FAM-ZINC CATALYZED ASYMMETRIC 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES
AND
FAM-TITANIUM CATALYZED ENANTIOSELECTIVE ALKYNYLATION OF ALDEHYDES

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ABSTRACT

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In the first part of this study, four new chiral ligands (FAM) were synthesized and used in catalytic amounts in asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides. This method leads to the synthesis of chiral pyrrolidines, which are found in the structure of many biologically active natural compounds and drugs. It was found that using 10 mol% of one of these chiral ligands with different dipolarophiles (dimethyl maleate, dimethyl fumarate, methyl acrylate, *tert*-butyl acrylate, and *N*-methylmaleimide), pyrrolidine derivatives could be synthesized in up to 94% yield and 95% ee.

In the second part of the study, the catalytic activity of these chiral ligands were tested with titanium in asymmetric alkynylzinc addition reactions to aldehydes. By this method, chiral propargylic alcohols, which are important precursors for the natural products and pharmaceuticals can be synthesized. Using our catalyst, chiral propargylic alcohols were obtained in up to 96% yield and 98% ee. Although, most of the catalyst systems in the literature worked only with aromatic or aliphatic aldehydes and phenylacetylene, the catalyst system developed in this study worked with four different types of aldehydes (aromatic, aliphatic, heteroaromatic and α,β-unsaturated) and two different aliphatic acetylenes very successfully. Additionally, chiral ligand can be recovered in more than 90% yield and reused without losing its activity.

Keywords: 1,3-dipolar cycloaddition reactions, azomethine ylides, pyrrolidine derivatives, alkynylzinc, chiral propargylic alcohols, Lewis acid.

ÖZ

AZOMETİN İLÜRLERİN FAM-ÇİNKO KATALİZÖRLÜĞÜNDE ASİMETRİK 1,3-DİPOLAR HALKASAL KATILMA TEPKİMELERİ
VE
ALDEHİTLERİN FAM-TİTANYUM KATALİZÖRLÜĞÜNDE ENANTİOSEÇİCİ ALKİNİLASYONU

Koyuncu, Hasan
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Eylül 2007, 201 sayfa

Bu çalışmanin ilk kısmında, dört yeni kiral ligand (FAM) sentezlenmiş ve katalitik miktarlarda azometin ilürlerin asimetrik 1,3-dipolar halkasal katılma tepkimelerinde kullanılmıştır. Bu yöntemle biyolojik aktiviteye sahip bir çok doğal ürün ve ilacın yapısında bulunan kiral pirolodinlerin sentezi gerçekleştirlebilir. Bu çalışma sonunda sentezlenen kiral ligandlardan bir tanesinin başarılı olduğu bulunmuş ve bu ligandın %10 mol oranında değişik dipolarofillerle (dimetil maleat, dimetil fumarat, metil akrilat, *tert*-bütil akrilat, ve *N*-metilmaleimid) kullanılmasıyla, pirolidin türevleri %93'e varan verim ve %95'e varan enantioseçicilikle sentezlenmiştir.

Çalışmanın ikinci kısmında, bu kiral ligandların titanyumla birlikte aldehitlere asimetrik alkinilçinko katılma tepkimelerinde katalitik aktiviteleri test edilmiştir. Bu yöntemle, birçok doğal ürün ve ilacın başlangıç maddesi olan kiral propargilik alkoller sentezlenebilir. Geliştirdiğimiz katalizörü kullanarak kiral propargilik alkoller %96'ya varan verim ve %98'e varan enantioseçicilikle elde edilmiştir. Literatürdeki katalizör sistemlerinin çoğu aromatik veya alifatik aldehitler ve fenilasetilen ile çalışmasına rağmen, bu çalışmada geliştirilen katalizör sistemi, dört farklı aldehit çeşidi (aromatic, alifatik, heteroaromatik ve α,β-doymamiş) ve iki farklı alifatik asetilen ile oldukça başarılı bir şekilde çalışmıştır. Ayrıca, kiral ligand %90'ın üzerinde verimle geri kazanılıp aktivitesini kaybetmeden tekrar kullanılmıştır.

Anahtar kelimeler: 1,3-dipolar halkasal katılma tepkimeleri, azometin ilürler, pirolidin türevleri, alkinilçinko, kiral propargilik alkoller, Lewis asidi.

To my parents, sister, and my girlfriend ÖZLEM……

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LIST OF ABBREVIATIONS

Ar	: aryl (also argon)
Bn	: benzyl
BINAP	: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bu	: butyl
^{t}Bu	: tert-butyl
TBS	: t-Butyldimethylsilyl (also TBDMS)
br	: broad singlet
^{o}C	: centigrade Celcius
Δ	: chemical shift in parts per million downfield from tetramethylsilane
c	: concentration
J	: coupling constant
c-Hex	: cyclohexyl
Cy	: cyclopentyl
de	: diastereomeric excess
DA	: Diels-Alder Reaction
DME	: 1,2-dimethoxyethane (glyme, solvent)
DMPU	: N,N'-dimethyl-N,N'-propylene urea
1,3-DC	: 1,3-Dipolar Cycloaddition
d	: doublet (spectral)
dt	: doublet of triplets (spectral)
dd	: doublet of doublet (spectral)
EI	: Electron Impact
EWG	: Electron Withdrawing Group
ee	: enantiomeric excess
ΔE	: energy gap

Et	: ethyl
equiv	: equivalent
Fc	: ferrocenyl
FAM	: Ferrocenyl substituted AziridinylMethanol
FMO	: Frontier Molecular Orbitals
g	: gram(s)
Hz	: hertz
HMPA	: hexamethylphosphoramide
Hex	: hexyl
HOMO	: Highest Occupied Molecular Orbital
HPLC	: High Pressure Liquid Chromatography
HRMS	: High Resolution Mass Spectrometry
h	: hour(s)
HC	: hydrocinchonine
IR	: infrared
^{i}Pr	: isopropyl
KHMDS	: potassium hexamethyldisilazane
LA	: Lewis Acid
LDA	: Lithium Diisopropylamide
LUMO	: Lowest Unoccupied Molecular Orbital
MS	: Mass Spectrometry
mp	: melting point
MHz	: megahertz
Me	: methyl
mL	: milliliter(s)
mmol	: millimole(s)
min	: minute(s)
m	: multiplet (spectral)
nm	: nanometer
NMR	: Nuclear Magnetic Resonance
ppm	: parts per million (in NMR)

Ph	: phenyl
Py	: pyridine; Solvent, base, catalyst
q	: quartet (spectral)
R_f	: retention factor (TLC)
t_R	: retention time (in HPLC)
rt	: room temperature
s	: singlet (spectral)
THF	: Tetrahydrofuran; solvent
TMS	; Tetramethylsilane, also Trimethylsilyl
TLC	: Thin Layer Chromatography
TES	: Triethylsilyl
Tf	: Triflate (CF_3SO_2)
t	: triplet (spectral)
UV	: ultraviolet

PART 1

FAM-ZINC CATALYZED ASYMMETRIC 1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES

CHAPTER 1.1

INTRODUCTION

1.1.1. Cycloaddition Chemistry

In synthetic organic chemistry, the complexity of synthetic targets which are originating from both natural and synthetic sources are increasing day by day. As a result of this fact, there is a great demand for new and easily applicable methods for the synthesis of these types of structures. For this reason, development of novel procedures or refinement of the already present methods are needed to achieve these goals.

In modern synthetic organic chemistry, cycloaddition chemistry is very popular for the construction of mono- and poly-cyclic systems. Because, it allows for the increased molecular complexity with high level of stereocontrol from often relatively simple and readily available precursors.

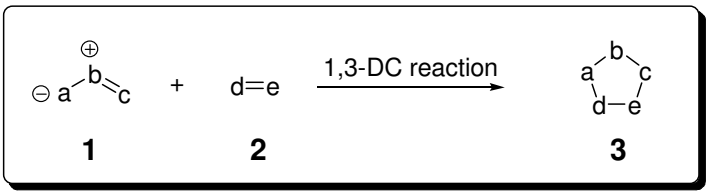
1.1.1.1. 1,3-Dipolar Cycloaddition (DC) Reactions

The 1,3-DC reaction is a very simple cycloaddition reaction in organic chemistry. It is a very powerful method for the synthesis of complex five membered heterocycles containing up to four stereogenic centers from simple starting materials. These five membered heterocycles are important for both academia and industry, because they

constitute the core unit of many complex natural products, pharmaceuticals, organocatalysts, biologically active compounds and building blocks in organic synthesis.[1]

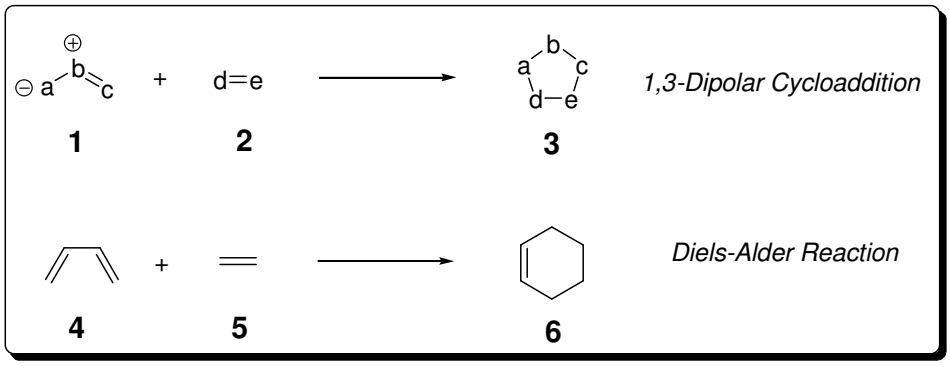
1.1.1.2. General Aspects of 1,3-DC Reactions

In 1,3-DC reaction, you need a 1,3-dipole or ylide, **1** (4π electron component) and a dipolarophile, **2** (2π electron component). They react in a $[_{\pi}4_s+_{\pi}2_s]$-fashion and concerted way to form five membered heterocyclic ring systems **3** (Scheme 1.1) .[2]



Scheme 1.1 General representation of 1,3-DC reactions.

The 1,3-DC reaction is similar to the very well known Diels Alder (DA) reaction, in which a diene (4π electron component) and a dienophile (2π electron component) react in again $[_{\pi}4_s+_{\pi}2_s]$-fashion to yield a six membered ring (Scheme 1.2) .



Scheme 1.2 Similarity between 1,3-DC Reaction and Diels-Alder (DA) Reaction.

If we deal with the background of 1,3-DC reactions, we can see that, Curtius discovered diazoacetic ester in 1883.[3] Five years later, Buchner studied the reaction of diazoacetic ester with α,β-unsaturated esters and described the first 1,3-DC reaction in literature.[4] Therefore, it is possible to say that, the chemistry of 1,3-DC reaction has evolved for more than 100 years, and variety of 1,3-dipoles have been discovered since then.[5]

In organic synthesis, general applications of 1,3-dipoles were established by Huisgen in 1960s.[6] At exactly the same time, concept of *'conservation of orbital symmetry'* was developed by Woodward and Hoffmann.[2] This study became very important for understanding the mechanism of cycloaddition reactions at that time. Later, the present understanding and ability to predict relative reactivity and regioselectivity of 1,3-DC reactions was explained by Houk et al.[7]

1.1.1.3. 1,3-Dipoles or Ylides

The 1,3-dipoles also known as ylides are generally represented as a-b-c structure and they have a positive and a negative charge distributed over three atoms. They are 4π-electron systems, having two filled and one empty orbitals.

1,3-Dipoles, mainly consist of elements from main groups IV, V, and VI. Nitrogen, carbon and oxygen are the most commonly used central atoms in these structures. Although some higher row elements, such as sulfur and phosphorus are present at the central atom, their asymmetric reactions are very limited in literature.

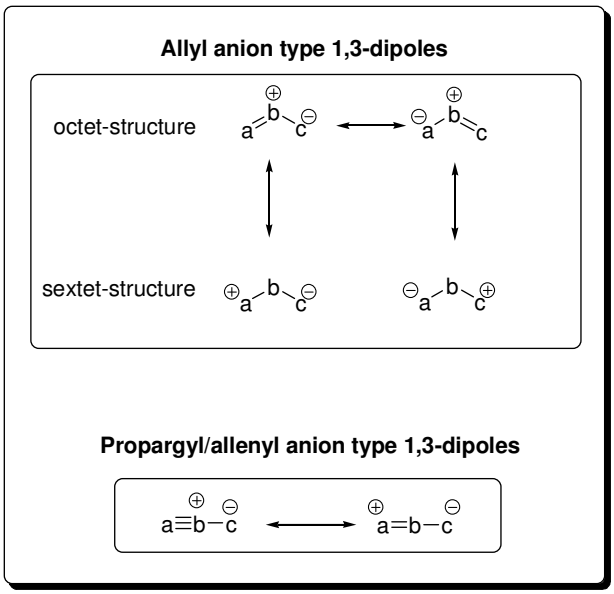
1,3-Dipoles may be divided into mainly two sub groups: the allyl anion type and propargyl/allenyl anion type of dipoles.[8]

1.1.1.3.1. Allyl Anion-Type Dipoles:

This type of dipoles have a bent type of structure (as shown in Scheme 1.3) and are characterized by four electrons located in three parallel pz orbitals, which are perpendicular to the plane of the dipole. Two resonance structures in which the three centers have an electron octet, and two structures in which *a* or *c* has an electron sextet, can be drawn. The central atom *b* can be mostly nitrogen, oxygen and sometimes sulfur (Figure 1.1).

1.1.1.3.2. Propargyl/Allenyl Anion-Type Dipoles:

The propargyl/allenyl anion type of 1,3-dipoles are linear (Scheme 1.3) and have an extra π orbital located in the plane orthogonal to the allenyl anion type molecular orbital (MO). The former orbital is not directly involved in the resonance structures and reactions of the dipole. In this type of 1,3-dipoles the central atom *b* is limited to nitrogen only (Scheme 1.3). Some examples for allyl anion type and propargyl/allenyl anion type 1,3-dipoles are given in Figure 1.2.



Scheme 1.3 The basic types and resonance structures of 1,3-dipoles.

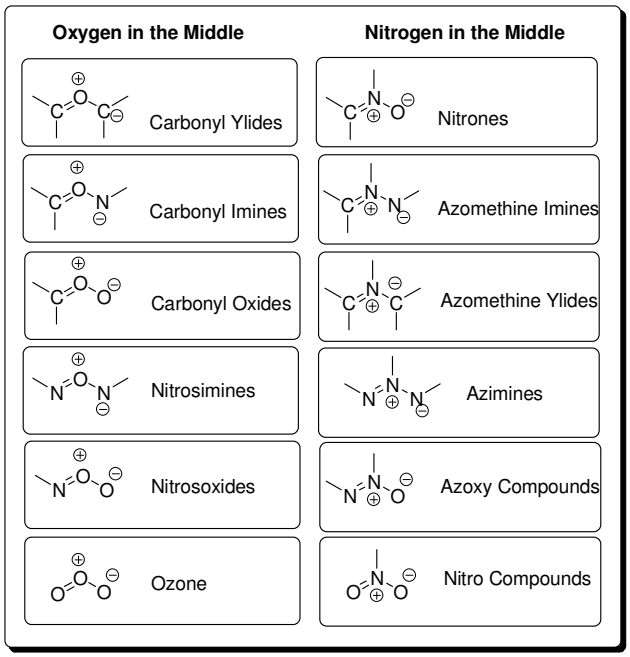


Figure 1.1 Allyl anion type of 1,3-dipoles.

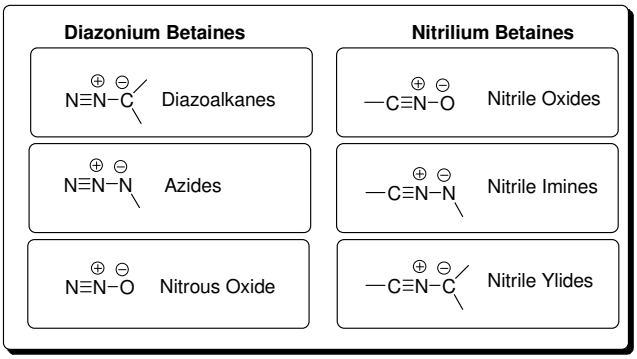


Figure 1.2 Propargyl/allenyl anion type of 1,3-dipoles.

1.1.1.4. Dipolarophiles

In 1,3-DC reactions, the dipolarophile is a 2π-electron specie that reacts with 1,3-dipoles in a concerted manner. Generally electron deficient dipolarophiles role model as dipolarophiles in 1,3-DC reactions. Specific examples to generally used electron deficient dipolarophiles can be given as: α,β-unsaturated carbonyl compounds (**7**), allylic alcohols (**8**), allylic halides (**9**), alkynes (**10**), vinylic ethers (**11a**), vinylic esters (**11b**), imines (**12**), and ketones (**13**) (Figure 1.3). [9]

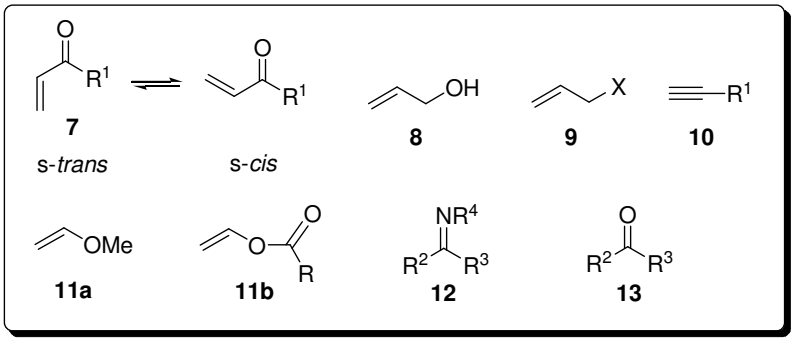
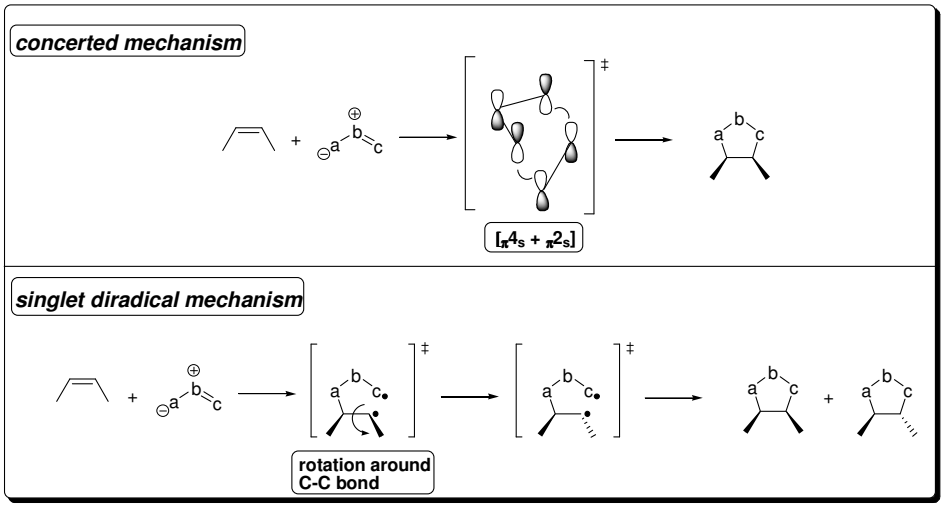


Figure 1.3 Various C-C, C-N and C-O Dipolarophiles Used in 1,3-Dipolar Cycloadditions.

1.1.1.5. Mechanistic Approaches to 1,3-DC Reactions

In the 1960s, the 1,3-DC reaction mechanism was subject to a great debate.[10] As a result of serious collection of experimental data, Huisgen et al. claimed that, 1,3-DC reactions proceed through a concerted mechanism, which means that all the bonds were created simultaneously, but not necessarily to the same extent at a certain time (Scheme 1.4).[5,6]

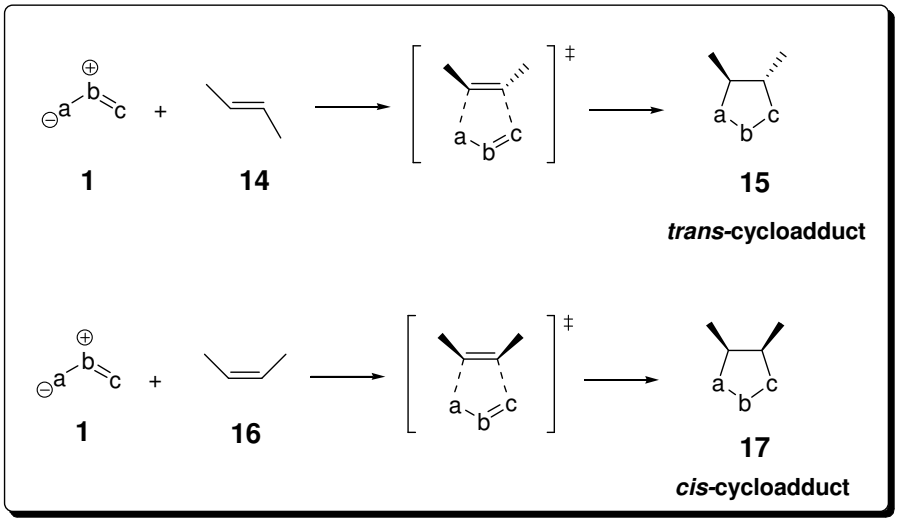


Scheme 1.4 Concerted versus singlet diradical mechanism of 1,3-DC reactions.

Firestone et al. claimed that, the 1,3-DC reaction proceeds through a singlet diradical intermediate (Scheme 1.4). When *cis*- or *trans*-alkene is used, a 180° rotation of the C-C bond is possible in this diradical intermediate and thus be expected to yield a mixture of the *cis*- and *trans*- isomers of the cycloadduct.

According to the Woodward-Hoffmann[2] rules, 1,3-DC reaction proceeds over concerted mechanism and thermally allowed with the description of $[_{\pi}4_s + _{\pi}2_s]$. This means that the three p*z* orbitals of the 1,3-dipole and the two p*z* orbitals of the dipolarophile both combine suprafacially.

In concerted 1,3-DC reaction, the stereochemistry of the dipole and the dipolarophile are retained in the final product. This is exemplified in Scheme 1.5, where the dipolarophile *trans*-2-butene **14** reacts with the hypothetical dipole **1** furnishing exclusively *trans*-cycloadduct **15**. Starting from the *cis* alkene **16** will thus yield only the *cis*-cycloadduct **17**.



Scheme 1.5 Retaining the stereochemistry of dipolarophile during a concerted 1,3-DC reaction.

Concerted cycloaddition reactions are very important in synthetic organic chemistry. This type of reactions are mostly employed in the creation of stereospecific chiral centers. The transition state of the concerted 1,3-DC reaction is controlled by the frontier molecular orbitals (FMO) of dipole and dipolarophile. It is possible that, while dipole and dipolarophile reacts, the $HOMO_{dipole}$ can interact with the $LUMO_{dipolarophile}$ and the $LUMO_{dipole}$ with the $HOMO_{dipolarophile}$. According to the basis of the relative FMO energies between the dipole and the dipolarophile interactions, 1,3-DC reactions have been classified by Sustman into three types (Figure 1.4) .[11,12]

The dominant FMO interaction in the case of type I reactions is between the $HOMO_{dipole}$ and the $LUMO_{dipolarophile}$ and this type of 1,3-DC reactions are typical for azomethine imines and azomethine ylides.

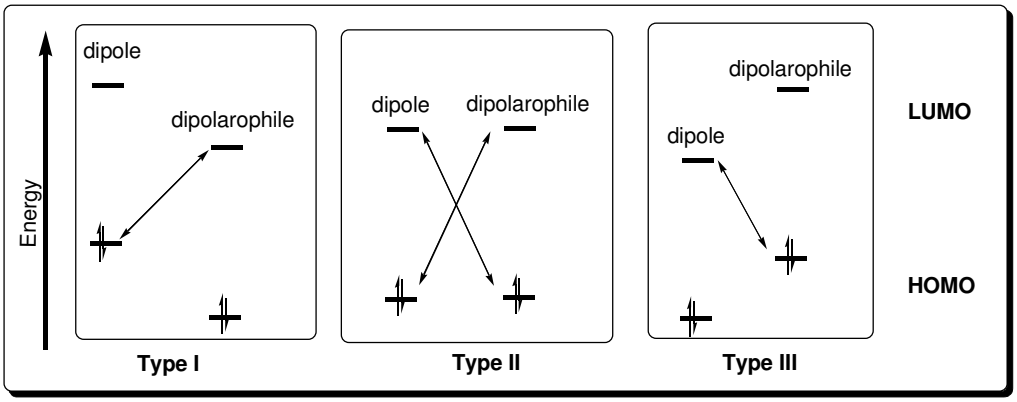


Figure 1.4 The classification of 1,3-DC reactions on the basis of FMOs.

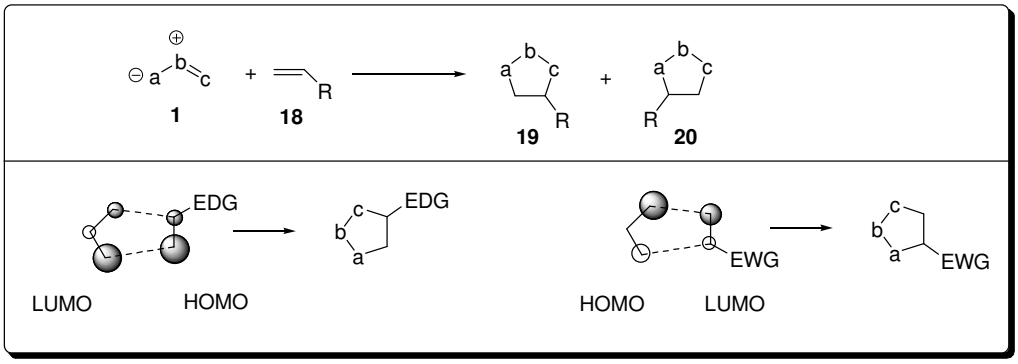
In the case of type II reactions, both reactants have similar interfrontier energy gaps and as a result, the HOMO-LUMO interactions of both dipole-dipolarophile and dipolarophile-dipole are important. This type of reactions is typical for the reactions of nitrones.

In type III reactions, the dominant interacton is between the $HOMO_{dipolarophile}$ and the $LUMO_{dipole}$. Nitrile oxide reactions are generally classified as type II but since their

HOMO energies are low lying, their reactions are between the borderline of type II and type III. Other examples to type III are given as nitrous oxide and ozone.

1.1.1.6. Effect of Substituents on 1,3-Dipoles and Dipolarophiles

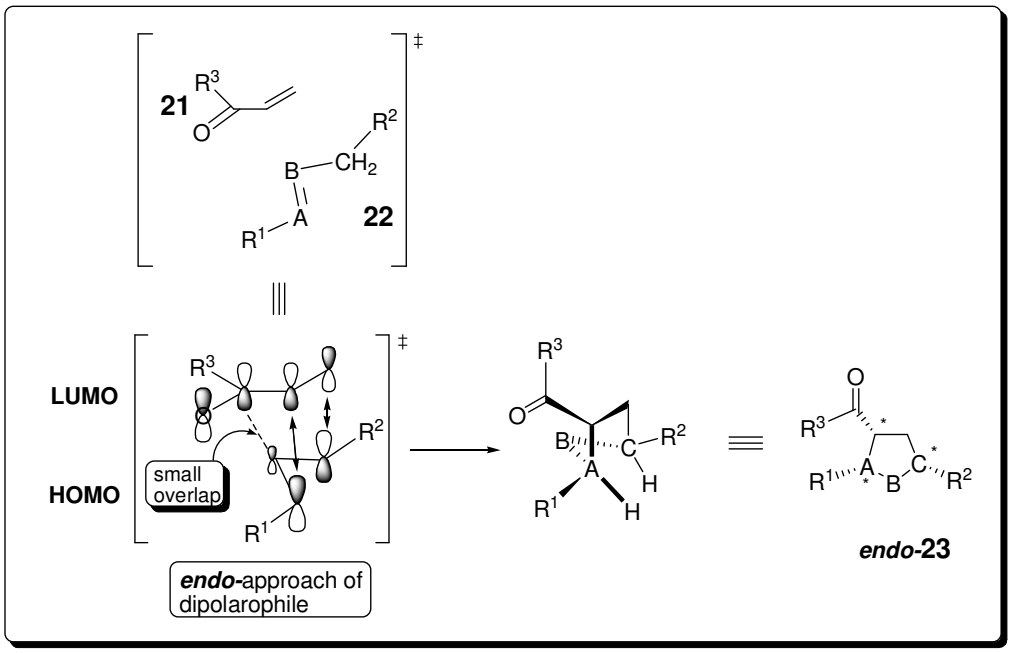
Depending upon the presence of substituents (electron donating or electron withdrawing) on dipole and dipolarophile, the FMO energies and as a result the type of 1,3-DC reactions may change. For example, when methyl acrylate reacts with *N*-methyl-*C*-phenylnitrone, the reaction is controlled by the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ interaction (type I). However, the reaction of methyl vinyl ether with the same nitrone is controlled by the $LUMO_{dipole}$-$HOMO_{dipolarophile}$ interaction (type III). As it has been seen in this example, substituents influence and perturb the FMO energies of the dipolarophile. Additionally, the perturbation of FMO energies of reactants may effect the regio- and the diastereo-selectivity of the reaction. The steric and electronic factors can affect the regioselectivity. However, the electronic properties of the substrates sometimes predominate in terms of selectivity, and the atom with the largest HOMO in the dipole interacts with the atom with the largest LUMO in the dipolarophile (Scheme 1.6).[13]

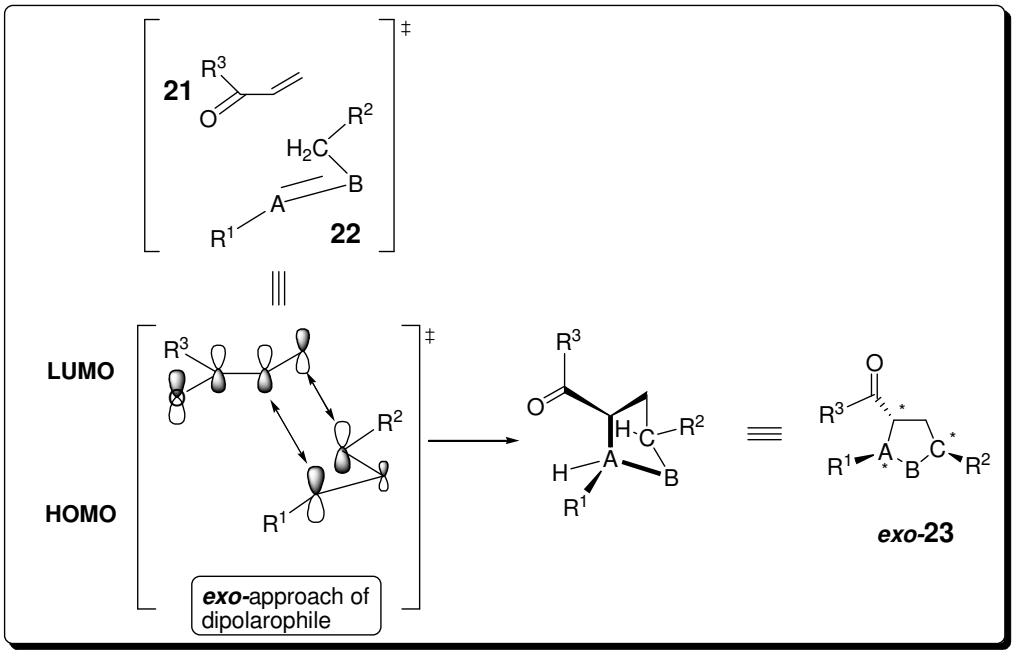


Scheme 1.6 Regioselectivity in 1,3-DC reactions.

It is possible that when a dipolarophile **21** reacts with an allyl anion type dipole **22**, the reaction could either go through an ***endo***- or an ***exo***-transition state and produce two diastereomeric cycloadducts, ***endo*-23** or ***exo*-23** as depicted in Scheme 1.7. It is

very well known that, in Diels-Alder reaction, ***endo-*** transition state is stabilized with a secondary π-orbital interaction. Here, it can be seen clearly that ***endo***-approach of the dipolarophile is stabilized by a small secondary π-orbital interaction between the $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ which contributes to the ***endo*/e*xo*** selectivity of the reaction (Type II and III).





Scheme 1.7 Diastereoselectivity in 1,3-DC reactions. Possible ***endo***- and ***exo***-approaches involved in the reaction of dipolarophile (**8**) and dipole (**9**).

1.1.1.7. Azomethine Ylides

1.1.1.7.1. 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides

1.1.1.7.1.1. General Aspects

As it was seen in Figure 1.1, azomethine ylides are planar, allyl anion type 1,3-dipoles. They include two terminal carbon atoms adjacent to a central nitrogen atom and have the general structure **27** given in Scheme 1.8.[14] Although there are some examples of stable and isolable azomethine ylides in literature[15], they are generally very reactive, unstable and short lived species and must be prepared from a stable precursor in situ and trapped with any multiple C-C or C-X bonds.[14] The 1,3-DC reactions of azomethine ylides give pyrrolidines or pyrrolines in one step and these types of structures can be synthesized in longer and more sophisticated routes unless otherwise.

Azomethine ylides constitute one of the most important classes of 1,3-DC reactions and their reactions have become very popular in recent years. Various methods have been developed based on their cycloaddition chemistry. For the synthesis of saturated, nitrogen containing, five membered heterocycles (pyrrolidines), the 1,3-DC reaction of azomethine ylides is the most simple and efficient method.

Lots of methods have been developed for the generation of azomethine ylides in literature. Such as;

*ring opening of aziridines,[16]

*desilylation of various silylamino derivatives,[17]

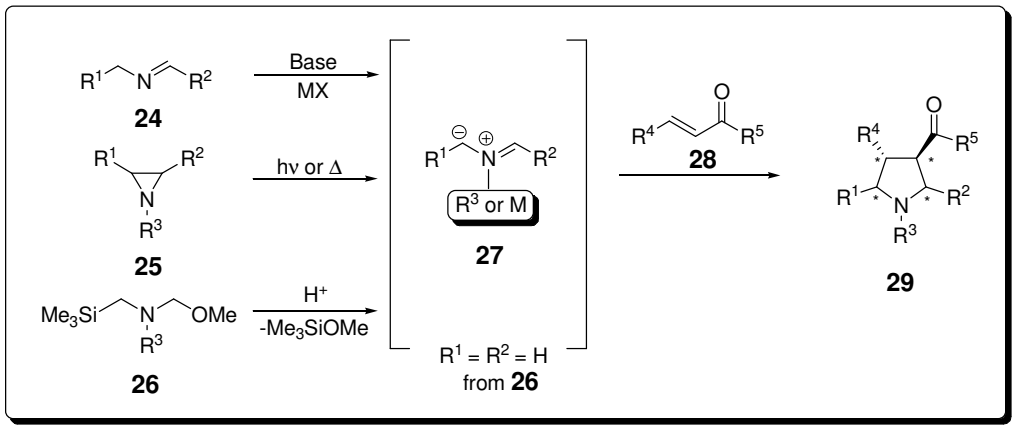
*1,2-prototropy/metallo-azomethine ylides of amino acids derived imines,[18]

*decarboxylative condensation of amino acids,[19]

*deprotonation of iminium salts,[20]

*and others.[21]

The three most commonly employed procedures; such as proton abstraction from imine derivatives **24**, photolysis or thermolysis of aziridines **25**, and acid catalysed decomposition of N-alkyl-N-methoxymethyl-N-(trimethylsilyl)methylamines **26** are given in Scheme 1.8.[22]



Scheme 1.8 Some examples for the generation of azomethine ylide (**27**) from stable precursors. Reaction with an electron deficient dipolarophile (**28**) results the pyrrolidine derivative (**29**).

1.1.1.7.1.2. Asymmetric Applications of 1,3-DC Reactions

Asymmetric synthesis is one of the hot subjects in synthetic organic chemistry. The synthesis of enantiomerically pure compounds and creating the maximum number of stereogenic centers in one step and in atom economical method is the main challenge in asymmetric synthesis. For these reasons, asymmetric catalysis is very powerful tool especially for cycloaddition reactions, where the absolute and relative configurations of several carbon atoms are established at the same time (concertedly). In recent years, the novel and very popular research fields in 1,3-DC

reactions is their asymmetric applications. The enantio-, diastereo-, and regio-selectivity controls in 1,3-DC reactions are very important.

The asymmetric versions of 1,3-DC reactions can be obtained generally in three ways;

* by attaching a chiral auxiliary to the dipole,[16c,23]

* by attaching a chiral auxiliary to the dipolarophile,[24] or

* by employing a chiral Lewis acid (LA) capable of complexing with both 1,3-dipole and dipolarophile.[25,26]

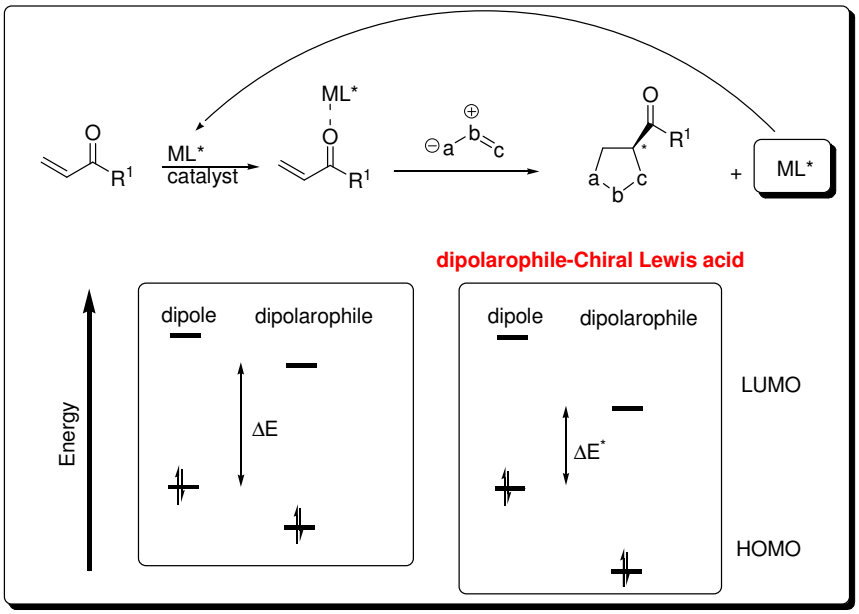
There are lots of studies published in the literature including the first two approaches. In the earlier studies of the last one, stoichiometric amount of a chiral metal complex was used.[25] However, it has been shown in recent years that, very high yield and enantioselectivities can be obtained in the synthesis of pyrrolidines when chiral ligands and metal salts are used in catalytic amounts.[26] Even though, asymmetric metal-catalyzed carbo- and hetero-Diels-Alder reactions are compared with metal catalyzed 1,3-DC reactions, the development in the last one is several years behind.

The presence of a Lewis acid in the case of an asymmetric 1,3-DC reactions is important because it can alter both the orbital coefficients of the reacting atoms and the FMO energies of both dipolarophile and 1,3-dipole. Additionally, it can also play a major role in the selectivity of the 1,3-DC reactions; enantio-, regio- and diastereo-selectivity can be controlled by the presence of a metal-ligand complex.

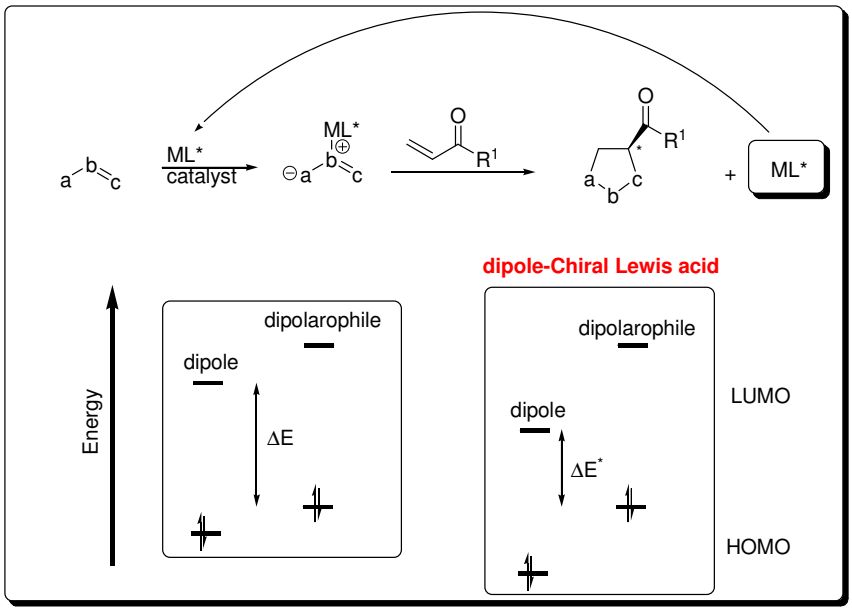
1.1.1.7.1.3. Enantioselective 1,3-DC Reactions Using Chiral Catalysts

In recent years, one of the rapidly growing research fields in 1,3-Dipolar Cycloaddition chemistry is its enantioselective version. These reactions are becoming very popular because it allows the chirality in the presence of only catalytic amount of a chiral, non-racemic complex (i.e. a catalyst). In contrast to the chiral auxiliary reactions, attachment and removal of a chiral auxiliary steps are not required in these reactions.

When a catalyst was coordinated to the dipole or dipolarophile, the FMO characteristics of the dipole and/or the dipolarophile may change. It means, a decrease or an increase in the energy gap (ΔE) between the LUMO (or HOMO) and HOMO (or LUMO) of the dipole and dipolarophile is observed.[27] Compared to the uncatalyzed reaction, when the energy gap narrows, reaction goes on faster. An example for the $HOMO_{dipole}$-$LUMO_{dipolarophile}$ controlled reaction (type 1) is given in Scheme 1.9. When chiral Lewis acid coordinates to the carbonyl oxygen of the dipolarophile, the energy level of $LUMO_{dipolarophile}$ decreases, and energy gap between $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ decreases ($\Delta E^{*} < \Delta E$). This decrease in energy gap increases the reaction rate compared to the uncatalyzed reaction. It is clear that when Lewis acid coordinates to the dipole, the reaction goes on again faster when compared to the uncoordinated one and the reaction is controlled by $HOMO_{dipolarophile}$-$LUMO_{dipole}$ interaction. When the reaction is completed, dissociation of the catalyst from the product occurs and it is ready for another catalytic cycle. (Scheme 1.10)



Scheme 1.9 The change in FMO energies of the dipolarophile when a catalyst is coordinated to the carbonyl oxygen.



Scheme 1.10 The change in FMO energies of the dipole when a catalyst is coordinated to the dipole.

It is clear that, if the catalyst used in 1,3-DC reaction is chiral, one of the π-faces of the dipole or dipolarophile may be more shielded than the other face and by this way one of the π-faces is discriminated by the dipolarophile or dipole. As a result an enantioselective reaction occurs giving rise to unequal amounts of two enantiomeric products.

1.1.1.7.1.4. Applications of Asymmetric 1,3-DC Reactions in Organic Synthesis

Many of the natural alkaloids and biologically active compounds contain pyrrolidine rings in their complex structures.[28] There are numerous examples for the successful synthesis of naturally occurring alkaloids and their analogues. In the synthesis of these types of structures, asymmetric 1,3-DC reaction of azomethine ylides with a dipolarophile play a major role. Some important examples are (+)- and (–)-spirotryprostatin B (**30**),[29] (–)-2α-tropanol (**31**),[30] (–)-cucurbitine (**32**),[31] (–)-horsfiline (**33**),[32] a precursor to the alkaloid (+)-conessine (**34**) (used in the treatment of dysentery),[24a] the total synthesis of the antitumor antibiotic (–)-quinocarcin (**35**),[33] the analgesic alkaloid epibatidine (**36**)[34] (nonopiate analgesic, 200 times more potent than morphine), kainic acid (**37**) (important in physiological and pharmacological studies of the central nervous system), cephalotaxine (**38**) (shows antileukaemeic activity), and acromelic acid (**39**) (has potential neurotoxicity) (Figure 1.5). Asymmetric 1,3-dipolar cycloadditions of azomethine ylides have also been utilized as key steps in the total syntheses of many unnatural bioactive substances, for example some cocaine antagonists,[35] antibacterial compounds[36] and glucosidase inhibitors.[37] 3,4-Disubstituted pyrrolidines have found applications as receptor antagonists.[38]

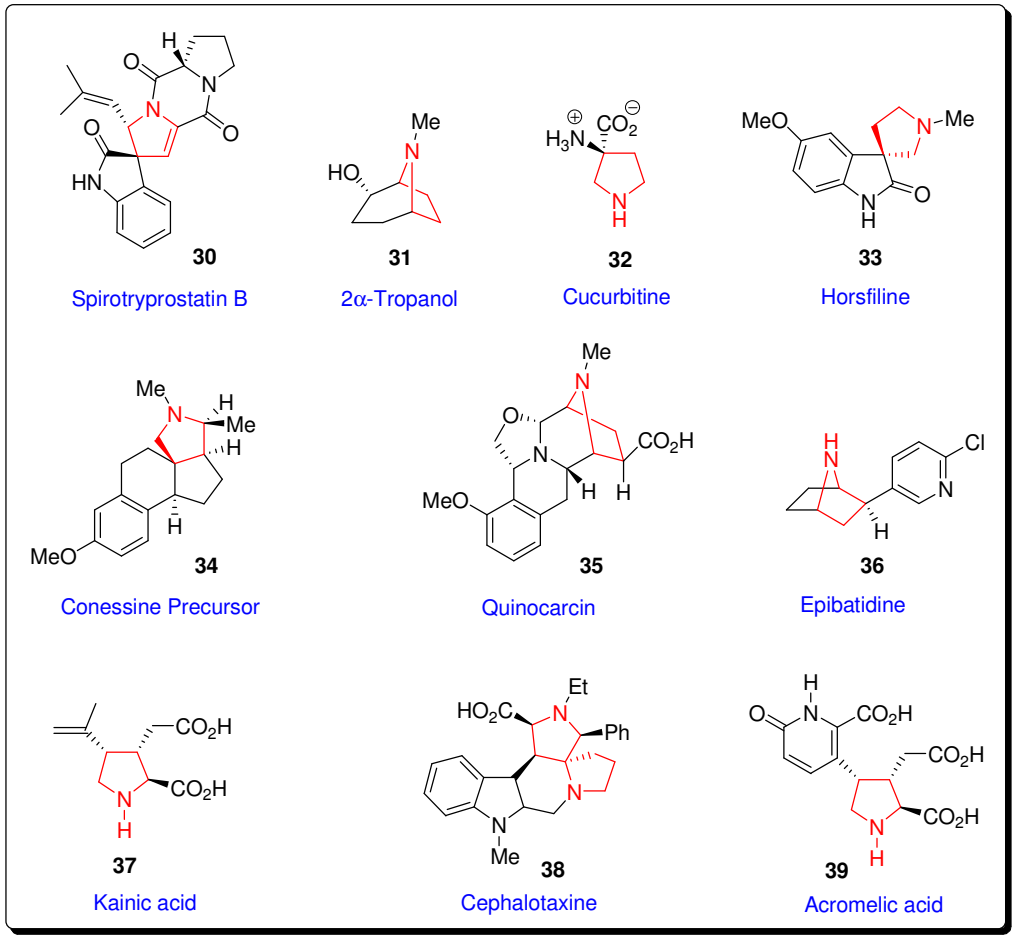
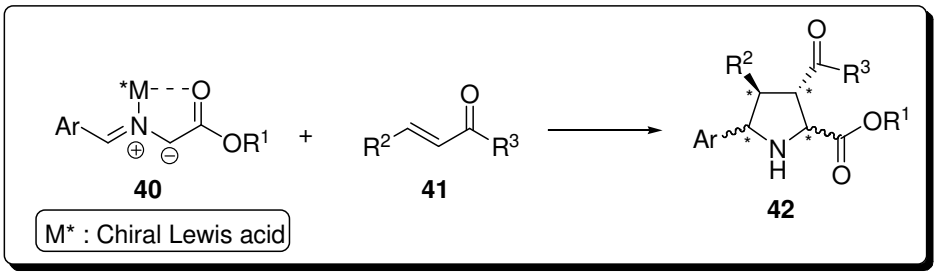


Figure 1.5 Examples of some alkaloids and biologically active compounds synthesized via asymmetric 1,3-DC reaction of an azomethine ylide as a key step. (The pyrrolidine unit obtained in this step is marked in **red**).

1.1.1.7.1.5. Metal Catalyzed 1,3-DC Reactions of Azomethine Ylides in Literature

In the literature, there are only limited numbers of metal-catalysts, which are used in enantioselective manner for the synthesis of 1,3-dipolar cycloaddition reactions of azomethine ylides with different electron deficient dipolarophiles. In general, the azomethine ylides of α-iminoesters are used. Because, these types of azomethine ylides (**40**) can be stabilized due to the presence of adjacent electron acceptor. As it is shown in Scheme 1.11, in the presence of a Lewis acid catalyst, this type of azomethine ylides coordinate to the catalyst in bidentate fashion in the transition state. Then, cycloaddition with an electron deficient dipolarophile (**41**) results a functionalized pyrrolidine derivative.

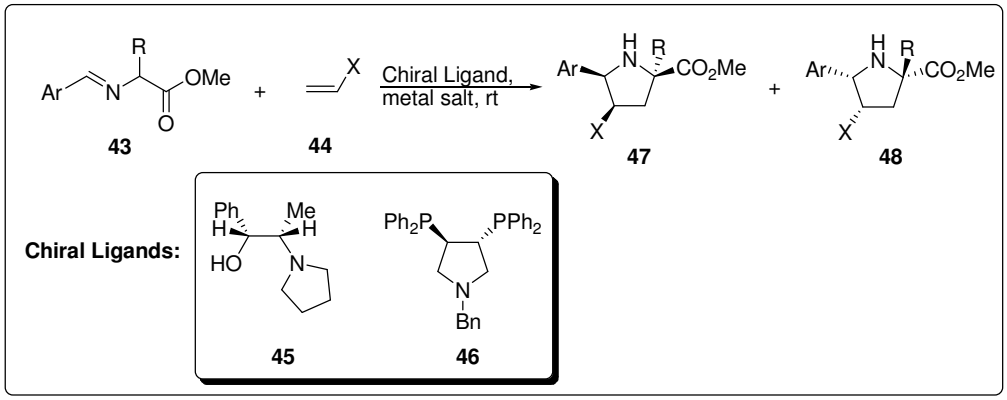


Scheme 1.11 Coordination of a chiral Lewis acid to a stabilized azomethine ylide and subsequent cycloaddition with an electron-deficient dipolarophile.

As it is mentioned before, there are several procedures for generating azomethine ylides. The metallation of azomethine ylides of imino ester types are mostly studied in recent years.[39,40] Metallo azomethine ylides are valuable because they can be prepared very easily from α-imino esters in basic media and at room temperature in the presence of a metal salt.

The first reported example of a metal catalyzed asymmetric 1,3-Dipolar Cycloaddition reaction in the literature was published by Grigg and co-workers as a seminal work in 1991.[25a] This study is very important, because in asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides it has become a milestone to different groups in the literature.

In this study, they have observed that, chiral manganese and cobalt complexes are capable of showing enantioselectivity in 1,3-Dipolar Cycloaddition reactions of azomethine ylides derived from α-amino ester. The azomethine ylide precursor (**43**) and methyl acrylate (**44**, X=CO_2Me) reacted in the presence of stoichiometric amounts of cobalt salt and the two equivalents of chiral ephedrine ligand (**45**). The 1,3-DC reaction product (**47**) was obtained up to 96% ee (Scheme 1.12).



Scheme 1.12 The reaction of the azomethine ylide precursor (**43**) and the dipolarophile (**44**) in the presence of stoichiometric amounts of metal salt and chiral ligands (**45**) and (**46**).

The yields of the product **47** were ranged between 45-84% depending upon the dipolarophile used and the highest enantioselectivities were obtained when Ar = 2-naphthyl, 4-BrC_6H_4, 4-$MeOC_6H_4$ and when methyl acrylate (**44**, X=CO_2Me) was used as the solvent and dipolarophile at the same time in this study.

Table 1.1 The results of the asymmetric 1,3-DC reactions of Grigg and co-workers

Ar	R	X	Ligand[a]	Metal Salt	product	yield(%)	ee(%)
2-Naphthyl	H	CO_2Me	**45**	$CoCl_2$	**47**	84	96
2-Naphthyl	Me	COMe	**46**	AgOTf	**48**	83	70
2-Naphthyl	Me	SO_2Ph	**46**	AgOTf	**48**	64	70

[a]100 mol%

At the end of the study, they recognized that both the reaction time and the enantioselectivity were dependent on the counterion. They have obtained good results in terms of yield and enantioselectivity when they used $CoCl_2$ catalyst instead of CoF_2.

Their results were explained according to the following working model as shown in Figure 1.6**A**.

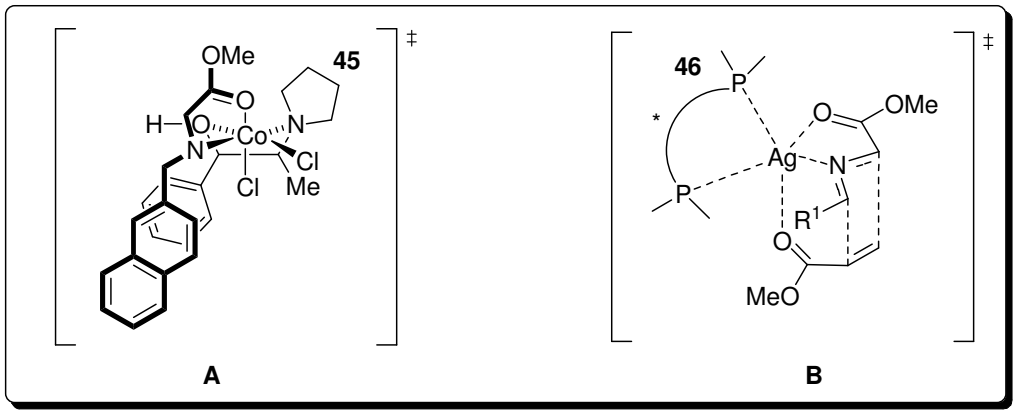


Figure 1.6 The transition states of Co(II) (**A**), and Ag(I) (**B**) in the presence of chiral ligands (**45**) and (**46**).

In this model, they claim that, the *cis*-methyl and phenyl groups of the ligand (**45**) in the transition structure (**A**) results in a pseudo equatorial conformation of the phenyl group and this effectively blocks one face of the dipole.[25a]

In a second study, they also studied the catalysis of Ag(I) salts and chiral phosphine ligand (**46**) involving the azomethine precursor (**43**) and methyl vinyl ketone (**44**, X=COMe).[25b] Again in this reaction, the catalyst was used in stoichiometric amount, and the reaction proceeded to give the cycloadduct in a good yield with 70% ee (Table 1.1). The offered transition state in this study is given in Figure 1.6**B**.

1.1.1.7.1.5.1. Ag(I)-Based Protocols

The Ag(I) salts are probably the most effective Lewis acids in the cycloaddition reactions of azomethine ylides. The reaction times with silver salts are generally fast, and a few hours is enough for the completion of the reaction. The products are generally isolated in very high yields and enantioselectivities.

In recent years, several chiral ligands have been used in catalytic asymmetric silver-catalyzed 1,3-DC reactions of azomethine ylides.[26]

The first use of catalytic chiral metallic complex was published by Zhang[26a] and co-workers. In this study, silver acetate was screened with several bisphosphine chiral ligands such as; (*R*)-BINAP (**47**), (*R*,*R*)-Me-DuPhos (**48**), (*R*,*S*,*R*,*S*)-PennPhos (**49**), (*R*,*R*,*R*,*R*)-BICP (**50**) (Figure 1.7), and they obtained very poor enantioselectivities and diastereoselectivities, in the cyclization reaction of imino ester (**52**) and dimethyl maleate (**53**) (Scheme 1.13).

The Trost's ligand (**51**) (Scheme 1.13) gave higher enantioselectivity compared to the previous bisphosphine ligands and this result could be probably due to the weak interaction of nitrogen atom of the bisamide unit with silver atom when chiral complex forms.

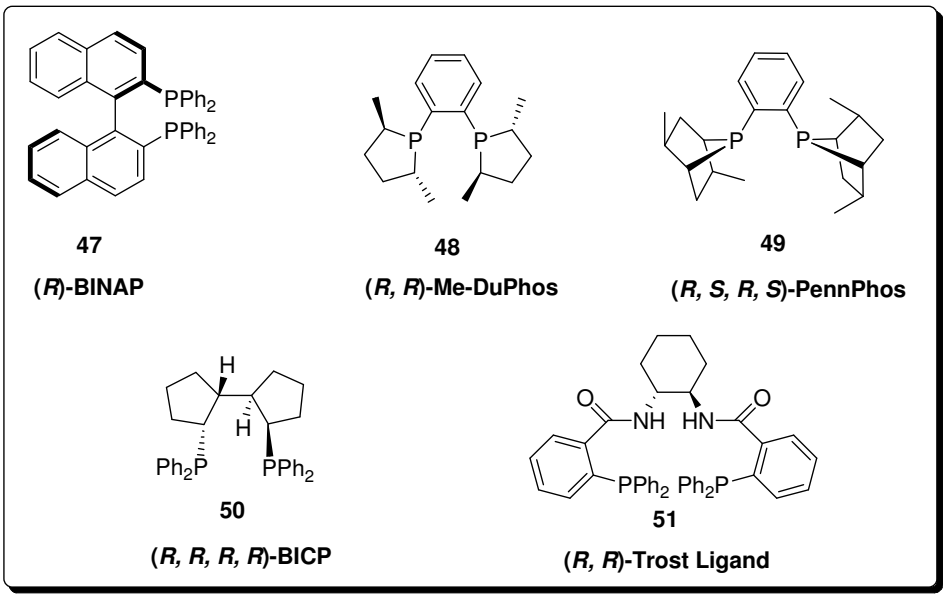
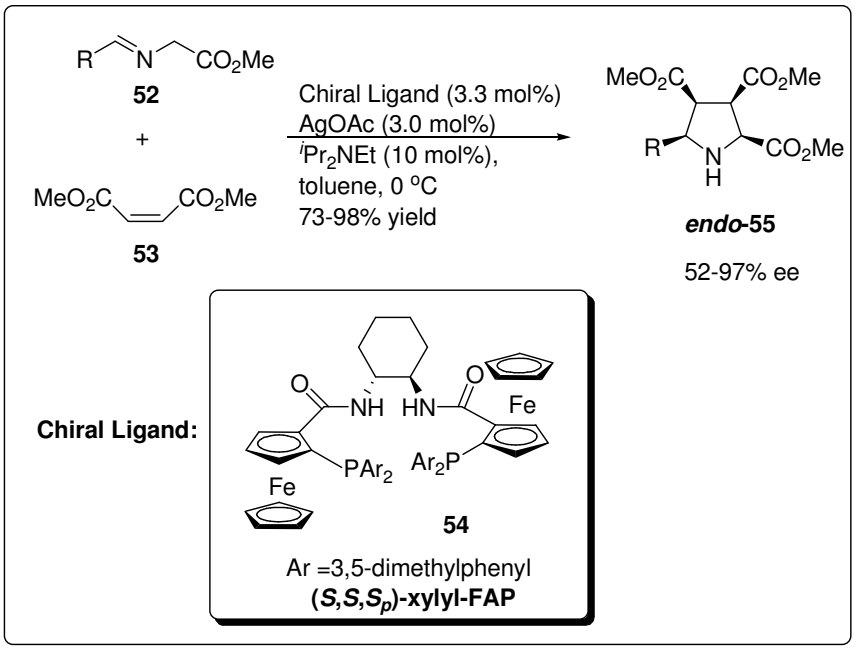


Figure 1.7 The different types of chiral ligands used by Zhang and co-workers.



Scheme 1.13 The reaction of imino ester (**52**) and dimethyl maleate (**53**) in the presence of 3.3 mol% of chiral ligand (**54**) and 3.0 mol% Ag(I).

After having this result, they synthesized a new type of chiral ligand (**54**), which is similar to the Trost's ligand and has an additional planar chirality due to the presence of ferrocene units. The best results for the cycloadduct ***endo*-55** were obtained when this chiral ligand (**54**) and dimethyl maleate (**53**) were reacted. The cycloadduct ***endo*-55** was again obtained in high yield and enantioselectivities, when R on the ylide precursor (**52**) was chosen as different aromatic and aliphatic units (Table 1.2). The results of the experiments when azomethine ylide precursor (**52**) (R=Ph) was used with different dipolarophiles under optimized reaction conditions are summarized in Figure 1.8.

Table 1.2 The results of the asymmetric 1,3-DC reactions of Zhang and co-workers.

R	**yield (%)**	**ee (%)**
Ph	87	87
p-MeC_6H_4	93	88
p-$MeOC_6H_4$	98	92
p-ClC_6H_4	96	92
p-FC_6H_4	96	90
p-CNC_6H_4	90	96
o-ClC_6H_4	96	86
o-Tolyl	97	90
1-Naphthyl	73	85
2-Naphthyl	98	97
3-Pyridyl	98	84
Isopropyl	82[a]	70
c-Hex	82[a]	81

[a] reactions were run at room temperature.

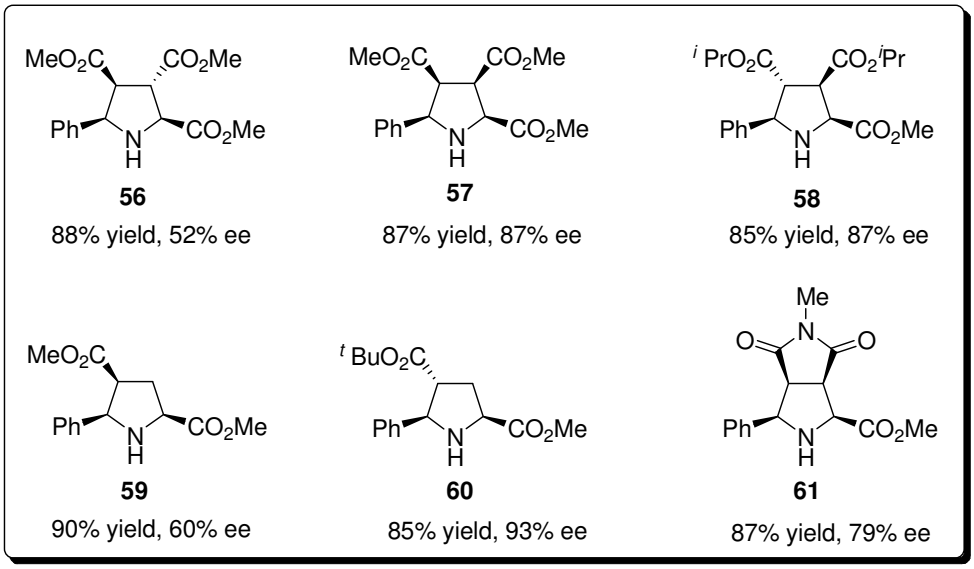
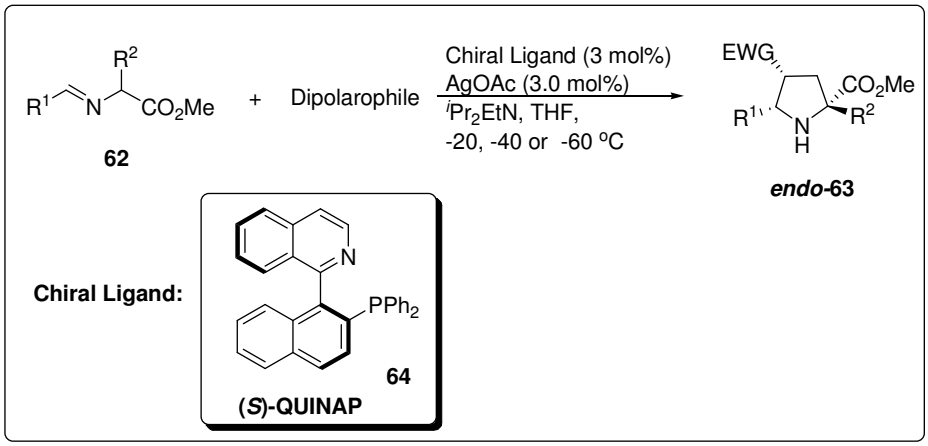


Figure 1.8 Results of the asymmetric 1,3-DC reaction of azomethine ylides when the chiral ligand (**54**) was used with different dipolarophiles under optimized reaction conditions.

Using Ag(I) catalyzed enantioselective 1,3-DC reaction of azomethine ylides, Schreiber[26b] and co-workers developed a new 1,3-DC reaction of azomethine ylides of α-iminoesters and acrylates furnished 3-substituted pyrrolidines (***endo*-63**) in excellent yields and enantioselectivities (Scheme 1.14). They have used series of chiral mono-phosphines and among them, the P,N-ligand (*S*)-QUINAP (**64**) worked very efficiently (Scheme 1.14). This is a good indication that **64** forms a stable complex with Ag(I) at transition state. They proposed for this result that, the corresponding azomethine ylides are formed *in situ* by the deprotonation in the α-position by diisopropylethylamine, followed by a formation of bidentate complexation of the chiral catalyst to the imine nitrogen and the enolate oxygen (as shown in Figure 1.9). The results of the catalytic asymmetric 1,3-DC reactions of azomethine ylides with various dipolarophiles under optimized reaction conditions are given in Table 1.3.



Scheme 1.14 Ag(I) catalyzed asymmetric 1,3-DC reactions of azomethine ylides.

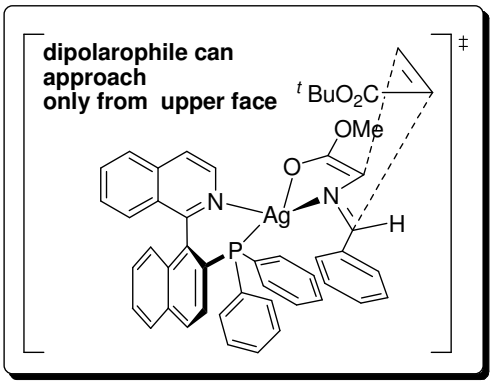


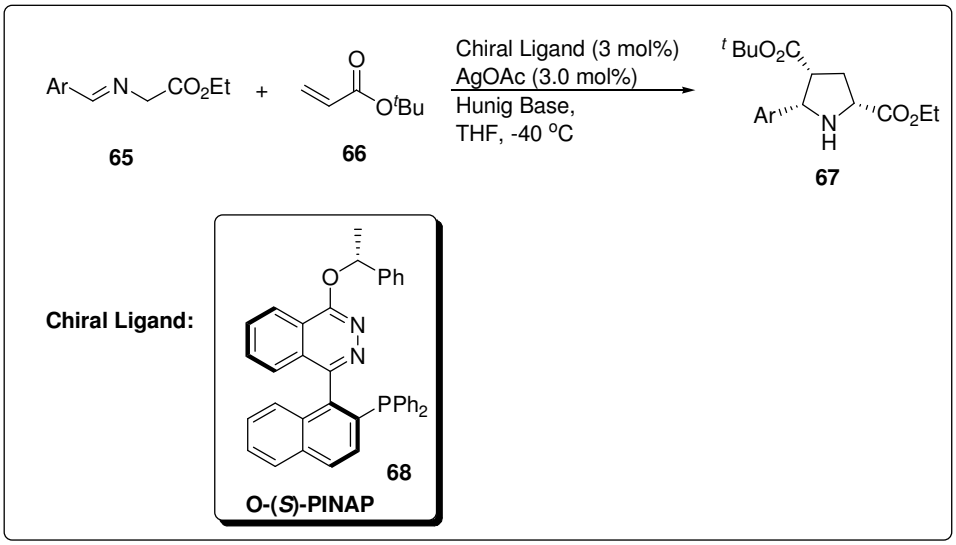
Figure 1.9 Proposed transition state for the silver(I)/(*S*)-QUINAP catalyzed azomethine ylide cycloaddition.

The chiral ligand O-(*S*)-PINAP (**68**), which is similar to (*S*)-QUINAP (**64**) was synthesized by Carreira[26c] and co-workers and it was used under the same conditions as the Schreiber's reaction conditions (3 mol% catalyst loading) (Scheme 1.15). When tert-butylacrylate (**66**) was reacted with the azomethine ylide at -40 °C, they obtained comparable results to (*S*)-QUINAP/Ag(I) catalyst system. This is again a good indication that O-(*S*)-PINAP also forms a stable complex with Ag(I) in the reaction medium. The results of this study are summarized in Table 1.4.

Table 1.3 The results of the catalytic asymmetric 1,3-DC reactions of azomethine ylides with different dipolarophiles under optimized reaction conditions with catalyst system silver(I)/(*S*)-QUINAP (3 mol%).

R^1	R^2	T (^oC)	dipolarophile	*endo*/*exo*	yield (%)	ee (%)
p-$MeOC_6H_4$	H	- 45	*tert*-butyl acrylate	only ***endo***	93	95
p-BrC_6H_4	H	- 45	*tert*-butyl acrylate	only ***endo***	89	95
p-CNC_6H_4	H	- 45	*tert*-butyl acrylate	only ***endo***	92	96
2-Naphthyl	H	- 45	*tert*-butyl acrylate	only ***endo***	89	94
o-Tolyl	H	- 45	*tert*-butyl acrylate	only ***endo***	95	89
Ph	H	- 60	dimethyl maleate	> 20:1	88	60
Ph	H	- 20	*tert*-butyl crotonate	> 20:1	97[a]	84
Ph	H	- 20	*tert*-butyl cinnamate	2:1	62[b]	81
Ph	Me	- 20	*tert*-butyl acrylate	only ***endo***	98	80
Ph	isobutyl	- 20	*tert*-butyl acrylate	only ***endo***	77	80
Ph	benzyl	- 20	*tert*-butyl acrylate	only ***endo***	93	77
Ph	3-indolylmethyl	- 20	*tert*-butyl acrylate	only ***endo***	47	81(50)[c]

[a] Catalyst loading: 10 mol%, [b] total yield of ***endo*** and ***exo*** products, [c] enantioselectivity of the ***exo*** product.



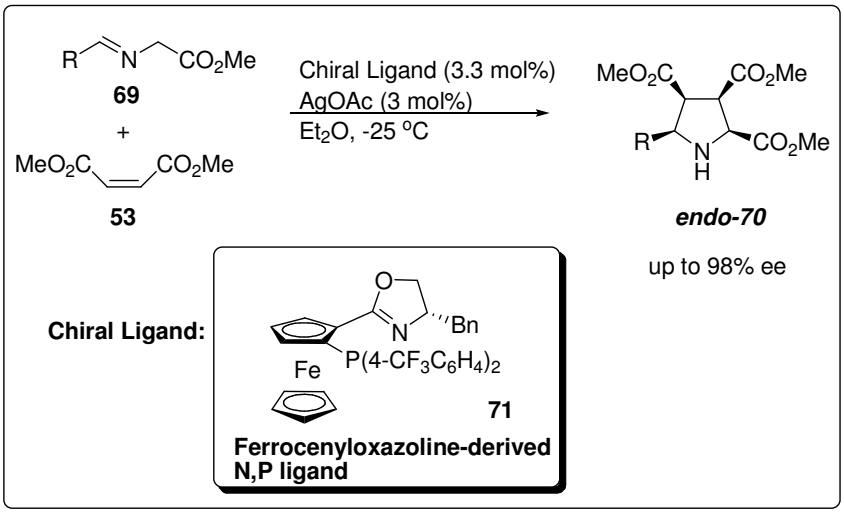
Scheme 1.15 Ag(I) and O-(*S*)-PINAP (**68**) catalyzed asymmetric 1,3-DC reactions of azomethine ylides with *tert*-butylacrylate (**66**).

Table 1.4 The results of the catalytic asymmetric 1,3-DC reactions of *tert*-butylacrylate, Ag(I) and O-(*S*)-PINAP (**68**) with two different azomethine ylide precursors.

Ar	yield (%)	ee (%)
p-CNC_6H_4	94	95
p-$MeOC_6H_4$	88	92

Recently, a chiral ferrocenyloxazoline derived P,N ligand (**71**) depicted in Scheme 1.16 was used as an efficient chiral catalyst in the presence of AgOAc by Zhou and co-workers.[26d] An extra base was not needed in this study, since the reactive metal-bound azomethine ylide dipole was formed by deprotonation with acetate ion which played the role of base. It was postulated in this study that, AgOAc bearing a weakly basic charged acetate ion facilitated the deprotonation of imino esters to generate the azomethine ylides. This method resulted a total ***endo***- diastereoselectivity in all cases, furnished enantio-pure highly substituted pyrrolidine derivatives. The results

of this reaction with different azomethine ylide precursors are given in Table 1.5. The results of the reaction under optimized conditions with different dipolarophiles are given in Figure 1.10.



Scheme 1.16 Ag(I) and ferrocenyloxazoline derived P,N ligand (**71**) catalyzed asymmetric 1,3-DC reactions of different azomethine ylides with dimethyl maleate (**53**).

Table 1.5 The results of the catalytic asymmetric 1,3-DC reactions of different azomethine ylides with dimethyl maleate (**53**) under optimized reaction conditions.

R	yield(%)	ee(%)
Ph	85	97
p-$MeOC_6H_4$	94	98
p-ClC_6H_4	99	97
p-FC_6H_4	96	97
p-CNC_6H_4	91	97
o-ClC_6H_4	98	97
o-Tolyl	99	98
1-Naphthyl	85	98
2-Naphthyl	95	98
3-Pyridyl	76	93
i-Pr	56	88

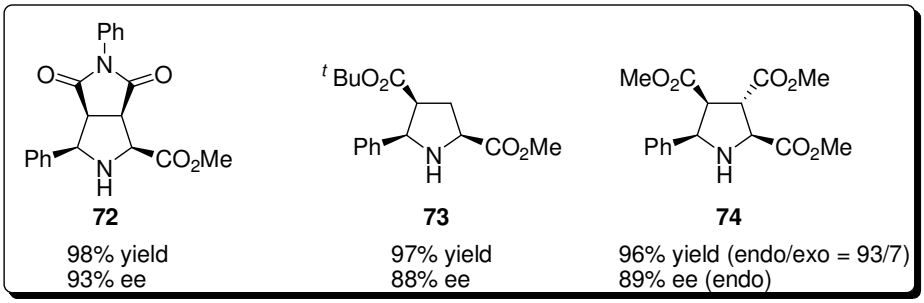
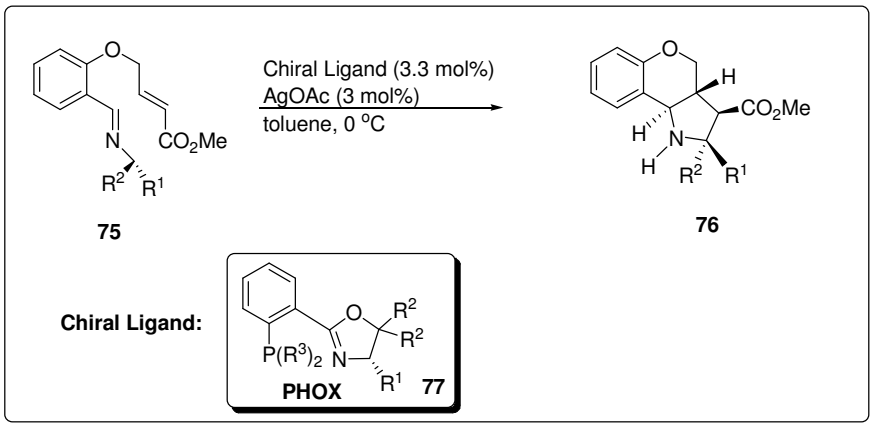


Figure 1.10 The asymmetric 1,3-DC reaction of Ag(I) and ferrocenyloxazoline derived P,N ligand (**71**) with other dipolarophiles under optimized reaction conditions.

1.1.1.7.1.5.2. The Intramolecular Ag(I)-Based Protocol

The intramolecular version of the enantioselective Ag(I) catalyzed 1,3-DC reaction was performed in the presence of a chiral ligand by Pfaltz et al.[26e] in 2005. They used a phosphino-oxazoline (PHOX) structure (**77**) as the chiral ligand, and at the end of the reaction chiral tricyclic compound (**76**) with perfect diastereoselectivity and high levels of enantiocontrol was obtained (Scheme 1.17). The results of the catalytic asymmetric intramolecular 1,3-DC reactions are summarized in Table 1.6.



Scheme 1.17 Ag(I) and phosphino-oxazoline (PHOX) (**77**) catalyzed intramolecular asymmetric 1,3-DC reaction.

Table 1.6 The results of the catalytic asymmetric 1,3-DC reactions of Ag(I) and phosphino-oxazoline (PHOX) (**77**) catalyzed intramolecular asymmetric 1,3-DC reaction.

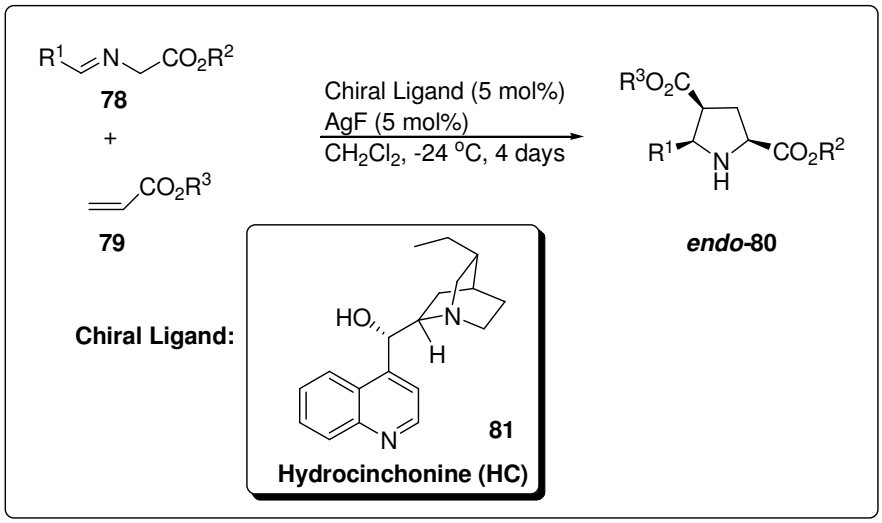
R^1	R^2	yield (%)	ee (%)
CO_2Me	H	74	96
CO_2t-Bu	H	66	99
CO_2Me	Me	61	96
Py	H	70	83

In this study, Pfaltz and co-workers have tried also various chiral PHOX ligands in intermolecular Ag(I)-catalyzed reaction of N-(2-naphthylidene)glycine methyl ester and methyl acrylate. By using 3 mol% of catalyst, which is prepared *in situ* from standard PHOX ligands, in toluene at 0 ^{o}C the desired pyrrolidine was obtained in high yield and high diastereoselectivity but very low enantioselectivities were obtained.

Up to now, the corresponding cycloadducts were obtained in very high yields and enantioselectivities. However, the glovebox techniques, deoxygenated and dried solvents, preformation of the catalysts were normally the standard reaction conditions in these studies. Additionally, the reactions were carried out under inert atmosphere which limited their application from a practical point of view.

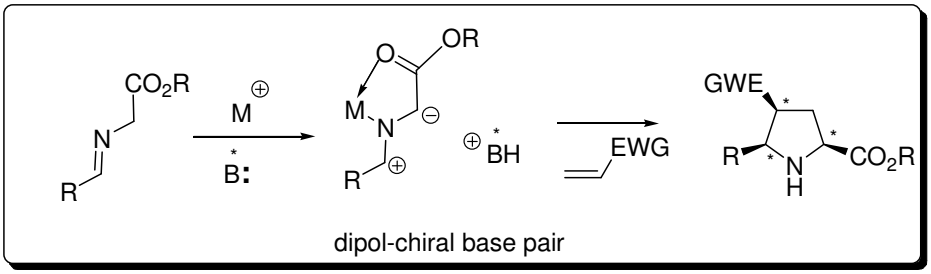
In 2005, Jorgensen[26f] and co-workers reported a novel and convenient catalytic procedure, for the enantioselective 1,3-DC reactions of azomethine ylides (obtained from **78**) and acrylate derivatives (**79**). In this procedure, by using AgF and hydrocinchonine (**81**) as the catalyst system, the ***endo*-80** cycloadducts were obtained in very high yields and enantioselectivities without requiring specific precautions such as drying and degassing of solvent, using an inert atmosphere (Scheme 1.18). They offered that, chelation of the metal to the imino ester followed by deprotonation by a cinchona alkaloid acting as the chiral base would form a

metallo-azomethine ylide-chiral base ion pair. The dipolarophile then reacted with this chiral environment to afford the cycloadduct stereoselectively (Scheme 1.19).



Scheme 1.18 Ag(I) and hydrocinchonine (HC) (**81**) catalyzed asymmetric 1,3-DC reaction.

The results of the AgF and hydrocinchonine (**81**) catalyzed 1,3-DC reactions of various azomethine ylides and dipolarophiles are summarized in Table 1.7.



Scheme 1.19 The asymmetric 1,3-DC reaction of azomethine ylide, which is activated by a metal salt and a chiral base.

Table 1.7 The results of the catalytic asymmetric 1,3-DC reactions of Ag(I) and hydrocinchonine (**81**) catalyzed asymmetric 1,3-DC reaction.

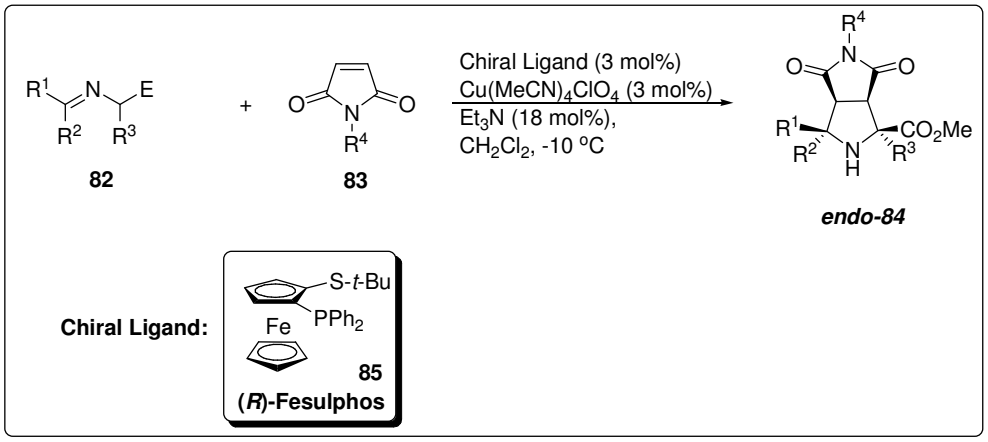
R^1	R^2	R^3	yield (%)	ee (%)
p-MeC_6H_4	Me	Me	>95[a]	41
p-MeC_6H_4	*t*-Bu	Me	93[a]	32
p-MeC_6H_4	Me	*t*-Bu	>95[a]	50
p-MeC_6H_4	Me	*t*-Bu	89	70
o-MeC_6H_4	Me	*t*-Bu	97	64
Ph	Me	*t*-Bu	88	64
o-$MeOC_6H_4$	Me	*t*-Bu	63	56
m-$MeOC_6H_4$	Me	*t*-Bu	93	70
p-$MeOC_6H_4$	Me	*t*-Bu	89	56
o-$Me_2NC_6H_4$	Me	*t*-Bu	86 (41)[b]	67 (92)[b]
p-BrC_6H_4	Me	*t*-Bu	88	66
p-NCC_6H_4	Me	*t*-Bu	86	70
p-$MeO_2CC_6H_4$	Me	*t*-Bu	82 (41)[b]	61 (85)[b]
2-Furyl	Me	*t*-Bu	86	73
1-Naphthyl	Me	*t*-Bu	88	64
2-Naphthyl	Me	*t*-Bu	86	62
c-Hex	Me	*t*-Bu	65	41
t-Bu-CH_2	Me	*t*-Bu	78	41
i-Pr	Me	*t*-Bu	67	52

[a] room temperature overnight 20 mol% base, 20 mol% metal salt, [b] yield and ee after recrystallization.

1.1.1.7.1.5.3. Cu-Based Protocols

In recent years, some methods have been developed using Cu-Lewis acids or Cu-based reagents, which are valuable synthetic tools with a wide application in enantioselective cycloadditions of azomethine ylides. Copper is one of the most important transition metal in terms of its efficiency and diversity of these methods in organic synthesis.

Carretero[26g] and his group showed that, the combination of chiral ligand (*R*)-Fesulphos (**85**) and copper(I) salts resulted in a highly reactive catalyst system. In this study, maleimide dipolarophiles (**83**) and a broad range of the azomethine ylide precursors (**82**) were used and high enantioselectivities were obtained (Scheme 1.20).



Scheme 1.20 The Cu(I) and (*R*)-Fesulphos (**85**) catalyzed asymmetric 1,3-DC reaction.

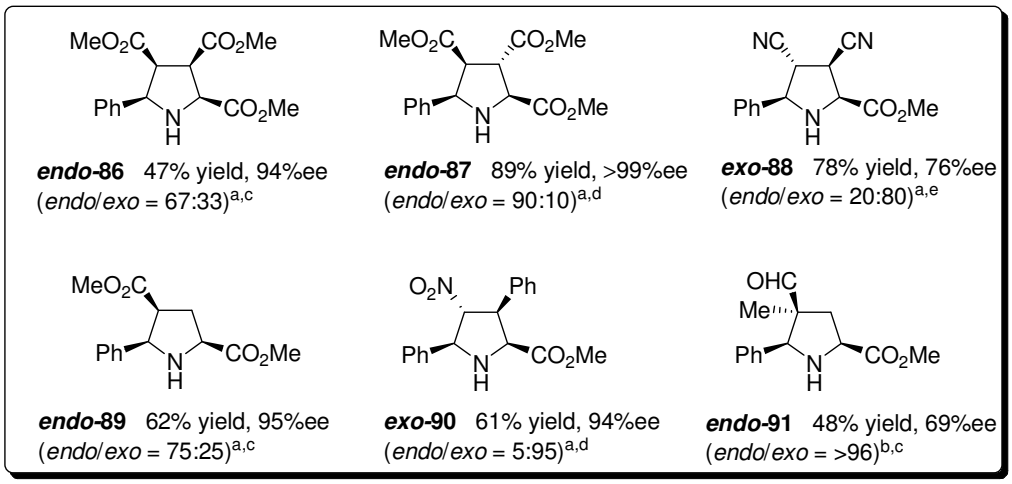
Dipolarophiles other than maleimides, such as dimethyl maleate, dimethyl fumarate and fumarodinitrile were also studied in order to explore more deeply the scope and

generality of this new methodology. It was seen that, high asymmetric inductions (76-99% ee) were obtained which proved that these are the excellent susbstrates for this reaction. However, the ***endo/exo*** selectivity was poorer than that of the maleimide dipolarophile (Figure 1.11).

The results of the Cu(I) and (*R*)-Fesulphos (**85**) catalyzed 1,3-DC reactions of various azomethine ylides and maleimides are summarized in Table 1.8.

Table 1.8 The results of the catalytic asymmetric 1,3-DC reactions of Cu(I) and (*R*)-Fesulphos (**85**) catalyzed asymmetric 1,3-DC reaction.

R^1	R^2	R^3	R^4	E	yield (%)	de (%)	ee (%)
Ph	H	H	Ph	CO_2Me	81	>96	>99
2-Naphthyl	H	H	Ph	CO_2Me	81	94	>99
p-FC_6H_4	H	H	Ph	CO_2Me	82	>96	>99
p-$MeOC_6H_4$	H	H	Ph	CO_2Me	81	>96	>99
o-Tolyl	H	H	Ph	CO_2Me	85	>96	>99
Ph	H	H	Me	CO_2Me	97	>96	>99
2-Naphthyl	H	Me	Ph	CO_2Me	78	>96	92
p-ClC_6H_4	Me	H	Ph	CO_2Me	80	>96	>99
Ph	Me	H	Ph	CO_2Me	78	>96	94
Ph	Ph	H	Ph	CO_2Et	92	>96	93
Ph	H	Me	Ph	CO_2Me	50	>96	80

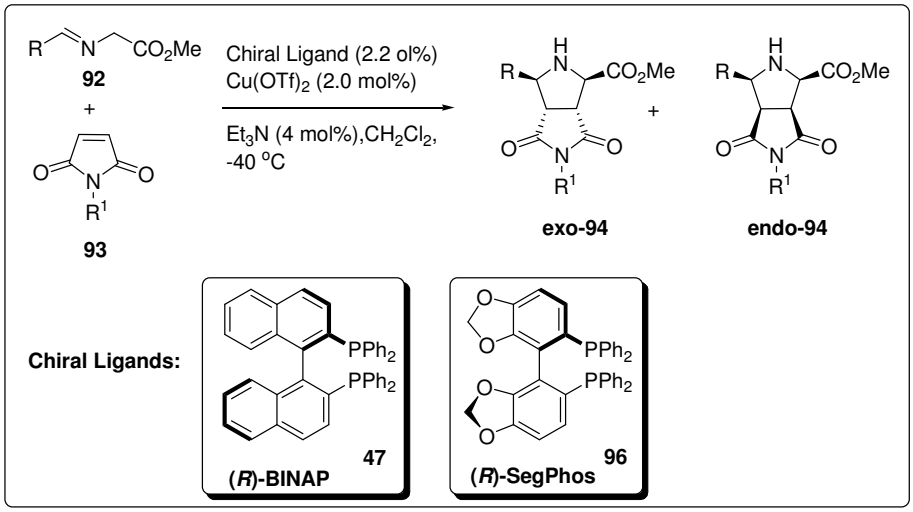


[a] in THF, [b] in DCM, [c] at room temperature, [d] reaction at -10 °C, reaction at -30 °C.

Figure 1.11 The results of the catalytic asymmetric 1,3-DC reactions of Cu(I) and (*R*)-Fesulphos (**85**) with different dipolarophiles.

Later, it has been demonstrated by Komatsu[26h] and co-workers that, compared to silver, copper forms a more stable complex with chiral bisphosphine ligands. They observed ***exo***-selectivity in their reactions, which were performed at –40 °C using chiral bisphosphine ligands and $Cu(OTf)_2$. The ratio of ***exo*-94/*endo*-94** up to 95/5 was obtained when N-phenylmaleimide was employed as dipolarophile. Among the chiral bisphosphine ligands used, (*R*)-BINAP (**47**) and (*R*)-SegPhos (**96**) gave the highest enantioselectivities obtained (Scheme 1.21).

When dimethyl fumarate or fumaronitrile were used ***endo*-94** instead of ***exo*-94** was obtained in higher proportion. This means that ***exo/endo*** selectivity depends on the dipolarophile used in the reaction (Figure 1.12).



Scheme 1.21 The Cu(II) and (*R*)-BINAP (**47**) or (*R*)-SegPhos (**96**) catalyzed asymmetric 1,3-DC reaction.

The results of the Cu(II) and (*R*)-BINAP (**47**) or (*R*)-SegPhos (**96**) catalyzed 1,3-DC reactions of various azomethine ylides with maleimides are summarized in Table 1.9.

Table 1.9 The results of the catalytic asymmetric 1,3-DC reaction of azomethine ylides with maleimide dipolarophiles when $Cu(OTf)_2$ and (*R*)-BINAP (**47**), or (*R*)-SegPhos (**96**) catalyst systems are used.

R	R^1	Ligand	yield (%)	*exo/endo*	ee (*exo* %)
Ph	Ph	(*R*)-BINAP	71	>96	64
Ph	Ph	(*R*)-SegPhos	78	85/15	72
p-$MeOC_6H_4$	Ph	(*R*)-BINAP	83	>96	87
p-$MeOC_6H_4$	Ph	(*R*)-SegPhos	0	-/-	-
p-$NO_2C_6H_4$	Ph	(*R*)-BINAP	77	>96	62
p-$NO_2C_6H_4$	Ph	(*R*)-SegPhos	32	>96	19
p-ClC_6H_4	Ph	(*R*)-BINAP	83	>96	65
p-ClC_6H_4	Ph	(*R*)-SegPhos	94	>96	75
Ph	Me	(*R*)-BINAP	64	72/28	55
Ph	Me	(*R*)-SegPhos	64	86/14	62

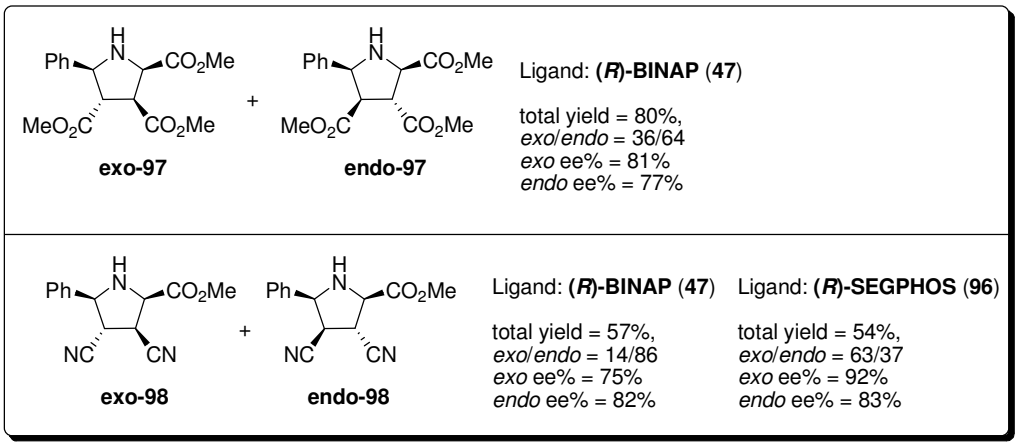
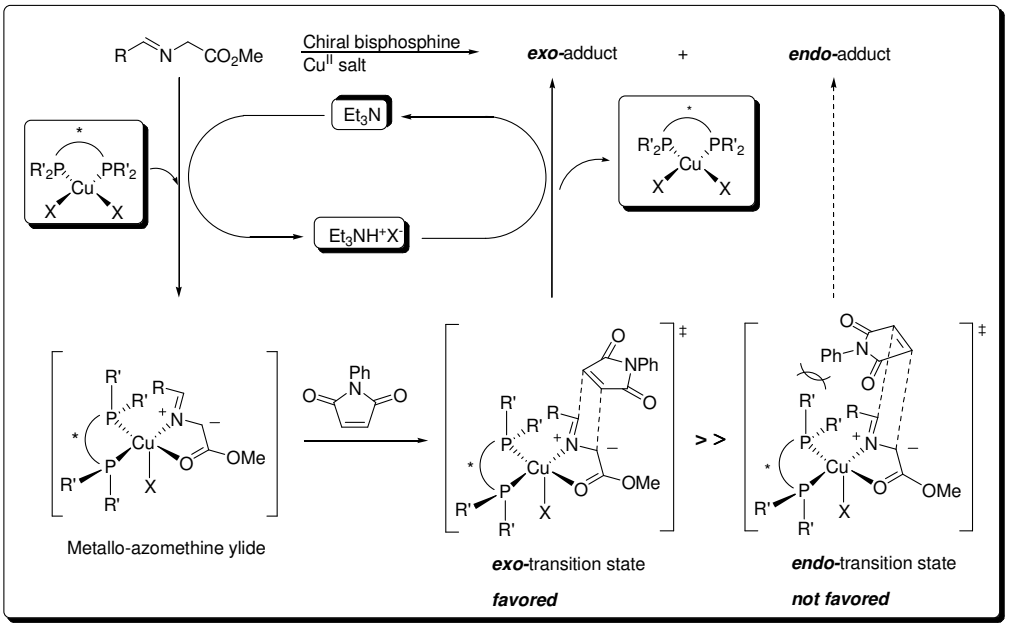


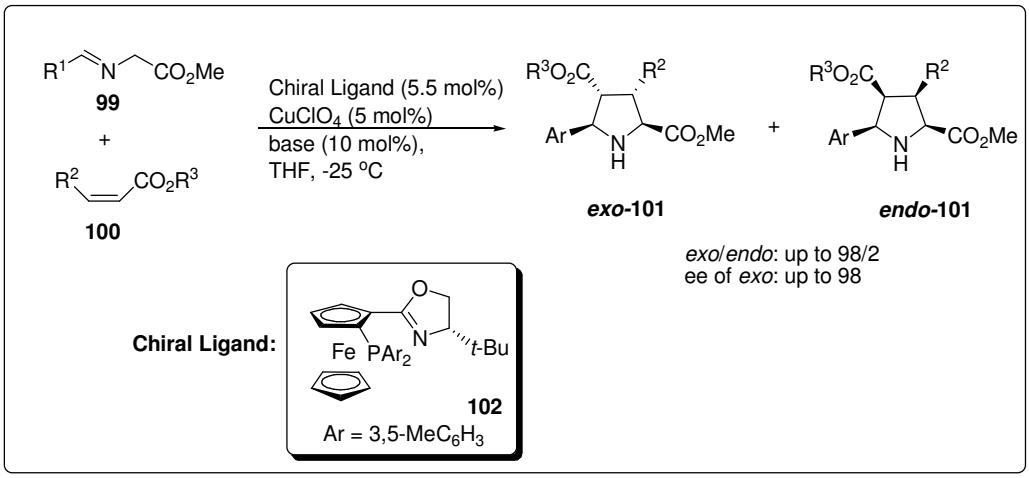
Figure 1.12 The results of the catalytic asymmetric 1,3-DC reactions of Cu(II) and (*R*)-BINAP (**47**), or (*R*)-SegPhos (**96**) with different dipolarophiles.



Scheme 1.22 Plausible mechanism of the 1,3-DC reaction of azomethine ylides catalyzed by chiral phosphine-Cu(II) complexes.

Komatsu and co-workers offered a plausible mechanism about the ***exo***-selectivity of the reaction (Scheme 1.22). In this mechanism, the azomethine ylide is formed in basic media and then it complexes with the chiral Lewis acid. Then in the transition state, it reacts with the dipolarophile (N-Phenylmaleimide) in ***exo-***approach rather than ***endo-*** one. As can be seen in ***endo-***transition state, it is clear that there is a bigger overlap between the Ph group of the dipolarophile and the bisphosphine ligand. However, in the ***exo-***transition state there is no such an overlap and this transition state is favored. This hypothesis about the mechanism of the reaction was also supported by ZINDO calculations.

Zhang[26i] and co-workers developed a new method including chiral phosphinooxazoline ligand (**102**) in combination with Cu(I) in the enantioselective 1,3-DC reaction of azomethine ylides with acrylates. Very high ***exo***-**101**/***endo***-**101** selectivities and enantioselectivities were obtained (Scheme 1.23).



Scheme 1.23 The Cu(I) and chiral phosphinooxazoline ligand (**102**) catalyzed asymmetric 1,3-DC reaction.

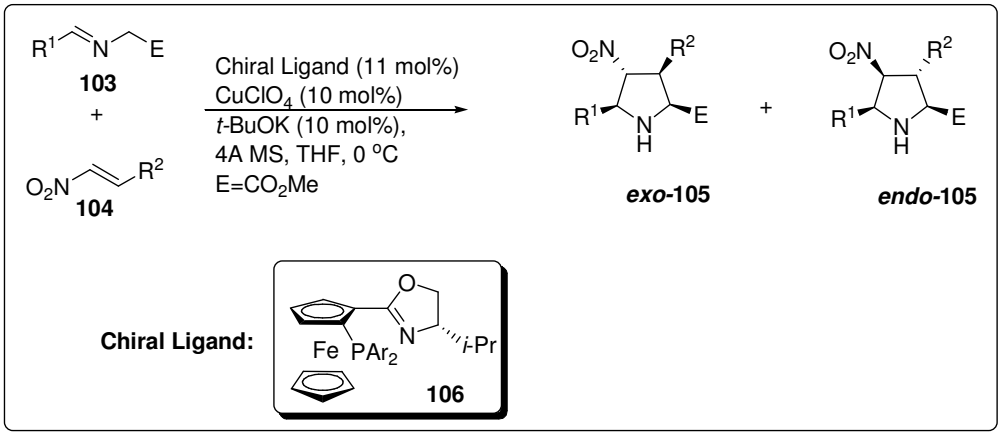
The results of the Cu(I) and chiral phosphinooxazoline ligand (**102**) catalyzed 1,3-DC reactions of various azomethine ylides with different dipolarophiles are summarized in Table 1.10.

Table 1.10 The results of the catalytic asymmetric 1,3-DC reaction of azomethine ylides with different dipolarophiles when Cu(I) and chiral phosphinooxazoline ligand (**102**) catalyst systems are used.

R^1	R^2, R^3	base	yield of *exo* (%)	*exo*/*endo*	ee of *exo* (%)
p-ClC_6H_4	H, ^{t}Bu	Et_3N	85	96/4	91
o-ClC_6H_4	H, ^{t}Bu	Et_3N	71[a]	76/24	98
m-ClC_6H_4	H, ^{t}Bu	Et_3N	80	96/4	91
p-FC_6H_4	H, ^{t}Bu	Et_3N	70	94/6	91
p-CNC_6H_4	H, ^{t}Bu	DBU	84	95/5	91
Ph	H, ^{t}Bu	DBU	65	95/5	84
p-MeC_6H_4	H, ^{t}Bu	DBU	61	97/3	89
p-$MeOC_6H_4$	H, ^{t}Bu	DBU	82	97/3	91
β-Naphthyl	H, ^{t}Bu	DBU	84	98/2	90
p-ClC_6H_4	H, Me	Et_3N	77[b]	83/17	91
p-ClC_6H_4	H, Et	Et_3N	79[c]	84/16	91
p-ClC_6H_4	CO_2Me, Me	Et_3N	87[d]	98/2	93

[a] 20% of ***endo***-cycloadduct (42% ee) was isolated, [b] 13% of ***endo***-cycloadduct (67% ee) was isolated, [c] 16% of ***endo***-cycloadduct (58% ee) was isolated, [d] reaction was carried out at 0 ^oC, 1mol% $CuClO_4$, and 1.1 mol% of chiral ligand was employed.

$CuClO_4$-P,N-ferrocene catalyst system was employed by Hou[26j] et al. in the reactions of nitroalkenes (**104**). Exclusively, the ***exo*-105** cycloadducts were obtained in high yield and high ee values ranging from 92 to 98% ee's (Scheme 1.24).



Scheme 1.24 The $CuClO_4$-P,N-ferrocene catalyzed asymmetric 1,3-DC reaction.

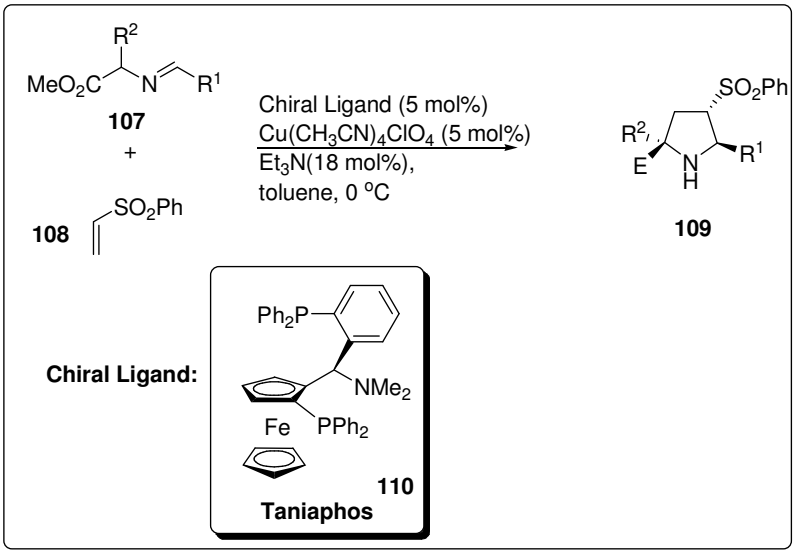
The results of the $CuClO_4$-P,N-ferrocene catalyzed 1,3-DC reactions of various azomethine ylides with different dipolarophiles are summarized in Table 1.11.

Table 1.11 The results of the catalytic asymmetric 1,3-DC reaction of azomethine ylides with different nitroalkenes (**104**) when $CuClO_4$-P,N-ferrocene catalyst systems are used.

R^1	R^2	Ar	yield (%)	*exo*/*endo*	ee (%)
Ph	Ph	Ph	87	only ***exo***	95
Ph	*p*-$NO_2C_6H_4$	Ph	70	only ***exo***	96
Ph	*p*-$MeOC_6H_4$	Ph	77	only ***exo***	96
Ph	*p*-MeC_6H_4	Ph	73	only ***exo***	96
Ph	*p*-ClC_6H_4	Ph	64	only ***exo***	92
Ph	*m*-ClC_6H_4	Ph	74	only ***exo***	95
Ph	*i*Pr	Ph	75	only ***exo***	98
p-$MeOC_6H_4$	Ph	Ph	96	89/11	97
m-ClC_6H_4	Ph	Ph	97	88/12	92
2-Naphthyl	Ph	Ph	92	92/8	92
p-BrC_6H_4	Ph	Ph	77	86/14	83(99)[b]
Ph	Ph	3,5-$(CF_3)_2$-C_6H_3	85	14/86	98
Ph	*p*-$MeOC_6H_4$	3,5-$(CF_3)_2$-C_6H_3	79	30/70	95
Ph	*m*-ClC_6H_4	3,5-$(CF_3)_2$-C_6H_3	82	11/89	92
Ph	*i*Pr	3,5-$(CF_3)_2$-C_6H_3	88[a]	6/94	97
p-$MeOC_6H_4$	Ph	3,5-$(CF_3)_2$-C_6H_3	79	18/82	96
m-ClC_6H_4	Ph	3,5-$(CF_3)_2$-C_6H_3	98	17/83	84
2-Naphthyl	Ph	3,5-$(CF_3)_2$-C_6H_3	98	19/81	97
p-BrC_6H_4	Ph	3,5-$(CF_3)_2$-C_6H_3	71	18/82	88(96)[b]

[a] yield of ***endo***-cycloadduct, [b] the ee value obtained after one recrystallization.

A generally applicable procedure for the catalytic asymmetric 1,3-DC reactions of azomethine ylides with arylvinyl sulfones (**108**) were developed by Carretero[26k] et al. in 2006. Very high ***exo***-selectivity and enantioselectivities up to 85% were obtained using $Cu(MeCN)_4ClO_4$/Taniaphos catalyst system (Scheme 1.25). The results of the experiments are summarized in Table 1.12.



Scheme 1.25 The $Cu(MeCN)_4ClO_4$/Taniaphos (**110**) catalyzed asymmetric 1,3-DC reaction.

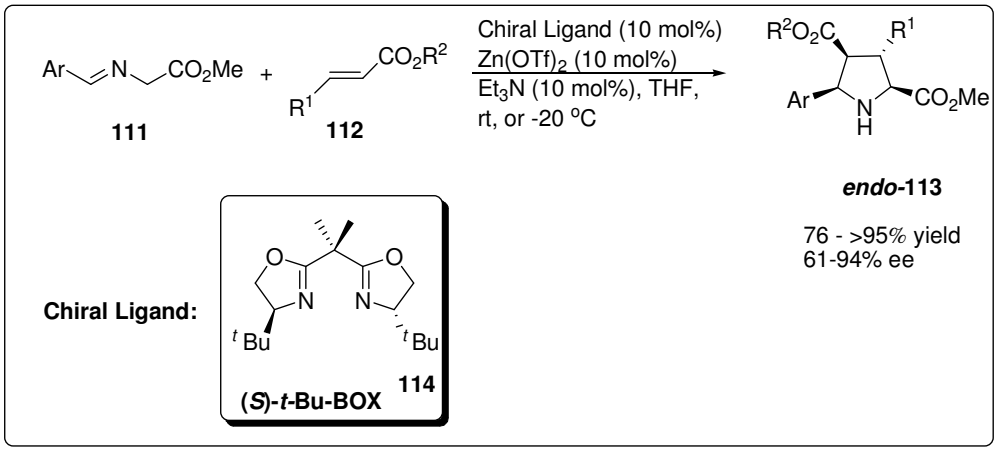
Table 1.12 The results of the catalytic asymmetric 1,3-DC reaction of azomethine ylides with arylvinyl sulfones (**108**) when $Cu(MeCN)_4ClO_4$/Taniaphos (**110**) catalyst system was used.

R^1	R^2	yield (%)	ee (%)
p-FC_6H_4	H	91	82
p-$MeOC_6H_4$	H	71	84
m-FC_6H_4	H	83	85[a]
m-$MeOC_6H_4$	H	71	85
m-Tolyl	H	74	79[a]
2-Naphthyl	H	71	65
o-Tolyl	H	92	41
c-Hex	H	50	69
Ph	Me	38[b]	80

[a] Determined by HPLC from its N-methyl derivative, [b] The other isomer was isolated in 4% yield.

1.1.1.7.1.5.4. Zn(II)-Based Protocol

Chiral bisoxazolines were used by Jorgensen[26l] and co-workers in the catalytic asymmetric 1,3-DC reactions of azomethine ylides in conjunction with Zn(II)-Lewis acids. The Lewis acid $Zn(OTf)_2$ was used with different electron deficient dipolarophiles in basic media and reaction was conducted at rt or -20 ^oC (Scheme 1.26). As a result of the study, it was seen that only ***endo*-113** was obtained in high yields and enantioselectivities (Table 1.13).



Scheme 1.26 The Zn(II)/(*S*)-^{t}Bu-BOX (**114**) catalyzed asymmetric 1,3-DC reaction.

Table 1.13 The catalytic asymmetric 1,3-DC reaction with a catalyst system comprising chiral bisoxazoline (*S*)-^{t}Bu-BOX (**114**) and $Zn(OTf)_2$.

Ar	R^1	R^2	yield (%)	ee (%)
Ph	H	Me	>95	78
Ph	H	Me	80[a]	88
2-Naphthyl	H	Me	93	78
2-Naphthyl	H	Me	84[a]	91
2-Naphthyl	H	Me	86[a,b]	87
2-Naphthyl	H	Et	76	68
2-Naphthyl	H	^{t}Bu	12	<5
p-BrC_6H_4	H	Me	89	61
p-BrC_6H_4	H	Me	89[a]	94
Ph	CO_2Me	Me	78[a]	76
2-Naphthyl	CO_2Me	Me	84	90
p-BrC_6H_4	CO_2Me	Me	87	68

[a] reaction at – 20 °C, [b] reaction in the absence of solvent.

Compared to the previous studies, the catalyst loading in this reaction was a little bit higher (10 mol%). Jorgensen and co-workers observed that, the amount of base used did not effect the reactions but the substituent on the dipolarophile did effect the results of the experiments. When *tert*-butylacrylate was used, the enantioselectivity obtained was < 5%.

To determine the absolute configuration, they got the X-ray structure analysis of N-tosylated cycloadduct. Based on this X-ray structure, they offered a transition state for the cycloaddition chemistry of their chiral complex. In this transition state, the azomethine ylide coordinates to the chiral Zn(II)-*t*Bu-BOX complex and forms an 18 electron complex with a tetrahedral arrangement of the ligand around the metal center (Figue 1.13).

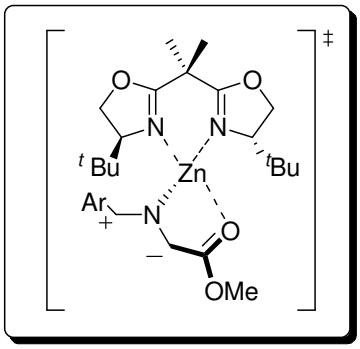


Figure 1.13 Proposed transition state for Zn(II)-^{t}Bu-BOX catalyzed cycloaddition.

As it was mentioned before, the catalytic asymmetric versions of 1,3-DC reaction of azomethine ylides is very important in terms of organic synthesis. While doing reactions, one has to control lots of parameters at the same time. In terms of coordination, the metal to chiral ligand coordination must be very strong compared to the dipole and metal center. When the reaction was completed, the cycloadduct must be able to get rid of the chiral catalyst very easily, to have a very effective

catalytic cycle. While the dipolarophile attacks to the dipole, the chiral catalyst must effectively block one face of the dipole very efficiently to have a high enantioselectivity. The substituents on the dipole, the dipolarophile, and the chiral ligand are also important to have a good enantioselectivity. Finally, the selection of solvent and the temperature must be adjusted carefully to have a good enantioselection.

The studies performed up to now showed us that, Ag(I), Cu(II), and Zn(II) metals were studied with N,P-ligands, P,P-ligands and N,N-ligands respectively in 1,3-DC reactions and gave the products in good yield and enantioselectivity. However there are some drawbacks with some of the existing methods:

a) longer reaction times and specific temperatures are required,

b) the yields and ee's are dependent on the structure of 1,3-dipole and the dipolarophile,

c) synthesis of the chiral ligands require longer steps and the ligands are not recoverable.

1.1.1.8. Aim of Our Study

The aim of this study is to develop a new chiral ligand and use this ligand with a metal as a chiral catalyst for:

* the catalytic enantioselective 1,3-dipolar cycloaddition reactions of azomethine ylides with dipolarophiles to synthesize chiral pyrrolidine derivatives.

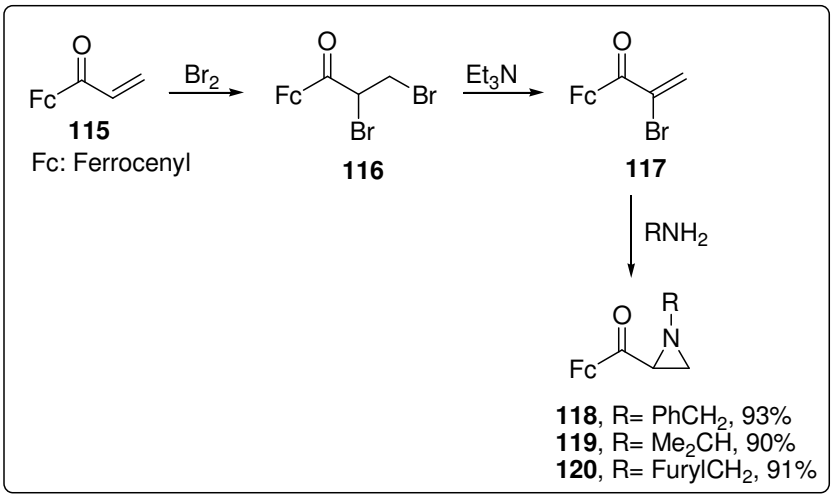
* the alkynylzinc addition reactions to aldehydes to synthesize chiral propargylic alcohols.

CHAPTER 1.2

RESULTS AND DISCUSSION

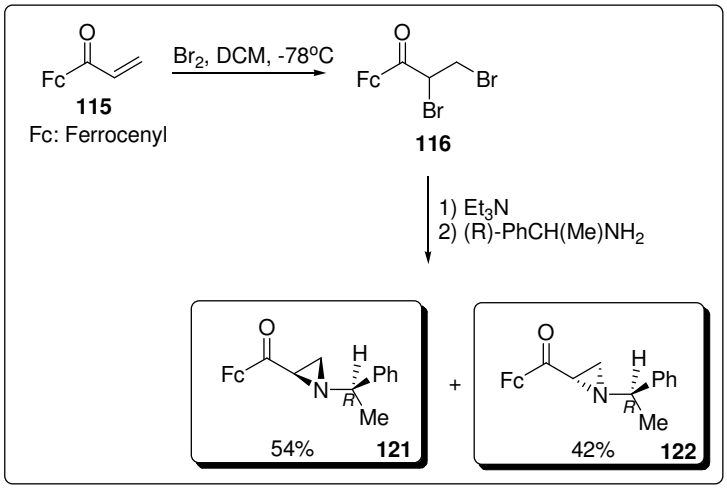
1.2.1. The Synthesis of Aziridinyl Ketones

Our group have previously synthesized racemic ferrocenyl aziridinyl ketones (**118**, **119** and **120**) starting from acryloyl ferrocene (**115**) and benzyl, isopropyl, and furylamines (Scheme 1.27).[41]



Scheme 1.27 Synthesis of ferrocenyl aziridinyl ketones.

In order to synthesize chiral derivatives of these compounds we have used chiral amine, (*R*)-1-phenylethylamine, which introduces asymmetry to the molecule. To synthesize chiral ketones **121** and **122**, acryloyl ferrocene (**115**) was brominated first to give the dibromo-compound **116** in more than 95% isolated yield. In the second step, this compound was treated first with Et_3N to obtain monobromo-compound **117** and then (*R*)-1-phenylethylamine was added to the same reaction flask. After stirring the reaction mixture overnight at room temperature, the ketones **121** and **122** were obtained in 54% and 42% yields respectively (Scheme 1.28). This reaction is known as Gabriel-Cromwell aziridination.[42] These ketones can be separated easily by flash column chromatography on silica gel. Ferrocene group on these ligands impart a red color to these compounds for this reason, the purification can be monitored visually (Figure 1.14).



Scheme 1.28 Synthesis of aziridinyl ketones (**121**) and (**122**).

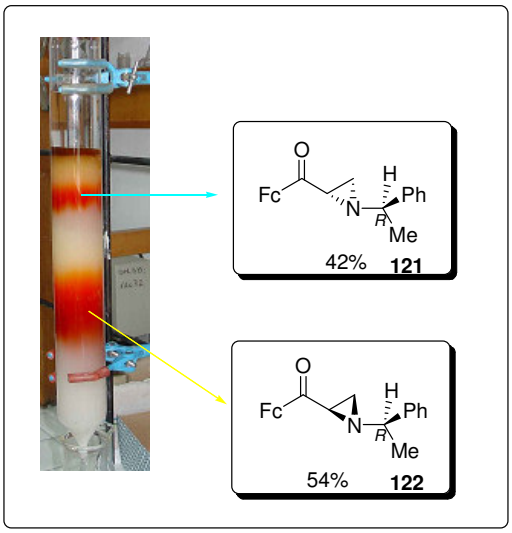
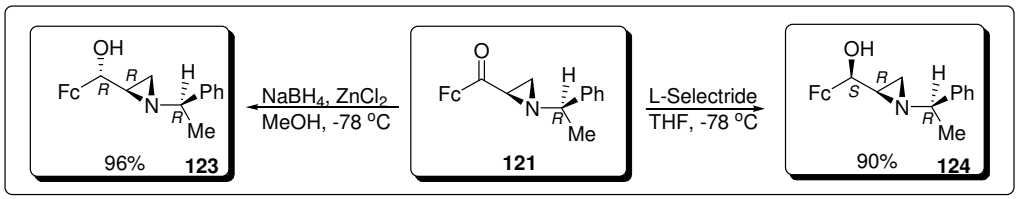


Figure 1.14 The flash column chromatography separation of (**121**) and (**122**).

1.2.2. The Synthesis of Chiral FAM Ligands

To finish the synthesis of chiral FAM ligands, ketone group was reduced to alcohol using the procedure reported by Korean group.[43] Stereocontrolled reduction of the aziridinyl ketone **121** with $NaBH_4$+$ZnCl_2$ (chelation control) gave aziridinyl alcohol **123** in 96% yield as a single diastereomer which is a stable and yellow crystalline solid (mp 83-85 ^oC) (Scheme 1.29). The configuration of this compound was confirmed by X-ray crystallography (Figure 1.15).



Scheme 1.29 The synthesis of chiral ligands (**123**) and (**124**) from aziridinyl ketone (**121**) under different reduction conditions.

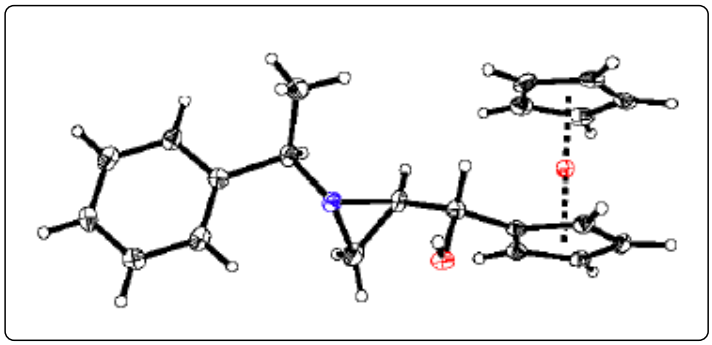
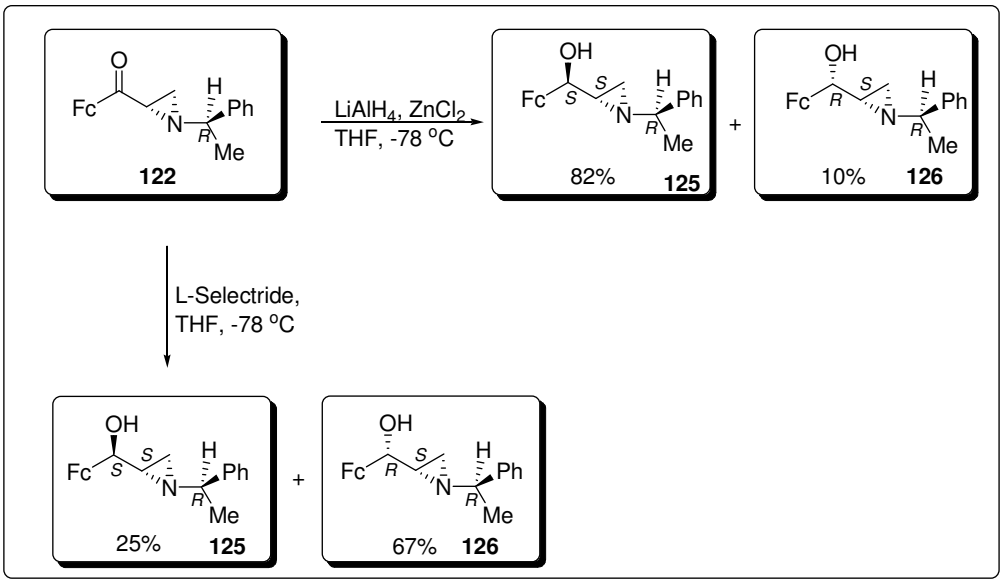


Figure 1.15 ORTEP diagram from the X-ray crystallographic analysis of ligand (**123**).

The chiral ligand **124**, which is the (*S*)-configured diastereomer of **123** at the alcohol carbon center, was synthesized in 90% yield again as a single diastereomer by using L-Selectride at -78 ^{o}C. This ligand is also yellow colored crystalline compound (Scheme 1.29).

The stereocontrolled reduction of the ferrocenyl aziridinyl ketone **122** was also tried with $NaBH_4$+$ZnCl_2$ (chelation control) under the same reaction conditions. In this case, the reduction of the carbonyl group was not successful compared to the reduction of ketone **121**. Reduction reaction was very slow and mostly the starting material was regained at the end of the reaction. Although the amount of the $NaBH_4$ in the reaction medium was increased, we did not observe any change. Therefore, the reduction procedure was changed and more powerful reducing agent $LiAlH_4$ was used instead of $NaBH_4$ under the same reaction conditions. The reduction of the ketone became successful and two diastereomeric products, **125** and **126** were obtained in 82% and 10% yield respectively (dr~8:1) (Scheme 1.30). They are both yellow in color and oily. Again, their separation on flash column chromatography was easy and could be monitored visually. Although both of the diastereomers were very pure, their crystallization could not be possible.



Scheme 1.30 The reduction of aziridinyl ketone (**122**) under different reduction conditions to synthesize either (**125**) or (**126**) as a major product.

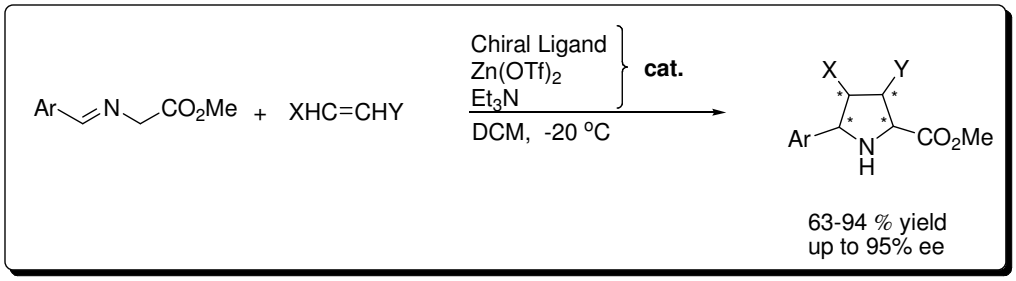
When reduction of the same ketone was done using L-Selectride, the diastereomeric alcohols **125** and **126** were obtained as a yellow oil in 25% and 67% yields respectively (dr~1:2.7).

Although the reduction of ketone **122** by $LiAlH_4$-$ZnCl_2$ or L-Selectride was not as selective as that of ketone **121**, we did not worry about the selectivity and tried to optimize the conditions to improve the selectivity. Because these diasteromeric alcohols can be separated easily by simple flash column chromatography on silica gel and had to be synthesized anyway.

1.2.3. The Asymmetric Synthesis of Pyrrolidine Derivatives by Using Chiral FAM Ligands

After the synthesis of all of the four stereoisomers of Ferrocenyl AzirinylMethanol (FAM) chiral ligands **123**, **124**, **125**, and **126**, they were ready to be tested in the

catalytic enantioselective synthesis of organic compouds. Since our group has experience in the synthesis of pyrrolidine derivatives by 1,3-DC reactions of azomethine ylides, we first tried all of the newly synthesized FAM-chiral ligands in catalytic asymmetric versions of this reaction (Scheme 1.31).



Scheme 1.31 General reaction scheme of 1,3-DC reactions of azomethine ylides with dipolarophiles.

At the beginning of this study, the catalytic asymmetric 1,3-DC reactions were performed as in Jorgensen's[261] original reaction procedure using THF as the solvent at -20 °C. However, as the reaction proceeded, due to the lower solubility of the product in THF, the reaction medium became cloudy. Although the reactions were resulted with very high yields (~90%), the enantioselectivities were low and not reproducable due to the inhomogeneity of the reaction. To have a homogeneous reaction medium, the solvent was changed to DCM (dichloromethane) and the reaction was performed at the same temperature.

With the modified reaction conditions the catalytic performance of the newly synthesized chiral ligands **123**, **124**, **125** and **126** were tested using $Zn(OTf)_2$ as the Lewis acid. The results of these experiments are summarized in Table 1.14.

Table 1.14 The results of catalytic asymmetric 1,3-DC reactions of azomethine ylides with dipolarophiles using chiral ligands (**123**), (**124**), (**125**), and (**126**).

Entry	chiral ligand[a]	aldimine	dipolarophile	yield (%)	ee (%)	cycloadduct
1	**123**	Ph, N, CO_2Me	MeO_2C, CO_2Me	**88**	**90**	**127**
2	**124**	”	”	60	18	**127**
3	**125**	”	”	80	48	**ent-127**
4	**126**	”	”	70	22	**127**
5	**123**	”	O, N, O, Me	**92**	**70**	**128**
6	**124**	”	”	81	12	**128**
7	**125**	”	”	84	46	**ent-128**
8	**126**	”	”	**93**	**76**	**ent-128**
9	**124**	”	MeO_2C	54	34	**ent-129**
10	**125**	”	$^tBuO_2C$	80	44	**ent-130**

[a] 10 mol% catalyst was used in all of the reactions.

As seen from Table 1.14, when dimethyl maleate was reacted in the presence of catalytic amount of chiral ligand **123**, the expected cycloadduct **127** was obtained in very high yield and enantioselectivity (entry 1). However, when the other ligands **124**, **125**, or **126** were used under the same reaction conditions with dimethyl maleate, the corresponding cycloadduct was obtained in reasonable yield but low enantioselectivity (entries 2-4). When the dipolarophile was changed to N-methylmaleimide, good results in terms of both yield and ee were obtained only with ligands **123** and **126** (entries 5 and 8). The other ligands **124** and **125** gave the products in good yields but low ee's (entries 6 and 7). Interestingly, the chiral ligands **123** and **124** with (*R*)-configuration at the aziridine center gave one enantiomer of the cycloadduct (entries 5 and 6) while the ligands **125** and **126** with (*S*)-configuration at the aziridine center gave the other enantiomer of the cycloadduct (entries 7 and 8). These results show that the stereochemistry of the

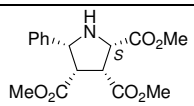
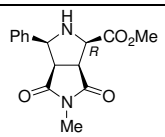
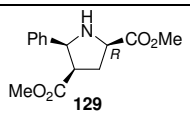
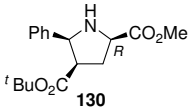
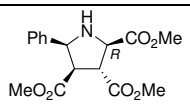
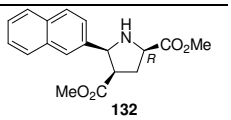
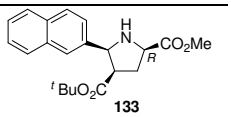
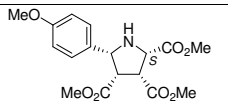
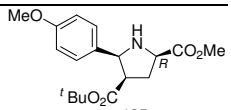
aziridine carbon is very effective in determining the enantioselectivity of the asymmetric 1,3-DC reactions.

We have also tested the catalytic performances of chiral ligands **124** and **125** with unsymmetrical dipolarophiles (entries 9 and 10) but again the cycloadducts were obtained in reasonable yields but low ee's.

Based on the results summarized in Table 1.14, chiral ligand **123** is the best choice for the catalytic asymmetric 1,3-DC reactions of azomethine ylides.

In order to show the applicability of the new catalyst system [chiral ligand **123-**Zn(II)] in asymmetric 1,3-DC reactions, various azomethine ylides and dipolarophiles were screened. The results of these studies were summarized in (Table 1.15). Three well known aldimines $ArCH{=}NCH_2CO_2Me$ (Ar= phenyl, 2-naphthyl, and 4-methoxyphenyl)[44] were used as the precursor of azomethine ylides with electron deficient dipolarophiles (dimethyl maleate, dimethyl fumarate, methyl acrylate, *tert*-butyl acrylate and N-methylmaleimide) in DCM at -20 ^{o}C with 10 mol % of ligand **123**. Enantioselectivities of the products were determined by chiral HPLC. In each of these reactions, single cycloaddition product was observed.

Table 1.15 The results of the three known aldimines with electron deficient dipolarophiles using catalytic amount of chiral ligand (**123**) and $Zn(OTf)_2$ under optimized reaction conditions.

Entry	aldimine	dipolarophile	catalyst loading (mol%)	yield (%)	ee (%)	product
1a	Ar=N–CO_2Me (Ar= Ph)	dimethyl maleate	10.0	88	90	 **127**
1b	”	dimethyl maleate	5.0	88	82	
2	”	N-methylmaleimide	10.0	92	70	 **128**
3	”	methyl acrylate	10.0	83	46	 **129**
4a	”	*tert*-butyl acrylate	10.0	93	88	 **130**
4b	”	*tert*-butyl acrylate	5.0	94	88	
5	”	dimethyl fumarate	10.0	85	68	 **131**
6a	Ar=N–CO_2Me (Ar= 2-Naphthyl)	methyl acrylate	10.0	92	37	 **132**
6b	”	methyl acrylate	5.0	85	36	
7a	”	*tert*-butyl acrylate	10.0	85	78	 **133**
7b	”	*tert*-butyl acrylate	5.0	63	76	
8a	Ar=N–CO_2Me (Ar= *p*-$MeOC_6H_4$)	dimethyl maleate	10.0	70	95	 **134**
8b	”	dimethyl maleate	5.0	67	90	
9a	”	*tert*-butyl acrylate	10.0	79	84	 **135**
9b	”	*tert*-butyl acrylate	5.0	63	80	

1.2.4. Effect of Catalyst Loading

When the reaction conditions were tested in terms of catalyst loading, it was seen that, similar yields and enantioselectivities were obtained with 10.0 and 5.0 mol% of the catalyst (Table 1.15). Using 10 mol% of chiral ligand **123** the enantioselectivities were ranged from 90-95% with dimethyl maleate (entries 1a-8a) and from 78% to 88% with *tert*-butyl acrylate (entries 4a, 7a and 9a), and 68% for dimethyl fumarate, and 70% for *N*-methylmaleimide (entries 2 and 5).

Although similar yields and enantioselectivities were obtained by using 5 mol% ligand, the reaction was slower as compared to the reaction carried out with 10 mol% ligand.

When the relative stereochemistry of the cycloadducts were considered, all of the reactions proceeded over ***endo-*** approach of the dipolarophile to the corresponding (*E*,*E*)-configured N-metalated azomethine ylide. The regioselective 2,4,5-trisustituted pyrrolidine derivatives were obtained when acrylate dipolarophiles were reacted with azomethine ylides (Figure 1.16). Except for the reactions with methyl acrylate, high enantioselectivities were obtained with all the remaining dipolarophiles. Preferentially, all the Zn(II)-catalyzed 1,3-DC reactions of azomethine ylides with chiral ligand **123** resulted (2*R*)-configured pyrrolidines except for dimethyl maleate. Absolute configurations of all the products obtained from the asymmetric 1,3-DC reactions were derived from comparison of their optical rotations and chiral HPLC data with the values reported in the literature (see experimental part).

The absolute configuration of the cycloadduct **127**, obtained from the reaction of dimethyl maleate with phenyl substituted azomethine ylide was confirmed by chemical correlation with a compound that has been characterized previously by X-

ray crystallography.[45] Literature assignments for all cycloadducts except **128** were based on analogy with structurally related compounds that had been characterized by X-ray crystallography.

The experimentally observed *re*-facial selectivity with acrylate, fumarate, and maleimide dipolarophiles can be explained by the pre-transition state (TS) shown in Figure 1.16.

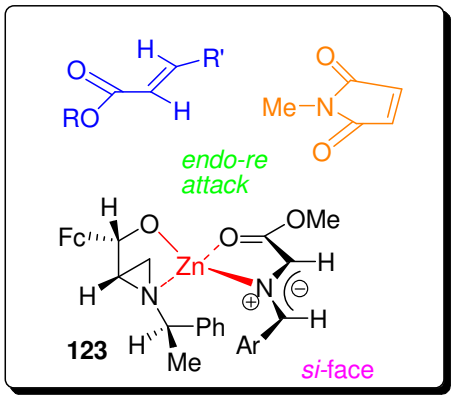


Figure 1.16 The proposed ***endo***-*re* pre-transition state leading to cycloadducts (**128-133**) and (**135**).

According to this working model, the Zn(II) atom is four coordinate and the stereocenter at C2 of the aziridine determines the chirality of the complex. The (*E*,*E*)-dipole is oriented such that the phenyl group is positioned on the convex face of the bicyclic ring system formed by the Zn(II)-chelation to aziridino alcohol (**123**). In such a complex, the N-substituent of ligand **123** effectively blocks the bottom *si*-face of the ylide and dipolarophile can not approach from this face. Therefore, the dipolarophile can approach only from the *re*-face of the ylide. Although the ***endo***-selectivity can be ascribed to a stereoelectronic effect, a five coordinate Zn(II) complex with the ester dipolarophiles acting as ligands is also possible.[26l] Such an

ensemble may be preferred over *si*-favoring alternatives with a bulky *tert*-butyl ester. At present, we do not have an adequate explanation for the ***endo***-*si* selectivity that is observed with dimethyl maleate.

CHAPTER 1.3

CONCLUSION

As a result, we developed a new catalyst system [FAM **123**-Zn(II)] that can be used as a catalyst for catalytic asymmetric 1,3-DC reactions of azomethine ylides with four different aldimines and dipolarophiles to synthesize pyrrolidine derivatives. The yields of the products varied between 63-94% and the enantioselectivities varied between 36-95%. These results are compared well with the results reported by Jorgensen's group which is the only group using Zn as the metal source. In the similar studies in literature, the ligands used are the phosphorous derivatives that work well with the Ag and Cu metals but not with Zn. Although phosphorous based ligands gave the best results in terms of yield and selectivity, their synthesis was not so easy, and required multistep synthesis. In addition, they are very sensitive to oxygen, therefore the reactions has to be carried out at oxygen free conditions. Also, for most cases, the recovery and recycle are not possible.

Compared to the phosphorous based ligands in literature, the advantages of our ligand (**123**) is the ease of synthesis. It can be synthesized in three easy steps starting from acryloyl ferrocene on a gram scale. It is a stable solid. Additionally, ferrocene unit on the structure imparts a yellow color to the ligand and makes the purification easier. Furthermore, the ligands synthesized in this thesis are open to further development and use in other catalytic enantioselective synthesis of organic compounds (see the next part of this thesis). The enantiomers of these ligands can easily be synthesized starting from (*S*)-(-)-1-phenylethylamine. This is very important for the catalytic asymmetric synthesis which warrants the synthesis of the chiral compounds with desired stereochemistry.

CHAPTER 1.4

EXPERIMENTAL

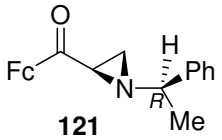
1.4.1. General Consideration

Reactions were performed in flame-dried glassware under an atmosphere of argon. Dichloromethane (DCM) was dried and distilled over calcium hydride prior to use. Commercial $Zn(OTf)_2$ was benzene-azeotroped, placed under vacuum for about 1 h and stored under Ar in a desiccator. Chiral FAM (Ferrocenyl substituted Aziridinyl Methanol) ligands **123**, **124**, **125**, and **126** were benzene-azeotroped and dissolved in dry DCM before transferring into the reaction flask. Liquid dipolarophiles were distilled and kept under Ar prior to use. Stock solutions of the solid N-methyl maleimide and solid dimethyl fumarate in dry DCM were transferred *via* syringe. Et_3N was distilled and kept over NaOH pellets under Ar. Products were purified by flash column chromatography on silica gel 60 (Merck, 230–400 mesh ASTM). TLC analyses were performed on 250 μm Silica Gel 60 F254 plates and visualized by quenching of the UV fluorescence at 254 nm. All melting points were taken in open-end capillary tubes and are uncorrected. IR spectra are reported in reciprocal centimeters (cm^{-1}). Unless indicated otherwise, ^{1}H-NMR and ^{13}C-NMR samples were prepared in 1:1 $CDCl_3$-CCl_4 and recorded at 400 MHz and 100 MHz, respectively. ^{1}H-NMR data are reported as chemical shifts (δ, ppm) relative to tetramethylsilane (δ 0.00), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad singlet), coupling constant (Hz) and integration. Proton decoupled ^{13}C-NMR data are reported as chemical shifts. High resolution

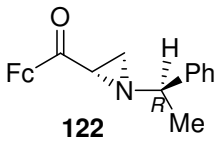
MS data were obtained using electron impact (EI) ionization. Enantiomeric excess (ee) was determined by chiral HPLC analysis using a chiral stationary phase (Daicel Chiralcel OD or Chiralpak AS), eluting with *i*-PrOH-hexanes, and using UV detection at 210 nm or 230 nm.

1.4.2. Characterization Data

1.4.3. The Synthesis of Aziridino Ketones (121) and (122):



121



122

Br_2 (4.57 mmol in 9.0 mL DCM) was added to a stirred solution of **115** (1.00 g, 4.17 mmol) in DCM at –78 °C over 5 min, at which point the reaction was judged to be complete by TLC. The crude mixture was filtered through a short plug of silica gel using $CHCl_3$ as the eluent. Evaporation of the solvent gave pure 1,2-dibromopronionylferrocene **116** (1.63 g, 98% yield). To a stirred solution of this material (1.0 g, 2.5 mmol) in $CHCl_3$ (0.1 M) was added Et_3N (0.592 mL, 4.25 mmol). After 4-5 h at rt, TLC analysis signified complete conversion to α-bromoacryloylferrocene **117**. To this solution was added (*R*)-(+)-1-phenylethylamine (0.574 mL, 4.45 mmol) and the mixture was stirred at rt overnight. The solvent was removed by rotary evaporation and the crude reaction mixture was flash chromatographed on silica gel (3:1 hexanes-EtOAc) to afford aziridine **121** (54% yield) and **122** (42%).

1.4.3.1. Aziridino Ketone (121):

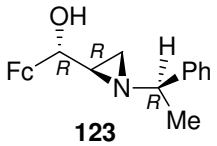
R_f = 0.17, 3:1 hexanes-EtOAc; mp 123-125 °C; $[\alpha]_D^{25}$ = 74.9 (*c* 0.5, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.4 Hz, 2H, Ph), 7.34 (t, *J* = 7.4 Hz, 2H, Ph), 7.26 (t, *J* = 7.2 Hz, 1H, Ph), 5.03 (br, 1H, ferrocene), 4.94 (br, 1H, ferrocene), 4.52 (br, 2H, ferrocene), 4.23 (s, 5H, ferrocene), 2.62 (q, *J* = 6.5 Hz, 1H), 2.57 (dd, *J* = 6.5 & 3.0 Hz,1H), 2.26 (br, 1H), 1.66 (d, *J* = 6.5 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.8, 143.8, 128.4, 127.3, 126.9, 78.07, 72.32, 72.21, 70.36, 69.88, 69.82, 43.50, 35.64, 23.72; IR (neat) 2939, 1660, 1450, 1251, 818, 796, 701. HRMS (EI) for $C_{21}H_{21}FeNO$ calculated 359.0973, found 359.0971.

1.4.3.2. Aziridino Ketone (122):

R_f = 0.1, 3:1 hexanes-EtOAc; mp: 114-116 °C ; $[\alpha]_D^{25}$ = 185.9 (*c* 0.4, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 2H, Ph), 7.25 (t, *J* = 7.6 Hz, 2H, Ph), 7.14 (t, *J* = 7.3 Hz, 1H, Ph), 4.59 (br, 2H, ferrocene), 4.32 (br, 2H, ferrocene), 3.81 (s, 5H, ferrocene), 2.51 (q, *J* = 6.5 Hz, 1H), 2.44 (dd, *J* = 6.5 & 3.1 Hz, 1H), 2.33 (dd, *J* = 2.6 & 1.5 Hz, 1H), 1.74 (dd, *J* = 6.5 & 1.3 Hz, 1H), 1.45 (d, *J* = 6.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 199.1, 144.3, 137.3, 128.7, 127.6, 126.9, 78.60, 72.28, 72.11, 71.12, 69.72, 69.49, 69.37, 41.51, 37.07, 23.58; IR(neat) 2969, 1660, 1455, 1251, 823, 755, 696. HRMS (EI) for $C_{21}H_{21}FeNO$ calculated 359.0973, found 359.0971.

1.4.4. The Synthesis of Chiral Ligand FAM-(123):

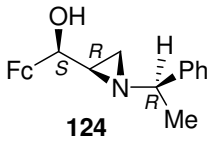


123

Aziridino ketone **121** (1.34 g, 3.73 mmol) was dissolved in MeOH (0.1 M) and cooled to -78 °C. To this stirred solution $ZnCl_2$ (762 mg, 5.59 mmol) was added. After 1 h, $NaBH_4$ (282 mg, 7.46 mmol) was added and stirring continued at -78 °C for 2 hours when TLC analysis showed the reaction to be complete. The reaction mixture was partitioned between DCM (2 x 25 mL) and water (25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give crude **123**. Purification by flash column chromatography on silica gel eluting with 4:1 hexane-EtOAc gave pure **123** (1.29g) in 96% yield. R_f = 0.5, 2:1 hexanes-EtOAC; mp: 83-85 °C; $[\alpha]_D^{25}$ = 77.4 (*c* 1.3, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H, Ph), 4.47 (d, *J* = 3.8

Hz, 1H), 4.26 (br, 1H, ferrocene), 4.23 (br, 1H, ferrocene), 4.17 (s, 5H, ferrocene), 4.13 (br, 2H, ferrocene), 2.61 (br, 1H, OH), 2.57 (q, J = 6.5 Hz, 1H), 1.83-1.80 (m, 1H), 1.80 (d, J = 2.8 Hz, 1H), 1.31 (d, J = 6.6 Hz, 3H), 1.29 (d, J = 7.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.2, 128.2, 126.9, 126.5, 89.7, 68.8, 68.4, 68.2, 67.8, 67.6, 67.0, 65.7, 43.8, 30.0, 23.5; IR (neat) 3431, 3100, 2969, 1494, 1445, 1221, 1100, 812, 759, 691, 481; HRMS (EI) for $C_{21}H_{23}FeNO$ calculated 361.1129, found 361.1123.

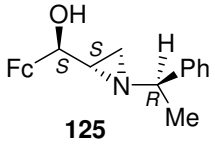
1.4.5. The Synthesis of (*S*,*R*,*R*) FAM-(124):



124

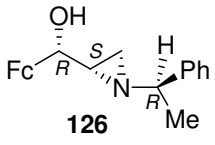
Ketone **121** (1.00 g, 2.78 mmol) was dissolved in THF (16 mL, distilled over Na-benzophenone) in a reaction flask. The flask was cooled to -78 ^{o}C and L-Selectride (4 mL, from 1M THF solution) was added slowly over 30 min. After stirring about 1h, TLC showed no starting material. To the reaction flask was added 10% NaOH solution (15 mL) followed by EtOAc (20 mL) and the two layers were separated. The aqueous layer was extracted one more time with EtOAc (25 mL). The combined organic layers were dried over $MgSO_4$ concentrated and purified by flash chromatography on silica gel using 3:1 hexane/EtOAc. Ligand **124** was obtained in 90% yield as yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 3H, Ph), 7.24-7.19 (m, 2H, Ph), 4.30 (br, 1H), 4.18 (s, 5H, ferrocene), 4.13-4.10 (m, 4H, ferrocene), 2.70 (br, 1H, OH), 2.49 (q, J = 6.5 Hz, 1H), 1.79-1.76 (m, 1H), 1.72 (d, J = 3.4 Hz, 1H), 1.37 (d, J = 6.6 Hz, 3H) 1.34 (d, J = 6.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.4, 128.3, 127.0, 126.7, 90.9, 70.2, 69.2, 68.6, 67.8, 67.7, 66.3, 65.8, 45.5, 31.5, 23.8. HRMS (EI) for $C_{21}H_{23}FeNO$ calculated 361.1129, found 361.1123.

1.4.6. The Synthesis of (*S*,*S*,*R*) FAM-(125):



Ketone **122** (1.34 g, 3.73 mmol) was dissolved in THF (37 mL) in a reaction flask (100 mL). Reaction flask was then cooled to -78 ^{o}C and $ZnCl_2$ (762 mg, 5.59 mmol) was added and the reaction mixture was stirred for 1 h at this temperature. Then $LiAlH_4$ (282 mg, 7.46 mmol) was added and stirring continued for about 2 h at which point TLC showed that no starting material was left. The contents of the reaction flask was hydrolyzed with distilled water and then extracted with DCM (25 mL). The aqueous layer was extracted one more time with DCM (25 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatograhy on silica gel using 4:1 hexane/EtOAc. Alcohol **125** was obtained as a light yellow oil in 82% yield along with 10% of the *R*,*S*,*R*- diastereomer **126**. Chiral ligand **125**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.27 (m, 3H, Ph), 7.25-7.21 (m, 2H, Ph), 4.30 (d, *J* = 3.4 Hz, 1H), 4.07 (s, 5H, ferrocene), 4.05-4.04 (m, 2H, ferrocene), 4.03-4.02 (m, 2H, ferrocene), 2.64 (br, 1H, OH), 2.59 (q, *J* = 6.5 Hz, 1H), 2.02 (d, *J* = 3.4 Hz, 1H), 1.77-1.73 (m, 1H), 1.42 (d, *J* = 6.7 Hz, 1H), 1.40 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 145.0, 129.2, 127.9, 127.3, 90.0, 70.1, 69.1, 68.5, 68.3, 67.5, 67.4, 67.0, 43.1, 30.6, 23.0. HRMS (EI) for $C_{21}H_{23}FeNO$ calculated 361.1129, found 361.1127.

1.4.7. The Synthesis of (*R*,*S*,*R*) FAM-(126):



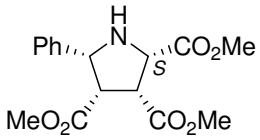
Ketone **122** (1.00 g, 2.78 mmol) was dissolved in dry THF (0.17 M) under Ar and cooled to -78 ^{o}C. L-Selectride (4 mL, 1 M in THF) was added slowly over 30 min. After stirring about 1h, TLC analysis indicated presence of no starting material. The reaction was partitioned between 10% NaOH solution (15 mL) was and EtOAc (2 x 25 mL). The

combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel (3:1 hexanes-EtOAc). Ligand **126** was obtained as a yellow oil in 67% yield along with 25% of the *S*,*S*,*R*-diastereomer **125**. Chiral ligand **126**: R_f = 0.29, 2:1 hexanes-EtOAc; $[\alpha]_D^{25}$ = 8.67 (*c* 1.30, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H, Ph), 4.05 (s, 5H, ferrocene), 4.03 (br, 1H, ferrocene), 3.97 (br, 1H, ferrocene), 3.94 (br, 2H, ferrocene) 3.76 (br, 1H), 2.50 (q, *J* = 6.5 Hz, 1H), 1.98 (d, *J* = 4.0 Hz, 1H), 1.90 (d, *J* = 3.4 Hz, 1H), 1.77-1.73 (m, 1H), 1.5 (d, *J* = 6.5 Hz, 1H) 1.44 (d, *J* = 6.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.4, 128.7, 127.6, 127.0, 90.0, 70.5, 69.8, 68.5, 67.6, 66.3, 66.1, 43.9, 32.0, 29.8, 22.8. IR (neat) 3412, 3086, 2960, 1489, 1455, 1378, 1280, 1105, 817, 754, 696, 482; HRMS (EI) for $C_{21}H_{23}FeNO$ calculated 361.1129, found 361.1135.

1.4.8. General Procedure for Catalytic Asymmetric Cycloaddition:

Dry $Zn(OTf)_2$ (10 or 5 mol%) was weighed in a glove bag into a pre-dried reaction flask under Ar. (Commercial $Zn(OTf)_2$ was dried by azeotroping with benzene under Ar and then removing the residual solvent under vacuum). The reaction flask was then connected to a vacuum line and heated with a heat gun for 10-15 min. Benzene-azeotroped chiral ligand (11.5 or 5.8 mol%) dissolved in freshly distilled DCM (1.8 mL per mmole of imine) was added to the reaction flask at rt. The homogeneous mixture was stirred at this temperature for about 1 h and then cooled to -20 ^oC. To this mixture was added sequentially, the imine (1 equiv), dry Et_3N (10 mol%) and the dipolarophile (1.1 equiv). The resulting mixture was stirred ~ 6h for the higher and ~14h for the lower catalyst loadings at -20 ^oC under Ar atmosphere, at which point the solvent was removed under reduced pressure and the crude product was isolated by flash column chromatography on silica gel. The reaction can be performed on up to 500 mg of imine.

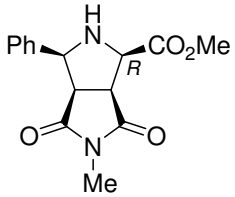
1.4.8.1. (2*S*,3*R*,4*S*,5*R*) 2,3,4-Tricarbomethoxy-5-phenylpyrrolidine (127).



127

90% ee as determined by HPLC, Chiralpak AS column, 7:3 hexanes-*i*-PrOH, t_R(major) = 6.9 min, t_R(minor) = 15.7 min; $[\alpha]_D^{25}$ = 61.9 (*c* 1.44, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.24 (m, 4H, Ph), 7.20-7.17 (m, 1H, Ph), 4.38 (d, *J*= 6.7 Hz, 1H, H-5), 4.05 (d, *J*= 8.9 Hz, 1H, H-2), 3.74 (s, 3H, 2- CO_2Me), 3.62 (s, 3H, 3- CO_2Me), 3.61 (t, *J*= 8.4 Hz, 1H, H-3), 3.46 (t, *J*= 7.4 Hz, 1H, H-4), 3.28 (br, 1H, N-H), 3.16 (s, 3H, 4-CO_2Me); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170,8 170.6, 170.5, 137.2, 128.3, 127.6, 126.7, 65.47, 62.18, 52.49, 52.24, 51.92, 51.16, 51.04.

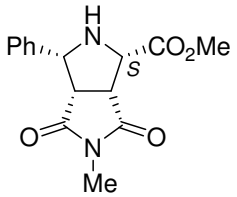
1.4.8.2. (1*S*,2*R*,4*S*,5*R*)-Methyl-4-phenyl-7-methyl-6, 8-dioxo-3,7-diazabicyclo[3.3.0]octane-2-carboxylate (128).



128

70% ee as determined by HPLC, Chiralpak AS column + guard column, 4:1 *i*-PrOH-hexanes, t_R(minor) = 7.3 min, t_R(major) = 16.5 min; $[\alpha]_D^{25}$ = -61.9 (*c* 1.24, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.19 (m, 5H), 4.40 (dd, *J* = 8.5 and 5.8 Hz, 1H, H-4), 3.95 (t, *J* = 6.1 Hz, 1H, H-2), 3.80 (s, 3H, CO_2Me), 3.45 (t, *J* = 7.2 Hz, 1H, H-1), 3.32 (t, *J* = 8.1 Hz, 1H, H-5), 2.79 (s, 3H, N-Me), 2.30 (t, *J* = 5.2 Hz, 1H, N-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.7, 174.5, 169.9, 136.6, 128.4, 128.3, 127.0, 64.12, 61.69, 52.23, 49.54, 48.25, 24.94.

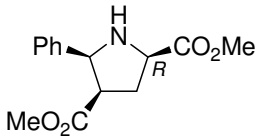
1.4.8.3. (1*R*,2*S*,4*R*,5*S*)-Methyl-4-phenyl-7-methyl-6, 8-dioxo-3,7-diazabicyclo[3.3.0]octane-2-carboxylate (ent-128).



ent-128

76% ee as determined by HPLC, Chiralpak AS column + guard column, 4:1 *i*-PrOH-hexanes, t_R(minor) = 7.3 min, t_R(major) = 16.7 min; $[\alpha]_D^{25}$ = 63.3 (*c* 1.29, DCM).

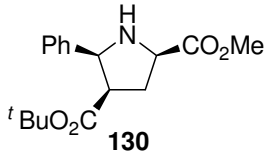
1.4.8.4. (2*R*,4*R*,5*S*) 2,4-Dicarbomethoxy-5-phenylpyrrolidine (129).



129

46% ee as determined by HPLC, Chiralcel OD column, 9:1 hexanes-*i*-PrOH, t_R(minor) = 14.2 and t_R(major) = 29.7 min; $[\alpha]_D^{25}$ = -20.9 (*c* 0.46, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27-7.22 (m, 5H, Ph), 4.51 (d, *J* = 7.8 Hz, 1H, H-5), 3.94 (t, *J* = 8.1 Hz, 1H, H-2), 3.82 (s, 3H, 2- CO_2Me), 3.28 (q, *J* = 7.2 Hz, 1H, H-4), 3.20 (s, 3H, 4- CO_2Me), 2.74 (br, 1H, NH), 2.42 (t, *J* = 7.3 Hz, 2H, H-3); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.8, 173.0, 139.6, 128.8 (2xC), 127.8, 127.1 (2xC), 66.12, 60.13, 52.43, 51.38, 49.98, 33. 59.

1.4.8.5. (2*R*,4*R*,5S) 2-Carbomethoxy-4-carbo-*tert*-butoxy-5-phenylpyrrolidine (130).

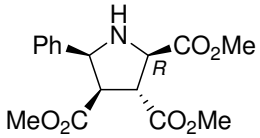


130

88% ee as determined by HPLC, Chiralpak AS + guard column, 95:5 hexanes-*i*-PrOH, t_R(minor) = 13 min, t_R(major) = 24.8 min; $[\alpha]_D^{25}$ = -28.6 (*c* 1.36, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.3 Hz, 2H, Ph) 7.23 (t, *J* = 7.5 Hz, 2H, Ph),

7.15 (t, J = 7.1 Hz, 1H, Ph), 4.38 (d, J = 7.8 Hz, 1H, H-5), 3.84 (t, J = 8.3 Hz, 1H, H-2), 3.74 (s, 3H, 2-CO_2Me), 3.16 (q, J = 7.7 Hz, 1H, H-4), 2.55 (br, 1H, NH), 2.38-2.31 (m, 1H, H-3), 2.27-2.20 (m, 1H, H-3), 0.95 (s, 9H, *t*-Bu); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4, 171.5, 139.4, 128.1, 127.3, 80.3, 65.67, 59.88, 52.04, 50.17, 34.17, 30.75, 27.53.

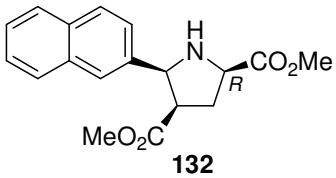
1.4.8.6. (2*R*,3*R*,4*R*,5*S*) 2,3,4-Tricarbomethoxy-5-phenylpyrrolidine (131).



131

68% ee as determined by HPLC, Chiralcel OD column, 9:1 hexanes-*i*-PrOH, t_R(minor) = 25.4 min, t_R(major) = 50.7 min; $[\alpha]_D^{25}$ = -11.5 (*c* 1.49 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.28 (m, 4H, Ph), 7.26-7.24(m, 1H, Ph), 4.62 (t, J = 6.8 Hz, 1H, H-5), 4.15 (t, J = 6.0 Hz, 1H, H-2), 3.84 (s, 3H, 2-CO_2Me), 3.77 (s, 3H, 3- CO_2Me), 3.61 (t, J = 6.6 Hz, 1H, H-3), 3.53 (t, J = 6.8 Hz, 1H, H-4), 3.19 (s, 3H, 4-CO_2Me), 2.76 (br, 1H, N-H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.4, 171.8, 171.3, 138.2, 137.2, 128.2, 127.8, 126.9, 65.48, 63.33, 53.81, 52.38, 52.34, 51.37, 50.68.

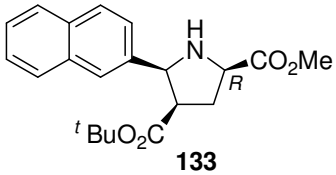
1.4.8.7. (2*R*,4*R*,5*S*)-5-Naphthalen-2´-yl-pyrrolidine-2,4-dicarboxylic acid dimethyl ester (132).



132

37% ee as determined by HPLC, Chiralpak AS column, 9:1 hexanes-*i*-PrOH, t_R(minor) = 12.4 min, t_R(major) = 25.3 min; $[\alpha]_D$ = -15.2 (*c* 1.04 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82-7.74 (m, 4H), 7.45-7.38 (m, 3H), 4.65 (d, J = 7.7 Hz; 1H), 3.99 (t, J = 8.1 Hz; 1H), 3.85 (s, 3H), 3.36 (dd, J = 14.0 & 7.1 Hz; 1H), 3.11 (s, 3H), 2.50-2.39 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.5, 172.7, 136.6, 133.2, 132.9, 128.0, 127.7, 127.5, 126.0, 125.8, 125.5, 125.1, 66.0, 59.9, 52.1, 51.1, 49.6, 33.4.

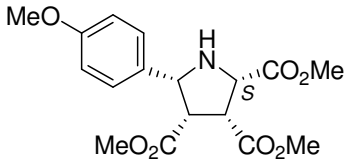
1.4.8.8. *tert*-Butyl-(2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-(2-naphthyl)pyrrolidin-4-carboxylate (133).



133

78% ee as determined by HPLC, Chiralpak AS column 95:5 hexanes-*i*-PrOH, t_R(minor) = 9.3 min, t_R(major) = 17.3 min; $[\alpha]_D$ = -21.4 (*c* 0.73 g/100mL, DCM). ^{1}H-NMR and ^{13}C-NMR data were consistent with previously reported values.[26b]

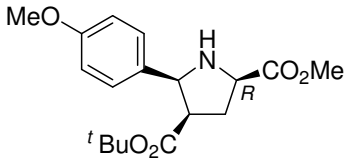
1.4.8.9. (2*S*,3*R*,4*R*,5*R*)-2,3,4-tricarbomethoxy-5-(4-methoxyphenyl)pyrrolidine (134).



134

95% ee as determined by HPLC, Chiralpak AS column 85:15 hexanes-*i*-PrOH, t_R(major) = 15.7 min, t_R(minor) = 30.5 min; $[\alpha]_D$ = +72.6 (*c* 0.74 g/100mL, DCM); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 4.40 (d, *J* = 6.9 Hz, 1H), 4.09 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.64 (t, *J* = 8.4 Hz, 1H), 3.48 (t, *J* = 7.4 Hz, 1H), 3.26 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 170.6, 159.1, 129.2, 127.9, 113.7, 65.0, 62.2, 55.0, 52.5, 52.2, 51.9, 51.2, 50.9.

1.4.8.10. *tert*-Butyl-(2*R*,4*R*,5*S*)-2-methoxycarbonyl-5-(4-ethoxyphenyl)pyrrolidin-4-carboxylate (135).



135

84% ee as determined by HPLC, Chiralpak AS column 9:1 hexanes-*i*-PrOH, t_R(minor) = 6.6 min,

t_R(major) = 9.6 min; $[\alpha]_D$ = -22.9(*c* 0.96 g/100mL, DCM). ^{1}H-NMR and ^{13}C-NMR data were consistent with previously reported values.[26b]

PART 2

FAM-TITANIUM CATALYZED ENANTIOSELECTIVE ALKYNYLATION OF ALDEHYDES

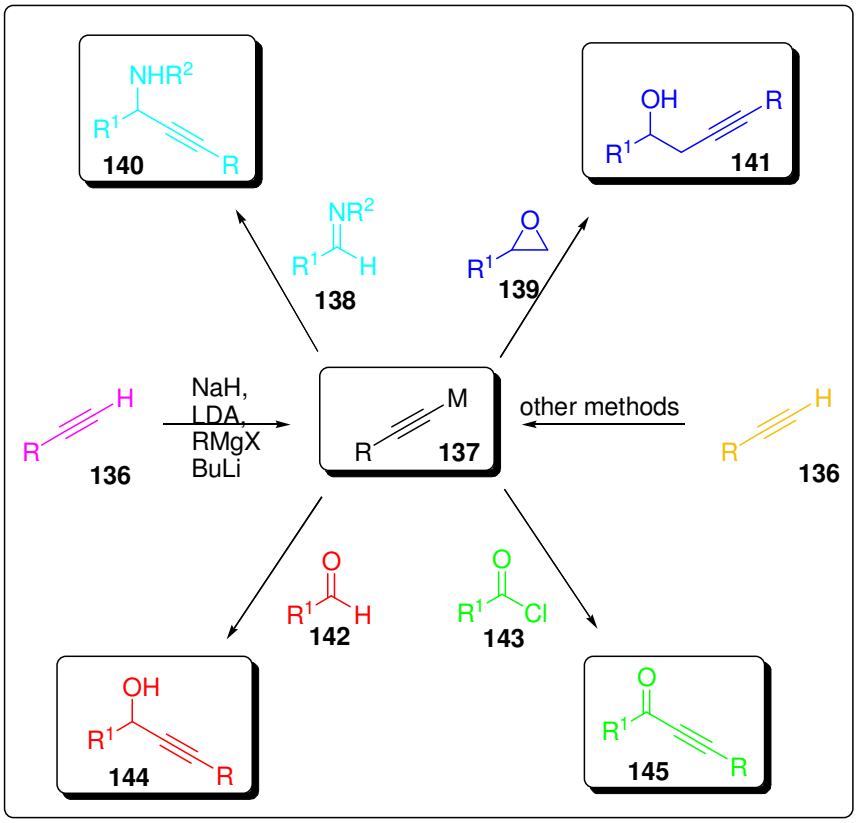
CHAPTER 2.1

INTRODUCTION

2.1.1. C-C Bond Formation in Organic Chemistry

One of the most important reactions in synthetic organic chemistry is a C-C bond formation and metalated terminal alkynes can be used as a nucleophile in C-C bond formation.[46] The reaction of terminal acetylenes with alkali or alkaline earth metal compounds may create metalated terminal alkyne derivatives (**137**), which are carbanionic and very reactive. They react with a broad range of electrophiles, such as; nitrones, imines (**138**), epoxides (**139**), acid chlorides (**143**) and even aldehydes (**142**) (Scheme 2.1). In addition, metalated alkyne derivatives can react in Pd(0)-catalyzed C(sp^2)-C(sp) and C(sp)-C(sp) couplings[47] which is very important in modern organic synthesis.[48]

The pKa of the terminal alkynes relative to H_2O is around 25.[49] Therefore the deprotonation of terminal alkynes is rapid and quantitative with RLi, RMgBr, or LDA. Additionally, hydroxides and alkalimetal alkoxides are basic enough for the deprotonation. Even amine bases (pKa~11) can deprotonate terminal alkynes when it is activated by forming a π-complex with metals such as Ag(I) or Cu(I). Concomitant formation of the corresponding silver or copper acetylide and deprotonation can take place at room temperature.[50]



Scheme 2.1 The synthesis of metalated terminal alkynes (**137**) and their reactions with broad range of electrophiles.

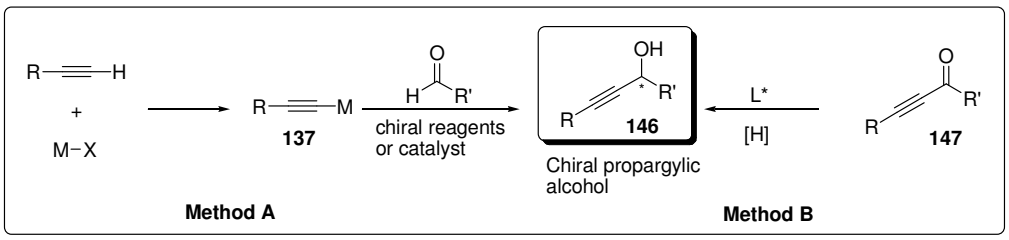
If specific examples are to be given, the metalated terminal alkynes can be prepared from the following strong bases and even Lewis acid (EtMgBr[51], BuLi[52], Me_2Zn[53]), hydroxides (NaOH, KOH, CsOH)[54], alkoxides (KO^{t}Bu)[55] and metalated amides (LDA, Et_2NLi, KHMDS).

The strong bases, which are used in the traditional preparation of metalated terminal alkynes and most of the electrophiles (imines, aldehydes and etc.) can not be together in the same reaction medium. In order to prevent the formation of side reaction, except for KOH, NaOH and CsOH, the deprotonation of the alkyne must

be carried out in a separate step. If this is possible, the C-C bond formation is obtained in a second step and this method does not simplify the addition process.

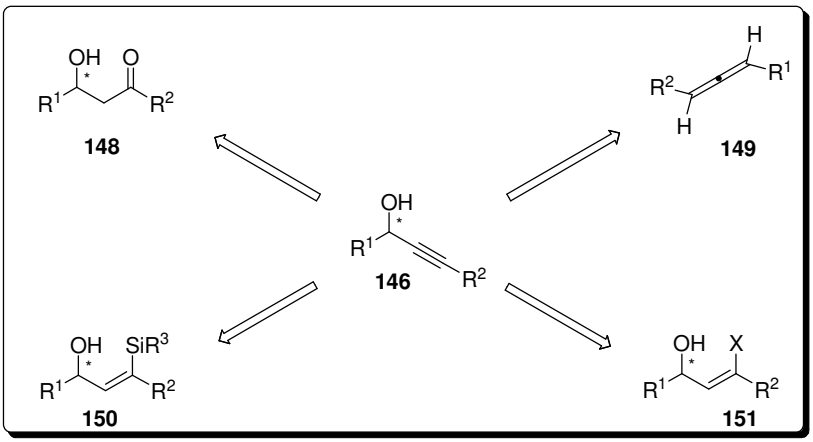
2.1.2. Optically Active Propargylic Alcohols

Optically active propargylic alcohols (**146**) are versatile precursors to many organic molecules including natural products and pharmaceutical compounds.[56] In order to synthesize chiral propargylic alcohols, two general methods are used in synthetic organic chemistry. Although, the direct reduction of alkynyl ketones (**147**) (also known as ynone reduction)[57] (Method B in Scheme 2.2) is the most common approach to the synthesis of these compounds, the alkynylation of aldehydes by organometallic reagents (**137**) (Method A in Scheme 2.2) has a strategic synthetic advantage. In method A, a new C-C bond and a chiral alcohol center are created simultaneously in a single transformation, while in method B, the C-C bond and the new chiral center are created separately. For this reason, method A is the most efficient method used in the synthesis of chiral propargylic alcohols.



Scheme 2.2 Two general methods used in the synthesis of optically active propargylic alcohols.

The acetylene and hydroxyl functions of the chiral propargylic alcohols can be used to construct very diverse molecular structures as shown in Scheme 2.3.[58]

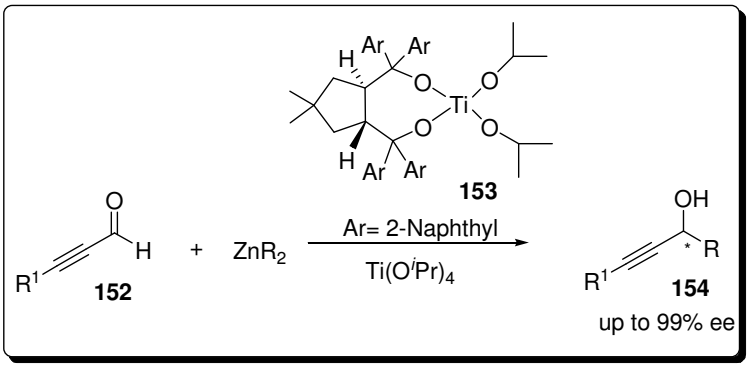


Scheme 2.3 Acetylenic alcohols as precursors to various valuable compounds.

2.1.3. Enantioselective Alkynylation of Aldehydes

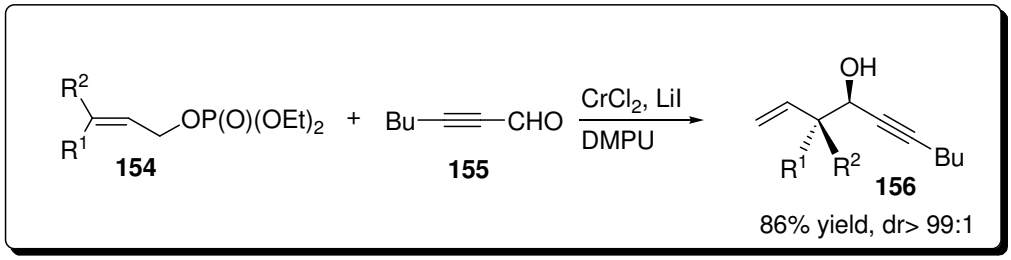
2.1.3.1. Enantioselective Alkylation of Alkynyl Aldehydes

By the addition of dialkyzinc to alkynyl aldehydes (**152**) in the presence of chiral Ti-TADDOLate (**153**), Seebach and co-workers obtained secondary propargylic alcohols (**154**) with very high enantioselectivity (up to 99% ee) (Scheme 2.4) .[59]



Scheme 2.4 The enantioselective alkylation of alkynyl aldehyde (**152**) in the presence of chiral Ti-TADDOLate (**153**).

Knochel and co-workers reported the reaction of alkynyl aldehydes (**155**) with γ-disubstituted allylic phosphonates (**154**) and $CrCl_2$ in the presence of catalytic amounts of LiI in DMPU. This reaction proceeded with high stereoselectivity and **156** was obtained in 86% yield (Scheme 2.5).[60]

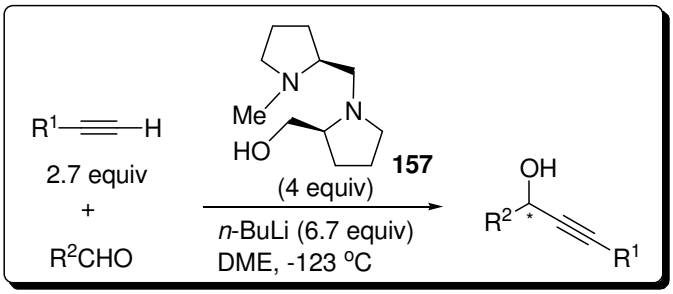


Scheme 2.5 The enantioselective alkylation of alkynyl aldehyde (**155**) with γ-disubstituted allylic phosphonate (**154**).

2.1.3.2. Enantioselective Alkynylation of Aldehydes with Other Alkynyl Organometallic Reagents

Various organometallic-acetylides have been used in the addition to carbonyl compounds in literature. However, to control the stereoselectivity of the addition step, stoichiometric amounts of chiral reagents have been used in the previous studies.

The first reported study in this subject was the lithium-acetylide addition to aldehydes, which was conducted by Mukaiyama et al.[61] (Scheme 2.6). They used 4 equivalents of a chiral diamino alcohol (**157**) at -123 ^{o}C to produce propargylic alcohols with up to 92% ee. The results of the experiments are summarized in Table 2.1.



Scheme 2.6 The asymmetric alkynylation of aldehydes in the presence of chiral ligand (**157**).

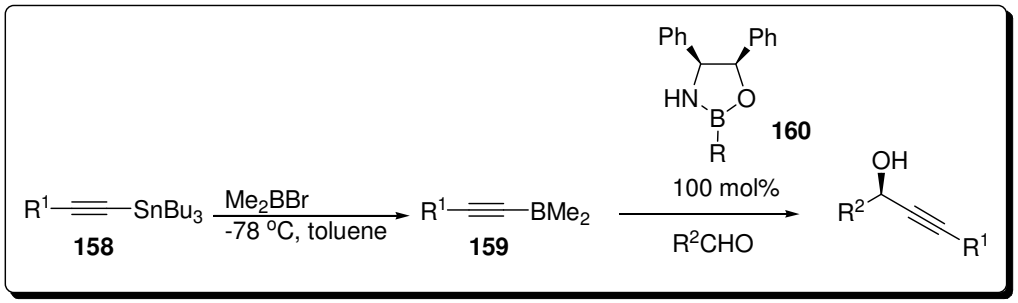
Table 2.1 The results of the asymmetric alkynylation reactions of Mukaiyama and co-workers.

Entry	R^1	R^2	yield (%)	ee (%)
1	H	Ph	76	54
2	TMS	Ph	87	92
3	TES	Ph	93	80
4	TBS	Ph	67	72
5	Ph_2MeSi	Ph	88	80
6	TPS	Ph	83	76
7	TMS	Et	77	68
8	TMS	*n*-Pent	87	76
9	TMS	*n*-Octyl	83	80
10	TMS	$n\text{-}C_{11}H_{23}$	82	70
11	TMS	$n\text{-}C_{13}H_{27}$	76	73
12	TMS	$(CH_3)_2CHCH_2$	54	65
13	TMS	$CH_3(CH_2)_2CH{=}CH$	74	40

Aromatic aldehydes gave (*S*)-alcohol, whereas aliphatic aldehydes gave (*R*)-alcohol.

Corey and Cimprich developed a catalytic process by using chiral oxazaborolidine (**160**) to catalyze the addition of alkynylboranes (**159**) to aldehydes.[62] They used very large range of alkynes and aldehydes and obtained up to 97% ee. In this study,

alkynylstannanes (**158**) were prepared first and then converted to alkynylboranes (**159**) before addition to aldehydes (Scheme 2.7). The results of the experiments are summarized in Table 2.2.



Scheme 2.7 The enantioselective alkynylation of aldehydes in the presence of 100 mol% of chiral oxazaborolidine (**160**).

Table 2.2 The results of the asymmetric alkynylation reactions of Corey and Cimprich.

Entry	R^1	R^2	R(equiv)	yield (%)	ee (%)
1	Ph	*c*-Hex	Bu(1)	96	90
2	*n*-Pent	*c*-Hex	Bu(1)	82	95
3	Ph	Ph	Bu(1)	78	96
4	*n*-Pent	Ph	Bu(1)	28	94
5	Ph	*n*-Pent	Bu(1)	90	96
6	*n*-Pent	*n*-Pent	Bu(1)	80	96
7	Ph	*c*-Hex	Me(1)	95	90
8	Ph	*t*-Bu	Bu(1)	71	97
9	Ph	*n*-Pent	Ph(0.25)	77	93
10	Ph	Ph	Ph(0.25)	72	97
11	Ph	*c*-Hex	Ph(0.25)	80	85
12	Ph	*p*-MeO_2C-Ph	Me(1)	80	96
13	Ph	*p*-NO_2-Ph	Ph(1)	86	96

In another study, Schäfer et al.[63] used substituted cyclohexanones and lithium trimethylsilylacetylide in the presence of stoichiometric amounts of (2*S*,2′*S*)-2-hydroxy-methyl-1-[(1-methylpyrrolidin-2-methyl]pyrrolidine as chiral ligand to synthesize tertiary propargylic alcohols with enantioselectivities up to 82%.

The total synthesis of efavirenz, (**161**) which is the potent nonnucleosidal HIV reverse transcriptase inhibitor, has attracted considerable interest in recent years and the scientists from Merck have published the addition of lithium cyclopropylacetylide to a suitable precursor in the presence of chiral ligands (Figure 2.1).[64]

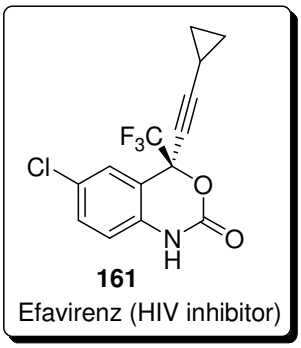
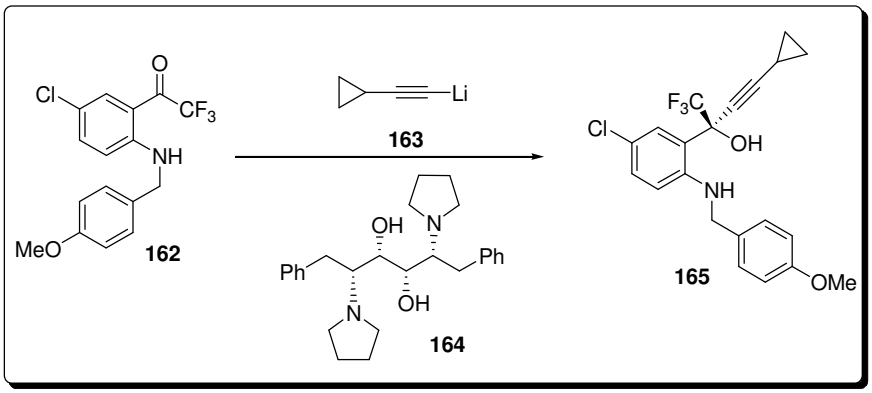


Figure 2.1 The chemical structure of efavirenz (**161**).

A second study included the synthesis of a precursor of Efavirenz (**165**). This study was published by Jiang and his co-workers. They employed a stoichiometric amount of the chiral C_2 symmetric diol (**164**) in the presence of lithium acetylides (**163**) (Scheme 2.8).[65]



Scheme 2.8 Asymmetric synthesis of the precursor of Efavirenz (**165**) in the presence of C_2-symmetric diol (**164**).

The highly diastereoselective reaction (at least 85:15) of a steroidal aldehyde with stannylacetylene was reported by Yamamoto et al.[66] Krause and Seebach used RC≡CTi(O^{i}Pr)$_3$ in the alkynylation of aldehydes with only low to moderate diastereoselectivity.[67] Baldoli and co-workers reacted chiral ortho-substituted benzaldehyde-tricarbonylchromium complex with lithium acetylides and ethynyl magnesium bromide.[68] At the end they obtained alkynyl alcohols in good yields with excellent diastereoselectivity (≥98% de).

2.1.3.3. Enantioselective Alkynylation of Aldehydes With Alkynylzinc Reagents

Although the catalytic asymmetric addition of alkenyl and dialkylzinc compounds to aldehydes have been studied extensively with different catalyst systems, the asymmetric alkynylation methods are less developed. Previous studies on the alkynylation of aldehydes required stoichiometric amounts of catalysts, used limited source of reagents, and suffered from the formation of considerable amounts of alkylated byproducts.[69] However, some new methods including highly enantioselective catalytic alkynylmetal addition to aldehydes have been developed in recent years.

In asymmetric additions to aldehydes, zinc-acetylides are the mostly studied ones in recent years since they are easily prepared *in situ* from the reaction of terminal alkynes with the easily available alkylzincs or $Zn(OTf)_2$. In addition, unlike the organolithium and Grignard reagents, the organozinc reagents can tolerate the presence of many functional groups such as esters, amides, nitro groups and nitriles. This property renders the organozinc species as an attractive useful alternative to the highly active reagents.

The first enantioselective addition of alkynylzinc reagents to benzaldehyde was reported by Soai and co-workers.[69a,70] They used enantiomerically pure amino alcohols (**166** and **167**) or amines (**168** and **169**) in this reaction (Figure 2.2). At the end of the reaction, the chiral ligand **166** was chosen as the best ligand and used in 5 mol% in asymmetric addition to aldehydes (Scheme 2.9). The propargylic alcohol products were obtained in 36-99% yield and 7-34% enantioselectivities. The results of the experiments are summarized in Table 2.3.

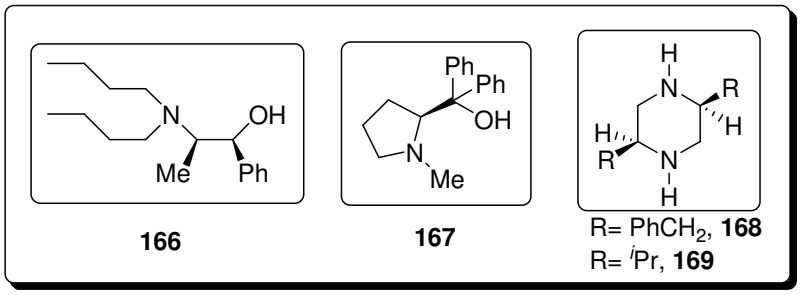
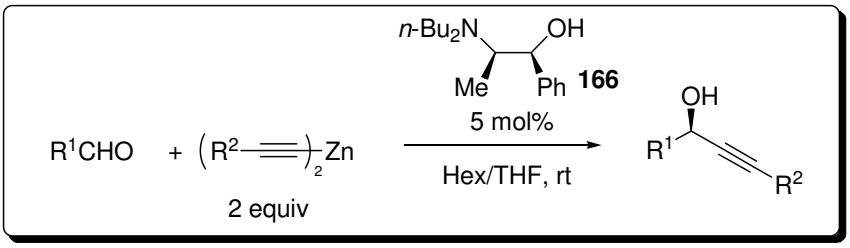


Figure 2.2 The chiral ligands (**166**-**169**) used by Soai and Niwa in the enantioselective alkynylation of aldehydes with alkynylzinc reagents.

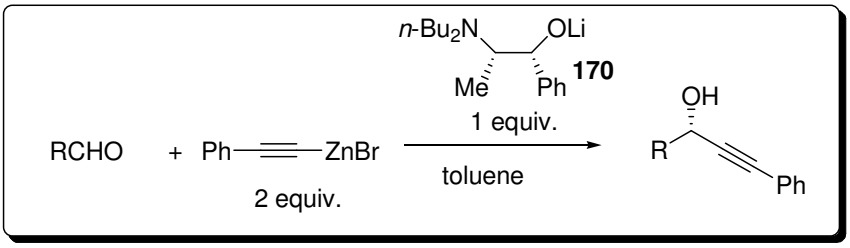


Scheme 2.9 The enantioselective alkynylation of aldehydes performed by Soai and Niwa using chiral ligand (**166**).

Table 2.3 The results of the enantioselective alkynylation reactions of Soai and Niwa.

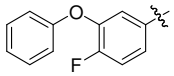
Entry	R^1	R^2	Time (h)	yield (%)	ee (%)
1	Ph	Ph	14	99	34
2	*n*-Octyl	Ph	5	78	9
3	PhCH=CH	Ph	14	97	10
4	Ph	*n*-Hex	44	81	22
5	Ph	Bu	52	93	20
6	Ph	Me_3Si	168	36	21
7	*n*-Octyl	Me_3Si	48	80	24
8	Ph	*c*-Hex	48	88	7

Tombo et al.[71] used 2 equivalents of PhC≡CZnBr and stoichiometric amount of chiral ligand **170** in asymmetric addition reactions to aldehydes (Scheme 2.10). They reported up to 90% yield and 88% enantioselectivity, Table 2.4.



Scheme 2.10 The asymmetric alkynylation reactions of aldehydes by using (**170**).

Table 2.4 The results of the asymmetric alkynylation reactions performed by Tombo and co-workers.

Entry	R	T (°C)	Time (h)	yield (%)	ee (%)
1	Ph	-30	19	70	80
2	*t*-Bu	-30	24	50	67
3	*n*-Pent	-30	20	90	19
4		0-5	20	80	88

In a similar study, Ishizaki and Hoshino[72] used pyridyl amine **171** and pyridyl alcohol ligands **172**-**174** in the alkyne addition reactions (Figure 2.3). Chiral ligand **172** was found to be the best and up to 88% yield and 95% enantioselectivity was obtained using 10 mol% of this ligand in the asymmetric alkyne addition reactions to aldehydes (Scheme 2.11). The results of the experiments are summarized in Table 2.5. In some cases, ethylated byproduct was also observed (entries 5, 6 and 7).

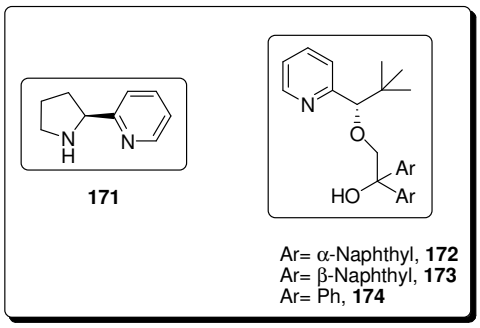
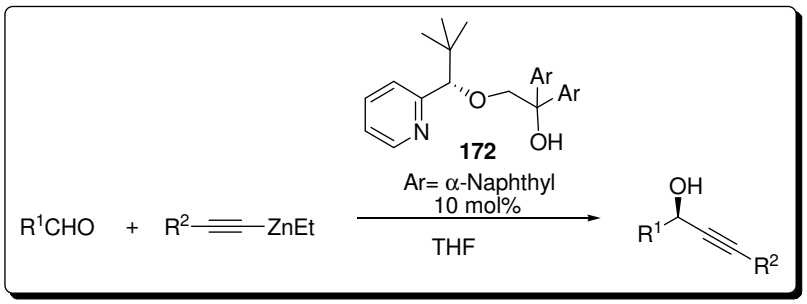


Figure 2.3 The chiral ligands (**171**-**174**) used by Ishizaki and Hoshino in the enantioselective alkynylation of aldehydes with alkynylzinc reagents.



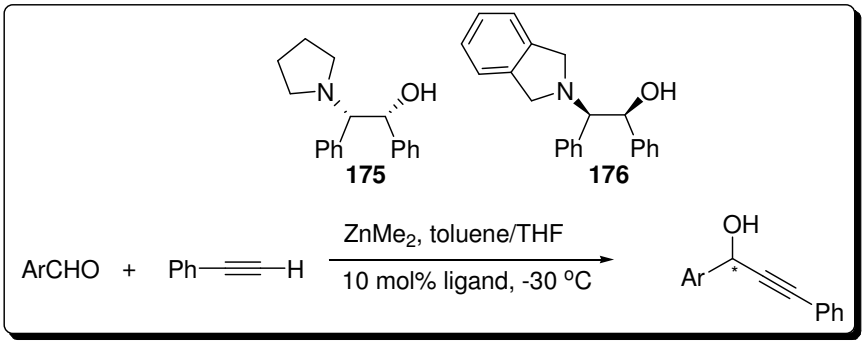
Scheme 2.11 The asymmetric alkynylation reactions of aldehydes by using **172**.

Table 2.5 The results of the asymmetric alkynylation reactions performed by Ishizaki and Hoshino.

Entry	R^1	R^2	Temp. (°C)	Time (h)	yield (%)	ee (%)
1	Ph	Ph	0	15	64	90
2	*n*-Octyl	Ph	0	4	65	83
3	*c*-Hex	Ph	0	10	88	91
4	*t*-Bu	Ph	0	10	61	95
5	Ph	*n*-Hex	rt	2	41(52)[a]	78
6	*n*-Octyl	*n*-Hex	rt	1	62(22)[a]	73
7	*c*-Hex	*n*-Hex	rt	3	79(18)[a]	82
8	*t*-Bu	*n-Hex*	rt	3	67	87
9	*c*-Hex	Ph_3Si	rt	5	55	91

[a] The values given in paranthesis are yields of the ethylated products.

Li et al.[73] used 10 mol% of aminoalcohol ligands **175** or **176** in the asymmetric alkyne addition to various aldehydes (Scheme 2.12). Up to 94% yield and 82% ee were obtained with these ligands, Table 2.6.



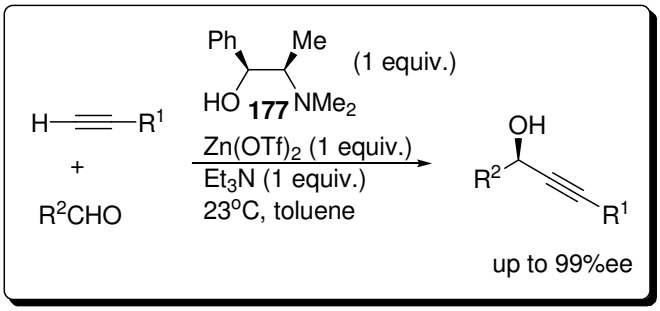
Scheme 2.12 The asymmetric alkynylation reactions of aldehydes by using (**175**) or (**176**).

Table 2.6 The results of the asymmetric alkynylation reactions using 10 mol% of (**175**) or (**176**).

Entry	Ar	Ligand	yield (%)	ee (%)
1	Ph	**175**	70	68(-) (*S*)
2	*o*-FC_6H_4	**176**	90	82(-)
3	*m,o*-di-F C_6H_3	**176**	94	81(+)
4	*o*-ClC_6H_4	**175**	77	80(+)
5	*o*-BrC_6H_4	**175**	77	80(+)
6	*o*-$NO_2C_6H_4$	**175**	81	76(+)
7	*o*-$MeOC_6H_4$	**175**	74	82(+)
8	*o*-MeC_6H_4	**175**	65	62(+)
9	2-Naphthyl	**176**	87	75(-)

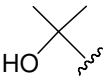
Highly enantioselective alkynylzinc additions to aldehydes were reported by Carreira and co-workers in various studies.[74] They used stoichiometric amount of chiral ligand N-methylephedrine (**177**) and $Zn(OTf)_2$ in order to promote the reaction of terminal alkynes with various aliphatic aldehydes and benzaldehyde.[29a]

High enantioselectivites were obtained at the end of these reactions. The yield and enantioselectivity for the reaction of an α,β-unsaturated aldehyde was significantly lower. It is important to mention here that, these reactions can be run in commercial grade solvent and do not need air sensitive atmospheres, which made this method very convenient and practical (Scheme 2.13). The results of the experiments are summarized in Table 2.7.

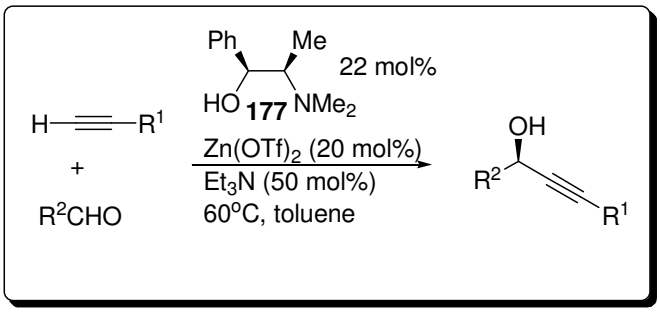


Scheme 2.13 The general reaction scheme for enantioselective alkynylation of aldehydes in the presence of stoichiometric amounts of $Zn(OTf)_2$, Et_3N and chiral ligand (**177**).

Table 2.7 The results of the experiments performed by Carreira and co-workers.

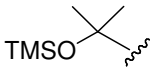
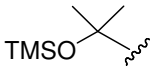
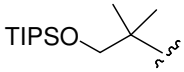
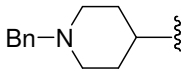
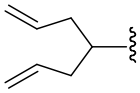
Entry	R^1	R^2	yield (%)	ee (%)
1	Ph	*c*-Hex	99	96
2	$Ph(CH_2)_2$	*c*-Hex	98	99
3	$Ph(CH_2)_2$	*i*-Pr	90	99
4	Ph	*i*-Pr	95	90
5	$Ph(CH_2)_2$	PhCH=CH	39	80
6	$Ph(CH_2)_2$	*t*-Bu	84	99
7	Ph	*t*-Bu	99	95
8	$Ph(CH_2)_2$	Ph	52	96
9	Ph	Ph	53	94
10	TMS	*c*-Hex	93	98
11	$Ph(CH_2)_2$	Me_3CCH_2	72	99
12	Ph	Me_3CCH_2	90	97
13	$TMSCH_2$	*c*-Hex	84	98
14	$TBDMSOCH_2$	*c*-Hex	83	98
15	$(EtO)_2CH$	*c*-Hex	90	98
16		*c*-Hex	94	98
17		*i*-Pr	97	98

In a second study,[74d] they used catalytic amounts of **177** and $Zn(OTf)_2$ to promote the reaction of alkynylzincs with various aliphatic aldehydes at 60 °C to overcome the problem of low turnover in the catalytic cycle (Scheme 2.14). The catalyst system was excellent for aliphatic aldehydes, and chiral propargylic alcohols were obtained in high yields and up to 99% enantioselectivity was achieved. On the other hand, aromatic aldehydes gave Cannizzaro products. These reactions were also tolerant to air and moisture and they could be conducted in the absence of solvent maintaining high yield and enantioselectivity. The results of the experiments are summarized in Table 2.8.



Scheme 2.14 The general reaction scheme for enantioselective alkynylation of aldehydes in the presence of catalytic amounts of $Zn(OTf)_2$, Et_3N and chiral ligand (**177**).

Table 2.8 The results of the experiments performed by Carreira and co-workers in the presence of catalytic amounts of $Zn(OTf)_2$, Et_3N and chiral ligand (**177**).

Entry	R^1	R^2	yield (%)	ee (%)
1	Bn_2NCH_2	*c*-Hex	91	97
2	$Ph(CH_2)_2$	*c*-Hex	89	94
3	Ph	*c*-Hex	94	86
4		*i*-Pr	77	98
5	$Ph(CH_2)_2$	*n*-Heptyl	45	92
6	$Ph(CH_2)_2$	*t*-Bu	77	93
7	$TBSOCH_2$	*t*-Bu	81	93
8	$(EtO)_2CH$	*c*-Hex	88	94
9	*n*-Bu	*c*-Hex	81	93
10		*c*-Hex	80	99
11	TES	*c*-Hex	85	96
12	Bn_2NCH_2		80	95
13	$TBSOCH_2$	*c*-Hex	88	90
14	Bn_2NCH_2		81	94
15	$Ph(CH_2)_2$		80	93
16	Bn_2NCH_2	*n*-Heptyl	55	91

Different rigid binaphthtyl amino alcohol ligands (**178**-**181**), which can be synthesized in a few steps from commercially available BINOL, were synthesized by Chan et al (Figure 2.4).[75] These ligands were used in asymmetric addition of alkynylzinc to aldehydes (Scheme 2.15). One of them, (1*R*,2*S*,3*R*)-**178** was found to be highly effective in the asymmetric alkynylation of aldehydes.

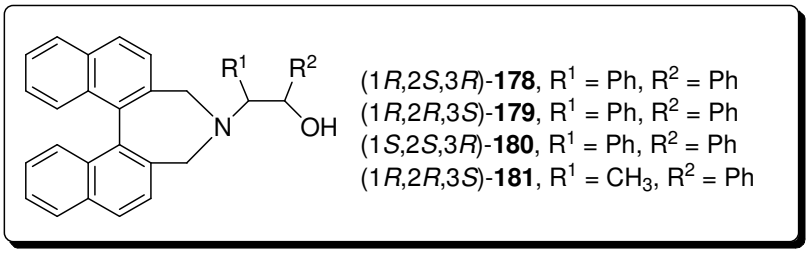
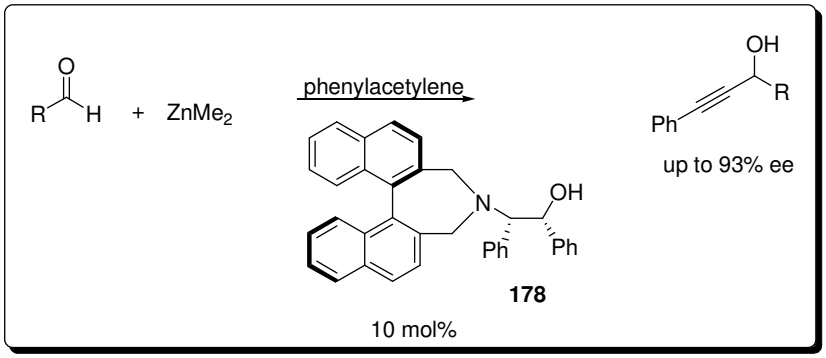


Figure 2.4 The chemical structures of four different rigid binaphthtyl amino alcohol ligands (**178**-**181**) synthesized by Chan et al.



Scheme 2.15 The general reaction scheme for enantioselective alkynylation of aldehydes in the presence of $ZnMe_2$ and 10 mol% chiral ligand (**178**).

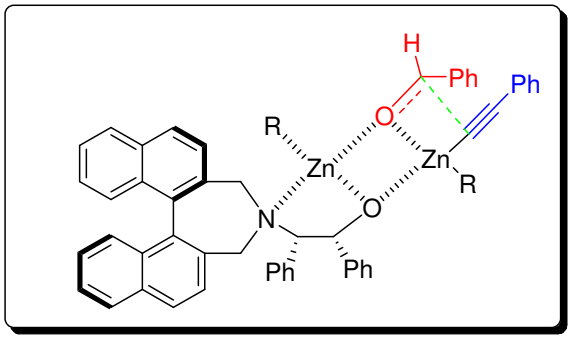


Figure 2.5 The proposed transition state in this reaction.

The proposed transition state in this reaction consist of a bimetallic specie that is also common for other reactions of dialkylzinc with aldehydes (Figure 2.5).

In this study, various aldehydes were converted to the corresponding propargylic alcohols, in the presence of dimethylzinc in 61-93% ee's. Both aliphatic and aromatic alkynylzincs give good results with aromatic aldehydes in the presence of the catalyst-**178**. However, with aliphatic aldehydes, very low enantioselectivities were obtained (36% ee was obtained with cyclohexanecarboxaldehyde). Although in the presence of amino alcohols, other alkylzinc reagents react easily with aldehydes, the Lewis acid Me_2Zn does not add to aldehyde but only forms the active alkynylzinc complex and deprotonates the acetylene derivative.

2.1.3.4. The Use of Ti(O^{i}Pr)$_4$ in Enantioselective Alkynylzinc Addition to Aldehydes

Chan group[76] used chiral Ti(O^{i}Pr)$_4$-(*R*)-BINOL and Ti(O^{i}Pr)$_4$-(*R*)-H$_8$-BINOL catalysts and various aromatic aldehydes were converted to the corresponding propargylic alcohols with very good yields and enantioselectivities (up to 96% ee was achieved). The titanium complex was prepared by stirring (*R*)-BINOL or (*R*)-

H_8-BINOL (Figure 2.6) with $Ti(O^iPr)_4$ at room temperature in THF. This mixture was added to the mixture of phenylacetylene, Me_2Zn and aldehyde. This procedure could also be applied to aliphatic aldehydes and moderate to good enantioselectivities were obtained. The higher enantioselectivities were achieved when (*R*)-H_8-BINOL (**180**) was used as a catalyst (Scheme 2.16). The results of the experiments are summarized in Table 2.9.

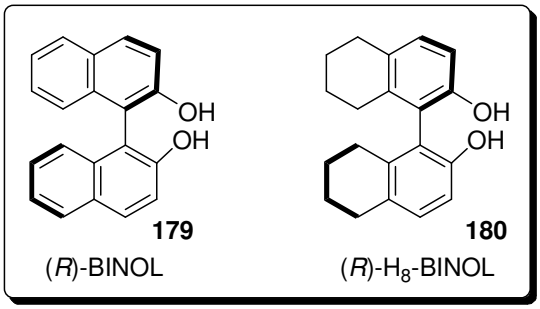
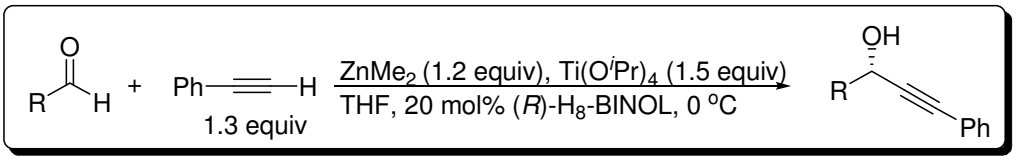


Figure 2.6 The chemical structures of (*R*)-BINOL (**179**) and (*R*)-H_8-BINOL (**180**).



Scheme 2.16 The general reaction scheme for enantioselective alkynylation of aldehydes in the presence of 20 mol% chiral ligand (**180**).

Table 2.9 The results of the experiments performed by Chan and co-workers.

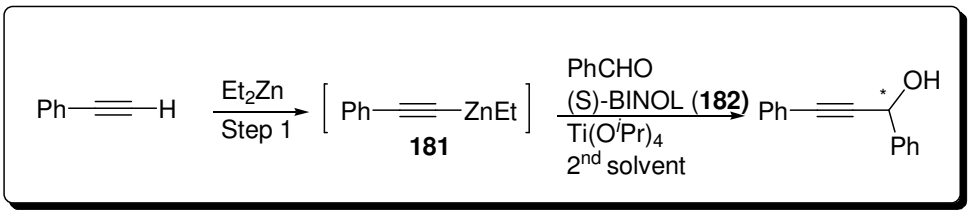
Entry	R	yield (%)	ee (%)
1	Ph	85	92(*S*)
2	*o*-Cl-Ph	90	76
3	*m*-Cl-Ph	87	95
4	*p*-Cl-Ph	91	94
5	*p*-Me-Ph	84	86
6	*p*-F-Ph	82	87
7	*p*-Br-Ph	89	94
8	*p*-NO_2-Ph	89	95
9	*m*-NO_2-Ph	88	96
10	2-naphthyl	75	80
11	*p*-CF_3-Ph	89	93
12	*i*-Pr	84	82
13	*c*-Hex	86	74
14	*n*-Pr	87	77

At about the same time, an analogous BINOL-Ti(O^iPr)$_4$ system to that of Chan and co-workers was reported by Moore and Pu[77] in a series of papers. They also found that (*S*)-BINOL in combination with Ti(O^iPr)$_4$ could effect the highly enantioselective alkynylzinc additions to aldehydes. In this system, up to 98% ee was obtained with aromatic aldehydes. In contrast to Chan's procedure, the reactive alkynylzinc was prepared by refluxing diethylzinc with phenylacetylene before the reaction in toluene. By this way, they also prevent the ethyl addition to aldehydes. This procedure was applicable to phenylacetylene and aromatic aldehydes and 92-98% ee's were obtained.[77a] In addition to this study, they have further demonstrated that Ti(O^iPr)$_4$-BINOL catalyst system is also highly enantioselective for the phenylacetylene addition to aliphatic and α,β-unsaturated aldehydes.[77b] In each of these studies, the asymmetric alkynylzinc addition was conducted in two steps:

Step (1) The terminal alkyne was treated with Et_2Zn in refluxing toluene,

Step (2) (*S*)-BINOL, $Ti(O^iPr)_4$, an aldehyde and a secondary solvent was added into the reaction flask.

This two step reaction using phenylacetylene, Et_2Zn and benzaldehyde catalyzed by (*S*)-BINOL (**182**) and $Ti(O^iPr)_4$ is given in Scheme 2.17. Here, the first step generates the alkynylzinc intermediate (**181**), which then adds to benzaldehyde in the presence of the catalyst to form the chiral propargylic alcohol.



Scheme 2.17 The reaction of phenylacetylene with benzaldehyde in the presence of Et_2Zn, (*S*)-BINOL, $Ti(O^iPr)_4$ and a second solvent.

Chiral ligands (*R*)-**183** and (*S*)-**184** were synthesized by further structural modifications on BINOL ligand by Pu and co-workers (Figure 2.7).[78] Although they gave reasonable enantioselectivities (up to 92% ee) in the asymmetric alkynylation, they were not as efficient as simple chiral BINOL. They recognized that the active catalyst can also be prepared at room temperature by stirring phenylacetylene and Et_2Zn in the presence of the chiral ligand (*R*)-**183**. In this study, they suggested that a zinc complex is formed by the reaction of this ligand and Et_2Zn, which catalyzes the formation of the alkynylzinc reagent from phenylacetylene and Et_2Zn.

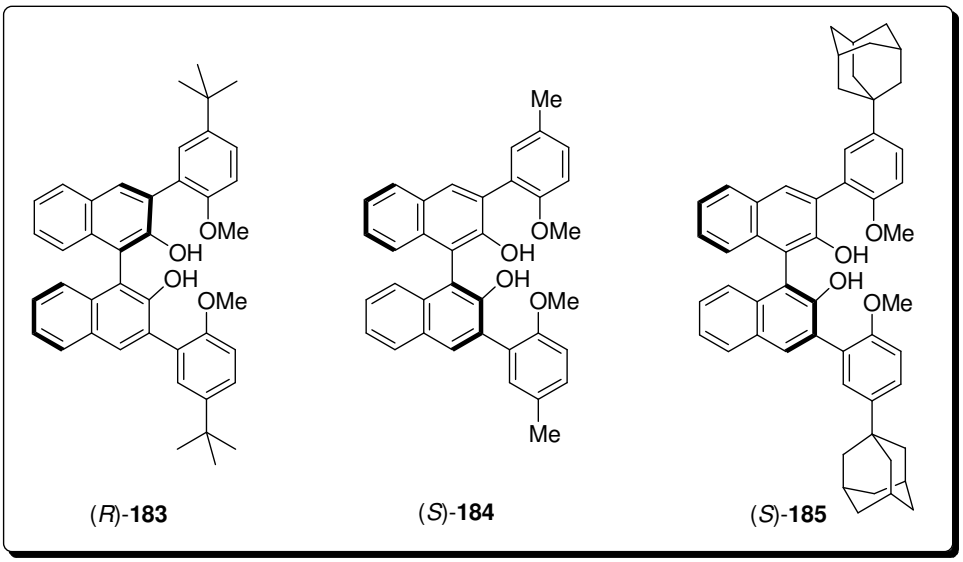
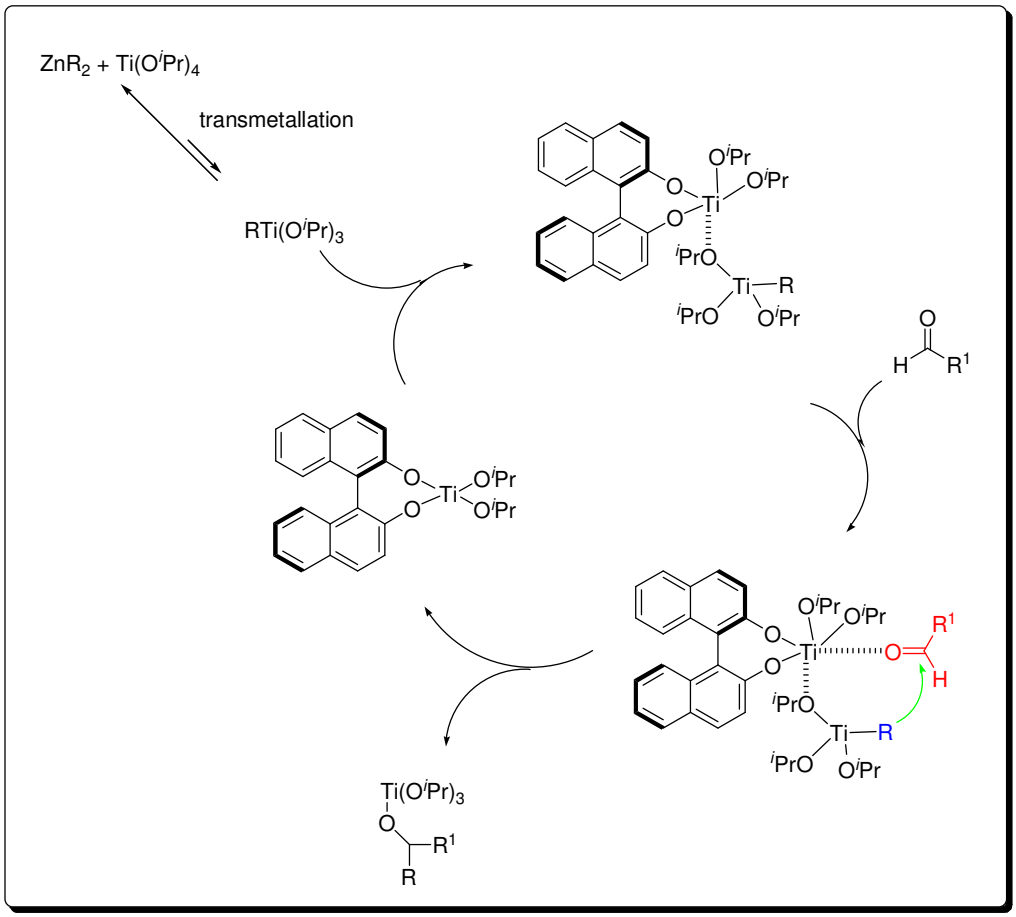


Figure 2.7 The chiral ligands (**183**-**185**) synthesized by Pu and co-workers.

In another study, Pu and co-workers[79] used 1,1′-binaphthyl compound (*S*)-**185**. This ligand contains a more bulky 3,3′-aryl substituents which catalyzed the reaction of terminal alkyne with various aromatic aldehydes (80-94% ee's) even without using the titanium compound.

2.1.3.5. The Role of Ti(O^{i}Pr)$_4$ in Asymmetric Alkynylation

The role of Ti(O^{i}Pr)$_4$ is to produce the active catalyst and to facilitate the transmetallation. For the addition of alkylzinc reagents in the presence of Ti(O^{i}Pr)$_4$, recent studies suggested such a mechanism (Scheme 2.18). In this mechanism it is suggested that the role of Ti(O^{i}Pr)$_4$ is to receive an alkyl group from the zinc reagent and to bind the chiral titanium catalyst in a present form.[80]



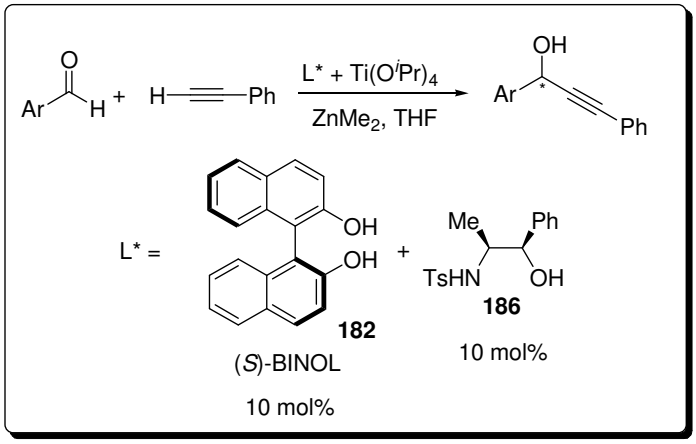
Scheme 2.18 The proposed catalytic cycle when alkyl adds to aldehyde in the presence of $Ti(O^iPr)_4$.

It is seen in Scheme 2.18 that, in all cases, a bimetallic catalyst with two titanium atoms seems to be necessary in order to achieve stereoselectivity at the addition of R group to aldehyde. However, this hypothesis needs to be proven by detailed kinetic studies.

2.1.3.6. Self-Assembly of Several Chiral Ligands in the Asymmetric Alkynylation of Aldehydes

The self-assembly of several chiral ligands into a highly enantioselective catalyst for asymmetric reaction is a new frontier in organic synthesis. Mikami et al.[81] first introduced this idea and several chiral ligand components were self-assembled into a highly enantioselective titanium catalyst for carbonyl-ene reactions. Several chiral ligands and titanium was used *in situ* preparation of self-assembled titanium catalyst and it increased reaction rates and enantioselectivites.

After the publication of this work, a chiral self-assembled titanium catalyst for asymmetric alkynylation was reported by Chan group.[82] In this study, best results were obtained by combination of (*S*)-BINOL (**182**) and chiral sulfonamide (**186**) (Scheme 2.19). With respect to previously reported studies, both the enantioselectivity (99.7% ee) and catalytic activity were better (Table 2.10). In this method, it is explained that a complex mixture of several titanium catalysts is formed in solution. The role of additive is to modify the equilibrium between different species and form a selective and highly active catalyst and reaction goes on over this active catalyst.



Scheme 2.19 The general reaction scheme for asymmetric alkynylation of aldehydes when (*S*)-BINOL and chiral sulfonamide are self-assembled.

Table 2.10 The results of the self-assembly experiments performed by Chan and co-workers.

Entry	aldehyde	yield (%)	ee (%)
1	benzaldehyde	83	96(*R*)
2	2-nitrobenzaldehyde	83	88(*R*)
3	3-nitrobenzaldehyde	82	99.7(*R*)
4	4-nitrobenzaldehyde	82	99(*R*)
5	4-bromobenzaldehyde	85	99(*R*)
6	3-chlorobenzaldehyde	84	97(*R*)
7	4-chlorobenzaldehyde	86	95(*R*)
8	2-naphthaldehyde	81	95(*R*)
9	4-anisaldehyde	78	95(*R*)
10	4-tolualdehyde	79	92(*R*)

2.1.3.7. Addition of Catalytic Amounts of Achiral Compounds (Achiral Activators)

In literature, it is given that catalytic asymmetric reactions are sometimes very sensitive to small changes. For example, addition of catalytic amounts of achiral compounds increases the yield and enantioselectivities.[83]

Chan group[84] reported that, chiral $Ti(O^iPr)_4$-BINOL complexes were activated by addition of phenol. Addition of this achiral activator increased the enantioselectivity compared to the reactions catalyzed by using the enantiopure chiral catalyst alone in the alkynylation of both aliphatic and aromatic aldehydes.

Pu and co-workers also reported that, addition of HMPA (hexamethylphosphoramide) to the catalyst system generated the alkynylzinc reagent at room temperature and the reaction afforded high enantioselectivity.[85]

Recent attempts to improve the activity and enantioselectivity of the asymmetric alkynylation led to the development of other types of chiral ligands including sulfonamide, N-terminal protected amino acid, cinchonidine, salen and ferrocenyl oxazoline (Figure 2.8). [86-94]

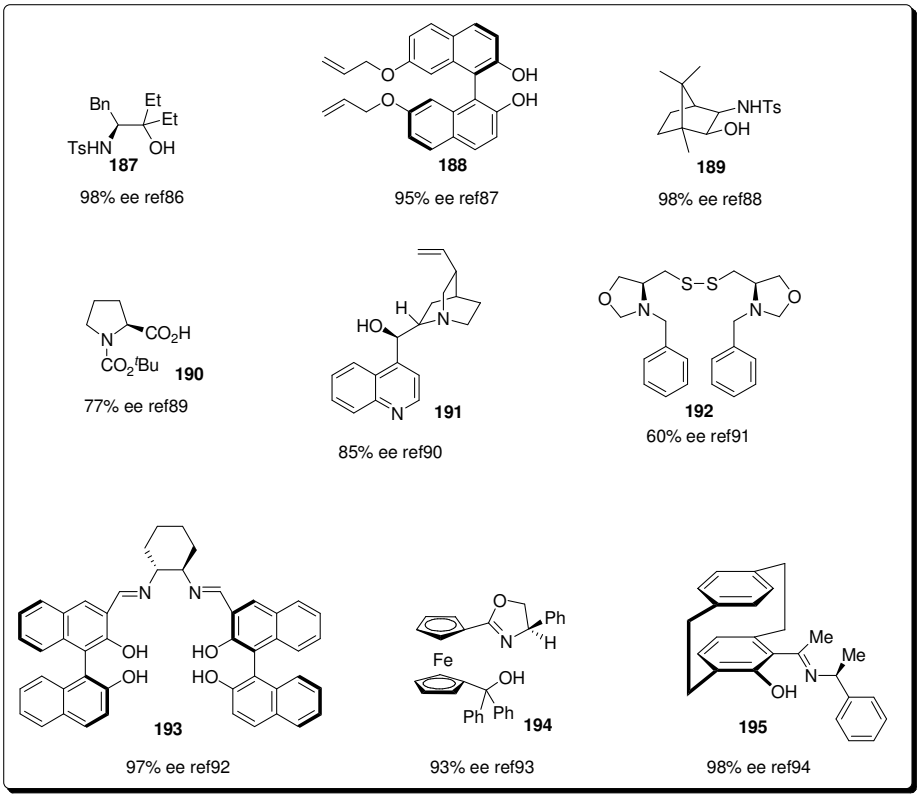
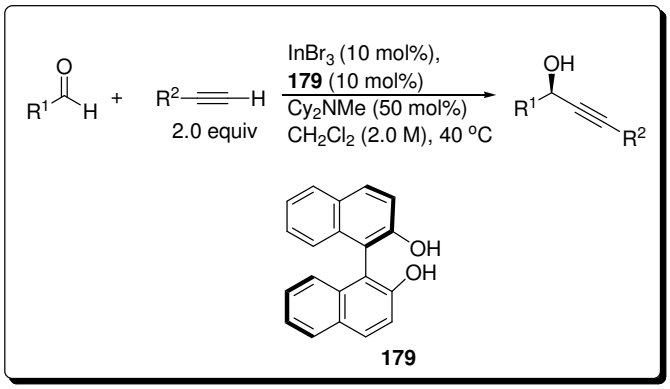


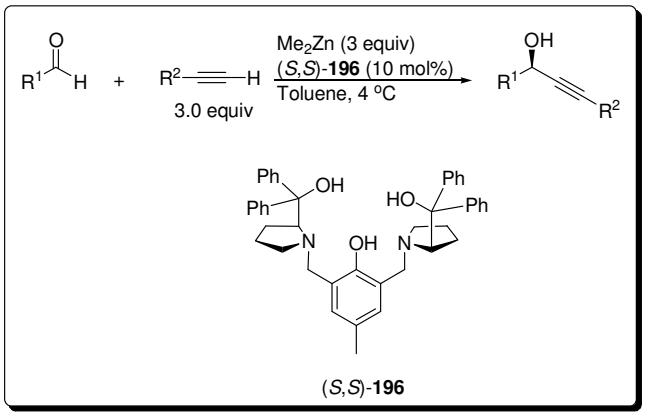
Figure 2.8 The various chiral ligands used by different research groups in the asymmetric alkynylation of aldehydes.

Shibasaki et al.[95] described a catalytic asymmetric alkynylation of both aliphatic and aromatic aldehydes, which are promoted by a chiral In(III)/BINOL complex (Scheme 2.20). This catalytic system has generality to phenylacetylene, alkenylacetylene and alkylacetylenes. Although 46-95% yield and up to >99% ee was achieved with aliphatic aldehydes, 61-85% yield and 83-99% ee was achieved with aromatic aldehydes.



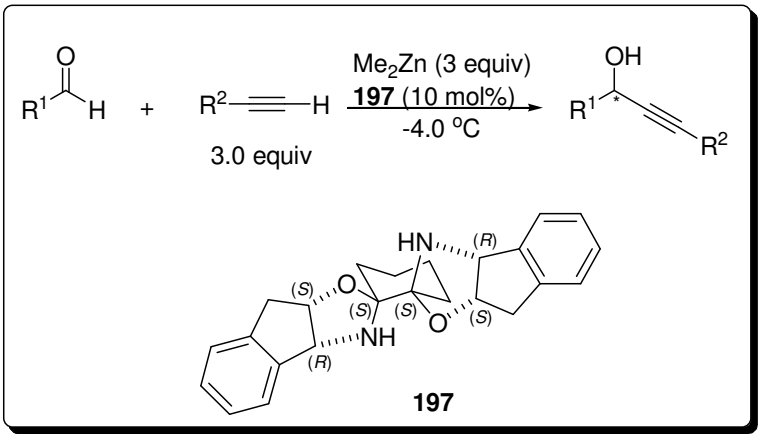
Scheme 2.20 The general reaction scheme for asymmetric alkynylation of aldehydes when (*R*)-BINOL and $InBr_3$ were used in catalytic amounts.

Trost et al.[96] used proline-derived chiral ligand (*S*,*S*)-**196** in asymmetric alkynylation of aromatic and α,β-unsaturated aldehydes in the presence of various acetylene derivatives (Scheme 2.21). Using 10 mol% of **196** in the presence of 3 equivalents of Me_2Zn, up to 95% yield and 99% ee was achieved with aromatic aldehydes. Use of α,β-unsaturated aldehydes for the same reaction gave the propargylic alcohols in better yields (100%) and similar ee's (95%).



Scheme 2.21 The general reaction scheme for asymmetric alkynylation of aldehydes when (*S*,*S*)-(**196**) was used in catalytic amount.

Another excellent catalyst was reported by Wolf and co-workers.[97] They used C_2-symmetric chiral ligand **197** in asymmetric alkynylation of aromatic, aliphatic and heteroaromatic aldehydes with phenylacetylene (Scheme 2.22). They observed that, aromatic and heteroaromatic aldehydes with phenylacetylene in the presence of 10 mol% of **197** gave the corresponding propargylic alcohols in excellent yields (up to 95%) and ee's (up to 94%). Their catalytic system was also suitable to both linear and branched aliphatic acetylenes, up to 96% yields and 95% ee's were reported with these acetylenes. When aliphatic aldehydes were used with phenylacetylene, products were obtained in excellent yields (99%) and good ee's (83%) by lowering the temperature to -15 ^{o}C.



Scheme 2.22 The general reaction scheme for asymmetric alkynylation of aldehydes by Wolf and co-workers.

2.1.4. Aim of This Study

As it was mentioned in Part I of this thesis, the aim of this study was to develop new chiral ligands and use these ligands with a metal as a chiral catalyst for the catalytic enantioselective synthesis of organic compounds.

In the first part of this thesis, aziridine based FAM (Ferrocenyl substituted AziridinylMethanols) ligands were synthesized for the first time. These ligands were used as a catalyst with zinc in 1,3-Dipolar Cycloaddition reactions of azomethine ylides with various dipolarophiles to synthesize chiral pyrrolidine derivatives.[45]

In the second part of this thesis, we aimed to use these chiral ligands in enantioselective synthesis of propargylic alcohols by the reaction of alkynylzinc addition to aldehydes.

CHAPTER 2.2

RESULTS AND DISCUSSION

2.2.1. Asymmetric Alkynylation of Aldehydes

Development of novel and more efficient catalysts for alkynylation of aldehydes is still needed.[56,69b,86-99] Most of the catalysts developed up to now concentrate on the asymmetric alkynylation of only one or two types of aldehydes (aromatic or aliphatic) with only phenylacetylene.

Limitations to some of the currently existing methods can be listed as:

- works only with aromatic aldehydes
- works only with phenylacetylene
- requires higher concentration of acetylenes and zinc reagents
- ligands require multistep synthesis
- requires longer reaction times (one to two days)

Therefore, there is still a demand for development of a catalyst system which can successfully alkynylate the broad range of aldehydes (aliphatic, aromatic, heteroaromatic, and α,β-unsaturated) and applicable to the acetylene derivatives other than phenylacetylene by using lower concentration of zinc reagents or terminal

acetylenes with shorter reaction times. [77b,88,94,96,97] In addition, the ligands should be synthesized on a gram scale with easy steps.

2.2.2. Some Applications of FAM Chiral Ligands in Organic Synthesis

Our group recently developed a set of Ferrocenyl substituted AziridinylMethanol (FAM) chiral ligands and used in catalytic enantioselective 1,3-DC reactions of azomethine ylides to obtain pyrrolidines in up to 95% ee (first part of this theses).[45] These ligands were also used in diethylzinc addition reactions to aldehydes[100] to obtain secondary alcohols in up to 99% ee's and enones[101] to obtain β-ethylated ketones in up to 80% ee's. Here, the FAM chiral ligands (**123**-**126**, for the synthesis of these ligands; see pages 51, 52, and 54 of this theses) (Figure 2.9) are tested in catalytic asymmetric alkynylation of various aldehydes.

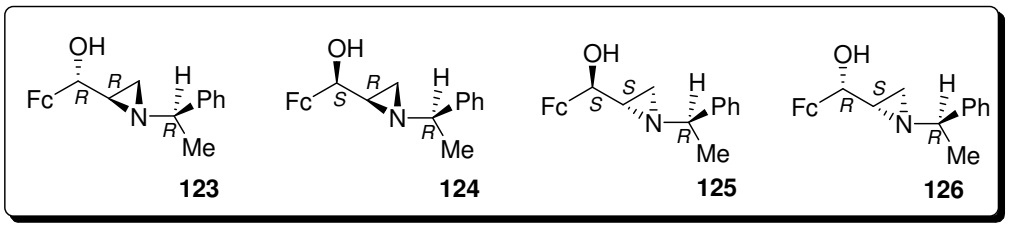


Figure 2.9 The chemical structures of chiral FAM ligands (**123**-**126**).

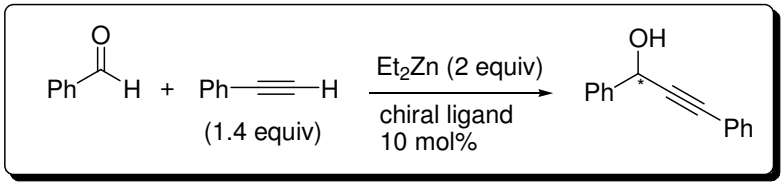
2.2.3. Asymmetric Alkynylation of Aldehydes by Using Chiral FAM Ligands

At the beginning of this study, the catalytic effect (10 mol%) of all four chiral ligands **123-126** were tested in enantioselective alkynylzinc addition to benzaldehyde (as shown in Scheme 2.23) under various reaction conditions. The results of these experiments are summarized in Table 2.11.

As seen from this table, benzaldehyde was treated with 1.4 equivalents of phenylacetylene, 2.0 equivalents of diethylzinc and 10 mol% of FAM-ligands (**123**,

124, **125**, or **126**). The reaction mixture was stirred at various temperatures for 18 to 28 hours. Using FAM-ligand **123**, the (*S*)-configured product was obtained in 92% yield and 22% ee at room temperature (entry 1). Enantioselectivity of the reaction was determined by chiral HPLC. Lowering the temperature to 0 ^{o}C, both yield and ee remained almost the same (entry 2). At -20 ^{o}C, the asymmetric addition product was obtained in 75% yield and 44% ee (entry 3). Since this was the highest ee obtained, we decided to use same reaction conditions to find out the catalytic effect of other chiral ligands (**124**, **125**, and **126**).

Although all the remaining ligands gave very similar results, the highest yield was obtained with chiral ligand **124** and highest ee was obtained with chiral ligand **125** (entries 4 and 5 respectively, for the configuration of the product obtained in each case see Table 2.11). We also searched for the amount of diethylzinc. Thus repeating the reaction at the same temperature and at a lower diethylzinc concentration (1.2 equivalents), the yield remained almost the same but the ee increased to 38% (entry 7). The increase in ee can be explained as follows: At low (1.2 equiv) diethylzinc concentration, the amount of alkynylzinc is low compared to high (3.0 equiv) diethylzinc concentration, as a result the reaction is slower and more selective.



Scheme 2.23 The general reaction scheme for testing the catalytic effects of chiral ligands (**123**-**126**).

Table 2.11 Optimization of the reaction conditions with different chiral ligands.

Entry	ligand	Et_2Zn(equiv)	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	**123**	2.0	rt	18	92	22 (*S*)
2	**123**	2.0	0	20	90	26 (*S*)
3	**123**	2.0	–20	28	75	44 (*S*)
4	**124**	2.0	–20	28	78	32 (*S*)
5	**125**	2.0	–20	28	60	46 (*R*)
6	**126**	2.0	–20	28	72	34 (*R*)
7	**123**	1.2	0	28	93	38 (*S*)

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

2.2.4. Asymmetric Alkynylation of Aldehydes in The Presence of Catalytic Amounts of $Ti(O^iPr)_4$

In the literature, various chiral ligand-Ti complexes[76,77b,88] were reported in asymmetric addition reactions of alkynylzinc to aromatic and aliphatic aldehydes in very high enantioselectivities.

Therefore, we decided to use titanium with our FAM ligands in the asymmetric alkynylzinc addition to benzaldehyde. Results of the experiments are summarized in Table 2.12. Thus using 0.5 equivalents of titanium under the same reaction conditions, the chiral product was obtained in 91% yield and 96% ee (entry 1). This was the highest ee obtained so far. Here, we also observed that the configuration of the addition product changed to (*R*) in the presence of $Ti(O^iPr)_4$. Encouraged with this result, we repeated the reaction with lower concentration of titanium complex (0.25 equiv) and obtained the product in about the same yield and ee (entry2). Then we have done another reaction at a shorter reaction time (5h) which gave the product again in about the same yield and ee (entry 3). Finally we looked for the results with lower ligand concentration. When 5 mol% ligand **123** was used, the product was

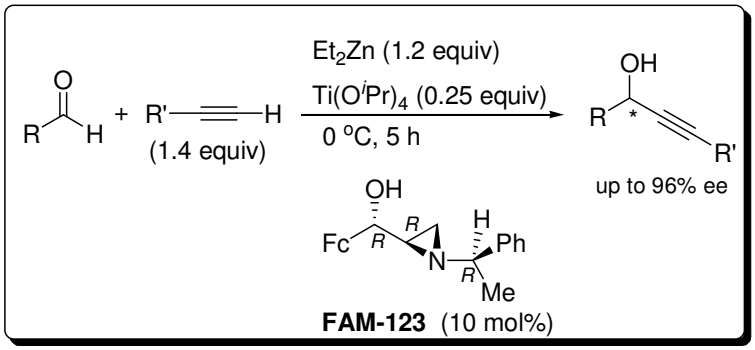
obtained in 35% yield and 82% ee (entry 4). Increasing the reaction time with 5 mol% ligand, increased the yield but the ee remained almost the same (entry 5). The decrease in ee at low ligand loading can be attributed to the background reaction. After determining that the best conditions are 1.2 equivalents of diethylzinc, 10 mol% ligand, 0.25% titanium, 0 ^{o}C, and 5h reaction time, the other chiral ligands **124**, **125**, and **126** were also tried under these optimized conditions. Ligand **124** gave the product with low yield but with acceptible ee. Ligand **125** gave the product with satisfactory yield and good ee. In the case of ligand **126**, the reaction was almost non-stereoselective. (entries 6, 7, and 8 respectively).

Table 2.12 Optimization of the reaction conditions in the presence of $Ti(O^{i}Pr)_4$.

Entry	ligand	Et_2Zn (equiv)	$Ti(O^{i}Pr)_4$ (equiv)	temp (^{o}C)	time (h)	yield (%)[a]	ee (%)[b]
1	**123**	1.2	0.50	0	18	91	96 (*R*)
2	**123**	1.2	0.25	0	18	91	92 (*R*)
3	**123**	1.2	0.25	0	**5**	**92**	**96 (*R*)**
4[c]	**123**	1.2	0.25	0	5	35	82 (*R*)
5[c]	**123**	1.2	0.25	0	10	66	82 (*R*)
6	**124**	1.2	0.25	0	5	53	70 (*R*)
7	**125**	1.2	0.25	0	5	71	86 (*S*)
8	**126**	1.2	0.25	0	5	57	8 (*R*)

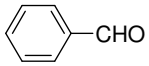
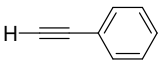
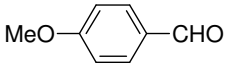
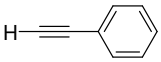
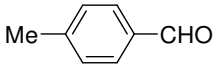
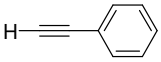
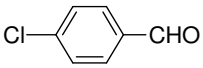
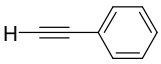
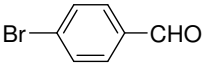
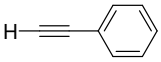
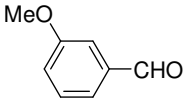
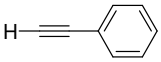
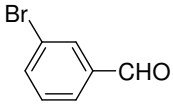
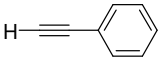
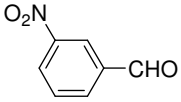
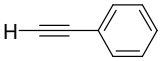
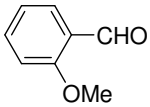
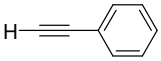
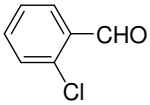
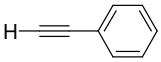
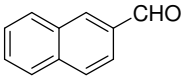
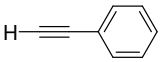
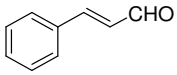
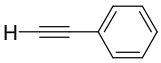
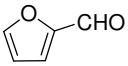
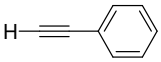
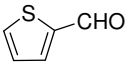
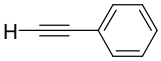
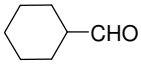
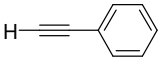
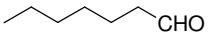
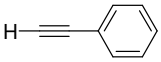
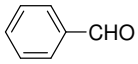
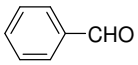
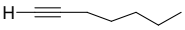
[a] Isolated yields. [b] Determined by chiral HPLC. [c] 5 mol % ligand was used.

In order to find out the scope and limitations of our catalyst system [FAM **123**-Ti], the reactions were repeated with different aldehydes and acetylenes (Scheme 2.24). The results of these studies are summarized in Table 2.13.



Scheme 2.24 The general reaction scheme using catalytic amounts of $Ti(O^iPr)_4$ and FAM-(**123**).

Table 2.13 The results of the asymmetric alkynylation reactions of various aldehydes and acetylenes.

Entry	aldehyde	alkyne	yield (%)[a]	ee(%)[b]
1			92[c]	96[c]
2			90	96
3			93	92
4			91 (89)[c]	94 (92)[c]
5			91	92
6			91	96
7			91	92
8			85	78
9			91	92
10			96	64
11			90 (90)[c]	96 (98)[c]
12			87	92
13[d]			93	96
14[d]			92	96
15			96	86
16			93	88
17[d]			84	94
18[d]			80	94

[a] Isolated yields. [b] Determined by chiral HPLC. [c] Obtained with recovered ligand. [d] 2.0 equiv of Et_2Zn and alkyne were used, reaction time was 17 h for entries 17and 18.

As can be seen from Table 2.13, this catalytic system worked very efficiently in asymmetric alkynylation of aromatic (*ortho*-, *meta*-, and *para*-substituted), α,β-unsaturated, heteroaromatic and aliphatic aldehydes. The *para*-substituted benzaldehyde derivatives were alkynylated in very high yields and enantioselectivities (entries 2, 3, 4 and 5). In the case of *meta*-methoxy and *meta*-bromo-substituents, the corresponding propargylic alcohols were also obtained in very high yields and enantioselectivities (entries 6 and 7). With the strong electron withdrawing NO_2 group at the *meta*-position, the yield was good but the ee was low (entry 8).

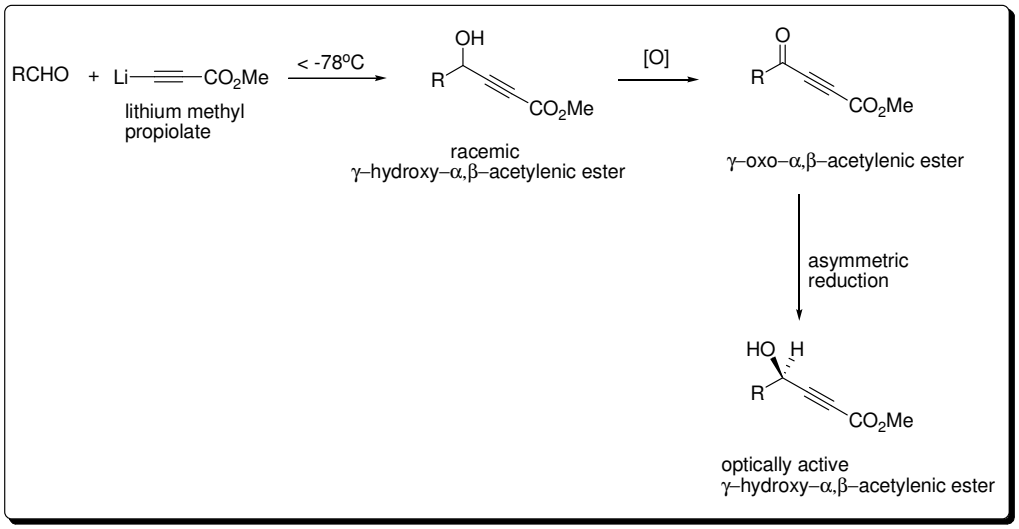
In the *ortho*-substituted benzaldehyde cases, methoxy substituent gave the product in high yield and ee, but the chloro-substituent gave the product in good yield and poor ee (entries 9 and 10). We do not have a good explanation for this observation. When 2-naphthaldehyde was used, again the expected product was obtained in 90% yield and 96% ee (entry 11). This catalyst system also worked very efficiently with α,β-unsaturated and heteroaromatic aldehydes. From these aldehydes, the corresponding propargylic alcohols were obtained in excellent enantioselectivities and yields (entries 12, 13 and 14). Our catalyst system also gave very good results with aliphatic aldehydes as well. Using cyclohexanecarbaldehyde, the product was obtained in 96% yield and 86% ee (entry 15). In the case of heptanal, propargylic alcohol was obtained in 93% yield and 88% ee (entry 16). Besides phenylacetylene, as an acetylene source, 1-hexyne and 1-heptyne were also tried. In the first case, the product was obtained in 84% yield and 94% ee (entry 17). In the second case, the product was obtained in 80% yield and 94% ee (entry 18). With the last two acetylenes in order to reach high yields of products, it was necessary to use 2.0 equivalents of diethylzinc and alkylacetylenes at a longer reaction times (17h).[102]

In our study, it is important to note that, FAM-**123** can be recovered in more than 90% yield and recycled without losing its activity. Repeating the reactions with recovered ligand with some of the previously used aldehydes, the corresponding

products were obtained in 89-92% yield and in 92-98% ee (entries 1, 4 and 11). Another important point is the selectivity of the ligands. Based on the HPLC results, we can say that, chiral ligands **123** and **124** with (*R*)-configuration at aziridine center gives the product with (*R*)-configuration when benzaldehyde was used as the starting material. On the other hand, chiral ligand **125** with (*S*)-configuration at aziridine center gives the product in low yield and ee with (*S*)-configuration.

2.2.5. The Synthesis of chiral γ-Hydroxy-α,β-Acetylenic Esters

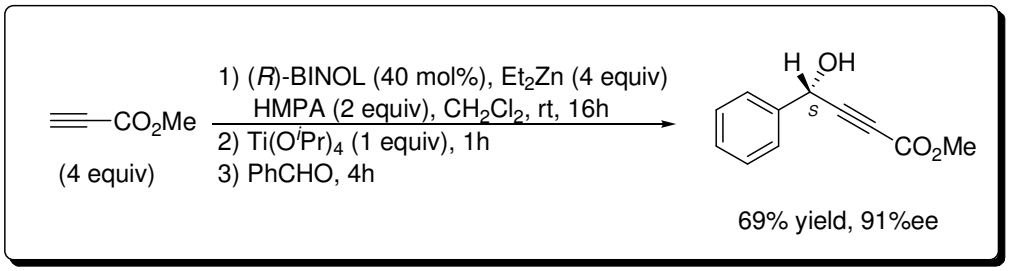
In addition to the synthesis of chiral propargylic alcohols, we tried to synthesize chiral γ-hydroxy-α,β-acetylenic esters in the catalytic presence of chiral FAM ligands. It is known that, γ-hydroxy-α,β-acetylenic esters are very useful in the synthesis of highly functionalized organic molecules. Because they are containing three adjacent and structurally very different functional groups.[103,104] It is known that, asymmetric γ-hydroxy-α,β-acetylenic esters are generally prepared in three steps. In the first step, alkyl propiolate is treated with *n*BuLi at ≤ -78 ^{o}C to obtain lithium alkyl propiolate and it is added to aldehyde to obtain racemic γ-hydroxy-α,β-acetylenic ester. In the second step, γ-hydroxy-α,β-acetylenic ester is oxidized to γ-oxo-α,β-acetylenic ester. Finally the asymmetric reduction of γ-oxo-α,β-acetylenic ester leads to chiral γ-hydroxy-α,β-acetylenic ester (Scheme 2.25).[103] A milder method was reported recently by Shahi and Koide in which, $AgC{\equiv}CCO_2Me$ was reacted in the presence of $[Cp_2ZrCl_2]$ and AgOTf with aldehydes at room temperature.[105]



Scheme 2.25 The general synthesis of γ-hydroxy-α,β-acetylenic esters.

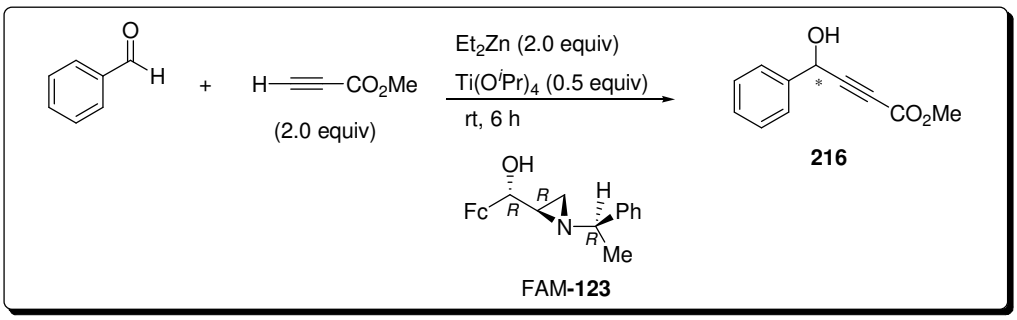
Although there has been a major progress in terms of asymmetric alkyne addition to aldehydes, limited studies were published in terms of enantioselective addition reaction of alkynoates to aldehydes. The direct synthesis of chiral γ-hydroxy-α,β-acetylenic esters by the enantioselective alkynoate addition to aromatic and α,β-unsaturated aldehydes was reported by Pu and co-workers (Scheme 2.26).[106] This was the first systematic study for the direct synthesis of chiral γ-hydroxy-α,β-acetylenic esters in the literature.

In this study, they reported a highly enantioselective method for the addition of methyl propiolate to aromatic and α,β-unsaturated aldehydes. Up to 96% yield and 95% ee was achieved by using 40 mol% of the ligand with 4 equivalents of diethylzinc and methyl propiolate.



Scheme 2.26 The general reaction scheme of asymmetric addition of methyl propiolate to benzaldehyde in the presence of (*R*)-BINOL, Et_2Zn, HMPA and $Ti(O^iPr)_4$.

We have also tried methyl propiolate addition to benzaldehyde using our chiral ligand FAM-**123** to synthesize chiral γ-hydroxy-α,β-acetylenic esters (Scheme 2.27).



Scheme 2.27 The general reaction scheme for the reaction of methyl propiolate in the presence of chiral ligand (**123**).

At the beginning of the study, we used our standard reaction conditions, 10 mol% of chiral ligand **123,** 1.2 equiv of Et_2Zn, 1.4 equiv of methyl propiolate and 0.25 equiv of $Ti(O^iPr)_4$ at 0 ^oC. Although the reaction mixture was stirred for 24 h at this temperature, the product formation was very slow. In a second study, the same reaction was repeated by increasing the amounts of Et_2Zn and methyl propiolate to

2.0 equivalents, but there was no observable change in the reaction (TLC showed no increase on the product formation). Since the reaction was very slow at 0 ^{o}C, another experiment was carried out at room temperature by doubling the amount of $Ti(O^{i}Pr)_4$ and keeping others at the same amounts. The reaction mixture was stirred at room temperature for 6h and then worked-up. Analysis of the product showed that the yield was 40% and ee was 90% (Table 2.14, entry 1). Increasing the amount of chiral ligand (under the same reaction conditions) to 20 mol%, the yield and ee was almost the same, 42% and 92% respectively (entry 2). When the time of stirring was increased to ~20 h, the yield and enantioselectivity was not effected significantly. We have also increased the amounts of Et_2Zn, and methyl propiolate to 3 equivalents. But, again very similar results were obtained (40% yield and 86% ee, entry 3).

Table 2.14 The results of the reaction of methyl propiolate with benzaldehyde.

Entry	chiral ligand	time (h)	yield (%)	ee (%)
1	**123**[a]	6h rt	40	90
2	**123**[b]	6h rt	42	92
3	**123**[a]	6h rt	40	86

[a] chiral ligand was used 10 mol%. [b] chiral ligand was used 20 mol%.

Finally we have also tried adding HMPA to the reaction medium (0.25 equiv to 1.00 equiv) as in the study of Pu[106] and co-workers. Unfortunatelly, there was no improvement in the yield of the reaction.

CHAPTER 2.3

CONCLUSION

As a conclusion, it is possible to say that a novel catalyst system was developed by using FAM-**123** and the titanium complex that can catalyze alkynylzinc addition reactions to aldehydes to yield chiral propargylic alcohols in good to excellent yields and enantioselectivities. When compared to the similar studies in the literature, the reactions can be conducted at a lower concentration of Et_2Zn and acetylene derivative and at a shorter reaction times. Although, most of the catalyst systems reported in literature worked with aromatic or aliphatic aldehydes with only phenylacetylene, the catalyst system developed in this study worked with four different types of aldehydes (aromatic, aliphatic, heteroaromatic and α,β-unsaturated) and with two aliphatic acetylenes very efficiently.[110] Additionally, chiral γ-hydroxy-α,β-acetylenic ester can be synthesized using benzaldehyde and methyl propiolate in the catalytic presence of chiral ligand **123** in low yields but very high ee's.

Also, it is important to note that, FAM-chiral ligands can be synthesized from acryloyl ferrocene in very high yields and enantiopurity in three easy steps. It is also possible to synthesize both enantiomers of these ligands easily starting from commercially available (*R*)-(+)-1-phenylethylamine or (*S*)-(-)-1-phenylethylamine. Finally the chiral ligand can be recovered and recycled without losing its activity.

CHAPTER 2.4

EXPERIMENTAL

2.4.1. General Consideration

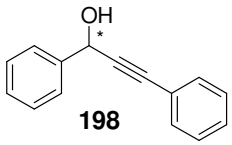
All reactions were performed under a nitrogen or argon atmosphere in oven-dried glassware unless reported. Tetrahydrofuran (THF) was dried and distilled over Na-benzophenone prior to use. All reagents were purchased commercially and used without further purification unless stated otherwise. Chiral Ligand Fam (ferrocenyl substituted aziridinyl methanol) was weighed into a pre-dried flask attached to a vacuum line and heated with a heat gun to remove any moisture and then dissolved in dry THF before transferring into the reaction flask. Liquid aldehydes were used directly from their commercial bottles unless stated otherwise (only benzaldehyde and furfural were distilled before use). Solid aldehydes were also directly used from their commercial bottle (only 4-chlorobenzaldehyde was distilled via bulb to bulb distillation). Solid aldehydes were weighed into a pre-dried sample tube which was attached to a vacuum-argon line. Sample tube was filled with argon atmosphere and aldehyde was dissolved in THF and transferred via syringe into the reaction medium. All of the products were purified by flash column chromatography on silica gel 60 (Merck, 230–400 mesh ASTM). TLC analyses were performed on 250 µm Silica Gel 60 F254 plates and visualized by quenching of the UV fluorescence at 254 nm. Unless indicated otherwise, ^{1}H-NMR and ^{13}C-NMR samples were prepared in 1:1 $CDCl_3$-CCl_4 and recorded at 400 MHz and 100 MHz, respectively. ^{1}H-NMR data are reported as chemical shifts (δ, ppm) relative to tetramethylsilane (δ 0.00), multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad

singlet), coupling constant (Hz) and integration. Proton decoupled ^{13}C-NMR data are reported as chemical shifts. Enantiomeric excess (ee) was determined by chiral HPLC analysis using a chiral stationary phase (Daicel Chiralcel OD-H, Daicel Chiralcel OJ-H or Daicel Chiralcel OD), eluting with *i*-PrOH-hexanes, and using UV detection at 254 nm unless stated otherwise.

2.4.2. Representative General Procedure For The Addition of Acetylene Derivatives to Aldehydes

Chiral ligand Fam-**123** (0.0554 mmol, 20 mg) was weighed into a pre-dried flask which was attached to a vacuum-argon line. After vacuum, the flask was filled with argon and freshly distilled THF (1.15 mL, dried over sodium-benzophenone), Et_2Zn (0.665 mmol, 1M solution in hexanes) and phenylacetylene (0.776 mmol, 85.2 μL) were added. This homogenous mixture was stirred at room temperature for 2 hours. Then, freshly distilled $Ti(O^iPr)_4$ (0.139 mmol, 41 μL) was added and this final mixture was stirred for 1 hour. At the end of this period, reaction mixture was cooled to 0 ^oC and aldehyde (0.554 mmol) was added and the reaction was allowed to proceed for 5h at this temperature. Saturated ammonium chloride (3 mL) was added to quench the reaction, and ethyl acetate (3x10 mL) was used for extraction. The organic phase was combined, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with hexane/ethyl acetate (10:1) as the eluent to afford the propargylic alcohol. Enantiomeric excess valus were determined by chiral HPLC.

2.4.2.1. 1,3-Diphenyl-prop-2-yn-1-ol (198):

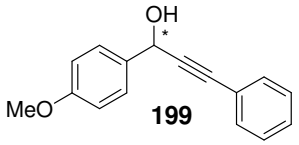


198

92% isolated yield, 96% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 13.9 min and t_R(minor)= 19.9 min. $[\alpha]_D^{27}$ = + 2.4 (*c* 1.67, $CHCl_3$), lit[95]. $[\alpha]_D^{23}$ = + 3.1 (*c* 3.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59-7.57 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.46-

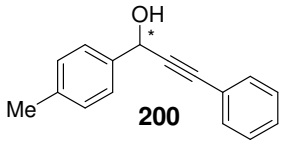
7.43 (m, 2H, Ar-H), 7.39-7.35 (m, 2H, Ar-H), 7.31-7.29 (m, 4H, Ar-H), 5.64 (s, 1H), 2.16 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 131.8, 128.6, 128.5, 128.3, 128.2, 126.7, 122.6, 89.0, 86.6, 65.0.

2.4.2.2. 1-(4-Methoxyphenyl)-3-phenyl-prop-2-yn-1-ol (199):



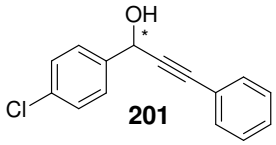
90% isolated yield, 96% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 17.5 min and t_R(minor)= 28.9 min. $[\alpha]_D^{28}$ = + 5.6 (*c* 2.26, $CHCl_3$), lit[88]. $[\alpha]_D^{15}$ = + 3 (*c* 0.93, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52-7.50 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.48-7.45 (m, 2H, Ar-H), 7.31-7.30 (m, 3H, Ar-H), 6.90-6.88 (d, *J* = 8.6 Hz, 2H, Ar-H), 5.60 (d, *J* = 4.4 Hz, 1H), 3.81 (s, 3H), 2.24 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 133.1, 131.7, 128.4, 128.2, 128.1, 122.7, 113.9, 89.2, 86.4, 64.6, 55.1.

2.4.2.3. 3-Phenyl-1-p-tolyl-prop-2-yn-ol (200):



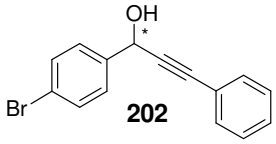
93% isolated yield, 92% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 11.1 min and t_R(minor)= 19.9 min. $[\alpha]_D^{28}$ = + 4.8 (*c* 1.00, $CHCl_3$), lit[107]. $[\alpha]_D^{20}$ = + 4.02 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (m, 4H, Ph), 7.30-7.29 (m, 3H, Ph), 7.19-7.17 (d, *J* = 7.9 Hz, 2H), 5.61 (d, *J* = 6.1 Hz, 1H), 2.37 (s, 3H), 2.12 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 131.8, 129.3, 128.4, 128.2, 126.7, 122.6, 89.1, 86.5, 64.9.

2.4.2.4. 1-(4-Chlorophenyl)-3-phenyl-prop-2-yn-1-ol (201):



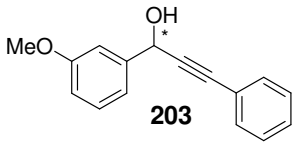
91% isolated yield, 94% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 14.8 min and t_R(minor)= 47.8 min. $[\alpha]_D^{28}$ = + 7.2 (*c* 1.25, $CHCl_3$), lit[88]. $[\alpha]_D^{15}$ = + 6 (*c* 0.72, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.44-7.42 (m, 2H, Ar-H), 7.35-7.29 (m, 5H, Ar-H), 5.62 (s, 1H), 2.27 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 134.3, 131.7, 128.7, 128.6, 128.3, 128.0, 122.3, 88.4, 86.9, 64.3.

2.4.2.5. 1-(4-Bromophenyl)-3-phenyl-prop-2-yn-1-ol (202):



91% isolated yield, 92% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 14.5 min and t_R(minor)= 47.5 min. $[\alpha]_D^{28}$ = + 6.2 (*c* 1.39, $CHCl_3$), lit[88]. $[\alpha]_D^{15}$ = + 4 (*c* 0.76, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.41 (m, 6H, Ar-H), 7.33-7.27 (m, 3H, Ar-H), 5.60 (s, 1H), 2.35 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 131.7, 131.6, 128.7, 128.3, 128.2, 122.4, 122.2, 88.4, 87.0, 64.3.

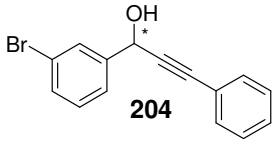
2.4.2.6. 1-(3-Methoxyphenyl)-3-phenyl-prop-2-yn-1-ol (203):



91% isolated yield, 96% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 24.8

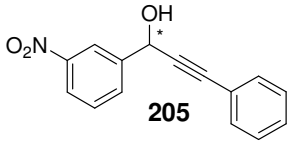
min and t_R(minor)= 38.3 min. $[\alpha]_D^{28}$ = + 15.7 (*c* 1.03, $CHCl_3$), lit[77a]. $[\alpha]_D^{27}$ = + 11.4 (*c* 1.32, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H, Ar-H), 7.30-7.25 (m, 4H, Ar-H), 7.17-7.14 (m, 2H, Ar-H), 6.84 (d, *J* = 8.2 Hz, 1H), 5.62 (d, *J* = 6.0 Hz, 1H), 3.83 (s, 3H), 2.18 (d, *J* = 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 142.3, 131.8, 129.6, 128.5, 128.2, 122.6, 118.9, 114.1, 112.1, 88.9, 86.6, 64.9, 55.1.

2.4.2.7. 1-(3-Bromophenyl)-3-phenyl-prop-2-yn-1-ol (204):



91% isolated yield, 92% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 14.7 min and t_R(minor)= 53.8 min. $[\alpha]_D^{25}$ = + 12.9 (*c* 1.52, $CHCl_3$), lit[88]. $[\alpha]_D^{15}$ = + 6 (*c* 0.92, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H, Ar-H), 7.50 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.45-7.43 (m, 3H, Ar-H), 7.31-7.29 (m, 3H, Ar-H), 7.24 (t, *J* = 7.8 Hz, 1H, Ar-H), 5.61 (s, 1H), 2.34 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9, 131.8, 131.3, 130.0, 129.8, 128.7, 128.3, 125.2, 122.7, 122.2, 88.2, 87.1, 64.2.

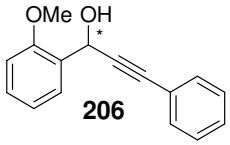
2.4.2.8. 1-(3-nitrophenyl)-3-phenylprop-2-yn-1-ol (205):



85% isolated yield 78% ee determined by HPLC analysis (Chiralcel OJ-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 42.6 min and t_R(minor)= 73.5 min. $[\alpha]_D^{26}$ = + 34.6 (*c* 1.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H, Ar-H), 8.17 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.92 (d, *J* = 7.6 Hz,

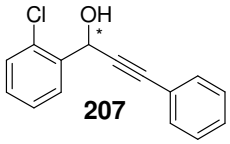
1H, Ar-H), 7.54 (t, J = 7.9 Hz, 1H, Ar-H), 7.44 (d, J = 7.4 Hz, 2H, Ar-H), 7.35-7.29 (m, 3H, Ar-H), 5.76 (s, 1H), 2.71 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 142.8, 132.5, 131.8, 129.4, 129.0, 128.4, 123.1, 121.8, 121.7, 87.7, 87.6, 63.9.

2.4.2.9. 1-(2-Methoxyphenyl)-3-phenyl-prop-2-yn-1-ol (206):



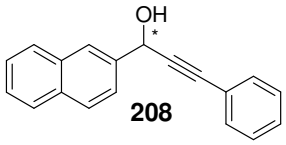
91% isolated yield, 92% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 16.3 min and t_R(minor)= 19.9 min. $[\alpha]_D^{28}$ = - 11.8 (c 1.22, $CHCl_3$), lit[88]. $[\alpha]_D^{18}$ = - 8 (c 0.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.8 Hz, 1H, Ar-H), 7.46-7.43 (m, 2H, Ar-H), 7.30-7.24 (m, 4H, Ar-H), 6.97 (t, J = 7.5 Hz, 1H, Ar-H), 6.90 (d, J = 8.2 Hz, 1H, Ar-H), 5.86 (br, 1H), 3.92 (s, 3H), 2.85 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 131.8, 129.5, 129.2, 128.2, 128.1, 128.0, 123.0, 121.0, 110.8, 88.7, 85.9, 61.5, 55.5.

2.4.2.10. 1-(2-chlorophenyl)-3-phenylprop-2-yn-1-ol (207):



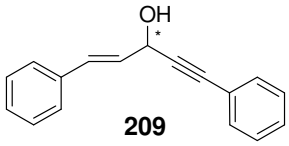
96% isolated yield, 64% ee determined by HPLC analysis (Chiralcel OD column 2% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 37.7 min and t_R(minor)= 55.5 min. $[\alpha]_D^{26}$ = - 30.5 (c 1.48, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.4 Hz, 1H, Ar-H), 7.44-7.42 (m, 2H, Ar-H), 7.37 (d, J = 7.7 Hz, 1H, Ar-H), 7.32-7.23 (m, 5H), 6.00 (s, 1H), 2.57 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 132.8, 131.8, 129.7, 129.5, 128.5, 128.4, 128.2, 127.2, 122.4, 87.8, 86.6, 62.4.

2.4.2.11. 1-(Naphthalen-2-yl)-3-phenyl-prop-2-yn-1-ol (208):



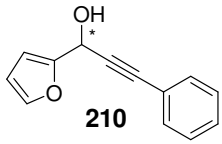
90% isolated yield, 96% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 16.5 min and t_R(minor)= 49.7 min. $[\alpha]_D^{28}$ = - 7.8 (*c* 1.30, $CHCl_3$), lit[88]. $[\alpha]_D^{19}$ = - 12 (*c* 2.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, Ar-H), 7.84-7.78 (m, 3H, Ar-H), 7.68 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.47-7.44 (m, 4H, Ar-H), 7.30-7.26 (m, 3H, Ar-H), 5.80 (s, 1H), 2.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 133.3, 133.2, 131.8, 128.5, 128.3, 127.7, 126.2, 125.5, 124.7, 122.6, 88.9, 86.9, 65.2.

2.4.2.12. 1,5-Diphenyl-pent-1-en-4-yn-3-ol (209):



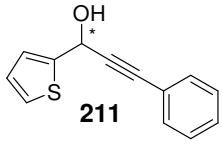
87% isolated yield 92% ee determined by HPLC analysis (Chiralcel OD column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 24.1 min and t_R(minor)= 66.3 min. $[\alpha]_D^{26}$ = + 0.5 (*c* 1.25, $CHCl_3$), lit[88]. $[\alpha]_D^{15}$ = + 1 (*c* 2.58, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (m, 2H. Ar-H), 7.39 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.30-7.20 (m, 6H, Ar-H), 6.79 (d, *J* = 15.8 Hz, 1H), 6.34 (dd, *J* = 15.8 & 5.9 Hz, 1H), 5.23 (d, *J* = 5.5 Hz, 1H), 2.08 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 131.9, 131.8, 128.5, 128.4, 128.3, 128.2, 128.0, 126.8, 122.6, 88.2, 86.4, 63.4.

2.4.2.13. 1-(Furan-2-yl)-3-phenyl-prop-2-yn-1-ol (210):



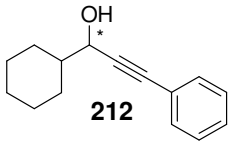
77% isolated yield, 96% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 13.4 min and t_R(minor)= 27.1 min. $[\alpha]_D^{28}$ = + 10.4 (*c* 1.12, $CHCl_3$), lit[107]. $[\alpha]_D^{25}$ = + 34 (*c* 0.58, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 2H, Ar-H), 7.40 (s, 1H, Ar-H), 7.30-7.24 (m, 3H, Ar-H), 6.48 (d, *J* = 2.8 Hz, 1H), 6.34 (s, 1H), 5.63 (s, 1H), 2.46 (br, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.1, 142.8, 131.8, 128.6, 128.2, 122.3, 110.4, 107.7, 86.4, 85.7, 58.6.

2.4.2.14. 3-Phenyl-1-(thiophen-2-yl)prop-2-yn-1-ol (211):



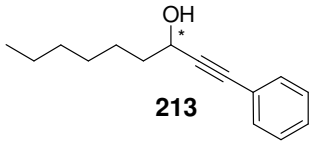
73% isolated yield 96% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 11.3 min and t_R(minor)= 21.1 min. $[\alpha]_D^{28}$ = + 20.7 (*c* 1.07, $CHCl_3$), lit[108]. $[\alpha]_D$ = + 20 (*c* 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H, Ar-H), 7.25-7.21 (m, 4H, Ar-H), 7.15 (d, *J* = 3.2 Hz, 1H, Ar-H), 6.91 (t, *J* = 4.2 Hz, 1H, Ar-H), 5.77 (br s, 1H), 2.27 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 131.8, 128.7, 128.3, 126.7, 126.0, 125.5, 122.3, 88.2, 86.0, 60.7.

2.4.2.15. 1-Cyclohexyl-3-phenyl-prop-2-yn-1-ol (212):



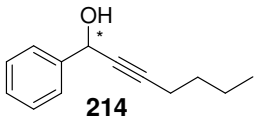
96% isolated yield 86% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 7.7 min and t_R(minor)= 14.9 min. $[\alpha]_D^{27}$ = - 8.8 (*c* 1.29, $CHCl_3$), lit[74a]. $[\alpha]_D^{26}$ = - 9.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.38 (m, 2H, Ar-H), 7.28-7.26 (m, 3H, Ar-H), 4.33 (d, *J* = 5.9 Hz, 1H, Ar-H), 1.93-1.91 (m, 2H), 1.81-1.78 (m, 2H), 1.72-1.58 (m, 2H), 1.34-1.08 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 128.2, 122.9, 89.4, 85.7, 67.5, 44.3, 28.7, 28.3, 26.5, 26.0.

2.4.2.16. 1-Phenylnon-1-yn-3-ol (213):



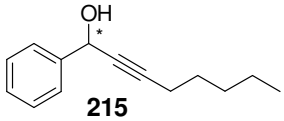
93% isolated yield 88% ee determined by HPLC analysis (Chiralcel OD-H column 10% IPA in hexanes, flow rate = 1.0 mL/min, 254 nm). Retention time: t_R(major)= 7.2 min and t_R(minor)= 16.5 min. $[\alpha]_D^{26}$ = - 4.6 (*c* 1.41, $CHCl_3$), lit[109]. $[\alpha]_D^{23}$ = - 1.5 (*c* 0.69, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H, Ar-H), 7.28-7.25 (m, 3H, Ar-H), 4.55 (t, *J* = 6.5 Hz, 1H), 1.85 (bs, 1H), 1.82-1.71 (m, 2H), 1.56-1.47 (m, 2H), 1.40-1.32 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.7, 128.2, 122.8, 90.4, 84.8, 62.9, 37.9, 31.8, 29.0, 25.2, 22.6, 14.1.

2.4.2.17. 1-Phenylhept-2-yn-1-ol (214):



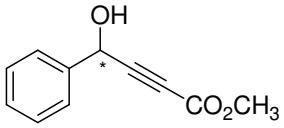
80% isolated yield 94% ee determined by HPLC analysis (Chiralcel OD-H column 6% EtOH in hexanes, flow rate = 1.0 mL/min, 214 nm). Retention time: t_R(minor)= 6.7 min and t_R(major)= 10.2 min. $[\alpha]_D^{28}$ = + 16.8 (*c* 1.13, $CHCl_3$), lit[70]. $[\alpha]_D$ = + 5.44 (*c* 5.08, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.35-7.24 (m, 3H, Ar-H), 5.39 (bs, 1H), 2.27 (dt, *J* = 1,8 & 7.0 Hz, 2H), 2.01 (bs, 1H), 1.49-1.39 (m, 2H), 1.57-1.50 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 128.4, 128.0, 126.6, 87.3, 80.3, 64.7, 30.7, 22.0, 18.5, 13.6.

2.4.2.18. 1-Phenyloct-2-yn-1-ol (215):



84% isolated yield 94% ee determined by HPLC analysis (Chiralcel OD-H column 6% EtOH in hexanes, flow rate = 1.0 mL/min, 214 nm). Retention time: t_R(minor)= 6.5 min and t_R(major)= 9.9 min. $[\alpha]_D^{28}$ = + 15.5 (*c* 1.14, $CHCl_3$), lit[62]. $[\alpha]_D$ = + 16.1 (*c* 1.1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.36-7.24 (m, 3H, Ar-H), 5.40 (bs, 1H), 2.25 (dt, *J* = 1,8 & 7.1 Hz, 2H), 2.01 (bs, 1H), 1.59-1.49 (m, 2H), 1.42-1.29(m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 128.4, 128.0, 126.6, 87.4, 80.3, 64.7, 31.1, 28.3, 22.2, 18.8, 14.0.

2.4.2.19. Methyl 4-hydroxy-4-phenylbut-2-ynoate (216):



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42% yield, and 92% ee determined by HPLC analysis (Chiralcel OD column 10% *i*PrOH in hexane flow rate = 1 mL/min, 230 nm). Retention time: t_R(minor)= 12.9 min, and t_R(major)= 16.6 min. ^{1}H NMR (400 MHz, $CDCl_3$) 7.43 (d, J = 7.1 Hz, 2H, Ar-H), 7.33 (m, 3H, Ar-H), 5.47 (bs, 1H), 3.71 (s, 3H), 2.44 (s, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 138.1, 128.3, 126.1, 86.1, 77.1, 63.7, 52.1.

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APPENDIX

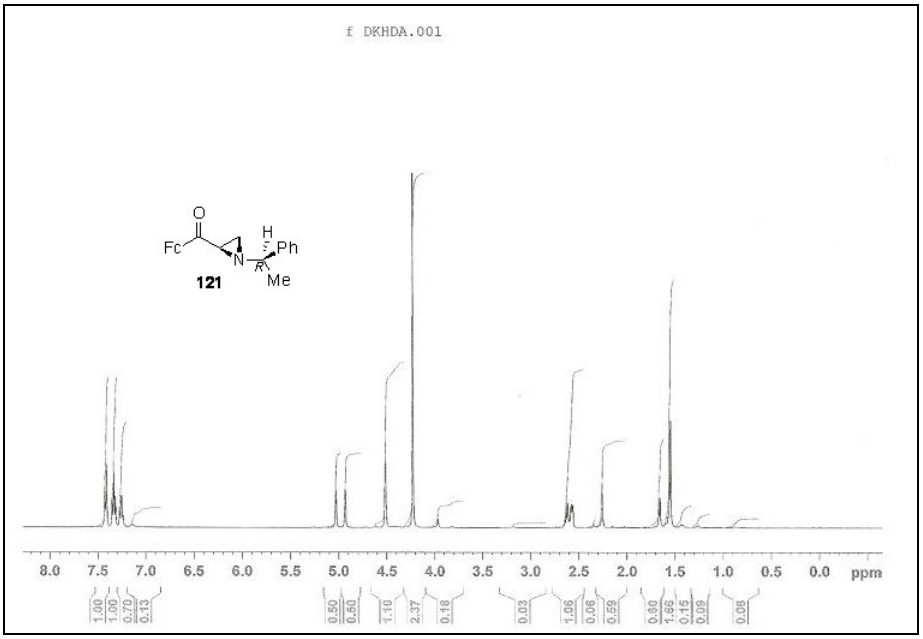


Figure A.1 ^{1}H-NMR spectrum of compound **121**.

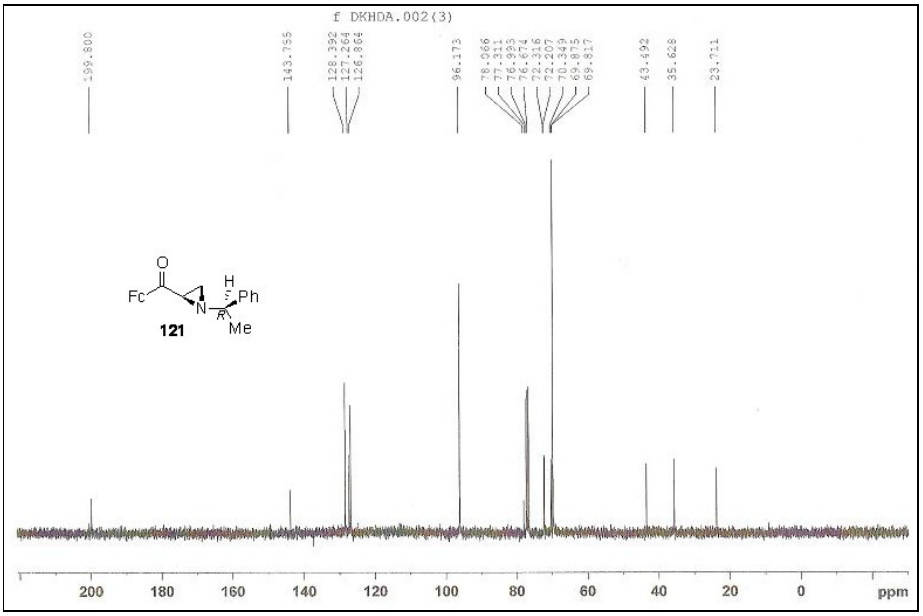


Figure A.2 ^{13}C-NMR spectrum of compound **121**.

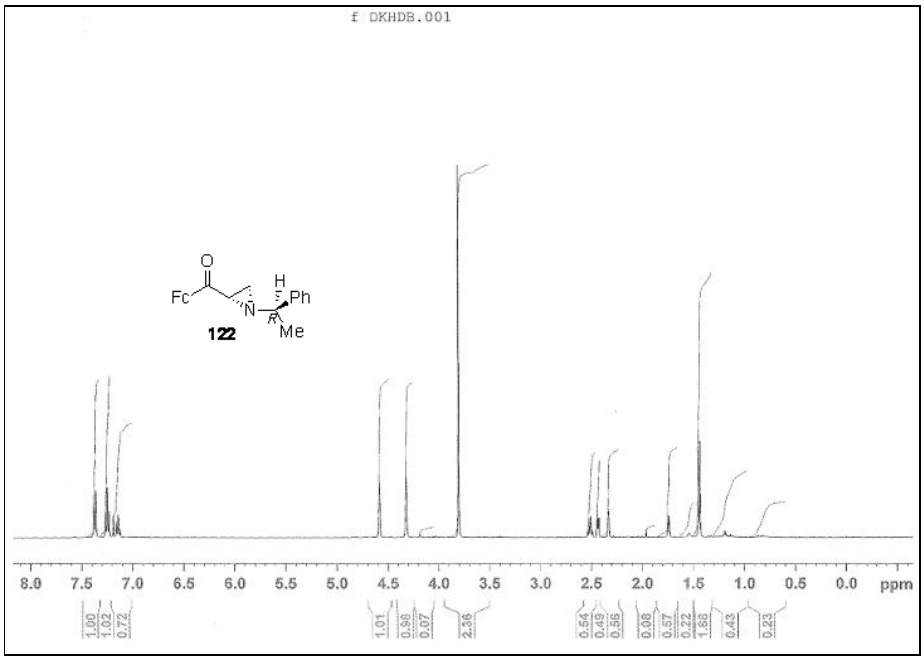


Figure A.3 ^{1}H-NMR spectrum of compound **122**.

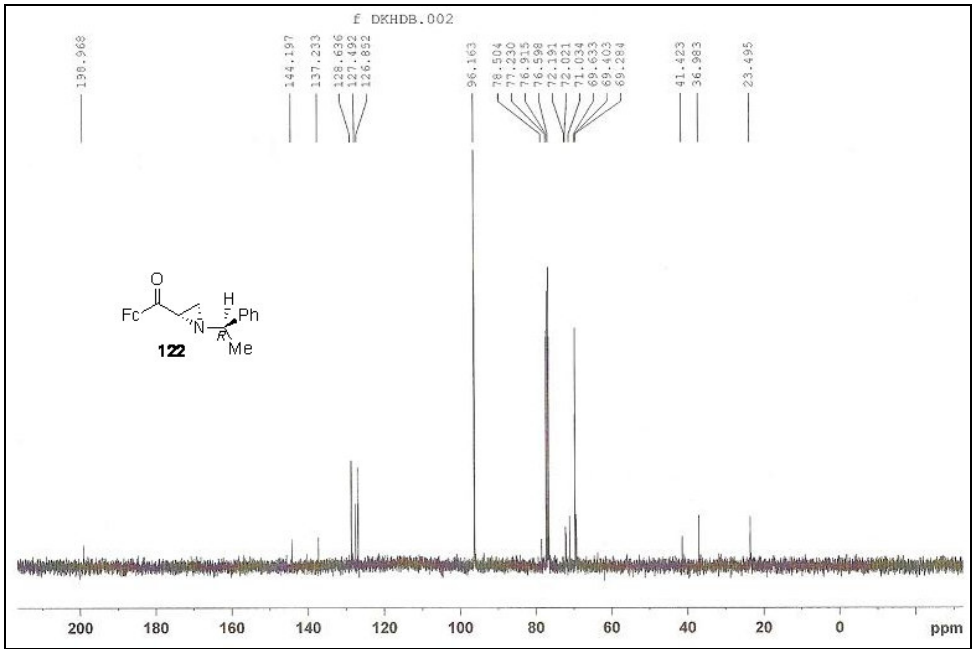


Figure A.4 ^{13}C-NMR spectrum of compound **122**.

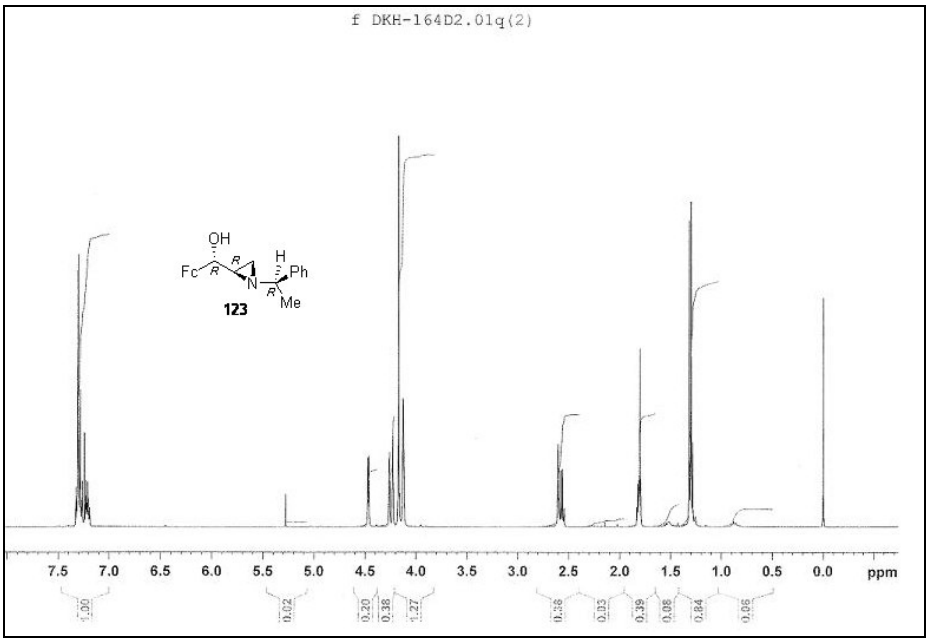


Figure A.5 ^{1}H-NMR spectrum of compound **123**.

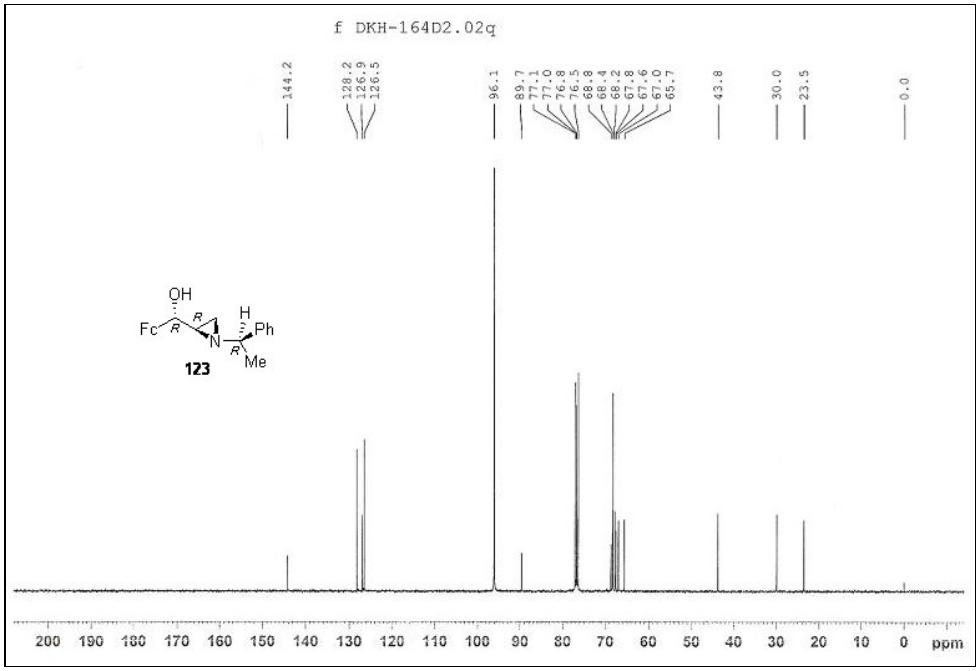


Figure A.6 ^{13}C-NMR spectrum of compound **123**.

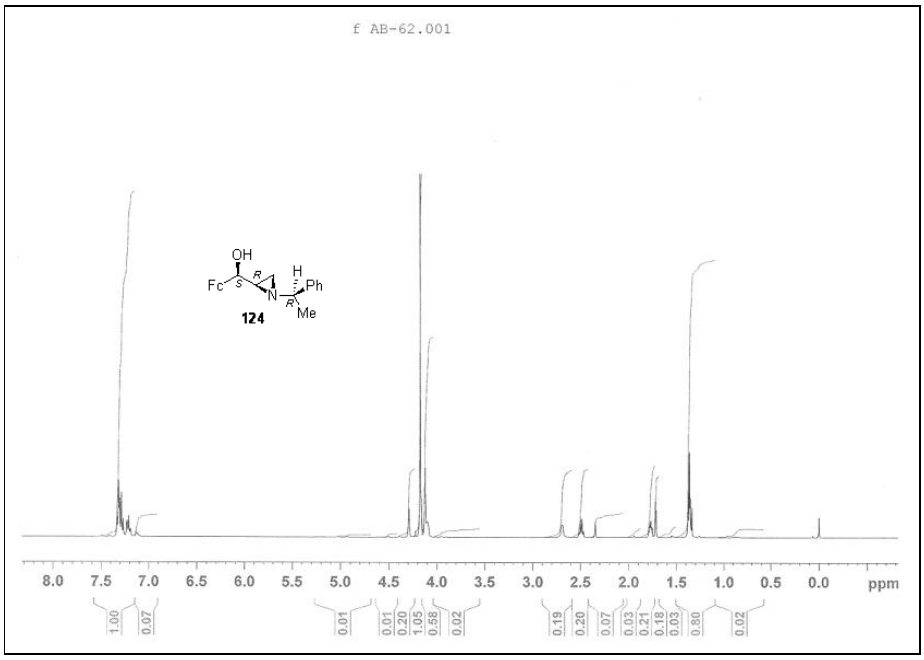


Figure A.7 ^{1}H-NMR spectrum of compound **124**.

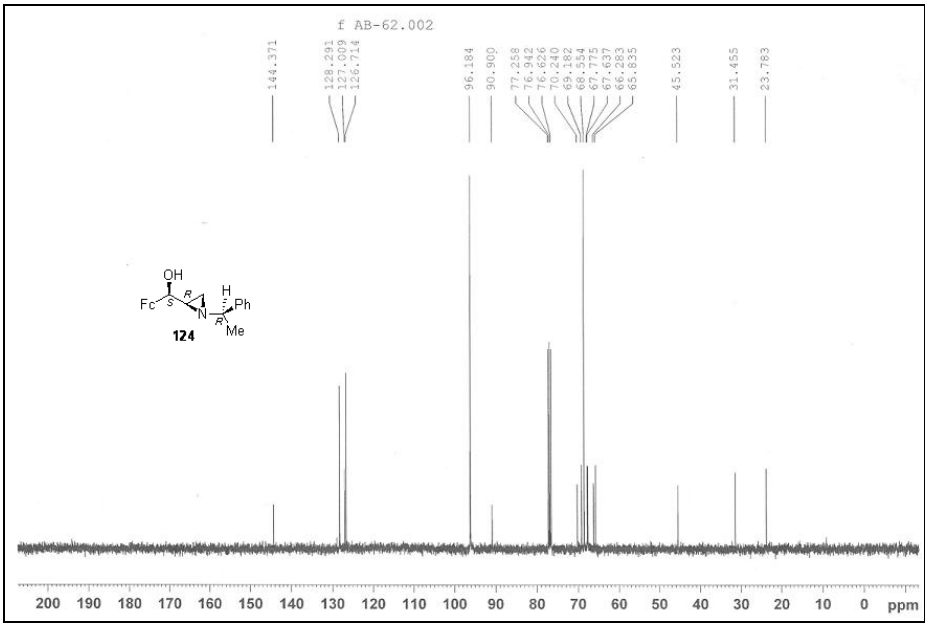


Figure A.8 ^{13}C-NMR spectrum of compound **124**.

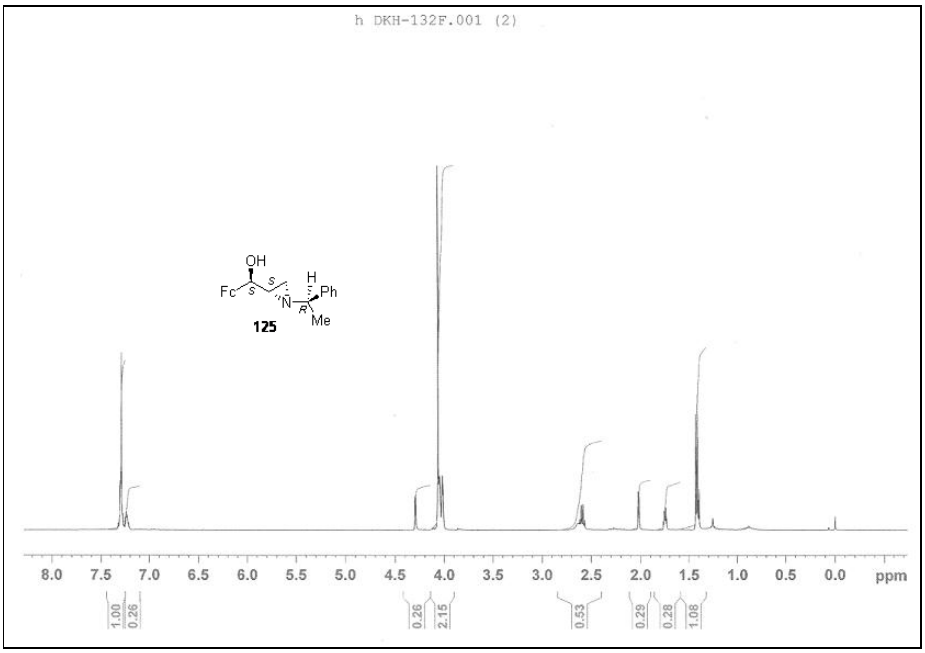


Figure A.9 ^{1}H-NMR spectrum of compound **125**.

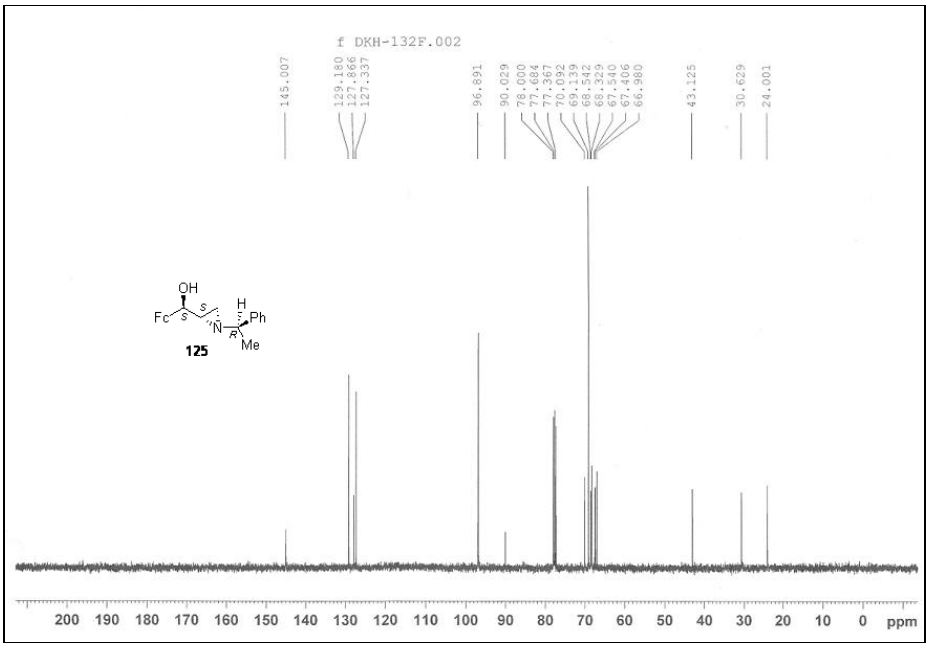


Figure A.10 ^{13}C-NMR spectrum of compound **125**.

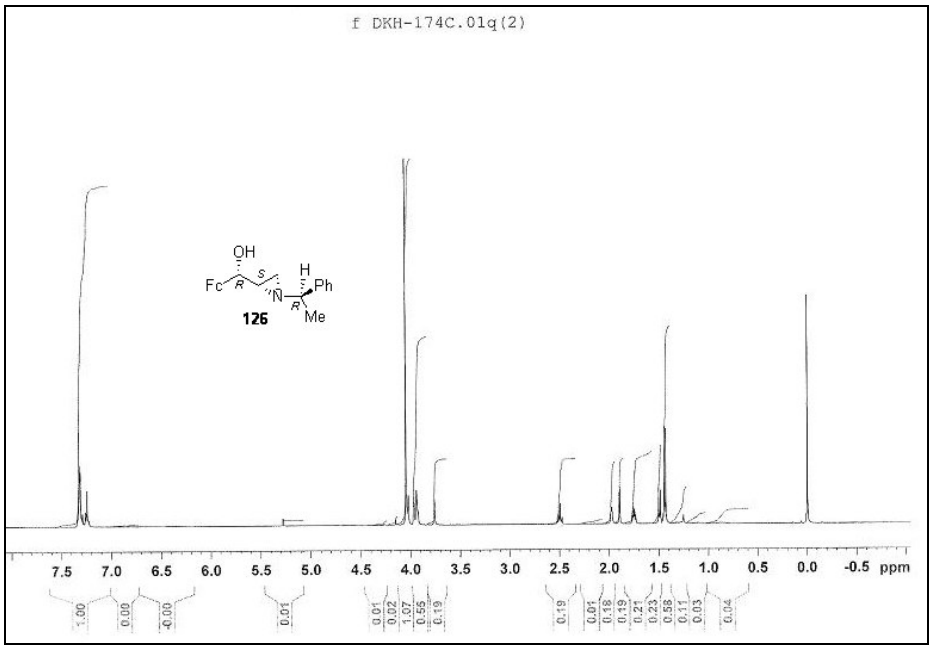


Figure A.11 ^{1}H-NMR spectrum of compound **126**.

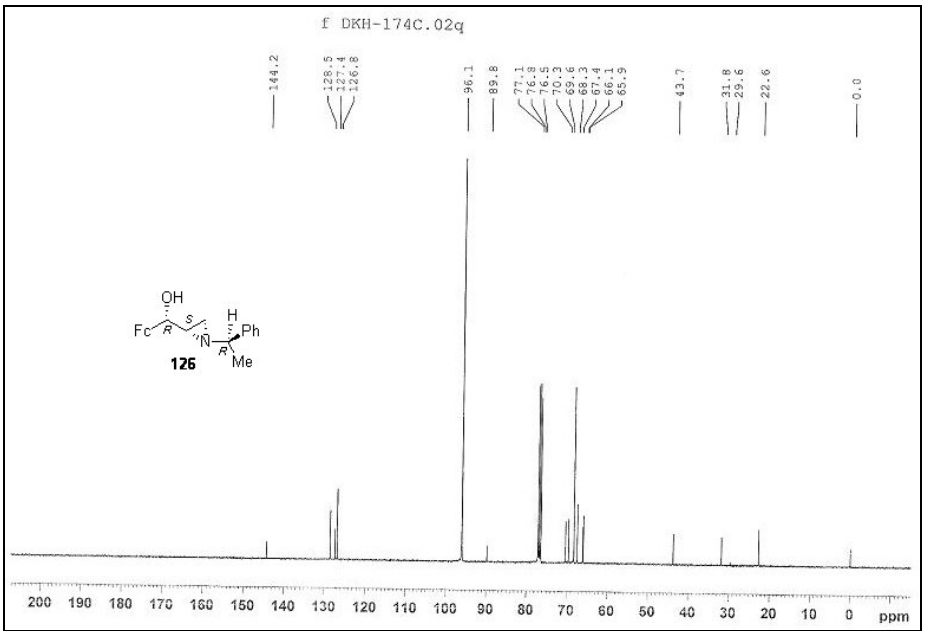


Figure A.12 ^{13}C-NMR spectrum of compound **126**.

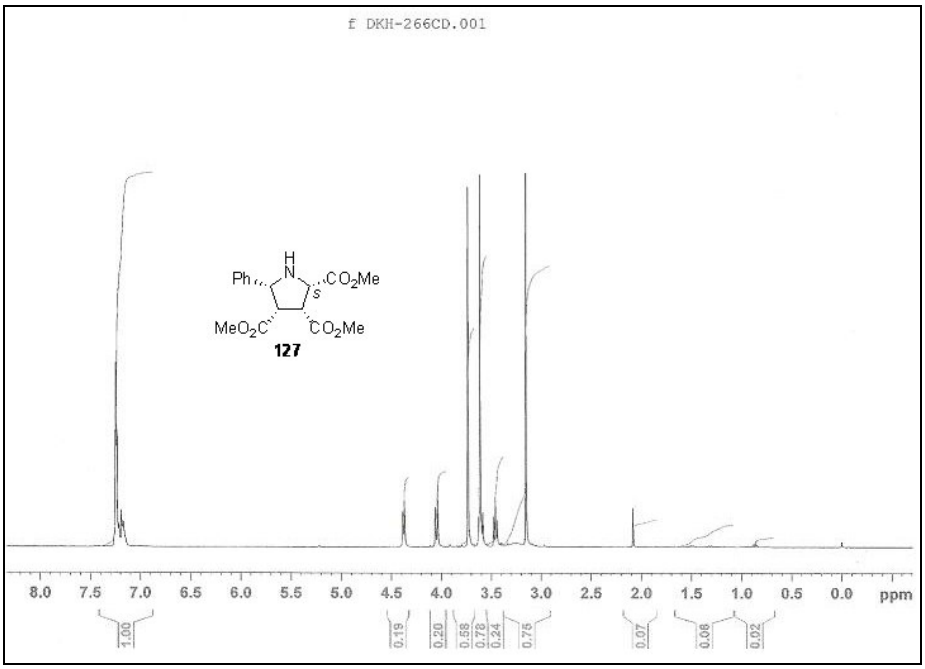


Figure A.13 ^{1}H-NMR spectrum of compound **127**.

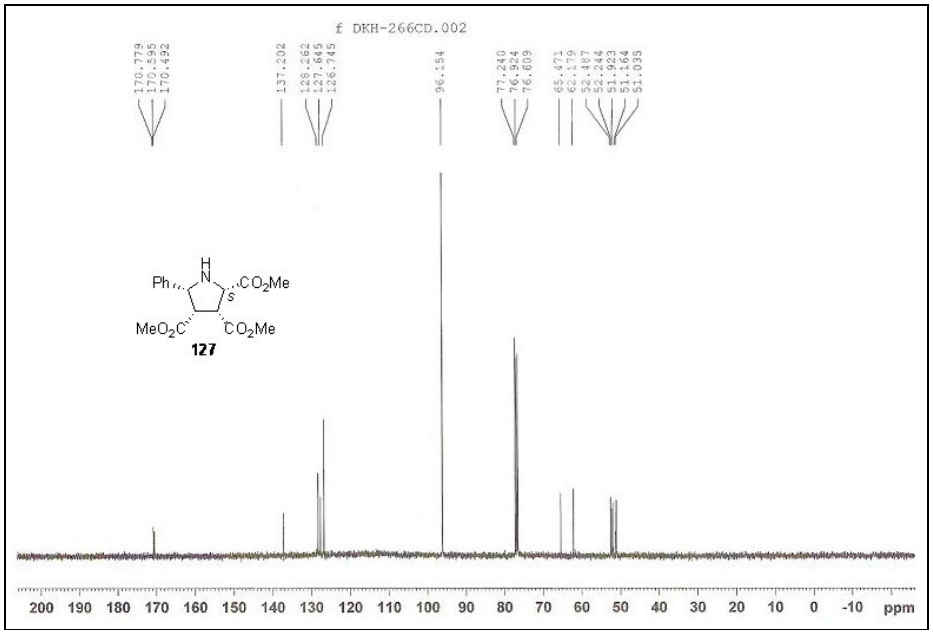


Figure A.14 ^{13}C-NMR spectrum of compound **127**.

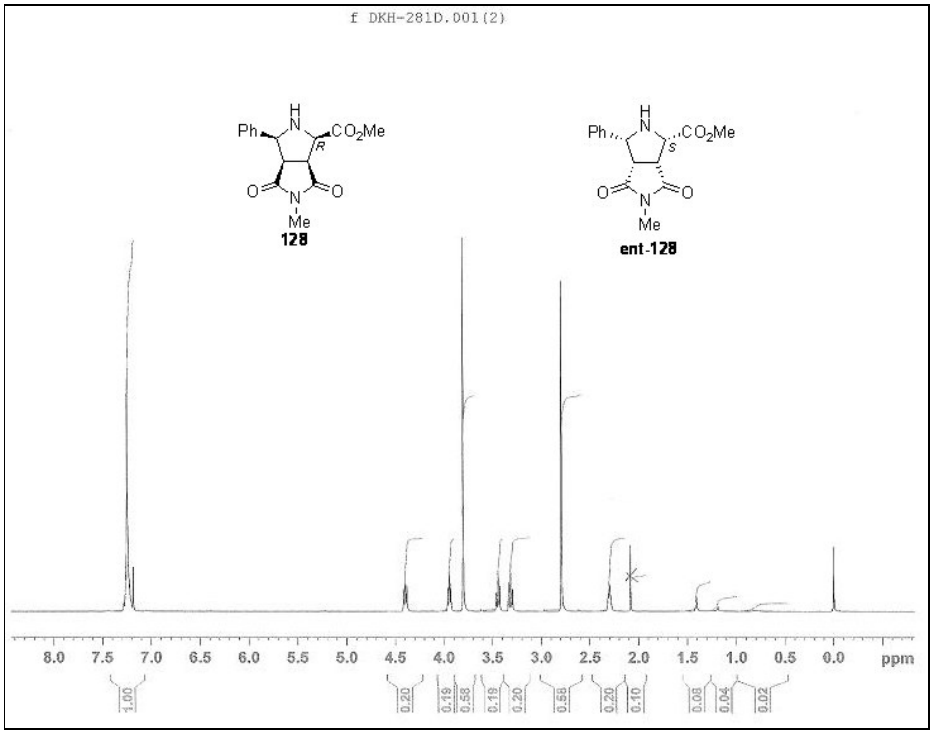


Figure A.15 ^{1}H-NMR spectrum of compound **128** and **ent-128**.

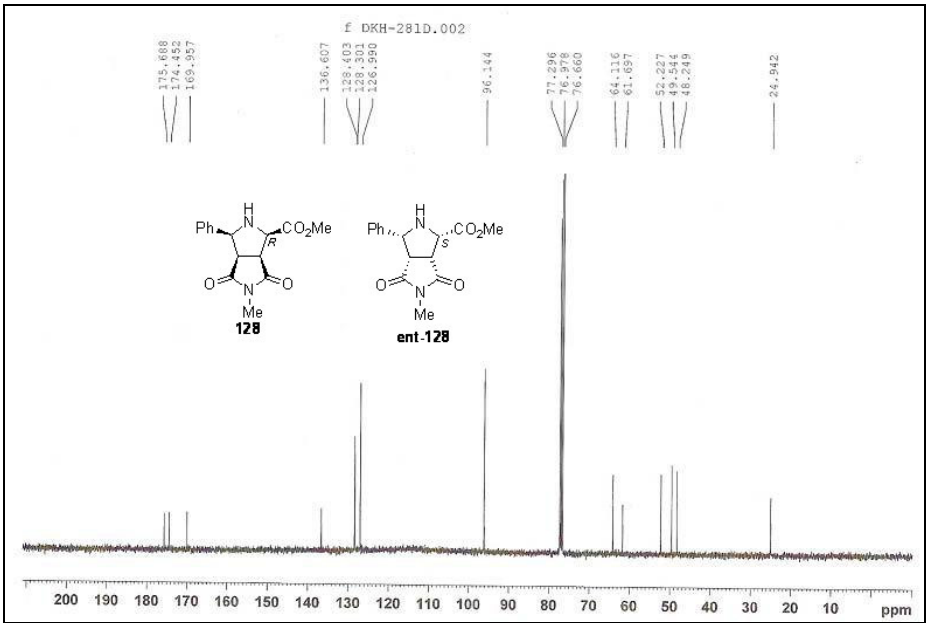


Figure A.16 ^{13}C-NMR spectrum of compound **128** and **ent-128**.

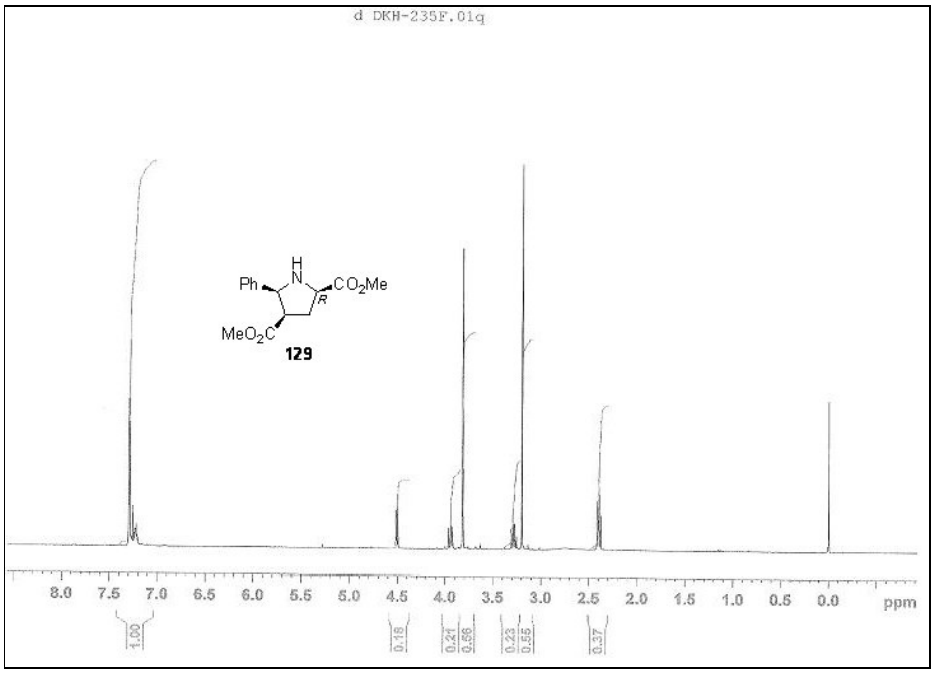


Figure A.17 ^{1}H-NMR spectrum of compound **129**.

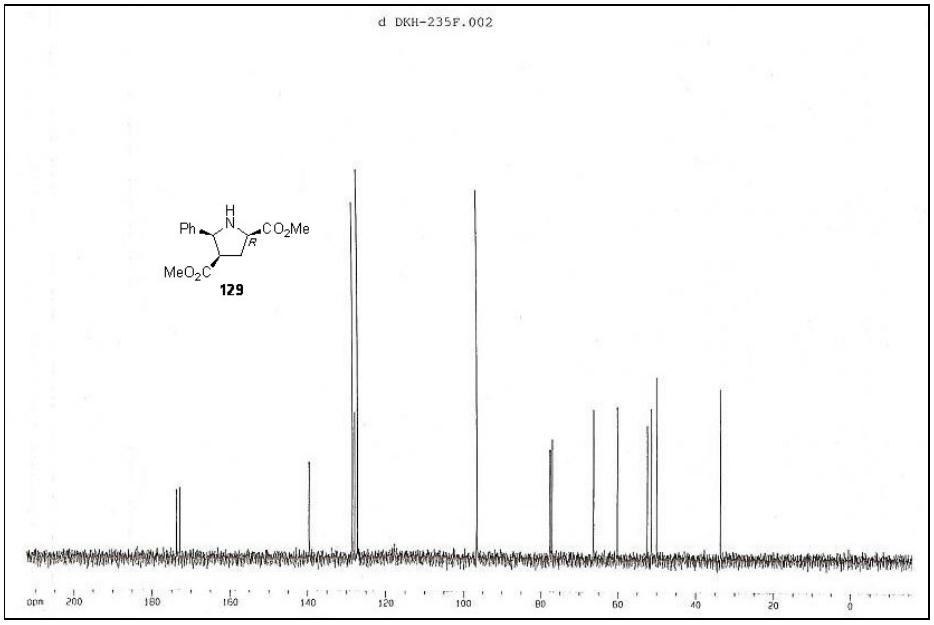


Figure A.18 ^{13}C-NMR spectrum of compound **129**.

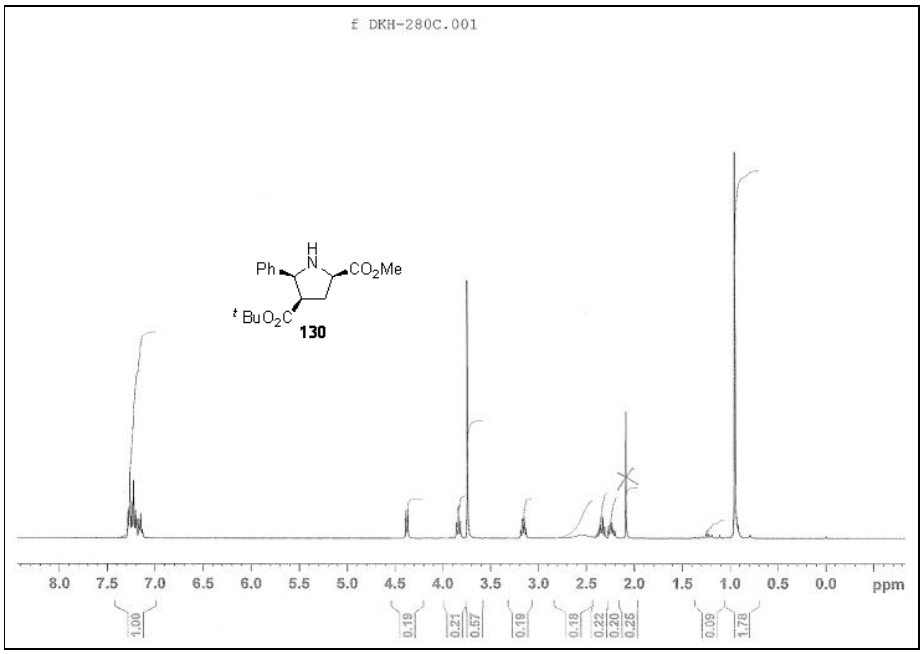


Figure A.19 ^{1}H-NMR spectrum of compound **130**.

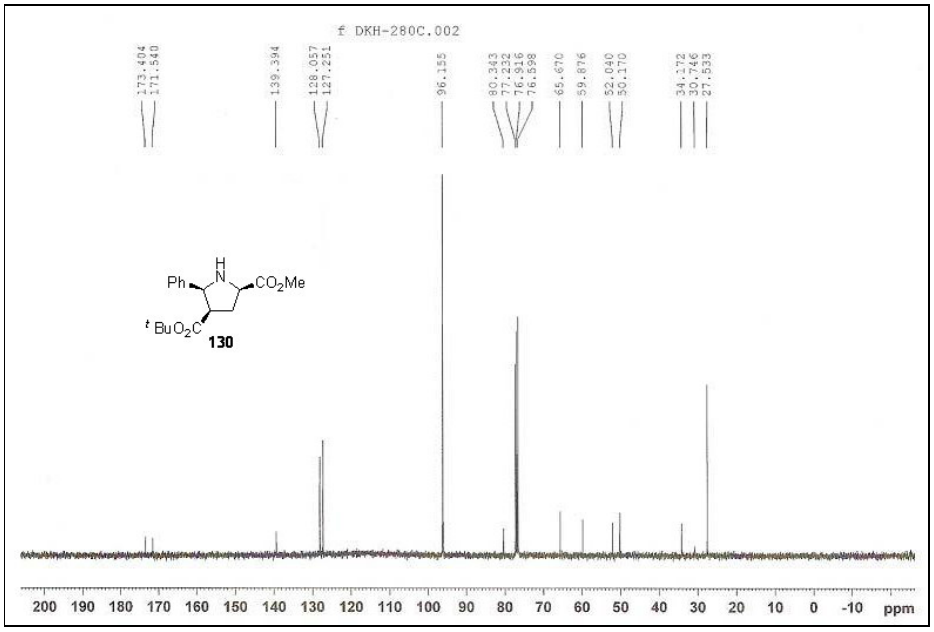


Figure A.20 ^{13}C-NMR spectrum of compound **130**.

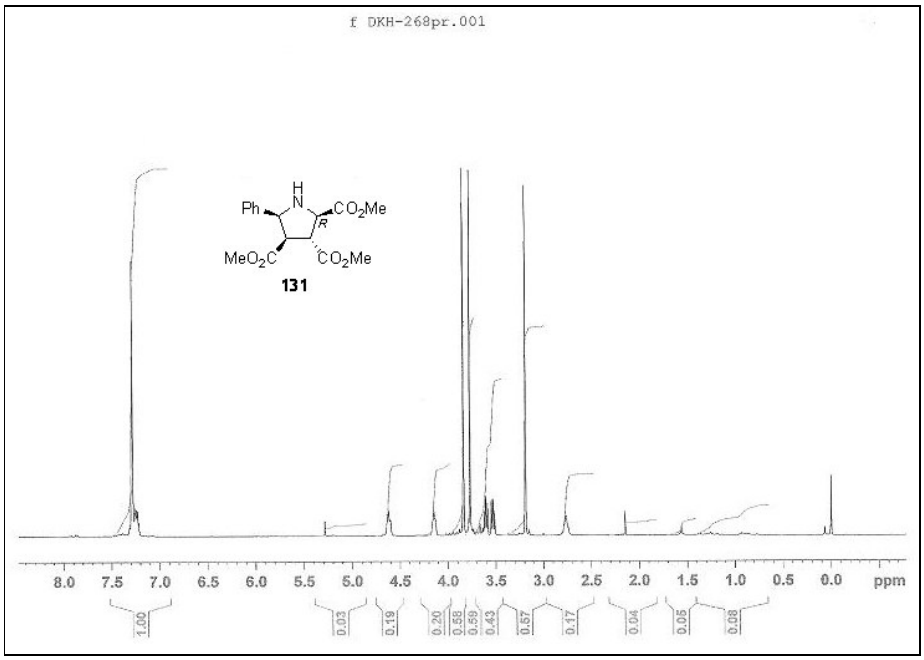


Figure A.21 ^{1}H-NMR spectrum of compound **131**.

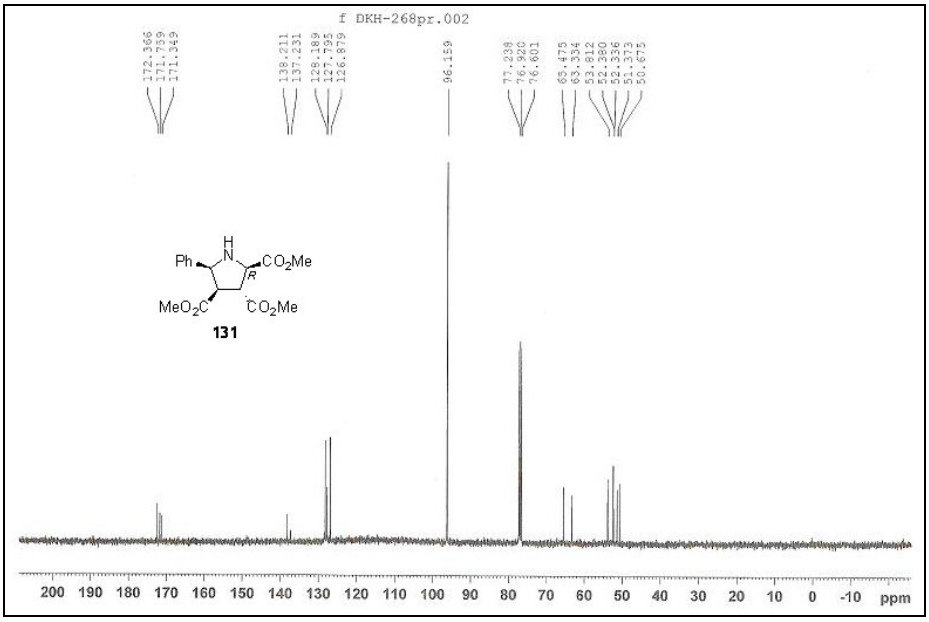


Figure A.22 ^{13}C-NMR spectrum of compound **131**.

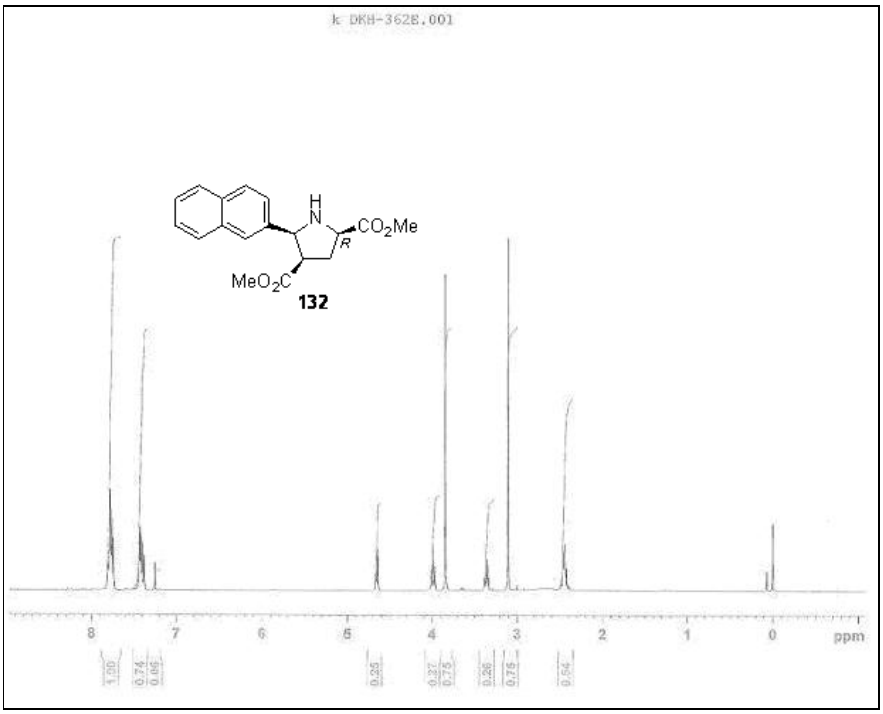


Figure A.23 ^{1}H-NMR spectrum of compound **132**.

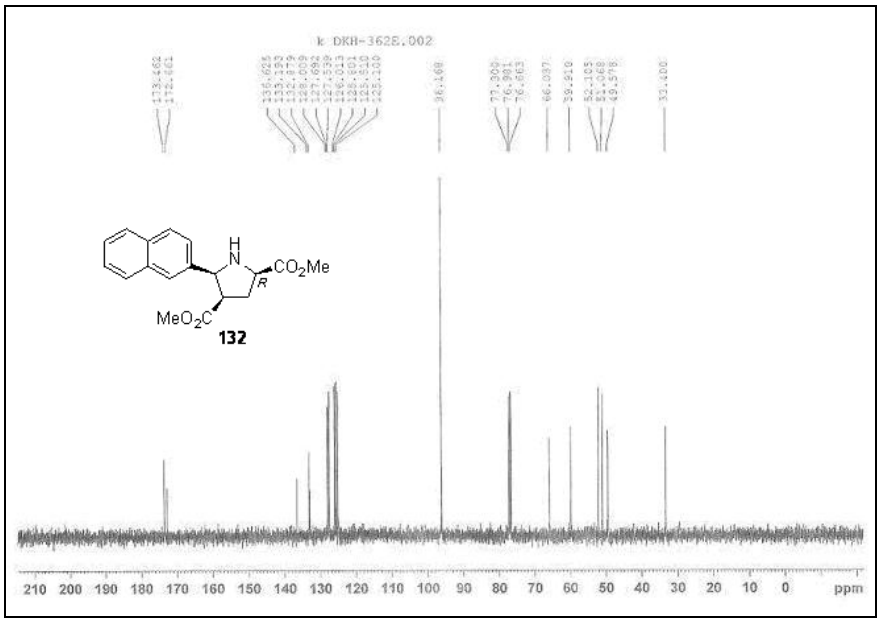


Figure A.24 ^{13}C-NMR spectrum of compound **132**.

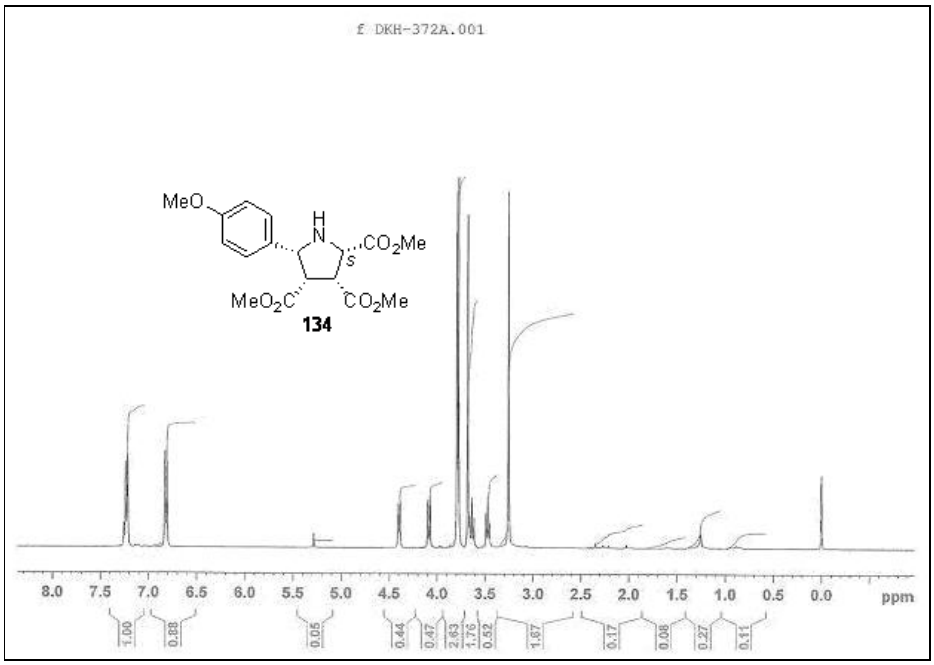


Figure A.25 ^{1}H-NMR spectrum of compound **134**.

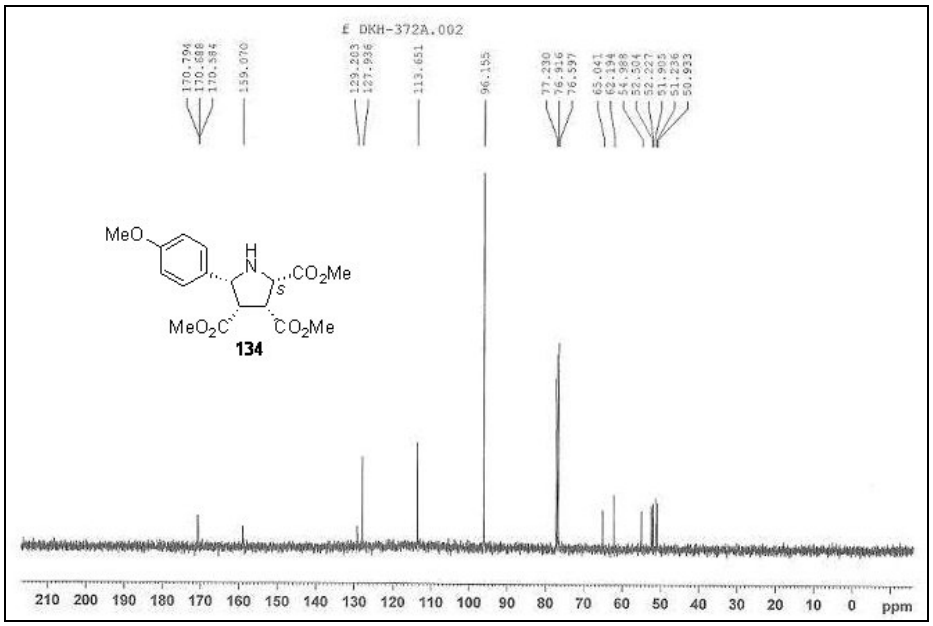


Figure A.26 ^{13}C-NMR spectrum of compound **134**.

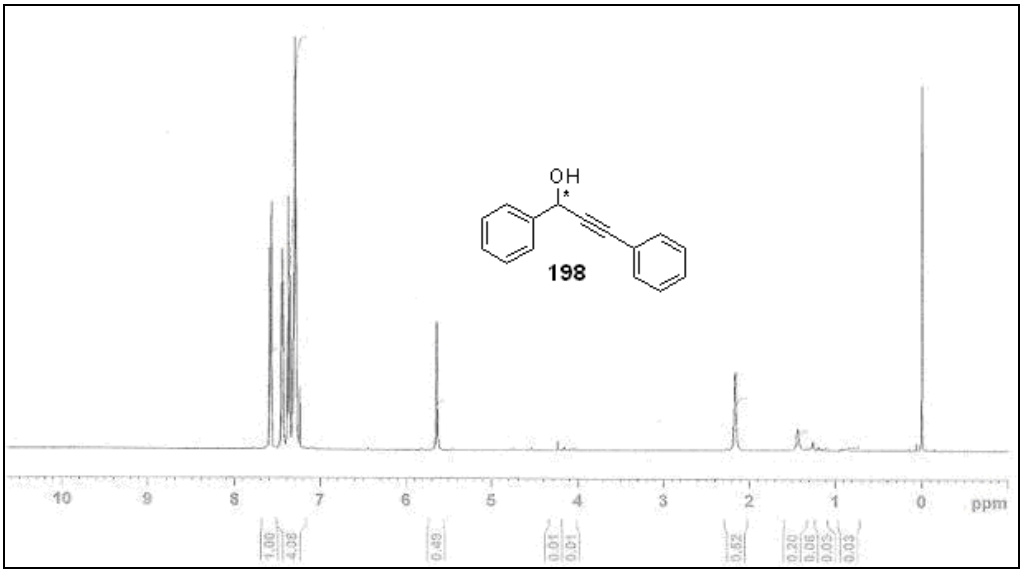


Figure A.27 ^{1}H-NMR spectrum of compound **198**.

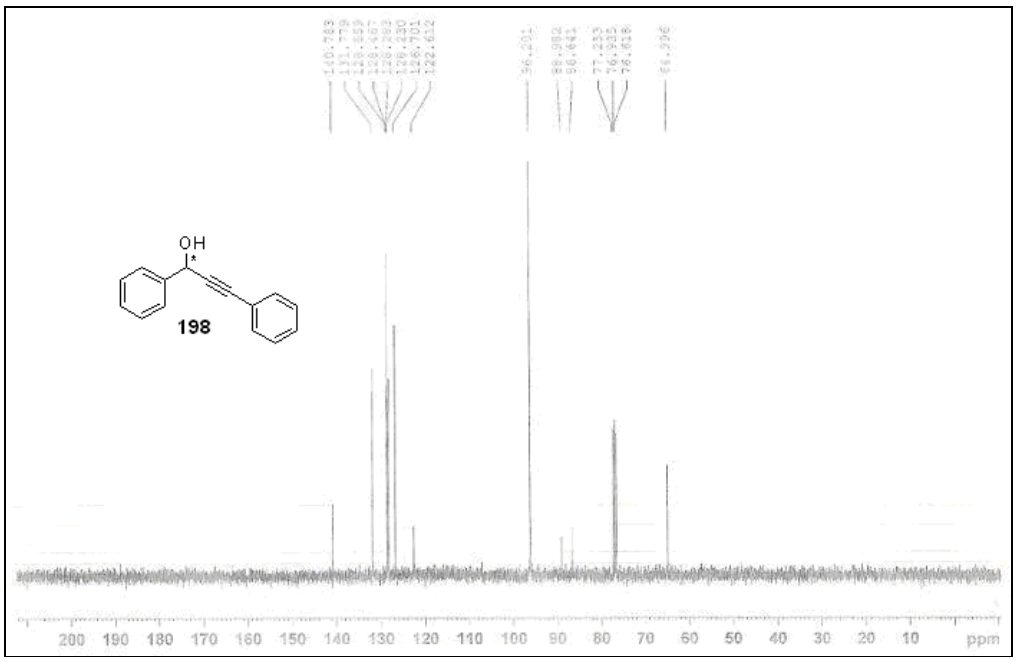


Figure A.28 ^{13}C-NMR spectrum of compound **198**.

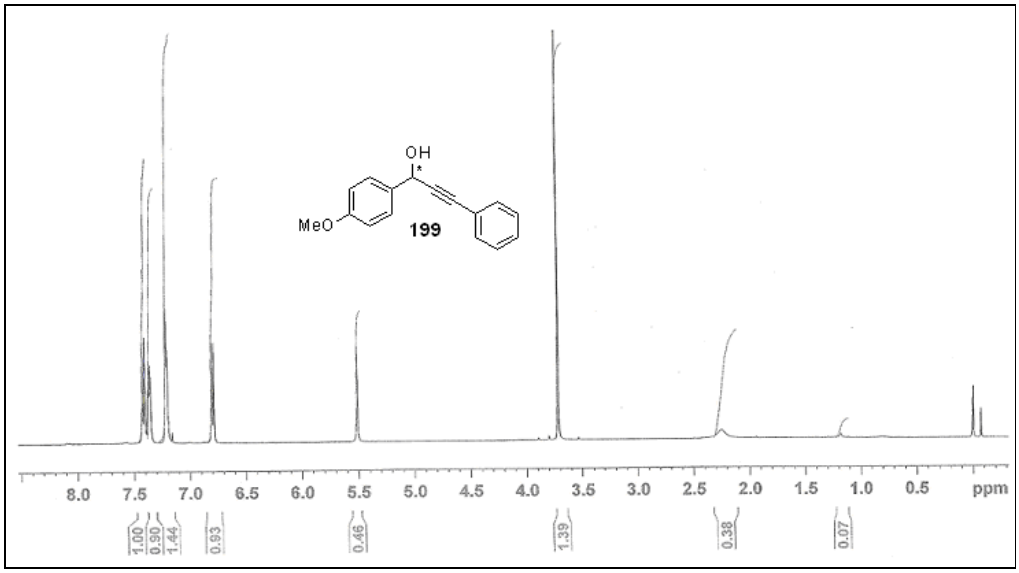


Figure A.29 ^{1}H-NMR spectrum of compound **199**.

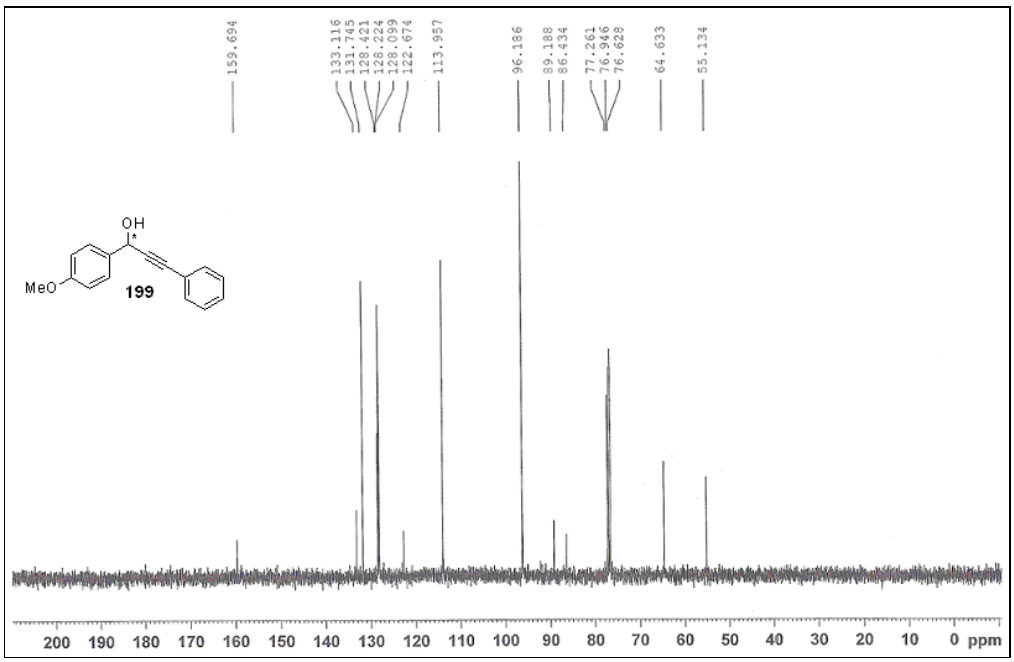


Figure A.30 ^{13}C-NMR spectrum of compound **199**.

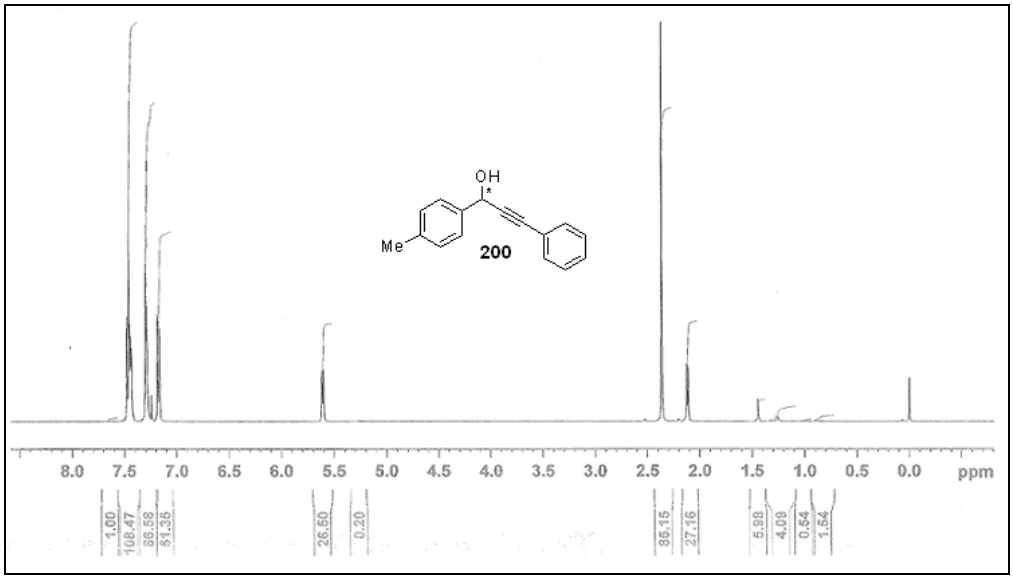


Figure A.31 ^{1}H-NMR spectrum of compound **200**.

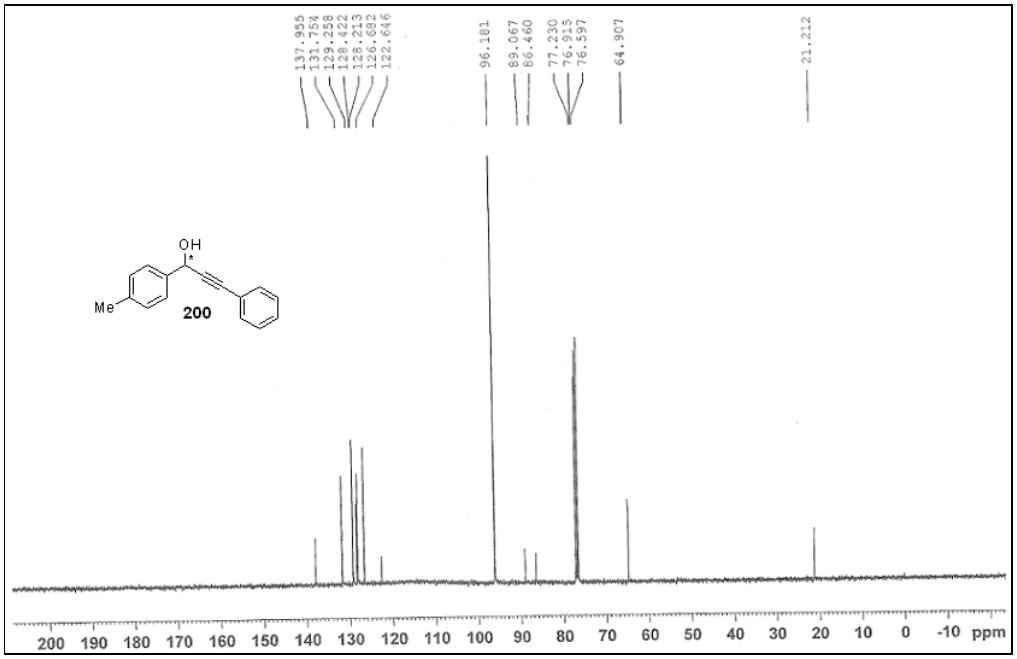


Figure A.32 ^{13}C-NMR spectrum of compound **200**.

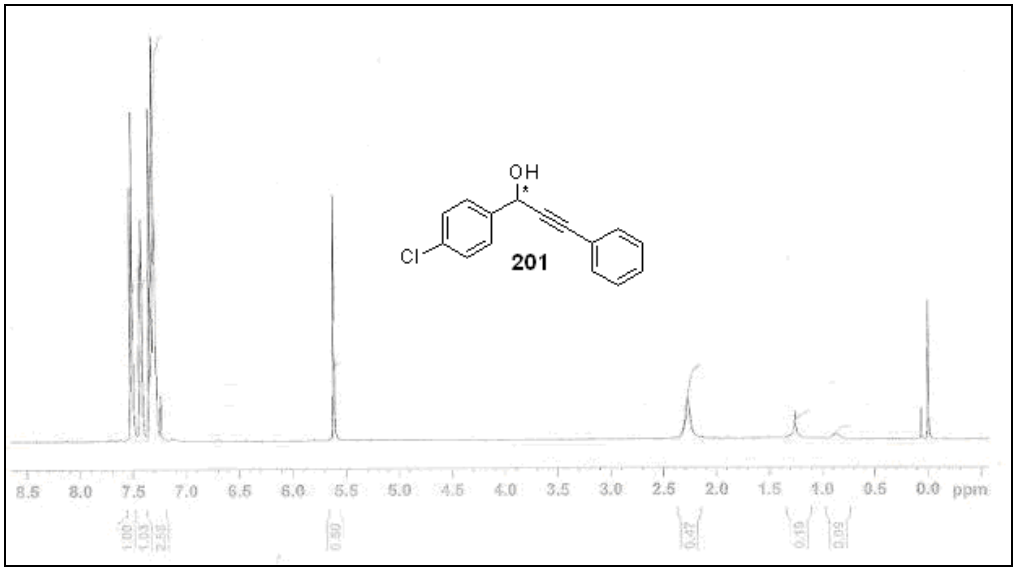


Figure A.33 ^{1}H-NMR spectrum of compound **201**.

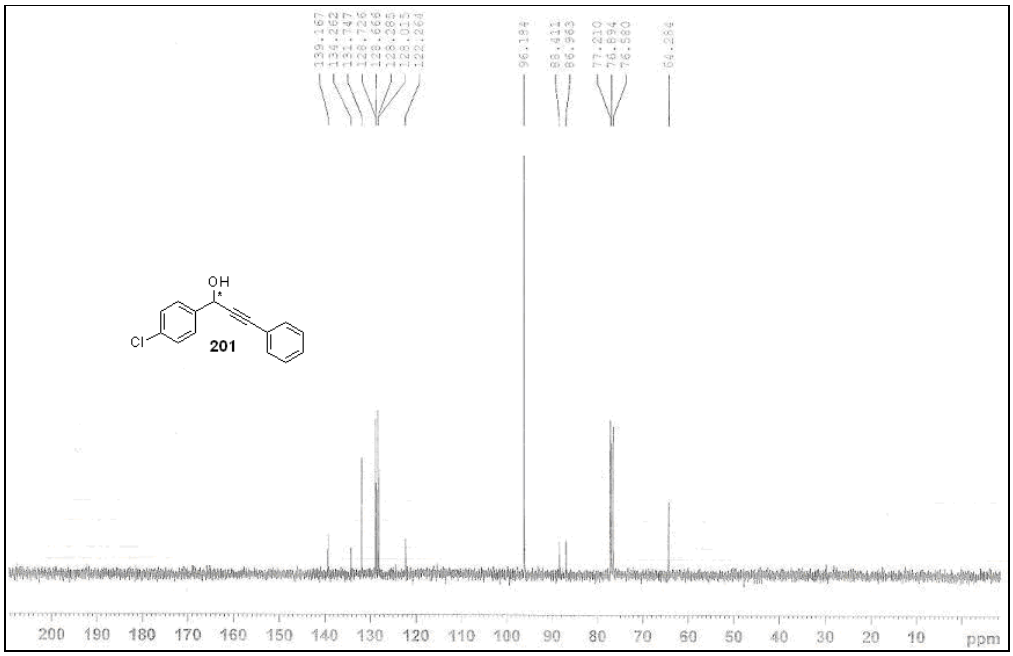


Figure A.34 ^{13}C-NMR spectrum of compound **201**.

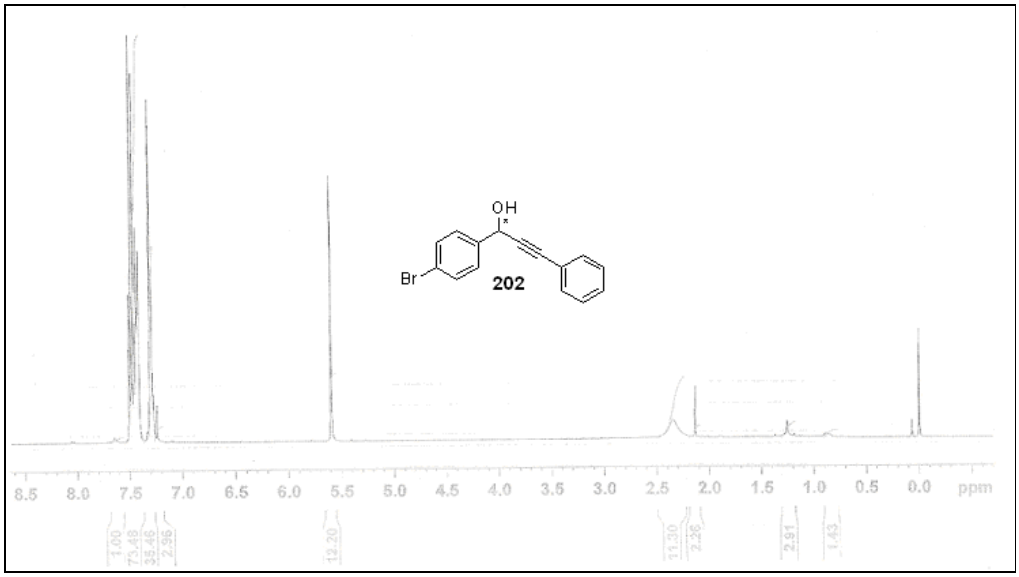


Figure A.35 ^{1}H-NMR spectrum of compound **202**.

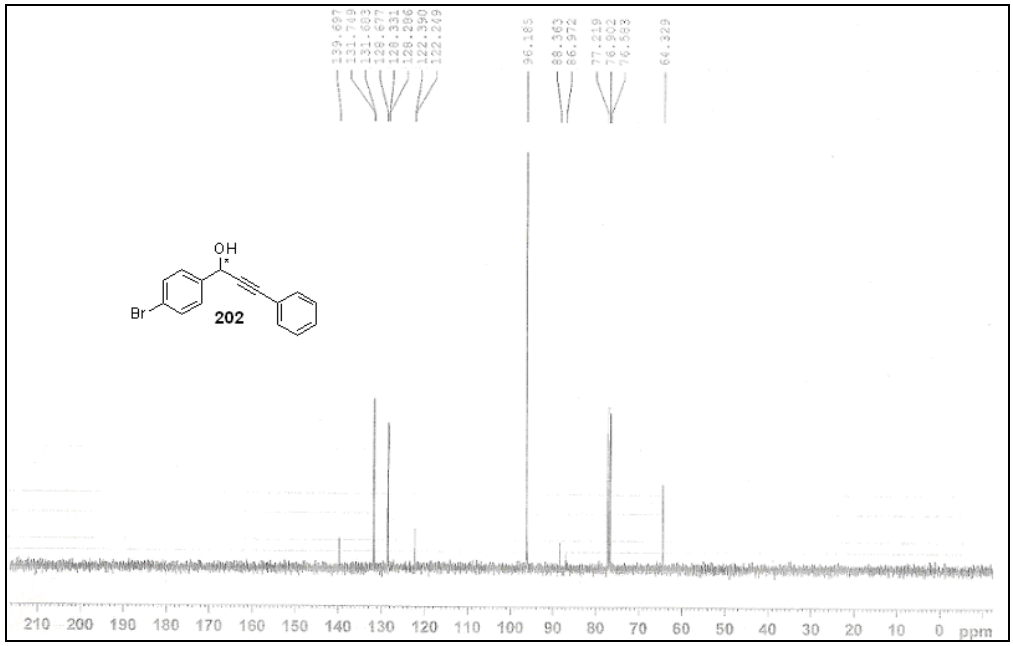


Figure A.36 ^{13}C-NMR spectrum of compound **202**.

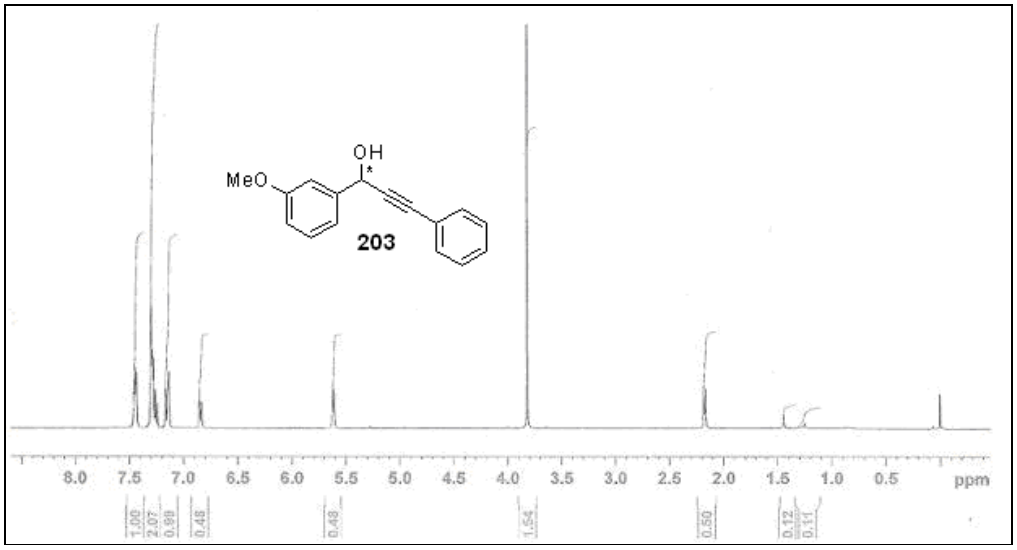


Figure A.37 ^{1}H-NMR spectrum of compound **203**.

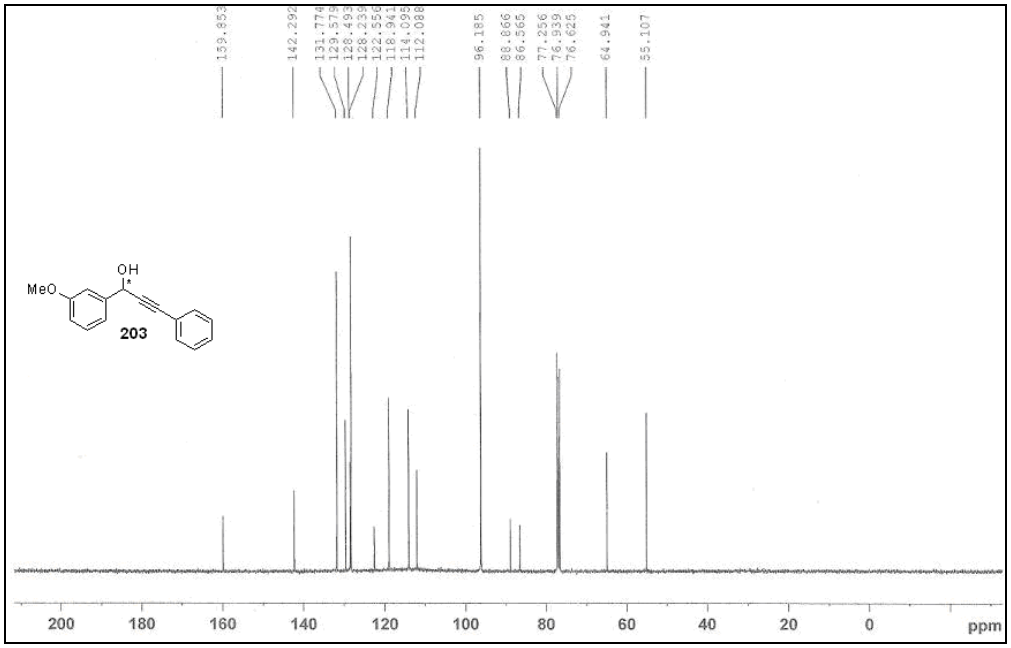


Figure A.38 ^{13}C-NMR spectrum of compound **203**.

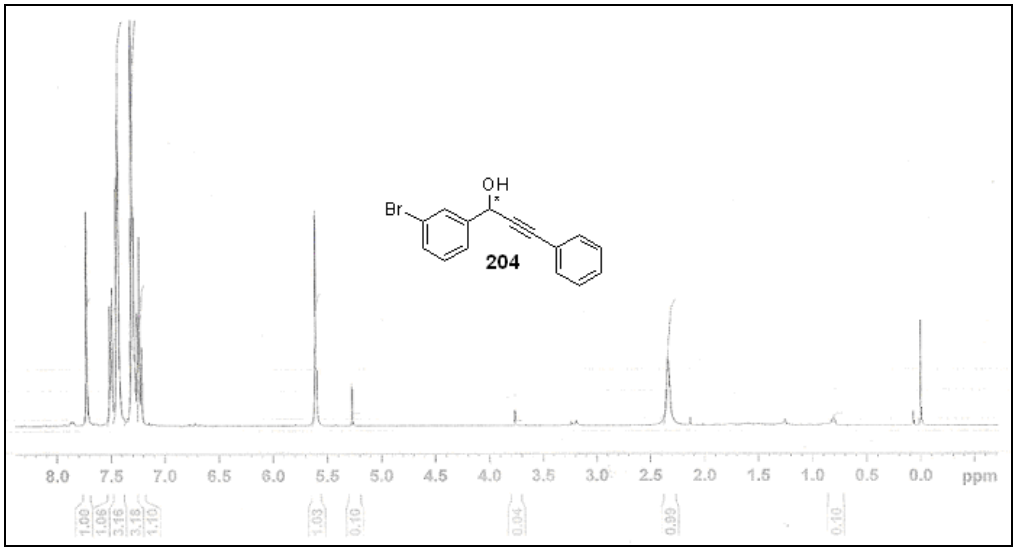


Figure A.39 ^{1}H-NMR spectrum of compound **204**.

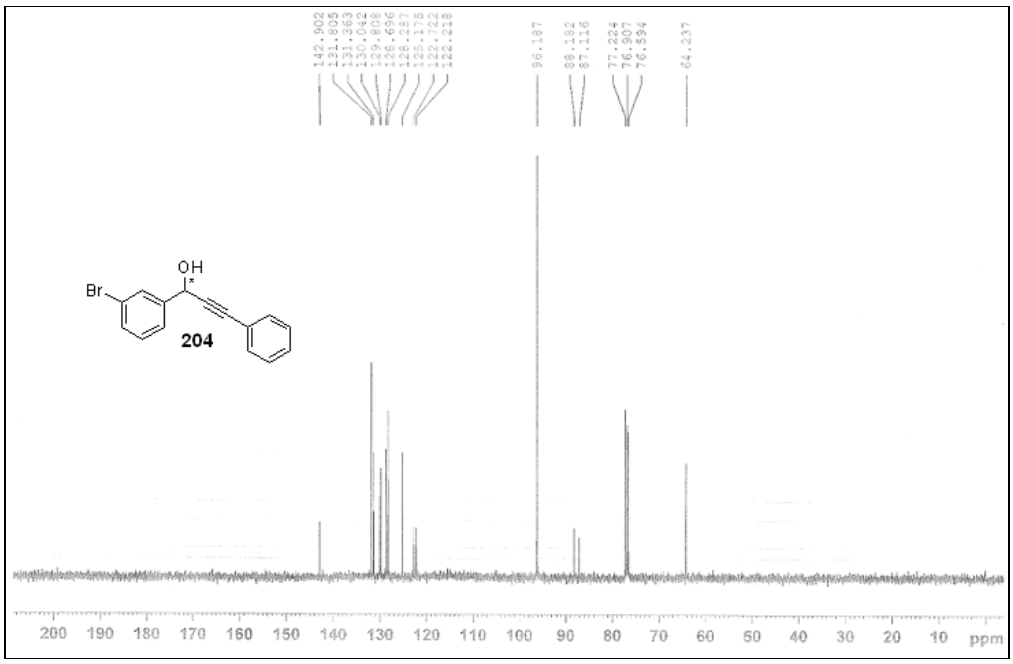


Figure A.40 ^{13}C-NMR spectrum of compound **204**.

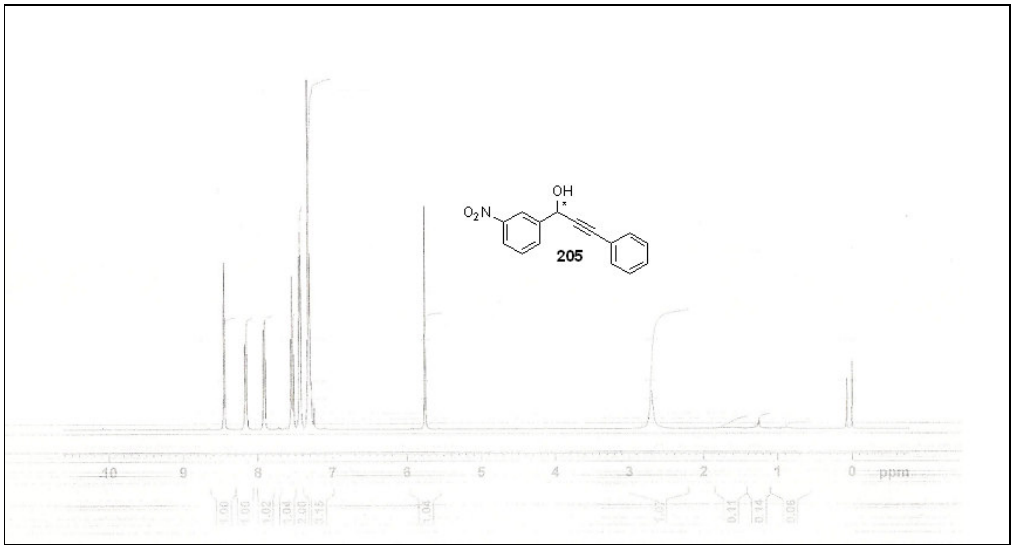


Figure A.41 ^{1}H-NMR spectrum of compound **205**.

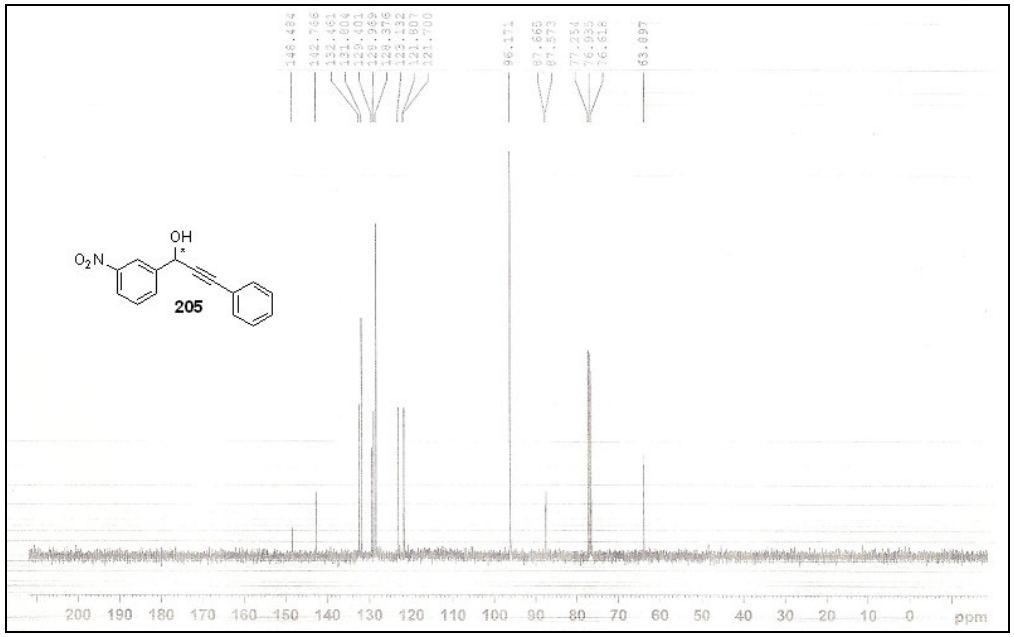


Figure A.42 ^{13}C-NMR spectrum of compound **205**.

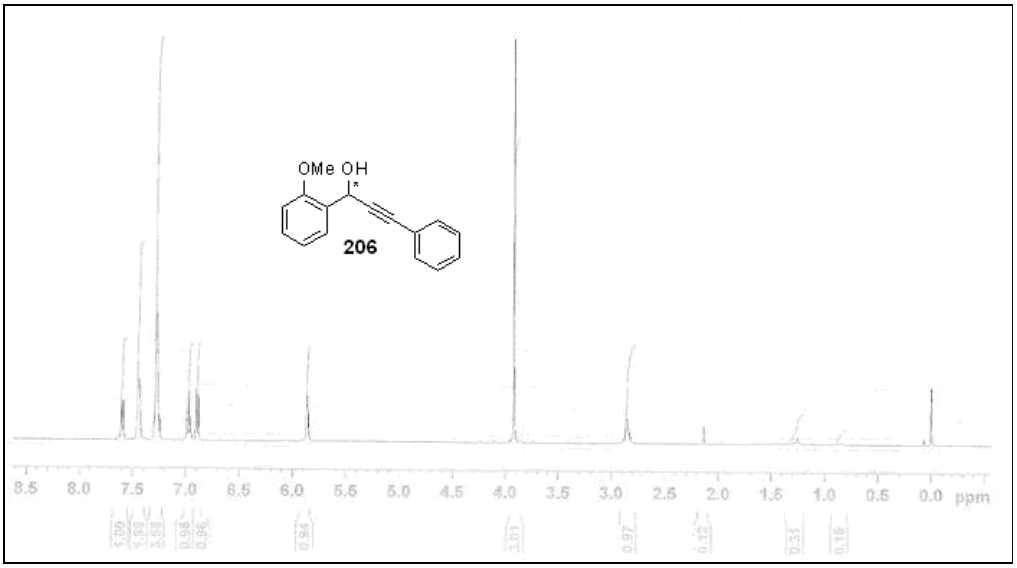


Figure A.43 ^{1}H-NMR spectrum of compound **206**.

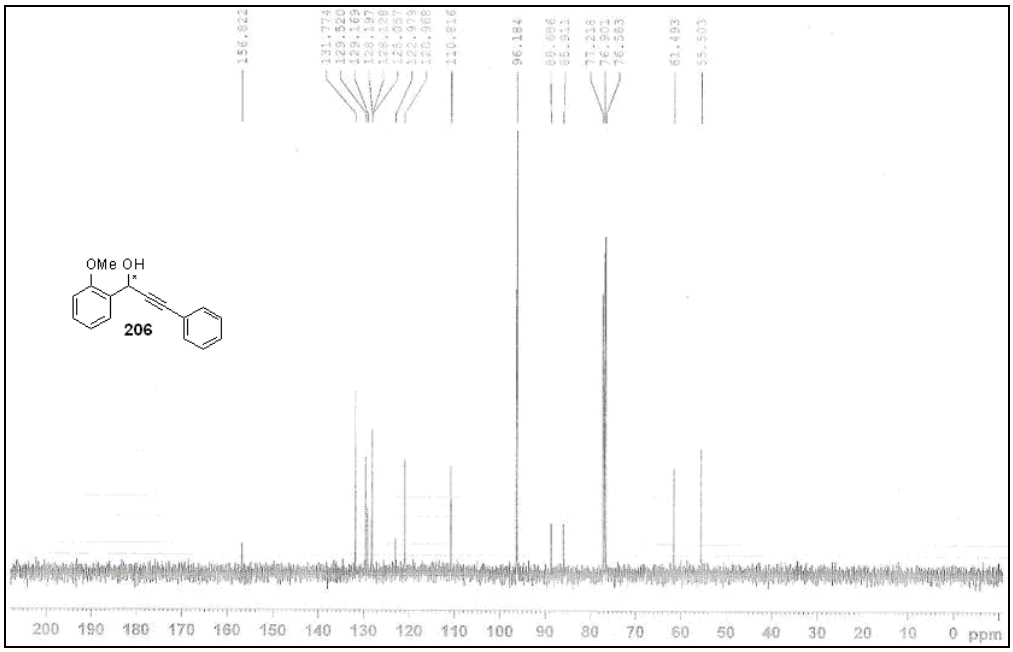


Figure A.44 ^{13}C-NMR spectrum of compound **206**.

Figure A.45 ^{1}H-NMR spectrum of compound **207**.

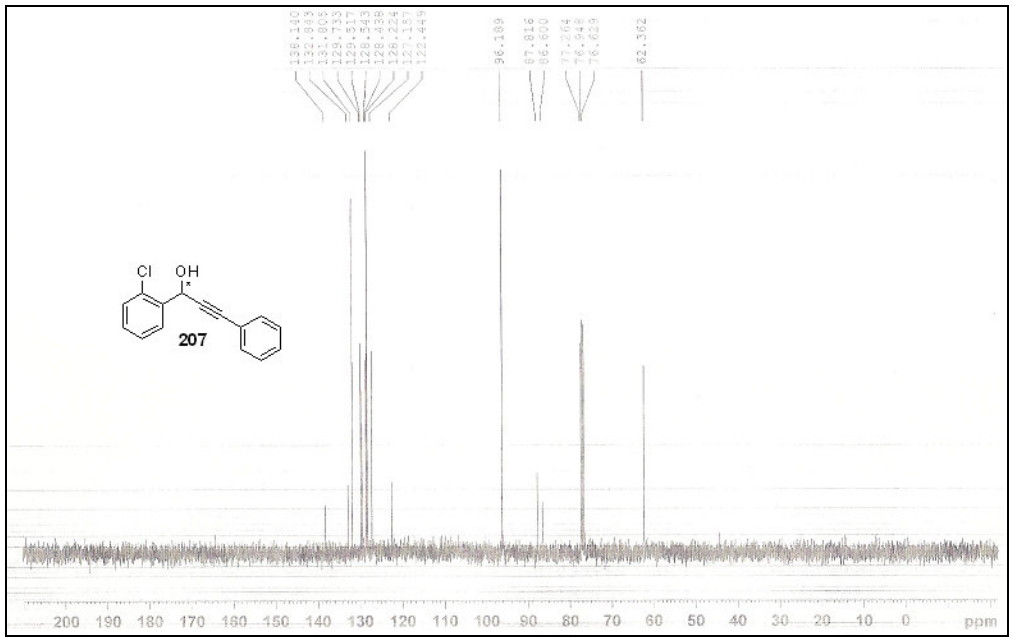


Figure A.46 ^{13}C-NMR spectrum of compound **207**.

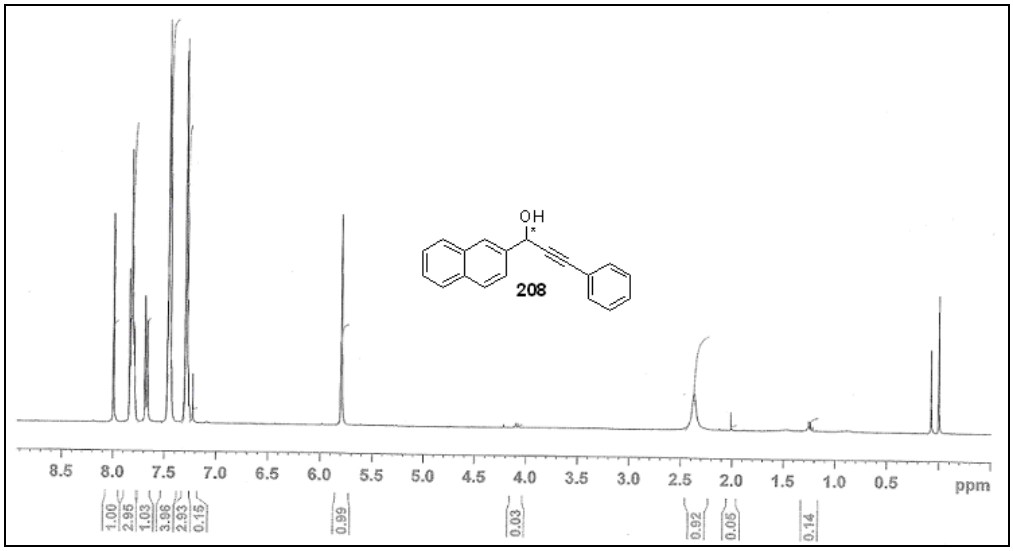


Figure A.47 ^{1}H-NMR spectrum of compound **208**.

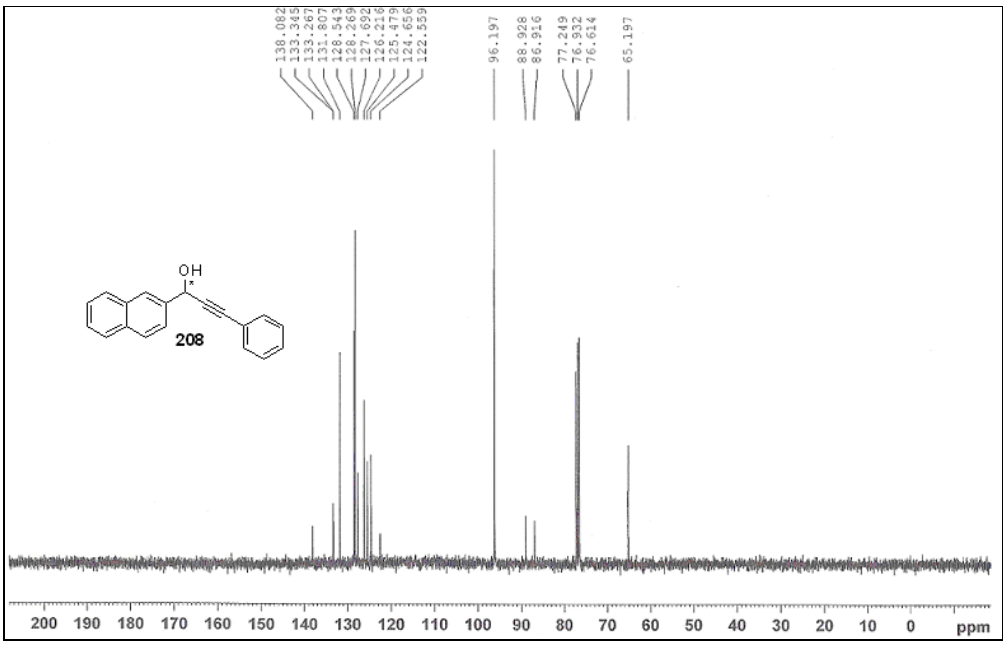


Figure A.48 ^{13}C-NMR spectrum of compound **208**.

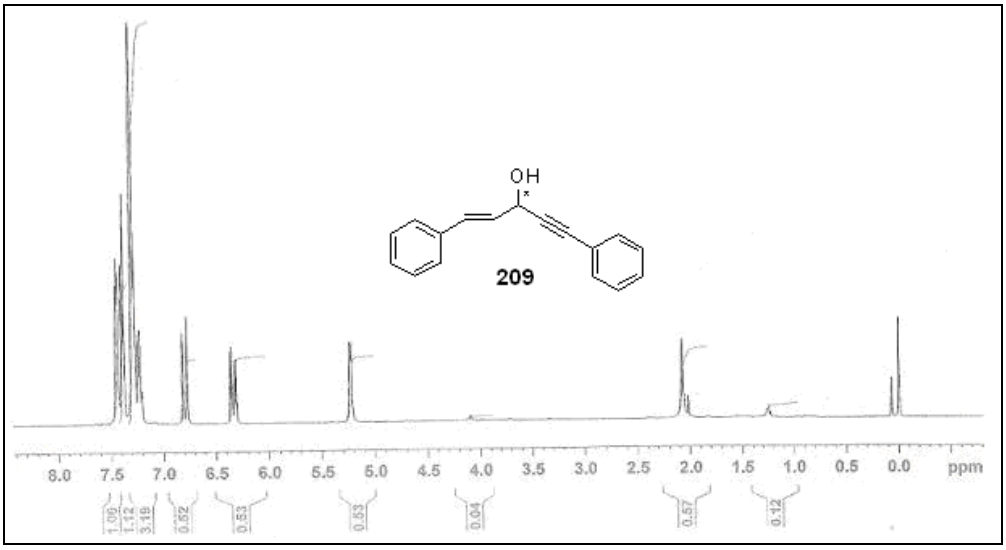


Figure A.49 ^{1}H-NMR spectrum of compound **209**.

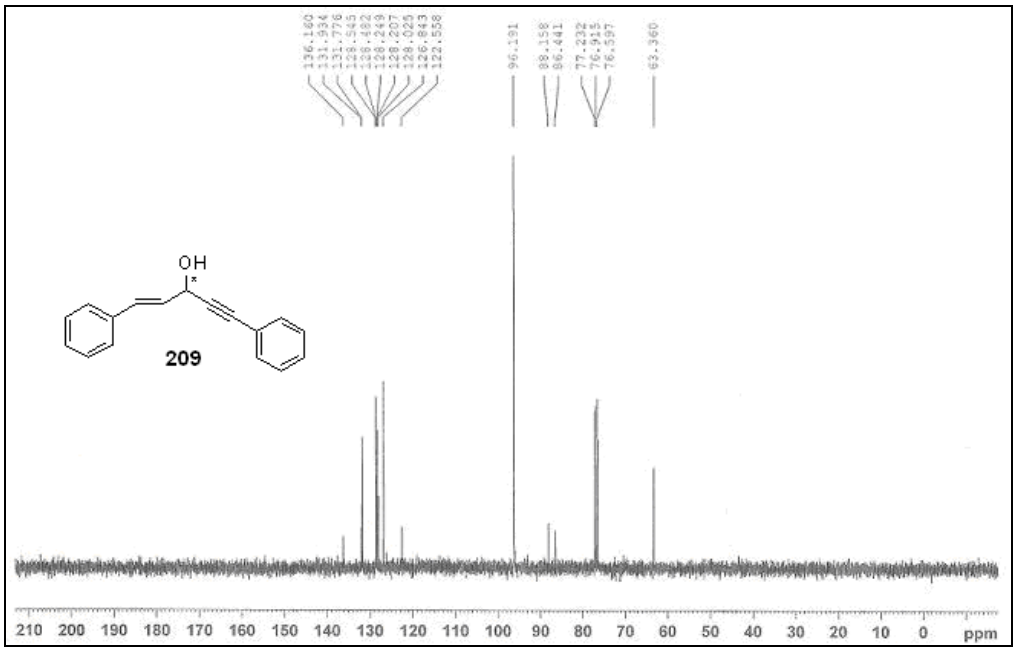


Figure A.50 ^{13}C-NMR spectrum of compound **209**.

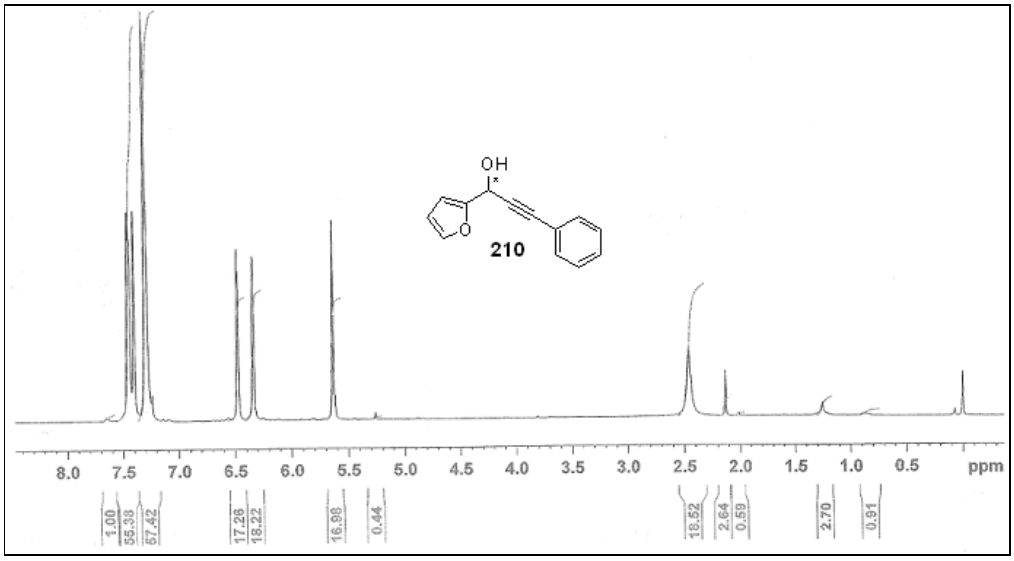


Figure A.51 ^{1}H-NMR spectrum of compound **210**.

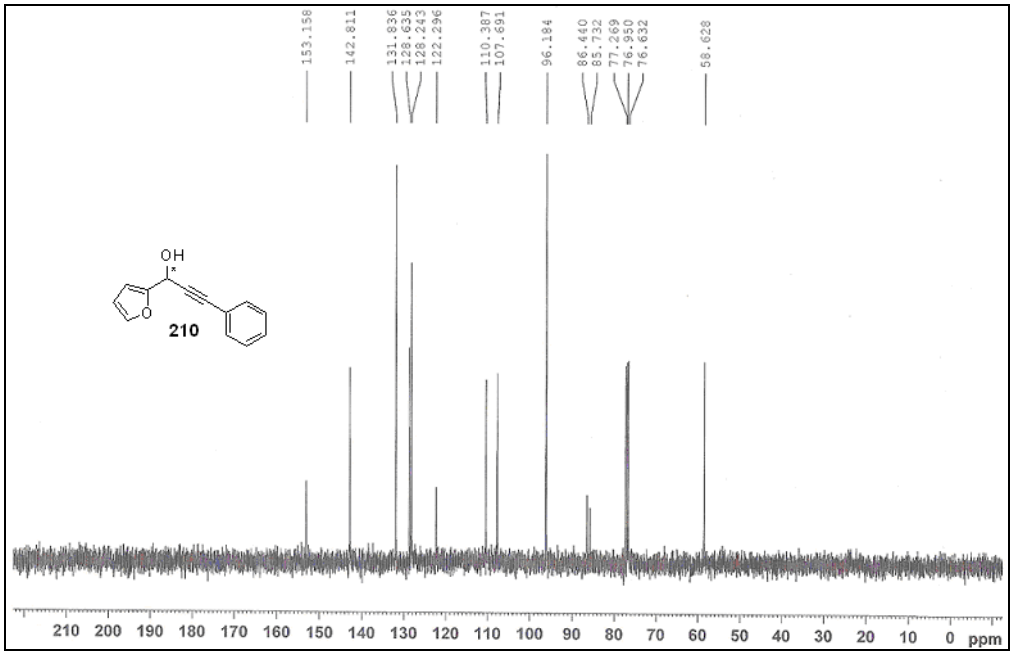


Figure A.52 ^{13}C-NMR spectrum of compound **210**.

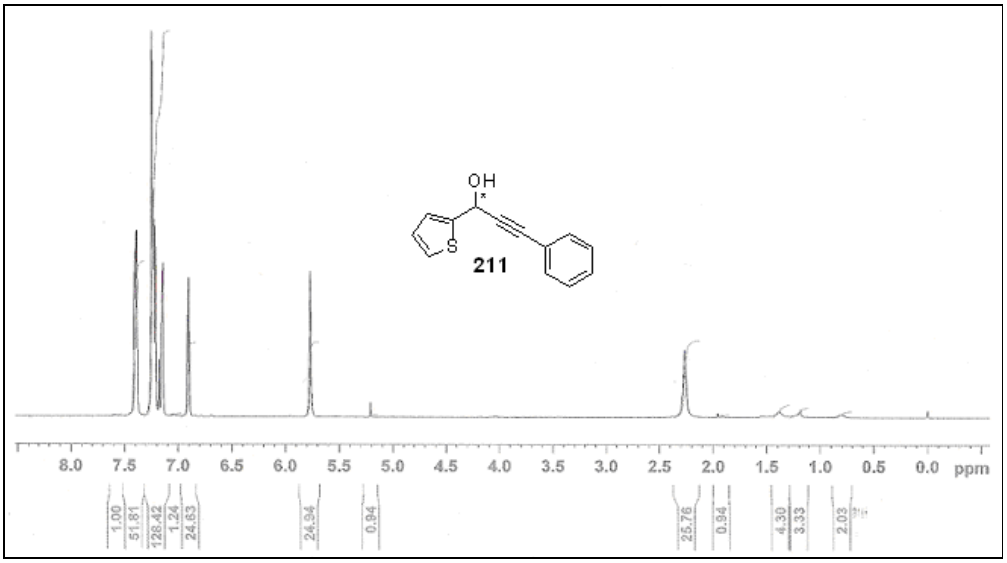


Figure A.53 ^{1}H-NMR spectrum of compound **211**.

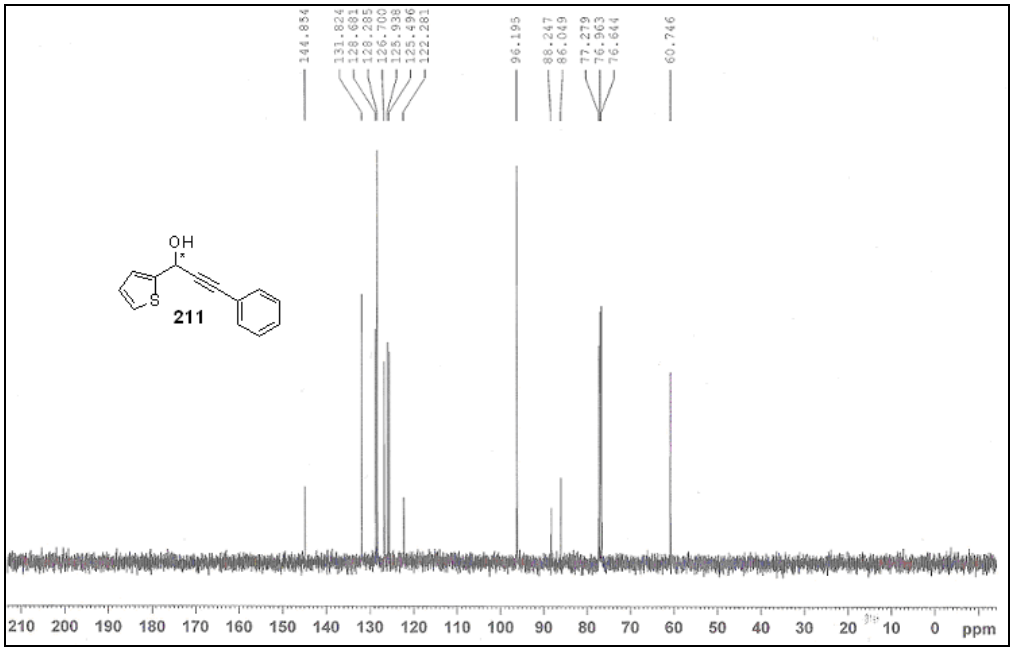


Figure A.54 ^{13}C-NMR spectrum of compound **211**.

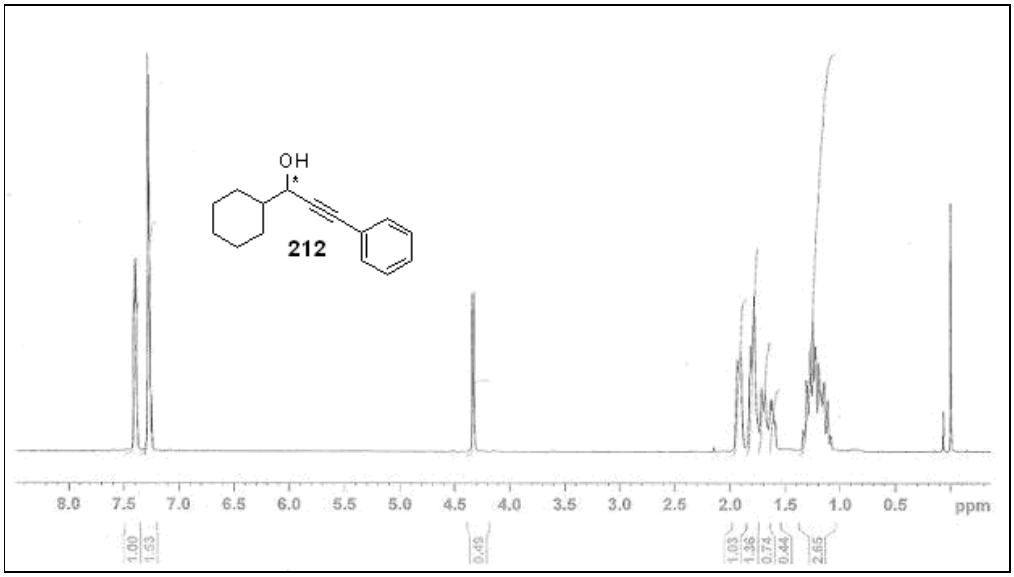


Figure A.55 ^{1}H-NMR spectrum of compound **212**.

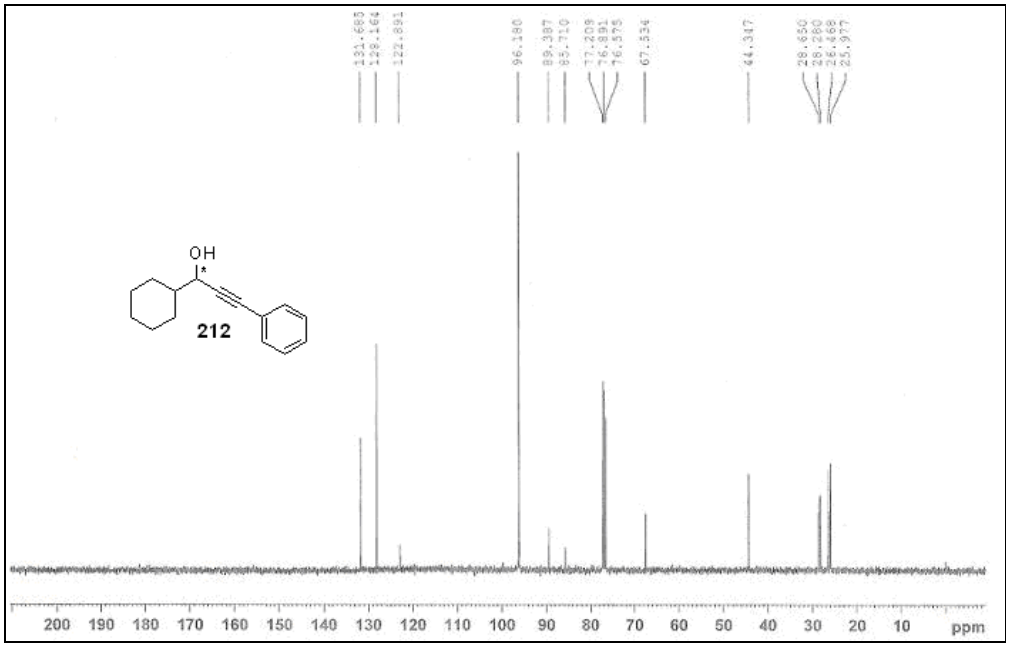


Figure A.56 ^{13}C-NMR spectrum of compound **212**.

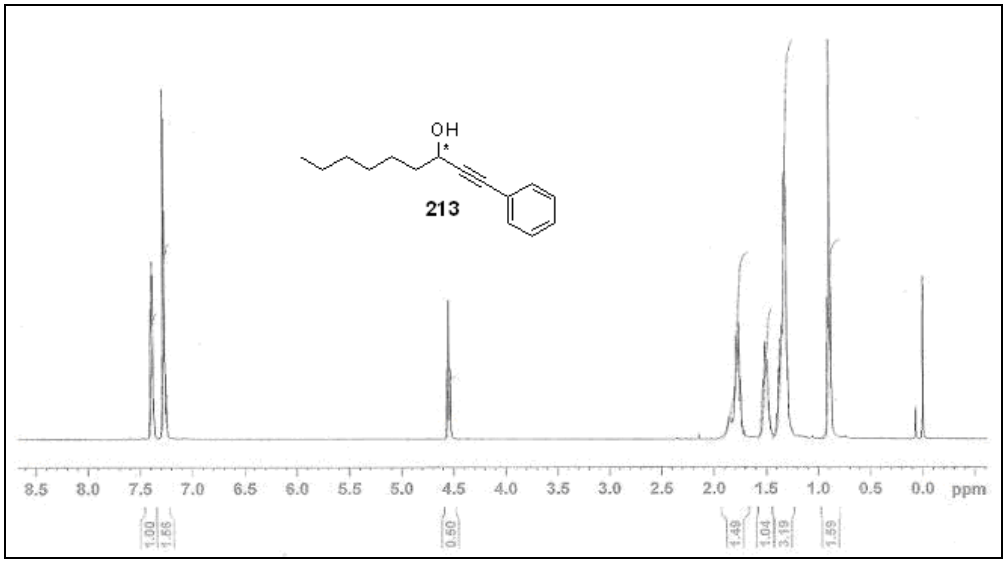


Figure A.57 ^{1}H-NMR spectrum of compound **213**.

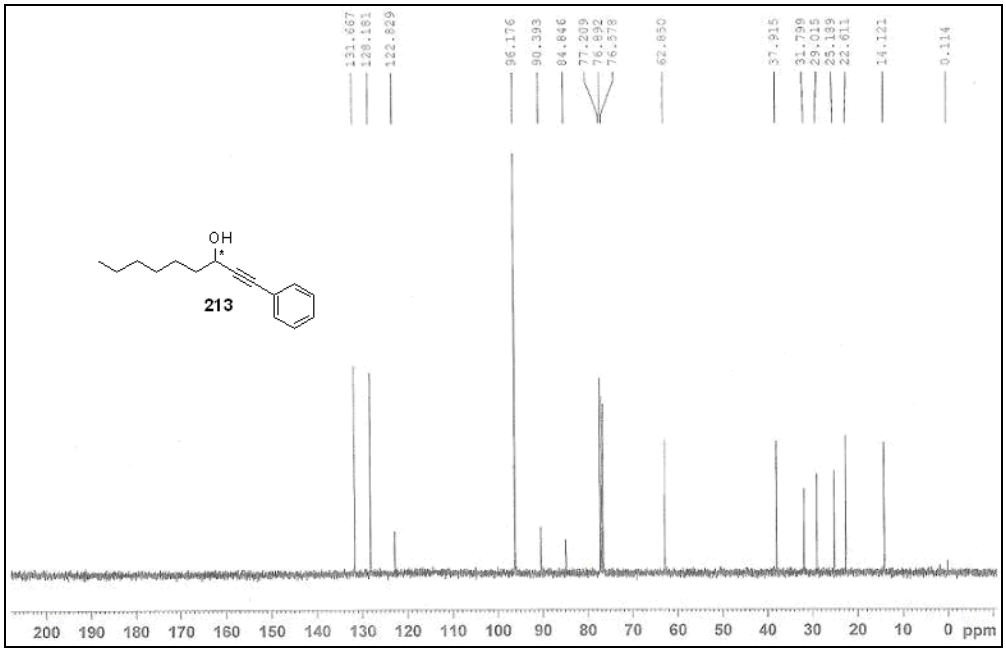


Figure A.58 ^{13}C-NMR spectrum of compound **213**.

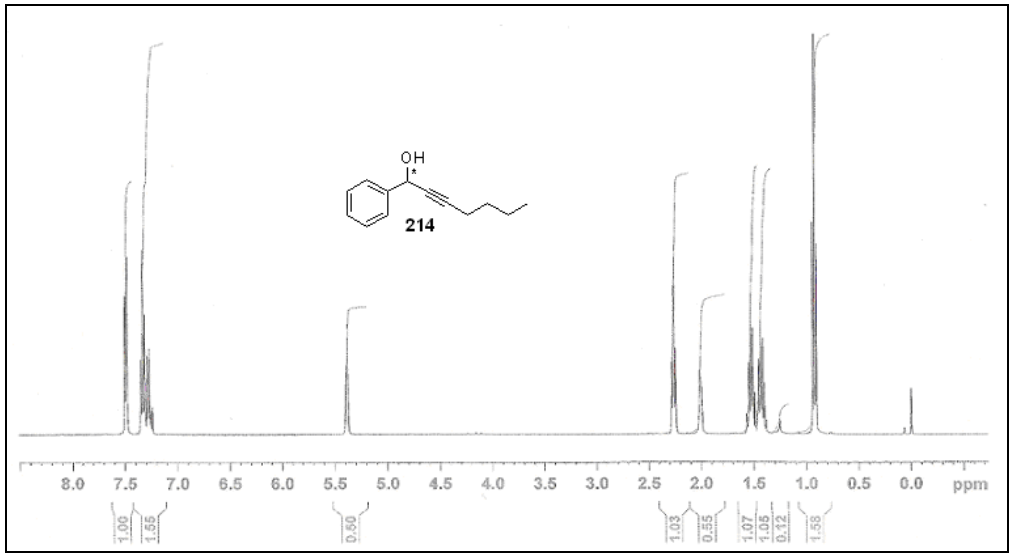


Figure A.59 ^{1}H-NMR spectrum of compound **214**.

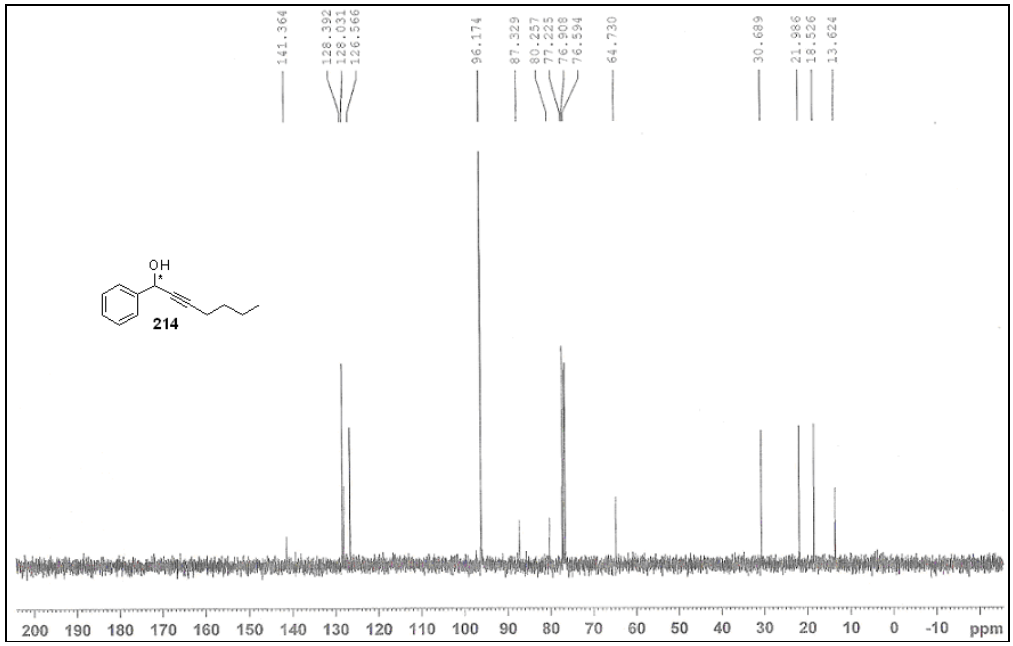


Figure A.60 ^{13}C-NMR spectrum of compound **214**.

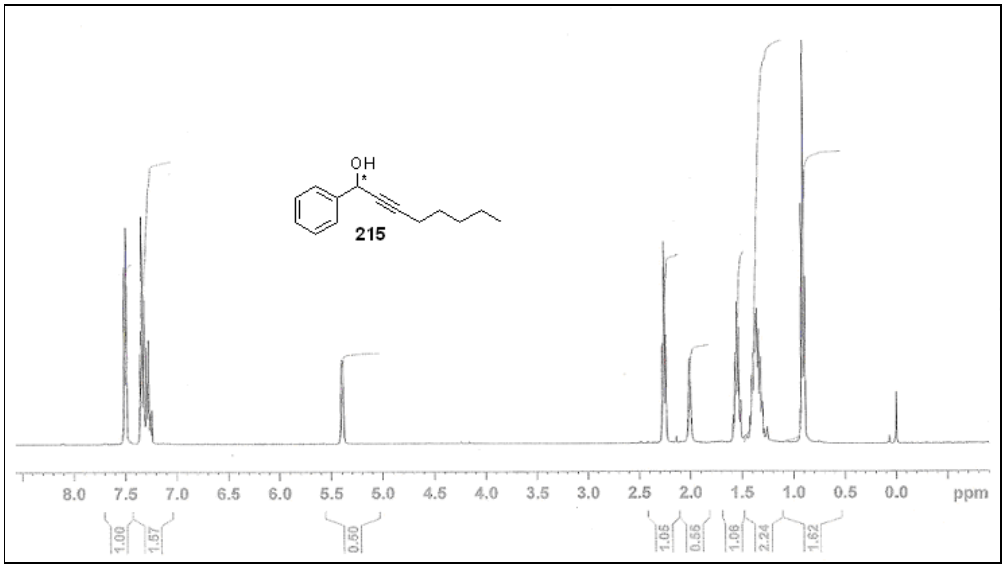


Figure A.61 ^{1}H-NMR spectrum of compound **215**.

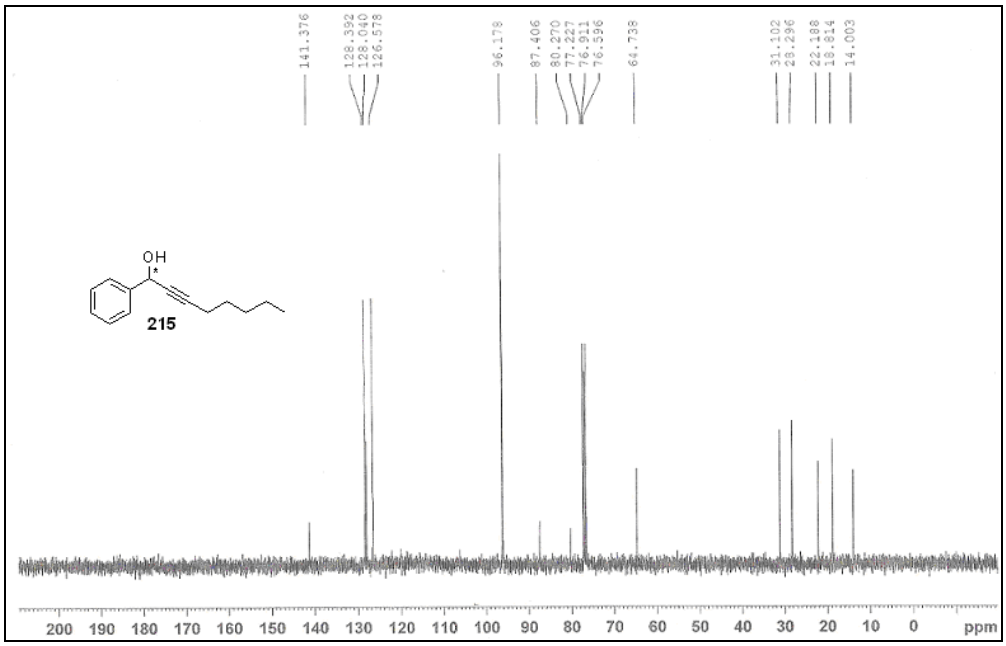


Figure A.62 ^{13}C-NMR spectrum of compound **215**.

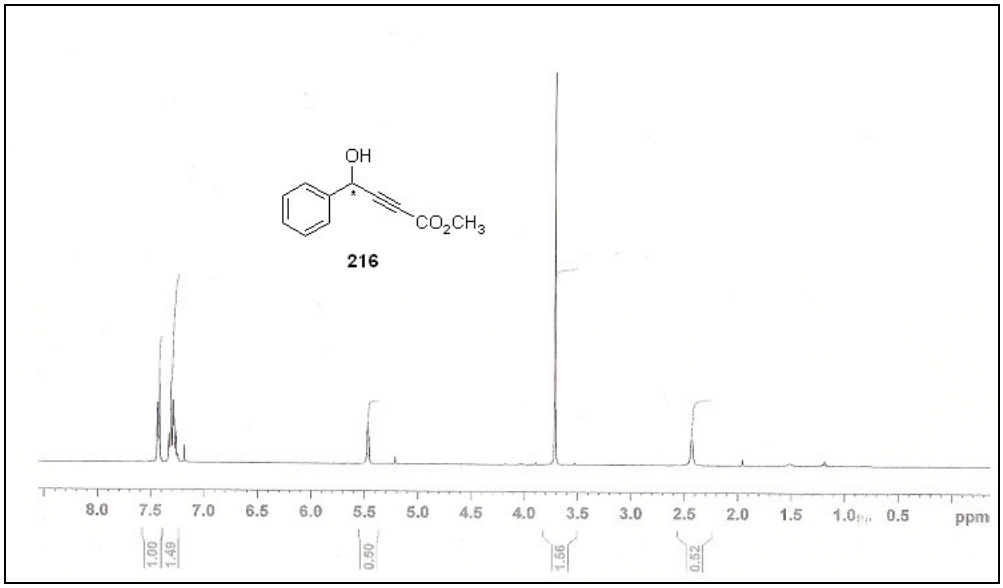


Figure A.63 ^{1}H-NMR spectrum of compound **216**.

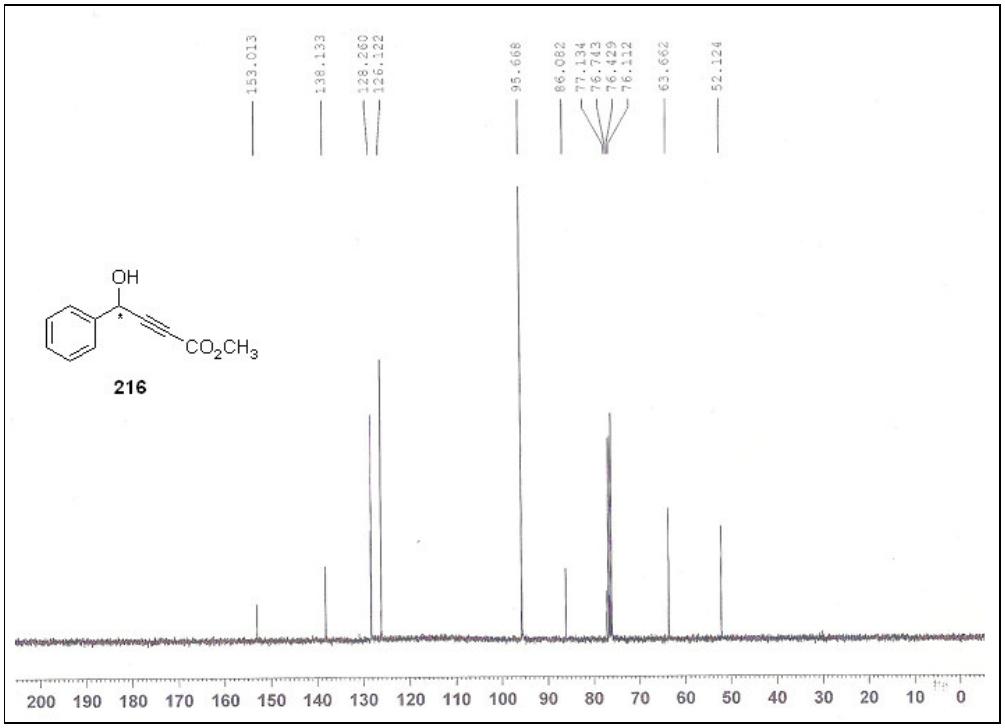
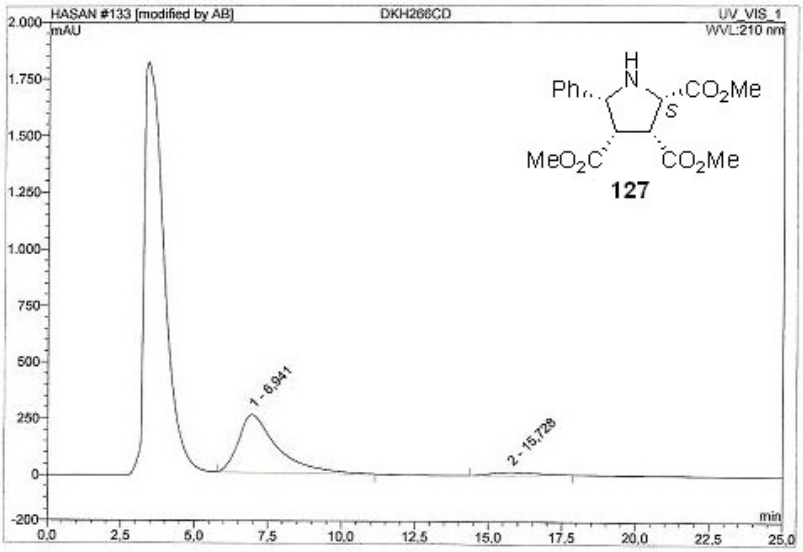
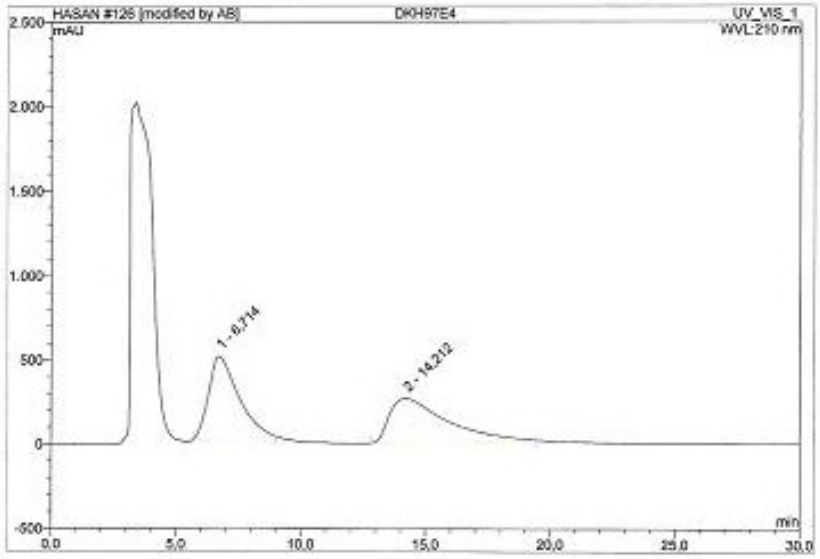


Figure A.64 ^{13}C-NMR spectrum of compound **216**.



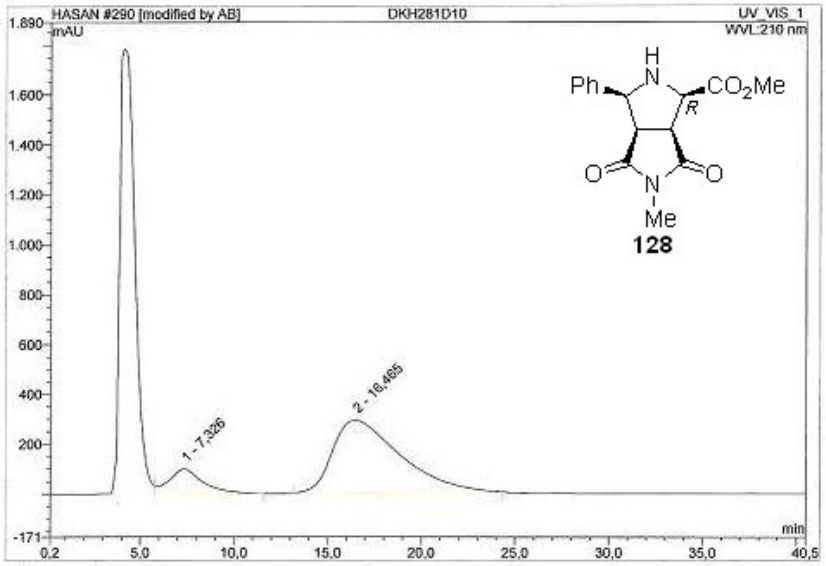
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6,94	n.a.	253,365	381,646	94,43	n.a.	BMB*
2	15,73	n.a.	12,786	22,523	5,57	n.a.	BMB*
Total:			266,151	404,169	100,00	0,000	

Figure A.65 HPLC chromatogram of compound **127**.



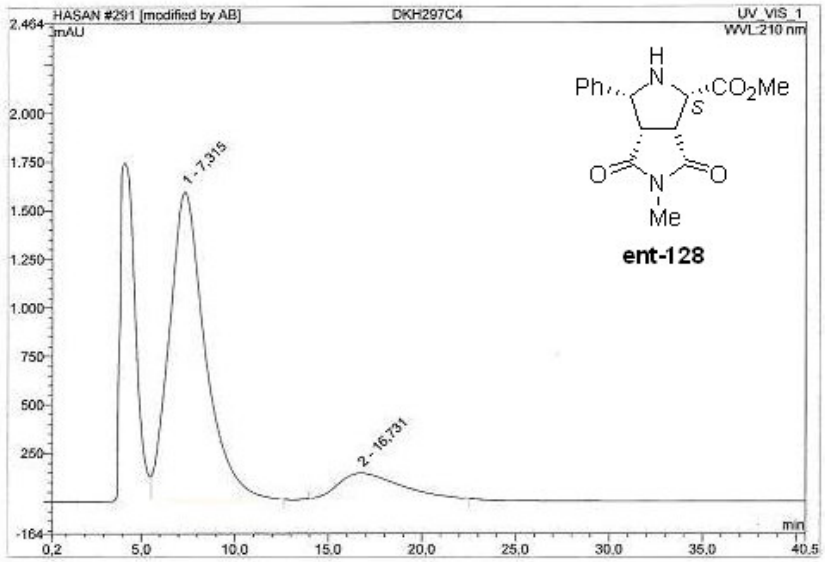
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6,71	n.a.	489,233	663,006	49,21	n.a.	BMB*
2	14,21	n.a.	262,278	684,202	50,79	n.a.	BMB*
Total:			751,511	1347,208	100,00	0,000	

Figure A.66 HPLC chromatogram of ***racemic* 127 + *ent*-127**.



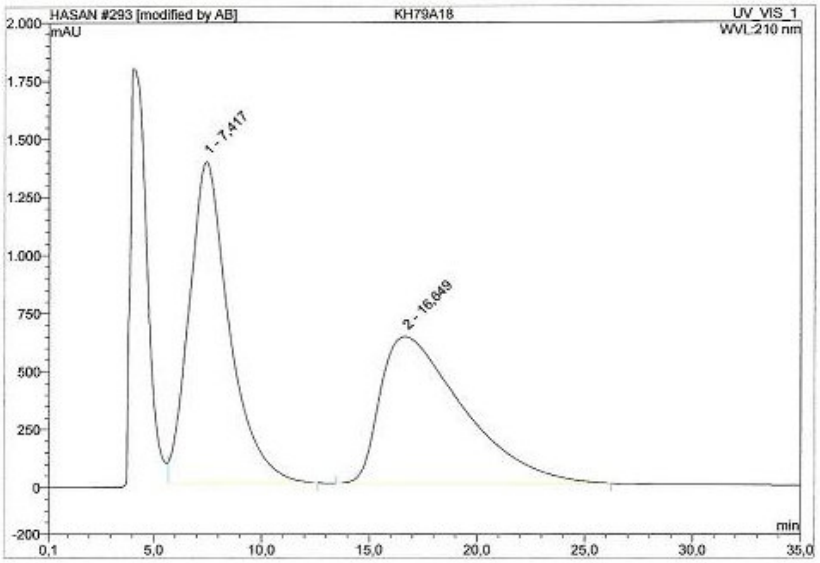
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7,33	n.a.	96,634	202,066	14,30	n.a.	MB*
2	16,46	n.a.	290,169	1210,597	85,70	n.a.	BM *
Total:			386,803	1412,662	100,00	0,000	

Figure A.67 HPLC chromatogram of compound **128**.



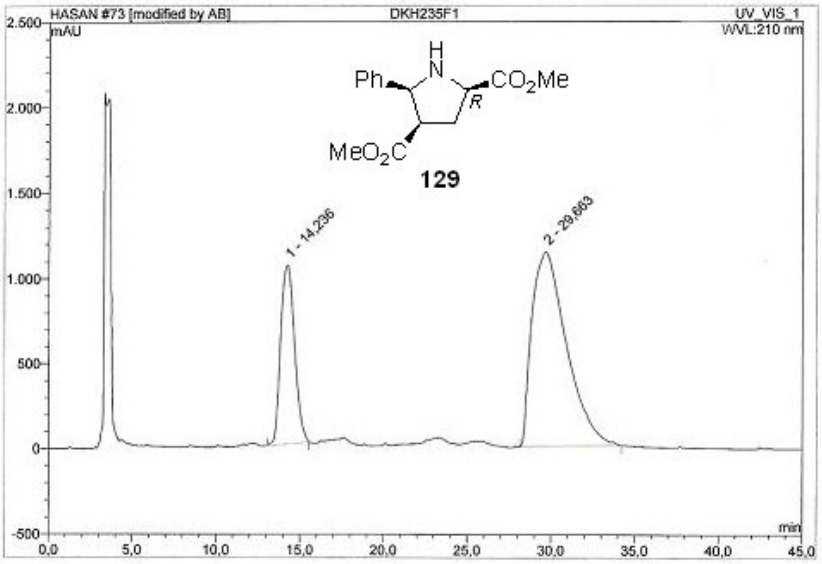
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7,31	n.a.	1580,896	3495,635	87,60	n.a.	MB*
2	16,73	n.a.	130,833	494,910	12,40	n.a.	BMB*
Total:			1711,729	3990,545	100,00	0,000	

Figure A.68 HPLC chromatogram of compound ***ent*-128**.



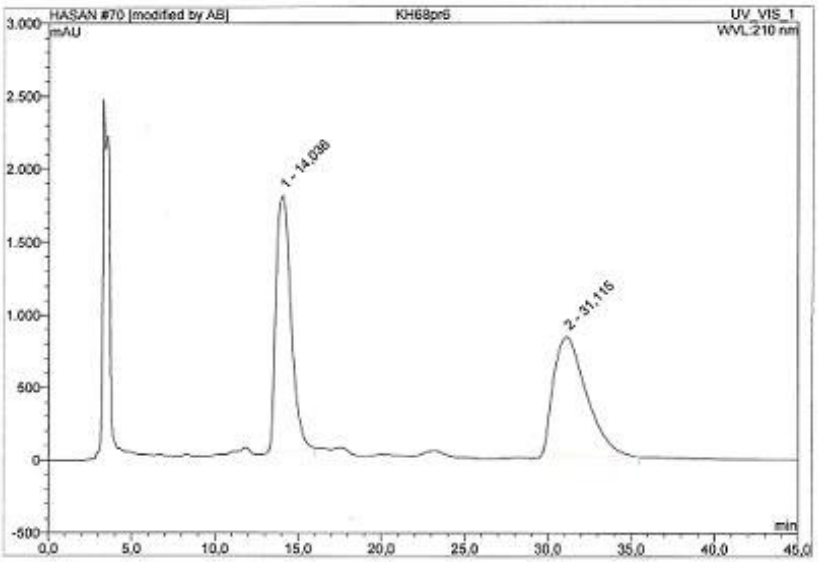
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7,42	n.a.	1382,056	2981,798	51,40	n.a.	M *
2	16,65	n.a.	631,836	2819,539	48,60	n.a.	BMB*
Total:			2013,892	5801,337	100,00	0,000	

Figure A.69 HPLC chromatogram of ***racemic* 128 + *ent*-128**.



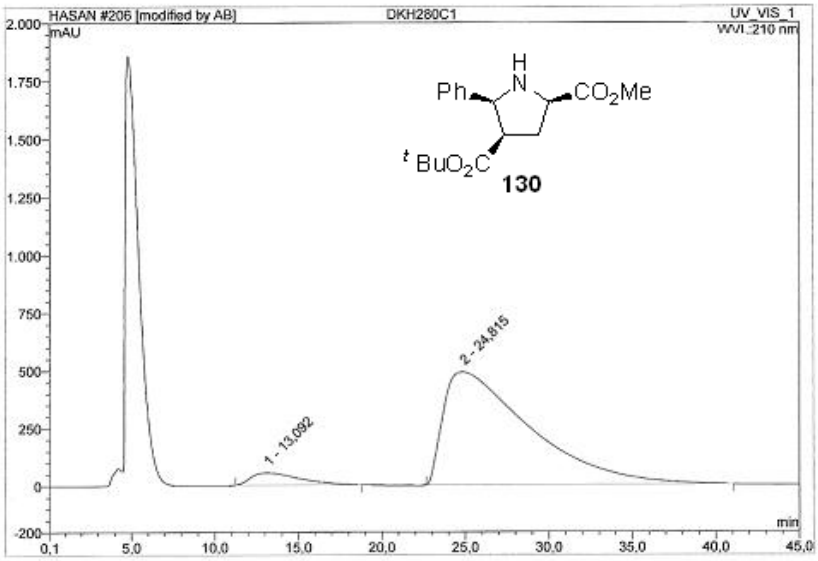
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,24	n.a.	1047,791	1005,721	27,01	n.a.	BMB*
2	29,66	n.a.	1139,569	2718,134	72,99	n.a.	BMB*
Total:			2187,360	3723,855	100,00	0,000	

Figure A.70 HPLC chromatogram of compound **129**.



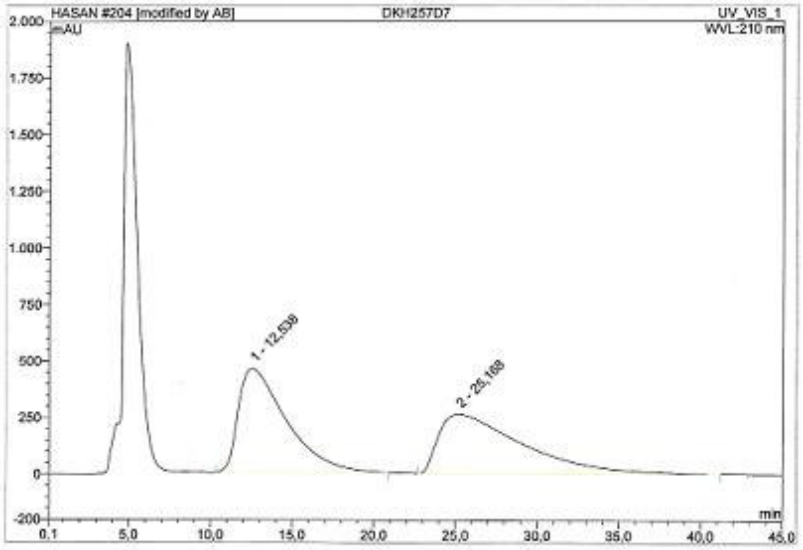
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,04	n.a.	1755,249	1825,978	49,51	n.a.	BMB*
2	31,12	n.a.	813,046	1862,221	50,49	n.a.	BMB*
Total:			2568,295	3688,199	100,00	0,000	

Figure A.71 HPLC chromatogram of ***racemic* 129 + *ent*-129**.



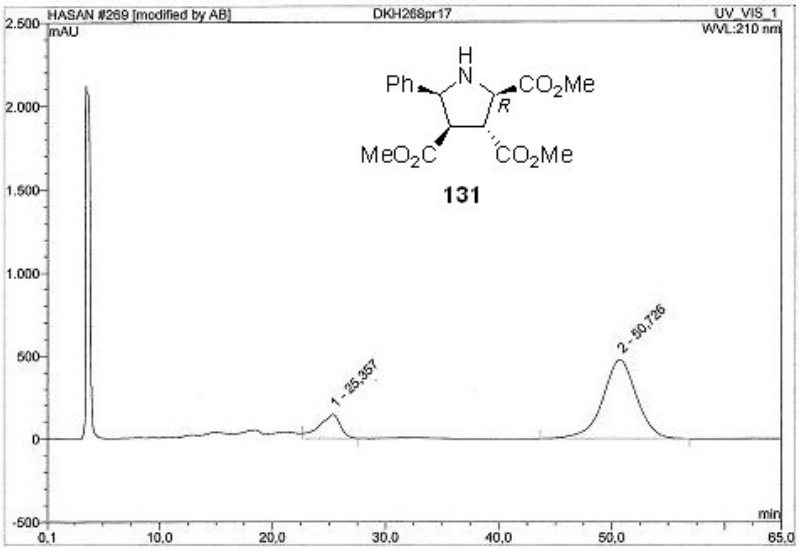
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13,09	n.a.	52,840	175,845	5,66	n.a.	BMB*
2	24,82	n.a.	488,235	2933,124	94,34	n.a.	BMB*
Total:			541,076	3108,969	100,00	0,000	

Figure A.72 HPLC chromatogram of compound **130**.



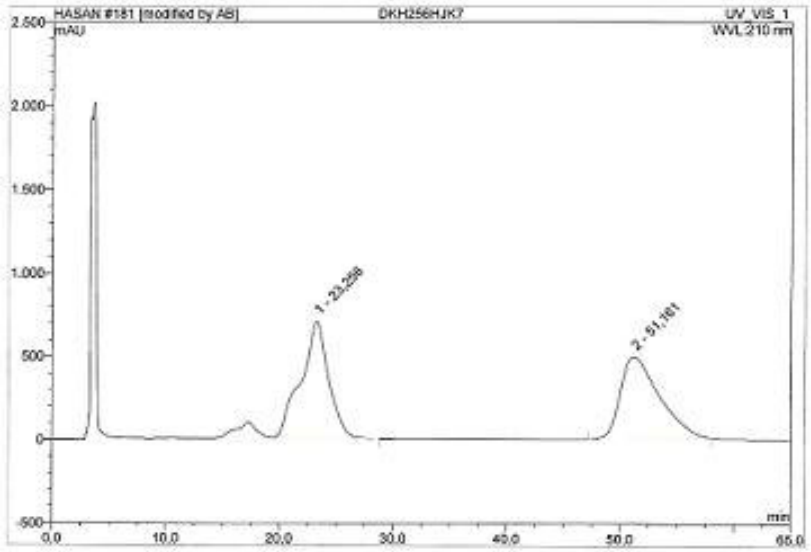
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,54	n.a.	458,211	1561,514	50,26	n.a.	BMB*
2	25,17	n.a.	260,501	1545,320	49,74	n.a.	BMB*
Total:			718,712	3106,834	100,00	0,000	

Figure A.73 HPLC chromatogram of ***racemic* 130 + *ent*-130**.



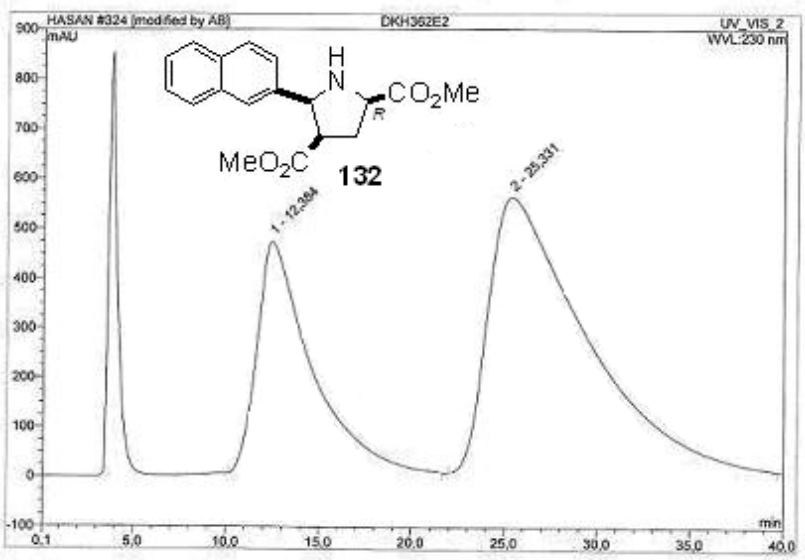
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25,36	n.a.	143,307	306,484	15,80	n.a.	MB*
2	50,73	n.a.	472,401	1633,011	84,20	n.a.	BMB*
Total:			615,708	1939,495	100,00	0,000	

Figure A.74 HPLC chromatogram of compound **131**.



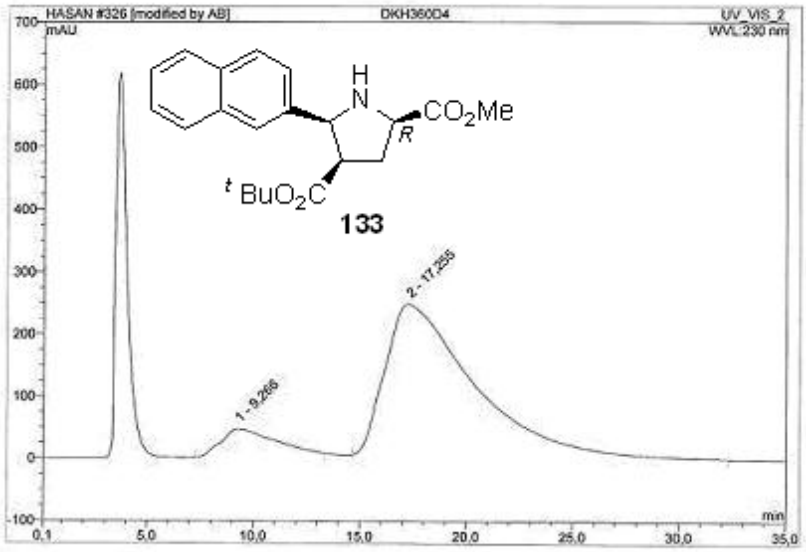
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	23,26	n.a.	698,190	1956,426	49,91	n.a.	BMB*
2	51,16	n.a.	491,976	1963,405	50,09	n.a.	BMB*
Total:			1190,165	3919,832	100,00	0,000	

Figure A.75 HPLC chromatogram of ***racemic* 131 + *ent*-131**.



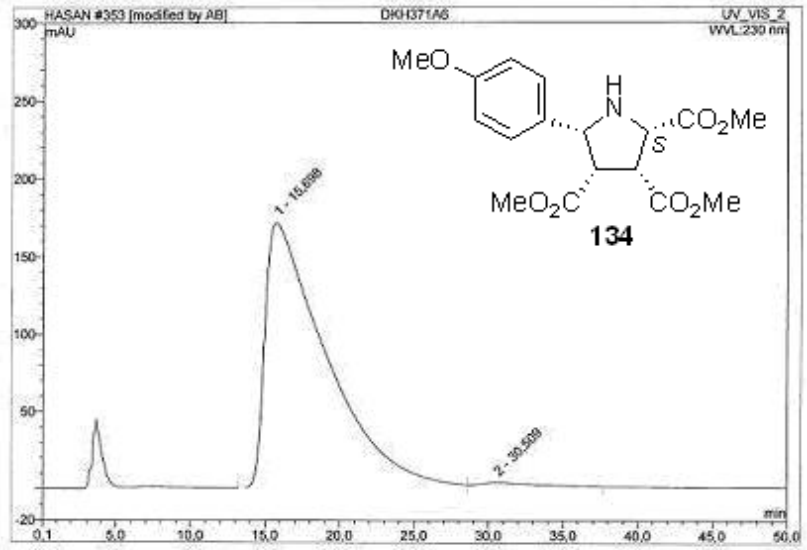
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,38	n.a.	466,457	1575,325	31,55	n.a.	BMB*
2	25,33	n.a.	555,038	3417,460	68,45	n.a.	BM *
Total:			1021,494	4992,785	100,00	0,000	

Figure A.76 HPLC chromatogram of compound **132**.



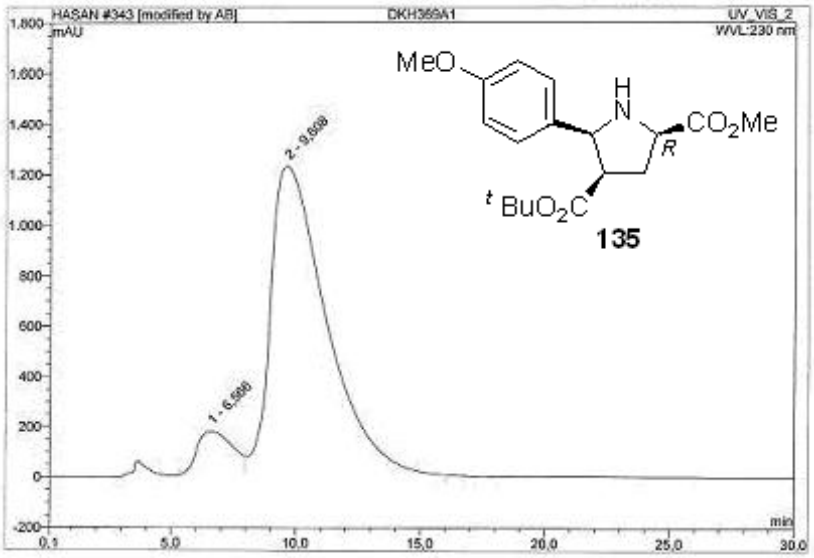
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	9,27	n.a.	46,213	147,748	10,82	n.a.	M *
2	17,25	n.a.	247,323	1218,076	89,18	n.a.	M *
Total:			293,536	1365,825	100,00	0,000	

Figure A.77 HPLC chromatogram of compound **133**.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	15,70	n.a.	171,230	819,623	97,29	n.a.	BM *
2	30,51	n.a.	3,783	22,856	2,71	n.a.	M *
Total:			175,014	842,478	100,00	0,000	

Figure A.78 HPLC chromatogram of compound **134**.

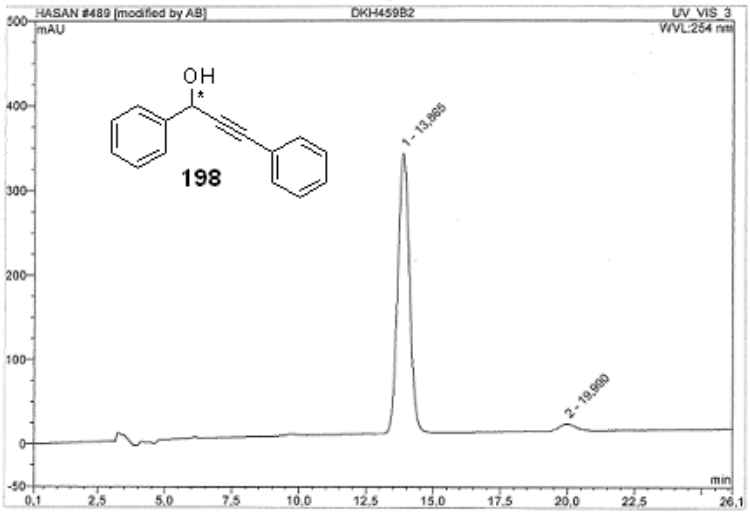


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6,57	n.a.	172,667	284,786	8,23	n.a.	BM *
2	9,61	n.a.	1222,447	3173,671	91,77	n.a.	MB*
Total:			1395,113	3458,457	100,00	0,000	

Figure A.79 HPLC chromatogram of compound **135**.

489 DKH459B2

Sample Name:	**DKH459B2**	*Injection Volume:*	**20,0**
Vial Number:	**501**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**23.2.2007 21:56**	*Sample Weight:*	**1,0000**
Run Time (min):	**26,03**	*Sample Amount:*	**1,0000**

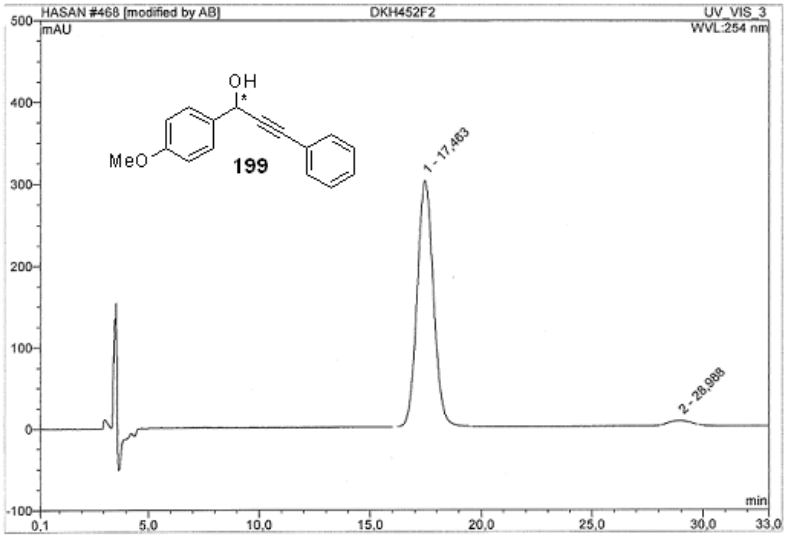


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13,86	n.a.	331,137	169,128	97,75	n.a.	BM *
2	19,99	n.a.	6,839	3,888	2,25	n.a.	BMB*
Total:			337,976	173,015	100,00	0,000	

Figure A.80 HPLC chromatogram of compound **198**.

468 DKH452F2

Sample Name:	**DKH452F2**	*Injection Volume:*	**20,0**
Vial Number:	**480**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**1.2.2007 20:32**	*Sample Weight:*	**1,0000**
Run Time (min):	**32,83**	*Sample Amount:*	**1,0000**

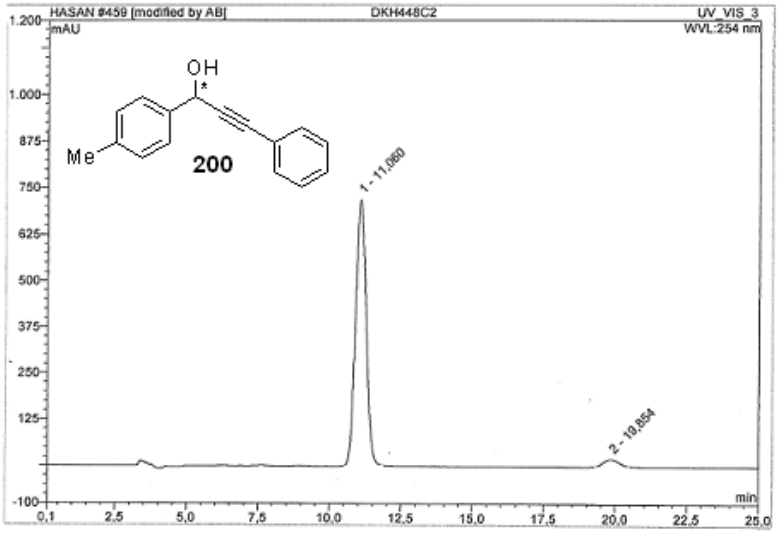


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	17,46	n.a.	302,410	258,535	97,90	n.a.	BM *
2	28,99	n.a.	5,744	5,537	2,10	n.a.	BMB*
Total:			308,154	264,072	100,00	0,000	

Figure A.81 HPLC chromatogram of compound **199**.

459 DKH448C2

Sample Name:	**DKH448C2**	*Injection Volume:*	**20,0**
Vial Number:	**469**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**17.1.2007 18:31**	*Sample Weight:*	**1,0000**
Run Time (min):	**24,88**	*Sample Amount:*	**1,0000**

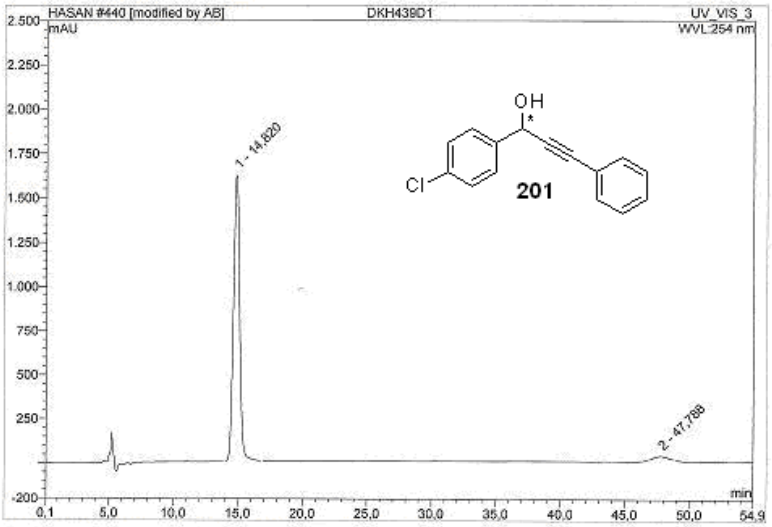


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11,06	n.a.	715,563	306,841	96,40	n.a.	BMB*
2	19,85	n.a.	18,720	11,469	3,60	n.a.	BMB*
Total:			734,282	318,309	100,00	0,000	

Figure A.82 HPLC chromatogram of compound **200**.

440 DKH439D1

Sample Name:	**DKH439D1**	*Injection Volume:*	**20,0**
Vial Number:	**450**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**28.12.2006 23:45**	*Sample Weight:*	**1,0000**
Run Time (min):	**54,82**	*Sample Amount:*	**1,0000**

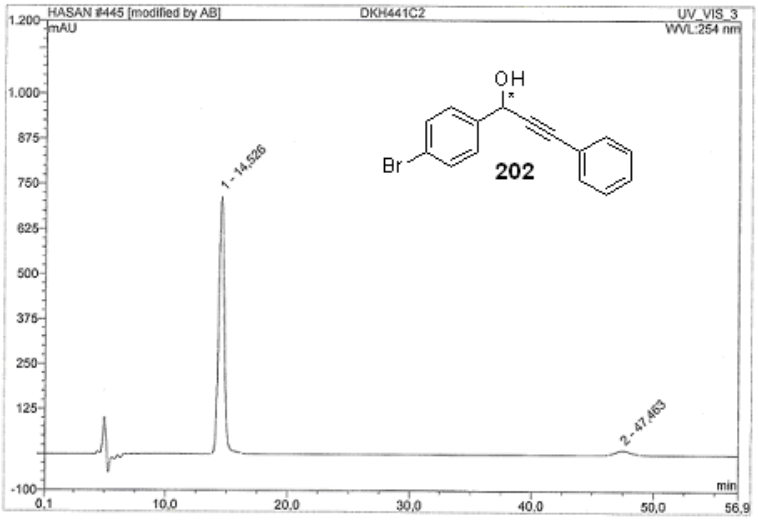


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,82	n.a.	1618,131	907,709	97,27	n.a.	BMB*
2	47,79	n.a.	20,963	25,481	2,73	n.a.	BMB*
Total:			1639,094	933,189	100,00	0,000	

Figure A.83 HPLC chromatogram of compound **201**.

445 DKH441C2

Sample Name:	**DKH441C2**	*Injection Volume:*	**20,0**
Vial Number:	**455**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**29.12.2006 3:46**	*Sample Weight:*	**1,0000**
Run Time (min):	**56,80**	*Sample Amount:*	**1,0000**

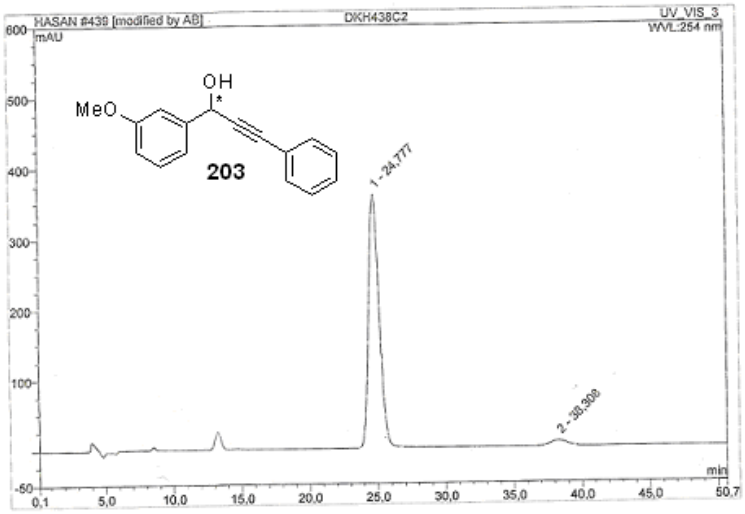


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,53	n.a.	711,981	377,871	96,10	n.a.	BMB*
2	47,46	n.a.	11,001	15,341	3,90	n.a.	BMB*
Total:			722,982	393,212	100,00	0,000	

Figure A.84 HPLC chromatogram of compound **202**.

439 DKH438C2

Sample Name:	**DKH438C2**	*Injection Volume:*	**20,0**
Vial Number:	**449**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**26.12.2006 11:52**	*Sample Weight:*	**1,0000**
Run Time (min):	**50,54**	*Sample Amount:*	**1,0000**

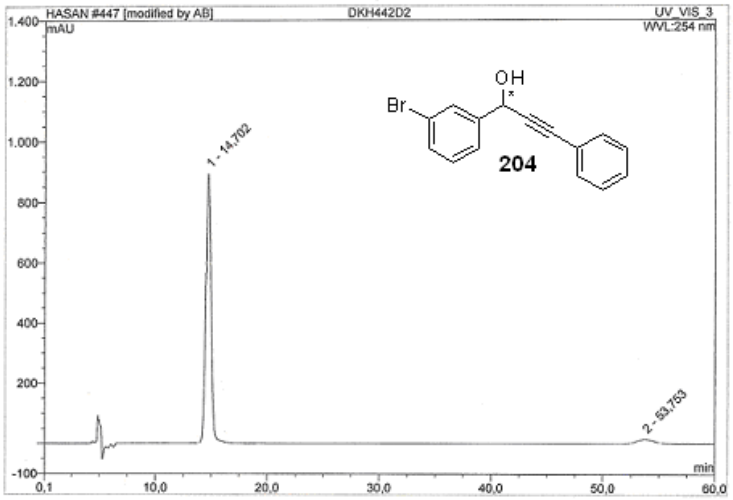


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24,78	n.a.	358,815	321,079	97,55	n.a.	BMB*
2	38,31	n.a.	6,736	8,047	2,45	n.a.	BMB*
Total:			365,551	329,126	100,00	0,000	

Figure A.85 HPLC chromatogram of compound **203**.

447 DKH442D2

Sample Name:	**DKH442D2**	*Injection Volume:*	**20,0**
Vial Number:	**457**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**29.12.2006 5:44**	*Sample Weight:*	**1,0000**
Run Time (min):	**59,88**	*Sample Amount:*	**1,0000**

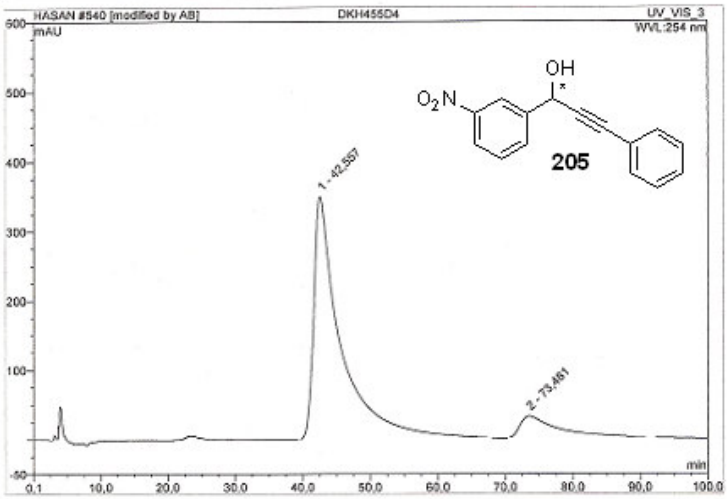


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	14,70	n.a.	891,810	482,647	96,05	n.a.	BMB*
2	53,75	n.a.	12,868	19,858	3,95	n.a.	BMB*
Total:			904,678	502,505	100,00	0,000	

Figure A.86 HPLC chromatogram of compound **204**.

540 DKH455D4

Sample Name:	**DKH455D4**	*Injection Volume:*	**20,0**
Vial Number:	**556**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**2.4.2007 17:44**	*Sample Weight:*	**1,0000**
Run Time (min):	**99,88**	*Sample Amount:*	**1,0000**

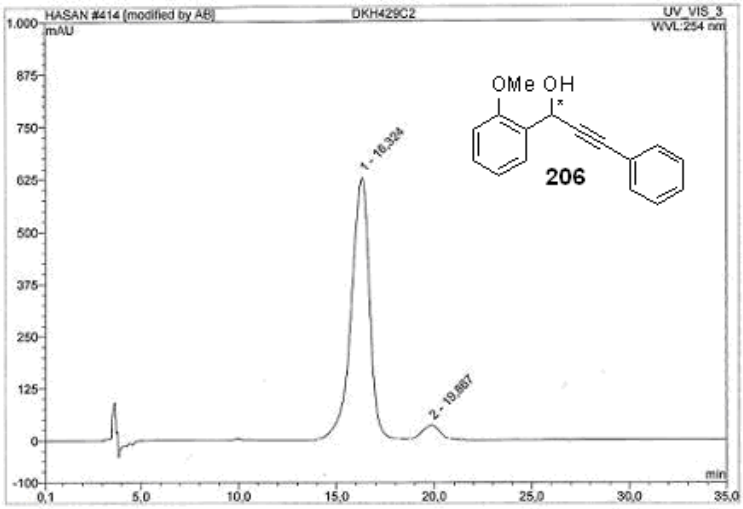


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	42,56	n.a.	349,989	1623,152	88,83	n.a.	BMB*
2	73,48	n.a.	31,116	204,105	11,17	n.a.	BMB*
Total:			381,105	1827,258	100,00	0,000	

Figure A.87 HPLC chromatogram of compound **205**.

414 DKH429C2

Sample Name:	**DKH429C2**	*Injection Volume:*	**20,0**
Vial Number:	**423**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**11.12.2006 5:27**	*Sample Weight:*	**1,0000**
Run Time (min):	**34,84**	*Sample Amount:*	**1,0000**

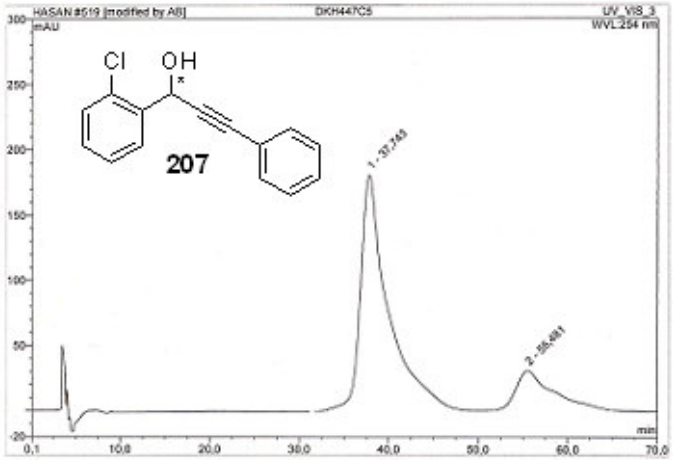


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16,32	n.a.	623,648	672,205	95,59	n.a.	BMB*
2	19,87	n.a.	31,691	31,042	4,41	n.a.	BMB*
Total:			655,339	703,247	100,00	0,000	

Figure A.88 HPLC chromatogram of compound **206**.

519 DKH447C5

Sample Name:	**DKH447C5**	*Injection Volume:*	**20,0**
Vial Number:	**534**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**24.3.2007 16:28**	*Sample Weight:*	**1,0000**
Run Time (min):	**69,88**	*Sample Amount:*	**1,0000**

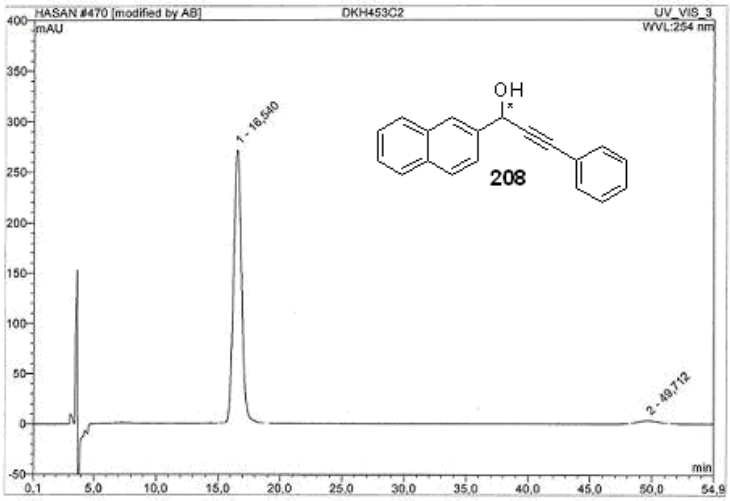


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	37,74	n.a.	181,578	668,945	82,31	n.a.	BM *
2	55,48	n.a.	30,240	143,813	17,69	n.a.	BMB*
Total:			211,818	812,758	100,00	0,000	

Figure A.89 HPLC chromatogram of compound **207**.

470 DKH453C2

Sample Name:	**DKH453C2**	*Injection Volume:*	**20,0**
Vial Number:	**482**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**1.2.2007 22:02**	*Sample Weight:*	**1,0000**
Run Time (min):	**54,83**	*Sample Amount:*	**1,0000**

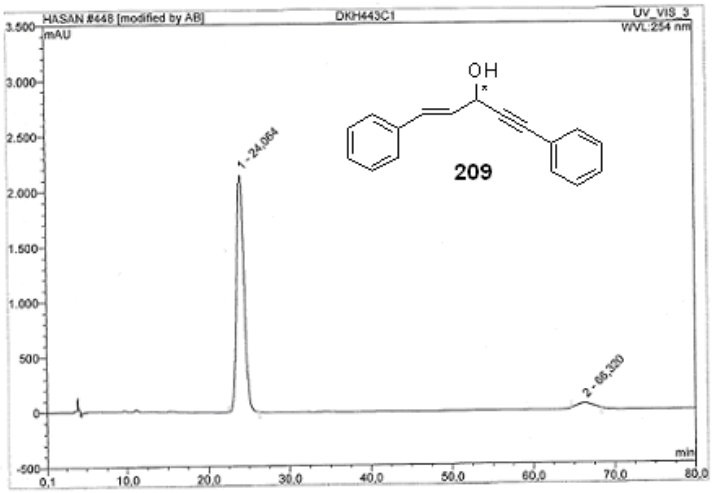


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16,54	n.a.	271,035	204,438	97,61	n.a.	BMB*
2	49,71	n.a.	2,875	5,010	2,39	n.a.	BMB*
Total:			273,910	209,448	100,00	0,000	

Figure A.90 HPLC chromatogram of compound **208**.

448 DKH443C1

Sample Name:	**DKH443C1**	*Injection Volume:*	**20,0**
Vial Number:	**458**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**9.1.2007 12:11**	*Sample Weight:*	**1,0000**
Run Time (min):	**79,88**	*Sample Amount:*	**1,0000**

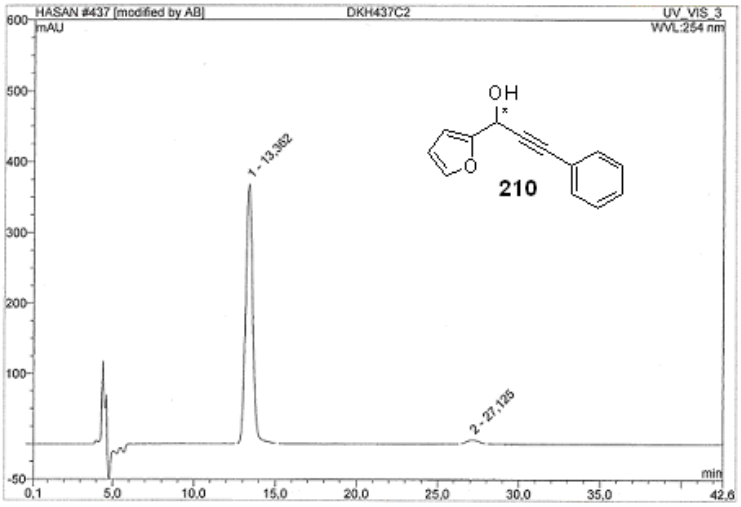


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	24,06	n.a.	2146,602	2298,192	96,43	n.a.	BMB*
2	66,32	n.a.	40,358	84,960	3,57	n.a.	BMB*
Total:			2186,959	2383,152	100,00	0,000	

Figure A.91 HPLC chromatogram of compound **209**.

437 DKH437C2

Sample Name:	**DKH437C2**	*Injection Volume:*	**20,0**
Vial Number:	**447**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**26.12.2006 9:47**	*Sample Weight:*	**1,0000**
Run Time (min):	**42,45**	*Sample Amount:*	**1,0000**

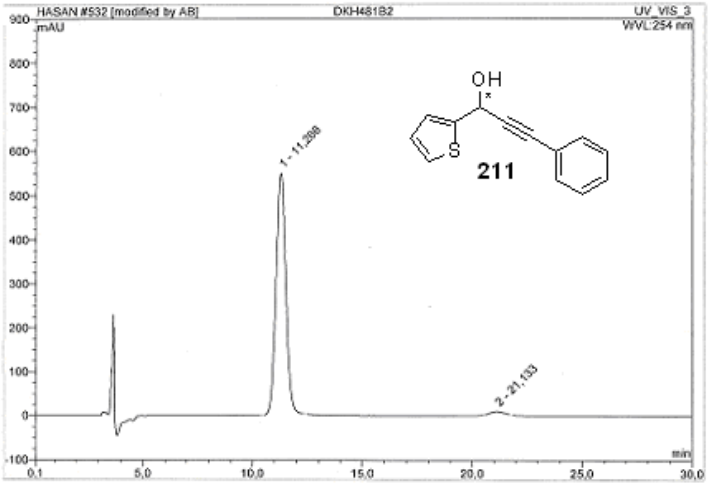


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	13,36	n.a.	366,898	184,758	97,67	n.a.	BMB*
2	27,13	n.a.	5,151	4,404	2,33	n.a.	BMB*
Total:			372,049	189,162	100,00	0,000	

Figure A.92 HPLC chromatogram of compound **210**.

532 DKH481B2

Sample Name:	**DKH481B2**	*Injection Volume:*	**20,0**
Vial Number:	**548**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**30.3.2007 13:45**	*Sample Weight:*	**1,0000**
Run Time (min):	**29,88**	*Sample Amount:*	**1,0000**

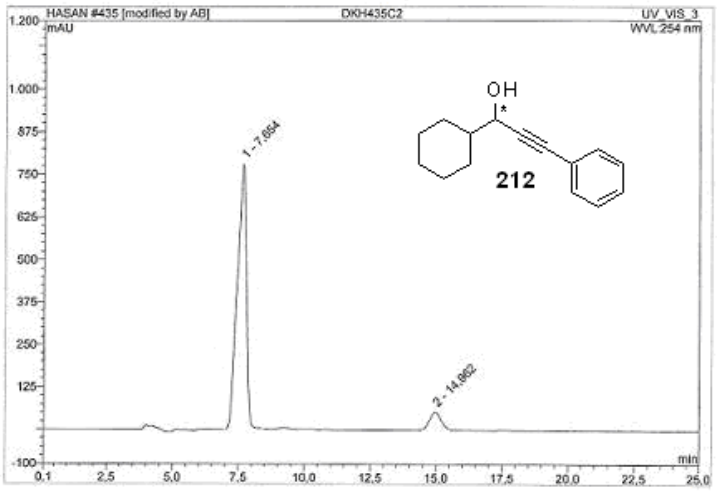


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	11,27	n.a.	548,512	283,242	98,21	n.a.	BMB*
2	21,13	n.a.	7,148	5,161	1,79	n.a.	BMB*
Total:			555,660	288,403	100,00	0,000	

Figure A.93 HPLC chromatogram of compound **211**.

435 DKH435C2

Sample Name:	**DKH435C2**	*Injection Volume:*	**20,0**
Vial Number:	**444**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**26.12.2006 6:31**	*Sample Weight:*	**1,0000**
Run Time (min):	**24,83**	*Sample Amount:*	**1,0000**

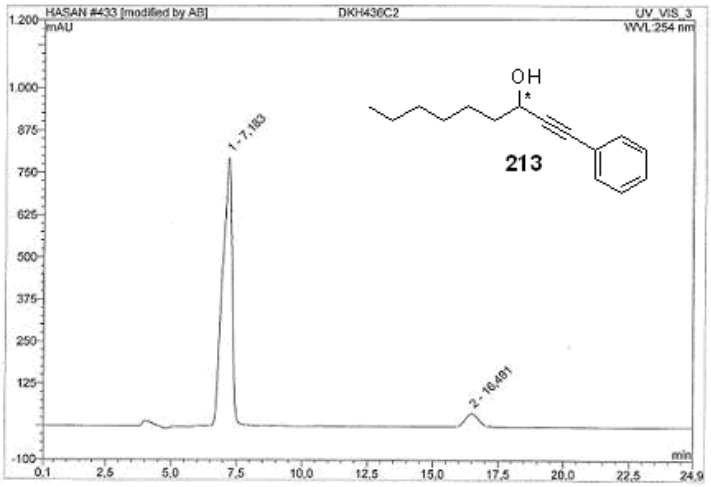


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7,65	n.a.	777,205	311,420	92,68	n.a.	BMB*
2	14,96	n.a.	49,630	24,585	7,32	n.a.	BMB*
Total:			826,834	336,005	100,00	0,000	

Figure A.94 HPLC chromatogram of compound **212**.

433 DKH436C2

Sample Name:	**DKH436C2**	*Injection Volume:*	**20,0**
Vial Number:	**442**	*Channel:*	**UV_VIS_3**
Sample Type:	**unknown**	*Wavelength:*	**254**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**26.12.2006 5:39**	*Sample Weight:*	**1,0000**
Run Time (min):	**24,81**	*Sample Amount:*	**1,0000**

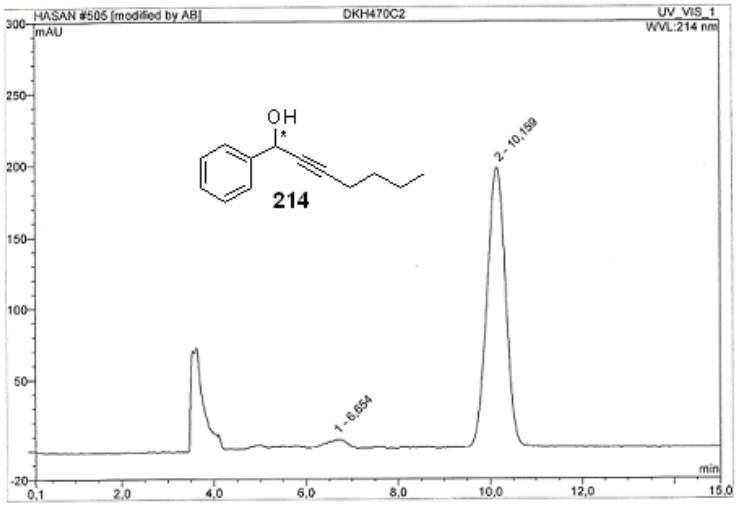


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	7,18	n.a.	791,330	332,234	94,28	n.a.	BMB*
2	16,49	n.a.	36,625	20,151	5,72	n.a.	BMB*
Total:			827,955	352,386	100,00	0,000	

Figure A.95 HPLC chromatogram of compound **213**.

505 DKH470C2

Sample Name:	**DKH470C2**	*Injection Volume:*	**20,0**
Vial Number:	**520**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**214**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**15.3.2007 19:58**	*Sample Weight:*	**1,0000**
Run Time (min):	**14,88**	*Sample Amount:*	**1,0000**

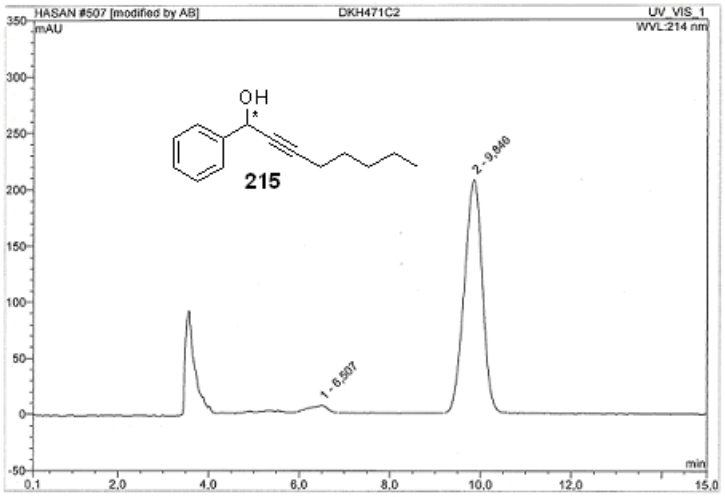


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6,65	n.a.	5,341	2,513	2,69	n.a.	BMB*
2	10,16	n.a.	195,716	90,970	97,31	n.a.	BMB*
Total:			201,057	93,483	100,00	0,000	

Figure A.96 HPLC chromatogram of compound **214**.

507 DKH471C2

Sample Name:	**DKH471C2**	*Injection Volume:*	**20,0**
Vial Number:	**522**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**214**
Control Program:	**PROGRAM01**	*Bandwidth:*	**2**
Quantif. Method:	**METHOD01**	*Dilution Factor:*	**1,0000**
Recording Time:	**15.3.2007 20:43**	*Sample Weight:*	**1,0000**
Run Time (min):	**14,88**	*Sample Amount:*	**1,0000**

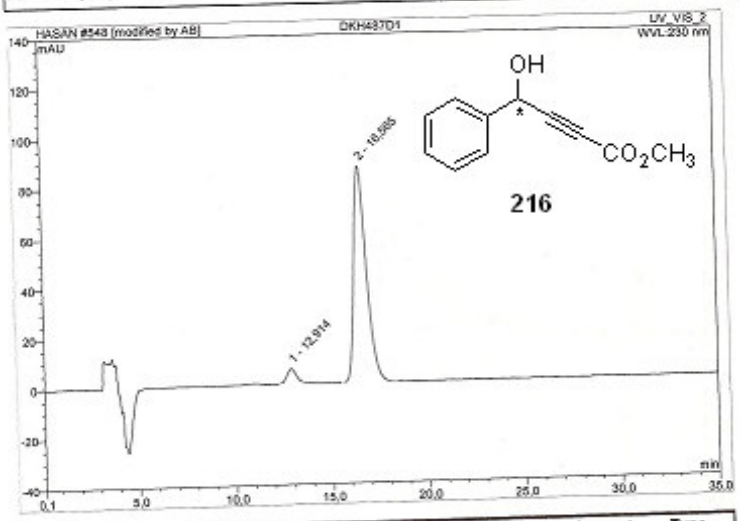


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	6,51	n.a.	6,717	3,433	3,48	n.a.	MB*
2	9,85	n.a.	207,082	95,182	96,52	n.a.	BM *
Total:			213,799	98,615	100,00	0,000	

Figure A.97 HPLC chromatogram of compound **215**.

549 DKH487D1

Sample Name:	DKH487D1	Injection Volume:	20,0
Vial Number:	569	Channel:	UV_VIS_2
Sample Type:	unknown	Wavelength:	230
Control Program:	PROGRAM01	Bandwidth:	2
Quantif. Method:	METHOD01	Dilution Factor:	1,0000
Recording Time:	10.4.2007 22:29	Sample Weight:	1,0000
Run Time (min):	34,88	Sample Amount:	1,0000



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12,91	n.a.	5,640	3,014	4,40	n.a.	BMB*
2	16,57	n.a.	86,754	65,501	95,60	n.a.	BM *
Total:			92,394	68,515	100,00	0,000	

Figure A.98 HPLC chromatogram of compound **216**.

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1997 July-August	FAKO Drug Company	Summer Intern Training

FOREIGN LANGUAGE

English

PUBLICATIONS

1. Koyuncu, H.; Doğan, Ö. *Org. Lett,* **2007**, *9*, 3477-3479.
2. Doğan, Ö.; Koyuncu, H.; Garner, P. P.; Bulut, A.; Youngs, W.; Panzner, M. *Org. Lett.* **2006**, *8*, 4687-4690.
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4. Koyuncu, H.; Doğan, Ö. *J. Organomet. Chem.* **2001**, *631 (1-2)*, 135-138.
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