SHORT-TIME SUZUKI REACTIONS OF ARYL HALIDES CATALYZED BY PALLADIUM-LOADED NaY ZEOLITE UNDER AEROBIC CONDITIONS

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ABSTRACT

SHORT-TIME SUZUKI REACTIONS OF ARYL HALIDES CATALYZED BY PALLADIUM-LOADED NaY ZEOLITE UNDER AEROBIC CONDITIONS

The palladium-catalyzed Suzuki cross-coupling reaction is a powerful methods used in the synthesis of biaryl compounds.

In this study, the Suzuki reactions of aryl bromides and chlorides with arylboronic acid were carried out over a $Pd(NH_3)_4^{2+}$-loaded NaY type zeolite. On the basis of our results, the $Pd(NH_3)_4^{2+}$-loaded NaY zeolite was found to be highly active for the Suzuki reactions of wide range of aryl bromides and electron poor aryl chlorides at low Pd concentrations (0.1-0.001mol %Pd), in air and at short times (5-45 minutes). The presence of relatively large amount of zeolite (1-4 g) was crucial for the success of the reactions with aryl chlorides. It was determined that there was a synergistic effect of the water- zeolite pair on the reaction rate.

It was found that reactions were catalyzed dissolved palladium species. However, the palladium was largely recovered and only traces of palladium remained within the solution at the end of reaction (<0.8 ppm).

ÖZET

ARİL HALOJENÜRLERİN HAVA ALTINDA PALADYUM YÜKLÜ NaY ZEOLİT KATALİZLİ KISA SÜRELİ SUZUKİ TEPKİMELERİ

Paladyum katalizli Suzuki kenetlenme tepkimeleri biaril bileşiklerinin sentezinde kullanılan etkili bir metotdur.

Bu çalışmada arilboronik asitlerle aril bromür ve klorürlerin Suzuki tepkimeleri $Pd(NH_3)_4^{2+}$-yüklü NaY tipi zeolit ile gerçekleştirilmiştir. Sonuçlarımız doğrultusunda, $Pd(NH_3)_4^{2+}$-yüklü NaY tipi zeolitin, hava altında ve düşük paladyum konsantrasyonunda (0.1-0.001 mol %Pd), kısa süre içerisinde (5-45 dakika). çeşitli aril bromür ve elektronca fakir klorürlerin Suzuki tepkimelerinde oldukça aktif olduğu gözlenmiştir. Göreceli olarak büyük miktarlarda zeolit varlığı (1-4 g) aril klorürlerin reaksiyonlarının başarısında kritik bir role sahipti. Tepkime verimliliğine zeolit-su bileşiminin sinerjistik etkisi olduğu saptanmıştır.

Reaksiyonların çözünmüş paladyum ile katalizlendiği bulunmuştur. Bununla birlikte paladyum büyük ölçüde kazanılmış ve reaksiyon sonunda, çözelti içerisinde iz miktarda paladyuma rastlanmıştır (<0.8ppm).

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CHAPTER 1

INTRODUCTION

The palladium catalyzed Suzuki reaction is one of the most powerful methods for the formation of C-C bond in the synthesis of biaryl compounds which are important building blocks of numerous agrochemicals, pharmaceuticals, natural produts, polymers, advanced materials, liquid crystals, and ligands.

Phosphine/Pd complexes are commonly used catalyst systems for the reaction (Miyaura and Suzuki 1995). Sterically demanding, electron-rich phosphines, such as tri-*tert*-butylphosphine, have shown high cross-coupling activities for a variety of substrates (Shen 1997, Littke and Fu 1998, Bellina et al. 2004, Kirchhoff et al. 2002, Christmann et al. 2005, Nishiyama et al. 1998). However, many phosphines complexes require air-free handling to prevent their oxidation, and P-C bond degradation is possible at elevated temperatures (Yu et al. 2006).

As alternative to phosphine ligands, some types of palladacycles and Pd-*N*-heterocyclic carbene complexes have been used in the cross-coupling reactions to a large extent (Hermann and Böhm 1999, Hermann et al. 1999, Ohff et al. 1999, Albisson et al. 1998, Zim et al 2000, Bedford et al. 2003, Botella and Najera 2002, Gong et al. 2005, Arduengo et al. 1992, Hermann et al. 1998, Hermann et al. 2003, Böhm et al. 2000, Selvakumar et al. 2002, Frisch et al. 2004).

In spite of their high activities and selectivities, it is the difficult to separate these homogeneous catalyst systems from the reaction mixture and to reuse them in consecutive reactions. Palladium and ligands are expensive and toxic in many cases, which severely restrict their industrial use. In this aspects, heterogeneous catalysis is emerging as an alternative to homogeneous processes so that catalysts can be recovered after the reaction and re-used several times to achieve very high turnover numbers (Ruiz et al. 2006, Kotha et al. 2002).

Among studies involved in heterogeneous catalyst systems, recoverable catalysts for the Suzuki-Miyaura reactions have been achieved by immobilization of palladium catalyst to liquid phases (Genet and Saignac 1999, Dupuis et al. 2001, Li et al. 2005, Mathews et al. 2000, Mcnulty et al. 2002, Okubo et al. 2002) and insoluble supports such as inorganic oxides (Kabalka et al. 1999, Kabalka et al. 2003,), carbon (Leblond et al. 2001, Tagata et al. 2003, Sakurai et al. 2002, Arvela and Leadbeater 2005, Mori and Seki 2002, Conlon et al. 2003), clays (Varma et al. 1999, Varma and Naicker 1999a, Varma and Naicker 1999b,), polymers (Parrish and Buchwald 2001, Hu et al. 2003, Wang et al. 2004, Bedford et al. 2005), silica (Bedford et al. 2005, Blanco et al. 2006, Baleizao et al 2003, Baleizao et al. 2004, Mobufu et al. 2001, Paul and Clark 2003, Yamada et al. 2003), hydrotalcite (Ruiz et al. 2006), sepiolites (Corma et al. 2004, Shimizu et al. 2004), dendrimers (Dahan and Portnoy 2003), resin (Uozumi et al. 1999, Phan et al. 2004, Inada and Miyaura et al. 2000, Jang 1997), layered double hydroxide supports (Choudary et al. 2002), chitosan (Hardy et al. 2004) and perovskites (Smith et al. 2003).

In addition to heterogeneous catalysts abovementioned, zeolites are also very good supporting material since they posses high specific surface area and well-defined micropores and mesopores for encapsulation of the Pd species. The Pd-loaded NaY zeolite has been found to be highly active catalyst toward C-C coupling reactions; such as Heck reaction (Djakovitch and Koehler 1999, Djakovitch et al. 1999, Djakovitch and Koehler 2001), arylation of malonate (Djakovitch and Koehler 2000), amination reactions (Djakovitch et al. 1999) and recently Suzuki reactions (Artok and Bulut 2004, Bulut et al. 2003).

In the previous studies first reported by Artok et. al that the Pd-loaded NaY zeolites were found to be very active catalysts in Suzuki reactions of aryl bromides and iodides, affording excellent product formation at room temperature, however, at relatively high palladium concentrations (2.5mol% Pd). But, in their studies, moderate yields were obtained with chloroarenes even for activated ones (Artok and Bulut 2004, Bulut et al. 2003).

In this study, we prepared a catalyst easily by loading of $Pd(NH_3)_4^{2+}$ onto a NaY zeolite and investigated its activity over Suzuki reactions of aryl bromides and aryl chlorides. The activation parameters, turnover frequency (TOF) and turnover number (TON) limits of the catalyst were investigated. We observed that the catalyst was highly active at very low palladium concentration and tolerable toward air and moisture.

CHAPTER 2

PALLADIUM CATALYSTS IN SUZUKI CROSS-COUPLING REACTION

Catalysis is important academically and industrially. It plays an essential role in the production of a wide range of products, frm gasoline and plastics to fertilizers and herbicides.

A catalyst can be defined as a chemical substance which transforms reactants into products via an uninterrupted and repeated cycle of elementary steps and regenerated in its original form at the end of cycle during its life (Weitkamp and Puppe 1999). In general, there are three classes of catalysts including heterogeneous, homogeneous and biological catalysts (Figure 2.1.) (Smith and Notheisz 1995).

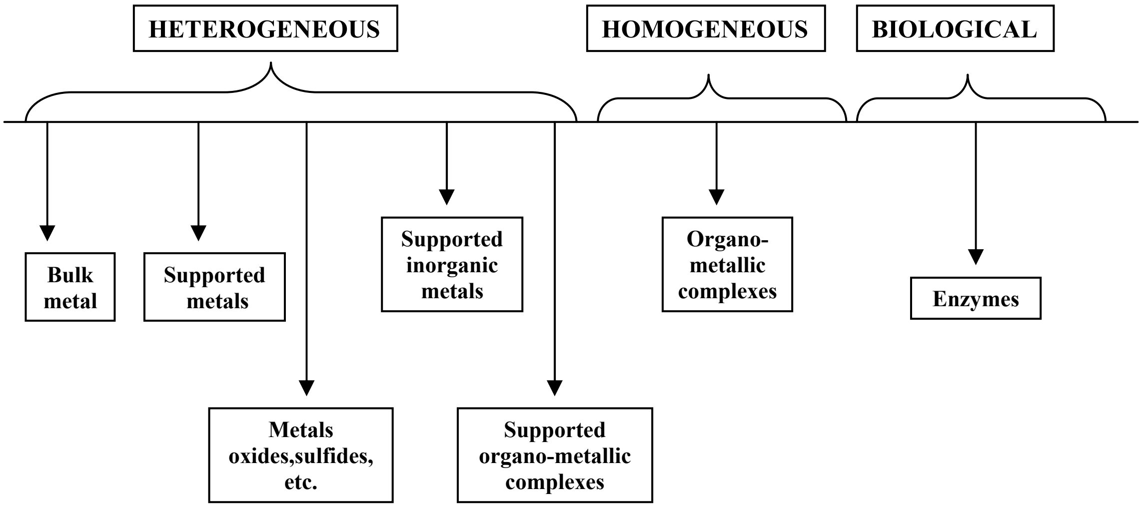


Figure 2.1. General kinds of catalysts.

(Source: Smith and Notheisz 1995)

Homogeneous catalysis means that a catalyst is in the same phase (usually liquid or gas solution) as the reactants and products. In contrast, heterogeneous catalysis involves the use of a catalyst in a different phase from the reactants. Typical examples involve a solid catalyst with the reactants as either liquids or gases.

Catalyst is a compound that affects the transition state and activation path by complexing one of the reagents. Due to their partially filled-orbitals, transition metals are used as catalysts, providing electrons or withdrawing electrons from the transition state of the reaction. During the reaction the transition metal ion is oxidized by one reactant to a higher oxidation state then reduced back to the original form by another reactant.

The study of catalysis dates back to the early 1800’s. Faraday was one of the first scientists to examine the ability of platinum to facilitate oxidation reactions (Smith and Notheisz 1995). Until now, many transition metals have been used in organic synthesis, but it is widely recognized that palladium is the most versatile in promoting or catalyzing reactions, particularly those involving carbon-carbon bond formation, which is not always easy to achieve with other transition metals (Tsuji 1995).

2.1. Palladium Metals as Catalysts in Organic Syntheses

2.1.1. Palladium as a Transition Metal

Palladium is, as a d^{10} element, one of the nine elements in Group 8 of the periodic table. It was discovered by William Hyde Wollaston in 1803.

Modern palladium chemistry started in 1960 with the invention of an industrial process for acetaldehyde production by the air oxidation of ethylene, catalyzed by $PdCl_2$ and $CuCl_2$, which is called the Wacker process (Tsuji 1995).

In addition to its use as a catalyst, there are many other applications of palladium;

- Gold is decolorized by addition of palladium, forming white gold.
- Hydrogen easily diffuses through heated palladium. Thus, it purifies the gas.
- Telecommunications switching-system equipments use palladium.
- Palladium is also used in dentistry, watches, in aircraft spark plugs and in the production of surgical instruments and electrical contacts.

2.1.2. The Coordination Geometry of Organopalladium Compounds

The geometry of organopalladium compounds depends on the oxidation state of palladium. In the organopalladium compounds, the transition metal may have 0, +2, +3, +4 oxidation state. All possible geometries of palladium depending upon its oxidation states are shown in Table 2.1.

Table 2.1. The geometries of organopalladium compounds

Oxidation Step	**Electronic Configuration**	**Geometry**
0	d^{10}	Tetrahedral
2+	d^8	Square planer
4+ (rarely)	d^6	Octahedral

2.1.3. The Characteristic Features of Pd and Pd-C Bonds

The most characteristic feature of the Pd-C bonds in intermediates of catalytic reactions is their reaction with nucleophiles. Pd(0) is generated by accepting two electrons from nucleophiles. Unlike palladium, some other metal-carbon bonds such as those with Mg, Al, Zn are attacked by electrophiles and metals are oxidized to M(II). Therefore, reaction can not carried out with a catalytic amount of these metals. Whereas, the catalytic reaction is possible via the regeneration of an active Pd (0) catalyst. In this respect, Pd is very unique.

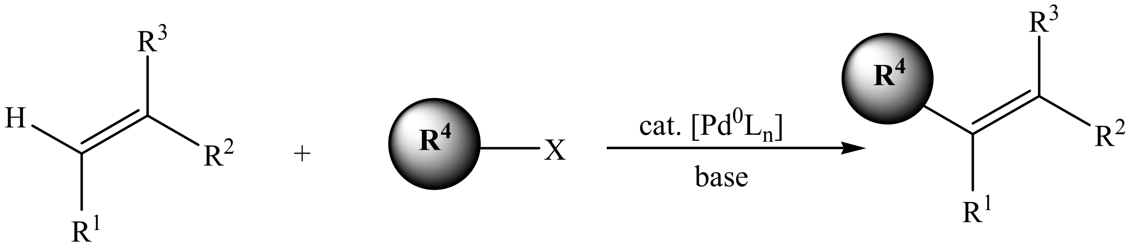
Organopalladium species tolerate many functional groups, such as carbonyl and hydroxyl groups, (except alkene, alkynes and iodide and bromides attached to sp^2 carbons), which allows them to be employed in the synthesis of highly complex molecules. Thus, Pd-catalyzed reactions do not need any protection of these functional groups. They are also not sensitive to water, alcohols and carboxylic acids.

Pd is much less expensive a compared to other metals such as Rh, Pt, and Ir and its toxicity has posed no problem so far. Pd forms complexes with a wide variety of organic ligands with P, N, and O atoms; many of these complexes are relatively easy to prepare and to handle. These advantages make palladium, among the transition metals, arguably the most versatile and the most widely applied catalytic metal in the field of fine chemicals (Tsuji 1995).

2.1.4. Palladium-Catalyzed Cross-Coupling Reactions

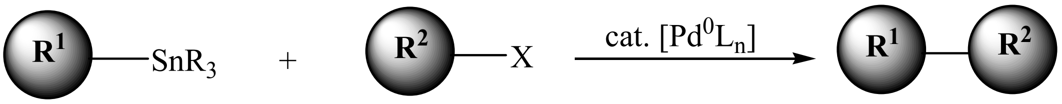
Commonly utilized palladium-catalyzed cross-coupling reactions are depicted in Figure 2.2. (Nicolaou et al. 2005).

1. Heck Reaction:



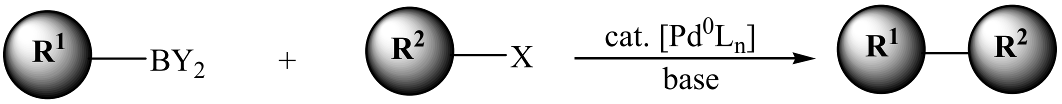
R^4= aryl,benzyl,vinyl
X= Cl, Br, I, OTf

2. Stille Reaction:



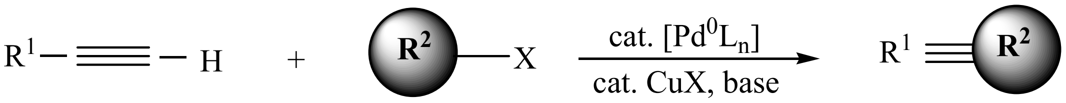
R^1= alkyl, alkynyl, aryl, vinyl
R^2= acyl, alkynyl, allyl, aryl, benzyl, vinyl
X= Br, Cl, I, OAc, $OP(=O)(OR)_2$, OTf

3. Suzuki Reaction:



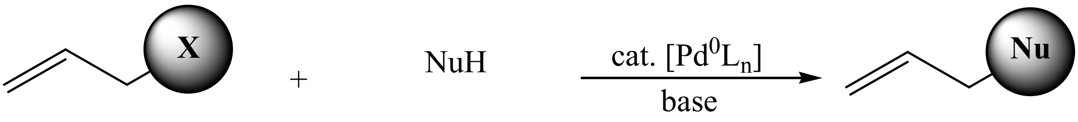
R^1= alkyl, alkynyl, aryl, vinyl
R^2= alkyl, alkynyl, aryl, benzyl, vinyl
X= Br, Cl, I, $OP(=O)(OR)_2$, OTf, OTs

4. Sonogashira Reaction:



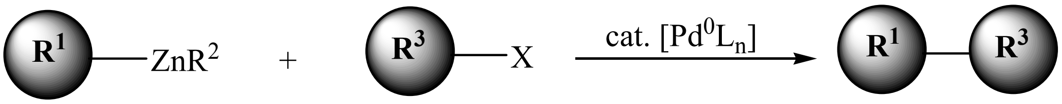
R^1= alkyl, aryl, vinyl
R^2= aryl, benzyl, vinyl
X= Br, Cl, I, OTf

5. Tsuji-Trost Reaction:



X= Br, Cl, OCOR, OCO_2R, OSO_2R, $P(=O)(OR)_2$
NuH= ß-dicarbonyls, ß-ketosulfones, enamines, enolates

6. Negishi Reaction:



R^1= alkyl, alkynyl, aryl, vinyl
R^3= acyl, aryl, benzyl, vinyl
X= Br, I, OTf, OTs

Figure 2.2. Palladium-catalyzed cross-coupling reactions
(Source: Nicolaou et al. 2005)

Among these reactions catalyzed by palladium, four main catalytic methods are used for the synthesis of biaryls which are important building blocks of numerous agrochemicals, pharmaceuticals, natural products, polymers, advanced materials, liquid crystals, and ligands. These are Kharasch Reaction, Negishi Reaction, Stille Reaction and Suzuki Reaction. Compared to other methods of biaryl synthesis, Suzuki cross-coupling reaction is the most important one for industrial and academic area.

2.2. The Suzuki Reactions

The coupling reactions of organoboron compounds with aryl, alkenyl, and alkynyl halides, which is referred to as Suzuki or Suzuki-Miyaura reaction, was first applied by Suzuki and Miyaura. In their study, cross-coupling reactions of 1-alkenylboronic esters and 1-bromo or 1-iodo-1-alkenes were performed. Later on, the methodology has found wide acceptance for the synthesis of biaryl reagents.

$$\mathbf{Ar\text{-}X} \quad + \quad \mathbf{Ar'\text{-}B(OH)_2} \xrightarrow{\text{Pd, Base}} \mathbf{Ar\text{-}Ar'}$$

X = Halogen, OTf

Figure 2.3. General representation of Suzuki reaction

The Suzuki coupling reactions have many advantages (Suzuki 2005, Suzuki 1999, Kotha et al. 2002). These are;

- The reactants are readily available, nontoxic, and air-stable.
- Reactions are largely unaffected by the presence of water.
- Reactions can be performed under mild conditions and are amenable to a variety of reaction conditions, including the use of aqueous solvents and substrate supports.
- The boron-containing byproduct is environmentally safe and can be easily removed after the reaction when compared to byproducts of other organometallic reagents.
- Most important of all, the coupling reaction proceeds with high regio- and stereo selectivity, and is little affected by steric hindrance. It does not affect other functional groups in the molecule.

2.2.1. Mechanism of Suzuki Coupling Reactions

The catalytic cycle of Suzuki reaction involves three steps, oxidative addition of a halide, followed by transmetallation and then reductive elimination of the two carbon ligands added to the palladium.

A general catalytic cycle for the Suzuki cross-coupling reaction is depicted in Figure 2.4.

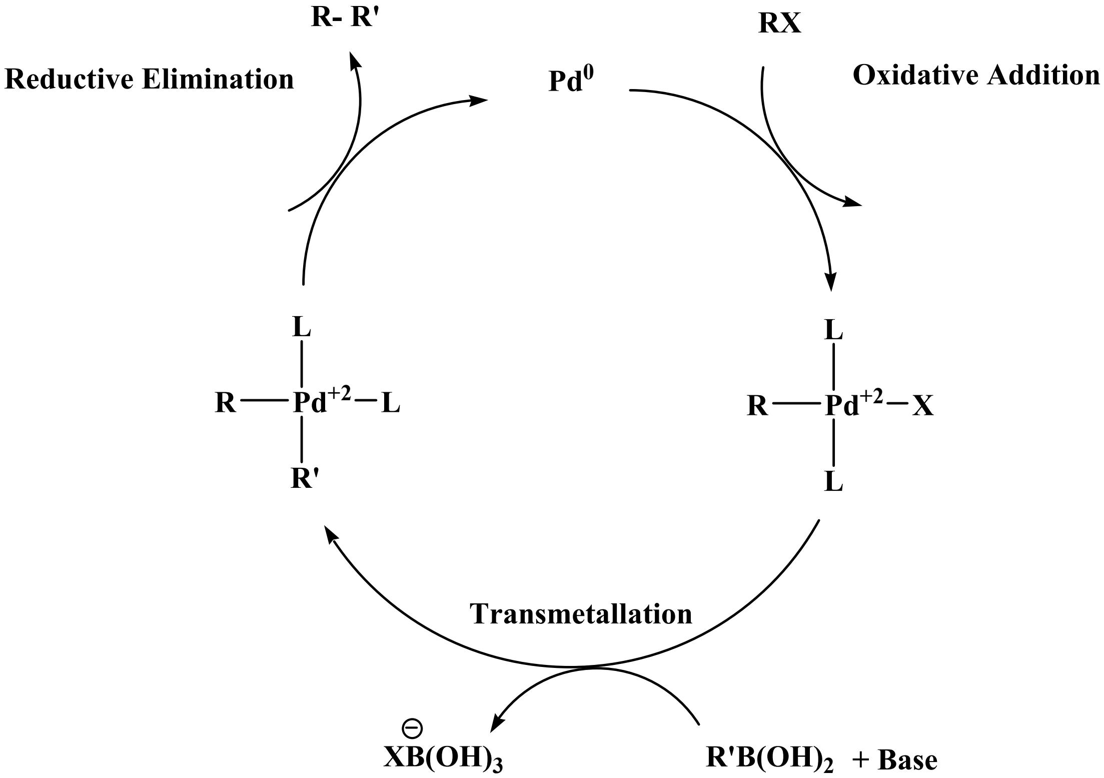
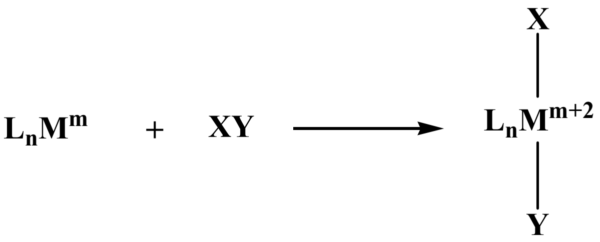


Figure 2.4. A general catalytic cycle for the Suzuki cross-coupling reaction

2.2.1.1. Oxidative Addition

In an oxidative addition step an electrophilic compound X-Y adds to a metal complex. In this step, the XY bond is broken and two bonds are formed; M-X and M-Y, and meanwhile, oxidation state of the metal is raised by two. The coordination number of the metal also increases by two (Tsuji 1995).



$$L_nM^m + XY \longrightarrow L_nM^{m+2}(X)(Y)$$

Figure 2.5. Oxidative Addition

In Suzuki reactions, oxidative addition involves the insertion of palladium metal into an aryl halide. The empty ligand field orbital (LFO) of metal interacts with the carbon halogen bonding orbital, while a second orbital overlap occurs between the non-bonding t_{2g} orbital containing an electron pair and the carbon-halogen antibonding orbital. This destabilizes the carbon-halogen bond leading to cleavage and eventually oxidative addition to the palladium. The palladium catalyst in the reaction must be ‘0’ oxidation state as an 18 electron system and after oxidative addition, it would be oxidation state of II as a 16 electron system (Figure 2.6).

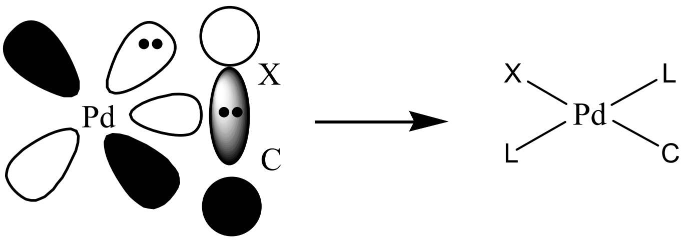


Figure 2.6. The Carbon- halogen bond cleavage in oxidative addition

This step is often the rate-determining step in a catalytic cycle. The relative reactivity of aryl halides decreases in the order of C- I > C-OTf > C-Br >> C-C1>>> C-F. Aryl and 1-alkenyl halides bearing electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups (Miyaura and Suzuki 1995).

2.2.1.2. Transmetallation

Ar-Pd-X complexes formed by oxidative addition react with organic compounds (M-R) and hydrides (M-H) of main group metals such as Mg, Zn, B, Al, Sn, Si, and Hg.

As a result, organic group or hydride is transferred to Pd (Figure 2.7.). A driving force for the reaction called transmetallation, is due to the difference in the electro negativities of two metals (Tsuji 1995).

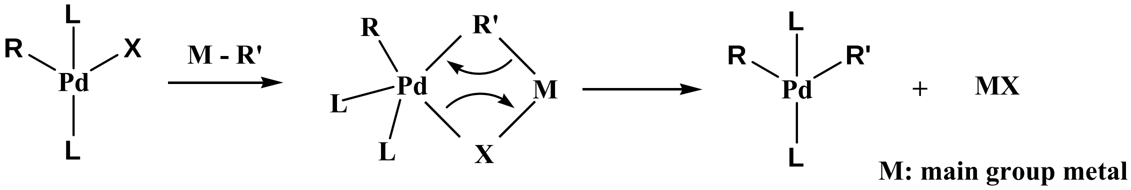


Figure 2.7. Transmetallation
(Source: Tsuji 1995)

In Suzuki reactions, transmetallation between organopalladium (II) halides and organoboron compounds does not occur readily due to the low nucleophilicity of organic group on boron atom. However, the nucleophilicity of organic group on boron atom can be enhanced with base giving the corresponding "ate" complexes (Miyaura and Suzuki 1995).

2.2.1.3. Reductive Elimination

Reductive elimination is simply the reverse reaction of oxidative addition. In this step, two carbon metal bonds are broken (Tsuji 1995). The catalytic cycle is completed by reduction of the Pd^{II} species into a Pd^0 species and finally coupling product forms (Figure 2.8.).

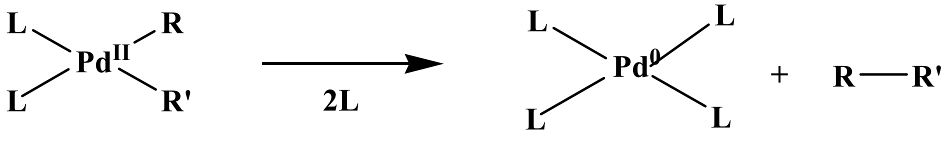


Figure 2.8. Reductive Elimination
(Source: Tsuji 1995)

The active re-generated Pd^0 undergoes oxidative addition and starts another catalytic cycle. Generally in catalytic cycles these reactions are relatively fast (Tsuji 1995).

2.2.2. Reaction Conditions Affecting the Suzuki Reactions

There are several parameters that can be changed to increase the efficiency of the Suzuki reactions. These are substrate type, ligand type, solvent type, additives and other reaction conditions such as base, temperature, time, pressure and microwave heating.

2.2.2.1. Substrate Effect

One of the most important parameters for the activity of the reaction is substitution group of the substrate. Electron-rich aryl halides those with electron donating groups such as $-OCH_3$, $-CH_3$, -OH, $-NH_2$, are reluctant to the oxidative addition where Ar-X bond is broken by the insertion of palladium metal, because increased electron density would enhance the strength of C-X bond (Miura 2004). Unlike electron-donating groups, carbon-halide bond cleaves more easily in the presence of electron-withdrawing group ($-COCH_3$, -CN, $-NO_2$, -CHO, $-CF_3$ etc) on the aryl halide, because of weakness of the bond C-X. As a result, electron-withdrawing groups are more reactive to the oxidative addition than those with-donating groups (Miyaura and Suzuki 1995).

Another important aspect for activation of coupling reactions is the position of substitution group on the aryl compounds. An electronegative group would decrease electron density on C-X bond more effectively when substituted on the *p*-position.

Aryl halides with one electron-withdrawing group at the *meta* position are less reactive than those with electron-withdrawing substitutions at the *ortho* or *para* positions (Shen 1997). However, it is generally observed the opposite situation for *ortho* and *meta* position due to the steric effect on aryl compound.

2.2.2.2. Halogen Effect

Nearly all reports of palladium-catalyzed coupling reactions utilized aryl bromides, iodides, and triflates (-OTf) succesfully as substrates. On the other hand, although chlorides are of lower cost and have wider diversity of available compounds, the use of aryl chlorides was not very common compared to other reactants because of their low reactivity toward Suzuki reactions.

The oxidative addition of palladium into carbon-halogen bonds mainly depends on the strength of the bond between C-X. Bond energies for Ph-X; Cl: 96 kcalmol^{-1}; Br: 81 kcalmol^{-1}; I: 65 kcalmol^{-1} (Grushin and Alper 1994). Differences in bond energies are due to size of halogens. The size of halogen atom increases as we go down the periodic table. Fluorine atom is the smallest and iodine is the largest. The low reactivity of chlorides is related to the strength of the C-Cl bond. Fluorine is unreactive with any of the known catalysts. Unlike chlorine or fluorine, aryl iodides need low activation energy and no ligands are required to undergo oxidative addition.

As mentioned in section 2.2.1.1, the relative reactivity towards cross-coupling reactions decreases in the order of (Littke and Fu 2002).

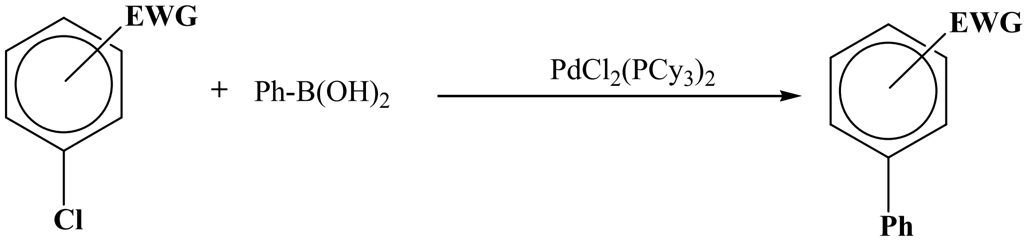
$$\text{C-I} > \text{C-OTf} > \text{C-Br} \gg \text{C-C1} >\!>\!> \text{C-F}$$

2.2.2.3. Ligand Effect

In the case of aryl iodides and bromides containing electron-withdrawing groups, even ligandless palladium catalyst precursors are sufficient to promote cross-coupling in high turnovers. However, in the case of less reactive aryl chlorides and electron-rich aryl bromides, the presence of added ligands is necessary to effectively promote these cross-couplings (Zim et al. 2000).

Since the first report on coupling reactions of aryl iodides or bromides with phenylboronic acid, $Pd(PPh_3)_4$ have become commonly used complex for Suzuki reactions.

Years later, Shen showed that aryl chlorides could be activated in Suzuki reaction in the presence of a bulky, electron-rich trialkylphosphane (PCy_3, Cy: cyclohexyl) at 100 °C (Table 2.1, entry 1.) (Figure 2.9). It was speculated that the electron-richness of PCy_3 might facilitate oxidative addition of the Ar-Cl bond to Pd(0) and that the steric demand of PCy_3 might favor ligand dissociation to give an active monophosphine Pd complex (Shen 1997). Later on, there are various types of ligands that were shown to be activating Pd for the reactions of aryl chlorides. Some of which are illustrated in Figure 2.10.



(EWG= 3-MeCO, 4-CHO, 3-CHO, 2-CHO, 3-NO_2, 3-(*E*)-CH=CH-COOMe)

Figure 2.9. The example of Suzuki reactions of aryl chlorides from literature (Source: Shen 1997)

In 1998, Fu and co-workers described the use of the electron-rich trialkylphosphine P(*t*-Bu)$_3$ as a ligand in Suzuki coupling reactions of deactivated and hindered aryl chlorides with arylboronic acid. It was also found that P(*t*-Bu)$_3$:Pd ratio between 1:1 or 1.5 :1 was the most effective (Littke and Fu 1998) (Table 2.1, entry 2).

Prior to 1998, there were no reports on the palladium catalyzed Suzuki reactions of electron-neutral or electron-rich aryl chlorides. In 1998, Buchwald and co-workers reported that aminophosphane, **1** (Figure 2.10), is a very effective ligand for palladium-catalyzed Suzuki reactions of electron-neutral and electron-rich aryl chlorides (Table 2.1, entry 3) (Old et al. 1998).

Buchwald and co-workers subsequently determined that biphenyl ligands, **2** and **3** (Figure 2.10), can be even more effective than **1** in palladium-catalyzed Suzuki reactions of aryl chlorides (Table 2.1, entry 4) (Wolfe and Buchwald 1999a, Wolfe and Buchwald 1999b, Wolfe et al. 1999).

A variety of ligands containing P-O bonds have proven to be useful in Heck and Suzuki coupling reactions (Zapf and Beller 2000). Pd(II)-phosphate complexes were found to be excellent complexes for the activation of aryl chlorides in Suzuki couplings reactions, and air-stable phosphine oxides have been shown to be useful in the Suzuki coupling reactions of aryl chlorides by Li and co-workers (Li 2001, Li 2002, Li et al. 2001). In their study, the catalyst system, **4** (Figure 2.10), was found to be highly effective for Suzuki reactions of hindered and electron-rich aryl chlorides (Li 2001) (Table 2.1, entry 5).

Recently, Teo et al. synthesized some new 1,1'-phosphine-ether-functionalized ferrocenyl ligands, **5-8** (Figure 2.10), and Pd complexes of these ligands have been shown to promote the Suzuki cross-couplings of a range of arylboronic acids and aryl chlorides to give the desired biaryl products in high isolated yields in the presence of CsF and in 1,4-dioxane solvent under N_2 atmosphere at 90 °C for 16 h (Teo et al. 2006).

Despite tertiary phosphines are effective in controlling reactivity and selectivity in organometallic chemistry and homogeneous catalysis, they require air-free handling to prevent their oxidation. Moreover, they are also subject to P-C bond degradation at elevated temperatures (Yu et al. 2006).

As alternative to phosphine ligands, different palladacycles are also used in the cross-coupling reaction to large extent.

Monteiro et al. have established that sulfur-containing palladacycles, **9** (Figure 2.10), are effective catalysts for Suzuki reactions of activated aryl chlorides (Table 2.2, entry 6). The addition of tetrabutylammonium bromide was found to be beneficial for the reaction rate (Zim et al. 2000).

A Convenient oxime-carbapalladacycle **10**-catalyzed Suzuki cross-coupling has been performed in water in the presence of TBAB at 100 ºC (Table 2.2, entry 7) with activated and deactivated aryl or heteroaromatic chlorides as well as benzylic chlorides (Botella and Najera 2002).

In 2005, a novel, simple PCy_3 adducts of cyclopalladated ferrocenylimines, **11** and **12** (Figure 2.10), have been synthesized and successfully used in palladium-catalyzed Suzuki cross-coupling reactions of aryl chlorides with phenylboronic acid, providing coupled products in excellent yields (Table 2.2, entry 8). For activated chlorides such as 4-chloronitrobenzene and 4-chloroacetophenone, the catalyst loadings could be lowered to 0.01mol % without loss of activity (Gong et al. 2005).

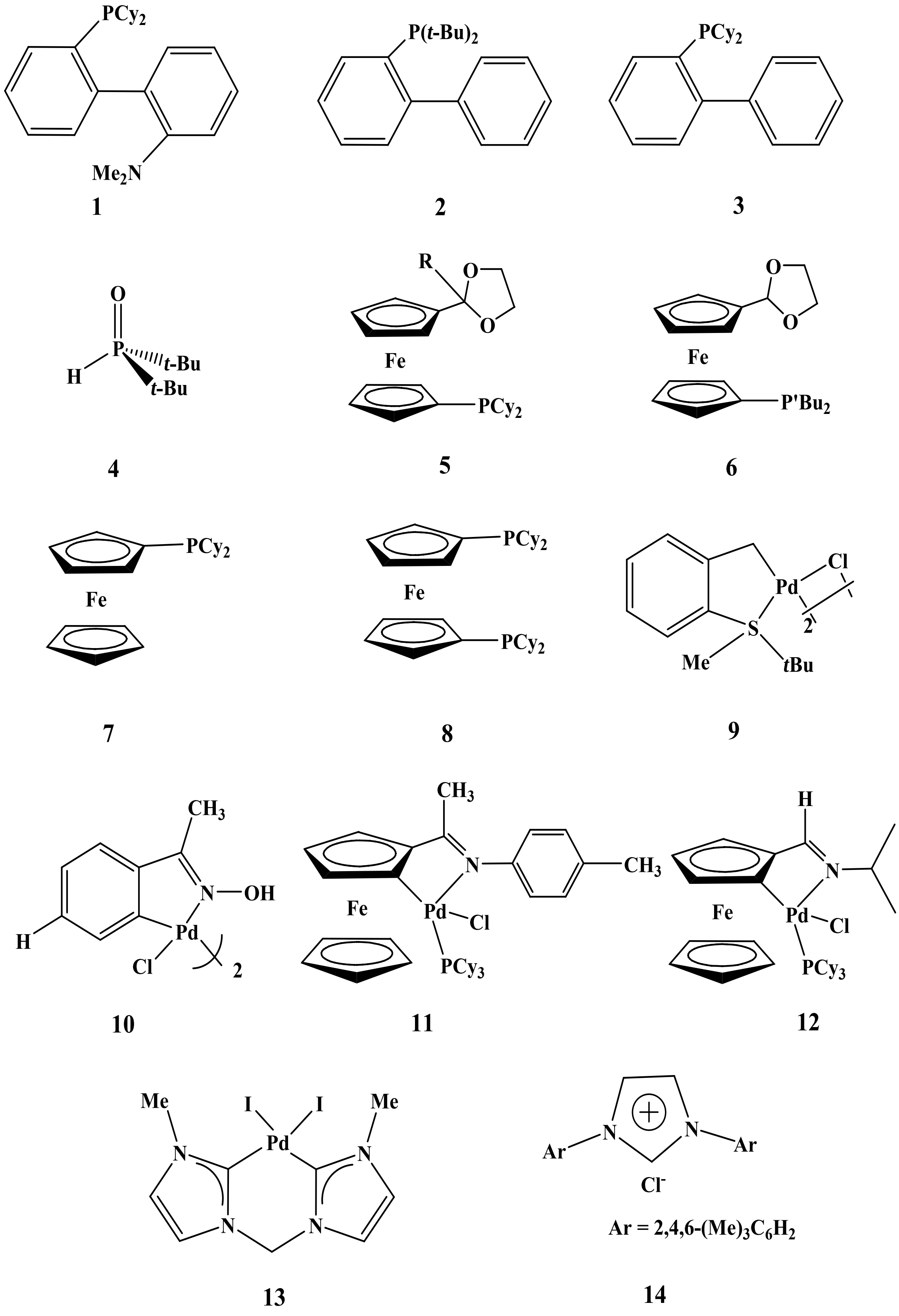
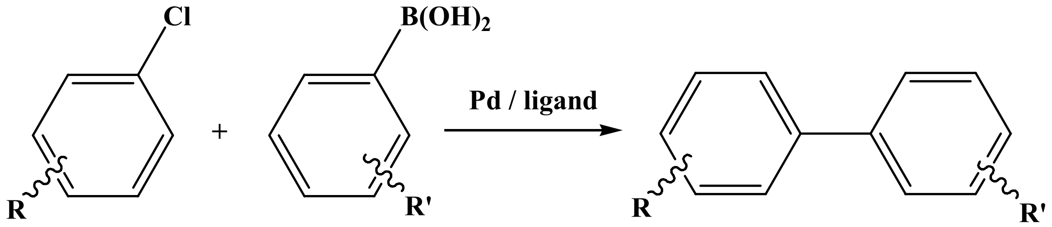


Figure 2.10. Different types of ligands and palladium complexes used in Suzuki reactions

Table 2.2. Examples from literature on Suzuki reactions of aryl chlorides



Entry	R	Catalyst/ligand	Reaction Conditions	Yield	*Ref.*
1	4-CHO, 3-CHO, 2-CHO, 3-MeCO	$PdCl_2(PCy_3)_2$	CsF, NMP, 100 °C	83-98	Shen 1997
2	4-COMe, 4-Me, 2-Me, 4-OMe,	$[Pd_2(dba)_3]$/ $P(t\text{-}Bu)_3$	Cs_2CO_3, dioxane, 80-90 °C	82-92	Littke and Fu 1998
3	4-OMe	$Pd(OAc)_2$/ **1**	CsF, dioxane, RT	92	Old et al. 1998
4	$-NO_2$, CN, CO_2Me, 2-COMe	$Pd(OAc)_2$/ **2, 3**	KF, THF, RT	88-98	Wolfe and Buchwald 1999
5	4-H, OMe, 2-OMe	$[Pd(dba)_3]$/ **4**	CsF/ Cs_2CO_3, dioxane, 100 °C	83-99	Li 2001
6	4-COMe, CN, NO_2	**9**	K_3PO_4, DMF,130 °C	90-95	Zim et al. 2000
7	4-COMe	**10**	Met. A: K_2CO_3, TBAB, water, 100 °C Met. B: KOH , TBAB methanol/ water (3:1), RT		Botella and Najera 2002
8	4-NO_2, COMe	**11, 12**	Cs_2CO_3, dioxane, 100 ° C		Gong et al. 2005
9	4-COMe	**13**	K_2CO_3, toluene, 120 °C	60	Hermann 1998
10	4-CO_2Me, Me, OCH_3	$[Pd(dba)_3]$/ **14**	Cs_2CO_3, dioxane, 80 °C	88-99	Zhang et al. 1999

Since the discovery of stable *N*-heterocyclic carbene (NHC) by Arduengo et al. (Arduengo et al. 1992), *N*-heterocyclic carbene complexes (NHCs) have become commonly used ligand type in the literature since NHCs have high electron-donor characteristics, promoting oxidative addition step. Even deactivated aryl chlorides can be used effectively in the presence of NHCs (Miura 2004).

The application of NHC ligands, **13** (Figure 2.10), to the Suzuki–Miyaura coupling was first reported in 1998 by Hermann (Hermann 1998) (Table 2.2, entry 9).

Palladium adducts of 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, **14** (IMes) (Figure 2.10), have been reported to be active catalysts for Suzuki cross-couplings of a wide variety of aryl chlorides with arylboronic acids (Zhang et al. 1999) (Table 2.2, entry 10).

2.2.2.4. Base Effect

Unlike other cross-coupling reactions involving transmetallation, the Suzuki reaction requires the use of a base (Leadbeater 2005, Miyaura 2002).

Although the mechanism of oxidative addition and reductive elimination are reasonably well understood, less is known about the transmetallation step because the mechanism highly depends on reaction conditions, especially base used for the coupling (Miyaura and Suzuki 1995). It has been suggested that there are mainly two role of the base during the transmetallation;

1. to form a more electron-rich intermediate with the boronic acid which is more reactive than the original boronic acid towards attack of Pd(II) complexes.

2. to form an alkoxy palladate from arylpalladium halide (Genet and Saignac 1999) (Figure 2.11).

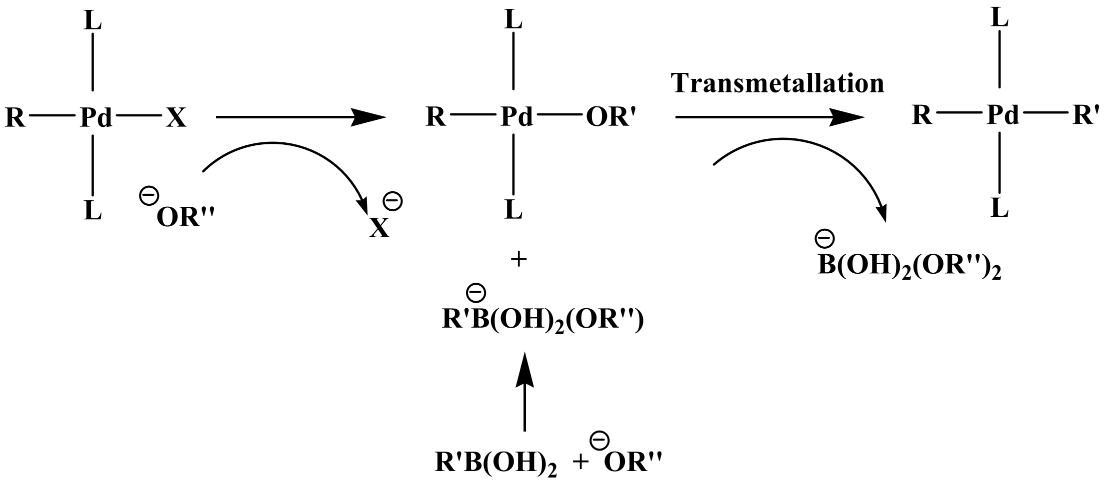


Figure 2.11. The role of base in transmetallation
(Source: Genet and Saignac 1999)

The most commonly used base in the cross-coupling reaction is Na_2CO_3 but this is often ineffective with sterically demanding substrates. In such instances, $Ba(OH)_2$ or K_3PO_4 has been used to generate good yields of the cross-coupling products. Other bases utilized in the Suzuki-Miyaura coupling reaction include Cs_2CO_3, K_2CO_3, KF and NaOH. However, 1-2 molar equivalents of bases are often required. The best choice of both solvent and amount of base chosen must be determined on an individual basis.

2.2.2.5. Additive Effect

Additives have a critical role in Suzuki reactions. Phase transfer catalysis enables reactions between anions or molecules soluble in one phase (usually aqueous) and organic substrates soluble in organic phase. The phase-transfer catalysts such as crown esters, cryptates, ammonium salts such as tetrabutylammonium bromide (TBAB) or phosphonium salts could significantly promote the cross-coupling reaction.

The role of the ammonium salt is thought to be twofold although not clear yet. Firstly, it facilitates solvation of the organic substrates in the solvent medium. Secondly, it enhances the rate of the coupling reaction by activating the boronic acid towards reaction by the formation of a boronate complex $[ArB(OH)_3]^-[R_4N]^+$ (Leadbeater 2005, Leadbeater and Marco 2003, Zim et al. 2000). In addition, it is also proposed that the

TBAB delivers Br^- ion to anionic palladium species; $[Br\text{-}Pd\text{-}ligand]^-$ to activate Pd (Amatore and Jutand 2000).

2.2.2.6. Solvent and Temperature Effects

Most of typical reaction components like aryl, allyl or benzyl halogenides and their coupling products are very sparingly soluble in water. So, most of these components are realized in organic solvents. The Suzuki-Miyaura cross-coupling reactions generally employ organic solvents such as THF and diethyl ether in the presence of Pd(II) or Pd(0) catalysts which are soluble in these solvents (Kotha et al. 2002, Paetzold et al. 2001).

Although the solubility of the majority of organic compounds is low in water, from industrial and environmental points of view, the reactions performed in water are desired. Because the use of water as solvent is safe and inexpensive. In literature, there have been several examples related to the Suzuki reactions carried out in water (Uozumi et al. 1999, Li et al. 2000, Paetzold et al. 2001, Sakurai et al. 2002, Baleizao et al. 2003, Baleizao et al. 2004, Shimizu et al. 2004, Jang and Ragauskas 2006).

Reaction temperatures of the Suzuki reaction range from room temperature to 140 °C.

2.2.2.7. Pressure and Microwave Heating Effects

Microwave-promoted synthesis is an area of increasing interest in both academic and industrial laboratories. Although people had been using microwaves in their homes for many years, it was not until 1986 that the first reports of microwave-heating in organic synthesis appeared in the literature. As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. Also, many reactions can be performed by using microwave heating that cannot be achieved by using ‘conventional’ heating methods (Leadbeater 2005).

Recently, Arvela et al. have shown that by using microwave promotion and water as a solvent, the Suzuki reaction of potassium organotrifluoroborates with aryl bromides and iodides is performed efficiently (Arvela et al. 2006). In addition to microwave heating effect, high pressure can also have useful effect on Suzuki reaction of especially unactivated choloroarenes.

CHAPTER 3

THE HETEROGENEOUS SUZUKI CROSS-COUPLING REACTIONS

Two types of catalysts are used in the Suzuki reactions; heterogeneous catalysts where metallic Pd is supported on a carrier and homogeneous catalysts consisting of mononuclear Pd (ligand) complexes.

Homogeneous palladium catalysts are widely used in many cross-coupling reactions. These catalytic systems generally exhibit better activity and selectivity than heterogeneous systems. Although homogeneous techniques are certainly important in terms of their substrate tolerance, catalyst loading and reactivity, their complexity preclude the large-scale applications. Palladium ligands and precursors are also expensive, which severely restrict their industrial use and it is often difficult to remove these reagents at end of reactions (Ruiz et al. 2006). Moreover, undesired byproducts and/or scrambled products may also form in the presence homogeneous catalysts (Kotha et al. 2002) (Figure 3.1.).

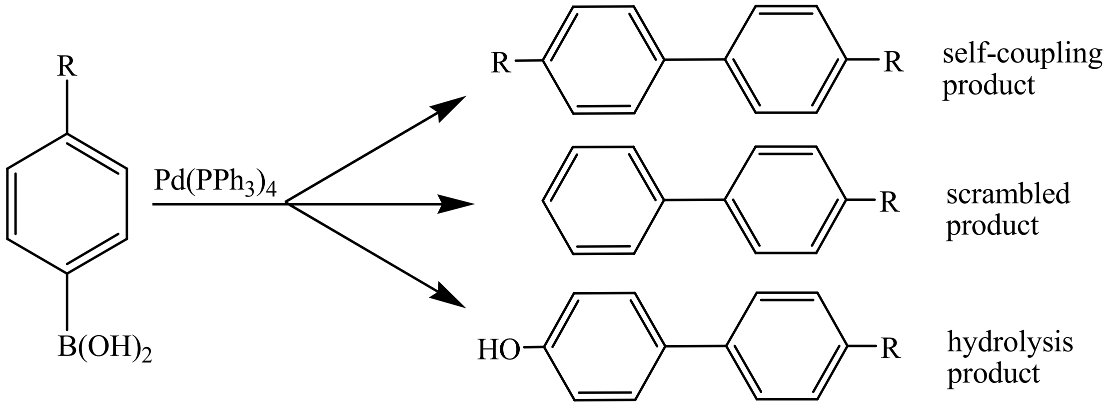


Figure 3.1. Generally observed side-reactions with Pd-catalyzed Suzuki-Miyaura cross-coupling

(Source: Kotha et al. 2002)

In this aspect, heterogeneous catalysts have many advantages over homogeneous counterparts so that it can be easily removed from reaction mixtures and re-used several times for the transformation of a large amount of reactants until they become eventually deactivated (Baleizao et al. 2003, Kim et al. 2002, Corma et al. 2002). That's why, heterogeneous catalysts are preferred for industrial processes and heterogenization methods have been also investigated (Smith and Notheisz 1995).

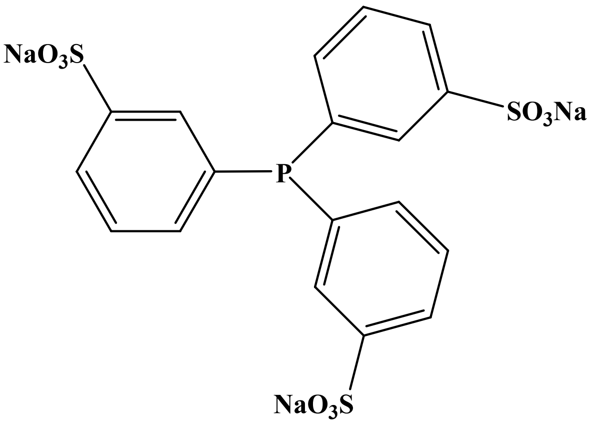
The commonly used two methods for homogeneous system to heterogenize is immobilization to liquid phase and insoluble support.

3.1. The Immobilization to Liquid Phase

The immobilization of catalysts in liquid phases has been widely used in the coupling reactions. The principle of the liquid/liquid biphasic catalysis system is related to solubility of reaction components like aryl, allyl or benzyl halogenides and boronic acids as well as their coupling products. The most important advantage of such processes is the facile recovery of catalysts from the reaction mixture, which is done by a simple phase separation of two immiscible solutions, of which one contains the product of the catalytic transformation and the other one palladium catalyst. Moreover, this approach also limits contamination of the organic products by catalyst metal (Heiden and Plenio 2004, Paetzold et al. 2001).

There are several different concepts studied by research groups; organic/organic liquid biphasic catalysis often with polymer-supported catalysts, fluorous/organic systems, ionic liquids, supercritical solvents, and aqueous/organic solvent systems (Heiden and Plenio 2004, Paetzold et al. 2001).

Phosphines which commonly used in cross-coupling reactions as homogeneous ligands can be converted into water-soluble derivatives by introduction of polar groups, including carboxylate, sulfonate and ammonium, providing easy removability from reaction mixture by extraction with organic solvent (Figure 3.2).



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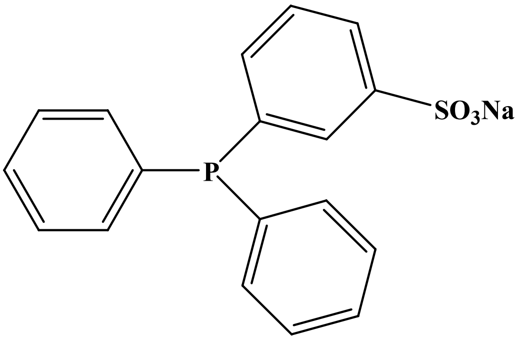

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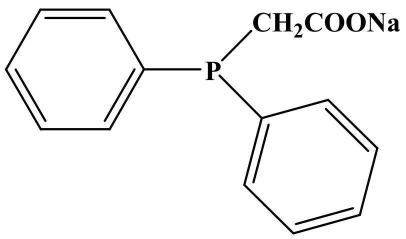

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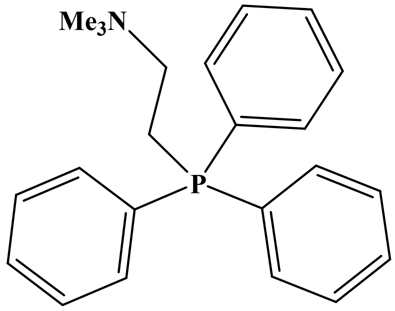

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Figure 3.2. The water soluble phosphine derivatives used in Suzuki reactions

Sulfonated triphenylphosphines **15** and **16** (TPPTS and TPPMS respectively) are the most commonly used as water-soluble ligands (Figure 3.2), with which palladium goes into aqueous phase and catalytic reaction proceeds therefore in water (Genet and Saignac 1999).

Dupuis et al. reported the Suzuki cross-coupling reactions between aryl bromides and arylboronic acids using a water soluble Pd(0)/TPPTS catalyst under mild conditions (Figure 3.3) (Dupuis et al. 2001).

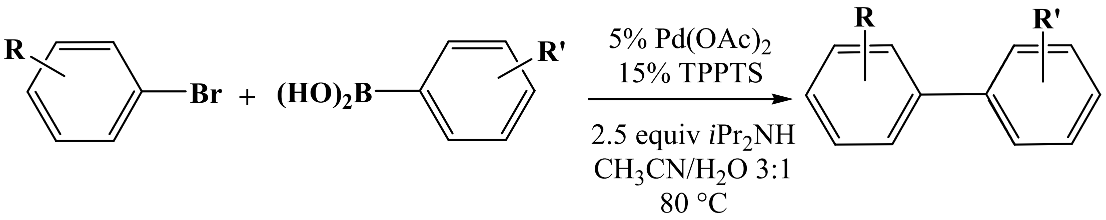


Figure 3.3. The Suzuki reactions of aryl bromides performed in TPPTS
(Source: Dupuis et al. 2001)

The solid polyethlene glycol (PEG) commonly utilized for heterogeneous catalyst systems becomes liquid at temperatures higher than 40 °C, exhibits high chemical stability to a wide range of reagents and can dissolve many organic compounds as well as inorganic salts. Since PEG is immiscible with hexane, ethyl ether and even cold methanol, substrates and reaction products can be recovered by liquid–liquid extraction in hot (Corma et al. 2005).

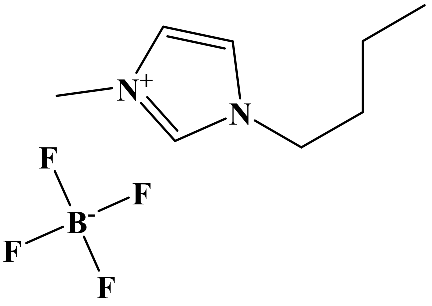
The catalytic system of Pd(OAc)$_2$ and 1,4-diazobicyclo[2.2.2]octane (DABCO) as ligand in PEG-400 was developed for Suzuki-Miyaura cross-coupling reaction of aryl bromides, iodides and chlorides with arylboronic acids. The reactions proceeded with excellent yield formation and high turnover numbers (TONs). Moreover, the Pd(OAc)$_2$/DABCO/PEG-400 system was recycled and reused five times without any loss of catalytic activity for aryl iodides and bromides (Li et al. 2005).

Under organic/organic biphasic conditions (DMSO/heptane), the Suzuki-Miyaura coupling of aryl chlorides with PhB(OH)$_2$ was performed successfully over several cycles by polymeric Pd catalysts with soluble polyethylene glycol phase tags (Heiden and Plenio 2004).

Imidazolium ionic liquids appear as promising green media for the purpose of developing heterogeneous, reusable catalytic systems since they have negligible vapor pressure, ease of handling and potential for recycling. Furthermore, their high compatibility with transition metal catalysts and limited miscibility with common solvents, enables easy product and catalyst separation with the retention of the stabilized catalyst in the ionic phase by liquid–liquid extraction using some conventional immiscible organic solvents such as ethyl ether and hexane (Corma et al. 2005).

The 1-Butyl-3-methylimidazolium tetrafluoroborate [bmim][BF$_4$], **19** (Figure 3.4), is one of the ionic liquid type that is used. It is stable in air and is known to solubilize many organometallic compounds. These properties, in addition to its controllable miscibility with water and immiscibility with ether, make [bmim][BF_4] a potential solvent for Suzuki reactions (Mathews et al. 2000).

Mathews et al. have demonstrated that Suzuki cross-coupling reactions of electron-rich and electron-deficient aryl bromides with arylboronic acids and their derivatives can be successfully conducted in **19** and at ambient temperature (Mathews et al. 2000).



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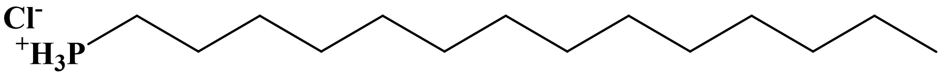

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Figure 3.4. Ionic liquid types used in the Suzuki reactions
(Source: McNulty et al. 2002, Mathews et. al 2000)

The Suzuki cross-coupling reactions of aryl chlorides with arylboronic acids were also achieved in a phosphonium salt ionic liquid, tetradecylphosphonium chloride, **20** (Figure 3.4), in 1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim][BF_4] in the presence of K_3PO_4 and a catalytic amount of $Pd_2(dba)_3$, as well as in the ionic liquid (McNulty et al. 2002).

3.2. The Immobilization to Insoluble Support

One another general strategy to transform a homogeneous catalyst into a heterogeneous catalyst is to anchor the active site onto an insoluble support. Two types of insoluble solids are among the most useful supports to anchor complex catalyst, *inorganic solids* and *polymers* (Baleizao et al. 2003, Baleizao et al. 2004).

3.2.1. Attachment to Polymer Supports

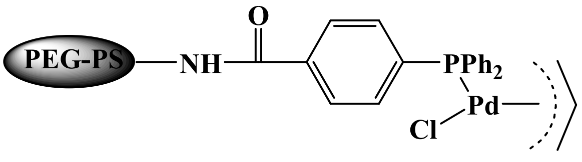
Polymers present a high hydrophobicity that makes them suitable for reactions in organic (Baleizao et al. 2003, Baleizao et al. 2004). Attachment of catalytic groups to the polymer support can be achieved by well-known organic and organometallic synthesis (Smith and Nontheisz 1999).

In the literature, there have been many heterogeneous catalysts prepared by this method.

The amphiphilic poly(ethyleneglycol)-polystyrene resin-supported palladium-monophosphine complex, **21** (Figure 3.5), was found to be active catalyst in the reaction of aryl halides and allyl acetates with aryl boron compounds in aqueous media (Table 3.1, entry 1). This catalyst could be easily removed from the reaction mixture and reused with no decrease in activity (Uozumi et al. 1999).

In another study, the Merrifield resin-supported salen-type palladium catalyst, **22** (Figure 3.5), prepared was found to be effective recyclable heterogeneous catalyst for the Suzuki cross-coupling reaction without the use of ligands. The Suzuki reactions were performed with activated aryl bromides in the presence of 0.5mol% Pd resin catalyst (Table 3.1, entry 2). The supported precatalyst was found to be significantly more useful than the corresponding homogeneous analogue (Phan et al. 2004).

An assembled complex of palladium and a non cross-linked amphiphilic polymer, denoted as PdAS, was prepared from $(NH_4)_2PdCl_4$ and non-cross-linked amphiphilic polymer poly[(N-isopropylacrylamide)-*co*-(4-diphenylstyrylphosphine)], **23** (Figure 3.5). The material was found to be an excellent catalyst precursor for heterogeneous Suzuki reactions of aryl and alkenyl halides and benzylic chlorides with arylboronic and alkenyl boronic acids and alkyl-9-borabicyclo[3.3.1]nonanes with high turnover numbers, PdAS was reused 10 times without any decrease in its catalytic activity (Yamada et al. 2003).



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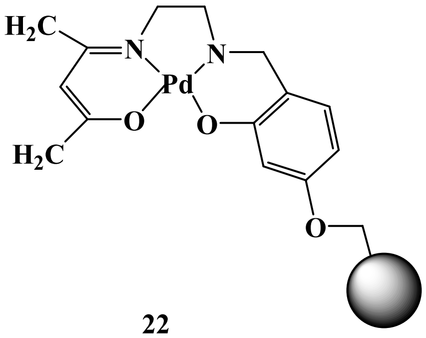

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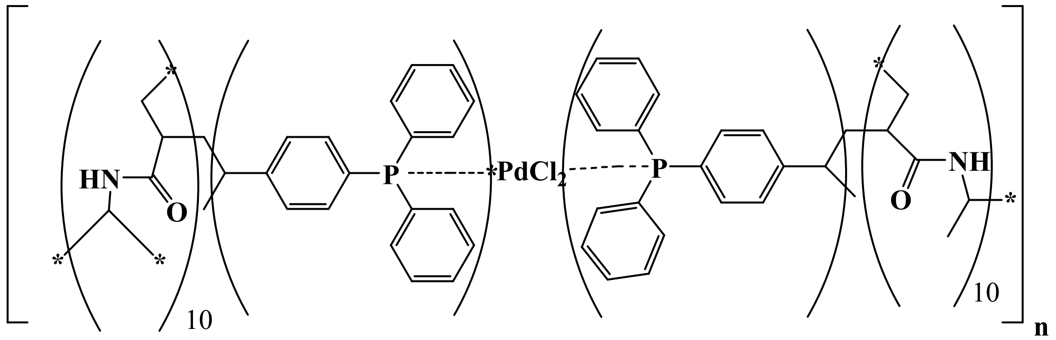

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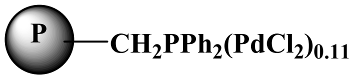

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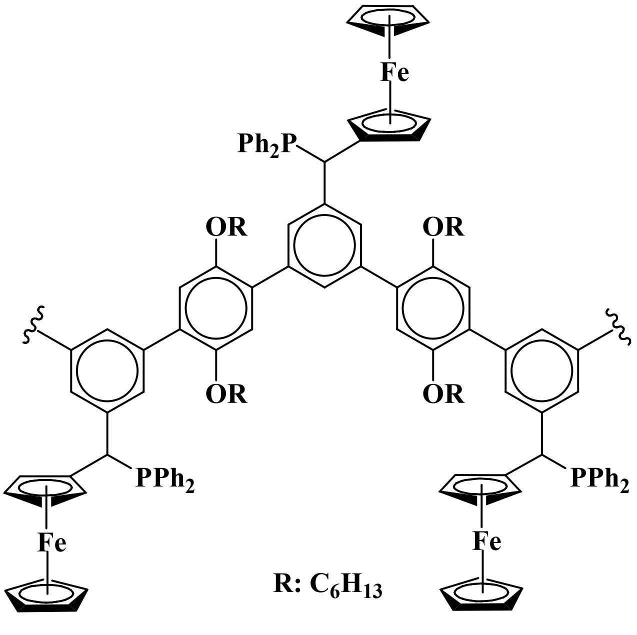

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Figure 3.5. Polymer-supported palladium complexes

Miyaura and Inada reported the use of PPh_3-functionalized polymer resins as supports for $PdCl_2$, **24** (Figure 3.5), in the Suzuki coupling of aryl chlorides and arylboronic acids (Inada and Miyaura 2000). The authors reported that the solid material could be reused multiple times. The cross-coupling reaction of tolyl boronic acid with chloropyridines, chloroquinoline, or activated chloroarenes having an electron-withdrawing group was carried out in toluene, aqueous K_3PO_4 at 80 °C in the presence of a polymer-bound $PdCl_2$ catalyst. The resin catalyst was recovered by filtration (Table 3.1, entry 3).

Hu et al. designed and synthesized monophosphine-containing polymer, **25** (Figure 3.5)**,** which was then used for the room-temperature palladium catalyzed reaction between aryl chlorides and arylboronic acids (Hu et al. 2003).

Sauer and Wang studied palladium complexes anchored on polyethylene-based supports known as FibreCat catalysts for Suzuki coupling of aryl chlorides, bromides and iodides under microwave heating conditions. A wide variety of aryl halides were effectively converted in 10-25 minutes (Wang and Sauer 2004).

Triphenylphosphine based polymer-supported FibreCat precatalysts **26-29** (Figure 3.6) can be used to achieve room-temperature couplings of activated and inactivated aryl bromides with phenylboronic acid in nearly quantitative conversions (Colacot et al. 2002).

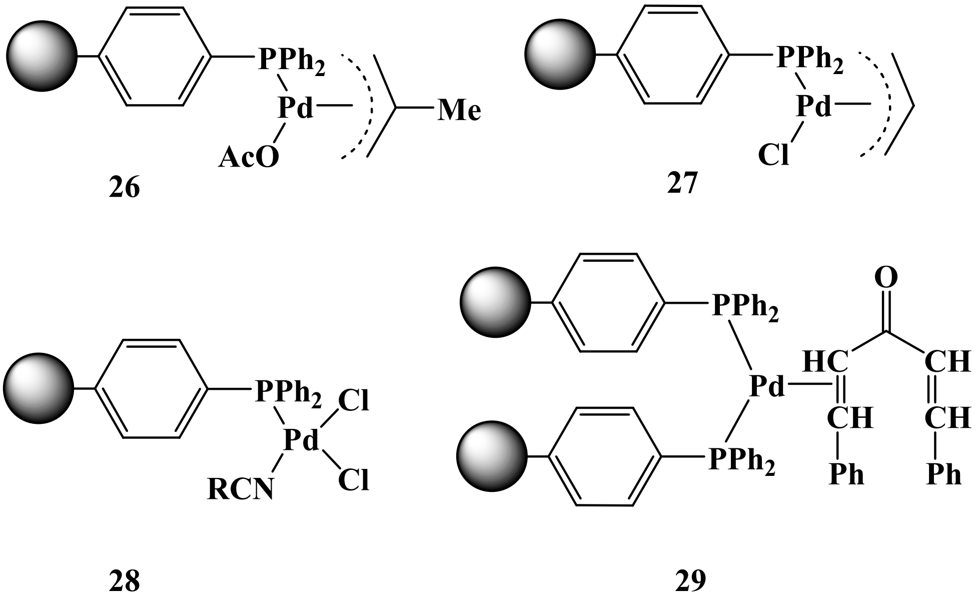

Figure 3.6. Polymer-supported FibreCat precatalysts

In recent years, palladium nanoparticles have also been used as catalysts for Suzuki reactions. In fact, these particles have characteristically high surface-to-volume ratio and, consequently, a large fraction of the palladium atoms are at the surface and available for catalysis (Li et al. 2000, Kim et al. 2002, Liu et al. 2004). Li and co-workers have demonstrated that palladium nanoparticles stabilized by poly (*N*-vinyl-2-pyrrolidone) (PVP) are efficient catalysts for the linear dependence of reaction rate on Pd concentration, suggesting that the catalysis eventually occurs on nanoparticle surface (Figure 3.7).

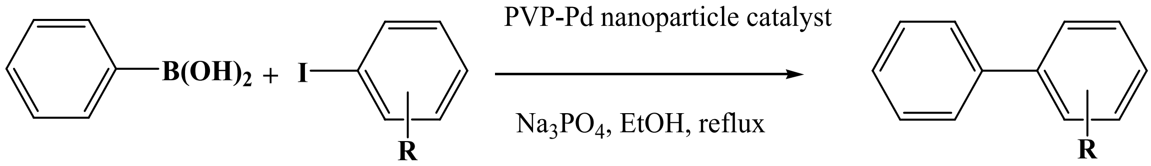

Figure 3.7. PVP-Pd catalyzed the Suzuki reactions
(Source: Li et al. 2004)

Macquarie and co-workers immobilized an imino pyridine ligand on the sugar-based polymer chitosan, metalated it with $Pd(OAc)_2$, **30** (Figure 3.8), and found that it was an excellent and reusable precatalyst for Suzuki reactions involving aryl and heteroaryl bromides (Hardy et al. 2004).

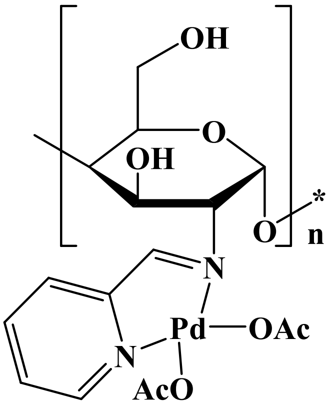

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Figure 3.8. The sugar-based polymer chitosan supported palladium complex
(Source: Hardy et al. 2004)

3.2.2. Catalysts Anchored to Inorganic Solids

It has been accepted that inorganic solids, unlike polymers, prevent the intermolecular aggregations of the active surface species by means of their rigid structures. Moreover, inorganic solids have the advantage that they can be prepared with larger surface areas, have periodic structured porosity, and can resist thermal regeneration (Baleizao et al. 2003, Baleizao et al. 2004).

In literature recently, some cross-coupling processes have used palladium supported on various types of supports such as sepiolites, silica, zeolites, zeolitic materials, layered double hydroxides and carbon.

Palladium powder has also been used as a catalyst precursor for Suzuki reactions. Kabalka et al. found that aryl iodides readily couple with arylboronic acids in refluxing methanol for 4 hour under air, in the presence of a catalytic amount of Pd powder (Kabalka et al. 2001).

Kabalka and his research group developed a novel, solventless Suzuki coupling methodology including the use of a commercially available KF–Al_2O_3 mixture, doped with a ligandless Pd(0) catalyst for cross-coupling reactions of aryl, allyl halides and aryl- or alkenyl boronic acids (Table 3.1, entry 4) (Kabalka et al. 1999). Moreover, with these reaction conditions optimized, it was observed that the use of microwave irradiation accelerated the reactions by decreasing the reaction times from hours to minutes (Kabalka et al. 2000, Kabalka et al. 2003).

With the advantage of its relatively inexpensive, stable, easily removable and reusable characteristics, palladium on carbon has been found to be another effective precatalyst for Suzuki reactions (Gruber et al. 2004, Dyer et al. 2001).

The Pd/C catalyzed the Suzuki coupling of an 8-bromo-6-(2-(methylsulfonyl)propan-2-yl)quinoline and 3-formylphenylboronic acid (Figure 3.9). The reaction was shown to give coupling product in excellent yield with low levels of residual palladium after a simple filtration and precipitation (Conlon et al. 2003).

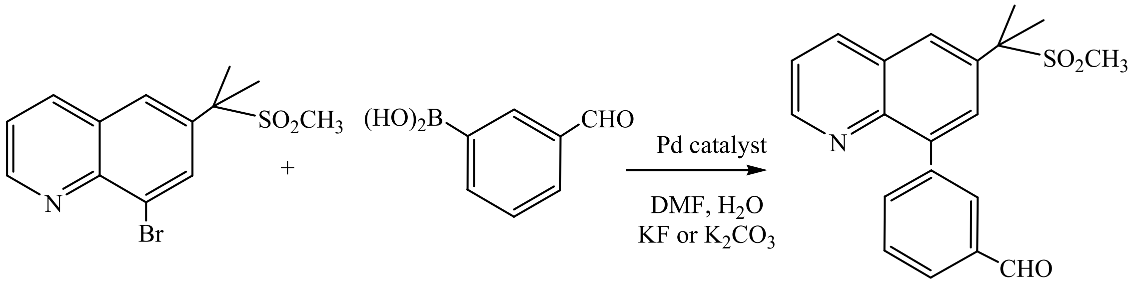


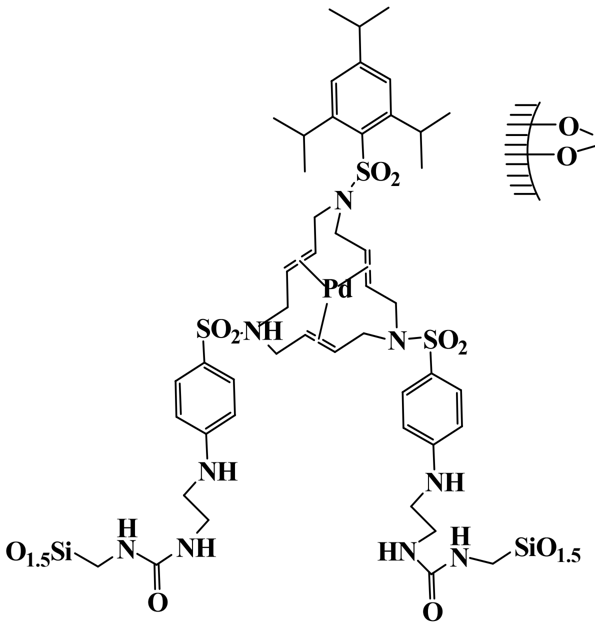
Figure 3.9. The Suzuki coupling of an 8-bromo-6-(2-(methylsulfonyl)propan-2-yl)quinoline and 3-formylphenylboronic acid
(Source: Conlon et al. 2003)

Leblond et al. also studied Pd/C catalysts for Suzuki couplings, focusing their studies on the conversions of aryl chlorides (Table 3.1, entry 5). They observed that addition of small amounts of triphenylphosphine inhibited the reaction significantly, concluding that the heterogeneous metal particle surface was the true active catalyst, and that activation of metal halides was made possible by synergistic anchimeric and electronic effects occurring in the presence of adsorbed species on the catalyst surface (Leblond et al. 2001).

The majority of the heterogeneous catalyst is related to silica materials since they have excellent stability, high surface area, good accessibility, and organic groups can be anchored to the surface. However, it has limited stability in aqueous, especially basic conditions.

Blanco et al. first prepared a hybrid organic–inorganic material containing a macrocyclic triolefinic palladium(0) complex covalently bonded to a silica matrix, **31** (Figure 3.10), and tested catalytic activity in Suzuki cross-coupling reactions with cinnamyl bromide and activated aryl iodides, resulting high product formation (Table 3.1, entry 6). Heterogeneous catalyst has been reused up to five cycles, although a progressive decrease in activity has been observed (Blanco et al. 2006).

Baleizao et al. demonstrated that a silica or MCM-41 anchored oxime–carbapalladacycle complex, **32** (Figure 3.10), was highly active and reusable heterogeneous catalyst (Table 3.1, entry 7). They enabled to perform the Suzuki reaction of chloroarenes and phenylboronic acid in water and the catalyst could be reused eight times without loss of activity or leaching of the Pd from the solid to the liquid phase (Baleizao et al. 2003, Baleizao et al. 2004).



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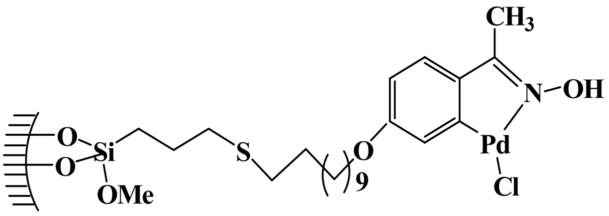

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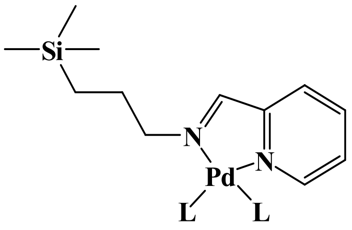
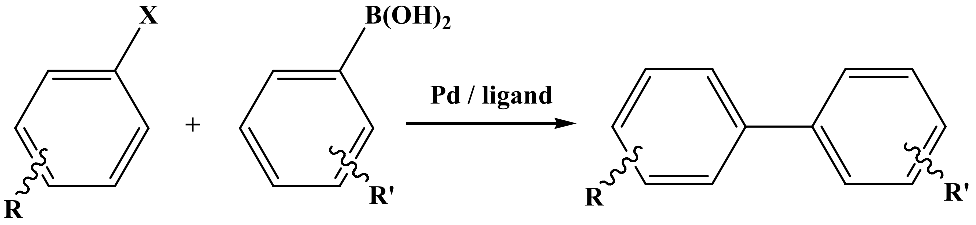


33

Figure 3.10. Silica-supported palladium complexes used in the Suzuki reactions

Silica-supported iminopyridine-based palladium complexes, **33** (Figure 3.10), were shown to have very good catalyst recyclability in Suzuki reactions of aryl bromides (Mobufu et al. 2001) (Table 3.1, entry 8).

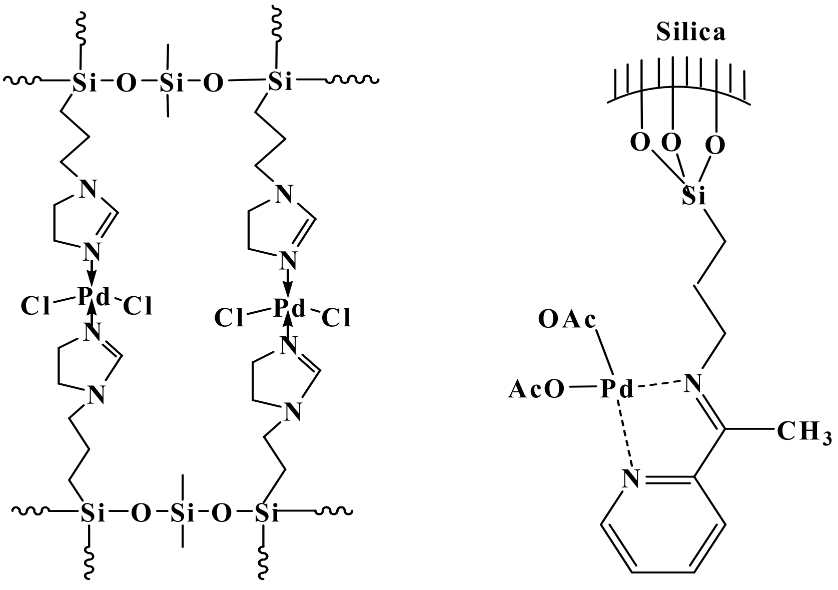
Table 3.1. Examples from literature on Suzuki reactions of aryl halides



Entry	R	Catalyst/ Ligand	Reaction Conditions	Yield%	*Ref.*
1	H, 2-CH_3, 4-CH_3	**21**	aq.KOH, 25 °C	67-91	Uozumi et al. 1999
2	4-: CHO, $COCH_3$, CN	**22**	K_3PO_4, DMF, 90 °C, 24h,	100	Phan et al. 2004
3	4-: $COCH_3$, CH_3, OMe	$Pd(OAc)_2$/ **24**	KF, THF, RT, 48-60 h	42-75	Inada and Miyaura 2000
4	Ph	Pd(0) on KF/Al_2O_3	100 °C, 4h	29-99	Kabalka et al. 1999
5	4-: NO_2, CF_3, CN,	Pd/C	DMA/H_2O, K_2CO_3, 80°C	79-95	Leblond et al. 2001
6	4-: NO_2, OCH_3	**31**	Cs_2CO_3, dioxane, 100 °C, Ar atm, 2h	49- 97	Blanco et al. 2006
7	4-: $COCH_3$, COOH, CH_3 , H, 2-: CN, NO_2	**32**	K_2CO_3, water, 2h, 100 °C	73-99	Baleizao et al. 2003
8	H, CN, Cl, OCH_3, CH_2Br	**33**	xylene, K_2CO_3, 95 °C	88-98	Mobufu et al. 2001
9	4-: H, -OCH_3, -CN,	**35**	o-xylene, N_2 atm, 95 °C	75-100	Paul and Clark 2003

Gurbuz et al. prepared and characterized silica supported 3-(4,5-dihydroimidazol-1-yl)-propyltriethoxysilanedichloropalladium(II), **34** (Figure 3.11), and utilized them in Heck and Suzuki coupling reactions of iodo-, bromo- and chloroarenes (Figure 3.11). The heterogeneous catalyst was reusable many times (Gurbuz et al. 2003).

In 2003, Paul and Clark used a novel silica-supported palladium catalyst, **35** (Figure 3.11), for Suzuki reactions of aryl and polyaryl bromides with phenylboronic acid (Table 3.1, entry 9). The key features of the catalyst included rapid reactions, excellent catalyst recyclability and total stability under reaction conditions. The catalyst which has a very low loading of palladium was defined as completely heterogeneous and highly stable under reaction conditions (Paul and Clark 2003).



34

35

Figure 3.11. The immobilized Pd(II) species on silica supports

Clays are also special inorganic solids since they have well-defined structures and pores with molecular dimensions, which can solvate the adsorbed molecules and provide solvent-like environments (Smith and Nontheisz 1999).

Varma et al. reported $PdCl_2$/tetraphenylphosphonium bromide-intercalated clay as a heterogeneous catalyst for Suzuki coupling of aryl bromides and iodides (Varma et al. 1999, Varma and Naicker 1999a, Varma and Naicker 1999b).

The deposition of palladium salts on hydrotalcite which is a naturally occurring mineral of the layered double hydroxide family that constitutes a major class of anionic clay materials was found to be an effective method for preparing active catalysts in Suzuki cross coupling reactions. They also tested the reusability of the catalyst. It was observed that after three catalytic cycles the catalyst lost some activity after each reuse (Ruiz et al. 2006).

Corma et al. tested bifunctional (palladium and basic sites) sepiolites clay for their catalytic activities for the Heck and Suzuki reactions in the absence of any extrinsic base at 145 °C. However, irreversible depletion of the basic sites of the sepiolite was considered to be responsible for the deactivation of the catalyst (Corma et al. 2004).

Shimizu et al. reported that $[Pd(NH_3)_4]^{+2}$-exchanged sepiolite clay was highly active for Suzuki reactions of 4-bromophenol with phenylboronic acid or sodium tetraphenylborate in water (Shimizu et al. 2004).

The recyclable nanopalladium particles supported on layered double hydroxide (LDH) were designed and developed by a simple ion-exchange technique following reduction processes. This heterogeneous palladium catalyst showed high activity for Heck-, Suzuki-, Sonogashira-, and Stille-type coupling reactions of chloroarenes to afford good to excellent yields of coupling products (Choudary et al. 2002).

Researchers synthesized palladium hollow spheres showing good catalytic activities in Suzuki cross coupling reactions of iodothiophene and phenylboronic acid and can be reused at least for 7 cycles at 78 °C with no apparent leaching (Kim et al. 2002). They reported that Pd shell is not active enough to catalyze the reaction of aryl chloride (Figure 3.12).

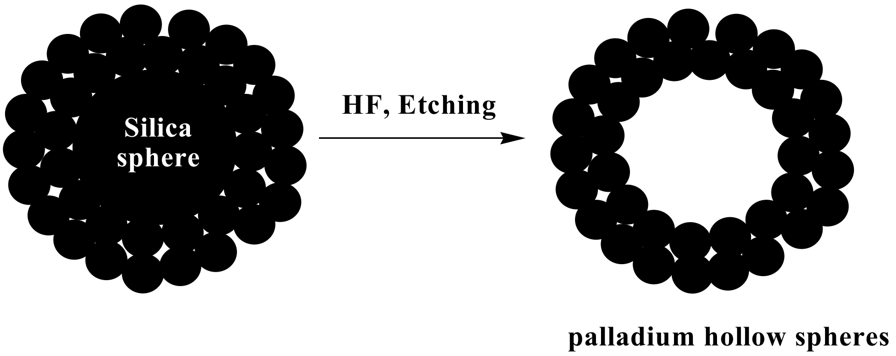


Figure 3.12. Preparation of palladium hollow spheres
(Source: Kim et al. 2002)

Smith et al introduced the use of Pd(II)-exchanged perovskites ($LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$) as a new class of catalysts in the Suzuki coupling of 2-bromoanisole, 2-bromo pyridine and arylboronic acids with low levels of Pd leaching at 80 °C (Smith et al. 2003).

Zeolites, which have specific properties because of their well-defined structure and pores with molecular dimensions, have been also used as a support material (Smith and Nothesisz 1995).

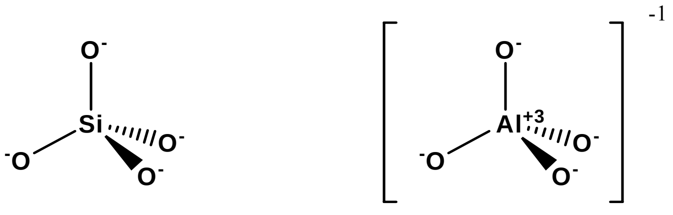
3.3. Zeolite supported palladium catalysts in the Suzuki Reactions

3.3.1. Structural Features of Zeolite

Zeolites are three-dimensional, microporous, crystalline solids with well-defined structures that contain aluminum, silicon, and oxygen in their regular framework; cations and water are located in the pores. Zeolites have a uniform pore structure (Weitkamp and Puppe 1999).

The formula of zeolite is written as $\mathbf{M_{2/\mathit{n}}.\ Al_2O_3.\ \mathit{x}SiO_2.\ \mathit{y}H_2O}$ where n is the cation valence; M is the cation which balances the negative charge.

The framework of zeolites consists of $(SiO_4)^{4-}$ and $(AlO_4)^{5-}$, combined with each other at the corners by sharing their oxygen, resulting in the general formula of $(AlO_2)_x.\ (SiO_2)_{(n-x)}$, Where n is the number of tetrahedra per unit cell, and $x \leq n/2$ (Weitkamp and Puppe 1999).



Silica Tetrahedron

Alumina Tetrahedron

Figure 3.13. Silica and alumina tetrahedron structures

While the SiO_4 units are neutral, the AlO_4 results in a net negative charge since the trivalent aluminum is bonded to four oxygen anions. Negative charge is neutralized by a cation generally from the groups IA or IIA. These cations are highly mobile and can be exchanged for other cationic species.

There are two building blocks so-called the sodalite and pentasil units which are shown in Figure 3.14.

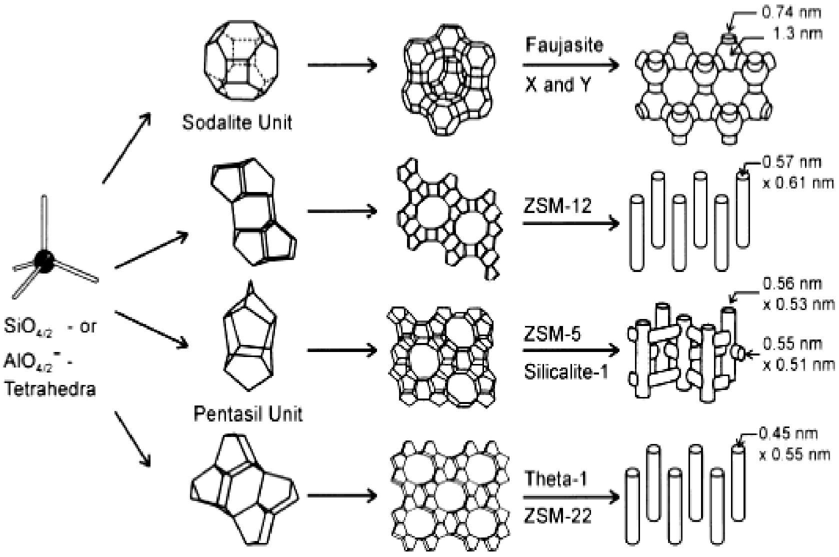


Figure 3.14. SiO_4 and AlO_4 building blocks of zeolites
(Source: Weitkamp and Puppe 1999)

The position, size, and numbers of cations and the position and number of water molecules located in the cages, cavities, and channels of the zeolites can significantly change the properties of the zeolite.

3.3.2. The Advantages of Zeolites

Due to high thermal stability, ease of handling, ready availability, being environmental friendly, inexpensive cost of zeolites, they have been used as the support materials for immobilization of the catalysts. Moreover, the use of zeolite as support material should have the following advantages (Sen et al. 1999);

- Complexes immobilized in zeolite super cages may have almost the same activity as the free complexes in solution.
- The zeolite microstructure (micro-reactor) could help to overcome the problems of metal leaching.
- Zeolites are capable of stabilizing intermediate active species retained in their cavities and may show the product shape-selectivity.
- They should regenerate the catalyst after deactivation.

In the literature, [Pd]-loaded NaY zeolites were used for C-C coupling reactions for the first time by Djakovitch and Koehler (Figure 3.15) (Djakovitch and Koehler 1999). They reported that the catalysts exhibited a high activity and selectivity toward the Heck reaction of aryl bromides with olefins in low palladium concentrations (0.1 mol% of Pd). In another study, the Heck reactions were performed for industrially more interesting chloroactophenone with styrene at 100 ºC (Djakovitch et al. 1999). The authors observed that the catalysts could be separated from the reaction mixture. However it could not be reused with same activity. The catalyst used in a first run at 100 ºC was regenerated by increasing temperature to 140 ºC under reaction conditions (Djakovitch and Koehler 2001).

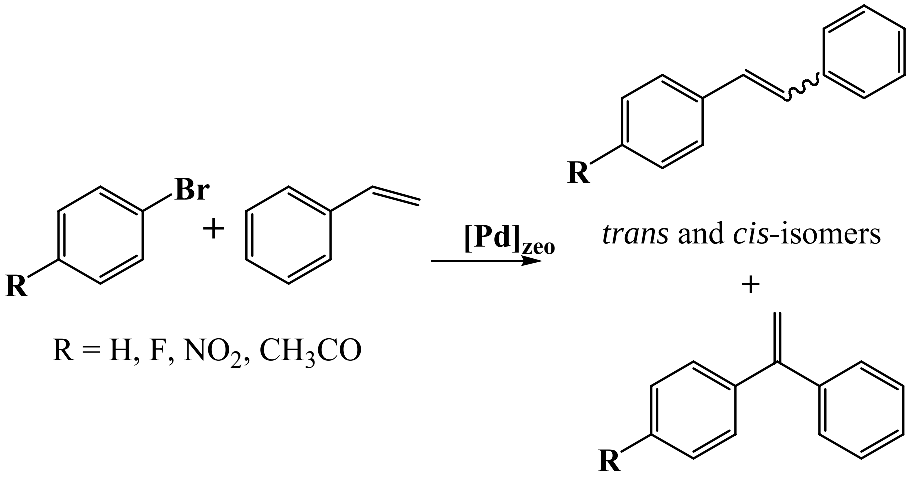


Figure 3.15. The Heck reactions of aryl bromides with olefins
(Source: Djakovitch and Koehler 1999)

The leaching test was also performed and it was found that only small amount of palladium was leached, depending on temperature of the reaction and the nature of the Pd species immobilized in the zeolite cage. For the $[Pd(NH_3)_4]^{2+}$-NaY which we also investigated for its activity over Suzuki reaction in thesis study, Pd leaching was higher at 140 °C (6% ppm) than at 100 °C (0.5% ppm). It was found that the $[Pd(NH_3)_4]^{2+}$ complex decomposed in two step as $T_1 = 158$ °C and $T_2 = 285$ °C which explained the better stability of the catalyst obtained at 100 °C (Djakovitch and Koehler 2001).

They proposed the active palladium species was formed in-situ by decomposition of Pd complexes entrapped in zeolite and catalyzed reaction homogeneously.

Djakovitch and Koehler also reported that Pd loaded NaY zeolites activates aryl halides toward arylation of malonate (Djakovitch et al. 2000) and amination reactions (Djakovitch et al. 1999).

In another study, the immobilization of the $PdCl_2[Ph_2P(CH_2)_2S(CH_2)_3SO_3Na]_2$ complex on propylsilylsulfonated mesoporous Al-MCM-41 has been investigated over Suzuki reactions (Kosslick et al. 2001).

Paetzold et al. reported the coupling reaction of *p*-iodoanisole and phenylboronic acid in the presence of palladium complexes containing water-soluble phosphine ligands anchored onto MCM-41 and alumina supports (Paetzold et al. 2001).

Corma et al. reported the Suzuki reaction of bromobenzene with phenylboronic acid catalyzed by bifunctional basic zeolites impregnated with palladium chloride. Their system also had the innovation to avoid the use of an extrinsic base, since the zeolite framework oxygens can act as efficient basic site. The solids could be reused after water washings with only a minor decrease in the catalytic activity of the zeolite (Corma et al. 2002).

It was first reported by Artok and Bulut that the Suzuki coupling of aryl bromides and phenylboronic acid performed over Pd(II)-loaded and Pd(0)-loaded NaY in water/DMF mixture at room temperature and relatively high Pd concentration (2.5mol % Pd) (Artok and Bulut 2004, Bulut et al. 2003). In the beginning of their study, reaction conditions were optimized by using 4-bromoanisole as electron-donating substrate. Under optimal conditions several aryl bromides were tested towards Suzuki reactions. But activities of these catalysts were not enough to catalyze Suzuki reactions of aryl chlorides which are of great importance for industrial due to their lower cost.

3.3.3. Preparation of Zeolite-Supported Metal Catalysts

Metals can be introduced into a zeolite by basically two procedures according to the chemical composition of metal ion; the ion exchange and sorption method. If the metal forms cations, negative charge carried by AlO_2 unit is neutralized by these cations through ion exchange. In the sorption method, neutral metal compounds are treated with zeolite. As for synthesis of metal complexes which dimensions exceed pore size, the ship-in-bottle method is used to immobilize such complexes within the zeolite cavities (Figure 3.16). The ship in bottle is used to immobilize such complexes within the zeolite cavities providing an opportunity to heterogenize a homogeneous catalyst system (Weitkamp and Puppe 1999).

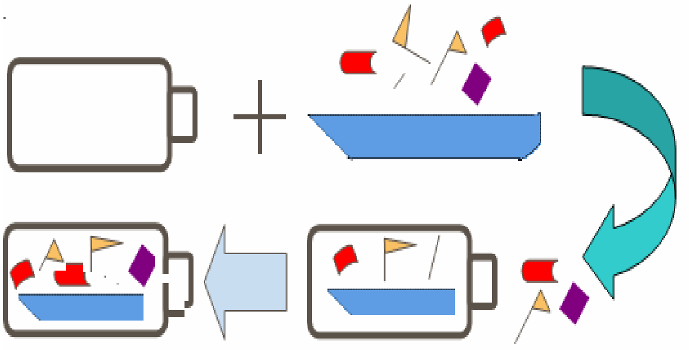


Figure 3.16. Ship in bottle synthesis

(Source: Weitkamp and Puppe 1999)

In their study, Djakovitch et al. prepared [Pd]-exchanged NaY zeolite by ion-exchange method and characterized by MAS-NMR (Figure 3.17) (Djakovitch et al. 2001, Djakovitch et al. 1999).

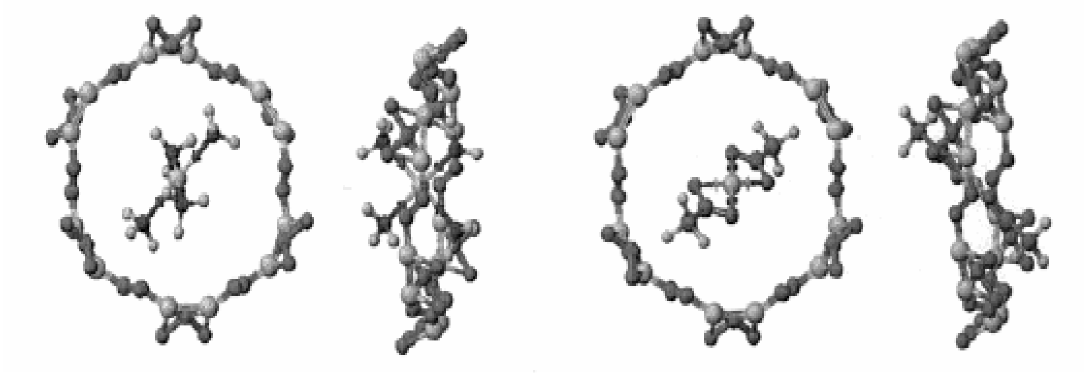


Figure 3.17. Molecular modeling of the Pd complexes ($[Pd(NH_3)_4]^{2+}$, $[Pd(OAc)_2]$, $[Pd(C_3H_5)Cl]_2$ in Na-Y zeolite using the CAChe^{TM} software with extended MM2 molecular force field and molecular mechanics methods (Source: Djakovitch et al. 2001, Djakovitch et al. 1999)

CHAPTER 4

EXPERIMENTAL STUDY

4.1. Palladium-Loaded Zeolite Catalyst Preparation

$Pd(NH_3)_4Cl_2$ complex was synthesized from $PdCl_2$ (Fluka, 47% purum) and a commercial ammonia solution (Merck, 25%). NH_3 solution was added over $PdCl_2$ complex and some water was added drop wise to this solution while stirring until the solution color turned to yellow from tobacco color. This solution was boiled to remove water and yellow crystals were obtained. Then this complex was recrystalized with extra pure ethanol (Riedel, 95%).

$Pd(NH_3)_4^{2+}$ was introduced into the NaY zeolite (Zeolyst International, CBV100, SiO_2/Al_2O_3 mol ratio: 5.1) by ion exchange with 200 mL 0.1 M NH_4OH solution of $Pd(NH_3)_4Cl_2$ for two grams of zeolite in as-received form, corresponding, approximately, to 0.8 or 0.2 wt% of Pd on the zeolite. The Pd solution and zeolite mixture was stirred at room temperature for 2 h, filtered and washed with water until no chloride ion was detectible within the filtrate. The solid was left under ambient conditions to eliminate its excess water content. The application of higher temperatures and high vacuums resulted in less active catalyst.

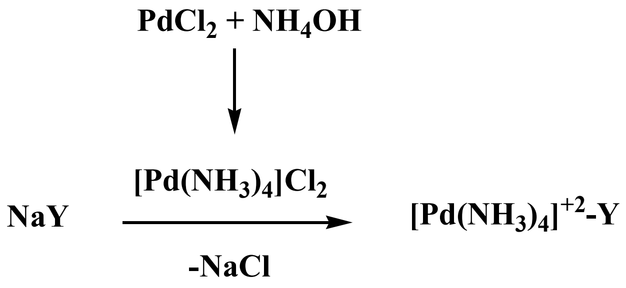


Figure 4.1. Preparation of $[Pd(NH_3)_4]^{+2}$-Y catalyst from NaY zeolite

4.1.1. Palladium-Loaded Zeolite Catalyst Characterization

In order to determine the palladium content of the zeolite, Pd-NaY was dissolved in a mixture of concentrated HBF_4, HNO_3, and HCl (3:3:2) in a Teflon reactor. This mixture was heated in Ethos Plus Microwave Lab station furnace according to the following heating program.

The mixture was heated to 180 °C in 5 minutes under 600 W power and in the next step, hold at 180 °C for 10 minutes under 650 Watt microwave power. At the end of the program, the solutions were diluted to approximately 1:50. Standard solutions (0.5, 1, 2, 3, 4 ppm) were prepared from standard stock palladium(II) solution (Pd(II) nitrate in nitric acid 0.5mol/l) in nitric acid (%1). The samples were analyzed by Atomic Adsorption Spectroscopy (AAS). The wt% Pd in zeolite was determined by using the formula given below.

$$\text{wt \% Pd} = \frac{V_{\text{final}}\,(\text{ml}) \times \text{Concentration(mg/L)}}{1000(\text{ml})} \times \frac{100}{m_{\text{catalyst}}(\text{mg})} \qquad (4.1)$$

Although the catalyst was analyzed by X-Ray Diffraction, any palladium couldn’tbe observed due to its low concentration (<0.2wt %Pd).

4.2. General Procedures for the Suzuki Coupling Reactions

Aryl halide, boronic acid, hexadecane (as an internal standard), base, solvent, Bu_4NBr for aryl chlorides, catalyst and zeolite were introduced into a two-necked round bottomed flask which was equipped with a condenser and a septum (Figure 4.2). The flask was then placed in a preheated oil bath and vigorously stirred during the reaction in an inert or ambient atmosphere.

Small amounts of samples were periodically withdrawn by syringe during the reaction, diluted in ethyl acetate and analyzed by GC. The conversion was calculated based on internal standard. The course of the reaction was followed until no further increase in the formation of coupling product was observed. After cooling to room temperature, the catalyst was recovered by filtering through a membrane filter with 0.2 μm porosity and washed with ethyl acetate.

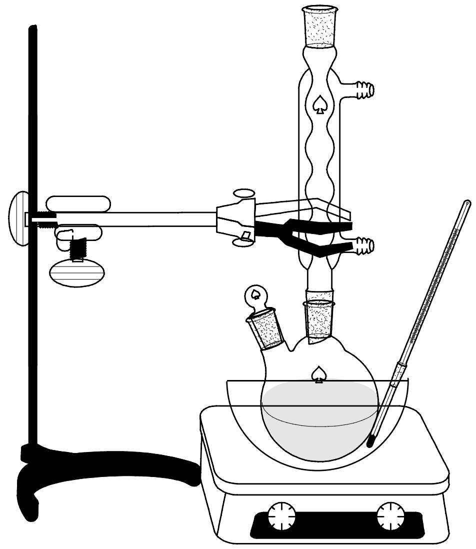


Figure 4.2. The experimental set-up for Suzuki coupling reactions

4.3. Characterization of Products

4.3.1. GC Method

The samples were analyzed by GC/MS (HP GC/MS 6890/5973N on a HP-5MS, 30m, 0.25 mm capillary column, 5% phenylmethoxysiloxane with 0.25μm film thickness) 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 250 °C, then it was kept at this temperature for 3 min. Throughout the analysis the injector and detector temperatures were kept constant at 280 °C and 300 °C, respectively. The analysis was performed on split mode with a split ratio of 1/50. A sample gas chromatogram of the reactant and reaction products according to this temperature program is given in Figure 4.3.

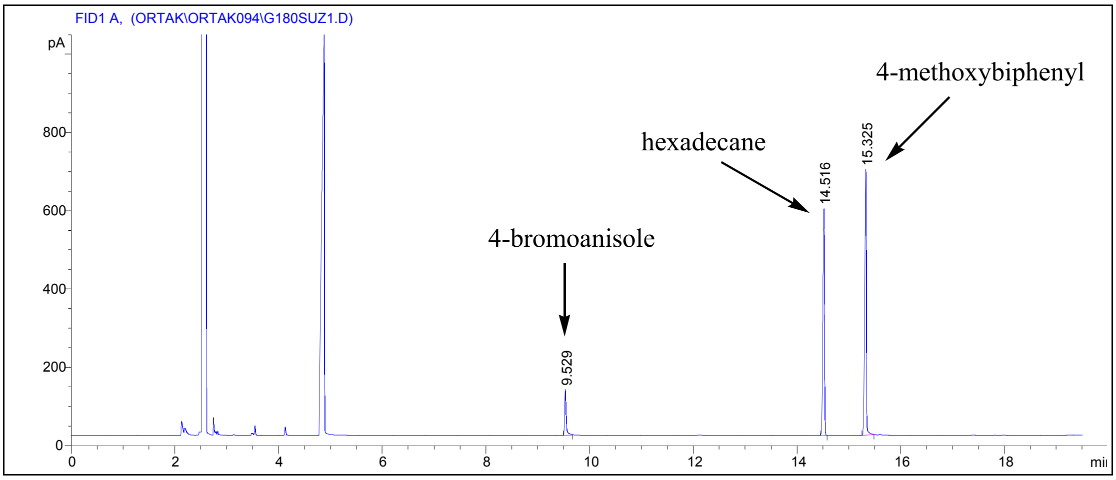


Figure 4.3. GC chromatogram of a selected Suzuki Reaction (4-bromoanisole and phenylboronic acid)

4.3.1.1. Calculation of Reactant and Product Amount on GC

For the calculation of amount of reactants and products, response factor of each reactant and product for the set temperature program of GC was determined. As internal standard, hexadecane was used. The amount of internal standard does not change throughout the reaction, so 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. For the determination of response factor of a compound, 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 then was injected to GC. After the analysis is complete according to the set temperature program, the following equation is used for the determination of response factor of that compound:

$$\text{R.F.} = \frac{\text{internal standart area}}{\text{compound area}} \times \left(\frac{\text{compound amount}}{\text{internal standart amount}} \right) \qquad (4.2)$$

In Suzuki experiments response factor values for the reactant and products were determined with respect to hexadecane as internal standard. In order to calculate the amount of both reactant and products at the end of 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 hexadecane and the area under the hexadecane peak into account, the following equation was used in order to calculate the amount of reactant and products at the end of reaction:

$$\text{amount of compound} = \left(\frac{\text{internal standart amount}}{\text{internal standart area}}\right) \text{ x R.F. x compound area} \qquad (4.3)$$

4.3.1.2. Calculation of Reactant Conversion, Product Yield and Recovery

Reactant conversion at any time is calculated using equation 4.4:

$$(\text{Reactant Conversion})_t\ \% = \frac{\left((\text{Reactant})_i - (\text{Reactant})_t\right)}{(\text{Reactant})_i} \text{ x } 100 \qquad (4.4)$$

where $(\text{reactant})_i$ 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 4.5:

$$\text{Product Yield} = \frac{\text{mole of product}_t}{\text{initial mole of aryl halide}} \qquad (4.5)$$

4.4. Purification of the Products

In this study, various types of products were purified by using column chromatography.

At end of reaction, the catalyst was separated from the reaction mixture by filtration. Water phase was extracted with ethyl acetate for three times. Organic phase was dried over sodium sulphate and solvent was removed by using evaporator. Then, it was extracted with saturated NaCl solution to remove solvent (DMA; *N,N*-dimethylacetamide). It must be noted that in the Suzuki reactions of aryl chlorides, organic phase extracted with HCl (10%) to remove both DMA and tributylamine which were formed in the course reaction. Products were isolated by using column chromatography (diameter of column 1.5cm) on silica gel (Merck, Silica Gel 60) with a 0.63mm-0.200mm (20g) or 0.40mm-0.63mm (35g) .

The purity of products was determined through GC, GC/MS and NMR techniques.

All products are known compounds and products were determined by ^{1}H NMR, ^{13}C NMR (Varian AS Mercury + MHz spectrometer) and GC-MS. The values are represented below and NMR and GC-MS spectrums are given Appendix A and Appendix B respectively.

4-Acetylbiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01-8.05 (m, 2H), 7.70-7.60 (m, 4H,), 7.50-7.38 (m, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ: 197.9, 146.0, 140.1, 136.1, 129.2, 129.1, 128.5, 127.5, 127.4, 26.8; MS: 196 (M^+), 181, 152.

4-Cyanobiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.73-7.66 (m, 4H), 7.60-7.57 (m, 2H), 7.51-7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.9, 139.4, 132.8, 129.3, 128.9, 128.0, 127.5, 119.1; 111.2; MS: 179 (M^+).

4-Nitrobiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31-8.27 (m, 2H), 7.75-7.71 (m, 2H), 7.64-7.60 (m, 2H); 7.52-7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.9, 147.3, 139.0, 129.4, 129.1, 128.0, 127.6, 124.3; MS: 199 (M^+), 169, 152, 141.

4-Phenylbenzaldehyde: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.1 (s, 1H, CHO); 7.96 (d, 2H); 7.64 (d, 2H); 7.98 (d, 2H); 7.51-7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.1, 147.4, 140.0, 135.5, 130.5, 129.2, 128.7, 127.9, 127.6. MS: 181 (M^+), 152, 76.

4-Methoxybiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63-7.58 (m, 4H); 7.49-7.45 (m, 2H); 7.38-7.34 (m, 1H); 7.05-7.03 (d, 2H); 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.5, 141.1, 134.1, 129.0, 128.4, 127.0, 126.9, 114.5, 55.6; MS: 184 (M^+), 169, 141, 115.

3-Acetylbiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20-8.19 (m, 1H); 7.95-7.92 (m, 1H); 7.79-7.77 (m, 1H); 7.64-7.60 (m, 2H); 7.55-7.45 (m, 3H); 7.41-7.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.2, 141.9, 140.4, 137.9, 131.9, 129.3, 129.2, 128.1, 127.4, 127.2, 26.9; MS: 196 (M^+), 181, 152.

3-Methoxybiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.65 (m, 2H); 7.5-7.47 (m, 2H); 7.43-7.39 (m, 2H); 7.26-7.20 (m, 2H); 6.98-6.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 143.1, 141.4, 130.0, 129.0, 127.7, 127.5, 119.9, 113.2, 112.9, 55.5; MS: 184 (M^+), 154, 141, 115.

2-Methoxybiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57-7.59 (d, 2H); 7.43-7.47 (t, 2H); 7.34-7.38 (t, 3H); 7.09-7.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 138.8, 131.2, 131.0, 129.8, 128.9, 128.2, 127.2, 121.1, 111.6, 55.8; MS: 184 (M^+), 169, 141, 115.

2-Methylbiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47-7.25 (m, 9H); 2.32-2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.3, 142.2, 135.6, 130.6, 130.0, 129.4, 128.3, 127.5, 127.0, 126.0, 20.7; MS: 168 (M^+), 165, 153.

3-Phenylpyridine: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85-8.84 (m, 1H); 8.58-8.57 (m, 1H); 7.86-7.83 (m, 1H); 7.57-7.55 (m, 2H); 7.48-7.44 (m, 2H); 7.41-7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.6, 148.5, 138.0, 136.9, 134.6, 129.3, 128.3, 127.4, 123.8; MS: 155 (M^+).

1-Phenylnaphthalene: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99-7.91 (m, 3H); 7.6-7.47 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.1, 140.6, 134.1, 131.9, 130.4, 128.5, 127.9, 127.5, 127.2, 126.3, 126.3, 126.0, 125.7; MS: 204 (M^+), 101.

2-Phenylnaphthalene: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11-8.10 (s, 1H); 7.97-7.91 (m, 3H); 7.82-7.77 (m, 3H); 7.58-7.51 (m; 4H); 7.46-7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.4, 138.9, 134.0, 132.9, 129.1, 128.7, 128.5, 127.9, 127.7, 127.6, 126.6, 126.2, 126.1, 125.9; MS: 204 (M^+), 101.

4-Acetyl-4’-methoxybiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01-7.99 (m, 2H); 7.65-7.56 (m, 4H); 7.01-6.98 (m, 2H); 3.86-3.83 (s, 3H); 2.62-2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.9, 160.2, 145.6, 135.6, 132.5, 129.2, 128.6, 126.8, 114.7, 55.6, 26.8; MS: 226 (M^+), 211, 183, 168, 152, 139.

2-Acetylbiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57-7.49 (m, 4H); 7.45-7.38 (m, 3H); 7.37-7.33 (m, 2H); 2.01-1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.0, 141.2, 140.9, 140.8, 130.9, 130.5, 129.1, 128.9, 128.1, 127.7, 30.6; MS: 196 (M^+), 181, 152.

4-Methylbiphenyl: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.67-7.26 (m, 9H); 2.49-2.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.5, 138.7, 137.3, 129.8, 129.0, 127.3, 127.3, 21.4; MS: 168 (M^+), 152.

4-Phenylaniline: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.62-7.59 (d, 2H); 7.49-7.44 (m, 4H); 7.35-7.31 (m, 1H); 6.79-6.77 (m, 2H); 3.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 141.5, 131.8, 128.9, 128.3, 126.7, 126.5, 115.7; MS: 169 (M^+).

Table 4.1. Purification of coupling products by column chromatography.

Product	**Gradient Elution**	**Melting Point (°C)**	**Appearance**	**Purity %**
4-Acetylbiphenyl	Hexane/ethyl acetate (12:1)	119.2-121.2	white	>99
4-Methylbiphenyl	Hexane/ethyl acetate (12:1)	45.5-47.4	colorless	>99
4-Methoxybiphenyl	Hexane/ethyl acetate (16:1)	85.8-88.4	white	>99
4-Nitrobiphenyl	Hexane/CH_2Cl_2 (9:3)	112.6-115.1	yellow	99
4-Cyanobiphenyl	Hexane/CH_2Cl_2 (9:3)	86.4-88.8	white	>99
1-Phenylnaphthalane	Hexane/ethyl acetate (16:1)	oily	colorless	99
2-Phenylnaphthalane	Hexane/ethyl acetate (15:1)	101-102.1	white	>99
3-Acetylbiphenyl	Hexane/ethyl acetate (14:1)	oily	yellow	>99
2-Methoxybiphenyl	Hexane/ethyl acetate (14:1)	oily	colorless	>99
3-Methoxybiphenyl	Hexane/ethyl acetate (16:1)	oily	light yellow	98
4-Phenylbenzaldehyde	Hexane/ethyl acetate (13:1)	59.6-61.3	white	>99
2-Methylbiphenyl	Hexane/ethyl acetate (17:1)	oily	colorless	99
3-Phenylpyridine	Hexane/ethyl acetate (7:1)	oily	light yellow	97
2-Acetylbiphenyl	Hexane/ethyl acetate (12:1)	oily	light yellow	98
4-Phenylaniline	Hexane/ethyl acetate (1:4)	52.6-55.9	orange	98

4.5. Leaching Test

After the reaction, catalyst was removed from reaction medium by filtration. The filtrate was concentrated by evaporating organic solvent. The filtrate was digested in the presence of H_2O_2 (Merck, 99%) and HNO_3 (conc.). The filtrate was diluted to (1/50) and analyzed by The Inductively Coupled Plasma Mass Spectrometry (ICP-MS). (Standard solutions were prepared as 1, 2, 4, 8, 10, 20 ppb from standard stock solution).

CHAPTER 5

RESULTS AND DISCUSSIONS

In this thesis, activity of $Pd(NH_3)_4^{2+}$-loaded NaY was investigated for Suzuki reactions at low Pd concentrations.

The $Pd(NH_3)_4^{2+}$-loaded NaY type zeolite showed high activity in the Suzuki cross-coupling reactions of less expensive aryl chlorides and bromides at low palladium concentrations in air and within very short reaction time. Turnover frequencies (TOF) and turnover number (TON) limits of the catalyst were also investigated.

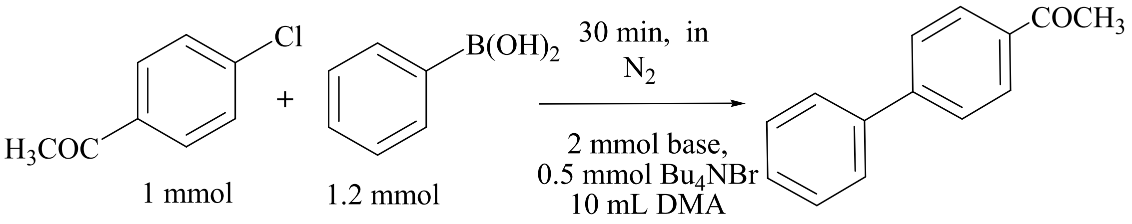
5.1. The Suzuki Reactions of Aryl Chlorides

5.1.1. Pd-NaY Catalyzed Suzuki Reaction of 4-Chloroacetophenone with Phenylboronic Acid

At the beginning of our study, optimization was performed for Suzuki reaction of 4-chloroacetophenone with phenylboronic acid over $Pd(NH_3)_4^{+2}$ modified zeolite containing 0.68% Pd (0.064 mmol Pd/g NaY zeolite) under an inert atmosphere. The zeolite content of the reaction medium was brought to 1 g upon addition of NaY zeolite in an as-received form.

In the course of optimization, the effect of tetrabutylammonium bromide (TBAB) additive and temperature was first investigated using Na_2CO_3 as a base in *N,N*-dimethylacetamide (DMA). Product formation was increased from 36% to 46% by addition of 0.5 equivalent Bu_4NBr into reaction medium at 140 ^{o}C under inert atmosphere (Table 5.1, entry1-2). Under this condition, it was observed that increasing the water content (DMA: water ratio of 9:1) lowered the yield to 14 % (entry 3). No activity was observed when the ratio was 1:1. A higher yield (57%) and conversions were obtained at 160 °C in the presence of Bu_4NBr (Table 5.1, entry 4).

Table 5.1. The effect of additive, temperature and DMA: water ratio on Pd-NaY catalyzed Suzuki reaction of 4-chloroacetophenone over the Pd concentration of 0.68%[a]



Entry	***T* (°C)**	**Bu_4NBr**	**Conversion%[b]**	**Yield%[b]**
1	140	-	49	36
2	140	+	54	46
3[c]	140	+	20	14
4	160	+	70	57

[a] $PhB(OH)_2$ was supplied from Aldrich. [b] GC yield. [c] Performed in a sealed glass reactor and in a DMA/water solvent mixture (9:1).

Under the defined conditions (Table 5.1, entry 4), the effect of base type on the reaction efficiency was also screened. Table 5.2. shows that alkoxides (entries 5-7) are more effective than the carbonates (entries 1-3), K_3PO_4 (entry 4) and hydroxides (entries 8-10). As a result, $NaOC_2H_5$ was chosen as optimal base for activation of Suzuki reaction (Table 5.2, entry 5).

Table 5.2. The effect of base on Pd-NaY catalyzed Suzuki reaction of 4-chloroacetophenone

Entry	**Base**	**Conversion%**[a]	**Yield%**[a]
1	Na_2CO_3	70	57
2	K_2CO_3	69	53
3	Cs_2CO_3	50	35
4	K_3PO_4	76	64
5	$NaOC_2H_5$	95	82
6	$NaOC(CH_3)_3$	96	81
7	$KOC(CH_3)_3$	93	79
8	NaOH	42	29
9	KOH	67	37
10	$Ca(OH)_2$	47	40

[a] GC yield.

All the experiments described above were performed with phenylboronic acid reagent from Aldrich (cat# P2,000-9). However it was determined that the reaction efficiency was influenced depending on the source of phenylboronic acid. While product formation was lower when a Fluka sample (cat# 78181) was used (Table 5.3, entry 2), Merck reagent (cat# 820131) has been found to be most effective (Table 5.3, entry 3). We have no brief explanation for the effects of phenylboronic acid reagents. However, reagents may have different types of impurities that may influence the activity of the catalyst in different extent. Under the established conditions, the reaction was repeated in the absence of Bu_4NBr to understand whether it is needed or not (Table 5.3, entry 4). That lower yield was obtained in the absence of the salt concludes that the addition of bromide salt is essential for the reaction.

Table 5.3. The effect of phenylboronic acid reagent on Pd-NaY catalyzed Suzuki reaction of 4-chloroacetophenone[a]

Entry	**$PhB(OH)_2$**	**Conversion%[b]**	**Yield%[b]**
1	Aldrich	95	82
2	Fluka	87	75
3	Merck	100	90
4[c]	Merck	82	64

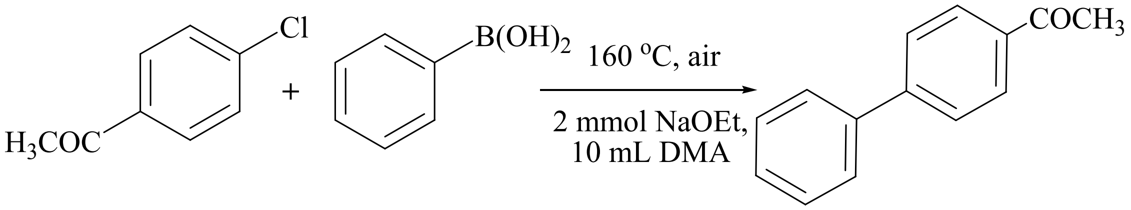
[a] $NaOC_2H_5$ was used as base. [b] GC yield. [c] In the absence of Bu_4NBr.

We tried to lower Pd concentration under the optimized reaction condition (i.e., 2 equiv. NaOEt, 1.2 equiv. $PhB(OH)_2$ (Merck), 0.5 equiv. Bu_4NBr, 160°C, in N_2). It was found that reduction of the catalyst loading from 0.68 to 0.1mol % Pd (0.018 mmol Pd/g NaY zeolite) lowered the yield of the Suzuki product (Table 5.4, entry 1). Interestingly, changing atmosphere condition from N_2 to ambient atmosphere improved the coupling yield (Table 5.4, entry 2).

It was reported recently that a Pd-NaY catalyst displayed higher activity in Mizoroki-Heck reaction under O_2 atmosphere. The promotive effect of O_2 was ascribed to the reduced propensity of Pd to agglomerate inactive Pd clusters by keeping most of its fraction in Pd(II) state. This may also account for the promotive effect of air. In our case, however, O_2 atmosphere turned out to be highly detrimental for the reaction.

Since the addition of tetraalkylammonium salts enhanced the rate of the coupling reaction, tetrabutylammonium salts of chloride and iodide were also screened under defined conditions (Table 5.4, entries 3-5). Among salts tested, the best result was obtained by using bromide salt (entry 4). Increasing the amount of Bu_4NBr and $PhB(OH)_2$ to 1 and 2 molar equivalents, respectively, gave the yield of desired product at 0.1% Pd concentration (Table 5.4, entries 4, 6). It is worth noting that only 5 minutes of reaction period was sufficient to achieve 90 % of coupling product (Table 5.4, entry 7).

Table 5.4. The Optimization of Pd-NaY catalyzed Suzuki reaction of 4-chloroacetophenone over the Pd concentration of 0.1%



Entry	Additive (mmol)	Boronic acid (mmol)	t (min)	Conv.%	Yield%[a]
1[b]	Bu_4NBr (0.5)	1.2[c]	15	38	32
2	Bu_4NBr (0.5)	1.2[c]	15	74	67
3	Bu_4NCl (0.5)	1.2[c]	15	44	36
4	Bu_4NBr (1)	1.2[c]	15	100	80
5	Bu_4NI (1)	1.2[c]	15	97	74
6	Bu_4NBr (1)	2.0[c]	15	100	92
7	Bu_4NBr (1)	2.0[c]	5	100	90
8	NaBr (1)	2.0[c]	5	57	51
9	KBr (1)	2.0[c]	5	64	46
10	LiBr (1)	2.0[c]	5	100	64
11	LiBr(1)+Bu_3N (1)	2.0[c]	5	100	64
12	Bu_4NBr (1)	2.0[d]	5	100	89
13	Bu_4NBr (1)	2.0[e]	5	97	80

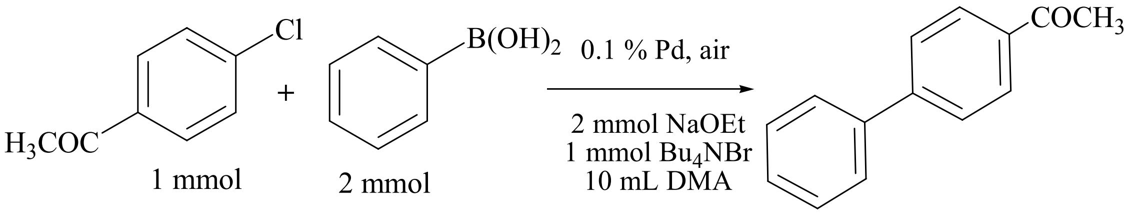
[a] GC yield. [b] In N_2. [c] Merck reagent. [d] Aldrich reagent. [e] Fluka reagent.

The addition of NaBr, KBr, or LiBr instead of tetrabutylammonium salts appeared to be the least effective for the reaction (Table 5.4, entries 8-10). It was noticed that Bu_4NBr underwent decomposition to yield Bu_3N in the course of Suzuki reactions possibly via Hofmann elimination. However, the presence of a Bu_3N secondary product seems to have no effect on the reaction process (compare entries 10, 11). $PhB(OH)_2$ of different sources was tested again under the improved reaction conditions which were applied in the case of entry 7. The result from the Aldrich product was comparable with that obtained with Merck's whereas the reagent from Fluka resulted about 10% lower yield (Table 5.4, entries 12, 13).

To understand the role of the zeolite itself in reactions (i.e., whether it plays an active role), the reaction was performed with only ~60 mg of Pd-loaded zeolite in the absence of extra amount of zeolite. Surprisingly, no product formation was observed (Table 5.5, entry 1). Moreover, when the zeolite additive which was vacuum dried at 140 °C for 2 h prior to the reaction (Table 5.5, entry 2) was used, the catalyst displayed no activity. As a result of these data, we concluded that the intrinsic water content of the zeolite (which was measured to be around 23% based on the weight loss during vacuum drying at 140 °C for 2 h) was crucial for the activity of the system. When 230 mg of water (which is equal to the amount of water that would be introduced by the addition of 1 g of NaY zeolite in as-received form) was added into reaction medium without the zeolite additive, a moderate product formation (61%) was observed (Table 5.5, entry 3), indicating that the reaction can operate only in moist medium and, suggesting the existence of a synergism between water and zeolite combination.

Also, the effect of zeolite amount (in as-received form) was examined at 140 ºC (Table 5.5, entries 4-7). The yield formation was modest (48%) when the reaction was carried out with an overall zeolite amount of 1 g for 5 min (Table 5.5, entry 4). About 3 to 4 grams of the zeolite seemed to be required for the optimum product recovery (compare entries 5-7) and the reaction proceeded smoothly even at a lower reaction temperature of 120 ºC to give 88% coupling product after 15 min (Table 5.5, entry 8). Four grams of NaY zeolite would introduce nearly 1 g of water into the reaction medium. Therefore, a reaction was conducted in the presence of 1 g of zeolite along with 1 g of added water in order to clarify if the yield improvement was solely due to the increased water amount in the system. The yield was identical to that obtained in the experiment performed with 1 g original zeolite alone (Table 5.5, compare entries 4, 9).

Table 5.5. Effect of zeolite and water additives on the reaction efficiency



Entry	Zeolite (g)	Water (g)	*T* (°C)	*t* (min)	Conv.%	Yield%[a]
1	0.06	-	160	60	17	< 1
2[b]	1	-	160	60	18	< 1
3	0.06	0.23	160	5	70	61
4	1	-	140	5	63	48
5	2	-	140	10	87	75
6	3	-	140	5	100	90
7	4	-	140	5	94	91
8	3	-	120	15	94	88
9[c]	1	1	140	5	60	49
10[d]	1	3	140	45	95	2

[a] GC yield. [b] Dried under vacuum at 140 °C for 2 h. [c] With 9 mL of DMA. [d] With 7 mL of DMA.

Moreover, the presence of a larger amount of water (with DMA: water ratio of 7:3) completely destroyed the activity of the catalyst (Table 5.5, entry 10). These results clearly show that improvement gained by introducing higher amount of original zeolite is not solely due to the increased amount of water within the reaction medium, but rather due to synergistic effect in the zeolite-water system.

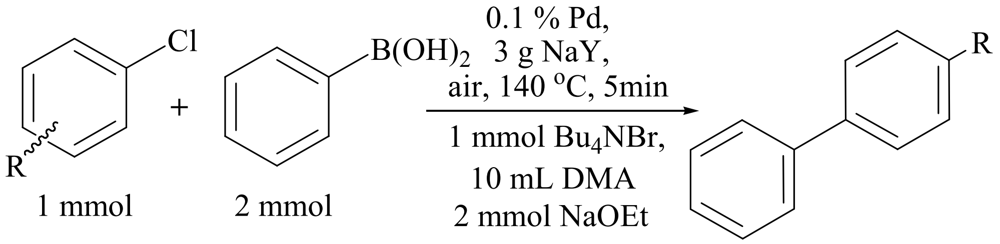
The underlying reasons for the observed synergism seem to be complicated. However, the fact remains that the presence of little amount of water was crucial for the activation of the reaction system. The presence of excess amounts of zeolite in the reaction medium might have retarded the transformation of Pd to inactive Pd agglomerates during dissolution/re-precipitation processes on the zeolite surface and water from the zeolite will be released in a timely and localized manner (slowly) since it is in the pores, whereas water alone (without added zeolite) reacts in an uncontrolled way.

In order to check whether the coupling reactions were catalyzed heterogeneously or not, the reaction was carried out with addition of 30,000 molar equivalent of an insoluble cross-linked poly(vinyl pyridine) polymer (PVPy) under optimized condition. After 4 h of reaction, only 20% coupling product was obtained, indicating that PVPy greatly reduced the activity of the catalyst by strongly coordinating the soluble Pd(II) species while remaining inert towards the solid Pd. Therefore, if the reaction was performed by heterogeneous catalyst, no change in the reaction progress should be expected. Consequently, the coupling reactions were proven to be catalyzed by the dissolved Pd species leached from the Pd-NaY catalyst.

5.1.2. $Pd(NH_3)_4^{2+}$-loaded NaY type Zeolite Catalyzed Suzuki Cross-Coupling Reaction of Aryl Chlorides

The Suzuki reaction of variety aryl halides with $PhB(OH)_2$ were investigated under the optimal conditions determined (2 equiv. of $PhB(OH)_2$, 2 equiv. sodium ethoxide, 1 equiv. Bu_4NBr, 3g NaY zeolite and, for 5 minutes, under aerobic conditions). The results obtained with activated aryl chlorides were quite good at 140 °C (Table 5.6). However, at 120 °C, the catalyst reserved its high activity on reactions of 4-chloroacetophenone and 4-nitrobenzene (entry 1, 4). On the other hand, moderate yields were obtained for other *p*-substituted chloroarenes (entry 2, 3). The result was not satisfactory in the case of 2-substituted aryl chlorides (entry 5).

Table 5.6. $Pd(NH_3)_4^{2+}$-loaded NaY type zeolite catalyzed Suzuki cross-coupling reaction of aryl chlorides



Entry	R	140°C		120°C	
		Isolated Yield%	**TOF h^{-1b}**	**Yield%^{a}**	**TOF h^{-1b}**
1	4-$COCH_3$	86	10,320	90	1,205
2	4-CHO	78	9,360	40	400
3	4-CN	90	10,800	56	562
4	4-NO_2	92	11,040	95	949
5	2-$COCH_3$	80	9,600	22	217

[a] GC yield. [b]TOF = TON/h, TON = [yield]/[Pd].

5.1.3. The Leaching Test for Suzuki Reaction of Aryl Chlorides

The Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analyses revealed Pd concentration was only <0.8 ppm (0.01% loss based on the initial Pd quantity) within the filtrates after the reactions since zeolite also acted as a very affective scavenger for the dissolved Pd species, eliminating the need for post-reaction removal for Pd.

5.2. The Suzuki Reactions of Aryl Bromides

We also performed the Suzuki reaction of aryl bromides at very low catalyst concentrations in an aqueous solvent.

5.2.1. The Optimization of $Pd(NH_3)_4^{2+}$-Loaded NaY Type Zeolite Catalyzed Suzuki Reactions of 4-Bromoanisole with Phenylboronic Acid

Initially, 4-bromoanisole (a deactivated aryl bromide) was chosen as the main test substrate as it is usually difficult to be activated in cross-coupling reactions. To determine the optimal conditions at 0.005% Pd concentration, various conditions on the Suzuki reaction were examined.

In previous studies, Pd-NaY zeolite displayed high activity for aryl bromides by using Na_2CO_3 as base in *N,N*-dimethylformamide (DMF)/water (1:1) solvent mixture at room temperature (Artok and Bulut 2004, Bulut et al. 2003). At the beginning our study for optimatization, we performed experiments under these optimized reaction conditions.

In the Suzuki reactions experiments of aryl chlorides, we have observed phenylboronic acid reagents affected efficiency of the reaction and the Fluka reagent was the worst among them. In case of aryl bromides, different results were obtained. While the catalyst showed high activity in the presence of phenylboronic acid from Fluka (cat# 78181), the lowest product formation was obtained by using Aldrich reagent (cat# P2,000-9) (Table 5.7, entries 1, 2). We decided to use Fluka reagent of phenylboronic acid during optimization of reaction conditions.

Artok and Bulut observed that the Pd-NaY showed either no or poor activity in the presence of bases such as sodium acetate, potassium phosphate, sodium fluoride etc. while carbonates bases worked best. They concluded that efficiency of reaction didn't depend on basicity of bases (Artok and Bulut 2004, Bulut et al. 2003). That's why, we screened only inexpensive carbonate bases and among them, Na_2CO_3 was found to be effective (Table 5.7, entry 2). Moderate yields were obtained in the presence of Cs_2CO_3 and K_2CO_3 (entry 3, 4).

The type of other organic co-solvent was investigated in the organic solvent-water mixture in the ratio of 1:1. *N,N*-dimethylacetamide (DMA) resulted in the highest product formation (entry 6), while the use of *N*-methylpyrolidone (NMP) with water gave a slightly lower coupled product yield (entry 5). It was reported by Artok and Bulut that amides acted as ligands to activate the palladium species. In the view of these results, DMA was chosen as organic solvent.

Another crucial factor for the efficiency of their action was the DMA/water ratio. It is apparent that the reaction is tolerable to one higher ratio DMA/water (Table 5.7, entries 7, 8). However, the ratio of 1/1 was the optimum for the reaction (entry 6).

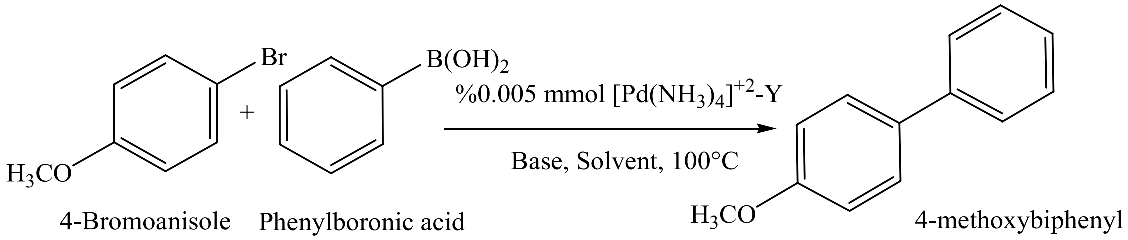
It was observed in the Suzuki reaction of aryl chlorides that extra amount of zeolite increased product formation. The reaction was performed with the addition of 1g of zeolite in as-received form under defined final conditions and 1g of zeolite was useful for the product formation under inert atmosphere (Table 5.7, entry 10).

All the experiments mentioned above were conducted under inert atmosphere. When the reaction was carried out under air, the catalyst also successfully activated the reaction, resulting in the highest yield of 4-methoxybiphenyl as coupling product (Table 5.7, entry 11).

To control whether the addition of extra amount of zeolite was useful or not under final conditions (Na_2CO_3 , DMA/H_2O(1:1), under air, at 100 °C), we performed reaction without extra amount of zeolite, resulting slightly lower product formation (Table 5.7, entry 12). It was indicated that there was useful effects of zeolite for Suzuki reactions.

Under optimized conditions, we tested effect of phenylboronic acid reagent from Merck (cat # 820131). The yield and reaction time were nearly same with that of Fluka reagent (Table 5.7, entry 13). However, we also observed that the Suzuki reaction of 4-bromobenzonitrile was complete in shorter time when the Fluka reagent was used.

Table 5.7. The Optimization of Pd-NaY catalyzed Suzuki reaction of 4-bromoanisole over the Pd concentration of 0.005%[a]



Entry	Base	Solvent (Solvent/H_2O)	Conversion%[b]	Yield%[b]
1[c,d]	Na_2CO_3	DMF(1/1)	75	71
2[c]	Na_2CO_3	DMF(1/1)	87	86
3	Cs_2CO_3	DMF(1/1)	52	52
4	K_2CO_3	DMF(1/1)	62	62
5	Na_2CO_3	NMP(1/1)	81	81
6	Na_2CO_3	DMA(1/1)	96	89
7	Na_2CO_3	DMA(1/2)	82	82
8	Na_2CO_3	DMA(1/3)	74	74
9	Na_2CO_3	DMA(2/1)	63	63
10[e]	Na_2CO_3	DMA(1/1)	94	94
11 [e,f]	Na_2CO_3	DMA(1/1)	93	94 (92) [g]
12[f]	Na_2CO_3	DMA(1/1)	95	87
13[h]	Na_2CO_3	DMA(1/1)	96	91

[a] Typical reaction conditions: 10 mmol of 4-bromoanisole, 12 mmol of $PhB(OH)_2$ (Fluka), 0.005% Pd, 20mmol Na_2CO_3 , 20ml Solvent/H_2O, under inert atmosphere at 100 °C, 30min. [b] GC yield based on 4-bromoanisole. [c] 5 mmol 4-bromoanisole, 6mmol $PhB(OH)_2$, 10mmol Na_2CO_3, 10ml DMF/water(1/1) was used. [d] $PhB(OH)_2$ was supplied from Aldrich. [e] In the presence of zeolite (1g). [f] Open to the atmosphere. [g] Isolated yield. [h] $PhB(OH)_2$ was supplied from Merck.

We also tried to lower Pd concentration to 0.001% and performed reaction using the Merck reagent of phenylboronic acid under optimized conditions. However, the yield was very low (Table 5.8, entry 1). The use of 2 or 3 g of zeolite has no effect on the reaction (Table 5.8, entries 2, 3). Nevertheless, presence of 4 g zeolite in the reaction medium decreased product formation (Table 5. 8, entry 4). We also increased amount of phenylboronic acid reagent to 2 mmol in the presence of 1g extra amount of zeolite. The catalyst could not show activity (entry 5). Reaction was repeated in the presence of NaOEt (entry 6). We increased reaction temperature to 130 ºC (entry 7). They didn't work. Finally, moderate yield was obtained by using Fluka reagent (Table 5.8, entry 8). We concluded that Pd concentration of 0.005% was optimum in the presence of 1g of zeolite and Fluka reagent for Suzuki reactions of 4-bromoanisole.

Table 5.8. The Optimization of Pd-NaY catalyzed Suzuki reaction of 4-bromoanisole over the Pd concentration of 0.001 %[a]

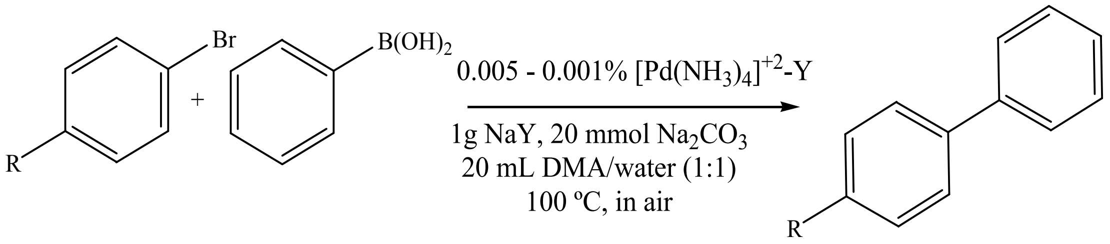
Entry	**Zeolite (g)**	**Ratio of $PhB(OH)_2$**	**Conversion%[b]**	**Yield%[b]**
1	1	1.2	49	33
2	2	1.2	55	33
3	3	1.2	68	31
4	4	1.2	18	18
5	1	2	20	14
6[c]	1	1.2	25	8
7[d]	1	1.2	41	14
8[e]	1	1.2	78	61

[a] Reaction conditions: 5mmol 4-bromoanisole, 6mmol $PhB(OH)_2$ (Merck), 10mmol Na_2CO_3, 10mL DMA: water (1:1) under air at 100 ºC. [b] GC yield. [c] NaOEt was used as base. [d] at 130 ºC. [e] $PhB(OH)_2$ was supplied from Fluka and amount of all reagents was increased by two.

5.2.2. $Pd(NH_3)_4^{2+}$-Loaded NaY Type Zeolite Catalyzed Suzuki Reactions of Aryl Bromides and ArylBoronic Acids

After optimization of reaction conditions, we investigated the substrate scope of the reaction for a range of aryl bromides with $PhB(OH)_2$ (Table 5.9).

Table 5.9. $Pd(NH_3)_4^{2+}$-loaded NaY type zeolite catalyzed Suzuki reaction of 4-substituted aryl bromides with arylboronic acid



Entry	**Aryl Halide**	**Isolated Yield%**	**Pd% (mmol)**	**Time (min)**	**TOF^{-1a}**	**TON^{a}**
1	$4\text{-}COCH_3C_6H_4Br$	95	0.005	15	76,000	19,000
2	$4\text{-}COCH_3C_6H_4Br$	97^b	0.001	30	194,000	97,000
3	$4\text{-}COCH_3C_6H_4Br$	30^b	0.0001	120	150,000	300,000
4	$4\text{-}NO_2C_6H_4Br$	97	0.001	30	194,000	97,000
5	$4\text{-}CNC_6H_4Br$	91	0.001	105	52,000	91,000
6	$4\text{-}CHOC_6H_4Br$	100	0.001	30	200,000	100,000
7	$4\text{-}OCH_3C_6H_4Br$	92	0.005	30	36,800	18,400
8	$4\text{-}CH_3C_6H_4Br$	93^b	0.005	15	74,400	18,600
9	$4\text{-}CH_3C_6H_4Br$	76^b	0.001	15	304,000	76,000
10	$4\text{-}NH_2C_6H_4Br$	94	0.005	45	25,067	18,800
11	C_6H_6Br	90^b	0.001	45	120,000	90,000
12^c	$4\text{-}COCH_3C_6H_4Br$	99	0.001	45	132,000	990,000

[a] TOF = TON/h, TON = [yield]/[Pd]. [b] GC yield. [c] 4-methoxyphenylboronic acid was used.

The optimization of reaction conditions was determined at the Pd concentration of 0.005%. In the case of the activated aryl bromides, we were able to perform the reaction even at 0.001% Pd (Table 5.9, entries 2, 4-6). Unfortunately, product formation was not good at much lower (0.0001%) Pd concentration (entry 3). However, the catalyst showed high activity for the reactions of the inactivated aryl bromides (Table 5.9, entries 7, 8, 10) and also nonactivated bromobenzene (entry 11) at 0.005% Pd and 0.001% of Pd concentrations, respectively. Moderate yield was obtained in the presence of 0.001% Pd concentration for 4-bromotoluene (entry 9). 4-Bromoacetophenone also revealed excellent reactivity towards the coupling reactions with 4-methoxy phenylboronic acid (Table 5.9, entry 12).

Meta- substituted aryl bromides were well tolerated by catalytic system, providing the corresponding coupled product in high yields in 15 minutes (Table 5.10, entries 1, 3). We observed that the uses of slightly higher catalyst amount was necessary for reaction of 2-bromoanisole to be completed (compare entries 4, 5). Coupling product of 2-bromotoluene was isolated in excellent yield at 0.01% Pd (entry 6). Moreover yield was also good at lower Pd concentration in 15 minutes (Table 5.10, entry 7).

Table 5.10. $Pd(NH_3)_4^{2+}$-loaded NaY type zeolite catalyzed Suzuki reaction of 3- and 2-substituted aryl bromides with arylboronic acid

Entry	**Aryl Halide**	**Isolated Yield%**	**Pd% (mmol)**	**Time (min)**	**TOF^{-1b}**	**TON^{b}**
1	3-$COCH_3C_6H_4Br$	96	0.005	15	76,800	19,200
2	3-$COCH_3C_6H_4Br$	57^{a}	0.001	110	31,091	57,000
3	3-$OCH_3C_6H_4Br$	95	0.005	15	76,000	19,000
4	2-$OCH_3C_6H_4Br$	91	0.01	30	18,200	9,100
5	2-$OCH_3C_6H_4$ Br	66^{a}	0.005	45	17,600	13,200
6	2-$CH_3C_6H_4$ Br	93	0.01	15	37,200	9,300
7	2-$CH_3C_6H_4$ Br	85^{a}	0.005	15	17,000	68,000
8	3-BrC_5H_4N	78	0.01	30	15,600	7,800
9	3-BrC_5H_4N	30^{a}	0.005	6^{c}	6,000	1,000
10	1-Bromonaphthalene	100	0.005	60	20,000	20,000
11	1-Bromonaphthalene	42^{a}	0.001	11.5^{c}	3,652	42,000
12	2-Bromonaphthalene	93	0.001	90	62,000	93,000

^{a} GC yield. ^{b}TOF = TON/h, TON = [yield]/[Pd]. ^{c} hour.

It is difficult to perform reactions of 3-bromopyridine as heteroaromatic since substrate can act as ligand to coordinate palladium. Furthermore, the Suzuki reaction of 3-bromopyridine with phenylboronic acid donated good yield at slightly higher palladium concentration (compare entries 8-9). While the coupling products of 2-bromonaphthalene (Table 5.10, entry 12) was also recovered in excellent yields at

0.001% Pd, reaction of 1-bromonaphthalene was carried out at 0.005% Pd concentrations due to steric effect (compare entries 10, 11).

5.2.3. The Leaching Test for the Suzuki Reactions of Aryl Bromides

The palladium leaching was investigated after the reaction. In view of the results obtained from the Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analyses, Pd concentration of filtrate were found only <0.02 ppm (wt 0.001% loss).

CHAPTER 6

CONCLUSIONS

In this thesis study, $Pd(NH_3)_4^{2+}$ ion was easily loaded into the NaY zeolite. Activity of catalyst was investigated over Suzuki coupling reactions of aryl bromides and chlorides.

The $Pd(NH_3)_4^{2+}$-loaded NaY zeolite was observed to activate the C-Cl bond of the electron poor aryl chlorides in Suzuki reactions at low Pd concentrations in air within minutes. The excess amounts of zeolite provided the necessary water for the reaction when employed in as-received form. The results pointed out to a synergistic effect due to use of the water-zeolite pair for the reaction. The underlying reasons for the observed synergism seem to be complicated. However, the fact remains that the presence of little amount of water was crucial for the activation of the reaction system. In addition to water effect, the presence of excess amounts of zeolite in the reaction medium had important roles. We thought that it might have retarded the transformation of Pd to inactive Pd agglomerates during dissolution/re-precipitation processes on the zeolite surface and water from the zeolite will be released in a timely and localized manner (slowly) since it is in the pores, whereas water alone (without added zeolite) reacts in an uncontrolled way.

Zeolite catalyst was also found highly active for Suzuki cross-coupling reactions of various bromoarenes with arylboronic acids without added ligands. The reactions were proceeded at very low Pd concentrations (0.01- 0.001% Pd). The presence of water was essential within the reaction medium.

In both reactions of aryl chlorides and bromides, the catalyst was stable in air. The commercial source of phenylboronic acid reagent was found to be highly effective for the catalyst activity. Probably, variation types of impurities had different effects on the catalyst activity.

It must also be noted that no dechlorination or self-coupling products were produced by the reactions performed under the established conditions.

In the view of our results, the coupling reactions were seemed to be catalyzed by the dissolved Pd species leached from the Pd-NaY catalyst. On the other hand, ICP-MS analyses revealed only <0.8 ppm amounts of Pd within the filtrates after the reactions since zeolite also acted as a very affective scavenger for the dissolved Pd species, eliminating the need for post-reaction removal for Pd.

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APPENDIX A

^{13}C AND ^{1}H NMR OF SUZUKI CROSS-COUPLING PRODUCTS

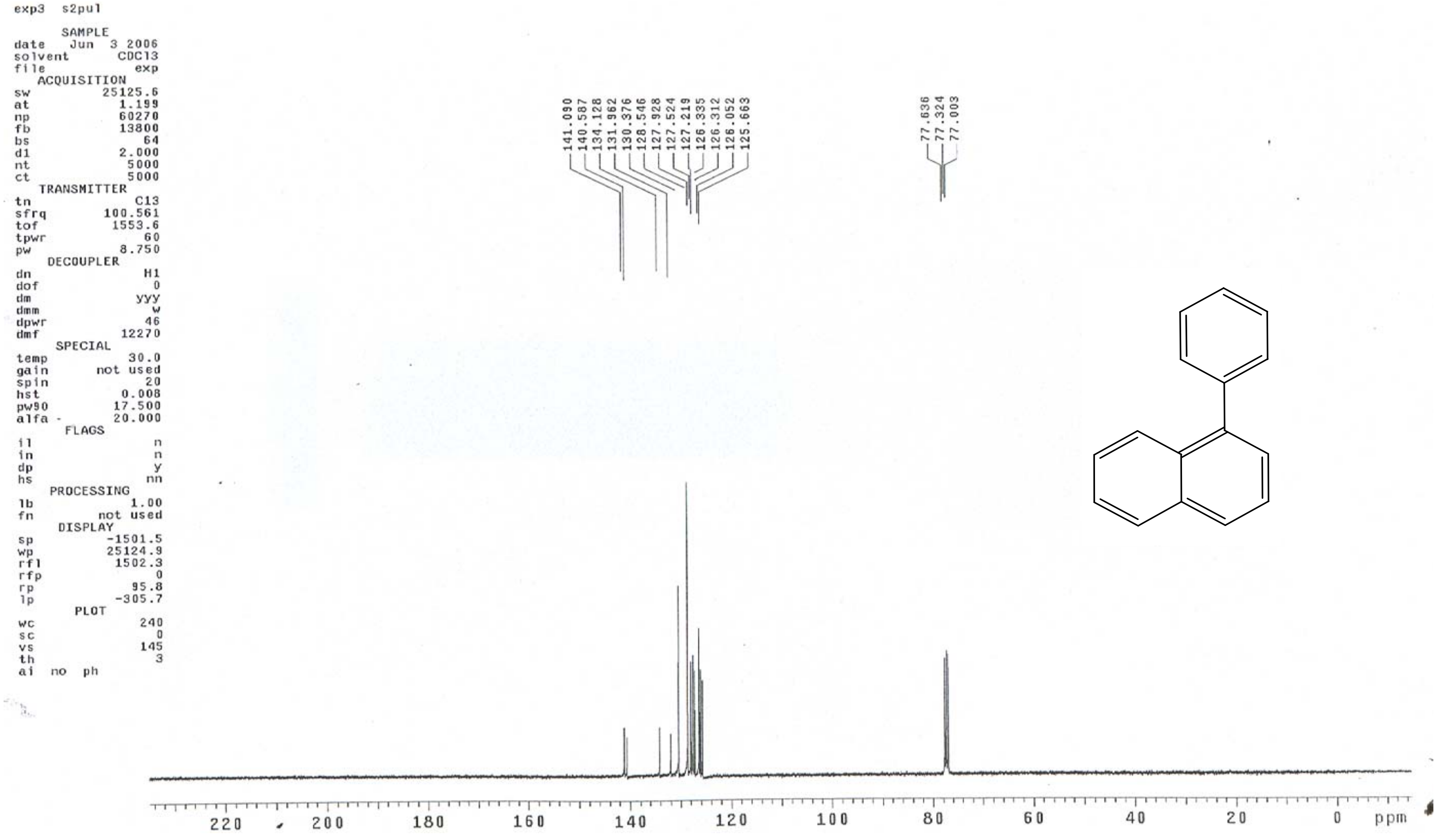
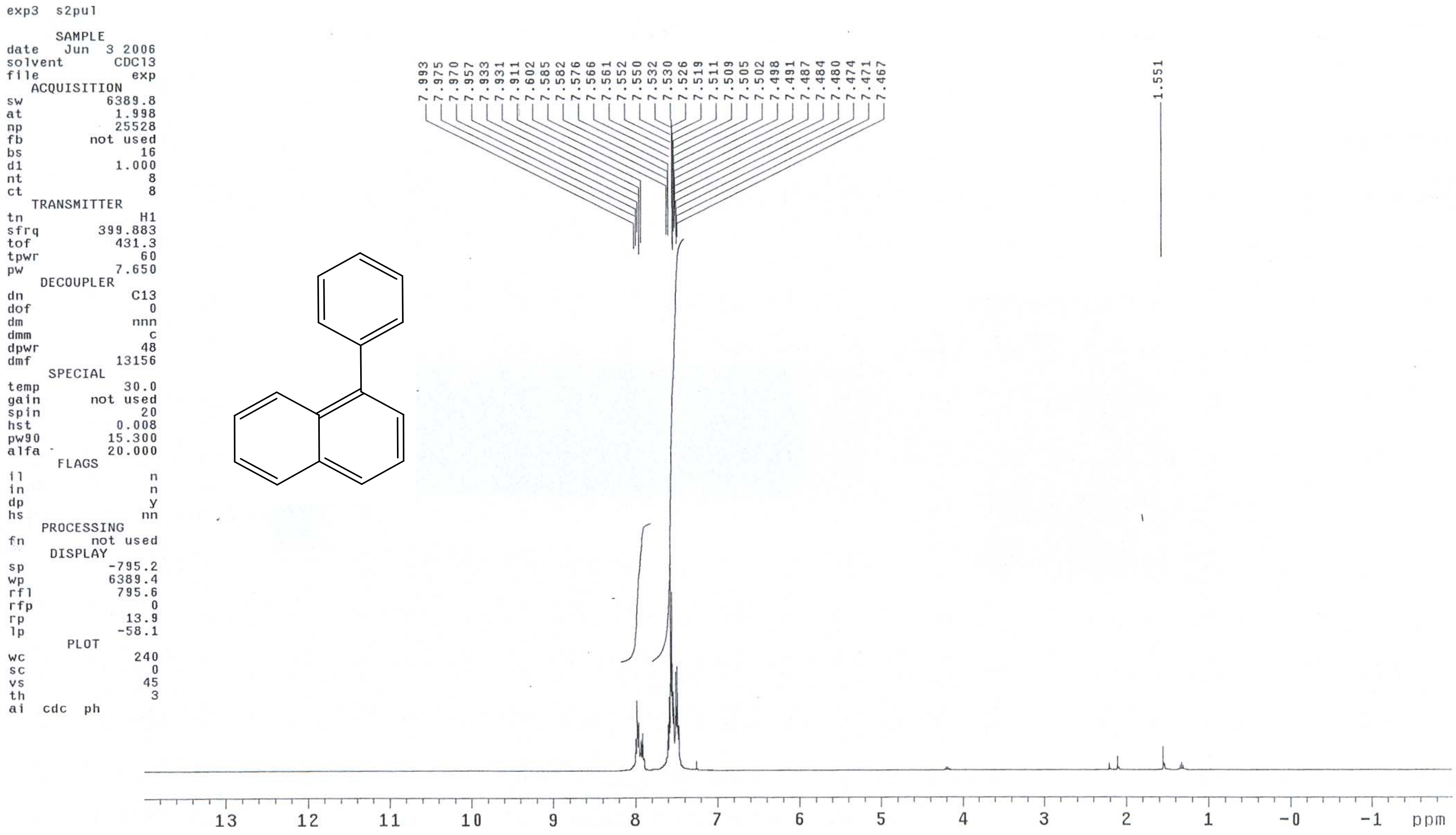


Figure A.1. ^{13}C NMR of 1-phenylnaphthalene



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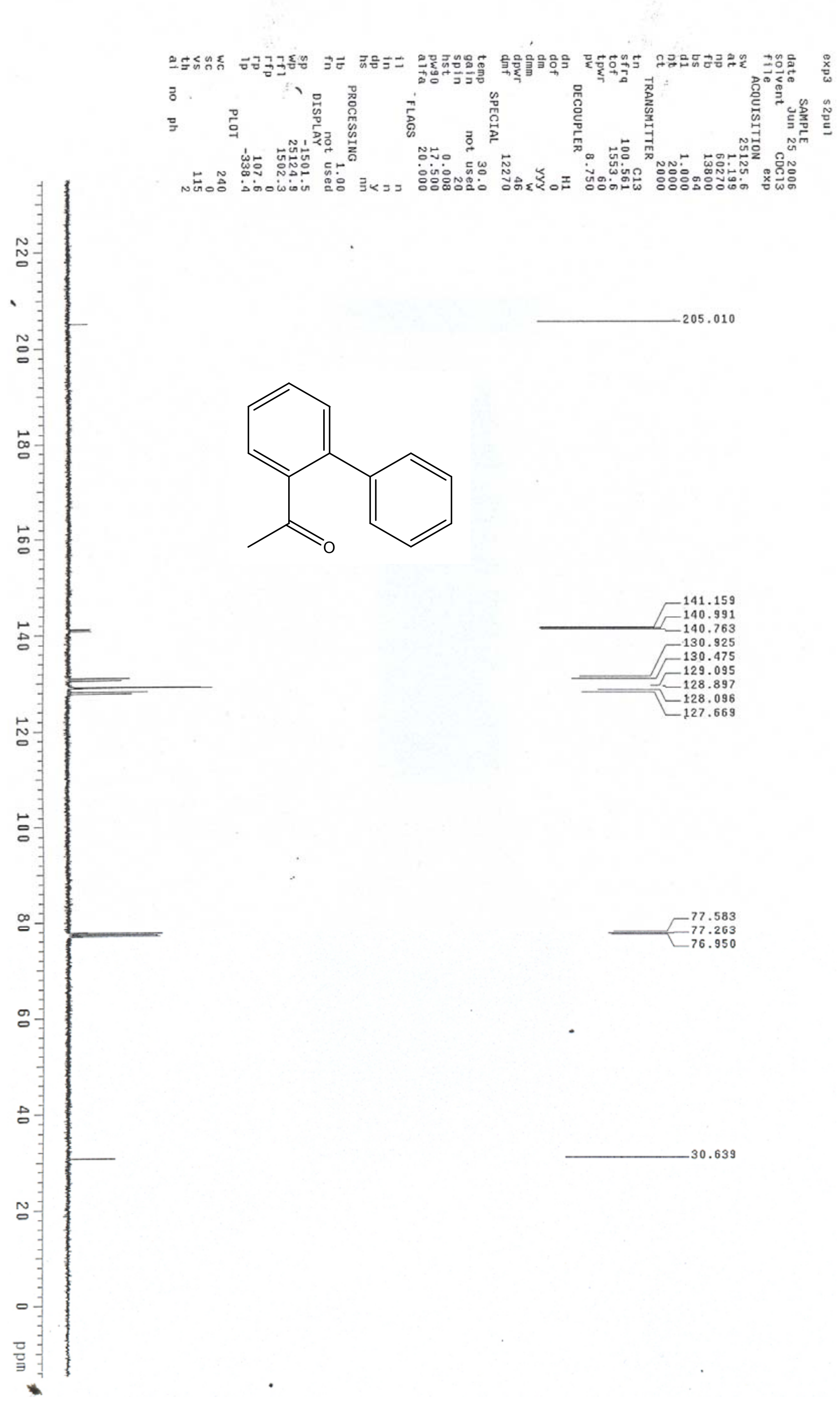

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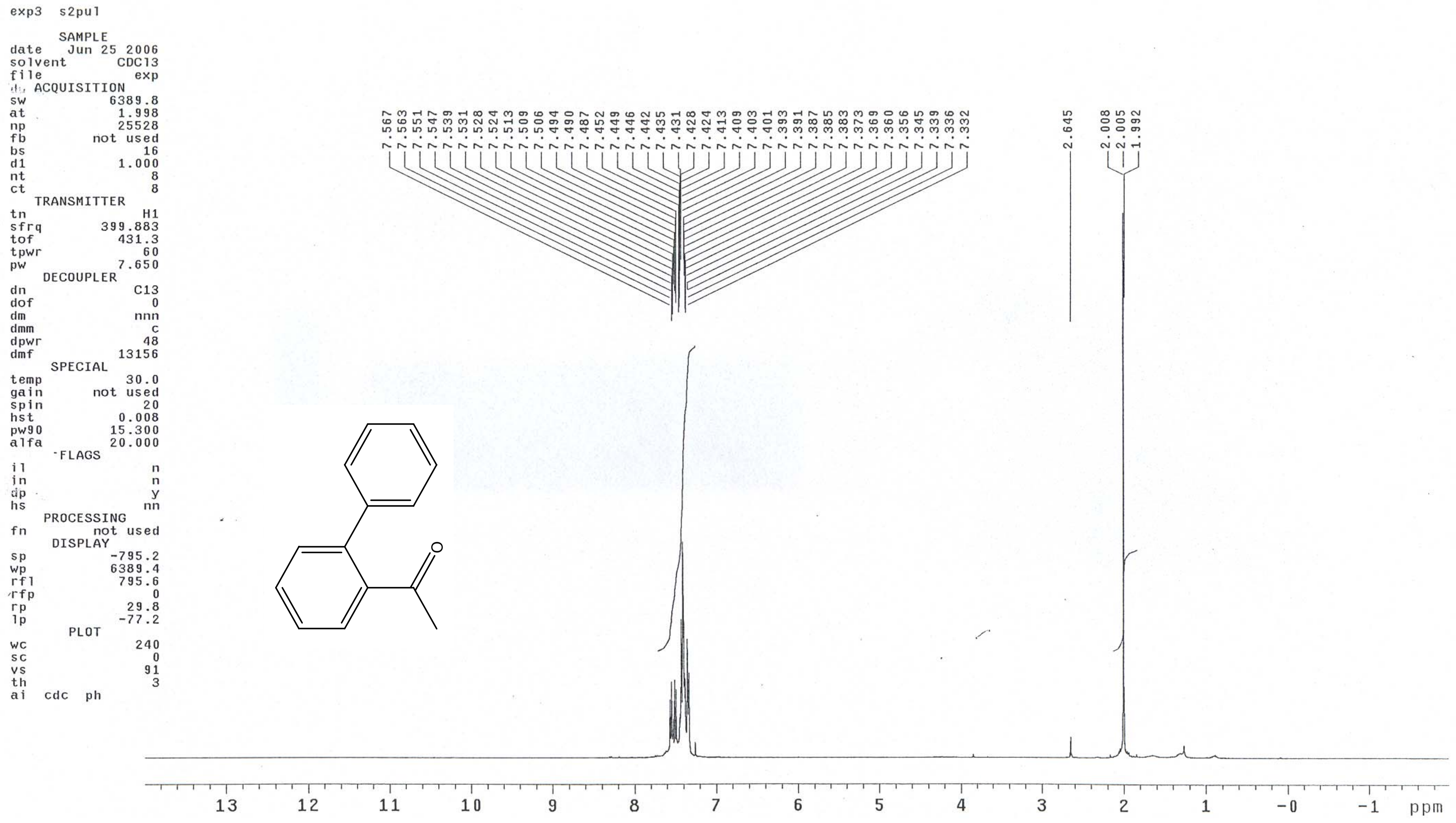

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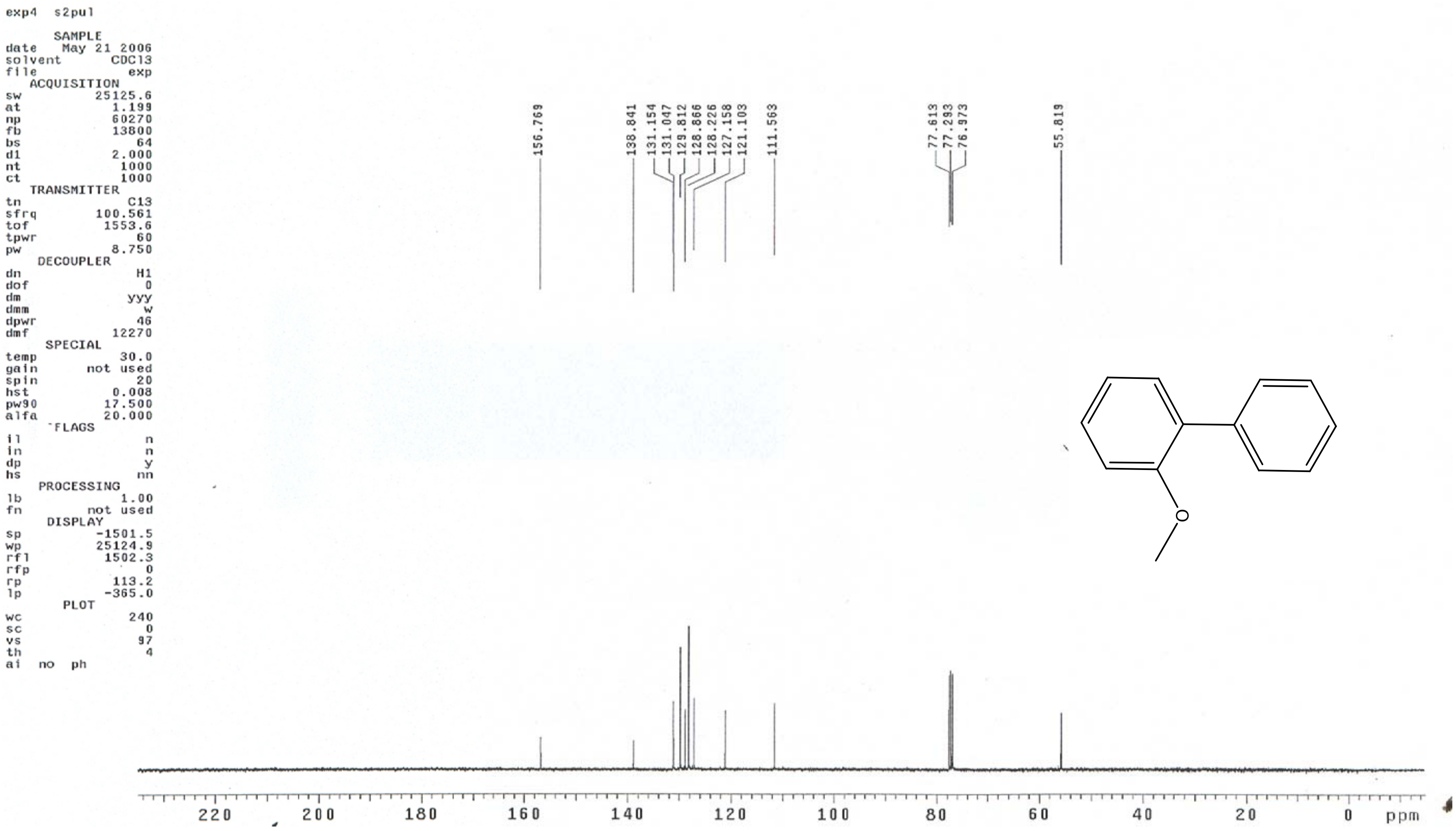

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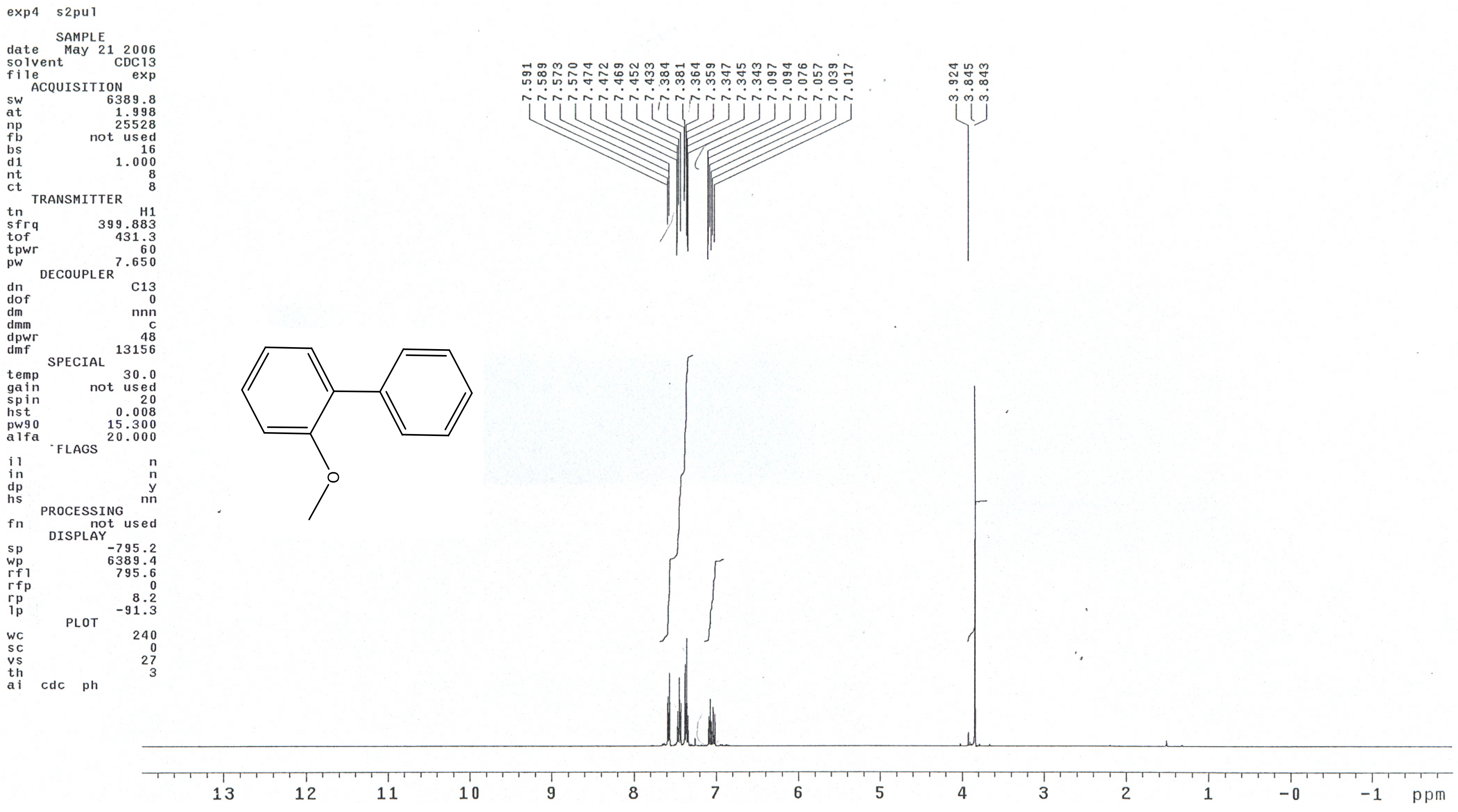

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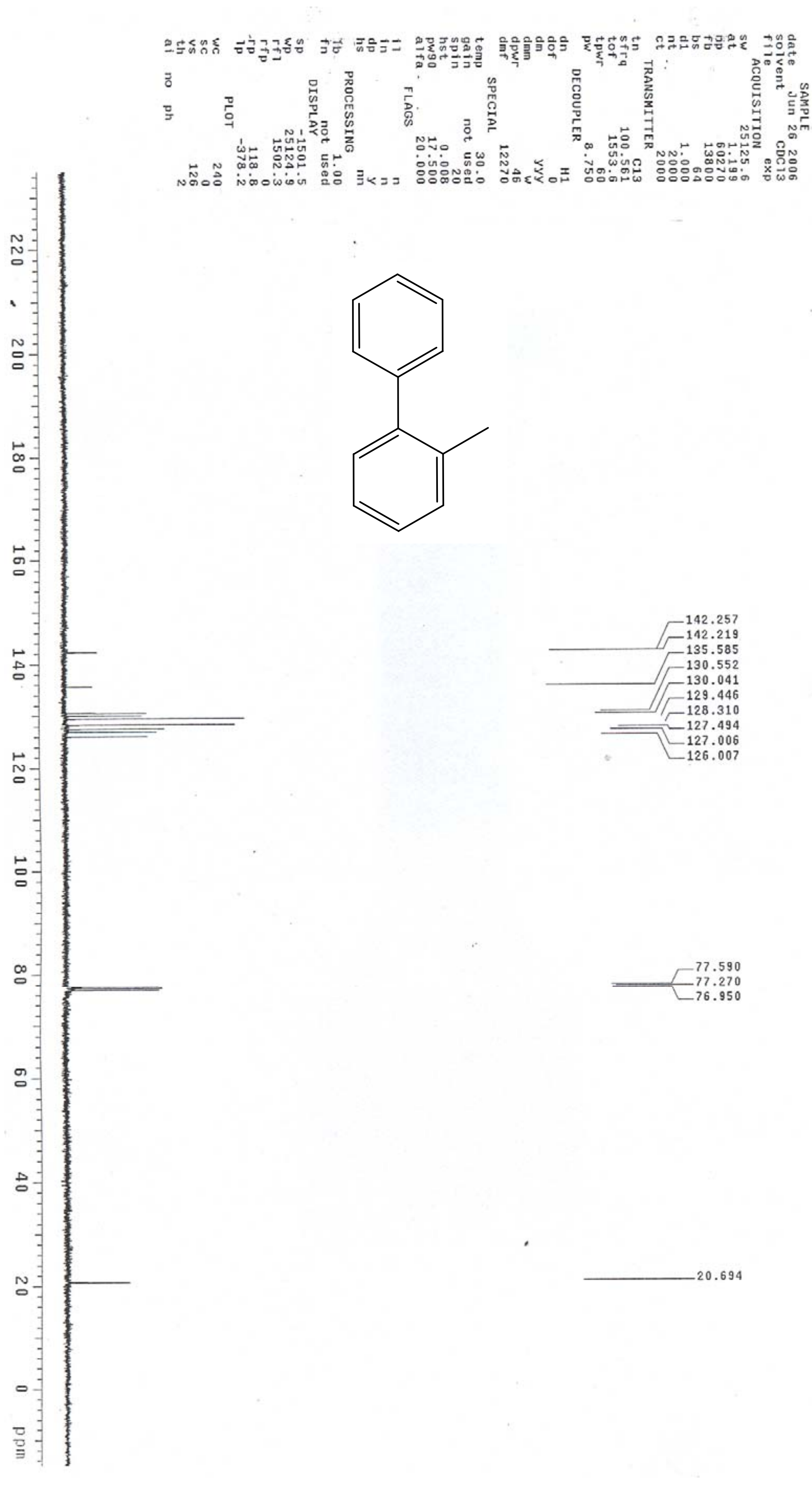

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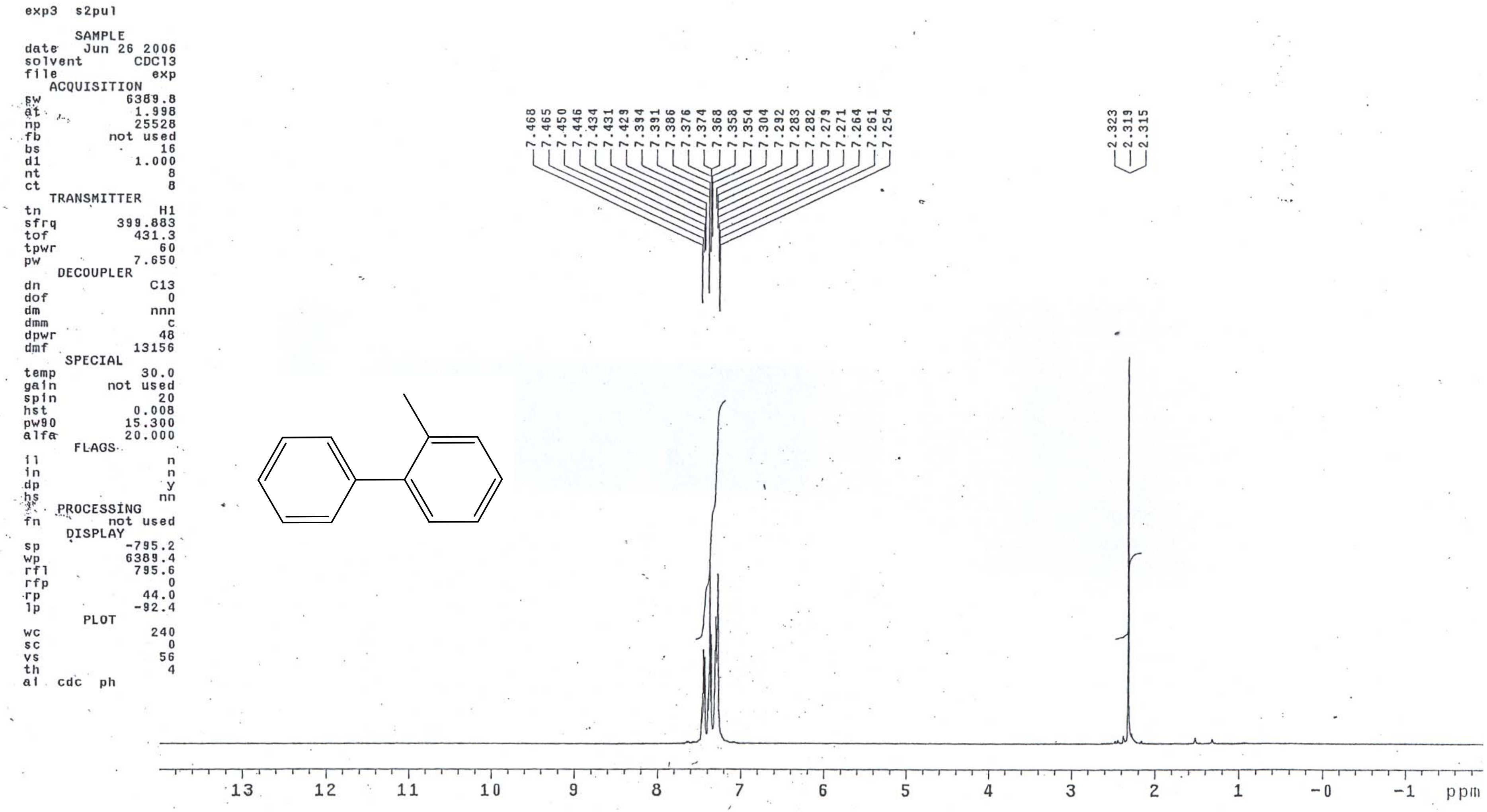

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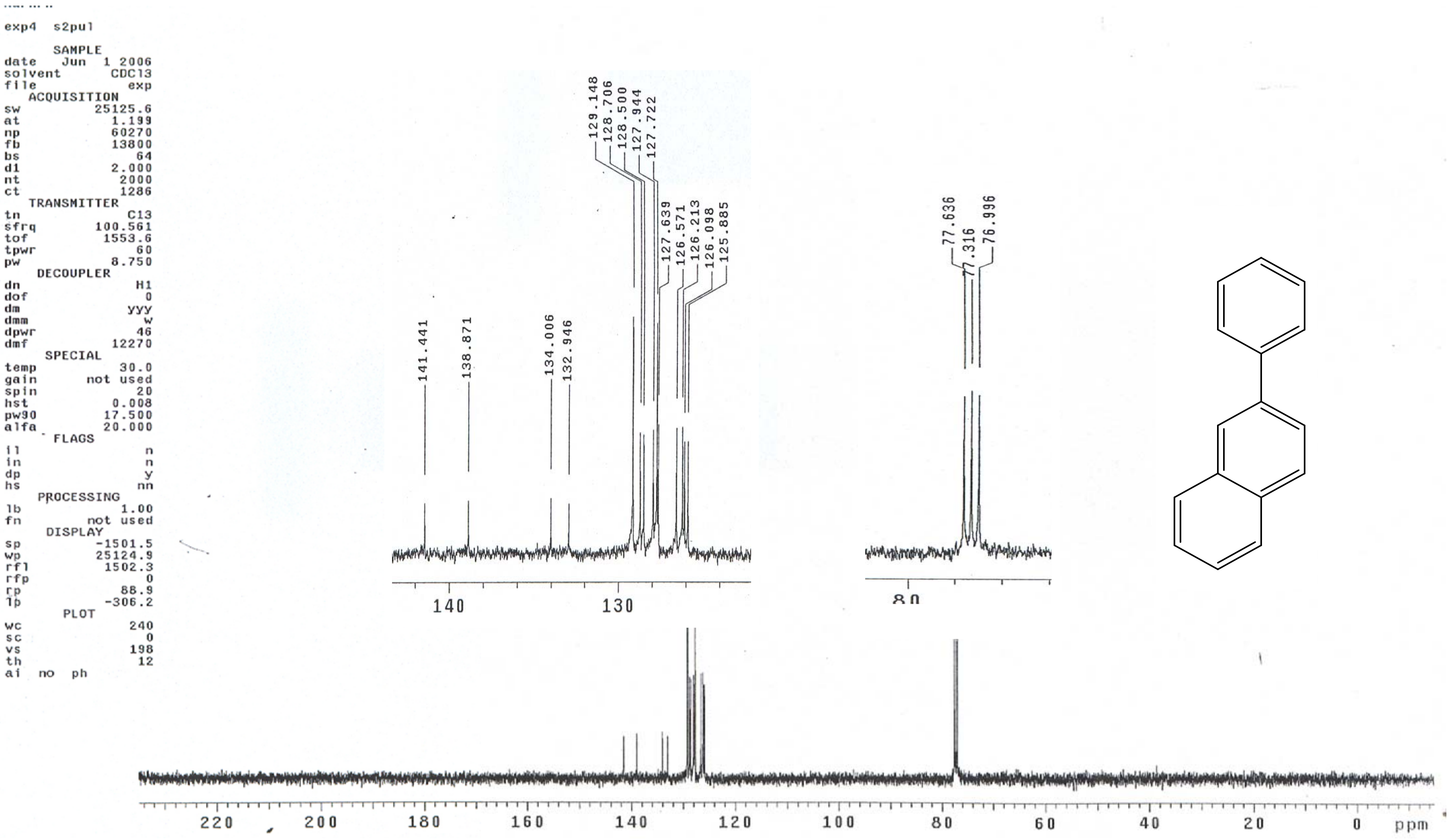

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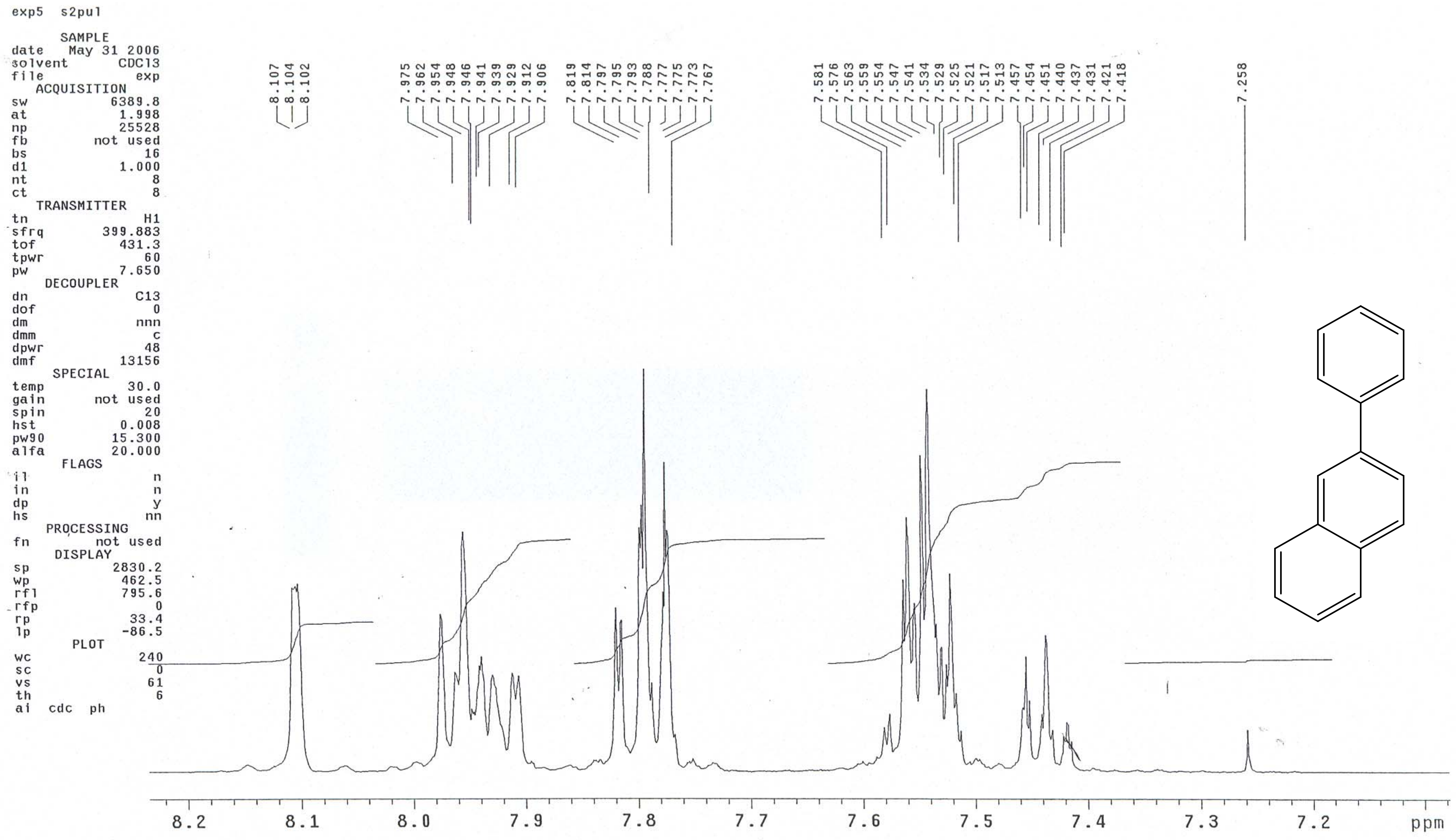

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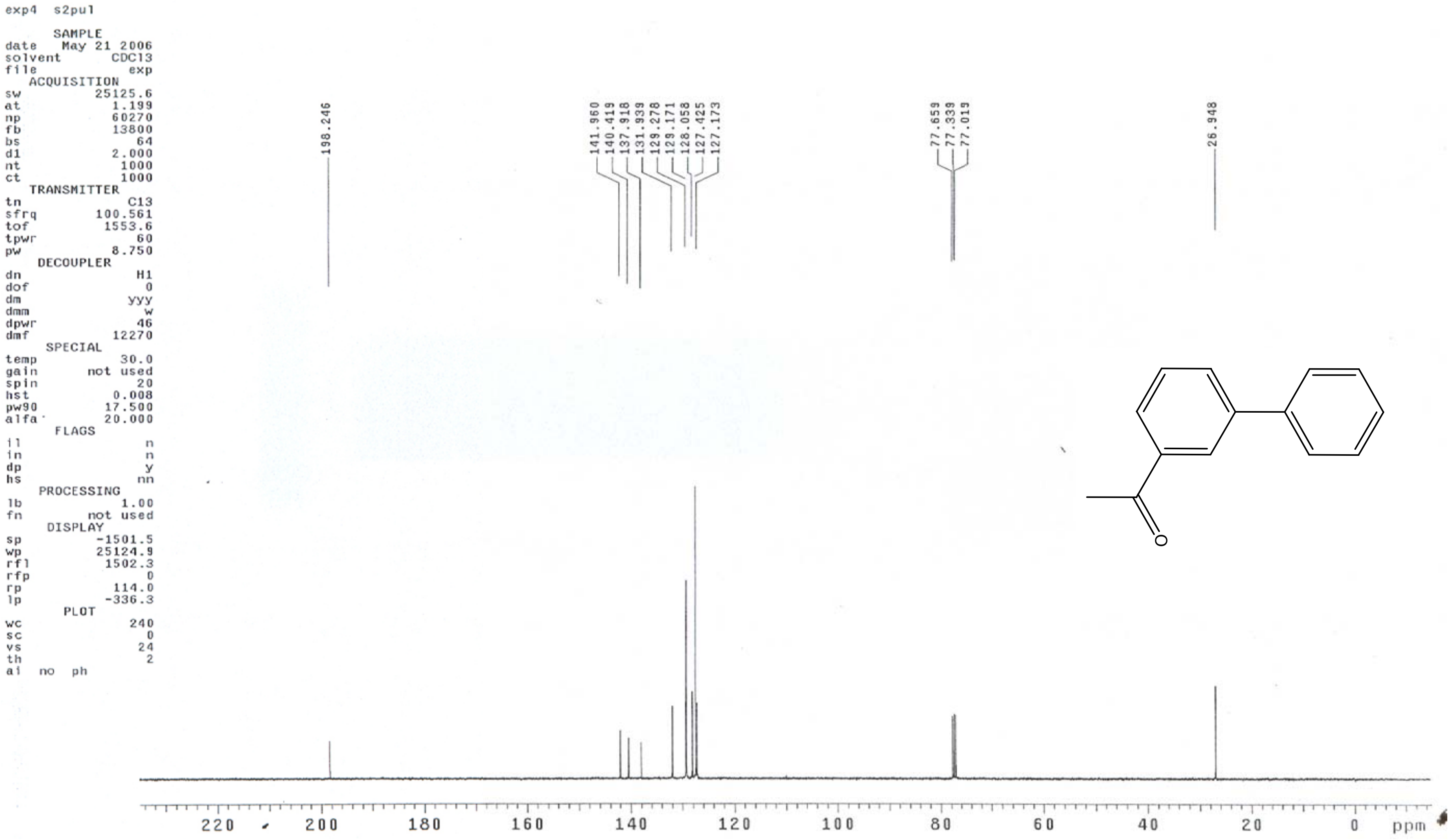


Figure A.11. ^{13}C NMR of 3-acetylbiphenyl

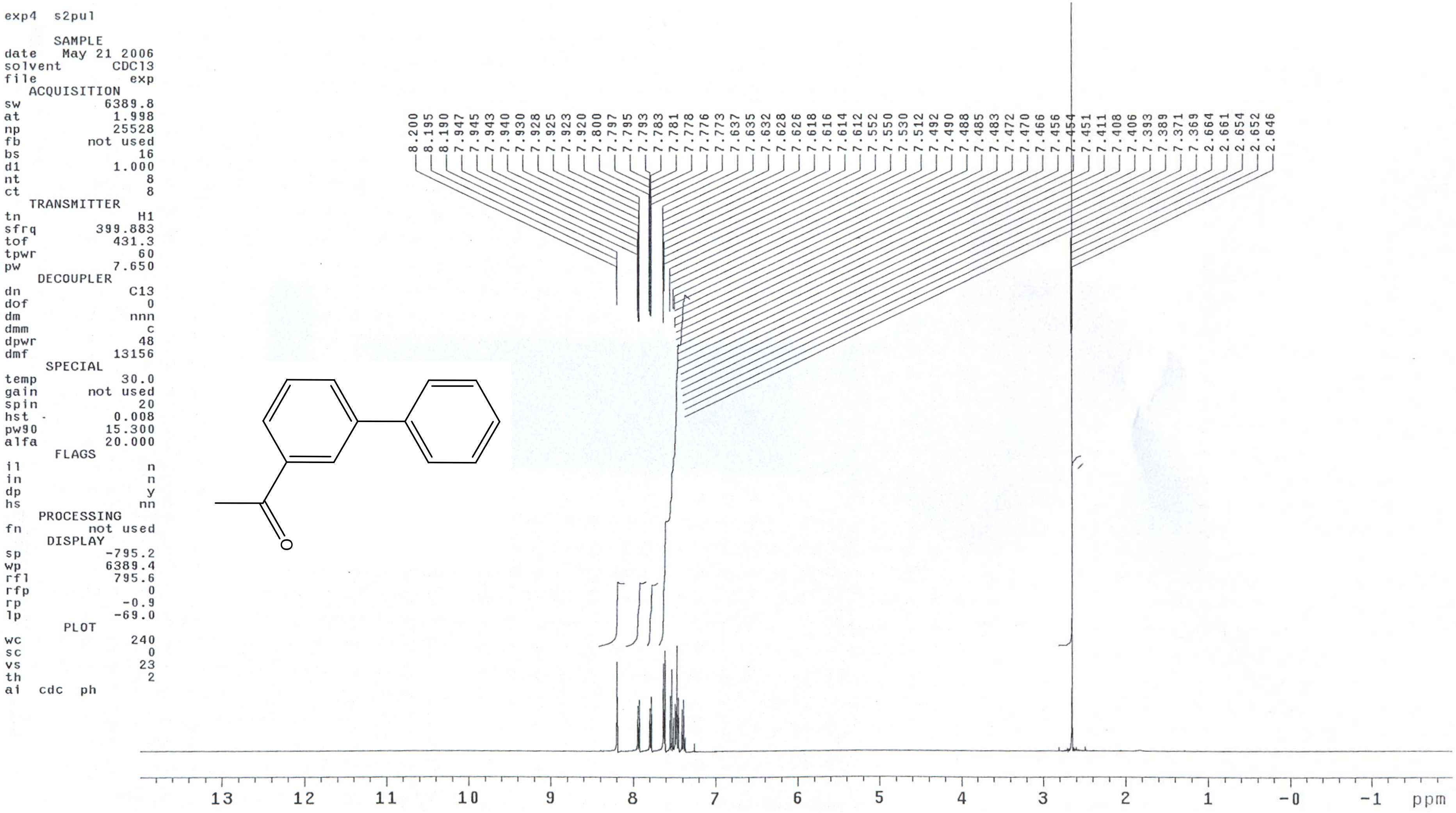


Figure A.12. ^{1}H NMR of 3-acetylbiphenyl

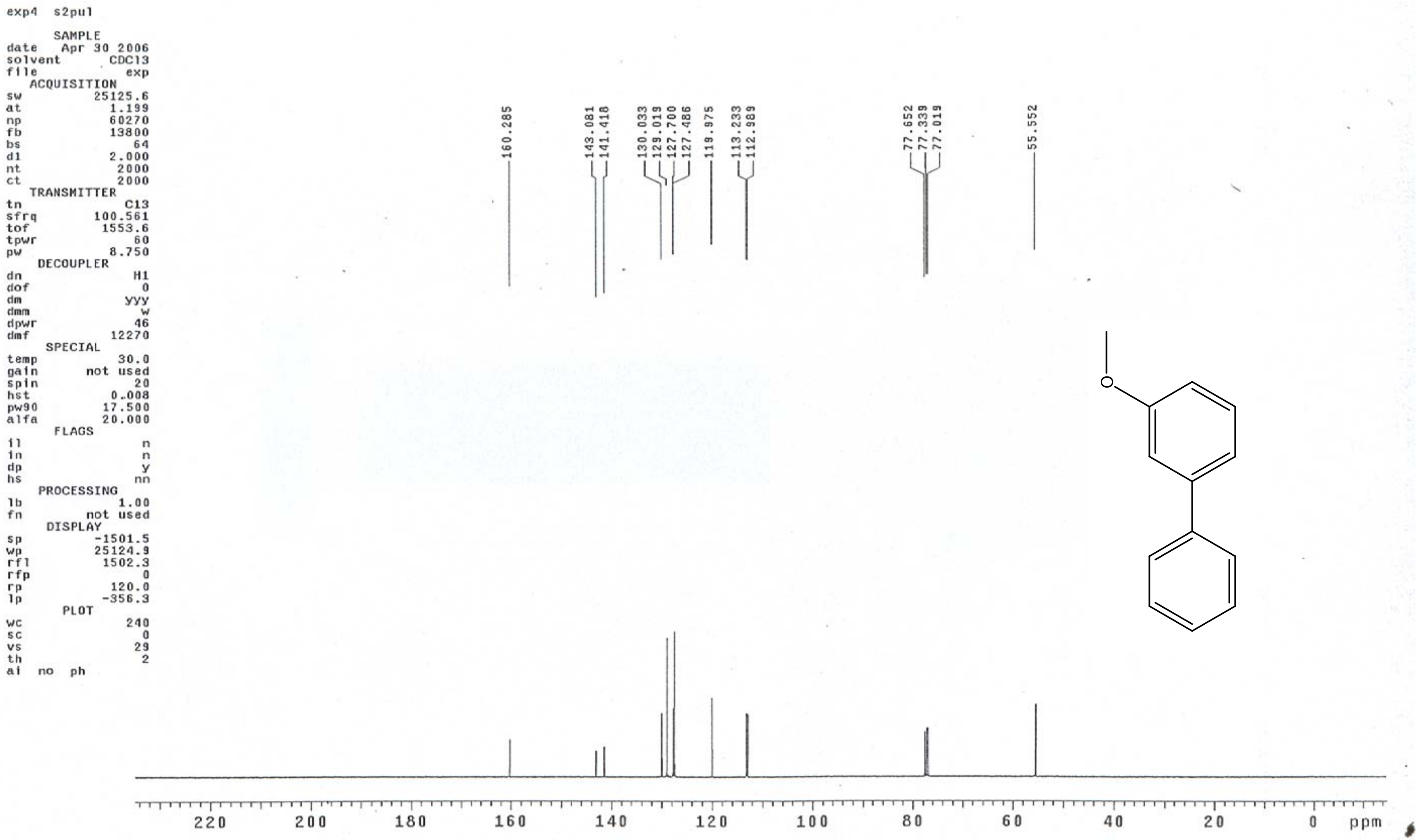
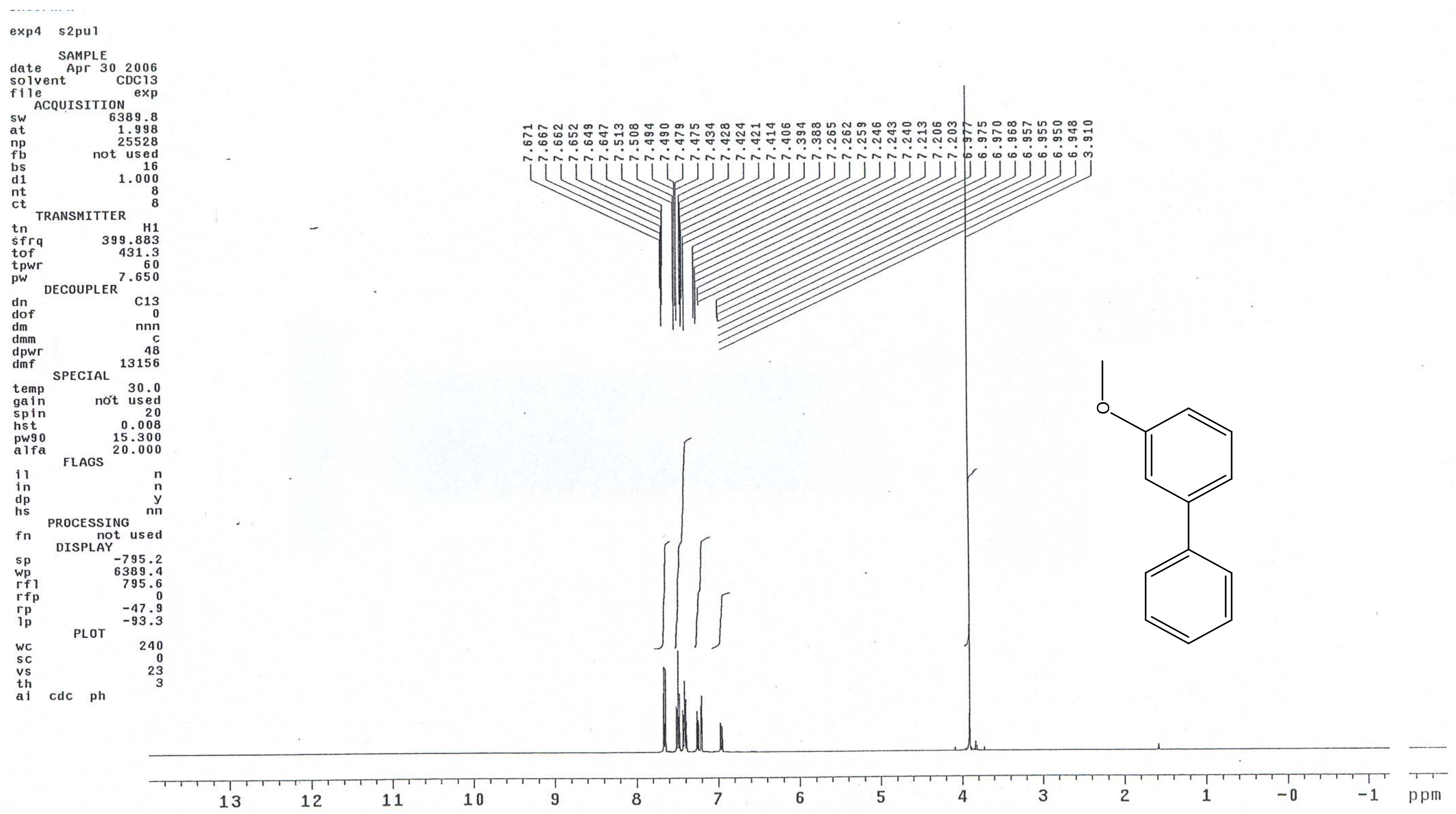


Figure A.13. ^{13}C NMR of 3-methoxybiphenyl



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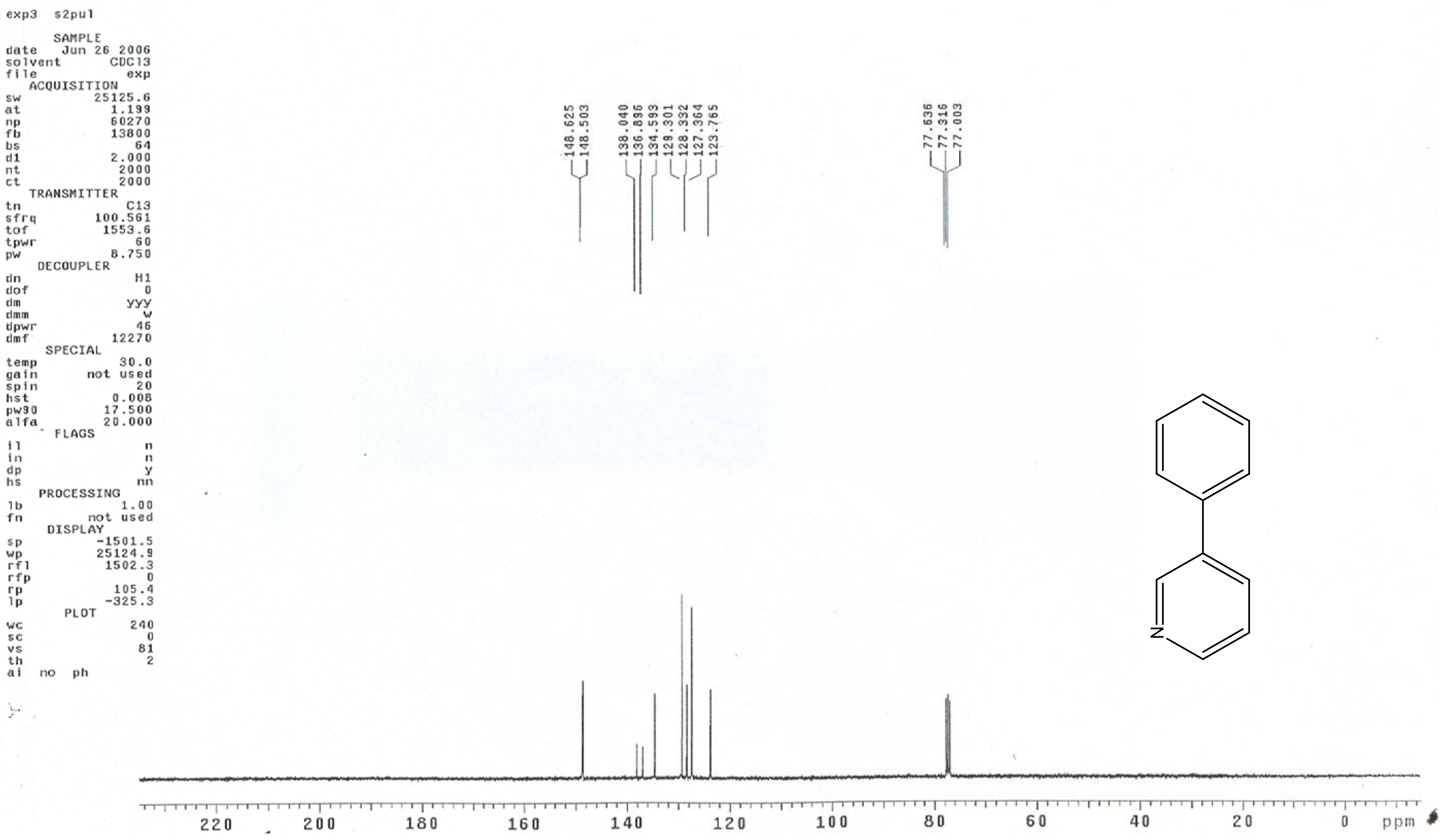

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sc               0
vs              81
th               2
ai   no   ph
```

Figure A.15. ^{13}C NMR of 3-phenylpyridine

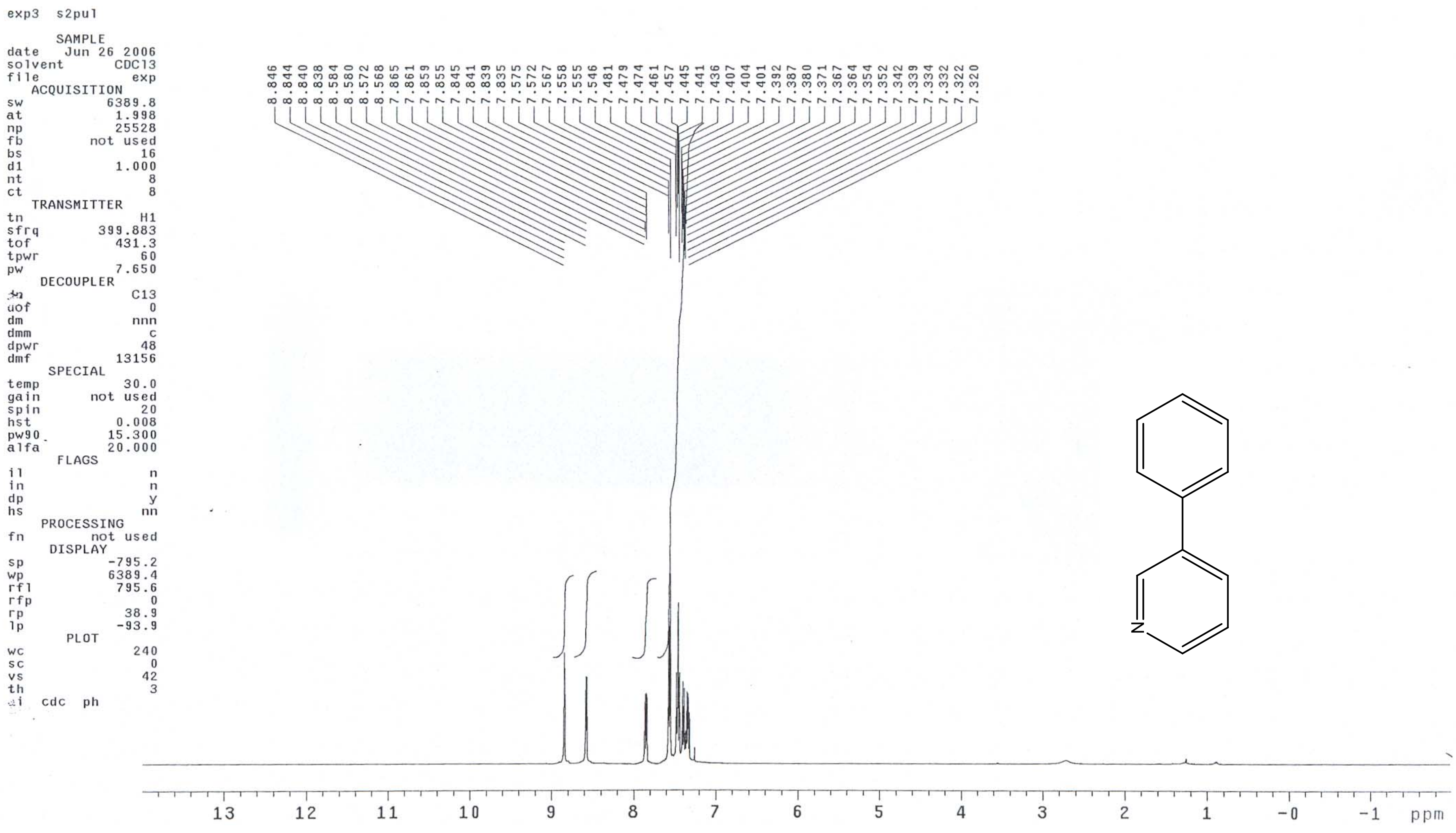
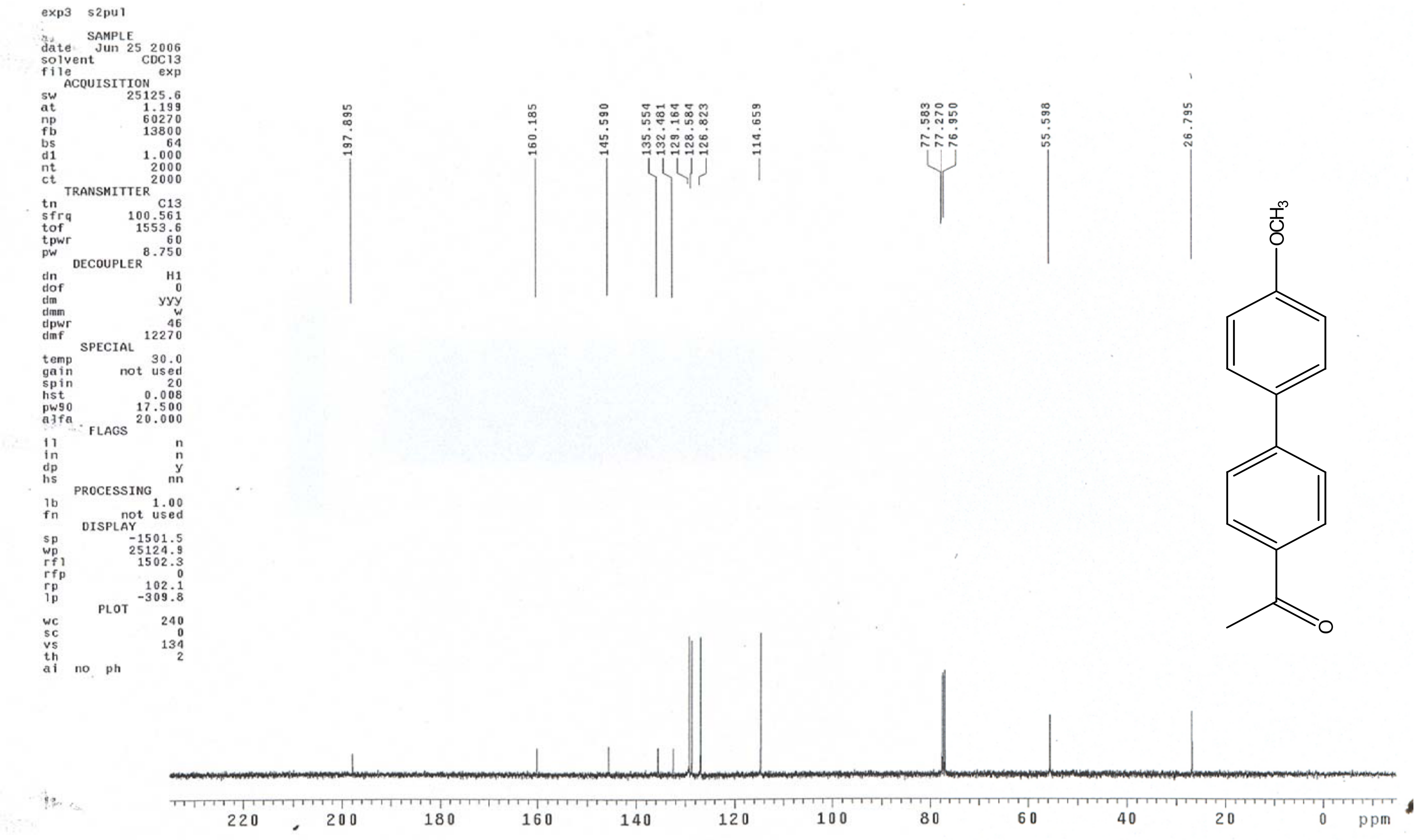


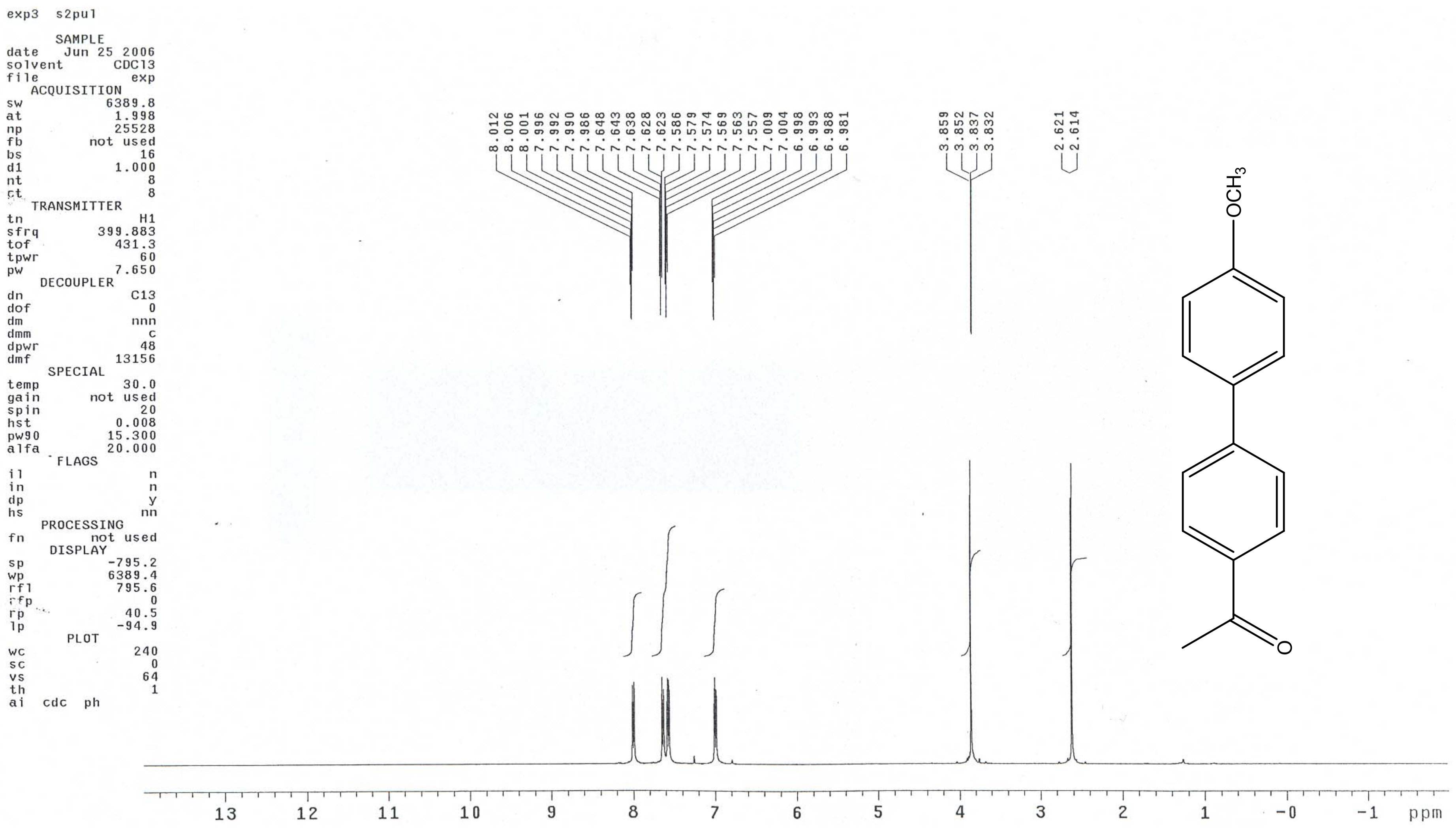
Figure A.16. ^{1}H NMR of 3-phenylpyridine



```
exp3  s2pul

      SAMPLE
date   Jun 25 2006
solvent      CDCl3
file           exp
   ACQUISITION
sw         25125.6
at           1.199
np           60270
fb           13800
bs              64
d1           1.000
nt            2000
ct            2000
   TRANSMITTER
tn             C13
sfrq       100.561
tof         1553.6
tpwr            60
pw           8.750
    DECOUPLER
dn              H1
dof              0
dm             yyy
dmm              w
dpwr            46
dmf          12270
     SPECIAL
temp          30.0
gain      not used
spin            20
hst          0.008
pw90        17.500
alfa        20.000
      FLAGS
il               n
in               n
dp               y
hs              nn
    PROCESSING
lb            1.00
fn        not used
     DISPLAY
sp         -1501.5
wp         25124.9
rfl         1502.3
rfp              0
rp           102.1
lp          -309.8
       PLOT
wc             240
sc               0
vs             134
th               2
ai   no  ph
```

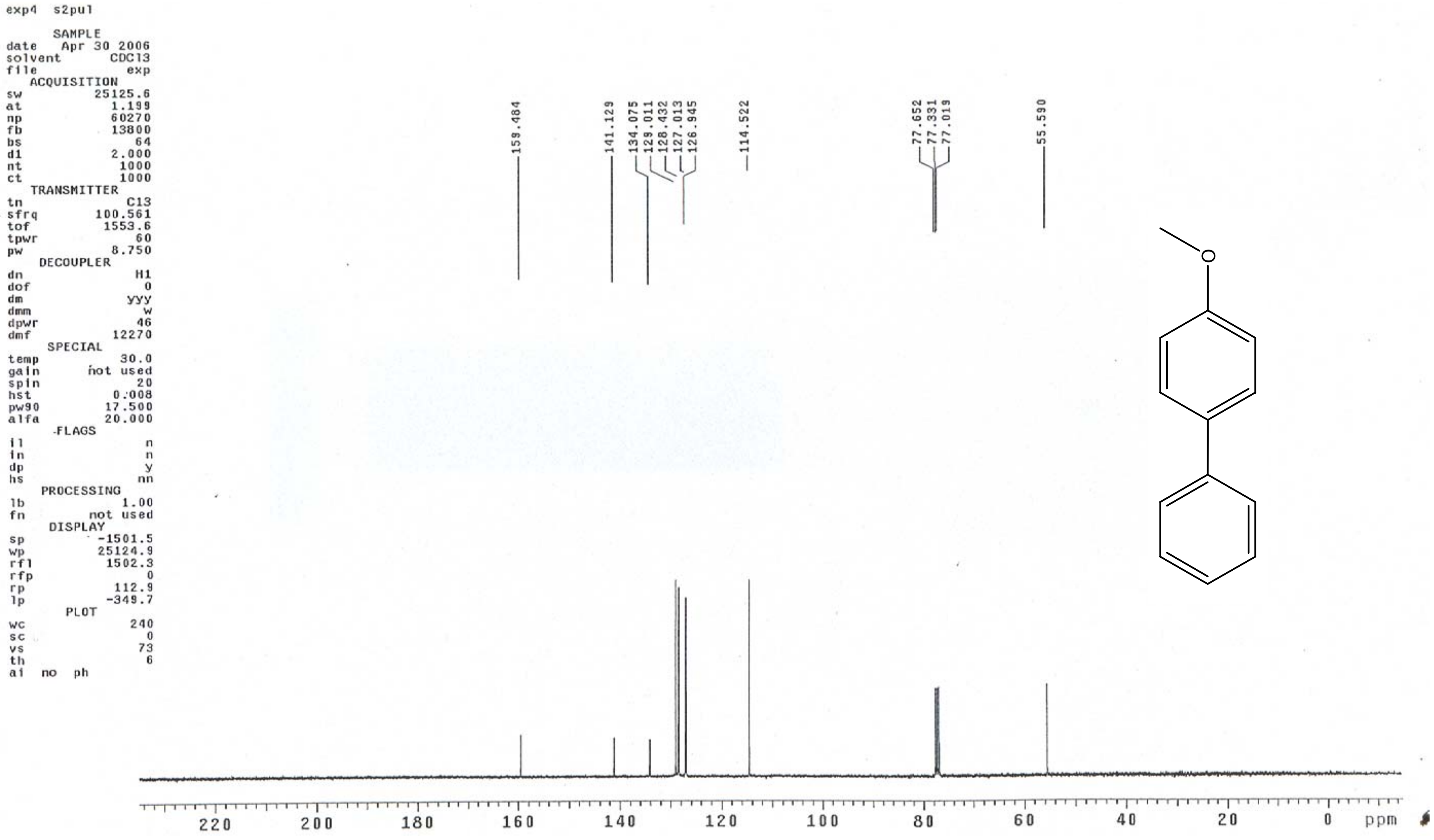
Figure A.17. ^{13}C NMR of 4-acetyl-4'-methoxybiphenyl



```
exp3  s2pul

       SAMPLE
date   Jun 25 2006
solvent      CDCl3
file           exp
    ACQUISITION
sw          6389.8
at           1.998
np           25528
fb        not used
bs              16
d1           1.000
nt               8
ct               8
    TRANSMITTER
tn              H1
sfrq       399.883
tof          431.3
tpwr            60
pw           7.650
     DECOUPLER
dn             C13
dof              0
dm             nnn
dmm              c
dpwr            48
dmf          13156
       SPECIAL
temp          30.0
gain      not used
spin            20
hst          0.008
pw90        15.300
alfa        20.000
       FLAGS
il               n
in               n
dp               y
hs              nn
     PROCESSING
fn        not used
      DISPLAY
sp          -795.2
wp          6389.4
rfl          795.6
rfp              0
rp            40.5
lp           -94.9
        PLOT
wc             240
sc               0
vs              64
th               1
ai   cdc   ph
```

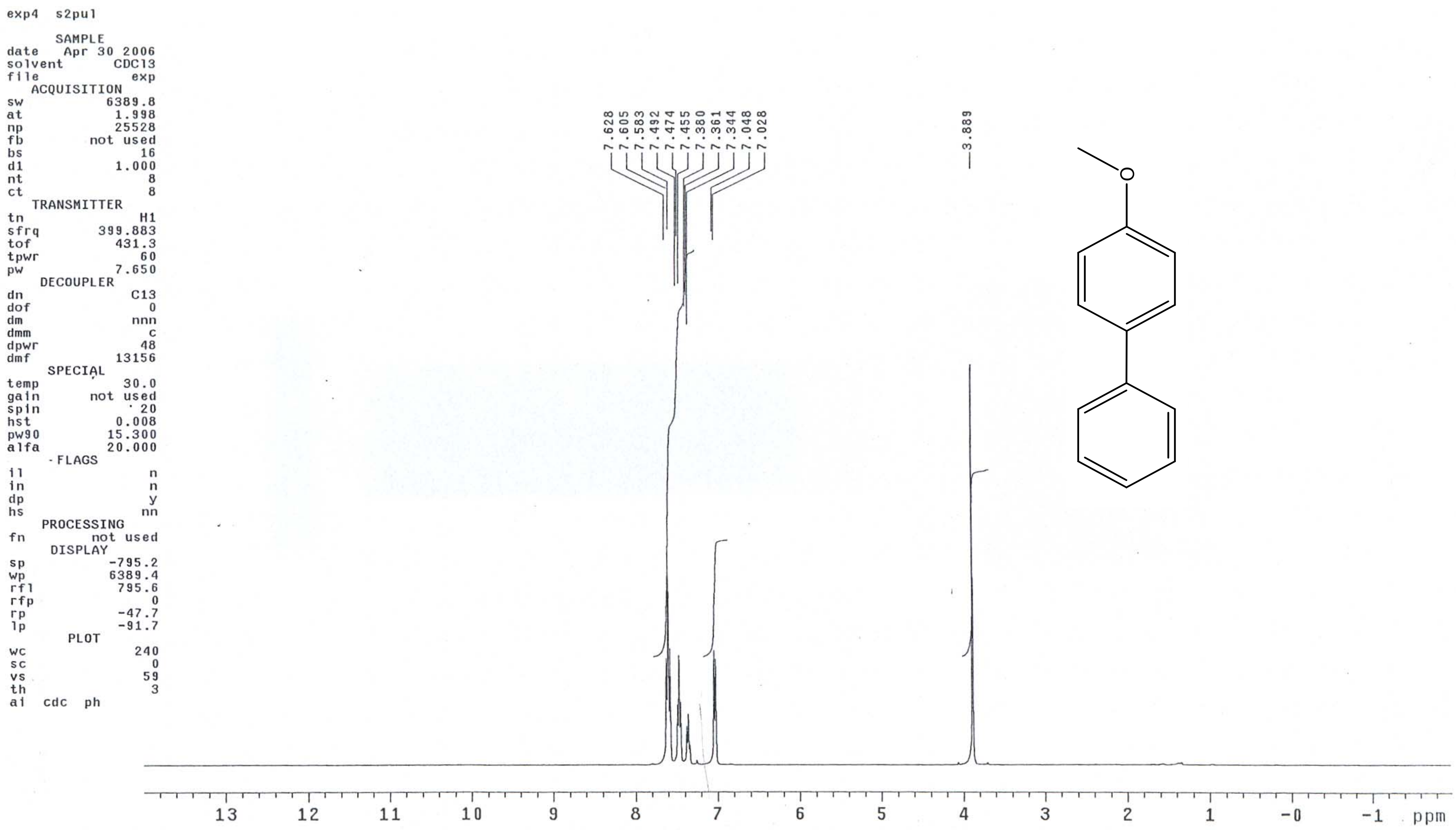
Figure A.18. ^{1}H NMR of 4-acetyl-4’-methoxybiphenyl



```
exp4  s2pul

       SAMPLE
date    Apr 30 2006
solvent        CDCl3
file             exp
    ACQUISITION
sw           25125.6
at             1.199
np             60270
fb             13800
bs                64
d1             2.000
nt              1000
ct              1000
    TRANSMITTER
tn               C13
sfrq         100.561
tof           1553.6
tpwr              60
pw             8.750
      DECOUPLER
dn                H1
dof                0
dm               yyy
dmm                w
dpwr              46
dmf            12270
       SPECIAL
temp            30.0
gain        not used
spin              20
hst            0.008
pw90          17.500
alfa          20.000
      FLAGS
il                 n
in                 n
dp                 y
hs                nn
     PROCESSING
lb              1.00
fn          not used
       DISPLAY
sp           -1501.5
wp           25124.9
rfl           1502.3
rfp                0
rp             112.9
lp            -349.7
        PLOT
wc               240
sc                 0
vs                73
th                 6
ai  no  ph
```

Figure A.19. ^{13}C NMR of 4-methoxybiphenyl



```
exp4  s2pul

      SAMPLE
date   Apr 30 2006
solvent      CDCl3
file           exp
   ACQUISITION
sw          6389.8
at           1.998
np           25528
fb        not used
bs              16
d1           1.000
nt               8
ct               8
   TRANSMITTER
tn              H1
sfrq       399.883
tof          431.3
tpwr            60
pw           7.650
   DECOUPLER
dn             C13
dof              0
dm             nnn
dmm              c
dpwr            48
dmf          13156
     SPECIAL
temp          30.0
gain      not used
spin            20
hst          0.008
pw90        15.300
alfa        20.000
     FLAGS
il               n
in               n
dp               y
hs              nn
   PROCESSING
fn        not used
     DISPLAY
sp          -795.2
wp          6389.4
rfl          795.6
rfp              0
rp           -47.7
lp           -91.7
       PLOT
wc             240
sc               0
vs              59
th               3
ai   cdc  ph
```

Figure A.20. ^{1}H NMR of 4-methoxybiphenyl

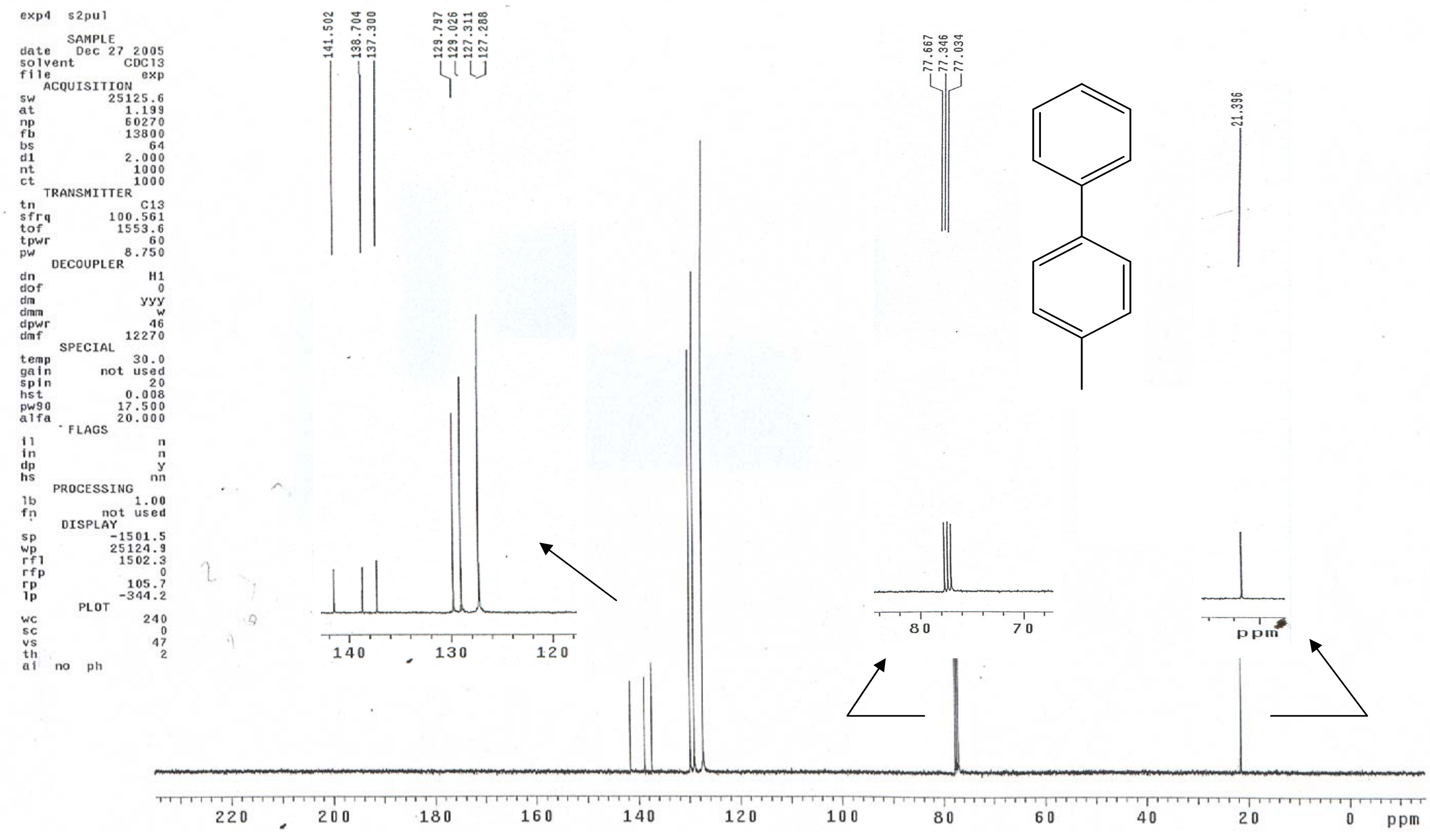


Figure A.21. ^{13}C NMR of 4-methylbiphenyl

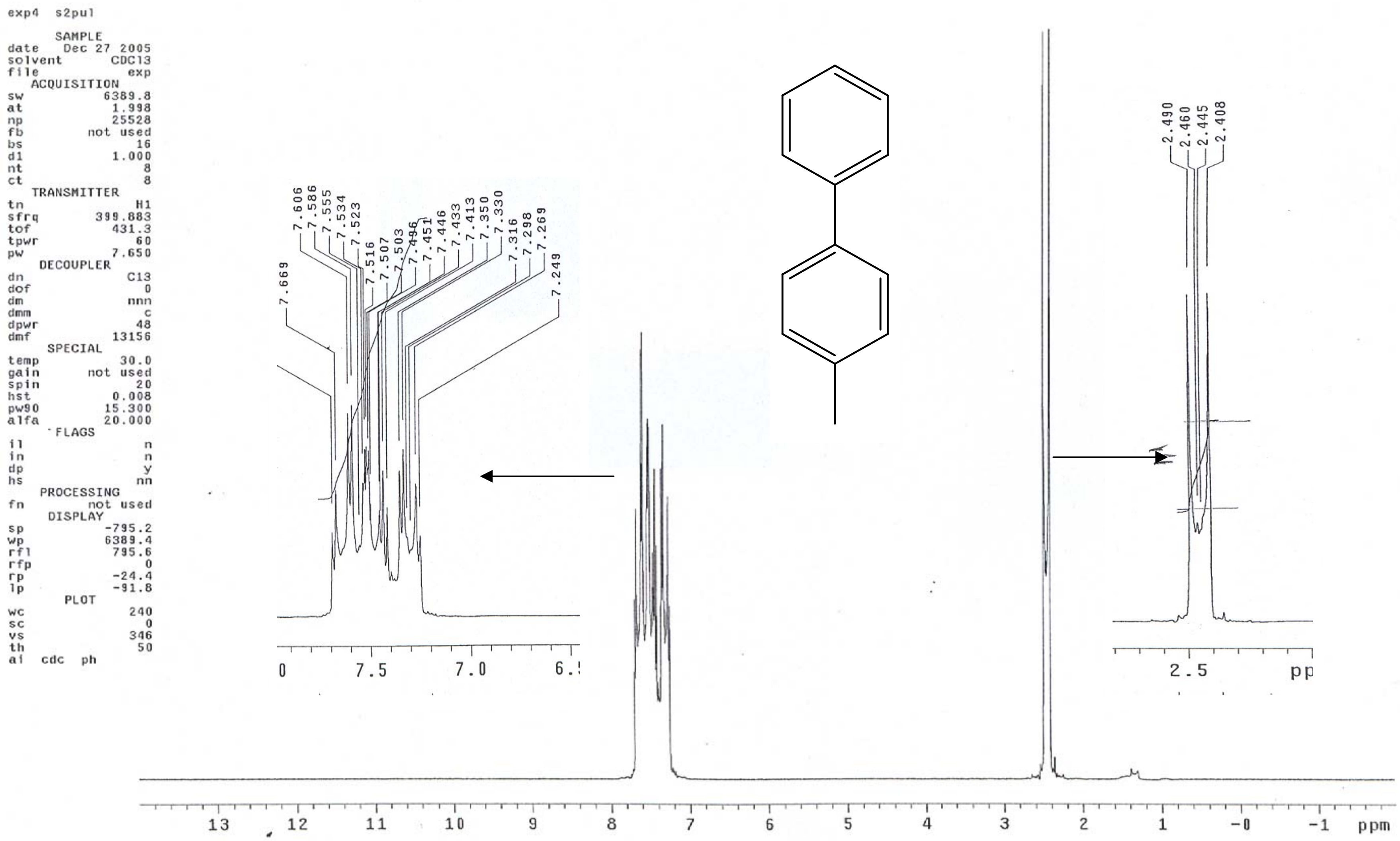


Figure A.22. ^{1}H NMR of 4-methylbiphenyl

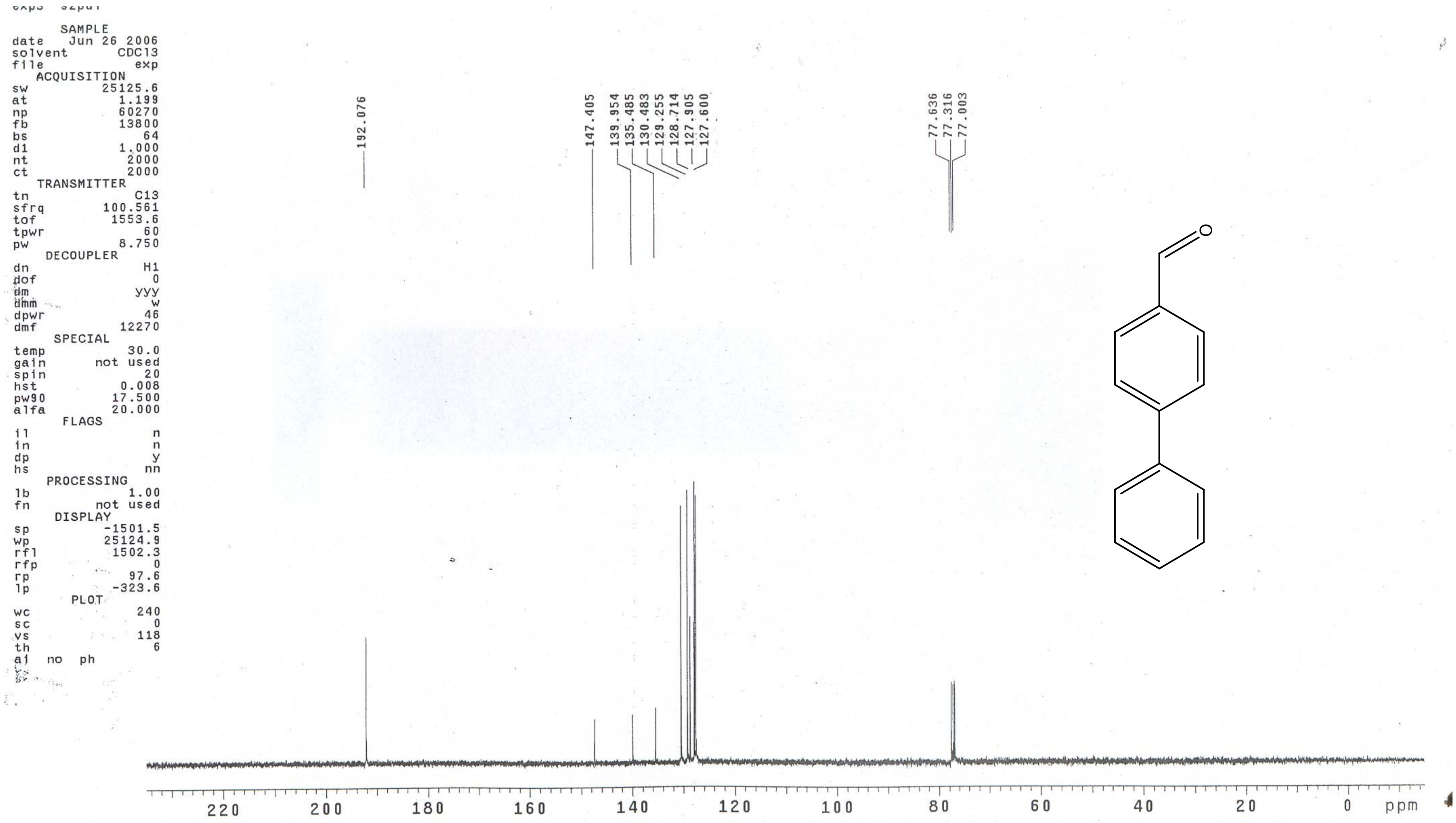


Figure A.23. ^{13}C NMR of 4-phenylbenzaldehyde

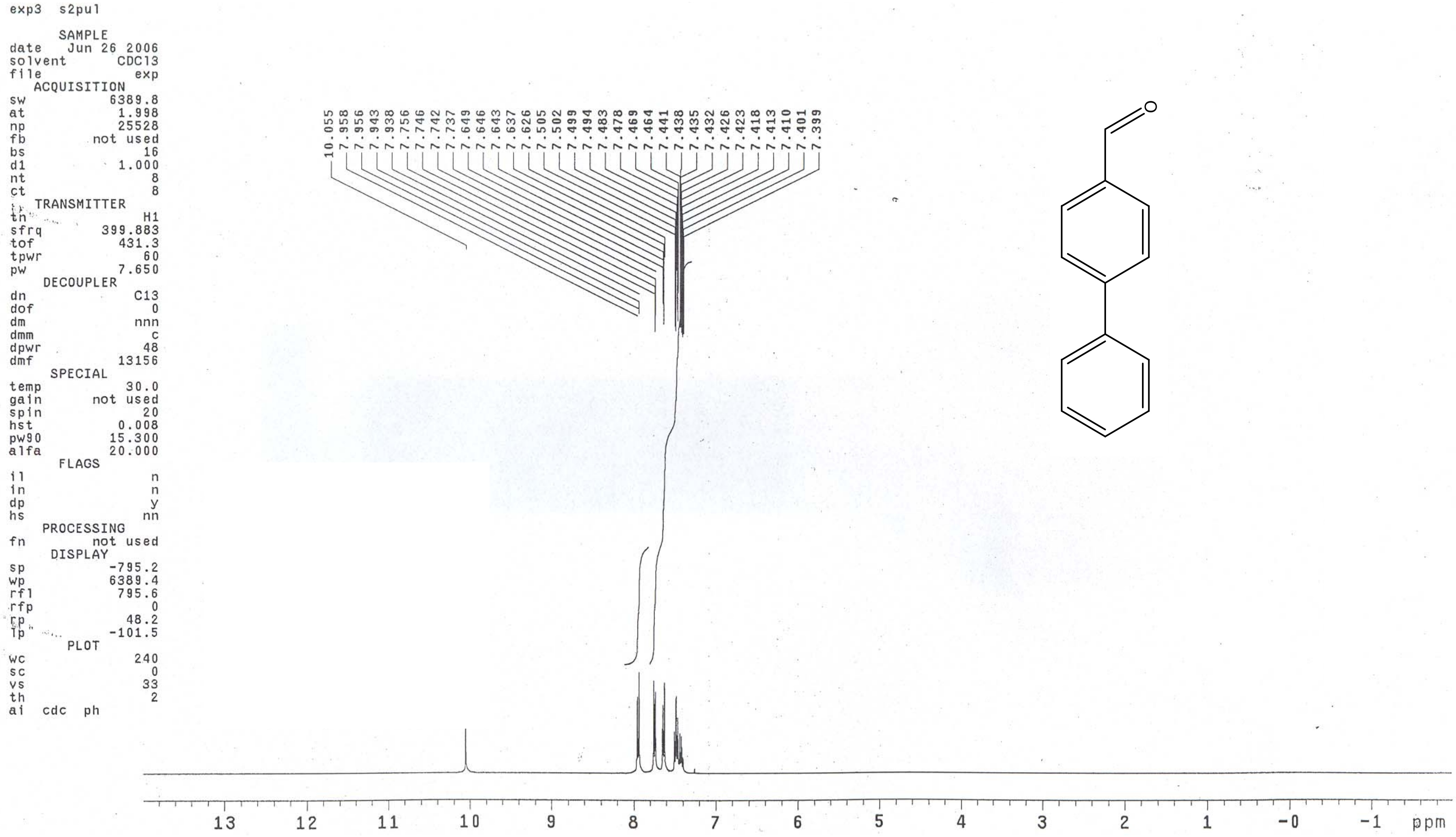
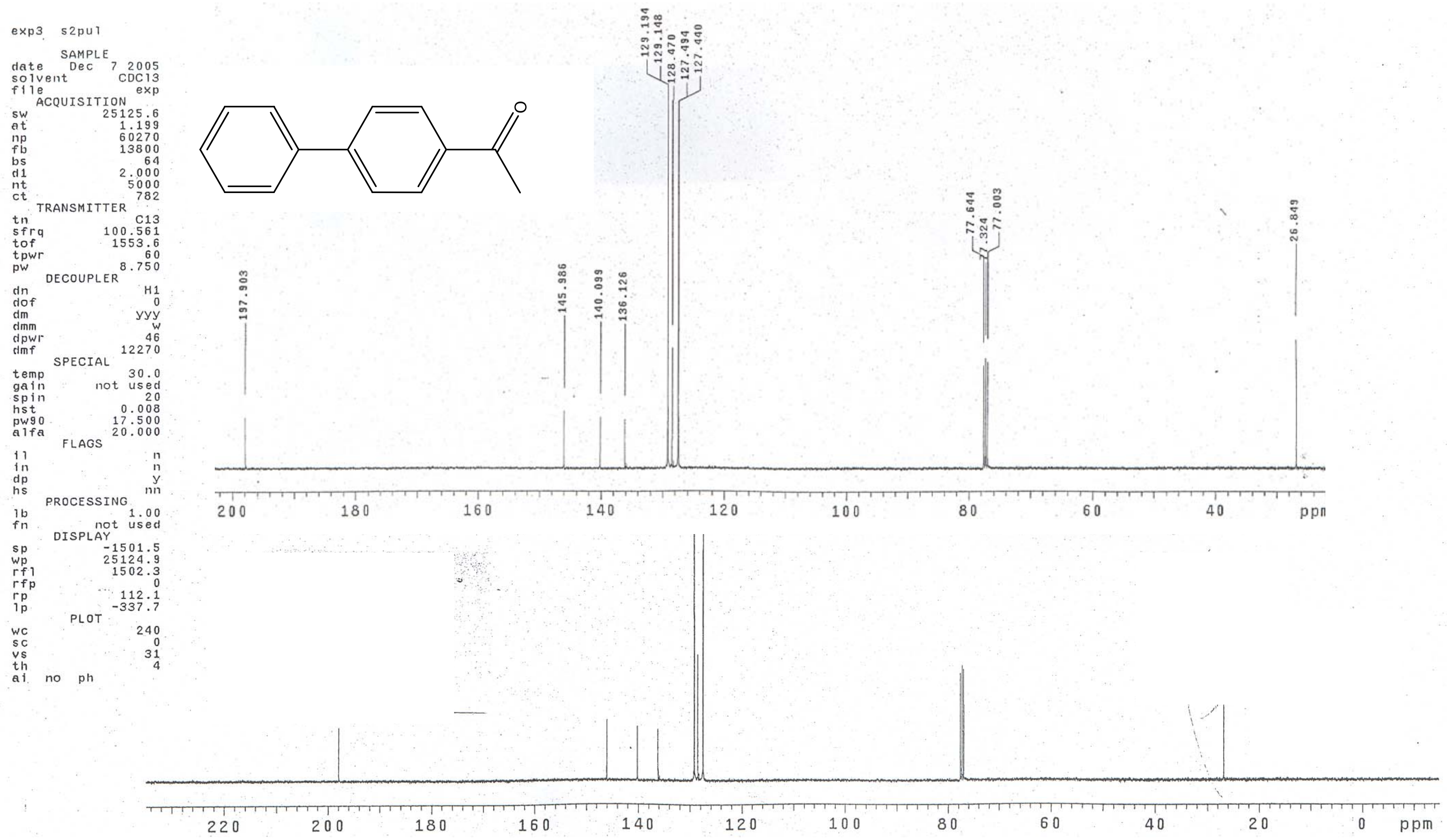


Figure A.24. ^{1}H NMR of 4-phenylbenzaldehyde



```
exp3  s2pul

      SAMPLE
date   Dec  7 2005
solvent      CDCl3
file           exp
   ACQUISITION
sw         25125.6
at           1.199
np           60270
fb           13800
bs              64
d1           2.000
nt            5000
ct             782
   TRANSMITTER
tn             C13
sfrq       100.561
tof         1553.6
tpwr            60
pw           8.750
    DECOUPLER
dn              H1
dof              0
dm             yyy
dmm              w
dpwr            46
dmf          12270
     SPECIAL
temp          30.0
gain      not used
spin            20
hst          0.008
pw90        17.500
alfa        20.000
      FLAGS
il               n
in               n
dp               y
hs              nn
    PROCESSING
lb            1.00
fn        not used
     DISPLAY
sp         -1501.5
wp         25124.9
rfl         1502.3
rfp              0
rp           112.1
lp          -337.7
       PLOT
wc             240
sc               0
vs              31
th               4
ai  no  ph
```

Figure A.25. ^{13}C NMR of 4-acetylbiphenyl

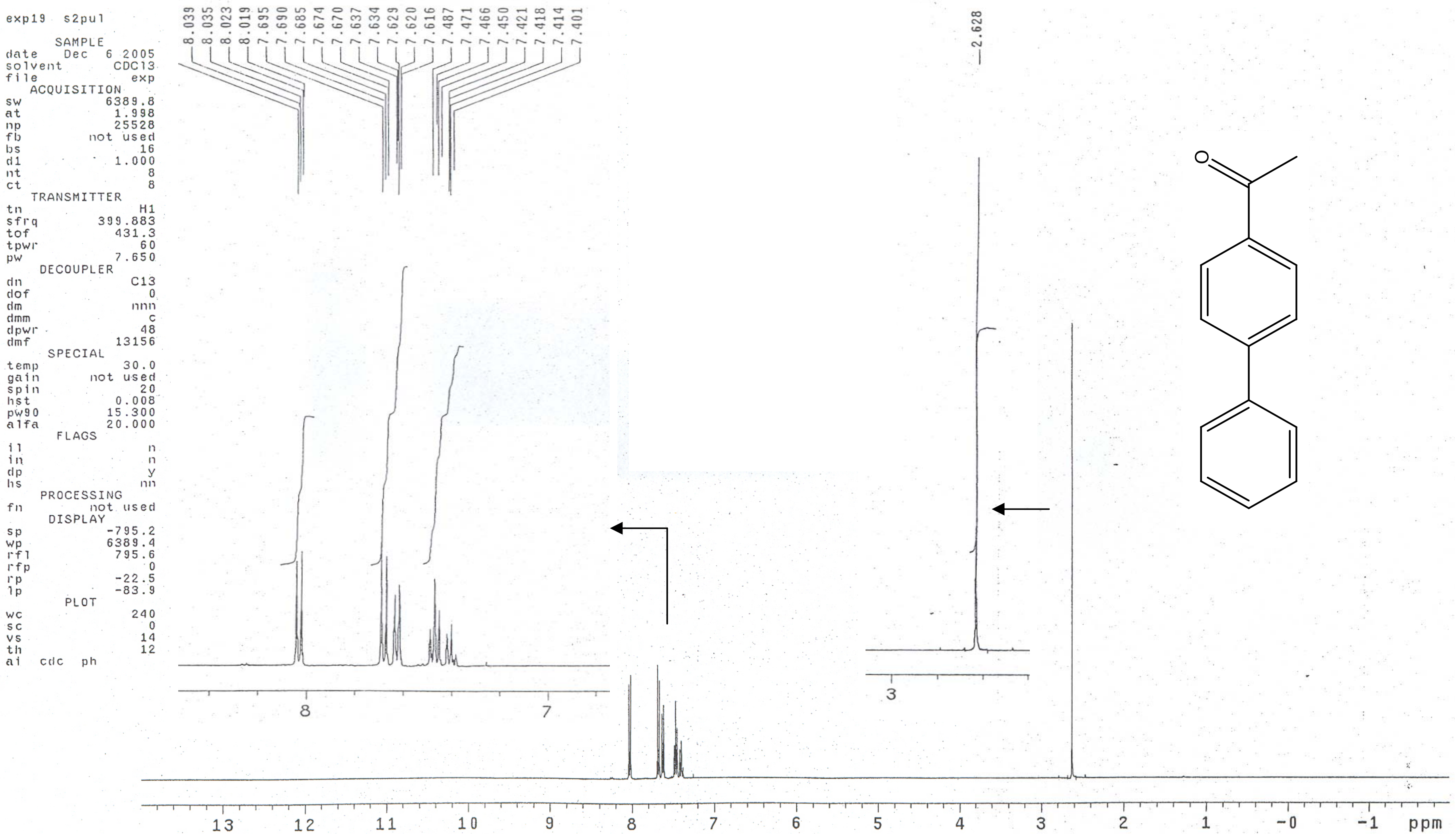
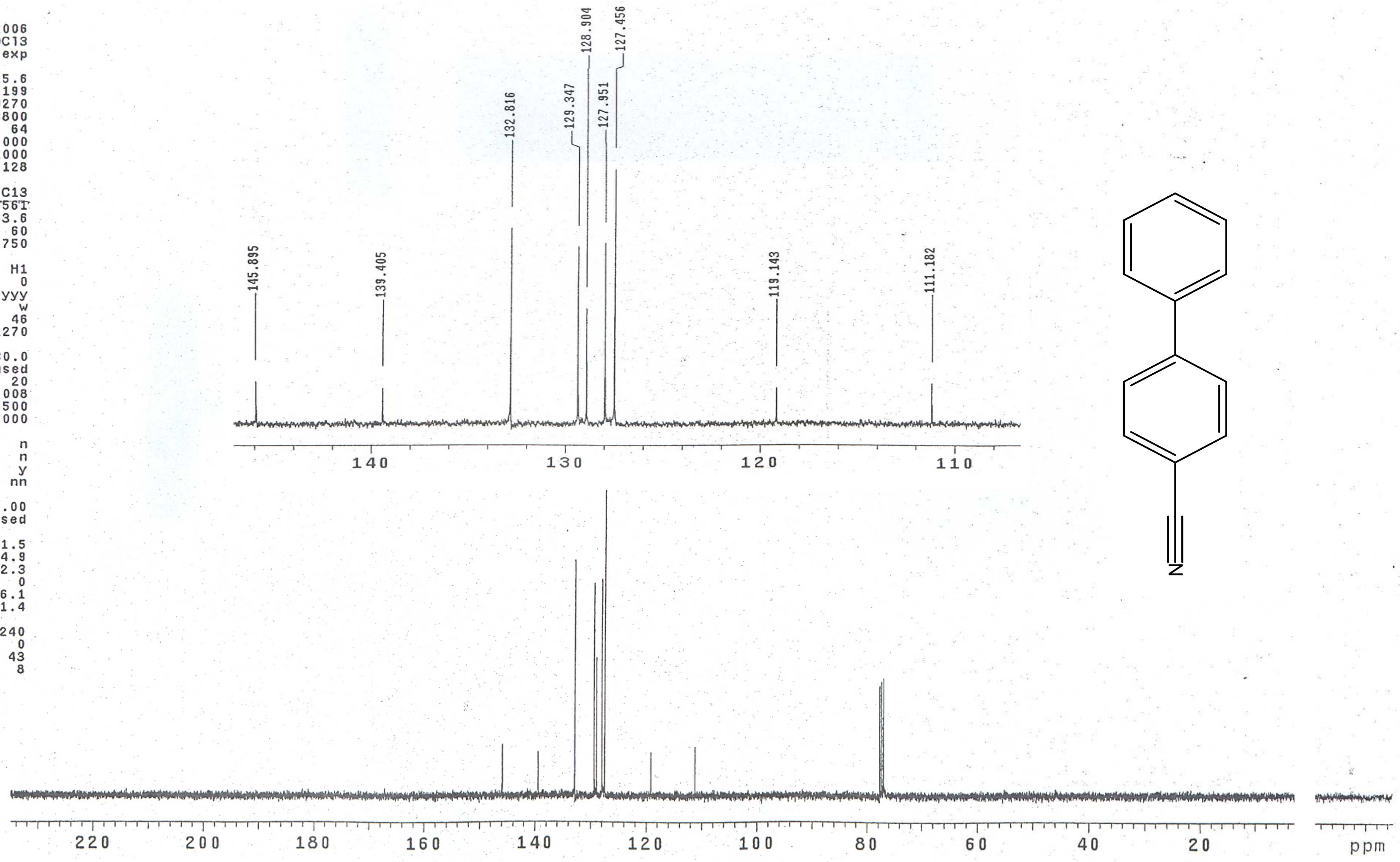


Figure A.26. ^{1}H NMR of 4-acetylbiphenyl



```
exp5  s2pul

      SAMPLE
date    Feb 27 2006
solvent       CDCl3
file            exp
    ACQUISITION
sw          25125.6
at            1.199
np            60270
fb            13800
bs               64
d1            1.000
nt             1000
ct              128
    TRANSMITTER
tn              C13
sfrq        100.561
tof          1553.6
tpwr             60
pw            8.750
     DECOUPLER
dn               H1
dof               0
dm              yyy
dmm               w
dpwr             46
dmf           12270
      SPECIAL
temp           30.0
gain       not used
spin             20
hst           0.008
pw90         17.500
alfa         20.000
      FLAGS
il                n
in                n
dp                y
hs               nn
    PROCESSING
lb             1.00
fn         not used
     DISPLAY
sp          -1501.5
wp          25124.9
rfl          1502.3
rfp               0
rp             86.1
lp           -271.4
       PLOT
wc              240
sc                0
vs               43
th                8
ai   no  ph
```

Figure A.27. ^{13}C NMR of 4-cyanobiphenyl

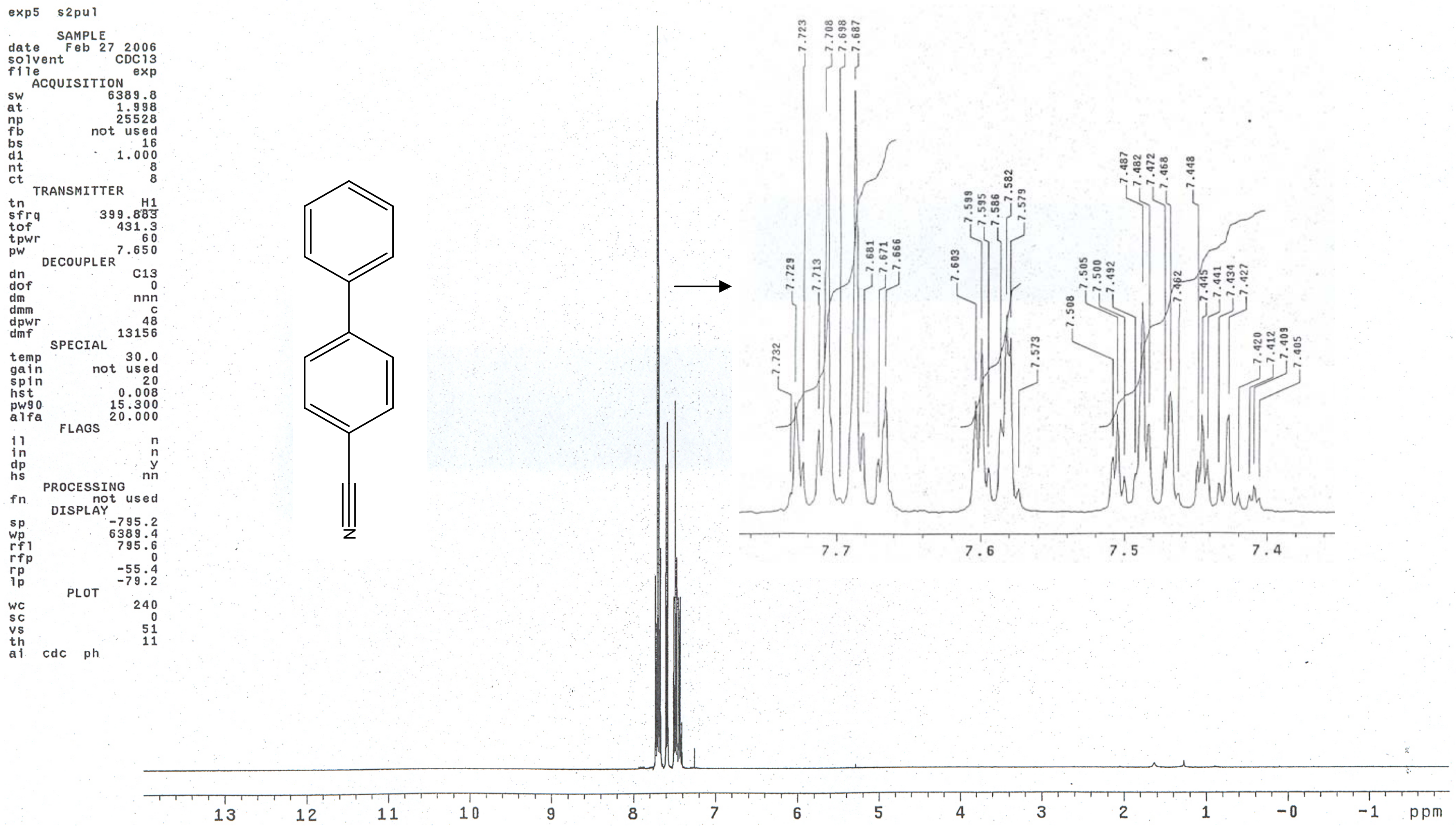
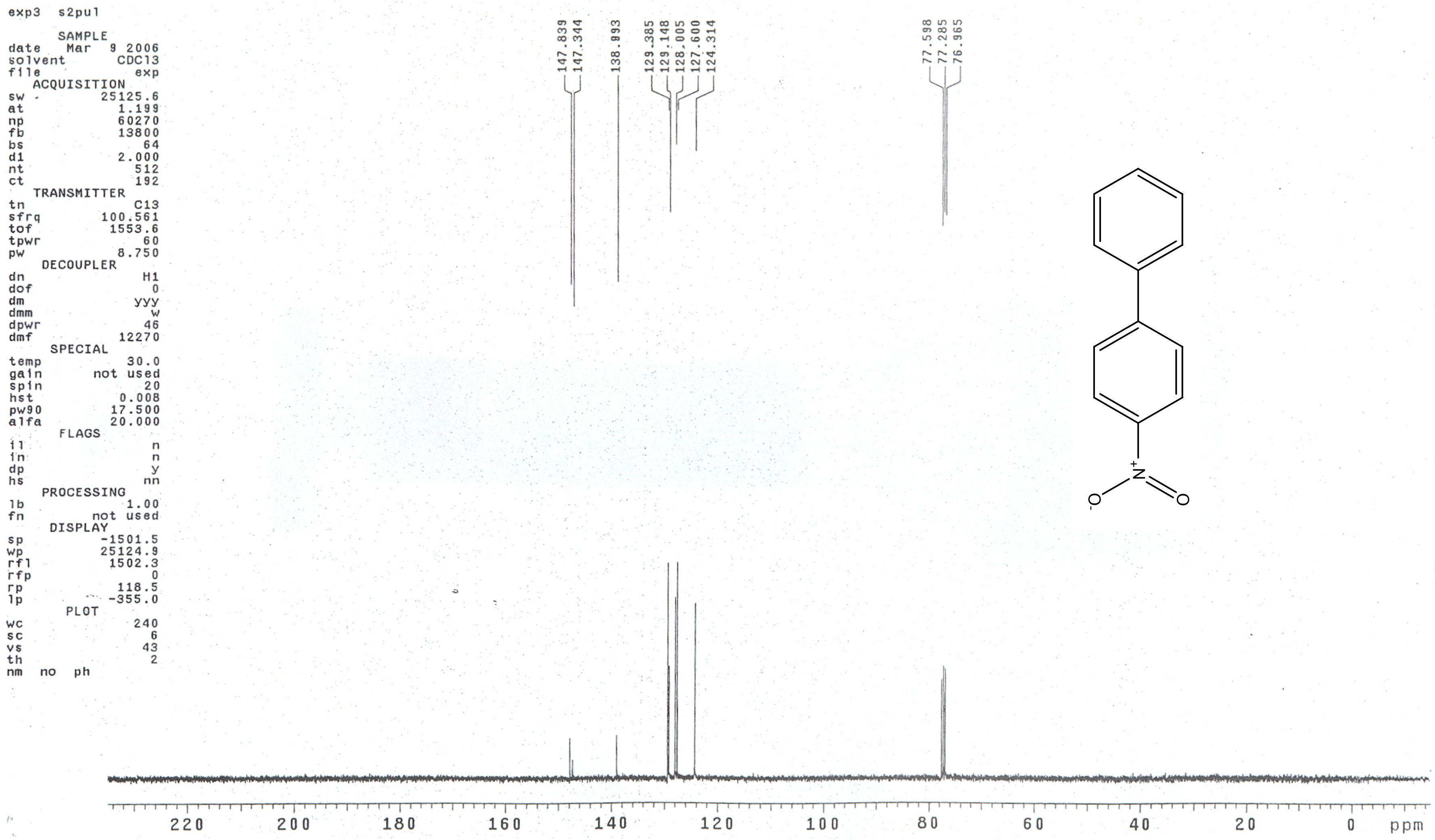


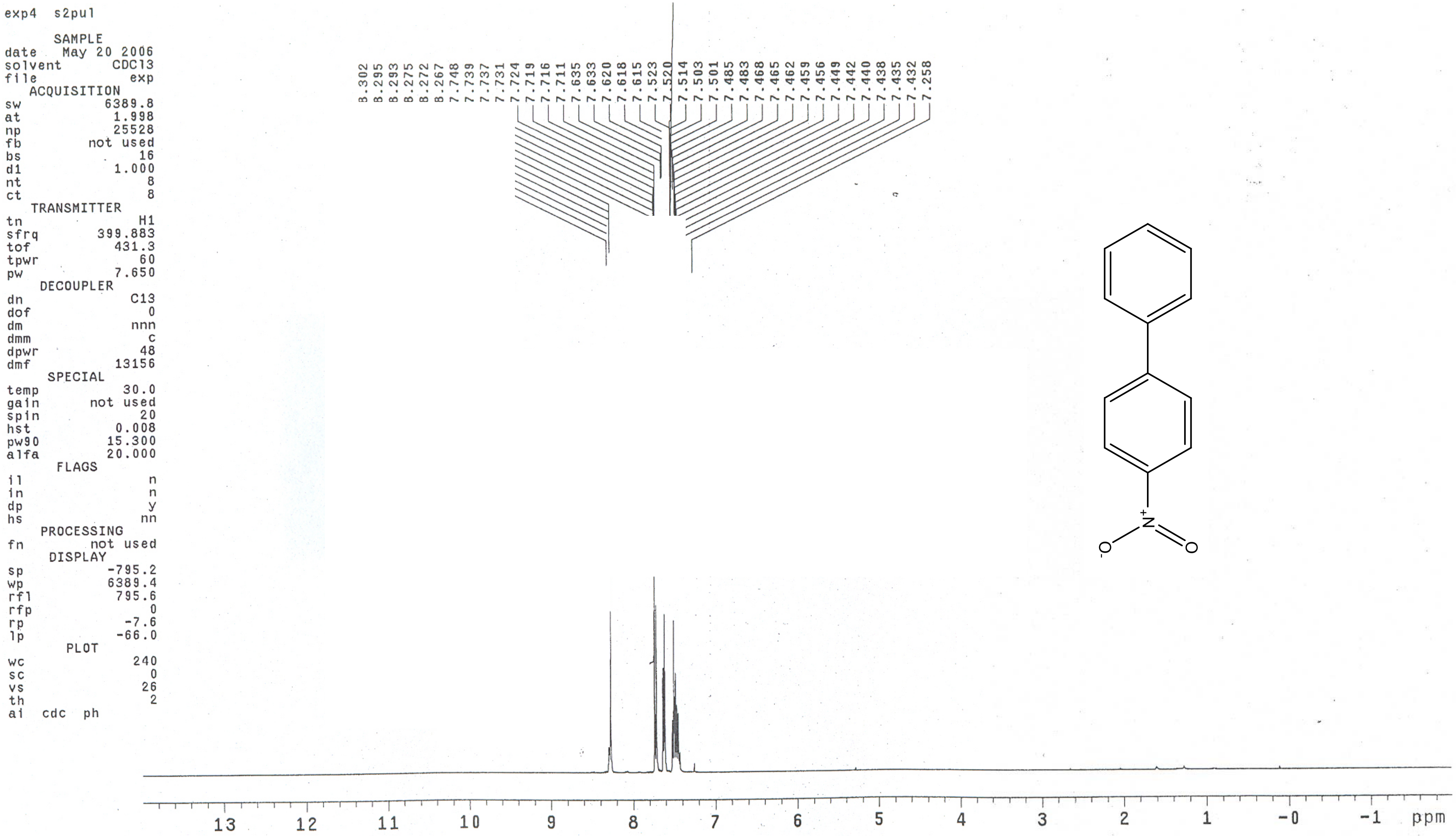
Figure A.28. ^{1}H NMR of 4-cyanobiphenyl



```
exp3  s2pul

      SAMPLE
date    Mar  9 2006
solvent       CDCl3
file            exp
   ACQUISITION
sw -        25125.6
at            1.199
np            60270
fb            13800
bs               64
d1            2.000
nt              512
ct              192
   TRANSMITTER
tn              C13
sfrq        100.561
tof          1553.6
tpwr             60
pw            8.750
    DECOUPLER
dn               H1
dof               0
dm              yyy
dmm               w
dpwr             46
dmf           12270
      SPECIAL
temp           30.0
gain       not used
spin             20
hst           0.008
pw90         17.500
alfa         20.000
      FLAGS
il                n
in                n
dp                y
hs               nn
    PROCESSING
lb             1.00
fn         not used
     DISPLAY
sp          -1501.5
wp          25124.9
rfl          1502.3
rfp               0
rp            118.5
lp           -355.0
       PLOT
wc              240
sc                6
vs               43
th                2
nm  no  ph
```

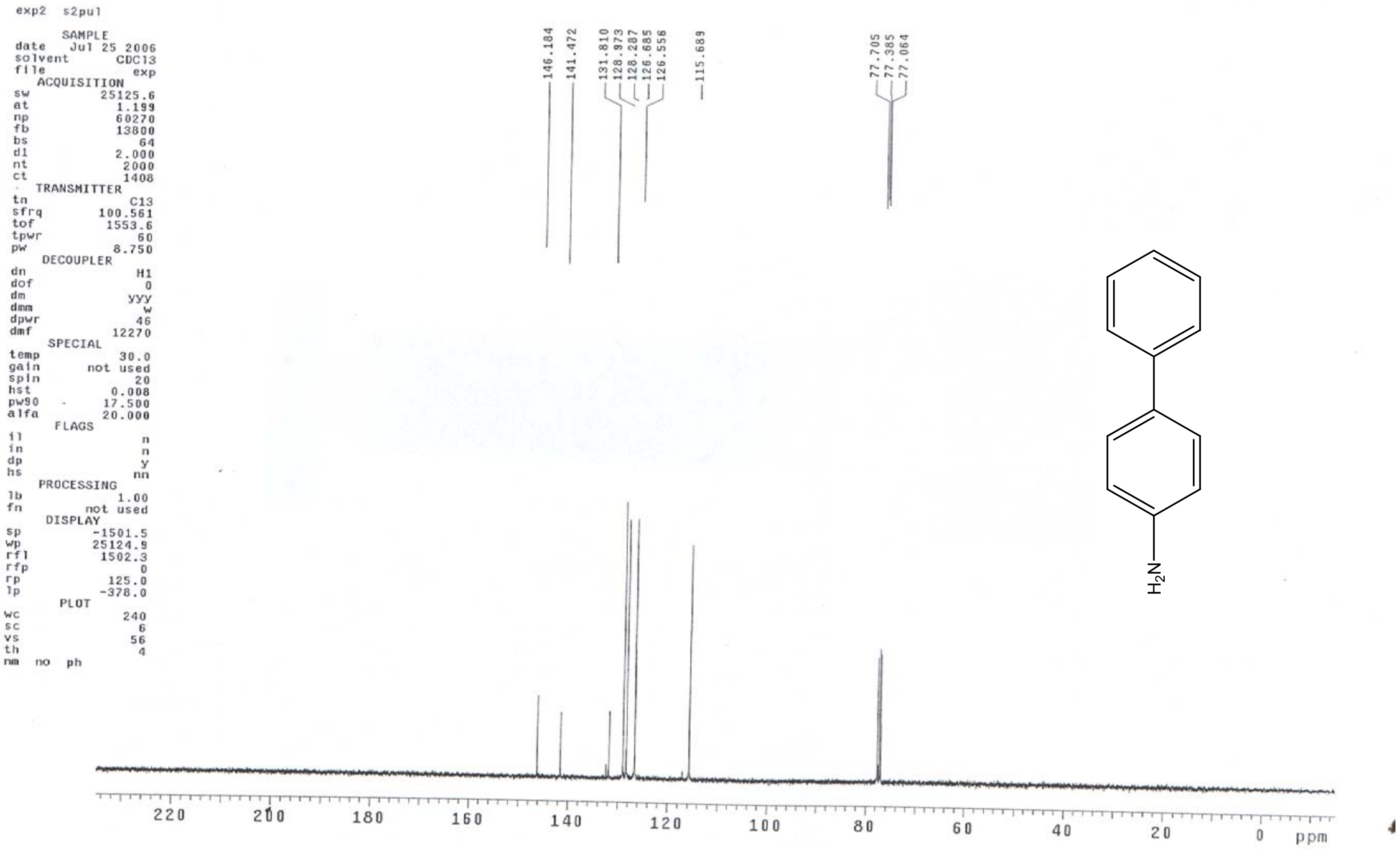
Figure A.29. ^{13}C NMR of 4-nitrobiphenyl



```
exp4  s2pul

      SAMPLE
date   May 20 2006
solvent      CDCl3
file           exp
    ACQUISITION
sw          6389.8
at           1.998
np           25528
fb        not used
bs              16
d1           1.000
nt               8
ct               8
    TRANSMITTER
tn              H1
sfrq       399.883
tof          431.3
tpwr            60
pw           7.650
     DECOUPLER
dn             C13
dof              0
dm             nnn
dmm              c
dpwr            48
dmf          13156
      SPECIAL
temp          30.0
gain      not used
spin            20
hst          0.008
pw90        15.300
alfa        20.000
       FLAGS
il               n
in               n
dp               y
hs              nn
    PROCESSING
fn        not used
      DISPLAY
sp          -795.2
wp          6389.4
rfl          795.6
rfp              0
rp            -7.6
lp           -66.0
        PLOT
wc             240
sc               0
vs              26
th               2
ai   cdc   ph
```

Figure A.30. ^{1}H NMR of 4-nitrobiphenyl



```
exp2  s2pul

      SAMPLE
date    Jul 25 2006
solvent       CDCl3
file            exp
   ACQUISITION
sw          25125.6
at            1.199
np            60270
fb            13800
bs               64
d1            2.000
nt             2000
ct             1408
   TRANSMITTER
tn              C13
sfrq        100.561
tof          1553.6
tpwr             60
pw            8.750
   DECOUPLER
dn               H1
dof               0
dm              yyy
dmm               w
dpwr             46
dmf           12270
      SPECIAL
temp           30.0
gain       not used
spin             20
hst           0.008
pw90         17.500
alfa         20.000
      FLAGS
il                n
in                n
dp                y
hs               nn
   PROCESSING
lb             1.00
fn         not used
   DISPLAY
sp          -1501.5
wp          25124.9
rfl          1502.3
rfp               0
rp            125.0
lp           -378.0
      PLOT
wc              240
sc                6
vs               56
th                4
nm  no  ph
```

Figure A.31. ^{13}C NMR of 4-phenylaniline

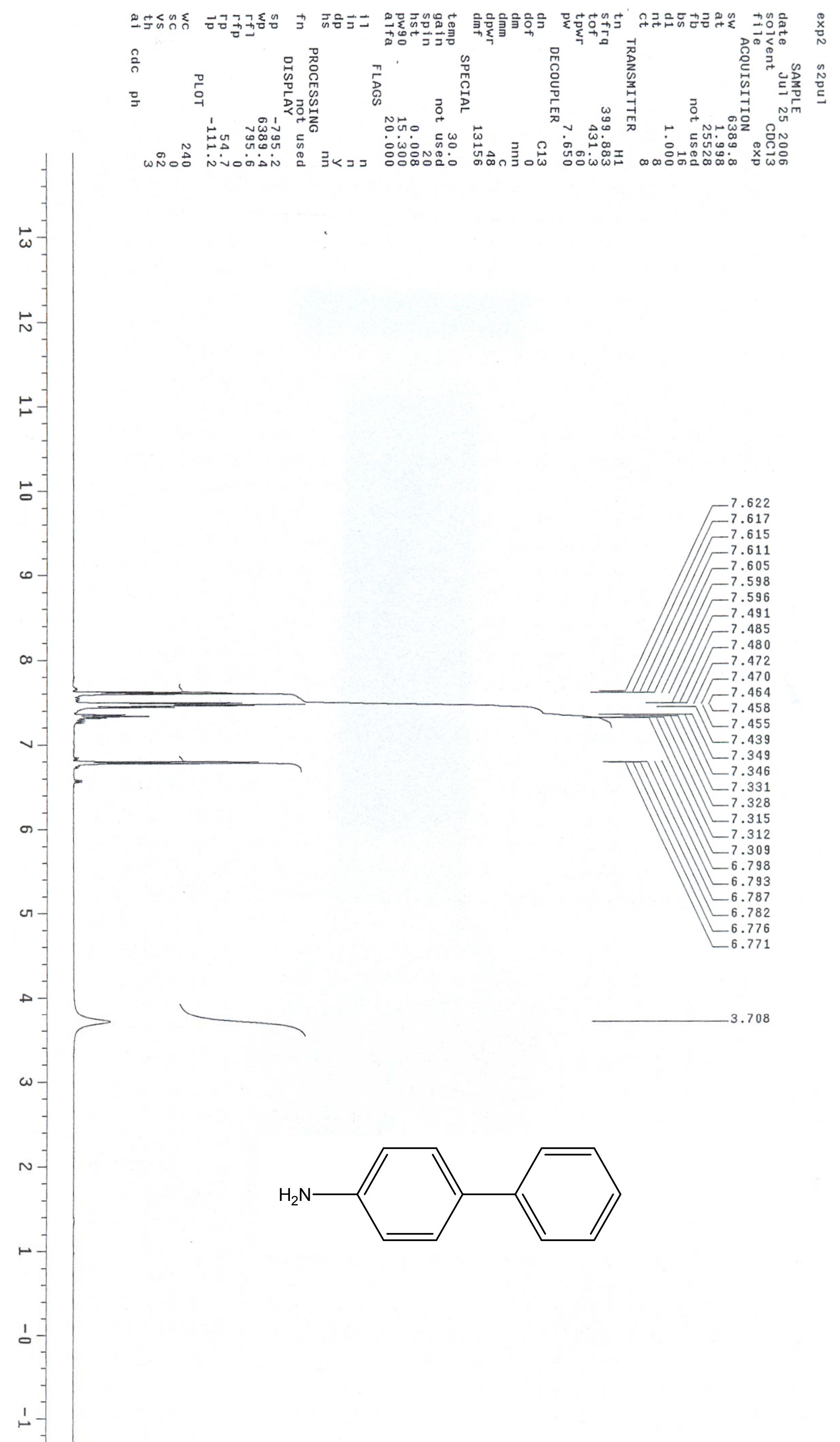


Figure A.32. ^{1}H NMR of 4-phenylaniline

APPENDIX B

MASS SPECTRUMS OF SUZUKI CROSS-COUPLING PRODUCTS

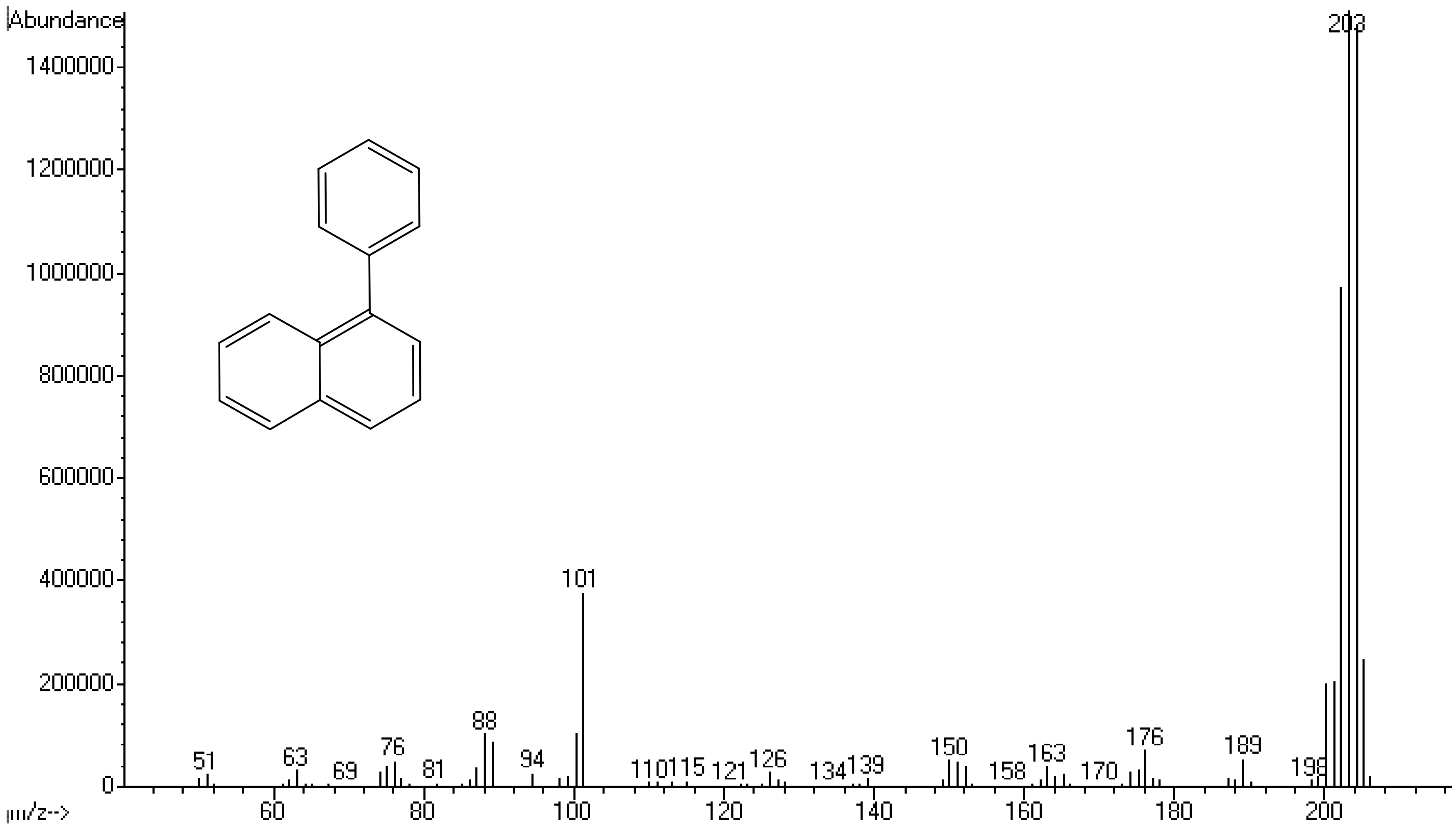


Figure B.1. Mass spectrum of 1-phenylnaphthalene

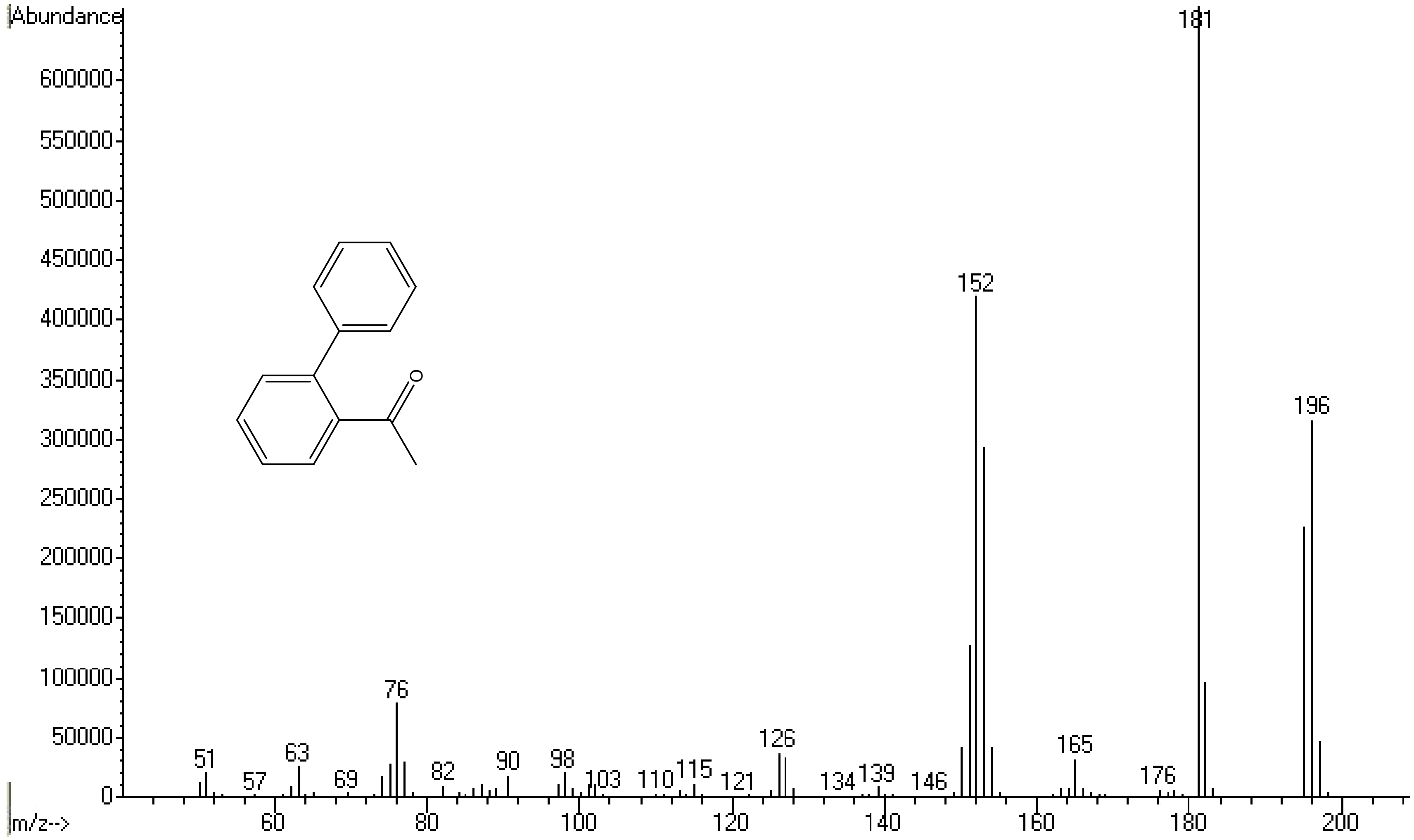


Figure B.2. Mass spectrum of 2-acetylbiphenyl

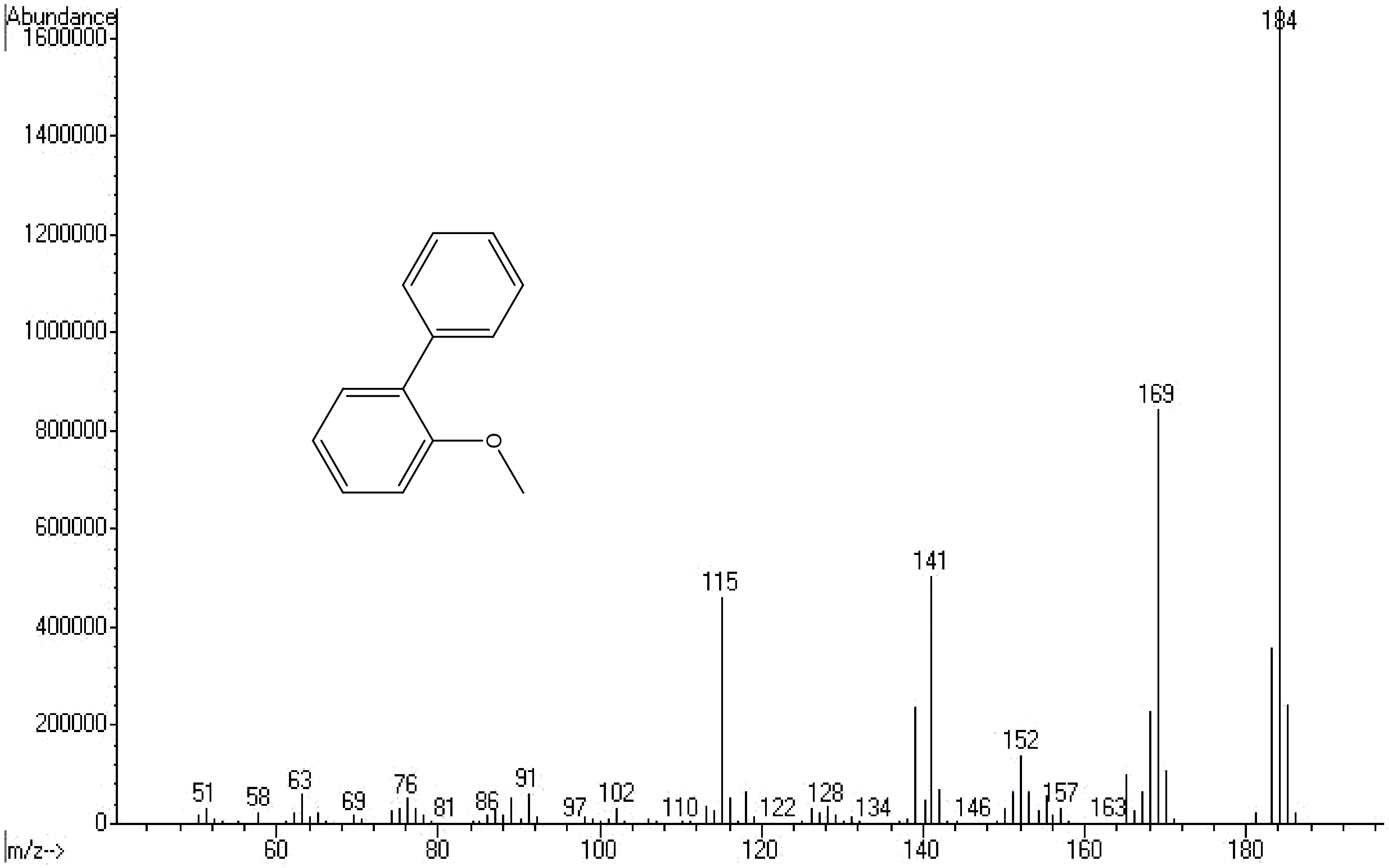


Figure B.3. Mass spectrum of 2-methoxybiphenyl

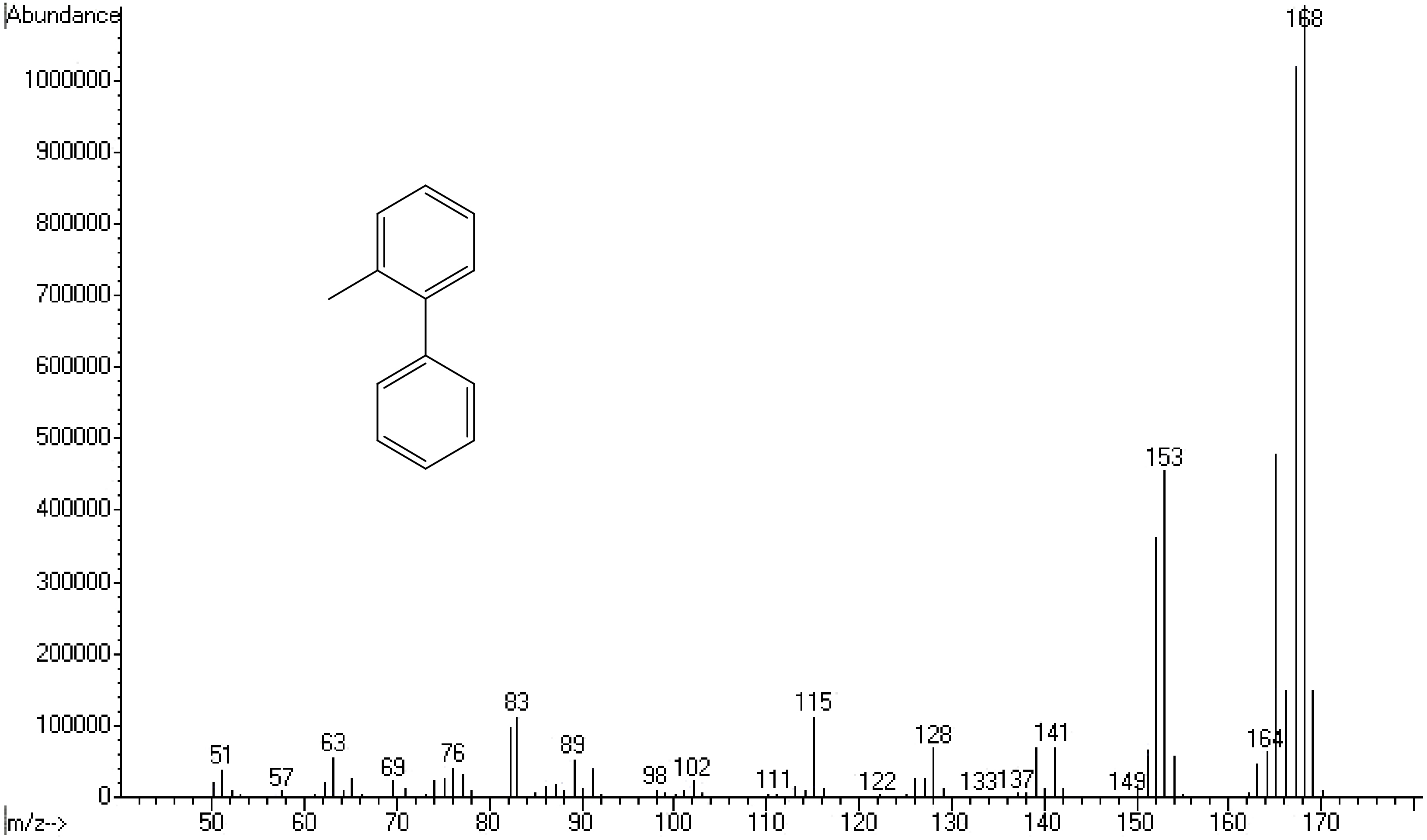


Figure B.4. Mass spectrum of 2-methylbiphenyl

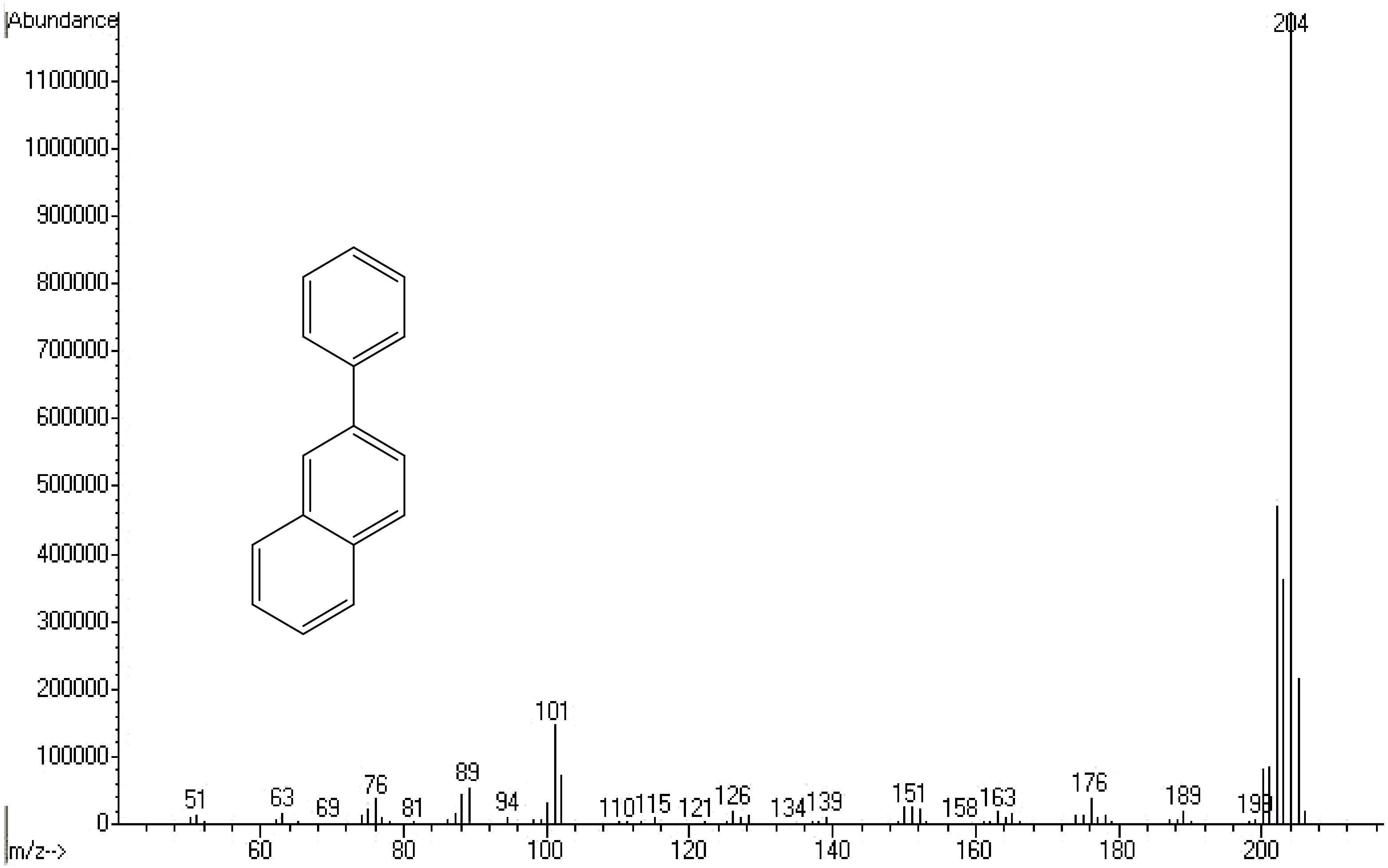


Figure B.5. Mass spectrum of 2-phenylnaphthalene

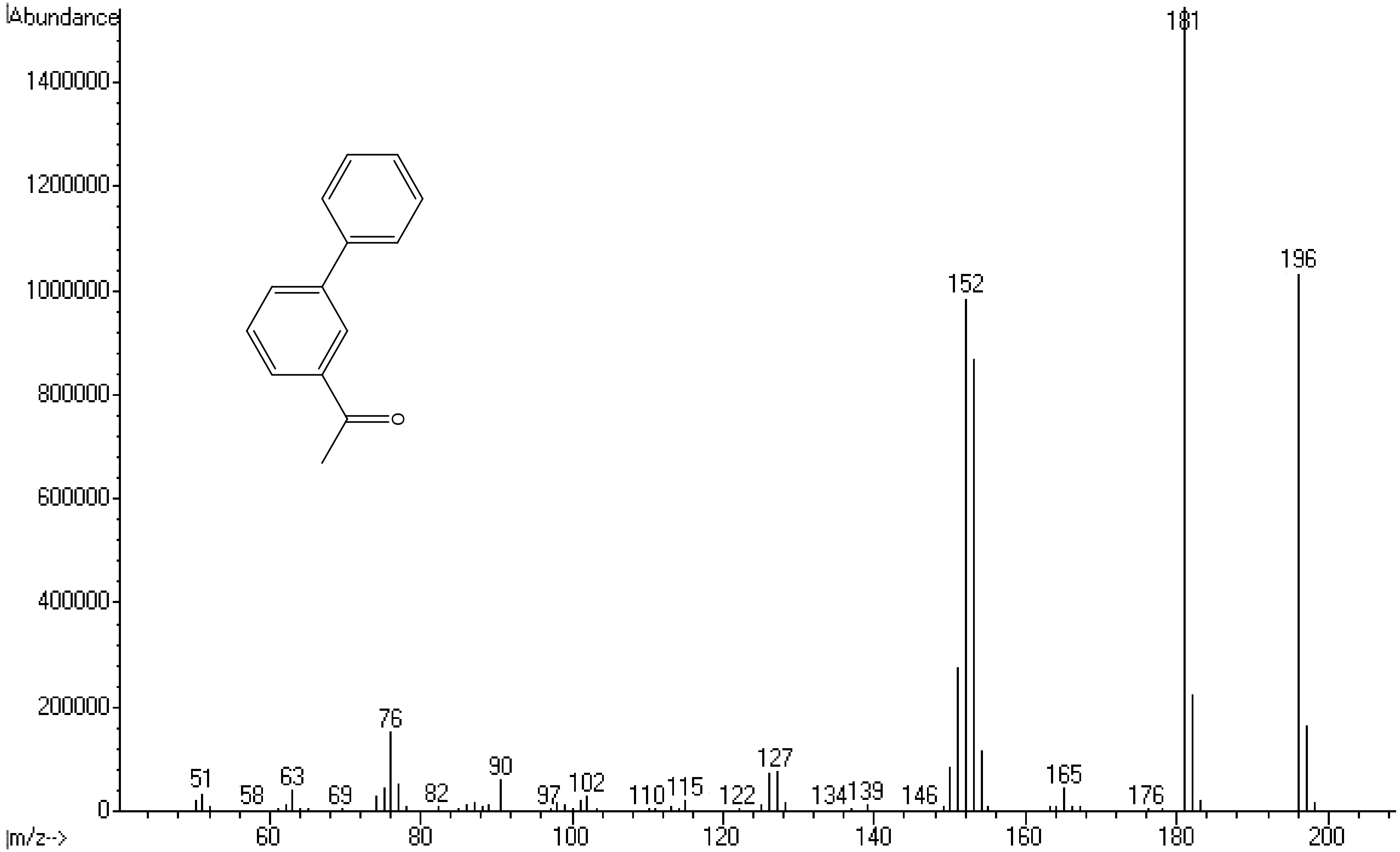


Figure B.6. Mass spectrum of 3-acetylbiphenyl

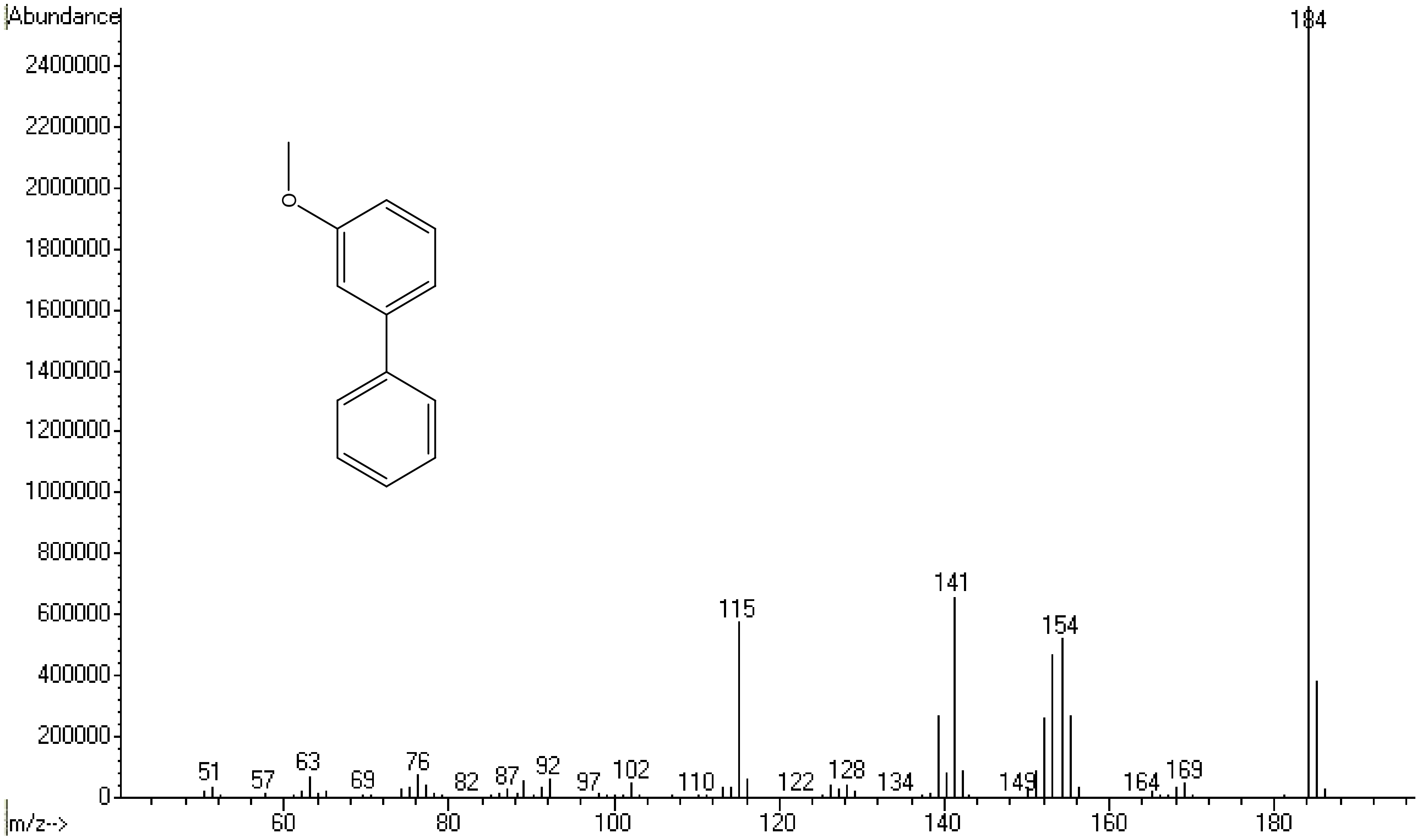


Figure B.7. Mass spectrum of 3-methoxybiphenyl

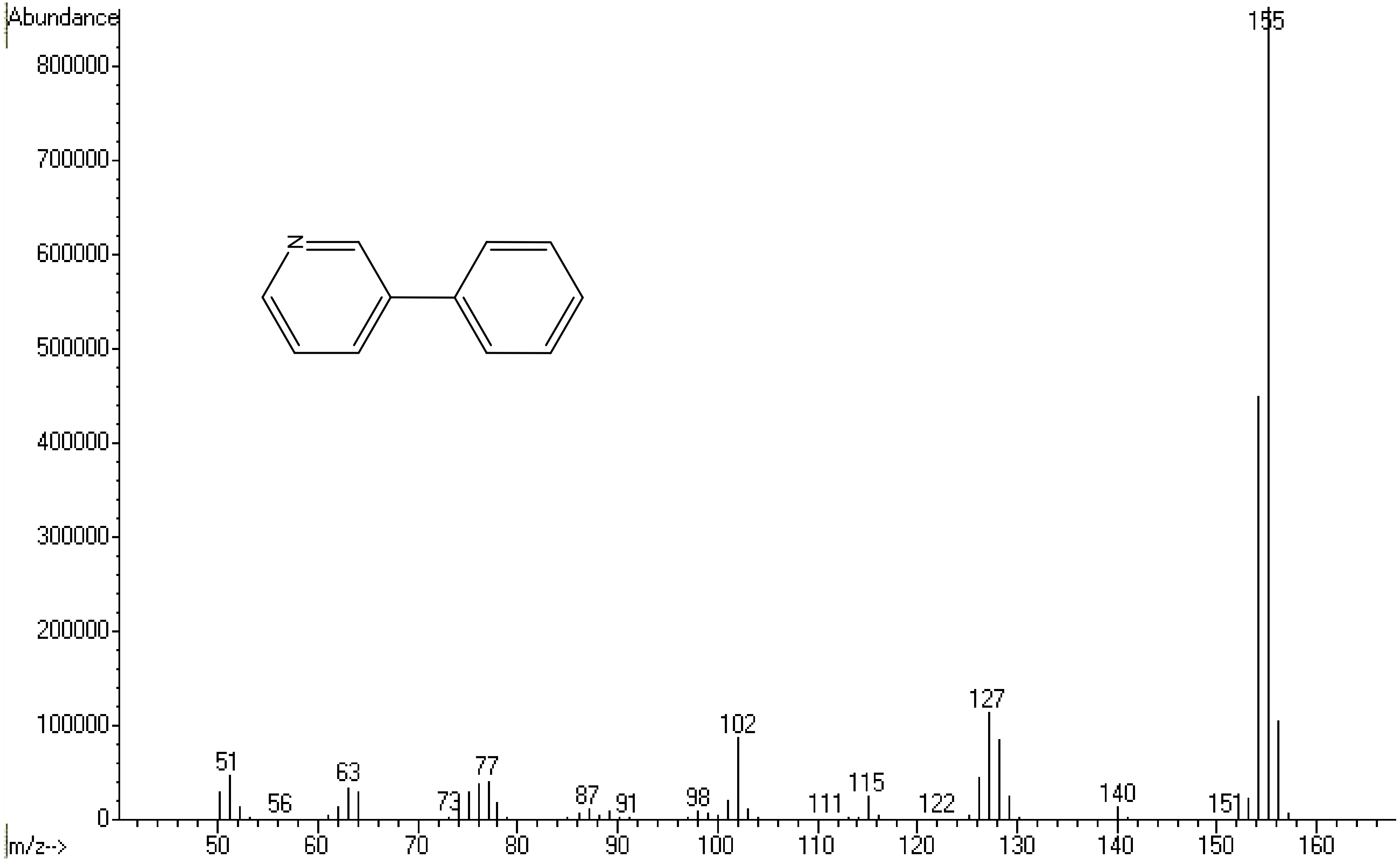


Figure B.8. Mass spectrum of 3-phenylpyridine

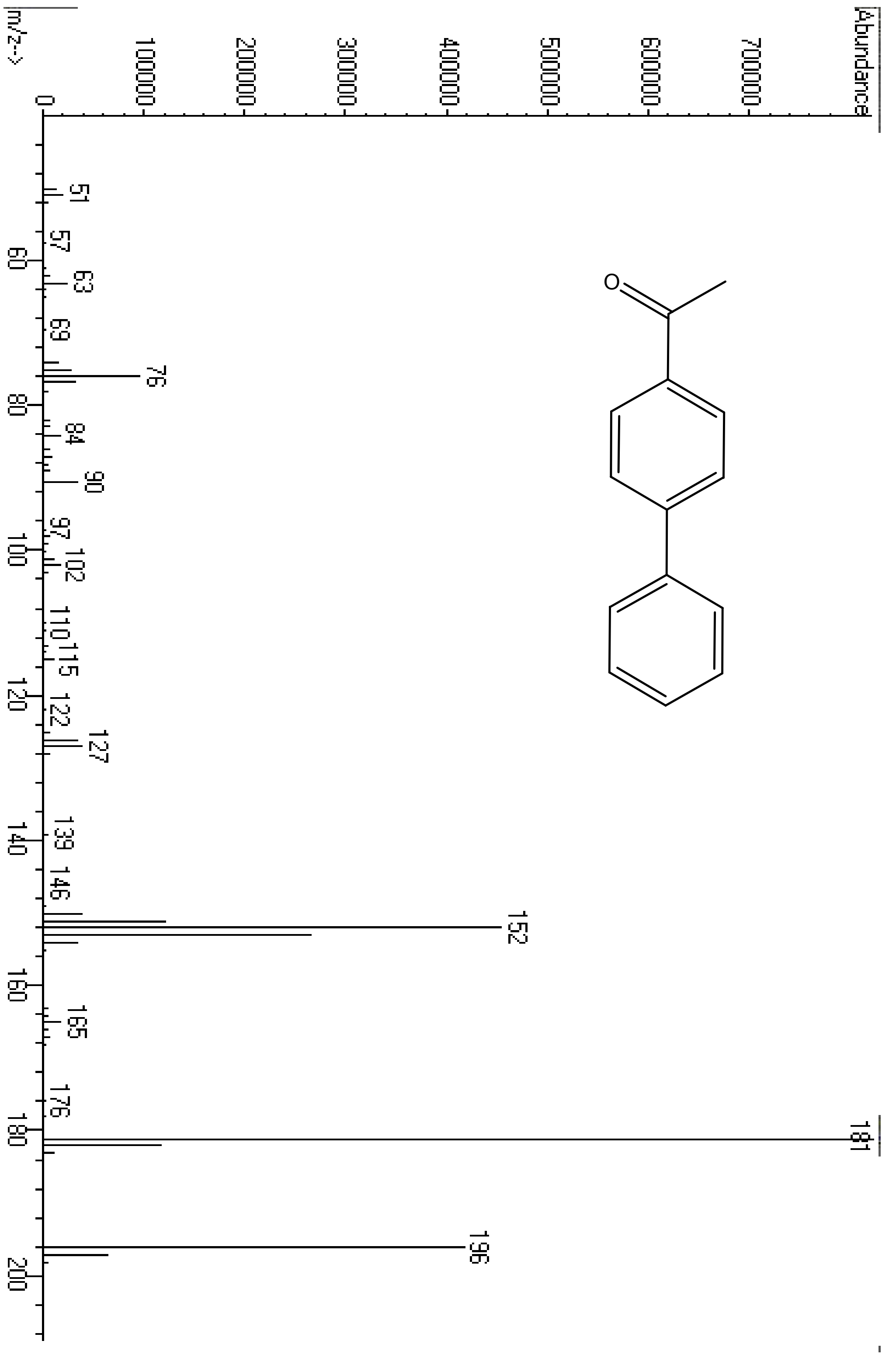


Figure B.9. Mass spectrum of 4-acetylbiphenyl

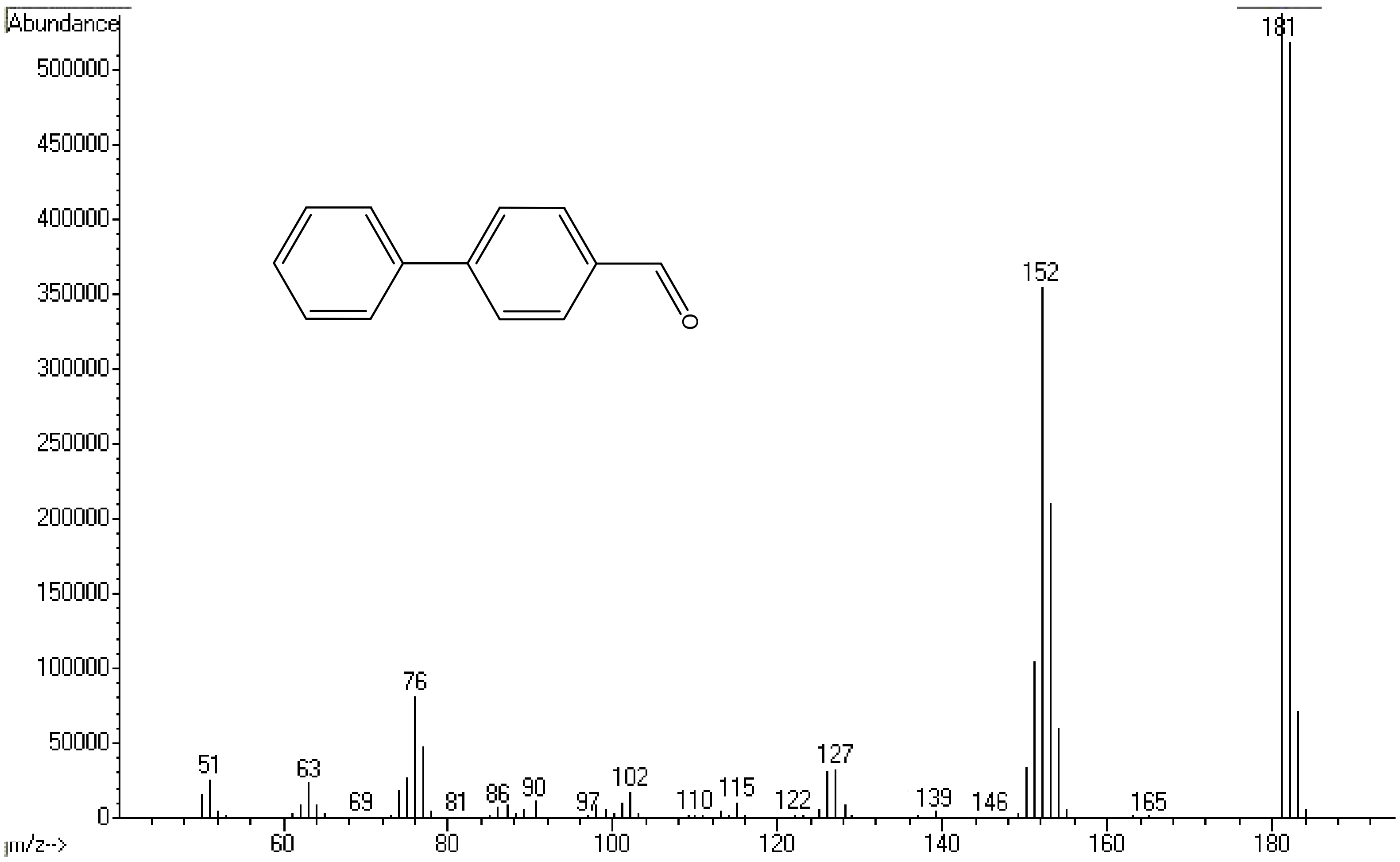


Figure B.10. Mass spectrum of 4-phenylbenzaldehyde

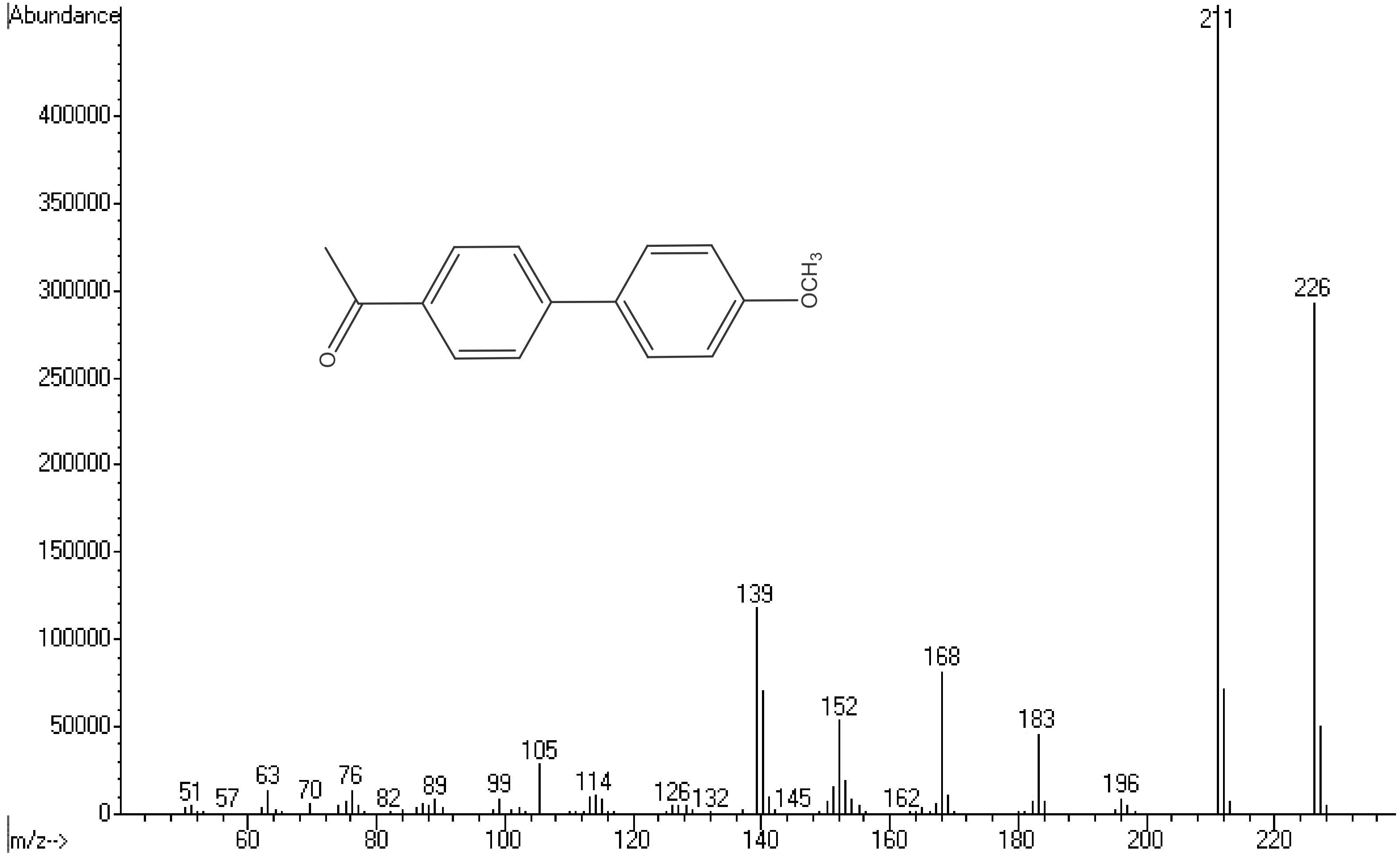


Figure B.11. Mass spectrum of 4-acetyl-4’-methoxybiphenyl

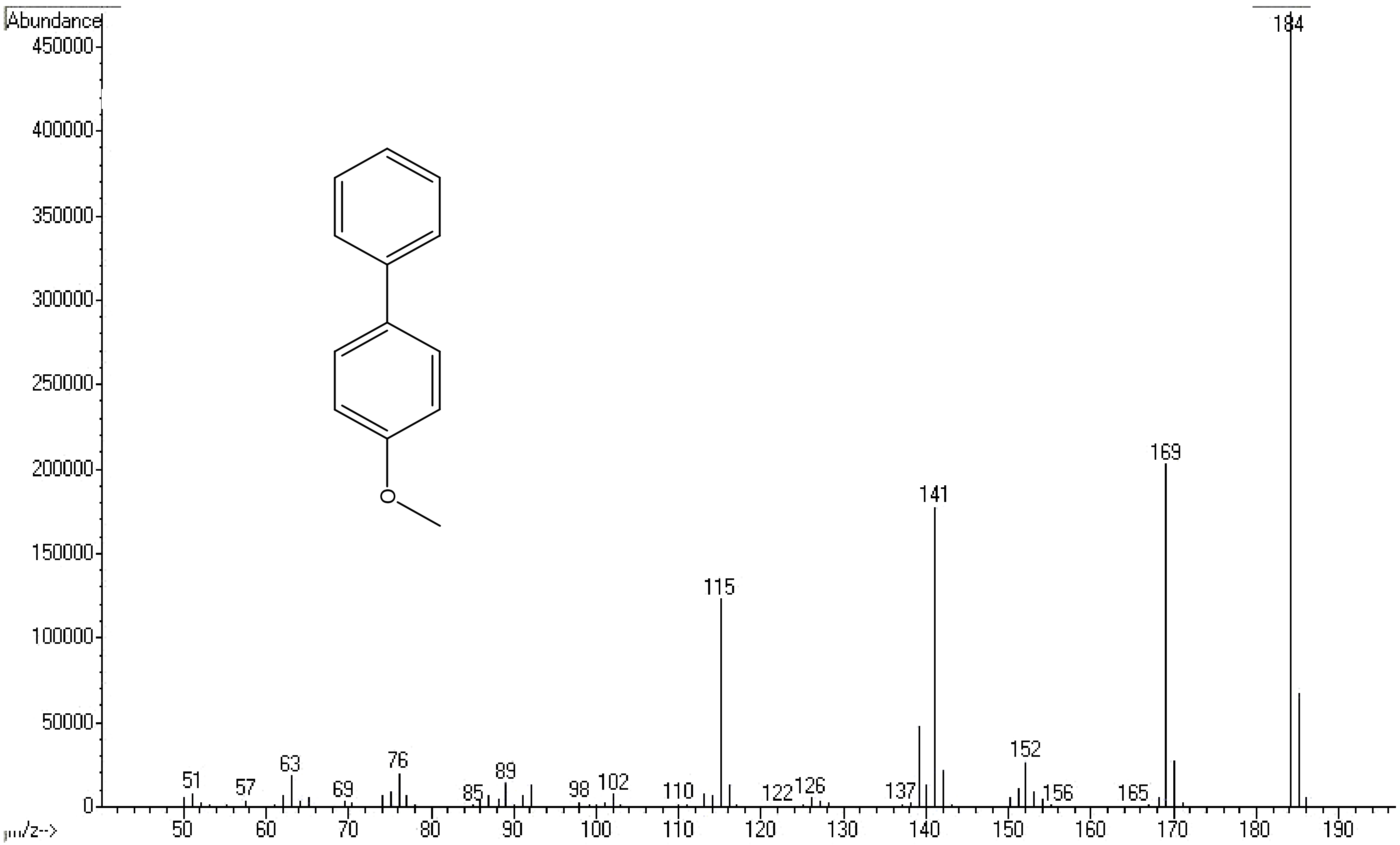


Figure B.12. Mass spectrum of 4-methoxybiphenyl

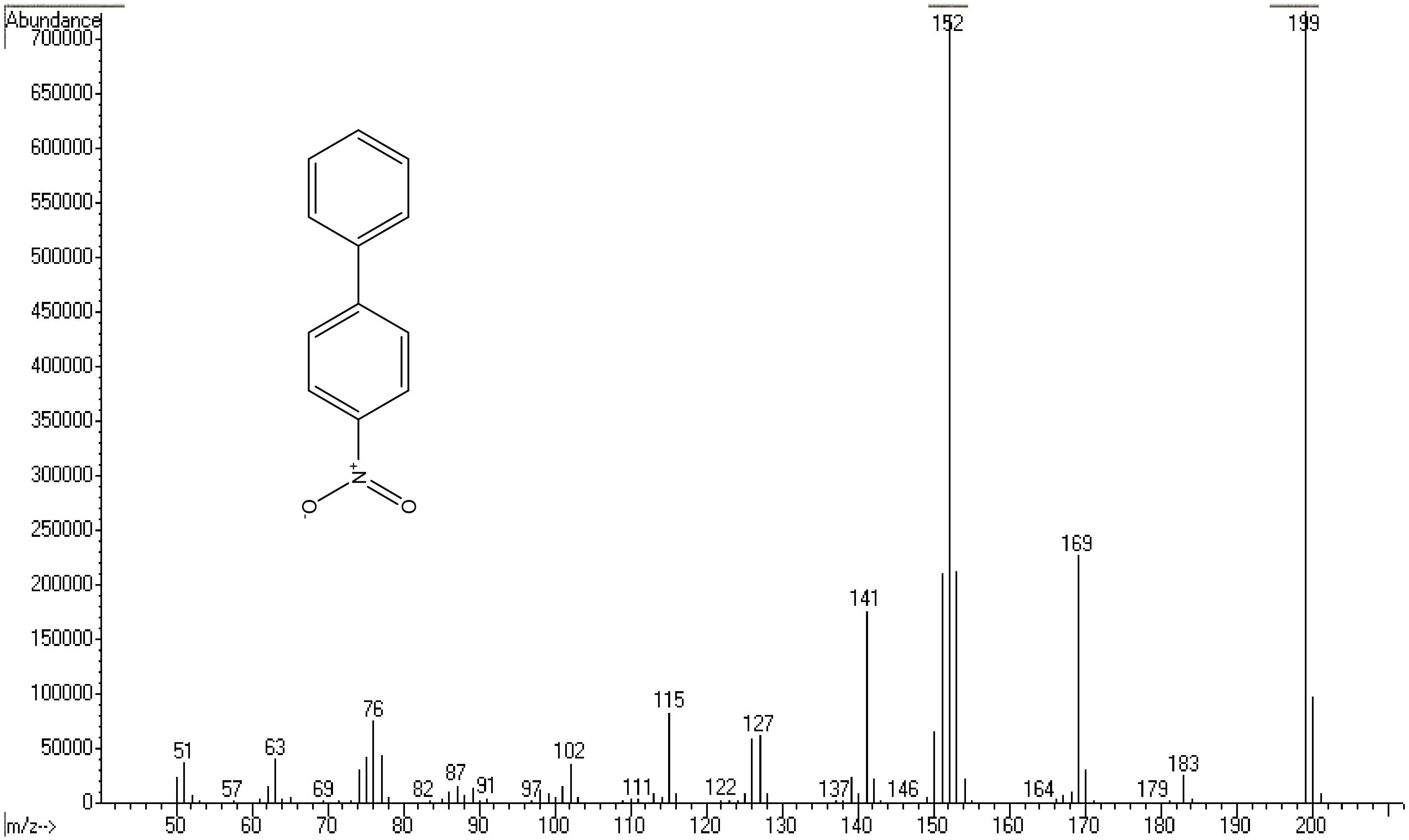


Figure B.13. Mass spectrum of 4-nitrobiphenyl

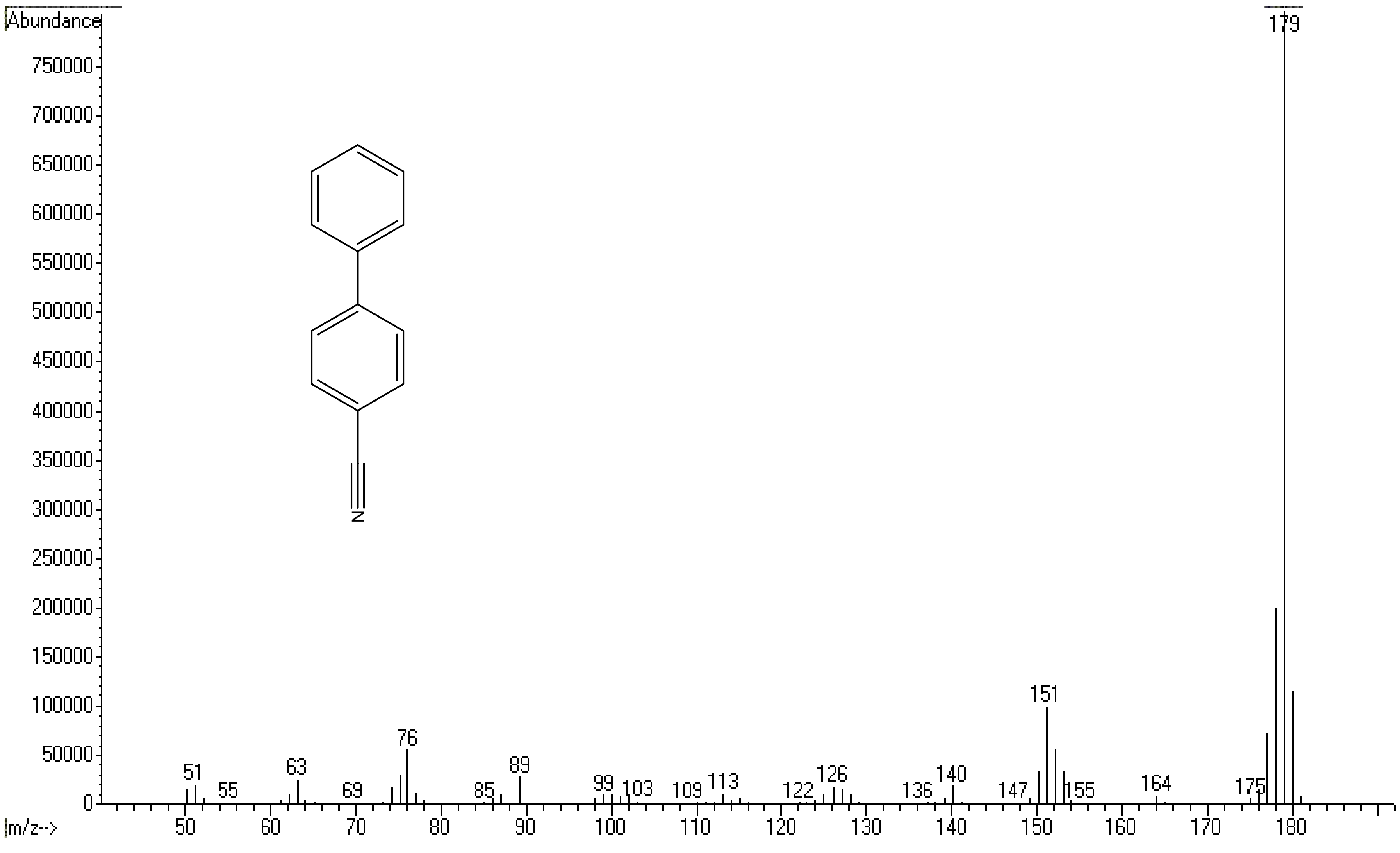


Figure B.14. Mass spectrum of 4-cyanobiphenyl

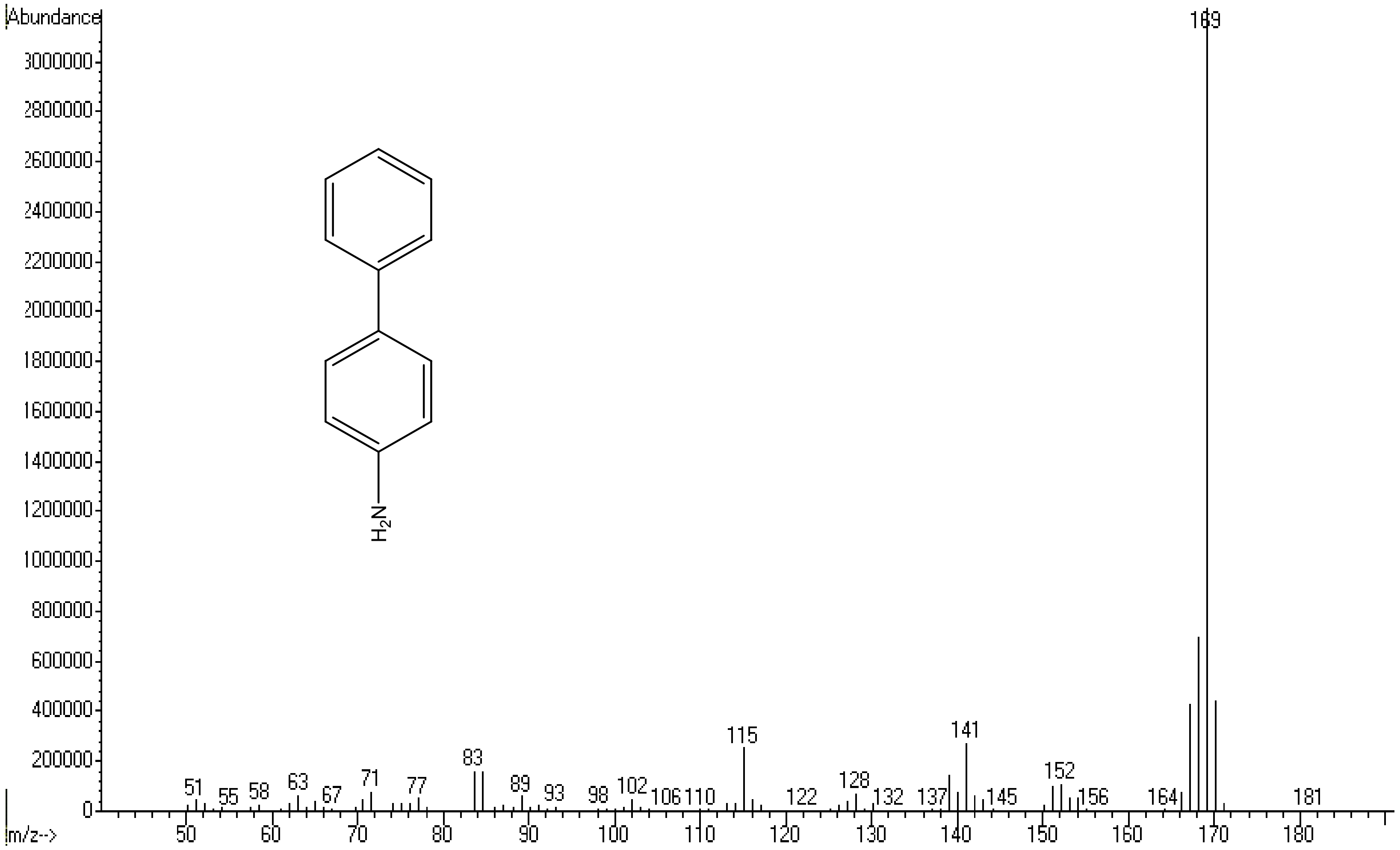


Figure B.15. Mass spectrum of 4-phenylaniline

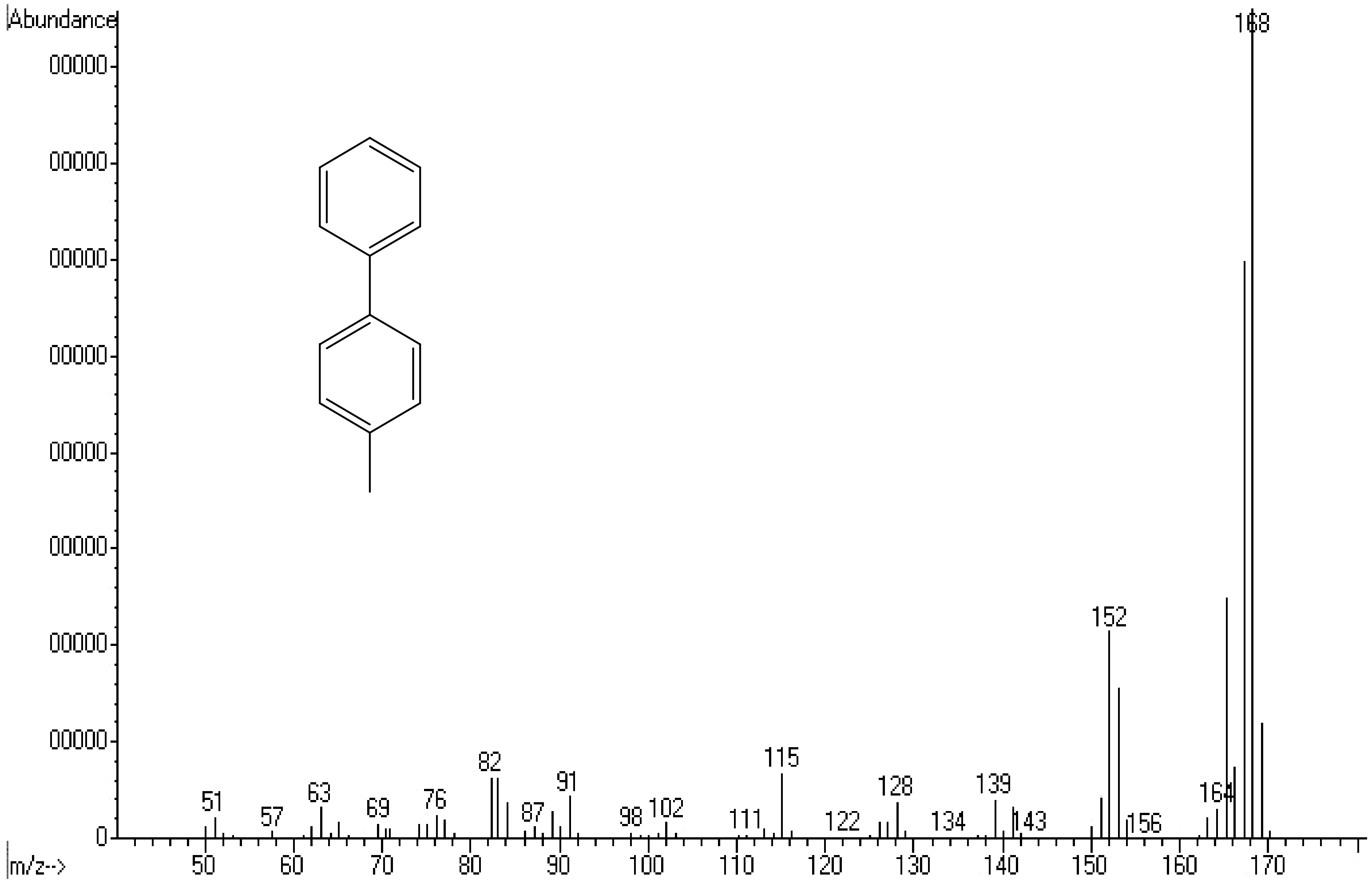


Figure B.16. Mass spectrum of 4-methylbiphenyl