THE SYNTHESES OF INDANONES AND INDENONES VIA RHODIUM CATALYZED CARBONYLATIVE ARYLATION OF ALKYNES
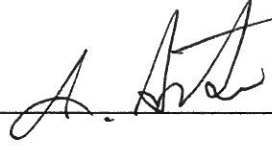
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ABSTRACT

THE SYNTHESES OF INDANONES AND INDENONES VIA RHODIUM CATALYZED CARBONYLATIVE ARYLATION OF ALKYNES

Indanones and indenones are important classes of compounds in organic chemistry. These structural motifs are found in various types of natural compounds and also can be used as intermediates in the synthesis of a variety of molecules.

In this study, indanones and indenones were synthesized via rhodium catalyzed reaction of alkynes with arylboroxines under a CO atmosphere. Reactions were performed using *para-* and *meta-* substituted phenylboroxines. Higher yields were obtained for indanones with methyl- substitution on *para-* and *meta-*positions of phenylboroxines than methoxy-substituted ones. However, by using phenylboroxine with an electron withdrawing group, a lower yield of indanone was observed. Higher yields of indanone were obtained with electron poor diaryl acetylenes than electron rich ones.

As a general result, the yields of indanone were higher than the yields of indenones at the end of the reaction. The desired products were purified with silica gel column chromatography and the structure of indanones and indenones were determined using GC, GC-MS, NMR, FT-IR and HRMS techniques.

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ÖZET

ALKİNLERİN RODYUM KATALİZİ KARBONİLATİF ARİLASYONU YOLU İLE İNDANON VE İNDENON SENTEZİ

İndanon ve indenonlar organik kimyada önemli bileşik sınıflarıdır. Bu yapısal motifler çeşitli doğal bileşik tiplerinde bulunmaktadırlar ve ayrıca çeşitli moleküllerin sentezinde ara madde olarak kullanılabilmektedirler.

Bu çalışmada, alkinlerin arilboroksinler ile rodyum katalizli reaksiyonu yolu ile CO gazı altında indanon ve indenonlar sentezlendi. Reaksiyonlar *para-* ve *meta-*sübstitüyeli fenilboroksinler kullanılarak gerçekleştirildi. *Para-* ve *meta-* posizyonunda metil substitüyeli fenilboroksin ile metoksi sübstitüyeliye oranla daha yüksek indanon verimi elde edildi. Buna karşın elektron çekici gruplu fenilboroksin kullanılarak daha düşük indanon verimi gözlendi. Elektronca fakir diaril asetilenler ile elektronca zengin olanlara göre daha yüksek indanon verimi elde edilmiştir.

Genel bir sonuç olarak; reaksiyon sonunda, indanon verimleri indenonlara oranla daha yüksekti. İstenen ürünler silica jel kolon kromotografisi ile saflandırıldı ve indanon ve indenonların yapıları GC, GC-MS, NMR, FT-IR ve HRMS teknikleri ile belirlendi.

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CHAPTER 1

INTRODUCTION

Organoboron reagents have been used in many useful chemical reactions from metal-catalyzed processes (Fagnou and Lautens 2003) to acid catalysis, asymmetric transformations, and multicomponent reactions. Arylboronic acids, an organoboron reagent, are highly useful organometallic reagents because they are stable compounds that can easily be prepared displaying a wide arrange of functionality.

Using a combination of a metal catalyst, such as rhodium, and organoboron reagents in the reactions became popular for the carbon-carbon bond formation via the transmetallation between organo/main group metal reagents and transition metal compounds in organic synthesis. Organoboron reagents readily undergo transmetallation with rhodium to form arylrhodium (I) species which have capacity to react with many electrophilic sides (Sakai, et al. 1997, Fagnou and Lautens 2003). After first example of the Rh-catalyzed addition reactions of organoborones to enones was reported (Sakai, et al. 1997), addition of arylboronic acids and their analogues to the carbon-carbon double bond (Oguma, et al. 2000, Lautens, et al. 2001), carbon-carbon triple bond, (Hayashi, et al. 2001) carbon-heteroatom double bonds (Sakai, et al. 1998, Ueda, et al. 2000, Fürstner, et al. 2001) and also the other systems such as unsaturated carbonyl compounds (esters, amids, anhydride etc…) was developed.

Recently, six-membered triorganoboroxine rings have been used as boronic acid alternatives in various organic reactions such as Suzuki-Miyaura coupling reactions (Miyaura, et al. 1995), Rh catalyzed arylation reactions (Miura, et al. 2007, Duursma, et al. 2005, Tokunaga, et al. 2004, Kuruyama, et al. 2004), and nickel catalyzed reactions (Arao, et al. 2007).

Transition metal catalyzed carbonylation reactions have become essential tools for the synthesis of a wide variety of carbonyl compounds (Colquhoun 1991). There are many studies in the literature for the synthesis of compounds having carbonyl groups such as ketones, aldehydes, carboxylic acids, esters, amids, lactones, lactams and carbamates.

Indanones and indenones are important classes of compounds in organic chemistry. In the literature, there are many studies for the synthesis of indanones (Allen, et al. 1943, Frank, et al. 1944, Kraft, et al. 1948, House, et al. 1960, Witiak, et al. 1974, Pines, et al. 1976, Suzuki, et al. 1997, Hassan, et al. 2000, Nguyen, et al. 2003, Fillion, et al. 2003, Park, et al. 2004, Wessig, et al. 2004, Fillion, et al. 2005, Womack, et al. 2007, Sharma, et al. 2007, Konstantin, et al. 2007, Senaiar, et al. 2007, Kerr, et al. 2007, Sani, et al. 2008, Saxena, et al. 2008, Zawisza, et al. 2008, Sheng, et al. 2009). But, there are few examples of carbonylative synthesis of indanones. 1-Indanone and its derivatives can be used as useful intermediates in the synthesis of (R) and (S)- 2 – hydroxy- indanone (Kajiro, et al. 1998), indenones (Hauser, et al. 2001), 6-substituted 3,4-benzotropolones (Iwaya, et al. 2003), dimer of 2-(4-pyridylmethyl)-1-indanone displaying potent aromatase inhibitory activity (Grupta, et al. 2004), biphenyl-carboxylic acid indanones (Bonnefous, et al. 2005), substituted indenes (Silver et al. 2005), the estrogen receptor beta selective agonist (Scott, et al. 2008), 1-indanone thiosemicarbazone derivatives (Finkielsztein, et al. 2008), dibromo-indenone derivatives (Tutar, et al. 2008). 2-Indanone was used for the synthesis of indeno-chromones and indeno-thiochromone (Townsend, et al. 2000).

In the literature, there are many studies for the synthesis of indenones. (House, et al. 1960, Murray, et al. 1976, Anstead, et al. 1988, Anstead, et al. 1989, Vicente, et al. 1996, Hauser, et al. 2001, Tutar, et al. 2008). There are few studies regarding the carbonylative synthesis of indenones.

In this thesis, we developed a method for rhodium catalyzed carbonylative synthesis of indanones and indenones using various alkynes and arylboroxine derivatives.

CHAPTER 2

CARBONYLATION REACTIONS

Carbonylation means introduction of carbon monoxide into organic and inorganic substrates, by which a C=O group can be introduced to the compound. Carbonylations are the basis of two main types of reactions. These are: *hydroformylation and Reppe Chemistry.*

Hydroformylation refers to reaction of transition metal catalyzed of carbon monoxide and hydrogen with an alkene. The first study about hydroformylation reaction was done by Otto Roelen (1938). He showed that propanal can be synthesized by the cobalt catalyzed addition of ethene to the gas mixture of carbon monoxide and hydrogen (Figure 2.1).

$$H_2C = CH_2 \ + CO \ + \ H_2 \ \xrightarrow{\text{HCo(CO)}_4} \ CH_2CH_2CHO$$

Figure 2.1. The synthesis of propanal by the hydroformylation reaction
(Source: Roelen 1938)

After the studies of Roelen, Reppe et al. (1939) reported that many types of organic carbonyl compound such as carboxylic acids and esters could be obtained from the unsaturated hydrocarbons by the reaction involving metal carbonyl compound. These processes entails addition of carbon monoxide and an acidic hydrogen donor to the organic substrate in presence of metal catalyst which binds and activates to CO. Hancock (1973) made a study regarding this process and synthesized acrylic acid from acetylene using nickel carbonyl (Figure 2.2).

$$HC\!\!\equiv\!\!CH \ + \ CO \ + \ H_2O \ \xrightarrow{\ Ni(CO)_4\ } \ H_2C\!\!=\!\!CHCOOH$$

Figure 2.2. The synthesis of acrylic acid via nickel carbonyl catalyzed reaction in presence of CO and H_2O (Source: Hancock 1973)

Transition metal catalyzed carbonylation reaction involves metal-carbon bond formation followed by insertion of carbon monoxide and giving an acyl-metal intermediate. Finally, this process goes to form the carbonyl product and regenerates the catalyst complex in its orginal form.

The potential applications of carbon monoxide in carbonylation reaction are illustrated in Figure 2.3.
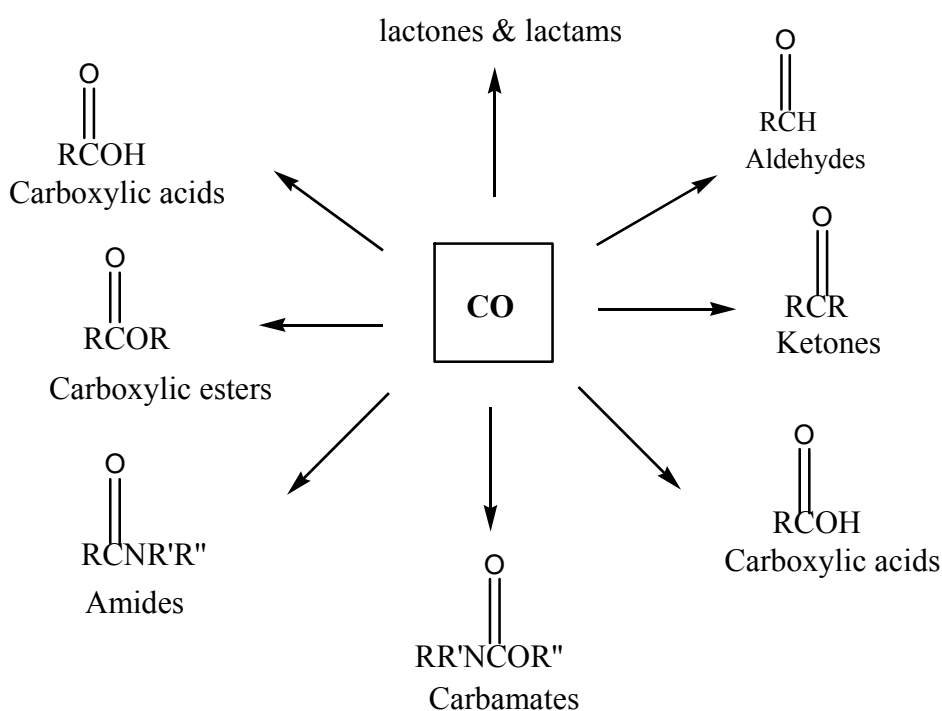
Figure 2.3. The application of carbon monoxide in carbonylation reactions

There are many studies about the transition metal catalyzed carbonylation reactions in the literature. Here, some examples of them will be given.

A common carbonylation reaction is the palladium (0) catalyzed nucleophilic carbonylation reaction of aryl halides (Heck 1985) (Figure 2.3). In this type of reaction, formed arylpalladium intermediate product by the oxidative addition of palladium (0) to aryl halide insert into carbon monoxide and aroylpalladium intermediate is formed.

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Finally, from the reaction of nucleophilic reagent, products such as amides, carboxylic acids and esters are formed.

$$ArX \xrightarrow{\text{Pd(0)}} Ar\text{-}Pd\text{-}X \xrightarrow{\text{CO}} ArCHPdX \xrightarrow{\text{HNu}} ArCNu$$

X=I, Br, Cl

HNu=ROH,H$_2$O , RNH$_2$
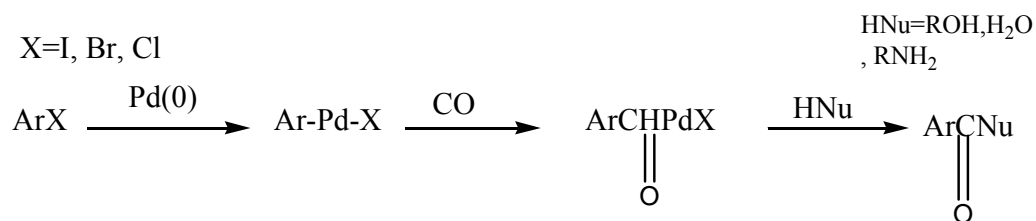
Figure 2.4. Palladium catalyzed carbonylation reaction of aryl halides
(Source: Heck 1985)

In another study, α-methylene-β-lactams were synthesized in good yields by the carbonylation of 2-bromo-3-propene derivatives using palladium acetate as a catalyst under CO atmosphere (Mori, et al. 1985) (Figure 2.4).
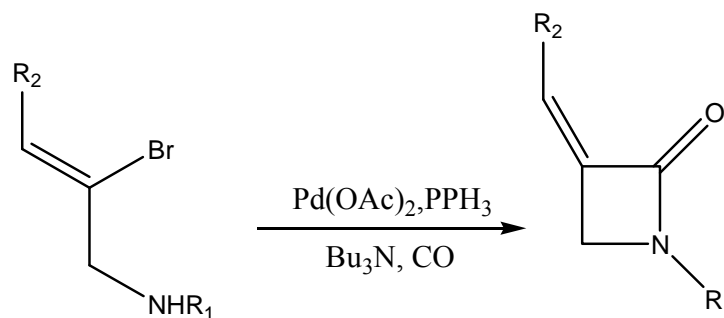
Figure 2.5. Carbonylation of 2-bromo-3-propene derivatives in presence of palladium acetate and triphenylphosphine (Mori, et al. 1985)

Also, in the literature, there are studies regarding nucleophilic palladium catalyzed carbonylation reactions of alkynes (Scrivanti, et al. 1998).
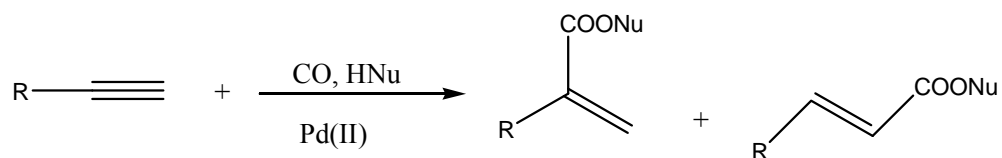
Figure 2.6. The nucleophilic carbonylation reaction of alkynes in presence of palladium
(Source: Scrivanti, et al. 1998)

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Huang and Alper (1991) reported the cross cyclocarbonylation reaction of 3-aryl-1-propyne with iodoarenes using palladium catalyst (Figure 2.7).
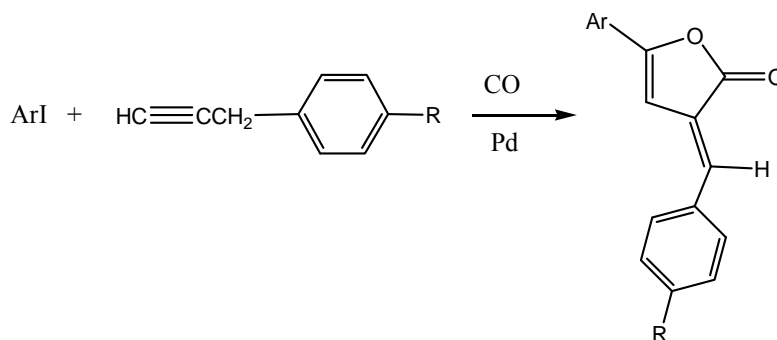
Figure 2.7. Palladium catalyzed cyclocarbonylation of 3-aryl-1-propyne with iodoarenes (Source: Huang and Alper 1991)

γ-lactones were synthesized by the palladium catalyzed carbonylative reaction of aryl halides with internal alkynes (Negishi, et al. 1995) (Figure 2.8).
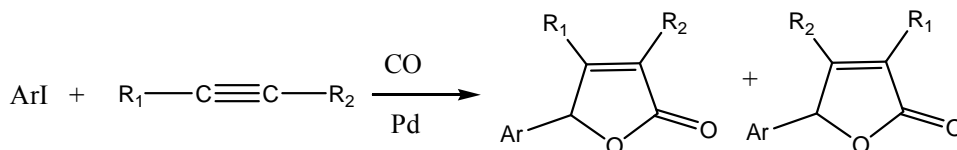
Figure 2.8. The synthesis of γ-lactones from the reaction of aryl halides with internal alkynes using palladium catalyst (Source: Negishi, et al. 1995)

Miura et al. (1992) showed that 3-aroylfuran compounds could be synthesized via cross coupling carbonylation reaction of aryl halides with 1-aryl-2-alkyne-1-one (Figure 2.9). In another study of Miura et al. (1995), ketones were synthesized via palladium catalyzed carbonylative reaction of five membered ring olefins.
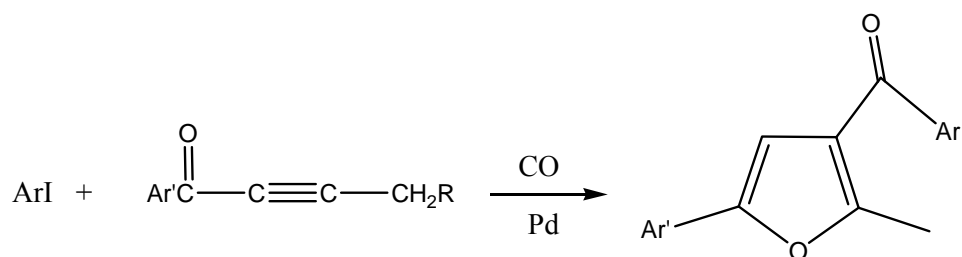
Figure 2.9. Palladium catalyzed carbonylative reaction of 1-aryl-2-alkyne-1-one with aryl halides (Source: Miura, et al. 1992).

Diaryl ketones were obtained by the palladium catalyzed carbonylative coupling reaction of arylboronic acids with aryl halides (Mingji, et al. 2004).
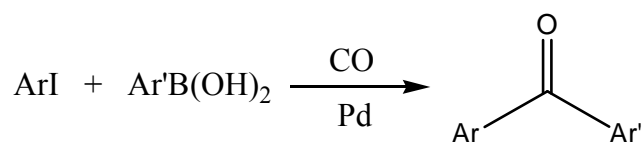
Figure 2.10. The synthesis of diaryl ketones via palladium catalyzed carbonylative coupling reaction of arylboronic acids an aryl halides (Source: Mingji, et al. 2004).

There are a few studies about the rhodium catalyzed carbonylative addition reaction of organoborons. It is observed that under a CO atmosphere, rhodium catalyzed addition reaction of organoborons can yield different organic materials such as ketones, furans, pyrrols, indenones.

Sauthier et al. (2004) observed that 1,4-diketones can be synthesized via rhodium catalyzed addition reaction of arylboronic acids to α,β unsaturated ketones under CO atmosphere. After Sauthier et al. (2004) reported a study about synthesis of 1,4-diketones, Chochois et al. (2006) developed a new route that allows simple and fast access to the pyrrole and furan compounds which are based on formation of diketone via carbonylation with an extra cyclization step (Figure 2.11).
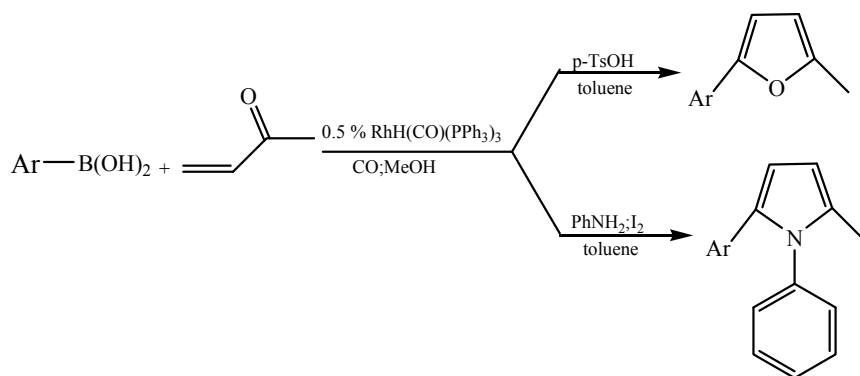
Figure 2.11. Rhodium catalyzed addition reaction of α,β unsaturated ketones under CO atmosphere and the formation of pyrrole and furan (Source: Chochois, et al. 2006)

Aksın et al. (2006) synthesized 5-aryl-2($5H$)-furanones via the Rh-catalyzed reactions of arylboronic acids with internal alkynes under a CO atmosphere (Figure 2.12).
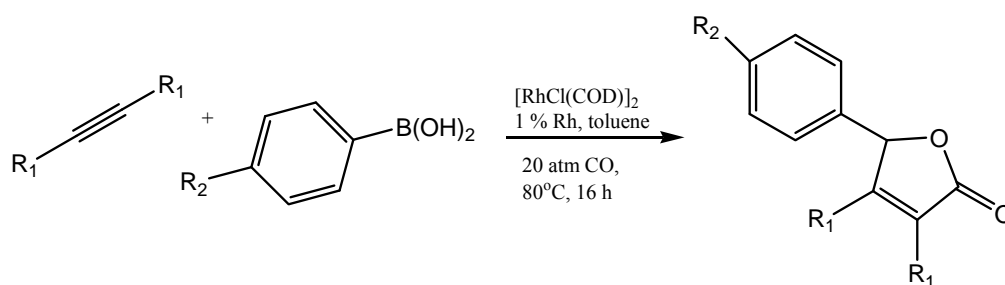
Figure 2.12. Rhodium catalyzed reaction of arylboronic acids to alkynes under CO pressure (Source: Aksın, et al. 2006).

Dheur et al. (2007) reported that α,β unsaturated ketones can be generated via rhodium catalyzed carbonylative addition reaction of arylboronic acids to terminal alkyne under CO atmosphere (Figure 2.13).
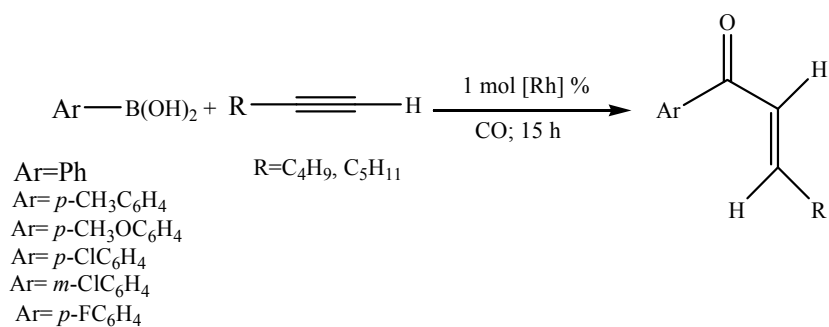
Figure 2.13. Rh catalyzed carbonylative addition reaction of arylboronic acids to terminal alkynes (Source: Dheur, et al. 2007).

Recently, α,β unsaturated ketones have been synthesized by the rhodium catalyzed reaction of arylboronic acids to internal alkynes under CO atmosphere in the presence of an acid additive (Kus, et al. 2008).
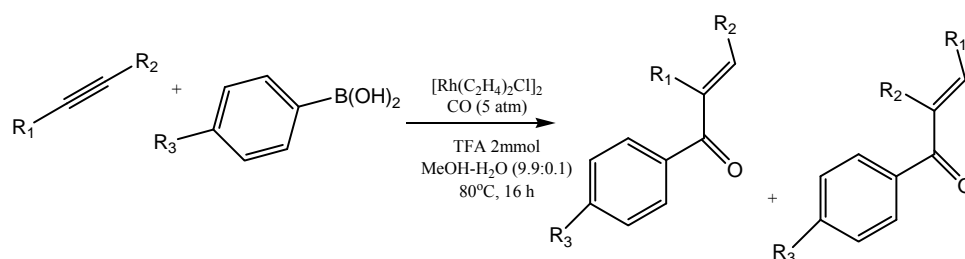
Figure 2.14. The synthesis of enones by carbonylation of phenylboronic acids to alkynes under CO pressure (Source: Kus, et al. 2008)

The Rh-catalyzed reaction of alkynes with 2-bromophenylboronic acids under CO atmosphere gave indenones of which regioselectivity depends on electronic and the steric nature of the substituents on the alkynes (Harada, et al. 2007) (Figure 2.15).
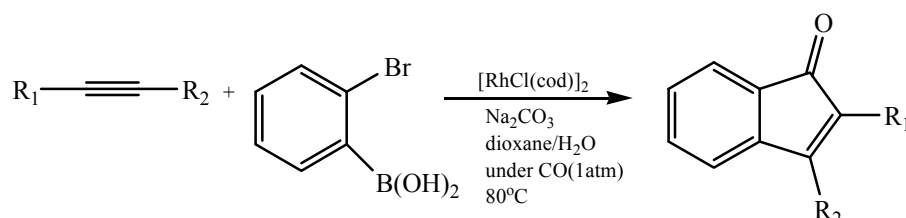
Figure 2.15. Rh catalyzed carbonylative cyclization reaction of 2-bromophenylboronic acids to alkynes (Source: Harada, et al. 2007)

CHAPTER 3

ORGANOBORONS

3.1. Boron

Boron is the fifth chemical element in the periodic table with atomic number 5 and the chemical symbol B. Naturally, boron exists as ^{10}B (19,78%) and ^{11}B (80,22%). Boron which is a metalloid element has several forms, the most common of which is amorphous boron, a dark powder, unreactive to oxygen, water, acids and alkalis. Also, it exists in many polymorphs (different crystal lattice structures).

Elemental boron is a poor electrical conductor at room temperatures, but is a good electrical conductor at high temperatures. Metallic boron is extremely hard and has a high melting point. Boron can transmit portions of infrared light. Boron is not present in nature in elemental form. It is found combined in borax, boric acid, kernite, ulexite, colemanite and borates. Chemically boron is electron-deficient, possessing a vacant p-orbital and it is an electrophile. Compounds of boron often behave as Lewis acids, readily bonding with electron-rich substances to compensate for boron's electron deficiency.

3.2. Organoboron

Organoboron compounds are the compounds which have at least one C-B bond. Organic compounds containing boron are important reagents for their chemical properties and reactivities because of enabling many chemical transformations such as hydroboration. Strategic position on the periodic table adjacent to carbon and electronic structure of boron makes trivalent boron compounds behave as electrophilic molecules with trigonal planar structures that are neutral yet isoelectronic to carbocations. In this

way, formation of an additional bond to boron produces anionic tetravalent boron compounds having tetrahedral structures and behave as nucleophilic molecules (Figure 3.1). Thanks to electronic, structural, and reactivity behaviour of organoborons, they can be used in many useful chemical reactions such as asymmetric synthesis, metal-catalysis, acid-catalysis, multicomponent reactions, biological and medicinal applications and in many areas from pharmaceuticals to materials.

Figure 3.1. The structure of organoboron compounds
(Source: Petasis, et al. 2007)

Some of the important organoborons are: trialkyl and arylboranes (R_3B), chlorodialkylboranes (R_2BCl), dichloro(alkyl)borane ($RBCl_2$), organoboranes with carbon replaced by oxygen are alkoxydialkylboranes (R_2BOR), dialkoxyalkylboranes ($RB(OR)_2$), borates or trialkoxyalkylboranes $RB(OR)_3$, hydroxydialkylborane (R_2BOH), dihydroxy(alkyl)borane and aryl or alkylboronic acids ($RB(OH)_2$ or $ArB(OH)_2$), boroxines ($R_3(BO)_3$).

3.3. Boronic Acids

Boronic acids are the most extensively used form of organoboron derivatives because of their stability and easy of handling in organic synthesis. Also, their low toxicity and their final breaking down into the environmentally friendly boric acid allow them to be regarded as green compounds. This reactivity profile as mild organic Lewis acids makes boronic acids an important class of synthetic intermediates. As a result,

boronic acids have some advantages such as increasing availability of reagents, ease of use in both aqueous and heterogeneous conditions, compatibility with a broad range of functional groups and electrophilic substituents, mild reaction conditions, air stability.

Boronic acids are trivalent boron-containing organic compounds that possess one alkyl substituent and two hydroxyl groups to fill the remaining valences on the boron atom (Figure 3.2).
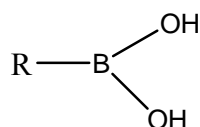
Figure 3.2. The structure of boronic acids

Boronic acids are the products of the second oxidation of boranes. The first oxidation products of boranes are borinic acids and third oxidation products are boric acids (Figure 3.3).

Borane   Borinic acids   Boric acids
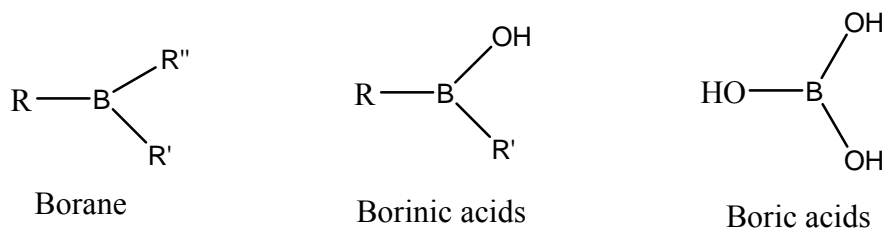
Figure 3.3. The structure of some oxygenated organoboron compounds.

Boronic acids are solids that tend to exist as mixtures of hydrates or free boronic acids or oligomeric anhydrides, especially the cyclic six-membered boroxines (Figure 3.4).
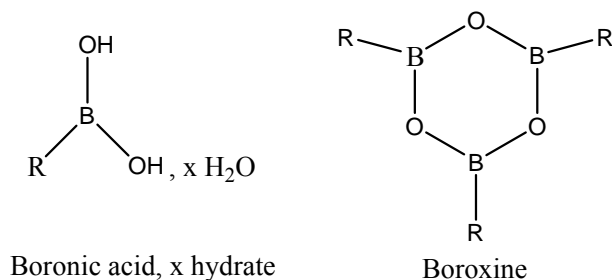
Figure 3.4. The structure of boroxine and boronic acids hydrate

The type of carbon group (R) which directly bonded to boron has an important effect on the reacivity and properties of boronic acids. Boronic acids are classified as alkyl-, alkenyl-, alkynyl-, and aryl- boronic acids.

Most boronic acids exist as white crystalline solids that can be handled in air without special precautions; boronic acids are chemically stable at ambient temperature and most display shelf-stability for long periods. Also, at high temperatures, they do not tend to disproportionate into their corresponding borinic acid and boric acid.

3.4. Boroxines

Boroxines are the cyclotrimeric anhydrides (boroxine:1,3,5,2,4,6-trioxatriborinane) and dehydration product of organoboronic acids. Simple dehydration of boronic acids results in the formation six-membered triorganoboroxine $(RBO)_3$ rings through azeotropic removal of water or by comprehensive drying over sulfuric acid or phosphorus pentoxide (Snyder, et al. 1938) (Figure 3.5). They can be operated invariably as substrates in many of the same synthetic transformations known to affect boronic acids, but they are rarely sought as synthetic products.

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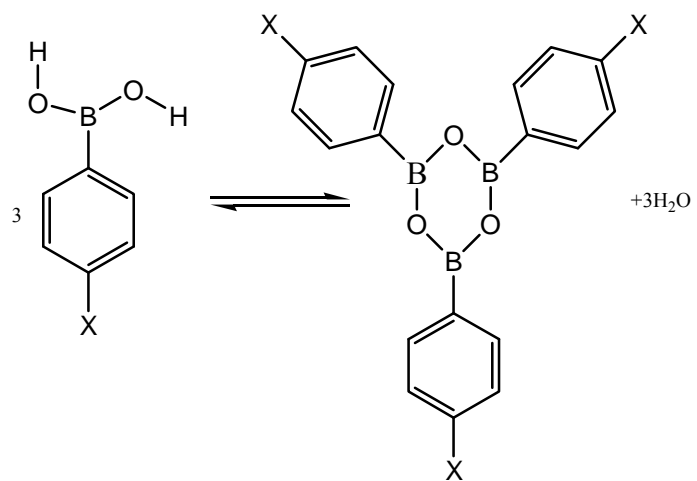
Figure 3.5. The formation of the triphenylboroxine

CHAPTER 4

TRANSITION METAL CATALYZED ADDITION REACTIONS OF ORGANOBORONS

4.1. Transition metal catalyzed addition reaction of Organoborons

Transition metals and their compounds are often good catalysts because of their ability to change oxidation state. Use of transition metals as catalyst is important in the synthesis of organic compounds. In the past twenty five years, transition metal catalysts have been used for the formation of carbon carbon bonds in organic synthesis reactions. In the literature, there are studies about addition reactions of organoborons using transition metal catalyst.

In 1995, Cho et al. (1995) reported a study about conjugate addition of aromatic compounds to α,β unsaturated ketones and aldehydes with sodium tetraphenylborate and arylboronic acids. A mild method was developed for the first enantioselective palladium catalyzed conjugate addition of arylboronic acids to a variety of α,β - unsaturated compounds such as aldehydes, ketones, and esters using a ligand (Gini, et al. 2005). Cylic substrates gave higher yields than linear ones. In another study, conjugate addition of arylboronic acids to α,β -unsaturated carbonyl compounds with high yields was performed in presence of palladium/bipyridine catalyst in aqueous media (Lin, et al. 2006). Arcadi et al. (2008) synthesized 2,4-diarylquinolines via the Pd-catalyzed hydroarylation of α,β -ynones with organoboron derivatives. The reaction catalyzed by both Pd(II) and Pd(0) precatalysts.

The palladium-catalyzed ring-opening addition of arylboronic acids to heterobicyclic alkenes aza- and oxabicyclic alkenes was reported (Lautens and Dockendorff 2003).

Palladium compounds can catalyze the addition of organoboronic acids to alkyne was shown for the first time (Oh, et al. 2003). Horiguchi et al. (2008) reported

oxidative coupling of arylboronic acids with alkynes in presence of palladium/phosphite or phosphate as a catalyst for the synthesis of 2:2 coupling products.

Arao et al. (2007) reported arylation of aromatic aldehydes with arylboroxines in presence of Ni-phosphine ligand.

Recently, copper(II) acetate-catalyzed addition of arylboronic acids to aromatic aldehydes was developed for the synthesis of carbinol using air-stable dppf ligand with high yields (Zeng, et al. 2009).

4.1.1. Rhodium-catalyzed Addition Reactions of Organoborons

Transition metals such as Pd, Pt, Ni and Rh etc… have an important meaning in the synthesis of organic compounds for C-C bond forming processes. Using rhodium, as a catalyst with organometallic reagents became popular for carbon carbon bond formation, because it allows developing environmentally benign processes in which the reactions occurs in water or in presence of water additive.

Also, rhodium has a different possible behavior in catalytic cycles different from the other transition metals.
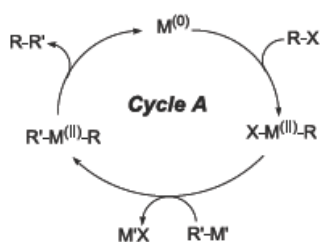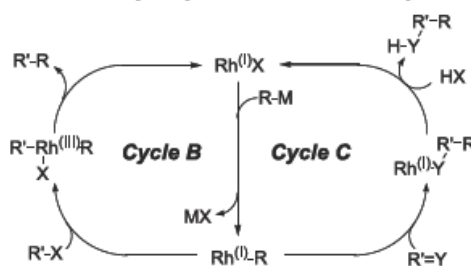
Figure 4.1 The catalytic cycle of transition metals.
(Source: Fagnou and Lautens 2003)

Ni, Pd, Pt operate at one point in a catalytic cycle between the (0) and (II) oxidation states. As a result, transmetallation can only occur with these metals (II) species, Rh(I) allows for two possible points of transmetallation in the cycle between Rh (I) and Rh (III).

4.1.1.1. Rhodium Catalyzed Addition Reactions of Organoborons to Cyclic and Acyclic Enones

In this research field, the first study is made in 1997 by Sakai et al. (1997). Rh(I) catalyzed conjugate addition of aryl and alkenylboronic acids to enones at 50°C and in aqueous solvent was reported. They observed that although the yields are high for β-unsubstituted enones, the yields are moderate for β-substituted enones. With various ligands, they obtained best yields with bis-phosphine ligands in their reactions (Figure 4.2).
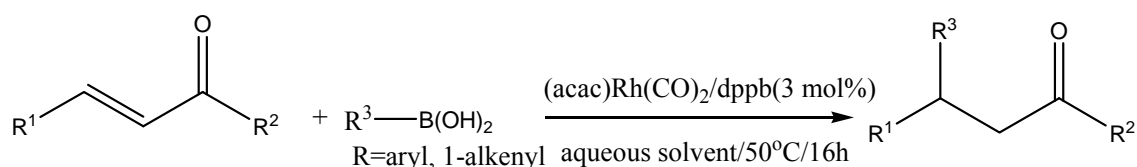
Figure 4.2. Rh-catalyzed addition of aryl and alkenylboronic acids to enones
(Source: Sakai, et al. 1997)

In 1998, Hayashi et al. (1998) modified these reaction conditions by changing temperature, solvent, rhodium precursor and using chiral ligand such as (S) - BINAP (Figure 4.3), they obtained high enantioselectivity.
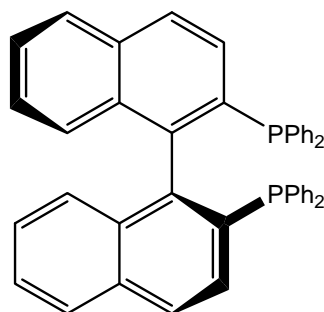
Figure 4.3. Structure of (S)-BINAP, a chiral ligand
(Source: Hayashi, et al.1998)

Kuruyama et al. (2001) reported a study about Rh catalyzed asymmetric 1,4 addition reaction of arylboronic acids with cycloalkenones. In this study, by using amidomonophosphine as a chiral ligand (Figure 4.4), high yield and enantioselectivity are obtained (Figure 4.5). Rh-catalyzed addition reactions of boronic acids to cyclic and acylic enones has been performed by using the Rh(I) complex derived from the new bisdiphenylphosphine diphonane (Figure 4.6) (Vandyck, et al. 2005).
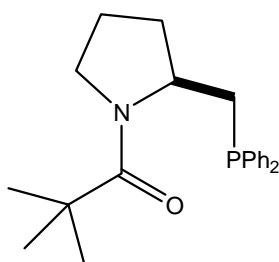
Figure 4.4. Structure of amidomonophosphine ligand
(Source: Kuruyama, et al. 2001)
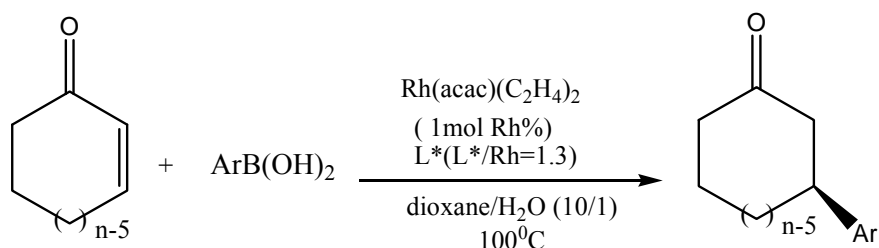
Figure 4.5. Rh catalyzed addition of arylboronic acids to cycloalkenones
(Source: Kuruyama, et al. 2001)
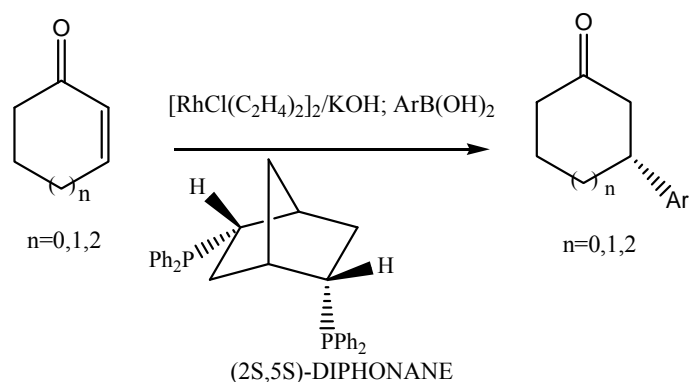
Figure 4.6. Rh-catalyzed addition reactions of boronic acids to cyclic and acylic enones by using bisdiphenylphosphine diphonane (Source: Vandyck, et al. 2005)

Morgan et al. (2008) showed that terphspan ligand such as a wide bite angle diphosphine ligand (Figure 4.7) can be used in rhodium-catalyzed 1,4-addition reaction of arylboronic acids to α,β unsaturated ketones.

E=CH$_2$, R=Ph
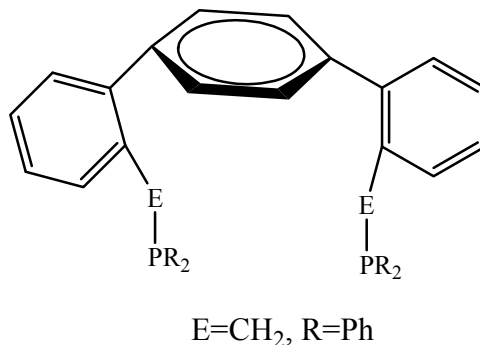
Figure 4.7 Structure of wide angle diphosphine ligand
(Source: Morgan, et al. 2008)

Boiteau et al. (2003) showed that monodentate phosphoramidites (Figure 4.8) can be used as chiral ligands in the Rh-catalyzed enantioselective conjugate addition of arylboronic acids to enones, unsaturated esters, lactones, and nitro alkenes. It is observed that reaction yields and enantioselectivity were high in this study.
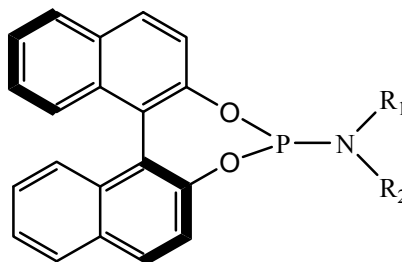
Figure 4.8. Structure of (*S*)-bisphenol-based monodentate ligands
(Source: Boiteau, et al. 2003)

Rhodium-catalyzed conjugate addition of arylboronic acids to enones which are the bifunctional Michael acceptors was achieved under basic reaction conditions and using monodentate phosphoramidites which is a chiral ligand (Mediavilla, et al. 2006). This method is also suitable for cycloenones (Figure.4.9).
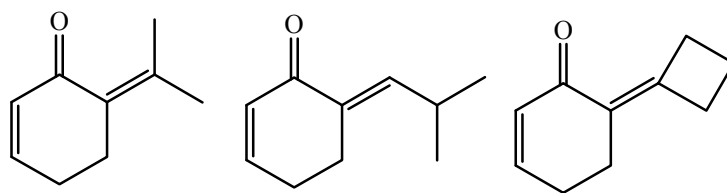
Figure.4.9. Structure of Michael acceptors
(Source: Mediavilla, et al. 2006)

Other than monodentate phosphoramidite ligands, also bidentate phosphoramidite ligands can be used in rhodium catalyzed reactions. Kurihara et al. (2007) reported a study about usage of bidentate phosphoramidite ligands in 1,4-addition reaction of arylboronic acids to α,β - unsaturated carbonyl compounds. They investigated that bidentate phosphoramidite is a suitable ligand for both cyclic and acyclic enones and allows the reaction to be completed in a short time at room temperature (Figure 4.10).

R=Me, Et, *i*-Pr
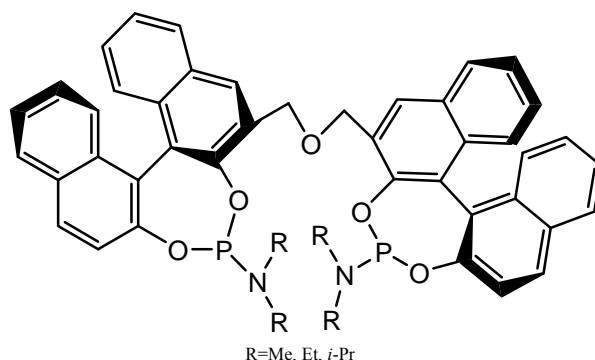
Figure 4.10. Structure of bidentate phosphoramidite ligand.
(Source: Kurihara, et al. 2007)

Ma et al. (2003) obtained high reaction yield and high selectivity by using chiral imidazolium ligand. They proposed that by using different imidazolium ligands, new routes can be developed for rhodium-based processes and asymmetric, transition- metal-catalyzed reactions that have high yield at low temperatures.

Defieber et al. (2004) reported that new substituted [2.2.2] diene ligands display high selectivity in Rh (I) catalyzed conjugate addition reactions of boronic acids to cyclic and acyclic enones (Figure 4.11).
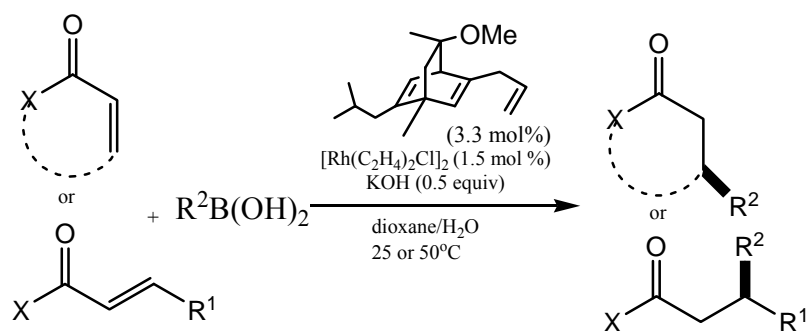
Figure 4.11. Rh catalyzed conjugate addition of arylboronic acid to cyclic and acyclic enones with [2.2.2] chiral ligands. (Source: Defieber, et al. 2004)

Monosubstituted chiral dienes can also be used as ligands in Rh catalyzed 1,4 addition reactions (Gendrineau, et al. 2008). These ligands allow high enantioselectivities to be obtained for the formation of a new C-C bond in the β position of Michael acceptors. Feng et al. (2008) reported that C_2-symmetric chiral diene ligands with a nonbridged bicyclic [3.3.0] backbone can be used in Rh catalyzed 1,4 addition reactions (Figure 4.12). In another study, 2- heteroarylzinc donors can be used in rhodium-catalyzed conjugate addition reaction was explained (Notre, et al. 2008).
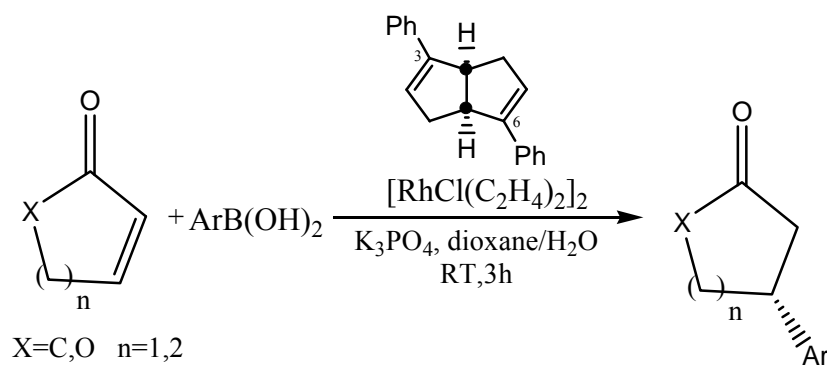
Figure 4.12. Asymmetric 1,4-addition of arylboronic acids to α,β unsaturated cyclic carbonyl compounds (Source: Feng, et al. 2008)

Recently, Lukin et al. (2009) have showed that using an in situ generated rhodium-binap catalyst, asymmetric addition of arylboronic acids to enones can be occurred (Lukin, et al. 2009).

4.1.1.2. Rhodium Catalyzed Addition Reactions of Organoborons to Aldehydes

Sakai et al. (1998) reported that rhodium catalyzed addition of aryl or alkenylboronic acids to aldehyde gives secondary alcohols in good yields (Figure 4.13). Ueda et al. (2000) showed that using a ligand such as tri(tert-butyl)phosphine, which is a bulky ligand, in the addition reaction of boronic acids to aldehyde has a important effect in accelerating reaction (Ueda, et al. 2000).

$$RB(OH)_2 + R'CHO \xrightarrow[\text{DME/H}_2\text{O or dioxane/H}_2\text{O}]{[\text{Rh(acac)L}_n]} R \overset{R'}{\underset{OH}{\diagup}}$$
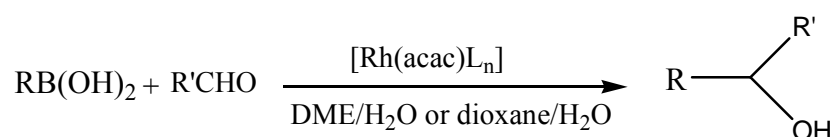
Figure 4.13. Rhodium catalyzed addition of organoboronic acids to aldehyde
(Source: Sakai, et al. 1998)

Fürstner et al. (2001) demonstrated that rhodium catalyzed addition of organoboronic acids to aldehydes is affected by a catalyst, an aqueous base and a imidazolium salt. They explained that this method is chemoselective for aldehydes and compatible with various functional groups. Özdemir et al. (2004) showed that if rhodium- carben complexes are used in the addition of boronic acids to aldehydes, the reaction has high yields and becomes faster. Son et al. (2005) reported that π-bonded rhodium quinonoid complex plays a bifunctional role and suitable catalyst for coupling of aryl boronic acids and aldehydes.

The asymmetric addition of arylboronic acids to cinnamaldehyde derivatives using Rh (I)-diene complexes gives optically active 3,3-diaryl-substituted aldehydes (Paquin, et al. 2005). Chen et al. (2006) reported that multidentate NHC–rhodium complexes can be used in the addition of boronic acids to aldehydes and the reaction results in high yields. Asymmetric synthesis of diarylmethanols using phosphoramidites as chiral ligands in the rhodium catalyzed addition of arylboronic acids to aldehydes was achieved (Jagt, et al. 2006). Mora et al. (2007) showed that diaryl ketones can be synthesized via a tandem catalytic process in the cross-coupling reaction of arylboronic acids with aryl aldehydes.

4.1.1.3. Rhodium Catalyzed Addition Reactions of Organoborons to Other Unsaturated Carbonyl Compounds

After Sakai et al. (1997) reported that rhodium-catalyzed 1,4 conjugate addition reactions of aryl and 1-alkenylboronic acids to enones in an aqueous solvent, Sakuma et al. (2000) reported a study about the rhodium catalyzed 1,4 addition reaction of α,β unsaturated esters using a rhodium(I)-(S) binap catalyst giving β aryl esters (Figure 4.14).
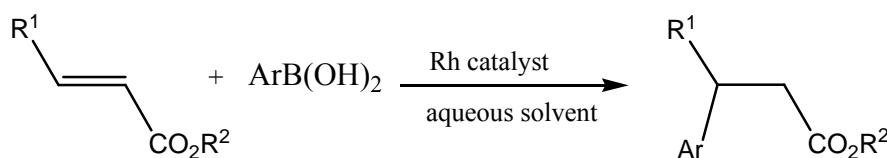
Figure 4.14. Rhodium catalyzed asymmetric conjugate addition of α,β unsaturated esters. (Source: Sakuma, et al. 2000)

Sakuma et al. (2001) made an another study about rhodium catalyzed asymmetric 1,4 addition of arylboronic acids with α,β unsaturated amids using chiral rhodium catalyst and an aqueous base. The reaction resulted in optically active β-aryl amides. It is observed that using a aqueous base, such as K_2CO_3, has a significant effect on high yields (Figure 4.15).
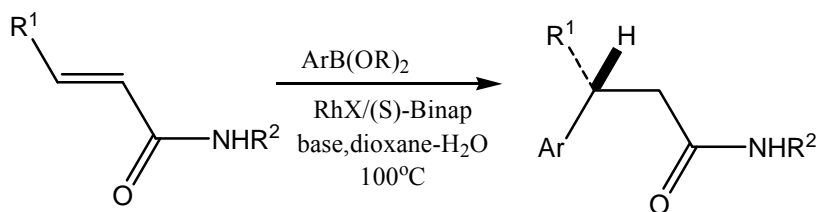
Figure 4.15.Rhodium catalyzed conjugate addition of α,β unsaturated amids (Source: Sakuma, et al. 2001)

Frost et al. (2001) reported that aryl and alkenyl ketones can be synthesized via rhodium catalyzed addition reaction of boronic acids to anhydrides (Figure 4.16).

Oguma et al. (2002) made a similar study by using sodium tetraphenylborate instead of boronic acids and observed that the reaction resulted in the formation of phenyl ketones. Miura et al. (2005) reported rhodium (I)-catalyzed acyl 1,3 migration reaction of acetylenic β-ketoesters and two carbon atom ring-expansion reaction
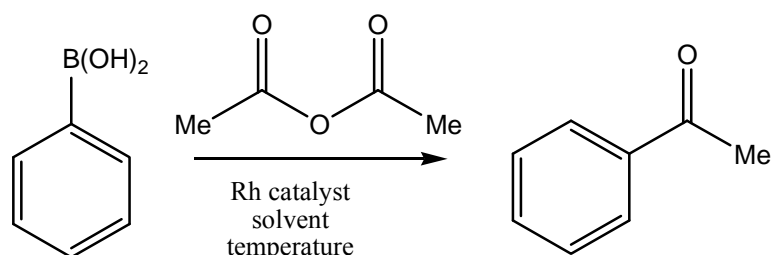
Figure 4.16. Rhodium catalyzed reaction of arylboronic acids to anhydrides.
(Source: Frost, et al. 2001)

Toullec et al. (2006) developed a method to synthesize 3-aryl-3-hydroxyoxindole via 1,2-addition of aryl and alkenylboronic acids to isatins using a rhodium(I)/triphenylphosphite catalyst (Figure 4.17).
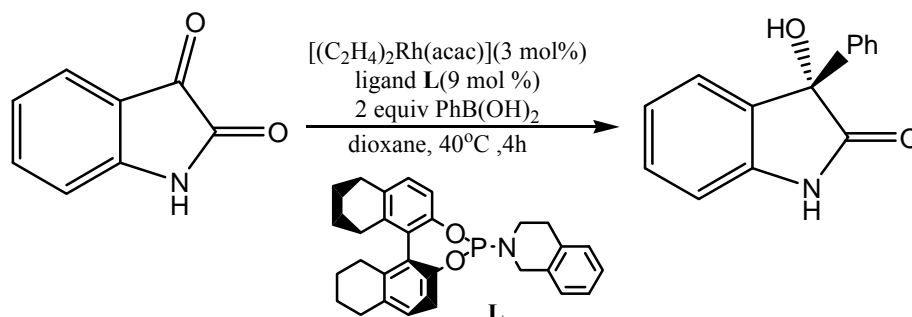
Figure 4.17. Phosphoramidite-rhodium catalyzed addition of arylboronic acid to isatin
(Source: Toullec, et al. 2006)

Iyer et al. (2007) showed that rhodium catalyzed conjugate addition of arylboronic acids can be performed by using unprotected maleimides in microwave (Figure 4.18). Miura et al. (2007) synthesized secondary amides under mild conditions using isocyanides in Rh catalyzed addition reaction of boronic acids. Duan et al. (2007) demonstrated a rhodium-catalyzed asymmetric 1,4-addition with a very high stereoselectivity by using Rh/(R,R)-Ph-bod catalyst and using substituted maleimides as starting agents (Figure 4.19).
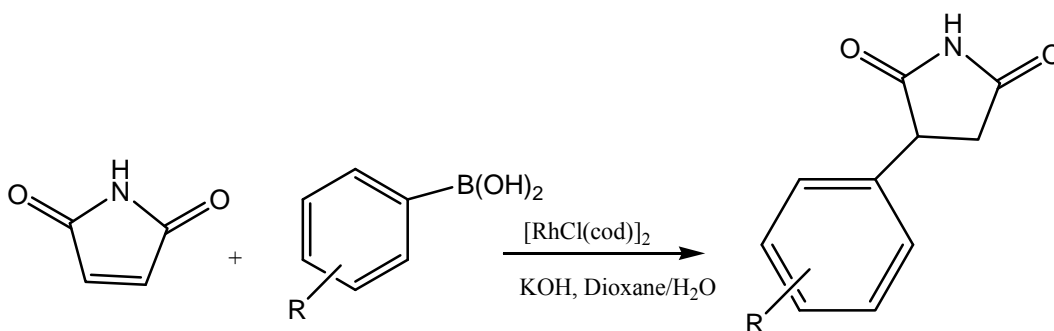
Figure 4.18. Rh catalyzed conjugate addition of boronic acids to maleimides
(Source: Iyer, et al. 2007)
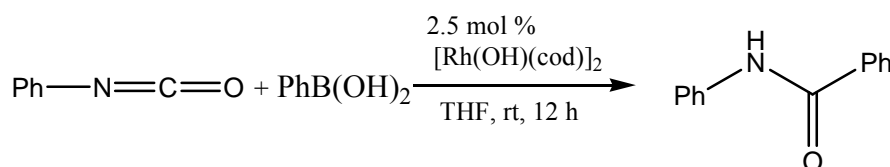
Figure 4.19. Rh catalyzed addition reaction of boronic acids to isocyanides
(Source: Miura, et al. 2007)

Tertiary α-hydroxy ketones can be synthesized via rhodium catalyzed addition of boronic acids such as aryl or vinyl boronic acids to 1,2 diketones and 1,2 diketoesters under mild conditions (Ganci, et al. 2007) (Figure 4.20). Miyamura et al. (2007) performed a similar study with Ganci et al.'s study (2007) using sodium tetrakis(4-methylphenyl)borate and dialkyl oxalates instead of boronic acid and 1,2 diketones and 1,2 diketoesters and obtained α-hydroxydiarylacetates. Duan et al. (2008) used rhodium catalyst spirophosphite ligands in addition of arylboronic acids to α-ketoesters.
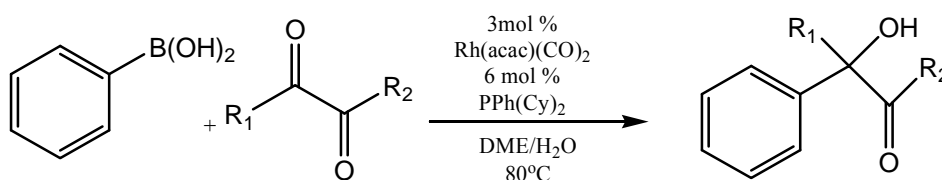
Figure 4.20. Rh catalyzed addition of boronic acids to 1,2 diketones and 1,2 diketoesters
(Source: Ganci, et al. 2007)

Miura et al. (2007) synthesized four- and five-membered-ring cyclic alcohols equipped with a tetrasubstituted exocyclic olefin by the addition reaction of alkynones with arylboronic acids using rhodium (I) catalyst (Figure 4.21).
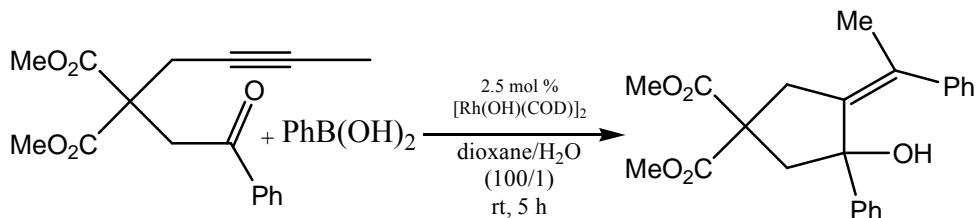
Figure 4.21. Rh catalyzed addition reaction of arylboronic acids to alkynones
(Source: Miura, et al. 2007)

Srgel et al. (2008) synthesized 3,3-diaryl-2-cyanopropanoates up to 99% enantioselectivity using a rhodium catalyst coordinated with a chiral diene ligand in 1,4-addition reaction of arylboronic acids to arylmethylene cyanoacetates.

Recently, Navarro et al. (2009) derived a method to synthesize (-)-7-oxamuricatacin by using δ-hydroxy-γ- butanolides substituted at the β-position by aryl and alkenyl groups (Figure 4.22).
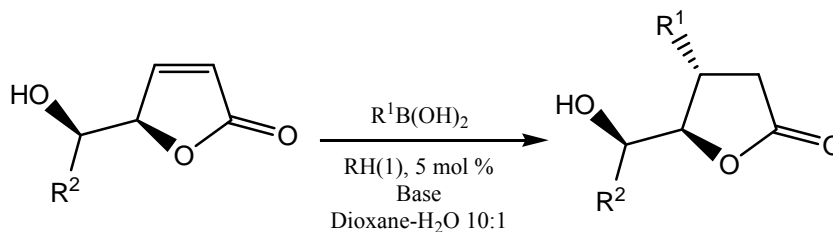
Figure 4.22. Rhodium-catalyzed conjugate addition of boronic acids to unprotected δ-hydroxy-γ-butenolides (Source: Navarro, et al. 2009)

4.1.1.4. Rhodium Catalyzed Addition Reactions of Organoborons to Alkenes

Rhodium catalyzed addition reaction of organoborons cannot be limited only to α,β unsaturated ketones, unsaturated carbonyl compounds and aldehydes. These reactions can be performed by using different organic reagents such as alkenes.

In early studies, Oguma et al. (2000) reported a study about rhodium series of reactions which is a multiple alkylation reaction which is known as "merry-go-round type" sequential alkylation. By this way, they synthesized a unique class of sterically encumbered aromatic molecules in a single process (Figure 4.23).
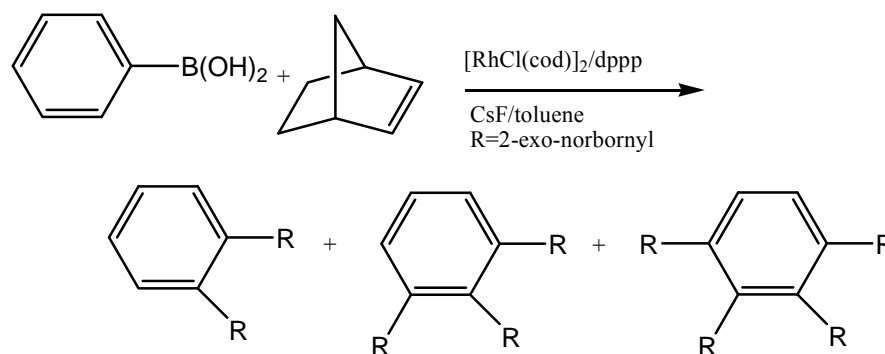
Figure 4.23. Addition of phenylboronic acids to 2-norbornene
(Source: Oguma, et al. 2000)

Hayashi et al. (2000) reported a study about rhodium catalyzed asymmetric conjugate addition of boronic acids to nitroalkenes.

Rhodium catalyzed coupling reaction of arylboronic acids with olefins was performed in aqueous media by using water-soluble phosphine ligands such as TPPDS and TPPTS (Figure 4.24) (Lautens et al. 2001). In the reaction, styrenyl olefins as a olefin were used, Heck-type products were formed but when a olefin bearing a aromatic ring was used, addition-hydrolysis process was observed (Figure 4.25).
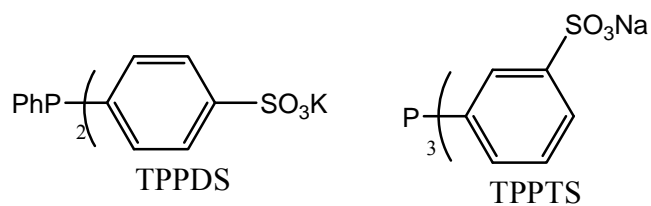
Figure 4.24. The structure of water soluble phophine ligands
(Source: Lautens et al. 2001)
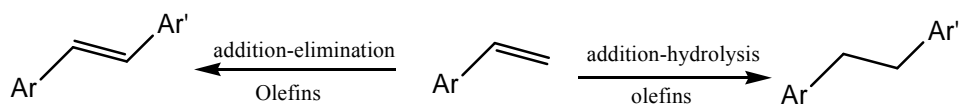
Figure 4.25. Rh catalyzed coupling reaction of phenylboronic acids in aqueous media
(Source: Lautens et al. 2001)

Mauleon et al. (2007) reported rh catalyzed asymmetric conjugate addition of boronic acids to vinyl sulfones. β- substituted 2-pyridyl sulfones were synthesized (Figure 4.26).
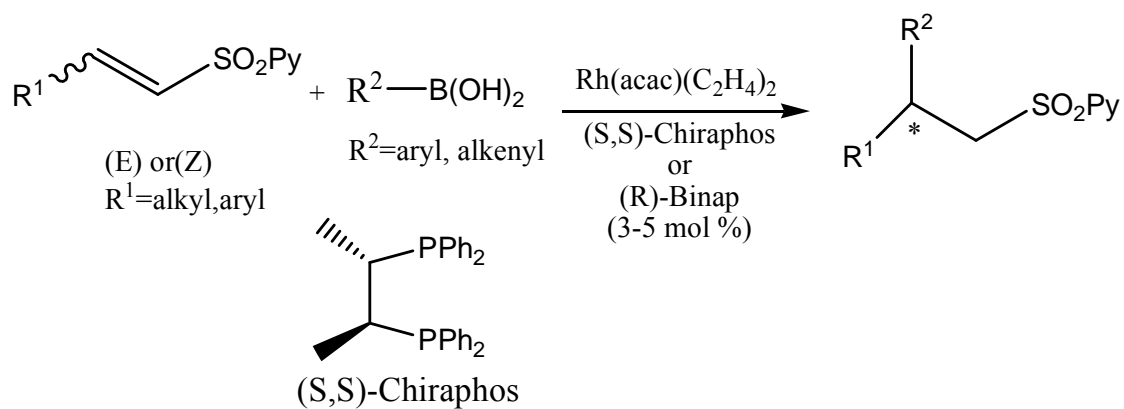
Figure 4.26. Rhodium catalyzed conjugate addition of aryl or alkenylboronic acids to vinyl sulfones (Source: Mauleon, et al. 2007)

4.1.1.5. Rhodium Catalyzed Addition Reactions of Organoborons to Alkynes

Hayashi et al. (2001) reported a study about rhodium catalyzed hydroarylation of alkynes. It was observed that the addition has *syn* selectivity (Figure 4.27).

$R^1=R^2=n\text{-Pr}$
$R^1=R^2=Et$
$R^1=R^2=Ph$
$R^1=Me, R^2=Ph$
$R^1=n\text{-Bu}, R^2=COOMe$
$R^1=Me_3Si, R^2=COOMe$
$R^1=n\text{-Hex } R^2=P(O)(OEt)_2$

$Ar=Ph$
$Ar=4\text{-}CF_3C_6H_4$
$Ar=4\text{-}MeC_6H_4$
$Ar=4\text{-}MeOC_6H_4$
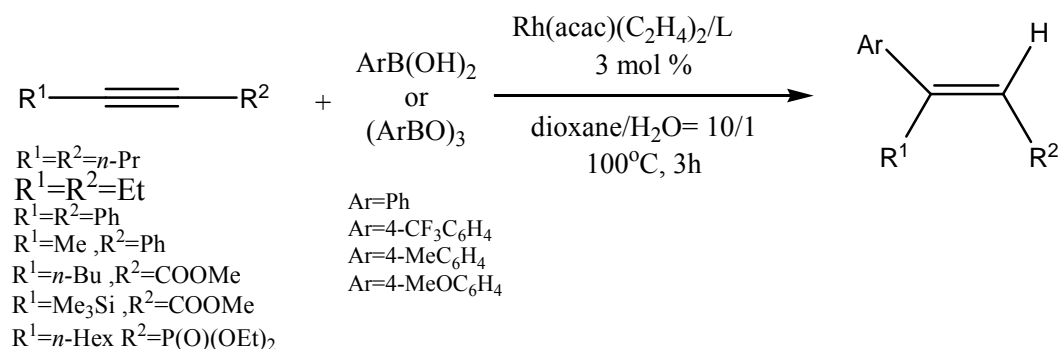
Figure 4.27. Rh catalyzed hydroarylation reaction of alkynes
(Source: Hayashi, et al. 2001)

In another study, Lautens et al. (2003) performed the rhodium catalyzed addition reactions of alkynes using a heteroatomic alkyne. By this way, tri substituted alkenes were synthesized. Also, it was observed that by using pyridine substituted phosphine ligands (Figure 4.28), which are water soluble, better yields were gained (Figure 4.29). In a different way, tri substituted alkenes were synthesized in biphasic system (Toluene – water mixture) (Genin, et al. 2004).
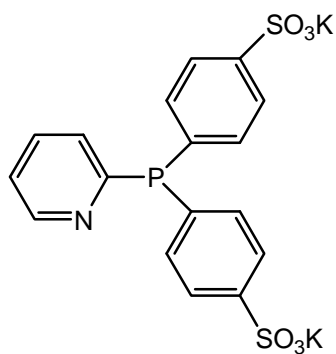
Figure 4.28. The structure of pyridine substituted phosphine ligand
(Source: Lautens, et al. 2003)
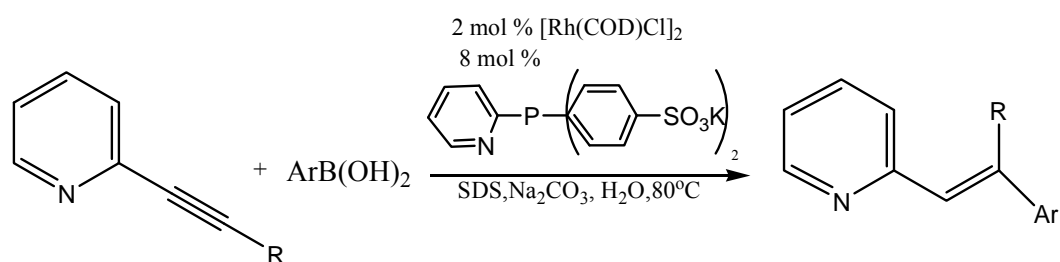
Figure 4.29. Rh catalyzed reaction of arylboronic acids to heteroatomic
alkynecompound. (Source: Lautens, et al. 2003)

Rhodium catalyzed arylative cyclization reaction of alkyne-tethered electron-deficient olefins with arylboronic acids was performed using a chiral diene ligand (Shintani, et al. 2005) (Figure 4.30). In another study of Shinta et al. (2005) indenols were synthesized via a rhodium/diene-catalyzed coupling reaction of alkynes with ortho-carbonylated arylboronic acids (Figure 4.31).
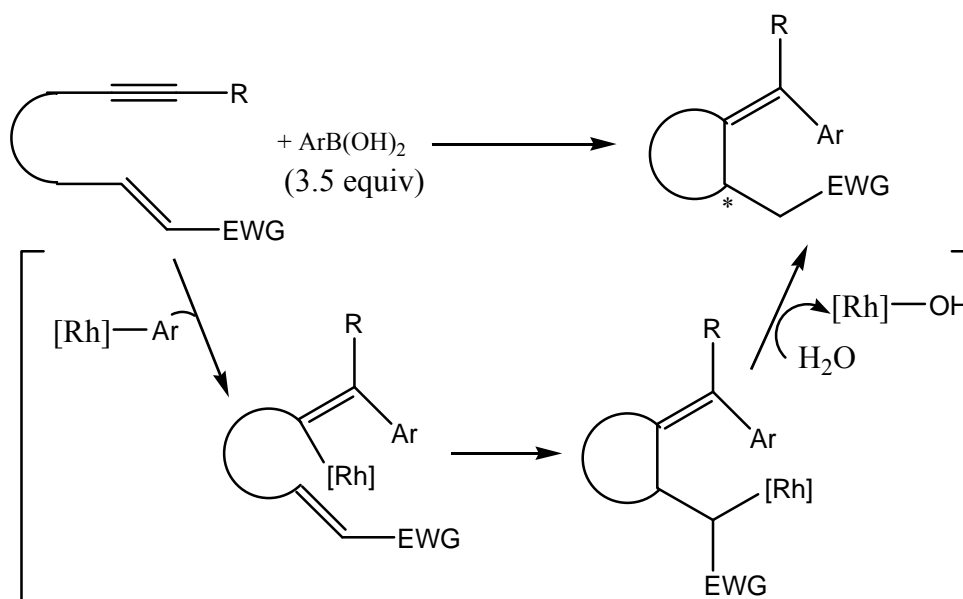
Figure 4.30. Rhodium catalyzed arylative cyclization reaction of alkyne tethered olefins with arylboronic acids (Source: Shintani, et al. 2005)
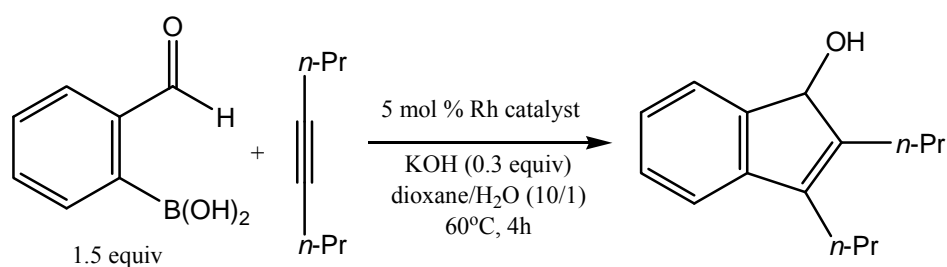
Figure 4.31. Rhodium catalyzed reaction of alkynes with *ortho*-carbonylated arylboronic acids using a chiral diene ligand (Shintani et al. 2005)

Miura et al. (2007) reported a study about the synthesis of syn α-allenols from the rhodium catalyzed reaction of alkynyl oxiranes and phenylboronic acids (Figure 4.32).
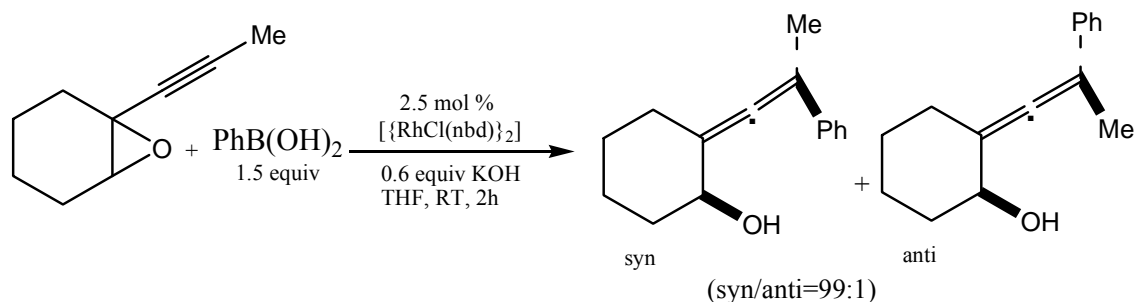
Figure 4.32. Rh catalyzed reaction of phenylboronic acid to alknyl oxirane.
(Structure: Miura, et al.2007)

Miyamuta et al. (2008) showed that indene derivatives can be synthesized from the reaction of 2-(chloromethyl)phenylboronic acid with alkynes in the presence of a Rh (I) complex (Figure 4.33).
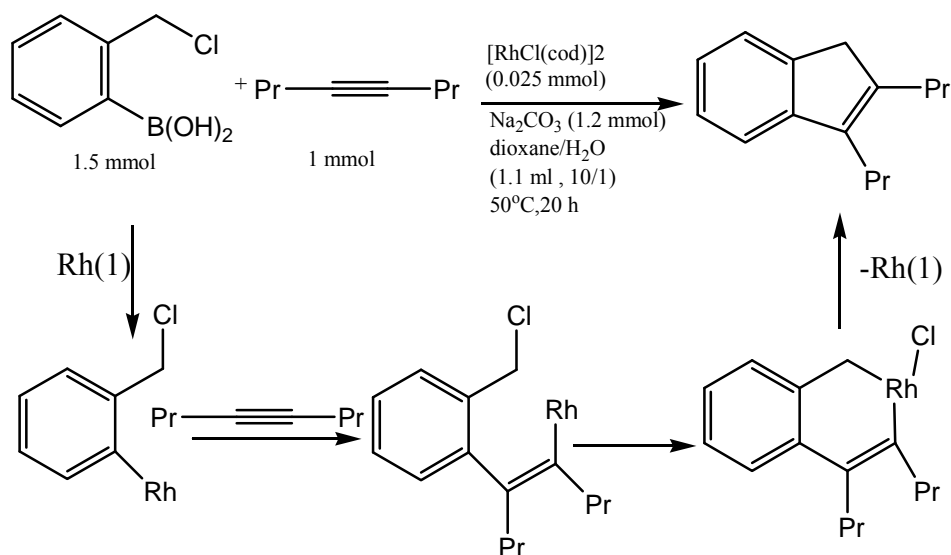
Figure 4.33. The reaction mechanism and conditions of rhodium catalyzed reaction of 2-
(chloromethyl)phenylboronic acid with alkynes. (Source: Miyamuta, et al.
2008)

4.1.1.6. Rhodium-Catalyzed Addition of Organoborons to Other Unsaturated Systems

Daniel et al. (2005) synthesized α- branched amines in two ways which are rhodium catalyzed diastereoselective addition of arylboronic acids to aliphatic and aromatic *N*-sulfinyl imines and enantioselective addition of arylboronic acids to *N*-diphenylphosphinoyl imins. Bolshan et al. (2005) made a study about rhodium catalyzed diastereoselective addition of organoboronic acids to chiral sulfinimines in the presence of water as a cosolvent and enantiomerically enriched diarylmethylamines were synthesized via formed sufinamide reagent (Figure 4.34). In another study, asymmetric synthesis of arylglycines was developed via rhodium catalyzed addition of arylboronic acids to *N*-tert-butanesulfinyl imino esters (Beenen, et al. 2006).
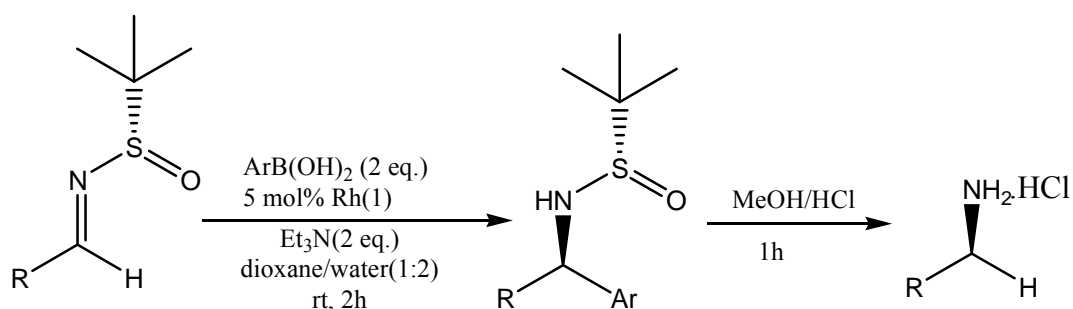
Figure 4.34. Rhodium catalyzed addition of organoboronic acids to chiral sulfinimines
(Source: Bolshan, et al. 2005)

Rhodium catalyzed arylation and alkenylation of C_{60} was reported using organoboron (Nambo, et al. 2007).

4.1.2. Rhodium Catalyzed Addition Reactions of PhenylBoroxine and Derivatives

Hayashi et al. (1999) reported that rhodium catalyzed asymmetric 1,4-addition to α,β-unsaturated phosphonates can be done by using chiral phosphine-rhodium catalyst and triarylcyclotriboroxanes instead of arylboronic acids.

4-aryl-2-piperidinones were synthesized via rhodium catalyzed asymmetric 1,4-addition of arylboron reagents to 5,6-dihydro-2(1H)-pyridinones using a chiral bisphosphine-rhodium catalyst (Senda, et al. 2001) (Figure 4.35).
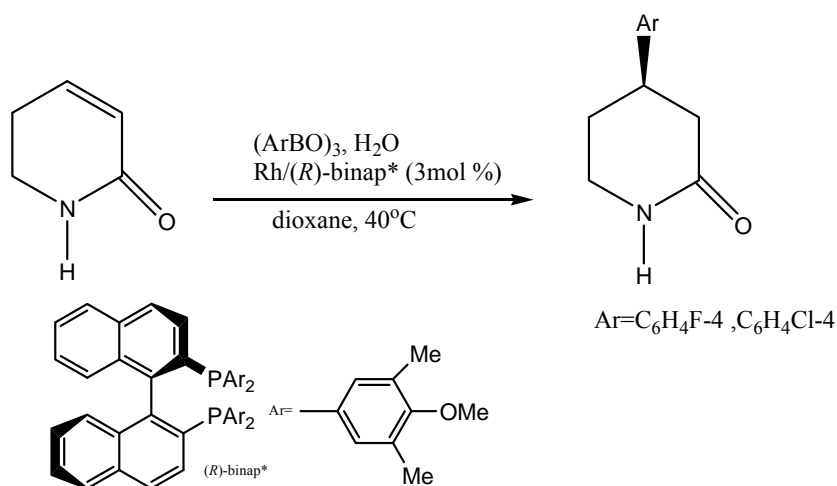
Figure 4.35. Rhodium catalyzed 1,4 addition of boroxine to 5,6-dihydro-2(1H)-pyridinones using a chiral ligand. (Source: Senda, et al. 2001)

Duursma et al. (2003) showed that combination of chiral monodentate phosphoramidite ligands can be used in the rhodium catalyzed conjugate addition of boronic acids to cyclohexenone, benzylidene acetone and 4-methyl-nitrostyrene and chiral catalysts based on hetero-combinations of ligands were more effective than the homo-combinations were observed. In another study of Duursma et al. (2005), rhodium catalyzed boronic acid addition of 2-cyclohexenone and 4-methyl-nitrostyrene was performed using a combination of a chiral and an achiral monodentate ligand (Figure 4.36).
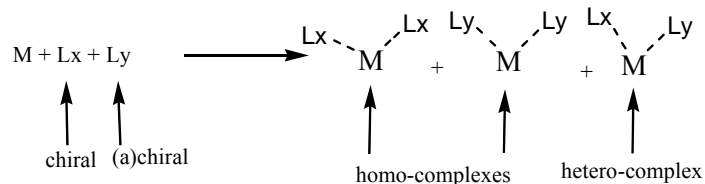
Figure 4.36. Ligand combination approach
(Source: Duursma, et al. 2005)

Asymmetric synthesis of diarylmethylamines was performed using a C_2-symmetric diene ligand as a chiral ligand in the rhodium catalyzed arylation of arylboroxine to *N*-tosylarylimines (Tokunaga, et al. 2004). In another study, asymmetric 1,4-addition of arylboroxines to cyclic α,β-unsaturated ketones was reported using a rhodium complex (Figure 4.37) (Chen, et al. 2006).

[RhCl((*S*,*S*)-Bn-bod*)]₂
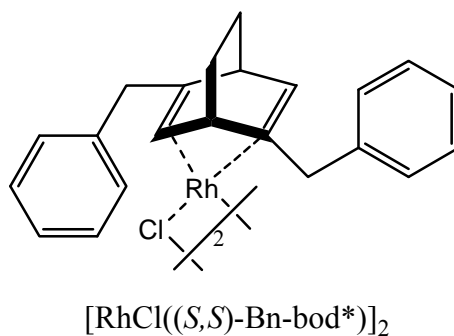
Figure 4.37. The structure of chiral rhodium complex
(Source: Chen, et al. 2006)

Miura et al. (2007) performed the rhodium catalyzed arylation reaction of cis-allylic diols with arylboroxines.

CHAPTER 5

INDANONES and INDENONES

5.1. Nomenclature of Indanones and Indenones

Indanone is an organic compound which has unstable cyclopentanone and benzene in its structure. Depending on the position of carbonyl functional group on the cyclopentanone ring, the indanone structure is called as either 1-indanone (Figure 5.2) or 2-indanone (Figure 5.1).
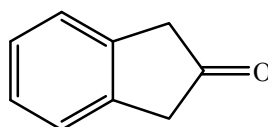
Figure 5.1. The structure of 2-indanone
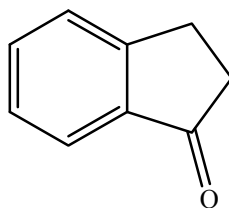
Figure 5.2. The structure of 1-indanone

1-indanone has two active centers. Depending on the reaction conditions (ionic or radical), the groups bear to these centers (Figure 5.3). The addition of groups in ionic conditions occurs in the center close to carbonyl group which is 1st center and the addition in radicalic conditions occurs in the center far from the carbonyl group which is 2nd center.
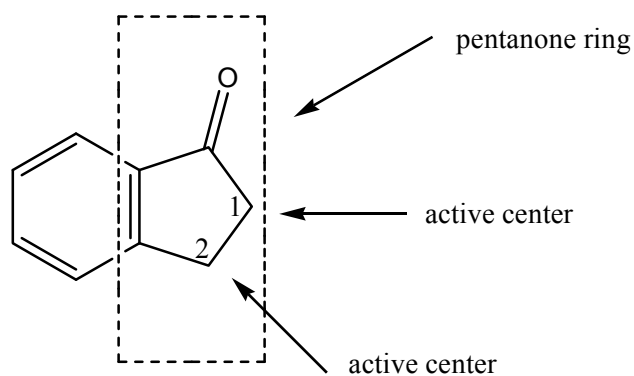
Figure 5.3. The active centers in 1-indanone

Indanones are named by labeling the carbon atoms. The labeling begins from the carbonyl carbon. First carbon atom after carbonyl-carbon atom is labeled as 2 and the second atom is labeled as 3 and carbon atom of benzene ring which is the closest carbon atom to the 3rd labeled carbon atom is labeled as 4 and so forth (Figure 5.4). When nomenclature is done, firstly the number of the group which is bonded to corresponding numbered carbon is given, then the names of groups are pronounced, lastly "1-indanone" is added such as 2,3- diphenyl -1-indanone (Figure 5.5). Also the nomenclature can be done by giving numbers to hydrogens which are numbers of carbons that hydrogens are bonded to. Nomenclature and labeling of indenones are done in the same way.
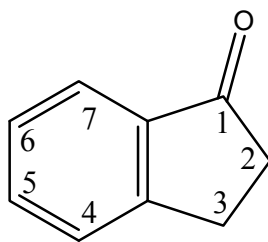
Figure 5.4. The labelling in indanone compound
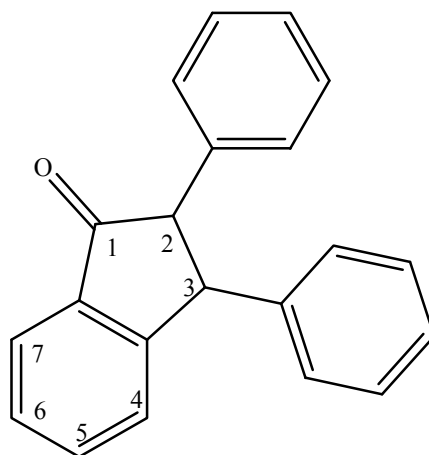
Figure 5.5. 2,3- diphenyl -1-indanone or 2,3-dihydro-2,3-diphenylinden-1-one

The carbonyl group in 2-indanone are labeled as 2 when the nomenclature are done. 2 –indanone can be called as 1*H*-inden-2(3*H*)-one. As in the nomenclature of 1-indanone, the numbers of the groups are numbers which are numbers of carbons that groups are bonded to (Figure 5.6).
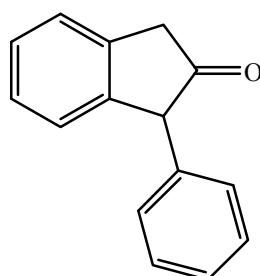
Figure 5.6. 1-phenyl-1*H*-inden-2(3*H*)-one or 1-phenyl-2-indanone

5.2. Indanones in Use

Indanones and related compounds are important bioactive molecules. They are important substrates for preparation of many biologically active compounds such as indacrinone (Hanna, et al. 1989), indanoyl isoleucine conjugates (Mithofer, et al. 2005), indanocines which are developed to combat drug-resistant malignancies (Figure 5.7)

(Leoni, et al. 2000) and other medicinally important products such as phenyl-tetrazolyl and 4-thiopyridyl indanones as allosteric potentiators of the metabotropi glutamate receptor 2 (Pinkerton, et al. 2005) and monoquaternary neuromuscular blocking agents based on 1-indanone (Biggs, et al. 1976). Indanones have been studied for various biological activities including cancer and Alzheimer's type of diseases.
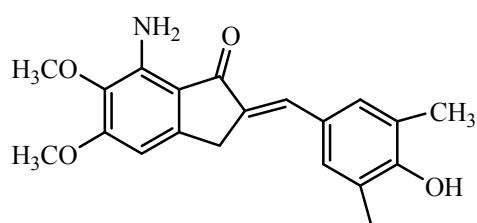
Figure 5.7. The structure of indanocine
(Source: Leoni, et al. 2000)

Indanone analogue such as donepezil hydrochloride has been used for the treatment of Alzheimer's disease. It acts as AChE (Acetylcholinesterase) inhibitor (Sugimoto, et al. 1999) (Figure 5.8).
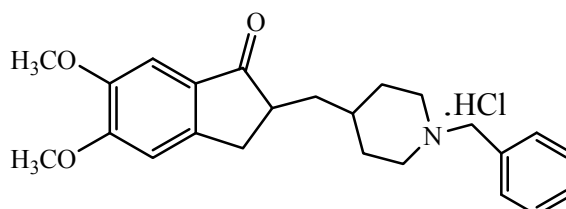
Figure 5.8. The structure of donepezil hydrochloride
(Sugimoto, et al. 1999)

1-indanone and its analogues are useful intermediates for the synthesis of compounds some of which have applications as pharmaceuticals, especially as analgesics (Hammen, et al. 1977) and antihypertensives (Bhattacharya, et al. 1986), as well as tobacco flavoring agents (Schumacher, et al. 1974). Indanones are commonly used as starting agent for the synthesis of ninhydrin which is used determination of fingerprints (Joullie, et al. 1991).

Camps et al. (2006) reported a study about the synthesis of spiro{cyclopenta[a]indene-2,2'-indene}diones in connection with the synthesis of novel

donepezil-based anti-Alzheimer agents by the reaction of 1-indanones with aromatic aldehydes under NaOEt base catalysis in THF (Figure 5.9).

R=OMe,H
R'=2-,3-, and 4-pyridyl, 2-furyl,2-thienyl,*N*-methyl-2-pyrrolyl,phenyl
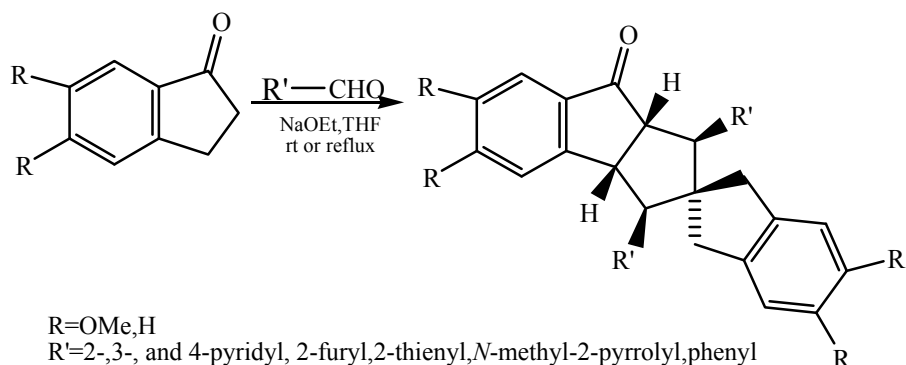
Figure 5.9. The reaction of 1-indanones with aldehyde using NaOEt base
(Source: Camps, et al. 2006)

In another study, It was reported that a novel series of 1-indanone a_1-adrenoceptor antagonists were synthesized relative to reasoning of ligand-based drug design (Li, et al. 2007) (Figure 5.10).

R=3,4-dimethoxy
R=4-methoxy
R=3,4,5-trimrthoxy

R=1-naphtyl
R=2,4-dimethyphenyl
R=2,6-dimethylphenyl
R=4-*t*-butylphenyl
R=2,4-dichlorophenyl

R=4-methoxyphenyl
R=3,4-dimethylphenyl
R=phenyl
R=2-chlorophenyl
R=4-chlorophenyl
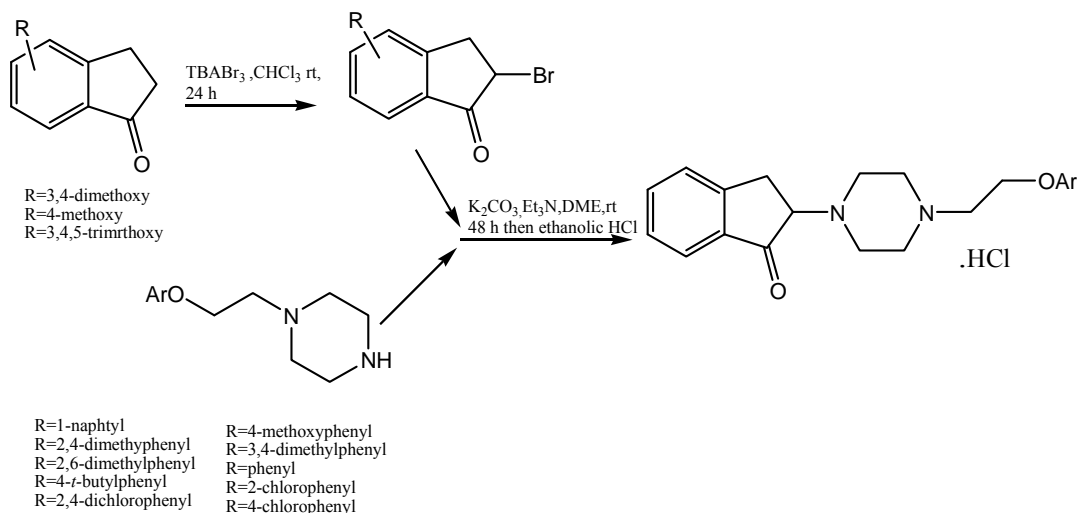
Figure 5.10. The synthesis processes of 1-indanone a_1-adrenoceptor antagonists
(Source: Li, et al. 2007)

Finkielsztein et al. (2008) developed a series of 1-indanone thiosemicarbazone derivatives for new antiviral compounds by the reaction of 1-indanone with thiosemicarbazide in ethanol (Figure 5.11). They examined the synthesized 1-indanone

thiosemicarbazone derivatives against bovine viral diarrhoea virus as a surrogate model for hepatitis C virus and observed that these derivatives were as antiviral agents for the cure of infections brought about by other highly related members of Flaviviridae family, as hepatitis C virus.
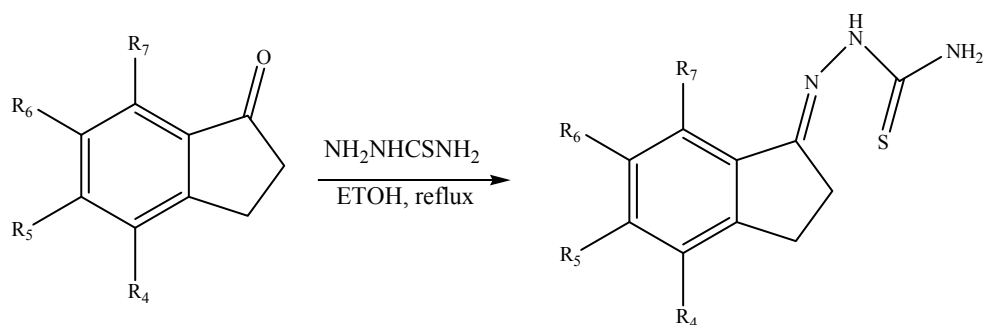
Figure 5.11. The synthesis of 1-indanone thiosemicarbazone derivatives by the reaction of 1-indanones with thiosemicarbazide in ethanol (EtOH) (Source: Finkielsztein, et al. 2008).

Also, Saxena et al. (2008) reported that gallic acid-based indanone derivatives showed potent anticancer activity against hormone-dependent breast cancer, oral and liver cancer cell lines (Figure 5.12) (Source: Saxena, et al. 2008).
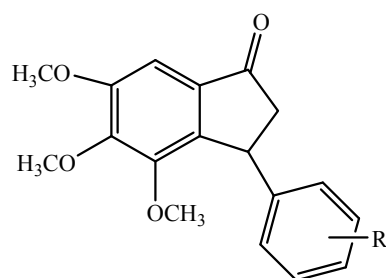
Figure 5.12. The structure of gallic acid-based indanone (Source: Saxena, et al. 2008)

In a another study, Grupta et al. (2004) synthesized novel dimer of 2-(4-pyridylmethyl)-1-indanone which showed strong inhibition of human placental aromatase by the aldol condensation of 1-indanone with pyridine-4-carboxaldehyde in alkaline conditions (Figure 5.13).
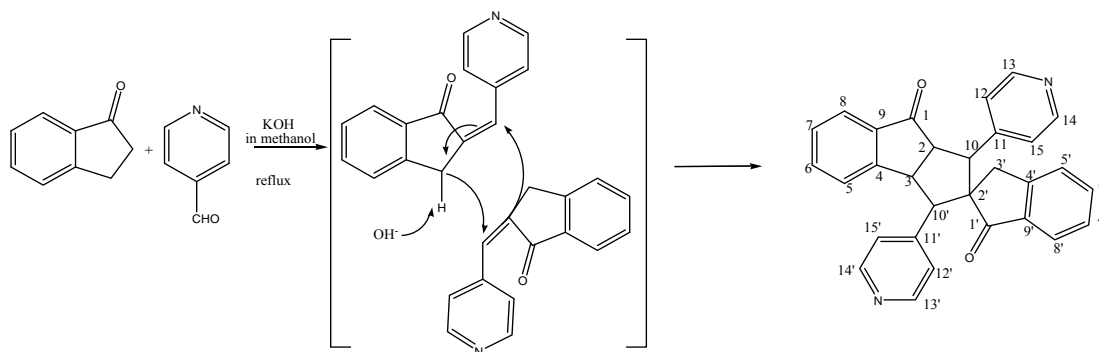
Figure 5.13. The synthesis of 2-(4-pyridylmethyl)-1-indanone by the aldol condensation of 1-indanone with pyridine-4-carboxaldehyde (Source: Grupta, et al. 2004)

5.3. Synthesis of Indanones

There are many studies about synthesis of indanones with various synthesis methods.

In 1999, Gevorgyan et al. (1999) developed a method to synthesize indanols by the cyclic vinylpalladiation of aromatic aldehyde with alkynes by using a palladium catalyst and DMF as reaction medium at 60°C. But, when the reaction time was extended, it was observed that indenol was converted to indanone (Figure 5.14).
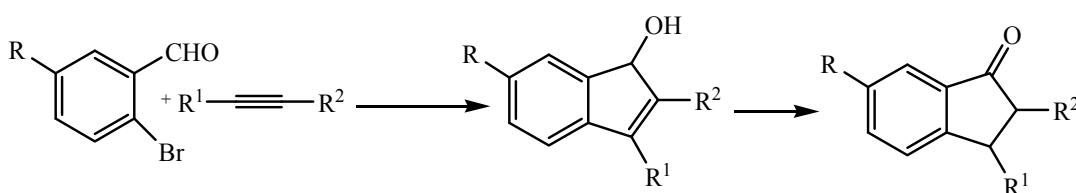
Figure 5.14. The synthesis of indanones via converting indenols to indanones by reaction time extension (Source: Gevorgyan, et al. 1999)

2-indanones were synthesized by the reaction of (trialkylsilyl)arylketenes with (trimethylsilyl)diazomethane in [4 + 1] annulation process at room temperature (Dalton, et al. 2002). When meta-alkyl substituents arylketenes were used , mixtures of isomeric indanones were obtained. However, desired procuct, 1,3-bis(silyl)-indanone was synthesized but after purification step, 1,3-bis(silyl)-indanone was converted to

mono(silyl)indanone due to the cleavage of Me₃Si groups by silica gel treatment or depending on conditions such as acidic or basic (Figure 5.15)
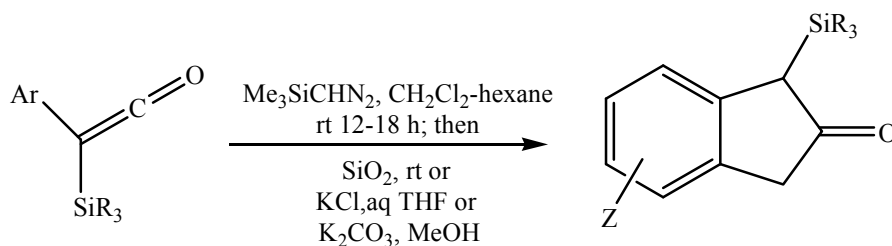
Figure 5.15.The reaction conditions for synthesizing 2-indanones from the reaction of (trialkylsilyl)arylketenes with (trimethylsilyl)diazomethane in [4+1] annulation process (Source: Dalton, et al. 2002)

In another study, 1-indanones were synthesized via Friedel Crafts reaction of p-methylphenol with α,β-unsaturated carboxylic acids using AlCl₃ as a lewis acid in chlorobenzene with conventional heating and also, the reaction was carried out in microwave without using a solvent. In this case, it was observed that the reaction time became shorter. (Silva, et al. 2002). Superacid such as trifluoromethanesulfonic acid (CF₃SO₃H) catalyzed cycli-acyalkylation of aromatics with unsaturated carboxylic acids resulted in the formation of 1-indanones (Prakash, et al. 2003). Cui et al. (2004) reported that 1-indanones can be synthesized via intramolecular Friedel–Crafts acylation reaction of 3-arylpropionic acids using Tb(OTf)₃ at 250°C.

Shintani et al. (2005) synthesized β-monosubstituted indanones with high yields by the rhodium catalyzed isomerization of α-arylpropargyl alcohols in THF. Among different substrates, they observed that when meta-substituted substrates are used, cyclization occurs selectively at the less hindered site of the aromatic ring. Also, this study reported that the reaction showed 1,4 hydrogen shift in the proposed mechanism of the reaction (Figure 5.16). Also, they reported rhodium catalyzed isomerisation of racemic α-arylpropargl alcohols using chiral bisphosphine ligand.
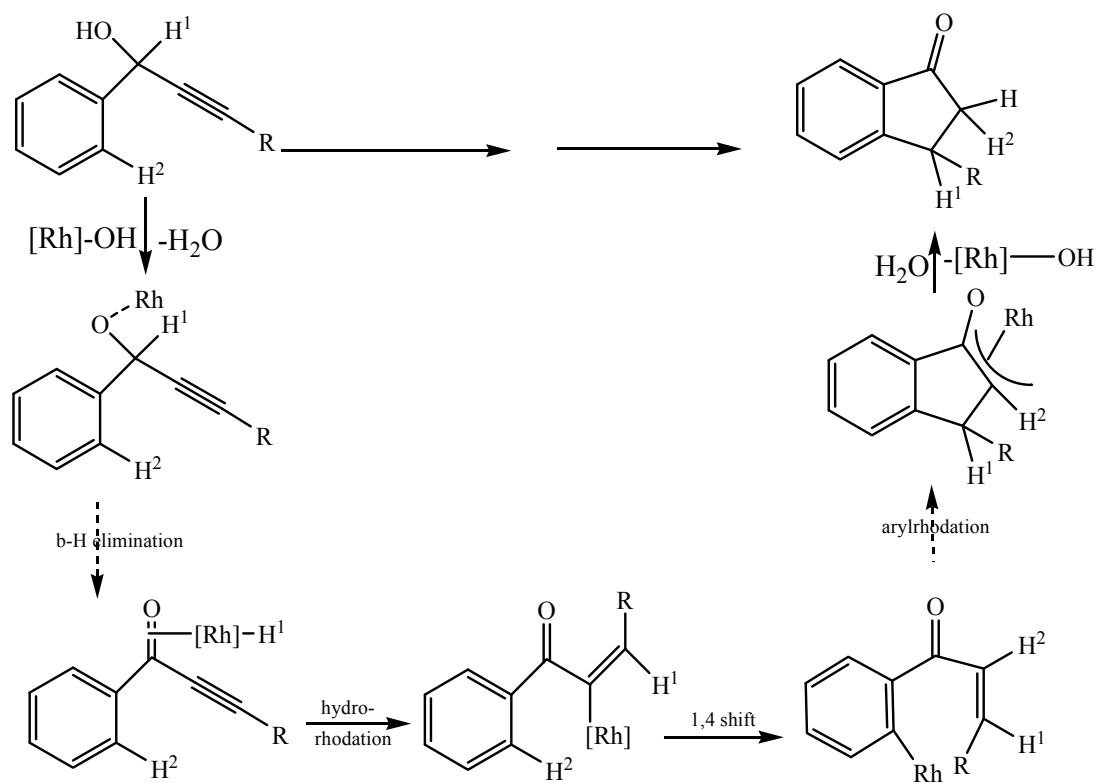
Figure 5.16.Proposed mechanism for rhodium catalyzed isomerization of a-
arylpropargyl alcohols. (Source: Shintani, et al. 2005)

In another study, Shintani et al. (2005) synthesized β,β -disubstituted indanones with high yields via rhodium catalyzed addition of arylzinc reagents to aryl alkynyl ketone using dppf [1,1'-bis(diphenylphosphanyl) ferrocene] as a ligand in 1,2-dichloroethane. Also, they developed a study about the addition of aryl boronates to aryl alkynyl ketones using rhodium catalysis. They reported that this study enables the formation of enantio enriched indanones (Shintani, et al. 2007). Another study about synthesis of 3-substituted indanones was performed by hydroacylation of 2-vinyl benzaldehyde using rhodium catalyst in dichloromethane (Kundu, et al. 2005). They reported that the concentration of the substrate plays an important role in the reaction (Figure 5.17).
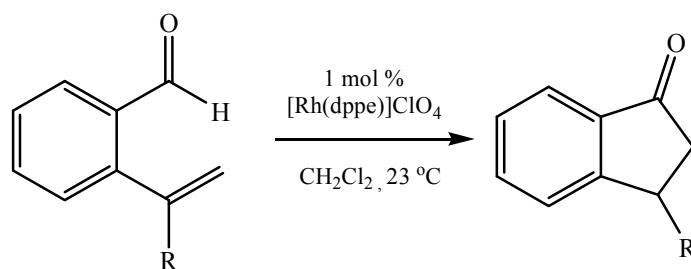
Figure 5.17. Rhodium catalyzed hydroacylation of 2-vinylbenzaldehyde
(Source: Kundu, et al. 2005)

Lawrence et al. (2006) demonstrated that indanones can be synthesized by the dry TFA catalyzed microwave-assisted Nazarov cyclization of chalcones (Figure 5.18).
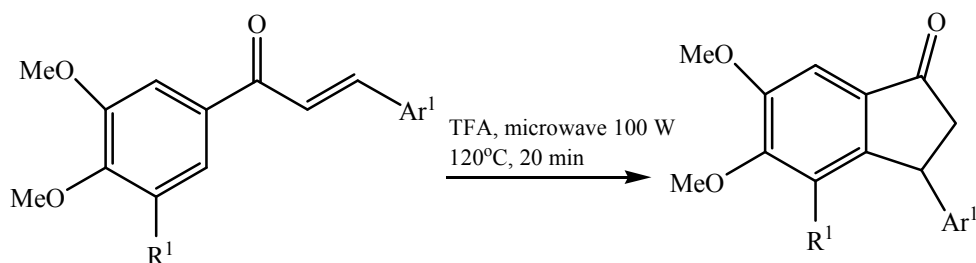
Figure 5.18. The synthesis of indanones via TFA catalyzed microwave-assisted Nazarov cyclization of chalcones (Source: Lawrence, et al. 2006).

Chiral 3-substituted indanones were synthesized by palladium catalyzed enantioselective reductive-heck reaction using a chiral ligand such as (*R*)-3,5-XylMeOBIPHEP and base (Minatti, et al. 2007). They observed that when a proton songiny reagent is used, *trans*-2-alkyl-3-aryl-substituted indanones were obtained in high yields but, by using 1,2,2,6,6-pentamethylpiperidine, α-exo-methylene indanones were obtained (Figure 5.19).
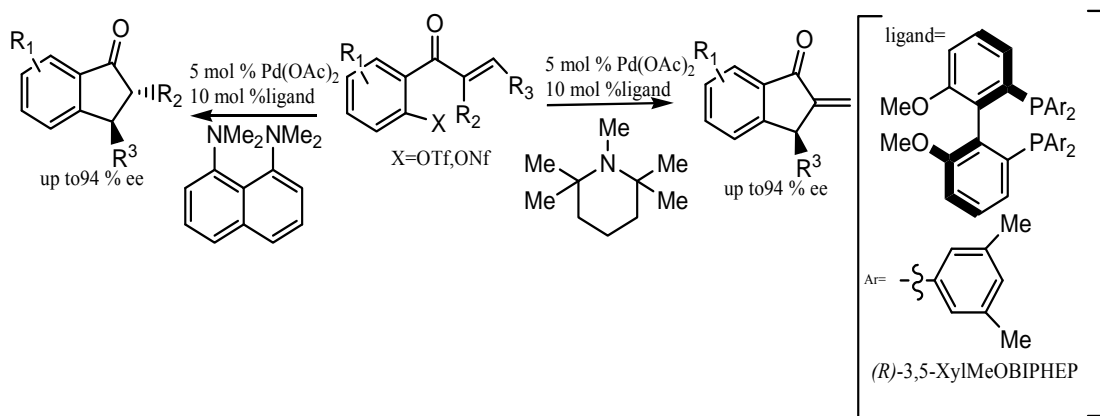
Figure 5.19. Palladium-catalyzed asymmetric reductive-Heck reaction for the synthesis of chiral 3-substituted indanones and α-exo-methylene indanones (Source: Minatti, et al. 2007)

Tandem transformation via Nazarov cyclization and electrophilic fluorination of polarized enones such as alkylidene β-ketoester in the presence of Cu(OTf)$_2$ as a catalyst and fluorinating reagent in dichloromethane led to formation of fluorine-containing 1-indanone derivatives with two new stereocenters (Nie, et al. 2007). The reaction occured with high diastereoselectivity (Figure 5.20). Another study about fluorinated indanone derivatives was performed by way of a Lewis acid-catalyzed Knoevenagel condensation/Nazarov cyclization/electrophilic fluorination sequence (Cui, et al. 2007). It was reported that the reaction occured with high stereoselectivity to afford *trans*-fluorinated 1-indanones (Figure 5.21).
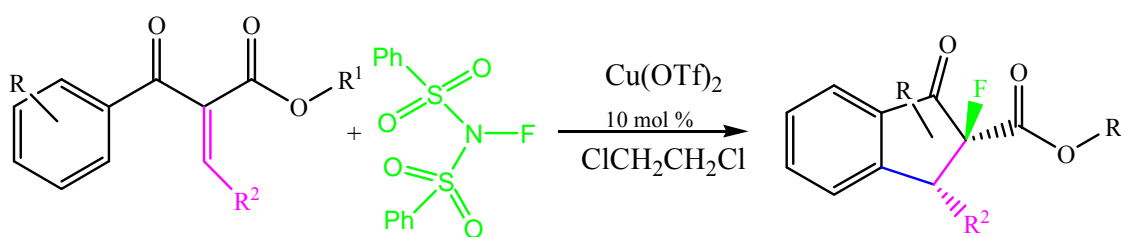
Figure 5.20. Catalytic tandem Nazarov cyclization and electrophilic fluorination trapping of alkylidene β-ketoester (Source: Nie, et al. 2007)
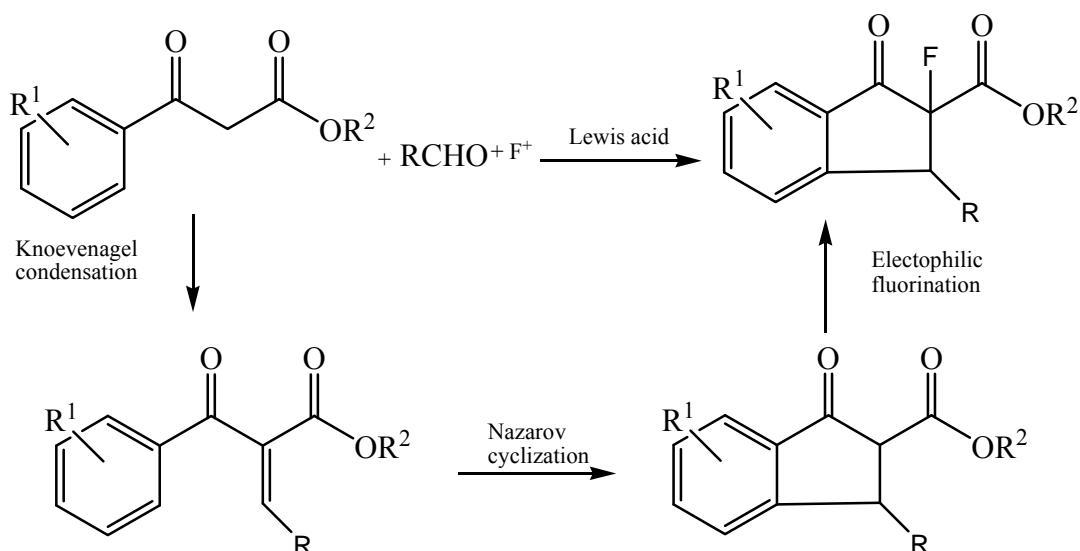
Figure 5.21.Lewis acid catalyzed triple cascade reaction of aromatic β-ketoester with aldehyde using a lewis acid and fluorinating reagent (Source: Cui, et al. 2007).

Recently, 2,3-disubstituted indanones as single *trans*-isomer were synthesized from the reaction of phenylalkyne derivatives with aldehydes using SbF_5 and ethanol as an additive at 90^oC in dichoromethane in one pot (Saito, et al. 2008). They observed that when the reaction is performed at 60^oC, enone is obtained in high yields. But, it can be converted to indanone whether reaction was carried out at 90^oC (Figure 5.22).
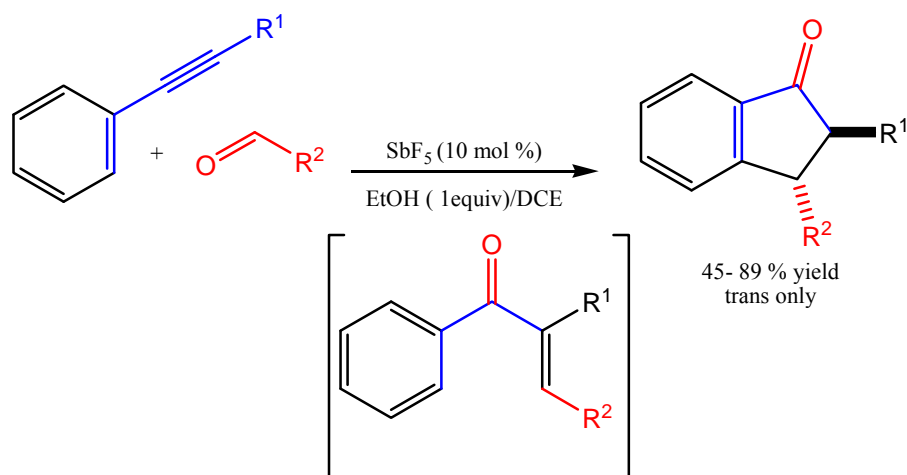
Figure 5.22.The synthesis of 2,3 disubstituted indanones from the reaction of phenylalkyne and aldehyde using SbF_5 and EtOH (Source: Saito, et al. 2008)

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5.4. Carbonylative Synthesis of Indanones

There are also few examples for the carbonylative synthesis of indanones.

In 1988, 1-indanones were synthesized via cobalt catalyzed cyclocarbonylation of acetylene in THF in present of phosphine as a ligand under 100 atmosphere CO at 220°C (Doyama et al. 1988). The selectivity of indanones was depending on the concentration of the reactant (Figure 5.23).
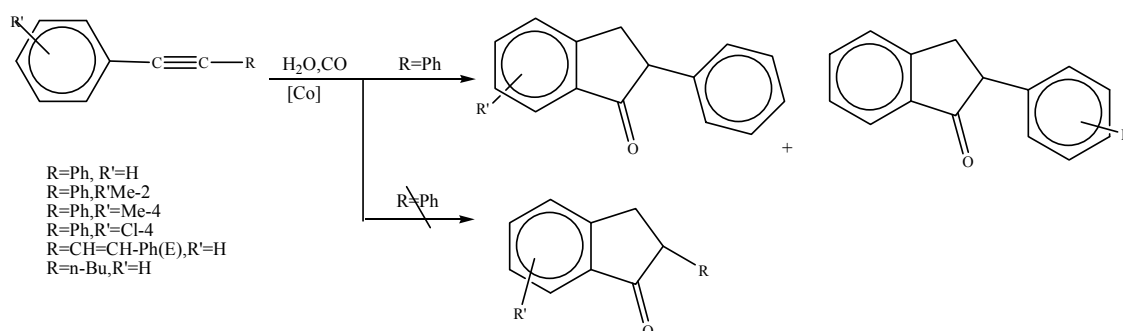
Figure 5.23.The cyclocarbonylation of acetylene under water gas shift for the synthesis of 1-indanones (Source: Doyama, et al. 1988)

Takeuchi et al. (1993) made a study about the rhodium catalyzed desilylative cyclocarbonylation of l-aryl-2-(trimethylsilyl) acetylenes using amine as a base under water-gas shift reaction to synthesize 2,3-dihydro-l*H*-inden-l-ones (Figure 5.24).
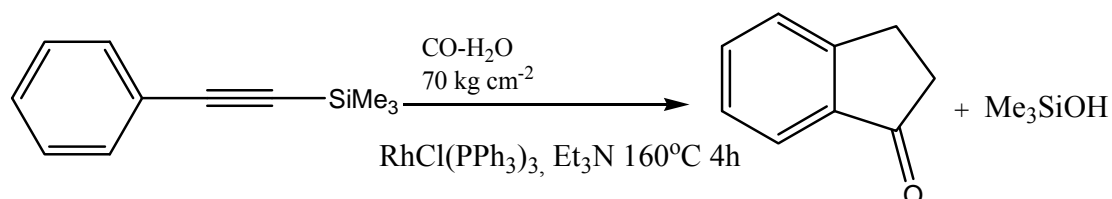
Figure 5.24.The desilylative cyclocarbonylation of l-aryl-2-(trimethylsilyl)acetylenes under water -gas shift for the synthesis of 2,3-dihydro-l*H*-inden-l-ones (Source: Takeuchi, et al. 1993)

Rhodium catalyzed cyclic carbonylation of alkynes gave 3-alkoxycarbonylindanones in the presence of alcohols (Yoneda, et al. 1999). The type of

used alcohol affected the reaction. It was reported that higher yields of indanone were obtained in primary alcohols than secondary alcohols whereas indanone derivatives were not obtained in t-butyl alcohol.

Palladium catalyzed carbonylative cyclization of unsaturated aryl iodides, dienyl triflates and bromides led to formation of indanones (Gagnier, et al. 2003). It was reported that carbonylative cyclization has important effect on substrates containing a terminal olefin (Figure 5.25).
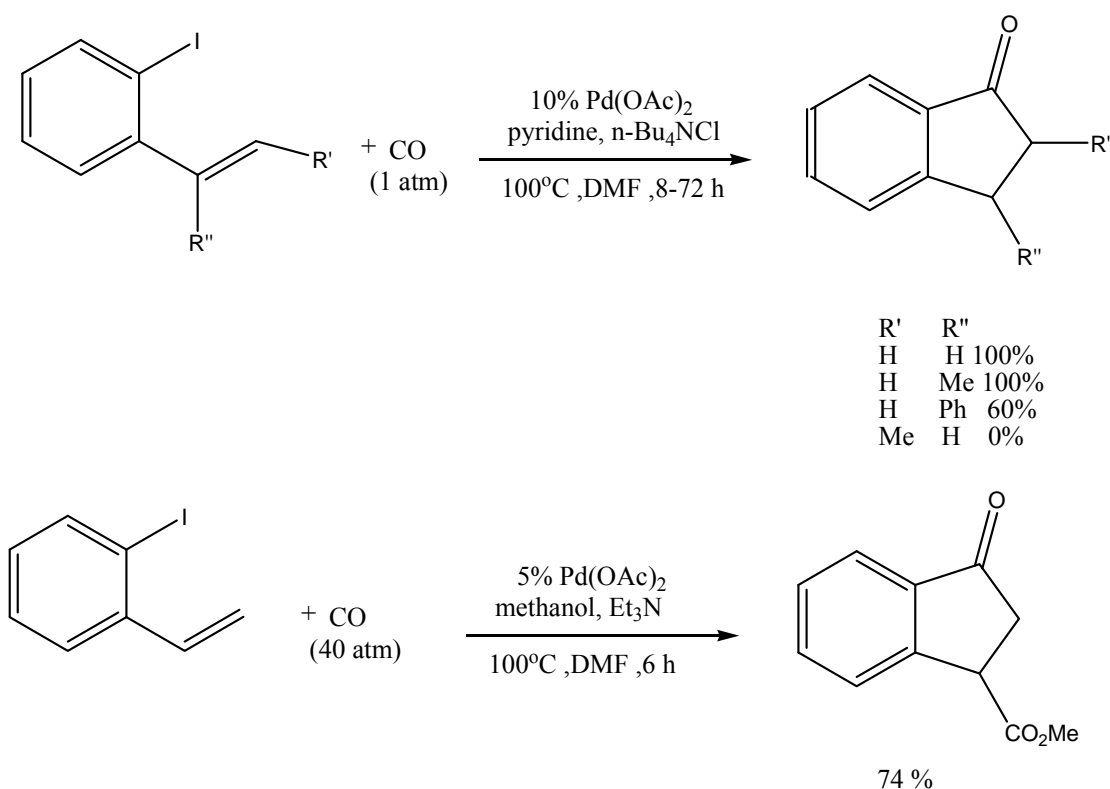
Figure 5.25.Palladium catalyzed carbonylative cyclization of unsaturated aryl iodides for the synthesis of 1-indanones (Source: Gagnier, et al. 2003).

Wu et al. (2005) synthesized indan-1-ones and 3-acylaminoindanones via carbonylative cyclization of unsaturated aryl bromides and chlorides using molybdenum hexacarbonyl as a solid source of carbon monoxide in presence of palladium catalyst. Neutral and electron-rich o-halostyrene derivatives gave 1-indanones in high yields. Internal Heck arylations of enamides with o-bromoaryl triflates gave 3-amidoindan-1-ones.

Carbonylative cyclization of organic halides with a tethered carbon nucleophile with aldehydes as a substitute for carbon monoxide in present of rhodium catalyst resulted in the formation of indanones (Morimoto, et al. 2007) (Figure 5.26).
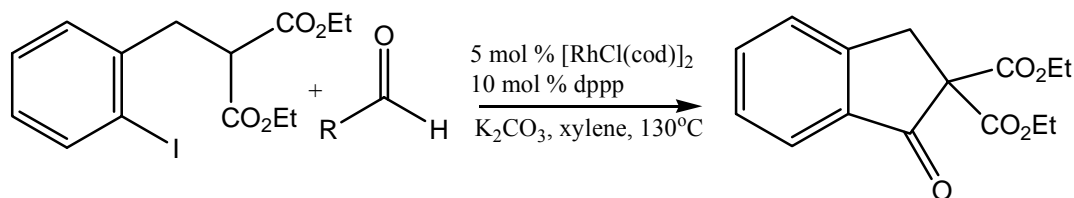
Figure 5.26. The synthesis of indanones via Rh (I)-catalyzed CO gas-free carbonylative cyclization of organic halides with tethered nucleophiles using aldehydes as a substitute for carbon monoxide (Source: Morimoto, et al. 2007).

5.5. Indenones in Use

Indenones can be used as intermediates for the synthesis of natural molecules such as C-nor-D-homosteroids (Chatterjee, et al. 1970, Martens, et al. 1972), photochromic indenone oxides (Ullman, et al. 1966) and indanones (Zimmerman, et al. 1956) (Figure 5.27).

2,3-Diphenylindenone Oxide.   C-Nor-D-homo Steroid System
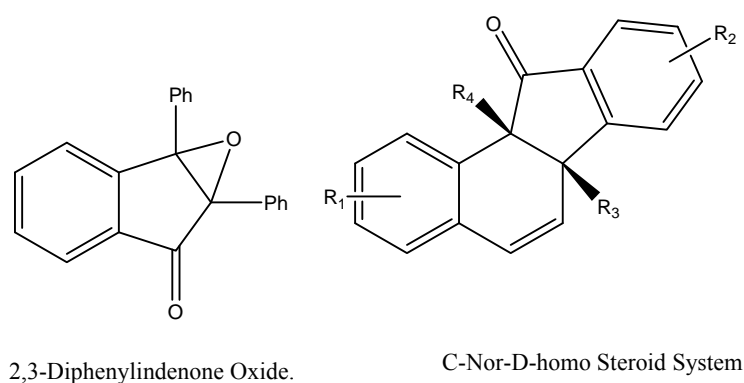
Figure 5.27. The structure of some natural molecules

Indenones have been used as alcolic fermantation activators (Franck, et al. 1944) and estrogenbinding receptors (Anstead, et al. 1989).

5.6. Synthesis of Indenones

There are many studies about the synthesis of indenones especially 2,3 disubstituted indenones in the litrature.

In 1970, 2-alkylindenones were synthesized by the intramoelcular Friedel-Crafts acylation of α-alkyl-β-aryl-β-chloropropionyl chlorides. (Floyt, et al. 1970)

Larock et al. (1993) developed a method for synthesis of 2,3 disubstituted indenones from the reaction of internal alkynes with o-iodo- or o-bromobenzaldehyde using palladium catalyst under mild conditions in moderate yields. They used two procedure which are called A and B procedure. A procedure which concludes 5 mol % Pd(OAc)$_2$, 4 equiv of NaOAc, 1 equiv of n-Bu$_4$NCl, 10 mL of DMF at 100°C was suitable for diarylalkynes and gave better yields. B procedure which concludes 5 mol Pd(OAc)$_2$, 1 or 4 equiv of Na$_2$CO$_3$, 1 equiv of n-Bu$_4$NCl, 10 mL of N,N-dimethylacetamide was general method for variety of alkynes containing aryl, silyl and tert-alkyl groups. It was observed that when the alkyne having tertiary alkyl, trimethylsilyl or other hindered groups was used, the more sterically demanding group favored the 2-position of the indenone but, less hindered alkynes, such as 1-phenyl-1-propyn gave 1:1 mixture of regioisomers (Figure 5.28). In Larock et al.'s another study, 2,3 diphenylindenone with high yields were synthesized by the reaction of o-iodobenzonitrile with alkyne using palladium catalyst and base such as Et$_3$N in DMF-H$_2$O at 130°C for 24 h (Larock, et al. 1999).
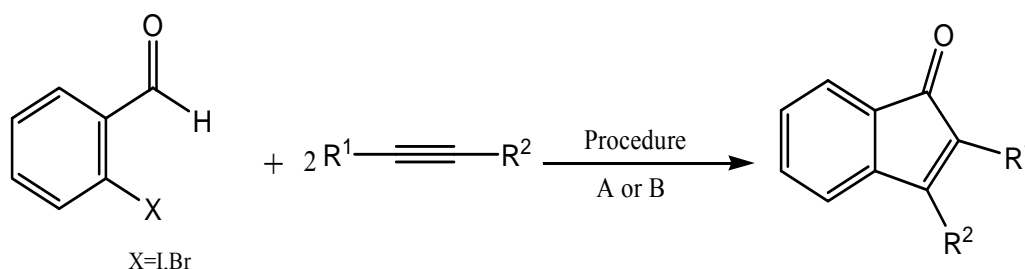
Figure 5.28. The synthesis of 2,3 disubstituted indenones via palladium catalyzed reaction of alkynes with o-iodo- or o-bromobenzaldehyde (Source: Larock, et al. 1993)

2,3-disubstituted-1-indenones were also synthesized from the reaction of aroyl chlorides with alkynes using rhodium catalyst in presence of ligand such as triphenylphosphine (PPh$_3$) (Kokubo, et al. 1996). It is observed that with unsymmetrical alkynes, two regioisomers were formed. They reported that the precedence of the reaction courses resulting in vinyl chlorides and indenones depends on the structure of acid chlorides as well as that of alkynes (Figure 5.29).

R^1=R^2=Pr
R^1=R^2=Et
R^1=R^2=Ph
R^1=Ph,R^2=Me
R^1=Bu,R^2=Me
R^1=Ph,R^2=SiMe$_3$
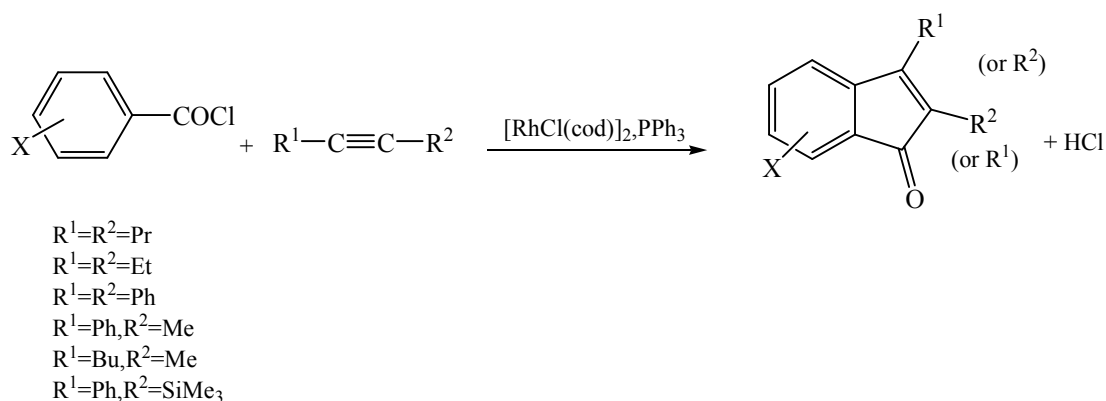
Figure 5.29. The synthesis of 2,3-disubstituted-1-indenones by the rhodium catalyzed reaction of aroyl chlorides with alkynes (Source: Kokubo, et al. 1996)

Zengin et al. (2001) developed a simple method for efficient synthesis of indenone by the reaction of dichloroketone with NEt$_3$. In another study, indenones were synthesized in high yields via the conversion of indanones to indenones using Et$_3$N in presence of palladium catalyst in CH$_3$CN (Hauser, et al. 2001). They observed that all of the indenones were unstable, the synthesized indenones should be used immediately because indenones lacking substituents at the 2- and 3-positions were notoriously unstable.

Pletnev et al. (2002) synthesized 2,3-diarylindenones by Pd catalyzed annulation of alkynes with 2-iodoarenenitriles in presence of a amin such as Et$_3$N at 100°C in DMF-H$_2$O. With various alkynes such as 1-phenyl-1-propyne, 4,4-dimethyl-2-pentyne, 2,2,7,7-tetramethyl-3,5-octadiyne, poor yields were obtained at 100°C. But, they reported that when the temperature at which reaction occurred was increased from 100°C to 130°C, yields were increased (Figure 5.30). Vasilyev et al. (2004) developed a simple and fast method for the synthesis of 3-aryl indenones by the intramolecular cyclization of 1,3-diarylpropynones in superacidic media.
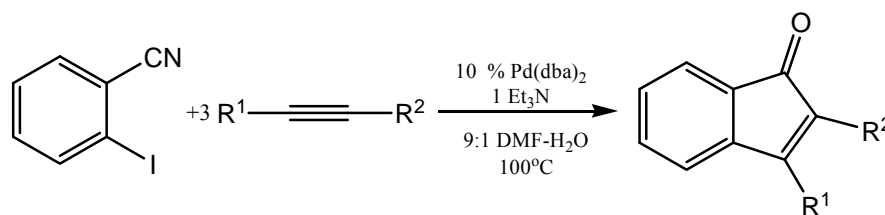
Figure 5.30 . Palladium catalyzed annulation of alkynes with 2-iodoarenenitriles for synthesis of 2,3-diarylindenones (Source: Pletnev, et al. 2002)

For the synthesis of substituted indenones or indanones, Miura et al. (2005) developed [3 + 2] annulation reaction using 2-cyanophenylboronic acid and internal alkynes in presence of rhodium catalyst at 100°C in dioxane-H_2O. It was observed that terminal alkynes were unsuccesful for this annulation reaction (Figure 5.31). In another study, 2,3-disubstituted indenones were obtained via Pd(II)-catalyzed reaction of internal alkynes with phenylboronic acids bearing ortho ester (Tsukamoto, et al. 2007).
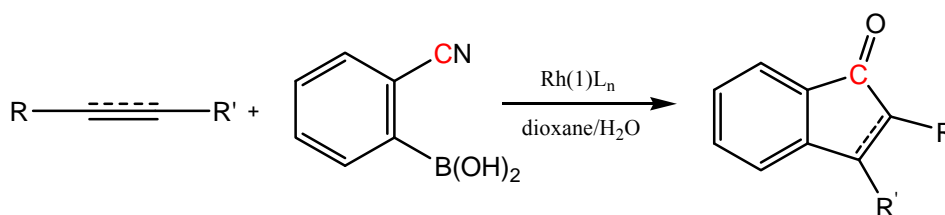
Figure 5.31. Synthesis of indanones via rh catalyzed [3+2] annulation reaction of 2-cyanophenylboronic acid with alkynes (Source: Miura, et al. 2005)

In the literature, there are also studies about the photochemical and thermal synthesis of indenones.

2,3-diaryl-[lH]-inden-1-ones were performed by the thermal and photolytic reactions of Fp-(SnAr$_3$) (Fp = dicarbonyl(-η^5- cyclopentadienyl)iron, Ar = phenyl, p-tolyl) with diphenylacetylene (Nesmeyanov, et al. 1971). In another study, Kolobova and Goncharenko (1979) synthesized thienyl and furanyl indenone isosteres from the photochemical reaction of Fp-(2-thienoyl) and Fp-(2-furanoyl) with diphenylacetylene (Kolobova and Goncharenko 1979). In 1990, Butler et al. (1990) reported that the thermal and photochemical reactions of Fp-(1- and 2-naphthoyls) with diphenylacetylene and 1-phenylprop-2-yne gave indenones (Figure 5.32). They showed that insertion of diphenylacetylene came before that of carbon monoxide.
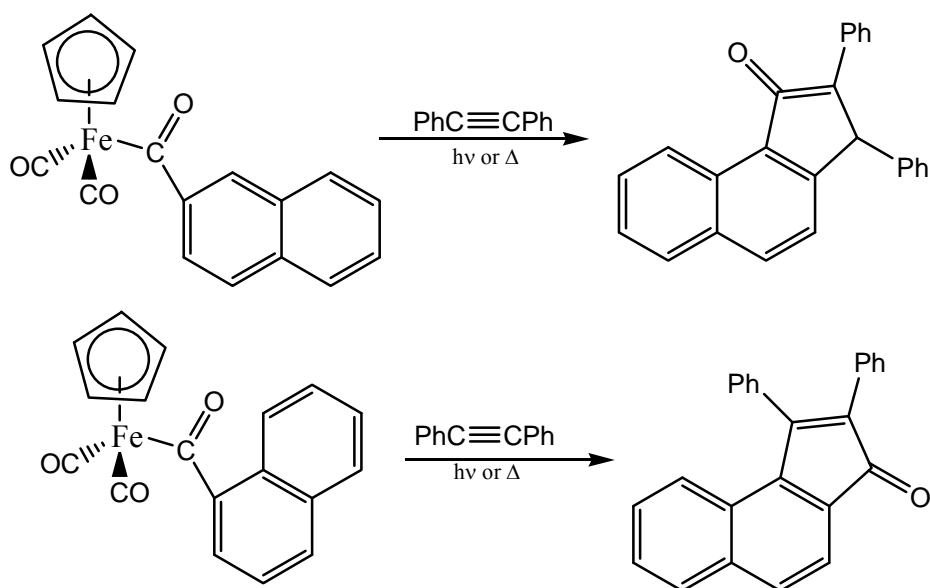
Figure 5.32. The synthesis of indenones via photochemical and thermal reaction of Fp-
(1- and 2-naphthoyls) with diphenylacetylene (Source: Butler, et al. 1990)

5.7. Carbonylative Synthesis of Indenones

In 1980, Liebeskind et al. (1980) found a method for the synthesis of indenones. It was reported that the reaction of *o*-dihalo aromatics with nickel carbonyl in the presence of an alkyne at 120$^{\text{o}}$C led to the formation of indenones. Also, in this study, palladium-catalyzed variant of the indenone synthesis using zinc dust as the terminal reductant in EtOH under 88 psi of CO was demonstrated.

Fukuyama et al. (1997) developed a simple method for synthesis of 2-substituted inden-1-ones by the $Ru_3(CO)_{12}$-catalyzed reaction of aromatic imines with olefins under CO atmosphere. (Figure 5.33).
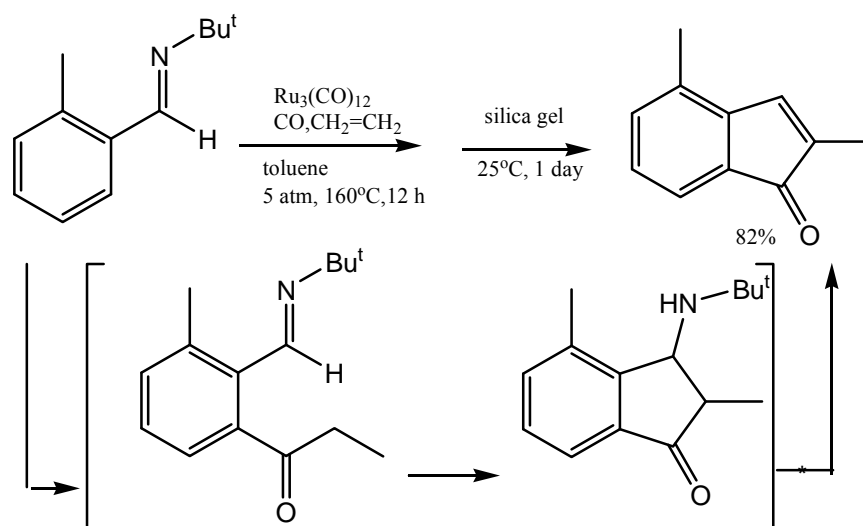
Figure 5.33. The synthesis of 2-substituted inden-1-ones via $Ru_3(CO)_{12}$-catalyzed carbonylation of aromatic imines with olefins (Source: Fukuyama, et al. 1997)

Harada et al. (2007) synthesized indenones via rhodium(I) catalyzed carbonylative cyclization reactions of alkynes with 2-bromophenylboronic acids (Figure 5.34). It was reported that regioselectivity was affected by the steric and electronic factors and sterically bulky and electron-withdrawing groups favored the α-position of indenone.
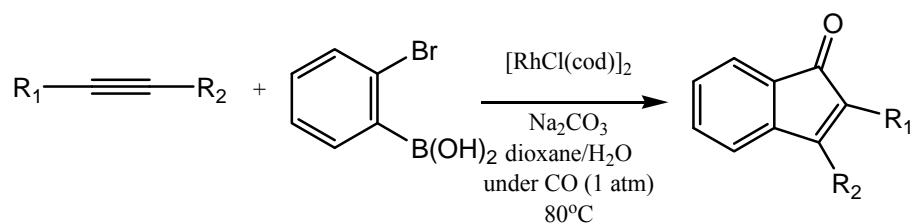
Figure 5.34. Rhodium(I) catalyzed carbonylative cyclization reaction of alkynes with 2-bromophenylboronic acids (Source: Harada, et al. 2007)

Recently, the synthesis of indenones was performed by rhodium catalyzed CO gas-free carbonylative cyclization reactions of alkynes with 2-haloarylboronic acids in presence of formaldehyde (Morimoto, et al.2009). It was reported that $[RhCl(BINAP)]_2$ and $[RhCl(cod)]_2$ were responsible for the decarbonylation of formaldehyde. Also, when unsymmetrically substituted alkynes were used, sterically bulky and electron-withdrawing groups favored the α-position of indenones was observed (Figure 5.35).
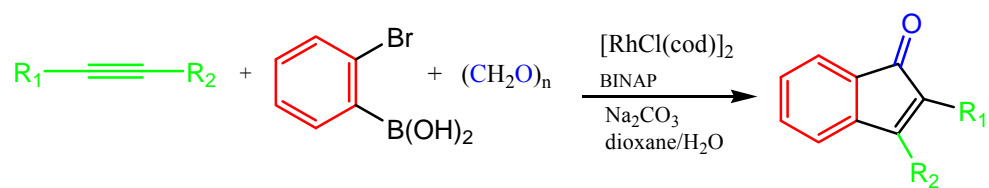
Figure 5.35. The synthesis of indenones via rhodium catalyzed CO gas- free
carbonylative cyclization reaction of alkynes with 2-haloarylboronic acids
using formaldehyde (Souce: Morimoto, et al. 2009).

CHAPTER 6

EXPERIMENTAL STUDY

6.1. General Procedures for Synthesis of Alkynes by a Modification of Sonogashira Coupling Reactions

Two different procedures were applied for the synthesis of alkynes.

Teflon-coated magnetic stir bar was put into a 25 mL round bottom flask. This flask was closed with a rubber septum and flame dried under vacuum. After that, the flask was purged with dry argon and $PdCl_2(PPh_3)_2$ (16.8 mg, 6 mol%), CuI (15.2 mg, 10 mol%), 4-iodobenzotrifluoride as starting material (1 equiv, 0.80 mmol) were added into the flask. After that, dry benzene (4.0 mL, starting material is 0.20 M in dry benzene) ,which was sparged with dry argon, was added by the help of syringe while the mixture being stirred. After that, DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) (718 μL, 6 equiv), which was sparged with argon, was added by syringe and the reaction media was purged with argon. At the end, cooled thrimethylsilylethynylene (57 μL, 0.50 equiv) was added into reaction flask by syringe and distilled water (5.8 μL , 40 mol%) was added into reaction media immediately after adding of thrimethylsilylethynylene. The reaction flask was covered with aluminum foil and left for stirring at a high rate of speed for 18 h at room temperature. Small amounts of samples were periodically taken by the help of a syringe during the reaction, diluted in ethyl acetate and analyzed by GC to check whether all alkyne and starting material were consumed in the reaction. The course of the reaction was followed until no further increase in the formation of coupling product was observed. Then, the reaction mixture was partitioned in ethyl ether and distilled water (50 mL each). The organic layer was washed with 10% HCl (3X 75 mL), saturated aqueous NaCl (1X75 mL), dried over $MgSO_4$, gravity-filtered and the solvent removed with rotary evaporator. The crude product was purified by silica gel column chromatography to give pure product. Alkyne A2 was synthesized with this procedure (See: appendices D and E) (Mio, et al. 2002).

In a different procedure, teflon-coated magnetic stir bar was put into a 8 mL thick walled sealed tube and this flask was closed with a rubber septum and flame dried under vacuum. After that, the tube was purged with dry argon and PdCl$_2$(PPh$_3$)$_2$ (27.4 mg, 6 mol%), CuI (24.8 mg, 10 mol%) and 4-bromoanisol as starting material (1 equiv, 1.3 mmol) were added into flask. After that, dry benzene (6.5 mL, starting material is 0.20 M in dry benzene) ,which was sparged with dry argon, was added by syringe while the mixture being stirred. After this step, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (1.17 mL, 6 equiv) ,which was sparged with argon, was added by syringe and the reaction media was purged with argon. In the next step, distilled water (5.6 μL, 40 mol%) was added by syringe and the septum was removed. At the end, immediately, cooled thrimethylsilylethynylene (92 μL,0.50 equiv) was added by syringe and the sealed tube was closed tightly. The reaction tube was placed in preheated mineral oil bath at 60°C, protected from day light, and left stirring at a high rate of speed for 18 h (Figure 6.1). Small amounts of samples were periodically taken by the help of a syringe during the reaction, diluted in ethyl acetate and analyzed by GC to check whether all alkyne and starting materal were consumed in the reaction. The course of the reaction was followed until no further increase in the formation of coupling product was observed. Then, the tube was removed from the oil bath and the solution was allowed to cool to the room temperature. The reaction mixture was partitioned in ethyl ether and distilled water (50 mL each). The organic layer was washed with 10% HCl (3X 75 mL), saturated aqueous NaCl (1X 75 mL), dried over MgSO$_4$, gravity-filtered and the solvent was removed with rotary evaporator. The crude product was purified by silica gel column chromatography to give the pure product. Alkyne A1 was synthesized by using this procedure (See: appendices D and E) (Mio, et al. 2002).
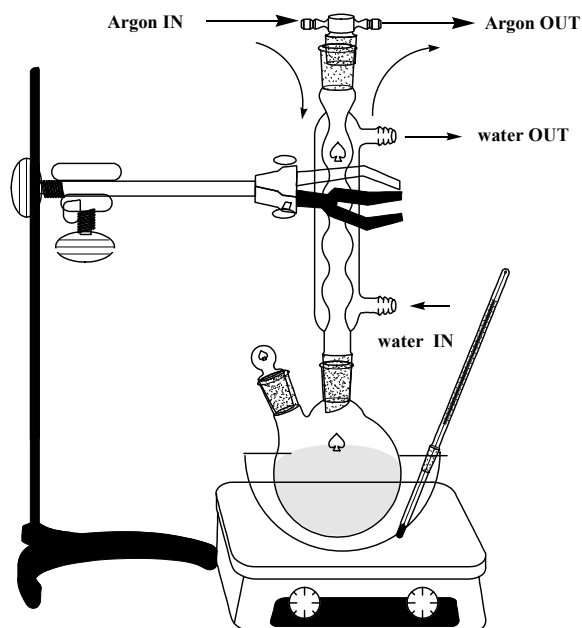
Figure 6.1. The experimental set uf for synthesis of alkynes by the modification of Sonogashira coupling reaction for elevated temperature

6.2. General Procedure for the Synthesis of Arylboroxines derivatives

For the preparation of phenylboroxine, at first, to remove H_2O azeotropically, a solution of phenylboronic acid (5.0 g, 40 mmol) in benzene (100 mL) was refluxed for 2h. (Figure 6.2). After that, the mixture was heated until the white crystals were occured. Then it was cooled to room temperature and was filtrated to obtain to crude product. The precipitate obtained was washed 5 times with hexane to give boroxine as a white crystal (Chen, et al. 2006).
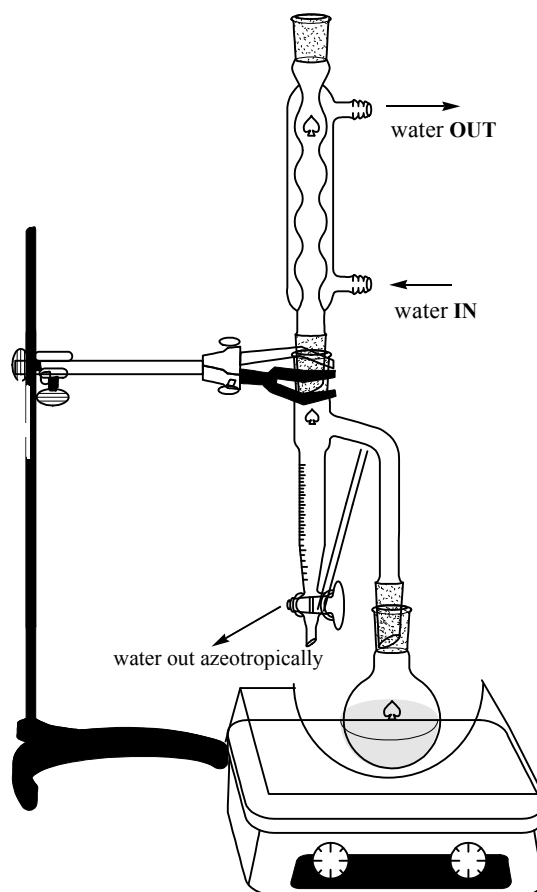
Figure 6.2. The experimental set up for the synthesis of phenylboroxine derivatives.

6.3. General Procedure for Drying of Solvents

Methanol was dried by using magnesium turnings and iodine. To dry 200 mL MeOH, first of all, 1.00 mg Mg-turnings, 100 mg iodine and 10 mL methanol were placed in 250 ml round-bottom flask. The mixture was heated under argon atmosphere until iodine disappears. If stream of bubbles was not observed, more iodine was added (100 mg). Heating was continued until all Mg-turnings were consumed. After that, the remainder MeOH (190 ml) was added into the flask and the mixture was refluxed for 3 hours (Figure 6.3). The distilled methanol was collected on 3A sieve beads (10% w/v). The dried methanol was kept on 3A sieve beads for at least 1 day after drying without using (Leonard, Lygo and Procter 1998).

Figure 6.3. The experimental set up for drying methanol

6.4. General Procedure for Rh-Catalyzed Carbonylative Addition Reactions of Arylboroxines to Alkynes

Bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate was supplied from Alfa Aesar. Diphenylacetylene, phenylboronic acid, tetradecane were supplied from Merck. 4-methoxyphenylboronic acid was supplied from Aldrich. Other phenylboronic acids were supplied from Fluka. trimethyl(2-phenylethynyl)silane was supplied from Aldrich.

A mixture of arylboroxine (0.5 mmol), alkyne (1 mmol), tetradecane (as an internal standard, 0.56 mmol), [Rh(cod)$_2$BF$_4$] (1.5 mol% Rh) and 10 mL methanol (pre-dried and degassed before use) was added into glass insert with a magnetic bar which was then placed into a stainless-steel reactor. After reactor was closed, it was evacuated and purged with 5 atm CO twice. Finally, the reactor was pressurized to 1 atm with CO and the reactor was placed into pre-heated oil bath at 120°C and left magnetically stirring for 16 h (Figure 6.4). After 16 hour, the reactor was removed from the oil bath and allowed to cool to the room temperature. The reaction mixture was recovered with ethyl acetate. A sample was taken from reaction mixture and diluted with ethyl acetate, then analyzed by GC and GC-MS.

Figure 6.4. The experimental set up for rh-catalyzed carbonylative addition reactions of arylboroxines to alkynes

6.5. Characterization of Products

6.5.1. GC Method

The samples were analyzed by GC/MS (GC-Varian star 3400CX, MS-VarianSaturn 2000 Gc-ms) and GC (19091J-413 HP-5 6890N on a 30m, 0.25 mm capillary column (5% dimetylsiloxane, 95% phenyldimethylsiloxane with a 0.25 μm film thickness and FID detector). The GC program applied throughout the analysis is as follows: the column temperature was 40 °C at the beginning of the program and it was heated with a rate of 10 °C/min up to 300 °C, then it was kept at this temperature for 15 min. Throughout the analysis the injector and detector temperatures were kept constant at 280 °C and 300 °C, respectively. The analysis was performed on a split mode with a split ratio of 1/50.

6.5.2. Calculation of Reactant and Product Amount on GC

Response factor of each reactant and product for the set temperature program of GC was determined for the calculation of amount of reactants and products. Tetradecane was used as internal standard. The response factor of each compound was determined according to the amounts and areas under the peaks of internal standard and standard compound of interest because the amount of internal standard does not change during the reaction.

To determine the response factor, a known amount of standard compound together with a known amount of internal standard dissolved in the reaction solvent and diluted with ethyl acetate and was injected to GC. After the analysis is completed according to the set temperature program, for the determination of response factor, following equation (5.1) was used.

$$\text{R.F.} = \frac{\text{internal standard area}}{\text{compound area}} \times \left(\frac{\text{compound amount}}{\text{internal standard amount}} \right) \quad (5.1)$$

To calculate the amount of both reactant and products at the end of the reaction, aliquots of reaction sample taken from the reaction flask and diluted samples were injected to GC. At the end of GC analysis, taking the amount of tetradecane and the area under the tetradecane peak into account, the following equation (5.2) was used in order to calculate the amount of reactant and products at the end of reaction.

$$\text{amount of compound} = \left(\frac{\text{internal standard amount}}{\text{internal standard area}} \right) \times \text{R.F.} \times \text{compound area} \quad (5.2)$$

6.5.3. Calculation of Reactant Conversion, Product Yield and Recovery

Reactant conversion at any time was calculated using following equation (5.3):

$$(\text{Reactant Conversion})_t \% = \frac{\left((\text{Reactant})_i - (\text{Reactant})_t\right)}{(\text{Reactant})_i} \times 100 \qquad (5.3)$$

In equation (5.3), $(\text{reactant})_i$ is the weight of reactant at the beginning of the reaction and $(\text{reactant})_t$ is the weight of reactant at time t.

Product yield of a molecule was calculated according to the following equation (5.4):

$$\text{Product Yield} = \frac{\text{mole of product}_t}{\text{initial mole of alkyne}} \qquad (5.4)$$

6.5.4. Purification of the Products

In this study, many types of products were purified by column chromatography. At the end of reaction, reactor was washed with ethyl acetate and solvent was removed by using evaporator. The product was purified by using column chromatography. The purity of products was determined by GC, GC-MS-NMR and Elemental Analysis techniques.

All products were determined by NMR (Varian VnmrJ 400), FT-IR (Perkin-Elmer Spectrum 100), GC-MS (GC-Varian star 3400CX, MS-VarianSaturn 2000 Gc-ms) Elemental Analysis (Leco CHNS 932), Melting Point Apparatus (Electrothermal 9200). High-resolution mass spectral (HRMS) analyses were performed by HPLC-ESI-HRMS, GC-EI-HRMS and DI-EI-HRMS (direct inlet ionisation) techniques at Dortmund University of Technology Mass Spectrometry Laboratories. ^{19}F NMR spectra

were recorded in the presence of CF_3COOH as standard. [19]F signal of the acid was set to -76.55 ppm The values are represented below.

(1) 2,3-dihydro-2,3-diphenylinden-1-one: Hexane/ethyl acetate; orange paste; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3,81 (d, $J = 4,8$ Hz, 1H); 4,57 (d, $J = 4,8$ Hz, 1H); 7,07-7,13 (m, 4H); 7,23-7,82 (m, 4H); 7,48 (t, $J = 7,4$ Hz, 1H); 7,64 (dt, $J = 1,0$ Hz, $J = 7,6$ Hz, 1H); 7,89 (d, $J = 8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55,1; 64,9; 124,3; 126,9; 127,4; 127,4; 128,1 (2C); 128,5; 128,6 (2C); 129,1 (2C); 129,2 (2C); 135,7; 136,4; 138,8; 142,8; 156,4; 205,5; MS (EI, m/z): 284 (100, M[+]), 206 (20), 178 (25); FTIR (ATR) ν (cm^{-1}) CO: 1711; analytical calculation for $C_{21}H_{16}O$ C: 88.70 %, H: 5.67 %; found C: 80.23%, H: 5.54%; HRMS (m/z, M[+]) calculated: 284.1196; found: 284.1206.

(2) 2,3-dihydro-6-methoxy-2,3-diphenylinden-1-one: Hexane/ethyl acetate; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3,80 (d, $J = 4,4$ Hz, 1H); 3,88 (s, 3H); 4,5 (d, $J = 4,4$ Hz, 1H); 7,06-7,34 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 54,5; 56,0; 65,6; 105,2; 125,1; 127,4; 127,4; 127,7; 128,0 (2C); 128,6 (2C); 129,1 (2C); 129,1 (2C); 137,7; 138,9; 143,0; 149,3; 160,3; 205,5; MS(EI, m/z): 314 (100, M[+]), 223 (10); FTIR (ATR) ν (cm^{-1}) CO: 1698; analytical calculation for $C_{22}H_{18}O_2$ C: 84.05 %, H: 5.77 %; found C: 84.385 %, H: 6.0855 %; HRMS (m/z, M[+]) calculated: 314.1301; found 314.1290. **(2a) 6-methoxy-2,3-diphenyl-1_H_-inden-1-one:** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3,85 (s, 3H); 6,80 (dd, $J = 2,2$ Hz, $J = 8,0$ Hz, 1H); 7,04 (d, $J = 8,0$, 1H); 7,17-7,26 (m, 6H); 7,34-7,43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55,8; 110,6; 116,3; 122,2; 127,5; 128,0; 128,4; 128,7; 129,3; 129,8; 131,0; 131,4; 133,0; 136,9; 156,4; 161,1; 196,2; MS: 312 (M[+]); 270; HRMS (m/z, M[+]) calculated 312.1301; found 284.1290.

(3) 2,3-dihydro-6-methyl-2,3-diphenylinden-1-one: Hexane/ethyl acetate; orange paste; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2,46 (s, 3H); 3,79 (d, $J = 4,8$ Hz, 1H); 4,53 (d, $J = 4,8$ Hz, 1H); 7,05-7,11 (m, 4H); 7,19 (d, $J = 7,6$ Hz, 1H); 7,23-7,33 (m, 6H); 7,46 (dd, $J = 1,4$ Hz, $J = 7,8$, 1H); 7,69 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21,4; 54,8; 65,2; 124,2; 126,6; 127,3; 127,4; 128,1 (2C); 128,6 (2C); 129,1 (2C), 129,1 (2C); 136,6; 136,9; 138,6; 139,0; 143,0; 153,9; 205,6; MS (EI, m/z): 298 (100, M[+]); 221 (40), 178 (23), FTIR (ATR) ν (cm^{-1}) CO: 1711; analytical calculation for $C_{22}H_{18}O$ C: 88.56 %, H: 6.08 %; found C: 86.995 %, H: 6.358 %; HRMS (m/z, M[+]) calculated 298.1352; found 298.1341.

(4) 2,3-dihydro-5-methoxy-2,3-diphenylinden-1-one: Hexane/ethyl acetate; white solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3,78 (d, J = 4,8 Hz, 1H); 3,80 (s, 3H); 4,49 (d, J = 4,8 Hz, 1H); 6,69 (d, J = 1,2 Hz, 1H); 7,0 (dd, J = 2,4 Hz, J = 8,4 Hz, 1H); 7,09 (d, J = 7,6 Hz, 4H); 7,22-7,34 (m, 6H); 7,82 (d, J = 8,4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 55,0; 55,8; 64,8; 109,6; 116,5; 125,8; 127,1; 127,2; 127,9 (2C); 128,3 (2C); 128,8 (2C); 128,9 (2C); 129,6; 139,0; 142,6; 159,2; 165,9; 203,4; MS (EI, m/z): 314 (100, M$^+$); 238 (30), 165 (20); FTIR (ATR) ν (cm^{-1}) CO: 1702; analytical calculation for C$_{22}$H$_{18}$O$_2$ C: 84.05 %, H, 5.77 %; found C:82.8%, H:5.92%; HRMS (m/z, M$^+$) calculated 314.1301; found 284.1287.

(5) 2,3-dihydro-5-methyl-2,3-diphenylinden-1-one: Hexane/ethyl acetate; pale yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 2,40 (s, 3H); 3,79 (d, J = 4,8 Hz, 1H); 4,51 (d, J = 4,8 Hz, 1H); 7,06-7,12 (m, 5H); 7,2-7,34 (m, 7H); 7,78 (d, J = 7,6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 22,2; 54,8; 64,7; 123,9; 126,9; 127,1; 127,9; 123; 128,8; 128,9; 129,6; 134,0; 138,8; 142,7; 146,8; 156,7; 204,8; MS (EI, m/z): 298 (M$^+$), 221 (40), 178 (23); FTIR (ATR) ν (cm^{-1}) CO: 1696; analytical calculation for C$_{22}$H$_{18}$O C:88.56 %, H: 6.08 %; found C: 87.76%, H: 6.33%; HRMS (m/z, M$^+$) calculated: 298.1352; found 298.1340.

(6) 6-(trifluoromethyl)-2,3-dihydro-2,3-diphenylinden-1-one: Hexane; pale yellow solid; ^{1}H NMR (400 MHz, CDCl$_3$); δ 3,89 (d, J =5,2, 1H); 4,62 (d, J = 5,2, 1H); 7,06-7,11 (m, 4H); 7,28-7,37(m, 6H); 7,45 (d, J = 7,6 Hz, 1H); 7,80 (d, J =8 Hz, 1H) ; 8,16 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 54,8; 64,8; 121,3; 121,4; 122,3; 125,0; 127,5; 127,5; 127,9; 128,3; 128,9; 129,1; 130,9; 131,3; 131,8; 136,5; 137,7; 141,4; 159,1; 203,9; MS(EI, m/z): 352 (100, M$^+$); 274 (28), 246 (12), 205 (14); FTIR (ATR) ν (cm^{-1}) CO: 1724; analytical calculation for C$_{22}$H$_{15}$F$_3$O C: 74.99 %, H: 4.29 %; found C: 73.77 %; H: 4.68 %; HRMS (m/z, M$^+$) calculated: 352.1075; found: 352.1070; ^{19}F NMR (376 MHz, CDCl$_3$): δ: -63.5. **(10) 1-benzyl-5-(trifluoromethyl)-1,2,3-triphenyl-1H-indene:** white solid; M.P.: 138-140 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3,57 (d, J = 12,4 Hz, 1H); 3,96 (d, J = 12,4 Hz, 1H); 6,35 (d, J = 7,2 Hz, 2H); 6,74 (d, J = 8,4 Hz, 2H), 6,89 (t, J = 7,6 Hz, 2H), 6,98-7,05 (m, 6H), 7,2 (s. 1H), 7,28-7,46 (10H); MS(EI, m/z): 502 (4, M$^+$), 483 (6), 411 (100), 334 (25), 91 (27); HRMS (m/z, M$^+$) calculated: 502.1908; found: 502.1890; ^{19}F NMR (375.9 MHz, CDCl$_3$) δ: -63.4.

(7) 2,3-dihydro-2,3-bis(4-methoxyphenyl)inden-1-one: Hexane/ethyl acetate; orange solid; ^{1}H NMR (400 MHz, CDCl$_3$); δ 3,71 (d, J =4,8 Hz, 1H); 3,78 (s, 3H); 3.79

(s, 3H); 4,47 (d, J =4,8 Hz, 1H); 6,83 (d, J =2,0, 2H); 6.86 (d, J = 2.8 Hz, 2H), 7,0 (m, 4H); 7,02 (d, J =4,4, 2H); 7.29 (d, J = 8.0 Hz, 1H); 7,46 (t, J = 7,4 Hz, 1H), 7,62 (t, J =7,4 Hz, 1H); 7,86 (d, J =7,4, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 54,3; 55,3; 114,3; 123,9; 126,6; 128,2; 128,9; 129,4; 134,5; 135,3; 136,1; 156,2; 158,7; 205,6; MS (EI, m/z): 344(97, M$^+$), 237 (100), 208 (40), 166 (40), 122 (35), 73 (63); FTIR (KBr) ν (cm$^-$^{1}) CO: 1709; analytical calculation for C$_{23}$H$_{20}$O$_3$ C: 80.21%; H: 5.85 %; found C: 78.47 %, H: 5.58%; HRMS (m/z, M$^+$) calculated: 344.1407; found: 344.1406. **(7a) 2,3-bis(4-methoxyphenyl)-1H-inden-1-one:** Hexane/ethyl acetate; red, paste; ^{1}H NMR (400 MHz, CDCl3); δ: 3,79 (s, 3H); 3,85 (s, 3H); 6,82 (d, J =9,2 Hz, 2H); 6,94 (d, J =8,8 Hz, 2H); 7,16 (d, J =7,2 Hz , 1H); 7, 21-7,28 (m, 3H); 7,31-7,37 (m, 3H); 7,55 (d, J =6,8 Hz , 1H); ^{13}C NMR (100 MHz, CDCl3) 55,1; 55,2; 113,7; 114,2; 120,9; 122,7; 123,4; 125,1; 128,6; 130,2; 131,0; 131,2; 133,2; 134,9; 145,5; 153,8; 159,1; 160,3; 196,9; MS (EI, m/z): 342 (100, M$^+$), 280, 208; FTIR (KBr) ν (cm-1) CO: 1703; analytical calculation for C$_{23}$H$_{18}$O$_3$ C: 80.68%; H: 5.30%; found C:73.92 %, H:5.02%; HRMS (m/z, M$^+$) 342.1250 (calculated); 342.1244 (found).

(8) 2,3-bis(4-(trifluoromethyl)phenyl)-2,3-dihydroinden-1-one: Hexane/ethyl acetate; pale yellow solid: ^{1}H NMR (400 MHz, CDCl$_3$); δ:3,84 (d, J = 5,6 Hz, 1H); 4,63 (d, J = 5,6 Hz, 1H); 7,20-7,33 (m, 5H); 7,52-7,72 (m, 6H); 7,93 (d, J = 7,6 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 54,4; 64,2; 122,6; (d, J = 24,8Hz); 124,4; 125,3; 126,0; 126,1; 126,5; 128,2 (2C); 128,9 (2C); 129,8; 129,7; 129,9; 130,0; 135.9; 135,9; 141,8; 145,9; 154,7; 203,4; MS (EI, m/z): 420 (100, M$^+$), 421 (15), 351 (10), 275 (30), 261 (18); ^{19}F NMR (376 MHz, CDCl$_3$); δ:-63,5 (d, J = 19,2 Hz); δ:-63,7 (d, J = 21,8 Hz); FTIR (KBr) ν (cm-1) CO: 1704; analytical calculation for C$_{23}$H$_{14}$F$_6$O C: 65.72%; H: 3.36 %; found C: 63.95 %, H: 3.16 %; HRMS (m/z, M$^+$) calculated: 420.0943; found: 420.0934. **(11) 1-(4-(trifluoromethyl)benzyl)-1,2,3-tris(4-(trifluoromethyl)phenyl)-1H-indene**: white solid; M.P.: 229-234°C; ^{1}H NMR (400 MHz, CD$_2$Cl$_2$) δ: 3,56 (d, J = 12,4 Hz, 1H); 3,98 (d, J = 12,8 Hz, 1H); 6,36 (d, J = 7,6 Hz, 2H); 6,69 (d, J = 8,0 Hz, 2H), 6,90-6,94 (m, 1H), 7,00 (d, J = 8,0 Hz, 2H); 7,10 (d, J = 8,0 Hz, 2H); 7,17-7,27 (m, 5H); 7,45-7,60 (m, 6H); MS (EI, m/z): 706 (8, M$^+$), 687 (5), 547 (100), 401 (12); HRMS (m/z, M$^+$): 706.153 (calculated), 706.143 (found); ^{19}F NMR (375.9 MHz, CD$_2$Cl$_2$) δ: -63,5; -63,3;-63,2; -63,17.

(9) 2,3-dihydro-3-phenylinden-1-one: Hexane/ ethyl acetate; yellow solid: ^{1}H NMR (400 MHz, CDCl$_3$); δ:2,69 (dd, J =19,2, J = 4 Hz, 1H); 3,23 (dd, J = 19,2, J =8

Hz, 1H); 5,57 (dd, J = 8, J = 3,6 Hz, 1H); 7,10-7,14 (m, 2H); 7,20-7,33 (m, 4H); 7,41 (t, J = 7,4, 1H); 7,81 (d, J = 8, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ: 44,4; 46,8; 123,4; 126,9; 127,0; 127,6; 127,9; 128,9; 135,1; 136,7; 143,7; 158,0; 206.1; MS (EI, m/z): 208 (M^+), 193 (13), 178 (25), 165 (20), 130 (10); FTIR (KBr) ν (cm-1) CO: 1705; analytical calculation for C$_{15}$H$_{12}$O C: 86.51%; H: 5.81 %; found C: 85.85 %, H: 5.81 %; HRMS (m/z, M^+): 178; calculated: 208.0883; found: 208.0874.

Table 6.1. Purification of indanone and indenones by column chromatography

Product#	Gradient Elution	Melting Point (°C)	M.P. Literature(°C)	Appearance
1	Hexane/ethyl acetate (100:1.5)			orange, paste
2	Hexane/ethyl acetate (40:1)	137.1-146.8		white, solid
2a	Hexane/ethyl acetate (110:1)			red, paste
3	Hexane/ethyl acetate (40:1)	67.4-74.8		white,solid
4	Hexane/ethyl acetate (10:1)	139-143.5		white, solid
5	Hexane/ethyl acetate (10:1)	113.9.-117.5		Pale yellow, solid
6	Hexane	81-83		Pale yellow, solid
7	Hexane/ethyl acetate (10:1)	115-118.9		orange, solid
7a	Hexane/ethyl acetate (100:1)			red,paste
8	Hexane/ethyl acetate (30:1)	137-140		Pale yellow, solid
9	Hexane/ethyl acetate	72.8-75.7	75-78	Yellow, solid

CHAPTER 7

RESULTS AND DISCUSSIONS

7.1. Rh-Catalyzed Carbonylative Addition of Phenylboronic Acid to Diphenyl Acetylene

Carbonylation of mixture of phenylboronic acid (3 mmol) **(2a)** and diphenylacetylene (1mmol) **(1a)** in presence of [Rh(cod)Cl]$_2$ (3 % Rh) as catalyst in dioxane under 20 atm at 120°C pressure afforded mainly major product 3,4,5-triphenylfuran-2(5H)-one **(4aa)** and the other carbonylation products which are (E/Z)-1,2,3-triphenylprop-2-ene-1-one **(3aa)**, 2,3-diphenyl-1H-inden-1-one **(5aa)**, 2,3-dihydro-2,3-diphenylinden-1-one **(6aa)** (Aksın, et al. 2006) (Figure 7.1).
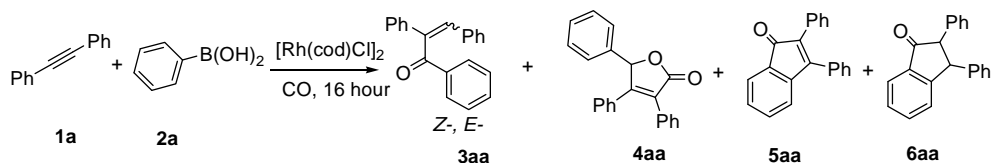
Figure 7.1. The rhodium catalyzed carbonylative arylation reaction of alkynes with phenylboronic acids (Source: Aksın, et al. 2006)

At the outset of this study, to increase the selectivity of indanone **6aa** and indenone **5aa**, reaction conditions were optimized. Carbonylation of phenylboronic acid (3 mmol) with diphenyl acetylene (1 mmol) using [Rh(cod)Cl]$_2$ (3 % Rh) as catalyst prescursor was performed in different solvents. The reaction showed less selectivity for the formation of indanone and indenone when dry dioxane was used (Table 7.1, entry 2). It was observed that using pre-dry methanol increased the formation of indanone **6aa**, indenone **5aa** and product **3aa** (Table 7.1, entry 1). When the reaction occured in metanol:water solvent mixture at 80°C, the formation of indanone **6aa** increased,

however the formation of indenone **5aa** diminished. Also, side product formation **3aa** decreased (Table 7.1, entry 3). It was observed that the reaction temperature, 80°C, was not enough to be formed of indanone **6aa** and indenone **5aa** but, increasing the reaction temperature to 120°C increased the formation of indanone **6aa** and indenone **5aa** and reduced the formation of product **3aa** (Table 7.1, entry 4). When the NaBPh$_4$ was used instead of PhB(OH)$_2$ as organoboron presurcor, the formation of indanone **6aa** and side products **3aa, 4aa, 7aa, 8aa** decreased, but the formation of indenone **5aa** and **9a** increased (Table 7.1, entry 5). Also, when the reaction was performed using KPhB$_4$, despite the formation of indenone **5aa** decreased a little, formation of indanone **6aa** increased considerably and also, side products formation decreased (Table 7.1, entry 6). Then, optimum reaction temperature was determined as 120 °C with dry methanol as solvent, KPhBF$_4$ as organoboron. After these optimization experiments, the reaction conditions at Table 7.1, entry 6 were chosen for the rest of optimization study.

Table 7.1. The effect of temperature, solvent and additives on [Rh(cod)Cl]$_2$ catalyzed carbonylative addition reaction of diphenyl acetylene to organoboron species

Entry	Organoboron	Solvent[a]	T°C	Conversion of 2a %[b]	3aa%[a]	4aa%[a]	5aa%[a]	6aa%[a]	7aa%[a]	8aa%[a]	9a%[a]
1	PhB(OH)$_2$	CH$_3$OH	80	100	50	6	12	20	5	-	-
2	PhB(OH)$_2$	Dioxane	80	52	11	7	2	9	1	-	-
3	PhB(OH)$_2$	CH$_3$OH/H$_2$O	80	100	47	6	-	22	-	-	-
4	PhB(OH)$_2$	CH$_3$OH	120	100	32	4	11	34	<1	4	3
5	NaBPh$_4$	CH$_3$OH	120	100	-	1	25	7	-	-	16
6	KPhBF$_4$	CH$_3$OH	120	100	3	2	19	31	2	6	8

[a]: dry Solvent;   [b]: GC yield

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Table 7.2. The effect of solvent on [Rh(cod)Cl)]₂ catalyzed carbonylative addition reaction of diphenyl acetylene to KPhBF₄
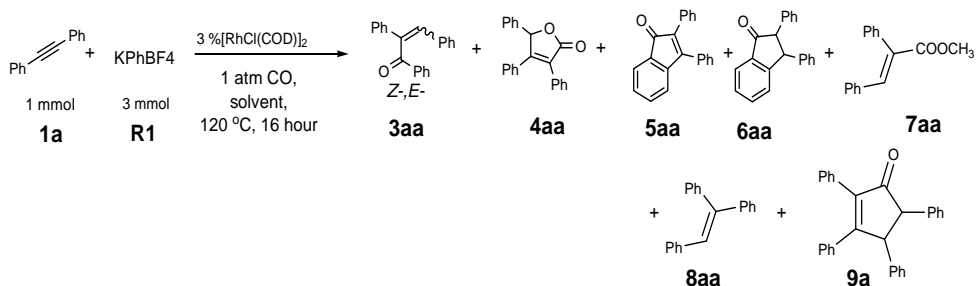
Entry	Solventᶜ	Conversion of R1%ᵃ	3aa%ᵃ	4aa%ᵃ	5aa%ᵃ	6aa%ᵃ	7aa%ᵃ	8aa%ᵃ	9aa%ᵃ
1	CH₃OH	100	3	2	19	31	2	6	8
2	CH₃OHᵇ	100	4	5	2	23	-	-	3
3	Toluene	75	1	33	3	-	-	40	-
4	THF	55	-	1	9	-	-	1	2
5	DMF	100	-	4	12	1	1	7	21
6	o-xylene	100	1	4	7	3	-	59	3

ᵇ: PPh₃ ᵃ: GCyield ᶜ: dry solvent

The reaction performed using different solvents in presence of KPhBF₄ as organoboron. It was observed that THF and toluene were not effective for the formation of indanone **6aa** and indenone **5aa** (Table 7.2, entry 3 and 4). In toluene, product **3aa** and **8aa** were formed as major products (Table 7.2, entry 3). Also, when DMF and o-xylene were used as solvent, the reaction was not effective for the formation of indanone (Table 7.2, entry 5 and 6) but, **9aa** formed as the major product when the reaction was performed in DMF and indenone formation was little (Table 7.2, entry 5). Also, **8aa** was major product in o-xylene (Table 7.2, entry 6). Other than toluene, THF, DMF, o-xylene, the reaction was performed in methanol as solvent. It was observed that the methanol was suitable solvent to form the product indanone **6aa** and indenone **5aa** (Table 7.2, entry 1) as major products. Addition of PPh₃ to reaction medium reduced the formation of indanone **6aa** and indenone **5aa** (Table 7.2, entry 2). As a result, the reaction solvent was determined as methanol.

Table 7.3. Effect of rhodium catalysts on carbonylative addition of KPhBF$_4$ to diphenyl acetylene

Entry	Catalyst	Conversion of R1%[a]	3aa%[a]	4aa%[a]	5aa%[a]	6aa%[a]	7aa%[a]	8aa%[a]	9aa%[a]
1	[Rh(cod)OH]$_2$	100	2	2	17	31	1	2	11
2	Rh(C$_2$H$_4$)$_2$acac	100	2	3	24	26	-	1	11
3	[Rh(C$_2$H$_4$)$_2$Cl]$_2$	100	3	1	15	29	2	4	7
4	[Rh(CO)$_2$Cl]$_2$	100	4	2	18	24	3	1	9
5	Rh(cod)$_2$BF$_4$	100	1	2	17	40	1	2	8

[a]: GC yield

In the optimization study, the effect of rhodium source was also investigated by using various rhodium complexes in presence of KPhBF$_4$ as organoboron (Table 7.3). The reaction was more efficient for the formation of indanone **6aa** and indenone **5aa** when Rh(cod)$_2$BF$_4$ was used as a catalyst precursor (Table 7.3, entry 5). It should be due to the cationic form of rhodium activated the bond of Ar-H more effectively.

Table 7.4. The effect of organoboron on carbonylative addition of diphenyl acetylene
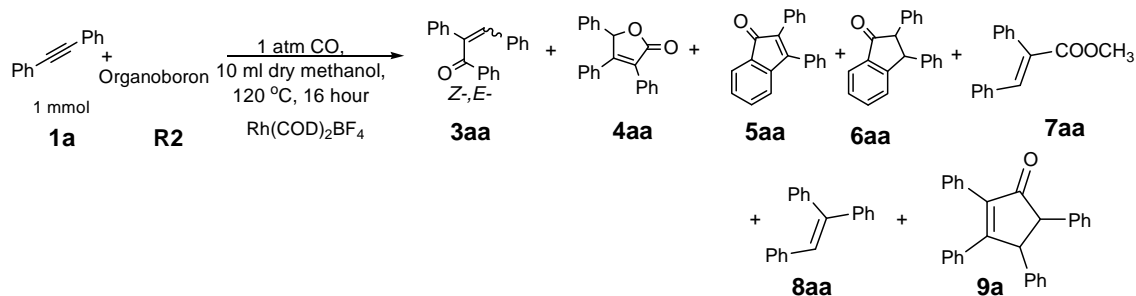
Entry	Catalyst	Organoboron	Conversion of R2%[g]	3aa%[g]	4aa%[g]	5aa%[g]	6aa%[g]	7aa%[g]	8aa%[g]	9aa%[g]
1	Rh(cod)$_2$BF$_4$	KPhBF$_4$	100	1	2	17	40	1	2	8
2	Rh(cod)$_2$BF$_4$	Ph$_3$(BO)$_3$ [a]	100	11	1	8	56	0	9	3
3	Rh(cod)$_2$BF$_4$[d]	Ph$_3$(BO)$_3$ [b]	100	12	<1	3	65	0	10	4
4	Rh(cod)$_2$BF$_4$[d]	Ph$_3$(BO)$_3$[b,c]	100	9	<1	4	55	0	7	3
5	Rh(cod)$_2$BF$_4$ [e]	Ph$_3$(BO)$_3$ [b]	100	5	<1	6	36	0	8	3
6	Rh(cod)$_2$BF$_4$ [f]	Ph$_3$(BO)$_3$[b]	100	3	0	1	53	0	9	2

[a]: 1 mmol phenylboroxine, [b]: 0.5 mmol phenylboroxine, [c]: 2 atm, [e]: 10 Rh %, [f]: 1 Rh %, [d]: 1.5 Rh % [g]: GC yield

In the last part of the optimization study, we used different organoboron, phenylboroxine instead of KPhBF$_4$, it was observed that the formation of indanone **6aa** increased but, the formation of indenone **5aa** decreased (Table 7.4, entry 2). When rhodium amount decreased up to 1.5% and phenylboroxine amount decreased up to 0.5 mmol, the formation of indanone **6aa** increased (Table 7.4, entry 3). Under the same conditions, the increase of the CO pressure was up to 2 atm caused the decreased formation of indanone product **6aa** (Table 7.4, entry 3 and entry 4). Using 10 % or 1 % rhodium amount reduced the formation of indanone **6aa** (Table 7.4, entry 5 and entry 6). Phenylboroxine was determined as the appropriate organaboron to be used.

7.2. Rh-catalyzed Carbonylative Reactions of Different Arylboroxines with Diphenyl Acetylene

Rh-catalyzed carbonylative reactions of various *p-,* and *m*-arylboroxines with diphenyl acetylene were investigated under the optimal conditions determined (0.5 mmol arylboroxines, 1 mmol diphenylaceylene with Rh(cod)$_2$BF$_4$ (1.5 % Rh) in 10 mL dry-methanol at 120 ^{o}C under 1 atm CO for 16 h (Table 7.5) .

Table 7.5. The reaction of arylboroxines with diphenylacetylene under CO pressure
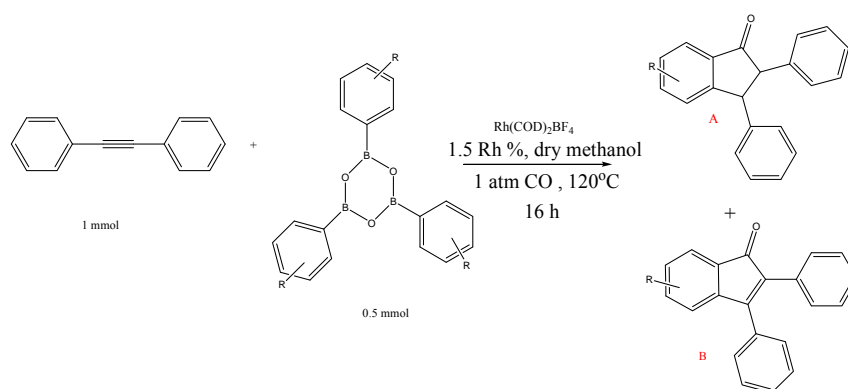
Entry	Product#	organoboron	R	Isolated yield product A %	GC yield product B %
1	*1*	Ph$_3$(BO)$_3$	H	43	7
2	*2*	(*p*-CH$_3$OPh)$_3$(BO)$_3$	OCH$_3$	26	7[a]
3	*3*	(*p*-CH$_3$Ph)$_3$(BO)$_3$	CH$_3$	41	8
4	*4*	(*m*-CH$_3$OPh)$_3$(BO)$_3$	OCH$_3$	24	<1
5	*5*	(*m*-CH$_3$Ph)$_3$(BO)$_3$	CH$_3$	43	4
6	*6*	(*p*-CF$_3$Ph)$_3$(BO)$_3$	CF$_3$	13	7 (4[a])

[a]: isolated yield

When $Ph_3(BO)_3$ was used as organoboron, 41 % yield of indanone A was isolated and the GC yield of indenone was 7% (Table 7.5, entry 1). It was observed that using phenylboroxines substituted with an electron-donating group, methoxy group, at *meta*- or *para*- positions reduced the formation of indanone (Table 7.5, entry 2 and 5). But, when the reaction was performed using phenylboroxines substituted with electron-donating group, methyl group, at *meta*- or *para*- positions increased yield of indanone and GC yield of indenone (Table 7.5, entry 3 and entry 5). Stronger electron-withdrawing groups CF_3- on the *para*- positions of phenyboroxine reduced the formation of indanone.

Table 7.6. The yields of side products in reaction of arylboroxines with
diphenylacetylene under CO pressure

Entry	R^1	Arylboroxine	$3aa^b$	$8aa^b$
			Yield %	
1	Ph	$(PhBO)_3$	10	9
2	Ph	$(p\text{-}OCH_3C_6H_4BO)_3$	15	3
3	Ph	$(p\text{-}CH_3C_6H_4BO)_3$	6	15
4	Ph	$(m\text{-}OCH_3C_6H_4BO)_3$	25	7
5	Ph	$(m\text{-}CH_3C_6H_4BO)_3$	<1	13
6	Ph	$(p\text{-}CF_3C_6H_4BO)_3$	2	7

[b]:GC yield.

Also, formation of side products was observed during the synthesis of indanones and indenones (Table 7.6). When $Ph_3(BO)_3$ was used as organoboron, higher yield was obtained for the keton product **3aa** than the yield of arylation product **8aa** (Table 7.6, entry 1). It is observed that when phenylboroxines substituted with an electron-donating

group, methoxy group, at *meta-* or *para-* position were used, higher yields were obtained for the keton products **3aa** than yields of arylation products **8aa** (Table 7.6, entry 2,3,4,5). But, stronger electron-withdrawing groups CF₃- on the *para-* positions of phenyboroxine gave higher yield for arylation product **8aa** than yield of keton product **3aa** (Table 7.6, entry 6).

The reaction of diphenylactylene with *p*-CF₃ substituted phenylboroxine produced the corresponding indenone and indanone products only at an overall yield of 20% (Table 7.5, entry 6) and low side product yields for keton and arylation products (Table 7.6, entry 6). The reaction, however, yielded a significant amount of an indene product (42% yield). The formation of this type of indene structure was shown and well discussed for the rhodium catalyzed reaction of 4-octyne and phenylboroxine by Hayashi et al. (2001) previously. However, the reaction conditions and the use of diphenylacetylene in our case led to the hydrodemetallation of a cyclic alkylrhodium intermediate instead of α-hydrogen elimination during the last step of the reaction cycle (Figure 7.2).
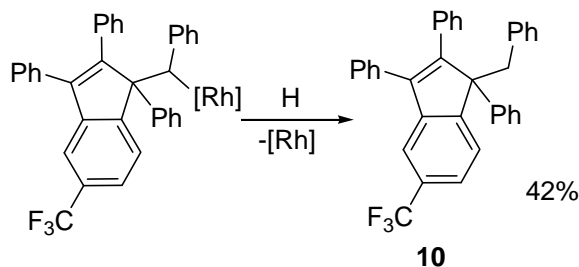

Figure 7.2. The formation of indene structure from the reaction of diphenylactylene with *p*-CF₃ substituted phenylboroxine under optimized conditions

7.3. Rh-catalyzed Carbonylative Reactions of Alkynes with Phenylboroxine

We performed the rhodium-catalyzed carbonylative reactions of different alkynes with phenylboroxine under the optimized conditions.

7.3.1. Rh-catalyzed Carbonylative Reactions of Alkynes with Phenylboroxine

The reaction of 4-octyne with phenylboroxine under the optimized conditions was not selective for the formation of indanone and indenone. It was observed that a complex mixture was formed at the end of the reaction.

Reactions were also performed with dimethylacetylenedicarboxylate as alkyne in the rhodium catalyzed carbonylative reactions with phenylboroxines, but this reaction yielded no indanone and indenone compounds.

When the alkyne having two aryl groups which are substituted by methoxy groups on the *para-* positions was used, 24 % yield of indanone was obtained. The presence of an electron-donating methoxy group at the *p*-position on both of the phenyl groups of the alkyne led to an increased amount of indenone product and it was isolated with 10 % yield (Table 7.7, entry 1). The presence of stronger electron-withdrawing groups on the *para-* positions of phenyl rings on alkyne increased the formation of indanone (34.6% yield) but, decreased the formation of indenone (Table 7.7, entry 2).

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Table 7.7. The activity of different diaryl-substituted symmetric alkynes
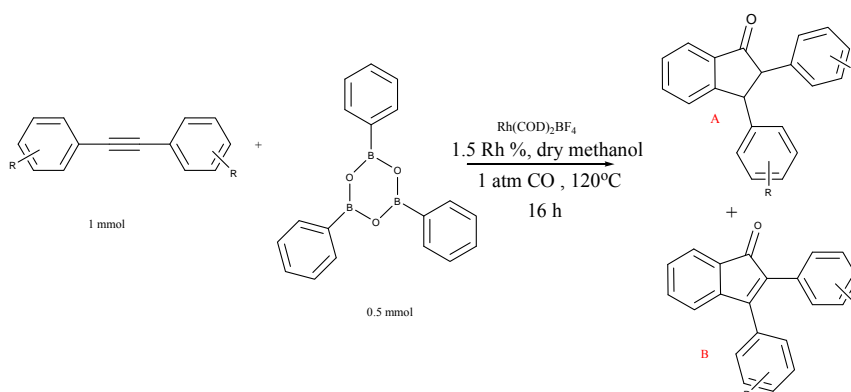
Entry	Product#	R	Isolated Yield % (A:B)
1	*7*	*p*-CH$_3$O	27:10
2	*8*	*p*-CF$_3$	33:1.6

Also, formation of side products was observed during the synthesis of indanones and indenones (Table 7.8). Electron rich diphenylacetylenes gave higher yields for ketone **3aa** and arylation product **8aa** than electron poor diphenylacetylenes (Table 7.8, entry 1). Both of these reactions gave higher yields for arylation product **8aa** (Table 7.8, entry 1 and 2). *p*-CF$_3$ substitution on both ends of the diphenylacetylene substrate, however, also rendered the indene (**11**) formation in significant quantity (Figure 7.3).
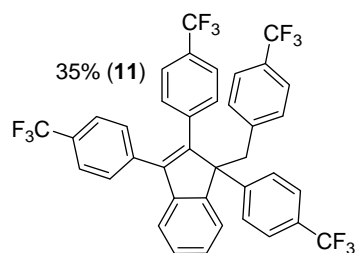
Figure 7.3. The structure of inden which was obtained from the reaction of 1,2-bis(4-(trifluoromethyl)phenyl)ethyne with phenylboroxine under optimized conditions

Table 7.8. The yields of side products in reaction of phenylboroxines with diphenylacetylene derivatives under CO pressure

Entry	R^1	Arylboroxine	3aa[b]	8aa[a]
1	p-CH$_3$O	(PhBO)$_3$	18	20
2	p-CF$_3$Ph	(PhBO)$_3$	3	9

[a] isolated yield, [b] GC yield

7.3.2. Rh-catalyzed Carbonylative Reactions of Asymmetric Alkynes with Phenylboroxines

Reactions were performed with 1-phenyl-propyne, 1-hexyne, methyl-2-heptoanate as alkynes under the optimized condition but, these reactions produced either complex mixture of products or yielded no indanone and indenone compounds.

The reaction with trimethyl(2-phenylethynyl)silane proceeded in a regioselective manner, affording a desilylated indanone product (**Product# 9**) together with a hydrophenylated product (Figure 7.4). Differently from our synthesized indanones, obtained product had only one substitue at β position of indanone. It was observed that silyl group was desilylated and phenyl group favored β-position of indanone.
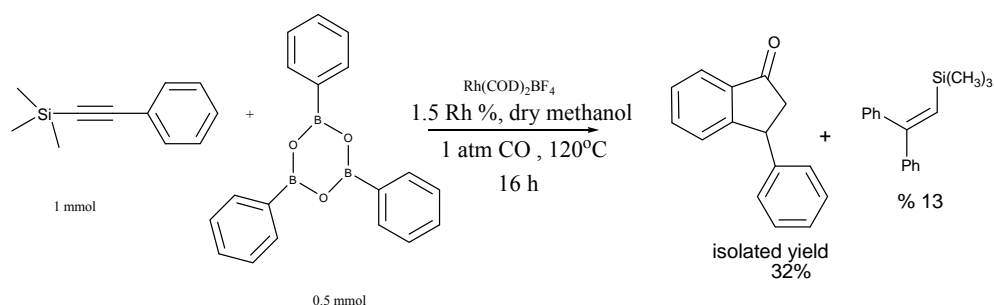

Figure 7.4. The reaction of trimethyl(2-phenylethynyl)silane with phenylboroxine under optimized conditions

7.4. Proposed Mechanism of Rh-catalyzed Carbonylative Reactions of Arylboroxines with Alkynes

In Figure 6.3, proposed mechanism for formation of indanones and indenones is shown.
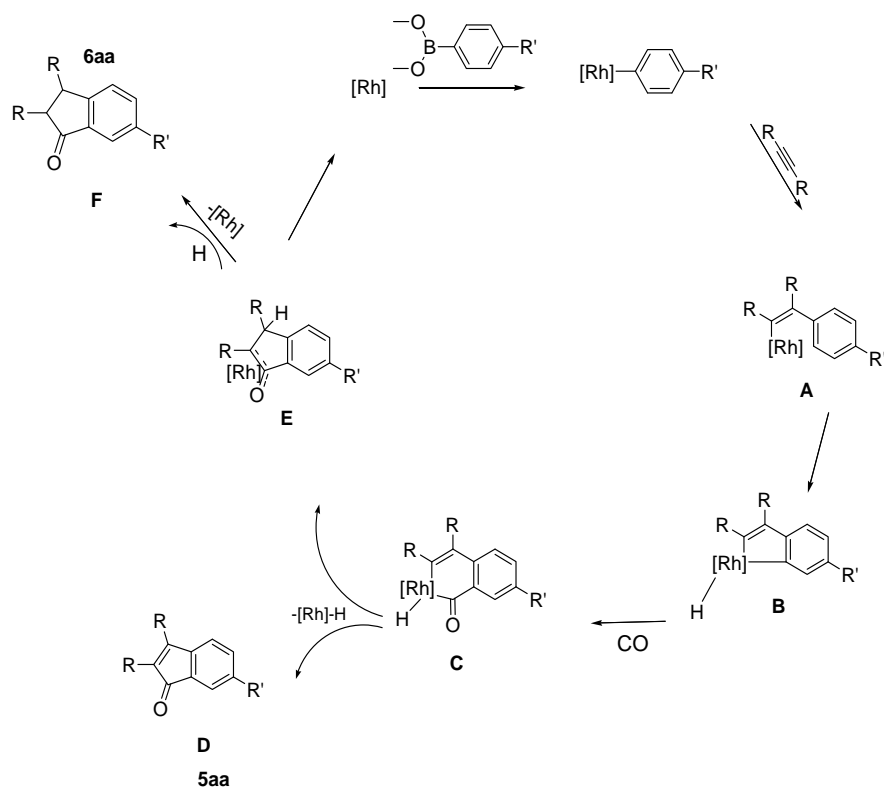
Figure 7.5. Proposed mechanism for the Rh-catalyzed carbonylative reaction of arylboroxines with alkynes

The regioisomeric structures of products **5aa** and **6aa** implies that the reaction mechanisms involve a rhodoarylation step, analogous to the carbonylative reaction of *o*-haloarylboronic acids with alkynes which gives rise to indenones as was reported by Chatani et al. Firstly, arylrhodium(I) species can be formed by the transmetallation of Rh (I) compounds with arylboroxines. Formed arylrhodium undergoes 1,2-addition to the carbon-carbon triple bond of alkyne which results in the formation of alkenylrhodium(I) complex (**A**). Then this alkenylrhodium(I) which undergoes oxidative addition to a C-H bond on the *o*-position of the aryl ring that is contributed by the arylboroxine reagent to generate the Rh(III) species (**B**). The insertion of CO followed by reductive elimination produces **5aa.** Indanone **6aa** should form through protonation of intermediate. But it was invalid. Because, it was observed that when a control experiment conducted using the rhodium catalyst in the presence of a preformed indenone produced, no hydrogenation product was obtained and the starting material was recovered in high yield. As a result, **6aa** could not obtained by hydrogenation of **5aa.**

7.5. Identification of Position of Indanone Rings

Dihedral angles of indanone ring hydrogens were <1° for *cis* isomeric structure and 124° for *trans* isomeric structure according to AM1 calculations. So, the indanones should be on the structure of *trans*-stereoisomeric according to interaction constant of ring hydrogens determined by ^{1}H NMR.

CHAPTER 8

CONCLUSION

In this study, rhodium catalyzed carbonylative arylation of alkynes with various phenylboroxines derivatives were investigated. Rh(cod)$_2$BF$_4$ was found to be the most effective complex in catalyzing the reactions.

The yield of indanones was higher when phenylboroxines substituted with electron-donating groups, methyl group, at *meta-* or *para-* positions were used. However, an methoxy -substituted phenylboroxine at *meta-* or *para-* was found to give lower yields for the corresponding indanone products. But, higher indenone yields were obtained for *para-* substituted phenylboroxines. The presence of stronger electron-withdrawing group, -CF$_3$, on *para* position also reduced the yield of indanone.

When reaction was performed with an alkyne having two aryl goups which are substituted by an electron-withdrawing group, -CF$_3$, on the *para-* position, reaction yielded higher yield than an electron-donating group, -CH$_3$O, on the *para-* position on aryl groups but, yield of indenone was decreased.

For the reaction of alkyne substituted with both aryl and alkyl moieties, aryl group favored β position of indanone and alkyl group was desilylated.

Some of synthesized indenones were not isolated in column chromatography and the yields of indenones were determined using GC method. The presence of electron donating group, -CH$_3$O, substituted on *para-* position of phenylboroxine or aryl groups on alkyne resulted in the exact isolation of indenones from the other products.

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APPENDIX A

^{13}C, ^{1}H, ^{19}F NMR SPECTRUMS OF INDANONES AND INDENONES

Figure A.1. ^{1}H NMR 2,3-dihydro-2,3-diphenylinden-1-one

Figire A.2. ^{13}C NMR of 2,3-dihydro-2,3-diphenylinden-1-one

1

YO-I205KC

Sample Name:
  YO-I205KC
Data Collected on:
  nmr400-vnmrs400
Archive directory:
  /home/walkupl/vnmrsys/data
Sample directory:
  YO-I205KC_13May2008
FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: May 13 2008

Temp. 27.0 C / 300.1 K
Operator: walkupl

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
512 repetitions
OBSERVE C13, 100.4598839 MHz
DECOUPLE H1, 399.5239862 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min

54.878
64.611
76.716
77.034
77.351
124.034
126.692
126.932
127.196
127.382
127.715
127.855
127.901
128.087
128.118
128.289
128.358
128.847
128.916
129.056
129.218
131.233
135.410
136.193
138.526
142.501
156.125

Peak list (ppm):
0.000, 0.076, 3.794, 3.805, 3.855, 3.880, 4.497, 4.508, 5.281, 7.043, 7.062, 7.065, 7.069, 7.076, 7.082, 7.086, 7.098, 7.103, 7.108, 7.178, 7.199, 7.207, 7.216, 7.222, 7.237, 7.240, 7.243, 7.247, 7.255, 7.262, 7.268, 7.272, 7.276, 7.281, 7.283, 7.296, 7.302, 7.309, 7.313, 7.323, 7.326, 7.331, 7.335

Integrations: 5.34, 15.50, 5.04, 22.46, 51.65

Figure A.3. ¹H NMR of 2,3-dihydro-6-methoxy-2,3-diphenylinden-1-one

Figure A.4. ^{13}C NMR of 2,3-dihydro-6-methoxy-2,3-diphenylinden-1-one

Figure A.5. ^{1}H NMR of 6-methoxy-2,3-diphenyl-1H-inden-1-one

Figure A.6. ^{13}C NMR of 6-methoxy-2,3-diphenyl-1*H*-inden-1-one

2a

55.816

76.685
77.003
77.320

110.597
113.588
116.323
122.244
127.467
128.025
128.436
128.555
128.723
129.296
129.691
129.815
130.970
131.381
132.520
132.938
132.954
136.945
156.365
161.053

YELDA-YOI220KB

Sample Name:
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Data Collected on:
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Archive directory:
  /home/walkupl/vnmrsys/data
Sample directory:
  YELDA-YOI220KB_15Mar2008
FidFile: CARBON

Pulse Sequence: CARBON (s2pul)
Solvent: cdcl3
Data collected on: Mar 19 2008

Temp. 25.0 C / 298.1 K
Operator: walkupl

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
512 repetitions
OBSERVE C13, 100.4598839 MHz
DECOUPLE H1, 399.5239862 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 19 min

ppm

220 200 180 160 140 120 100 80 60 40 20

106

Figure A.7. ¹H NMR of 2,3-dihydro-6-methyl-2,3-diphenylinden-1-one
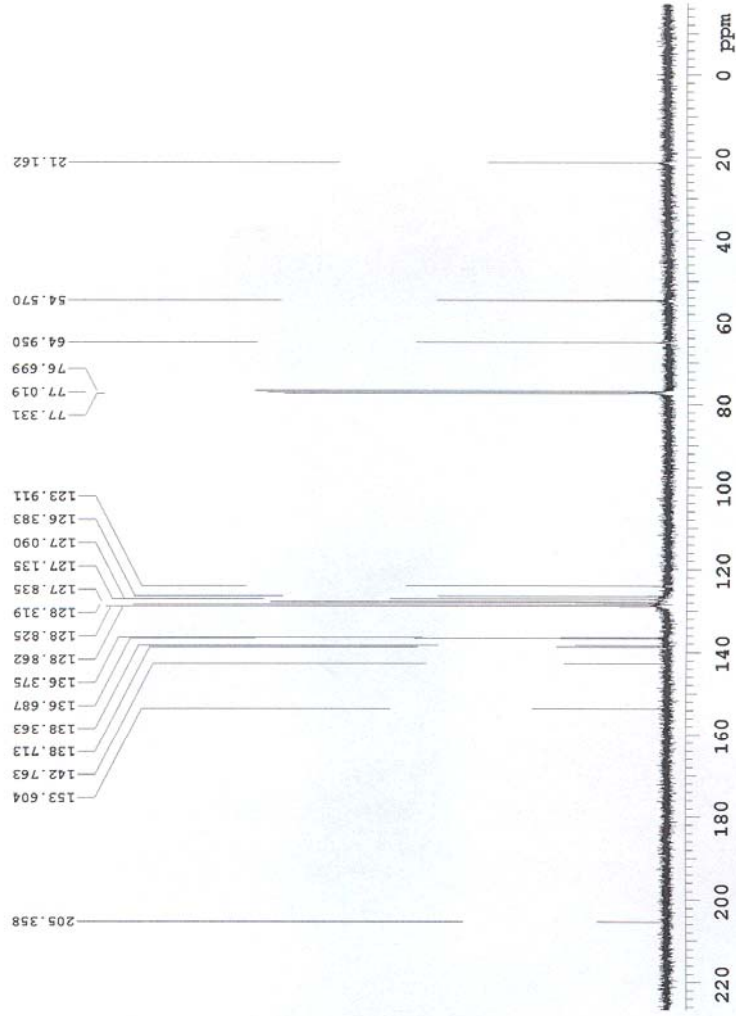
Figure A.8. ^{13}C NMR of 2,3-dihydro-6-methyl-2,3-diphenylinden-1-one
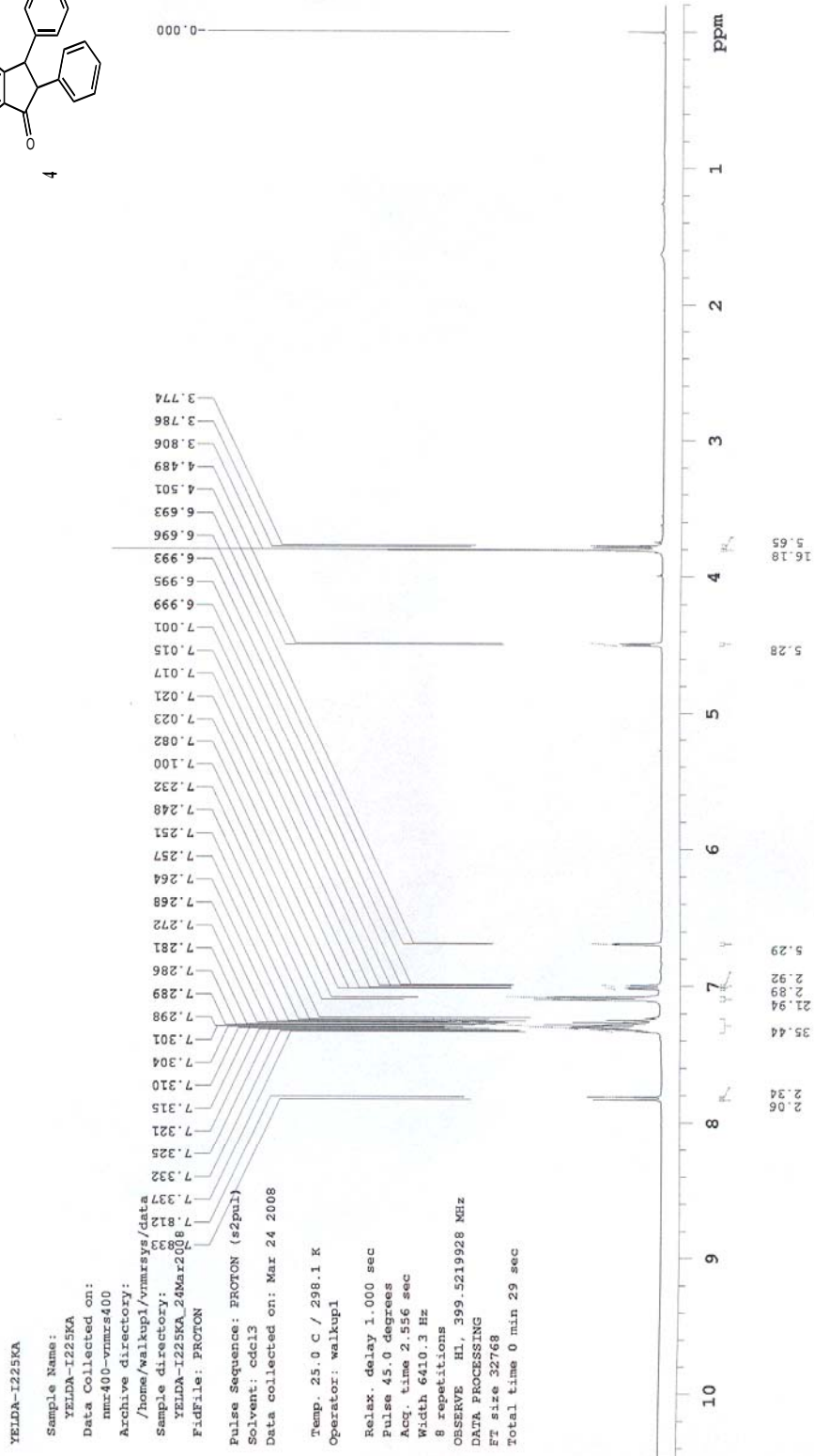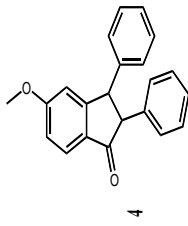
Figure A.9. ¹H NMR of 2,3-dihydro-5-methoxy-2,3-diphenylinden-1-one
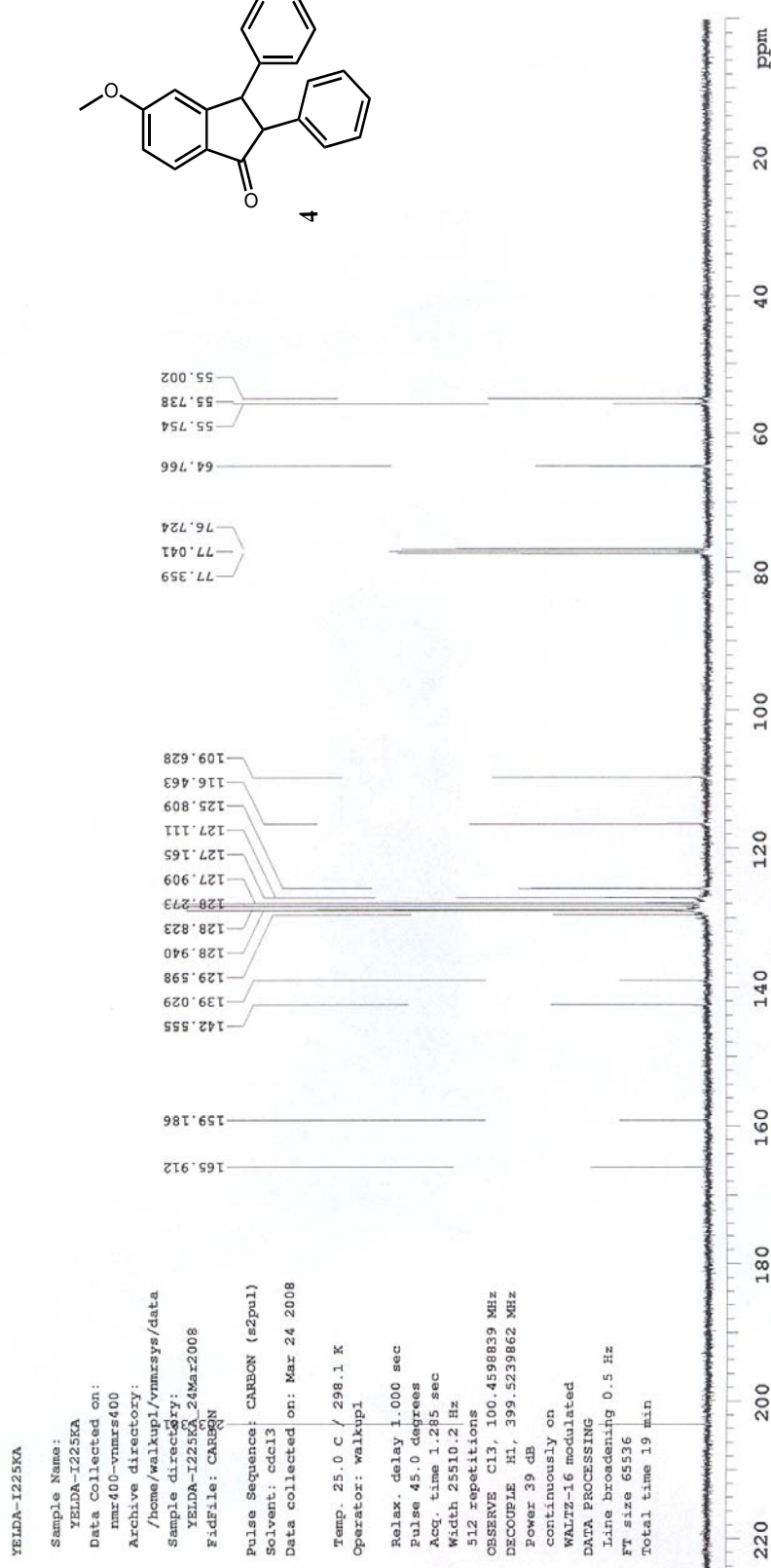
Figure A.10. ^{13}C NMR of 2,3-dihydro-5-methoxy-2,3-diphenylinden-1-one
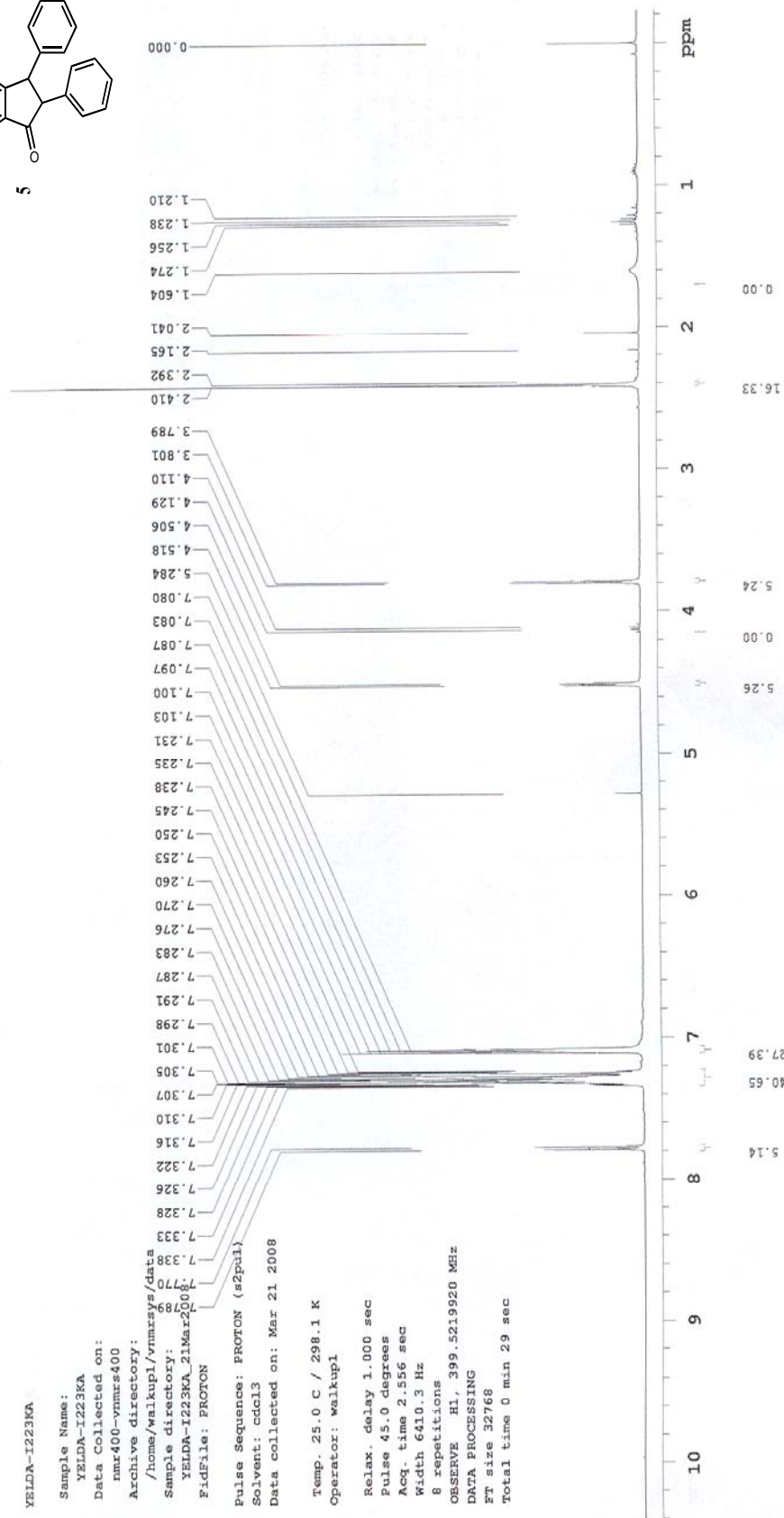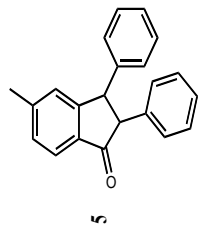
Figure A.11. ^{1}H NMR of 2,3-dihydro-5-methyl-2,3-diphenylinden-1-one
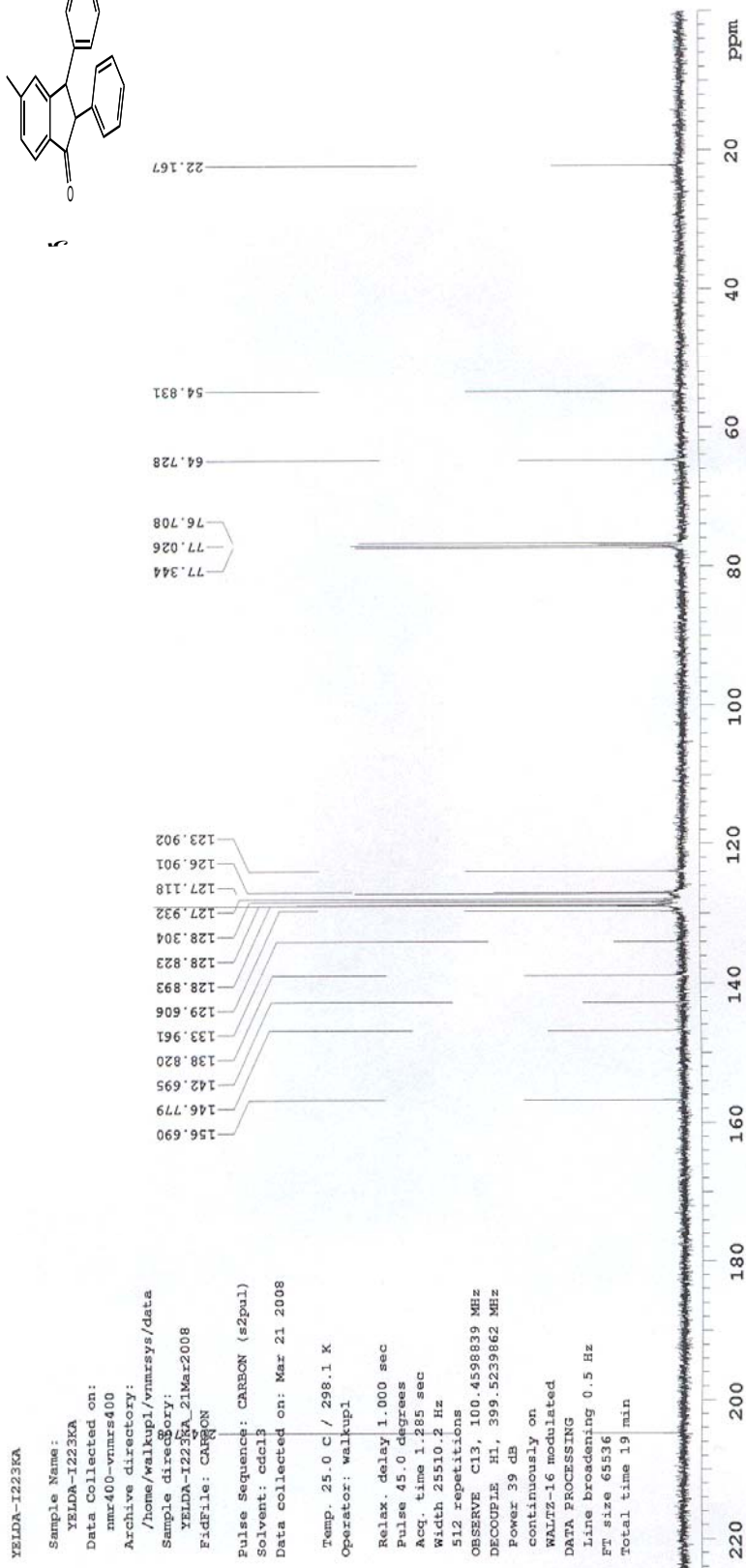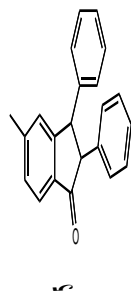
Figure A.12. ^{13}C NMR of 2,3-dihydro-5-methyl-2,3-diphenylinden-1-one
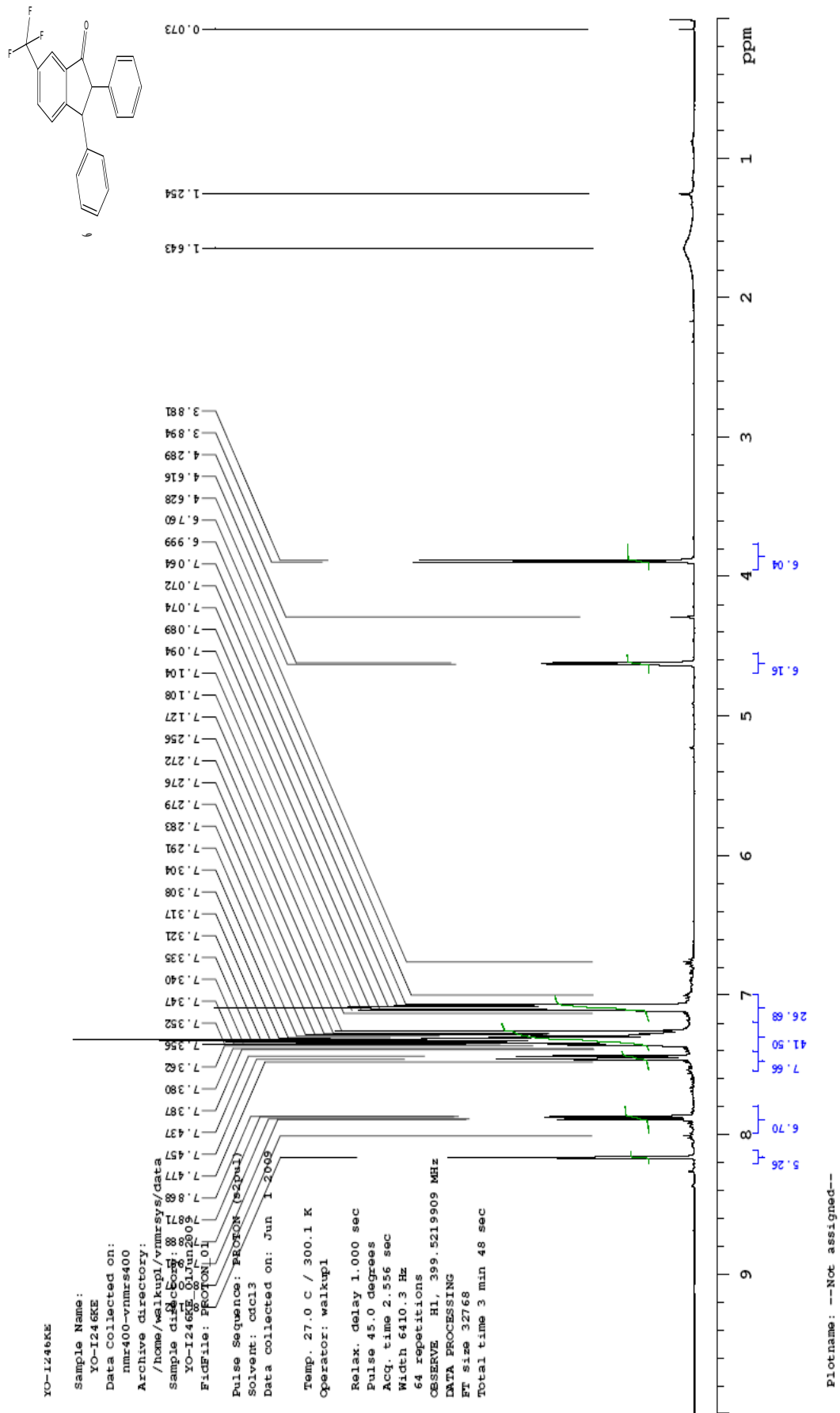
Figure A.13. ^{1}H NMR of 6-(trifluoromethyl)-2,3-dihydro-2,3-diphenylinden-1-one
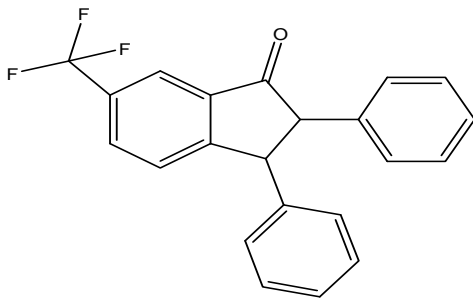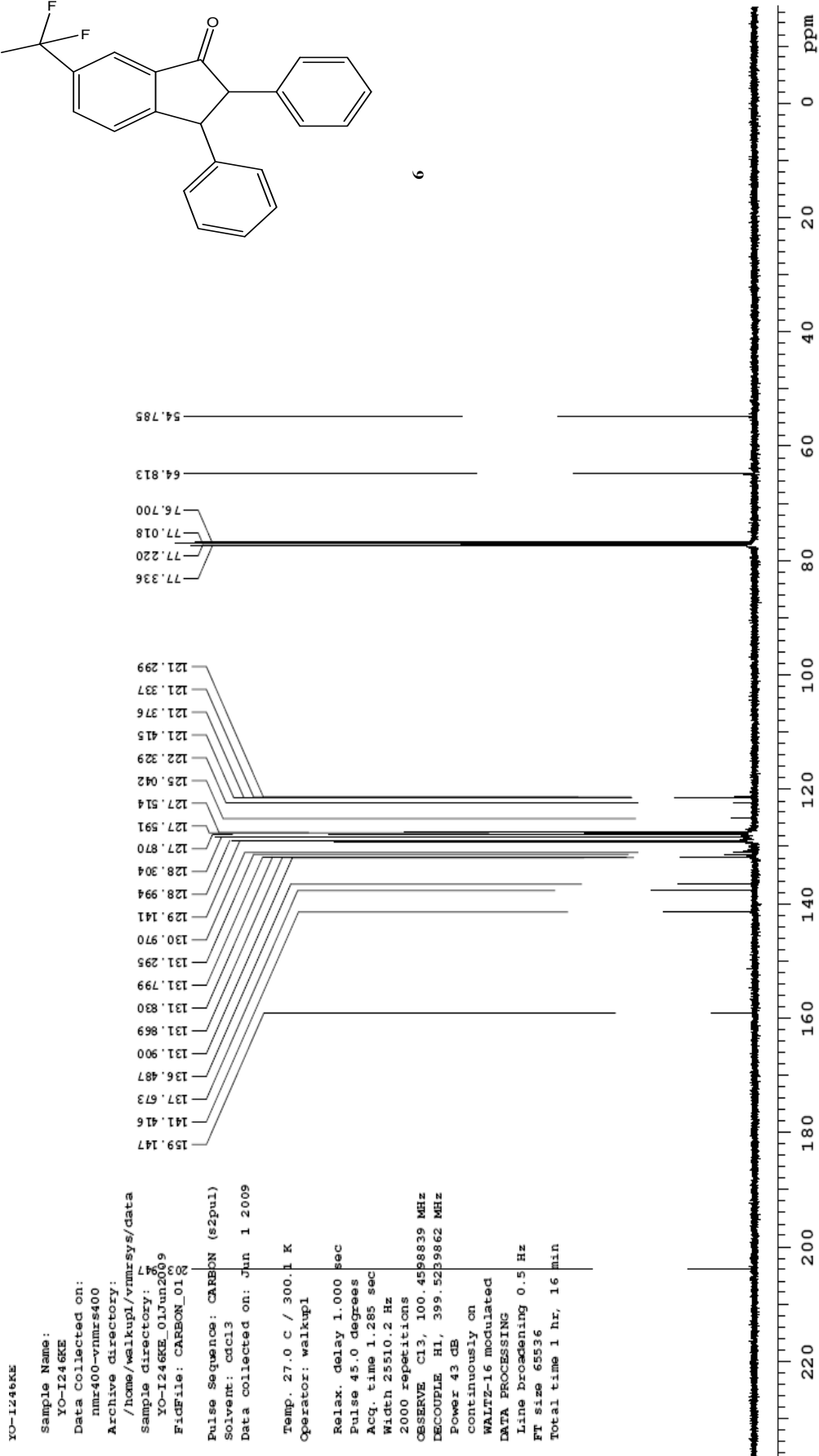
Figure A.14. ^{13}C NMR of 6-(trifluoromethyl)-2,3-dihydro-2,3-diphenylinden-1-one

Figure A.15. ^{19}F NMR of 6-(trifluoromethyl)-2,3-dihydro-2,3-diphenylinden-1-one
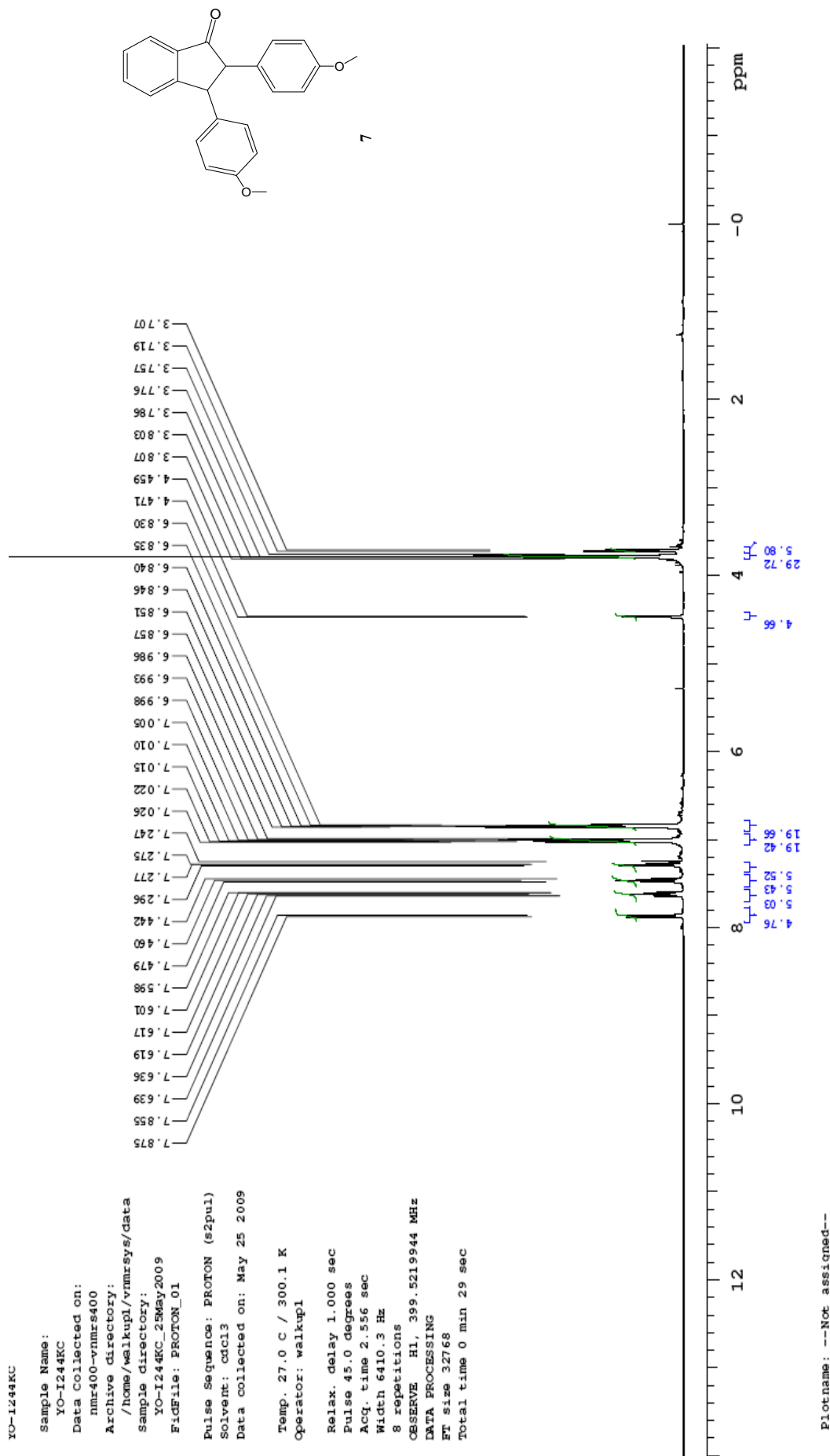
Figure A.16. ^{1}H NMR of 2,3-dihydro-2,3-bis(4-methoxyphenyl)inden-1-one

YO-I244KC

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Data Collected on:
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Archive directory:
    /home/walkup1/vnmrsys/data
Sample directory:
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FidFile: PROTON_01

Pulse Sequence: PROTON (s2pul)
Solvent: cdcl3
Data collected on: May 25 2009

Temp. 27.0 C / 300.1 K
Operator: walkup1

Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
8 repetitions
OBSERVE H1, 399.5219944 MHz
DATA PROCESSING
FT size 32768
Total time 0 min 29 sec

116

Figure A.17. ^{13}C NMR of 2,3-dihydro-2,3-bis(4-methoxyphenyl)inden-1-one
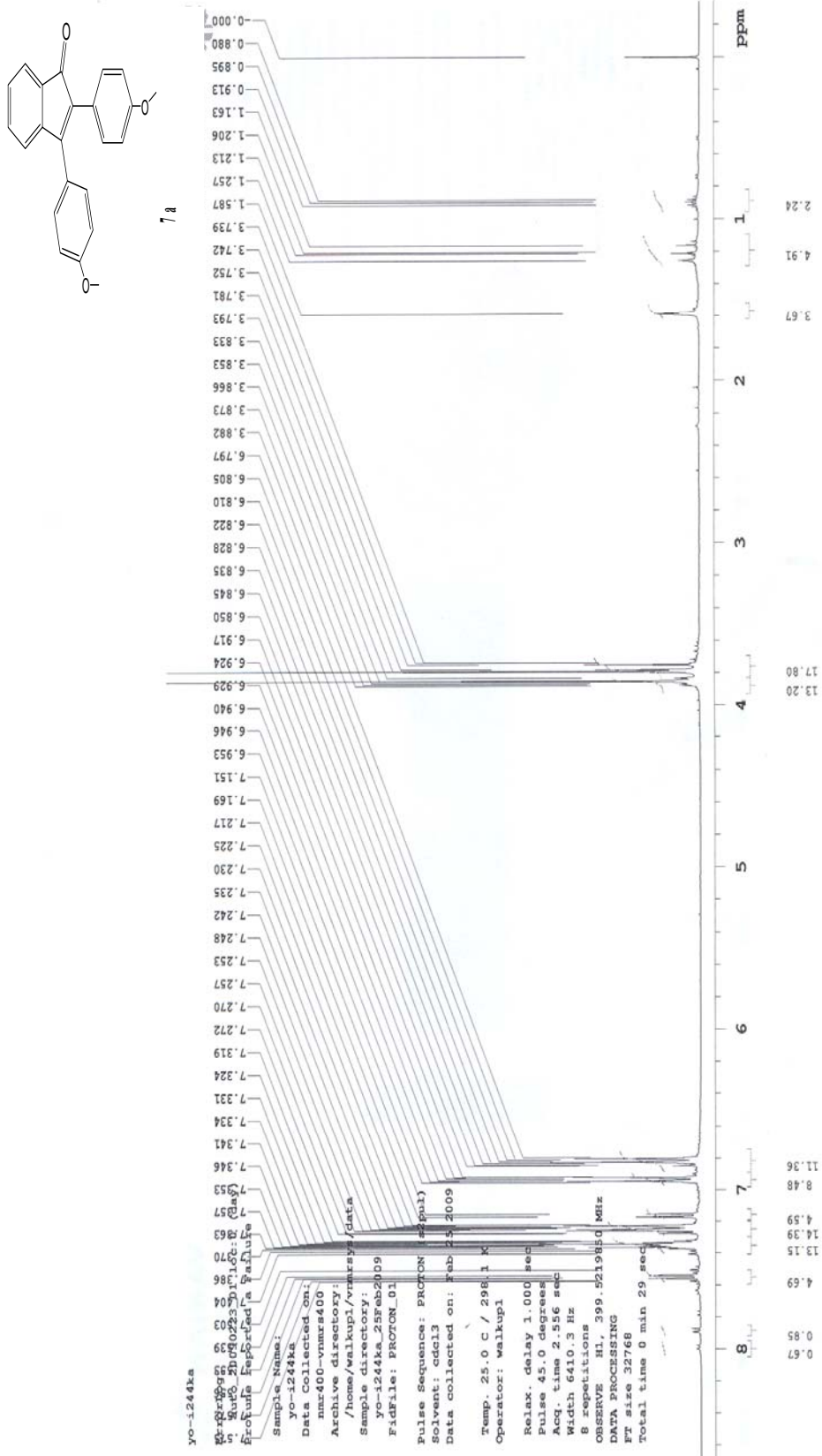
Figure A.17. ^{1}H NMR of 2,3-bis(4-methoxyphenyl)-1*H*-inden-1-one

118
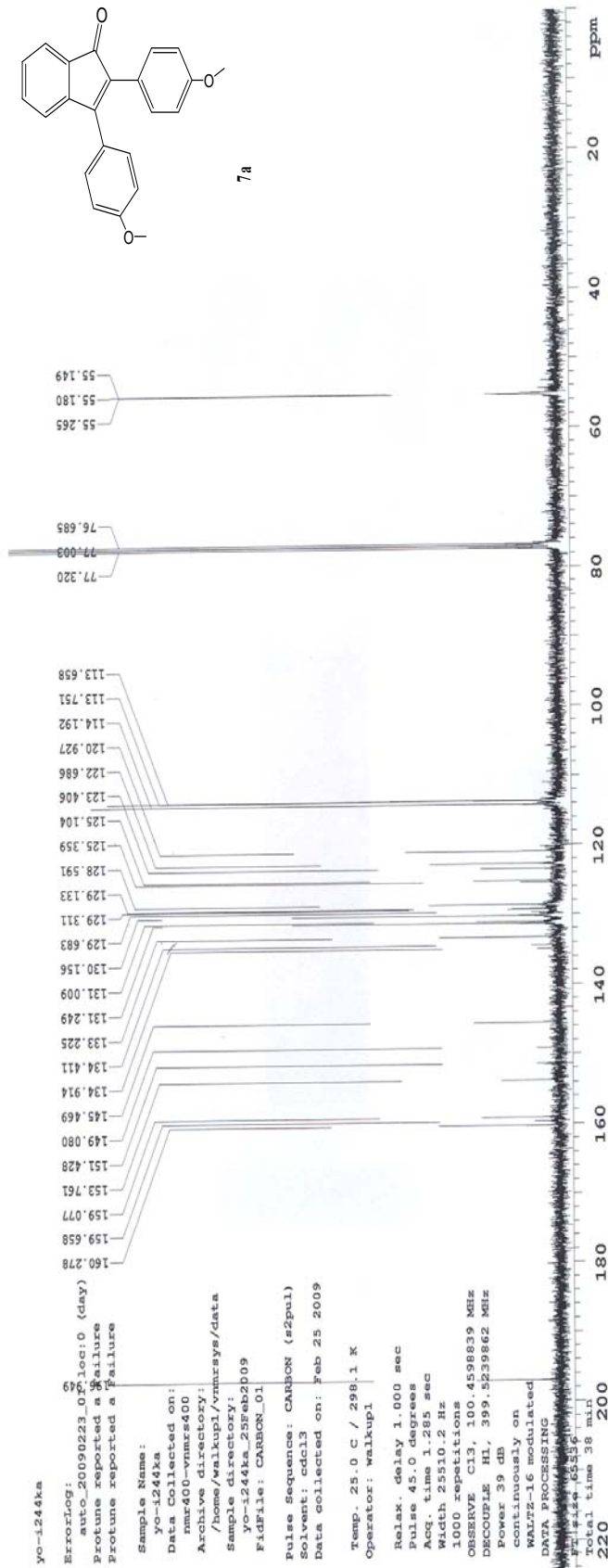
Figire A.18. ^{13}C NMR of 2,3-bis(4-methoxyphenyl)-1*H*-inden-1-one
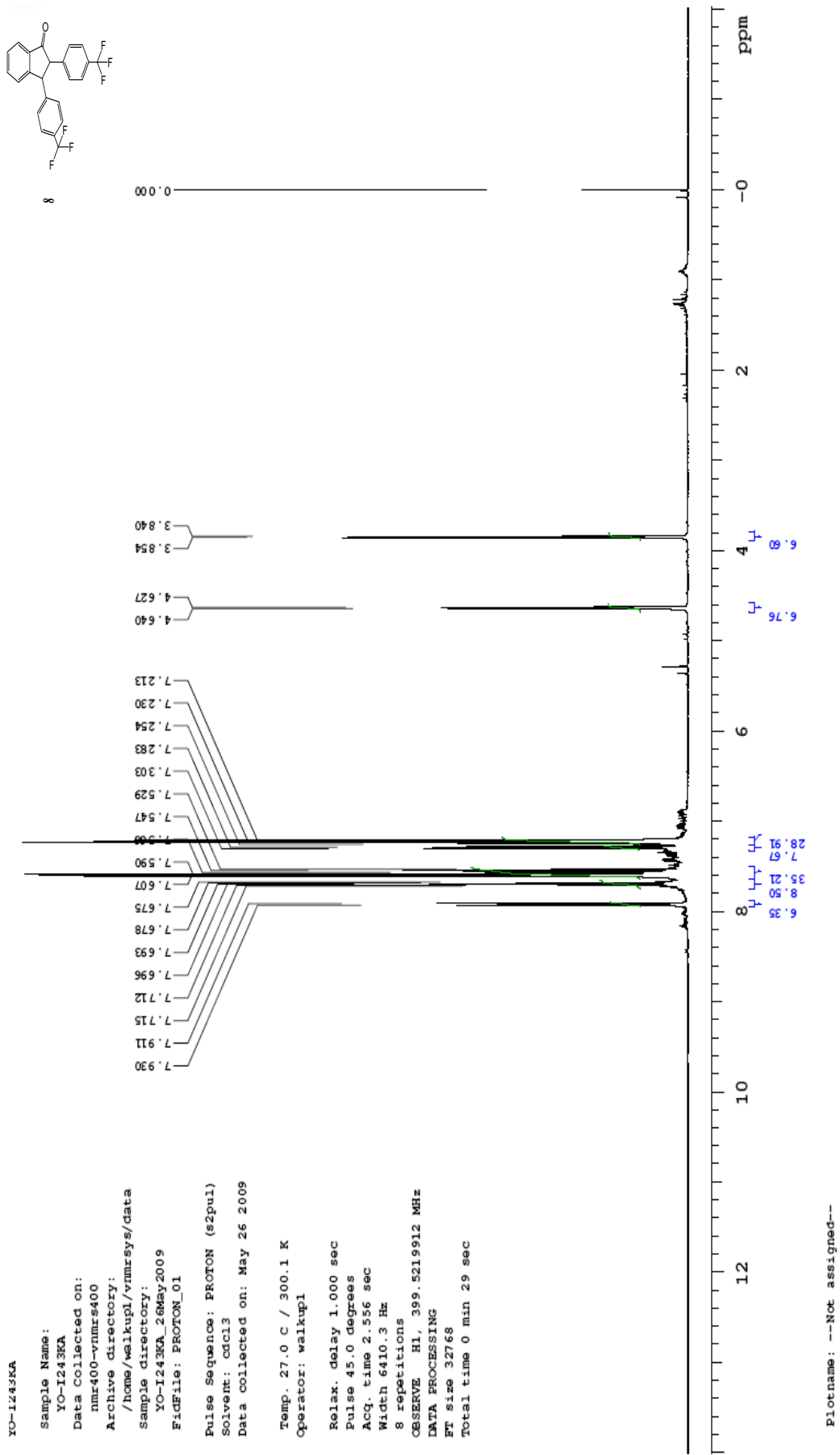
Figure A.19. ^{1}H NMR of 2,3-bis(4-(trifluoromethyl)phenyl)-1H-inden-1-one
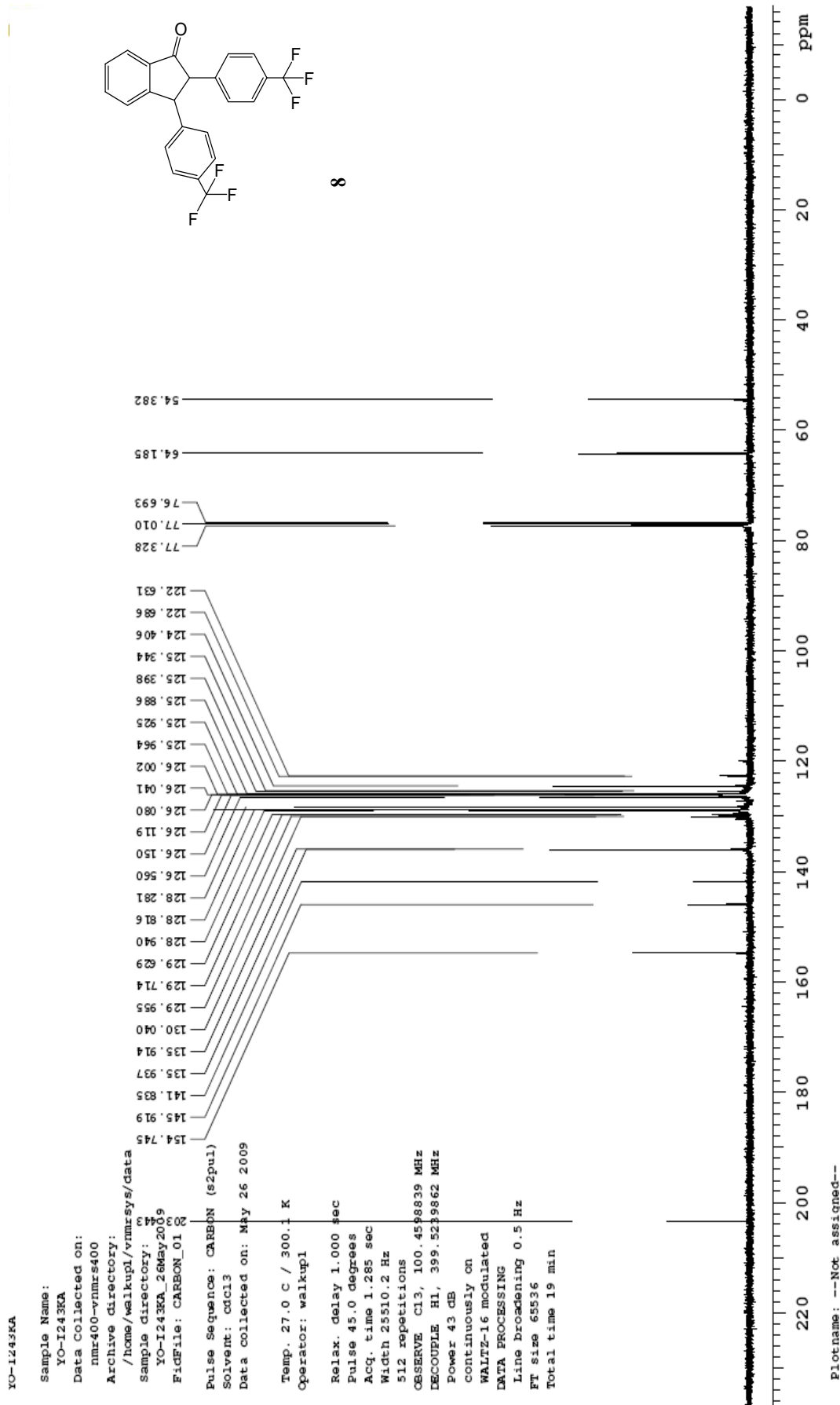
Figure A.20. ^{13}C NMR of 2,3-bis(4-(trifluoromethyl)phenyl)-1H-inden-1-one
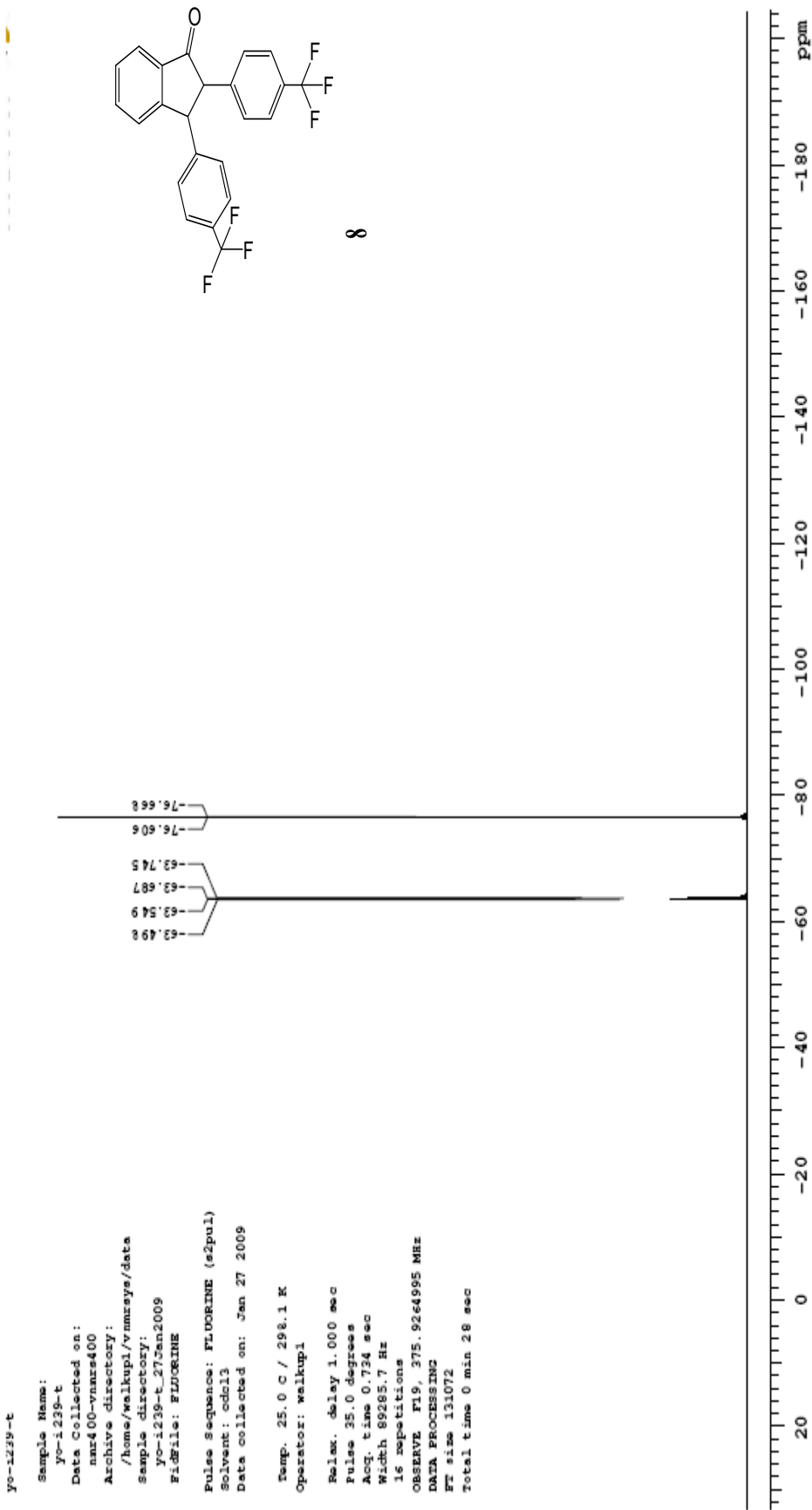
Figure A.21. ^{19}f NMR of 2,3-bis(4-(trifluoromethyl)phenyl)-1H-inden-1-one
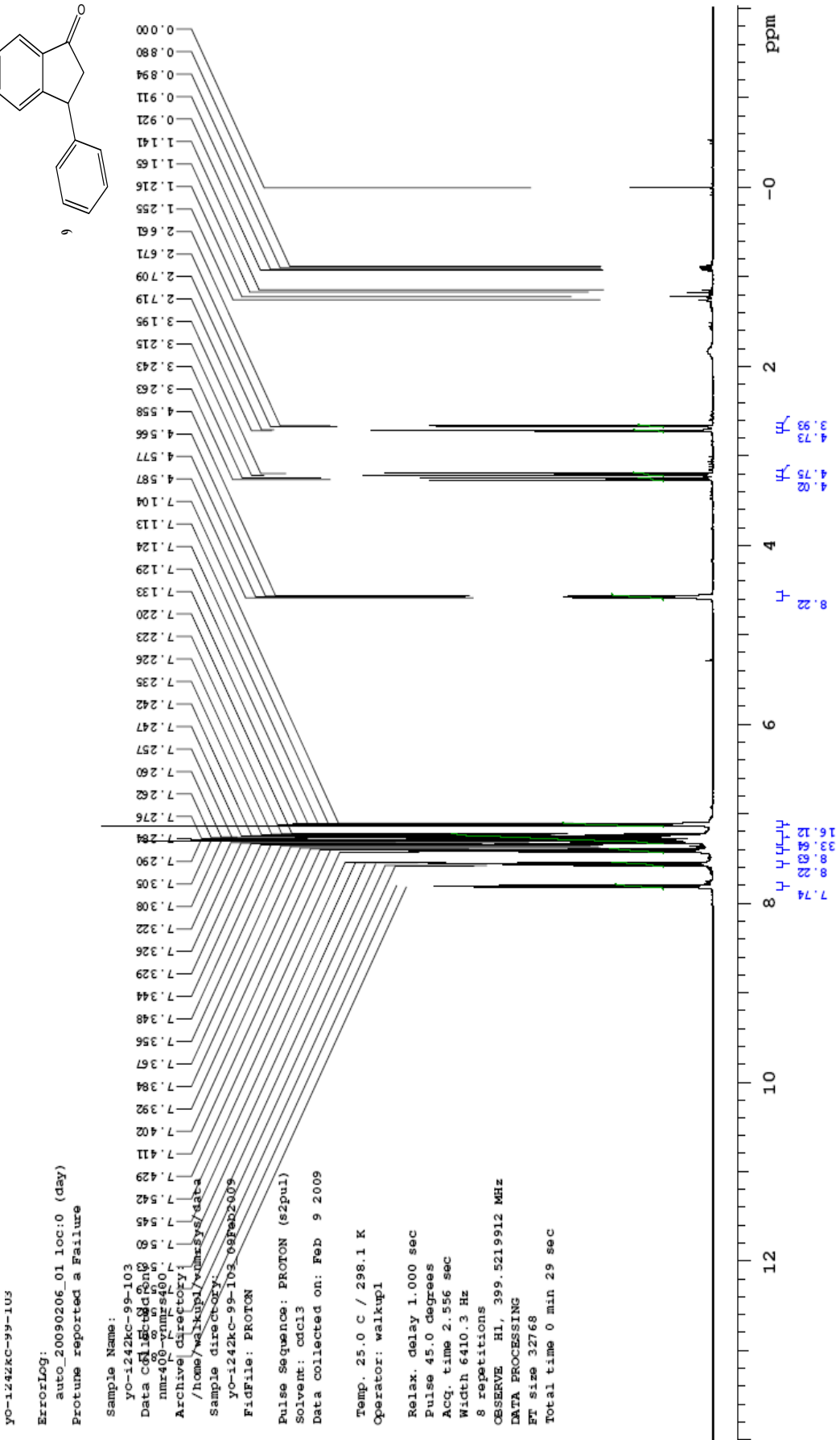
Figure A.22. ^{1}H NMR of 2,3-dihydro-3-phenylinden-1-one
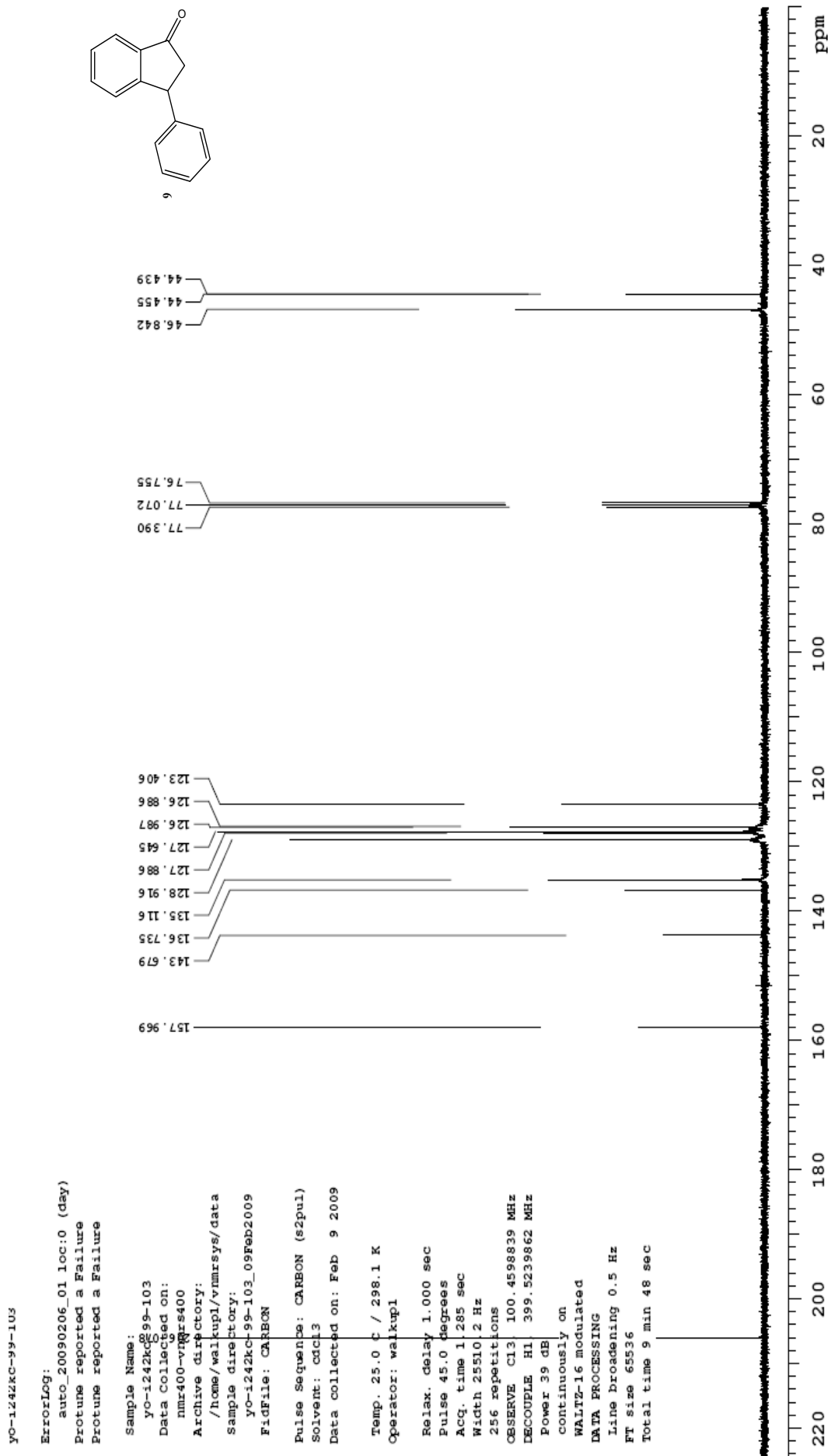
Figure A.23. ^{13}C NMR of 2,3-dihydro-3-phenylinden-1-one

151.969

143.679
136.735
135.116
128.916
127.886
127.645
126.987
126.886
123.406

77.390
77.072
76.755

46.842
44.455
44.439

220 200 180 160 140 120 100 80 60 40 20 ppm

APPENDIX B

MASS SPECTRUMS OF INDANONES AND INDENONES
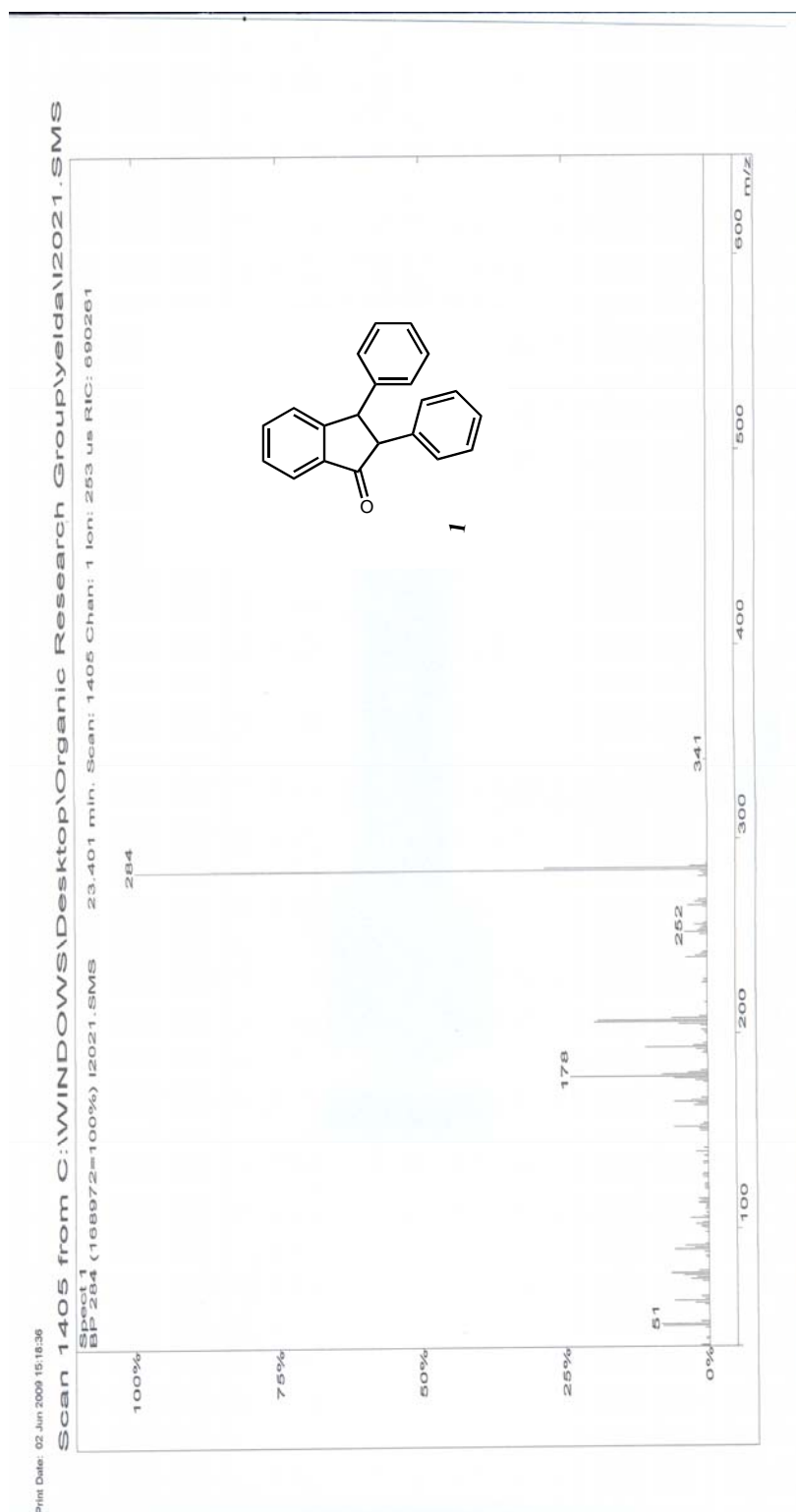
Figure B.1. Mass spectrum of 2,3-dihydro-2,3-diphenylinden-1-one
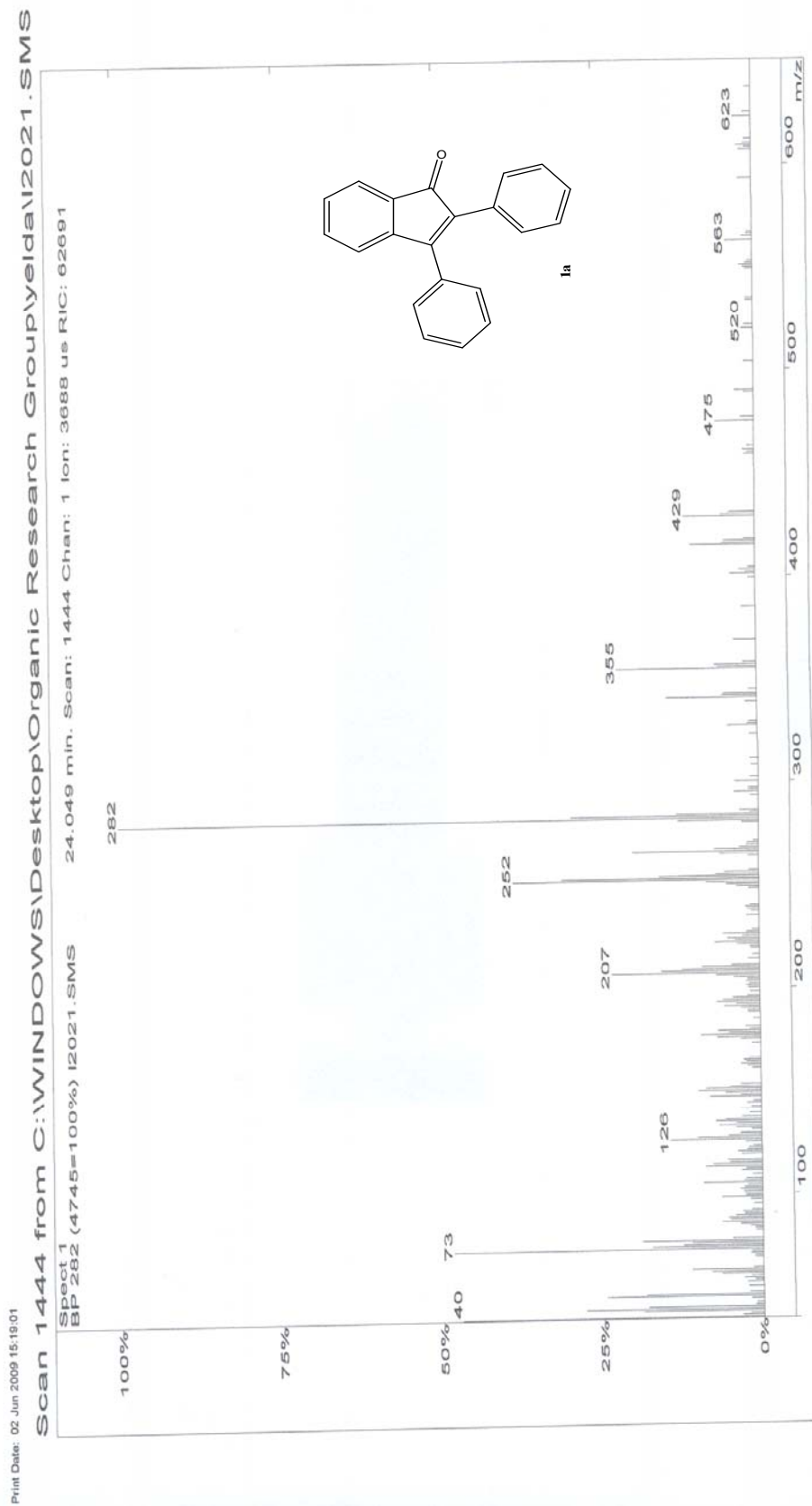
Figure B.2. Mass spectrum of 2,3-diphenyl-1*H*-inden-1-one

126
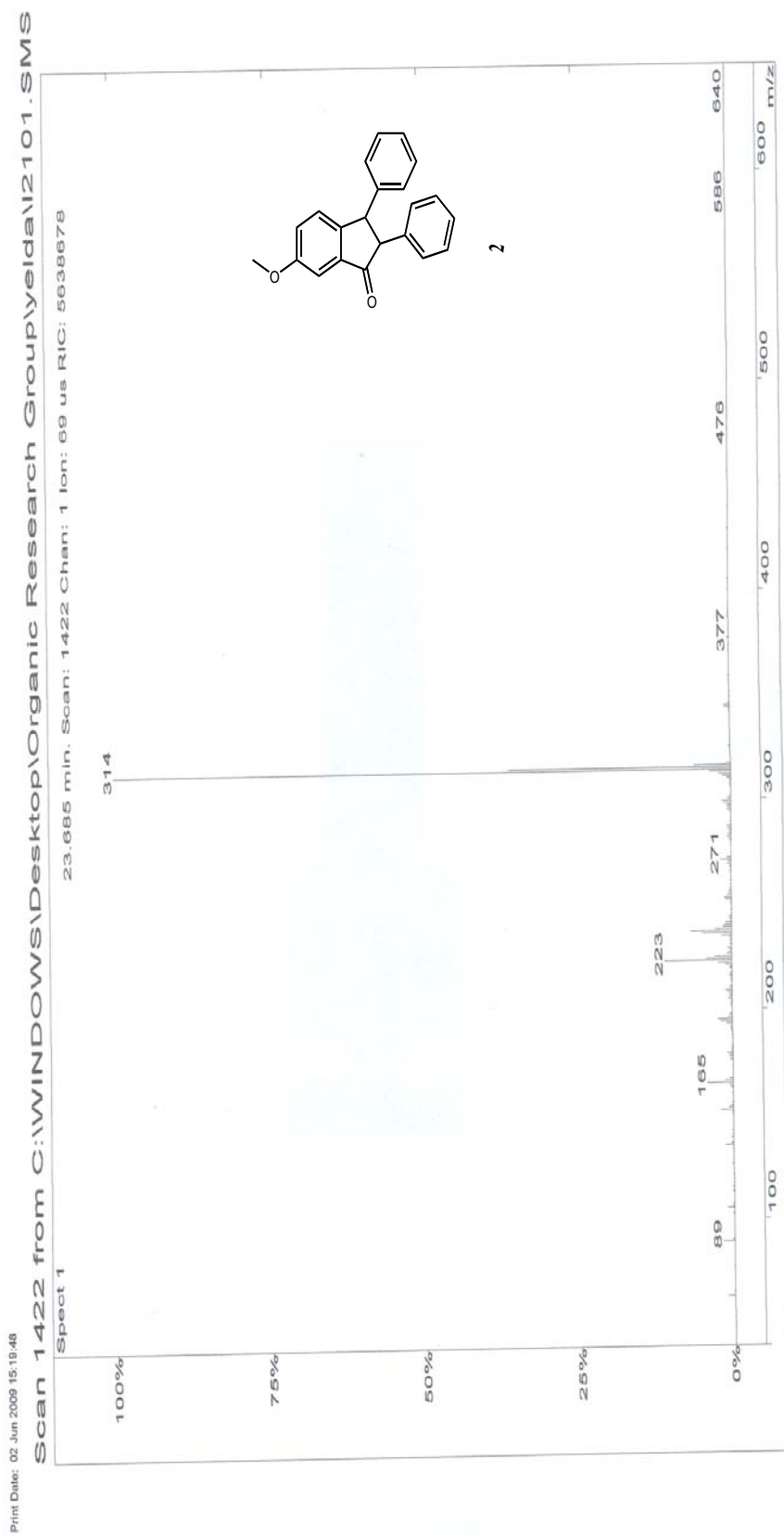
Figure B.3. Mass spectrum of 2,3-dihydro-6-methoxy-2,3-diphenylinden-1-one
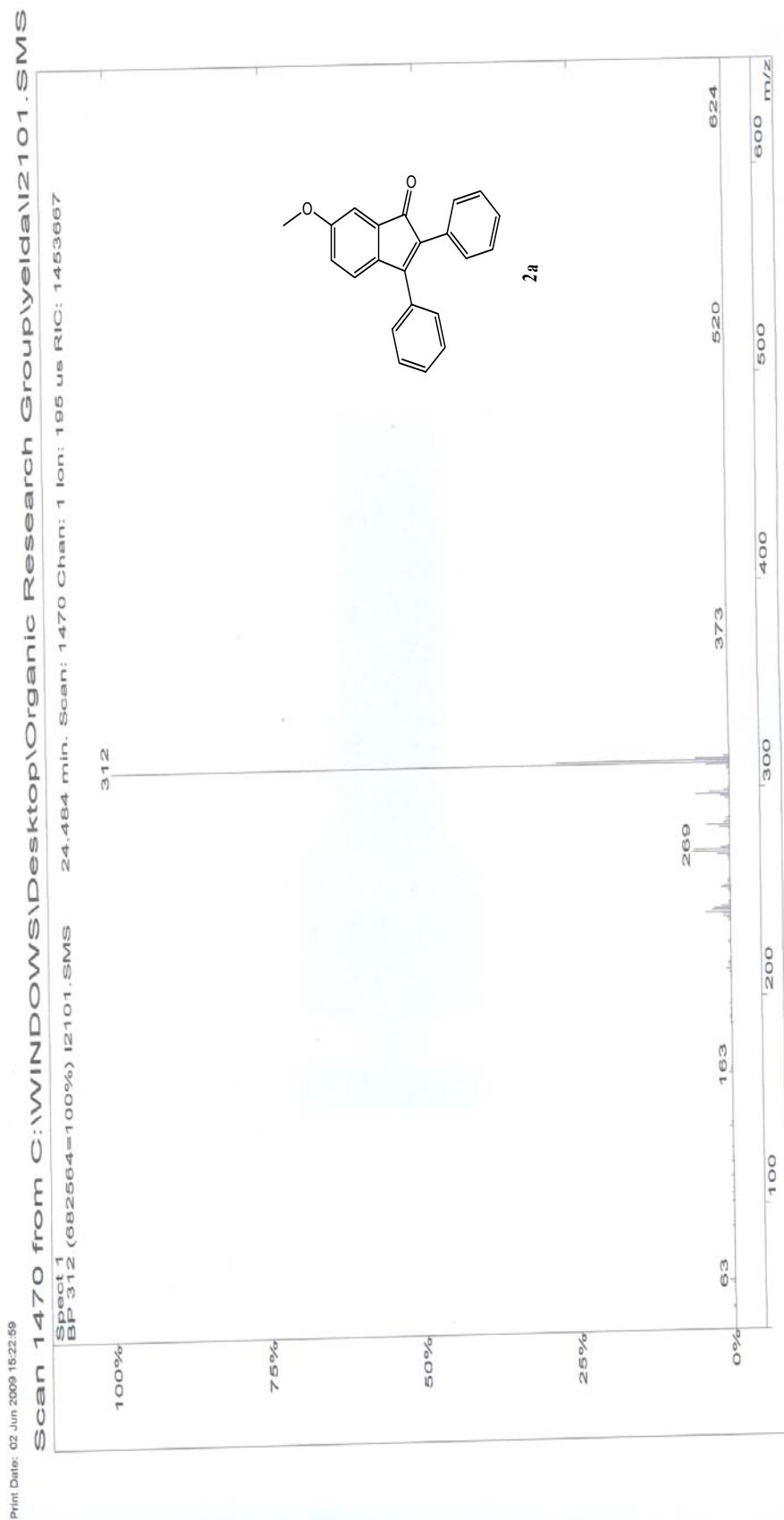
Figure B.4. Mass spectrum of 6-methoxy-2,3-diphenyl-1*H*-inden-1-one
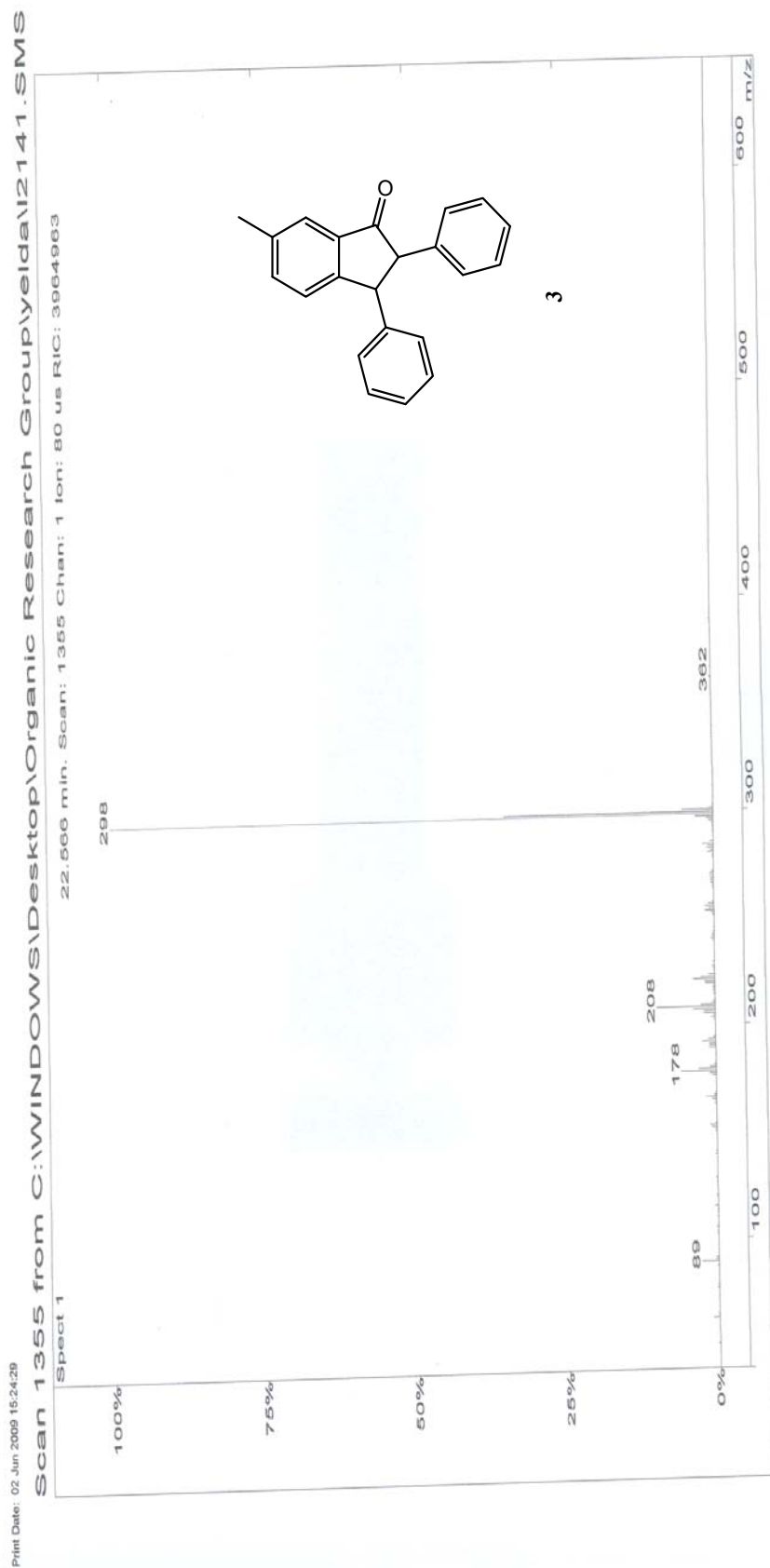
Figure B.5. Mass spectrum of 2,3-dihydro-6-methyl-2,3-diphenylinden-1-one
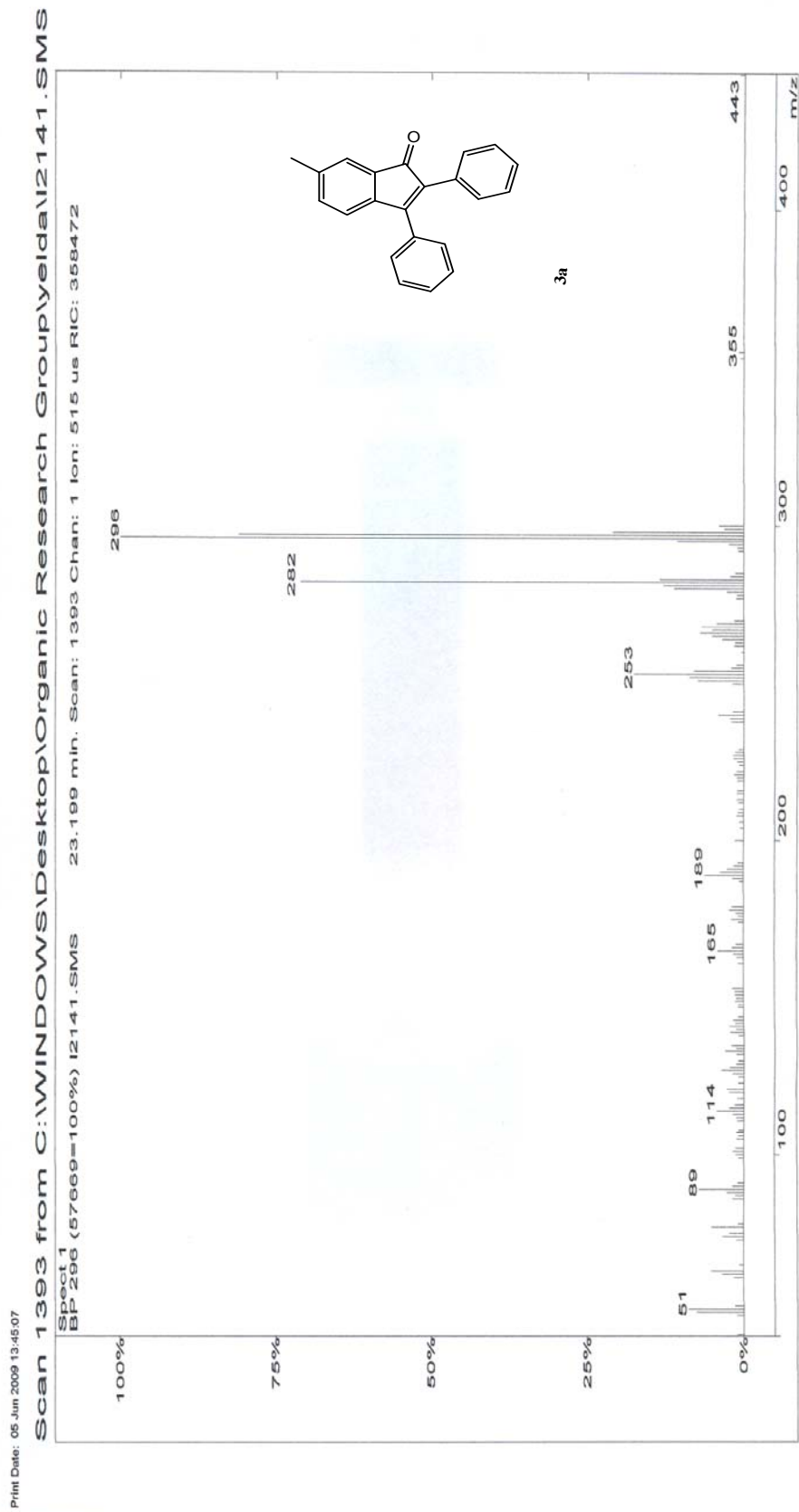
Figure B.6. Mass spectrum of 6-methyl-2,3-diphenyl-1*H*-inden-1-one
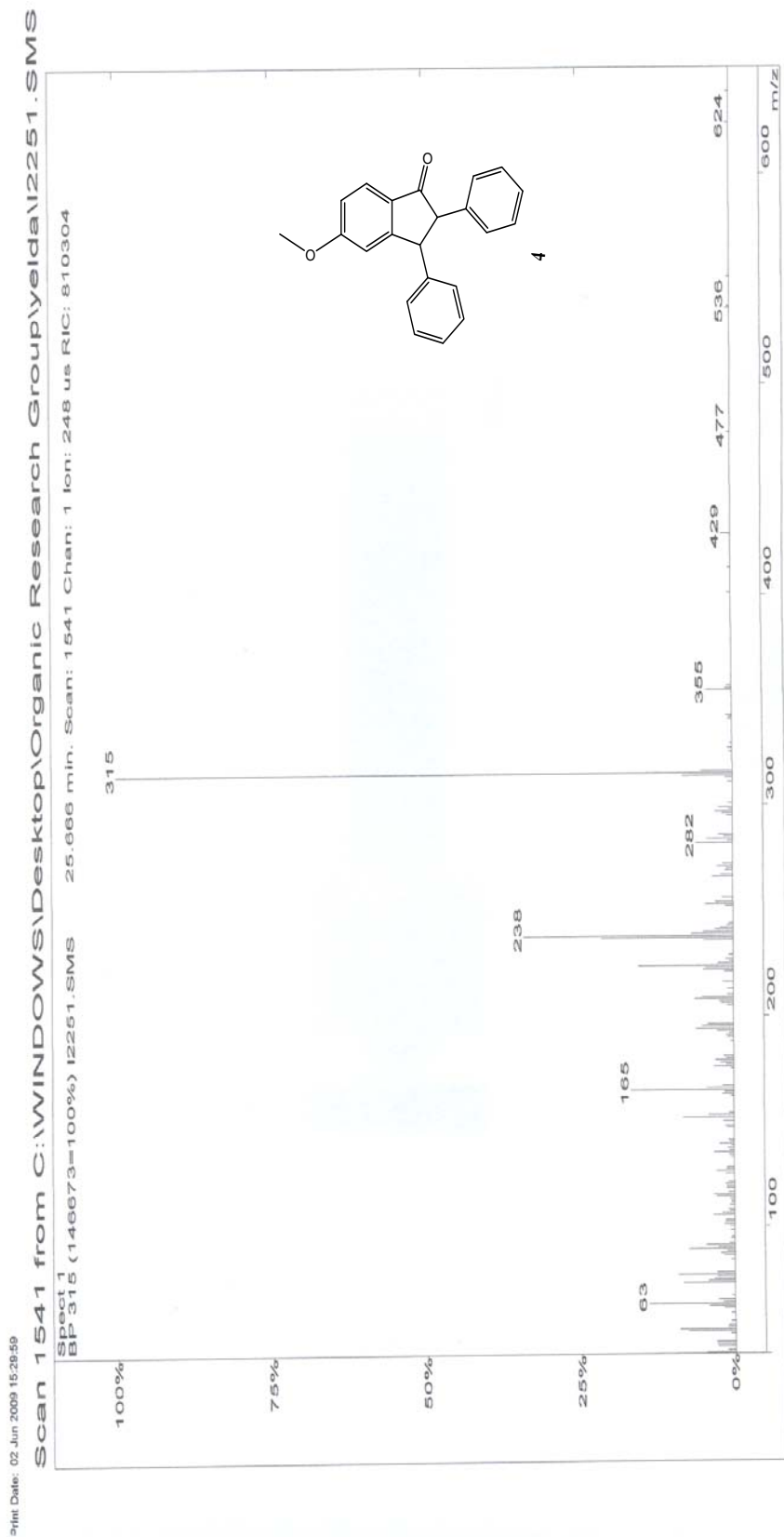
Figure B.7. Mass spectrum of 2,3-dihydro-5-methoxy-2,3-diphenylinden-1-one

131
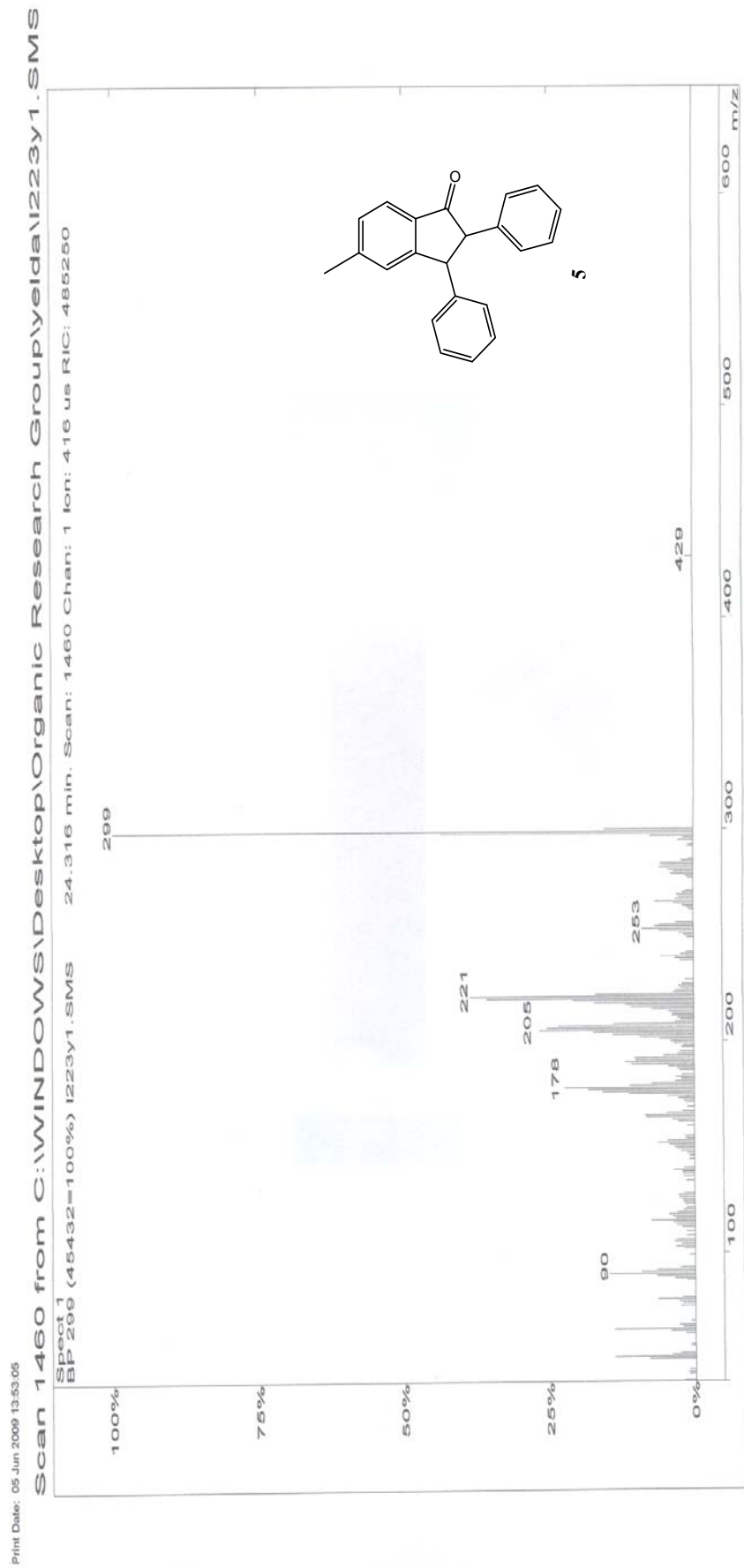
Figure B.8 Mass spectrum of 2,3-dihydro-5-methyl-2,3-diphenylinden-1-one
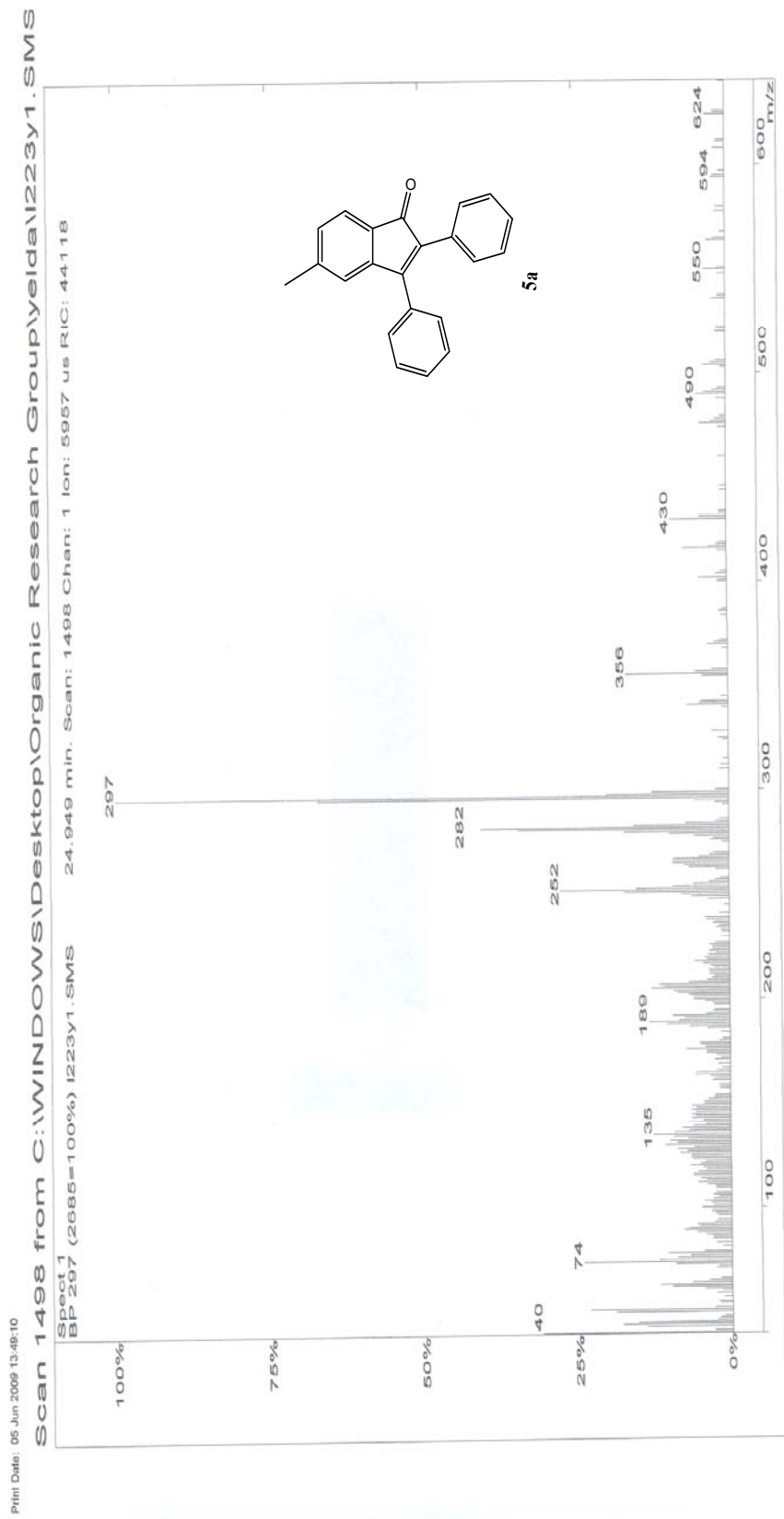
Figure B.9 Mass spectrum of 5-methyl-2,3-diphenyl-1*H*-inden-1-one
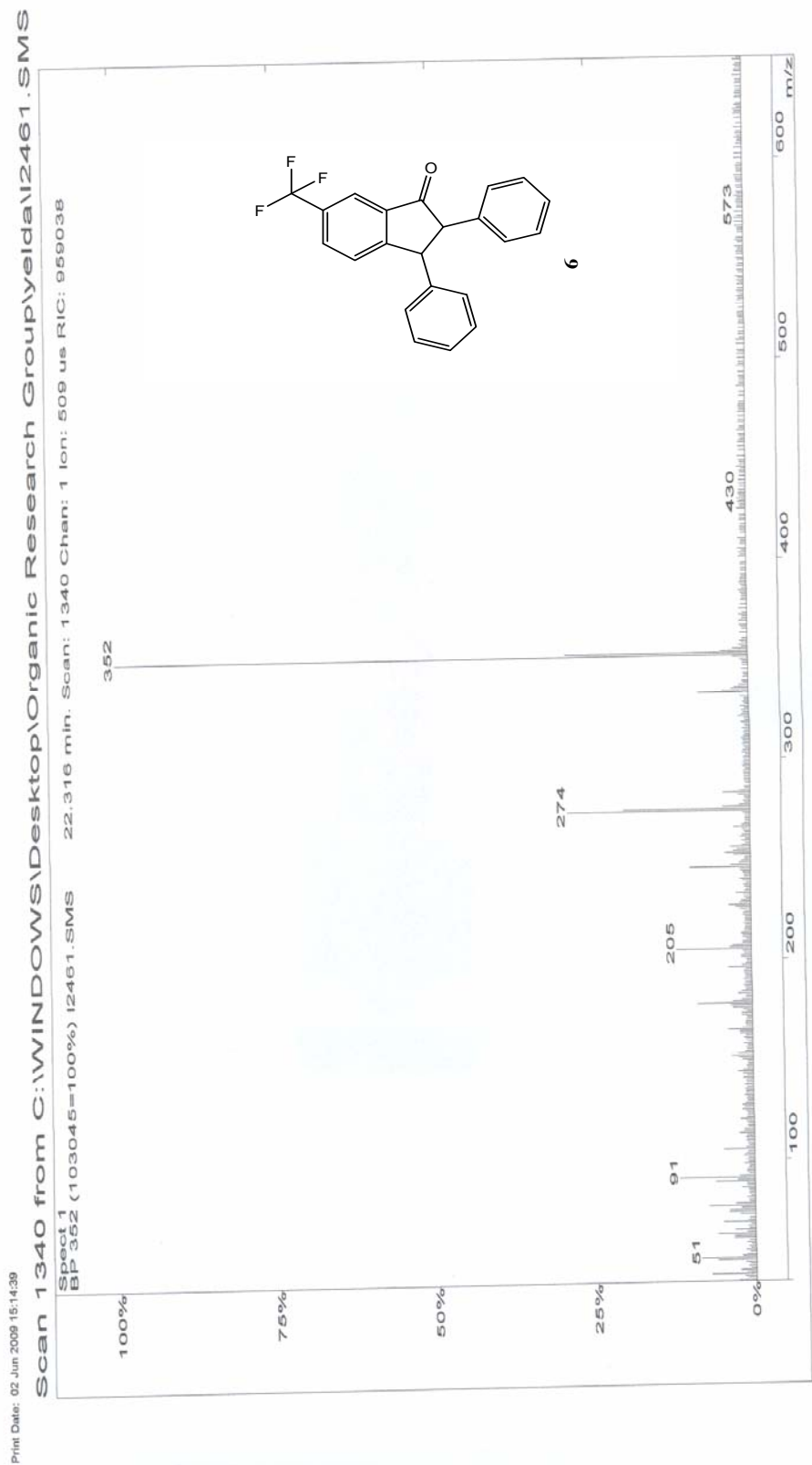
Figure B.10. Mass spectrum of 6-(trifluoromethyl)-2,3-dihydro-2,3-diphenylinden-1-one

134
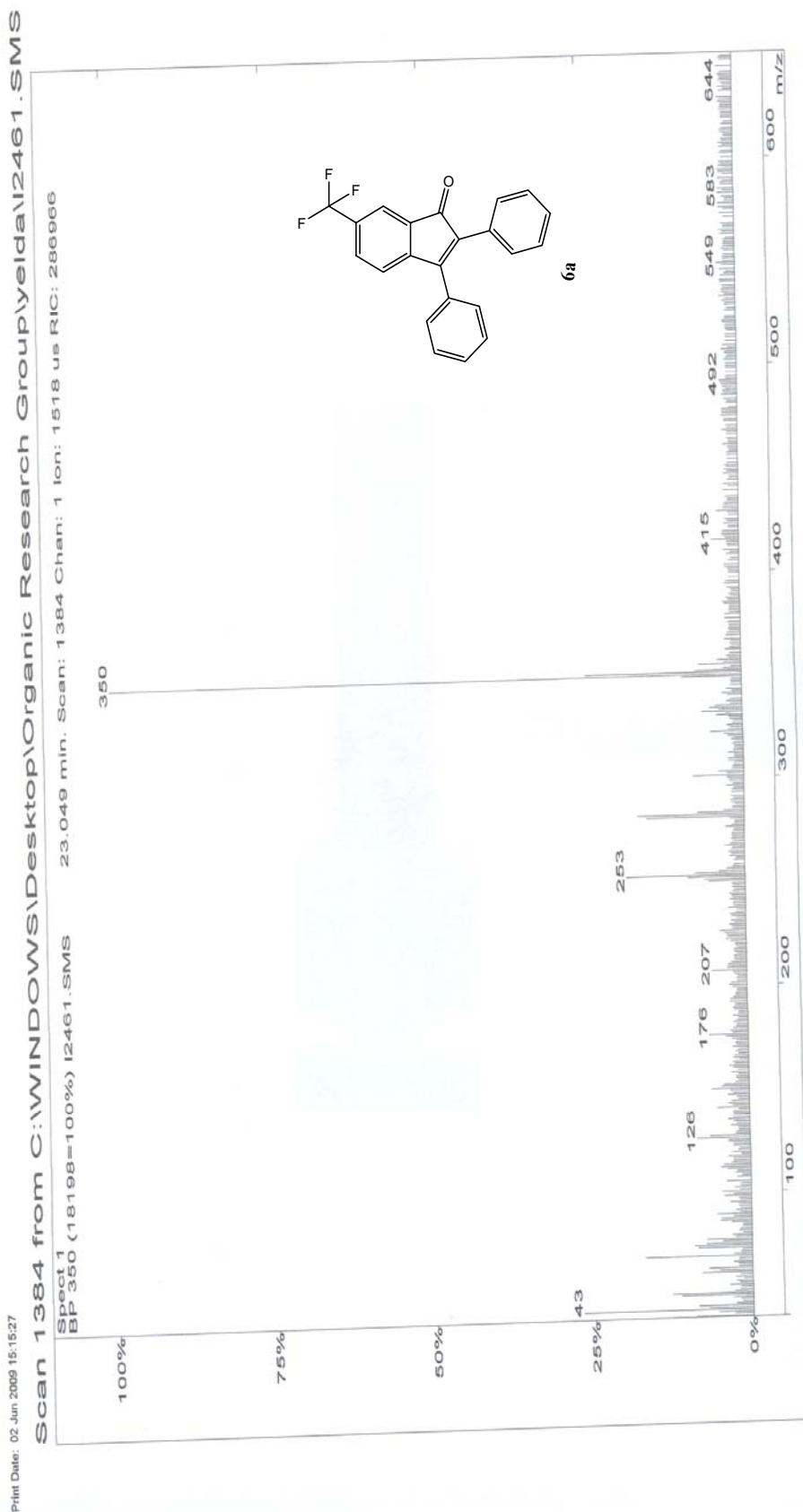
Figure B.11. Mass spectrum of 6-(trifluoromethyl)-2,3-diphenyl-1*H*-inden-1-one
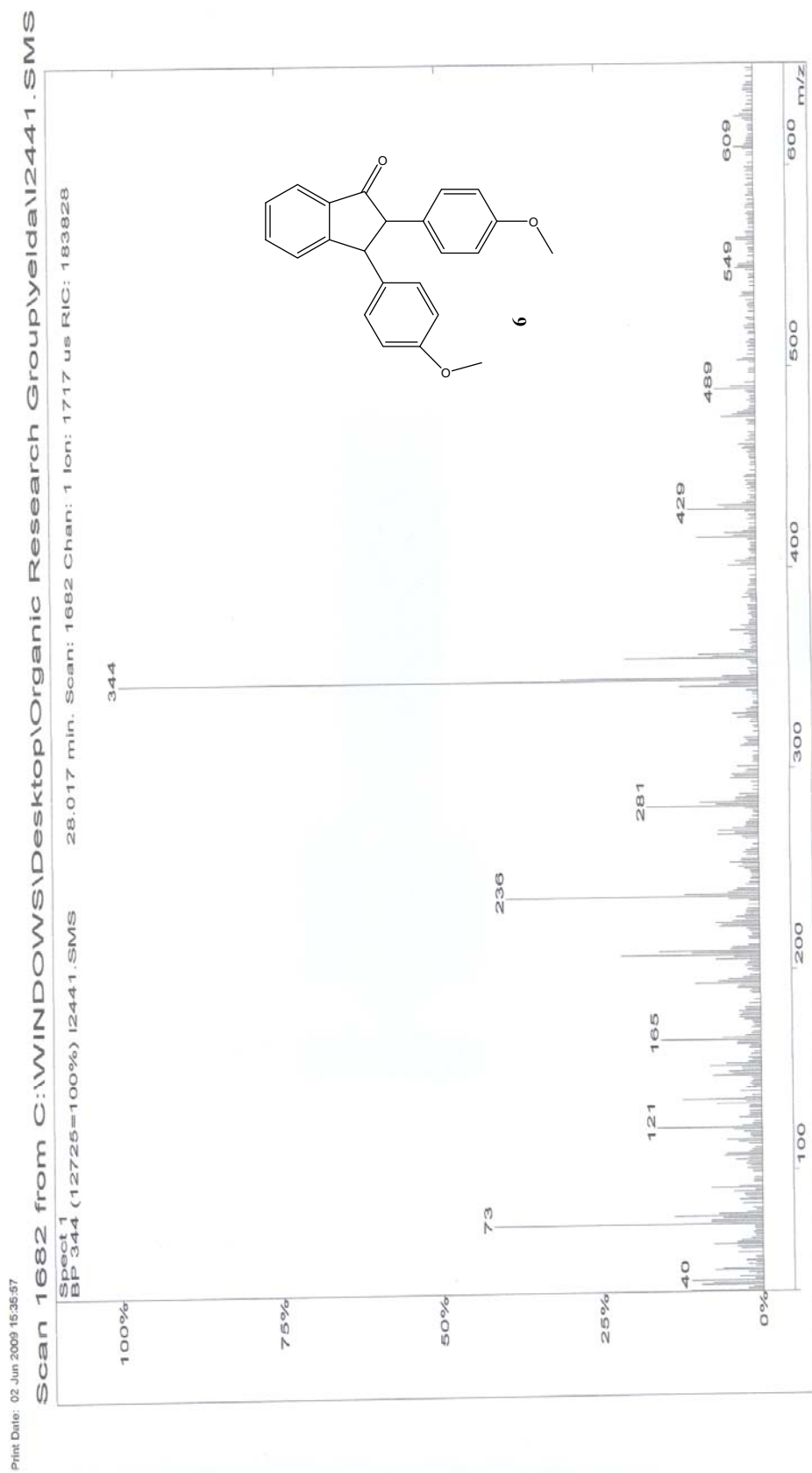
Figure B.12. Mass spectrum of 2,3-dihydro-2,3-bis(4-methoxyphenyl)inden-1-one

136
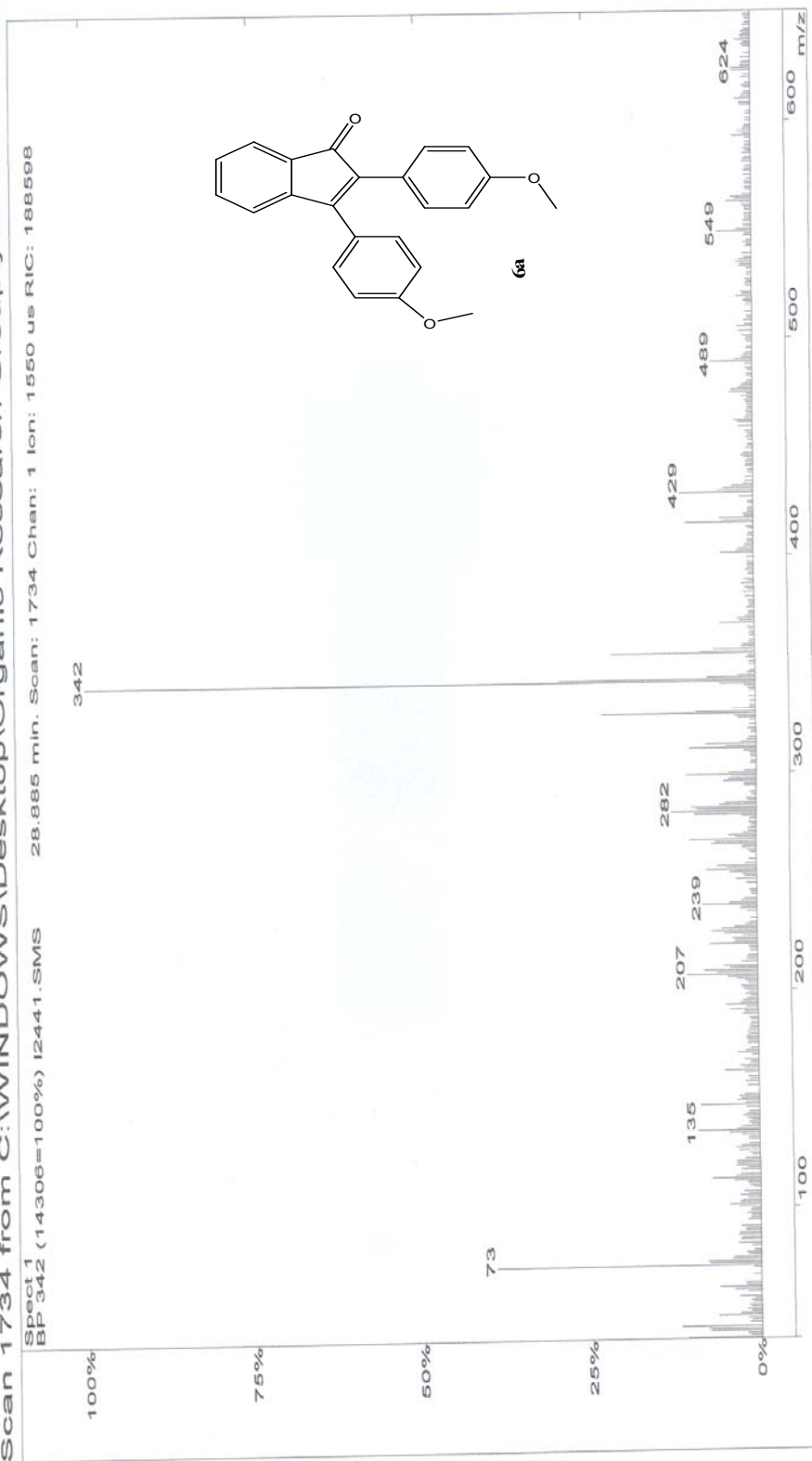
Figure B.13. Mass spectrum of 2,3-bis(4-methoxyphenyl)-1*H*-inden-1-one
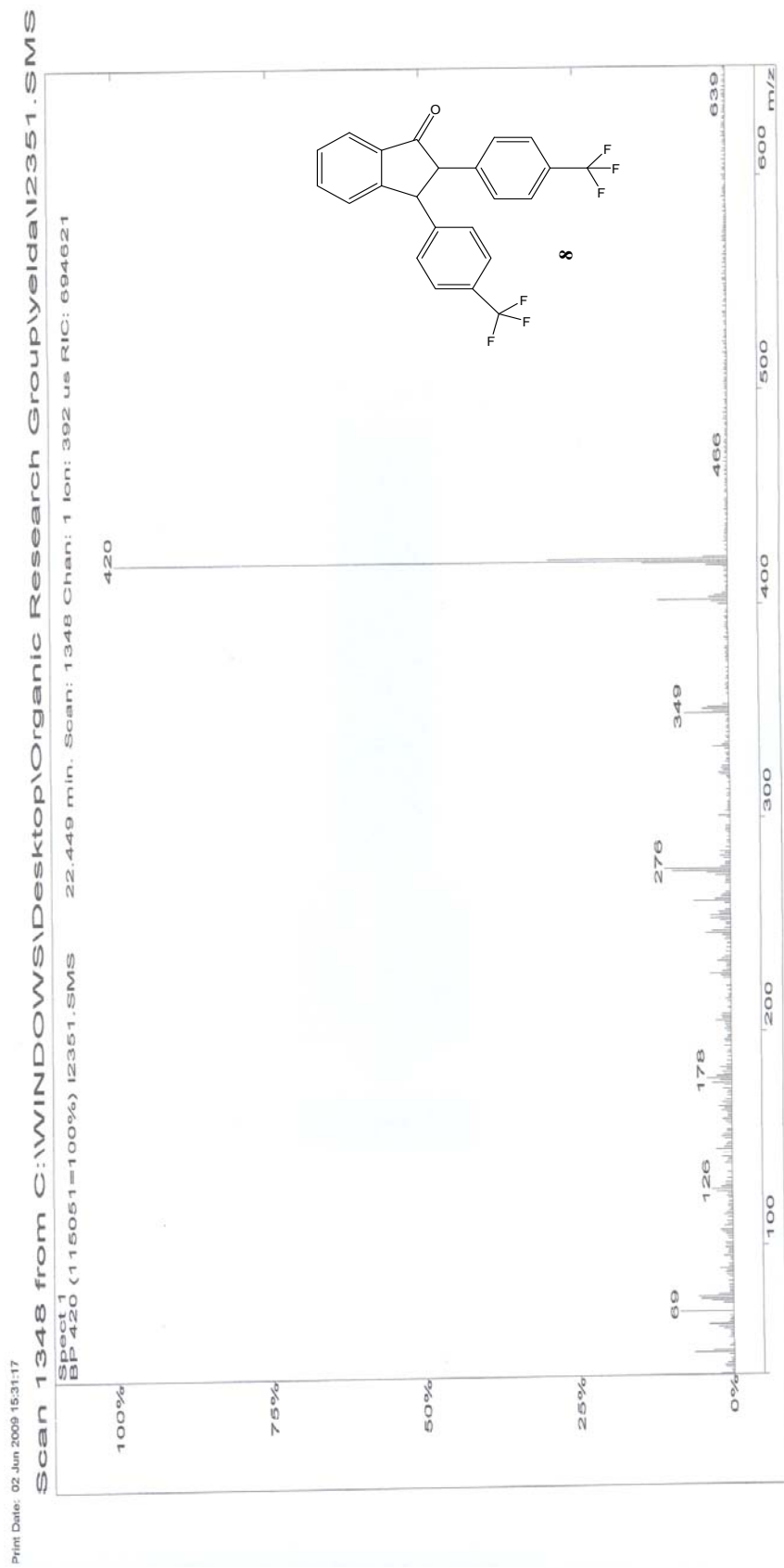
Figure B.14. Mass spectrum of 2,3-bis(4-(trifluoromethyl)phenyl)-2,3-dihydroinden-1-one
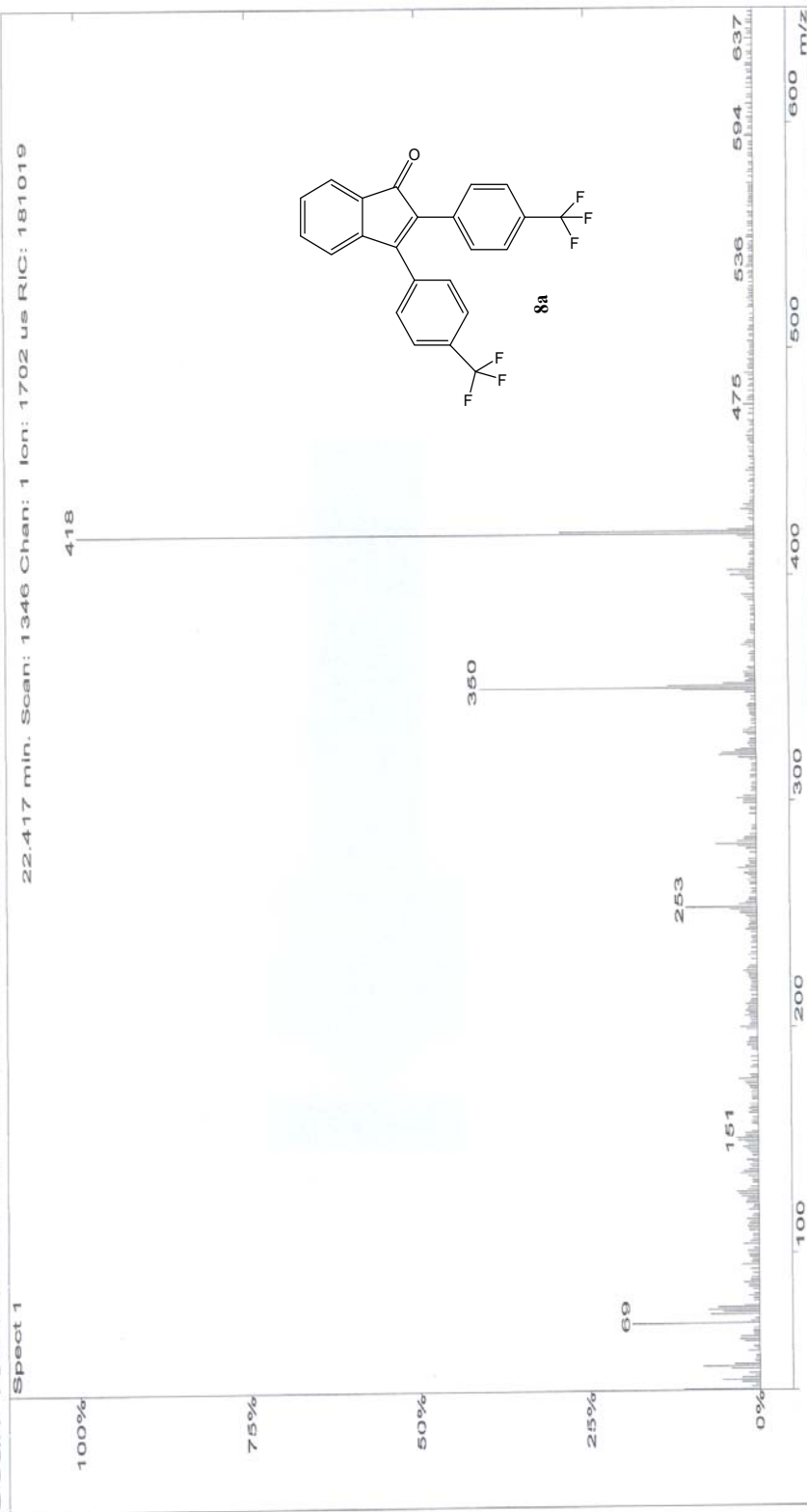
Figure B.15. Mass spectrum of 2,3-bis(4-(trifluoromethyl)phenyl)-1*H*-inden-1-one
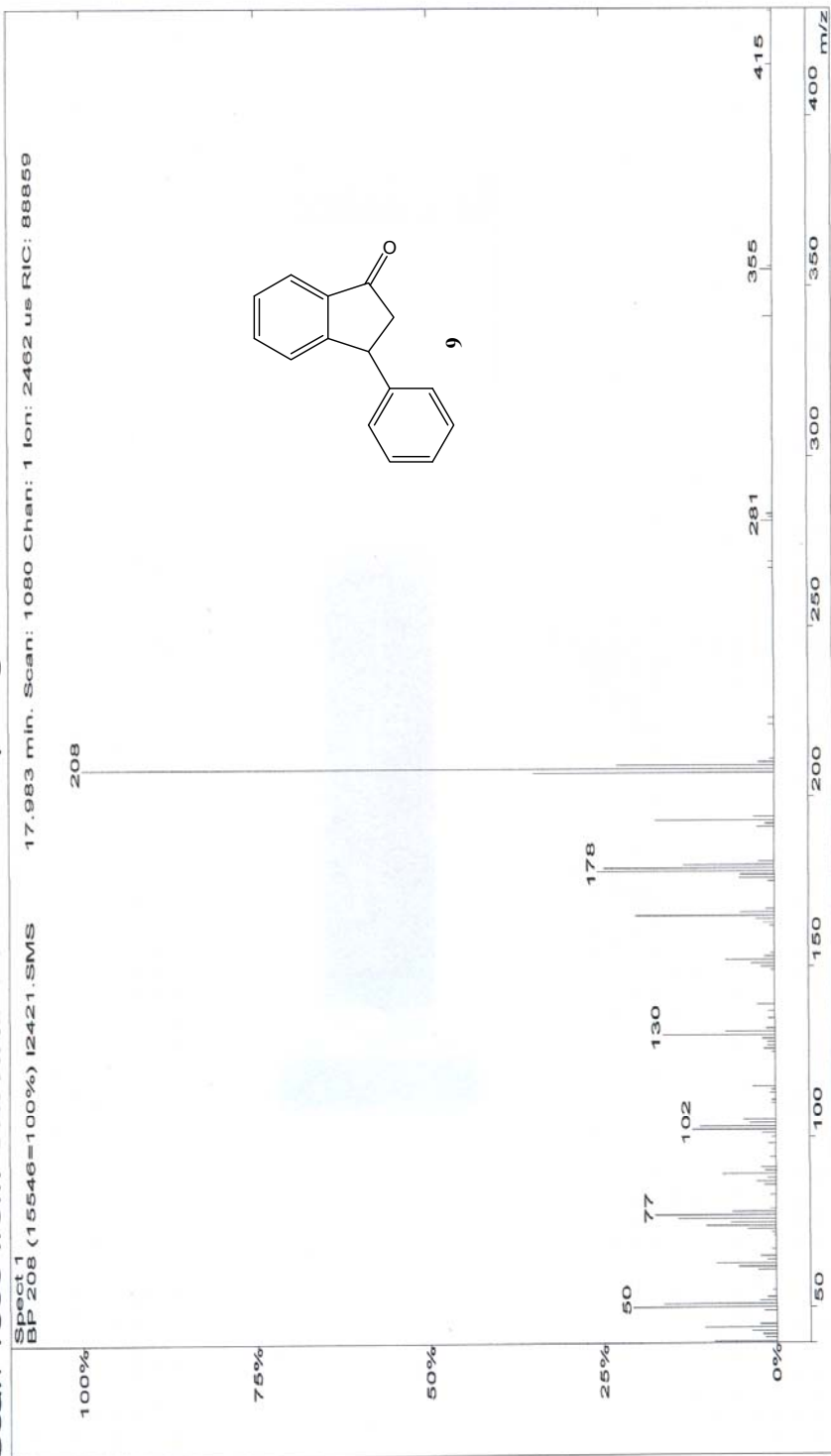
Figure B.16. Mass spectrum of 2,3-dihydro-3-phenylinden-1-one1*H*-inden-1-one

APPENDIX C
FT-IR SPECTRUMS OF INDANONES AND
INDENONES
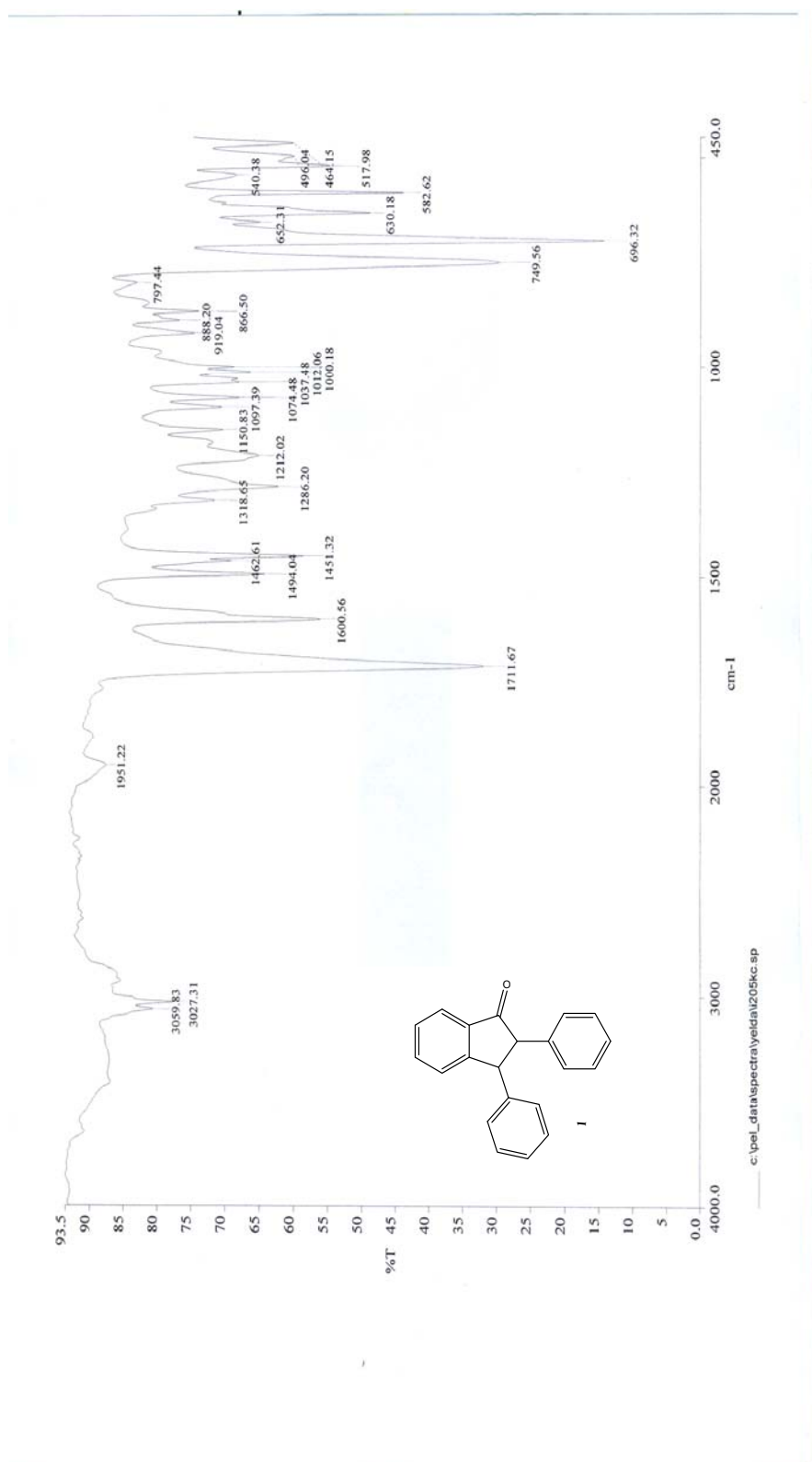
Figure C.1. FT-IR spectrum of 2,3-dihydro-2,3-diphenylinden-1-one
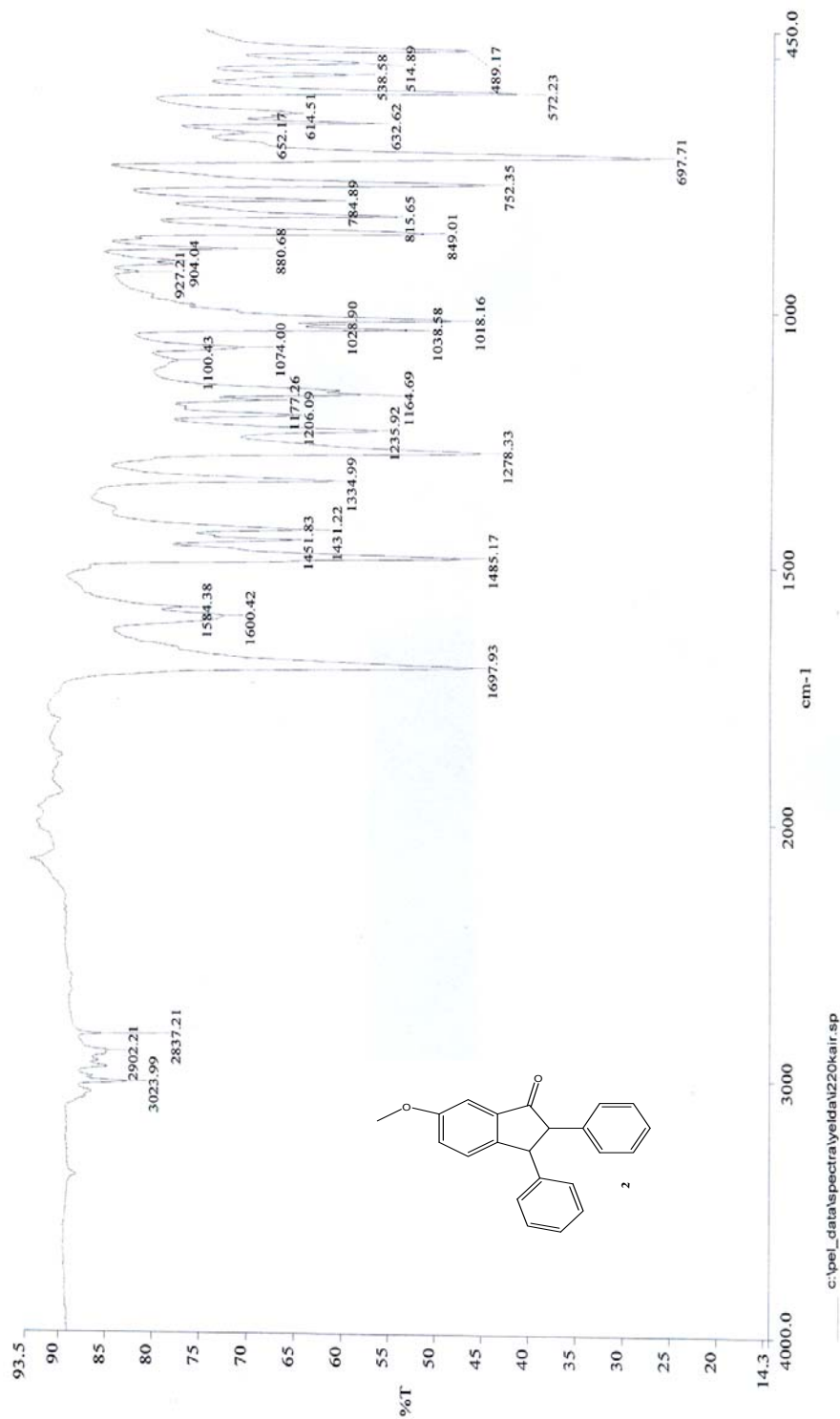
Figure C.2. FT-IR spectrum of 2,3-dihydro-6-methoxy-2,3-diphenylinden-1-one
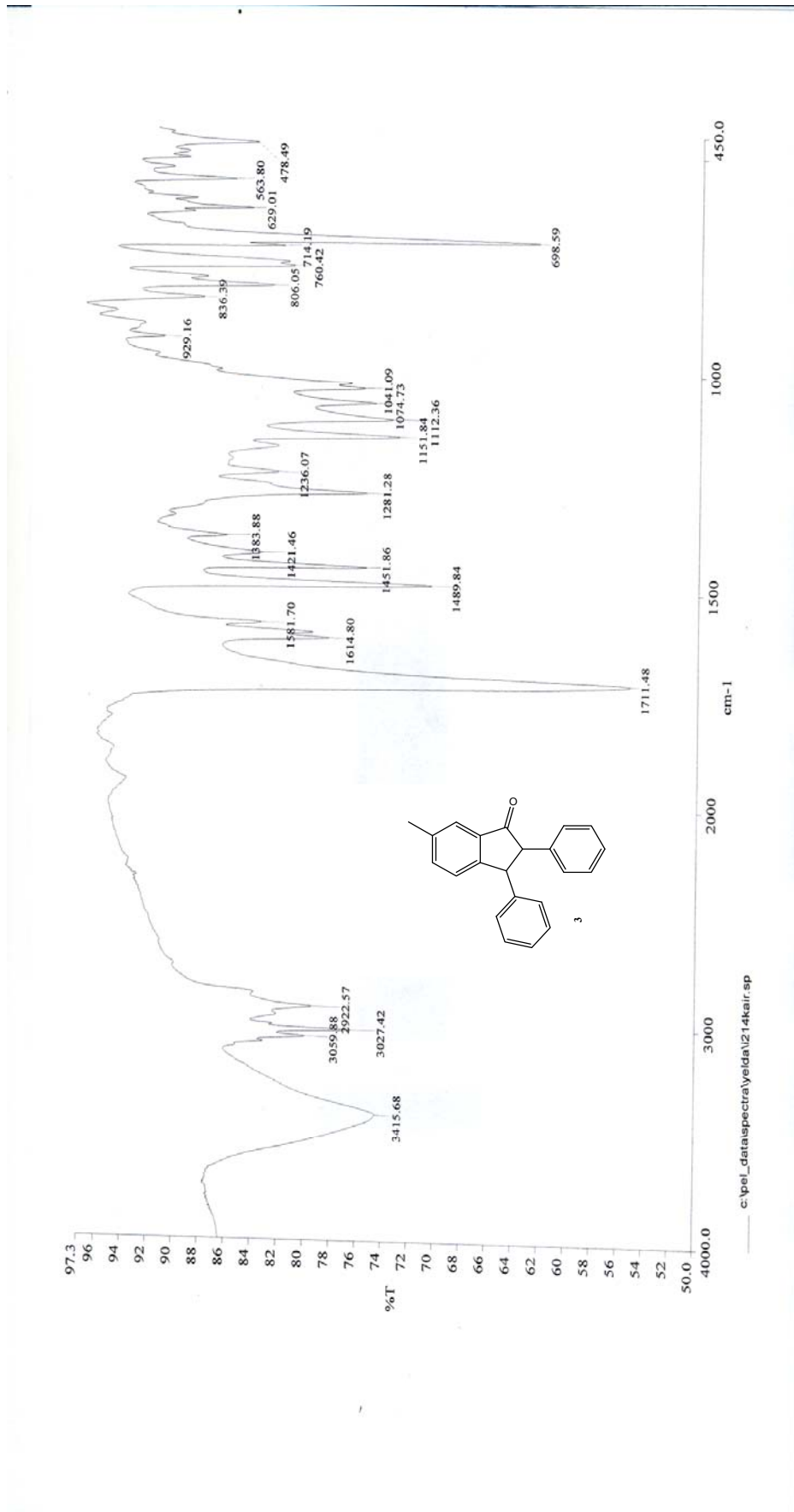
Figure C.3. FT-IR spectrum of 2,3-dihydro-6-methyl-2,3-diphenylinden-1-one
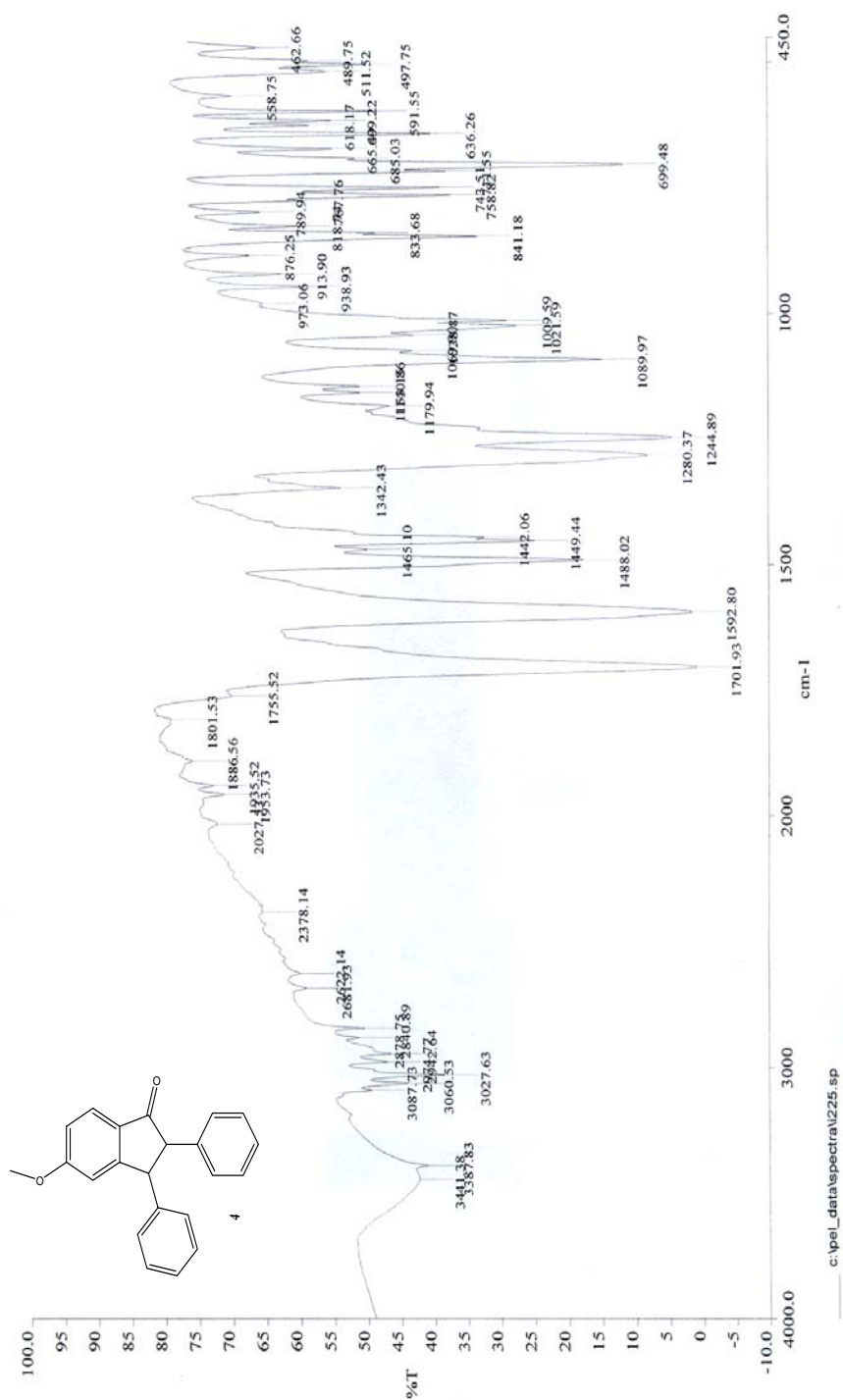
Figure C.4. FT-IR spectrum of 2,3-dihydro-5-methoxy-2,3-diphenylinden-1-one

144

Figure C.5. FT-IR spectrum of 2,3-dihydro-5-methyl-2,3-
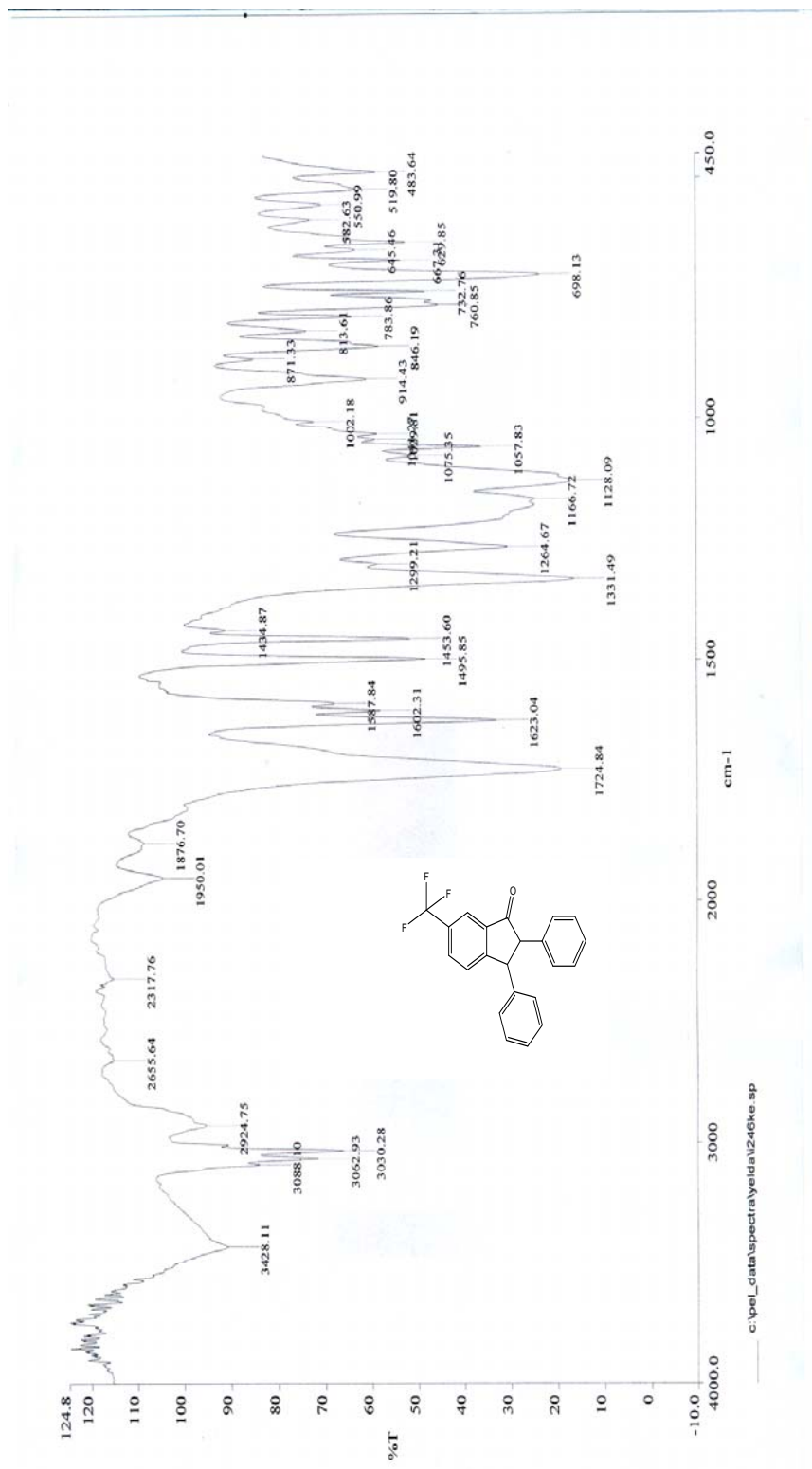
Figure C.6. FT-IR spectrum of 6-(trifluoromethyl)-2,3-dihydro-2,3-diphenylinden-1-one
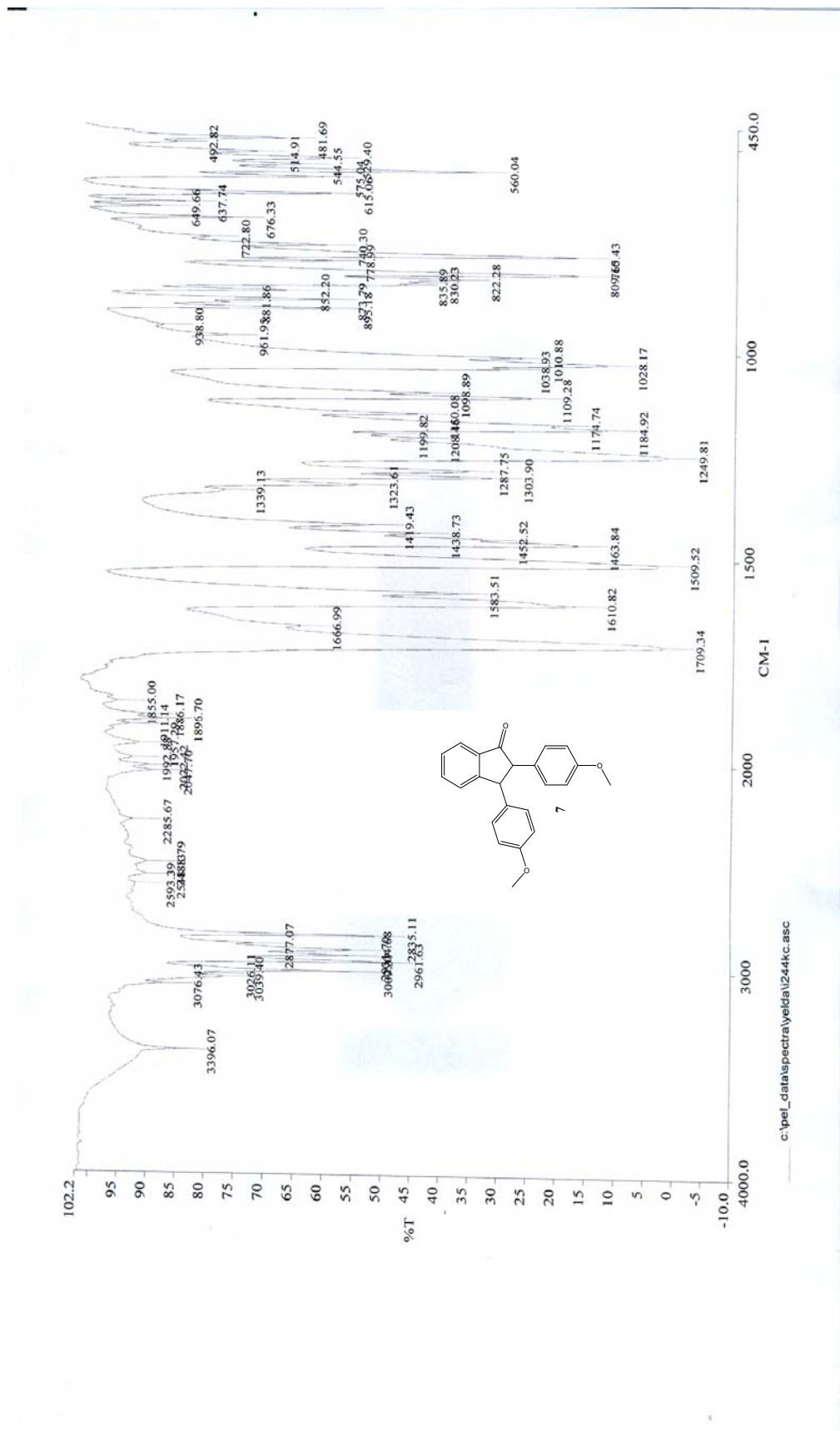
Figure C.7. FT-IR spectrum of 2,3-dihydro-2,3-bis(4-methoxyphenyl)inden-1-one

147
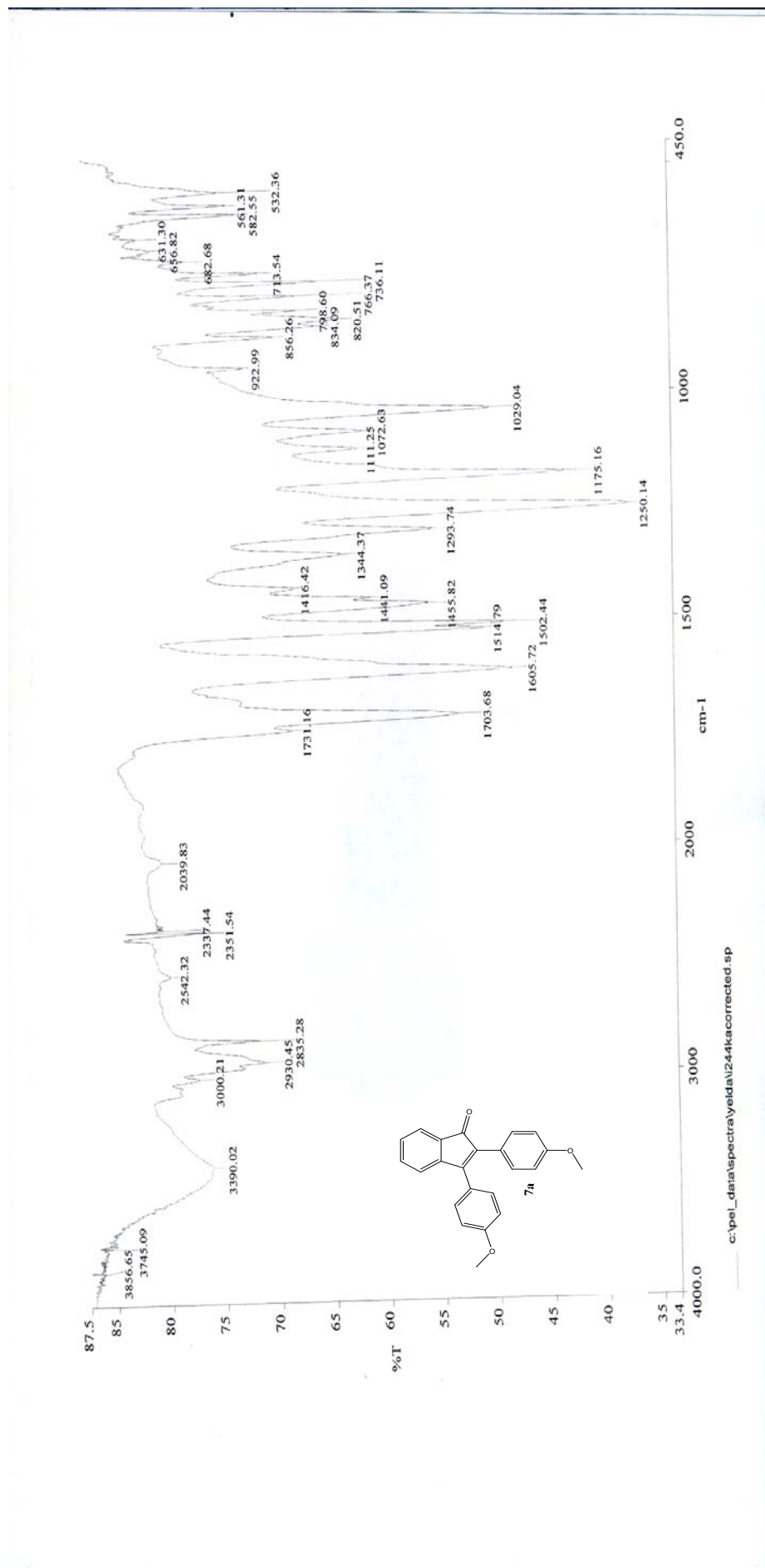
Figure C.8. FT-IR spectrum of 2,3-bis(4-methoxyphenyl)-1H-inden-1-one

148
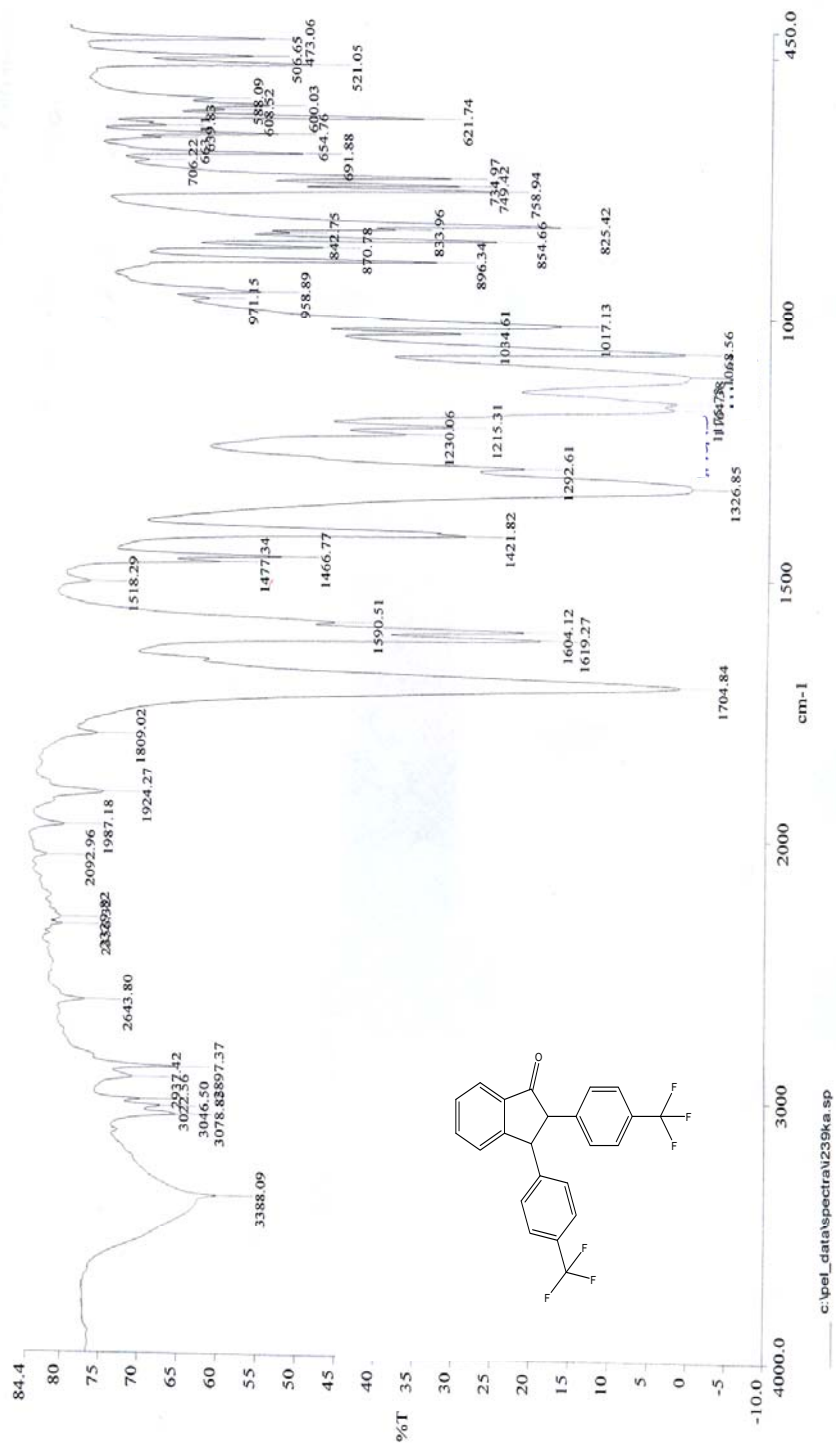
Figure C.9. FT-IR spectrum of 2,3-bis(4-(trifluoromethyl)phenyl)-2,3-dihydroinden-1-one
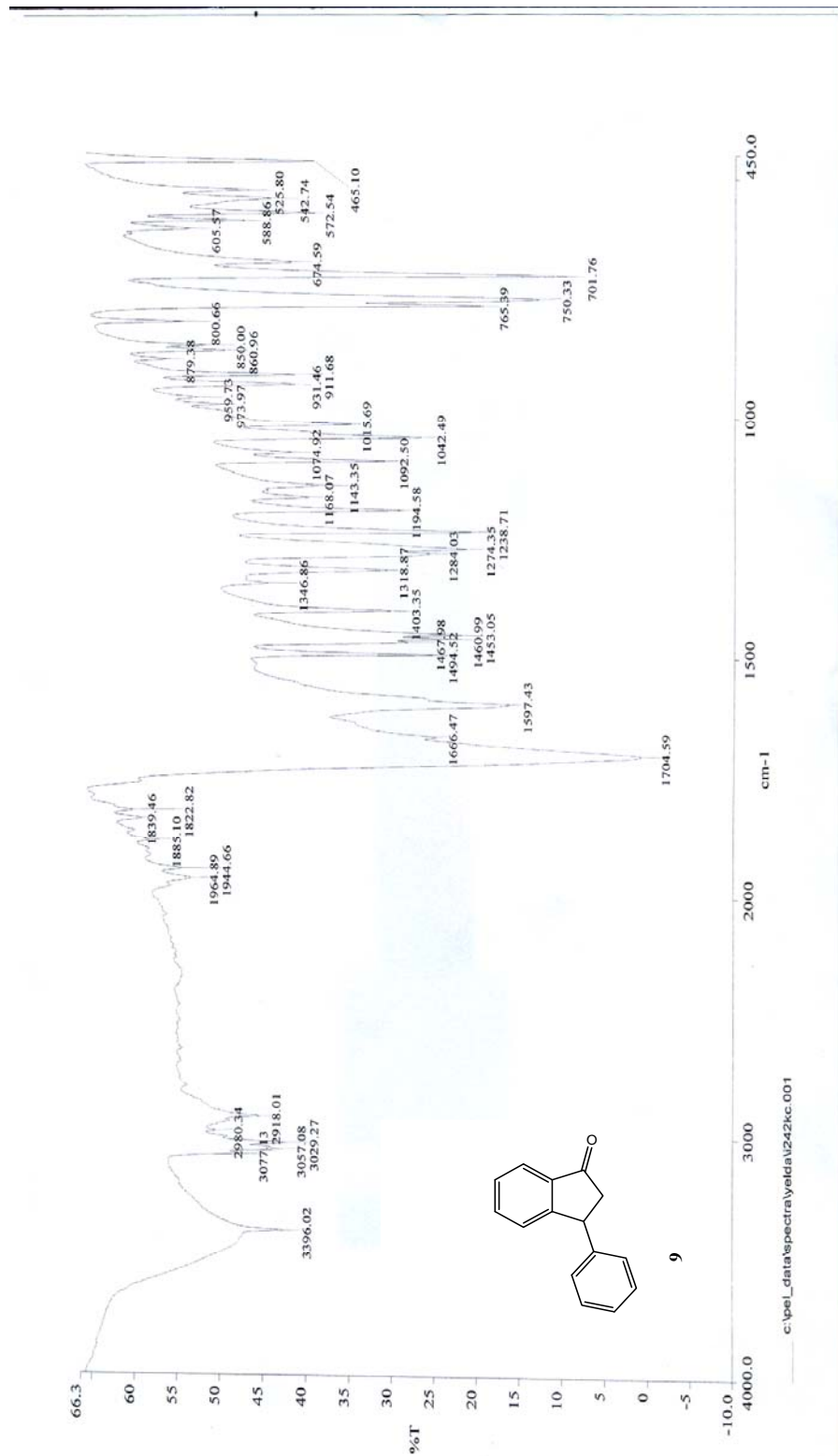
Figure C.10. FT-IR spectrum of 2,3-dihydro-3-phenylinden-1-one

^{13}C NMR AND ^{1}H NMR OF SONOGASHIRA PRODUCTS

Figure D.1. ^{1}H NMR of 1,2-bis(4-methoxyphenyl)ethyne

Figure D.2. ^{13}C NMR of 1,2-bis(4-methoxyphenyl)ethyne

Figure D.3. ^{1}H NMR of 1,2-bis(4-(trifluoromethyl)phenyl)ethyne

A2

1.529

5.289

7.253
7.609
7.625
7.632
7.638
7.644
7.660

5.76

94.24

ppm

153
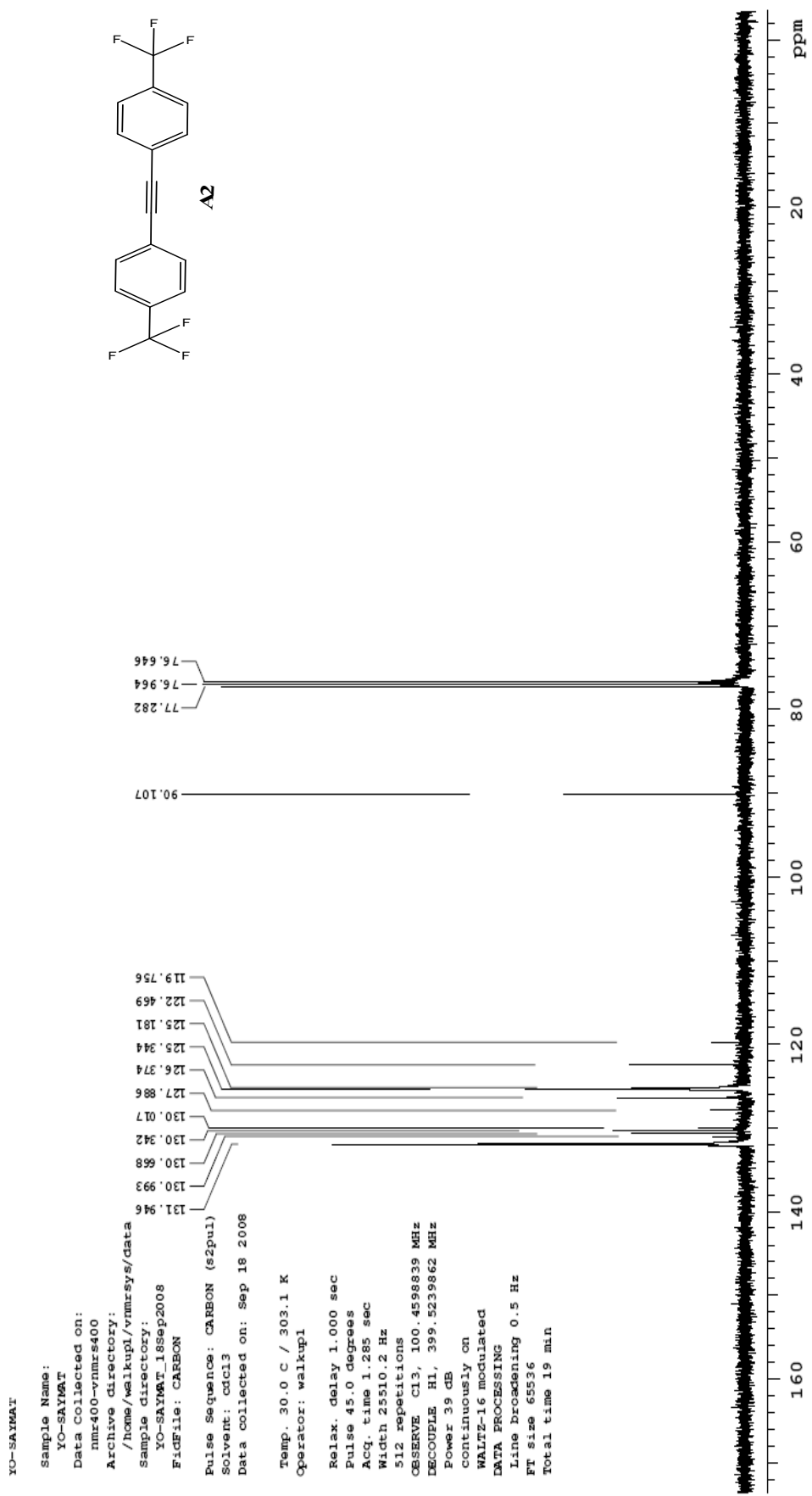
Figure D.4. ^{13}C NMR of 1,2-bis(4-(trifluoromethyl)phenyl)ethyne
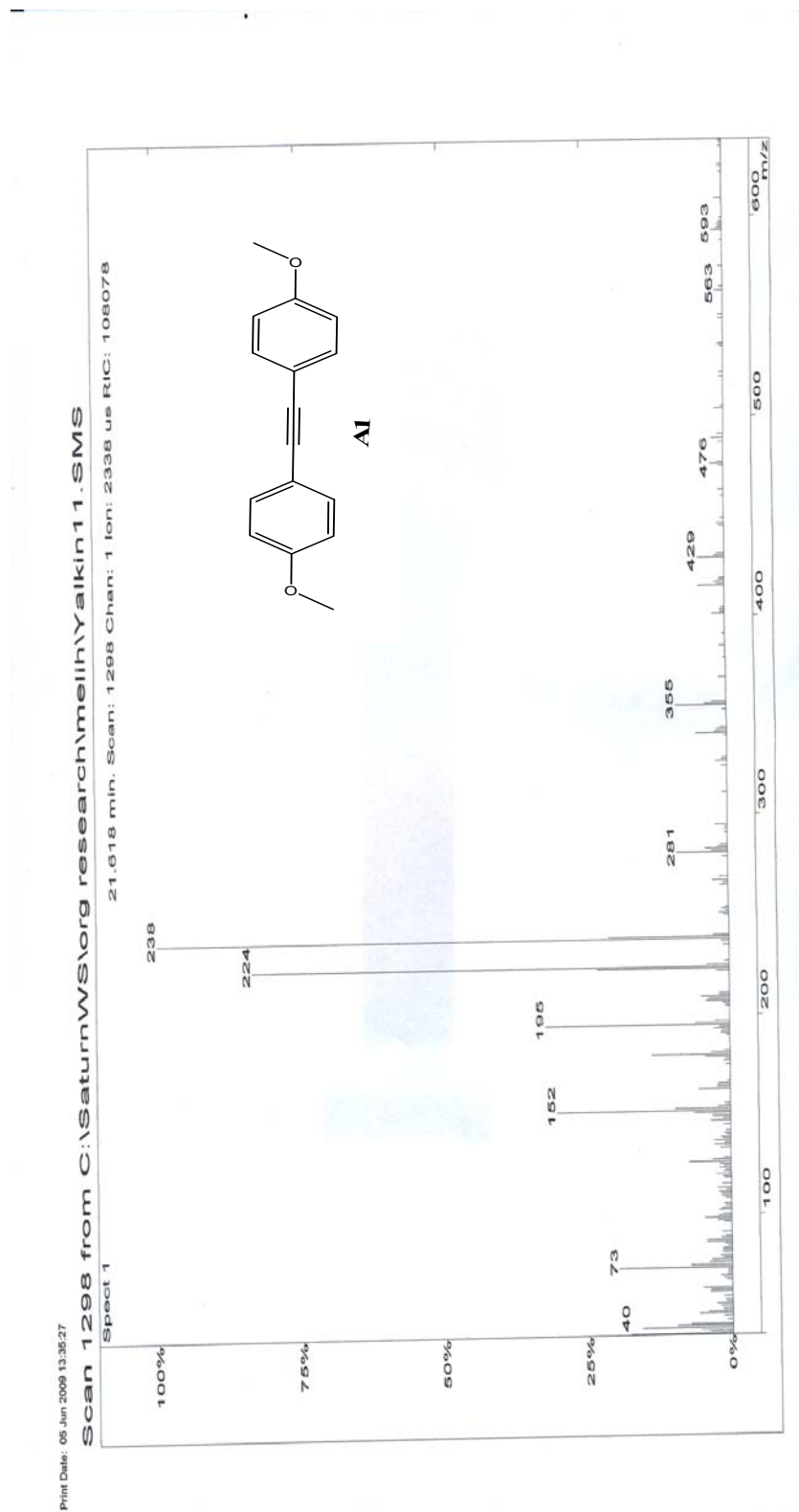
Figure E.1. Mass spectrum of 1,2-bis(4-(trifluoromethyl)phenyl)ethyne
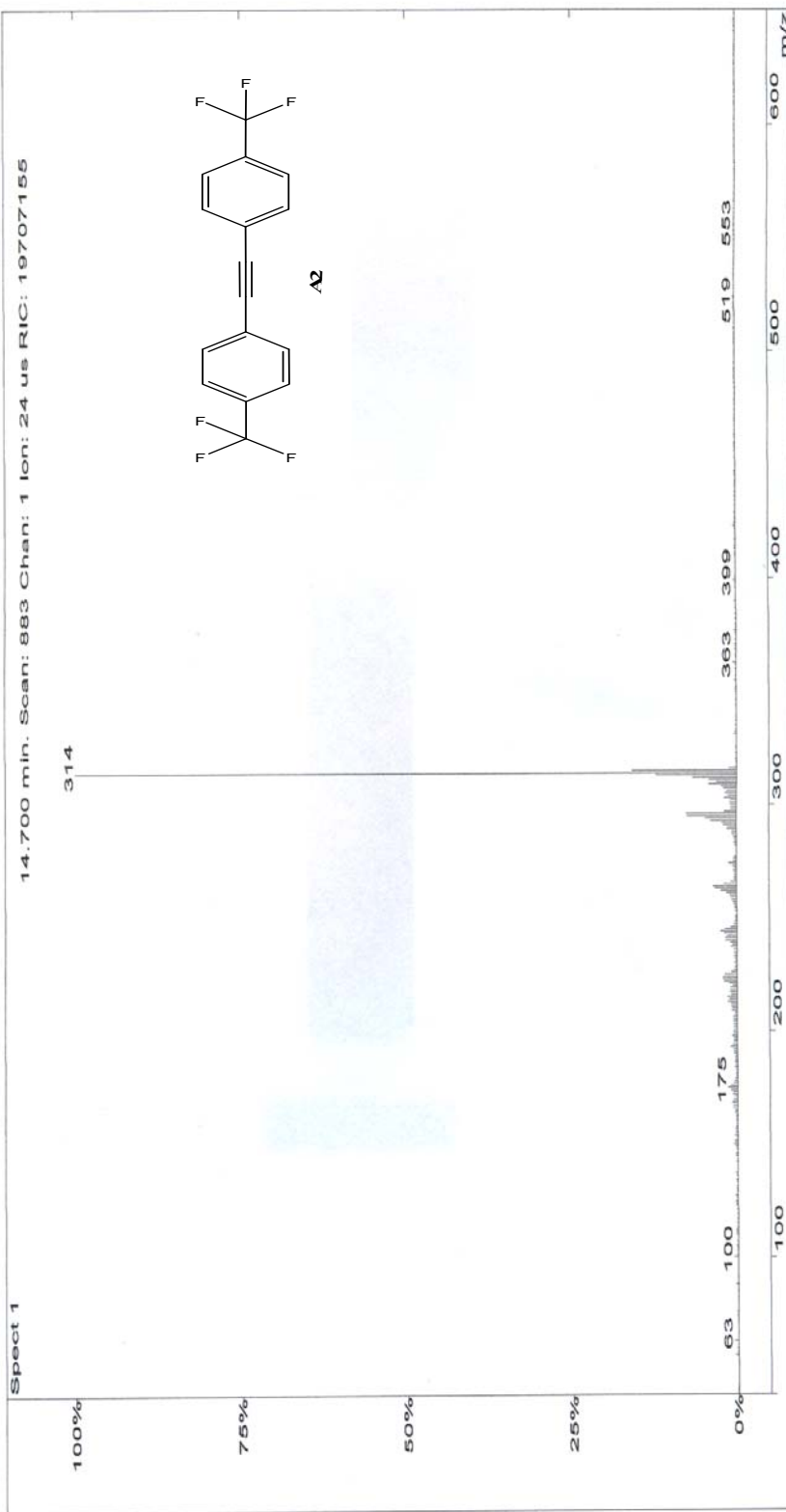
Figure E.2. Mass spectrum of 1,2-bis(4-(trifluoromethyl)phenyl)ethyne