SYNTHESIS OF NEW SQUARAMIDE BASED ORGANOCATALYST AND ITS APPLICATIONS FOR ENANTIOSELECTIVE SYNTHESIS OF ORGANIC COMPOUNDS

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ÖZGE ÖZDEMİR

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submitted by **ÖZGE ÖZDEMİR** in partial fulfillment of the requirements for the degree of **Master of Science** i**n Chemistry, Middle East Technical University** by,

Prof. Dr. Halil Kalıpçılar
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. Özdemir Doğan
Head of the Department, **Chemistry** _____

Prof. Dr. Özdemir Doğan
Supervisor, **Chemistry, METU** _____

Examining Committee Members:

Prof. Dr. Cihangir Tanyeli
Chemistry, METU _____

Prof. Dr. Özdemir Doğan
Chemistry, METU _____

Prof. Dr. Akın Akdağ
Chemistry, METU _____

Prof. Dr. Sıdıka Polat Çakır
Chemical Engineering, ÇOMÜ _____

Asst. Prof. Dr. Çağatay Dengiz
Chemistry, METU _____

Date:19.08.2022

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Name Last name: Özge Özdemir

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ABSTRACT

SYNTHESIS OF NEW SQUARAMIDE BASED ORGANOCATALYST AND ITS APPLICATIONS FOR ENANTIOSELECTIVE SYNTHESIS OF ORGANIC COMPOUNDS

Özdemir, Özge
Master of Science, Chemistry
Supervisor: Prof. Dr. Özdemir Doğan

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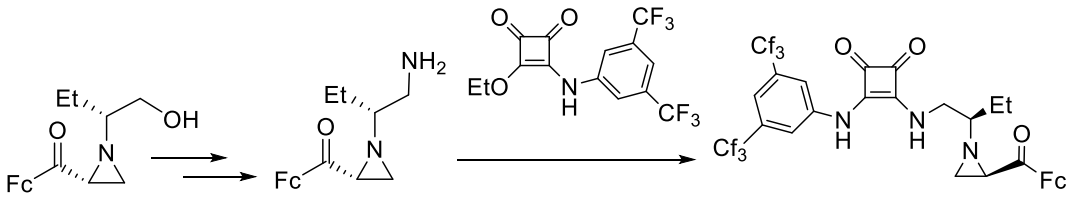
Organocatalytic asymmetric synthesis of organic compounds is one of the important fields of synthetic organic chemistry. Organocatalysts are small chiral organic molecules having certain functional groups, such as hydroxy, amino, amido etc. These catalysts are environmentally more friendly than the alternative chiral metal catalysts. Therefore, they are more popular and studied more than the metal catalysts. On the other hand, there are no organocatalysts that work well for every organic reaction. Here in thesis, we wanted to design and synthesize new squaramide based chiral organocatalyst starting with previously developed ferrocenyl aziridinyl methanol which in few steps is converted to amine and reacted with squarate. Additionally, we aimed to apply organocatalyst to the enantioselective synthesis of organic compounds.



Keywords: Squaramide organocatalyst, 1,3-diketones, nitroolefins, Michael reaction

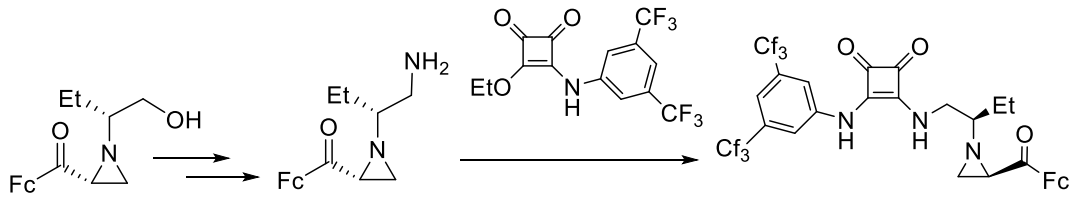
ÖZ

SKUAR AMİT TEMELLİ ORGANOKATALİZÖR SENTEZİ VE ORGANİK BİRLEŞİKLERİN ENANTİOSEÇİCİ SENTEZİNDE UYGULANMASI

Özdemir, Özge
Yüksek Lisans, Kimya
Tez Yöneticisi: Prof. Dr. Özdemir Doğan

Ağustos 2022, 78 sayfa

Organokatalizörlerle organik bileşiklerin asimetrik sentezi sentetik organik kimyanın önemli alanlarından biridir. Organokatalizörler hidroksi, amino, amido gibi belli fonksiyonel grupları olan küçük moleküllerdir. Bu tür katalizörler alternatifleri olan metal katalizörlere göre daha çevrecidir. Bu nedenle bu katalizörler hem daha popüler hem de daha fazla çalışılmaktadır. Diğer taraftan henüz tüm organik tepkimeler için oldukça iyi çalışabilen organokatalizör geliştirilememiştir. Bu tez kapsamında daha önce geliştirilmiş ferrosenil aziridinil metanol ile başlayan ve birkaç adımda amine dönüştürülerek yeni skuar amit temelli organokatalizör tasarlayıp organik bileşiklerin enantioseçici sentezinde uygulamayı planladık.



Anahtar kelimeler: Skuar amit organokatalizörü, 1,3-diketonlar, nitroolefinler, Michael tepkimesi

To my family …

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LIST OF ABBREVIATIONS

ABBREVIATIONS

NMR: Nuclear Magnetic Resonance

R_f: Retention Factor (TLC)

t_R: Retention Time

DPEN: Diphenylethylenediamine

CFAM: Cyclohexyl-Substituted Ferrocenyl Aziridinyl Methanol

HSQC: Heteronuclear Single Quantum Coherence

Fc: Ferrocenyl

MTBE: Methyl tert-butyl ether

CHAPTER 1

INTRODUCTION

1.1 History of Asymmetric Synthesis

In 1815, Jean-Baptiste Biot, who discovered that when light passes through organic liquid solutions its polarization is affected, was interested in the property of optical activity.[1] Later, Pasteur discovered that the sodium ammonium salt of an optically inactive tartaric acid can be divided into two salts, which are called optically active D-(-)-tartaric acid **1** and L-(-)-tartaric acid ***ent*-1** (Figure 1). Pasteur observed the presence of two mirror-image crystals in tartaric acid. He found that one group of molecules rotates plane polarized light clockwise, while the other rotates plane polarized light counterclockwise.[2]

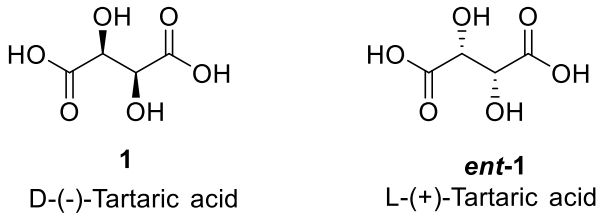
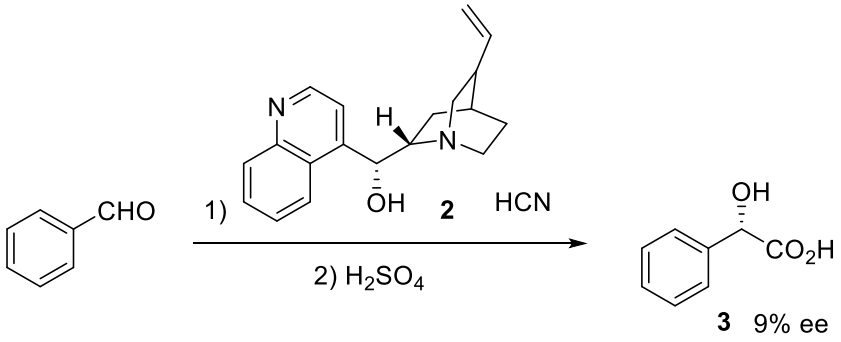


Figure 1. Tartaric acid enantiomers

In 1874, Jacobus Henricus Van 't Hoff and Joseph Le Bel independently proposed the tetrahedral geometry of carbon. Van't Hoff and Le Bel theorized that the arrangement of groups around this tetrahedron could determine the optical activity of the resulting compound by what is known as the Le Bel–Van't Hoff rule. The term for carbon with four different groups, chirality was introduced by Thomson William only 20 years later, in 1894.[3] The same year, H. E. Fischer has proposed a concept of asymmetric induction. He described it as the preferential formation in a

chemical reaction of one enantiomer or diastereoisomer over the other. The term also refers to the formation of a new chiral feature preferentially in one configuration under such influence.

The first example of asymmetric synthesis was described in 1908 by Rosenthaler, who used emulsin to catalyze the HCN addition on benzaldehyde. In his work he was able to isolate cyanohydrin. In 1913, the first enantioselective reaction, in the absence of an enzyme, on a prochiral substrate was performed by Bredig and Fiske with 9% ee (Scheme 1).[4]



Scheme 1. Bredig and Fiske's hydrocyanation reaction

1.2 Importance of Asymmetric Synthesis

Asymmetric synthesis is a reaction that provides the formation of one or more stereogenic center configurations relative to the other configuration.[5] It is a useful method to produce stereoisomeric compounds for different purposes especially pharmaceutical application. Chemical synthesis of drugs generally brings about the form of two configurations in asymmetric center. They can be active or inactive. The desired effect can be enhanced by using differences in activity to adapt a drug with a certain ratio of isomers. Enantiomers show different biological activities.[6] For instance, (*S*,*S*)-(+)-ethambutol **4** is widely used drug for treatment of tuberculosis in the 1960s. On the other hand, (*R*,*R*)-(-)-ethambutol ***ent*-4** leads to blindness (Figure 2).[7]

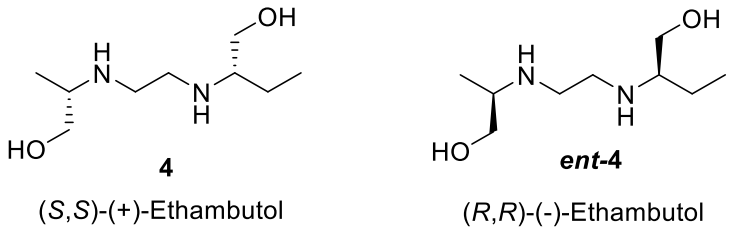


Figure 2. Enantiomers of ethambutol

Another example is thalidomide, synthesized in 1954 by CIBA pharmaceutical company. Whereas (*R*)-(+)-thalidomide **5** was prescribed as a sedative and antiemetic for morning sickness, (*S*)-(-)-thalidomide ***ent*-5** form prevents the release of tumor necrosis factor (TNF) from peripheral mononuclear blood cells (Figure 3).[8]

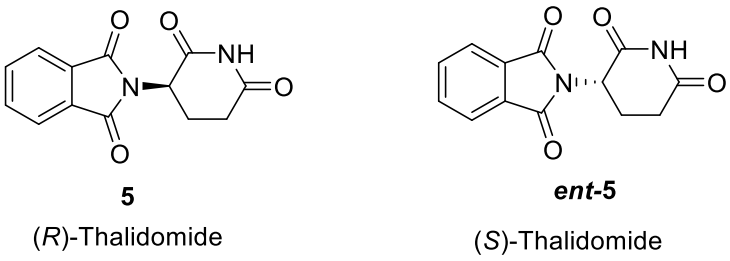


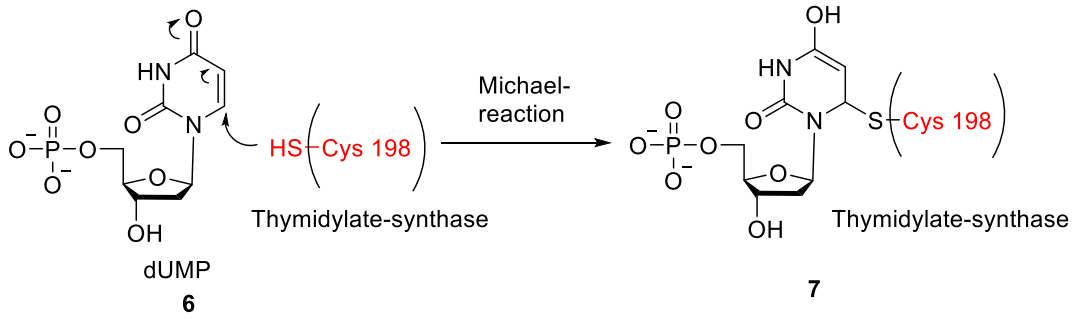
Figure 3. Enantiomers of thalidomide

In asymmetric synthesis, the catalytic asymmetric synthesis has gained importance for enantioselective pharmaceutical, agrochemicals and natural product synthesis.[9] There are mainly three common alternative ways for the asymmetric synthesis, enzyme catalyst, metal catalyst and organocatalyst.

1.2.1 Enzyme Catalysts

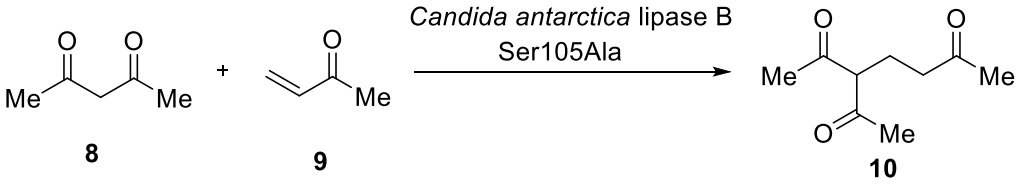
One of the catalytic methods to achieve asymmetric synthesis is by using enzymes. It has been understood from much evidence such as its directivity by the surrounding environment and temperature that enzymes have internal movements and flexible structure. There is a relation between enzymes structure and activity.[10] According to 'lock and key' and 'stimulated adaptation' hypothesis, substrate and enzyme have structural interaction.[11] All of these properties play an important role in enzyme catalysis reactions. Enzyme catalysis provides high catalytic activity and selectivity.[12]

To give an example, *thymidylate synthase* is one of the enzymes that regulates the balanced nutrition of four DNA precursors in normal DNA replication. It is significant for chemotherapeutic drugs.[13] The enzyme catalyzes a synthesis of deoxythymidine monophosphate (dTMP) **7** from deoxyuridine monophosphate (dUMP) **6** (Scheme 2).[14]



Scheme 2. Thymidylate synthase catalyzed Michael reaction

Another example for the enzyme catalyst is *Candida antarctica* lipase B. In Michael reaction, strong base can be used to catalyze; however, some unwanted side products can be produced. To prevent it, enzyme is an alternative catalyst (Scheme 3).[15]

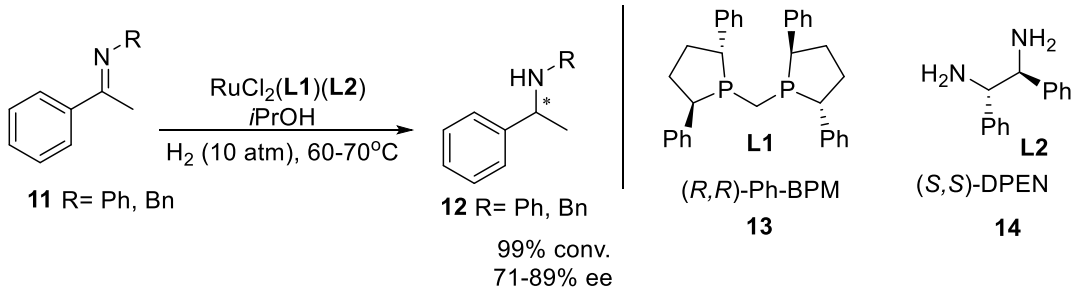


Scheme 3. Michael reaction catalyzed by *C. Antarctica* Lipase B mutant

However, enzymes have some limitations such as limited substrate choice and one enantiomer formation.[12]

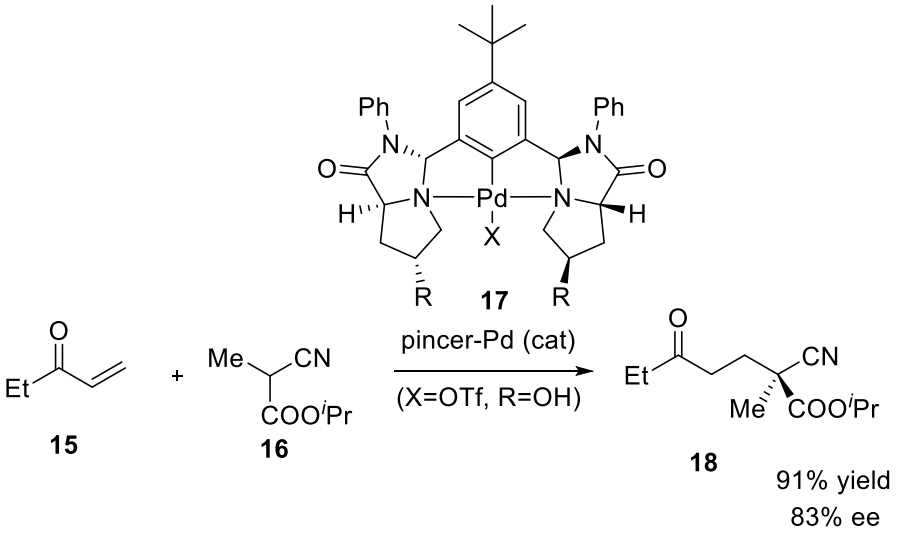
1.2.2 Transition Metal Catalysts

Another widely used and effective way to achieve asymmetric synthesis is to use of transition metal catalysts. In the literature, there are many examples of variety of organic transformations performed in the presence of transition metal catalysis. One example for the metal catalyzed asymmetric reaction is the ruthenium catalyzed hydrogenation of imines (Scheme 4). In this work, authors used ruthenium complex of chiral (*R*,*R*)-PhBPM **13** and (*S*,*S*)-DPEN **14** ligands to reduce different imines in high convergence of 99% and moderate to good enantioselectivities of 71−89% ee.[16]



Scheme 4. Aza-Michael addition reaction with metal catalyst

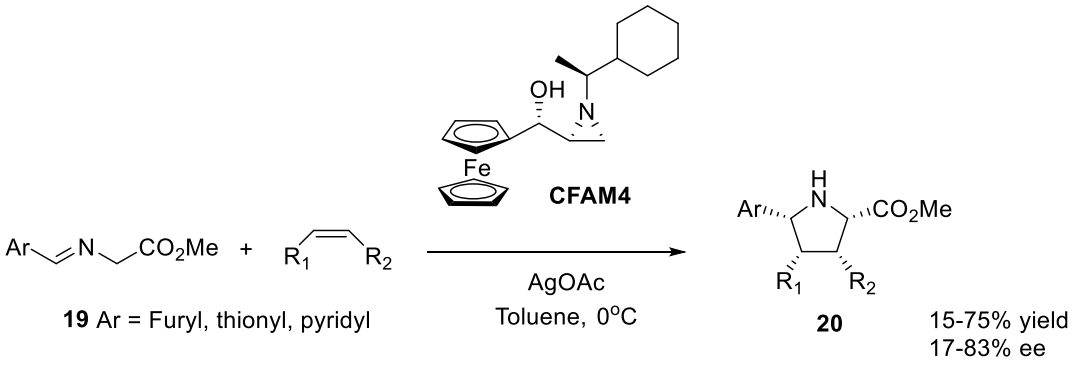
Another example is the study of Takenaka and Uozumi.[17] In this study, novel chiral pincer palladium complexes were used in asymmetric Michael reaction with a pincer-Pd complexes **17** having pyrroloimidazolone units, which provided the product in high yield of 91% and with 83% enantioselectivity (Scheme 5).[17]



Scheme 5. Study of Takenaka and Uozumi in 2004

Our research group has wide experience in working with the transition metal catalysts. Ferrocenyl aziridine based chiral ligands developed in our group has proven to be effective in various organic transformations such as aldol, asymmetric alkynylation of aldehydes[18], Henry reaction[19], addition of diethylzinc to aldehydes[20] etc.

Most recently, cyclohexyl substituted aziridinyl methanol ligand (**CFAM4**) has shown good catalytic activity in asymmetric 1,3-dipolar cycloaddition (1,3-DC) reaction of heteroaryl substituted azomethine ylides with various dipolarophiles (Scheme 6).[21]



Scheme 6. Asymmetric 1,3-DC reaction studied by our group

Although transition metal catalysts, have wide choice of substrate, and shows high catalytic activity, they may cause heavy metal pollution.[12]

1.2.3 Organocatalysts

Another alternative way for asymmetric synthesis is to use organocatalysts in organic synthesis. Unlike metal catalysts, organocatalysts, small organic molecules, are nontoxic, inexpensive, and environmentally friendly.[12] They play two roles besides accelerating the reaction. One of them is in the transition state, it coordinates either the electrophilic or nucleophilic centers of the substrate and the other one is to introduce the asymmetrical environment responsible for inducing chirality in the product.[9] There are also organacatalysts that can activate both nucleophilic and electrophilic substrates which are called bifunctional organacatalysts.[22] Working principle of organocatalysts are undertaken by H-bond.[23] They show their catalytic effect by making H-bonds and its stereoselective effect with chiral R* groups. Organocatalysts have been applied in very different types of organic reactions in the literature up to date. The most widely known organocatalysts are proline derivatives, thiourea/urea derivatives, BINAP phosphoric acid derivatives and squaramide derivatives (Figure 4).[24–27]

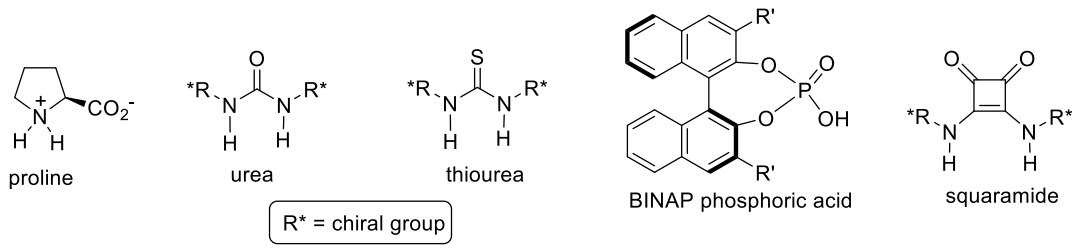
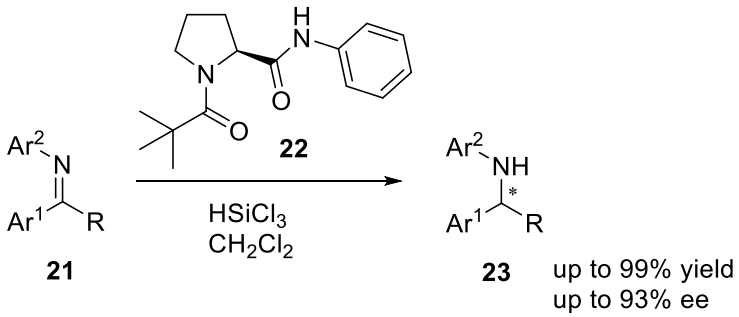


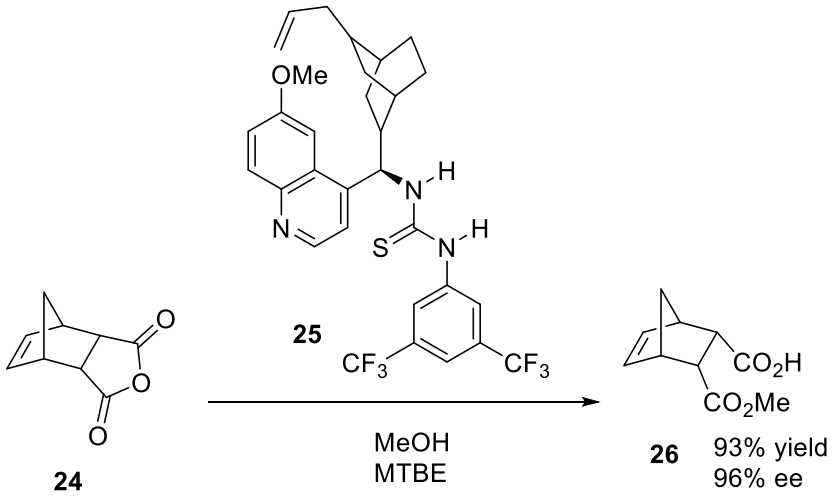
Figure 4. Examples of organocatalyst

Kanemitsu and coworkers studied in 2012 on proline based organocatalyst.[24] They tried to reduce imines with trichlorosilane in up to 99% yield and 93% ee (Scheme 7).



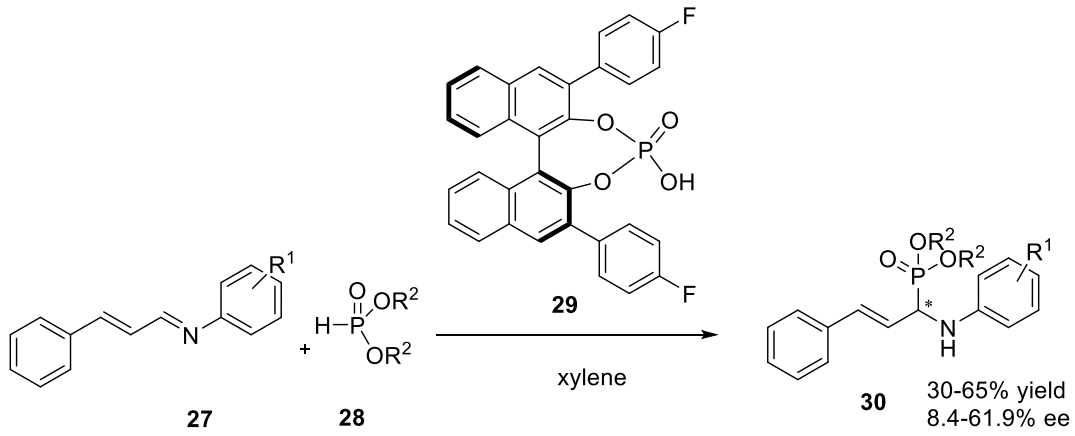
Scheme 7. Reaction with proline based organocatalyst

Another example of organocatalyst is thiourea based organocatalyst. Peschiulli and coworkers worked on the enantioselective desymmetrization of anhydrides in 2007.[25] They obtained the product in 93% yield with 96% ee (Scheme 8).



Scheme 8. Reaction with thiourea based organocatalyst

Xu and coworkers studied the asymmetric synthesis of α-aminophosphonates in 2010. They achieved 30-65% yield and 8.4-61.9% ee (Scheme 9).[26]



Scheme 9. Reaction with binaphtylphosphoric acid based organocatalyst

Herein we focus on the synthesis of new squaramide based organocatalyst and its application on asymmetric Michael reaction to synthesize chiral organic molecules.

1.3 Squaramide Based Organocatalysts

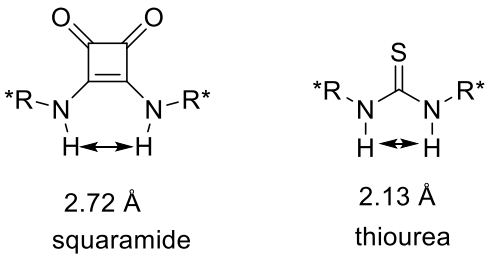
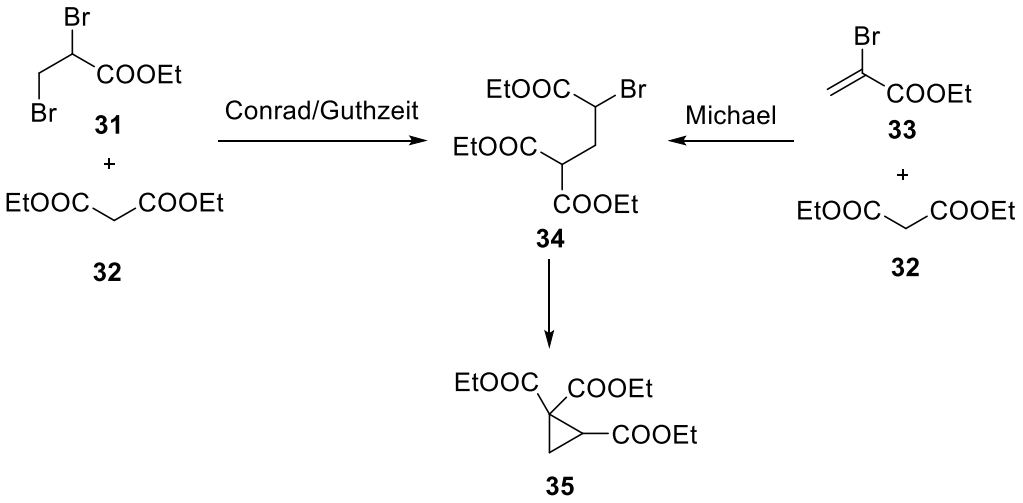


Figure 5. Squaramide and thiourea compounds

The working principle of squaramides are similar to thiourea compounds. In both cases they are examples of organocatalysts that detect molecules by making H-bonds. Their ability to form hydrogen bonds depends on the acidity of the amide hydrogens. The degree of acidity varies depending on the R* group. The fact that the acidity of squaramides (pKa = 8.4-16.5) is higher than that of thiourea (pKa = 8.5-21.2) which strengthens the hydrogen bonding feature. Therefore it is thought that the catalytic and selectivity effects of squaramide based organocatalysts are higher for the reactions. On the other hand, it has been suggested that the inter-hydrogen bond distance also plays a role in the catalytic effect.[28] Studies have shown that the bond distance in squaramide structures is approximately 0.6 Å longer than the bond length in thiourea structures (Figure 5).[27] It is claimed that the H-bond dynamics and stiffness of squaramide derivatives is better for asymmetric reactions.[29]

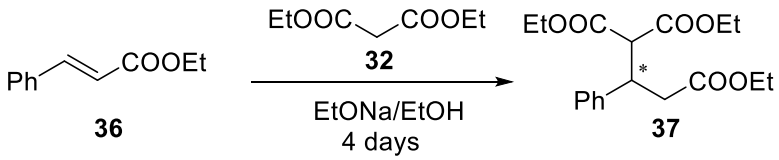
1.4 History of Asymmetric Michael Reaction

In 1884 publication done by Conrad and Guthzeit the reaction of ethyl 2,3-dibromopropionate with diethyl sodium malonate formed cyclopropane adduct (Scheme 10).[30]



Scheme 10. Foundation of Michael reaction in 1887

Michael was able to obtain the same product by replacing the propionate by 2-bromacrylic acid ethyl ester.[31] Then he realized that this reaction could only work by assuming an addition reaction to the double bond of the acrylic acid.[31] He confirmed this assumption by reacting diethyl malonate and the ethyl ester of cinnamic acid, which formed the first Michael adduct in 1887 (Scheme 11).[32]

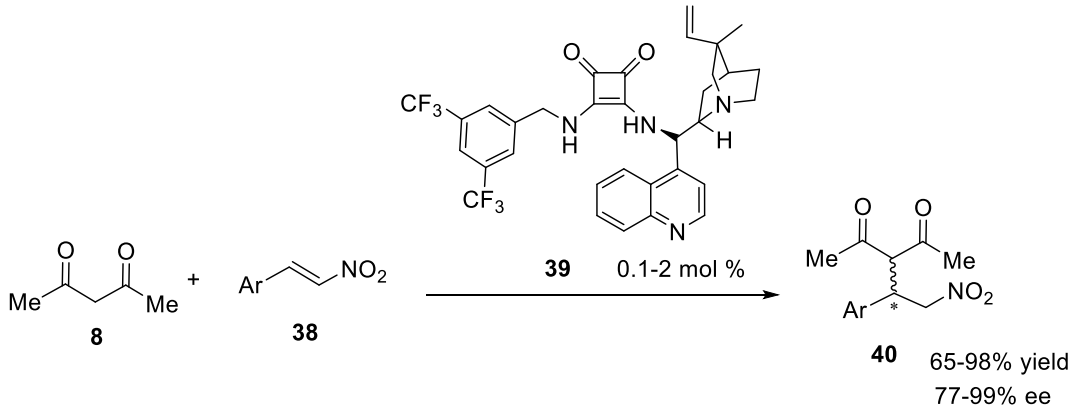


Scheme 11. Study of Michael in 1887

Since the first publication of asymmetric Michael reaction there has been a tremendous development in this field. The literature reports many studies that involve both metals catalyzed and organocatalytic asymmetric Michael reaction.

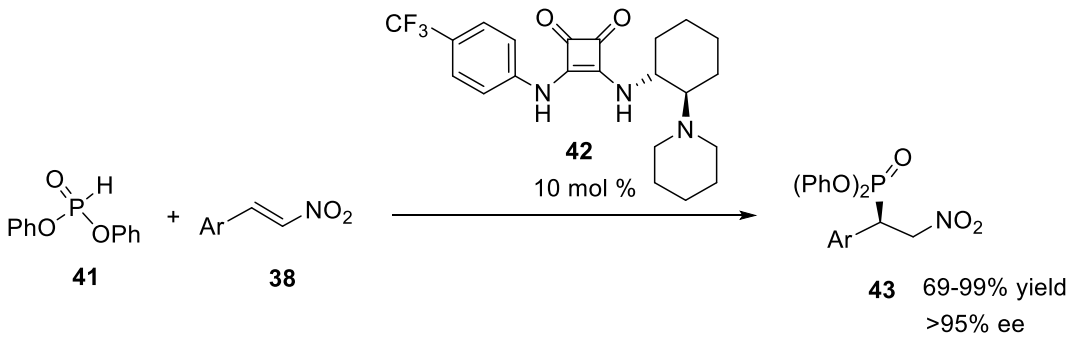
1.4.1 Asymmetric Michael Reaction Using Squaramide Based Organocatalysts

Michael addition reaction is a useful and efficient method to trigger the formation of carbon-carbon bonds.[15] The first squaramide structure was presented to the literature by Rawal in 2008,[27] in which by using a small amount of squaramide based organocatalyst 77-99% enantioselectivity was achieved (Scheme 12). Then the interest in squaramide-derived organocatalysts has increased considerably.



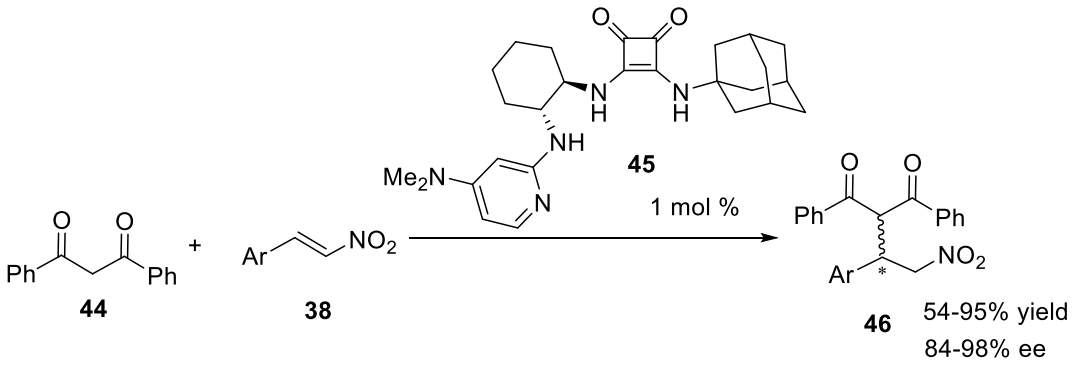
Scheme 12. The first study conducted by Rawal and coworkers in 2008

In another study, the same group performed the Michael addition reaction of diphenyl phosphite to nitroolefins in the presence of a new squaramide organocatalyst. The adducts were obtained in the range of 69-99% yields and enantioselectivity >95% (Scheme 13).[29]



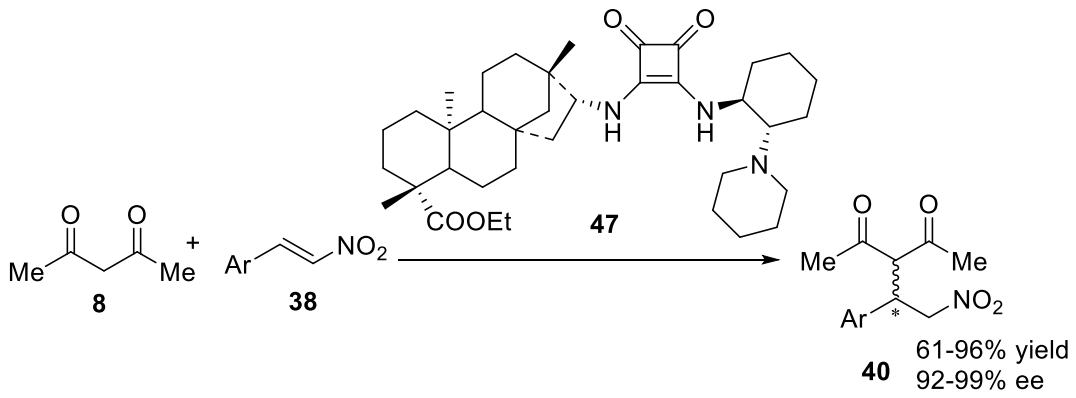
Scheme 13. The organocatalytic addition of diphenyl phosphate to nitroolefins

Tanyeli and coworkers have also reported interesting finding on asymmetric Michael reaction of 1,3-diketones with nitrostyrene derivatives using bifunctional squaramide based organocatalyst.[33] They reported that the products were obtained in up to 98% yield with 95% enantioselectivity (Scheme 14).



Scheme 14. The study of the Tanyeli group

A more recent study, by Ma et al. reported in 2021, gives an example of chiral squaramide derived from the natural product of the stevioside used in asymmetric Michael addition of acetylacetone to nitroolefins.[34] This asymmetric reaction performed well, and a series of enantiomerically enriched compounds were obtained in high yields (up to 96%) with excellent enantioselectivities (up to 99% ee) (Scheme 15).

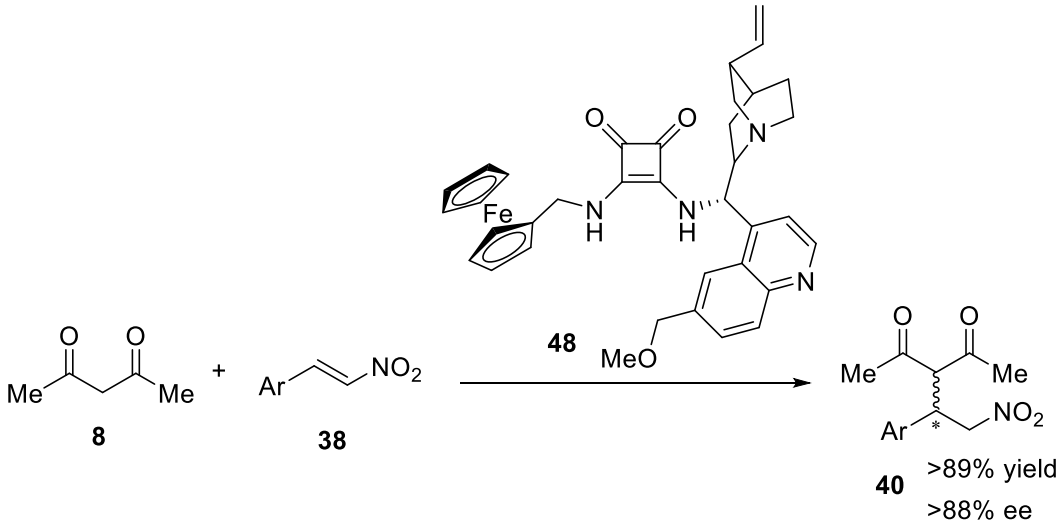


Scheme 15. Study of Ma et al. in 2021

1.5 Ferrocene based organocatalysts

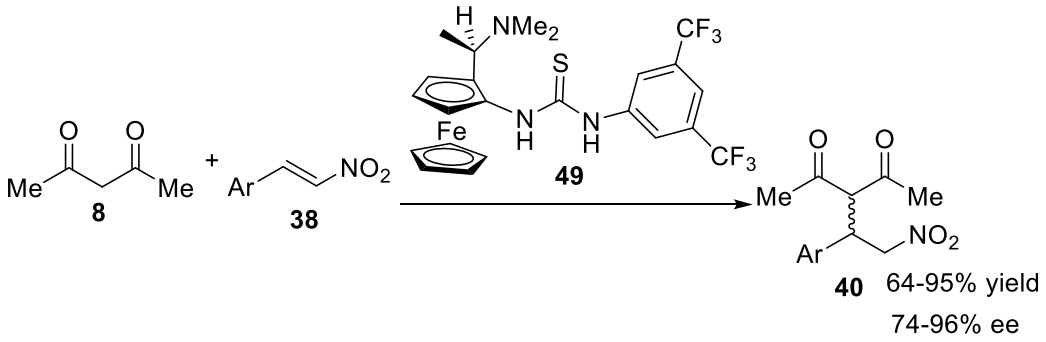
Chiral ferrocene derivatives have been extensively studied in asymmetric catalysis. Notably, chiral ferrocenyl phosphine ligands have been used in asymmetric hydrogenation reactions of alkenes, in the synthesis of enantiopure *β*-amino acids, and in the synthesis of *β*-amino ketones.[35] It has been suggested that the ferrocene moiety in this type of ligand might induce rigidity in the chiral molecule, which in turn enhances the interaction of the reactant with the catalyst.[36]

A good example for ferrocene based organocatalyst was published by Rao et al. in 2015.[37] In this study, bifunctional catalysts were used in asymmetric Michael additions of 1,3-dicarbonyl compounds to *β*-nitrostyrenes. The corresponding products were obtained in high yields and in good to excellent enantioselectivities and diastereoselectivities under mild conditions by using 1 mol% of the catalyst (Scheme 16).



Scheme 16. The study of Rao and coworkers reported in 2015

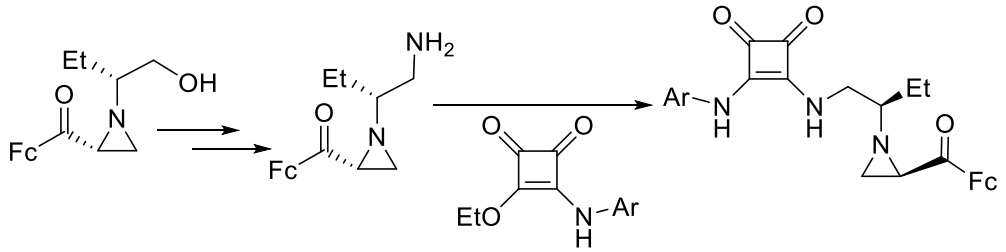
The work published by Yao et al. in 2014 demonstrates that, in accord with metal catalysis, ferrocene could be an excellent scaffold for chiral organocatalysts.[38] In their study, ferrocene-based bifunctional amine–thiourea organocatalyst provided high enantioselectivity in the Michael addition of acetylacetone to nitroolefins, giving the enantioselectivity of up to 96% ee (Scheme 17).



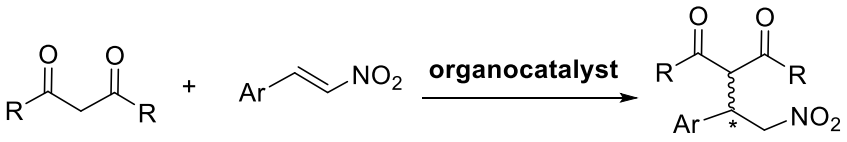
Scheme 17. The study of Yao and coworkers reported in 2014

1.6 Aim of the Study

Organocatalysts are small organic compounds which generally contain C, S, O, P, N atoms[39] and can catalyze reactions in the absence of metals or metal ions. In this thesis we aimed to design and synthesize a new squaramide based chiral organocatalyst starting with previously developed ferrocenyl aziridinyl methanol. For this purpose, we planned to convert alcohol, introduced to the literature by our group, to primary amine first then couple with known mono-squaramide derivative to reach the target organocatalyst as shown below.



After the synthesis of the desired organocatalyst we wanted to use it for the enantioselective organocatalytic synthesis of organic compounds specifically for the asymmetric Michael addition reaction of 1,3-diketones to nitroolefins as indicated.



Scheme 18. The Michael addition reaction of 1,3-diketones to nitroolefins

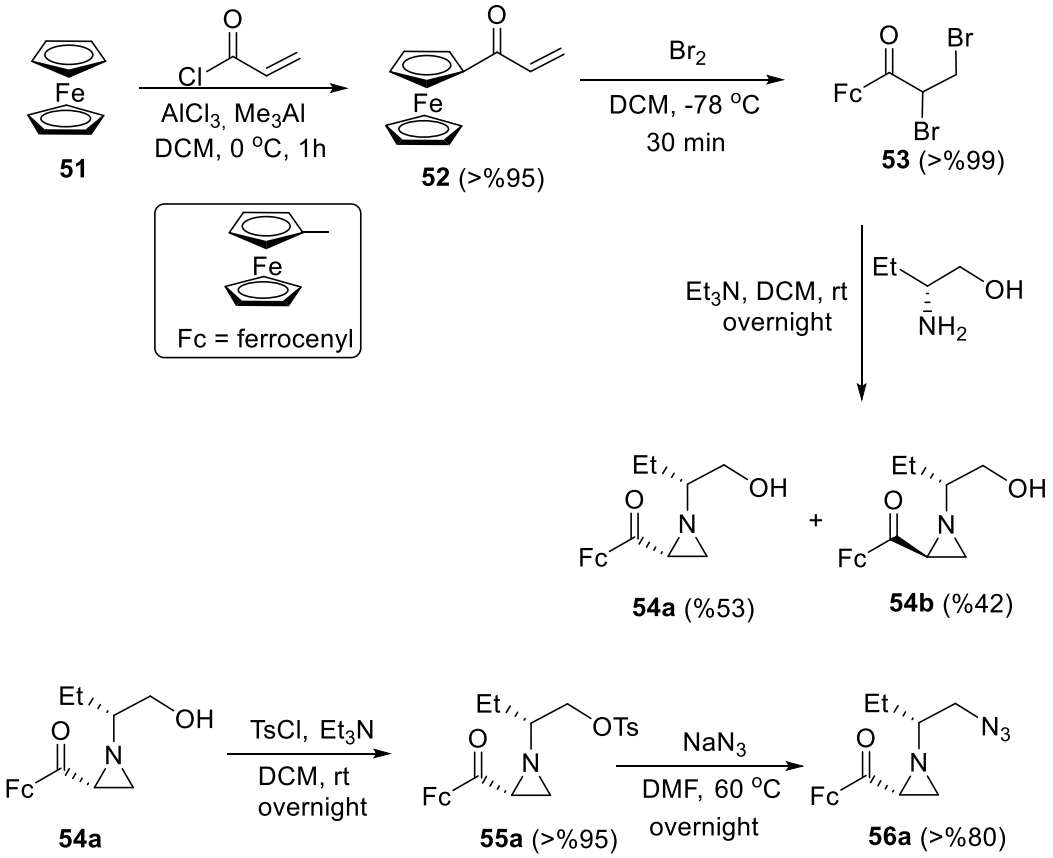
CHAPTER 2

RESULT AND DISCUSSION

2.1 Synthesis of Squaramide Catalyst

The synthesis of the target squaramide organocatalyst is shown in Scheme 34. According to this synthetic plan, ferrocenyl substituted aziridines were achieved by using Gabriel-Cromwell reaction as reported previously by our group.[40–42]

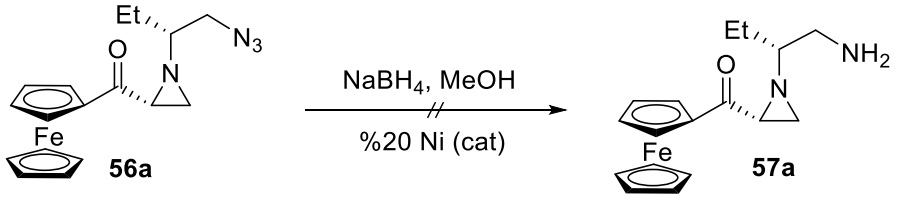
Starting with the ferrocene **51** and acryloyl chloride, in the presence of Lewis acid (Me_3Al-$AlCl_3$), acryloyl ferrocene **52** was synthesized in high yield (>95%). Then bromine was added to acryloyl ferrocene at low temperature to obtain dibromo compound **53** in almost quantitative yield. In the aziridination step, compound **3** was treated with triethylamine first then subsequent addition of chiral (*R)*-2-amino-1-butanol yielded a diastereomeric mixtures of ketones **54a** and **54b**, which were easily separated by silica column chromatography. In order to convert the hydroxyl group of compound **54a** to amino group it was tosylated by *p*-toluene sulfonyl chloride. This reaction went smoothly to provide desired tosylate **55a** in >95% yield. In the next step, tosylate was replaced with azide by using NaN_3 to get azido compound **56a** in more than 80% yield.



Scheme 19. Synthesis of compound **56a**

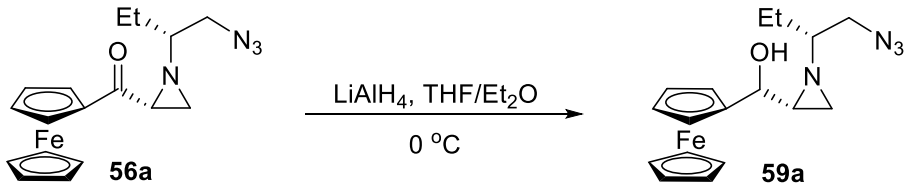
2.1.1 Reduction of azide group

To reduce azide group to amine, reducing agents such as $NaBH_4$ and $LiAlH_4$ have been tested. The reduction of compound **56a** under $NaBH_4$ with 20% Nickel catalyst conditions did not take place, the starting material was recovered (Scheme 20).



Scheme 20. The reaction of compound **56a** with $NaBH_4$

In the case of the reduction with a stronger reducing agent $LiAlH_4$ only the carbonyl group was reduced to corresponding alcohol **59a**, but the azide group was remained (Scheme 21).[43]



Scheme 21. The reaction of compound **56a** with $LiAlH_4$

The structure of compound **59a** was confirmed by the fact that the sharp carbonyl signal around 1700 cm^{-1} disappeared in the IR analysis and the broad OH signal around 3092 cm^{-1} was formed. In addition, the sharp azide signal at about 2100 cm^{-1} remained (Figure 6).

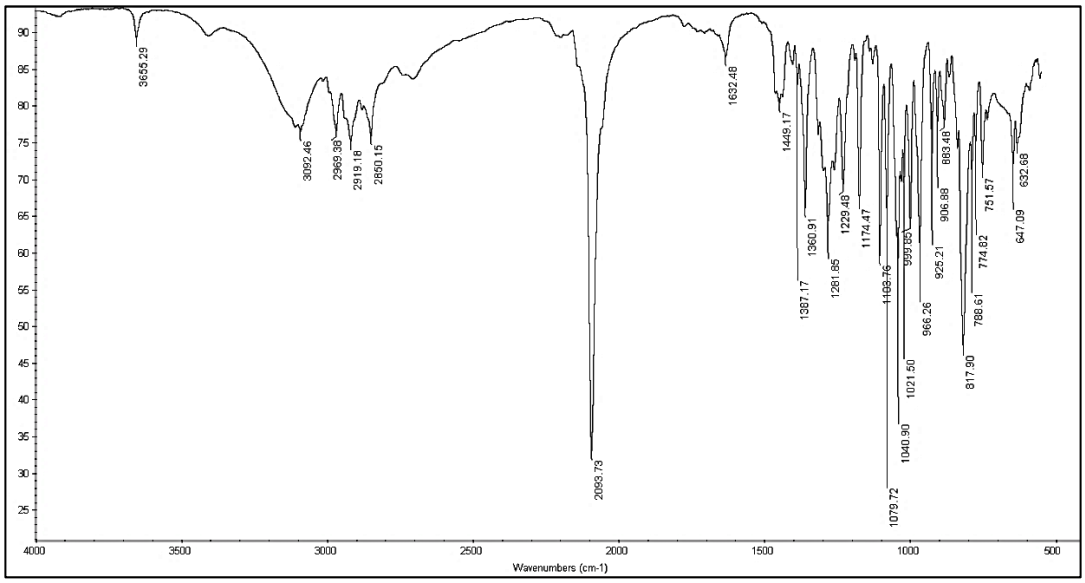
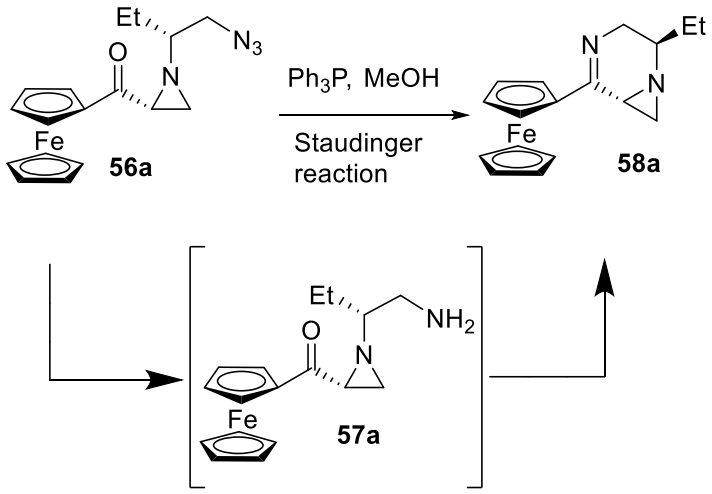


Figure 6. IR spectrum of compound **59a**

As an alternative, Staudinger reaction was used to reduce azide to amine. Surprisingly, amine product **57a** was not observed instead aziridine fused piperazine precursor **58a** was isolated. Compound **57a** believed to be formed as an intermediate but could not be observed or isolated from the reaction medium. Supposedly as soon as the amine is formed, it undergoes intramolecular condensation reaction through the ketone carbonyl group to form compound **58a** (Scheme 22).



Scheme 22. The Staudinger reaction of compound **56a**

The structure of newly formed imine **58a** was determined by using various spectroscopic methods, such as ^{1}H NMR, ^{13}C NMR (Appendix A, Figure 7) and HSQC to correlate ^{1}H signals with corresponding ^{13}C signals. As given in HSQC spectrum (Figure 7), the characteristic triplet and quartet of ethyl group belonging to C_8 and C_9 at 1.1 ppm and 1.55 ppm are correlated with expected carbon signals at 11.0 ppm and 26.9 ppm, respectively. The diastereotopic protons of aziridine ring H_7 and $H_{7'}$ appearing at 2.01 and 2.16 ppm, correlates with the carbon atom at 24.5 ppm. Same goes for diastereotopic protons H_3 at 2.85 ppm and $H_{3'}$ at 3.67 ppm that are related with one carbon at 48.3 ppm. The multiplet of H_2 proton at 2.67 ppm correlates with C_2 at 51.3 ppm. The CH of aziridine ring is clearly observed as a

multiplet at 2.97 ppm with corresponding carbon at 30.9 ppm. Five proton signals of lower Cp ring of ferrocene group appear at 4.19 ppm and correlate with five carbon signals at 69.5 ppm. The signals of other ferrocene protons are observed between 4.38-4.73 ppm correlating with carbons between 65-75 ppm. The carbon of specific C=N group appeared in ^{13}C NMR spectrum at 167.1 ppm (Appendix A, Figure 14).

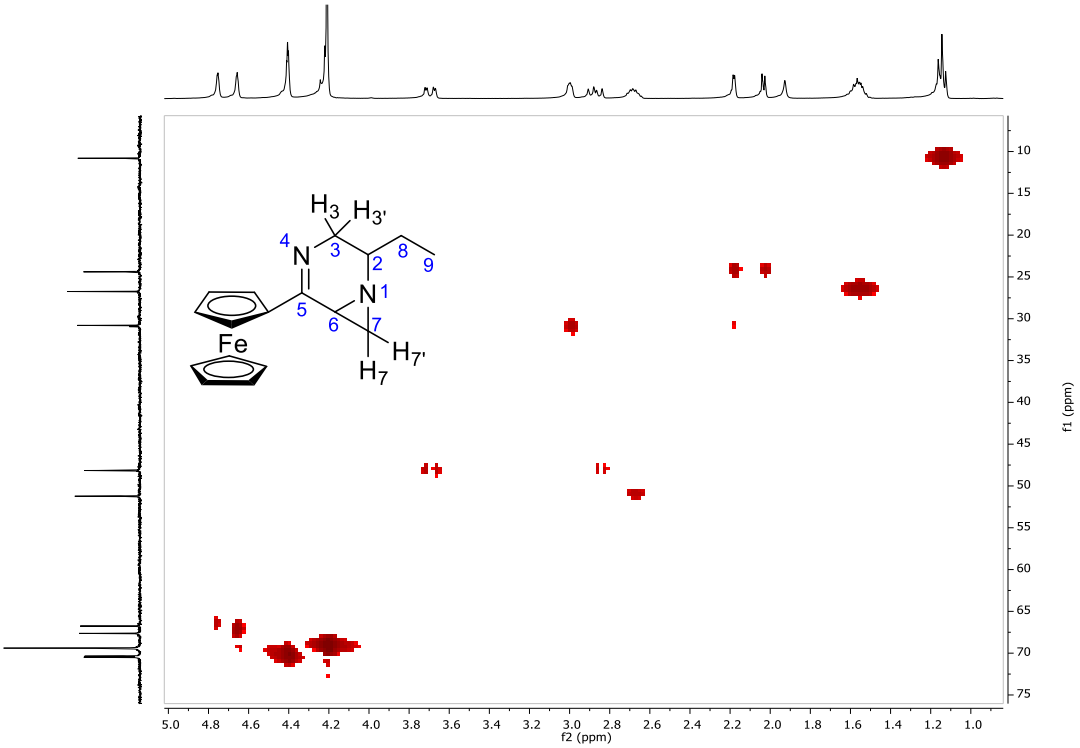


Figure 7. HSQC spectra of compound **58a**

The IR spectrum of compound **58a** (Figure 8), was also helpful in determination of compound **58a**. The carbonyl signals around 1700 cm^{-1} and azide signals around 2100 cm^{-1} disappeared and a sharp signal at 1621 cm^{-1} was observed, which was assigned to C=N group of compound **58a**.

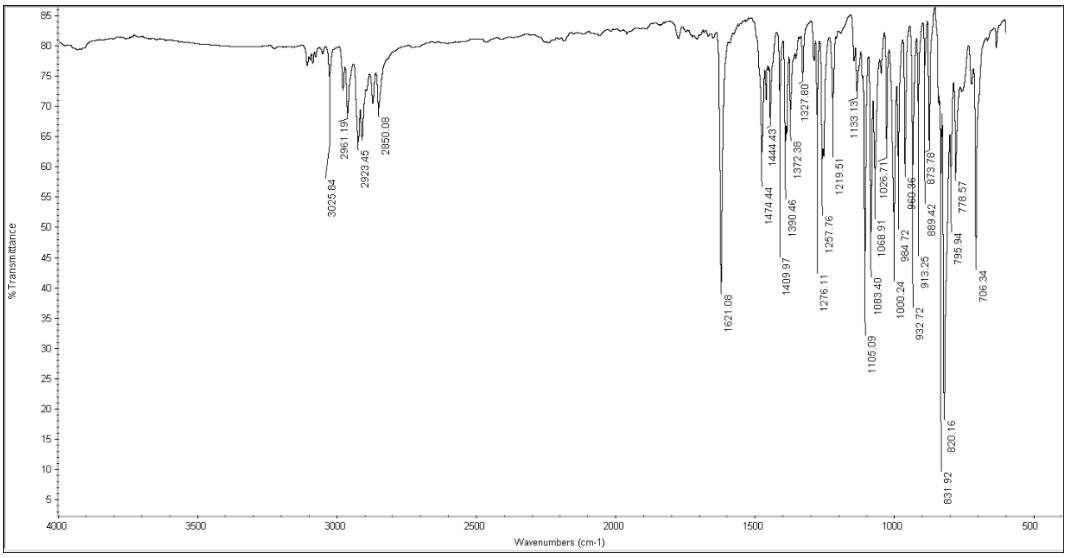


Figure 8. IR spectrum of compound **58a**

Finally, the structure of compound **58a** was confirmed undoubtedly by single crystal X-Ray analysis which also proved the absolute stereochemistry (Figure 9).

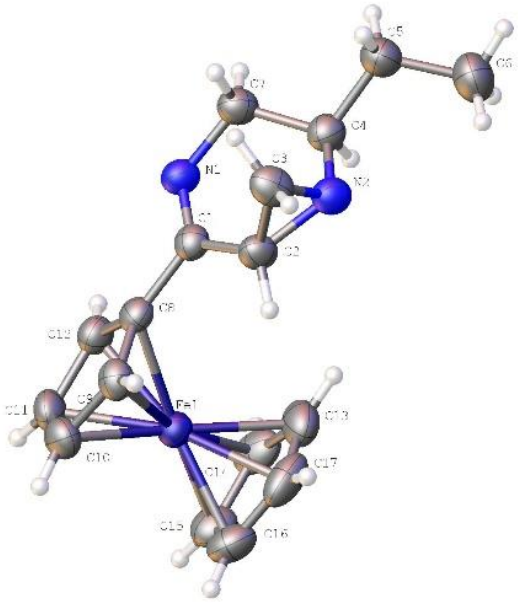
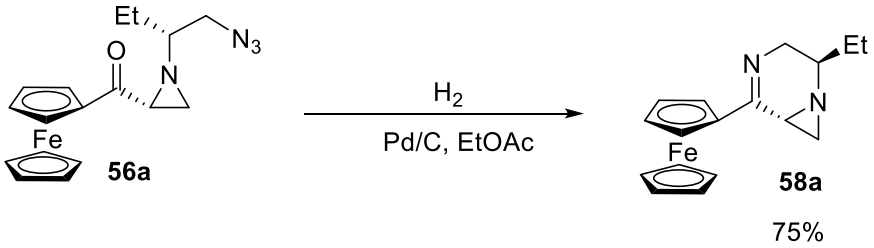


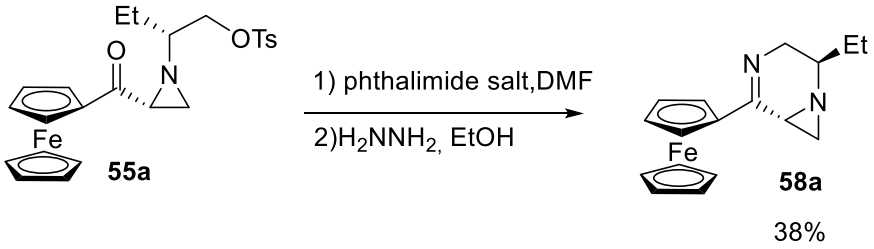
Figure 9. The X-Ray structure of the compound **58a**

To reduce the azide group of compound **56a** standard hydrogenation reaction was also used (Scheme 23). This reaction formed compound **58a** was isolated in 75% yield.



Scheme 23. Pd-catalyzed hydrogenation of compound **56a**

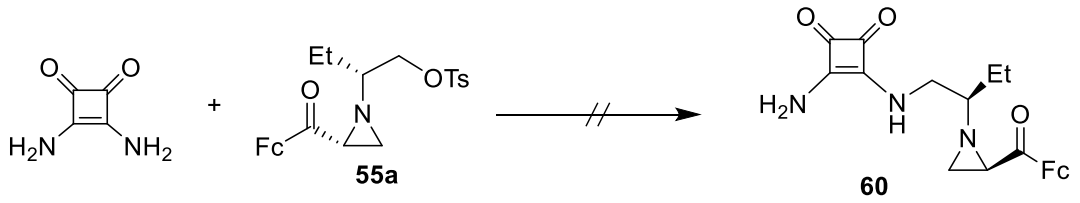
Another attempt to obtain amino compound **57a**, was tried starting directly from tosylate **55a** which was reacted with phthalimide salt and hydrazine monohydrate. This reaction also gave compound **58a** in 38% isolated yield (Scheme 24).



Scheme 24. Reaction of phthalimide with tosylate **55a**

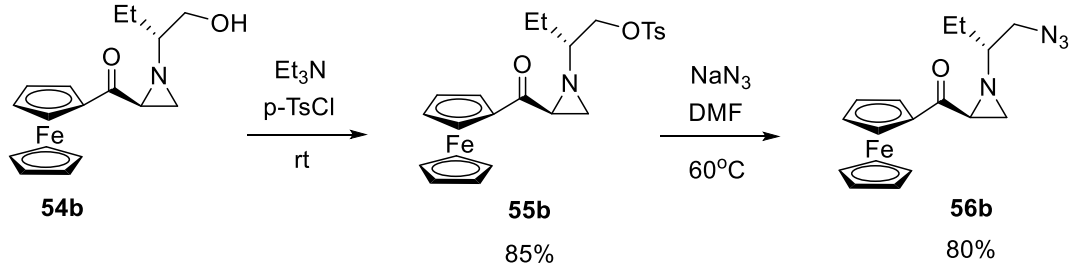
The failure in the synthesis of amine **57a** made us try direct reaction of squaramide with tosylate **55a** by adapting the literature procedure (Scheme 25).[42] For this reaction different reaction conditions[44] were also tested. For example **55a** and squaramide were reacted directly in methanol at room temperature first then refluxed. In another attempt squaramide was reacted with NaH in DMF and then

tosylate **55a** was added to the reaction mixture. In the third reaction, n-BuLi was reacted with squaramide in THF then tosylate **55a** was added to the reaction medium. However, none of these reactions provided expected squaramide product, in all cases, starting materials were recovered.



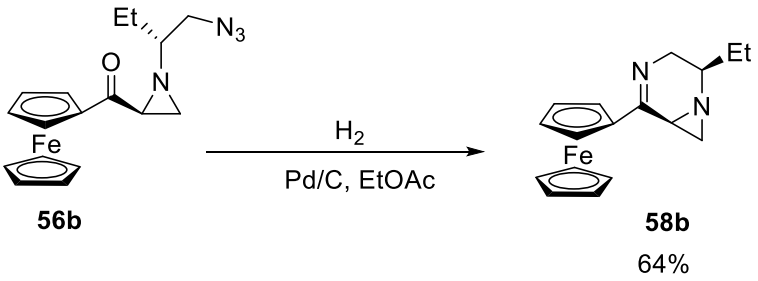
Scheme 25. Reaction of compound **55a** and squaramide

In order to find out whether the ketones **54a** and **54b** behave differently against reduction, all the steps were carried out with ketone **54b**; tosylation, azidation and reduction. First two steps took place smoothly and azide **56b** was obtained in 80% yield (Scheme 26).



Scheme 26. Synthesis of compound **56b**

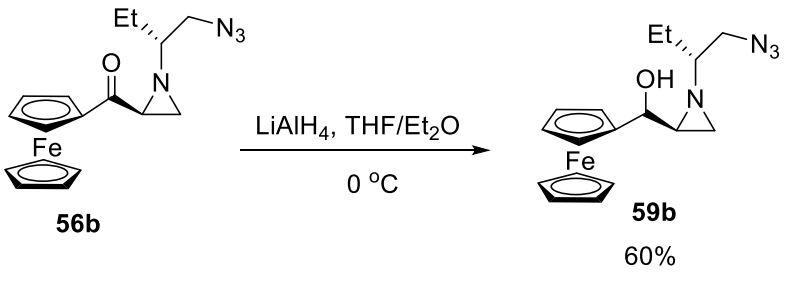
The hydrogenation reaction under similar conditions used for **56a** was repeated for **56b**. The result was very similar by providing cyclic imine **58b** through condensation reaction as observed for compound **56a** (Scheme 27).



56b **58b** 64%

Scheme 27. Cyclic imine formation from compound **56b**

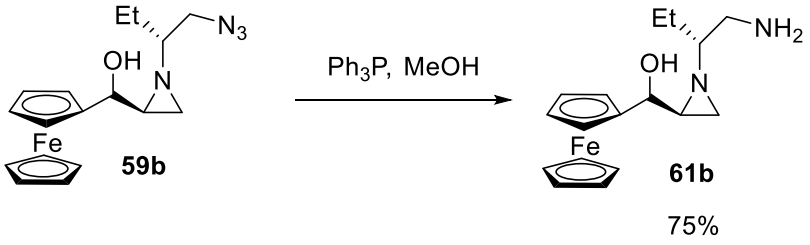
All attempts to reduce azide to amine group was unsuccessful. As mentioned before, we believe that the reduction of azide group in compounds **56a** or **56b** produced primary amine as an intermediate which underwent condensation reaction with carbonyl group to yield cyclic imine **58a** or **58b** respectively. Since it was not possible to convert the azide group to the amine group in the presence of the ketone group, the problematic ketone group was reduced to alcohol first (Scheme 28). The reduction of the azido compound **56b** with $LiAlH_4$ led to the formation of alcohol **59b** in 60% yield.



56b **59b** 60%

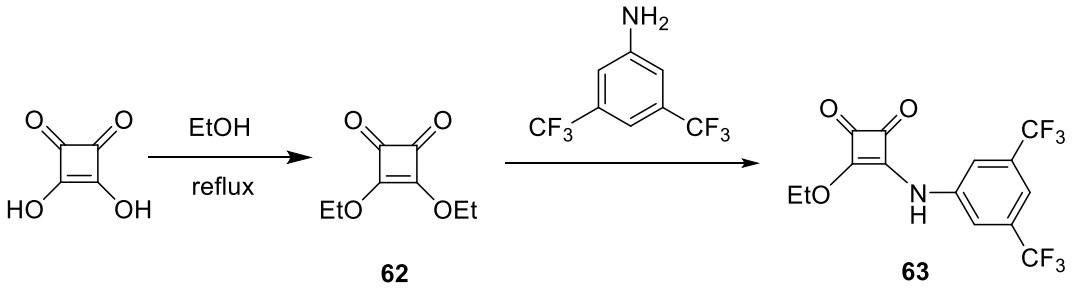
Scheme 28. Reduction of azide carbonyl to alcohol to obtain **59b**

After reduction of the carbonyl group, reduction of the azide was carried out under Staudinger conditions. This reaction produced desired amine easily by forming product **61b** (Scheme 29). Simply the IR analysis of compound **61b** showed the disappearance of azide signal at 2100 cm^{-1} in the IR spectrum.



Scheme 29. Reduction of azide group to amine group

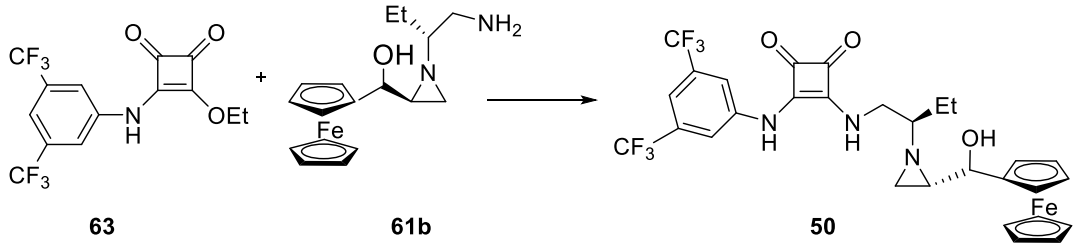
In order to synthesize the desired squaramide organocatalyst, squaric acid was converted to diethyl squarate **62**. Then compound **62** was reacted with 3,5-bis trifluoromethyl aniline to get compound **63** by using literature procedure (Scheme 30).[45]



Scheme 30. Synthesis of compound **62**

After obtaining the desired compound **63**, the next step was the introduction of the second amine group to the compound **63**. For this purpose compound **63** was

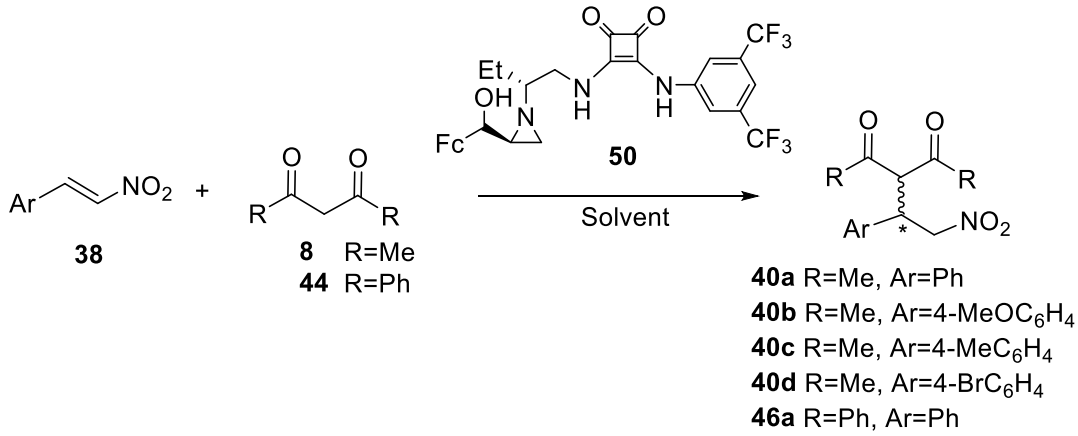
reacted with chiral amine **61b** which successfully provided desired squaramide compound **50** in 77% yield (Scheme 31).



Scheme 31. Synthesis of squaramide **50**

2.2 Asymmetric Michael Reaction

After the synthesis of target squaramide compound **50,** we wanted to test it's potential as an organocatalyst for the asymmetric Michael addition of 1,3-diketones to nitroolefins (Scheme 32).



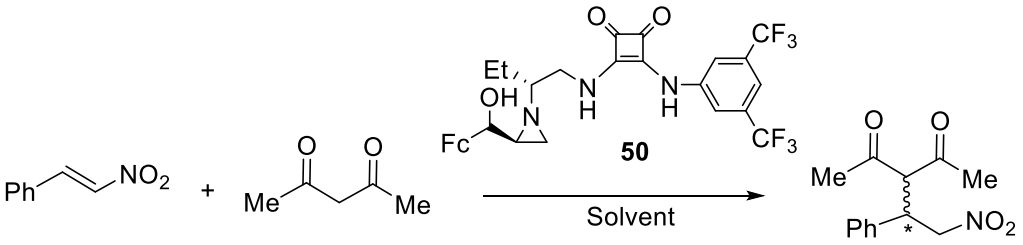
Scheme 32. Michael addition of 1,3-diketones to nitroolefins by the catalysis of squaramide **50**

For the enantioselective addition of 1,3-diketones to nitro olefins first we have done some optimization studies starting with the solvents.

2.2.1 Solvent Screening

For the solvent screening studies, we started with dichloromethane first. In this solvent we run the reaction without the catalyst just to see whether the reaction is taking place or not. If the reaction is taking place, we also wanted to observe how fast the progress of the reaction is. As can be seen from Table 1, reaction takes place without a catalyst but in low yield (61%). However, in the presence of organocatalyst under the same reaction conditions and time the yield was 86% (entry 2). This result indicated that the reaction rate is increased by the squaramide organocatalyst but with no selectivity. When acetonitrile was used as the solvent product was obtained in 44% yield (entry 3) with almost no enantioselectivity. In toluene yield was better as compared to acetonitrile but again no enantioselectivity (entry 4). As the last solvent, THF was used. Although the product was obtained in highest yield (95%) enantioselectivity was almost none (entry 5). From these studies it was decided to use THF as the solvent of the reaction for the further optimizations.

Table 1. Solvent screening studies for the Michael addition reaction



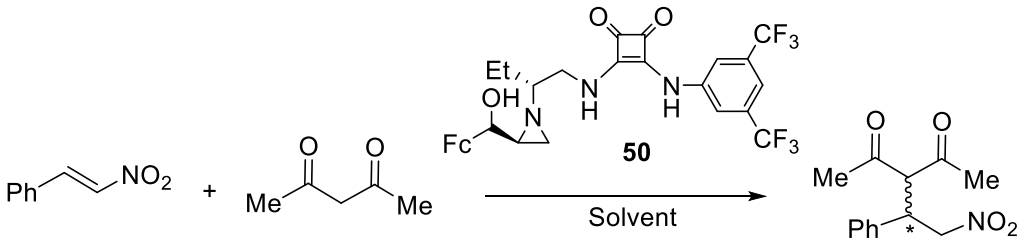
	Orgcat (mol %)	Solvent	ee[a]	Yield[b] (%)
1	-	DCM	rac	61
2	5	DCM	3	86
3	5	ACN	2	44
4	5	Toluene	2	76
5	5	THF	2	95

[a]Determined by chiral HPLC column. [b]Based on recovered nitrostyrene.

2.2.2 Catalyst Loading

After determining the solvent, different catalyst amounts were tested. In changing the catalyst load from 5, 10, and 20 mol% enantioselectivity (2%, 6%, and 9% respectively) and the yield (95%, 84%, and 90% respectively) were not affected significantly (Table 2). Therefore, we continued further optimization studies with 5 mol% catalyst loads.

Table 2. Michael addition reaction of acetyl acetone with nitrostyrene under different catalyst amount



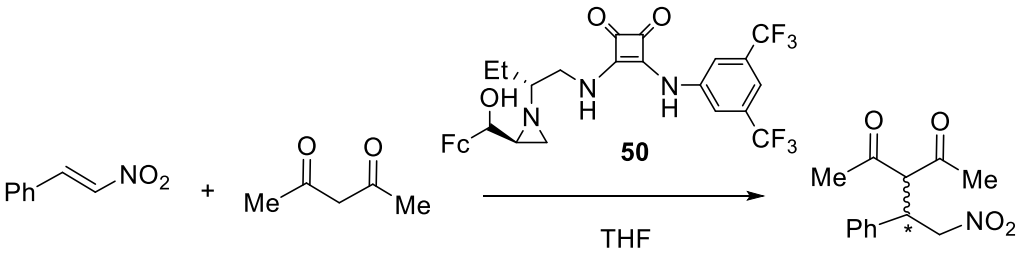
	Orgcat (mol %)	Solvent	ee	Yield (%)
1	5	THF	2	95
2	10	THF	4	84
3	20	THF	9	90

[a]Determined by chiral HPLC. [b]Based on recovered nitrostyrene.

2.2.3 Additive Screening

In order to find out whether the additives have some effect on the reaction, we tested Et_3N and pyridine. Using 15 mol% Et_3N as the additive, product was obtained in 97% yield but with the same ee where no additive was used (Table 3, entry 1). When pyridine was used as the additive the ee didn't change but the product was formed in low yield (43%, Table 3, entry 2). To see the effect of temperature on enantioselectivity, the reaction was repeated at -25℃ using Et_3N as the additive. However, the product was obtained with no enantioselectivity (entry 3).

Table 3. Additive screening table for Michael reaction of acetyl acetone with nitrostyrene



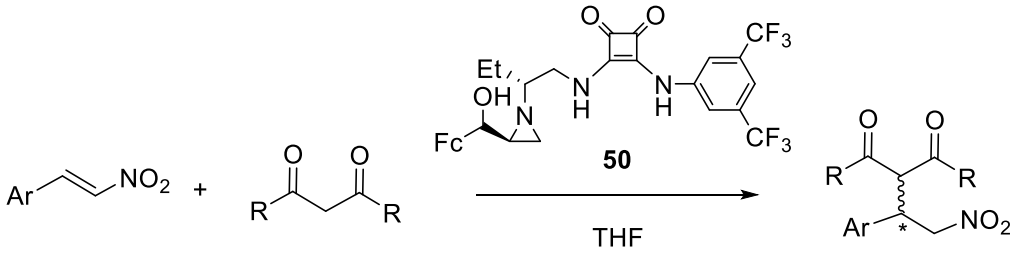
	Orgcat (mol %)	Solvent	Additive (15 mol %)	ee[a]	Yield[b]
1	5	THF	Et_3N	9	97
2	5	THF	Pyridine	9	43
3[c]	5	THF	Et_3N	rac	75

[a]Determined by chiral HPLC. [b]Isolated yield. [c]Reaction performed at -25°C.

2.2.4 Substrate Screening

As the last test of our squaramide compound as the organocatalyst we tried different substrates (Table 4). The nitroolefin having MeO-, Me-, and Br- groups on the para position of the aromatic unit were used under the same reaction conditions as the nitroolefin with no substituent. The results of these studies showed that the substituents on the aromatic group had no considerable effect on ee. Instead of using dimethyl-1,3-diketone, when diphenyl-1,3-dikotone was used the results were very similar to that of dimethyl-1,3-diketone case with the yield of 83% and an ee of 7% (entry 5).

Table 4. Substrate screening table for Michael reaction of acetyl acetone with nitrostyrene derivatives



	R	Ar	Additive (15 mol %)	ee[a]	Yield[b]
1	CH_3	Ph	Et_3N	9	97
2	CH_3	4-$MeOC_6H_4$	Et_3N	8	79
3	CH_3	4-MeC_6H_4	Et_3N	8	92
4	CH_3	4-BrC_6H_4	Et_3N	10	78
5	Ph	Ph	Et_3N	7	83

[a]Determined by chiral HPLC. [b]Isolated yield.

2.2.5 Proposed Transition State

Although no enantioselectivity was observed, it looks like the reaction rate was increased by the squaramide organocatalyst. The transition state model shown in Figure 10. According to this transition state nitrostyrene is attached to the catalyst from its oxygens *via* hydrogen bonding. Subsequently, the enolate form of 1,3-diketone was also attached to the catalyst from it's hydroxyl group by hydrogen bonding. As a result, the Michael reaction is taking place. The lower or no enantioselectivity of the catalyst can be attributed to the distance of chirality centers from the reaction site.

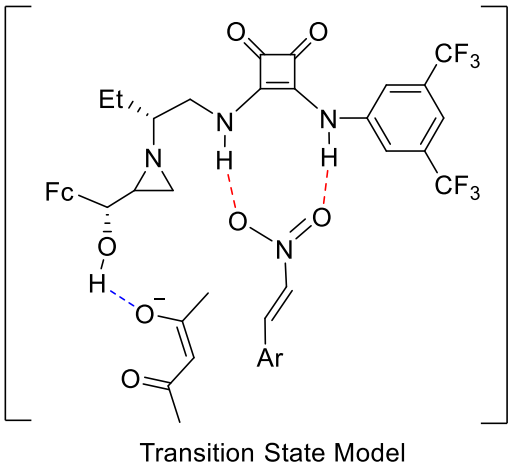
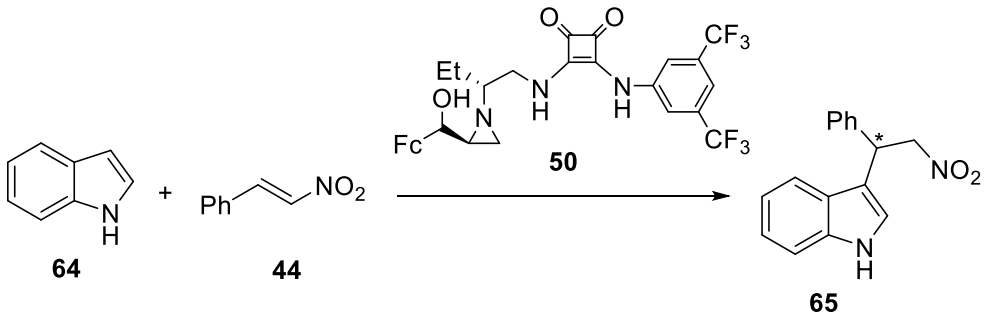


Figure 10. Proposed transition state model

2.3 Organocatalytic indole addition to nitrostyrene

Since the squaramide organocatalyst was not effective in asymmetric Michael addition reaction of 1,3-diketones with nitrostyrene we wanted to see it's effect in other organic reactions. For this purpose, we tried indole addition to nitrostyrene because there are many examples in the literature using squaramides for this reaction.[46–49] Following the literature procedure[49] the reaction between indole and nitroolefin was performed in DCM with 5 mol% of organocatalyst **50**. Unfortunately, product was formed as a racemic mixture in 49% yield.



Scheme 33. Organocatalytic indole addition to nitrostyrene

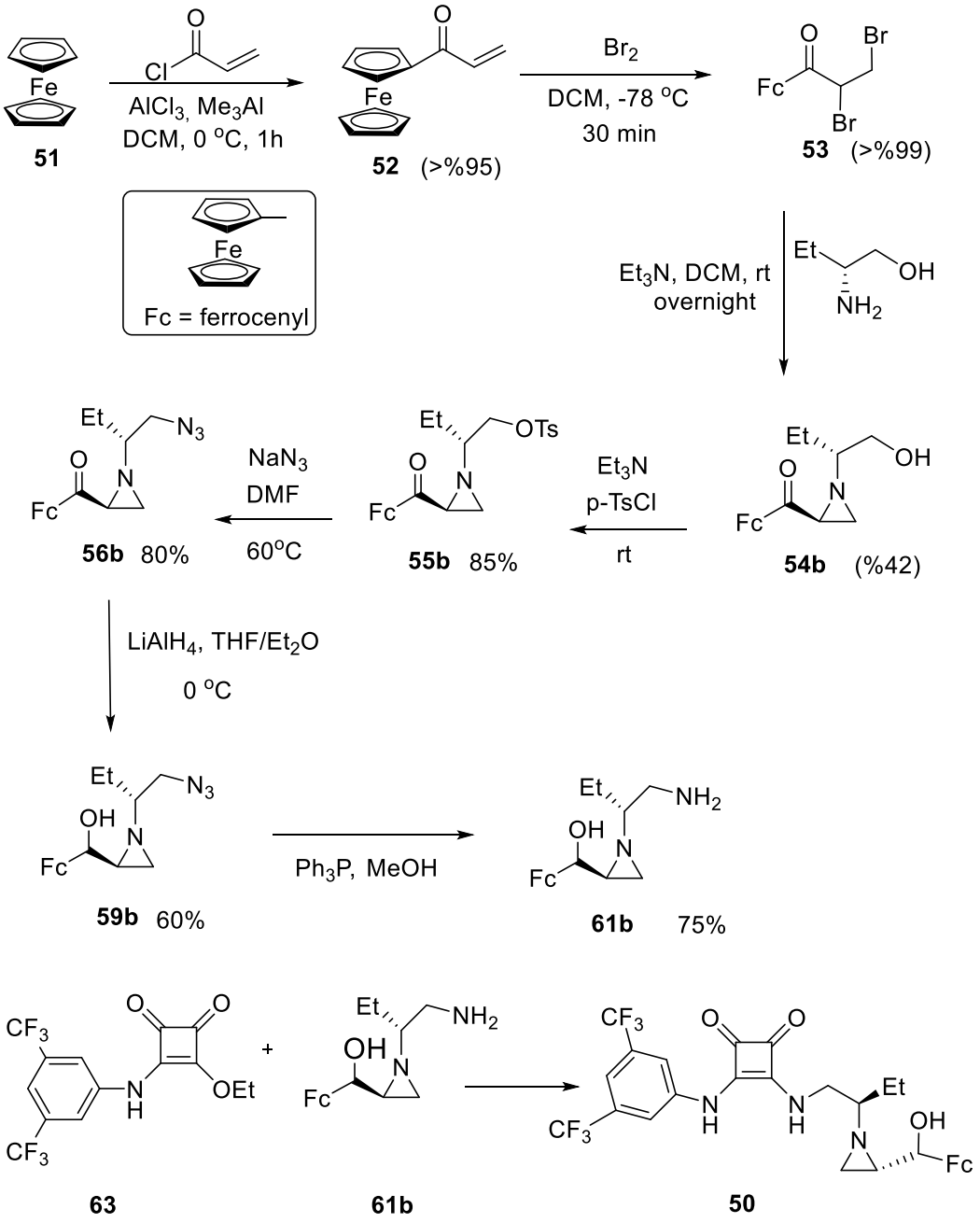
CHAPTER 3

CONCLUSION

Within the scope of this thesis, it was aimed to synthesize a new squaramide based organocatalyst **50** and investigate the catalytic effect of this compound mainly for the asymmetric Michael addition reaction of 1,3-diketones to nitroolefins. For the synthesis of squaramide **50**, chiral amine **61b** and compound **63** was reacted in the final step as outlined in Scheme 34. Chiral amine **61b** was obtained starting from ferrocene which was converted to acryloyl ferrocene **52** first. Bromination of **52** produced dibromo compound **53** which was treated with Et_3N then reacted with chiral amino alcohol in the same reaction flask to yield aziridinyl compounds **54a** and **54b** as a diastereomeric mixture. In the next step **54b** was tosylated to get **55b** then reacted with NaN_3 to get azido compound **56b** which was reduced to alcohol **59b** then to amino compound **61b**. In order to complete the synthesis of squaramide **50**, amine **61b** was coupled with monosquaramide **63** obtained from diethyl squarate **62**. After successful synthesis of squaramide **50**, it was used as an organocatalyst for the Michael addition reaction of 1,3-diketones to nitrostyrene. Although different reaction conditions and substrates were used enantioselectivity of the reaction could not be increased, it remained around 9%. The yield of the reaction, however, was good 78-97%.

We have also tested the catalytic activity of the squaramide **50** in indole addition to nitrostyrene but no enantioselectivity was observed.

There may be different reasons preventing selectivity of the squaramide, the most important reason could be attributed to the chiral control unit and larger group (such as the ferrocenyl group) which is far from the coordination center.



Scheme 34. General reaction scheme to synthesize compound **50**

As a future plan we want to modify the structure of organocatalyst and synthesize squaramides **66** and **67**. In addition, we will investigate the catalytical activity of organocatalyst **50** in different organic reactions.

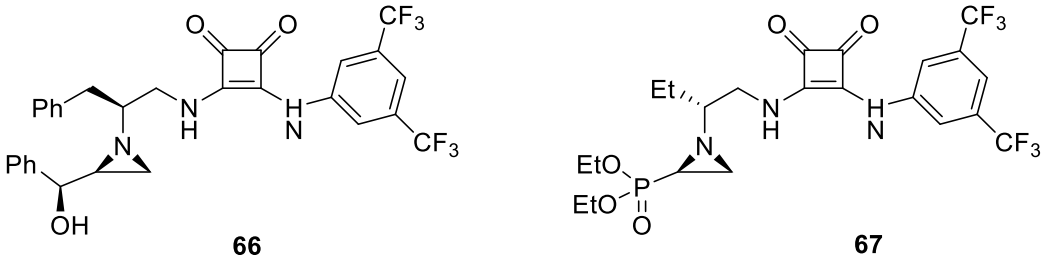


Figure 11. Squaramides that are planned to be synthesized

CHAPTER 4

EXPERIMENTAL

4.1 General Experimantal Procedure

The ^{1}H and ^{13}C NMR spectra of all the substances synthesized were obtained using Brucker spectroscopy Avance III DPX-400 ultra-shield NMR. The chemical shift values (δ) are given in terms of ppm, and the splitting constants (J) are given in Hz. The TMS signal was used as a reference in the proton NMR spectrum. The optical rotation values of chiral compounds were measured using Rudolph Research Analytical Autopol III Polarimeter. All reactions were carried out under nitrogen atmosphere. The synthesized compounds we purified on silica gel (Merck Silica Gel 60, part size: 0.040-0.063 mm, 230-400 mesh ASTM). Toluene and dichloromethane were distilled and dried over CaH_2. Diethyl ether and THF were dried over sodium/benzophenone. Et_3N and $^{i}Pr_2NEt$ were freshly distilled and stored over KOH pallets. The X-Ray diffraction data of Compound **58a** were obtained with the Agilent XCalibur X-ray diffractometer and the EOS CCD detector at room temperature with Mo-Kα radiation (graphite crystal monochromator λ=0.7107Å). The nitrostyrene derivatives were synthesized using the literature methods.[50]

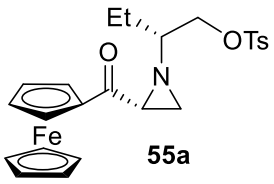
4.2 Synthesis and Characterization of Compounds

4.2.1 Synthesis of 54a and 54b

Acryloyl ferrocene **2** (1.00 g, 4.17 mmol) was dissolved in dichloromethane (DCM, 40 ml) and cooled to -78°C in round bottom flask. In another flask, dichloromethane (DCM, 40 ml) was cooled to -78°C and Br_2 (4.57 mmol in 10.0 ml DCM) was added on it. Bromine solutions was added to acryloyl ferrocene solution

quickly. Right after the addition TLC analysis showed that the starting material was finished. After hydrolysis of excess Br_2 with $Na_2S_2O_3$ extraction was carried out and the crude product was purified by flash column chromatography using silica gel. 1,2-dibromopropionylferrocene was obtained in 99% yield (1.63 g). To synthesize aziridinyl ketones, dibromo compound **53** (1.0 g, 2.5 mmol) was dissolved in DCM and Et_3N (0.6 ml, 4.3 mmol) was added and mixed in about half an hour. When all dibromo compound was converted to monobromo compound, (*R*)-2-amino-1-butanol (0.71 mL, 4.45 mmol) was added to the same reaction flask and stirred overnight. After removing the solvent all the contents of the flask was loaded on to the flash column chromatography using silica gel (3:1 hexane/EtOAc). From the column, aziridinyl ketones **54a** and **54b** were isolated as pure compounds in 53% and 42% yields respectively.

4.2.2 Synthesis and characterization of (*R*)-2-((*R*)-2-ferrocenoylaziridine-1-yl)butyl 4-methylbenzenesulfonate (55a)

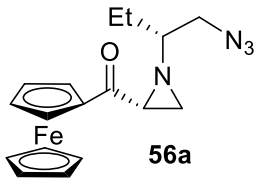


55a

Compound **55a** was synthesized using the literature method. (İşçi, M. Master's Thesis submitted to Middle East Technical University, 2012). The compound **54a** (145 mg, 0.4 mmol) was dissolved in round bottomed flask and dissolved in dichloromethane (2 ml) at room temperature. Triethylamine (0.1 ml, 1.0 mmol) was added and stirred for 15 min. Then *p*-toluenesulfonyl chloride (193.4 mg, 1.0 mmol) was added. The mixture was stirred overnight at room temperature. The reaction medium was extracted with dichloromethane and saturated NH_4Cl solution. After the organic phase was dried with $MgSO_4$, it was concentrated in *vacuo*. The crude product was purified by flash column chromatography using silica gel and eluting with hexane/EtOAc mixture solvent system to get tosylated compound **5a** in 95.0% yield as an orange oil. R_f = 0.65 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 5.04 (d, J = 1.9 Hz, 1H), 4.89 (d, J = 1.6 Hz, 1H), 4.60 (s, 2H), 4.22 (s, 5H), 4.16 (dd, J = 10.1, 3.7 Hz, 1H), 3.97 (dd, J = 10.1,

7.7 Hz, 1H), 2.85 (dd, *J* = 6.5, 3.3 Hz, 1H), 2.38 (s, 3H), 2.35 – 2.32 (m, 1H), 1.90 – 1.82 (m, 1H), 1.75 (dd, *J* = 6.5, 1.5 Hz, 1H), 1.69 – 1.49 (m, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 144.8, 132.3, 129.8, 127.7, 78.5, 72.6, 70.6, 69.7, 68.9, 68.5, 40.4, 33.7, 24.7, 21.4, 10.3. IR (cm^{-1}): 3095, 2970, 2880, 1661, 1757, 1355, 1256, 1714,1105, 948, 814, 748, 664.

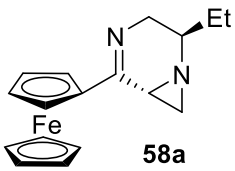
4.2.3 Synthesis and characterization of (*R*)-1-((*R*)-1-azidobutane-2-yl)aziridine-2-yl)(ferrocenyl)methanon (56a)



56a

NaN_3 (1.26 g, 20 mmol) was added to compound **55a** (1 g, 2 mmol) and dissolved in DMF (50 ml). The reaction was heated at 60°C and stirred for 4 hours. At the end of this perion the mixture was brought to room temperature and extracted by using ethyl acetate and saturated NH_4Cl solution. The organic phase was dried over $MgSO_4$, filtered and concentrated under *vacuo*. Then the crude product was purified by flash column chromatography using silica gel and hexane/EtOAc solvent system. Pure **56a** was isolated in 83% yield as a red solid. R_f = 0.82 (2:1 EtOAc:DCM). mp: 86-87°C. $[\alpha]_D^{26.0} = +0.736$ (c=0.008 in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.97 (d, *J* = 1.8 Hz, 1H), 4.92 (d, *J* = 2.2 Hz, 1H), 4.58 (d, *J* = 2.0 Hz, 2H), 4.25 (s, 5H), 3.56 – 3.44 (m, 2H), 2.78 (dd, *J* = 6.6, 3.2 Hz, 1H), 2.35 (dd, *J* = 3.2, 1.6 Hz, 1H), 1.77 (dd, *J* = 6.6, 1.5 Hz, 1H), 1.73 – 1.55 (m, 3H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.7, 78.7, 72.7, 70.2, 69.9, 69.2, 55.4, 41.3, 34.4, 26.0, 10.6. IR(cm^{-1}): 2974, 2929, 2877,2838, 2086, 1656, 1458, 1281, 1257, 1100, 1089, 821.

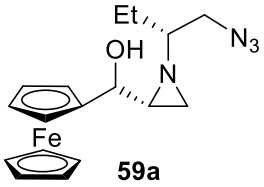
4.2.4 Synthesis and characterization of (2*R*,6*R*)-2-ethyl-5-ferrocenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (58a)



58a

Compound **56a** (50 mg, 0.1 mmol) was dissolved in EtOAc (2 ml) and Pd/C was added to the reaction flask at room temperature. Then H_2 gas filled in a small balloon was exposed to reaction medium. Stirring was continued until TLC analysis showed no starting material was remained in the reaction flask. Pd/C was removed by filtration and solvent was removed under vacuum. The crude product was purified by flash column chromatography using silica gel and hexane/EtOAc Compound **58a** was obtained in 75% yield as a red solid. R_f = 0.29 (5:2 EtOAc:DCM). mp: 110-111°C. $[\alpha]_D^{26.0} = +1.280$ (c=0.006 in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (d, *J* = 1.8 Hz, 1H), 4.63 (d, *J* = 1.9 Hz, 1H), 4.38 (s, 2H), 4.19 (s, 5H), 3.67 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.97 (d, *J* = 2.8 Hz, 1H), 2.85 (dd, *J* = 16.6, 11.0 Hz, 1H), 2.66 (dt, *J* = 11.0, 5.7 Hz, 1H), 2.16 (d, *J* = 3.2 Hz, 1H), 2.01 (d, *J* = 5.8 Hz, 1H), 1.59 – 1.50 (m, 2H), 1.12 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 83.4, 70.6, 69.5, 67.7, 66.8, 51.3, 48.3, 30.9, 26.9, 24.5, 11.0. IR (cm^{-1}): 3026, 2961, 2923, 2885, 2867, 2850, 1621, 1474, 1390, 1257, 1105, 1083, 1000, 820, 706.

4.2.5 Synthesis and characterization of (*R*)-((*R*)-1-((*R*)-1-azidobutan-2-yl)aziridin-2-yl)(ferrocenyl)methanol (59a)

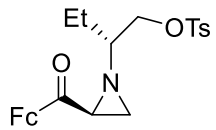


59a

The compound **56a** (60 mg, 0.16 mmol) was dissolved in dry diethyl ether (2 ml) and cooled to 0°C. Lithium aluminum hydride (10 mg, 0.27 mmol) was added to it. After stirring the mixture at this temperature for 2 hours, TLC analysis showed no starting material. The reaction was quenched with saturated ammonium chloride solution and extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated, then purified by flash column chromatography over silica gel with a hexane/EtOAc mixture. Compound **59a** was obtained in 65% yield as a

yellow liquid. R_f = 0.62 (2:1 EtOAc/DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.41 (d, J = 4.2 Hz, 1H), 4.24 – 4.22 (m, 1H), 4.18 (d, J = 1.9 Hz, 1H), 4.13 (s, 5H), 4.11 (s, 1H), 3.25 (dd, J = 12.5, 4.2 Hz, 1H), 3.15 (dd, J = 12.5, 5.9 Hz, 1H), 2.53 (s, 1H), 1.87 (d, J = 3.5 Hz, 1H), 1.80 (dt, J = 7.4, 3.8 Hz, 1H), 1.53 (p, J = 7.2 Hz, 2H), 1.44 (q, J = 5.6 Hz, 1H), 1.31 (d, J = 6.4 Hz, 1H), 1.19 (s, 1H), 0.87 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 89.7, 68.9, 68.6, 68.2, 68.2, 68.0, 67.2, 66.1, 54.8, 42.8, 29.3, 25.4, 10.3. IR (cm^{-1}): 3094, 2958, 2923, 2851, 2097, 1663, 1355, 1242, 1105, 1001,820

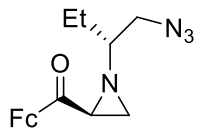
4.2.6 Synthesis and characterization of (*R*)-2-((*S*)-2-ferrocenoylaziridine-1-yl)butyl 4-methylbenzenesulfonate (55b)



55b

Compound **54b** (0.88mg, 2.5 mmol) was dissolved in DCM (12 ml) at room temperature. Then Et_3N (0.85 ml, 6.1 mmol) was added. *p*-toluene sulfonyl chloride (1.17 mg, 6.1 mmol) was added to stirred solution. Reaction was stirred at room temperature at overnight. Then extraction was done with EtOAc/saturated NH_4Cl. The crude product was purified by flash column chromatography using silica gel and hexane/EtOAc. Compound **55b** was obtained in 85% yield as an orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 4.87 (s, 2H), 4.54 (s, 2H), 4.19 (s, 5H), 4.17 – 4.11 (m, 2H), 2.57 – 2.49 (m, 1H), 2.45 (s, 3H), 2.24 (dd, *J* = 3.3, 1.5 Hz, 1H), 1.94 (dd, *J* = 6.7, 1.4 Hz, 1H), 1.87 – 1.82 (m, 1H), 1.65 – 1.56 (m, 3H), 0.94 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.7, 145.0, 132.8, 129., 127.90, 78.2, 72.6, 72.1, 69.8, 69.3, 68.7, 40.0, 35.7, 24.9, 21.6, 9.9. IR (cm^{-1}): 3095, 2970, 2880, 1661, 1597, 1355, 1256,1105, 948, 814, 748, 664.

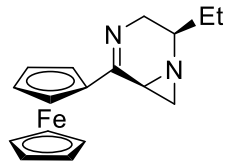
4.2.7 4.2.3 Synthesis and characterization of (*R*)-1-((*S*)-1-azidobutane-2-yl)aziridine-2-yl)(ferrocenyl)methanon (56b)



56b

Compound **55b** (1.1 g, 2.1 mmol) was dissolved in DMF (21 ml). Then NaN_3 (1.35 mg, 21.0 mmol) was added and stirred at 60℃ overnight. After cooling to room temperature, extraction was done with EtOAc/saturated NH_4Cl solution. Residue was purified by flash column chromatography using silica gel and hexane/EtOAc. Compound **56b** was obtained in 80% yield as an orange solid. mp: 65-66℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 – 4.91 (m, 2H), 4.56 (s, 2H), 4.23 (s, 5H), 3.55 – 3.43 (m, 2H), 2.56 (dd, *J* = 6.6, 3.2 Hz, 1H), 2.41 (dd, *J* = 3.2, 1.5 Hz, 1H), 1.94 (dd, *J* = 6.7, 1.5 Hz, 1H), 1.70 (q, *J* = 7.0 Hz, 2H), 1.61 (d, *J* = 5.5 Hz, 2H), 1.01 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.6, 77.9, 72.3, 69.5, 69.2, 69.0, 54.2, 40.2, 35.6, 25.4, 9.8. IR (cm^{-1}): 2963, 2946, 2920,2883, 2090, 1660, 1460, 1284, 1259, 1103, 1079, 812.

4.2.8 Synthesis and characterization of (2*R*,6*S*)-2-ethyl-5-ferrocenyl-1,4-diazabicyclo[4.1.0]hept-4-ene (58b)

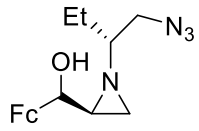


58b

Compound **56b** (100 mg, 0.3 mmol) was dissolved in EtOAc. Pd/C (20 mg) was added then hydrogen gas was passed until reaction was completed which was followed by TLC. After filtration, the reaction mixture was washed with DCM and purify by flash column chromatography over silica gel with a hexane/EtOAc mixture. Compound **58b** was obtained in 64% yield as an orange solid. R_f = 0.39 (EtOAc). $[\alpha]_D^{26.0} = -0.592$ (c=0.03 in DCM). mp: 115-116°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 – 4.67 (m, 1H), 4.58 (d, *J* = 1.8 Hz, 1H), 4.32 (s, 2H), 4.13 (s, 5H), 3.59 – 3.51 (m, 1H), 3.29 (dd, *J* = 16.5, 5.8 Hz, 1H), 2.72 (d, *J* = 6.1 Hz, 2H), 2.14 (d, *J* = 3.2 Hz, 1H), 2.12 (d, *J* = 5.9 Hz, 1H), 1.53 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.39 (dt, *J* = 13.9, 7.1 Hz, 1H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ

167.6, 83.1, 70.4, 70.3, 69.3, 67.6, 66.6, 53.9, 46.7, 29.4, 28.6, 27.4, 11.5. IR (cm^{-1}): 3091, 3048, 3021, 2955, 2912, 2879, 1617, 1407, 1271, 1257, 1105, 1079, 997, 820, 737.

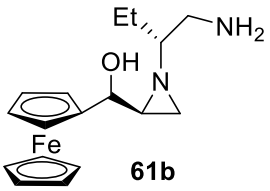
4.2.9 Synthesis and characterization of (*R*)-((*S*)-1-((*S*)-1-azidobutan-2-yl)aziridin-2-yl)(ferrocenyl)methanol (59b)



59b

The compound **56b** (360 mg, 0.9 mmol) was dissolved in dry tetrahydrofuran (THF, 1 ml) and cooled to 0°C. Lithium aluminum hydride (71.5 mg, 1.9 mmol) was added to it. After the mixture was stirred at the specified temperature for 4-5 hours, the reaction was controlled by TLC and terminated when the starting compound was finished. The lithium aluminum hydride was quenched with saturated ammonium chloride, extracted using saturated NH_4Cl solution. The combined organic phases were dried over $MgSO_4$ and concentrated, then purified by flash column chromatography over silica gel with a hexane/EtOAc mixture. It was obtained in 60% yield as an orange liquid. R_f = 0.38 (2:1 Hexane/EtOAc). $[\alpha]_D^{26.0} = +0.302$ (c=0.03 in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (s, 1H), 4.28 (d, *J* = 2.1 Hz, 1H), 4.22 (d, *J* = 3.0 Hz, 2H), 4.19 (s, 5H), 4.17 (d, *J* = 3.9 Hz, 2H), 3.41 (dd, *J* = 12.4, 4.1 Hz, 1H), 3.35 (dd, *J* = 4.9 Hz, 1H), 2.64 (s, 1H), 1.90 – 1.79 (m, 1H), 1.63 – 1.57 (m, 2H), 1.53 (d, *J* = 6.8 Hz, 2H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 89.3, 68.98, 68.5, 68.1, 67.9, 67.8, 67.1, 66.1, 54.3, 42.0, 29.8, 25.4, 10.1. IR (cm^{-1}): 3092, 2969, 2919, 2850, 2094, 1361, 1282, 1100, 966, 818.

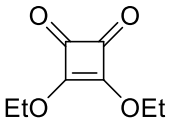
4.2.10 (*R*)-((*S*)-1-((*S*)-1-aminobutane-2-yl)aziridine-2-yl)(ferrocenyl)methanol (61b)



61b

The compound **59b** (110 mg, 0.29 mmol) was dissolved in methanol (5 ml), triphenylphosphine (114 mg, 0.43 mmol) was added to it at room temperature. The reaction was stirred 2 hours until the starting material was finished, which was checked with TLC. After the reaction micture was filtered, it was extracted with DCM and the solvent was concentrated in *vacuo*. The product was purified by hexane/EtOAc mixture over silica gel in flash column chromatography. It was obtained in 75% yield as a yellow liquid. R_f = 0.25 (1:3 MeOH/EtOAc). $[\alpha]_D^{26.1} = +3.448$ (c=0.03 in DCM). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (s, 1H), 4.30 (s, 1H), 4.22 (s, 1H), 4.19 (s, 5H), 4.17 (s, 1H), 2.67 (s, 2H), 1.82 (d, *J* = 7.2 Hz, 2H), 1.53 (t, *J* = 6.9, 2.3 Hz, 2H), 1.38 (d, *J* = 4.8 Hz, 1H), 1.35 – 1.26 (m, 1H), 0.89 (t, *J* = 7.0, 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 90.3, 77.5, 77.2, 76.8, 71.5, 69.5, 68.6, 68.3, 68.1, 67.4, 65.9, 45.0, 42.8, 30.0, 24.9, 10.7. IR (cm^{-1}): 3508, 3396, 2969, 2928, 2858, 1583, 1377, 1276, 1171, 1112, 882.

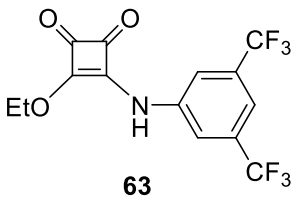
4.2.11 3,4-Diethoxy-3-cyclobutene-1,2-dione (62)



62

Squaric acid (2.5 g, 0.02 mol) was dissolved in ethanol (25 ml) and refluxed for 3 hours. After removing solvent under vacuum, another 25 ml of ethanol was added and refluxed 30 min. This procedure was repeated three times. Data are the same as reported in the literature.[51] ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.73 (q, *J* = 7.0 Hz, 3H), 1.47 (t, *J* = 7.1 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 184.1, 70.5, 15.5. IR (cm^{-1}): 2995, 1812, 1721, 1591, 1480, 1419, 1380, 1328, 1023,853, 799

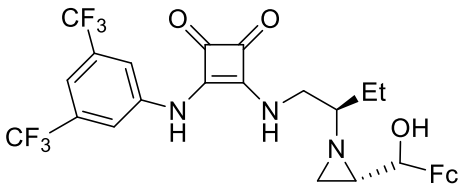
4.2.12 Synthesis of 3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-ethoxycyclobut-3-ene-1,2-dione (63)



63

3,5-bis(trifluoromethyl)aniline (0.25 ml, 1.60 mmol) was dissolved in methanol (4 ml). 3,4-diethoxy-3-cyclobutene-1,2-dione (0.27 g, 1.60 mmol) were added to it. Data are the same as reported in the literature.[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s(broad), 1H), 7.98 – 7.79 (m, 2H), 7.67 (s, 1H), 5.06 – 4.93 (q, 2H), 1.56 (t, J = 7.1 Hz, 3H).

4.2.13 3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((*R*)-2-((*S*)-2-((*S*)-hydroxy(phenyl) methyl) azirid of-1-il)butyl)amino)siklobut-3-en-1,2-dion (50)



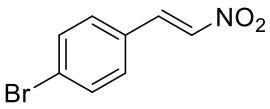
50

After dissolving compound **63** (117 mg, 0.3 mmol) in methanol (3 ml) at room temperature, compound **61b** (108 mg, 0.3 mmol) was added to the reaction mixture. The reaction was stirred overnight at room temperature. After the completion of the reaction indicated by TLC, the crude product was purified by flash column chromatography. It was obtained in 77% yield as an orange solid. R_f = 0.25 (1:1 MeOH/EtOAc). mp: 168-169°C. $[\alpha]_D^{25.5} = +1.625$ (c=0.01 in DCM). ^{1}H NMR (400 MHz, DMSO): δ 11.16 (broad, 1H, NH), 10.16 (s(broad), 1H, NH), 8.42 (d, J = 1.9 Hz, 2H), 7.63 (d, J = 2.0 Hz, 1H), 4.55 (d, J = 4.5 Hz, 1H, OH), 4.23 (s, 1H), 4.14 (s, 6H), 4.08 (d, J = 10.8 Hz, 3H), 3.80 (dd, J = 13.1, 4.9 Hz, 1H), 3.71 (dd, J = 13.1, 5.4 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.57 – 1.52 (m, 1H), 1.45 (d, J = 6.3 Hz, 1H), 1.34 (dt, J = 11.5, 6.3 Hz, 2H), 0.80 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO): δ 183.9, 171.6, 170.2, 141.0, 131.7, 131.4, 131.0, 130.7, 127.2, 124.5, 121.8, 118.7, 115.0, 68.9, 68.2, 67.0, 66.8, 66.6,

65.8, 59.7, 46.9, 43.2, 30.3, 24.4, 20.7, 14.0, 9.8. IR: 3509, 3396, 2969, 2929, 2858, 1625, 1583, 1377, 1276, 1112, 882.

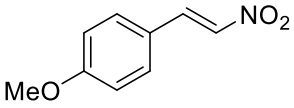
4.2.14 The general procedure for the synthesis of nitrostyrene derivatives

Nitromethane (5.36 ml, 0.1 mmol), benzaldehyde (10.2 ml, 0.1 mmol) and methyl alcohol (20 ml) were added into round bottom flask in the ice bath. NaOH (4.2 g, 0.11 mmol) was dissolved in water (20 ml). Then NaOH solution was added into other solution with dropping funnel. Temperature needed to keep at 10-15°C. After 15 min, reaction was dropped into HCl solution (30 ml H_2O, 20 ml HCl). Compound was filter by suction filtration and washed with water until free from chlorides. Precipitate was melted, water was decanted. The crude nitrosytrene derivatives was purified by dissolving hot ethyl alcohol. Then cooling until crystallization was completed.



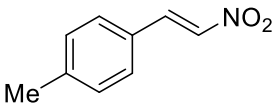
38a

Data are the same as reported in the literature.[52] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, J = 13.4 Hz, 1H), 7.56 (dd, J = 8.3 Hz, 3H), 7.39 (d, J = 8.2 Hz, 2H).



38b

Data are the same as reported in the literature.[52] ^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.01 (d, J = 13.5 Hz, 1H), 7.59 – 7.50 (m, 3H), 6.98 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H).

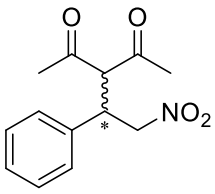


38c

Data are the same as reported in the literature.[52] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 13.7 Hz, 1H), 7.57 (d, J = 13.6 Hz, 1H), 7.47 – 7.42 (d, 2H), 7.28 – 7.25 (d, 2H), 2.41 (s, 3H).

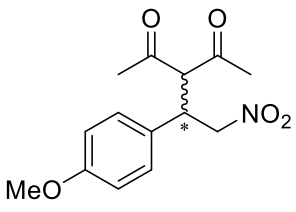
4.2.15 The general procedure for the Michael addition reaction of 1,3-diketones to nitrostyrenes

Nitrostyrene was added to catalyst **12** (5% mol or 10% mol) at room temperature in the solvent specified in Table 1. 1,3-diketone compound (2 equivalents) was added to the mixture and the reaction was stirred for 24 hours at the specified temperature. Whether the reaction was finished was controlled by TLC. The product was purified by hexane/EtOAc mixture over silica gel in flash column chromatography. The HPLC analysis of the product using the chiral column was determined by the chiral column Chiralpak AS-H column.



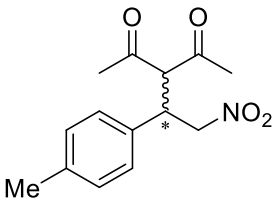
40a

Data are the same as reported in the literature.[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.31 (m, 2H), 7.21 (dd, J = 8.0, 1.7 Hz, 2H), 4.66 – 4.63 (m, 2H), 4.40 (d, J = 10.8 Hz, 1H), 4.27 (ddd, J = 10.8, 7.7, 4.9 Hz, 1H), 2.32 (s, 3H), 1.97 (s, 3H). The enantiomeric excess of the product was determined by chiral HPLC analysis on Daicel Chiralpak AS-H column, 85:15 Hexane-2-Propanol, 210 nm, flow rate = 1 ml/min, t_1 = 14 min, t_2 = 19 min.



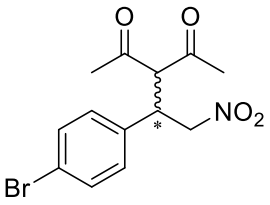
40b

Data are the same as reported in the literature.[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 4.52 (d, J = 6.3 Hz, 2H), 4.26 (d, J = 10.9 Hz, 1H), 4.13 (q, J = 5.6 Hz, 1H), 3.69 (s, 3H), 2.21 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 201.3, 159.6, 129.2, 127.7, 114.7, 78.6, 71.0, 55.3, 42.2, 30.5, 29.6. The enantiomeric excess of the product was determined by chiral HPLC analysis on Daicel Chiralpak AS-H column, 85:15 Hexane-2-Propanol, 210 nm, flow rate = 1 ml/min, t_1 = 19 min, t_2 = 26 min.



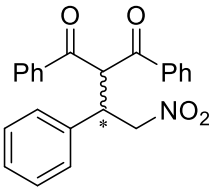
40c

Data are the same as reported in the literature.[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 7.9 Hz, 1H), 4.53 (d, J = 6.2 Hz, 1H), 4.28 (d, J = 10.8 Hz, 1H), 4.14 (q, J = 5.2 Hz, 1H), 2.22 (s, 2H), 2.21 (s, 2H), 1.86 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 201.3, 138.4, 132.9, 130.0, 127.9, 78.5, 70.8, 42.5, 30.5, 29.6, 21.1. The enantiomeric excess of the product was determined by chiral HPLC analysis on Daicel Chiralpak AS-H column, 85:15 Hexane-2-Propanol, 210 nm, flow rate = 1 ml/min, t_1 = 9 min, t_2 = 12 min.



40d

Data are the same as reported in the literature.[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 7.5 Hz, 2H), 7.01 (d, J = 7.9 Hz, 2H), 4.54 (d, J = 6.2 Hz, 2H), 4.27 (d, J = 10.6 Hz, 1H), 4.16 (q, J = 5.3 Hz, 1H), 2.21 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 200.8, 135.2, 132.6, 131.9, 130.2, 129.8, 122.7, 78.0, 70.5, 42.3, 30.6, 29.9. The enantiomeric excess of the product was determined by chiral HPLC analysis on Daicel Chiralpak AS-H column, 85:15 Hexane-2-Propanol, 210 nm, flow rate = 1 ml/min, t_1 = 9 min, t_2 = 12 min.



46a

Data are the same as reported in the literature.[27] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.43 (dt, J = 15.0, 7.2 Hz, 2H), 7.28 (dt, J = 14.3, 7.5 Hz, 4H), 7.19 – 7.05 (m, 5H), 5.77 (d, J = 7.8 Hz, 1H), 4.91 (d, J = 6.7 Hz, 2H), 4.55 (d, J = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 193.2, 136.8, 136.2, 135.9, 134.2, 133.9, 129.1, 128.9, 128.9, 128.7, 128.4, 128.2, 59.9, 44.1. The enantiomeric excess of the product was determined by chiral HPLC analysis on Daicel Chiralpak AS-H column, 85:15 Hexane-2-Propanol, 210 nm, flow rate = 1 ml/min, t_1 = 15 min, t_2 = 20 min.

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APPENDICES

A. NMR Spectra of Compounds

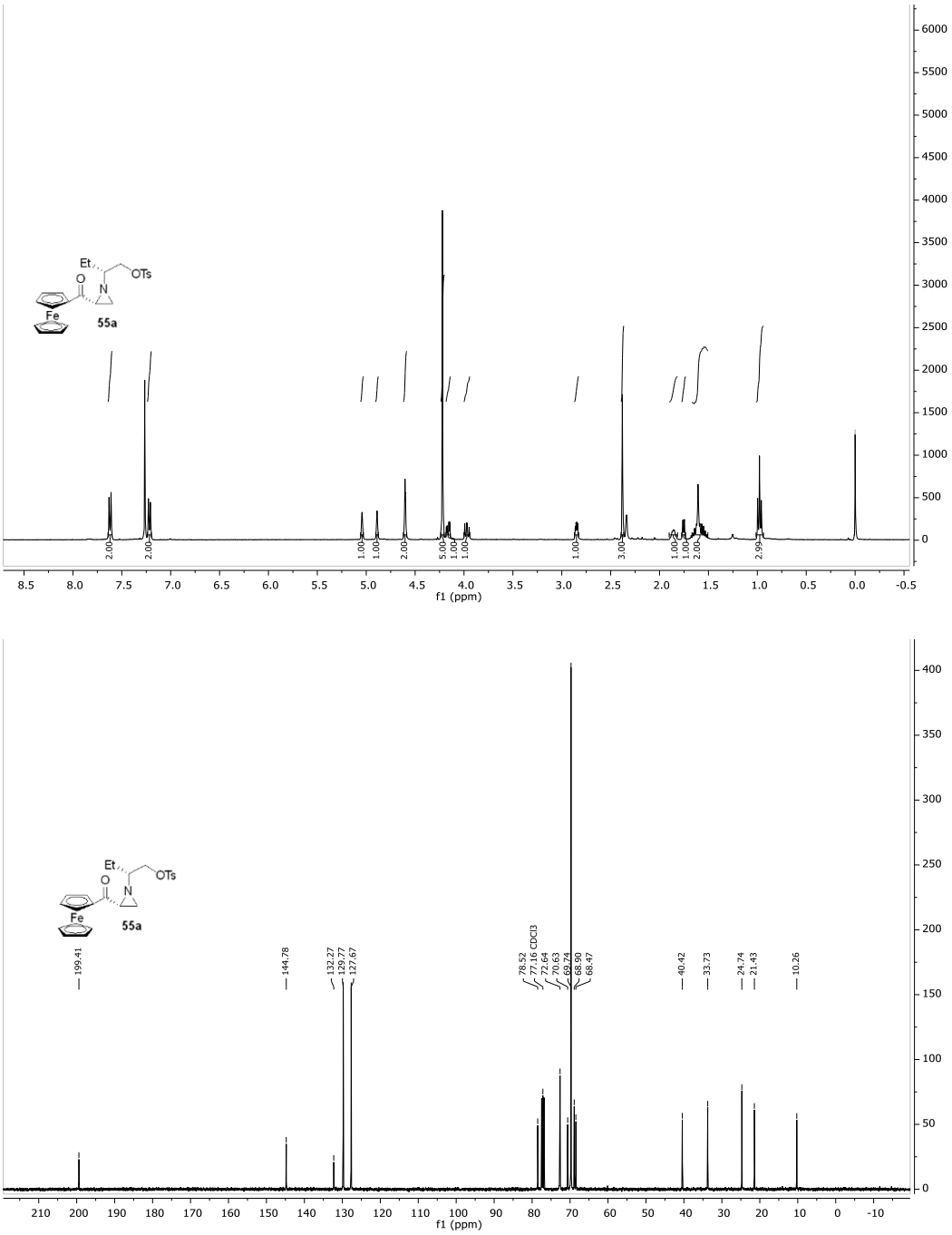


Figure 12. ^{1}H and ^{13}C NMR Spectra of Compound **55a**

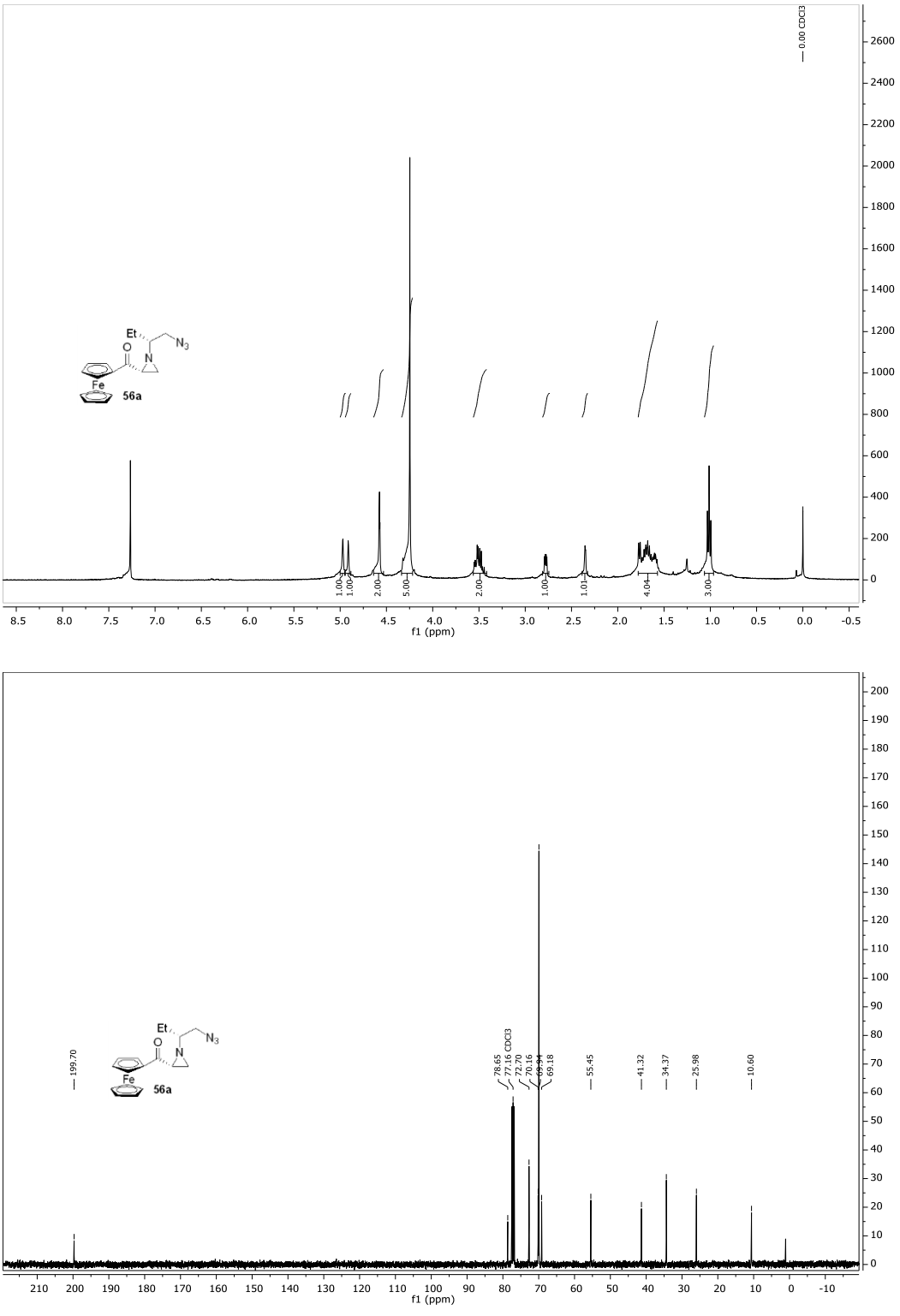


Figure 13. ^{1}H and ^{13}C NMR Spectra of Compound **56a**

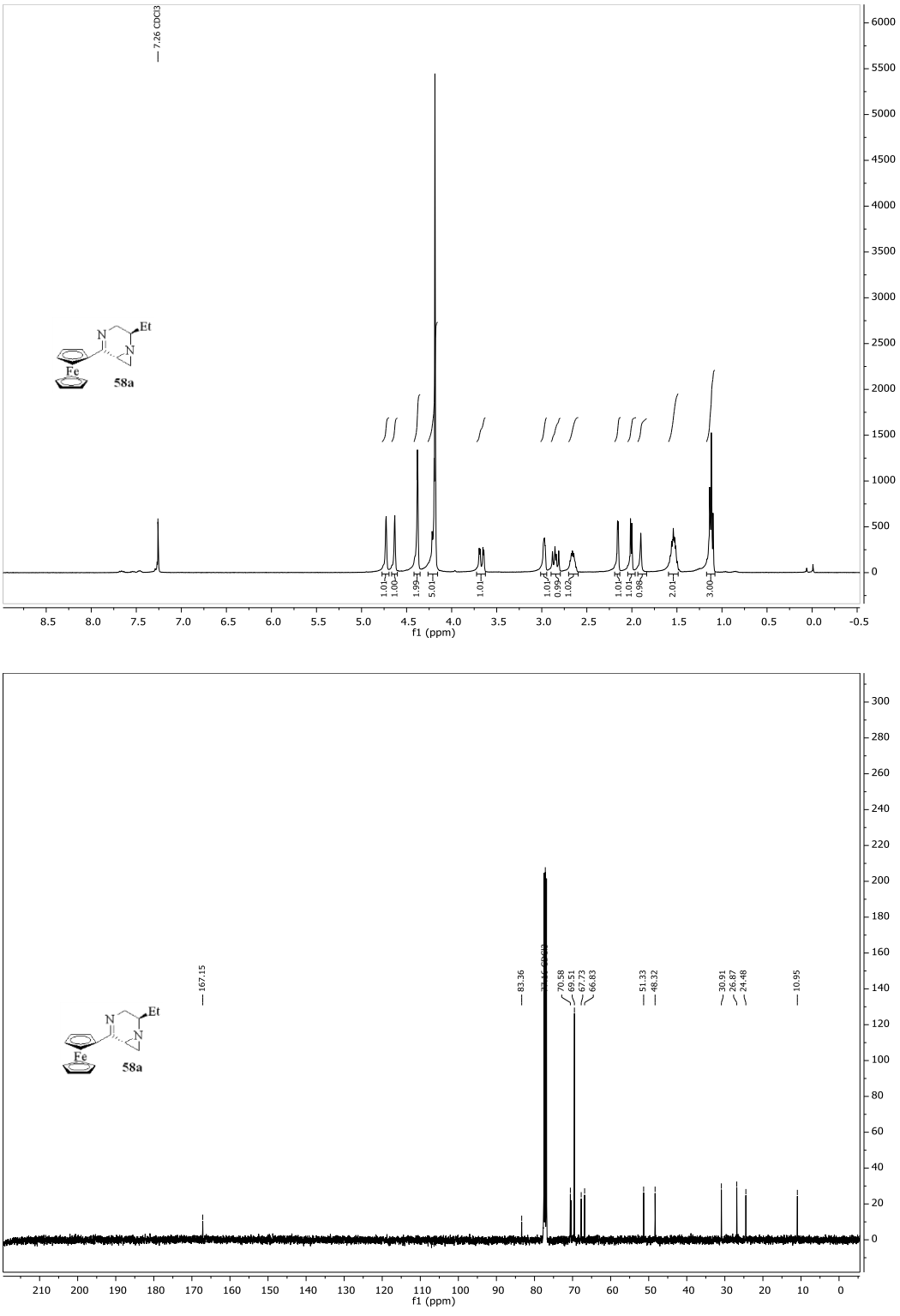


Figure 14. ^{1}H and ^{13}C NMR Spectra of Compound **58a**

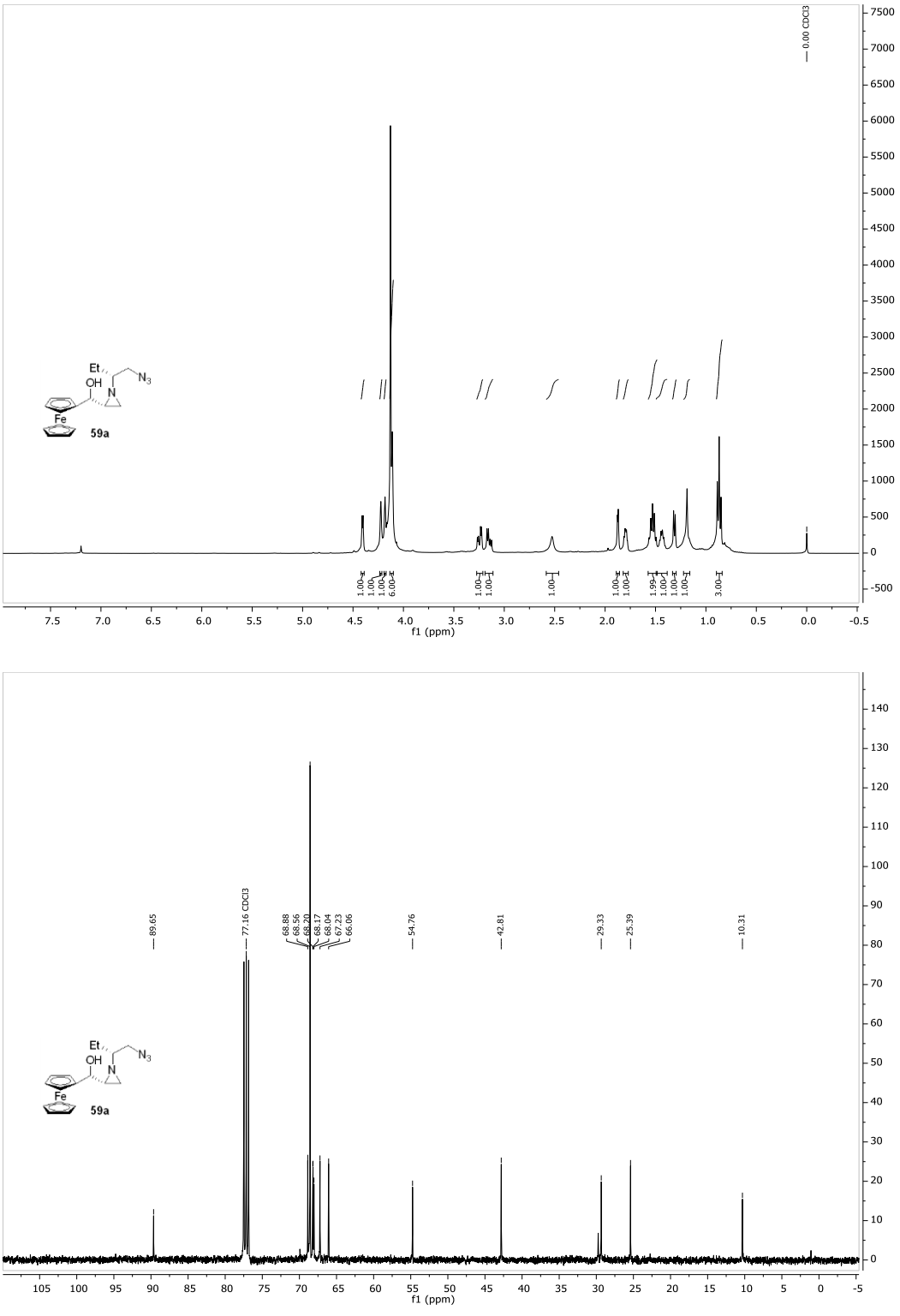


Figure 15. ^{1}H and ^{13}C NMR Spectra of Compound **59a**

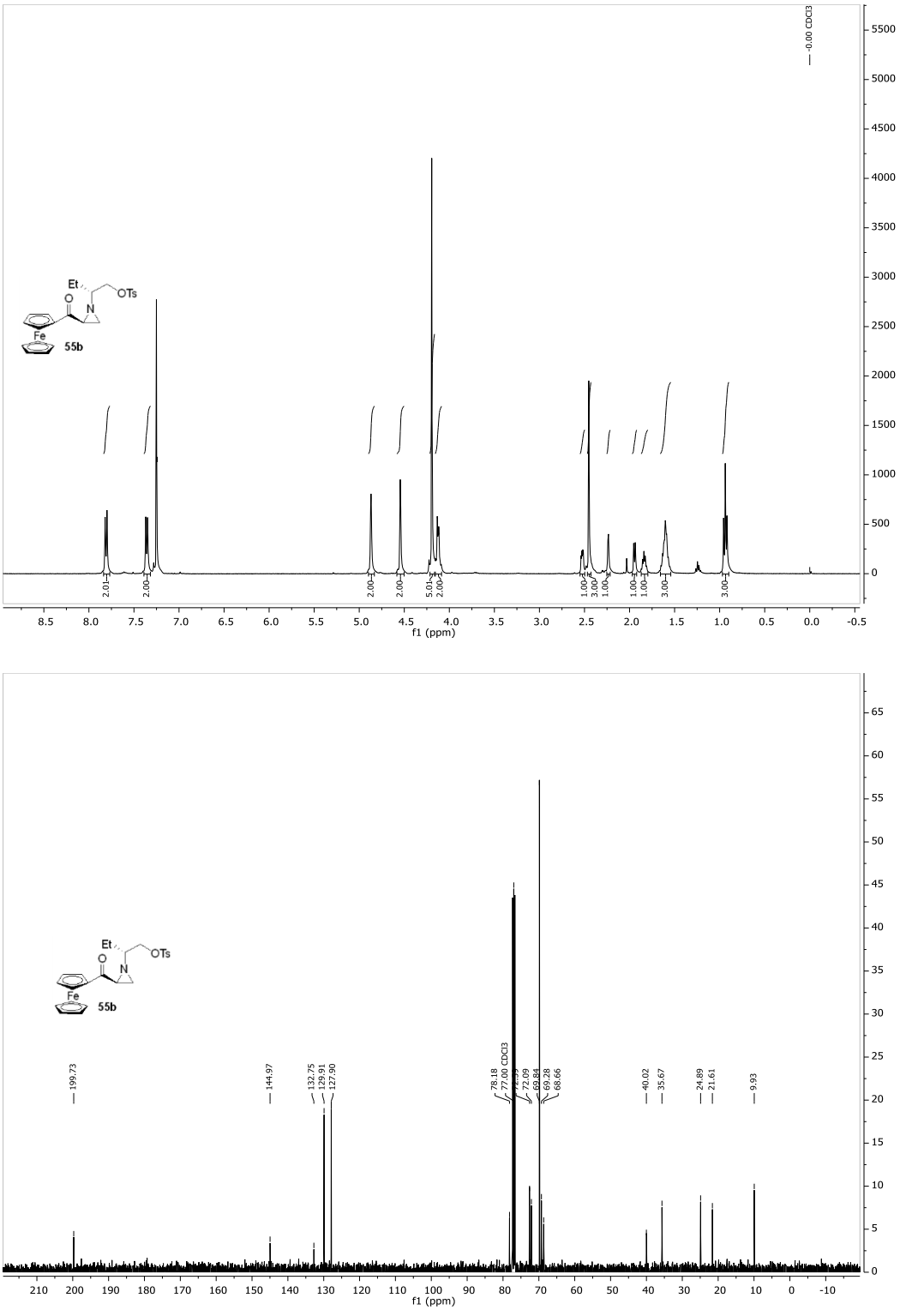


Figure 16. ^{1}H and ^{13}C NMR Spectra of Compound **55b**

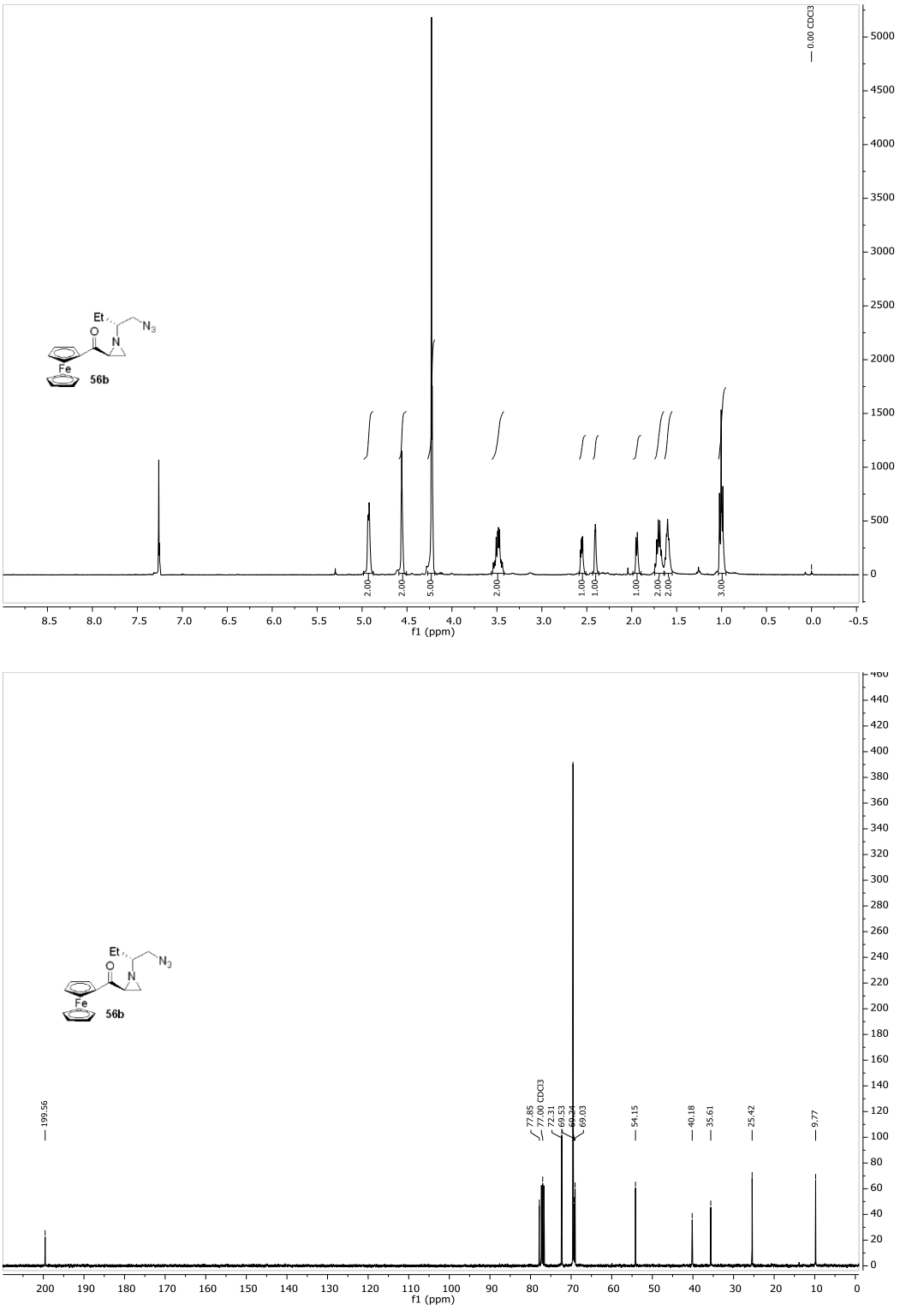


Figure 17. ^{1}H and ^{13}C NMR Spectra of Compound **56b**

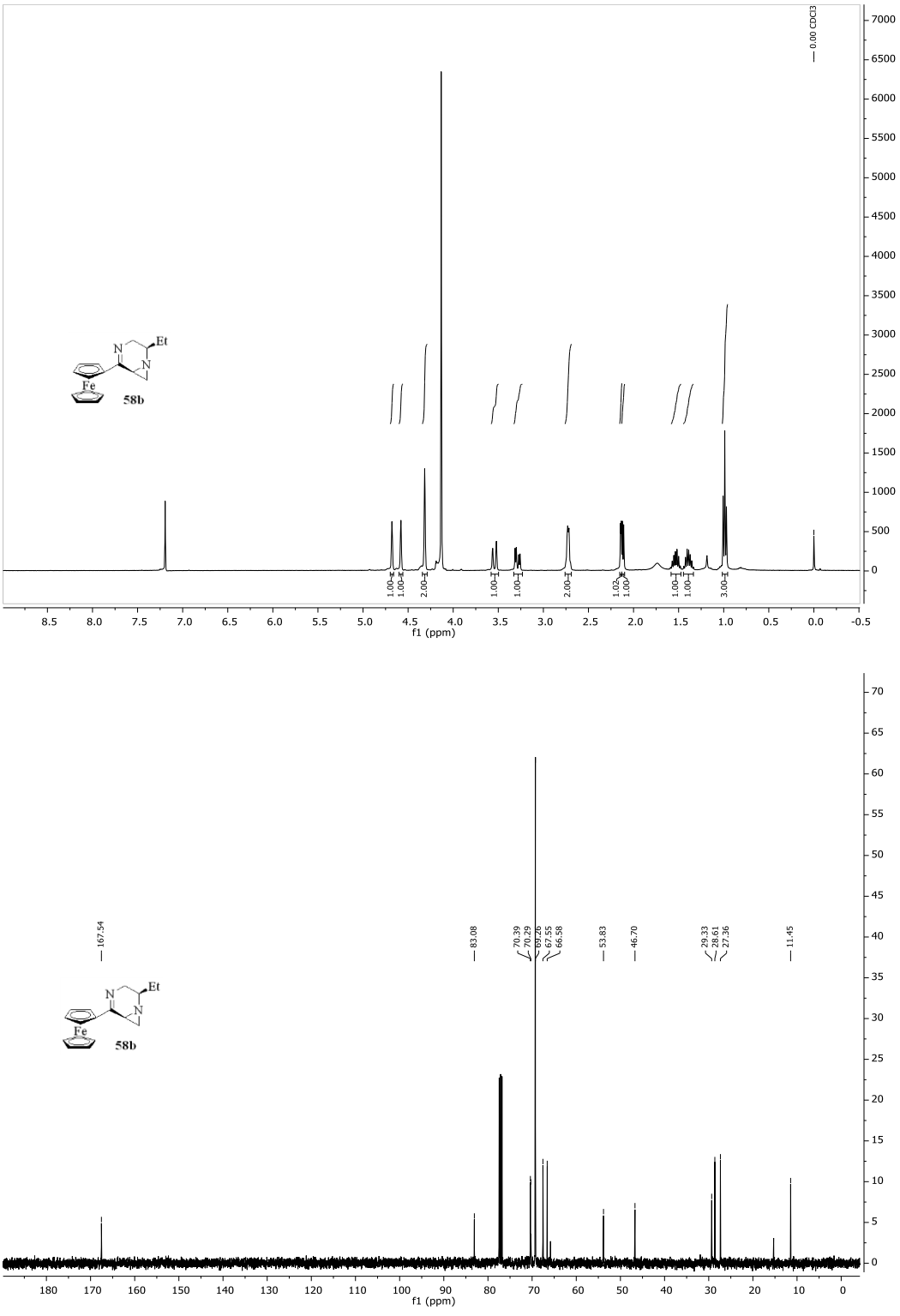


Figure 18. ^{1}H and ^{13}C NMR Spectra of Compound **58b**

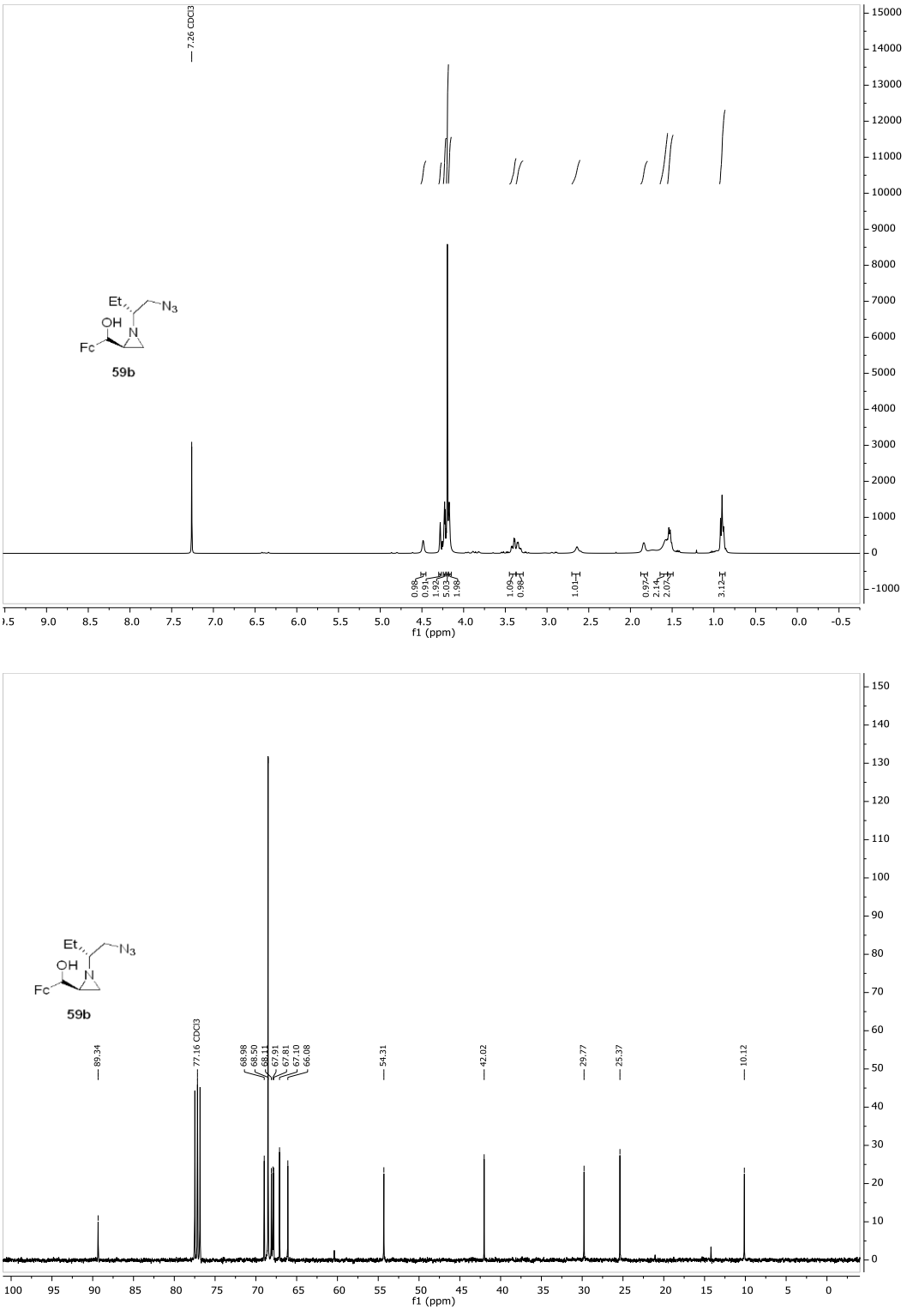


Figure 19. ^{1}H and ^{13}C NMR Spectra of Compound **59b**

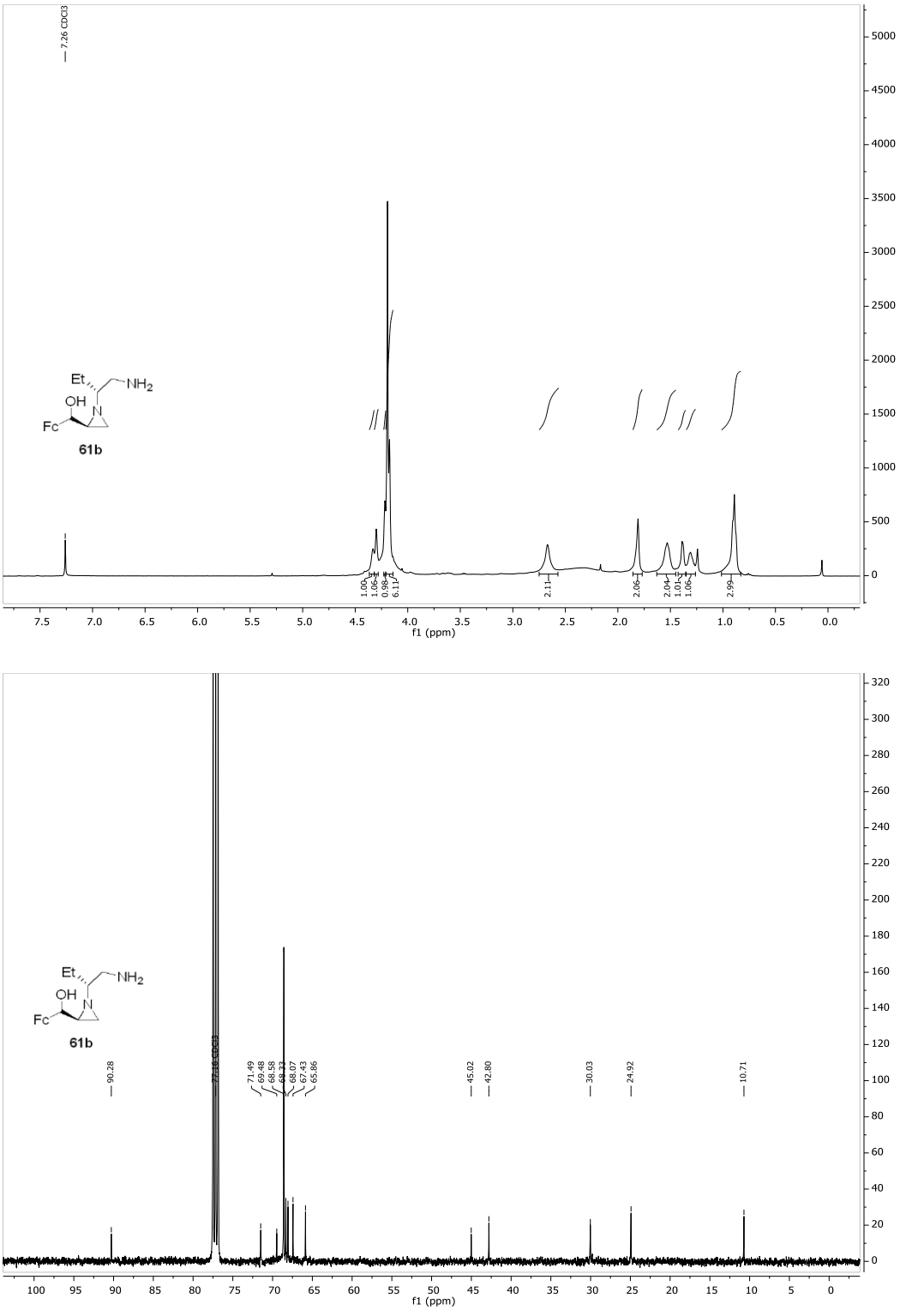


Figure 20. ^{1}H and ^{13}C NMR Spectra of Compound **61b**

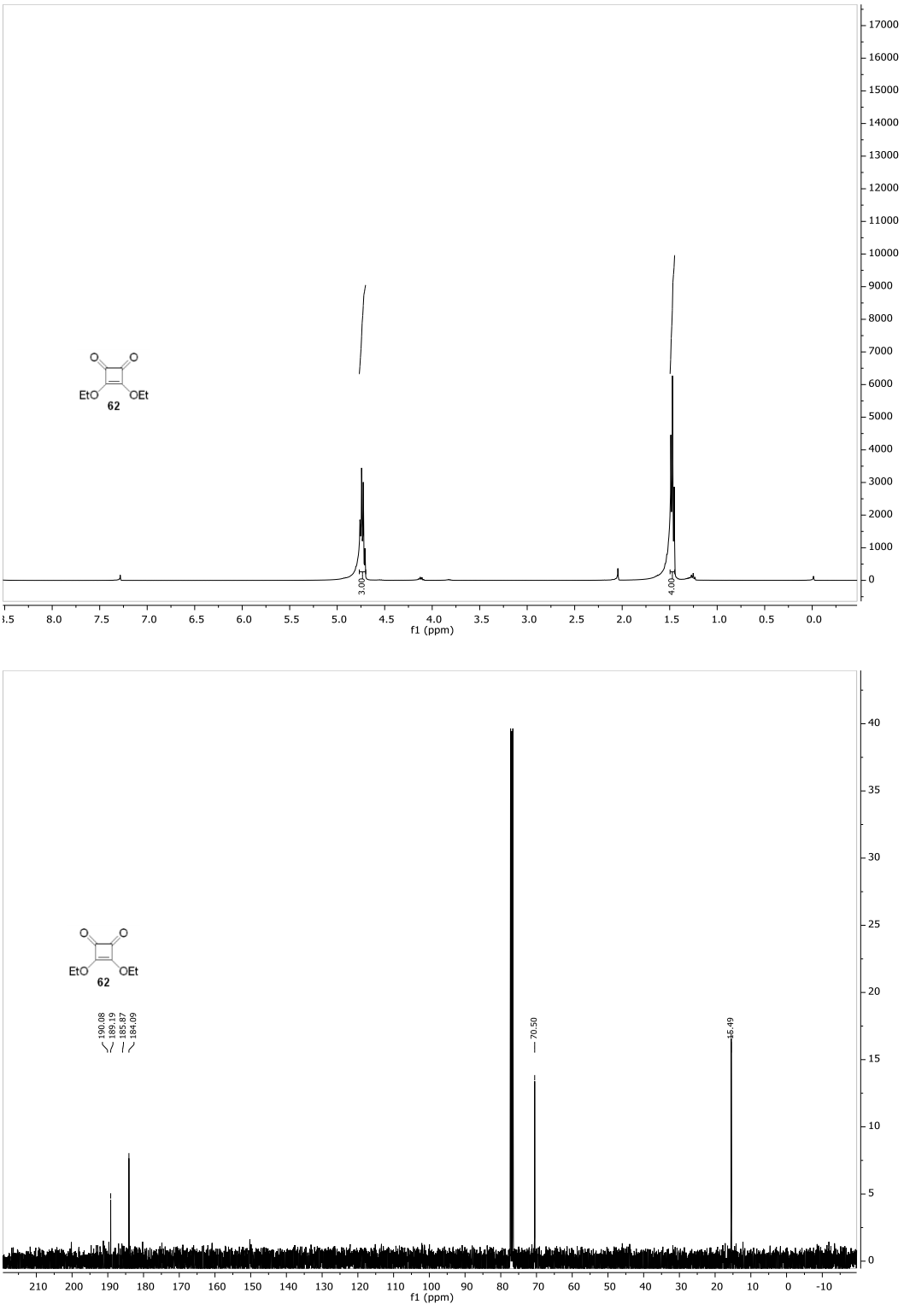


Figure 21. ^{1}H and ^{13}C NMR Spectra of Compound **62**

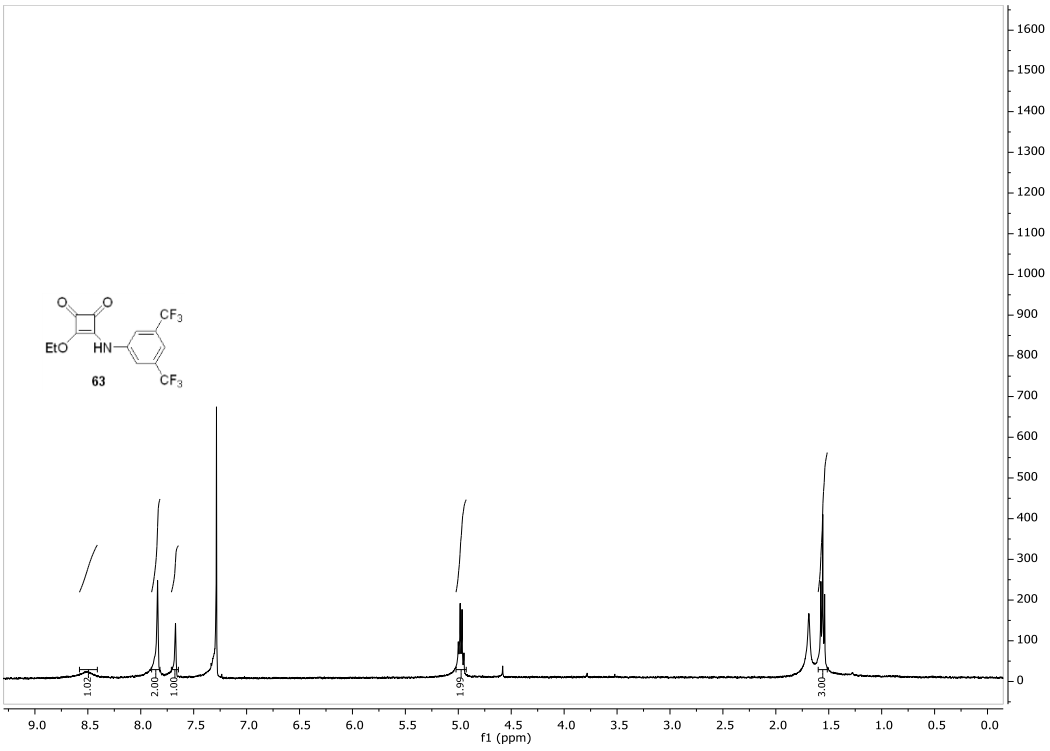


Figure 22. ^{1}H Spectrum of Compound **63**

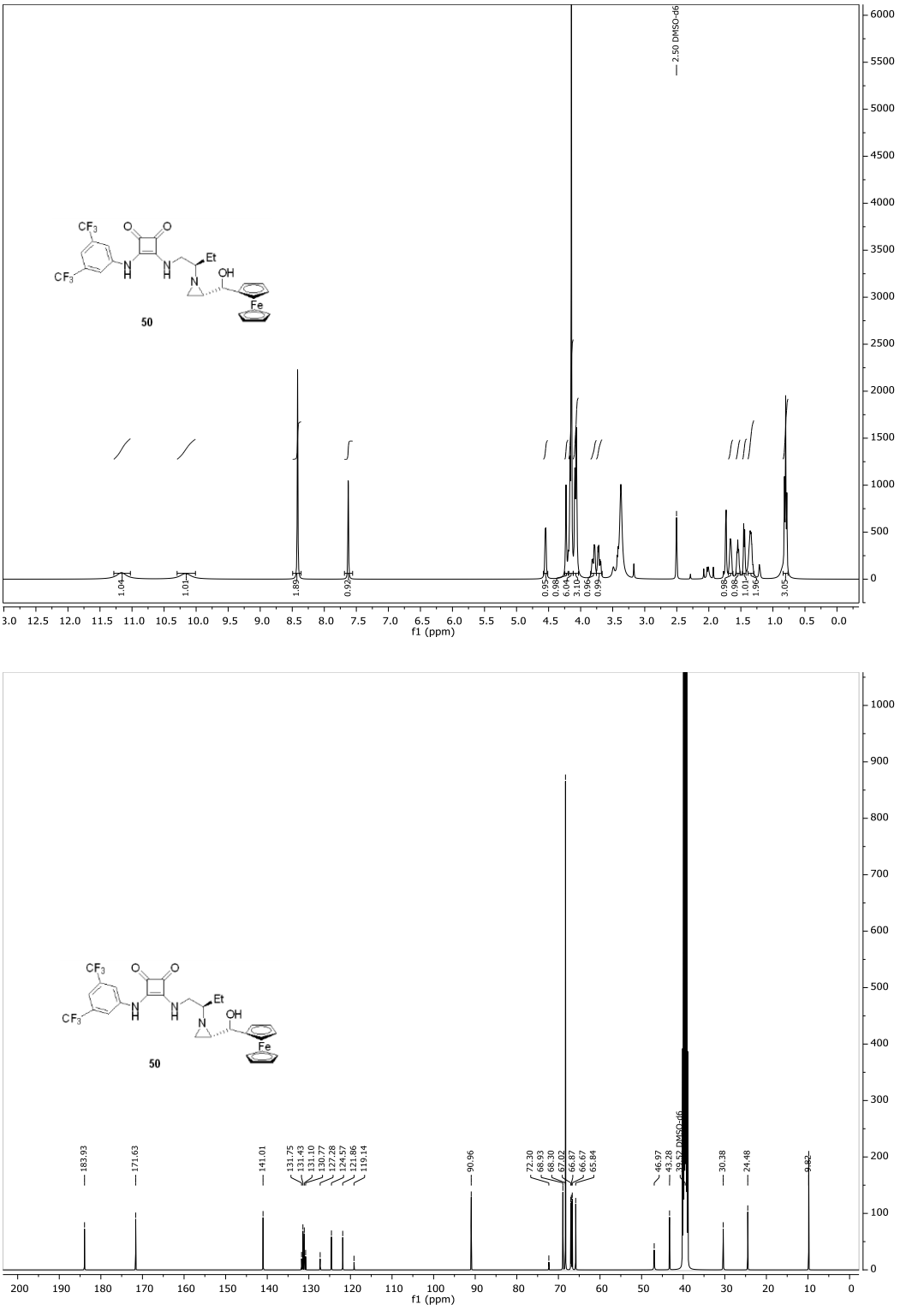


Figure 23. ^{1}H and ^{13}C NMR Spectra of Compound **50**

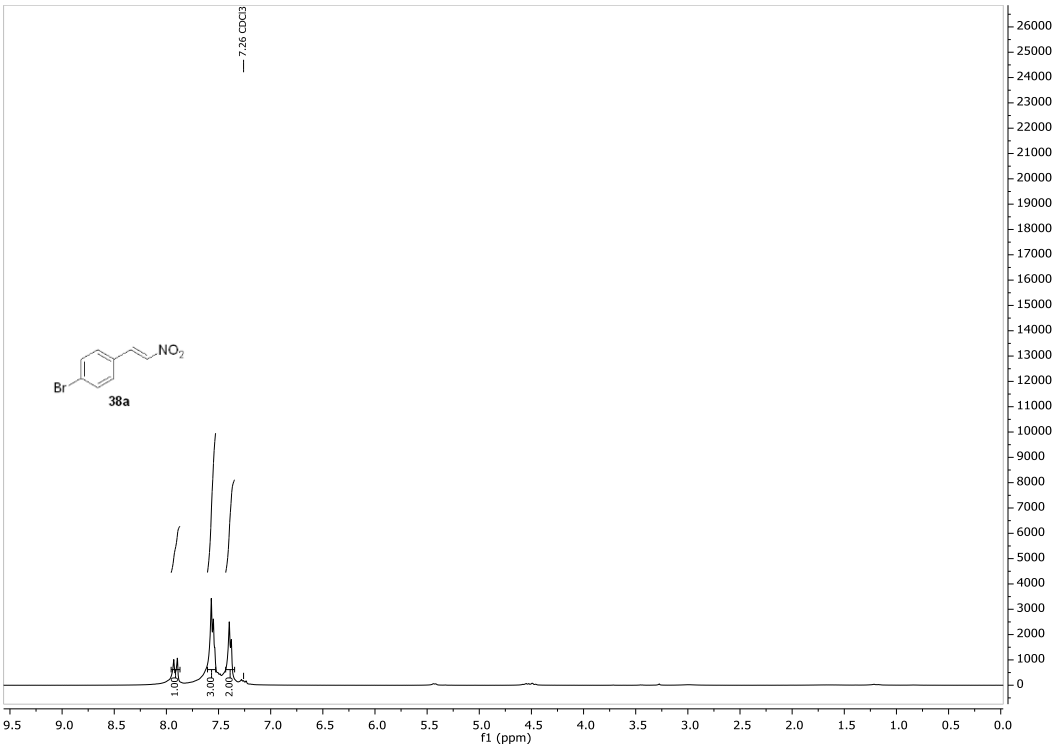


Figure 24. ^{1}H NMR Spectrum of Compound **38a**

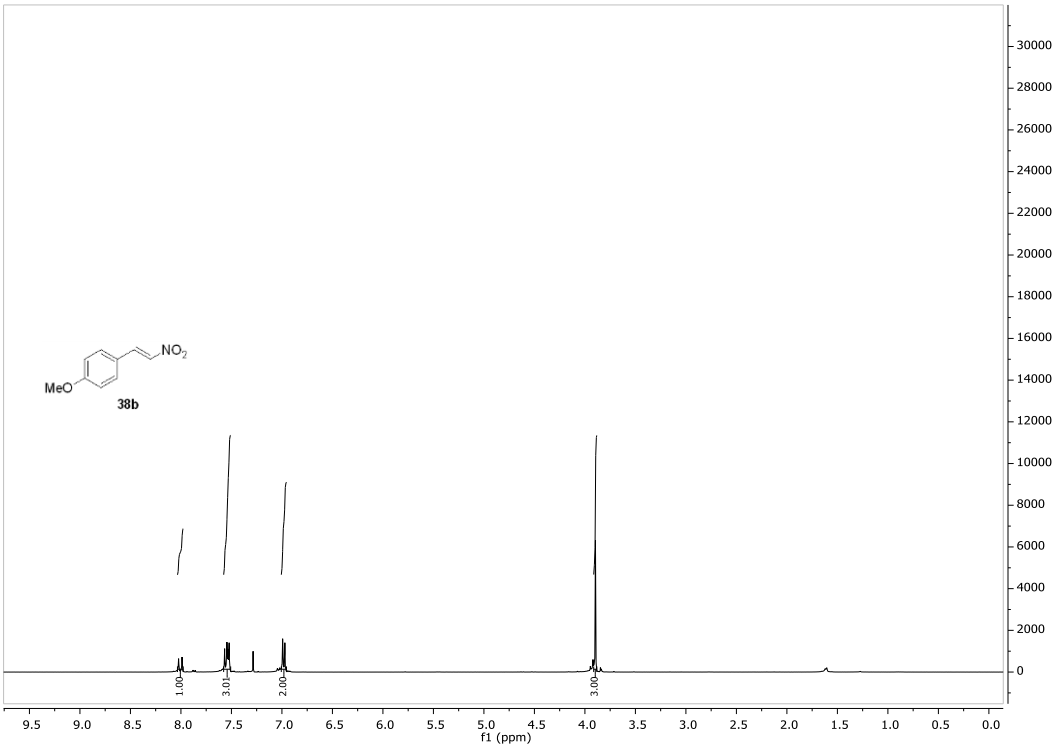


Figure 25. ^{1}H NMR Spectrum of Compound **38b**

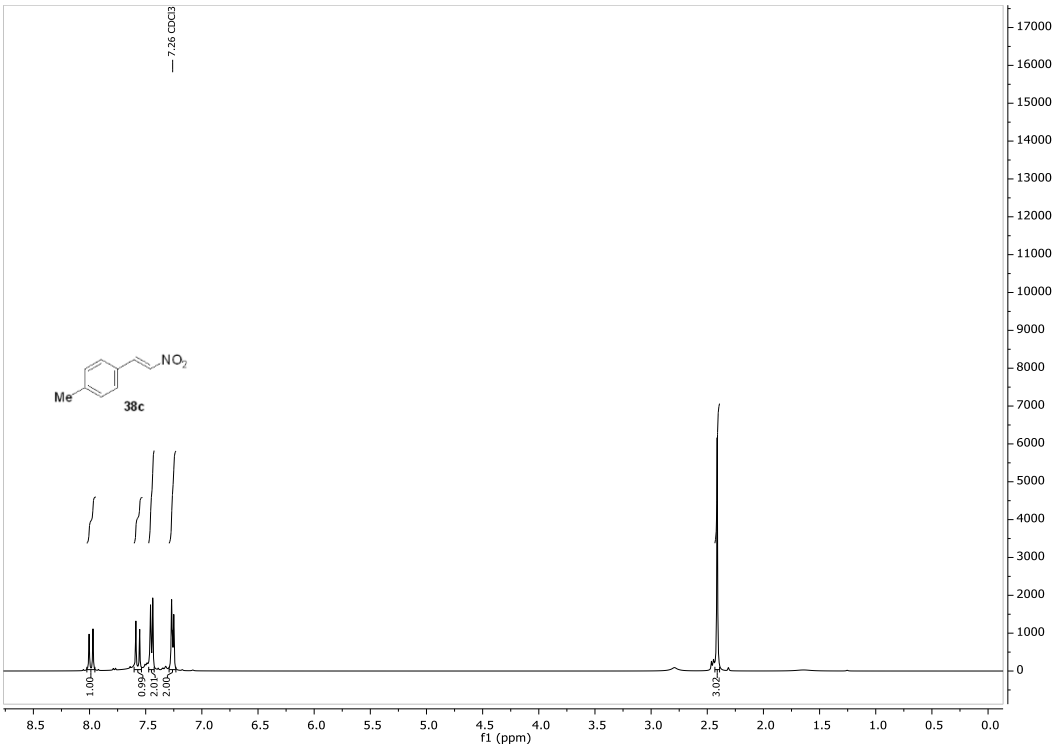


Figure 26. ^{1}H NMR Spectrum of Compound **38c**

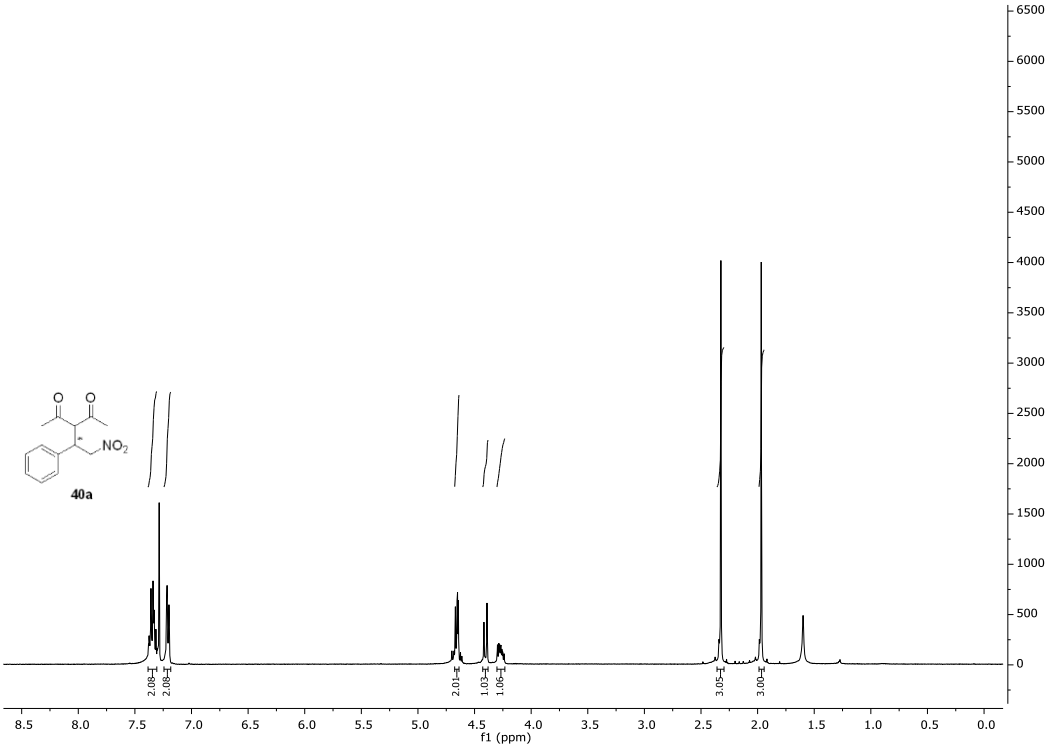


Figure 27. ^{1}H Spectrum of Compound **40a**

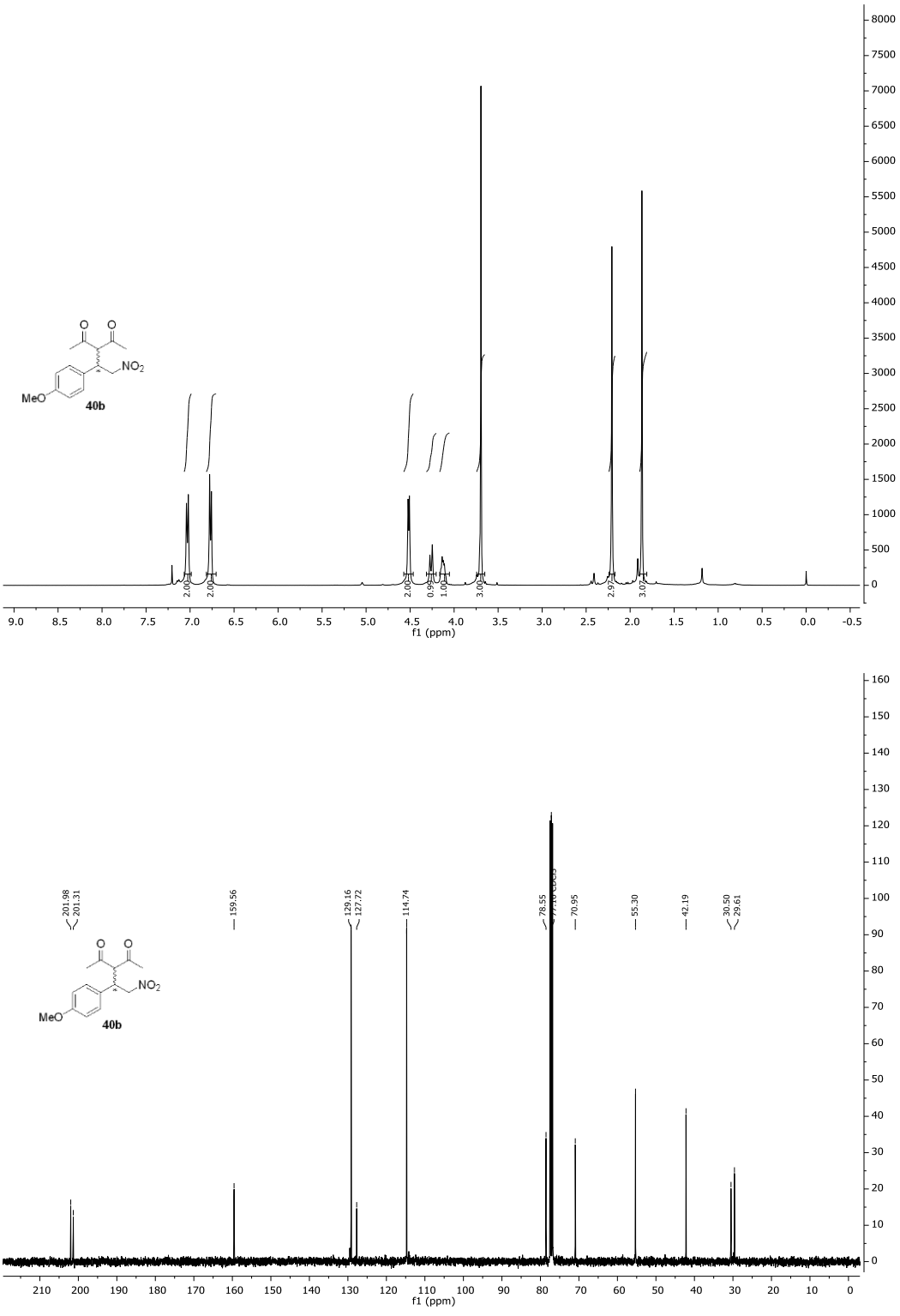


Figure 28. ^{1}H and ^{13}C NMR Spectra of Compound **40b**

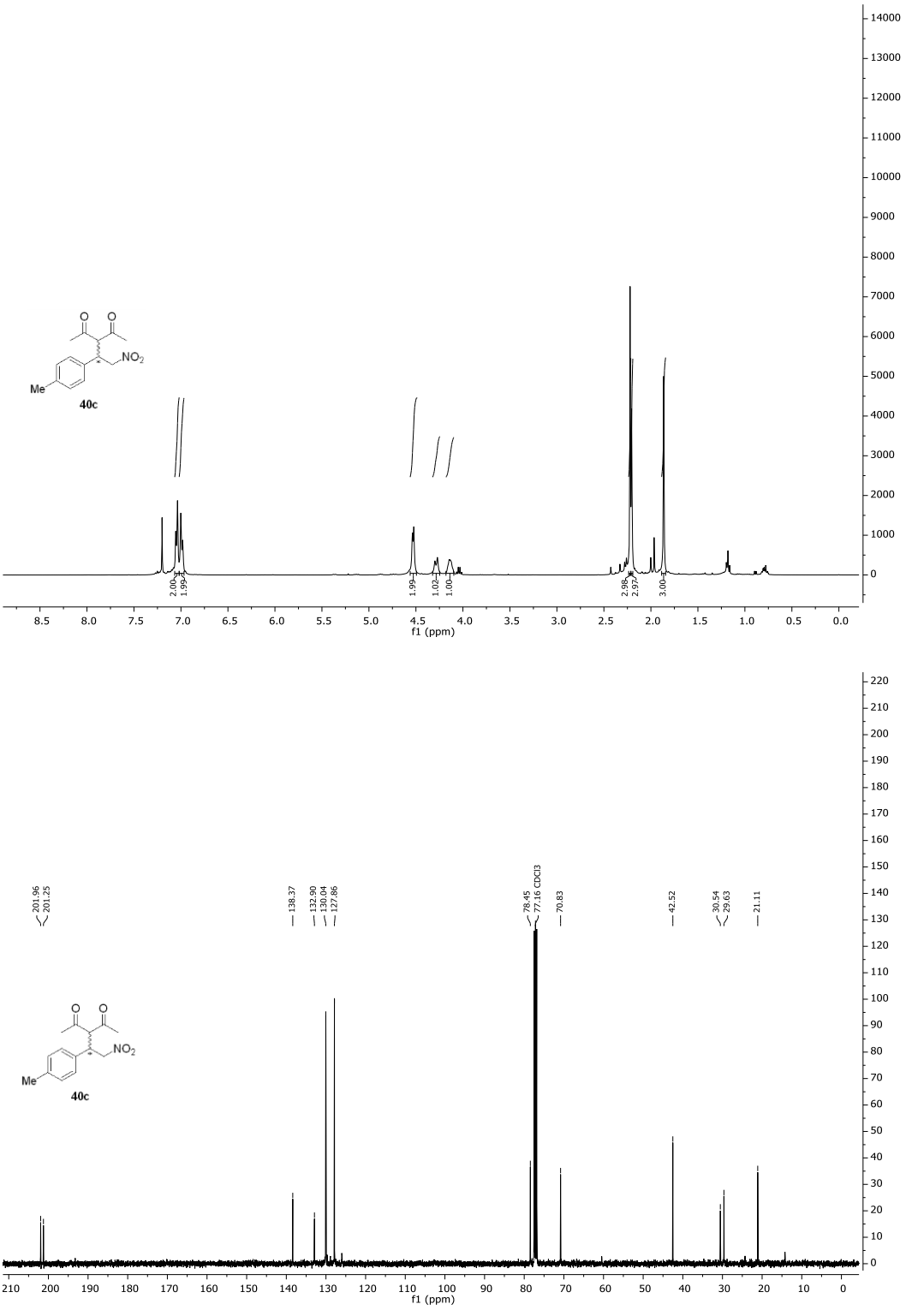


Figure 29. ^{1}H and ^{13}C NMR Spectra of Compound **40c**

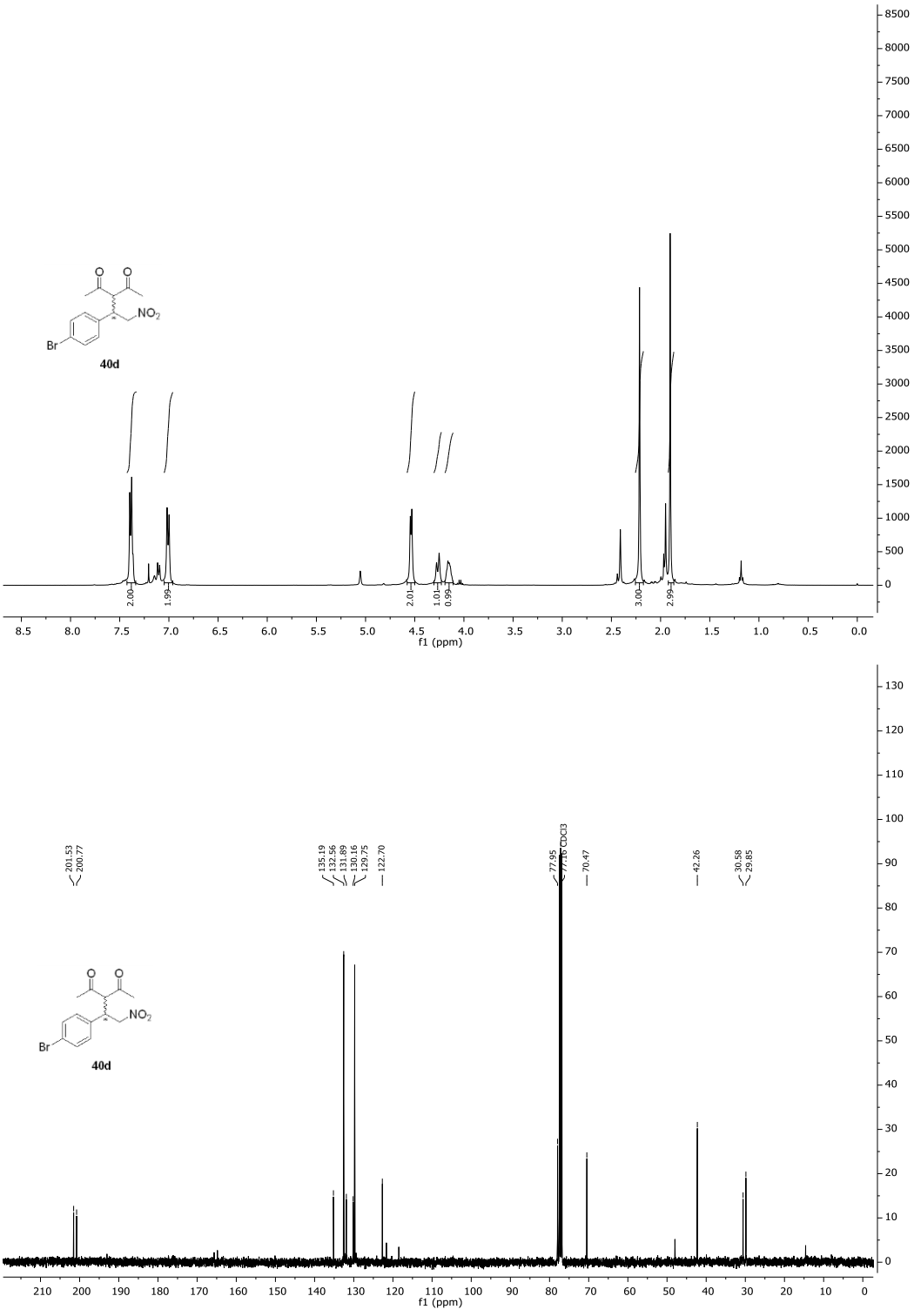


Figure 30. ^{1}H and ^{13}C NMR Spectra of Compound **40d**

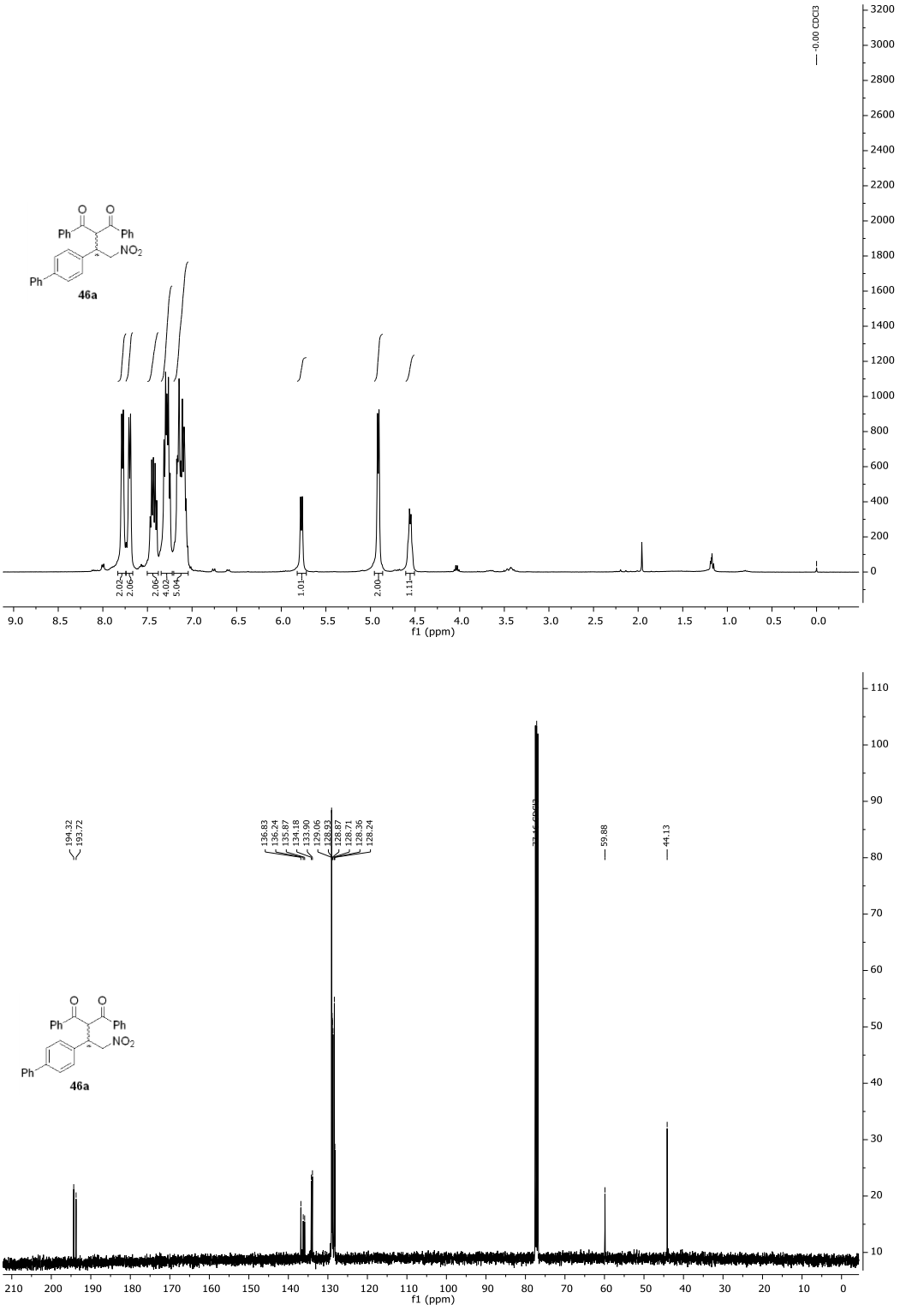
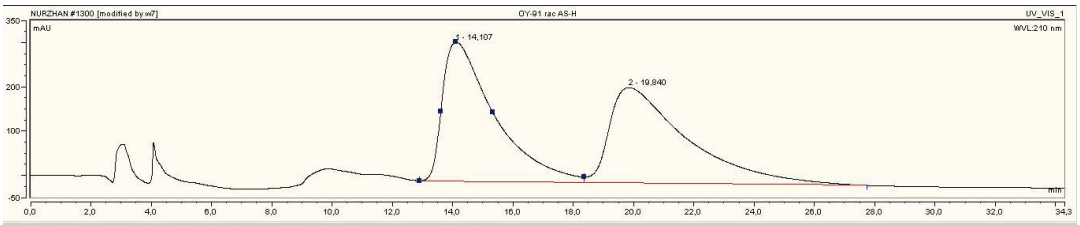


Figure 31. ^{1}H and ^{13}C NMR Spectra of Compound **46a**

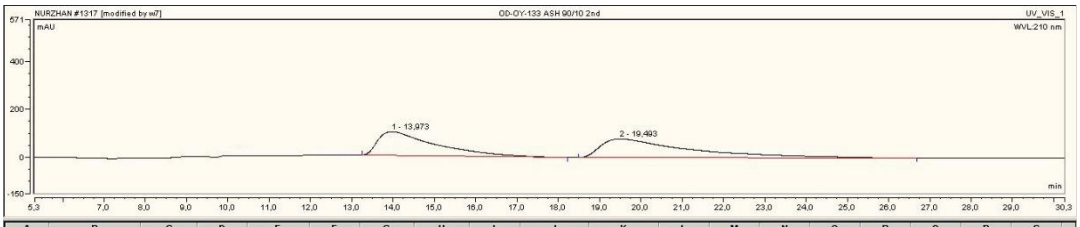
B. HPLC Chromatography

a)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	14,107	627,9616	n.a.	BM*	313,623	49,51	1,60
2	n.a.	19,840	640,2817	n.a.	MB*	215,126	50,49	n.a.
Total:			##########	0,0000		528,749	100,00	

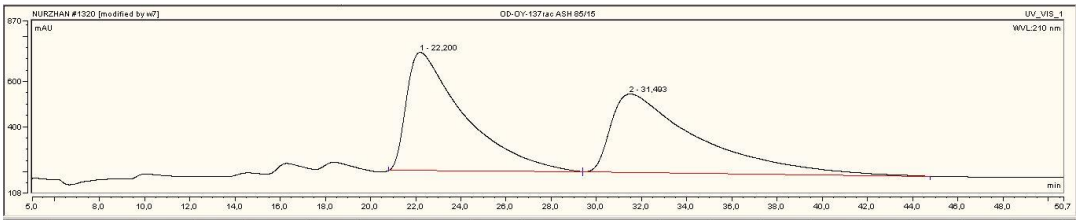
b)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	13,973	159,9726	n.a.	BMB*	98,068	45,46	1,93
2	n.a.	19,493	191,9630	n.a.	BMB*	78,321	54,54	n.a.
Total:			351,9356	0,0000		176,389	100,00	

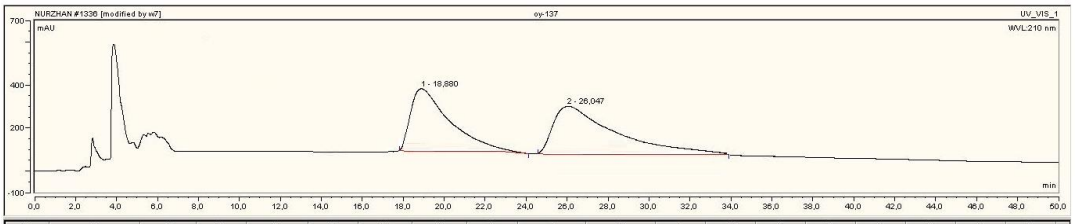
Figure 32. HPLC analysis of compound **40a**, a) racemic, b) 9% ee

a)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	22,200	##########	n.a.	BMb*	524,124	50,13	1,78
2	n.a.	31,493	##########	n.a.	bMB*	346,799	49,87	n.a.
Total:			##########	0,0000		870,923	100,00	

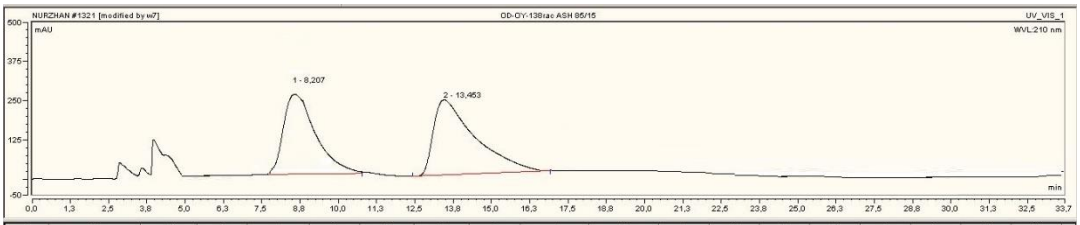
b)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	18,880	548,0471	n.a.	BMB*	257,694	45,92	1,96
2	n.a.	26,047	645,3722	n.a.	BMB*	207,710	54,08	n.a.
Total:			##########	0,0000		465,404	100,00	

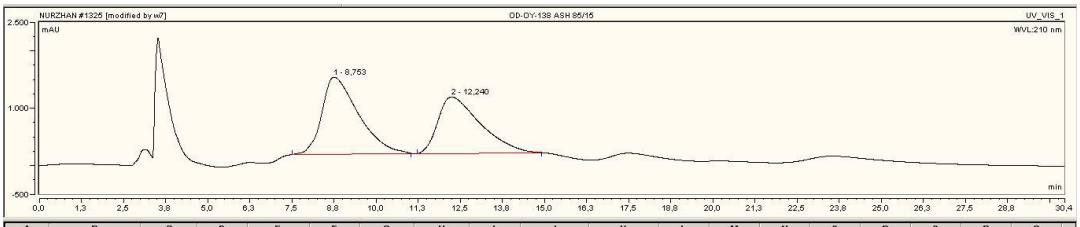
Figure 33. HPLC analysis of compound **40b**, a) racemic, b) 8% ee

a)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,207	377,2121	n.a.	BMB*	362,669	50,05	2,55
2	n.a.	13,453	376,5132	n.a.	BMB*	239,458	49,95	n.a.
Total:			753,7253	0,0000		602,127	100,00	

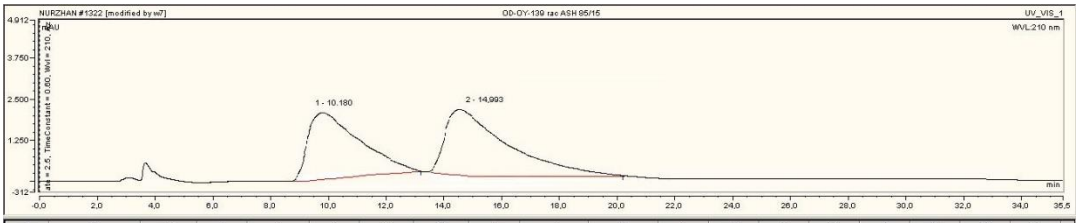
b)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,753	##########	n.a.	BMB*	1341,465	53,97	1,67
2	n.a.	12,240	##########	n.a.	BMB*	984,643	46,03	n.a.
Total:			##########	0,0000		2326,108	100,00	

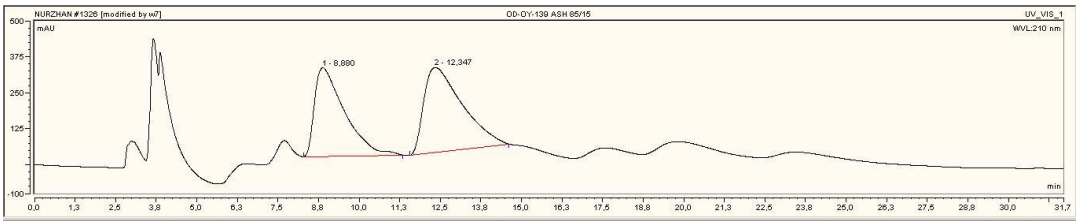
Figure 34. HPLC analysis of compound **40c**, a) racemic, b) 8% ee

a)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	10,180	234,4858		n.a. BMB*	309,988	49,50	3,06
2	n.a.	14,993	239,2623		n.a. BMB*	193,516	50,50	n.a.
Total:			473,7481	0,0000		503,504	100,00	

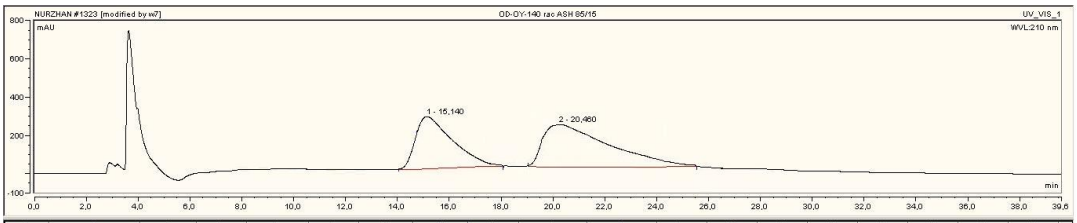
b)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	8,880	328,3957		n.a. BMB*	306,899	44,91	1,82
2	n.a.	12,347	402,7769		n.a. BMB*	295,005	55,09	n.a.
Total:			731,1726	0,0000		601,904	100,00	

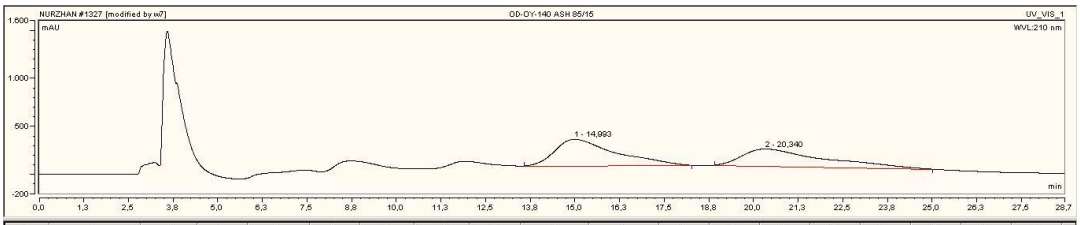
Figure 35. HPLC analysis of compound **40d**, a) racemic, b) 10% ee

a)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	15,140	63,6051	n.a.	BMB*	92,361	49,86	3,54
2	n.a.	20,460	63,9521	n.a.	BMB*	60,638	50,14	n.a.
Total:			127,5572	0,0000		152,999	100,00	

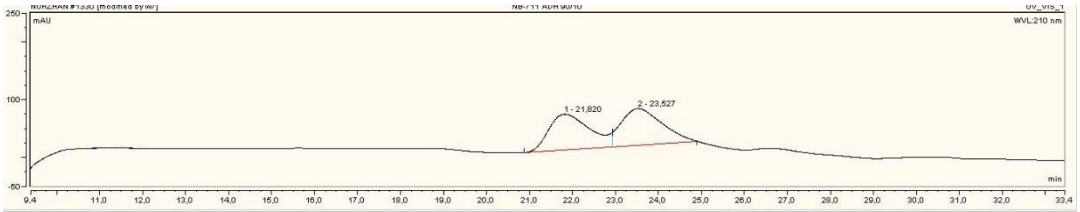
b)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	14,993	542,1645	n.a.	BMB*	275,336	53,37	1,61
2	n.a.	20,340	473,6631	n.a.	BMB*	177,485	46,63	n.a.
Total:			########	0,0000		452,821	100,00	

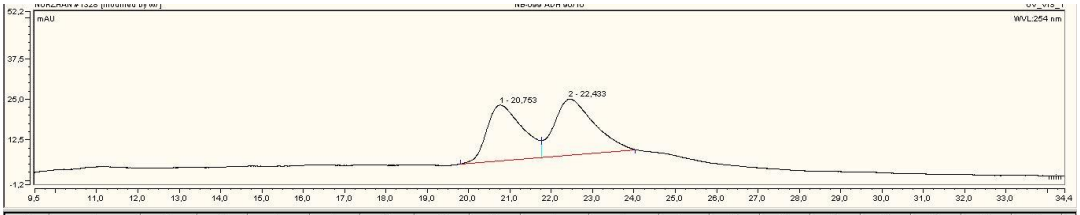
Figure 36. HPLC analysis of compound **46a**, a) racemic, b) 7% ee

a)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	21,820	68,3471		n.a.	BM *	61,730	49,78	0,93
2	n.a.	23,527	68,9592		n.a.	MB*	63,041	50,22	n.a.
Total:			137,3062	0,0000			124,771	100,00	

b)



No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	20,753	17,0319		n.a.	BM *	17,173	46,85	0,98
2	n.a.	22,433	19,3191		n.a.	MB*	17,213	53,15	n.a.
Total:			36,3509	0,0000			34,386	100,00	

Figure 37. HPLC analysis of compound **65**, a) racemic, b) 6% ee