SYNTHESIS OF NOVEL CHIRAL THIOUREA DERIVATIVES AND THEIR APPLICATIONS, SYNTHESIS OF SOME HDAC INHIBITORS, ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

GÜLÜZAR SAĞLAM

JANUARY 2008

SYNTHESIS OF NOVEL CHIRAL THIOUREA DERIVATIVES AND THEIR APPLICATIONS, SYNTHESIS OF SOME HDAC INHIBITORS, ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

GÜLÜZAR SAĞLAM

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

JANUARY 2008

Approval of the thesis;

SYNTHESIS OF NOVEL CHIRAL THIOUREA DERIVATIVES AND THEIR APPLICATIONS,
SYNTHESIS OF SOME HDAC INHIBITORS,
ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

submitted by **GÜLÜZAR SAĞLAM** in partial fulfillment of the requirements for the degree of **the master of science in Chemistry Department, Middle East Technical University** by,

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

Prof. Dr. Ahmet Önal _____
Head of Department, **Chemistry**

Prof. Dr. Ayhan S. Demir _____
Supervisor, **Chemistry Dept., METU**

Examining Committee Members

Prof. Dr. Lemi Türker _____
Chemistry Dept., METU

Prof. Dr. Ayhan S. Demir _____
Chemistry Dept., METU

Prof. Dr. Ali Usanmaz _____
Chemistry Dept., METU

Assoc.Prof.Dr.Nursen Çoruh _____
Chemistry Dept., METU

Asst. Prof. Dr. Servet Tural _____
Chemistry Education Dept., Dicle Univ.

Date: _____

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Name, Last name: Gülüzar Sağlam

Signature :

ABSTRACT

SYNTHESIS OF NOVEL CHIRAL THIOUREA DERIVATIVES AND THEIR APPLICATIONS,
SYNTHESIS OF SOME HDAC INHIBITORS,
ADDITION OF ACYL PHOSPHONATES TO ETHYLCYANOFORMATE

Sağlam, Gülüzar
M.S., Department of Chemistry
Supervisor: Prof. Dr. Ayhan S. Demir

January 2008, 68 pages

The thiourea derivatives have become a main focus of research in asymmetric synthesis as an organocatalyst in recent years. In the first part, the thiourea catalysts are synthesized starting from easily available L-tartaric acid and application of the catalysts to some addition reactions showed no significant asymmetric induction.

A number of HDAC inhibitors have been developed as anti-cancer agent at the present time.In the second part, some aryl butenoic acid derivatives are synthesized as HDAC inhibitors starting from substituted benzaldehyde and pyruvic acid. The HDAC activity studies showed comparable results with known molecules.

In the last part, some acyl phosphonates are synthesized and addition of ethylcyanoformate to acyl phosphonates furnished the products in good yields.

Keywords: Organocatalysis, Urea and Thiourea Derivatives, TADDOL, HDAC Inhibitors, Acyl Anion, Acylphosphonate, Cyanohydrin.

ÖZ

TİYOÜRE TÜREVLERİNİN SENTEZİ VE UYGULAMALARI,.
BAZI HDAC İNHİBİTÖRLERİNİN SENTEZLENMESİ,
AÇİL FOSFONATLARIN ETİLSİYANOFORMATA KATILIMI

Sağlam, Gülüzar
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Ayhan S. Demir

Ocak 2008, 68 pages

Son yıllarda tiyoüre türevleri asimetrik sentezde organokatalizör olarak ana çalışma konusu olmuştur.Çalışmanın ilk bölümünde, tiyoüre katalizörleri kolaylıkla elde edilebilen L-tartarik asitten sentezlenmiş ve kulanıldıkları bazı katılma tepkimelerinde önemli bir etki gösterememişlerdir.

Günümüzde, kansere karşı birçok HDAC inhibitörü geliştirilmiştir.Çalışmanın ikinci bölümünde, bazı aril bütenoik asit türevleri, fonksiyonlanmış benzaldehit ve pürivik asitten başlanarak HDAC inhibitörü olarak sentezlenmiştir.Yapılan aktivite testleri bilinen maddeler ile kıyaslanabilir sonuçlar göstermiştir.

Çalışmanın son bölümünde, bazı açil fosfonatlar sentezlenmiş ve bu açil fosfonatların etilsiyanoformata katılması ile yüksek verimli ürünler elde edilmiştir.

Anahtar kelimeler: Organokatalizör, Üre ve Tiyoüre Türevleri, TADDOL, HDAC İnhibitörleri, Açil Anyon, Açilfosfonat, Siyanohidrin.

To my parents,

ACKNOWLEDGEMENT

I am deeply indebted to my supervisor Prof. Dr. Ayhan S. Demir whose guidance, help, suggestions and encouragement helped me througout my study.

I would like to thank Ömer Reis for his guidance through my studies, helps on my chemistry and his friendship. I would like to thank Barbaros Reis and Mehmet Göllü for their guidance and good fellowship.

I wish also thank to Serkan Eymur for his support, patience and love not only this study but also all of my life.

I would like to thank Asuman Aybey for introducing me to chemistry world. I would like to thank all members of Demir's group and other friends from chemistry department.

I wish also thank to Tuğba Ayas and Canan Yücel for their indispensable friendship.

I would like to thank Fatoş Doğanel and M Seda Karayılan for their kind help for our routine and special NMR analysis.

.

TABLE OF CONTENTS

LIST OF FIGURES

FIGURES

CHAPTER 1

INTRODUCTION

PART I

1.1 Organocatalysts in Asymmetric Reactions

Catalytic enantioselective synthesis of organic compounds is a subject of intense research efforts. There has been a tremendous progress in the development of such strategies in the past decades. [1]

Until recently the catalysts used for enantioselective reactions in organic chemistry was mainly divided into two main categories, chiral transition metal complexes and enzymes. At the beginning of this decade, a new approach has been established which contends that small organic molecules, organocatalysts, can be highly selective and efficient catalysts [1, 2].

Organocatalysis is the acceleration of chemical reactions with a substoichiometric amount of an organic compound and no transition metals are required for this catalysis [1, 3]. Organocatalysts have a lot of advantages. First of all, they are usually powerful since they are not affected from moisture and oxygen, and moreover, necessary reaction conditions such as inert atmosphere, low temperatures, absolute solvents, etc. are, in many cases, not required. Addingly, they are cheap, readily accessible and non-toxic. Lastly, organocatalysis is a very effective method for preparation of compounds which do not tolerate metal contamination such as pharmaceutical products [1].

As a consequence, organocatalysis has gained great importance and become a main focus of research in asymmetric synthesis [2].

Most but not all organocatalysts can be abundantly categorized as either Lewis base, Lewis acid, Brønsted base, or Brønsted acid catalysts. The basic catalytic cycle is shown (Figure 1).

According to this cycles, Lewis base catalysts (B :) start the catalytic cycle with nucleophilic addition to the substrate (S). The resulting intermediate undergoes a transformation and releases product (P) and completes the catalytic cycle. Lewis acid catalysts (A) activate nucleophilic substares (S) in a similar way. Brønsted base and Brønsted acid catalysts start the cycles with the protonation or deprotonation of the substrate that activates it for further transformations [2].

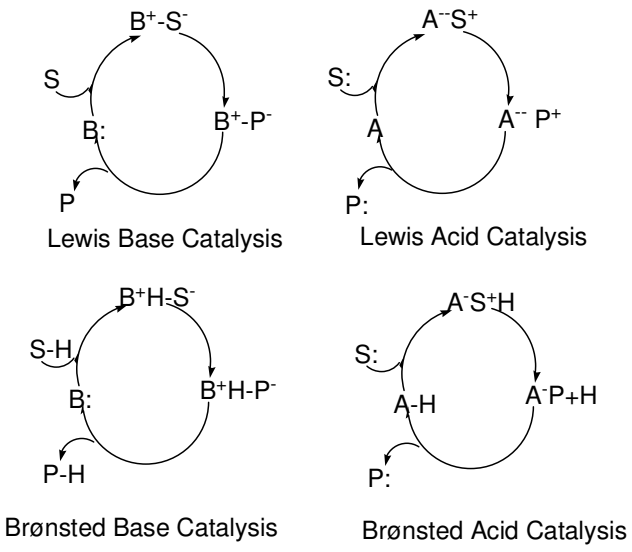
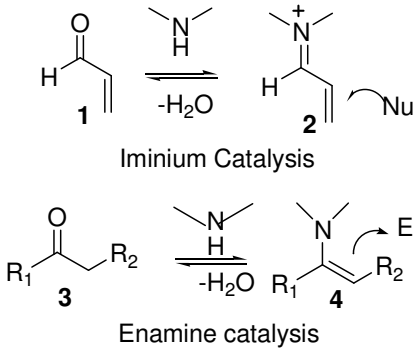


Figure 1 Organocatalytic cycles

1.1.1 Lewis Base Catalysis

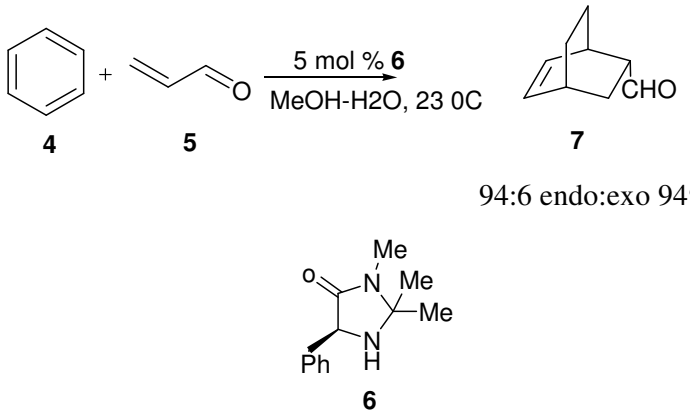
Lewis bases convert the substrates into activated nucleophiles or electrophiles and well-known reactive intermediates are iminium ions and enamines (Scheme 1) [2].



Scheme 1 Examples of Lewis base organocatalysis

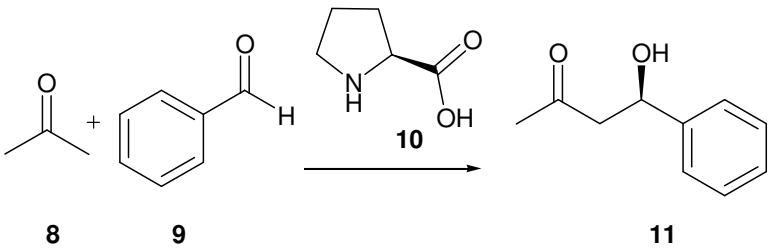
In *iminium catalysis*, the active reagent is an iminium ion, having high reactivitiy against nucleophiles, formed from a carbonyl compound and primary or secondary amines. The increased reactivity of iminium ions can be explained on the basis of decrease in the energy of LUMO orbital of conjugated double bonds upon formation of the iminium ion. This higher reactivity of iminium ion makes it possible the catalysis of various transformations such as Michael additions and cycloadditions.

The first example of enantioselective iminium catalysis was reported by Macmillan and co-workers in 2000. They introduced imidazolidinones **6** as effective iminium activation catalysis. This type of catalysis has been shown to be successful in various cycloadditions, Michael and Friedel-Craft type nucleophilic additions to α,β-unsaturated aldehydes and ketones (Scheme 2) [3].



Scheme 2 Diels-Alder reaction of α, β- unsaturated aldehydes

Enamine catalyts is observed followed by the deprotonation of an imine or iminium ion resulting in a strong nucleophilic character that can react with various electrophiles. Enamine catalysts are widely used in aldol and Mannich type reactions, Michael additions, α-heteroatom functionalizations of enolizable aldehyde and ketones. The first example of asymmetric enamine catalysis is discovered by Hajos, Parrish and Eder, Sauer and Wiechert in 1970's, an intramolecular aldol reaction catalyzed by proline [4]. Almost three decades later, List, Barbas and Lerner discovered intermolecular aldol reaction between aromatic aldehydes and acetone by using proline (Scheme 3) [5, 6].

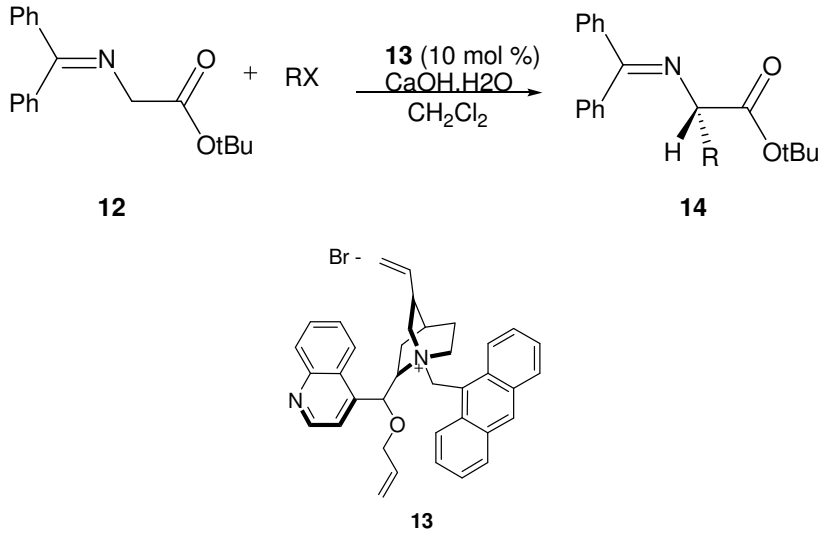


Scheme 3 Proline catalyzed aldol reaction

1.1.2. Lewis Acid Catalysis

An important class of organic catalysts that can be considered as Lewis acids are phase transfer catalysts.

Phase transfer catalysis is very successful approach because it is not only operates in mild reactions conditions and basic experimental methods but also it is inexpensive. [7]. Phase transfer reactions were firstly developed with the use of catalysts derived from cinchona alkaloids. The pioneering example of phase transfer catalyst was accomplished by using N-benzyl cinchonine salt for asymmetric α-methylation of indanone [8]. Same type of cinchonine and cinchonidine based catalysts were widely used for α-alkylation of glycine derivatives to form stereoselective α-aminoacids. Moreover, Corey and co-workers introduced new cinchonidium salts that brought a new approach to chiral phase transfer catalysts and they synthesized highly enantiomerically rich products via α-alkylation of glycine derivatives (Scheme 4) [9].

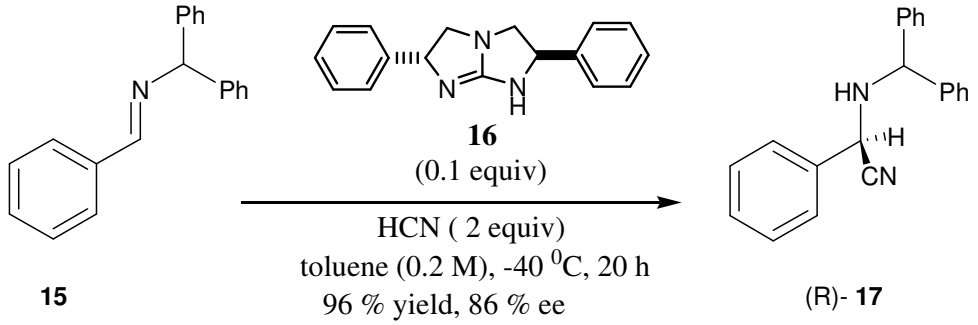


Scheme 4 Enantioselective catalytic Phase Transfer Alkylation

1.1.3. Brønsted base catalysis

Well-known reactions of Brønsted base in asymmetric synthesis is hydrocyanation such as cyanohydrin synthesis and Strecker reaction.

Corey and Grogan have shown the asymmetric synthesis of α-amino nitriles and α-amino acids by using bicyclic guanidine in Strecker reaction (Scheme 5). In this reaction, HCN interact with catalyst to generate a cyanide ion which can then serve as a hydrogen bond donor to the carbonyl compound or imine which is activated with hydrogen bonding [10].

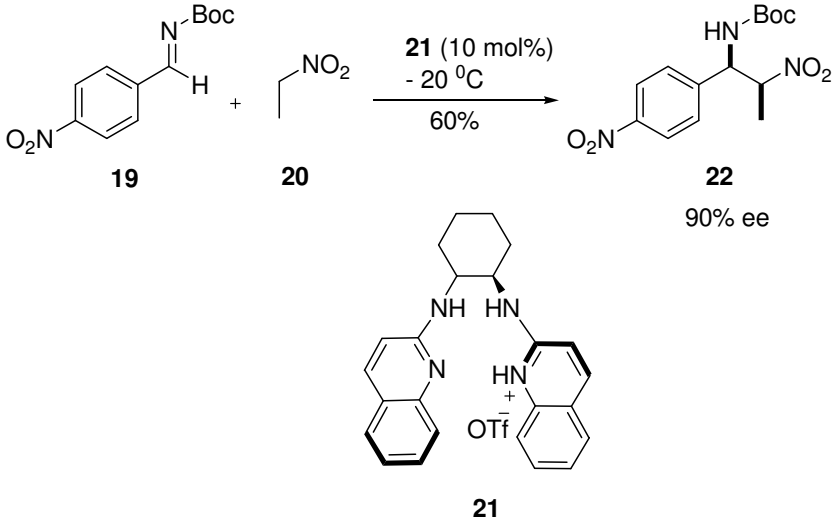


Scheme 5 Strecker reaction of α-amino nitriles

1.1.4 Brønsted acid catalysis

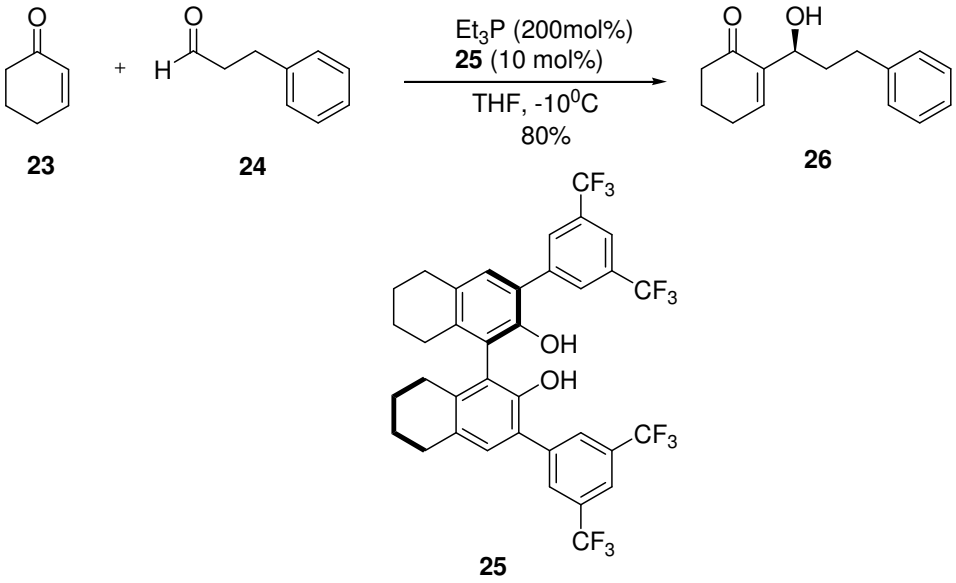
Recently, catalysis through hydrogen bonding **21** has been introduced as a powerful methodology for asymmetric catalysis. Similarly to enzymatic catalysis where H-bonding to a transition state occurs, this type of catalysis may be described as general acid catalysis.

The research was reported an enantioselective chiral proton source (containing a polar ionic hydrogen bond) as a catalyst for the aza-Henry reaction. For example, the reaction of nitroethane and the *p*-nitrobenzylimine **19** in the presence of **21** yielded the corresponding aza-Henry adduct in 90% *ee* (Scheme 6) [11].



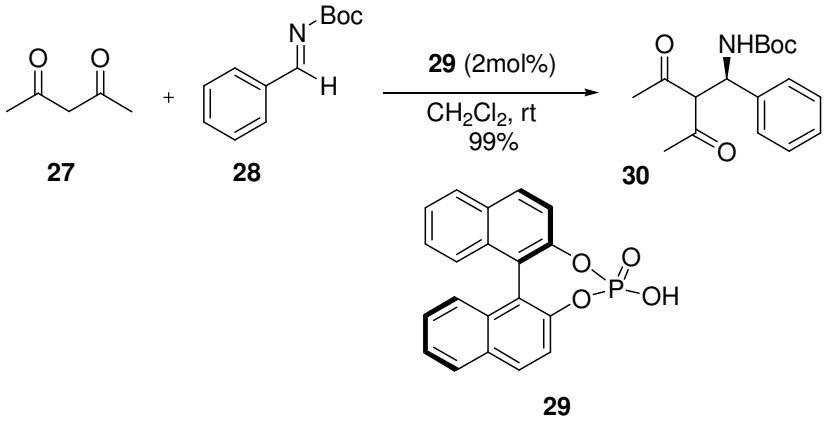
Scheme 6 Example of N-H- based Brønsted acid catalyst

The enantioselective asymmetric Morita–Baylis–Hillman reaction is catalyzed by a chiral BINOL-derived Brønsted acid **25** (Scheme 7) [12]. Here the Brønsted acid promotes the conjugate addition step of the reaction, and then remains hydrogen-bonded to the resulting enolate in the enantioselectivity-determining aldehyde addition step.



Scheme 7 Enantioselective asymmetric Morita–Baylis–Hillman reaction

Akiyama *et al*. have made the very exciting discovery that even relatively strong acids can be efficient asymmetric catalysts. Very recently, it has been reported Mannich reactions (Scheme 8) using chiral Brønsted acid catalyst [13].



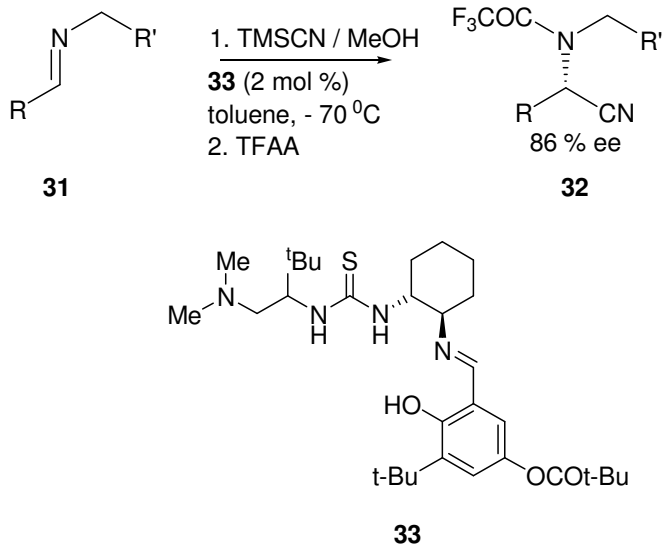
Scheme 8 Example of Mannich reaction

1.2 Catalysis by Chiral Hydrogen-Bond Donors

Nature uses hydrogen bonding as a main rate acceleration factor in enzyme-catalyzed reactions. In recent years, many research groups have reported that several asymmetric reactions can be catalyzed by organic compounds which have the ability to donate hydrogen bonds and many small organic species have been discovered as a class of privileged catalysts which are capable of donating two hydrogen bonds such as ureas and thioureas. Then, other effective strategies has been discovered for obtaining high enantiomeric excess using only a single hydrogen bond donation such as TADDOLs and their derivatives [14]

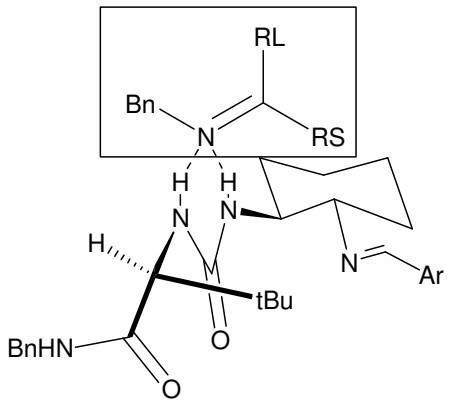
1.2.1 Chiral Ureas and Thioureas as Organocatalysts

The first discovery that urea and thiourea having the ability of facilitating highly an enantioselective reaction was the Strecker reaction (Scheme 9) [15].



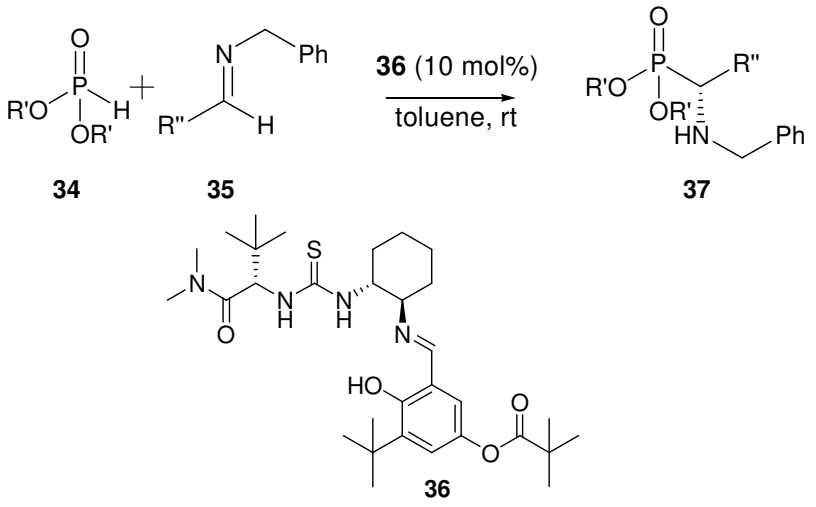
Scheme 9 Enantioselective Strecker eaction by Hydrocyanation of imines

The mechanism of imine activation by urea type catalysis was studied using many techniques such as NMR, kinetic and computational studies. Observed data show that there are two hydrogen bonds between the acidic NH protons of catalyst and imine lone pair and they operate to activate the electrophiles by forming an imine-catalyst complex (Scheme 10) [15].



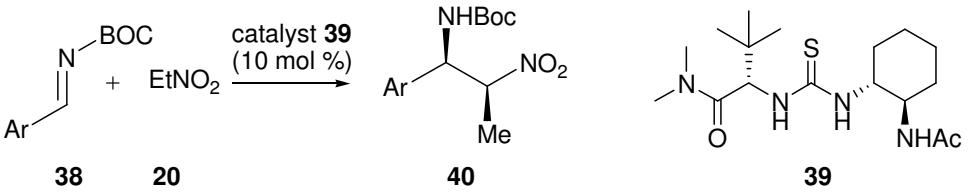
Scheme 10 The proposed mechanism of the strecker reaction using **33**

Besides Strecker reaction, a number of nucleophiles give enantioselective addition reactions with N-benzyl imines by using thiourea catalyst **36**. The addition of phosphite to N-benzyl imines to form asymmetric aminophosphonic acids was successfully achieved using thiourea **36** under optimized reaction conditions. High enantioselectivies were observed with a wide range of aliphatic and aromatic substrates (Scheme 11) [16].



Scheme 11 Enantioselective addition reaction of N-benzylimine

Because of the ability of thioureas to activate imines which have a wide range of protecting groups, they have been used in many enantioselective carbon-carbon bond-forming reactions. The enantioselective addition of range of nitroalkanes to aromatic N-Boc imines was accomplished in the presence of thiourea 39. This reaction improves the asymmetric nitro-Mannich reaction as regard to enantiselectivity and substrate scope. Actually, thioureas's acetamido cyclohexane group function is not well understood but the idea is suggested that this catalyst facilitiates a cooperative bifunctional mechanism, activating both nitroalkane and imine (Scheme 12) [17].

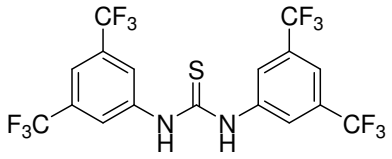


Scheme 12 Enantioselective addition reaction of nitroalkane to aromatic N-Boc imines

A number of characteristics and H-bonding ability of ureas provide a great importance as a catalyst for enantioselective reactions of wide range of electrophiles and nucleophiles. The double H- bonding interaction leads ureas to react with structurally diverse acceptors and in addition, ureas are easily available and highly tunable. Moreover, changing the substituents on nitrogen affects the catalyst's steric and electronic features and alters H-bond donating ability.

Use of additional acidic and basic functional groups on the urea scaffold can be used to design a wide range of bifunctional catalyst and so chiral ureas with these functional groups are easily prepared by the reactions between chiral amines and isotiocyanates.

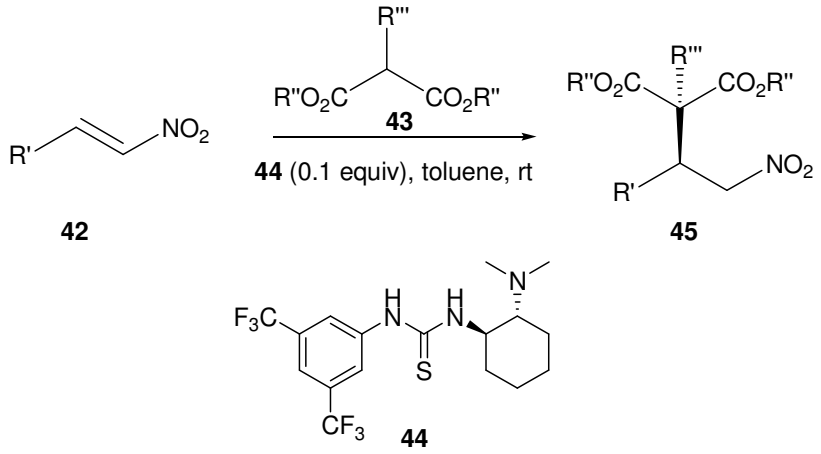
The idea that urea and thiourea could be used as a chiral catalysis by activating electrophiles by double hydrogen bonding creates a new concept for many research groups. In these studies, diaryl ureas and thioureas show maximum rate acceleration when there are electron- withdrawing groups in the 3- and 5- positions. The presence of electron-withdrawing groups leads to an increase in H-bond donating ability of N-H bonds by lowering the pKa value of these bonds. Such an opinion states that intramolecular H-bond between acidic ortho- C-H bonds of aromatic system and urea carbonyl group has a supporting role in activation. This interaction would diminish the basicity of the carbonyl group and would cause to increase H-bonding ability by acidifying the N-H bonds (Figure 2).



41

Figure 2 Thiourea catalysts with CF_3 group in the 3, 5 position

Takemoto's group demonstrated that introduction of an additional basic dimethylamino group which is a nucleophile-activating group in the thiourea catalyst can be used as an efficient catalyst for enantioselective Michael additions of malonates to nitroolefins (Scheme 13) [18].



Scheme 13 Enantioselective Michael addition malonates to nitro olefins

The mechanistic hypothesis suggests that the catalyst leads to activate both nucleophile by general base catalysis and electrophile by H-bonding to the nitro group. In other words, nitroolefins and nucleophiles are activated at the same time (Figure 3) [19].

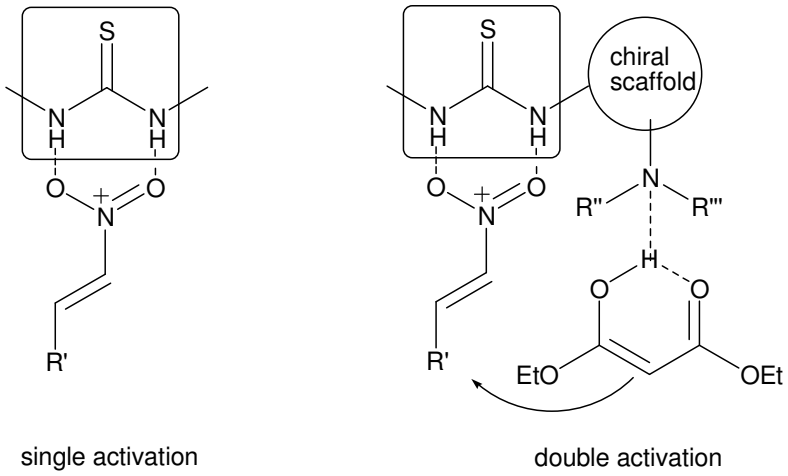


Figure 3 Multifunctional organocatalysts

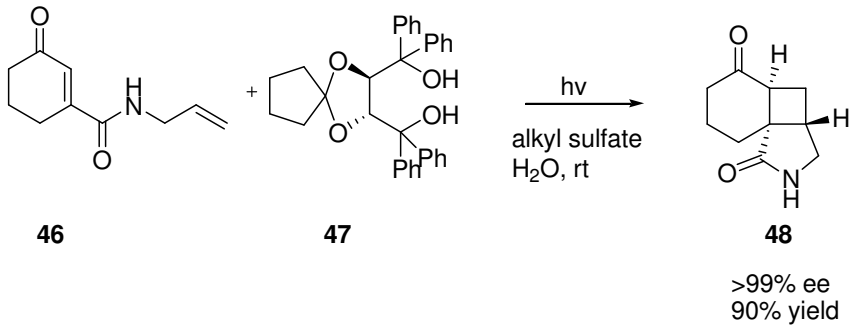
1.2.2. TADDOL and TADDOL's Derivatives as Organocatalysts

TADDOLs and their derivatives are considered as catalysts by single hydrogen bond donation and the mechanism of involving only single H-bond for activation is rare than those activating by either double H-bonding interactions or bifunctional catalysis. The diffuculties emerge from not only generating chiral single H-bond donors but also accomplishing a suitable rigid catalyst-substrate complex.

When the reactions are catalyzed by TADDOL derivatives, the transition state structure is accomplished by an intramolecular H-bonding interaction which increases the acidity of the second O-H bond and decides the position of substrate bonding with steric and electronic interactions. This type of catalysis is typically termed as "hydrogen bond assisted hydrogen bonding catalysis" in which an intramolecular hydrogen bonding increase the hydrogen bonding ability of the second moiety, that is an O-H in TADDOL system.

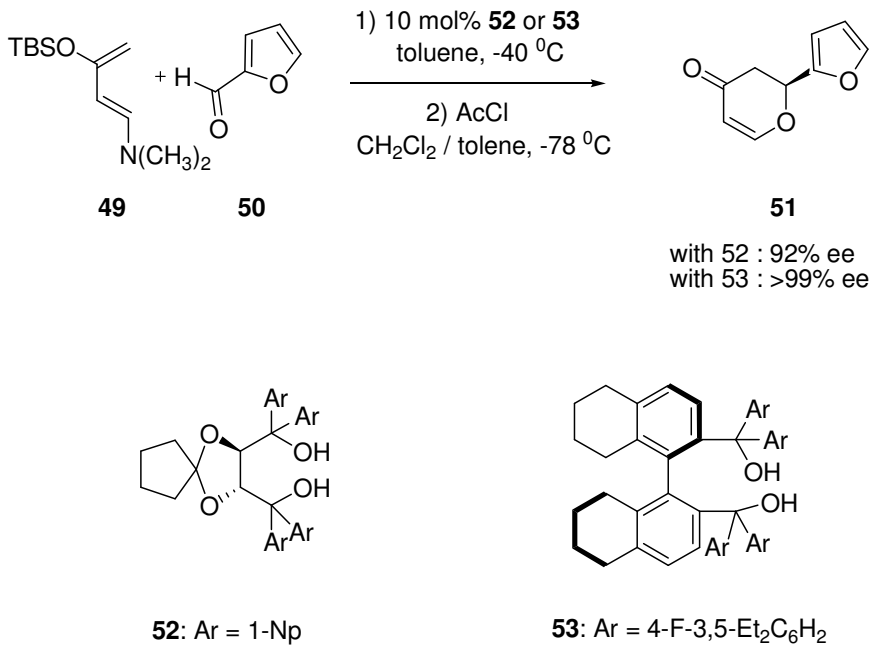
The pioneering example and identification of TADDOL derivatives was achieved by Toda and co-workers and they report that these species have capacity to solve basic substances such as amines, alcohols, carbonyl compounds with formation of H-

bonded. This observation is used in some reactions such as intermolecular [2+2] cycloaddition reaction of a diene (Scheme 14) [20].



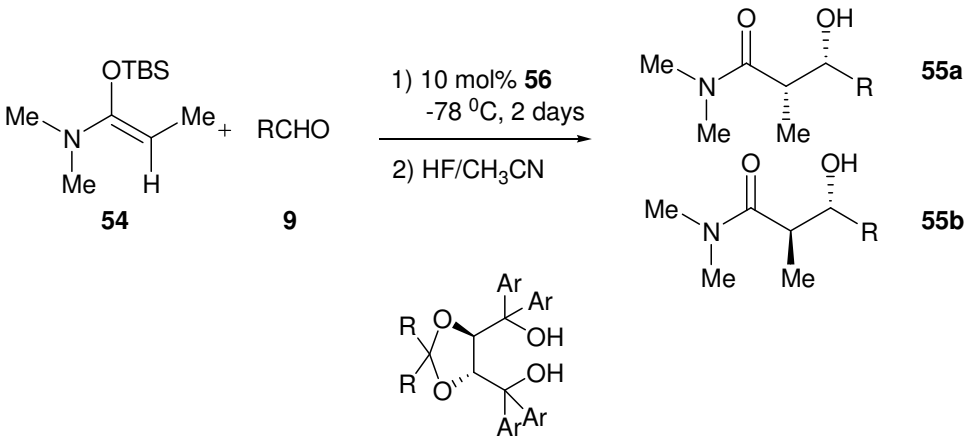
Scheme 14 Enantioselective intermolecular [2+2] cycloaddition reaction

Then, the first succesful application of TADDOL as enantioselective H-bonding catalyst is the highly enantioselective hetero-Diels-Alder reaction of aminodienes with aromatic and aliphatic aldehydes to afford the expected products with good yields and excellent ee's. In this reaction, TADDOL catalyzes the reaction by activating the aldehyde carbonyl group through a single hydrogen bonding (Scheme 15) [21].



Scheme 15 Enantioselective cycloadditions mediated by TADDOL derivatives

Rawal and co-workers extended this mode of catalysis and they reported that ketene acetals and wide range of aldehydes give products in synthetically useful yields and selectivities in Mukaiyama aldol reaction by using TADDOL as a catalyst (Scheme 16) [22].



56: Ar = 1-naphthyl, R= -(C_5H_{10})-

Scheme 16 Mukaiyama aldol reaction mediated by TADDOL

Crytallographic studies are very useful for explaining the structural characteristics of TADDOL and its function in reactions as a catalyst. Several TADDOL's derivative structures are defined with very few exceptions and demonstrated that there is an intramolecular H-bond between the two hydroxy groups. Because of this interaction the proton, which is not involved in H-bonding, is both acidified and orientationally defined. However, complexes' crystal structures which include chiral carbonyl and imino acceptors show that in each case, the 'free' TADDOL hydroxy proton engages in a single H-bond with the acceptor. Therefore, it can be understood that reactions including these catalysts similarly involves activation by means of a single H-bond interaction [14]

PART II

1.3 HDAC (Histone deacetylase) Inhibitors

Histone deacetylase (HDAC) inhibitors regulate the gene transcription by inhibiting the activity of enzymes which are known as histone deacetylases. The aim of HDAC enzymes is to remove the acetyl (CH_3CO) group on histones. Histones are proteins that play a role in the regulation of transcription and forming a scaffold around DNA when it is wrapped. Moreover, in the transcription process, the histones provide limited access to the DNA.

There are various enzymes in the cell and they control the binding of histones to DNA. Once a gene has to be transcribed in the DNA, the enzymes known as histone acetyltransferases add an acetyl group to the histone proteins and they make a confining access to the DNA emerge. While restricted access to DNA is left, transcription factors are capable of binding themselves to the DNA and facilitiate gene transcription. When the gene needs not to be transcribed anymore, histone deacetylases (HDAC) enzymes remove the acetyl group which is added by the histone acetyltransferases. After the removal of acetyl group, the histones can now bind to DNA and again cause to limiting access to the DNA.

In summary, histone acetyltransferases lead to transcription, HDAC enzymes prevent this transcription, HDAC inhibitors change this effect and again lead transcription to occur.

When there is a decrease in histone acetylation, this affects the genes and link to some diseases such as cancer or other gene disorders.

Inhibitors of HDACs increase histone acetylation in the cell and not surprisingly HDAC inhibitors can act as regulators of many diseases, including cancer. There are some desirable anti cancer effects provided by HDAC inhibitors such as the

decreasing of cancer cell proliferation, reduction of cell death of cancer cells and leading cell cycle regulation.

The HDACs are categorizing accoording to their sequence homology and functional properties. Class 1 HDACs (HDACs 1, 2, 3, 8); class 2 HDACs (HDACs 4, 5, 6, 7, 9, and 10) and class 4 HDAC 11 require zinc for acetylation while class 3 has unrelated deacetylases. Class 1 enzymes are generally small polypeptides and they involve at least 500 aminoacids but class 2 is larger polypeptides and they contain nearly 1000 aminoacids. Moreover; class 2 enzymes transport between nucleus and cytoplasm, whereas class 1 localize in the nucleus [23].

After identification of HDACs, it is proposed that HDACs may involve many cellular functions. However, little is known about these enzymes and their effectiveness in relation to the known inhibitors. The last and understood researches are about HDAC8 and there are many studies which reported the crystal structure of HDAC8 in complex with inhibitors.

The HDAC8's structure contains two molecules which are packed as head to head dimer and these two molecules stick one Zn^{+2} ion and two K^{+} ions. This settlement in the crystal is achieved by helping inhibitors with two capping groups (Figure 4) [24].

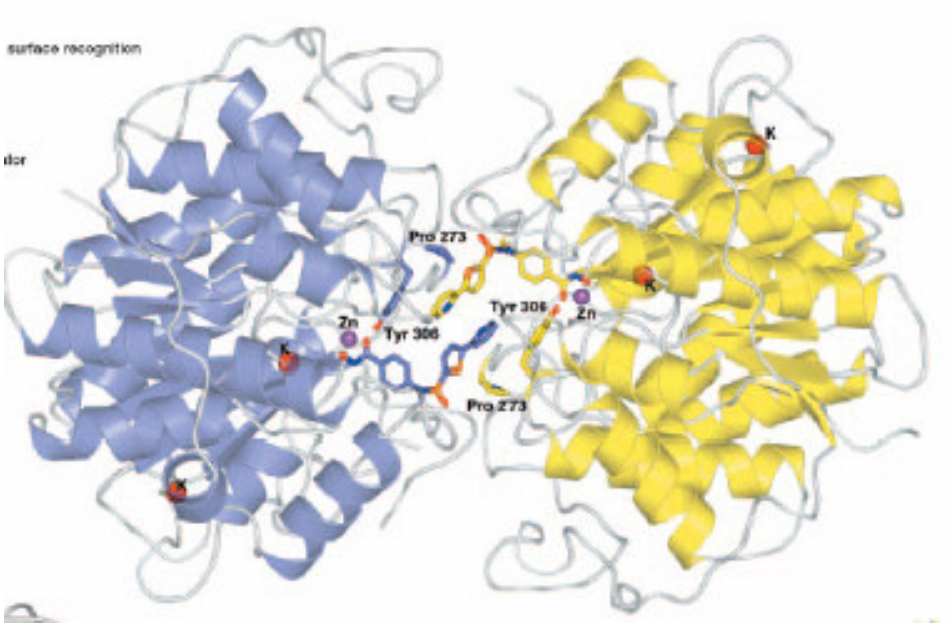
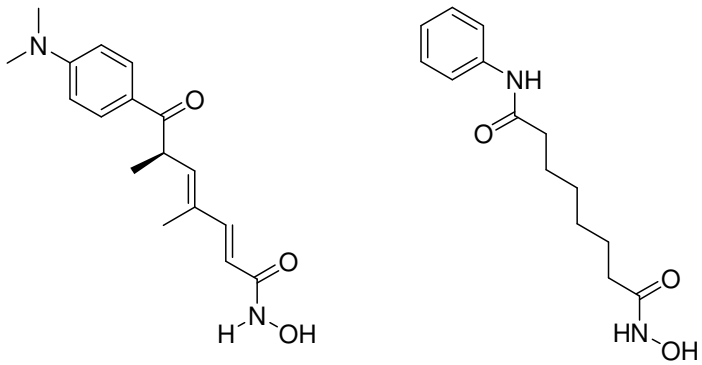


Figure 4 Overall structure of HDAC 8

Many HDAC8 inhibitors are discovered and reported, there are both naturally available such as trichostatin (TSA) and synthetically occuring such as SAHA. These inhibitors can be categorized as regard to their structural features such as hydroxamates and benzamides although two of them are hydroamic acid derivatives (Figure 5) [25].



TSA **57** SAHA **58**

Figure 5 Naturally occurring TSA and synthesized SAHA as HDAC inhibitors

Krem Hrubec and co-workers reported that efficient HDAC8 inhibitors should have three characteristics such as zinc binding group, cap group that binds the rim of active site and linker to connect these groups (Figure 6) [26].

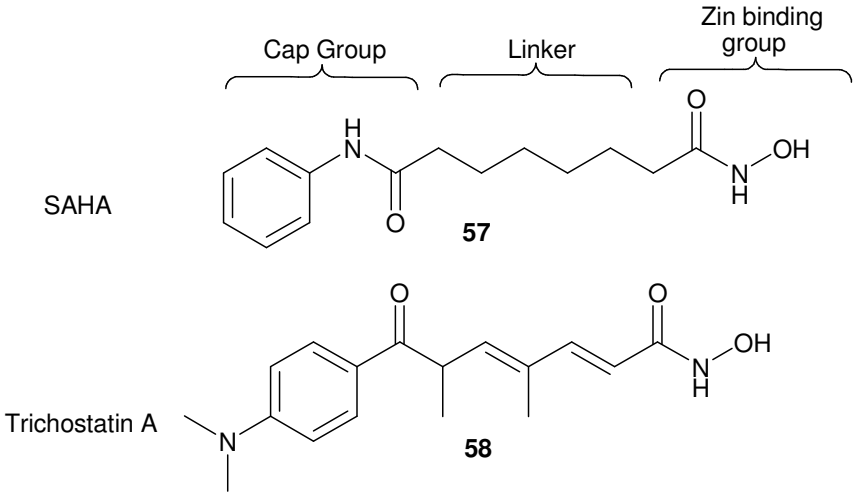


Figure 6 Common structural features of HDAC inhibitors SAHA and Trichostatin A

Paralleling the extention of HDAC researches, in additon to the hyroxamic acids (SAHA and Trichostatin), there exist various chemical compounds such as valproic acid, sodium phenylacetate and butyric acid that enable to inhibit HDACs (Figure 7).

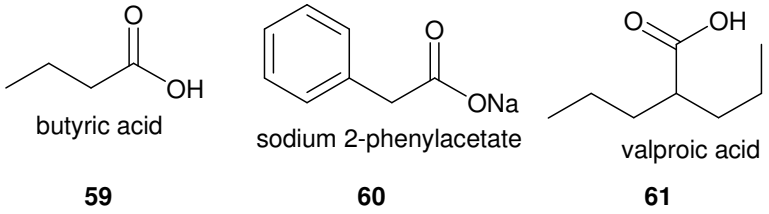


Figure 7 Some chemical compounds having inhibition activity

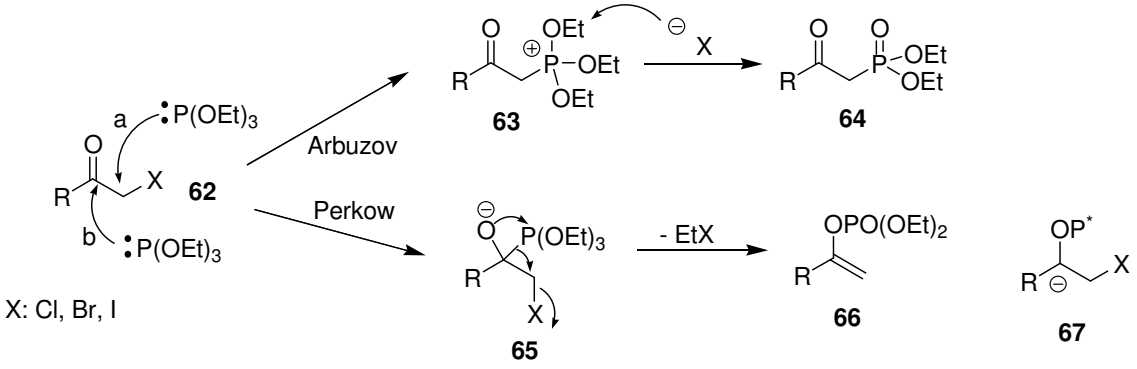
They are used in many researches and it is found that they can reduce cell arrest, differentiate the structure of cancer cell and showing the efficiency in inhibiting tumor growth.

PART III

1.4 Acylphosphonates as an Acyl Anion Equivalents

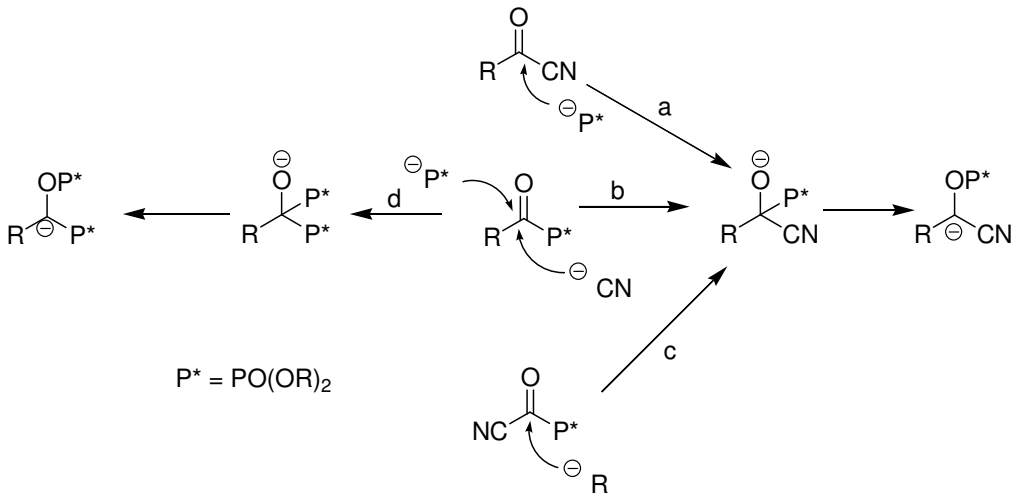
Phosphorus has a capacity to migrate both from carbon to oxygen and from oxygen to carbon under suitable conditions [27]. Although the phosphorus has this ability, until the last decades this knowledge was not used properly in the research studies. Indeed, acylphosphonates can be promoted to form acyl anion precursors that act as a nucleophile and can react with various electrophiles.

Certainly, the most fascinating example of migrating ability of phosphorus is the well-known Perkow reaction [28]. In spite of the fact that its mechanism is not known exactly, the reaction mechanism suggests that a trivalent-phosphorus ends up as a pentavalent-phosphorus with a migration of phosphorus from carbon to oxygen. Perkow reaction competes with the classical Arbuzov reaction and most of the time controls the main reaction routes. The mechanism of the Perkow reaction is represented as shown in scheme 17.



Scheme 17 Mechanism of Arbuzov and Perkow reactions

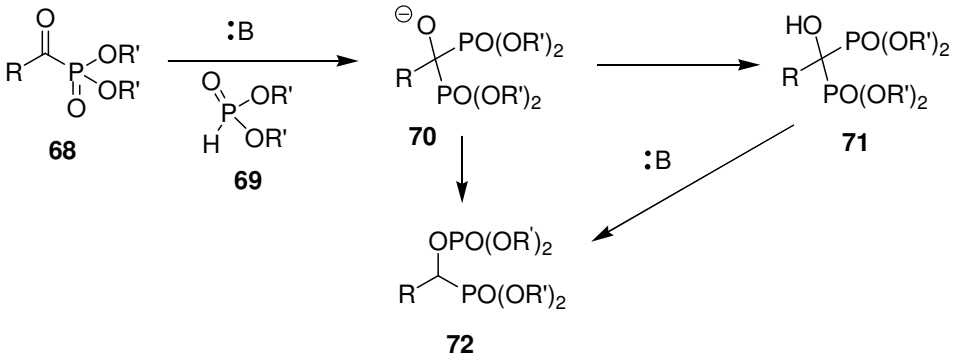
The rearrangement of phosphorus from carbon to oxygen is observed in Perkow reaction mechanism and this leads to form enol ether. The intermediates like **67** sometimes emerge and in fact it is acyl anion equivalent that is formed after eliminating a halogen group. It is suggested that placing a carbanion stabilizing group such as cyanide or phosphonate instead of the carbon bearing the leaving group (CH_2X) would give a chance to generate to a new acyl anion precursors. Our research group, based on this suggestion, recommended various strategies to form such intermediates. These strategies contain the additon of the phosphorus moiety in route a and d, addition of cyanide in route b or addition of the carbon nucleophiles in route c as represented in scheme 18.



Scheme 18

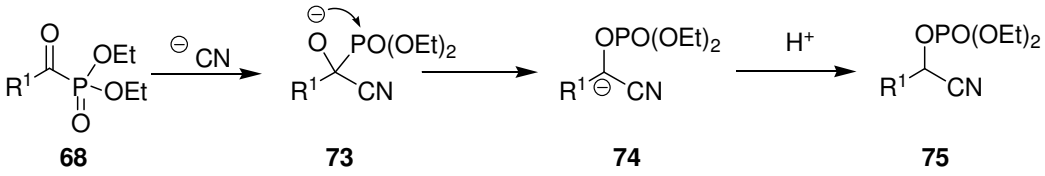
After this, information about the organophosphorus chemistry and each step of this method are collected from the literature for achievement of proposal method. In the literature, there are many studies that involve the 1, 2 rearrangement of phosphorus such as base caused migration of phosphorus from carbon to oxygen. A nice example of these rearrangements is phosphonate-phosphorus rearrangement and this is observed in synthesizing of controversial α-hydroxyalkylidenediphosphonate esters

71. McConnell and Coover achieved the synthesis of these compounds by the base catalyzed addition of dialkyl phosphites to acylphosphonates [29]. Then, it is understood that the adduct of this reaction was isomeric compound **72** and it contains two different phosphorus atoms [30]. It is formed by two ways such as from the rearrangement of intermediate **70** before protonated or isolated **71** rearranges to this compound (Scheme 19).



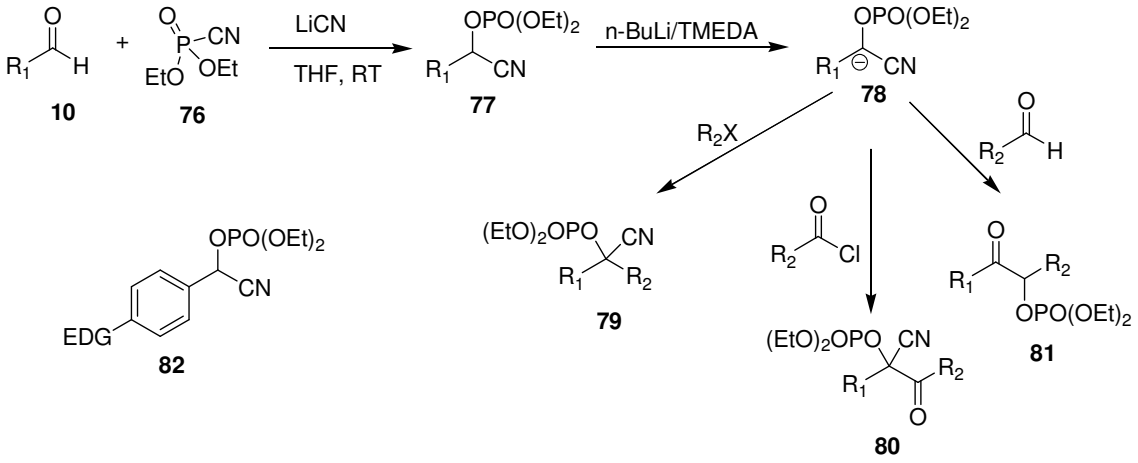
Scheme 19 Base promoted migration of phosphorus from carbon to oxygen

There is an example in that the cyanide ion is used for contributing the rearrangement of acylphosphonate in the presence of alkali cyanide solution [31]. As observing the other rearrangement, the presence of cyanide causes an important stabilization to carbanion **74** that forms **75** with protonation (Scheme 20). This is a very considerable and helpful example to show the ability of cyanide ion promoted rearrangement of acylphosphonate.



Scheme 20 Rearrangement of acyl phosphonate

Kurihara et el. show that the derivatives of **75** can be used as a acyl anion precursors. In this study, the cynophosphates are used and they are prepared by the reaction of aldehydes with diethylphosphorocyanidate and LiCN. After deprotonating of **75** to **74**, some reactions with various electrophiles containing alkylhalides, acylhalides and aldehydes give products such as alkylated, acylated and benzoin (acyloin), respectively. Even though this is the achievement for acyl anion precursors, it does not show advantage over available corresponding precursors. Moreover, aliphatic derivatives of **75** are unsuccesful for generating any adduct and only starting compunds are obtained again. Furthermore, when the **82** is substituted with electron donating group, it is failed to form of **74** because it is unstable (Scheme 21).



Scheme 21 Phosphate protected cyanohydrins as acyl anion equivalents

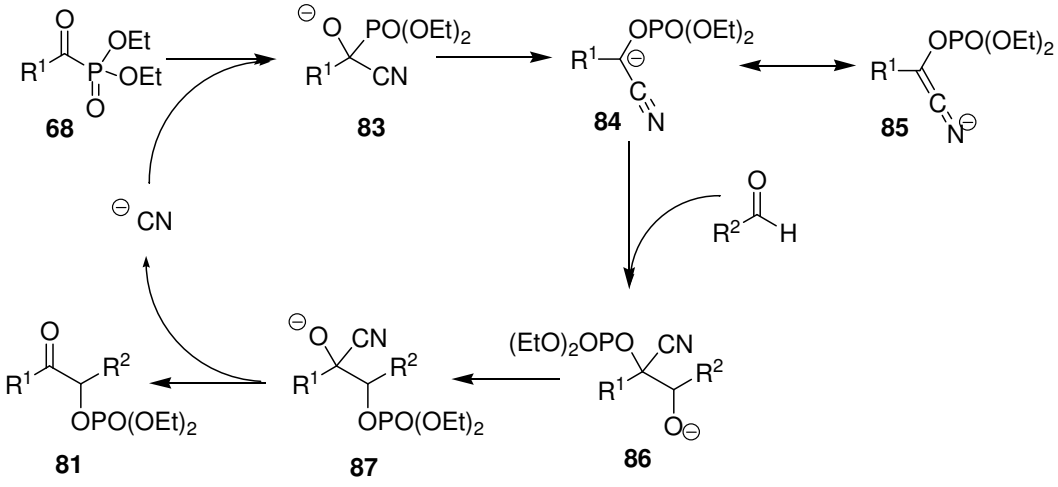
Based on this information and guided by initial proposal (Scheme 20), our group focus on the cyanide or phosphite anion promoted rearrangement of acylphosphonates (route b and d. Scheme 18).

1.5 Reactions of Acylphosphonates

1.5.1. Synthesis of Unsymmetrical Benzoins

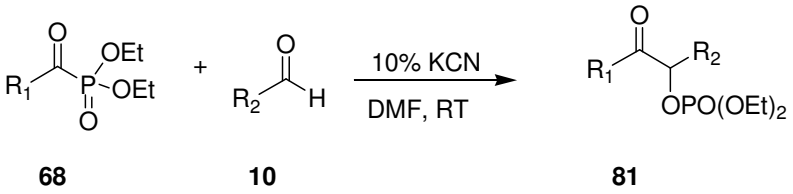
Demir *et al.* introduced acylphosphonates as a new type of acyl anion precursors in benzoin reaction [32]. While cyanide is promoting rearrangement from phosphonate to phosphate, corresponding acyl anion equivalents are formed. These acyl anion equivalents react with various aldehydes to produce varied benzoins..

The mechanism is similar to known benzoin reaction and in this mechanism the acyl anion is produced by the migration of phosphorus from carbon to oxygen after the addition of cyanide ion to carbonyl group. This acyl anion reacts with aldehyde and generates the intermediate **86.** After the 1, 4-O,O-phosphate migration , retrocyanates generate the benzoin product and join the catalytic cycle (Scheme 22).



Scheme 22 Mechanism of benzoin reaction of acyl phosphonates

This method provides various aromatic-aromatic, aromatic-aliphatic and aliphatic-aromatic acyloins (Scheme 23).



68 **10** **81**

a) R_1: Aryl R_2: Alkyl

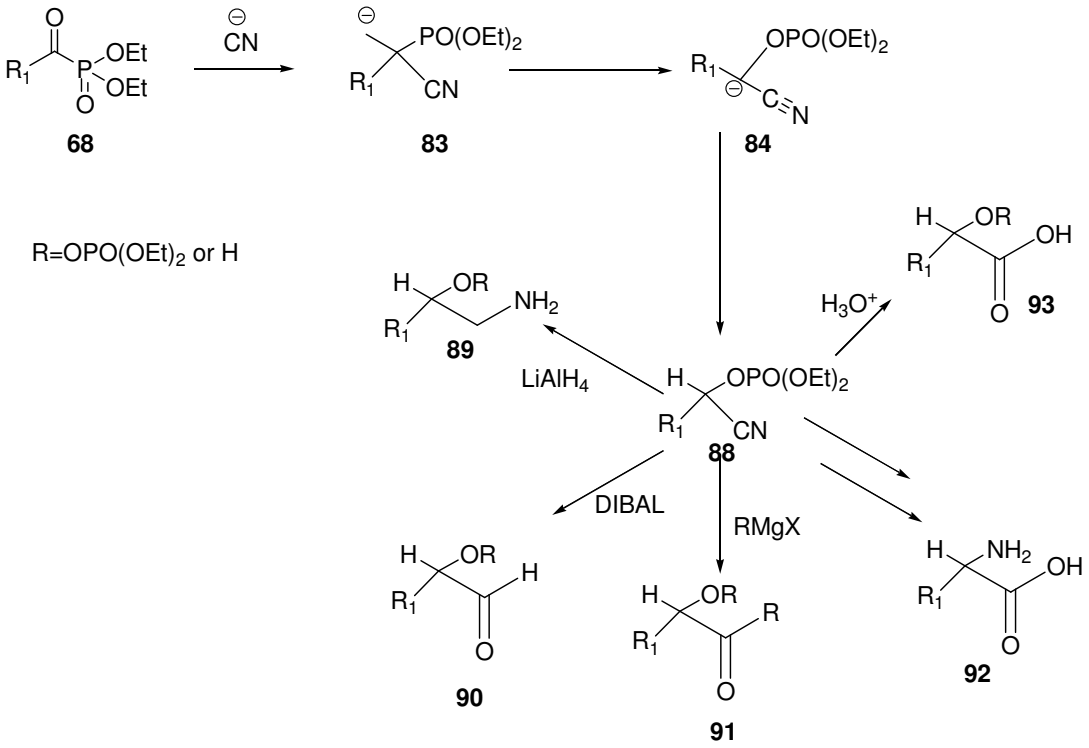
b) R_1: Aryl R_2: Alkyl

c) R_1: Alkyl R_2: Aryl

Scheme 23 Benzoin reaction of acyl phosphonate

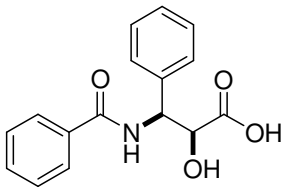
1.5.2. Protonation of Acyl Anion Equivalent

Protonation of acyl anion equivalent generated from acylphosphonates give valuable intermediates [33]. The main product is protected cyanohydrines and from these cyanohydrines a variety of compounds can be generated (Scheme 24).



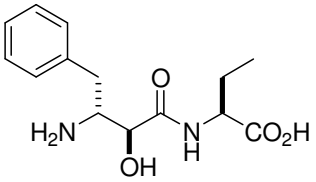
Scheme 24 Protonation of acyl anion equivalent and some transformations of the product

Moreover, protonation of acylphosphonates cyanide promoted rearrangement intermediates can give intermediate for the synthesis of α-amino aldehydes and α -hydroxy-β-amino acids. Because α-amino aldehydes and α -hydroxy-β-amino acids are highly considerable compounds which can be found in the structure of many biologically active compounds. For example, anticancer drug Taxol's side chain N-benzoyl-phenylisoserine and bestatin are just two of them (Figure 8)



phenylisoserine

94



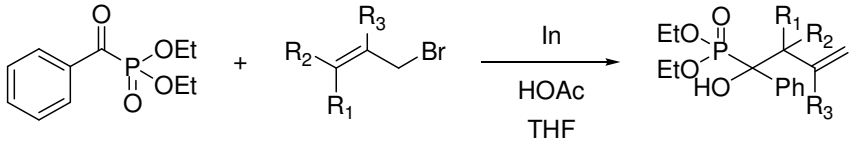
bestatin

95

Figure 8 Biologically active compounds

1.5.3. Addition of Carbon Nucleophiles to Acylphosphonates

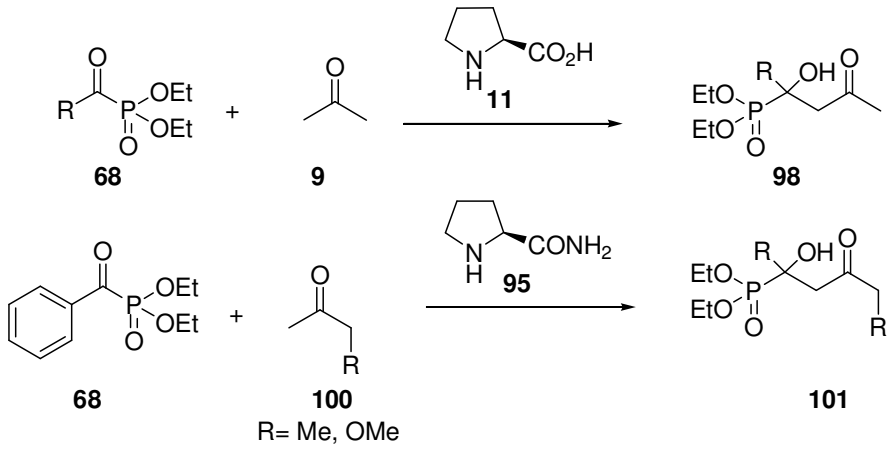
Wiemer group showed allylic addition to acylphosphonates by using allylic bromide in the presence of indium metal (Scheme 25) [34]. The expected adducts are observed in excellent yields in suitable conditions and the scope of the reaction is quite wide. Moreover, the method is used properly with both aliphatic and aromatic phosphonates.



68 **96** **97**

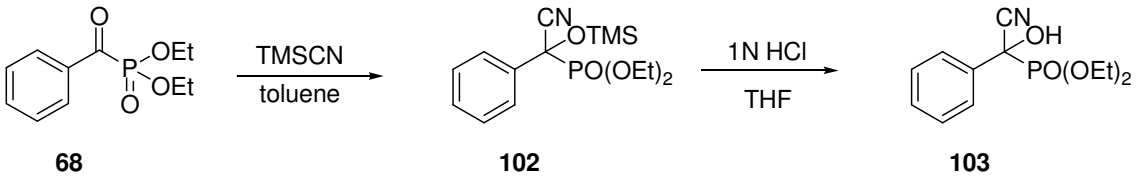
Scheme 25 Allylation of acyl phosphonates

Another type of reaction is aldol reaction of acylphosphonate which is catalyzed by L-proline (Scheme 26) [35]. Generally, although the acceptors are mainly aldehydes, the donors can become ketone or aldehydes in aldol reaction catalyzed by organocatalysts. Zhao and co-workers used acylphosphonate as an acceptor and acetone as a donor in this reaction. Both aliphatic and aromatic acylphosphonate is used and generate the products with high yields and excellent enantioselectivies.



Scheme 26 Aldol reaction with acyl phosphonates

By Demir *et al*, the new method is discovered for uncatalyzed addition of TMSCN to acylphosphonates. Until studies of our group the addition of TMSCN to the aldehydes or ketones could be achieved only in the presence of Lewis acid catalysis [36]. The new method has been found that TMSCN adds to acylphosphonates quantatively without any catalyst effect and the observed protected adduct can be hydrolyzed with HCl (Scheme 27).



Scheme 27 TMSCN addition to acyl phosphonate

1.6 Aim of the Work

Thiourea derivatives have gained great importance and become a main focus of research in asymmetric synthesis in recent years. In the first part of study, we have aimed to design new two-centered thiourea catalysts which can be synthesized from commercially available and relatively inexpensive L-tartaric acid and their use in asymmetric synthesis.

In addition; there are some desirable anti cancer effects provided by HDAC inhibitors. In the second part, because of the HDAC activity of resveratrol, the use of some aryl butenoic acid derivatives was aimed to synthesize as an analog of resveratrol for biological studies.

In the last part; some benzoyl phosphonates are synthesized for the study of ethylcyanoformate addition to aryl phosphonates.

CHAPTER 2

RESULTS AND DISCUSSION

PART I

2.1 Synthesis of Tartaric Acid Derivatives as an Organocatalysts

Electrophile activation by chiral small molecules which have ability to donate H-bond has become an important method for enantioselective catalysis with new applications.

Therefore, in this part of this study, we proposed new chiral H-bond donor catalysts that can be generated for some enantioselective transformations. Thus, we designed new two-centered thiourea catalysts which can be synthesized from commercially available and relatively inexpensive L-tartaric acid.

Our catalyst design is based on transition state structure which is proposed in Figure 9. When thiourea derivatives are used as catalysts, the electrophile is activated by double hydrogen bond between the acidic NH protons of catalyst and electrophiles.

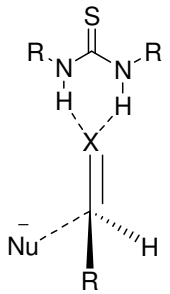
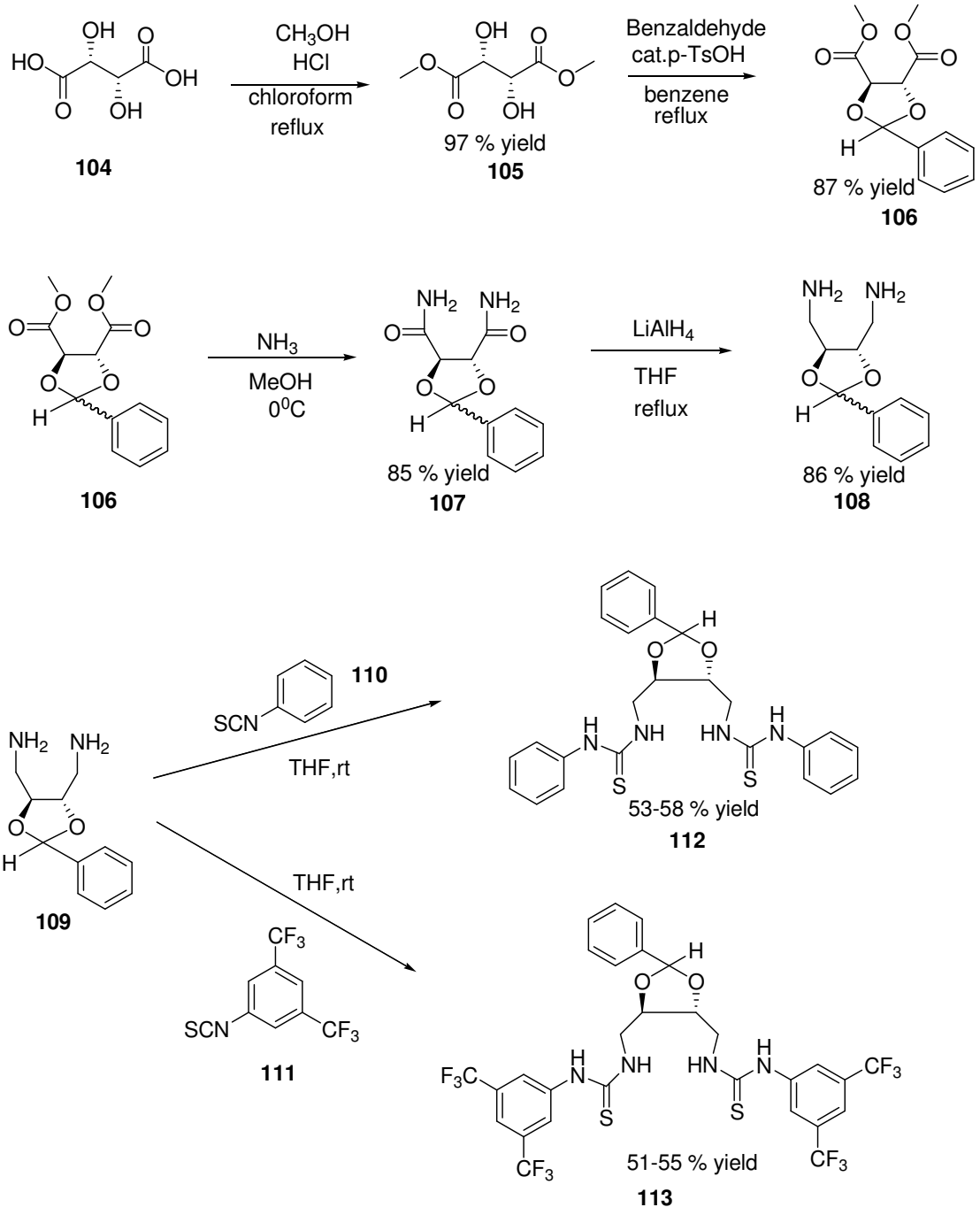


Figure 9 Activation by thiourea catalyst

As in the success of TADDOLs, many chiral catalysts and chiral ligands were syntesized from tartaric acid, which provides a structural diversity. Therefore, the L-tartaric acid serves as the chiral starting material for the target molecules.

Scheme 28 summarizes the synthesis of thiourea catalysts from L-tartaric acid. Several synthetic processes were examined and the present five-step synthesis, which needs only common and inexpensive reagents under operationally simple reaction conditions, was selected. According to the literature, carboxylic acids were converted to esters (Scheme 28**)** [37]. Then, the protection of the two hydroxyl groups of the tartarate was achieved by benzaldehyde by using Dean-Stark trap.

After the protection, the formation of his amide was carried out according to literature procedure and diamide derivative **107** is obtained in % 91 yield after purification by recrystallization. Reduction of amides with $LiAlH_4$ in THF gave the desired diamine **108** .Actually; the diamine compound **108** was used for the next step without any purification**.**



Scheme 28 Synthesis of thioureas catalysts

Finally, the reaction of **108** with 2 equiv. isothiocyanates in dry THF at room temperature furnished **112** and **113.** The product was obtained by recrystalization with diethylether-hexane (4:1).The catalysts appeared as a white solid and thus, the solid was easily separated from the reaction mixture by simple precipitation.

Treatment of **108** with 1 equiv. of isothiocyanates in dry THF did not lead to mono substituted products. Firstly, the catalyst **112** was generated by performing with 1-isothiocyanatobenzene, then, catalyst **113** was synthesized with 1, 3 bis (trifluoromethyl)-5- isothiocyanatobenzene since maximum rate acceleration is observed with thiourea derivatives which have strongly electron-withdrawing groups such as CF_3 in the 3-and 5-positions.The reaction of **108** with isothiocyanates accomplished the synthesis of thiourea catalysts, **112** and **113,** in 51-58 % yield.

The compounds are characterized by using ^{1}H-MNR analyses. In the ^{1}H-MNR spectrum, there are two signals belonging to four N-H protons. Of these signals at 8.54 belongs to two N-H protons, and the other peaks appeared at 6.95-7.15 belongs to other two N-H protons. In addition, the apperaence of thiourea carbon is observed by ^{13}C-MNR.It gives signal at 182 ppm.

2.2. Application of the catalysts

Although the thiourea derivatives are known to act as acid catalysts in many reactions, until the last decade the enantioselective reactions were rare. Takemoto *et el.* recently reported that thiourea derivatives facilitiate the Michael reaction of malonates to nitroolefins [18]. In this reaction, the thiourea seems to interact with nitro group and increases electrophilicity of nitroolefins.

This observation prompted us to investigate possible usage of thiourea derivatives **112** as and **113** catalysts in reactions between benzaldehyde and nitromethane. This reaction is known as Henry reaction and it provides the carbon-carbon bond formation. We expected that the corresponding nitronate could be produced from

nitroalkane with the thiourea catalyst via the hydrogen-bonding activation with the thiourea moiety. The other expectation was that our catalysts might be deprotanate the nitromethane with neighboring amin group as shown in figure 9. If they were accurate, so the catalysts would have been promoted the asymmetric Henry reaction.

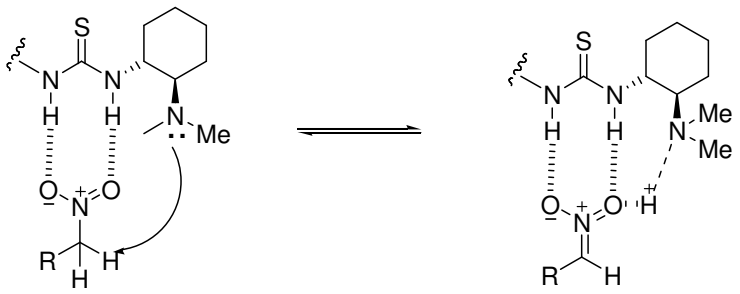
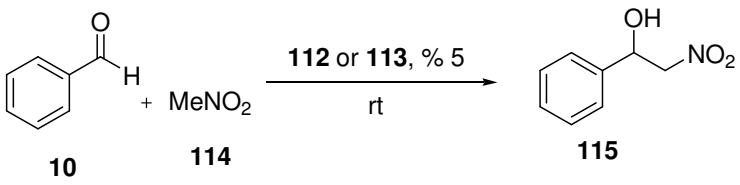


Figure 10 Dual activation of nitro alkane

Consequently, the reaction of benzaldehyde with nitromethane was investigated in the presence of thiourea catalyst without any base (Scheme 29).The mixture of benzaldehyde, nitromethane and thiourea catalysts **112** or **113** was stirred for 6 hours at room temperature. The reaction was monitored by TLC analysis and it was observed that the reaction did not proceed and so there was no product formation in the reaction. Then, the reaction temperature was changed and the reaction mixture was heated for 5 hours .However, the product formation was not observed. Lastly, use of microwave was decided for the reaction. Therefore, the reaction was performed in microwave (250 W, 80 ^{0}C, 4 min.) .The reaction was monitored by TLC; there was no product formation.

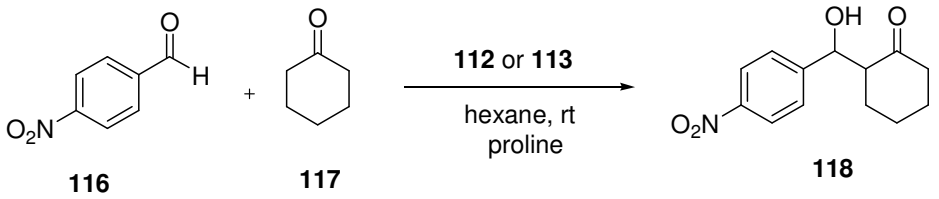


Scheme 29 Henry reaction mediated by our catalysts

This result indicated that our thiourea catalysts were not capable of deprotonation of nitromethane as thiourea derivatives having neighboring amino group. Thus, the same reaction was reperformed in the presence of Et_3N which can deprotanate the nitromethane. This time, the reaction underwent smoothly and a new product was generated. The product was observed by ^{1}H-MNR. The product was purified by column chromotography. Its specific rotation [α] was tested with polarimeter. Unfortunately, the adduct was not an optically active compound. The reaction furnished racemic product. Then, the solvent was changed and the reaction was performed in THF. The reaction mixture was stirred for 6 hours at room temperature. After completion the reaction (monitored by TLC), the product was obtained in racemic form.

In addition to this application, catalysts **112** and **113** were used in proline catalyzed aldol reaction. After the discovery of the proline as catalysts, enantioselective proline catalyzed reactions gain great importance. Although the proline has been used in several enantioselective reactions, it has some drawbacks such as low solubility that restricts the reactivity in common solvents, potential side reactions and low selectivity with aromatic aldehydes. Considering these drawbacks, it is not surprising that many proline catalysts obtained with modification of proline were reported so far in order to improve solubility and selectivity.

Thus, we proposed the idea that chiral thiourea catalysts **112** and **113** can be used with proline in aldol reaction (Scheme 30).The reaction was performed with cyclohexanone **117** and p-nitrobenzaldehyde **116**. The reaction was monitored with TLC analysis and it proceeded smoothly. After the work-up and the purification processes, the target compound **118** was obtained. The product was identified by ^{1}H-MNR spectrum.



Scheme 30 Aldol reaction used by our catalysts

As regard the enantiomeric excess, it was determined by HPLC analysis of **118** using a chiral column and racemic **118** was also synthesized using literature procedure as reference [38].The enantiomeric excess was observed under %5.Then, we started to investigate the reaction with other solvents and the reaction was performed in cyclohexane and toluene. The target compound **118** was observed with low yield and racemic form.

PART II

2.3 Synthesis and Inhibition of HDAC inhibitors

Histone deacetylases (HDAC) are enzymes that play an important role in modifying chromatin structure and regulating gene expression. A number of HDAC inhibitors have been developed as anti-cancer agents.

Structure of the HDAC inhibitors can be divided into three basic groups which are called the last group, linker group and polar group (Figure 10).

Figure 11 General structure of HDAC inhibitors

At the beginning of the study, the polar group was considered and the strategy was to change these polar groups while keeping the last groups and linker groups as they were. The compounds with different polar groups were then investigated for their inhibitory activity. These polar groups were carboxylic acid, boric acid, phosphoric acid and sulphonic acid.

Resveratrol which is a molecular produced by plants in response to stress is known to have anti-inflammatory, antioxidant and anti- cancer effects (Figure 11). In this preliminary study, HDAC inhibitory activities of resveratrol and its analogs were investigated in vitro by using HeLa nuclear ext. in a fluorimetric assay. High inhibitory activity was found in resveratrol in a concentration dependent manner. It showed more inhibitory effect than known HDAC inhibitors like short chain fatty acids. To display the inhibitor positioning in the active site of HDAC enzyme, molecular docking studies were performed and results showed that resveratrol had the most favorable free energy of binding and inhibition constant values.

Demonstration of HDAC inhibitory effect of resveratrol will provide new insights into pharmaceutical applications [39].

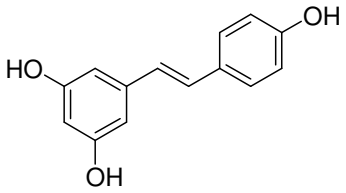
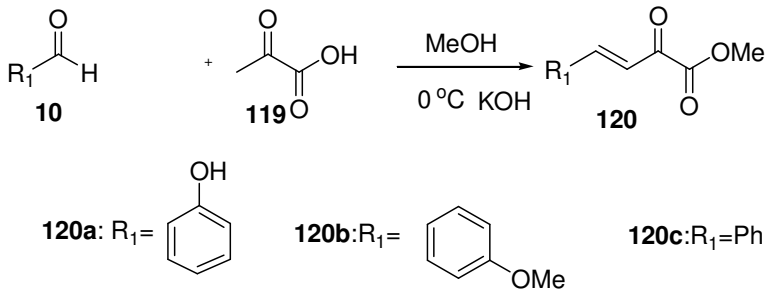


Figure 12 Resveratrol

.

Through the light of these findings with resveratrol derivatives, it was suggested that replace one of the aryl groups with carboxylic acid and design the structure **120** as shown in scheme 31. So, the first attention was paid to synthesize the carboxylic acid derivatives. In this context, benzaldehyde **10** and pyruvic acid **119** were selected as starting material to synthesize target molecule **120** (Scheme 31).



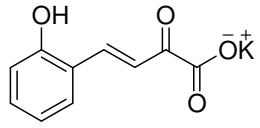
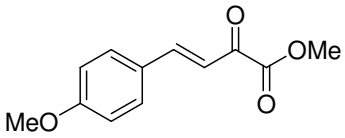
Scheme 31 Synthesis of HDAC inhibitors

The reaction of benzaldehyde **10** with pyruvic acid **119** is very exothermic. So, it was carried out at 0^0C in the ice bath. First, the potassium salt of benzylidenepyruvate was obtained, and then it was converted to ester by passing HCl gas. The other purpose was to functionalize the benzaldehyde by using salicylaldehyde and p-

anisaldehyde benzaldehyde with pyruvic acid. However, in the reaction of salicylaldehyde, the potassium salt could not have been converted to ester.

By using VMD (Visual Molecular Dynamics) program, inhibition constant and free energy of binding of the compounds **120 a** and **120 b** were calculated as in shown Table 1. Figure 12 and 13 show the binding mode of **120 a** and **120 b.**

Table 1. Calculation of free energy of binding and inhibition constant [40]

Inhibitors	**Free Energy of Binding (kcal/mol)**	**Inhibition constant (Ki)**	
 **120 a**	-7.24	Experimental: 4.79 μM	Calculated
 **120 b**	-7.97	1.45 μM	
TSA **57**	-9,9	0.5 μM	
SAHA **58**	-8.2	2.47 μM	

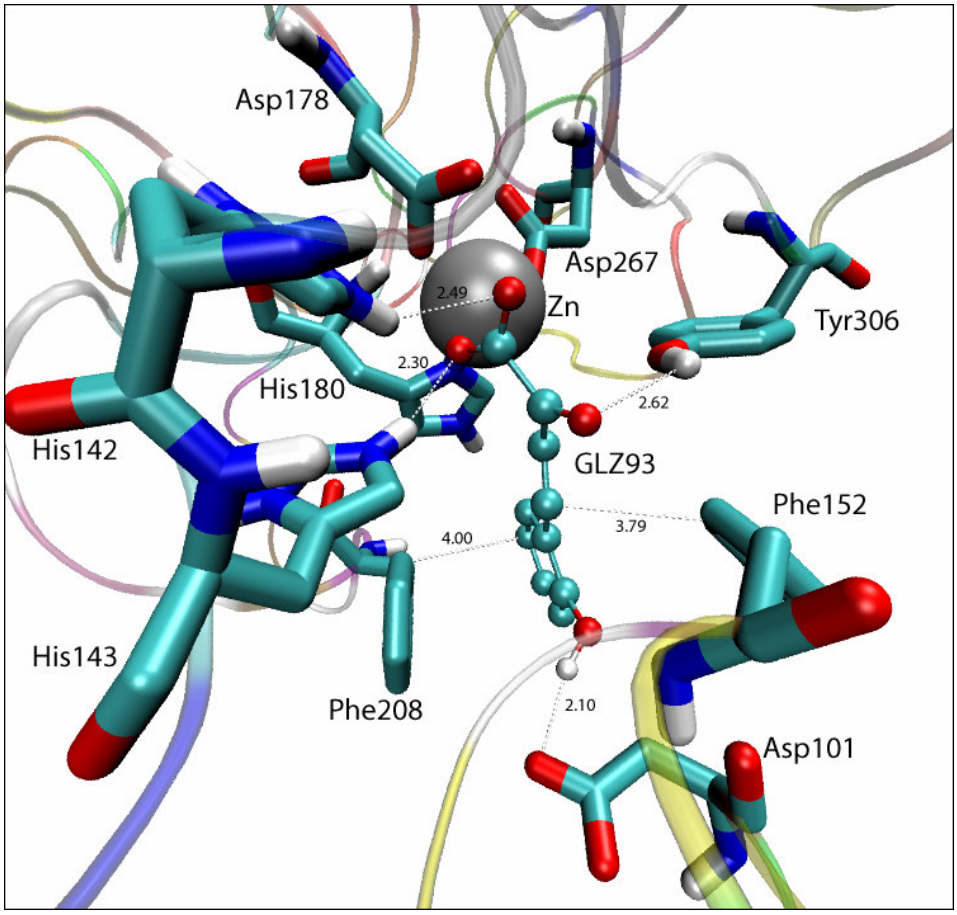


Figure 13 Binding mode of **120a** in the active site of HDAC8 enzyme. Ligand was designated in CPK, the important residues in the active site of the enzyme were presented by ligorice style and Zn was shown in VDW style. Part of the enzyme in the background was visualized in New Ribbon style using the VMD program [40].

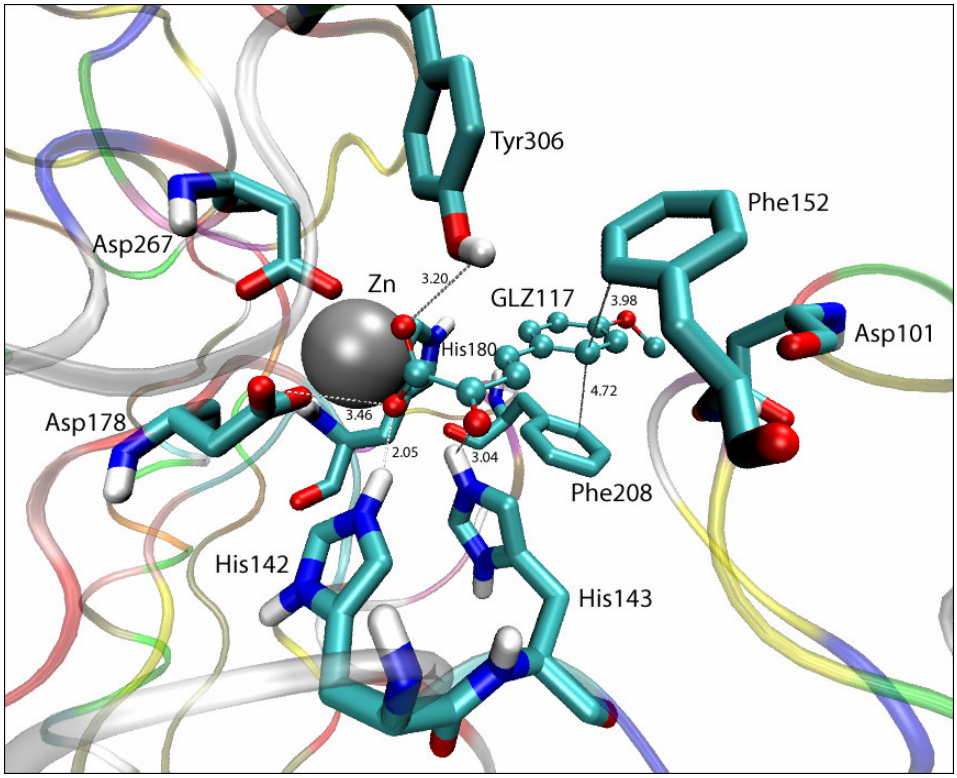


Figure 14 Binding mode of **120b** in the active site of HDAC8 enzyme. Ligand was designated in CPK, the important residues in the active site of the enzyme were presented by ligorice style and Zn was shown in VDW style. Part of the enzyme in the background was visualized in New Ribbon style using the VMD program [40].

The ester groups of compounds **120a** and **120 b** approach nearer as possible as to Zn and they form complex with Zn which is the important factor to increase inhibition activity. The other six interactions are shown in figures. In addition, the phenyl group of compound **120b** also makes π- π striking interaction between Phe 152 and Phe 208.The ester group of **120b** is nearer to Zn and there are close interactions with Tyr 306, Asp 178 and His 142.The carbonyl group of **120b** has also close interaction with His 143.Thus, **120b** has better inhibition value than **120a** with low inhibition constant.

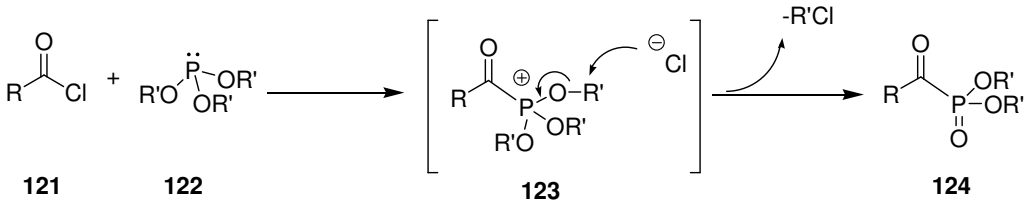
These results prove that our compounds have inhibition affect especially **120 b**, which has high inhibition with low inhibition constant, has become the most promising compound.

When we compare our results with the well-known HDAC inhibitors TSA and SAHA, inhibition constant of **120 b** is better than SAHA and its value is between TSA's and SAHA's inhibition constants which are 0.5 μM and 2.47 μM respectively. The other compound **120 a** is a near the SAHA with the value of 4.97 μM. Moreover, the cell-culture tests of the compounds are in progress.

PART III

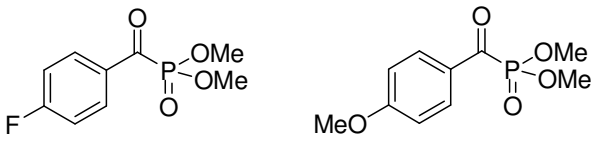
2.4 Synthesis of Acylphosphonates

Acylphosphonates (α-ketophosphonates) were used as precursors to biologically active α-aminophosphonic acids and α -hydroxyphosphonic acids. Acylphosphonates are easily available compounds. The most direct access to these compounds is the well-known Arbuzov reaction between acylchlorides **121** and trialkylphosphites **122** [41, 42]. Reaction proceeds via formation of unstable intermediate **123** that eventually leads to acylphosphonate **124** (Scheme 32). It is generally carried out by mixing neat reactants at or below room temperature. If one of the reactants is solid, it can be carried out in organic solutions. Gaseous alkyl chloride is the only side product.



Scheme 32 Synthesis of acyl phosphonates

Aryl acylphosphonates **124a** and **124b** were synthesized and used in this study (Figure 14). These compounds were synthesized with Arbuzov reaction according to literature procedures (Scheme 32).The products were purified by vacuum distillation and after syntesizing, these compounds were stored under argon filled flasks to prevent decomposition or hydrolysis, since they are so sensitive to moisture.



124a **124b**

Figure 15 Acylphosphonates synthesized and used in this study

2.5 Addition of the acylphosphonate to ethylcyanoformate

Acylphosphonates are precursors of acyl anion equivalents and in the presence of cyanide ion; nucleophilic acyl anion equivalent is generated. According to this information, the idea proposed was that the acylphosphonates could be used in carbonyl acylation with acyl cyanide compounds. With this proposed idea, we developed acyl phosphonates as acyl anion equivalents that formed the expected acyl anion equivalents in the presence of cyanide. Ethylcyanoformate **125** was chosen as the acylation agent due to the presence of cyanide as a leaving group in the molecule. This would provide a constant presence of cyanide anion in the reaction mixture throughout of the reaction (Scheme 33) [43].

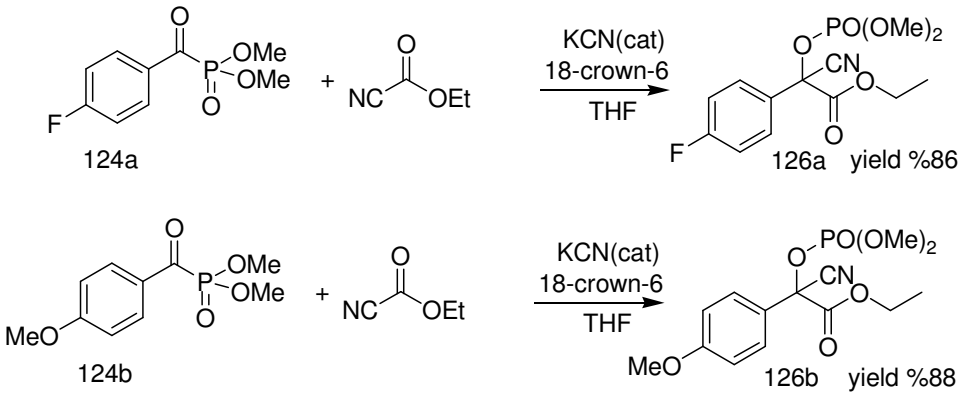
68 **125** **126**

Scheme 33 Addition of the acylphosphonate to ethylcyanoformate

The addition reaction did not provide any products in a variety of solvents. Considering the absence of an initiator to generate the very first acyl anion equivalents necessary for reaction to proceed, addition of catalytic amount of KCN was successful but limited. Since, there is a low solubility problem of KCN in typical

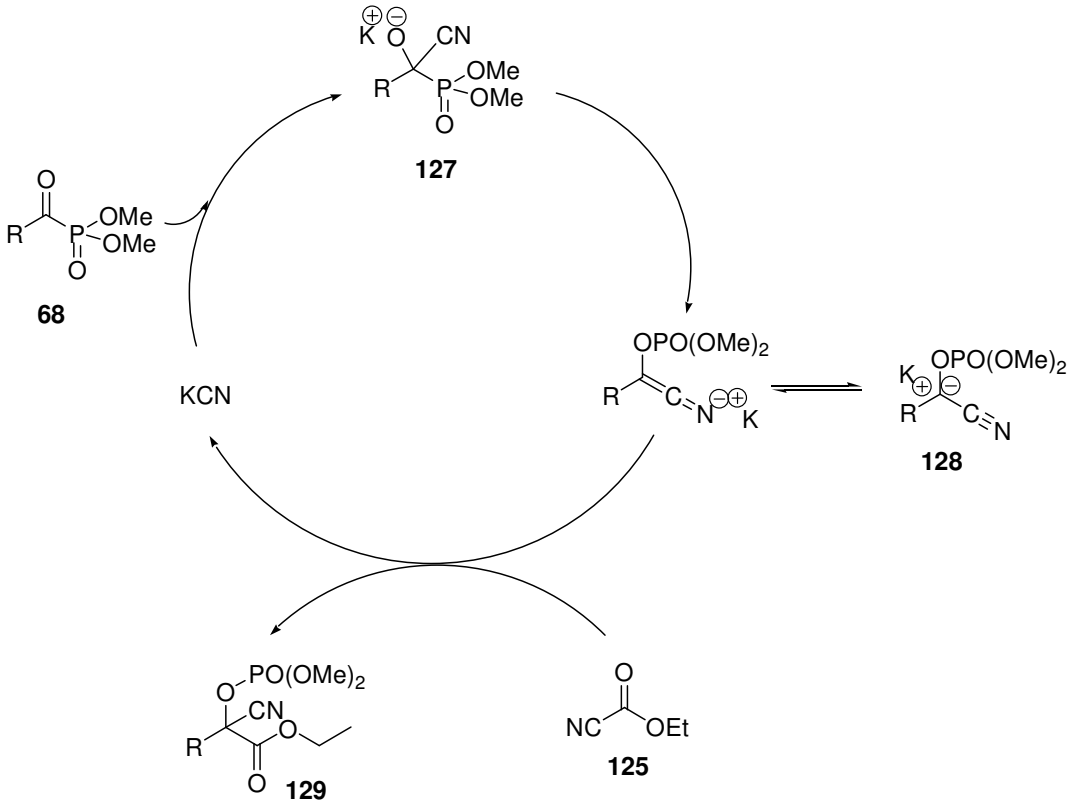
organic solvents. Thus, we decided to use phase transfer catalysis to increase the solubility of KCN. The use of crown ethers, such as 18-crown-6 is typical and it is widely used as a phase transfer catalyst. Therefore we examined the reaction in different organic solvents in the presence of catalytic amount of KCN and crown ether. All the reactions were complete in 15-20 min regardless of the solvent. Among the solvents tested, THF was the best in terms of yield and product purity.

After determining the optimum reaction conditions (5% 18-crown-6 and catalytic KCN in THF), two acylphosphonates **124a** and **124b** were tested with ethylcyanoformate in THF. The target compound **126a** and **126b** were obtained with high yield (Scheme 34).



Scheme 34 Addition of the acylphosphonate to ethylcyanoformate

The proposed reaction mechanism is that the cyanide ion's promoting rearrangement of acylphosphonates would provide the critical acyl anion equivalent. Reaction of this intermediate with ethylcyanoformate affords the product by releasing cyanide of ethylcyanoformate (Scheme 35) [43].



Scheme 35 Mechanism of addition of the acylphosphonate to ethylcyanoformate

CHAPTER 3

EXPERIMENTAL

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to C*H*Cl_3 (1H: δ= 7.26) and *C*DCl_3 (13C: δ = 77.0) as an internal standard; coupling constnats are reported in Hz. Column chromatography was conducted on silica gel 60 (mesh size 40-63 um). TLC was carried out on aluminum sheets precoated with silica gel 60F254 (Merck), and the spots were visualized with UV light (l = 254 nm).

3.1 Synthesis of Thiourea Catalysts

3.1.1 Synthesis of 2, 3-Dihydroxy-succinic acid dimethyl ester:

L-Tartaric acid (23.6 gr) and methanol (30 ml) was stirred in 50 ml $CHCl_3$. Then 0.1 ml of HCl was added to the solution and refluxed for 24 hours with a back Dean-Stark trap. The product was purified by vacuum distilation and obtained at 0.2 mmHg, 100°C. The product was obtained as a colorless dense liquid. MW: 178 Yield (% 97). ^{1}H NMR ($CDCl_3$) δ: 3.19 (d, 2H, J= 6.3 Hz), 3.86 (6H, s), 4.55 (d, 2H, J= 5.6 Hz)

3.1.2 Synthesis of 2-Phenyl-[1, 3] dioxalane-4, 5-dicarboxylic acid dimethyl ester:

Dimethyl tartarate (9.8 gr) and 5 ml benzaldehyde was dissolved in 120 ml benzene.

A catalytic amount of pTsOH was added to the solution and then the solution heated to reflux for 5 days under Dean-Stark trap. The product was purified by distillation and obtained at 1mmHg, 120°C. The product was obtained as a white crystall.
MW: 266.25 Yields (% 87).
^{1}H NMR ($CDCl_3$) δ: 3.71 (3H, s), 3.80 (3H, s), 4.74 (1H, s), 4.88 (1H, s), 6.01 (1H, s), 7.30-7.48 (5H, m).

3.1.3 Synthesis of 2-Phenyl-[1, 3] dioxalane-4, 5-dicarboxylic acid diamide :

NH_3 gas was passed over a solution of the diol protected dimethyl tartarate (4.5 gr) in 50 ml methanol for 15 minutes and then the solution was stirred for a night at 0°C. The solution was evaporated to dryness. MW: 236.22 Yield (%85)
^{1}H NMR ($CDCl_3$) δ: 4.72 (2H, s), 5.86 (1H, s), 6.08 (2H, d, J=48.83 Hz), 6.68 (2H, d, J=44.61 Hz), 7.30 (3H, broad s), 7.41 (2H, broad s); ^{13}C NMR ($CDCl_3$) δ:171.6, 170.4, 136.1, 129.6, 128.1, 127.2, 104.7, 77.9, 77.7

3.1.4 Synthesis of cis-(5-Aminoethyl-2-methy-2-phenyl-[1, 3]-dioxalan-4-yl)-methylamine:

Diamide **107** (3.45 g) was placed in a Soxhlet thimble and extracted into a refluxing suspension of lithium aluminum hydride (2.0 g) in anhydrous THF (200 mL). Refluxing was continued for 20 h and the suspension was cooled to room temperature. Water (2.0 mL) was added dropwise to the mixture, followed by 4N aqueous NaOH (2.0 mL) and water (6, 2 mL).The mixture was filtered, the resulting solid was washed with THF, and the combine filtrates were concentrated to afford the crude diamine (2.99 g) as pale brown oil. Crude ^{1}H NMR showed the formation of the product.

3.1.5. Synthesis of Thiourea Catalysts 112

Diamine **108** (258 mg) was dissolved in 5.6 mL THF and 1- isothiocynatobenzene (520 μL) was dropped via syringe to this reaction mixture at the room temperature. The mixture was then stirred at room temperature for overnight. Then, the volatile material was removed by rotary evaporation under reduced pressure. The remaining solid was dissolved in a minimum amount of diethylether and then n-hexane was added to prepicitate the desired product as nearly white solid. The solid was filtered off and washed with n-hexane several times and dried under reduced pressure. Yield (% 53)

^{1}H NMR ($CDCl_3$) δ: 3.85-3.97 (4H, m), 4.25-4.33 (2H, m), 5.82 (1H, s), 7.02 (2H, t, J= 7.3), 7.12-7.40 (15H, m), 8.83 (2H, b); ^{13}C NMR ($CDCl_3$) δ: 50.5, 51.2, 82.5, 83.5, 108.5, 129.5, 130.4, 130.5, 132.1, 133.4, 134.2, 134.4, 134.5, 143.1, 143.5, 143.8, 187.3, 187.4.

3.1.6 Synthesis of Thiourea Catalysts 113

Diamine **108** (115 mg) was dissolved in 2.5 mL THF and 1, 3-bis (trifluoromethyl)-5- isothiocyanatobenzene (364 μL) was dropped via syringe to this reaction mixture at the room temperature. The mixture was then stirred at room temperature overnight. Then, the volatile material was removed by rotary evaporation under reduced pressure. The remaining solid was dissolved in a minimum amount of diethylether and then was added n-hexane to prepicitate the desired product as nearly white solid. The solid was filtered and washed with n-hexane several times and dried under reduced pressure. Yield (% 51)

^{1}H NMR ($CDCl_3$) δ:3.79-4.01 (4H, m), 4.25-4.36 (2H, m), 5.91 (1H, s), 7.02-7.19 (2H, m), 7.32-7.36 (3H, m), 7.42-7.50 (2H, m), 7.62-7.67 (2H, m), 7.95-8.07 (4H, m), 8.54 (2H, b); ^{13}C NMR ($CDCl_3$) δ: 45.2, 45.7, 77.1, 77.8, 102.4, 123.2, 124.3 (d, J=11.8 Hz), 125.5, 126.8, 128.2, 128.6, 129.4, 137.3, 139.0 (d, J=18.7), 180.9.

3.1.7 Application of thiourea catalysts in Henry reaction

Benzaldehyde 0.1 mmol (10 μL) and catalysts **112** or **113** 0.02 mmol (3mg) were dissolved in 140 μL Et_3N.Then, 1 mmol (54.1 μL) nitromethane was added to reaction mixture. The reaction mixture was stirred for 6 hours at room temperature. After completion the reaction, mixture diluted with 5ml ether and 5 ml water. The aqueous phase was extracted with ether two times. Combined organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The product 2-nitro-1-phenylethanol **115** was obtained.

3.1.8 Application of thiourea catalysts in Aldol reaction

Proline 0.1 mmol (11.5 mg) and catalysts **112** or **113** 0.01 mmol (1.5 mg) was stirred in 1.6 ml hexane for 30 min. Then, 400 μL cyclohexanone was added to the reaction mixture. After addition of cyclohexanone, 0.5 mmol (75.5 mg) p-nitrobenzaldehyde was added. The reaction mixture was stirred over night. Then, the reaction mixture diluted with 5ml ether and 5 ml water. The aqueous phase was extracted with ether two times. Combined organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The product 2-(hydroxyl (4-nitrophenyl) methyl) cyclohexaneone **118** was obtained.

3.2 Synthesis of HDAC Inhibitors

3.2.1 (E)-methyl 2-oxo-4-phenylbut-3-enoate:

To a solution of pyruvic acid (20 mL), and benzaldehyde (31 mL) in 15 mL of methanol stirring in an ice bath, a solution of potassium hydroxide (24g) in 75 mL of methanol was added. The first 50 mL of the base solution was added slowly and the reaction temperature was kept below 25 ^{0}C. The ice bath was then removed and the rest of the base solution was added quickly. Firstly, yellow precipitate was formed. The reaction temperature was kept at 30 ^{0}C for 1 h and then the reaction was stirred

at zero temperature for overnight. The yellow crytals were filtered off and washed twice with cold methanol and once with ether. The yellow crystals were air dried to afford the potassium salt.

40 mL of sulfuric acid was added dropwise to 15 g of NaCl in 250 mL 2-necked round to generate hydrochloric acid. The hydrochloric acid gas was passing through mixture of the potassium salt and methanol. The mixture was stirred for five hours while the gas was passing. After then, the mixture was extracted with 20 mL of water and two times 20 mL of dicholoromethane. The combined organic phases were washed with saturated sodium bicarbonate and water. The organic phase was dried with anhydrous magnesium sulfate and evaporated. The yellow crystals were obtained. MW: 190.2

^{1}H NMR ($CDCl_3$) δ 3.8 (3H, s), 7.25 (1H, d, J=16Hz), 7.30-7.35 (3H, m), 7.52-7.56 (2H, m), 7.75 (1H, d, J=16 Hz); ^{13}C NMR ($CDCl_3$) δ 182.0, 162.5, 148.2, 134.0, 131.5, 129.1, 129.0, 120.5, 52.7.

3.2.2 (E)-methyl 4-(4-methoxyphenyl)-2-oxobut-3-enoate:

Pyruvic acid (20mL, 0.286 mol) and p-OMe benzaldehyde (0.286 mol) were stirred in 15 mL methanol at 0^0C in an ice bath.To cooled solution was added a solution of KOH in 5mL MeOH to maintain the temperature at 25 ^{0}C. After the addition of two-thirds of the alkali, the ice bath was removed and the rest of the alkali was run in rapidly. Immediately, the yellow color of the solution darkened to orange-red, the temperature rose to 35-40 ^{0}C and precipitiate of yellow potassium salt appeared.

24 mL of acetyl chloride was added to 140 mL of methanol at zero temperature to generate hydrochloric acid. The potassium salt (0.1 mol) was added and the mixture stirred for 30 min before the ice bath removed. After 2h the mixture was refluxed overnight. The reaction mixture was evaporated and the yellow solid was extracted with 20 mL of water and two times with 20 mL of dicloromethane. The combined organic phases were washed with saturated sodium bicarbonate and then 20 mL of water. The organic phase was dried with anhydrous magnesium sulfate and

evaporated. The yellow crystals were obtained via recrystallization from ethanol.MW:220.22

^{1}H NMR ($CDCl_3$) δ 3.78 (3H, s), 3.85 (3H, s), 6.84 (2H, d, J=8.6 Hz), 7.14 (1H, d, J= 16.0 Hz), 7.51 (2H, d, J=8.6 Hz), 7.74 (1H, d, J=16.0 Hz); ^{13}C NMR ($CDCl_{13}$) δ 181.8, 162.7, 162.5, 148.1, 130.9, 126.8, 118.2, 114.5, 55.2, 52.6.

3.3 Preparation of Acylphosphonate

Acylphosphonates **124a** and **124b** were synthesized according to literature procedures. Briefly, 1 equiv. of neat trimetylphosphite was added drop wise onto the neat acylchloride in a water bath under a positive inert atmosphere. After completion of the adddition, resulting mixture was stirred at room temperature for 60 min. The product was purified by vacuum distillation.

3.4 General Procedure for Addition of the Acylphosphonate to Ethylcyanoformate

An oven dried Schlenk flask with a magnetic stir bar was charged with 0.5 mmol of acylphosphonate. Subsequently, 1 mL dry THF, 0.6 mmol ethyl cyanoformate, 0.025 mmol 18-crown-6, and a tip of spatula KCN was added under argon. The reaction was monitored by TLC (completed within 15-20 min.). After the completion of the reaction, the reaction was extracted with ether and brine three times. The organic phases were combined and concentrated under reduced vacuum. If needed, the crude product was purified with automatic flash column chromatography ether-petroleum ether as eluent.

(Ethoxycarbonyl)(cyano)(4-fluorophenyl)methyl dimethyl phosphate(126a):

Yield (86%) yellow liq.; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, *J*=6.3 Hz), 3.79 (3H, d, *J*=11.7 Hz), 3.88 (3H, d, *J*=11.7 Hz), 4.20-4.31 (2H, m), 7.05-7.11 (2H, m), 7.60-7.65 (2H,m) ^{13}C NMR ($CDCl_3$) δ 13.6, 55.0 (d, *J*=6.0 Hz), 55.3 (d, *J*=6.0 Hz), 64.4, 76.1 (d, *J*=6.1

Hz), 115.2, 116.2 (d, *J*=22.4 Hz), 127.9 (d, *J*= 8.8 Hz), 128.6 (d, *J*=67 Hz), 163.4 (d, *J*=150.6 Hz), 165.1; ^{31}P NMR ($CDCl_3$) δ −1.64 ppm .

(Ethoxycarbonyl)(cyano)(4-methoxyphenyl)methyl dimethyl phosphate(126b):

Yield (88%) yellow liq.; ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, *J*=6.7 Hz), 3.76 (3H, s), 3.77 (3H, d, *J*=11.5 Hz), 3.86 (3H, d, *J*=11.5 Hz), 4.19-4.30 (2H, m), 6.88 (2H, d, *J*= 8.5 Hz), 7.54 (2H,d, *J*= 9.1); ^{13}C NMR ($CDCl_3$) δ 12.7, 53.9 (d, *J*= 6.6 Hz), 54.2 (d, *J*=6.6 Hz), 54.4, 63.2, 75.5 (d, *J*=6.7 Hz), 113.4, 114.4, 123.4 (d, *J*= 9.4 Hz), 126.3, 160.3, 163.4 ; ^{31}P NMR ($CDCl_3$) δ −2.29 ppm .

CHAPTER 4

CONCLUSION

This study can be divided in three parts. First one is the synthesis of new chiral urea derivatives as organocatalysis, second part is synthesis of some HDAC inhibitors and last part is synthesis and reaction of acylphosphonates.

At the beginning of this decade, a new approach has been established which contends that small organic molecules, organocatalysts, can be highly selective and efficient catalysts. In addition, thiourea derivatives have become a main focus of research in asymmetric synthesis as organocatalysts. Thus, in the first part of study, we designed and synthesized new two-centered thiourea catalysts. We applied these catalysts in some reactions, however; we did not observe any optically active products.

Moreover, histone deacetylases (HDAC) are enzymes that play an important role in modifying chromatin structure and regulating gene expression. A number of HDAC inhibitors have been developed as anti-cancer agents. In the second part of study, we synthesized aryl butenoic acid derivatives as HDAC inhibitors and their inhibition constant and free energy of binding were calculated. After calculation, we showed that the compounds are better or near the well-known HDAC inhibitors.

In the third part; since acylphosphonates were found so effective for carbonyl acylation in terms of yields, purity of product and reaction times, we synthesized acylphosphonates. Then, we used these acylphosphonates with ethylcyanoformate.

REFERENCES

1. Berkessel, A.; Gröger, H., *Asymmetric Organocatalysis*, VCH, Weinheim, **2004**

2. Seayad, J.; List,B., *Org. Biomol. Chem.*, **2005**, 3, 719-724

3. Jen ,W. S.; Wiener, J. J. M; MacMillan, D.W. C., *J. Am. Chem. Soc.* **2000,** 122, 9874-9875

4. (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed. Eng*. **1971**, 10, 496-497. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, 38, 3239-3243. (c) Hajos, Z.G.; Parrish, D. R. *J. Org. Chem.* **1974,** 39, 1615-1621.

5. (a) List, B.; Lerner ,R. A ; Barbas ,C. F., *J. Am. Chem. Soc.*, **2000,** *122,* 2395–2396; (*b*) Notz, W.; List, B.; *J. Am. Chem. Soc.*, **2000**, 122, 7386–7387; (*c*)List, B.; Pojarliev, P.; Castello, C., *Org. Lett.*, **2001**, 3, 573–575; (*d*) Bahmanyar, S.; Houk, K. N.; Martin ,H. J.; List, B., *J. Am. Chem. Soc.*, **2003,** 122, 2475–2479; (*e*) Pidathala ,C.; Hoang, L.; Vignola ,N.; List ,B. , *Angew. Chem., Int. Ed.*, **2003***,* 42, 2785–2788.

6. (*a*) Northrup, A. B. ;. MacMillan ,D. W. C, *J. Am. Chem. Soc.*, **2002,** 124, 6798–6799; (*b*) Bøgevig, A.; Kumaragurubaran, N.; Jørgensen ,K. A., *Chem.Commun.*, **2002**, 620–621; (*c*) Chowdari ,N. S.;.Ramachary ,D.B.; Cordova ,A.;.Barbas ,C.F,*Tetrahedron Lett.*, **2002,** 43*,* 9591–9595; (*d*) Cordova, A.; Notz ,W. ; Barbas, C. F., *J. Org. Chem.*, **2002,** *67,* 301

7. Maruoka , K.; Ooi ,T., *Chem. Rev.*, **2003**, 103*,* 3013–3028.

8. Dolling, U.-H.; Davis, P.; Grabowski, E. J. J., *J. Am. Chem. Soc.*,**1984,** 118, 446–447

9. Corey, E. J.; Xu, F.; Noe, M. C., *J. Am. Chem. Soc.*, **1997**, 119, 12414–12415

10. Corey, E. J.; Grogan, M. J., *Org. Lett.*, **1999**, 1, 157–160.

11. Nugent, B. M.; Yoder, R. A.; Johnston, J. N., *J. Am. Chem*. Soc., **2004**, 126, 3418–3419

12. McDougal, N. T. ; Schaus, S E., *J. Am. Chem. Soc.*, **2003**, 125, 12094–12095

13. Akiyama ,T.; Itoh, J.; Yokota, K.; Fuchibe K., *Angew. Chem.*, **2004**, 116, 1592–1594

14. Taylor, M. S.; Jacobsen, E. N. ,*Angew. Chem. Int. Ed*. **2006**, 45, 1520 – 1543

15. a) Sigman, M. S.; Jacobsen ,E. N., *J. Am. Chem. Soc***. 1998,** 120, 4901 – 4902; b) Vachal, P.; Jacobsen, E. N., *Org. Lett***. 2000**, 2, 867 – 870; c). Sigman ,M. S; Vachal, P. ;. Jacobsen ,E. N, *Angew. Chem***. 2000**, 112, 1336 – 1338; *Angew. Chem. Int. Ed.* **2000,** 39,
1279 – 1281.

16. Joly ,G. D.; Jacobsen ,E. N., *J. Am. Chem. Soc*. **2004**, 126, 4102 –4103

17. Yoon, T.P; Jacobsen, E. N., Angew. *Chem. Int. Ed*. **2005**, 44, 466 –468

18. Okino, T.; Hoashi, Y.; Takemoto, Y., *J. Am. Chem. Soc*. **2003**, 125, 12672-12673

19. Okino, T.; Hoashi Y.; Furukawa,T.; Xu ,X.; Takemoto,Y., *J. Am. Chem. Soc*. **2005**, 127, 119-125

20. Tanaka, K.; Toda, F., *J. Chem. Soc. Chem. Commun*. **1983,** 593 – 594.

21. Huang, Y. ; Unni, A. K; Thadani, A. N. ; Rawal, V. H. , *Nature* **2003,** 424, 146

22. Huang, Y. ; Rawal, V. H. ; *J. Am. Chem. Soc.* **2002,** 124, 9662 – 9663.

23. Somoza, J. R.; Skene, R. J.; Katz, B. A., *Structure*, **2004**. 12, 1325–1334.

24. KrennHrubec ,K.; Marshall, B.L.; Hedglin, M.;.Verdin ,E ; Ulrich, S.M. *Bioorg.Med.Chem. Lett. **2007***, 17 ,2874-2878

25.Liu ,T; Kapustin ,G.; Etzkorn, F.A. ,*J.Med.Chem*. **2007**, 50 ,2003-2006

26. Lee, H.;.Sengupta, N.; Villagra, A. ; Rezai-Zadeh, N.; Seto, E., *Mol. Cell. Biol.*,**2006**, 26, 5259-5269

27. (a) Hammerschmidt, F.; Schmidt, S. *Eur. J. Org. Chem*. **2000**, 2239. (b) Hammerschmidt, F.; Hanbauer, M. *J. Org. Chem*. **2000**, *65*, 6121.

28. Chopard, P. A.; Clark, V. M.; Hudson, R. F.; Kirby, A. J. *Tetrahedron*, **1965**, *21*, 1961

29. McConnell, R. L.; Coover Jr, H. W. *J. Am. Chem. Soc*. **1956**, *78*, 4450.

30. Fitch, S.; Moedritzer, K. *J. Am. Chem. Soc*. **1962**, *84*, 1876.

31. (a) Nicholson, A.; Vaughn, H. *J. Org. Chem.* **1971**, *36*, 3843. (b) Nguyen, L. M.; Niesor, E.; Bentzen, C. L. *J. Med. Chem.* **1987**, *30*, 1426. (c) Pachamuthu, K.; Schmidt, R. R. *Chem. Comm*. **2004**, 1078.

32. Demir A. S.; Reis O.; Iğdir A. C.; Esiringü İ.; Eymur S. *J. Org. Chem.*, **2005**, 10584.

33. Demir A. S.; Reis O.; Esiringü İ.; Reis B.; Baris S. *Tetrahedron*, **2007**,160

34. Kim,D. Y. ; Wiemer, D. F. *Tet. Lett.* **2003**, 44, 2803

35. Sampak Samanta, S.; Zhao, C. G. *J.Am.Chem. Soc* **2006**,128,7442

36. Demir A. S.; Reis O.; Kayalar M.; Eymur, S.;Reis B.; *Synlett* **2006** ,19,3329

37.. Kim, B. M.; Bae, S.J.; So, S.M.; Yoo, H.T.; Chang,S.K.; Lee,J.H.; Kang J.S.,*Org.Lett***. 2001**, 3, 2349-2351

38. List, B.; Lerner, D.A.; Barbas, C. F., *J. Am. Chem. Soc.* **2000**, 122, 2395-2396.

39.Dayangac E.D.; Ayhan, P.; Bora, G.; Yelekçi,K.;.Dalkara, S.; Demir, A.S., Abstracts of papers, 234th ACS National Meeting , Boston, MA, United States, August 19-23 **2007**

40. Humprey ,W.; Dalke, A.; Schulten, K.,*J.Molec.Graphics*, **1996,** 14, 33-38

41. Maeda, H.; Takahashi, K.; Ohmori, H. *Tetrahedron*, **1998**, *54*, 12233

42. (a) Berlin, K. D.; Taylor, H. A. *J. Am. Chem. Soc*. **1964**, *86*, 3862. (b) Kim, S.; Cho, C. H.; Lim, C. J. *J. Am.Chem. Soc*. **2003**, *125*, 9574.

43. Demir A. S.; Reis B.; Reis O.; Eymur S.; Tural S.; Göllü M.; Saglam G. *J. Org. Chem.*, **2007**, 7439.

APPENDIX A

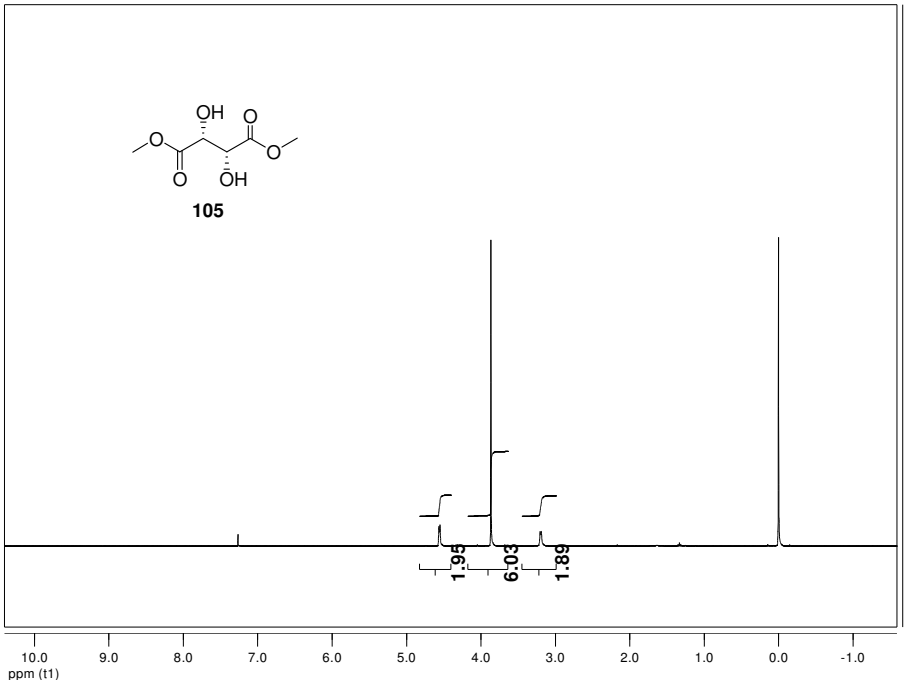


Figure 16 ^{1}H-NMR of **105**

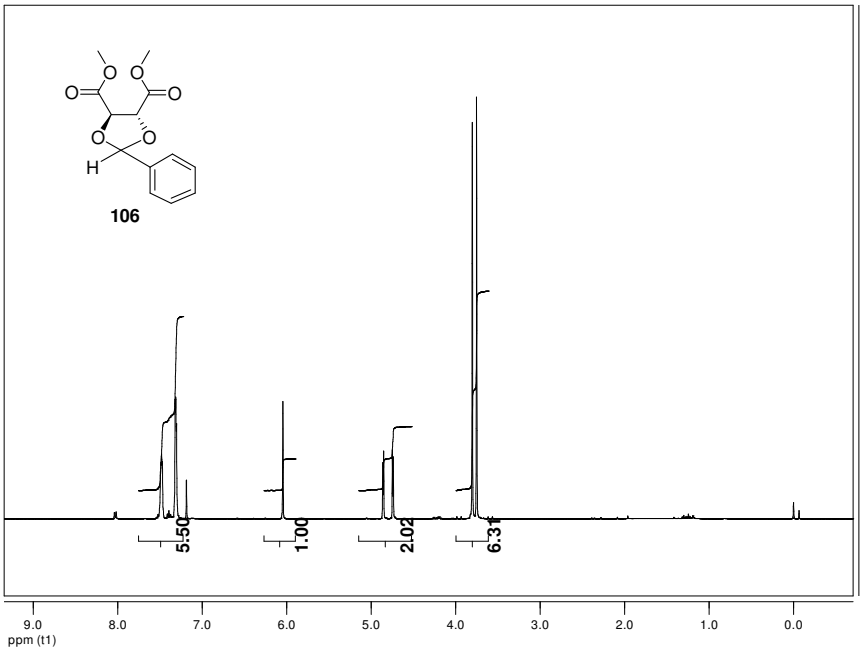


Figure 17 ^{1}H-NMR of **106**

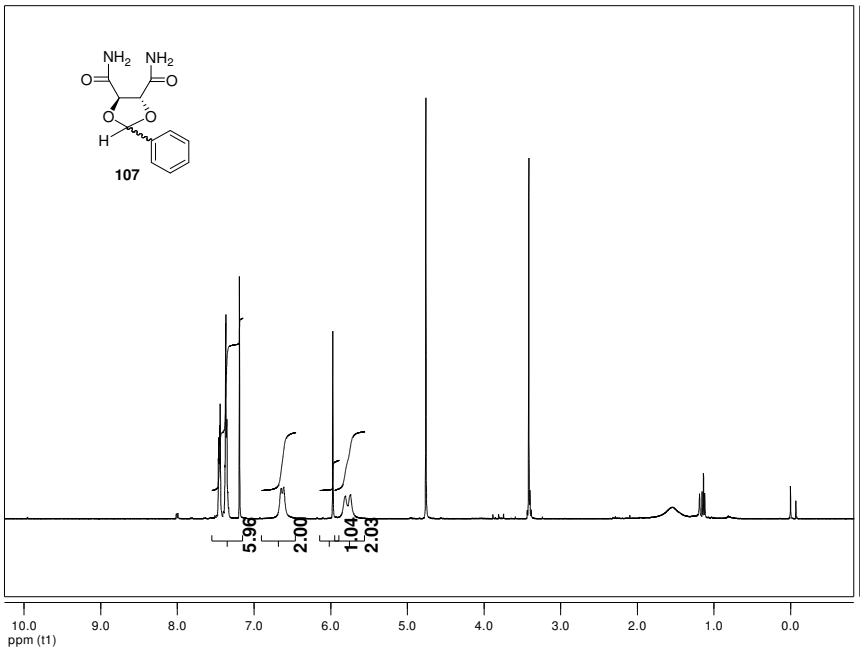


Figure 18 ^{1}H-NMR of **107**

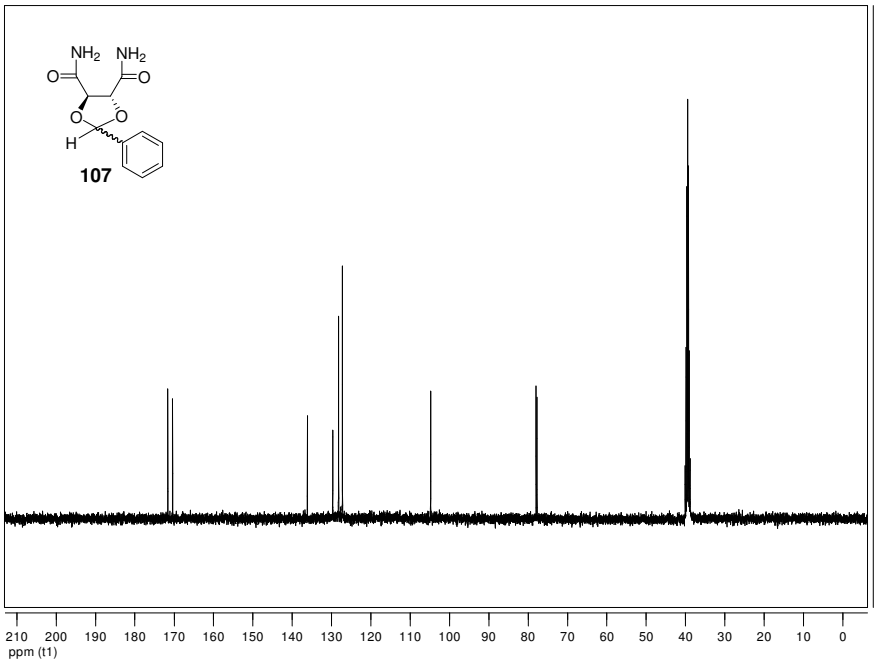


Figure 19 ^{13}C-NMR of **107**

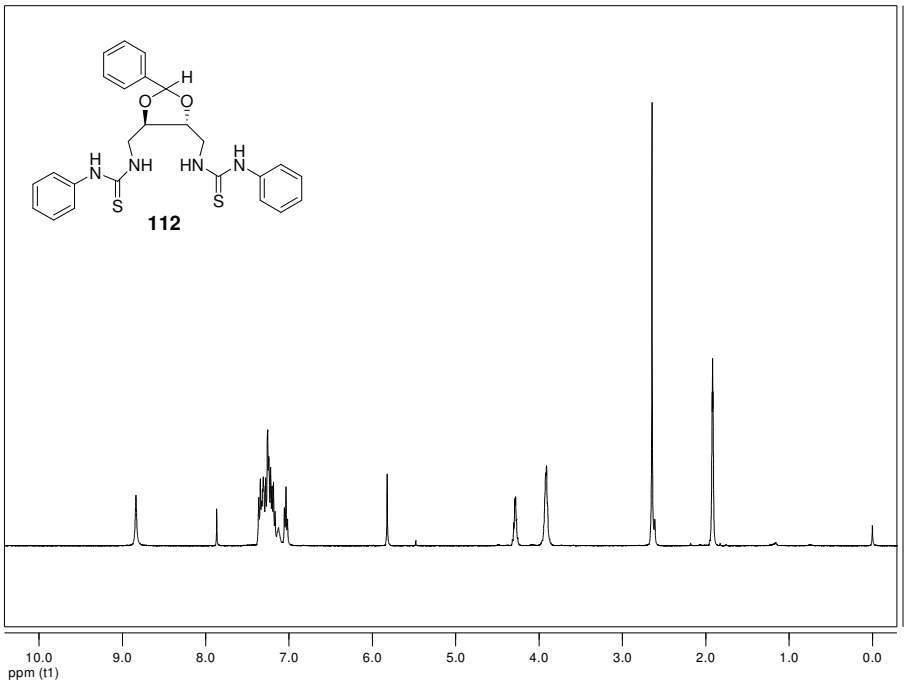


Figure 20 ^{1}H-NMR of **112**

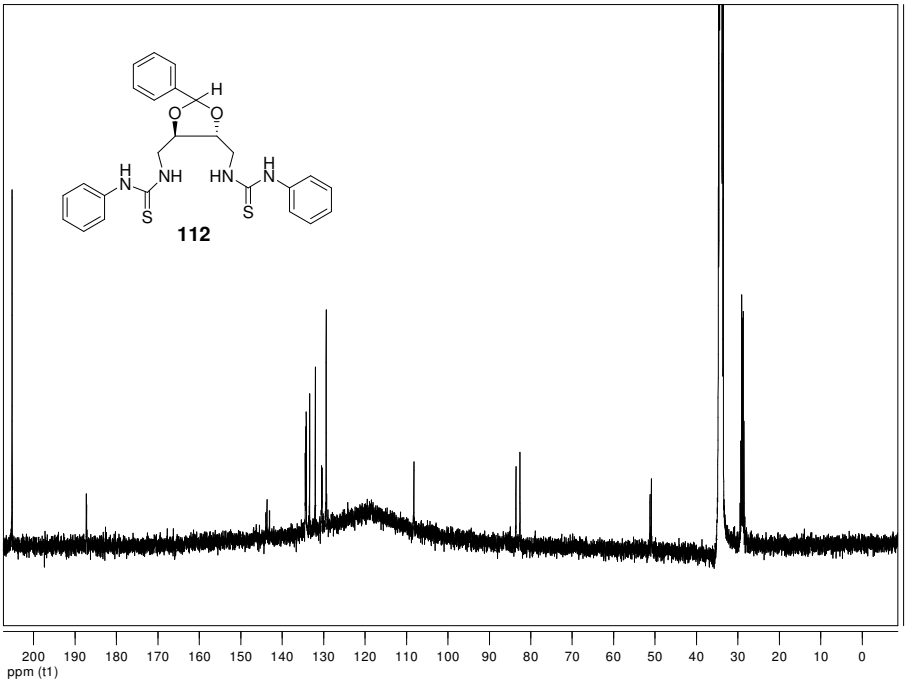


Figure 21 ^{13}C-NMR of **112**

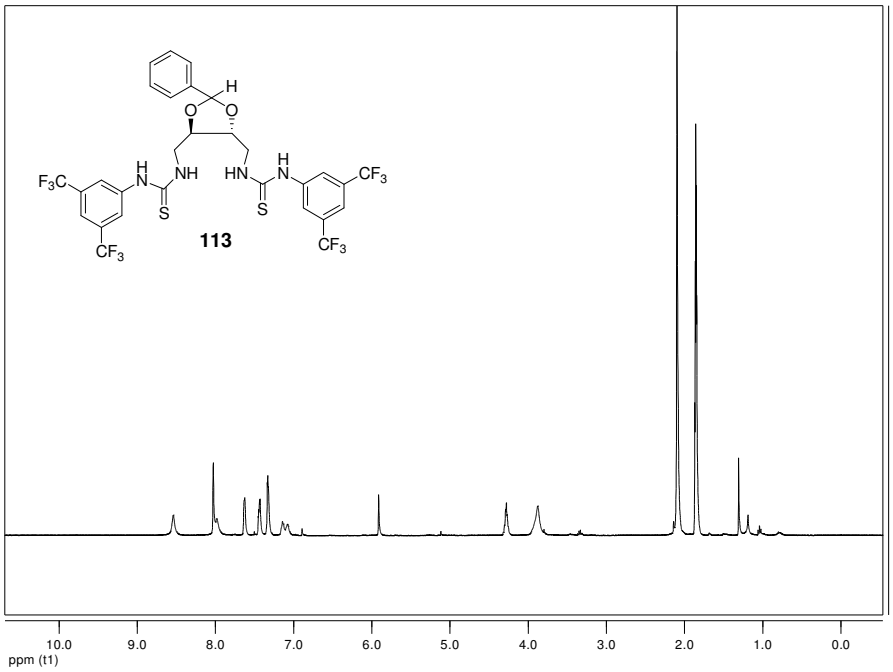


Figure 22 ^{1}H-NMR of **113**

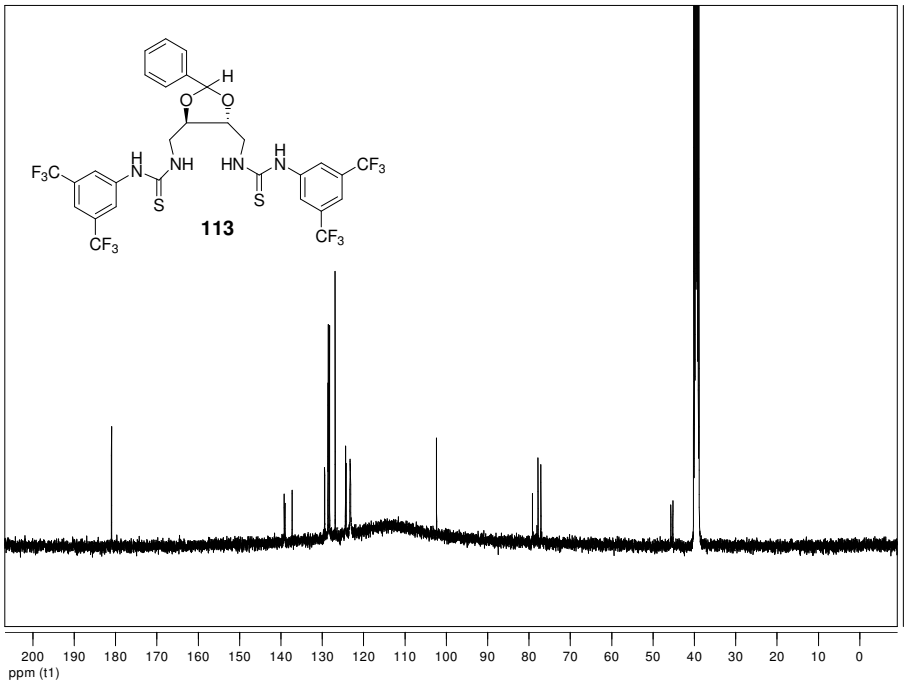


Figure 23 ^{13}C-NMR of **113**

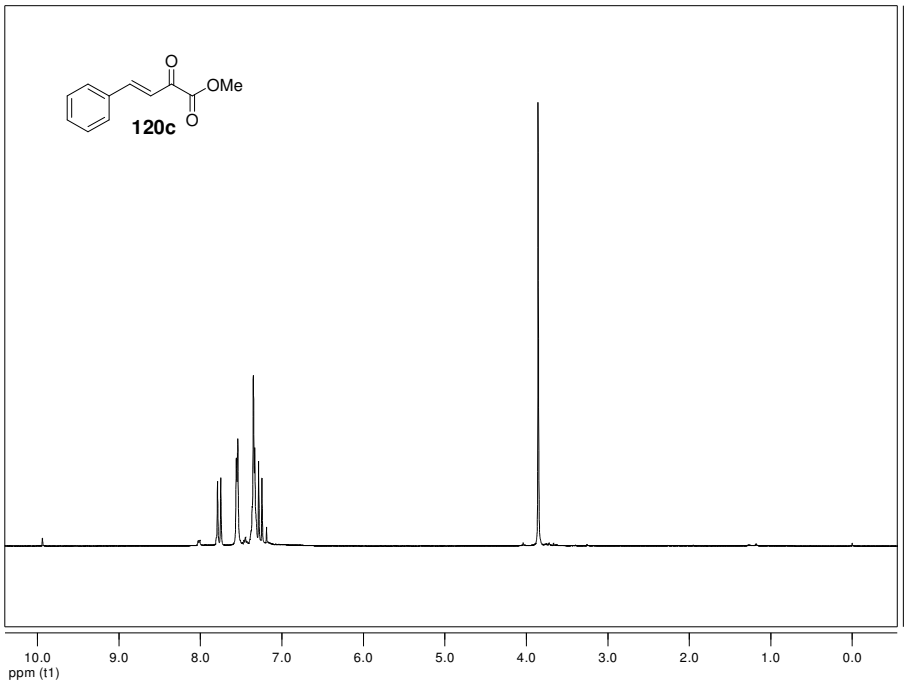


Figure 24 ^{1}H-NMR of **120c**

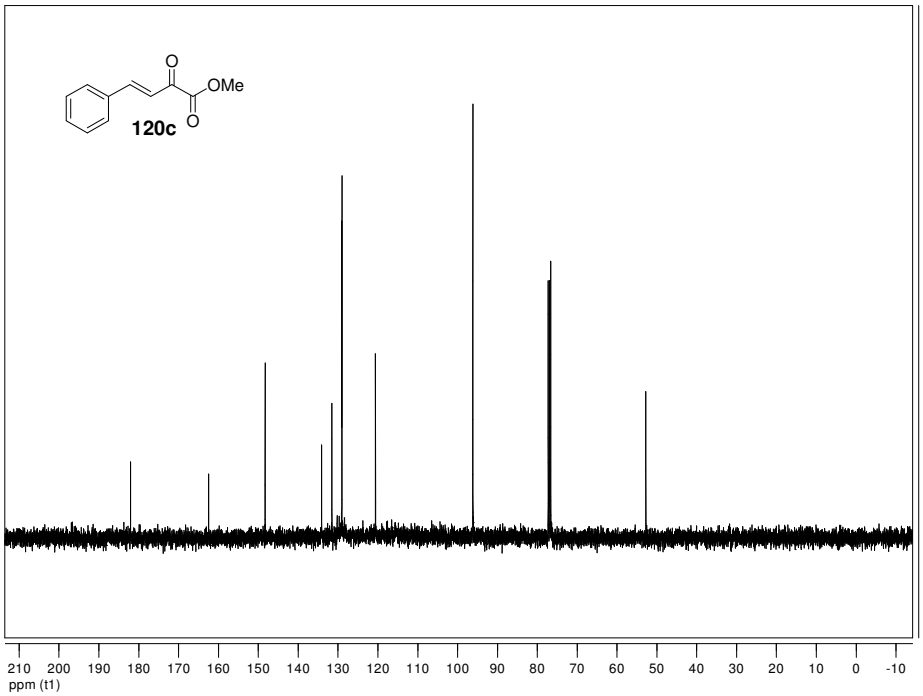


Figure 25 ^{13}C-NMR of **120c**

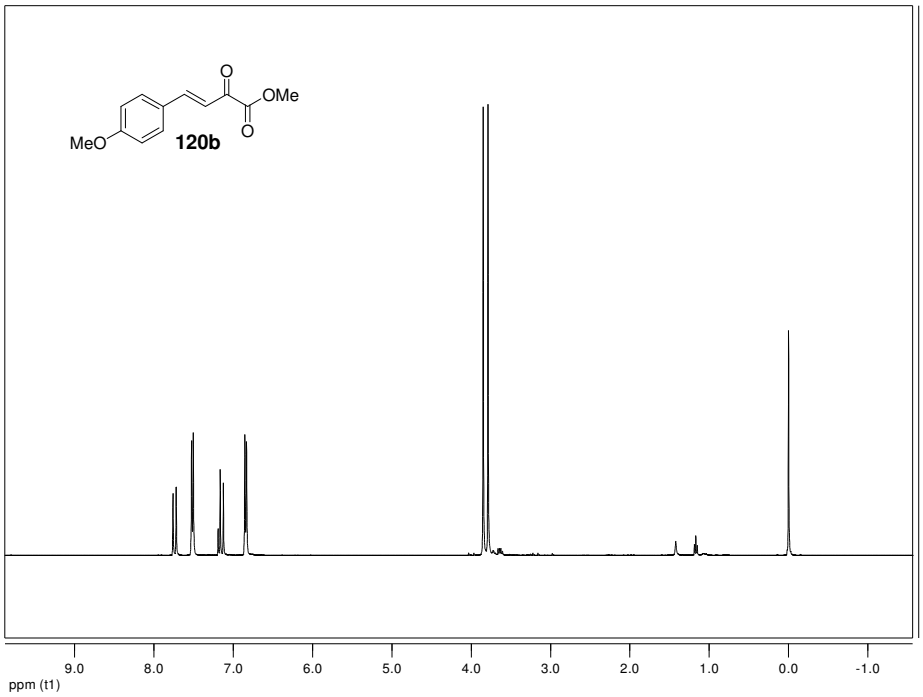


Figure 26 ^{1}H-NMR of **120b**

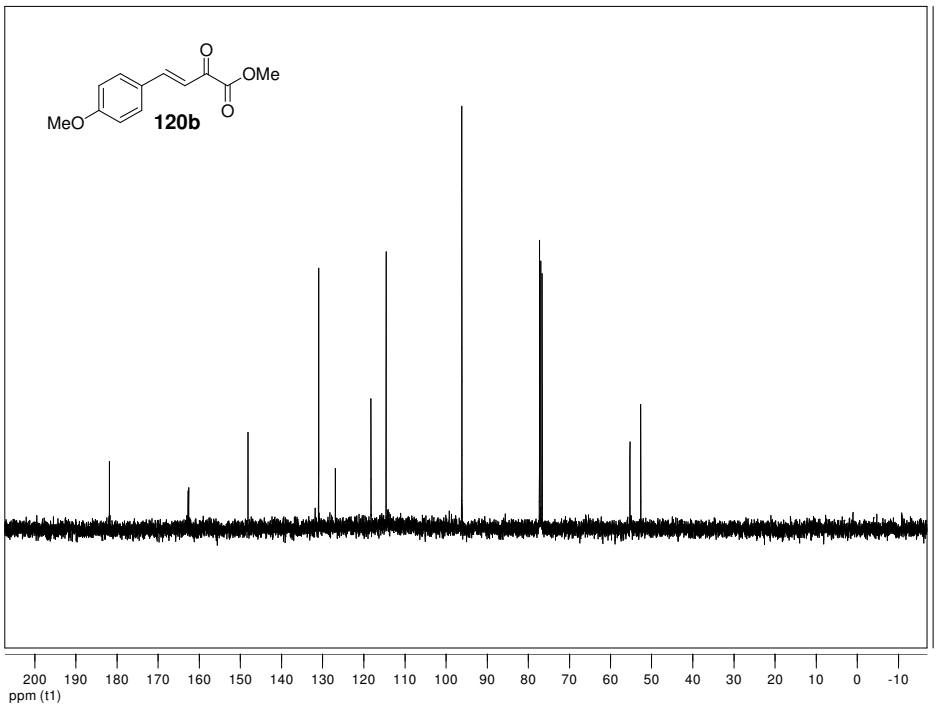


Figure 27 ^{13}C-NMR of **120b**

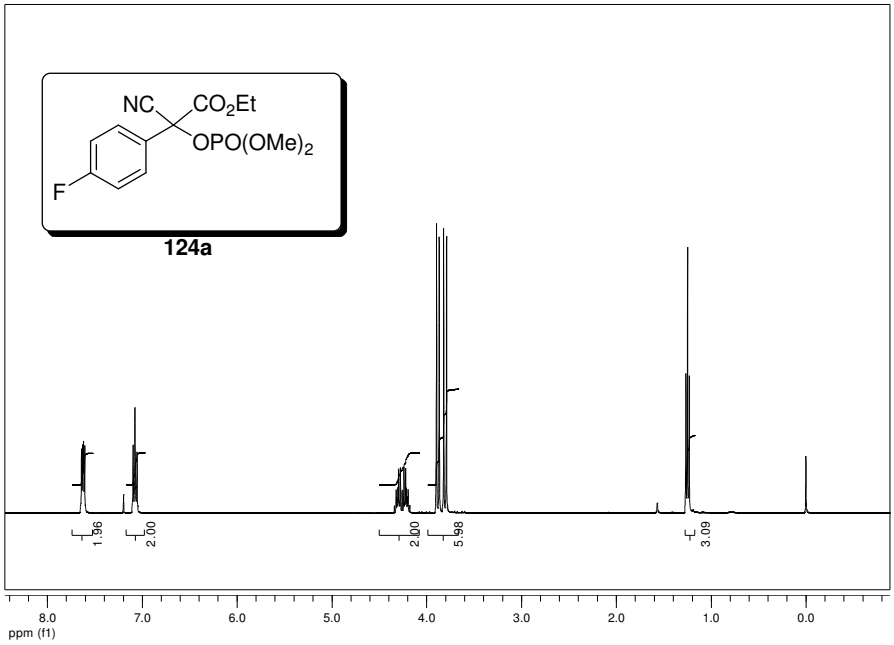


Figure 28 ^{1}H-NMR of **124a**

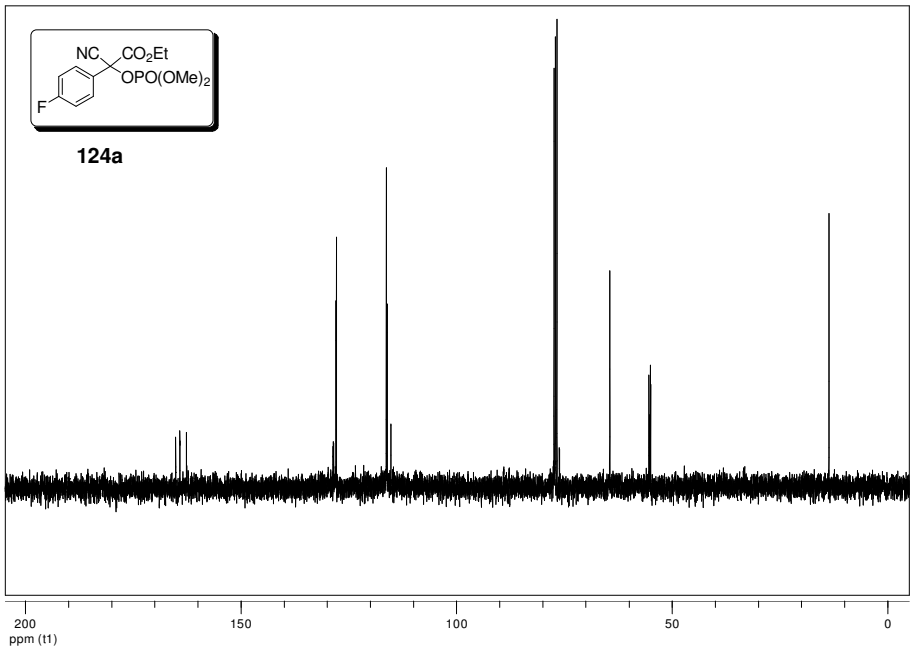


Figure 29 ^{13}C-NMR of **124a**

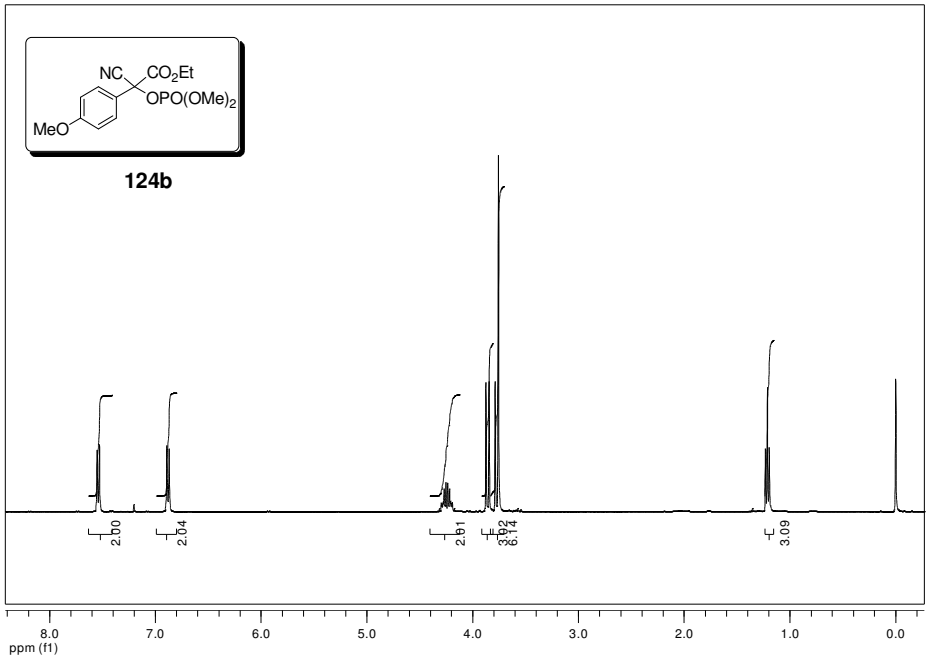


Figure 30 ^{1}H-NMR of **124b**

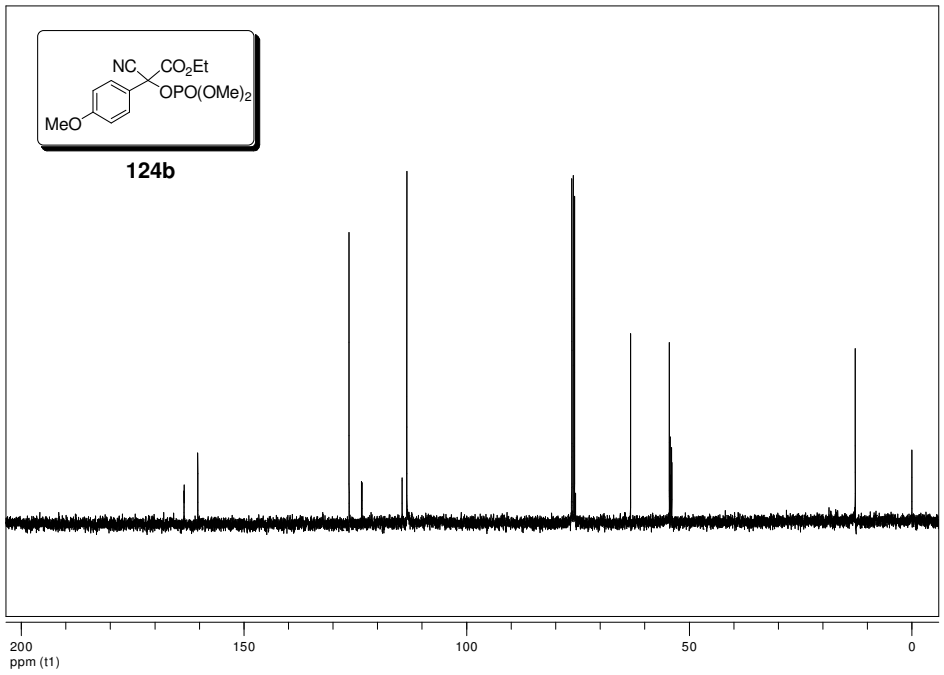


Figure 31 ^{13}C-NMR of **124b**