SYNTHESIS OF 1,2,3,5-TETRASUBSTITUTED PYRROLE DERIVATIVES VIA 5-EXO-DIG TYPE CYCLIZATION AND STEREOSELECTIVE FUNCTIONALISATION OF FERROCENE DERIVATIVES

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JANUARY 2005

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

BY

METİN KAYALAR

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

JANUARY 2005

Approval of the Graduate School of Natural and Applied Science

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ABSTRACT

SYNTHESIS OF 1,2,3,5-TETRASUBSTITUTED PYRROLE DERIVATIVES VIA 5-EXO-DIG TYPE CYCLIZATION AND STEREOSELECTIVE FUNCTIONALISATION OF FERROCENE DERIVATIVES

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January 2005, 102 pages

A convenient and new method for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives starting from 1,3,-dicarbonyl compounds through acid catalyzed cyclization reaction is described. Alkylation of 1,3-dicarbonyl compound with propargyl bromide followed by one step cyclization with the introduction of primary amines in the presence of catalytic amount of triflouroacetic acid (TFA) affords the corresponding pyrrole derivatives in high yields.

The investigations on the studies of developing a new method for catalytic and stereoselective functionalisation of ferrocene derivatives were summarized. Functionalisation studies were carried out in three main strategy the first one of which is carboxylation, second one is arylation and the last one is oxidative cross-coupling with α, β-unsaturated carbonyl compounds.

Keywords: nitrogen heterocycles, pyrrole, cyclization, dicarbonyl compounds, chiral ferrocene derivatives, stereoselective functionalisation.

ÖZ

1,2,3,5-TETRASUBSTİTUE PİROL TÜREVLERİNİN 5-EXO-DİG TİPİ HALKALAŞMA TEPKİMESİ İLE SENTEZİ VE FERROSEN TÜREVLERİNİN STEREOSEÇİCİ OLARAK FONKSİYONLANDIRILMASI

Metin Kayalar
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Ayhan S. Demir
Ocak 2005, 102 sayfa

Bu çalışmanın ilk bölümünde, 1,3-dikarbonil bileşiklerinden başlayarak asitle katalize edilmiş halkalaşma tepkimesiyle 1,2,3,5-tetrasübstitie pirol türevleri sentezleme konusunda yeni ve kolay uygulanabilir bir yöntem geliştirilmiştir. İlk olarak 1,3-dikarbonil bileşikleri propargil bromür ile alkillenmiş daha sonra da primer amin ve katalitik miktarda TFA (trifloroasetik asit) eklenmesiyle tek basamakta gerçekleşen dönüşümle yüksek verimlerle pirol türevleri sentezlenmiştir.

Çalışmanın ikinci bölümünde ise, ferrosen türevlerinin katalitik ve de stereoseçici olarak fonsiyonlanırılması için geliştirilmesi planlanan metodun şimdiye kadar çalışmaları özetlenmiştir. Bu çalışmalar karboksilleme, arilleme ve α, β doymamış karbonil bileşiklerinin oksitleme ile çapraz bağlanması ana başlıkları altında incelenmiştir.

Anahtar kelimeler: azot hetroçiklikleri, pirol, halkalaşma, dikarbonil bileşiği, kiral ferrosen bileşikleri, stereoseçici foksiyonlandırma.

To my family

ACKNOWLEDGEMENT

I would like to thank my supervisor Prof. Dr. Ayhan S. Demir for giving chance to study with him and for encouraging me throughout this study.

I would like to express my deep gratitude to Ömer Reis for his skillful guidance, endless support, encouragement and patience throughout this study.

I express my sincere appreciation to Asuman Aybey.

I am also thankfull to Çiğdem İğdir and Neşe Duygu for their valuable supports during this study.

I would like to all my friends in Organic Chemistry Research Group whose discussion, cooperation and friendship were extremely helpful.

I am indepted to our group members for their friendship, encouragement and helps whenever I need.

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INTRODUCTION

1.1 The Importance of Pyrrole Derivatives

The existence of pyrrole in coal tar, bone oil, and, in general, in products obtained by the dry distillation of proteins was first surmised by Runge[1] in 1834, when he noticed that a substance was present in the ammonia liberated which would impart a red color to a wood splint moistened with mineral acid. Because of the fiery red color obtained, he called this unknown substance "pyrrole" (derived from Greek for red), meaning fiery oil, although he did not know its chemical constitution and supposed it to be a gas. Pyrrole obtained from bone tar was first purified and analyzed in 1857.

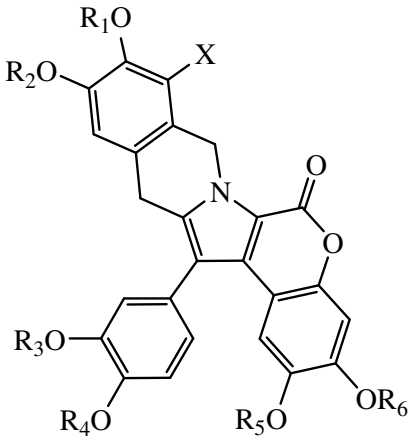
The discovery that pyrrole ring was an integral part of hemain and of chlorophyll molecules[2] not only created intense interest in the chemistry of pyrrole and its derivatives, but also resulted in the majority of investigations conducted during the latter part of the nineteenth century and the early years of the twentieth century being dominated by this relationship of pyrrole with naturally occurring compounds.

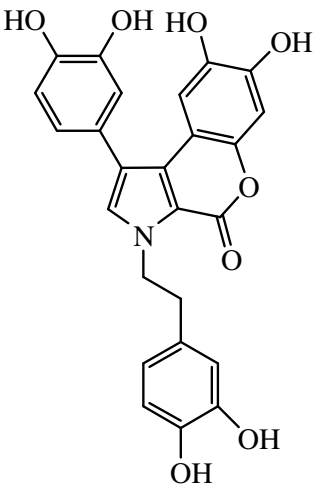
The importance of pyrrole derivatives can be summarized in following basic concepts the first one of which is the existence of them in the structure of many natural products possessing biological activity beside the fact that many of them have biological activities on their own. Secondly, they are versatile building blocks in

organic synthesis. Moreover, they are important starting materials for various synthetic transformations. Finally, they are widely used in materials science. These properties of pyrrole derivatives let them be crucial in the synthesis of many drugs-particularly anticancer drugs.

The most specific examples to the pyrrole containing natural compounds are Ningalins and Lamellarins which belong to the marine natural products. The common feature of many compounds of these groups has potential multidrug resistance (MDR) reversal property by means of showing cytotoxic activity. MDR is a persistent problem limiting the effectiveness of a wide variety of anticancer drugs, antibiotics, and protease inhibitors.[3, 4, 5] Ningalin B (Figure1) is the second member of recently identified ningalin class of marine natural products possessing a 3,4-diaryl-substituted pyrrole nucleus bearing a 2-carboxylate. It was isolated by Fenical (1997) from an ascidian of the genus *Didemnum* collected in western Australia.[7] It shows multidrug resistance reversal activity against L1210 and HCT116 cell lines.[8]

The Lamellarins are a related rapidly growing class of marine natural products which were first isolated from the prosobranch mollusc *Lamellaria sp*., and important members of this class have been disclosed by Bowden, Faulkner, Fenical, Capon, and Scheuer.[9,10] Recent investigations of several lamellarins demonstrated their cytotoxic activity, revealed equally effective cytotoxic activity against multidrug-resistant (MDR) cell lines, and revealed MDR reversal even at noncytotoxic concentrations by inhibition of P-glycoprotein (P-gp)-mediated drug efflux.[10] Lamellarins K and L (Figure 1) posses biological activities which include cytotoxicity, HIV-1 integrase inhibition, and multidrug-resistance reversal.[11, 12]





Lamellarin	R_1	R_2	R_3	R_4	R_5	R_6	X
K	Me	Me	Me	H	Me	H	OH
L	H	Me	H	Me	Me	H	H

Ningalin B

Figure 1 Ningalin & Lamellarin derivatives

Another natural product bearing pyrrole nucleus is Roseophilin (Figure 2). In 1992, Seto *et al*. disclosed the structure of roseophilin, a novel antibiotic isolated from *Streptomyces griseoViridis*.[13] This alkaloid possesses a topologically unique skeleton combining a rather strained macrocyclic entity with an extended heterocyclic chromophore and exhibits very promising cytotoxicity in vitro against K562 human erythroid leukemia and KB human epidermoid carcinoma cell lines in the sub-micromolar range. These properties render roseophilin a new lead structure in the search for anticancer agents and a rewarding target for total synthesis.

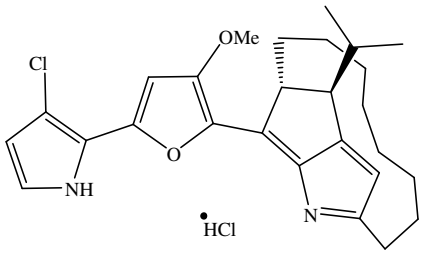


Figure 2 Roseophilin

Pyrrole moiety exists not only in the structure of many naturally occurring biologically active compounds, but also in the structure of some biologically active compounds with no natural source. From this point of view, pyrroles are very important building blocks in organic synthesis so in the drug industry. A good example for this case is atorvastatin calcium, the active material of famous drug named as "Atorvastatin" (produced by Pfizer drug company) (Figure 3). This drug has the blood cholesterol lowering activity.

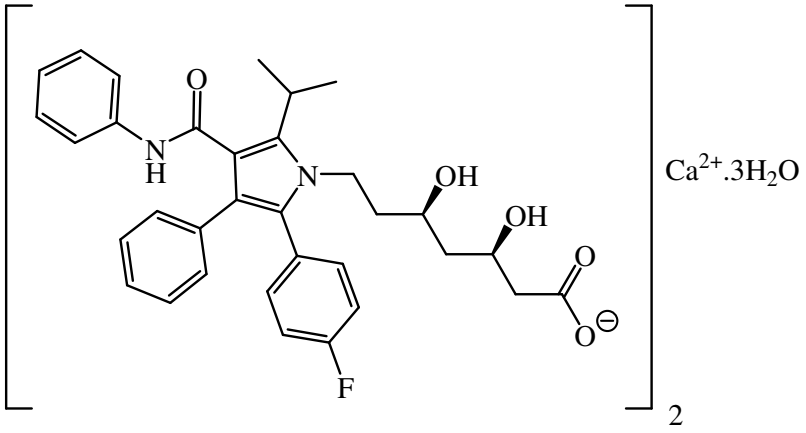


Figure 3 Atorvastatin calcium

Pyrroles being useful building blocks in organic synthesis makes them efficient starting materials for many kinds of synthetic transformations. Pyrroles take important role in the synthesis of porphyrin systems. Porphyrins and other closely related tetrapyrrolic pigments occur widely in nature, and they play very important roles in various biological processes. Heme [the iron(II) protoporphyrin-IX complex] is the prosthetic group in hemoglobins and myoglobins, which are responsible for oxygen transport and storage in living tissues (Figure 4).

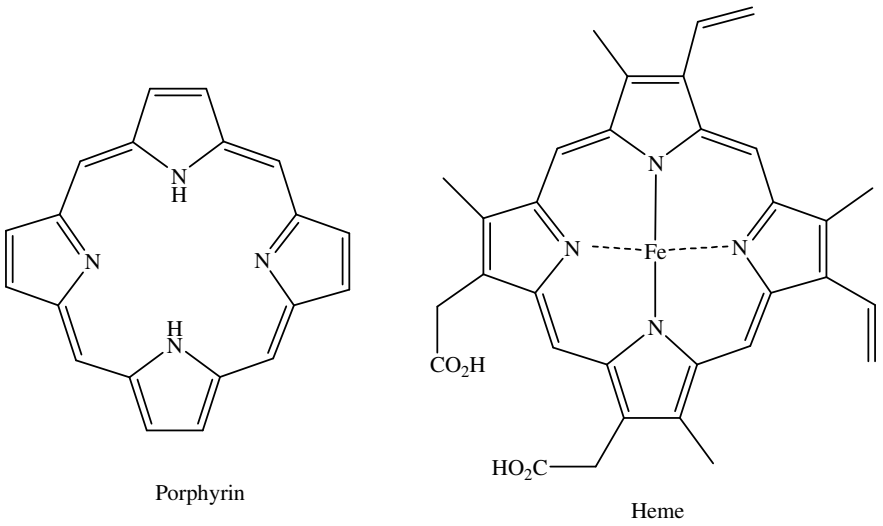


Figure 4 Porphyrin & Heme

Reduction of one of the pyrrole units on the porphyrin ring leads to a class of porphyrin derivatives called chlorins. Chlorophylls (e.g. chlorophyll-a), found abundantly in green plants, belong to this category. They play very important roles in the process of photosynthesis (Figure 5).

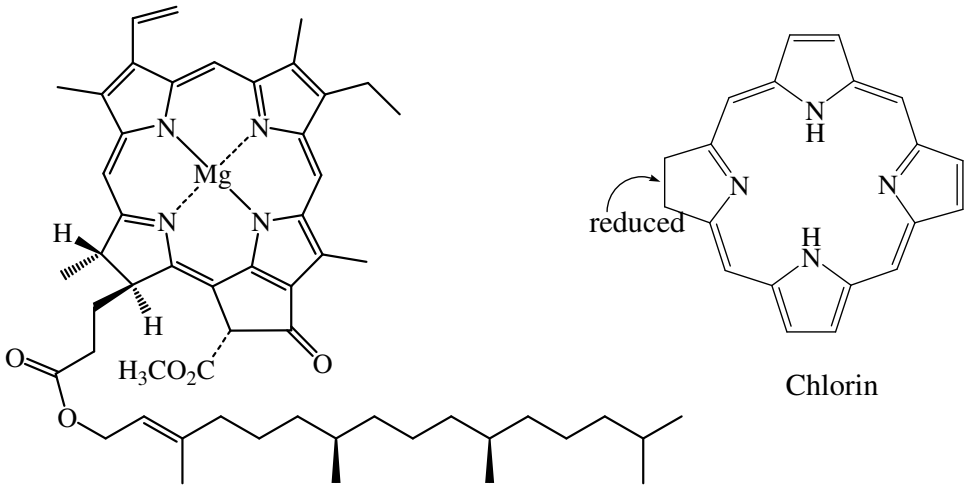


Figure 5 Chlorophyll-a & Chlorin

Vitamin B_{12} (Figure 6) contains a porphyrin-like unit called corrin, a reduced form of corrole (Scheme 1).

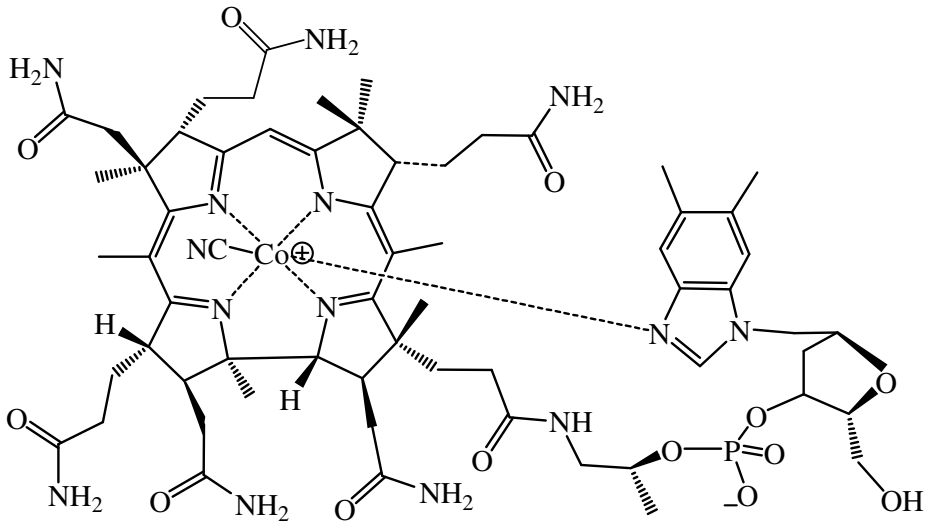
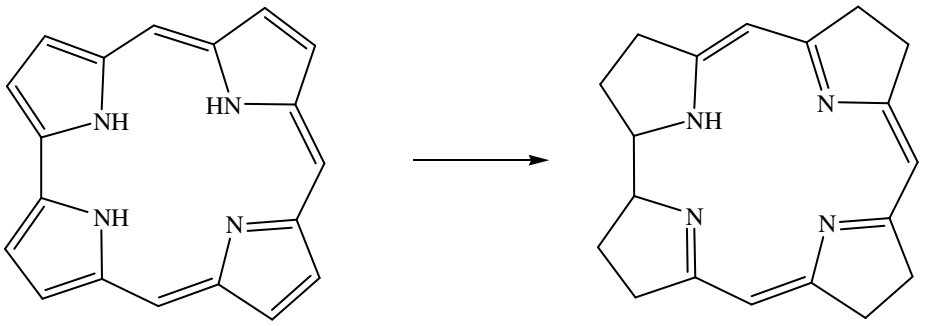


Figure 6 Vitamin B_{12}

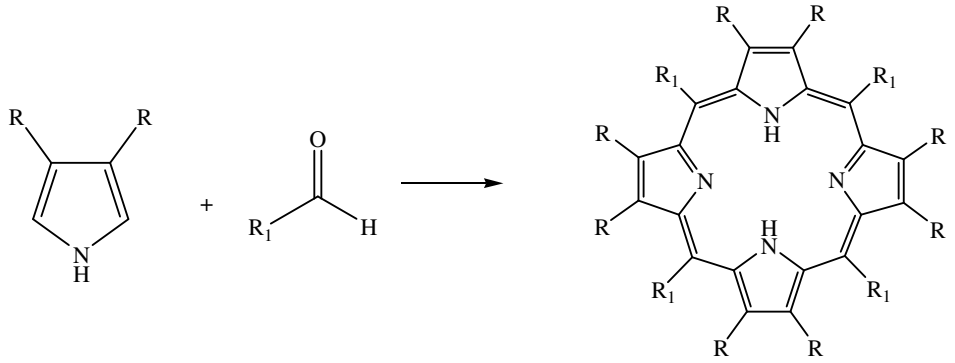


Corrole Corrin

Scheme 1

There are two general approaches to obtain a desired porphyrin: (1) by modification of a naturally occurring porphyrin (e.g. heme); or (2) by total synthesis. Although it is convenient, modification of naturally occurring porphyrins posses great limitations on the choice of peripheral substituents because certain substituents can not be modified easily. In most cases, such limitations can be overcome by total

synthesis, which involves the syntheses of the pyrrole subunits having the required substituents. Tetramerization of monopyrroles is commonly used method in porphyrin total syntheses (Scheme 2). In addition to this method, condensation of dipyrrolic intermediates is another convenient and frequently applied synthetic route being used in recent publications.[13b]



Scheme 2

One more important feature of pyrrole derivatives is the frequent use of them in material science. An example to this is the use of pyrroles in oligoaryl systems. Oligoaryl is an important class of compounds which exhibit a variety of fascinating properties for optoelectronic interests.[14] Incorporation of five-membered heteroaromatic moieties into these conjugated molecules will occasionally increase fluorescence quantum yields and the optoelectronic properties of the oligomers can be tuned.[14] For this purpose, desired substituted pyrroles or furans are synthesized in order to incorporate them into the oligoaryls.[15]

Moreover, pyrroles theirselves display a variety of physiological activities;[16] in particular, 1,2,3,5-tetrasubstituted pyrrole derivatives[17] are biologically active and have been proven to display antibacterial,[18] antiviral,[19] antiinflammatory[20] and antioxidant activities and to inhibit cytokine-mediated diseases.[21] Additionally, they have been found to show potent inhibiting platelet aggregation[22] and hypertensive activities.[23]

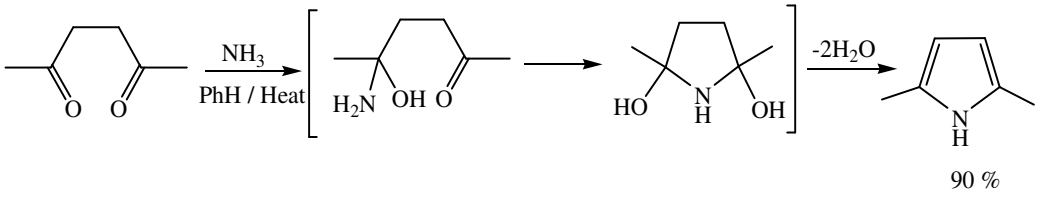
1.2 Synthesis of Pyrroles

1.2.1 General Synthesis of Pyrrole Derivatives

Apart from the commercial synthesis of pyrroles there are three generally important approaches to pyrroles from nonheterocyclic precursors. These are; Paal-Knorr, Hantzsch and Knorr synthesis of pyrrole. In addition to these famous methods, metal mediated cyclization reactions have become popular recently.

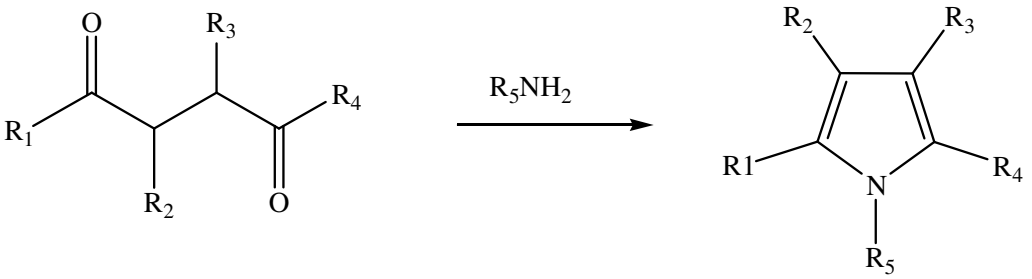
1.2.1.1 Paal-Knorr Pyrrole Synthesis

Pyrroles are formed by the reaction of ammonia or a primary amine with 1, 4-dicarbonyl compound. Nucleophilic addition of the amine to the two carbonyl carbon atoms and the loss of the two moles of water afford the pyrrole (Scheme 3). This method provides a convenient method for the synthesis of pyrroles having alkyl or aryl substituents in both 2- and 5- positions. In particular, a wide variety of 1-substituted 2, 5-dimethyl pyrroles have been prepared from hexane-2,5-dione.



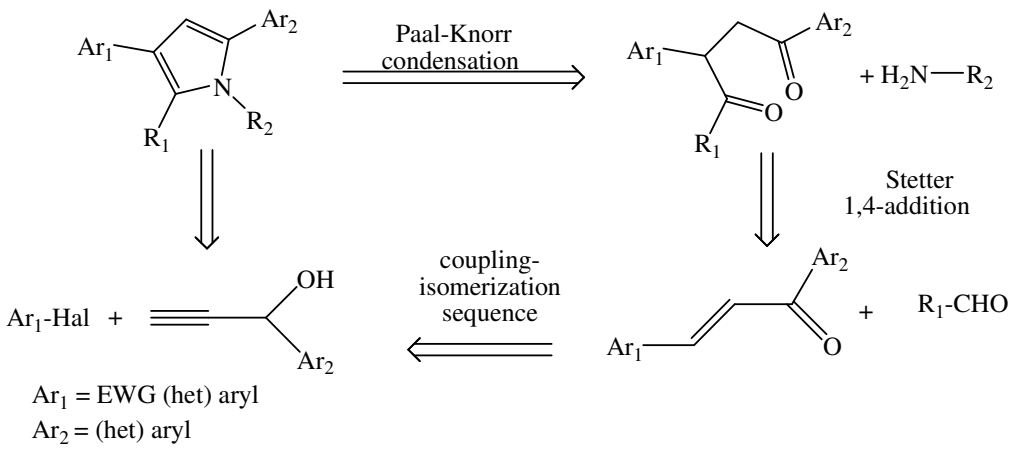
Scheme 3

When the reaction route is simplified as in the case summarized in Scheme 4, it will be easily recognized that the substitution pattern of resulting pyrrole can be determined by means of making modifications on the 1,4-dicarbonyl compound and primary amine. The key strategy for the synthesis of desired pyrrole derivative is the construction of modified 1,4-dicarbonyl compound with desired substituents. It is the striking property of Paal-Knorr synthesis to lead many pyrrole synthesis methods for the construction of 1,4-dicarbonyl skeleton.

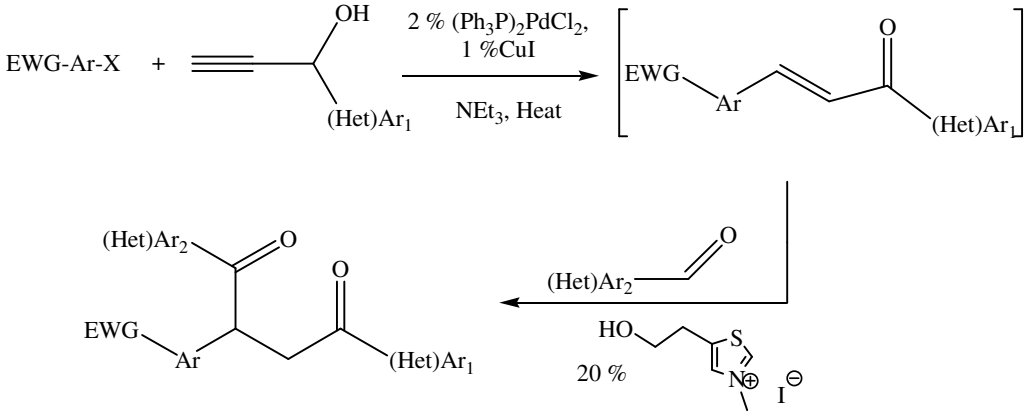


Scheme 4

In the literature there are many studies in which Paal-Knorr synthesis is chosen as the model method for pyrrole synthesis. They differ only in the way that the 1,4-dicarbonyl skeleton is formed. For instance, Müller *et al.*[24] developped a novel one pot pyrrole synthesis method using the Paal-Knorr strategy . According to this method 1,2,3,5-tetrasubstituted pyrroles can be synthesized in good yields in a one-pot, three-step, four-component process by a coupling-isomerization- Stetter reaction-Paal-Knorr sequence of an electron-poor (hetero)aryl halide, a terminal propargyl alcohol, an aldehyde, and a primary amine (Scheme 5). The detailed course of the reaction constitutes the coupling of aryl substituted propargyl alcohol with aryl halide containing electron withdrawing group, spontaneous isomerization with the use of catalytic amount of $(Ph_3P)_2PdCl_2$ and CuI in the presence of boiling triethylamine that provide the formation of 1,4-enone skeleton respectively Then the 1,4-addition of aldehyde in the presence of thiazolium salt (known as Stetter reaction) afford the 1,4-carbonyl moiety required for the Paal-Knorr type cyclization with primary amine (Scheme 6).



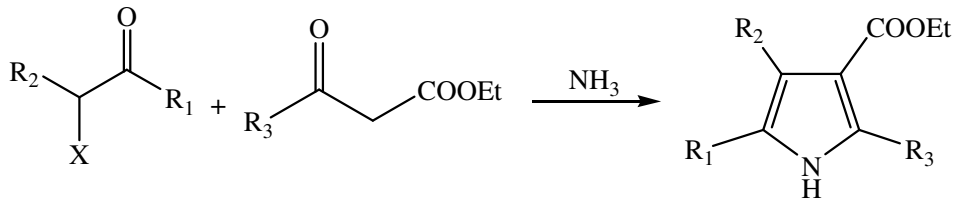
Scheme 5



Scheme 6

1.2.1.2 Hantzsch Pyrrole Synthesis

Substituted 2-alkylpyrrole-3-carboxylic esters are conveniently prepared from the reaction of a α-haloketone or aldehyde with a, β-ketoester and ammonia by a procedure generally referred as the Hantzsch synthesis (Scheme 7). Actually Hantzsch synthesis is just the modification of the Feist-Benary synthesis of furans.



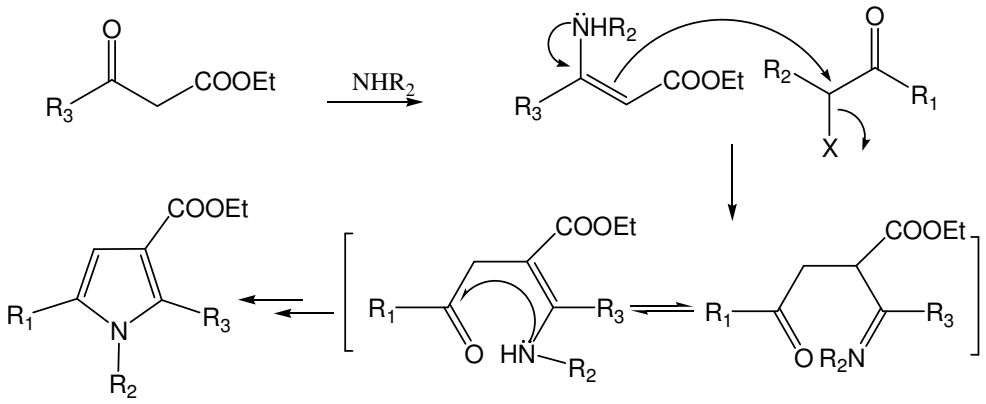
Scheme 7

The versatility of the reaction is illustrated in Table 1

Table 1 Hantzsch synthesis of pyrroles

R_1	R_2	R_3	X	% Yield
Me	H	Me	Cl	50
Me	H	Et	Cl	9
Me	H	*n*-C_3H_7	Cl	2
Et	Me	Me	Br	7
H	Et	Me	Cl	30
H	Et	Me	Br	45
H	Et	Et	Br	15
H	Et	*n*-C_3H_7	Br	16
H	*n*-C_6H_{11}	Me	Br	55
H	*n*-C_6H_{11}	Et	Br	49

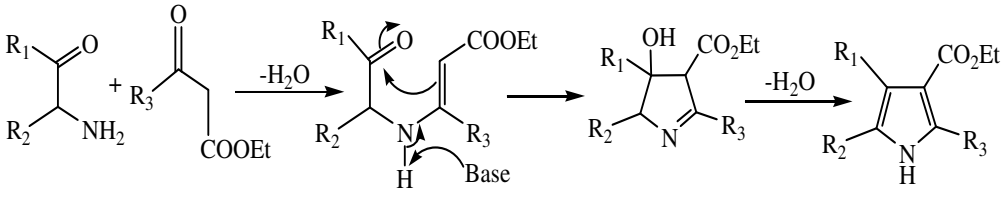
Since nucleophilic attack by ammonia on a α-chloroketone may occur either at the α-carbon atom, with the displacement of the halide ion, or on carbonyl group, there is the possibility that two isomeric pyrroles may be formed. The first reaction pathway leading to the initial formation of a α-amino ketone followed by the Knorr condensation is not observed. The first step of Hantzsch pyrrole synthesis is not the formation of the α-aminoketone or the attack of the carbanion on the α-haloketone, but the formation of an aminocrotonic ester (β-amino acrylic ester) (Scheme 8).



Scheme 8

1.2.1.3 Knorr Pyrrole Synthesis

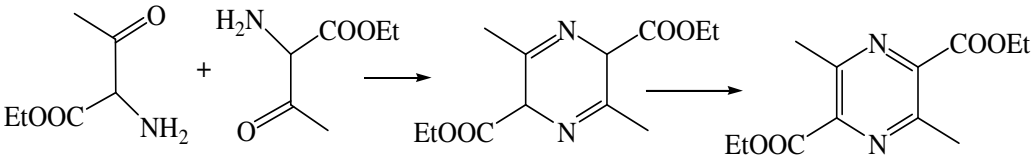
The most widely applied ring closure reaction method in the pyyrole chemistry was discovered by Knorr. The reaction involves the condensation of an α-amino ketone with a ketone having a reactive methylene group alpha to the carbonyl group (Scheme 9). This method utilizes two components the first one of which is the α-aminocarbonyl component supplying the nitrogen and the carbon atoms at the second and third position of the pyrrole ring. The second component supplies carbon atoms at the fourth and fifth position and must have a methylene group α to carbonyl.



Scheme 9

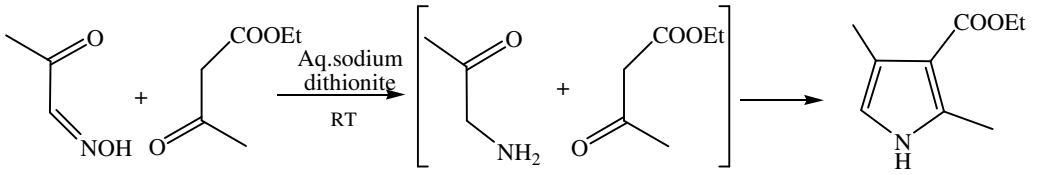
The utility of the reaction is limited by the tendency of α-aminoketones towards self condensation.[25] If the methylene ketone is not sufficiently reactive, the

amino ketone will condense to form a pyrazine instead of pyrrole (Scheme 10).[26] This condensation proceeds so readily that α-amino ketones are, in general, not capable of independent existence and must be isolated as hydrochlorides.

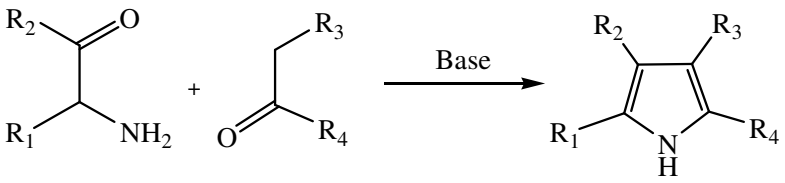


Scheme 10

The Knorr synthesis works well only if the methylene group of the second component is further activated (for example as in the case of acetoacetic ester) to enable the condensation leading to pyrrole to compete effectively with self-condensation of the α-aminocarbonyl component. An alternative way of avoiding the difficulty in handling α-aminocarbonyl compounds is to prepare them in the presence of the second component, with which they are to react. Zinc-acetic acid or sodium dithionite can be used to reduce oximino groups to amino while leaving ketone and ester groups untouched (Scheme 11).



Scheme 11



Scheme 12

If we consider the generalized reaction as represented in Scheme 12, then the limitations of the reaction is as follows;

When R_1 is H or alkyl or aryl and the other substituents are favorable, the reaction is frequently useful but the yields may not be wholly satisfactory.

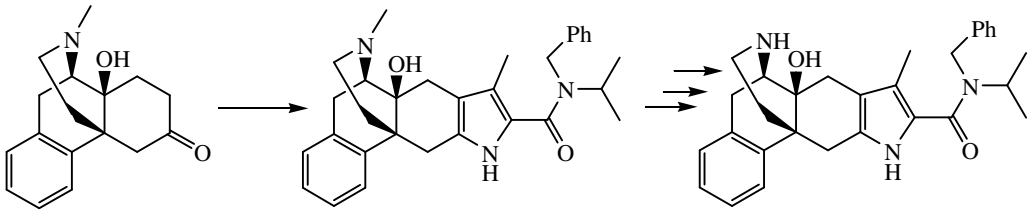
When R_1 is acyl or ester and the other substituents are favorable, the yields are excellent.

R_2 may be alkyl, aryl, acyl or ester without seriously affecting the yield.

When R_3 is alkyl, the yields are poor or the reaction may fail. When it is acyl or ester the yields are excellent.

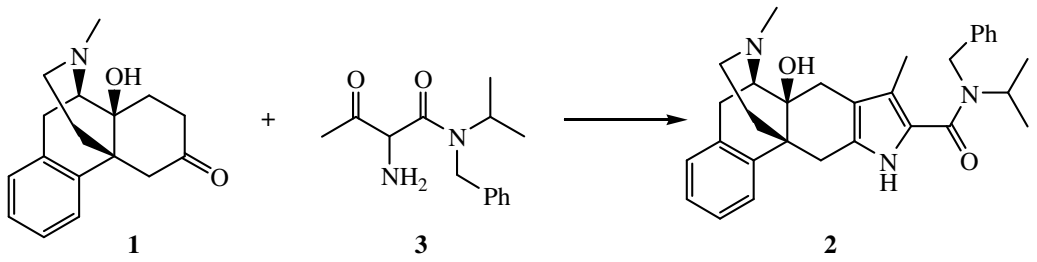
When R_4 is alkyl, aryl, acyl or ester the yields are excellent.

As mentioned before Knorr synthesis is the most frequently applied method for the synthesis of pyrrole moiety. An example to the recent study in which Knorr synthesis is used for the construction of pyrrole ring was performed by Carey *et al.*[27] on the synthesis of ***SB-342219*** which is a selective δ-opioid receptor antagonist and as such has undergone preclinical evaluation for the potential treatment of neuropathic pain[28]. The synthetic pathway for this synthesis requires formation of pyrrole moiety in compound **2** starting from ketone **1** (Scheme 13).



Scheme 13

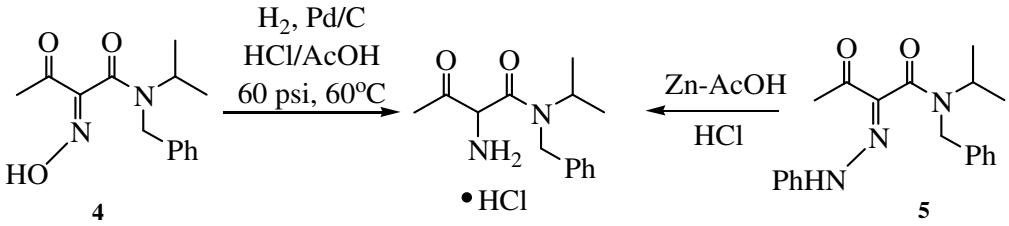
To form such kind of pyrrole moiety, Knorr synthesis is very convenient and applicable one. For the synthesis of compound **2** starting from ketone **1** by means of applying Knorr method α-amino ketone **3** is required (Scheme 14).



1 **3** **2**

Scheme 14

Because of the fact that this α-amino ketone may undergo self-condensation which is the classical handicap of Knorr pyrrole synthesis, α-amino ketone **3** can be isolated as hydrochloride. Therefore, Carey and his co-workers synthesized the α-amino ketone via hydrogenation of corresponding oxime **4** and isolated as hydrochloride which can also be synthesized through the reduction of corresponding phenylhydrazone derivative **5** through the use of zinc in acetic acid (Scheme 15). However, the use of zinc may cause some problems associated with scale-up for the synthesis of ***SB-342219***. Therefore, the reduction of oxime **4** was preferred in this synthesis.



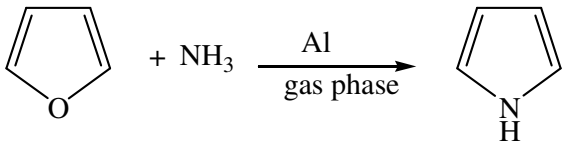
4 **5**

Scheme 15

This study is a good example for application of Knorr synthesis and the tricks to overcome the self-condensation of α-amino ketone which is a serious limitation.

1.2.1.4 Commercial Process

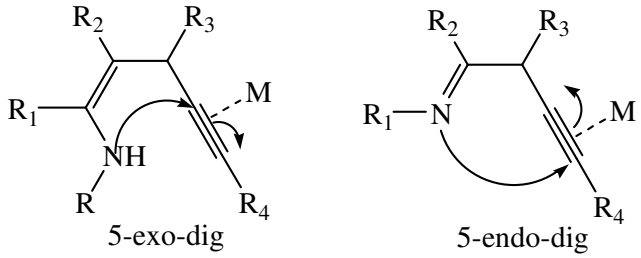
Pyrroles manufactured by alumina-catalyzed gas-phase interaction of furan and ammonia (Scheme 16).



Scheme 16

1.2.1.5 Metal-Mediated Ring Closure

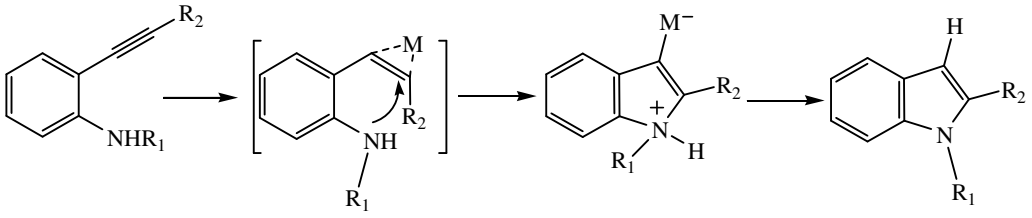
In many recent studies on the construction of the pyrrole ring, attack of nitrogen to the activated triple bond is the original idea for the pyrrole ring closure. This is valid for the construction of other heterocyclic five-membered rings in many recent studies. This attack may lead to either 5-exo-dig or 5-endo-dig type cyclization according to the number of carbon atoms nitrogen and triple bond. If there exist 3 carbon atom between nitrogen and triple bond 5-exo-dig type cyclization takes place. In the case of 4 carbon atom ring closure is 5-endo-dig one (Scheme 17).



Scheme 17

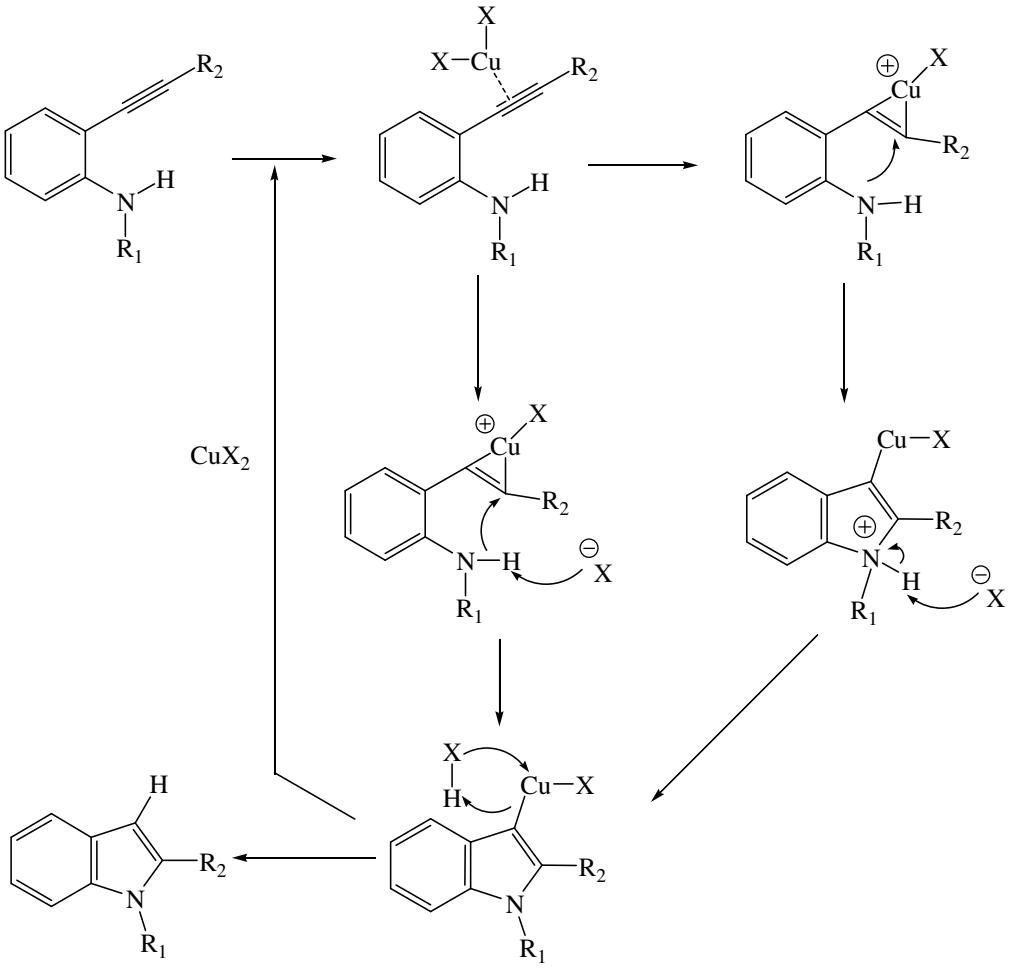
Attack of nitrogen to triple bond often requires high activation energy.[29] To overcome this drawback, triple bond must somehow be activated. For this purpose Lewis acids are used frequently.

A representative study for the 5-endo-dig type ring closure of pyrrole moiety has been performed by Hiroya *et al.* for the synthesis of indoles starting from 2-ethynylaniline derivatives with the use of Cu (II) salts in catalytic amount.[30] General reaction is illustrated in Scheme 18.



Scheme 18

First of all various Lewis acids with different metal atoms were tested for effective cyclization on the model compound (the case in which R_1 is –methylsulfonyl and R_2 is –Ph) and $Cu(OTf)_2$ was found to be the best among them. After that different Cu(II) salts were tested for effective cyclization again with the use of model substrates (R_1= methylsulfonyl, R_2= -Ph and R_1= *p*-toluenesulfonyl, R_2 = -Ph) and $Cu(OAc)_2$ was found to be best catalyst among them. After optimizing the conditions various indoles were synthesized with high yields. The suggested mechanism for the Cu (II) salts catalyzed cyclization is summarized in Scheme 19.

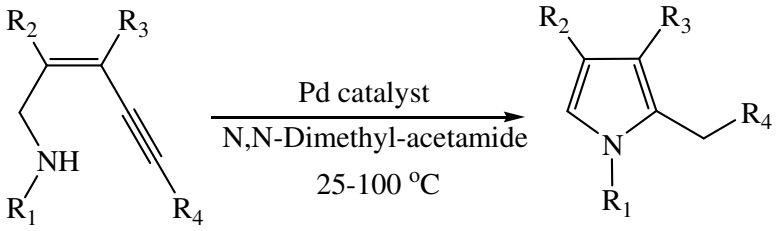


Scheme 19

Another study on 5-endo-dig type cyclization mediated by potassium or cesium bases has been carried out by Knochel *et al*. again on the synthesis of indole derivatives.[31]

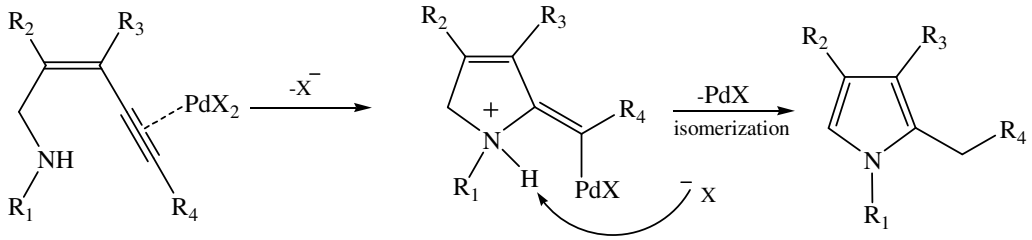
Since the formation of the 5-membered ring is very favorable especially in the case of pyrrole ring construction which in terms leads to the formation of an aromatic compound when compared to formation of 6-membered ring in the same case. Since formation of pyrrole ring is more favorable process than 6-membered ring construction without aromacity, the distinctive criteria for 5-exo or endo dig type cyclization is the number of carbon atom between nitrogen and the triple bond.

In the case of 4 carbons atom between "N" and triple bond 5-exo-dig cyclization takes place. A nice study was carried out by Gabriele *et al*. with the Pd catalyzed cycloisomerization reaction to form pyrrole ring (Scheme 20).[32]



Scheme 20

The conversion of (*Z*)-(2-en-4-ynyl)amine to the substituted pyrrole derivatives was performed with the use of $PdCl_2$ + KCl combination as the catalyst with high yields. According to the results, the reactivity of (*Z*)-(2-en-4-ynyl)amines substituted at C-2 and unsubstituted at C-3 are higher than the analogous ones substituted at C-3. This suggests that the triple bond coordinates to Pd (II) from the opposite side of $–CH_2NHR_1$ moiety and for this reason affected by steric hindrance. The activated triple bond then undergoes 5-exo-dig cycloisomerization to form pyrrole derivative (Scheme 21).



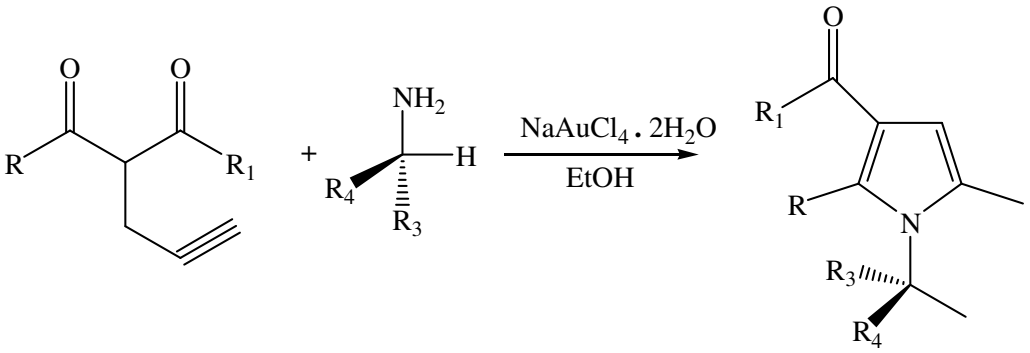
Scheme 21

The versatility of the substituents together with the metal catalysts used in the reaction was investigated and reported later.[33]

Although Pd and Cu is frequently used for activation of triple bond for cyclization[34], Ru and Pt[35], Au[36], Ag[37] metals have been used as well for both exo and endo type cyclizations.

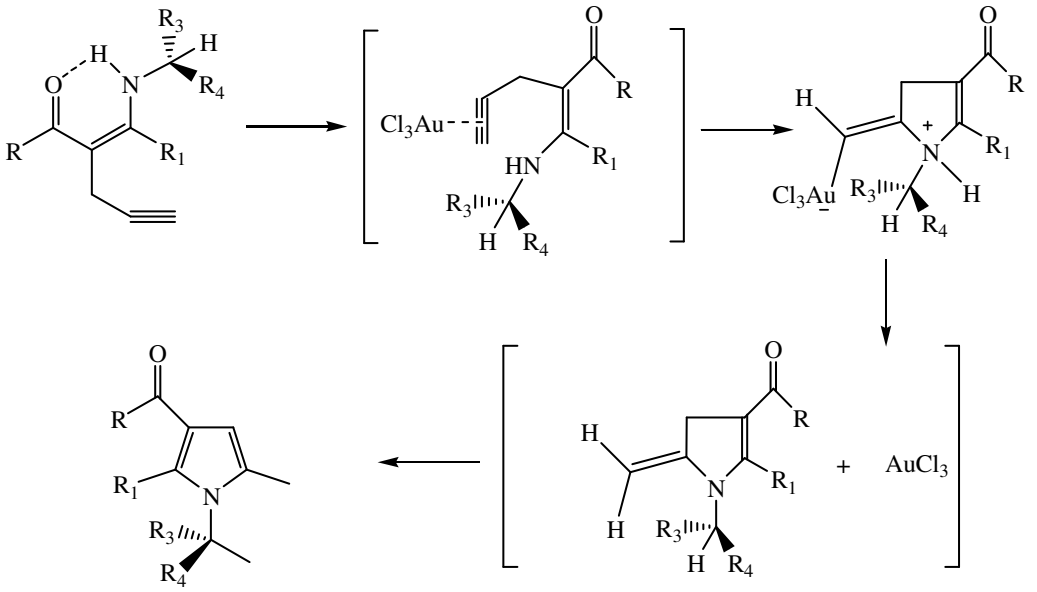
1.2.2 Synthesis of 1,2,3,5-Tetrasubstituted Pyrrole Derivatives

Synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives has become an attractive goal owing to the fact that they particularly show biological activity. Recently, Arcadi *et al.*[38] described the synthesis of chiral 1,2,3,5-substituted pyrrole derivatives via gold catalyzed amination/annulation reactions of 2-propynyl-1,3-dicarbonyl compounds (Scheme 22).



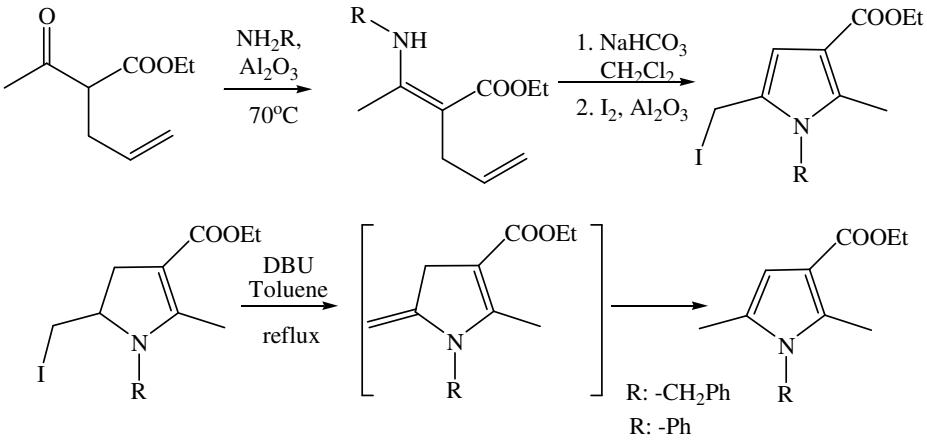
Scheme 22

Enantiomerically pure amines, amino alcohols and amino esters were used as the starting materials for the synthesis of the chiral pyrrole derivatives. The reaction of primary amines with 2-propynyl-1,3-dicarbonyls led to enaminone derivatives, which undergo regioselective cycloamination to pyrroles under the catalytic action of $NaAuCl_4 \cdot 2H_2O$ (Scheme 23). The above formation of pyrrole derivatives has been suggested to proceed by the anti-addition of nitrogen and gold moieties in a 5-exo-dig manner to the acetylenic bond to give the vinylaurate species. Then the protonolysis of the Csp^2-Au bond and the isomerization afford the pyrrole derivatives (Scheme 23).



Scheme 23

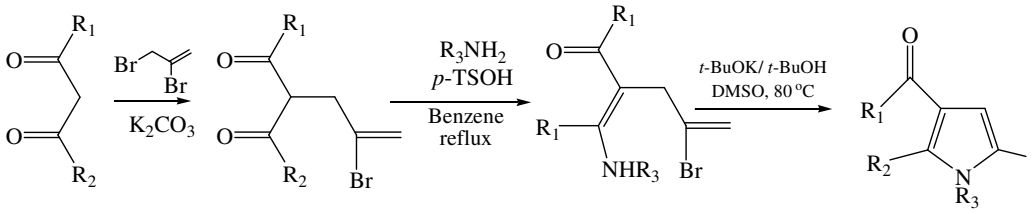
In addition to the method developed by Arcadi *et al*.,[38] Ferraz *et al.* described the synthesis of N-substituted pyrrole and tetrahydroindole derivatives from alkenyl 1,3-dicarbonyl compounds via the formation of iodo-1,3-enamino esters followed by dehydroiodination (Scheme 24).[39]



Scheme 24

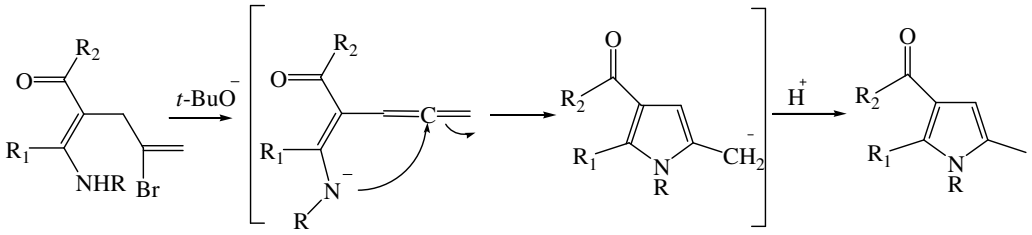
Another study on the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives was performed by Demir *et al*. starting from 2-(2-bromoallyl)-1,3-dicarbonyl

compounds.[40] In this study, 1,3-dicarbonyl compounds were α-alkylated with 2,3-dibromoprop-1-ene followed with enamine formation. Then the isolated enamines were led to the cyclization reaction to form pyrrole derivatives (Scheme 25).

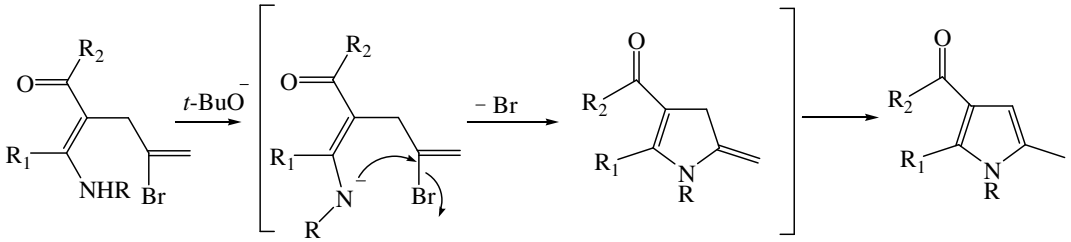


Scheme 25

In this method there exists two separate suggested cyclization mechanism the first one of which goes through the allene intermediate (Scheme 26) and the second through the nucleophilic vinylic substitution reaction (Scheme 27).

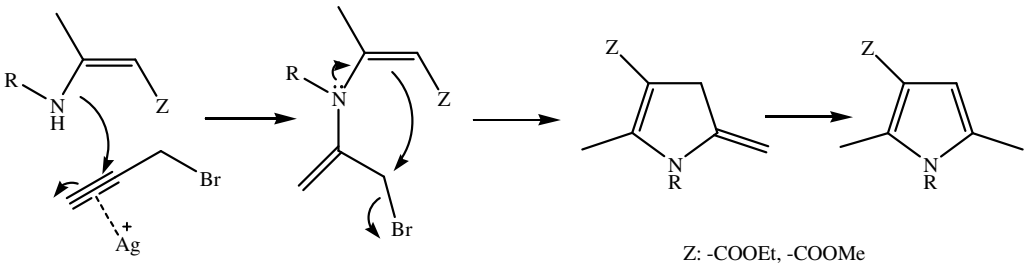


Scheme 26



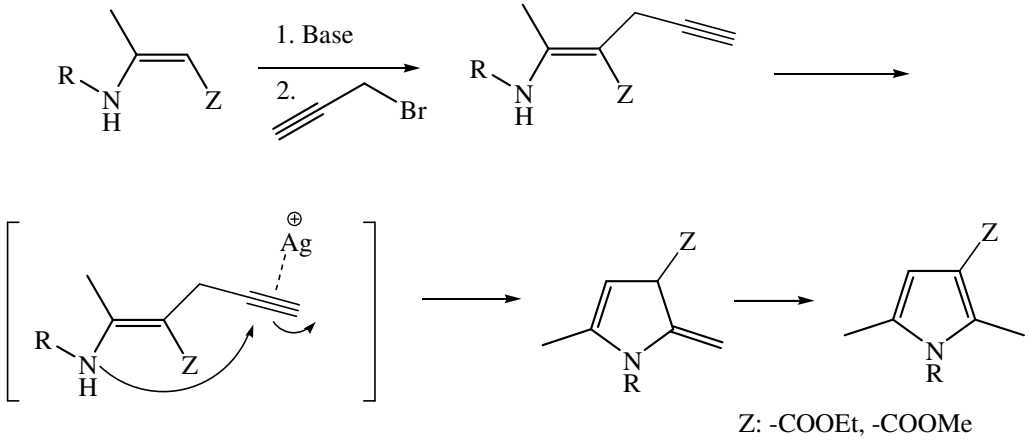
Scheme 27

Attack of nitrogen to the activated triple bond has become common strategy of synthesis of many heterocyclic derivatives, in particular pyrroles. A very recent publication from Dovey *et al.* is another example to this strategy.[37] In this study activation of triple bond was carried out by means of using $AgNO_3$ and the synthesis was achieved one pot. The general mechanism is illustrated in Scheme 28.



Scheme 28

Owing to the fact that the yields are not high at all, a new strategy was developed to overcome this drawback. The new strategy was to perform C-propargylation of vinylogous carbamates and amides followed by the silver mediated hydroamination that caused the improvements in the yields (Scheme 29).



Scheme 29

1.3 Stereoselective Functionalisation of Ferrocene Derivatives

1.3.1 Importance of Ferrocene Derivatives

Since the discovery of ferrocene in 1951,[41, 42] thousands of its derivatives have been prepared. The chemistry of ferrocene is very rich and diversified and is of interest in many areas such as material science, electrochemistry, asymmetric catalysis, etc.[43] Because of the unique structure of ferrocene, it is possible to create chiral compounds, especially 1,2-disubstituted derivatives. Enantiopure 1,2-disubstituted ferrocene derivatives are widely used as ligands in homogeneous transition metal catalysts.[43, 44] Typical examples are the aminophosphine ppfa,[45] the diphosphine Josiphos[46] and the industrially important Xyliphos[47] (Figure 7).

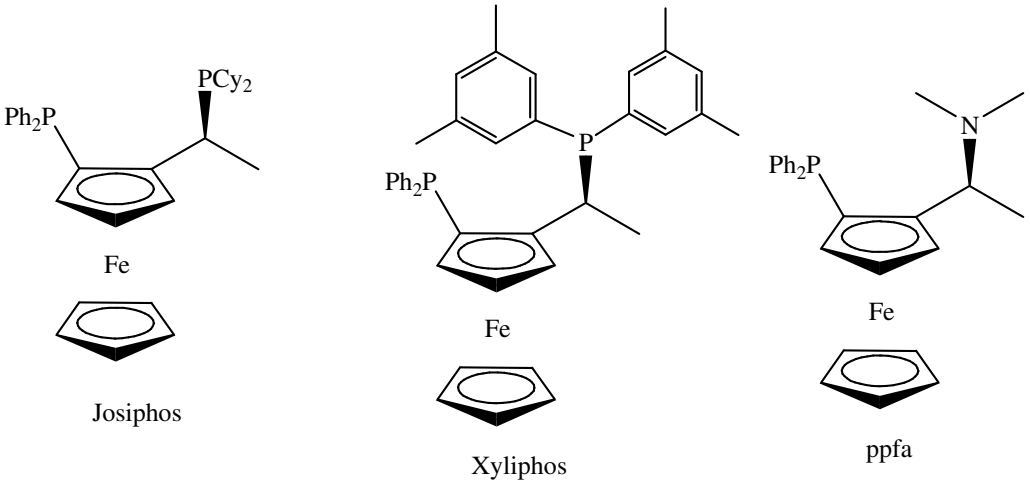


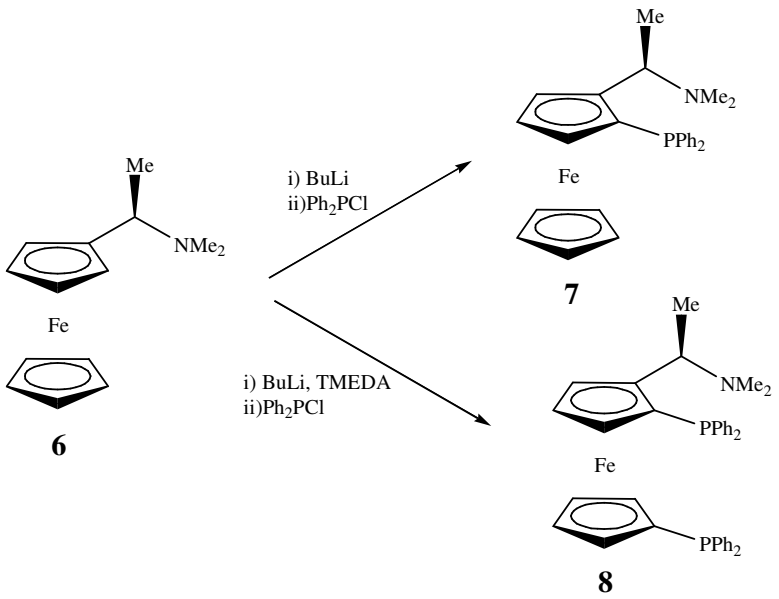
Figure 7 Enantiopure 1, 2-disubstituted ferrocene derivatives

1.3.2 Synthesis of ferrocene derivatives

It is noteworthy that most of the chiral ligands currently used posses of plane chirality. After the leading study of Hayashi *et al.,*[45] the use of planar chiral ferrocene ligands has grown rapidly,[43, 48] reaching to the point of development of two industrial

asymmetric hydrogenation processes.[49] Recently, several new approaches have appeared for the introduction of planar chirality to ferrocene, the most important of which are Sammakia,[50] Richards,[51] Uemura[52] (oxazoline system), Kagan[53] (acetal and sulfate system), Enders[54] (SAMP system), and Snieckus[55] (sparteine system). Although many excellent results were derived from planar chiral ferrocene ligands, the role of planar chirality was still unclear. Some examples showed that the planar chirality had a significant effect on the enantioselectivity,[56] while in other examples it was not so apparent.[57]

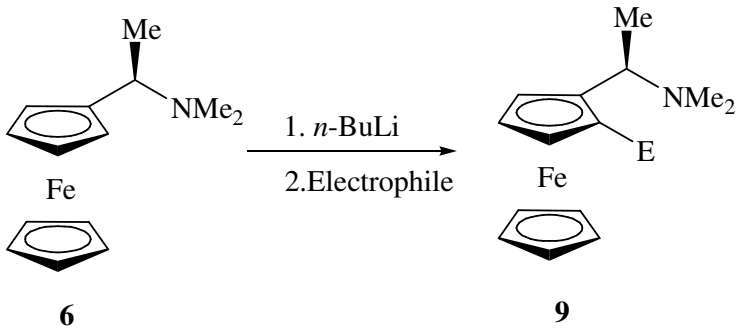
Untill now, the principle method available for the synthesis of non-racemic ferrocene derivatives is the highly diastereoselective lithiation of N,N-dimethyl-ferrocenylethylamine followed by the introduction of an appropriate electrophile, such as chlorodiphenylphosphine. Depending on the lithiation conditions, this can result in either the monophosphine or diphosphine which are themselves starting materials for large number of derivatives obtained through the replacement of diethylamino group (Scheme 30). Such compounds have been successfully applied as ligands for many catalytic asymmetric reactions.



Scheme 30

1.3.2.1 Diastereoselective Synthesis

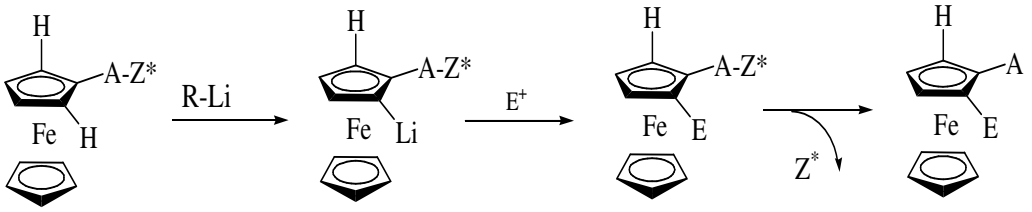
Pioneering work on the synthesis of ferroceneyl compounds with plane chirality was carried out by Ugi *et al.*[58] who discovered that *ortho*-lithiation of N,N-dimethyl-ferrocenylethylamine **6** (Scheme 31) by *n*-BuLi, followed by electrophilic quenching, gave a 96:4 ratio of the two possible diastereomers of **9.** The Ugi method has been widely applied to prepare ferrocenyl compounds with planar chirality, for example the chiral diphosphine **8** (Scheme 30) synthesized by Hayashi *et al.*[59] in 1974 and used as a chiral ligand in asymmetric catalysis.



6 **9**

Scheme 31

So far, there has been a great interest in the synthesis and application of chiral ferrocene derivatives. Although many of these methods rely on N,N-dimethyl-ferrocenylethylamine **6** as the starting material, there has been large number of publications on the alternative *ortho*-directing groups for the synthesis of non-racemic ferrocene displaying planar chirality. The strategy of using an *ortho*-directing group is a key process for the creation of planar chirality from the attached chiral auxiliary. This diastereoselective *ortho*-metalation is illustrated in a simplified way in Scheme 32. To create the chirality with the recovery of chiral auxiliary Z* is the ideal case which is not fulfilled in Ugi's method because of the fact that the chiral center comes from the starting material or it is destroyed in the course of reaction (*e.g.* by hydrogenolysis or β-elimination of nitrogen).



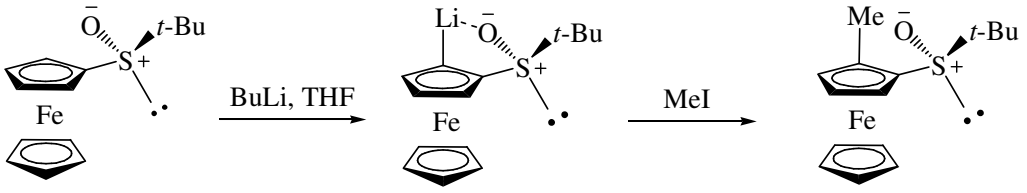
Scheme 32

1.3.2.1.1 Alternative *Ortho*-Directing Groups

Herein, examples of some *ortho*-directing groups and their applications are illustrated:

- ***Sulfoxide Ortho-Directing Groups***:

The mechanism for *ortho*-lithiation of sulfoxide attached ferrocene derivative **10** is thought to have similarity with that of N,N-dimethyl-ferrocenylethylamine **6** with a small difference which is the coordination of lithium to sulfoxide oxygen. The *t*-Bu moiety prefers to occupy anti position to the ferrocene system leading to the methylation of ortho position with a diastereoisomeric excess of > 96 % (Scheme 33).[53b]

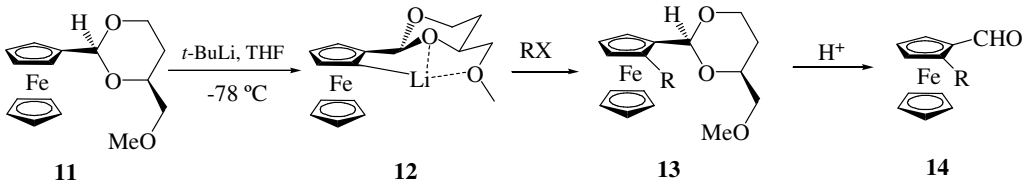


10

Scheme 33

- ***Acetal Ortho-Directing Groups:***

Acetal moiety attached ferrocene derivative **11,** which can be synthesized from ferrocenecarboxaldehyde and (*S*)-1,2,4-butanetriol, has great synthetic value. Addition of *t*-BuLi at -78 ºC and warming to room temperature results in the formation of kinetically controlled, highly diastereoselective lithiation (98:5 d.e.) rationalized by transition state leading to **12.** This can be treated with wide range of electrophiles leading the formation of 2-substituted ferrocene derivatives **13**. From this derivative 2-substituted ferrocenecarboxaldehydes (**14**) can be synthesized with the removal of recoverable auxiliary from **13** (Scheme 34).[53a, c]

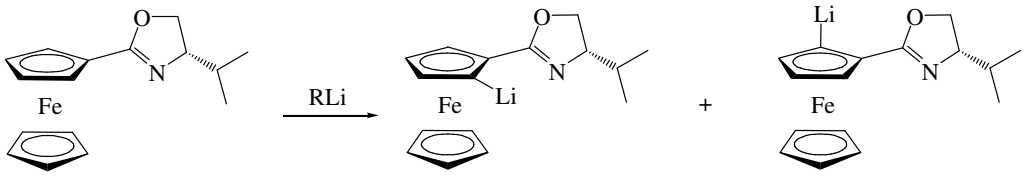


11 **12** **13** **14**

Scheme 34

- ***Oxazoline Ortho-Directing Groups:***

Synthesis of planar chiral ferrocene derivatives via *ortho*-lithiation of ferrocenyloxazolines is an attracting method and has generated great deal of interest since 1995. Ferrocenyloxazolines can be synthesized from ferrocenecarboxylic acid and amino alcohols. The first examples of the use of oxazolines as *ortho*-directing group were published simultaneously by three groups who examined the ratio of diasetereoisomers obtained by the use of BuLi and *sec*-BuLi followed with the addition of appropriate electrophile.[51, 52, 60] Common feature of these three studies was the *iso*-propyl substituted ferrocenyl oxazoline **15** for which the ratio of lithiated oxazolines **16** to **17** varied from 2.5:1 using BuLi at room temperature,[51] through 8:1 with *sec*-BuLi at -78 ºC in THF,[52] and finally 39:1 with *sec*-BuLi used at -78 ºC in Et_2O (Scheme 35).[60] In each study **16** was reported to be the major product satisfyingly.

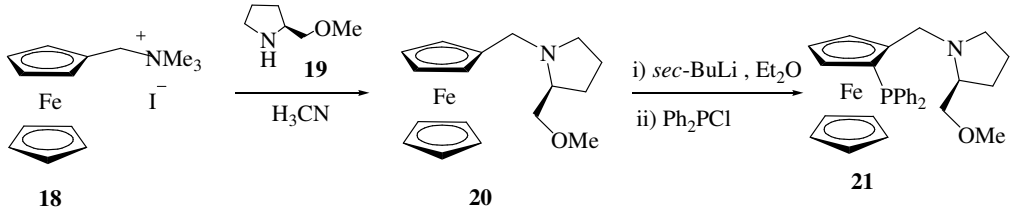


Scheme 35

- ***Other Auxiliary Ortho-Directing Groups:***

Two important *ortho*-directing auxiliaries are (*S*)-2-methoxymethyl pyrrolidine (SMP) and (*S*)-1-Amino-2 methoxymethylpyrrolidine (SAMP) used in the diastereoselective synthesis of various ferrocene derivatives.

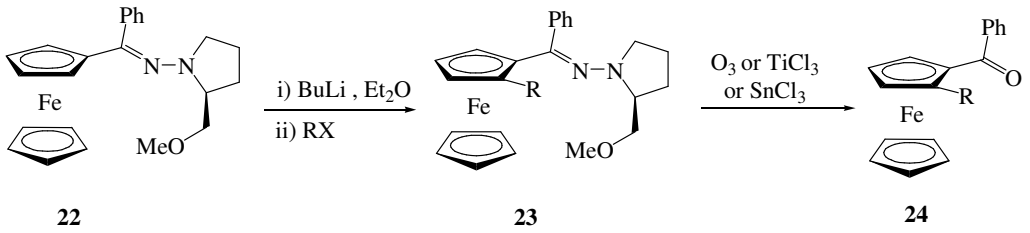
Lithiation of (*S*)-(2-methoxymethylpyrrolidin-1-yl)ferrocene (FeSMP) **20**, which can be prepared from ammonium iodide **18** and (*S*)-2-methoxymethyl pyrrolidine (SMP) **19,** with *sec*-BuLi at -78 ºC in Et_2O and the subsequent addition of Ph_2PCl result the formation of **21** with a diastereoisomeric excess of 98 % (Scheme 36).[61]



Scheme 36

(*S*)-1-Amino-2 methoxymethylpyrrolidine (SAMP) hydrazone substituted ferrocene derivative is another system frequently applied for the diastereoselective functionalization of ferrocene. Lithiation of SAMP hydrazone **22**, which can be prepared from benzoyl ferrocene according to the procedure reported by Enders e*t al*.

in 73 % yield,[54] with BuLi at -78 ºC in Et_2O and quenching with various electrophiles affords ortho-substituted ferrocenes **23** with high diastereoselectivities. Going one step further with either oxidative cleavage with ozone or reductive cleavage with $SnCl_2$ or $TiCl_3$, provides wide range of benzoylferrocene derivatives **24** (Scheme 37).

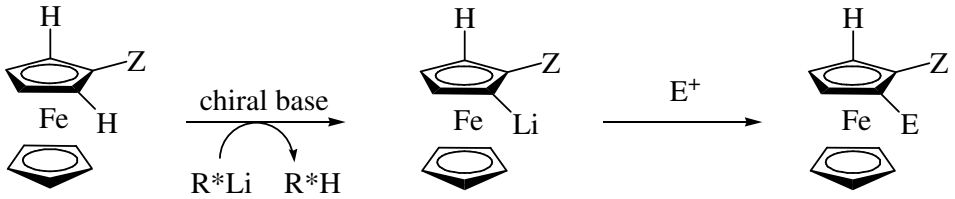


22 **23** **24**

Scheme 37

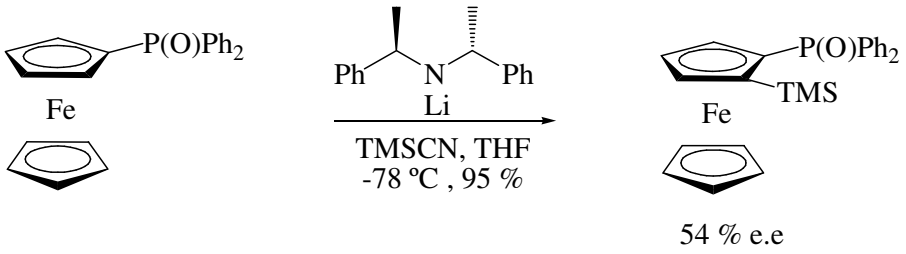
1.3.2.2 Enantioselective Synthesis

An alternative strategy for creating planar chirality in a ferrocene system is based on the enantioselective metalation of an achiral monosubstituted ferrocene such as in Scheme 38 which summarizes the enantioselective *ortho*-metalation process. If Z is an *ortho*-directing group, there exists the possibility of chiral recognition in the deprotonation of one of the two enantiotopic protons by chiral base.

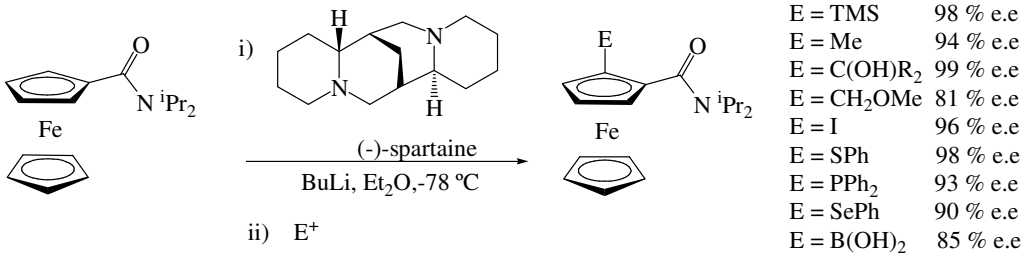


Scheme 38

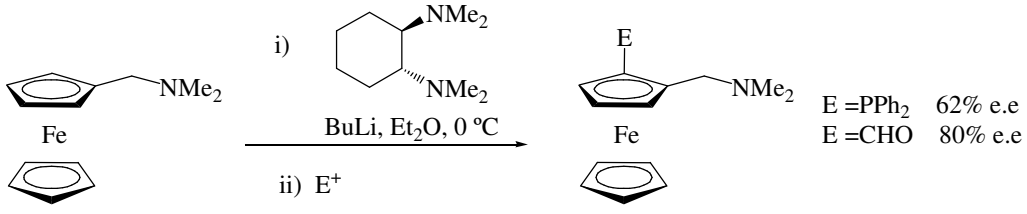
The first study concerning with this strategy was performed by Nozaki *et al.* in 1969 in the case of Z = *i*-Pr.[62] The isopropyl groups acted as *meta*-orientating groups, but 1,3-disubstituted ferrocenes were isolated in very low enantiomeric excess. The first positive results in directed enantioselective *ortho*-metalation were obtained only very recently with Z = $P(O)Ph_2$, $C(O)N$*i*-Pr_2, or CH_2NR_2 by Simpkins *et al.* (Scheme39),[63] Snieckus *et al.* (Scheme 40),[64] and Uemura *et al.* (Scheme 41),[65] respectively.



Scheme 39



Scheme 40



Scheme 41

1.4 Aim of the Work

Because of the high importance of pyrrole derivatives which exist in the structure of many natural products possessing biological activity beside their valuable feature of being versatile building blocks in organic synthesis and important starting materials for various synthetic transformations, there exists a constant demand for the development of new methods for the synthesis of them. Synthesis of pyrroles in high yields with minimum number of steps through metal-free catalytic reaction has become an attractive goal for many synthetic organic chemistry research groups.

Being aware of the importance of pyrrole derivatives and the importance of development of new and efficient synthetic method for them, we aimed to develop an efficient methods for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives through acid catalyzed cyclization reaction in the first part of this study.

In the second part, it is aimed to develop a catalytic stereoselective functionalisation method for the ferrocene derivatives which are widely used as ligands in homogeneous transition metal catalysts.

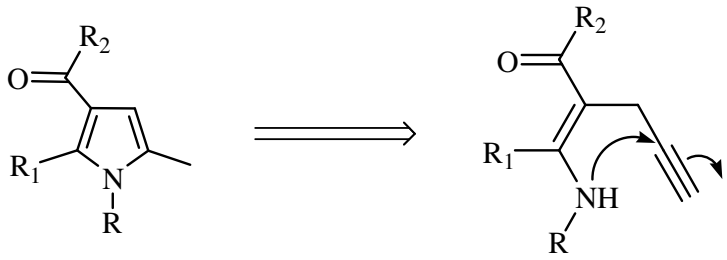
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of 1,2,3,5-Tetrasubstituted Pyrrole Derivatives

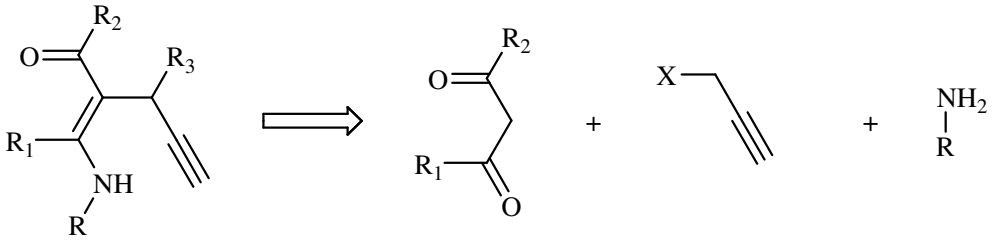
2.1.1 Retrosynthetic Pathway for Synthesis of 1,2,3,5-tetrasubstituted Pyrrole Derivatives

The strategy for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives can be divided into subgroups. The first one is to find out new and easily synthesized acyclic precursors and the second one is to develop practical and flexible cyclization method. For this purpose an acyclic precursor such as in Scheme 42 can be suggested.



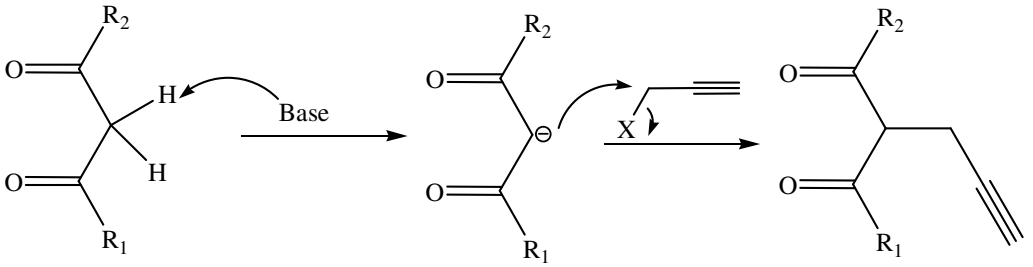
Scheme 42

Acyclic precursor being easily available or synthesizable from readily available starting materials is of importance. To synthesize such an acyclic precursor, 1,3-dicarbonyl compounds are good starting materials. It can be constructed via the α-alkylation of 1,3-dicarbonyl compounds with propargyl halide followed by the condensation reaction with corresponding amine (Scheme 43)



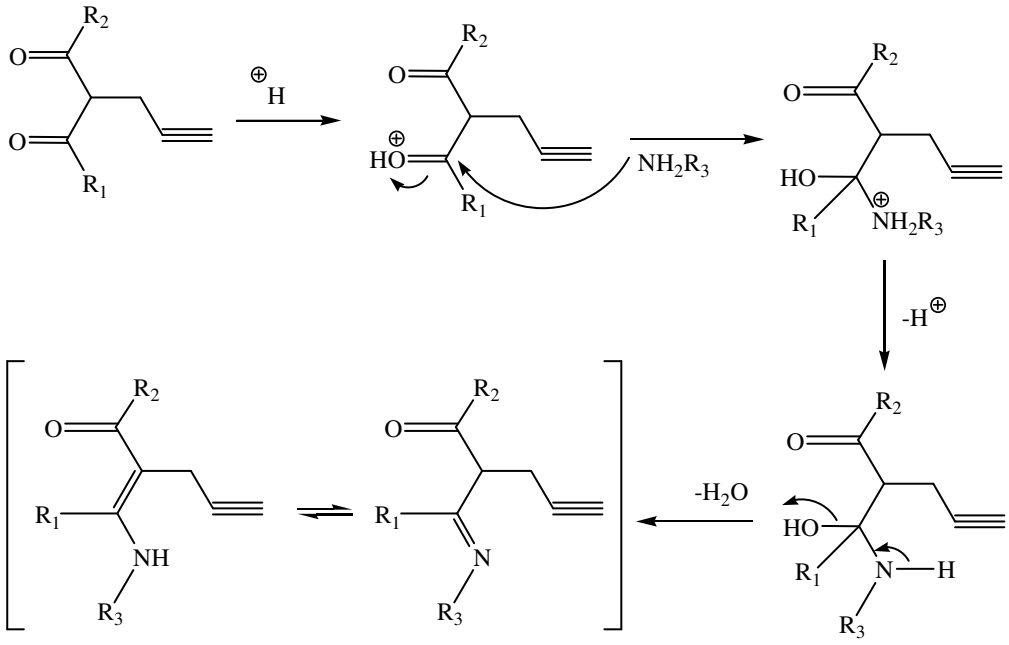
Scheme 43

First step of the synthesis of the acyclic precursor is to alkylate the 1,3-dicarbonyl compound at the carbon between two carbonyl moiety. Since the hydrogen atoms attached to this carbon atom are very acidic it is very easy to alkylate this carbon atom by just taking the proton with a base and making substitution reaction with the addition of propargyl halide (Scheme 44).



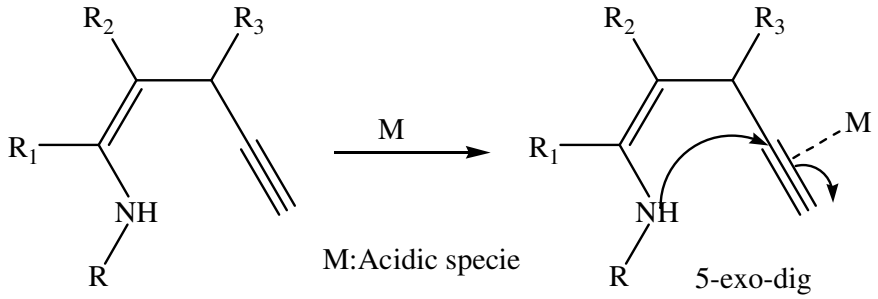
Scheme 44

Second step in the synthesis of acyclic precursor is the formation of enaminone via the condensation reaction of alkylated 1,3-dicarbonyl compound and amine, usually in the presence of catalytic amount of acid (Scheme 45).



Scheme 45

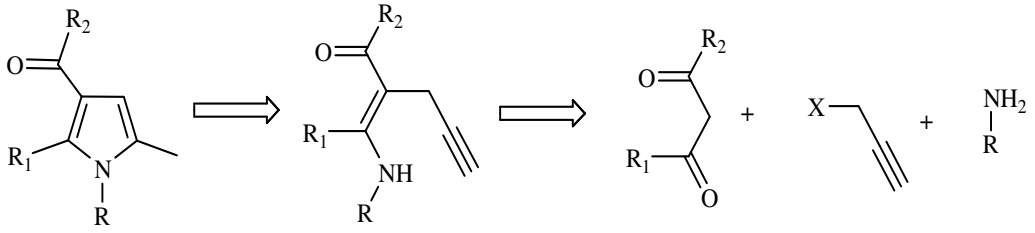
After constructing the acyclic precursor, finding out an appropriate cyclization method is the subsequent step for the synthetic strategy. As it can be noted easily, there are 3 carbon atoms between acetylenic moiety and nitrogen, so the ring construction must be a 5-exo-dig type cyclization reaction. In order to carry out such a cyclization, the triple bond must be activated somehow due to the fact that attack of nitrogen to triple bond is a high activation energy requiring process. As discussed in the introduction part, this energy lowering process can be achieved by means of using acidic species such as Lewis acids (Scheme 46).



Scheme 46

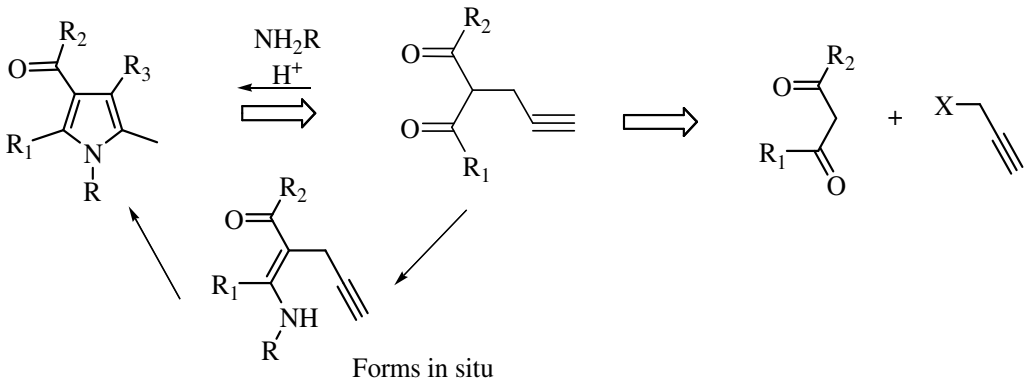
Among the Lewis acids used for this kind of reaction, Cu containing ones operates properly according to recent studies.[30, 33, 34]

Then the overall retrosynthetic pathway for synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives become as in Scheme 47.



Scheme 47

Although this synthetic pathway seems reasonable for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives, it can be modified so that number of the steps can be reduced and the use of metal can be prevented. The enaminone formation requires addition of catalytic amount of acid (Scheme 45) to increase the partial positive character of carbon atom at which nitrogen will attack. Similarly, cyclization step requires acidic specie (frequently Lewis acids) to lower the activation barrier of attack of nitrogen to triple bond. In the light of these pieces of information the idea of combining these two separate steps into one single step by using acid itself arises. Then the new synthetic route becomes as in Scheme 48.



Scheme 48

According to this new strategy 1,2,3,5-tetrasubstituted pyrrole derivatives can be synthesized in two steps without the use of metal which can be considered as green chemistry.

2.1.2 Alkylation of 1,3-Dicarbonyl Compounds

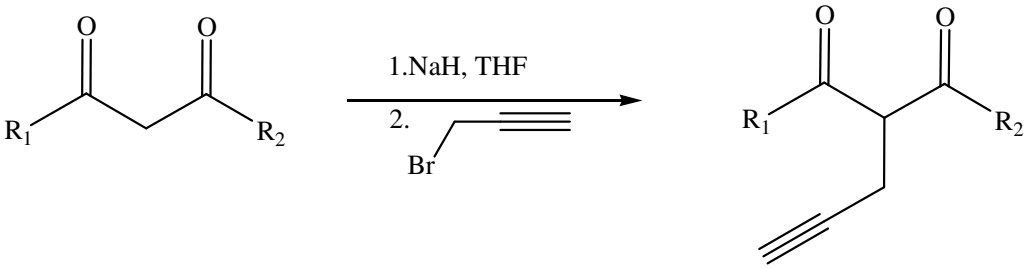
In order to construct the acyclic precursor which will enable us to synthesize desired 1,2,3,5-tetrasubstituted pyrrole derivative, 1,3-dicarbonyl compounds must be alkylated with propargyl bromide. The α-hydrogens in 1,3-dicarbonyl compounds being acidic is a key advantage for making substitution at this carbon atom. Taking one of the protons attached to that carbon with a proper base and making a substitution reaction with the addition of propargyl bromide is the strategy for the alkylation of 1,3-dicarbonyl compounds studied in this project.

Two important parameters must be determined for the substitution reaction the first one of which is the base and the second one is the solvent. The total harmony of base and solvent increases the effectivity of the substitution reaction.

The choice of solvent for the substitution reactions is of importance. Since propargyl bromide is primary halide, it will most likely undergo SN_2 type substitution reaction. It is very well known that polar aprotic solvents increase the rate of SN_2 reactions by dissolving the ionic nucleophile and yet not solvating the nucleophile by H-bonding. Therefore, solvent must be polar aprotic type that can solvate not only propargyl bromide and 1,3-dicarbonyl compound but also the base that will be used for the proton abstraction from 1,3-dicarbonyl compound without any problem. For this purpose THF can be used with the proper base that can be solvated by it.

As the base case, any base which is both strong enough to take proton and appropriate for the solvent can be used. For example, NaH can be used. Then the applicability of THF-NaH pair was tested on the alkylation of ethylacetoacetate and

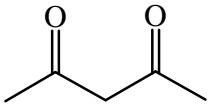
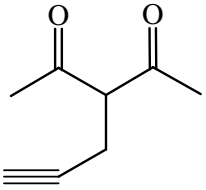
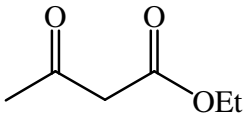
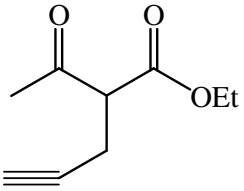
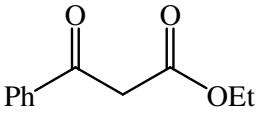
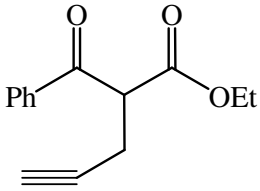
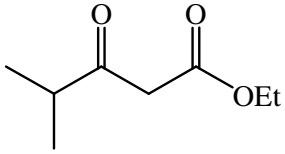
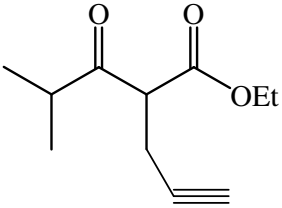
this pair was decided to be good for alkylation. Then the conditions for alkylation step become as in Scheme 49.



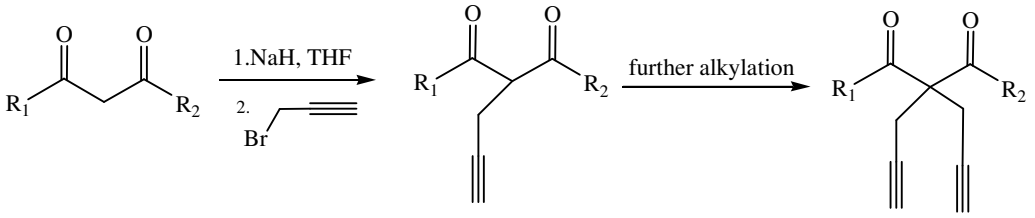
Scheme 49

The alkylation of 1,3-dicarbonyl compounds was performed according to the conditions summarized in Scheme 50 with moderate yields. Results of the alkylation were summarized in Table 2. The yields' being moderate is due to the steric interference of the substituents on the dicarbonyl compounds as well as effect of dialkylation

Table 2 Alkylation of 1,3-dicarbonyl compounds

1,3-Dicarbonyl compound	Alkylated 1,3-Dicarbonyl compound	% Yield
	 **25**	75
	 **26**	66
	 **27**	62
	 **28**	64

Main problem encountered during the alkylation step is the dialkylation of the carbon atom between two carbonyl carbons. Owing to the high acidity of the protons attached to that carbon, second proton is abstracted from the monoalkylated product leading to the dialkylation of 1,3-dicarbonyl compound (Scheme 50).



Scheme 50

Although this problem could not be sort out completely, it was minimized by means of addition of propargyl bromide in small portions. By doing so, 1,3-dicarbonyl compounds were alkylated with moderate yields (62-75 % yield).

Characterization of the alkylated compounds was carried out by considering the ^{1}H-NMR spectra. The common peaks of all alkylated dicarbonyl compounds are triplets belonging to the H_2 proton around 3.5-4.0 ppm and doublets belonging to the H_1 protons around 2.5-3.0 ppm as illustrated in Figure 8.

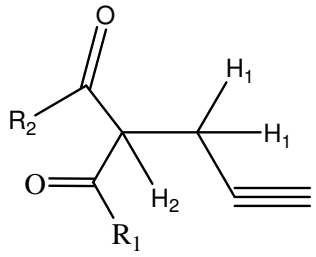


Figure 8 Common protons of 1,3-dicarbonyl compounds

2.1.3 Cyclization Reactions

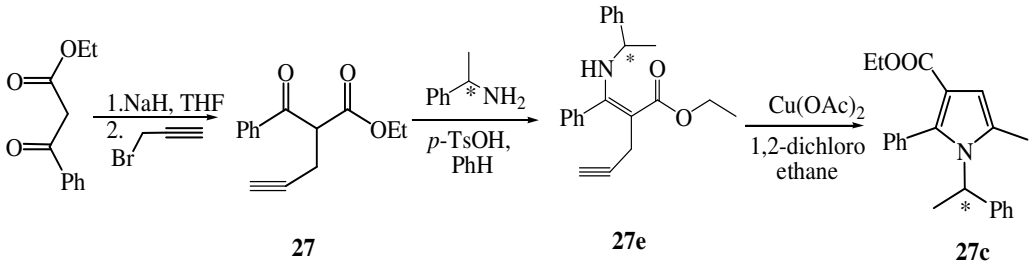
Cyclization of the acyclic precursor can be achieved by either by using Lewis acid which can be considered as metal-mediated cyclization or by using acid that can be named as acid catalyzed cyclization. It must be kept in mind that for the metal-mediated cyclization, acyclic precursor (enaminone system) must be isolated while

for acid catalyzed cyclization there is no need for the isolation of the acyclic precursor.

2.1.3.1 Metal Mediated Cyclization

As mentioned in the introduction part the attack of nitrogen to triple bond requires high activation barrier to overcome and does not process spontaneously. So it must be lowered by means of activation of triple bond. This is usually achieved by means of lowering the electron density of triple bond with the coordination of a metal to the triple bond.

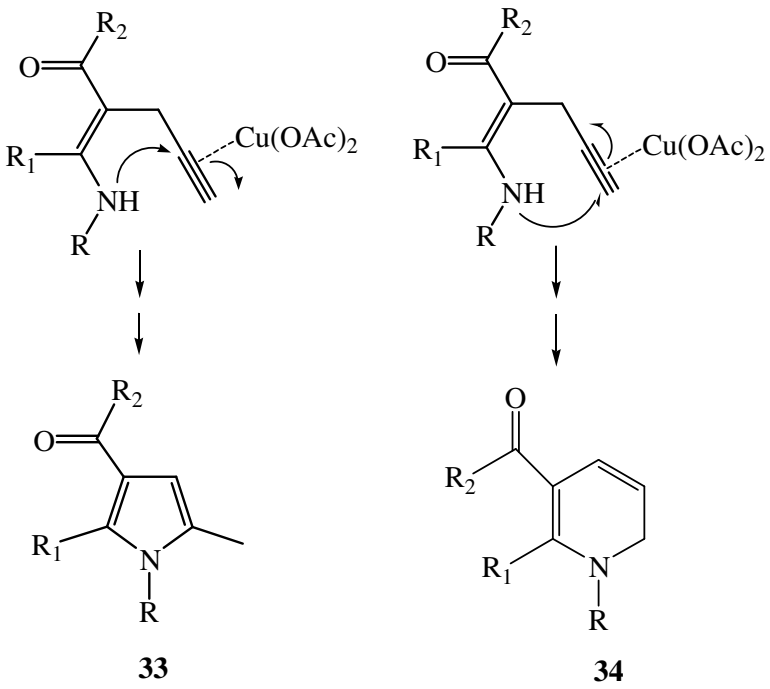
The recent study performed by Hiroya *et al.* [31] for the synthesis of indoles starting from 2-ethynylaniline derivatives with the use of Cu (II) salts in catalytic amount prompted us to carry out the cyclization step with $Cu(OAc)_2$. The use of $Cu(OAc)_2$ was tried at the early stages of the study and resulted in the synthesis of moderate to poor yields which then prompted us to find a new method. $Cu(OAc)_2$ was used only in the case of synthesis of pyrrole derivative **27c** started from ethylbenzoylacetate and (*R*)-phenylethylamine in moderate yield (70 %) owing to the fact that this derivative could not be synthesized by acid catalyzed cyclization reaction in good yields. The synthesis of this derivative was performed by alkylation followed with the formation of enaminone **27e** through simple condensation reaction in the presence of catalytic amount of *p*-TsOH. Remaining part is the cyclization with the use of catalytic amount of $Cu(OAc)_2$ in the presence of 1,2-dichloroethane (Scheme 51).



27 **27e** **27c**

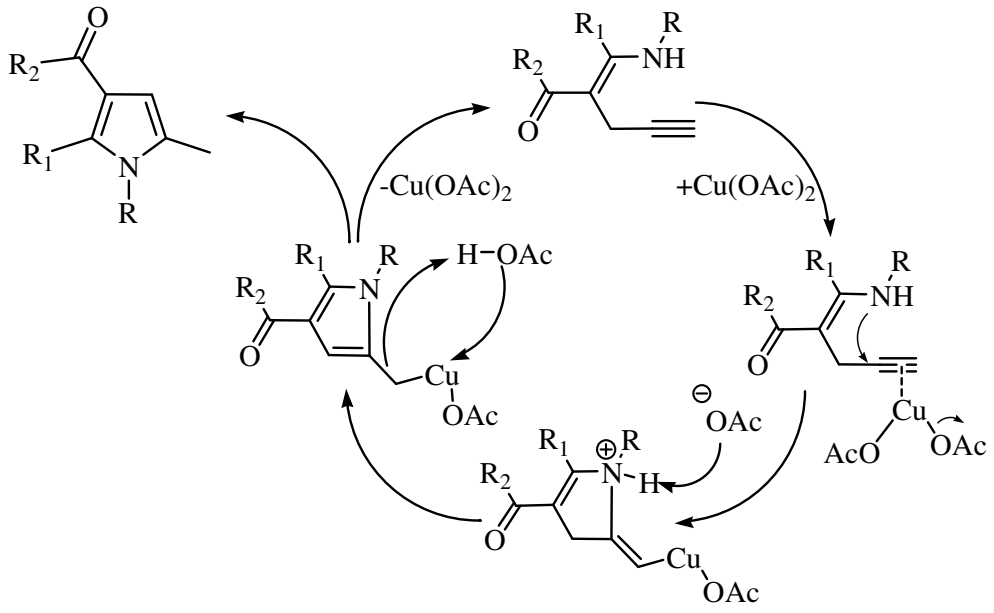
Scheme 51

When the mechanism of the $Cu(OAc)_2$ mediated cyclization is considered, there happens two possible attack of nitrogen to the triple bond. The first case is attack of nitrogen to the carbon atom that leads to 5-exo-dig type cyclization which leads to pyrrole derivative **33** and the other one is 6-endo-dig type cyclization leading to compound **34** (Scheme 52)**.**



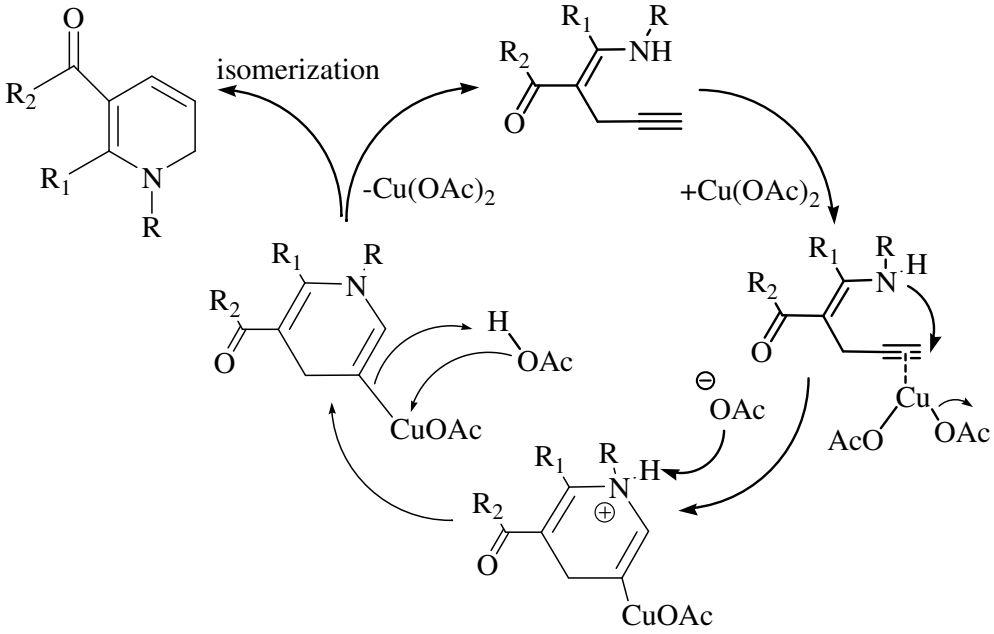
Scheme 52

Mechanism of the reaction that will end up with the pyrrole derivative is summarized in Scheme 53.



Scheme 53

In the same manner, the mechanism of attack of nitrogen to the other carbon atom to give 6-endo-dig type cyclization reaction is illustrated in Scheme 54.



Scheme 54

Even though both 5-exo-dig type and 6-endo-dig type cyclizations are favored according to Baldwin's rules [66], the formation of only pyrrole derivative was observed. The main reason for the 5-exo-dig type cyclization being exclusive mechanism can be explained in terms of the comparisons of the activation energy of two cyclization route. No doubt the activation barrier for formation of 5 membered ring has lower activation energy compared to that of 6 membered ring so that 5-exo-dig type cyclization is dominating route. Moreover, when the final products of both cyclization processes are taken into account, the formation of aromatic pyrrole derivative has priority over the formation of a compound which is not aromatic. Although it has conjugation between double bonds and carbonyl group, it is not applicable when compared with the stability of the aromatic compound.

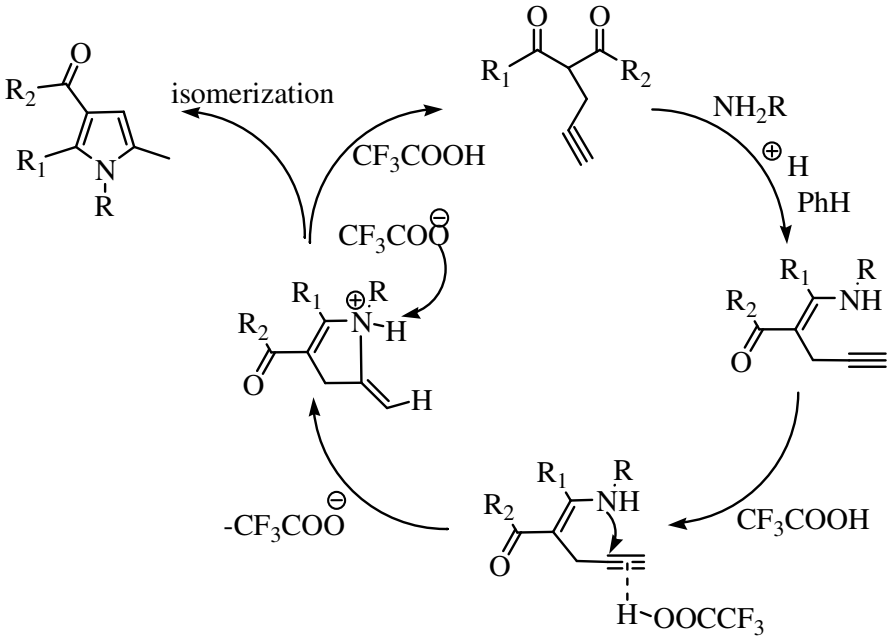
The main drawback of this metal-mediated cyclization reaction is the requirement of isolation of acyclic precursor (enaminone compound) and carrying out cyclization as a single step. When compared to acid catalyzed cyclization, this strategy requires 3 steps, which are alkylation, enamine formation and cyclization, while acid catalyzed cyclization requires 2 steps, which are alkylation and pyrrole formation step. From synthetic point of view, decreasing the number of steps means escaping from workups, saving chemicals especially solvents for work-up and isolation, and saving the time. Another important point is that use of metal even though in catalytic amount is not desired for environment. Moreover, yields are not high at all. No doubt, this does not mean metal mediated cyclization is not applicable when compared to acid catalyzed one. The advantage of acid catalyzed cyclization stems from the fact that reacting species do not have functional groups sensitive to acidic condition. In such a case, use of metal-mediated cyclization strategy become applicable rather than acid catalyzed one.

2.1.3.2 Acid Catalyzed Cyclization

The results obtained from the metal-mediated cyclization reactions were not satisfactory in terms of percent yield. Moreover, isolation of the enaminone derivatives (acyclic precursors for pyrrole derivative synthesis) brought some

difficulties that led to the loss of some amount of it in the isolation step (flash column chromatography). Together with these difficulties, idea of combining the enaminone formation with cyclization step prompted us to carry out the conversion with one single step starting from alkylated 1,3-dicarbonyl compounds.

Since activation of triple bond is the main requirement for the attack of nitrogen to it catalytic amount of trifluoroacetic acid (TFA) was used as proton source for both activation of triple bond and catalysis of enaminone formation. The mechanism of the conversion starting from alkylated 1,3-dicarbonyl compounds is summarized in Scheme 55.

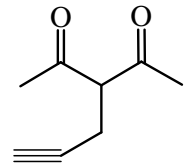
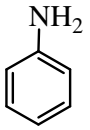
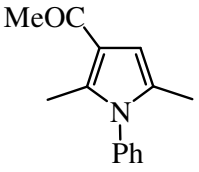
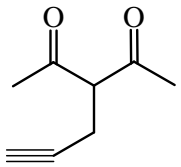
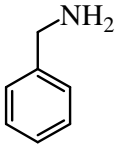
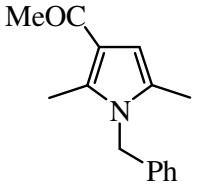
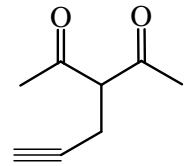
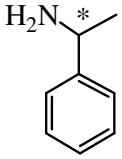
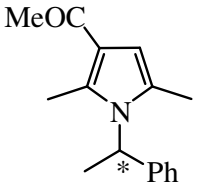
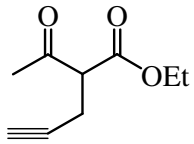
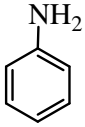
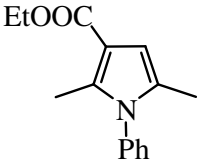
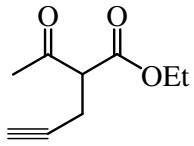
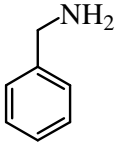
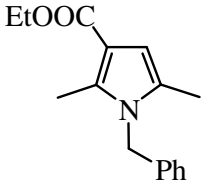
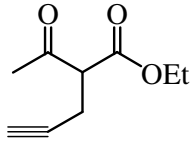
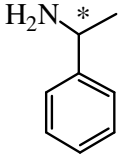
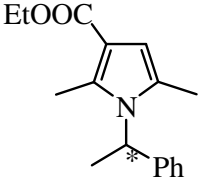


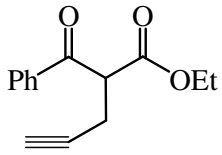
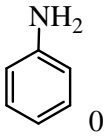
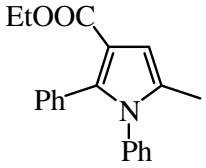
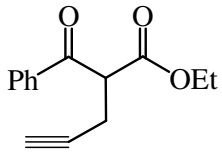
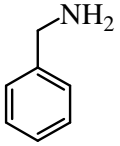
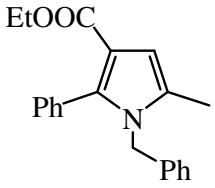
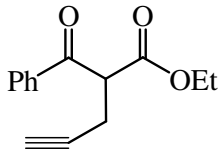
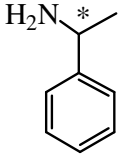
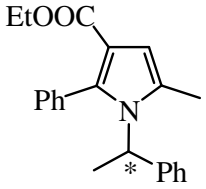
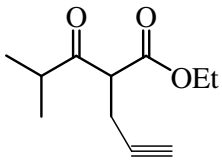
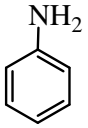
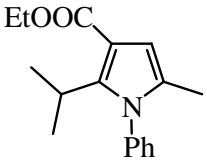
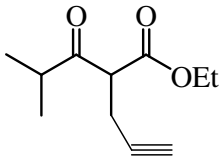
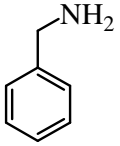
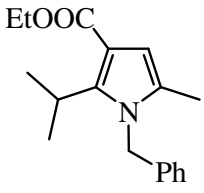
Scheme 55

The possibility of attack of nitrogen to the other carbon atom of the triple bond to give 6-endo-dig type cyclization is very low because of the reasons discussed in metal mediated cyclization case. Therefore, the exclusive products were expected to be pyrrole derivatives as it was observed. The pyrrole derivatives were synthesized

in high yields. The results of the acid catalyzed cyclization of alkylated 1,3-dicarbonyl compounds are summarized in Table 3.

Table 3 Acid catalyzed synthesis of pyrrole derivatives

1,3-Dicarbonylcompounds	Amine	Pyrrole	%Yield
 **25**	 **a**	 **25a**	**65**
 **25**	 **b**	 **25b**	**97**
 **25**	 **c**	 **25c**	**93**
 **26**	 **a**	 **26a**	**96**
 **26**	 **b**	 **26b**	**92**
 **26**	 **c**	 **26c**	**94**

 **27**	 **a**	 **27a**	**92**
 **27**	 **b**	 **27b**	**94**
 **27**	 **c**	 **27c** (synthesized by metal mediated cyclization)	**70**
 **28**	 **a**	 **28a**	**70**
 **28**	 **b**	 **28b**	**95**

Characterization of the pyrrole derivatives were done from the ^{1}H and ^{13}C NMR spectra. For ^{1}H-NMR spectra there are two kind of characteristic protons. These are illustrated in Figure 9. H_1 proton of the different pyrrole derivatives

resonate between 6.17-6.60 ppm as singlet. Moreover, H_2 protons resonate around 2 ppm as singlet.

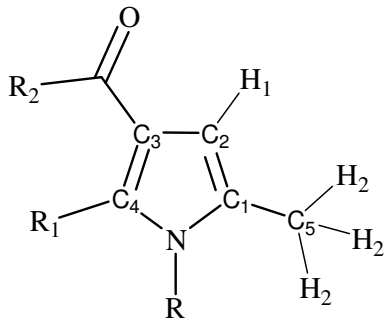


Figure 9 Characteristic protons and carbons of pyrrole derivatives

When the ^{13}C NMR spectra of different pyrrole derivatives are interpreted, C_1, C_2, C_3, C_4 belonging pyrrole ring and C_5 belonging methyl group are common in all pyrrole derivatives and resonate around similar values. C_1 usually resonates around 127 ppm, C_2 around 105-110 ppm, C_3 aroun134-139 ppm, C_4 around 128-132 ppm and C_5 around 12 ppm.

Beside ^1H and ^{13}C NMR spectra, IR spectra are useful for reception of some characteristic functional groups such as ketone, ester and aromatic C-H stretching of C_2-H bond. For example in the IR spectrum of **25a,** characteristic peak due to the presence of ketone functionality at 1649 cm^{-1}, in that of **26a,** ester functionality at 1685 cm^{-1} help us to characterize the synthesized pyrrole derivatives.

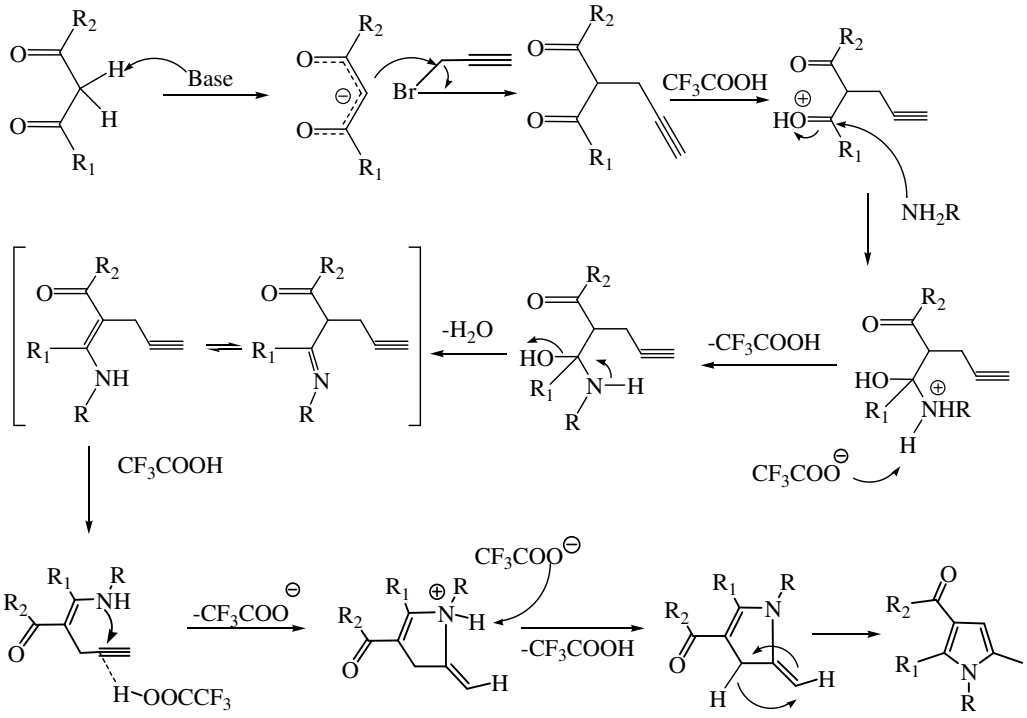
The yields can be considered as high except for **25a, 27c** and **28a** whose yields are good. They are **25a, 27c** and **28a.** The synthesis of **27c** could not be achieved by acid catalyzed cyclization, but by addition of catalytic amount of $Cu(OAc)_2$ to the formed enaminone

Considering the high yields with the metal-free cyclization, acid catalyzed cyclization seems to be better synthetic way for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives in the case of presence of no acid sensitive

functional groups in the starting materals. In addition to these, this process does not require the isolation of acyclic precursor which forms in situ and undergoes cyclization at the same reaction medium. To sum up, synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives starting from 1,3-dicarbonyl compounds is very straightforward when this new method is followed

2.1.3.3 Mechanism of the Reaction

The overall mechanism is summarized in Scheme 58.



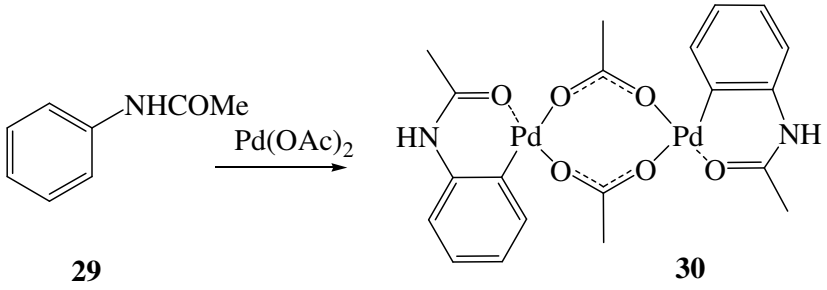
Scheme 56

2.2 Catalytic Stereoselective Functionalisation of Ferrocene Derivatives

Functionalization of directing group substituted aromatic compounds with the formation of new C-C bond through transition metal catalyzed activation of normally unreactive aromatic C-H bond has become an interesting area of search recently.

Most frequently used transition metal is Pd for this kind of study. There are large numbers of publications on the C-H activation of aromatic compounds with the use of Pd. In addition to Pd; Ru, Rh, Ir, Ti, Zr, Ni [67], Hg [68], Sn, Pt [68d] involved activations has been published in the literature.

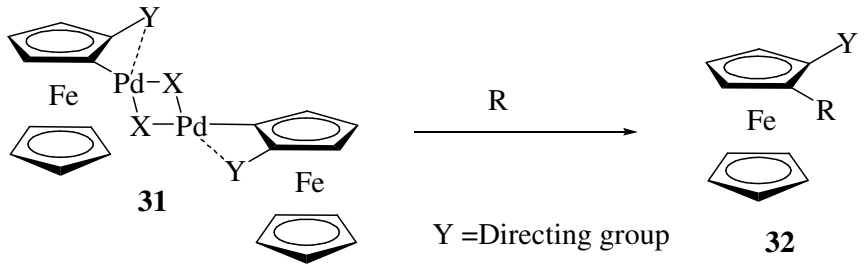
When Pd assisted activations are considered, the first step of the process is cyclopalladation of the aromatic compound to form a dimeric cyclopalladated complex involving coordination of Pd to the directing group as well as normally inactive C-H carbon of aromatic compound. A very good example to this activation was performed by Horino *et al*. in the study of ortho vinylation of aromatic amides via cyclopalladation complexes (Scheme 57).[69] The formation of the dimeric cyclopalladate complex is a common feature of many of the activation of C-H bond studies on the aromatic compounds [70].



29 **30**

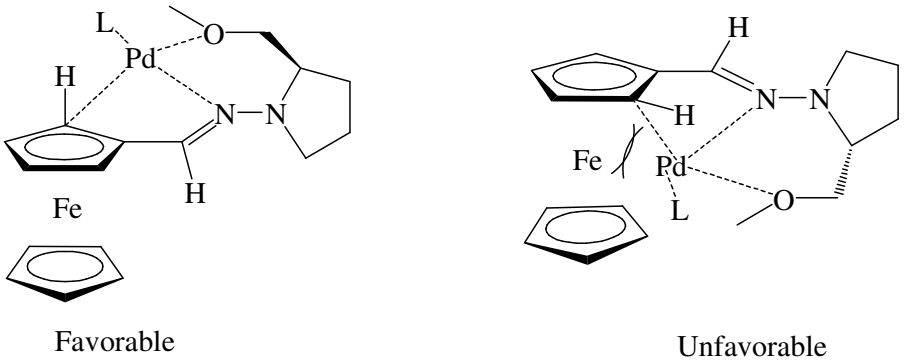
Scheme 57

In the light of this idea, cyclopalladation has been performed on the ferrocene systems having directing groups. With the coordination of Pd to the aromatic carbon of ferrocene derivative, the coordinated carbon gets somehow more negative character. This is a very good property from synthetic point of view. This additional electron density on the activated carbon makes functionalisation easier in quenching with species having positive characters that is, electrophiles or quenching with nucleophiles.(Scheme 58).



Scheme 58

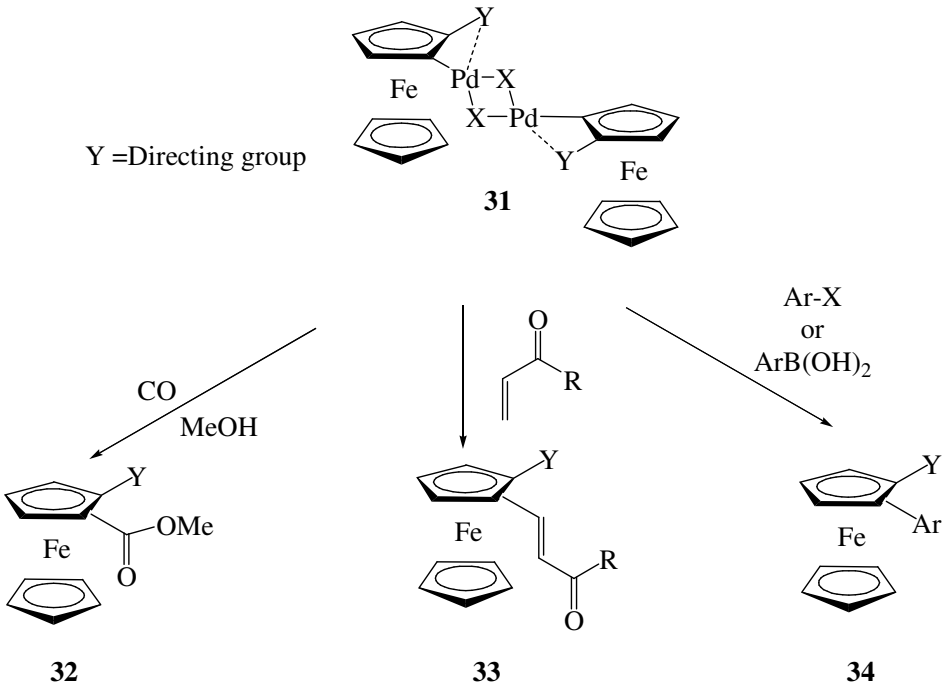
Our aim in this study is to follow the same strategy and stereoselectively functionalize the ferrocene system with the use of catalytic amount of Pd source. To make a stereoselective functionalization, we need a good ortho directing group attached to the ferrocene. Imines and hydrazones are very useful directing groups for this kind of jobs. To make a stereoselective functionalization, the imine or hydrazone group must have some kind of chirality to differ two carbon atoms that have the possibility of being activated. Fe-SAMP hydrazone was chosen to be the good system in that it has both asymmetric center and directing property for the cyclopalladation. The stereoselectivity arises from the chiral property of SAMP as illustrated in Scheme 59.



Scheme 59

The functionalisation studies we focused on can be summarized in three subgroups, the first one of which is carboxylation with CO, the second one is

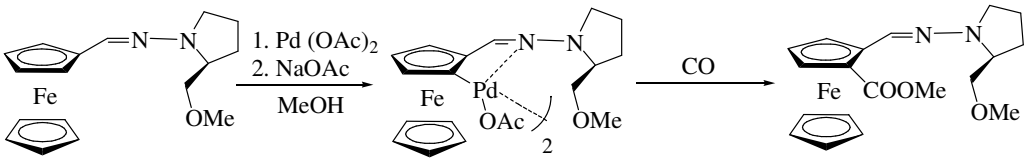
oxidative cross-coupling with α, β-unsaturated carbonyl compounds and the third one is arylation. All of them were planned to be achieved by catalytic amount of Pd source. They are summarized in Scheme 60.



Scheme 60

2.2.1 Carboxylation with CO

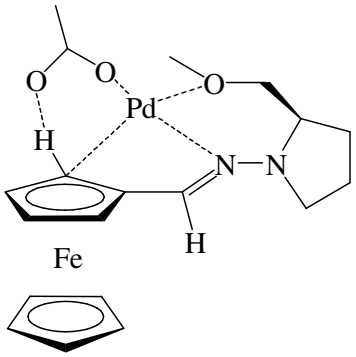
To be able to carboxylate ferrocene-SAMP hydrazone **35** catalytically, the applicability of the reaction was tested stoichiometrically. Since formation of dimeric cyclopalladated complex is the first step for activation of inactive C-H bond of ferrocene system, **35** was cyclopalladated with 1 eq $Pd(OAc)_2$ and 1 eq NaOAc in methanol. After the formation of the complex **36** which was monitored by TLC, CO was introduced to the reaction medium for carboxylation (Scheme 61).



35 **36** **37**

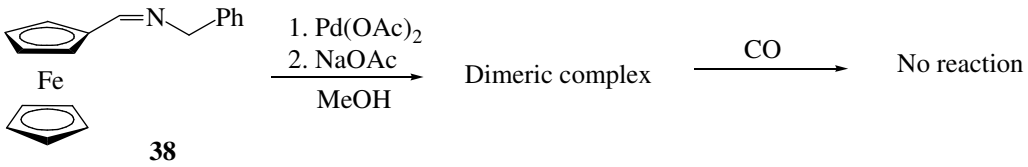
Scheme 61

Introduction of CO to the medium caused Pd to precipitate with the formation of **37.** This clearly indicates that stereoselective functionalization of **35** was achieved in case of stoichiometric addition of $Pd(OAc)_2$. Characterization of **37** was done by its ^{1}H-NMR spectrum (Figure37). When compared with ^{1}H-NMR spectrum of **35** (Figure 36), the appearance of a singlet, the integration of which corresponds to 3H at 3.71 ppm, and the shift of olefinic proton to the low field of the spectrum in Figure 38 clearly indicate the formation of **37**. The singlet corresponds to 1H at 7.59 ppm is the result of existence of cis and trans isomer of **37** in the final product. Precipitation of Pd means that oxidation state of Pd is reduced to Pd(0) from Pd(2) that is, Pd(2) is consumed up for the functionalization as expected. NaOAc is the weak base frequently used to accelerate the cyclopalladation process. The acetate group of the Pd is intramolecularly takes the proton attached to the carbon of ferrocene system at which Pd coordinates (Scheme 62). If the same reaction is tried with another Pd source such as $PdCl_2$ without NaOAc the rate of the reaction would drop drastically. However, the addition of NaOAc will lead to the insertion of acetate anion to the ligand sphere of Pd where from it promoted intramolecularly the abstraction of proton. To sum up, use of NaOAc is crucial for the cyclopalladation process.



Scheme 62

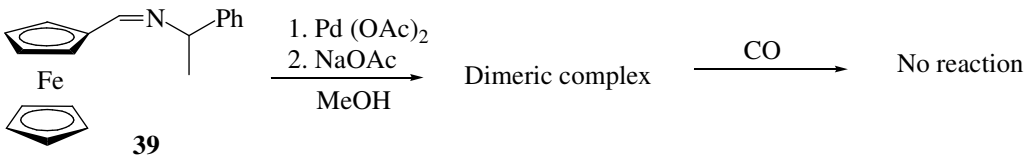
Then the question of changing the directing group will give the same response arises. For this pupose, applicability of the diastereoselective functionalisation of **38** was explored with stoichiometric addition of $Pd(OAc)_2$ and NaOAc. Although the formation of dimeric complex had taken place, which was monitored by TLC, introduction of CO to the medium did not lead to the formation of the desired product. Possibly, imine moiety is not durable to this kind of reaction and decomposed to its aldehyde (Scheme 63).



38

Scheme 63

Another imine derivative **39** was tested with stoichiometric ratios and failed (Scheme 64).



39

Scheme 64

Since stoichiometric functionalization of **38** and **39** failed, **35** was decided to be the model system for the remaining experiments for the catalytic stereoselective functionalization.

After the prove of applicability of the selective carboxylation of **35**, the studies focused on performing the same reaction with catalytic amount of $Pd(OAc)_2$ and NaOAc. The first attempt of catalytical functionalization was failed. Therefore, a series of modifications were made and tested for the validity of the conditions for the catalytic conversion.

First of all, the effects of different solvents (methanol, ethanol, toluene, DMF, THF and acetic acid) on the stoichiometric conversion examined and methanol and ethanol were found to be the best solvents (methanol is a little better). Moreover, in THF, DMF and toluene formation of the product was observed but acetic acid is not applicable.

There are two main reasons for the failure of the catalytic conversion. First one is the precipitation of Pd, and the second one is the possibility that existence of CO prevents the formation of cyclopalladated dimeric complex. After the selection of the best solvent, these two reasons were taken into account.

To test the possible block of the formation of dimer by CO, CO gas was introduced to the reaction medium just before the addition of $Pd(OAc)_2$ and NaOAc**.** Formation of the dimeric complex was observed. This apparently means that existence of CO does not block the formation of dimeric complex.

After elimination of the first possible reason for the failure, we concentrated on the second possibility; precipitation of palladium. In other words, the oxidation state of Pd reduces to 0 and can not be converted to 2. Thus, possible ways to overcome this handicap was explored.

In many catalytic reactions involving Pd, Cu(II) and O_2 are used, to reoxidate Pd (0) by Cu(II) (Scheme 65).[71]

$$Pd(0) + 2\,CuX_2 \longrightarrow PdX_2 + 2\,CuX$$

$$2\,CuX + 2HX + 1/2\,O_2 \longrightarrow 2\,CuX_2 + H_2O$$

Scheme 65

Therefore, reaction was performed in the presence of $Cu(OAc)_2$ and O_2. Unfortunately, catalytic conversion could not be achieved. Then the effect of $Cu(OAc)_2$ presence on the formation of dimeric complex was explored. This was done by performing the reaction with stoichiometric amounts of $Pd(OAc)_2$ and NaOAc in the presence of $Cu(OAc)_2$. It was found that presence of $Cu(OAc)_2$ does not have negative effect on the formation of the dimeric complex.

There are some examples in the literature in which benzoquinone (BQ) is used in the catalytic reactions of palladium. van Leeuwen *et al.* explained the success of BQ as follows. It either reoxidizes Pd (0) or acts as ligand to stabilize the Pd complexes forming during the course of reaction.[72]

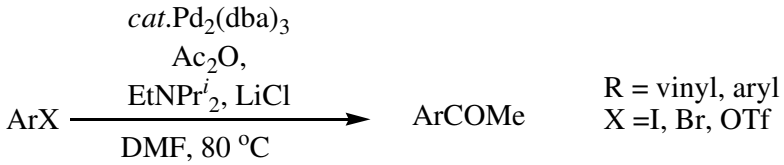
In the light of these pieces of information, we made a series of experiment on catalytic reaction. In these reactions $Cu(OAc)_2$**,** O_2 and BQ were used together as the oxidizing species and other parameters such as effect of solvent, temperature, and addition sequence of reactants were investigated. Unfortunately, all the reactions failed.

Fujiwara and co-workers reported that benzene and other aromatic compounds can be carboxylated by using CO in the presence of catalytic palladium source in triflouroacetic acid by using K_2S_8 (potassium peroxodisulfate) as oxidant.[73] This study prompted us to use K_2S_8 and acetic acid as oxidant and solvent respectively. Beside that some combinations of K_2S_8 and BQ in methanol were tested. Unfortunately they did not succeed.

Another oxidant tested was AgOAc. It did not reoxidize Pd(0) either.

So far, introducing CO to the reaction medium had been performed by passing CO gas either through reaction atmosphere or through reaction mixture. No doubt, the pressure of CO in these cases is equal to a fixed value. Therefore, the pressure fixed to atmospheric pressure by adjusting a balloon apparatus to the head of the reaction vessel. Some selected reactions which had already tried were reinvestigated with the balloon apparatus. Unfortunately no positive result was obtained.

Another possible way to introduce CO to the medium is to generate it in situ. Recently, Cacchi *et al* described hydrocarbonylation of vinyl and aryl halides with this strategy. The generation of CO was achieved by using Pd(0)-acetic anhydride pair. (Scheme 66).[74]



Scheme 66

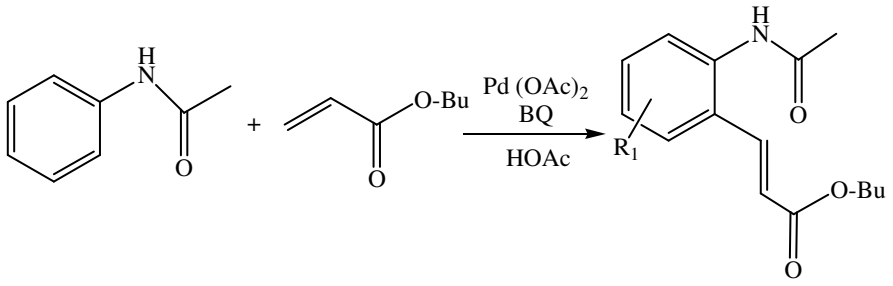
We generated CO as described in Cacchi's publication for catalytic carbonylation of **35**. Reaction failed.

Ultimately, in order to check the effect of Pd source on the reaction, catalytic conversion was performed with allyl palladium acetate dimer in different solvents (methanol, dioxane, THF and toluene). The formation of the cyclopalladated complex was observed in methanol and dioxane. Then CO introduced to the formed complexes. Precipitation of Pd was observed as in the previous cases. Therefore the source of Pd is decided not to have enormous effect on catalytic conversion.

Catalytic version of the selective functionalization of **35** with CO requires time for testing other parameters and combination of each parameter separately. This study is still under investigation.

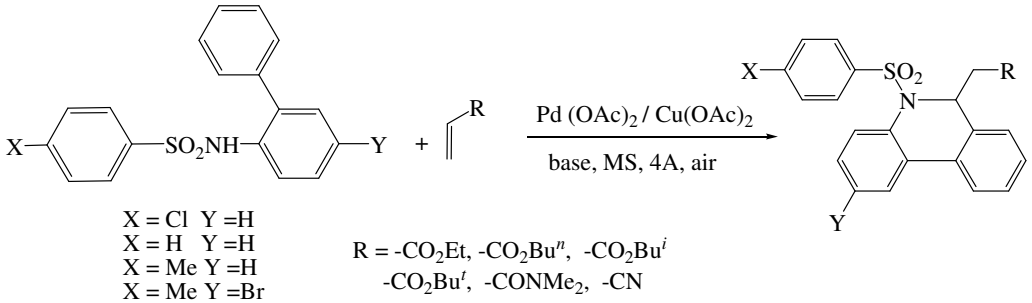
2.2.2 Oxidative Cross-Coupling with α, β-Unsaturated Carbonyl Compounds

Recently, van Leeuwen and co-workers reported that it is possible to make an oxidative coupling between anilides and olefins through C-H bond activation with the use of catalytic amount of $Pd(OAc)_2$ (Scheme 67).[72]



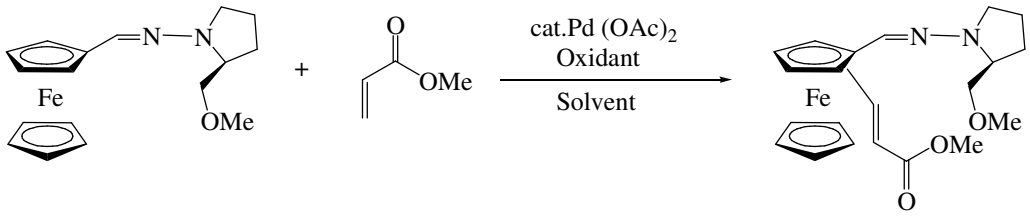
Scheme 67

Another study related to this concept was performed by Miura *et al*. on the oxidative cross-coupling of N-(2'-Phenylphenyl)benzene sulfonamides or benzoic and naphthoic acids with alkenes using a palladium-copper catalyst system under air (Scheme 68).[75]



Scheme 68

These studies encouraged us to achieve similar functionalization in the ferrocene system catalytically and stereoselectively. The reaction of **35** with methyl acrylate was chosen as the model reaction for this purpose (Scheme 69).



35 **40**

Scheme 69

First of all, stoichiometric reaction of **35** with methyl acrylate was performed in different solvents together with the addition of NEt_3. The reason for addition of NEt_3 is that, it acts as base which accelerates the formation of cyclopalladated dimeric complex and acts as ligand to stabilize Pd complexes forms throughout the reaction. The tested solvents were methanol, acetic acid, toluene, THF, DMF, and TFA. The reactions did not work in these solvents with $Pd(OAc)_2$ - NEt_3 pair.

Then, to test applicability of the reaction functionalisation of **35**, the reaction was performed with the conditions described by Miura *et al.* [75] Low yield formation of the product was observed (Monitored by TLC). In spite of the low yield, the reaction was found to be applicable due to the formation of expected product with low conversion.

Solvent screening was performed for this catalytic conversion and dioxane or dioxane/ water system seemed to be useful. Another parameter to be tested is the oxidant. The combination of $Cu(OAc)_2$ and BQ in different solvents was tested. None of the tested combination led to the catalytical conversion of **35** to **40**.

During the test of the corresponding parameters, it was observed that as the equivalence of $Cu(OAc)_2$ changed from catalytic to stoichiometric, the formation of

40 decreases. Moreover, the formation of ferrocene carboxaldehyde decomposition of **35** was observed. This may be due to the ability of Cu species to decompose hydrazones to their corresponding hydrazines.

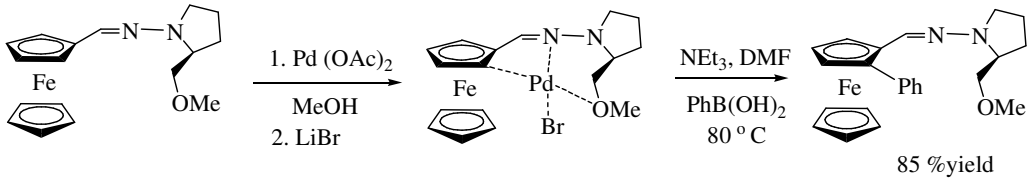
This negative effect of Cu(II) led us to test another oxidant: AgOAc. The solvent screening is applied for AgOAc case and found to be unsuccessful oxidant for the catalytic conversion.

As in the case of carboxylation, this synthetic route requires some time for the test of different combinations of oxidant-solvent which will enable the catalytic conversion of **35** to **40**. This project is still under investigation.

2.2.3 Arylation

In this part of the study, our aim was to make a catalytic and stereoselective functionalization of **35** with Pd source through *ortho* arylation reaction. The arylation can be performed either by means of using aryl boronic acids or using aryl halides. In each case aryl group has positive character to which activated carbon can attack.

To make a catalytic reaction, one must explore the applicability of the reaction in stoichiometric ratios. Hence, we first synthesized the aryl substituted ferrocene derivative through the reaction pathway summarized in Scheme 70.



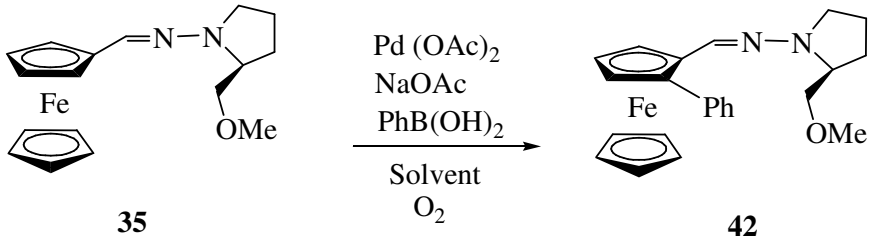
35 **41** **42**

Scheme 70

Synthesis of **41** works in two steps. First one is the formation of the cyclopalladated dimeric complex as usual. The second step is cleavage of dimer with LiBr. The reason for using NEt_3 was same as discussed in previous section. Aryl substituted ferrocene derivative **42** was synthesized in 85 % yield. Characterization of **42** was made from ^{1}H-NMR spectrum (Figure 39). We achieved to make diastereoselective arylation of ferrocene derivative stoichiometrically.

After that, we focused on the catalytic version of the same synthesis. For a catalytic design of the synthetic route described above, cleavage of dimeric cyclopalladated complex with LiBr to form **41** and isolation of it for another step is out of the scope of catalytic conversion study. For the completion of the catalytic cycle, reaction must go through the formation of cyclopalladated dimeric complex rather than the isolation **41** and using it in another step.

For this purpose, first of all stoichiometric version of mentioned strategy was tested with different solvents (THF, DMF, toluene) as summarized in Scheme 71.

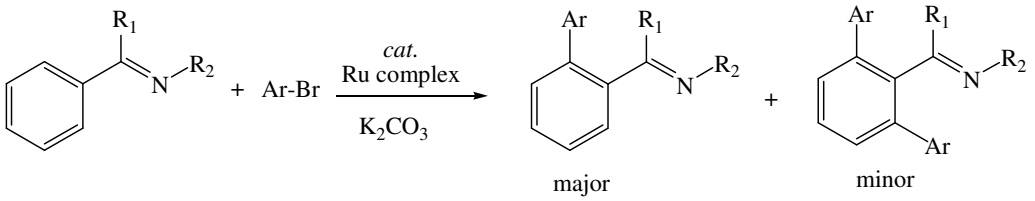


35 **42**

Scheme 71

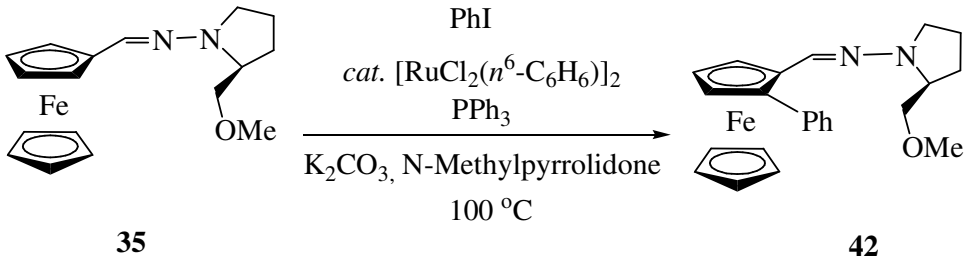
Unfortunately, all the reactions gave the biphenyl product as the result of homocoupling reaction. This result shifted our expectations to achieve catalytic arylation with aryl halides rather than testing all the parameters and finding optimum combinations of them in aryl boronic acid strategy.

Oi *et al*. has described the *ortho* arylation of aromatic imines with organic halides through ruthenium complex catalyzed reaction recently (Scheme 72).[76]



Scheme 72

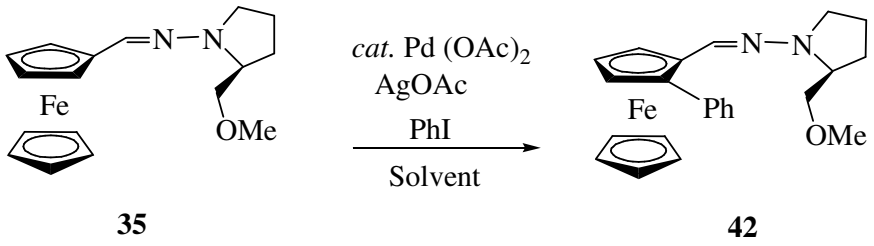
This study prompted us to make the same arylation on ferrocene system. First of all, the same reaction conditions described by Oi *et al* were tried on the arylation of **35** with phenyl iodide (Scheme 73). The reaction failed.



35 **42**

Scheme 73

After the failure of this reaction together with the failure of $Pd(OAc)_2$ - $PhB(OH)_2$ combination we concluded that forming cationic palladium with the use of AgOAc may be effective for further activation of carbon to which Pd will coordinate (Scheme 74). Then the new strategy became use of $Pd(OAc)_2$- AgOAc combination for arylation with phenyl iodide.



35 **42**

Scheme 74

A series of experiments were carried with the different solvents. (dioxane, dioxane /water, methanol, acetic acid, DMF and THF) None of the tried condition succeeded in making catalytic arylation to **35.**

Similar to the carbonylation and oxidative coupling with α, β-unsaturated carbonyl compound, arylation project requires time for exploring the parameters for providing optimum conditions for the catalytic functionalization of ferrocene derivative **35.**

CHAPTER 3

EXPERIMENTAL

The structure determination of the compounds in this study was done by the instruments mentioned below.

NMR spectra were recorded on a Brucker DPX 400 spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane, which is used as internal standart; the ^{1}H-NMR data is presented in the order: δ value of the signal, peak multiplicity (abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br , broad) and coupling constants in Hertz integrated number of protons.^{13}C-NMR spectra were measured at 100 MHz and the chemical shifts were reported relative to $CDCl_3$ triplet centered at 77.0 ppm.

IR spectra were recorded on a Perkin Elmer 1600 FTIR series instrument.

Optical rotations were recorded in $CHCl_3$ solution of a 1dm cell using a Krüss P3002RS Automatic digital polarimeter.

Column chromatography was conducted on silica gel 60 (mesh size 40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light (λ = 254 nm). Solvents were either technical or high grade and they were distilled when necessary.

All extracts were dried over $MgSO_4$ and concentrated under vacuum

3.1 Synthesis of 1,2,3,5-Tetrasubstituted Pyrrole Derivatives

3.1.1 Alkylation of 1,3-Dicarbonyl Compounds

3.1.1.1 General Procedure for Alkylation of 1,3-Dicarbonyl Compounds

5.0 mmol of 1,3-dicarbonyl compound was dissolved in 10 ml THF and stirred. Under Ar atmosphere NaH (120 mg, 5.0 mmol,) was added carefully and stirred for 2-3 hours. After that, propargyl bromide (655 mg, 5.0 mmol) was added in 4 or 5 portions during 4 hours. The formation of products was monitored by TLC using 1:7 ethyl acetate:hexane solvent system.

After completion of the reaction, unreacted NaH was neutralized with water, reaction mixture was acidified with 2-3 drops of concentrated HCl, extracted with ethylacetate three times (3x30ml), dried over $MgSO_4$, and concentrated under reduced pressure. Further purification was achieved by flash column chromatography (1:7 ethyl acetate:hexane) to afford the alkylated 1,3-dicarbonyl compounds.

3.1.1.2 3-(Prop-2-ynyl) pentane-2,4-dione, 25

500 mg (5.0 mmol) acetyl acetone was alkylated according to the general procedure in 75 % yield. Alkylated form exists in both keto and enol form according to the ^{1}H-NMR spectrum.

^{1}H-NMR ($CDCl_3$): δ (ppm): 1.93 (t, J=2.1 Hz, 1H), 2.14 (s, 3H), 2.16 (s, 3H), 2.57 (dd, J=12 and j=2.6 Hz, 2H), 3.75 (t, J=7.5 Hz, 2H).

These values are in agreement with the literature values.[78, 79]

3.1.1.3 Ethyl 2-acetylpent-4-ynoate, 26

840 mg (5.0 mmol) ethyl acetoacetate was alkylated according to the general procedure in 66 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.23 (t, J=7.2 Hz, 3H), 1.92 (s, 1H), 2.22 (s, 3H), 2.60 (d, J=8.7 Hz, 2H), 3.60 (t, J=7.5 Hz, 1H), 4.15 (q, J=7.0 Hz, 2H).

These values are in agreement with the literature values.[80, 81, 82]

3.1.1.4 Ethyl 2-(benzoyl)pent-4-ynoate, 27

1.150 g (5.0 mmol) ethyl benzoylacetate was alkylated according to the general procedure in 62 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.09 (t, J=7.1 Hz, 3H), 1.86 (t, J=2.5 Hz, 1H), 2.74-2.83 (m, 2H) 4.45 (t, J=7.5 Hz, 1H), 4.08 (q, J=3.7 Hz, 2H) 7.21-7.42 (m, 2H), 7.49-7.52 (m, 2H), 7.95 (d, J=7.8, 1H).

These values are in agreement with the literature values.[83]

3.1.1.5 Ethyl 2-(isobutyryl)pent-4-ynoate, 28

980 mg (5.0 mmol) ethyl *iso*-butyrylacetate was alkylated according to the general procedure in 64 % yield. Alkylated form exists in both keto and enol form according to the ^{1}H-NMR spectrum. Signals mix and forms as multiplets for some protons.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.03-1,07 (m, 6H), 1.18 (t, J=7 Hz, 3H), 1.94 (t, J=2.7 Hz, 1H), 2.59-2.62 (m, 1H), 2.80-2.83 (m, 1H), 3.41 (d, J=7.2 Hz, 1H), 3.83 (t, J=3.2 Hz, 1H), 4.10 (q, 3.2 Hz, 2H)

3.1.2 Cyclization reactions

3.1.2.1 $Cu(OAc)_2$ Catalyzed Cyclization Ceaction: Ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate, 27c

3.1.2.1.1 (*R*)-(*Z*) Ethyl 2-((1-phenylethylamino)(phenyl)methylene)pent-4-ynoate, 27e

300 mg (1.3 mmol) of **27** was condensed 158 µL (1.56 mmol) (*R*)-phenylethylamine in the presence of catalytic amount of *p*-TsOH in 10 ml benzene by using Dean-Stark trap to remove water from the medium. The formation of products was monitored by TLC using 1:10 ethyl acetate:hexane solvent system.

After completion of the reaction, the reaction mixture extracted with ethylacetate three times (3x10ml), dried over $MgSO_4$, and concentrated under reduced pressure. Then purification performed via flash column chromatography (1:10 ethyl acetate:hexane solvent system) to isolate (*R*)- (Z)-ethyl 2-((1-phenylethylamino)(phenyl)methylene)pent-4-ynoate (**27e)** in 80 % yield. According to the ^{1}H-NMR, small amount of keto form of the **27e** exists.

^{1}H-NMR ($CDCl_3$): 1.35 (t, J=7.2 Hz, 3H), 1.38 (d, J=6.9 Hz, 3H), 1.93-1.95 (br, 1H), 2.55 (dd, j=2.7 Hz, J=18.2 Hz, B part of A-B system, 1H), 2.62 (dd, j=2.7 Hz, J=18.2 Hz, A part of A-B system, 1H), 1.02 (q, J=19 Hz, 2H), 4.15-4.20 (m, 2H), 6.66 (d, J=7.6 Hz, 1H), 6.91 (d, J=7.0 Hz, 1H), 7.06-7.21 (m, 4H), 7.24-7.31 (m, 2H), 7.34-7.40 (m, 1H), 9.53 (d, J=9.0 Hz, 1H)

3.1.2.1.2 (*R*)-Ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate, 27c

150 mg (0.45 mmol) **27e** was dissolved in 6 ml 1,2-dichloroethane and 16 mg (0.09 mmol) $Cu(OAc)_2$ was added. Then it was refluxed for 6 hours. The formation of products was monitored by TLC using 1:7 ethyl acetate:hexane solvent system.

After completion of the reaction, the reaction mixture extracted with diethylether three times (3x5ml), dried over $MgSO_4$, and concentrated under reduced pressure. Then purification performed via flash column chromatography (1:10 ethyl acetate:hexane) to afford (*R*)-Ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate (**27c)** in 70 % yield.
$[\alpha]_D^{20}$: +185.1 (0.047 *c,* $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.09 (t, J=7.0 Hz, 3H), 1.77 (d, J=7.1 Hz, 3H), 1.88 (s, 3H), 4.06 (q, J=7.1 Hz, 2H), 5.29 (q, J=7.0 Hz, 1H), 6.38 (s, 1H), 7.0 (d, J=7.5 Hz, 2H), 7.2-7.43 (m, 8H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 14.1, 14.2, 19.1, 53.2, 58.9, 108.6, 112.5, 125.9, 127.1, 127.9, 128.1, 128.3, 128.5, 128.7, 128.8, 129, 130.1, 130.9, 133.1, 139.1, 141.2, 164.4

3.1.2.2 General Procedure for the Acid Catalyzed Cyclization Reaction

1 mmol Alkylated 1,3-dicarbonyl compound was dissolved in 10 ml benzene. 1.2 mmol amine together with 77.5 μL (0.01 mmol) TFA was added to the stirring mixture and refluxed 12-15 hours by using Dean-Stark trap. The formation of products was monitored by TLC using 1:10 ethyl acetate:hexane solvent system.

After completion of the reaction, the reaction mixture extracted with ethyl acetate three times (3x10ml), dried over $MgSO_4$, and concentrated under reduced

pressure. When further purification needed, flash column chromatography was performed (1:10 ethylacetate:hexane) to afford the pyrrole derivatives.

3.1.3 3-Acetyl-2,5-dimethyl-1-phenyl-1H-pyrrole, 25a

138 mg (1.0 mmol) **25** was condensed with 111 mg (1.2 mmol) aniline according to the general procedure to afford **25a** in 65 % yield.

IR: ν_{max} 3052, 3018, 2985, 1649, 1503, 1419, 1261, 1216 cm^{-1}

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.91 (s, 3H), 2.22 (s, 3H), 2.31 (s, 3H), 6.19 (s, 1H), 7.10 (d, J=7.0 Hz, 2H), 7.36-7.43 (m, 3H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 12.7, 12.9, 28.5, 108.1, 120.5, 128.1, 128.2, 128.6, 129.4, 135.6, 137.6, 194.3

These values are in agreement with the literature values.[40, 77]

3.1.3.1 3-Acetyl-1-benzyl-2,5-dimethyl-1H-pyrrole, 25b

138 mg (1.0 mmol) **25** was condensed with 128 mg (1.2 mmol) benzylamine according to the general procedure to afford **25b** in 97 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.04 (s, 3H), 2.30 (s, 3H), 2.39 (s, 3H), 4.95 (s, 2H), 6.17 (s, 1H), 6.78 (d, J=7.2 Hz, 2H), 7.13-7.23 (m, 3H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 12.1, 12.6, 28.8, 46.9, 108.9, 120.7, 125.8, 127.8, 127.9, 129.3, 135.3, 137.2, 194.8

These values are in agreement with the literature values.[40, 77, 39a]

3.1.3.2 3-Acetyl-2,5-Dimethyl-1(1-H-phenyl ethyl)-1H-pyrrole, 25c

138 mg (1.0 mmol) **25** was condensed with 145 mg (1.2 mmol) (*R*)-phenyl ethylamine according to the general procedure to afford **25c** in 93 % yield.
$[\alpha]_D^{20}$:-254.6 (*c* 0.172, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.75(d, J=7.0, Hz, 3H), 1.90 (s, 3H), 2.23 (s, 3H), 2.34 (s, 3H), 5.43 (q, J=7.0 Hz, 1H), 6.08 (s, 1H), 6.90 (d, J=7.8 Hz, 2H), 7.09-7.20 (m, 3H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 12.5, 13.6, 28.0, 52.3, 96.1, 109.6, 120.2, 125.8, 127.2, 127.5, 128.6, 134.9, 140.8, 194.1

These values are in agreement with the literature values.[40, 38, 39a]

3.1.3.3 Ethyl 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate, 26a

168 mg (1.0 mmol) **26** was condensed with 111 mg (1.2 mmol) aniline according to the general procedure to afford **26a** in 96 % yield.

IR: ν_{max} 3035, 2986, 2311, 1685, 1536, 1420, 1269, 1219, 1163, 1071 cm^{-1}

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.28 (t, J=7.1 Hz, 3H), 1.90 (s, 3H), 2.21 (s, 3H), 4.21 (q, J=7.1 Hz, 2H), 6.26 (s, 1H), 7.1-7.38 (m, 5H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 12.3, 12.6, 14.5, 59.2, 107.5, 111.5, 115.1, 128.1,128.4, 128.7, 129.2,129.3, 136.1, 137.8, 165.2.

These values are in agreement with the literature values.[40, 39a]

3.1.3.4 Ethyl 1-benzyl-2,5-dimethyl-1H-pyrrole-3-carboxylate, 26b

168 mg (1.0 mmol) **26** was condensed with 128 mg (1.2 mmol) benzylamine according to the general procedure to afford **26b** in 92 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.33 (t, J=7.1 Hz, 3H), 2.11 (s, 3H), 2.44 (s, 3H), 4.23 (q, J=7.2 Hz, 2H), 5.03 (s, 2H), 6.3 (s, 1H), 6.8 (d, J=7.3 Hz, 2H), 7.2-7.3 (m, 3H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 11.3, 12.2, 14.6, 46.7, 58.9, 108.1, 111.3, 125.5, 127.4, 127.9, 128.3, 128.8, 120, 135.3, 137.1, 165.3

These values are in agreement with the literature values.[40, 39, 77]

3.1.3.5 (*R*)-Ethyl 2,5-dimethyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate, 26c

168 mg (1.0 mmol) **26** was condensed with 145 mg (1.2 mmol) (*R*)-phenyl ethylamine according to the general procedure to afford **26c** in 94 % yield.
$[\alpha]_D^{20}$: +64.55 (*c* 0.079, $CHCl_3$).

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.26 (t, J=7.0, 3H), 1.8 (d, J=7.2 Hz, 3H), 1.94 (s, 3H), 2.35 (s, 3H), 4.16 (q, J=7.1Hz, 2H), 5.46 (q, J=7.2 Hz, 1H), 6.17 (s, 1H), 6.96 (d, J=7.8Hz, 2H), 7.16-7.25 (m, 3H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 12.2, 13.7, 14.6, 18.9, 52.5, 58.9, 109.1, 111.4, 125.8, 127.2, 127.6, 128.6, 135.5, 141.1, 165.3

3.1.3.6 Ethyl 5-methyl-1,2-diphenyl-1H-pyrrole-3-carboxylate, 27a

230 mg (1.0 mmol) **27** was condensed with 111 mg (1.2 mmol) aniline according to the general procedure to afford **27a** in 92 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.2 (t, J=7.2 Hz, 3H), 2.1 (s, 3H), 4.2 (q, J=7.2, 2H), 6.6 (s, 1H), 7.2-7.34 (m, 10H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 13.0, 14.3, 59.2, 109.2, 113.2, 120.7, 125.5, 127.2, 127.4, 127.8, 128.5, 128.8, 128.9, 129.8, 131.2, 132.0, 138.0, 138.4, 164.6

3.1.3.7 Ethyl 1-benzyl-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate, 27b

230 mg (1.0 mmol) **27** was condensed with 128 mg (1.2 mmol) benzylamine according to the general procedure to afford **27b** in 94 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.04 (t, J=7.1 Hz, 3H), 2.04 (s, 3H), 4.01 (q, J=7.1 Hz, 2H), 4.83 (s, 2H), 6.40 (s, 1H), 6.75 (d, J=7.3 Hz, 2H), 7.11-7.23 (m, 8H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 12.4, 14.2, 47.6, 59.0, 109.2, 112.9, 125.5, 127.2, 127.7, 128.1, 128.7, 128.8, 130.7, 132.3, 137.8, 138.5, 164.5

3.1.3.8 Ethyl 2-isopropyl-5-methyl-1-phenyl-1H-pyrrole-3-carboxylate, 28a

196 mg (1.0 mmol) **28** was condensed with 111 mg (1.2 mmol) aniline according to the general procedure to afford **28a** in 70 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.14 (d, j=7.1 Hz, 6H), 1.26 (t, j=7.1 Hz, 3H), 1.80 (s, 3H), 2.87-3.00 (m, 1H), 4.17 (q, j=7.2 Hz, 2H), 6.26 (s, 1H), 7.3 (d, j=7.3 Hz, 2H), 7.33- 7.41 (m, 3H)

^{13}C-NMR ($CDCl_3$): δ (ppm) 12.6, 14.6, 20.7, 22.0, 26.8, 59.0, 108.9, 110.7, 127.7, 128.5, 128.6, 129.0, 129.1, 138.6, 145.5, 164.8

3.1.3.9 Ethyl 1-benzyl-2-isopropyl-5-methyl-1H-pyrrole-3-carboxylate, 28b

196 mg (1.0 mmol) **28** was condensed with 128 mg (1.2 mmol) benzylamine according to the general procedure to afford **28b** in 95 % yield.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.17 (d, J=7.2 Hz, 6H), 1.27 (t, J=7.1 Hz, 3H), 2.0 (s, 3H), 3.34-3.39 (m, 1H), 4.16 (q, J=7.1 Hz, 2H), 5.1 (s, 2H), 6.26 (s, 1H), 6.8 (d, J=7.5 Hz, 2H), 7.13-7.23 (m, 3H)
^{13}C-NMR ($CDCl_3$): δ (ppm) 12.2, 14.6, 20.7, 25.9, 43.8, 47.5, 59.0, 109.4, 110.6, 127.1, 127.3, 127.6, 128.1, 128.4, 128.6, 137.7, 144.6, 164.9

3.2 Stereoselective Functionalization of Ferrocene Derivatives

3.2.1 (+)-(*S*)-FcCH=NNCH$_2$CH$_2$CH$_2$-CHCH$_2$OCH$_3$, 35

Ferrocenecarboxaldehyde (1.6 g, 7.7 mmol), (+)-(*S*)-1-amino-2-(methoxy-methyl)pyrrolidine [(+)- (*S*)-**1**] (1.0 g, 7.7 mmol) was dissolved in dry benzene (100 mL). The flask containing the reaction mixture was connected to a condenser equipped with a Dean-Stark apparatus. The red solution was refluxed over an oil bath for about 6 h and then transferred into a Schlenk tube, into which 5 Å molecular sieves (3.0 g) were introduced. The mixture was further refluxed for 6 h and carefully filtered. The filtrate was reduced to dryness and then washed with *n*-hexane.Hexane was evaporated under vacuum Yield: 1.83 g (73%).

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.75-1.77 (br, 1H), 1.86-1.93 (br, 3H), 2.78-2.83 (br, 1H), 3.32 (s, 4H), 3.35-3.40 (br, 2H), 3.53 (d, J=18 Hz, 1H), 4.02 (s, 5H), 4.08 (s, 2H), 4.37 (d, J=9.6 Hz, 2H), 6.96 (s, 1H).

3.2.2 (+)-(*S*)-Fc(COOMe)CH=NNCH$_2$CH$_2$CH$_2$-CHCH$_2$OCH$_3$, 37

33 mg of (0.1 mmol) of **35**, 22 mg (0.1 mmol) $Pd(OAc)_2$ and 8.2 mg (0.1 mmol) NaOAc was dissolved in 3 ml methanol and mixed. Formation of **36** was monitored by TLC. After that, CO was introduced to the solvent by syringe and mixed overnight. Completion of the reaction was checked with TLC using 1:7 ethylacetate: hexane solvent system.

After completion of the reaction, the reaction mixture extracted with ethylacetate three times (3x10ml), dried over $MgSO_4$, and concentrated under reduced pressure. For further purification flash column chromatography was performed (1:10 EtOAc:Hex) to afford **37**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.77-1.79 (br, 1H), 1.99-1.99 (br, 3H), 2.98-3.03 (br, 1H), 3.30 (s, 3H), 3.39 (s, 2H), 3.53 (br, 1H), 3.71 (s, 3H), 4.05 (s, 2H), 4.07 (s, 1H), 4.19 (s, 1H), 4.31 (s, 1H), 4.91 (s, 1H), 7.19 (s, 1H),7.59 (s, 1H)

3.2.3 (+)-(*S*)-Fc(Ph)CH=NNCH$_2$CH$_2$CH$_2$-CHCH$_2$OCH$_3$, 42

3.2.3.1 Fc-SAMP-Pd-Br complex, 41

33 mg of (0.1 mmol) of **35**, 22 mg (0.1 mmol) $Pd(OAc)_2$ was dissolved in 5 ml methanol and mixed for 1 hour. Then, 8.6 mg (0.1 mmol) LiBr was added to the reaction mixture. Formation of **41** was monitored by TLC.

After completion of the reaction, the reaction mixture extracted with ethylacetate three times (3x5 ml), dried over $MgSO_4$, and concentrated under reduced pressure. For further purification flash column chromatography was performed (1:3 ethyl acetate: hexane) to afford 40 mg (80 % yield) of **41.**

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.94 (br, 2H), 2.07 (s, 1H), 2.83 (br, 1H), 3.47-3.52 (br, 2H), 3.70 (s, 4H), 4.20 (s, 4H), 4.30 (s, 4H), 4.80-4.83 (br, 1H), 6.96 (br, 1H), 7.19 (s, 1H).

3.2.4 (+)-(*S*)-Fc(Ph)CH=NNCH$_2$CH$_2$CH$_2$-CHCH$_2$OCH$_3$, 42

40 mg (0.08 mmol) of **41** and 11 μL triethylamine (0.08 mmol) was dissolved in 2 ml DMF and stirred. After the addition of 97 mg (0.08 mmol) of phenyl boronic acid resulting mixture was heated to 80 ºC. The formation of **42** was monitored with TLC by using 1:7 ethy lacetate: hexane solvent system.

After completion of the reaction, the reaction mixture extracted with diethyl ether four times (4x5 ml), dried over $MgSO_4$, and concentrated under reduced pressure. For further purification flash column chromatography was performed (1:7 ethy lacetate: hexane) to afford 27 mg (85 % yield) of **42.**

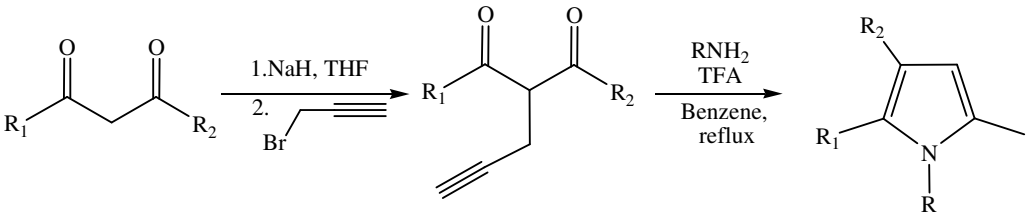
^{1}H-NMR ($CDCl_3$): δ (ppm) 1.76-1.96 (br, 4H), 2.78-2.85 (br, 1H), 3.30 (s, 2H), 3.32 (s, 2H), 3.35 (s, 1H), 3.40-3.57 (br, 2H), 3.98 (s, 2H), 4.00 (s, 2H), 4.02 (s, 2H), 4.16 (s, 1H), 4.38 (s, 1H), 4.73 (s, 1H), 7.13-7.24 (m, 4H), 7.44 (d, J=2 Hz, 2H).

CHAPTER 4

CONCLUSION

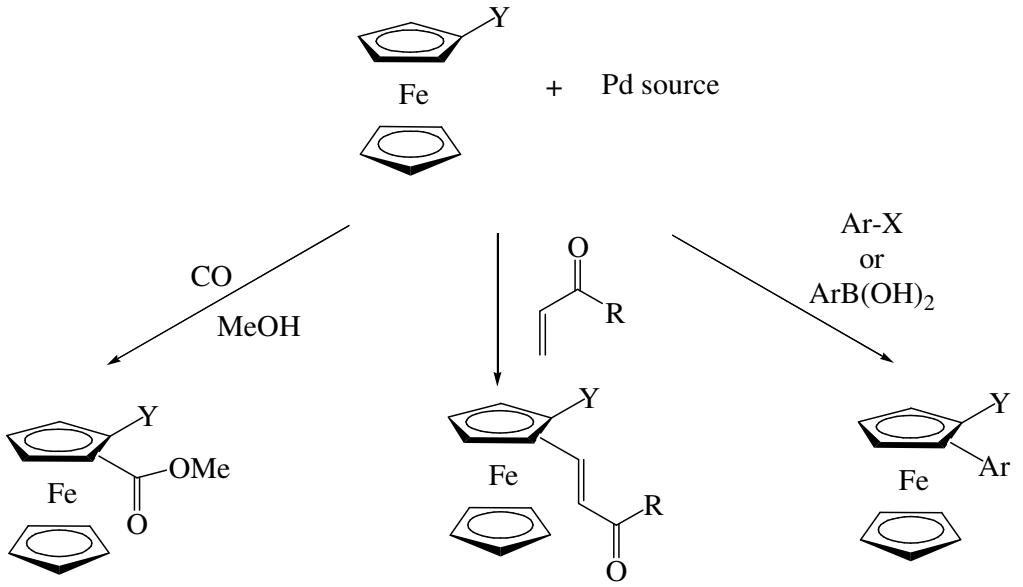
Since pyrroles represent a class of heterocycles that posses biological activity and present in many naturally occurring compounds as well as being building blocks for many important synthetic organic transformations, there happens a continuous demand for the development of a new and applicable method for the synthesis of them.

In the first part of the study, we accomplished to develop a new and efficient synthetic method for the synthesis of 1,2,3,5-tetrasubstituted pyrrole derivatives in two steps through acid catalyzed cyclization reactions enabling the synthesis of them in high yields. We showed that, alkylation of 1,3-dicarbonyl compounds with propargyl bromide followed with the introduction of primary amine results in cyclization with metal free catalytic manner. Compared with the similar synthetic ways consisting of cyclization via catalysts, this method removes the use of metal catalysts making a contribution the idea of green chemistry in syntheses.



Scheme 75

Ferocene derivatives are widely used as ligands in homogeneous transition metal catalysts. In the second part of the study, stereoselective functionalization of ferrocene derivative by means of carboxylation and arylation was achieved with stoichiometric use of $Pd(OAc)_2$. For the catalytic and stereoselective functionalisation of the corresponding ferrocene derivative, various parameters with different strategies were tested. Owing to the vast amount of parameters to be tested, the catalytic functionalisation studies require time and it is still under investigation



Scheme 76

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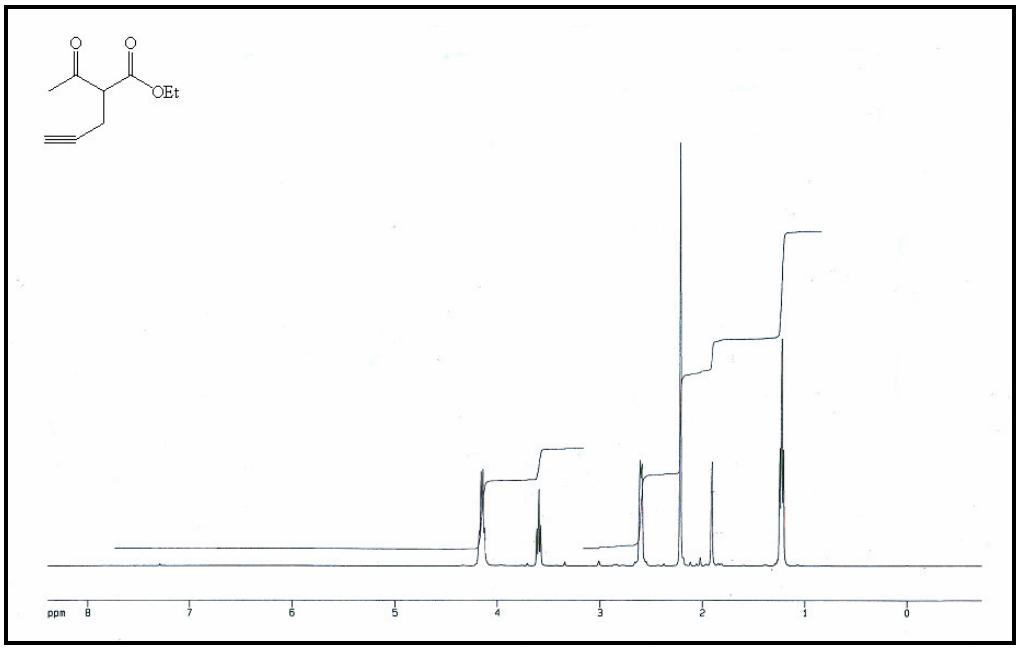

Figure 10 ^{1}H-NMR spectrum of ethyl 2-acetylpent-4-ynoate (**26**)

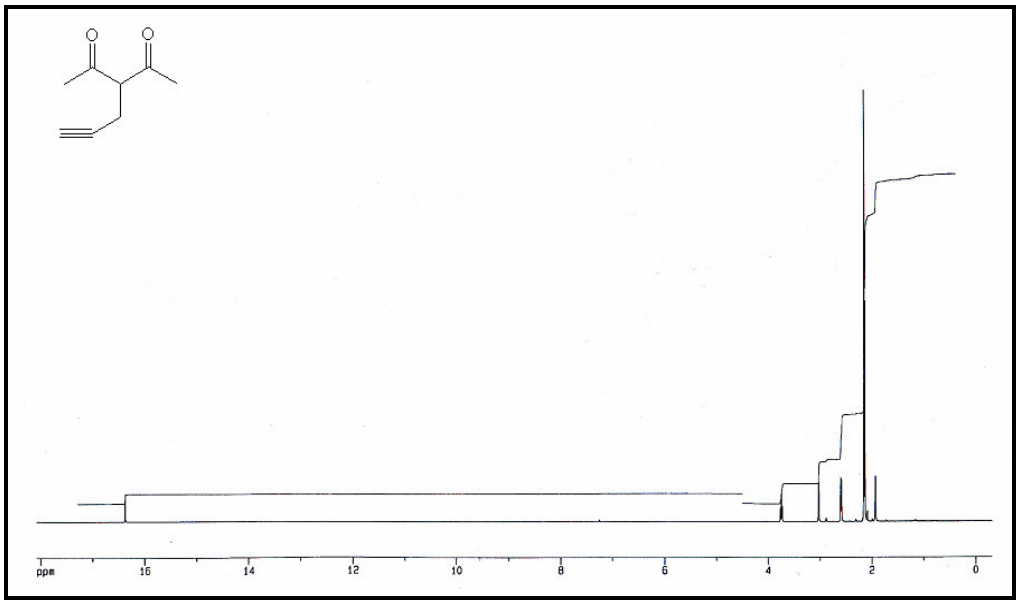

Figure 11 ^{1}H-NMR spectrum of 3-(prop-2-ynyl) pentane-2,4-dione (**25**)

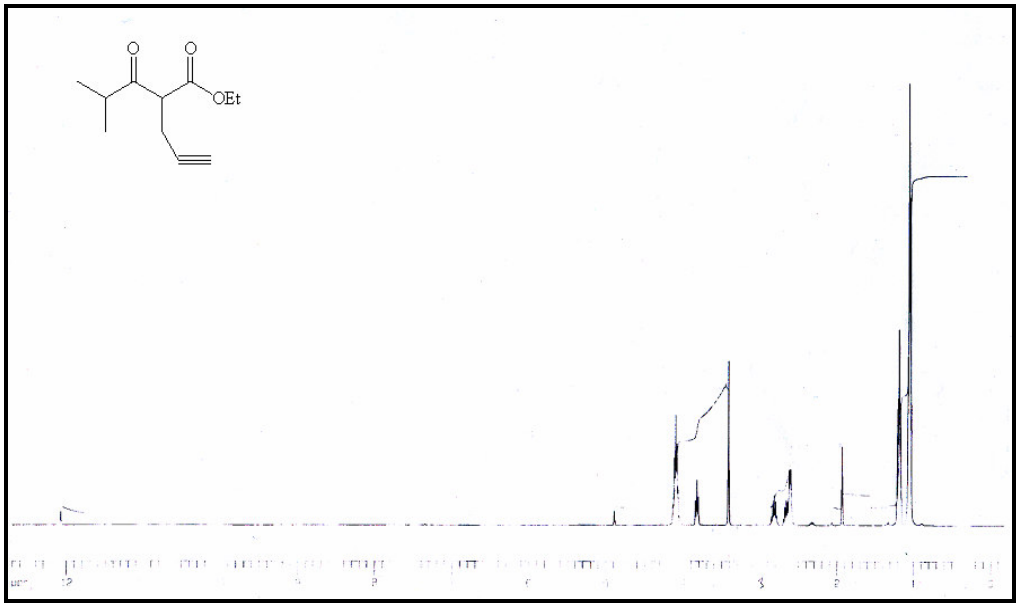

Figure 12 ^{1}H-NMR spectrum of ethyl 2-(isobutyryl) pent-4-ynoate (**28**)

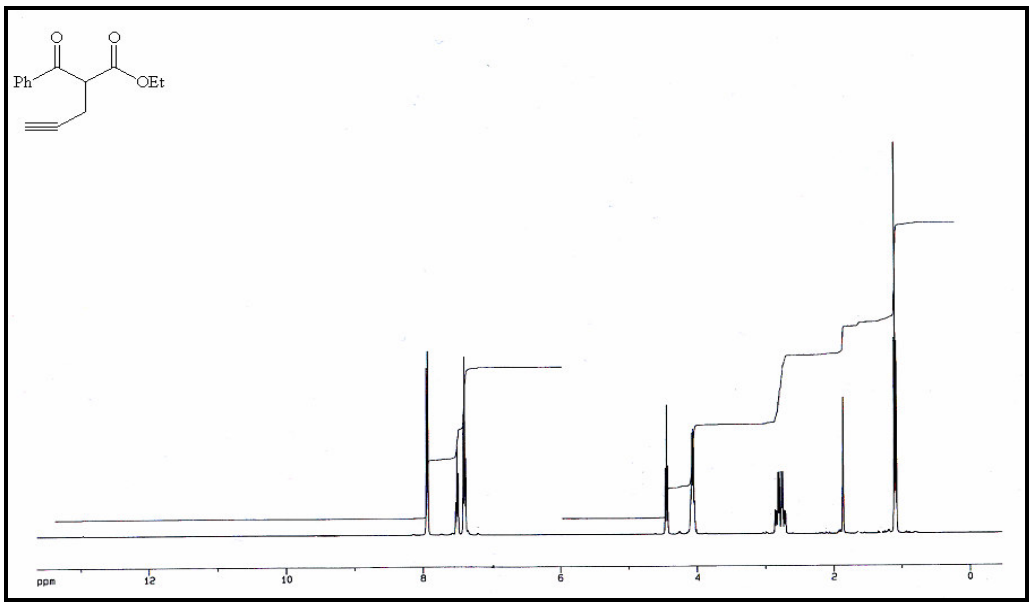

Figure 13 ^{1}H-NMR spectrum of ethyl 2-(benzoyl)pent-4-ynoate, (**27**)

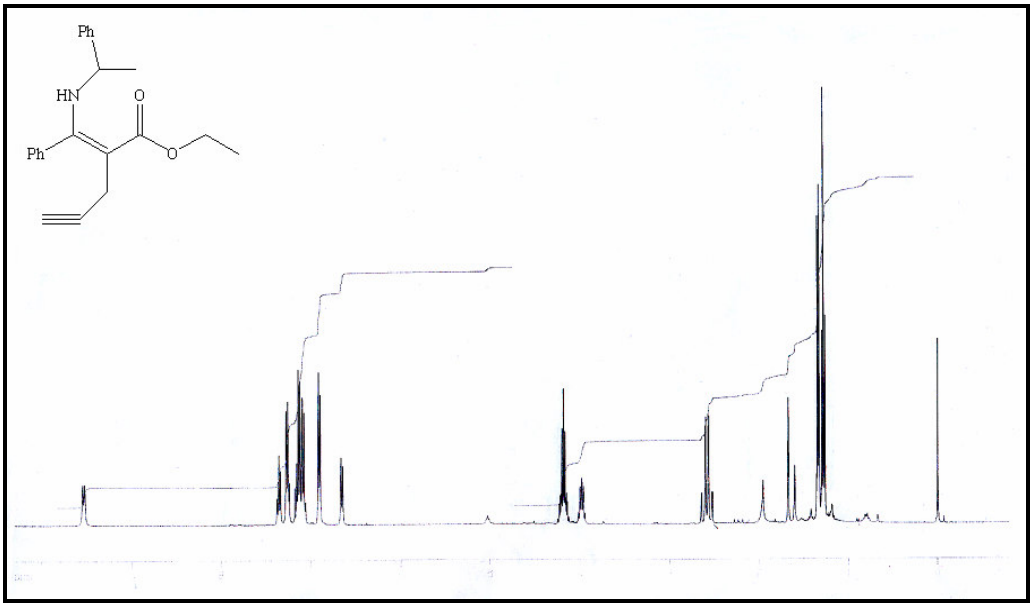

Figure 14 ^{1}H-NMR spectrum of (*R*) - (*Z*)-ethyl 2-((1-phenylethylamino)(phenyl)methylene)pent-4-ynoate, **27e**

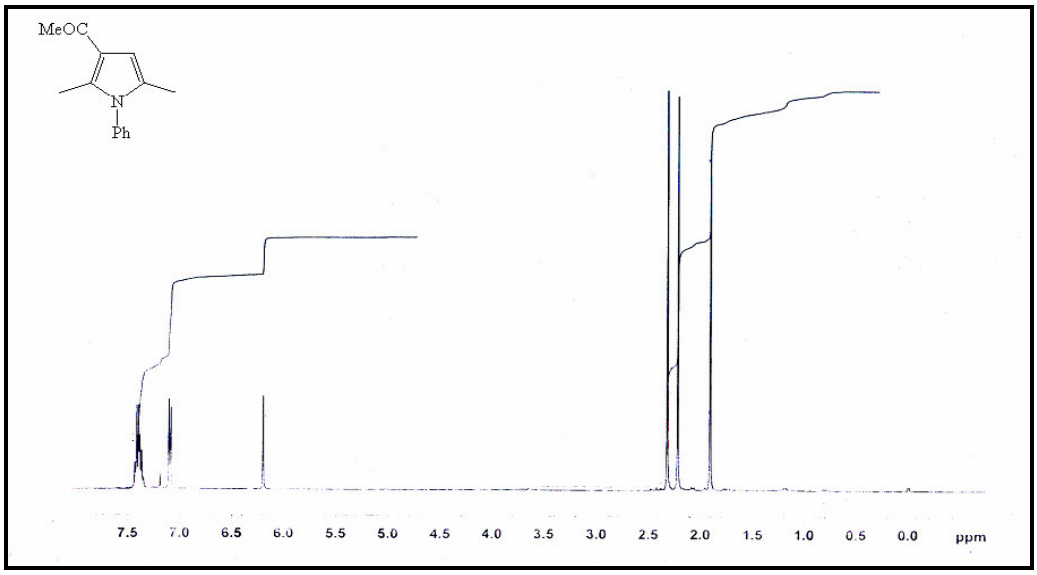

Figure 15 ^{1}H-NMR spectrum of 3-Acetyl-2,5-dimethyl-1-phenyl-1H-pyrrole (**25a**)

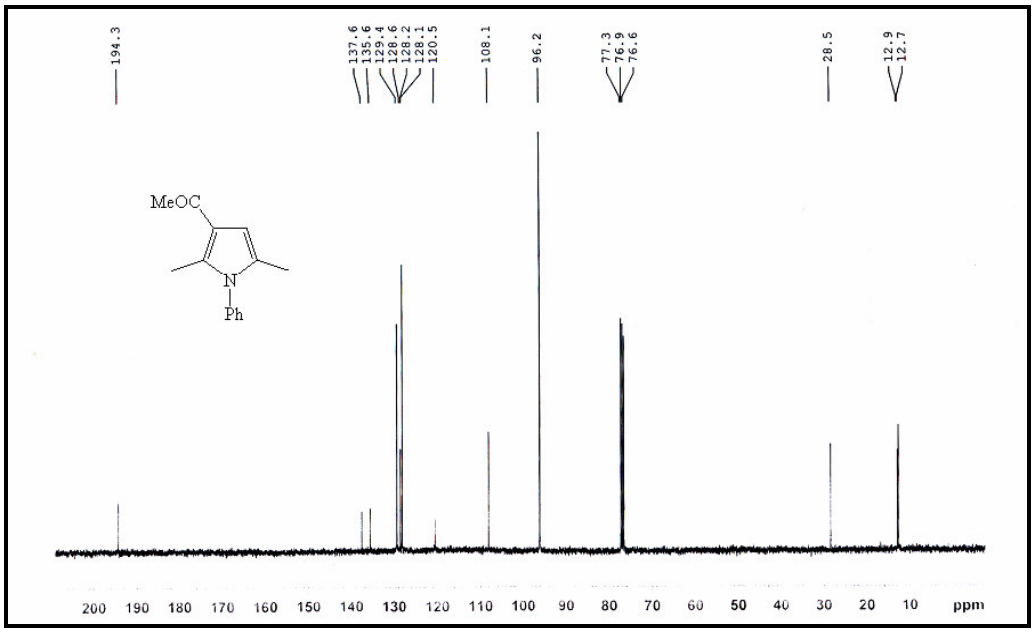

Figure 16 ^{13}C-NMR spectrum of 3-Acetyl-2,5-dimethyl-1-phenyl-1H-pyrrole(**25a**)

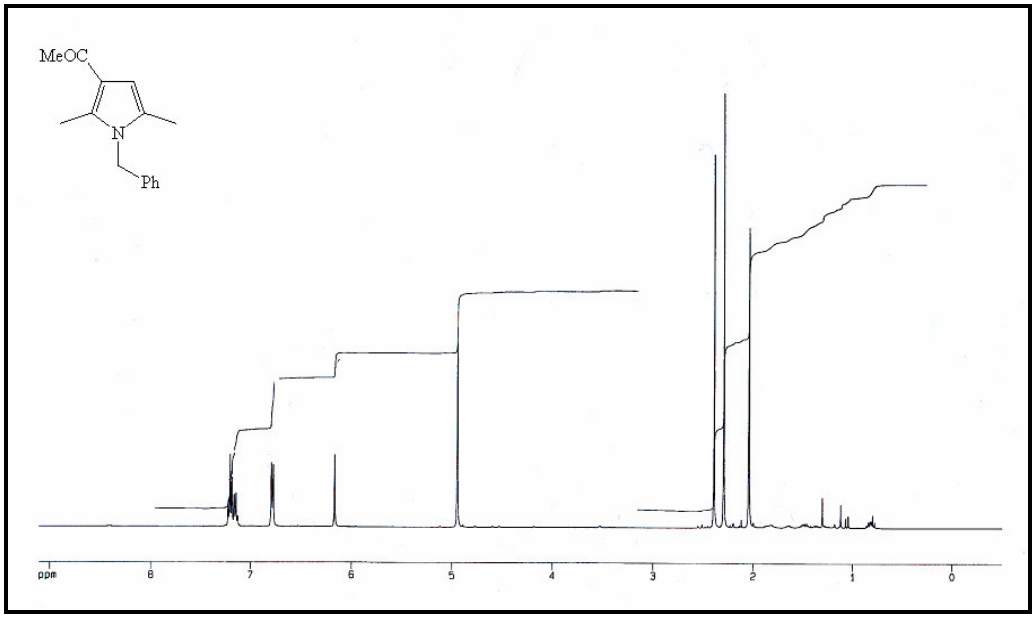

Figure 17 ^{1}H-NMR spectrum of 3-Acetyl-1-benzyl-2,5-dimethyl-1H-pyrrole**,** (**25b**)

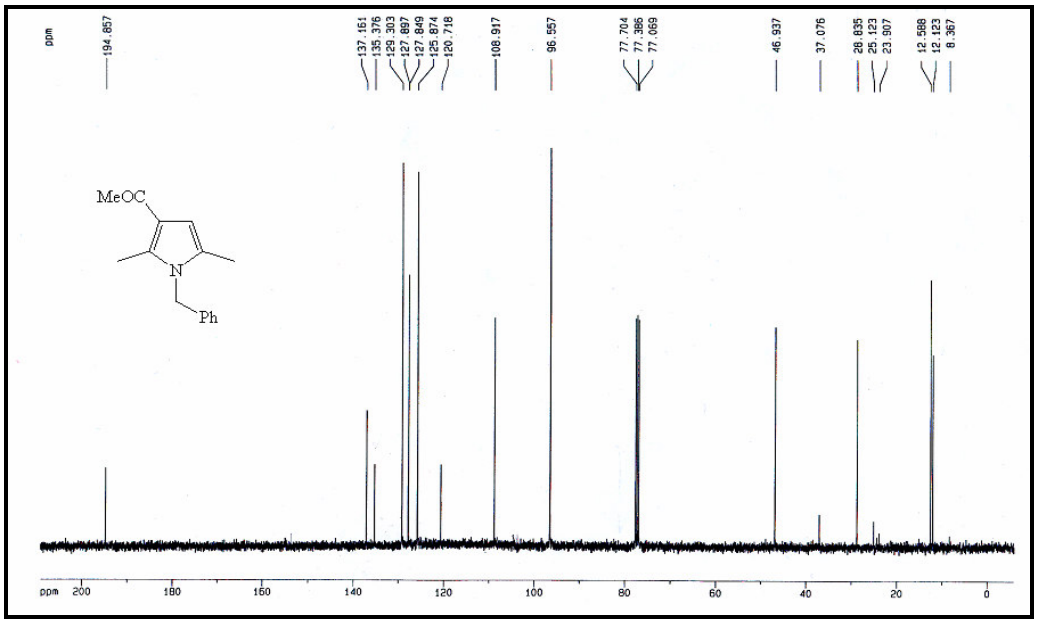

Figure 18 ^{13}C-NMR spectrum of 3-Acetyl-1-benzyl-2,5-dimethyl-1H-pyrrole**,** (**25b**)

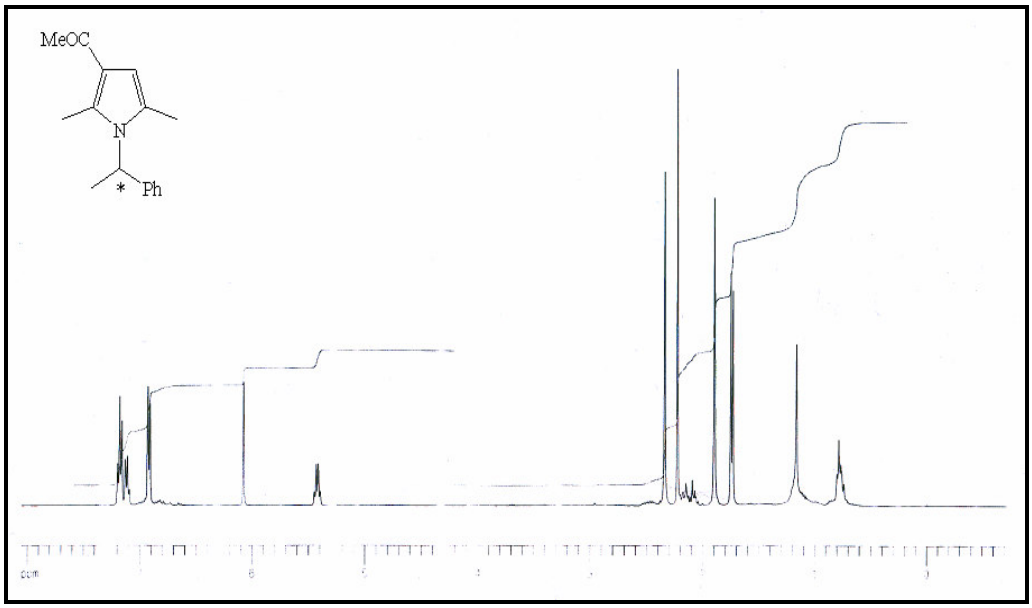

Figure 19 ^{1}H-NMR spectrum of (*R*)- 3-Acetyl-2,5-Dimethyl-1(1-H-phenyl ethyl)-1H-pyrrole (**25c**)

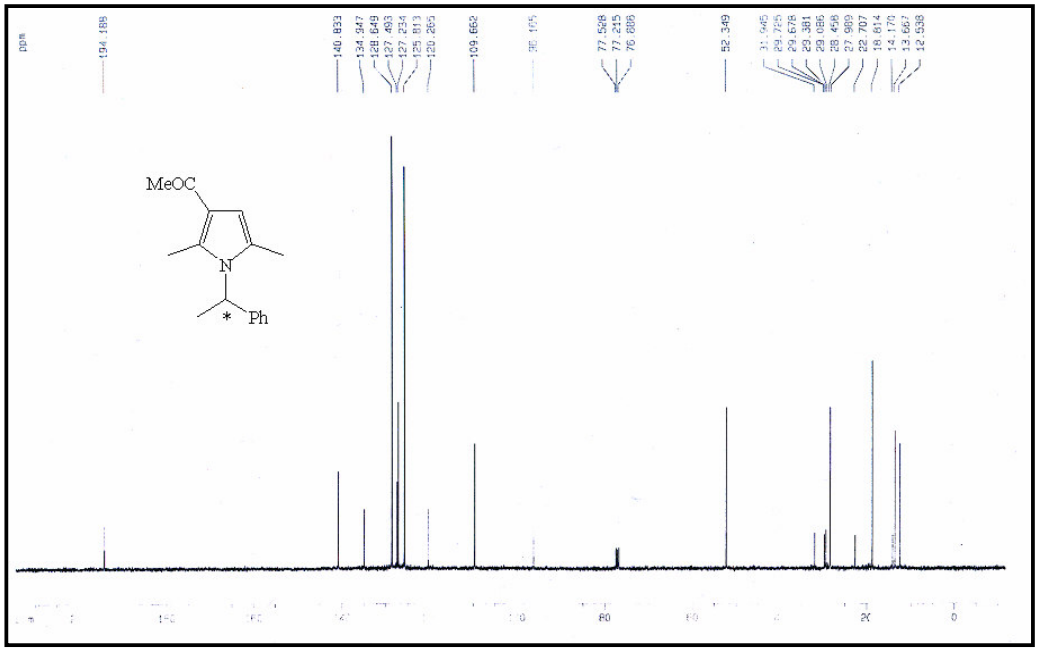

Figure 20 ^{13}C-NMR spectrum of (*R*)- 3-Acetyl-2,5-Dimethyl-1(1-H-phenyl ethyl)-1H-pyrrole (**25c**)

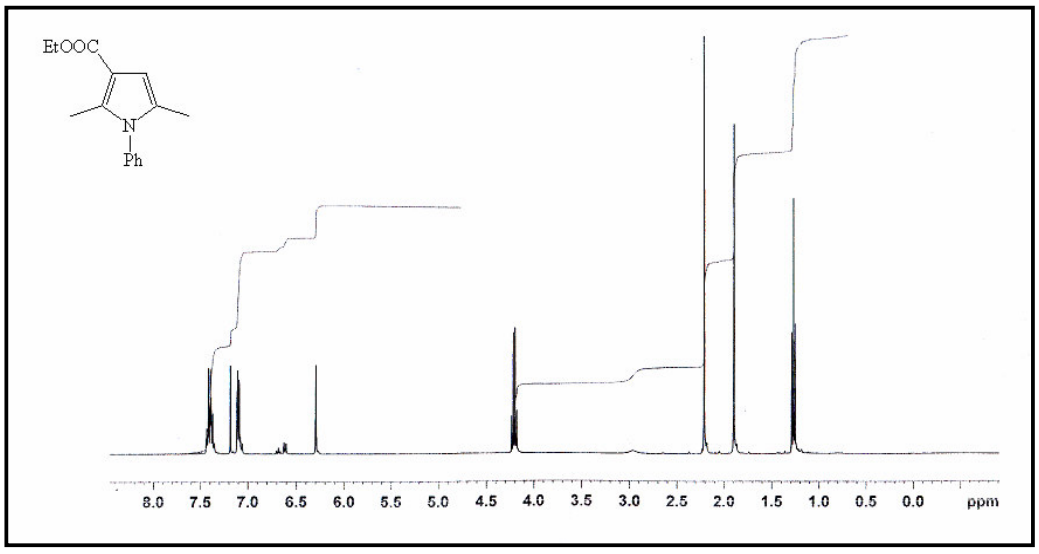

Figure 21 ^{1}H-NMR spectrum of ethyl 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate (**26a**)

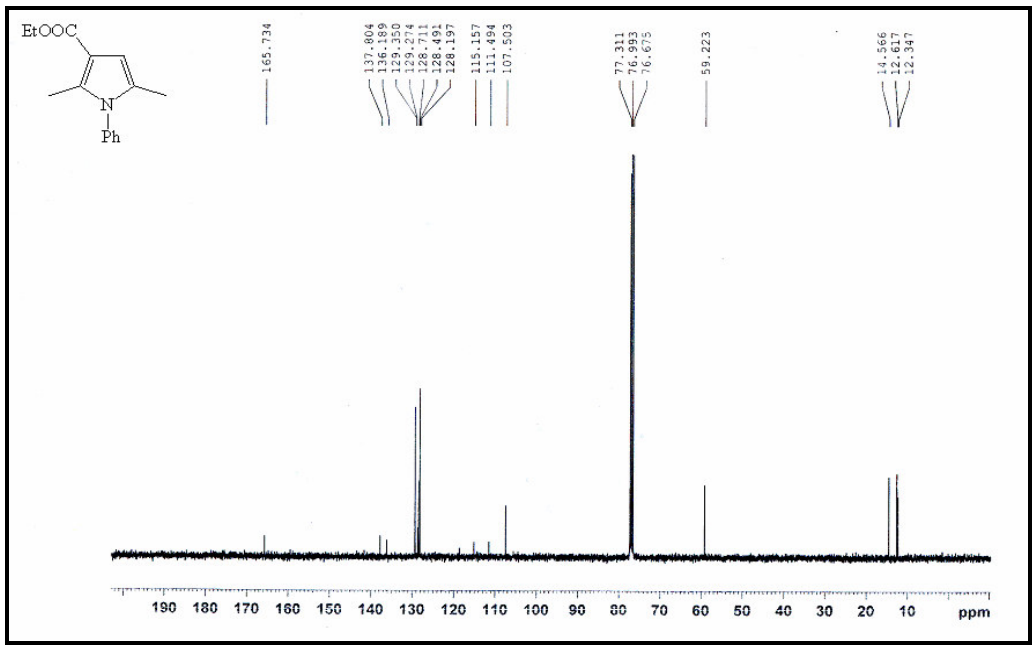

Figure 22 ^{13}C-NMR spectrum of ethyl 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylate (**26a**)

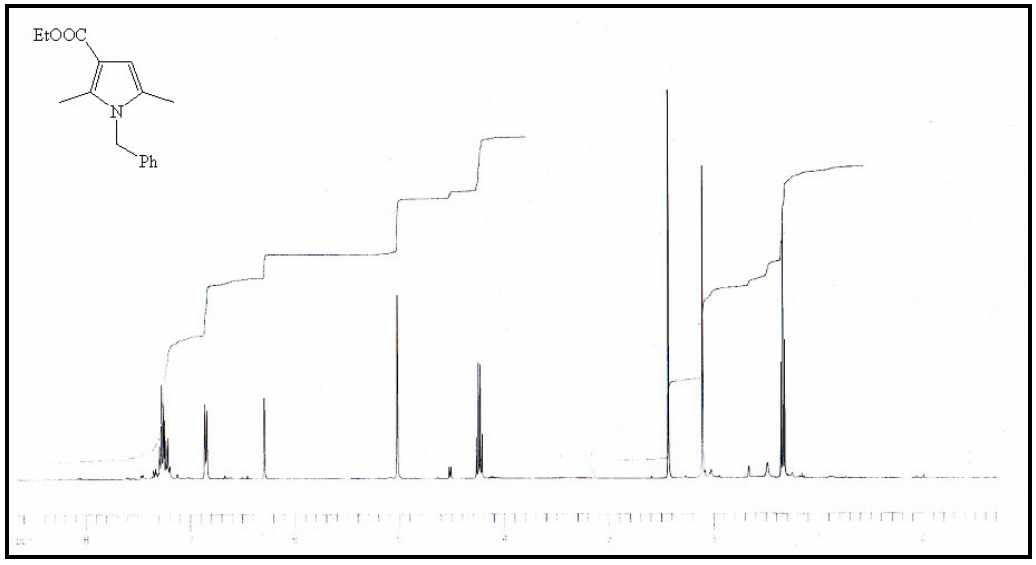

Figure 22 ^{1}H-NMR spectrum of ethyl 1-benzyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (**26b**)

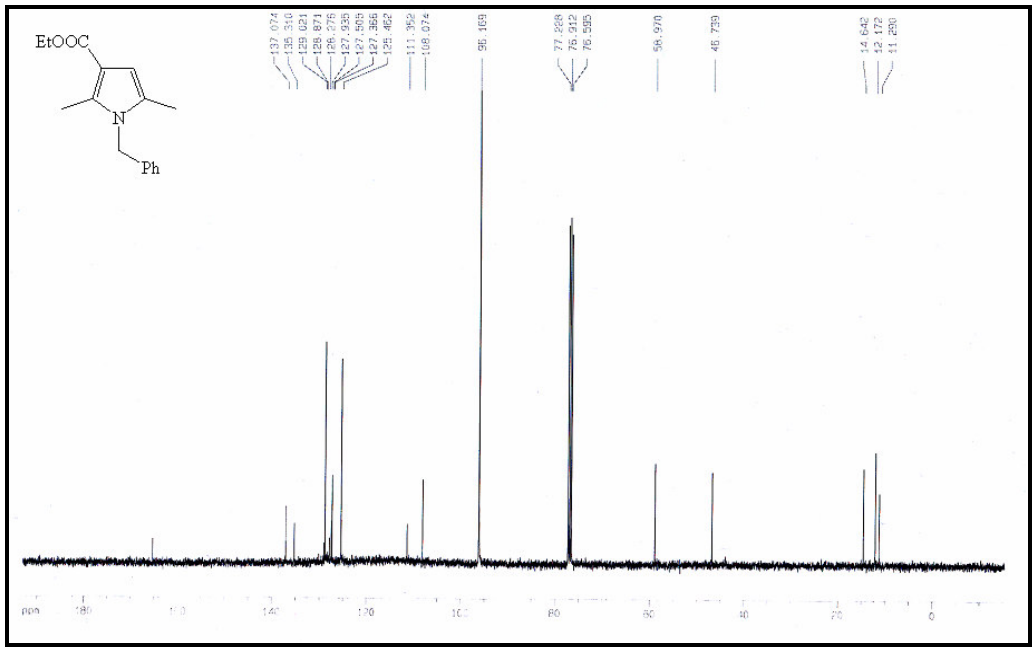

Figure 23 ^{13}C-NMR spectrum of ethyl 1-benzyl-2,5-dimethyl-1H-pyrrole-3-carboxylate (**26b**)

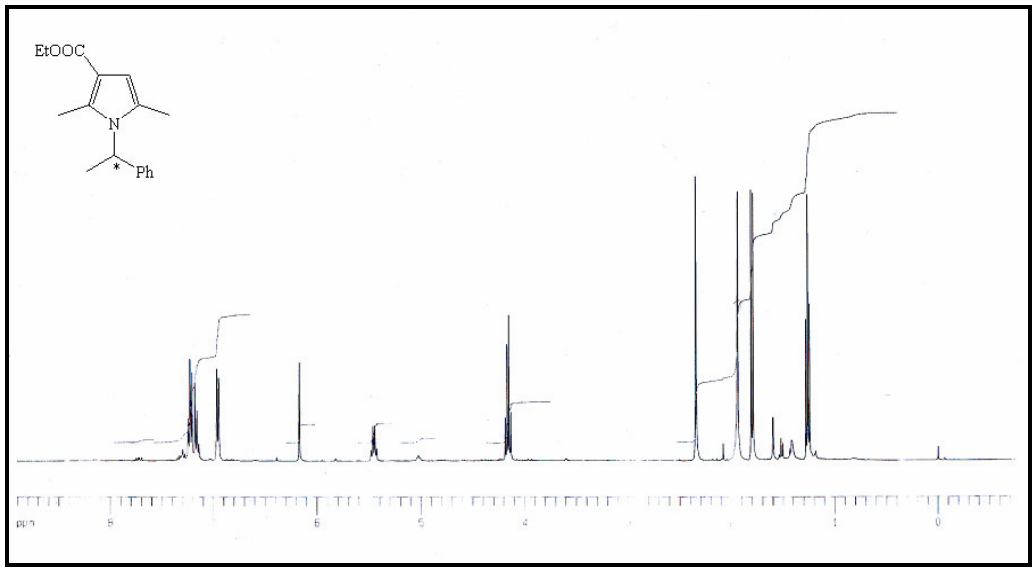

Figure 24 ^{1}H-NMR spectrum of (*R*)-ethyl 2,5-dimethyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate (**26c**)

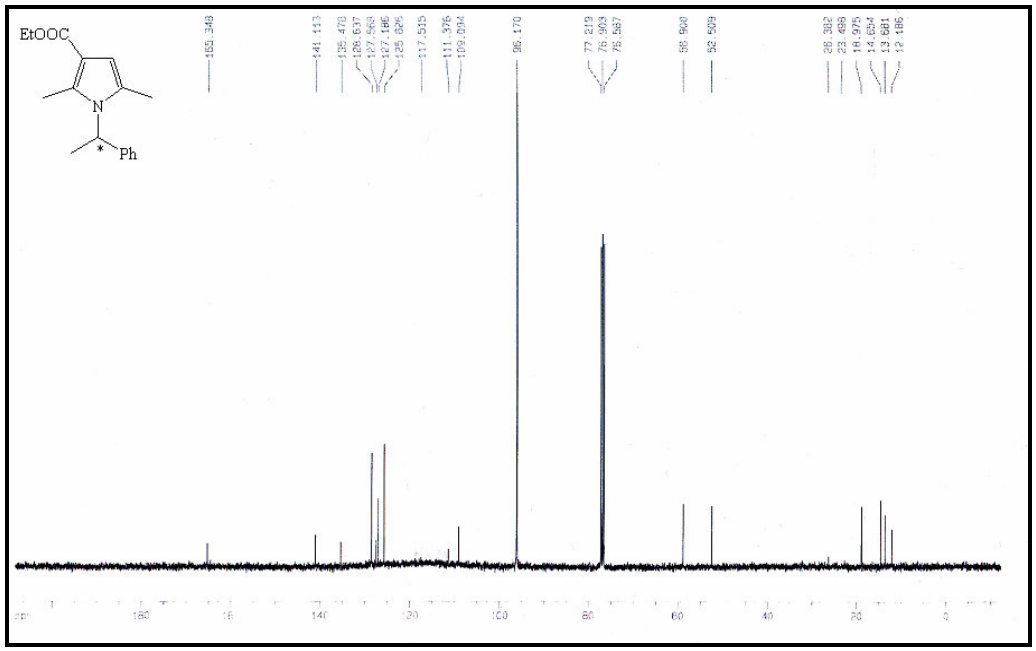

Figure 25 ^{13}C-NMR spectrum of (*R*)-ethyl 2,5-dimethyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate (**26c**)

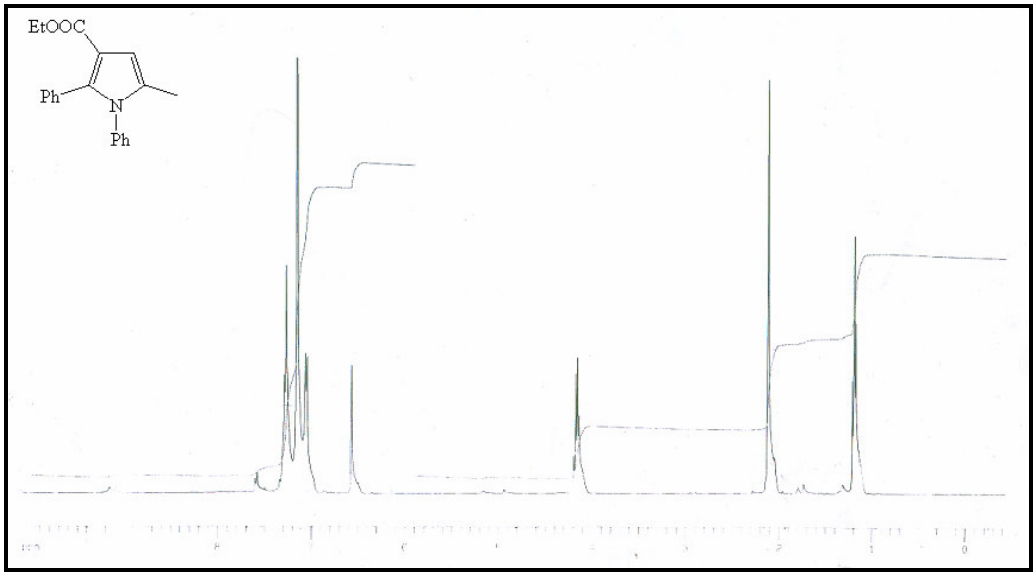

Figure 26 ^{1}H-NMR spectrum of ethyl 5-methyl-1,2-diphenyl-1H-pyrrole-3-carboxylate (**27a**)

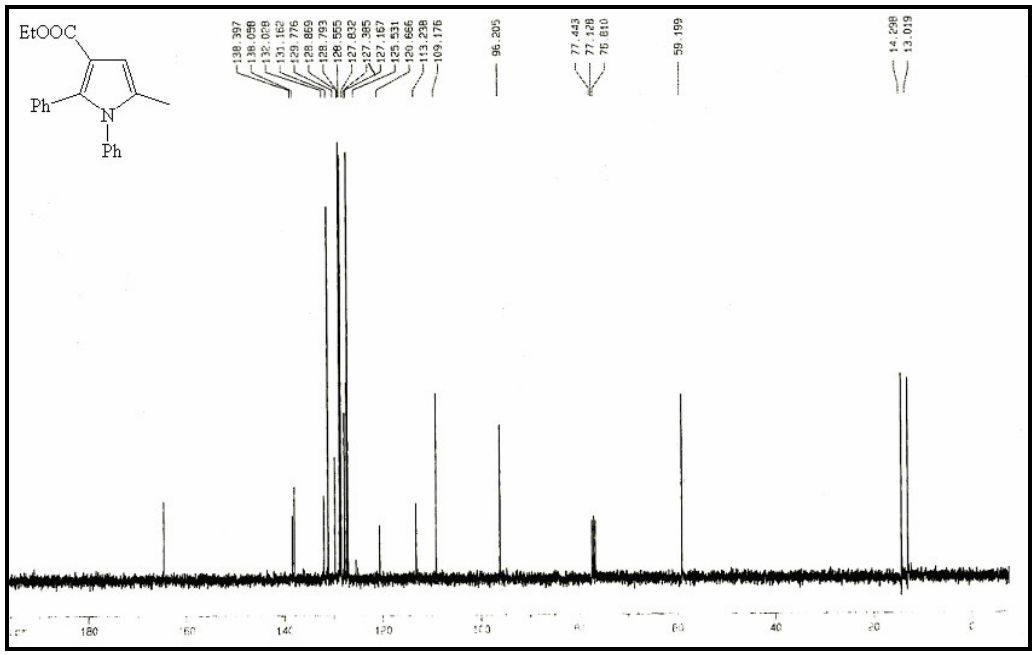

Figure 27 ^{13}C-NMR spectrum of ethyl 5-methyl-1,2-diphenyl-1H-pyrrole-3-carboxylate (**27a**)

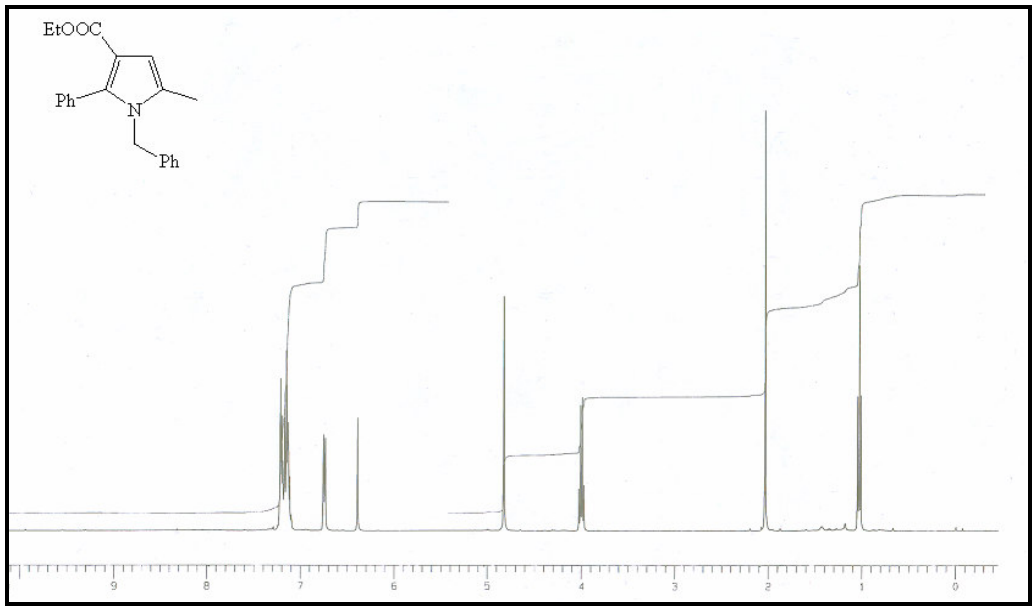

Figure 28 ^{1}H-NMR spectrum of ethyl 1-benzyl-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**27b**)

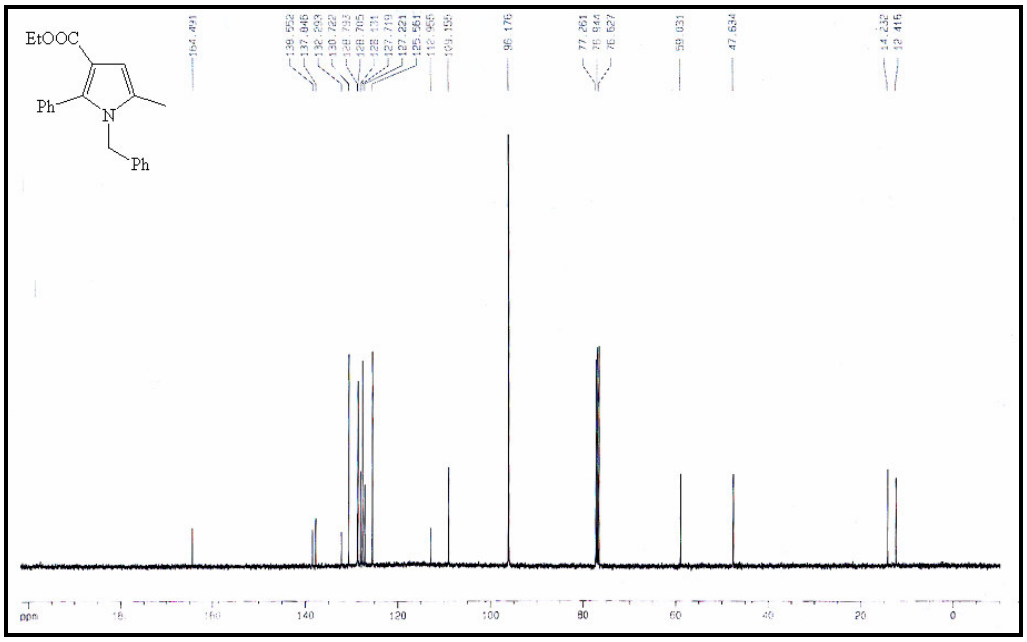

Figure 29 ^{13}C-NMR spectrum of ethyl 1-benzyl-5-methyl-2-phenyl-1H-pyrrole-3-carboxylate (**27b**)

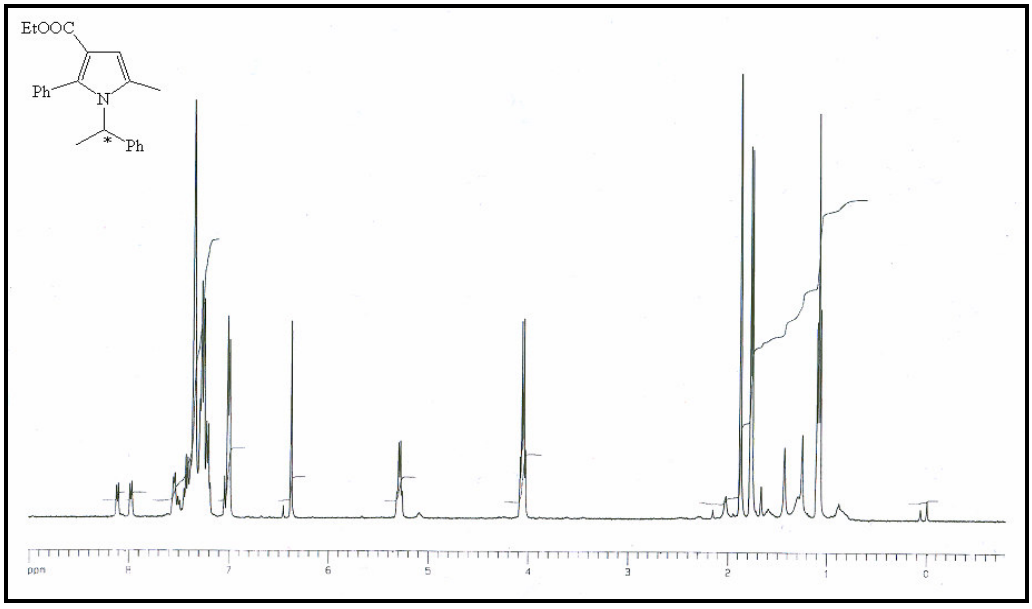

Figure 30 ^{1}H-NMR spectrum of (*R*)-ethyl-5-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate (**27c**)

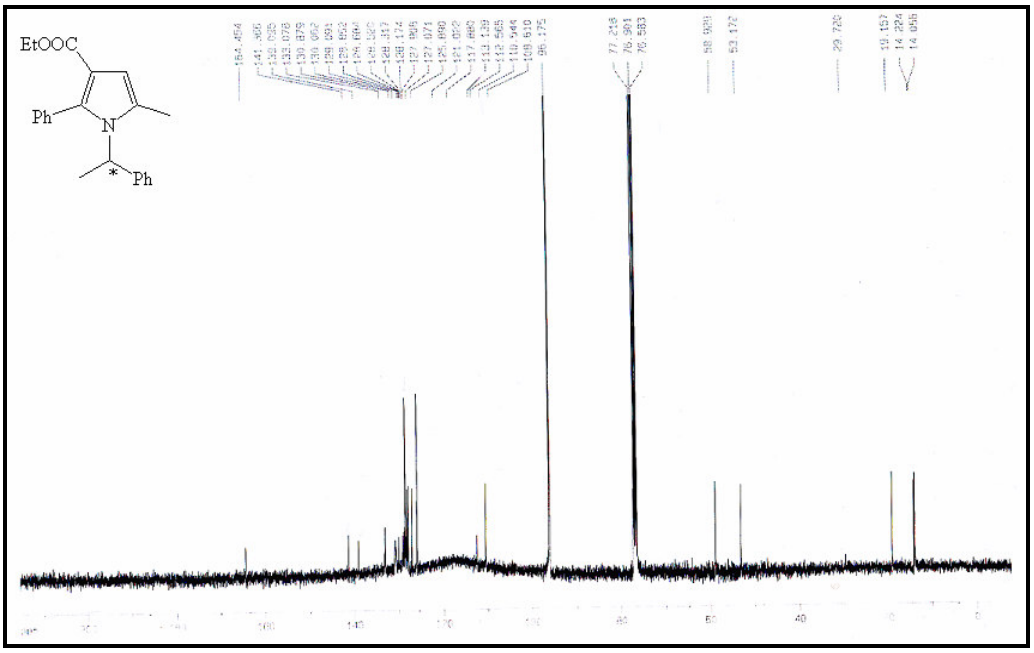

Figure 31 ^{13}C-NMR spectrum of (*R*)-ethyl 5-methyl-2-phenyl-1-(1-phenylethyl)-1H-pyrrole-3-carboxylate (**27c**)

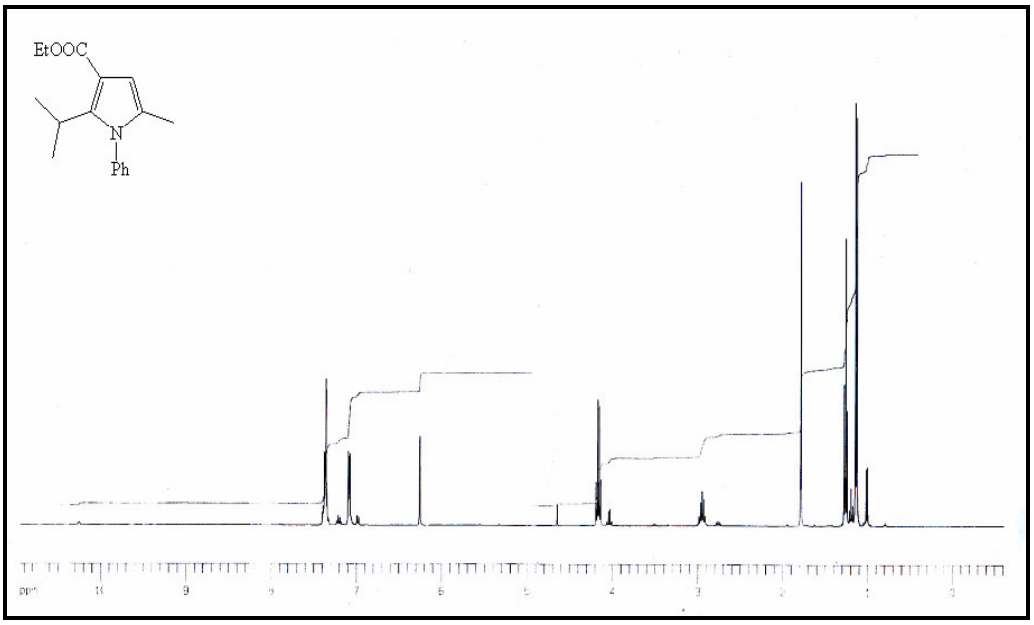

Figure 32 ^{1}H-NMR spectrum of ethyl 2-isopropyl-5-methyl-1-phenyl-1H-pyrrole-3-carboxylate **(28a)**

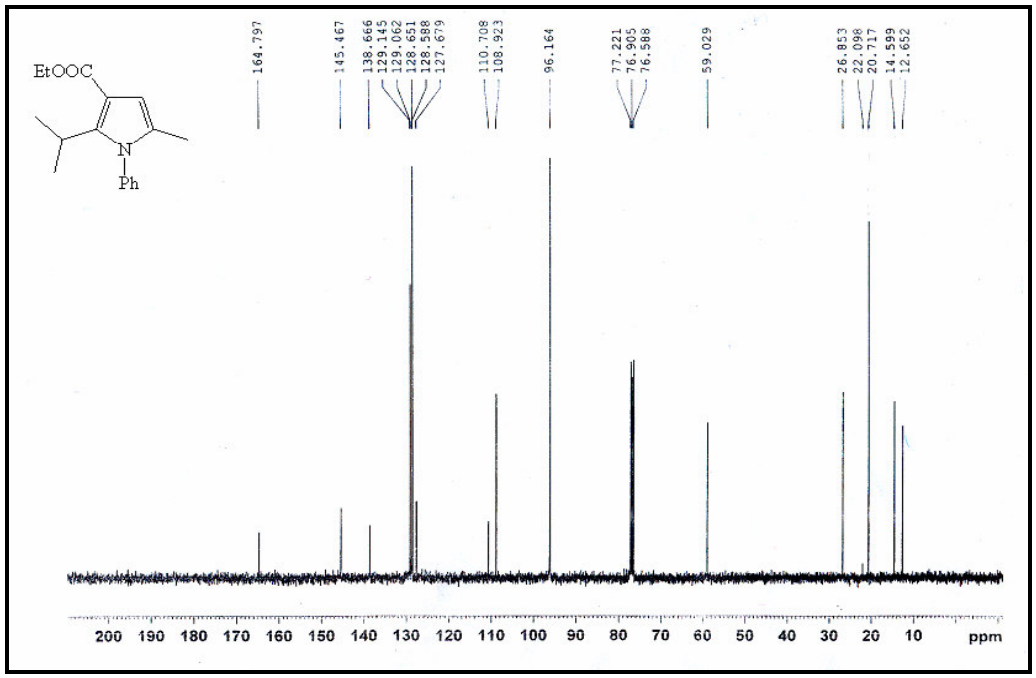

Figure 33 ^{13}C-NMR spectrum of ethyl 2-isopropyl-5-methyl-1-phenyl-1H-pyrrole-3-carboxylate (**28a**)

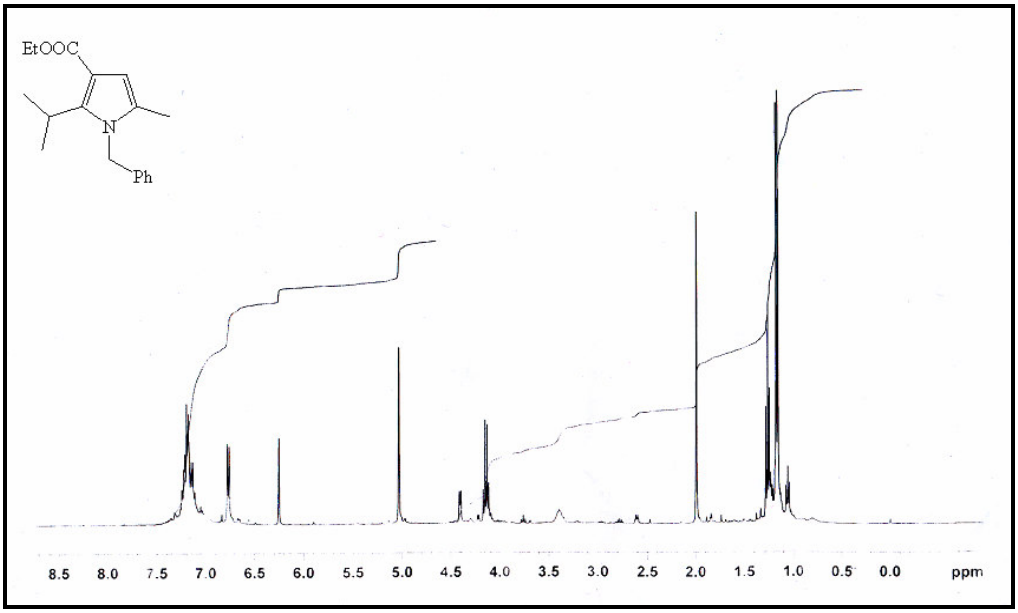

Figure 34 ^{1}H-NMR spectrum of ethyl 1-benzyl-2-isopropyl-5-methyl-1H-pyrrole-3-carboxylate (**28b**)

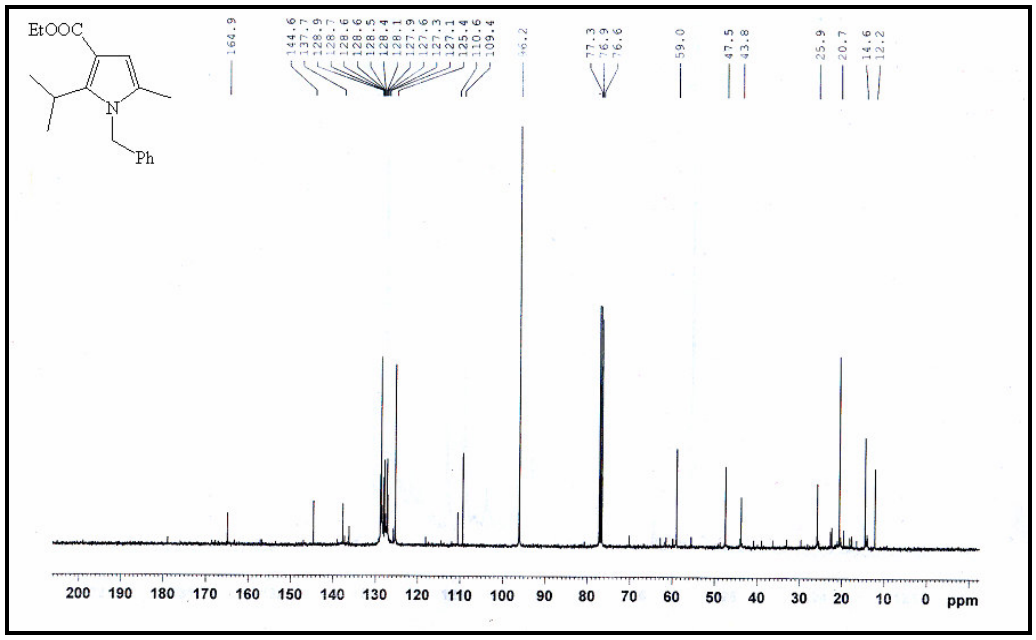

Figure 35 ^{13}C-NMR spectrum of ethyl 1-benzyl-2-isopropyl-5-methyl-1H-pyrrole-3-carboxylate (**28b**)

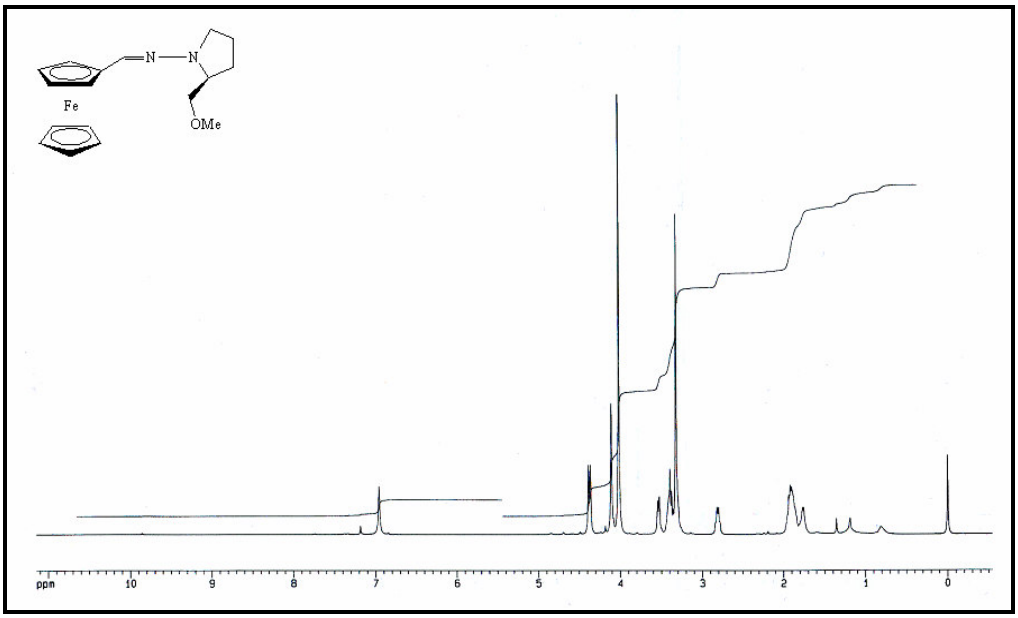

Figure 36 ^{1}H-NMR spectrum of of (+)-(*S*)-FcCH=NNCH$_2$CH$_2$CH$_2$-CHCH$_2$OCH$_3$, (**35**)

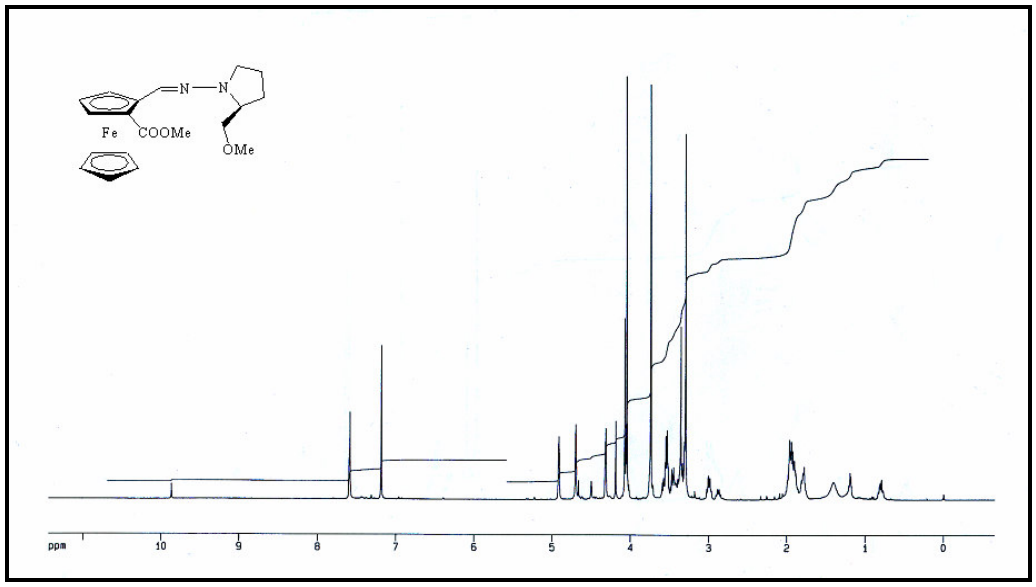

Figure 37 ^{1}H-NMR spectrum of (+)-(*S*)-Fc(COOMe)CH=NNCH$_2$CH$_2$CH$_2$-CHCH$_2$OCH$_3$, (**37**)

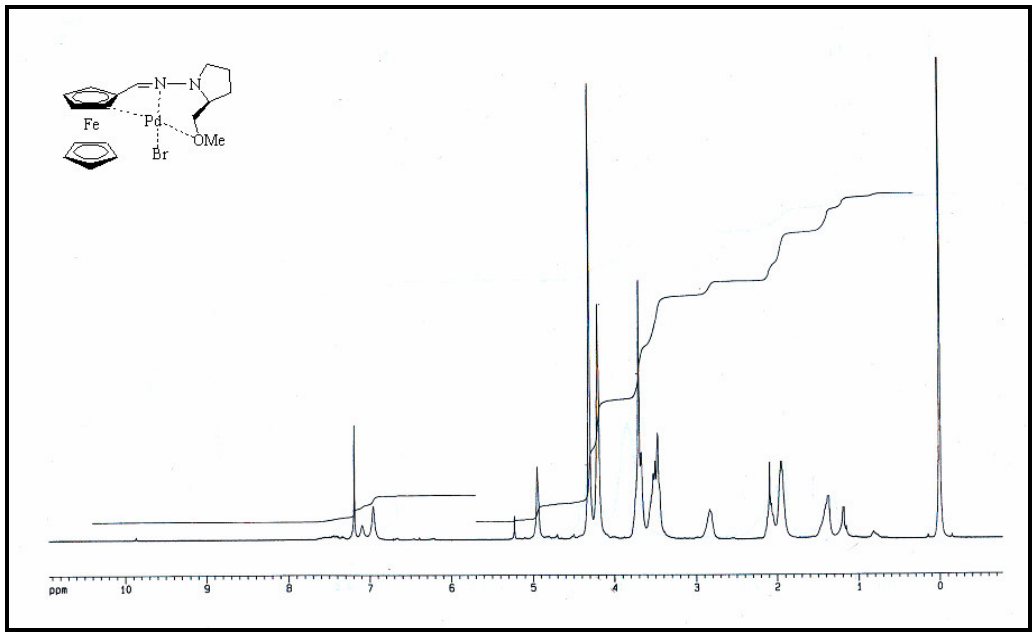

Figure 38 ^{1}H-NMR spectrum of Fc-SAMP-Pd-Br complex, (**41**)

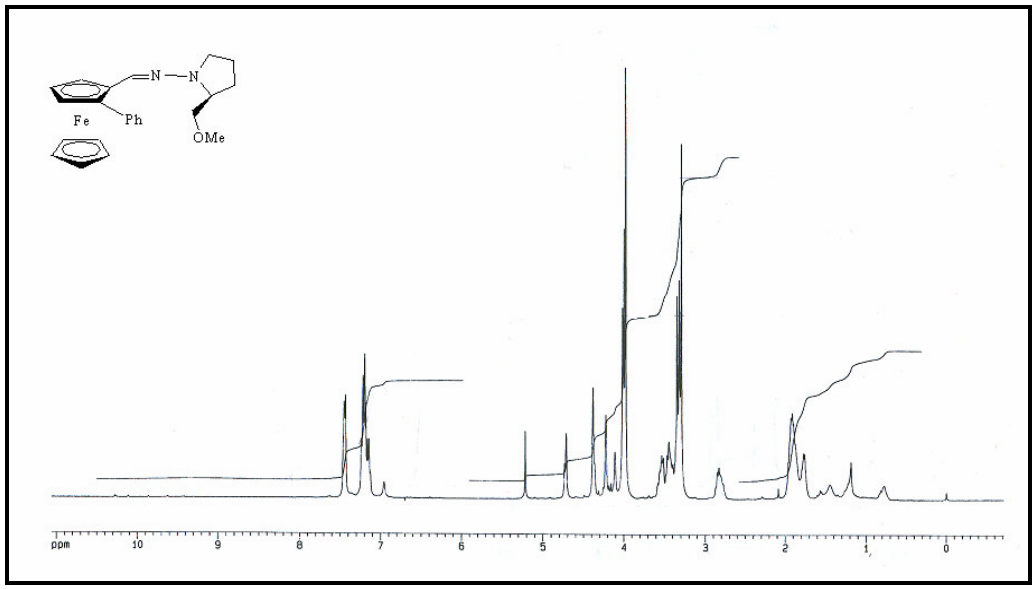

Figure 39 ^{1}H-NMR spectrum of (+)-(*S*)-Fc(Ph)CH=NNCH$_2$CH$_2$CH$_2$-CHCH$_2$OCH$_3$, (**42**)

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