NOVEL SUPRAMOLECULAR ORGANOCATALYSTS FOR ASYMMETRIC ALDOL REACTIONS

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NOVEL SUPRAMOLECULAR ORGANOCATALYSTS FOR ASYMMETRIC ALDOL REACTIONS

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ABSTRACT

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The proline–calix[4]arene thiourea host–guest complex catalyzed intermolecular aldol reaction of aromatic aldehydes with cyclohexanone is developed. The anti-configured products were obtained in good yields and high enantioselectivities. The reaction is proposed to work via modified Houk–List model, where the carboxylate part of the proline constitutes a supramolecular system with the thiourea. The outcome of the study indicates the influence of the calix[4]arene thiourea on the reactivity and selectivity in a non-polar reaction medium, even in the presence of water at moderate temperatures.

Keywords: Asymmetric Catalysis, Organocatalysis, Proline, Calix[4]arene.

ÖZ

ASİMETRİK ALDOL REAKSİYONLARI İÇİN YENİ SUPRAMOLEKÜLER ORGANOKATALİZÖR

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Yüksek Lisans, Kimya Bölümü

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Haziran 2013, 55 sayfa

Prolin-kaliks[4]aren tiyoüre konuk-konak kompleksi katalizörlüğünde siklohekzanon ve aromatik aldehitlerin moleküller arası aldol reaksiyonu geliştirilmiştir. *Anti*- konfigürasyona sahip ürünler yüksek verim ve özellikle yüksek enansiyoseçicilikle elde edilmiştir. Reaksiyonun prolin'in karboksilat kısmı ile kaliks[4]aren tiyoürenin bir birliktelik oluşturduğu değiştirilmiş Houk-List modeline göre ilerlediği önerilmiştir. Bu sonuçlar, kaliks[4]aren tiyoürenin apolar reaksiyon ortamında, hatta su bulunan ortamda, reaktivite ve seçicilik üzerine olan etkisini göstermektedir.

Anahtar Kelimeler: Asimetrik Kataliz, Organokataliz, Prolin, Kaliks[4]aren

To Ayhan Sıtkı Demir

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TABLE OF CONTENTS

LIST OF FIGURES

Figures

LIST OF TABLES

Tables

LIST OF SCHEMES

Schemes

LIST OF ABBREVIATIONS

Ee	Enantiomeric excess
Dr	Diasteromeric ratio
HOMO	Highest Occupied Molecular Orbital
LUMO	Lowest Unoccupied Molecular Orbital
r.t	Room Temperature
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectra
S-	Sinister (from latin)
R-	Rectus (from latin)
Rac-	Racemic

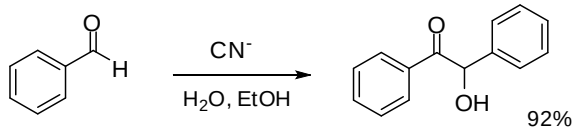
CHAPTER 1

INTRODUCTION

1.1 Asymmetric C-C Bond Forming Reactions

Organic synthesis is the operation of constructing organic molecules from simpler precursors, which can be aimed due to many reasons such as, discovering effective molecules in pharmaceutical field, to prove suggested reaction mechanisms or understanding metabolic reactions. To do so, there are two possible choices in organic synthesis. One of them is to use reactions that transfrom functional group to one another and the second choice is to use reactions that create new C-C bonds.[1] To achieve building of organic molecules, C-C bond forming reactions have always been the fundemental approach in organic chemistry, as combining a nucleophile and an electrophile is one of the most effective way to attain the target molecule.

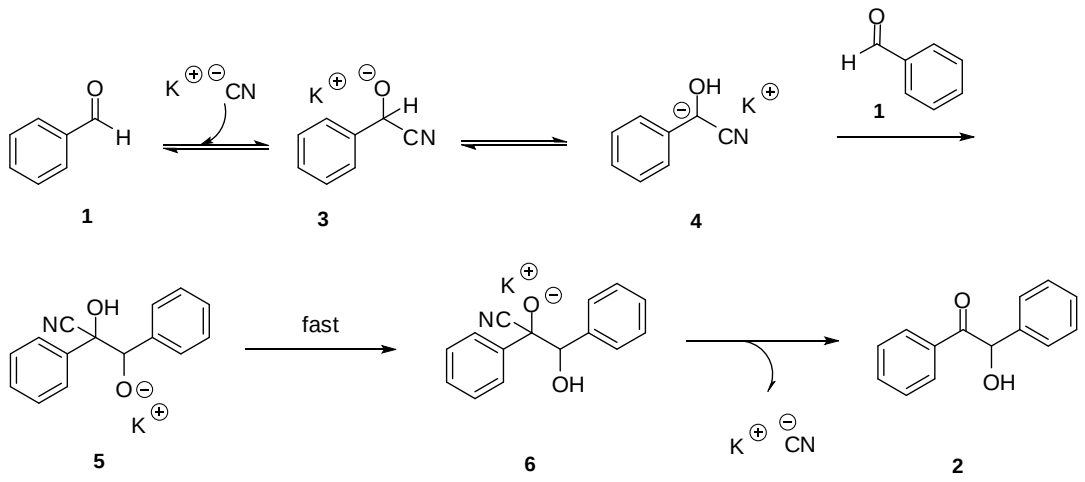
The history of C-C bond forming reactions began with benzoin condensation reaction, before 'asymmetry' term was introduced to organic chemistry. It was found in 1832 by Liebig and Wöhler, where two aldehydes were dimerized by using cyanide ion, being both a reactive nucleophile and a good leaving gorup (Scheme 1).[2]



1 2

Scheme 1. Benzoin condensation reaction

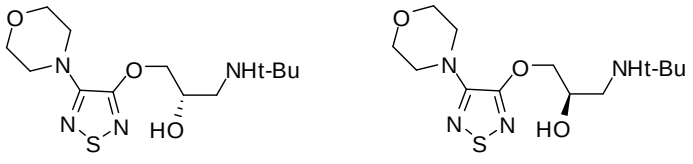
The significance of benzoin reaction actually comes from the importance of α-functionalized product. The mechanism of the reaction, as seen in Scheme 2**,** was explained by Lapworth later in 1903, in which the addition of cyanide ion is followed by proton transfer giving a carbanion structure and attack of this carbanion to another aldehyde resulting in benzoin product.[3]



Scheme 2. Suggested mechanism of benzoin condensation reaction by Lapworth

C-C bond forming reactions allow us to synthesize many important compounds such as α-hydroxy ketones as in the example of benzoin condensation, yet there should be a much more powerful speciality to be that essential and this speciality should definitely be the possibility of possesion of chiral information by the product at the end of the reaction.[4] At this point, the term 'asymmetry' gains meaning. In 1971, eloquent definiton of asymmetric synthesis came from Morrison and Mosher; [5] *''Asymmetric synthesis is a reaction where an achiral unit is converted by a reactant into a chiral unit, such that the stereoisomeric products are formed in unequal amounts.''*

When the importance of the chiral information is realized, asymmetric C-C bond forming reactions have started to draw growing attention, because synthesis of enantiomerically pure compounds is known to be crucial for both pharmaceuticals and academic researches as the biological activity of each enantiomers differs from each other. It is astonishing that nature bears only one of the enantiomer of a chiral compound, many of which also play a role in the metabolic reactions. Timolol can be an illustration to the different effect of enantiomers. Its *(S)*-enantiomer **(*S*)-7** was proved to be an adrenergic blocker, whereas its *(R)*-enantiomer **(*R*)-7** is not.[7] The molecular structures of the enantiomers are given below in Figure 1.



(*S*)-7

(S)-Timolol

Adrenegic blocker

(*R*)-7

(R)-Timolol

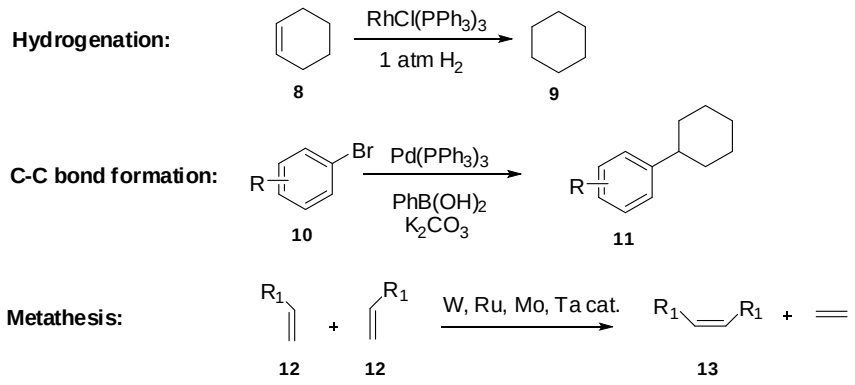
Ineffective

Figure 1. Enantiomers and their functions

Finding new methodologies or developing the already existing ones for synthesis of pure enantiomers, become more and more essential due to their participation in fundemental structures of pharmaceuticals, agrochemicals and synthetic intermediates, *etc*. In the history of organic chemistry, it is seen that the common method for preparing enantiomerically pure compounds was kinetic resolution, which gives only 50% yield of the desired enantiomer. Other methods were also tried in order to devise the best, yet simplest way for this purpose. Transition metal catalysis and biocatalysis were the two general categories which definetely direct chemists for further improvement in such methods.

1.2 Transition Metal Catalysis

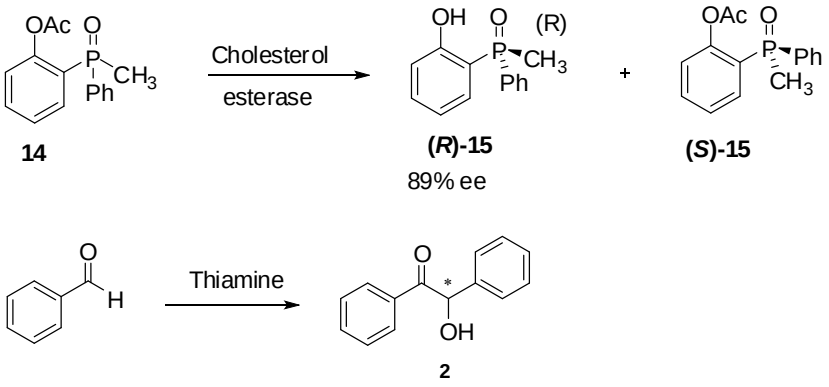
Transition metal catalysis has been participating in many important organic reactions.[8] Transition metal complexes has been mainly preferred due to their potential in getting high selectivity and atom economy in the reactions. Moreover, infinite combinations with ligands make them a useful library of catalysts for organic chemists.[9] Variability of oxidation state and coordination numbers are other factors effective to be chosen.[10] Hence, it is not surprising that transition metal catalysis field was considered worthy to be reward with Nobel Prize; in 2001 for ''Chirally catalyzed hydrogenation and oxidation states'',[11] in 2005 for ''The metathesis method in organic synthesis''[12] and in 2010 for ''Palladium-catalyzed cross couplings in organic synthesis''.[13] General reaction schemes of transition metal catalyzed reactions that won Nobel Prize can be found in Scheme 3.



Scheme 3. General reaction schemes of transition metal catalyzed hydrogenation, C-C bond formation and metathesis reactions

1.3 Biocatalysis

Biocatalysis has become one of the main components in organic chemistry, especially in pharmaceuticals. In this type of catalysis, enzymes are used as catayst. Hence, biocatalysis owes its growing interest to be environmentally friendly. Enzymes are generally used because they provide very high enantioselectivity, regioselectivity, transformation under mild conditions and for being green as water can be used as solvent in the reactions.[15] Yet, they have some drawbacks also. Examples of reactions catalyzed by enzymes can be seen in Scheme 4.[17,18]



Scheme 4. General scheme of cholesterol esterase and thiamine catalyzed reaction

1.4 Organocatalysis

The reaction which is accelerated by small organic molecules, where an inorganic element is not part of the active principle, is called organocatalysis.[19] Although there were evidences about the catalytic activity of small organic compounds, it was not until 2000, that utilizing them in asymmetric transformations become popular, or in other words organocatalysis has just gathered a great potential and significant spot in organic chemistry. The rising interest in organocataysis in the world can easily be understood from the data given in Figure 2.[20]

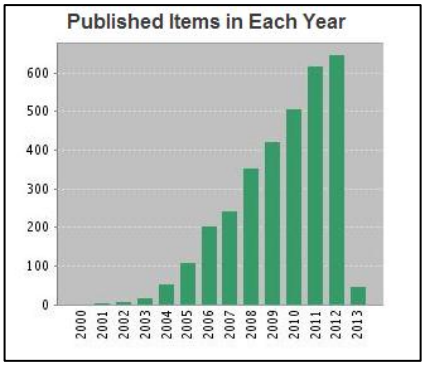


Figure 2. Number of publications in organocatalysis field according to years.

The main reason why organocatalysis has become very popular is the advantages of organocatalysts. The fundemental advantage is that organocatalysts are generally nontoxic which makes them environmetally friendly.[21] Therefore, nontoxic compounds can be better choice for catalyst in both academic field and industry. Furthermore, being cheaper than metal based catalysts is just as important as being environmentally friendly, because they can be used in larger quantities in laboratories with the same cost. Moreover, it is known that organic molecules such as amino acids are inert to moisture and oxygen which makes them suitable candidates for catalysts, as they eliminate the difficult procedures, many of which require special storage conditions, experimental technique or ultra dry reagents and solvents.[22] Availabilty is another crucial advantage of organocatalysts. Actually, vast majority of the organic compunds are existing in nature which makes them suitable for small scale to industrial processes.[23] Besides, organocatalysts provides generality, robustness and convenience in many applications.

To sum up, the discovery of organocatalysis has brought a different aspect to many organic chemist, as it needs less money, time and energy. It provides easier procedure in experiments and less chemical waste. Hence, the aforementioned advantages of organocatalysts lead chemists to explore new methodologies for C-C bond formation reactions by using small organic compounds, organocatalysts.

1.4.1 Types of Organocatalysis

It was not that simple to categorize the types of asymmetric organocatalysis as this area bears such a wide variety of mechanistic views. On the other hand, classifying organocatalysts which are used in this kind of synthesis was much better and easier way to distinguish between the types of organocatalysis according to Benjamin List.[24] He categorized organocatalysts into four different types namely; Lewis Bases, Lewis Acids, Brønsted Bases and Brønsted Acids. The working principle of the classified organocatalysis can be seen in Figure 3 simply, where B stands for a base catalyst and A stands for an acid catalyst

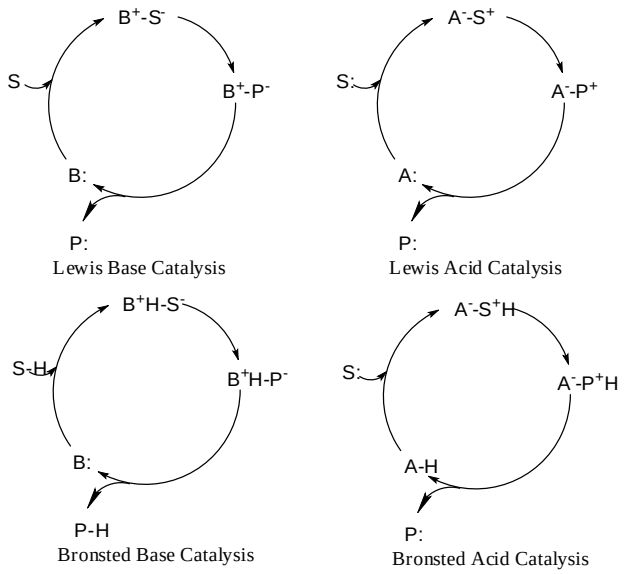


Figure 3. Classification of organocatalysis by Benjamin List

If a Lewis base catalyst is used, the catalytic cycle starts with the nucleophilic attack to the substrate which is defined as S in all catalytic cycles above, in order to yield the product (P) at the end. If acid catalyst is used, this time nucleophilic substrate is attacked to give the product. The distinctive characteristic of the Bronsted acid or base catalysts is that the catalytic cycle contains partial protonation or deprotonation steps. Macmillan catalyst **16**, thiourea catalyst **17**, phosphoric acid catalyst **18**, formamide catalyst **19**, phase transfer catalyst **20** Maruoka catalyst **21** are examples of common organocatalysts[25] according to this classification, which are seen in Figure 4.

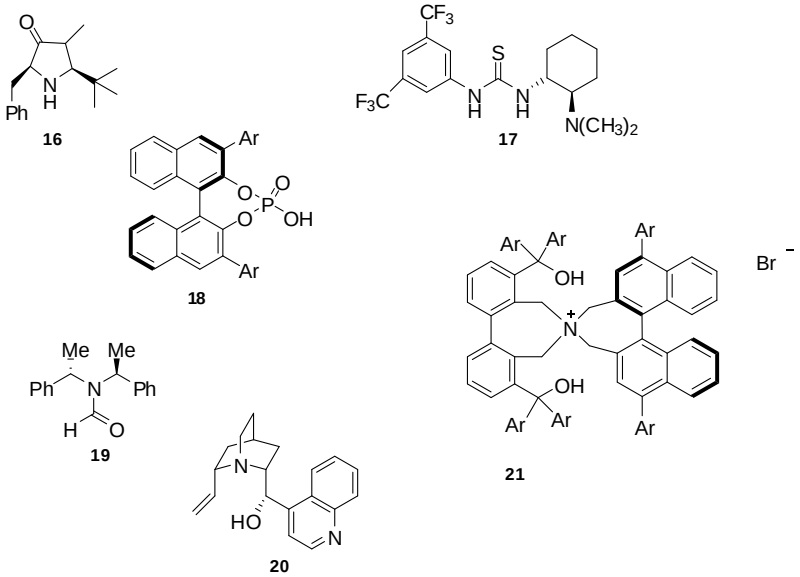


Figure 4. Common organocatalysts

Although this basic classification gives an idea about the types of organocatalysis, MacMillan used a different approach to categorize the types of organocatalysis.[26] He suggested that the major point in this issue should be the identification of the generic activation modes of the catalysts. He explained the generic activation mode as the reactive species which anticipates in different reactions with permanently high enantioselectivities. This species can form when a single chiral catalyst interacts with a main functional group in a highly organized and predictable manner. In Figure 5**,** enamine catalysis is described according to this categorization which is used in this study.

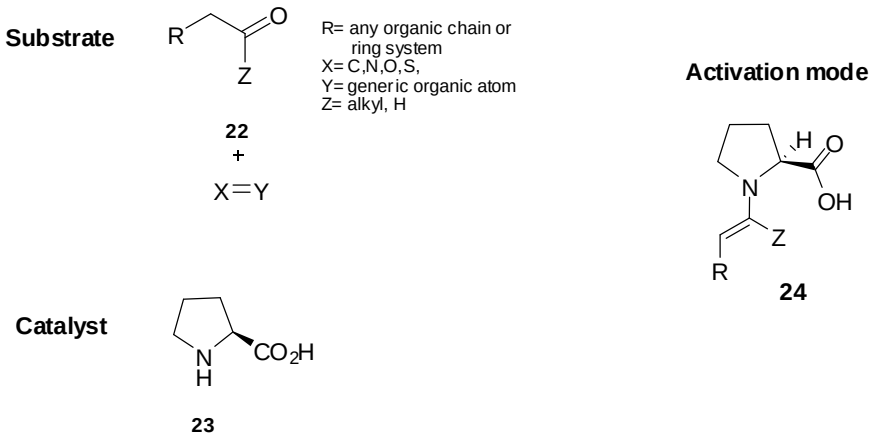
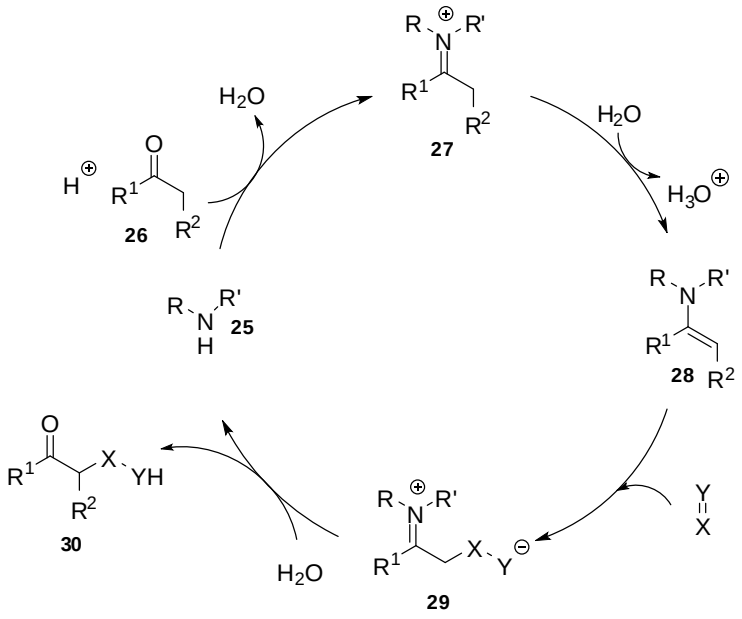


Figure 5. Activation mode of enamine catalysis

1.4.2 Enamine Catalysis

In asymmetric C-C bond forming reactions, the way of generating carbanion equivalents might change according to the type of organocatalyst used and its generic activation mode. For this purpose, one of the most popular methods can be accepted as the enamine catalysis. The principle of enamines actually came from the reaction between carbonyl compounds and secondary amines, found by Stork.[27]

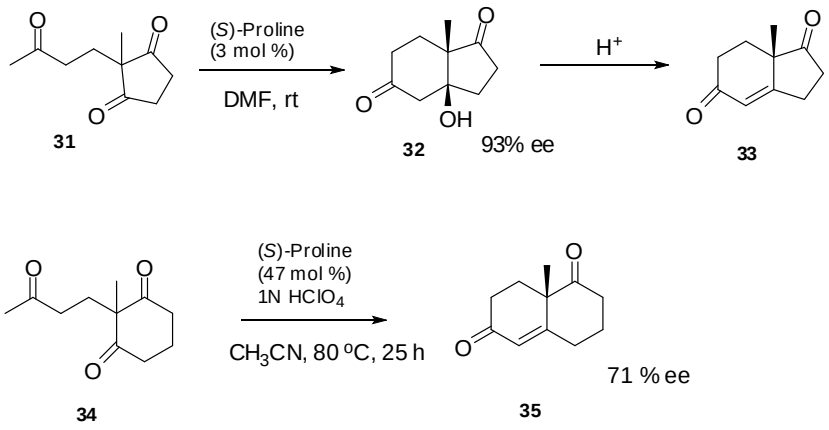
The activation mode of the enamine catalysis can be explained as in Scheme 5 below. The first step of the catalytic cycle starts with the nucleophilic attack of the secondary amine **26** to the carbonyl compound **26** which results in iminium ion **27**. Protonation of this iminium ion gives enamine intermediate **28**, which is able to undergo addition reactions with many different electrophiles forming the new iminium ion **29**. Hydrolysis of the iminium ion provides the α-substituted carbonyl compound **30** at the end of the catalytic cycle. It is not so hard to realize and understand the mechanism underlying this catalytic cycle. In enamine catalysis, HOMO of the carbonyl compound is raised, leading much more activated nucleophiles and this activation makes easier the attack of nucleophile to the electrophile for combining its LUMO than actual nucleophile namely aldehyde or ketone **26**.[28]



Scheme 5. Mechanism of enamine catalysis

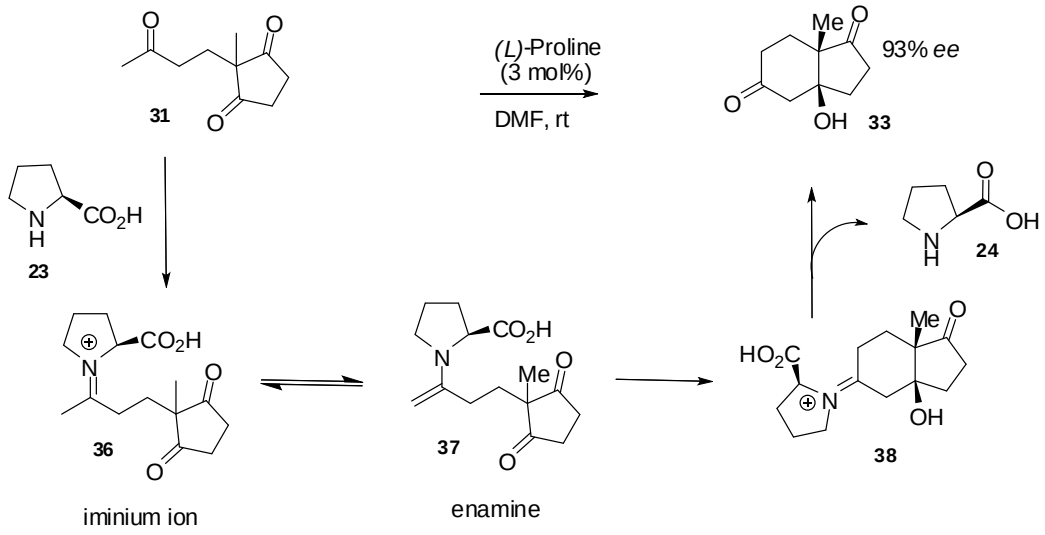
1.4.3 Enantioselective Organocatalytic Aldol Reactions by Enamine Catalysis

Aldol reaction has been one of the most useful methods for carbon-carbon bond forming reactions in organic chemistry. The acquired products, β-hydroxy ketones, are involved in the structure of many biologically important compunds which also concerns pharmaceutical field.[28] Although much affords has already been given in order to find new methodologies including new types of organocatalysts for improving the enantioselectivities of the aldol reaction products, it is still a thriving area in organocatalysis. The first example of enamine catalyzed asymmetric aldol reaction was introduced by two independent reports from Eder-Sauer-Wiechert[29] and Hajos-Parrish[30] (Scheme 6)



Scheme 6. Eder-Sauer-Wiechert and Hajos-Parrish reaction respectively

This reaction, being a milestone in the asymmetric synthesis, elegantly showed that small chiral molecules may catalyze intramolecular aldol reactions and improve the control of the stereoselectivity. The reaction mechanism of Hajos-Parrish-Eder-Sauer-Wiechert reaction is given in Scheme 7.



Sheme 7. The mechanism of the Hajos-Parrish-Eder-Sauer-Wiechert reaction

Surprisingly, the mechanism of this reaction was controversial at the time it was introduced and different groups suggested different ideas about the effect on stereoselectivity as shown in Figure 6.

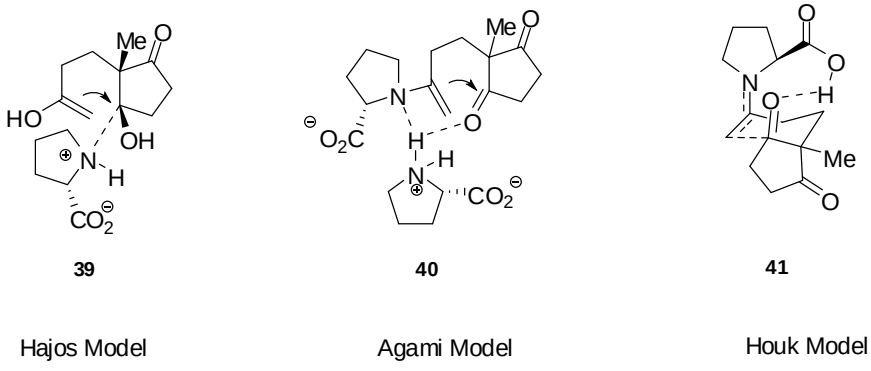
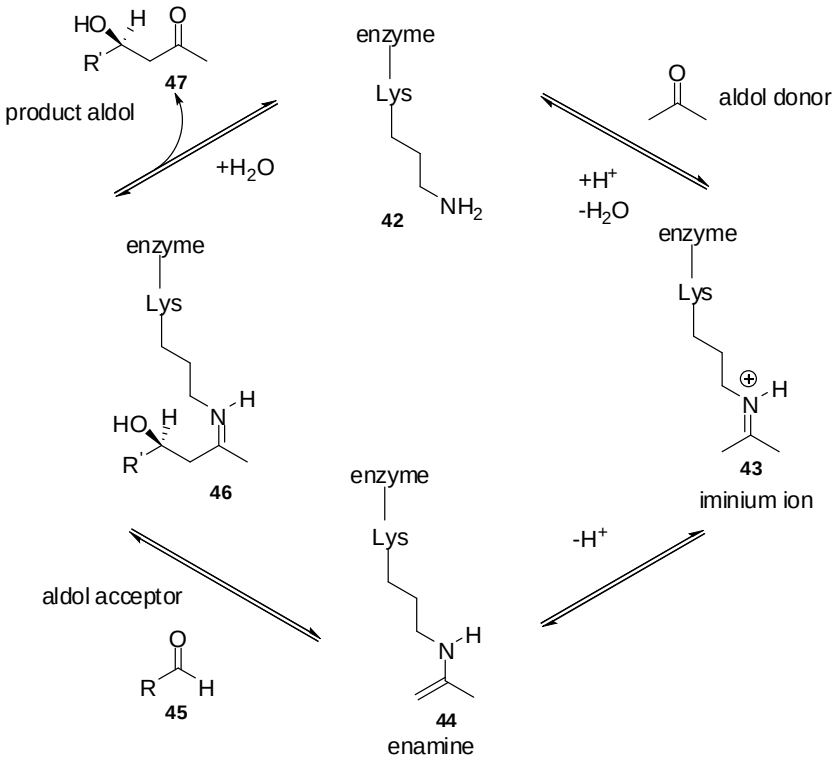


Figure 6. Suggested transition states for proline catalyzed direct asymmetric aldol reaction

Initially, in the mechanism suggested by Hajos, there was not an enamine structure in the transition state.[29,30] Later, according to the studies conducted by Agami existence of enamine with the side chain ketone **40** formed by proline was stated, yet there was another proline molecule in the transtion state, which takes part in proton transfer.[31] On the other hand, Houk and List proposed a different mechanism which includes only one proline molecule for both intramolecular aldol reaction and intermolecular type, where the transition state **41** was fixed by hydrogen bonding between the carboxylic acid part and acceptor aldehyde.[32] Further studies showed that Houk-List model is the best explanation for aldolization process.

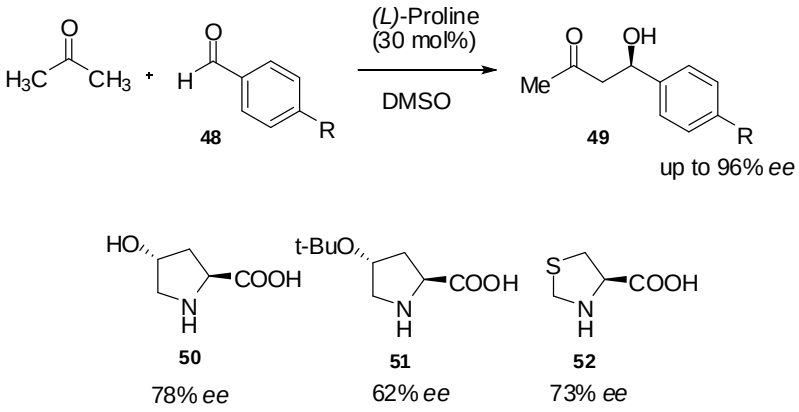
Nevertheless, developed in 1970's, Hajos-Parrish-Eder-Sauer-Wiechert reaction was a breakthrough for both organocatalysis and modern asymmetric catalysis.[33] When the Hajos-Parrish-Eder-Sauer-Wiechert reaction was introduced to the organocatalysis field, there has not been any studies on asymmetric intermolecular aldol reaction but, the ambiguity of the reaction mechanism slowed down the affords given to this issue.

After decades, Lerner and Barbas sugessted that the significance of enamine catalysis for organocatalytic reactions may arise from the nature itself indeed. Their studies about the Class I Aldolase enzymes gave inspiration for the possibility of the intermolecular aldol reaction to have significant value in organic synthesis field (Scheme 8). [34,35]



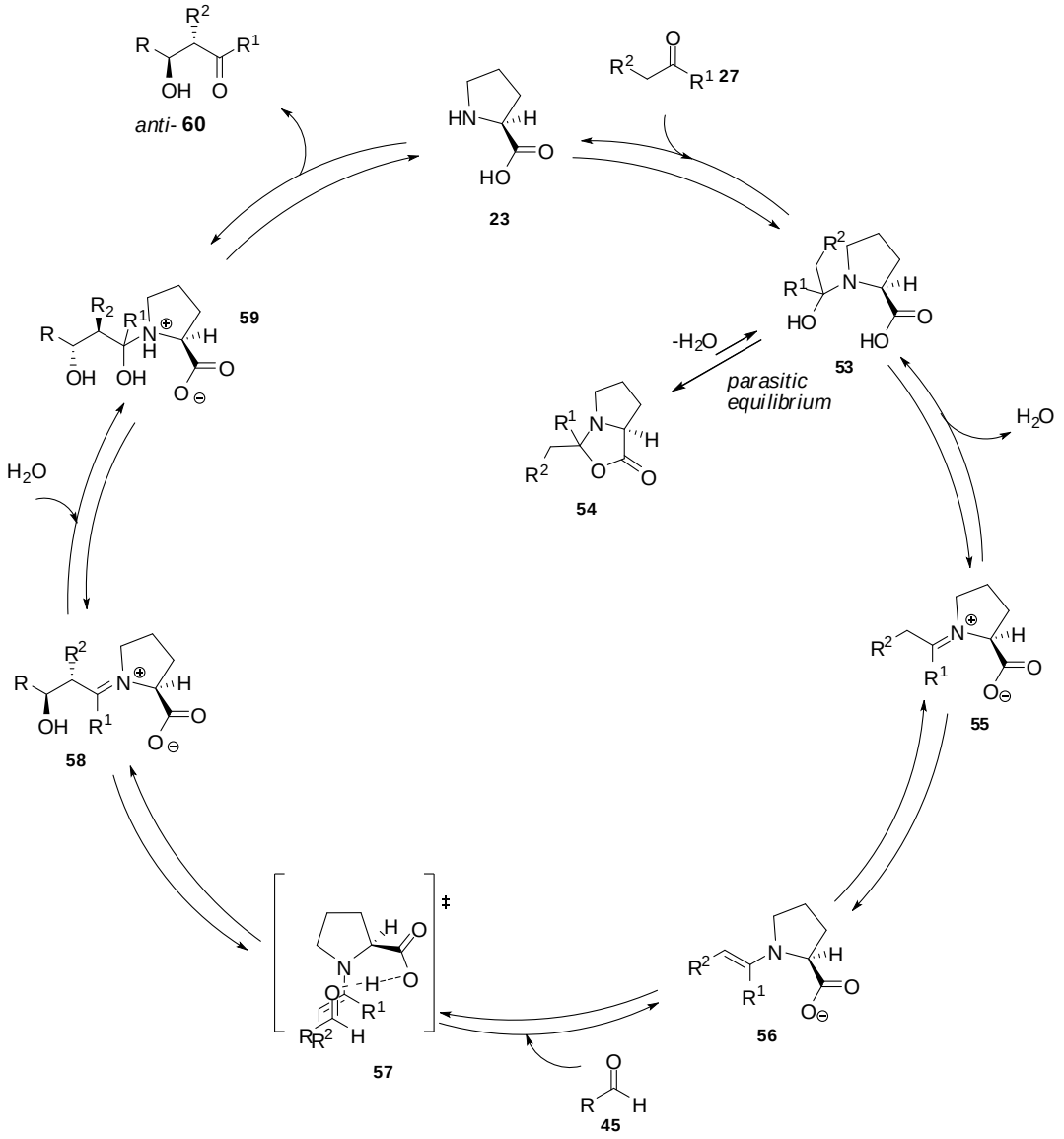
Scheme 8. Suggested mechanism of class I Aldolase catalyzed aldol reaction

This work inspired List and co-workers to investigate the proline catalysis of the direct asymmetric aldol reaction between ketones and aldehydes. In this study different types of catalysts, primary amino acids or acyclic secondary amino acids, were tried in order to understand their function in direct asymmetric aldol reactions.[36] Surprisingly, primary amino acids, acyclic secondary amines and 2-pyrollidine carboxamide were found to be ineffective to give the desired product (Scheme 9). This evidence obviously indicated that both the pyrrolidine ring and the carboxylate part is essential for reaction to proceed with high stereoselectivity. What is more, derivatives of proline also did not give better results than proline itself which gave up to 96% ee.



Scheme 9. Direct asymmetric intermolecular aldol reactions

The owners of the study claimed that proline act as a 'micro-aldolase', beacuse both carboxylic acid due to its acid/base cocatalyst property and nucleophilic amine part play role in the mechanism. In other words, it was explained that carboxylic acid part helps the nucleophilic attack step. It is added that carboxylic part of the proline assists also the nucleophilic attack of amino group on **23**, the dehydration of the carbinol amine intermediate **55**, deprotonation of iminium species **55** and **58**, carbon-carbon bond forming step and hydrolysis of the iminium-aldol intermediate(Scheme 10).



Scheme 10. Mechanism of proline catalyzed direct asymmetric aldol reaction

The effect of proline as a catalyst was proven with this studies. Actualy there are many reasons to be chosen as an organocatalayst by most of the scientists. To begin with, nontoxicity, inexpensiveness and availability make proline a suitable organocatalyst. Besides, its high solubility in water provides easy removal by aqueous extraction. Furthermore, there is no need to prior modification of carbonyl substrates such as deprotonation steps.[36]

On the other hand, further studies showed that the drawback of this organocatalyst can not be ignored and it was understood that more affords should be given to find solutions to difficulties obsered. Although proline can be accepted as the simplest and one of the most effective organocatalyst, it has low solubility in organic solvents. More importantly, there

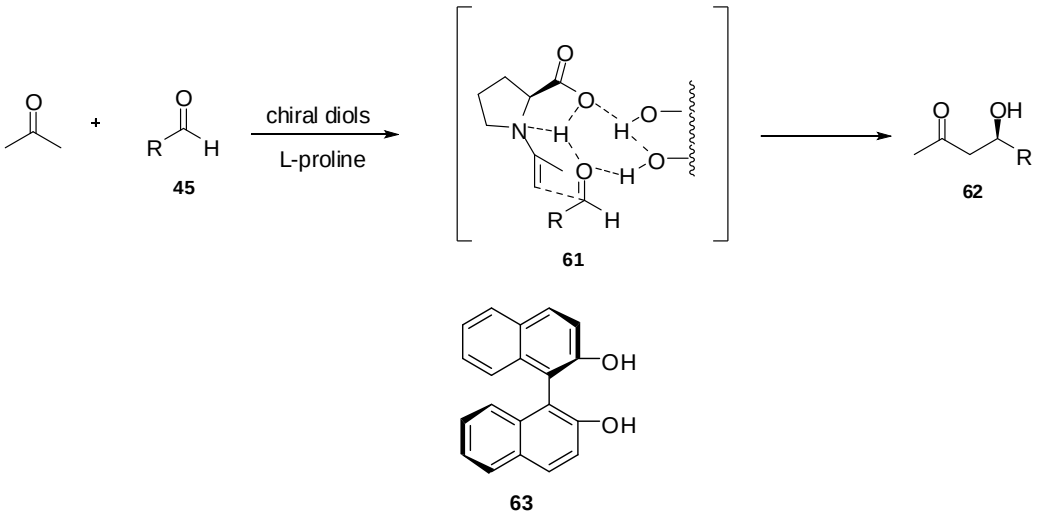
exists a parasitic equilibria which entails the high loadings of the catalyst in order to be overcome. Another point is that, its low selectivity which make it hard to work with, especially in direct asymmetric aldol reactions. All the aforementioned difficulties pushed chemists to find new methodologies in this area and some of these studies related to the subject of the thesis will be covered from now on.

1.5 Role of Additives in Asymmetric Organocatalytic Aldol Reactions

Once the mechanism of enamine catalysis was understood and the drawbacks of the proline were realized, much attention has been given to find different catalyst systems and to apply them in different kind of reactions in order to increase the enantioselectivity. At this point nature has always been inspirational to most of the scientists to find out solutions. Therefore, most of the time, they tried to mimmic the nature.

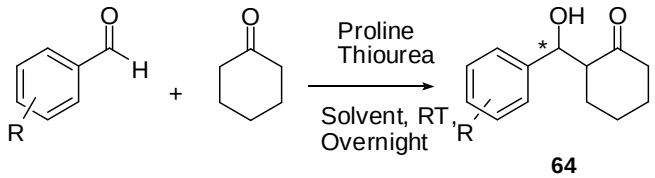
Hydrogen bond is widely accepted as the most powerful noncovalent bond, which can be seen in many important biochemical environments. Hence, it is thought that this kind of strong but noncovalent interaction may alter the function of the small organocatalysts, improving the selectivities in the reactions they are used. One of the popular work in this field belongs to Zixing Shan.[37] At that time proline had been used in many different reactions including Diels-Alder reaction,[38] Michael reaction,[39] Mannich reaction[40] *etc*. but, asymmetric direct aldol reaction has drawn much more attention among these reactions.

Poor solubility of proline was one of the problems that should be solved. For this purpose, newly designed catalysts, derived from proline's structure most of the time, were synthesized, but they did not give better results.[41] So, chemists started to give much attention to other solutions in order to thrive the enantioselectivities or accelerate the reaction and using additives was an option according to the researches. Houk and co-workers suggested that the additives can enhance the enantioselectivity as the additive may promote the formation of the enamine intermediate.[42] Inspired by this study, Shan and Zhou chose chiral diol **63** in their study as shown in Scheme 11. Surprisingly, they managed to get 98% ee and 90% yield. Another impressive result was that the configuration of the products does not depend on the chirality of the additives. The results, when racemic proline was used, showed that the chiral induction did belong to proline, but it was also explained that additives absolutely improved enantioselectivity by chiral supramolecular system through hydrogen bonding interactions. It is also indicated with this work that mimmicing the nature could be the right way to choose for further improvements.

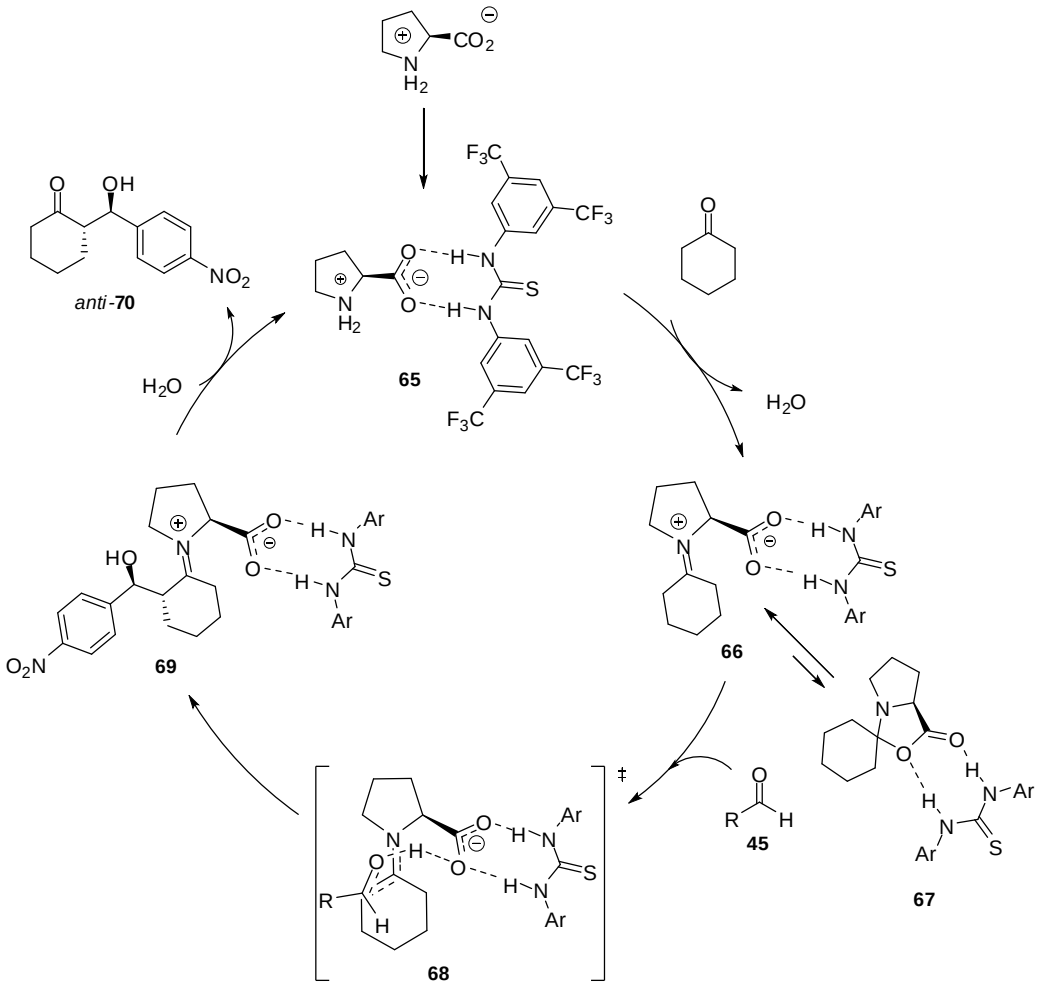


Scheme 11. Possible transition state for chiral diol additives

When the effect of additives was proven, the supramolecular catalyst systems become quite popular. Most of the time, studies focused on the problems encountered when proline is used. Another study in this field belongs to Demir and his group.[43] They used thiourea derivative as additive to see its impact on both stereoselectivity and enantioselectivity. It was suggested that, if a functional group could interact with the carboxylate part of the proline, it may both increase the solubility of the proline in organic solvents and make the possible transtion state more plausible, which will enhance the selectivity. For this purpose, they used cyclohexanone as donor and substituted benzaldehydes as acceptor (Scheme 12). The results with the thiourea-proline host-guest complex were impressive; 99% ee and very high stereoselectivities were obtained in nonpolar solvents. The suggested mechanism of the reaction can be seen in Scheme 13.



Scheme 12. Proline thiourea host guest complex catalyzed direct enantioselective aldol reaction



Scheme 13. Suggested reaction mechanism for proline thiourea host guest complex catalyzed direct enantioselective aldol reaction

In another work, Barbas preferred to use water as the solvent,[44] which is a desirable solvent in organic reactions because it is safer, cheaper and greener.[45] Yet, it disturbs the interactions and hydrogen bonding which can be crucial for the stabilization of the transition state. In order to achieve the desired goal, they used specially designed catalysts in this study (Figure 7).

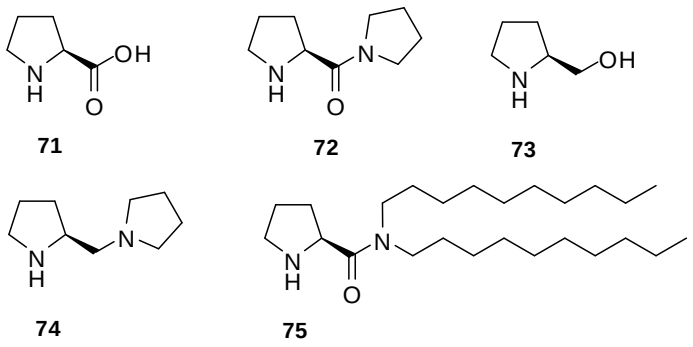
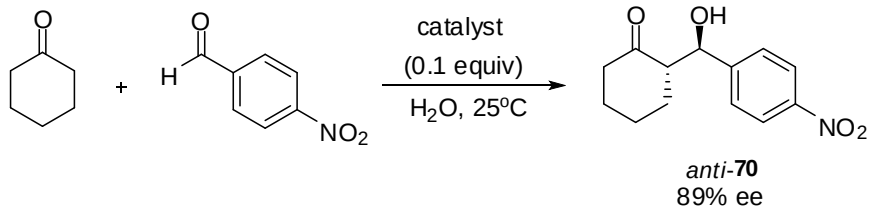


Figure 7. Examples of catalysts used in the presence of water

It is explained that hydrophobic active part of an enzyme is responsible for the occurance of the reactions in Class I Aldolase type reaction. It may be due to decreasing interaction between water and reaction transition state which affects enantioselectivity. Hence, if the hydrophobic alkyl chain in the structure of amine based catalyst **75** helps having hydrophobic interaction between the reactants, water molecules should be excluded and biphasic system should increase enantioselectivity. The trials were successful and reaction between cyclohexanone and 4-nitrobenzaldehyde in given condition produced 89%ee (Scheme 14).



Scheme 14. General reaction scheme of enantioselective aldol reaction

in the presence of water

1.5.1 Calix[4]arenes in Asymmetric Synthesis

Calixarenes are macromolecules which can be synthesized starting from phenols and aldehydes.[46] Actually, the reaction between phenols and aldehydes which gives cyclic oligomers at the end of the reaction, was found by Zinke and Ziegler in 1940.[47] The name calix (chalice) actually came from the resemblence of a vase and the name stands for the aromatic building block (Figure 8). The common structure consists of two distinguishable parts called upper and lower rim where substituted phenol rings constitutes the upper rim and the phenolic hydroxyl groups form the lower rim. Although it is said that these huge

molecules can exist in different chemical conformations as rotation is easy around methylene bridge, it is also possible to limitate them. Replacing hydroxyl groups with other molecules, make calixarenes have higher rotational barriers. Besides, having bulky groups on the upper rim as on the one which is used in this study, can also decrease the rotation hence decrease the number of conformations. The reason for using *p*-tert Butyl groups on the upper rim of calix[4]arene therefore can be explained that phenomena. Due to that, these molecules have rigid structures. Benzene units on the structure provides an enhanced π-π interaction. Furthermore, OH groups creates possibility for hydrogen bonding with other molecules. Most importantly, hydrophobic cavities of calix[4]arenes makes them good candidates for taking place in host-guest chemistry due to possible noncovalent interactions and possibility of holding smaller molecules.

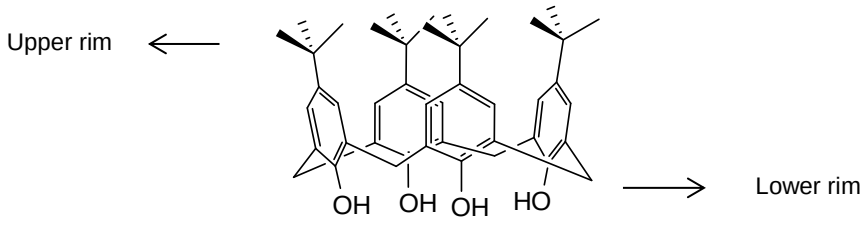
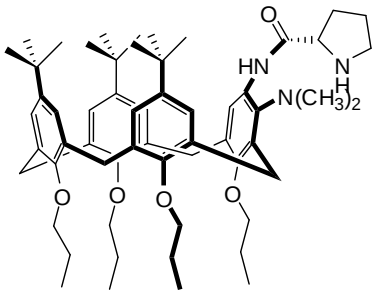


Figure 8. Common structure of p-tert butyl Calix[4]arene

According to their different structures and properties, calixarenes may be used as optical or ion sensitive sensors, chiral recognition devices or as stationary phase. Those huge molecules allow modification only from two places on the structure; *p*-substituted groups and hydroxyl groups. Besides, benzene units of the calixarene structure results in have high π-π interactions, gathering them prominence. Furthermore, hydroxyl groups may be used for making hydrogen bonding that can be effective in the reaction course.[48]

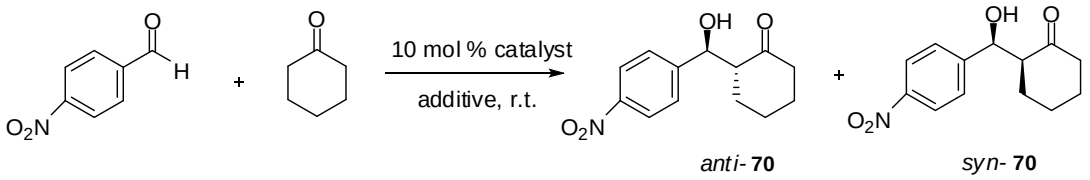
Once the possibility of modification for this chiral macromolecules make them suitable for asymmetric reactions, studies were started to be reported in this field. In 2008, a specific calixarene structure was modified and used in direct enantioselective aldol reactions,[49] which is seen in Figure 9.



76

Figure 9. Modified calix[4]arene based catalyst

The *m*-dimethylamino substituted chiral calix[4]arene derivative **76** was synthesized, having an L-prolinamido group, and it was able to catalyze the reaction between aromatic aldehydes and ketone in the presence of acetic acid which gave 75% ee with 4-nitrobenzaldehyde (Scheme 15).



Scheme 15. General reaction scheme

1.6 Aim of the Work

α-Hydroxy ketones has take place in the structure of important pharmaceutical intermedaites. Due to the functional groups it bears such as hydroxyl group or carboxyl group, they can be easily modified to different target molecules. Therefore, new methodologies for enantioselective synthesis of α-hydroxy ketones have been tried and to get maximum enantioselectivity host-guest chemistry has been tried in the literature lately.

The main target of the study was to accomplish direct asymmetric aldol reaction between aromatic aldehydes and cyclohexanone, by using a host-guest complex. For this purpose, proline was chosen as the host molecule and calix[4]arene thiourea was selected for the guest molecule. It was aimed to increase the solubility of the aminoacid in organic solvents due to noncovalent interaction between proline and thiourea. It was thought that the hydrogen bonding should also influence the catalytic properties of proline and make the transition state more stable. The effect of calix[4]arene moiety on the selectivity of the reaction in the presence of water was also wanted to be investigated, because the hydrophobic cavity can help the reaction to proceed. At the end, the results of modification on the structure of the host-guest complex by using calix[4]arene moiety can be effective for further improvements in synthesis of enantiomerically pure compounds.

CHAPTER 2

RESULTS AND DISCUSSION

Based on these information, it was thought that the hydrophobic cavity of calix[4] arene can be used for the reaction to proceed and increase the solubility of proline with the help of thioureas attached to calix[4]arene molecule which could also stabilize the transition state due to hydrogen bonding interactions, which can be seen in Figure 10.

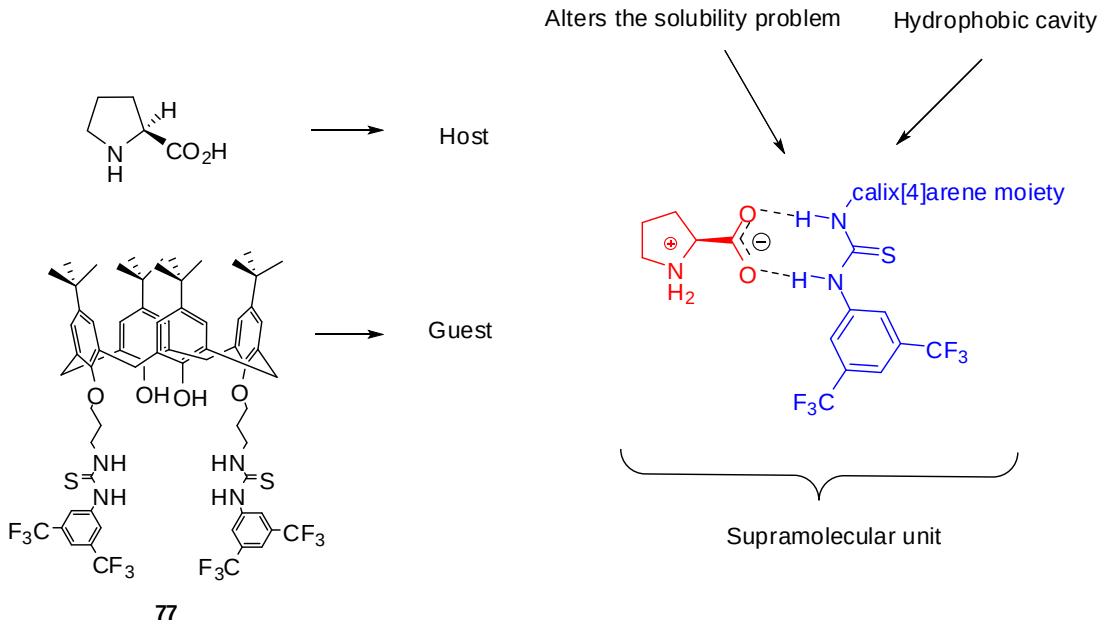
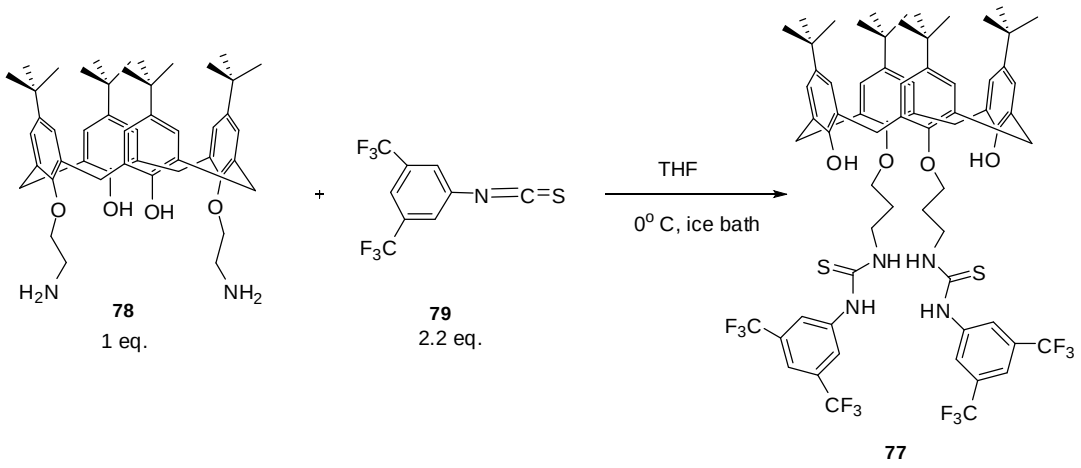


Figure 10. Supramolecular unit aimed to use in the study

In order to achieve that, *p*-tertbutyl calix[4]arene diamine **78** which can be synthesized starting from calix[4]arene was supplied from Selçuk University for synthesis of thiourea guest molecule. By using 3,5–*bis* (trifluoromethyl) phenyl isothiocyanate **79**, the product **77** was obtained (Scheme 16) and characterized by ^{1}H NMR, ^{13}C NMR and HRMS .



Scheme 16. Synthesis of *p*-tertbutyl calix[4]arene thiourea guest molecule

After the characterization of calix[4]arene based thiourea guest molecule **77**, NMR experiments were conducted to prove the interaction between the thiourea and the proline, where $CDCl_3$ was used as solvent. The ^1H NMR spectra of proline-thiourea complex in Figure 11 showed that addition of proline makes N-H protons of the thiourea give downfield shift due to H-bonding, which also indicates the incresing solubility of proline when thiourea is used as guest molecule. It was also observed that furher addition leads further downfiled shift.

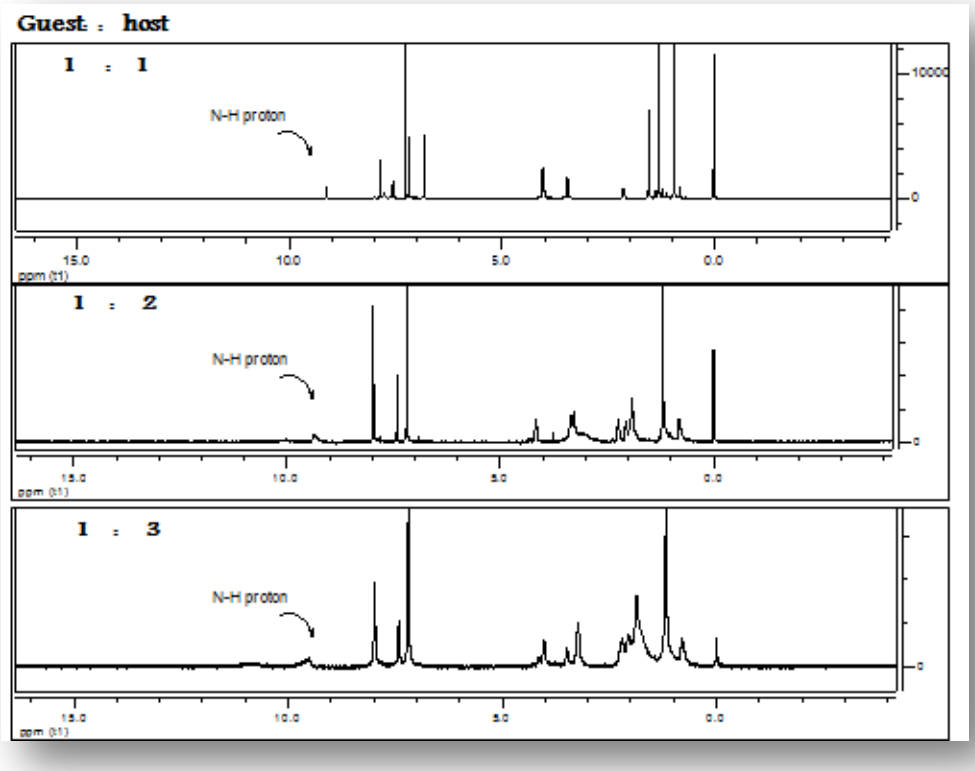
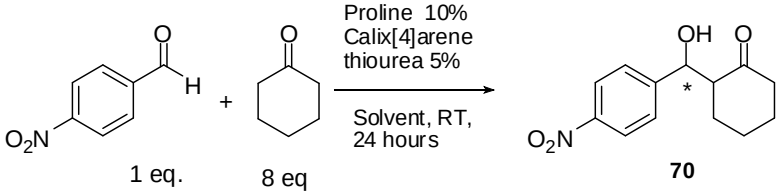


Figure 11. The ^{1}H NMR spectra of proline-thiourea complex

Cyclohexanone (8 equivalent) was chosen as the donor and 4-nitrobenzaldehyde (1 equivalent) was decided to be used as acceptor for early investigation. In order to determine the best solvent for the reaction, variety of solvents having different polarities were screened, although previous studies pointed out that polar solvents most probably disturb the H-bonding interaction between proline and thiourea (Scheme 17). The expected results were obtained in which more polar solvents gave lower diastereoselectivities and enantioselectivities (Table 1). The lowest stereoselectivity belongs to chloroform because of high polarity which decrase the possibility of the interaction between the host and the guest molecule. The best result was acquired by using a nonpolar solvent, hexane, and it was chosen as the solvent for the direct asymmetric enantioselective aldol reaction for further studies.



Scheme 17. Aldol reaction catalyzed by proline- calix[4]arene based supramolecular catalyst

Table 1: Solvent screening for direct asymmetric aldol reaction catalyzed by proline-calix[4]arene complex

Entry	Solvent	Conversion[a]	anti: syn[a]	ee%[b]
1	Chloroform	90%	80:20	92%
2	Hexane	99%	90:10	96%
3	DCM	87%	77:23	89%
4	Cyclohexane	95%	88:12	92%
5	Toluene	95%	87:13	90%

a: Determined from crude ^{1}H NMR

b: Determined from HPLC with appropriate chiral columns

Another issue was to see the effect of guest loading. In the former studies, the percantages of the host and guest molecule were found to be same most of the time, but the structure of the *p*-tertbutyl calix[4]arene give the possibility to use proline in half amount of the thiourea due to two thiourea moieties. Therefore it was decided that the ratio between host and the guest molecule should be 2:1. After that, catalyst loading was investigated as given in Table 2 and it was observed that the enantioselectivities increased when the amount of complex (mol percent) was decreased. As the convenience of amount of proline was considered also, the minimum amount for proline was chosen as 10 mol % . To sum up 5 mol % calix[4]arene based thiourea and 10 mol % proline was used as host guest complex for the reaction.

Table 2: Guest screening for 24 hours using hexane as solvent.

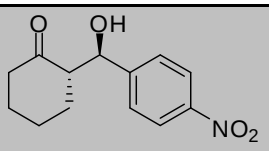
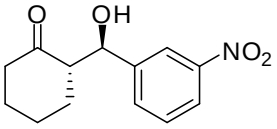
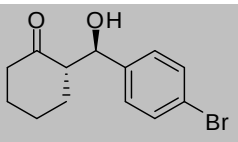
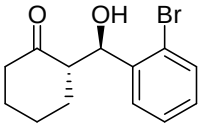
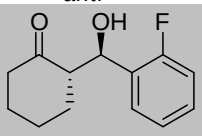
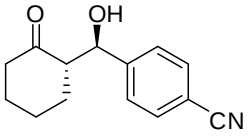
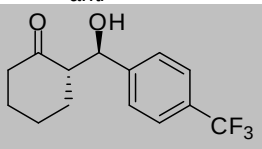
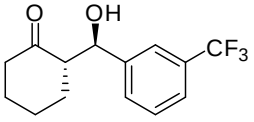
Entry	Calix[4]arene thiourea	Proline	Conversion[a]	anti: syn[a]	ee%[b]
1	20%	20%	90%	80:20	92%
2	10%	20%	97%	86:14	96%
3	5%	10%	98%	95:5	99%

a: Determined from crude ^{1}H NMR

b: Determined from HPLC with appropriate chiral columns

After optimization of the solvent and catalyst loading for the reaction as indicated in Table 1 and Table 2, different substituted aromatic aldehydes were tried for the substrate scope. As can be seen in Table 3, aromatic aldehydes having highly electron withdrawing groups gave the best results as expected. Moreover, it was proved that the reaction is tolerable with *ortho* substituted aldehydes such as *o*-bromo, *o*-methyl and *o*-fluorobenzaldehyde.

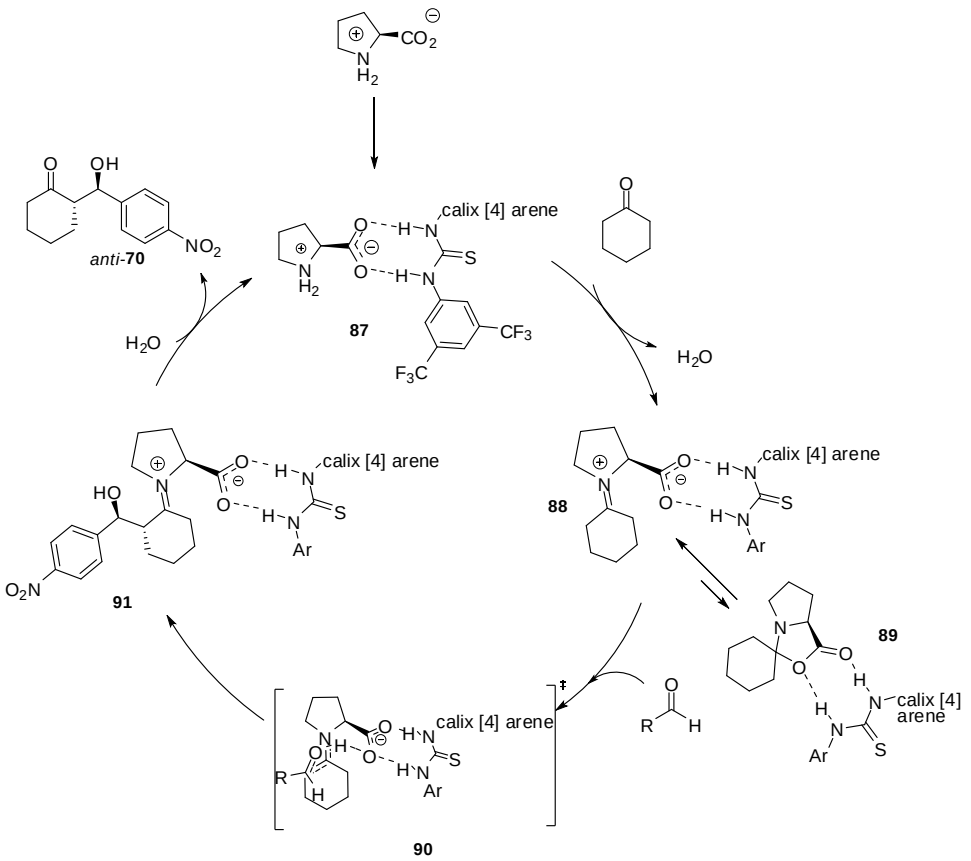
Table 3: Substrate Scope for direct asymmetric aldol reaction with proline-calix[4]arene thiourea host-guest complex.

Entry	Product	Conversion %[a]	anti:syn[a]	Yield	ee%[b]
1	 *anti*-**70**	98	97:3	95	99
2	 *anti*-**80**	96	96:4	90	99
3	 *anti*-**81**	84	94:6	79	99
4	 *anti*-**82**	87	96:4	83	99
5	 *anti*-**83**	86	90:10	84	94
6	 *anti*-**84**	65	70:30	63	87
7	 *anti*-**85**	80	86:14	78	95
8	 *anti*-**86**	93	94:6	90	99

a: Determined from crude ^{1}H NMR

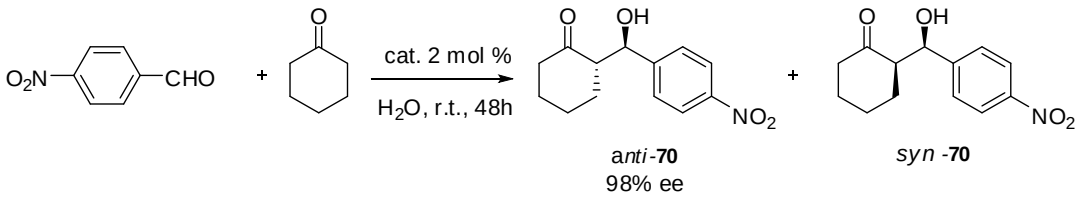
b: Determined from HPLC with appropriate chiral columns

All the aforementioned results lead us to propose a mechanism based on general enamine catalysis. The transition state can be explained according to a modified Houk-List model, because thiourea generates a supramolecular unit due to hydrogen bonding with the carboxylic acid moiety of the proline, which participates in improving the catalytic properties of proline. The hydrogen bonding also plays a role in decreasing the possibility of presence of parasitic equilibria which results in oxazalidinone compound. What is more, the hydrogen on the amine moiety of proline becomes much more acidic which also assits to stabilize the transition state. Furthermore, the chair conformation in the trasition state explains the stability and stereoselectivity seen in the reaction. Lastly, nonpolar thiourea moiety helps to increase the solubility properties of proline in non-polar solvents as in hexane or toluene. In the mechanism shown in Scheme 18, the supramolecular complex **87** is formed by hydrogen bonding. Then, iminium ion **83** is generated resulting from the dehydration reaction of the nucleophile. After the deprotonation step enamine intermediate is obtained which has a higher HOMO level, therefore much more activated than the original nucleophile - cyclohexanone in this case. The suggested transition state **90** before the formation of C-C bond can be seen also. Hydration of iminium ion **91** gives the anti aldol product *anti*-**70** and the complex **87**.



Scheme 18. Proposed mechanism for aldol reaction using proline-calix[4]arene thiourea host-guest complex.

The possibility of using water as solvent in asymmetric reactions has always been interesting and attracting and in 2009, similar structure based on calixarene moiety bearing proline was found to be effective catalyst in water for direct asymmetric aldol reactions (Scheme 19). The suggested mechanism seen in Figure 12 helps to explain that hydroxyl groups on calix[4]arene based catalyst makes additional hydrogen bonding with water molecules which creates boundary between hydrophobic and hydrophilic region and assist the rection to proceed in that region. It was possible to achieve high diastereoselectivity and 98% ee in the presence of 28 equivalent water.[50]



Scheme 19. Aldol reaction catalyzed by calix[4]arene catalyst in the presence of water[50].

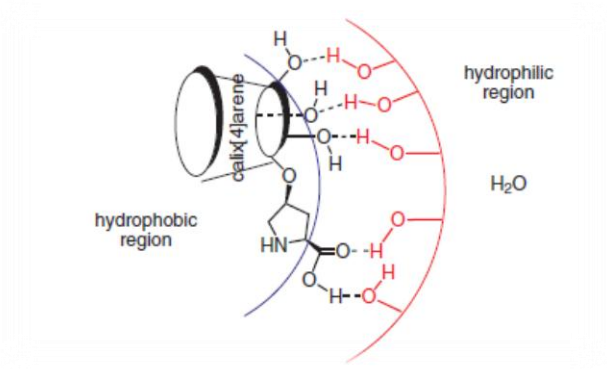
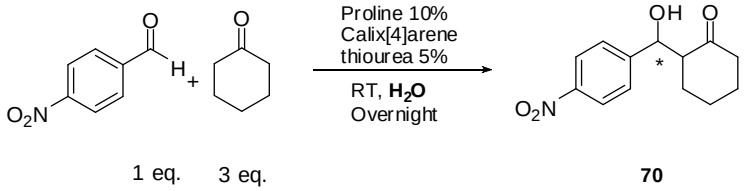


Figure 12. Hydrophilic and hydrophobic reagions created by calix[4]arene based catalyst.[50]

The hydrophobic cavity of calix[4]arenes makes them potential choice for this purpose. To understand the effect of calix[4]arene moiety of thiurea guest molecule, the reaction of cyclohexanone and 4-nitrobenzaldehyde was tried in the presence of water under the same conditions (Scheme 20).



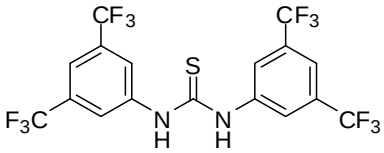
Scheme 20. Direct asymmetric aldol reaction in the presence of water

Although the ratio between the donor and acceptor was decreased to 3:1 the reaction proceed with high enantioselectivity even in the presence of water, where solvent was not used. It was also proved that the reaction did not take place when 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea is used (Table 4).

Table 4: Results of reaction in the presence of water

Entry	Water	Proline	Additive	Conversion[a] %	Anti:Syn[a]	ee % [b]
1	45 µL water	10%	5%	60	65:35	92
2	45 µL water	10%	5%[a]	-	-	-

a:



b: Determined from 1H Crude NMR

c: Determined from HPLC by using appropriate chiral columns

The results of the experiments clearly demonstrates that the reaction takes place in the hydrophobic cavity provided by calix[4]arene moiety. It is proven that there is hydrogen bonding between the thiouera and the proline with NMR experiments. Yet, there are two other hydroxyl groups on calix[4]arene molecule which may also form hydrogen bonding with other molecules. Therefore, when water is introduced into the medium without disturbing the interaction between the host and the guest molecule, hydroxyl groups interacts with water molecules. As the calix[4]arene have a rigid structure, when thiourea moieties are attached to it, the hydrophobic cavity is extended and the motion of thioureas is restricted becuase of the rigidity. Hence, the reaction can proceed through enamine catalysis inside of the cavity with high stereoselectivity and enantioselectivity, whereas it is not possible when Shriener's thiourea is used instead of calix[4]arene with the same amount of water. In addition, it can be explained that although proline is soluble in water, it takes place in the hydrophobic region and catalyze the reaction in the presence of water, due to the enormous effect of calixarene structure on the reaction (Figure 13).

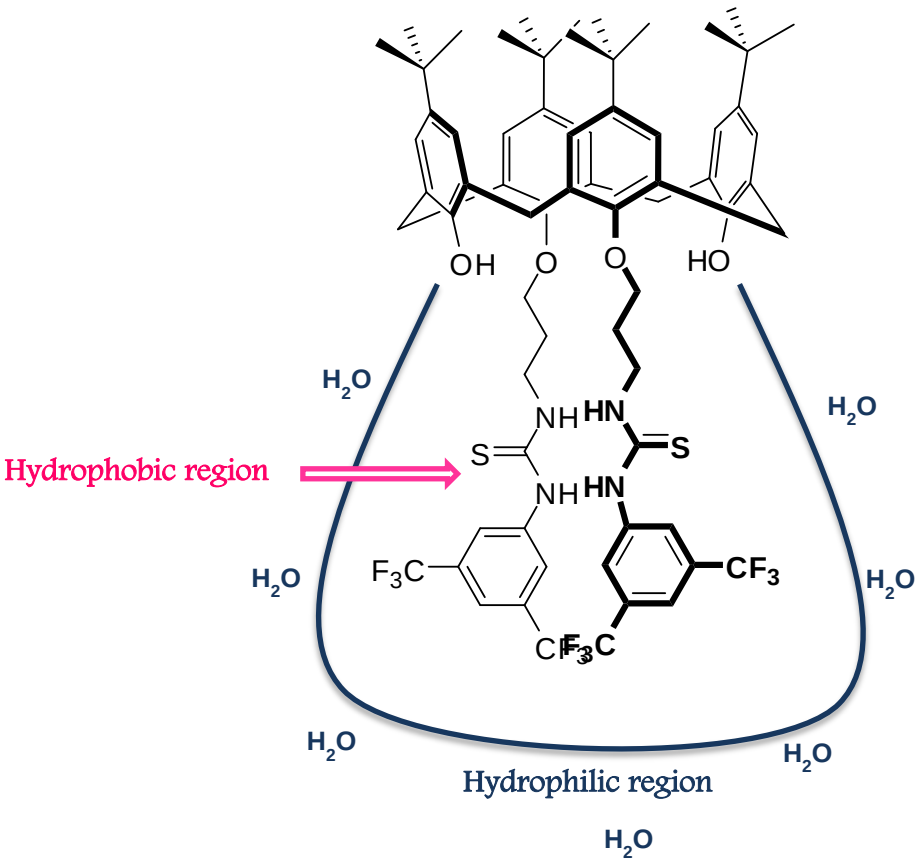


Figure 13. Illustration of hydrophobic reagion reaction takes place

CHAPTER 3

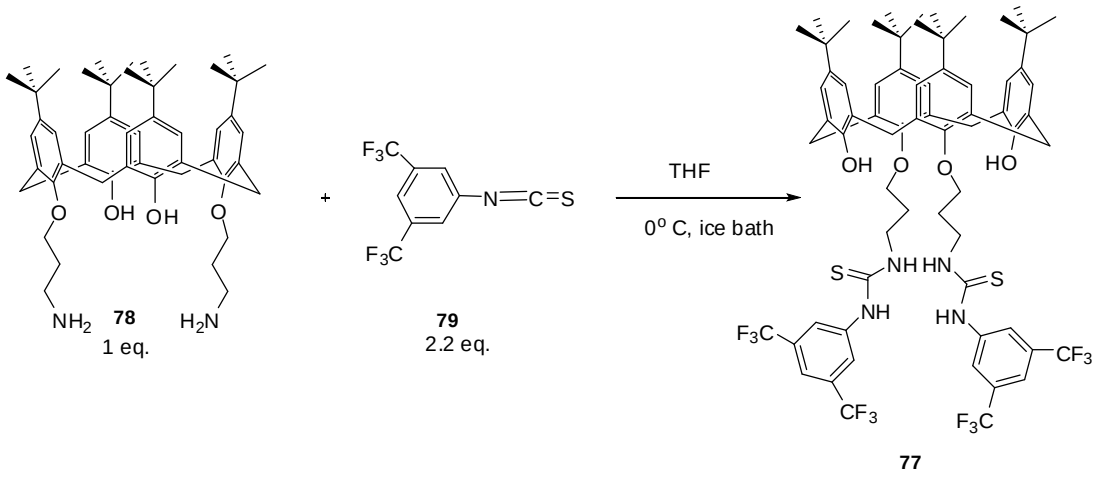
EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 400. ^{1}H NMR spectra are reported in ppm using solvent as an internal standard ($CHCl_3$ at 7.26 ppm). Data are reported as (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm).Column chromatography was conducted on silica gel 60 (mesh size 40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck). HRMS were recorded on Agilent 6224 TOF LC/MS, UNAM, Bilkent University.

3.1 Synthesis of Calix[4]arene Based Thiourea Catalysis

3.1.1 General Procedure for *p*-tertButyl calix[4]arene thiourea guest molecule

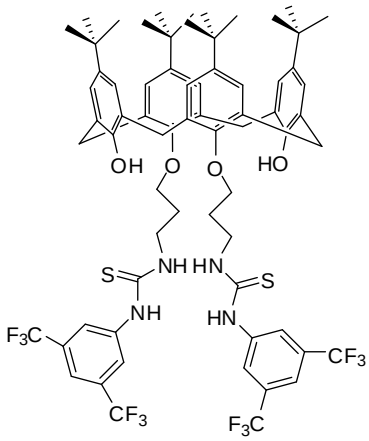
p-t-Butylcalix[4]arene diamine (1.0 mmol, 0.762 mg) was dissolved in 30 ml dried THF. Then, 3,5 –*bis* (trifluoromethyl) phenyl isothiocyanate (2.2 mmol, 400 μL) was added via syringe in ice bath and the mixture was stirred at room temperature until the completion of the reaction. The completion of reaction was monitored by TLC (Thin Layer Chromatography). After completion of reaction, volatile material was removed and remaining solid dissolved in a minimum amount of EtOAc. By using column chromatography the desired product was taken with 4:1 (Hexane:EtOAc) solvent system. Finally *n*-hexane was added for precipitation. The solid product was filtered and washed with hexane several times. Then crystallization procedure was applied to the filtered product. The reaction scheme can be seen in the following scheme.



Scheme 21: Calix[4]arene derived thiourea synthesis.

3.1.2. Characterization of Calix[4]arene Based Thiourea

The characterization of calix[4]arene based thiourea catalyst was done by ^{1}H NMR Spectra, ^{13}C NMR Spectra and High Resolution Mass Spectra.



^{1}H NMR (400 MHz, *$CDCl_3$* δ ppm): 9.17-9.07 (m, 2H), 7.87-7.85 (m, 4H), 7.81-7.74 (m, 2H), 7.61-7.57 (m, 2H), 7.57-7.53 (m, 2H), 7.18-7.16 (m, 4H), 6.86-6.81 (m, 4H), 4.10-3.97 (m, 12H), 3.51-3.39 (m, 4H), 2.24-2.03 (m, 4H), 1.35-1.27 (m, 18H), 0.99-0.93 (m, 18H)

^{13}C NMR (101 MHz, *$CDCl_3$* δ ppm): 181.6, 148.6, 148.5, 148.0, 144.7, 140.4, 132.0, 131.7, 126.18 126.2, 124.4, 122.7, 117.9, 44.7, 34.1, 31.9, 30.9, 28.3.

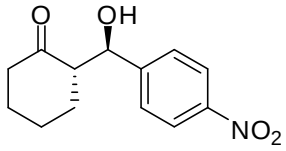
HRMS: Calculated mass: 1304.2003 g/mole

Measured $[M-H]^{+}$: 1305.5212 g/mole

3.2 General Procedure for the Enantioselective Direct Aldol Reaction

L-proline (0.025 mmol, 2.8 mg), calix[4]arene thiourea (0.0125 mmol, 16.25 mg) and 1.8 mL hexane were placed in a screw capped vial, then cyclohexanone (2 mmol, 0.2 mL) was added, in which the resulting mixture was stirred for 15 min. at ambient temperature followed by addition of aldehyde (0.25 mmol) wherein stirring was continued until no further conversion was observed by TLC. After completion of the reaction, the reaction mixture was treated with saturated aqueous ammonium chloride solution and the whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a crude residue, which was purified with column chromatography over silica gel using hexane-ethyl acetate as an eluent to afford pure product. Diastereoselectivity and conversion were determined by ^{1}H NMR analysis of the crude aldol product. The enantiomeric excess of product was determined by chiral-phase HPLC analysis all of which are in accordance with the data given in the literature. The absolute configuration of aldol products were determined by comparing the values with those previously reported in the literature.

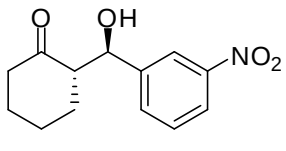
3.2.1 (S)-2-((R)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one[51]



anti-**70**

Yield: 95%. **Conversion:** 98% **Anti/syn:** 97/3, *anti*-diastereomer, **^{1}H NMR (400 MHz, $CDCl_3$ δ ppm)**: 1.46-1.31 (m, 1H), 1.71-1.52 (m, 3H), 1.93-1.77 (m, 1H), 2.16-2.07 (m, 1H), 2.42-2.31 (m, 1H), 2.54-2.45 (m, 1H), 2.66-2.55 (m, 1H), 4.09 (s, 1H), 4.90 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H). 98.8 %ee was obtained. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min, anti: t_{minor} = 24.6 min and t_{major} = 32.3 min

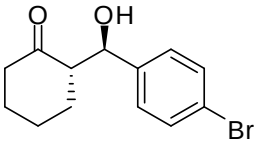
3.2.2. (S)-2-((R)-Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one [51]



anti-**80**

Yield: 90%. **Conversion:** 96%. **Anti/syn:** 96/4, *anti*-diastereomer, **^{1}H NMR (400 MHz, $CDCl_3$ δ ppm):** 1.47-1.32 (m, 1H) 1.76-1.51 (m, 4H), 1.91-1.78 (m, 1H), 2.17-2.07 (m, 1H), 2.44-2.31 (m, 1H), 2.56-2.46 (m, 1H), 2.72-2.58 (m, 1H), 4.13 (d, *J* = 3.0 Hz, 1H), 4.91 (d, *J* = 8.5 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.22 (s, 1H), 99% ee was obtained. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min, anti: t_{major} = 19.9 min and t_{minor} = 25.2 min

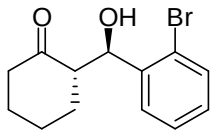
3.2.3. (S)-2-((R)-Hydroxy(4-bromophenyl)methyl)cyclohexan-1-one[52]



anti-**81**

Yield:60% **Conversion:** 65%. **Anti/syn:**94/6, *anti*-diastereomer**. ^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm):** 1.37-1.21 (m, 1H), 1.62-1.54 (m, 3H), 1.86-1.75 (m, 1H), 2.15-2.04 (m, 1H), 2.34 (d, *J* = 7.2 Hz, 1H), 2.64-2.43 (m, 2H), 3.98 (d, *J* = 2.72 Hz, 1H), 4.75 (d, *J* = 8.7 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H) 99% ee was obtained. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0mL/min, anti: t_{major} = 14.4 min and t_{minor} = 16.7 min.

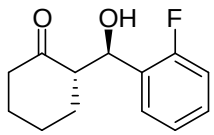
3.2.4. (S)-2-((R)-Hydroxy(2-bromophenyl)methyl)cyclohexan-1-one[52]



anti-**82**

Yield: 83% **Conversion:** 87% **Anti/Syn:** 96:4 *anti*-diastereomer**. ^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm):** 2.14-2.05 (m, 1H), 2.41-2.28 (m, 1H), 2.52-2.41 (m, 1H), 2.76-2.62 (m, 1H), 4.04 (d, *J* = 4.09 Hz, 1H), 5.30 (dd, *J* = 7.96 Hz, 1H), 7.13 (t, *J* = 7.44 Hz, 1H), 7.34 (t, *J* = 7.70 Hz, 1H), 7.52 (d, *J* = 7.97 Hz, 1H). 99% ee was obtained. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 0.3 mL/min, anti: t_{major} = 37.2 min and t_{minor} = 43.5 min.

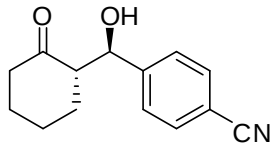
3.2.5(S)-2-((R)-Hydroxy(2-fluorophenyl)methyl)cyclohexan-1-one[52]



anti-**83**

Yield: 84%. **Conversion:** 86% **Anti/syn:** 90:10 *anti*-diastereomer**. ^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm)**: 2.42-2.30 (m, 1H), 2.53-2.44 (m, 1H), 2.75-2.60 (m, 1H), 3.99 (d, *J* = 3.4 Hz, 1H), 5.18 (d, *J* = 8.7 Hz, 1H), 7.06-6.97 (m, 1H), 7.21-7.13 (m, 1H), 7.30-7.23 (m, 1H), 7.53-7.43 (m, 1H). 94% ee was obtained. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 95.0:5.0]; flow rate 1.0 mL/min, anti: t_{major} = 8.9 min and t_{minor} = 12.0 min.

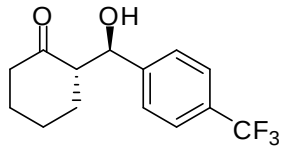
3.2.6. (S)-2-((R)-Hydroxy(4-cyanophenyl)methyl)cyclohexan-1-one[51]



anti-**84**

Yield: 63% **Conversion:** 65%. **Anti/syn:** 70/30, *anti*-diastereomer**. ^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm)**: 1.43-1.30 (m, 1H), 1.64-1.51 (m, 1H), 1.90-1.77 (m, 1H), 2.16-2.07 (m, 1H), 2.42-2.30 (m, 1H), 2.62-2.45 (m, 1H), 4.07 (d, 1H), 4.84 (d, *J* = 8.5 Hz, 1H), 7.46-7.43 (m, 2H), 7.68-7.63 (m, 1H) 87% ee was obtained. The optical purity was determined by HPLC on chiralpak AD-H column [hexane/2-propanol 90.0:10.0]; flow rate 1.0 mL/min, anti: t_{major} = 24.5 min and t_{minor} = 31.1 min.

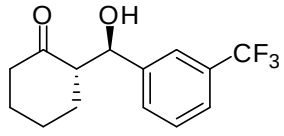
3.2.7 (S)-2-((R)-Hydroxy(4-trifluoromethylphenyl)methyl)cyclohexan-1-one[53]



anti-**85**

Yield: 78% **Conversion:** 80% **Anti/syn:** 86/14, *anti*-diastereomer. **^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm)** : 1.66-1.51 (m, 4H), 1.86-1.76 (m, 1H), 2.16-2.05 (m, 1H), 2.43-2.31 (m, 1H), 2.54-2.44 (m, 1H), 2.66-2.55 (m, 1H), 4.04 (d, *J* = 2.8 Hz, 1H), 4.85 (d, *J* = 8.6 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 95 % ee was obtained. The optical purity was determined by HPLC on chiralpak OD-H column [hexane/2-propanol 95.0: 5.0]; flow rate 0.5 mL/min, anti: t_{major} = 11.5 min and t_{minor} = 14.9 min.

3.2.8. (S)-2-((R)-Hydroxy(3-trifluoromethylphenyl)methyl)cyclohexan-1-one[53]



anti-**86**

Yield: 90% **Conversion:** 93%. **Anti/syn:** 94/6 *anti*-diastereomer**. ^{1}H NMR (400 MHz, *CDCl$_3$* δ ppm):** 1.33-1.14 (m, 2H), 1.68-1.55 (m, 2H), 1.80-1.69 (m, 1H), 2.10-1.99 (m, 1H), 2.37-2.24 (m, 1H), 2.47-2.37 (m, 1H), 2.59-2.5 (m, 1H), 4.01 (d, 1H(syn)), 4.77 (d, *J* = 8.7 Hz, 2H), 7.46-7.37 (m, 1H), 7.55-7.47 (m, 2H) The optical purity was determined by HPLC on chiralpak AS-H column [hexane/2-propanol 95.0: 5]; flow rate 0.5 mL/min, anti: t_{major} = 19.6.

CHAPTER 4

CONCLUSION

In this study, direct enantioselective aldol reaction of cyclohexanone and benzaldehyde derivatives was achieved, as α-Hydroxy ketones are important due to their participation in pharmaceuticals. The developped methodology give chance to improve the catalytic properties of proline where an achiral additive was used. Solvents with different polarities were screened and hexane was chosen as the solvent. The following aim was to decide the ratio between proline and calix[4]arene thiourea that would be used in the reaction. It was explained that proline–calix[4]arene thiourea host–guest complex was able to catalyze direct enantioselective aldol reactions in nonpolar solvent with high enantioselectivity and diostereoselectivity, the results of which were better than proline itself (up to 99 % ee and 97:3 *dr*).

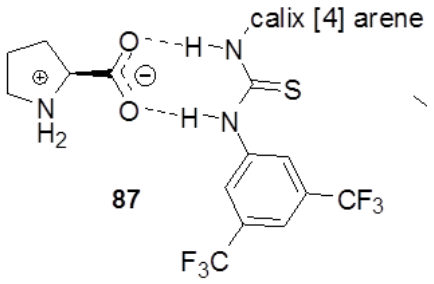


Figure 14. Representative illustration of hydrogen bonding between proline and the additive

In addition it was shown that the reaction was tolerable to water up to a certain level where hydrophobic cavity created by the calix[4]arene moiety was extended because of the thiourea molecules attached that makes the reaction proceed with high enantioselectivity.

REFERENCES

1. Solomons, G; Frhyle, C., *Organic Chemistry*, John Wiley & Sons, Inc., New York, **1999**, 174.
2. Wöhler, F.; Liebig, *J. Ann. Pharm*. **1832**, *3*, 249.
3. Lapworth, A. *J. Chem. Soc*. **1903**, *83*, 995.
4. Carruthers, W; Coldham, J., *Modern Methods of Organic Synthesis*, Cambridge University Press.,**2004**.
5. Morrison, D. J., Mosher, S. H., *Asymmetric Organic Reactions*, Prentice Hall, **1971**.
6. Solomons, G; Frhyle, C., *Organic Chemistry*, John Wiley & Sons, Inc., New York **1999**, 193.
7. Koskinen, A. *Chirality, Topology and Asymmetric Synthesis. In Asymmetric Synthesis of Natural Products*; Wiley: New York, **1993.**
8. Masters, C., *Homogeneous Transition Metal Catalysis: A Gentle Art*, Chapman and Hall, New York, **1981**.
9. Beller, M.; Bolm, C., *Transition Metals for Organic Synthesis*, Wiley-VCH; Weinheim, Germany, **2004.**
10. Jacobsen, E.N.; Pfaltz. A.; Yamamato, H., *Comprehensive Asymmetric Catalysis*, Springer-Verlag, Berlin, Heidelberg, **1999**.
11. Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A*, **1966**, 1711.
12. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.
13. Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760.
14. Grubbs, R. H., *Handbook of Metathesis*, Wiley-VCH: Weinheim, Germany, **2003**.
15. D. Enders, K.-E. Jaeger, *Asymmetric Synthesis with Chemical and Bioblogical Methods*, Wiley-VCH, **2007.**
16. A. S. Bommarius, B. R. Riebel, *Biocatalysis*,Wiley-VCH, **2004**
17. Davis, B. G.; Boyer, V., *Nat. Prod. Rep.* **2001**, *18*, 618.
18. Enders, D.; Balensiefer, T., *Acc. Chem. Res*. **2004**, *3*, 534.
19. B. List, *Chem. Rev.*, **2007**, *107*, 5413.
20. Available at: www.webofknowledge.com.
21. Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed*., **2008**, *47*, 6138.
22. List, B.; *Tetrahedron* **2002**, *58*, 5573.
23. Dalko, I. P.; *Enantioselective Organocatalysis: Reactions and Experimental Procedures*, Wİley-VCH Verlag GmbH & Co. KGaA, Weinheim, **2007.**
24. Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719.
25. Jacobsen, E. N.; Doyle, G. A.; *Chem. Rev*. **2007**, *107*, 5713.
26. MacMillan, D. W. C. Nature **2008**, *455*, 304.
27. Solomons, G; Frhyle, C., *Organic Chemistry*, John Wiley & Sons, Inc., New York **1999**, 904.
28. List, B., *Acc. Chem. Res*., **2004**, 37, 548.
29. Eder, U., Sauer, G., Wiechert, R., *Angew. Chem., Int. Ed. Engl*., **1971**, *10*, 496.
30. Hajos, Z. G.; Parrish, D. R., *J. Org. Chem*. **1974**, *39*, 1615.
31. Agami, C., Meynier, F.; Puchot, C.; Guilhem, J.; Pascard, C. *Tetrahedron*, **1984**, *40*, 1031.

32. Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B., *J. Am. Chem. Soc*. **2003**, *125*, 16.
33. List, B.; *Acc. Chem. Res*. **2004**, *37*, 548.
34. Barbas, C. F. III.; Heine, A.; Lerner, A., *Science* **1997**, *278*, 2085.
35. Berkessel, A.; Gröger, H., *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley- VCH Verlag GmbH &Co., Weinheim, Germany, **2005**, 11.
36. List, B.; Lerner, R. A.; Barbas, C. F. III., *J. Am. Chem. Soc.* , **2000**, *39*, 2395.
37. Zhou, Y., Shan, Z.; *J. Org. Chem*., **2006**, *71*, 9510.
38. a) Thayumanavan, R.; Dhevalappaly, B; Sakthivel, K.; Tanaka, F.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 3817. b) Ramachary, D.B.; Chodwari, N.S.; Barbas, C.F., III. *Tetrahedron Lett.* **2002**, *43*, 6743.
39. a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett*. **2001**, *3*, 2423. b) Betancort, J.M.; Barbas, C. F., III. *Org. Lett*. **2001**, *3*, 3737. c) Enders, D.; Seki, A. *Synlett* **2002**, *6*, 26.
40. a) List, B. *J. Am. Chem. Soc*. **2000**, 122, 9336. b)List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc*. **2002**, *124*, 827.
41. a) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 3055. b) Kano, T.; Tokuda, o.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 7423.
42. a) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc*. **2003**, *125*, 16. b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Org. Chem. Soc.* **2003**, *125*, 2475.
43. Reis, Ö.; Eymur, S.; Reis, B.; Demir, A. S. *Chem Commun*., **2009**, 1088.
44. Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734.
45. (a) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209.
46. David, G. C.; *Royal Soc. Chem.*, **1989**, 1.
47. Zinke, A.; Ziegler, E.; Ber, B74, 1944, 264.
48. Agrawal, Y. K.; Pnacholi, J. P.; Vyas, J. M.; *Journal of Scientific and Industrial Research*, **2009**, *68*, 745.
49. Xu, Z.-X. *Tetrahedron*, **2008**, *64*, 8668.
50. Xu, Z. X.; Li, G. K.; Chen, C. F.; HuangS, Z. T. *Synlett* **2009**, *14*, 2356.
51. Tian, H.; *Tetrahedron:Asymmetry*, **2011**, *22*, 1074.
52. Chimni, S. S; *Tetrahedron:Asymmetry*, **2008**, *19*, 2276.
53. J. Z.; Y.H.; H. X**.;** *Org. Biomol. Che. ;***2010,** *8***,** 1368.

APPENDIX A

NMR SPECTRA

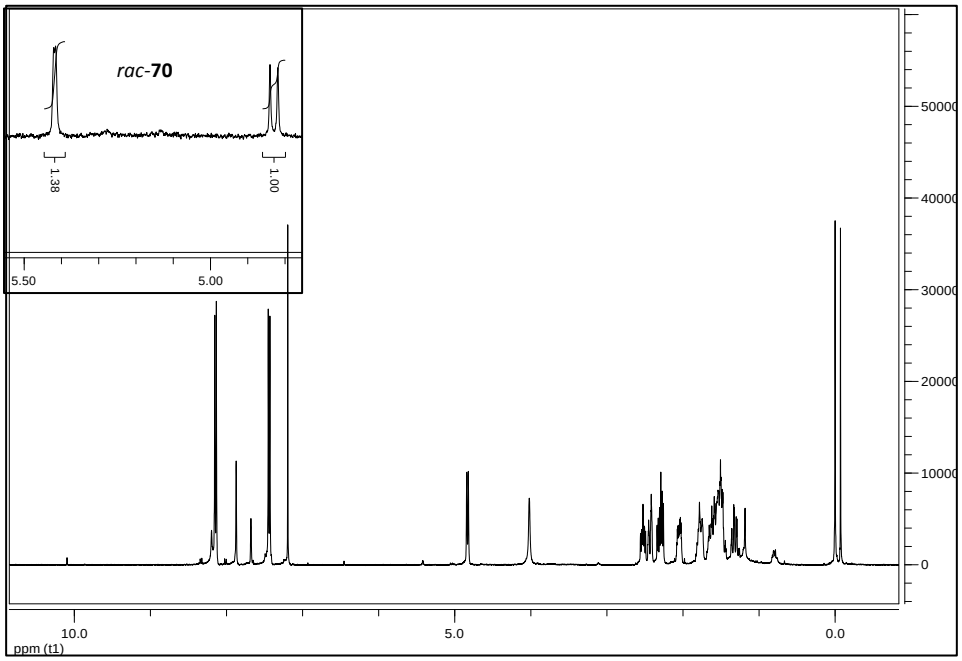


Figure 15. ^{1}H NMR Spectrum of crude product 70

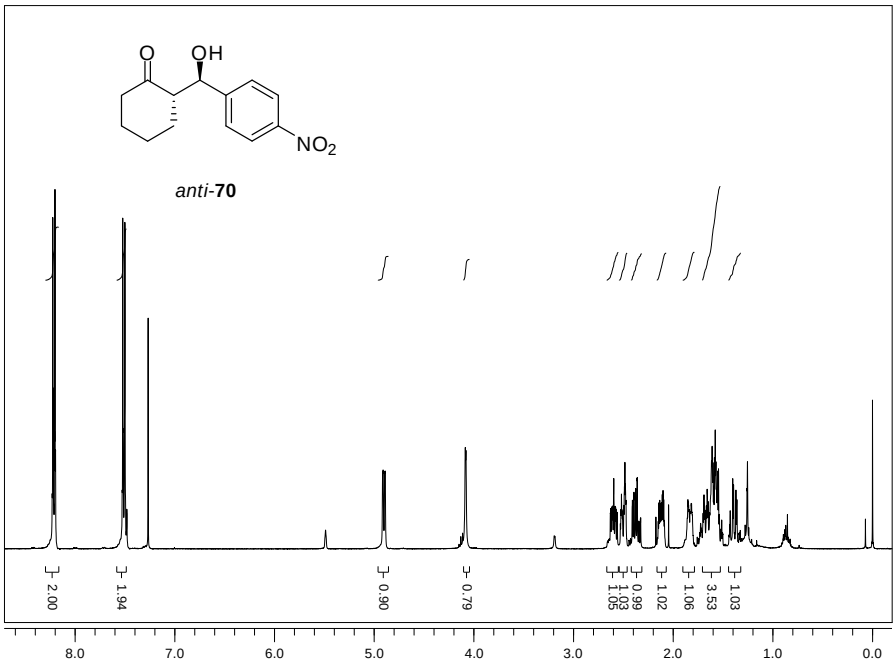


Figure 16. ^{1}H NMR Spectrum of isolated product 70

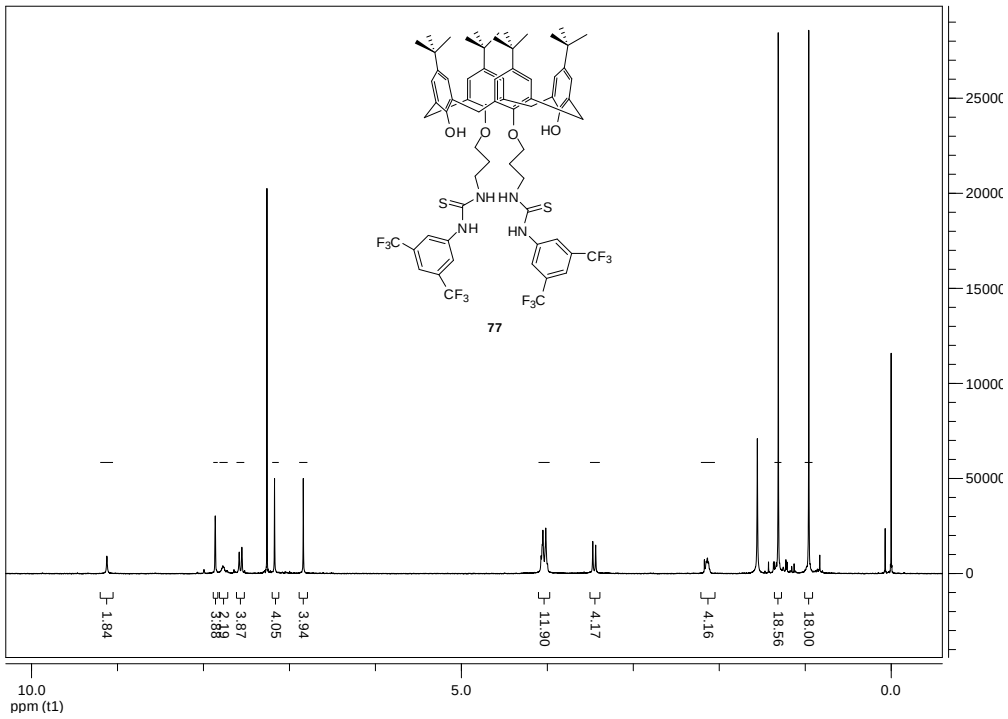


Figure 17. ^{1}H NMR Spectrum of product 77

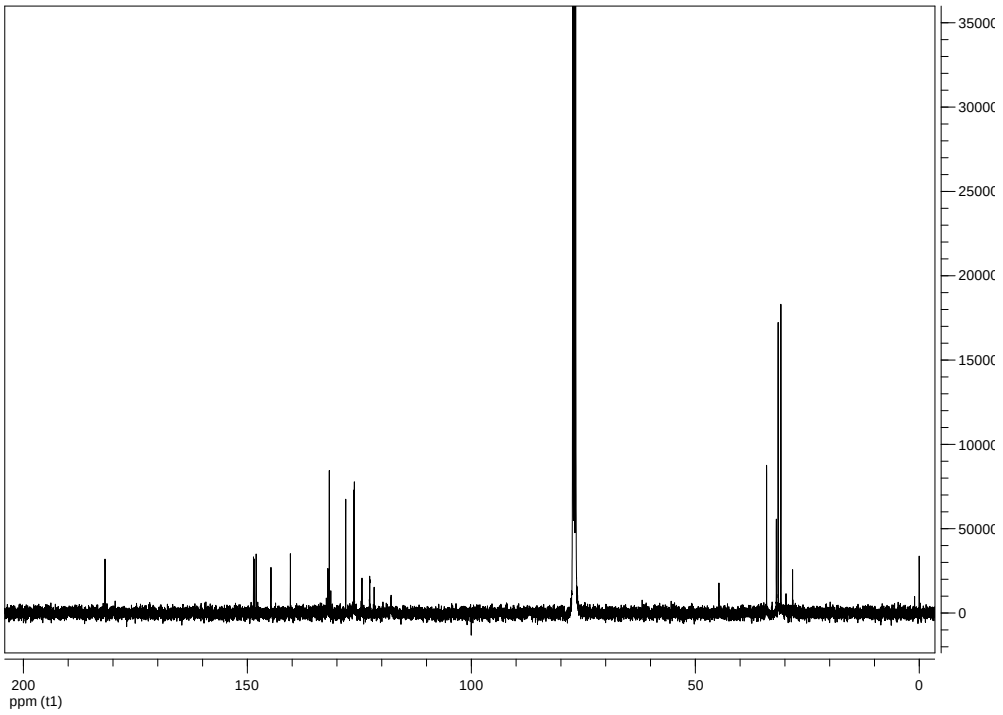


Figure 18. ^{13}C NMR Soectrum of product 77

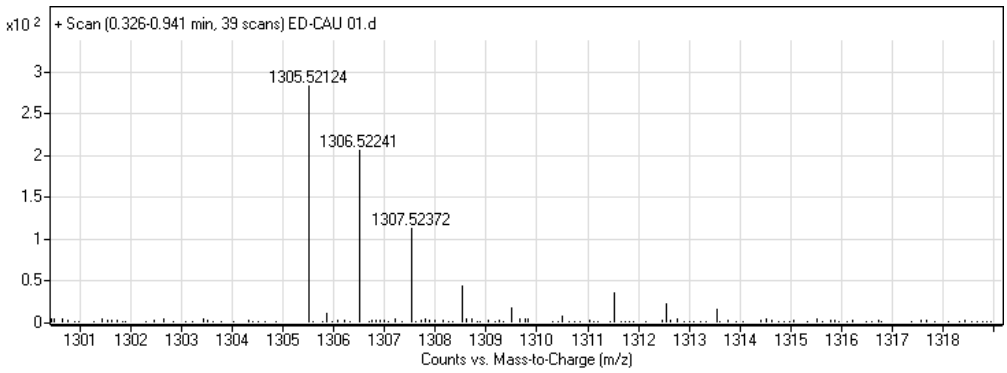


Figure 19. HRMS of product 77

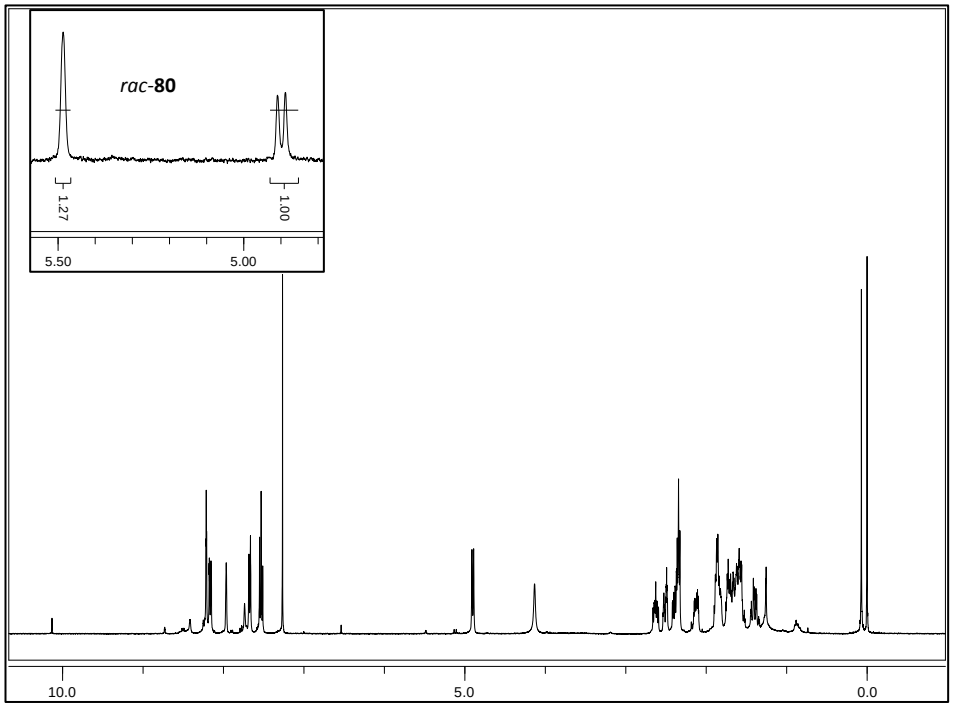


Figure 20. ^{1}H NMR Spectrum of crude product 80

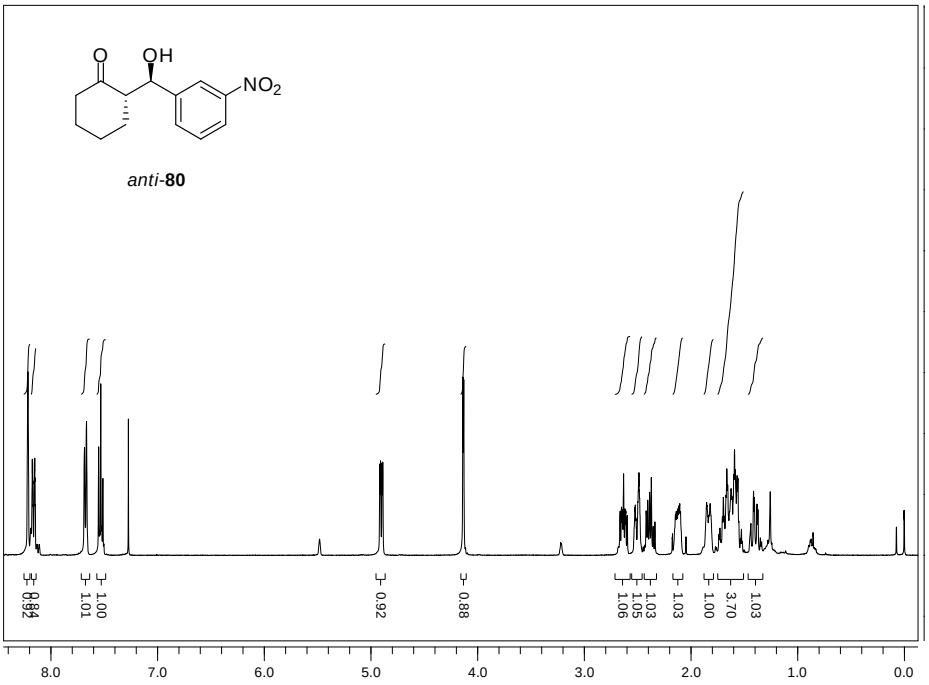


Figure 21. ^{1}H NMR Spectrum of isolated product 80

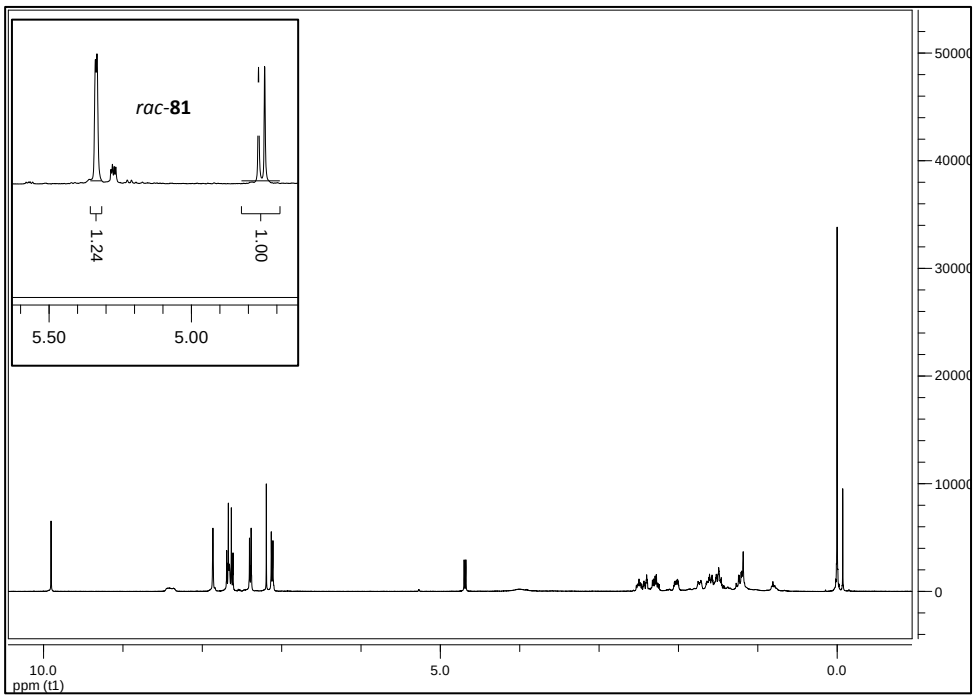


Figure 22. ^{1}H NMR Spectrum of crude product 81

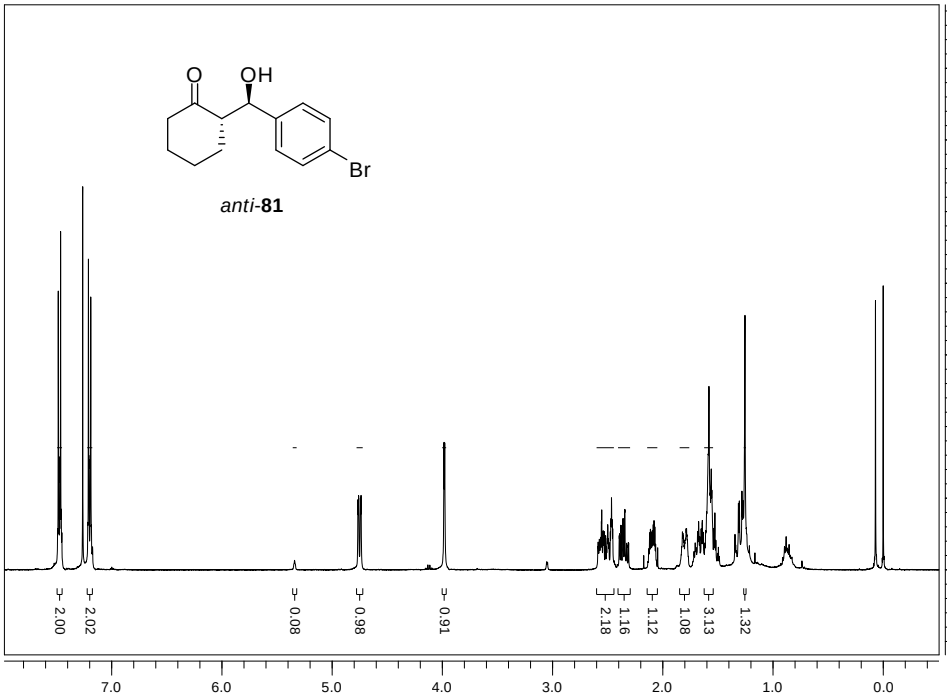


Figure 23. ^{1}H NMR Spectrum of isolated product 81

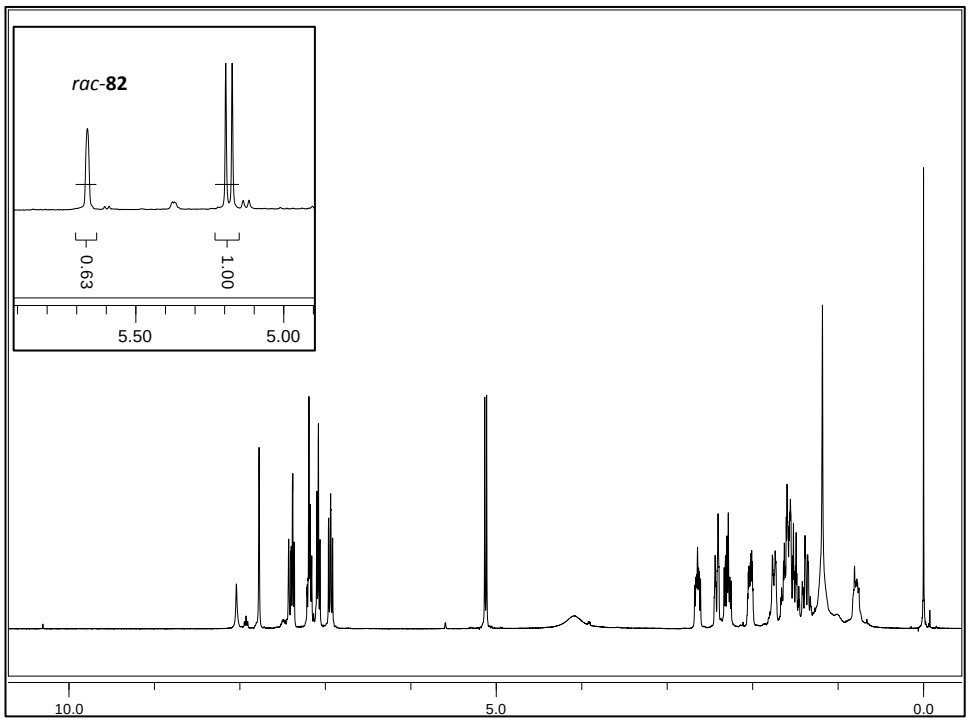


Figure 24: ^{1}H NMR Spectrum of crude product 82

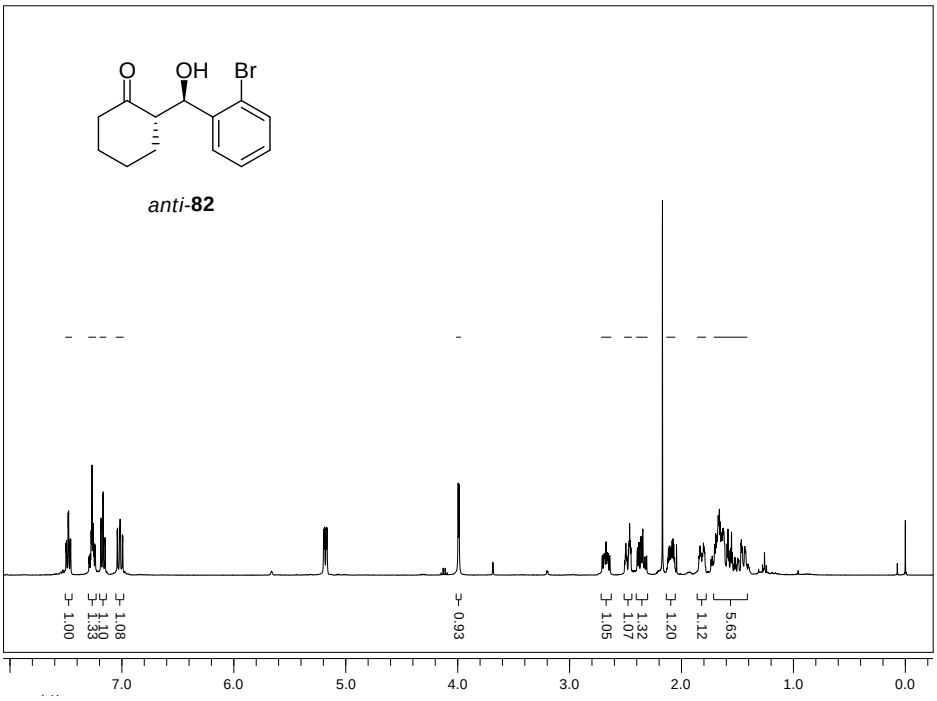


Figure 25: ^{1}H NMR Spectrum of isolated product 82

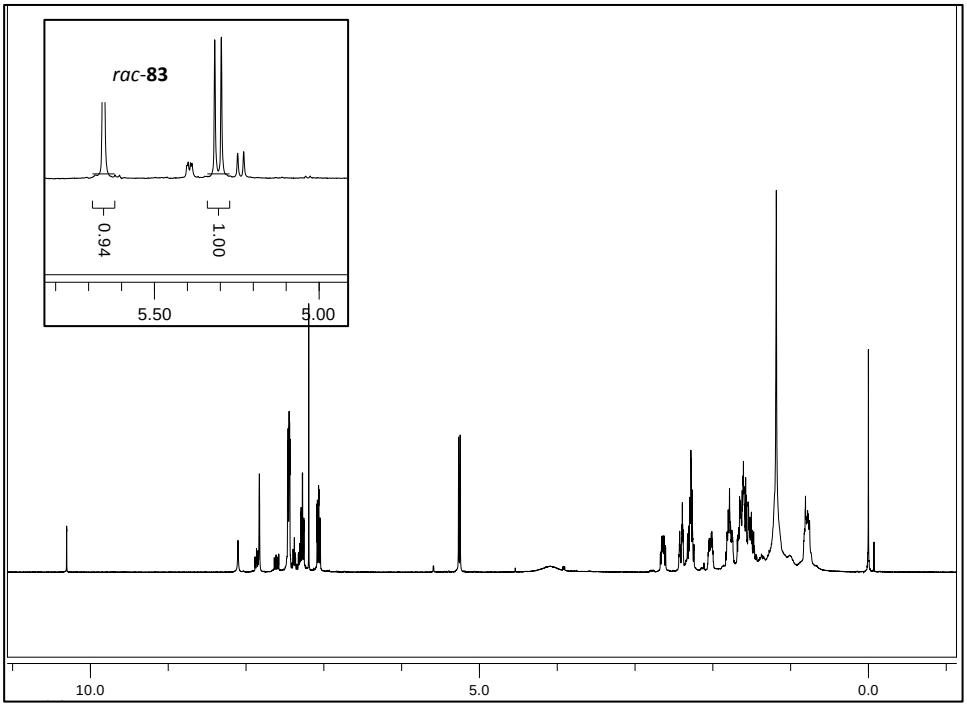


Figure 26. ^{1}H NMR Spectrum of crude product 83

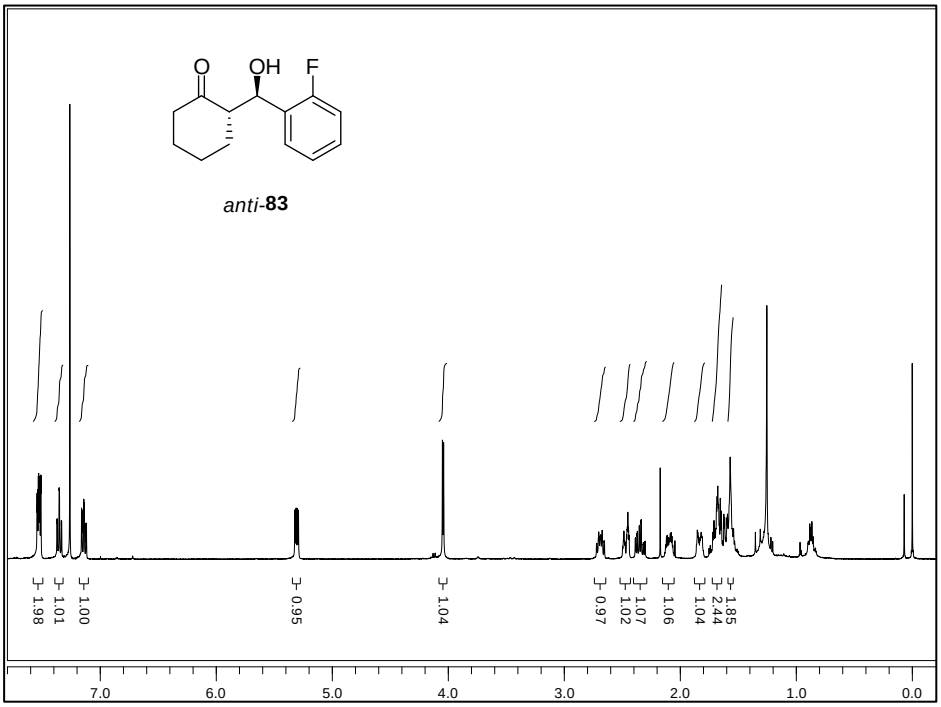


Figure 27. ^{1}H NMR Spectrum of isolated product 83

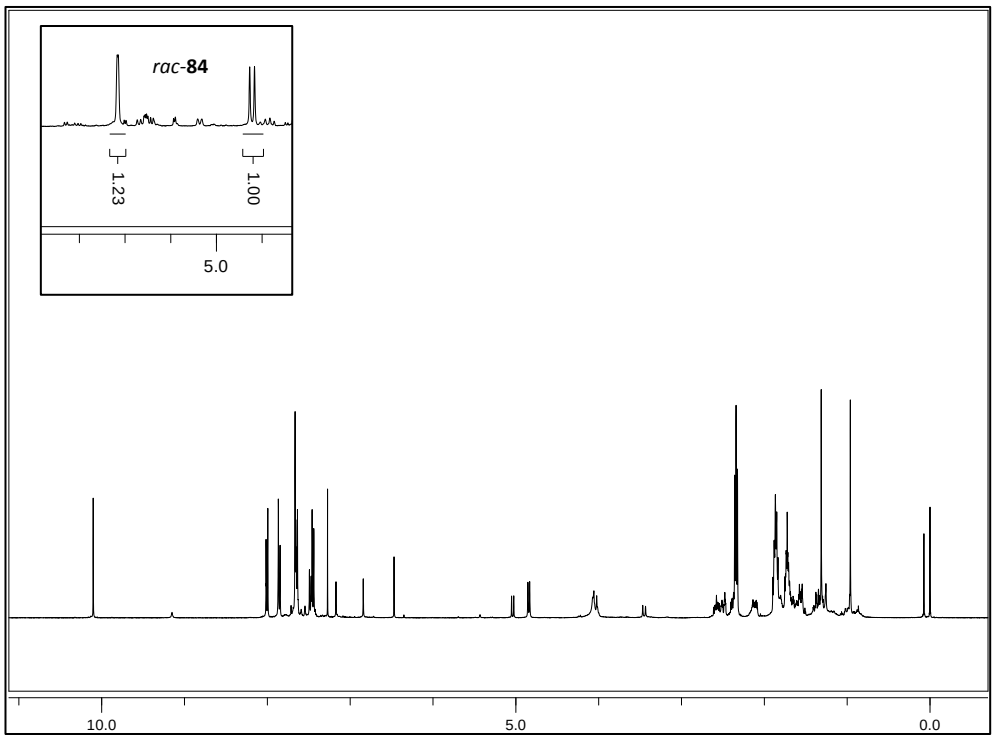


Figure 28. ^{1}H NMR Spectrum of crude product 84

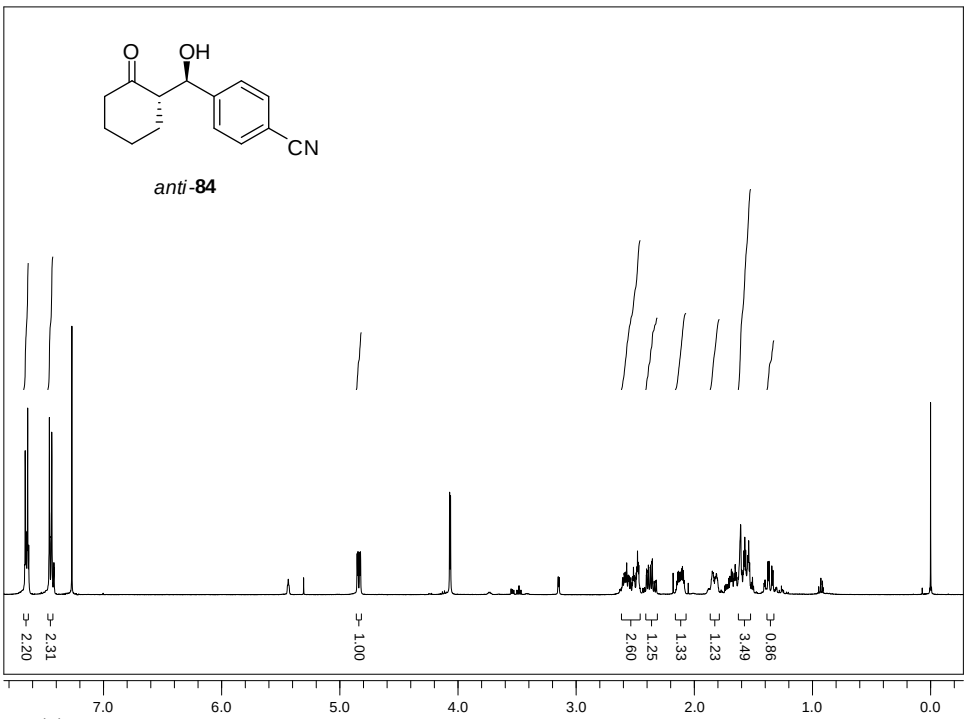


Figure 29. ^{1}H NMR Spectrum of isolated product 84

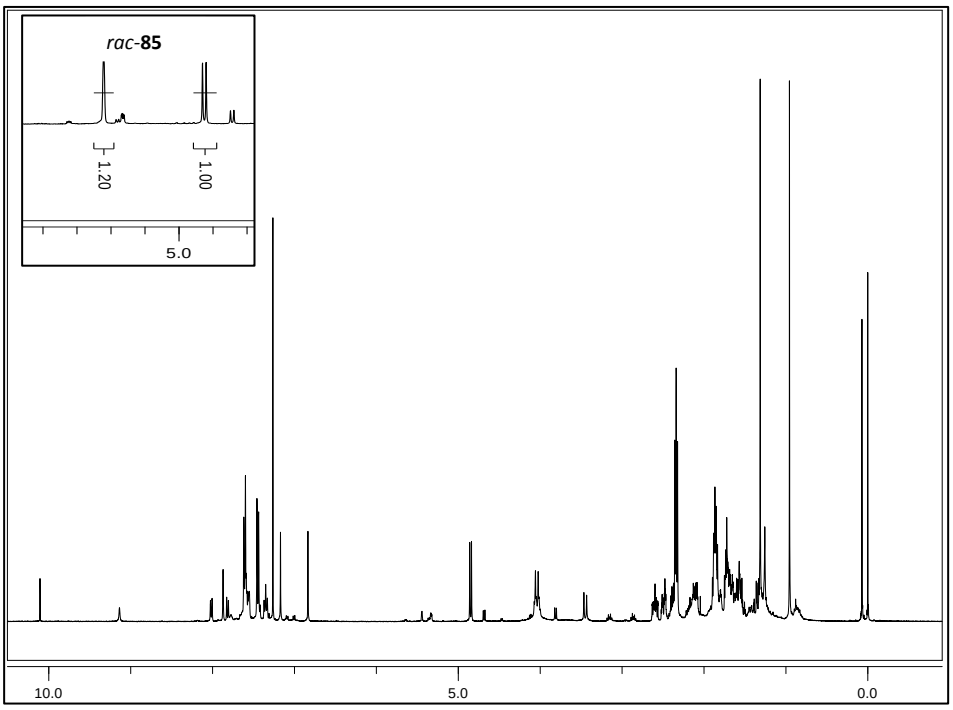


Figure 30. ^{1}H NMR Spectrum of crude product 85

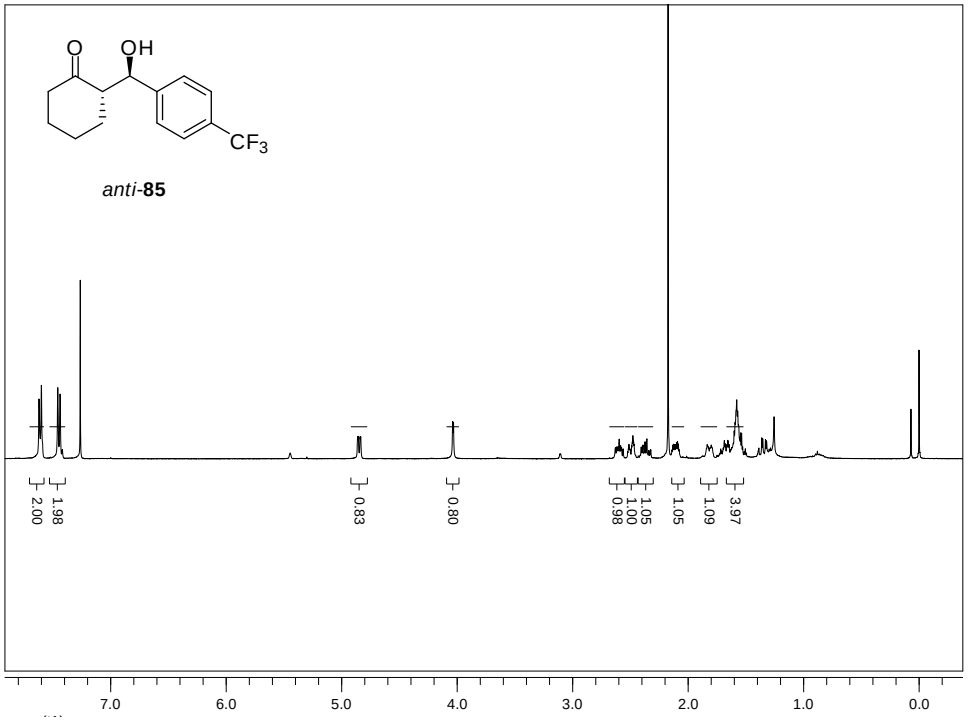


Figure 31. ^{1}H NMR Spectrum of isolated product 85

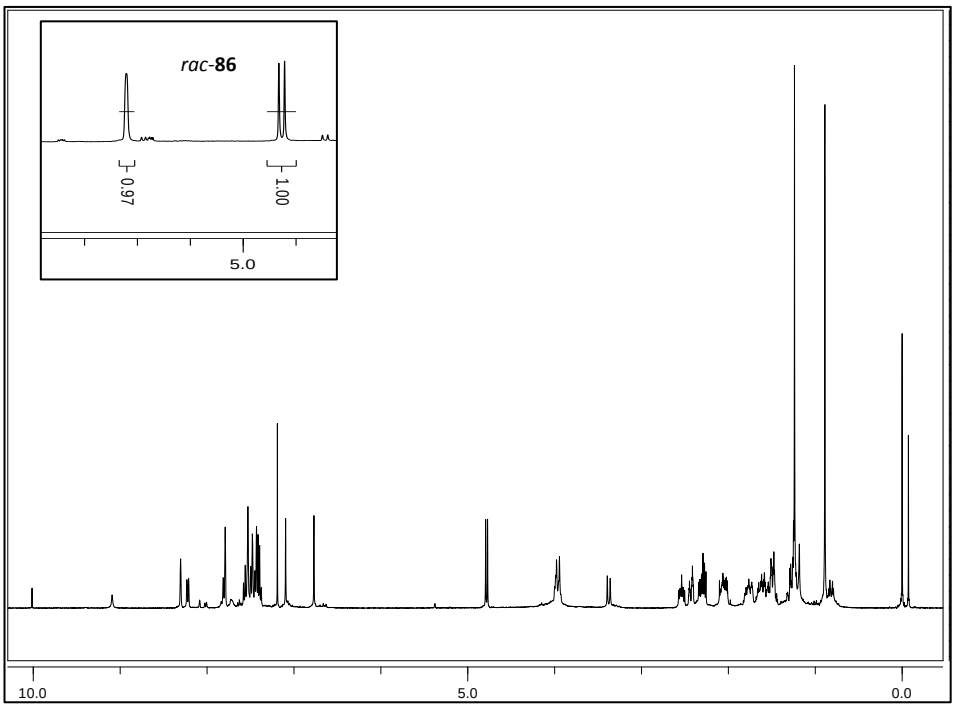


Figure 32. ^{1}H NMR Spectrum of crude product 86

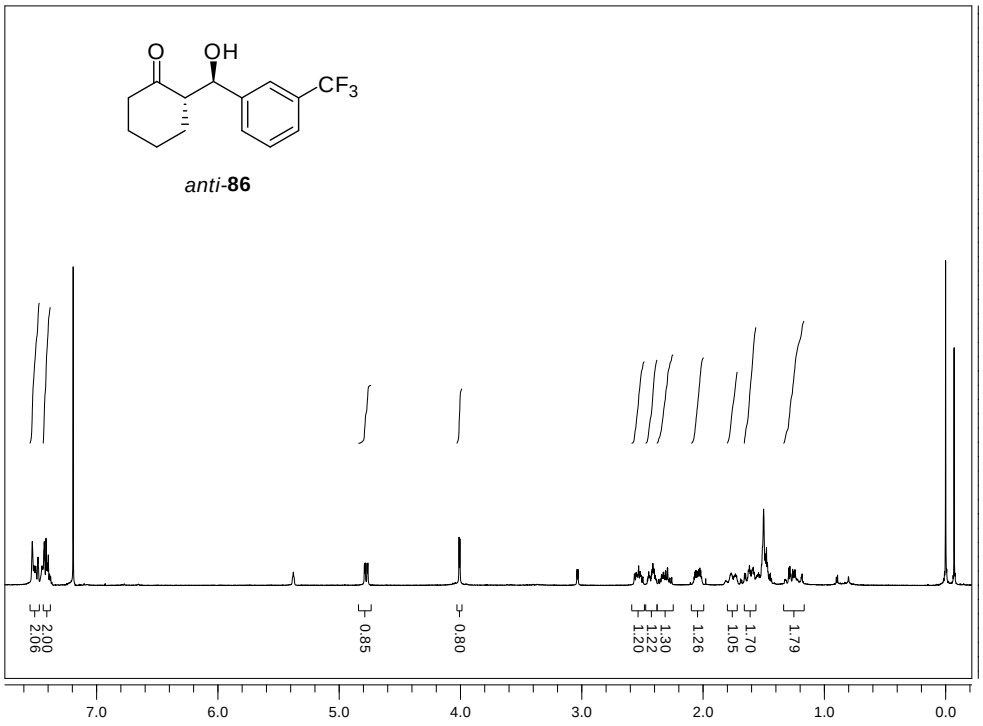
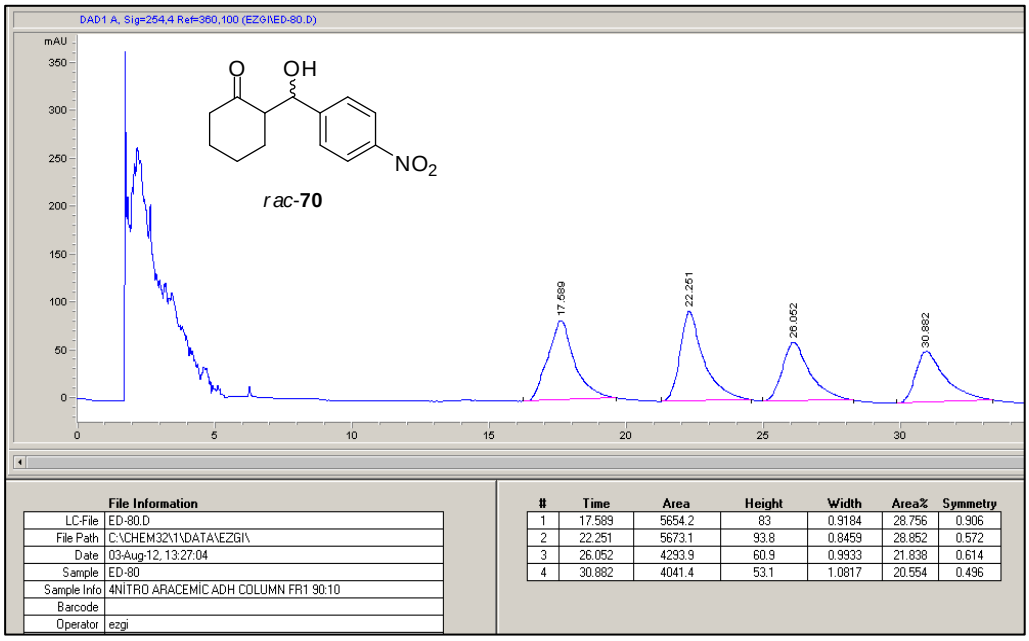


Figure 33. ^{1}H NMR Spectrum of isolated product 86

APPENDIX B

HPLC

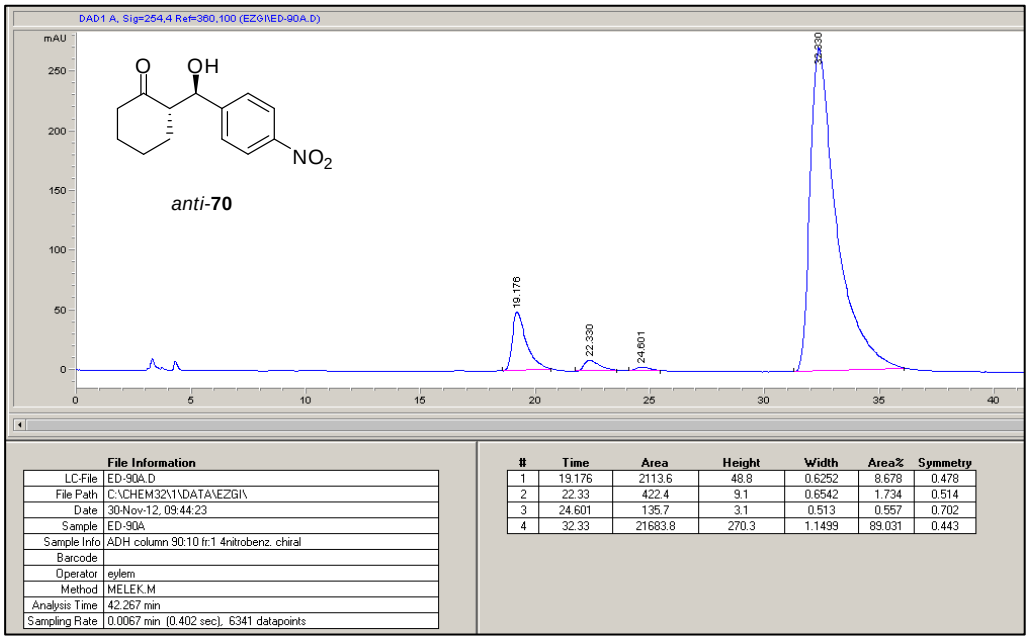


File Information

LC-File	ED-80.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	03-Aug-12, 13:27:04
Sample	ED-80
Sample Info	4NİTRO ARACEMİC ADH COLUMN FR1 90:10
Barcode	
Operator	ezgi

#	Time	Area	Height	Width	Area%	Symmetry
1	17.589	5654.2	83	0.9184	28.756	0.906
2	22.251	5673.1	93.8	0.8459	28.852	0.572
3	26.052	4293.9	60.9	0.9933	21.838	0.614
4	30.882	4041.4	53.1	1.0817	20.554	0.496

Figure 34. HPLC Chromatogram of *rac*-70



File Information

LC-File	ED-90A.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	30-Nov-12, 09:44:23
Sample	ED-90A
Sample Info	ADH column 90:10 fr:1 4nitrobenz. chiral
Barcode	
Operator	eylem
Method	MELEK.M
Analysis Time	42.267 min
Sampling Rate	0.0067 min (0.402 sec), 6341 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	19.176	2113.6	48.8	0.6252	8.678	0.478
2	22.33	422.4	9.1	0.6542	1.734	0.514
3	24.601	135.7	3.1	0.513	0.557	0.702
4	32.33	21683.8	270.3	1.1499	89.031	0.443

Figure 35. HPLC Chromatogram of *anti*-70

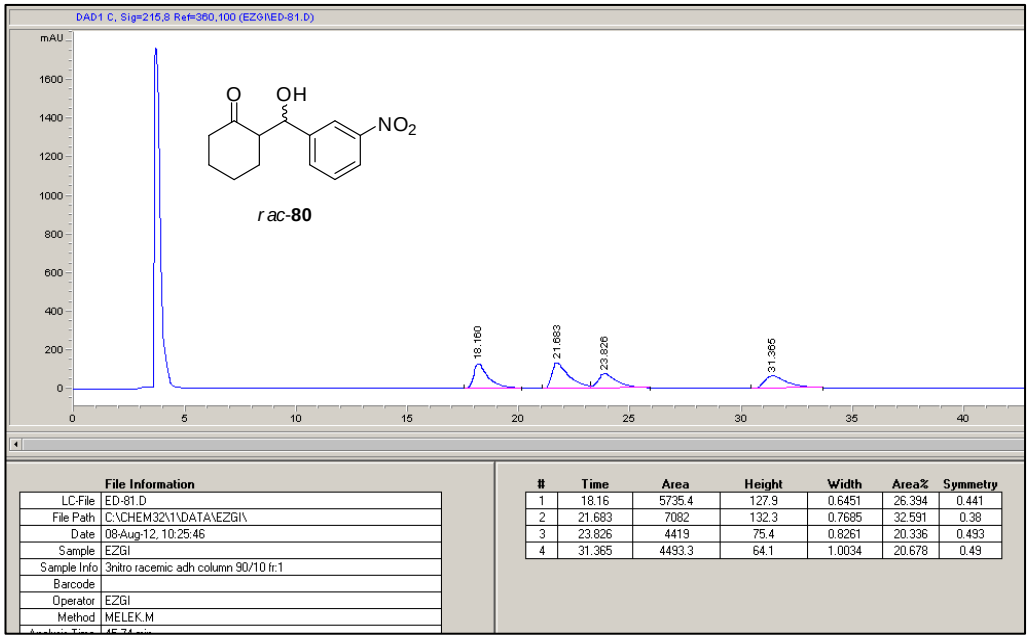


Figure 36. HPLC Chromatogram of *rac*-80

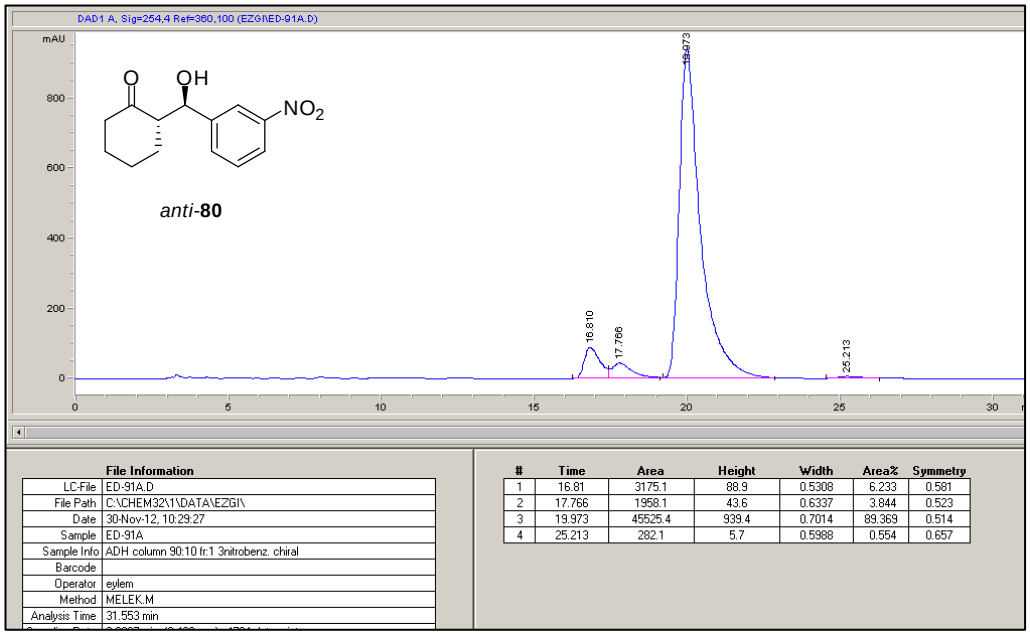
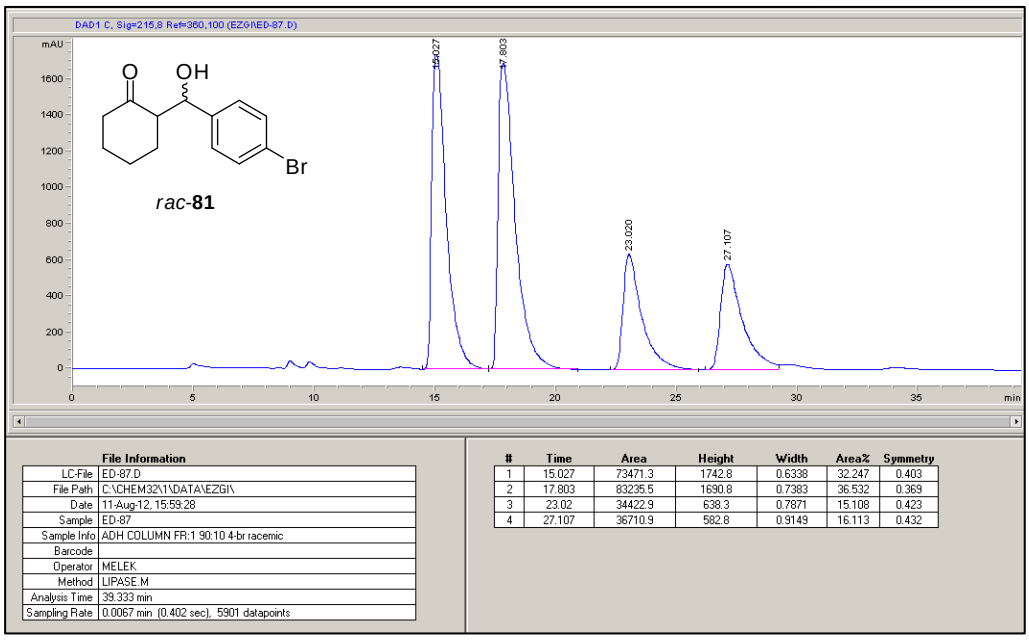


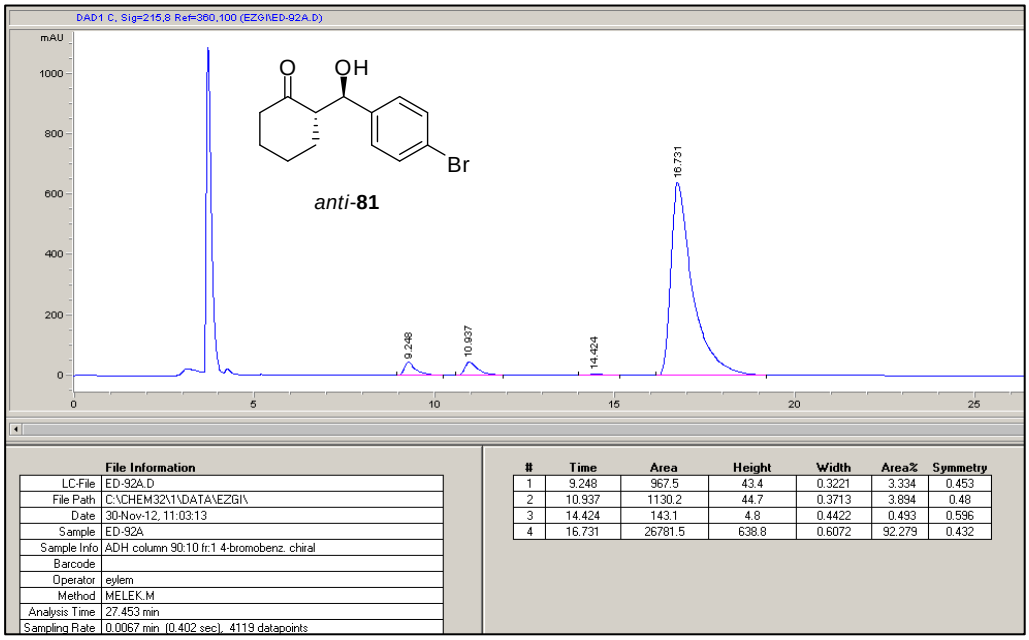
Figure 37. HPLC Chromatogram *anti*-80



File Information	
LC-File	ED-87.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	11-Aug-12, 15:59:28
Sample	ED-87
Sample Info	ADH COLUMN FR:1 90:10 4-br racemic
Barcode	
Operator	MELEK
Method	LIPASE.M
Analysis Time	39.333 min
Sampling Rate	0.0067 min (0.402 sec), 5901 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	15.027	73471.3	1742.8	0.6338	32.247	0.403
2	17.803	83235.5	1690.8	0.7383	36.532	0.369
3	23.02	34422.9	638.3	0.7871	15.108	0.423
4	27.107	36710.9	582.8	0.9149	16.113	0.432

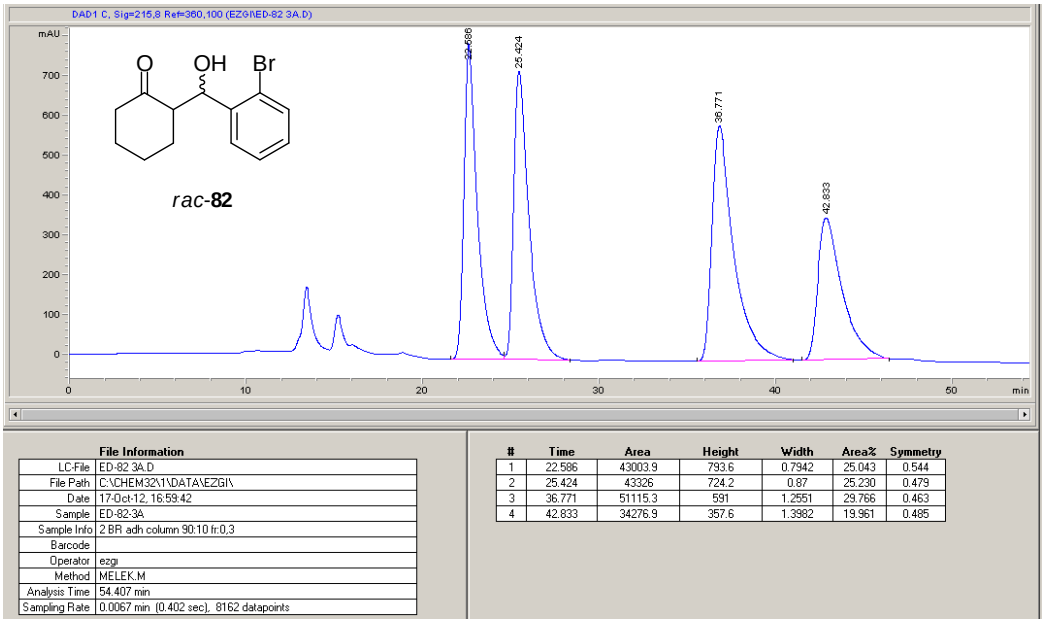
Figure 38. HPLC Chromatogram of *rac*-81



File Information	
LC-File	ED-92A.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	30-Nov-12, 11:03:13
Sample	ED-92A
Sample Info	ADH column 90:10 fr:1 4-bromobenz. chiral
Barcode	
Operator	eylem
Method	MELEK.M
Analysis Time	27.453 min
Sampling Rate	0.0067 min (0.402 sec), 4119 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	9.248	967.5	43.4	0.3221	3.334	0.453
2	10.937	1130.2	44.7	0.3713	3.894	0.48
3	14.424	143.1	4.8	0.4422	0.493	0.596
4	16.731	26781.5	638.8	0.6072	92.279	0.432

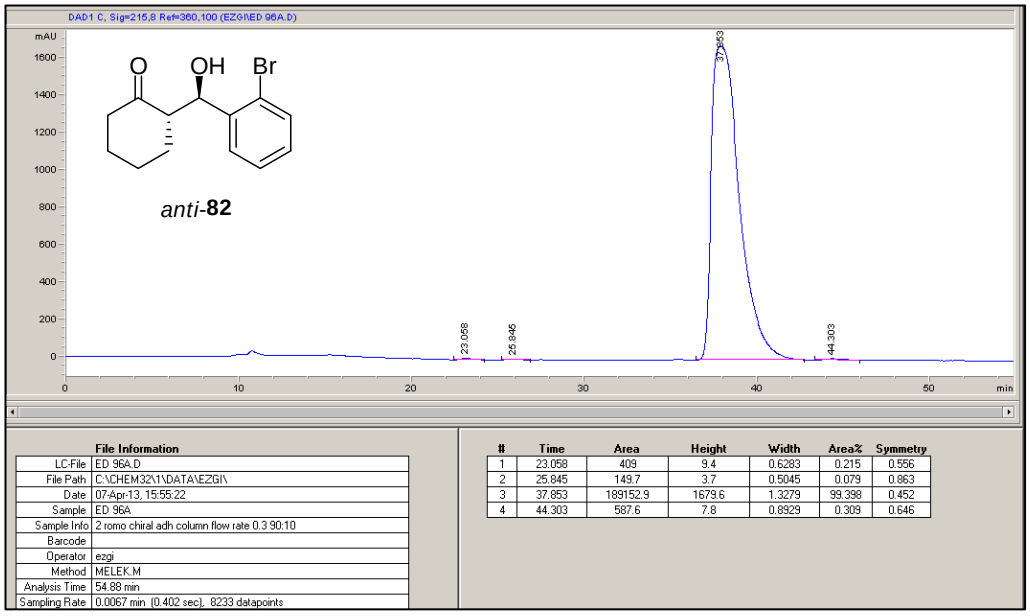
Figure 39. HPLC Chromatogram of *anti*-81



File Information	
LC-File	ED-82 3A.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	17-Oct-12, 16:59:42
Sample	ED-82-3A
Sample Info	2 BR adh column 90:10 fr:0,3
Barcode	
Operator	ezgi
Method	MELEK.M
Analysis Time	54.407 min
Sampling Rate	0.0067 min (0.402 sec), 8162 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	22.586	43003.9	793.6	0.7942	25.043	0.544
2	25.424	43326	724.2	0.87	25.230	0.479
3	36.771	51115.3	591	1.2551	29.766	0.463
4	42.833	34276.9	357.6	1.3982	19.961	0.485

Figure 40. HPLC Chromatogram of *rac*-82



File Information	
LC-File	ED 96A.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	07-Apr-13, 15:55:22
Sample	ED 96A
Sample Info	2 romo chiral adh column flow rate 0.3 90:10
Barcode	
Operator	ezgi
Method	MELEK.M
Analysis Time	54.88 min
Sampling Rate	0.0067 min (0.402 sec), 8233 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	23.058	409	9.4	0.6283	0.215	0.556
2	25.845	149.7	3.7	0.5045	0.079	0.863
3	37.853	189152.9	1679.6	1.3279	99.398	0.452
4	44.303	587.6	7.8	0.8929	0.309	0.646

Figure 41. HPLC Chromatogram of *anti*-82

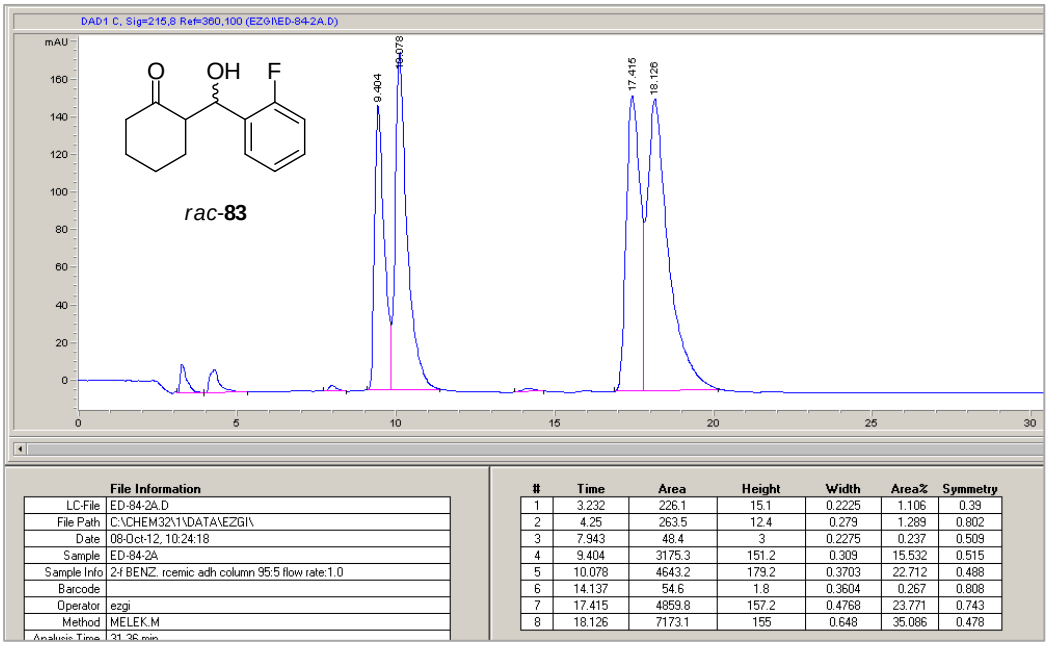


Figure 42. HPLC Chromatogram of *rac*-83

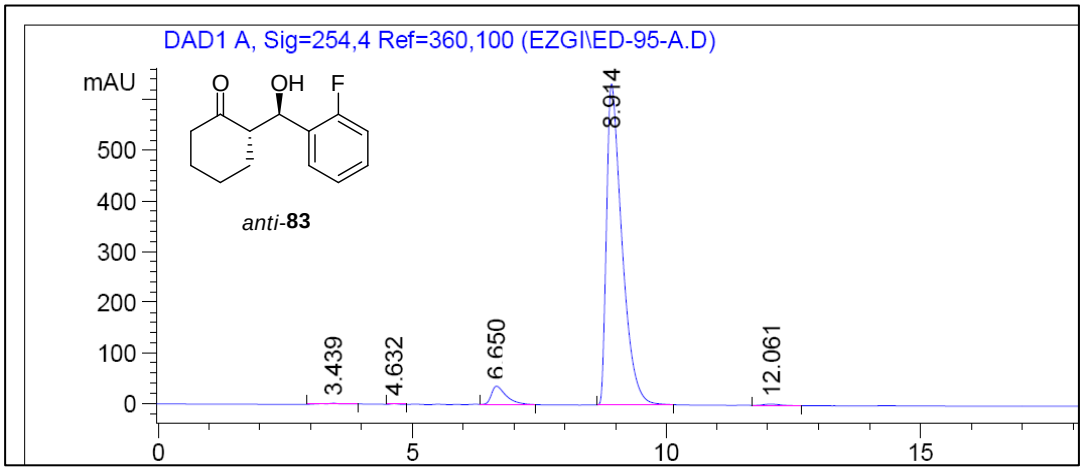


Figure 43. HPLC Chromatogram of *anti*-83

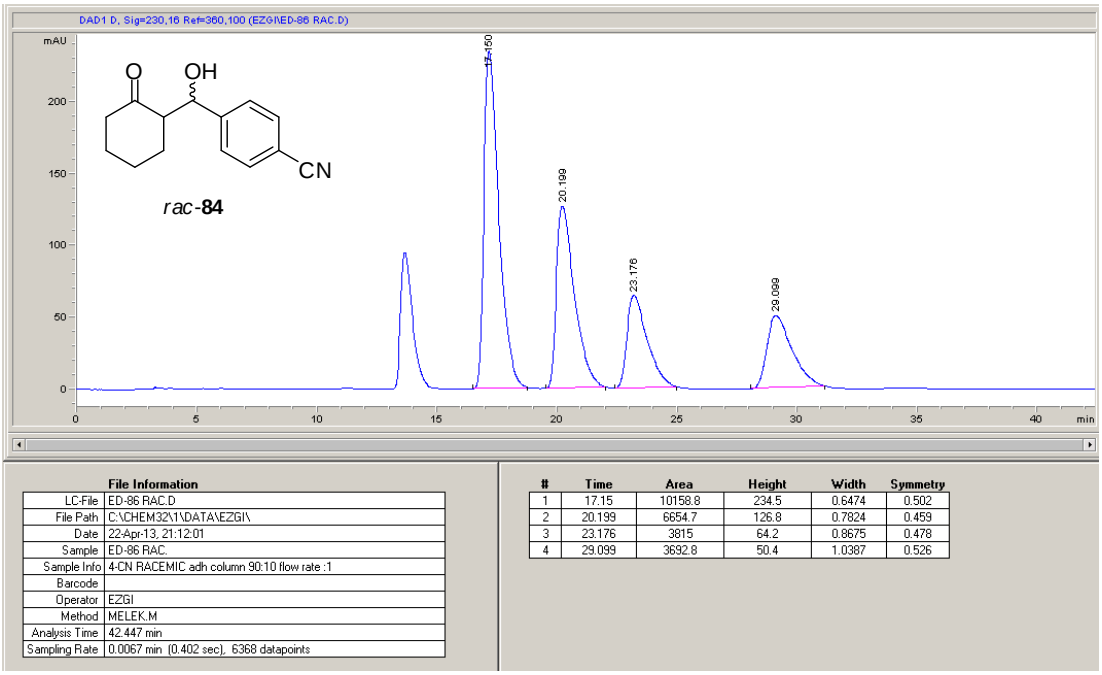


Figure 44. HPLC Chromatogram of rac-84

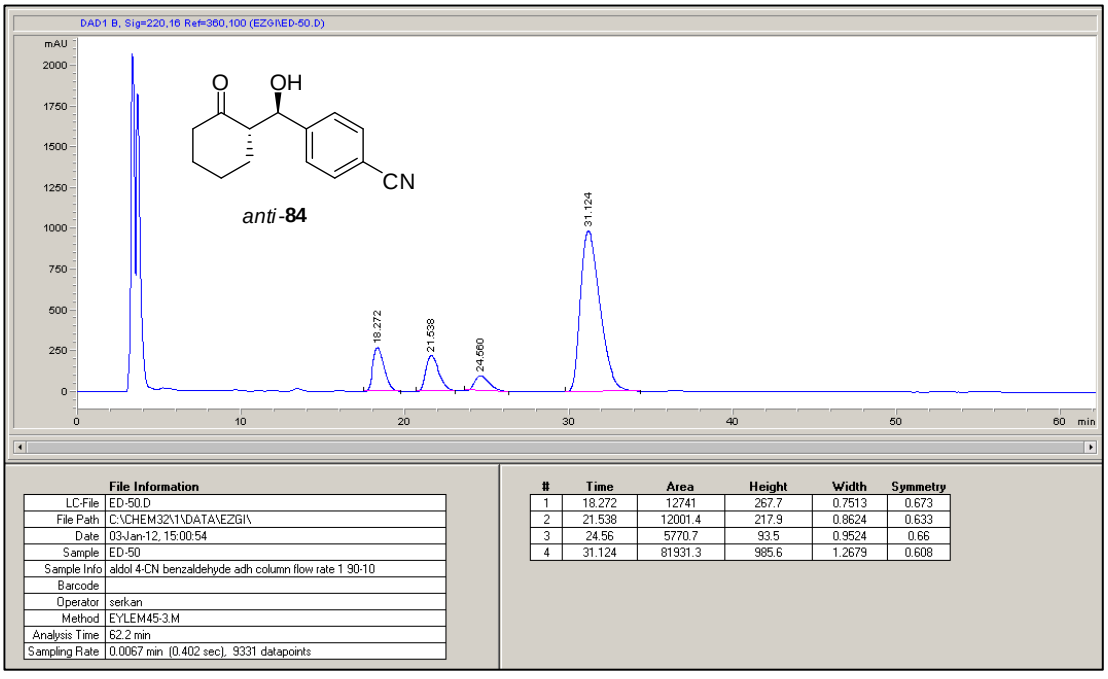
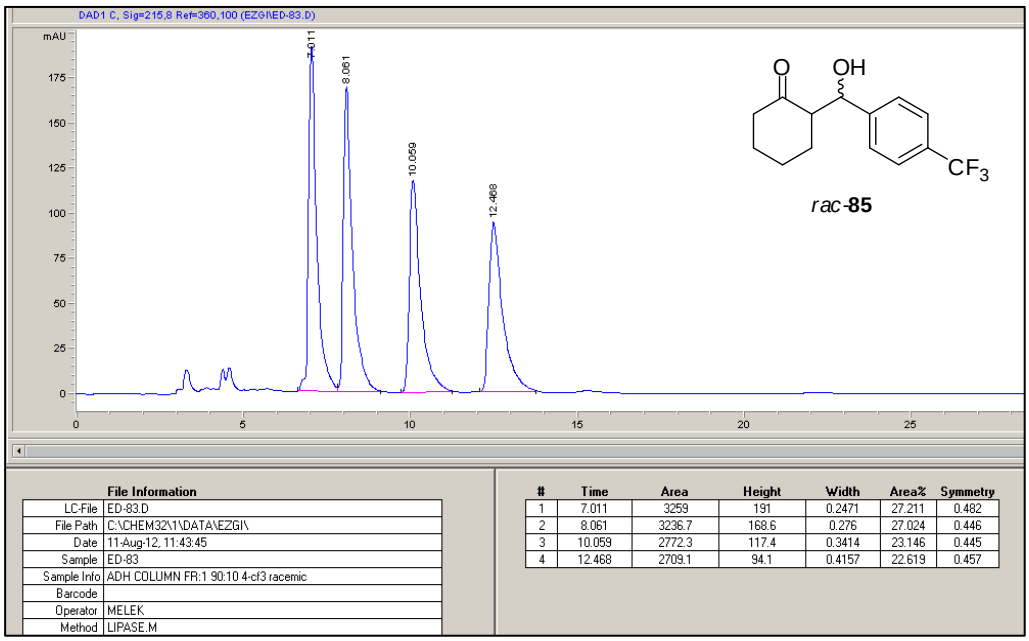


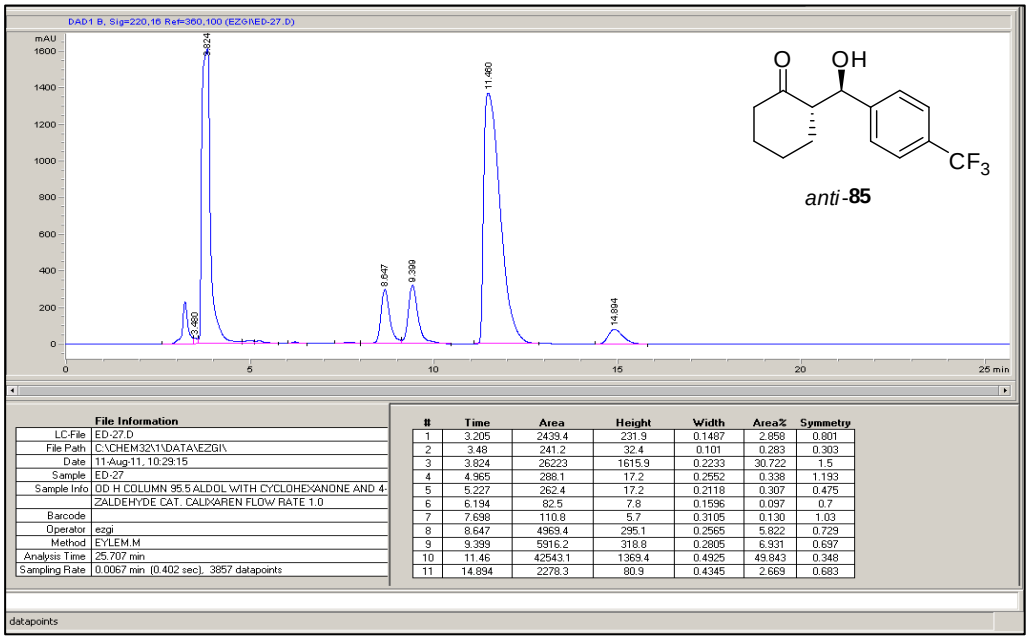
Figure 45. HPLC Chromatogram of *anti*-84



File Information	
LC-File	ED-83.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	11-Aug-12, 11:43:45
Sample	ED-83
Sample Info	ADH COLUMN FR:1 90:10 4-cf3 racemic
Barcode	
Operator	MELEK
Method	LIPASE.M

#	Time	Area	Height	Width	Area%	Symmetry
1	7.011	3259	191	0.2471	27.211	0.482
2	8.061	3236.7	168.6	0.276	27.024	0.446
3	10.059	2772.3	117.4	0.3414	23.146	0.445
4	12.468	2709.1	94.1	0.4157	22.619	0.457

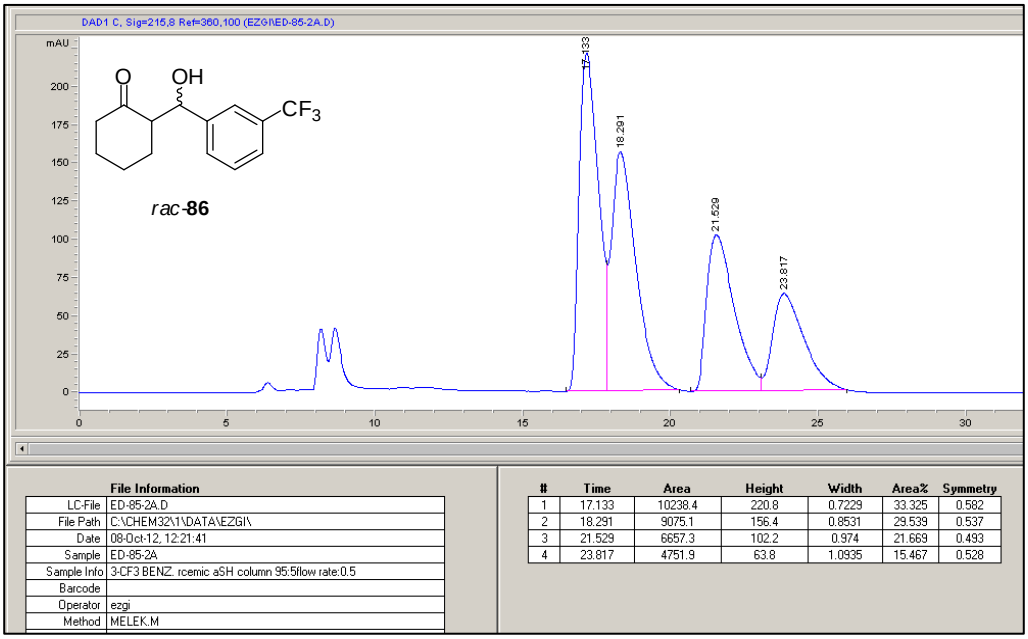
Figure 46. HPLC Chromatogram of *rac*-**85**



File Information	
LC-File	ED-27.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	11-Aug-11, 10:29:15
Sample	ED-27
Sample Info	OD H COLUMN 95:5 ALDOL WITH CYCLOHEXANONE AND 4-
	ZALDEHYDE CAT. CALIXAREN FLOW RATE 1.0
Barcode	
Operator	ezgi
Method	EYLEM.M
Analysis Time	25.707 min
Sampling Rate	0.0067 min (0.402 sec), 3857 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	3.205	2439.4	231.9	0.1487	2.858	0.801
2	3.48	241.2	32.4	0.101	0.283	0.303
3	3.824	26223	1615.9	0.2233	30.722	1.5
4	4.965	288.1	17.2	0.2552	0.338	1.193
5	5.227	262.4	17.2	0.2118	0.307	0.475
6	6.194	82.5	7.8	0.1596	0.097	0.7
7	7.698	110.8	5.7	0.3105	0.130	1.03
8	8.647	4969.4	295.1	0.2565	5.822	0.729
9	9.399	5916.2	318.8	0.2805	6.931	0.697
10	11.46	42543.1	1369.4	0.4925	49.843	0.348
11	14.894	2278.3	80.9	0.4345	2.669	0.683

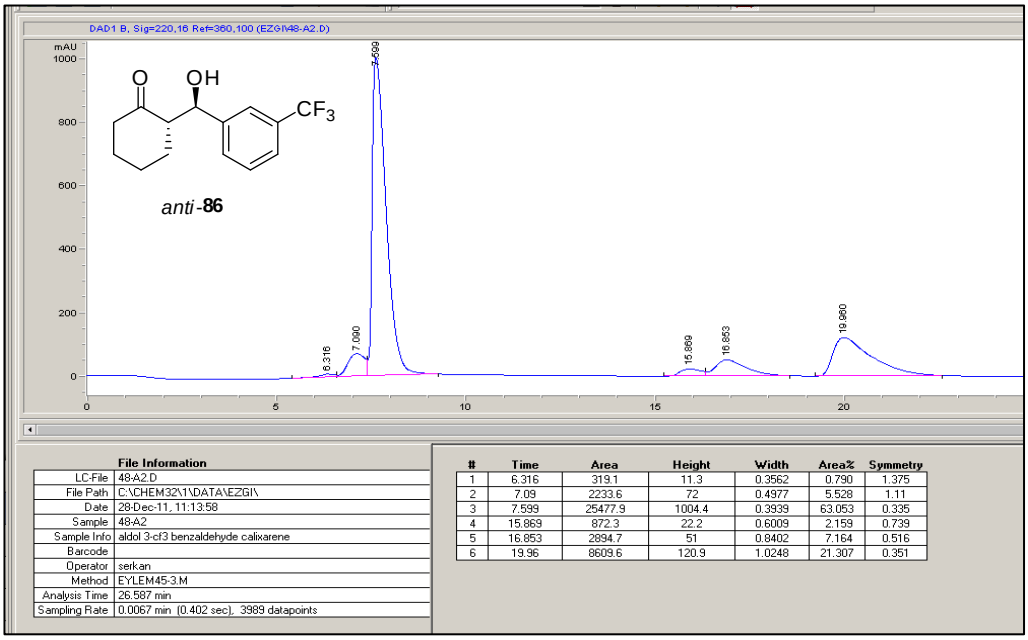
Figure 47. HPLC Chromatogram of *anti*-85



File Information	
LC-File	ED-85-2A.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	08-Oct-12, 12:21:41
Sample	ED-85-2A
Sample Info	3-CF3 BENZ. rcemic aSH column 95:5flow rate:0.5
Barcode	
Operator	ezgi
Method	MELEK.M

#	Time	Area	Height	Width	Area%	Symmetry
1	17.133	10238.4	220.8	0.7229	33.325	0.582
2	18.291	9075.1	156.4	0.8531	29.539	0.537
3	21.529	6657.3	102.2	0.974	21.669	0.493
4	23.817	4751.9	63.8	1.0935	15.467	0.528

Figure 49. HPLC Chromatogram of *rac*-86



File Information	
LC-File	48-A2.D
File Path	C:\CHEM32\1\DATA\EZGI\
Date	28-Dec-11, 11:13:58
Sample	48-A2
Sample Info	aldol 3-cf3 benzaldehyde calixarene
Barcode	
Operator	serkan
Method	EYLEM45-3.M
Analysis Time	26.587 min
Sampling Rate	0.0067 min (0.402 sec), 3989 datapoints

#	Time	Area	Height	Width	Area%	Symmetry
1	6.316	319.1	11.3	0.3562	0.790	1.375
2	7.09	2233.6	72	0.4977	5.528	1.11
3	7.599	25477.9	1004.4	0.3939	63.053	0.335
4	15.869	872.3	22.2	0.6009	2.159	0.739
5	16.853	2894.7	51	0.8402	7.164	0.516
6	19.96	8609.6	120.9	1.0248	21.307	0.351

Figure 50. HPLC Chromatogram of *anti*-86