Cu-CATALYZED SELECTIVE MONO-*N*-HETEROARYLATION OF CHIRAL DIAMINES
&
ASYMMETRIC CONJUGATE ADDITION OF DIBENZOYLMETHANE TO TRANS-*BETA*-NITROSTYRENE

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MUHAMMET YAĞIZ ÜNVER

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ABSTRACT

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In the first part of the thesis, a new methodology has been developed to desymmetrize *trans*-(*R*,*R*)-cyclohexane-1,2-diamine, a C_2-symmetrical most demanding chiral backbone, by using copper chemistry (modified Ullman). Various halo substituted nitrogen heteroaromatic compounds were selectively introduced to one of the diamine unit. 10 novel coupling products were synthesized in a single step procedure. These resultant coupling products have amidine motifs which can be valuable candidates as a basic catalophoric part in the context of bifunctional organocatalyst.

The second part of the thesis comprises the asymmetric organocatalytic Michael addition of dibenzoylmethane to various β-nitroolefins. 2-AminoDMAP/Squaramide type bifunctional acid/base organocatalyst, developed in our research group, has been used under optimized condition with very low catalyst loading and short reaction duration. Enantioselectivities of 14 chiral Michael addition products are varied between 80-98% ee.

Keywords: asymmetric synthesis, organocatalyst, copper catalysis, Michael addition, chiral mono amidine

ÖZ

BAKIR KATALİZÖRÜ İLE KİRAL DİAMİNLERE HETEROAROMATİKLERİN SELEKTİF OLARAK TAKILMASI
&
DİBENZOİLMETANIN TRANS-*BETA*-NİTROSTİREN ASİMETRİK KONJUGE KATILMA REAKSİYONU

Ünver, Muhammet Yağız

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Cihangir Tanyeli

Ağustos 2013, 91 sayfa

Bu çalışmanın ilk kısmında bakır katalizörlüğünde en yaygın olarak kullanılan kiral C_2-simetrik *trans*-(*R,R*)-siklohekzan-1,2-diaminden C_1-simetrik yapıya geçişi sağlayacak bir metod geliştirilmiştir. Bu metod ile halojen takılı azot içeren heteroaromatikler kiral C_2-simetrik diamine seçici olarak takılarak 10 adet yeni ürün tek basamakta sentezlenmiştir. Bu amidin motifine sahip 10 adet ürün bifonksiyonel organokatalizör alanında önemli aday bazik katalaforlardır.

Çalışmanın ikinci kısmında, dibenzoilmetanın nitrostirene conjuge katılma reaksiyonunda grubumuzda geliştirilmiş olan 2-AminoDMAP/Skuaramit bifonksiyonel organokatalizörü denenmiş, 14 adet kiral Michael ürünü çok düşük katalizör miktarı ve kısa reaksiyon süresinde yüksek enantiyomerik zenginliklerde sentezlenmiştir. Enantiyomerik zenginliklerin 80-98% arasında olduğu gözlemlenmiştir.

Anahtar Kelimeler: Asimetrik sentez, organokatalizör, bakır katalizörü, konjüge katılma, kiral mono amidin

To my dear family…

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LIST OF ABBREVIATIONS

DMAP: 4-Dimethylaminopyridine

SOMO: Singly Occupied Molecular Orbital

HOMO: Highest Occupied Molecular Orbital

LUMO: Lowest Unoccupied Molecular Orbital

DMSO: Dimethyl sulfoxide

THF: Tetrahydrofuran

DCM: Dichloromethane

DMF: Dimethylformamide

PG: Protecting Group

BINAM: 1,1'-Binaphthalene-2,2'-diamine

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CHAPTER 1

INTRODUCTION

1.1 An Overview to Chirality and Asymmetric Synthesis

Chirality concept was firstly introduced by Lord Kelvin in 1884.[1] Very simply, in order to be *chiral* system or molecule must be nonsuperimposable with its mirror image. The term was derived from a Greek word which has a meaning of hand. Human hands are the best example for chiral molecules, both hands look same at first but they are actually nonsuperimposable mirror images of each other. These two mirror images are called enantiomers.

Chirality can be observed in living systems, i.e. in enzymes, in receptors, in DNA and RNA structures etc. containing only one enantiomeric form. For example, a molecule which is a biologically active compound interacts with its receptor in a chiral manner. Therefore, a drug having both forms of enantiomers may lead to a side effect due to the different interaction of both enantiomers with receptor site.[2]

There are some examples of enantiomers showing some different and interesting behaviors. For instance, one enantiomer of Carvone smells like spearmint and the other one smells like caraway. The other interesting example is Brevicomine. One enantiomeric form of Brevicomine (+) is attractive for western pine beetles but the other one is not (Figure 1).

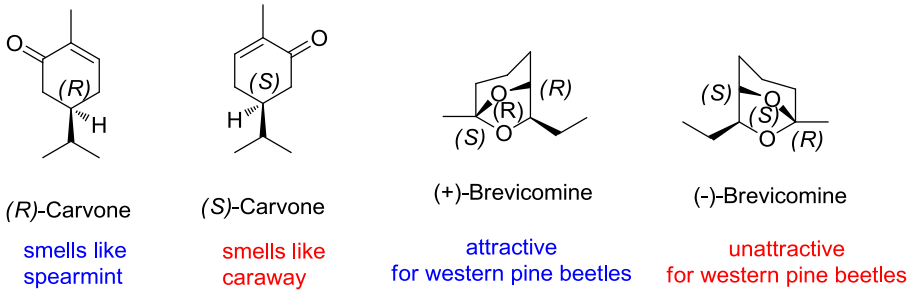


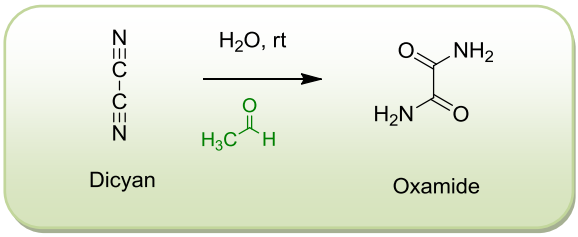
Figure 1. Examples for different, interesting behaviours of enantiomers

Asymmetric synthesis broadly can be defined as a reaction in which an achiral substance is converted into chiral one by producing unequal amount of stereoisomeric products. Stereoisomeric products can be obtained in different ways such as using transition metal catalysts with chiral ligands, biocatalysts or organocatalysts.[3] In this thesis the focus will be on organocatalysis. Asymmetric synthesis has been an important and popular field because high enantiomeric purity is needed in the production of especially drugs or agrochemicals.

1.2 Organocatalysis

Very simply, the term, *organocatalysis*, comes from *organic* and *catalysis*. Organocatalysis has gained a great popularity in recent years. Organocatalysts are pure compounds containing mainly carbon, hydrogen, nitrogen, oxygen, sulphur and sometimes phosphorous atoms and no transition metal is used in their active sites. The term was firstly introduced by David MacMillan in 2000. He described organocatalysis as speeding up a reaction by using catalytic or substoichometric quantity of small organic molecules.[4a]

Although popularity of organocatalysis has arisen recently, the history dates back to 1860. The first organocatalyst was acetaldehyde and firstly used by Justus von Liebig in the synthesis of oxamide from dicyan and water (Scheme 1).[5]



Scheme 1. First organocatalytic oxamide synthesis

1.2.1 Advantages of Organocatalysis

In asymmetric synthesis, there are some different methods to get optically pure compounds. These are bio-catalysis, transition metal catalysis and organocatalysis.[6]

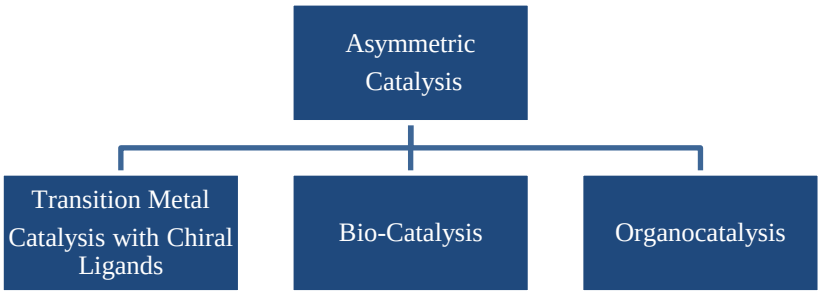


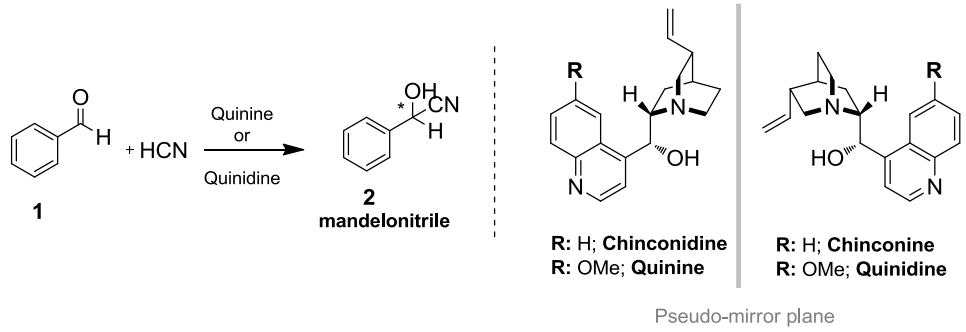
Figure 2. Three techniques in asymmetric synthesis

In biocatalysis chiral biological molecules are used as catalyst and also it is possible to get high enantioselectivity by using synthetic transition metal complexes. The third type is organocatalysis and it has some advantages over transition metal catalysis and bio-catalysis.

Organocatalysts are usually robust, inexpensive, nontoxic compounds and are readily available small organic molecules. They are quite inert molecules toward moisture and air, in this way most troublesome reaction conditions such as inert atmosphere, very low temperatures and dry solvents and chemicals are not needed. In addition, in pharmaceutical products, due to the absence of metal residues they are much more valuable and attractive because there is no tolerance for metal in pharma industry.[4a]

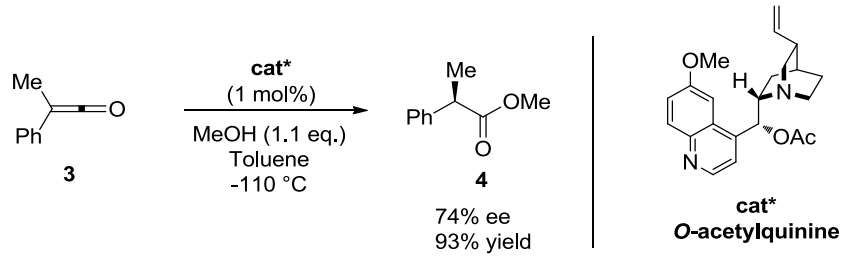
1.2.2 History of Asymmetric Organocatalysis

The first example in the field of asymmetric organocatalysis was reported in 1912. It was the enantioselective addition of HCN to benzaldehyde **(1)** *via* cinchona alkaloids quinine and quinidine published by Bredig and Fiske.[7] Unfortunately, the enantioselectivity was not high enough. These two catalysts are the first examples opened the doors widely for next generation organocatalysts (Scheme 2).



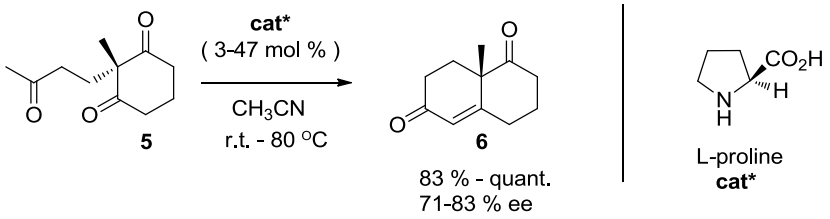
Scheme 2. First asymmetric organocatalytic reaction

Until the 1960's, there was no remarkable improvement in that field. In 1960, Paracejus et al. published a paper about enantioselective addition of methanol to phenylmethylketene **(3)** by using alkaloids as catalyst. The results were quite remarkable. In that reaction, *O*-acetylquinine was used as catalyst with 1 mol% catalyst loading, and 74% ee was achieved for the desired product **4** (Scheme 3).[8]



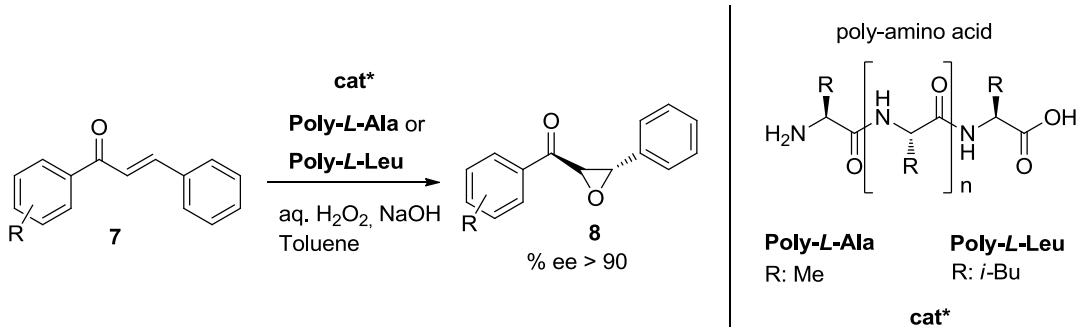
Scheme 3. First remarkable work on asymmetric organocatalysis

In 1971, a new enantioselective organocatalytic reaction was discovered by Hajos, Parrish, Eder, Sauer and Wiechert. They accomplished an intramolecular asymmetric aldol cyclodehydration of an achiral trione **5** *via* L-proline to afford bicyclic product **6** up to 83% ee (Scheme 4).[9]



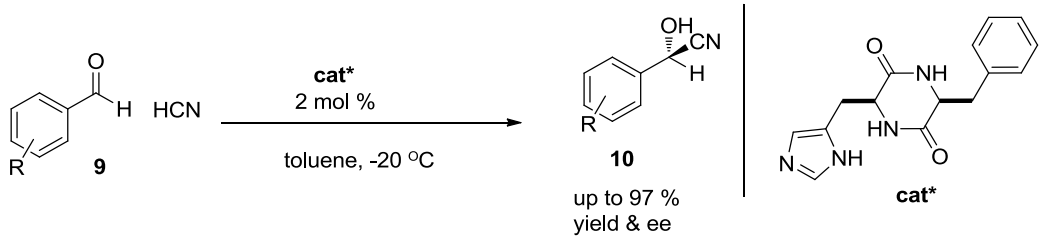
Scheme 4. The Hajos-Parrish-Eder-Sauer-Wiechert reaction

At around 1980s, organocatalytic epoxidation of chalcones **7** with alkaline peroxide catalyzed by poly aminoacids, known as Julia-Colonna epoxidation, gave the corresponding products **8** greater than the 90% ee values (Scheme 5).[4b,c]



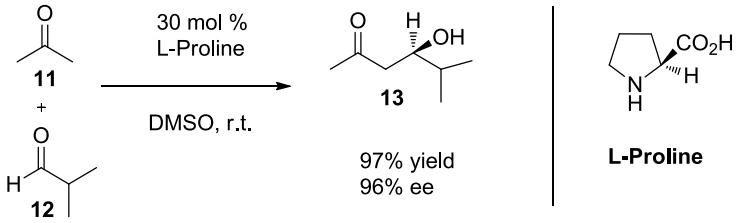
Scheme 5. The Juliá-Colonna epoxidation of chalcones

In 1981, another remarkable event was published by Inoune et al. They solved the enantioselectivity problem in mandelonitrile **(2)** formation, as indicated in Scheme 2, by using cyclic dipeptide type organocatalyst instead of cinchona alkaloids used by Bredig and Fiske.[7] Organocatalytic HCN addition to benzaldehyde derivatives **9** resulted in the corresponding mandelonitrile **10** up to 97% ee (Scheme 6).[10]



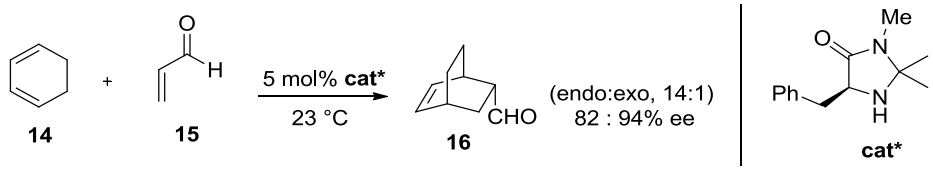
Scheme 6. Enantioselective addition of HCN to benzaldehyde *via* cyclic dipeptide catalyst

In 2000's, two scientists, David MacMillan and Benjamin List, have drawn great attention of chemical society. The potential of proline as a catalyst was not discovered until these years although a few examples were reported in the past. List et al. presented a pioneering study about intermolecular aldol reactions by using L-proline as catalyst. For instance, aldol reaction of acetone with a variety of aldehydes can give aldol products with excellent enantiomeric purity and yields. As can be seen from the work of List,[11] the aldol reaction of acetone **(11)** with *iso*-butyraldehyde **(12)** gave a 97% yield and 96% enantiomeric excess for the aldol product **13** (Scheme 7).



Scheme 7. Proline catalyzed enantioselective intermolecular aldol reaction

Meanwhile, MacMillan introduced the definitions of organocatalyst and organocatalysis terms.[12] He reported an enantioselective Diels-Alder reaction of *α,β*- unsaturated aldehydes catalyzed by phenylalanine-derived secondary amine with high enantioselectivities. In this paper, Diels Alder reaction of cyclohexa-1,3-diene **(14)** and acrolein **(15)** catalyzed by imidazolidone was reported with 94% ee for the desired product **16**. This preliminary results were the first step and opened the doors for further secondary amine catalysis (Scheme 8).



Scheme 8. Imidazolidone catalyzed enantioselective Diels Alder reaction

1.2.3 Classification of Asymmetric Organocatalysis

In the literature, there are some different classifications of organocatalysis. Generally these classifications were done according to reactions which are catalyzed or according to the types of organocatalysts which are used. In addition, there are also other classifications which look from other perspectives. These definitions were done by Berkessel,[4a] List[11] and MacMillan.[12] Ambiguity in classification can be attributed to insufficient kinetic works in organocatalysis field.

Berkessel[4a] made classification by looking at the character of bonding in transition states. He categorized organocatalysis into two parts as covalent catalysis and non-covalent catalysis. In covalent catalysis, within the catalytic cycle there is covalent interaction between catalyst and substrates. In the case of non-covalent interaction, there is no covalent bonding; instead there may be a hydrogen bond formation or formation of ion pairs. Thus, he define the terminologies *covalent catalysis* for the first case and *non-covalent catalysis* for the second case (Figure 3).

In the covalent catalysis, substrate-catalyst adducts can form in two different ways. It may occur by Lewis acid-Lewis base interaction in a single step or by some multistep enamine formation from aldehydes and secondary amines. In the case of non-covalent catalysis, most interactions are primarily based on formation of hydrogen bonding between catalyst and substrate.[4]

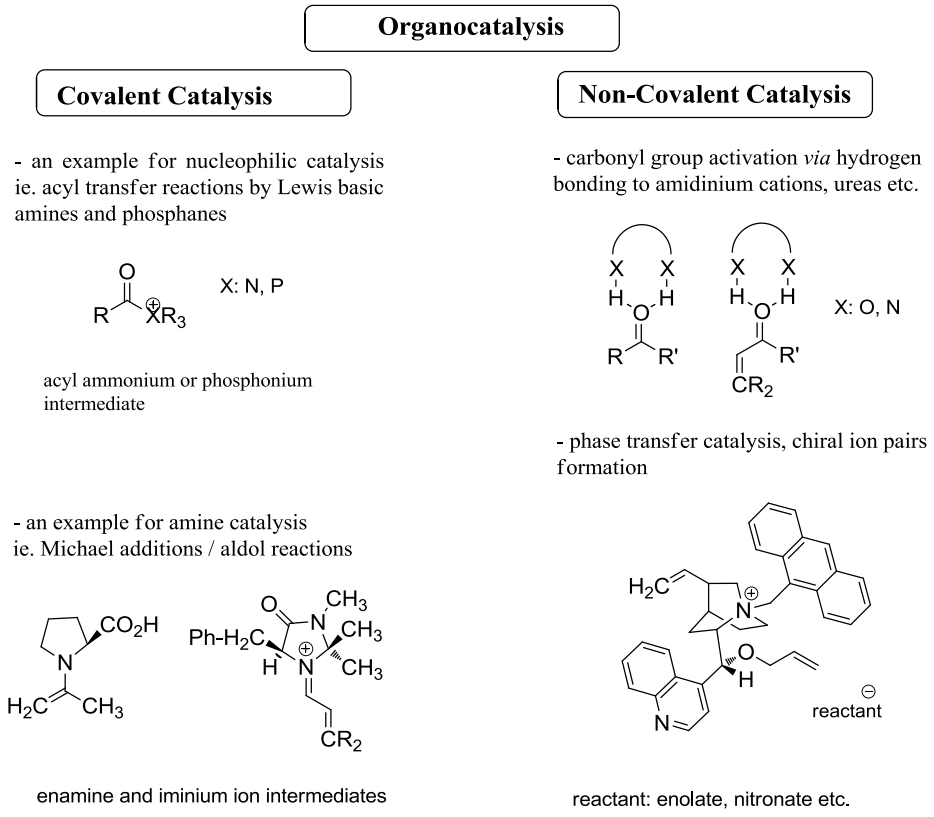


Figure 3. Berkessel's classification of organocatalysis

Another important and most widely accepted classification was done by Benjamin List in 2005.[11] According to List, not all but most of the organocatalysis can be broadly divided into four types. These are Lewis acid, Lewis Base, Brønsted acid and Brønsted base catalysis depending on the catalophoric nature of organocatalysis (Figure 4). Lewis basic and acidic catalysis proceeds in a similar manner. For example, in Lewis basic catalysis, the basic catalyst is doing a nucleophilic attack to the substrate first. These results in the initiation of the catalytic cycle. After reaction proceeds, product formation occurs and catalyst can be recovered at the end of the reaction. In similar case, Lewis acidic catalyst initiates catalytic

cycle *via* activation of nucleophilic substrate. In the Brønsted acidic and basic case, initiation is done by protonation or deprotonation respectively. Although this classification is good at giving logical ideas of structure but in terms of mechanistic information it is not sufficient.

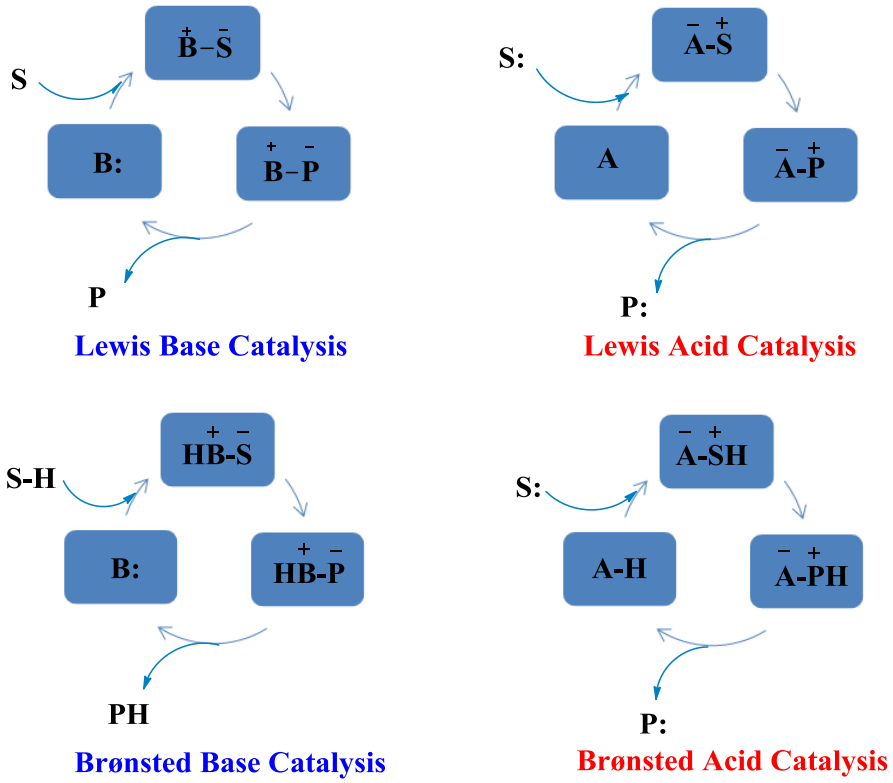


Figure 4. List's classification of organocatalysis according to the catalophoric nature of organocatalysis

In 2008, MacMillan reported a work, which attracted great attention from chemical society, on generic modes of activation of catalytic systems.[12] In this study, the great increase in popularity of organocatalysis can be seen and most critically all of the reactions which are published are directly fitting to six types of generic modes. These generic modes which are commonly used in organocatalysis can be classified as enamine catalysis, iminium catalysis, hydrogen bonding catalysis, counterion catalysis and SOMO catalysis. The most common generic modes of activations are enamine, iminium and hydrogen bond catalysis. Hydrogen bonding catalysis is very important because it is the key of multifunctional, in other words bifunctional organocatalysis.

1.2.4 Bifunctional Organocatalysis

In 2003, Takemoto and co-workers[13] introduced bifunctionality for organocatalysis inspired by the efficient and selective nature of enzymes. Bifunctional organocatalysis refers to dual activation of electrophile and nucleophile in a variety of enantioselective reactions. A

bifunctional organocatalyst has a basic catalophoric unit to activate highest occupied molecular orbital (HOMO) of nucleophiles to increase the HOMO level, it also has an acidic site to decrease the lowest unoccupied molecular orbital (LUMO) of the electrophile at the same time and consequently to decrease the gap between HOMO and LUMO levels that renders the reaction possible.

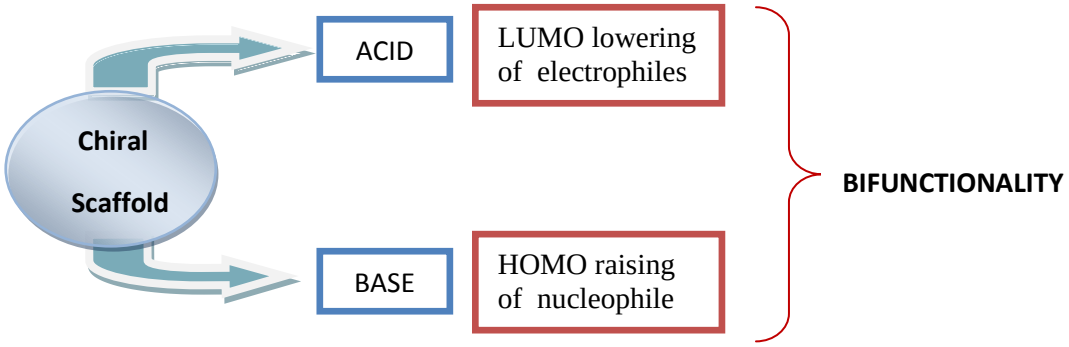


Figure 5. Bifunctionality of organocatalysts

Inspiring the Schreiner's work[14] which comprises symmetrical thioureas **17, 18, 19** (Figure 6) as a catalyst in the Diels-Alder reaction of chalcone with cyclopentadiene, Takemoto has introduced tertiary amine/thiourea catalyst and first optimization studies was done on asymmetric conjugate addition of malonates to nitroolefins.

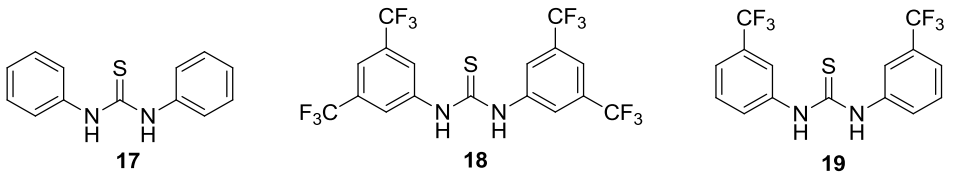
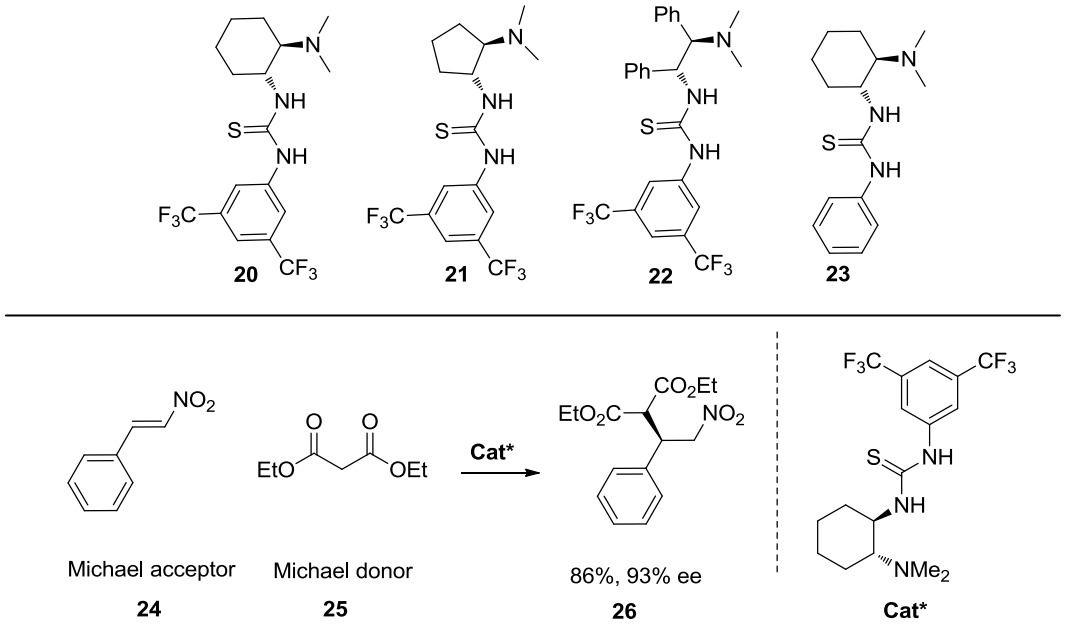


Figure 6. Schreiner's symmetrical thioureas to catalyze Diels-Alder reactions

Nitroolefins have two oxygen atoms which can be activated *via* thiourea's acidic hydrogens. Starting from this idea Takemoto et al.[13] was able to anticipate the effect of additional nucleophile activating groups in the thiourea catalysts which may facilitate efficient catalysis for Michael additions and authors designed various thiourea based bifunctional organocatalysts **20-23** as shown in Scheme 9. Those catalysts were tested in the asymmetric conjugate addition of diethyl malonate **(25)** to *trans-β*-nitrostyrene **(24)** yielding Michael adduct **26** with 86% yield and 93% ee.



Scheme 9. Takemoto's bifunctional *tert*-amine/thiourea catalysts in asymmetric conjugate addition

1.2.5 Squaramides as Bifunctional Organocatalysts

Catalysis *via* hydrogen bonding has grown very rapidly in recent years.[15] There are some hydrogen bond donor catalysts in literature namely thiourea or ureas. Until recently, the potent of squaramides as hydrogen donor has not been able to explored. Today, squaramides are accepted as excellent hydrogen bond donors because of several differences over the other analogues, thiourea/urea. Squaramides have significant functionality differences in terms of some aspects.[16] The first difference is the duality of squaramides having two N-H protons for hydrogen bonding meanwhile two carbonyl groups as a hydrogen bond acceptor. In fact, this family is also bifunctional in hydrogen bonding abilities (Figure 7).[17]

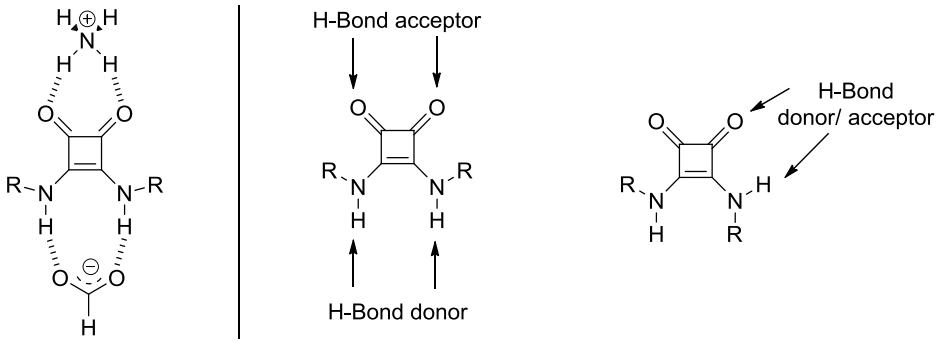
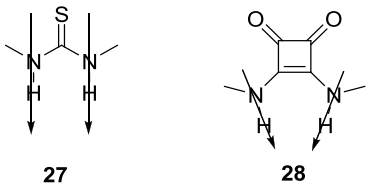


Figure 7. Dual character of squaramides, different H-bonding abilities

Another interesting property of squaramides beyond dual character is its rigid structure. It can be said vinylogous amide to squaramide whereas the other types, ureas/thioureas, are called normal amides. In both cases, there is a strong delocalization starting from the lone pairs of nitrogen atoms through carbon-oxygen double bond resulting in restriction in the rotation of C-N bonds. However, in the case of squaramides, delocalization is further improved over partially aromatic cyclobutenedione system. Therefore, the further restriction in the structure conformation of squaramide let this molecule be more rigid.[18]

The third difference of squaramides compared to thioureas/ureas is that there is a significant difference between the two N-H bond distances and their space. Some calculations was done to measure the distance between the N-H protons by Rawal[19] and Takemoto[13] and reported as approximately 2.13Å for *N,N'*-dimethylthiourea **27**, 2.72Å for *N,N'*- dimethylsquaramide **28**. Different disposition of squaramide hydrogen bonds gives an excellent linear hydrogen bonding ability and also provides different transition state in terms of binding property (Figure 8).



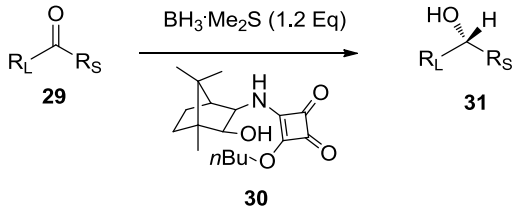
27 **28**

Figure 8. Orientation of hydrogen bonds in thioureas and squaramides

Finally the other important property is the acidity of squaramides due to strong delocalization and pKa_1 and pKa_2 values are estimated as 1.5 and 3, respectively.[20]

1.2.5.1 Asymmetric Reactions with Squaramide Catalysts

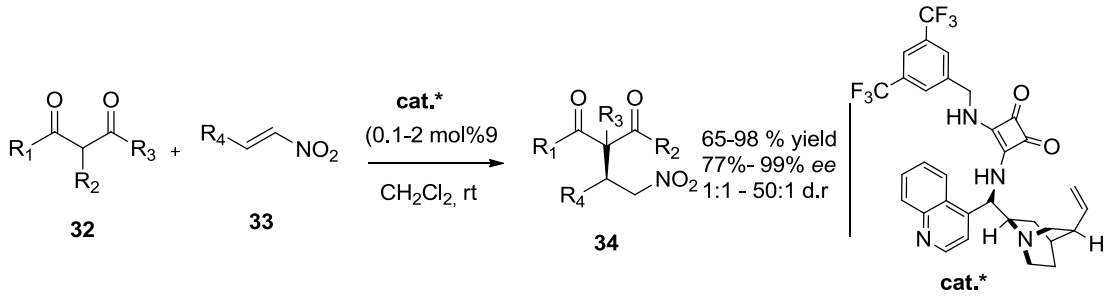
The first reported example of an asymmetric synthesis applying squaramide skeleton as a catalyst was introduced by Xie et al.[21] in 2005. Prochiral ketone **29** was reduced with borane dimethyl sulfide in combination with chiral squaric amino alcohols in substoichiometric amounts. In this reaction the squaric amino alcohol **30** was a ligand, not a bifunctional organocatalyst but it is remarkable in terms of being a first representative structure of these catalysts in asymmetric catalysis. The enantioselectivity of this reaction was very high (up to 99% ee) (Scheme 10).



Scheme 10. Reduction of a prochiral ketone *via* squaramide ligand

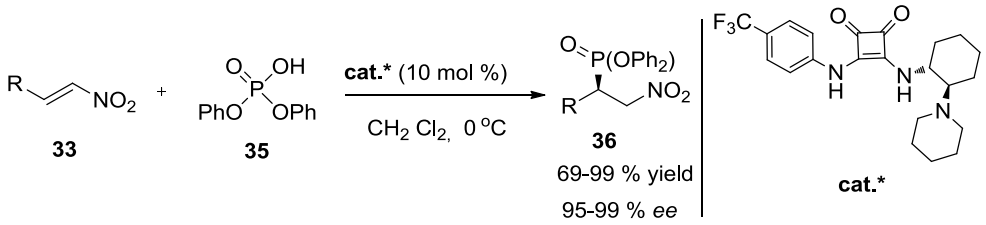
The first example of squaramide bifunctional organocatalysis was introduced by Rawal et al.[22,23] in 2008. Rawal designed a cinchona alkaloid based squaramide bifunctional organocatalyst and tested it in asymmetric conjugate addition of dicarbonyl compounds **32** to nitroolefines **33.**

The desired products **34** have enantiomeric purity up to 99% with good chemical yields. According to the authors, using low catalyst enhances the full conversion of products in 8-24 h. Moreover, the reaction proceeds smoothly in the addition of less reactive nucleophiles such as *α*-branched *β*-ketoesters by using low catalyst loadings (Scheme 11).



Scheme 11. Asymmetric addition of active methylene compounds to nitroolefines

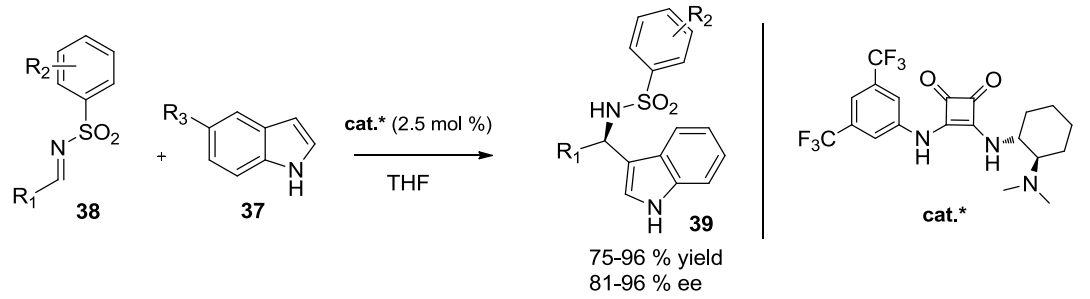
After this work, Rawal developed a new bifunctional squaramide organocatalyst inspiring the Takemoto's thioureas[13] in 2010. In this work, Rawal used a chiral 1,2- diaminocyclohexane scaffold instead of cinchona alkaloid derivatives and used it in a different Michael reaction of diphenylphosphite **(35)** and nitroolefines **33** (Scheme 12). The yields and the enantiomeric excess values for this interesting reaction were up to 99% for each.[23]



Scheme 12. Asymmetric Michael addition of diphenylphosphite to nitroalkenes with squaramide catalyst

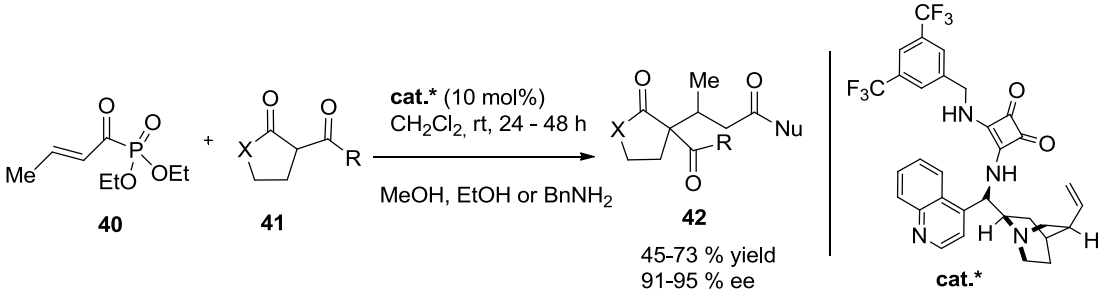
The same group, a few months later, published a new article[24] regarding enantioselective Friedel-Craft reaction of indoles **37** with arylsulfonylimines **38**. In this reaction, desired

products **39** were achieved with good to excellent yields and enantioselectivities by using again cyclohexanediamine scaffold in the structure of catalyst. The reaction was tested over a range of different indoles and imines and reaction proceeded well only when unsubstituted or electron rich indoles were reacted (Scheme 13).



Scheme 13. Friedel-Crafts reaction of indoles with *N*-sulfonylimines

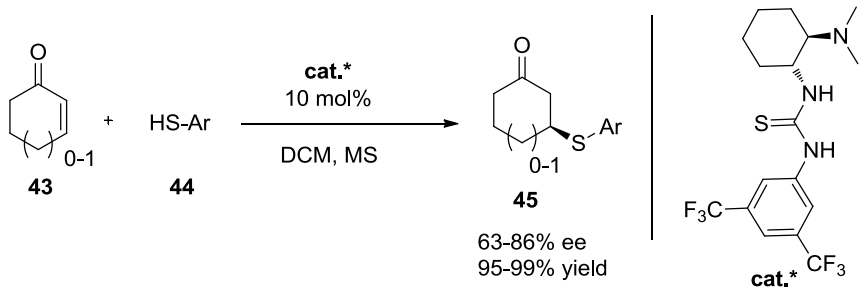
In 2010, Jørgensen[25] reported a 1,4-addition reaction of azalactones, indoles and dicarbonyl compounds to *α,β*-unsaturated acylphosphonates. In these reactions, both squaramide and thiourea motifs were used and showed a complementary reactivity. As a representative example of cyclic dicarbonyls **41** with unsaturated acylphosphonates **40** catalyzed by squaramide catalyst gave the better ee values whereas thiourea catalyst did not work (Scheme 14).



Scheme 14. Conjugate addition of cyclic dicarbonyls to unsaturated acylphosphonates

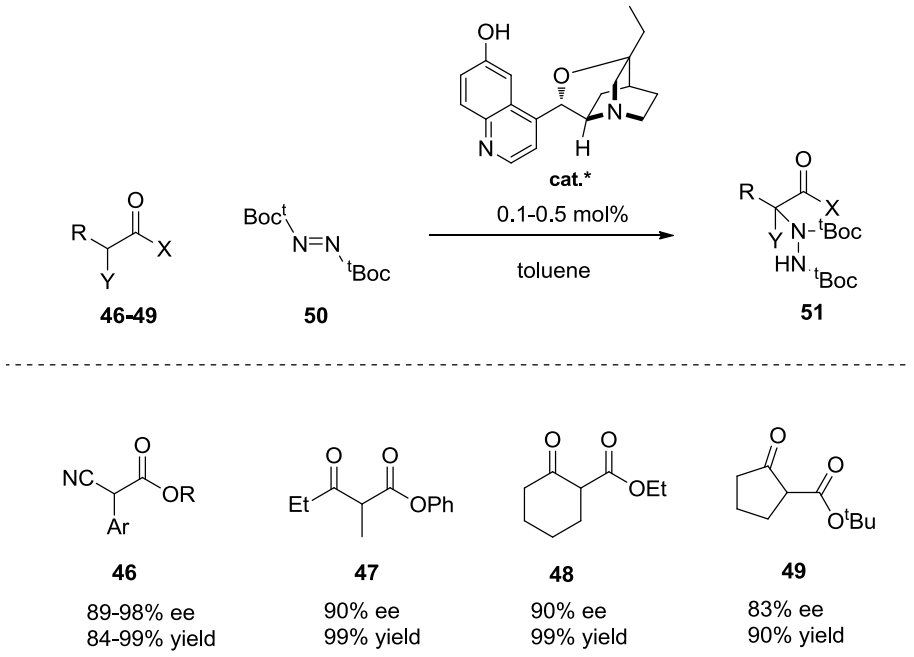
1.3 Enantioselective Michael Addition Reactions

The interest in designing bifunctional organocatalysts has increased very much by inspiring the Takemoto's first work in conjugate addition of 1,3-dicarbonyls to nitroolefines.[26-28] Chen et al. adapted the Takemoto's catalyst **20** to the reaction of arylthiols **44** to cyclic enones **43** to get *β*-thiolated ketones **45** in the range of 63-86% enantioselectivity (Scheme 15).[29]



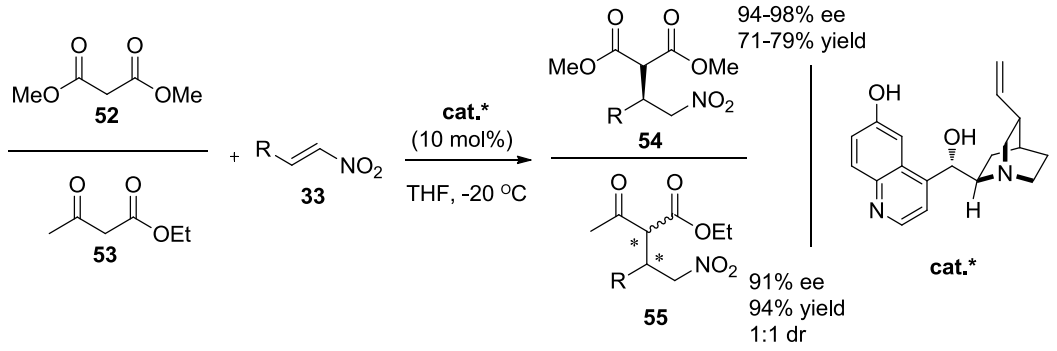
Scheme 15. Michael additions of thiols *via* Takemoto's catalyst.

After one year, Jørgensen et al. introduced a cinchona alkaloid type organocatalyst named *β*-isocupreidine which was used to catalyze promoted *α*-amination of unsymmetrical 1,3-dicarbonyls **46-49** with di-tert-butyl azodicarboxylate **(50)** to form various *α*-aminoacid analogues **51** (Scheme 16).[30]



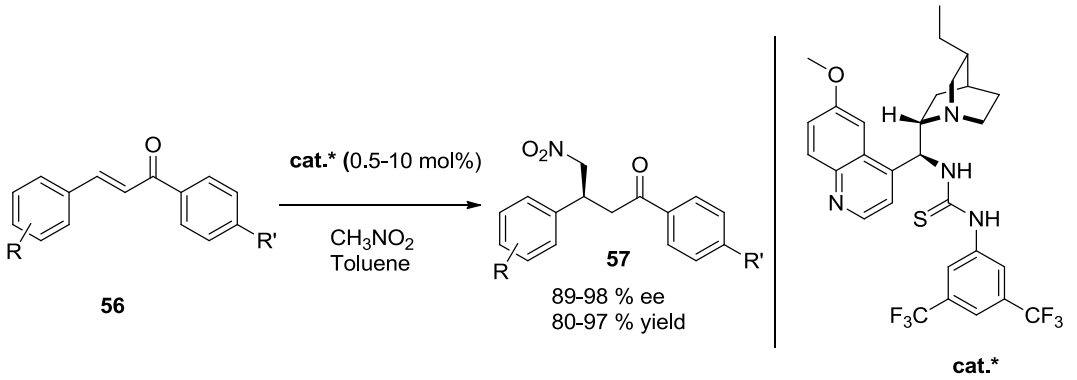
Scheme 16. Jørgensen's *α*-amination of unsymmetrical 1,3-dicarbonyls

Deng et al.[31] introduced a new cinchona alkaloid type catalyst functioned very well in 1,4-addition of dimethyl malonate **(52)** and ethyl acetoacetate **(53)** to different nitroalkenes by forming enantiomerically enriched products **54** and **55,** respectively (Scheme 17).



Scheme 17. Deng's catalyst in Michael reaction

SoóS et al. reported the asymmetric conjugate addition of nitromethane to chalcones **56** with thiourea modified cinchona alkaloid type bifunctional acid/base catalyst affording γ-nitroketone derivatives **57** up to 98% ee and 97% chemical yields (Scheme 18).[32]

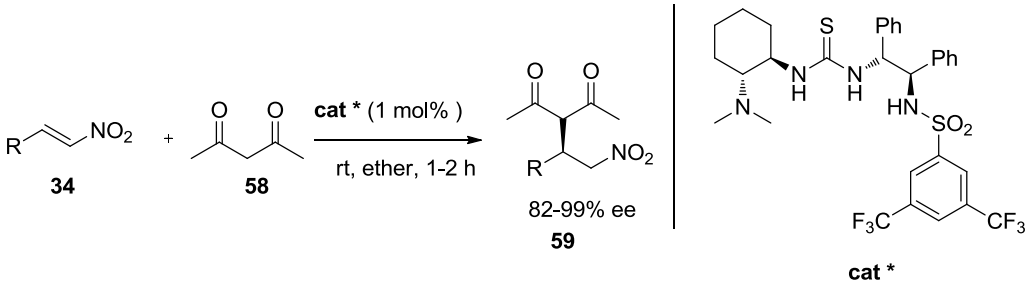


Scheme 18. Conjugate addition of nitromethane to chalcones

1.3.1 Asymmetric Conjugate Addition of Dibenzoylmethane to *trans*-(*β*)-Nitrostyrene

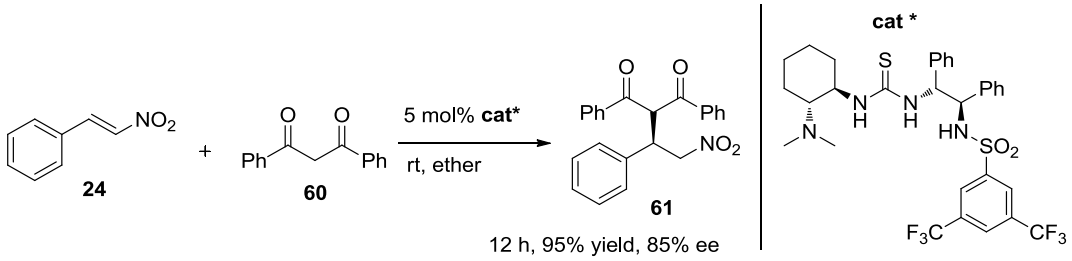
Michael addition reactions done with a wide array of carbon nucleophiles and nitroolefines acted as electrophile are crucial because of being an access for different functionalities due to nitro unit[27] which can be converted to amines *via* reduction[33] or can be converted into nitrile oxide,[34] ketone,[35] and carboxylic acid.[36] In literature there are many examples for Michael additions of carbon nucleophiles to nitroolefines to get enantiomerically enriched compounds. Most encountered carbon nucleophiles after deprotonation are aldehydes, ketones or active methylene compounds.[37] Among the active methylene compounds such as acetylacetone, diethyl malonate, dimethyl malonate or dibenzoylmethane, dibenzoylmethane addition to nitroolefins is challenging. There are only a couple of examples reported up to now.

Wang et al.[38] in 2008, illustrated the efficient use of chiral amine-thioureas as a catalyst for the addition of acetylacetone **(58)** to nitroolefins **34**. The reaction were conducted with very low catalyst loading (1%) at room temperature and in very short reaction duration (1-2 h) to afford addition products **59** up to 99% ee (Scheme 19).



Scheme 19. Asymmetric conjugate addition of acetylacetone to nitroalkens

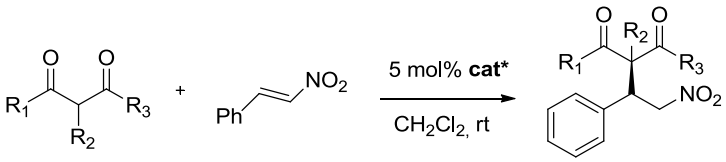
In contrast to these excellent results, the same catalyst did not properly work with dibenzoylmethane **60**. Comparing with the results obtained by acetylacetone addition, dibenzoylmethane **(60)** addition required prolonged reaction duration (12h) and relatively high catalyst loading (5 mol%) to afford addition product **61** up to 85% ee (Scheme 20).

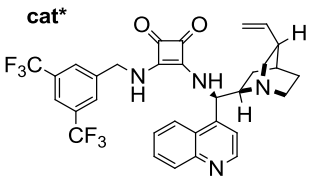


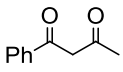
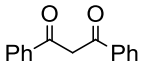
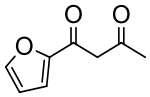
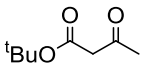
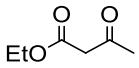
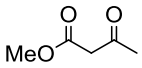
Scheme 20. Asymmetric Michael addition of dibenzoylmethane to *trans-β*-nitrostyrene

Another work conducted by Rawal[19] is also supporting the challenge in dibenzoylmethane (**60)** addition. Squaramide type organocatalysts were used to catalyze the addition reaction of different range of *β*-diketones to nitroolefins. The range of enantioselectivity in between the reaction of acetylacetone and various nitroolefins is from 97% to 98%. In addition, various *β*-diketones were also tried and as can be seen from Table 1, dibenzoylmethane addition was again lower in terms of enantioselectivity than the other different diketones.

Table 1. Variation of nucleophile in conjugate addition to nitroolefins

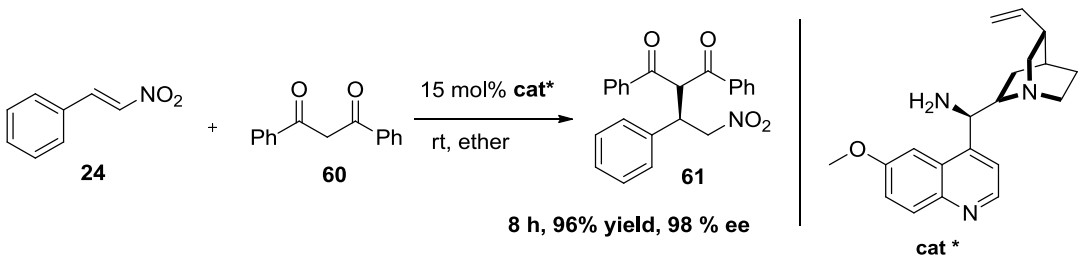




Nucleophile	time	yield (d.r)	ee [a]
	9 h	91% (2:1)	95%, 94%
	24 h	93%	88%
	8 h	97% (1.4:1)	92%,81%
	12 h	95% (1.6:1)	96%, 96%
	8h	89% (1.6:1)	97%, 96%
	18	75% (1.1)	96%, 98%

[a] Values are listed for major and minor diastereomers respectively

In 2009, Zhong et al. demonstrated highly enantioselective Michael addition reaction of 1,3-diphenyl-1,3-propandiones **(60)** to nitroolefines by using a recyclable organocatalyst.[39] However, dibenzoylmethane **(60)** addition required high catalyst loading (15 mol%) (Scheme 21).



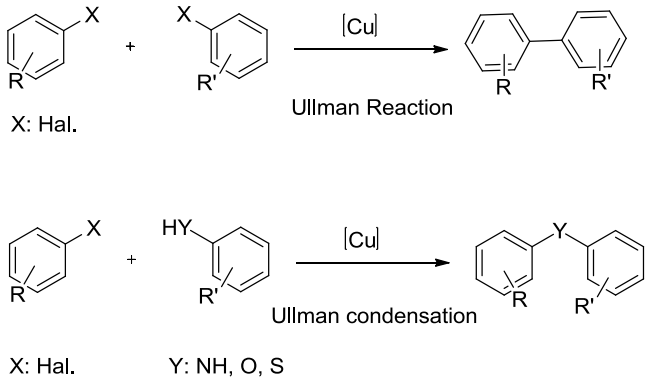
Scheme 21. Enantioselective conjugate addition of dibenzoylmethane to *trans-β*-nitrost

With the pioneering work of Takemoto,[13] there is an increasing interest toward bifunctional organocatalysis which provide dual activation of electrophile and nucleophile. In this respect, in our group, we anticipated the effect of DMAP unit as a Lewis basic catalophore on one site of the most common chiral backbone, C_2-symmetrical chiral cyclohexanediamine, and by introducing the acidic moiety with modifications on the remaining amine unit would provide the discovery of a new bifunctional organocatalyst in asymmetric organocatalysis. Hence, direct access to mono-heteroarylated diamines was a crucial step to facilitate an easy and direct method in bifunctional organocatalyst design. In literature, the difficultly in that step can easly be noticed.

1.4 Copper Catalyzed C-N Bond Forming Reactions

1.4.1 History from Pd to Cu Coupling Reactions

The formation of C-N bond in the arylation of nucleophiles *via* copper chemistry has been known for more than a century. The idea dates back to 1903. Ullman,[40] Ullman- Goldberg,[41] Ullman-Hurtley[42] condensation reactions were pioneering studies for C-C, C-heteroatom bond formation. Those name reactions required copper salts as catalyst in mostly stoichiometric amounts, besides, very high temperatures were needed. Also the reaction times were very long.[43] Basically, Ullman condensation reactions are reactions in which aryl halides and an amine, ether or thioether are reacted in the presence of copper as a catalyst in stoichiometric or substoichiometric amounts.



Scheme 22. Ullman reaction and Ullman condensation

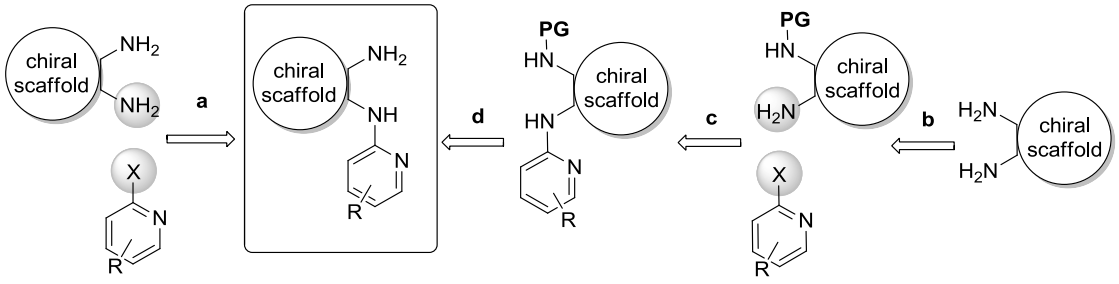
The other related types of reactions are known as Goldberg[51] and Hurtley[44] condensation reactions. In Goldberg condensation, C (aryl)-N bond formation occurs in a reaction of aryl halide and an amide with copper catalyst, whereas Hurtley condensation occurs when 2-halobenzoic acids react with diketones.

The interest for Ullman type reactions has increased tremendously and some new methodologies supporting that type of reaction were arisen. The new methods developed in

2000s by Buchwald and Hartwig.[47] They used palladium in such coupling reactions of haloarenes with various nucleophiles. This method had some drawbacks such as using very high priced metal as well as ligands to activate it. Hence, scientists turn back to use more environmentally friendly, lower cost metal, copper. Therefore, a new method, *Modified Ullman Reaction*, in which copper can be used as in old fashion with catalytic amount was gained great attention from scientists. [45,46]

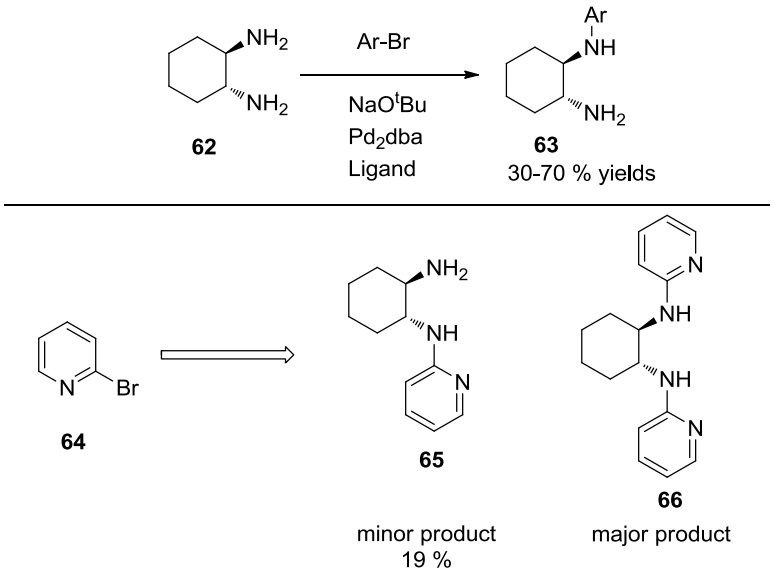
1.4.2 Palladium Catalyzed Selective Mono-*N*-Heteroarylation of C_2-Symmetrical Chiral Diamines

Selective mono-*N*-heteroarylation of C_2- symmetrical chiral diamines have been done *via* Pd chemistry initiated by the pioneering work of Buchwald and Hartwig in 1995.[47] In literature there are two synthetic approach which are the direct coupling and protecting group strategy as shown in Scheme 23.
In the first approach (**a)**, heteroaryl unit can be attached to the one amine unit selectively by controlling the equivalency *via* palladium chemistry. When mono-heteroarylation fails, protection of one amine unit comes to aid. After protection steps **(b)**, Buchwald-Hartwig protocol is applicable (**c)** and finally deprotection (**d)** is needed at the end of these steps.



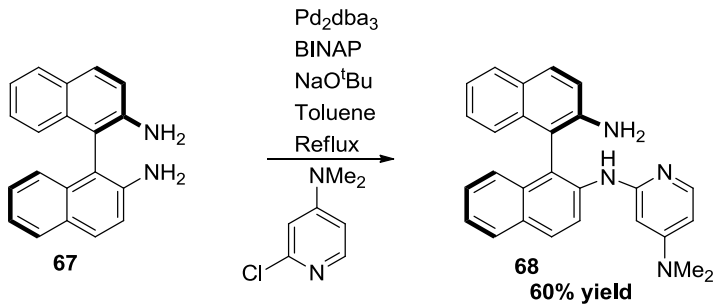
Scheme 23. Synthetic pathway to get mono-heteroarylated products

Mono heteroarylation has gained great importance due to the increasing demand in organocatalyst field. C_2-symmetrical diamines[49] are the most common candidates for the construction of bifunctional organocatalysts. There are only few examples for selective couplings done with palladium. Frost et al[48] applied Buchwald-Hartwig protocol for selective-*N*-arylation. Yields are varied between 30-70%. Among these *N*-arylated derivatives **63**, there is only one *N*-heteroaryl derivative **65** isolated as minor product with 19% chemical yield as shown in Scheme 24.



Scheme 24. Frost's work of selective coupling (only one heteroarylated product)

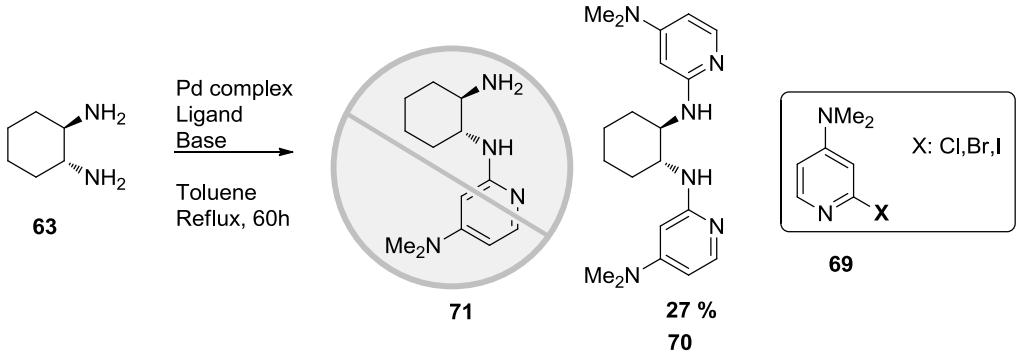
The second example to get mono heteroarylated C_1-symmetrical diamines *via* palladium chemistry is the Wulf's work. Wulf et al. succeeded to introduce DMAP unit to *R*-BINAM (**67)** to afford C_1-symmetrical derivative **68** with 60% yield.[49]



Scheme 25. Wullf's selective mono-heteroarylation

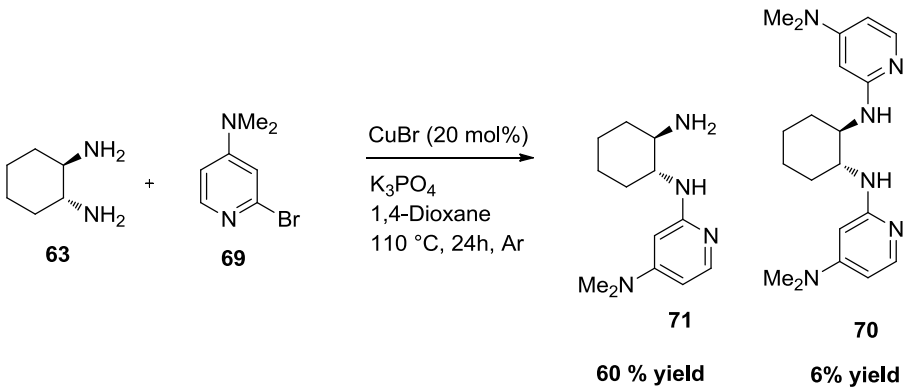
1.4.3 Copper Catalyzed Selective Mono-*N*-Heteroarylation

Preliminary studies to generate a methodology for copper catalyzed coupling reactions of chiral cyclohexanediamine were done in Tanyeli's research group in 2011.[50] They first applied Buchwald-Hartwig[47] protocol to introduce selectively 2-halo DMAP to (1*R*, 2*R*)-1,2-diaminocyclohexane **63,** only isolated compound was the diheteroarylated C_2-symmetrical product **70** (27% chemical yield) instead of C_1-symmetrical product **71 (**Scheme 26).



Scheme 26. Pd trials to access C_1-symmetrical compound **71**

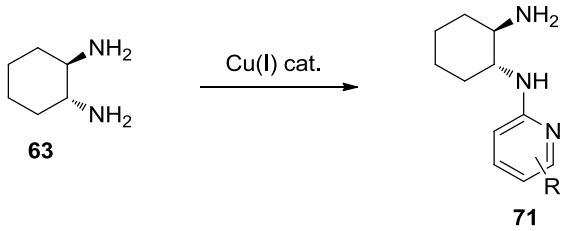
Pd chemistry is not feasible method for direct selective mono-heteroarylation of (1*R*, 2*R*)-1,2-diaminocyclohexane **63**, subsequently, they applied modified Ullman type reaction catalyzed by Cu (I) salt and achieved direct selective mono-*N*-pyridilation of (1*R*, 2*R*)-1,2-diaminocyclohexane **63** with 60% chemical yield (Scheme 27).



Scheme 27. First direct mono-pyridylation *via* copper chemistry

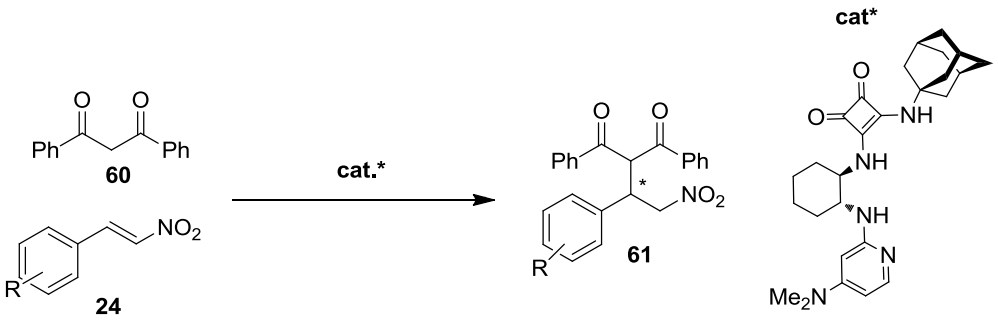
1.5 Aim of the Work

In the first part of the thesis, we aimed to extend the applicability of copper catalyzed selective mono-*N*-heteroarylation of (1*R*, 2*R*)-1,2-diaminocyclohexane **63** developed in Tanyeli's research group by using various halo substituted heteroaromatic compound. The developed methodology could offer a unique alternative single step procedure for the desymmetrization of most demanding C_2-symmetrical (1*R*, 2*R*)-1,2-diaminocyclohexane **63** to C_1-symmetrical amidine derivatives which are able to be candidates for wide range of bifunctional acid/base type organocatalysts (Scheme 28).



Scheme 28. Cu- catalyzed selective mono-*N*-heteroarylation of (1*R*, 2*R*)-1,2 diaminocyclohexane **63**

We also aimed to test the effectiveness of 2-AminoDMAP/Squaramide type bifunctional organocatalyst as shown in Scheme 29, already designed and synthesized in Tanyeli's research group, in asymmetric conjugate addition of dibenzoylmethane **(60)** to various *trans*-*β*-nitrostyrene derivatives **24**. Our challenge was to improve the dibenzoylmethane **(60)** addition in terms of low catalyst loading, short reaction duration and high enantioselectivity.



Scheme 29. Enantioselective addition of dibenzoylmethane to nitrostyrene

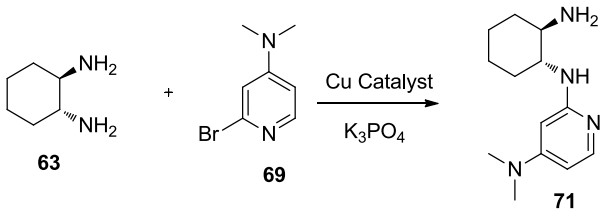
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Copper Catalyzed Selective C_1-Symmetrical Chiral Amidine Synthesis

As given in the introduction part, selective mono-*N*-DMAP functionalization of C_2-symmetrical (1*R*,2*R*)-1,2-diaminocyclohexane has been achieved in Tanyeli's research group.[51] Our aim in this theses is to extend the applicability of that method in the synthesis of wide range of C_1 symmetrical (1*R*,2*R*)-1,2-diaminocyclohexane based amidine synthesis.

Keeping the method [51]developed in our research group as a reference point, to improve the chemical yield of mono pyridilation by using 2-bromoDMAP **(69)** substrate, optimization studies have been done firstly (Scheme 30).



Scheme 30. Screening studies for the synthesis of 2-AminoDMAP **71**

As the first parameter, the effect of solvent on the chemical yield was checked by using 20 mol% CuBr as a catalyst at 110 °C (Table 2). Of the screened solvents, 1,4-dioxane proved to be the best one with 60% chemical yield.

Table 2. Solvent screening results of selective mono-*N*-heteroarylation of (1*R*,2*R*)-1,2-diaminocyclohexane

Solvents	CuBr(mol%)	Temperature(°C)	Time (h)	yield %
THF	20	110	24	36.3
DMSO	20	110	24	39.7
Toluene	20	110	24	26
DMF	20	110	24	25
1,4-Dioxane	20	110	24	60

After choosing the best solvent, our attention was turned to check catalyst loading as 1, 5, 10 and 20 mol% of CuBr. If we could decrease the catalyst (copper) amount, the work would be more valuable in terms of green chemistry approach and decreasing cost. As can be seen from the Table 3, 1 mol% CuBr afforded the product with very low yield, on the other hand

5 mol% and 10 mol% catalyst loading showed a sharp increase in yields, 43.5% and 46%, respectively. The best catalyst loading for the reaction was found as 20 mol% CuBr with 60% yield.

Table 3. Catalyst loading results of selective mono-*N*-heteroarylation of (1*R*,2*R*)-1,2-diaminocyclohexane

CuBr(mol%)	Temperature (°C)	Time (h)	Yield %
1	110	24	5
5	110	24	43.5
10	110	24	46
20	110	24	60

The next optimization parameter was the temperature screening. Four different temperatures were checked starting from room temperature up to 110 °C which is the most preferred value in the literature (Table 4).[47] It was observed that as the temperature increases there is parallel increase in chemical yields up to 60%. Therefore, the best reaction temperature was fixed at 110 °C as similar in literature examples of those coupling reactions.

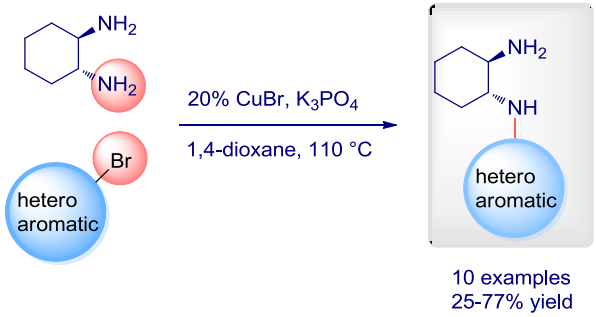
Table 4. Temperature screening results of selective mono-*N*-heteroarylation of (1*R*,2*R*)-1,2-diaminocyclohexane

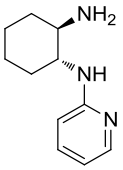
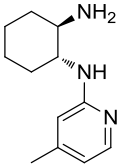
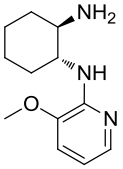
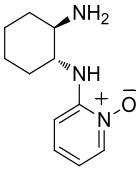
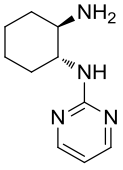
CuBr(mol%)	Temperature (°C)	Time (h)	yield %
20	rt	24	8.5
20	60	24	26
20	90	24	41
20	110	24	60

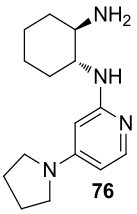
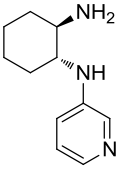
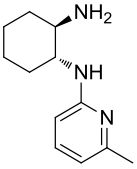
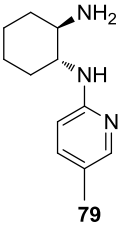
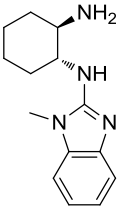
2.1.1 Synthesis of Mono-Heteroarylated Lewis Basic Catalophores (C_1-Symmetrical Amidines)

After optimization studies, best condition for the *N*-pyridilation was found as 20 mole% catalyst loading, 1,4-dioxane as solvent and 110°C as reaction temperature. With the optimized conditions, our aim was to extend our basic catalophore library by changing C_2-symmetrical cyclohexanediamine to C_1-symmetrical *via* attaching different heteroaromatics with a single step protocol. Under the optimized condition, 10 new mono-heteroarylated products having amidine motifs were synthesized in the range of 25-77% chemical yields. Results are summarized in Table 5.

Table 5. New Lewis Basic Catalophores



Entry	Product	Yield (%)
1	 **66**	53
2	 **72**	77
3	 **73**	44
4	 **74**	38
5	 **75**	42

Entry	Product	Yield (%)
6	 **76**	40
7	 **77**	44
8	 **78**	36
9	 **79**	42
10	 **80**	25

First of all, it should be noted that the yields of those coupling products **66, 72-80** are given as isolated yields. The most encountered problem in the coupling reactions was observed in the purification step since all products are highly polar.It was quiet difficult to be sure regarding the purity of products by just monitoring with TLC because the side products such as diheteroarylated ones had almost the same R_f values. Therefore, the column chromatography was done with highly polar systems such as DCM saturated with ammonia and gradient elution was generally needed. Structure elucidations were done by ^{1}H NMR, ^{13}C, IR and HRMS. In particular, the existence of six carbon signals at high field region which belong to cyclohexane ring carbons strongly supports accomplishment of C_2 to C_1 symmetry transformation.

As a representative example, ^{1}H and ^{13}C NMR spectrum of the synthesized product with highest yield, (*1R,2R*)-*N*^{1}-(4-methylpyridin-2-yl)cyclohexane-1,2-diamine **(72)**, are given below. In ^{1}H NMR spectrum the characteristic sets of pyridine moiety are observed at 7.82 ppm as doublet (J = 5.2 Hz, 1H), 6.30 ppm as doublet (J = 5.2 Hz, 1H), 6.19 ppm as singlet. Methyl protons resonates at 2.12 ppm as singlet (Figure 9).

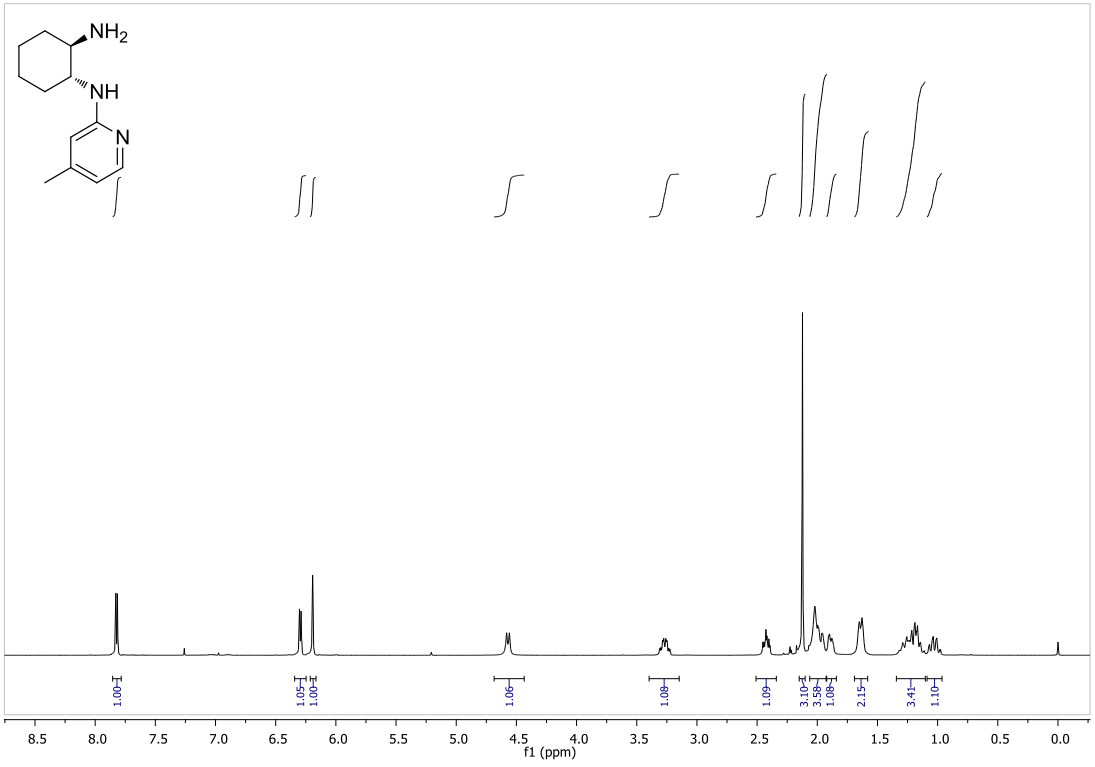


Figure 9. ^{1}H NMR spectrum of product **72**

^{13}C NMR spectrum shows seven signals in the high field region. As mentioned before, six carbon signals of the cyclohexane ring strongly proves the C_1-symmetrical character of the product **74** (Figure 10).

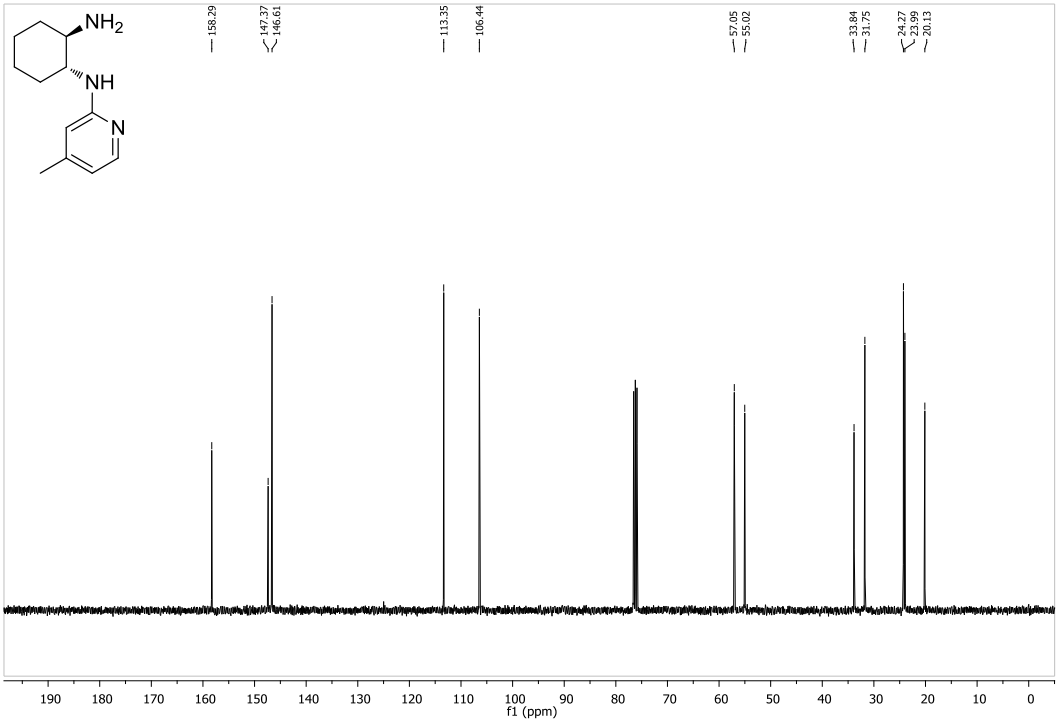
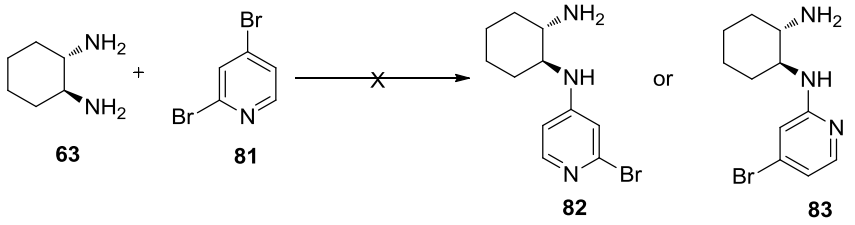


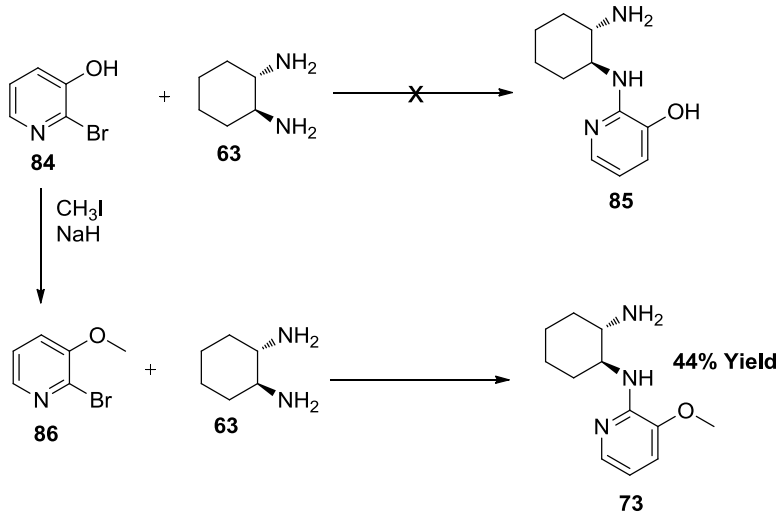
Figure 10. ^{13}C NMR spectrum of product **74**

During the desymmetrization studies some unfruitful results have been obtained. For instance, 2,4-diboromopyridine **(81)** was choosen as the heteroaromatic substrate. Due to the existence of second halogen unit, pyridine unit would gain a modular characteristic. It can be possible to attach some units from halogen substituted part of amidine motif. Unfortunately, we could isolate neither compound **82** nor **83** under our standart condition (Scheme 33).



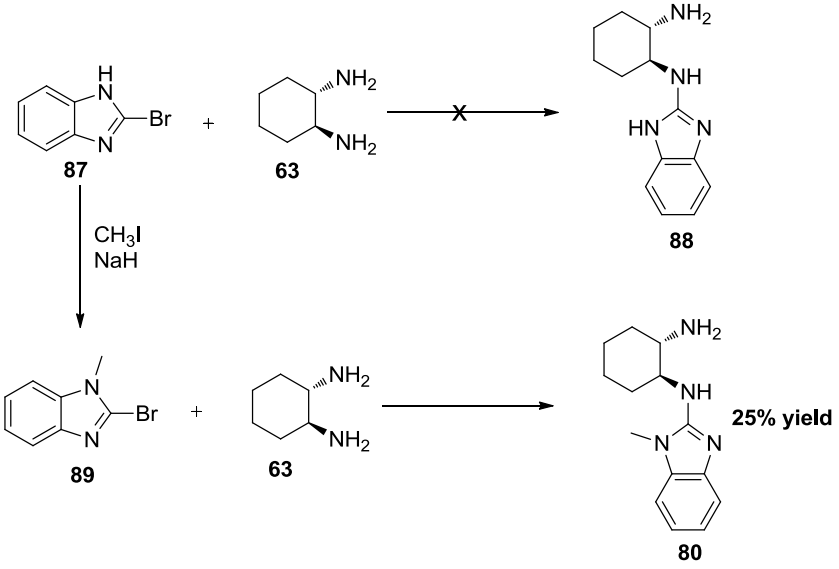
Scheme 31. Unsuccessful coupling reaction of 2,4-dibromopyridine **(81)**

In parallel with our modular approach discussed above, second attempt was done with 2-bromo-3-pyridinol **(84)** which can be functionalized from -OH unit, we would not isolate compound **85**. We thought that unsuccessful result can be arisen from phenolic proton, therefore, -OH unit was first methylated with methyl iodine in the presence of NaH to afford 2-bromo-3-methoxy-pyridine **(86)**, subsequent reaction with (1*R*,2*R*)-1,2-diaminocyclohexane **(63)** resulted in C_1-symmetrical product **73** with 44% chemical yield. This finding could support the effect of phenolic proton on reactivity (Scheme 34).



Scheme 32. Modification of compound **84**

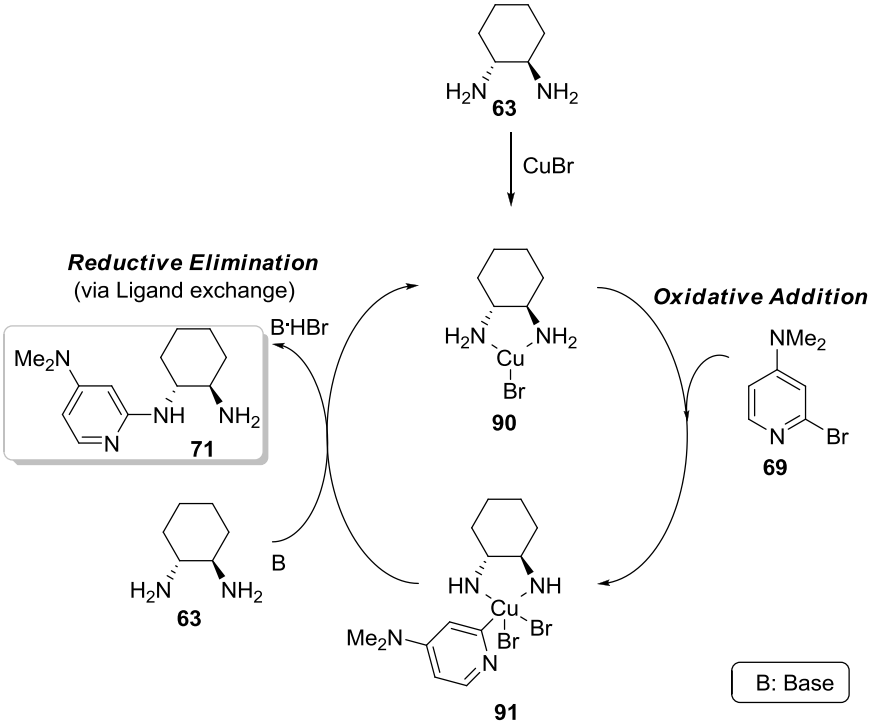
Third attempt has been done with 2-bromo-1H-benzimidazole **(87)** to get guanidine equivalent basic catalophoric site on C_1-symmetrical organocatalyst candidate. Our attempt was failure. Hence, benzimidazole derivative **87** was metyhlated again with methyl iodine in the presence of NaH. Subsequent C-N modified Ullman coupling reaction afforded desymmetrized product **80** in 25% isolated yield. Although TLC monitoring showed relatively more mono-heteroarylated product, such low amount of the product was isolated (Scheme 35).



Scheme 33. Modification of compound **87**

The proposed mechanism for the reaction was shown in Scheme 36 by adopting the previous literature examples.[52-54] The first step in the mechanism is the chelation of diamine **63** with copper bromide by forming activated copper complex **90**, after that oxidative addition of halo heteroaromatic **69** would result in formation of five coordinated unstable complex **91**.

By using a base the intermediate could afford a reductive elimination to form compound **71**. Then the catalytically active copper complexes would be ready for turnover. It is important to note that, in our methodology there is no need to use any ligand to activate copper salt since (1*R*,2*R*)-1,2-diaminocyclohexane **(63)** act as a ligand by itself which was proven in Buchwald mechanistic studies.[53]



Scheme 27. Proposed catalytic cycle affording compound **71**

To sum up, our methodology is quiet practical because of several reasons. Firstly, it is a single step reaction so that there is no need for protection steps. It is more economical. Comparing with the Sigma Aldrich prices of copper and palladium chemicals, copper chemistry is 100 fold cheaper than the palladium chemistry. Such economical issues are very important, especially in the industrial applications.

2.2 Asymmetric Conjugate Addition of Dibenzoylmethane to *trans*-*β*-Nitrostyrene Derivatives *via* 2-AminoDMAP/Squaramide Bifunctional Organocatalyst

In literature there are many examples of asymmetric conjugate addition of active methylene compounds to nitroolefines. However, a challenge in the addition of dibenzoylmethane to nitroolefins is standing out. There are very limited works in that area. Wang[48], Rawal[19] and Zhong[49] were reported first trials in that field. Wang and Rawal generally focused on conjugate additions of other methylene containing compounds and reported very good enantioselectivities for those Michael donors but in the case of dibenzoyl methane addition they were not successful as well as the other ones. In 2009, Zhong reported the first detailed study for dibenzoylmethane addition to a variety of nitroolefins with very good enantioselectivities. Although it seems very good to obtain highly enantiomerically enriched

products, the 15 mol% catalyst loading is the main drawback of the organocatalysis. By realizing those kind of information, low catalyst loading, and higher enantioselectivity with shorter reaction duration was aimed to fill the missing parts of puzzle.

2.2.1 Synthesis of 2-AminoDMAP/Squaramide Bifunctional Organocatalyst

We have chosen a 2-AminoDMAP/Squaramide bifunctional organocatalyst **92** from Tanyeli's[51] research group catalyst library since squaramide part has bulky adamantly unit which would assist to improve enantioselectivity of Michael addition reaction.

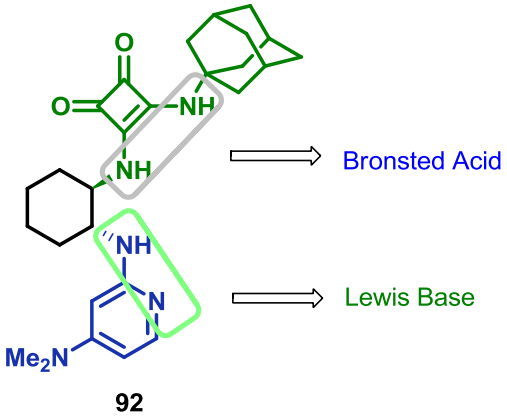
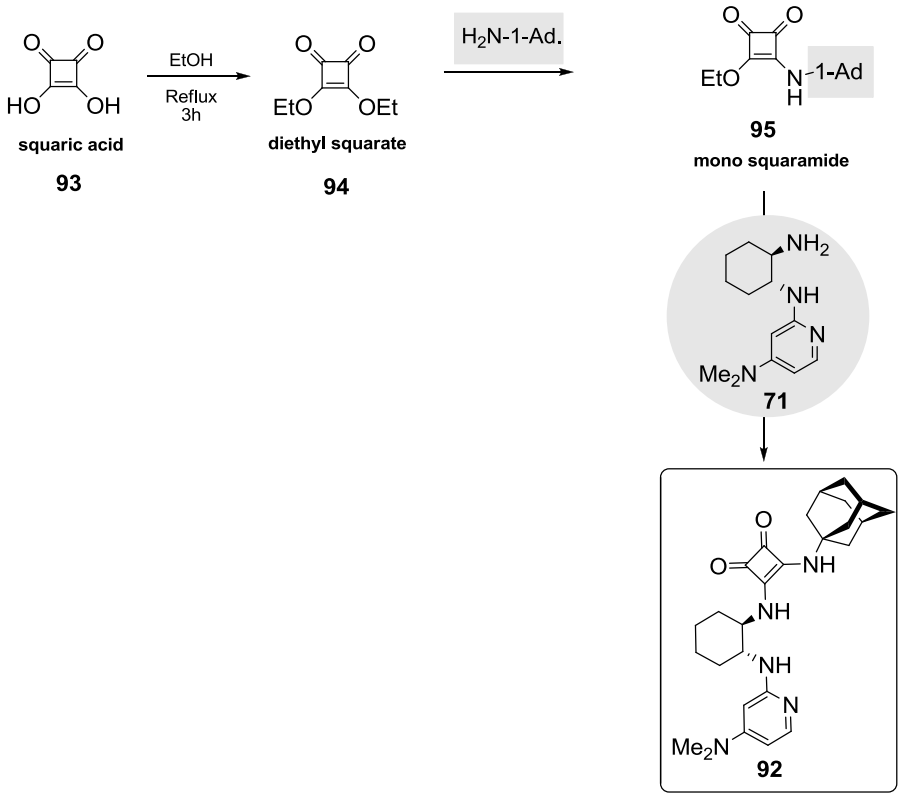


Figure 11. 2-AminoDMAP/Squaramide bifunctional organocatalyst

The bifunctional organocatalyst has acidic hydrogens on squaramide moiety and can activate nitroolefin type electrophile to decrease the LUMO level. The basic catalaphoric site (DMAP) can activate the dibenzoylmethane nuchleophile by increasing the HOMO level. Consequently, decreasing the energy gap between HOMO and LUMO levels would favor the reaction.

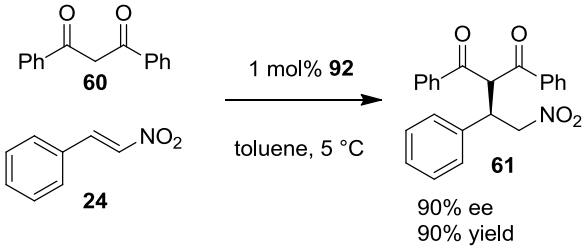
The synthesis of organocatalyst was started from sqauaric acid **(93)**. Refluxing squaric acid in absolute ethanol easily afforded diethylsquarate **(94)**. 1-Adamantyl amine moiety was reacted with diethylsquarate **(94)** in one to one ratio in dichloromethane at room temperature. The final step was the mixing of our basic catalophore **71** and mono-squaramide **94** at room temperature. The structure of organocatalyst **92** was characterized by ^{1}H NMR,^{13}C NMR, HRMS, IR. The total chemical yield of the bifunctional organocatalyst **92** was quiet good in spite of the multi step reactions (66%). The synthetic route is given in Scheme 37.



Scheme 28. Synthetic pathway for bifunctional organocatalyst **92**

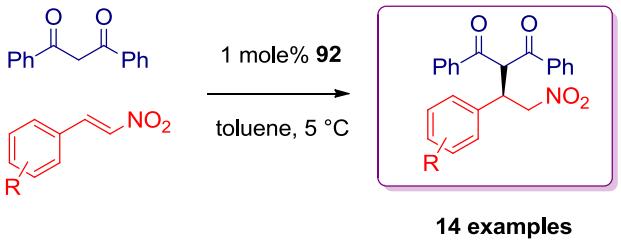
2.2.2 Evaluation of Bifunctional Organocatalyst 92 in Asymmetric Conjugate Addition of Dibenzoylmethane to *trans*-*β*-Nitrostyrene Derivatives

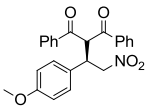
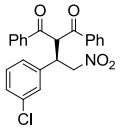
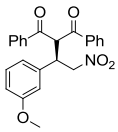
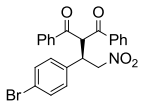
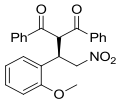
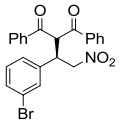
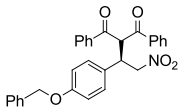
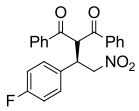
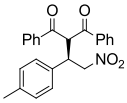
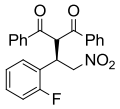
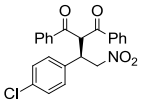
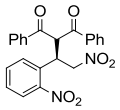
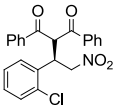
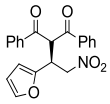
Being aware of the limited results in the literature, it was a good chance to improve this reaction with our catalyst. Using very low catalyst loading, getting high enantioselectivity in short reaction duration were aimed. The best condition for this reaction was optimized previously[51] in the reaction of dibenzoylmethane **(60)** with *trans*-*β*-nitrostyrene **(24)** as 1% mol catalyst loading, toluene as a solvent at 5 °C (Scheme 38). This promising preliminary result (90% ee) in our hand, we have used a wide array of *trans*-*β*-nitrostyrene type acceptors having electron donating and withdrawing groups on different positions of aromatic ring to prove effectiveness of 1-adamantyl subtstituted 2-AminoDMAP/Squaramide bifunctional organocatalyst. The results are summarized in Table 6.



Scheme 29. Optimized condition affording product **61**

Table 6. Results of different derivatives



Ent.	Product		h	Yield (%)	ee (%)	Ent.	Product		h	Yield (%)	ee (%)
1		**96**	4	70	80	8		**103**	3	74	84
2		**97**	6	94	90	9		**104**	4	75	94
3		**98**	6	70	85	10		**105**	5	60	83
4		**99**	10	54	86	11		**106**	7	75	95
5		**100**	2	85	92	12		**107**	3	95	95
6		**101**	3	90	87	13		**108**	18	68	95
7		**102**	3	86	94	14		**109**	6	58	98

When the results given in Table 6 are roughly inspected, it can be concluded that the choosen bifunctional organocatalyst **92** shows better effectiveness than the literature examples in terms of catalyst loading, reaction duration and enantioselectivity. Comparing our catalyst loading amount (1 mol%) with Wang et al.[48] (5mol%), Rawal et al.[19] (5 mol%) and Zhong et al.[49] (15 mol%) proves the excellent effectiveness of 1-adamantyl substituted 2-AminoDMAP/Squaramide bifunctional organocatalyst **92**.

When we compare the reaction duration parameter with the literature results, most of the reactions were completed between 2-7 h except compound **99** (Entry 4, Table 6) as 10 h and

product **108** (entry 13, Table 6) as 18 h. In literature, reaction durations varied 8-24 h. Short reaction duration could prove the higher reactivity of organocatalyst **92** over the literature examples.

In asymmetric organocatalysis field, enantioselectivity is the most important and widely used criteria to show the value of the catalyst system. The enantioselectivity results obtained are varied between 80-98% ee. Among the electron donor methoxy substituted *trans-β*-nitrostyrene derivatives, *o*- **98** and *p*-methoxy **96** derivatives (entry 1 and 3, Table 6) gave lower enantioselectivity as 85% and 80%, respectively, than the *m*-methoxy substituted derivative **97** (entry 2, Table 6) in 90% ee.

p-Methyl substituted product **100** (entry 5, Table 6) was obtained in the shortest reaction duration as 2 h in 92% ee.

In the halogen substituted series, *p*- and *o*-F substituted derivatives **106-107**, respectively, (Entries 2-3) resulted in the best enantioselectivities as 95% ee's for both by comparing with the chloro and bromo substituted derivatives.

We observed a drastic increase in enantioselectivity for *p*-,*o*-, and *m*-chloro substituted derivatives **101-103,** respectively (Entries 6-8) depending up on their substitution pattern. *o*-chloro substituted *trans-β*-nitrostyrene **102** afforded the best enantioselectivity as 94% ee.

The similar effect arisen from the position of the bromide was observed in *p*-bromo **104** and *m*-bromo **105** derivatives in terms of enantioselectivity as 94% ee and 83% ee, respectively (entries 9-10).

The only example for *o*-NO_2 substituted *trans-β*-nitrostyrene **108** and furyl substituted nitroolefin derivative **109** resulted in excellent enantioselectivities as 95% ee and 98% ee, respectively (entries 13-14).

The absolute configurations were found to be *R* for Michael addition products **96-108** and *S* for the **109** according to the specific rotations reported in literature.[49]

According to the dual activation model of Takemoto,[13] we proposed the activation modes of nucleophile and electrophile *via* our catalyst as given in Figure 12. The squaramide unit was presumed to activate nitroalkene *via* hydrogen bonding through nitro unit's oxygens. On the other hand, it was proposed that there is a six membered hydrogen bonding network in between the 2-AminoDMAP basic catalophore and dibenzoylmethane **(60)** after deprotonation.

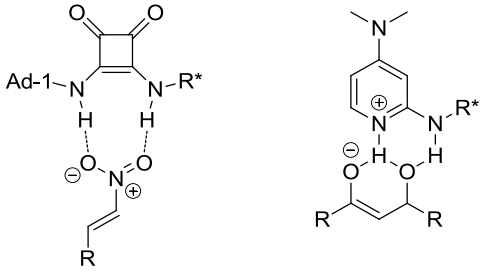


Figure 12. Proposed activation modes of electrophile and nucleophile

To understand the enantioselectivity with the assistance of the catalyst **92**, based on our proposed activation modes shown in Figure 12, the most reasonable transition state was proposed in Figure 13.

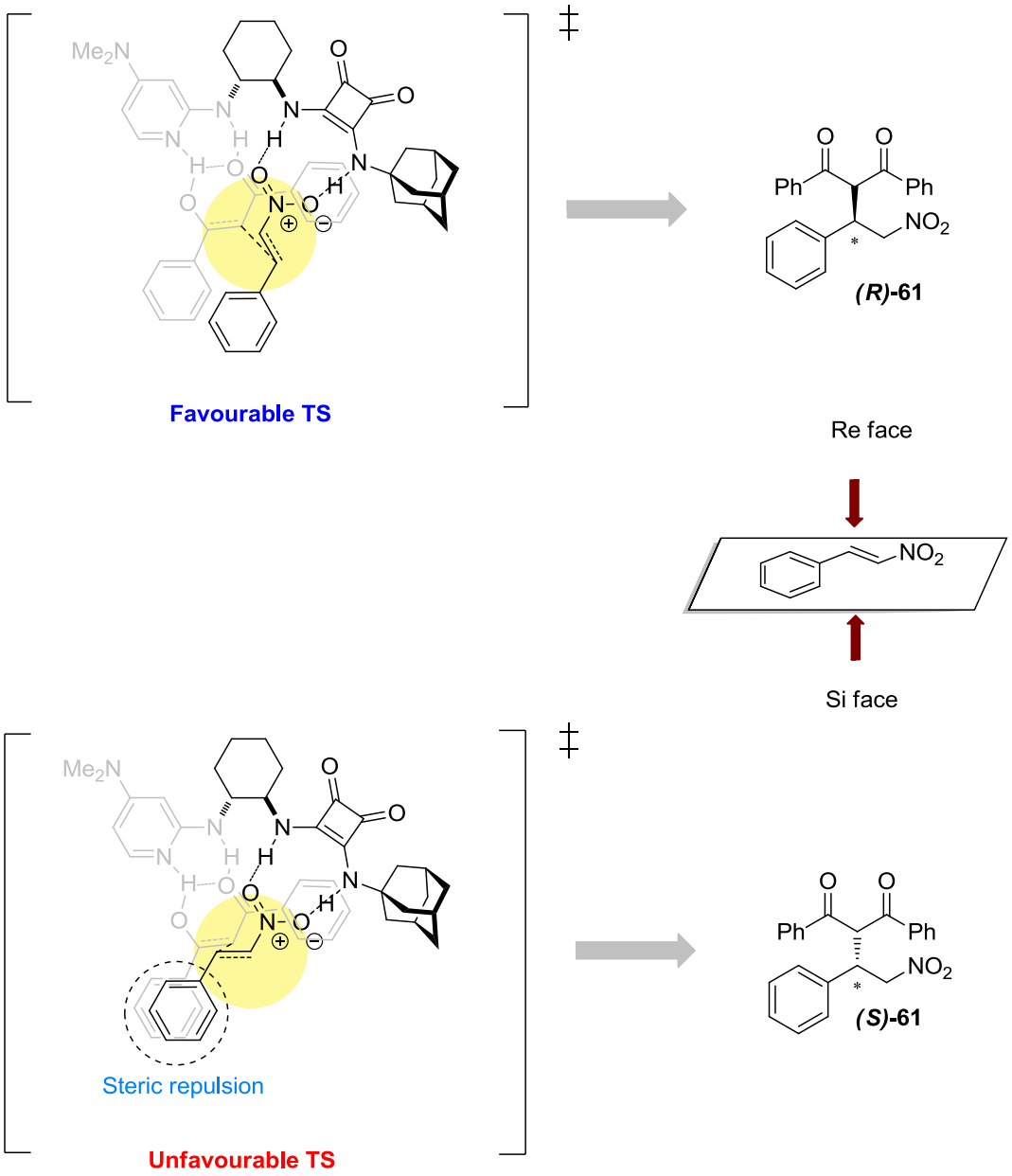


Figure 13. Proposed transition state model explaining enantioselectivity

It can be concluded that the steric repulsion between the two benzene rings of nitroolefin and diketone results in attacking of diketone to the *Re* face of the nitrostyrene to afford product **61**. According to our transition state model, it is difficult to afford *S* enantiomer due to the same reason. In addition, this picture figures out why dibenzoylmethane addition is challenging most of the time (Figure 13).

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

Structural elucidations of compounds were done with the instruments as written below.

^{1}H and ^{13}C nuclear resonance spectrums of compounds were recorded in $CDCl_3$ on Bruker Spectrospin Advance DPX 400 spectrometer. Chemical shifts are given in parts per million (ppm) with TMS as internal reference. Spin multiplicities were specified as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dq (doublet of quartet), t (triplet), q (quartet), m (multiplet), sept (septet) and coupling constants (*J*) were reported in Hertz (Hz). ^{1}H and ^{13}C NMR spectra of products are given in Appendix A.

Polarimetric measurements were made by Rudolph Scientific Autopol III polarimeter and reported as follows $[\alpha]_D^T$ (*c* in g per ml, solvent). HPLC chromatograms were recorded Thermo-Finnigan HPLC system. Daicel AD-H and AS-H chiral columns were used with different solvent systems. HPLC chromatograms of chiral products and racemic forms of them were given in Appendix B.

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

All reactions were monitored by TLC using precoated silica gel plates (Merck Silica Gel 60 F_{254}), visualized by UV-light. Chromatographic seperations were performed by glass precoated silica gel -200 purchased from Macherey-Nagel and column chromatography was performed on silica gel 60 with a particle size of 0.063–0.200 mm.

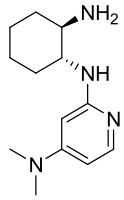
Compounds were named by using ChemDraw Ultra 12.0

3.2 General Procedure for Cu-Catalyzed Coupling Reaction

An oven-dried resealable Schlenk tube was charged with CuBr (0.2 mmol) and K_3PO_4 (2.0 mmol), evacuated, and backfilled with argon thrice. (*R,R*)-cyclohexane-1,2-diamine (1.20 mmol), Br-Heteroaromatic (1.0 mmol), and dioxane that was distilled over Na-benzophenone under Ar atmosphere (1.0 mL) were added by Schlenk line. The Schlenk tube was sealed, and the reaction mixture was stirred at 110 °C for 24 h. The resulting green-blue suspension was allowed to reach room temperature. Then 2 mL of water and 2 mL of conc ammonia were added consecutively. The resulting Prussian blue solution was extracted with dichloromethane thrice (3 × 25 mL). The combined dichloromethane phase was dried with brine and $MgSO_4$, respectively. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel using dichloromethane that was saturated with conc aqueous ammonia to afford C_1 symmetrical coupling products.

3.2.1 Synthesis of 2-AminoDMAP 71

General procedure starting from 2-BrDMAP (1 mmol, 201 mg) afforded the desired product **71** as a brown solid in 60% yield. Spectroscopic data have been reported previously.[51]

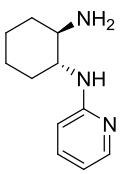


^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93−1.09 (m, 1H), 1.09−1.43 (m, 3H), 1.65 (dd, *J* = 2.5, 10.0 Hz, 2H), 1.75 (bs, 2H), 1.85−1.95 (m, 1H), 1.97−2.07 (m, 1H), 2.41 (dt, *J* = 4.1, 10.4 Hz, 1H), 2.87 (s, 6H), 3.24 (dq, *J* = 4.0, 9.6 Hz, 1H), 4.15 (d, *J* = 9.5 Hz, 1H), 5.53 (d, *J* = 2.2 Hz, 1H), 5.91 (dd, *J* = 2.3, 6.1 Hz, 1H), 7.69 (d, *J* = 6.1 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 25.4, 32.9, 34.9, 39.2, 56.3, 58.4, 87.8, 99.2, 148.0, 156.1, 160.1.

3.2.2 Synthesis of Compound 66

General procedure starting from commercially available 2-bromo-pyridine (1 mmol,95.8µl) afforded the desired product **66** as a brown solid in 53% yield.



Mp: 110-114 °C $[\alpha]_D^{30}$= -54° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (ddd, *J* = 5.0, 1.8, 0.6 Hz, 1H), 7.29 (ddd, *J* = 8.6, 7.1, 1.9 Hz, 1H), 6.45 (ddd, *J* = 7.1, 5.0, 0.8 Hz, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 4.58 (d, *J* = 9.1 Hz, 1H), 3.36 – 3.19 (m, 1H), 2.43 (td, *J* = 10.4, 4.1 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.93 – 1.84 (m, 1H), 1.73 (bs, 2H), 1.60-1.68 (m, 2H), 1.34 – 1.10 (m, 3H), 1.10 – 0.96 (m, 1H).

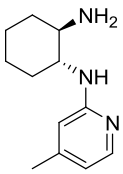
^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 147.9, 137.3, 112.6, 107.2, 58.0, 56.0, 34.92, 32.6, 25.2, 24.9

IR (neat) 3266, 2929, 2885, 1666, 1587, 1531, 1452, 1418, 800 cm^{-1}

HRMS calcd for $C_{11}H_{18}N_3$ [M + H]+ 192.1422, found 192.1427.

3.2.3 Synthesis of Compound 72

General procedure starting from commercially available 2-bromo-4-methylpyridine (1 mmol,111.3µl) afforded the desired product **72** as a viscous solid in 77% yield.



$[\alpha]_D^{30}$= -61° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 5.2 Hz, 1H), 6.30 (d, *J* = 5.2 Hz, 1H), 6.19 (s, 1H), 4.57 (d, *J* = 9.3 Hz, 1H), 3.27 (qd, *J* = 9.6, 4.0 Hz, 1H), 2.51 – 2.34 (m, 1H), 2.12 (s, 3H), 2.06-1.93 (m, 3H), 1.92–1.84 (m, 1H), 1.69–1.58 (m, 2H), 1.34–1.10 (m, 3H), 1.08-0.96 (m, 1H).

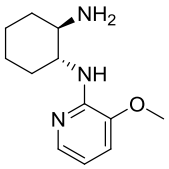
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 147.4, 146.6, 113.4, 106.4, 57.1, 55.0, 33.8, 31.8, 24.3, 23.9, 20.1

IR (neat) 3260, 2927, 2855, 1665, 1613, 1564, 1525, 1486, 795 cm^{-1}

HRMS calcd for $C_{12}H_{20}N_3$ [M + H]+ 206.1657, found 206.1650

3.2.4 Synthesis of Compound 73

Starting material 2-bromo-3-methoxypyridine was synthesized from commercially available 2-bromo-3-pyridinol by applying the procedure available in literature.[55] General procedure starting from 2-bromo-3-methoxypyridine (1 mmol, 210 mg) afforded the desired product **73** as a brown solid in 44% yield.



Mp : 67-69 °C $[\alpha]_D^{33}$= -59° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 5.1, 1.3 Hz, 1H), 6.73 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.41 (dd, *J* = 7.7, 5.1 Hz, 1H), 4.69 (d, *J* = 9.0 Hz, 1H), 3.74 (s, 3H), 2.41 (td, *J* = 10.4, 4.0 Hz, 1H), 2.05–1.89 (m, 2H), 1.74–1.53 (m, 5H), 1.42–1.13 (m, 4H), 1.13–0.99 (m, 1H).

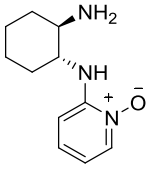
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 142.0, 138.4, 113.6, 111.3, 56.8, 56.5, 55.0, 35.1, 33.2, 25.4, 25.3

IR (neat) 3423, 2976, 2927, 2854, 1663, 1604, 1500, 1451, 1417, 1176, 755 cm^{-1}

HRMS calcd for $C_{12}H_{20}N_3O$ [M + H]+ 222.1606, found 222.1610

3.2.5 Synthesis of Compound 74

General procedure starting from commercially available 2-bromopyridine-*N*-oxide (1 mmol,189 mg) afforded the desired product **74** as a brown solid in 38% yield.



Mp: 115-117 °C $[\alpha]_D^{30}$= +28° (c=0.25, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 6.5, 1.2 Hz, 1H), 7.15 – 7.05 (m, 1H), 6.70 (dd, *J* = 8.5, 1.5 Hz, 2H), 6.46 (td, *J* = 7.5, 1.7 Hz, 1H), 3.04 (qd, *J*

= 9.9, 4.2 Hz, 1H), 2.71 (td, *J* = 9.8, 3.9 Hz, 1H), 2.44 (bs, 3H), 1.97–1.85 (m, 2H), 1.76–1.62 (m, 2H), 1.32–1.17 (m, 4H).

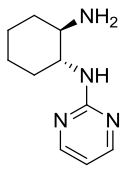
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 137.4, 128.8, 111.1, 106.4, 58.8, 55.4, 34.4, 32.2, 25.1, 24.5

IR (neat) 3261, 2933, 2859, 1623, 1571, 1526, 1445, 1194, 806, 751 cm^{-1}

HRMS calcd for $C_{11}H_{18}N_3O$ [M + H]+ 208.1450, found 208.1420

3.2.6. Synthesis of Compound 75

General procedure starting from commercially available 2-bromopyrimidine (1 mmol,159 mg) afforded the desired product **75** as a brown solid in 42% yield.



Mp: 110-112 °C. $[\alpha]_D^{29}$= -93° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 4.8 Hz, 2H), 6.43 (t, *J* = 4.8 Hz, 1H), 5.52 (d, *J* = 9.0 Hz, 1H), 3.69–3.49 (m, 1H), 2.43 (td, *J* = 14.4, 7.2 Hz, 1H), 2.05–1.96 (m, 1H), 1.96–1.88 (m, 1H), 1.72–1.57 (m, 4H), 1.35–1.14 (m, 3H), 1.14–1.04 (m, 1H).

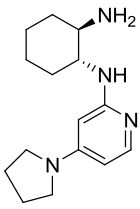
^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 157.9, 110.5, 57.6, 55.9, 34.9, 32.7, 25.2, 25.1

IR (neat) 3263, 2928, 2855, 1666, 1587, 1531, 1452, 1418, 800 cm^{-1}

HRMS calcd for $C_{10}H_{17}N_4$ [M + H]+ 193.1453, found 193.1450

3.2.7 Synthesis of Compound 76

Starting material 2-bromo-4-(pyrrolidin-1-yl)pyridine was synthesized from commercially available 4-(pyrrolidin-1-yl)pyridine by applying the procedure available in literature.[56] General procedure starting from 2-bromo-4-(pyrrolidin-1-yl)pyridine (1 mmol, 227 mg) afforded the desired product **76** as a brown solid in 40% yield.



Mp: 117-120 °C. $[\alpha]_D^{36}$= -54° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.0 Hz, 1H), 5.81 (dd, *J* = 6.0, 2.0 Hz, 1H), 5.43 (d, *J* = 2.0 Hz, 1H), 4.08 (d, *J* = 9.3 Hz, 1H), 3.27–3.14 (m, 5H), 2.42 (td, *J* = 10.3, 4.0 Hz, 1H), 2.09–1.96 (m, 1H), 1.99–1.83 (m, 5H), 1.75 (bs, 2H), 1.69-1.59 (m, 2H), 1.37–1.10 (m, 3H), 1.12–0.94 (m, 1H).

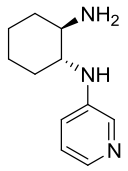
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 153.4, 147.8, 99.6, 87.5, 58.5, 56.3, 46.9, 34.8, 32.8, 25.4, 25.3 25.0.

IR (neat) 3297, 2976, 2925, 2854, 1606, 1527, 1485, 1284, 803 cm^{-1}

HRMS calcd for $C_{15}H_{25}N_4$ [M + H]+ 261.2001, found 261.1931

3.2.8 Synthesis of Compound 77

General procedure starting from commercially available 3-bromo-pyridine (1 mmol,96.3µl) afforded the desired product **77** as a semisolid in 44% yield.



$[\alpha]_D^{35}$= -73° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (t, *J* = 3.3 Hz, 1H), 7.84 (dd, *J* = 7.7, 3.1 Hz, 1H), 7.01 – 6.93 (m, 1H), 6.90–6.82 (m, 1H), 3.82 (d, *J* = 7.5 Hz, 1H), 2.86 (bs, 1H), 2.48 (td, *J* = 9.8, 4.4 Hz, 1H), 2.07-1.97 (m, 1H), 1.94-1.84 (m, 1H), 1.76–1.61 (m, 2H), 1.56 (bs, 2H), 1.32–1.10 (m, 3H), 1.08–0.90 (m, 1H)

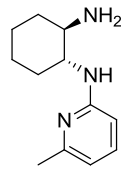
^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 138.5, 136.8, 123.7, 119.1, 59.7, 55.8, 35.2, 32.1, 25.1, 24.9

IR (neat) 3265, 3101, 3046, 2928, 2855, 1666, 1585, 1483, 1321, 792 cm^{-1}

HRMS calcd for $C_{11}H_{18}N_3$ [M + H]+ 192.1501, found 192.1498

3.2.9. Synthesis of Compound 78

General procedure starting from commercially available 2-bromo-6-methylpyridine (1 mmol,110µl) afforded the desired product **78** as a semisolid in 36% yield.



$[\alpha]_D^{33}$= -64° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* =7.71 Hz, 1H), 6.33 (d, *J* = 7.3 Hz, 1H), 6.20 (d, *J* = 8.3 Hz, 1H), 4.37 (d, *J* = 9.3 Hz, 1H), 3.14 (qd, *J* = 9.6, 4.0 Hz, 1H), 2.54–2.37 (m, 1H), 2.27 (s, 3H), 2.03–1.93 (m, 3H), 1.93–1.84 (m, 1H), 1.70–1.59 (m, 2H), 1.32–1.11 (m, 3H), 1.09–0.96 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.9, 136.9, 111.2, 102.1, 57.4, 55.1, 33.9, 31.6, 24.3, 23.9, 23.3

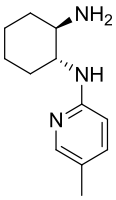
IR (neat) 3270, 2929, 2850, 1599, 1522, 1464, 1337, 778 cm^{-1}

HRMS calcd for $C_{12}H_{20}N_3$ [M + H]+ 206.1579, found 206.1593

3.2.10. Synthesis of Compound 79

General procedure starting from commercially available 2-bromo-5-methylpyridine (1 mmol,172 mg) afforded the desired product **79** as a semisolid in 42% yield.

$[\alpha]_D^{30}$= -65° (c=1, CH_2Cl_2).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.33 (d, *J* = 8.0 Hz, 1H), 4.18 (bs, 1H), 3.24 (d, *J* = 8.0 Hz, 1H), 2.43 (bs, 1H), 2.08 (s, 3H), 1.99 (d, *J*=12.6 Hz, 1H), 1.91 (d, *J*=9.2 Hz, 1H), 1.66 (bs, 4H), 1.37–1.10 (m, 3H), 1.10–0.92 (m, 1H).

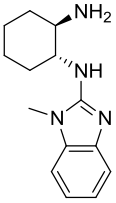
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 146.8, 137.6, 120.7, 106.2, 57.7, 55.4, 34.1, 31.9, 24.5, 24.2, 16.5

IR (neat) 3266, 2978, 2926, 2856, 1614, 1500 1359, 1020, 819 cm^{-1}

HRMS calcd for $C_{12}H_{20}N_3$ [M + H]+ 206.1657, found 206.1653

3.2.11. Synthesis of Compound 80

Starting material 2-bromo-1-methyl-1H-benzo[d]imidazole was synthesized from commercially available 2-bromo-1-H-benziimidazole by applying the procedure available in literature.[55] General procedure starting from2-bromo-1-methyl-1H-benzo[d]imidazole (1 mmol,197 mg) afforded the desired product **80** as a brown solid in 25% yield.



Mp: 73-75 °C. $[\alpha]_D^{30}$= -28° (c=0.25, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.6 Hz, 1H), 7.09 – 6.92 (m, 3H), 3.43 (s, 3H), 2.54-2.40 (m, 1H), 2.37–2.26 (m, 1H), 2.01–1.80 (m, 3H), 1.72-1.59(m, 2H), 1.45–1.00 (m, 6H).

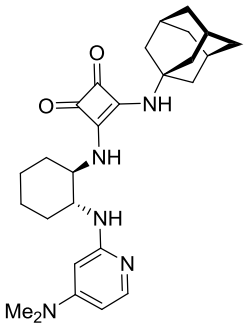
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 133.7, 119.9, 118.2, 115.1, 105.7, 94.9, 58.2, 54.7, 34.9, 31.9, 27.1, 24.1, 23.8

IR (neat) 3330, 3053, 2859, 1618, 1570, 1448, 1281, 1236, 1128, 739 cm^{-1}

HRMS calcd for $C_{14}H_{20}N_4$ [M + H]+ 245.1688, found 245.1778

3.3 Synthesis of Bifunctional Organocatalyst 92

To a solution of (*R*,*R*)-configurated 2-aminoDMAP **71** (47 mg, 0.2 mmol) in one to one (volume) mixture of DCM:MeOH (1 mL) was added solid 3-(1-adamantylamino)-4-ethoxycyclobut-3-ene-1,2-dione **(95)** (55 mg, 0.2 mmol) at rt. The solution was stirred for 48 hours at this temperature. The mixture was directly loaded on to a silica gel column and eluted with DCM:MeOH (90 : 10) to afford solid 2-aminoDMAP/Squaramide bifunctional organocatalyst **92** in 66% yield. Spectroscopic data have been reported previously.[50]



^{1}H NMR (400 MHz, DMSO) δ 1.01 – 1.45 (m, 10H), 1.46 – 1.56 (m, 1H), 1.57 –1.87 (m,6H), 1.90 – 2.10 (m, 2H), 2.85 (s, 6H), 3.59 – 3.87 (m, 4H), 5.52 (s, 1H), 5.85 (d, *J* = 7.6 Hz, 1H), 5.99 (dd, *J* = 2.0, 6.2 Hz, 1H), 7.41 (bs, 2H), 7.59 (d, *J* = 6.2 Hz, 1H).

Two protons could not be located.

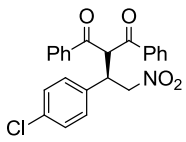
^{13}C NMR (100 MHz, DMSO) δ 23.8, 24.3, 24.7, 32.1, 33.4, 33.6, 38.7, 51.7, 53.8, 54.8, 57.5, 88.4, 98.9, 146.0, 155.3, 158.7, 166.9, 167.5, 181.6, 182.2.

3.4 General Procedure for Asymmetric Conjugate Addition of Dibenzoylmethane to *trans*-(*β*)-nitrostyrene Derivatives

To a solution of *trans*-*β*-nitrostyre derivative (0.20 mmol) in toluene (1.0 mL) was added 2-aminoDMAP/Squaramide (0.002 mmol, 0.98mg) and dibenzoylmethane **60** (134 mg, 0.6 mmol). Upon consumption of limiting reagent (monitored by TLC) at 5 °C, the reaction mixture was directly subjected to column chromatography using 1:10 EtOAc:Hexanes as the eluent to afford the conjugate addition products.

3.4.1 Synthesis of (*R*)-2-(1-(4-chlorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3 dione

General procedure starting from (*E)*-1-chloro-4-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **101** in 90% yield and 89% ee in 3 hours. Spectroscopic data have been reported previously.[49]



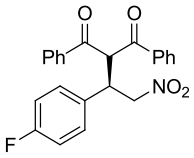
HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =33.8 min, t_{minor}=24.6, $[\alpha]_D^{20}$= -6.5° (c=0.25, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.85 (m, 2H), 7.77-7.74 (m, 2H), 7.54-7.48 (m, 2H), 7.41-7.32 (m, 4H), 7.15 (m, 4H), 5.78 (d, J = 10.8 Hz, 1H), 4.93-4.91 (m, 2H), 4.57 (dd, J = 7.2, 19.2 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 193.4, 136.0, 135.7, 135.3, 134.3, 134.1, 134.0, 129.7, 129.2, 129.1, 129.0, 128.8, 128.6, 77.3, 59.7, 43.5

3.4.2 Synthesis of (*R*)-2-(1-(4-fluorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-fluoro-4-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **106** in 75% yield and 95% ee in 7 hours.



Mp: 115-119 °C

HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =34.1 min, t_{minor}=23.3, $[\alpha]_D^{20}$= -9.1° (c=0.25, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.78 (m, 2H), 7.73–7.68 (m, 2H), 7.51–7.40 (m, 2H), 7.36-7.26 (m, 4H), 7.16–7.10 (m, 2H), 6.86-6.76 (m, , 2H), 5.73 (d, *J* = 8.3 Hz, 1H), 4.93–4.78 (m, 2H), 4.55 (td, *J* = 8.3, 5.3 Hz, 1H).

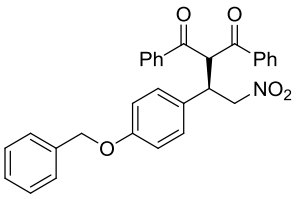
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 192.5, 161.3 (d, $J_{(C-F)}$= 247.7 Hz), 134.96 (d, $J_{(C-F)}$= 30.6 Hz), 133.1 (d, $J_{(C-F)}$= 27.3 Hz), 131.5 (d $J_{(C-F)}$= 3.5 Hz), 129.1, 129.0, 128.0, 127.9, 127.8, 127.7, 127.6, 126.2, 115.0, 114.8,76.5, 58.8, 42.4.

IR (neat) 2954, 2950, 1690, 2595, 1551, 1509, 1447, 1377, 1258, 970,820, 687 cm^{-1}

HRMS calcd for $C_{23}H_{18}FNO_4$, [M - H]+ 390.1220, found 390.1239

3.4.3 Synthesis of (*R*)-2-(1-(4-(benzyloxy)phenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-(benzyloxy)-4-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **99** in 54% yield and 86% ee in 10 hours.



Mp: 156-159

HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =59.1 min, t_{minor}=47.9, $[\alpha]_D^{20}$= -22.0° (c=0.25, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.4 Hz, 2H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.51–7.38 (m, 2H), 7.36–7.20 (m, 9H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.76-6.69 (m, 2H), 5.73 (d, *J* = 8.1 Hz, 1H), 4.97–4.75 (m, 4H), 4.50 (dd, *J* = 14.2, 7.6 Hz, 1H

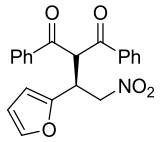
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 192.7, 157.5, 135.7, 135.2, 134.9, 134.8, 133.0, 132.7, 128.4, 127.9, 127.8, 127.8, 127.6, 127.6, 126.9, 126.4, 114.2, 68.9, 59.1, 42.4

IR (neat) 2965, 2960, 1691,1595, 1546, 1513, 1448, 1286, 1117, 1039, 821, 733, 689 cm^{-1}

HRMS calcd for $C_{30}H_{25}NO_5$, m/z 479.1733, found 479.1760

3.4.4 Synthesis of (*S*)-2-(1-(furan-2-yl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-2-(2-nitrovinyl)furan (0.2 mmol) afforded the desired chiral product **109** in 58% yield and 98% ee in 6 hours. Spectroscopic data have been reported previously.[49]



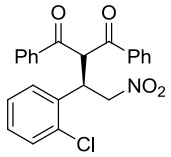
HPLC (AD-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =38.4 min, t_{minor}=48.5, $[\alpha]_D^{19}$= -29.5° (c=1, CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89-7.85 (m, 4H), 7.58-7.55 (m, 2H), 7.45-7.39 (m, 4H), 7.23 (m, 1H), 6.13 (m, 2H), 6.04 (d, *J* = 7.6 Hz, 1H), 5.01-4.90 (m, 2H), 4.77-4.72 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.7, 149.8, 142.5, 135.9, 135.4, 134.1, 133.9, 129.0, 128.9,128.6, 110.7, 108.9, 75.6, 56.7, 37.8

3.4.5 Synthesis of (*R*)-2-(1-(2-chlorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-chloro-2-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **102** in 86% yield and 94% ee in 3 hours.



Mp: 110-115 °C

HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =24.6 min, t_{minor}=23.1, $[\alpha]_D^{20}$= 31.5° (c=0.25, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 2H), 7.35–7.25 (m, 5H), 7.17-7.12 (m, 1H), 7.08-7.03 (m, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 5.99 (d, *J* = 6.5 Hz, 1H), 5.21–4.91 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 192.3, 135.2, 134.6, 133.2, 133.1, 132.9, 132.8, 129.4, 129.4, 128.6, 128.3, 127.9, 127.9, 127.7, 127.6, 126.2, 74.2, 56.1, 39.2

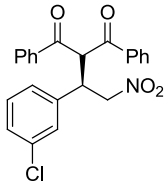
IR (neat) 2921, 2850, 1686, 1549, 1447, 1376, 1258, 1179, 756, 684 cm^{-1}

HRMS calcd for $C_{23}H_{18}ClNO_4$, m/z 407.0924, found 407.0943

3.4.6 Synthesis of (*R)*-2-(1-(3-chlorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-chloro-3-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **103** in 74% yield and 84% ee in 2.5 hours.

Mp: 86-88 °C



HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =43.9 min, t_{minor}=24.7, $[\alpha]_D^{19}$= -25° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.76 (m, 2H), 7.74–7.67 (m, 2H), 7.51–7.39 (m, 2H), 7.36–7.24 (m, 4H), 7.15 (s, 1H), 7.07–7.00 (m, 3H), 5.74 (d, *J* = 8.2 Hz, 1H), 4.98–4.80 (m, 2H), 4.52 (td, *J* = 8.2, 5.4 Hz, 1H).

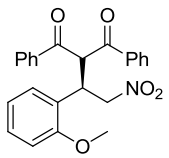
^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 192.4, 137.8, 134.9, 134.6, 133.7, 133.2, 132.9, 129.2, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 125.6, 75.9, 58.4, 42.6

IR (neat) 2820, 1689, 1656, 1593, 1544, 1446, 1379, 1255, 958, 683 cm^{-1}

HRMS calcd for $C_{23}H_{18}ClNO_4$, m/z 407.0921, found 407.0941

3.4.7 Synthesis of (*R*)-2-(1-(2-methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-methoxy-2-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **98** in 70% yield and 85% ee in 6.5 hours. Spectroscopic data have been reported previously.[49]



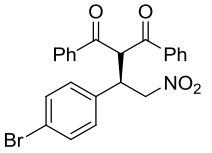
HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =20.4 min, t_{minor}=16.6, $[\alpha]_D^{20}$= -35.7° (c=1, CH_2Cl_2).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91-7.87 (m, 4H), 7.55-7.51 (m, 2H), 7.43-7.37 (m, 4H), 7.20-7.13 (m, 2H), 6.81-6.76 (m, 2H), 6.09 (d, *J* = 8.0 Hz, 1H), 5.25 (dd, *J* = 9.6, 12.8 Hz, 1H), 4.94 (dd, *J* = 4.0, 13.2 Hz, 1H), 4.86-4.80 (m, H), 3.87 (s, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.4, 194.2, 157.1, 136.4, 136.0, 133.8, 133.7, 131.0, 129.4, 128.9, 128.7, 128.6, 128.6, 124.2, 121.1, 110.9, 75.8, 57.2, 55.3, 40.9

3.4.8 Synthesis of (*R*)-2-(1-(4-bromophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-bromo-4-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **104** in 75% yield and 94% ee in 4 hours. Spectroscopic data have been reported previously.[49]



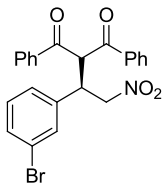
HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =37.0 min, t_{minor}=26.7, $[\alpha]_D^{24}$= -16.2° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.85 (m, 2H), 7.77-7.74 (m, 2H), 7.59-7.52 (m, 2H),7.54-7.47 (m, 2H), 7.41-7.29 (m, 6H), 7.11-7.08 (m, 2H), 5.78 (d, *J* = 10.8 Hz, 1H), 4.93-4.90 (m, 2H), 4.57 (dd, *J* = 7.2, 19.6 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 193.3, 136.0, 135.8, 135.7, 134.3, 134.0, 132.1, 130.0, 129.1, 129.0, 128.8, 128.6, 122.3, 77.2, 59.6, 43.6

3.4.9 Synthesis of (*R*)-2-(1-(3-bromophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-bromo-3-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **105** in 60% yield and 83% ee in 5 hours.



Mp: 102-105 °C

HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =46.8 min, t_{minor}=26.4, $[\alpha]_D^{24}$= -14.6° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.53–7.43 (m, 2H), 7.38–7.26 (m, 5H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 5.72 (d, *J* = 8.0 Hz, 1H), 4.98–4.80 (m, 2H), 4.51 (td, *J* = 8.2, 5.2 Hz, 1H).

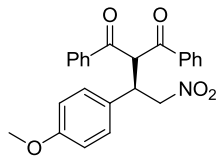
^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 192.3, 138.0, 134.9, 134.6, 133.2, 132.9, 130.4, 130.3, 129.4, 128.1, 127.9, 127.7, 127.6, 126.1, 121.9, 75.9, 58.3, 42.6

IR (neat) 2960, 1686, 1539, 1256, 1189, 1176, 958, 799, 771, 711, 666 cm^{-1}

HRMS calcd for $C_{23}H_{18}BrNO_4$, m/z 451.0419, found 451.0443

3.4.10 Synthesis of (*R*)-2-(1-(4-methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-methoxy-4-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **96** in 70% yield and 80 % ee in 6.5 hours. Spectroscopic data have been reported previously.[49]



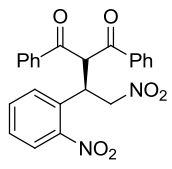
HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =49.7min, t_{minor}=35.7, $[\alpha]_D^{24}$= -17.9° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.57-7.51 (m, 2H), 7.44-7.36 (m, 4H), 7.17 (d, *J* = 8.8 Hz, 2 H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.84 (d, *J* = 8.0 Hz, 1H), 5.00-4.96 (m, 2H), 4.61 (dd, *J* = 7.2, 14.4 Hz, 1H), 3.72 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 193.7, 159.3, 136.2, 135.9, 134.1, 133.8, 129.4, 129.0, 128.84, 128.81, 128.6, 128.5, 114.3, 77.7, 60.1, 55.2, 43.5

3.4.11 Synthesis of (*R*)-2-(2-nitro-1-(2-nitrophenyl)ethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-nitro-2-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **108** in 68% yield and 95% ee in 18 hours. Spectroscopic data have been reported previously.[49]



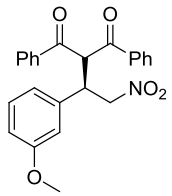
HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =32.6min, t_{minor}=27.2, $[\alpha]_D^{24}$= 93.2° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.84 (m, 5H), 7.60-7.52 (m, 2H), 7.43-7.36 (m, 7H),6.28 (d, *J* = 6.0 Hz, 1H), 5.28-5.26 (m, 1H), 5.12-5.09 (m, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.4, 193.4, 150.0, 136.2, 135.6, 134.3, 133.2, 131.7, 130.1, 129.1, 129.1, 128.9, 128.9, 128.6, 128.6, 125.4, 75.1, 58.0, 439.0

3.4.12 Synthesis of (*R*)-2-(2-Nitro-1-(2-nitrophenyl)ethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-methoxy-3-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **97** in 94% yield and 90% ee in 6 hours. Spectroscopic data have been reported previously.[49]



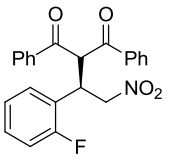
HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =49.6 min, t_{minor}=64.8, $[\alpha]_D^{19}$= -16.2° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 2H), 7.59-7.52(m, 2H), 7.44-7.37 (m, 4H), 7.16-7.12 (m, 1H), 6.85-6.71 (m, 3H), 5.85 (d, *J* = 8.0 Hz, 1H), 5.02-4.99 (m, 2H), 4.64-4.58 (m, 1H), 3.70 (s,3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 193.6, 159.8, 138.3, 136.2, 135.8, 134.1, 133.8, 130.0, 128.8, 128.8, 128.6, 128.1, 120.3, 114.3, 113.6, 77.2, 59.7, 55.2, 44.0

3.4.13 Synthesis of Synthesis of (*R*)-2-(1-(2-fluorophenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-fluoro-2-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **107** in 95% yield and 95% ee in 3 hours.



Mp: 88-91 °C

HPLC (OJ-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =53.9 min, t_{minor}=80.4, $[\alpha]_D^{19}$= -49.1° (c=1, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H), 7.80–7.75 (m, 2H), 7.50–7.39 (m, 2H), 7.36-7.24(m, 4H), 7.16 (dt, *J* = 7.6, 1.7 Hz, 1H), 7.09–7.01 (m, 1H), 6.91–6.82 (m, 2H), 5.92 (d, *J* = 8.6 Hz, 1H), 5.02 (dd, *J* = 13.2, 10.2 Hz, 1H), 4.87–4.70 (m, 2H).

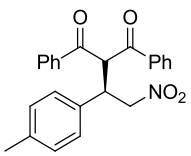
^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 193.4, 161.1 (d, $J_{(C-F)}$= 245.3 Hz), 135.9 (d, $J_{(C-F)}$= 41.7 Hz), 134.1 (d, $J_{(C-F)}$= 17.6 Hz), 131.3 (d, $J_{(C-F)}$= 4.1 Hz), 130.1, 130.1, 129.1, 128.9, 128.7, 128.6, 124.6, 124.7, 123.5 (d, *J* = 13.0 Hz), 115.9 (d, *J* = 22.1 Hz), 75.9, 57.5, 39.9

IR (neat) 2950, 2945, 1685, 1593, 1555, 1469, 1448, 1258, 1204, 682 cm^{-1}

HRMS calcd for $C_{23}H_{18}FNO_4$, m/z 391.1220, found 391.1247

3.4.14 Synthesis of (*R*)-2-(2-nitro-1-(p-tolyl)ethyl)-1,3-diphenylpropane-1,3-dione

General procedure starting from (*E*)-1-methyl-4-(2-nitrovinyl)benzene (0.2 mmol) afforded the desired chiral product **100** in 85% yield and 92% ee in 2 hours. Spectroscopic data have been reported previously.[49]



HPLC (AS-H, 80:20 n-Hexane:Isopropanol, 1 mL / min, 254 nm): t_{major} =30.6 min, t_{minor}=23.0, $[\alpha]_D^{24}$= -13° (c=1, CH_2Cl_2).

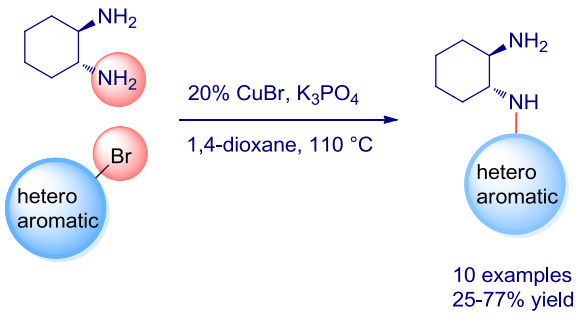
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.57-7.52 (m, 2H), 7.44-7.37 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 2 H), 7.03 (d, *J* = 7.6 Hz, 2H), 5.85 (d, *J* = 8.0 Hz, 1H), 5.00-4.98 (m, 2H), 4.62 (dd, *J* = 5.2, 8.0 Hz, 1H), 2.25 (s, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 193.6, 137.9, 136.2, 135.9, 134.1, 133.8, 133.7, 129.6,129.0, 128.83, 128.81, 128.7, 128.1, 77.5, 60.1, 43.7, 21.0

CHAPTER 4

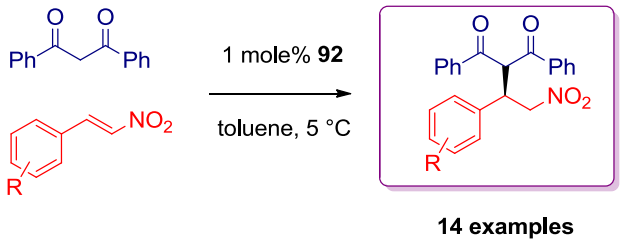
CONCLUSION

In this work, a novel methodology for selective mono-*N*-heteroarylation of chiral C_2-symmetrical cyclohexanediamine *via* copper chemistry was developed firstly. It is unique in terms of being a challenging step to build a variety of bifunctional organocatalysts with the most demanding chiral backbone (1*R*, 2*R*)-1,2-diaminocyclohexane. The developed methodology would provide a direct access to bifunctionality in novel organocatalyst design by transforming C_2-symmetrical nature of chiral backbone into C_1. Each C_1-symmetrical amidine can be a good candidate in future works.



Scheme 37. C_1-symmetrical amidine synthesis

In the second part of the thesis, we showed the effectiveness of squaramide type acid catalophoric unit in Michael addition of dibenzoylmethane to *β*-nitroolefines. 14 examples have been done by using 1 mol% organocatalyst. The enantioselectivities are varied between 80-98% ee. Consequently, we obtained better results than the literature studies in terms of reaction duration and enantioselectivity.



Scheme 38. Enantioselective Michael addition

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APPENDIX A

NMR DATA

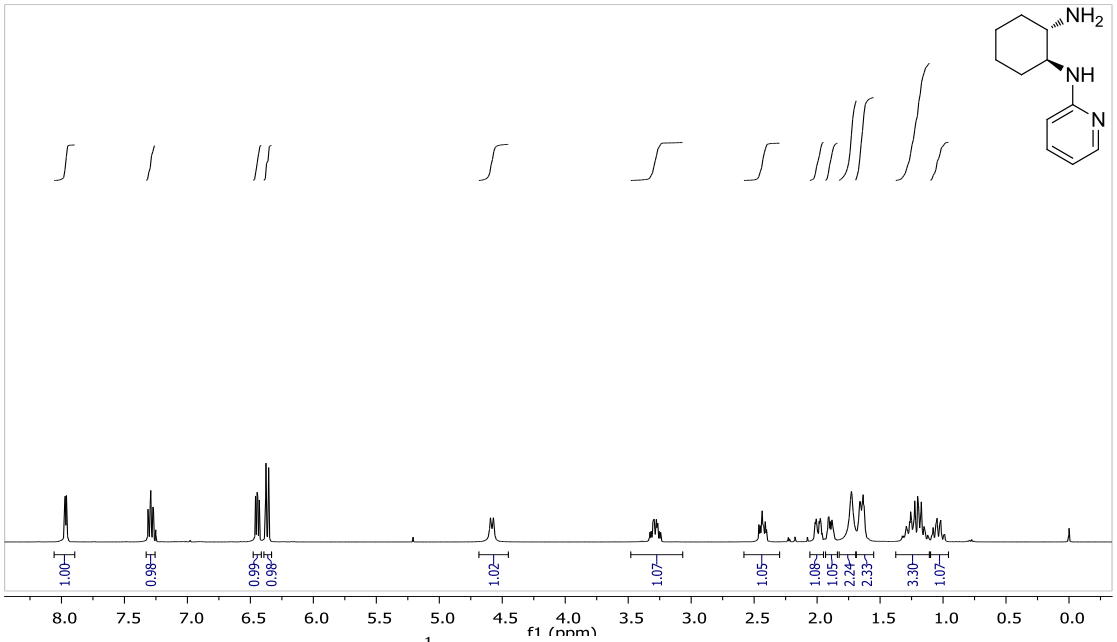


Figure A. 1 ^{1}H NMR spectrum of compound **66**

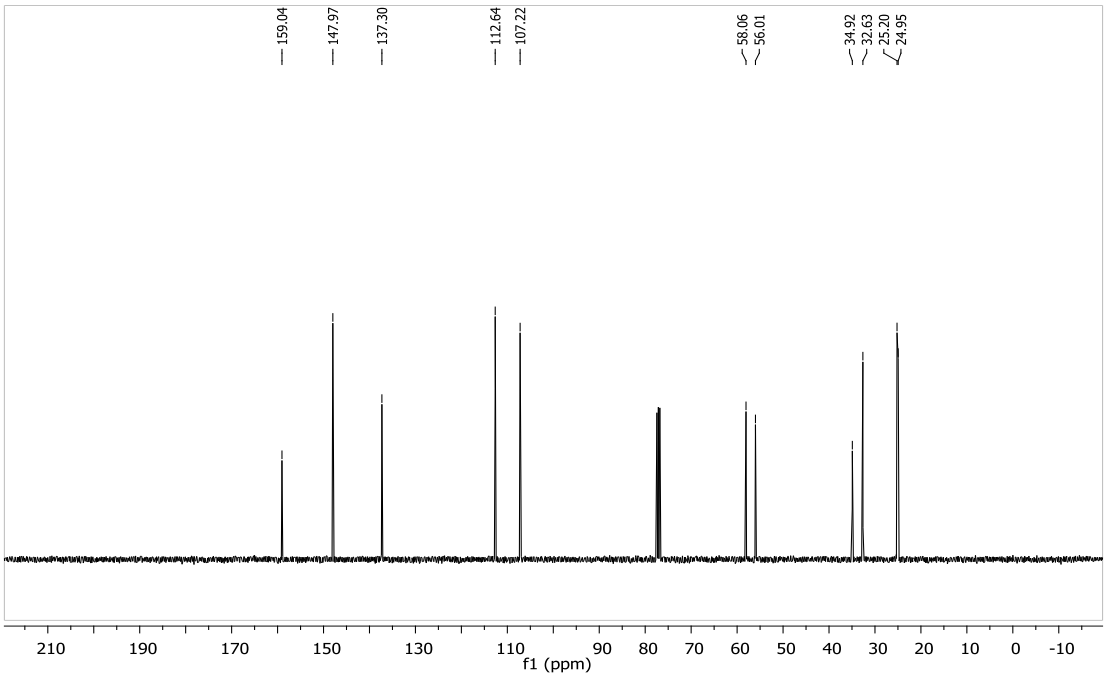


Figure A. 2 ^{13}C NMR spectrum of compound **66**

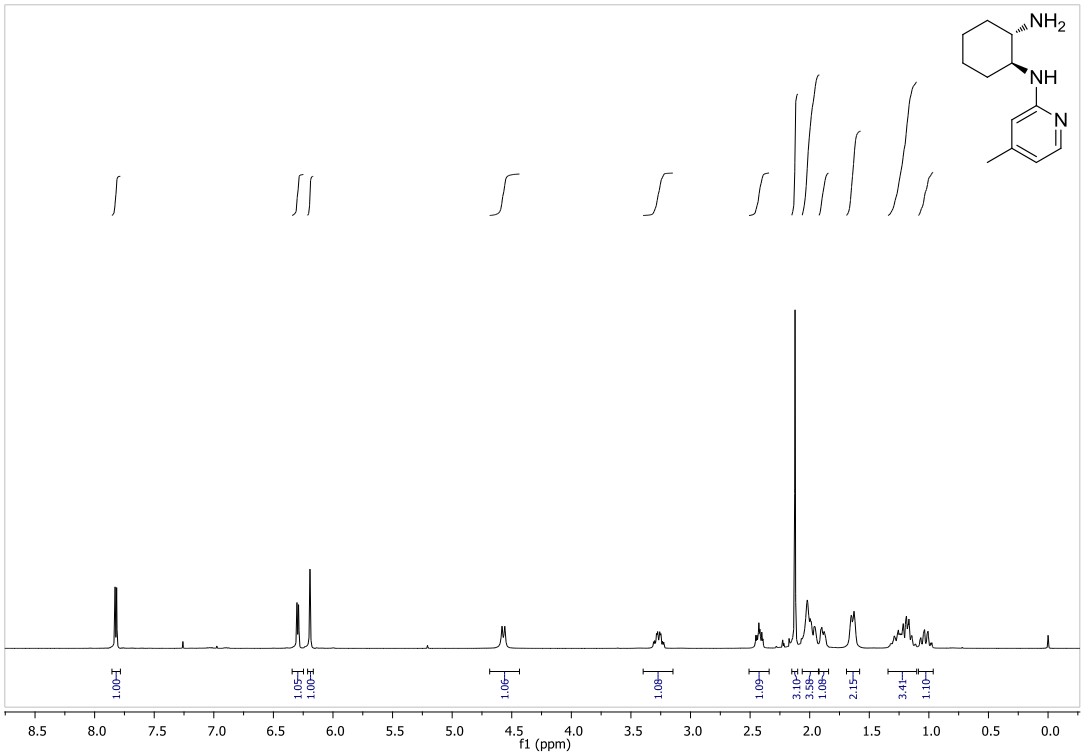


Figure A. 3 ^{1}H NMR spectrum of compound **72**

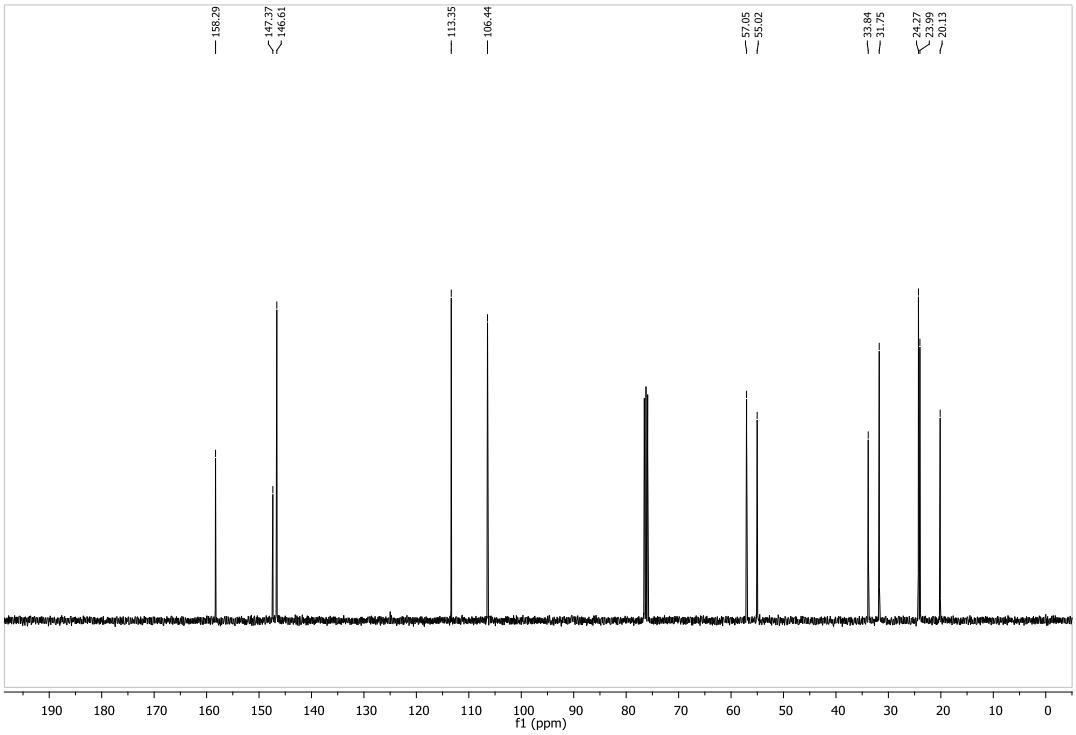


Figure A. 4 ^{13}C NMR spectrum of compound **72**

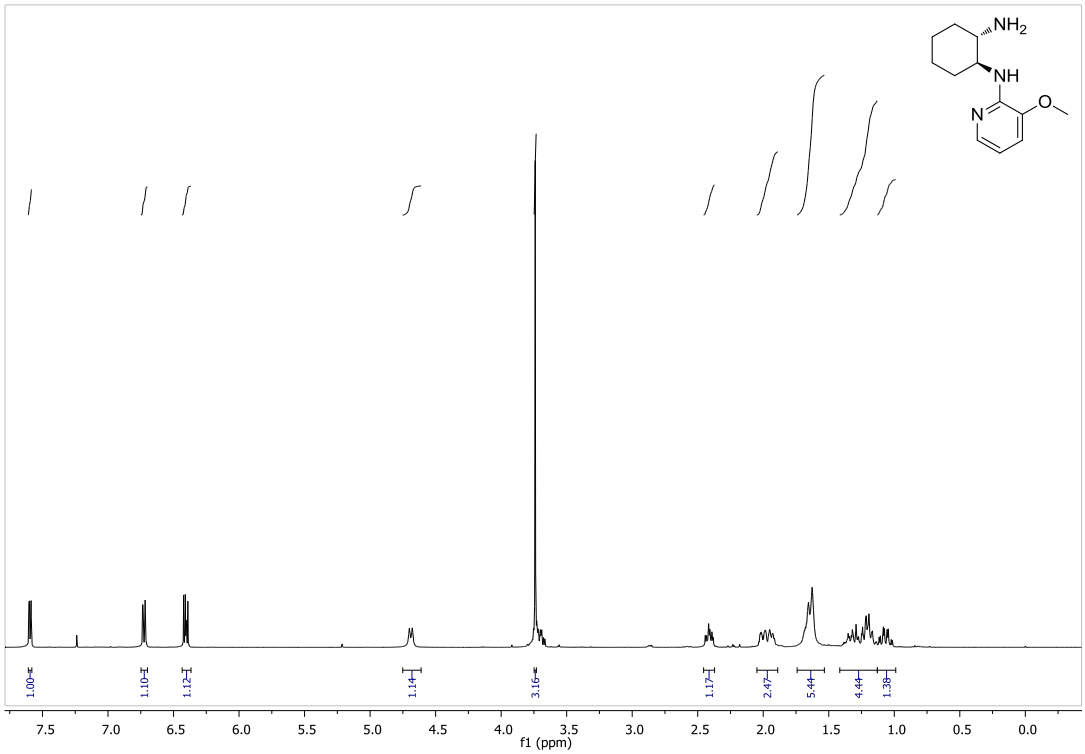


Figure A. 5 ^{1}H NMR spectrum of compound **73**

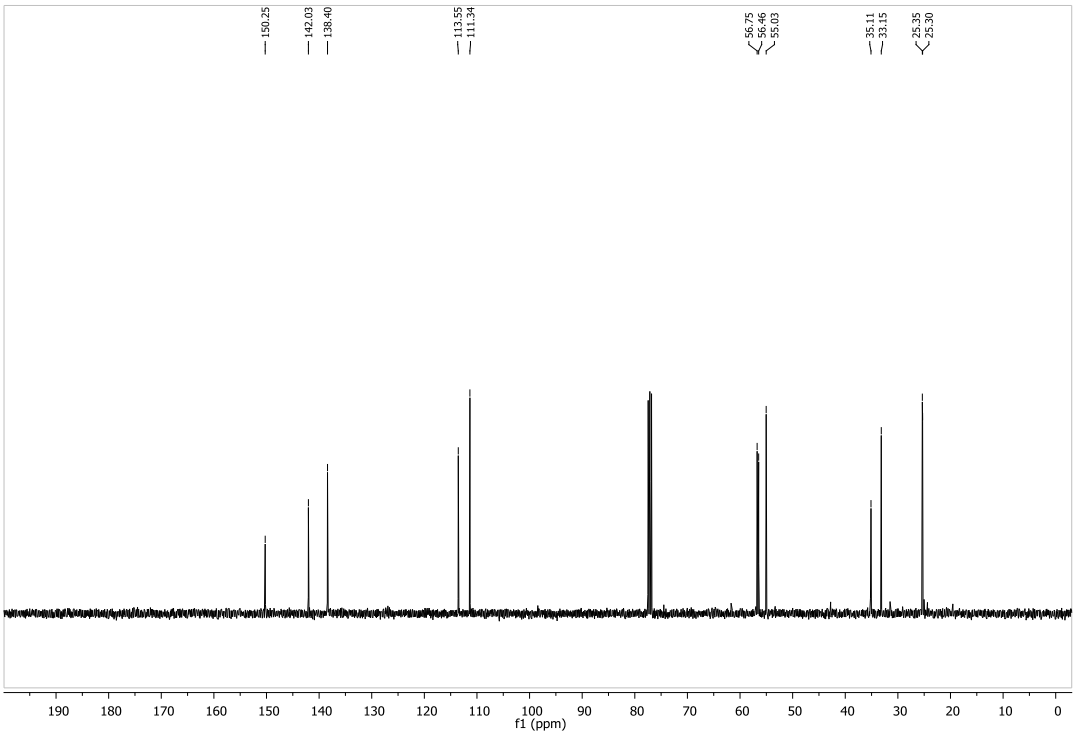


Figure A. 6 ^{13}C NMR spectrum of compound **73**

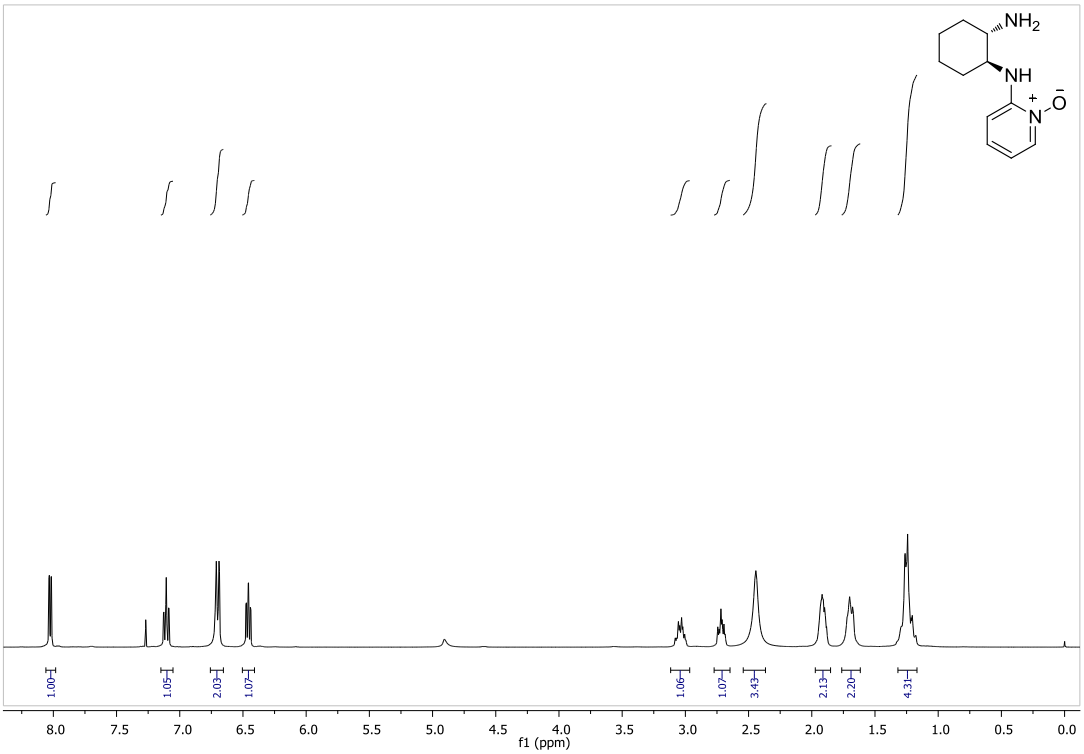


Figure A. 7 ^{1}H NMR spectrum of compound **74**

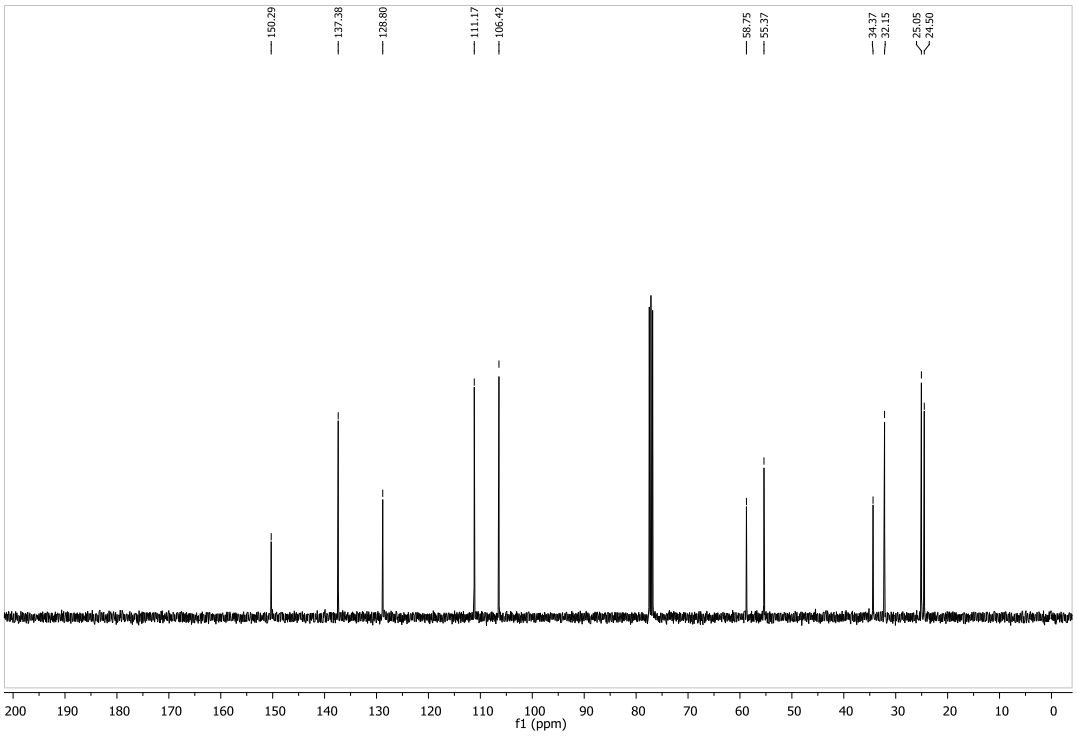


Figure A. 8 ^{13}C NMR spectrum of compound **74**

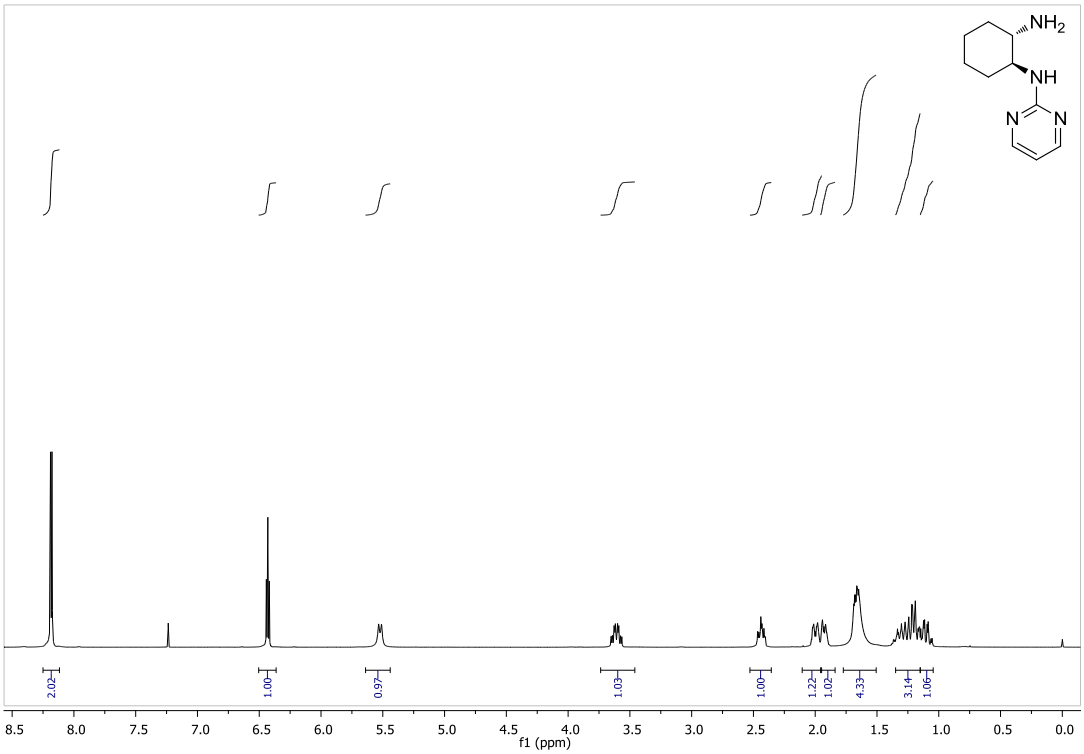


Figure A. 9 ^{1}H NMR spectrum of compound **75**

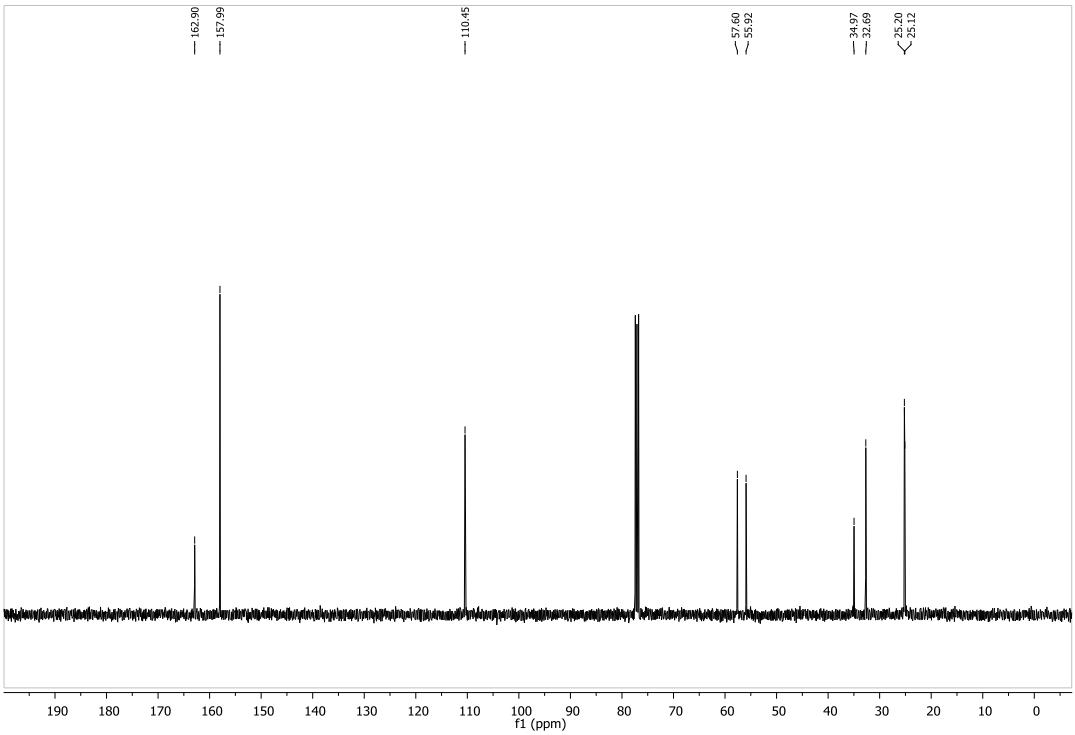


Figure A. 10 ^{13}C NMR spectrum of compound **75**

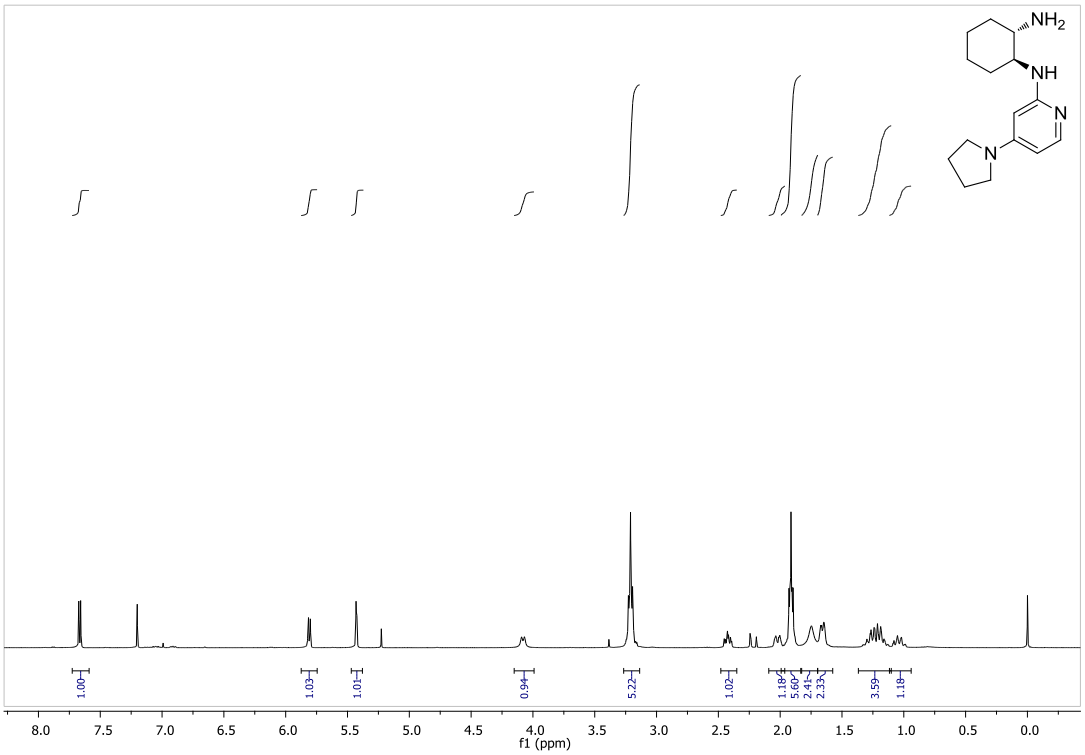


Figure A. 11 ^{1}H NMR spectrum of compound **76**

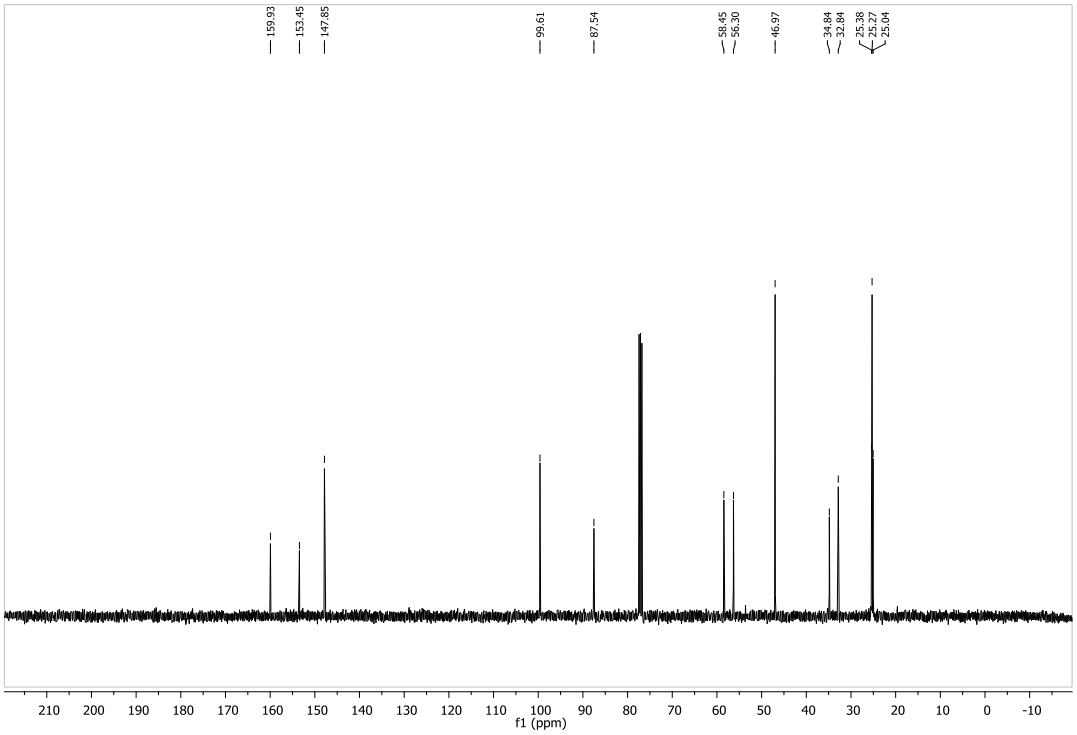


Figure A. 12 ^{13}C NMR spectrum of compound **76**

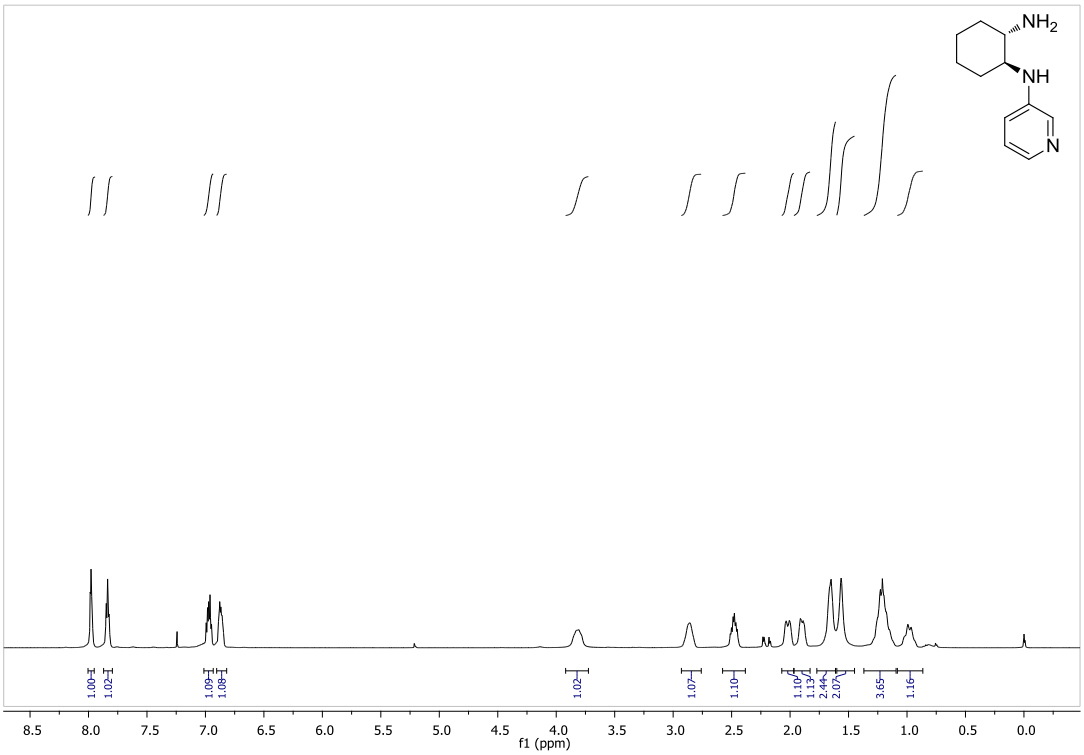


Figure A. 13 ^{1}H NMR spectrum of compound **77**

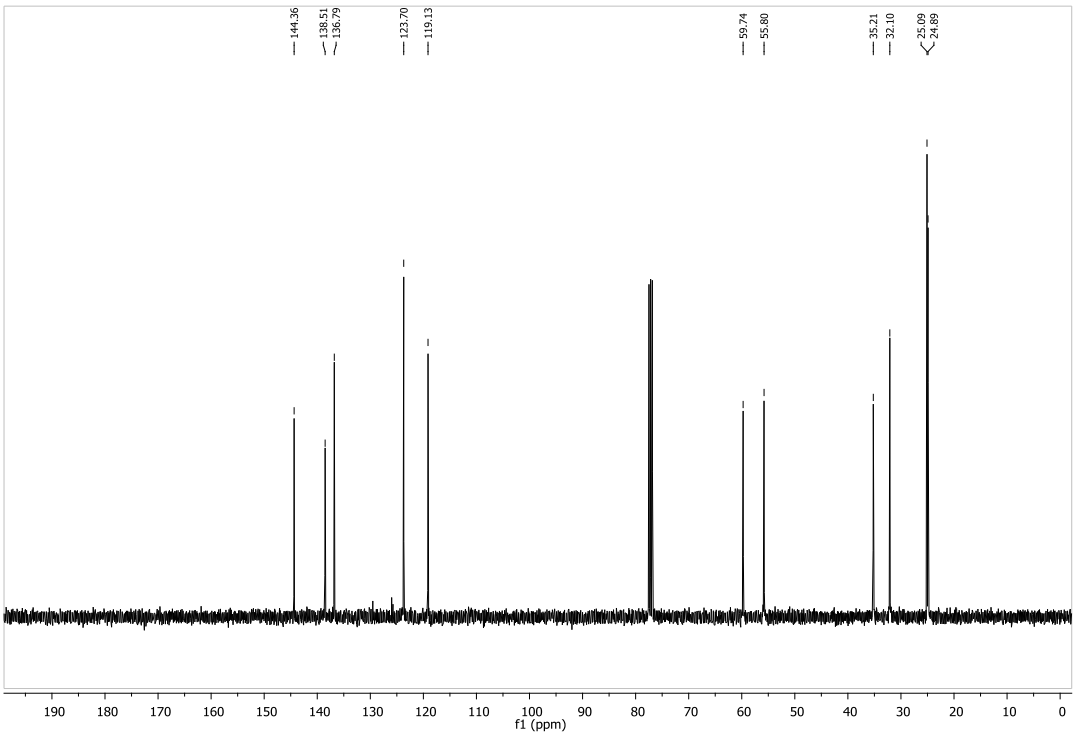


Figure A. 14 ^{13}C NMR spectrum of compound **77**

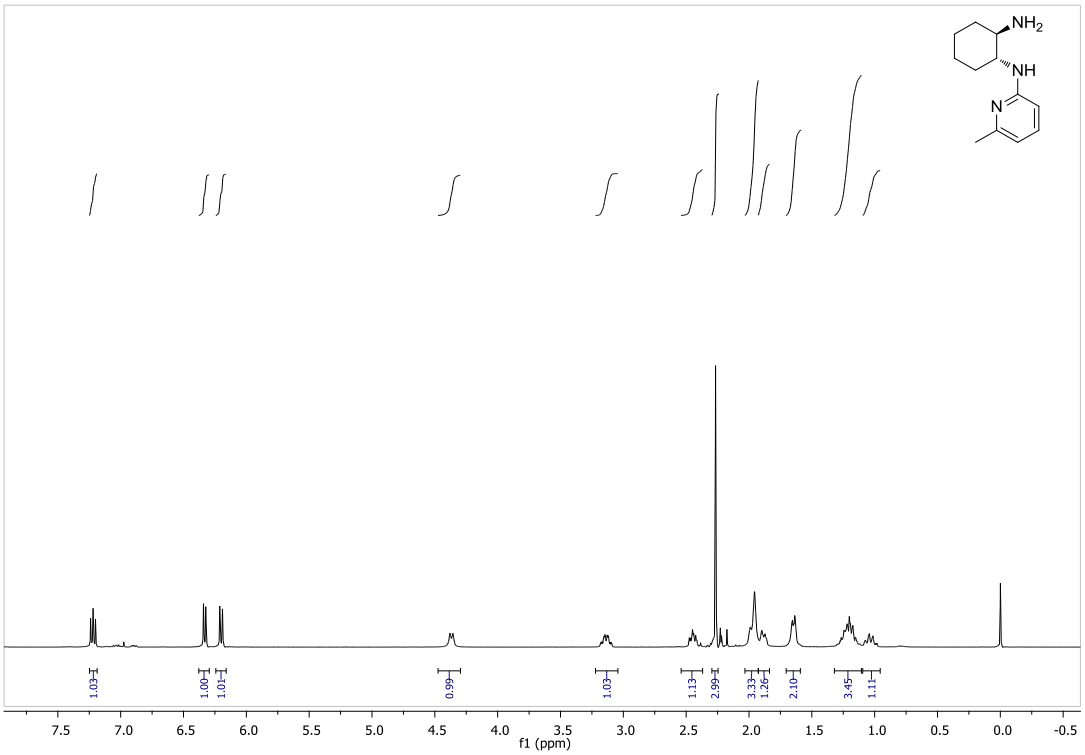


Figure A. 15 ^{1}H NMR spectrum of compound **78**

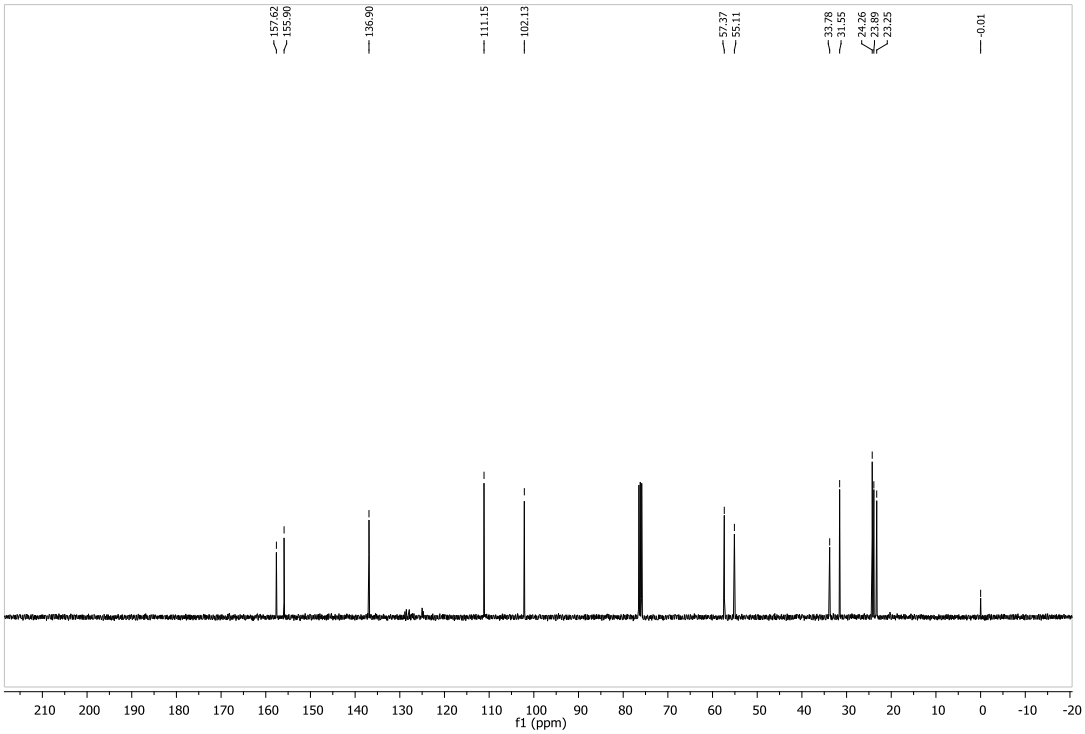


Figure A. 16 ^{13}C NMR spectrum of compound **78**

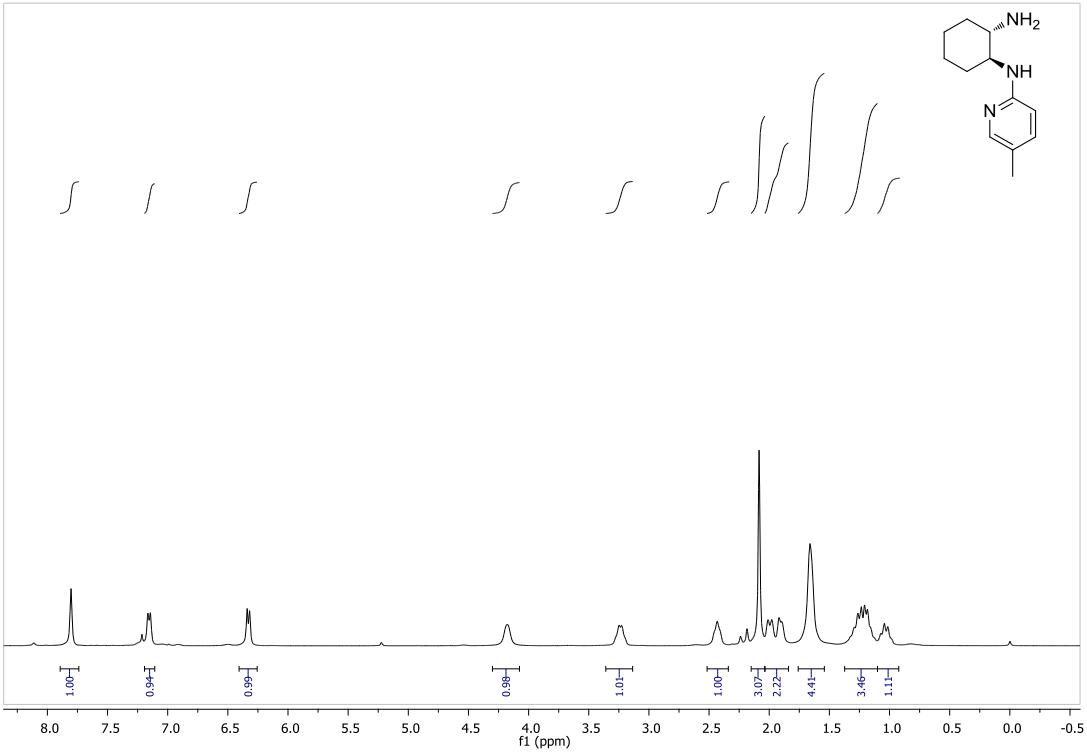


Figure A. 17 ^{1}H NMR spectrum of compound **79**

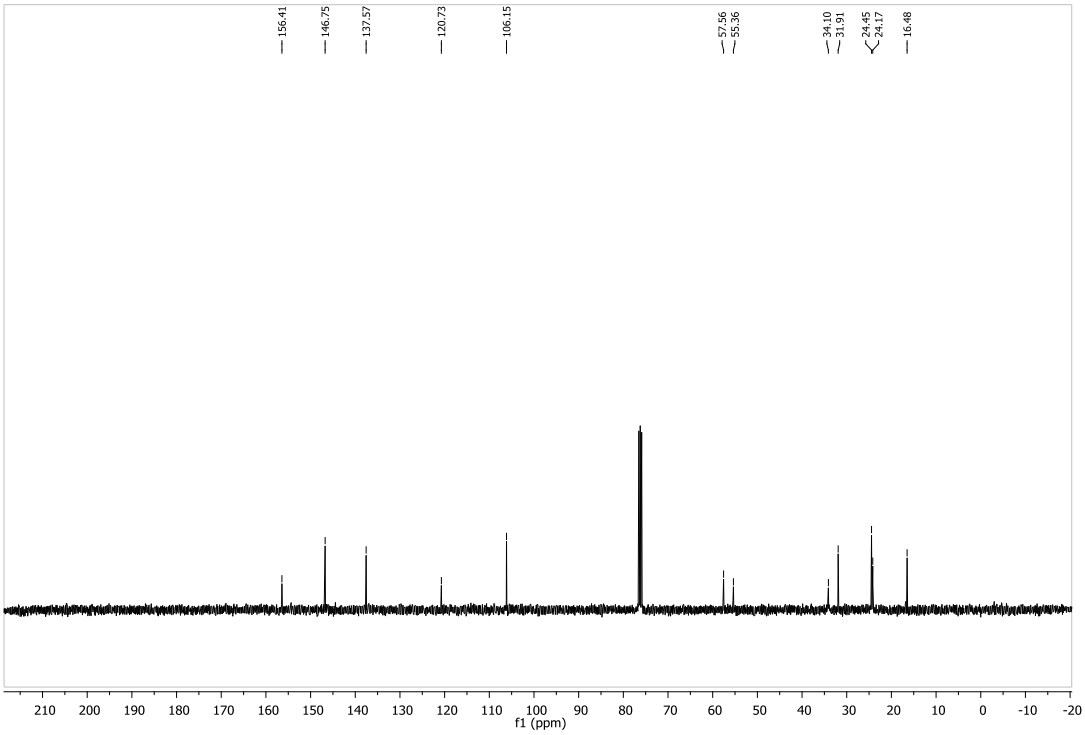


Figure A. 18 ^{13}C NMR spectrum of compound **79**

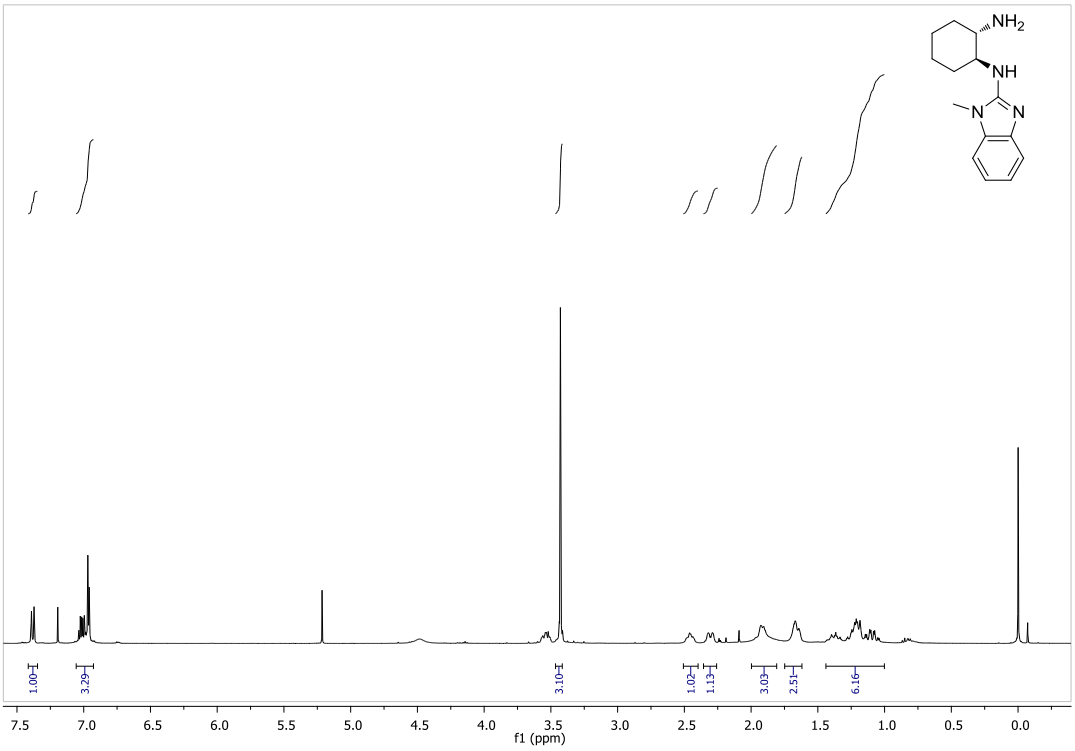


Figure A. 19 ^{1}H NMR spectrum of compound **80**

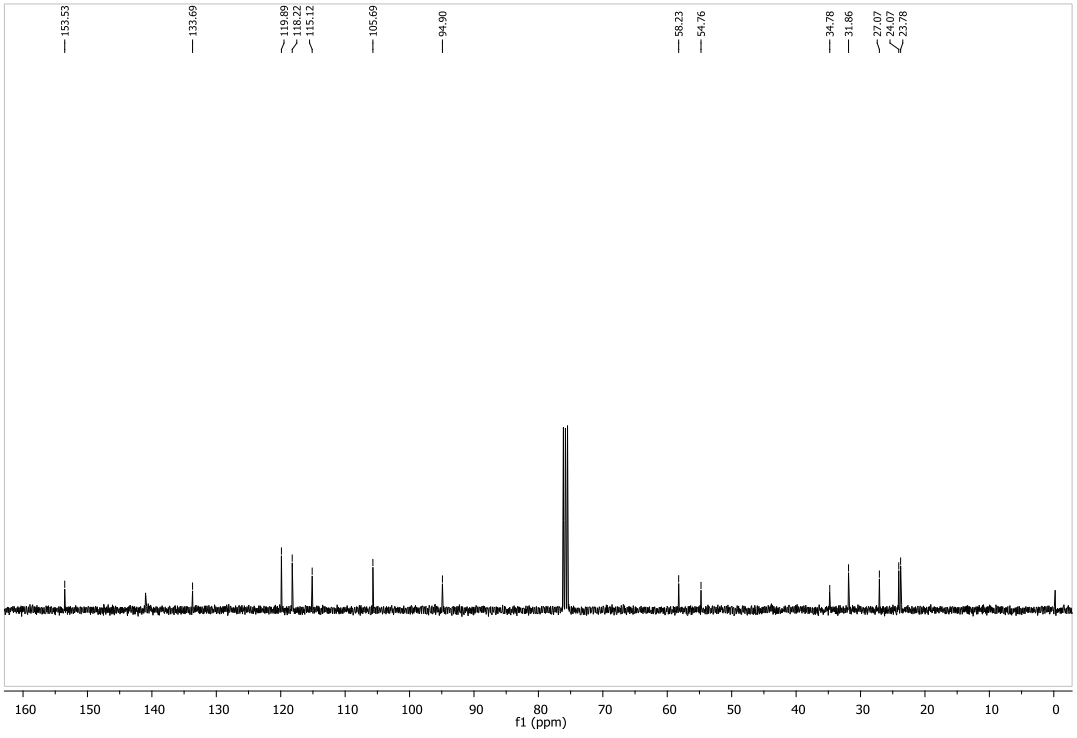


Figure A. 20 ^{13}C NMR spectrum of compound **80**

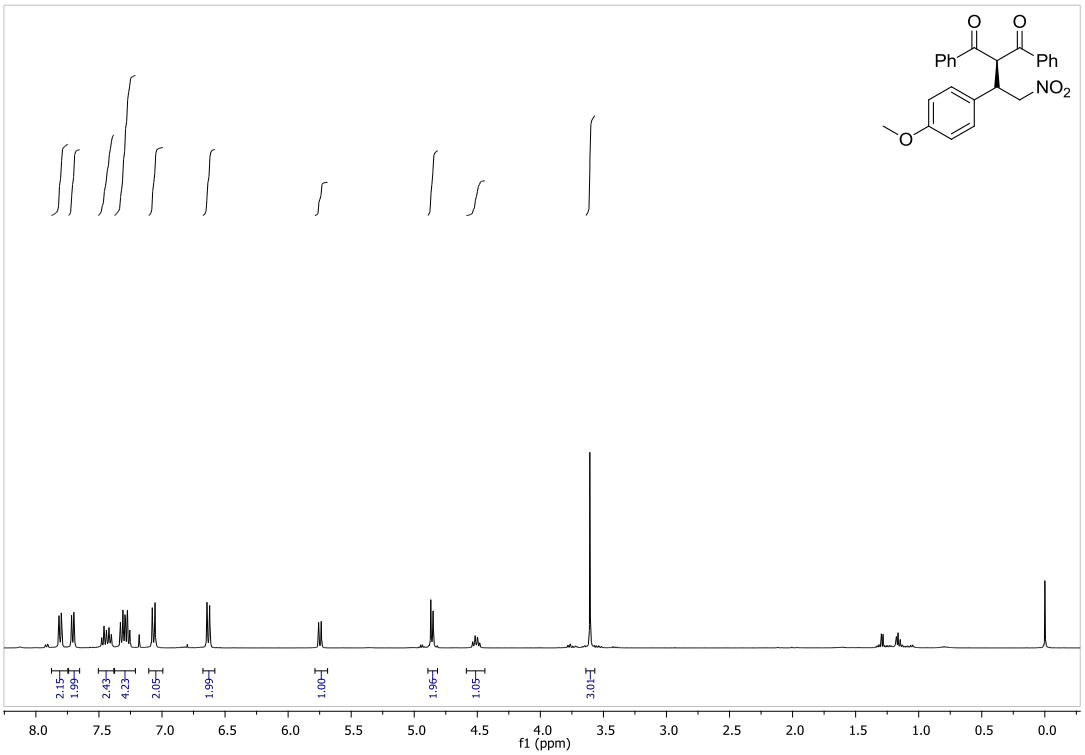


Figure A. 21 ^{1}H NMR spectrum of compound **96**

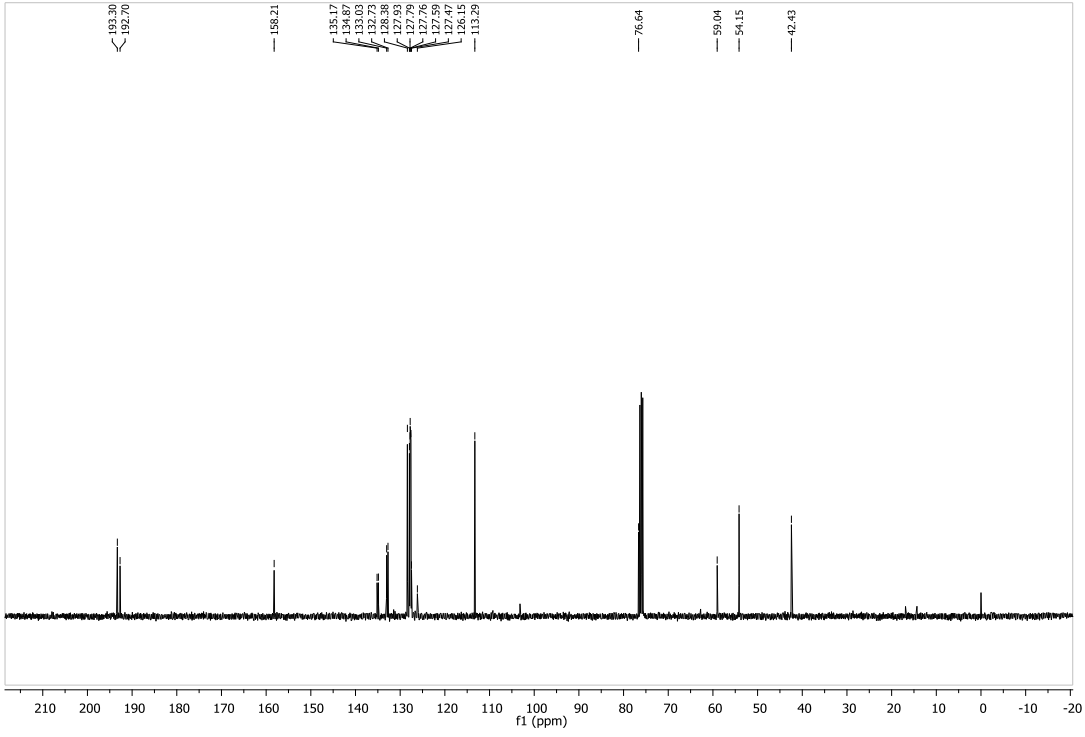


Figure A. 22 ^{13}C NMR spectrum of compound **96**

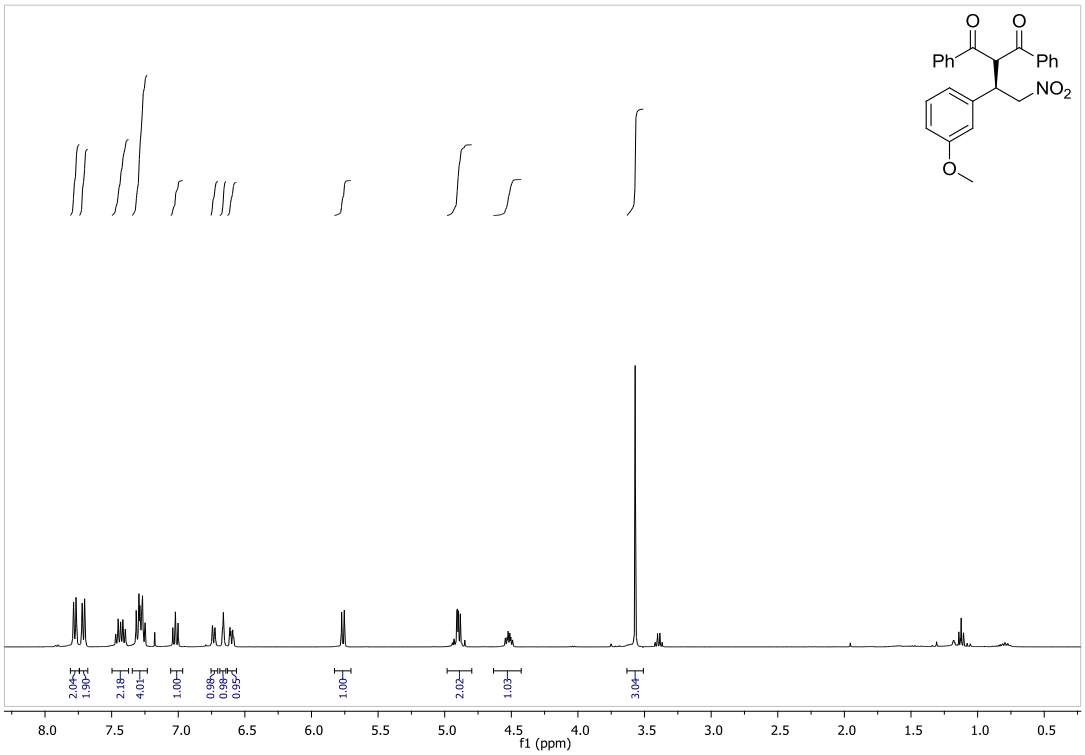


Figure A. 23 ^{1}H NMR spectrum of compound **97**

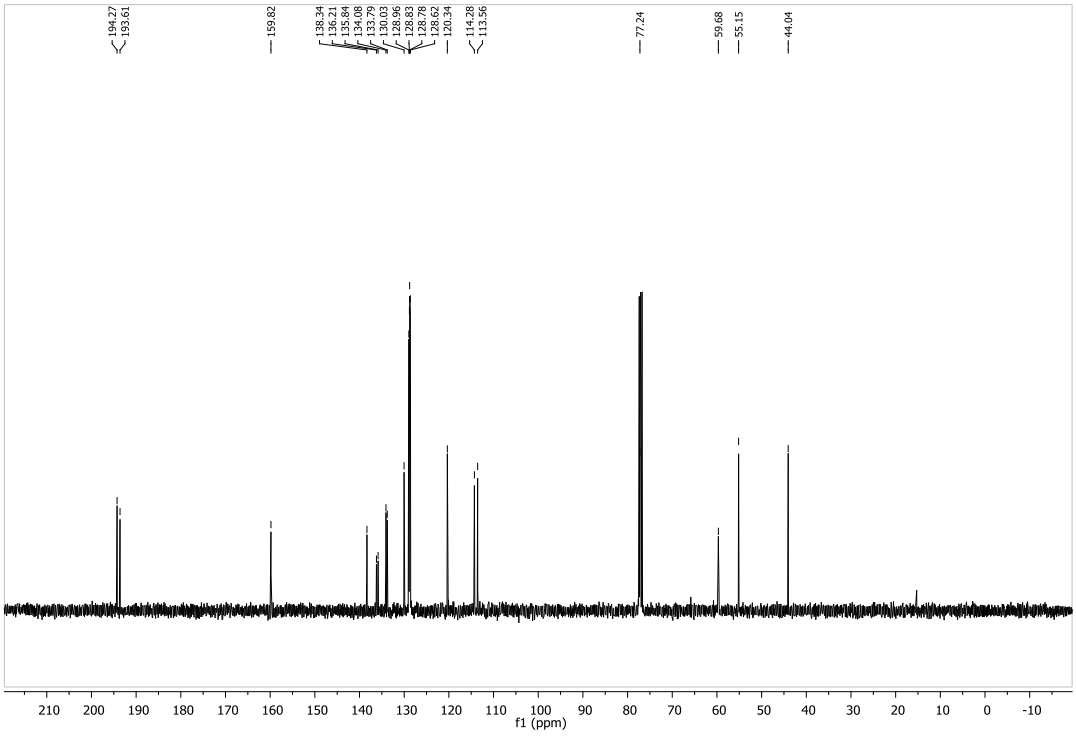


Figure A. 24 ^{13}C NMR spectrum of compound **97**

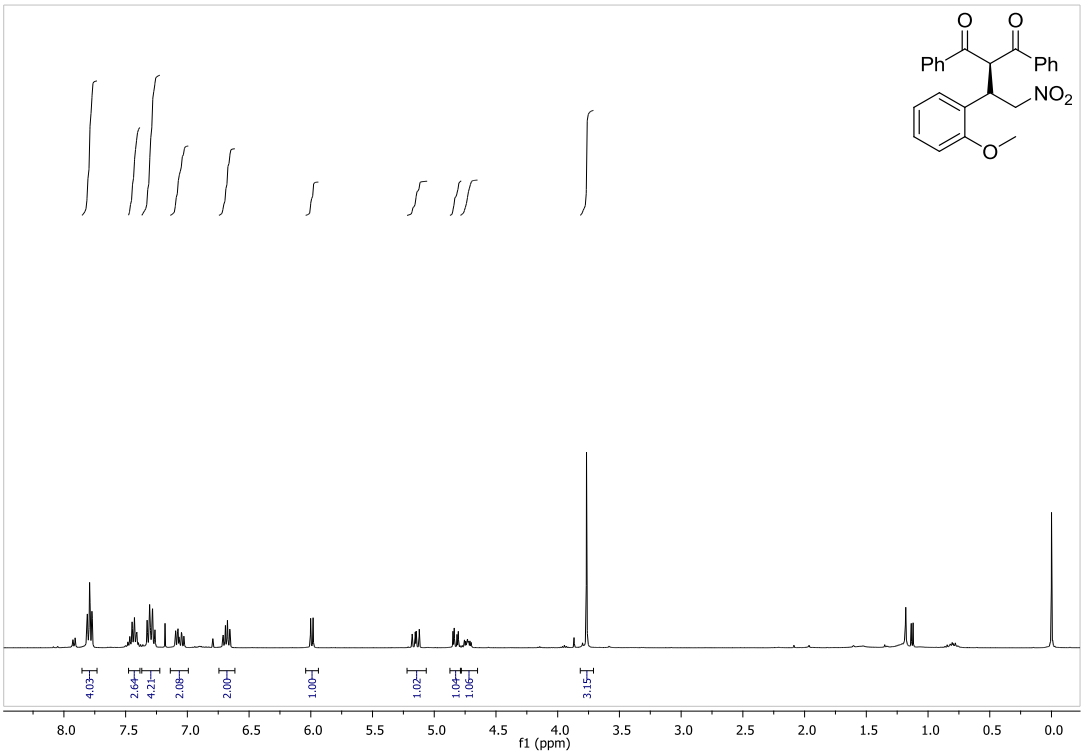


Figure A. 25 ^{1}H NMR spectrum of compound **98**

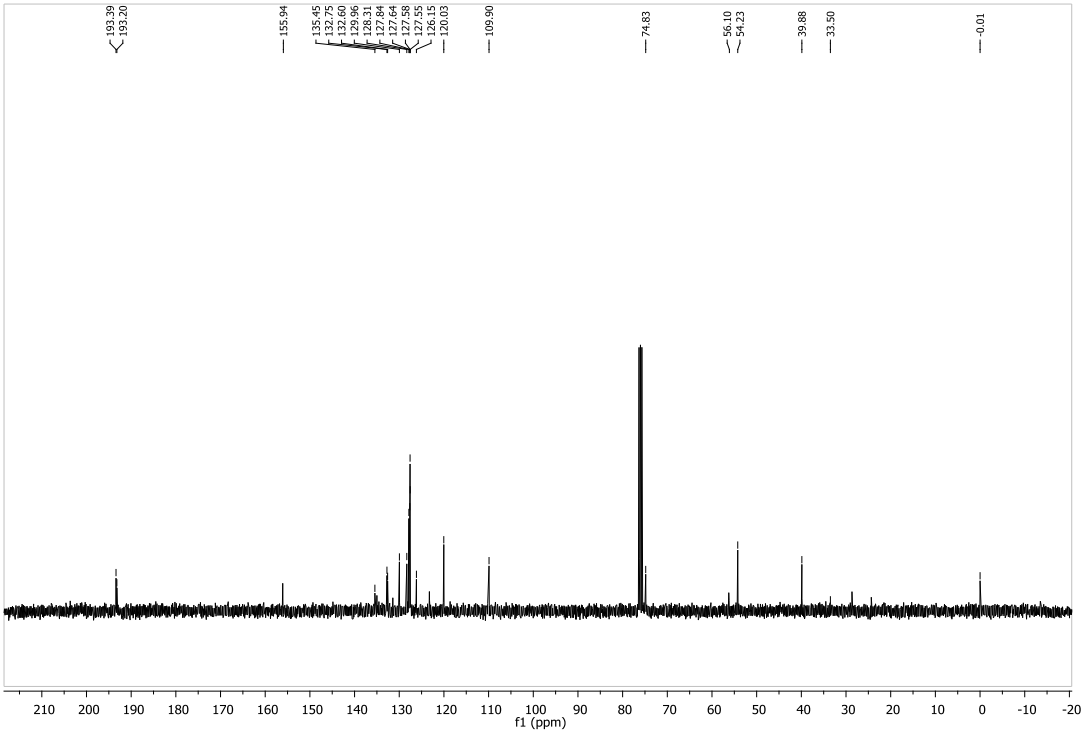


Figure A. 26 ^{13}C NMR spectrum of compound **98**

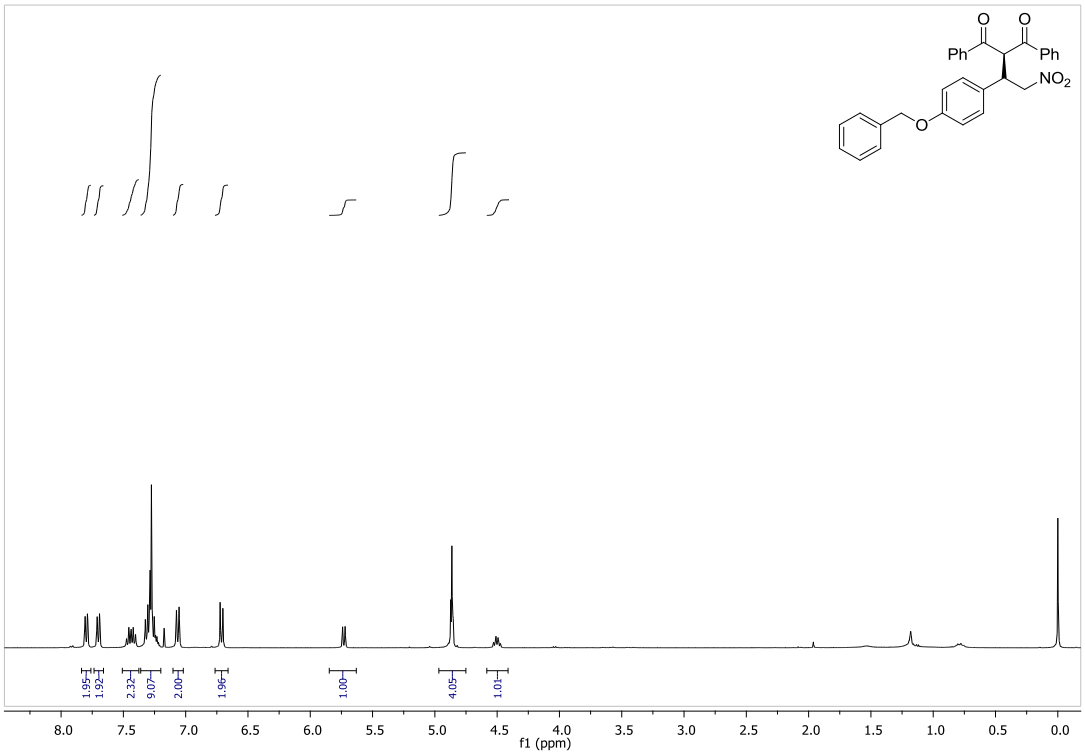


Figure A. 27 ^{1}H NMR spectrum of compound **99**

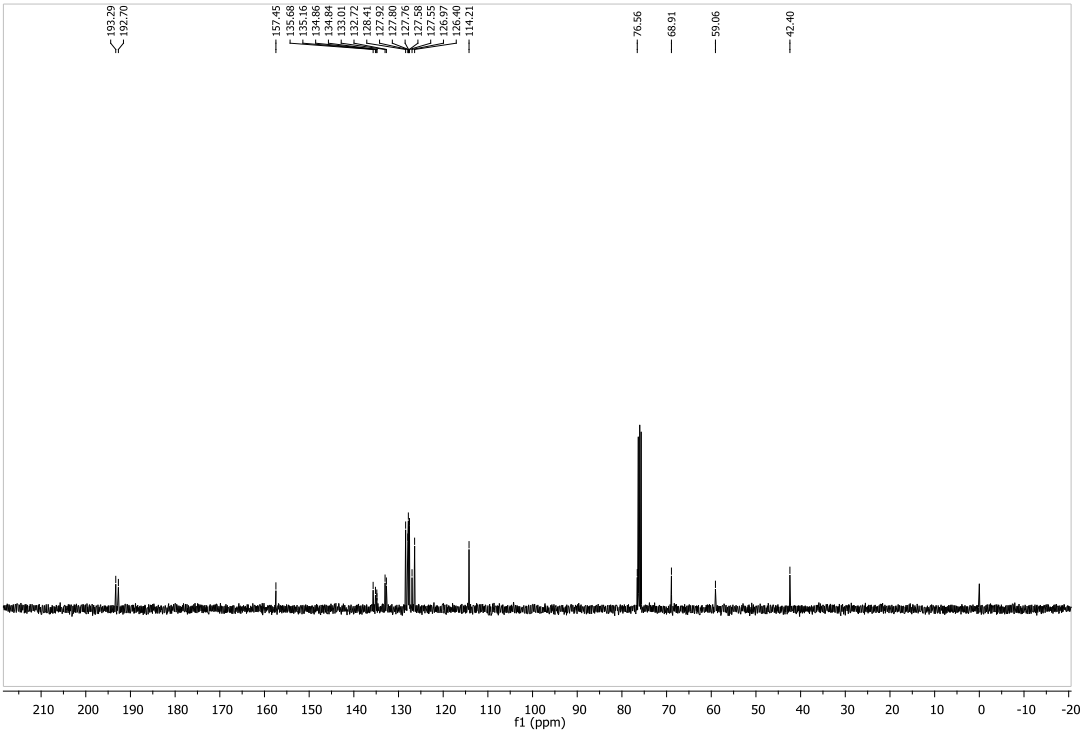


Figure A. 28 ^{13}C NMR spectrum of compound **99**

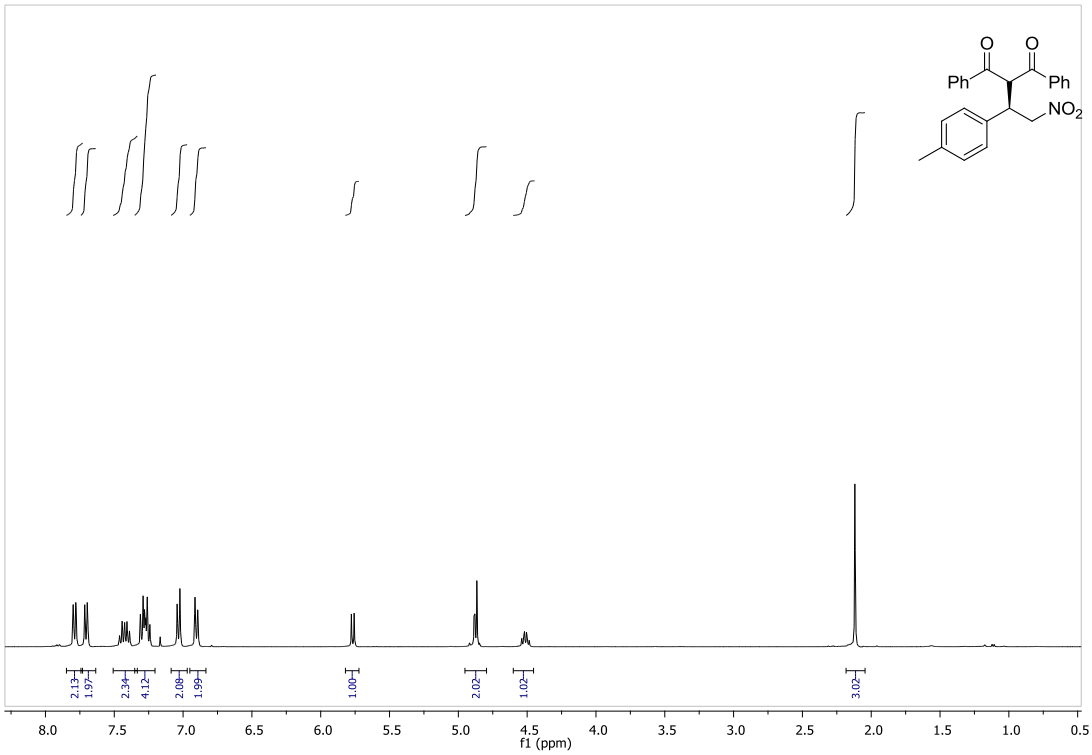


Figure A. 29 [1]HNMR spectrum of compound **100**

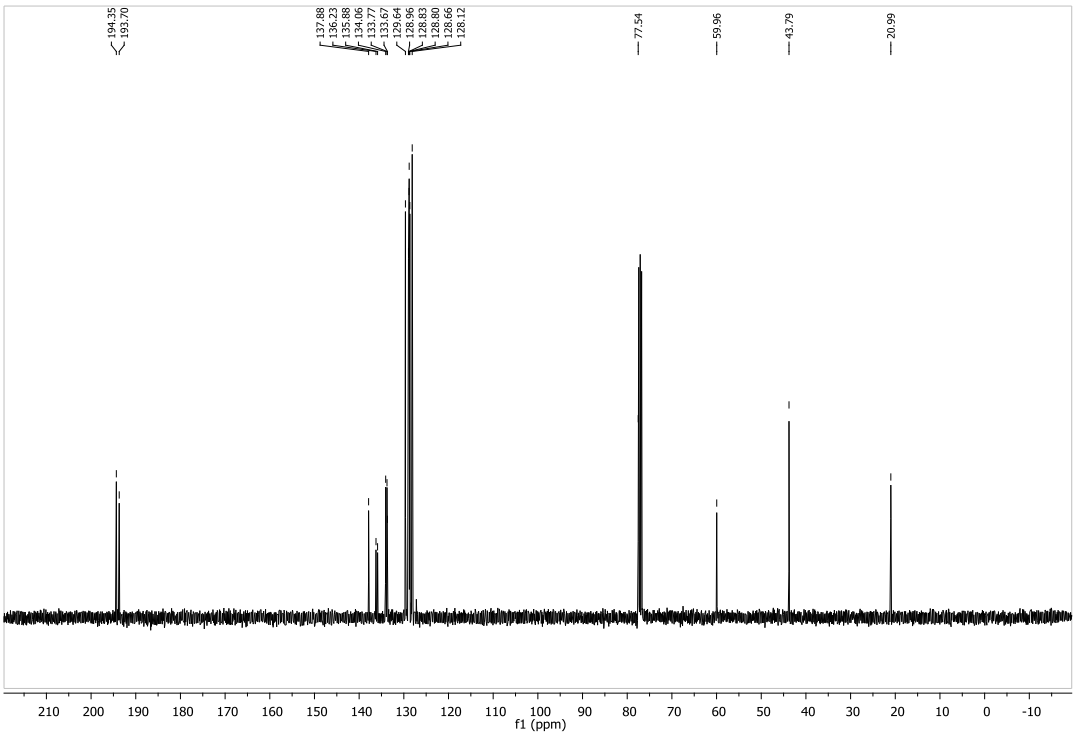


Figure A. 30 [13]C NMR spectrum of compound **100**

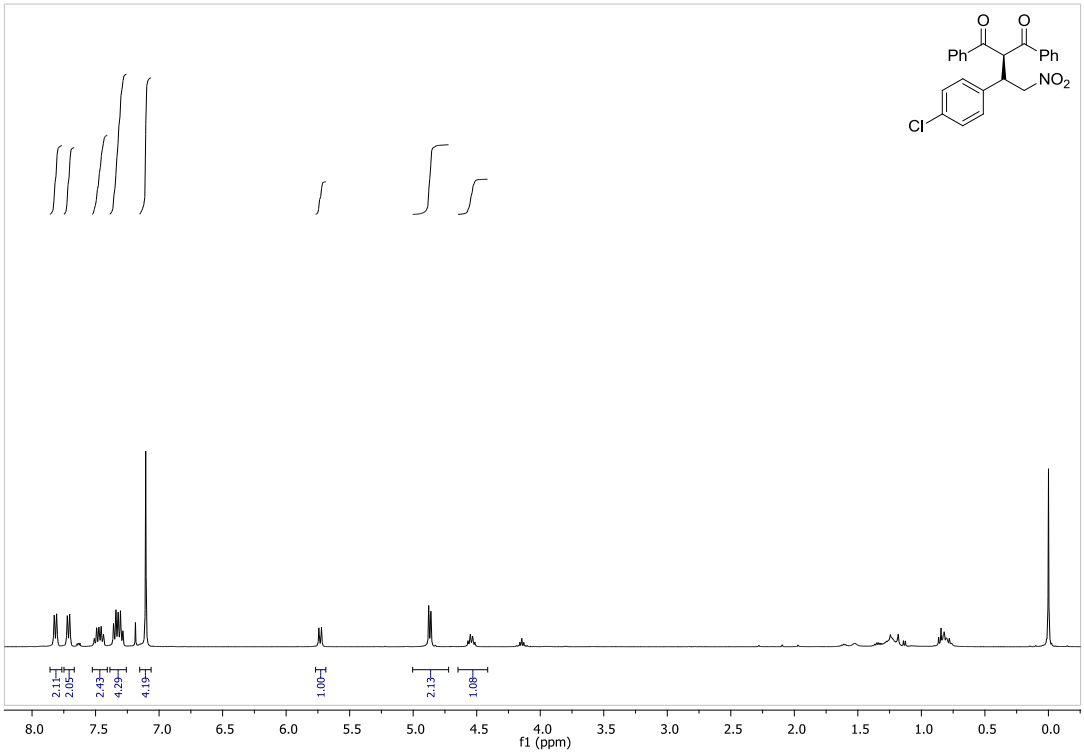


Figure A. 31 ^{1}H NMR spectrum of compound **101**

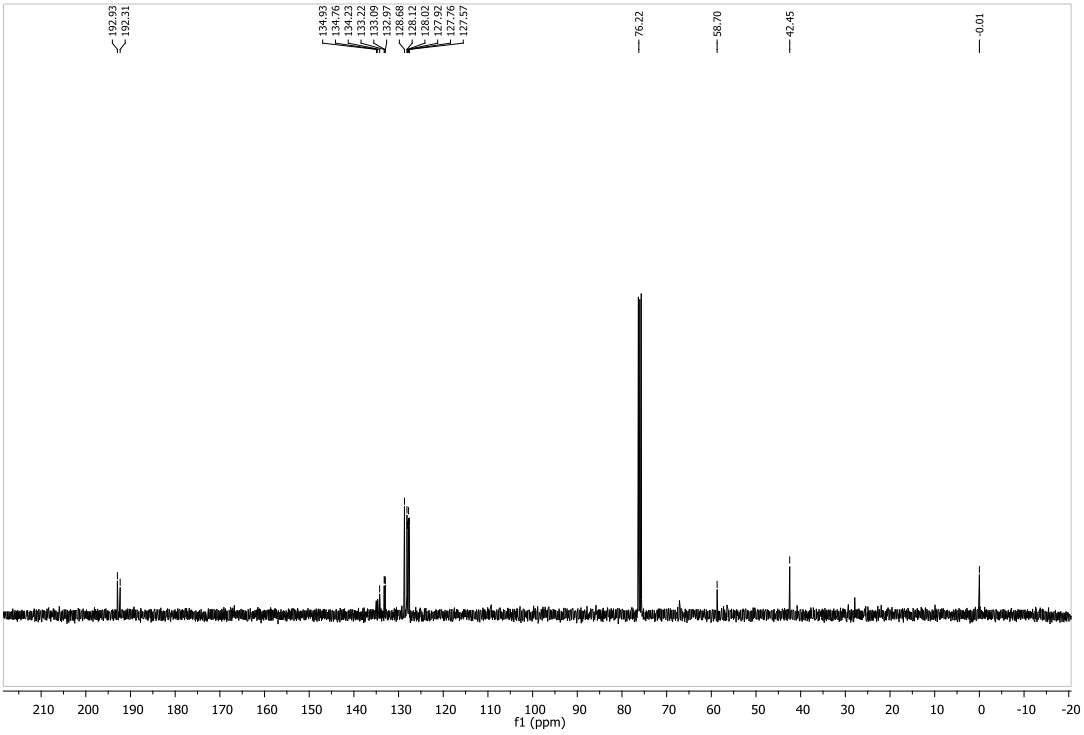


Figure A. 32 ^{13}C NMR spectrum of compound **101**

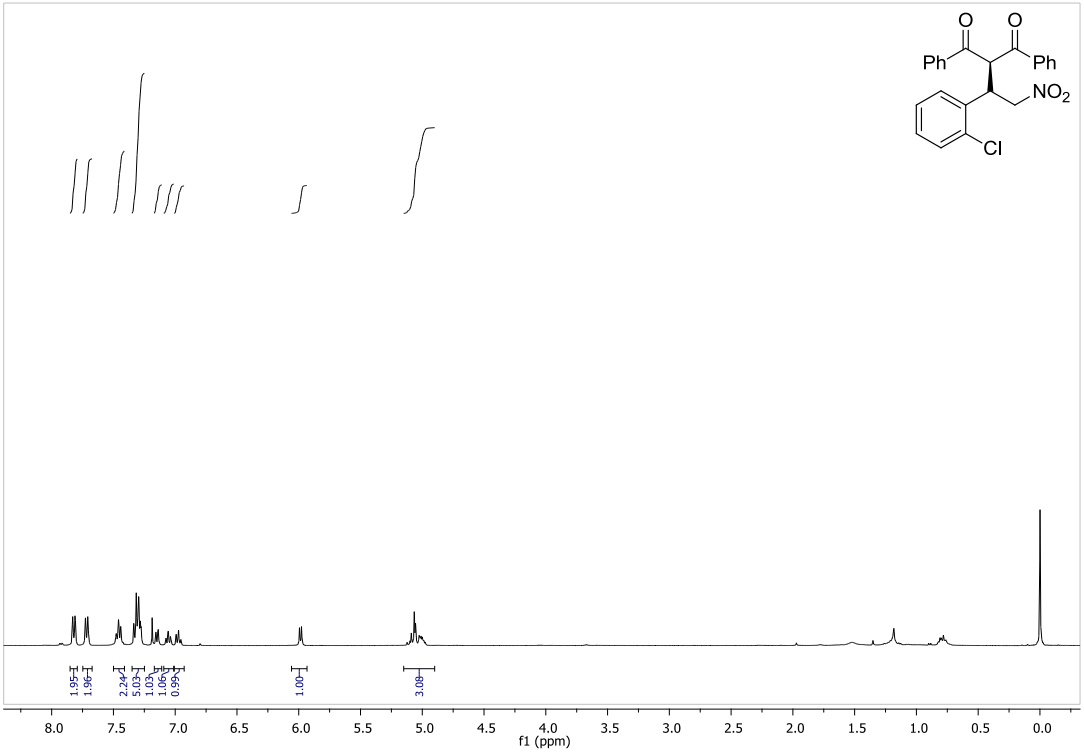


Figure A. 33 ^{1}H NMR spectrum of compound **102**

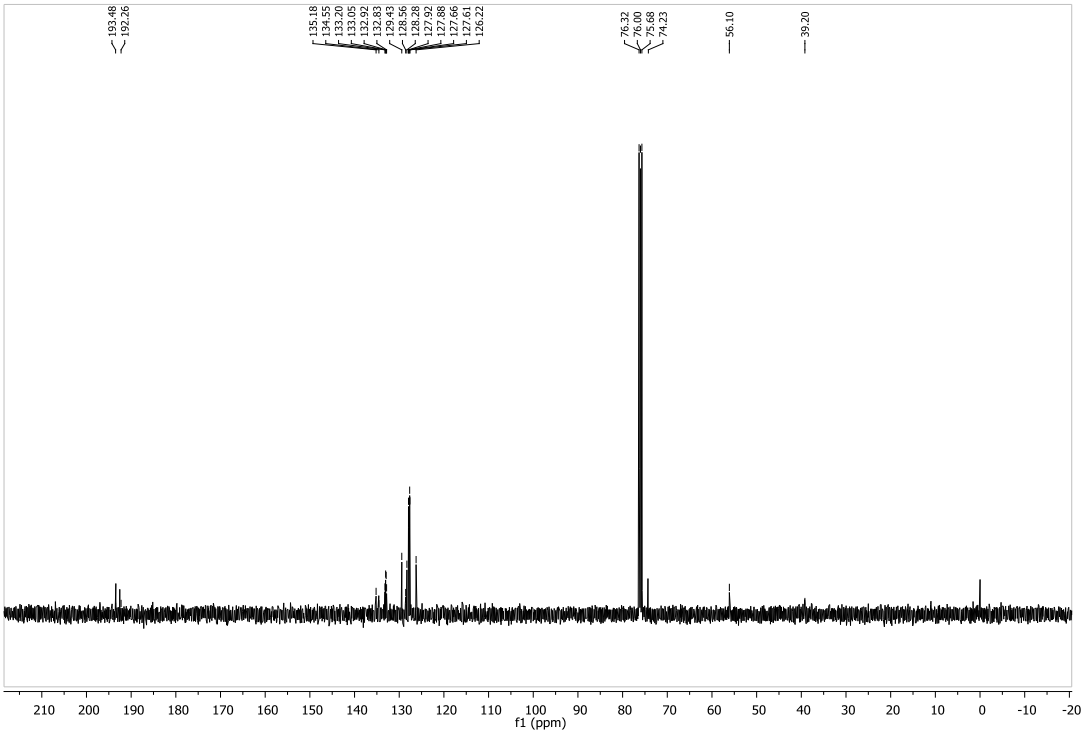


Figure A. 34 ^{13}C NMR spectrum of compound **102**

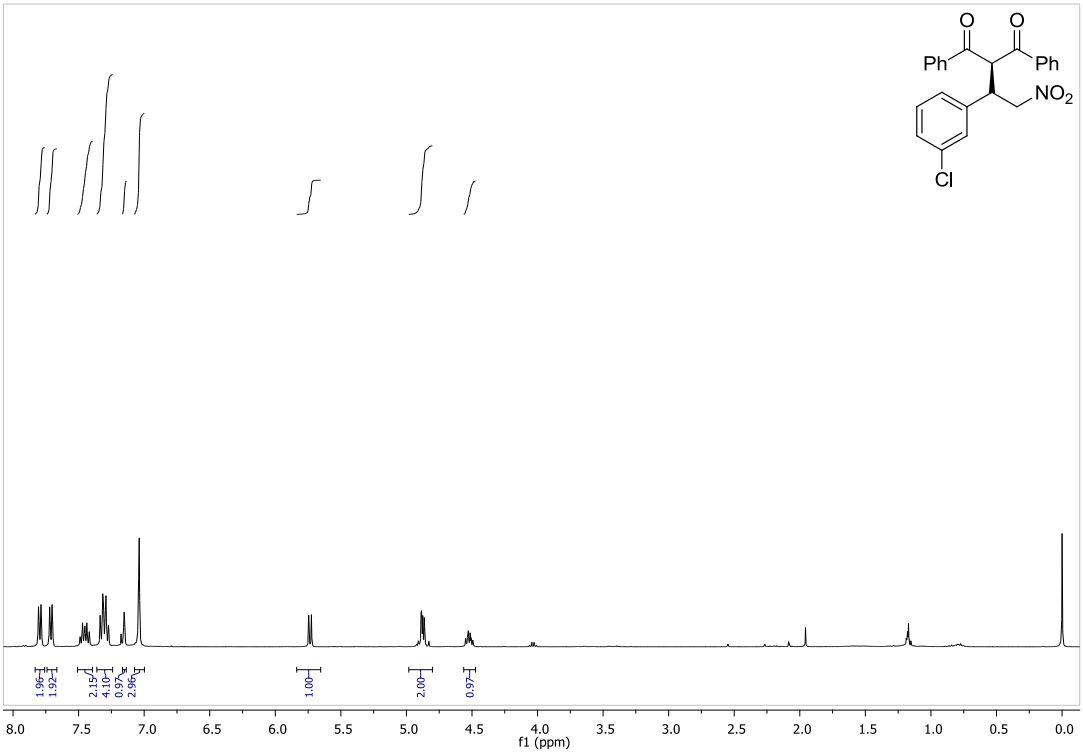


Figure A. 35 ^{1}H NMR spectrum of compound **103**

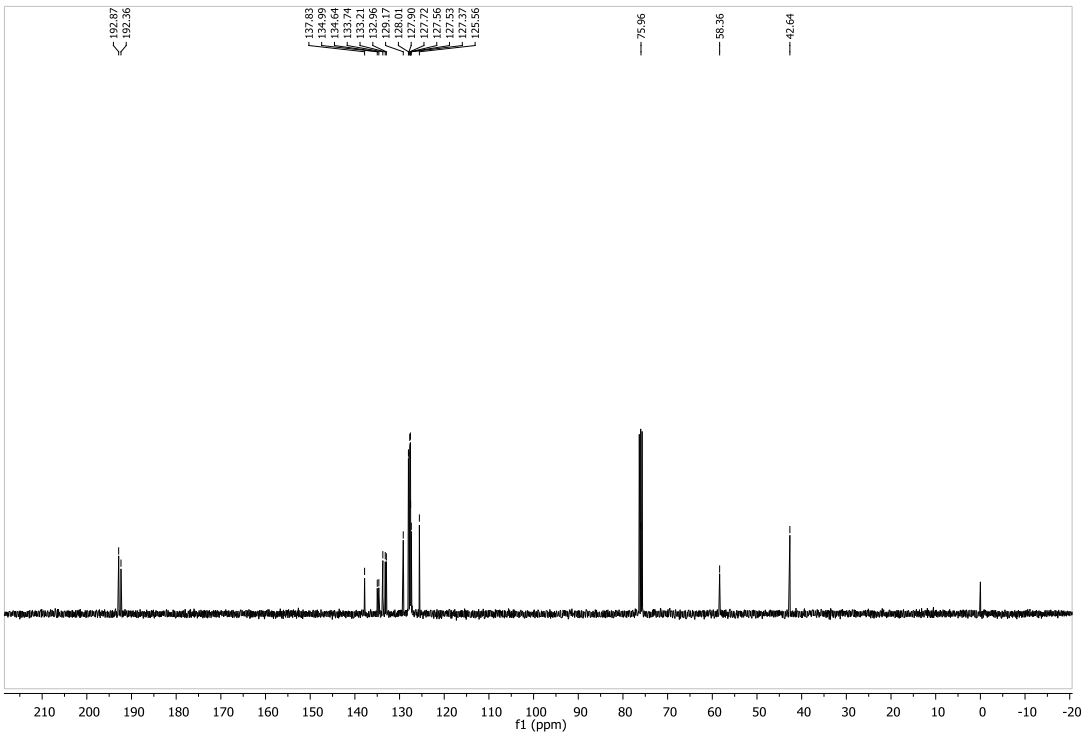


Figure A. 36 ^{13}C NMR spectrum of compound **103**

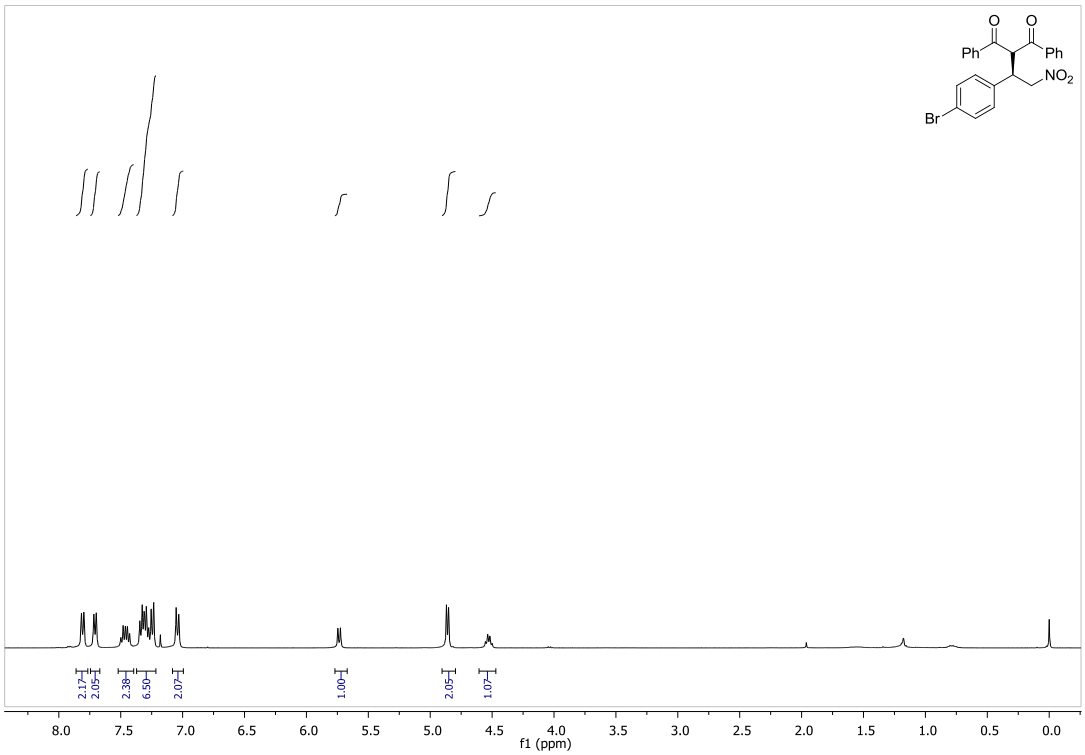


Figure A. 37 ^{1}H NMR spectrum of compound **104**

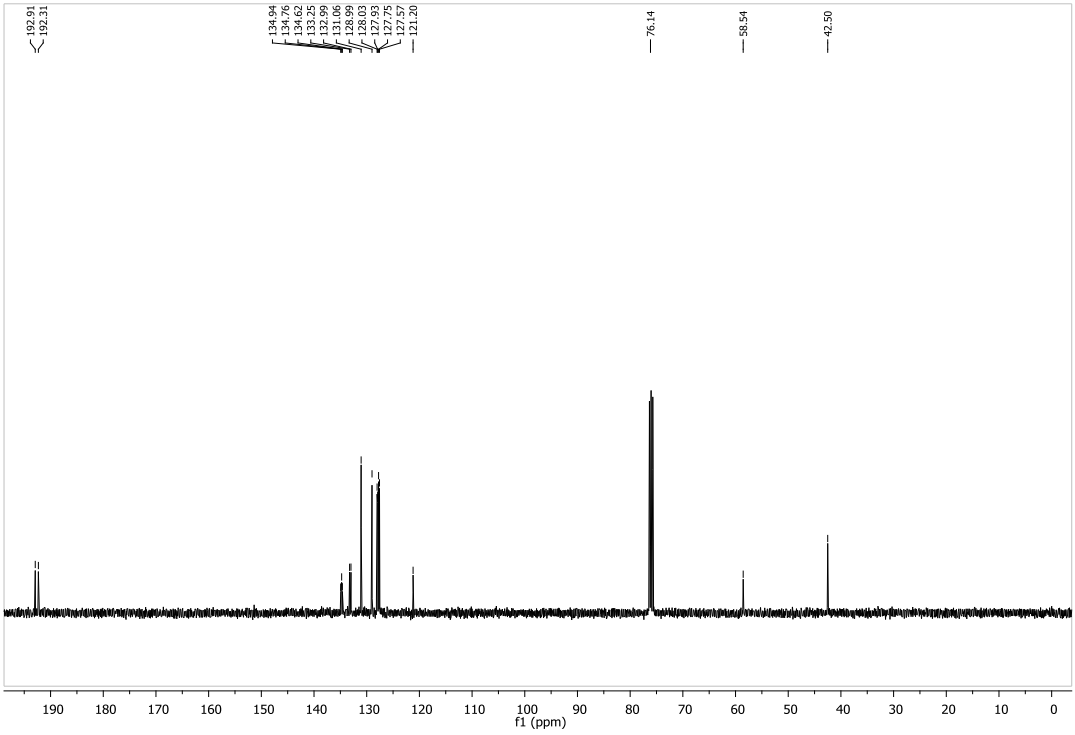


Figure A. 38 ^{13}C NMR spectrum of compound **104**

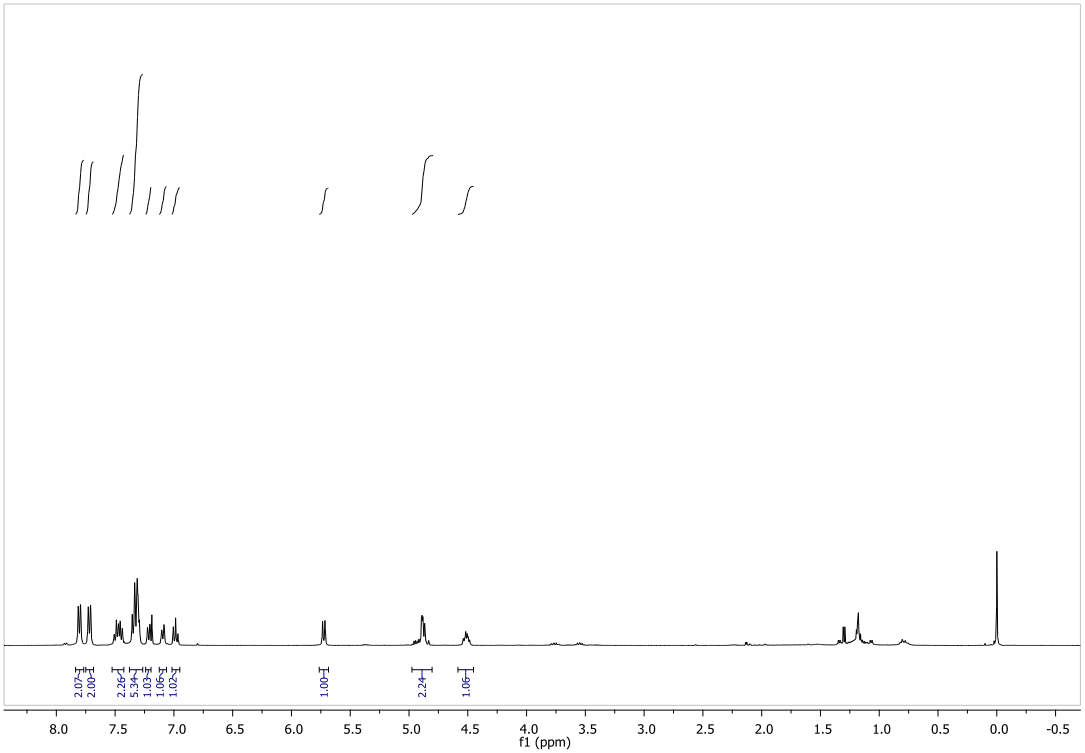


Figure A. 39 ^{1}H NMR spectrum of compound **105**

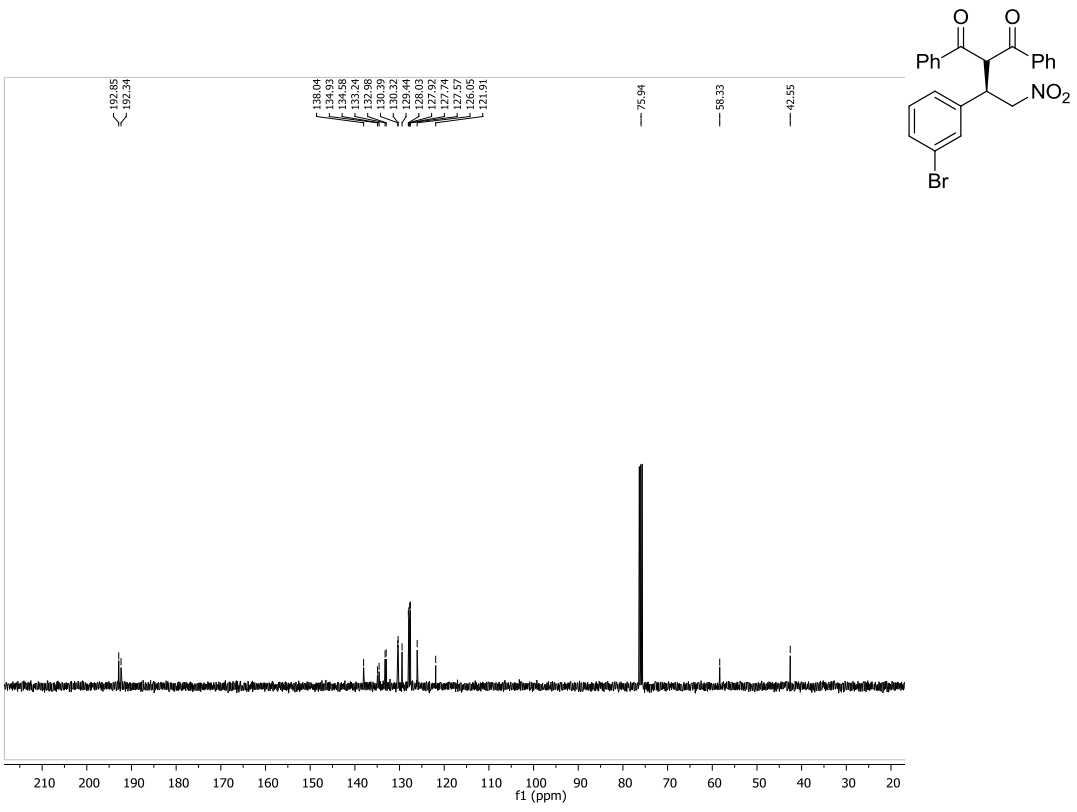


Figure A. 40 ^{13}C NMR spectrum of compound **105**

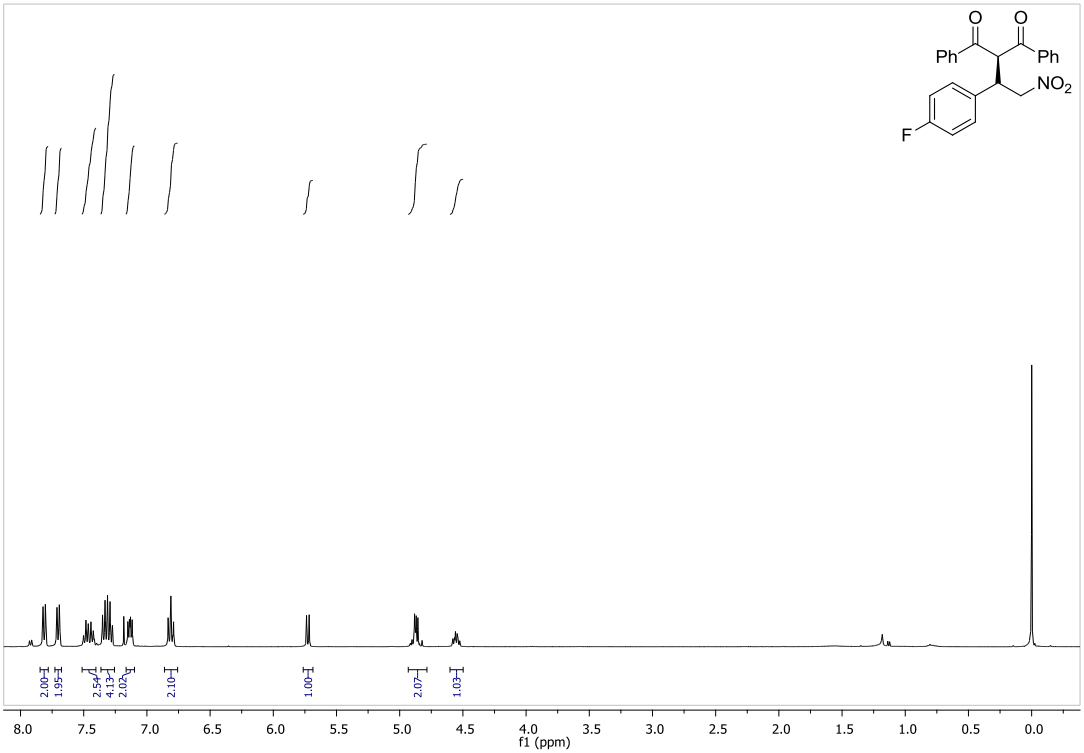


Figure A. 41 ^{1}H NMR spectrum of compound **106**

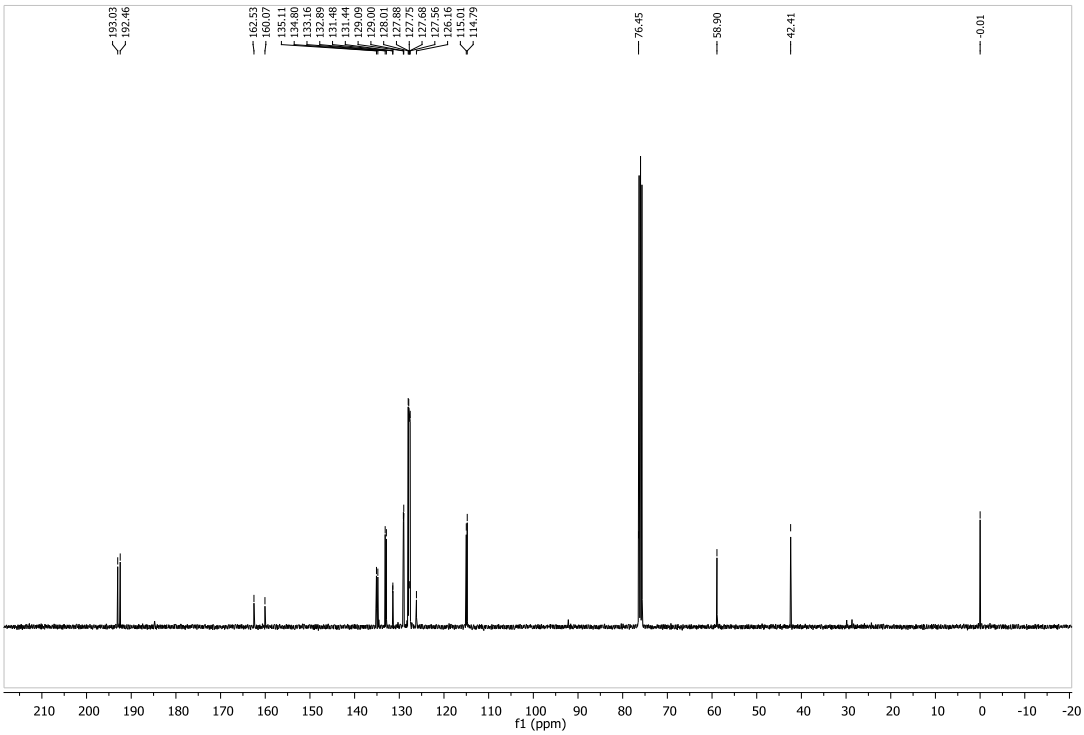


Figure A. 42 ^{13}C NMR spectrum of compound **106**

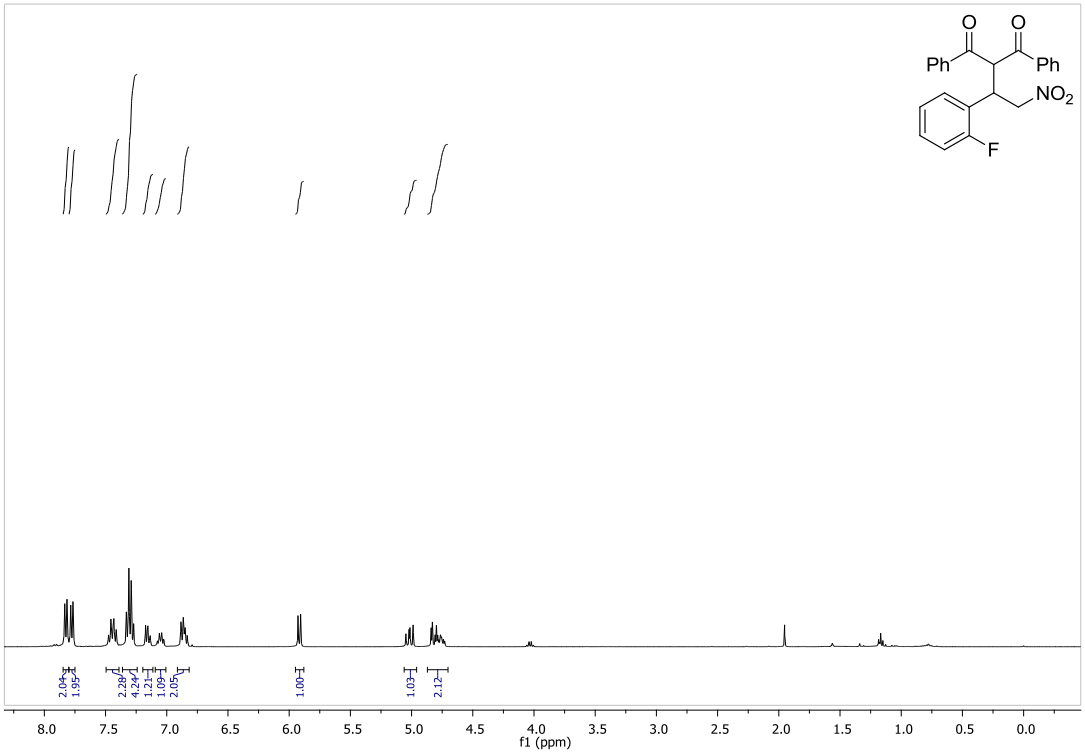


Figure A. 43 ^{1}H NMR spectrum of compound **107**

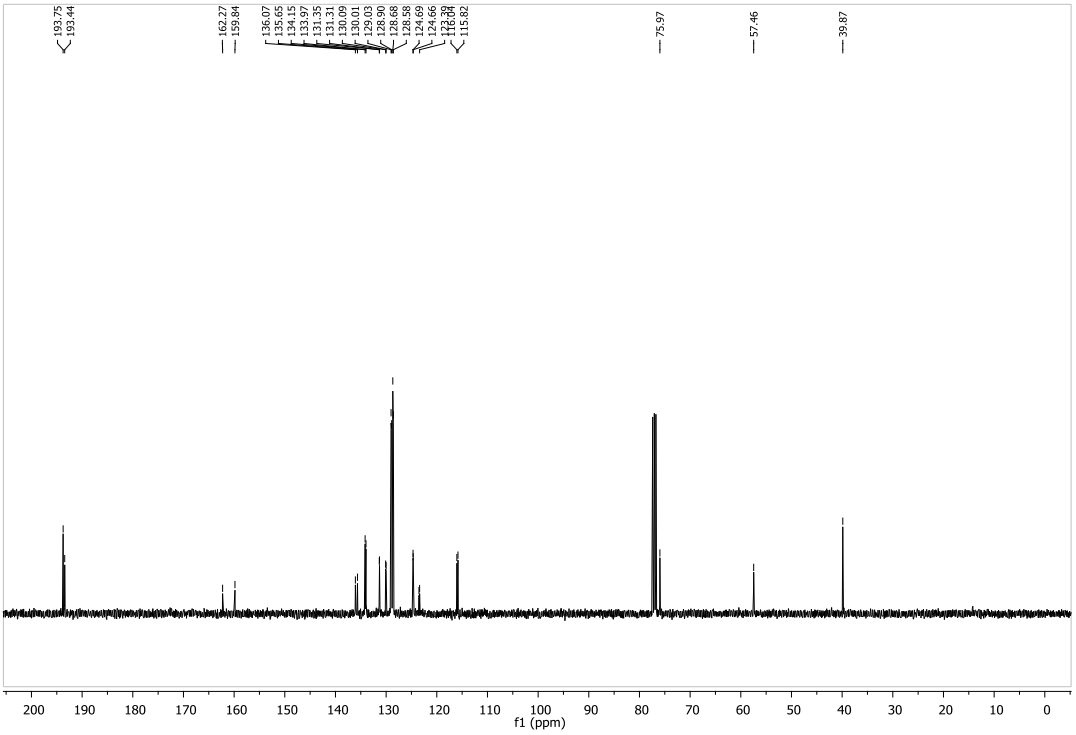


Figure A. 44 ^{13}C NMR spectrum of compound **107**

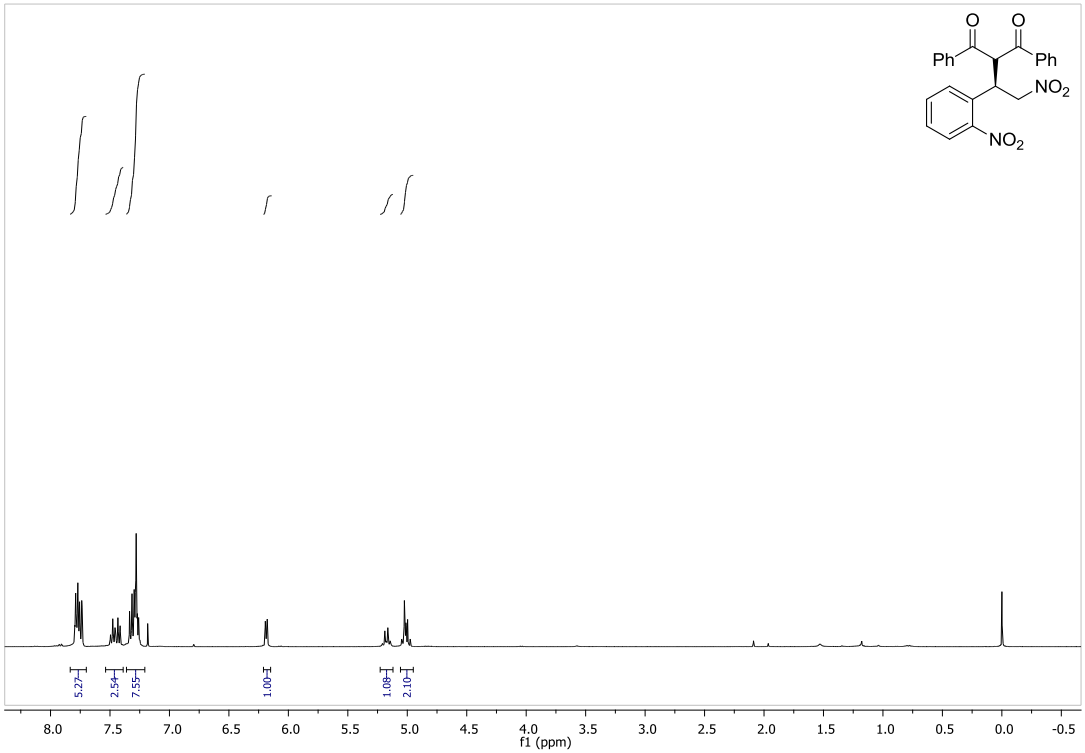


Figure A. 45 ^{1}H NMR spectrum of compound **108**

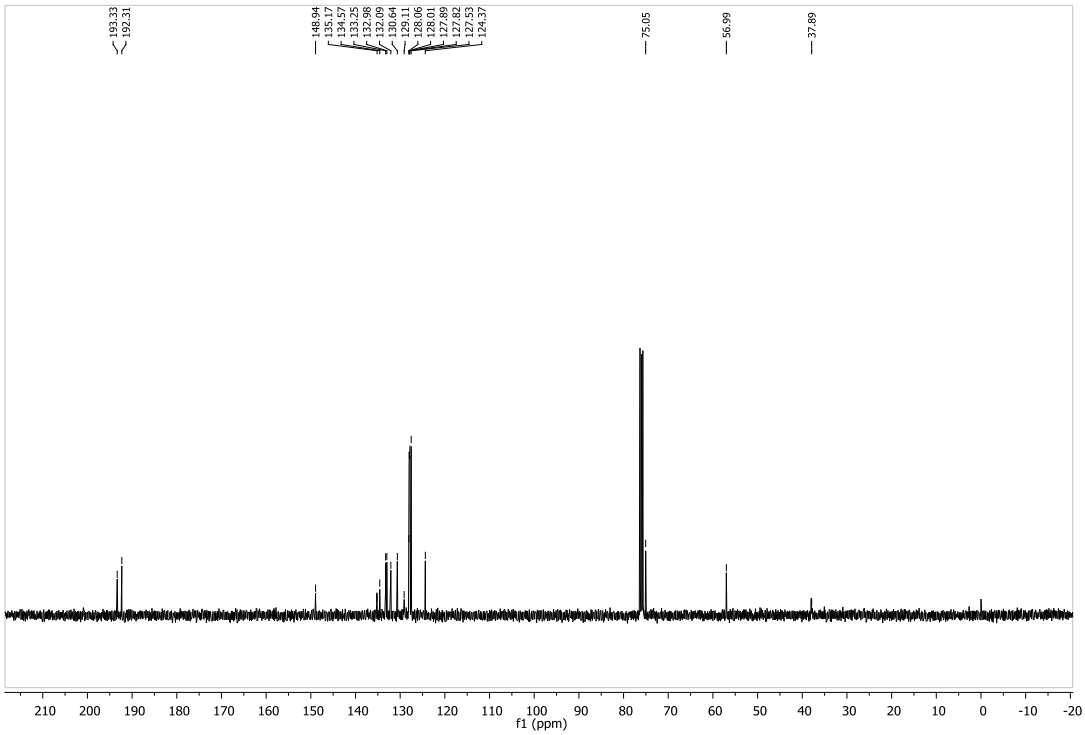


Figure A. 46 ^{13}C NMR spectrum of compound **108**

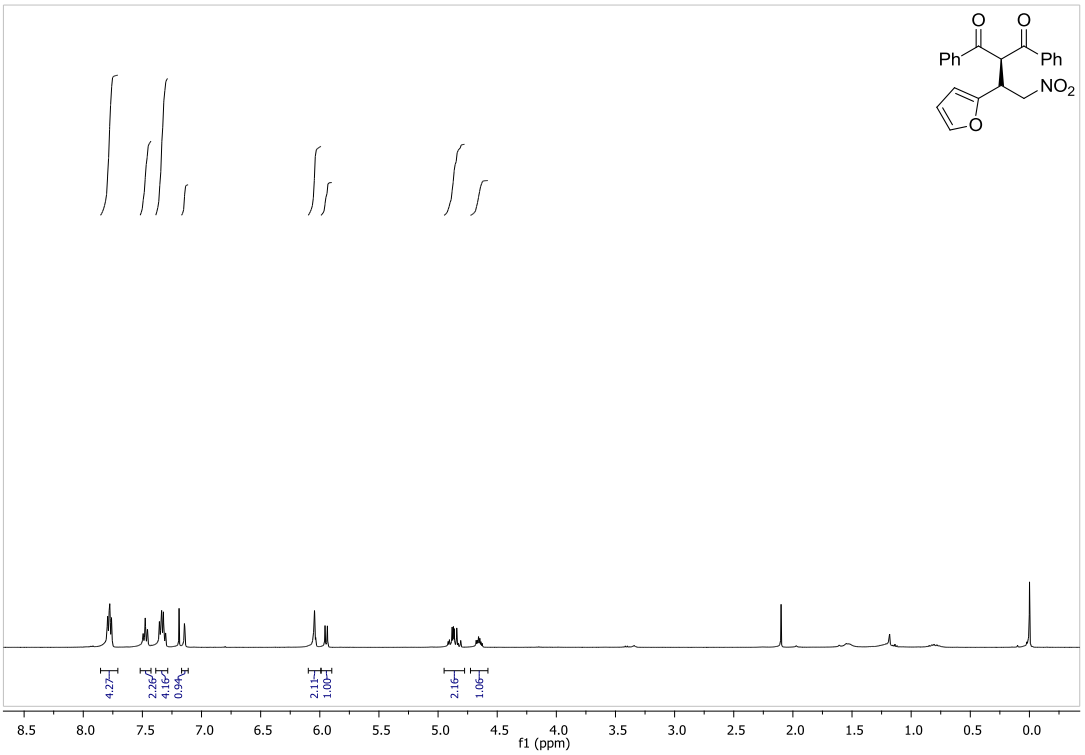


Figure A. 47 ^{1}H NMR spectrum of compound **109**

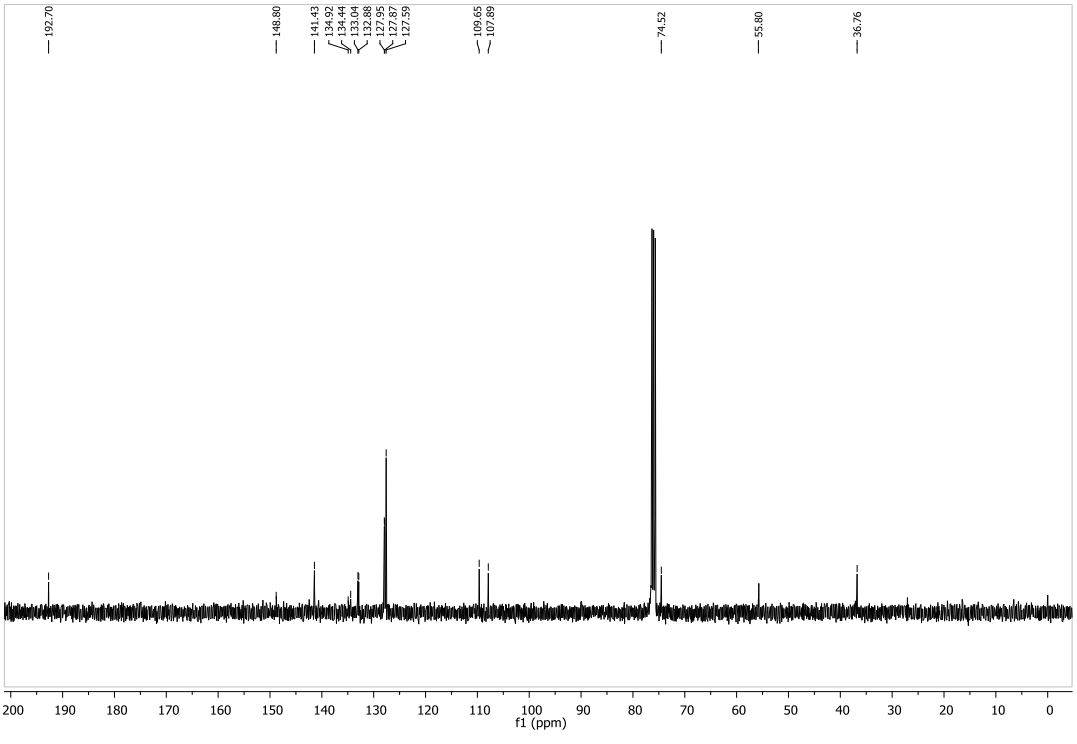
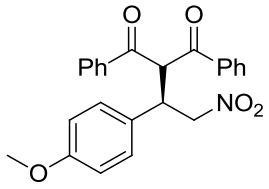


Figure A. 48 ^{13}C NMR spectrum of compound **109**

APPENDIX B

HPLC DATA



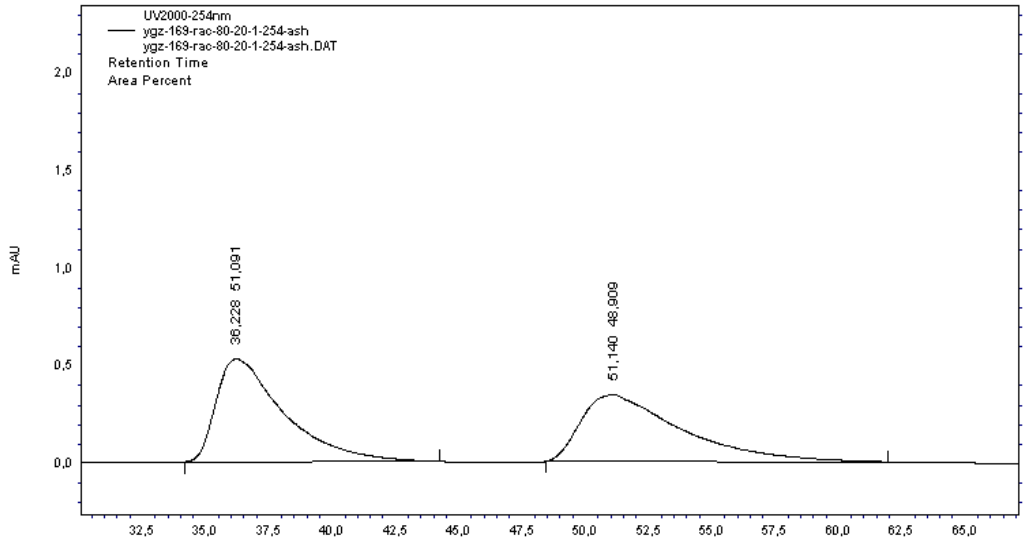


Figure B. 1 HPLC chromatogram of ***rac*-96**

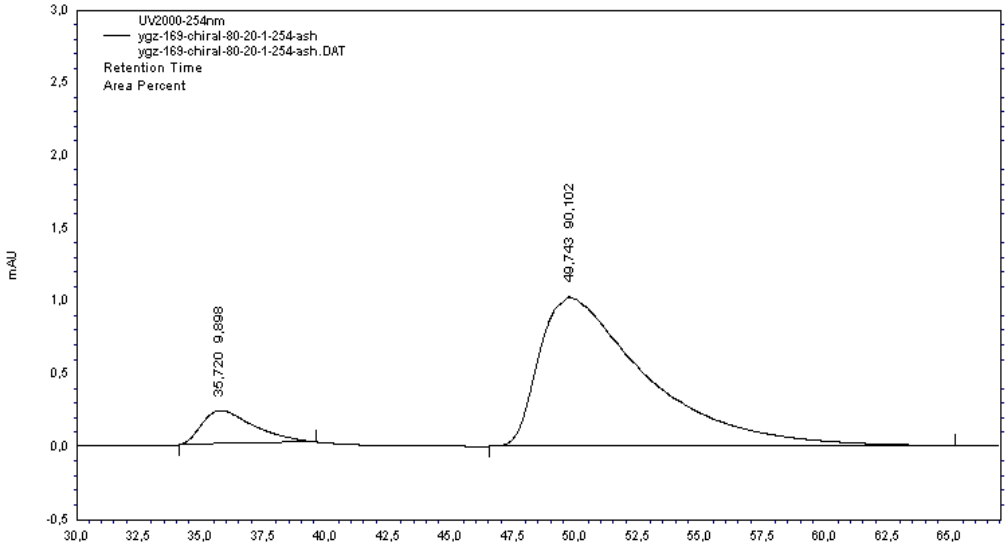
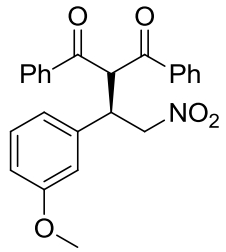


Figure B. 2 HPLC chromatogram of **96**



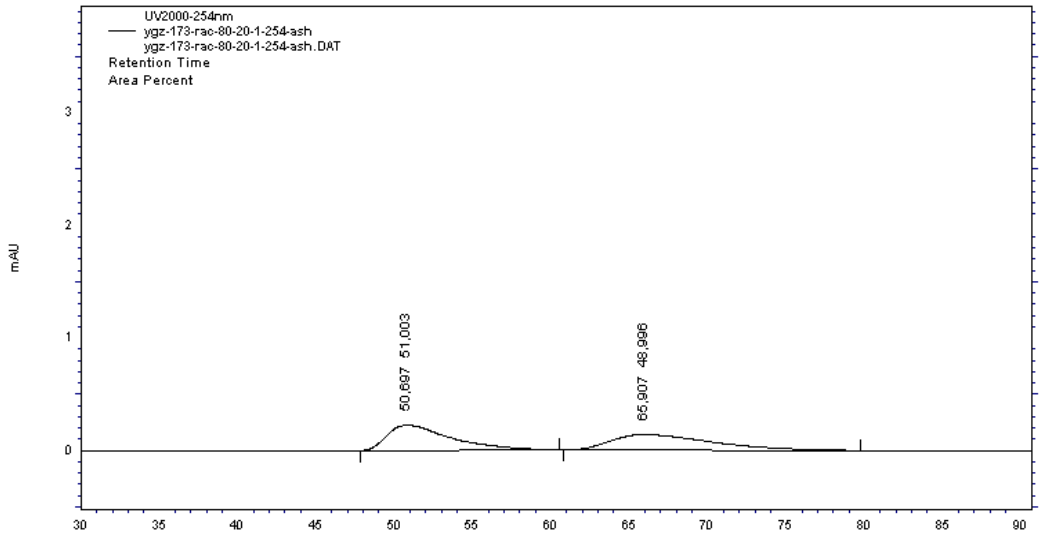


Figure B. 3 HPLC chromatogram of ***rac*-97**

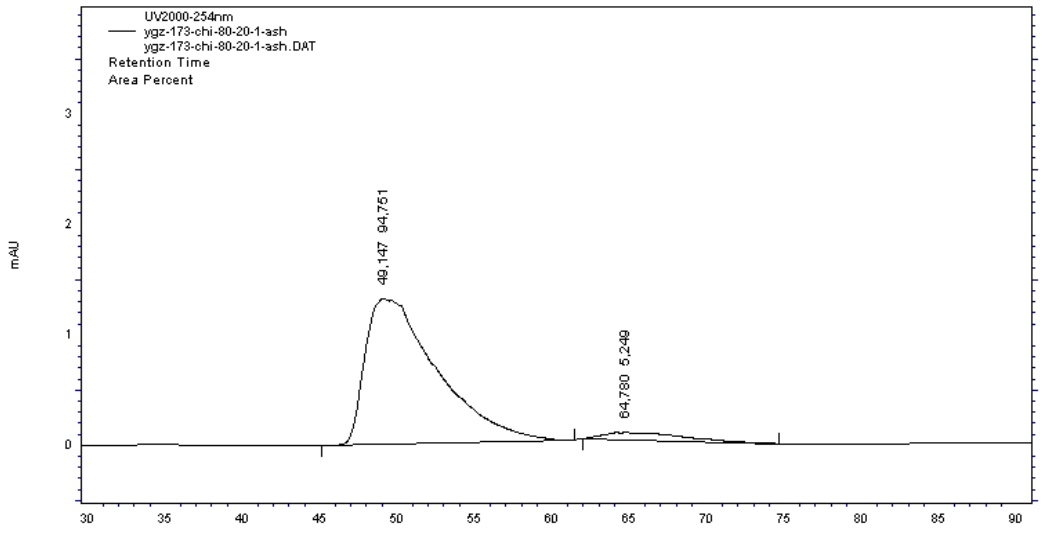
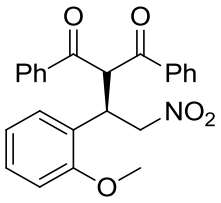
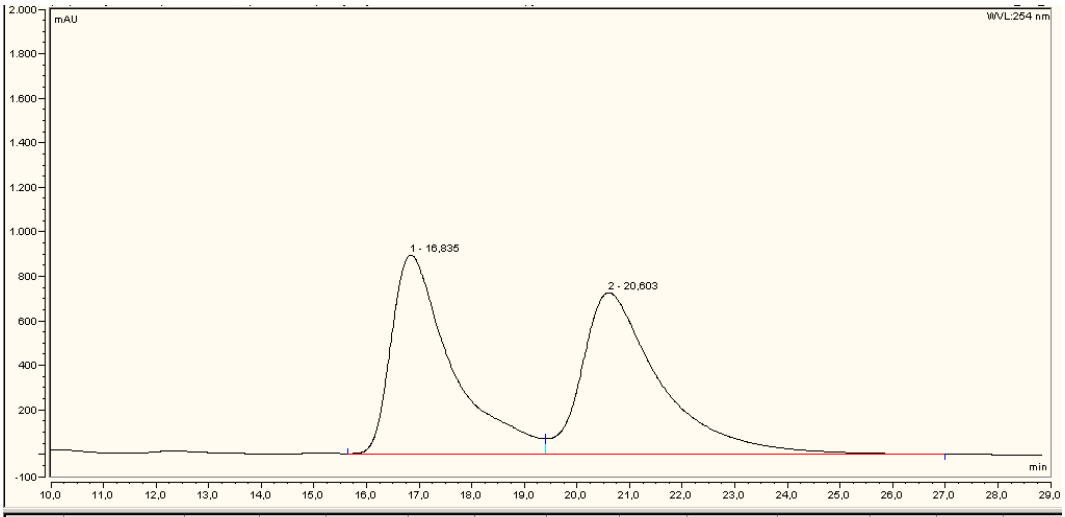


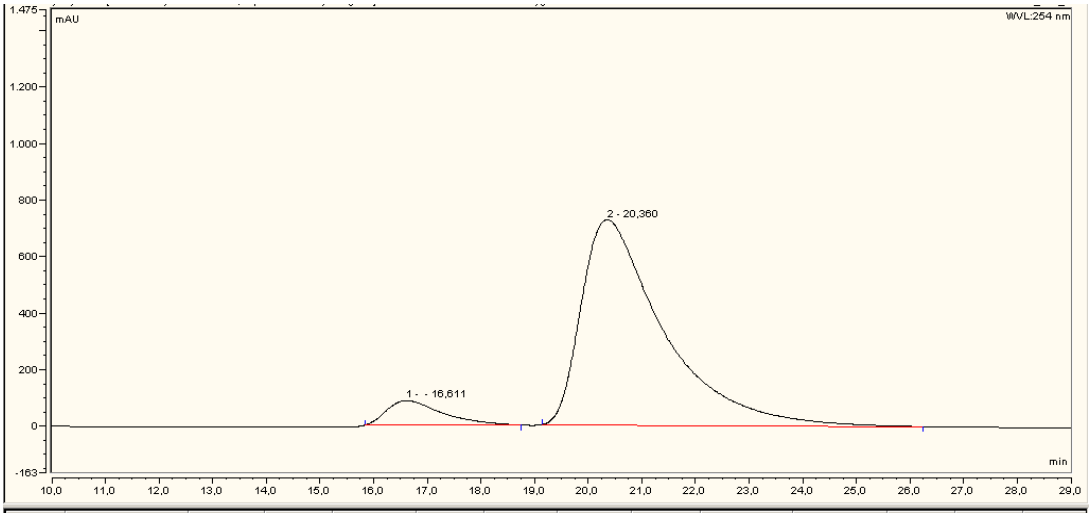
Figure B. 4 HPLC chromatogram of **97**





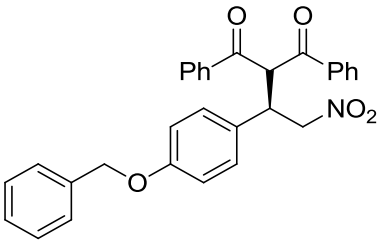
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	16,835	##########	n.a.	BM A	891,942	48,960	1,78
2	n.a.	20,603	##########	n.a.	MB	724,491	51,040	n.a.
Total:			##########	0,0000		1616,433	100,00	

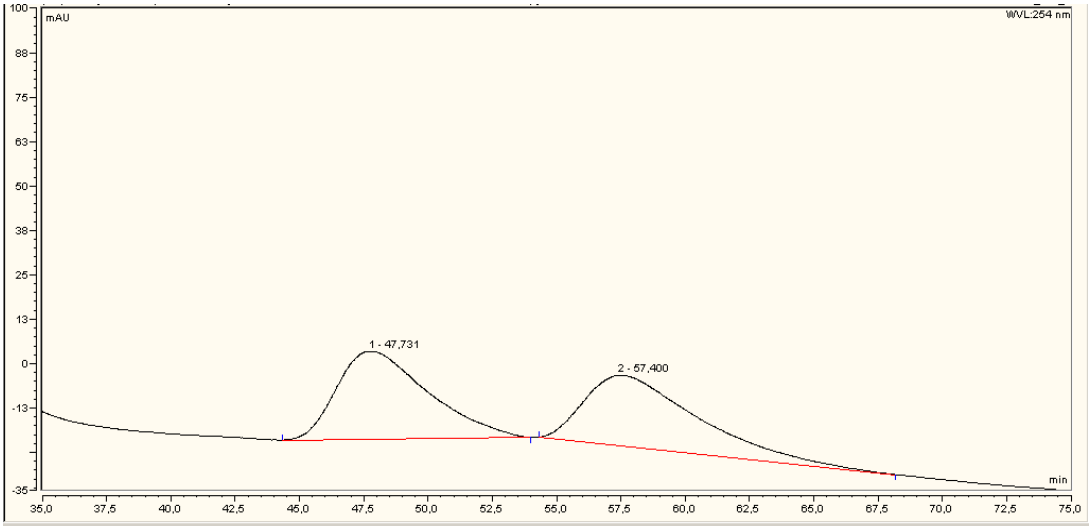
Figure B. 5 HPLC chromatogram of ***rac*-98**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1		16,611	103,2797	n.a.	BMB*A	86,599	7,425	1,71
2	n.a.	20,360	##########	n.a.	BMB*	725,416	92,575	n.a.
Total:			##########	0,0000		812,015	100,00	

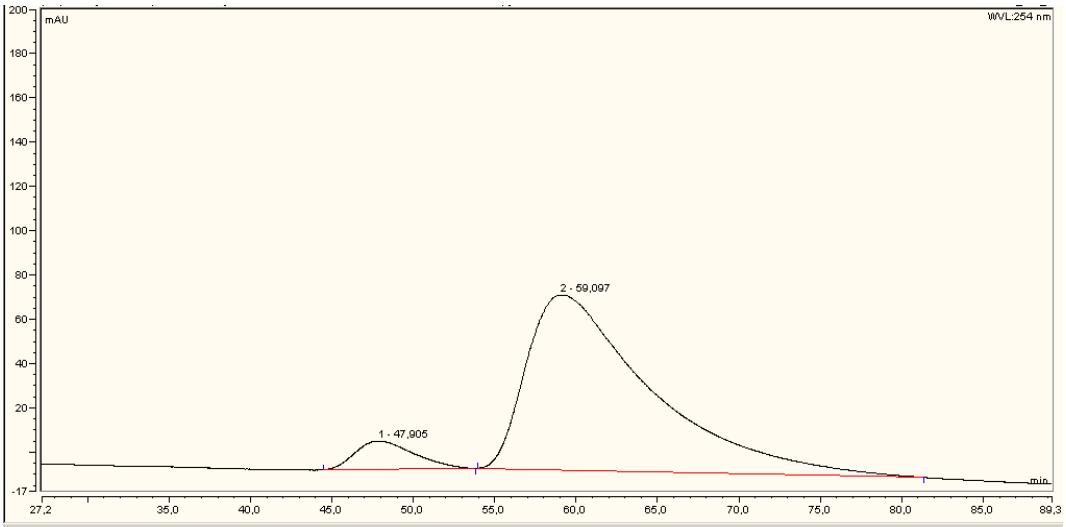
Figure B. 6 HPLC chromatogram of **98**





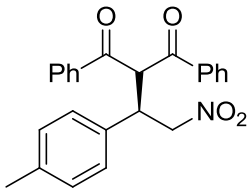
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	47,731	101,4445	n.a.	BMB	24,739	49,874	1,34
2	n.a.	57,400	101,9559	n.a.	BMB*	19,743	50,126	n.a.
Total:			**203,4005**	**0,0000**		**44,483**	**100,00**	

Figure B. 7 HPLC chromatogram of ***rac*-99**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	47,905	53,3133	n.a.	BMB*	12,799	7,092	1,14
2	n.a.	59,097	698,3738	n.a.	BMB*	79,086	92,908	n.a.
Total:			**751,6871**	**0,0000**		**91,884**	**100,00**	

Figure B. 8 HPLC chromatogram of **99**



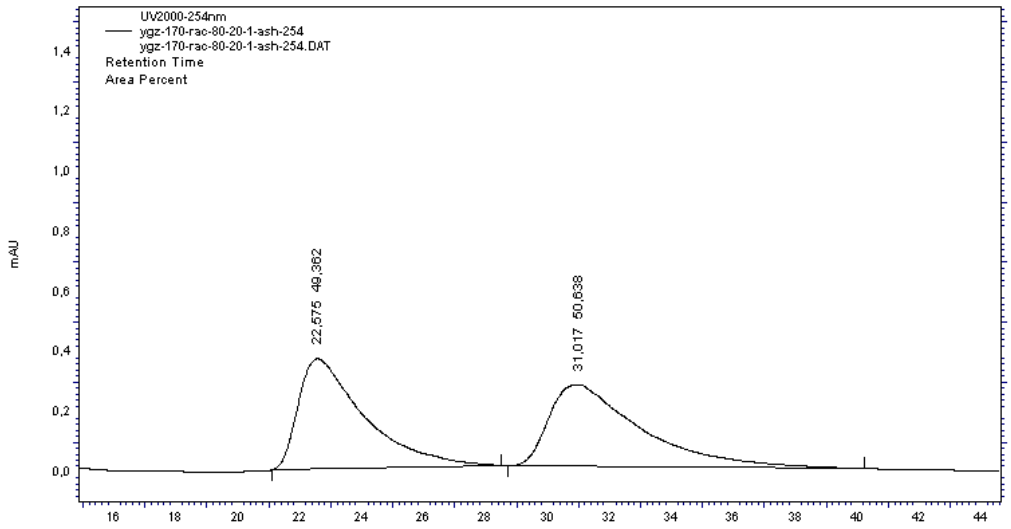


Figure B. 9 HPLC chromatogram of ***rac*-100**

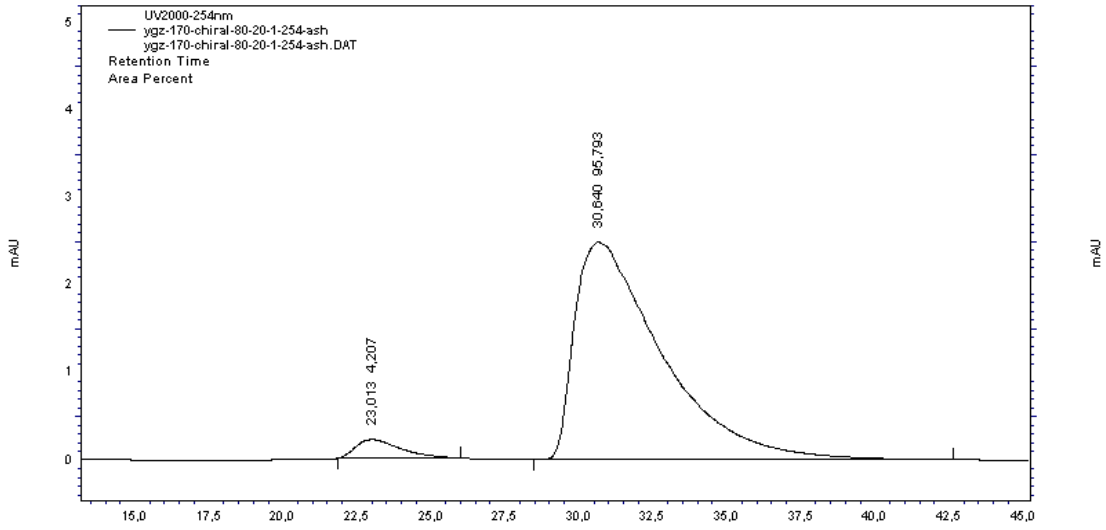
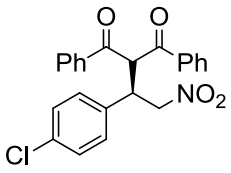
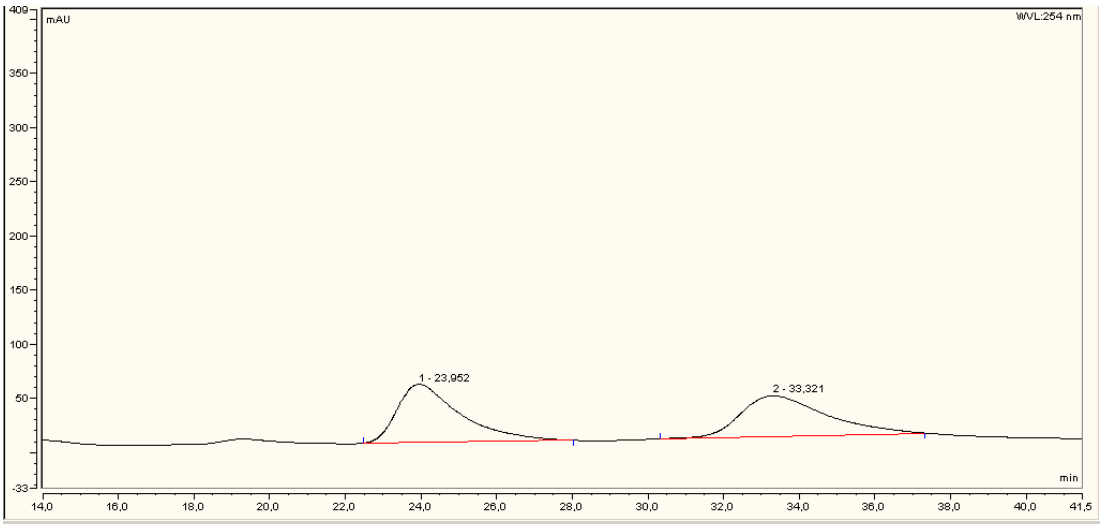


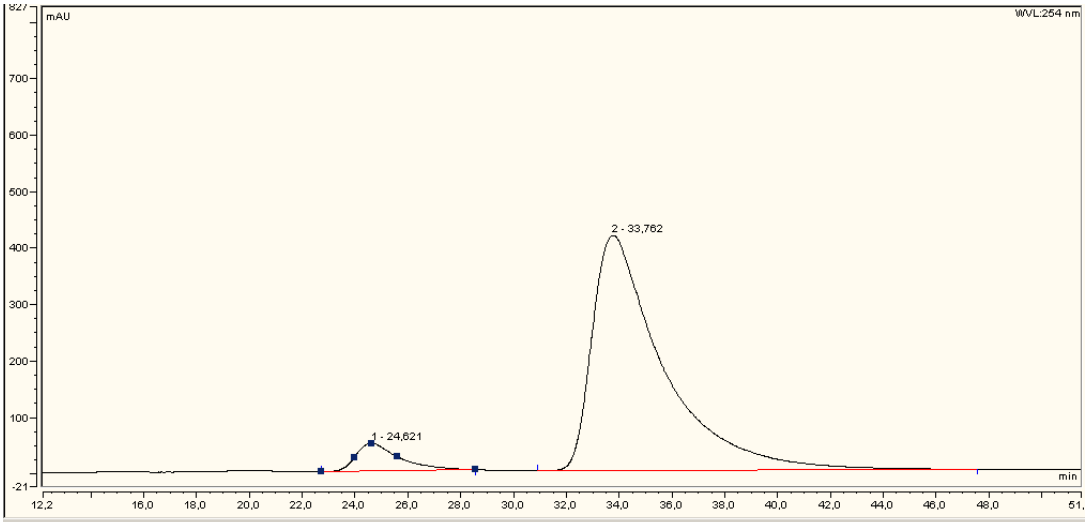
Figure B. 10 HPLC chromatogram of **100**





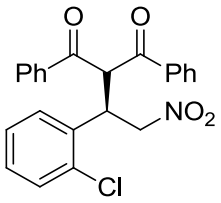
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	23,952	103,3673	n.a.	BMB*	53,702	51,536	2,75
2	n.a.	33,321	97,2063	n.a.	BMB*	37,425	48,464	n.a.
Total:			**200,5736**	**0,0000**		**91,128**	**100,00**	

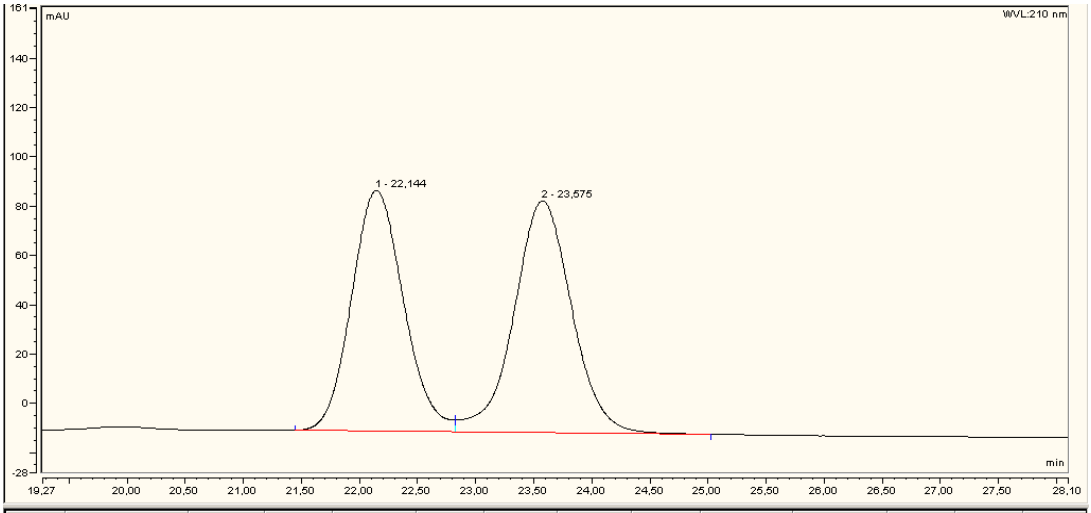
Figure B. 11 HPLC chromatogram of ***rac*-101**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	24,621	92,0089	n.a.	BMB*	48,963	6,652	2,59
2	n.a.	33,762	##########	n.a.	BMB*	415,862	93,348	n.a.
Total:			*********	**0,0000**		**464,825**	**100,00**	

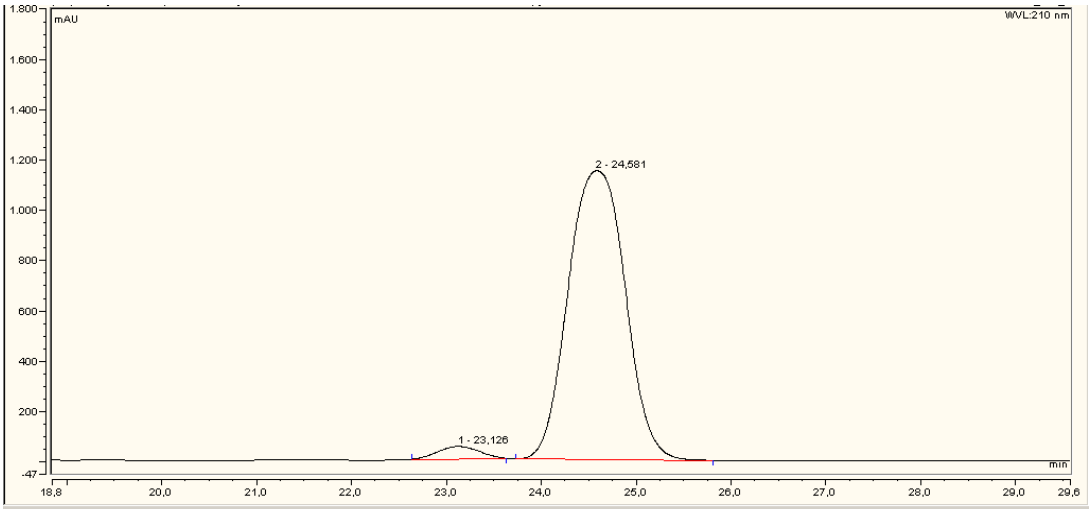
Figure B. 12 HPLC chromatogram of **101**





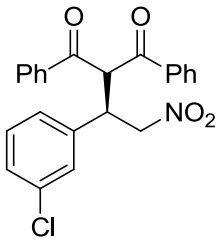
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	22,144	50,7367	n.a.	BM	97,674	48,317	1,69
2	n.a.	23,575	54,2718	n.a.	MB	94,101	51,683	n.a.
Total:			105,0086	0,0000		191,775	100,00	

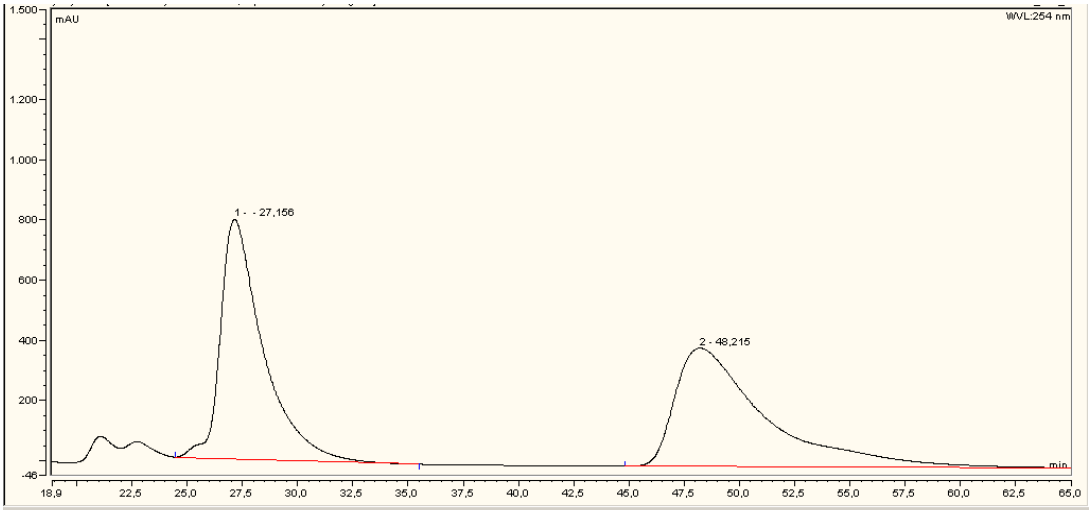
Figure B. 13 HPLC chromatogram of ***rac*-102**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	23,126	24,5287	n.a.	BMB*	48,940	2,973	1,48
2	n.a.	24,581	800,6231	n.a.	BMB*	1147,717	97,027	n.a.
Total:			825,1518	0,0000		1196,657	100,00	

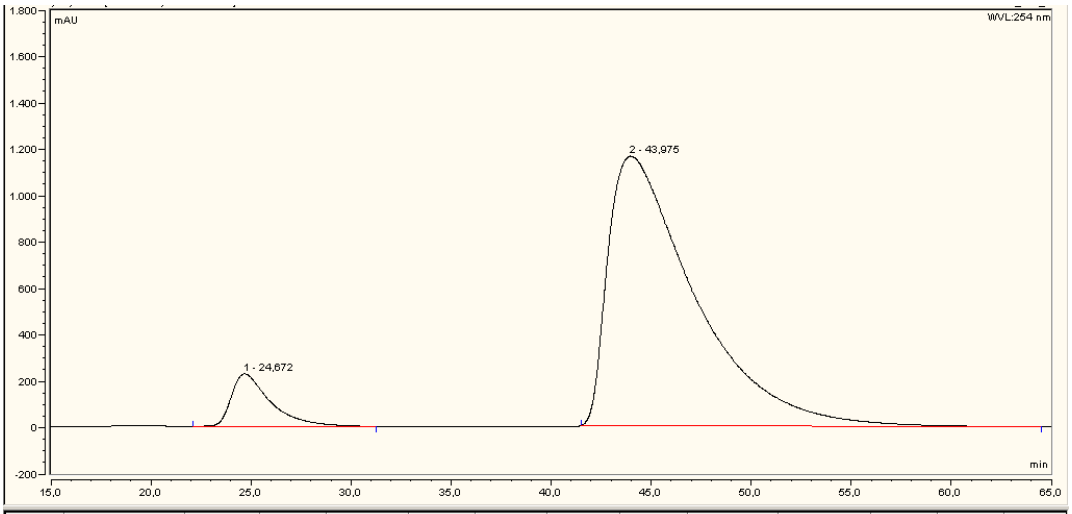
Figure B. 14 HPLC chromatogram of **102**





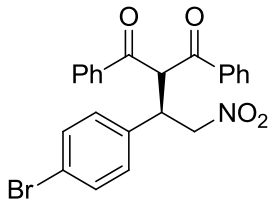
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1		27,156	##########	n.a.	BMB*^A	795,537	49,061	4,42
2	n.a.	48,215	##########	n.a.	BMB	393,010	50,939	n.a.
Total:			#########	0,0000		1188,547	100,00	

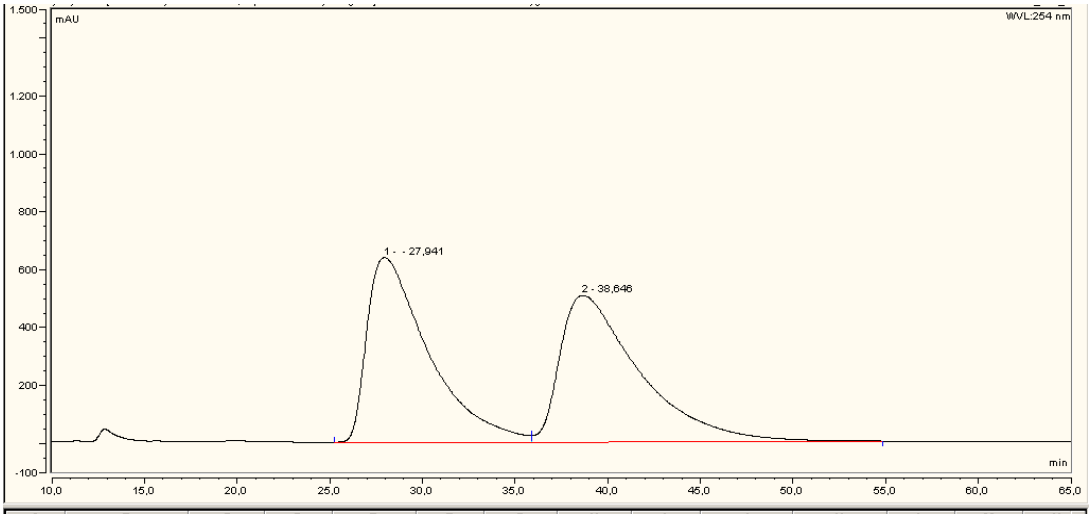
Figure B. 15 HPLC chromatogram of ***rac*-103**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	24,672	513,4271	n.a.	BMB	226,439	8,075	3,60
2	n.a.	43,975	##########	n.a.	BMB*	1161,839	91,925	n.a.
Total:			#########	0,0000		1388,278	100,00	

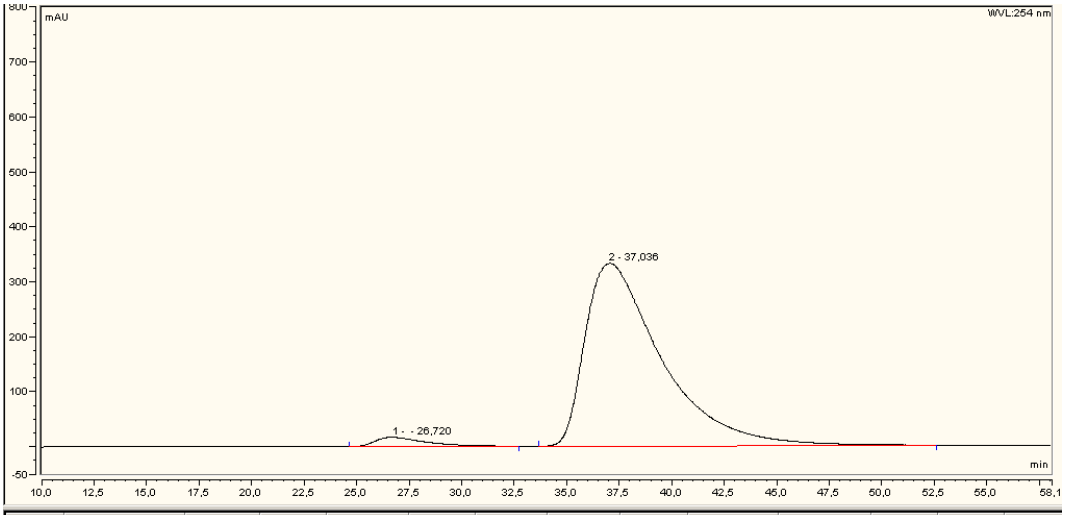
Figure B. 16 HPLC chromatogram of **103**





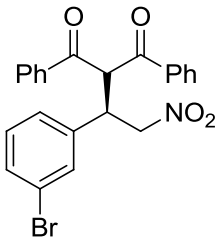
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1		27,941	##########	n.a.	BM ^	637,248	49,568	1,65
2	n.a.	38,646	##########	n.a.	MB	504,978	50,432	n.a.
Total:			#########	0,0000		1142,227	100,00	

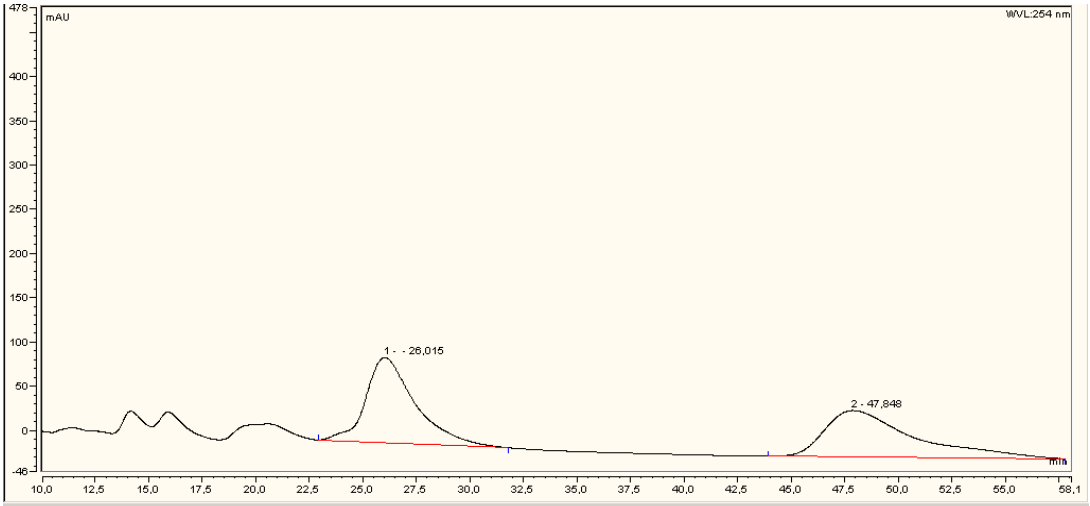
Figure B. 17 HPLC chromatogram of ***rac*-104**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1		26,720	46,8335	n.a.	BMB^	16,919	3,238	1,99
2	n.a.	37,036	##########	n.a.	BMB*	332,305	96,762	n.a.
Total:			#########	0,0000		349,224	100,00	

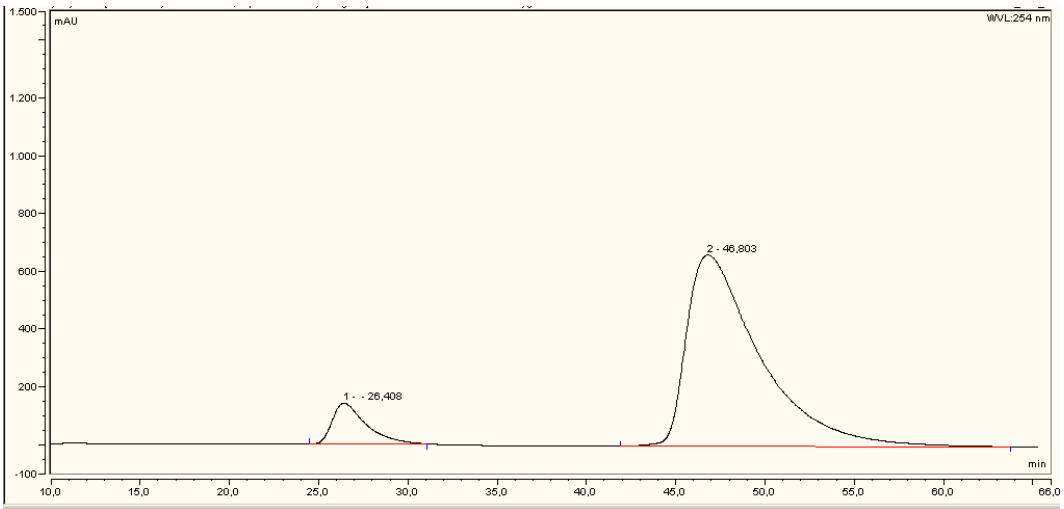
Figure B. 18 HPLC chromatogram of **104**





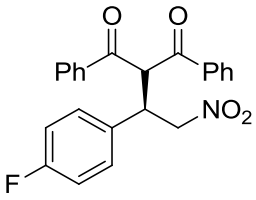
A	B	C	D	E	F	G	H	I	J	K	L	M	N
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution					
1		26,015	257,0753	n.a.	BMB*^	96,086	50,448	4,17					
2	n.a.	47,848	252,5118	n.a.	BMB	52,449	49,552	n.a.					
Total:			509,5871	0,0000		148,535	100,00						

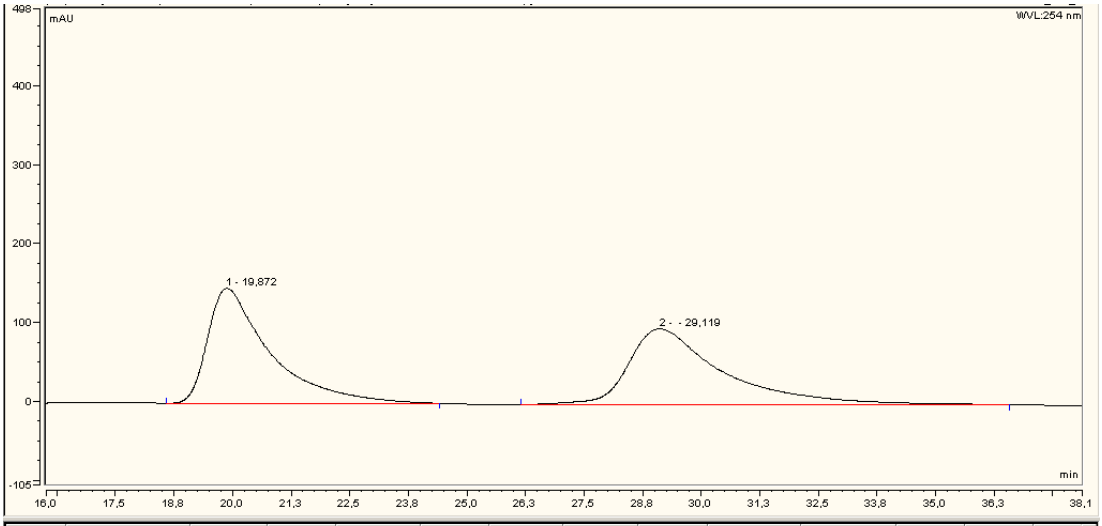
Figure B. 19 HPLC chromatogram of ***rac*-105**



A	B	C	D	E	F	G	H	I	J	K	L	M	N
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution					
1		26,408	307,8963	n.a.	BMB*^	141,448	8,886	4,02					
2	n.a.	46,803	##########	n.a.	BMB	662,190	91,114	n.a.					
Total:			##########	0,0000		803,637	100,00						

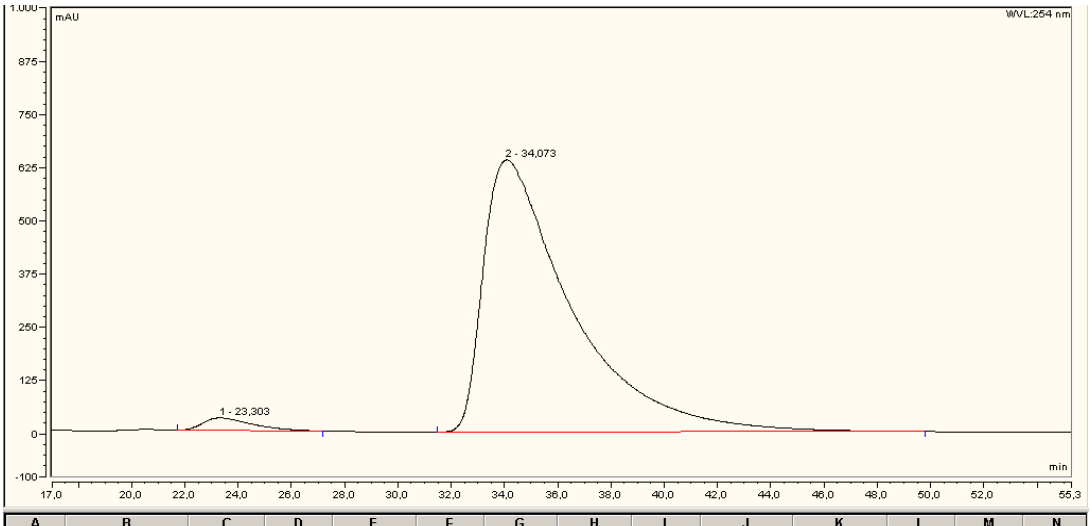
Figure B. 20 HPLC chromatogram of **105**





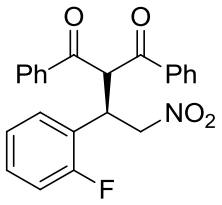
No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	19,872	223,2050	n.a.	BMB	145,525	50,062	3,50
2		29,119	222,6556	n.a.	BMB^	95,919	49,938	n.a.
Total:			445,8606	0,0000		241,444	100,00	

Figure B. 21 HPLC chromatogram of ***rac*-106**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	23,303	62,5534	n.a.	BMB	29,356	2,492	2,47
2	n.a.	34,073	##########	n.a.	BMB	639,104	97,508	n.a.
Total:			##########	0,0000		668,460	100,00	

Figure B. 22 HPLC chromatogram of **106**



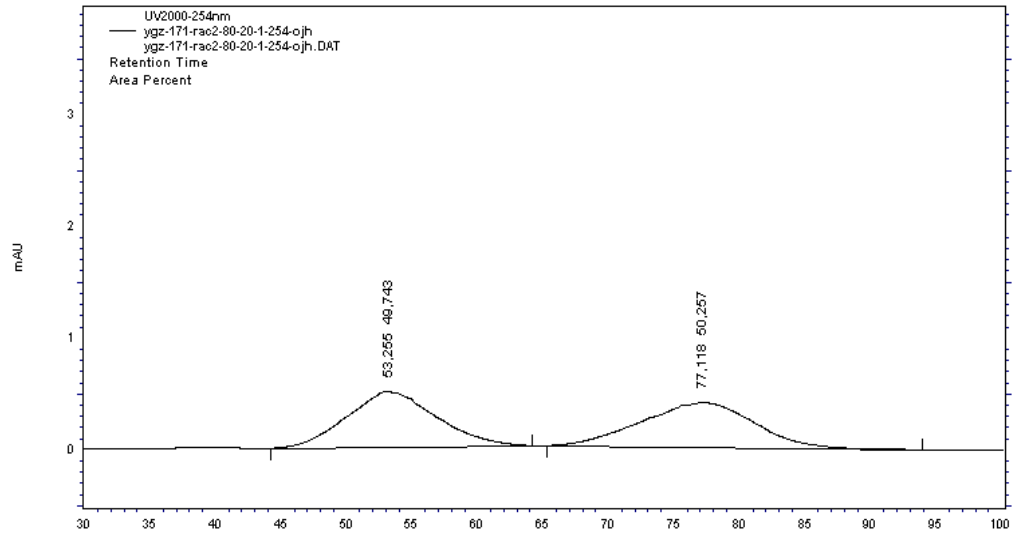


Figure B. 23 HPLC chromatogram of ***rac*-107**

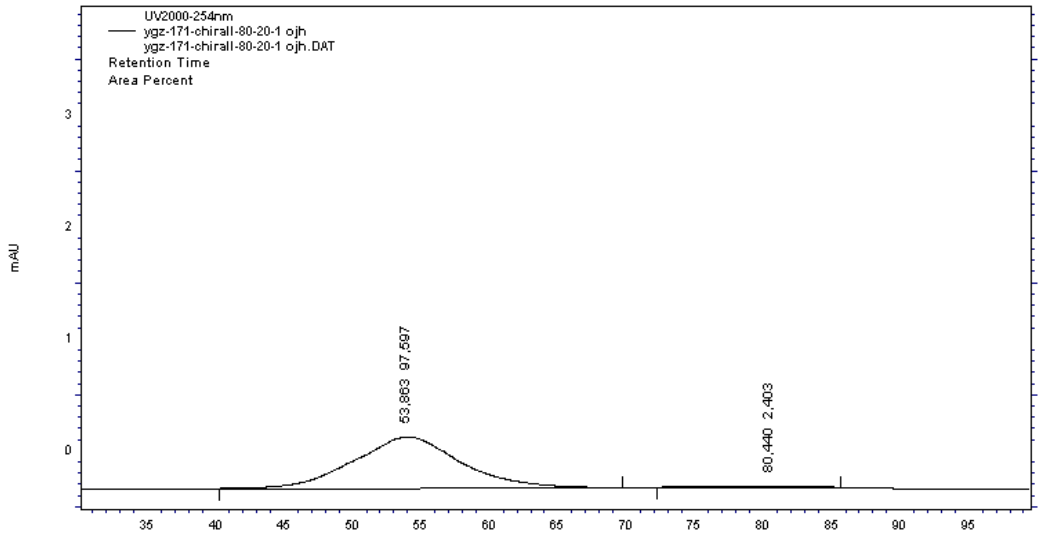
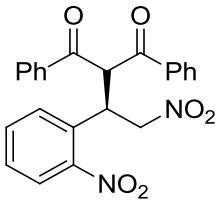
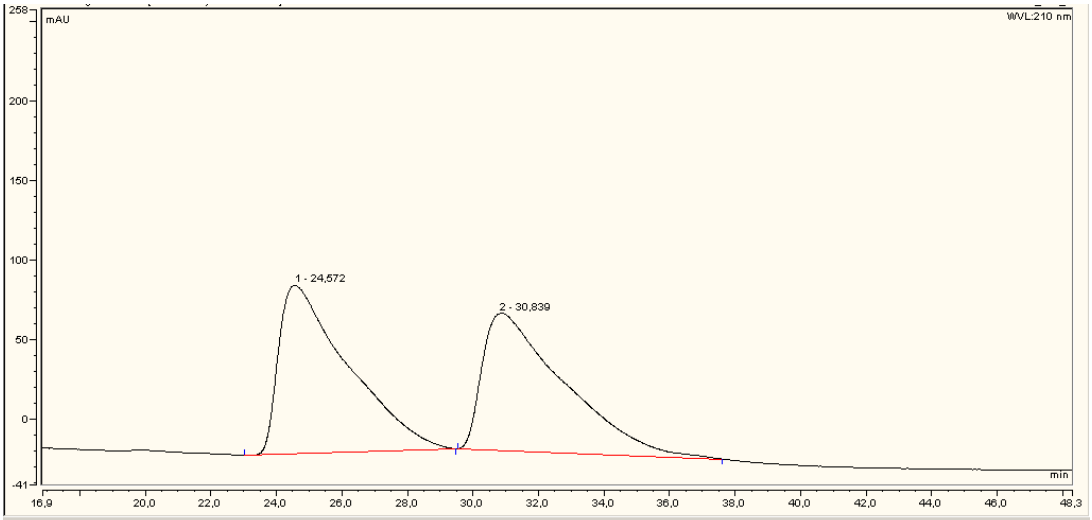


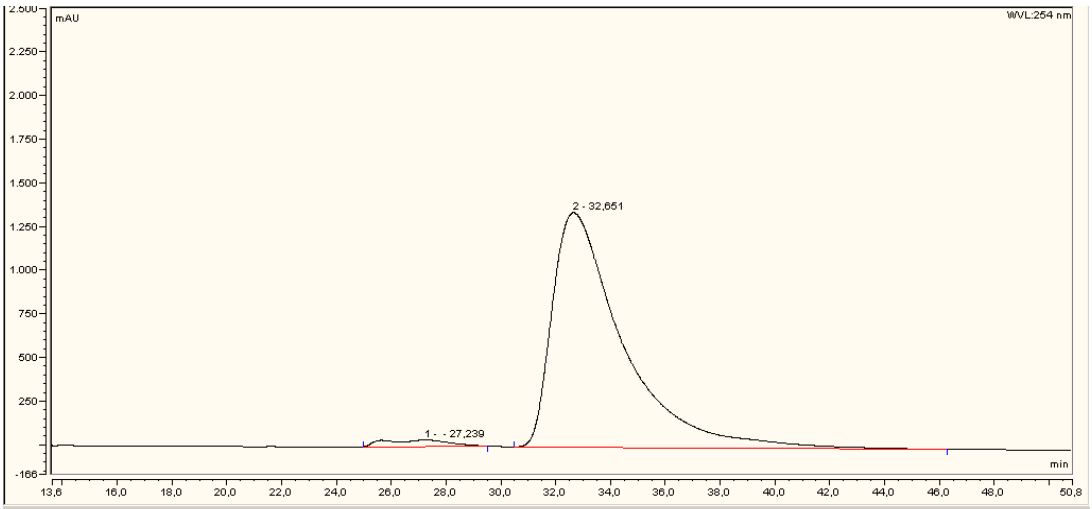
Figure B. 24 HPLC chromatogram of **107**





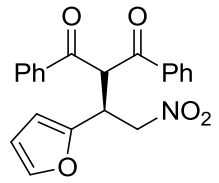
No.	Peakname	Ret.Time min	Area mAU*min	Amount n.a.	Type	Height mAU	Rel.Area %	Resolution
1	n.a.	24,572	257,9413	n.a.	BMB*	105,798	50,950	1,51
2	n.a.	30,840	248,3179	n.a.	BMB*	86,342	49,050	n.a.
Total:			506,2591	0,0000		192,140	100,00	

Figure B. 25 HPLC chromatogram of ***rac*-108**



No.	Peakname	Ret.Time min	Area mAU*min	Amount	Type	Height mAU	Rel.Area %	Resolution
1		27,239	101,7979	n.a.	BMB*^	36,750	2,474	1,18
2	n.a.	32,651	##########	n.a.	BMB*	1342,987	97,526	n.a.
Total:			##########	0,0000		1379,736	100,00	

Figure B. 26 HPLC chromatogram of **108**



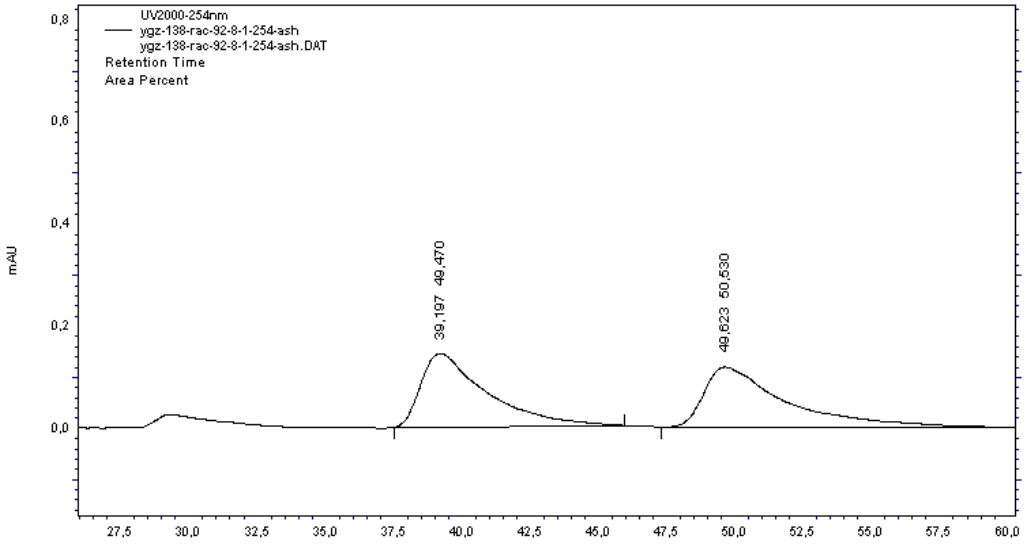


Figure B. 27 HPLC chromatogram of ***rac*-109**

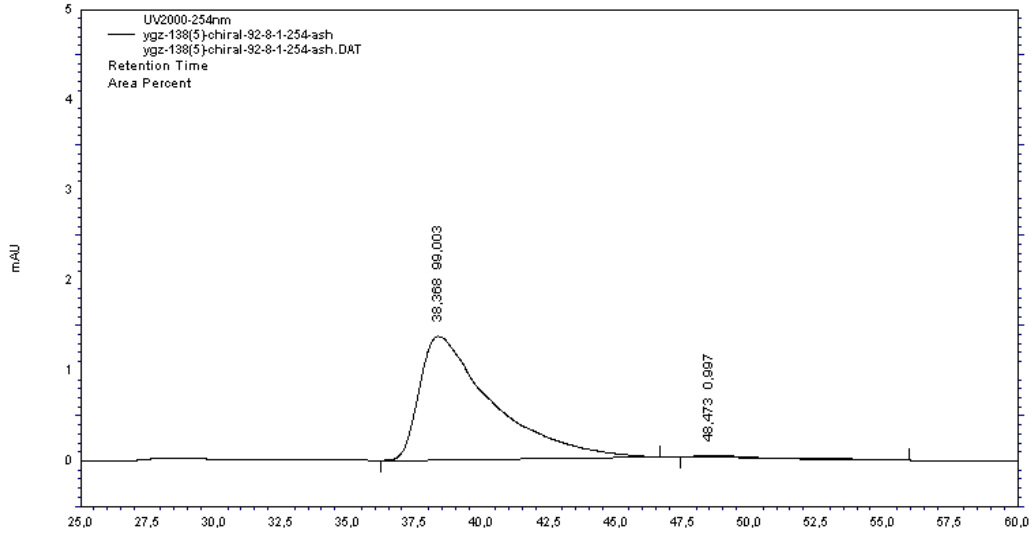


Figure B. 28 HPLC chromatogram of **109**