SYNTHESIS OF FERROCENYL CYCLOHEPTADIENONES

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Approval of the Graduate School of Natural and Applied Sciences

_____

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I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

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This is to certify that we have read this thesis and in our opinion it is full adequate, in scope and quality, as a thesis for the degree of Master of Science.

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ABSTRACT

SYNTHESIS OF FERROCENYL CYCLOHEPTADIENONES

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Synthesis of seven-membered ring systems such as cycloheptadienones has attracted a great deal of attention in organic chemistry since they are present in a variety of biologically important molecules. Incorporation of the essential structures of such compounds with a ferrocene moiety instead of an aryl group could provide subtances with enhanced antitumor activities since some ferrocene derivatives have already proved to be active against a number of tumors. To develop a ferrocenyl-substituted seven-membered ring forming reaction, we have investigated the reaction of cyclopropylcarbene-molybdenum complex with ferrocenyl-substituted alkynes. As ferrocenyl-substituted alkyne, ferrocenyl-propyne (**25B**), (2-ferrocenylethynyl)trimethylsilane (**25C**), 1-ferrocenyl-3-phenylprop-1-yne (**25D**), 1-ferrocenyl-2-phenylethyne (**25E**), diferrocenylethyne (**25F**), ferrocenyl(formyl)acetylene (**25G**) were synthesized starting from ethynylferrocene (**25A**).

The reaction between cyclopropylcarbene-molybdenum complex and ferrocenyl alkynes produced ferrocenyl-substituted cycloheptadienones **26**, hydrolysis product of cycloheptadienones, **27**, α-hydroxycycloheptadienones **28** and cyclobutenones **29**, depending on the substitution pattern of the alkyne moiety. Interestingly, α-hydroxycycloheptadienone product **28B** was isolated from these types of reactions for the first time. Terminal alkynes, trimethyl- and formyl-substituted alkynes did not produce any expected product, possibly depending on the steric and electronic effects, and/or the polymerization of the alkyne. Proposed mechanism for the formation of cycloheptadienones involves metallacyclobutene formation, electrocyclic ring opening, electrocyclic ring closure, CO insertion, reductive elimination.

Keywords: Ferrocene, ferrocenyl cycloheptadienones, ferrocenyl alkynes metal-carbene complexes, cyclopropylcarbene-molybdenum complex, Dötz reaction.

ÖZ

FERROSENİL SİKLOHEPTADİENONLARIN SENTEZİ

Açıkgöz, Canet
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Doç. Dr. Metin Zora

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Yedi üyeli halkalı bileşikler, biyolojik açıdan önemli olan birçok maddede bulunduklari için, organik kimyada bu bileşiklerin sentezleri büyük öneme sahiptir. Boyle oluşan, Aril grubunun ferrosenil grubu ile değiştirilmesinden olusan bu önemli yapılar, gelişmiş antitümör aktiviteye sahip moleküllerin elde edilmesine imkan tanır. Çünkü ferrosen ve türevlerinin potansiyel antitümör özelliğe sahip olduğu daha önce yapılan çalışmalarla kanıtlanmıştır. Bu nedenle biz yedi üyeli halkalı bileşiklerin sentezi için siklopropilkarben-molibden kompleksinin ferrosen sübstitüe alkiller ile olan tepkimesini inceledik. Etinil ferrosenden **25A** başlayarak, ferrocenilpropin **25B**, 3-metil(2-ferrosenilletinil)silane **25C,** 1-ferrosenil-3-fenilnilprop-1-in **25D,** 1-ferrosenil-2-feniletin **25E,** diferroseniletin **25F,** ferrosenil(formil)asetilen **25G** sentezlendi. Ferrosen sübstitutüe alkinler ile karben kompleksinin **17** reaksiyonundan, ferrosen bağlı siklohepta dienon **26,** hidroliz ürünü **27,** α-hidroksisikloheptadienon **28** ve siklobutenon **29,** kullanılan ferrosen bağlı alkinin yapısına bağlı olarak elde edilmiştir. Bu reaksiyonlardan ilk defa α-hidroksisikloheptadienon **28B** bileşigi sentezlenmistir.

Ayrıca terminal alkinler, üçmetil- and formil bağlı alkinlerin, reaksiyonlari sonucunda beklenen ürünlerin oluşmadığı da tespit edilmiştir. Bunun nedeni büyük olasılıkla elektronik ve sterik etkenler ya da polimerleşme olayları olabilir. Metallosiklobüten oluşumu, elektrosiklik halka açılımı ve elektrosiklik halka kapanması (CO insersiyon, redüktif eliminasyon) önerilen mekanizmadır.

Anahtar kelimeler: Ferrosen, Ferrosen sikloheptadienonlar, Ferrocenil alkinler, metal-karben kompleksleri, siklopropilkarben-molibden kompleksi, Dötz tepkimesi.

To Bitros &Nurelhide Açıkgöz

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LIST OF ABBREVIATIONS

bp	boiling point
br	broad (spectral)
Bn	benzyl
Bu	butyl
^{o}C	degrees Celcius
Cp	cyclopentadienyl ligand
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
Et	ethyl
g	gram(s)
h	hour(s)
Hz	hertz
IR	infrared
i-Pr	isopropyl
J	coupling constant
m	multiplet (spectral)
Me	methyl
mL	milliliter(s)
mHz	megahertz
min	minutes
mmol	millimole(s)
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million (in NMR)
Pr	propyl
q	quartet

R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
THF	tetrahydrofuran
TMS	trimethylsilane
TLC	thin layer chromatography

CHAPTER 1

INTRODUCTION

One of the most attractive research areas in chemistry for recent years has involved studying the compounds which possess direct, more or less polar bonds between metal and carbon atom. The field of organometallic chemistry combines aspects of organic chemistry and inorganic chemistry and has led to many important applications in organic synthesis [1,2].

The development of transition–metal organometallic chemistry dates back to 1827 when Zeise [3] reported the first transition transition–metal organometallic compound, the ethylene-platinum complex $K[PtCl_3C_2H_4]$. Subsequent developments in this area of organometallic chemistry arose not in orderly steps from this original discovery but, instead, from several other initially unrelated discoveries. These include the discovery of nickel tetracarbonyl in 1890 by Mond, Langer, and Quincke [4], which led to the area of metal carbonyl chemistry, developed further largely by Hieber and his co-workers from about 1920 to present. Another initially unrelated discovery was that of the polyphenylchromium compounds by Hein in 1919 [5]. These compounds represented one of the great enigmas in inorganic chemistry for several decades until Fischer and Hafner [6] discovered dibenzenechromium in 1955. Subsequently, the bonding in dibenzenechromium was shown to be similar to that in the polyphenylchromium compounds of Hein. Meanwhile, another key event in transition-metal organometallic chemistry had occured: the discovery of the ferrocene.

Discoveries of ferrocene and Ziegler [7] catalyst brought a new era to organometallic chemistry since the chemical bonding of the compounds have allowed theoreticians to gain more profound understanding of the role of the d-orbitals in determining molecular structure and properties.

The sandwich structure of ferrocene revealed after its serendipitous discovery was fascinating and aroused the interest of both theoretical and synthetic chemists [8]. The scope of organometallic chemistry is extraordinarily broad so that it has become a mature area of science that will obviously continue to grow.

Transition–metal organometallic compounds have been found to have certain applications of practical or potentially practical interest. Some types have catalytic applications, such as certain organotitanium systems acting as components of Ziegler-Natta polymerization catalysts for the preparation of unusual olefins mediate in the palladium-catalyzed oxidation of olefins. Two metal carbonyls manufactured in tonnage quantities are iron pentacarbonyl, from which special iron powders are prepared by thermal decomposition, and methyl cyclopentadienylmanganese tricarbonyl for use as an additive to improve the combustion of certain liquid fuels. Further applications of metal carbonyls as vehicles for the transport and deposition of metals are exemplified by the role of nickel tetracarbonyl in the Mond process for nickel refining and by the use of the thermal decomposition of molybdenum hexacarbonyl as a means of depositing metallic molybdenum [9].

The use of organometallic compounds is widespread in industry despite their sensitivity to solvolysis and oxidation, their flammable and poisonous character, and the expense of the necessary starting materials, such organometallic compounds as those of aluminum, lithium, magnesium, mercury, and cobalt are now made on a large scale. Now not only are such compounds used stoichiometrically in industrial chemistry but, more interestingly, they can be used as catalyst or promoters in many organic oligomerization and polymerization processes [10].

The reactivity of the carbon-metal bond forms a convenient site in an organic molecule for many facile and important reactions [11]. The chemical versatility of Grignard reagents, organolithium compounds, and metal hydrides of group III has become so extensive in organic chemistry. The fundamental organometallic chemistry now presents one of the most fruitful contributors of novel synthetic methods and mechanistic studies to the discipline of organic chemistry. It would appear that these unnatural products have taken the role of natural products because of the diversity of organometallic structure. The electron-deficient, bridging structure of metal alkyls, the sandwich configuration of ferrocene types, the metal adducts of conjugated organic compounds have necessitated in this manner [10].

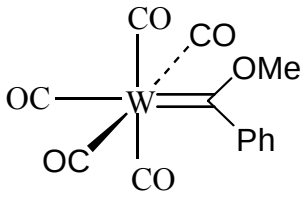
There are many reasons for using transition metals in complex synthesis. Generally, every organic functional group will coordinate to some transition metal, and on coordination, the reactivity of that functional group is often dramatically changed. Electrophilic species can become nucleophilic and vice versa, stable compounds can become reactive and highly reactive compounds can become stabilized. Normal reactivity patterns of functional groups can be inverted and unconventional (impossible, under “normal” conditions) transformations can be achieved with facility.

Highly reactive, normally unavailable reaction intermediates can be generated, stabilized, and used as efficient reagents in organic synthesis. Most organometallic reactions are highly specific, able to discriminate between structurally similar sites, thus reducing the need for bothersome "protection-deprotection" sequences that plague conventional organic synthesis. Finally, by careful selection of substrate and metal, multistep cascade sequences can be generated to from several bonds in a single process in which the metal "stitches together" the substrate [12].

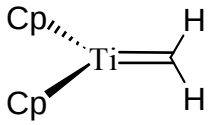
Carbene-complexes having formal metal-to-carbon double bonds are known for metals across the entire transitions series and they are useful in the field of synthetic organic chemistry [12]. The first stable transition metal carbene complex was reported by Fischer in 1964 [13], however prior to that time, complexes of carbenes with transition metals had been proposed as intermediates in metal-catalyzed reactions of diazo compounds and in other carbene transfer reactions [14]. Since the first report by Fischer, studies of the synthesis and reactivity of metal-carbene complexes has been a very active area of research.

The more useful transformations accomplished by carbene complexes include the conversion of alkenes to cyclopropanes [15], the conversion of carbonyl compounds to alkenes [16], and novel construction of highly substituted aromatic rings from alkynes [17-19]. Metal carbenes are also key intermediates in the industrially important olefin metathesis reactions [20]. Moreover, metal carbenes have been involved in various biological processes such as cyctochrome reduction/oxidation [21].

The metal carbene complexes are generally divided into two classes. 'Fischer-type' carbene complexes and 'Schrock-type' carbene complexes (Figure 1) [22]. Fischer carbene complexes exhibit the following features: (1) the carbene carbon is electrophilic which is stabilized by π–acceptor ligands (e.g., carbon monoxide); (2) the metal is in a relatively low oxidation state; and (3) the metal is typically toward the right side of the transition block. On the other hand, Schrock carbenes exhibit the following features: (1) the carbene carbon is nucleophilic which is stabilized by π–donor ligands; (2) the metal is in a relatively high oxidation state; and (3) the metal is typically toward the left side of the transition block [23].



A Fischer carbene complex



A Schrock carbene complex

Figure 1. Schematic representation of metal carbene complexes

Among the vast number of carbene complexes, Fischer type compounds of group 6 metals (Cr, Mo, W) are of a major synthetic importance [24]. These are easily synthesized by the reaction of the crystalline metal hexacarbonyl with a range of organolithium reagents (Figure 2). One of the six equivalents CO groups undergoes attack to produce the stable, anionic lithium acylate complex, in which the negative charge is stabilized and delocalized into the remaining five, π-accepting, electron withdrawing CO groups. These acylate complexes are normally isolated as the stable tetramethyl ammonium salt, which can be prepared on a large scale and stored for months without decomposition.

Treatment with hard alkylating agents such as methyl triflate or trimethlyoxonium salts (Meerwein's reagent) results in alkylation at oxygen, producing alkoxycarbene complex in excellent yield [25]. These yellow to red crystalline solids are easily purified by crystallization or chromatography on silica gel. As solids, they are quite air-stable and easy handle. In solution, they are slightly air-sensitive, particularly in the presence of light, and reactions are best carried out under inert atmosphere. The heteroatom is required for stability, and this stability results from extensive delocalization of the lone pair on the heteroatom into the strongly electron withdrawing metal carbonyl fragment. For delocalization, the orbital of the lone pair must be collinear with the p orbital of the carbene carbon because the chromium pentacarbonyl fragment presents the carbene carbon with a "wall" of CO's, α-branching of the substituents on the carbene carbon results in steric congestion which may prevent efficient overlap and compromise the stability of the carbene complex [12].

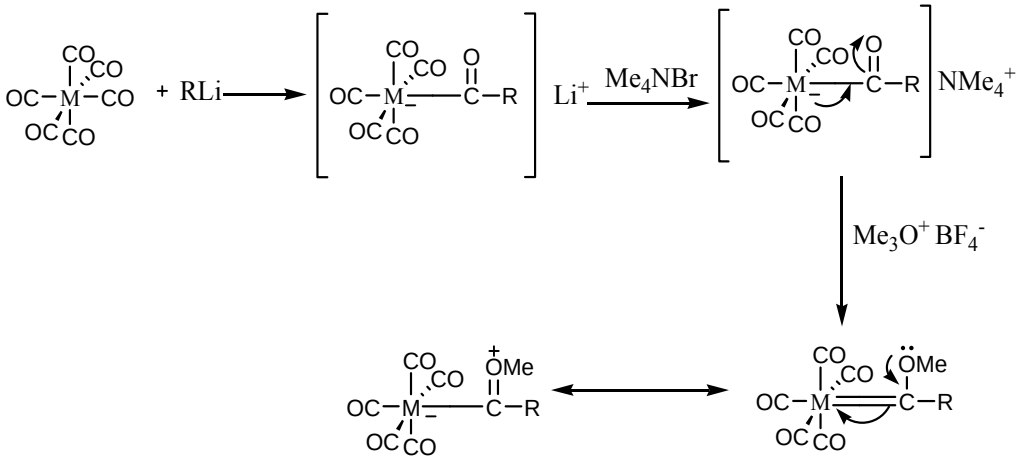


Figure 2. The attack of organolithium reagents at the carbenes and delocalization in carbene

Electrophilic carbene complexes have a very rich chemistry, and undergo reaction at several sites. The general reactivity profile for Fischer carbene complexes is depicted in Figure 3 [24].

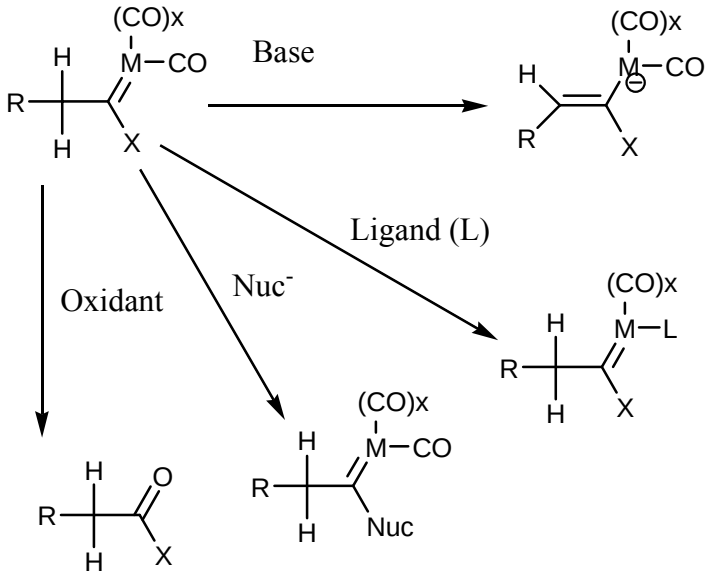


Figure 3. The general reactivity profile for Fischer carbene complexes

Fischer carbene complexes are coordinatively saturated, metal(0) d^6 complexes which undergo ligand exchange (CO loss) by a dissociative process (Figure 4). Since loss of CO is a prerequisite for substrate coordination and subsequent reaction, this exchange process is central to most synthetically useful reactions.

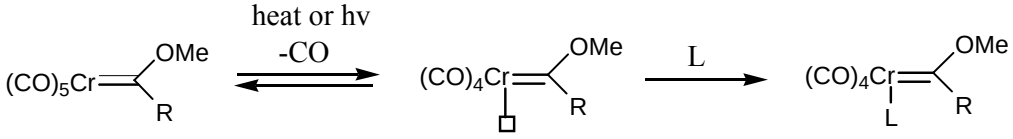
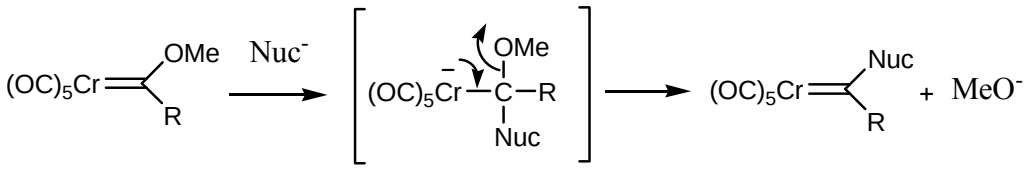


Figure 4. The dissociative process for Fischer carbene complexes

Because CO groups are strongly electron withdrawing, the metal carbene carbon bond is polarized such that the carbene carbon is electrophilic, and generally subject to attack by a wide range of nucleophiles (Figure 5) [26]. In most cases the resulting tetrahedral intermediate is unstable, and the alkoxy group is removed, producing a new carbene complex. This is one of the best ways to prepare a Fischer carbene complex containing heteroatoms other than oxygen, and the process is quite analogous to “transesterification” of organic esters. In fact, in many of their reactions, the analogy between alkoxycarbene complexes and organic esters is remarkable. It is the one of the major uses of the Fischer carbene complex functionality is as an ester surrogate, which is usually accompanied by a substantial enhancement of the electrophilic reactivity; the term `super ester' has often been used to describe this behavior. The diverse array of demetallation reactions for the carbene complex functionality further enhances the synthetic utility of this functional group [27].



Nuc= RO^-, NH_3

Figure 5. The synthesis of metal-carbene complexes according to Fischer’s original procedure

The reactivity of alkylidene (carbene) complexes has been extensively investigated and a number of general and useful transformations have been reported [28]. Transition metal carbene complexes are capable of reacting with alkenes in a number of different ways. Two major reaction pathways that have been reported are alkene cyclopropanation and olefin metathesis. Many transition metal carbene complexes readily react with alkenes, often via [2+2] cyclization to generate a metallacyclobutane intermediate (Figure 6). Such an intermediate can undergo a variety of subsequent transformations, one of which is reductive elimination to form a cyclopropane [29].

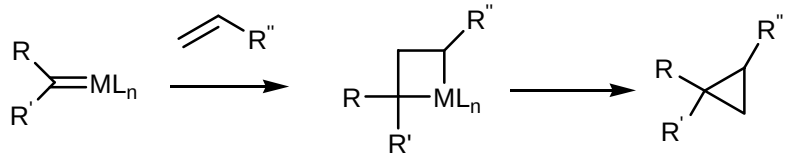


Figure 6. The reaction of metal carbene complexes with alkenes

Fischer and Dötz described the first reactions of chromium and tungsten arylalkoxycarbene complexes with electron-rich and electron-deficient alkenes to produce substituted cyclopropanes [30]. The scope and limitations of these original observations have since been further explored and it has been found that a broad variety of substituted cyclopropanes are accessible by this approach [31]. Monosubstituted alkenes bearing ester, amide, nitrile, phosphonic ester and sulfone functionality all react smoothly to give substituted cyclopropanes in good yields (Figure 7).

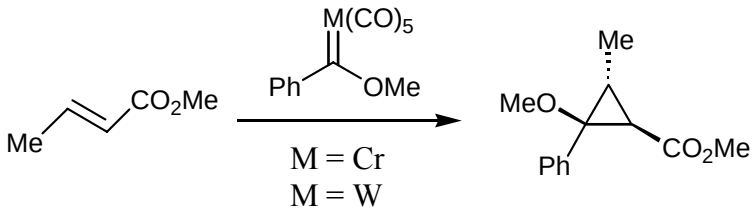


Figure 7. The synthesis of substituted cyclopropanes with metal arylalkoxycarbene complexes

It has been amply demonstrated that a variety of transition metal complexes are capable of catalyzing olefin metathesis reactions and olefin metathesis has found many industrial uses. The general mechanism for this reaction involves [2+2] cyclization of the alkene with the metal-carbon double bond to form a metallacyclobutane intermediate. Subsequent retro [2+2] cyclization leads to a new alkene and a new carbene complex (Figure 8).

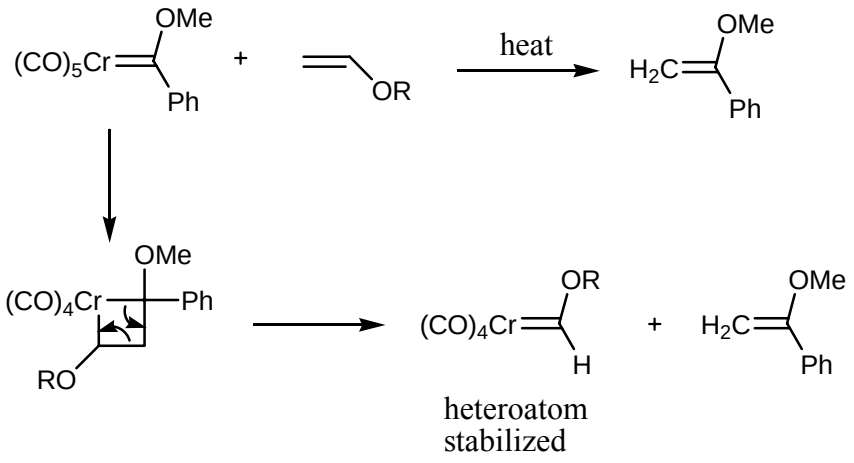
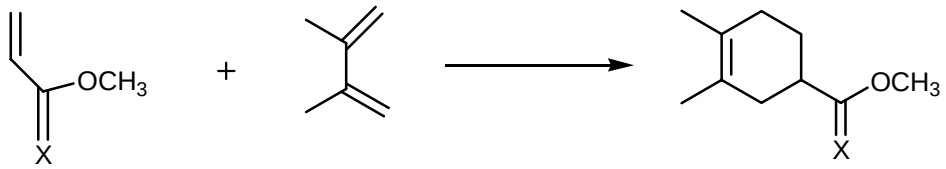


Figure 8. Olefin metathesis reaction

The other major synthetic uses of carbene complexes is the Dies-alder reaction between α,β-unsaturated carbene complexes and dienes [32] (Figure 9). These complexes are extremely reactive intermediates; their reactivity resembles that of α,β-unsaturated esters in the presence of Lewis acids, and offer superior regio and stereoselectivity in reactions with unsymmetrical dienes. This reaction can also be conducted asymmetrically if a chiral auxiliary is present on the heteroatom substituent [33]. Successful oxidation of the carbene complex adducts to the corresponding esters or amides has been demonstrated in most examples. Other reactions similar of α,β-unsaturated esters have also been reported, including 1,3-dipolar cycloadditions with diazo compounds [34,35], nitrones [36] and nitrile ylides [37] and Micheal addition reactions [38], [2+2]-cycloadditions [39], and cyclopropanation [40].



X, conditions

$Cr(CO)_5$, 25 °C, 5h, 74%

$W(CO)_5$, 25 °C, 1.5h, 80%

Figure 9. Diels-Alder reaction between α,β-unsaturated carbene complexes and dienes

Another thermal reaction of carbene complexes of great use in synthesis is the reaction of carbene complexes with alkynes. It is the Dötz benzannulation reaction [41], which involves the coupling of an α,β-unsaturated carbene complex with an alkyne (Figure 10). It has been reported that phenols [42,43], cyclopentenones [23], indenes [44], furans [45], cyclobutenones [46], vinylketenes [47] have resulted from these reactions under appropriate conditions.

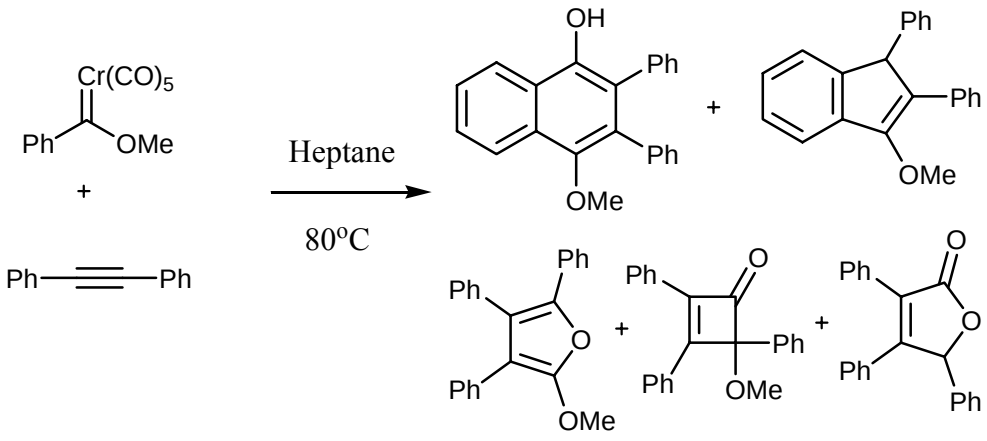


Figure 10. The reaction of carbene complexes with alkynes *via* Dötz reaction

The Dötz reaction has been employed as a key step in the total synthesis of a variety of natural products, including vitamins E (Figure 11) [48], and K_1 [49], nanaomycin, deoxyfrenolicin [50], angelicin, sphondin, thiosphondin [51], daunomycinone, 11-deoxydaunomycinone [52], khellin [53] (Figure 12). Moreover, the Dötz reaction has been extensively utilized to make quinone derivatives.

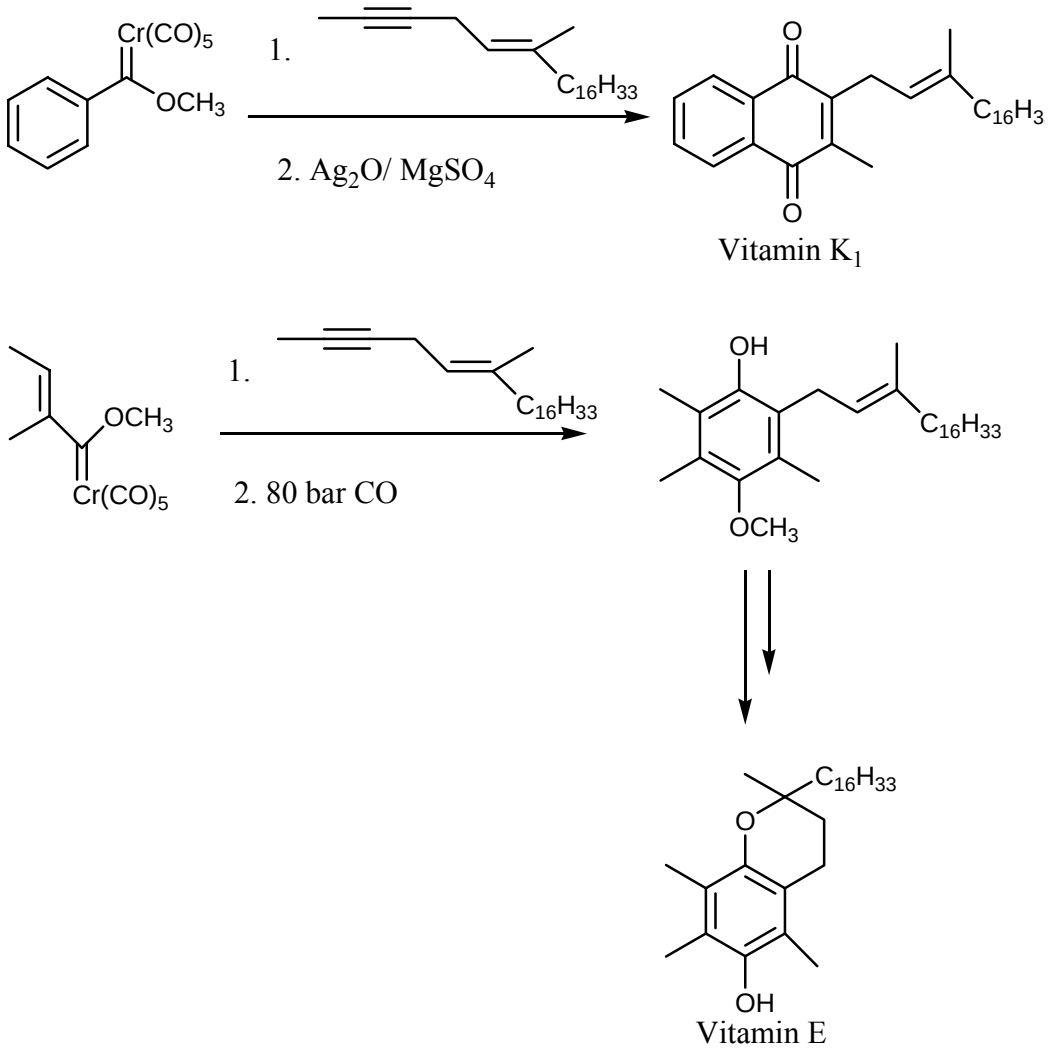
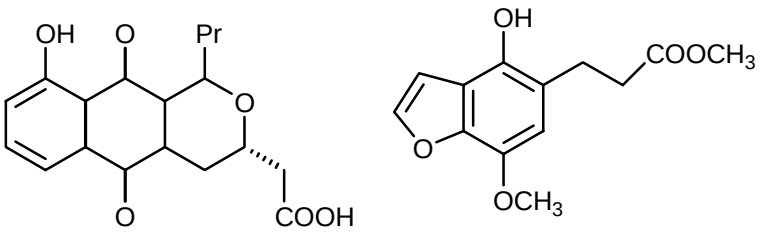
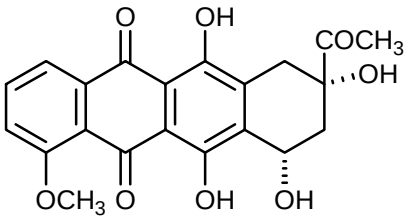


Figure 11. Synthesis of Vitamin K and Vitamin E by Dötz reaction

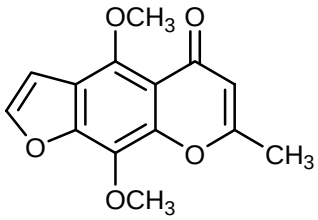


Deoxyfrenolicin

Angelicin



Daunomycinone



Khellin

Figure 12. Some examples of natural products synthesized by Dötz reaction

Dötz reaction is a well established for the preparation of phenol derivatives [41]. The reaction begins with a thermal loss of one CO to generate a vacant coordination site in carbene complex **1** (Figure 13). Coordination of the alkyne followed by cycloaddition generates the metallacyclobutene **4** [54], which inserts CO to give a metallacyclopentenone **5**. Fragmentation of this metallacycle generates a metal bound vinyl ketene **6**. Cyclization of this vinyl ketene followed by enolization produces the hydroquinone derivatives **8** (Figure 13). Phenol and five-membered ring formation are related, and differ only in the incorporation of carbon monoxide in a late step of the reaction process, where intermediate vinylcarbene complex **5** can either undergo CO insertion to form vinylketene **6** and eventually the phenol **8**, or undergo direct cyclization to **9** and eventually form the indene **10** (Figure 14) [27].

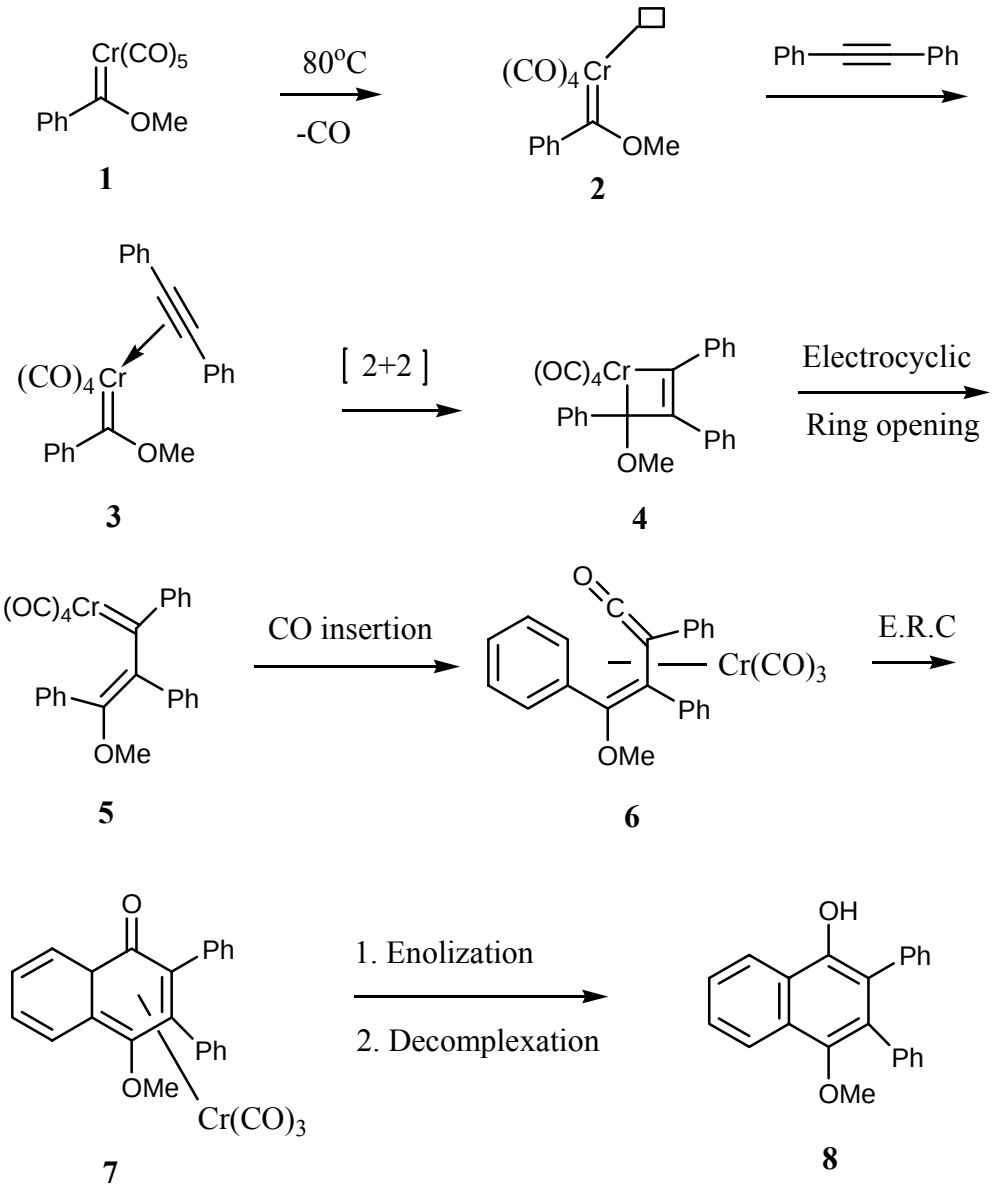


Figure 13. The mechanism of the Dötz reaction

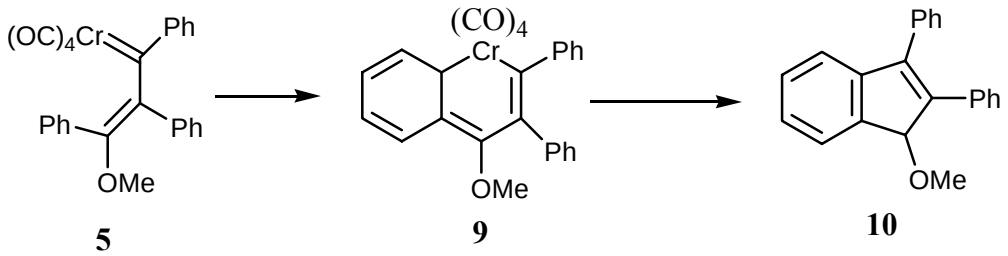
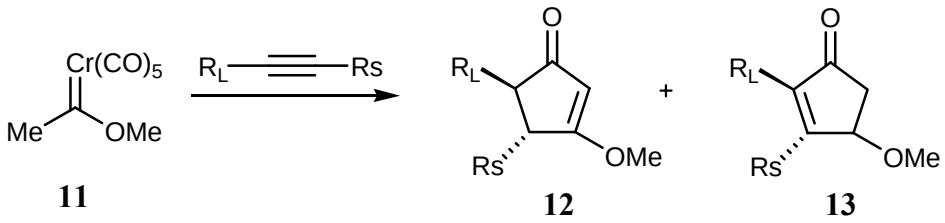


Figure 14. The formation of indene product

The reactivity of phenylmethoxy Fischer carbene complexes of group VI metals with alkynes has been extensively investigated. When the metal is chromium, hydroquinone formation is generally favored over indene formation. When molybdenum or tungsten is employed in place of chromium, indene formation is generally favored. The order of selectivity for the CO-insertion product is Cr > W > Mo, which correlates with the metal-CO bond strengths of the metal hexacarbonyls for chromium ($\Delta H_{\text{Cr-CO}}$ = 36.8 kcal/mol) and tungsten ($\Delta H_{\text{W-CO}}$ = 46.0 kcal/mol), but not for molybdenum ($\Delta H_{\text{Mo-CO}}$ = 40.5 kcal/mol) [55]. This difference is attributed to the tendency of molybdenum to undergo ligand substitution at a faster rate than either chromium or tungsten [56].

Relatively minor modifications to the structure of the carbene complex, the alkyne, or the reaction conditions can dramatically alter the observed reaction pathway. Since Dötz's initial observations, several groups have investigated reactions of group VI carbene complexes with alkynes. In their extensive studies of the reactions of alkylalkoxy chromium carbene complexes, Wulff and colleagues observed that when methylmethoxy chromium carbene complex **11** is treated with simple alkynes in hexane, cyclopentenones **12** and **13** are produced (Figure 15) [57,58].



11 **12** **13**

Figure 15. The reaction of methylmethoxy chromium carbene complex with simple alkynes

Herndon and co-workers have reported that cyclopentenone products are obtained upon reaction of cyclopropyl-substituted chromium complexes with alkynes (Figure 16) [59,60]. The coupling of alkynes with cyclopropylcarbene-chromium complexes affords cyclopentenone derivatives (**14 → 16)**; both intermolecular and intramolecular versions of this reaction have been demonstrated [61]. The reaction produces a cyclopentadienone intermediate **15** through a complex mechanistic process, which is reduced by the chromium byproduct of the cycloaddition process (Figure 16). This process has been used as cornerstone for the preparation of vitamin D synthetic intermediates. The cyclopentanone and cyclopentenone structural units are present in a wide range of important natural products such as jasmonoids, cyclopentanoid antibiotics and prostaglandins [62].

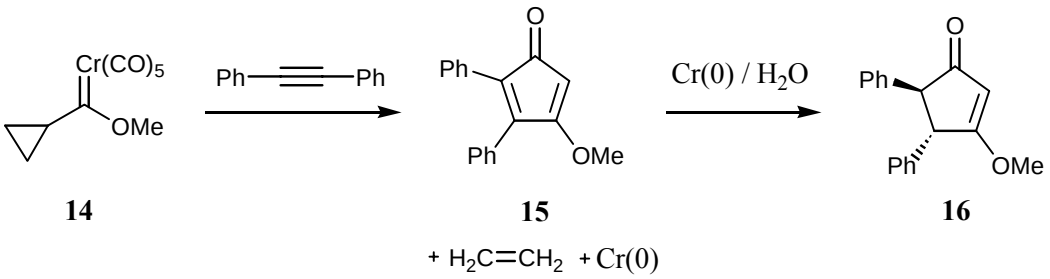


Figure 16. The reaction of cyclopropyl-substituted chromium complexes with alkynes

The coupling of alkynes with the molybdenum and tungsten anologs of complex **14** afford cycloheptadienone derivatives **18** (Figure 17) [63].

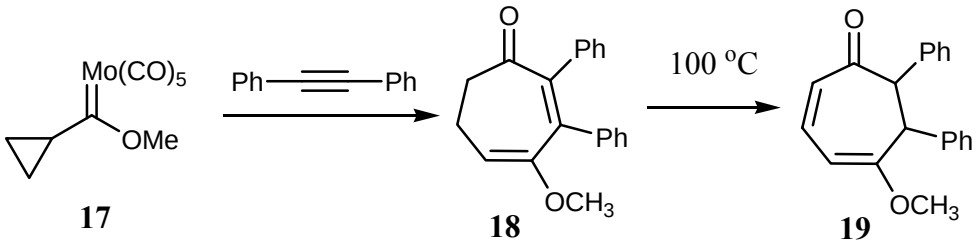


Figure 17. The reaction of cyclopropyl-substituted molybdenum complexes with alkynes

The cycloheptane ring system is an important structural feature in a variety of biologically-important molecules, including cholchicine, tigliane and daphnane (Figure 18) [64]. They are typically constructed by ring expansion reactions, cyclization reactions, reactions of other seven-membered rings, and occasionally cycloaddition reactions [65].

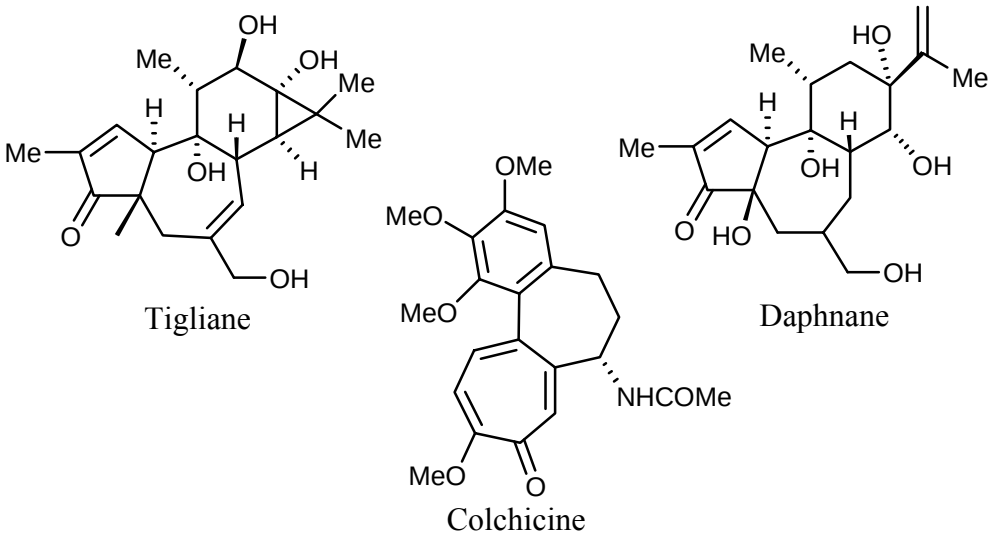


Figure 18. Some biologically-important molecules including seven-membered ring system

Tigliane and the daphnane are the phorbol esters and the phorbol esters have been vigorously studied over the past half-century since the discovery that these noncarcinogenic compounds amplify the effect of certain carcinogens in animals [66]. The phorbol esters have emerged as important leads in the formulation of a molecular mechanism for carcinogenesis as well as in the development of hemotherapeutic agents for cancer and other diseases, most notably including AIDS. The cholcine is used to relieve intense pain and as antitumor agent [67].

Metallocenes are organometallic compounds which consist of a metal atom between two polyhapto rings [68]. They are called “sandwich compounds”. Frequently encountered ligand in metallocenes is the cyclopentadienide anion which forms complexes known as the metal cyclopentadienyls with these metals. In most of these compounds, all five carbon atoms of the cyclopentadienyl ring are bonded to the metal atom. Compounds of this type are known as the π-cyclopentadienyls and they are utilized in various areas of chemistry and technology [69]. A very stable and familiar compound of this type is biscyclopentadienyliron, $(C_5H_5)_2Fe$, which has the more convenient trivial name ferrocene.

Ferrocene, an orange, crystalline, diamagnetic solid was the first π-cyclopentadienyl derivative to be prepared. It was discovered by Kealy and Pauson [70] as an expected product of the reaction between cyclopentadienyl-magnesium bromide and ferric chloride in diethyl ether solution in an unsuccessful attempt to prepare the still unknown dihydrofulvalene, C_5H_5- C_5H_5, by a coupling reaction. At about the same time, ferrocene was independently prepared by Miller, Tebboth, and Tremaine [71] in low yield by passing cyclopentadiene vapor over a special iron-molybdenum catalyst at elevated temperatures.

The original discoverers of ferrocene did not recognize its unusual structure. However, shortly after its initial discovery was reported, Wilkinson, Rosenblum, Whiting, and Woodward [72] postulated the pentagonal antiprismatic structure for ferrocene.

Since the original discovery of the ferrocene, a wide variety of methods for its preparation have been developed. Some of the more interesting and useful methods for the preparation of ferrocene are summarized in the following equations:

$$NaC_5H_5 + FeCl_2 \xrightarrow{THF} (C_5H_5)_2Fe + 2NaCl$$

$$2C_6H_5 + FeO \xrightarrow{Heat} (C_5H_5)_2Fe + H_2O$$

Ferrocenes have wide application in many fields: they are used in supramolecular chemistry, as magnetic materials and liquid crystals, in asymmetric catalysis [73], and as oil additives [74]. Ferrocenyl compounds function as enzyme inhibitors and can act as cancer therapeutic agents [75,76]. The ferrocene molecule is a lipophilic one and can easily cross cellular membranes.

The stability of the ferrocene is sufficiently high that a variety of reactions can be performed on the ferrocene system without breaking either metal-carbon bond. This enables numerous substitued ferrocenes to be prepared. The C_5H_5 rings in ferrocene possess an aromacity similar to that benzene. Ferrocene undergoes electrophilic substitution reactions similar to those of benzene except for the following differences: (a) ferrocene is more reactive than benzene toward electrophilic substitution, and (b) the instability of ferrocene to strong oxidizing agents makes the electrophilic nitration, sulfonation, and halogenation of ferrocene impossible, since the strongly oxidizing concentrated nitric acid, concentrated sulfuric acid and free halogens destroys the ferrocene system [9]. Since ferrocene has a rich aromatic chemistry, undergoing Friedel-Crafts acylation and alkylation, Vilsmeier formylation and mercuration [77]. Some of the basic reactions of ferrocene (**20**) are shown in Figure 19.

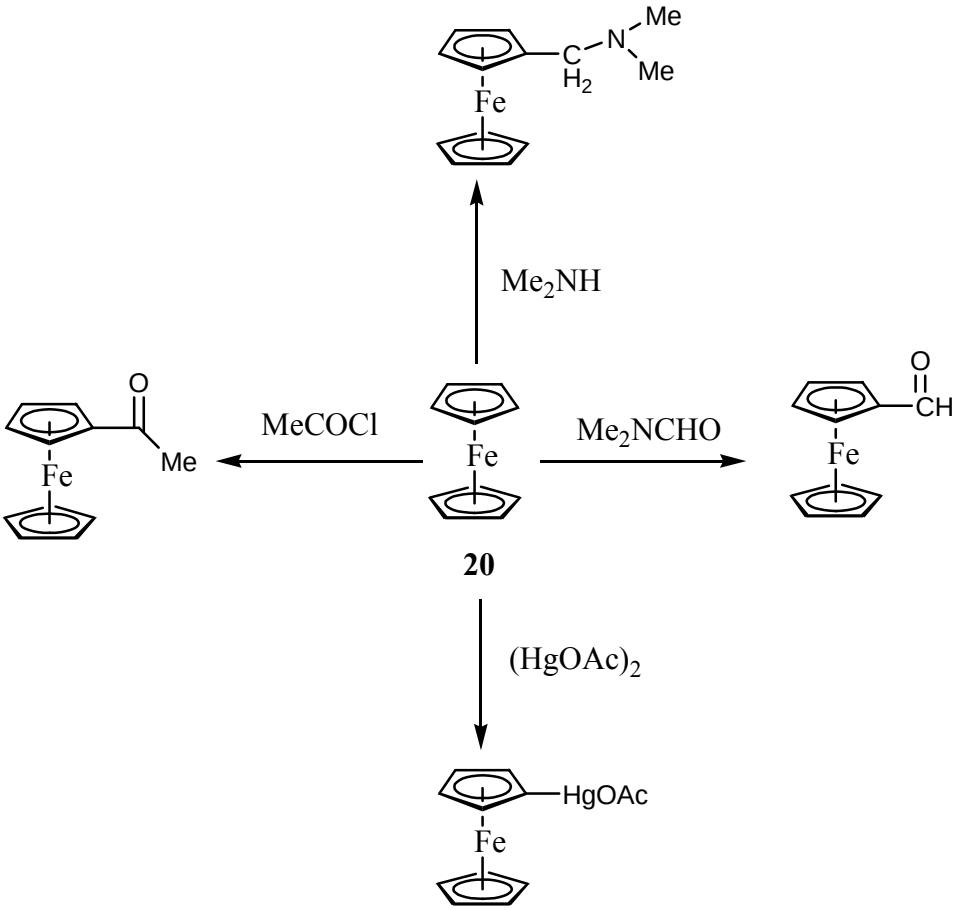


Figure 19. Typical electrophilic substitution reactions of ferrocene

Ferrocenium compounds play important role in the inhibition of the tumor cell growth. The antineoplastic activity of ferrocenes and their ferrocenium salts has been much less studied and the mechanism by which drugs become active towards cancer cells is not known clearly. In 1984, Köph-Maier reported on the antineoplastic activity of some ferrocenium salts against Ehrlich ascites tumor (EAT) cell line [78,79]. Ferrocene and ferrocenium salts had been tested *in vivo* for their inhibitory activity towards the EAT cell line. Studies showed that only

the ferrocenium salts, in which the central iron atoms have the oxidation state +3 (as in ferrocenium cations) exhibit tumor inhibitory effects [80].

Small polyphenolic molecules such as stilbenes, flavonoids, proanthocyanidines, and their derivatives are found throughout the vegetable world (for example, in grapes, green tea, and cocoa) and are recognized for their beneficial effects [81,82] Although they are most well known for their antioxidant action [83] against free radicals which have been associated with diseases related to aging (certain cancers, cardiac, ocular, and degenerative problems, etc.), these entities also act as specific modulators of certain protein functions [84]. For example, resveratrol **21** (3,4,5-trihydroxy-*trans*stilbene), present in red wine, is an endocrine modulator that recognizes estrogen receptors alpha and beta (ERα and ERβ) [85], as well as a free radical scavenger [86]. Among synthetic diphenolethylenes, compound **22**, (1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene, likewise presents estrogenic effects [87], a feature that is confirmed in the biological experiments. When the compound **22** is modified by replacing the phenyl unit with ferrocene, the resultant **23** compound shows surprising in vitro antiproliferative effects on breast cancer cells classified as hormone-independent (ERα negative) (Figure 20). Diphenol compounds **21-22** are known to be estrogenic, contributing to cell proliferation through interactions with the ER. In the experiments, compound **22** indeed showed a proliferative effect on the hormone dependent cells and had no significant effect on the hormon inedependent cells. Compound **23,** however**,** yielded strong antiproliferative effects in *both* hormone-dependent and independent breast cancer cells. Ferrocene itself exhibits interesting properties as an anti-anemic or cytotoxic agent [88]. Conjugates of ferrocene with well-known drugs were reported, for example, with antibiotics such as penicillins and cephalosporins [89]. In addition, structural variations of established drugs with the ferrocenyl moiety were reported, such as ferrocenyl aspirin [90], the anti-malarial drugs chloroquine (termed ferroquine) [91], and the anti-cancer drug tamixofen to give ferrocifen [92] (Figure 21).

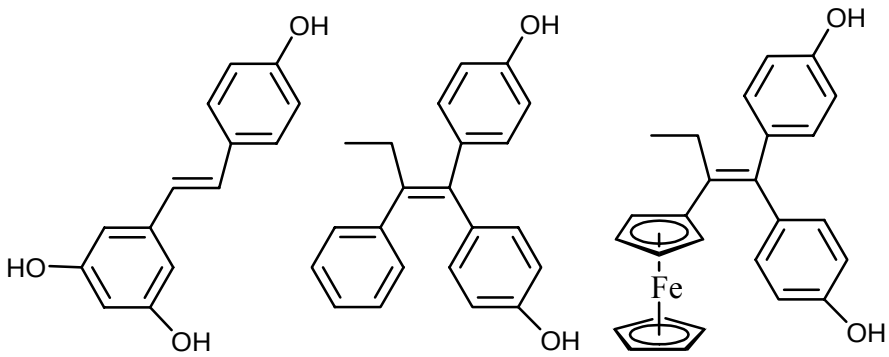


Figure 20. Cooperation of ferrocene moiety in the compound **22**

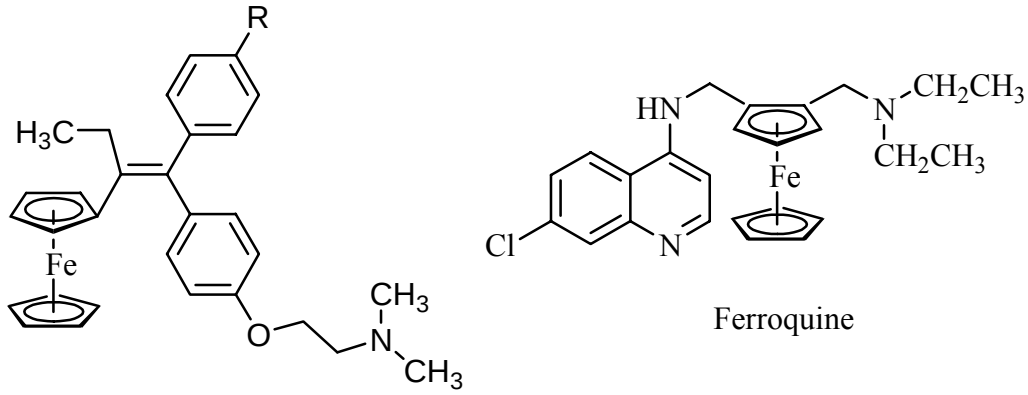


Figure 21. Ferrocifen and ferroquine

Since the discovery of ferrocene in the 1950s, the fascinating structural properties of ferrocene and its derivatives have been the subject of increasing interest in all fields of organometallic chemistry. One of the most important properties of ferrocene chemistry is that it is easy lithiation by *n*-butyllithium or *t*-butyllithium to prepare functionalized ferrocenes. Mono and dilithio derivatives are formed, depending on the reaction conditions. Ferrocenyllithium, like other organolithium compunds, is very reactive and can be converted to numerous other ferrocene derivatives as shown in Figure 22.

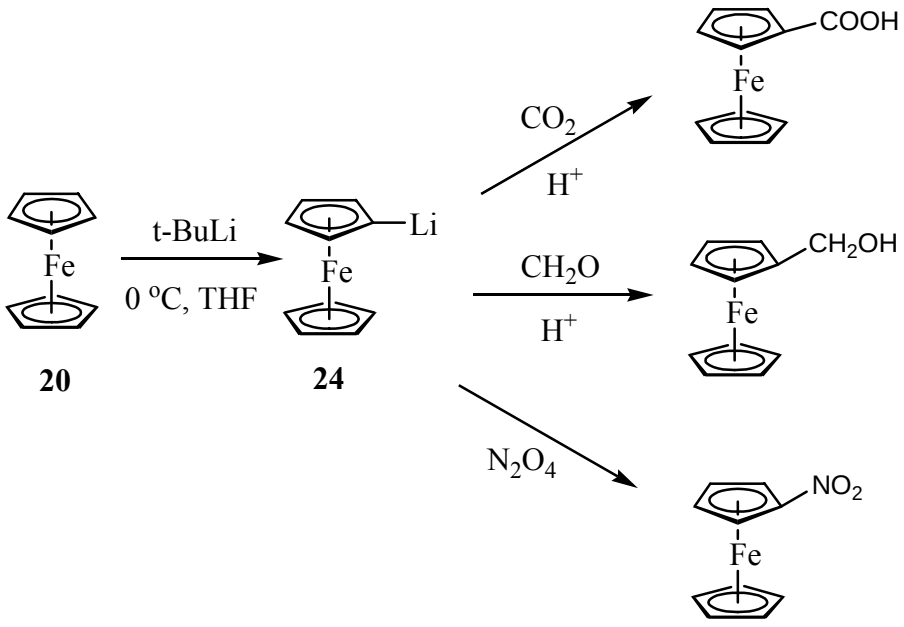


Figure 22. Some reactions of ferrocenylithium

Although, since its discovery, ferrocene and its derivatives have found large application in number of areas, most notably in materials chemistry and asymmetric catalysis [73], but few studies on the biological properties of molecules bearing ferrocene moiety have been reported. In this study, we aimed to synthesize ferrocenyl-substitued cycloheptadienones in order to increase the potential antitumor activity of the molecule.

As mentioned before, since highly funtionalized cycloheptanes are present in a variety of important natural products, new procedures for their formation have been actively sought. Cycloaddition reactions have greatest potential, but few leading to direct formation of a seven-membered ring have been reported. In this study, to develope a ferrocenyl-substituted seven-membered ring forming reaction, the reaction between cyclopropylmolybdenum-carbene complex **17** and Ferrocenyl-substitued alkynes **25** was examined (Figure 23). Since both ferrocene and cycloheptadienones show antitumor activity, we expect to increase the biological activities and potential antitumor activities of the molecules. In this study, the scope, limitations and the mechanism of this seven-membered ring forming reaction are discussed.

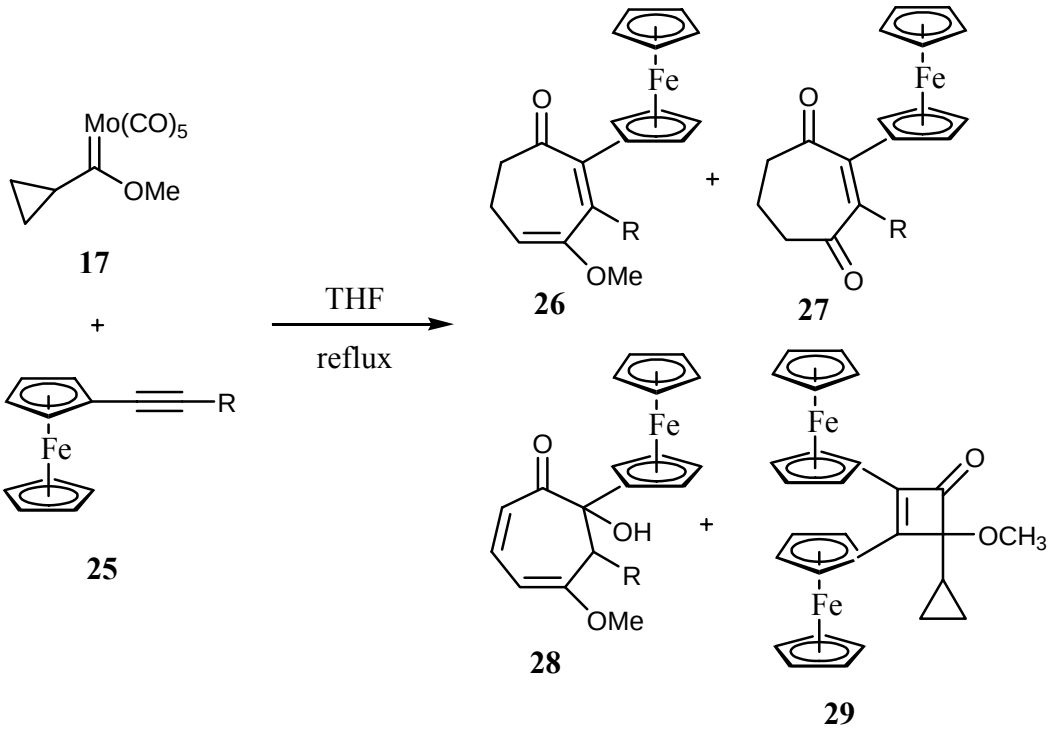


Figure 23. The reaction of molybdenum carbene complex **17** with ferrocenyl alkynes **25**

CHAPTER 2

RESULTS AND DISCUSSION

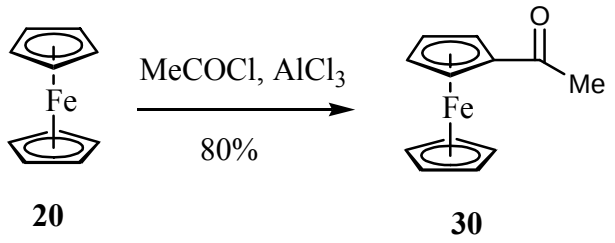
2.1. Synthesis of ferrocenyl cycloheptadienones.

The main objective of this study was to investigate the reaction between cyclopropylcarbene-molybdenum complex **17** and ferrocenyl-substituted alkynes **25** to afford ferrocenyl-substituted cycloheptadienone derivatives, which have some potential biological activities.

2.1.1. Synthesis of ferrocenyl-substitued alkyne derivatives.

For the synthesis of ferrocenyl-substituted seven-membered ring derivatives, the starting materials, ferrocenyl-substitued alkyne derivatives, were first synthesized. For this reason, the synthesis of ethynylferrocene (**25A**) was firstly carried out starting from ferrocene according to known literature procedures (Figures 24 and 25) [93,94]. In particular, ferrocenyl acetylenes constitute an interesting class of ferrocene derivatives since they serve as starting materials for the construction of more complex organometallic compounds.

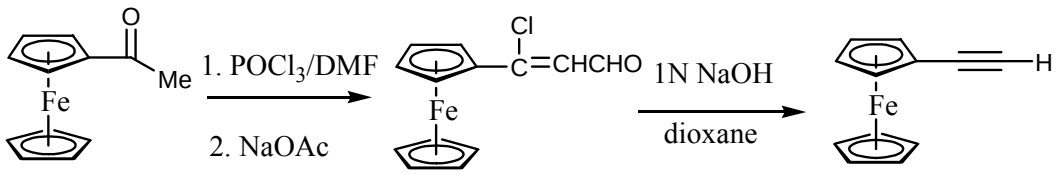
Initially, the synthesis of acetylferrocene (**30**) was performed. Ferrocene (**20**) was subjected to Friedel-Crafts acetylation by treating with acetyl chloride in the presence of aluminum chloride to form acetylferrocene (**30**) in 80% yield (Figure 24) [94].



20 **30**

Figure 24. Synthesis of acetylferrocene (**30**) from ferrocene (**20**)

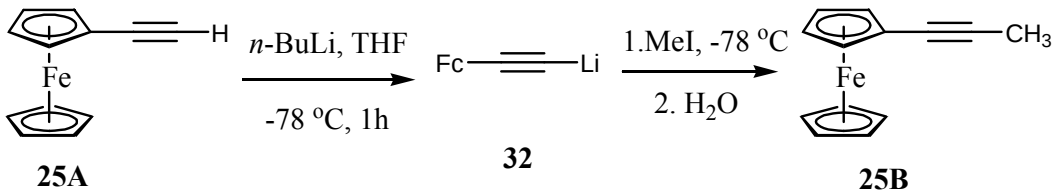
Then, two step synthesis of ethynylferrocene (**25A**) was carried out. Treatment of acetylferrocene (**30**) with phosphorus oxychloride in dimethyl-formamide, followed by the addition of sodium acetate, led to (2-formyl-1-chlorovinyl)ferrocene (**31**) in 85% yield (Figure 25). The mechanism involves the attack of carbonyl oxygen to phosphorus atom displacing a chloride ion. After the coordination of oxygen to phosphorus atom, the acetate ion attacks the methyl hydrogen in acetylferrocene which is quite acidic. The enol formed in the medium attacks to DMF. Then chloride ion acts as a nucleophile to displace the leaving group to form (2-formyl-1-chlorovinyl)ferrocene (**31**). After refluxing the (2-formyl-1-chlorovinyl)ferrocene (**31**) in dioxane in the presence of NaOH resulted in the formation of ethynylferrocene (**25A**) in 74% yield (Figure 25).



30 **31** **25A**

Figure 25. Synthesis of ethynylferrocene (**25A)** from acetylferrocene **30**

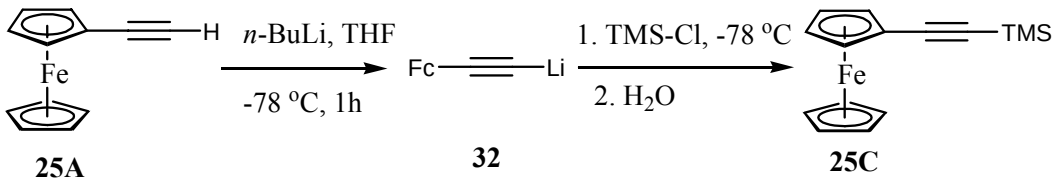
After synthesizing the ethynylferrocene (**25A**), six different ferrocenyl-substitued alkynes were prepared. To synthesize ferrocenylpropyne (**25B**), lithiation was firstly undertaken in the reaction medium (Figure 26). For the generation of lithiated form of ethynylferrocene (**32**), the ethynylferrocene (**25A**) was treated with a solution of *n*-butylithium at -78 ^{o}C in THF. After generation of lithiated form of ethynylferrocene (**32**), the addition of excess methyl iodide gave exclusively ferrocenylpropyne (**25B**) (Figure 26) [95].



25A **32** **25B**

Figure 26. Synthesis of ferrocenylpropyne **25B** from ethynylferrocene (**25A**)

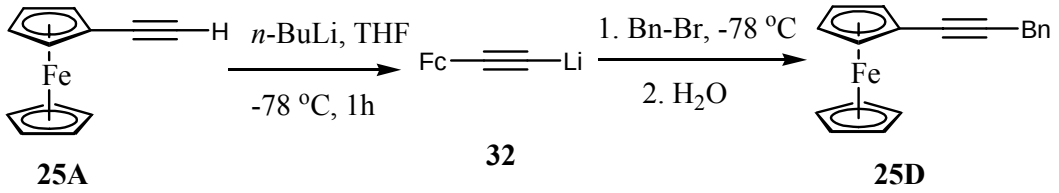
After synthesizing ferrocenylpropyne (**25B**), (2-ferrocenylethynyl)-trimethylsilane (**25C**) was prepared with the same procedure (Figure 27). The addition of trimethylsilyl chloride to the compound **32** afforded product **25C**. In the NMR-spectrum of the substance, we see a singlet peak at 0.2 ppm, which belongs to the nine protons of methyl groups. The peaks belong to the ferrocene protons appear between 4 and 5 ppm.



25A **32** **25C**

Figure 27. Synthesis of (2-ferrocenylethynyl)trimethylsilane (**25C**) from ethynylferrocene (**25A**)

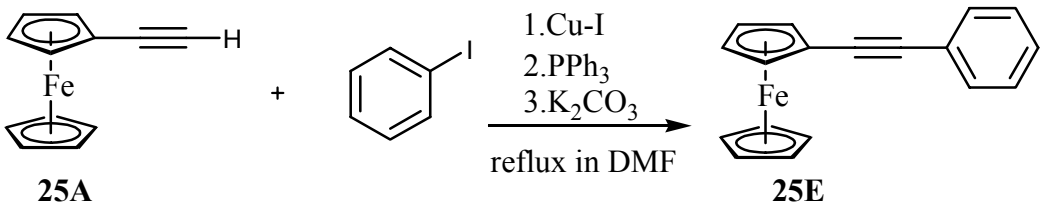
For the synthesis of 1-ferrocenyl-3-phenylprop-1-yne (**25D**), similar procedure was used (Figure 28). After lithiation, benzyl bromide was added and the subsequent addition of water into the reaction medium terminated the reaction to afford compound **25D** (Figure 28).



25A **32** **25D**

Figure 28. Synthesis of 1-ferrocenyl-3-phenylprop-1-yne (**25D**) from ethynylferrocene (**25A**)

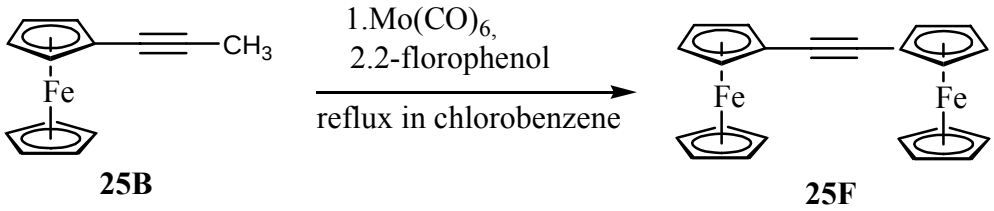
On the other hand, for the synthesis of 1-ferrocenyl-2-phenylethyne (**25E**), the reaction between iodobenzene and ethynylferrocene (**25A**) was next investigated (Figure 29), which is known as Suzuki coupling. To a mixture of copper(I) iodide, triphenylphosphine, potassium carbonate and DMF were added iodobenzene and ethynylferrocene (**25A**) under nitrogen. The resulting mixture was further stirred at 120 ^{o}C for 16 h to give compound **25E**. Suzuki *et al.* have reported that aryl and vinyl iodides smoothly react with terminal alkynes in the presence of a catalytic amount of copper(I) iodide using potassium carbonate as base when an appropriate amount of triphenylphosphine is added, giving the corresponding coupling products in good yields. The reactivity of the compound here is enhanced or modified in the presence of the catalytic amounts of a transition metal, leading to new forms of reactivity. The key step for these reactions is the transmetalation from the stoichiometric metal carbene reagent to the catalyst. This process generates a new metal-carbene complex that leads to enhanced reactivity of new reaction modes [96].



25A **25E**

Figure 29. Synthesis of 1-ferrocenyl-2-phenylethyne (**25E**) from ethynylferrocene (**25A**) and iodobenzene

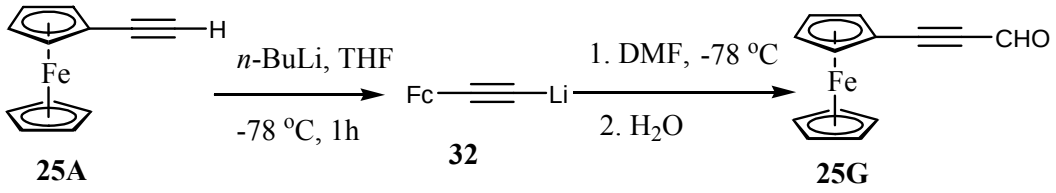
To synthesize 1,2-diferrocenylethyne (**25F**), a solution of alkyne **25B**, $Mo(CO)_6$ and 2-fluorophenol in chlorobenzene was refluxed for 2h (Figure 30). This reaction is one of the most intensively studied and applied transformations in organic chemistry which is transition-metal-catalyzed olefin metathesis. However, one disadvantage of alkene metathesis is that mixture of (*E*)- and (*Z*)-C=C isomers are typically obtained. This constitutes a significant drawback in target oriented synthesis. For this and other reasons, increasing attention is being focused on the sister reaction: alkyne metathesis. Although some applications of these transformations in the synthesis of organic and organometallic compounds and in material science are very promising, alkyne metathesis in general is still its infancy as compared with the alkene metathesis. So that, this methodology requires developing improved, more stable, and active catalyst. Thus, for the transformation of **25B** to **25F,** the molybdenum/2-fluophenol system was used as a catalyst [97].



25B **25F**

Figure 30. Synthesis of 1,2-diferrocenylethyne (**25F**) from ferrocenylpropyne (**25B**)

Finally, the synthesis of ferrocenyl(formyl)acetylene (**25G**) was performed**.** In this synthesis, first ethynylferrocene (**25A**) was treated with *n*-BuLi, and then excess DMF was added to the reaction medium. The reaction was ended by the addition of water (Figure 31).

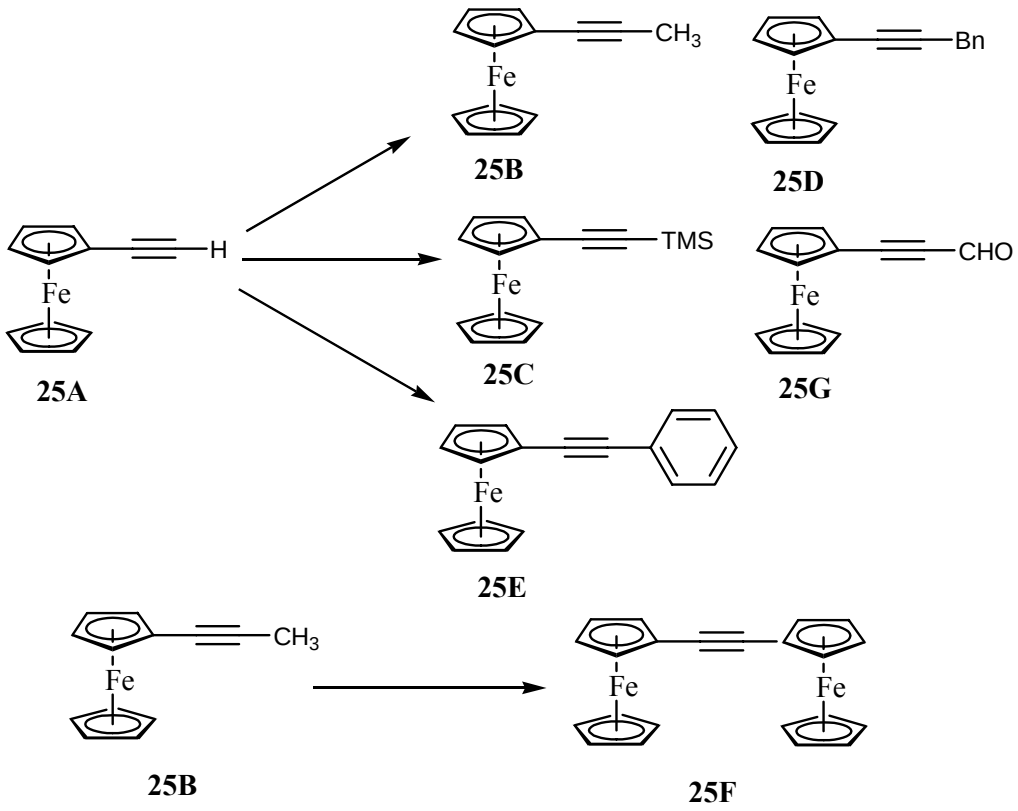


25A **32** **25G**

Figure 31. Synthesis of ferrocenyl(formyl)acetylene (**25G**) from ethynylferrocene (**25A**)

The overall yields for ferrocenyl alkyne derivatives are summarized in Table 1. The best yield was observed for the methyl-substituted alkyne **25B** while the lowest yield was obtained for diferrocenyl alkyne **25F**.

Table 1. The overall yields for ferrocenyl alkyne derivatives **25**



Products	Yield (%)
25B	96
25C	84
25D	56
25E	47
25F	26
25G	50

2.1.2. Synthesis of cyclopropylcarbene-molybdenum complex.

Cyclopropylcarbene-molybdenum complex **17** was synthesized starting from cyclopropyl bromide according to a known literature procedure (Figure 31) [98]. For this purpose, cyclopropyl bromide **33** was treated with the *tert*-BuLi in dry THF at -78 ^{o}C, to produce cyclopropyllithium **34,** which was then directly added to a suspension of the molybdenum hexacarbonyl in THF at 0 ^{o}C to afford lithium metal enolate **35.** Treatment of this enolate with methyl triflate produced cyclopropylcarbene-molybdenum complex **17** in 74% yield (Figure 32).

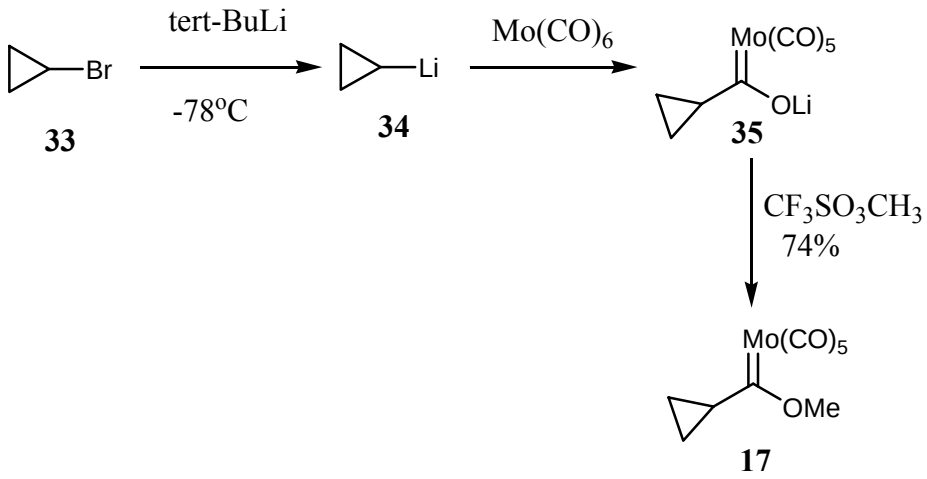


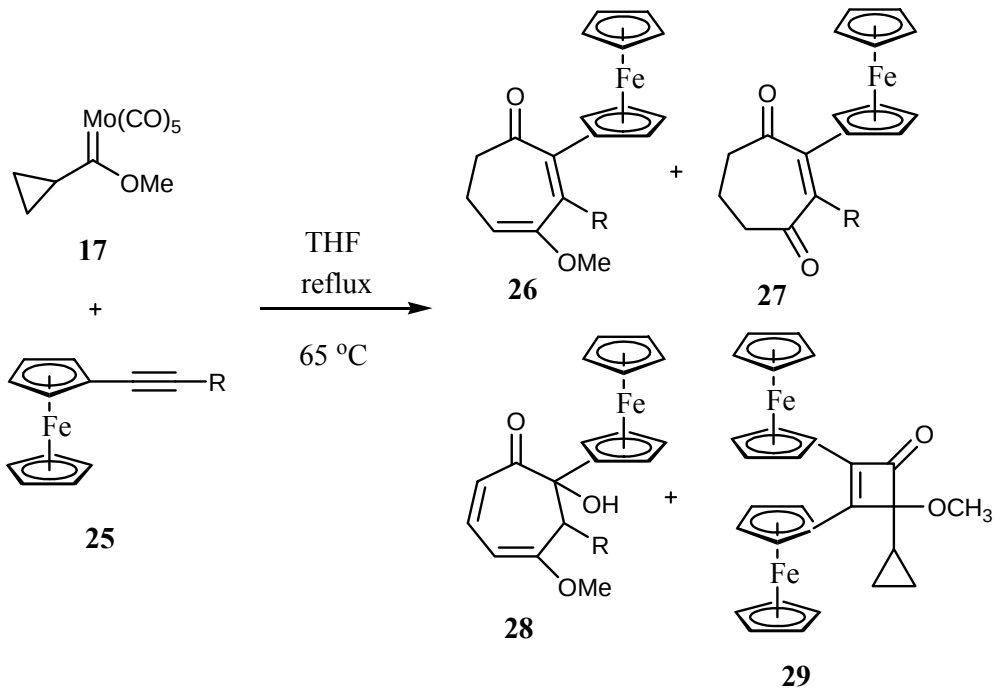
Figure 32. Synthesis of cyclopropylcarbene-molybdenum complex **17**

2.1.3. Synthesis of ferrocenyl cycloheptadienones.

We have demonstrated that the reactions of cyclopropylcarbene complex **17** with ferrocenyl alkynes give ferrocenyl cycloheptadienones **26**, **27** and/or **28**, and/or **29** as byproduct**.** First of all, the reaction between cyclopropylcarbene complex **17** with alkynes **25** was examined**.** It was found that the optimal conditions require heating a 1:1.5 mole ratio of carbene complex **17** and alkyne **25** in THF at 65 ^{o}C. The reaction products were isolated from these reactions by flash column chromatography and characterized by means of ^{1}H- and ^{13}C-NMR, IR, MS and HRMS spectroscopy. The results of this study are summarized in Table 2.

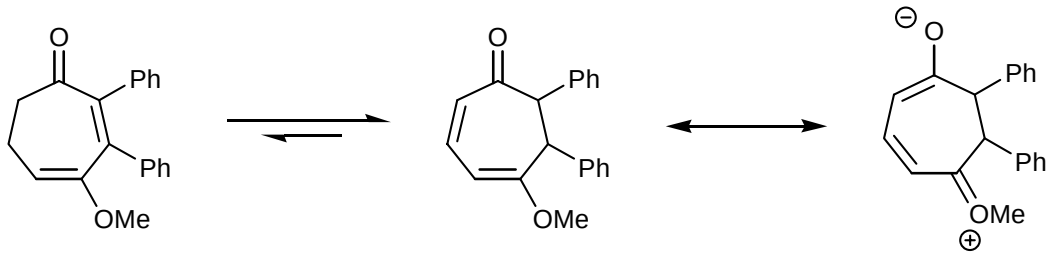
Initially, the reaction between cyclopropylcarbene complex **17** with ethynylferrocene (**25A**) was examined (Table 2, Entry A). Unfortunately, this reaction did not produce any products, possibly due to the polymerization of the terminal alkyne. In fact, this is in accord with the findings of Herndon [98]. Early studies carried out with cyclopropylcarbene-molydenum complex **17** and terminal alkynes gave similar results [98].

Table 2. The reaction of cyclopropylcarbene-molydenum complex **17** with ferrocenyl alkynes **25**



Entry	Starting Materials	R	Rxn times, Additives	Products (Yield %)
A	**25A+17**	H	6h	-
B	**25B+17**	Me	5h	**26B**(47) + **27B**(12)+ **28B**(12)
C	**25B+17**	Me	5h, PPh_3	**27B** (12) + **28B** (14)
D	**25C+17**	TMS	5h	-
E	**25D+17**	Bn	4h	**26D** (70)
F	**25E+17**	Ph	4h	**26E** (72) + **27E** (10)
G	**25F+17**	Fc	3h	**26F** (15) + **29F** (8)
H	**25G+17**	CHO	4h	-

Then, the reaction between cyclopropylcarbene complex **17** and ferrocenylpropyne **25B** was investigated by refluxing at the same conditions in THF at 65 ^{o}C for 6 hours (Table 2, Entry B). From this reaction, cycloheptadienone **26B** was obtained in 42% yield, accompanied by a substantial amount of unreacted alkyne, hydrolysis product of cycloheptadienone, **27B**, in 12% yield and reduced and rearranged product **28B** in 12% yield. In the ^{1}H-NMR spectrum of cycloheptadienone **26B,** the peak for the vinylic proton appeared at 5.13 ppm as a triplet and that for methoxy protons at 3.49 ppm as a singlet. On the other hand, in the ^{1}H-NMR spectrum of cycloheptadienone **27B,** the peaks for vinylic proton and methoxy protons disappeared. Another triplet occurred instead which is due to two protons adjacent to carbonyl group. Since two carbonyls groups are present in the hydrolysis product **27B**, the carbonyl carbons have been seen at 204.2 and 203.3 ppm in the ^{13}C-NMR spectrum. The product **28B** results from the reduction of cycloheptadienone intermediate with water followed by the rearrangement of double bonds, or vice versa, during the course of the reaction. Although we have not studied in detail, this reduction may be favored by the presence of an iron metal or ferrocenyl moiety. It should be mentioned that α-hydroxycycloheptadienones are very important compounds in terms of organic synthesis and biological activity. In similar studies, Herndon and his coworkers have shown that cycloheptadienone product **36K** is the kinetic product of the reaction and converts into thermodynamically more stable product **36T** under reaction conditions (Figure 33). The cycloheptadienone **36T** is more stable than **36K** due to the resonance interaction. In our case, for the formation of product **28B**, the reduction with water and rearrangement of the compound was observed. Such reductions with water are not so common in literature.



36K **36T**

Figure 33. Conversion of cycloheptadienone **36K** to **36T** and resonance stabilization of cycloheptadienone **36T**

In general, phosphine ligands are used in organometallic reactions to increase the yield of main products by assisting metal carbene reactions by aiding in the displacement of a carbon monoxide ligand. By the addition of phosphine ligands to the reaction mixture, the extent of the side reaction may also be suppressed. Since cycloheptadienone **26** was the main product from these reactions, we expected to increase its yield by the addition of phosphine ligands such as triphenyl phosphine. Herndon and his coworkers reported that in the reaction of cyclopropylmolybdenum-carbene complex with phenylpropyne, furan formation is the major competing reaction pathway, but the use of triphenyl phosphine as additive suppresses the furan formation [98].

As suggested by Herndon [98] phosphine complexation to the metal might simply alter the *E*:*Z* ratio of the vinylcarbene complexes (Figure 34); however, increasing the steric bulk of the metal should increase the proportion of the less sterically less congested *Z*-vinylcarbene complex (**38-Z**). Formation of *Z*-vinylcarbene causes an increase in the formation of furan product **40**. Alternatively, if the cyclopropyl ring opening step is kinetically faster than the ring-closure step of the furan-forming reaction, and phosphine could effect an *E*-*Z* isomerization, then the apparent result would be the an increase in the cycloheptadienone:furanone ratio.

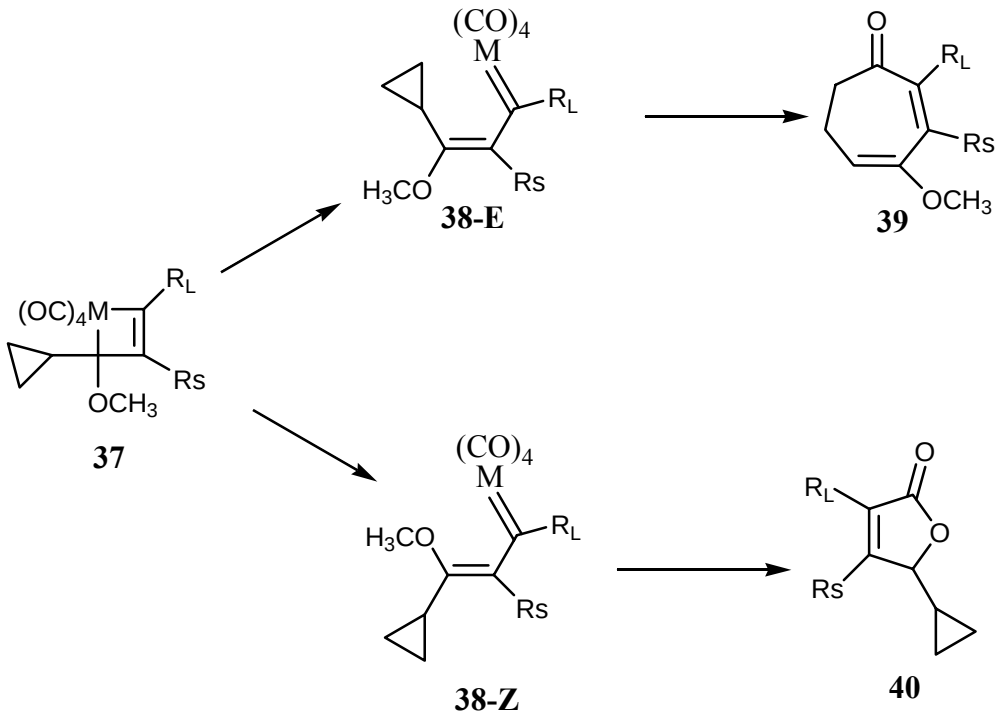


Figure 34. The potential role of triphenylphosphine in the *E-Z* isomerization of vinylcarbene complexes

However, this was not the result in the reaction of cyclopropylcarbene complex **17** and ferrocenylpropyne **25B** with triphenylphosphine (Table 2, Entry C). The results were surprising since we did not get any **26B** as a product or furanone product. Instead, hydrolysis product of cycloheptadienone **27B** and **28B** were isolated from this reaction. Clearly, the use of triphenyl phosphine as an additive neither lead any increase in the yields of the reaction, nor cause a change in the reaction pathway (Table 2, Entry C).

The structure elucidation of **28B** is based on ^{1}H and ^{13}C NMR spectra. In the ^{1}H-NMR spectrum of the compound **28B**, the singlet peak at 4.39 reveals the presence alcoholic proton. The peaks at δ 6.58, 5.99, 4.94 ppm, related to carbon signals at 138.42, 118.86, 93.38 ppm, show the presence of the double bond protons. Signals on 4.23, 4.13, 4.07, 3.92 ppm belong to the ferrocenyl group, which appear at δ 65.60, 65.14, 64.93 and 64.27 ppm in ^{13}C-NMR spectrum. Since there is a chiral center in the molecule, we see different shifts for ferrocene carbons. Ferrocenyl ipso carbon gives resonance at δ 66.67 ppm. The shift of the ipso carbon can be easily understood from the DEPT-90. Since only CH protons are seen in the DEPT-90, the missing signal is the ipso carbon.

Since terminal alkynes did not lead to cycloheptadienones, we would like to alleviate this problem by employing a trimethylsilly-substitued ferrocenyl alkyne. But, from the reaction of the cyclopropylcarbene complex **17** and (2-ferrocenylethynyl)trimethyl silane (**25C**), we did not get any product (Table 2, Entry D). This result was also not expected since the reaction of cyclopropylcarbene complex **17** and (2-phenylethynyl)trimethyl silane was known to give phenyl-substitued cycloheptadienones. The reason can be the steric effects coming from both the trimethysilyl and ferrocenyl groups since both groups are relatively large and bulky groups. As expected, the presence of large groups blocks the coordination of alkyne to the metal for steric reasons, which prevents the reaction.

Investigation of the reaction between cyclopropylcarbene complex **17** and 1-ferrocenyl-3-phenylprop-1-yne (**25D**)**,** gave the cycloheptadienone derivative **26D** in 70% yield**.** The structure of compound **26D** was also analyzed by X-ray single crystal analysis as depicted in Figure 34. X-Ray crystallographic data for compound **26D** is summarized in Table 3.

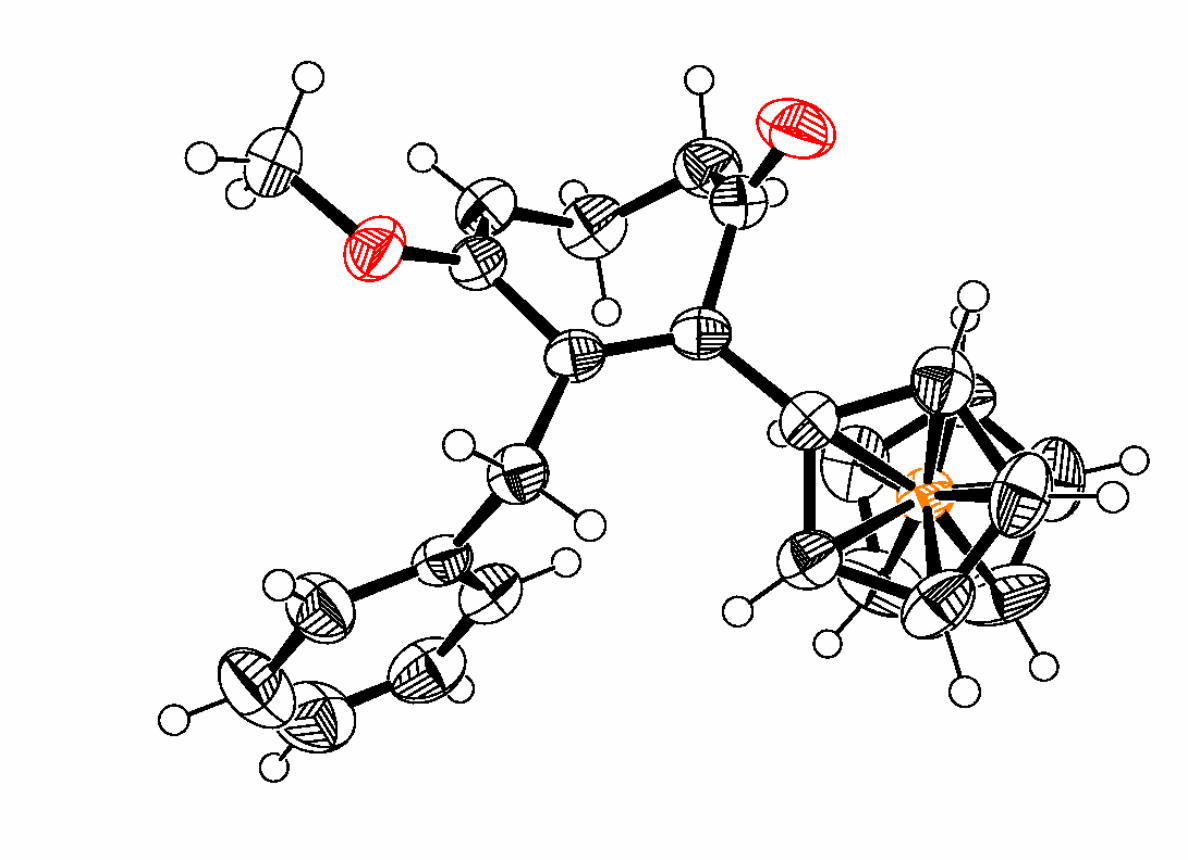


Figure 35. Ortep crytal structure of compound 2-ferrocenyl-3-benzyl-4-methoxycyclohepta-2,4-dienone (**26D**)

Table 3. X-Ray crystallographic data for compound **26D**

Chemical formula	$C_{25}H_{24}FeO_2$
Molecular weight	412.29
Crstal system	triclinic
Space group	'P -1'
Unit cell dimensions	
a	7.7443(5) Å
b	11.3769(7) Å
c	11.5864(7) Å
α	76.372 °
β	80.118 (7) °
γ	89.386 °
Cell volume	976.90(11) ($Å^3$)
Z (Molecule number in unit cell)	2
Density (calculated)	1.402 Mg/m**3
F_{000}	432.0
Cell measurement temperature	293
Cell measurement theta min	2.27
Cell measurement theta max	26.00
$S(F^2)$	1.000
R, R_W	0.026

A similar trend was observed when the carbene complex **17** was refluxed with 1-ferrocenyl-2-phenylethyne (**25E**) in THF for 4 hours. The reaction produced cycloheptadienone derivative **26E** in 72 % yield and hydrolysis product **27E** in 10% yield (Table 2, Entry F).

It is interesting to note that, in reaction with carbene complex **17** and 1,2-diferrocenylethyne (**25F**)**,** cycloheptadienone derivative **26F** was observed but in very low yield (15%) when compared to other substituents (Table 2, Entry G). The reason might be the steric effects since both groups were ferrocenyl, which are relatively larger groups and possibly prevents the coordination of alkyne to the metal during the course of the reaction. Surprisingly, the product **29F** was also isolated from this reaction. It should be noted that such products were previously observed in the reactions of similar metal carbene complexes [99].

Finally, we have performed the reaction of carbene complex **17** and **25G** (Table 2, Entry H). The reaction did not yield any isolable product. The reason was due to the electron withdrawing property of the aldehyde group. The electron deficiency in the alkyne diminished the [2+2] cycloaddition reaction.

2.1.4. Mechanism

The mechanism for the formation of cycloheptadienone derivative **26** is shown below (Figures 36-38). Two variations in this mechanism can be envisaged, which differ in their timing of CO insertion vs cyclopropane ring opening steps. The mechanism in path A more closely resembles the currently favored mechanism for the Dötz reaction (Figure 36).

The reaction begins with a thermal loss of one CO, to generate a vacant coordination site in the carbene complex **17** (Figure 34). Coordination of the alkyne followed by [2+2] cycloaddition to the metal-carbon double bond generates the metallocyclobutene **43**. Electrocyclic ring opening of the metallocyclobutene **43** results in the formation of intermediate **44**. Seven-membered ring derivative **26** could be formed from the intermediate **44** by two ways as shown in Figures 37 and 38.

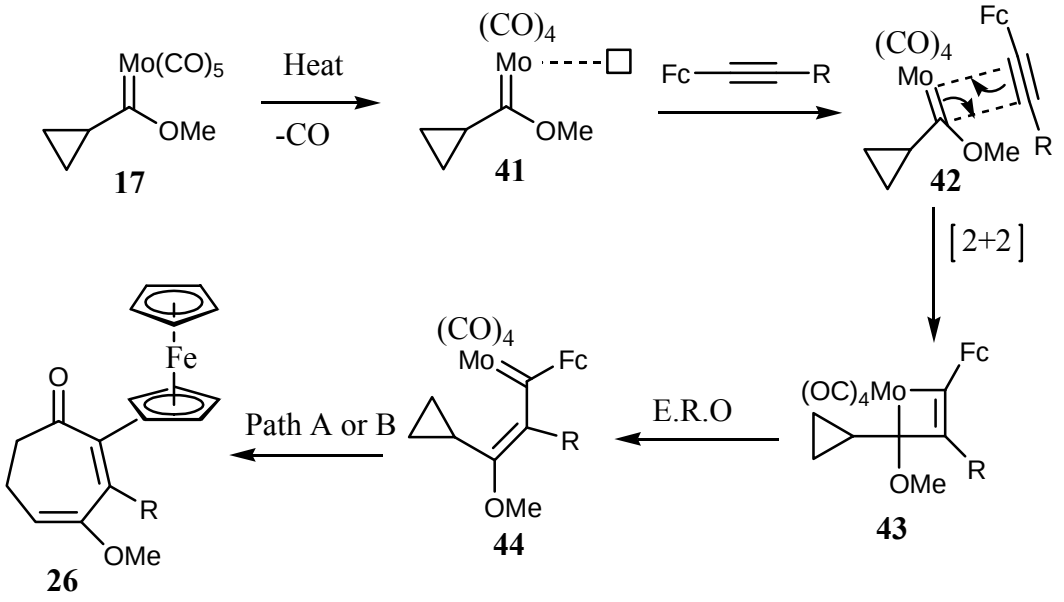


Figure 36. Proposed mechanism for the reaction of carbene complex **17** with ferrocenyl alkynes **25**

In the path A, first CO insertion occurs to form vinylketene **45** (Figure 37). Electrocyclic ring closure of **45,** followed by decomplexation, leads to the formation of cycloheptadienone derivative **26**.

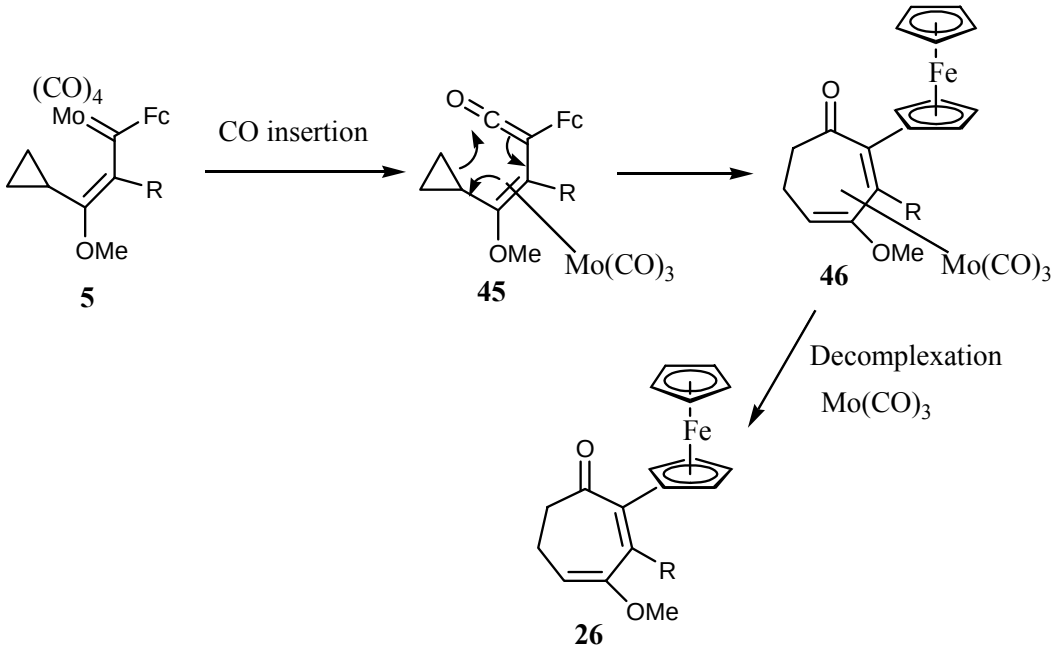


Figure 37. Proposed mechanism for the formation of cycloheptadienone **26** via Path A

In the path B, first cyclization occurs, and then CO insertion takes place to give eight-membered ring compound **48** (Figure 38). Reductive elimination in **48** eventually forms the cycloheptadienone **26.** In particular, reductive elimination is important for organic synthetic applications since it is the major way for transition metals to make carbon-carbon bonds. Anything which reduces the electron density at the metal facilitates reductive elimination. This can be as simple as the dissociation of a ligand, either spontaneously or by the application of heat or light.

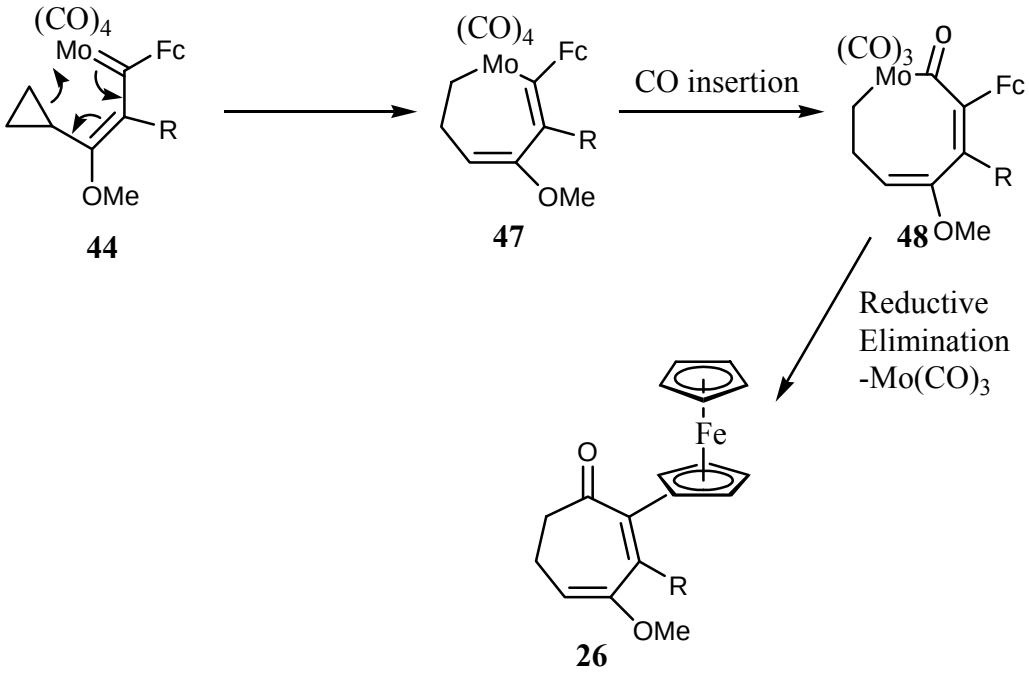


Figure 38. Proposed mechanism for the formation of cycloheptadienone **26** via Path B

According to the mechanism, overall regiochemistry of the reaction is set in the metallacyclobutene ring forming step (**42** to **43**), where the larger group of the alkyne ends up α to the metal in order to minimize steric interactions.

CHAPTER 3

CONCLUSION

A methodology for the synthesis of ferrocenyl-substituted cyclohepta-dienones was developed. For this purpose, the reaction between cyclopropylmolybdenum-carbene complex **17** and ferrocene-substitued alkynes **25** was investigated. In the first phase of the study, the starting materials, cyclopropylmolybdenum-carbene complex **17** and ferrocene-substituted alkynes **25**, were prepared according to well known literature procedures starting from ethynylferrocene (**25A**). As alkyne derivatives, ferrocenylpropyne (**25B**), (2-ferrocenylethynyl)trimethylsilane (**25C**), 1-ferrocenyl-3-phenylprop-1-yne (**25D**), 1-ferrocenyl-2-phenylethyne (**25E**), diferrocenylethyne (**25F**), ferrocenyl(formyl)acetylene (**25G**) were synthesized starting from ethynylferrocene (**25A**). First, the reaction between the carbene complex **17** and ethynylferrocene (**25A**) was investigated. This reaction did not give any isolable product, presumably due to the polymerization of the terminal alkyne. However, the reaction between carbene complex **17** and ferrocenylpropyne (**25B**) yielded cycloheptadienone **26B**, hydrolysis product **27B** and cycloheptadienone derivative **28B**. When the same reaction was carried out in the presence of triphenylphosphine, α-hydroxycycloheptadienone derivative **28B** was obtained in addition to **27B**. Importantly, α-hydroxycycloheptadienone product **28B** was not reported previously from these types of reactions by other researchers.

Unfortunately, the reaction of (2-ferrocenylethynyl)trimethylsilane (**25C**) with carbene complex **17** did not yield any cycloheptadienone derivatives, possibly due to steric bulkiness in alkyne moiety. In the reaction of carbene complex **17** with 1-ferrocenyl-3-phenylprop-1-yne (**25D**)**,** we observed only cycloheptadienone derivative **26D.** In the reaction of carbene complex **17** with 1-ferrocenyl-2-phenylethyne (**25E**), cycloheptadienone derivative **26E** and hydrolysis product **27E** were observed. The reaction with 1,2-diferrocenylethyne (**25F**) afforded cycloheptadienone derivative **26F** but in very low yield. Finally, we have carried out the reaction of carbene complex **17** and **25G**, which did not yield any isolable product, possibly due to electron-withdrawing property of aldehyde moiety.

Proposed mechanism involves metallacyclobutene ring formation, electrocyclic ring opening, electrocyclic ring closure, CO insertion, reductive elimination.

In conclusion, we showed that the reaction of cyclopropylmolybdenum-carbene complex **17** with ferrocene-substitued alkynes affords corresponding cycloheptadienone derivatives. These studies will be of value in the development of synthetic pathways for ferrocenyl-substituted cycloheptadienones.

CHAPTER 4

EXPERIMENTAL

General. Nuclear Magnetic Resonance (^{1}H and ^{13}C) spectra were recorded on a Brucker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. Chemical shifts are reported in parts per million downfield from an internal tetramethylsilane reference. Coupling constants (*J* values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). DEPT ^{13}C-NMR information is given in parenthesis as C, CH, CH_2 and CH_3. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band, and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak), vw (very weak). Mass spectra (MS) were obtained on a Micromass UK Platform-II spectrometer using electron impact (EI); *m/e* values are reported, followed by the relative intensity in parantheses. Flash coloumn chromatography was performed using thick-walled glass columns and "flash grade" silica (Merck 230-400 mesh). Routine thin layer chromatography (TLC) was effected by using precoated 0.25 mm silica gel plates purchased from Merck. The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. All commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF and dioxane were distilled from sodium/benzophenone kettle. The inert atmosphere is created by slight positive pressure (ca. 0.1 psi) of argon.

4.1 Synthesis of Ferrocenyl Alkynes

4.1.1. Acetylferrocene (30). To a solution of ferrocene **20** (10.00 g, 54 mmol) in CH_2Cl_2 (45 ml) was added acetyl chloride (4.62 g, 59 mmol). Then it was immersed in an ice-water bath at 0°C. To the resultant solution anhydrous aluminium chloride (7.2 g, 54 mmol) was added in 10 portions. After stirring the reaction mixture at room temperature for 2 h, it was recooled by placing it in a fresh ice-water bath. Then the solution was hydrolysed by the addition of cold water and extracted with CH_2Cl_2 (2 x 25 ml). Combined organic layers were washed with water and saturated aq. NaCl solution, respectively. After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. The crude red/orange solid was purified by flash chromatography on silica gel using hexane-ethyl acetate (9:1) as the eluent. The orange fraction was collected to give acetylferrocene (9.8 g, 80%).

30: ^{1}H-NMR ($CDCl_3$): δ 4.78 (s, 2H), 4.51 (s, 2H), 4.21 (s, 5H), 2.40 (s, 3H). The spectral data are in agreement with those reported previously for this compound [94].

4.1.2. (2-Formyl-1-chlorovinyl)ferrocene (31). To a solution of acetylferrocene (**30**) (2.28 g, 10 mmol), DMF (2.5 ml, 32 mmol) was added and the system was flushed with argon. Then it was cooled to 0°C, and the reaction mixture was stirred for several minutes. Separately, a solution of DMF (2.5 ml, 32 mmol) and $POCl_3$ (2.5 ml, 27 mmol) was prepared. The resulting viscous complex was transferred to the dropping funnel and added to the reaction mixture dropwise over 30 min. After stirring the mixture at 0°C for 2 h, a 7.5 ml portion of diethyl ether was added, and the viscous mixture was stirred vigorously for several minutes. Then sodium acetate trihydrate (11.6 g, 85 mmol) was added to the solution in one portion followed by addition of 1 ml of water.

The ice bath was removed whereupon the organic layer undergone a striking color change from colorless to ruby red.

After 1 h, an additional 1 ml of ether was added, and the stirring was continued for 3 h at room temperature. The reaction mixture was extracted with ether (3 x 20 ml). Combined organic phases were washed with saturated aq. Na_2CO_3 solution and water, respectively. The organic phase was dried over $MgSO_4$ and the solvent was removed on a rotary evaporator affording 2.34-2.56 g (85-93%) of (2-formyl-1-chlorovinyl)ferrocene (**31**) as deep purple crystals after drying under high vacuum.

31: ^{1}H-NMR ($CDCl_3$): δ 10.09 (d, 1H), 6.40 (d, 1H), 4.75 (s, 2H), 4.57 (s, 2H), 4.24 (s, 5H). The spectral data are in agreement with those reported previously for this compound [94].

4.1.3. Ethynylferrocene (25A). To (2-formyl-1-chlorovinyl)ferrocene (**31**) (2.6 g, 9.5 mmol), anhydrous 1,4-dioxane (30 ml) was added after flushing it with argon. The reaction mixture was heated to reflux and after 5 min at reflux, a boiling 1 N solution of NaOH (25 ml) was added as rapidly as possible in one portion, and the mixture was heated at reflux for another 25 min. Then the reaction mixture was allowed to cool to room temperature and it was cautiously poured into ice and neutralized with 1 N HCl. The aqueous mixture was extracted with hexane (5 x 10 ml). Combined organic extracts were washed with 10 mL portions of saturated aqueous sodium bicarbonate solution and water, respectively. The organic phase was dried over $MgSO_4$, and the solvent was removed on a rotary evaporator affording an orange residue of crude ethynylferrocene (**25A**). The crude product was purified by flash chromatography on silica gel with elution by hexane giving 1.48-1.50 g (74-75%) of pure ethynylferrocene which crystallized as an orange solid.

25A: ^{1}H-NMR ($CDCl_3$): δ 4.46 (s, 2H), 4.21 (s, 5H), 4.19 (s, 2H), 2.71 (s, 1H). The spectral data are in agreement with those reported previously for this compound [93].

4.1.4. Ferrocenylpropyne (25B). A solution of *n*-BuLi (1.30 ml, 1.6 M, 2 mmol) in hexane was added to ethynylferrocene (**25A**) (0.4 g, 1.9 mmol) in THF (30 ml) at -78°C. After 30 min, an excess of MeI (0.5 ml, 8 mmol) was added. The solution was brought to room temperature and stirred for 1 h, and then hydrolysed at 0°C followed by the extraction with CH_2Cl_2 (2 x 25 ml). Combined organic layers were washed with water. After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. The crude product was purified by flash chromatography on silica gel using hexane as the eluent. The orange fraction was collected to give ferrocenylpropyne (410 mg, 96%).

25B: ^{1}H-NMR ($CDCl_3$): δ 4.29 (s, 2H), 4.20 (s, 5H), 4.07 (s, 2H), 1.86 (s, 3H). The spectral data are in agreement with those reported previously for this compound [95].

4.1.5. (2-ferrocenylethynyl)trimethylsilane (25C). A solution of *n*-BuLi (1.30 ml, 1.6 M, 2 mmol) in hexane was added to ethynylferrocene (**25A**) (0.4 g, 1.9 mmol) in THF (30 ml) at -78°C. After 30 min, an excess of TMSCl (1.02 ml, 8 mmol) was added. The solution was brought to room temperature and stirred for 1 h, and then hydrolysed at 0°C followed by the extraction with CH_2Cl_2 (2 x 25 ml). Combined organic layers were washed with water. After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. The crude product was purified by flash chromatography on silica gel using hexane as the eluent. The orange fraction was collected to give (2-ferrocenylethynyl)trimethylsilane (450 mg, 84%).

25C: ^{1}H-NMR ($CDCl_3$): δ 4.40 (t, 2H), 4.17 (s, 5H), 4.15 (t, 2H), 0.1 (s, 9H). The spectral data are in agreement with those reported previously for this compound [100].

4.1.6. 1-Ferrocenyl-3-phenylprop-1-yne (25D). A solution of *n*-BuLi (1.30 ml, 1.6 M, 2 mmol) in hexane was added to ethynylferrocene (**25A**) (0.4 g, 1.9 mmol) in THF (30 ml) at -78°C. After 30 min, an excess of BnBr (0.9 ml, 10 mmol) was added. The solution was brought to room temperature and stirred for 1 h, and then hydrolysed at 0°C followed by the extraction with CH_2Cl_2 (2 x 25 ml). Combined organic layers were washed with water. After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. The crude product was purified by flash chromatography on silica gel using hexane as the eluent. The orange fraction was collected to give 1-ferrocenyl-3-phenylprop-1-yne (320 mg, 56%).

25D: ^{1}H-NMR ($CDCl_3$): δ 7.45-7.43 (m, 3H), 7.39-7.33 (m, 2H), 4.68 (s, 2H), 4.49 (s, 2H), 4.49 (s, 5H), 3.10 (s, 2H). The spectral data are in agreement with those reported previously for this compound [101].

4.1.7. 1-Ferrocenyl-2-phenylethyne (25E). To a mixture of copper(I) iodide (23 mg, 0.13 mmol), triphenylphosphine (62.4 mg, 0.25 mmol), potassium carbonate (493 mg, 3.7 mmol), and DMF (5 ml) were added ethynylferrocene (**25A**) (2.5 mmol) and iodoferrocene (2.5 mmol) under argon. The resulting mixture was stirred at 120°C for 16 h after which it was poured into water, extracted with ether (2 x 25 ml). Combined organic layers were washed with water. After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. The crude product was purified by flash chromatography on silica gel using hexane as the eluent. The orange fraction was collected to give 1-ferrocenyl-2-phenylethyne (320 mg, 47%).

25E: ^{1}H-NMR ($CDCl_3$): 7.20-7.60 (m, 5H), 4.53 (s,2H), 4.27 (s, 7H). The spectral data are in agreement with those reported previously for this compound [96].

4.1.8. 1,2-diferrocenylethyne (25F). A solution of ferrocenylpropyne (**25B**) (437 mg, 1.95 mmol), $Mo(CO)_6$ (25.75 mg, 0.1 mmol) and 2-fluorophenol (0.18 ml, 1.4 mmol) in chlorobenzene (40 ml) was refluxed for 2 h using electric heating mantle. After evaporation of the solvent on rotary evaporator, the residue was purified by flash chromatography on silica gel using hexane as the eluent. The orange fraction was collected to give 1,2-diferrocenylethyne (200 mg, 26%).

25F: ^{1}H-NMR ($CDCl_3$): δ 4.45 (t, 2H), 4.23 (s, 5H), 4.20 (t, 2H). The spectral data are in agreement with those reported previously for this compound [97].

4.1.9. Ferrocenyl(formyl)acetylene (25G). A solution of *n*-BuLi (3.2 ml, 1.6 M, 5 mmol) in hexane was added to ethynylferrocene (**25A**) (1 g, 4.8 mmol) in THF (30 ml) at -78°C. After 30 min at -78°C , an excess of DMF (1 ml, 13 mmol) was added. After 1 h at -78°C, the solution was brought to the room temperature and poured over 50 ml of an ice-water mixture containing 5 ml of conc HCl. A violet coloration was observed. The solution then neutralised with $NaHCO_3$, and the red solution so formed was extracted with ether, dried and 1.05 g (4.4 mmol, 93%) of red crystalline solid was obtained upon removal of solvent.

25G: ^{1}H-NMR ($CDCl_3$): δ 9.27 (s, 1H), 4.60 (s, 2H), 4.41 (s, 2H), 4.25 (s, 5H). The spectral data are in agreement with those reported previously for this compound [95].

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4.2. Synthesis of Cyclopropylcarbene-molybdenum Complex (17). A solution of *t*-butyllithium (1.7 M in hexane, 12 mL, 20 mmol) was added dropwise to cyclopropylbromide (0.8 mL, 10 mmol) in 10 mL of THF at 0^{o}C. After 45 min at 0^{o}C the solution was transferred dropwise via cannula to a suspension of molybdenum hexacarbonyl (2.6 g, 10.0 mmol) in THF (20 mL). After 1h at rt, methyl triflate (1.7 mL, 15 mmol) was slowly added to the reaction mixture at 0 ^{o}C. When the addition was complete, the mixture was stirred for another 0.5 h at 0 ^{o}C The reaction was quenched by adding 20 mL of saturated $NaHCO_3$ and stirred for 10 min.

The organic layer was separated and the aqueous layer was extracted with ether (3 *x* 20 mL). The organic solutions were combined, washed with water (30 mL) and brine (30 mL), and dried ($MgS0_4$). After removal of solvents, the crude product was flashed chromatographed on silica gel using hexane as the eluent. A dark purple low melting solid was collected in 74% yield (2.3 g, 7.1 mmol).

17: ^{1}H-NMR ($CDCl_3$): δ 4.54 (s, 3H), 3.45 (s, 1H J = 4.4 Hz), 1.39 (t, 2H, J = 3.7 Hz), 1.19 (t, 2H, J = 3.7 Hz). The spectral data are in agreement with those reported previously for this compound [98].

4.3. Synthesis of ferrocenyl substitued cycloheptadienones

4.3.1. General Procedure I. Synthesis of ferrocenyl substitued cycloheptadienones (Table 2). A solution of molybdenum carbene complex (1.00 mmol) and alkyne (1.50 mmol) in THF was refluxed under nitrogen until all carbene complex was consumed. The progress of the reaction was monitored by routine TLC for the disappearance of carbene complex.

The mixture was then cooled to 25°C, and the solvent was removed on a rotary evaporator, final purification was achieved by flash chromatography on silica gel. Eluting with 29:1 hexane-ethyl acetate yielded unreacted alkyne. Eluting with 19:1 hexane-ethyl acetate followed by 9:1 hexane-ethyl acetate yielded the cycloheptadienone derivatives.

4.3.2. Reaction of carbene complex 17 with ethynylferrocene (25A) (Table 2, Entry A). General procedure I was followed using carbene complex **17** (0.1 g, 0.311 mmol) and ethynylferrocene (**25A**) (0.1 g, 0.476 mmol). No product other than decomposition and/or starting material was isolated.

4.3.3. Reaction of carbene complex 17 with ferrocenylpropyne (25B) (Table 2, Entry B). General procedure I was followed using carbene complex **17** (0,14 g, 0.446 mmol) and ferrocenylpropyne (**25B**) (0.15 g, 0.66 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, three fractions were isolated. The product in the first fraction (R_f = 0,56 in 9:1 hexane/ethyl acetate) was assigned as (2*Z*,4*E*)-2-ferrocenyl-4-methoxy-3-methylcyclohepta-2,4-dienone (**26B**) (0.07g, 47%). The product in the second fraction (R_f = 0,32 in 9:1 hexane/ethyl acetate) was identified as (2*Z*,4*E*)-7-ferrocenyl-7-hydroxy-5-methoxy-6-methylcyclohepta-2,4-dienone (**28B**) (0.02 g, 14%). The product in the third fraction (R_f = 0,21 in 9:1 hexane/ethyl acetate) was assigned as (*Z*)-3-ferrocenyl-2-methyl-cyclohept-2-ene-1,4-dione (**27B**) (0.017 g, 12%).

26B: ^{1}H-NMR ($CDCl_3$): δ 5.13 (t, 1H, *J* = 7.3 Hz), 4.41 (s, 2H), 4.28 (s, 2H), 4.08 (s, 5H), 3.49 (s, 3H), 2.86 (t, 2H, *J* = 6.4 Hz), 2.36 (q, 2H, *J* = 6.8), 1.93 (s, 3H); ^{13}C-NMR: ($CDCl_3$): δ 206.1 (C), 158.1 (C), 137.7 (C), 132.1 (C), 98.5 (CH), 79.2 (C), 69.7 (CH), 69.5 (CH), 68.8 (CH), 54.6 (CH_3), 51.6 (CH_2), 20.1 (CH_2), 16.5 (CH_3); IR (CH_2Cl_2): 3052 (w), 1683 (m), 1629 (vw), 1422 (w), 1362 (w), 1272 (vs), 1258 (vs), 1203 (w), 1130 (w), 1105 (vw), 893 (w) cm^{-1}. MS (EI): 336.2 (M^+), 334.2, 308.2, 293.1, 255.0, 227.0, 199.1, 186.0, 153.1, 129.1, 121.0, 115.1; HRMS (EI); Calculated for $C_{19}H_{20}FeO_2$: 336.0813. Found: 336.0816.

27B: ^{1}H-NMR ($CDCl_3$): δ 4.49 (s, 2H), 4.43 (s, 2H), 4.16 (s, 5H), 2.83 (t, 2H, *J* = 6.8 Hz), 2.61 (t, 2H, *J* = 6.0 Hz), 2.04 (p, 2H, *J* = 6.3 Hz), 2.01 (s, 3H); ^{13}C-NMR: ($CDCl_3$): δ 204.2 (C), 203.3 (C), 148.5 (C), 134.7 (C), 70.6 (CH), 70.3 (CH), 69.7 (CH), 43.2 (CH_2), 41.6 (CH_2), 17.2 (CH_2), 16.3 (CH_3); IR (CH_2Cl_2): 3052 (s), 2985 (vw), 1696 (m), 1663 (m), 1420 (w), 1272 (vs), 1260 (vs) 1108 (vw), 895 (w), 826 (vw) cm^{-1}. MS (EI): 322.1 (M^+), 320.1, 294.1, 277.1, 258.0, 257.0, 229.0, 199.0, 167.1, 149.1, 121.0; HRMS (EI); Calculated for $C_{18}H_{18}FeO_2$: 322.0656. Found: 322.0659.

28B: ^{1}H-NMR ($CDCl_3$): δ 6.58 (q, 1H, *J* = 8.7 Hz), 5.99 (d, 1H, *J* = 12.5 Hz), 4.94 (d, 1H, *J* = 8.7 Hz), 4.39 (s, 1H), 4.23 (s, 1H), 4.13 (s, 1H), 4.07 (s, 6H), 3.92 (s, 1H), 3.42 (s, 3H), 2.53 (q, 1H, *J* = 6.3 Hz), 1.12 (d, 3H, *J* = 7.3 Hz); ^{13}C-NMR: ($CDCl_3$): δ 196.2 (C), 172.2 (C), 138.4 (CH), 118.9 (CH), 93.4 (CH), 87.9 (C), 66.7 (C), 65.6 (CH), 65.1 (CH), 64.9 (CH), 64.2 (CH), 53.6 (CH_3), 46.4 (CH), 9.08 (CH_3); IR (CH_2Cl_2): 3053 (s), 2981 (m), 2352 (w), 1569 (m), 1426 (w), 1277 (vs), 1259 (vs), 1168 (w), 1073 (vw), 898 (m) cm^{-1}. MS (EI): 352.2 (M^+), 336.2, 322.1, 287.1, 269.1, 243.1, 214.1, 186.1, 139.1, 121.0, 1151; HRMS (EI); Calculated for $C_{19}H_{20}FeO_3$: 352.0762. Found: 352.0759.

4.3.4. Reaction of carbene complex 17 with ferrocenylpropyne (25B) in the presence of triphenylphosphine (Table 2, Entry C). General procedure I was followed using carbene complex **17** (0,14 g, 0.446 mmol), ferrocenylpropyne (**25B**) (0.15 g, 0.66 mmol) and triphenylphosphine (0.446 mmol, 0.12 g). After chromatographic purification using 9:1 hexane-ethyl acetate as the eluent, two fractions were collected. The product in the first fraction (R_f = 0,32 in 9:1 hexane/ethyl acetate) was assigned (2Z,4E)-7-ferrocenyl-7-hydroxy-5-methoxy-6-methylcyclohepta-2,4-dienone (**28B**) (0.02 g, 14%). The product in the second fraction (R_f = 0,21 in 9:1 hexane/ethyl acetate) was assigned as (Z)-3-ferrocenyl-2-methyl-cyclohept-2-ene-1,4-dione (**27B**) (0.031 g, 22%).

4.3.5. Reaction of carbene complex 17 with 25C (Table 2, Entry D). General procedure I was followed using carbene complex **17** (0.113 g, 0.354 mmol) and (2-ferrocenylethynyl)trimethylsilane (**25C)** (0.2 g, 0.708 mmol). No product other than decomposition and/or starting material was isolated.

4.3.6. Reaction of carbene complex 17 with 1-ferrocenyl-3-phenylprop-1-yne (25D) (Table 2, Entry E). General procedure I was followed using carbene complex **17** (0.082 g, 0.25 mmol) and 1-ferrocenyl-3-phenylprop-1-yne (**25D**) (0.12 g, 0.38 mmol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, one fraction was isolated. The product in the fraction (R_f = 0.51 in 4:1 hexane/ethyl acetate) was assigned as 3-benzyl-2-ferrocenyl-4-methoxycyclohepta-2,4-dienone (**26D**) (0.072g, 70%).

26D: ^{1}H-NMR ($CDCl_3$): δ 7.34-7.28 (m, 3H), 7.19 (dd, 2H, J = 7.8 Hz), 5.13 (t, 1H, J = 7.3 Hz), 4.41 (t, 2H, J = 2.0 Hz), 4.25 (t, 2H, J = 1.8 Hz), 4.08 (s, 5H), 3.80 (s, 2H), 3.36 (s, 3H), 2.98 (t, 2H, J = 6.7 Hz), 2.45 (q, 2H, J = 7.0 Hz). ^{13}C-NMR: ($CDCl_3$): δ 205.728 (C), 157.135 (C), 139.764 (C), 133.505 (C), 128.347 (CH), 128.039 (CH), 125.895 (CH), 99.739 (CH), 78.266 (C), 69.545 (CH), 69.254 (CH), 69.102 (CH), 67.077 (C), 54.593 (CH_3), 51.651 (CH_2),

35.126 (CH_3), 20.297 (CH_2). IR (CH_2Cl_2): 3056 (vs), 2981 (m), 2682 (w), 2301 (m), 1688 (m), 1627 (w), 1424 (s), 1260 (vs), 1049 (w), 902 (s) cm^{-1}. MS (EI): 412.2 (M^+), 398.2, 384.2, 370.2, 331.1, 318.1, 303.1, 275.1, 253.1, 217.1, 213.0, 186.1, 151.2; HRMS (EI); Calculated for $C_{25}H_{24}FeO_2$: 412.1126. Found: 412.1130

4.3.7. Reaction of carbene complex 17 with 1-ferrocenyl-2-phenylethyne (25E) (Table 2, Entry F). General procedure I was followed using carbene complex **17** (0,112 g, 0.35 mol) and 1-ferrocenyl-2-phenylethyne (**25E**) (0.15 g, 0.53 mol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, two fractions were isolated. The product in the first fraction (R_f = 0,57 in 4:1 hexane/ethyl acetate) was identified as 2-ferrocenyl-4-methoxy-3-phenylcyclohepta-2,4-dienone (**26E**) (0,100g, 72%). The product in the second fraction (R_f = 0,18 in 4:1 hexane/ethyl acetate) was identified as 2-ferrocenyl-3-phenylcyclohept-2-ene-1,4-dione (**27E**) (0,113g, 10%).

26E: ^{1}H-NMR ($CDCl_3$): δ 7.29-7.26 (m, 3H), 7.05 (did, 2H, J = 7.3 Hz), 5.46 (t, 3H, J = 7.3 Hz), 4.15 (t, 2H, J = 1.7 Hz), 4.09 (s, 5H), 3.87 (t, 2H, J = 1.7 Hz), 3.38 (s, 3H), 3.03 (t, 2H, J = 6.7 Hz), 2.67 (q, 2H, J = 1.7 Hz) ^{13}C-NMR: (Aseton-d_6): δ 204.6 (C), 157.5 (C), 139.1 (C), 138.6 (C), 133.6 (C), 129.5 (CH), 127.9 (CH), 127.1 (CH), 100.4 (CH), 77.5 (C), 69.6 (CH), 69.3 (CH), 68.9 (CH), 54.1 (CH_3), 51.5 (CH_2), 19.9 (CH_2); IR (CH_2Cl_2): 3049 (vs), 2988 (s), 2680 (vw), 2521 (vw), 2407 (vw), 2298 (m), 1682 (w), 1418 (m), 1259 (vs), 1158 (w), 900 (s) cm^{-1}. MS (EI): 398.2 (M^+), 370.2, 339.2, 317.1, 303.1, 261.1, 226.1, 202.1, 186.1, 165.1, 127.2, 119.1; HRMS (EI); Calculated for $C_{24}H_{22}FeO_2$:398.0969. Found: 398.0972.

27E: ^{1}H-NMR ($CDCl_3$): δ 7.34-7.29 (m, 3H), 7.02 (did, 2H, J = 6.5 Hz), 4.19 (t, 2H, J = 1.8 Hz), 4.08 (s, 5H), 3.80 (t, 3H, J = 1.8 Hz), 2.90 (t, 2H, J = 6.0 Hz), 2.58 (t, 2H, J = 6.5 Hz), 2.15 (p, 2H, J = 6.3 Hz). ^{13}C-NMR: ($CDCl_3$): δ 197.578 (C), 156.268 (C), 137.793 (C), 135.324 (C), 130.173 (CH), 128.330 (CH), 127.121 (CH), 81.718 (C), 70.501 (CH), 70.198 (CH), 69.629 (CH), 38.201 (CH_2), 30.721 (CH_2), 22.715 (CH_2); IR (CH_2Cl_2): 3048 (vs), 2985 (s), 2680 (vw), 2305 (m), 1650 (m), 1578 (w), 1422 (s), 1358 (w), 1265 (vs), 1175 (w), 891 (s) cm^{-1}. MS (EI): 356.2 (M^+), 400.2, 384.2, 357.2, 300.2, 291.1, 263.1, 235.1, 202.1, 178.1, 165.1, 152.1, 112.0; HRMS (EI); Calculated for $C_{23}H_{20}FeO_2$: 384.0813. Found: 384.0816.

4.3.8. Reaction of carbene complex 17 with 1,2-diferrocenylethyne (25F) (Table 2, Entry G). General procedure I was followed using carbene complex **17** (0,054 g, 0.17 mol) and 1-ferrocenyl-2-phenylethyne (**25E**) (0.10 g, 0.25 mol). After chromatographic purification using 9:1 hexane-ethyl acetate as eluent, two fractions were isolated. The product in the first fraction (R_f = 0,42 in 9:1 hexane/ethyl acetate) was assigned as (2*Z*,4*E*)-2,3-diferrocenyl-4-methoxycyclohepta-2,4-dienone (**26F**) (0,012g, 15%). The product in the second fraction (R_f = 0,22 in 9:1 hexane/ethyl acetate)was identified as 4-cyclopropyl-2,3-diferrocenyl-4-methoxy-cyclobut-2-enone (**29F**) (0.006g, 8%).

26F: ^{1}H-NMR ($CDCl_3$): δ 5.09 (t, 1H, J = 7.4 Hz), 4.21 (s, 2H), 4.17 (s, 2H), 4.12 (s, 2H), 4.11 (s, 5H), 4.08 (s, 5H), 3.98 (s, 2H), 3.64 (s, 3H), 2.91 (t, 2H, J = 3.2 Hz), 2.44 (q, 2H, J = 6.9 Hz); IR (CH_2Cl_2): 3054 (vs), 2989 (s), 2682 (vw), 2406 (w), 2304 (m), 1700 (w), 1418 (s), 1266 (vs), 1102 (w), 897 (s). cm^{-1}. MS (EI): 394.1 (M^+), 522.2, 506.2, 476.2, 438.1, 394.1, 362.2, 308.1, 242.1, 186.0, 113.1; HRMS (EI); Calculated for $C_{28}H_{26}Fe_2O_2$: 506.0632. Found: 506.0636.

29F: ^{1}H-NMR ($CDCl_3$): δ 5.02 (t, 1H), 4.91 (s, 2H), 4.89 (s, 1H), 4.61 (s, 1H), 4.58 (s, 1H), 4.39 (t, 2H), 4.27 (s, 5H), 4.18 (s, 5H), 3.27 (s, 3H), 0.71-0.68 (m, 2H), 0.66-0.55 (m, 2H), 0.52-0.41 (m, 1H). MS (EI): 506.2 (M^+), 478.2, 464.2, 436.1, 396.1, 394.1, 281.1, 253.1, 203.1, 186.1, 165.1, 121.0; HRMS (EI); Calculated for $C_{28}H_{26}Fe_2O_2$: 506.0632. Found: 506.0629.

4.3.9. Reaction of carbene complex 17 with 25G (Table 2, Entry H). General procedure I was followed using carbene complex **17** (0.127 g, 0.397 mol) and **25G** (0.142 g, 0.596 mol). No product other than decomposition and/or starting material was isolated.

4.4. Data Collection for X-Ray Crystal Structure Analysis. X-Ray crystal structure analysis of compound **26D** was performed at Ondokuz Mayıs University, Deparment of Physics, by using the Stoe IPDS-II diffractometer. Data collection: *X-AREA* [102]; cell refinement: *X*- Area; data reduction: *X-RED32* [102]; program(s) used to solve structure: *SHELX97* [103]; program(s) used to refine structure: *SHELXL97* [104]; molecular graphics: *ORTEP-3* [105], CAMERON [106] and PLUTON [107]; software used to prepare material for publication: *WinGX* [108].

REFERENCES

[1] Hart, H.; Hart, D. J.; Craine, L. E. *Organic Chemistry*, 9th Ed., Houghton Muflin: New York, 1995.

[2] Elschenbroich, Ch.; Salzer, A. *Organometallics*, 2th Ed., VCH Puplisher Inc: New York, 1992.

[3] Birmingham, J. M.; Wilkinson, G. *J. Am. Chem. Soc*. **1956**, *78*, 42.

[4] Fischer, E. O.; Fischer, H. *J. Organomet. Chem.* **1966**, *6*, 141.

[5] Calderazzo, F.; Pappalardo, R.; Cosi, S. *J. Inorg. & Nucl. Chem.* **1966**, 28, 987.

[6] Fischer, E. O.; Fischer, H. *J. Organomet. Chem.* **1965**, *3*, 181.

[7] Yamamoto, A. *J. Organomet. Chem.* **2000**, *1*, 600.

[8] Yamamoto, A. *Pure Appl. Chem*. **2001**, *2*, 205.

[9] King, B. R. *Transition-Metal Organometallic Chemistry*, Academic Press, New York, 1969.

[10] Eisch, J. *The Chemistry of Organometallic compounds,* Macmillan Press, New York, 1967.

[11] (a) Bruner, H. *J. Organomet. Chem*. **1986**, *300*, 39-56. (b) Knowles, W. S. *Acc Chem. Res*. **1983**, *16*, 106-112. (c) Halpern, J. *Pure App. Chem* **1983**, *55*, 99.

[12] Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules* 2th Ed., University Science Books, CA, 1999.

[13] Fischer, E. O.; Maasböl, A. *Angew. Chem. Int. Ed. Engl*. **1964**, *8*, 580.

[14] Kirmse, W. *Carbene Chem.* Academic Press, New York, 1971.

[15] Brookhart, M.; Studabaker, W. B. *Chem. Rew.* **1987**, *87*, 411.

[16] Brown-Wensley, K. A.; Buchwald, S. L.; Cannizzo, L.; Clowson, L.; Ho, S.; Meinhardt, D.; Stille, J. R.; Staus, D,; Grubbs, R. H. *Pure Appl. Chem.* **1983**, *55*, 1733.

[17] de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed*. **2000**, *39*, 3964.

[18] (a) Dötz, K. H.; Fischer E. O.; Hoffman, P.; Kreissel, F. R.; Schubert, U.; Weiss, K. *Transition Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, Fl, 1984. (b) Dötz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689.

[19] (a) Wullf, W. D. In *Advances in Metal-Organic Chemistry;* Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1. (b) Wullf, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813.

[20] Mol, J. C. *J. Mol. Catal.* **1982**, *15*, 35.

[21] (a) Mansuy, D. *Pure Appl. Chem.* **1987**, *59*, 759. (b) Groves, J. T.; Avaria Neisser, G. E.; Fish, K. M.; Imachi, M.; Kuczkowski, R. L. *J. Am. Chem. Soc*. **1986,** *108*, 3837.

[22] Schrock, R .R. *J. Am. Chem. Soc*. **1974**, *96*, 6796.

[23] Herndon, J. W. *Coordination Chem. Rew*. **2000**, *206*, 237.

[24] (a) Herndon, J. W. *Tetrahedron* **2000**, *56*, 1257. (b) Barluenga, J.; Florez, J.;Fananas, F. J. *J. Organomet. Chem*. **2001**, *5*, 624. (c) Sierra, M. A. *Chem. Rev.* **2000**, *100*, 591. (d) Aumann, R. *Eur. J. Org. Chem*. **2000**, 17.

[25] For a rewiev of transition metal carbene complexes, see: Wullf, W.D., In *Comprehensive Organometallic Chemistry II;* Abel, E. W.; Stone, F. G. A.; Wilkonson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 470-484.

[26] Schubert, U.; Hartley, F. R.; Patai, S., *The Chemistry of the Metal-Carbon Bonds* Wiley: Chichester, 1982; p 233.

[27] Herndon, J. W. *Tetrahedron* **2000**, 56.

[28] Wulff, W. D.; Yang, D. C.; Murray, C. K. *Pure Appl. Chem*. **1988**, *60*, 137

[29] Daniel, F.; Sigano, M. *Chem. Rew.* **1996**, *96*, 271.

[30] (a) Dötz, K. H.; Fischer, E. O. *Chem. Ber.* **1972**, *105*, 1356-1367. (b) Dötz, K. H.; Fischer, E. O. *Chem. Ber.* **1972**, *105*, 3966-3973. (c) Dötz, K. H.; Fischer, E. O. *Chem. Ber.* **1970**, *103*, 1273-1278.

[31] Wienand, A.; Reissig, H. U. *Organometallics* **1990**, *9*, 3133-3142.

[32] Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc*. **1990**, *112*, 3642.

[33] Wulff, W. D. *Organometallics* **1998**, *17*, 3116.

[34] Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc*. **1986**, *108*, 5229.

[35] Kreissel, F. R.; Fischer, E. O.; Kreiter, C. G. *J. Organomet. Chem*. **1973**, *57*, 9.

[36] Chan, K. S.; Yeung, M. L.; Chan, W. K.; Wang, R. J.; Mak, T. C. W. *J. Org. Chem*. **1995**, *60*, 1741.

[37] Barluenga, J.; Ferneandez-Mary, F.; Aguilar, E.; Vindo, A. L.; Olano, B. *Tetrahedron Lett*. **1998**, *39*, 4887.

[38] Barluenga, J.; Montserrat, J.; Florez, J.; Garcya-Granda, S.; Martin, E. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1392.

[39] Wulff, W. D.; Faron, K. L.;. Rheingold, A. L. *J. Chem. Soc. Perkin Trans* **1999**, *1*, 197.

[40] Barluenga, J.; Bernad, P. L.; Concellon, J. M.; Pineranicolas, A.; Garcia-Granda, S. *J. Org. Chem*. **1997**, *62*, 6870.

[41] Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rew*. **1999**, *28*, 187.

[42] Dötz, K. H.; *Angew. Chem. Int. Ed. Engl.* **1984,** *23***,** 587-608.

[43] Wullf, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming I.; Paquatte , L. A., Eds.; Pergamon Press: Oxford, 1991.

[44] (a) Yamashita, A.; Toy, A.; Watt, W.; Munchmore, C. R. Tetrahedron Lett. **1988**, *28*, 3403-3406. (b) Yamashita, A. Tetrahedron Lett. **1986,** *27,* 5915. (c) Pruskill, I.; Schubert, U.; Ackerman, K.; *Dötz, K. H. Chem. Ber.* **1983,** *116*, 2337-2343.

[45] Wulff, W. D; McCallum J. S.; Kunng F.; Gilbertson, S. R. A. *Organometallics* **1988**, *7*, 2346-2360 and references cited there. (b) Semmelhack, M. F.; Park, *Organometallics* **1986,** *5***,** 2550**.**

[46] (a) Chan, K. S.; Peterson, G. A.; Branvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wullf, W. D. *J. Organomet. Chem.* **1987**, *334*, 9-56.

[47] Wullf, W. D.; Gilbertson, S. R.; Springer, J. P. J. Am. Chem. Soc. **1985**, *107*, 5823-5824. (b) Tang, P. C.; Wullf, W. D. *J. Am. Chem. Soc*. **1984,** *106*, 1132-1133.

[48] Dötz, K. H.; Kuhn, W. *Angew. Chem. Int. Ed. Engl*. **1983**, *22*, 732.

[49] Dötz, K. H.; Pruskill, I.; Mühlemeier, J.; *Chem. Ber*. **1982**, *115*, 1278.

[50] Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Speiss, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*, 5803.

[51] Wulff, W. D; McCallum J. S.; Kunng F. A. *J. Am. Chem. Soc*. **1988**, *110*, 7419.

[52] Dötz, K. H.; Popall, M. *Chem. Ber*. **1988**, *121*, 665.

[53] Yamashita, A. *J. Am. Chem. Soc*. **1985**, *107*, 665.

[54] Wulff, W. D; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461.

[55] Lewis, K. E.; Golden, D. M.; Smith, G. P. *J. Am. Chem. Soc*. **1984**, *106*, 3905-3912.

[56] (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry,* 2nd Ed., University Science Books, Mill Valley, CA. **1987** (b) Li, J.; Schreckenbach, G.; Ziegler, T. *J. Am. Chem.* **1995***, 117,* 486.

[57] Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Chamberlin, S.; Faron, K L.; Kim, O. K.; Murray, C. K.; Xu, Y.-C.; Yang, D. C.; Darling, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 1359-1376.

[58] Anderson, B. A.; Wulff, W. D. *J. Am. Chem. Soc*. **1990**, *112*, 8615-8617.

[59] Herndon, J. W.; Tumer, S. U.; Schnatter, W. F. K. *J. Am. Chem. Soc*. **1988,** *110*, 3334-3335.

[60] Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc*. **1992**, *114*, 8394.

[61] Yan , J.; Zhu, J.; Matasi, J.J.; Herdon, J. W. *J. Org. Chem.* **1999**, *64*, 400.

[62] Mikolajzyk, M.; Mikina, M.; Zurawinski, R. *Pure Appl. Chem.* **1999**, 473.

[63] Herndon, J. W.; Zora, M.; Patel, P. P.; Chatterjee, G.; Matasi, J. J.; Tumer, S. U. *Tetrahedron* **1993**, *53*, 550.

[64] (a) Colchicine synthesis: Muzaffar, A.; Brossi, A. *Pharmacol. Ther*. **1991**, *49*, 105. (b) Phorbol synthesis: Wender, P. A.; Mcdonald, F.E. *J. Am. Chem. Soc*. **1990**, *112*, 4956.

[65] Herndon, J. W.; Patel, P. P.; Chatterjee, G.; Matasi, J. J.; Tumer, S. U.; Harp, J.; Reid, M. D. *J. Am. Chem. Soc*. **1991,** 113, 7808.

[66] (a) Naturally Occurring Phorbol Esters*;* Evans, F. J., Ed.; CRC: Boca Raton, FL, 1986. (b) Mechanism of Tumor Promotion*;* Slaga, T. J., Ed.; CRC: Boca Raton, FL, 1984; Vols. I-IV. (d) Weinstein, I. B.; Galtoni-Celli, S.; Kirschmeier, P.; Lambert, M.; Hsiao, W. In *Biochem. Basis Chem Carcinogenesis;* Greim, H. et al., Eds.; Raven: New York, 1984; pp 193.

[67] (a) Harada, **S.;** Yamamoto, N.; Fujiki, H. *AIDS Res. Hum. Retroviruses* **1988,** *4* **,** 99**.** Poli, G.; Orenstein, J. M.; Kinter, A,; Folks, T. M.; Fauci, A. S. *Science* **1989,** 2*44***,** 575**.** (b) Weede, R. P. Posion in the Pot *: The Legacy of Lead S*outhern Illinios University Press: Carbondale and Edwardswille, **1984**, 83.

[68] Shriver, D. F.; Atkins, P. W.; Langford, C. H. Inorganic Chemistry, 2nd Ed., Oxford University Press: Oxford, 1994.

[69] Jonas, K. *Angew. Chem. Int. Ed. Engl*. **1985,** *24,* 295-297.

[70] Kealy, T. J.; Pauson, P. L. *Nature* **1961**, *168*, 1039.

[71] Miller, S. A.; Tebboth, J. A.; Tremaine, J. F. *J. Chem. Soc*. **1952,** 632.

[72] Wilkonson, G.; Rosenblum, M.; Whiting, M. C.; Woodward, R. B.; *J. Am. Chem. Soc*. **1952**, *74*, 2125.

[73] Togni, A.; Hayashi, T. Eds. *Ferrocenes*; VCH: Weinheim, Germany **1995**.

[74] Kajdas, C.;Domonik, M.; Firkowski, A.; Dybrowski, J. R.; Misterkiewicz, B. Tribochemistry Alcohols Based on Ether and Homomorphs. *Fluid Phase Equilib.* **1986**, *25*, 113-128.

[75] Mason, R. W.; McGrouther, K.; Ranatunge-Bandarage, P. R.; Robinson B. H.; Simpson, J. Toxicology and Antitumor Activity of Ferrocenylamines and Platinum Derivatives. *Appl. Organomet. Chem.* **1999**, *13*, 163-173.

[76] Haiduc, I.; Silvestru, C. *Organometallics in Cancer Chemotherapy*; CRC. Press: Boca Raton, FL, 1989.

[77] Little, W. F. In Comprehensive Organometallic Chemistry; Scott, A. Ed.; Academic: New York, 1963, Vol. 1, pp 133.

[78] Köpf-Maier, P.; Köpf, H.; Neuse, E. W. *Cancer Res. Clin. Oncol.* **1984**, *108*, 336.

[79] Köpf-Maier, P.; Naturforsch, Z. *Biosci.* **1985**, *40*, 843-850.

[80] Osella, D.; Ferrali, M.; Zanello, P.; Laschi, F.; Fontani, M.; Nervi, C.; Cavigiolio G. *Inorg. Chim. Acta* **2000**, *306*, 42.

[81] Haslam, E. *Practical Polyphenolics-From Structure to Molecular Recognition and Physiological Action*; Cambridge University Press: Cambridge, 1998.

[82] Okuda, T.; Yoshida, T.; Hatano, T. Hydrolyzable tannins and related polyphenols. *Prog. Chem. Org. Nat. Prod.* **1995**, *66*, 1-117.

[83] Santos-Buelga, C.; Williamson, G. *Methods in Polyphenol Analysis*; RSC: Cambridge, **2003.**

[84] (a) Corder, R.; Douthwaite, J. A.; Lees, D. M.; Khan, N. Q.; Visen dos Santos, A. C.; Wood, E. E.; Carrier, M. J. Red *Nature* **2001**, *414*, 863-8 864. (b) Fremont, L. Biological effects of resveratrol. *Life Sci.* **2000**, *66*, 663-673.

[85] (a) Mueller, S. O.; Simon, S.; Chae, K.; Metzler, M.; Korach, K. S Phytoestrogens and their human metabolites show distinct agonistic a antagonistic properties on estrogen receptor alpha (ERalpha) and (ERbeta) in human cells. *Toxicol. Sci.* **2004**, *80*, 14-25. (b) Bowers, J. L.; Tyulmenkov, V. V.; Jernigan, S. C.; Klinge, C. M. *Endocrinology* **2000**, *141*, 3657-3667.

[86] M. J.; Duncan, J. *Arch. Biochem. Biophys.* **2000**, *381*, 253-263.

[87] Schrager, S.; Potter, B. E.. *Am. Fam. physician* **2004**, *69*, 2395-2400.

[88] (a) Köpf-Maier, P.; Köpf, H. *Chem. Rev.* **1987**, *87*, 1137. (b) Köpf Maier, P.; H. *Struct. Bond.* **1988**, *70*, 105.

[89] (a) Shen, W.-C.; Beloussow, K.; Meirim, M. G.; Neuse, E. W.; Caldwell, G. *J. Inorg. Organomet. Polym.* **2000**, *10*, 51. (b) Neuse, E. W. *Macromol. Symp.* **2001**, *172*, 127. (c) Edwards, E. I.; Epton, R.; Marr, G. *J. Organomet. Chem.* **1976**, *122*, C49.

[90] (a) Edwards, E. I.; Epton, R.; Marr, G. *J. Organomet. Chem.* **1976**, *107*, 351. (b) Edwards, E. I.; Epton, R.; Marr, G. *Chem. Abstr.* **1977**, *87*, 728. (c) Edwards, E. I.; Epton, R.; Marr, G.; Rogers, G. K.; Thompson, K. J. *Spec. Publ. Chem. Soc.* **1977**, *128*, 92. (d) Edwards, E. I.; Epton, R.; Marr, G. *J. Organomet. Chem.* **1979**, *168*, 259.

[91] (a) Epton, R.; Marr, G.; Rogers, G. K. *J. Organomet. Chem.* **1976**, *110*, C42. (b) Epton, R.; Marr, G.; Rogers, G. K. *J. Organomet. Chem.* **1978**, *150*, 93. (c) Sawamura, M.; Sasaki, H.; Nakata, T.; Ito, Y. *Bull. Chem. Soc. Jpn.* **1993** *66*, 2725.

[92] (a) Delhaes, L.; Biot, C.; Berry, L.; Delcourt, P.; Maciejewski, L. A.; Camus, D.; Brocard, J. S.; Dive, D. *ChemBioChem* **2002**, *3*, 418. (b) Atteke, C.; Ndong, J. M. M.; Aubouy, A.; Maciejewski, L. A.; Brocard, J. S.; Lebibi, J.; Deloron, P. *J. Antimicrob. Chemother.* **2003**, *51*, 1021. (c) Beagley, P.; Blackie, M. A. L.; Chibale, K.; Clarkson, C.; Meijboom, R.; Moss, J. R.; Smith, P. J.; Su, H. *Dalton Trans.* **2003**, 3046. (d) Jaouen, G.; Top, S.; Vessieres, A.; Leclercq, G.; Quivy, J.; Jin, L.; Croisy, A. *C. R Acad. Sci. Paris* **2000**, *SerieIIc*, 89. (e) Top, S.; Vessie`res, A.; Cabestaing C.; Laios, I.; Leclercq, G.; Provot, C.; Jaouen, G. *J. Organomet. Chem.* **2001**, *637-639*, 500. (f) Top, S.; Vessie`res, A.; Leclercq, G.; Quivy, J.; Tang, J.;Vaissermann, J.; Huche´, M.; Jaouen, G. *Chem. Eur. J.* **2003**, *9*, 5223.

[92] Grevels, F. W.; Kuran, A.; Ozkar, S.; Zora, M. *J. Organomet. Chem*. **1999** *587*, 122.

[93] Polin, J.; Schottenberger, H.; Anderson, B.; Martin, S. F. *Org. Synt*. **1995**, *73*, 262.

[94] Gibson, S. E. *Transition Metals in Organic Synthesis*; Oxford University Press: Oxford, 1997.

[95] Doisneau, G.; Balavoine, G.; Khan-Fillebeen T. *J. Organomet. Chem*. **1992**, *425*, 113.

[96] Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura M. *J. Org. Chem.* **1993,** *58***,** 4716-4721.

[97] Sashuk, V.; Ignatowska, J.; Grela, K. *J. Org. Chem,* **2004.**

[98] Herndon, J. W.; Zora, M.; Patel, P. P.; Chatterjee, G.; Matasi, J. J.; Tumer, S. U. *Tetrahedron* **1993**, *49*, 5507-5530.

[99] Herndon, J. W; Tumer, S. U.; McMullen A. L. *J. Am. Chem. Soc.* **1992**, *114*, 8394-8404.

[100] Muthali, C.; Praveen, K. *J. Org. Chem.* **2000**, *65*, 3733.

[101] Schloegl, K.; Mahar, A. *Monatshefte fuer Chemie* **1962**, *93*, 861.

[102] *X-AREA* (Versions 1.18) and *X-RED32* (Versions 1.04). Stoe and Cie, Darmstadt, Germany.

[103] Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467-473.

[104] Sheldrick, G. M. *SHELXL97* **1997**, University of Gottingen, Germany.

[105] Farrugia, L. J. *J. Appl. Cryst*. **1997**, *30*, 565.

[106] Watkin, D. M.; Pearce, L. and Prout, C. K. *CAMERON* **1993,** Chemical Crystallography Laboratory, Oxford, England.

[107] Spek, A. L. *PLATON* **1998,** University of Utrecht, The Netherlends.

[108] Farrugia, L. J. *J. Appl. Cryst*. **1999**, *32*, 837-838

APPENDIX A

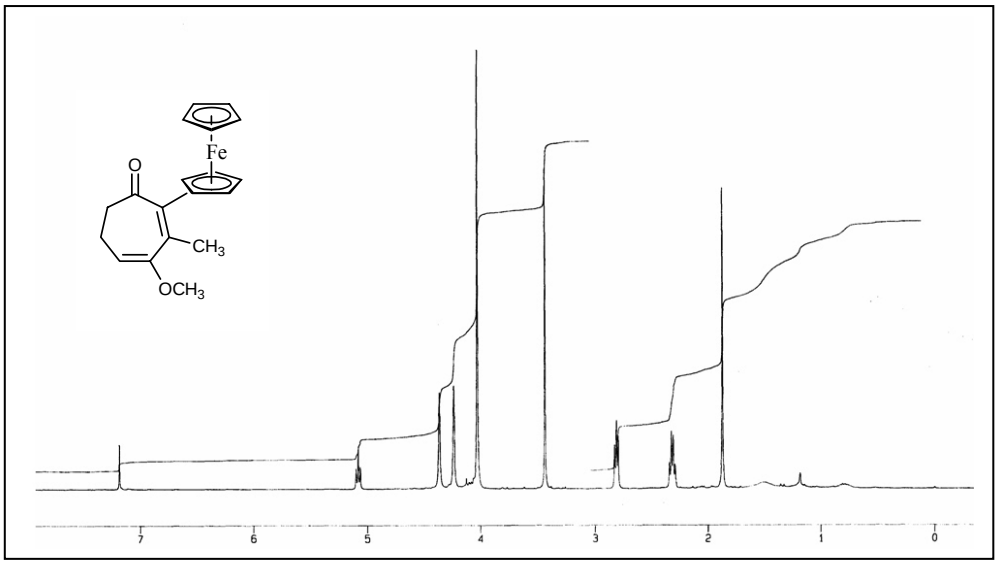

Figure A1. ^{1}H-NMR Spectrum of ferrocenyl cycloheptadienone **26B**

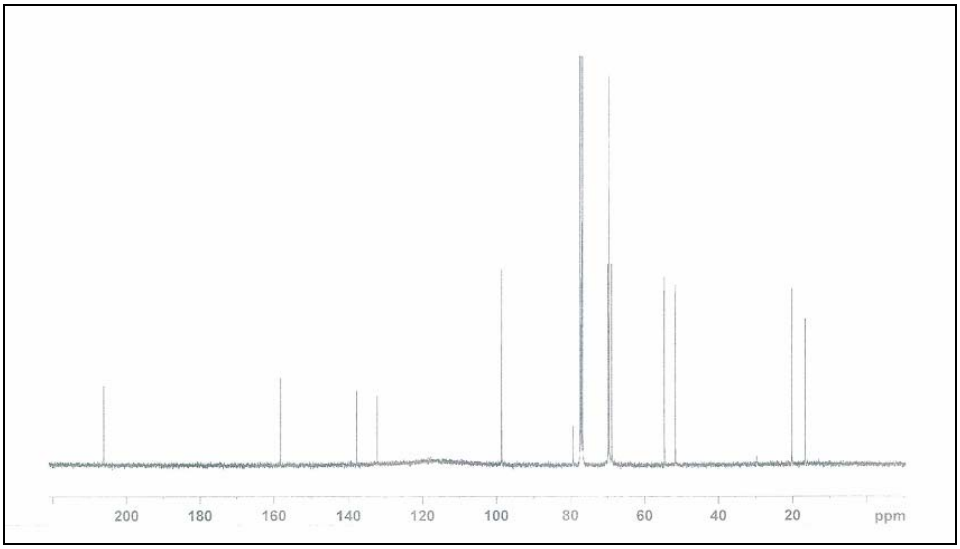

Figure A2. ^{13}C-NMR Spectrum of ferrocenyl cycloheptadienone **26B**

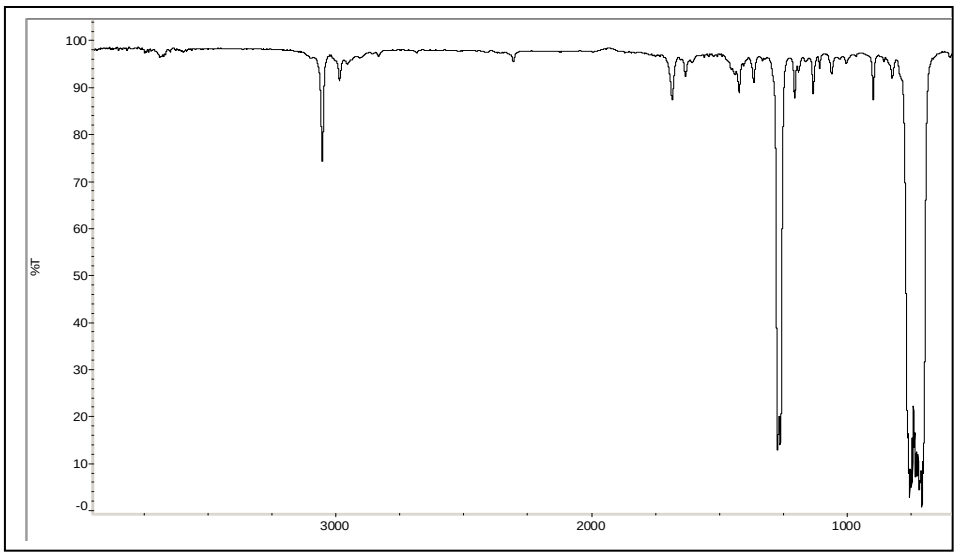

Figure A3. IR Spectrum of ferrocenyl cycloheptadienone **26B**

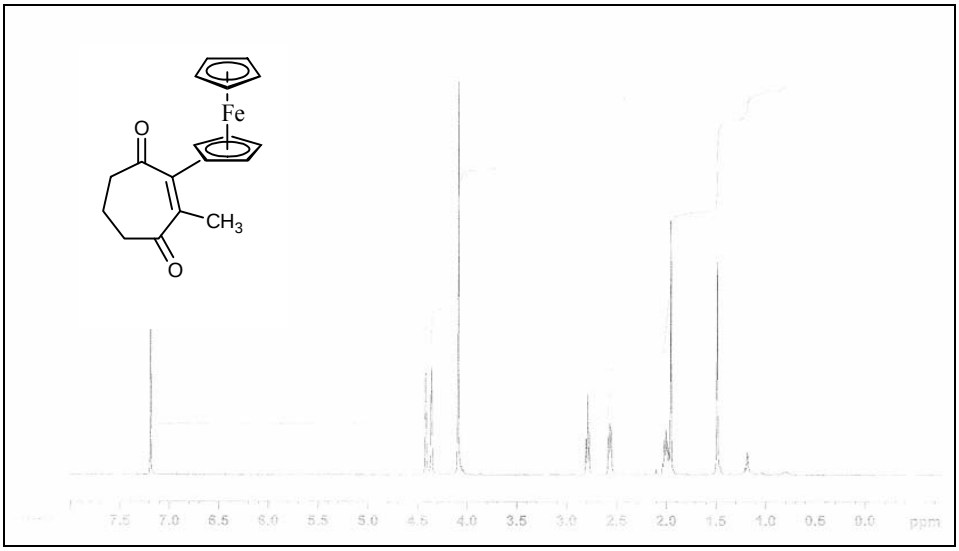

Figure A4. ^{1}H-NMR Spectrum of ferrocenyl cycloheptadienone **27B**

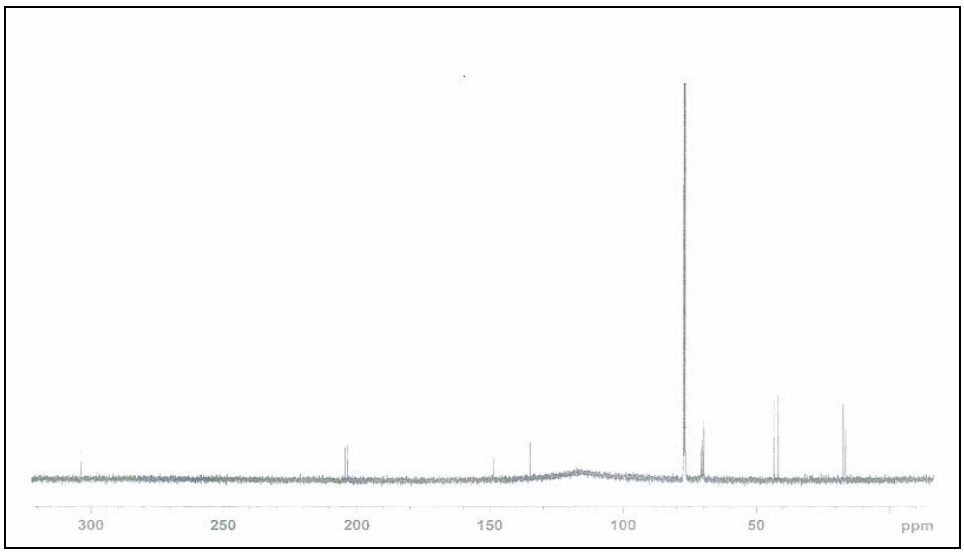

Figure A5. ^{13}C-NMR Spectrum of ferrocenyl cycloheptadienone **27B**

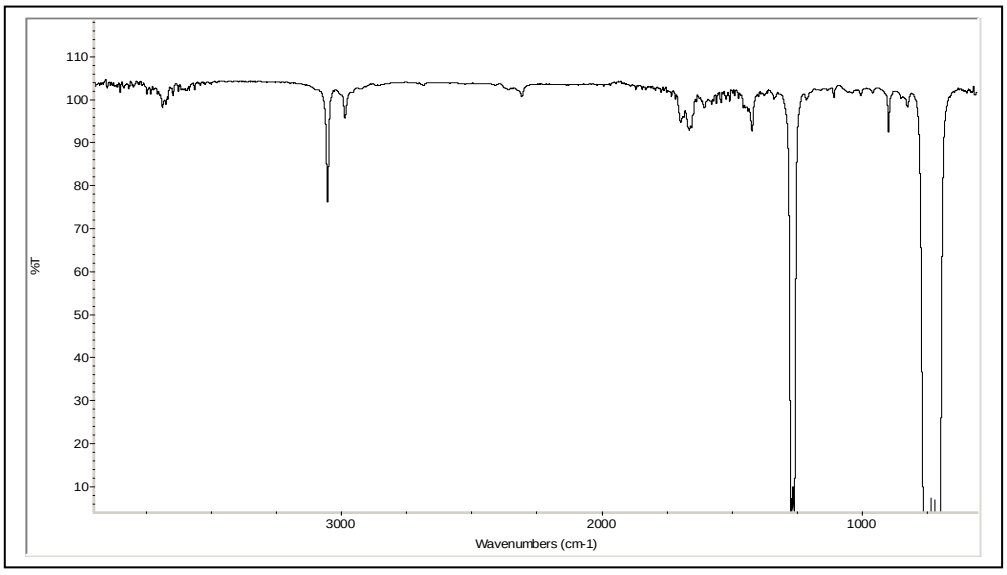

Figure A6. IR Spectrum of ferrocenyl cycloheptadienone **27B**

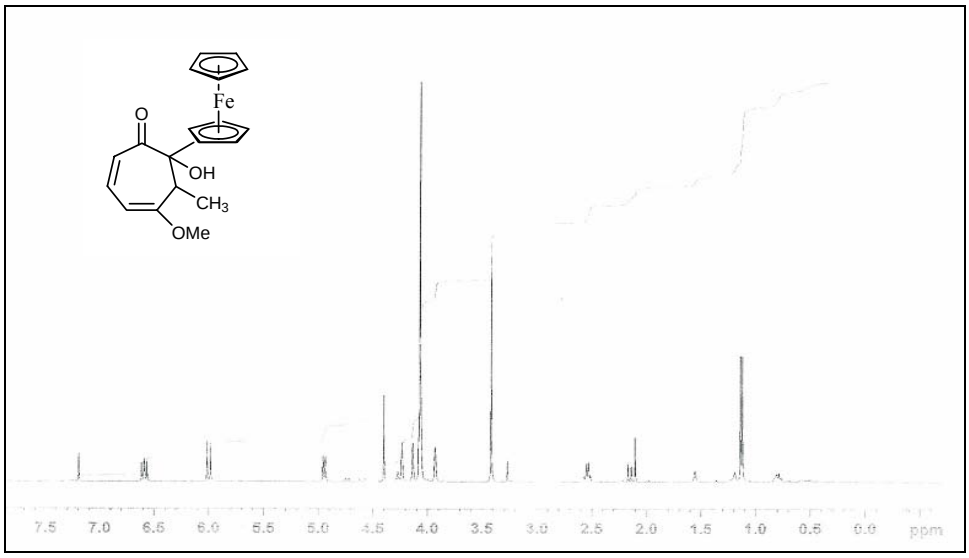

Figure A7. ^{1}H-NMR Spectrum of ferrocenyl cycloheptadienone **28B**

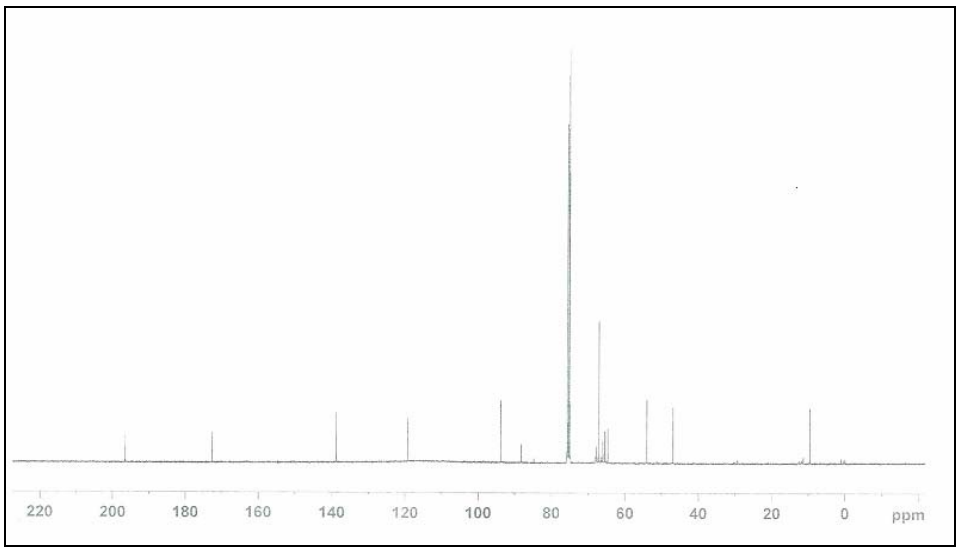

Figure A8. ^{13}C-NMR Spectrum of ferrocenyl cycloheptadienone **28B**

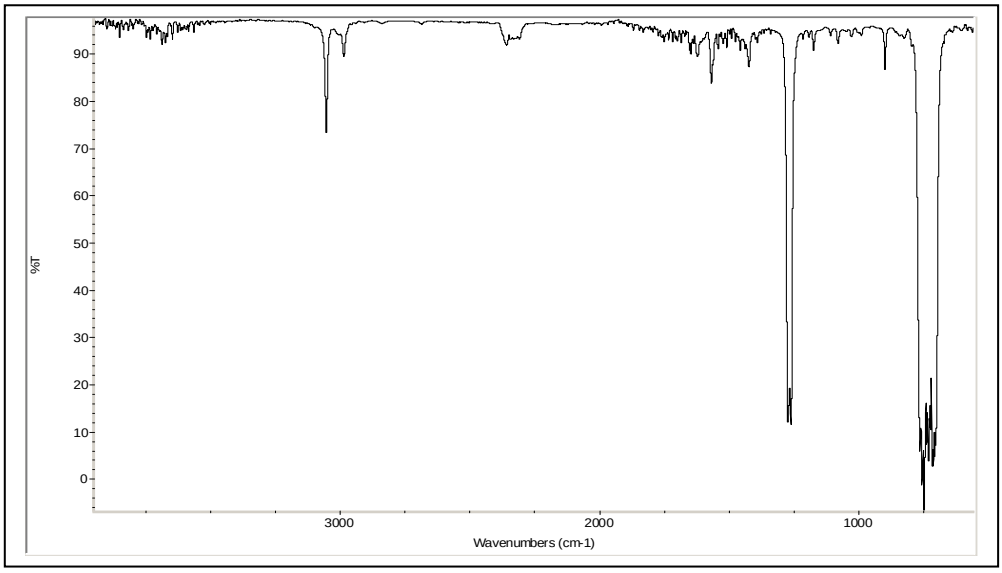

Figure A9. IR Spectrum of ferrocenyl cycloheptadienone **28B**

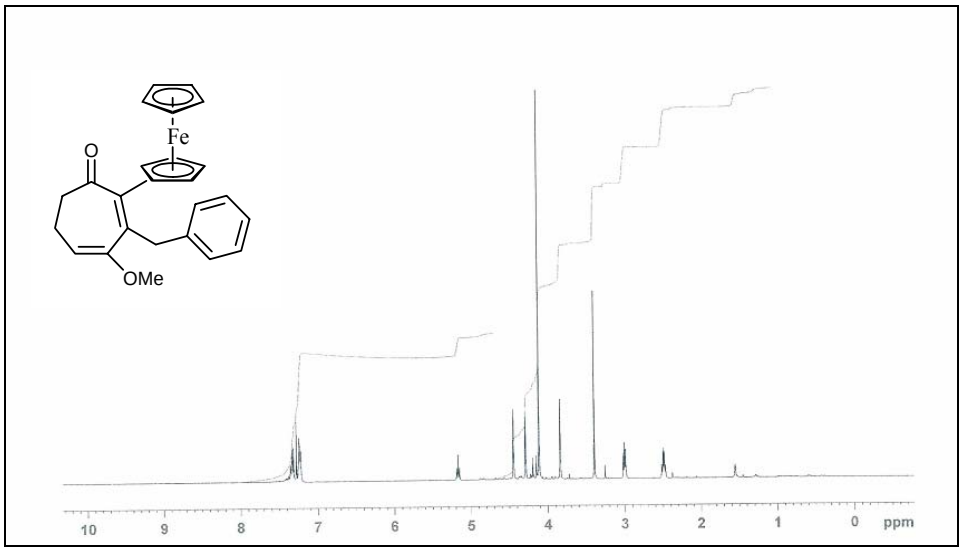

Figure A10. ^{1}H-NMR Spectrum of ferrocenyl cycloheptadienone **26D**

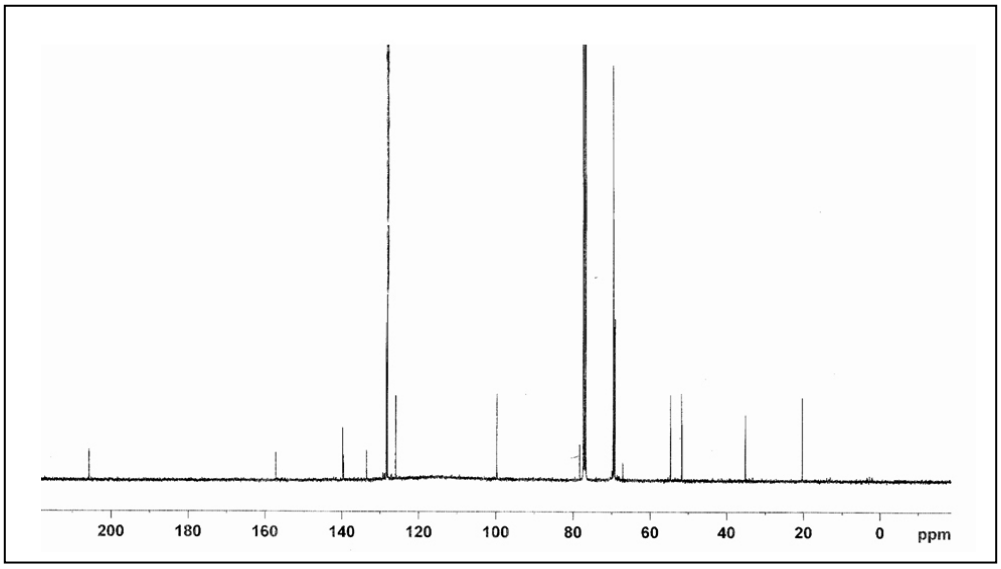

Figure A11. ^{13}C-NMR Spectrumof ferrocenyl cycloheptadienone **26D**

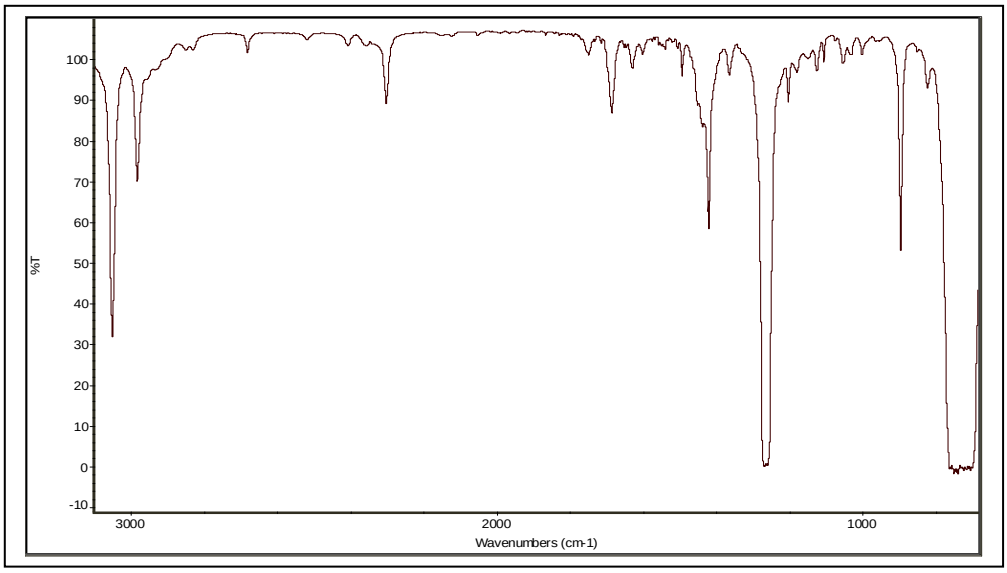

Figure A12. IR Spectrum of ferrocenyl cycloheptadienone **26D.**

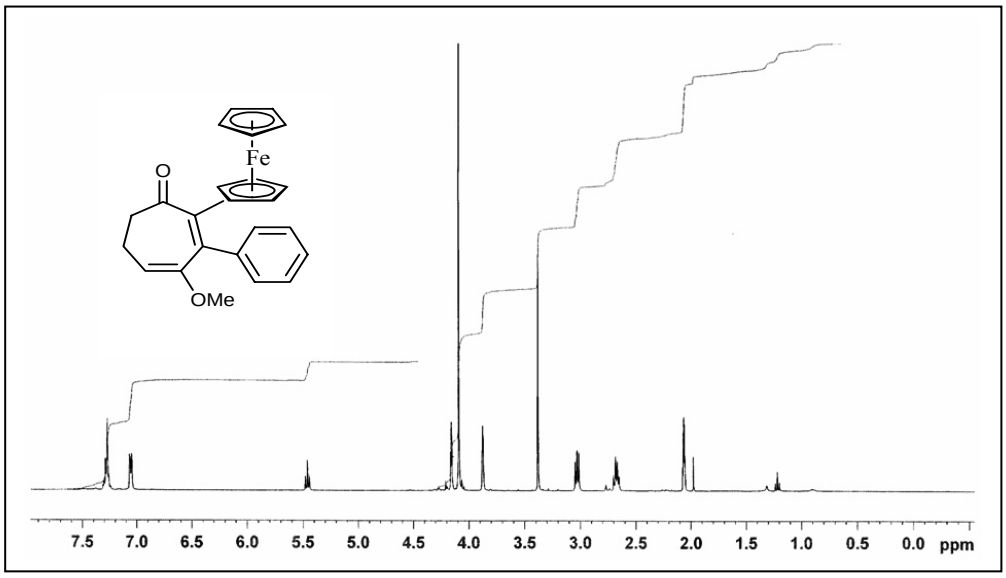

Figure A13. ^{1}H-NMR Spectrum of ferrocenyl cycloheptadienone **26E**

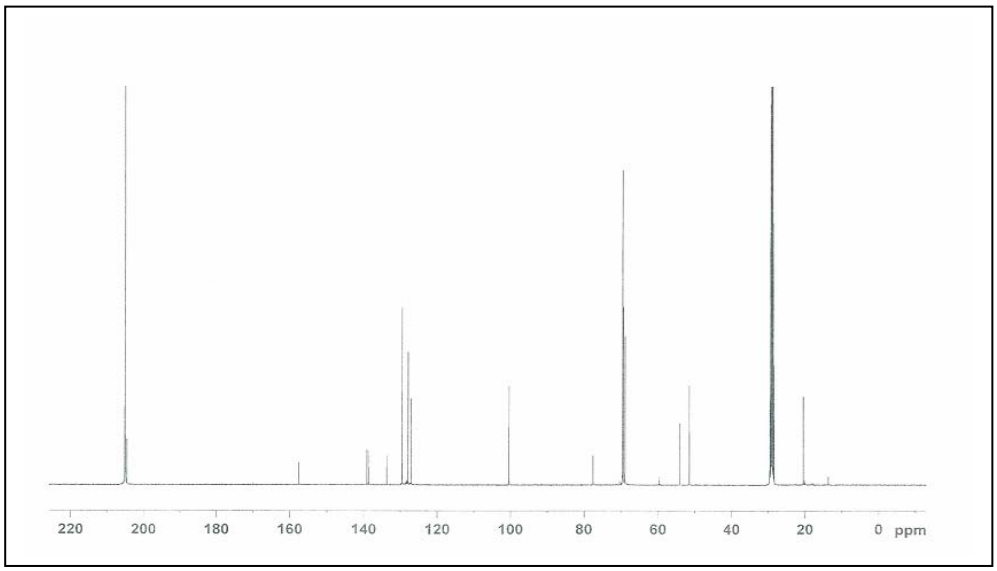

Figure A14. ^{13}C-NMR Spectrum of ferrocenyl cycloheptadienone **26E**

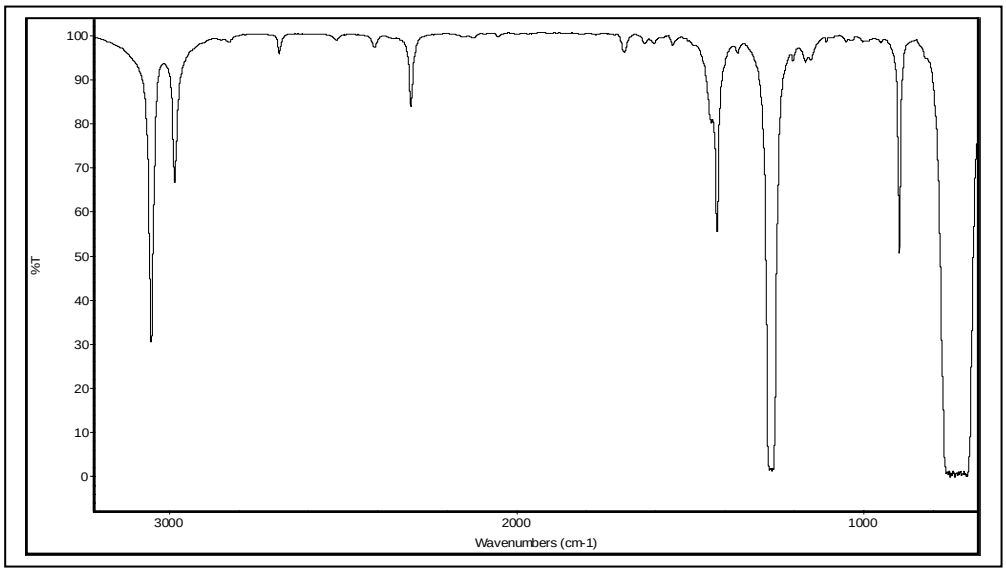

Figure A15. IR Spectrum of ferrocenyl cycloheptadienone **26E.**

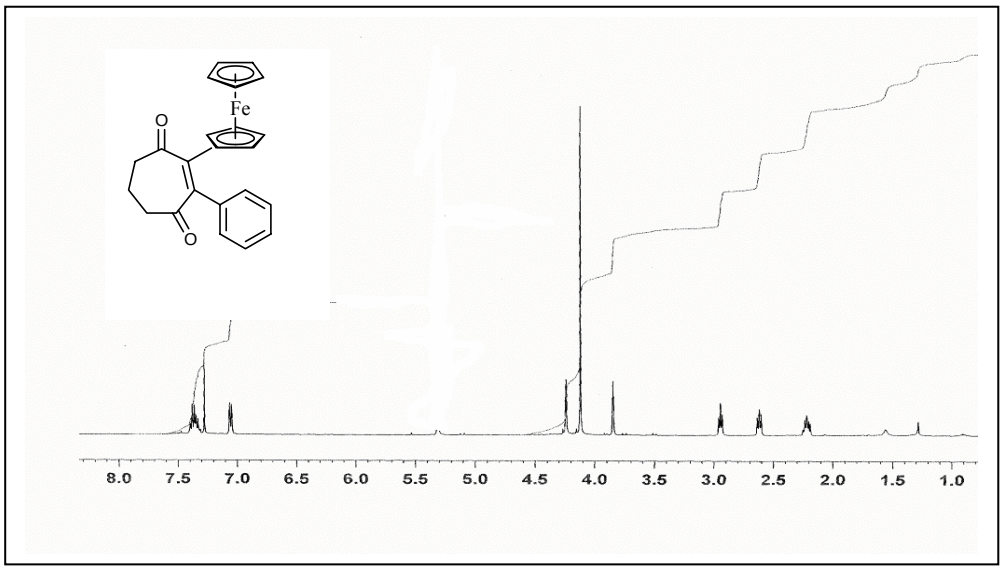

Figure A16. ^{1}H-NMR Spectrum of ferrocenyl cycloheptadienone **27E**

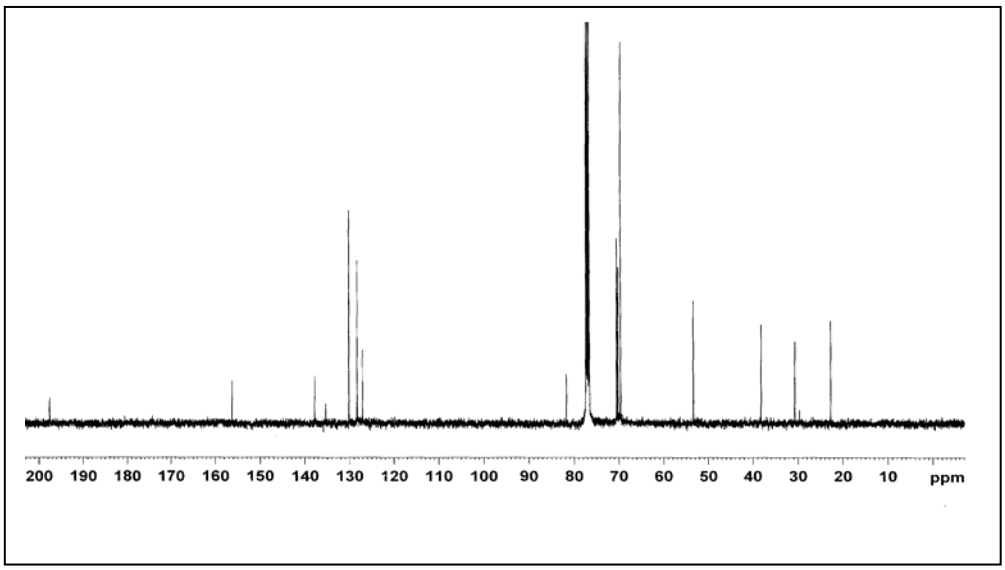

Figure A17. ^{13}C-NMR Spectrum of ferrocenyl cycloheptadienone **27E**

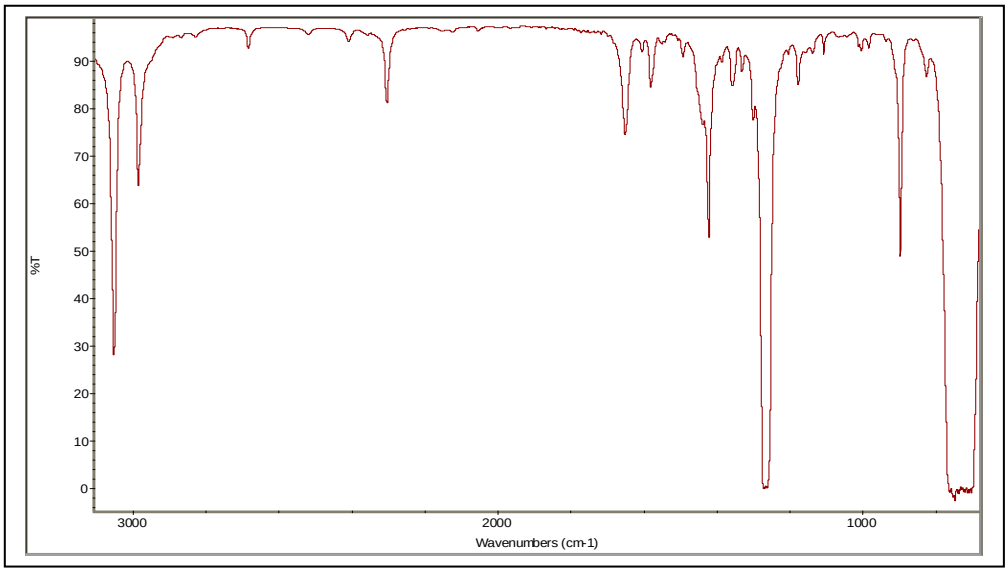

Figure A18. IR Spectrum of ferrocenyl cycloheptadienone **27E**

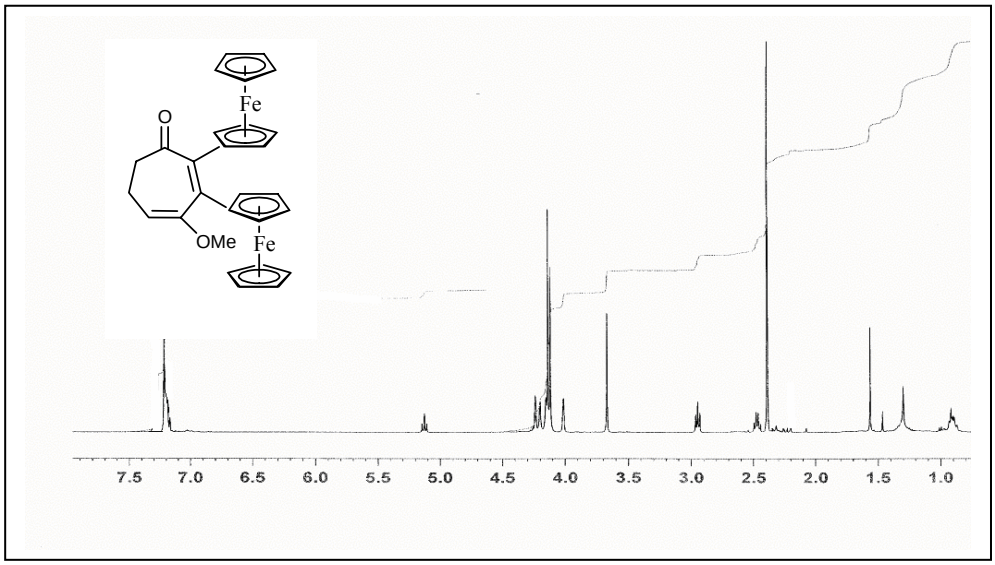

Figure A19. ^{1}H-NMR Spectrum of ferrocenyl cycloheptadienone **26F**

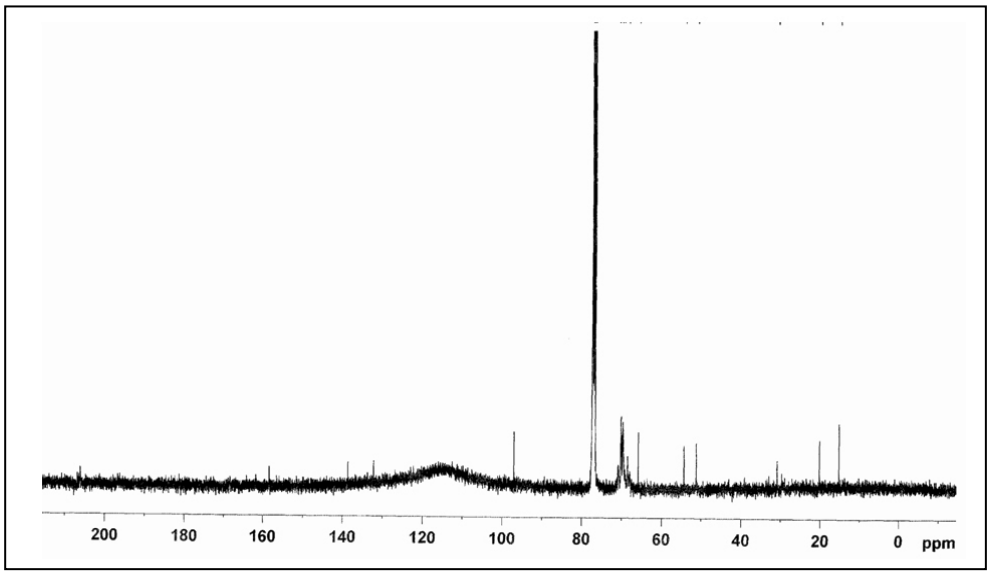

Figure A20. ^{13}C-NMR Spectrum of ferrocenyl cycloheptadienone **26F**

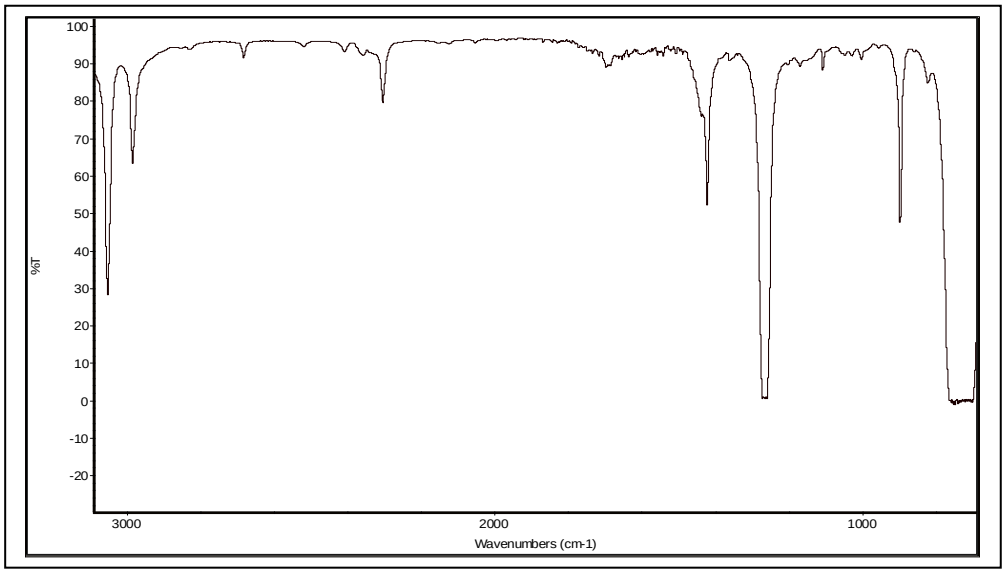

Figure A21. IR Spectrum of ferrocenyl cycloheptadienone **27F**

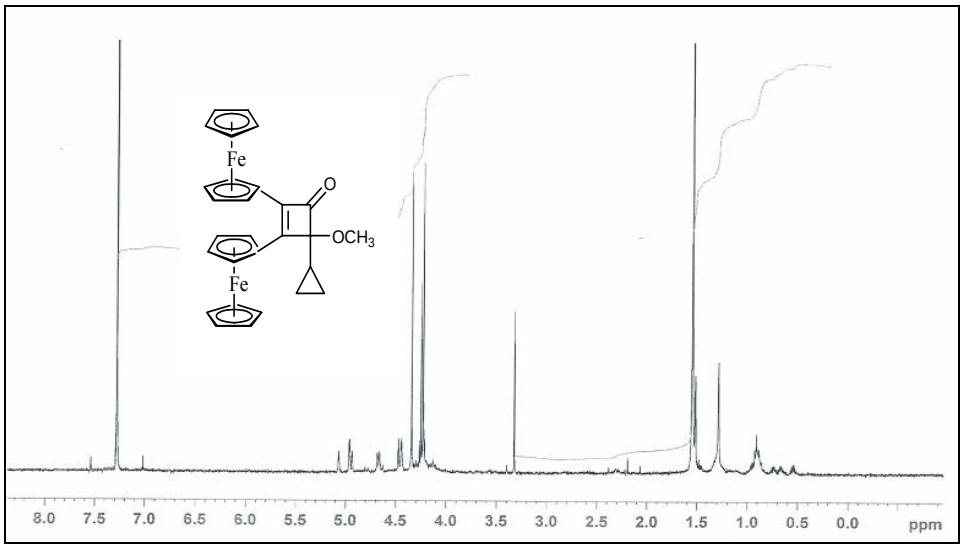

Figure A22. IR Spectrum of ferrocenyl cycloheptadienone **29F**