CINCHONA ALKALOID BASED BIFUNCTIONAL UREA CATALYZED ENANTIOSELECTIVE ALDOL REACTIONS BETWEEN ALPHA AZIDO KETONES AND ALPHA OXO ESTERS

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

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ABSTRACT

CINCHONA ALKALOID BASED BIFUNCTIONAL UREA CATALYZED ENANTIOSELECTIVE ALDOL REACTIONS BETWEEN ALPHA AZIDO KETONES AND ALPHA OXO ESTERS

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2-Azido-3-hydroxy-1,4-diones are valuable multifunctional synthons for many synthetic transformations. Selective manipulations of different functionalities of these compounds make them potential precursors for the synthesis of α-amino ketones, azido alcohols, 1,2-amino alcohols, phosphoranes and 1,2,3-triazoles. Chemoselective reduction of azide group leads to 1,2-amino alcohols which are great importance in pharmacological research on analgesics, anaesthetics etc. Due to the well-known stereoselectivity of receptorial centers in the cell, asymmetric synthesis of enantiopure drug intermediates are essential. In this project, we developed a new method for the asymmetric synthesis of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates by chiral base promoted aldol addition of α-azido ketones to ethyl pyruvate. By the deprotonation of highly acidic alpha protons, α-azido ketones gain nucleophilic property and resulting carbanion readily reacts with electrophilic carbonyl moiety. Moreover, chiral bifunctional cinchona alkaloid-urea organocatalyst offers not only chiral induction in the product, but also simultaneous activation of nucleophile and electrophile. In the first part, after the synthesis of α-azido ketones according to the literature procedure, several parameters such as solvent, catalyst loading, substrate concentration and temperature were screened for the aldol addition. In the second part, derivatization of products was performed at optimized reaction conditions. Consequently, high diastereoselectivities up to 18: 1 and good enantioselectivities up to 81% enantiomeric excess were achieved in the desired products.

Keywords: aldol addition, asymmetric organocatalysis, α-azido ketones, bifunctional urea, cinchona alkaloids

ÖZ

BİFONKSİYONEL KİNKONA ALKALOİT-ÜRE KATALİZÖRLÜĞÜNDE ALFA AZİDO KETON VE ALFA OKSO ESTERLERİN ENANTİYOSEÇİCİ ALDOL REAKSİYONU

Okumuş, Seda
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Mayıs 2013, 76 sayfa

2-Azido-3-hidroksi-1,4-dionlar çoklu fonksiyonel gruplara sahip olduklarından sentetik dönüşümler için kıymetli yapı birimleridir. Yapı içinde fonksiyonel grupların seçiçi olarak başka fonksiyonel gruplara dönüştürülmesi bu yapıları α-amino ketonlar, azido alkoller,1,2 diamino alkoller, fosforanlar ve 1,2,3- triazollerin sentezi için önemli öncü maddeleri haline getirmiştir. Azit grubunun kemoselektif indirgenmesi sonucunda elde edilen 1,2-amino alkoller analjezik, anestezik v.b. ilaçları kapsayan farmakolojik araştırmalarda önemli bir yere sahiptir. Hücre reseptörlerinin stereoseçici yapılara sahip olması ilaç hammaddelerinin enantiosaf bir şekilde sentezlenmesini gerektirmektedir. Bu projede, kiral baz eşliğinde α-azido ketonların, etil purivata aldol katılmasıyla, 4-aril-3-azido-2-hidroksi-2-metil-4-oksobütanoatların asimetrik sentezi için yeni bir metod geliştirilmiştir. α-azido ketonların oldukça asidik alfa protonlarının deprotonasyonu sonucunda elde edilen nükleofilik karbanyon, elektrofilik karbonil grubuyla kolaylıkla reaksiyona girer. Kullanılan kiral bifonksiyonel kinkona alkaloit-üre organokatalizörü kiraliteyi sağlamanın yanı sıra reaksiyon sırasında nükleofil ve elektrofilin eşzamanlı aktivasyonunu gerçekleştirmektedir. İlk kısımda α-azido ketonların literatürde bilinen yöntemlerle sentezinden sonra, aldol reaksiyonu için çözücü, katalizör miktarı, substrat konsantrasyonu ve sıcaklık gibi parametreler tarandı. İkinci kısımda ise ilk aşamada belirlenen optimum reaksiyon şartlarında ürünler türevlendirildi. Sonuç olarak istenilen ürünlerin sentezi, 18:1'e kadar yüksek diastereoseçicilik ve 81% kadar iyi düzeyde enantiomerik fazlalıkla başarıyla gerçekleştirilmiştir.

Anahtar Kelimeler: aldol reaksiyonu, asimetrik organokataliz, α-azido ketonlar, bifonksiyonel üre, kinkona alkaloitler

To my beloved mother and Prof. Dr. Ayhan Sıtkı Demir

Rest in Peace…

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LIST OF ABBREVIATIONS

DOPA: 3,4-dihydroxyphenylalanine

DABCO: 1,4-diazabicyclo[2.2.2]octane

QN: Quinine

QD: Quinidine

CN: Cinchonine

CD: Cinchonidine

DHQD: Dihydroquinidine

DIAD: Diisopropyl azodicarboxylate

BOC: *tert*-Butyloxycarbonyl

TBS: tert-Butyldimethylsilyl

LG: Leaving group

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DMAD: Dimethyl acetylenedicarboxylate

TMEDA: *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine

$(DHQD)_2AQN$: Hydroquinidine (anthraquinone-1,4-diyl) diether

$(DHQD)_2Pyr$: Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether

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CHAPTER 1

INTRODUCTION

1.1 Organocatalysis

"Organocatalysis" as a term states the acceleration of a chemical reaction by the assistance of a stoichiometric or catalytic amount of small organic molecules [1]. The birth of "organocatalysis" was almost 50 years ago and it received the attention it had deserved by the pioneering contributions of chemists such as Barbas, List, Jacobsen and Jørgensen. Over the last 15 years the growth of the field so astonishing that there is hardly any day without a publication on a new organocatalytic reaction [2].

In various enantioselective transformations, such low-molecular weight organic molecules serve as efficient and selective catalysts. Acceleration in transformations occurs as a result of the covalent or non-covalent interactions between the catalysts and the organic substrates. The former type of interaction includes the generation of covalent adducts through the catalytic cycle and named as covalent catalysis. The subsequent type, non-covalent interaction, is based on hydrogen bonding or the ionic interaction of charged species [3]. In both cases, organocatalyst, as any catalyst, accelerates the transformation by offering a new reaction pathway with lower activation barrier (Figure 1).

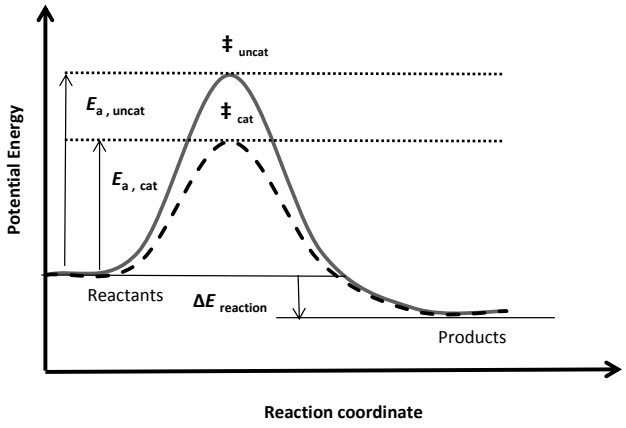


Figure 1. A reaction coordinate diagram for catalyzed and uncatalyzed reactions

Enantioselective organocatalysis has become a useful synthetic tool and hastened the expansion of new strategies to make a variety of chiral compounds. Its ease in application, ready availability and low toxicity, makes enantioselective organocatalysis attractive for the generation of complex structures. Providing mild, simple and practical paradigm for the synthesis of functionalized molecules with high enantiopurity, enantioselective catalysis has had significant effect especially on pharmaceutical industry over the past decade [4].

1.1.1 Advantages of organocatalysis

Until recently, the catalysts employed for enantioselective transformations have been classified in two groups mainly; metal complexes and enzymes. Previously there was a certain belief such that only man-made transition metal complexes can be employed to form either enantiomer of a chiral adduct whereas enzymes cannot. However, this view has changed after the advances in biocatalysis such as the discovery of preperatively useful enzymes from novel organisms and application of them in industrial scale for the production of enantiomerically pure fine chemicals [2].
Besides the extremes of transition metal catalysis and biocatalysis, a third class of asymmetric catalysis, which is organocatalysis, has arisen. In contrary to organic ligands with transition metal complexes, organocatalysts catalyze the reactions itself, no transition metals are required. No need for metals prevents the residue of toxic traces of heavy metals in compounds intolerant of contamination, e.g. pharmaceuticals. Addition to this they are readily available, robust, low-cost and non-toxic. Because of being inert toward moisture and oxygen, generally it does not require demanding reaction conditions such as inert atmosphere, low temperature or extra dry solvents [2].

1.1.2 The advent and development of organocatalysis

The interest in the field of organocatalysis has increased dramatically over the past decade. Besides its advantages mentioned before, according to MacMillan (2008) there are mainly two more factors implementing the sudden birth and impressive evolution of organocatalysis as a field [5];

1. Conceptualization of the field
2. Generic modes of catalyst activation, induction and reactivity

Although the use of small organic molecules as catalysts has been known for more than a century, its acceptance as research area is almost new. The main reason for this oversight is that researchers cannot work on undefined problems. Even though a few works on the low molecular weight molecules used as catalysts for asymmetric transformations were reported between 1968 and 1997, these were not enough to extrapolate general concepts on organocatalysis.

However at the end of the 1990s, works of Yian Shi [6], Scott Denmark [7] and Dan Yang [8] on enantioselective epoxidation of simple alkenes, description of hydrogen-bonding catalysis in an asymmetric Strecker reaction by Eric Jacobsen [9] and Elias J. Corey [10] and then the peptide catalyzed kinetic resolution of alcohols by Scott Miller [11] and his co-workers enlightened that the use of small organocatalysts can solve important problems in chemical synthesis. Recognition of organocatalysis as a concept by chemical synthesis communities has happened just after two important publications; one of them was on enamine catalysis, by Carlos Barbas, Richard Lerner and Benjamin List [12], and the other on iminium catalysis, by MacMillan research group in 2000 [13]. Describing the underlying

mechanisms and general activation strategy, these works showed that broader application of organocatalysis for extended transformations are possible [5].

According to the research conducted by ISI Web of Knowledge in 2008, the word "organocatalysis" or related words has been used in the title of more than 600 articles and become the subject of more than 40,000 web pages (Figure 2) [5].

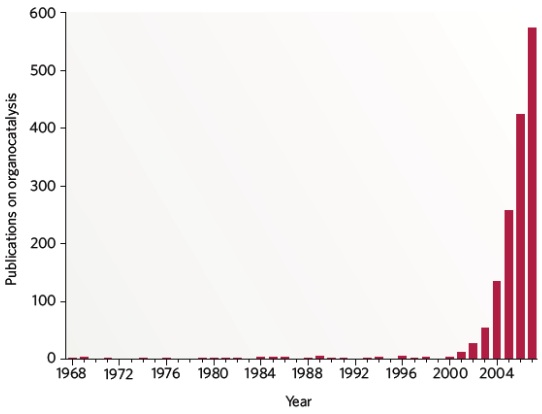


Figure 2. An explosion of interest: the increase in the number of publications on the topic of organocatalysis between 1968 and 2008 [5]

Having generic activation modes is another reason for the development of organocatalysis. Generic activation mode can be defined as reactive species formed by the interaction of a chiral catalyst with a certain functional group (ketone, aldehyde, alkene, imine etc.) in an arranged and predictable manner. Generic activation modes can be employed in various reaction types with high stereoselectivity. Formation of a generic activation mode brings about straightforward platform to use them in new various enantioselective reactions. It is a strong evidence for the easy application of organocatalysts that among 130 organocatalytic reactions reported since 1998 to 2008, only five or six generic activation modes were utilized [5].

1.2 Why we do asymmetric synthesis

"The world is chiral and clinal, enjoy symmetry wherever you find it."
Vladimir Prelog

The most quoted words of Prelog, who is an organic chemist with great contributions on stereochemistry of organic and natural compounds, symmetry and chirality, indicates that the world is chiral and so are the most organic compounds [14]. Selectivity of enzymes and structure of information carrier molecules (RNA and DNA) requires a uniform chirality of their monomeric units such as amino acids and nucleotides. Additionally, enantiomerically pure compounds are required in perfumes, cosmetics, nutrients, flavors, pesticides, vitamins and pharmaceuticals [15]. Especially in drugs, chirality and the activity of drugs are so

related that roughly half of the pharmaceuticals on the market are sold as single enantiomer. In order to be active, a drug must match chiral hole of the receptor in the cell. Since the human enzymes and the surfaces of receptors are chiral, absorption, activation or degradation processes of two enantiomers may be different and may cause diverse consequences in the body [16]. Therefore, stereoisomeric discrimination is very essential in biological systems.

An interesting illustration to the different effects of enantiomers is L- DOPA **(1)** which is used for treatment of Parkinson's sickness. Actually the active drug is the dopamine which is obtained by the in vivo decarboxylation of **(1)**. Since dopamine cannot cross the blood-brain barrier to reach the site of action, L-DOPA **(1)** is used as "prodrug". During the enzyme catalyzed decarboxylation of DOPA, the enzyme L-DOPA decarboxylase distinguishes the enantiomers of DOPA. While specifically and merely L-DOPA is transformed into dopamine, the accumulation of D-DOPA **(2)** may cause adverse effects since it is not metabolized in the body. Therefore it is essential to synthesize L-DOPA in enantiomerically pure L- form (Figure 3) [17].

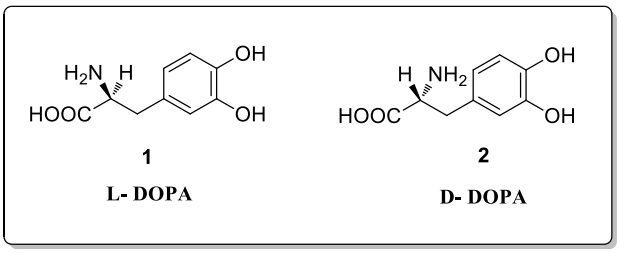


Figure 3. Enantiomers of DOPA

1.2.1 Catalytic and stoichiometric asymmetric synthesis

One of the main purposes of chemistry is to form valuable products compounds from readily available starting materials by using a controlled and economic process. In organic chemistry, worth of the product is related to purity and in asymmetric synthesis, it is related to enantiopurity. Among the enantioselective transformations introduced to the literature in recent years, chemists make use of catalytic asymmetric synthesis. In catalytic fashion the chiral auxiliary is used in fewer amounts than stoichiometric quantities. In other words, a small amount of chiral reagent is capable of producing larger amounts of enantiopure products. It is obvious that when "atom economy" is considered, catalytic asymmetric synthesis is more cost-effective than the stoichiometric asymmetric synthesis [2, 18]. In catalytic manner, either asymmetry may be induced by the covalently attached intermediate of chiral auxiliary and the substrate in the catalytic cycle or by the intermolecular fashion.

1.3 Noncovalent organocatalysis based on hydrogen bonding

In various asymmetric transformations, hydrogen bonding is used to activate electrophiles by decreasing the electron density and activating it toward nucleophilic attack. This principle is originated from enzymes which activates a variety of chemical processes in the nature. Recently, organic chemists have started to mimic the marvelous potential offered by hydrogen bonding in the catalytic asymmetric synthesis of small molecules [19].

Substrate coordination to metal-based Lewis acid and iminium ion formation have been commonly used for the electrophilic activation of carbonyl compounds, imines etc. A third type of electrophilic activation is hydrogen bonding (Figure 4) [3].

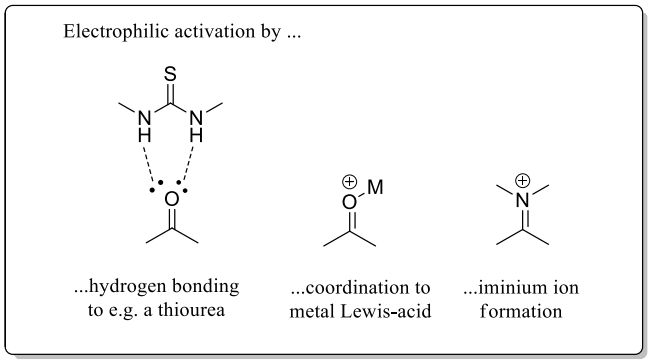


Figure 4. Three modes of carbonyl activation towards nucleophilic attack

Substrate activation by hydrogen bonding catalysis is related to, but different from Brønsted acid catalysis. In Brønsted acid catalysis, there is a proton transfer from catalyst to the substrate. Two different terms are used based on whether proton transfer occurs to the substrate in its ground state or to the transition state. In "specific Brønsted acid catalysis", the electrophile is reversibly protonated in a pre-equilibrium step before the nucleophilic attack. While in "general Brønsted acid catalysis" the proton is transferred in the transition state of rate-determining step (Figure 5) [3].

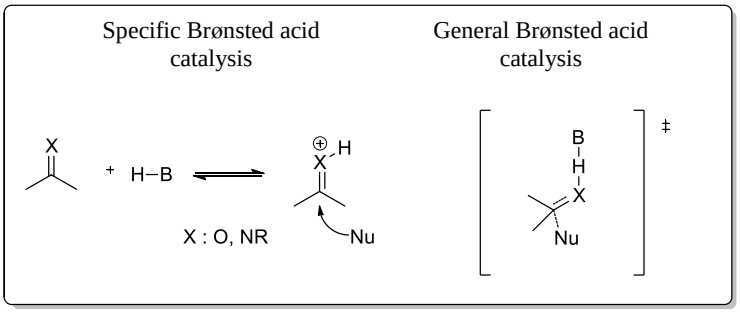
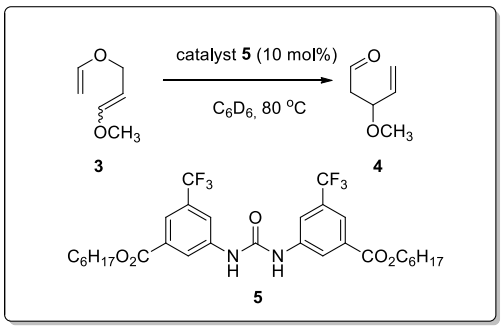


Figure 5. Specific and general Brønsted acid catalysis

Investigation of electrophile activation mechanism of enzymes through hydrogen bonding aspired organic chemist to design well-defined chiral H-bond donors to catalyze various asymmetric reactions. Also solid-state and solution-state studies in the field of molecular recognition clarified that dual H-bond catalysts can be directly used to control the assembly of molecules as much as covalent bonds do [20].

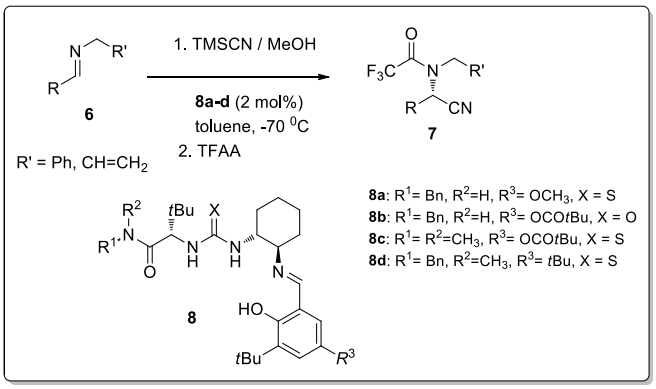
1.3.1 (Thio)urea as asymmetric catalysts

Claisen rearrangement of ally vinyl ethers **3**, reported by Curran and Kuo in 1994, is the first example of using achiral urea derivative **5** as competent organic catalysts (Scheme 1) [21].



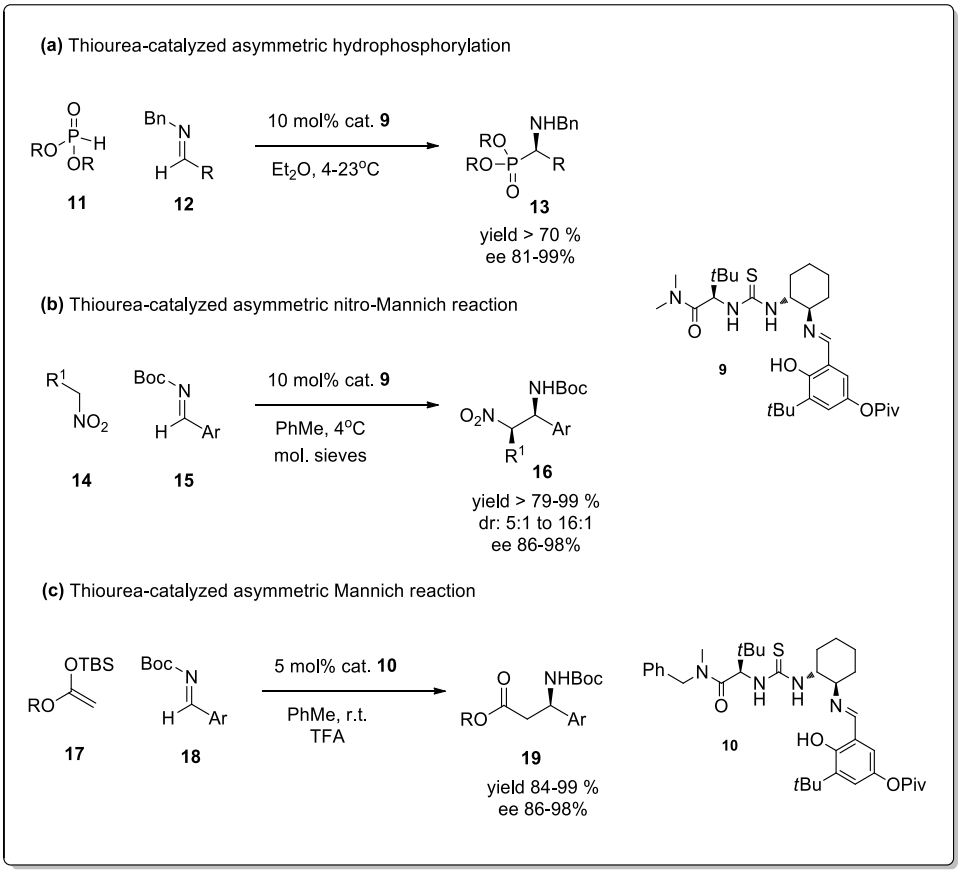
Scheme 1. Claisen Rearrangement catalyzed by an achiral urea

Afterwards Jacobsen's group has developed several derivatives of chiral (thio)ureas to activate imines through hydrogen bonding. These chiral urea and thiourea derivatives had been initially designed as potential ligands to Lewis acidic metals. Unexpectedly, Jacobsen and co-workers investigated that in the absence of metals, moderate to high enantioselectivities can also be achieved in the Strecker reaction of several imine derivatives (Scheme 2) [9]. Thereafter, the presence of double hydrogen bonding between the -NH protons of (thio)urea **8** and lone pairs of imine **6** was proven by structural modification, NMR, kinetic and computational studies [22].



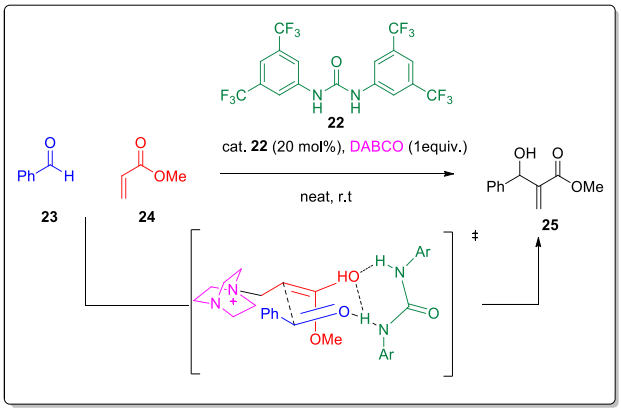
Scheme 2. Enantioselective Strecker reactions catalyzed by urea and thiourea Schiff bases

Furthermore, Jacobsen's catalysts were examined in addition reactions of wide range of nucleophiles to activated imines and brought about high enantiomeric excesses in the product. Some examples to these reactions were hydrophosphorylation [23], nitro-Mannich [24] and Mannich reactions [25]. The utilization of same activation mode through several transformations indicates that chiral (thio)urea catalysts have versatile properties as general catalysts for asymmetric synthesis (Scheme 3).



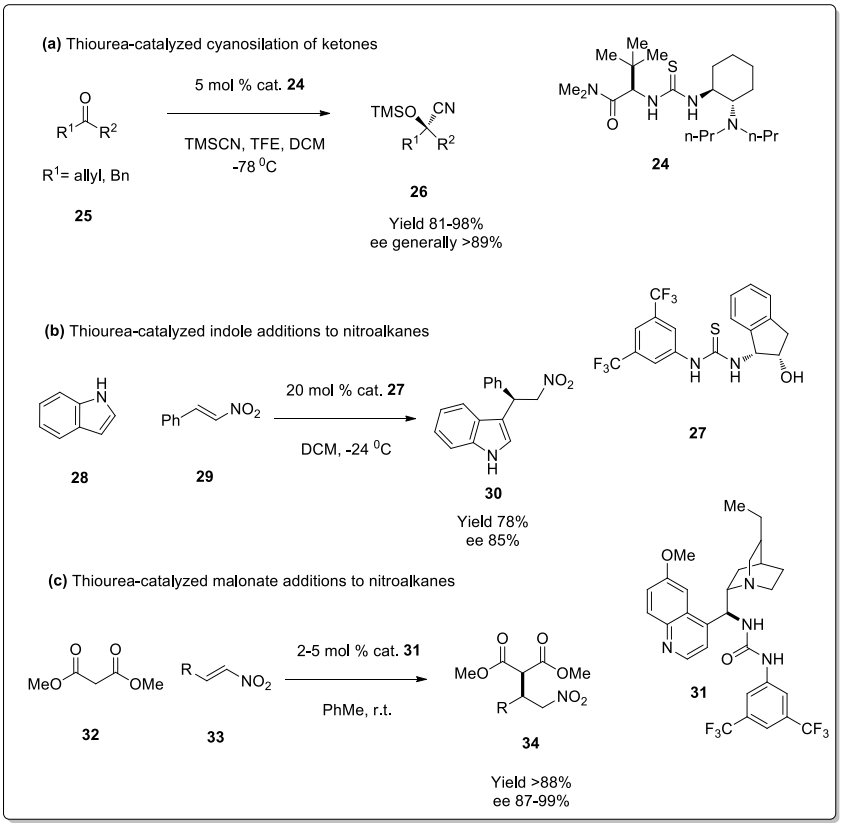
Scheme 3. Asymmetric reactions catalyzed by Jacobsen's catalysts

Apart from the bifunctional urea catalysts, chiral (thio)urea/amine catalysts systems were examined by Connon group in Morrita-Baylis-Hillman reactions of benzaldehyde **(21)** and methyl acrylate **(22)**. Activation of both electrophile and nucleophile is achieved by the simultaneous use of urea, or thiourea and DABCO catalyst. It is dedicated that both ureas and thioureas accelerate the reaction relative to the uncatalyzed process. Although urea was superior to thiourea in terms of stability and efficiency, better enantioselectivitiy was obtained in the case of thiourea as hydrogen bond donor. For the addition of the resulting enolate anion to the aldehyde, they suggested that catalysts follow Zimmerman- Traxler-type transition state which is a chair-cyclohexane like model for predicting the stereochemical outcome of enolate addition (Scheme 4) [26].



Scheme 4. DABCO and urea promoted Morita-Baylis-Hillman reaction

After the inspiring works of Jacobsen, others also achieved highly enantioselective asymmetric transformations by using slightly different (thio)urea catalysts. In 2005, Fuerst and co-workers achieved the cyanosilylation of ketones in both high yields and enantiomeric excesses [27]. In addition, (thio)urea catalyzed enantioselective indole and malonate additions to nitroalkenes were reported in the same year. In the subsequent reaction, it was investigated that the use of epimeric form of the naturally occurring alkaloid structure in the bifunctional cinchona alkaloid-thiourea catalyst resulted in higher enantiomeric excess in the product (Scheme 5) [28, 29].



Scheme 5. (Thio)urea catalyzed asymmetric reactions

1.4 Brønsted base catalysts

In enantioselective synthesis, chiral organic Brønsted bases have been widely used to achieve high stereoselectivity and catalytic activity for a century. Chiral Brønsted base catalysts firstly emerged in 1913, for enantioselective hydrocyanation of aldehydes and then it was developed by Wynberg in the 1970s and 1980s. Comprehension of mode of activation and catalyst designs has made chiral organic Brønsted base catalysis useful tools to overcome challenges in asymmetric transformations. Over the past two decades, new methodologies have been developed considering the mechanistic studies and insightful observations on Brønsted base and hydrogen bond donor activation. Combination of two activation modes leads to bifunctional catalysts by which simultaneous activation of both electrophile and nucleophile is possible (Figure 6) [30].

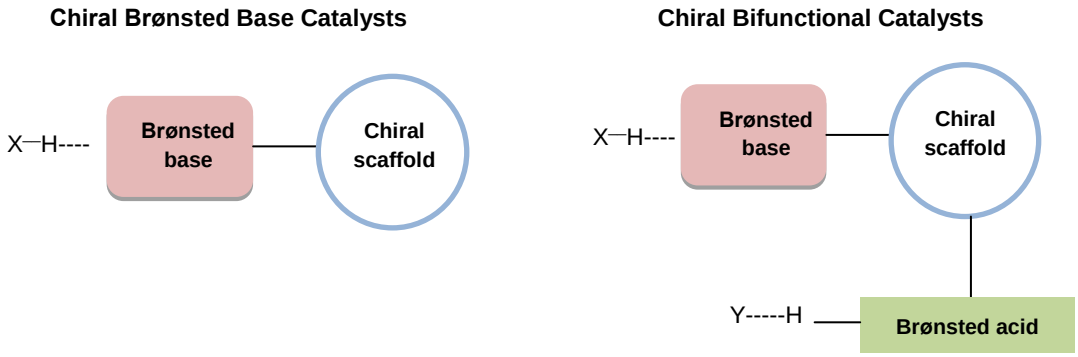


Figure 6. Chiral Brønsted bases catalysts design

The advent of chiral Brønsted base catalysis started with the discovery that Cinchona alkaloids function as excellent catalysts and have privileged structures. Evaluation of functionality of rigid quinuclidine ring with basic property and the absence or presence of a hydrogen bond donor within the same catalysts have led to design and synthesis of novel cinchona alkaloid-based catalysts [30].

1.4.1 Cinchona alkaloids as asymmetric catalysts

Progress of the asymmetric organocatalysis has been accompanied by investigation of several synthetic methodologies making use of cinchona alkaloid derived compounds. Cinchona alkaloids are natural products extracted from the bark of the trees belonging to the Cinchona genus and have biological activities. From a structural point of view, they are relatively lower in molecular weight and densely functionalized with stereogenic centers, quinuclidine ring and alcohol, vinyl and quinoline units. Quinine (QN) **(35a)**, quinidine (QD) **(36a)**, cinchonine (CN) **(36b)**, and cinchonidine (CD) **(35b)** are main components of

cinchona alkaloids. They are readily available amine catalysts and used to generate either enantiomer of a chiral compound (Figure 7) [31].

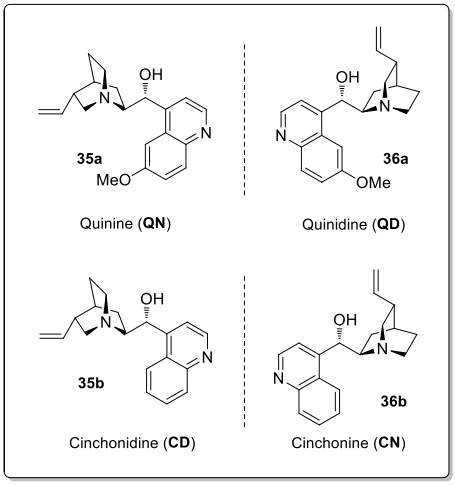


Figure 7. The structure of Cinchona alkaloids

In asymmetric organocatalysis, quinuclidine unit has mainly three roles. In the first mode of activation, quinuclidine ring behaves as a Brønsted base for the deprotonation of a pronucleophile. Secondly, it reacts with one of the substrates to create nucleophilic species. Thirdly, quaternary ammonium salts of cinchona forms ion pairs with deprotonated substrates and create a chiral environment for subsequent attack as a phase transfer catalyst (Figure 8) [31].

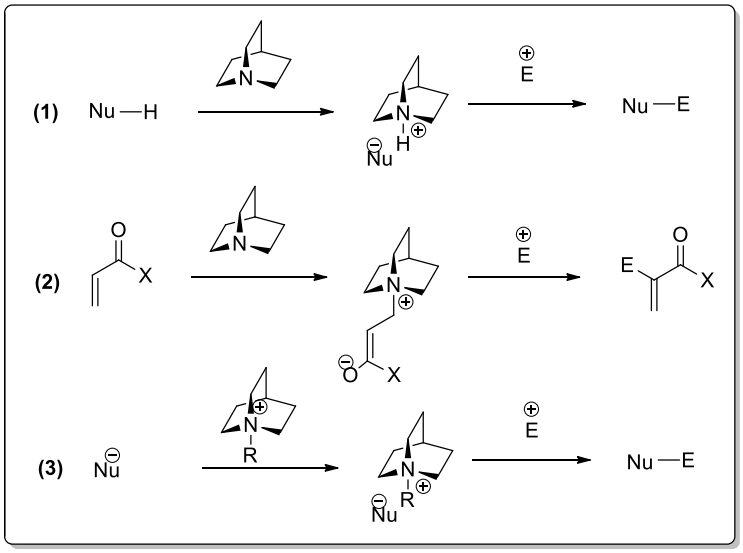
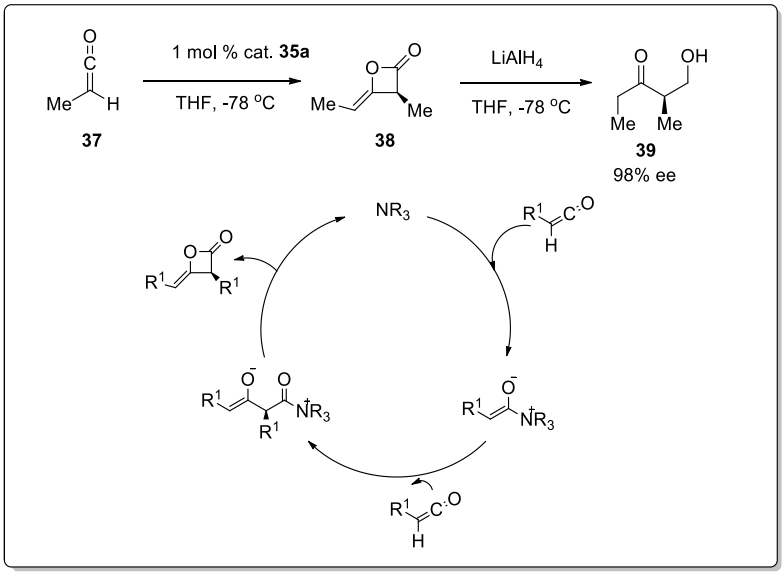


Figure 8. Modes of action of Cinchona organocatalysts

The unique molecular recognition abilities of cinchona alkaloids and cinchona derivatives make them invaluable in almost every field of chemistry related with chirality [31]. Especially, transformation of carbonyl compounds by enolate formation in a catalytic enantioselective manner has received significant attention within the synthetic organic chemists. Recently, chiral tertiary amine catalysts have been utilized as a source to generate asymmetric ammonium enolates. Most commonly, cinchona alkaloids are used for this aim since they possess a catalytically active nucleophilic quinuclidine nitrogen atom which is also responsible for asymmetric induction [32].

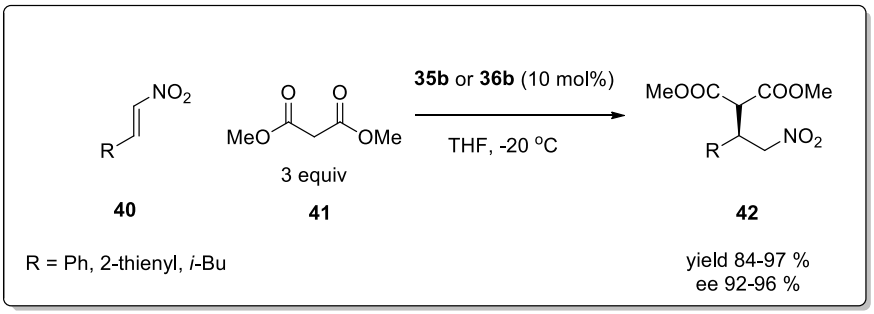
The early work with cinchona alkaloid catalyzed ammonium enolate generation was mainly carried out by Pracejus and Sauer and exploited ketene dimerization reactions. This work was used as a route in the synthesis of *β*-lactones. The dimerization mechanism starts with the attack of the nucleophilic amine catalyst **(35a)** (shown in Figure 7) to the methyl ketene **(37)** and continues with the attack of the resulting zwitterionic ammonium enolate to another molecule of reactive ketene. By intramolecular *O*-acylation of acyl ammonium intermediate, amine catalyst is recovered and the ketene dimer **38** is formed (Scheme 6) [33].



Scheme 6. Enantioselective ketene dimerization mechanism

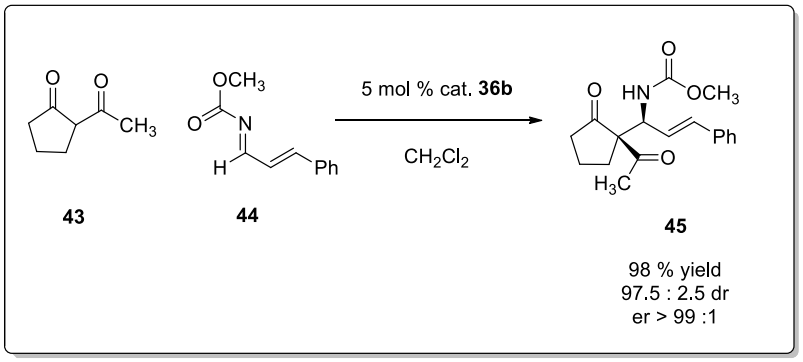
Additionally, catalysts **(35b)** and **(36b)** depicted in Figure 7, obtained by the modification of quinine and quinidine, respectively, were used by Deng and co-workers in the catalytic asymmetric Michael additions of malonates to nitroolefins. High enantioselectivities and yields were achieved in the conjugate additions of methylmalonate **(41)** to a wide range of aromatic, heteroaromatic and aliphatic *β*-substituted nitroolefins **40**. Since two catalysts are pseudoenantiomeric forms of each other, both enantiomers of the addition product were observed. It is also investigated that enantiomeric excess values are higher in the presence of 6′-hydroxyquinoline-derived catalysts when it is compared to 6′-methoxyquinoline derivatives (92-96% ee versus 6-24% ee) (Scheme 7). Considering this observation, authors suggested that phenolic hydroxyl functions as hydrogen bond donor and play a key role in

the transition state. This situation is also evidence to belief that cinchona-derived compounds behave as bifunctional catalysts [34].



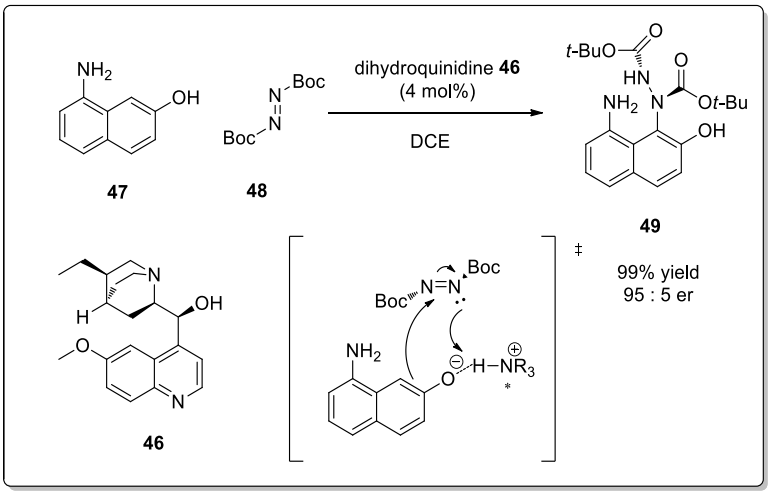
Scheme 7. Cinchona alkaloid catalyzed Michael reactions of nitroolefins

Cinchona alkaloids were previously shown to be active catalysts in malonate additions. Later Schaus et al. worked on the Mannich reactions of cyclic 1,3- dicarbonyl donors **43** to *N*-acyl aldimines **44**. Multifunctional secondary amine adducts **45** was obtained in excellent yields and stereoselectivities in the presence of 5 mol% cinchonine as catalyst (Scheme 8) [35].



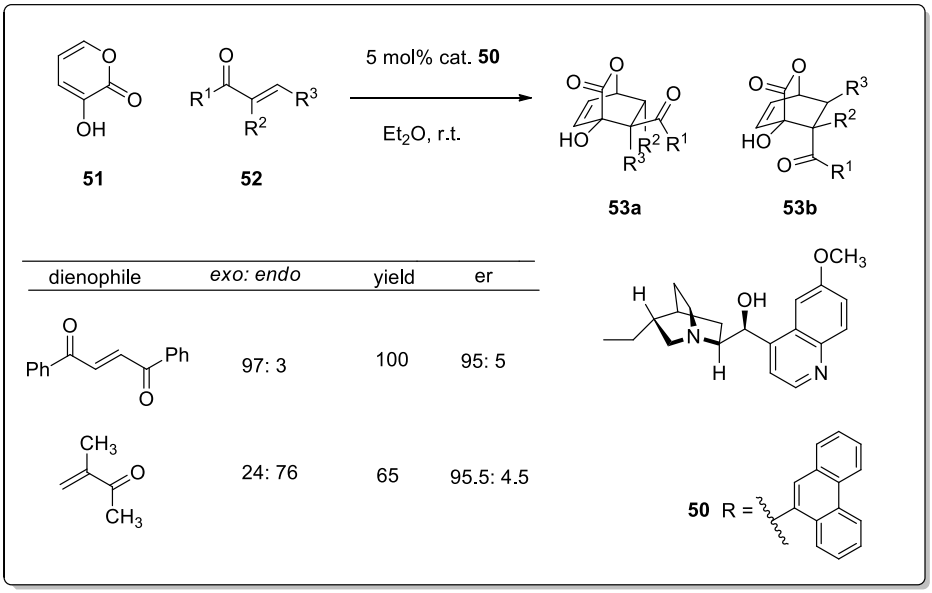
Scheme 8. Cinchona alkaloid catalyzed Mannich reaction

Until the study of Jørgensen, there were a few reports in which the nitrogen atom is directly attached to the aromatic ring. In his work, deprotonation of the hydroxyl group on 8-amino-2-naphthol **(47)** and following addition of tert-butyl-azodicarboxylate **(48)** were utilized by dihydroquinidine (DHQD) **(46)** catalyst. Consequently, aminated naphthol product **49** was obtained in 99% yield and 95:5 enantiomeric ratio (Scheme 9) [36].



Scheme 9. Dihydroquinidine catalyzed Friedel Crafts amination

Diels-Alder reaction of 2-pyrones is an efficient method for the synthesis of bridged cyclohexene derivatives. In early studies, *endo* selective cycloaddition reactions of 3-hydroxy-2-pyrone **(51)** with electron deficient dienophiles in the presence of base catalyst were known. Although reaction proceeds under triethylamine catalysis, superior selectivity is obtained by modified cinchona alkaloids [Scheme 10]. From a mechanistic point of view, cinchona alkaloids catalyze reaction by raising the HOMO of the 2-pyrone via multiple hydrogen bonding while lowering the LUMO of the dienophile with simultaneous control over the substrates (Scheme 10) [30].

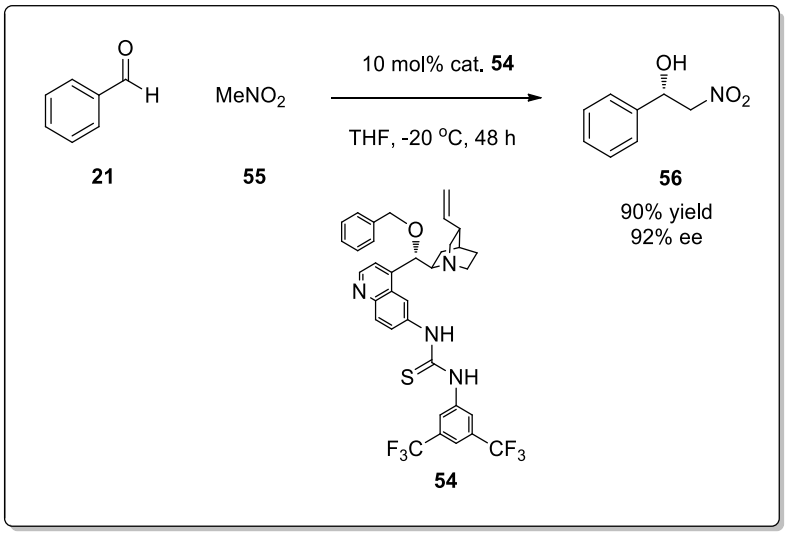


Scheme 10. Cinchona alkaloid catalyzed Diels-Alder reaction

1.4.2 Cinchona alkaloid derived chiral (thio)urea catalysts

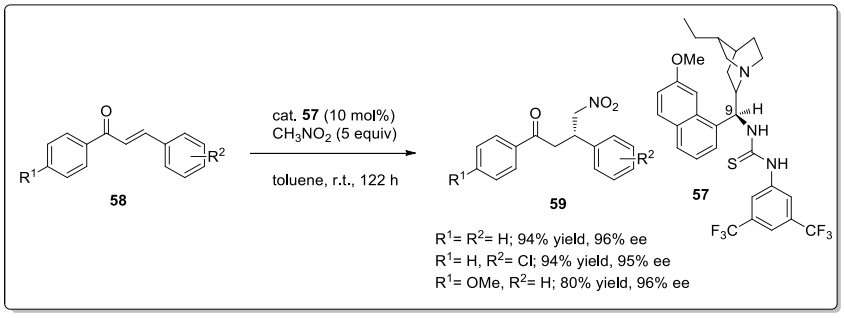
Hydrogen bonding activity of urea and thiourea derivatives have been known for a long time. However, these catalysts were relatively limited in terms of stereoselectivity and reaction types. To develop the catalyst performance many groups have worked on combining cinchona alkaloids and (thio)ureas with strong electron withdrawing groups [30].

Although excellent yields and asymmetric induction was obtained by metal catalysts in 1990s, discovery of organocatalytic Henry reaction was in 2005. The first evaluation of the reaction of nitromethane with aldehydes or trifluoromethyl ketones was done in the presence of unmodified cinchona alkaloid catalysts; however, high-pressure was required and enantioselectivities was low (35% ee). Replacement of C6′- hydroxyl with an activated thiourea moiety **54** increased both reactivity (90-99% yield) and the selectivity (85-92% ee) of Henry reaction of nitromethane with various aromatic and heteroaromatic aldehydes (Scheme 11) [37].



Scheme 11. Cinchona alkaloid derived thiourea catalyzed Henry reaction

Similarly, by the cinchona alkaloid-derived thiourea catalyst **57** developed by Soós and co-workers, high yields (80- 94%) and enantiopurities (89- 96% ee) were obtained in conjugate addition of nitromethane to *trans*-chalcones **58**. The absolute configuration of C9-stereocenter plays a crucial role in selectivity and spatial orientation of the thiourea-enone complex and the ammonium nitronate nucleophile (Scheme 12) [38].



Scheme 12. Thiourea catalyzed Michael additions of nitromethane to chalcones

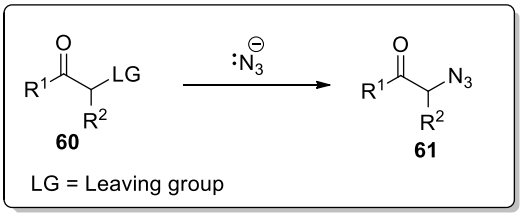
1.5 Alpha azido ketones

Organic azides are an important class of organic compounds and they can be utilized as amine precursors, nitrene sources and starting materials of phosphoranes. Moreover, 1,3-dipolar cycloadditions can be employed due to the dipole of azide moiety.

Besides synthetically valuable properties of organic azides, α-azido ketones, special subclass within the azides, have different properties offering extra synthetic opportunity for chemists. Many researchers have employed the synthetic potential of α-azido ketones in the synthesis of pharmaceuticals and naturally occurring compounds. The enhanced acidity of α-azido ketones is a valuable feature for C-C bond formation. The enhanced acidity is the consequence of oxo functionality on adjacent position of azide [39].

1.5.1 Synthesis of α-azido ketones

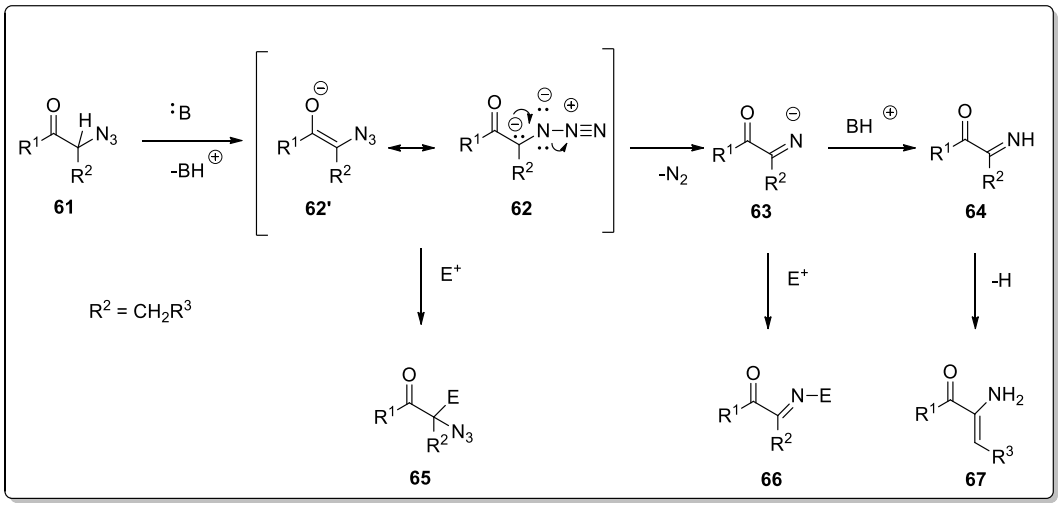
According to the review of Patonay, the most frequently α-azido ketones **61** are synthesized by the nucleophilic substitution reaction of α-substituted ketone with good leaving group. Leaving groups for this reaction are commonly halides or, much more rarely, a sulfonyloxy unit (Scheme 13). According to literature, the most widely used starting materials for the synthesis of α-azido ketones are 1-aryl-2-halo-1-ethanone derivatives (**60**, LG = halogen, R^1 = aryl, hetaryl, R^2 = H), 1-aryl-2-halo-1-alkanones (**60**, LG = halogen, R^1 = aryl, hetaryl, R^2 = alkyl, aryl) or related compounds. It is also reported that substitution generally takes place with high chemoselectivitiy and yield [39].



Scheme 13. Synthesis of α-azido ketones via nucleophilic substitution

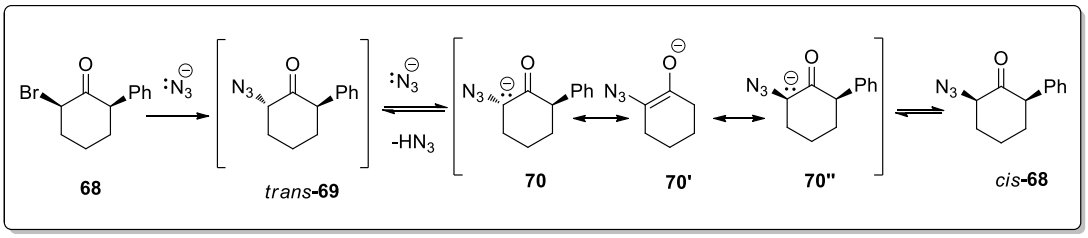
Most commonly sodium azide is used as azide source in the synthesis of α-azido ketones. Lithium azide, potassium azide, tetramethyl guanidinium azide and polymer-supported quarternary ammonium azide are also used rarely. As the solvent, dipolar aprotic solvents (DMF, DMSO, acetone) are preferred in ambient or subambient temperature. Use of chloroform or dichloromethane as solvent has also been reported but it should be avoided due to the formation of highly explosive diazidomethane in these solvents. In order to improve the solubility of sodium azide and increase the yield, phase transfer catalysts such as Aliquat 336 and 18-crown-6 are also used [39].

During the synthesis of α-azido ketones **61**, due to highly acidic alpha proton, undesired side products may be observed. According to the mechanism offered by Boyer and Canter, if the deprotonated ketone loses nitrogen, imino anion **63** is obtained. Protonation of imino anion leads to imino ketones **64** which can tautomerize into α-enaminones in the presence of electron-withdrawing R^3 group. Additionally, enolate **62** and imino anion **63** can be trapped by using carbonyl electrophiles which leads to formation of **65** and **66**, respectively (Scheme 14) [39, 40].



Scheme 14. Formation mechanism of imino ketones and α-enaminones

Kinetic studies on the mechanism of nucleophilic substitution of α-halo carbonyl compounds to yield α-azido ketones proved that reaction has second-order (S_N2) kinetics, first-order in each component. S_N1 type mechanism should be very unlikely since electron-deficient alpha carbon of carbonyl compounds is unstable. In accordance with S_N2 reaction, generally inversion of configuration is observed; however, retention product in diastereomeric mixture is also possible in some cases due to the epimerization into thermodynamically stable diastereomer via enolisation (Scheme 15) [39].



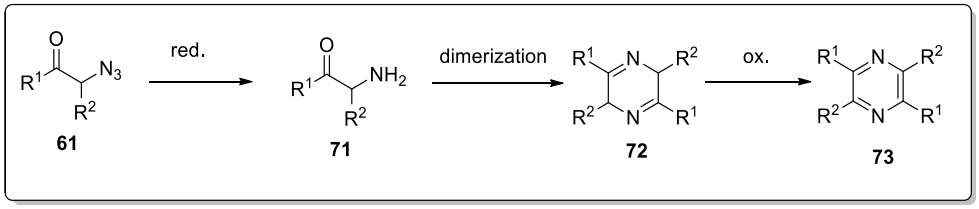
Scheme 15. Examples to the retention of configuration in α-azido ketone synthesis

1.5.2 Reactions of α-azido ketones

α-azido ketones can be reduced to corresponding 1,2-amino alcohols. According to literature, this transformation occurs in two steps. That is to say, either the azide group or the carbonyl can be reduced chemoselectively.

1.5.2.1 Synthesis of α-amino ketones

Chemoselective reduction of α-azido ketones to α-amino ketones is possible but the main difficulty is their tendency to undergo intermolecular condensation followed by oxidation. As a result, pyrazines are obtained rather than α-amino ketones. In the study of Anselme *et. al*. the catalytic reduction of phenacyl azides (R^1 = Ph, 4-OMe-C_6H_4, R^2 = H) and aliphatic α-azido ketones (R^1 = iPr, R^2 = H; R^1 = Me, R^2 = Et) were examined in the presence of Pd-C catalysis. Due to the dimerization of initial product followed by oxidation, isolated product was the corresponding pyrazines **73** in 61-95% yields (Scheme 16) [39].



Scheme 16. Formation of pyrazines from α-azido ketones

However, in some cases, the catalytic reduction over Pd-C, Pd-calcium carbonate or platinum oxide leads to quite stable α-amino ketones **74**, **75** and **76**. Comparison of obtained yields reveals that when the steric hindrance around the amino group increases, probability of dimerization decreases (Figure 9) [39].

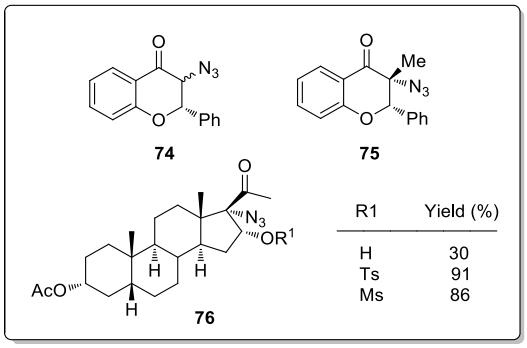
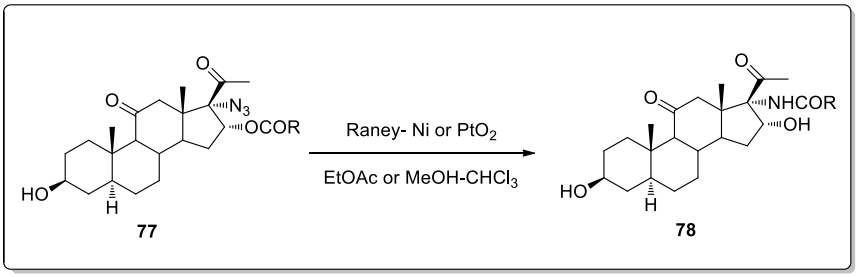


Figure 9. Azido ketones giving stable α-amino ketones by catalytic reduction

Immediate protection of them via salt formation or acetylation to avoid the dimerization of α-amino ketones is known in the literature. Most frequently, hydrogen chloride is added to the solution before or just after the hydrogenation. Acetylation or aroylation by an active ester immediately after the reduction is also reported [39, 41].

RANEY-Ni or Adams platinum oxide catalyzed hydrogenation of steroidal α-azido ketones with β-acyloxy groups led to not only α-amino ketones but also acyl migration from oxygen to nitrogen (Scheme 17) [42].

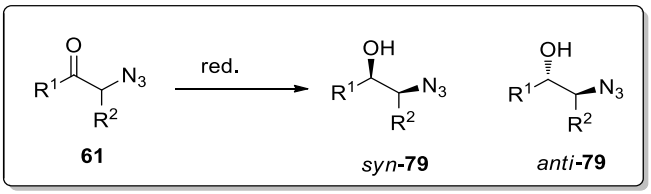


Scheme 17. Reduction of steroidal α-azido ketones

1.5.2.2 Synthesis of 2-azido alcohols

The higher reactivity of azide group through catalytic hydrogenation has been mentioned previously. Chemoselective reduction of carbonyl group of α-azido ketones is also possible by sodium borohydride or other boranes. Since these reagents are mild compared to lithium aluminum hydride, rate of reduction of azide group is very slow.

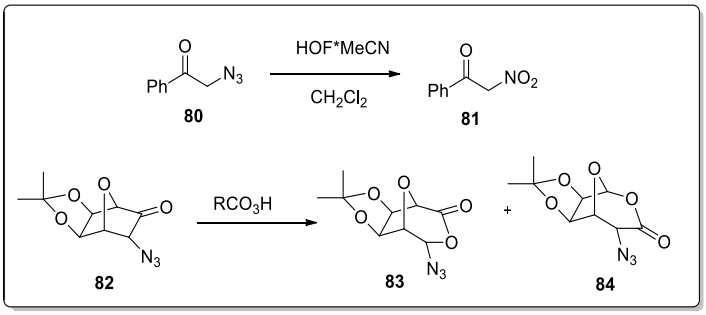
An alternative method for the synthesis of azido alcohols is enzymatic reduction of α-azido ketones. An efficient methodology for the synthesis of enantiomerically pure azido alcohols is the reduction of prochiral phenacyl azides into racemic mixture of alcohols **79** followed by lipase catalyzed kinetic resolution (Scheme 18) [39].



Scheme 18. Chemoselective reduction of carbonyl moiety of α-azido ketones

1.5.2.3 Oxidation of α-azido ketones

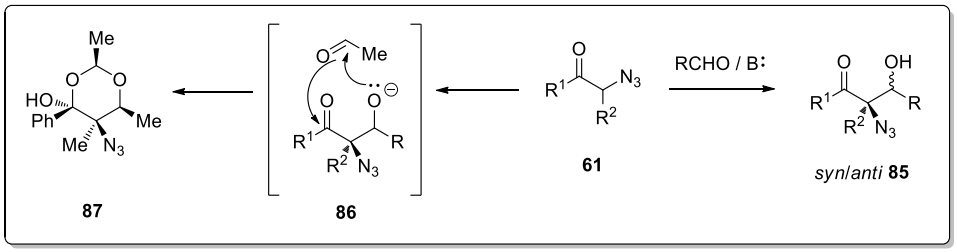
In the literature there are few examples to the oxidation of α-azido ketones. One of them is the oxidation of 2-azidoacetophenone **(80)** into 2-nitroacetophenone **(81)** by HOF.acetonitrile complex generated *in situ*. The second example is the Baeyer-Villiger oxidation of bicyclic azido ketone **82** with mCPBA and sodium bicarbonate led to isomeric mixture of **83** and **84** in a ratio 55:45 (Scheme 19) [43, 44].



Scheme 19. Oxidation of α-azido ketones

1.5.2.4 Reactions of α-azido ketones with carbonyl electrophiles

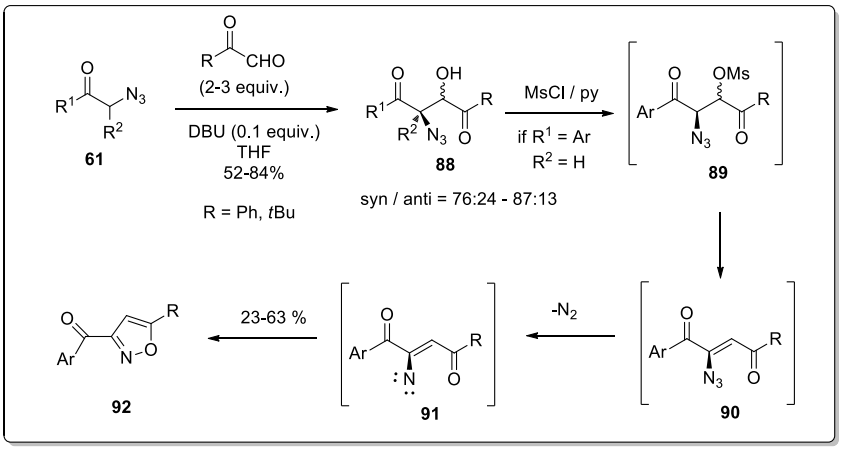
The anionic species **62** and **62′** (shown in Scheme 14) offer an interesting possibility for the C-C bond forming reactions of α-azido ketones. In 1995, the reaction of α-azido ketones and aldehydes affording α-azido-β-hydroxy ketones was reported in the presence of base. Since the reaction was thermodynamically controlled, the products were obtained as the diastereomeric mixture of *syn* and *anti* adduct **85**. Although the obtained diasteroselectivity was low (dr ≤ 76:24), an increase in diastereoselectivity was observed when bulkier aldehydes were used. Besides the desired product and interesting by-product **87** was obtained in the aldol addition of α-azidopropiophenone (R^1= Ph, R^2= Me). This transformation was explained by the attack of the aldol product to aldehyde molecule **86** (Scheme 20) [40].



Scheme 20. Reactions of α-azido ketones and aldehydes

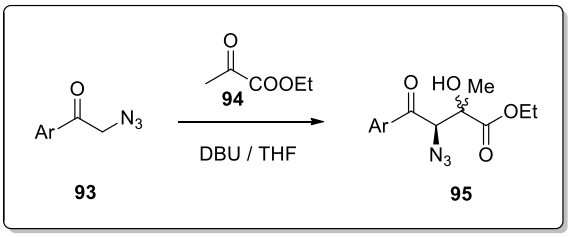
The reaction of aliphatic α-azido ketones synthetically less valuable since secondary reactions such as dehydration giving α-acylvinyl azides or 1,3-dioxanes are more probable. It is noteworthy to indicate that α-azido-β-hydroxyketones **85** are important multifunctionalized synthons.

Addition of enolates generated from phenacyl azides or 3-azidochromanones to more complex carbon electrophiles such as 2-oxoaldehydes or α-oxo esters were also examined. The addition reactions occurred in complete regioselectivity so that addition took place only with more electron deficient carbonyl group. The obtained 1-aryl-2-azido-3-hydroxy-1,4-diones **(88)** were transformed into isooxazoles **92** when treated with mesyl chloride in pyridine. Isooxazole formation mechanism was explained by elimination of methanesulfonic acid followed by nitrene formation and ring closure. Since the protons at C-2 and C-3 are highly acidic, epimerization of them allows the formation of thermodynamically more stable *Z* -vinyl azide **90** (Scheme 21) [45].



Scheme 21. Reactions of α-azido ketones with carbon electrophiles

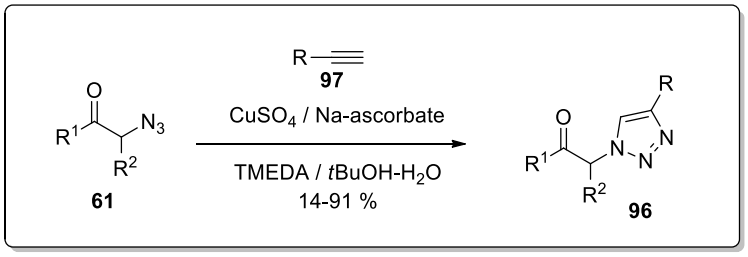
Reactions of phenacyl azides **93** with ethyl pyruvate **(94)** afforded to the expected product ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates **95** in the presence of DBU. However, it is reported that only 4(4-methoxyphenyl) derivative was relatively stable and other derivatives undergo retro-aldol reaction due to the steric hindrance around the quaternary C-2 atom. Similarly, product **95** is transformed into α-acylvinyl azides (Scheme 22) [46].



Scheme 22. Reactions of phenacyl azides with ethyl pyruvate

1.5.2.5 Click chemistry with α-azido ketones

Five-membered nitrogen heterocycles are important in biological systems. 1,2,3-triazole heterocycles is a class of such biologically active molecules and they are useful building blocks in chemistry. One way of synthesizing 1,2,3-triazoles is the 1,3-dipolar cycloaddition of azides to alkynes. For the first time, the reaction of substituted 2-azidoacetophenone with dimethyl acetylenedicarboxylate (DMAD) in hot xylene leading to 1,2,3-triazole was reported in 2005 [39]. Later, Kumar and co-workers reported one-pot synthesis of 1,2,3-triazoles starting from α-bromo ketones or α-tosyloxy ketones with sodium azide and terminal alkynes **97** in the presence of copper source [47]. Finally, Patonay and co-workers achieved the click reaction of the isolated phenacly azides **61** (R^1= Ar, R^2 = H) with different terminal alkynes to obtain desired 1,2,3-triazoles **96** (Scheme 23). Also reaction of 3-azidochromanone and -1-thiochromanone afforded to corresponding 1,2,3-triazoles. It is investigated that the rate of click reaction changes with respect to substituents of azide, the reaction solvent and the bidentate ligand [39].

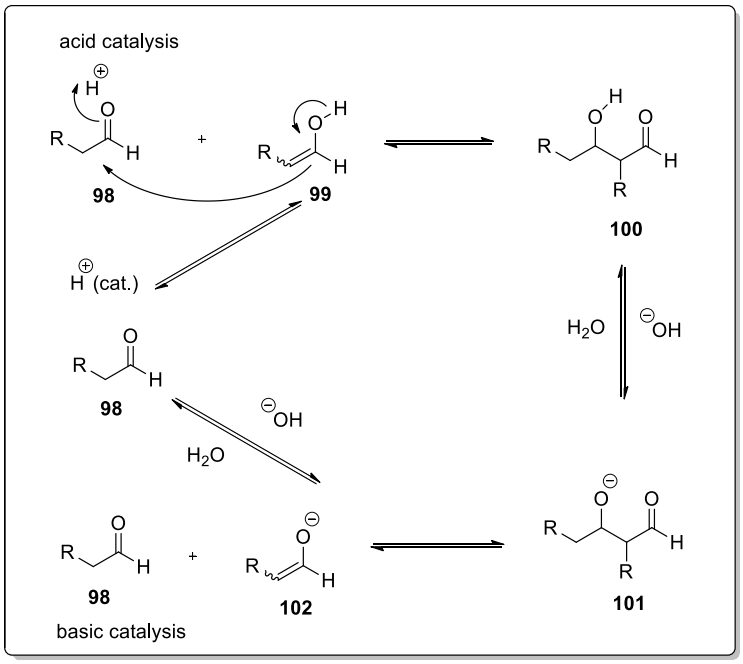


Scheme 23. 1,3-Dipolar cycloaddition of the α-azido ketones leading to 1,2,3-triazoles

1.6 Aldol reactions

Aldol reaction is a kind of C-C bond forming reaction in which an enolizable carbonyl compound reacts with another aldehyde or ketone. The enolizable carbonyl compound is one with at least one acidic proton at alpha position. By the formation of enolate, alpha carbon of enolizable carbonyl compound gains a nucleophilic property and attacks to the electrophilic carbonyl carbon of other component [48].

Aldol reaction may take place either self or cross manner between identical or nonidentical carbonyl compounds, respectively. The primary product of aldol reaction is always β-hydroxycarbonyl compounds and they may undergo water elimination to form conjugated α-β-unsaturated carbonyl compounds. If the final adduct is β-hydroxycarbonyl compound reaction is called as "aldol addition" while the process with water elimination is denoted "aldol condensation". The traditional aldol reaction is thermodynamically controlled and reversible. Aldol reaction can be catalyzed by either acid or base catalysts (Scheme 24) [29].



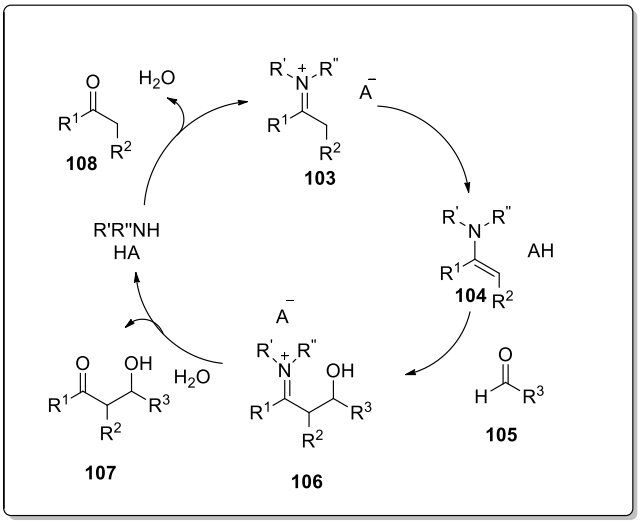
Scheme 24. Aldol addition: general acidic and basic catalysis

1.6.1 Asymmetric organocatalytic aldol reactions

The asymmetric aldol reaction is very popular in the field of modern catalytic synthesis since the products, β-hydroxycarbonyl compounds, have synthetic importance in pharmaceutical industry. Although the discovery and the initial improvements on asymmetric aldol addition were metal-catalyzed, organocatalytic asymmetric aldol reactions of modified and unmodified ketones have been attracting chemists since 1990s [2]. In the literature, many types of organocatalysis selectively accelerating the aldol reaction are known; however, in this section, a few examples of these organocatalysts will be mentioned.

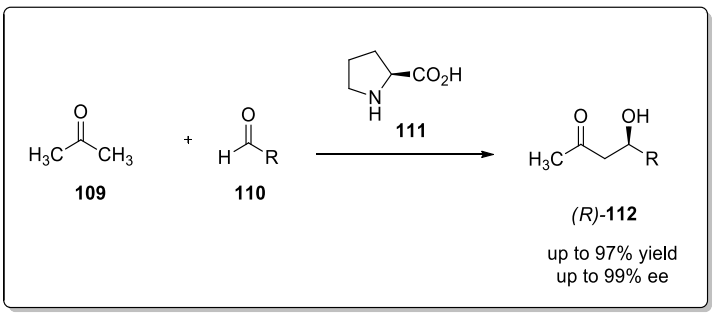
Chiral amines and amino acids, as enamine catalysts, have been used as catalysts for aldol reactions for years. Catalytic cycle of enamine-based aldol reaction is shown in Scheme 25. The cycle starts with the formation of iminium intermediate **103** between aldol donor and the amine catalyst, and then continues with the formation of enamine intermediate **104** from the

iminium. C-C bond formation occurs between the enamine intermediate **104** and the aldol acceptor carbonyl compound **105**. Hydrolysis of resulting iminium affords the product (Scheme 25) [2].



Scheme 25. The enamine catalytic cycle

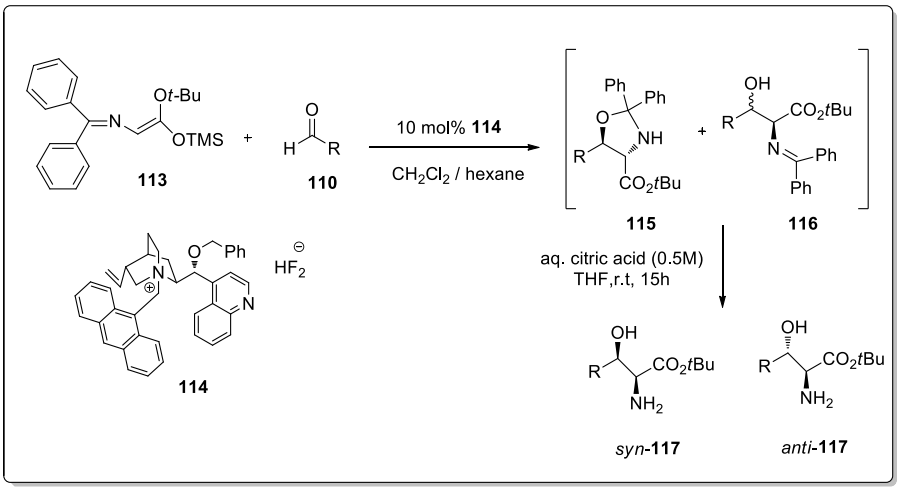
At the beginning of 2000s, List and Barbas reported the use of L-proline **(111)** for the enzyme-mimetic catalytic intermolecular aldol reaction of acetone **(109)** with aldehyde **110**. Proline catalyzed aldol reaction yielded in the generation of desired product **112** with very good yields and excellent selectivities up to >99% ee (Scheme 26) [12].



Scheme 26. L-proline catalyzed intermolecular aldol reaction of acetone

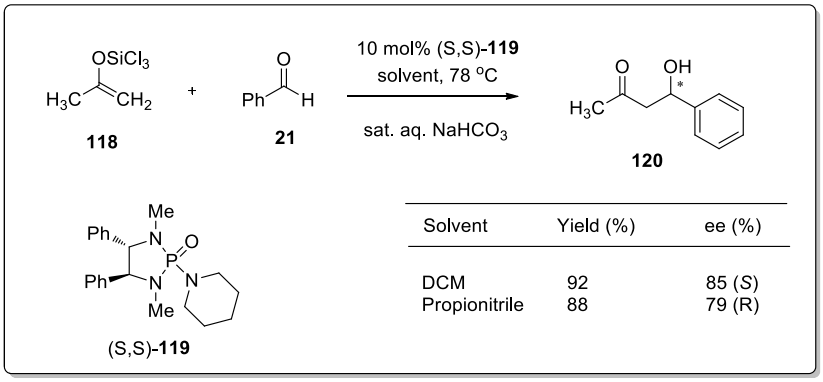
Chiral quaternary ammonium salts are a powerful class of metal-free organocatalysts in which chiral induction is provided by the 3-D structure of chiral ammonium cations and counteranions. This kind of organocatalysis may function in either homogeneous or heterogeneous systems [22]. An important example to the cinchonidine-derived quaternary ammonium catalyzed aldol reaction was introduced by Corey group. In his study, aldol

donor trimethylsilyl enol ether derivative of tert-butyl-glycinate-benzophenone Schiff base **(113)** reacts with a broad variety of aldehydes in the presence of 10 mol% catalyst **114**. In the first step, isomeric mixture of oxazolidine **115** and β-hydroxy-α-amino acid ester Schiff base **116** is formed and subsequent cleavage by citric acid led to desired products **117**. Although the syn/anti ratios vary from 1:1 to 13:1, good to excellent enantioselectivities up to 95% ee were obtained in derivatives of **117** (Scheme 27) [49].



Scheme 27. Quaternary ammonium catalyzed aldol reaction

Trichlorosilylenolates are powerful nucleophiles and they readily react with several aldehydes. In the presence of phosphoramides **119**, chiral Lewis-base catalysts, the acetone-derived enolate **118** and benzaldehyde **(21)** gave the desired aldol product **120** in high yields and stereoselectivity. It was investigated that solvent has significant effect on enantioselectivity so that while the use of dichloromethane yields (*S*)-**120** with 85% ee, propionitrile leads to (*R*)-**120** with 79% ee (Scheme 28) [50].



Solvent	Yield (%)	ee (%)
DCM	92	85 (*S*)
Propionitrile	88	79 (R)

Scheme 28. Phosphoramide catalyzed aldol reaction of trichlorosilylenolate

1.7 Aim of the work

The main objective of this thesis is to achieve the stereoselective synthesis of chiral multifunctional ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates **95** starting from phenacyl azides **93**. It is known that due to the highly acidic alpha protons of α-azido ketones, they can be used to generate nucleophile for the aldol additions to carbonyl electrophiles. Having different functionalities, obtained products can be employed for the synthesis of α-amino ketones, azido alcohols, 1,2-amino alcohols, phosphoranes and 1,2,3-triazoles. Within these compounds, 1,2-amino alcohols have pharmaceutical importance due to their well-known biological activity. Because of aforementioned stereoisomeric discrimination of cell receptors, stereoselective synthesis of precursors of biologically active compounds is also valuable. Although the base induced coupling of α-azido ketones and 1,2-dicarbonyl compounds are known in the literature, it is reported that most of the derivatives could not be isolated since the increased steric hindrance around the C-2 atom lead to retro-aldol cleavage in basic medium. Also the diastereoselectivity in isolated products was low in the presence of DBU as base [38, 39]. Therefore, the first diastereo- and enantioselective synthesis of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates was aimed by the aldol additions of phenacyl azides **93** to ethyl pyruvate **(94)** in the presence of chiral base catalyst.

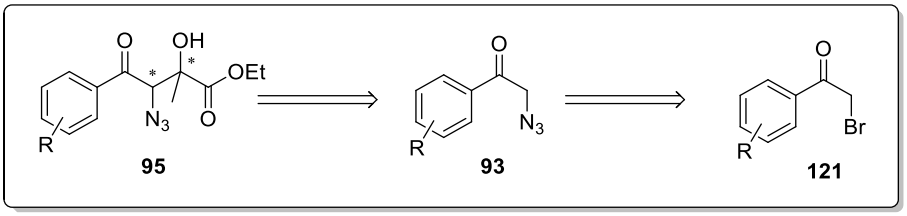
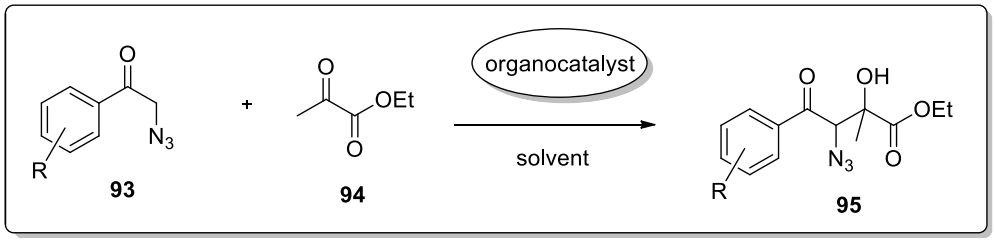


Figure 10. Retro synthesis of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates

In the first part, the synthesis of 2-azido-1-phenylethanone derivatives **93** were planned by the nucleophilic substitution reaction of 2-bromoacetophenone derivatives **121** and sodium azide according to the literature procedure (Figure 10) [39]. Then the purpose was to detect the best chiral base catalyst and determine the optimum conditions for the aldol additions (Scheme 29). In the second part, synthesis of aryl substituted derivatives of compound **95** at optimized conditions was planned to observe the effect of substituents on selectivity and improve the enantiomeric purity.



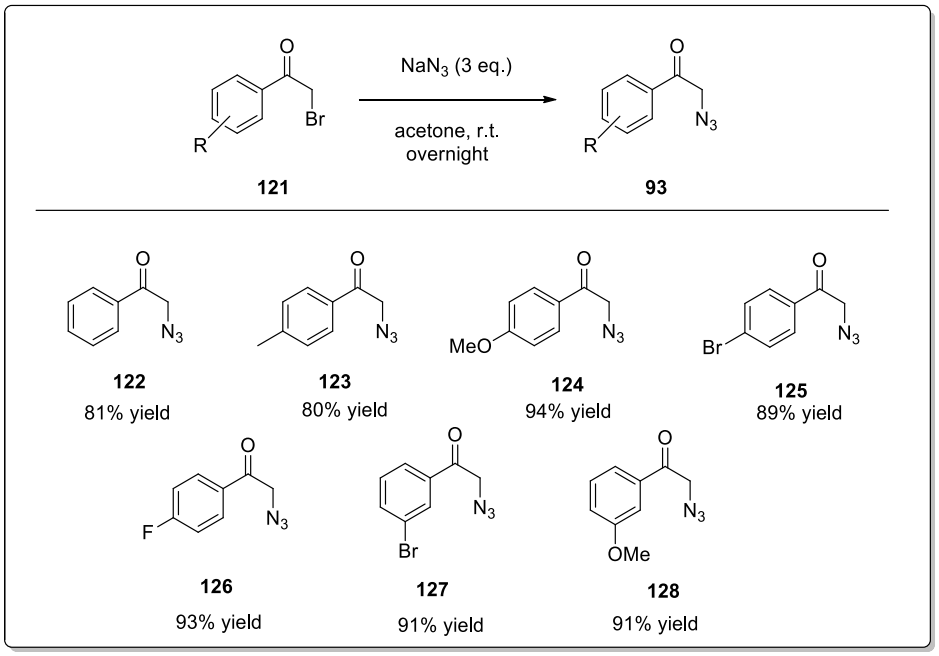
Scheme 29. Aldol addition of phenacyl azides **93** to ethyl pyruvate **(94)**

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of alpha azido ketones

In the first part of this study, alpha azido ketone derivatives **93** were synthesized according to the literature [39] by the nucleophilic substitution reaction of commercially available 2-bromoacetophenone derivatives **121**. As the azide source, sodium azide, which is most commonly used in the literature, was used in excess amount due to the low solubility in organic solvents. Acetone was our solvent of choice because of reported better solubility of sodium azide and slower rate of deprotonation of product in this medium (Scheme 30).



Scheme 30. Synthesis and derivatives of α-azido ketones

Following the procedure given in experimental part, alpha azido ketones shown in Scheme 30 were obtained in good yields (80-94% yield). Although azides are known to be thermally and photochemically labile compounds, isolated alpha azido ketones could be stored at low temperatures and in dark medium without decomposition for a long time. ^{1}H and ^{13}C NMR spectra of alpha azido ketones which are not known in the literature are depicted in Appendix A. Formation of alpha azido ketones were supported by the resonance of α-protons as singlet at lower field (4.40-4.60 ppm) compared to 2-bromoacetophenone precursors. In addition to NMR data, IR spectra of the substitution products revealed a characteristic azide peak around 2100 cm^{-1}.

2.2 Synthesis of chiral ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates via aldol addition

As reported by Patonay in 1995 [40], it was previously known that α-protons of α-azido ketones are highly base sensitive and their base-promoted deprotonation leads to formation of carbanion intermediate. Thus, so far α-azido ketones have been coupled with Michael acceptors, aldehydes and various in situ generated imines. The aldol reactions of enolate between α-azido ketone and various aldehydes, ketones, 2-oxoaldehydes and α-oxo esters in the presence of base catalyst were known in the literature. In his subsequent studies [45, 46], Patonay reported that although the reaction of phenacyl azides **93** with ethyl pyruvate **(94)** resulted in the expected ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates, only the 4(4-methoxyphenyl) derivative could be isolated. The failure in isolation of other derivatives was attributed to the rapid retro-aldol reaction in the presence of DBU as base due to the crowdedness around the C-2 atom. Also the diastereoselectivity in the isolated 4(4-methoxyphenyl) derivative was very low with a diastereomeric ratio of 67:33 *syn*/*anti* diastereomers.

Therefore, in this study we aim to achieve both enantioselective and highly diastereoselective synthesis of such synthetically valuable multifunctional compounds besides decreasing the rate of retro-aldol reaction by chiral base catalysis.

2.2.1 Optimization studies for the asymmetric aldol addition of alpha azido ketones

Effect of parameters on selectivity was checked and optimized for the aldol addition of unsubstituted phenacyl azide **122** and ethyl pyruvate **(94)** (Scheme 31)

Scheme 31. Control reaction for optimization studies

In order to detect the organocatalyst inducing the best stereoselectivity, Brønsted basic organocatalysts which are available in our laboratory were screened in the aldol addition of unsubstituted phenacyl azide **122** and ethyl pyruvate **(94)**. Hydroquinidine (anthraquinone-1,4-diyl) diether **(130)**, $(DHQD)_2AQN$, hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether **(131)**, $(DHQD)_2Pyr$, quinidine (QD) **(36a)**, bifunctional cinchona-(thio)urea catalyst **132** and 1,4-Diazabicyclo[2.2.2]octane (DABCO) **(133)** were selected as catalyst (Figure 11).

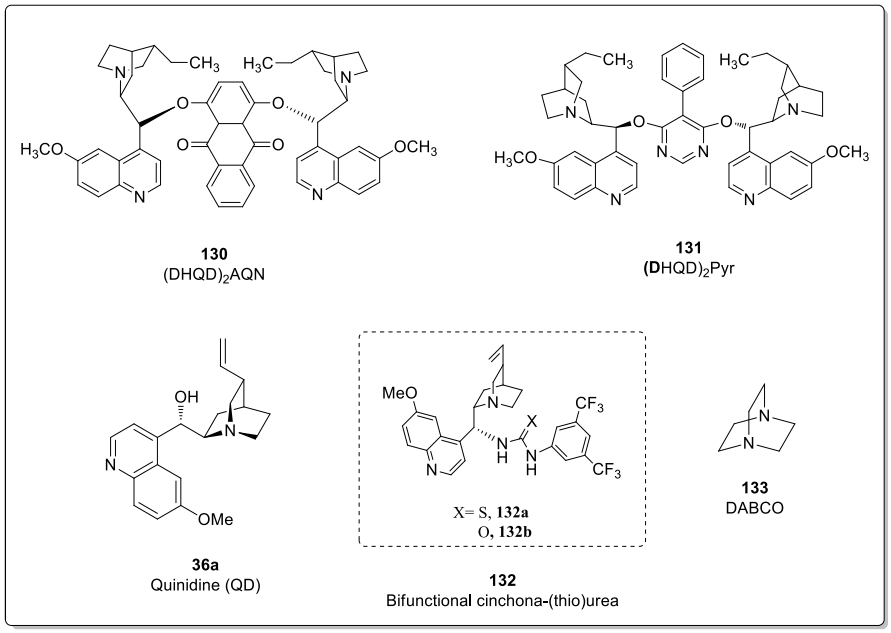


Figure 11. Brønsted basic organocatalysts screened in aldol reaction

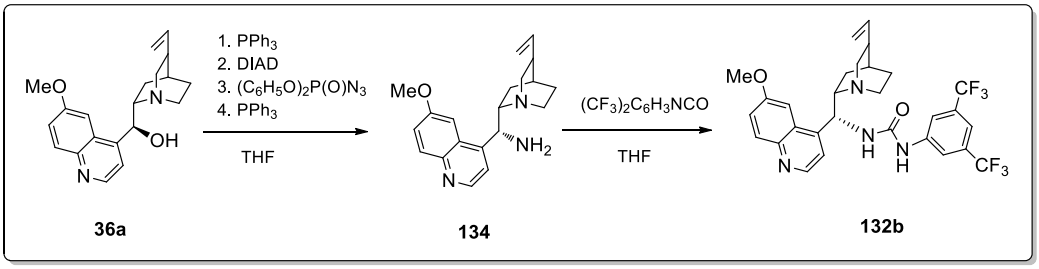
In this part, catalyst loading was kept constant at 10 mol % and reactions were performed in acetonitrile at room temperature. Besides these parameters, 4 eq. of ethyl pyruvate was used and the amount of solvent was adjusted so that the concentration of phenacyl azide was 0.55 M.

Table 1. Catalyst screening results.

catalyst	eq. of **94**	molarity of **122**	solvent	catalyst loading	T (°C)	time	conversion[a]	dr[a] *syn*:*anti*	ee %[b]
36a	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	87	5.2 : 1	-17
130	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	92	3.2 : 1	-29
131	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	93	3.0 : 1	-27
132a	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	60	4.1 : 1	54
132b	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	64	4.7 : 1	56
133	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	95	2.7 : 1	rac

[a] Determined by crude ^{1}H NMR.
[b] minus (-) sign indicates the excess of the opposite enantiomer compared to enantiomer obtained by **132**.

According to the obtained data shown in Table 1, bifunctional cinchona-urea catalyst **132b** was detected as the best one in terms of enantioselectivity. Although the enantiomeric excess was observed in the presence of C_2–symmetrical catalysts **130** and **131**, it was relatively low compared to bifunctional catalyst **132**. DABCO **(133)** catalyzed reaction afforded racemic product as expected since the catalyst is achiral and small compared to others. Additionally, the poorer enantioselectivity in the case of quinuclidine catalyst supports the idea that bifunctionality enhances the selective substrate binding in the course of aldol addition reaction. In accordance with our aim of study, although the obtained conversions are relatively low, optimization studies were continued by using bifunctional cinchona-urea catalyst **132b** due to better diastereo- and enantioselectivity (Table 1). Bifunctional-urea catalyst **132b** was synthesized according to literature procedure [38] starting from quinidine. Firstly, transformation of secondary hydroxyl moiety of quinidine into primary amine via Mitsunobu reaction afforded 9-amino(9-deoxy)quinidine **(134).** Then the nucleophilic attack of primary amine to the 3,5-bis(trifluoromethyl)phenyl isocyanate leads to formation of bifunctional-cinchona urea catalyst **132b** (Scheme 32).



Scheme 32. Synthesis route for catalyst **132b**

Table 2. Screening results of ethyl pyruvate **(94)** in different equivalencies.

catalyst	eq. of **94**	molarity of **122**	solvent	catalyst loading	T (^oC)	time	conversion [a]	dr [a] *syn*: *anti*	ee %
132b	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	64	4.7 : 1	56
132b	2	0.55 M	CH_3CN	10 mol %	r.t.	2d	70	3.3 : 1	47
132b	6	0.55 M	CH_3CN	10 mol %	r.t.	2d	69	3.4 : 1	48
132b	0.25	0.55 M	CH_3CN	10 mol %	r.t.	2d	29	1.9 : 1	15

[a] Determined by crude ^1H NMR.

As the second parameter, the effect of ethyl pyruvate **(94)** equivalency on the selectivity and conversion was monitored. For this purpose, both higher and lower amounts of ethyl pyruvate, such as 2 eq., 6 eq. and 0.25 eq. were examined in the same reaction by using catalyst **132b**. Although, small increase in conversions (70% and 69%) was detected in the

case of 2 eq. and 6 eq. of **94**, respectively, there was a decrease in both diastereo- and enantioselectivity. Since no valuable change was detected in these trials, previously determined 4 eq. was accepted as the best amount for ethyl pyruvate (Table 2).

Table 3. Solvent screening results.

catalyst	eq. of **94**	molarity of **122**	solvent	catalyst loading	T (^oC)	time	conversion [a]	dr [a] *syn*: *anti*	ee %
132b	4	0.55 M	CH_3CN	10 mol %	r.t.	2d	64	4.7 : 1	56
132b	4		Neat	10 mol %	r.t.	4d	78	3.2 : 1	14
132b	4	0.55 M	Toluene	10 mol %	r.t.	4d	77	4.3 : 1	62
132b	4	0.55 M	DCM	10 mol %	r.t.	4d	86	4.0 : 1	58
132b	4	0.55 M	$CHCl_3$	10 mol %	r.t.	4d	84	4.4 : 1	54
132b	4	0.55 M	THF	10 mol %	r.t.	4d	70	3.0 : 1	32
132b	4	0.55 M	Xylene	10 mol %	r.t.	4d	62	4.6 : 1	58
132b	4	0.55 M	1,4-Dioxane	10 mol %	r.t.	4d	77	4.4 : 1	11
132b	4	0.55 M	Cyclohexane	10 mol %	r.t.	4d	78	4.7 : 1	41
132b	4	0.55 M	n-Heptane	10 mol %	r.t.	4d	76	4.0 : 1	56

[a] Determined by crude ^1H NMR.

Thirdly, several solvents and neat condition were examined to detect the best solvent in terms of conversion and selectivity. In general, an increase in conversions was detected at the end of the fourth day except for xylene as a solvent. Though polar aprotic solvents chloroform and dichloromethane resulted for higher conversion (84%, 86%, respectively) obtained enantioselectivity (54% ee, 58% ee) was poorer than the reaction in toluene (77% conversion, 62% ee) (Table 3). Investigating that stereoselectivity is better in relatively nonpolar solvent, toluene; xylene which has similar polarity was also tried. Although the diastereoselectivity is better (dr = 4.6 : 1), enantioselectivity was poorer (58% ee). Finally, other solvents, n-heptane and cyclohexane, having lower polarity than toluene were also checked, but any jump in enantioselectivity could not be detected. Hexane solvent was also considered for our reaction, yet solubility of the catalyst **132b** and the phenacyl azide **122** was problematic. Consequently, toluene solvent of choice led to both higher conversion and enantiomeric excess (77% conversion, 62% ee) than the ones in acetonitrile (64% conversion, 56% ee) (Table 1). Although the diastereomeric ratio in toluene (dr = 4.3 : 1),

determined by ^{1}H NMR) was poorer than in acetonitrile (dr = 4.7 :1), this decrease was attributed to possible epimerization of product due to different reaction times (Table 3). This possibility was then approved by checking the change in diastereomeric ratio of the products at the end of certain time intervals in subsequent screening studies.

Table 4. Screening results of different phenacyl azide **122** concentrations.

catalyst	eq. of **94**	molarity of **122**	solvent	catalyst loading	T (^{o}C)	time	conversion [a]	dr [a] *syn*: *anti*	ee %
132b	4	0.55 M	Toluene	10 mol %	r.t.	4 d	77	4.3 : 1	62
132b	4	1.0 M	Toluene	10 mol %	r.t.	12 h	68	6.6 : 1	59
						1 d	68	7.0 : 1	65
						2 d	73	6.2 : 1	60
						4 d	80	6.2 : 1	57
132b	4	0.60 M	Toluene	10 mol %	r.t.	12 h	68	7.9 : 1	68
						1 d	79	8.1 : 1	65
						2 d	72	7.2 : 1	64
						4 d	78	6.9 : 1	57
132b	4	0.20 M	Toluene	10 mol %	r.t.	12 h	56	12.0 : 1	72
						1 d	66	9.3 : 1	68
						2 d	66	10.8 : 1	68
						4 d	69	8.1 : 1	57
132b	4	0.10 M	Toluene	10 mol %	r.t.	12 h	16	1.5 : 1	70
						1 d	62	8.2 : 1	67
						2 d	62	8.3 : 1	66
						4 d	69	7.6 : 1	48

[a] Determined by crude ^{1}H NMR.

Afterward, solvent amount was monitored to discover the best concentration for the substrate **122**. In previous trials, phenacyl azide concentration was kept constant at 0.55 M. In this stage, different molarities (0.10 M, 0.20 M, 0.60 M, and 1.0 M) of **122** were screened at formerly optimized conditions. Hereafter, conversions, diastereomeric ratio and enantiomeric purity were controlled in certain time intervals via ^{1}H NMR. Considering entries given in Table 4, as the amount of solvent increases and the concentration of **122** decreases, an increase in enantiomeric excess in 12th hour is significant. Our attempt to decrease concentration from 0.20 M to 0.10 M required prolonged reactions times for acceptable conversions. However, long reaction time was disadvantageous due to the epimerization causing decrease in stereoselectivity clearly shown in Table 4. The reason why at high concentrations selectivity was low is the self-aggregation of urea since in the presence of less solvent also urea becomes concentrated. According to the theoretical calculations

represented in the literature, in concentrated solutions urea has tendency to make strong H-bonding with itself. This situation decreases the effective coordination of catalyst **132b** with electrophilic ethyl pyruvate **(94)** via H-bonding, so selectivity of reaction decreases. This situation will also be encountered in the cases for which catalyst loading is relatively high [51]. In the light of mentioned studies and results, the best concentration was concluded to be 0.20 M which led to highest enantioselectivity with 72 % ee and diastereoselectivity with dr = 12.0 : 1 (Table 4).

As the fifth parameter, effect of catalyst loading to the selectivity was checked by using four different catalyst amounts (5 mol%, 15 mol%, 2 mol% and 1 mol%). When the catalyst loading was the highest (15 mol%), though the conversion is the maximum among the other cases (Table 5), both diastereo- and enantioselectivity were poorer again due to the elevated self-aggregation of urea shown in Figure 12. In the presence of 5 mol% and 2 mol% catalyst loading, similar enantiomeric purity by 74% ee was detected at the end of 12th hour. However diastereomeric ratio was better (14.0 : 1) in the presence of 2 mol% catalyst loading. Although there was a decrease in conversion by 4%, (52% conversion in 5 mol% catalyst loading and 48% conversion in 2 mol% catalyst loading), this decrease was negligible since lower catalyst loading is more valuable in catalytic asymmetric synthesis in terms of atom-economy. Our effort to decrease the catalyst loading to 1 mol% brought about very low conversion without any increase in selectivity. Consequently, the optimum catalyst loading was decided to be 2 mol %.

Table 5. Screening results for catalyst loading.

catalyst	eq. of **94**	molarity of **122**	solvent	catalyst loading	T (^{o}C)	time	conversion [a]	dr [a] *syn*: *anti*	ee %
132b	4	0.2M	toluene	10 mol %	r.t.	12h	56	12.0 : 1	72
132b	4	0.2 M	toluene	5 mol %	r.t.	3h	52	10.0 : 1	72
						12h	52	10.0 : 1	74
						1d	52	13.0 : 1	73
132b	4	0.2 M	toluene	15 mol %	r.t.	3h	67	5.7 : 1	67
						12h	67	5.5 : 1	69
						1d	67	7.4 : 1	68
132b	4	0.2M	toluene	2 mol %	r.t.	3h	48	10.2 : 1	71
						12h	47	14.0 : 1	74
						1d	48	14.2 : 1	72
132b	4	0.2 M	toluene	1 mol %	r.t.	3h	32	10.0 : 1	70
						12h	34	12.0 : 1	67
						1d	34	12.0 : 1	65

[a] Determined by crude ^{1}H NMR.

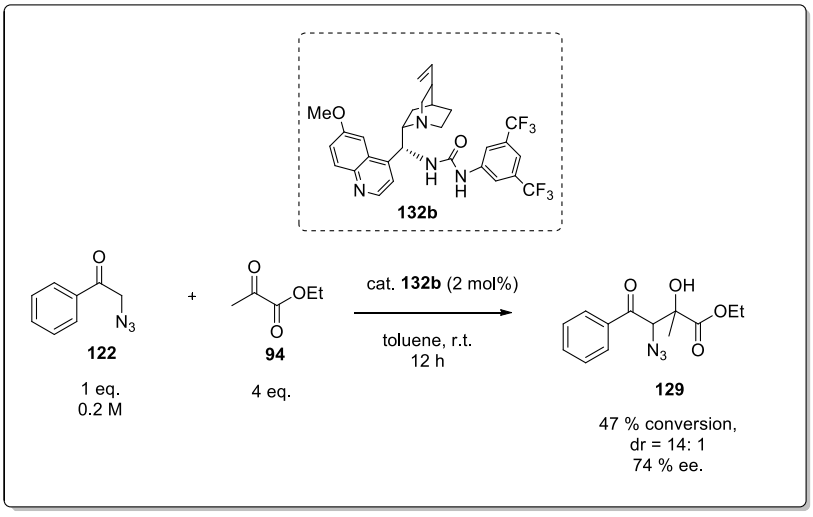
Lastly, effect of temperature was checked. Generally at reduced temperatures, selectivity increases since lower reactivity enhances better selectivity. However, it is not always the case as in our reaction. Reducing the temperature to 0 ^{o}C, a significant decrease in both enantioselectivity and diastereoselectivity, compared to Table 5 (74% ee, dr = 14.0 : 1), was noticed (66% ee, dr = 12.0 : 1) as shown in Table 6. Conditions higher than ambient temperature were not tried due to the thermally labile nature of azides and possibility of transformation to the aldol condensation product.

Table 6. Effect of reduced temperature on selectivity.

catalyst	eq. of **94**	molarity of **122**	solvent	catalyst loading	T (^{o}C)	time	conversion [a]	dr [a] *syn*: *anti*	ee %
132b	4	0.2M	toluene	2 mol %	r.t.	12h	47	14.0 : 1	74
132b	4	0.2 M	toluene	2 mol %	0^{o} C	3h	33	12.0 : 1	60
						12h	33	12.0 : 1	66
						1d	45	9.3 : 1	66

[a] Determined by crude ^{1}H NMR.

As a result of screening studies, the optimum condition for the aldol addition was chosen to be toluene as solvent, 2 mol% catalyst loading and ambient temperature. Also 0.2 M phenacyl azide **122** concentration, 4 eq. of ethyl pyruvate **(94)** were conserved in the following derivatization studies (Scheme 33).



Scheme 33. Optimized conditions for aldol addition of phenacyl azide **122** to ethyl pyruvate

Throughout optimization studies, particularly as shown in Table 4, 5 and 6, decrease in the enantiomeric purity after reaching a maximal value is an important finding supporting our anticipation on possible racemization of the desired product. When only racemization of the major enantiomer by the deprotonation of C-2 proton is presumed, it is normal to expect a decrease in % ee and no change in conversion. However, this prediction partially fails when the fluctuations in conversions and diastereomeric ratios are carefully investigated. That is to say, there are some examples in which diastereomeric ratio increases as % ee decreases. At this point, the possibility of the racemization of minor diastereomer also comes to mind. However, any certain conclusion about the epimerization of the minor diastereomer cannot be derived only considering the conversion and diastereomeric ratio results given in tables since no drastic change was detected. Furthermore, following the reactions by NMR spectroscopy may bring about error in results to some extent.

2.2.2 Derivatization of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates

In this part, various derivatives of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates **95** with electron-donating or electron withdrawing groups on meta- and para- positions are synthesized at optimized conditions. During the reaction course conversions and diastereomeric ratios were similarly monitored by ^{1}H NMR and enantiomeric excess value by chiral HPLC.

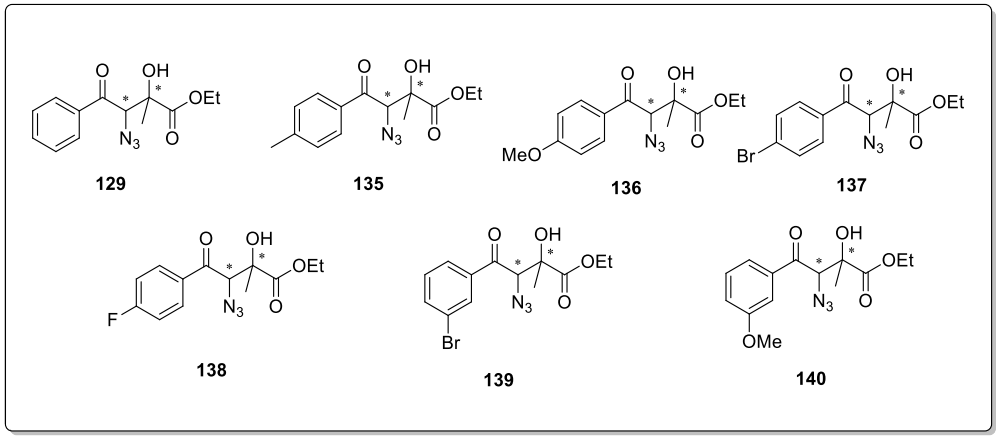


Figure 12. Derivatives of chiral ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates

Results of derivatization studies are summarized in Table 7 indicating the products, time, conversion, diastereomeric ratio and enantiomeric excess. As shown in Table 7, the best enantioselectivity (81% ee) among other derivatives was obtained when the mesomerically electron donating methoxy group is on para-position. However, the conversion was very low (21 %). This situation can be attributed to the electronic effect of methoxy group, because methoxy group at para-position is a deactivating group and relatively decreases the acidity of α-proton. This situation results with a decrease in reactivity, so conversion, and an increase

in selectivity. On the other hand, when the methoxy is on meta- position although conversion is relatively high (41%) (compared to **136**), enantioselectivity is relatively low (68% ee). In the case of 4-Br substituted ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoate **137**, maximum enantiomeric excess obtained was 50%). On the other hand, in spite of having almost same conversions, 3-Br substituted adduct **139** led to 60% ee. The structure of all derivatives was analyzed by ^{1}H and ^{13}C NMR spectroscopy spectra which are available in Appendix A. Similar affinities of both starting material phenacyl azides and adducts toward stationary and mobile phase used in chromatography caused difficulty in the isolation of the adduct. This problem directed us to determine the conversion by ^{1}H NMR of crude product. However for the adduct **139**, since the characteristic peaks of the related phenacyl azide **127** and adduct **139** overlap, only for this compound, the conversion was determined after repeated separation techniques. Therefore, the data given for adduct **139** (55% conversion and dr = 7: 1) is lower than actually obtained ones. Also characterization of compounds was supported by IR spectroscopy and high resolution Mass Spectroscopy data given in experimental part.

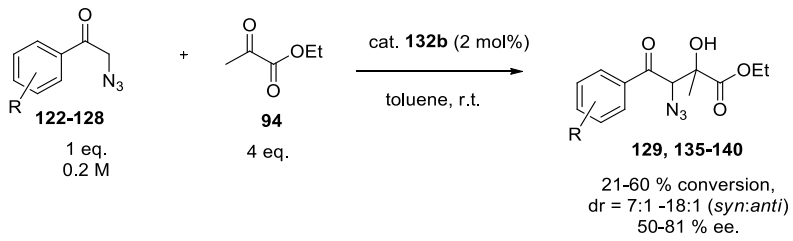


Table 7. Results for various derivatives of ethyl-4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutonates.

product	-R	time	conversion [a,b]	dr [a, b] *syn*: *anti*	ee %
129	H	12 h	47[a]	14 : 1[a]	74
135	4-Me	18 h	27 [a]	18 : 1[a]	78
136	4-OMe	18 h	21 [a]	12 : 1[a]	81
137	4-Br	16 h	60 [a]	10 : 1[a]	50
138	4-F	24 h	44 [a]	12 : 1[a]	75
139	3-Br	18 h	55[b]	7 : 1[b]	60
140	3-OMe	24 h	41 [a]	11: 1[a]	68

[a] Determined by crude ^{1}H NMR.
[b] Determined after column chromatography.

Control of enantiomeric excess values among the derivatization studies reveals that enantiomeric purity of each derivative decreases after reaching a maximum. Graph displaying the change in % ee with reaction duration, clearly represents the racemization of the major enantiomer via deprotonation of alpha acidic (C-2) proton in the presence of Brønsted basic bifunctional cinchona-urea catalyst **132b** (Figure 13).

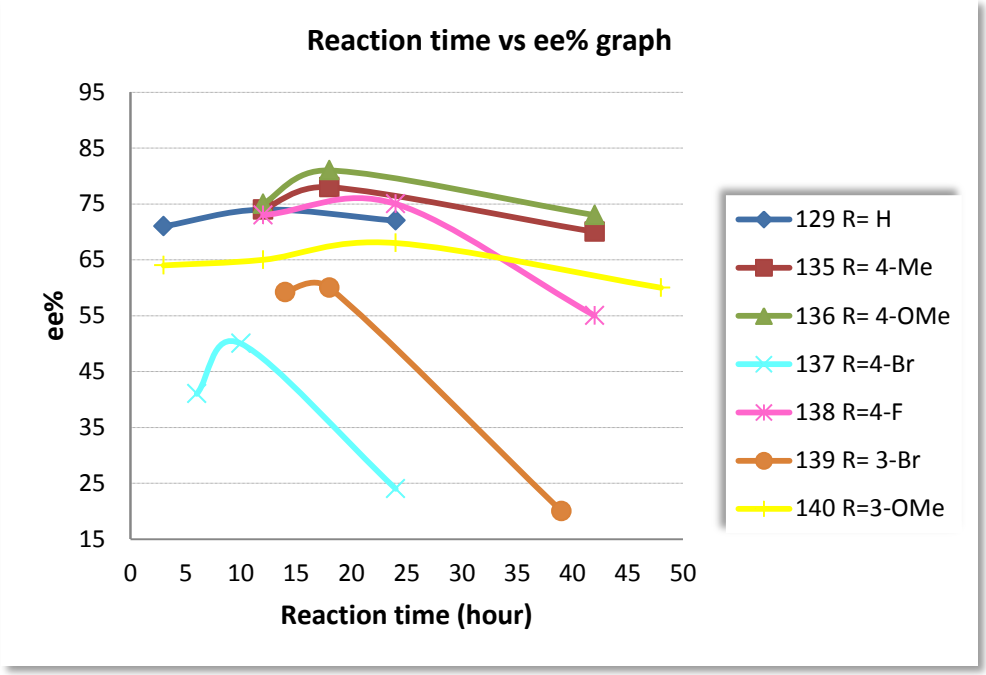


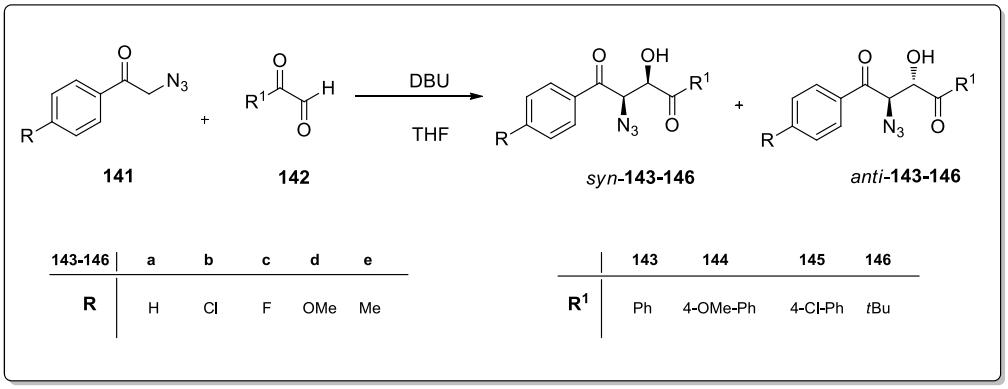
Figure 13. Change in percent enantiomeric excess with reaction time

2.2.3 Determination of relative configuration

In 2008, Patonay and co-workers reported that the reaction of 2-azido-1-(4-methoxyphenyl)ethanone **(124)** and ethyl pyruvate in the presence of stoichiometric amount of DBU as base resulted in the formation of adduct as mixture of *syn* and *anti* isomers. Repeated chromatography afforded diastereopure *syn* and *anti* products separately. Then single-crystal X-ray analysis of the minor product revealed that it has *anti* relative configuration [46].

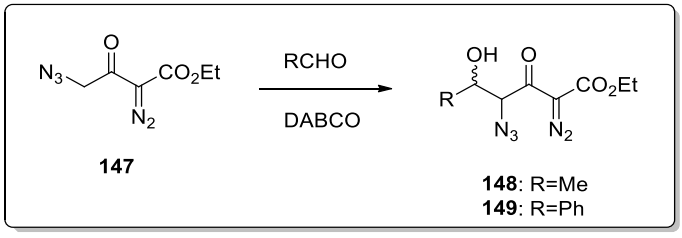
Since ^{1}H NMR and ^{13}C NMR of the product **136** obtained by the reaction of **124** and ethyl pyruvate in the presence of chiral bifunctional catalyst **132b** are in accordance with the reported *syn*-isomer, it is obvious that there is a preference for the formation of *syn*-configuration during C-C bond coupling.

Previous study of Patonay on the aldol reaction of 2-azido-4'-substituted-acetophenones **141** and α-oxo aldehydes **142** afforded 2-azido-3-hydroxy-1,4-diones **143-146** with *syn*-configuration of major product. Furthermore; to assign the diastereomers in the whole series diagnostic differences in their NMR spectra in [D_6] acetone as solvent were used. Characteristically, chemical shifts of the 2-H and 3-H hydrogen atoms of the *syn*-isomers appeared at lower field (Δδ = 0.03-0.06 ppm and Δδ = 0.12-0.15 ppm, respectively). Similarly, in 13C NMR spectra, C-2 carbon atoms of the *syn*-isomers observed at significantly lower field (Δδ = 1.8-2.7 ppm) than their counterparts (Scheme 34) [45].



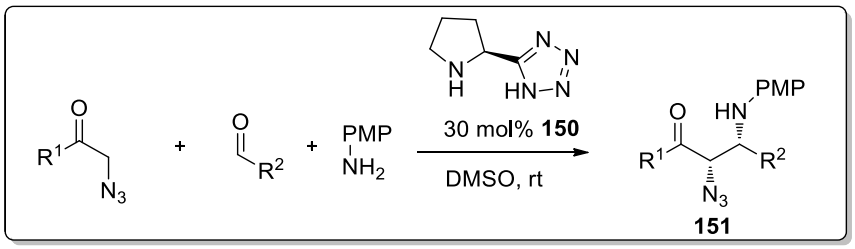
Scheme 34. Aldol reaction of 2-azido-4'-substituted-acetophenones and α-oxo aldehydes

Furthermore, the preference for the *syn*-configuration was also observed in the base promoted reaction of ethyl 4-azido-2-diazo-3-oxo-butanoate **(147)** with both acetaldehyde and benzaldehyde. The resulted mixed aldol products were assigned as *syn* or *anti* by comparison of coupling constants (*syn*-isomer J = 3.5-5.7 Hz and *anti*-isomer J = 7.0-9.5 Hz) of the methine protons at C-2 and C-3 carbon atoms. Due to the thermodynamic control, low diastereoselectivity is typical in the coupling of α-azido ketones with carbon electrophiles but still there is a preference for the *syn*-configuration (Scheme 35) [52].



Scheme 35. Reaction of ethyl 4-azido-2-diazo-3-oxo-butanoate with aldehydes

Moreover, in 2006, Chowdari et al. studied the Mannich reactions of different azido ketones and various aldehydes in the presence of L-proline derived tetrazole **150**. And high diastereoselectivity up to *syn*/*anti* = 94/6 was obtained in the products **151** (Scheme 36) [53].



Scheme 36. Mannich reaction for the synthesis of various 1,2-Azidoamines

Considering our products, since we do not have methine protons coupling each other, coupling constants cannot be used as a tool for the diagnosis of *syn* and *anti* isomers. But, if ^{1}H NMR spectra, reported in the experimental part and Appendix A, are compared with throughout the all series, methine proton (2-H) of the major diastereomers appears at higher field ($\Delta\delta$ = 0.11-0.13 ppm) of minor diastereomers, Similarly, 2-H proton of 4-OMe substituted *syn*-adduct which is in accordance with literature [46] resonates at higher field (δ = 4.55 ppm, 2-H) than its *anti* counterpart (δ = 4.67 ppm, 2-H). Likewise, C-2 carbon atoms of the s*yn*-isomer observed at higher field ($\Delta\delta$ = 1.1-1.7 ppm) than C-2 carbons of *anti*-isomers. On the basis of the mentioned studies we can also say that in the aldol reaction of the alpha azido ketones to ethyl pyruvate, formation of the *syn*-adduct is favored.

CHAPTER 3

EXPERIMENTAL

3.1 Materials and Methods

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

Polarimetric measurements were made by Rudolph Scientific Autopol III polarimeter and reported as follows $[\alpha]_D^T$ (*c* in g per mL, solvent). HPLC chromatograms were recorded on an Agilent 1100 Series. Daicell AD-H and AS-H chiral columns were used with different solvent systems. HPLC chromatograms of chiral products and racemic forms of them were given in appendix B.

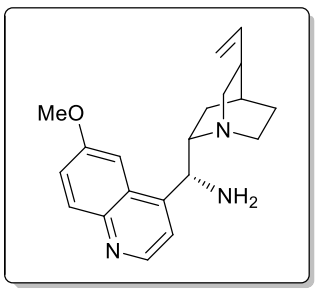
HRMS data were detected on a Agilent 6224 TOF LC/ MS at UNAM, Bilkent University.

Infrared Spectra were recorded on Bruker Alpha Platinum ATR. Band positions were reported in reciprocal centimeters (cm^{-1}).

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

Compounds were named by using ChemDraw Ultra 12.0

3.2 Synthesis of 9-amino(9-deoxy)quinidine (134)



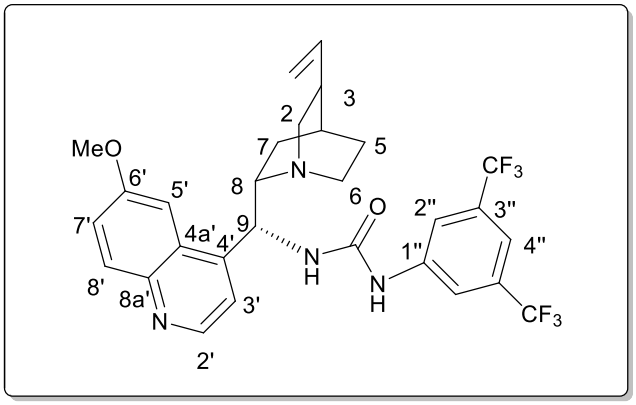
According to literature procedure [38], quinidine (3.24 g, 10 mmol) and 1.2 eq triphenylphosphine (3.15 g, 12.0 mmol) were dissolved in 50 mL of dry THF and the solution was cooled to 0 °C. Then 1.2 eq. diisopropyl azodicarboxylate (2.43 g, 12.0 mmol) was added all at once to the initial solution. In another flask, diphenyl phosphoryl azide (3.30 g, 12.0 mmol) solution in 20 mL THF was cooled to 0 °C in ice bath. The second

solution was added to the original flask dropwise at 0 ^{o}C . The mixture was allowed to warm to room temperature. After 12 h stirring, the solution was heated to 50 ^{0}C for 2 h. Then 1.3 eq. triphenylphosphine (3.41 g, 13.0 mmol) was added and heating was continued until the gas evolution has finished. The solution was cooled to room temperature and 1 mL of water was added. The resulting mixture was stirred at room temperature for 3 h. After removing the solvents *in vacuo*, the residue was dissolved in CH_2Cl_2 and 10% hydrochloric acid (1:1, 100 mL). The aqueous phase was washed with CH_2Cl_2 (4 x 50 mL). Later aqueous phase was made alkaline with excess cc. aqueous ammonia and washed with CH_2Cl_2 (4 x 50 mL). The combined organic phases was dried of $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/ MeOH/ NEt_3 = 50/ 50/ 1 as eluent). Chromatography afforded the title compound as yellowish viscous oil with 70% yield).

Spectroscopic data have been reported previously [38].

3.3 Synthesis of urea catalyst 132b

According to literature procedure [38], to a solution of 9-amino(9-deoxy)quinidine **(134)** (6.8 mmol, 2.20 g) in dry THF (20 mL) was slowly added to a solution of 3,5-bis(trifluoromethyl)phenyl isocyanate (6.8 mmol) in 10 mL of dry THF at room temperature. The mixture was allowed to stir overnight. Then the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/ MeOH/ NEt_3 = 300/ 5/ 1 as eluent) affording urea **132b** (85% yield) as white solid.



^{1}H NMR (400 MHz, CD_3OD) δ: 8.64 (d, *J* = 4.7 Hz, 1H, H-2′), 7.91 (bs, 2H, H-2″), 7.90 (d, *J* = 9.5 Hz, 1H, H-8′), 7.79 (d, *J* = 2.5 Hz, 1H, H-5′), 7.51 (d, *J* = 4.7 Hz, 1H, H-3′), 7.39 (bs, 1H, H-4″), 7.37 (dd, J_1 = 9.3 Hz, J_2 = 2.6 Hz, 1H, H-7′), 5.85 (ddd, J_1 = 17.2 Hz, J_2 = 10.5 Hz, J_3 = 6.2 Hz, 1H, CH=CH_2), 5.61 (bs, 1H, H-9), 5.02(d, *J* =17.2 Hz, 1H, CH=CH_2), 4.97 (d, *J* = 10.5 Hz, 1H, CH=CH_2), 3.96 (s, 3H, -OCH_3), 3.60-3.45 (m, 2H), 3.32-3.26 (m, 1H), 2.90-2.77 (m, 2H), 2.40-2.30 (m, 1H), 1.74-1.50 (m, 3H), 0.90-0.70 (m, 2H)

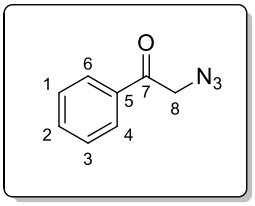
^{13}C NMR (100 MHz, CD_3OD) δ: 159.9 (C=O), 158.7, 148.3, 147.3, 143.3, 142.3, 133.1 (q, $^{3}J_{CF}$ =33.0 Hz, C-3″), 131.5, 130.0, 124.8, (q, $^{1}J_{CF}$ =271.8, CF_3), 123.7, 119.1, 119.0, 115.6, 115.3, 115.6 (sept, $^{4}J_{CF}$ = 3.7 Hz, C-4″), 115.3, 103.1, 60.7, 56.8, 56.3, 42.3, 40.5, 28.8, 28.2, 27.4

3.4 General Procedure for the synthesis of phenacyl azides 93

To a stirred solution of appropriate 2-bromo-1-phenylethanone **121** (5.02 mmol) in 40 mL acetone, 3 eq. of sodium azide (0.979 g, 15.06 mmol) was added at room temperature. The resulting solution was stirred overnight at room temperature. The reaction was checked by TLC. After the completion of reaction, the solvent was evaporated. Then the mixture was poured into water and extracted by ethyl acetate (3 x 50 mL). The organic layer was dried over $MgSO_4$, and concentrated *in vacuo.* After the evaporation of solvent the crude product was purified by column chromatography eluting with ethyl acetate: hexane (1:5) to give 2-azido-1-phenylethanone **93**.

3.4.1 Synthesis of 2-azido-1-phenylethanone (122)

General procedure starting from 2-bromo-1-phenylethanone afforded pure product **122**. (81% yield, yellow oil. Spectroscopic data have been reported previously [54].



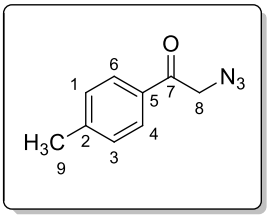
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.54 (s, 2H, H-8), 7.45-7.50 (m, 2H, H-1,3), 7.58-7.62 (m, 1H, H-2), 7.86-7.90 (m, 2H, H-1,3), 4.72-4.41 (m, 3H, H-6,4).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.8, 127.9, 129.0, 134.1, 134.4, 193.3

IR: 2195 (N_3), 2105, 1698 (C=O), 1286 cm^{-1}

3.4.2 Synthesis of 2-azido-1-(*p*-tolyl)ethanone (123)

General procedure starting from 2-bromo-1-(*p*-tolyl)ethanone afforded pure product **123.** (80% yield, white solid) (m.p. 63-65 ^{0}C) Spectroscopic data have been reported previously [55].



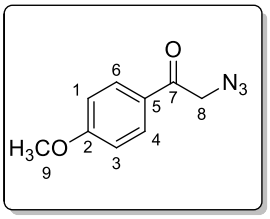
^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.42 (s, 3H, H-9), 4.53 (s, 2H, H-8), 7.28 (d, *J* = 8.2 Hz, 2H, H-1,3), 7.80 (d, *J* = 8.2 Hz, 2H, H-6,4)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.7, 54.8, 128.0, 129.6, 131.9, 145.1, 192.8

IR: 2969, 2100 (N_3), 1686 (C=O) cm^{-1}

3.4.3 Synthesis of 2-azido-1-(4-methoxyphenyl)ethanone (124)

General procedure starting from 2-bromo-1-(4-methoxyphenyl)ethanone afforded pure product **124.** (94% yield, yellowish-white crystals) (m.p. 68-69 ^{0}C). Spectroscopic data have been reported previously [56].



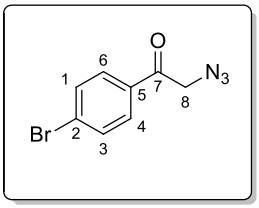
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.88 (s, 3H, H-9), 4.50 (s, 2H, H-8), 6.95 (d, *J* = 8.9 Hz, 2H, H-1,3), 7.88 (d, *J* = 8.9 Hz, 2H, H-6,4)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.5, 55.6, 114.1, 127.4, 130.3, 164.2, 191.7

IR: 2124 (N_3), 1684 (C=O), 1600, 1240 (C-O-C), 1178, 826 cm^{-1}

3.4.4 Synthesis of 2-azido-1-(4-bromophenyl)ethanone (125)

General procedure starting from 2-bromo-1-(4-bromophenyl)ethanone afforded pure product **125.** (89% yield, orange crystals) (m.p. 86-87 ^{0}C). Spectroscopic data have been reported previously [57].



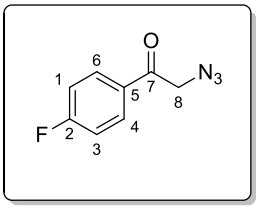
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.54 (s, 2H, H-8), 7.65 (d, *J* = 6.8 Hz, 2H, H-1,3), 7.77 (d, *J* = 6.8 Hz, 2H, H-6,4)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.8, 129.4-133.1 (Ar-C), 192.3

IR: 2107 (N_3), 1700 (C=O) cm^{-1}

3.4.5 Synthesis of 2-azido-1-(4-fluorophenyl)ethanone (126)

General procedure starting from 2-bromo-1-(4-fluorophenyl)ethanone afforded pure product **126**. (93% yield, yellow crystals) (m.p. 49-50 ^{0}C). Spectroscopic data have been reported previously [54].



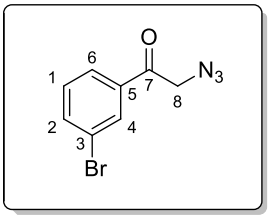
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.47(s, 2H, H-8), 7.18 (dd, *J* = 9.0 Hz, J_{HF} = 8.9 Hz, 2H, H-1,3), 7.97 (dd, *J* = 9.0 Hz, J_{HF} = 5.4 Hz, 2H, H-6,4)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.5, 116.3 (d, J_{CF} = 22.2 Hz), 130.8 (d, J_{CF} = 9.5 Hz), 130.9, 166.5 (d, J_{CF} = 256 Hz), 192.0

IR: 2100 (N_3), 1689 (C=O), 1594, 1226, 1217, 834 cm^{-1}

3.4.6 Synthesis of 2-azido-1-(3-bromophenyl)ethanone (127)

General procedure starting from 2-bromo-1-(3-bromophenyl)ethanone afforded pure product **127**. (91% yield, yellow crystals) (m.p. 51-53 ^{0}C)



^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.47 (s, 2H, H-8), 7.32 (t, *J* = 7.8 Hz, 1H, H-1), 7.69 (ddd, *J* = 7.8, 1.2, 1.0 Hz, 1H, H-6), 7.76 (dt, *J* = 8.9, 1.0 Hz, 1H, H-2), 7.98 (t, *J* = 1.8 Hz, H-4)

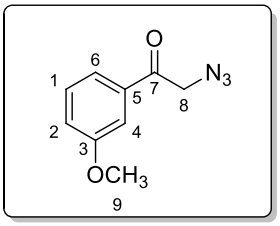
^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.9, 123.3, 126.4, 130.5, 131.0, 136.1, 137.0, 192.0

IR: 2104 (N_3), 1692 (C=O), 1568, 1287, 1209, 923 cm^{-1}

HRMS: C_8H_7BrNO (MH^+- N_2): Calcd 211.9633, found 211.9654

3.4.7 Synthesis of 2-azido-1-(3-methoxy)ethanone (128)

General procedure starting from 2-bromo-1-(3-methoxyphenyl)ethanone afforded pure product **128**. (91% yield, yellow oil)



^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (s, 3H, OCH_3), 4.43 (s, 2H, H-8), 7.08-7.11 (m, 1H), 7.30-7.40 (m, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 54.9, 55.5, 112.3, 120.3, 120.6, 130.0, 135.7, 160.1, 193.1

IR: 2121 (N_3), 1681 (C=O), 1596, 1515, 1236 (C-O-C), 1120 cm^{-1}

HRMS: $C_9H_{10}NO_2$ (MH^+- N_2): Calcd 164.0712, found 164.0727

3.5 General procedure for the racemic synthesis of 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates *rac*-95

To a 0.8 M solution of related phenacyl azide **93** (0.5 mmol) and catalyst DABCO **(133)** (10 mol %) in acetonitrile (0.625 mL) 4 eq. of ethyl pyruvate **(94)** (0.222 mL) was added at room temperature. Reaction progress was monitored by TLC. After the completion of the reaction, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in minimum amount of solvent for column chromatography on silica gel. For chromatography, gradient solvent system ethyl acetate: hexane (1:20), (1:15), (1:10) and (1:5) was used. Products were isolated as diastereomeric mixture of *rac*- **95** with 75-90 % yield.

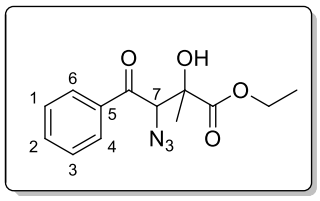
3.6 General procedure for the asymmetric organocatalytic synthesis of chiral ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates 95

To a 0.2 M solution of appropriate phenacyl azide **93** (1 mmol) and catalyst **132b** (2 mol %) in toluene (4.56 mL), 4 eq. of ethyl pyruvate **(94)** (0.444 mL) was added at room temperature. At the end of certain time intervals, conversions and diastereomeric ratios were monitored by crude ^{1}H NMR. Also enantiomeric excess values were checked by chiral HPLC as reaction proceeds. After the completion of the reaction, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in minimum amount of solvent for column chromatography on silica gel. For chromatography, gradient solvent system ethyl acetate:hexane (1:20), (1:15), (1:10) and (1:5) was used. Repeated column chromatography afforded generally diastereomeric mixture of **95** and pure diastereomers for one derivative.

3.6.1 Synthesis of ethyl 3-azido-2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate (129)

General procedure starting from 2-azido-1-phenylethanone afforded **129** as mixture of *syn*/*anti* isomers with ratio 14:1 (*syn*:*anti*) and 47% conversion (based on crude ^{1}H NMR) at the end of 12 h (yellow oil)

Diastereomeric mixture 129



^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.10 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***syn*-129**), 1.29 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***anti*-129**), 1.43 (s, 3H, -CH_3, ***anti*-129**), 1.54 (s, 3H, -CH_3), 3.70 (s, 1H, -OH, ***anti*-129**), 3.90 (s, 1H, -OH, ***syn*-129**), 3.99-4.10 (m, 2H, -OCH_2CH_3, ***syn*-129**), 4.24-4.33 (m, 2H, -OCH_2CH_3, ***anti*-129**), 4.54 (s, 1H, H-7, ***syn*-129**), 4.66 (s, 1H, H-7, ***anti*-129**) Inseparable signals: δ: 7.43-7.47 (m, 2H, H-1,3), 7.54-7.60 (m, 1H, H-2), 7.92-7.95 (m, 2H, H-4,6)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.9, 13.0, 22.5, 23.1, 61.0, 61.9, 64.5, 65.7, 75.2, 76.2, 127.9, 128.0, 128.1, 133.1, 133.3, 133.5, 133.9, 173.1, 173.3, 193.6, 195.4

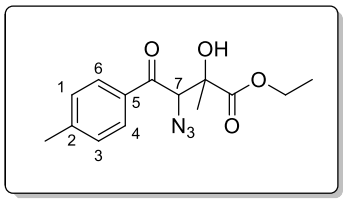
IR: 3481 (OH), 2137 (N_3), 1731, 1684, 1653, 1596, 1448, 1374, 1258, 1182, 1016 cm^{-1}

HRMS: $C_{11}H_{11}NO_3Cl$ (MH^+-N_2 +Cl -OEt): Calcd 240.0427, found 239.2272

3.6.2 Synthesis of ethyl 3-azido-2-hydroxy-2-methyl-4-oxo-4-(p-tolyl)butanoate (135)

General procedure starting from 2-azido-1-(*p*-tolyl)ethanone afforded **135** as diastereomeric mixture of *syn*/*anti* isomers with ratio: 18:1 (*syn*:*anti*) and 27% conversion (based on crude ^{1}H NMR) at the end of 18 h (yellow oil)

Diastereomeric mixture 135



^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.17 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***syn*-135**), 1.37 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***anti*-135**), 1.50 (s, 3H, -CH_3, ***anti*-135**), 1.60 (s, 3H, -CH_3, ***syn*-135**), 3.77 (s, 1H, -OH, **anti-135**), 4.02 (s, 1H, -OH, ***syn*-135**), 4.12 (q, *J* = 7.1 Hz, 2H, -OCH_2CH_3, ***syn*-135**), 4.31-4.40 (m, 2H, -OCH_2CH_3, ***anti*-135**), 4.59 (s, 1H, H-7, ***syn*-135**), 4.71 (s, 1H, H-7, ***anti*-135**) Inseparable signals: δ: 2.44 (s, 3H, -Ar-CH_3), 7.31 (d, *J* = 8.0 Hz, 2H, H-1,3), 7.89-7.92 (m, 2H, H-4,6)

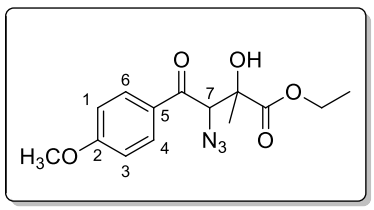
^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 21.8, 21.9, 23.4, 24.1, 62.0, 62.9, 65.2, 66.4, 76.2, 77.2, 116.0, 116.3, 129.2, 129.3, 129.7, 132.2, 145.6, 145.9, 174.1, 174.3, 194.1, 195.9

IR: 3469 (OH), 2100 (N_3), 1728, 1680, 1604, 1447, 1257, 1225, 1183, 1148, 1016 cm^{-1}

HRMS: $C_{14}H_{18}NO_4$ (MH^+- N_2): Calcd 264.1236, found 264.1256

3.6.3 Synthesis of ethyl 3-azido-2-hydroxy-4-(4-methoxyphenyl)-2-methyl-4-oxobutanoate (136)

General procedure starting from 2-azido-1-(4-methoxyphenyl)ethanone afforded diastereomeric mixture of **136** as mixture of *syn*/*anti* isomers with ratio 12:1 (*syn*:*anti*) and 21% conversion (based on crude ^{1}H NMR) at the end of 18 h. Repeated column chromatography afforded pure diastereomer *syn*-**136** as colorless oil. Unfortunately, *anti*-**136** could not be isolated. But it was reported as white solid (m.p. 87-90 ^{o}C) Spectroscopic data have been reported previously [46].



***syn*-136: ^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.13 (t, *J* = 7.2 Hz, 3H, -OCH_2CH_3), 1.57 (s, 3H, -CH_3) 3.86 (s, 3H, -OCH_3), 4.09 (q, *J* = 7.2 Hz, 2H, -OCH_2CH_3), 4.55 (s, 1H, H-7), 6.95 (d, *J* = 89.1 Hz, 2H, H-1,3), 7.97 (d, *J* = 9.1 Hz, 2H, H-4,6)

***syn*-136: ^{13}C NMR** (100 MHz, $CDCl_3$) δ: 13.9, 23.4, 55.6, 61.9, 64.0, 77.4, 114.2, 127.6, 131.7, 164.8, 174.2, 194.7

IR: 3500 (OH), 2100 (N_3), 1746, 1732, 1682, 1600, 1312, 1266, 1224, 1174, 1020 cm^{-1}

***anti*-136 : ^{1}H NMR** (400 MHz, $CDCl_3$) δ: 1.35 (t, *J* = 7.2 Hz, 3H, -OCH_2CH_3), 1.48 (s, 3H, -CH_3) 3.88 (s, 3H, -OCH_3), 4.33 (dq, *J* = 7.2 Hz, *J* = 2.2 Hz, 2H, -OCH_2CH_3), 4.67 (s, 1H, H-7), 6.96 (dd, *J* = 9.2, *J* = 2.1 Hz, 2H, H-1,3), 7.99 (dd, *J* = 9.2, 2.1 Hz, 2H, H-4,6) (Literature value)

***anti*-136 : ^{13}C NMR** (100 MHz, $CDCl_3$) δ: 13.9, 24.0, 55.5, 61.9, 66.2, 76.2, 114.1, 128.6, 131.6, 164.5, 174.3, 192.7 (Literature value)

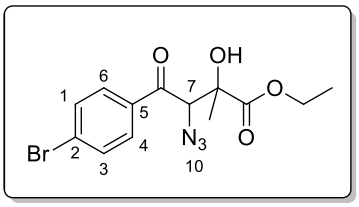
IR: 3470 (OH), 2101 (N_3), 1723, 1672, 1600, 1264, 1180 cm^{-1} (Literature value)

HRMS: $C_{14}H_{18}N_3O_5$ (MH^+): Calcd 308.1246, found 308.1256

3.6.4 Synthesis of ethyl 3-azido-4-(4-bromophenyl)-2-hydroxy-2-methyl-4-oxobutanoate (137)

General procedure starting from 2-azido-1-(4-bromophenyl)ethanone afforded diastereomeric mixture of **137** as mixture of *syn*/*anti* isomers with ratio 10:1 (*syn*:*anti*) and 60% conversion (based on crude ^{1}H NMR) at the end of 16 h (yellow oil)

Diastereomeric mixture 137



^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***syn*-137**), 1.30 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***anti*-137**), 1.43 (s, 3H, -CH_3, ***anti*-137**), 1.53 (s, 3H, -CH_3, ***syn*-137**), 3.69 (bs, 1H, -OH, ***anti*-137**), 3.83 (bs, 1H, -OH, ***syn*-137**), 4.07 (q, *J* = 7.1 Hz, 2H, -OCH_2CH_3, ***syn*-137**), 4.25-4.33 (m, 2H, -OCH_2CH_3, ***anti*-137**), 4.55 (s, 1H, H-7, ***syn*-137**), 4.67 (s, 1H, H-7, ***anti*-137**) Inseparable signals: δ: 7.57-7.60 (m, 2H, H-1,3), 7.79-7.83 (m, 2H, H-4,6)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 23.5, 24.1, 62.2, 63.1, 65.7, 67.3, 76.0, 77.2, 129.8, 130.1, 130.6, 130.7, 132.2, 132.3, 133.5, 134.5, 174.0, 174.2, 193.7, 195.4

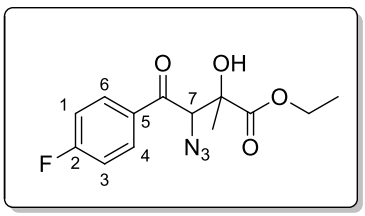
IR: 3467 (OH), 2099 (N_3), 1730, 1686, 1584, 1397, 1256, 1070 cm^{-1}

HRMS: $C_{11}H_9BrN_3O_4$ (M^+- C_2H_5): Calcd 325.9776, found 325.9770

3.6.5 Synthesis of ethyl 3-azido-4-(4-fluorophenyl)-2-hydroxy-2-methyl-4-oxobutanoate (138)

General procedure starting from 2-azido-1-(4-fluorophenyl)ethanone afforded diastereomeric mixture of **138** as mixture of *syn*/*anti* isomers with ratio 12:1 (*syn*:*anti*) and 44% conversion (based on crude ^{1}H NMR) at the end of 24 h (yellow oil)

Diastereomeric mixture 138



^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***syn*-138**), 1.37 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***anti*-138)**, 1.43 (s, 3H, -CH_3, ***anti*-138**), 1.53 (s, 3H, -CH_3, ***syn*-138**), 3.73 (s, 1H, -OH, ***anti*-138),** 3.89 (s, 1H, -OH, ***syn*-138**), 4.06 (q, *J* = 7.1 Hz, 2H, -OCH_2CH_3, ***syn*-138**),

4.24-4.32 (m, 2H, -OCH_2CH_3, ***anti*-138)**, 4.49 (s, 1H, H-7, ***syn*-138**), 4.61 (s, 1H, H-7, ***anti*-138)** Inseparable signals: δ: 7.09-7.14 (m, 2H, H-1,3), 7.96-8.01 (m, 2H, H-4,6)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 23.5, 24.0, 62.1, 63.0, 65.6, 67.1, 76.1, 77.2, 116.1 (d, J_{CF}= 22.1 Hz), 116.2 (d, J_{CF}= 22.1 Hz), 131.2 (d, J_{CF}= 9.7 Hz), 132.0 (d, J_{CF}= 9.7 Hz), 166.4, (d, J_{CF}= 257.7 Hz), 166.5, (d, J_{CF}= 257.7 Hz), 174.1, 174.2, 193.0, 194.7

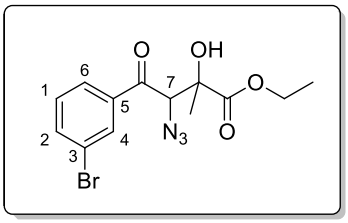
IR: 3484 (OH), 2099 (N_3), 2093, 1711, 1675, 1351, 1265, 1161, 1120, 1067, 1014 cm^{-1}

HRMS: $C_{13}H_{14}FN_3O_4$ (MNa^+): Calcd 318.0866, found 318.0876

3.6.6 Synthesis of ethyl 3-azido-4-(3-bromophenyl)-2-hydroxy-2-methyl-4-oxobutanoate (139)

General procedure starting from 2-azido-1-(3-bromophenyl)ethanone afforded diastereomeric mixture of **139** as mixture of *syn*/*anti* isomers with isolated ratio 7:1 (*syn*:*anti*) and 55% isolated yield at the end of 18 h (yellow oil)

Diastereomeric mixture 139



^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***syn*-139**), 1.30 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***anti*-139**), 1.43 (s, 3H, -CH_3, ***anti*-139**), 1.54 (s, 3H, -CH_3, ***syn*-139**), 3.57 (s, 1H, -OH, ***anti*-139**), 3.81 (s, 1H, -OH, ***syn*-139**), 4.00-4.11 (m, 2H, -OCH_2CH_3, ***syn*-139**), 4.25-4.32 (m, 2H, -OCH_2CH_3, ***anti*-139**), 4.47 (s, 1H, H-7, ***syn*-139**), 4.58 (s, 1H, H-7, ***anti*-139**), 7.32 (t, *J* =7.9 Hz, 1H, H-1, ***anti*-139**), 7.33 (t, *J* =7.9 Hz, 1H, H-1, ***syn*-139**), 8.05 (t, *J* =1.5 Hz, 1H, H-4, ***anti*-139**), 8.07 (t, *J* = 1.5 Hz, 1H, H-4, ***syn*-139**). Inseparable signals: δ: 7.70 (d, *J* = 8.7 Hz, 1H, H-6), 7.86 (d, *J* = 7.8 Hz, 1H, H-2)

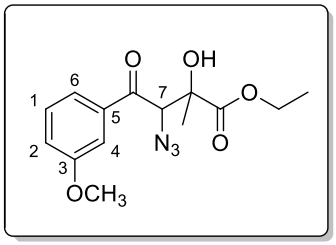
^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.9, 13.0, 22.5, 23.0, 61.2, 62.1, 64.7, 66.3, 75.0, 76.2, 122.2, 126.7, 129.4, 129.5, 131.0, 131.1, 135.4, 135.5, 136.3, 172.4, 173.0, 192.4, 194.0
IR: 3482 (OH), 2103 (N_3), 1731, 1687, 1588, 1566, 1456, 1210, 1016 cm^{-1}

HRMS: $C_{11}H_9BrN_3O_4$ (M^+- C_2H_5): Calcd 325.9776, found 325.9772

3.6.7 Synthesis of ethyl 3-azido-2-hydroxy-4-(3-methoxyphenyl)-2-methyl-4-oxobutanoate (140)

General procedure starting from 2-azido-1-(3-methoxyphenyl)ethanone afforded diastereomeric mixture of **140** as mixture of *syn*/*anti* isomers with ratio 11:1 (*syn*:*anti*) and 41% conversion (based on crude ^{1}H NMR) at the end of 24 h (yellow oil)

Diastereomeric mixture 140



^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***syn*-140**), 1.28 (t, *J* = 7.1 Hz, 3H, -OCH_2CH_3, ***anti*-140**), 1.41 (s, 3H, -CH_3, ***syn*-140**), 1.53 (s, 3H, -CH_3, ***anti*-140**), 3.70 (s, 1H, -OH, ***anti*-140**), 3.79 (s, 1H, -OH, ***syn*-140**), 4.03 (dq, *J* = 7.1, 3.3 Hz, 2H, -OCH_2CH_3, ***syn*-140**), 4.20-4.33 (m, 2H, -OCH_2CH_3, ***anti*-140**), 4.51 (s, 1H, H-7, ***syn*-140**), 4.64 (s, 1H, H-7, ***anti*-140**) Inseparable signals: δ: 3.78 (s, 3H, -OCH_3), 7.08-7.15 (m, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.41-7.46 (m, 1H), 7.50-7.53 (m, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.0, 23.5, 24.0, 55.5, 62.1, 62.9, 65.5, 66.6, 76.2, 77.3, 113.0, 113.2, 121.0, 121.1, 121.6, 121.7, 129.9, 136.1, 137.2, 160.0, 174.0, 174.3, 194.4, 196.2

IR: 3490 (OH), 2099 (N_3), 2099, 1730, 1680, 1596, 1580, 1430, 1249, 1199, 1018 cm^{-1}

HRMS: $C_{14}H_{17}N_3O_5$ (MNa^+): Calcd 330.1066, found 330.1085

3.7 HPLC conditions of chiral 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates 95

3.7.1 Ethyl 3-azido-2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate (129)

Enantiomerically enriched chiral ethyl 3-azido-2-hydroxy-2-methyl-4-oxo-4-phenylbutanoate **(129)** was obtained up to 74% ee . Enantiomeric purity was determined by chiral HPLC analysis (AS-H column, hexane/*i*-PrOH 99:1, flow rate 1 mL/min, λ= 254 nm) t_R = 17.56 min (major enantiomer of ***syn*-129**), t_R = 14.68 min (minor enantiomer of ***syn*-129**); t_R = 30.34 min (major enantiomer of ***anti*-129**),t_R = 25.98 min (minor enantiomer of ***anti*-129**).

Optical rotation of the diastereomeric mixture was determined as $[\alpha]_D^{22}$= +1.7° (*c* = 5.2 x 10^{-3} g/mL, $CHCl_3$)

3.7.2 Ethyl 3-azido-2-hydroxy-2-methyl-4-oxo-4-(p-tolyl)butanoate (135)

Enantiomerically enriched chiral ethyl 3-azido-2-hydroxy-2-methyl-4-oxo-4-(p-tolyl)butanoate **(135)** was obtained up to 78% ee . Enantiomeric purity was determined by chiral HPLC analysis (AS-H column, hexane/*i*-PrOH 99:1, flow rate 1 mL/min, λ= 254 nm) t_R = 12.93 min (major enantiomer of ***syn*-135**), t_R = 10.91 min (minor enantiomer of ***syn*-135**); t_R = 24.99 min (major enantiomer of ***anti*-135**), t_R = 20.00 min (minor enantiomer of ***anti*-135**).

Optical rotation of the diastereomeric mixture was determined as $[\alpha]_D^{23}$= +7.4° (*c* = 2.5 x 10^{-3} g/mL, $CHCl_3$)

3.7.3 Ethyl 3-azido-2-hydroxy-4-(4-methoxyphenyl)-2-methyl-4-oxobutanoate (136)

Enantiomerically enriched chiral ethyl 3-azido-2-hydroxy-4-(4-methoxyphenyl)-2-methyl-4-oxobutanoate **(136)** was obtained up to 81% ee Enantiomeric purity was determined by chiral HPLC analysis (AD-H column, hexane/*i*-PrOH 93:7, flow rate 1 mL/min, λ= 254 nm) t_R = 19.38 min (major enantiomer of ***syn*-136**),t_R =17.53 min (minor enantiomer of ***syn*-136**); t_R = 29.82 min (major enantiomer of ***anti*-136**),t_R = 24.53 min (minor enantiomer of ***anti*-136**).

Optical rotation of the ***syn*- 136** was determined as $[\alpha]_D^{22}$= +133.0^o (*c* = 2.6 x 10^{-3} g/mL, $CHCl_3$)

3.7.4 Ethyl 3-azido-2-hydroxy-4-(4-bromophenyl)-2-methyl-4-oxobutanoate (137)

Enantiomerically enriched chiral ethyl 3-azido-2-hydroxy-4-(4-bromophenyl)-2-methyl-4-oxobutanoate **(137)** was obtained up to 50% ee . Enantiomeric purity was determined by chiral HPLC analysis (AS-H column, hexane/*i*-PrOH 99:1, flow rate 1 mL/min, λ= 254 nm) t_R = 19.27 min (major enantiomer of ***syn*-137**),t_R =16.54 min (minor enantiomer of ***syn*-137**); t_R = 27.35 min (major enantiomer of ***anti*-137**),t_R = 31.70 min (minor enantiomer of ***anti*-137**).

Optical rotation of the diastereomeric mixture was determined as $[\alpha]_D^{23}$= +2.1^o (*c* = 14.8 x 10^{-3} g/mL, $CHCl_3$)

3.7.5 Ethyl 3-azido-2-hydroxy-4-(4-fluorophenyl)-2-methyl-4-oxobutanoate (138)

Enantiomerically enriched chiral ethyl 3-azido-2-hydroxy-4-(4-fluorophenyl)-2-methyl-4-oxobutanoate **(138)** was obtained up to 75% ee . Enantiomeric purity was determined by chiral HPLC analysis (AD-H column, hexane/*i*-PrOH 97:3, flow rate 1 mL/min, λ= 254 nm) t_R = 21.07 min (major enantiomer of ***syn*-138**),t_R =18.12 min (minor enantiomer of ***syn*-138**); t_R = 26.70 min (major enantiomer of ***anti*-138**),t_R = 24.68 min (minor enantiomer of ***anti*-138**).

Optical rotation of the diastereomeric mixture was determined as $[\alpha]_D^{23}$= +50.0^o (*c* = 3.1 x 10^{-3} g/mL, $CHCl_3$)

3.7.6 Ethyl 3-azido-2-hydroxy-4-(3-bromophenyl)-2-methyl-4-oxobutanoate (139)

Enantiomerically enriched chiral ethyl 3-azido-2-hydroxy-4-(3-bromophenyl)-2-methyl-4-oxobutanoate **(139)** was obtained up to 60% ee Enantiomeric purity was determined by chiral HPLC analysis (AD-H column, hexane/*i*-PrOH 99:1, flow rate 1 mL/min, λ= 254 nm) t_R = 28.72 min (major enantiomer of ***syn*-139**), t_R =25.26 min (minor enantiomer of ***syn*-139**); t_R = 39.07 min (major enantiomer of ***anti*-139**), t_R = 32.71 min (minor enantiomer of ***anti*-**

139).

Optical rotation of the diastereomeric mixture was determined as $[\alpha]_D^{25}$= +17.2^o (*c* = 4.0 x 10^{-3} g/mL, $CHCl_3$)

3.7.7 Ethyl 3-azido-2-hydroxy-4-(3-methoxyphenyl)-2-methyl-4-oxobutanoate (140)

Enantiomerically enriched chiral ethyl 3-azido-2-hydroxy-4-(3-methoxyphenyl)-2-methyl-4-oxobutanoate **(140)** was obtained up to 68% ee . Enantiomeric purity was determined by chiral HPLC analysis (AD-H column, hexane/*i*-PrOH 93:7, flow rate 1 mL/min, λ= 254 nm) t_R = 14.59 min (major enantiomer of ***syn*-140**), t_R =13.17 min (minor enantiomer of ***syn*-140**); t_R = 20.46 min (major enantiomer of ***anti*-140**), t_R = 18.66 min (minor enantiomer of ***anti*-140**).

Optical rotation of the diastereomeric mixture was determined as $[\alpha]_D^{23}$= +21.7^o (*c* = 2.4 x 10^{-3} g/mL, $CHCl_3$)

CHAPTER 4

CONCLUSION

In this study we developed a new methodology for the asymmetric synthesis of tetrafunctionalized ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates. Different functional groups of such compounds make them potential precursors for the synthesis of α-amino ketones, azido alcohols, 1,2-amino alcohols, phosphoranes and 1,2,3-triazoles.

Specifically, 1,2-amino alcohols have pharmaceutical importance due to their well-known biological activity. Because of the ability of cell receptors and body enzymes to discriminate stereoisomers, asymmetric synthesis of such precursors is also valuable. For this purpose, well-known acidity of alpha azido ketones was utilized to achieve the aldol addition alpha azido ketones to ethyl pyruvate in the presence of chiral bifunctional cinchona-urea organocatalyst. Besides activating both electrophile and nucleophile simultaneously, bifunctional catalyst provides selective substrate binding during the reaction course.

In the first part of this work, in order to improve stereoselectivity, screening studies were performed. Optimum conditions were detected by monitoring the effects of several parameters such as solvent, temperature, catalyst loading and substrate concentration. In the second part of thesis, the best condition in which diastereoselectivity and enantioselectivity enriched was applied in derivatization studies.

To sum up, the first organocatalytic asymmetric synthesis of ethyl 4-aryl-3-azido-2-hydroxy-2-methyl-4-oxobutanoates via chiral base induced aldol addition of α-azido ketones to ethyl pyruvate was achieved. A significant improvement in diastereoselectivity up to 18: 1 diastereomeric ratio and induction of enantioselectivity up to 81% ee were obtained in desired products via very low (2 mol %) catalyst loading.

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APPENDIX A

NMR DATA

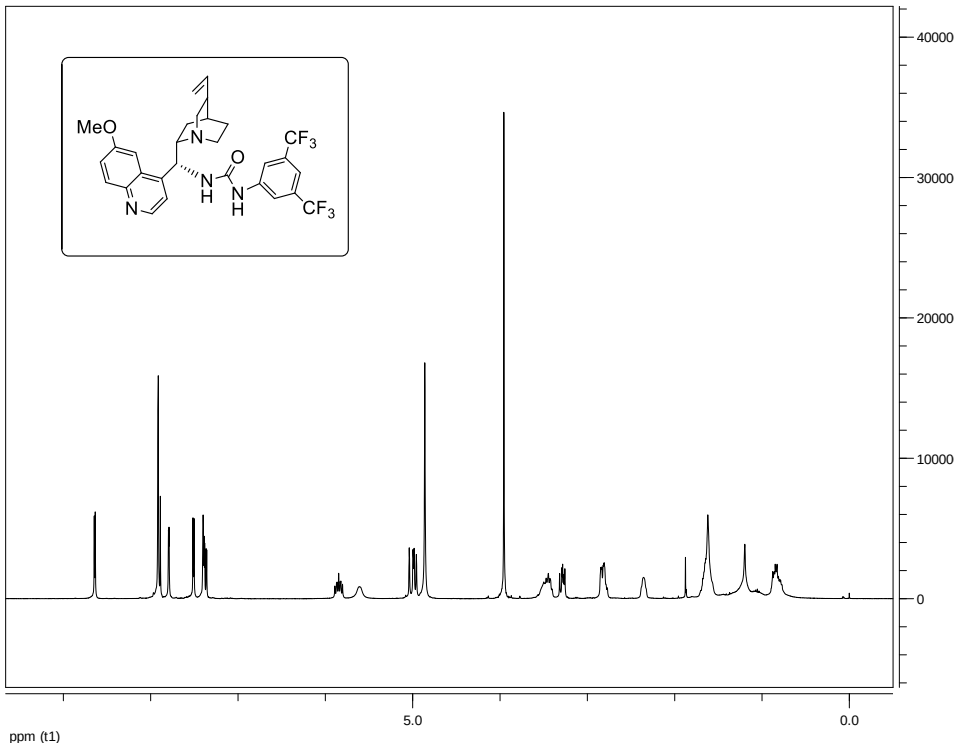

Figure A. 1 ^{1}H NMR spectrum of catalyst **132b**

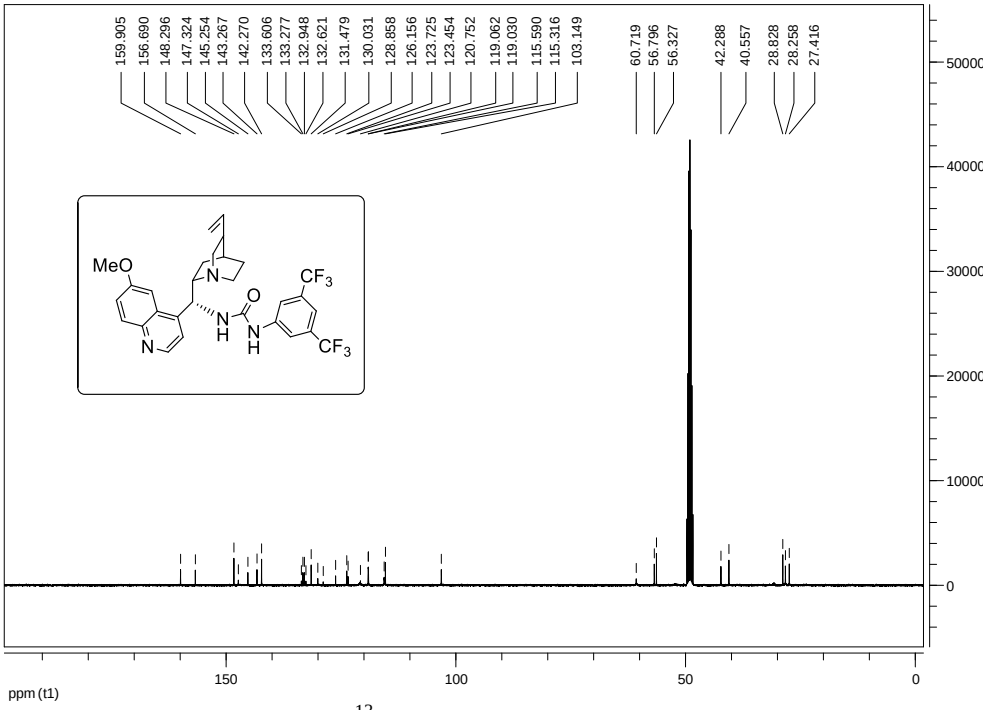

Figure A. 2 ^{13}C NMR spectrum of catalyst **132b**

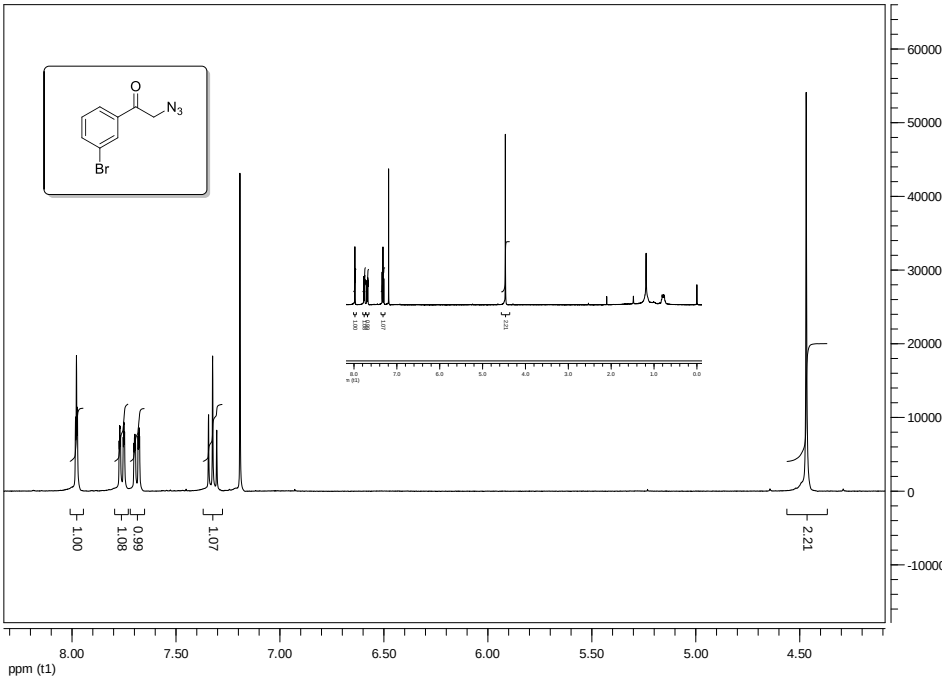

Figure A. 3 ^{1}H NMR spectrum of **127**

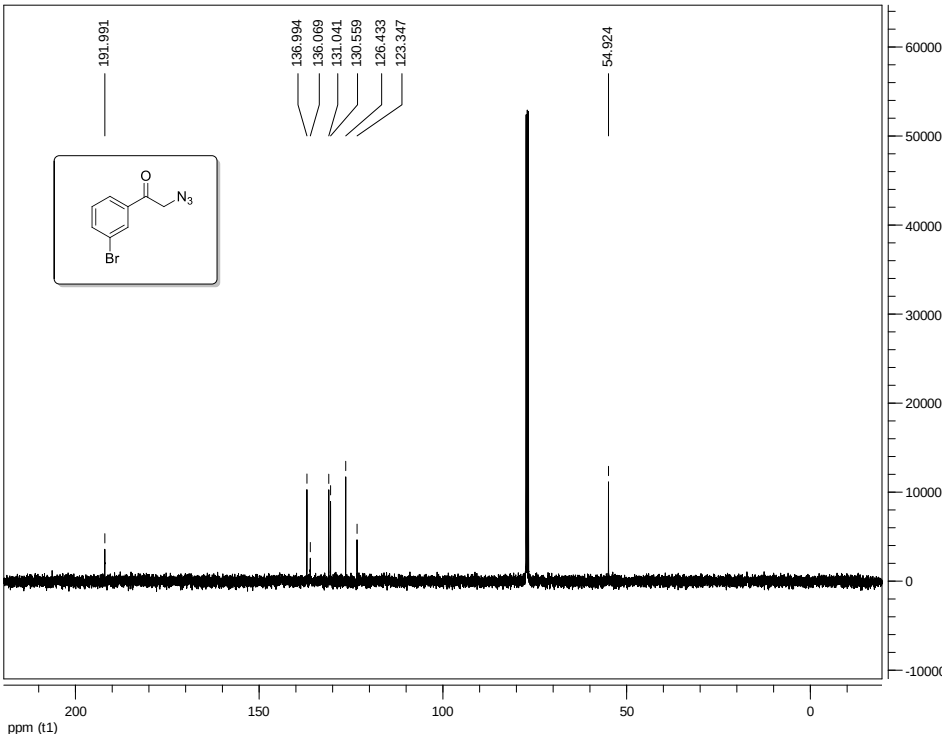

Figure A. 4 ^{13}C NMR spectrum of **127**

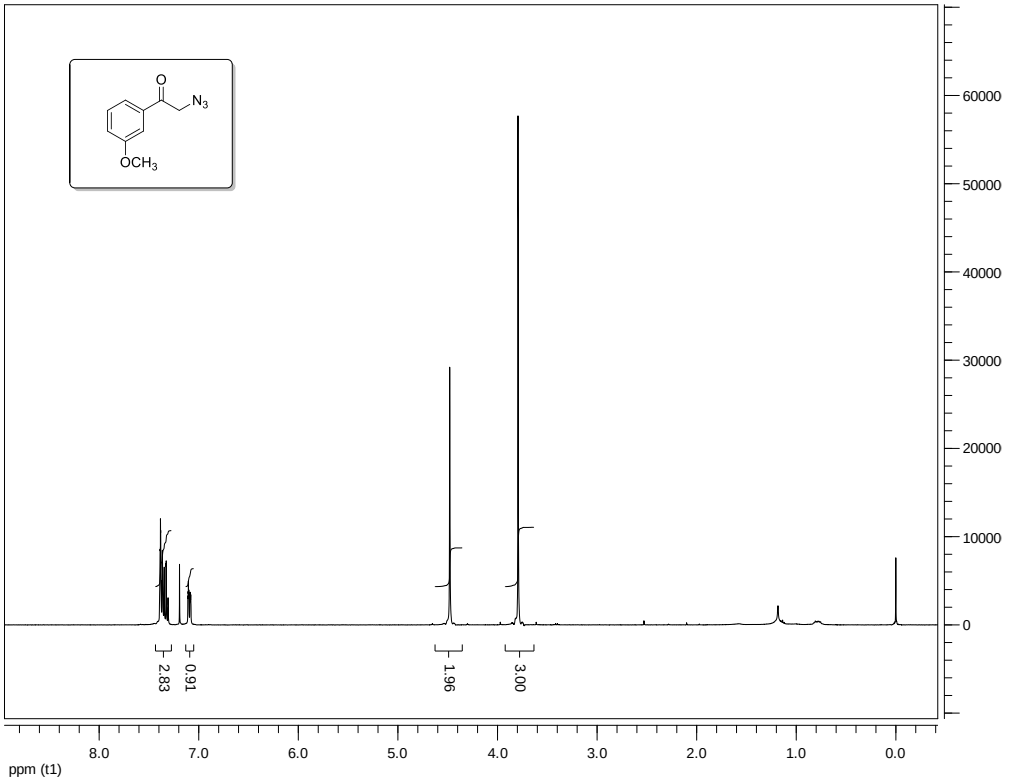

Figure A. 5 ^{1}H NMR spectrum of **128**

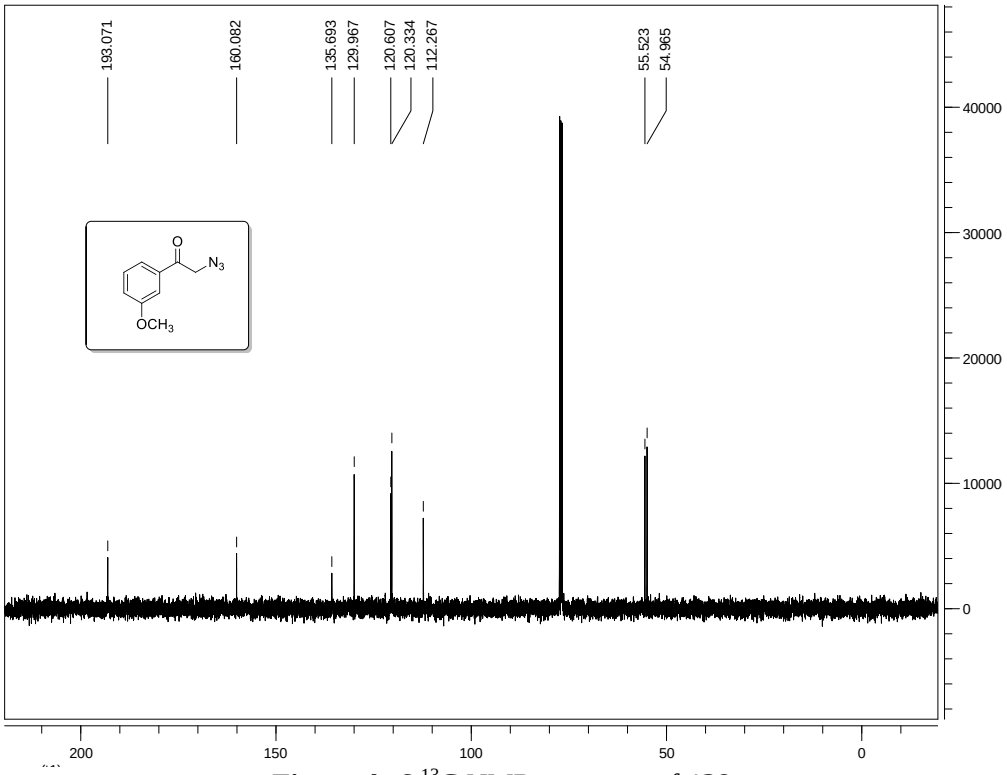

Figure A. 6 ^{13}C NMR spectrum of **128**

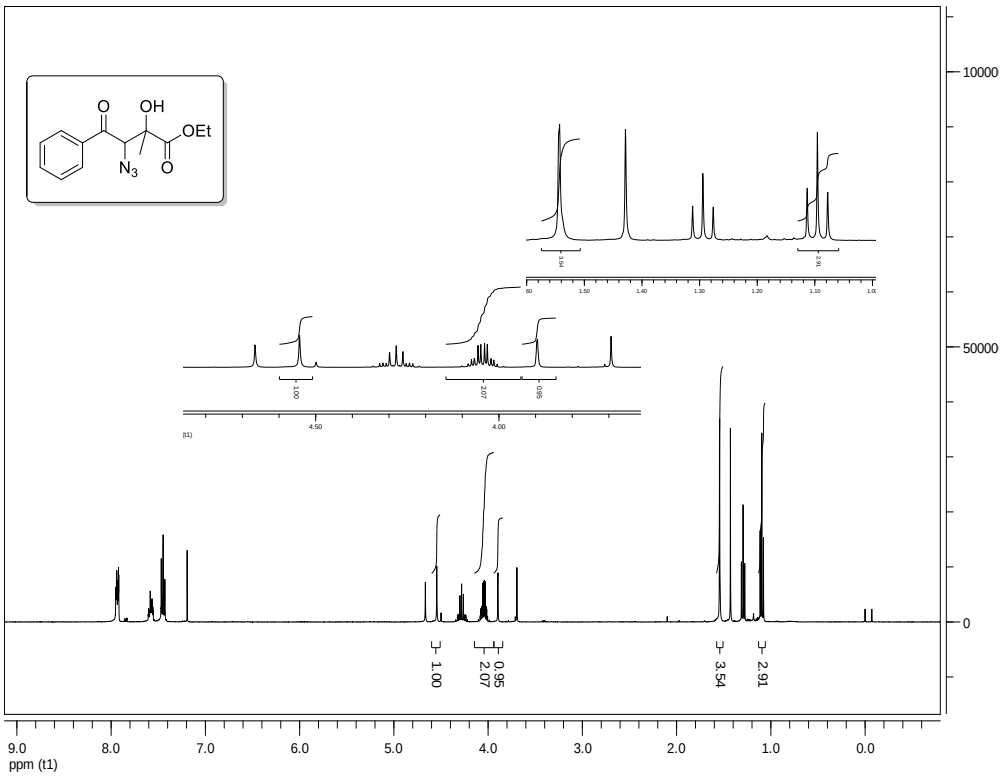

Figure A. 7 ^{1}H NMR spectrum of diastereomeric mixture **129**

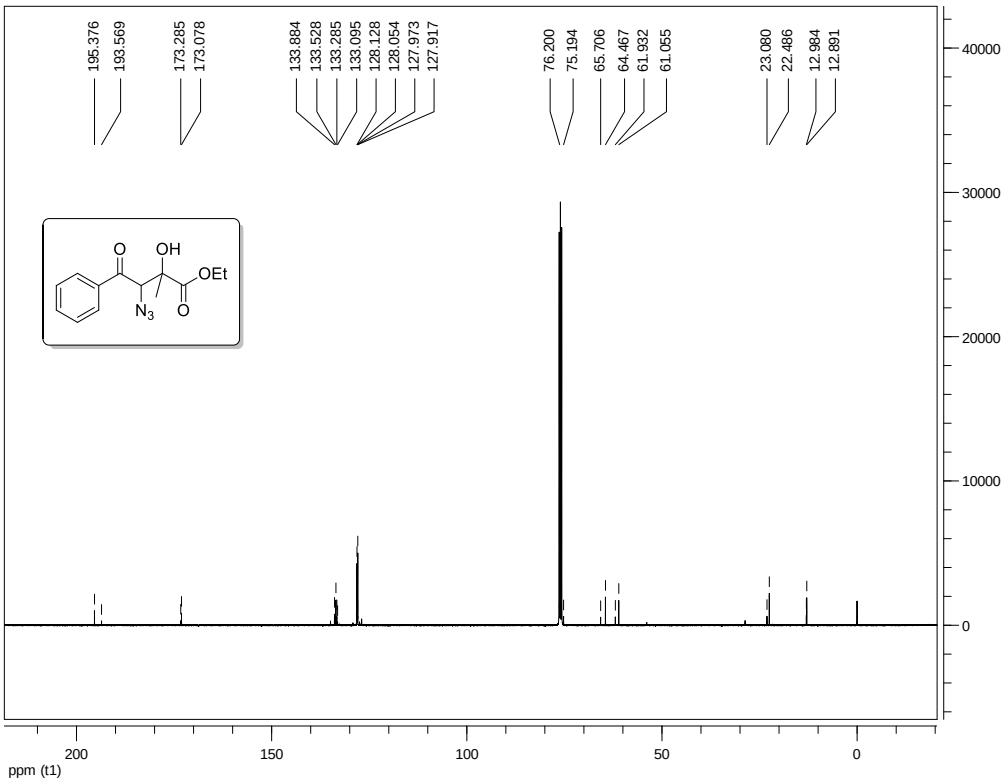

Figure A. 8 ^{13}C NMR spectrum of diastereomeric mixture **129**

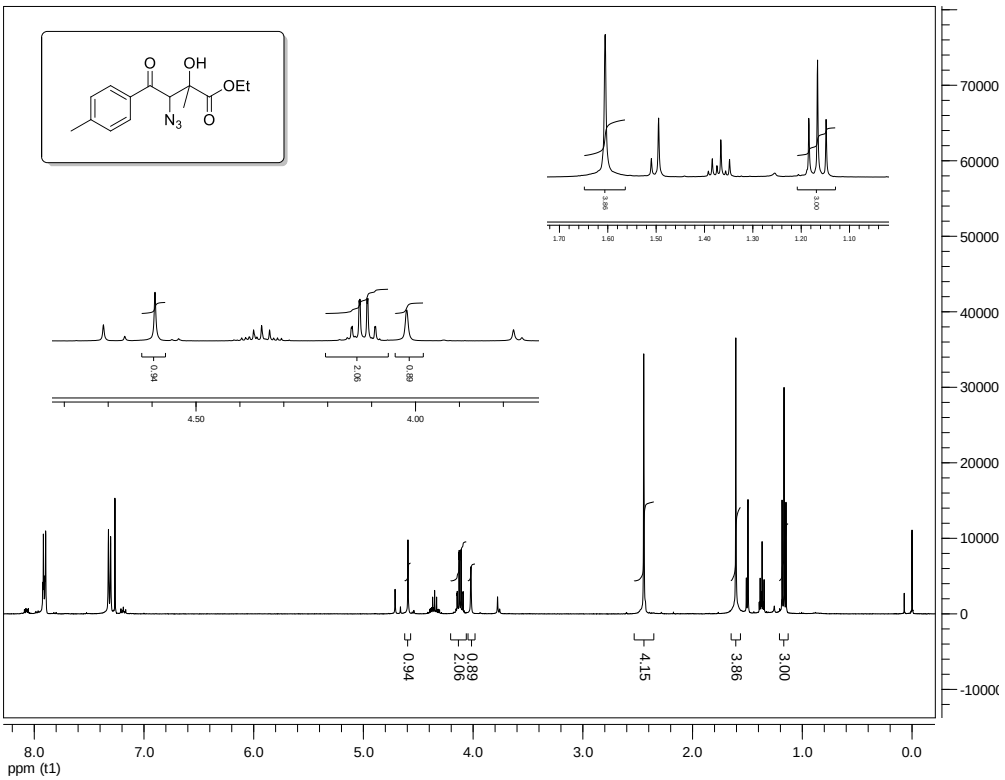

Figure A. 9 ^{1}H NMR spectrum of diastereomeric mixture **135**

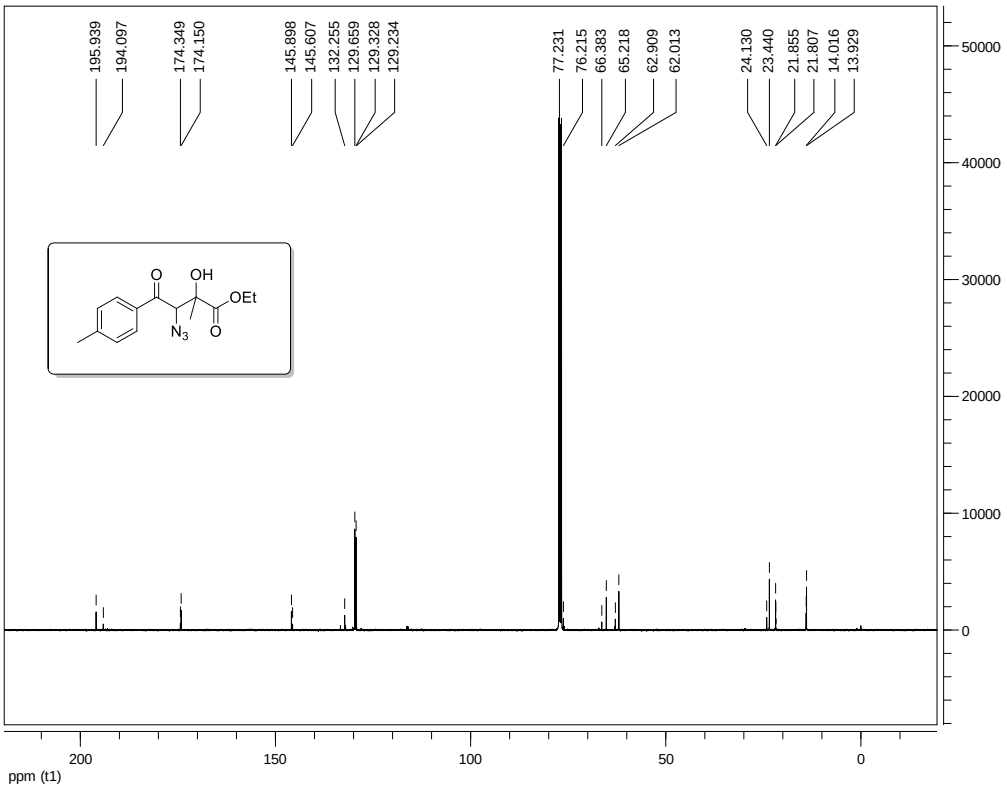

Figure A. 10 ^{13}C NMR spectrum of diastereomeric mixture **135**

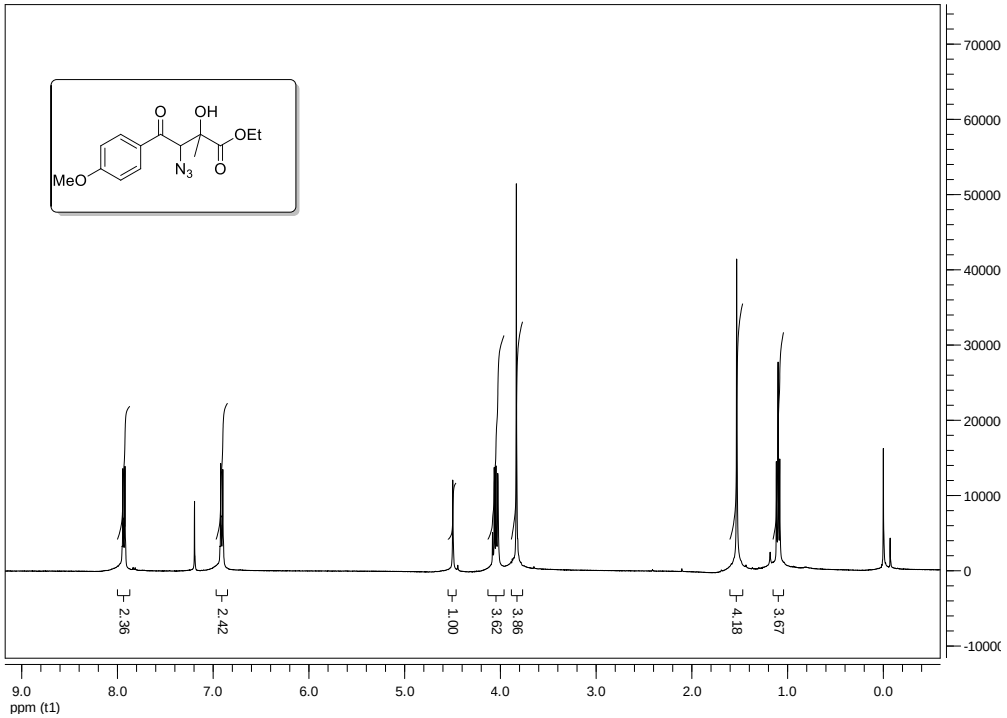

Figure A. 11 ^{1}H NMR spectrum of diastereopure ***syn*- 136**

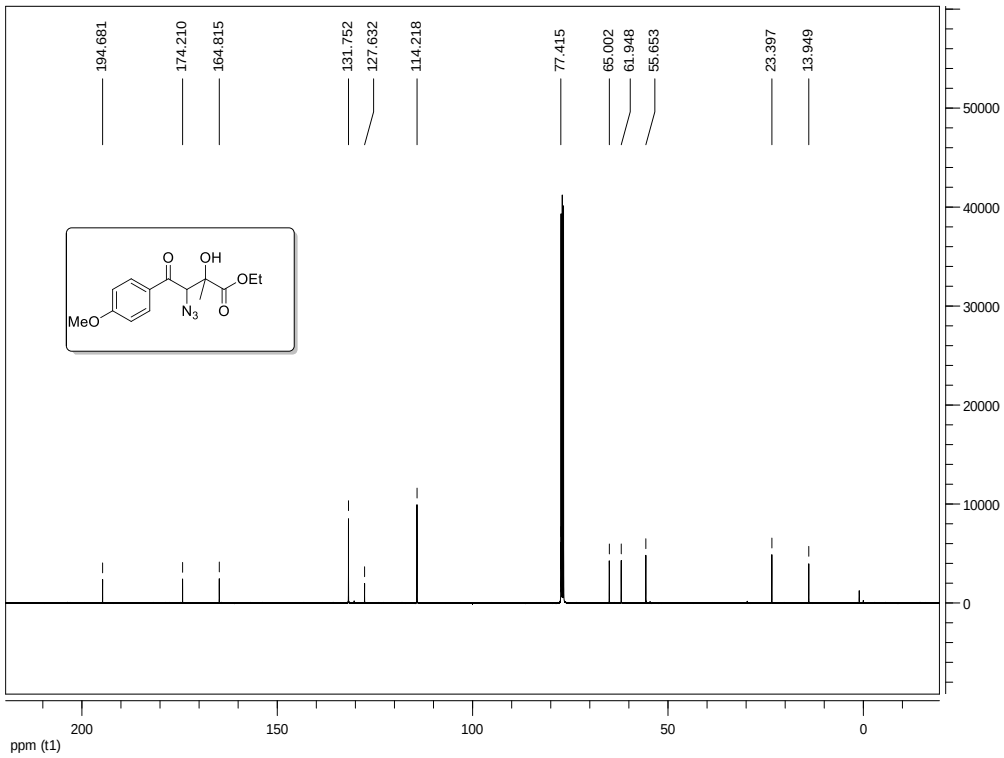

Figure A. 12 ^{13}C NMR spectrum of diastereopure ***syn*-136**

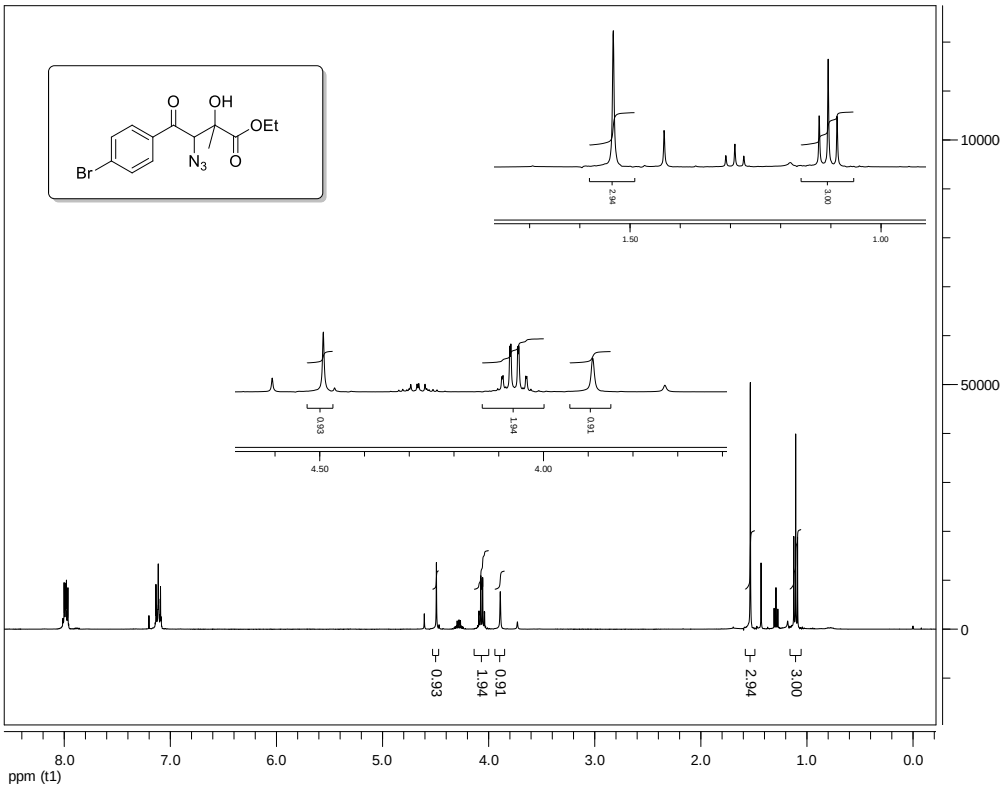

Figure A. 13 ^{1}H NMR spectrum of diastereomeric mixture **137**

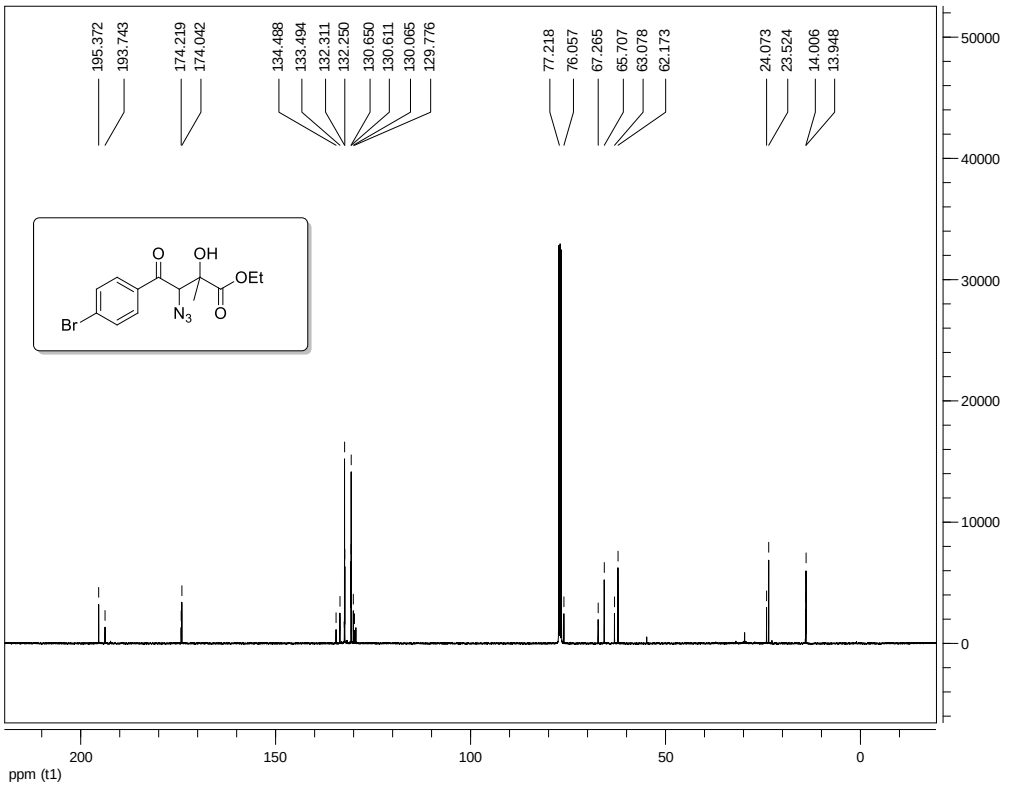

Figure A. 14 ^{13}C NMR spectrum of diastereomeric mixture **137**

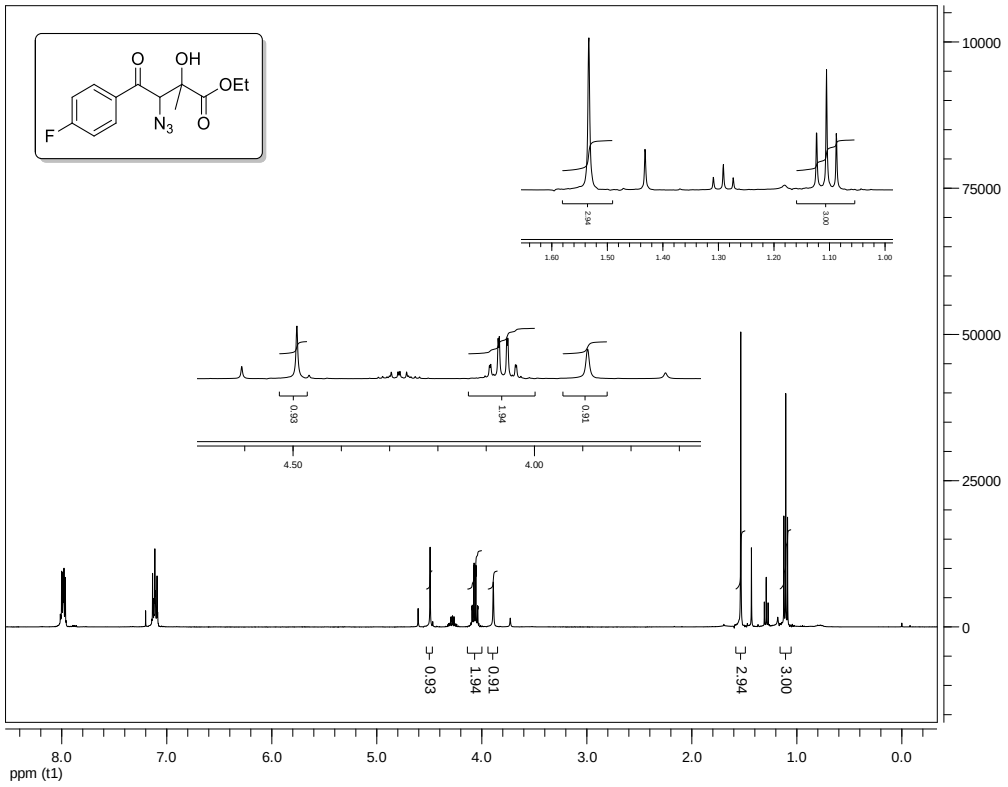

Figure A. 15 ^{1}H NMR spectrum of diastereomeric mixture **138**

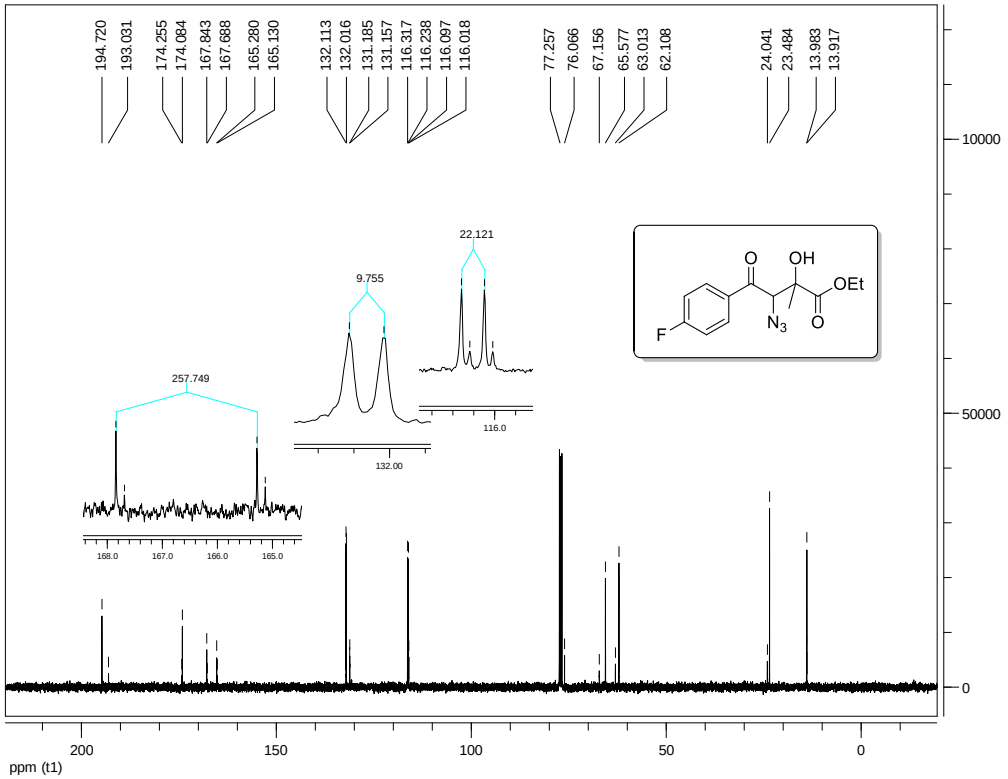

Figure A. 16 ^{13}C NMR spectrum of diastereomeric mixture **138**

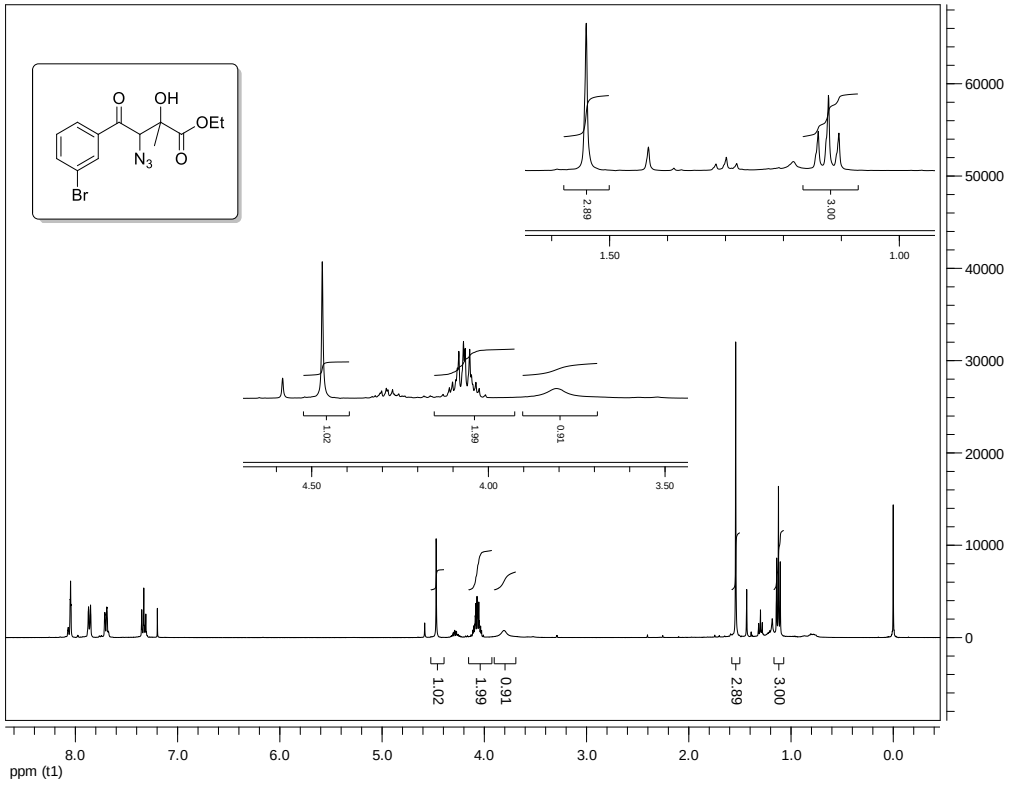

Figure A. 17 ^{1}H NMR spectrum of diastereomeric mixture **139**

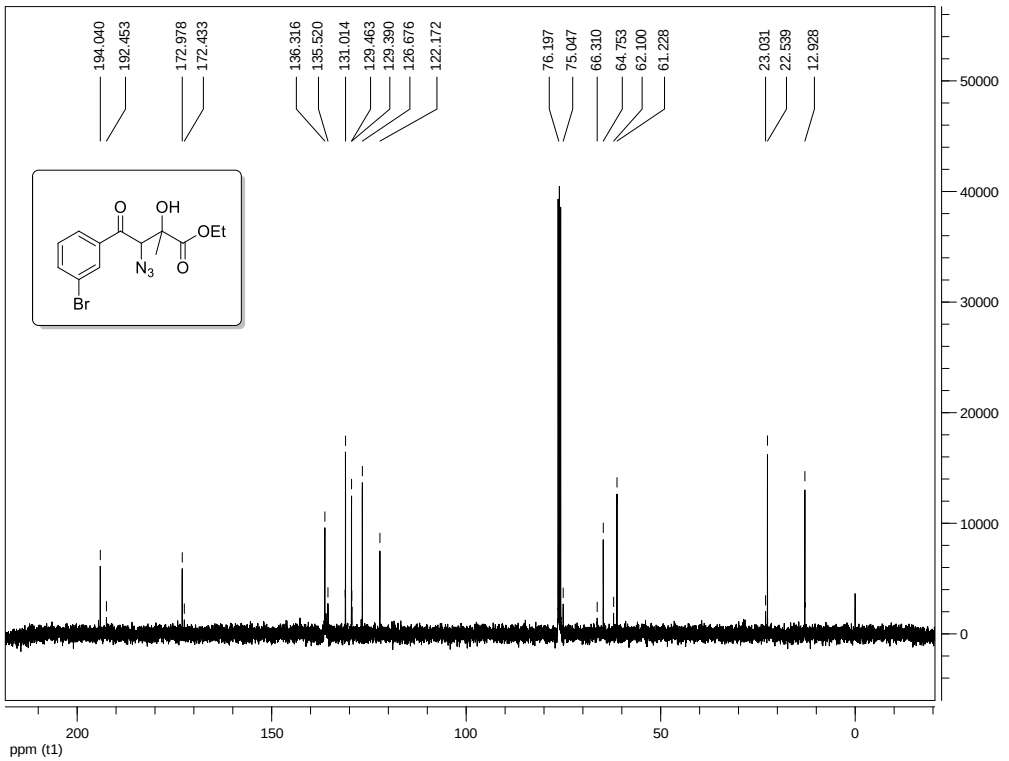

Figure A. 18 ^{13}C NMR spectrum of diastereomeric mixture **139**

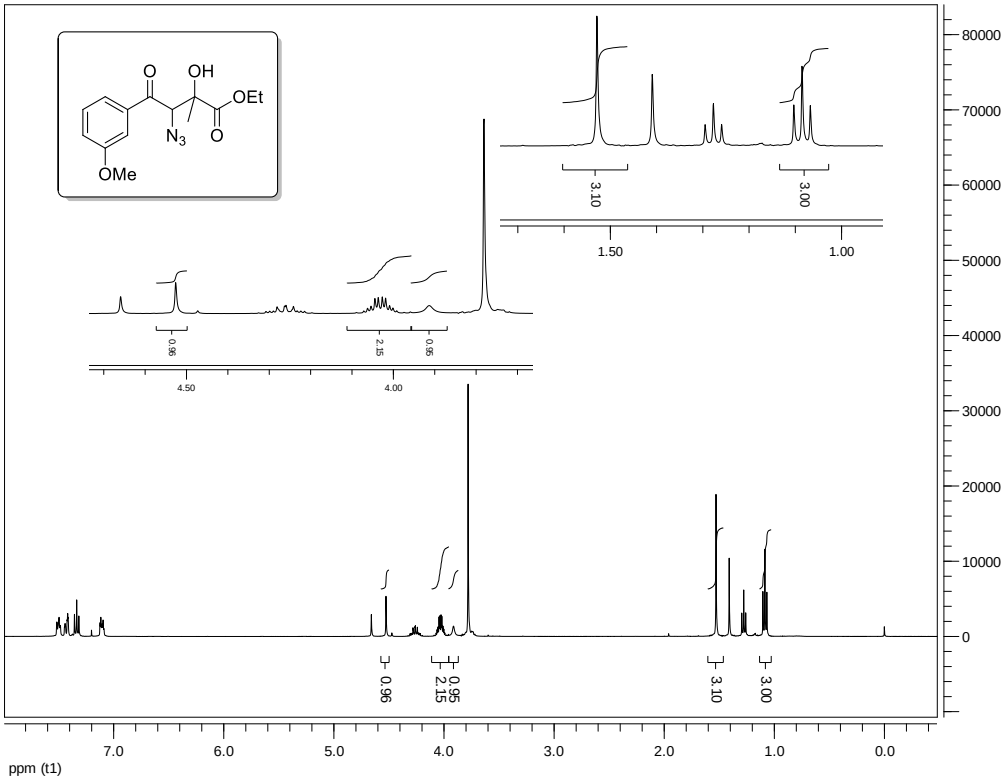

Figure A. 19 ^{1}H NMR spectrum of diastereomeric mixture **140**

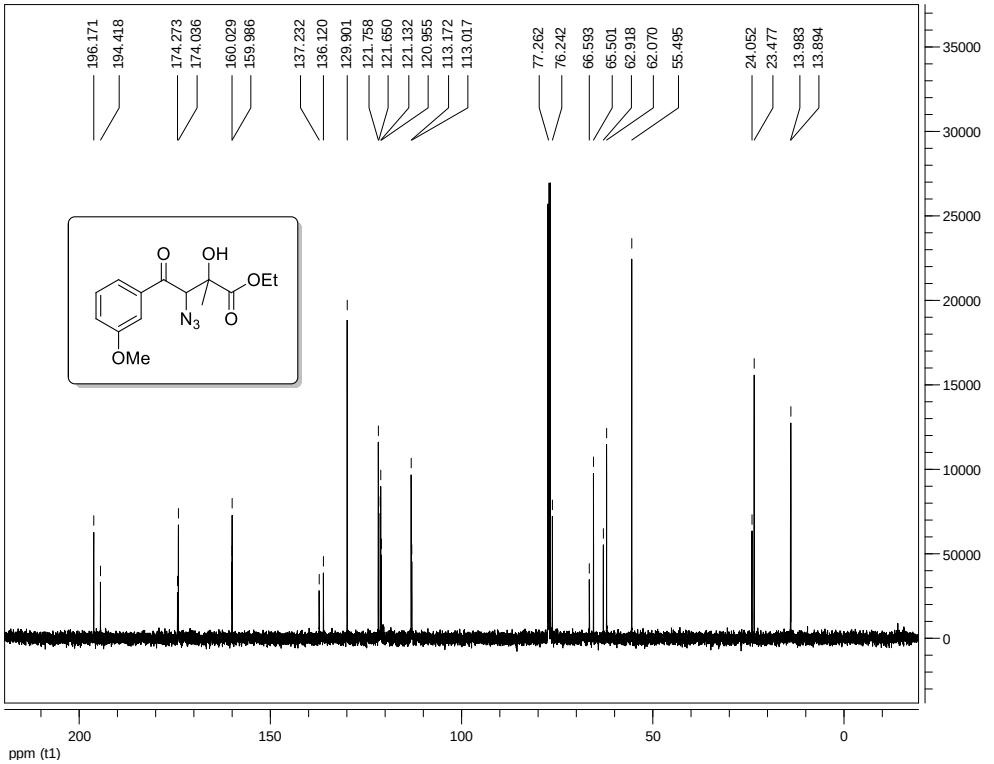

Figure A. 20 ^{13}C NMR spectrum of diastereomeric mixture **140**

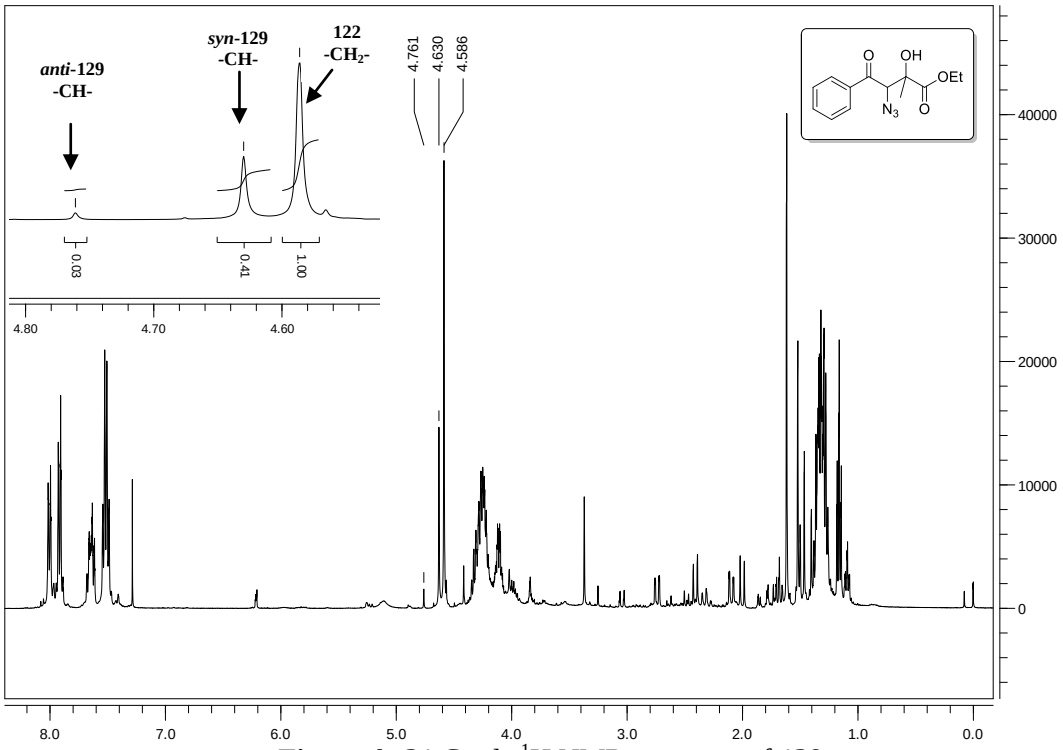

Figure A. 21 Crude ^{1}H NMR spectrum of **129**

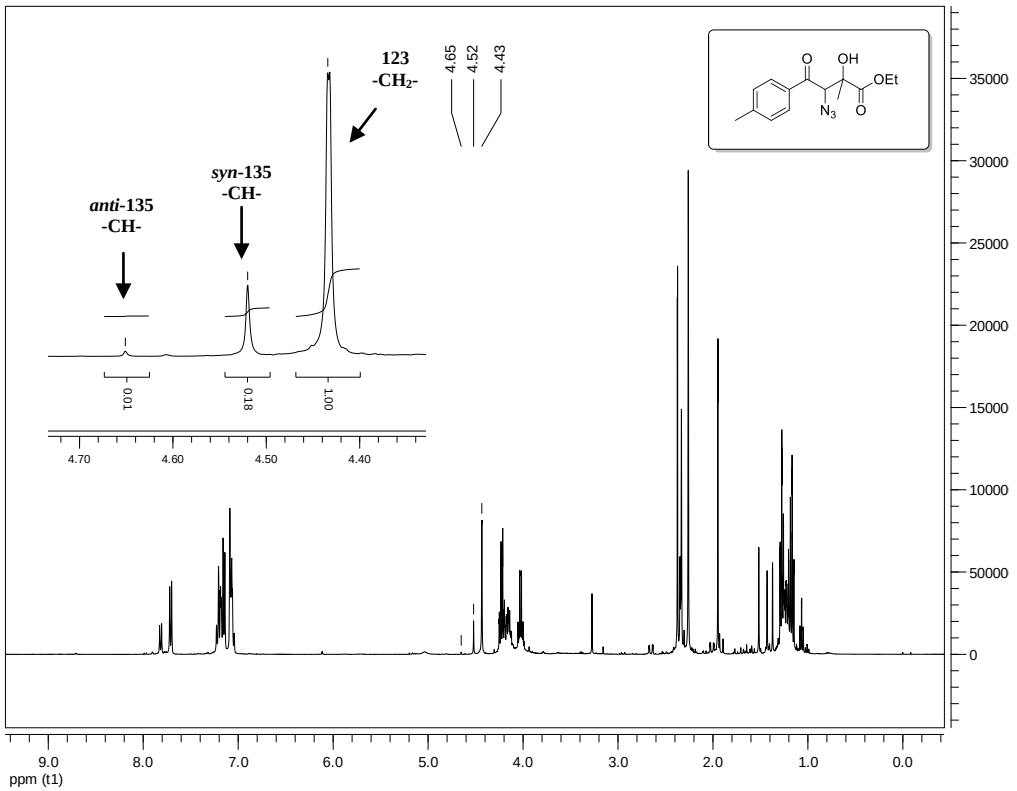

Figure A. 22 Crude ^{1}H NMR spectrum of **135**

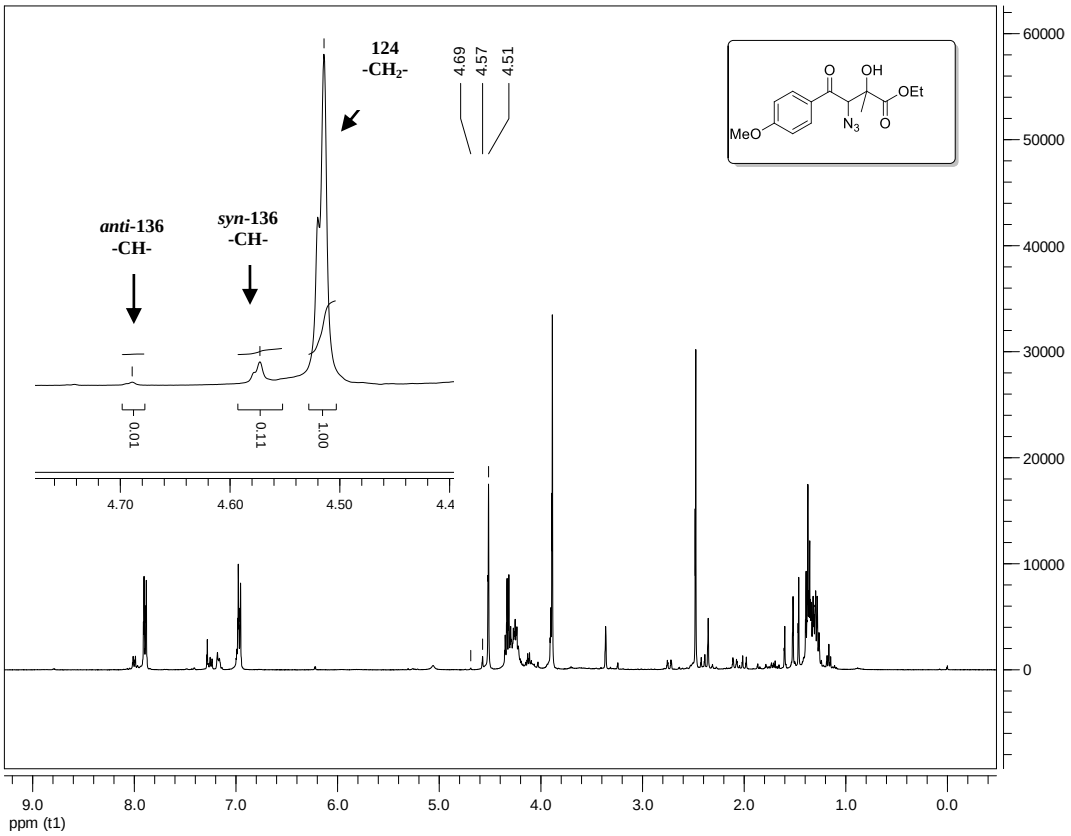

Figure A. 23 Crude ^{1}H NMR spectrum of **136**

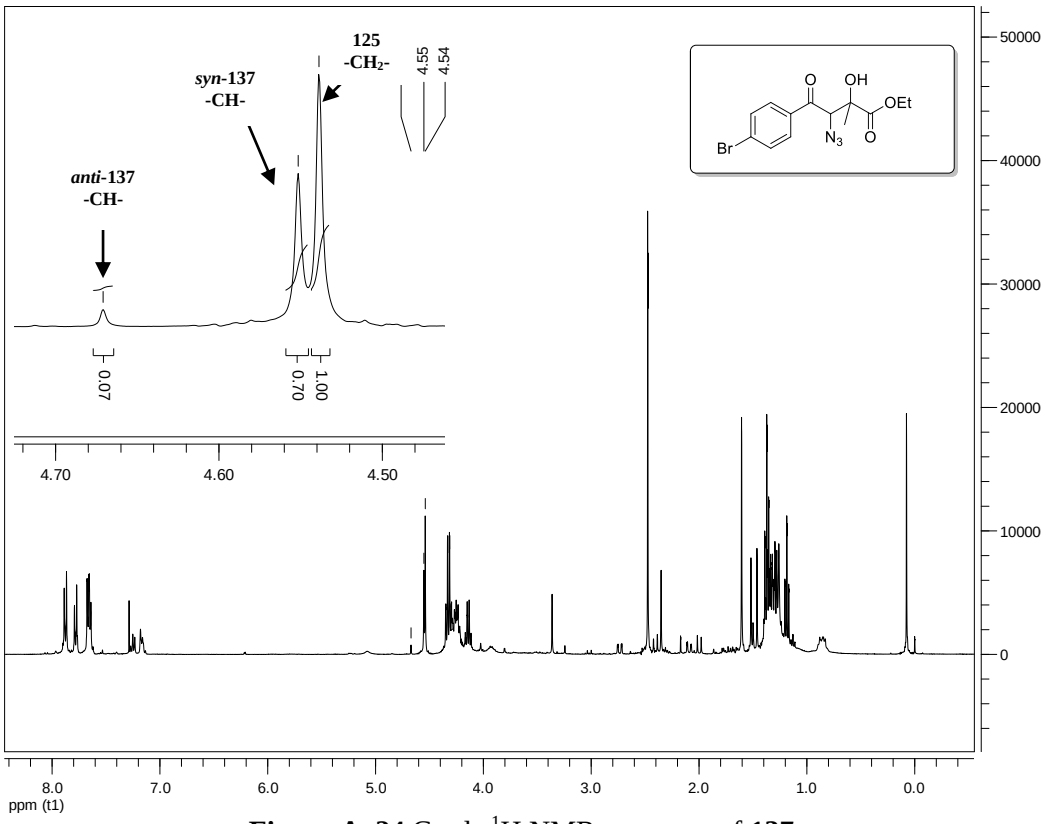

Figure A. 24 Crude ^{1}H NMR spectrum of **137**

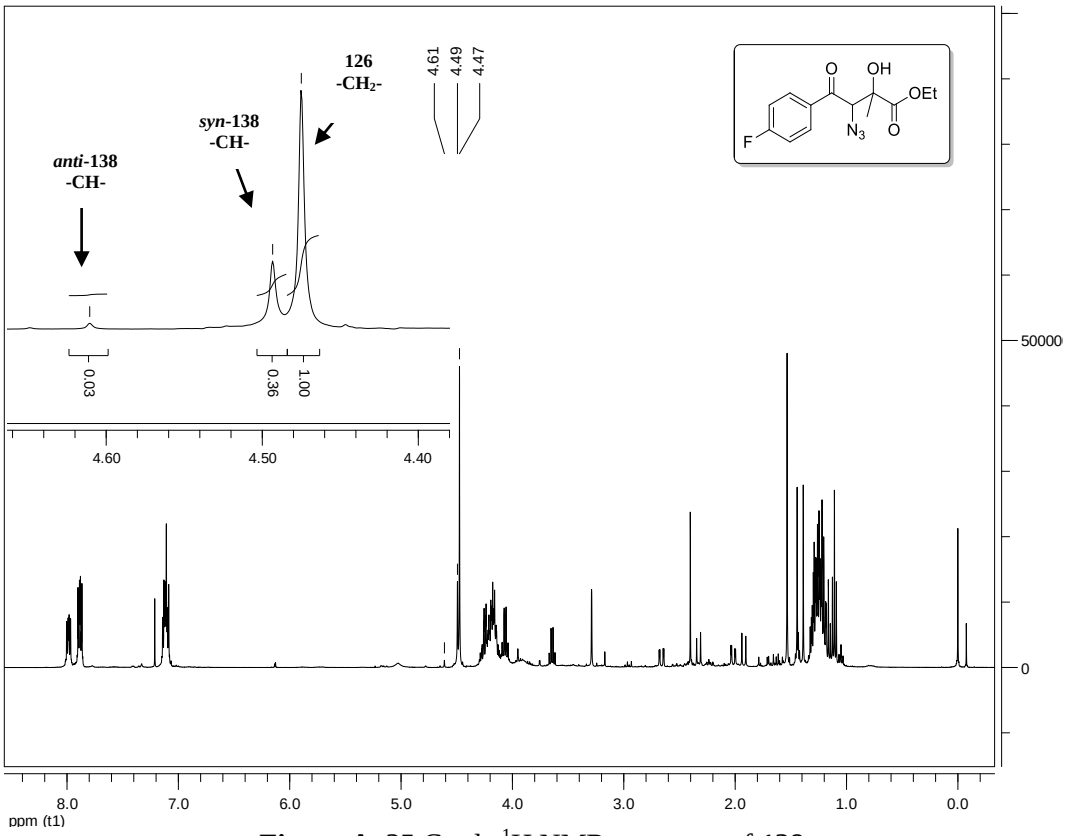

Figure A. 25 Crude ^{1}H NMR spectrum of **138**

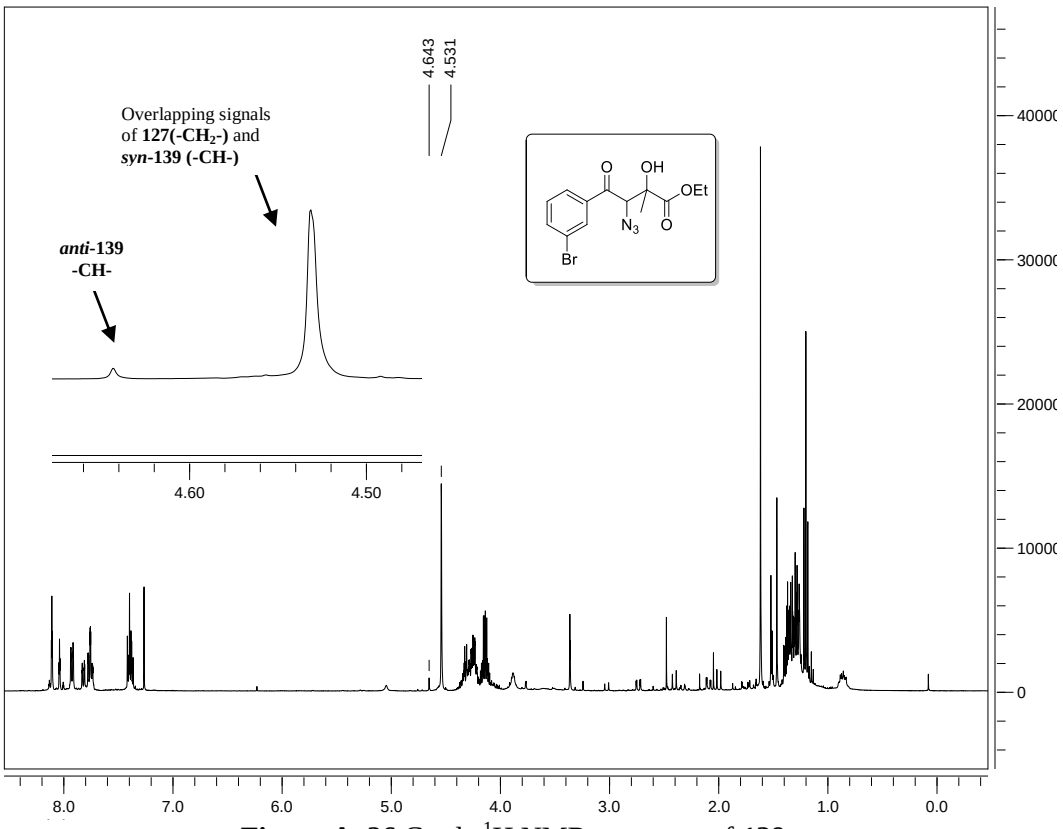

Figure A. 26 Crude ^{1}H NMR spectrum of **139**

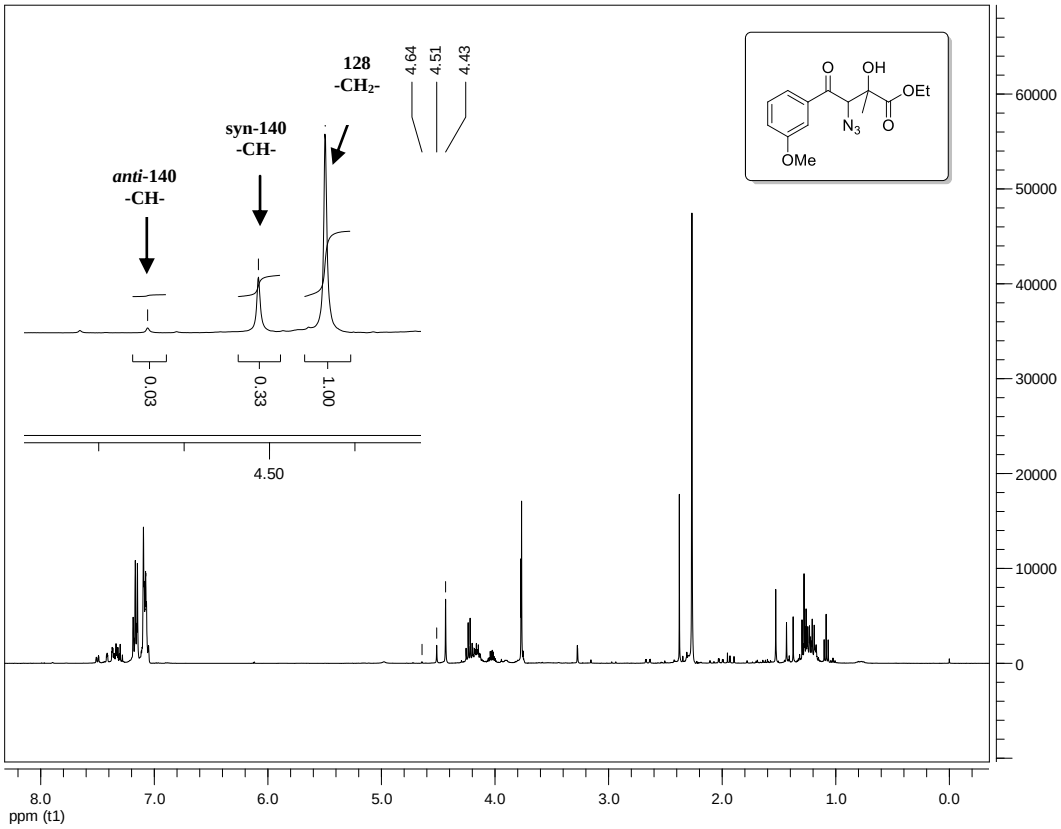

Figure A. 27 Crude ^{1}H NMR spectrum of **140**

APPENDIX B

HPLC DATA

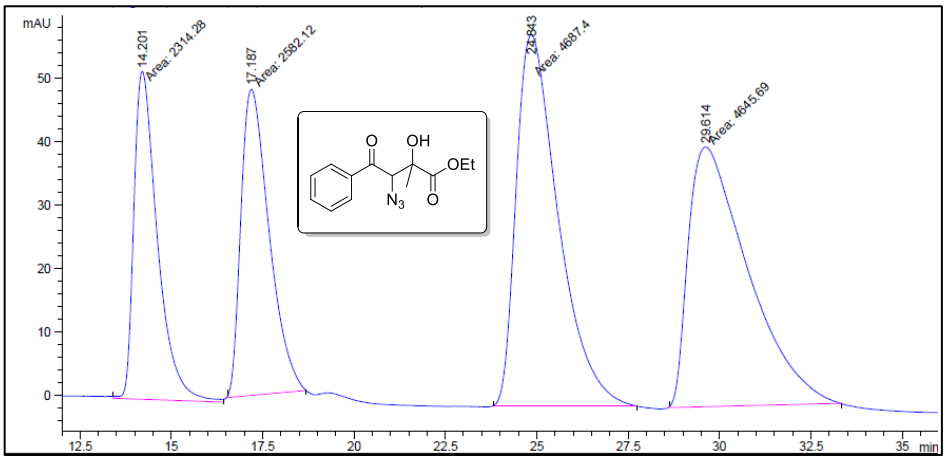

Figure B. 1 HPLC chromatogram of diastereomeric mixture of ***rac*- 129**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.201	MM	0.7460	2314.28369	51.70650	16.2640
2	17.187	MM	0.8919	2582.11865	48.25277	18.1463
3	24.843	MM	1.3344	4687.39893	58.54467	32.9414
4	29.614	MM	1.8919	4645.68506	40.92513	32.6483

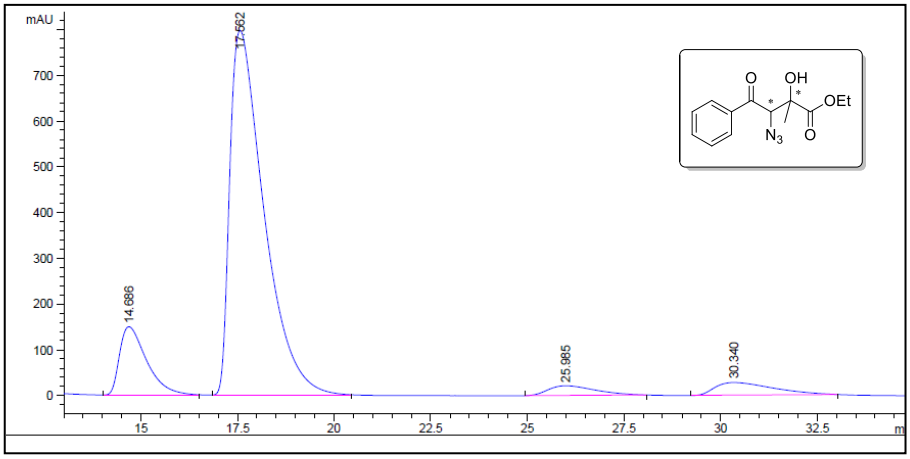

Figure B. 2 HPLC chromatogram of enantiomerically enriched **129**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.686	BB	0.7398	7235.70801	149.19319	11.8845
2	17.562	BB	0.9215	4.88663e4	796.79199	80.2616
3	25.985	BB	1.1255	1818.13586	21.22233	2.9862
4	30.340	BB	1.2473	2963.65137	28.03439	4.8677

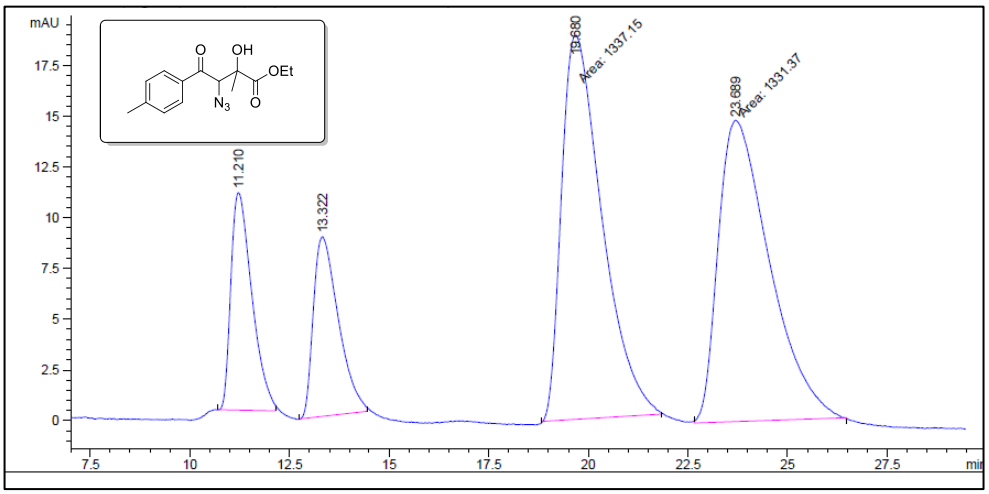

Figure B. 3 HPLC chromatogram of diastereomeric mixture of ***rac*- 135**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.210	BB	0.5217	392.90045	10.71673	11.3925
2	13.322	BB	0.5979	387.33945	8.86234	11.2313
3	19.680	MM	1.1781	1337.14612	18.91712	38.7719
4	23.689	MM	1.4938	1331.36829	14.85436	38.6043

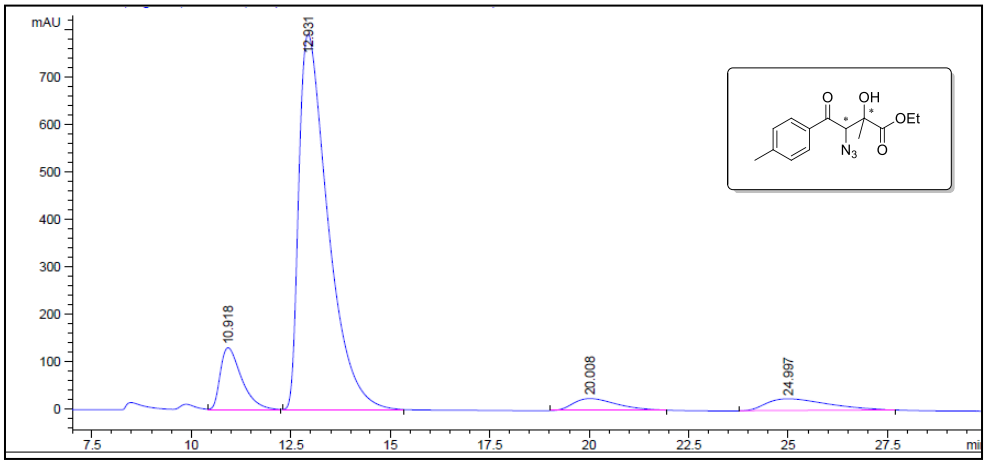

Figure B. 4 HPLC chromatogram of enantiomerically enriched **135**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.918	VB	0.5654	4880.31787	130.75781	9.7755
2	12.931	BB	0.7709	4.03730e4	791.74664	80.8693
3	20.008	BB	0.9210	1925.69434	25.21351	3.8573
4	24.997	BB	1.2926	2744.78491	25.04459	5.4979

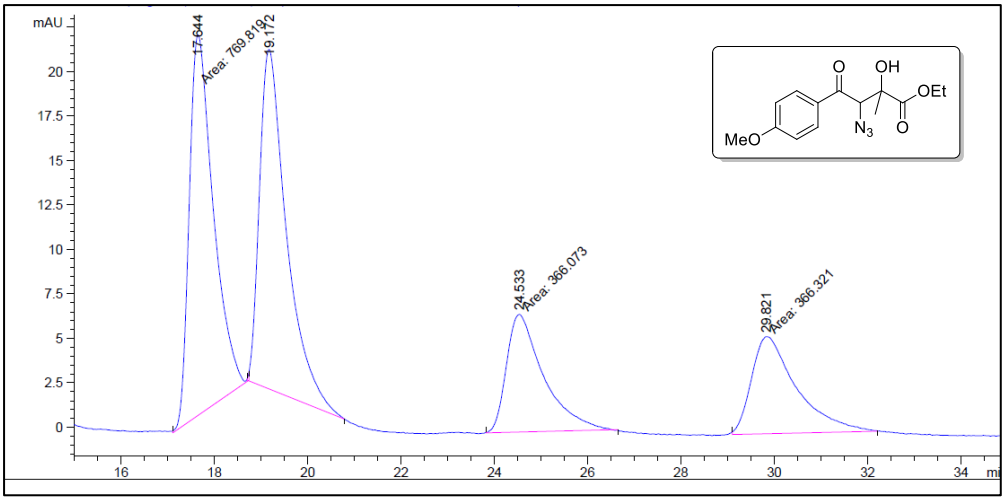

Figure B. 5 HPLC chromatogram of diastereomeric mixture of ***rac*- 136**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.644	MM T	0.5988	769.81927	21.42827	33.9261
2	19.172	MM R	0.6689	766.89575	19.10879	33.7972
3	24.533	MM	0.9208	366.07297	6.62588	16.1329
4	29.821	MM	1.1165	366.32132	5.46808	16.1438

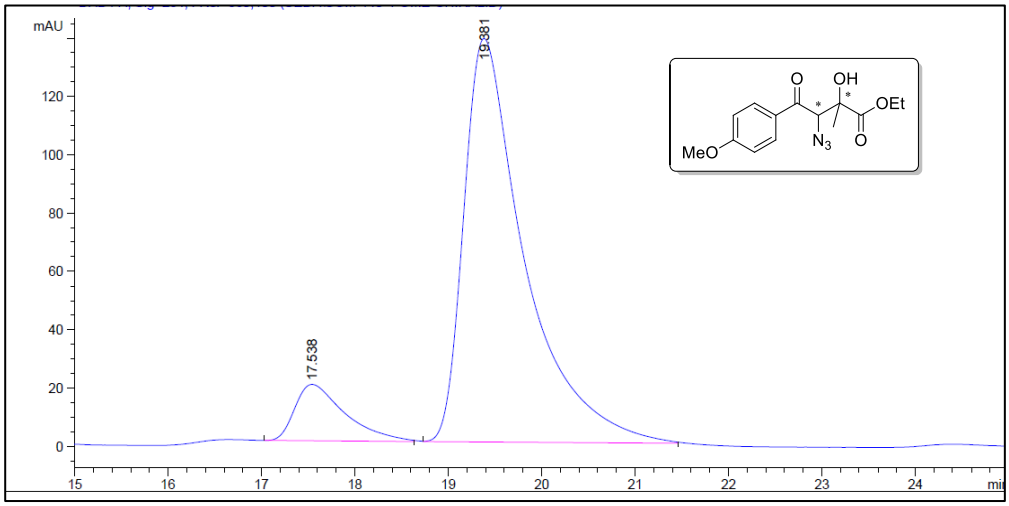

Figure B. 6 HPLC chromatogram of enantiomerically enriched product **136**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.538	MM	0.5745	630.60150	18.29348	9.2144
2	19.381	MM	0.7502	6213.06445	138.02315	90.7856

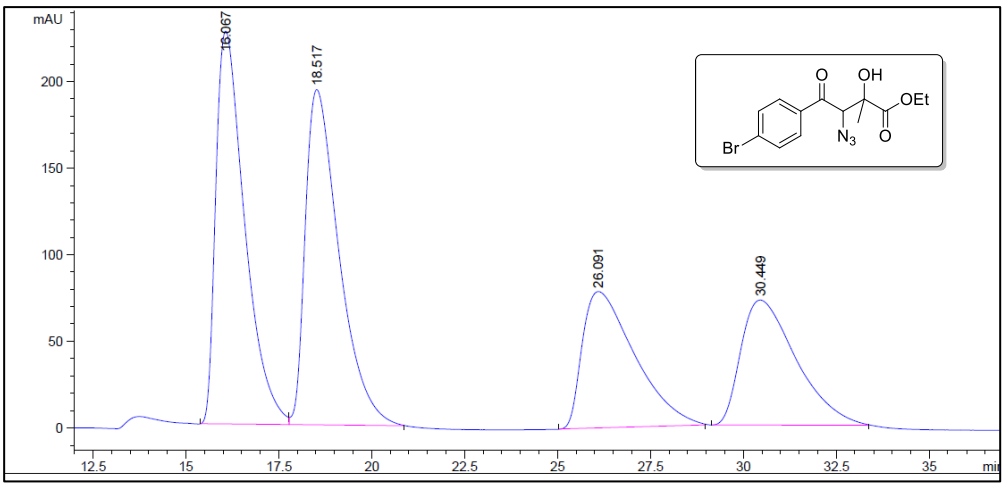

Figure B. 7 HPLC chromatogram of diastereomeric mixture of ***rac*- 137**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.067	BV	0.8208	1.22703e4	226.92470	30.8595
2	18.517	VB	0.9570	1.22747e4	193.77881	30.8706
3	26.091	BB	1.3451	7725.86230	78.85133	19.4303
4	30.449	BB	1.4039	7490.96826	72.23310	18.8396

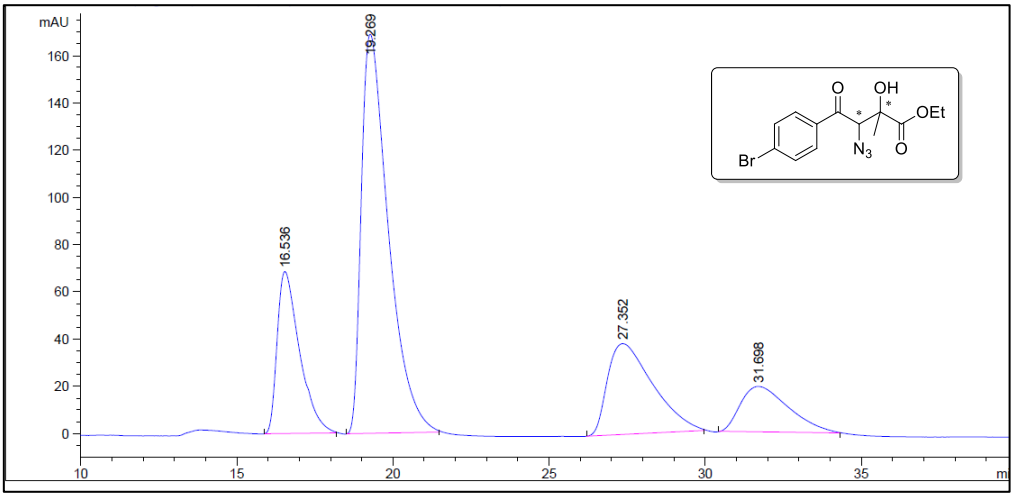

Figure B. 8 HPLC chromatogram of enantiomerically enriched product **137**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.536	BB	0.7410	3429.54639	68.63007	17.4760
2	19.269	BB	0.9111	1.02152e4	169.02205	52.0537
3	27.352	BB	1.4021	3892.04663	38.47865	19.8328
4	31.698	BB	1.2922	2087.53345	19.32657	10.6375

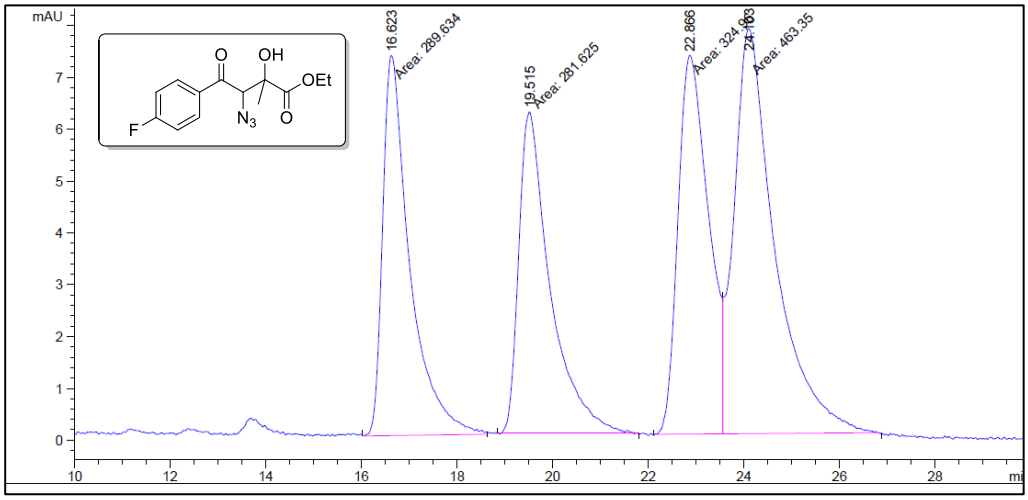

Figure B. 9 HPLC chromatogram of diastereomeric mixture of ***rac*- 138**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.623	MM	0.6580	289.63351	7.33574	21.3033
2	19.515	MM	0.7575	281.62476	6.19647	20.7143
3	22.866	MF	0.7407	324.96042	7.31169	23.9017
4	24.103	FM	0.9884	463.35019	7.81301	34.0807

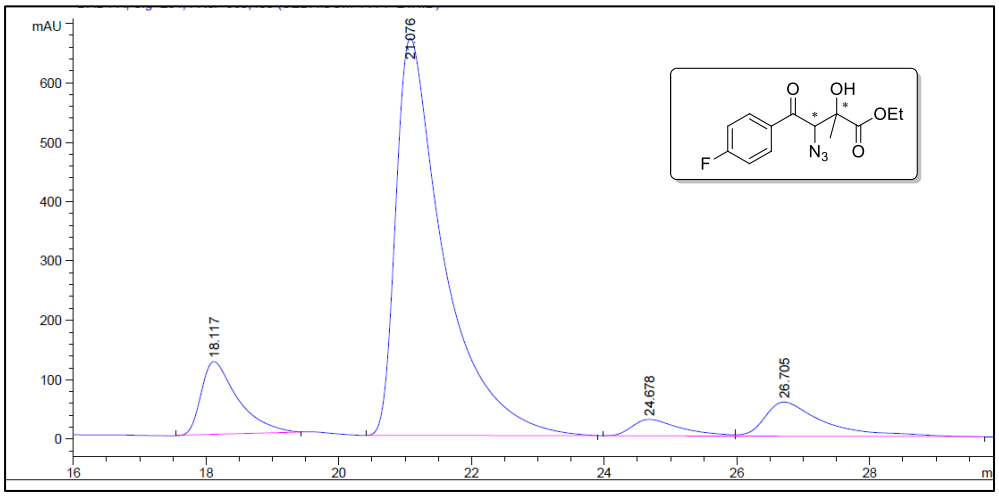

Figure B. 10 HPLC chromatogram of enantiomerically enriched product **138**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.117	BB	0.5620	4697.44873	122.89149	10.8343
2	21.076	BB	0.7265	3.36136e4	668.60443	77.5272
3	24.678	BV	0.7416	1438.52051	27.98893	3.3178
4	26.705	VB	0.8535	3607.57202	57.85696	8.3206

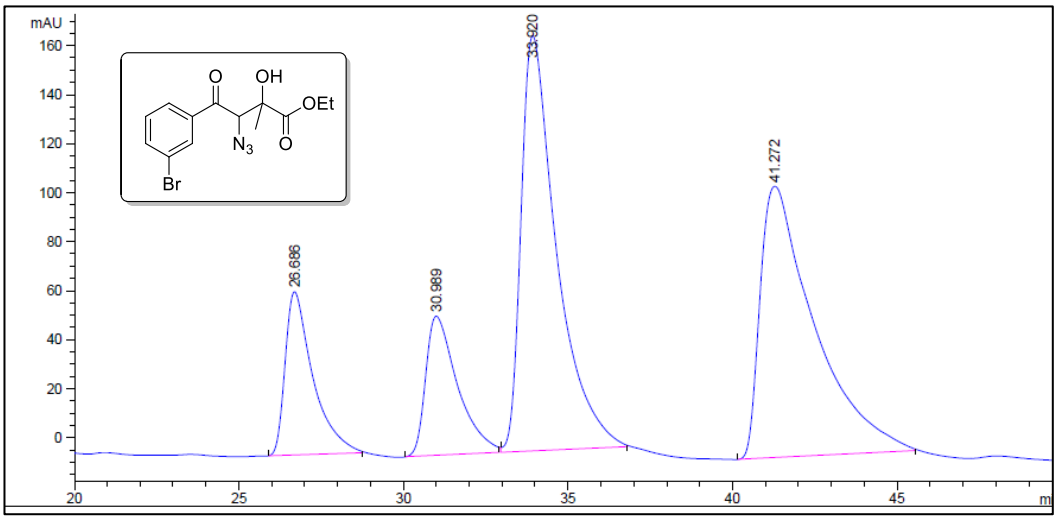

Figure B. 11 HPLC chromatogram of diasteromeric mixture of ***rac*- 139**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	26.686	BB	0.8267	3912.61475	66.66372	11.8097
2	30.989	BB	0.9777	3830.47754	56.87747	11.5617
3	33.920	BB	1.0900	1.27258e4	169.47487	38.4110
4	41.272	BB	1.5763	1.26617e4	110.71277	38.2176

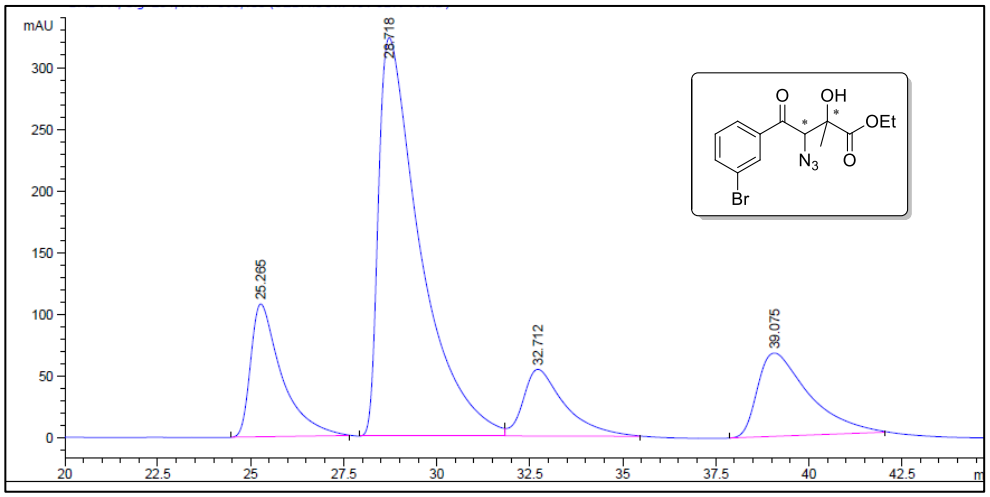

Figure B. 12 HPLC chromatogram of enantiomerically enriched product **139**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.265	BB	0.8360	6287.52734	107.87670	14.9132
2	28.718	BB	1.1082	2.51365e4	322.90213	59.6207
3	32.712	BB	1.0991	4237.30957	54.26036	10.0504
4	39.075	BB	1.3498	6499.38184	67.59026	15.4157

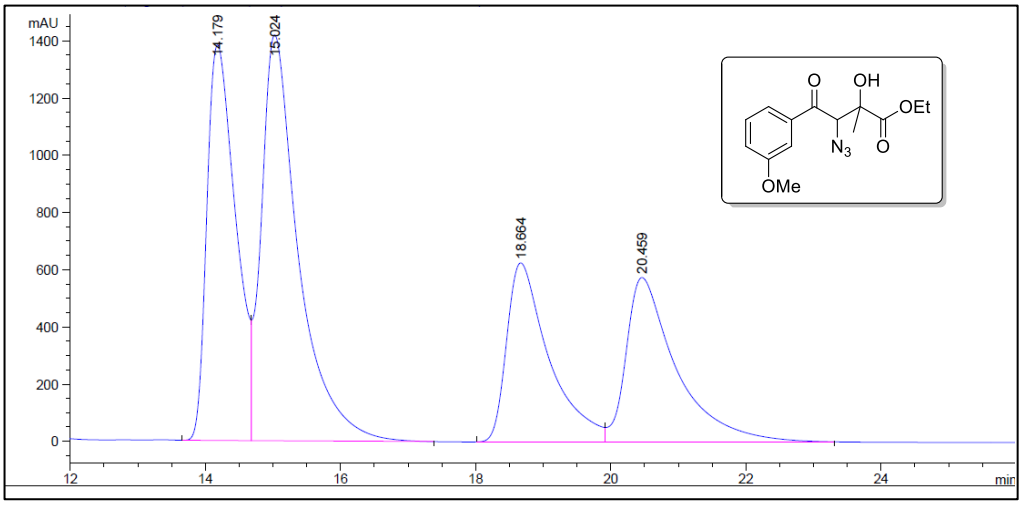

Figure B. 13 HPLC chromatogram of diastereomeric mixture of ***rac*- 140**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.179	VV	0.4428	4.08872e4	1383.61633	26.9407
2	15.024	VB	0.5505	5.40893e4	1419.59058	35.6396
3	18.664	BV	0.6328	2.72045e4	626.27338	17.9251
4	20.459	VB	0.7383	2.95865e4	575.01093	19.4946

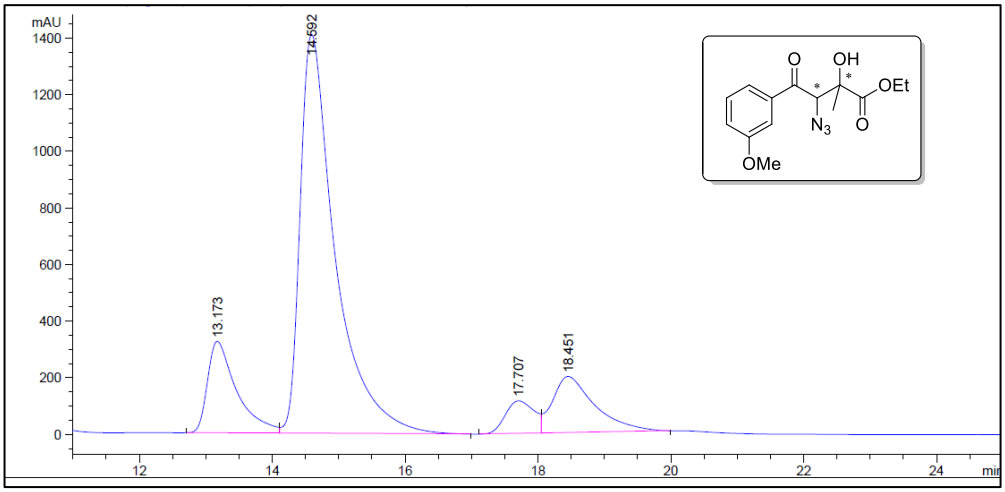

Figure B. 14 HPLC chromatogram of enantiomerically enriched product **140**

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.173	BV	0.4439	9877.37402	323.82074	13.3704
2	14.592	VB	0.5340	5.17155e4	1409.80896	70.0040
3	17.707	BV	0.4611	3468.98315	115.27213	4.6957
4	18.451	VB	0.6358	8813.23926	198.57903	11.9299