DEVELOPMENT OF HIGHLY EFFICIENT PALLADIUM CATALYSTS AND ORGANIC REACTIONS

by

CHENGGUO DONG

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy

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Abstract

DEVELOPMENT OF HIGHLY EFFICIENT PALLADIUM CATALYSTS AND ORGANIC REACTIONS

by

Chengguo Dong

Advisor: Dr. Qiao-Sheng Hu

Over the past decades, Palladium catalyzed bond-forming reactions including cross-coupling reactions are among the most powerful transformations in organic synthesis. It is of our primary concern to develop highly active Palladium catalysts and new reactions/processes to further enhance the efficiency of Palladium catalysis.

We have developed very highly active palladium catalysts that employ rigid and sterically regular monodentate phosphine containing polymers for Suzuki coupling reactions. To achieve extremely highly active palladium catalysts that will be widely applied both in pharmaceutical/chemical development and basic research, we carried out mechanistic studies directed at furnishing insights of the origin of the unusual catalytic activity of monophosphine/Palladium complex in the

coupling processes. Our study suggested that bridged dimeric palladiums complexes are relatively stable species with high catalytic activities and 1,3-dipalladium complexes have high catalytic activities in the ferrocenyl-methylphosphine-containing polymers/Palladium catalysts.

Based on our discovery of the reaction mechanism, we pinpointed that the individual elementary steps in each catalytic cycle could be controlled and such a control, especially combined with other bond forming processes, could provide us unprecedented opportunities to develop new reactions/processes; thus making the powerful Palladium-catalyzed cross-coupling reactions be even more powerful for organic synthesis.

We developed Pd(0)/*t*-Bu_3P-catalyzed Suzuki cross-coupling of dihaloarenes with arylboronic acids, a process that relies on the control of oxidative addition step, and defined the concept of "Preferential oxidative addition". The results lead to the development of new, efficient processes to conjugate polymers with controlled length which are potentially useful in molecular electronics. We have also development tandem cross-coupling-cyclization reactions by controlling transmetalation rate, a cyclization process that combines the control of the transmetalation step with sp^3 C-H activation as well as Palladium-Associated Aryne forming processes. This work provides a high yield, one-step access to substituted fluorenes from

readily available 1,2-dihalobenzenes and 2-haloaryl arenesulfonates and hindered Grignard reagents. It may find applications in the preparation of substituted fluorene-containing molecules including polymers.

To My Family

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I gratefully thank my thesis committee members, Professors Nan-Loh Yang and Klaus Grohmann, for their support and general comments over the years. I really gained a lot from their tutelage.

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I would like to thank my parents for their constant support and encouragement during the course of my studies. I owe them a lot since my

graduate study abroad. Their dedication, love and persistent confidence in me are important factors towards my success.

Especially, I would like to give my loving thanks to my wife Huiyu (Carol) Liu and my daughter Jessica M. Dong whose patient love enabled me to complete this work. They have lost a lot due to my research work. Without their encouragement and understanding it would have been impossible for me to finish this work. My special gratitude is due to my parents, my sisters and their families for their support.

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INTRODUCTION

Over the past decades, palladium-catalyzed carbon-carbon and carbon-heteroatom bond forming reactions such as the Suzuki coupling, the Kumada coupling are among the most powerful transformations in organic synthesis. They have been extensively used for the synthesis of a wide variety of organic compounds ranging from natural products, polymers, advanced materials, and pharmaceuticals.[1]

Scheme I-1 Palladium-Catalyzed Cross-Coupling Reactions

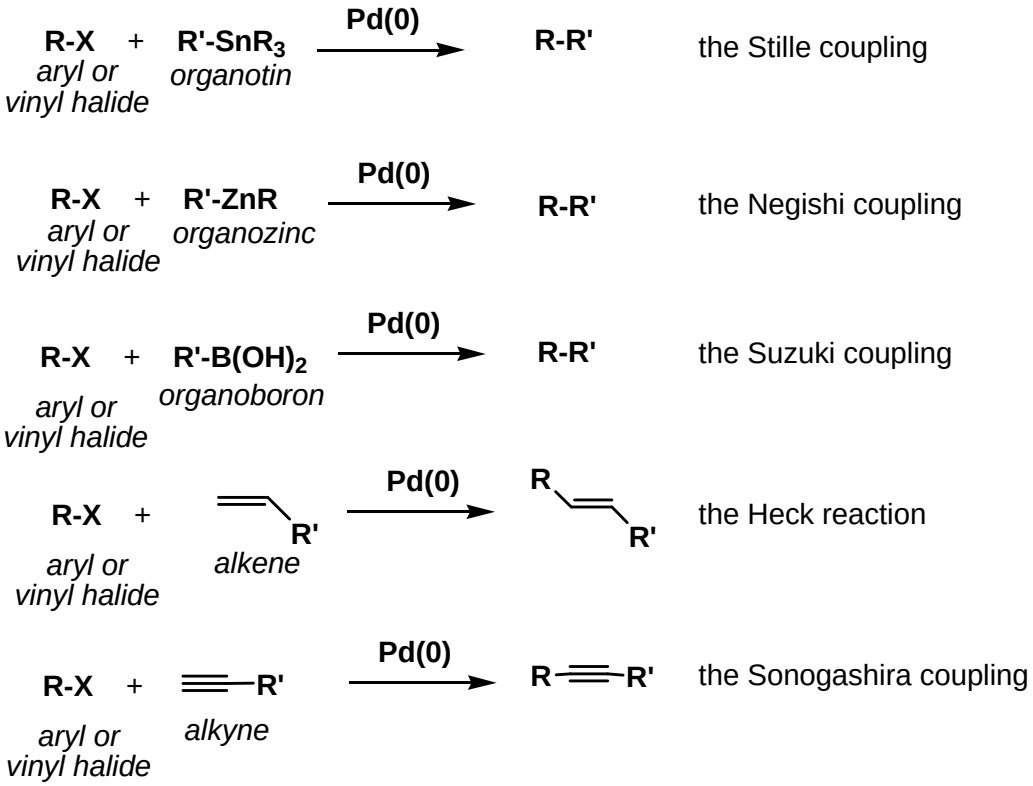
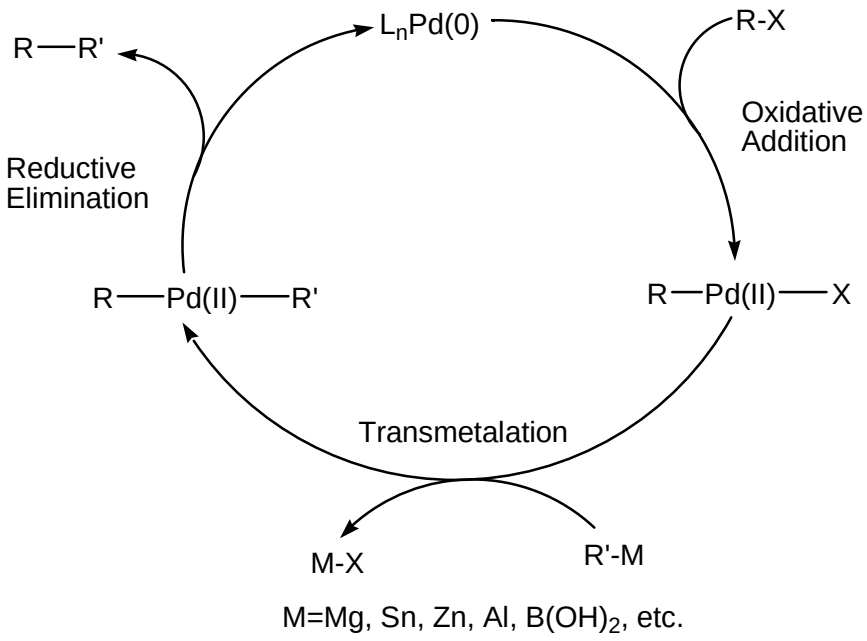


Figure I-1 Mechanism of Palladium Catalyzed Cross-coupling Reaction



Extensive study established that there are three key elementary steps in the catalytic cycles of Pd(0)-catalyzed cross-coupling reactions: oxidative addition of Pd(0) with an aryl halide to form Pd(II) complex; transmetalation of the Pd(II) complex with an organometallic reagent to form an diorganopalladate complex; and reductive elimination of the diorganopalladate complex to form the cross-coupling product and regenerate the Pd(0) catalyst (Figure 1).[2]

The catalytically active species of Pd(0) can be generated *in situ* to enter the reaction cycle. The oxidative addition of aryl/alkyl halides can

occur to these species to generate Pd (Π) or Ni (Π) complexes. The relative reactivity for aryl/alkenyl halides is R-I > R-Br > R-Cl (R=aryl/alkenyl group) due to the relative carbon halides bond strength. Electron-deficient substrates undergo oxidative addition more readily than those electron-rich ones because this step involves the oxidation of the metal and reduction of the organic aryl/alkenyl halides. Rate-determing step in the catalytic cycle could be the oxidative addition or the transmetallation step. Therefore, side reactions may occur during these two steps. Organometallic reagents and related nucleophiles used for the transmetalation step include Grignard reagents, organozincs, organotins, organoboron reagents and organocopper reagents.

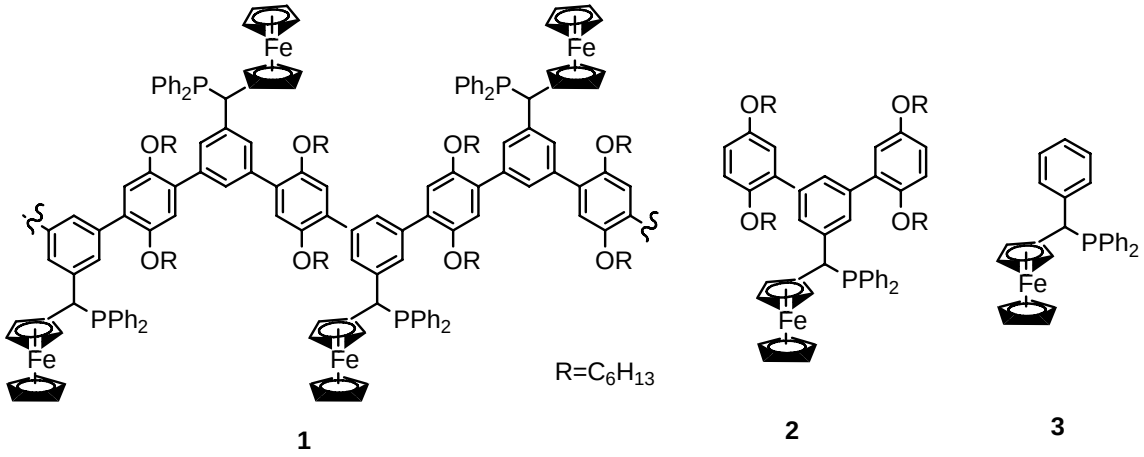
It is of our primary concern to develop highly active transition metal catalysts and new reactions/processes to further enhance the efficiency of transition metal catalysis. Among numerous transition metal catalysts developed, phosphine-coordinated transition metal complexes are the most used ones. Coordinatively unsaturated 14-electron transition metal complexes such as $(R_3P)_2Pd(0)$ complexes are generally accepted as the catalytically active species in most palladium catalyzed reactions. Compared to the extensively studied 14-electron palladium(0) complexes, coordinately unsaturated 12-electron palladium(0) complexes such as (monophosphine)-

Pd(0) complexes remain largely unexplored because of the lack of general method to access them, mainly due to the tendency of monophosphines, even every bulky ones, to form $(R_3P)_2Pd(0)$ complexes. It is therefore fundamentally interesting and synthetically useful to develop general approaches to coordinatively unsaturated (monophosphine)-Pd(0) complexes. Our group has developed rigid and sterically regular monophosphine-containing polymers ligands that could be a approach to $(R_3P)Pd(0)$ complexes.[3] We reason that the rigidity and stereoregularity of rigid and sterically regular polymers with suitable monophosphine installation could make the second monophosphine ligand unavailable for coordination, and thus only one, rather than two, monophosphine moiety will coordinate to one palladium center when they are used as ligands.

On the basis of this hypothesis, we have selected to construct rigid and sterically regular ferrocenylmethylphosphine-containing polymers **1** (Figure 2) as ligand for the room temperature Suzuki cross-coupling of unactivated aryl chlorides, a notable advance in organometallic chemistry in recent years. Our study showed that catalysts generated from **1**/Pd(0) can smoothly catalyze this transformation, while monomeric ferrocenylmethylphosphines **2** and **3** are ineffective ligands. We have also excluded Pd(0) itself as catalytically active species because no reaction was

observed when no phosphine ligand was used. It is thus believed that the catalytically active species in **1**/Pd(0) system is $(R_3P)Pd(0)$ or analogs. These studies formed the basis of part of my thesis research, aiming to understand the nature of the catalytically active species in **1**/Pd (0) complexes and to develop catalyst systems with even higher catalytic activities.

Figure I-2 Structure of the Ferrocenylmethylphosphine-containing Polymers **1**, Monomers **2** and **3**



1 **2** **3**

Based on our understanding of the reaction mechanism, we believed that the individual elementary steps in each catalytic cycle might be controlled. Such a control, especially combined with other bond forming processes, could provide us unprecedented opportunities to develop new reactions/processes; thus making the powerful transition metal-catalyzed cross-coupling reactions be even more powerful for organic synthesis. " The

usual procedure for the synthesis of organic compounds is the stepwise formation of the individual bonds in the target molecule. However, it would be much more efficient if several bonds could be formed in one sequence without isolating the intermediates, changing the reaction conditions, or adding reagents. It is obvious that this type of reaction would allow the minimization of waste and thus making the waste management unnecessary since compared to stepwise reactions the amount of solvents, reagents, adsorbents, and energy would be dramatically decreased. In addition the amount of labor would go down. Thus, these reactions would allow an ecologically and economically favorable production." [4] This type of transformation is called a domino reaction or tandem reaction. Transition metal-catalyzed transformations are of increasing importance in synthetic organic chemistry. Therefore, the use of this type of transformation as part of a tandem reaction will be of increasing interest. Transition metal-catalyzed C-H bond activation is an area of considerable current interest.[5] In particular, the ability of palladium to activate C-H bonds has been used extensively in organic synthesis.[6] Our study mainly focuses on this type of reaction.

References:

1) (a) Beller, M.;Bolm,C. *Transition Metals for Oragnic Synthesis*;Wiley-VCH: Weinheim, **1998**. (b) Stang, P.J. *Transition Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, **1998**. (c) Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, **1987**. (d) Trost, B.M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon: Elmsford, NY, **1991**. (e) Jacobsen, E.N.; Pfaltz, A.; Yamamoto,Y. *Comprehensive Asymmetric Catalysis*; Springer: New York, **1999**.

2) (a) Miyaura, N.; Suzuki; A. *Chem. Rev.*, **1995,** 95, 2457. (b) Suzuki, A. *J. Organomet. Chem.*, **1999, 57**6, 147.

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4) Tietze L. F. *Chem. Rev.* **1996,** 96, 115-136.

5) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731-1770.

6) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533-538.

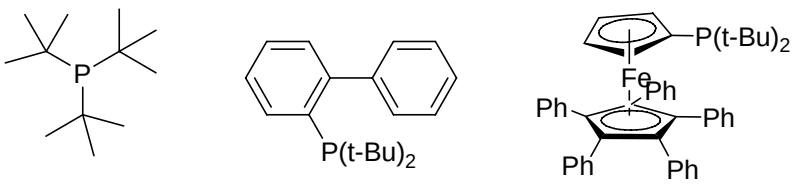
CHAPTER ONE

Synthesis and Catalytically Study of Ferrocenylmethylphosphine-Containing Ligands for Palladium-Catalyzed Cross- Coupling Reactions

1.1 Introduction

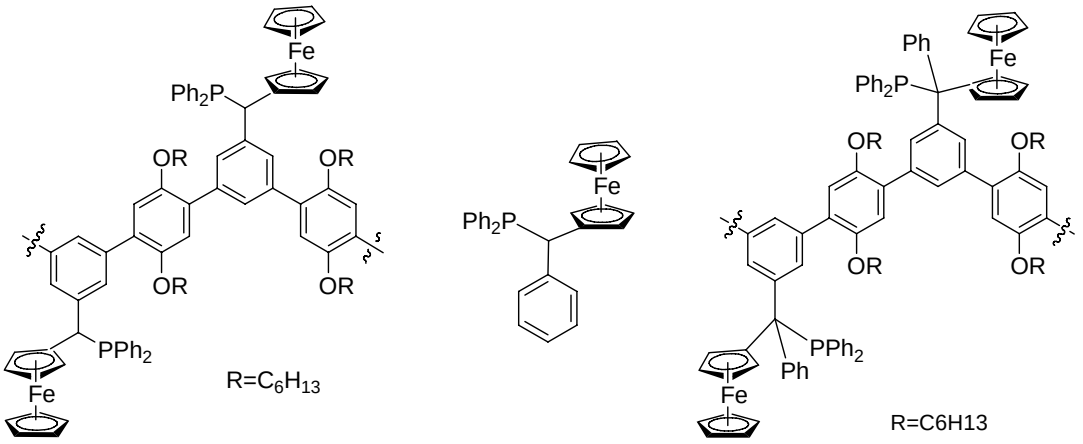
Palladium-catalyzed carbon-carbon and carbon-heteroatom bond formations are among the most powerful transformations in organic synthesis.[1,2] Coordinatively unsaturated palladium complexes such as 14-electron [$(R_3P)_2Pd(0)$], formed through either ligand dissociation or displacement, are generally accepted as the catalytically active species in most palladium(0)-catalyzed reactions. Recently, coordinately unsaturated [$(R_3P)Pd(0)$] complexes have been proposed as catalytically active species in Pd(0)-catalyzed cross-coupling reactions involving widely available, inexpensive aryl chlorides as coupling partners.[3-7] Under room temperature only high efficient catalysts can catalyze the Suzuki coupling reactions of aryl chlorides.

Figure 1.1 Bulky Electron-Rich Monophosphines Ligands for Cross-Coupling Reactions



1 2 3

Figure 1.2 Structure of the Ferrocenylmethylphosphine-containing Polymer **4, 6** and Monomer Moiety **5**



4 **5** **6**

Reported systems to access [(R_3P)Pd(0)] complexes involve the use of bulky, electron rich monophosphines such as **1**-**3** (Figure 1.1). In our laboratory, we are interested in developing highly active palladium catalysts that catalyze aryl chloride cross-couplings under mild conditions. Particularly, we are interested in developing alternative routes to access highly active [(R_3P)Pd(0)] complexes by employing macromolecules including polymer-supported monophosphines as ligands. We have designed and synthesized monophosphine-containing polymer **4** (Figure 1.2), which contains relatively small, not so electron-rich R-PPh_2 (**5**) moieties. Polymer **4** is an efficient ligand for the room-temperature Suzuki cross-coupling of unactivated aryl chlorides, a recent, notable advance in organometallic

chemistry.[8] Our study showed that catalysts generated from polymer **4**/Pd(0) can smoothly catalyze this transformation, while monomeric ferrocenylmethylphosphines **5** are ineffective ligands. We have also excluded Pd(0) itself as catalytically active species because no reaction was observed when no phosphine ligand was used. It is thus believed that the catalytically active species in polymer **4**/Pd(0) system is [(R_3P)Pd(0)] or analogs.

To gain more insights about the nature of the catalytically active species in polymer **4**/Pd (0) complexes and to develop catalyst systems with even higher catalytic activities, we did the systematically study in the catalysis system. We tuned the steric hindrance around the monophosphine moieties; synthesized dimmer and trimmer to mimic the catalytic system to further investigate the catalytical mechanism.

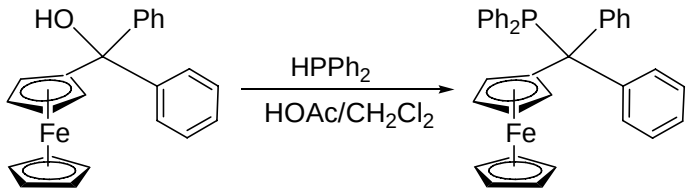
1.2 Tuning Steric Hindrance of α-Position of the Ferrocene Functionality

To study the Pd(0)/polymer **4** catalyst system including the nature of the catalytically active species, we decided to systematically tune the steric hindrance around the monophosphine moieties. As the first step of this systematic investigation, we synthesized polymer **6** (Figure 1.2), which

contains bulkier monophosphine moieties than polymer **4,** to examine the steric effect of the monohphosphine moieties.

The synthesis of polymer **6** is similar to the synthesis of polymer **4**. It is based on our recently developed protocol of direct conversion of ferrocenylmethyl alcohol **7** to ferrocenylmethylphosphine **8** under mild conditions (Scheme 1.1).[9]

Scheme 1.1 Direct Converion of Ferrocenylmethyl Alcohol **7** to Ferrocenylmethylphosphine **8**



7 **8**

Starting from 1,3,5-tribromobenzene, lithilation followed by treatment with benzoylferrocene yields dibromoferrocenylmethyl alcohol **9** in 76% yield.[10] Suzuki coupling polymerization of dibromoferrocenyl-methyl alcohol **9** with diboronic acid **10** under standard Suzuki coupling condition ($Pd(PPh_3)_4$, THF/2 M K_2CO_3, refluxing) generated polymer **11** in 90% yield (Scheme 1.2).[11] GPC (THF, polystyrene standard) analysis showed its molecular weight: Mw = 3,100, Mn = 2,000 (PDI = 1.56), which

is similar to molecular weight we obtained for polymer **4**. Treatment of **11** with acetic aicd in dichloromethane at room temperature gave polymer **6** in 80% yield. Polymer **6** is a yellow solid and can be easily dissolved in common organic solvents such as CH_2Cl_2, THF and toluene. ^{31}P NMR spectrum confirmed the existence of $RPPh_2$ moieties in the polymer.

Scheme 1.2 Synthesis of Monophosphine-containing Polymer **6**

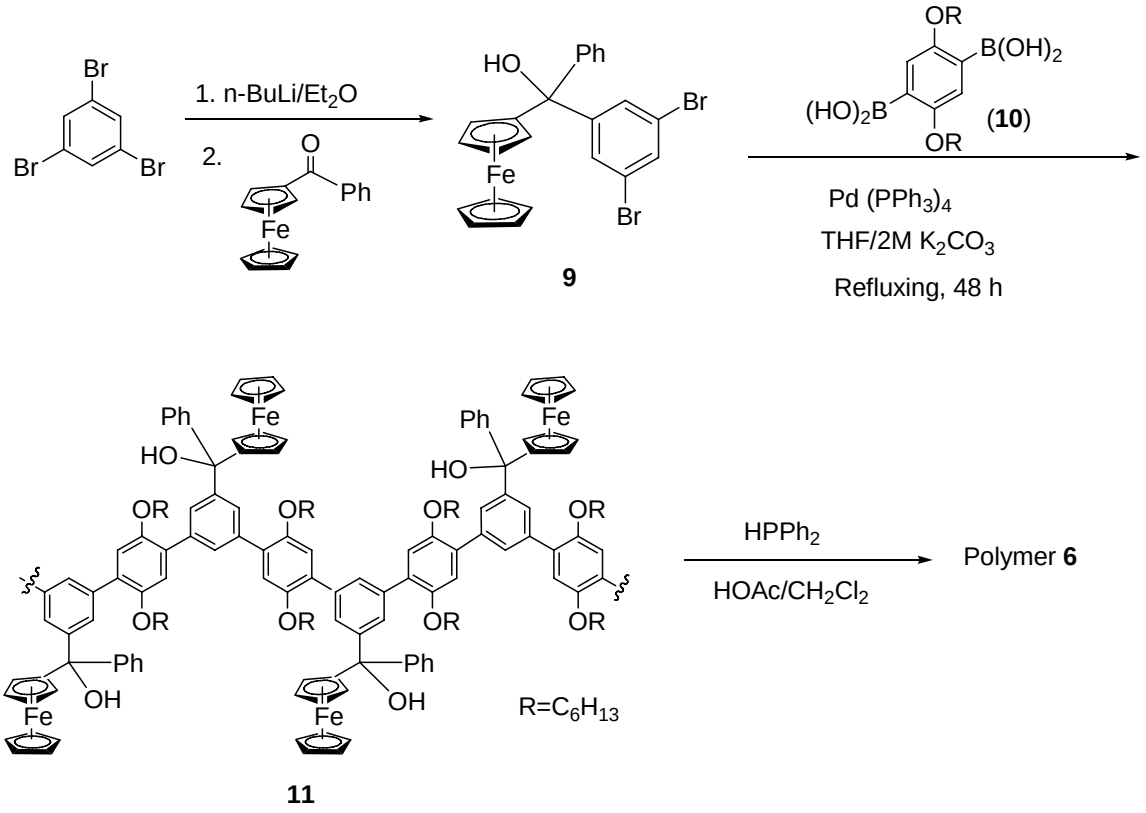
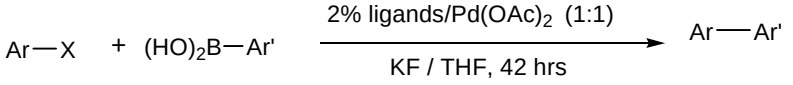


Table 1.1 Room Temperature Palladium(0)-catalyzed Cross-coupling of Aryl Halides with Arylboronic Acids [a]



Entry	Ar—X	(HO)$_2$B—Ar'	Ligand	Conversion (%)
1	MeO-C$_6$H$_4$-Br	C$_6$H$_5$-B(OH)$_2$	6	44
2	MeO-C$_6$H$_4$-Br	C$_6$H$_5$-B(OH)$_2$	8	90 [b]
3	MeO-C$_6$H$_4$-Br	C$_6$H$_5$-B(OH)$_2$	None	6
4	MeO-C$_6$H$_4$-Cl	C$_6$H$_5$-B(OH)$_2$	6	0
5	MeO-C$_6$H$_4$-Cl	C$_6$H$_5$-B(OH)$_2$	8	0

a. Reaction conditions: aryl halides (1.0 equiv.), phenylboronic acid (1.5 equiv.), KF (3.0 equiv.), THF (2 ml), room temperature. b. Reaction time: 48 hrs.

We have carried out the study of employing polymer **6** as ligand for Pd(0)-catalyzed coupling reactions of aryl halides with phenylboronic acids. We found that **6** was an effective ligand for Pd(0)-catalyzed couplings of bromobenzene with phenylboronic acid. However, our study showed that both monophosphine **8** and polymer **6** were ineffective ligands for the coupling of *p*-chloroanisole with phenylboronic acid. These results are in sharp contrast to the ones we obtained with polymer **4** and its corresponding monomeric monophosphine **5**: polymer **4** was an effective ligand for the same cross-coupling reaction while **5** was an ineffective one. These results suggested that increasing the steric hindrance at the α-position of ferrocenyl

groups likely deactivates the polymer ligand/palladium catalysts by decomposition and is thus detrimental to the catalytic property of the monophosphine-containing polymer as ligand for Pd(0)-catalyzed cross-coupling reaction of aryl chlorides with arylboronic acids.

1.3 Investigating on the Nature of Monodentate Phosphine Palladium Complex

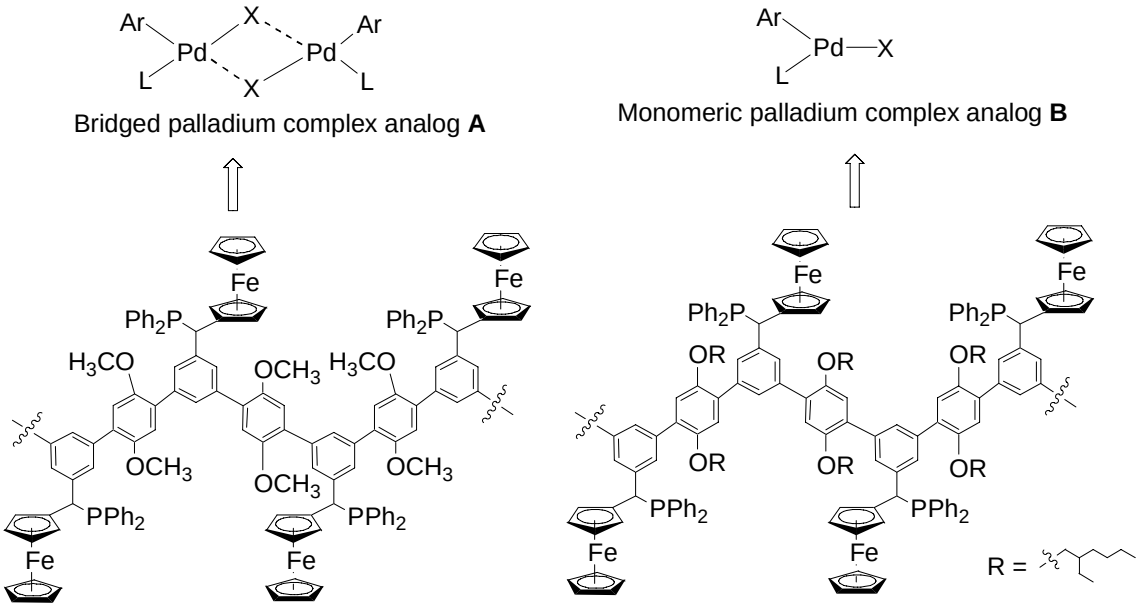
Although the [(R_3P)Pd(0)] being the real catalytically reactive species is generally accepted, the stabilities of catalytically active species during catalytic reactions, (R_3P)Pd(0) and [(R_3P)(Ar)Pd(II)X], are not fully understood. Recently, Hartwig and coworkers demonstrated that the bridged dimeric palladium complex act as has high catalytic activity for the coupling processes.[12]

To understand the decomposition or deactivation of the catalytst system, we have designed and synthesized two new ferrocenylmethylphosphine-containing polymers **12** and **13** (Scheme 1.3).

We envisioned that by using the more bulky group between phophines the formation of bridged complex analog **A** would not be favored due to the bulkness of the alkyl group, rather **B** would be favored. If the decomposition of **B** plays a role on the catalytic property, the catalyst longevity then would

not be good. On the other hand, the small size alkyl groups between phosphines allow Palladium complexes intramolecular communication. Therefore, the bridged palladium analog complex analog **A** could be formed, which could lead to greater catalyst longevity and thus better catalytic property.

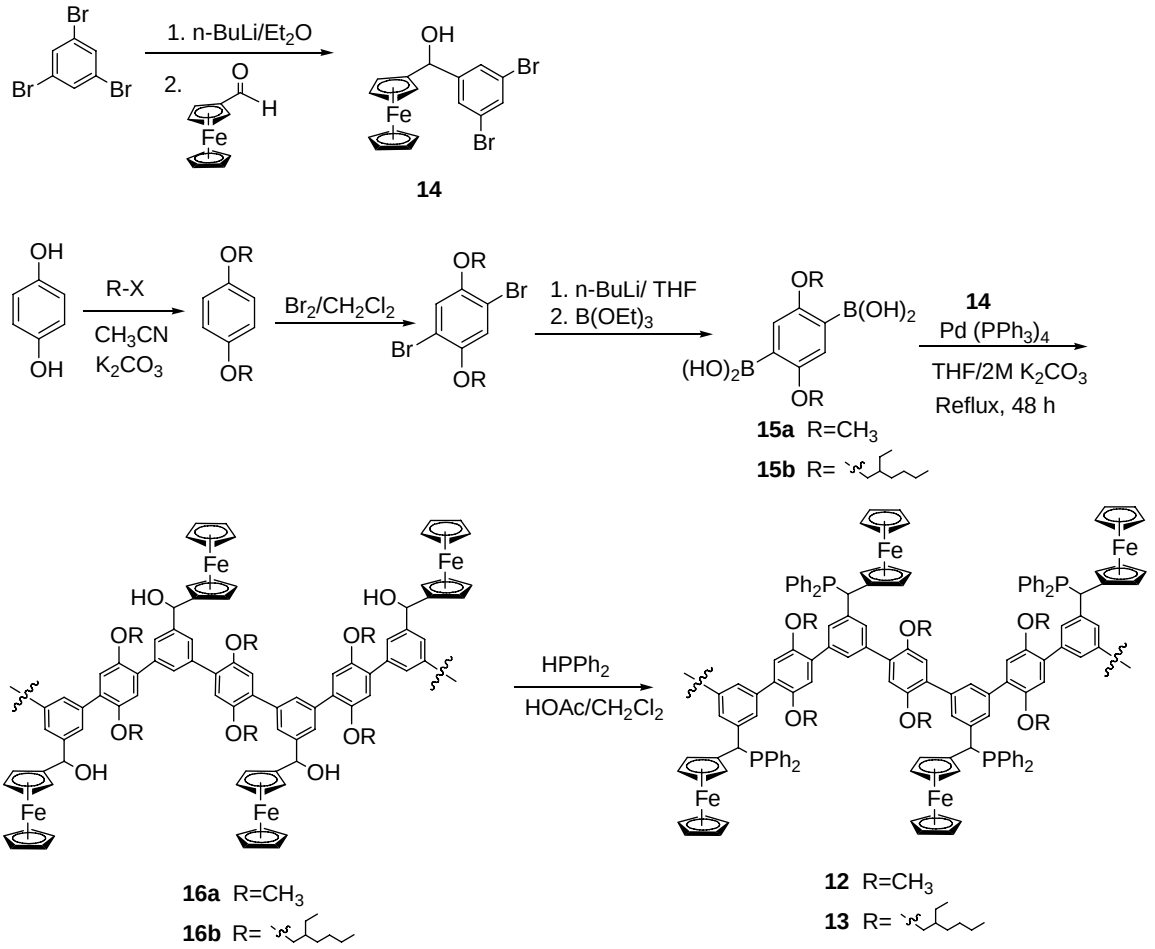
Scheme 1.3 Ferrocenylmethylphosphine-containing Polymer **12**, **13** Derived from Different Palladium Complex Structures



The synthetic routes of polymers **12, 13** and diboronic acid **15a, 15b** are shown on scheme 1.4. Reaction of 1,3,5-tribromobenzene with *n*-BuLi (1 equiv.) followed by treatment with ferrocenecarboxaldehyde generated ferrocenylmethyl alcohol **14** in 83% yield. Polymerization of **14** with diboronic acid **15** was carried out by using the Suzuki coupling

polymerization condition ($Pd(PPh_3)_4$, THF/2 M K_2CO_3). Treatment of the generated polymer **16** with excess $HPPh_2$ in $HOAc/CH_2Cl_2$ at room

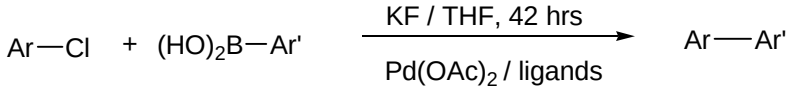
Scheme 1.4 Synthesis of a Ferrocenylmethylphosphine-containing Polymers **12**, **13**

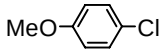
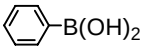
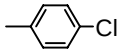
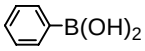
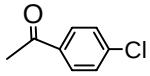
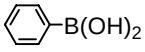
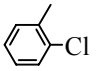
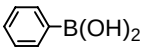
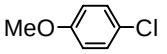
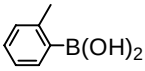
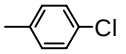
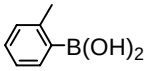


temperature afforded polymers in high yields. The ^1H NMR spectra of **9** showed complete conversion of -OH to -PPh_2 as evidenced by the disappearance of peaks of the methylene group that connects to the -OH group at 5.50 - 5.60 ppm and the OH peaks at about 2.4 ppm. ^{31}P NMR of **12/13** in $CDCl_3$ (H_3PO_4 as standard) shows one major peak along with a

minor peak, corresponding to the phosphine moieties at the end of the polymer chain. **12/13** are yellow to orange solids and relative stable in the solid state form. They are soluble in common organic solvents such as CH_2Cl_2, THF, and toluene.

Table 1.2 Room Temperature Palladium-catalyzed Cross-coupling of Aryl Chloride with Arylboronic Acids [a]



Entry	Ar—Cl	(HO)$_2$B—Ar'	Conversion (%) / Ligand 5	Conversion (%) / Ligand 6
1			30.4	20
2			38.9	20
3			63.8	59
4			52.8	27.8
5			23	5.8
6			69.3	10.7

a. Reaction conditions: aryl halides (1.0 equiv.), phenylboronic acid (1.5 equiv.), KF (3.0 equiv.), THF (2 ml), room temperature. b. Reaction time: 48 hrs.

Catalytic activities of ferrocenylmethylphosphine-containing polymers **12** and **13** for Suzuki coupling reaction have been studied by employing aryl chlorides as substrates. The results are shown on the table 1.2.

From the results it can be seen the catalytic activities are much different between ferrocenylmethylphosphine-containing polymers **12** and **13**. The ligand with small methyl group between phophines is much more reactive

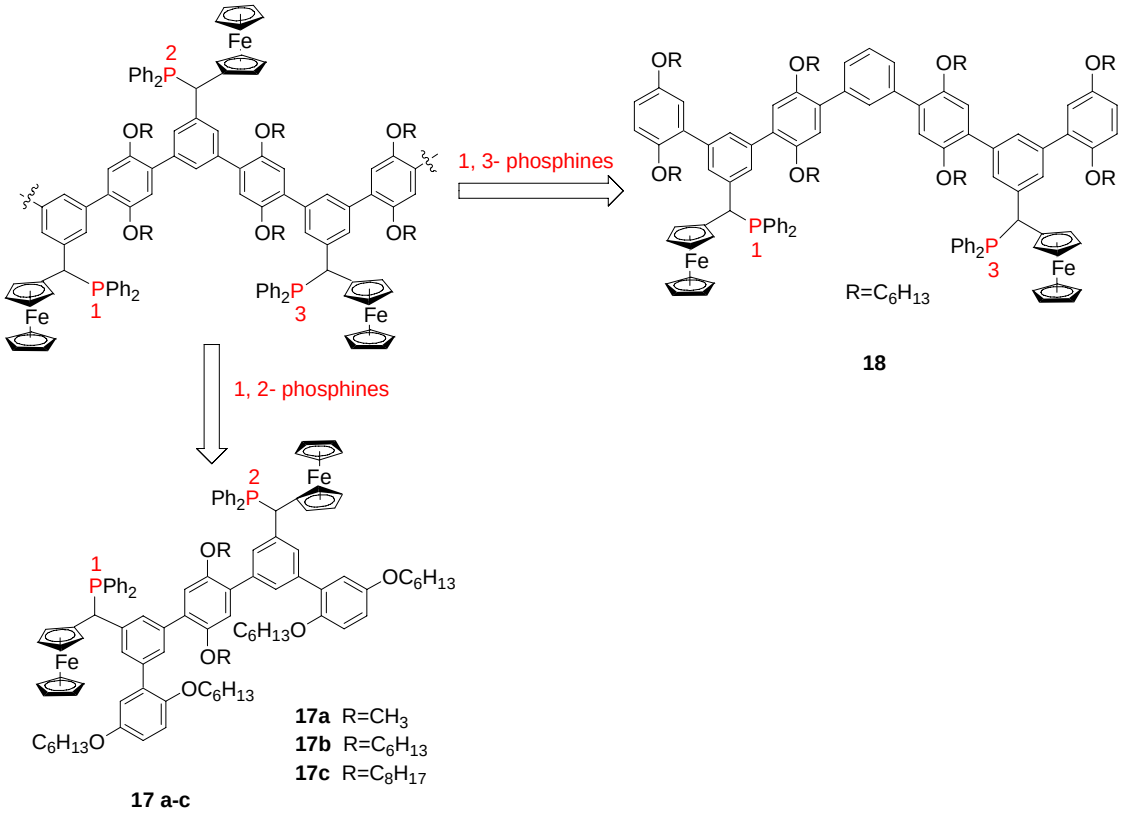
than that with bulky alkyl group (2-ethyl-hexyl), which suggest the bridged palladiums complex (complex **A**) is relative stable species with high catalytic activities. Monomeric palladium complex (complex **B**) would in charge of decomposition of palladium catalysts.

1.4 Study of Phophines Intramolecular Communications Effect

The bridged dimeric palladium complexes are relative stable species with high catalytic activities for the cross-coupling reactions. From the structure of ferrocenyl-methylphosphine-containing polymers we can see each phosphine has two possible intramolecular communications with its neighboring phosphines via palladium complexes (Scheme 1.5). Palladium complex coordinated by phosphine **1** may communicate with that coordinated by phosphine **2,** or phosphine **3**. To understand the intramolecular communications between palladium complexes, we designed and synthesized molecules **17a-c** and **18** with varied space between monophosphines to mimic these two types of intramolecular interaction. The synthesis of molecules **17a-c** is shown on Scheme 1.6. Reaction of 1,4-dibromo-2,5-dialkoxybenzene with *n*-BuLi (1 equiv.) followed by treatment with H_2O generated monobromobenzene **19** in 90% yield. Treat compound **19** with n-BuLi and $B(OEt)_3$ get monoboronic acid **20** in 50% yield. **20** coupled with **14 y**ields monobromo-ferrocenylmethyl alcohol **21** followed

by coupling with diboronic acid yields ferrocenylmethyl alcohol **22**. Treatment of the generated **22** with excess $HPPh_2$ in $HOAc/CH_2Cl_2$ afforded phosphine-containing **17a-c**.

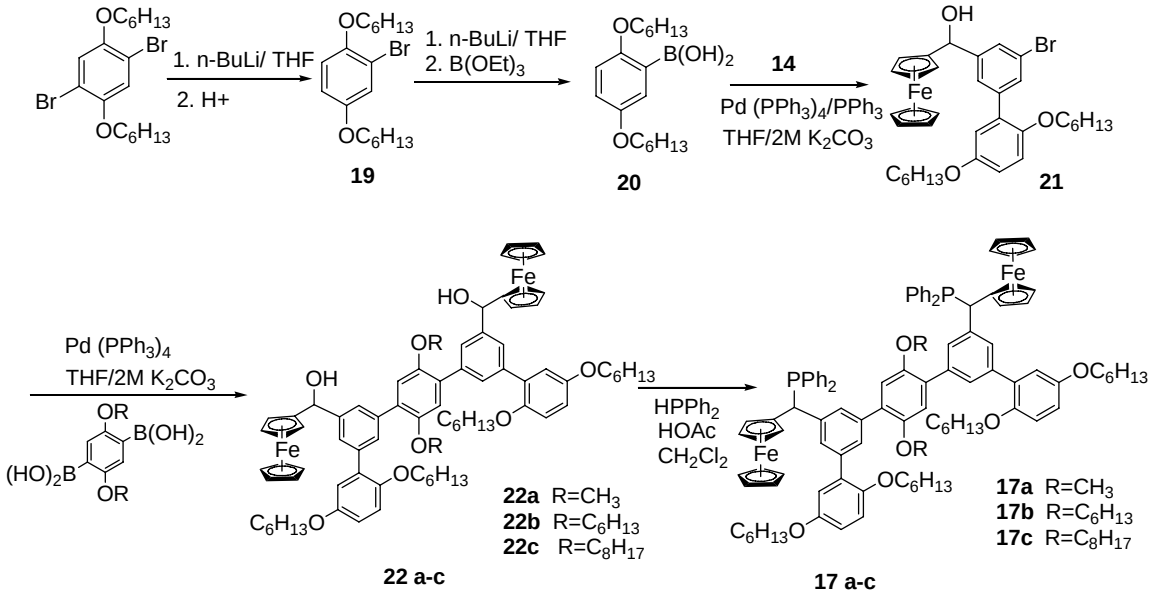
Scheme 1.5 Design of Ferrocenylmethylphosphine-containing Componds **17a-c** and **18**



The synthesis of molecule **18** is shown on scheme 1.7. Reaction of 1,4-dibromo-2,5-dialkoxybenzene with 1 equivalent of *n*-BuLi followed by treatment with $B(OEt)_3$ generated monoboronic acid **23** in 60% yield. Treat **23** with 1,3-diiodobenzene under normal Suzuki coupling condition yields compound **24**. **24** reacted with *n*-BuLi followed by $B(OEt)_3$ gets diboronic acid **25**. Then **21** coupled with **25** yields ferrocenylmethyl alcohol **26**.

Treatment of the generated **26** with excess $HPPh_2$ in $HOAc/CH_2Cl_2$ at room temperature afforded phosphine-containing **18**.

Scheme 1.6 Synthesis of a Ferrocenylmethylphosphine-containing Compounds **17a-c**



Scheme 1.7 Synthesis of a Ferrocenylmethylphosphine-containing Compound **18**

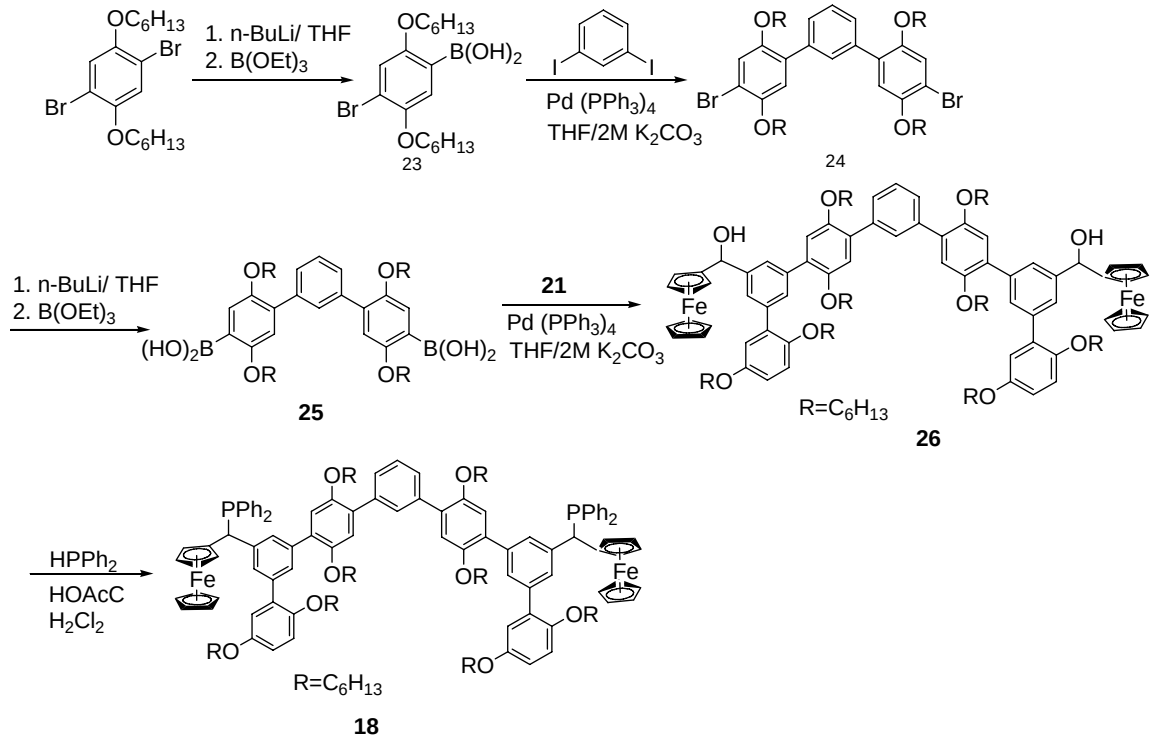
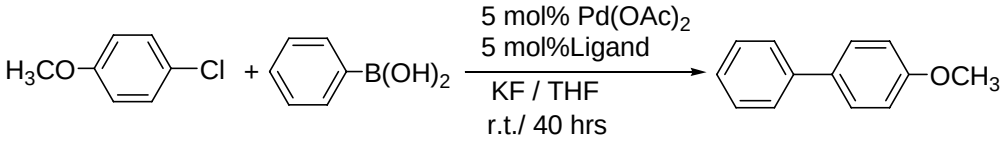


Table 1.3 Room Temperature Palladium-catalyzed Cross-Coupling of Aryl Chloride with Arylboronic Acids [a]



Entry	Ligand	Conversion (%)
1	17a	0
2	17b	5.5
3	17c	0
4	18	9.3

a. Reaction conditions: aryl halides (1.0 equiv.), phenylboronic acid (1.5 equiv.), KF (3.0 equiv.), THF (2 ml), room temperature.

By using ferrocenylmethylphosphine-containing compounds **17a-c, 18** and $Pd(OAc)_2$ as catalyst, Suzuki coupling reaction of 4-chloroanisole and phenylboronic acid was tested. (Table 1.3)

The results shows that 1,3-diphosphines molecule **18** has higher catalytic reactivity than 1,2-diphosphines molecules **17a-c**, which suggests that 1,3-diphosphines palladium complexes communication is the major catalytic effect in the ferrocenylmethylphosphine-containing polymers/Pd catalysts. Among 1,2-diphosphines molecules **17a-c**, less bulky alkyl group (methyl) between phosphines cannot prevent intermolecular phosphines communication, which leads to ineffective 14-electron palladium catalyst. Much bulky group makes it hard to form bridged palladium complex **A**,

which also lead to an ineffective catalyst. Medium size alkyl group is big enough to prevent intermolecular phosphines communications but allow intramolecular palladium complexes communication, from which catalytically active species could be generated. Catalytic activities of all these small molecules are worse than that of the polymer ligands because of the intermolecular phosophines interaction; 14-electron palladium complexes could be formed to some extent.

In summary, two kinds of ferrocenylmethylphosphine-containing polymers with different size alkyl groups have been synthesized. Their catalytic activities with palladium have been studied. The alkyl group between phosphines plays an important role in the catalytic species. Steric bulky group between phosphines worsen the catalytic activity, which suggest that monomeric palladium complexes B are not stable and they facilities decomposition or deactivation of the catalyst systems. On the other hand, bridged dimeric palladium complexes **A** are relative stable species with high catalytic activities. But we cannot exclude another possibility, that is, the bulky group might make it hard to access to the phosphines for palladium. Also, several ferrocenylmethylphosphine-containing molecules with different space between phosphines as well as different size of alkyl groups have been studied. 1,3-diphosphines compound **18** has higher

catalytic activity than 1,2-diphosphines compounds **17a-c**, which suggests that 1,3-diphosphines palladium complexes communication is better to stabilize the catalytic active species for the cross-coupling reactions. Among the 1,2-diphosphines molecules, both less bulky alkyl group and very bulky group between phosphines are ineffective ligands for palladium-catalyzed reaction. Medium size alkyl group ligand can catalyze the Suzuki coupling reaction of aryl chlorides, although the conversion is low, which suggests catalytic active species still could be generated in the system.

1.5 Experiments Section

1.5.1 General

NMR spectra were recorded on Varian 200 MHz or 600 MHz spectrometers. THF and Et_2O were dried with sodium/benzophenone. All air and water-sensitive synthetic manipulations were performed under nitrogen atmosphere using standard Schlenk techniques. 1,4-dibromo-2,5-dimethoxybenzene, 1,4-dibromo-2,5-bis(hexyloxy)benzene and 1,4-dibromo-2,5-bis(2-ethylhexyloxy)benzene have been prepared according to published synthetic protocols.[13] Diboronic acid **10, 15a** and **15b** were prepared according to reported method.[14] Compounds **19**, **20**, **23**, **24** and **25** were synthesized following the reported procedures.[15] Compound **14** was made exactly following the method established by our group.[16] $Pd(OAc)_2$,

$Pd(PPh_3)_4$, arylboronic acid, diphenylphopshine, and potassium fluoride were purchase from Strem and used directly. Other chemical reagents were purchased from Aldrich and used directly.

1,4-dibromo-2,5-dimethoxybenzene white solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.11 (s, 2H), 3.85 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.50, 117.10, 110.47, 57.00.

1,4-dibromo-2,5-bis(2-ethylhexyloxy)benzene colorless liquid. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.08 (s, 2H), 3.83 (d, *J* = 5.6 Hz, 4H), 1.740 (m, 2H), 1.490 (m, 8H), 1.323(m, 8H), 0.922 (m, 12H).

1,4-bis(hexyloxy)benzene white solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 6.82 (S, 4H), 3.90 (t, *J* = 6.4 Hz, 4H), 1.75 (m, 4H), 1.42(m, 4H), 1.36 (m, 8H), 0.90 (t, *J* = 6.4 Hz, 6H).

1,4-dibromo-2,5-bis(hexyloxy)benzene white solid. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.09 (s, 2H), 3.95 (t, *J* = 6.6 Hz, 4H), 1.80 (m, 4H), 1.48 (m, 4H), 1.34 (m, 8H), 0.91 (t, *J* = 6.6 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.14, 118.56, 111.19, 70.36, 31.47, 29.10, 25.60, 22.55, 13.97.

2,5-Dimethoxy-1,4-phenylenediboronic acid white solid. ^{1}H NMR (DMSO-d6, 200 MHz) δ 7.81 (s, 4H), 7.15 (s, 2H), 3.76 (s, 6H).

2,5-Bis(2-ethylhexyloxy)-1,4-phenylenediboronic acid white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.39 (s, 2H), 6.28(s, 4H), 4.01(d, *J* = 5.4 Hz, 4H), 1.76 (m, 2H), 1.45 (m, 8H), 1.35 (m, 8H), 0.93 (m, 12H).

2-Bromo-1,4-bis(hexyloxy)benzene 19 colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.11 (d, *J* = 6.0 Hz, 1H), 6.80 (d, *J* = 6.0 Hz, 1H), 6.79 (d, *J* = 6.0 Hz, 1H), 3.95 (t, (d, *J* = 7.2 Hz, 2H), 3.88 (t, *J* = 7.2 Hz, 1H), 1.77 (m, 4H), 1.46 (m, 4H), 1.34 (m, 8H), 0.90 (t, *J* = 7.8 Hz, 6H).

2,5-Bis(hexyloxy)phenylboronic acid 20 white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, *J* = 3.3 Hz, 1H), 6.96 (dd, J_1 = 9.0 Hz, J_1 = 3.3 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 6.12 (s, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 3.94 (t, *J* = 6.6 Hz, 2H), 1.80 (m, 4H), 1.46 (m, 4H), 1.34 (m, 8H), 0.91 (m, 6H).

4-Bromo-2,5-bis(hexyloxy)phenylboronic acid 23 white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 1H), 7.10 (s, 1H), 6.20 (s, 2H), 4.02 (t, *J* = 6.6 Hz, 2H), 4.01 (t, *J* = 6.6 Hz, 2H), 1.83 (m, 4H), 1.47 (m, 4H), 1.34 (m, 8H), 0.91 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.11, 150.07, 120.77,

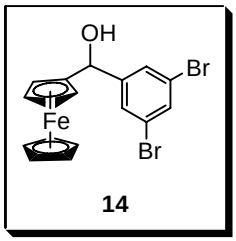
116.56, 116.46, 69.99, 69.34, 31.48, 31.39, 29.18, 29.14, 25.60, 25.58, 22.53, 22.44, 13.94, 13.88.

***p*-Triphenylene Dibromide 24** white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.64 (s, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.41 (t, J = 7.8 Hz, 1H), 7.16 (s, 2H), 7.94 (s, 2H), 3.99 (t, J = 6.6 Hz, 4H), 3.88 (t, J = 6.6 Hz, 4H), 1.81 (m, 4H), 1.65 (m, 4H), 1.49 (m, 4H), 1.34 (m, 12H), 1.20 (m, 8H), 0.90 (t, J = 6.6 Hz, 6H), 0.82 (t, J = 6.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.43, 149.89, 137.58, 130.84, 130.21, 128.27, 127.45, 118.31, 116.47, 111.32, 70.27, 69.59, 31.52, 31.42, 29.27, 29.16, 25.72, 25.66, 22.58, 22.51, 14.00, 13.96.

***p*-Triphenylene Diboronic Acid 25** white solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.72 (s, 1H), 7.57 (dd, J_1 = 7.8 Hz, J_1 = 1.2 Hz, 2H), 7.44 (m, 3H), 6.94 (s, 2H), 5.78 (s, 4H), 4.05 (t, J = 6.6 Hz, 4H), 3.96 (t, J = 6.6 Hz, 4H), 1.83 (m, 4H), 1.67 (m, 4H), 1.46 (m, 4H), 1.34 (m, 12H), 1.20 (m, 8H), 0.90 (t, J = 6.6 Hz, 4H), 0.82 (t, J = 6.6 Hz, 4H).

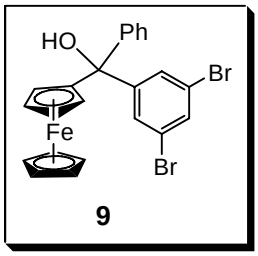
1.5.2 Tuning Steric Hindrance of α-Position of the Ferrocene Functionality Part

3,5-Dibromophenyl-hydroxymethylferrocene 14 yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.54 (t, *J* = 1.8 Hz, 1H), 7.470 (d, *J* = 1.8 Hz, 2H), 5.342 (d, *J* = 2.6 Hz, 1H), 4.27 (s, 5H), 4.24 (m, 3H), 4,18 (m, 1H), 2.49 (d, *J* = 2.6 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.30, 133.04, 128.22, 122.88, 93.70, 70.88, 68.75, 68.68, 67.75, 65.73.



14

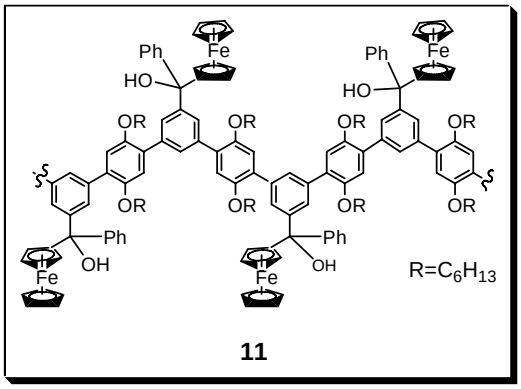
Synthesis of dibromide 9 Under N_2, to a mixture of 1,3,5-tribromobenzene (6.28g, 20.0 mmol) in Et_2O (140 ml) at -78ºC was added *n*-BuLi (12.5 ml, 1.6 M in hexane, 20.0 mmol). After stirring at -78ºC for 1h, a solution of benzoylferrocene (5.80g, 20.0 mmol) in THF (6 ml) was added to the mixture. The mixture was warmed to room temperature in 3 hrs. H_2O was added and the mixture was extracted with Et_2O. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane : Et_2O = 100:0 to 100:20) gave 9 as a light yellow solid 7.98g (76% yield). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.519(s, 1H), 7.41(s, 2H), 7.28-7.20(m, 5H), 4.253(s, 2H), 4.158(2, 5H),



9

3.994(s, 1H), 3.960(s, 1H), 3.483(s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 150.8 MHz): δ 150.79, 145.32, 132.29, 128.98, 127.67, 127.18, 122.08, 98.28, 77.66, 68.69, 68.64, 68.56, 68.25 ppm.

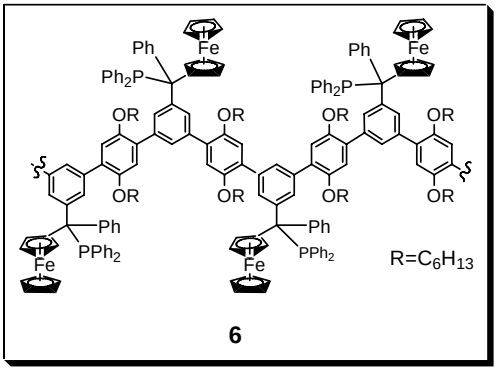
Synthesis of Polymer 11 To a mixture of dibromide **9** (1.574g, 3.0 mmol) and diboronic acid **10** (1.120g, 3.06 mmol) in 2M K_2CO_3 / THF (20ml/20ml) was added $Pd(PPh_3)_4$ (0.069mg, 0.06 mmol) under N_2. The mixture was refluxed for 48 h and bromobenzene was added to cap the end group. After another 12 h refluxing, the reaction mixture was cooled to room temperature and extracted with CH_2Cl_2. After washing with brine, the solvent was evaporated by using a rota-evaporator. The residue was redissolved in CH_2Cl_2 and precipitated from MeOH. The solid was collected by filtration. The dissolvation-precipitation-filtration procedure was repeated three times. After drying under vacuum, polymer **11** was obtained in 90% yield (1.82 g). GPC (THF, polystyrene standard): Mw = 3,100, Mn = 2,000 (PDI = 1.56). 1H NMR (CDCl3, 600 MHz): δ 7.589-7.500(m, 3H), 7.440-7.180(m, 5H), 6.951-6.907, 6.813, 6.781(m, 2H), 7.24.266-4.043(m. s, 9H), 3.811(m, 4H),



11

3.404(m, 1H), 1.594 (m, 4H), 1.258(m, 4H), 1.213(m, 8H), 0.827(m, 6H) ppm.

Synthesis of Polymer 6 To a solution of polymer **11** (0.675 g, 1.0 mmol) in HOAc/ CH_2Cl_2 (8 ml/ 4 ml) was added $HPPh_2$ (6 ml, 10% in hexane, 2.5 mmol) under N_2. The mixture was stirred at room temperature for 18h. The solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (2 ml, N_2 degassed) and precipitated from MeOH (10 ml, N_2 degassed). The process was repeated for three times. The precipitation was collected by filtration under air. After drying under vacuum, polymer **6** was obtained as a yellow solid (0.657 g), 80% yield. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.824- 7.594(m, 18H), 3.935-4.265(m, 9H), 3.820(m, 4H), 3.409(s, unreacted OH), 1.598 (m, 4H), 1.213(m, 12H), 0.824(m, 6H) ppm. ^{31}P NMR ($CDCl_3$, H_3PO_4 as standard): δ 32.6, 31.7 (1: 2.5) ppm.



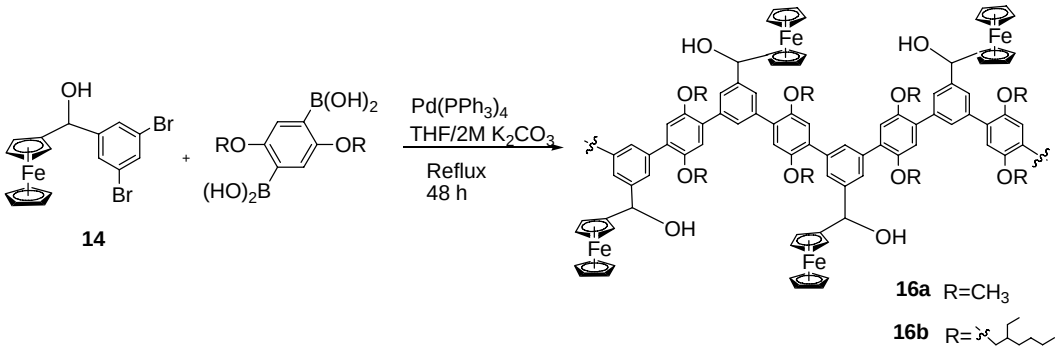
6

Polymer 6/Pd(0)-catalyzed Suzuki Cross-coupling Reaction of Aryl Halides with Phenylboronic Acids

In glove-box, to a vial containing Pd(OAc)2 (4.49 mg, 0.02 mmol) and polymer 6 (16.86 mg, 0.02 mmol), phenylboronic aicd (1.5 mmol) and KF (3 mmol) was added 2 ml THF. After stirring for a few minutes, 4-bromoanisole or 4-chloroanisole (0.125 ml, 1 mmol) was added. The mixture was stirred at room temperature in glove-box for 24 hrs. After adding water to the reaction mixture, the mixture was extracted with Et2O. The organic layer was washed with brine. The solvent was evaporated. The residure was analyzed by 1H NMR, for 4-bromoanisole, the conversion is 43.8%; for 4-chloroanisole, no reaction was observed. Without any ligand only Pd(OAc)2, the conversion of using 4-bromoanisole as substrate is 6%.

1.5.3 Investigating on the Nature of Monodentate Phosphine Palladium Complex Part

Synthesis of polymer 16a, 16b



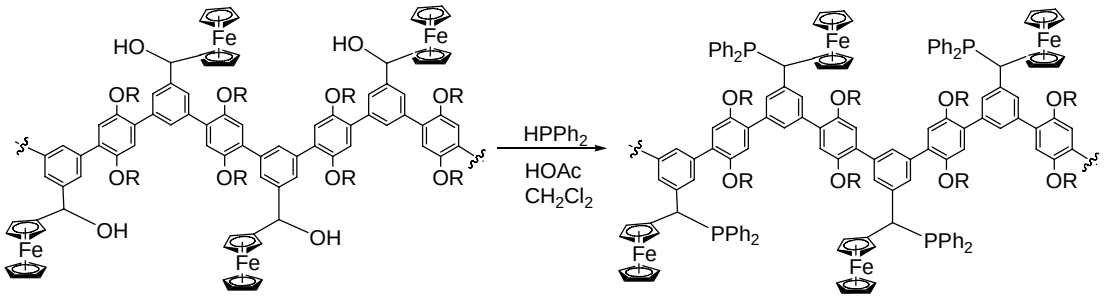
To a mixture of dibromide monomer **14** (3.0 mmol) and diboronic acid **8** (3.06 mmol) in 2M K_2CO_3 / THF (20ml/20ml) was added $Pd(PPh_3)_4$ (0.069mg, 0.06 mmol) under N_2. The mixture was refluxed for 48 h and bromobenzene was added to cap the end group. After another 6 hours refluxing, the reaction mixture was cooled down to room temperature and extracted with CH_2Cl_2. Washed by brine and evaporate the solvent. The residue was redissolved in CH_2Cl_2 and precipitated from methaol. The solid was collected by filtration. The dissolvation-precipitation-filtration procedure was repeated three times. After drying under vacuum, polymer **16a** and **16b** was obtained. The typical yield of the polymerization was 90~95%.

Polymer 16a: GPC (polystyrenes standards): Mw = 8,934; Mn = 3,186; PDI = 2.80. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.54 (s, 1H), 7.52 (s, 1H), 6.89 (s, 2H), 5.47 (br.s, 1H), 4.25(s, 7H), 4.22 (br.s, 1H), 4.20 (br.s, 1H), 3.75(s, 6H), 2.51 (br.s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.53, 145.02, 139.85, 131.18, 129.36, 127.95, 126.28, 121.95, 114.45, 93.80, 71.40, 68.52, 68.33, 68.31, 67.47, 65.95, 56.44. Anal. calcd for $C_{25}H_{22}FeO_3$: C 70.44, H 5.20. Found: C 67.92, H 5.02. The relative large difference

between the theoretical value and the experimental one is believed to be caused by the end groups as can be seen clearly from the ^{1}H NMR.

Polymer 16b: GPC (polystyrenes standards): Mw = 2,059; Mn = 1,569; PDI = 1.31. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (br.s, 1H), 7.61 (br.s, 2H), 7.01 (br.s, 2H), 5.56 (br.s, 1H), 4.31 (br.s, 1H), 4.26 (br.s, 1H), 4.24 (m, 5H), 4.15 (br.s, 2H), 3.77 (br. s, 4H), 2.43 (d, *J* = 3.0 Hz, 1H), 1.59 (m, 2H), 1.33 (m, 8H), 1.27 (m, 8H), 0.76 (m, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.40, 142.21, 138.03, 131.51, 130.77, 130.01, 126.30, 115.92, 94.40, 94.38, 71.84, 68.49, 68.44, 68.03, 67.91, 67.52, 66.19, 39.47, 30.47, 28.92, 23.78, 22.97, 14.10, 14.09, 10.98, 10.95. Anal. calcd for $C_{39}H_{50}FeO_3$: C 75.23, H 8.09. Found: C 73.61, H 7.82. The relative large difference between the theoretical value and the experimental one is believed to be caused by the end groups as can be seen clearly from the ^{1}H NMR.

Synthesis of polymer 12, 13



16a R=CH_3 **12** R=CH_3

16b R= **13** R=

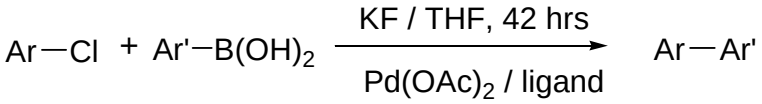
Under N_2 a solution of polymer **16a** or **16b** (1.0 mmol) in HOAc/ CH_2Cl_2 (8 ml/ 4 ml) was added $HPPh_2$ (6 ml, 10% in hexane, 2.5 mmol). The mixture was stirred at room temperature for 18h. The solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (2 ml, N_2 degassed) and precipitated from MeOH (10 ml, N_2 degassed). The process was repeated for three times. The precipitation was collected by filtration under air. After drying under vacuum, polymer **12** or **13** was obtained as a yellow solid, typical yield 60~70%.

Polymer 12 GPC (polystyrenes standards): Mw = 10,236; Mn = 4,651; PDI = 2.20. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77- 7.63(m, 3H), 7.42 – 7.22 (br.s,, 9H), 7.05- 6.87 (m, 3H), 4.44 (br.s, 1H), 4.09 (m, 1H), 3.85 – 3.78 (m, 12H), 3.51 (br.s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.79, 151.01, 150.91, 150.72, 141.17, 137.88, 137.66, 134.59, 134.45, 134.27, 133.37, 133.25, 130.70, 129.81, 128.80, 128.53, 128.18, 127.86, 121.53, 115.06, 69.73, 68.44, 68.03, 66.31, 56.64. ^{31}P NMR (81 MHz, $CDCl_3$, H_3PO_4 as standard) δ 5.42, 5.79 (minor peak). Anal. calcd for $C_{37}H_{31}FeO_2P$: C 74.76, H 5.26. Found: C 70.33, H 5.20. The relative large difference

between the theoretical value and the experimental one is believed to be caused by the end groups as can be seen clearly from the ^{1}H NMR.

Polymer 13 GPC (polystyrenes standards): Mw = 4,729; Mn = 2,859; PDI = 1.65. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (br.s, 1H), 7.67 (br.s, 2H), 7.40 (br.s, 2H), 7.31 (br.s, 3H), 7.27 (m, 3H), 7.17 (br.s, 2H), 6.99 (br.s, 2H), 4.42 (d, *J* = 5.4 Hz, 1H), 4.32 (s, 1H), 4.04 (s, 1H), 3.86 – 3.80 (m, 9H), 3.54 (s, 1H), 1.69 (br.s, 2H), 1.31 (m, 8H), 1.17 (br.s, 8H), 0.77 (m, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.44, 141.53, 137.94, 134.69, 134.56, 133.30, 133.19, 130.91, 129.32, 128.82, 128.52, 128.48, 127.88, 127.71, 127.67, 116.08, 71.97, 69.71, 68.40, 67.75, 66.13, 53.35, 39.37, 30.40, 28.92, 28.86, 23.74, 23.01, 14.15, 10.90 (observed complexity due to P-C splitting). ^{31}P NMR (81 MHz, $CDCl_3$, H_3PO_4 as standard) 4.52, 5.48 (minor peak). Anal. calcd for $C_{51}H_{59}FeO_2P$: C 77.46, H 7.52. Found: C 76.70, H 7.33. The relative large difference between the theoretical value and the experimental one is believed to be caused by the end groups as can be seen clearly from the ^{1}H NMR.

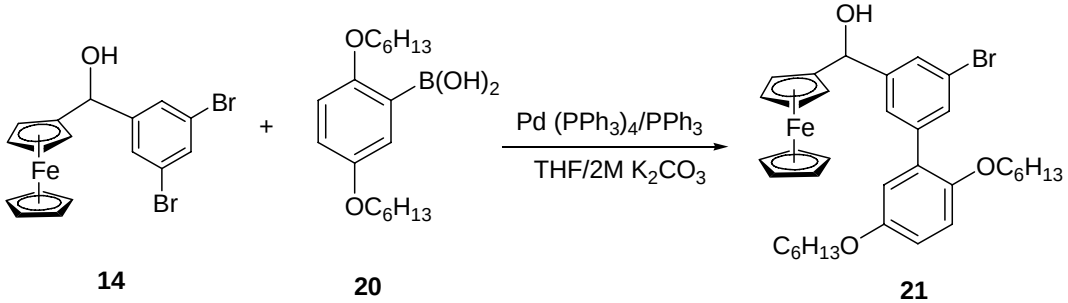
Polymer 12 or 13 / Pd(0)-catalyzed Suzuki cross-coupling reaction of aryl halide with arylboronic acids



In glove-box, to a vial containing $Pd(OAc)_2$ (5.61mg, 0.025 mmol) and polymer ligand 5 **or 6** (0.025 mmol), arylboronic aicd (1.5 mmol) and KF (3 mmol) was added 2 ml THF. After stirring for a few minutes, Ayl halide (1 mmol) was added. The mixture was stirred at room temperature in glove-box for 42 hrs. After adding water to the reaction mixture, the mixture was extracted with Et_2O and washed with brine. Evaporation of solvent gave the crude reaction mixture. Check NMR to find the conversion of the coupling products.

1.5.4 Study of Phophines Intramolecular Communications Effect Part

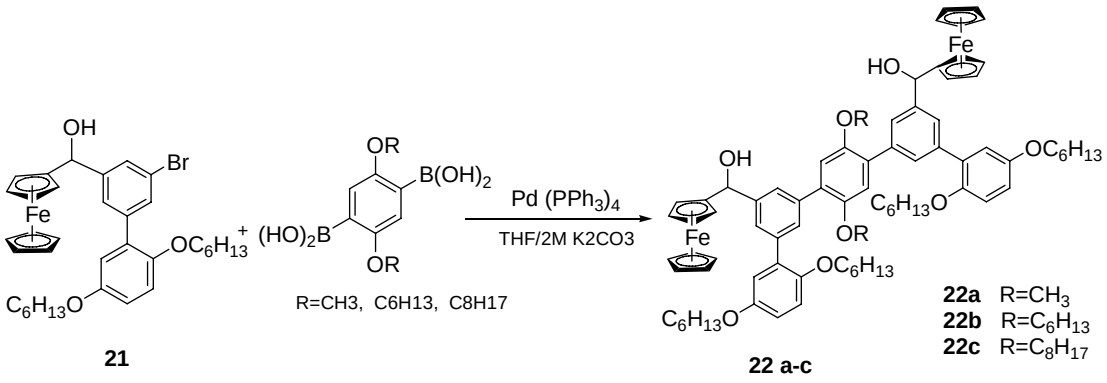
Synthesis of ferrocenylmethyl alcohol 21



14 **20** **21**

Under N_2, to a mixture of **14** (3.0 mmol) and monoboronic acid **20** (3.3 mmol) in 2M K_2CO_3 / THF (18ml/6ml) was added $Pd(PPh_3)_4$ (69 mg, 0.06 mmol) and PPh_3 (32 mg, 0.12 mmol). The mixture was refluxed for 20 h. The reaction mixture was cooled down to room temperature and extracted with EtOAc. After washing with brine, the solvent was evaporated. Flash chromatography on silica gel (hexanes: Et_2O = 100 : 0 to 100 : 20) gave **13** as a yellow solid in 66% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.62 (s, H), 7.59 (s, 1H), 6.96 (d, J = 3.6 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.81 (dd, J_1 = 8.4 Hz, J_2 = 3.6 Hz, 1H), 5.55 (d, J = 3.0 Hz, 1H), 4.31 (d, J = 1.2 Hz, 1H), 4.27 (d, J = 1.2 Hz, 1H), 4.24 – 4.23 (m, 5H), 4.16 (d, J = 8.4 Hz, 2H), 3.92 (t, J = 6.6 Hz, 2H), 3.85 (t, J = 6.6 Hz, 2H), 2.42 (d, J = 3.2 Hz, 1H), 1.76 (m, 2H), 1.65 (m, 2H), 1.32 (m, 4H), 1.21 (m, 8H), 0.89 (m, 3H), 0.82 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.36, 150.26, 142.27, 138.11, 132.10, 130.70, 129.66, 126.26, 117.23, 114.52, 113.99, 94.26, 72.39, 69.69, 69.63, 68.63, 68.45, 68.03, 67.94, 67.50, 66.24, 31.58, 31.55, 29.38, 29.37, 25.79, 25.72, 22.59, 22.56, 14.03, 14.01.

Synthesis of ferrocenylmethyl alcohol 22a-c



To a mixture of monobromide ferrocenylmethyl alcohol **21** (4.2 mmol) and diboronic acid (2.1 mmol) in 2M K_2CO_3 / THF (15 ml/ 15 ml) was added $Pd(PPh_3)_4$ (40 mg, 0.035 mmol) under N_2. The mixture was refluxed for 18 h. The reaction mixture was cooled down to room temperature and extracted with ethyl acetate. After washing with brine, the solvent was evaporated. Flash chromatography on silica gel (hexanes: Et_2O = 100 : 0 to 100 : 20) gave **14** as a yellow solid, typical yield is about 40 - 55%.

22a ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (s, 2H), 7.63 (d, J = 6.0 Hz, 2H), 7.59 (s, 2H), 7.00 (s, 2H), 6.96 (d, J = 3.6 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.82 (dd, J_1 = 8.4 Hz, J_2 = 3.0 Hz, 2H), 5.56 (d, J = 3.0 Hz, 2H), 4.32 (s, 2H), 4.28 (s, 2H), 4.24 (s, 10H), 4.18 (d, J = 7.2 Hz, 4H), 3.93 (t, J = 6.6 Hz, 4H), 3.88 (t, J = 6.6 Hz, 4H), 3.75 (s, 6H), 2.45 (d, J = 3.0 Hz, 2H), 1.76 (m,

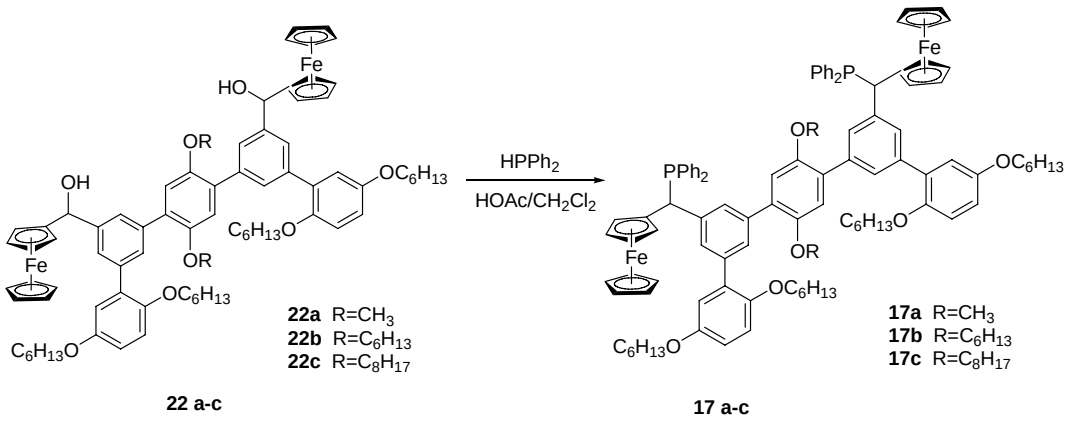
4H), 1.67 (m, 4H), 1.44 (m, 4H), 1.33 (m, 12H), 1.22 (m, 8H), 0.89 (m, 6H), 0.83 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.22, 150.64, 150.18, 142.33, 138.20, 137.76, 131.84, 130.33, 129.56, 126.43, 126.24, 117.24, 114.78, 114.28, 114.00, 94.01, 72.26, 69.48, 68.58, 68.44, 68.04, 67.98, 67.42, 66.34, 56.40, 31.54, 31.50, 29.31, 25.73, 25.68, 22.56, 22.52, 14.03, 14.00. Anal. calcd for $C_{78}H_{94}Fe_2O_8$: C 73.69, H 7.45. Found: C 73.75, H 7.55.

22b ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.62 (s, 2H), 7.59 (s, 2H), 7.00 (s, 2H), 6.96 (d, J = 3.0 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.81 (dd, J_1 = 8.4 Hz, J_2 = 3.0 Hz, 2H), 5.55 (d, J = 3.0 Hz, 2H), 4.32 (d, J = 1.2 Hz, 2H), 4.27 (d, J = 1.2 Hz, 2H), 4.29 – 4.23 (m, 10H), 4.17 (d, J = 1.2 Hz, 2H), 4.15 (d, J = 1.2 Hz, 2H), 3.92 (t, J = 6.6 Hz, 4H), 3.87 (t, J = 6.6 Hz, 4H), 3.86 (t, J = 6.6 Hz, 4H), 2.43 (d, J = 3.0 Hz, 2H), 1.76 (m, 4H), 1.65 (m, 8H), 1.44 (m, 4H), 1.32 (m, 16H), 1.21 (m, 16H), 0.89 (m, 6H), 0.84 – 0.80 (m, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.66, 150.61, 150.56, 142.60, 138.40, 138.25, 132.40, 131.02, 129.96, 126.56, 117.54, 116.63, 114.81, 114.28, 94.56, 72.68, 70.51, 69.98, 69.92, 68.90, 68.32, 68.23, 67.79, 66.56, 31.88, 31.86, 31.83, 29.71, 29.68, 26.11, 26.10, 26.02, 22.89, 22.86, 22.85,

14.36, 14.33, 14.32. Anal. calcd for $C_{88}H_{114}Fe_2O_8$: C 74.88, H 8.14. Found: C 75.05, H 8.00.

22c ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (s, 2H), 7.58 (s, 4H), 7.00 (s, 2H), 6.95 (d, J = 3.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 6.81 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 2H), 5.54 (d, J = 3.0 Hz, 2H), 4.31 (s, 2H), 4.26 (s, 2H), 4.23 (s, 10H), 4.17 (dd, J_1 = 10.2 Hz, J_2 = 1.2 Hz, 4H), 3.92 (t, J = 6.6 Hz, 4H), 3.85 (t, J = 6.6 Hz, 4H), 3.77 (d, J = 4.8 Hz, 4H), 2.42 (d, J = 3.0 Hz, 2H), 1.75 (m, 4H), 1.64 (m, 4H), 1.59 (m, 2H), 1.44 (m, 4H), 1.32 (m, 14H), 1.27 (m, 4H), 1.21 (m, 10H), 1.15 (m, 8H), 0.89 (t, J = 6.6 Hz, 6H), 0.83 (t, J = 6.6 Hz, 6H), 0.78 (t, J = 6.6 Hz, 6H), 0.76 (t, J = 6.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.32, 150.36, 150.23, 142.18, 138.03, 138.02, 138.00, 132.12, 130.68, 129.78, 129.79, 126.29, 126.20, 126.17, 117.21, 115.88, 114.50, 113.92, 94.32, 72.39, 72.37, 71.83, 70.20, 69.59, 68.60, 68.44, 68.03, 67.92, 67.50, 67.49, 22.25, 39.44, 31.59, 31.56, 30.45, 29.38, 29.37, 28.93, 28.91, 25.80, 25.72, 23.75, 22.96, 22.60, 22.57, 14.08, 14.07, 14.03, 10.93, 10.91. Anal. calcd for $C_{92}H_{122}Fe_2O_8$: C 75.29, H 8.38. Found: C 75.07, H 8.62.

Synthesis of phosphine-containing 17a-c



Under N_2 to a solution of ferrocenylmethyl alcohol **22a-c** (0.18 mmol) in HOAc (7 ml) was added $HPPh_2$ (2 ml, 10% in hexane, 0.72 mmol). The mixture was stirred at room temperature for 18h. The solvent was evaporated under vacuum. The residue was washed with MeOH (10 ml, N_2 degassed) several times. After drying under vacuum, **17a-c** was obtained as a yellow solid. Typical yield is about 6 0 - 70%.

17a ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 2H), 7.69 (s, 2H), 7.59 (s, 2H), 7.46 (br.s, 1H), 7.35 (m, 7H), 7.27 (t, *J* = 6.6 Hz, 3H), 7.24 (m, 4H), 7.17 (br.s, 5H), 6.98 (s, 2H), 6.93 (br.s, 4H), 6.84 (br.s, 2H), 4.38 (m, 3H), 4.05 (s, 1H), 3.96 (br.s, 4H), 3.88 – 3.83 (m, 9H), 3.78 (s, 6H), 3.48 (s, 1H), 1.79 (br.s, 4H), 1.69 (br.s, 4H), 1.48 (br.s, 4H), 1.35 (br.s, 12H), 1.21 (br.s, 8H), 0.91 (br.s, 6H), 0.81 (br.s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.29,

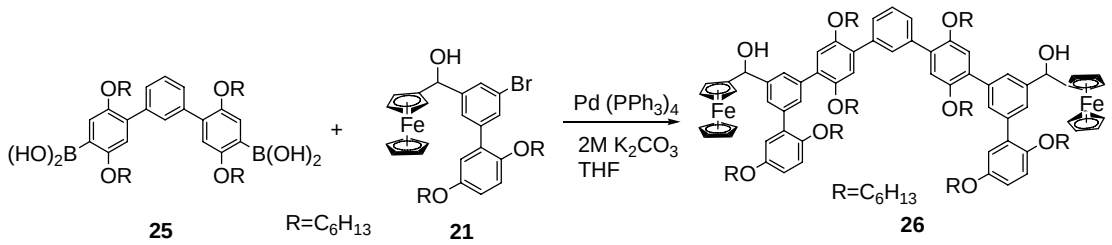
150.89, 150.30, 141.14, 141.06, 138.20, 137.73, 137.66, 134.62, 134.48, 133.26, 133.14, 132.36, 130.70, 129.94, 129.88, 129.38, 129.31, 128.80, 128.52, 128.44, 128.05, 127.84, 127.79, 127.76, 117.40, 115.07, 114.65, 113.76, 90.42, 90.29, 70.23, 69.76, 69.68, 68.59, 68.52, 68.38, 67.78, 67.68, 67.64, 66.19, 56.61, 47.18, 47.07, 31.58, 31.55, 29.40, 29.38, 25.73, 22.59, 22.52, 14.04. ^{31}P NMR (121 MHz, $CDCl_3$, H_3PO_4 as standard) δ 5.16. Anal. calcd for $C_{102}H_{112}Fe_2O_6P_2$: C 76.21, H 7.02. Found: C 76.02, H 6.95.

17b ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (br.s, 4H), 7.62 (s, 2H), 7.36 (s, 4H), 7.30 (br.s, 6H), 7.25 (br.s, 4H), 7.15 (br.s, 6H), 6.94 – 6.91 (m, 6H), 6.83 (br.s, 2H), 4.36 – 4.34 (m, 3H), 4.03 (s, 2H), 3.94 (s, 4H), 3.89 (br.s, 7H), 3.82 (br.s, 9H), 3.50 (s, 1H), 1.78 (br.s, 4H), 1.70 (br.s, 8H), 1.47 (br.s, 4H), 1.34 (br.s, 16H), 1.21 (br.s, 16H), 0.90 (br.s, 6H), 0.81 (br.s, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.36, 150.37, 141.30, 141.22, 138.07, 137.97, 137.92, 137.81, 137.70, 134.69, 134.56, 133.26, 133.15, 133.26, 133.15, 132.54, 132.50, 130.99, 130.75, 130.67, 129.60, 129.52, 129.45, 128.94, 128.82, 128.74, 127.98, 127.88, 127.84, 127.77, 127.72, 117.41, 116.62, 114.71, 113.78, 90.65, 90.52, 69.89, 69.82, 69.70, 68.63, 68.40, 67.88, 67.84, 67.77, 66.12, 47.28, 47.18, 31.63, 31.61, 29.54, 29.45, 25.86, 25.81, 25.78, 22.62, 22.58, 14.04. ^{31}P NMR (81 MHz, $CDCl_3$, H_3PO_4 as standard) δ

4.88. Anal. calcd for $C_{112}H_{132}Fe_2O_6P_2$: C 76.96, H 7.61. Found: C 76.99, H 7.47.

17c ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (s, 2H), 7.66 (s, 2H), 7.55 (s, 2H), 7.38 (t, *J* = 7.2 Hz, 4H), 7.30 (m, 6H), 7.26 (t, *J* = 7.2 Hz, 4H), 7.15 (s, 6H), 6.92 (br.s, 6H), 6.83 (d, J_1 = 8.4 Hz, J_2 = 8.4 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.31 (s, 2H), 4.03 (s, 2H), 3.94 (t, *J* = 6.6 Hz, 4H), 3.88 (t, *J* = 6.6 Hz, 4H), 3.83 – 3.78 (m, 12H), 3.51 (s, 2H), 1.78 (m, 4H), 1.69 (m, 4H), 1.66 (m, 2H), 1.47 (m, 4H), 1.34 (m, 14H), 1.27 (m, 4H), 1.22 (m, 10H), 1.15 (m, 8H), 0.90 (br.s, 6H), 0.82-0.72 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.31, 150.38, 141.36, 141.21, 138.10, 137.99, 137.90, 137.86, 137.82, 137.59, 134.76, 134.49, 133.32, 133.08, 132.53, 130.75, 129.50, 129.38, 129.28, 129.04, 128.83, 127.94, 127.90, 127.80, 127.74, 127.66, 117.44, 115.98, 114.60, 113.70, 90.67, 90.41, 71.86, 70.19, 69.78, 69.68, 68.58, 68.39, 67.89, 67.82, 67.74, 66.12, 47.31, 47.10, 39.42, 31.61, 31.59, 31.50, 30.40, 29.43, 28.91, 25.80, 25.76, 23.71, 22.97, 22.60, 22.57, 14.07, 14.05, 14.03, 10.92, 10.89, 10.86. ^{31}P NMR (121 MHz, $CDCl_3$, H_3PO_4 as standard) δ 4.68. Anal. calcd for $C_{116}H_{140}Fe_2O_6P_2$: C 77.23, H 7.82. Found: C 77.07, H 7.88.

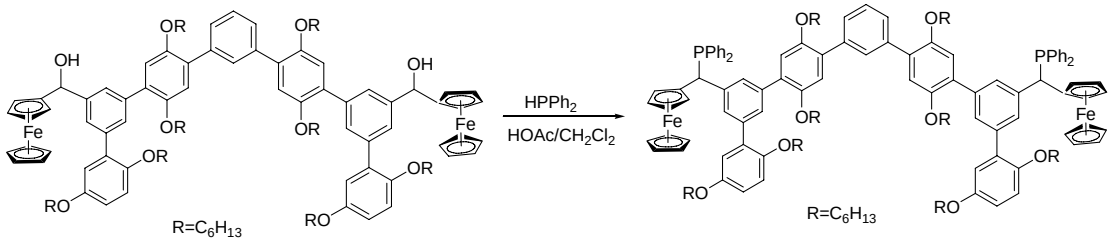
Synthesis of ferrocenylmethyl alcohol 26



Under N_2 to a mixture of monobromide ferrocenylmethyl alcohol **21** (1.68 mmol) and diboronic acid **25** (0.41 mmol) in 2M K_2CO_3 / THF (10 ml/ 10 ml) was added $Pd(PPh_3)_4$ (0.030mg, 0.03 mmol). The mixture was refluxed for 18 h. The reaction mixture was cooled down to room temperature and extracted with EtOAc. After washing with brine, the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexanes: Et_2O = 100 : 0 to 80 : 20) gave **26** as a yellow solid in 69% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.66 (d, *J* = 1.8 Hz, 2H), 7.64 (s, 2H), 7.61 (d, *J* = 1.8 Hz, 2H), 7.60 (s, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 4H), 6.97 (d, *J* = 3.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.82 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 2H), 5.56 (d, *J* = 3.3 Hz, 2H), 4.33 (t, *J* = 1.2 Hz, 2H), 4.28 (t, *J* = 1.2 Hz, 2H), 4.24 (s, 9H), 4.17 (m, 4H), 3.94 –3.90 (m, 13H), 3.86 (t, *J* = 6.6 Hz, 4H), 2.45 (d, *J* = 3.0 Hz, 2H), 1.76 (m, 4H), 1.67 (m, 12H), 1.45 (m, 4H), 1.33 (m, 20H), 1.22 (m, 24H), 0.90 (m, 6H), 0.85 – 0.80 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.35, 150.36, 150.28, 150.26, 142.29, 138.12, 137.93, 132.09, 130.80, 130.73, 130.34, 129.68, 128.26,

127.19, 126.26, 117.25, 116.30, 116.28, 114.51, 113.98, 94.27, 72.39, 69.65, 69.62, 68.62, 68.45, 68.03, 67.94, 67.59, 66.23, 31.58, 31.56, 31.53, 31.46, 29.41, 29.38, 25.82, 25.80, 25.75, 25.71, 22.58, 22.56, 22.54, 22.51, 14.05, 14.02, 14.01, 13.98. Anal. calcd for $C_{112}H_{146}Fe_2O_{10}$: C 76.26, H 8.34. Found: C 76.46, H 8.35.

Synthesis of phosphine-containing compound 18



26 **18**

Under N_2 to a solution of ferrocenylmethyl alcohol **26** (0.38 g, 0.216 mmol) in HOAc / CH_2Cl_2 (3 ml/2 ml) was added $HPPh_2$ (3.5 ml, 10% in hexane, 1.30 mmol). The mixture was stirred at room temperature for 18h. The solvent was evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (2 ml, N_2 degassed) and precipitated from MeOH (10 ml, N_2 degassed). The process was repeated for three times. The precipitation was collected by filtration under air. After drying under vacuum, **18** was obtained as a yellow solid in 58% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.69 (d, *J* = 6.6 Hz, 4H), 7.63 (s, 2H), 7.62 (d, *J* = 6.6 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.2 Hz, 4H), 7.32 – 7.28 (m, 6H), 7.25 (m, 5H),

7.15 (m, 5H), 7.07 (s, 2H), 6.96 (s, 2H), 6.93 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 3.0 Hz, 2H), 6.83 (dd, J_1 = 9.0 Hz, J_2 = 3.0 Hz, 2H), 4.36 (d, J = 6.6 Hz, 2H), 4.33 (s, 2H), 4.03 (s, J = 6.6 Hz, 2H), 3.95 – 3.91 (m, 12H), 3.87 (t, J = 6.6 Hz, 4H), 3.82 (s, 10H), 3.49 (s, 2H), 1.78 (m, 4H), 1.70 (m, 12H), 1.47 (m, 4H), 1.34 (m, 20H), 1.21 (m, 24H), 0.90 (m, 6H), 0.84 – 0.79 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.39, 150.49, 150.38, 150.30, 141.34, 141.26, 138.21, 138.13, 138.07, 137.95, 137.82, 137.70, 134.73, 134.59, 133.27, 133.16, 132.53, 131.10, 130.76, 130.40, 129.58, 129.51, 128.86, 128.79, 128.32, 127.99, 127.91, 127.86, 127.79, 127.75, 117.45, 116.51, 116.50, 114.77, 113.79, 90.66, 90.53, 69.87, 69.72, 69.69, 68.45, 68.42, 67.80, 66.16, 53.41, 47.32, 47.21, 31.65, 31.63, 31.59, 31.54, 29.53, 29.48, 29.46, 29.07, 25.87, 25.84, 25.80, 22.66, 22.64, 22.60, 22.58, 14.12, 14.06, 14.05, 14.04. ^{31}P NMR (121 MHz, $CDCl_3$, H_3PO_4 as standard) δ 4.62. Anal. calcd for $C_{136}H_{164}Fe_2O_8P_2$: C 77.77, H 7.87. Found: C 77.51, H 7.89.

References:

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CHAPTER TWO

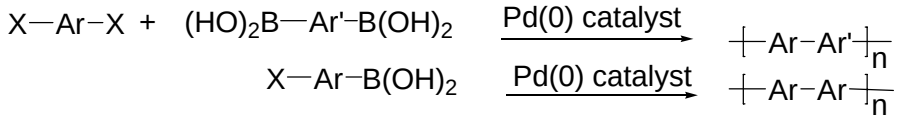
Palladium(0)-Catalyzed Cross-Coupling Reactions of Dihaloarenes with Arylboronic Acids and Grignard Reagents: Preferential Oxidative Addition Concept [1]

2.1 Introduction

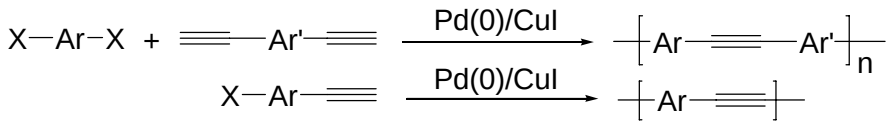
Conjugated polymers are important materials for electroluminesence and molecular electronics. Palladium-catalyzed cross-coupling polymerizations have become extremely powerful tools for building these macromolecules (scheme 2.1).[2,3] But the polymers obtained from palladium-catalyzed cross-coupling polymerizations processes have high Polydispersities.

Scheme 2.1 Palladium-Catalyzed Cross-Coupling Polymerizations

The Suzuki coupling polymerization

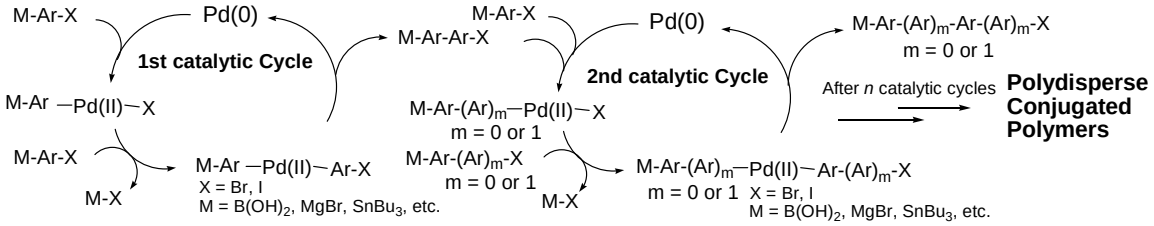


The Sonogashira coupling polymerization



Palladium-catalyzed cross-coupling polymerizations processes can be outlined as shown in scheme 2.2 for AB-type bifunctional monomers. During the cross-coupling polymerization processes, the catalytic cycle is repeated multiple times. In the second catalytic cycle, the reductively regenerated Pd(0) catalyst has two possibilities to insert into an aryl-halogen bond in the next oxidative addition step: One possibility is the reaction with the initial monomer; the second possibility is the intramolecular reaction with the newly generated dimer. Similar reactivity of these two molecules leads to non-selective reaction with the regenerated Pd(0) catalyst. In the third catalytic cycle the reductively regenerated Pd(0) catalyst has three options. We can imagine the more catalytic cycles, the more options for the regenerated Pd (0) catalyst. These non-selective reactions leads to random palladium-catalyzed polymerization processes.

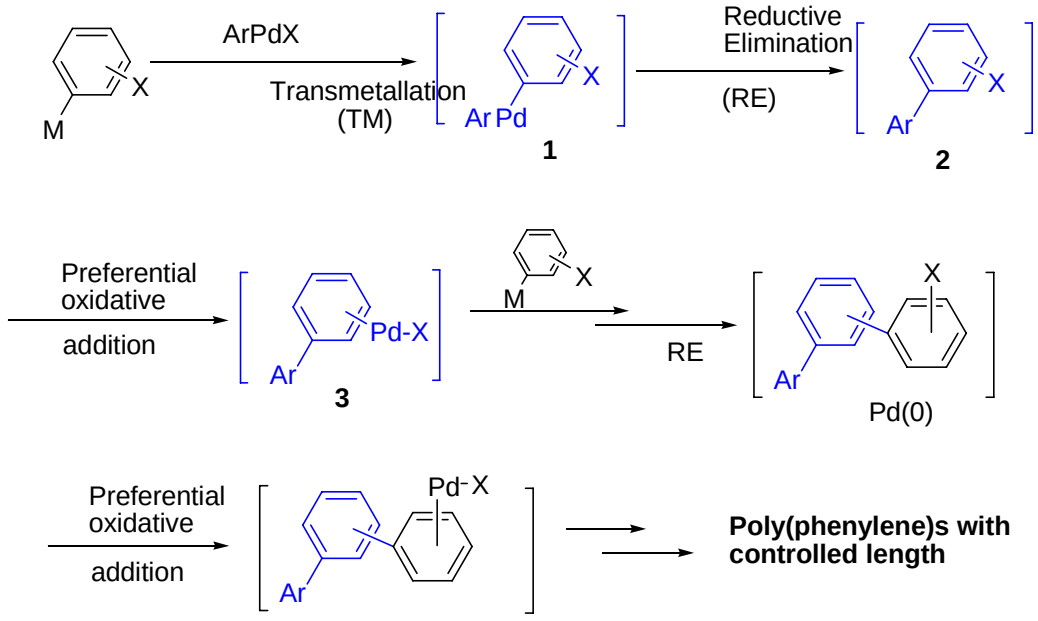
Scheme 2.2 Catalytic Cycle of Pd(0)-Catalyzed Cross-Coupling Polycondensations (AB Approach)



Controlled Pd(0)-catalyzed cross-coupling polymerizations for the synthesis of well-defined conjugated polymers is desired.[4] Scrutiny of the cross-coupling polymerization mechanism suggests that such controlled polymerizations would be possible if the fate of the regenerated Pd(0) catalyst could be controlled. For example, the polymerization of AB-type monomers would be controllable if the regenerated Pd(0) catalyst could be oriented to undergo oxidative addition preferentially with the coupling product just formed (Scheme 2.3). Because Pd(0)-catalyzed cross-coupling polymerizations proceed via repeating the oxidative addition-transmetalation-reductive elimination catalytic cycle, we reasoned that it should be appropriate to study one particular catalytic cycle of a polymerization process to address whether and how the preferential oxidative addition could be achieved. We also reasoned that cross-coupling reactions that possess the same particular preferential oxidative addition step as that of the hypothetical polymerization processes should be appropriate model reactions. We have studied one type of such model reactions, the cross-coupling reactions of dihalobenzenes with 1 equiv. of arylboronic acids (Scheme 2.4) to establish that it is possible to achieve such preferential oxidative addition when appropriate Pd(0) catalyst is employed. The use of 1 equiv or less of boronic acids is important for differentiating products of the

preferential oxidative addition pathway from the nonpreferential oxidative addition pathway. [5]

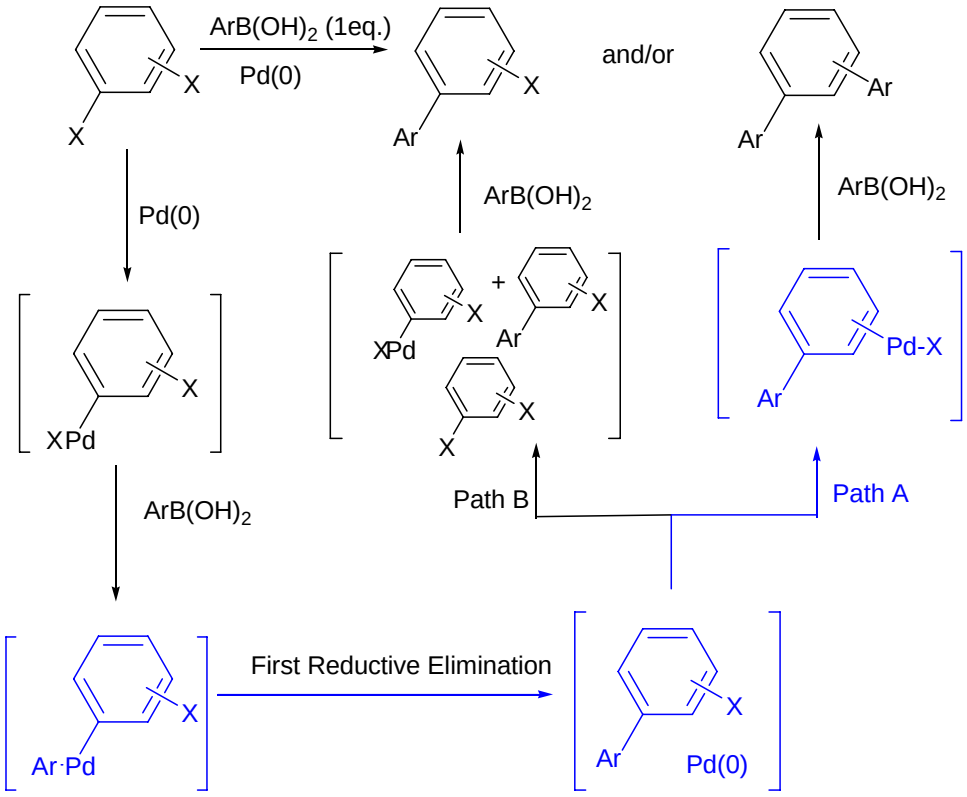
Scheme 2.3 Hypothetic Controlled Pd(0)-Catalyzed Cross-Coupling Polymerization of AB-Type Monomers



As shown in Scheme 2.4, mechanistically, the Pd(0) catalyst regenerated from the first reductive elimination is expected to situate nearby and interact with its homogenously formed 1-aryl-*n*-halobenzene (AHB) (*n*) 2, 3, or 4).[6] It could undergo oxidative addition with the AHB (Path A) or diffuse out of the vicinity of the AHB (Path B). The diffused Pd(0) catalyst is expected to undergo oxidative addition with a dihalobenzene, because the amount of dihalobenzene is in excess relative to that of AHB due to the use

of a limited amount of arylboronic acid, and is more reactive than AHB due to electronic and/or steric effects (Path B).

Scheme 2.4 Pd(0)-Catalyzed Cross-Couplings of Dihalobenzenes with 1 equiv. of Arylboronic Acids

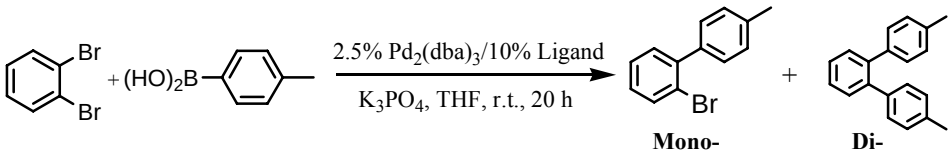


2.2 Catalyst Screening for Preferential Oxidative Addition

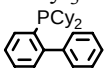
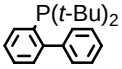
We envisioned that the key to achieve the preferential oxidative addition would lie in how to achieve faster oxidative addition of the regenerated Pd(0) with the AHB (Path A) over its diffusion process (Path B), and the efficiency of the preferential oxidative addition could be assessed by

examining the ratio of the Path A product (diarylbenzene) *vs.* the Path B product (AHB). It has been established that the nature of the ligands has great influence on the oxidative addition rate of a Pd(0) catalyst. We thus began our study by screening different ligands by using the cross-coupling

Table 2.1 Room Temperature Pd(0)-Catalyzed Cross-Couplings of 1,2-Dibromobenzene with *p*-Tolylboronic Acid [a]



Mono- **Di-**

Entry	Pd(0) + Ligand	Conversion(%) [b]	Mono: Di [b]
1	$Pd_2(dba)_3$ + 4 PPh_3	10	92 : 8
2	$Pd_2(dba)_3$ + 2 DPPF or DPPE	<2%	
3	$Pd_2(dba)_3$ + 4 *o*-$tolyl_3P$	99	49 : 51
4	$Pd_2(dba)_3$ + 4 	97	57 : 43
5	$Pd_2(dba)_3$ + 4 	93	38.5 : 61.5
6	$Pd_2(dba)_3$ + 4 PCy_3	66	35 : 65
7	$Pd_2(dba)_3$ + 4 *t*-Bu_3P	99	2 : 98 [c]

[a.] Reaction conditions (not optimized): 1,2-dibromobenzene (1.0 equiv.), p-tolylboronic acid (1.0 equiv.), K_3PO_4 (3 equiv.), THF (2 ml), room temperature. [b.] Based on ^1H NMR. [c].Based on GC-MS.

of 1,2-dibromobenzene with *p*-tolylboronic acid as the model reaction. Our results are listed in Table 2.1. We found that triphenylphoshine and bidentate DPPF or DPPE gave very poor results (Table 2.1, entries 1-2). More

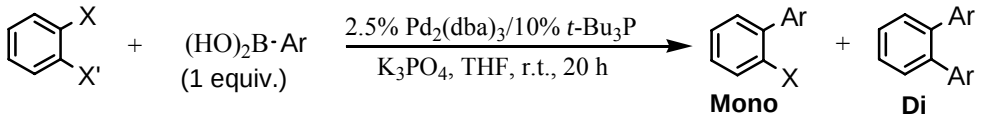
electron-rich monodentate phosphines including Buchwald-type monophosphines [7] gave high conversions with significant amount of diarylbenzene formations, suggesting the preferential oxidative addition occurred to some extent (Table 2.1, entries 3-6). Bulky, electron-rich *t*-Bu_3P [8] was found to give a very satisfying result, with excellent conversion and excellent percentage of diarylbenzene (Table 2.1, entry 7). These results clearly showed that the preferential oxidative addition for the regenerated Pd(0) can be achieved by careful selection of the catalyst system.

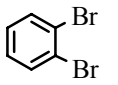
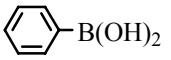
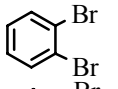
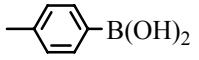
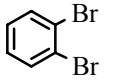
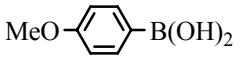
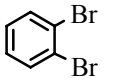
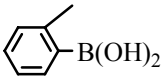
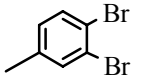
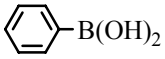
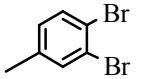
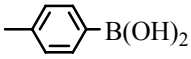
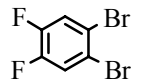
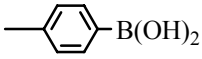
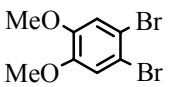
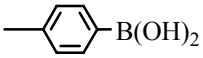
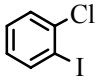
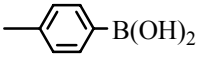
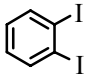
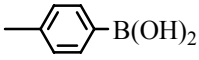
2.3 Pd(0)/*t*-Bu_3P Catalyzed the Cross-coupling Reactions of Dihaloarene with Arylboronic Acids

With Pd(0)-/*t*-Bu_3P as the catalyst system, the cross-coupling reactions of a number of 1,2-dibromobenzenes with arylboronic acids were examined, and our results are listed in Table 2.2. As shown in Table 2.2, all tested 1,2-dibromobenzenes including those with electron-withdrawing and electron-donating substitutents gave high disubstituted / monsubstituted product ratio, suggesting the preferential oxidative addition occurred efficiently. As expected, the cross-coupling of 1-chloro-2-iodobenzene with *p*-tolylboronic acid, which involves the oxidative addition of an inert C-Cl bond, gave exclusively the monosubstitued product (Table 2.2, entry 9),

suggesting the diffusion process was much faster than the oxidative addition process for the regenerated Pd(0) catalyst. Surprisingly, the coupling of 1,2-

Table 2.2 Room Temperature Pd(0)-Catalyzed Cross-Couplings of 1,2-Dihalobenzenes with Arylboronic Acids [a]



Entry	Dihalide	Ar-B(OH)$_2$	Mono : Di [b]	Yield(%) [c]
1			<1 : > 99	96
2			2 : 98	98
3			<1 : > 99	96.5
4			4 : 96	90
5			<1 : > 99	94
6			<1 : > 99	92
7			<1 : > 99	78
8			<1 : > 99	82
9			> 99 : < 1	99 [d]
10			21 : 79	72

a. Reaction conditions (not optimized): dibromoide (1.0 equiv.), arylboronic acids (1.0 equiv.), K_3PO_4 (3 equiv.), $Pd_2(dba)_3$ (2.5%), *t*-Bu_3P (10%), THF (2 ml), room temperature. b. Ratio based on GC-MS. c. Isolated yields of diarylbenzenes. d. Conversion of *p*-tolylboronic acid based on ^{1}H NMR.

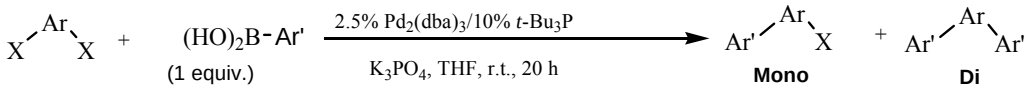
diiodobenzene with *p*-tolylboronic acid, which involves the oxidative addition with a very reactive C-I bond, gave only a 21:79 ratio of mono:di

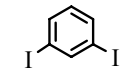
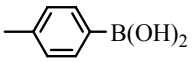
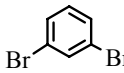
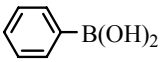
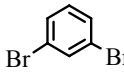
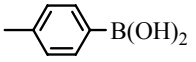
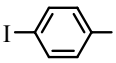
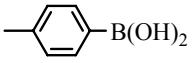
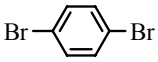
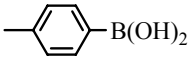
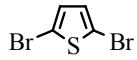
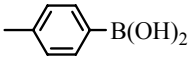
product (Table 2.2, entry 10). This less efficient preferential oxidative addition might suggest that the larger size of the second iodo group destabilizes the interaction of the regenerated Pd(0) catalyst with the homogenously generated product, leading to a formally faster diffusion process.

To address whether the preferential oxidative addition could occur for substrates with spatially separated reactive sites, we have examined the cross-couplings of 1,3- and 1,4-dihalobenzenes with 1 equiv. of arylboronic acids. We found that excellent ratios of diarylbenzenes *vs* monoarylbenzenes were observed for both 1,3-diiodobenzene and 1,3-dibromobenzene, suggesting the preferential oxidative addition also occurred efficiently (Table 2.3, entries 1-3). That the preferential oxidative addition occurred more efficiently for 1,3-diiodobenzene than for 1,2-diiodobenzene and 1,3-dibromobenzene suggests that the size of the second iodo group no longer interferes with the diffusion process and is consistent with the established results of C-I bonds having a higher oxidative addition rate with Pd(0) than C-Br bonds do. Such a trend was also observed for 1,4-dihalobenzenes. Table 2.3, entries 4-5). Interestingly, the 1,4-dihalobenzenes underwent much slower Suzuki crosscouplings than their 1,2- and 1,3-analogues (Table 2.3, entries 4-5). Such unusual results suggest that the oxidative addition of

the regenerated Pd(0) to C-Br or C-I bond, although faster than the diffusion process, occurs slower than the similar oxidative addition processes for the 1,2- and 1,3-analogues, and serves as the rate-limiting step. Finally, we have also carried out the cross-couplings of 2,5-dibromothiophene, and efficient preferential oxidative addition was also observed (Table 2.3, entry 6).

Table 2.3 Room Temperature Pd(0)-Catalyzed Cross-Couplings of Dihaloarenes with Arylboronic Acids[a]



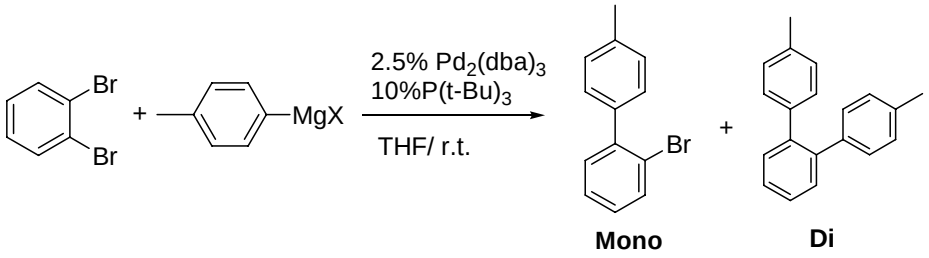
Entry	Dihalide	Ar-B(OH)$_2$	Mono : Di [b]	Yield(%) [c]
1			0.3 : 99.7 (1 : 332)	96
2			1.5 : 98.5	91
3			1 : 99	86
4			3 : 97	43
5			6 : 94	23
6			9 : 91	80

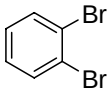
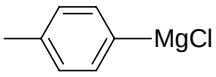
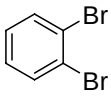
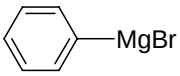
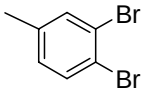
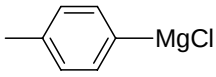
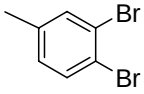
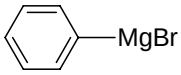
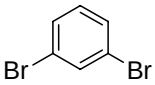
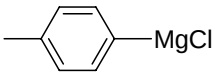
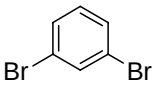
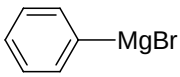
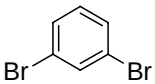
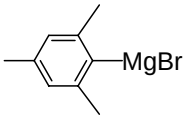
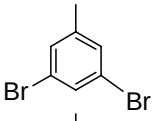
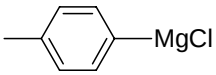
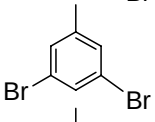
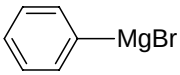
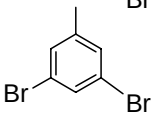
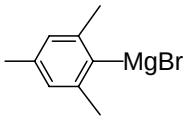
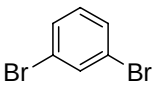
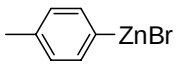
a. Reaction conditions (not optimized): dihalide (1.0 equiv.), arylboronic acid (1.0 equiv.), K_3PO_4 (3 equiv.), THF (2 ml), room temperature. b. Ratio based on GC-MS. c. Isolated yields of diarylbenzenes

2.4 Pd(0)/*t*-Bu$_3$P Catalyzed the Cross-coupling Reactions of Dihaloarene with Other Grignard Reagents

We also tested the preferential oxidative addition behavior of dihaloarenes with Grignard reagents (the Kumada coupling) and our results are list in Table 2.4. The results show that preferential oxidative addition

Table 2.4 Room-Temperature Pd(0)-Catalyzed Cross-Couplings of Dihalobenzene with Grignard Reagents [a]



Entry	Dihalobenzene	Grignard reagents	Mono : Di Ratio	Yield
1			8.0: 92.0	87%
2			3.7: 96.3	83%
3			4.5: 95.5	95.5%
4			< 1.0: 99.0	68.0%
5			2.3: 97.7	81.0%
6			3.2: 96.8	69.0%
7			4.5: 95.5	95%
8			< 1.0: 99.0	98.5%
9			1.5: 98.5	90.2 %
10			2.8: 97.2	98.2 %
11			4.9: 95.1	73.8 %

[a] Reaction conditions: dihalobenzene (1.0 equiv), Grignard reagents (1.0 equiv), THF (1 mL), room temperature, Reaction time: 3 h.

works well for the ortho- and meta-dihaloarenes. We observed that even for the bulky Grignard reagents, 2-mesitylmagnesium bromide, we still can get excellent ratio of diarylbenzene /monoarylbenzene (Table 2.4, entry 8, 11).

In summary, we have demonstrated that the regenerated Pd(0) catalyst in the cross-coupling of dihaloarenes with arylboronic acids or Grignard reagents could undergo oxidative addition preferentially with its homogenously formed coupling product when the appropriate Pd(0) catalyst system is employed. The Pd(0)/*t*-Bu_3P was identified as a powerful catalyst system to achieve efficient preferential oxidative addition. Our study may lead to the development of controlled Pd(0)-catalyzed cross-coupling polymerizations for the preparation of conjugated polymers with desired lengths. Future work in this direction is under active investigation.

2.5 Experimental Section

2.5.1 General

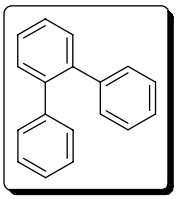
NMR spectra were recorded on Varian 200 MHz or 600 MHz spectrometers. All yields reported refer to isolated yields (average of two runs) unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by ^{1}H NMR. Experiments were carried out

using a Agilent GC/MS instrument consisting of a 6890N series GC and a 5973 Mass Selective Detector System. Compounds described in the literature were characterized by melting points, Mass Spectra, ^{1}H NMR and ^{13}C NMR spectra. THF were dried with sodium/benzophenone. $Pd_2(dba)_3$, phenylboronic acid, PPh_3, PCy_3, *n*-Bu_3P, *i*-Bu_3P, *t*-Bu_3P, DPPF, DPPE, and potassium phosphate were purchased from Strem and used directly. Other chemical reagents were purchase from Aldrich and used directly.

2.5.2 General procedure for the Suzuki couplings of dibromides with arylboronic acid

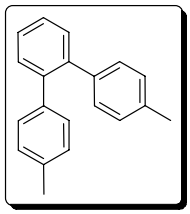
In a glove box with N_2-atmosphere, to a mixture of Arylboronic acid (1.0 mmol), potassium phosphate (3.0 mmol) and 3 ml THF (in a vial) were added tris(dibenzylideneacetone)dipalladium(0) (13.7 mg, 0.015 mmol) and tri(tert-butyl)phosphine (12.1 mg, 0.06 mmol). After stirred for 5-10 minutes, dibromide (1.0 mmol) was added. The mixture was allowed to stir for 6 hours. After quchening reaction with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) yielded the cross-coupling products.

o-Terphenyl (1) light yellow solid. m. p.: 85-87 ^{o}C. Ratio of mono: di : self-coupling of boronic acid based on GC-MS: 0.8: 99.2 : 0.3.



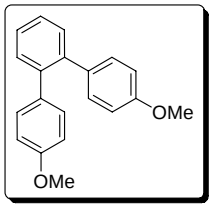
^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.441~7.405 (m, 4H), 7.196 (t, *J* = 7.8 Hz, 2H), 7.193 (t, *J* = 3.6 Hz, 2H), 7.137 (dd, *J* = 7.8 Hz, 4H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 141.482, 140.542, 130.579, 129.869, 127.833, 127.454, 126.419.

4,4″-Dimethyl-(1,1′,2′,1″)-Terphenyl (2) white solid. m.p.: 94-95 ^{o}C. Ratio of mono: di : self-coupling of boronic acid based on GC-MS: 1.7: 98.3: 1.6.



^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.406~7.368 (m, 4H), 7.033 (d, *J* = 1.2 Hz, 8H), 2.312 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 140.466, 138.745, 135.931, 130.623, 129.705, 128.591, 127.195, 21.087.

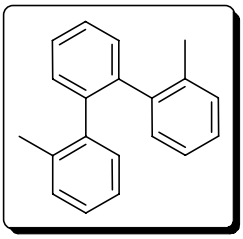
4,4″-Dimethoxyl-(1,1′,2′,1″)-Terphenyl (3) white solid. m.p.: 103-105 ^{o}C. Ratio of mono: di : self-coupling of boronic acid based on GC-MS: 0.9: 99.1: 0.



^{1}H NMR ($CDCl_3$, 600

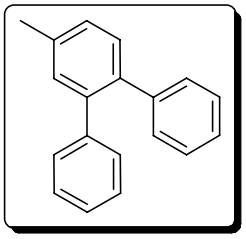
MHz) δ 7.392~7.352 (m, 4H), 7.063 (d, *J* = 8.4 Hz, 4H), 6.765 (d, *J* = 9.0 Hz, 4H), 3.780 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 158.200, 140.026, 134.068, 130.880, 130.540, 127.114, 113.349, 55.133.

2,2″-Dimethyl-(1,1′,2′,1″)-Terphenyl (4) white solid. m.p.: 39-41 °C.



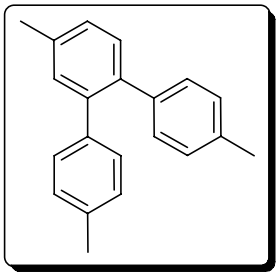
Ratio of mono: di: self-coupling of boronic acid based on GC-MS: 4: 96: 2.5. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.387 (br.s, 2H), 7.309 (br.s, 2H), 7.067 (br.s, 4H), 7.007 (br.s, 2H), 6.943 (br.s, 1H), 6.866 (br.s, 1H), 2.131 (br.s, 3H), 2.047 (br.s, 3H). 13C NMR (CDCl3, 150.9 MHz): δ 140.676, 135.550, 131.271, 130.681, 130.470, 129.846. 129.624, 126.749, 124.717, 20.470, 19.982.

4′-Methyl-(1,1′,2′,1″)-Terphenyl (5) white solid. m.p.: 80-81 °C.

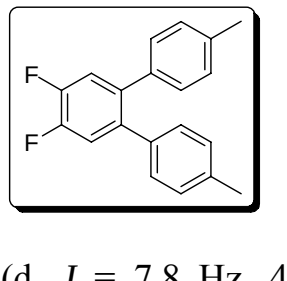


Ratio of mono: di: self-coupling of boronic acid based on GC-MS: 0.1: 99.9: 0. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.330 (d, *J* = 7.8 Hz, 2H), 7.250 (s, 1H), 7.063 (d, J=8.4 Hz, 4H), 6.765 (d, J=9.0 Hz, 4H), 2.435 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 141.617, 141.453, 140.399, 137.759, 137.170, 131.367, 130.556, 129.910, 129.868, 128.207, 127.821, 126.385, 126.245, 21.110.

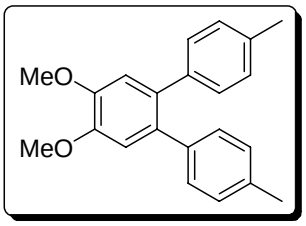
4′-Methyl-4,4″-Dimethyl-(1,1′,2′,1″)-Terphenyl (6) white solid. m.p.: 116-118 °C. Ratio of mono: di: self-coupling of boronic acid based on GC-MS: 0.1: 99.9: 0. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.291 (d, *J* = 7.8 Hz, 1H), 7.215 (s, 1H), 7.188 (d, *J* = 7.8 Hz, 1H), 7.041~6.997 (m, 8H), 2.408 (s, 3H), 2.297 (s, 3H), 2.293 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 140.214, 138.771, 138.606, 137.574, 136.851, 135.854, 135.699, 131.385, 130.567, 129.682, 129.647, 128.548, 127.941, 21.096, 21.085, 21.054.



4′,5′-Difluro-4,4″-Dimethyl-(1,1′,2′,1″)-Terphenyl (7) white solid. m.p.: 83-85°C. Ratio of mono: di: self-coupling of boronic acid based on GC-MS: 0.1: 99.9: 0. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.183 (t, 2H), 7.020 (d, *J* = 7.8 Hz, 4H), 6.968 (d, *J* = 7.8 Hz, 4H), 2.305 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 149.986, 148.358, 137.085, 136.818, 136.635, 129.512, 128.793, 21.109.

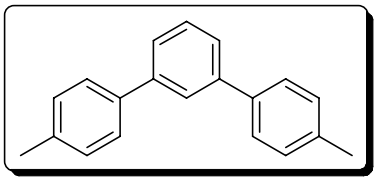


4′,5′-Dimethoxyl-4,4″-Dimethyl-(1,1′,2′,1″)-Terphenyl (8) white solid. m.p.: 128-130 °C. Ratio of mono: di: self-coupling of boronic acid based on GC-MS: 0.1: 99.9: 0. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.030 (m, 8H), 6.909



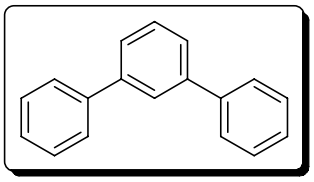
(s, 2H), 3.927 (s, 6H), 2.311 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 147.946, 138.586, 135.767, 132.805, 129.726, 128.613, 113.658, 56.000, 21.084.

4, 4″-Dimethyl-(1,1′,3′,1″)-Terphenyl (9) white solid. m. p.: 119-120 ^{o}C.



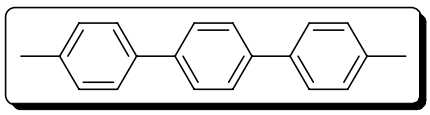
Ratio of mono: di : self-coupling of boronic acid based on GC-MS: from 1,3-diiodobenzene: 0.3: 99.7 : 0. from 1,3-dibormobenzene: 1: 99 : 0. ^{1}H NMR (CDCl3, 600 MHz) δ 7.767 (d, *J* = 1.8 Hz, 1H), 7.524 (d, *J* = 8.4 Hz, 6H), 7.248(d, *J* = 7.8 Hz, 4H), 2.388 (s, 6H). 13C NMR (CDCl3, 150.9 MHz) δ 141.622, 138.336, 137.108, 129.486, 129.075, 127.060, 125.737, 125.653, 21.097.

***m*-Terphenyl (10)** white solid. m. p.: 86-87 ^{o}C. Ratio of mono: di:



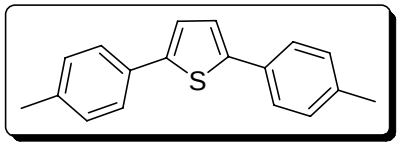
self-coupling of boronic acid based on GC-MS: 1.5: 98.5: 0.6. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.800 (s, 1H), 7.638 (d, *J* = 7.2 Hz, 4H), 7.557 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 2H), 7.495 (t, *J* = 7.8 Hz, 1H), 7.447 (t, *J* = 7.8 Hz, 4H), 7.355 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 141.738, 141.138, 129.156, 128.770, 127.369, 127.229, 126.127, 126.091.

1,4-Bis(4-methylphenyl)-benzene (11) white solid. m.p.: 213-214 ^{o}C.



Ratio of mono: di : self-coupling of boronic acid based on GC-MS: from 1,4-diiodobenzene (reaction at room temperature): 2.7: 97.3 : 5.4; from 1,4-diiodobenzene (reaction at 60^{o}C): 9 : 91 : 0.9; from 1,4-dibormobenzene: 6: 94 : 18. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.647 (s, 4H), 7.540 (d, J = 7.8 Hz, 4H), 7.267(d, J = 8.4 Hz, 4H), 2.407 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 139.738, 137.846, 137.056, 129.506, 127.233, 126.837, 21.108.

2,5-bis(4′-methylphenyl)-thiophene (12) yellow solid. m.p.: 177-178 ^{o}C.



Ratio of mono: di : self-coupling of boronic acid based on GC-MS: From 2,5-dibromothiophene: 8.8: 91.2 : 1.2. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.504 (d, J = 7.8 Hz, 4H), 7.210 (s, 2H), 7.172 (d, J = 8.4 Hz, 4H), 2.354 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 143.192, 137.245, 131.596, 129.532, 125.456, 123.382, 21.164.

2.5.3 Competition Reaction

In a glove box with N2-atmosphere, to a mixture of *p*-tolylboronic acid (0.5 mmol), potassium phosphate (1.5 mmol) and 2 ml THF (in a vial) were added tris(dibenzylideneacetone)dipalladium(0) (6.8 mg, 0.0075 mmol) and tri-*tert*butylphosphine (6.1 mg, 0.03 mmol). After stirred for 5-10 minutes, 1,2-dibromobenzene (0.5 mmol) and 2-bromobiphenyl (0.5 mmol) was added. The mixture was allowed to stir for 18 hours at room temperature. After quenching the reaction with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solution was analyzed by GC-MS directly. The conversions of 1,2-dibromobenzene and 2-bromobiphenyl are 55% and 45%, respectively.

Notes and References:

1) This chapter is mainly based on the paper published: Dong, C.-G.; Hu, Q.-S. *J. Am. Chem. Soc.* **2005**, 127, 10006-10007.

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3) (a) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.;Wiley-VCH: New York, **2004**. (b) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH:New York, **1998**. (c) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, **1987**.

4) For potential applications of conjugated molecules with desired length as molecular electronics, see: (a) Carroll, R. L.; Gorman, C. B. *Angew. Chem., Int. Ed.* 2002, *41*, 4378. (b) Tour, J. M. *Acc. Chem. Res*. 2000, *33*, 791-804.

5) For cross-couplings of dihalobenzenes with 2 equiv (or more) of arylboronic acids: (a) Berthiol, F.; Kondolff, I.; Doucet H.; Santelli. M. *J. Organomet. Chem.* **2004**, *689*, 2786-2798. (b) Simoni, D. et al., *Tetrahedron Lett*. **2003**, *44*, 3005-3008. (c) Basu, B.; Das, P.; Bhuiyan, M. M. H.; Jha, S. *Tetrahedron Lett.* **2003**, *44*, 3817- 3820. (d) van der Vlugt, J. I.; Bonet, J. M.; Mills, A. M.; Spek A. L.; Vogt. D. *Tetrahedron Lett.* **2003**, *44*, 4389-4392. (e) Paul, S.; Clark, J. H. *Green Chem*. **2003**, *5*, 635-638. (f) Oh, C. H.; Lim, Y. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 663-664. (g) Eastmond, G. C.; Paprotny, J.; Steiner, A.; Swanson, L. *New J. Chem.* **2001**, 379-384.

6) Recent examples: (a) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162-1163. (b) Kocovsky, P.; Vyskocil, S.; Cisarova, I.; Sejbal, J.; Tislerova, I.; Smrcina, M.; Lloyd-Jones, G. C.; Stephen, S. C.; Butts, C. P.; Murray, M.; Langer, V. *J. Am. Chem. Soc.* **1999**, *121*, 7714-7715.

7) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550-9561.

8) Pd(0)/*t*-Bu_3P for cross-coupling reactions: for a review: (a) Littke, A.F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176-4211. Selected recent examples: (b) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746-4748. (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

Chapter Three

Annulative Tandem Reactions Based on Palladium-Catalyzed Cross-Coupling/Csp^3-H Bond Activation: Synthesis of Substituted Fluorenes and Indenes [1]

3.1 Introduction

Recently transition metal-catalyzed carbon-carbon forming reaction via C*sp*^{3}-H bond activation have emerged as new efficient tools for synthetic organic chemistry.[2] The development of transition metal-catalyzed tandem or "domino" reactions, which combine two or more bond-forming reactions into one synthetic operation, represents one of the most attractive subjects in synthetic organic chemistry.[3,4] Such tandem/domino reactions allow the concomitant formation of two or more bonds with rapid increase in molecular complexity with minimized separation/purification efforts. In light of recent advancement in tandem or "Domino" reactions, we reasoned that these two types of powerful transition metal-catalyzed reactions could be transformed into even more powerful tools if they could be arranged to occur in a tandem or "Domino" fashion. Toward this end, on Chapter 2 we have developed Pd(0)/*t*-Bu_3P-catalyzed Suzuki cross-coupling of dihaloarenes with arylboronic acids, a process that relies on the control of oxidative addition step. We also envisioned that ring-forming tandem or

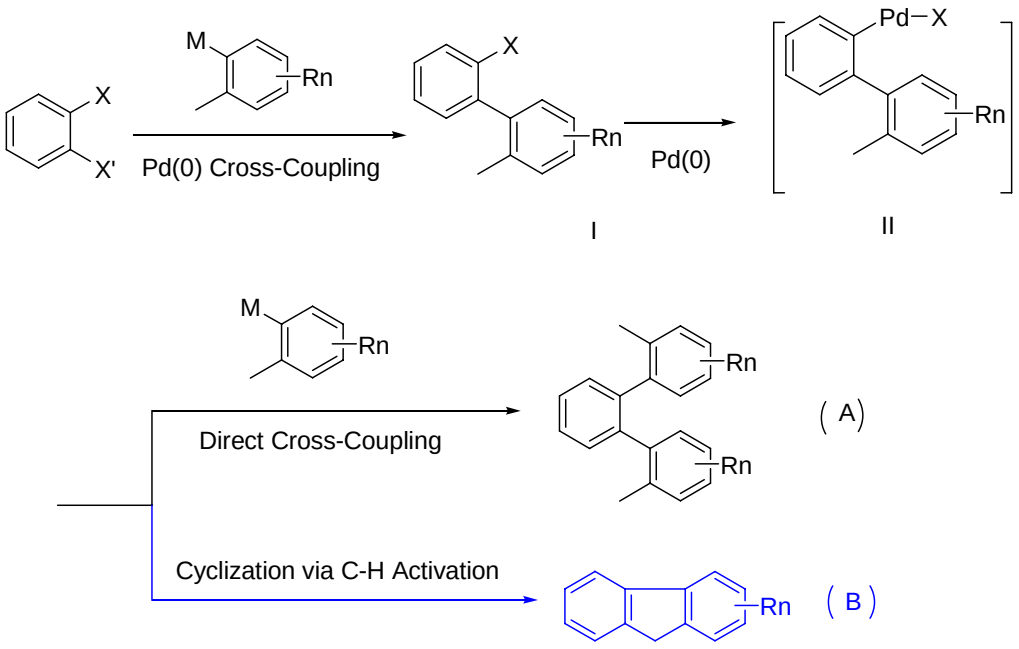
"Domino" reactions that combine transition metal-catalyzed cross-couplings and Csp^3-H bond activation strategy would provide extremely powerful tools for the synthesis of cyclic compounds because such annulative tandem or "Domino" reactions could not only concomitantly generate multiple bonds with rapid increase in molecular complexity but also allow us to access ring systems that are difficult to access by other methods. In connection with our interest to develop highly efficient catalysts/processes for organic synthesis, we studied such annulative tandem reactions, that is, Palladium-catalyzed tandem cross-coupling-cyclization via C-H activation of 1,2-dihalobenzenes and 1,2-dibromoalkenes with Grignard reagents, which provide efficient access to substituted fluorenes and indenes, which have been established as promising sensors and light-emitting materials. [5]

3.2 Exploring Cross-coupling-cyclization via C-H Activation Pathway Conditions

From the analysis of reaction mechanism, we recognized that Pd(II) complex **II**, the oxidative addition adduct of Pd(0) with the first cross-coupling step product 2-halobiaryl (**I**), could (a) couple with another equivalent of organometallic reagents to yield the direct cross-coupling product, and/or (b) undergo intramolecular C-H activation by the Pd(II)

species followed by cyclization (Scheme 3.1). Therefore, the challenge to realize ring-forming tandem cross-coupling-C-H activation reactions lies in how to achieve cyclization via intramolecular C-H activation (path B) over the intermolecular direct cross-coupling process (Path A, Scheme 3.1).

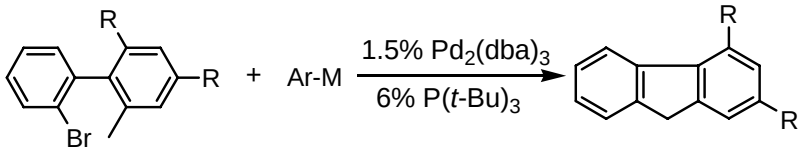
Scheme 3.1 Tandem Cross-Coupling-Cross-Coupling Reaction vs. Tandem Cross-Coupling-Cyclization via C-H Activation

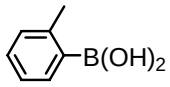
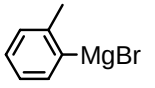
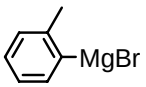
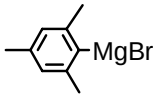
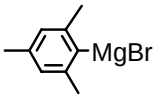
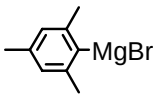
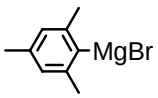


Based on reported results that sterically hindered substrates/reagents were more reluctant to undergo cross-coupling reactions, we surmised that the cyclization pathway should be more favored with bulkier substrates and/or reagents. We thus began our study by examining the cyclization behavior of 2-bromo-2'-methybiphenyls under cross-coupling reaction conditions (i.e., in the presence of ArM). With Pd/*t*-Bu_3P as our initial

catalyst, we found although 2-bromo-2'-methybiphenyl only yielded direct cross-coupling product with *o*-tolyoboronic acid (Table 3.1, entry 1), it indeed yielded more cyclization product with bulkier Grignard reagent, which served as both coupling reagent and base (Table 3.1, entries 2,3). The use of bulkier 2-bromo-2', 6'-dimethybiphenyl as substrate lead to clean cyclization in the presence of 2-mesitylmagnesium bromide, suggesting the cyclization pathway via C-H activation could be efficiently controlled over the direct cross-coupling process by adjusting the bulkiness of the substrates/reagents.

Table 3.1 Pd(0)-Catalyzed Cyclization of 2-Bromo-2'-methylbiaryl Compounds [a]



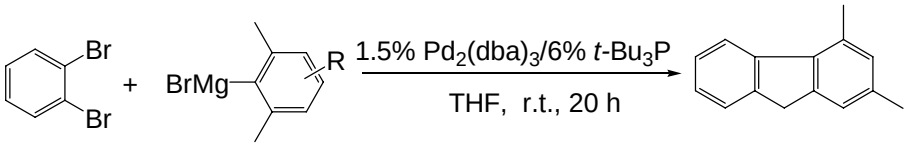
Entry	R	Ar-M	Base	Temp.	Yield
1	H		K_3PO_4	r.t.-Reflux	0 [b]
2	H			r.t.	trace [c]
3	H			r.t.	41 [d]
4	CH_3			r.t.	91 [e]

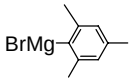
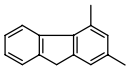
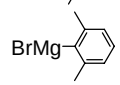
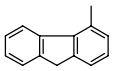
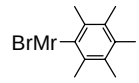
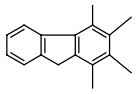
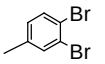
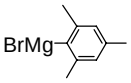
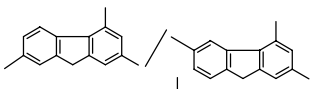
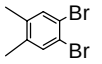
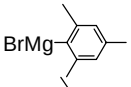
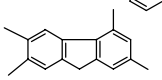
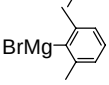
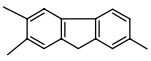
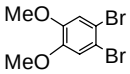
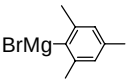
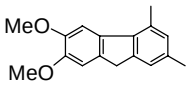
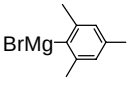
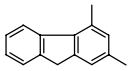
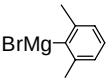
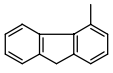
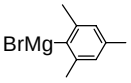
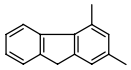
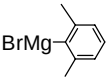
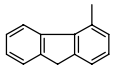
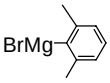
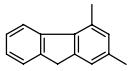
a. Reaction conditions (not optimized): Aryl bromide (1.0 equiv.) and either an aryboronic acid (1.5 equiv.) and K3PO_4 (3 equiv.) or Grignard reagent (2.5 equiv.), THF (2 ml). b.1,2-diarylbenzene was obtained in 37% conversion. c.1,2-diarylbenzene was obtained in 68% conversion. d. 1,2-diarylbenzene was obtained in 45% conversion. e. Isolated yiel.

3.3 Annulative Tandem Reactions of Dihaloarene with Grignard Reagents

Having established that cyclization via C-H activation pathway could be achieved by using bulky Grignard reagent, we next turned our attention to test the annulative tandem reaction of 1,2-dibromobenzene with 2-mesitylmagnesium bromide, which was expected to proceed via complex (**II**) as the intermediate. We were pleased to find that the annulative tandem reaction took place as expected in excellent yield (Table 3.2, entry 1). This result encouraged us to examine a number of 1,2-dihalobenzenes for this new type of annulative tandem reaction. We found good-to-excellent yields were observed for 1,2-dibromobenzenes (Table 3.2, entries 1–7) and 1-bromo-2-iodobenzene (Table 3.2, entries 8, 9). 1,2-Dibromo-4,5-dimethylbenzene and 1,2-dibromo-4,5-dime-thoxybenzene, which are more electron rich than 1,2-dibromobenzene, required heating to 60^{o}C for the reaction to go to completion. We also found that 1-chloro-2-halobenzenes only gave very low yields of fluorenes and excellent yields of 2-chlorobiphenyls (I, X=Cl) were obtained (Table 3.2, entries 10–12). Attempts to try and improve the yields of the cyclization products, including

Table 3.2 Pd-catalyzed Tandem Reaction of 1,2-Dihalobenzenes with Bulky Grignard Reagents [a]



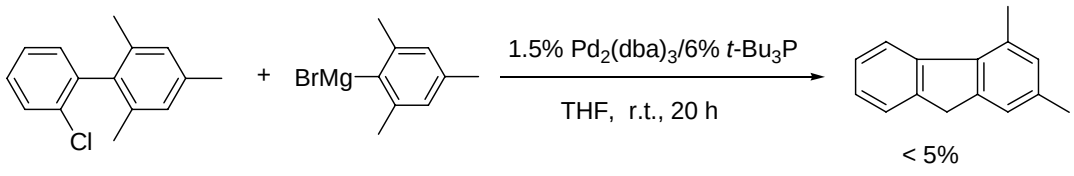
Entry	Dihalide	Griganrd Reagents	Product	Yield (%)[b]
1				99
2				99
3				93
4				99 (44/56)[c]
5				95 [d]
6				91 [d]
7				78 [d]
8				99
9				89
10				3[e] (94)[d, f]
11				2[e] (97)[d, f]
12				3[e] (96)[d, f]

[a] Reaction conditions (not optimized): aryl dihalide (1.0 equiv), Grignard reagent (2.5 equiv), Pd catalyst (3 mol%), THF (2 mL), room temperature. [b] Yields of the isolated products. [c] Ratio based on ^{1}H NMR spectroscopic analysis. [d] Reaction temperature: 60 8C. [e] Based on 1H NMR spectroscopic analysis. [f] In parenthesis: yields of the isolated product for 2-chlorobiaryl compounds **I**.

raising the temperature to reflux in THF or THF/dioxane were made, but no significant improvement in yield was observed (less than 5%).

We carried out preliminary studies on whether the first carbon–carbon bonding-forming step indeed proceeded through the envisioned cross-coupling strategy. As the formation of (**I)** and the subsequent oxidative addition of (**I)** with Pd(0) are involved in such a cross-coupling process, we reasoned that it could be validated by the detection of the existence of this intermediate. Reactions with 1-chloro-2-halobenzenes as the substrates were apparently consistent with the formation of the first carbon–carbon bond through the cross-coupling strategy, with (**I)** (X=Cl) being obtained in excellent yields (Table 3.2, entries 10–12) because of its reluctance to undergo oxidative addition with Pd(0)/*t*-Bu_3P under the new tandem reaction conditions (Scheme 3.2).

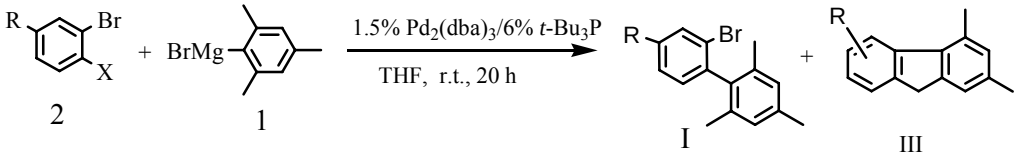
Scheme 3.2 Palldium-Catalyzed Reactions of 2-Chloro-2',4',6'-trimethylbiphenyls with 2-Mesitylmagnesium Bromide



Because (**I)** (X=Br) can readily undergo oxidative addition with Pd(0)/*t*-Bu_3P, the detection of the existence of I (X=Br) in Pd(0)/*t*-Bu_3P–

catalyzed tandem reactions of 1,2-dibromobenzenes would require the reactions to be stopped before completion by methods such as using a limited amount of Grignard reagent. We thus carried out the reaction of 1,2-

Table 3.3 Pd-catalyzed Reactions of 1,2-Dihalobenzenes with a Limited Amound of 2-Mesitylmagnesium Bromide [a]



2 1 I III

Entry	X	R	Conversion (%)[b]	I (%)	III (%)
1	Br	H	48	7	93
2	Br	CH_3	45	12	88
3	I	H	34	19.5	80.5

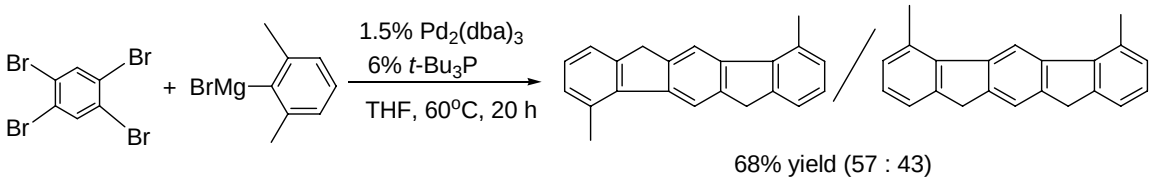
[a] Reaction conditions: aryl dihalide (1.0 equiv), Grignard reagent (0.5 equiv), Pd catalyst (3 mol%), THF (2 mL), room temperature, 20 h. Ratio **I/III** based on GC/MS data. [b] Based on 1,2-dihalobenzene.

dibromobenzene with 0.5 equivalents of 2-mesitylmagnesium bromide. Our results showed that I was observed in 7% yield (Table 3.3, entry 1). As the envisioned cross-coupling strategy also involves the oxidative addition of (**I**) with a regenerated Pd(0) species, substrates such as 1,2-dibromo-4-methylbenzene that yield less reactive (**I**), or substrates such as 1-bromo-2-iodobenzene that undergo oxidative addition faster than (**I**) (X=Br), should lead to the detection of greater amounts of (**I**) (X=Br); indeed, our study on these substrates showed that more of (**I**) was found (Table 3.3, entries 2, 3).

In combination with our recent observation of preferential oxidative addition with Pd(0)/*t*-Bu_3P, the detection of a significant amount of (**I**) strongly suggests that the cross-coupling strategy should be a main pathway, if not the only one, for the first carbon–carbon bond-forming step of the reaction of 1,2-dibromobenzenes and 1-bromo-2-iodobenzene with hindered Grignard reagents.

We also extended the tandem reaction to 1,2,4,5-tetrabromobenzene as a substrate and found that the tandem reaction occurred as expected to give indenofluorenes in good yield (Scheme 3.3).

Scheme 3.3 Pd-Catalyzed Tandem Reaction of 1,2,4,5-Tetrabromobenzene with 2,6-Dimethyphenylmagnesium Bromide



68% yield (57 : 43)

In Summary, we have demonstrated that cyclization through C(sp^3)-H bond activation in the Pd(0)/*t*-Bu_3P-catalyzed reactions of 2-bromo-2′-methylbiphenyls could be efficiently achieved by employing hindered substrates/reagents. Furthermore, we have developed a new type of Pd-catalyzed annulative tandem reaction of 1,2-dibromobenzenes and 1-bromo-2-iodobenzene with hindered Grignard reagents based on a Pd-catalyzed cross-coupling reaction and C-H activation strategy. This new type of

tandem reaction allows efficient access to potentially useful substituted fluorenes. Future work will focus on expansion of the reaction scope, elucidation of more detailed reaction mechanisms, and extension of the cyclization strategy for the preparation of other cyclic compounds and substituted oligofluorenes/polyfluorenes.

3.4 Experimental Section

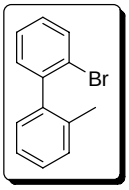
3.4.1 General

NMR spectra were recorded on Varian 200 MHz or 600 MHz spectrometers. GC-MS experiments were carried out using an Agilent GC/MS instrument consisting of a 6890N series GC and a 5973 Mass Selective Detector System. All yields reported refer to isolated yields (average of two runs) unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by ^{1}H NMR. Compounds described in the literature were characterized by comparison of their melting points, ^{1}H NMR and ^{13}C NMR spectra to reported data. Some of the new compounds were also characterized by elemental analysis.

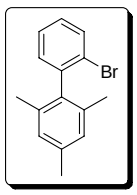
THF was dried with sodium/benzophenone. 2,6-dimethylpheny-lmagnesium bromide, 2-mesitylmagnesium bromide and *p*-tolylmagnesium bromide were purchased from Aldrich Chemical Co. and used directly.

$Pd_2(dba)_3$ and *t*-Bu_3P were purchased from Strem and used as received. 2-Bromo-2′-methylbiphenyl, 2-bromo-2′,4′,6′-trimethylbiphenyl, 2-chloro-2′,4′,6′-trimethylbiphenyl were prepared according to literature procedures.[6,7] Pentamethylphenylmagnesium bromide were prepared according to literature.[8,9] Other chemical reagents were purchased from Alfa Aesar and used directly.

2-Bromo-2′-methylbiphenyl (1) Colorless liquid. ^1H NMR ($CDCl_3$, 600 MHz) δ: 7.653 (d, J = 7.8 Hz, 1H), 7.348 (t, J = 7.2 Hz, 1H), 7.319 ~ 7.200 (m, 5H), 7.118 (d, J = 7.2 Hz, 1H), 2.108 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.871 MHz) δ: 142.638, 141.115, 135.947, 132.507, 130.836, 129.769, 129.218, 128.684, 127.876, 127.164, 125.461, 123.716, 19.835.

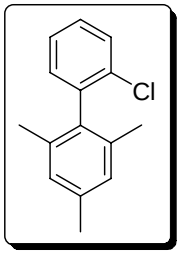


2-Bromo-2′,4′,6′-trimethylbiphenyl (2) Colorless liquid. ^1H NMR ($CDCl_3$, 600 MHz) δ: 7.663 (d, J = 7.8 Hz, 1H), 7.351 (t, J = 7.2 Hz, 1H). 7.193 (t, J = 7.2 Hz, 1H), 7.129 (d, J = 7.2 Hz, 1H), 6.945 (s, 2H), 2.335 (s, 3H), 1.951 (s, 6H). ^{13}C NMR ($CDCl_3$,



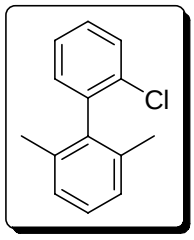
150.871 MHz) δ: 141.812, 137.929, 137.174, 135.717, 132.649, 130.831, 128.478, 127.976, 127.583, 124.189, 21.156, 20.166.

2-Chloro-2′,4′,6′-trimethylbiphenyl (3) Colorless liquid. ^{1}H NMR



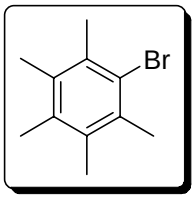
($CDCl_3$, 600 MHz) δ: 7.476 (d, J = 6.6 Hz, 1H), 7.306 ~ 7.278 (m, 2H), 7.134 (d, J = 4.2 Hz, 1H), 6.952 (s, 2H), 2.338 (s, 3H), 1.965 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.871 MHz) δ: 139.701, 137.194, 136.155, 135.948, 133.670, 130.984, 129.471, 128.351, 127.989, 126.933, 21.134, 20.130.

2-Chloro-2′,6′-trimethylbiphenyl (4) Colorless liquid. ^{1}H NMR



($CDCl_3$, 600 MHz) δ: 7.488 (d, J = 7.2 Hz, 1H), 7.325 (t, J = 7.8 Hz, 1H), 7.298 (t, J = 7.8 Hz, 1H), 7.203 (t, J = 7.2 Hz, 1H), 7.148 (d, J = 7.2 Hz, 1H), 7.145 (d, J = 7.2 Hz, 1H), 7.119 (d, J = 7.2 Hz, 1H), 1.995 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.871 MHz) δ: 139.654, 138.983, 136.115, 133.454, 130.691, 129.540, 128.452, 127.641, 127.163, 126.984, 20.227.

Bromopentamethylbenzene (5) white solid. m.p.: 161-163 ^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.442 (s, 6H), 2.267 (s, 6H), 2.202 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.868 MHz) δ 133.789, 133.757, 133.297, 126.669, 21.436, 17.697, 16.844.



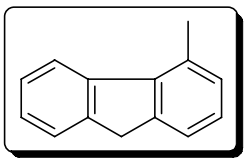
3.4.2 General Procedure for Palladium-Catalyzed Cyclization of 2-bromo-2′-methylbiaryls

In a glove box with nitrogen atmosphere, to a mixture of 2-Bromo-2′-methylbiphenyl or 2-bromo-2′,4′,6′-trimethylbiphenyl (0.25 mmol), and 1 ml THF (in a schlenk flask) was added $Pd_2(dba)_3$ (3.4 mg, 0.0037mmol) with *t*-Bu_3P (3.0 mg, 0.015 mmol). After stirred for 5-10 minutes, Grignard reagent (0.65 ml, 1M in THF, 0.65 mmol) was added. The mixture was allowed to stir under N_2-atmosphere. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. The reaction mixtures were analyzed by NMR and/or GC/MS. Flash chromatograph on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) gave the cyclization products.

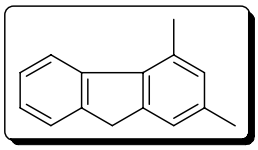
3.4.3 General Procedure for Palladium-Catalyzed Tandem Reactions of 1,2-Dihalobenzenes with Bulky Grignard Reagents

In a glove box with N_2-atmosphere, to a mixture of dihalobenzenes (1.0 mmol), and 1.0 ml THF (in a Schlenk flask) was added $Pd_2(dba)_3$ (13.7 mg, 0.015mmol) with *t*-Bu_3P (12.1 mg, 0.06 mmol). After stirred for 5-10 minutes, Grignard reagent (2.5 ml, 1M in THF, 2.5 mmol) was added. The mixture was allowed to stir under N_2-atmosphere for 20 h. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatograph on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) gave the reaction products.

4-Methylfluorene (6) white solid. m.p.: 69-71°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.907 (d, *J* = 7.2 Hz, 1H), 7.534 (d, *J* = 6.6 Hz, 1H), 7.368 (t, *J* = 6.6 Hz, 2H), 7.284 (t, *J* = 6.6 Hz, 1H), 7.187 (t, *J* = 6.6 Hz, 1H), 7.135 (t, *J* = 6.6 Hz, 1H), 3.872 (s, 2H), 2.709 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 143.617, 143.529, 142.630, 139.724, 132.990, 128.914, 126.559, 126.348, 125.962, 124.821, 123.066, 122.388, 37.018, 21.062.

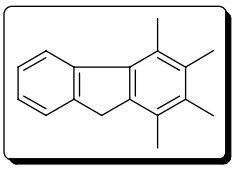


2,4-Dimethylfluorene (7) white solid. m.p.: 66.5-67.5°C. ^{1}H NMR



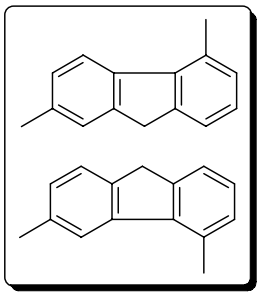
($CDCl_3$, 600 MHz) δ 7.873 (d, *J* = 7.2 Hz, 1H), 7.530 (d, *J* = 7.2 Hz, 1H), 7.363 (t, *J* = 7.8 Hz, 1H), 7.266 (t, *J* = 7.8 Hz, 1H), 7.209 (s, 1H), 6.969 (s, 1H), 3.859 (s, 2H), 2.686 (s, 3H), 2.392 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 143.900, 143.489, 142.713, 137.142, 136.212, 132.655, 129.896, 126.519, 125.525, 124.781, 123.103, 122.615, 36.887, 21.310, 20.882.

1,2,3,4-tetramethylfluorene (8) white solid. m.p.: 121.5-122.5°C. ^{1}H



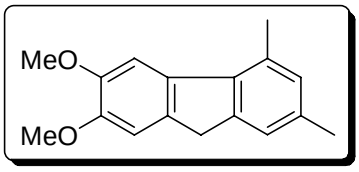
NMR ($CDCl_3$, 600 MHz) δ 7.969 (d, *J* = 8.4 Hz, 1H), 7.526 (d, *J* = 7.8 Hz, 1H), 7.342 (t, *J* = 7.8 Hz, 1H), 7.246 (t, *J* = 8.4 Hz, 1H), 3.760 (s, 2H), 2.663 (s, 3H), 2.318 (s, 6H), 2.287 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 143.712, 143.592, 139.927, 136.989, 133.700, 133.457, 129.438, 129.108, 126.348, 125.246, 124.705, 123.115, 36.593, 16.801, 16.541, 16.481, 16.200.

4,7-Dimethylfluorene & 4, 6-dimethylfluorene (9) light yellow solid. m.p.: 43-62°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.788 (d, *J* = 8.4 Hz, 1H), 7.728 (s, 2H), 7.428 (d, *J* = 7.8 Hz, 1H), 7.372 (d, *J* = 7.8 Hz, 1H), 7.366 (s, 2H), 7.185 (t, *J* = 7.8 Hz, 2H), 7.122 (t, *J* = 7.2 Hz, 2H), 3.845 (s, 4H), 2.726



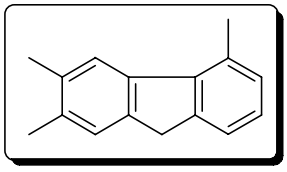
(s, 4H), 2.699 (s, 2H), 2.466 (s, 4H), 2.425(s, 2H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 144.009, 143.921, 143.356, 142.864, 140.709, 140.000, 139.842, 139.778, 136.033, 135.794, 132.943, 132.568, 128.874, 128.815, 127.393, 126.866, 126.199, 125.919, 125.620, 124.465, 123.812, 122.766, 122.401, 122.338, 36.883, 36.662, 21.798, 21.433, 21.145, 20.984.

2,3-Dimethoxy-5,7-dimethylfluorene (10) white solid. m. p.: 167-169°C.



^{1}H NMR ($CDCl_3$, 600 MHz) δ: 7.422(s, 1H), 7.172(s, 1H), 7.094 (s, 1H), 6.940 (s, 1H), 3.978 (s, 3H), 3.939(s, 3H), 3.779(s, 2H), 2.673(s, 3H), 2.378 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.871 MHz) δ: 148.080, 147.784, 143.955, 137.387, 136.113, 135.294, 134.991, 131.070, 129.758, 122.994, 108.214, 106.439, 56.206, 56.009, 36.686, 21.208, 20.571.

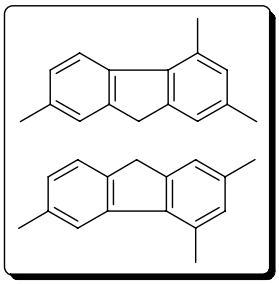
2,3,5-Trimethylfluorene (11) white solid. m. p.: 86.5- 87.5°C. ^{1}H NMR



($CDCl_3$, 600 MHz) δ: 7.682 (s, 1H), 7.355 (d, J = 7.2 Hz, 1H), 7.320 (s, 1H), 7.158 (t, J = 7.2 Hz, 1H), 7.114 (d, J = 7.2 Hz, 1H), 3.821 (s, 2H), 2.714 (s, 3H), 2.366

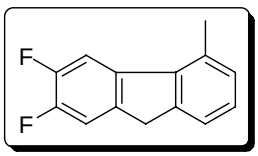
(s, 3H), 2.329 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.871 MHz) δ: 143.622, 141.351, 140.568, 139.975, 134.604, 134.467, 132.508, 128.758, 125.982, 125.771, 124.219, 122.313, 36.627, 21.057, 20.313, 19.983.

2,4,7-Trimethylfluorene and 2, 4, 6-trimethylfluorene (12) off-white



solid. m.p.: 43-57°C. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.740 (d, *J* = 7.8 Hz, 1H), 7.680 (s, 1H), 7.403 (d, *J* = 7.8 Hz, 1H), 7.341 (s, 1H), 7.188 (s, 1H), 7.180 (s, 1H), 7.160 (s, 1H), 7.083 (d, *J* = 7.2 Hz, 1H), 6.951 (s, *J* = 7.2 Hz, 2H), 3.808 (s, 4H), 2.686 (s, 4H), 2.659 (s, 2H), 2.457 (s, 4H), 2.418(s, 2H), 2.382 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 144.331, 143.744, 143.674, 142.874, 140.525, 140.002, 137.183, 137.123, 136.000, 135.933, 135.691, 135.259, 132.563, 132.194, 129.800, 129.727, 127.280, 126.374, 125.559, 124.387, 123.355, 123.088, 123.028, 122.274, 36.703, 36.475, 21.783, 21.397, 21.285, 21.274, 20.965, 20.800.

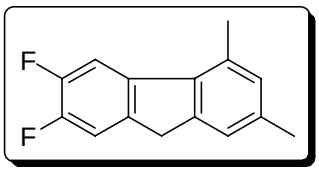
2,3-Difluoro-5-methyl-fluorene (13) white solid. m.p.: 51.5-52.5°C. ^1H



NMR ($CDCl_3$, 600 MHz) δ 7.665 (d, *J* = 7.2 Hz, 1H), 7.646 (d, *J* = 7.8 Hz, 1H), 7.372 (d, *J* = 7.2 Hz, 1H), 7.313 (t, *J* = 8.4 Hz, 1H), 7.211 (t, *J* = 7.8 Hz, 1H), 7.146 (d, *J* = 7.8 Hz, 1H), 3.833 (s, 2H), 2.661 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 150.528,

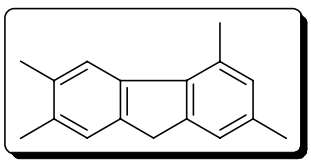
150.454, 149.997, 148.927, 148.853, 148.365, 148.281, 143.917, 139.395, 138.732, 138.444, 132.666, 129.204, 126.743, 122.481, 113.537, 113.417, 111.602, 111.472, 36.714, 20.632.

2,3-Difluoro-5,7-dimethyl-fluorene (14) white solid. m.p.: 81-83°C. ^{1}H



NMR ($CDCl_3$, 600 MHz) δ 7.582 (t, *J* = 8.4 Hz, 1H), 7.267 (t, *J* = 8.4 Hz, 1H), 7.168 (s, 1H), 6.955 (s, 1H), 3.763 (s, 2H), 2.601 (s, 3H), 2.377 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 150.491, 150.403, 149.680, 149.589, 148.880, 148.792, 148.048, 147.960, 144.246, 144.232, 139.211, 139.194, 139.169, 139.148, 138.801, 138.776, 138.755, 136.694, 135.810, 135.476, 132.271, 130.116, 128.157, 123.154, 113.451, 113.331, 111.074, 110.944, 36.527, 36.513, 21.273, 20.434.

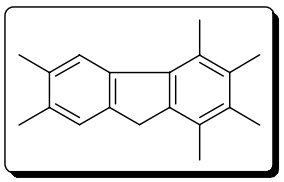
2,3,5,7-tetramethylfluorene (15) white solid. m.p.: 104-105°C. ^{1}H



NMR ($CDCl_3$, 600 MHz) δ 7.638 (s, 1H), 7.300 (s, 1H), 7.173 (s, 1H), 6.941 (s, 1H), 3.786 (s, 2H), 2.674 (s, 3H), 2.377 (s, 3H), 2.361 (s, 3H), 2.324 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 143.985, 141.204, 140.618, 137.350, 135.570, 134.520, 133.959,

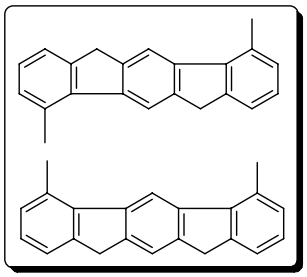
132.172, 129.707, 125.965, 123.813, 123.055, 36.487, 21.283, 20.890, 20.307, 19.959.

1,2,3,4,6,7-hexamethylfluorene (16) white solid. m.p.: 166-169°C. ^{1}H



NMR ($CDCl_3$, 600 MHz) δ 7.748 (s, 1H), 7.306 (s, 1H), 3.714 (s, 2H), 2.667 (s, 3H), 2.363 (s, 3H), 2.323 (s, 9H), 2.290 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 141.493, 141.434, 140.005, 137.228, 134.251, 133.644, 133.528, 132.847, 129.389, 128.690, 125.885, 124.348, 36.186, 20.406, 19.908, 16.825, 16.555, 16.436, 16.201.

4,6-Dimethyl-10,12-dihydroindeno[1,2b]fluorine & 4,10-dimethyl-6,12-



dihydroindeno[1,2b]fluorine (17) orange solid. m. p.: 193-210°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.498 (s, 1H), 8.073 (s, 2H), 7.705 (s, 1H), 7.408 (d, J=7.8 Hz, 4H), 7.208 (t, *J* = 7.2 Hz, 4H), 7.165 (t, *J* = 7.2 Hz, 4H), 3.973 (s, 4H), 3.937 (s, 4H), 2.823 (s, 6H), 2.782 (s, 6H). ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 144.129, 143.813, 142.588, 142.135, 141.489, 140.969, 140.046, 139.877, 132.797, 132.589, 129.075, 128.995, 126.088,

126.042, 122.489, 122.433, 121.380, 119.491, 117.719, 37.115, 36.845, 21.234, 21.121.

3.4.4 Exchanging and Trapping Experiments

(1) In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-chlorobenzene or 1,2-dibromobenzene (0.25 mmol), 1.0 ml THF was added 2-mesitylmagnesium bromide (0.65 ml, 1M in THF, 0.65 mmol). The mixture was allowed to stir at room temperature for 18 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR showed no reaction was observed.

(2) In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-iodobenzene (0.25 mmol), furan (0.5 mmol) and 1.0 ml THF was added *p*-tolylmagnesium bromide (0.65 ml, 1M in THF, 0.65 mmol) and 1,2,4,5-Tetramethybenzene (as internal standard). The mixture was allowed to stir under room temperature for 18 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. The Diels-Alder reaction product was clearly observed from ^{1}H NMR analysis (> 90%

yield), suggesting the reaction proceeded via benzyne intermediate and the benzyne intermediate could be trapped by furan.

(3) In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-chlorobenzene or 1,2-dibromobenzene (0.25 mmol), furan (0.5 mmol) and 1.0 ml THF was added 2-mesitylmagnesium bromide (0.65 ml, 1M in THF, 0.65 mmol) was added. The mixture was allowed to stir under room temperature for 18 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR showed there is no reaction for 1-bromo-2-chlorobenzene and 1,2-dibromobenzene.

(4) In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-chlorobenzene (0.25 mmol), furan (0.5 mmol) and 1.0 ml THF was added 2-mesitylmagnesium bromide (0.65 ml, 1M in THF, 0.65 mmol). The mixture was allowed to stir under 60^{o}C for 18 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. No reaction was observed.

(5) In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-iodobenzene (0.25 mmol), 1.0 ml THF were added 2-mesitylmagnesium bromide (0.65 ml, 1M in THF, 0.65 mmol) and1,2,4,5-Tetramethybenzene

(as internal standard). The mixture was allowed to stir under room temperature for 18 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR analysis showed that the formation of Diels-Alder reaction product, suggesting benzyne was formed in the reaction of 1-bromo-2-iodobenzene with 2-mesitylmagnesium bromide.

(6) In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-iodobenzene (0.25 mmol), furan (0.5 mmol) and 1.0 ml THF was added $Pd_2(dba)_3$ (7.8mg, 0.0075 mmol). After stirred for 5-10 minutes, 2-mesitylmagnesium bromide (0.65 ml, 1M in THF, 0.65 mmol) was added. The mixture was allowed to stir under room temperature for 18 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR showed that no Diels-Alder reaction product was formed; but annulative tandem reaction product was clearly observed.

3.4.5 General Procedure for Reactions of Dihalobenzenes with Limited Amount of 2-Mesitylmagnesium Bromide

In a glove box with N_2-atmosphere, to a mixture of aryl dihalide (1.0 mmol) and 2 ml THF (in a Schlenk flask) was added $Pd_2(dba)_3$ (13.7 mg, 0.015mmol) with *t*-Bu_3P (12.1 mg, 0.06 mmol). After stirred for 5-10 minutes, 2-Mesitylmagnesium bromide (0.5 ml, 1M in THF, 0.5 mmol) was added. The mixture was allowed to stir under N_2-atmosphere for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. The reaction mixtures were analyzed by GC/MS, from which the ratio of cyclization product to the mono-cross coupling product was obtained.

Notes and References:

1) This chapter is mainly based on the paper published:
Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289.

2) Recent reviews for C-H activation: (a) Kakiuchi, F.; Chatani,m N. *Advan. Synth. & Catal*. **2003**, 345, 1077-1101. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, 102, 1731-1770. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, 34, 633-639.

3) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001-1020. (b) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967-1983. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551-564. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195-206. (e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136; and references cited therein.

4) (a) de Meijere, A.; von Zezschwitz, P.; Brase, S. *Acc. Chem. Res.* **2005**, *38*, 413-422. (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731-1770. (c) Ikeda, S.-i. *Acc. Chem. Res.* **2000**, *33*, 511-519. (d) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467-473. (e) Heumann, A.; Reglier, M. *Tetrahedron* **1996**, *52*, 9289-9346. (f) Malacria, M. *Chem. Rev.* **1996**, *96*, 289-306; and references cited therein.

5) (a) Rathore R.; Chebny, V. J. Abdelwahed, S. H. *J. Am. Chem. Soc.* **2005**, 127, 8012-8013. (b) Marsitzky, D.; Vestberg, R.; Blainey P.; Tang, B.T.; Hawker, C. J.; Carter, K. R.; *J. Am. Chem. Soc.* **2001**, 123, 6965 - 6972.

6) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, 121, 9550-9561.

7) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207-10.

8) Miller, A.R.; Curtin D.Y. *J. Am. Chem. Soc.* **1976**, 98, 1860-1865.

9) Hawkins, R. T.; Lennarz, W. J.; Snyder, H. R. *J. Am. Chem. Soc.* **1960**, 82, 3053-305.

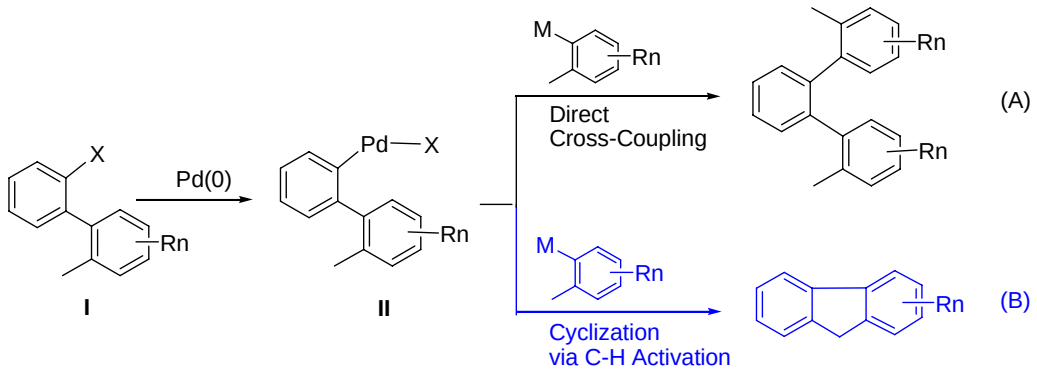
CHAPTER FOUR

$Pd(OAc)_2$-Catalyzed Domino Reactions of 1,2-Dihaloarenes and 2-Haloaryl Arenesulfonates with Grignard Reagents: Efficient Synthesis of Substituted Fluorenes [1]

4.1 Introduction

Fluorenes are the core structure of biologically active molecules, sensors and light-emitting materials.[2] On Chapter 3 we have reported Pd(0)/*t*-Bu_3P-catalyzed reaction of 2-bromobiphenyl with hindered Grignard reagents to form substituted fluorenes,[3] a cyclization process that combines the control of the transmetalation step with sp^3 C-H activation (Scheme 4.1).[4-6]

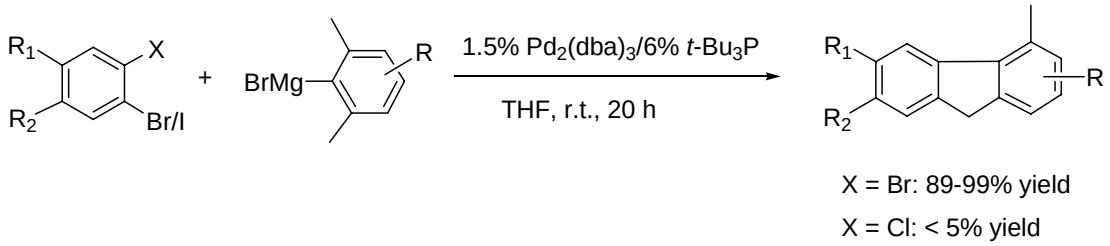
Scheme 4.1 Controlling Competition Between Direct Cross-Coupling and Cyclization via sp^3 C-H Bond Activation



We have further incorporated a cross-coupling step into the latter type of reaction and developed a new type of tandem reaction that combines the

cross-coupling strategy and cyclization via sp^3 C-H activation strategy (Scheme 4.2).[7,8] With Pd(0)/*t*-Bu_3P as catalyst, substituted fluorenes could be easily prepared in excellent yields from 1,2-dibromobenzenes and 1-bromo-2-iodobenzene.

Scheme 4.2 Pd(0)/*t*-Bu_3P-Catalyzed Tandem Reactions of 1,2-Dihalobenzenes with Hindered Grignard Reagents



Although Pd(0)/*t*-Bu_3P has been demonstrated to be a highly efficient catalyst system for the tandem reaction of 1,2-dibromobenzenes and 1-bromo-2-iodobenzene to form substituted fluorenes, we reasoned that further improvement of this new substituted fluorene making process could be possible. For example, the air-sensitivity of *t*-Bu_3P makes the handling of the catalyst very stringent. In addition and more importantly, Pd(0)/*t*-Bu_3P catalyst system was ineffective for substrates other than 1,2-dibromobenzenes and 1-bromo-2-iodobenzene, e.g., 1-chloro-2-halobenzenes. To expand the substrate scope and explore more practical catalyst systems, we envisioned a pathway other than the cross-coupling-

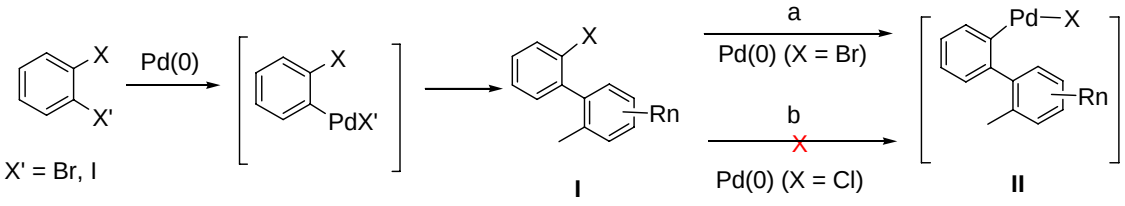
cyclization (via sp^3 C-H activation) strategy, namely palladium associated aryne forming pathway. We investigated factors that could influence the reaction to proceed via the palladium associated aryne forming pathway including the ligand effect and leaving group effect. We also investigated the substrates other than 1,2-dibromobenzenes and 1-iodo-2-bromobenzene, i.e., 1-chloro-2-halobenzenes, 1-bromo-2-fluorobezene and 2-haloaryl tosylates and benzenesulfonates for the reaction.

4.2 Palladium Associated Arynes as Intermediates for the Reaction of 1,2-Dihalobenzenes with Grignard reagents: ligand effect and leaving group effect

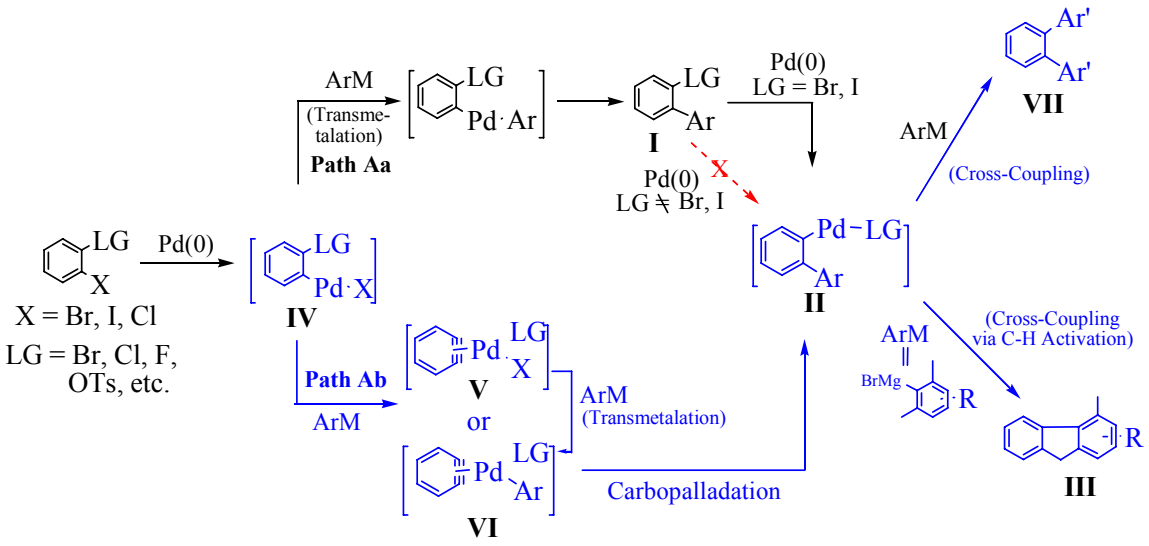
Our mechanistic study in Pd(0)/*t*-Bu_3P catalyst system suggested that the key obstacle to employ 1-chloro-2-halobenzenes as substrates for the reaction is the reluctance of the C-Cl bond in (**I)** to undergo oxidative addition with Pd(0) catalyst (Scheme 4.3). We thus envisaged that if no oxidative addition of C-Cl bond with Pd(0) was involved in the formation of ArPd(II)Cl (**II**), these substrates could then be suitable substrates for the new type of annulative tandem reactions. Recognizing that halo groups are known to function as leaving groups, we reasoned that this could be possible: as depicted in Scheme 4.4, *ortho*-leaving group (LG) bearing *o*-

aryl(LG)palladium(II) halides (**IV**), in addition to undergoing transmetalation with organometallic reagents to form (**I**) (Scheme 4.4, Path Aa), could undergo β-LG-elimination to form palladium associated arynes (**V**) (Scheme 4.4, Path Ab). The generated Pd(II)(LG)X associated arynes could then undergo transmatalation followed by carbopalladation to form intermediate (**II**), which could further undergo other transformations (Scheme 4.4, Path Ab). Therefore, through palladium associated aryne intermediates, intermediate (**II**) could be formed without undergoing the oxidative addition of C-LG bond with Pd(0), thus making it possible to employ 1-chloro-2-halobenzenes as suitable substrates for the domino reaction.

Scheme 4.3 Pd(0)/*t*-Bu_3P-Catalyzed Tandem Reactions of 1,2-Dihalobenzenes with Bulky Grignard Reagents



Scheme 4.4 Outline for 1-Halo-2-(leaving group)benzenes for Domino Reactions via Palladium(II)(LG)X Associated Aryne Intermediates



Arynes are very reactive and have recently been demonstrated as useful substrates for palladium-catalyzed carbon-carbon bond forming reactions.[9-13] Careful examination of aryne chemistry showed that the aryne generation strategy in reported reactions, in which arynes were generated *in situ* from expensive *o*-trimethylsilylaryl triflates, often does not work well with the use of catalytic amount of palladium because short-lived arynes needed to search for inherently unstable palladium intermediates for reactions to occur. Consequently, large excess of *o*-trimethylsilylaryl triflates were often required to achieve good yields. The pathway to generate arynes depicted in Scheme 4.4 (Path Ab) could employ widely available *o*-halo(LG)benzenes including 1,2-dihaloarenes as substrates with the

assurance of every generated aryne associated with a palladium. More importantly, in this strategy, because the formation of (**II**) does not involve the oxidative addition of C-leaving group bond, e.g., C-Cl bond, with Pd(0) species, the overall reactivity of *o*-halo(LG)benzenes would be governed by the reactivity of C-halo bonds that undergo the initial oxidative addition with Pd(0) catalysts. Thus, substrates that bear leaving groups other than -Br and -I groups might also be suitable substrates for tandem/domino reactions. Therefore, exploration of this palladium associated aryne generation strategy could be fundamentally interesting and synthetically useful.

As depicted in Scheme 4.4, the direct transmetalation of *o*-aryl(LG)palladium(II) halides (**IV**) to form cross-coupling product (**I**) (Scheme 4.4, Path Aa) would compete with the formation of Pd(II)(LG)X associated benzynes (Path Ab). Therefore, factors that could influence the transmetalation and/or the β-leaving group elimination of *o*-aryl(LG)Pd(II) halides, e. g., the steric hindrance and nucleophilicity of organometallic reagents, LG leaving ability, ligand effect, basicity of the base and reaction temperature, etc., were expected to affect the generation of Palldium associated arynes. We reasoned that for a given type of *o*-aryl(LG)Pd(II) halides with the same LG and a given type of organometallic regents such as Grignard reagents at a certain reaction temperature, the influential factors

could be narrowed down to steric hindrance and ligand effect. Since increasing the steric hindrance of Grignard reagents has been established to slow down the transmetalation process, we thus began our study by examining the ligand influence. The reaction of 1-bromo-2-chlorobenzene with bulky 2-mesitylmagnesium bromide was employed as the model reaction. As the initial oxidative addition was believed to occur at the C-Br bond[14] and 2-chloro-2′,4′,6′-trimethylbiphenyl (**Ia,** LG = Cl) was found to be inert under $Pd(OAc)_2$/Grignard reagent condition (Scheme 4.5), we expected that the domino reaction product 2,4-dimethylfluorene would be expected if the reaction proceeded via benzyne intermediate (Path Ab). The reaction product would be 2-chloro-2′,4′,6′-trimethylbiphenyl if the reaction occurred via transmetalation followed by reductive elimination (Path Aa). We screened a number of ligands and palladium source and our results are listed in Table 4.1. We found that with monodentate PPh_3, PCy_3, *t*-Bu_3P, a *N*-heterocyclic carbene (NHC),[15] or bidentate DPPE, DPPB and BINAP as ligands, 2-chlorobiaryl was obtained as the major product (Table 4.1, entries 1-8), suggesting the reactions proceeded predominately through Path Aa. However, 2,4-dimethylfluorene was observed as the major product with $Pd_2(dba)_3$, $Pd(OAc)_2$ or $Pd(PhCN)_2Cl_2$ as catalysts (Table 4.1, entries 9-11),

implying that the reaction proceeded predominately through Path Ab and Pd-associated benzynes were involved.

Scheme 4.5 $Pd(OAc)_2$-Catalyzed Reactions of 2-Halo-2',4',6'-trimethylbiphenyls with 2-Mesitylmagnesium Bromide

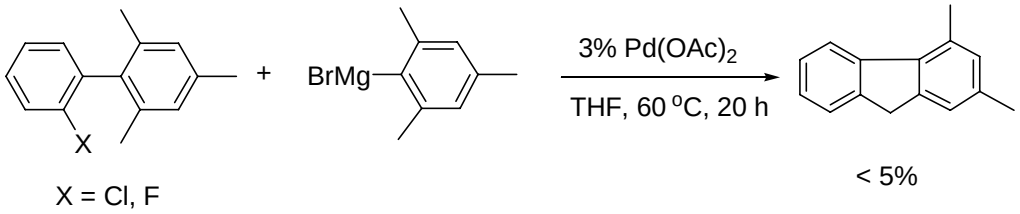
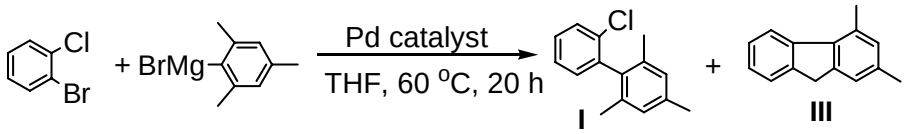
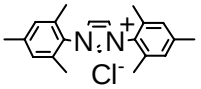


Table 4.1 Ligand Effect on Palladium-Catalyzed Reactions of 1-Bromo-2-chlorobenzene with Grignard Reagents [a]

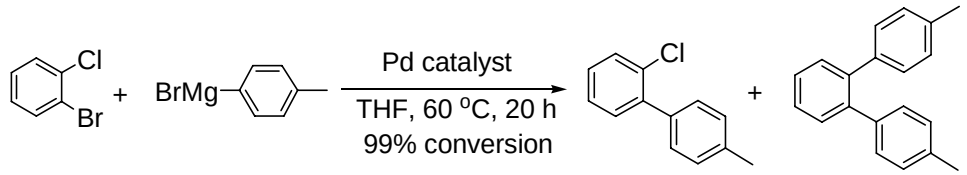


Entry	Catalyst	Conversion (%)	Ratio (%) [b] I	III
1	1.5% $Pd_2(dba)_3$ + 6% Ph_3P	99	69	31
2	1.5% $Pd_2(dba)_3$ + 6% Cy_3P	99	91	9
3	1.5% $Pd_2(dba)_3$ + 6% *t*-Bu_3P	99	90	10
4	3% $Pd(PPh_3)_4$	99	88	12
5	1.5% $Pd_2(dba)_3$ + 6% 	22	99	<1
6	1.5% $Pd_2(dba)_3$ + 3% DPPE	5	99	<1
7	1.5% $Pd_2(dba)_3$ + 3% DPPB	27	99	<1
8	1.5% $Pd_2(dba)_3$ + 3% BINAP	8	99	<1
9	1.5% $Pd_2(dba)_3$	99	<3	>97
10	3% $Pd(PhCN)_2Cl_2$	99	<3	>97
11	3% $Pd(OAc)_2$	99	<3	>97
12	None	0	-	-

a. Reaction conditions: 1-bromo-2-chlorobenzene (1.0 equiv.), Grignard reagent (2.5 equiv.), THF (2 ml). b. Ratio based on ^1H NMR.

The ligand effect on reaction pathways was further confirmed by the reaction results of 1-bromo-2-chlorobenzene with less sterically hindered *p*-tolylmagnesium bromide. We expected that 4,4′′-dimethyl-(1, 1′, 2′, 1′′)-terphenyl (**VII**) would be the product if the reaction occurs via palladium associated aryne pathway (Path Ab) and 2-chloro-4′-methylbiphenyl (**Ia**, LG = Cl) would be the product via transmetalation followed by reductive elimination (Path Aa) (Scheme 4.4). Our results showed that with *t*-Bu_3P as ligand, 4,4′′-dimethyl-(1, 1′, 2′, 1′′)-terphenyl and 2-chloro-4′-methyl-biphenyl were formed in a ratio of 7: 93 (based on ^1H NMR), suggesting Path Aa should be the major pathway. However, with only $Pd(OAc)_2$ as the catalyst, 4,4′′-dimethyl-(1, 1′, 2′, 1′′)-terphenyl was obtained as the major product (Scheme 4.6). These results further suggested that the absence of *t*-butylphosphine favored the reaction occur via palladium associated aryne intermediates. Comparing these results with the reaction result of 1-bromo-2-chlorobenzene with 2-mesitylmagnesium magnesium (Table 4.1, entry 11) further showed that increasing the steric hindrance of Grignard reagents would slow down the transmetalation process and favor the reaction to proceed via the aryne pathway.

Scheme 4.6 Pd(OAc)2-Catalyzed Reactions of 1-Bromo-2-chlorobenzene with p-Tolylmagnesium Bromide

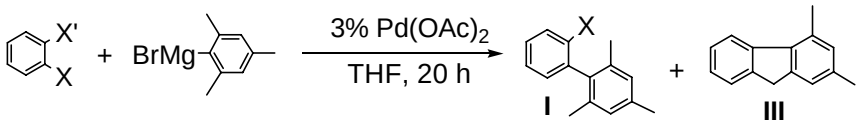


1.5% $Pd_2(dba)_3$ + 6% *t*-Bu_3P	93	:	7
3% $Pd(OAc)_2$	48	:	52

To gauge the leaving group effect on the reaction pathways, we chose 2-mesitylmagnesium bromide as the reagent and studied 1,2-dihalobenzenes with different leaving groups. We first examined 1-bromo-2-halobenzenes (halo = F, Cl, Br) as the substrates and found that the better the leaving group, the higher the ratio of **III** : **I**, suggesting benzyne intermediates formed easier with better leaving group. (Table 4.2, entries 1-4). With 1-fluoro-2-halobenzenes as substrates, as 2-fluoro-2′,4′,6′-trimethylbiphenyl (**Ib**) was found to be also inert under $Pd(OAc)_2$/Grignard reagent condition (scheme 4.5),[16] formation of 2,4-dimethylfluorene would be expected if the reaction proceeded via benzyne intermediate (Path Ab). With a bromo group as the leaving group, the reaction occurred smoothly at room temperature with exclusive formation of 2,4-dimethylfluorene (for the establishment of palladium associated benzyne pathway, see the section that describes the reactions of 1,2-dibromobenzenes with hindered Grignard reagents (vide infra)). For comparison purpose, room temperature reaction of 1-bromo-2-

chlorobenzene with 2-mesitylmagnesium bromide was also tested, a conversion of 61% was observed. As the oxidative addition of C-Br bond with Pd(0) for 1-bromo-2-chlorobenzene is expected to occur at the same rate as or higher than that of 1,2-dibromobenzene because of the more electron-withdrawing nature of -Cl group than -Br group, the lower conversion for 1-bromo-2-chlorobenzene suggested that the benzyne formation occurred slower with a -Cl leaving group than that with a -Br leaving group.

Table 4.2. Pd(OAc)2-Catalyzed Reactions of 1, 2-Dihalobenzene with 2-Mesitylmagnesium Bromide [a]



I **III**

Entry	X	X'	Temperature	Conversion (%)	**I : III** [b]
1	F	Br	60 °C	84	17 : 83
2	Cl	Br	60 °C	99	<3 : > 97
3	Cl	Br	rt	73	<3 : > 97
4	Br	Br	rt	99	0 : 100
5	F	Cl	60 °C	72	63 : 37
6	Cl	Cl	60 °C	24	3 : 97

a. Reaction conditions: 1,2-dihalobenzene (1.0 equiv.), Grignard reagent (2.5 equiv.), THF (2 ml). b. Ratio based on ^{1}H NMR.

We have also carried out the reactions of 1-chloro-2-fluorobenzene and 1,2-dichlorobenzene with 2-mesitylmagnesium bromide. Our results showed that higher ratio of **III** : **I** was observed for 1,2-dichlorobenzene than

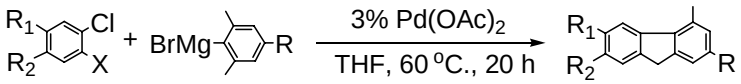
that for 1-chloro-2-fluorobenzene (Table 4.2, entries 5 and 6), and thus further confirmed that benzyne intermediates formed easier with better leaving groups. The higher conversion for 1-chloro-2-fluorobenzene than that of 1,2-dichlorobenzene might be explained by thinking of the C-Cl bond in 1-chloro-2-fluorobenzene being more activated than that in 1,2-dichlorobenzene because a -F group is more electron-withdrawing than a -Cl group.

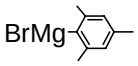
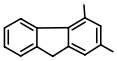
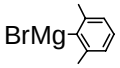
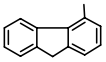
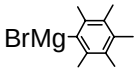
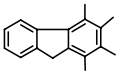
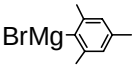
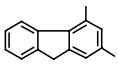
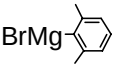
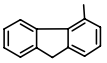
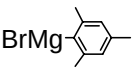
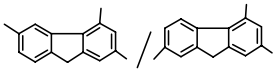
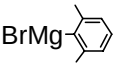
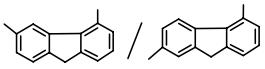
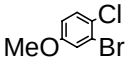
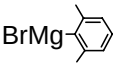
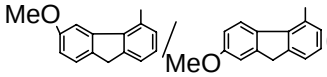
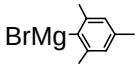
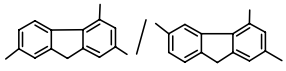
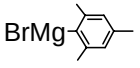
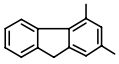
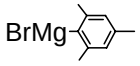
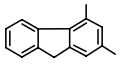
4.3 $Pd(OAc)_2$-Catalyzed Annulative Reactions of 1-Chloro-2-haloarenes and 1-Bromo-2-fluorobenzene with Hindered Grignard Reagents via Palladium Associated Arynes

After establishing $Pd(OAc)_2$, $Pd_2(dba)_3$ and $Pd(PhCN)_2Cl_2$ as excellent catalysts for 1-bromo-2-chlorobenzene to undergo annualtive reaction with 2-mesitylmagnesium bromide, we next examined other 1-chloro-2-halobenzenes and hindered Grignard reagents. Our results are listed in Table 4.3. We found that all tested 1-chloro-2-halobenzenes including 1,2-dichlorobenzene gave good to excellent yields of substituted fluorene products. For 1,2-dichlorobenzene, higher reaction temperature and longer reaction time is needed to achieve good yield, likely because the initial oxidative addition of C-Cl bond with Pd(0) is more difficulty than C-Br

bonds. We have also employed 1-bromo-2-fluorobenzene as substrate and a good yield of 2,4-dimethylfluorene was obtained (Table 4.3, entry 11).

Table 4.3 Pd(OAc)2-Catalyzed Cross-couplings of 1-Chloro-2-halobenzenes and 1-Bromo-2-fluorobenzene with Hindered Grignard Reagents [a]

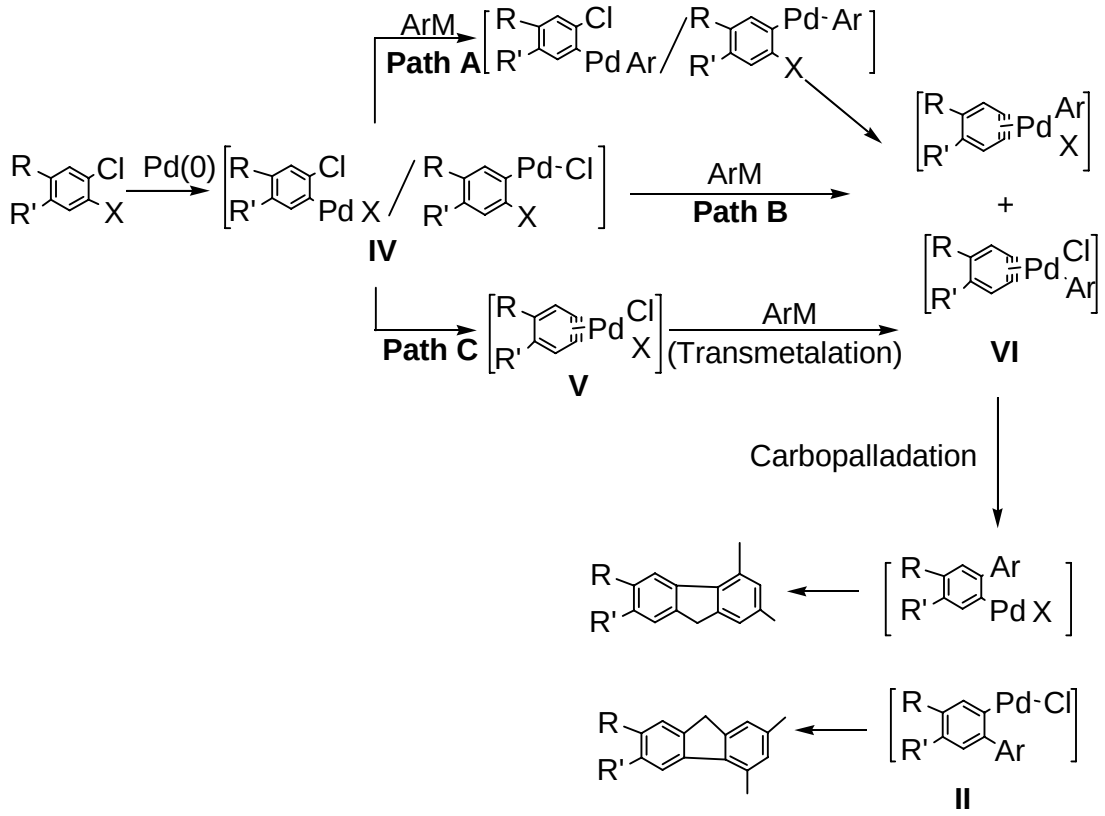


Entry	Dihalide	Grignard Reagents	Product	Yield(%)[b,c]
1				95
2				86
3				89
4				93
5				92
6			 (77:23) [e]	84 [d]
7			 (80:20) [e]	89 [d]
8			 (78:22) [e]	86
9			 (85:15) [e]	82
10				61[f]
11				59 [g]

a. Reaction conditions (not optimized): 1,2-dihalobenzene (1.0 equiv), Grignard reagent (2.5 equiv), $Pd(OAc)_2$ (3%), THF (2 mL). b. Isolated yields. c. 2-chlorobiaryls were observed in less than 5% yields. d. 1.5 %$Pd_2(dba)_3$ as catalyst. e. Ratio based on ^1H NMR. f. Refluxing in THF, 40 h, 16% 2-chloro-2',4',6'-trimethylbiphenyl was observed. g. 17% 2-fluoro-2',4',6'-trimethylbiphenyl was observed.

The palladium associated benzyne intermediates could be formed via several possible pathways, e.g., transmetalation followed by benzyne formation (Path A), transmetallation and benzyne formation occurred simultaneously (Path B), or benzyne formation first followed by transmetallation (Path C) (Scheme 4.7).

Scheme 4.7 Possible Pathways for the Formation of Palladium(II)ClX Associated Aryne Intermediates



We reasoned that these pathways could be differentiated by using unsymmetrical 1-halo-2-chlorobenzenes as substrates because these

pathways would give different ratio of isomeric substituted fluorenes. Both Path A and B would give a mixture of fluorene products in a ratio related to oxidative addition rate difference between C-X bond and C-Cl bond. The third pathway, Path C, is expected to give the ratio of products related to the transmetallation rates between Pd-Cl and Pd-X. Previous study on the reaction of 1-bromo-4-chlorobenzene with phenylboronic acid showed that the oxidative addition of Pd(0) occurred almost exclusively at C-Br bond (≥ 97%). Path A or B would yield the two isomeric fluorenes in a ratio of 97 : 3 or higher for unsymmetrical 1-bromo-2-chlorobenzenes. Our results with 3-bromo-4-chlorotoluene and 3-bromo-4-chloroanisole as substrates showed that the two isomeric fluorenes were formed in about 4 : 1 ratio (Table 4.3, entries 6-8), suggesting that the benzyne intermediates formed first followed by transmetalation. Since C-I bond has also been established to have higher oxidative addition rate than C-Br bond, *o*-chloroiodobenzenes would yield two isomeric fluorenes in a ratio close to 100 : 0 if the reaction proceeded via Path A or B. We thus tested 3-chloro-4-iodotoluene as the substrate and found that the two isomeric fluorenes were formed in about 85 : 15. This observation was consistent with that the palladium associated benzyne intermediates were formed via Path C. Comparison of results of 3-bromo-4-chlorotoluene with that of 3-chloro-4-iodotoluene indicated that the first C-C

bond formed mainly at the more reactive C-Br or C-I bond, suggesting that the formed benzyne species (**VI**) didn't undergo coordination flipping (dissociation followed by recoordination in a reversed way). Otherwise, substituted fluorenes with the same ratio would be observed for 3-bromo-4-chlorotoluene and 3-chloro-4-iodotoluene.

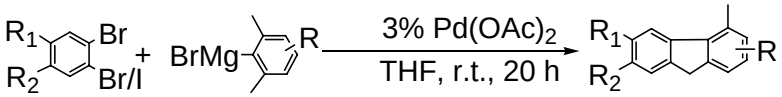
The observation of the formation of two isomeric fluorenes in a similar ratio (4~5 : 1) for 3-bromo-4-chlorotoluene, 3-bromo-4-chloroanisole and 3-chloro-4-iodotoluene (Table 4.3, entries 6-9) suggested that the transmetalation rates for Pd-Br and Pd-I bonds with hindered Grignard reagents were comparable to each other.

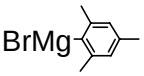
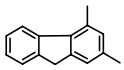
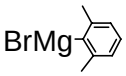
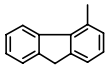
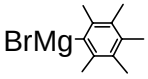
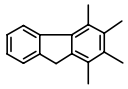
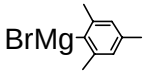
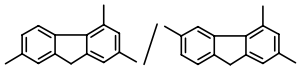
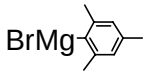
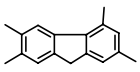
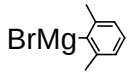
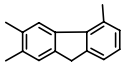
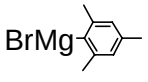
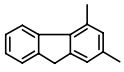
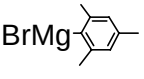
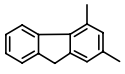
4.4 $Pd(OAc)_2$-Catalyzed Annulative Reactions of 1,2-Dibromoarenes and 1-Bromo-2-iodobenzene with Hindered Grignard Reagents

Our study on the leaving group ability effect suggested that 1,2-dibromoarenes should also be excellent substrates for the annulative reaction. We have thus also employed 1,2-dibromoarenes as substrates for the reaction and our results are listed in Table 4.4. We found with $Pd(OAc)_2$ as catalyst, the reaction could proceed at room temperature for 1,2-dibromobenzene and 3,4-dibromotoluene, and excellent yields of substituted fluorenes were obtained. Unsymmetrical 3,4-dibromotoluene gave two

isomeric fluorenenes in 42: 58 ratio, suggesting that the reactivity of two C-Br bonds is close to each other. For 1,2-dibromo-4,5-dimethylbenzene, heating to 60 ^{o}C was necessary to achieve high yields, likely because of slower initial oxidative addition of C-Br with Pd(0) species. We have also tested 1-bromo-2-iodobenzene as substrate and found it was also an excellent one for the reaction. Our study showed that $Pd(OAc)_2$ was a highly efficient, operationally convenient catalyst for this reaction.

Table 4.4 Pd-Catalyzed Cross-Couplings of 1,2-Dibromobenzenes and 1-Bromo-2-iodobenzene with Hindered Grignard Reagents [a]



Entry	Dihalides	Grigsnard Reagent	Products	Yield(%)[b]
1				99
2				99
3				92
4				99 (42/58)[c]
5				97[d]
6				94[d]
7				99
8				99

a. Reaction conditions (not optimized): 1,2-dihalobenzene (1.0 equiv.), Grignard reagent (2.5 equiv.), 3% Pd catalyst, THF (2 ml), room temperature. b. Isolated Yields. c. ratio based on ^{1}H NMR. d. Reaction temperature: 60 ^{o}C.

To establish that the reaction did not proceed via cross-coupling followed by C-H activation pathway, we adopted the same strategy we used for Pd(0)/*t*-Bu_3P catalyst system: to detect the existence of the intermediate (**I**) by interrupting the reactions before their completion by using limited amount of Grignard reagent. 2-Bromo-2',4',6'-trimethylbiphenyl (**I**) was found to be inert under the reaction condition (Scheme 4.8) and have been established to be detectable by GC-MS. We thus reasoned it could be detected if it was formed in the reaction as the intermediates. We have thus carried out the reaction of 1,2-dibromobenzene with 0.5 equivalent of 2-mesitylmagnesium bromide. Our result showed that no (**I**) was observed with $Pd(OAc)_2$ as catalyst (Table 4.5, entry 1). In contrary, 7% of (**I**) was observed with Pd(0)/*t*-Bu_3P as catalyst (Table 4.5, entry 2). The reaction of 3,4-dibromotoluene with 0.5 equivalent of 2-mesitylmagnesium bromide gave similar results: (**I**) was not detected with $Pd(OAc)_2$ as catalysts, and 12% (**I**) observed with Pd(0)/*t*-Bu_3P as catalyst (Table 4.5, entries 3, 4). In combination with our results that no reaction was observed when mixing (**I**) with 2-mesitylmagnesium bromide in the presence of $Pd(OAc)_2$ (Scheme 4.8), The absence of (**I**) strongly suggest that the pathway for the reaction of 1,2-dibromobenzenes as well as 1-bromo-2-iodobenzene with bulky

Grignard reagents should be benzyne formation pathway, rather that not the cross-coupling followed by C-H activation pathway.

Scheme 4.8 Pd-Catalyzed Reactions of 2-Bromo-2',4',6'-trimethylbiphenyls with 2-Mesitylmagnesium Bromide

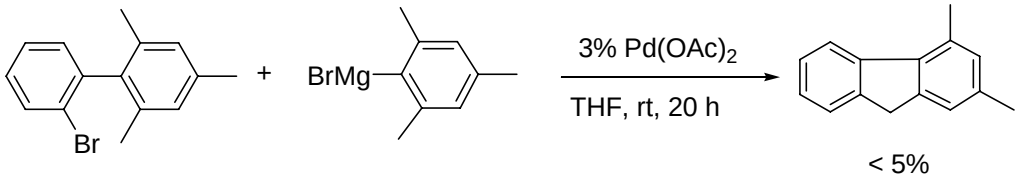
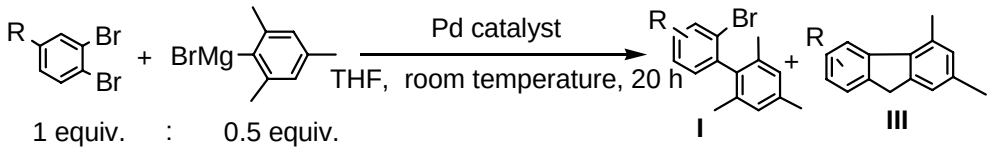


Table 4.5 Pd-Catalyzed Reactions of 1,2-Dihalobenzenes with Limited Amount of 2-Mesitylmagnesium Bromide [a]

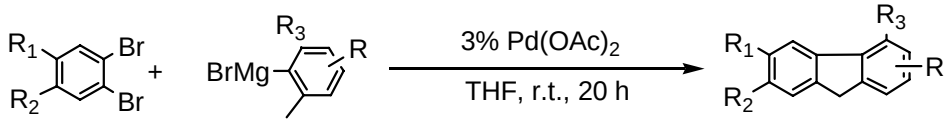


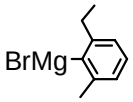
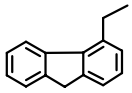
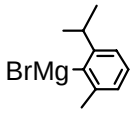
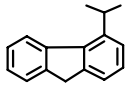
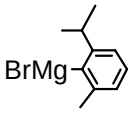
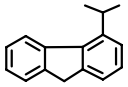
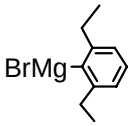
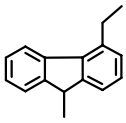
Entry	X	R	Pd Catalyst	Conversion(%)	Ratio I	Ratio III
1	Br	H	3 % $Pd(OAc)_2$	46	0	100%
2	Br	H	1.5% $Pd_2(dba)_3$/*t*-Bu_3P	48	7%	93%
3	Br	CH_3	3 % $Pd(OAc)_2$	49	0	100%
4	Br	CH_3	1.5% $Pd_2(dba)_3$/*t*-Bu_3P	45	12%	88%

a. Reaction conditions: 12-dibromobenzene (1.0 equiv.), Grignard reagent (0.5 equiv.), 3% Pd catalyst, THF (2 ml), r.t., 20 h. Ratios of **I** to **III** were based on GC-MS data.

To understand whether other types of carbon-hydrogen bonds (nonbenzylic C-(1^o)H bonds, benzylic C-(2^o)H bonds, and benzylic C-(3^o)H bonds) could also be activated under our condition, we have tested 2-ethyl-6-methylphenylmagnesium bromide and 2-isopropyl-6-methylphenyl-

Table 4.6 Pd-Catalyzed Cross-couplings of 1,2-Dibromobenzene with Hindered Grignard Reagents [a]



Entry	Dihalides	Grignard Reagents	Products	Yield(%)[b]
1				68
2				29
3				72 [c]
4				<1

a. Reaction conditions (not optimized): dihalide (1.0 equiv.), Grignard reagent (2.5 equiv.), 3% $Pd(OAc)_2$, THF (2 ml), room temperature. b. Isolated Yields. c. Reaction temperature: 60 ^{o}C.

magnesium bromide for the domino reaction. We found that the reaction with sterically more hindered Grignard reagents underwent slower (Table 4.4, entry 2; Table 4.6, entries 1-2), likely because of the slower transmetalation rate, and such a slower reaction could be improved by raising the reaction temperature (Table 4.6, entries 2 and 3). We also found that the sp^3 C-H activation occurred at the benzylic methyl groups, suggesting that benzylic C-(1^{o})H bonds preferentially be activated over

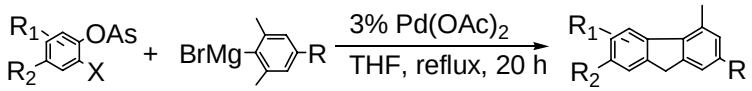
nonbenzylic C-(1^o)H bonds (nonbenzylic methyl group), benzylic C-(2^o)H bonds and C-(3^o)H bonds (Table 4.4, entry 2; Table 4.6, entries 1, 2). This observation was further confirmed by the fact that no reaction was observed for 2,6-diethylphenylmagnesium bromide (Table 4.6, entry 4).

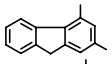
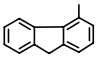
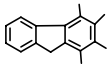
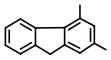
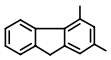
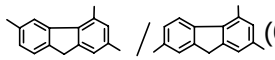
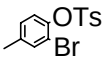
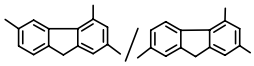
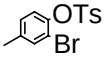
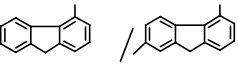
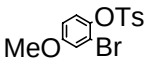
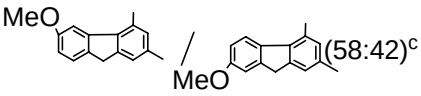
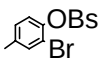
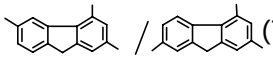
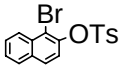
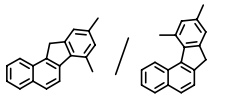
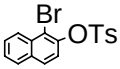
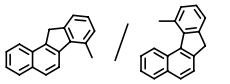
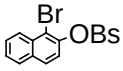
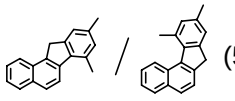
4.5 $Pd(OAc)_2$-Catalyzed Annulative Reactions of Hindered Grignard Reagents with 2-Haloaryl Arenesulfonates

Based on the hypothesis that the reactions of 1,2-dihalobenzenes proceeded with hindered Grignard reagents could proceed via palladium associated aryne intermediates, we found by omitting the use of phosphine and NHC ligands for palladium catalysts, a broad range of 1,2-dihalobenzenes including 1,2-dibromobenzenes, 1-bromo-2-iodobenzene, 1-chloro-2-halobenzenes, and 1-bromo-2-fluorobenzene could be suitable substrates for the preparation of substituted fluorenes. Our palladium associated aryne hypothesis suggested that other types of *o*-halo(LG)arenes, such as 2-haloaryl tosylates (Ts) and benzenesulfonates (Bs) which contain very inert Ar-OTs or Ar-OBs bonds, should also be suitable substrates for the tandem reaction because the oxidative addition of Palladium (0) with the very inert Ar-OTs or Ar-OBs bond would not be involved and the -OTs/-OBs group would only serve as a leaving group. We thus tested 2-haloaryl

tosylates and benzenesulfonates, which are readily available from 2-halophenols,[17] as substrates for the domino reactions (Table 4.7). We found that with $Pd(OAc)_2$ as catalyst, good to excellent yields of substituted fluorenes were obtained for 2-iodoaryl tosylates/benzenesulfonates and 2-bromoaryl tosylates/benzenesulfonates (Table 4.7, entries 1-13). However, 2-chloro-4-methylphenyl tosylate was found to be a poor substrate (Table 4.7, entry 14). Comparing the reaction results with 2-halo-4-methylphenyl tosylates as substrates (Table 4.7, entries 6, 7 and 14) revealed that 2-iodo-4-methylphenyl tosylate was a better substrate than 2-bromo-4-methylphenyl tosylate and 2-chloro-4-methylphenyl tosylate was virtually inactive. As the only difference for these substrates was the halo group and the chloro group was more electron-withdrawing than the bromo or iodo group, our results suggested that the initial oxidative addition should occur at the C-X bond, rather than at the C-OTs bond. 2-Chloro-4-methylphenyl tosylate would be the better substrate than 2-bromo-4-methylphenyl tosylate and 2-iodo-4-methylphenyl tosylate. Thus, the reluctance of the C-Cl bond in 2-chloro-4-methylphenyl tosylate to undergo the initial oxidative addition with Pd(0) species excluded it as a suitable substrate for the domino reaction. The observation of two isomers, rather than only one, in similar ratio for 2-bromophenyl tosylates/benzenesulfonates, 2-iodo-4-methylphenyl tosylate

Table 4.7 Pd(OAc)2-Catalyzed Reactions of 2-Haloaryl Arenesulfonates with Hindered Grignard Reagents [a]



Entry	Tosylate	ArMgBr	Product	Yield(%)[b]
1				92
2				87
3				83
4				95
5				86
6			 (62:38)[c]	92
7			 (58:42)[c]	82
8			 (63:37)[c]	74
9			 (58:42)[c]	69
10			 (71: 29)[c]	49
11			 (65:35)[c]	79
12			 (68: 32)[c]	71
13			 (55:45)[c]	47
14				< 2
15				< 2

a. Reaction conditions (not optimized): 2-haloaryl arenesulfonate (1.0 equiv), Grignard reagent (2.5 equiv), $Pd(OAc)_2$ (3%), THF (2 mL), reflux.
b. Isolated yields. c. Ratio based on ^1H NMR.

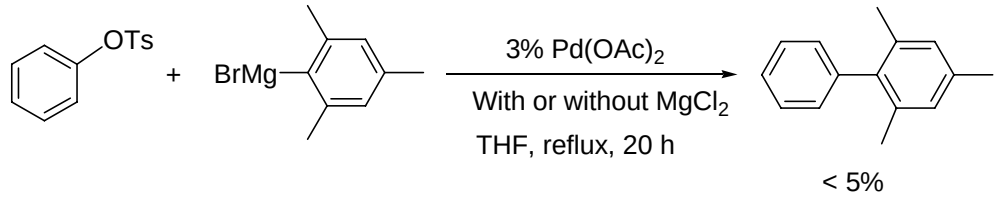
and 1-bromo-2-naphthyl tosylate/benzenesulfonate (Table 4.7, entries 6-13) further suggested that the transmetalation occurred with comparable transmetalation rates for Pd-Br and Pd-I bonds.

Aryl tosylates have been demonstrated to undergo cross-couplings with *para*-substituted phenylmagnesium bromides and *ortho*-tolymagnesium bromide catalyzed by Pd(0)/Josiphos ligand.[18] To establish whether aryl tosylates could undergo cross-coupling with hindered Grignard reagents, we have carried out the reaction of phenyl tosylate with 2-mesitylmagnesium bromide in the presence of 5% $Pd(OAc)_2$ at 60 ^oC for 20 h. We found that the cross-coupling product was formed in less than 5% yield, suggesting $Pd(OAc)_2$ cannot catalyze the cross-coupling of aryl tosylates with hindered Grignard reagents efficiently (Scheme 4.9). We also found that 2-(2', 4', 6'-trimethyl)-4-methylphenyl tosylate, intermediate that would be formed if the domino reaction proceeded via cross-coupling-oxidative addition-sp^3 C-H activation mechanism, was unable to be converted to 2,4,6-trimethylfluorene under $Pd(OAc)_2$/Grignard reagent or $Pd(OAc)_2/MgCl_2$/ Grignard reagent condition (Scheme 4.10).

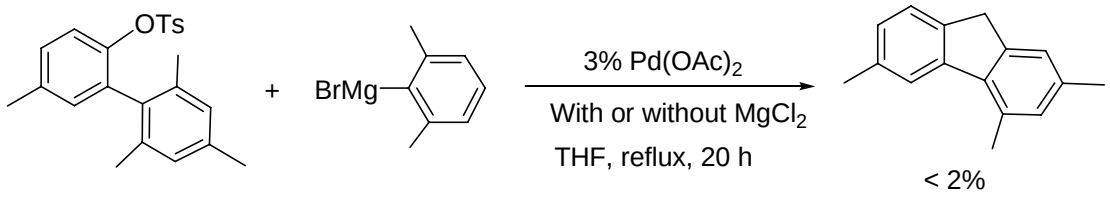
We have further carried out the $Pd_2(dba)_3$/*t*-Bu_3P-catalyzed reaction of 2-bromo-4-methylphenyl tosylate with 2-mesitylmagnesium bromide and 2-(2', 4', 6'-trimethyl)-4-methylphenyl tosylate was isolated in 82% yield with

no cyclized fluorene being observed (Scheme 4.11). These results strongly suggested that $Pd(OAc)_2$-catalyzed domino reactions of 2-haloaryl arenesulfonates with hindered Grignard reagents did not proceed through the cross-coupling-oxidative addition-sp^3 C-H activation mechanism.

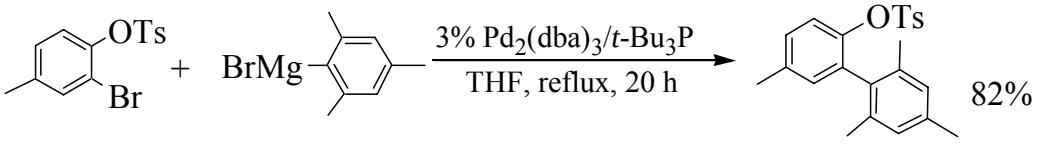
Scheme 4.9 $Pd(OAc)_2$-Catalyzed Reaction of phenyl tosylate with 2-Mesitylmagnesium Bromide



Scheme 4.10 $Pd(OAc)_2$-Catalyzed Reaction of 2-(2', 4', 6'-Trimethyl)-4-methylphenyl Tosylate with 2-Mesitylmagnesium Bromide



Scheme 4.11 Pd(0)/*t*-Bu_3P-Catalyzed Reaction of 2-Bromo-4-methylphenyl Tosylate with 2-Mesitylmagnesium Bromide



As our results supported that the initial oxidative addition should not occur at the C-OTs bond, the similar ratio of the substituted fluorenes

observed for unsymmetrical 2-bromoaryl tosylates/benzenesulfonates, 2-iodo-4-methylphenyl tosylate and 1-bromo-2-naphthyl tosylate/ benzenesulfonate excluded the pathway that the transmetalation occur first followed by aryne formation, in which only one isomer of substituted fluorenes would be expected. Our study further suggested that the pathway to form Pd(LG)X associated arynes first followed by transmetalation should be predominant, if not the only one.[19]

4.6 Summary

We demonstrated that simple palladium complexes such as $Pd(OAc)_2$ were excellent catalysts for 1,2-dihalobenzenes and 2-haloaryl arenesulfonates to undergo annulative reactions with hindered Grignard reagents to form substituted fluorenes. Our study was based on the hypothesis that two mechanistic pathways might be possible for the reaction of 1,2-dihalobenzenes with Grignard reagents, namely (a) the pathway that involves the cross-coupling of 1,2-dihalobenzenes with Grignard reagents to form 2-halobiphenyls followed by oxidative addition and sp^3 C-H activation, and (b) the pathway that involves the oxidative addition of 1,2-dihalobenzenes to form 2-haloarylPd(II)X complexes followed by β-halo elimination to form palladium associated arynes, transmetalation, carbopalladation and sp^3 C-H activation. We explored the ligand effect and

leaving group effect on these two pathways. We found that these two pathways were highly ligand dependent and the reaction pathway involving palladium associated arynes as intermediates could be controlled by omitting the use of phosphine and NHC ligands for palladium catalysts. We also found that a better leaving halo group favored the benzyne forming pathway and the sp^3 C-H activation preferentially occurred at benzylic C-(1^o)H bonds over nonbenzylic C-(1^o)H bonds (nonbenzylic methyl group), benzylic C-(2^o)H bonds and benzylic C-(3^o)H bonds. Our palladium associated aryne hypothesis allowed us to identify simple palladium complexes, e. g., $Pd(OAc)_2$, as the catalyst and a broad range of 1,2-dihalobenzenes including previously unsuitable 1-chloro-2-halobenzenes and 2-haloaryl arenesulfonates as substrates for high yield synthesis of substituted fluorenes. Our study also suggested that 2-(leaving group)arylPd(II) complexes most likely formed Pd(leaving group)X associated arynes first followed by transmetalation with Grignard reagents and carbopalladation, rather than undergo transmetalation with Grignard reagent first following by aryne formation and carbopalladation. The work described here provides a high yield, one-step access to substituted fluorenes from readily available 1,2-dihalobenzenes and 2-haloaryl arenesulfonates and hindered Grignard

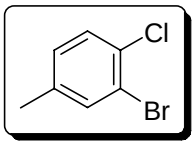
reagents, and our method may find applications in the preparation of substituted fluorene-containing molecules including polymers.

4.7 Experimental Section

4.7.1 General

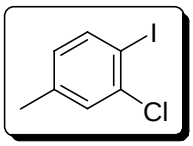
All yields reported refer to isolated yields (average of two runs) unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by ^{1}H NMR. Compounds described in the literature were characterized by comparison of their melting points, ^{1}H NMR and ^{13}C NMR spectra to reported data. THF was dried with sodium/benzophenone. 3-Bromo-4-chlorotolue,[20] 3-chloro-4-iodotoluene,[21] and 2-iodo-4-methylphenol[22] were prepared according to literature procedures. Aryl tosylates and benzenesulfonates were prepared by treating the corresponding phenols with *p*-toluenesulfonyl chloride or benzenesulfonyl chloride in dichloromethane containing excess of triethylamine at room temperature overnight. Bromopentamethylbenzene, pentamethyl phenylmagnesium bromide were prepared according to literature.[23,24]

3-Bromo-4-chlorotoluene Colorless liquid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.44(d, J = 1.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.04 (dd, *J* = 7.8,

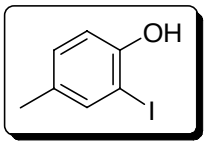


1.2 Hz, 1H), 2.30 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 138.1, 134.1, 131.2, 129.9, 129.2, 122.0, 20.5 ppm.

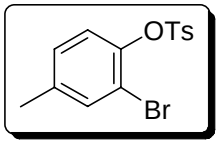
3-Chloro-4-iodotoluene Colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.28 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 2.29 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 139.9, 139.80, 138.1, 130.0, 129.00, 93.74, 20.75 ppm.



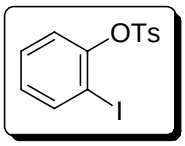
2-Iodo-4-methylphenol Colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.47 (s, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 5.11 (s, 1H), 2.25 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ 152.6, 138.2, 131.9, 130.8, 114.6, 85.4, 19.9 ppm.



2-Bromo-4-methylphenyl tosylate (1) White solid. m. p.: 117- 119^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.78 (d, *J* = 7.8 Hz, 2H), 7.32~ 7.31 (m, 3H), 7.19(d, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 8.4, 1.2 Hz, 1H), 2.45 (s, 3H), 2.301 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 145.6, 144.6, 138.4, 134.1, 132.7, 129.7, 129.1, 128.7, 123.6, 116.0, 21.7, 20.6 ppm.

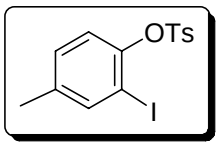


2-Iodophenyl tosylate (2) White solid. m. p.: 80- 81°C. ^{1}H NMR



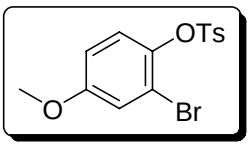
($CDCl_3$, 600 MHz): δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.34~ 7.33 (m, 4H), 6.99~ 6.96 (m, 1H), 2.46 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 146.0, 145.7, 140.1, 132.8, 129.8, 129.5, 128.8, 128.3, 123.0, 90.2, 21.8 ppm.

2-Iodo-4-methylphenyl tosylate (3) White solid. m. p.: 108-109°C.



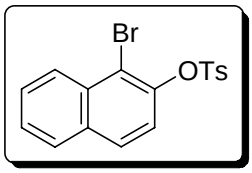
^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.80 (d, *J* = 7.8 Hz, 2H), 7.57 (s, *J* = 1.2 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.11 (dd, *J* = 8.4, 1.2 Hz, 1H), 2.46 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 147.8, 145.6, 140.3, 138.5, 132.9, 130.1, 129.7, 128.8, 122.5, 89.9, 21.7, 20.3 ppm.

2-Bromo-4-methoxyphenyl tosylate (4) White solid. ^{1}H NMR ($CDCl_3$,

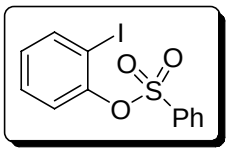


600 MHz): δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 9.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 6.80 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.77 (s, 3H), 2.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 158.3, 145.6. 140.4, 132.5, 129.7, 128.7, 124.4, 118.5, 116.9, 113.9, 55.8, 21.7 ppm.

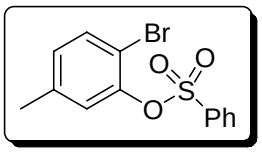
1-Bromonaphthyl *p*-toluenesulfonate (5) Light yellow solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.19 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 9.0 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.2 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.316 (d, J = 8.4 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 145.6, 145.0, 132.8, 132.6, 132.6, 129.8, 128.9, 128.7, 128.2, 128.0, 127.4, 126.9, 121.6, 116.0, 21.7 ppm.



2-Iodophenyl benzenesulfonate (6) White solid. m. p.: 85 – 86°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.93 (d, J = 3.6 Hz, 2H), 7.76 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.70 (t, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 2H), 7.36 ~ 7.33 (m, 2H), 7.00 ~ 6.97 (m, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 149.8, 140.0, 135.6, 134.5, 129.5, 129.2, 128.8, 128.4, 123.0, 90.1 ppm. Anal. calcd for $C_{12}H_9IO_3S$: C, 40.02%; H, 2.52%. Found: C, 40.14%; H, 2.47%.

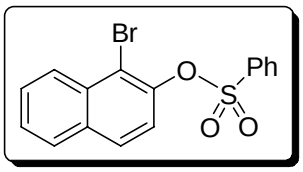


2-Bromo-5-methylphenyl benzenesulfonate (7) Colorless liquid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.91 (d, J = 7.8 Hz, 2H), 7.69 (t, J = 7.8 Hz,



1H), 7.54 (t, J = 7.8 Hz, 2H), 7.32 (d, J = 1.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.09 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.5, 138.6, 135.7, 134.4, 134.1, 129.1, 129.1, 128.7, 123.6, 115.9, 20.6 ppm.

1-Bromonaphthalen-2-yl benzenesulfonate (8) White solid. m. p.: 69 – 70°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.17 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.83 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.54 ~ 7.51 (m, 3H), 7.48 (d, J = 9.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.9, 135.7, 134.5, 132.6, 132.5, 129.2, 129.0, 128.7, 128.2, 128.1, 127.4, 126.9, 121.7, 116.0 ppm. Anal. calcd for $C_{16}H_{11}BrO_3S$: C, 52.91%; H, 3.05%. Found: C, 52.83%; H, 2.99%.



4.7.2 General Procedure for Palladium-Catalyzed Domino Reactions

(1) General Procedure of the Ligand Effect on Domino Reactions of 1-Bromo-2-chlorobenzene with Grignard Reagents

In a glove box with N_2-atmosphere, to a mixture of 1-bromo-2-chlorobenzene (1.0 mmol), and 2.0 ml THF (in a Schlenk flask) was added palladium source (0.015 mmol) and phosphine ligands (0.06 mmol). After stirred for 5-10 minutes, Grignard reagent (2.5 ml, 1M in THF, 2.5 mmol) was added. The mixture was allowed to stir under 60^{o}C for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate twice. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR analysis of the reaction mixture gave the conversion of the reaction, and the ratio of the products.

(2) General Procedure of the Leaving Group Effect on Domino Reactions of 1,2-Dihalobenzenes with Grignard Reagents

In a glove box with N_2-atmosphere, to a mixture of 1,2-halobenzene (1.0 mmol), and 2.0 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (0.015 mmol). After stirred for 5-10 minutes, 2-Mesitylmagnesium bromide (2.5 ml, 1M in THF, 2.5 mmol) was added. The mixture was allowed to stir at 60^{o}C or at room temperature for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate twice. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H

NMR analysis of the reaction mixture gave the conversion of the reaction, and the ratio of the products.

(3) General Procedure for Palladium-Catalyzed Domino Reactions of 1,2-Dihalobenzenes with Hindered Grignard Reagents

In a glove box with N_2-atmosphere, to a mixture of 1,2-dihalobenzenes (1.0 mmol) and 1.0 mL THF (in a Schlenk flask) was added palladium acetate (0.03 mmol) or $Pd_2(dba)_3$ (0.015 mmol). After stirred for 5-10 minutes, Grignard reagent (2.5 mL, 1M in THF, 2.5 mmol) was added. The mixture was allowed to stir at room temperature or 60^oC for 20 hours. After being quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100 : 0 to 90 : 10) gave the products.

(4) General Procedure for Palladium-Catalyzed Domino Reactions of 1,2-Dibromobenzene with 2,6-Dialkynlmagnesium Bromides

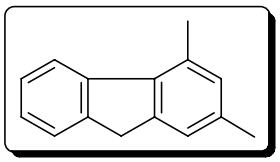
In a glove box with N_2-atmosphere, to a mixture of 1,2-dibromobenzene (1.0 mmol) and 1.0 mL THF (in a Schlenk flask) was added palladium acetate (0.03 mmol). After stirred for 5-10 minutes, 2,6-dialkynlmagnesium bromides (2.5 mmol, in THF) was added. The mixture

was allowed to stir at room temperature or 60°C for 20 hours. After being quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100 : 0 to 90 : 10) gave the products.

(5) General Procedure for $Pd(OAc)_2$-Catalyzed Domino Reaction of 2-Haloaryl Tosylates with Hindered Grignard Reagents

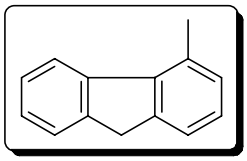
In a glove box with N_2-atmosphere, to a mixture of 2-haloaryl tosylate (1.0 mmol), and 1.0 ml THF (in a Schlenk flask) was added palladium acetate (6.7 mg, 0.03 mmol). After stirred for 5-10 minutes, Grignard reagent (2.5 ml, 1M in THF, 2.5 mmol) was added. The mixture was allowed to stir under refluxing for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) gave the products.

2,4-Dimethylfluorene (9) white solid m.p.: 66.5-67.5°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.87 (d, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 7.2 Hz,



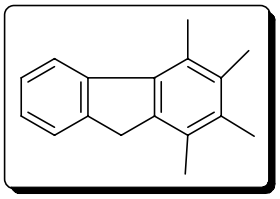
1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.21 (s, 1H), 6.97 (s, 1H), 3.86 (s, 2H), 2.69 (s, 3H), 2.39 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 143.9, 143.5, 142.7, 137.16, 136.2, 132.7, 129.9, 126.5, 125.6, 124.8, 123.1, 122.6, 36.9, 21.3, 20.9 ppm.

4-Methylfluorene (10) white solid. m.p.: 69-71^{o}C. ^{1}H NMR



($CDCl_3$, 600 MHz): δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 3.91 (s, 2H), 2.73 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 143.7, 143.6, 142.7, 139.8, 133.0, 129.0, 126.6, 126.4, 126.0, 124.9, 123.1, 122.4, 37.1, 21.1 ppm.

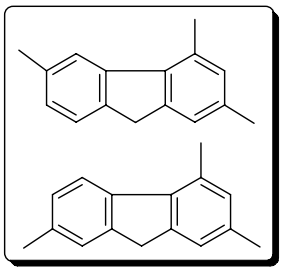
1,2,3,4-Tetramethylfluorene (11) white solid. m.p.: 121.5-



122.5^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.97 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.34 (dd, J_1 = 8.4, J_2 = 0.6 Hz, 1H), 7.25 (dd, J_1 = 8.4, J_2 = 0.6 Hz, 1H), 3.76 (s, 2H), 2.66 (s, 3H), 2.32 (s, 6H), 2.29 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 143.7, 143.6, 139.9, 137.0, 133.7, 133.5, 129.4, 129.1, 126.4,

125.3, 124.7, 123.1, 36.6, 16.8, 16.5, 16.5, 16.2 ppm. Anal. calcd for $C_{17}H_{18}$: C, 91.84%; H, 8.16%. Found: C, 91.58%; H, 8.19%.

2, 4, 6-Trimethylfluorene/2, 4, 7-Trimethylfluorene (12) off-white

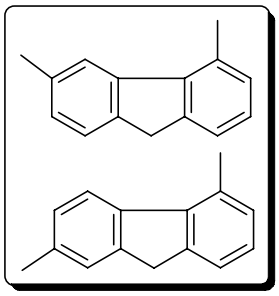


solid. m. p.: 43-57°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.68 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.34 (s, 1H), 7.19 (s, 1H), 7.18 (s, 1H), 7.18~ 7.16 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.95 (s, 1H), 3.81 (s, 4H), 2.69 (s, 4H), 2.66 (s, 2H), 2.46 (s, 4H), 2.42(s, 2H), 2.38 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.4, 143.8, 143.7, 142.9, 140.6, 140.1, 137.2, 137.2, 136.0, 136.0, 135.7, 135.3, 132.6, 132.2, 129.8, 129.8, 127.3, 126.4, 125.6, 124.4, 123.4, 123.1, 123.1, 122.3, 36.7, 36.5, 21.8, 21.4, 21.3, 21.3, 21.0, 20.8 ppm. Anal. calcd for $C_{16}H_{16}$: C, 92.26%; H, 7.74%. Found: C, 91.93%; H, 7.78%.

The structure of 2, 4, 6-Trimethylfluorene was established by NOE effect. Recrystallization on the mixture of 2,4,7-trimethylfluorene / 2, 4, 6-trimethylfluorene by hexanes gave >90% pure 2, 4, 6-trimethylfluorene (**4a**). ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.68 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.19 (s, 1H), 7.08 (d, J = 7.8 Hz, 1H), 6.95 (s, 1H), 3.80 (s, 2H), 2.68 (s, 3H),

2.46 (s, 3H), 2.38 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.4, 142.9, 140.6, 137.2, 136.1, 136.0, 132.6, 129.8, 126.4, 124.4, 123.4, 123.1, 36.5, 21.8, 21.3, 21.0 ppm. NOE effect observed when the peak at 3.80 ppm was irradiated: 3.5% for the peak with chemical shift of 7.40 ppm and 3.4% for the peak with chemical shift of 7.19 ppm.

3,5-Dimethylfluorene/2,5-Dimethylfluorene (13) Off-white solid.

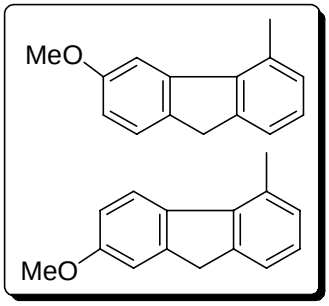


m.p.: 43-62°C. ^1H NMR ($CDCl_3$, 600 MHz) δ 7.78 (d, *J* = 7.8 Hz, 1H), 7.72 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.36~7.36 (m, 1H), 7.21~ 7.15 (m, 1H), 7.13~7.11 (m, 1H), 3.84 (s, 2H), 2.72 (s, 3H); 2.70 (s, 3H), 2.46 (s, 3H); 2.42 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.0, 143.9, 143.4, 142.9, 140.7, 140.0, 139.8, 139.8, 136.04, 135.8, 133.0, 132.6, 128.9, 128.8, 127.4, 126.9, 126.2, 125.9, 125.6, 124.5, 123.8, 122.8, 122.4, 122.3, 36.9, 36.7, 21.8, 21.4, 21.2, 21.0 ppm.

The structure of 3,5-Dimethylfluorene (**13a**) was established by NOE effect. Recrystallization of the mixture of 2,5-dimethylfluorene/3,5-dimethylfluorene by hexanes gave > 95% pure 3, 5-dimethylfluorene (**5a**). m. p.: 77-78.5°C. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.73 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 1H), 7.13 (m, 2H),

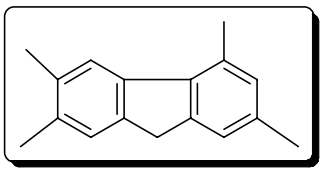
3.85 (s, 2H), 2.73 (s, 3H), 2.47 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 150.855 MHz): δ 144.0, 142.9, 140.7, 139.8, 136.1, 133.0, 128.9, 126.9, 126.2, 124.5, 123.8, 122.4, 36.7, 21.8, 21.2 ppm. NOE effect observed when the peak at 3.85 (s) ppm was irradiated: 2.9% for the peak with chemical shift of 7.43 ppm and 2.5% for the peak with chemical shift of 7.38 ppm.

3-Methoxy-5-methylfluorene/2-methoxy-5-methylfluorene (14)



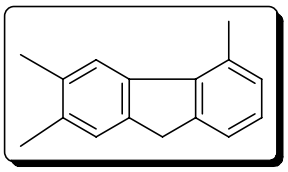
Obtained as a mixture with a ration of 78:22. The structure of 3-methoxy-5-methylfluorene was established by NOE effect. Recrystallization from the mixture of 3-methoxy-5-methylfluorene and 2-methoxy-5-methylfluorene in hexanes gave 3-methoxy-5-methylfluorene (**14a**) as a white solid. m.p.: 70-71°C. ^1H NMR ($CDCl_3$, 600 MHz): δ 7.49 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.87 (dd, J_1 = 8.4, J_2 = 2.4 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 2H), 2.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 151 MHz): δ 158.8, 144.7, 143.9, 139.6, 135.8, 133.0, 128.9, 126.5, 125.1, 122.5, 111.3, 109.4, 55.6, 36.3, 21.0 ppm. NOE effect observed when the peak at δ 3.84 ppm was irradiated: 7.45 (d, 0.3%), 7.38 (d, 0.3%).

2,3,5,7-tetramethylfluorene (15) white solid. m. p.: 104-105°C. ^{1}H



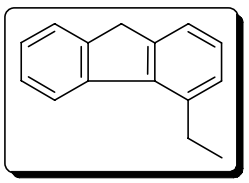
NMR ($CDCl_3$, 600 MHz) δ: 7.64 (s, 1H), 7.31 (s, 1H), 7.18 (s, 1H), 6.94 (s, 1H), 3.79 (s, 2H), 2.68 (s, 3H), 2.38 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.871 MHz) δ: 144.0, 141.2, 140.6, 137.4, 135.6, 134.5, 134.0, 132.2, 129.7, 126.0, 123.8, 123.1, 36.5, 21.3, 20.9, 20.3, 20.0 ppm.

2,3,5-Trimethylfluorene (16) white solid. m. p.: 86.5- 87.5°C. ^{1}H



NMR ($CDCl_3$, 600 MHz) δ: 7.68 (s, 1H), 7.36 (d, *J* = 7.2 Hz, 1H), 7.32 (s, 1H), 7.16 (t, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 3.82 (s, 2H), 2.71 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 150.871 MHz) δ: 143.6, 141.4, 140.6, 140.0, 134.6, 134.5, 132.5, 128.8, 126.0, 125.8, 124.2, 122.3, 36.6, 21.1, 20.3, 20.0 ppm.

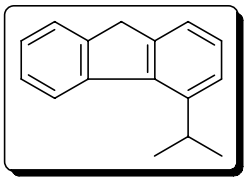
4-Ethylfluorene (17) White solid. m. p.: 35 - 36°C. ^{1}H NMR ($CDCl_3$,



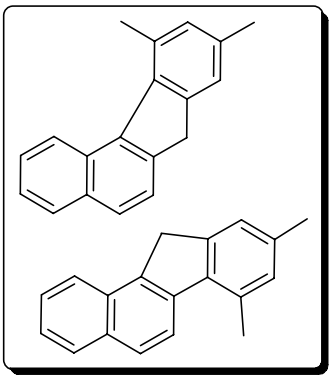
600 MHz) δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.27 ~ 7.24 (m, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 3.92 (s, 2H), 3.12 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.9, 143.7, 142.1, 139.4, 139.0, 127.1, 126.7, 126.6, 126.0, 124.9, 123.2, 122.5, 37.1, 27.2, 14.3 ppm.

4-Isopropylfluorene (18) Colorless liquid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.39 (d, *J* = 6.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.30 (t, *J* = 6.0 Hz, 2H), 3.90 (s, 2H), 3.84 (m, 1H), 1.41 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 144.3, 143.9, 143.8, 142.0, 138.5, 126.7, 126.6, 125.9, 124.9, 123.6, 123.0, 122.4, 37.1, 29.5, 22.8 ppm.

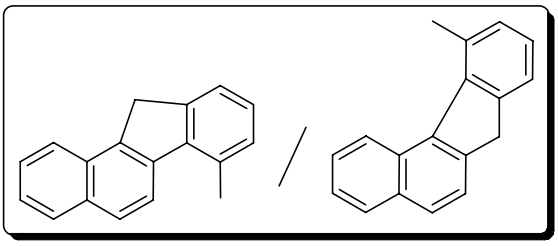


7,9-Dimethyl-11H-benzo[a]fluorene and 9,11-Dimethyl-7H-benzo[c]fluorene (19) Anal. calcd. for $C_{19}H_{16}$: C, 93.40%; H, 6.60%. Found: C, 93.60%; H, 6.54%. The structure of 7,9-dimethyl-11H-benzo[a]fluorene (**19a**) was established by NOE effect. Recrystalization from the mixture of 7,9-Dimethyl-11H-benzo[a]fluorene and 9,11-Dimethyl-7H-benzo[c]fluorene by using hexanes as solvent gave 7,9-dimethyl-11H-benzo[a]fluorene (**19a**) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.07 (d, *J* = 8.4 Hz, 1H), 8.00



(d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.29 (s, 1H), 7.00 (s, 1H), 4.14 (s, 2H), 2.77 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.0, 140.1, 139.9, 138.1, 135.9, 132.1, 131.9, 130.5, 130.1, 128.6, 127.3, 126.2, 125.1, 124.0, 123.2, 121.6, 35.6, 21.3, 20.8 ppm. NOE effect was observed when irradiated at the peak at δ 4.14 ppm: 8.00 (d, 0.5%), 7.29 (s, 0.3%). NOE effect observed when the peak at δ 2.77 ppm was irradiated: 8.07 (d, 0.5%), 7.00 (s, 0.29%). NOE effect observed when the peak at δ 2.42 ppm was irradiated: 7.29 (d, 0.22%), 7.00 (s, 0.19%).

9,11-Dimethyl-7H-benzo[c]fluorene (19b) off-white solid. Obtained from the mother liquid of the recrystalization of the mixture of 7,9-Dimethyl-11H-benzo[a]fluorene and 9,11-Dimethyl-7H-benzo[c]fluorene with >90% purity. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.51 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 7.07 (s, 1H), 3.90 (s, 2H), 2.82 (s, 3H), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 145.1, 142.3, 139.0, 138.4, 135.7, 133.7, 131.6, 131.4, 128.7, 128.6, 127.4, 126.8, 124.5, 124.5, 123.0, 122.9, 38.0, 25.1, 21.0 ppm. NOE effect observed when the peak at δ 3.90 ppm was irradiated: 7.58 (d, 0.5%), 7.21 (s, 0.3%).

7-Methyl-11H-benzo[a]fluorene and 11-methyl-7H-benzo[c]fluorene (20)  Anal. calcd. for $C_{18}H_{14}$: C, 93.87%; H, 6.13%. Found: C, 93.69%; H, 6.01%. The structure of 7-methyl-11H-benzo[a]fluorene was established by NOE effect. Recrystalization from the mixture of 7-methyl-11H-benzo[a]fluorene and 11-methyl-7H-benzo[c]fluorene by using hexanes as solvent gave 7-methyl-11H-benzo[a]fluorene (**20a**) as a white solid. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.10 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 4.17 (s, 2H), 2.80 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.6, 140.7, 140.3, 140.0, 132.5, 132.0, 130.4, 129.2, 128.6, 127.4, 126.3, 126.0, 125.3, 124.1, 122.4, 121.8, 35.7, 21.0 ppm. NOE effect observed when the peak at δ 4.17 ppm was irradiated: 8.10 (d, 0.9%), 7.47 (s, 0.3%).

11-Methyl-7H-benzo[a]fluorene (20b) off-white solid. Obtained from the mother liquid of the mixture of 11-methyl-7H-benzo[c]fluorene and 7-methyl-11H-benzo[a]fluorene by using hexanes as solvent with >85% purity. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.51 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* =

8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.26 (t, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 7.2 Hz, 1H), 3.97 (s, 2H), 2.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.7, 142.7, 141.6, 138.3, 133.7, 132.0, 130.6, 128.8, 128.6, 128.6, 127.9, 126.8, 125.9, 124.6, 123.0, 122.0, 38.2, 25.1 ppm. NOE effect was observed when the peak at δ 3.97 ppm was irradiated: 7.62 (d, 0.3%), 7.42 (s, 0.2%).

4.7.3 Other Palladium-Catalyzed Reactions for Mechanistic Study

(1) $Pd(OAc)_2$-Catalyzed Reaction of 1,2-Dichlorobenzene with 2-Mesitylmagnesium Bromide

In a glove box with N_2-atmosphere, to a mixture of 1,2-dichlorobenzene (0.5 mmol), and 1.0 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (3.4 mg, 0.015 mmol). After stirred for 5-10 minutes, Grignard reagent (1.25 ml, 1M in THF, 1.25 mmol) was added. The mixture was allowed to stir under 60^{o}C for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate twice. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) gave the products in 24% yield.

(2) $Pd(OAc)_2$-Catalyzed Reaction of 2-Halo-2′,4′,6′-trimethylbiphenyl with 2-Mesitylmagnesium Bromide

In a glove box with nitrogen atmosphere, to a mixture of 2-chloro-2′,4′,6′-trimethylbiphenyl or 2-fluoro-2′,4′,6′-trimethylbiphenyl (0.1 mmol), and 0.5 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (0.7 mg, 0.003 mmol). After stirred for 5-10 minutes, Grignard reagent THF solution (0.25 ml, 1M in THF, 0.25 mmol) was added. The mixture was allowed to stir under 60^{o}C for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. No reaction was observed by ^{1}H NMR.

(3) $Pd(OAc)_2$-Catalyzed Reaction of Phenyl Tosylate with 2-Mesitylmagnesium Bromide

In a glove box with nitrogen atmosphere, to a mixture of phenyl tosylate (62mg, 0.25 mmol), and 0.5 ml THF (in a schlenk flask) was added palladium acetate (1.7 mg, 0.007 mmol). After stirred for 5-10 minutes, 2-mesitylmagnesium bromide THF solution (0.6 ml, 1M in THF, 0.6 mmol) was added. The mixture was allowed to stir under 60^{o}C for 20 hours. After

quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. ^{1}H NMR showed that the yield of the cross-coupling product was less than 5%.

(4) $Pd(OAc)_2$-Catalyzed Reaction of 2-Chloro-5-methylphenyl Tosylate with 2-Mesitylmagnesium Bromide

In a glove box with nitrogen atmosphere, to a mixture of 2-chloro-5-methylphenyl tosylate (0.25 mmol), and 0.5 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol). After stirred for 5-10 minutes, Grignard reagent (0.65 ml, 1M in THF, 0.65 mmol) was added. The mixture was allowed to stir under refluxing for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. No reaction was observed by ^{1}H NMR.

(5) $Pd_2(dba)_3$/^{t}Bu$_3$P-Catalyzed Reaction of 2-Bromo-4-methylphenyl Tosylate with 2-Mesitylmagnesium Bromide

In a glove box with N_2-atmosphere, to a mixture of 2-Bromo-4-methylphenyl tosylate (170.5 mg, 0.5 mmol), and 1.0 ml THF (in a Schlenk flask) was added $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol) and *t*-Bu$_3$P (6.1 mg, 0.03

mmol). After stirred for 5-10 minutes, 2-mesitylmagnesium bromide (1.25 ml, 1M in THF, 1.25 mmol) was added. The mixture was allowed to stir under refluxing for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate twice. The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100: 0 to 90: 15) gave the cross-coupling product 2-(2', 4', 6'-Trimethylphenyl)-4-methylphenyl tosylate (**21**) in 82% yield. White solid. m.p.: 75-76^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.31 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.15 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 1.8 Hz, 1H), 6.80 (s, 2H), 2.40 (s, 3H), 2.35(s, 3H), 2.32 (s, 3H), 1.86 (s, 6H) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ 144.8, 144.3, 136.9, 136.6, 136.6, 133.7, 133.6, 133.1, 132.3, 129.2, 129.0, 127.9, 127.7, 122.6, 21.6, 21.0, 20.9, 20.3 ppm.

(6) Palladium-catalyzed reaction of 2-(2', 4', 6'-Trimethyl)-4-methylphenyl Tosylate with 2-Mesitylmagnesium Bromide

In a glove box with N_2-atmosphere, to a mixture of 2-(2', 4', 6'-trimethyl)-4-methylphenyl-tosylate (95 mg, 0.25 mmol), and 0.5 ml THF (in a Schlenk flask) was added $Pd(OAc)_2$ (1.7 mg, 0.0075 mmol). After stirred for 5-10 minutes, 2-mesitylmagnesium bromide (0.65 ml, 1M in THF, 0.65

mmol) was added. The mixture was allowed to stir under refluxing for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and the solvent was evaporated under vacuum. No 2,4,6-trimethylfluorene was observed by ^{1}H NMR.

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CHAPTER FIVE

Two Palladium-Catalyzed Domino Reactions from One Set of Substrates/Reagents: Efficient Synthesis of Substituted Indenes and *cis*-Stilbenoid Hydrocarbons from the Same Internal alkyne [1]

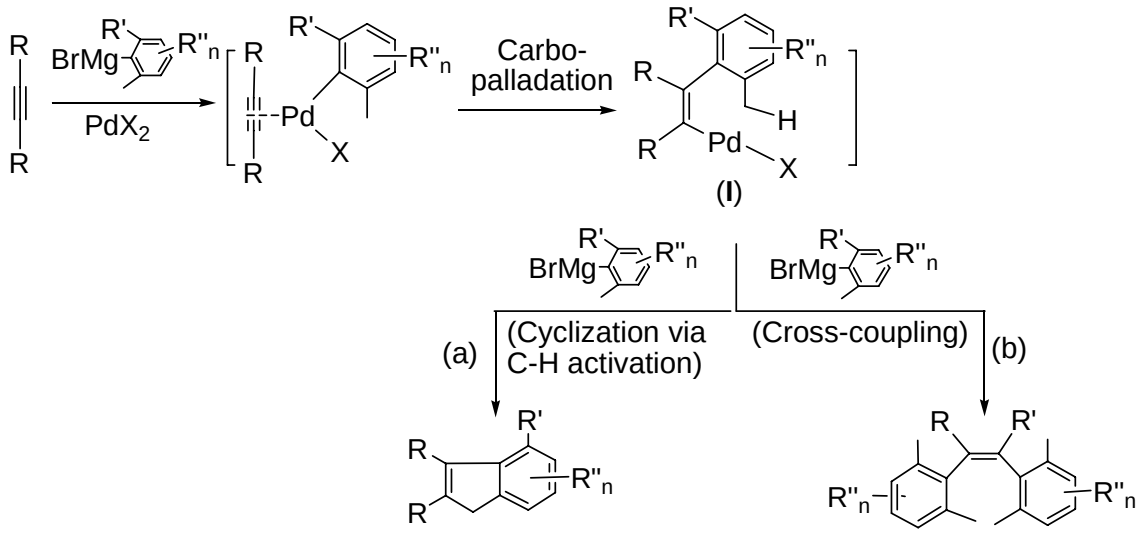
5.1 Introduction

Since arranging two or more bond-forming reactions to occur in a tandem or domino fashion is always challening, it is not surprising to observe that almost all tandem/domino reactions were developed on a basis of one type of tandem/domino reaction per one set of substrates/reagents.[2] Developing two or more types of tandem/domino reactions from the same substrates and reagents, which represents a strategy that could further heighten the efficiency of conducting reactions in a tandem/domino fashion, is apparently very attractive, but remains to be largely unexplored.[3]

On Chapter 4 we have discussed the palladium-catalyzed tandem reaction of 1,2-dihalobenzenes and 2-haloaryl tosylates with hindered Grignard reagents to form substituted fluorenes,[4] in which palladium-associated arynes were believed to be the intermediates when the reaction was carried out in the absence of phosphines or *N*-heterocyclic carbenes ligands. The triple bond nature of arynes led us to consider that alkynes might also function similarly as *in situ* generated arynes. We thus envisioned

that carbopalladation of alkynes could generate vinylpalladium(II)X complexes (**I**) (Scheme 5.1).[5]

Scheme 5.1 Domino Carbopalladation-Cyclization via sp^3 C-H Activation vs. Domino Carbopalladation-Cross-Coupling Reaction



Complexes (**I**) could then (a) undergo cyclization via C-H activation[6,7] to afford substituted indenes, which are structural constituents of metallocene-based catalysts for olefin polymerizations, of biologically active compounds and of functional materials;[8,9] and (b) undergo transmetalation followed by reductive elimination (cross-coupling process) to yield *cis*-stilbenoid hydrocarbons, which are potentially useful in the fields of molecular sensors and molecular electronics.[10,11] Therefore, two types of domino reactions, namely domino carbopalladation-cyclization to form polysubstituted indenes and domino carbopalladation–cross-coupling to

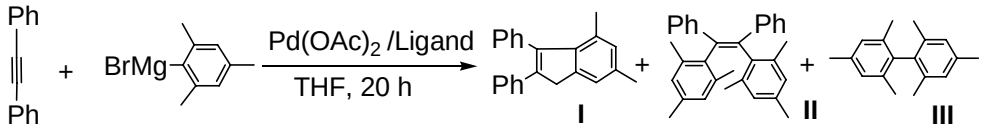
form *cis*-stilbenoid hydrocarbons containing highly substituted phenyl groups, might be developed from the same alkynes and hindered Grignard reagents if the two competing pathways could be controlled (Scheme 5.1).

5.2 Realization of Two Competing Pathways by Controlling the Use of Ligands and Reaction Temperature

Based on the consideration that the activation of C-H bond would involve the interaction of C-H bond with $Pd^{(II)}$ center and such interaction would be disfavored at higher reaction temperature and/or in the presence of ligands, we surmised the cyclization via sp^3 C-H activation process would be favored in the absence of ligands and at lower reaction temperature. We thus began our study by examining the reaction of diphenylacetylene with 2-mesitylPd(II)(OAc), *in situ* generated from 2-mesitylmagnesium bromide with $Pd(OAc)_2$. We found the domino carbopalladation-cyclization product 4,6-dimethyl-2,3-diphenylindene was the major product with only $Pd(OAc)_2$ as the promoter, either at room temperature, 60 ^oC or refluxing (Table 5.1, entries 1, 2, 5). The use of PPh_3 as a ligand decreases the formation of the cyclization product as well as slowed down the reaction (Table 5.1, entries 2-4). By using 4 equiv. of PPh_3 and in refluxing THF, the domino carbopalladation–cross-coupling product became the major product, along

with the self-coupling of Grignard reagent as the main side reaction (Table 5.1, entry 7). Our results suggested that by controlling the use of ligand and reaction temperature, it is possible to control the domino reaction pathways.

Table 5.1 $Pd(OAc)_2$-Promoted Domino Reaction of Diphenylacetylene with 2-Mesitylmagnesium Bromide [a]



Entry	Ligand	Temperature	Conversion	Ratio[b] I : II : III
1	None	R. T.	85%	97 : 2 : 1
2	None	60	99%	90 : 2 : 8
3	2 equiv PPh_3	60	75%	81 : 9 : 10
4	4 equiv PPh_3	60	60%	20 : 24 : 56
5	None	Reflux	99%	93 : 3.5 : 3.5
6	2 equiv PPh_3	Reflux	99%	69 : 12 : 19
7	4 equiv PPh_3	Reflux	81%	2 : 67 : 31

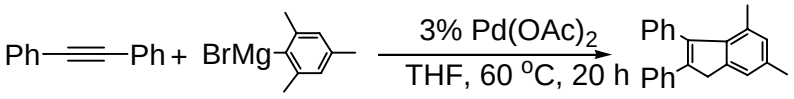
a. Reaction conditions: diphenylacetylene (1.0 equiv), Grignard reagent (2.5 equiv), $Pd(OAc)_2$ (1 equiv), THF (2 mL), 20 h. b. Based on ^1H NMR.

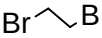
5.3 Palladium-Catalyzed Domino Reactions of Internal Alkyne with Hindered Grignard Reagents

As $Pd(II)X_2$ would be reduced to Pd(0) species after every reaction cycle, after establishing factors that influence the reaction competing pathways, we next turned our attention to develop the catalytic version of these two types of domino reactions by identifying oxidants that could

oxidize Pd(0) species to Pd(II) species. We have tested several commonly available oxidants and found 1,2-dibromoethane can be served as an excellent oxidizer (Table 5.2). By using a stoichiometric amount of 1,2-dibromoethane and 3% $Pd(OAc)_2$, the domino carbopalladation-cyclization process proceeded smoothly to give 4,6-dimethyl-2,3-diphenylindene in excellent yield (Table 5.2, entry 6).

Table 5.2 Pd(II)-Catalyzed Domino Reaction of Diphenylacetylene with Mesitylmagnesium Bromide [a]

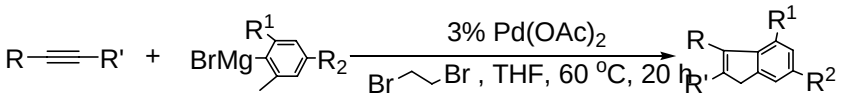


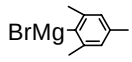
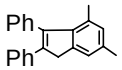
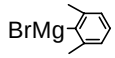
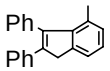
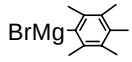
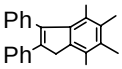
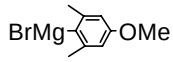
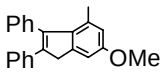
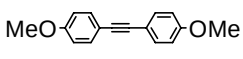
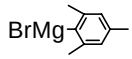
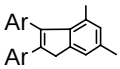
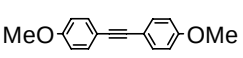
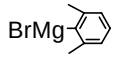
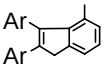
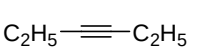
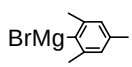
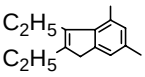
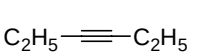
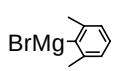
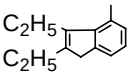
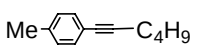
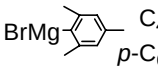
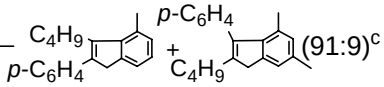
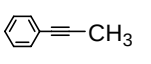
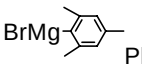
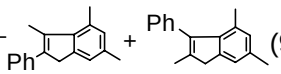
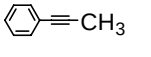
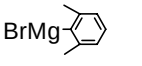
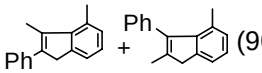
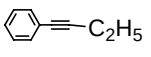
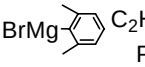
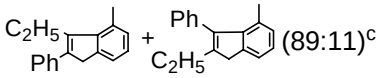
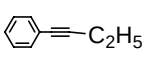
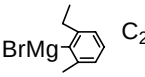
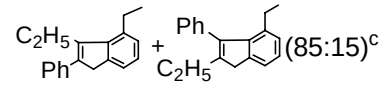
Entry	Additives	Yield (%)
1	None	< 2 [b]
2	$CuCl_2$	< 2 [b]
3	$CuSO_4$	< 2 [b]
4	$FeCl_3$	15
5	Ag_2CO_3	5
6		87

a. Reaction conditions: diphenylacetylene (1.0 equiv), Grignard reagent (2.5 equiv), THF (2 mL). b. Conversion based on ^1H NMR

With 1,2-dibromoethane as the oxidant, a number of alkynes were examined for the $Pd(OAc)_2$-catalyzed domino carbopalladation-cyclization reaction and our results are listed in Table 5.3. We found that diaryl-, dialkyl- and alkylarylacetylenes were all suitable substrates. When unsymmetrical alkylarylacetylenes were employed as the substrates, we

Table 5.3 Pd(OAc)2-Catalyzed Cyclizations of Internal Alkynes with Hindered Grignard Reagents [a]



entry	alkyne	ArMgBr	product	yield(%)[b]
1				87
2				85
3				81
4				87
5				97
6				94
7				71
8				77
9				78
10				72[d,e]
11				64[d,f]
12				85
13				67
14				69
15				78
16				< 2%[g]

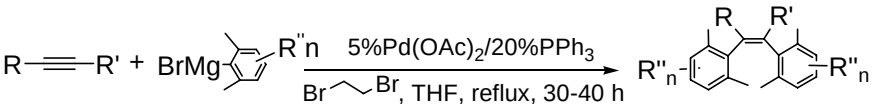
a. Reaction conditions: alkyne (1.0 equiv), Grignard reagent (2.5 equiv), $Pd(OAc)_2$ (3%), 1,2-dibromoethane (1.0 equiv.), THF (2 ml), 60 °C. b. Isolated yields. c. Ratio based on ^1H NMR. d. Reaction condition: room temperature, 30 h. e. 15% Crossc-oupling product was observed. f. 21% Cross-coupling product was observed. g. Reaction time: 45 h.

found the domino reaction occurred mainly from the alkyl sides of alkyarylacetylenes,[12] as evidenced by the ratio of two isomeric products (Table 5.3, entries 9-13). To determine whether other types of hydrogens (nonbenzylic 1^o hydrogens, benzylic 2^o, and 3^o hydrogens) could also be activated under our condition, we have tested 2-ethyl-6-methylphenylmagnesium bromide and 2-isopropyl-6-methylphenyl-magnesium bromide for the domino reaction. We found that the sp^3 C-H activation exclusively occurred at the benzylic methyl group, suggesting that nonbenzylic 1^o hydrogens (nonbenzylic methyl group), 2^o (ethyl group) and 3^o (isopropyl group) benzylic hydrogens could not be activated (Table 5.3, entries 14, 15). This was further confirmed by the fact that no reaction was observed for 2,6-diethylphenylmagnesium bromide with diphenyl-acetylene (Table 5.3, entry 16).

By using 1,2-dibromoethane as the oxidant, 4 equivalent of PPh_3 relative to $Pd(OAc)_2$ and in refluxing THF, we were also able to realize the second type of domino reaction, the carbopalladation followed by cross-coupling, to form *cis*-stilbenes,[13,14] in a catalytic fashion. *cis*-Substituted stilbenes containing highly substituted phenyl groups were obtained in good yields from the same alkynes and hindered Grignard reagents that form polysubstituted indenes (Table 5.4). Our results also suggested that

$Pd(PPh_3)_2Cl_2$-catalyzed reactions of *trans*-1,2-dibromoalkenes with Grignard reagents in refluxing THF to give *cis*-substituted stilbenes most likely also proceeded with alkynes and (**I**) as the reaction intermediates.

Table 5.4 Pd(OAc)2-Catalyzed Domino Carbopalladation-Cross-coupling of Internal Alkynes and Hindered Grignard Reagents [a]



entry	R—≡—R	BrMg	R, R' Ar, Ar	yield(%)[b]
1	Ph—≡—Ph	BrMg	Ph, Ph	71
2	Ph—≡—Ph	BrMg	Ph, Ph	65
3	MeO—≡—OMe	BrMg	*p*-$H_3COC_6H_4$, $C_6H_4OCH_3$-*p*	72
4	MeO—≡—OMe	BrMg	*p*-$H_3COC_6H_4$, $C_6H_4OCH_3$-*p*	69
5	C_2H_5—≡—C_2H_5	BrMg		60
6	C_2H_5—≡—C_2H_5	BrMg		81
7	Ph—≡—CH_3	BrMg	Ph	78
8	Ph—≡—CH_3	BrMg	Ph	74
9	Ph—≡—CH_3	BrMg	Ph	81

a. Reaction conditions: alkyne (1.0 equiv), Grignard reagent (4.0 equiv), 1,2-dibromoethane (1.5 equiv), $Pd(OAc)_2$ (5%), PPh_3 (20%), THF (2 mL), refluxing, 30-40 h. b. Isolated yields.

In summary, we developed two types of Pd-catalyzed domino reactions from the same alkynes and hindered Grignard reagents by controlling the use of ligand and the reaction temperature. We also showed that only benzylic methyl hydrogens might be activated by Pd(II) species. Our study provided an efficient access to useful polysubstituted indenes and *cis*-substituted stilbenes from simple, commercially available starting materials/ reagents. The ligand and temperature factors for controlling the domino reaction pathways identified in this study may also be applicable for other cross-coupling and C-H activation-based tandem/domino reactions. Work toward this direction is underway.

5.4 Experiment Section

5.4.1 General

NMR spectra were recorded on Varian 200 MHz or 600 MHz spectrometers. Chemical shifts were reported in ppm down field from internal tetramethylsilane. All yields reported refer to isolated yields (average of two runs) unless otherwise indicated, and the product purity was estimated to be greater than 95% as determined by ^{1}H NMR. Melting points

were measured on a Fisher-Johns Melting Point Apparatus and uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc. THF was distilled from sodium/benzophenone ketyl. 2,6-Dimethylphenylmagnesium bromide, 2-mesitylmagnesium bromide, 1-phenyl-1-propyne, 3-hexyne, 1,2-dibromethane, anhydrous iron(III) chloride were purchased from Aldrich and used directly. $Pd(OAc)_2$ was a gift from Frontier Scientific, Inc. PPh_3 was purchased from Acros Organics and used directly. Anhydrous copper(II) chloride, Anhydrous copper(II) sulfate, silver carbonate, and Iron(III) chloride were purchased from Stem Chemical Inc. and were used as received. Other chemical reagents were purchased from Alfa Aesar and used without further purification. Bromopentamethylbenzene, pentamethylphenylmagnesium bromide were prepared according to reported methods.[15,16] 2-Bromo-1-ethyl-3-methylbenzene, 2-bromo-1,3-diethyl-benzene and 2-bromo-1-isopropyl-3-methylbenzene were prepared according to literature procedures.[17] 1,2-Bis(4-methoxyphenyl)acetylene and 4-(1-Hexyn-1-yl)methylbenzene was prepared according to reported method.[18]

5.4.2 General Procedures for $Pd(OAc)_2$-Promoted Domino Reaction of Diphenylacetylene with Mesitylmagnesium Bromide

A. In glove box with nitrogen atmosphere, to a mixture of diphenylacetylene (44.5 mg, 0.25 mmol) and 0.5 ml THF (in a schlenk flask) was added palladium acetate (56 mg, 0.25 mmol). After stirred for 5-10 minutes, Grignard reagent (0.65 mL, 1M in THF, 0.65 mmol) was added. The mixture was allowed to stir at room temperature or 60^{o}C (oil bath) or refluxing for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine and the solvent was evaporated under vacuum. The reaction mixtures were analyzed by ^{1}H NMR, from which the reaction conversion and the ratios of cyclization product : cross-coupling product : self-coupling product were be obtained.

B. In glove box with nitrogen atmosphere, to a mixture of diphenylacetylene (44.5 mg, 0.25 mmol) and 0.5 mL THF (in a schlenk flask) was added palladium acetate (56 mg, 0.25 mmol) and PPh_3 (2 equiv., 131 mg, 0.5 mmol, or 4 equiv., 262 mg, 1.0 mmol). After stirred for 5-10 minutes, Grignard reagent (1.0 mL, 1M in THF, 1.0 mmol) was added. The mixture was allowed to stir under room temperature or 60^{o}C (oil bath) or refluxing for 20 hours. After quenched with water, the reaction mixture was

extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine and the solvent was evaporated under vacuum. The reaction mixtures were analyzed by ^{1}H NMR, from which the reaction conversion and the ratios of cyclization product: cross-coupling product : self-coupling product were be obtained.

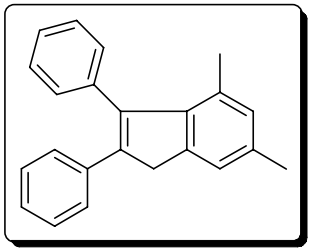
5.4.3 General Procedure of the Oxidant Screening for $Pd(OAc)_2$-Catalyzed Domino Reaction of Diphenylacetylene with Mesitylmagnesium Bromide

In glove box with nitrogen atmosphere, to a mixture of diphenylacetylene (89 mg, 0.5 mmol), oxidant (0.5 mmol) and 0.5 mL THF (in a Schlenk flask) was added palladium acetate (3.4 mg, 0.015 mmol). After stirred for 5-10 minutes, Grignard reagent (1.25 mL, 1M in THF, 1.25 mmol) was added. The mixture was allowed to stir under 60^{o}C (oil bath) for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine and the solvent was evaporated under vacuum. The crude reaction mixtures were analyzed by ^{1}H NMR. Flash chromatography on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) gave the cyclization products.

5.4.4 General Procedure for $Pd(OAc)_2$-Catalyzed Annulative Domino Reaction of Internal Alkynes with Hindered Grignard Reagents

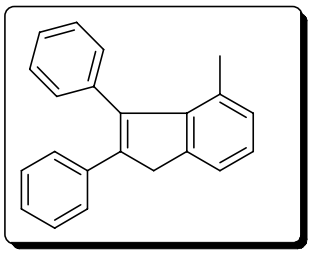
In glove box with nitrogen atmosphere, to a mixture of alkyne (0.5 mmol), 1,2-dibromoethane (0.75 mmol, 65 μl) and 0.5 mL THF (in a schlenk flask) was added palladium acetate (3.4 mg, 0.015 mmol). After stirred for 5-10 minutes, Grignard reagent (1.25 mL, 1M in THF, 1.25 mmol) was added. The mixture was allowed to stir under 60°C (oil bath) for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) gave the cyclization products.

4,6-Dimethyl-2,3-diphenyl-1H-indene (1) white solid. m. p.: 86 - 87°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.403~7.345 (m, 3H), 7.313 (d, *J* = 7.2 Hz, 2H), 7.209 (s, 1H), 7.178 (d, *J* = 8.4 Hz, 2H), 7.139 (t, *J* = 7.2 Hz, 2H), 7.097 (t, *J* = 7.2 Hz, 1H), 6.819 (s, 1H), 3.861 (s, 2H), 2.368 (s, 3H), 1.808 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.118, 141.612, 141.367, 140.054, 139.278, 136.729, 134.756, 131.576, 130.386,

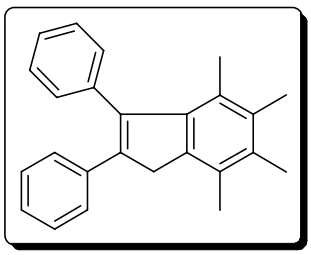


129.620, 128.560, 127.998, 127.851, 127.159, 126.457, 122.188, 40.595, 21.168, 19.834. Anal. calcd. for $C_{23}H_{20}$: C, 93.20%; H, 6.80%. Found: C, 93.00%; H, 6.69%.

4-Methyl-2,3-diphenyl-1H-indene (**2**) light yellow solid. M. p.: 118 - 119°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.412 ~ 7.367 (m, 4H), 7.325 (d, *J* = 7.8 Hz, 2H), 7.194 (d, *J* = 7.8 Hz, 2H), 7.160 (d, *J* = 7.8 Hz, 2H), 7.127 (t, *J* = 7.8 Hz, 2H), 6.992 (d, *J* = 7.8 Hz, 1H), 3.905 (s, 2H), 1.848 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.101, 142.721, 141.478, 141.152, 139.137, 136.584, 131.940, 129.669, 129.553, 128.563, 128.022, 127.969, 127.225, 126.639, 124.933, 121.334, 40.844, 20.012. Anal. calcd. for $C_{22}H_{18}$: C, 93.57%; H, 6.43%. Found: C, 93.35%; H, 6.47%.

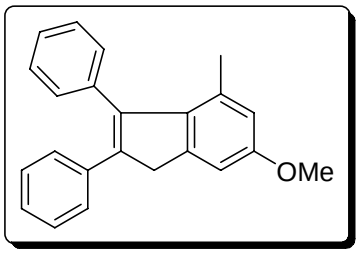


4,5,6,7-Tetramethyl-2,3-diphenyl-1H-indene (**3**) off-white solid. m. p.: 139 - 141°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.383 (t, *J* = 7.2 Hz, 2H), 7.345 (t, *J* = 7.2 Hz, 1H), 7.292 (d, *J* = 7.2 Hz, 1H), 7.160 (d, *J* = 7.8 Hz, 2H), 7.134 (t, *J* = 7.8 Hz, 2H), 7.090 (t, *J* = 7.8 Hz, 1H), 3.795 (s, 2H), 2.377 (s, 3H), 2.299 (s, 3H), 2.194 (s, 3H), 1.795 (s, 3H). ^{13}C

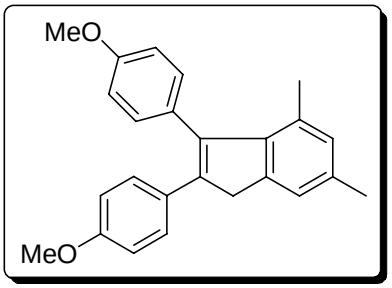


NMR ($CDCl_3$, 150 MHz): δ 142.156, 141.415, 140.474, 139.912, 139.147, 137.132, 134.573, 132.119, 129.676, 128.636, 128.205, 128.026, 127.906, 127.011, 126.319, 40.573, 16.368, 16.227, 16.119, 16.048. Anal. calcd. for $C_{25}H_{24}$: C, 92.54%; H, 7.46%. Found: C, 92.33%; H, 7.45%.

6-Methoxy-4-methyl-2,3-diphenyl-1H-indene (**4**) white solid. m. p.: 108 - 109°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.387 (t, *J* = 7.8 Hz, 2H), 7.361 (t, *J* = 7.2 Hz, 1H), 7.317 (d, *J* = 7.8 Hz, 2H), 7.167~ 7.121 (m, 4H), 7.087 (t, *J* = 7.2 Hz, 1H), 6.980 (d, *J* = 1.8 Hz, 1H), 6.560 (d, *J* = 1.8 Hz, 1H), 3.867 (s, 2H), 3.836 (s, 3H), 1.813 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.782, 144.656, 141.132, 139.239, 138.843, 137.561, 136.743, 132.815, 129.592, 128.585, 127.995, 127.686, 127.177, 126.275, 115.188, 107.412, 55.463, 40.813, 20.069. Anal. calcd. for $C_{23}H_{20}O$: C, 88.43%; H, 6.45%. Found: C, 88.34%; H, 6.34%.

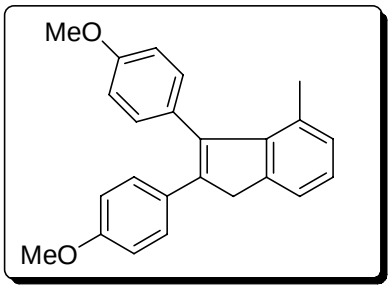


2,3-Bis(4-methoxyphenyl)-4,6-dimethyl-1H-indene (**5**) yellow solid. m. p.: 116-118°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.211 (d, *J* = 9.0 Hz, 2H), 7.179 (s, 1H), 7.139 (d, *J* = 9.0 Hz, 2H), 6.948 (d, *J* = 8.4 Hz, 2H),

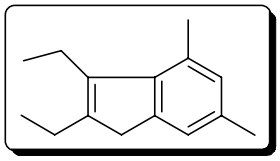


6.802 (s, 1H), 6.703 (d, *J* = 8.4 Hz, 2H), 3.868 (s, 3H), 3.807 (s, 2H), 3.745 (s, 3H), 2.359 (s, 3H), 1.831 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.670, 158.066, 142.778, 142.009, 139.741, 139.422, 134.233, 131.572, 131.182, 130.691, 130.301, 129.497, 128.890, 122.076, 114.012, 113.419, 55.115, 55.068, 40.419, 21.115, 19.875. Anal. calcd. for $C_{25}H_{24}O_2$: C, 84.24%; H, 6.79%. Found: C, 83.89%; H, 6.81%.

2,3-bis(4-methoxyphenyl)-4-methyl-1H-indene (**6**) white solid. m. p.: 131-132°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.354 (d, *J* = 7.8 Hz, 1H), 7.221 (d, *J* = 9.0 Hz, 2H), 7.152 (d, *J* = 8.4 Hz, 2H), 7.089 (t, *J* = 7.8 Hz, 1H), 6.971 (d, *J* = 7.2 Hz, 1H), 6.952 (d, *J* = 9.0 Hz, 2H), 6.710 (d, *J* = 8.4 Hz, 2H), 3.871 (s, 3H), 3.845 (s, 2H), 3.749 (s, 3H), 1.868 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.742, 158.226, 144.545, 142.407, 140.859, 139.577, 131.580, 131.457, 130.766, 129.499, 129.362, 129.049, 124.506, 121.210, 114.041, 113.466, 55.162, 55.113, 40.667, 20.056. Anal. calcd. for $C_{24}H_{22}O_2$: C, 84.18%; H, 6.48%. Found: C, 83.84%; H, 6.38%.

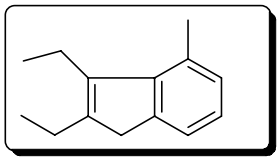


2,3-Diethyl-4,6-dimethyl-1H-indene (**7**) colorless liquid. ^{1}H NMR



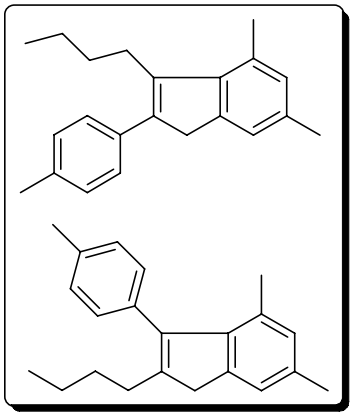
($CDCl_3$, 200 MHz): δ 7.056 (s, 1H), 6.825 (s, 1H), 3.217 (s, 2H), 2.640 (q, *J* = 7.6 Hz, 2H), 2.537 (s, 3H), 2.438 (q, *J* = 7.6 Hz, 2H), 2.320 (s, 3H), 1.130 (t, *J* = 7.6 Hz, 3H), 1.127 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.869, 143.233, 141.288, 139.182, 132.951, 129.939, 129.173, 122.138, 39.376, 21.261, 20.970, 19.889, 19.590, 15.290, 14.644.

2,3-Diethyl-4-methyl-1H-indene (**8**) colorless liquid. ^{1}H NMR ($CDCl_3$,



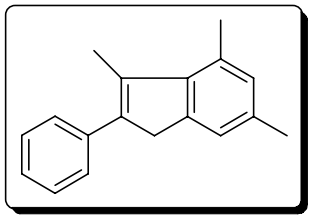
200 MHz): δ 7.230 (t, *J* = 3.6 Hz, 1H), 7.004 (d, *J* = 3.6 Hz, 1H), 7.699 (d, *J* =3.6 Hz, 1H), 3.256 (s, 2H), 2.667 (q, *J* = 7.2 Hz, 2H), 2.582 (s, 3H), 2.462 (q, *J* =7.2 Hz, 2H), 1.144 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.397, 143.993, 143.470, 139.447, 129.575, 129.175, 123.400, 121.185, 39.575, 21.298, 19.901, 19.750, 15.320, 14.625.

3-Butyl-4,6-dimethyl-2-*p*-tolyl-1H-indene/2-butyl-4,6-dimethyl-3-*p*-tolyl-1H-indene (**9**) ^{1}H NMR showed a 91: 9 ratio. Analytic sample of 3-butyl-4,6-dimethyl-2-*p*-tolyl-1H-indene was obtained by recrystalization of



the mixture of 3-butyl-4,6-dimethyl-2-*p*-tolyl-1H-indene and 2-butyl-4,6-dimethyl-3-*p*-tolyl-1H-indene in hexanes. white solid. M. p.: 81-82^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.276 (d, *J* = 7.8 Hz, 2H), 7.204 (d, *J* = 7.8 Hz, 2H), 7.127 (s, 1H), 6.890 (s, 1H), 3.600 (s, 2H), 2.733 (t, *J* = 7.8 Hz, 2H), 2.583 (s, 3H), 2.382 (s, 3H), 2.352 (s, 3H), 1.604 (m, 2H), 1.375 (m, 2H), 0.894 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 144.160, 141.320, 140.432, 140.397, 136.163, 135.401, 133.986, 130.434, 130.300, 128.973, 128.267, 122.222, 41.700, 33.074, 27.482, 22.795, 21.166, 21.051, 19.720, 13.889. The structure of 3-butyl-4,6-dimethyl-2-*p*-tolyl-1H-indene was established by NOE effect: NOE effect observed when irradiated at the peak at δ 3.600 ppm: 7.276 (d, 0.60%), 7.127 (s, 0.65%). Anal. calcd. for $C_{22}H_{26}$: C, 90.98%; H, 9.02%. Found: C, 90.74%; H, 9.05%.

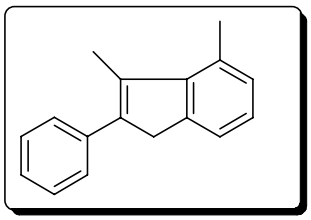
3,4,6-Trimethyl-2-phenyl-1H-indene (**10**) ^{1}H NMR showed a 92: 8 ratio.



Analytic sample of 3,4,6-trimethyl-2-phenyl-1H-indene was obtained by recrystalization of the mixture of 3,4,6-trimethyl-2-phenyl-1H-indene and 2,4,6-trimethyl-3-phenyl-1H-indene in hexanes. White solid. m.p.: 108-

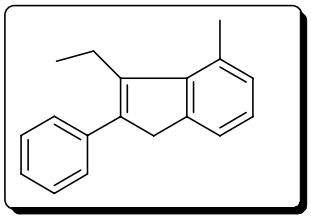
110°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.414 ~ 7.389 (m, 4H), 7.271 (t, *J* = 6.6 Hz, 1H), 7.130 (s, 1H), 6.881 (s, 1H), 3.633 (s, 3H), 2.618 (s, 3H), 2.419 (s, 3H), 2.357 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.6, 142.0, 140.2, 138.0, 136.0, 134.3, 130.9, 130.2, 128.6, 128.2, 126.4, 122.2, 41.2, 21.1, 20.3, 15.6. The structure of 3,4,6-trimethyl-2-phenyl-1H-indene was established by NOE effect: NOE effect observed when irradiated at the peak at δ 3.633 ppm: 7.400~7.390 (m, 0.9%), 7.130 (s, 0.65%).

3,4-Dimethyl-2-phenyl-1H-indene (**11**) ^{1}H NMR showed a 90: 10 ratio.

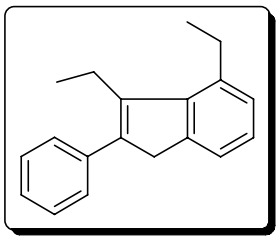


Analytic sample of 3,4-dimethyl-2-phenyl-1H-indene was obtained by recrystallization of the mixture of 3,4-dimethyl-2-phenyl-1H-indene and 2,4-dimethyl-3-phenyl-1H-indene in hexanes. White solid. m.p.: 75-77°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.426 ~ 7.390 (m, 4H), 7.311 (d, *J* = 7.2 Hz, 1H), 7.282 (d, *J* = 7.2 Hz, 1H), 7.093 (t, *J* = 7.2 Hz, 1H), 7.058 (d, *J* = 7.2 Hz, 1H), 3.674 (s, 2H), 2.665 (s, 3H), 2.440 (s, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 144.6, 143.3, 141.3, 137.9, 136.2, 131.3, 129.4, 128.6, 128.3, 126.6, 124.6, 121.4, 41.4, 20.4, 15.6. The structure of 3,4-dimethyl-2-phenyl-1H-indene was established by NOE effect: NOE effect observed when irradiated at the peak at δ 3.674 ppm: 7.421~7.410 (m, 0.8%), 7.311 (d, 0.6%).

3-Ethyl-4-methyl-2-phenyl-1H-indene (12) ^{1}H NMR showed a 89: 11 ratio. Analytic sample of 3-ethyl-4-methyl-2-phenyl-1H-indene was obtained by recrystallization of the mixture of 3-ethyl-4-methyl-2-phenyl-1H-indene and 2-ethyl-4-methyl-3-phenyl-1H-indene in hexanes. White solid. m. p.: 46-47^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.405 ~ 7.397 (m, 4H), 7.316 (d, *J* = 6.6 Hz, 1H), 7.297 (m, 1H), 7.103 (t, *J* = 7.2 Hz, 1H), 7.074 (d, *J* = 7.2 Hz, 1H), 3.659 (s, 2H), 2.789 (q, *J* = 7.2 Hz, 2H), 2.654 (s, 3H), 1.269 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.8, 143.6, 142.4, 141.2, 138.1, 130.8, 129.6, 128.4, 128.3, 126.7, 124.5, 121.4, 41.9, 20.6, 19.8, 15.6.

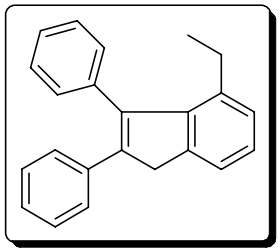


3,4-Diethyl-2-phenyl-1H-indene (13) ^{1}H NMR showed a 85: 15 ratio. Analytic sample of 3,4-diethyl-2-phenyl-1H-indene was obtained by recrystallization of the mixture of 3,4-diethyl-2-phenyl-1H-indene and 2,4-diethyl-3-phenyl-1H-indene in hexanes. white solid. m. p.: 65-66^{o}C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.425 ~ 7.389 (m, 4H), 7.323 (d, *J* = 7.8 Hz, 1H), 7.307 ~ 7.292 (m, 1H), 7.161 (t, *J* = 7.8 Hz, 1H), 7.144 (d, *J* = 7.2 Hz, 1H), 3.661 (s, 2H), 2.977 (q, *J* = 7.8 Hz, 2H), 2.768 (q, *J* = 7.2 Hz,

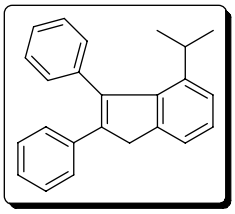


2H), 1.300 (t, *J* = 7.2 Hz, 3H), 1.261(t, *J* = 7.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 144.0, 142.4, 142.1, 141.6, 138.2, 137.7, 128.4, 128.3, 127.8, 126.7, 124.7, 121.3, 42.0, 25.5, 20.6, 17.1, 15.6. The structure of 3,4-diethyl-2-phenyl-1H-indene was established by NOE effect: NOE effect observed when irradiated at the peak at δ 3.661 ppm: 7.412~7.400 (m, 0.6%), 7.323 (d, 0.3%).

4-Ethyl-2,3-diphenyl-1H-indene (**14**) Off-white solid. m. p.: 80-81°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.403 ~ 7.365 (m, 4H), 7.344 (d, *J* = 7.8 Hz, 1H), 7.341 (d, *J* = 7.8 Hz, 1H), 7.181 (t, *J* = 7.2 Hz, 2H), 7.156 ~ 7.140 (m, 3H), 7.130 ~ 7.108 (m, 1H), 7.069 (d, *J* = 7.8 Hz, 1H), 3.902 (s, 2H), 2.216 (q, *J* = 7.2 Hz, 2H), 0.872 (t, *J* = 7.2 Hz, 3H).). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 143.4, 143.0, 141.5, 141.3, 139.2, 138.6, 136.6, 129.5, 128.5, 128.1, 128.0, 127.9, 127.3, 126.6, 125.1, 121.2, 41.0, 25.0, 16.3.



4-Isopropyl-2,3-diphenyl-1H-indene (**15**) white solid. m. p.: 79-80°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.400 ~ 7.358 (m, 4H), 7.337 ~ 7.323 (m, 2H), 7.238 ~ 7.221 (m, 2H), 7.144 ~ 7.137 (m, 4H), 7.120 ~ 7.097 (m, 1H), 3.895 (s, 2H), 2.739 (m, *J* = 6.6 Hz, 1H), 0.961 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR

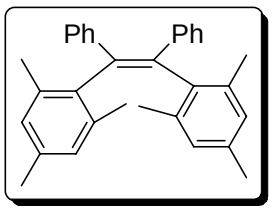


($CDCl_3$, 150 MHz): δ 143.7, 142.9, 142.8, 141.6, 141.3, 139.5, 136.7, 129.3, 128.6, 128.1, 127.9, 127.3, 126.6, 125.3, 124.2, 121.1, 41.0, 26.8, 24.1.

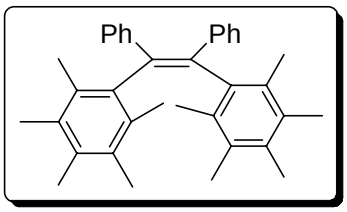
5.4.5 General Procedure for $Pd(OAc)_2$-Catalyzed Domino Carbopalladation-Cross-Coupling Reactions of Internal Alkynes with Hindered Grignard Reagents

In glove box with nitrogen atmosphere, to a mixture of alkyne (0.5 mmol), 1,2-dibromoethane (1.5 mmol, 130 μl and 0.5 mL THF (in a schlenk flask) was added palladium acetate (3.4 mg, 0.015 mmol) and PPh_3 (26.2 mg, 0.1 mmol). After stirred for 5-10 minutes, Grignard reagent (2.0 mL, 1M in THF, 2.0 mmol) was added. The mixture was allowed to stir under refluxing for 20 hours. After quenched with water, the reaction mixture was extracted with ethyl acetate (15 mL x 3). The organic layer was washed with brine and the solvent was evaporated under vacuum. Flash chromatography on silica gel (hexane: ethyl acetate = 100: 0 to 90: 10) gave the cross-coupling products.

1,2-Bis(2,4,6-trimethylphenyl)stilbene (16) white solid. m. p.: 177-178.5°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.047~ 7.025 (m, 6H), 6.928~ 6.911 (m, 4H), 6.641 (s, 4H), 2.167 (s, 6H), 2.052 (s, 12H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 142.812, 140.323, 138.228, 136.729, 135.893, 131.150, 128.595, 127.152, 125.828, 21.722, 20.890. Anal. calcd. for $C_{32}H_{32}$: C, 92.26%; H, 7.74%. Found: C, 92.22%; H, 7.78%.

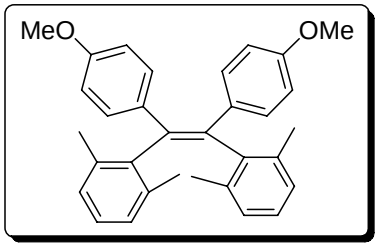


1,2-Bis(pentamethylphenyl)stilbene (17)[19] white solid. m.p.: 252-254°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.057~ 7.027 (m, 6H), 7.000~ 6.987 (m, 4H), 2.110 (s, 12H), 2.105 (s, 6H), 2.009 (s, 12H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.304, 141.545, 138.971, 132.803, 131.806, 131.761, 130.929, 127.176, 125.656, 20.026, 16.631, 16.413.



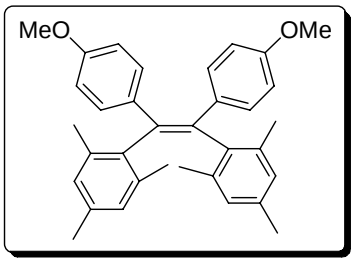
1,2-Bis(2,6-dimethylphenyl)-1,2-bis(4-methoxyphenyl)ethylene (18)

white solid. m. p.: 204 - 206°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.918 (t, *J* = 7.2 Hz, 2H), 6.873 (d, *J* = 9.0 Hz, 4H), 6.800 (d, *J* = 7.2 Hz, 4H), 6.621 (d, *J* = 9.0 Hz, 4H), 3.748 (s, 6H), 2.080 (s, 12H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 157.589, 141.201, 138.863,



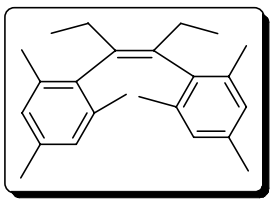
136.904, 135.054, 132.133, 127.587, 126.457, 112.713, 55.076, 21.782. Anal. calcd. for $C_{32}H_{32}O_2$: C, 85.68%; H, 7.19%. Found: C, 85.38%; H, 7.16%.

1,2-Bis(2,4,6-trimethylphenyl)-1,2-bis(4-methoxyphenyl)ethylene (**19**)

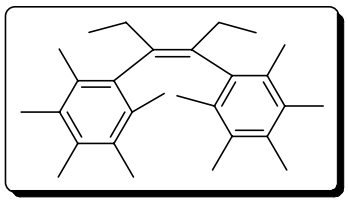


white solid. M. p.: 195.5-196.5°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.838 (d, J = 9.0 Hz, 4H), 6.627 (s, 4H), 6.598 (d, J = 9.0 Hz, 4H), 3.737 (s, 6H), 2.161 (s, 6H), 2.029 (s, 12H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 157.434, 138.892, 138.573, 136.715, 135.646, 135.585, 132.165, 128.540, 112.645, 55.079, 21.711, 20.900. Anal. calcd. for $C_{34}H_{36}O_2$: C, 85.67%; H, 7.61%. Found: C, 85.79%; H, 7.64%.

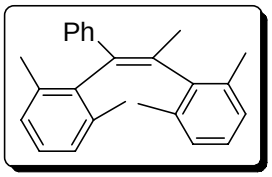
3,4-Bis(2,4,6-trimethylphenyl)hex-3-ene (**20**) white solid. m. p.: 165-166°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.648 (s, 4H), 2.472 (q, J = 7.2 Hz, 4H), 2.154 (s, 6H), 2.064 (s, 12H), 1.016 (t, J = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 138.615, 138.471, 135.697, 134,880, 128.083, 28.228, 20.926, 20.803, 13.382.



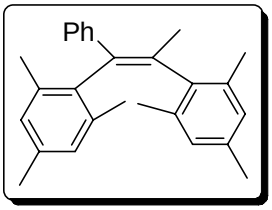
3,4-Bis(pentamethylphenyl)hex-3-ene (21) white solid. m. p.: 175-177°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 2.498 (q, *J* = 7.2 Hz, 4H), 2.112 (s, 6H), 2.025 (s, 12H), 2.004 (s, 12H), 1.059 (t, *J* = 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 139.449, 139.330, 131.965, 131.600, 131.112, 29.343, 19.647, 16.544, 16.442, 13.272.



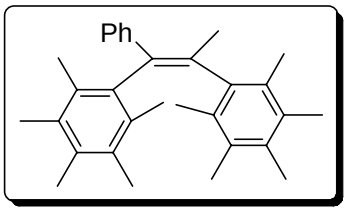
1,2-Bis(2,6-dimethylphenyl)phenylprop-1-ene (22) white solid. m.p.: 120- 121°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.295 (d, *J* = 4.2 Hz, 4H), 7.192 (q, *J* = 4.2 Hz, 1H), 6.929 (t, *J* = 7.8 Hz, 1H), 6.890 (t, *J* = 7.8 Hz, 1H), 6.852 (d, *J* = 7.8 Hz, 2H), 6.774 (d, *J* = 7.8 Hz, 2H), 2.216 (s, 3H), 2.202 (s, 6H), 2.084 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 141.991, 141.966, 140.920, 137.862, 136.641, 135.777, 135.257, 130.090, 127.404, 127.383, 127.355, 126.316, 126.102, 126.032, 22.750, 21.778, 21.068. The stereochemistry of 1,2-bis(dimethylphenyl)prop-1-ene was established by NOE effect: NOE effect observed when irradiated at the peak at δ 2.084 ppm: 7.295 (d, 0.33%), 6.774 (d, 0.32%), 2.202 (s, 0.75%). Anal. calcd. for $C_{25}H_{26}$: C, 91.97%; H, 8.03%. Found: C, 91.41%; H, 7.94%.



1,2-Bis(2,4,6-trimethylphenyl)phenylprop-1-ene (**23**) white solid. m. p.: 133- 135°C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.275~ 7.259 (m, 4H), 7.181~ 7.153 (m, 1H), 6.682 (s, 2H), 6.598 (s, 2H), 2.173 (s, 3H), 2.165 (s, 3H), 2.162 (s, 6H), 2.132 (s, 3H), 2.041 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 142.475, 139.287, 138.273, 137.883, 136.416, 135.686, 135.454, 135.296, 135.106, 130.086, 128.320, 128.306, 127.292, 125.842, 23.020, 21.697, 20.988, 20.837, 20.819. Anal. calcd. for $C_{27}H_{30}$: C, 91.47%; H, 8.53%. Found: C, 91.58%; H, 8.52%.



1,2-Bis(pentamethylphenyl)phenylprop-1-ene (**24**) white solid. m. p.: 177-179 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.329 (d, *J* = 7.2 Hz, 2H), 7.275 (t, *J* = 7.2 Hz, 2H), 7.156 (t, *J* = 7.2 Hz, 1H), 2.219 (s, 3H), 2.123(s, 6H), 2.118 (s, 3H), 2.085 (s, 3H), 2.073 (s, 6H), 2.053 (s, 6H), 1.996 (s, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 143.063, 140.114, 138.966, 138.927, 137.112, 132.447, 132.362, 131.962, 131.716, 131.615, 130.375, 129.933, 127.307, 125.598, 24.145, 20.062, 19.641, 16.611, 16.513, 16.453, 16.380. The stereochemistry of 1,2-bis(pentamethylphenyl)prop-1-ene was established



by NOE effect: NOE effect observed when irradiated at the peak at δ 2.219 ppm: 7.329 (d, 0.7%), 2.123 (s, 1.0%).

Notes and Reference:

1) This chapter is mainly based on the paper published:

Dong, C.-G.; Yeung, P.; Hu, Q.-S. *Org. Lett.* **2007**, *9*, 363-366.

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3) For examples: (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893-2901. (b) Ney, J. E.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 8644-8651.

4) (a) Dong, C.-G.; Hu, Q. –S. *Org. Lett.* **2006**, *8*, 5057-5060. (b) Dong, C.-G.; Hu, Q. –S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289-2292.

5) Recent reviews for carbopalladation of alkynes: (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285-2310. (b) de Meijere, A.; von Zezschwitz, P.; Brase, S. *Acc. Chem. Res.* **2005**, *38,* 413-422.

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8) (a) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205-1222. (b) Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, *13*, 2397-2399. and references therein. (c) Barbera, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296-299.

9) Substituted indenes were typically prepared in more than one step. For recent examples of one-pot access to substituted indenes with different substitution patterns: From 2-(2-(1-alkynyl)phenyl)malonates or 2-(2-halophenyl)malonate: (a) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* ***2006,*** *71,* 3325 -3327. (b) Zhang, D.; Yum, E. K.; Liu, Z.; Larock, R. C. *Org. Lett.* **2005**, *7,* 4963-4966. Also see: (c) Kuninobu, Y.; Nishina, Y.; Takai, K. *Org. Lett.* **2006,** *8,* 2891-2893. (d) Nakamura, I.; Bajracharya, G. B.; Wu, H.; Oishi, K.; Mizushima, Y.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 15423-15430.

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11) The most efficient preparation methods reported so far involve the use of 1,2-dibromoalkenes with hindered Grignard reagents: (a) Rathore,

R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832-14833. For other methods: (b) Maeda, K.; Okamoto, Y.; Morlender, N.; Haddad, N.; Eventova, I.; Biali,S. E.; Rappoport Z. *J. Am. Chem. Soc.* **1995**, *117*, 9686 – 9689. (c) Bottino, F. A.; Finocchiaro, P.; Libertini, E.; Reale, A.; Recca, A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 77-81.

12) A similar regioselectivity trend was observed in Pd-catalyzed three-component reactions of aryl iodides, internal alkynes and arylboronic acids: Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765-3777.

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14) The most efficient preparation methods reported so far involve the use of 1,2-dibromoalkenes with hindered Grignard reagents: (a) Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832-14833. For other methods: (b) Maeda, K.; Okamoto, Y.; Morlender, N.;Haddad, N.; Eventova, I.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.***1995**, *117*, 9686-9689. (c) Bottino, F. A.; Finocchiaro, P.; Libertini, E.;Reale, A.; Recca, A. *J. Chem. Soc., Perkin Trans. 2* **1982**, 77-81.

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APPENDIX ONE: Spectra Relevant to Chapter One

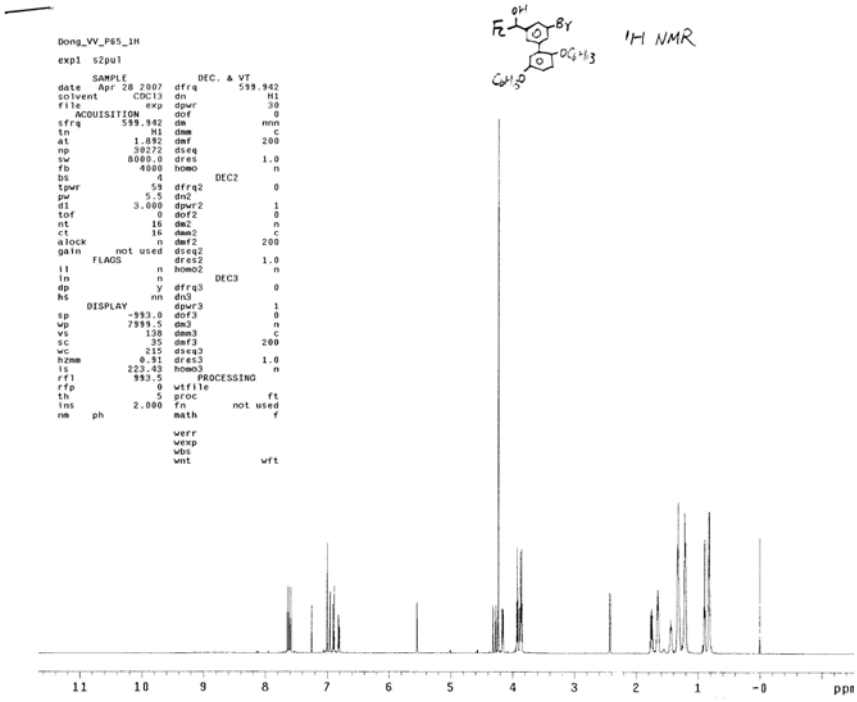

Figure A.1.1 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 21

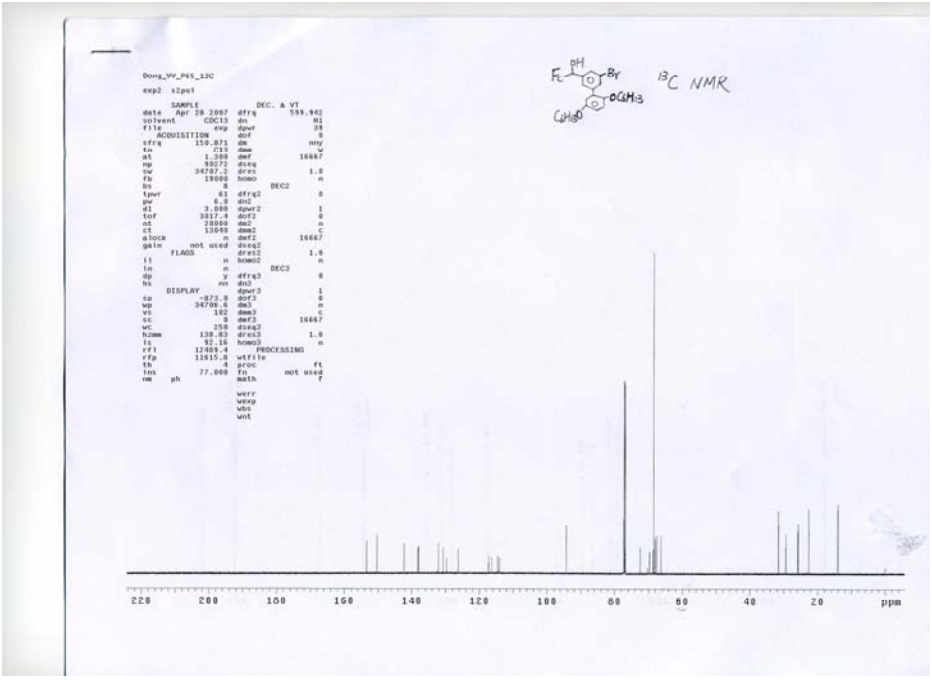

Figure A.1.2 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 21

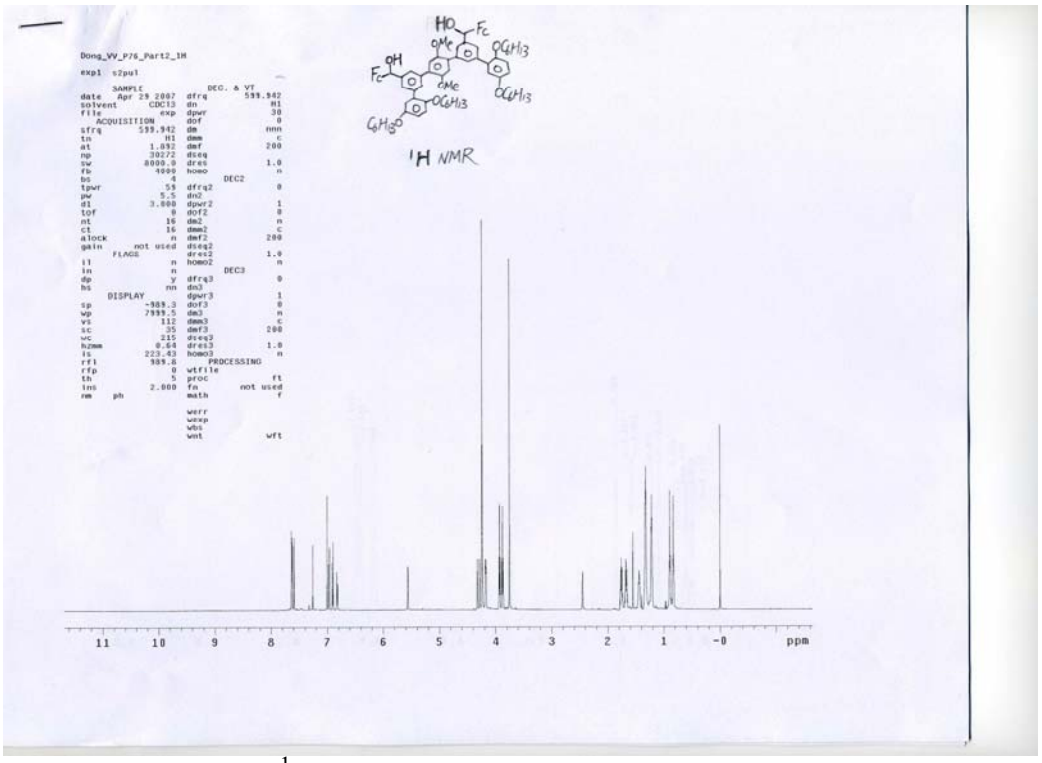

Figure A.1.3 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 22a

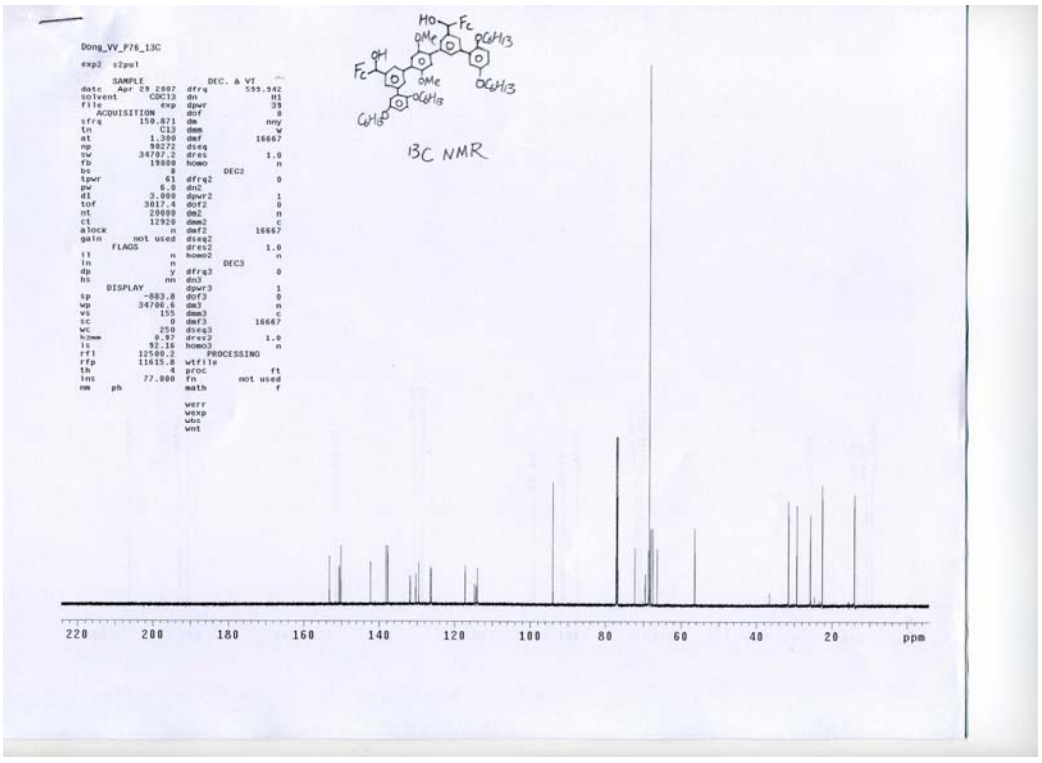

Figure A.1.4 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 22a

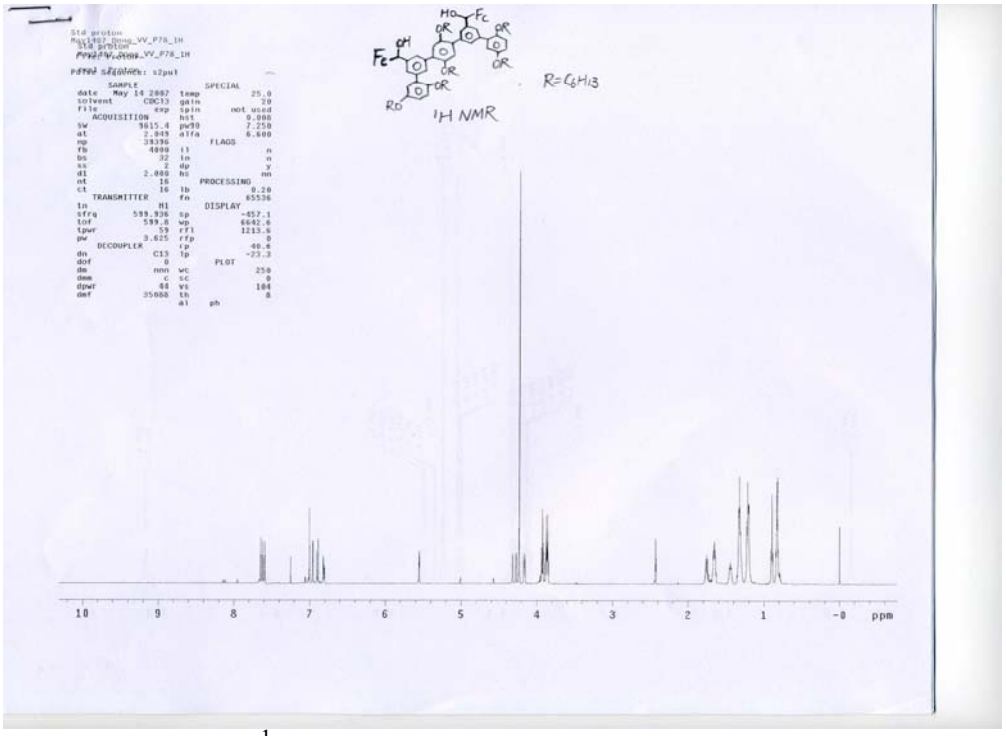

Figure A.1.5 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 22b

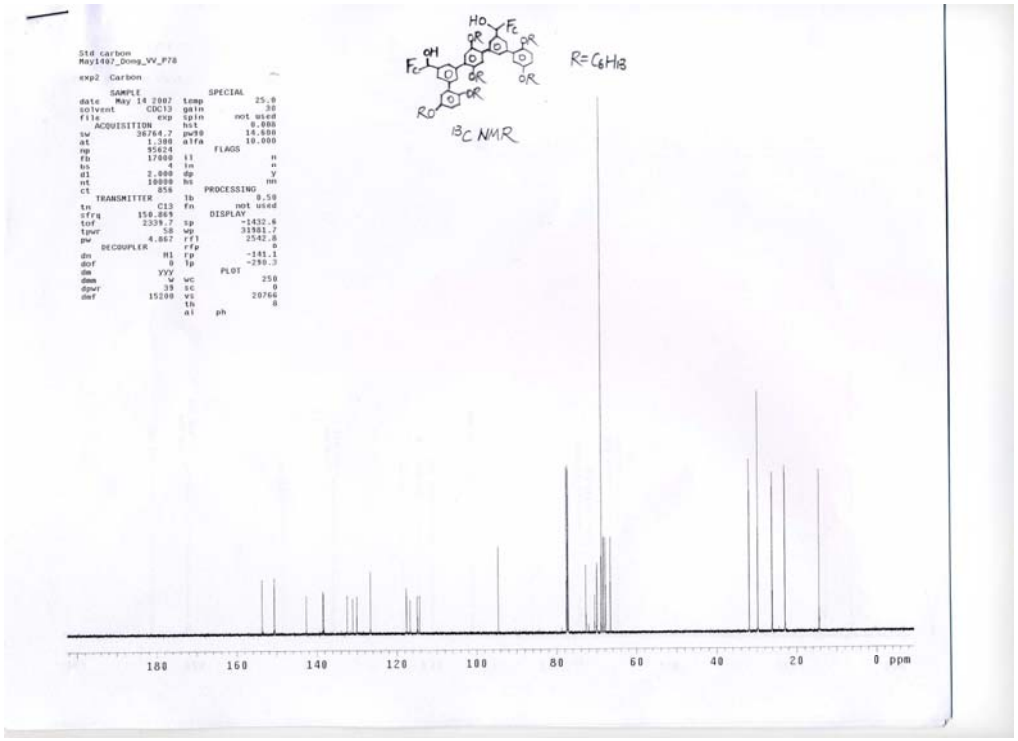

Figure A.1.6 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 22b

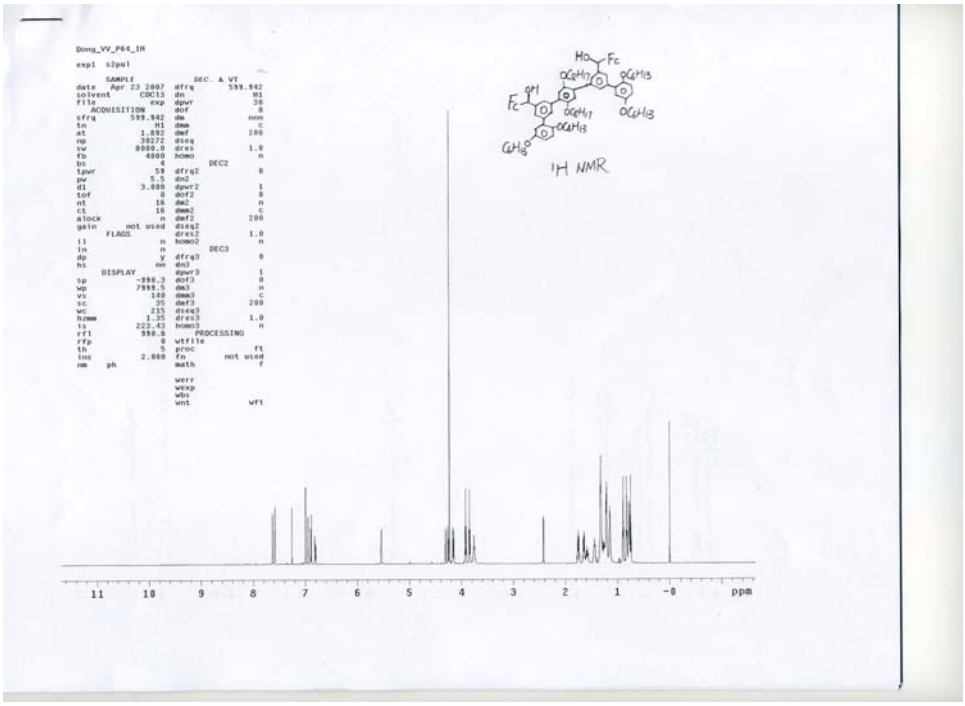

Figure A.1.7 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 22c

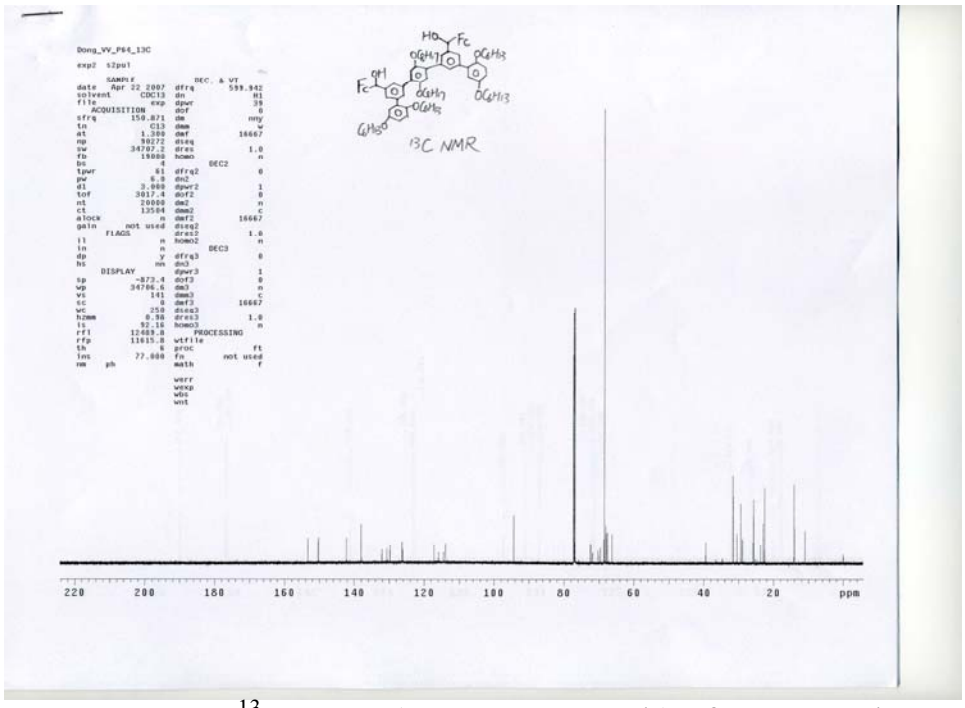

Figure A.1.8 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 22c

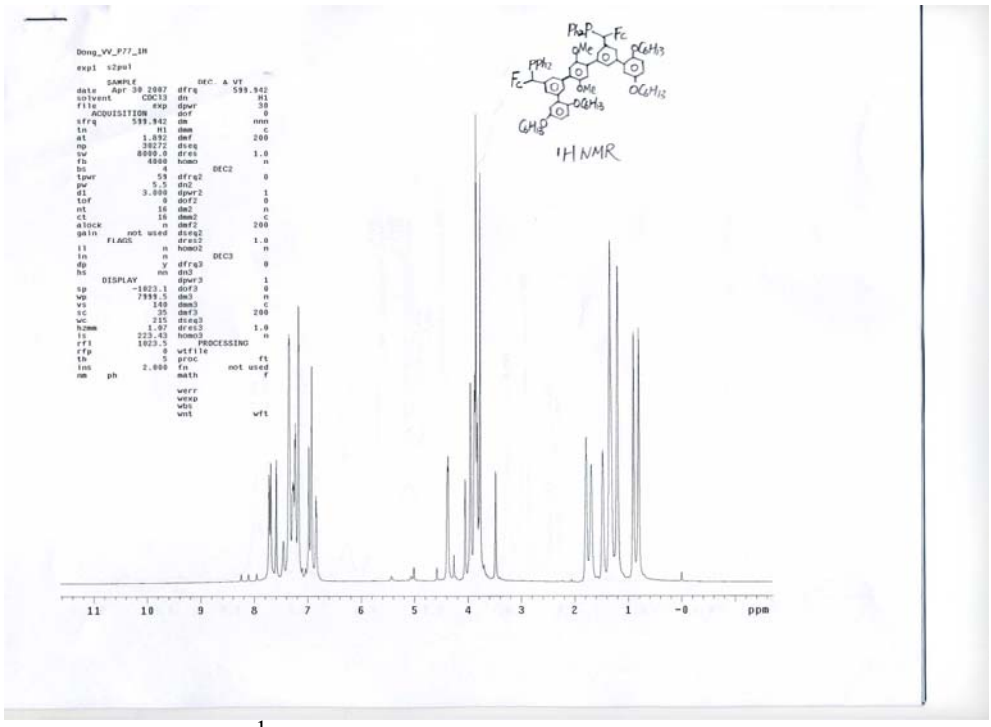

Figure A.1.9 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 17a

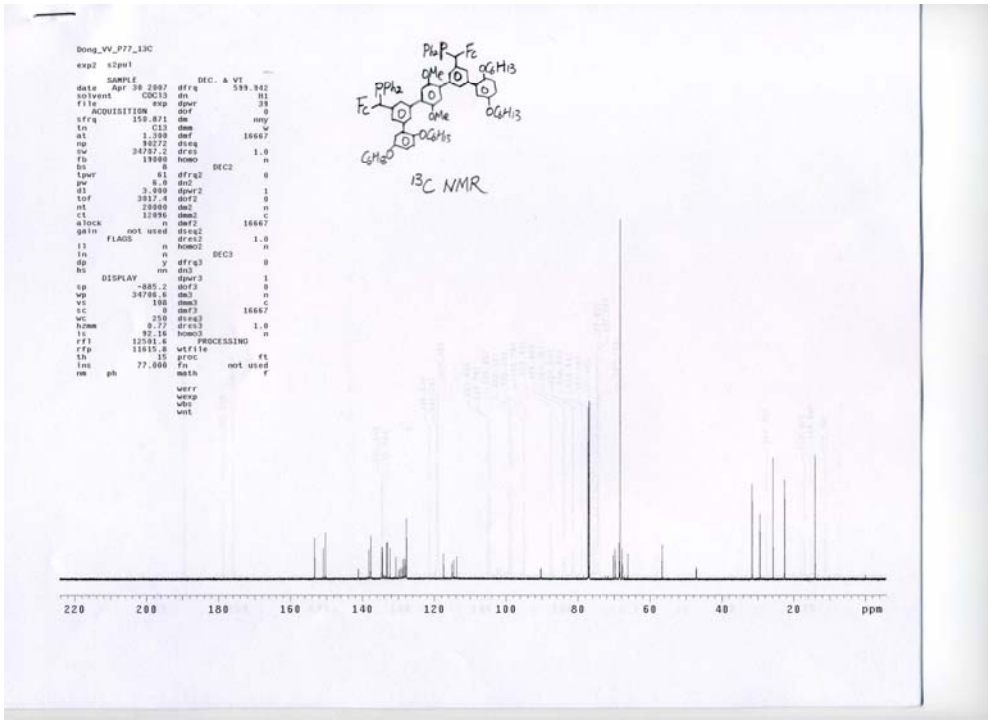

Figure A.1.10 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 17a

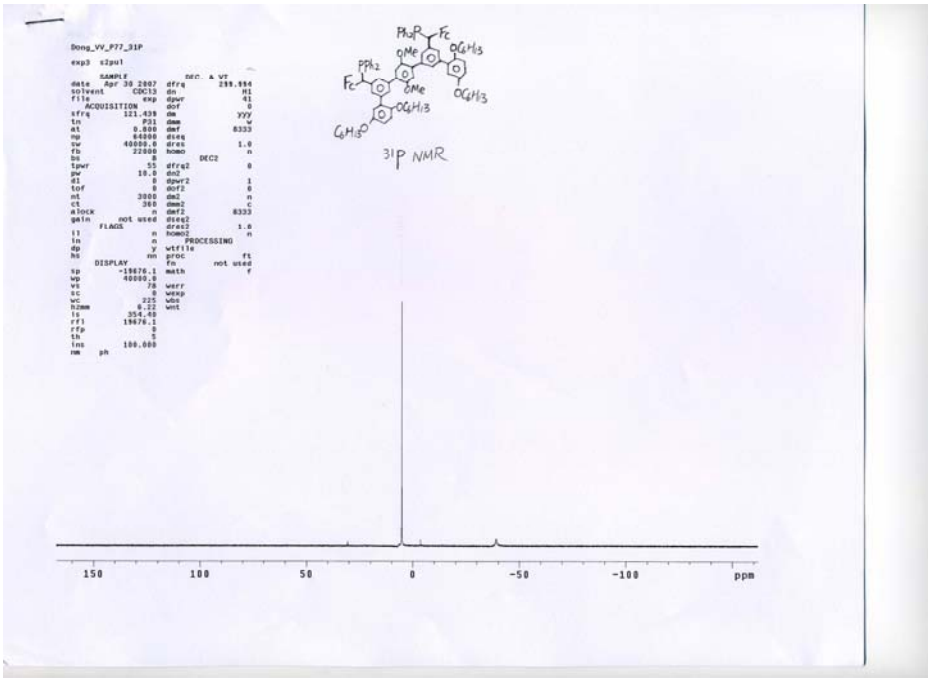

Figure A.1.11 ^{31}P NMR (121 MHz, $CDCl_3$) of compound 17a

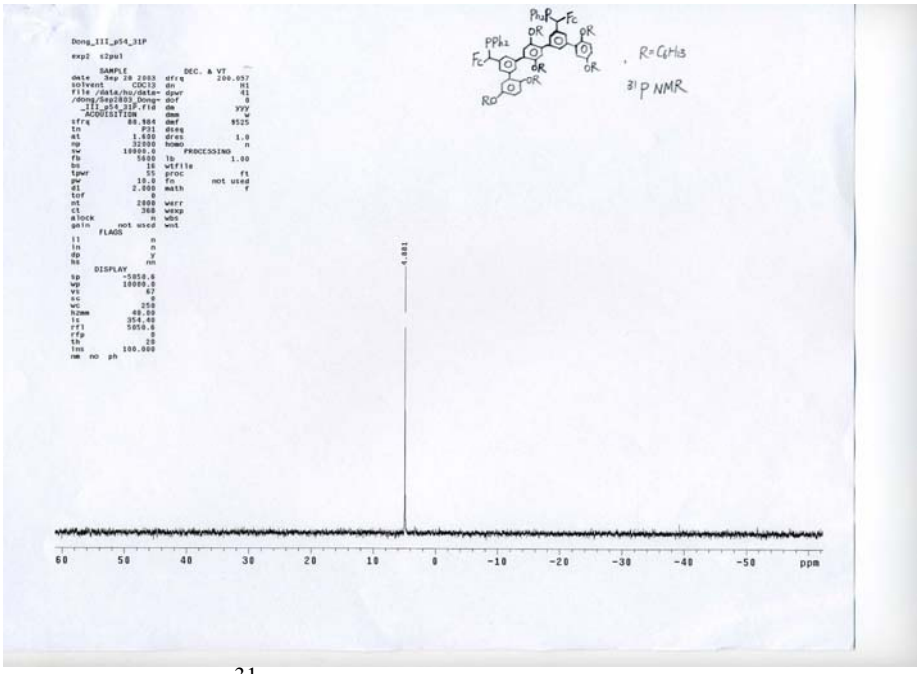

Figure A.1.12 ^{31}P NMR (81 MHz, $CDCl_3$) of compound 17b

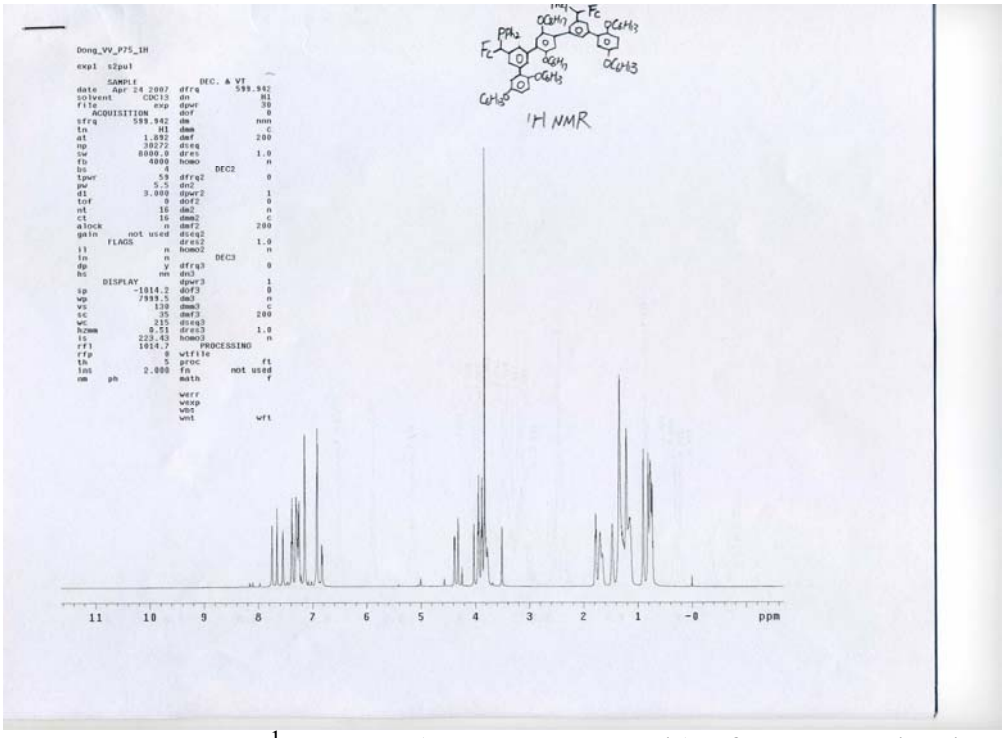

Figure A.1.13 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 17b

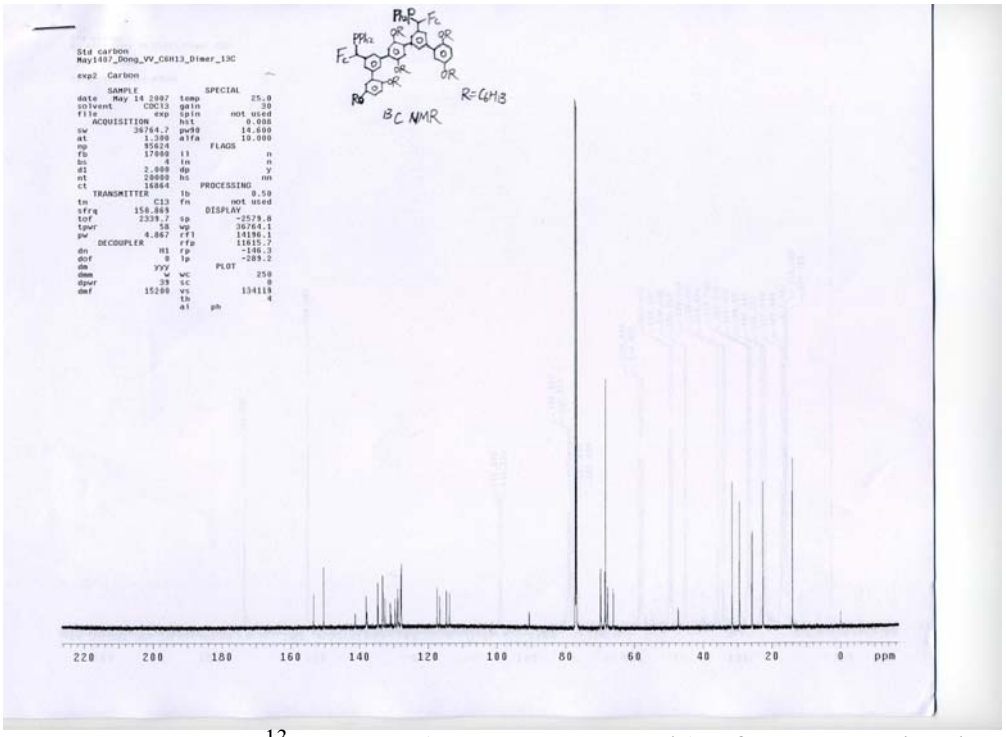

Figure A.1.14 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 17b

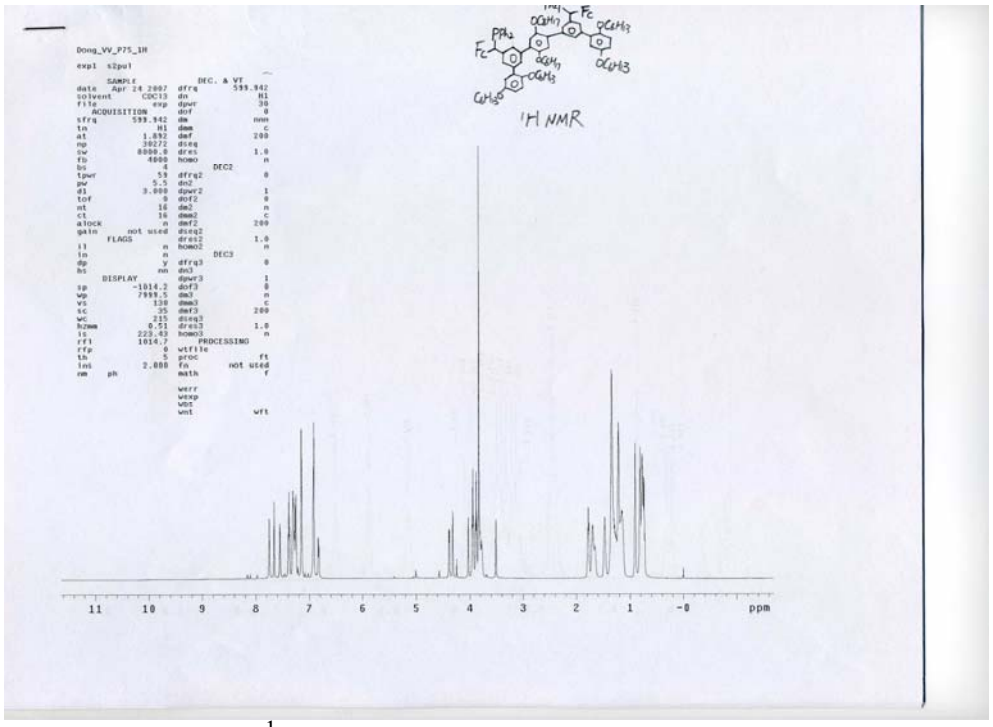

Figure A.1.15 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 17c

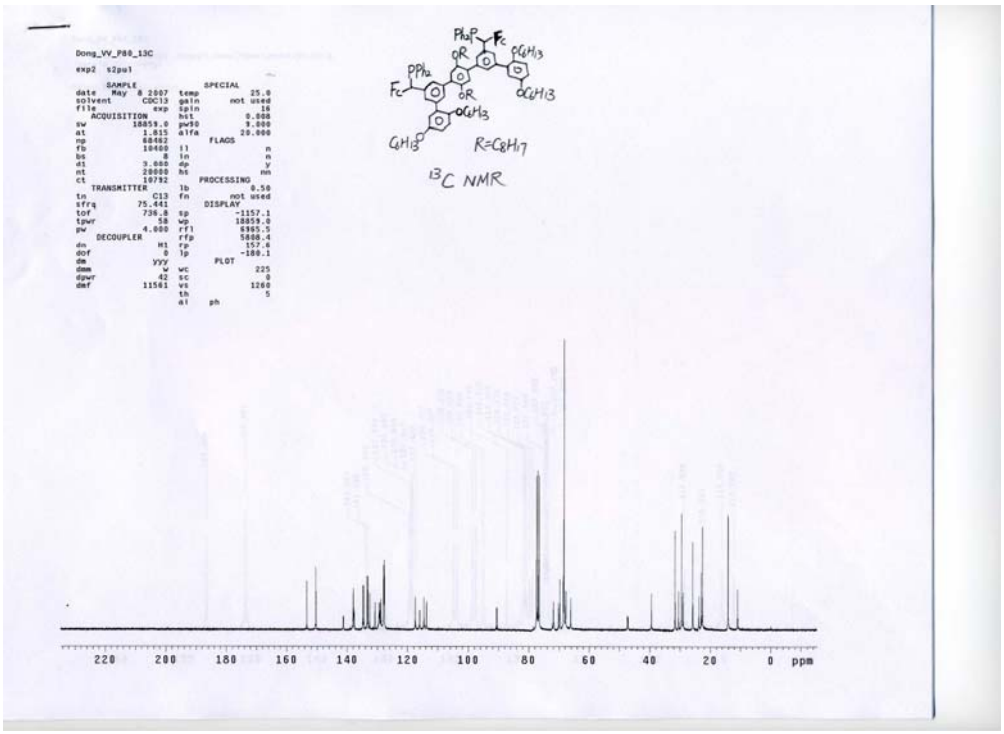

Figure A.1.16 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 17c

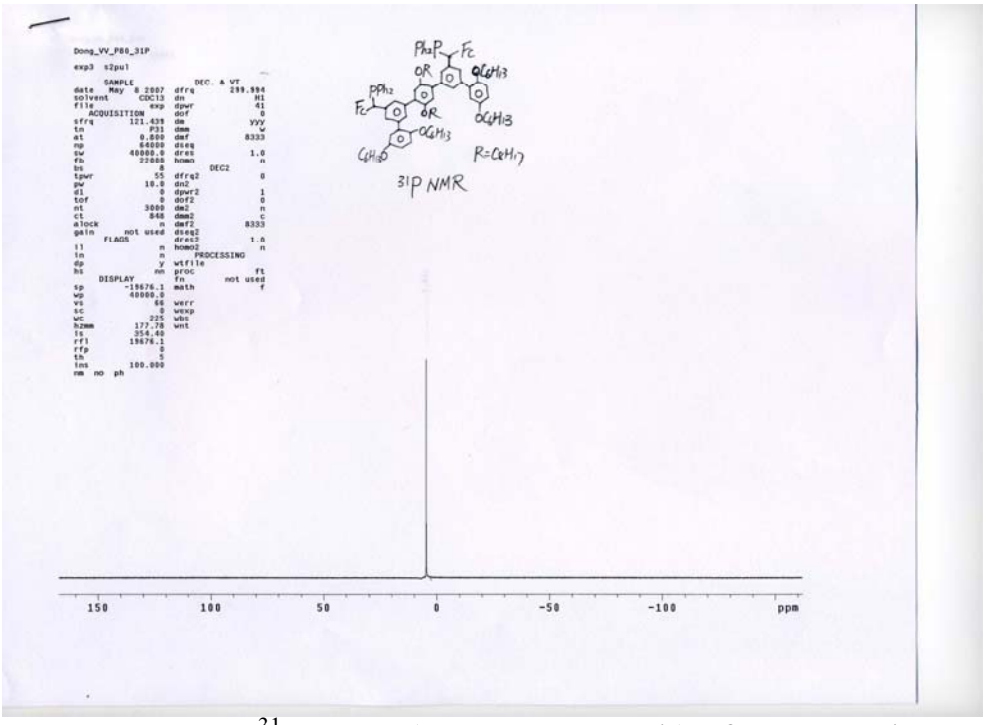

Figure A.1.17 ^{31}P NMR (121 MHz, $CDCl_3$) of compound 17c

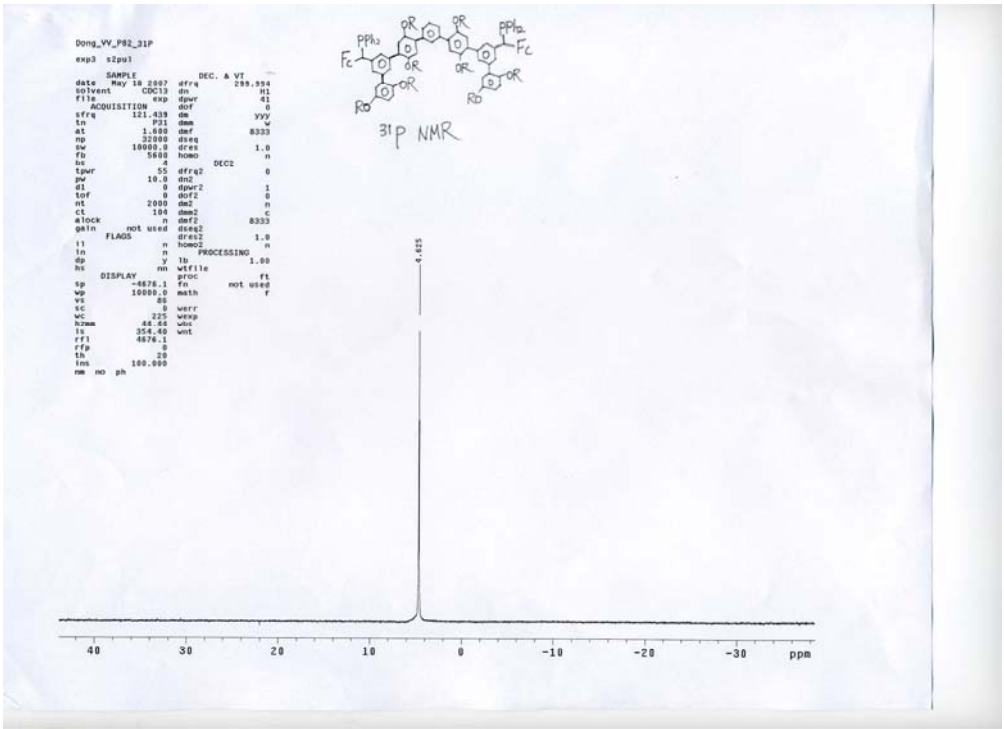

Figure A.1.18 ^{31}P NMR (121 MHz, $CDCl_3$) of compound 18

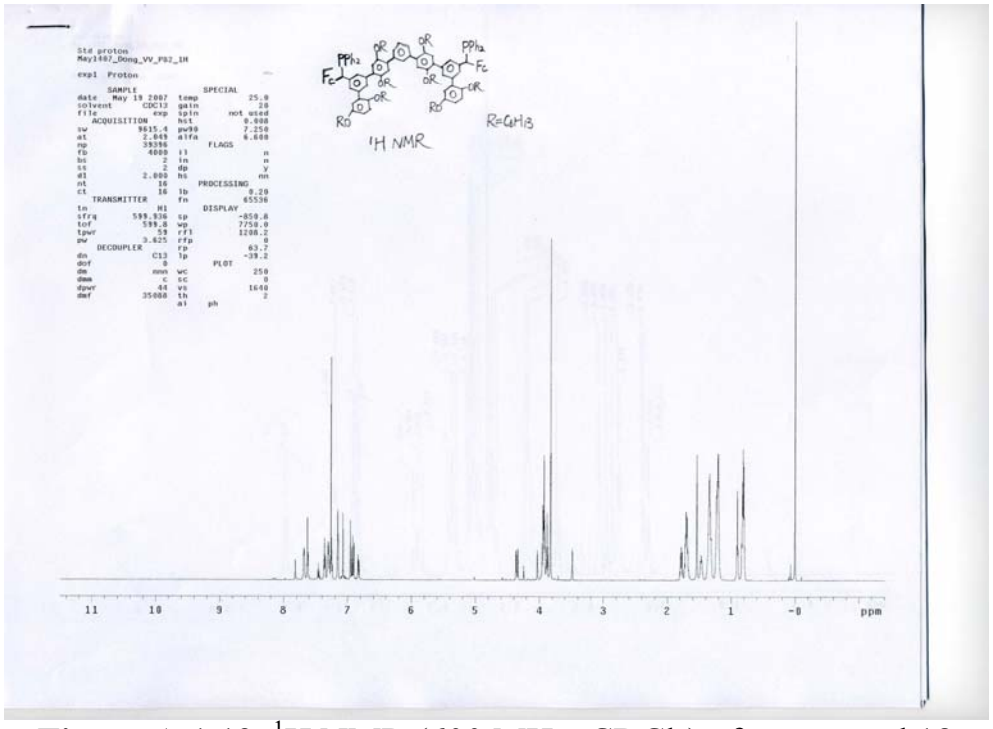

Figure A.1.19 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 18

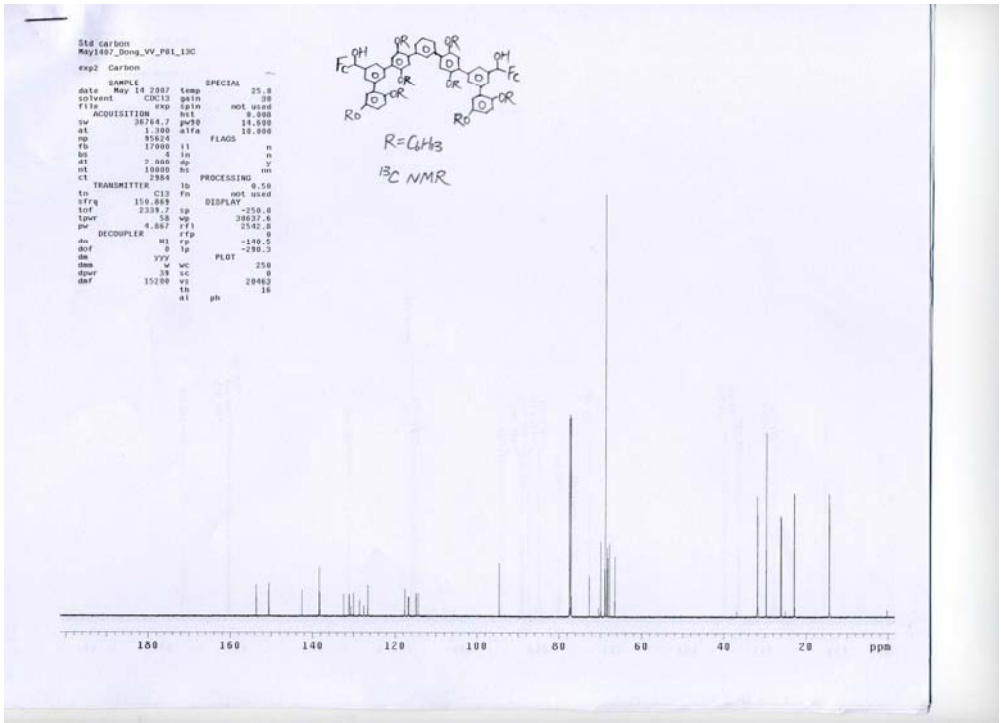

Figure A.1.20 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 18

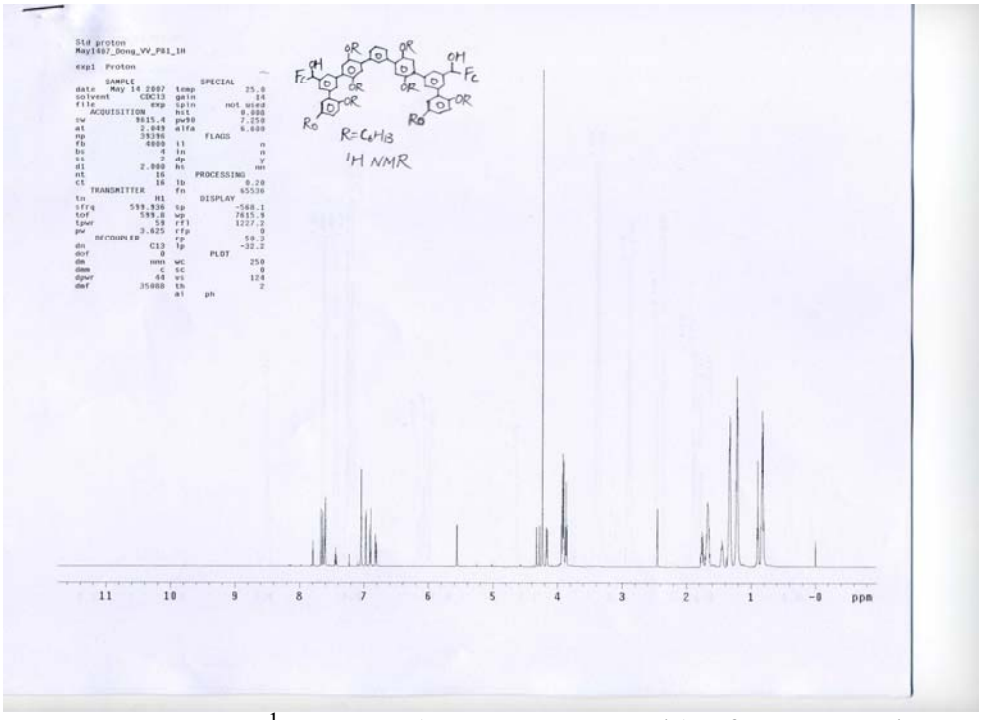

Figure A.1.21 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 26

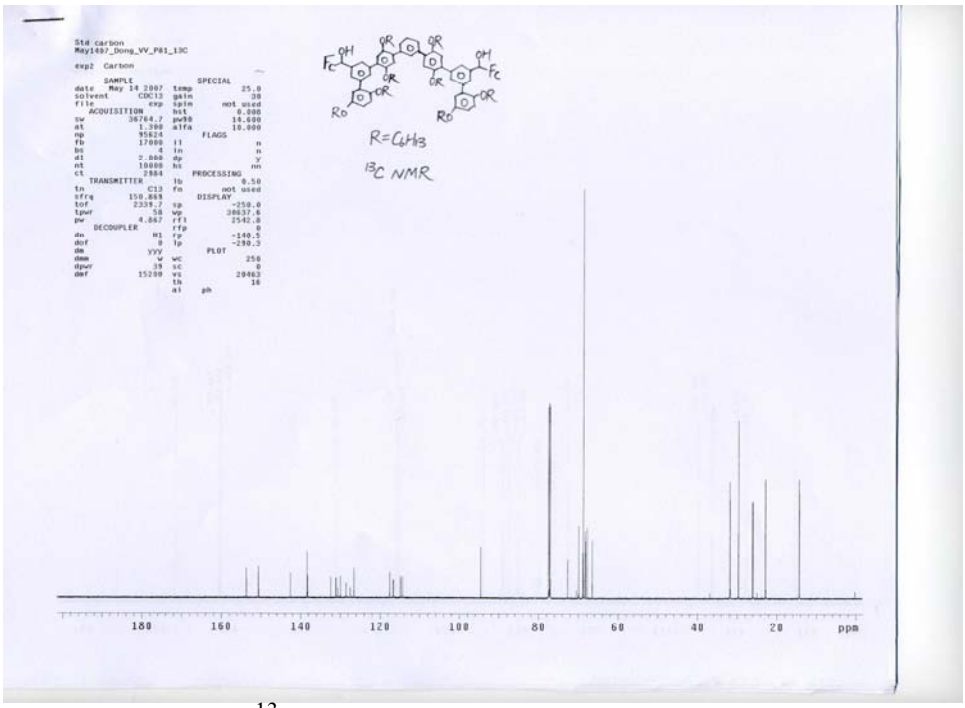

Figure A.1.22 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 26

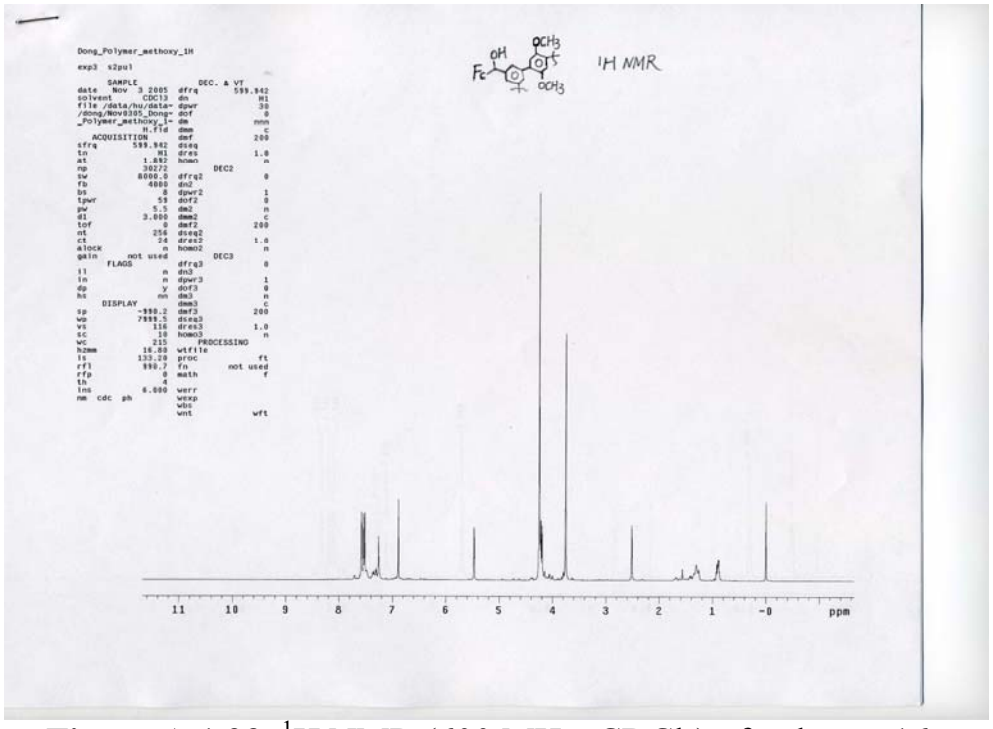

Figure A.1.23 ^{1}H NMR (600 MHz, $CDCl_3$) of polymer 16a

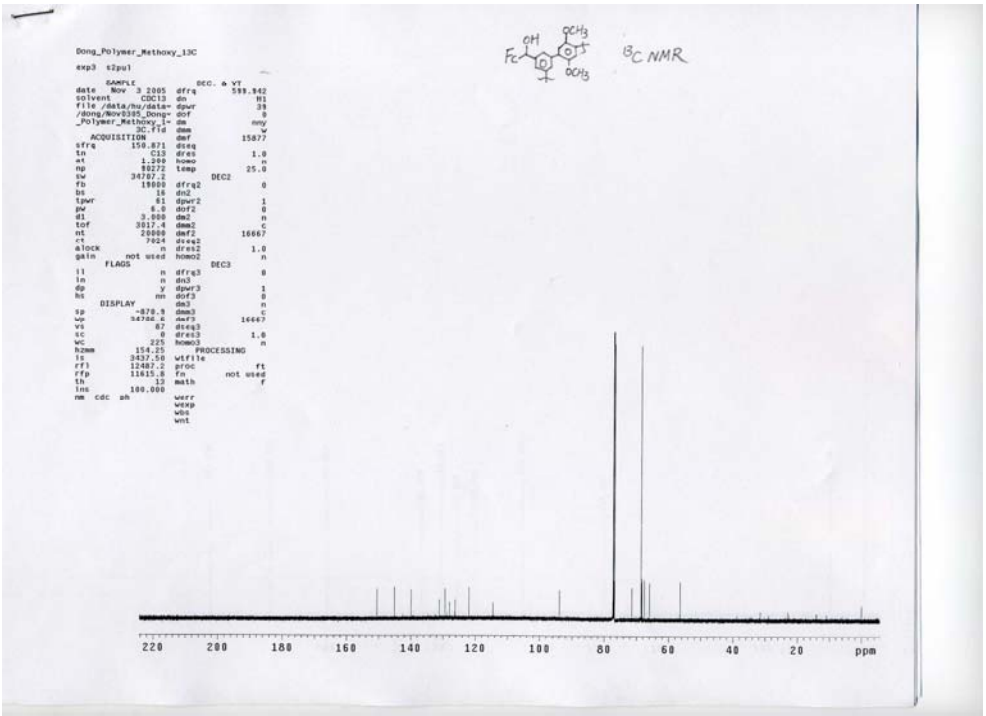

Figure A.1.24 ^{13}C NMR (150 MHz, $CDCl_3$) of polymer 16a

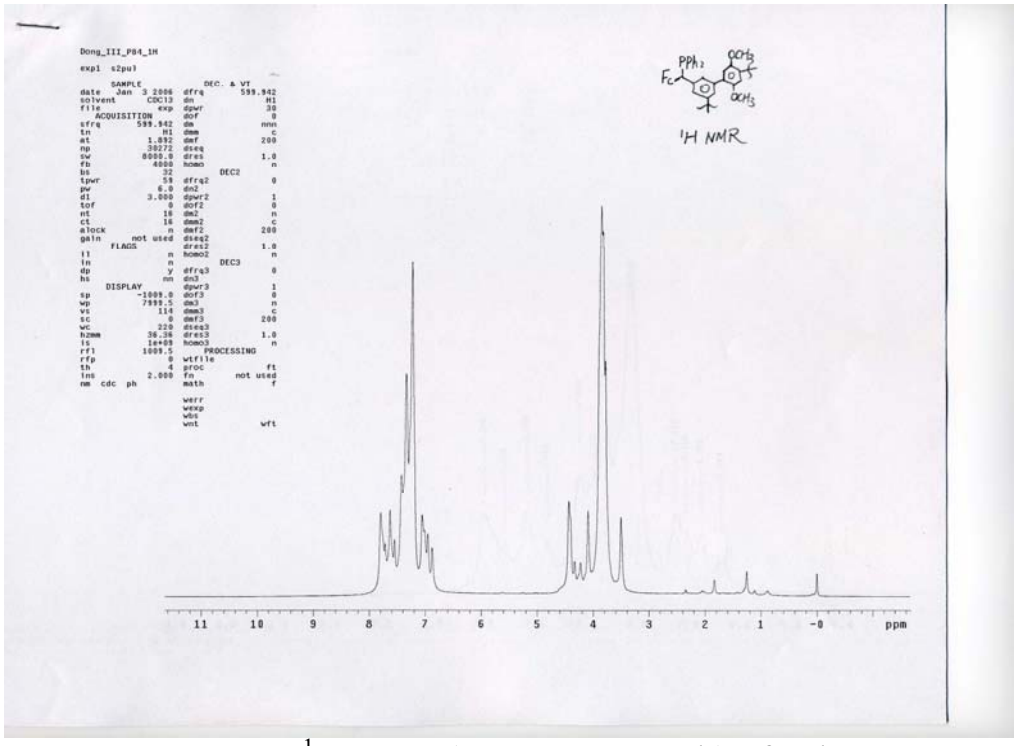

Figure A.1.25 ^{1}H NMR (600 MHz, $CDCl_3$) of polymer 12

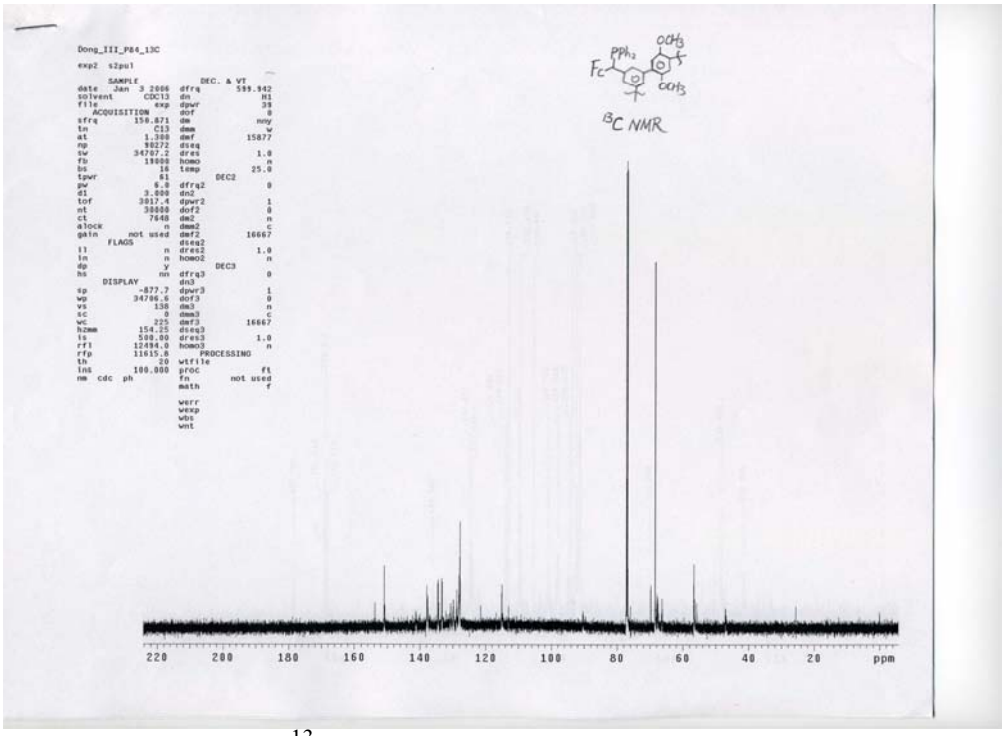

Figure A.1.26 ^{13}C NMR (150 MHz, $CDCl_3$) of polymer 12

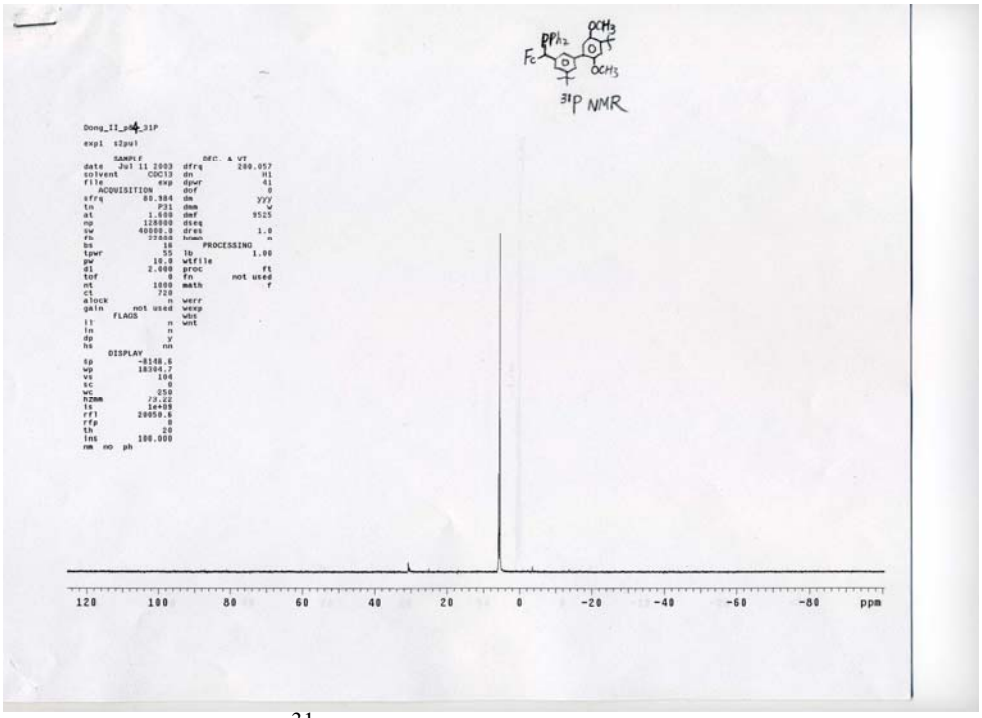

Figure A.1.27 ^{31}P NMR (81 MHz, $CDCl_3$) of polymer 12

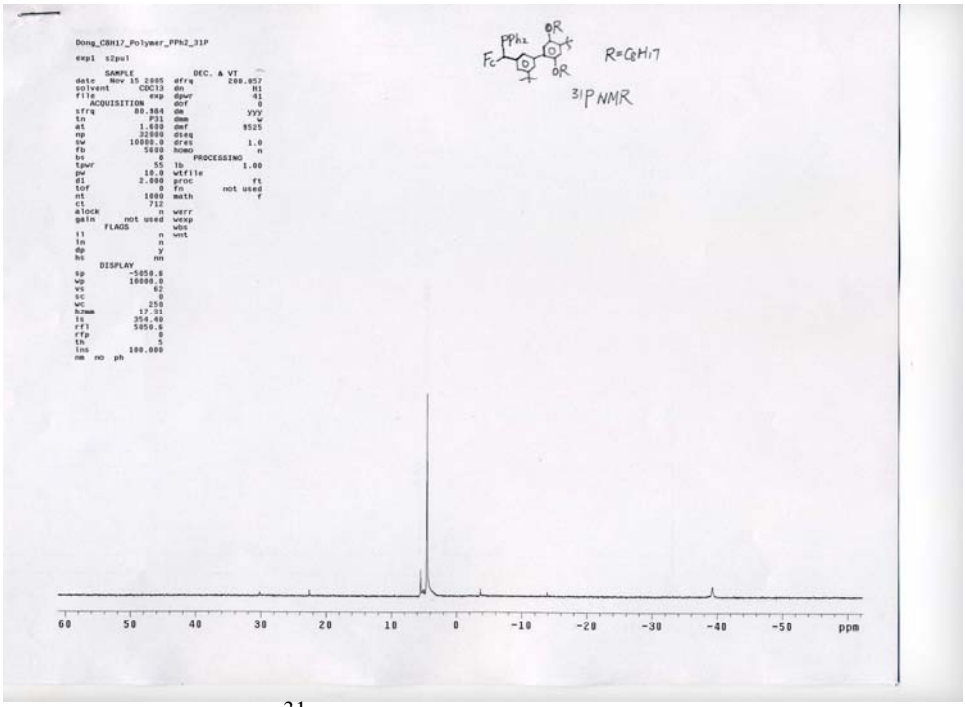

Figure A.1.28 ^{31}P NMR (81 MHz, $CDCl_3$) of polymer 13

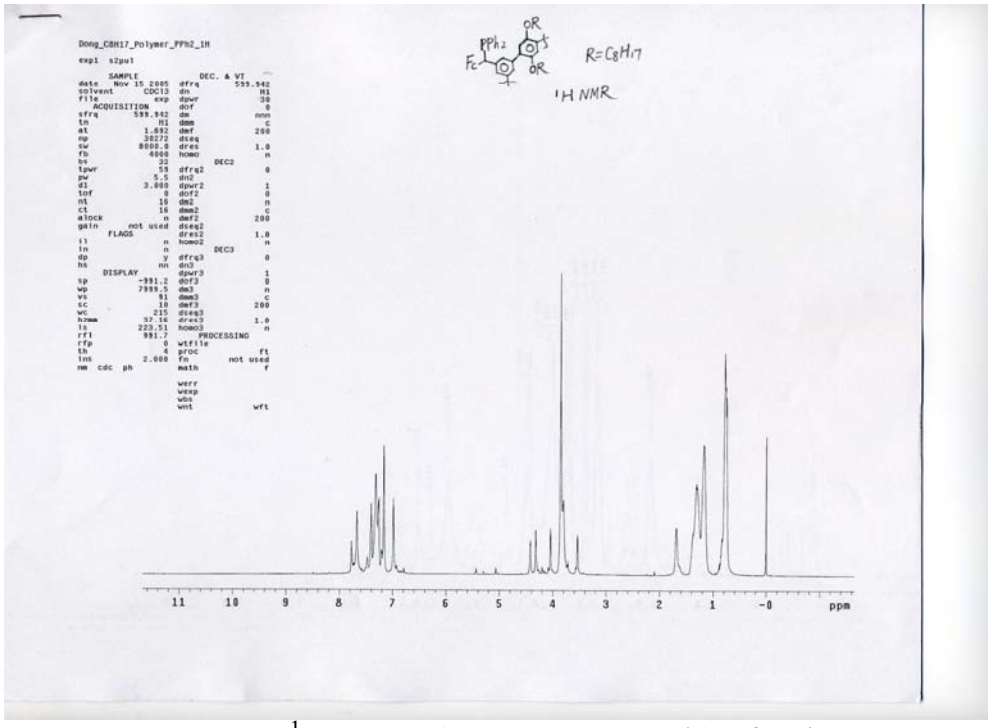

Figure A.1.29 ^{1}H NMR (200 MHz, $CDCl_3$) of polymer 13

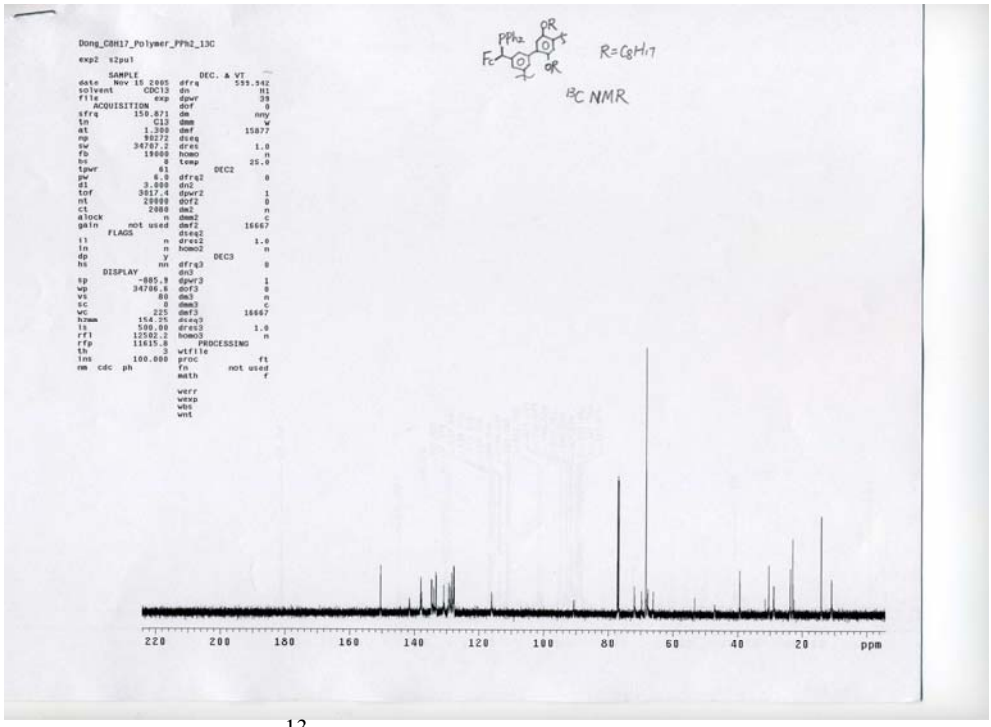

Figure A.1.30 ^{13}C NMR (150 MHz, $CDCl_3$) of polymer 13

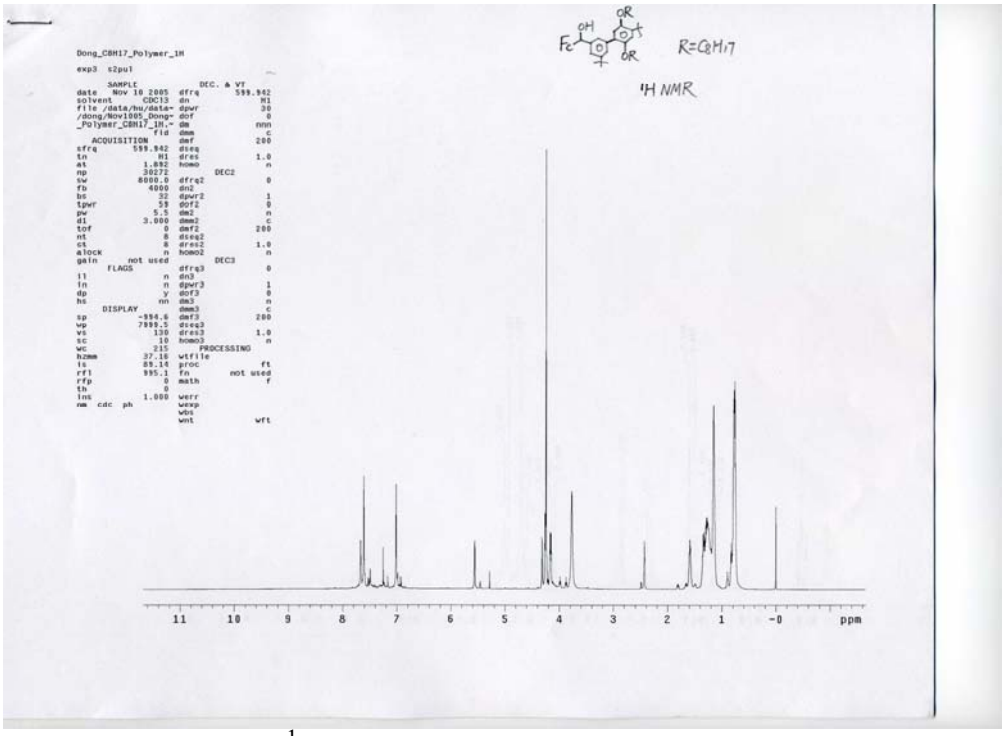

Figure A.1.31 ^{1}H NMR (600 MHz, $CDCl_3$) of polymer 16b

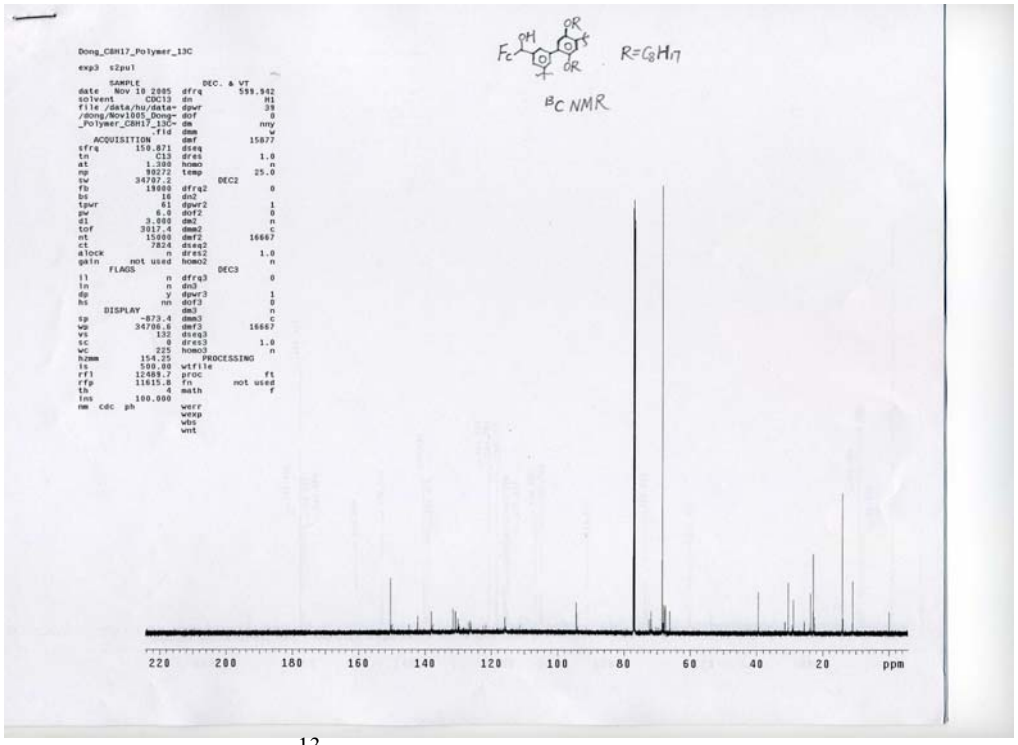

Figure A.1.32 ^{13}C NMR (50 MHz, $CDCl_3$) of polymer 16b

APPENDIX TWO: Spectra Relevant to Chapter Two

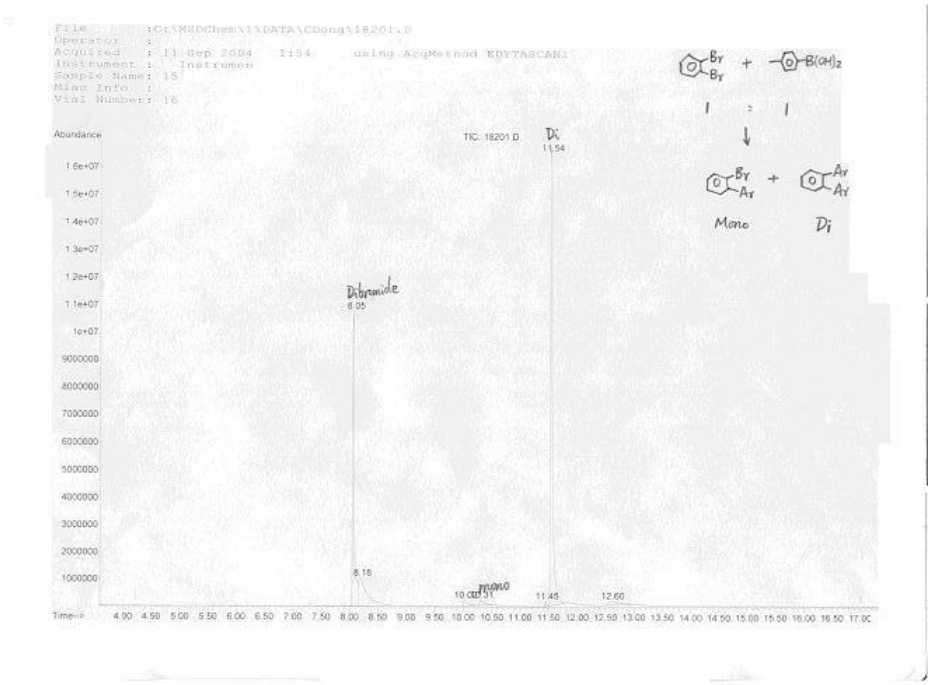

Figure A.2.1 GC-MS spectrum of Table 2.2 - Entry 2

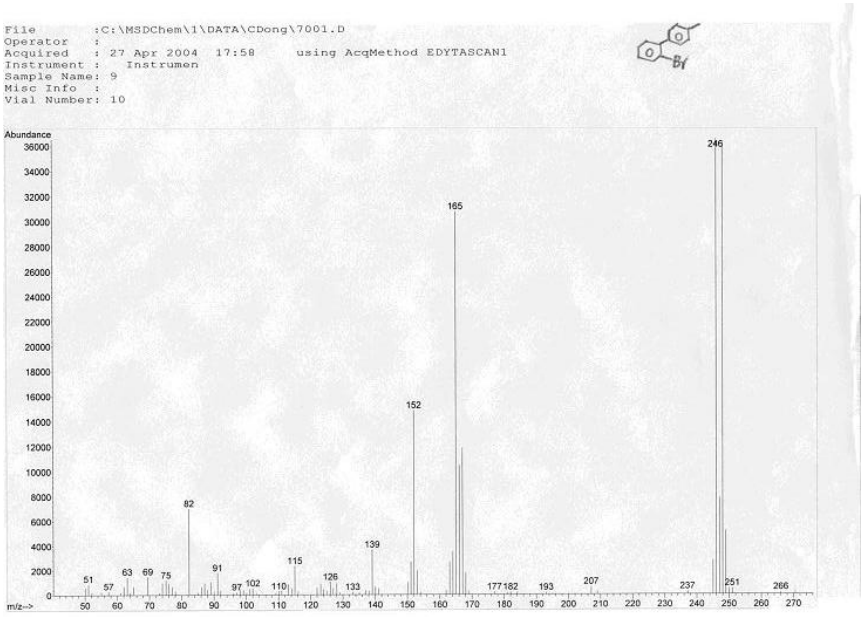

Figure A.2.2 GC-MS spectrum of Table 2.2 - Entry 2

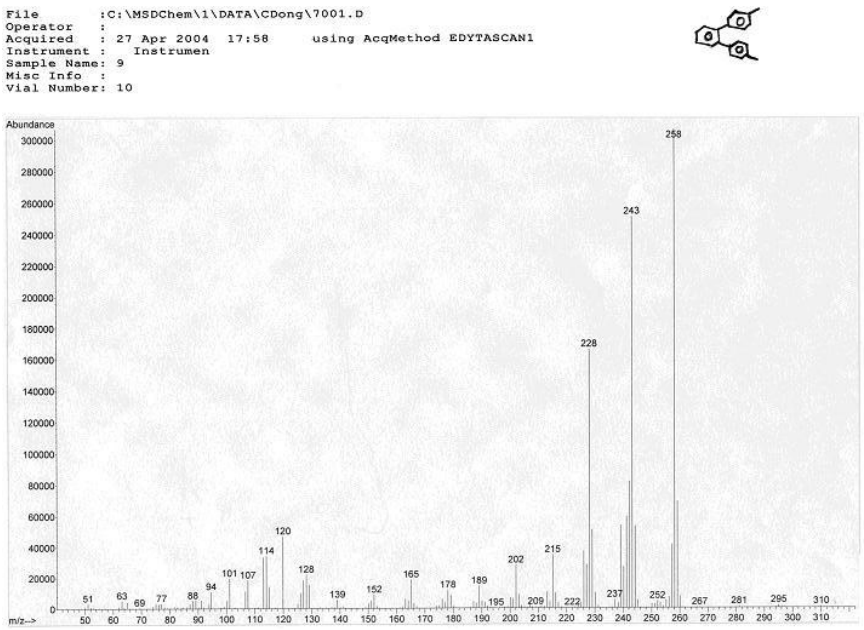

Figure A.2.3 GC-MS spectrum of Table 2.2 - Entry 2

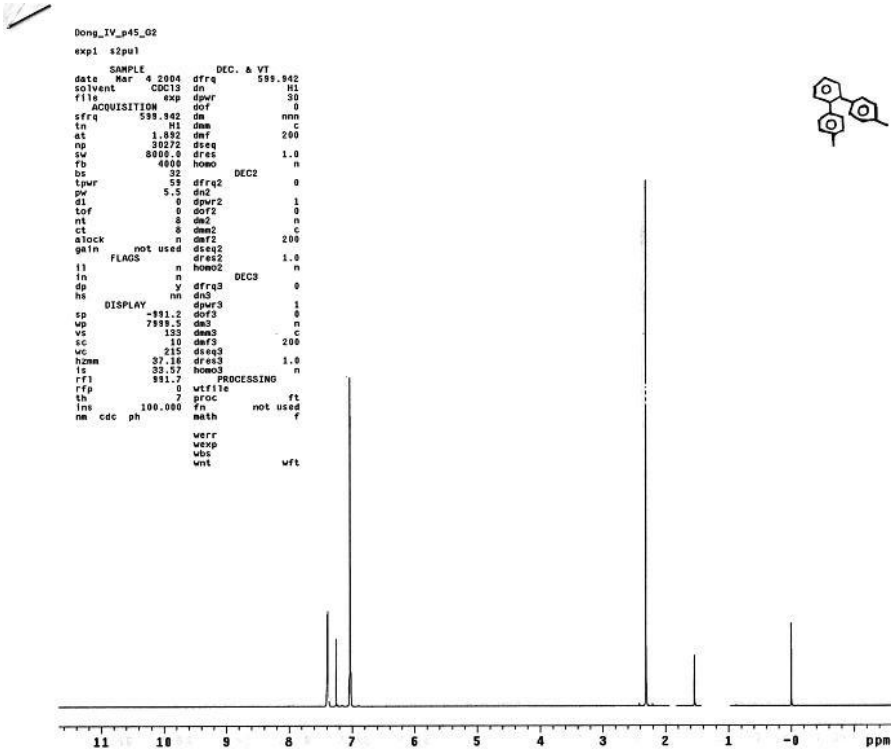

Figure A.2.4 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 2

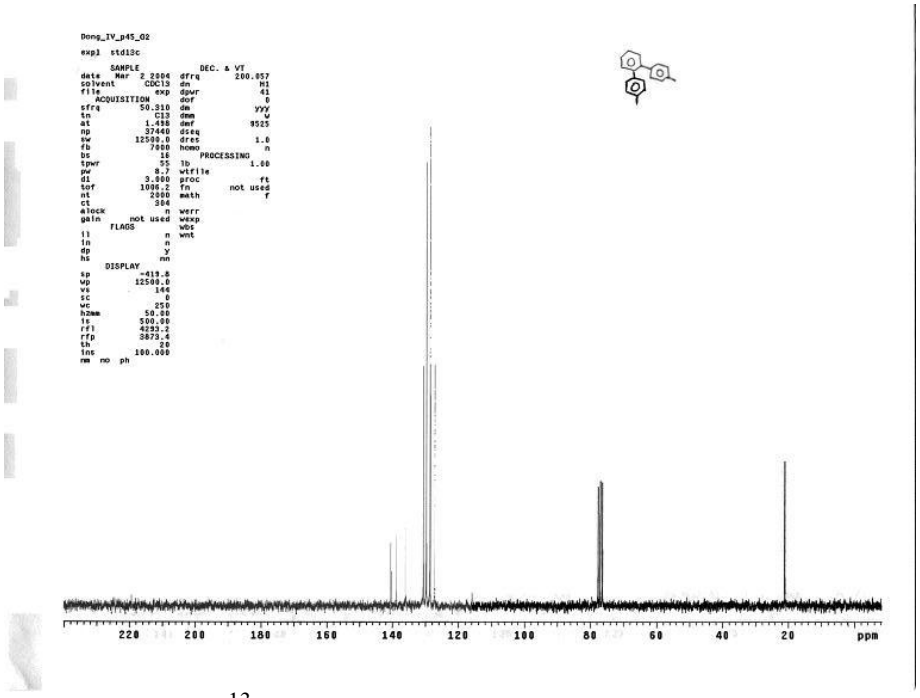

Figure A.2.5 ^{13}C NMR (150 MHz, $CDCl_3$) of Compound 2

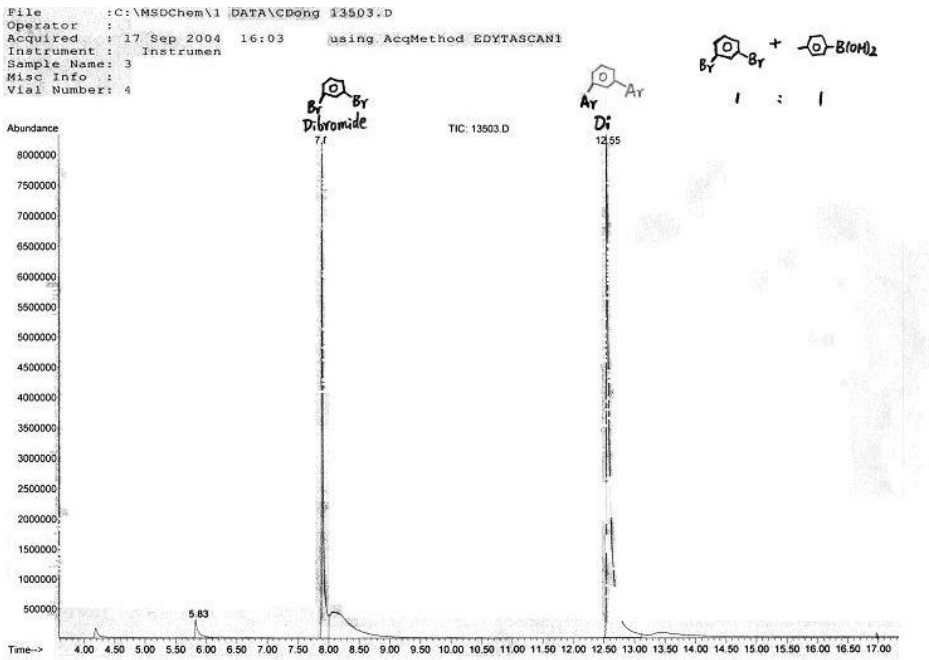

Figure A.2.6 GC-MS spectrum of Table 2.3 - Entry 3

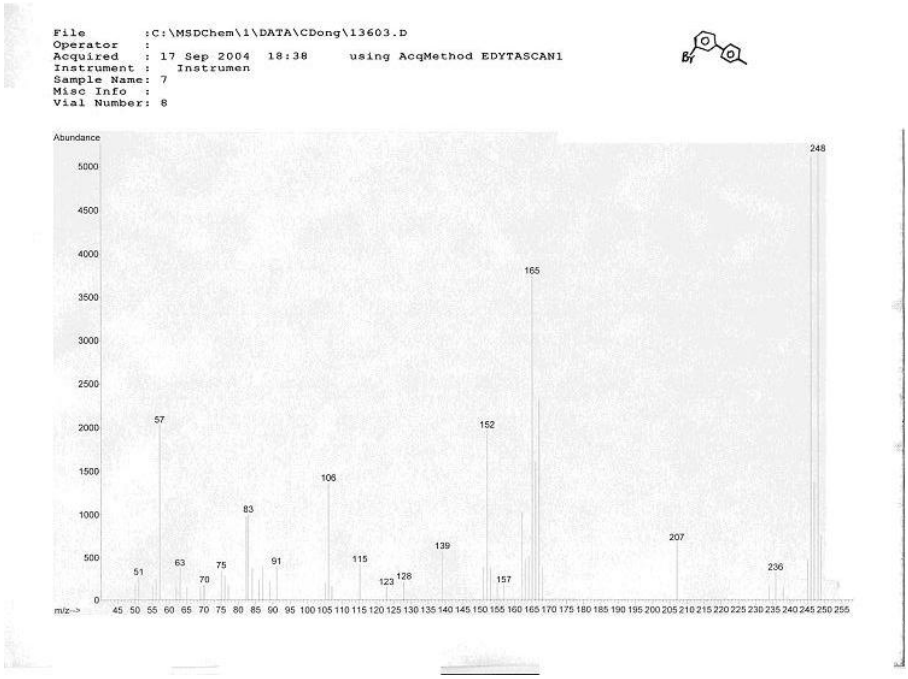

Figure A.2.7 GC-MS spectrum of Table 2.3 - Entry 3

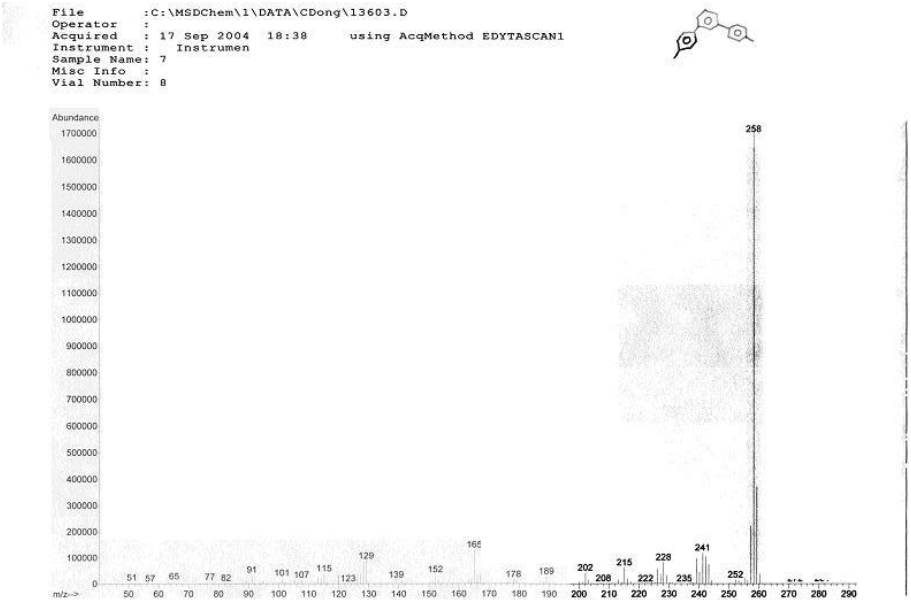

Figure A.2.8 GC-MS spectrum of Table 2.3 - Entry 3

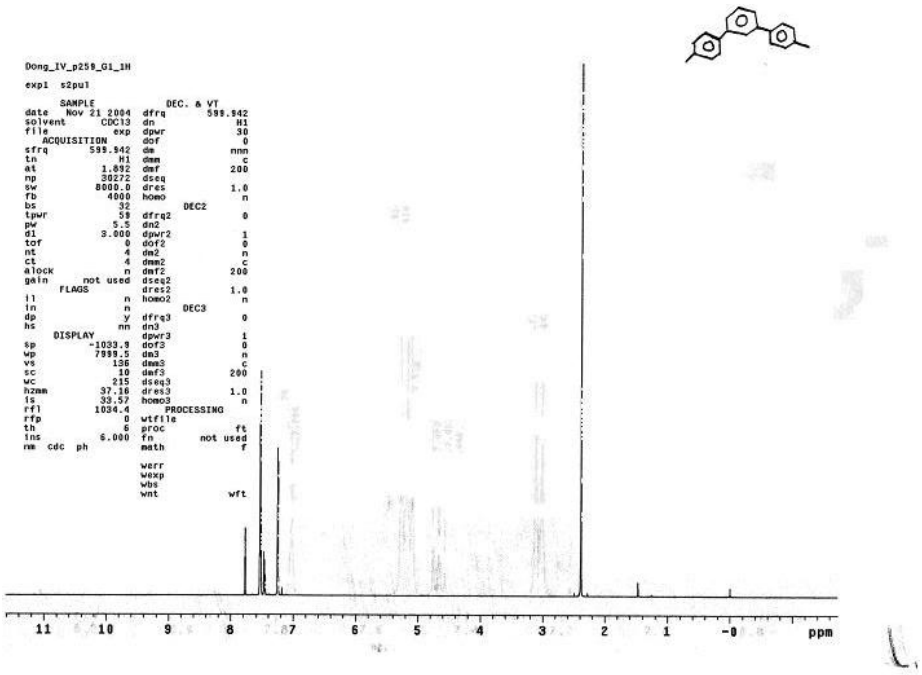

Figure A.2.9 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 9

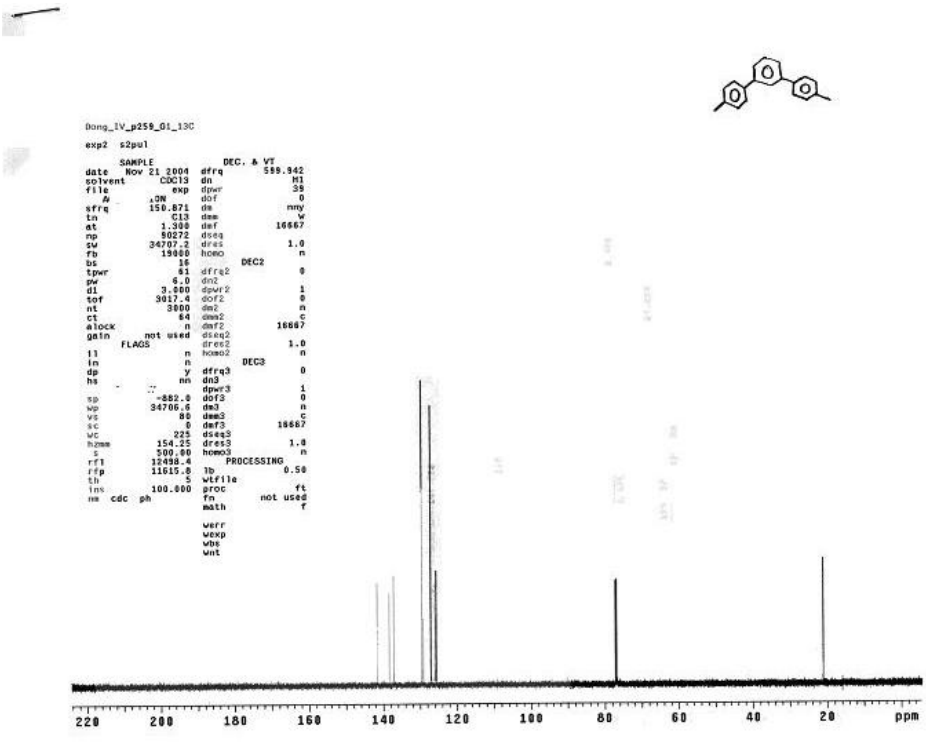

Figure A.2.10 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 9

APPENDIX THREE: Spectra Relevant to Chapter Three

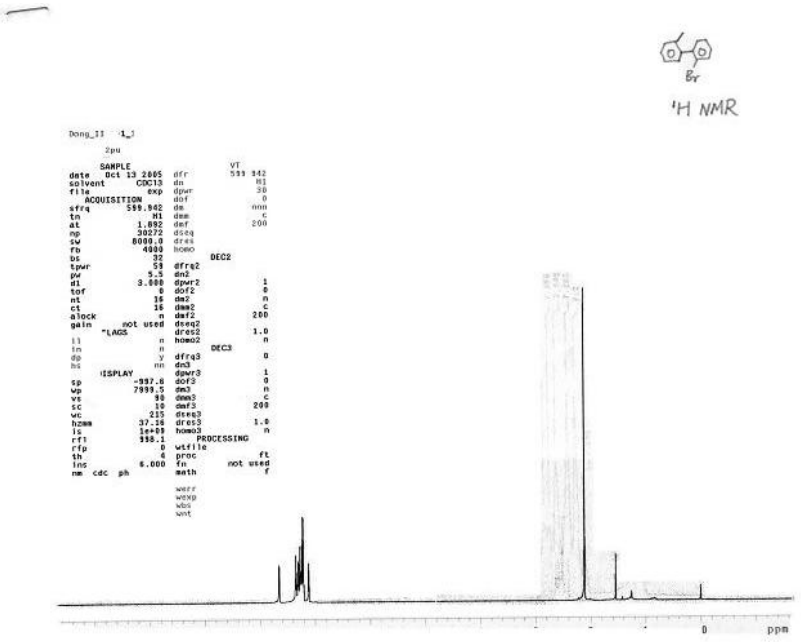

Figure A.3.1 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 1

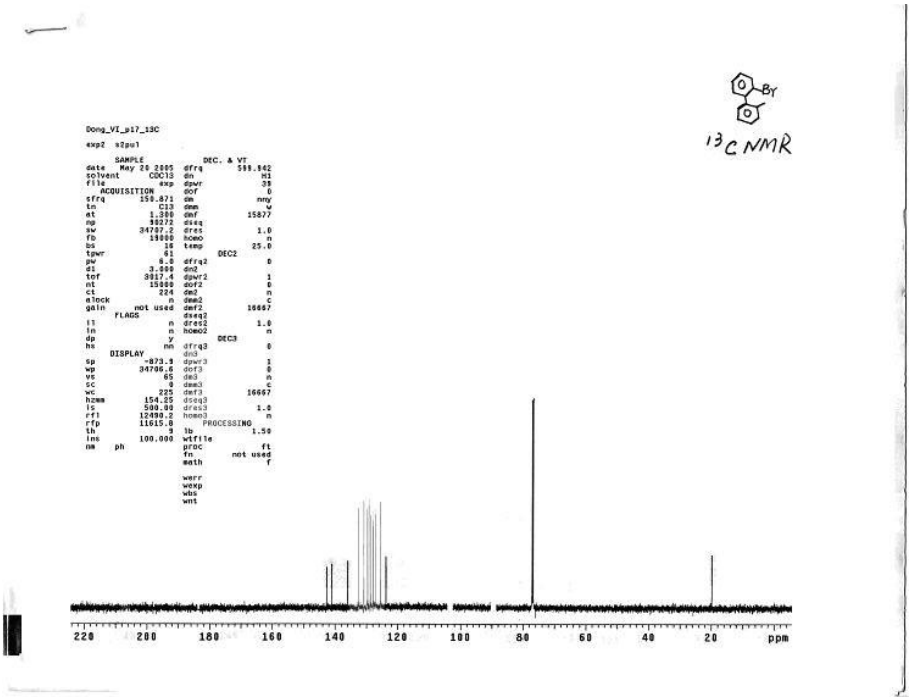

Figure A.3.2 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 1

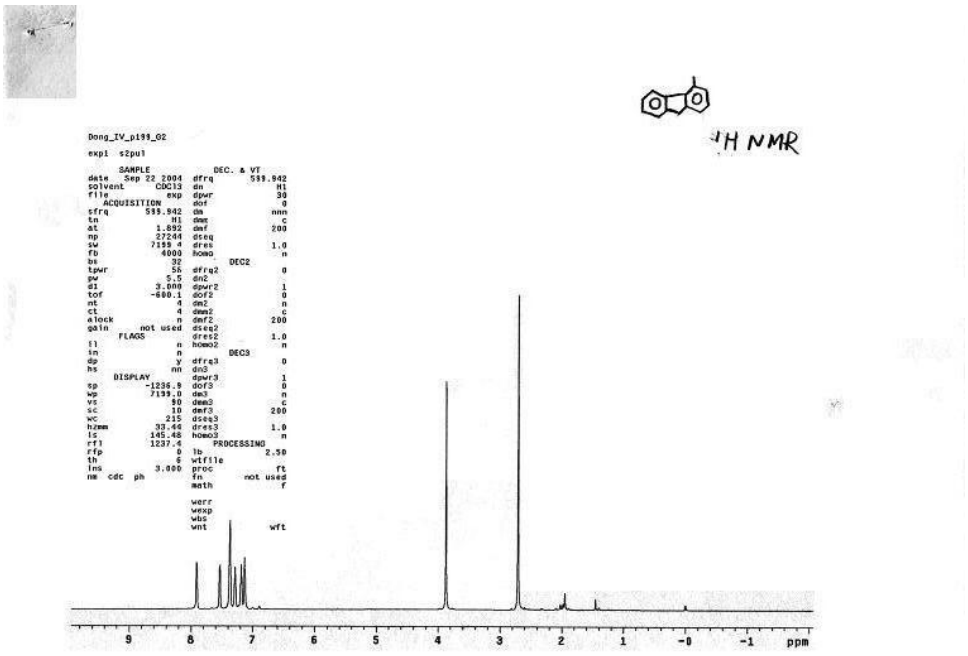

Figure A.3.3 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 6

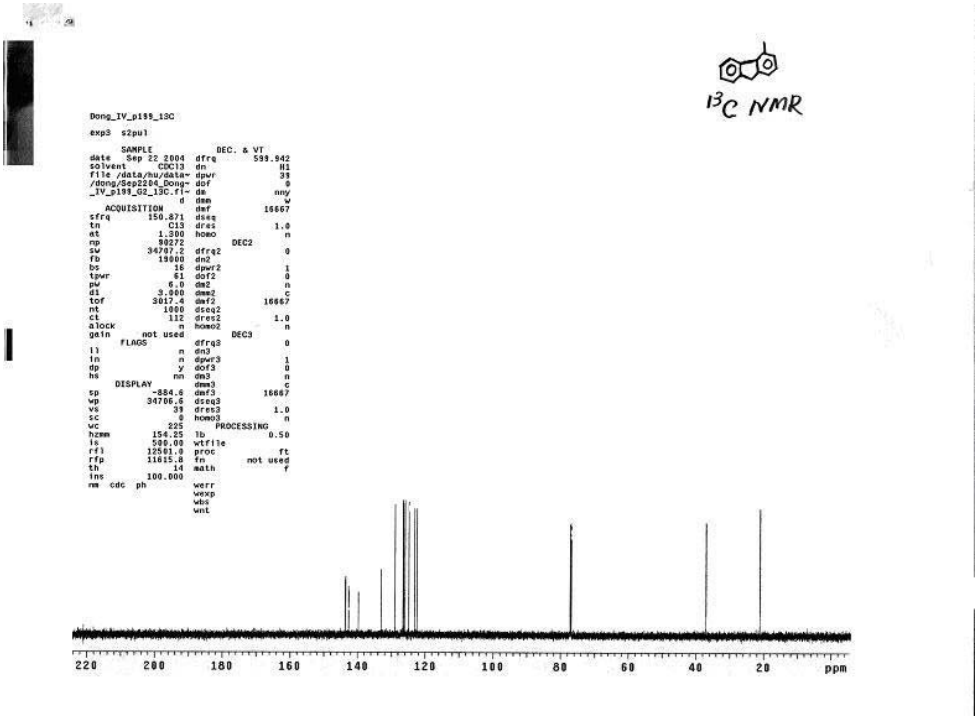

Figure A.3.4 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 6

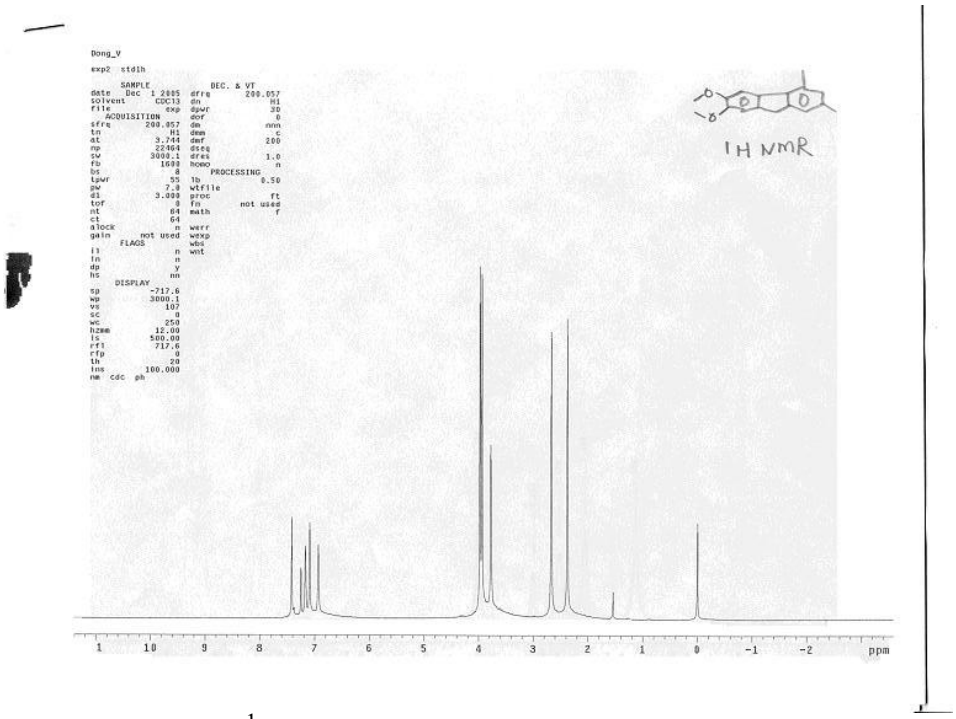

Figure A.3.5 ^{1}H NMR (200 MHz, $CDCl_3$) of compound 10

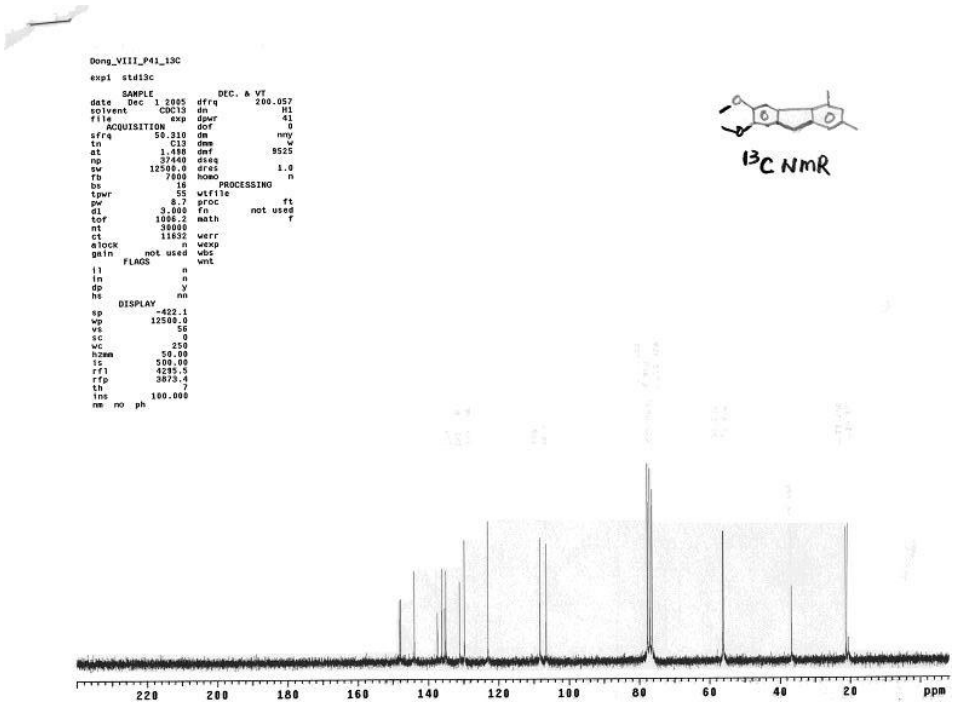

Figure A.3.6 ^{13}C NMR (50 MHz, $CDCl_3$) of compound 10

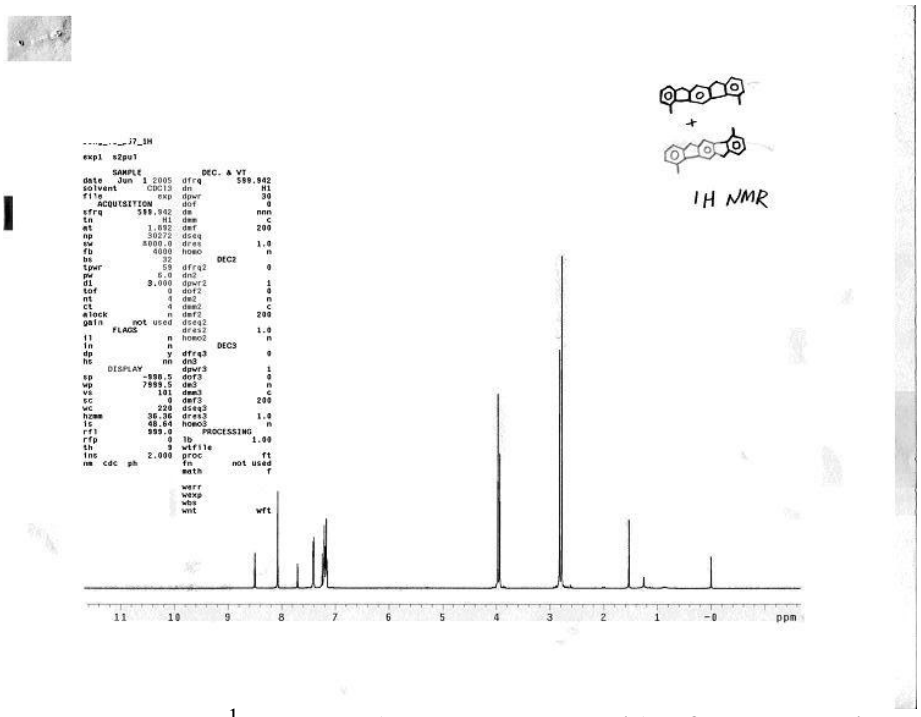

Figure A.3.7 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 17

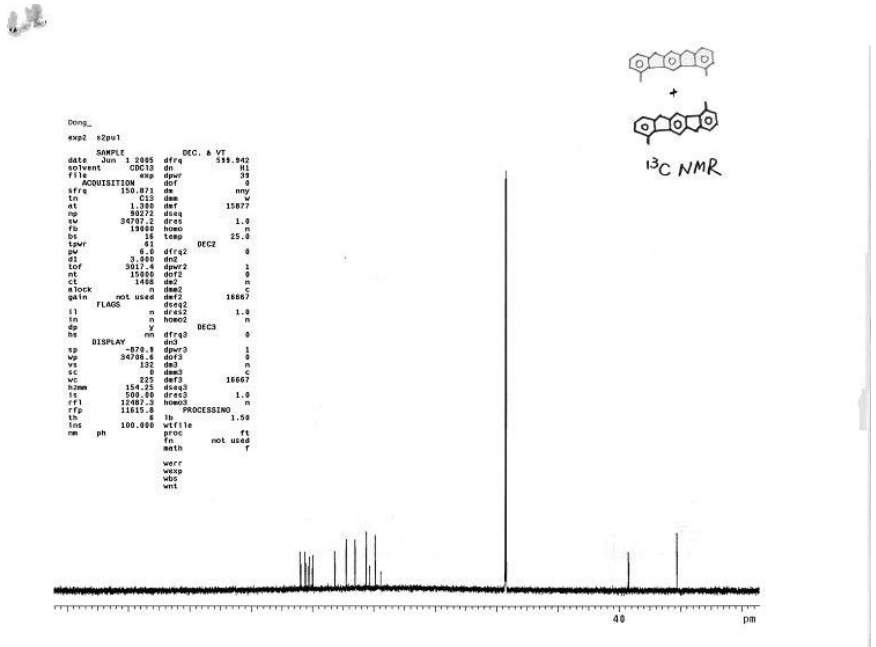

Figure A.3.8 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 17

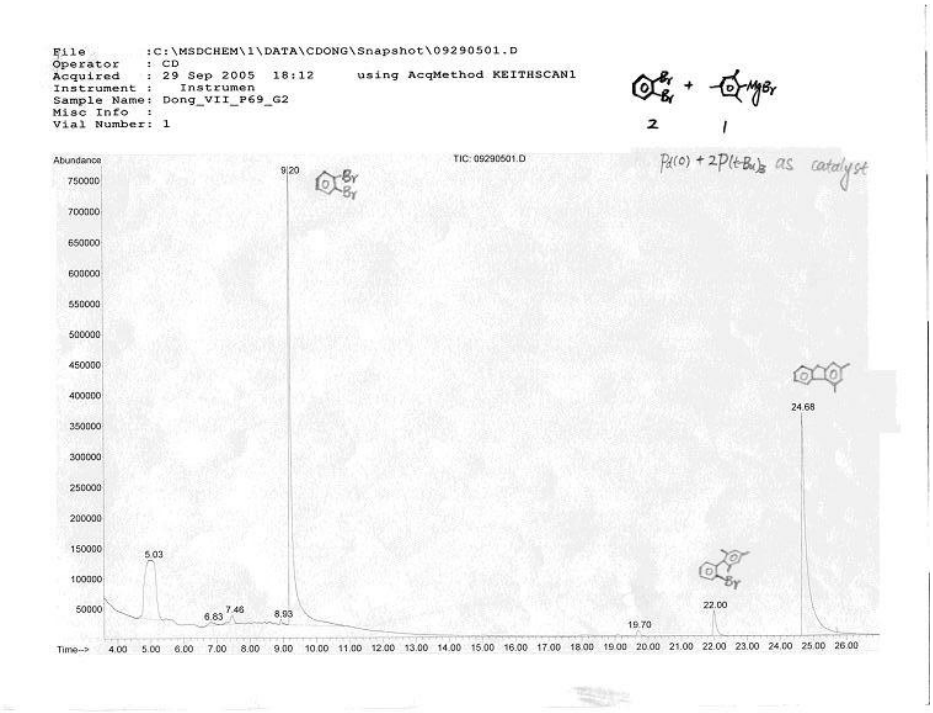

Figure A.3.9 GC-MS spectrum of the reaction between 1,2-Dibromobenzene with limited amont of Grignard Reagent

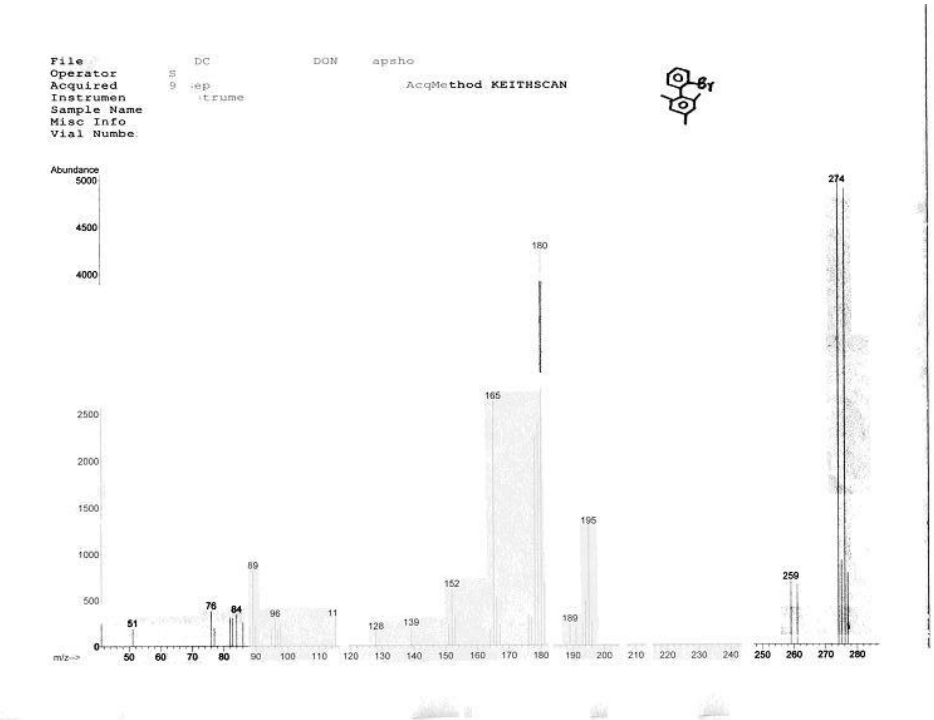

Figure A.3.10 GC-MS spectrum of the reaction between 1,2-Dibromobenzene with limited amont of Grignard Reagent

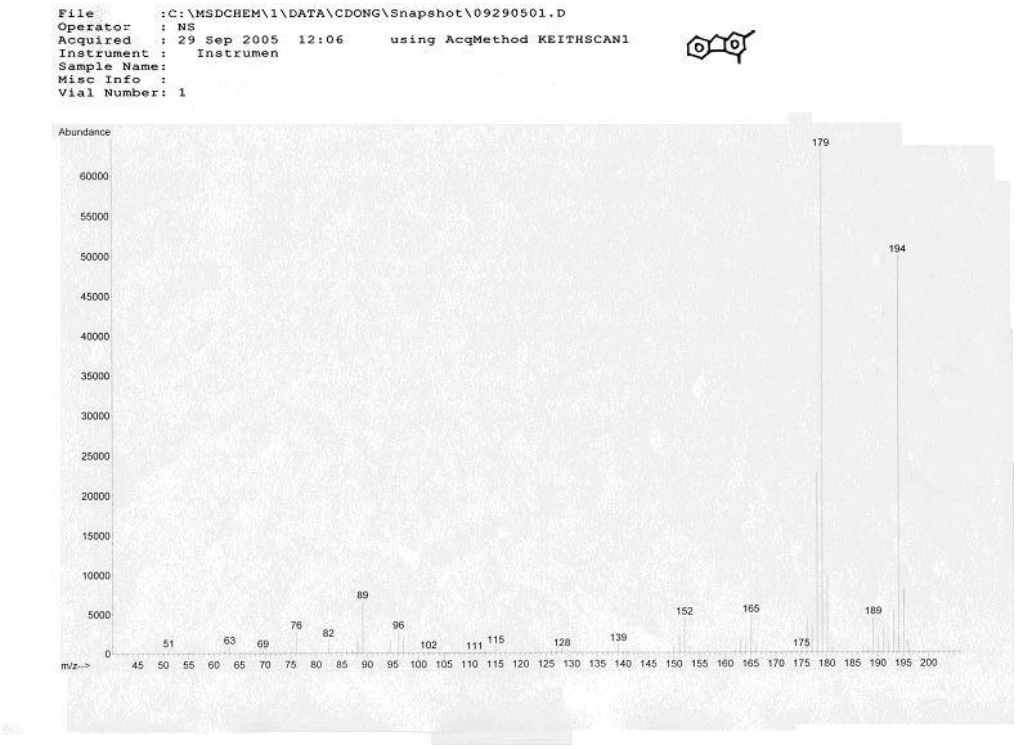

Figure A.3.11 GC-MS spectrum of the reaction between 1,2-Dibromobenzene with limited amont of Grignard Reagent

APPENDIX FOUR: Spectra Relevant to Chapter Four

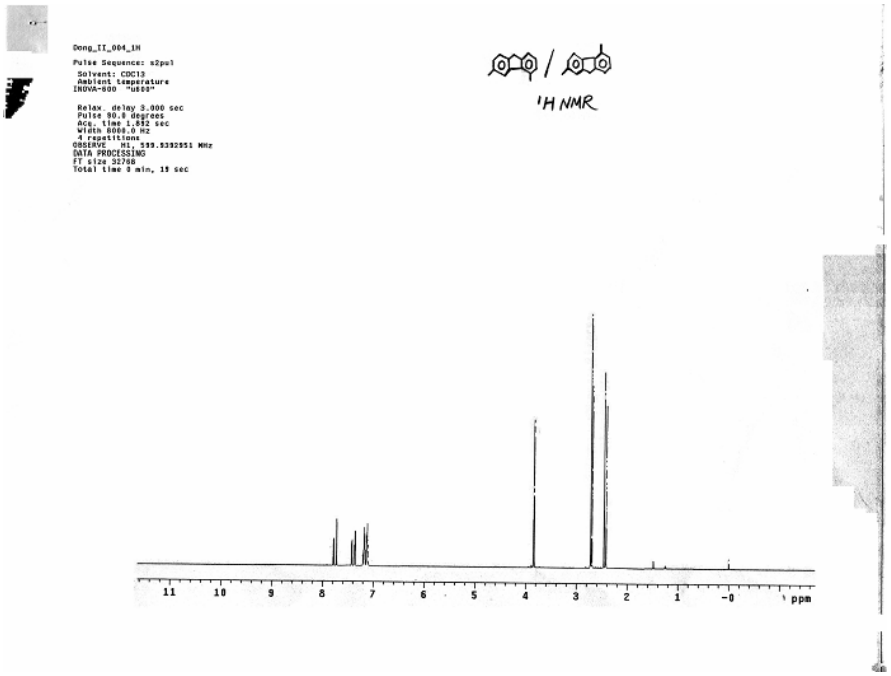

Figure A.4.1 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 13

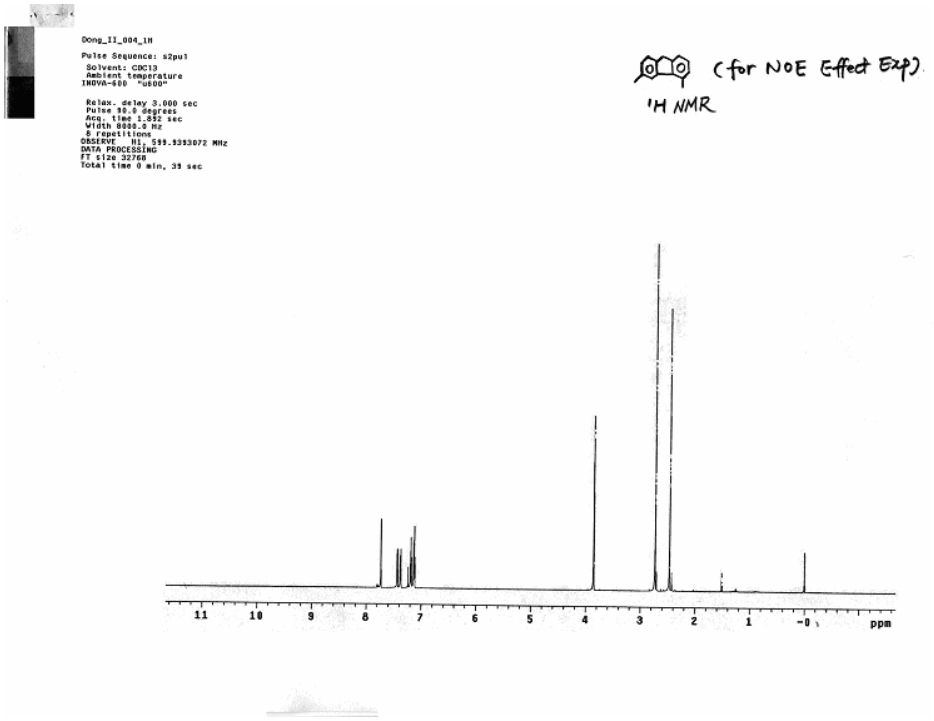

Figure A.4.2 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 13a

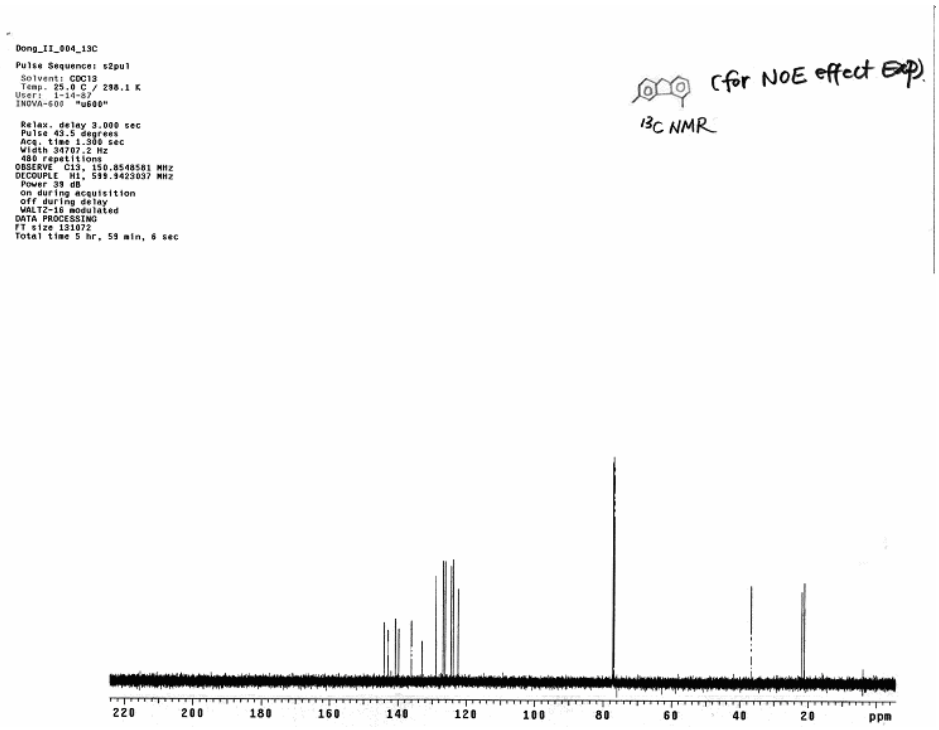

Figure A.4.3 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 13a

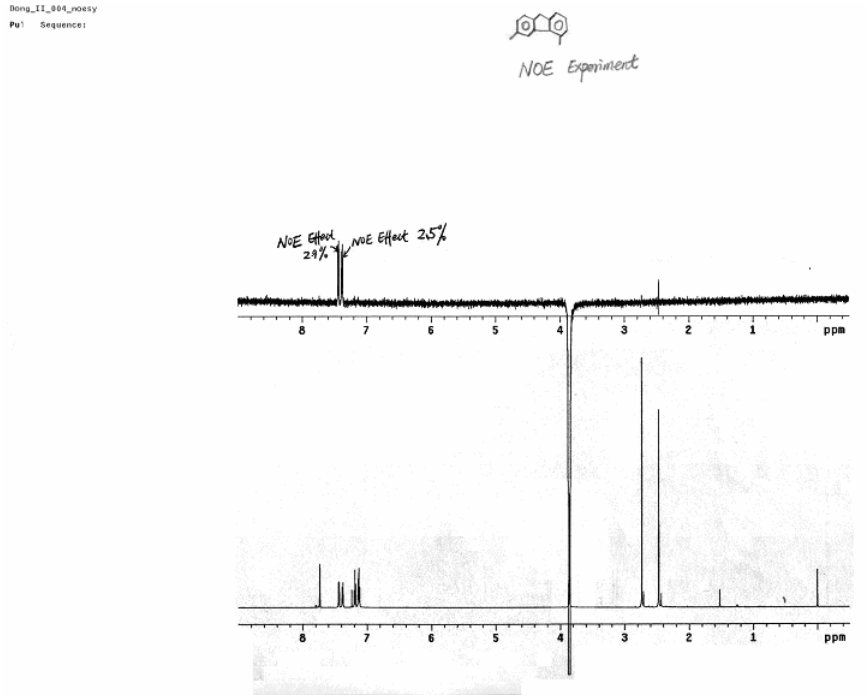

Figure A.4.4 NOE experiment of compound 13a

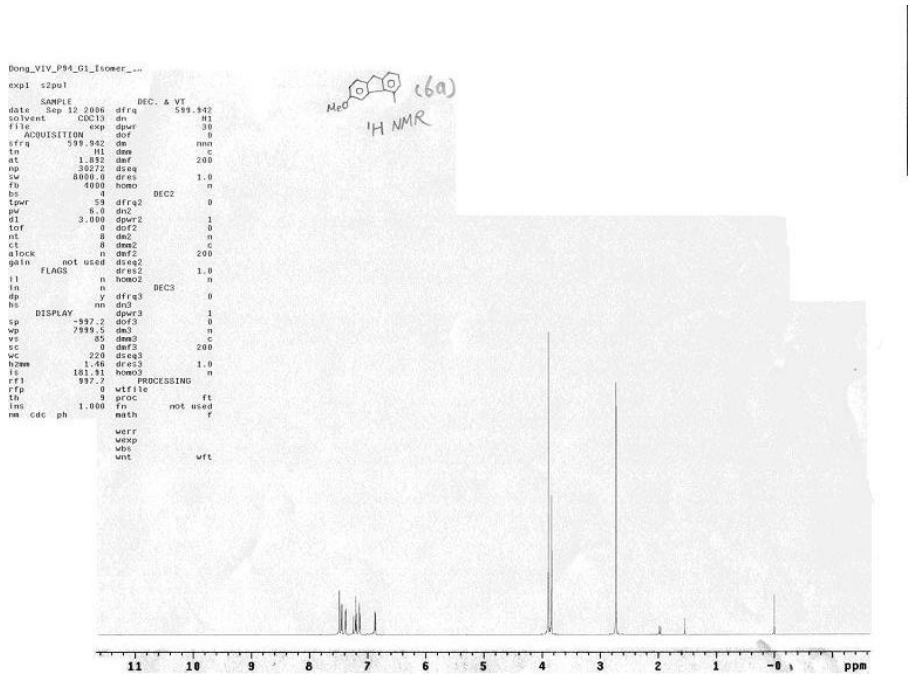

Figure A.4.5 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 14a

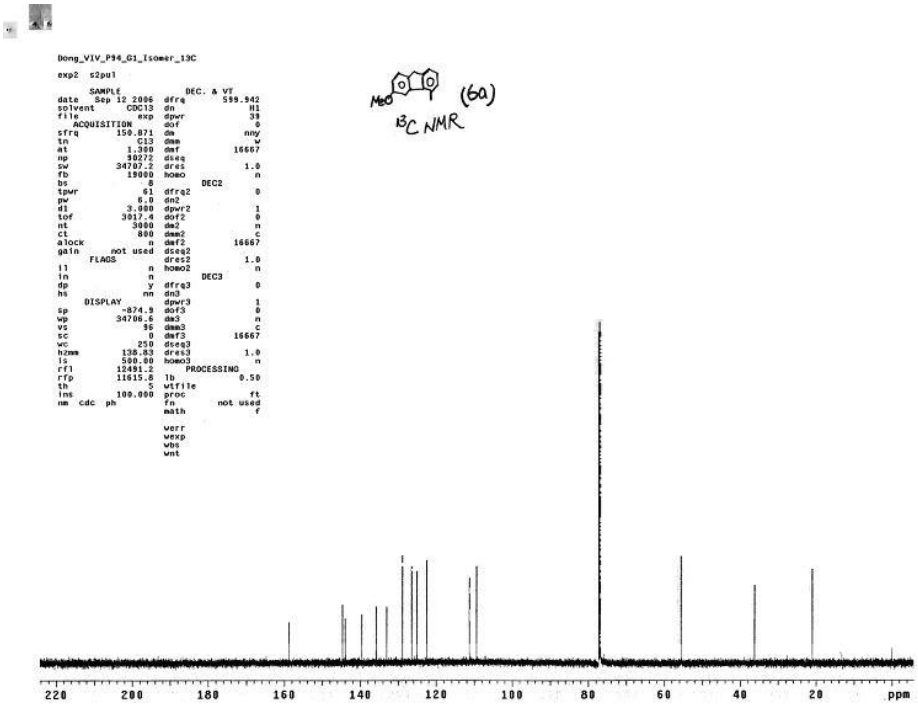

Figure A.4.6 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 14a

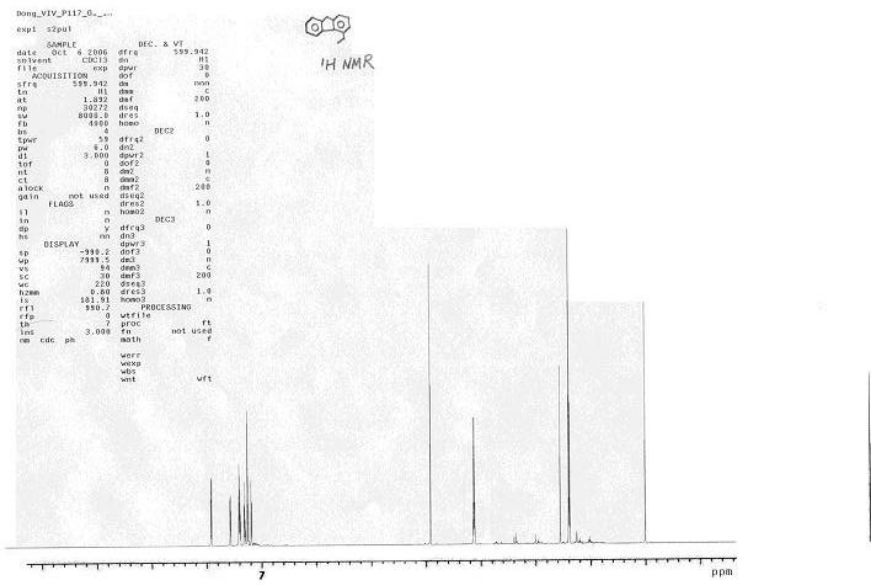

Figure A.4.7 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 17

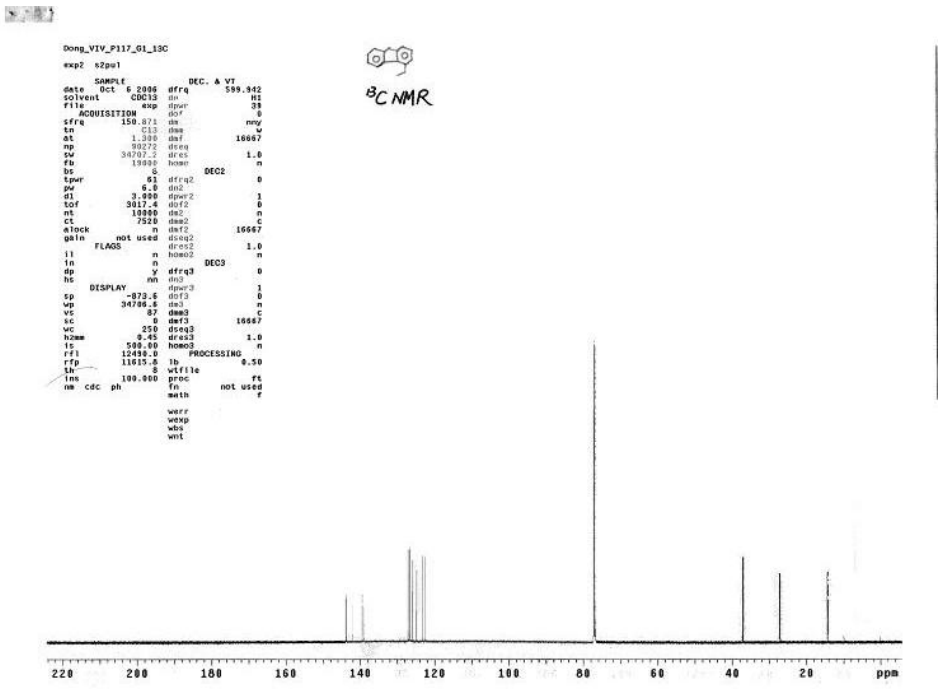

Figure A.4.8 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 17

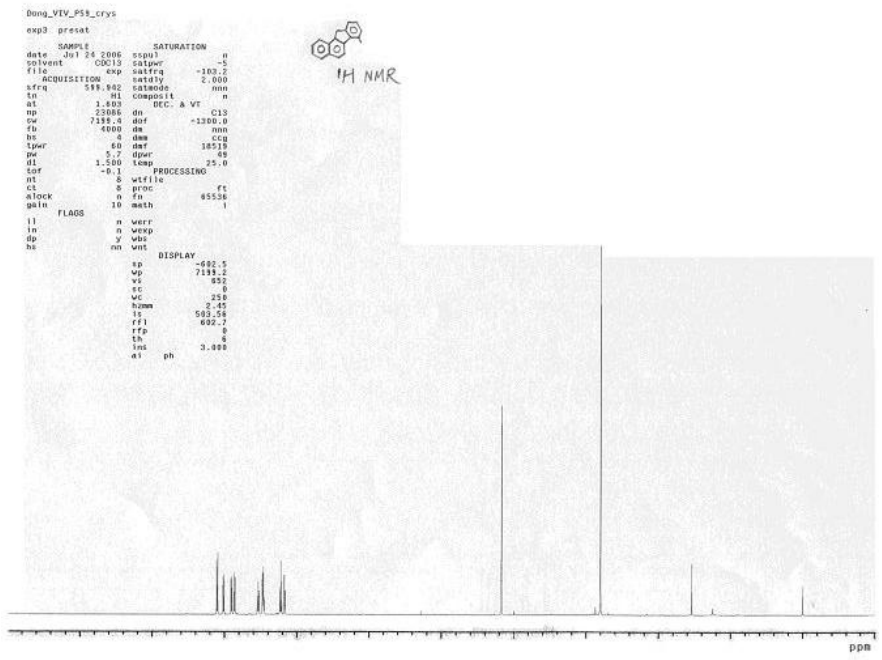

Figure A.4.9 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 20a

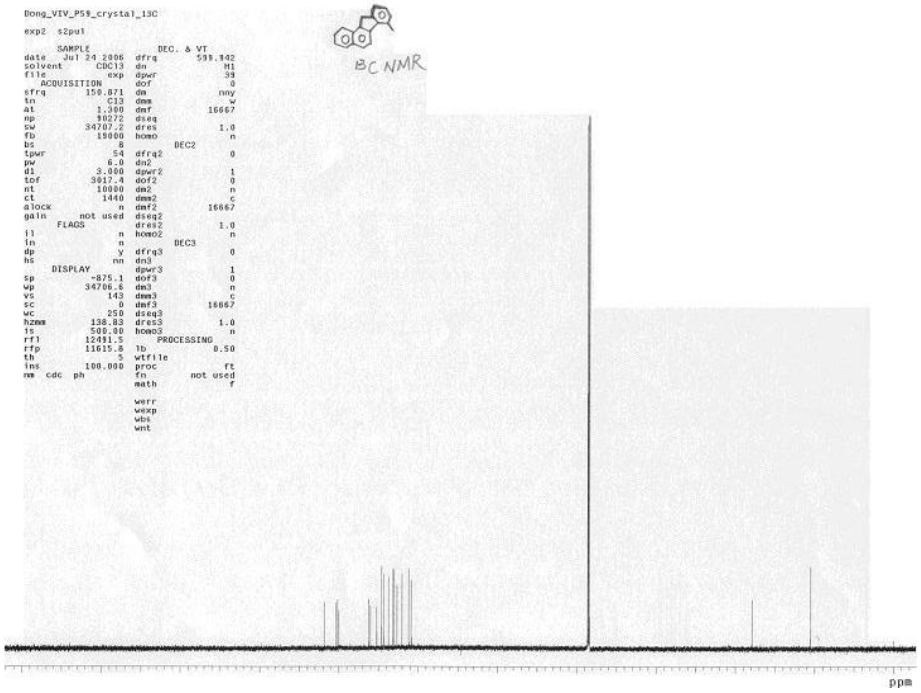

Figure A.4.10 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 20a

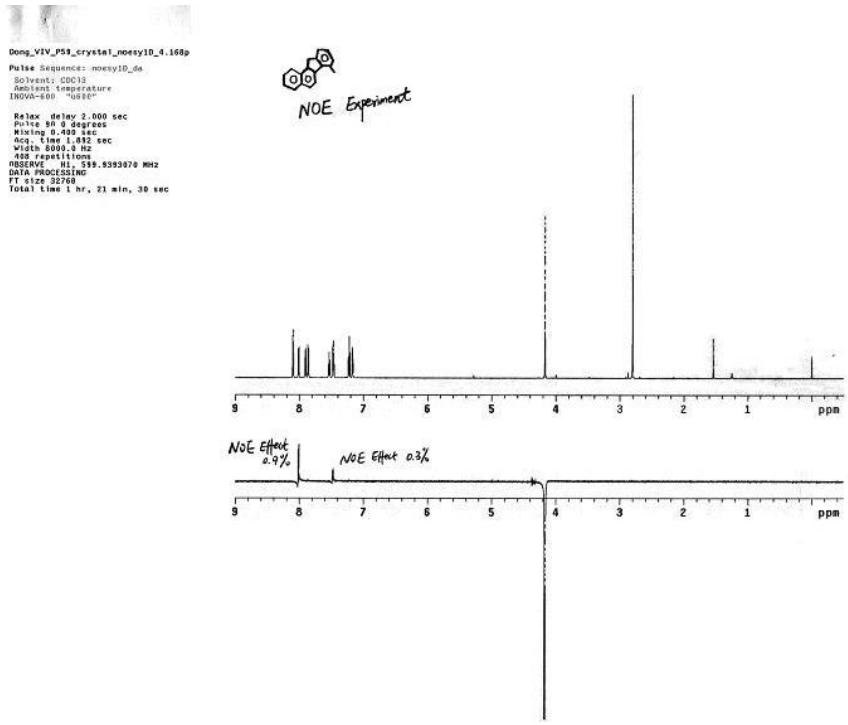

Figure A.4.11 NOE experiment of compound 20a

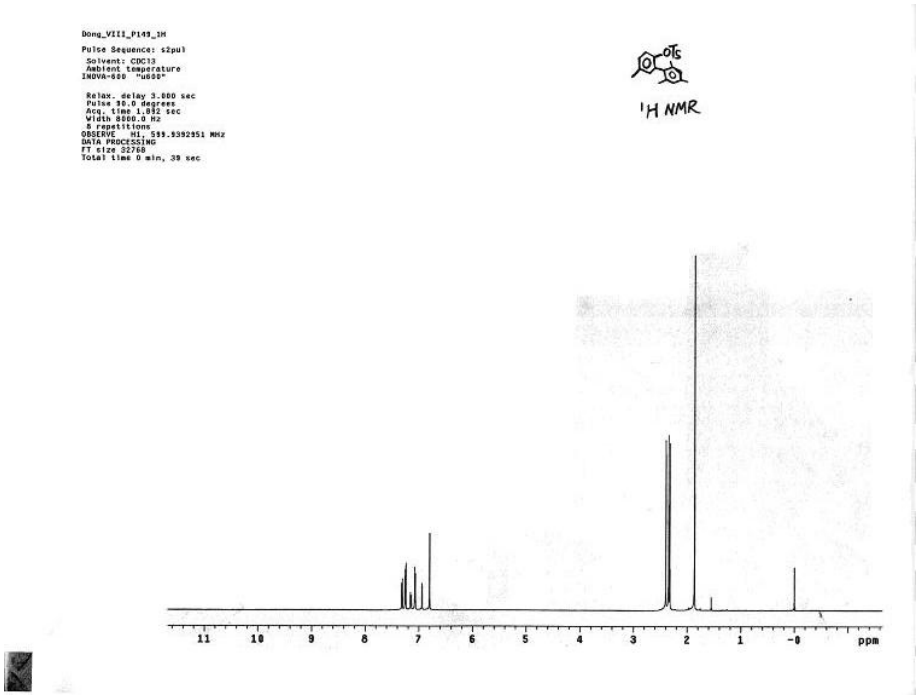

Figure A.4.12 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 21

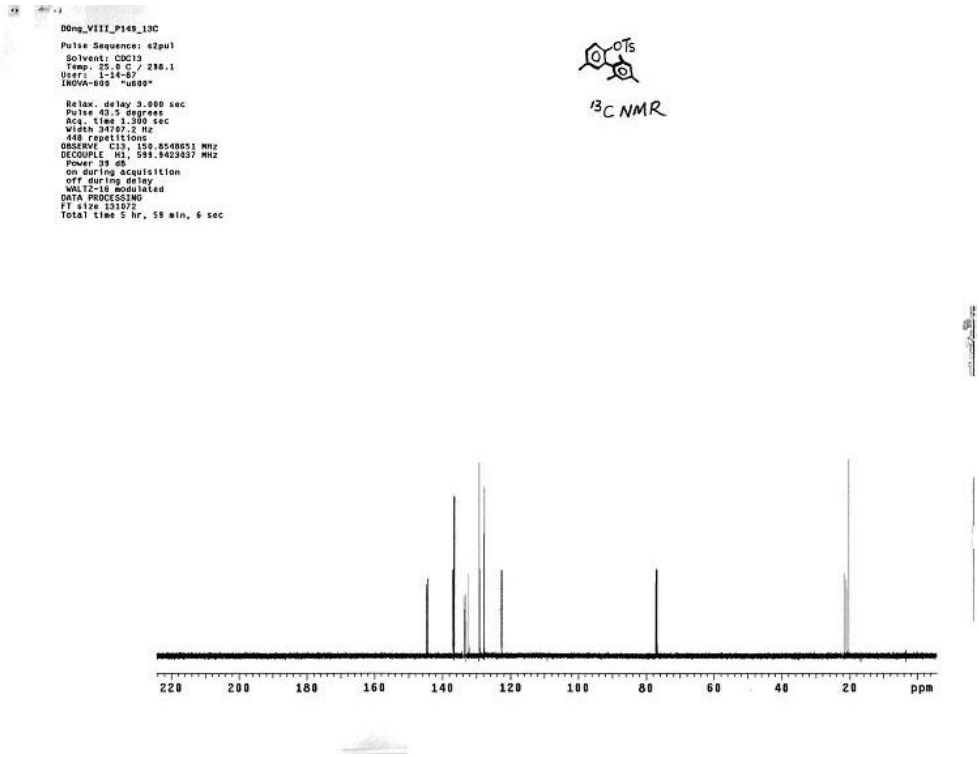

Figure A.4.13 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 21

APPENDIX FIVE: Spectra Relevant to Chapter Five

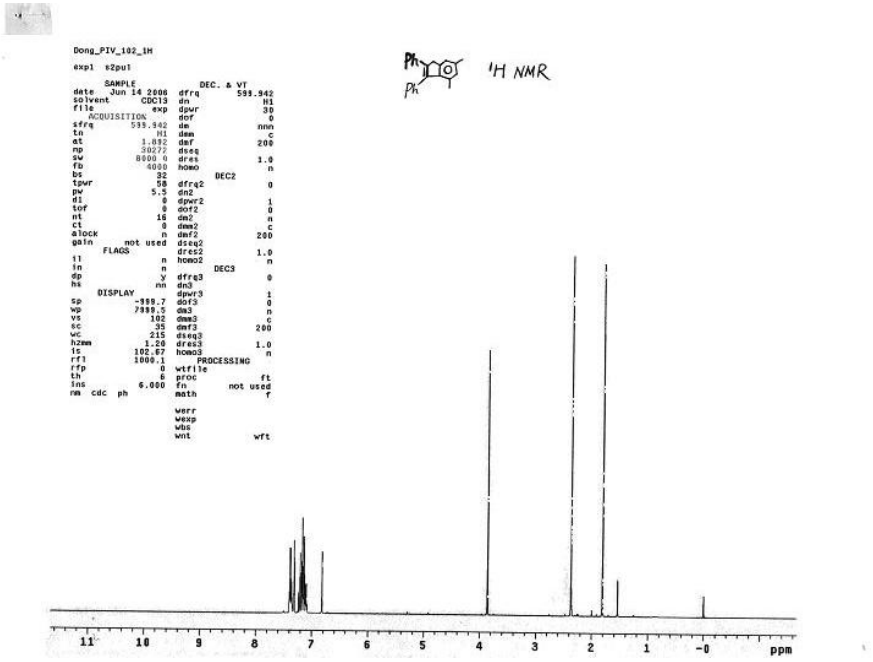

Figure A.5.1 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 1

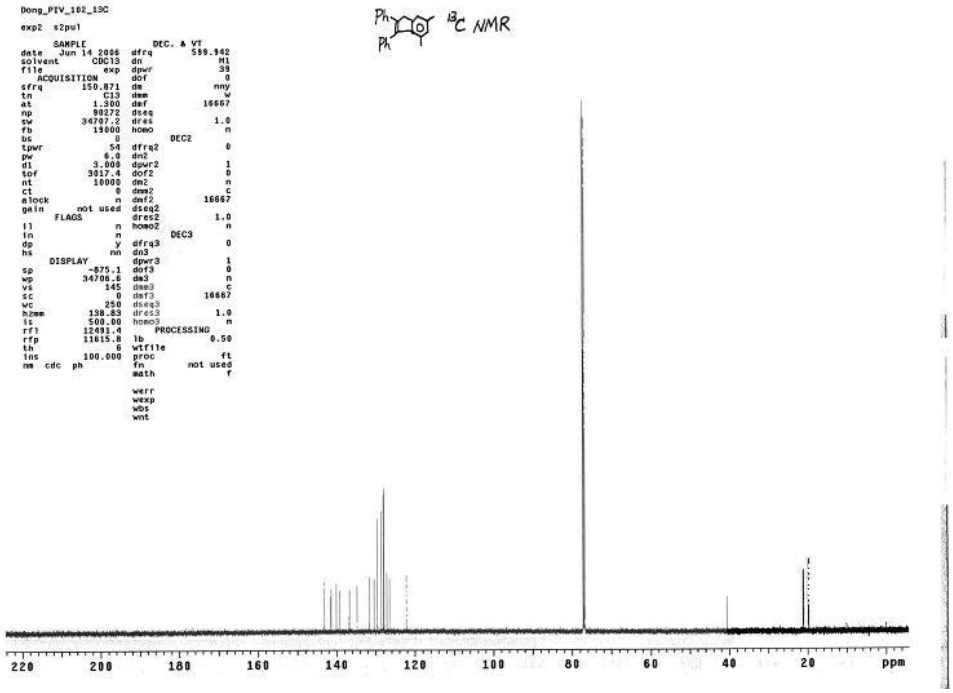

Figure A.5.2 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 1

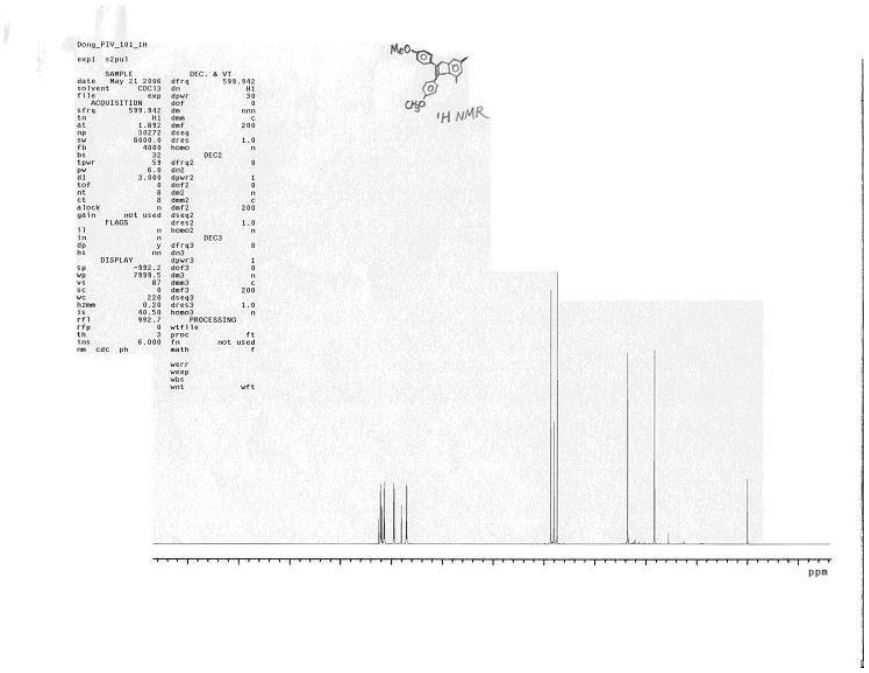

Figure A.5.3 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 5

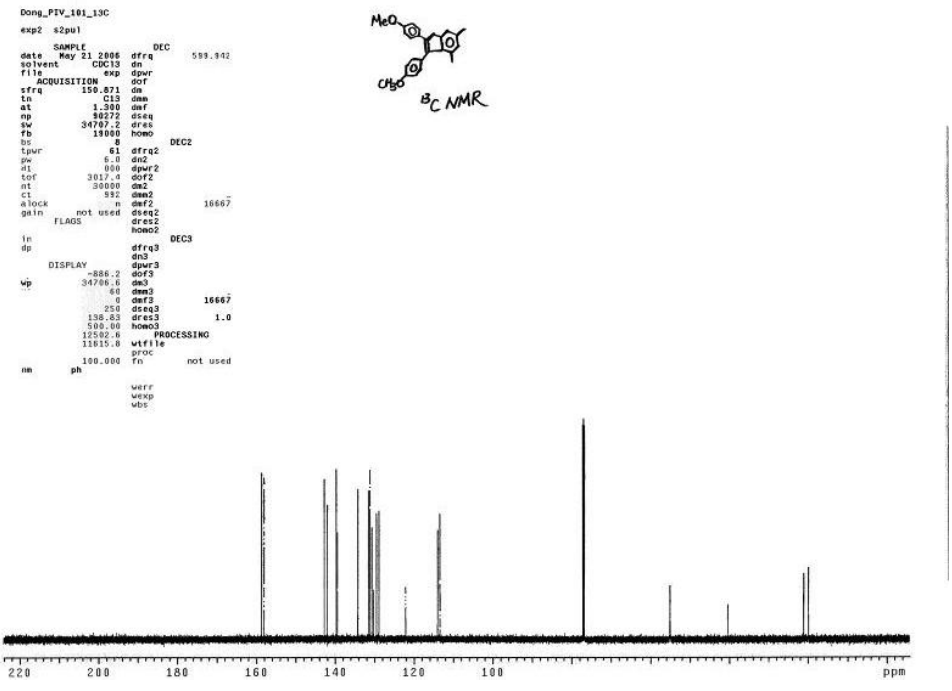

Figure A.5.4 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 5

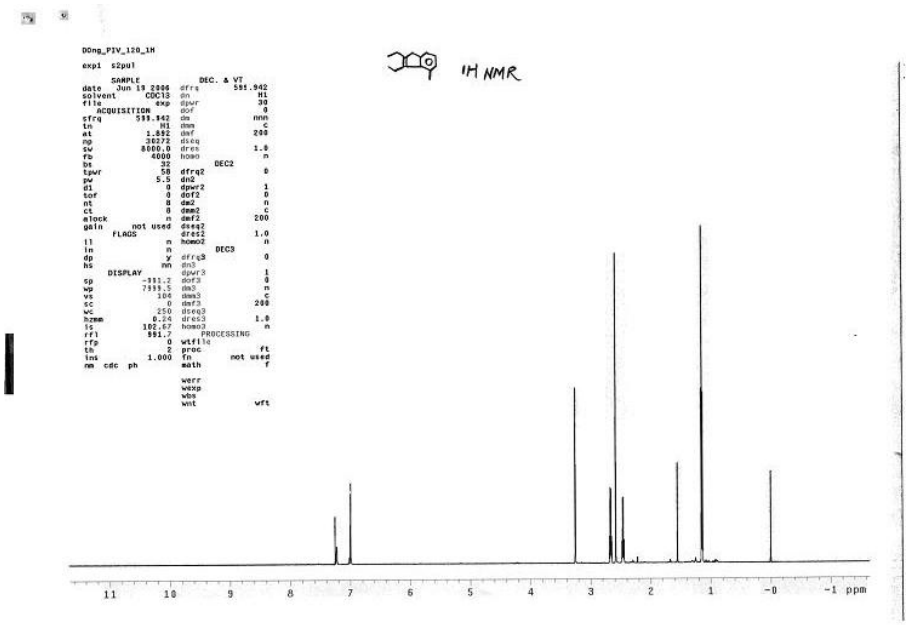

Figure A.5.5 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 8

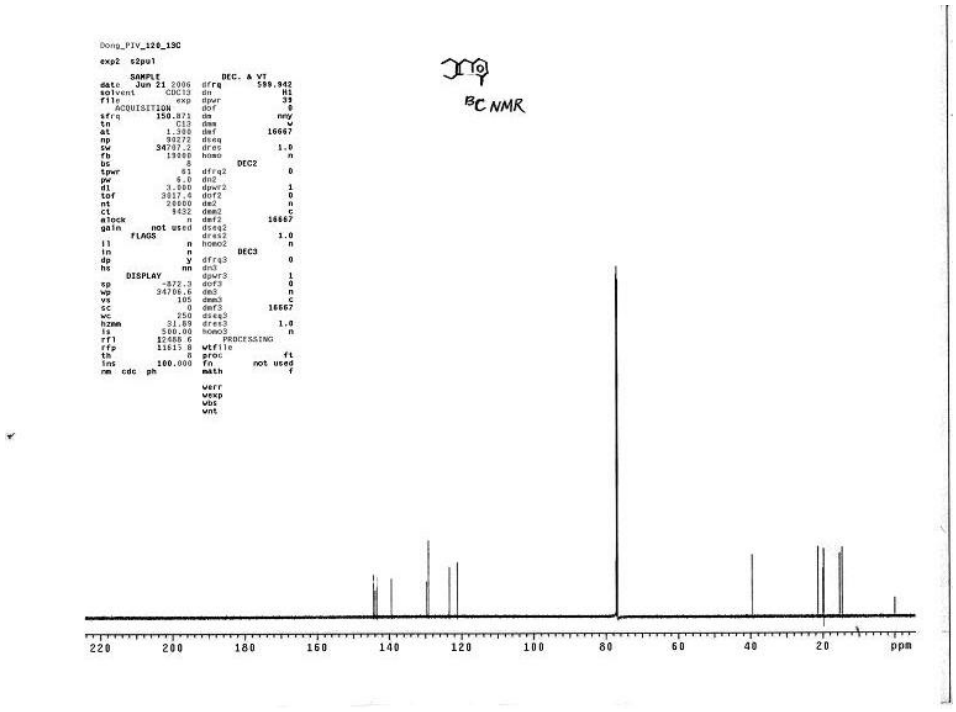

Figure A.5.6 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 8

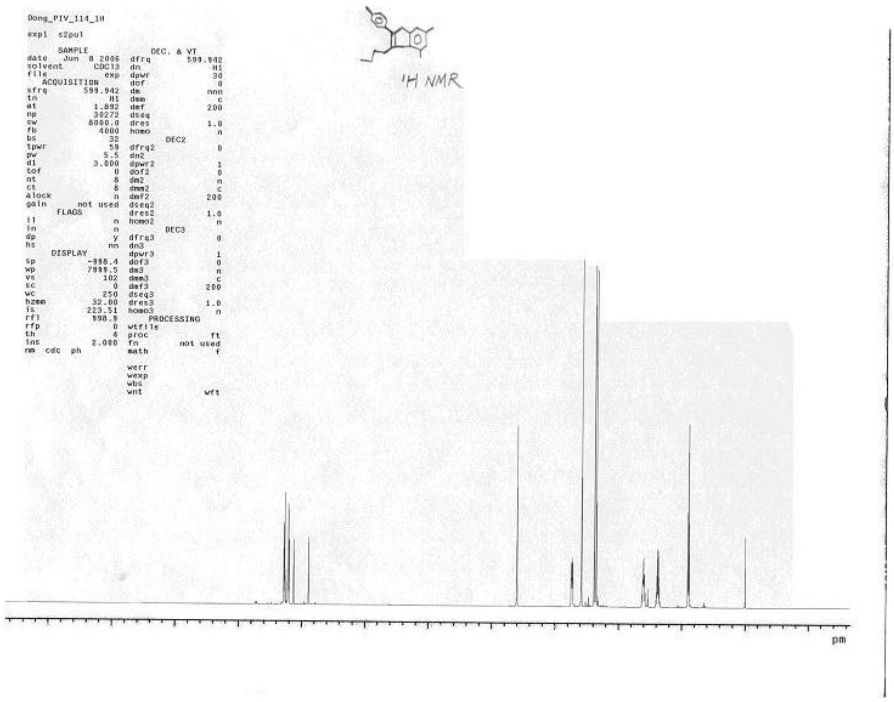

Figure A.5.7 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 9

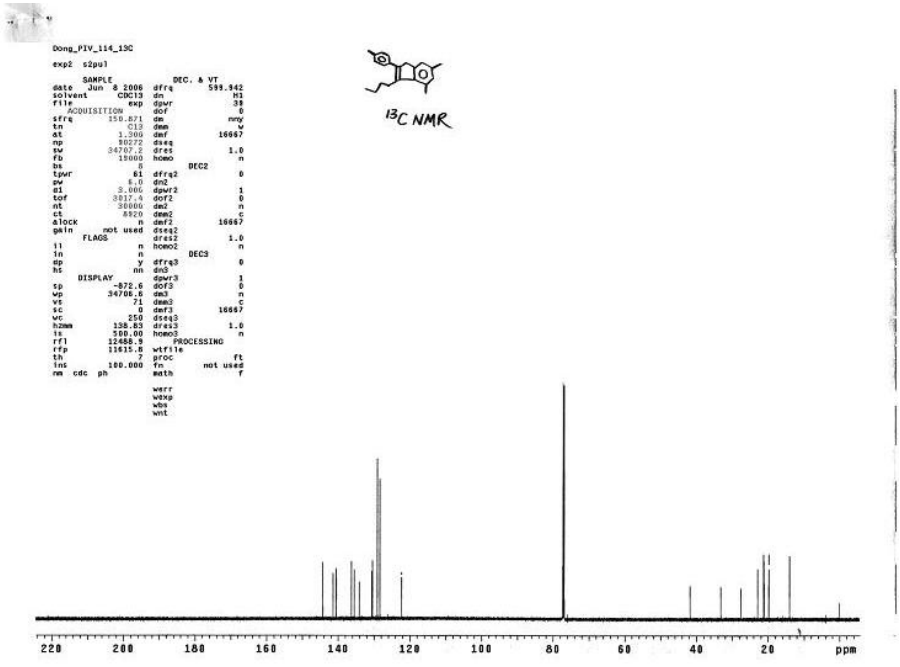

Figure A.5.8 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 9

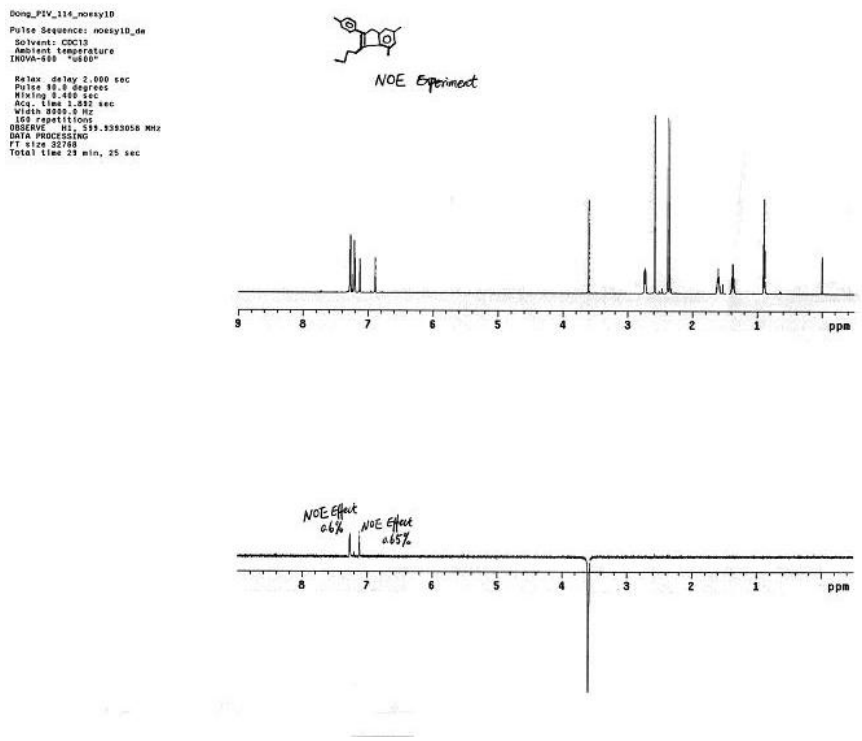

Figure A.5.9 NOE experiment of compound 9

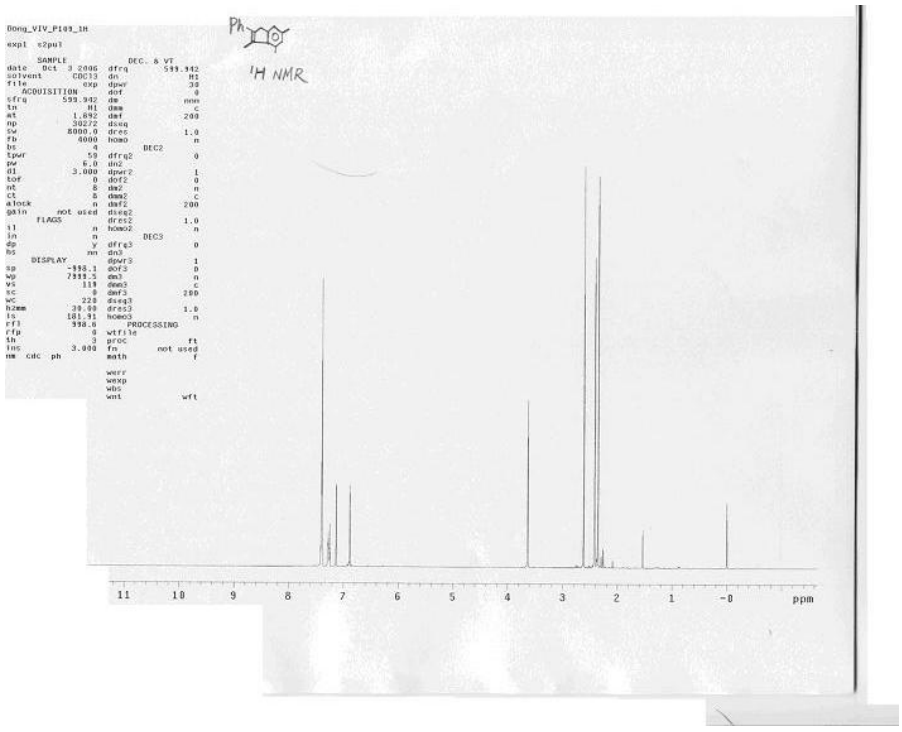

Figure A.5.10 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 10

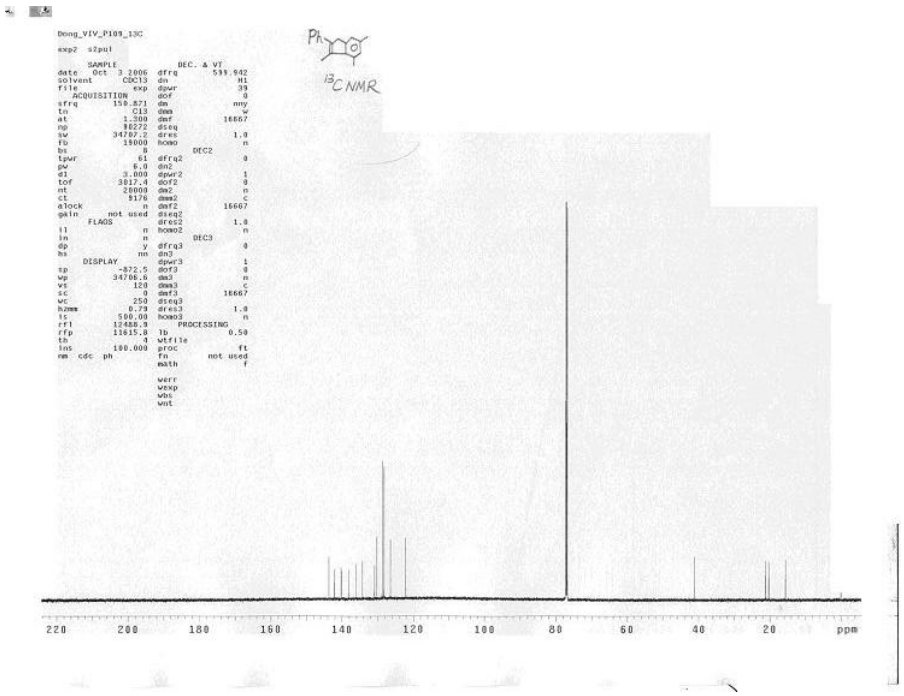

Figure A.5.11 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 10

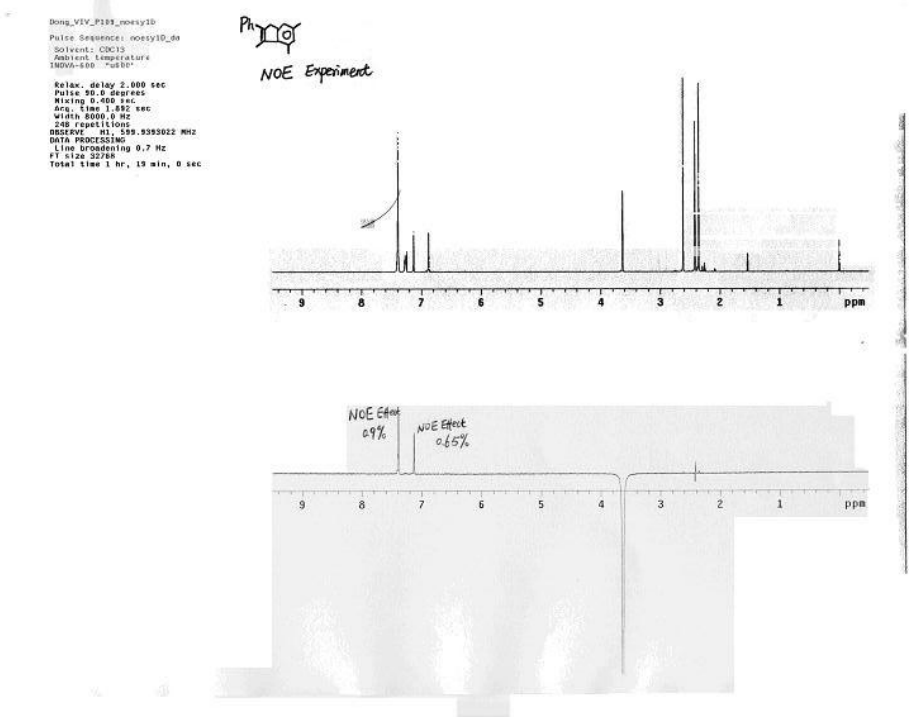

Figure A.5.12 NOE experiment of compound 10

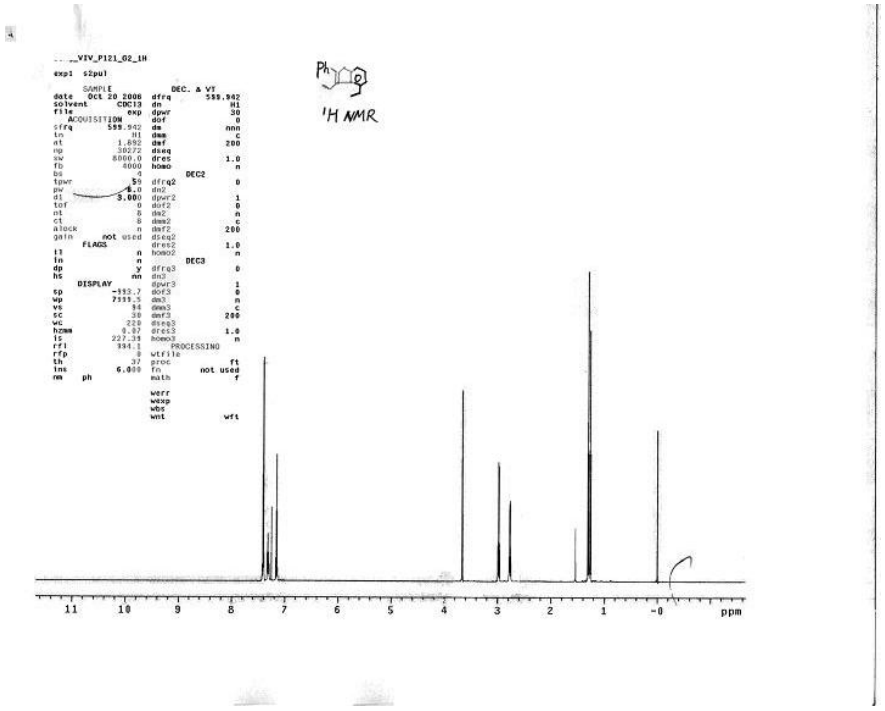

Figure A.5.13 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 13

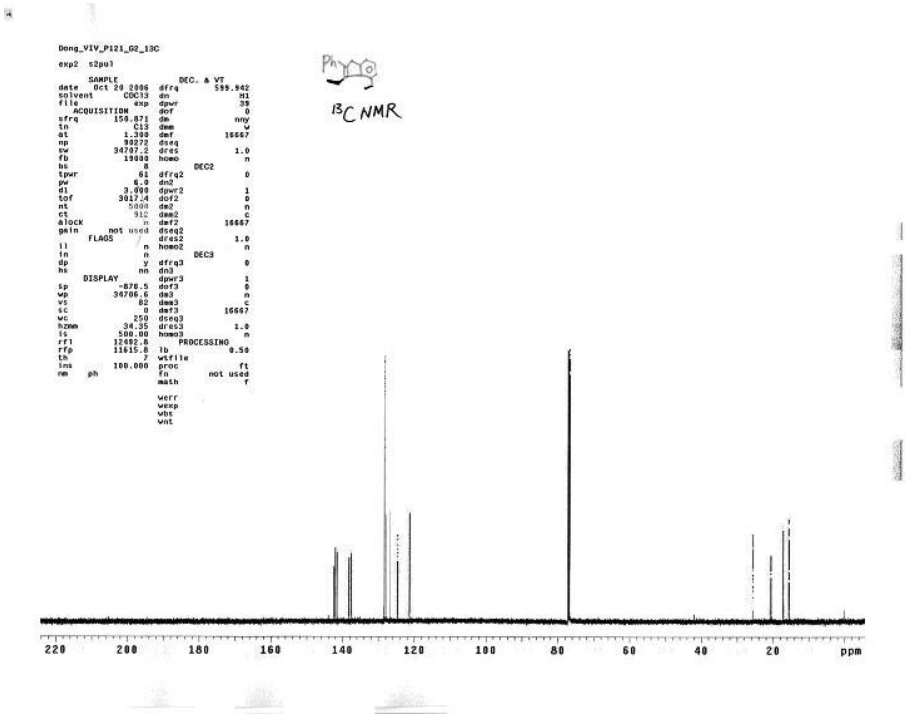

Figure A.5.14 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 13

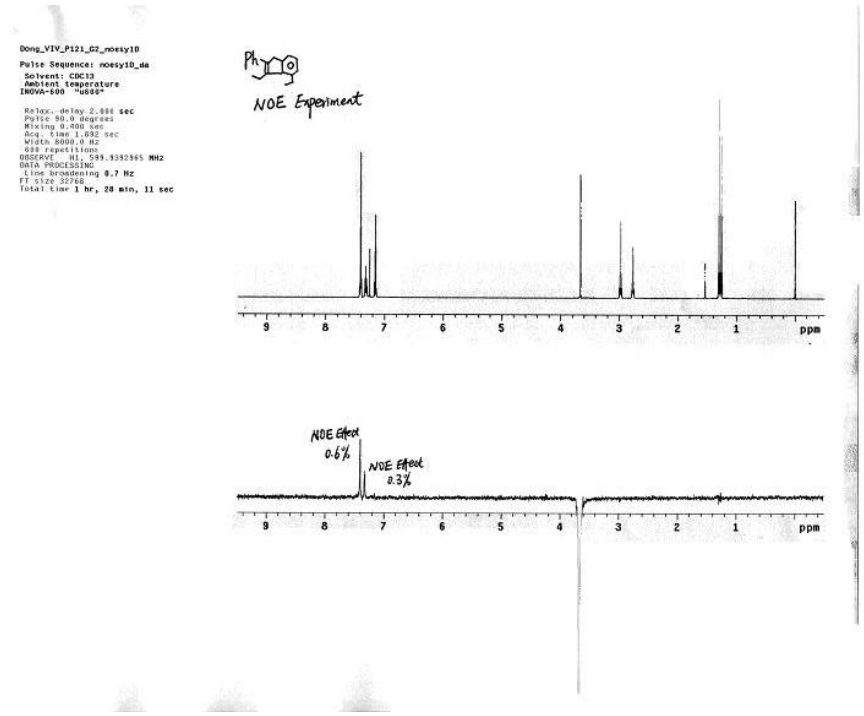

Figure A.5.15 NOE experiment of compound 13

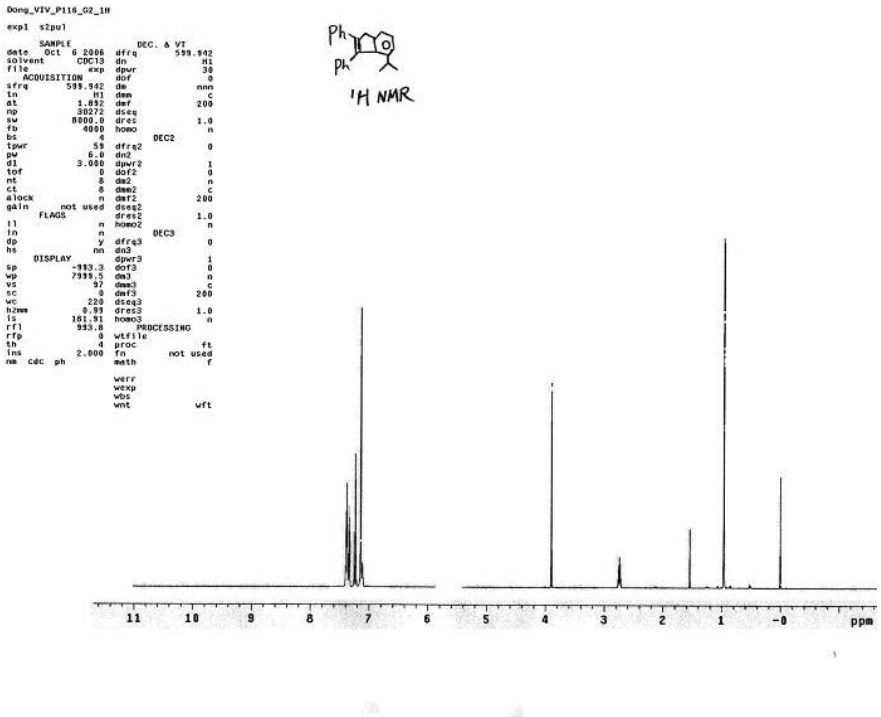

Figure A.5.16 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 14

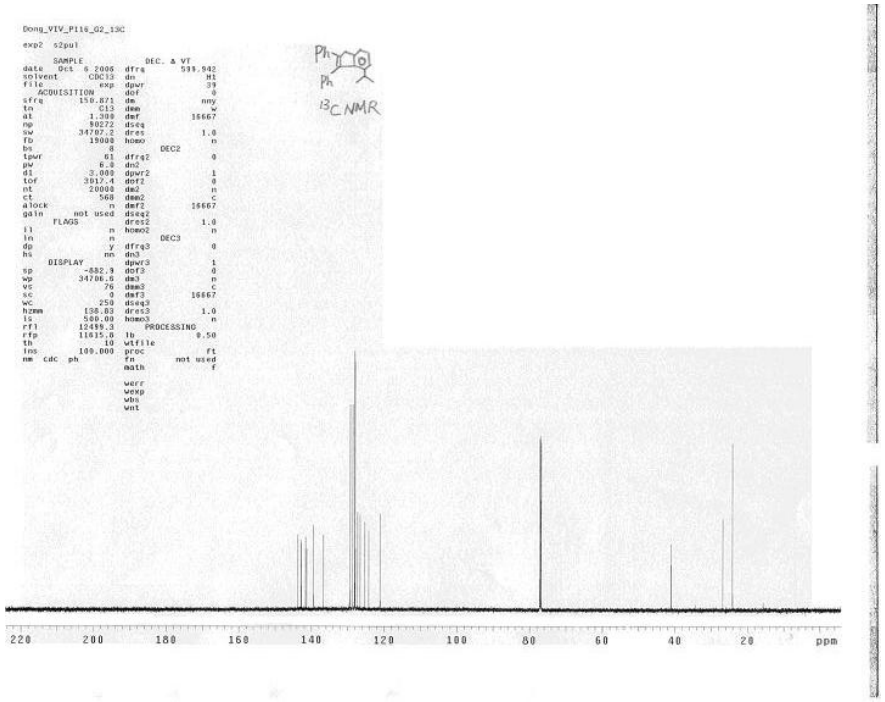

Figure A.5.17 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 14

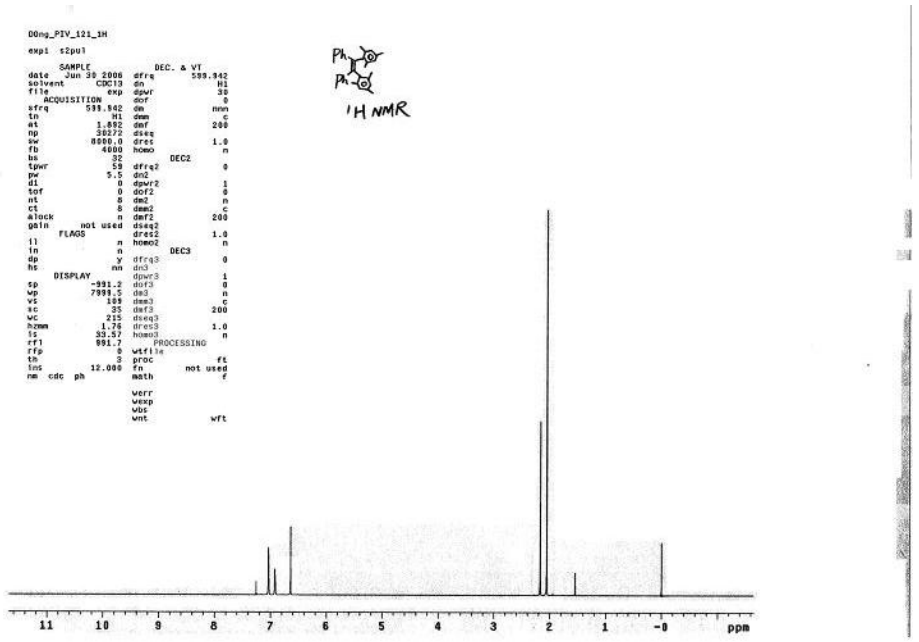

Figure A.5.18 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 16

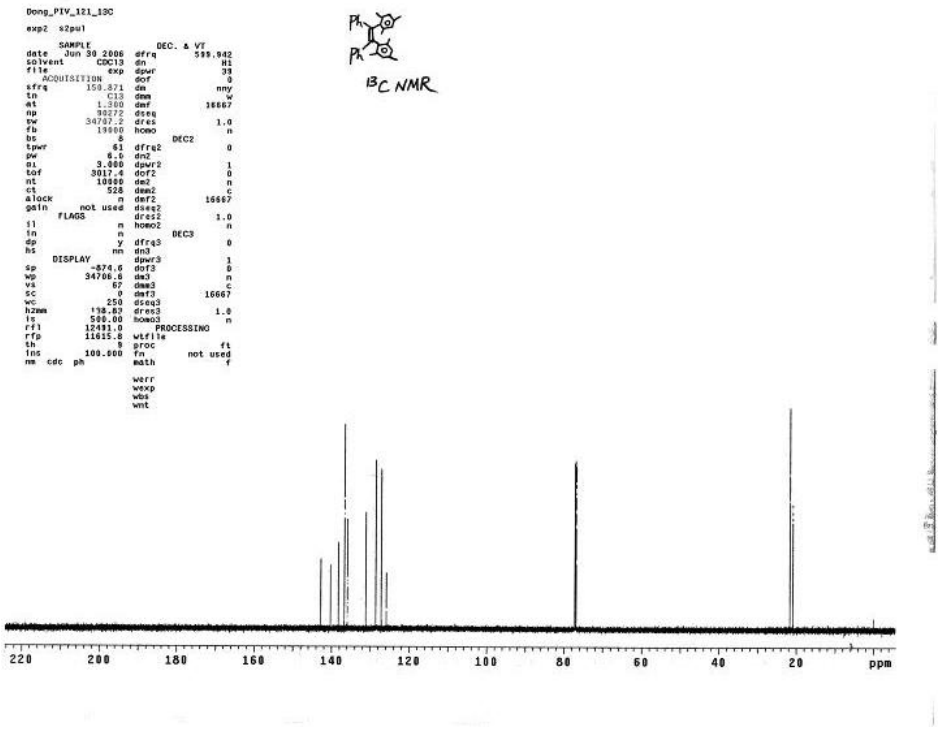

Figure A.5.19 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 16

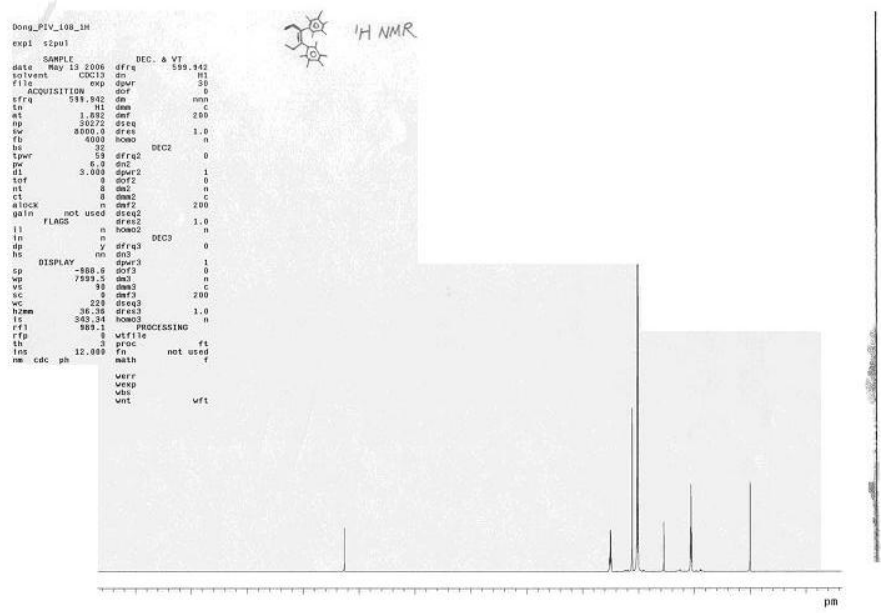

Figure A.5.20 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 21

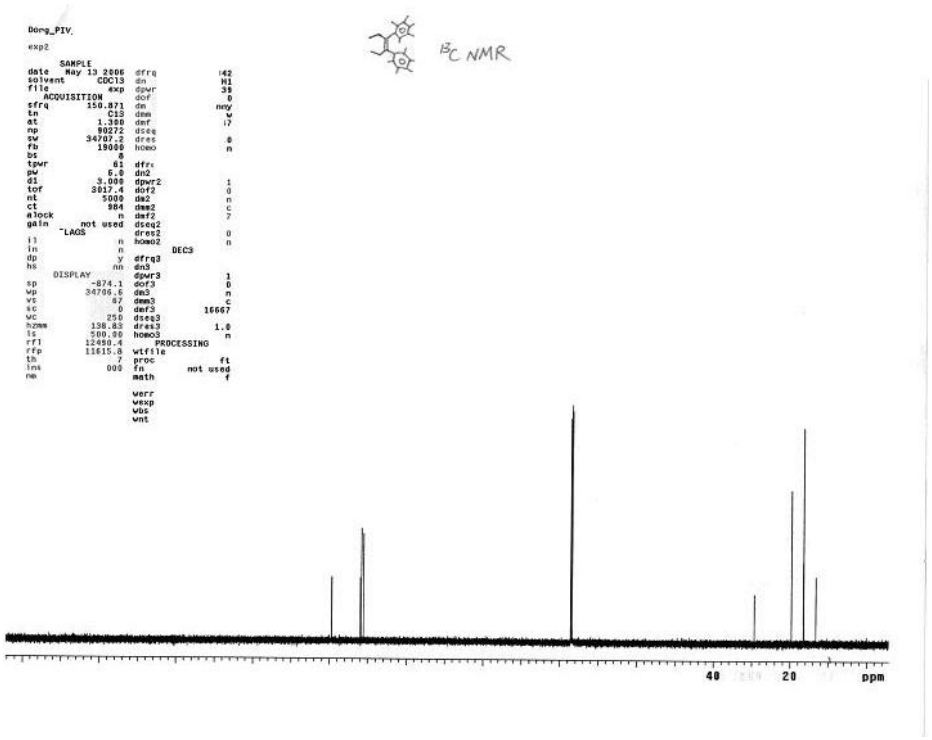

Figure A.5.21 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 21

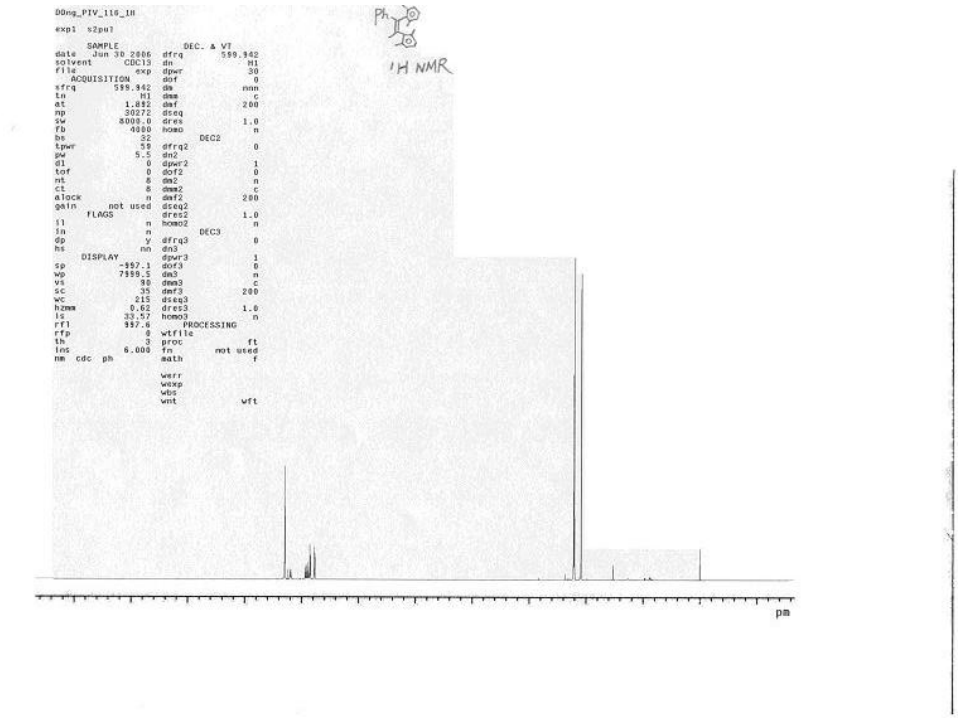

Figure A.5.22 ^{1}H NMR (600 MHz, $CDCl_3$) of compound 22

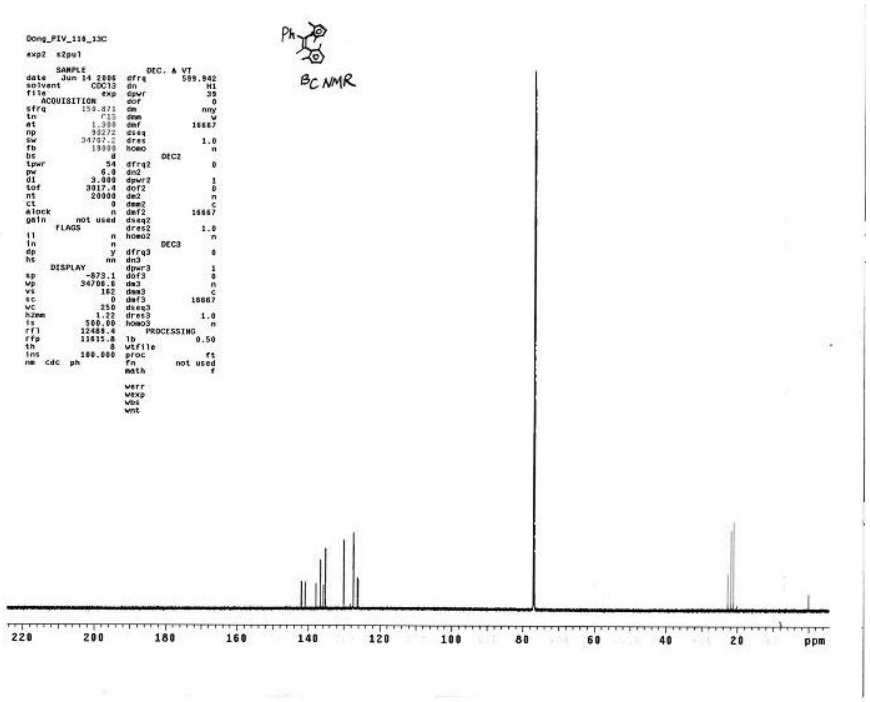

Figure A.5.23 ^{13}C NMR (150 MHz, $CDCl_3$) of compound 22

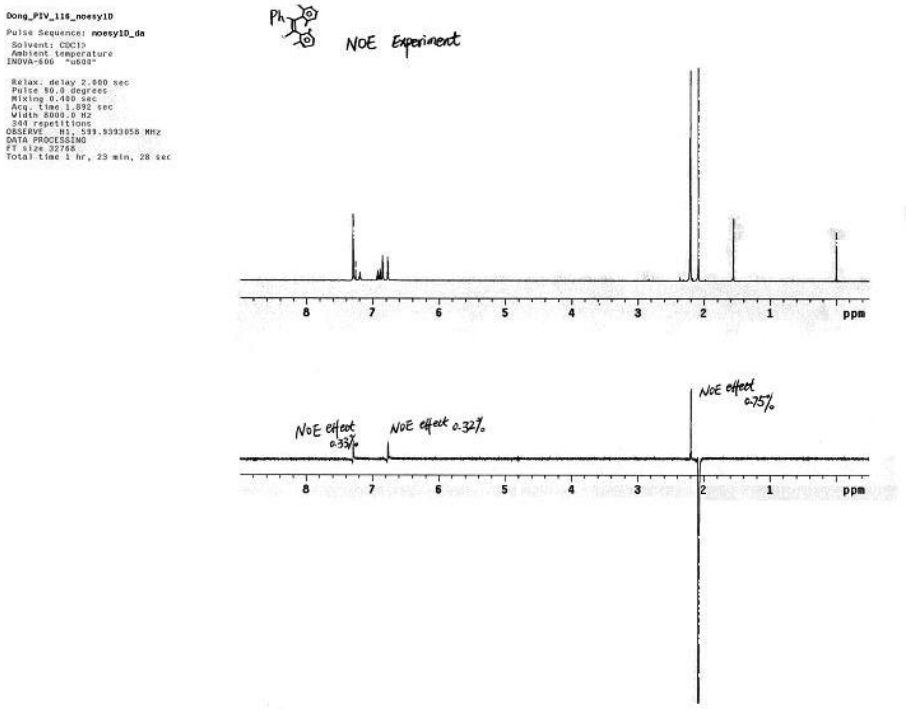

Figure A.5.24 NOE experiment of compound 22

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