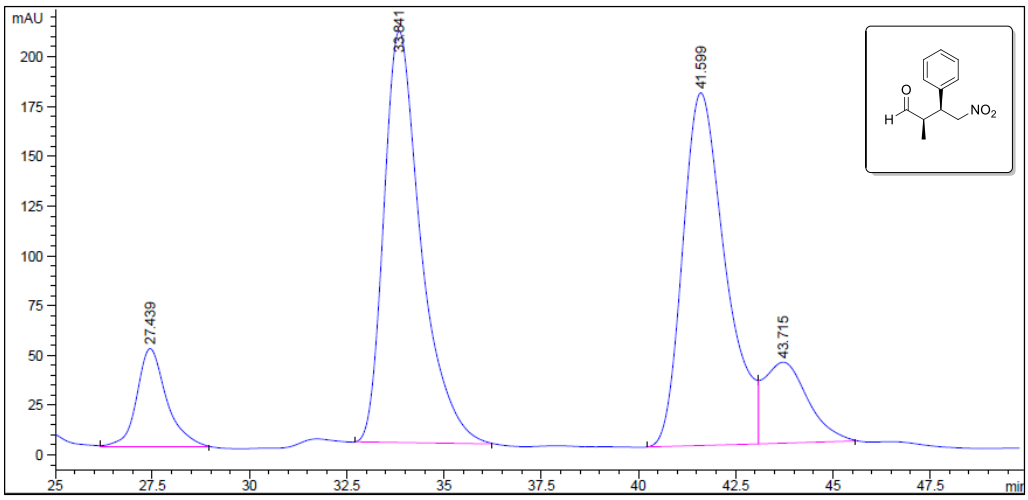

Figure B. 3 HPLC chromatogram of ***rac*- 76**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.439	VB	0.7950	2656.70776	49.43730	8.0062
2	33.841	BB	0.9975	1.37462e4	206.79556	41.4252
3	41.599	BV	1.1551	1.35591e4	177.11852	40.8611
4	43.715	VB	1.1021	3221.25122	40.75446	9.7075

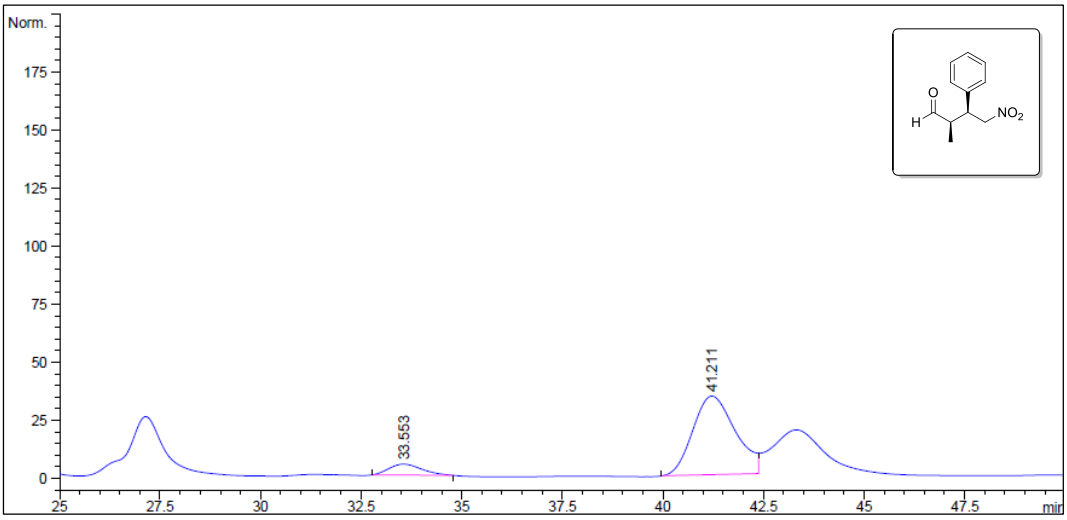

Figure B. 4 HPLC chromatogram of enantiomerically enriched **76**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.553	BB	0.7043	277.76151	4.77726	9.9548
2	41.211	BV	1.0765	2512.45898	33.98585	90.0452

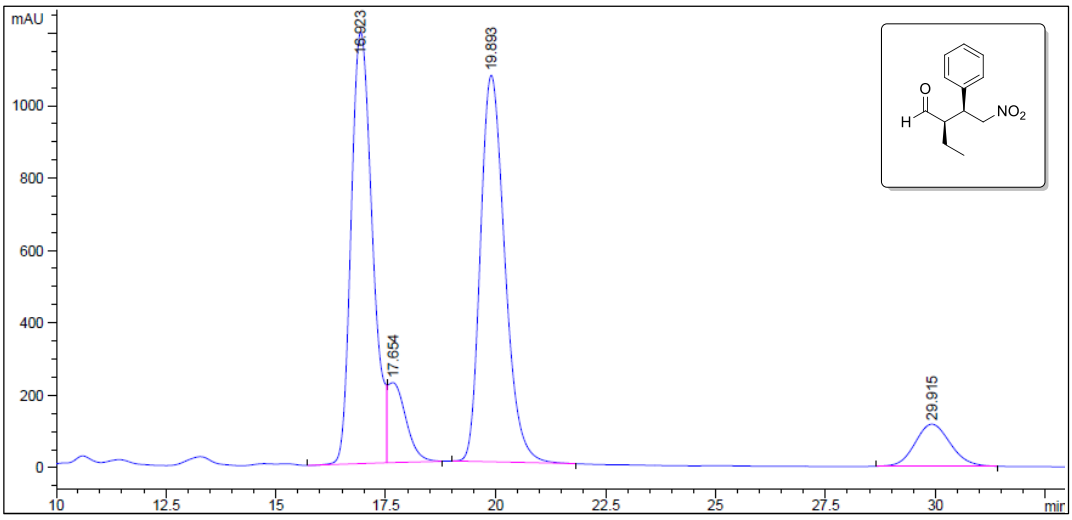

Figure B. 5 HPLC chromatogram of ***rac*- 77**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.923	VV	0.5253	4.01868e4	1192.18372	42.6249
2	17.654	VB	0.4324	6349.85400	221.53111	6.7351
3	19.893	BB	0.6000	4.12003e4	1068.14099	43.6999
4	29.915	BB	0.8545	6543.08496	116.62630	6.9401

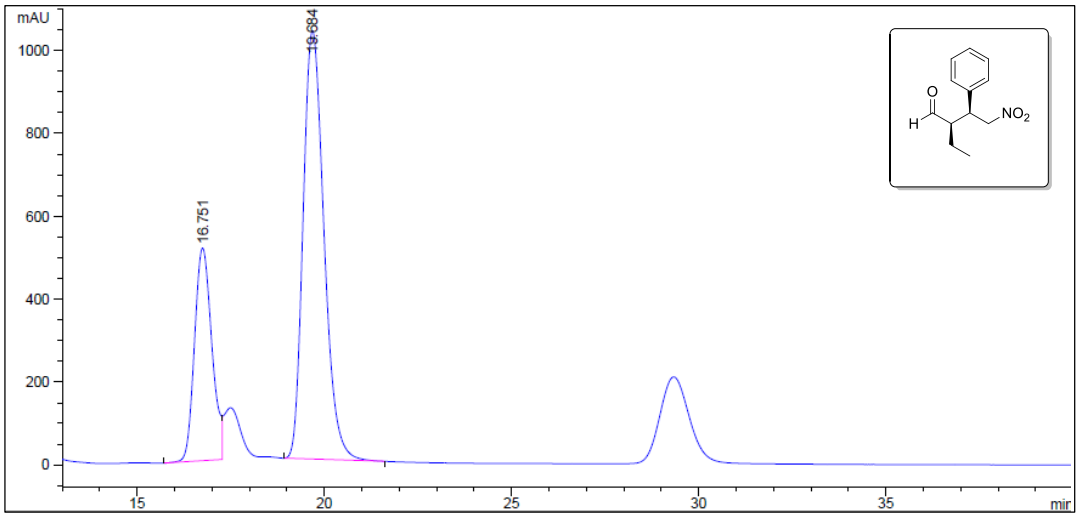

Figure B. 6 HPLC chromatogram of enantiomerically enriched **77**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.751	BV	0.5015	1.65161e4	513.15369	29.2715
2	19.684	BB	0.6047	3.99077e4	1032.97205	70.7285

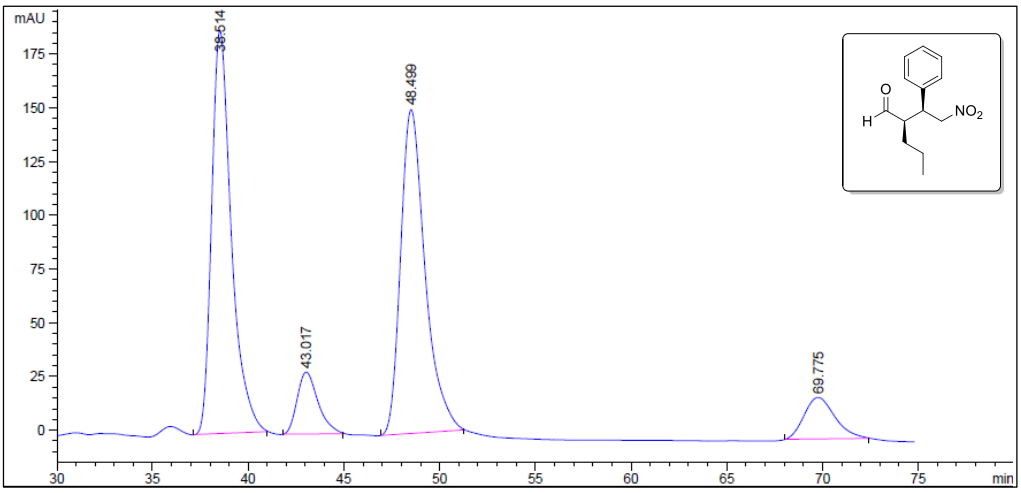

Figure B. 7 HPLC chromatogram of ***rac*- 78**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.514	VB	1.0766	1.34613e4	187.71912	43.0706
2	43.017	BB	1.0704	2197.98682	28.86347	7.0327
3	48.499	BB	1.3142	1.34137e4	150.74106	42.9184
4	69.775	BB	1.3342	2181.01807	19.39083	6.9784

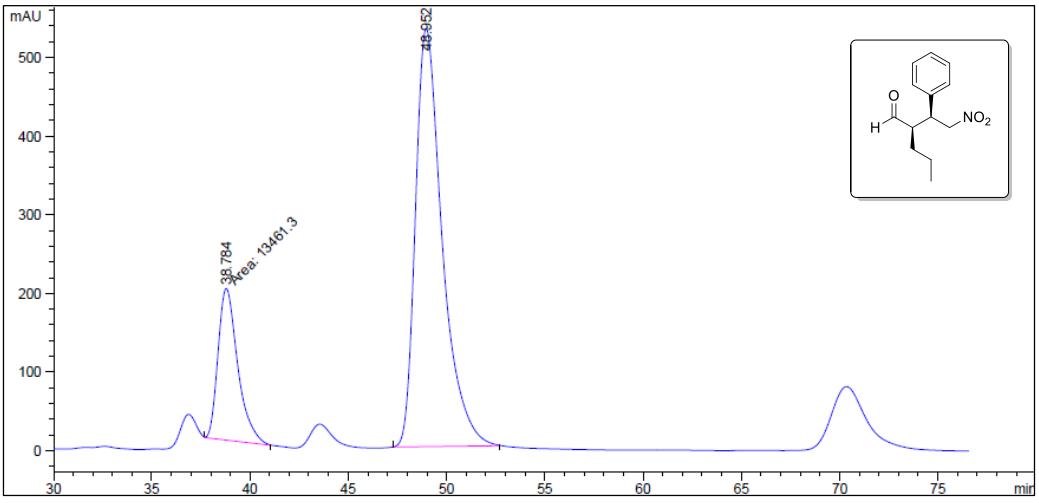

Figure B. 8 HPLC chromatogram of enantiomerically enriched **78**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.784	MM	1.1644	1.34613e4	192.68102	21.0622
2	48.952	BB	1.4132	5.04508e4	531.58856	78.9378

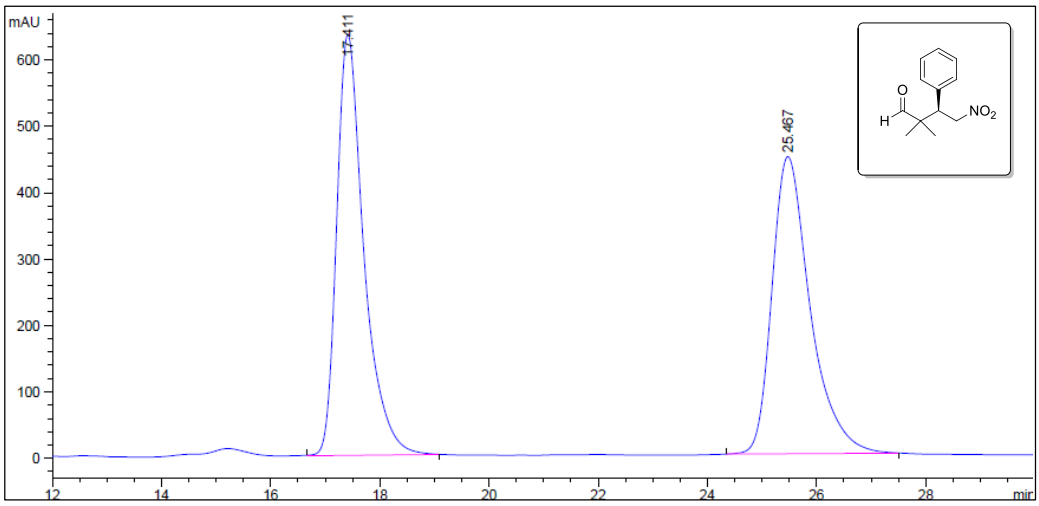

Figure B. 9 HPLC chromatogram of ***rac*- 79**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.411	BB	0.5223	2.19689e4	633.92493	50.1754
2	25.467	BB	0.7342	2.18153e4	447.90103	49.8246

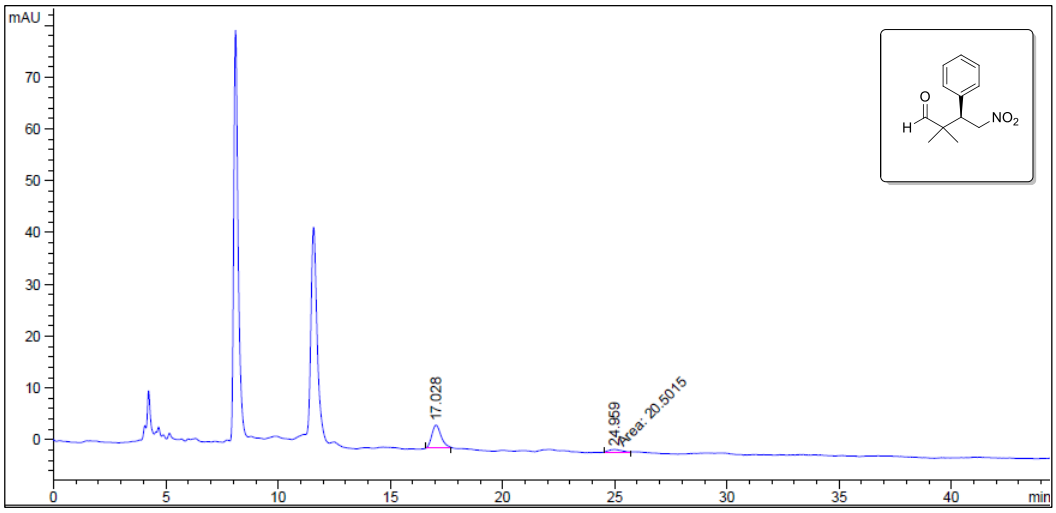

Figure B. 10 HPLC chromatogram of enantiomerically enriched **79** (crude product)

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.028	BB	0.4281	132.12132	4.47985	86.5672
2	24.959	MM	0.6439	20.50154	5.30692e-1	13.4328

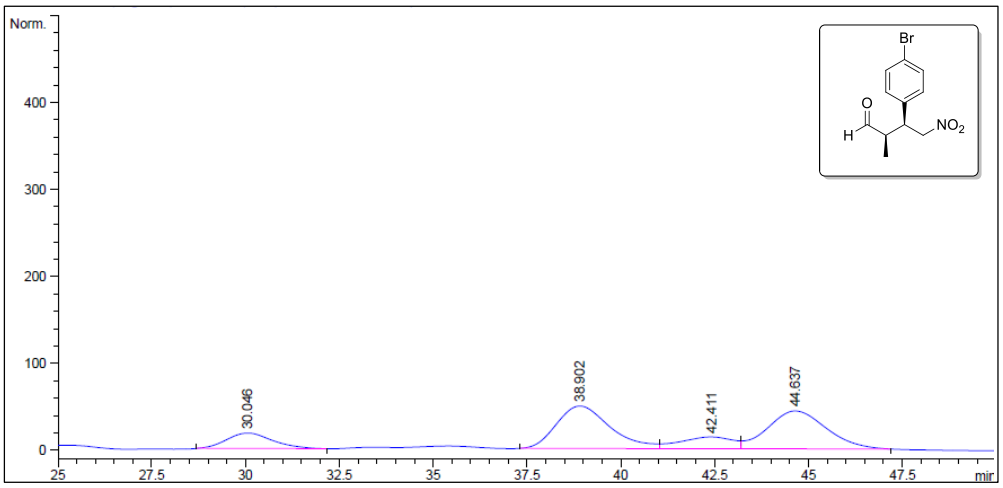

Figure B. 11 HPLC chromatogram of ***rac*- 80**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.046	BB	1.0719	1543.24304	17.93399	12.3166
2	38.902	BV	1.3771	4876.19238	48.91044	38.9169
3	42.411	VV	1.1498	1336.10828	13.70000	10.6635
4	44.637	VB	1.4010	4774.21191	43.75363	38.1030

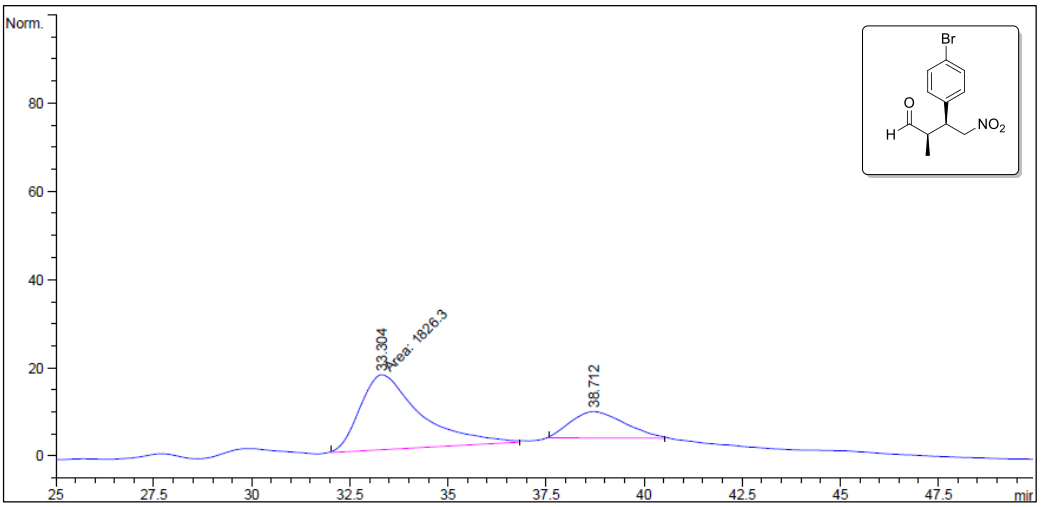

Figure B. 12 HPLC chromatogram of enantiomerically enriched **80**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.304	MM	1.7858	1826.30322	17.04466	75.8885
2	38.712	BB	1.1373	580.25928	6.02638	24.1115

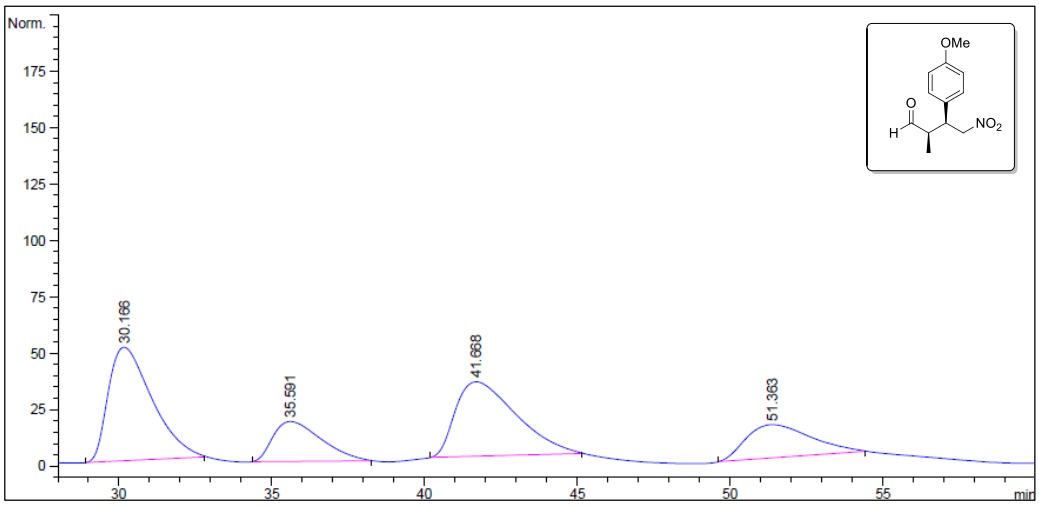

Figure B. 13 HPLC chromatogram of ***rac*- 81**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.166	BB	1.4044	5030.84570	50.32115	36.4707
2	35.591	BB	1.3130	1958.66174	17.69983	14.1992
3	41.668	BB	1.6807	4599.75928	33.15339	33.3456
4	51.363	BB	1.7336	2204.94360	14.87303	15.9846

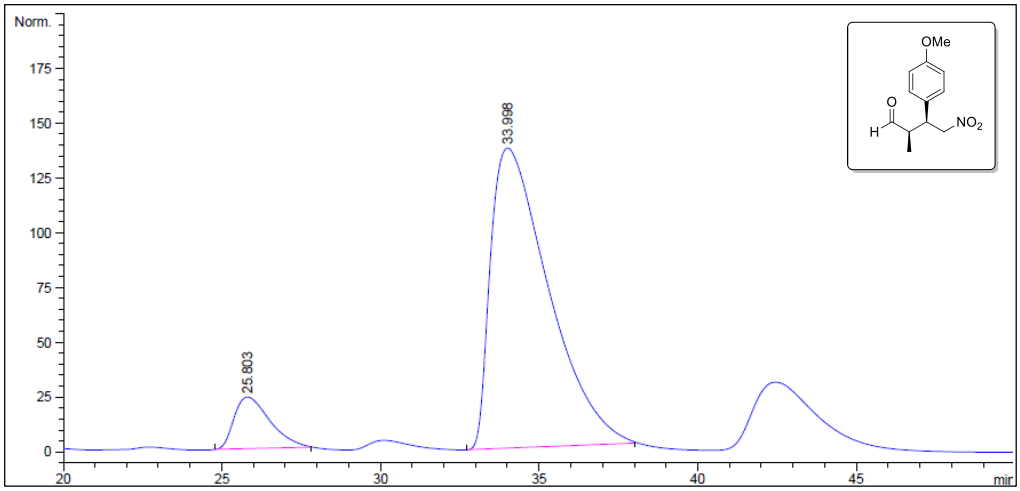

Figure B. 14 HPLC chromatogram of enantiomerically enriched **81**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.803	BB	1.1247	1864.32947	23.62343	9.6621
2	33.998	BB	1.7626	1.74310e4	136.97990	90.3379

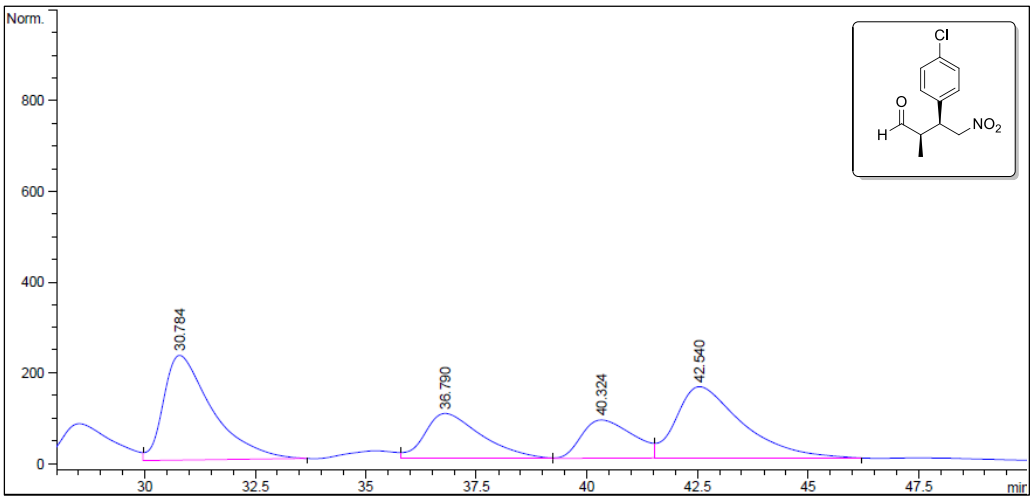

Figure B. 15 HPLC chromatogram of ***rac*- 82**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.784	VB	1.1353	1.77506e4	231.29869	35.4775
2	36.790	VV	1.2204	8873.93066	99.50970	17.7360
3	40.324	VV	1.1912	6888.80078	84.85091	13.7684
4	42.540	VB	1.5043	1.65201e4	158.20233	33.0181

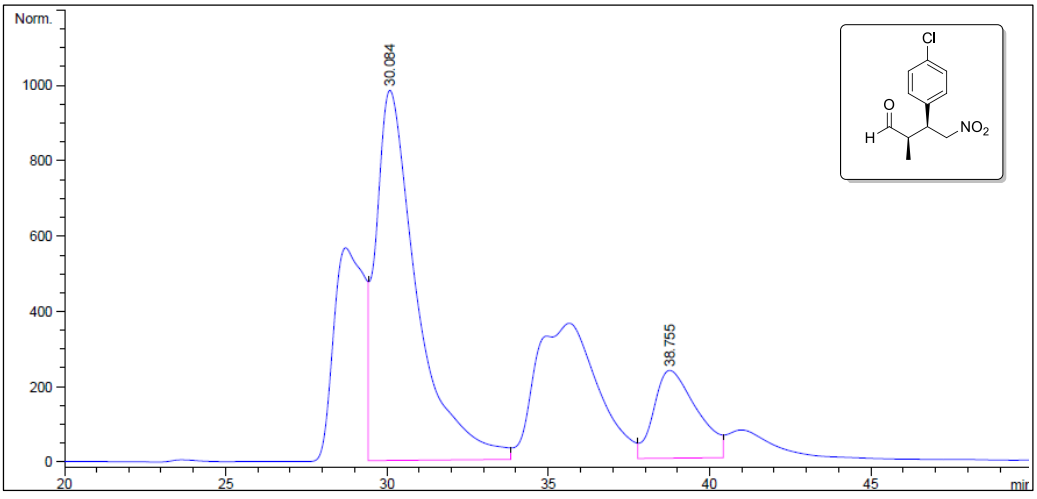

Figure B. 16 HPLC chromatogram of enantiomerically enriched **82**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.084	VB	1.2530	8.70853e4	983.52917	80.0500
2	38.755	VV	1.3188	2.17033e4	233.41095	19.9500

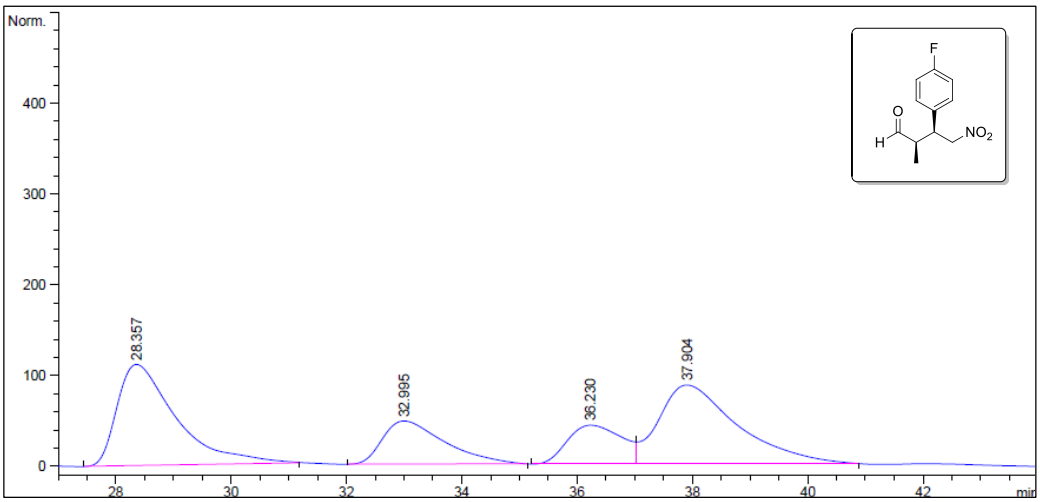

Figure B. 17 HPLC chromatogram of ***rac*- 83**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.357	BB	1.0227	7897.78809	111.45139	35.0121
2	32.995	BB	1.0513	3574.65625	47.53624	15.8470
3	36.230	BV	0.9587	2819.07861	42.78706	12.4974
4	37.904	VB	1.3403	8265.78516	87.00964	36.6435

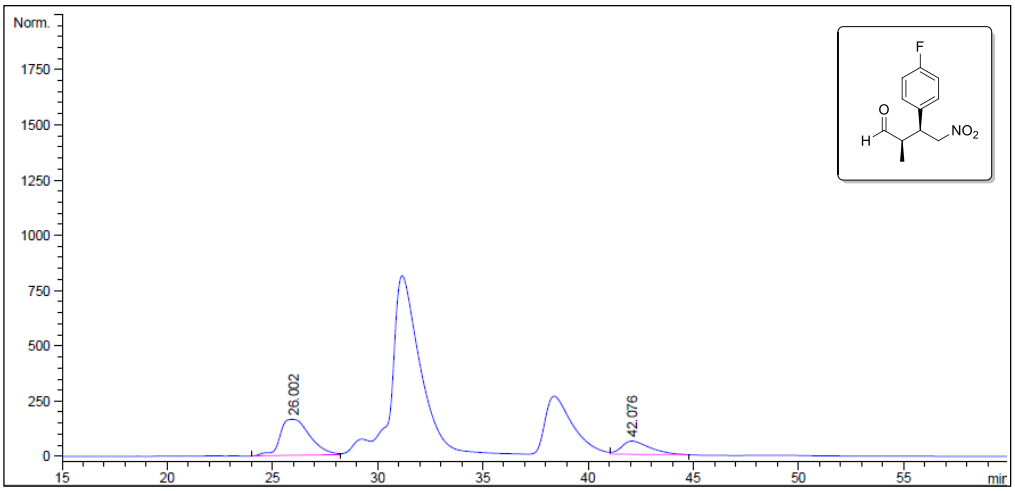

Figure B. 18 HPLC chromatogram of enantiomerically enriched **83**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.002	BV	1.3168	1.62512e4	162.77757	73.4856
2	42.076	BB	1.3483	5863.59619	61.17185	26.5144

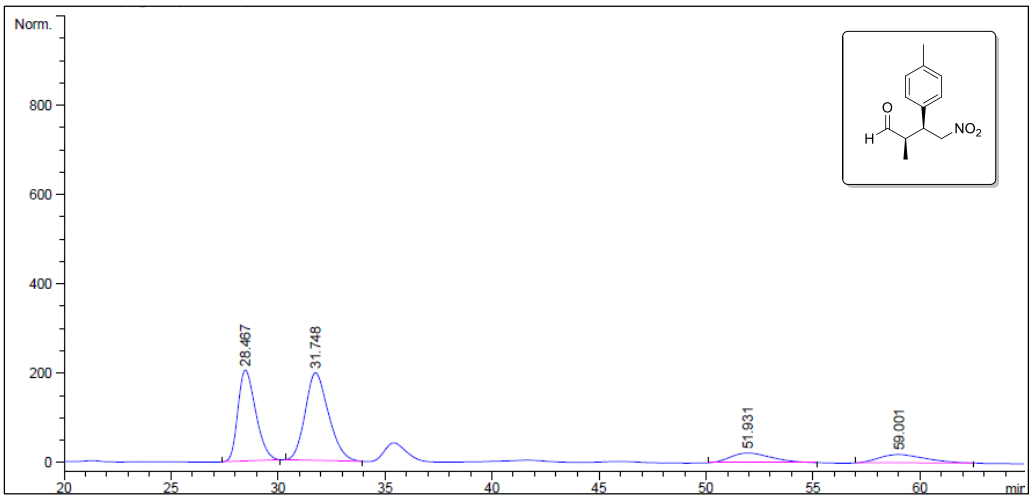

Figure B. 19 HPLC chromatogram of ***rac*- 84**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.467	BB	0.8839	1.17592e4	203.57562	36.1842
2	31.748	BB	1.0967	1.49132e4	196.22800	45.8894
3	51.931	BB	1.5958	2963.43701	21.82909	9.1188
4	59.001	BB	1.7531	2862.31958	19.15740	8.8076

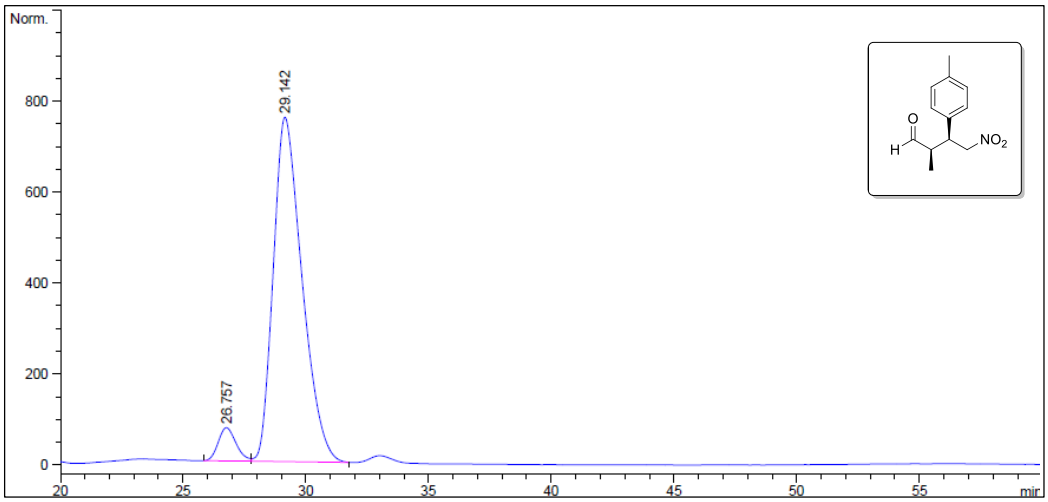

Figure B. 20 HPLC chromatogram of enantiomerically enriched **84**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.757	BV	0.7641	3726.00757	73.41658	5.6949
2	29.142	VB	1.1990	6.17009e4	756.90344	94.3051

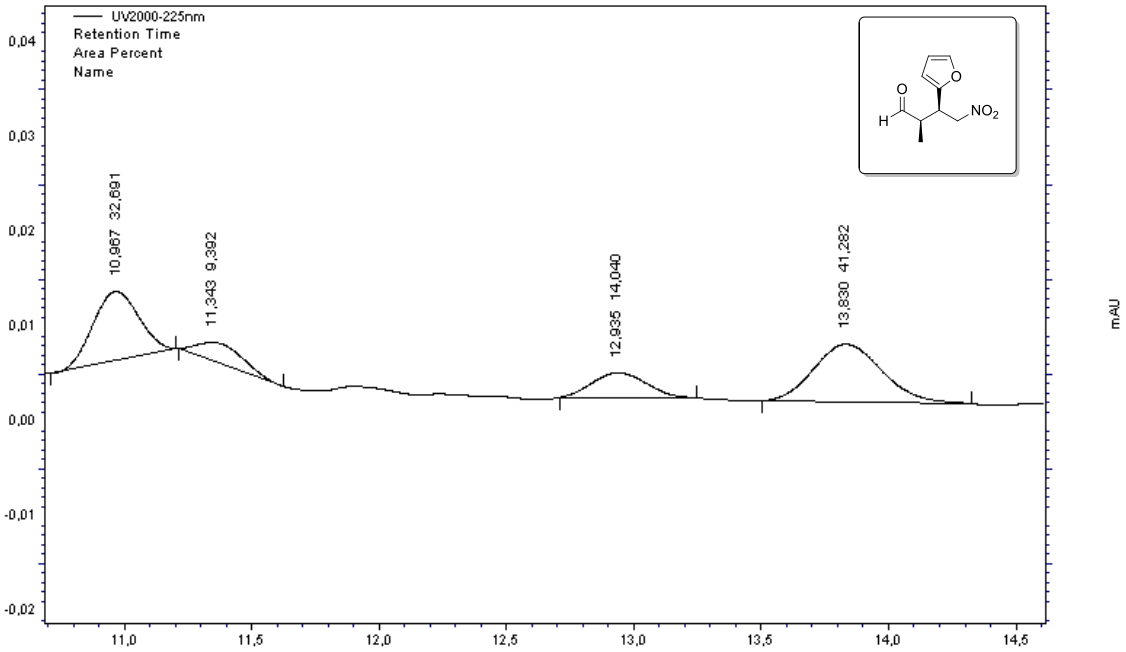

Figure B. 21 HPLC chromatogram of ***rac*- 85**

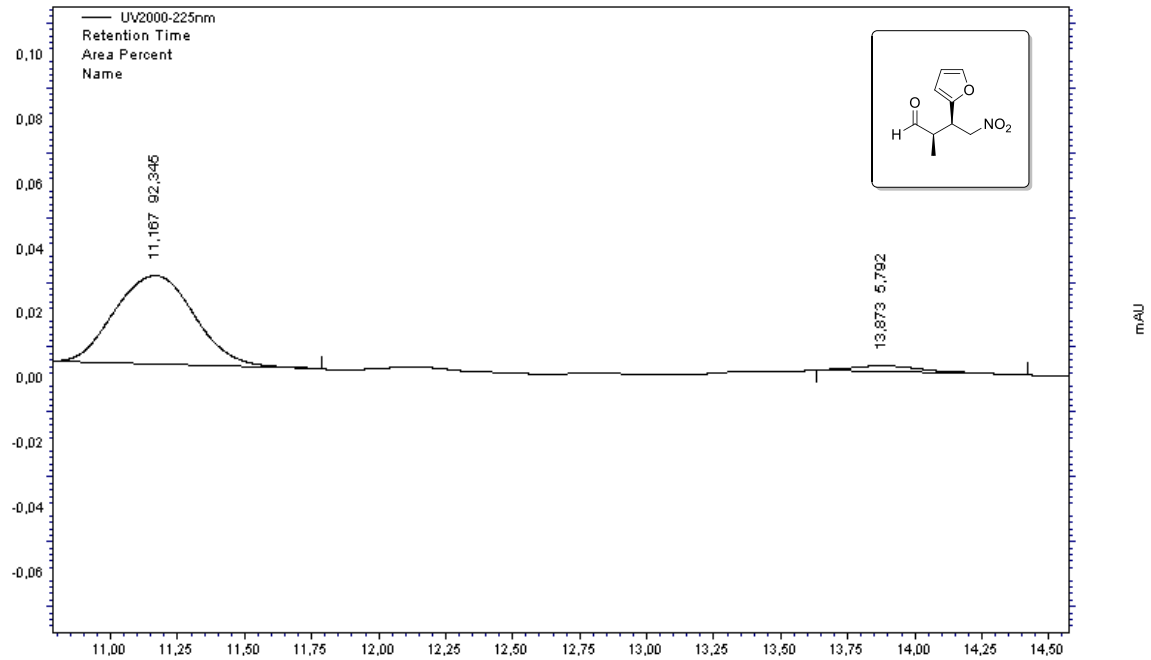

Figure B. 22 HPLC chromatogram of enantiomerically enriched **85**