Development of Transition-Metal-Catalyzed C–C and C–O Bond Forming Reactions: Synthesis of Aryl Vinyl Ethers and Benzofurans

A Thesis
Submitted for the degree of
DOCTOR OF PHILOSOPHY

By

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August, 2013

To

My Family & Friends

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STATEMENT

I hereby declare that the matter embodied in the thesis is the result of investigation carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of **Dr. Akhila Kumar Sahoo**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

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CERTIFICATE

Certified that the work contained in the thesis entitled "*Development of Transition-Metal-Catalyzed C–C and C–O Bond Forming Reactions: Synthesis of Aryl Vinyl Ethers and Benzofurans*" has been carried out by Mr. Malleswara Rao Kuram under my supervision and the same has not been submitted elsewhere for a degree.

Dr. Akhila Kumar Sahoo

(Supervisor)

Dean

School of Chemistry

Acknowledgements

There are people in everyone's lives who make success both possible and rewarding. Without them, pursuit of this advanced degree would never have been started.

Firstly, I would like to thank Dr. Akhila Kumar Sahoo, for giving me the opportunity to work within his research group. I would like to thank him for advice, guidance and support throughout my research career. I am very grateful for the passion he shows towards research. I appreciate the kind of motivation, freedom, and at the same time supervision if required. The academic freedom offers in creative thinking; this enables finding novel research problems. At last this helps me a lot proving my ability in tackling the challenges associated in research.

Foremost, I would like to thank all my family members. I am very grateful to my family members Amma (Pandamma), Nanna (Gangaraju), sisters (Ramachellamma and Swarnalatha) and brother (Venkateswara Rao). They always supported me in every aspect.

I take this opportunity to thank Prof. M. V. Rajasekharan, Dean, School of Chemistry for providing us the facilities needed for our research. I extend my sincere thank to former Deans Prof. D. Basavaiah and Prof. M. Periasamy, and all the faculty members, School of Chemistry for their co-operation on various aspects.

I feel fortunate to have friends Raveendra, Seshadri, Nagarjuna, Gupta Chandaluri, Murali, Nagarju Dokka, Nagakrishna, Suresh Ponguleti, Poseswara Rao, Ramkrishna Chary P, Bhagya Raju anna, who have been my close friends over the years, for keeping me sane, giving me perspective and who have made the time more enjoyable.

It is great pleasure to thank all my lab members. Sincere thanks to my co-worker and friend Bhanu for his help, pleasant company, and cooperation during my Ph.D. tenure. I thank to my friends and labmates Ramu Yadav, Nayan Ghosh, Sanatan Nayak, Raja Rit, Sudheer Kumar, Nagarjuna, Koushik, Shankar Majji, Prabagar, for their support throughout the tenure and creating cheerful work atmosphere. I wish to thank M.Sc project students Madhu and Ramarao to work with me. Special thanks to Dr. A. K. Sahoo family, Rashmita Sahoo and Amlesh (sonu) for hosting group dinners at their home.

I also thank all the non-teaching staff of the School of Chemistry for their assistance on various occasions. I thank DST and UGC for providing the required instruments and CSIR for the financial support. I would like to thank Prof. Kalidas Sen for providing DST-JC Bose fellowship.

I am lucky enough to have the support of many School of Chemistry friends and colleagues Seshu, Venu, Rama Krishna, Sudharani, Dr. Suresh, Madhu, Dinesh (PRS lab), Ganesh anna, Srinivas anna, Naveen, Ramana, Manoj, Vanaja (RB lab), Kishore, Bharat, Dr.GDP, Dr.Rambabu, Dr.Srinivas Rao, Ramakrishna, Sridevi, Poulami, Krishna (SKD lab), Gupta, Hari (Bakkodu), Keshav, Lavasya Dr. Ramesh (TPR lab), Dr. DK, Dr. Vikram, Dr. M. Ramu anna, Dr. Satish Anna, Dr. Vijji, Ramaraju, Ramesh, Ramkumar, Prakash (RN lab), Kishore Pilli, Anand, Prabhu, Nagarjuna, Yugandar (VB lab), Dr.Nagarju anna, Dr.Guru Braham, Dr.Laxaman, Mallesh anna, Sanjeev, Suresh (MP lab), Tirupathi Reddy, Kishore, Pavan, Siva, Sudheer (MJS lab), Naidu(Top 10), Sreenivas D, Vignesh, Sekhar Reddy, Haneesh, Ganesh, Vikas, Praveen (KMD lab), Sudhangshu, Malkappa, Raju, Billa, Kondareddy (TJ lab), Dr. Phani Pavan, Dr.Bhuvan, Dr.Venu, Dr.Rama Suresh, Dr. Anjaneyalu, Ramesh, Gangadhar, Nagarjuna reddy, Sreenivas (KCK lab), Ajay, Narayana, Chandrasekhar, Bashak, Pramithi, Krishna, Ramudu (RC lab), Karunakar (Bakka), Rajendar, Srinu (LGP lab), Krishna chary, Swamy, Balu, Nagaraju, Satish (SP lab), Suryanarayana, Rajesh, Maddy, Sudalai, Rajesh, Geeta (AN lab), Ashok, Chandu, Dr. Ravi, Dr.Santosh, Banarjee, Kara, Sowmya, Patra (AS lab), Yaseen, Sashi, Ramakrisha (AKB lab), Dr.Sekhar Reddy, Dr.Ramesh, Katta, Raghavaiah, Satpal, Sai, Lings (DB lab), Dr.Rajgopal Sr., Rajgopal Jr., N. P. Reddy, Krishna, Sugata, Rudro, Dr. Sivaranjan Reddy (SM lab), Sreedhar, Dinesh (MDP lab), Dr. Kishore, Dr. Ramkumar, Dr. Vijendhra Reddy, Chary, Bharani, Murali, Shivaprasad (assistant professor), Srinivas Reddy, Venky, Karthik DBR (lab), Sandeep, Tridib, Obaiah, Anup, Satish, Nanda Kishore, Sanjeev, Vikranth, (PKP lab).

I would like to thank Dr. P. Raghavaiah, Gupta, Bharat, Kishore who have helped me in XRD studies and Balavardhan for optical studies.

I would like to acknowledge the NRS hostel mates Malli, Sankar, Murali Manohar, Venkaiah, Dr. Majji, Shyam anna, Vijay matcha, Manoj anna, Johnson.

I would like to thank my college and childhood friends Gani (Rama Rao), Rambabu, Narender Reddy, Brahmi, Narotham, Narender, Krishna, Chidvi, Chinnam Naidu, Raj Kumar, Bhasha, Jittu, Rambabu(TVG), Devaraju, Koteswara Rao.

I would like to acknowledge all my teachers, Laxmaiah sir, Gnaneswari madam, Dr. Bidhu Bhusan Das, Somaiah sir, Narayana sir.

I thank to all my family friends and relatives, Suri, Papu and her family, Venky, Nagadurga, Durga, Venkata Laxmi, Kanaka akka and her family, Suri Vadina, Mutyalu

Vadina, Laxman anna, Gangajalam akka and her family, Devaraju (pedananna) and Ramulamma (peddamma), Mukaiah (chinnana), Atlamma (pinni), Papamma, Venteswara Rao master, Bhavani pinni, Pappamma pinni, Jogarao, Ramakrishna, Venkamma pinni, Seeta, Chandra akka and his family, Ramesh anna and his family, and my little sweet hearts Meghana, Jessy, Ramya, Naveen, Hema, Mounika, Manoj, Rakhi, Bharat, Sailu, Raaji, Puri and also all my church members.

I would like to acknowledge and thank one person specially, Lord Jesus who is my best friend, even though I'm not worthy and good. He always loves me, my comforter in all my situations and joy in all my life. Without Him, nothing is possible.

Malleswara Rao Kuram

University of Hyderabad
August, 2013

SYNOPSIS

The thesis entitled **"Development of Transition-Metal-Catalyzed C-C and C-O Bond Forming Reactions: Synthesis of Aryl Vinyl Ethers and Benzofurans"**, consists of three chapters: (**1**) Gold-catalyzed intermolecular hydrophenoxylation of unactivated internal alkynes, (**2**) Direct access to benzo[*b*]furans through palladium-catalyzed oxidative annulation of phenols and unactivated internal alkynes, (**3**) Design, synthesis and optoelectronic properties of fused furo-indole derivatives.

In this thesis, each chapter is subdivided into three parts: (a) Introduction (literature survey), (b) Results and Discussion (including future work), and (c) Experimental Section. All the new compounds are characterized by ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data followed by elemental analyses. The structure of the some of the compounds is unambiguously elucidated by X-ray crystallography studies.

Chapter 1

Gold-Catalyzed Intermolecular Hydrophenoxylation of Unactivated Internal Alkynes

In this chapter, a general and simple strategy for the synthesis of functionally diverse aryl vinyl ethers is reported through gold-catalyzed intermolecular addition of electronically and sterically substituted phenols with unactivated internal alkynes (Figure 1).

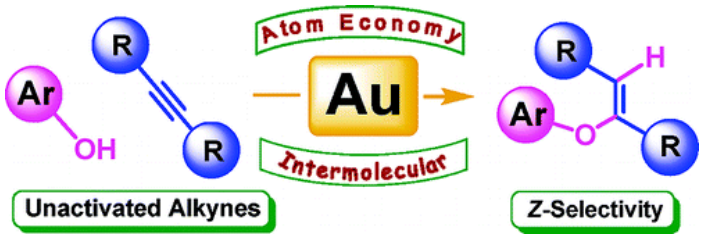
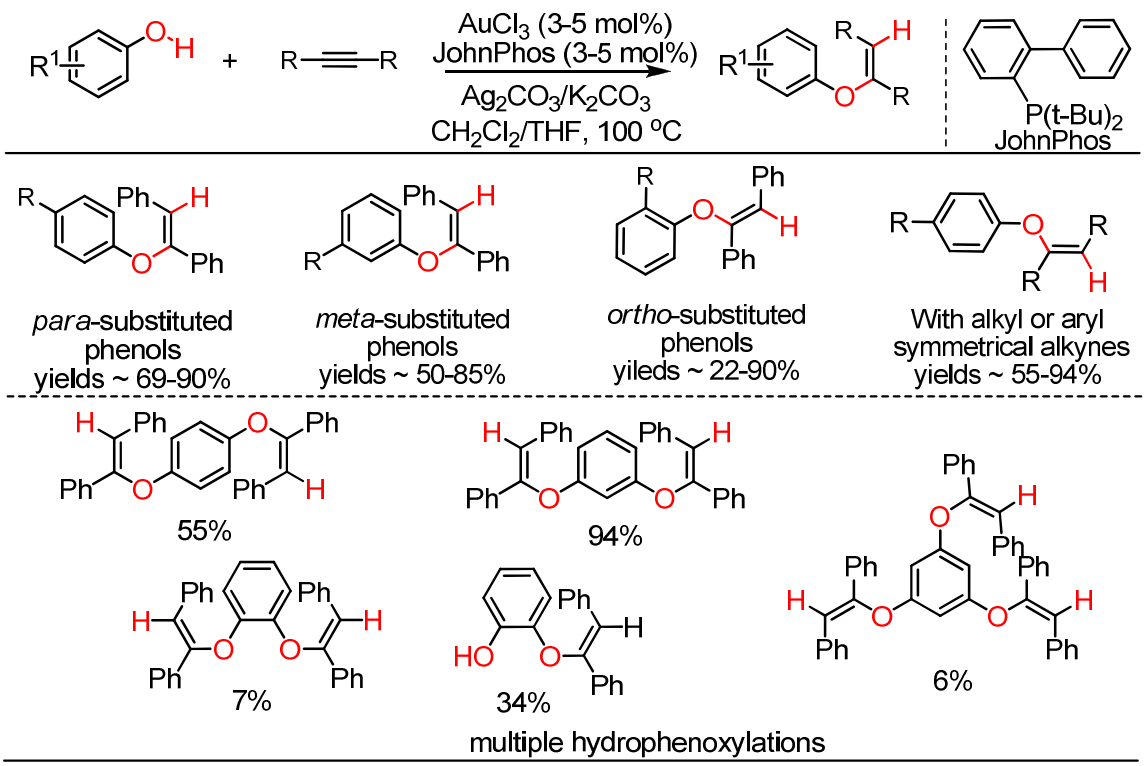


Figure 1. The gold-catalyzed synthesis of aryl vinyl ethers from phenols and unactivated internal alkynes.

The chapter begins in highlighting the importance of C–O bond in organic synthesis. The precedence on the transition-metal catalyzed C–O bond forming reactions is described in brief. The shortcomings in this survey inspired us to develop an addition reaction between *phenol and unactivated internal alkynes*, which to the best of our knowledge is the first report. Gratifyingly, an extensive screening of various combinations of catalysts, ligands, and bases led to an effective catalytic systems: Condition A [$AuCl_3$

(3 mol%), JohnPhos (3 mol%), and Ag_2CO_3 base in CH_2Cl_2 at 100 °C] useful for the hydrophenoxylation of activated phenols with unactivated internal alkynes and Condition B comprising of [$AuCl_3$ (5 mol%), JohnPhos (5 mol%), and K_2CO_3 base in THF at 100 °C] employed for the hydrophenoxylation of non-activated phenols with unactivated internal alkynes. This one-step synthetic protocol allows accessing a wide array of vinyl(1,2-disubstituted)aryl ethers easily. Addition of phenols to unsymmetrical alkynes provides the corresponding mixture of regioisomers of aryl-vinyl ethers with appreciable selectivity. The multiple hydrophenoxylations of polyphenols with diphenylacetylene are successfully demonstrated, highlighting the versatility and synthetic utility of the current strategy. The exclusive formation of *Z*-aryl-vinyl ethers suggests the anti-attack of the phenoxide on the gold-activated alkyne.



Scheme 1: Substrate scope for the synthesis of aryl-vinyl ethers.

Chapter 2

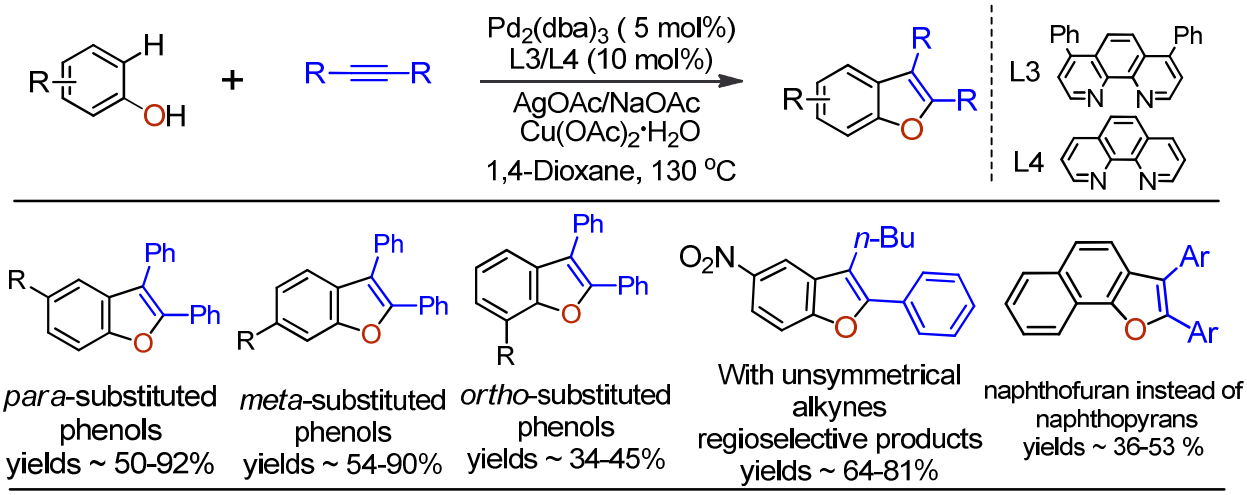
Direct Access to Benzo[*b*]furans through Palladium-Catalyzed Oxidative Annulation of Phenols and Unactivated Internal Alkynes

Chapter 2 describes the palladium-catalyzed oxidative annulation between commercially available phenols and readily accessible unactivated internal alkynes to provide 2,3-disubstituted benzo[*b*]furans (Figure 2).

Figure 2. The Pd-catalyzed synthesis of benzo[*b*]furans from phenols and unactivated internal alkynes.

The ubiquitous benzofuran skeleton is a privileged structure found in numerous natural products, biologically active compounds, and organic materials. Owing to the importance of benzo[*b*]furans and its derivatives, various synthetically viable strategies have been devised for the construction of benzo[*b*]furans. Some of the conceptually most interesting synthetic strategies including the transition-metal catalyzed C–H activation/C–O bond forming processes for benzo[*b*]furans are detailed at the beginning of this chapter. Pleasingly, the annulation between the phenols and the diphenyl acetylene is successfully achieved under the influence of Pd-catalysts. An extensive screening of various combinations of catalysts, bases and oxidants led to two effective catalytic systems: the Condition A [$Pd_2(dba)_3$, L3 (bathophenanthroline), AgOAc base, and $Cu(OAc)_2{\cdot}H_2O$ oxidant in 1,4-dioxane at 130 ºC] is suitable for the [3+2] annulations between the activated *p*-nitrophenol and unactivated internal diphenyl acetylene, whereas the Condition B [$Pd_2(dba)_3$, L4 (phenanthroline), NaOAc base, and $Cu(OAc)_2{\cdot}H_2O$ oxidant in 1,4-dioxane at 130 ºC] is selected for the [3+2] annulations between the non-activated *p*-methoxyphenol and internal diphenylacetylene. The electronic properties and acidity of the phenols significantly influence the reactivity: while the reaction of electron-poor phenols with alkynes proceeds in the presence of AgOAc, the base NaOAc is required in case of electron-rich phenols. This one-step method allows efficient access to a wide array of benzo[*b*]furans. The reaction conditions tolerated a variety of common functional

groups which greatly enhances the synthetic versatility of this strategy. Furthermore, the reaction of phenols with aryl-alkyl-substituted unsymmetrical alkynes resulted in regioselective benzofurans. The protocol could efficiently be applied in the installation of the benzofuran skeleton on biologically active complex molecules. The oxidative annulation of α-naphthol with internal unactivated alkynes resulted in naphthofurans rather than naphthopyrans. The preliminary investigations on a plausible reaction mechanism confirmed the involvement of a bis(aryloxo)palladium(II) complex and *ortho*-C–H bond cleavage of phenol.



Scheme 2: Substrate scope for the synthesis of benzofurans

Chapter 3

Design, Synthesis and Optoelectronic Properties of Fused Furo-Indole Derivatives

Chapter **3** depicts the synthesis of fused furo-indole derivatives using the developed method for benzo[*b*]furans described in Chapter 2. The optoelectronic property of the newly synthesized fused furo-indoles is also discussed in this chapter.

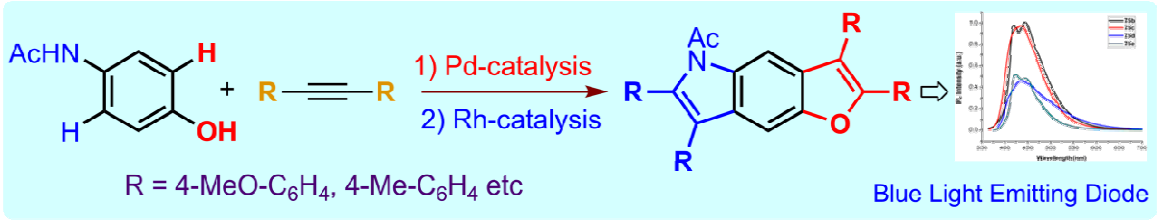


Figure 3: Synthesis of fused furo-indoles with the sequential installation of benzofuran and indole skeleton on *N*-acetyl-4-amino phenols.

Various fused furo-indole extended π-conjugated frameworks are successfully fabricated involving the multiple activations of C(sp^2)–H bonds. The synthesis of fused furo-indole skeleton is initiated with the installation of benzo[*b*]furans on *N*-acetyl-4-amino phenols employing the recently developed palladium-catalyzed oxidative annulation between phenols and unactivated internal alkynes (Chapter 2).

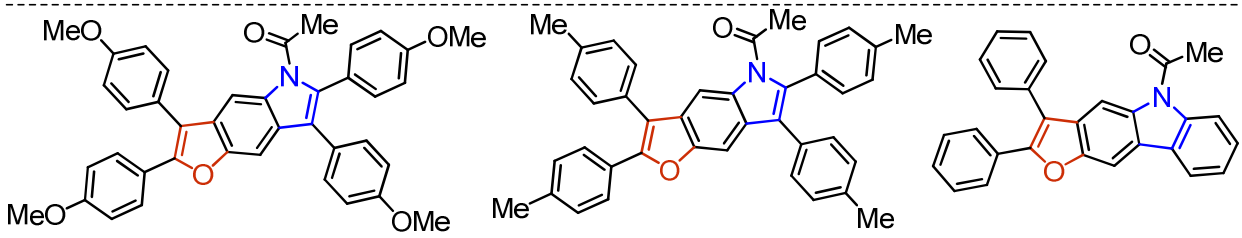


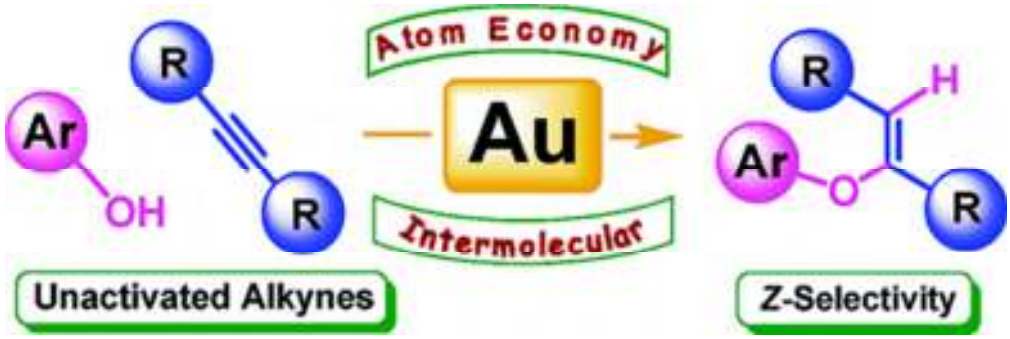
Figure 4: Extended π-conjugated molecular frameworks

The survival of the NHAc group allows the construction of indole-skeleton following the Fagnou's Rh-catalyzed oxidative annulations of anilides with internal alkynes. These two-step synthetic procedures useful in accessing a wide array of fused furo-indoles. The optical and electronic properties of these new molecular entities are studied by UV-vis and fluorescence spectroscopy. All the molecules showed strong absorption at UV range (300–400 nm) and strong blue emission. We therefore believe these molecules may find possible applications as blue light emitting diodes.

Gold-Catalyzed Intermolecular Hydrophenoxylation of Unactivated Internal Alkynes

1 Chapter

Abstract



A general and simple strategy for the synthesis of functionally diverse arylvinyl ethers is reported through gold-catalyzed intermolecular addition of electronically and sterically substituted phenols with unactivated alkynes. Addition of phenols to unsymmetrical alkynes provides the corresponding mixture of regioisomers with appreciable selectivity. Multiple hydrophenoxylations of polyphenols with diphenylacetylene are demonstrated successfully.

Reference:

Malleswara Rao Kuram, M. Bhanuchandra and Akhila K. Sahoo
J. Org. Chem. **2010**, *75*, 2247–2258

1.1. Introduction

Oxygen containing heterocyclic moieties are widely found in many important structural motifs of naturally occurring and pharmacologically active compounds (Figure 1.1).[1] Therefore development of novel methods for the formation of C–O bond is always demanding.[2] In particular, the enol-ethers are valuable precursors to cycloaddition, cyclopropanation, metathesis, and hydroformylation reactions; they are useful building blocks in the fabrication of complex natural products and its analogues.[3] The addition of an alcoholic O–H bond across alkynes either through inter- or intramolecular fashion provides general access to enol ethers or cyclic ethers with 100 % atom-efficiency.[4] Due to the decrease of disorder in the system, intermolecular reactions are entropically unfavorable over intramolecular reactions. Generally, the precursors for the intramolecular reactions are obtained through specialized protocols involving multiple synthetic steps, whereas simple starting materials are adequate for the intermolecular reactions.[5]

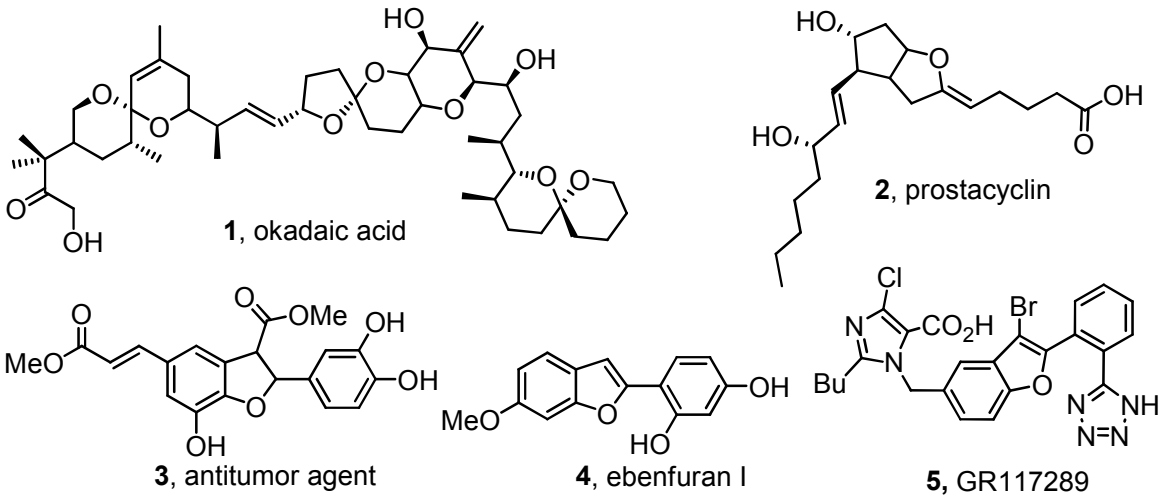
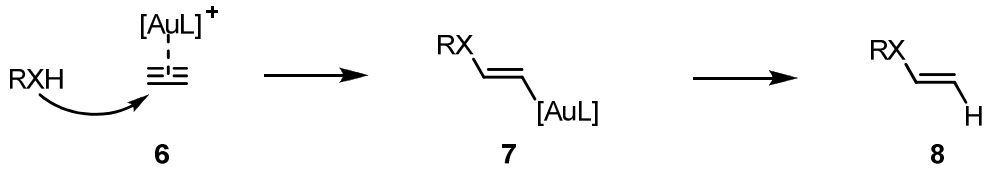


Figure 1.1: Representative oxygen-containing heterocyclic derivatives

The transition-metal-catalyzed C–C and C–X (X = N, O, S etc) bond forming reactions have shown profound impact in organic synthesis. Although transition-metal-catalyzed intramolecular hydroalkoxylations to alkynes are relatively well-known,[6] the intermolecular version is little explored.[7] The challenge lies in effecting the nucleophilic attack of the hard alkoxides obtained from the corresponding alcohols, on soft electron-rich alkynes. Since both the reactants are electron rich species, the attack of oxygen-nucleophiles to carbon-carbon multiple bonds are therefore not facile; unlikely the carbon-carbon multiple bonds are activated by electron withdrawing groups. A solution would be

to use soft and alkynophilic catalysts for the activation of carbon-carbon multiple bonds. The soft gold and platinum complexes are carbophilic Lewis acid catalysts efficiently activate the carbon-carbon π-bonds and useful in accomplishing complicated transformations with ease.[8] For instance: the strong σ-donor and weak π-acceptor of alkyne allows strong activation by gold complex forming the gold complexed alkyne **6** (Scheme 1.1). The gold complexed alkyne **6** is intrinsically electrophilic. The anti attack of nucleophile to **6** forms gold-vinyl complex **7**. Finally protodeauration of **7** results the product **8** (Scheme 1.1).



Scheme 1.1: General schematic representation of activation of alkynes by gold-catalysts

On the basis of the frontier orbitals and relativistic effect, gold is soft and carbophilic in nature.[9] The relativistic contraction of the 6s orbital and expanded 5d orbitals in gold accounts attributing the strength of the Au-Ligand bonds. Based on the computational studies of enthalpies of formation, the complexes between alkyne and gold catalyst showed the strongest binding energies over the bonding between the alkynes with electrophiles such as iodine and Ag salts.[10] As a consequence, gold salts have emerged as powerful and versatile Lewis acid catalysts invariably used for the C–C and C–X (X = O, N, S etc) bond formations.[8]

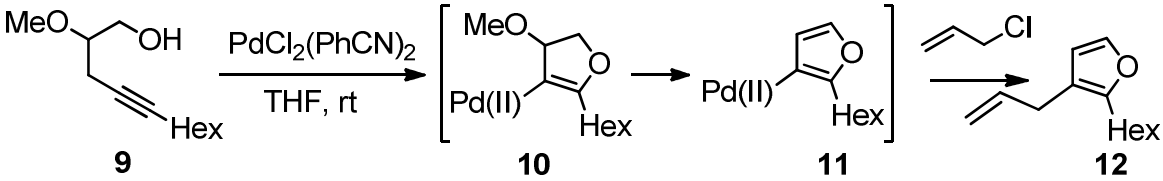
1.2. Precedents

The transition-metal catalyzed addition of oxygen nucleophiles to unactivted alkynes is a powerful strategy for direct formation of O–C(sp^2) bond. Accordingly, the development of novel methods for the hydroalkoxylation of unactivated alkynes has received much attention.[6]

1.2.1. Intramolecular Addition of Phenols and Alcohols to Alkynes

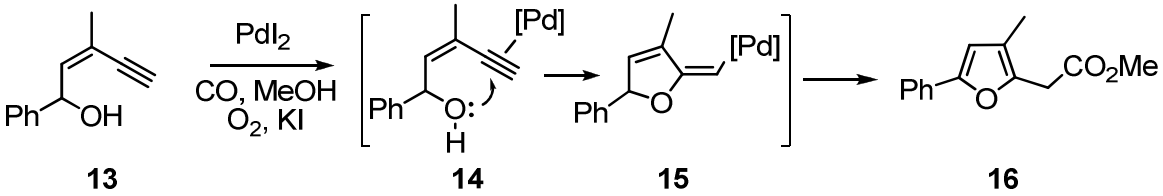
The transition-metal catalyzed intramolecular mode of attack of alcohol/phenol–OH moiety to the unactivated alkynes readily creates the oxygen-bearing heterocycles.

Utimoto and co-workers reported the palladium (Pd)-catalyzed intramolecular addition of alcohol moiety to alkynes for the synthesis of substituted-furans from 2-methoxy-3-alkyn-1-ols (**9**).[11] The reaction proceeds with the attack of the alcohol to the Pd-activated alkyne for the formation of the intermediate **10**. Subsequently, elimination of methanol from **10** generates **11**. Finally, trapping of an electrophile affords 2,3-disubstituted furans **12** (Scheme 1.2).



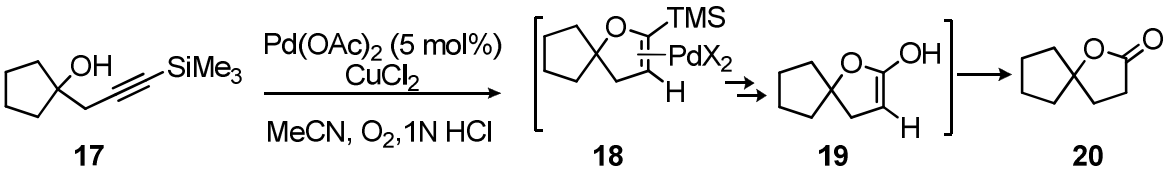
Scheme 1.2: Pd(II)-Catalyzed synthesis of di-substituted furans from alkynols

The highly-substituted furans are readily accessed via the intramolecular 5-*exo*-dig nucleophilic attack of the hydroxyl group of **13** to the Pd-activated triple bond. Finally, the alkoxycarbonylation of **15** followed by the aromatization deliver 2,3,5-trisubstituted furan **16** (Scheme 1.3).[12]



Scheme 1.3: Synthesis of tri-substituted furans from alkynols

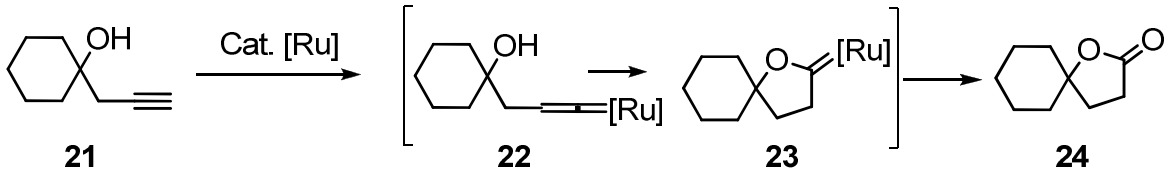
The 4-trimethylsilyl-3-alkyn-1-ols (**17**) swiftly transformed to γ-butyrolactones **20**. The reaction occurs through the intramolecular –OH attack to the activated alkyne-Pd species. The demetalation followed by coordination of Pd to the dihydrofuran forms η^2-olefin complex **18**. Then attack of water on **18** and elimination of $PdX/SiMe_3$ delivers **19**. The enolization of **19** produces lactone **20** (Scheme 1.4).[13]



Scheme 1.4: Pd(II)-Catalyzed formation of γ-butyrolactones from alkynols

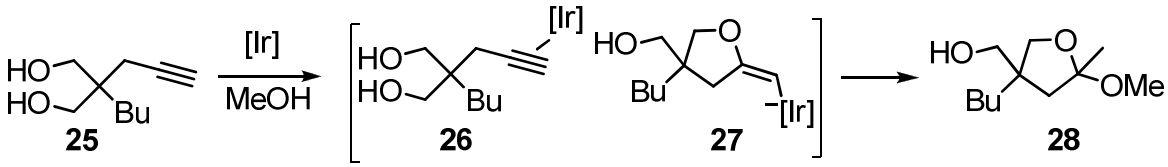
Trost and co-workers demonstrated the synthesis of γ-butyrolactones from propargyl alcohols under the influence of ruthenium catalyst.[14] The reaction initiates with the

oxidative insertion of Ru to the alkyne-moiety forming the vinylidene carbene intermediate **22**. Intramolecular –OH attack on the vinylidene carbene followed by hydrolysis of **23** produces the γ-butyrolactone **24** (Scheme 1.5).



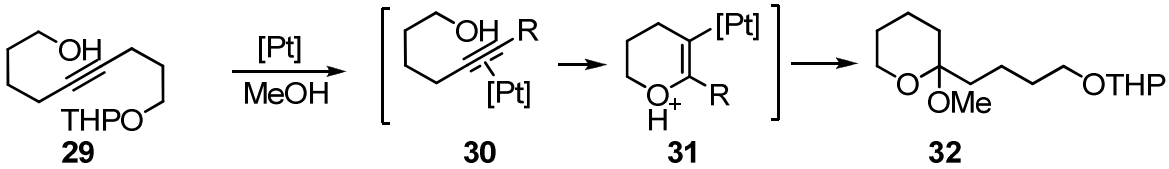
Scheme 1.5: Ru-Catalyzed cycloisomerization and oxidation of propargyl alcohols

The Genet group reported the Ir-catalyzed cyclization and hydroalkoxylation of bis-homopropargyl alcohols.[15] The reaction initiates with the formation of **27** by the attack of –OH group to the Ir-metal activated alkyne-moiety **26**. Intermolecular addition of MeOH to **27** and proton transfer leads to cyclic ketals **28** (Scheme 1.6).



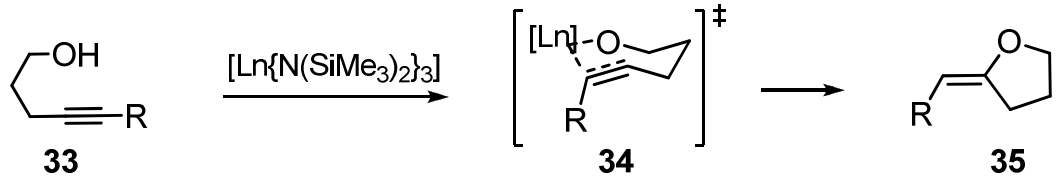
Scheme 1.6: Ir-Catalyzed cyclization/hydroalkoxylation of bis-homo propargyl alcohols

The intramolecular cyclization of alkynol is successfully demonstrated under the influence of Pt-catalysts. For example: 2-methoxy-2'-alkylpyran **32** is obtained from **29** in the presence of Pt-catalyst in methanol (Scheme 1.7). The carbophilic activation of alkyne moiety by Pt-catalyst triggers the attack of the tethered alkyl–OH delivering **31**. The hydromethoxylation of **31** delivers acetals **32**.[16]



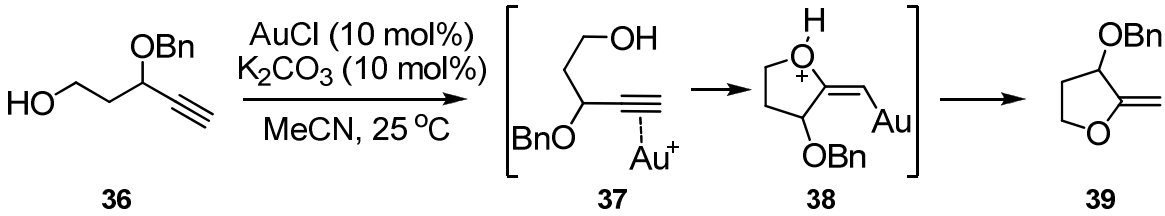
Scheme 1.7: Pt-Catalyzed cyclization of alkynyl alcohols

Recently, Marks and co-workers have shown the Lanthanides assisted intramolecular hydroalkoxylation of alkynol **33** towards the formation of tetrahydrofurans **35** (Scheme 1.8).[17] Authors have demonstrated the participation of the Ln–O bond (**34**) rather than the conventional Ln-alkyne activation in this study.



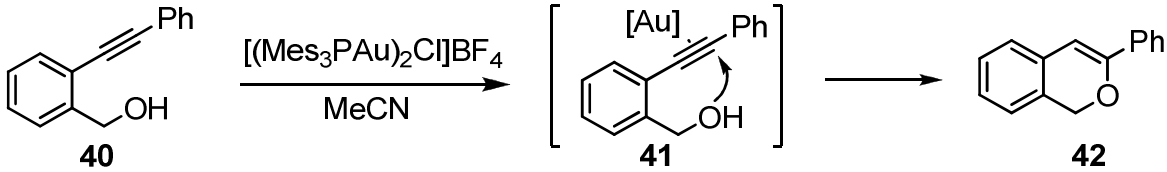
Scheme 1.8: Lanthanides mediated hydroalkoxylation/cyclization of alkynyl alcohols

Interestingly, the gold-catalyzed cyclization of yne-ols efficiently produces the oxygen-bearing heterocycles under mild reaction conditions. The reaction initiates with the electrophilic activation of the acetylene moiety by gold(I) catalyst. This triggers the nucleophilic attack of the tethered-alcohol to the formation of the reactive oxonium species **38**. Finally, protodeauration of **38** generates furan **39**.[18]



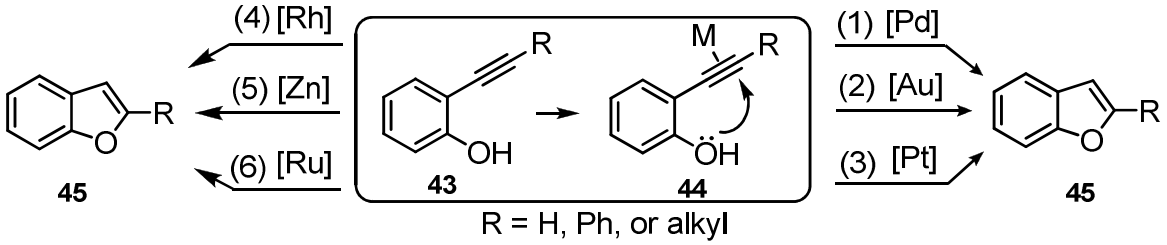
Scheme 1.9: Cyclization of acetylenic alcohols

The Hashmi and co-workers demonstrated the synthesis of isocromenes **42** from alkynyl benzyl alcohols **40**.[19] The attack of the –OH group to the carbophilic Au-activated alkyne-moeity delivers isocromenes (Scheme 1.10).



Scheme 1.10: Cyclization of acetylenic benzyl alcohols

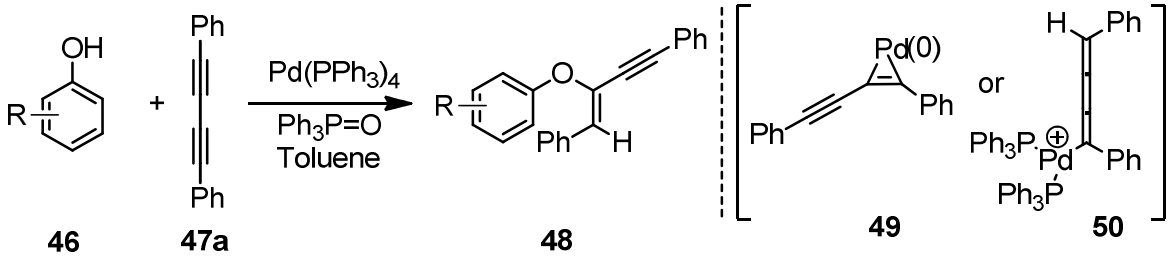
The transition-metal catalyzed intramolecular addition of phenol O–H to alkynes is a well developed method useful in the construction of the oxygen-bearing heterocycles. For example: palladium, platinum, rhodium, zinc and/or ruthenium catalyst assisted cyclization of 2-alkynyl phenols **43** readily deliver benzofuran and its derivatives.[20] The activation of alkyne by metal catalysts allows the intramolecular mode of attack of the oxygen nucleophile forming the oxygen-bearing heterocycles with ease (Scheme 1.11). The *ortho*-alkynyl phenol precursors **43** are easily accessed through Sonogashira coupling of 2-iodophenols.



Scheme 1.11: Cyclization of 2-alkynyl phenols to the formation of benzofurans

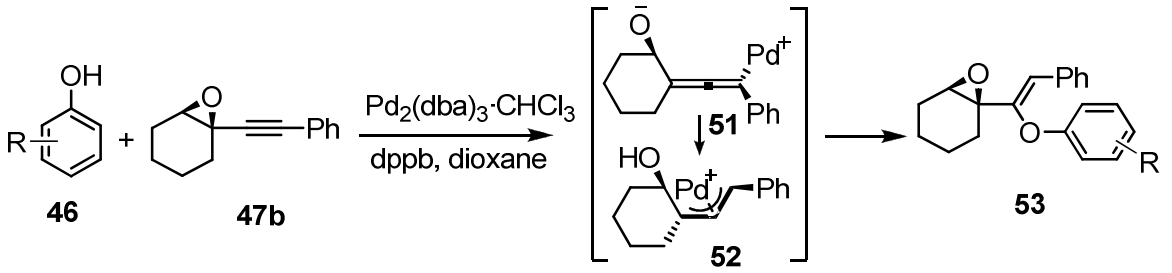
1.2.2. Intermolecular Addition of Phenols and Alcohols to Alkynes

Yamamoto group described the palladium-catalyzed addition of phenols to conjugated diynes (**47a)** producing alkoxylated enynes **48** (Scheme 1.12). The reaction proceeds with the participation of either η^2–coordinated Pd(0) complex **49** or the active σ–cumulenyl palladium intermediate **50**.[21]



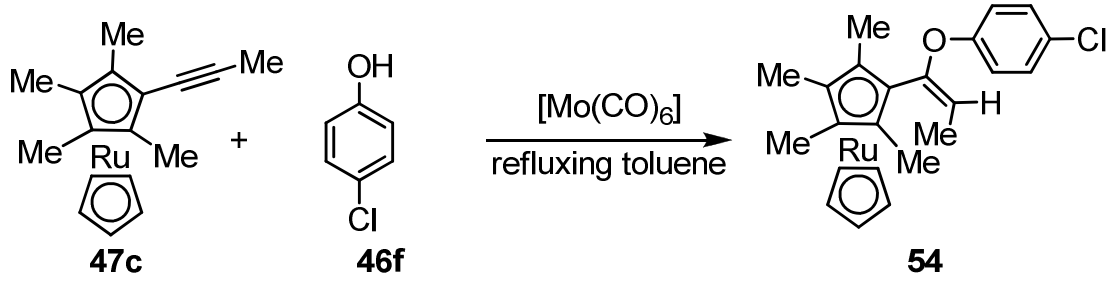
Scheme 1.12: Addition of phenols to diynes

The Pd–catalyzed addition of phenols to propargylic oxiranes **47b** furnishes phenol-substituted alkenes **53**. The π-propargyl and π-allyl palladium complexes **51** and **52**, obtained from oxirane through Pd-activation, are the possible intermediates participated in this reaction (Scheme 1.13).[22]



Scheme 1.13: Addition of phenols to propargylic oxiranes

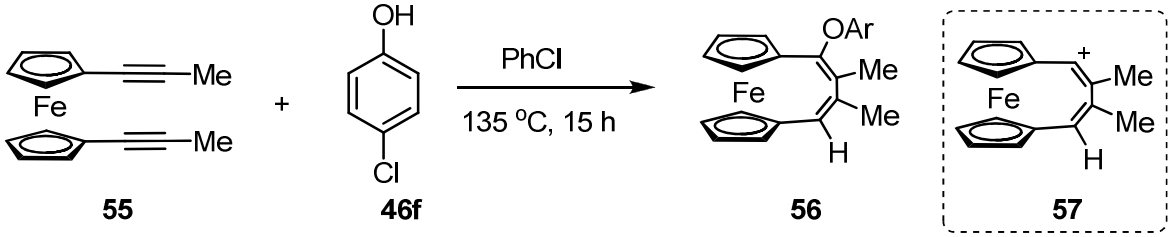
Under the influence of $Mo(CO)_6$ catalyst, a specific ruthenocene bearing alkyne **47c** undergo regioselective addition with activated 4-chlorophenol (**46f**) producing the desired hydropenoxylation product **54** (Scheme 1.14).[23]



47c **46f** **54**

Scheme 1.14: Addition of 4-chlorophenol to ruthenocene bearing alkyne

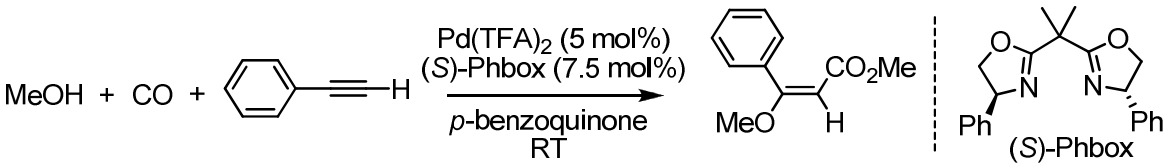
The transannular addition of 4-chlorophenol to 1,1'-dialkynylferrocene **55** proceeds in the presence of $Mo(CO)_6$.[24] The reaction involves the participation of vinylic cationic intermediate **57** (Scheme 1.15).



55 **46f** **56** **57**

Scheme 1.15: Addition of 4-chlorophenol to 1,1'-dialkynylferrocene

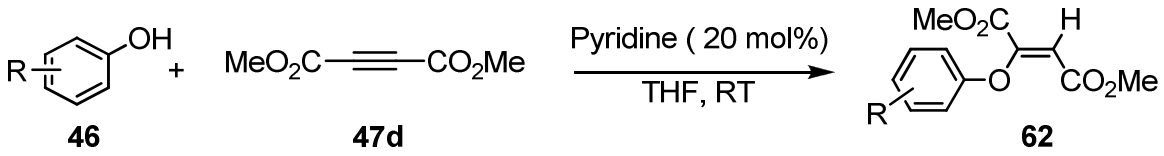
Kato group demonstrated the palladium(II)bis(oxazoline) catalyzed intermolecular methoxy-carbonylation of terminal alkynes.[25] The box ligand **61** is thought to enhance the π–electrophilicity of Pd(II) and activate the "soft" triple bond. The nucleophilic attack of methanol **58** to the Pd-coordinated-alkyne forms a vinylpalladium intermediate. The CO insertion into the C–Pd bond followed by methanolysis of the resulting acylpalladium complex affords β–methoxyacrylates (**60**) (Scheme 1.16).



58 **59** **60** **61**

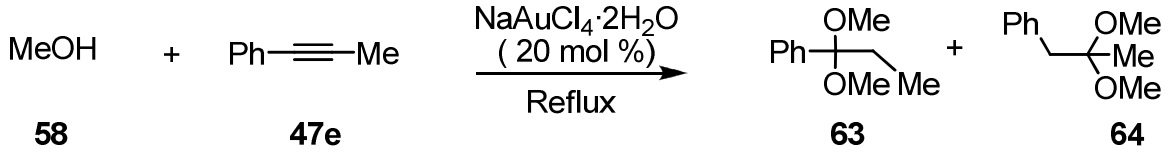
Scheme 1.16: Pd-Catalyzed methoxycarbonylation of alkynes

The base-assisted Michael-type addition of phenols to activated dimethylacetylene dicarboxylates (DMAD, **47d**) offers a straightforward approach for the C–O bond formation.[26] The reaction is diastereoselective, exclusively forming *Z*-aryl vinyl ethers **62** (Scheme 1.17).



Scheme 1.17: Addition of phenols to DMAD

The intermolecular addition of oxygen nucleophile methanol (**58**) to the unactivated phenyl methyl acetylene (**47e**) is successfully performed for the first time under the gold(III) salts.[27] This reaction deliver a mixture of two regioisomeric dimethylacetals **63** and **64** (Scheme 1.18).

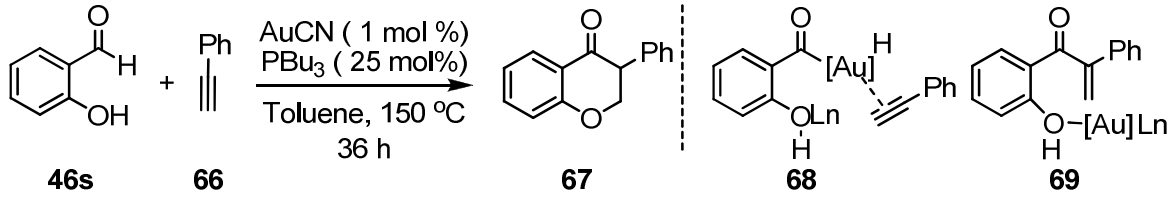


Scheme 1.18: Addition of alcohols to alkynes

The addition of primary and secondary alcohols to diphenylacetylene (**47f**) was efficiently conducted under the influence of Au(I)-catalyst at room temperature (Scheme 1.19). Unfortunately, *the tertiary alcohols and phenols failed to react with unactivated internal alkynes* under the reported conditions.[28]

Scheme 1.19: Addition of alcohols to alkynes using cationic gold species

Recently, gold(I)-catalyzed annulation of *o*-hydroxy benzaldehydes with terminal alkynes for the synthesis of isoflavanones is reported without direct formation of O–C bond.[29] Oxidative addition of the aldehyde C–H bond with Au-catalyst forms acyl gold(III) hydride at first, which simultaneously activates the alkyne triple bond forming the intermediate **68**. Hydrometalation of the activated **68** forms the enone **69**. Subsequently, conjugate addition of hydroxyl group to enone **69** followed by reductive elimination affords isoflavanone derivatives **67**.

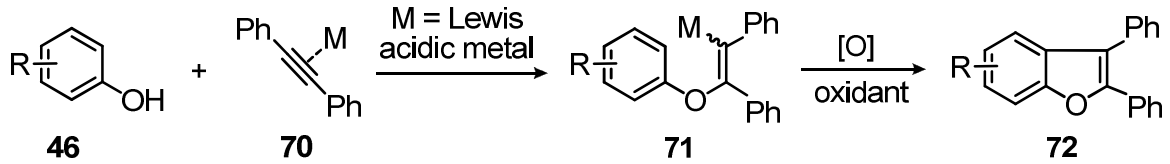


Scheme 1.20: Addition of salicylaldehydes to terminal alkynes

Survey of these reports reveals that the intramolecular hydroalkoxylation to alkynes is relatively well known, while the intermolecular mode of addition of oxygen nucleophiles to unactivated alkynes is little explored.

1.3. Problems and Design Plan

The addition of alcohols and phenols to activated alkynes has been well studied. Under the influence of gold-catalyst, the primary and secondary alcohols underwent 1,2-addition successfully with unactivated alkynes. The careful survey of literature revealed that the intermolecular mode of addition of phenols to unactivated alkynes remains elusive until 2009.[28] The problem lies in effecting the nucleophilic attack of the hard phenoxides obtained from the corresponding phenols, on soft electron-rich alkynes. We therefore envision the carbophilic activation of the unactivated alkynes by Lewis acid metal catalyst; this would trigger the attack of nucleophile such as phenol and forms the metal-vinyl intermediate **71a/71b**. The oxidative cyclization of **71** would then generate the interesting benzofurans in a single step (Scheme 1.21).



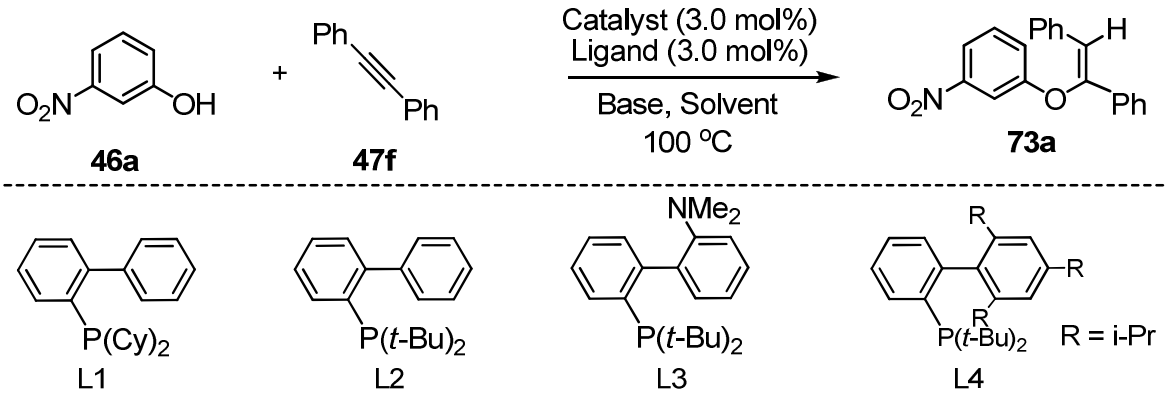
Scheme 1.21: Synthesis of benzofurans from phenols and alkynes

1.4. Results and Discussion

1.4.1. Reaction Optimization

During the course of our studies on the oxidative annulation between phenols and unactivated internal alkynes for the synthesis of benzofurans (discussed in Chapter 2), we decided to evaluate the influence of carbophilic Lewis acid gold-catalysts for the activation of alkynes. The reaction of 3-nitrophenol (**46a**) with diphenylacetylene (**47f**) under a catalytic mixture of $AuCl_3$ and biaryl ligand (2-biphenyl)dicyclohexylphosphine (CyJohnPhos, L1)/ (2-biphenyl)di-*tert*-butylphosphine (JohnPhos, L2), and Ag_2CO_3 base in nitromethane solvent surprisingly resulted the hydrophenoxylation product (*Z*)-(1-(3-nitrophenoxy)ethene-1,2-diyl)dibenzene (**73a**) as observed in GC-MS analysis (entries 1 and 2, Table 1.1). *To the best of our knowledge, the gold-catalyzed addition of phenols to unactivated alkynes is not yet disclosed*. Therefore, we sought to develop this interesting transformation and the optimization details are depicted in Table 1.1. Not even a trace of **73a** was detected in the absence of ligands (entry 3). The use of phosphine ligands such as PPh_3 and PCy_3 did not yield the product (entries 4 and 5). With Ag_2CO_3 base and L2 ligand, different solvents were then screened. Solvents such as toluene, 1,4-dioxane, THF, DMF and 1,2-dichloroethane (1,2-DCE) provided lower amounts of **73a**, as detected in GC, whereas CH_2Cl_2 appeared effective providing 98% conversion in 24 h (entries 6–11). With the optimal condition entry 11 in hand, we then screened other ligands, catalysts and bases. Among other Buchwald ligands examined (entries 11−14), L2 (JohnPhos) was found to be the best, and the yield of **73a** was 98% by GC (entry 11). In general, the sterically encumbered ligand *t*BuXPhos (L4) is more active than L2 in the cross-coupling reactions;[30] however, the reverse trend of ligand activity (L2 > L4) was observed in the current study. Explorations of various gold catalysts such as AuCl, PPh_3AuCl, PPh_3AuOTf, PPh_3AuSbF_6, and $AuBr_3$ with ligand L2 also led to poor yields of **73a** (entries 15–19). Next we screened the effect of silver salts in this reaction. The silver salts, such as AgOTf, AgOAc, $AgBF_4$, and $AgNO_3$, were found to be ineffective (entries 20–23). With the inorganic base K_2CO_3, only trace amount of product was observed (entry 24). Therefore, the reaction condition in entry 11 gave optimal yield of **73a** from 3-nitrophenol (**46a**) and diphenylacetylene.

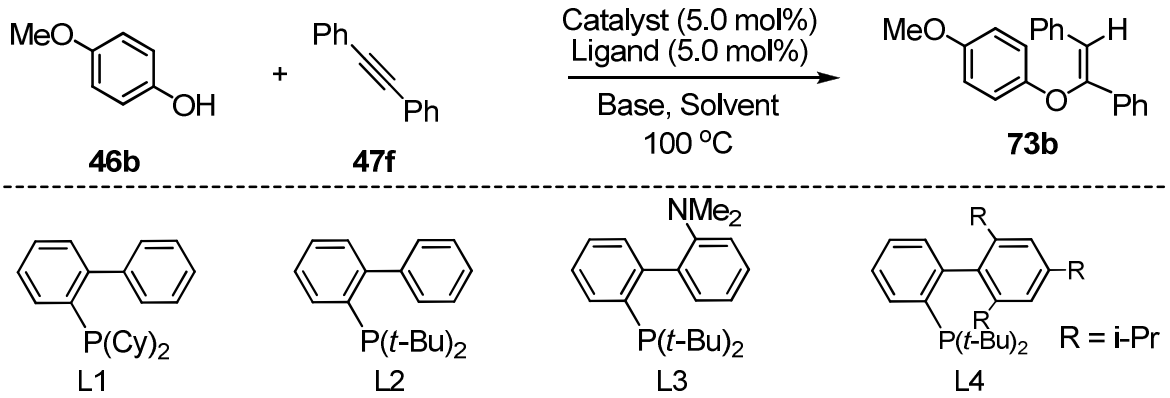
Table 1.1: Reaction between 3-nitrophenol and diphenylacetylene: Reaction optimization[a]



entry	46	catalyst	ligand	base	solvent	time (h)	yield of **73a** (%)[b]
1	46a	$AuCl_3$	L1	Ag_2CO_3	CH_3NO_2	36	4
2	46a	$AuCl_3$	L2	Ag_2CO_3	CH_3NO_2	36	16
3	46a	$AuCl_3$	--	Ag_2CO_3	CH_3NO_2	48	n.d.
4	46a	$AuCl_3$	PPh_3	Ag_2CO_3	CH_3NO_2	48	n.d.
5	46a	$AuCl_3$	PCy_3	Ag_2CO_3	CH_3NO_2	48	n.d.
6	46a	$AuCl_3$	L2	Ag_2CO_3	Toluene	48	trace
7	46a	$AuCl_3$	L2	Ag_2CO_3	1,4-dioxane	48	10
8	46a	$AuCl_3$	L2	Ag_2CO_3	THF	48	12
9	46a	$AuCl_3$	L2	Ag_2CO_3	DMF	48	n.d.
10	46a	$AuCl_3$	L2	Ag_2CO_3	1,2-DCE	48	20
11	**46a**	**$AuCl_3$**	**L2**	**Ag_2CO_3**	**CH_2Cl_2**	**24**	**98**
12	46a	$AuCl_3$	L1	Ag_2CO_3	CH_2Cl_2	36	11
13	46a	$AuCl_3$	L3	Ag_2CO_3	CH_2Cl_2	36	39
14	46a	$AuCl_3$	L4	Ag_2CO_3	CH_2Cl_2	36	52
15	46a	AuCl	L2	Ag_2CO_3	CH_2Cl_2	48	trace
16	46a	PPh_3AuCl	L2	Ag_2CO_3	CH_2Cl_2	48	trace
17	46a	$AuBr_3$	L2	Ag_2CO_3	CH_2Cl_2	36	13
18	46a	$Ph_3PAuOTf$	L2	Ag_2CO_3	CH_2Cl_2	48	trace
19	46a	$Ph_3PAuSbF_6$	L2	Ag_2CO_3	CH_2Cl_2	48	trace
20	46a	$AuCl_3$	L2	$AgNO_3$	CH_2Cl_2	48	trace
21	46a	$AuCl_3$	L2	AgOTf	CH_2Cl_2	36	28
22	46a	$AuCl_3$	L2	AgOAc	CH_2Cl_2	48	trace
23	46a	$AuCl_3$	L2	$AgBF_4$	CH_2Cl_2	36	35
24	46a	$AuCl_3$	L2	K_2CO_3	CH_2Cl_2	48	<5

[a] Reactions were carried out using **alkyne** (0.25 mmol), **phenol** (0.5 mmol) and base (0.5 mmol) in solvent (0.3 mL) at 100 °C. [b] GC yields based on alkynes using dodecane as internal standard. n.d. = not detected.

Table 1.2: Reaction between 4-methoxyphenol and diphenylacetylene: Reaction Optimization[a]



entry	**46**	catalyst	ligand	base	solvent	time (h)	yield of **73b** (%)[b]
1[c]	**46b**	$AuCl_3$	L2	Ag_2CO_3	CH_2Cl_2	24	7
2	**46b**	$AuCl_3$	L2	K_2CO_3	CH_2Cl_2	36	trace
3	**46b**	$AuCl_3$	L2	Na_2CO_3	CH_2Cl_2	48	trace
4	**46b**	$AuCl_3$	L2	K_3PO_4	CH_2Cl_2	48	20
5	**46b**	$AuCl_3$	L2	K_3PO_4	THF	48	84
6	**46b**	$AuCl_3$	L2	Cs_2CO_3	THF	48	51
7	**46b**	**$AuCl_3$**	**L2**	**K_2CO_3**	**THF**	**48**	**95**
8	**46a**	$AuCl_3$	L2	K_2CO_3	THF	36	15

[a] Reactions were carried out using **alkyne** (0.25 mmol), **phenol** (0.5 mmol) and base (0.5 mmol) in solvent (0.3 mL) at 100 °C. [b] GC yields based on alkynes using dodecane as internal standard. [c] $AuCl_3$ and ligand (3 mol% each) were used for 24 h.

The acidic nature of phenols varies with the substituent on the aromatic ring. With this in mind, the optimized reaction condition is applied in the reaction of electron-rich phenol with diphenylacetylene (**47f**) (Table 1.2). Indeed, under the optimized condition shown in entry 11 (Table 1.1), addition of unactivated 4-methoxyphenol (**46b**) with **47f** produced (*Z*)-(1-(4-methoxyphenoxy)ethene-1,2-diyl)dibenzene (**73b)** in only 7% yield (entry 1). Further screening of various bases revealed that inorganic bases are found to be better compared to silver salts (entries 2–4). Better conversion of reaction was observed, when THF was employed instead of CH_2Cl_2 (entries 5–7). Further screening of bases revealed that K_2CO_3 in THF improved the yield of **73b** to 95% (entry 7). With disappoint, when the optimal conditions for the unactivated 4-methoxyphenol in entry 7 was applied for the activated 3-nitrophenol, only 15% yield was observed (entry 8). Therefore, the reaction conditions are very selective for the acidic nature of the phenols. In addition, the effective

addition of respective phenols to alkynes solely depends on the nature of bases and solvents used. Such divergence in the behavior of bases is interesting; however, the origin of this effect is unclear. It appears that relatively strong bases, such as K_2CO_3, are required in the case of electron-rich phenols having higher pK_a, and a milder base, such as Ag_2CO_3, is sufficient for activated phenols with lower pK_a.[31, 32]

1.4.2. Reaction Scope

To investigate the generality of the addition of various phenols with symmetrical and unsymmetrical alkynes, Condition A [$AuCl_3$ (3 mol%), ligand L2 (3 mol%), Ag_2CO_3 base in CH_2Cl_2 at 100 ^oC] is used for activated phenols and Condition B [$AuCl_3$ (5 mol%), ligand L2 (5 mol%), K_2CO_3 base in THF at 100 ^oC] is employed for non-activated phenols. The effect of substitution on the phenols in the hydrophenoxylations with diphenylacetylene (**47f)** was surveyed at first. The results are detailed in Table 1.3. Electron-donating substituent at the 4-position on phenols reacted effectively with **47f** in good yields; 4-methoxyphenol (**46b**), *p*-cresol (**46c**), and 4-*sec*-butylphenol (**46d**) were reacted with **47f** under the conditions B, effectively produced the corresponding hydrophenoxylation products **73b**, **73c**, and **73d**, respectively. The *Z*-selectivity of **73b** is established based on the NOESY studies; intramolecular NOEs between vinyl-H (δ = 6.62 ppm; H_x) and the *ortho*-hydrogens (δ = 7.60, 7.68 ppm; H_a, H_b) of the phenyl groups of **73b** are clearly seen, whereas the NOEs between vinyl-H and *ortho*-hydrogens (δ = 6.78 ppm; H_c) of the 4-methoxyphenyl moiety of **73b** are not observed (Figure 1.2). The reaction of **47f** with *para*-halo groups bearing phenols such as 4-fluorophenol (**46e**) and 4-chlorophenol (**46f**) under the conditions B furnished **73e** and **73f** in excellent yields. The *Z*-selectivity of **73f** is established based on the NOESY studies (Figure 1.2).

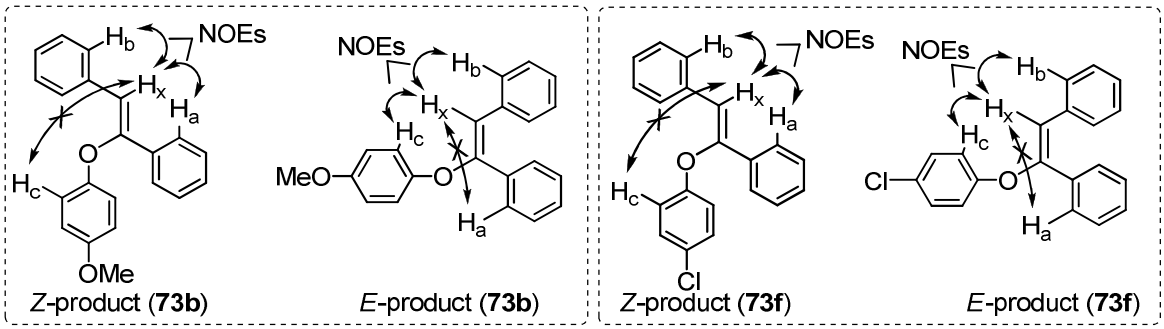
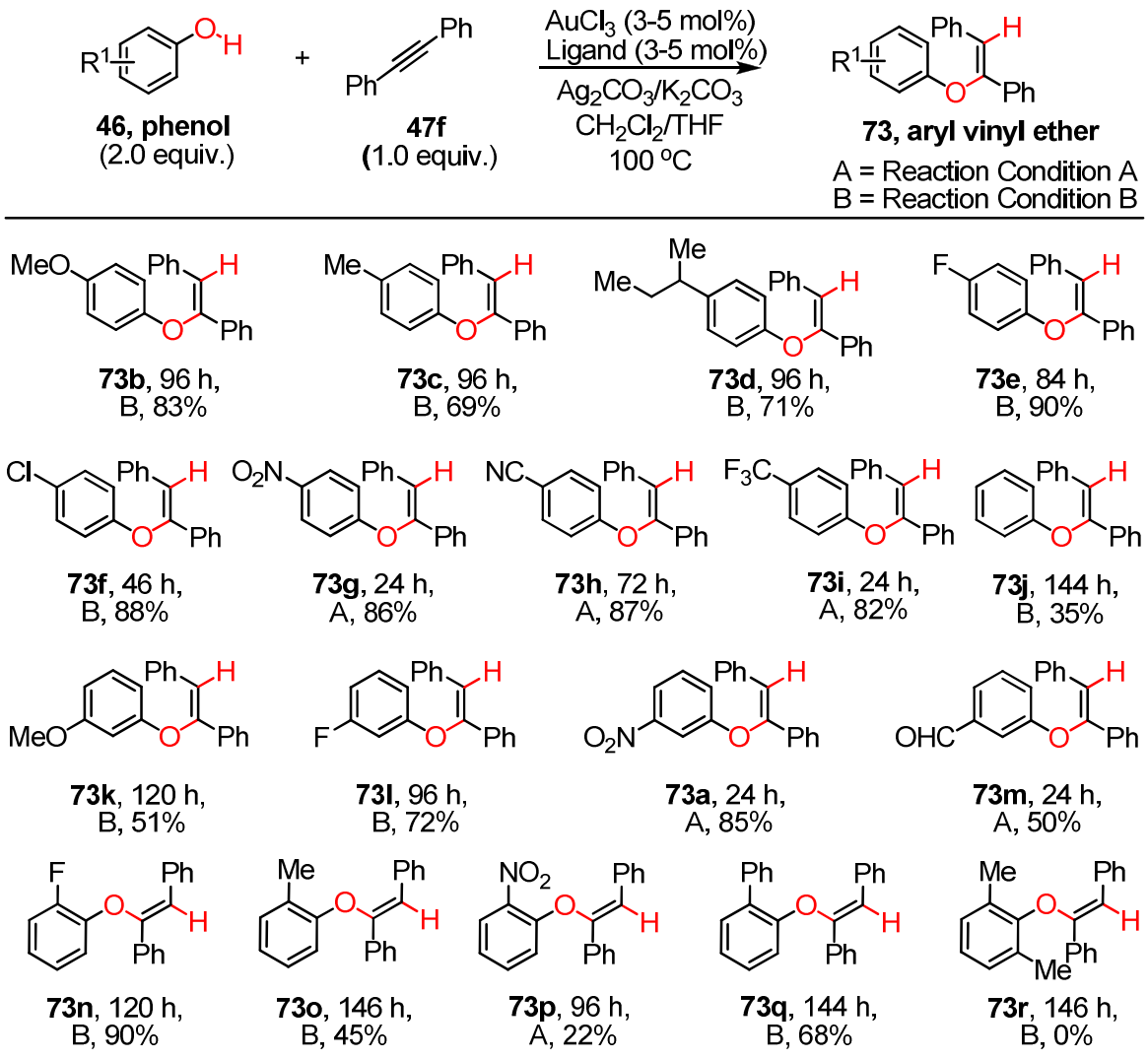


Figure 1.2: NOESY studies of **73b** and **73f**

Table 1.3: Hydrophenoxylation of phenols with diphenylacetylene[a,b]



[a] Reactions were performed employing **46** (2.0 mmol), **47f** (1.0 mmol) at 100 °C; Condition A: Ag_2CO_3 (2.0 mmol), $AuCl_3$ and **L2** (3 mol% each) in CH_2Cl_2 (1.0 mL) was used. Condition B: K_2CO_3 (2.0 mmol), $AuCl_3$ and **L2** (5 mol% each) in THF (1.0 mL) was used. [b] Isolated yields based on alkynes; average of two runs.

Similarly, the electron withdrawing groups bearing activated phenols reacted efficiently with **47f** under the conditions A, furnishing excellent yields of the desired addition products. The presence of common electron withdrawing groups such as nitro, cyano, and trifluromethyl on phenols (**46g**, **46h** and **46i**) was well-tolerated, and the respective products **73g**, **73h**, and **73i** were obtained in excellent yields. However, the addition of electronically neutral phenol (**46j**) to **47f** proceeded with poor yield of **73j**, and incomplete conversion of **46j** was observed even with the extended reaction time.

In the case of *meta*-substituted phenols, the reaction proceeded with overall moderate yields. The addition of electron donating 3-methoxyphenol (**46k**) to **47f** afforded the corresponding product **73k** in 51% yield; incomplete conversion of **47f** was noticed even with prolonged reaction time, justifying the moderate yield encountered in this reaction. However, activated phenols bearing -F, -NO_2, or -CHO groups at the 3-positions (**46l**, **46a** and **46m**) gave the desired hydrophenoxylation products **73l**, **73a**, and **73m** in good to excellent yields, respectively. The Z-configuration of **73m** is established based on the NOESY studies (See page 36).

These experimental results reveal that the *para*-substituent's on phenol leads to better yield, while *meta*- and unsubstituted phenols are less effective in the hydrophenoxylations of alkynes. Presumably, the electronic effect of the functional group in the *para*-position decides the rate and stability of the phenolate and therefore influences the attack on alkynes. To evaluate the steric effect in the hydrophenoxylation, the *ortho*-substituted phenols were reacted with **47f**. The presence of a compact electron-poor *o*-substituent, such as -F group (**46n**), did not affect the reaction efficiency, and the product **73n** was obtained in 90% yield under the optimized condition B. The Z-configuration of **73n** is established based on the NOESY studies (See page 37). However, the bulky *ortho*-moiety on phenols inhibits the effective addition to **47f**. Reaction of **47f** with sterically demanding substrates such as 2-methyl- and 2-nitrophenols (**46o** and **46p**) proceeded in low to moderate yields (**73o** and **73p**). Similarly, hydrophenoxylation of 2-phenylphenol (**46q**) with **47f** gave **73q** in 68% yield. Unfortunately, the reaction failed completely when the sterically encumbered substrate 2,6-dimethylphenol (**46r**) was run with **47f**.

Next, we investigated the scope of the alkynes (Table 1.4). Symmetrical dialkyl alkynes as well as diaryl alkynes having electron-donating and electron-withdrawing groups reacted with various phenols. Electron-rich 4-methoxyphenol (**46b**) or electron deficient 3-nitrophenol (**46a**) reacted with 3-hexyne (**47g**) to produce hydrophenoxylation products **74a** and **74b** in 94% and 55%, under the optimized conditions B and A, respectively. Formation of moderate amount of **74b** is a consequence of the *meta*-substitution on phenols. The *para*-substituted phenols such as *p*-cresol (**46c**), 4-phenylphenol (**46t**) and 4-fluorophenol (**46e**) were efficiently added across 4-octyne (**47h**) furnishing corresponding hydrophenoxylation products **74c**, **74d** and **74f**, respectively in good yields. Interestingly, the reaction of 3-methoxyphenol (**46k**) or 2-phenylphenol (**46q**) with 4-octyne (**47h**)

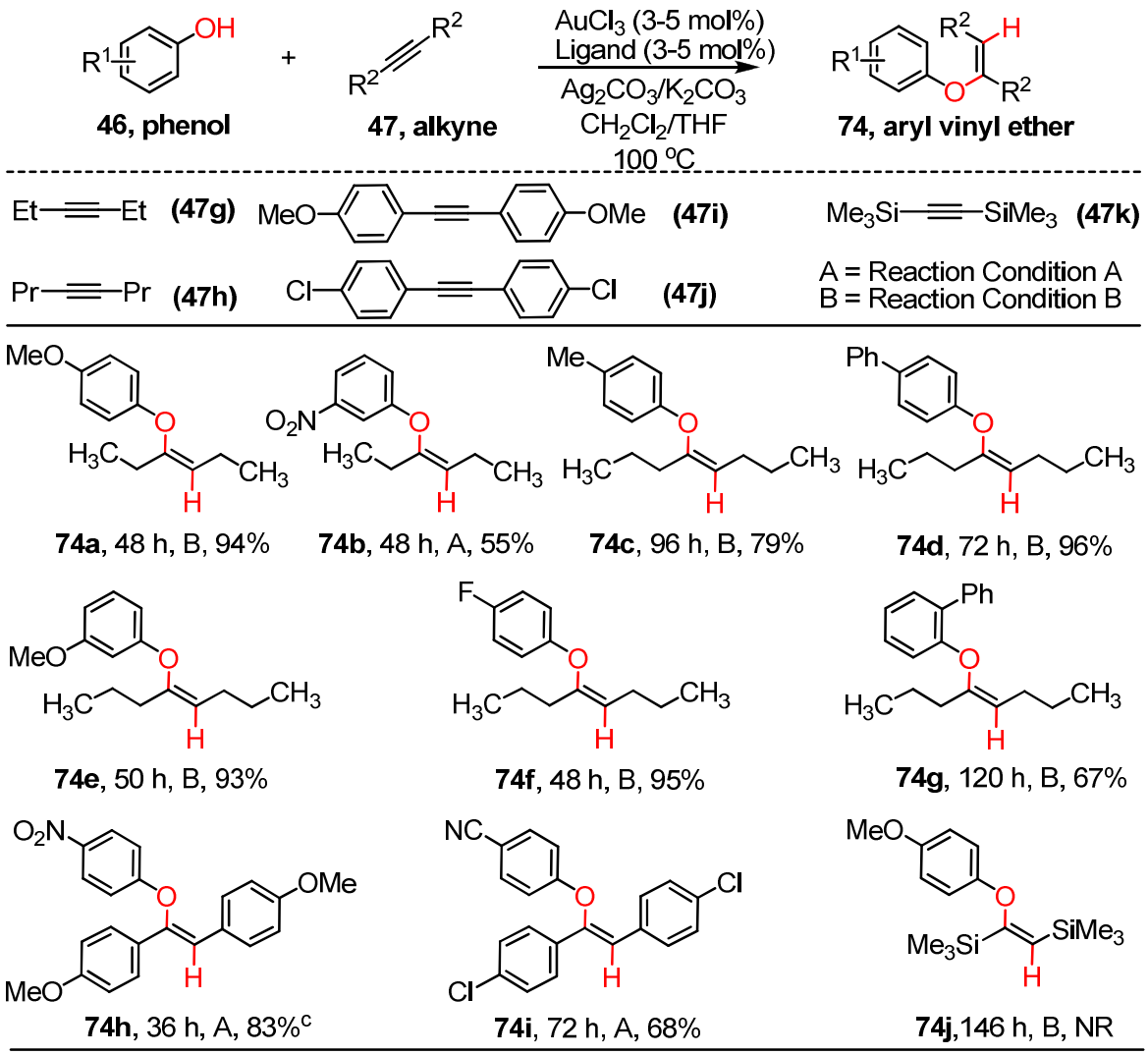
affords **74e** (93%) and **74g** (67%), respectively. The Z-configuration of **74b** and **74c** are established based on the NOESY studies (See page 40).

These results suggest that the addition of phenols to alkyl-substituted alkynes is more effective than to aryl-substituted alkynes. We also believe that the efficiency of the reaction depends primarily on the facile attack of phenol nucleophile on the activated electrophilic Au-alkyne-π intermediate. Moreover, carbophilic gold preferably activates the electron-rich alkynes over the electron-deficient alkynes.[33] The inductively donating alkyl group would enhance the electron density on alkynes, thereby promoting activation by cationic gold. However, the electron density migration is reversed by neutral or electron-deficient aryl group, diminishing the effective activation by cationic-gold. Therefore, we conclude that electron-rich alkynes would show better reactivity in this transformation.[33]

Next, we explored the scope of the reaction by examining the symmetrical electron-rich and -deficient aryl substituted internal alkynes. Addition of 4-nitrophenol (**46g**) to the electron-rich 4-methoxyphenyl-substituted alkyne (**47i**) was performed under the conditions A and **74h** was isolated in 83% yield. The Z-configuration of **74h** is established based on the NOESY studies (See page 43). However, moderate yield of **74i** was produced when electron-deficient 4-chlorophenyl-substituted alkyne **47j** reacted with 4-cyanophenol (**46h**) under the optimized condition A. Unfortunately, attempt to obtain the expected product from the addition of 4-methoxyphenol (**46b**) to the electronically and sterically demanding substrate bis(trimethylsilyl)acetylene (**47k**) turned out futile (**74j**).

We have further explored the scope of the reaction by examining the utility of electron-rich and electron-deficient aryl-substituted unsymmetrical internal alkynes. It is very important in the sense that it would provide two new molecular entities corresponding to the regioisomeric products. Preferential formation of regioselective products is highly desirable in the application of synthetic chemistry. Our observation of hydrophenoxylation of symmetrical alkynes revealed that the gold catalyst activates electron-rich-substituted alkynes efficiently. Therefore, we decided to evaluate the reactivity of electron-rich unsymmetrical alkynes toward the addition of phenols. Table 1.5 summarizes the scope of the hydrophenoxylation of substituted phenols with unsymmetrical alkynes.

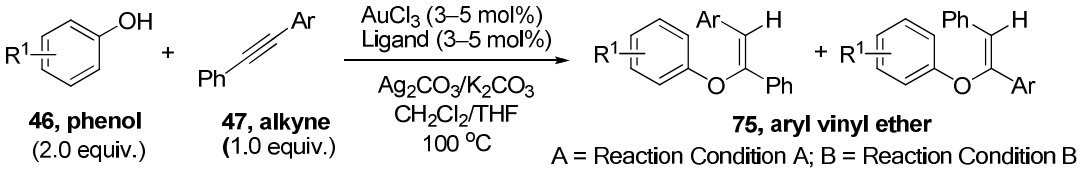
Table 1.4: Hydrophenoxylation of phenols with symmetrical alkynes[a,b]



[a] Reactions were performed employing **46** (2.0 mmol), **47** (1.0 mmol) at 100 °C; Condition A: Ag_2CO_3 (2.0 mmol), $AuCl_3$ and L2 (3 mol% each) in CH_2Cl_2 (1.0 mL) was used. Condition B: K_2CO_3 (2.0 mmol), $AuCl_3$ and L2 (5 mol% each) in THF (1.0 mL) was used. [b] Isolated yields based on alkynes; average of two runs. [c] **47i** (0.5 mmol) was used.

The reaction of 4-nitrophenol (**46g**) with electron-rich unsymmetrical alkyne 1-methoxy-4-(phenylethynyl)benzene (**47l**) afforded the corresponding mixture of products in 94% yield with moderate regioselectivity (Table 1.5, entry 1). Excellent yields of the desired regioisomeric products were isolated in the hydrophenoxylation of **46g** with phenyl alkyl acetylenes (**47e** and **47m**) (entries 2 and 3); this observation clearly demonstrates the effective addition of phenols to the unsymmetrical alkyl-substituted alkynes. Pure products **75b** and **75b′** (entry 2) could be successfully isolated by column chromatography. The Z-configuration of **75b** and **75b′** are established based on the NOESY studies (See page 46).

Table 1.5: Hydrophenoxylation of phenols with unsymmetrical alkynes

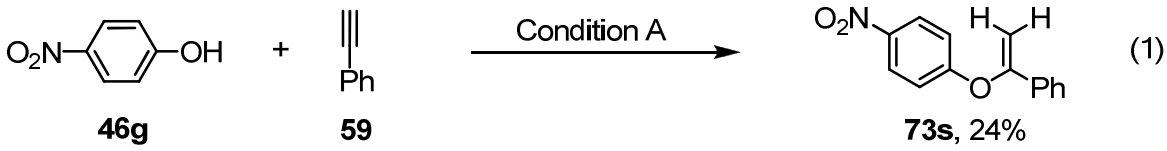


entry	phenol	alkyne	products[c]
1[a]	**46g**	**47l**	**75a** + **75a'** (Ar^1 = 4-MeO-C_6H_4-) 96 h; 94% [75a/75a' = 37/63][d]
2[a]	**46g**	**47e**	**75b** + **75b'** 72 h; 93% [75b:75b' = 32:68][d,e]
3[a]	**46g**	**47m**	**75c** + **75c'** 72 h; 81% [75c/75c' = 38/62][d]
4[b]	**46k**	**47l**	**75d** + **75d'** 120 h; 63% [75d/75d' = 91/9][d]
5[b]	**46t**	**47n**	**75e** + **75e'** (Ar^2 = 3-F_3C-C_6H_4-) 120 h; 35% [75e/75e' = 30/70][d]

[a] Reactions were carried out using condition A. [b] Reactions were performed employing condition B. [c] Isolated yields of the mixture of regioisomers. [d] Ratios of regioisomers were determined by HPLC analysis. [e] Regioisomers are purified.

When the reaction was run between *meta*-substituted 3-methoxyphenol (**46k**) and electron-rich unsymmetrical alkyne **47l**, the product was obtained in modest yield with better regioselectivity (91:9; Table 1.5, entry 4). This again demonstrates the reduction in reactivity with *meta*-substituted phenols. *The regioselectivity observed in these reactions warrants further investigations of the mode of addition of phenols to unsymmetrical alkynes*. It is likely that electronic effects of unsymmetrical alkynes and phenols contribute to the moderate regioselectivity. Gold and other catalytic systems used in the hydration and hydroalkoxylations of unsymmetrical alkynes have led to moderate regioselectivity in

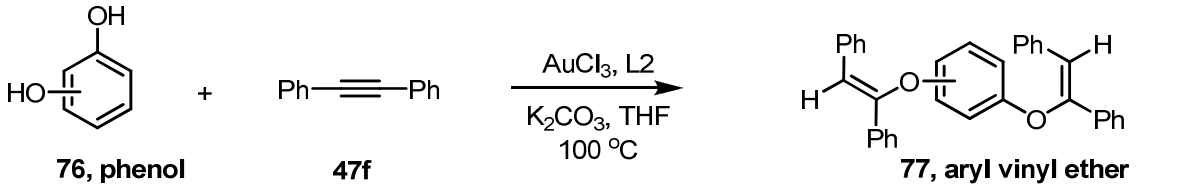
the product,[23,33,34] and our current observations are consistent with this. However, electron-deficient alkyne **47n** reacted sluggishly with **46t**, and an inseparable mixture of regioisomers **75e** and **75e′** was produced in poor yield (Table 1.5, entry 5); a substantial amount of precursor **47n** was recovered even after continuing the reaction for 4 days. This indicates poor reactivity of phenolic−OH to electron-poor alkynes under the optimized gold-catalyzed reaction condition. Hydrophenoxylations of phenols with terminal alkyne was then explored; a reaction of 4-nitrophenol (**46g**) with phenylacetylene (**59**) under the optimized catalytic condition A gave the corresponding Markovnikov's addition product **73s** in poor yield (eq. 1).



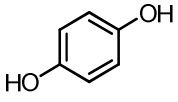
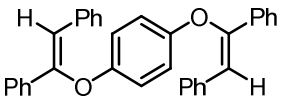
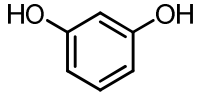
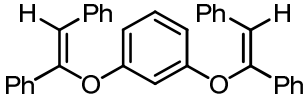
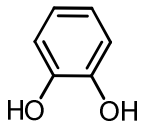
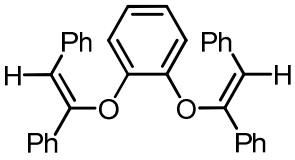
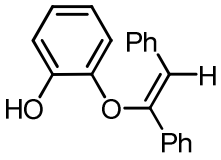
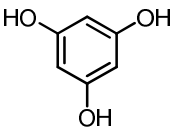
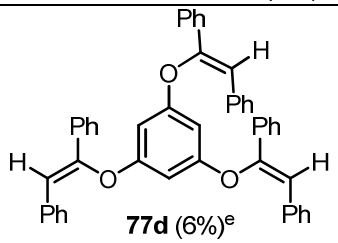
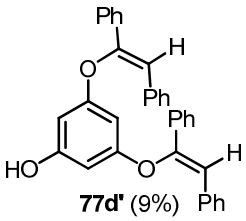
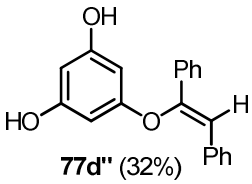
46g **59** **73s**, 24% (1)

We envisaged that multiple hydrophenoxylation of polyphenols would result in enlarging the molecular diversity which eventually extends the conjugation. With this in mind, we have evaluated the addition of electron-rich polyphenols with diphenylacetylene under the optimized conditions B, and the results are shown in Table 1.6. The addition of hydroquinone (**76a**) to **47f** gave the corresponding di-*O*-vinylated product **77a** in 55% yield along with trace amount of mono-adduct (entry 1). The reaction could not be completed even after 4 days; we assume that the addition of the potential intermediate, benzene-1,4-bis(olate), to the electrophilic Au-alkyne-π complex is inefficient, leading in producing moderate yield of the product.[35] X-ray crystallographic analysis unambiguously elucidated the structure of **77a** having *Z*-olefin stereochemistry (Figure 1.3). Efficient addition was observed in case of resorcinol (**76b**) with **47f** under the optimized condition to furnish the desired di-*O*-vinylated product **77b** in 94% yield. The *Z*-configuration of **77b** is established based on the NOESY studies (See page 51). Further, we were interested in examining the possibility of hydrophenoxylations of sterically encumbered catechol (**76c**) with **47f**. Apparently, because of close proximity of the −OH groups in the catechol, the bond formation between **76c** and **47f** would be difficult. Indeed, di-*O*-vinylated catechol (**77c**) was isolated in only 7% yield after continuing the reaction for 7 days (entry 3). Moderate yield of the corresponding mono-*O*-vinylated catechol (**77c′**) was also produced along with unreacted **76c**.

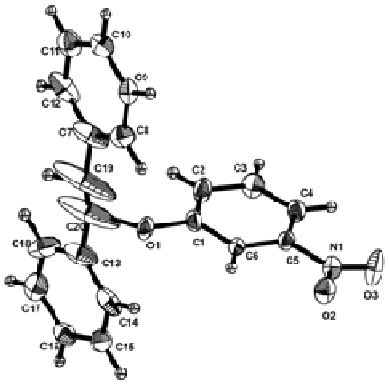
Table 1.6: Hydrophenoxylation of polyphenols[a,b]



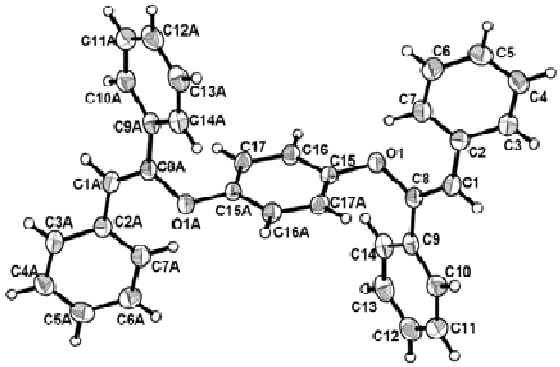
76, phenol **47f** **77, aryl vinyl ether**

	Phenol	Product		Phenol	Product
1	 **76a**	 **77a** (55%)[c]	2	 **76b**	 **77b** (94%)[c]
3	 **76c**	 **77c** (7%)[c,d]			 **77c'** (34%)
4	 **76d**	 **77d** (6%)[e]		 **77d'** (9%)	 **77d''** (32%)

[a]Reactions were performed using **76** (1.0 mmol), THF (2.0 mL) in condition B. [b] Isolated yields based on **76**. [c] Reaction was carried out employing **47f** & K_2CO_3 (4.0 mmol each), $AuCl_3$ & **L2** (10 mol% each), and continued for 96 h. [d] Reaction was continued for 168 h, mono-adduct (**77c'**) was also obtained. [e] Reaction was performed using **47f** & K_2CO_3 (6.0 mmol each), $AuCl_3$ & **L2** (15 mol% each), and continued for 168 h; di- (**77d'**) and mono-*O*-vinylated phloroglucinols (**77d''**) were obtained.



73a

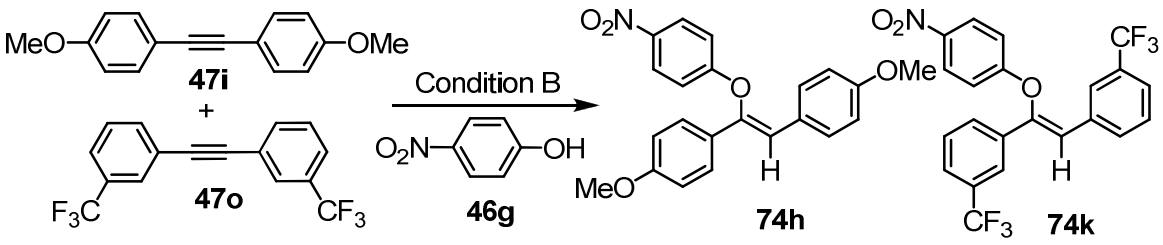


77a

Figure 1.3: Thermal ellipsoidal plot of compounds **73a** and **77a** with atom labeling scheme

More challenging substrate phloroglucinol (**76d**) with **47f** was then examined for hydrophenoxylation. Tri-*O*-vinylated phloroglucinol (**77d**) was obtained, although in poor yield, when the reaction between **76d** and **47f** was performed under the optimized condition B for 7 days; the corresponding di- and mono-*O*-vinylated phloroglucinols were also produced in 9% and 32% yield, respectively (entry 4). To the best of our knowledge, these new molecular entities are prepared for the first time *via* gold-catalyzed simultaneous addition of phenols to the alkynes.

1.4.3. Competition Experiment



Scheme 1.22: Competition experiment between alkynes **47i** and **47o**.

A competition experiment was performed reacting 4-nitrophenol (**46g**, 0.2 mmol) with 1,2-bis(4-methoxyphenyl)ethyne (**47i**, 0.2 mmol) and 1,2-bis(3-(trifluoromethyl)phenyl)ethyne (**47o**, 0.2 mmol) in the presence of $AuCl_3$, ligand L2 , and Ag_2CO_3 at 100 ^oC for 72 h. The respective vinyl-H integration in the crude ^1H NMR spectrum showed the formation of the corresponding products **74h** and **74k** in 2:1 ratio. This signifies that the reaction of 4-nitrophenol with electron-rich alkyne **47i** is preferred over the electron-deficient alkyne **47o**.

1.4.4. Mechanistic Studies

Even though the detailed mechanism of this reaction is not yet established, we have proposed the following catalytic cycle, as shown in Figure 1.4. The gold catalyst complex with JohnPhos ligand (L2) forms the soft and carbophilic JohnPhos ligated Au complex which activates the alkyne to provide gold-alkyne-π complex **78**.[30,33] This ligand is found to be very crucial for the present reaction, suggesting that its bulkiness enhances the reactivity and stability of the gold complex and triggers the subsequent nucleophilic addition of phenols.[36] Two mechanistic scenarios can be possible for the nucleophilic addition of phenols to gold-alkyne-π-complex **78**. *Following the path A*, phenolate attacks

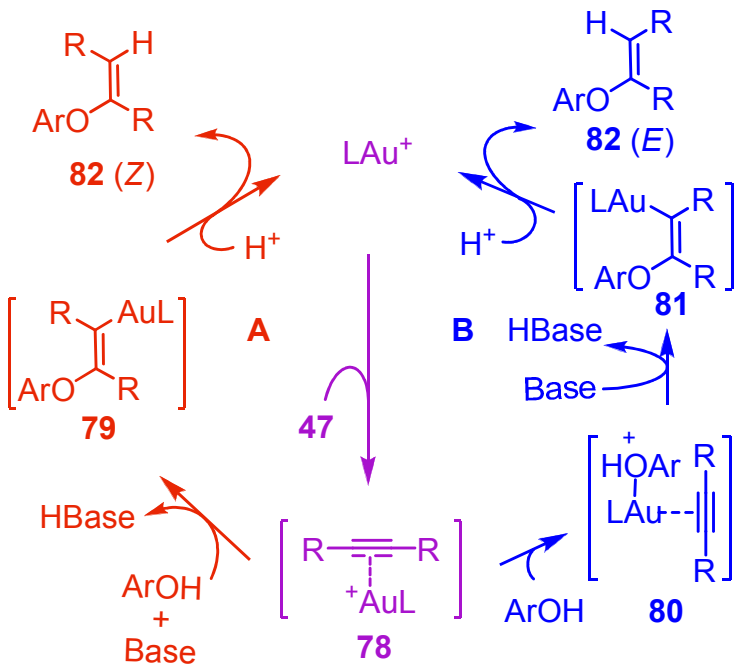
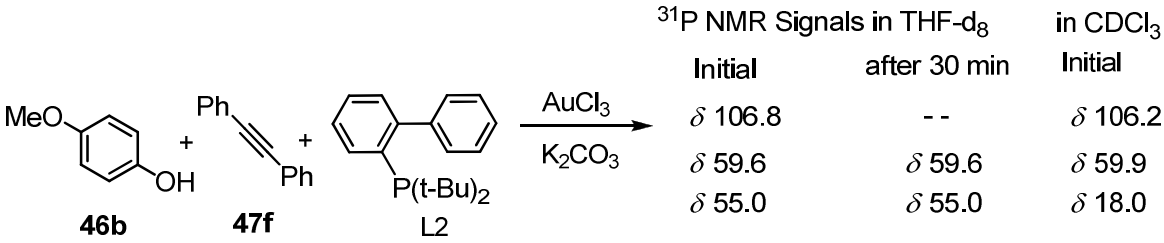


Figure 1.4: Proposed catalytic cycle

from the opposite side of **78** to yield *O*-vinyl-Au species **79**.[32,37] Protodeauration furnishes arylvinyl ethers with *Z*-olefins **82** and regenerates the active gold catalyst. *An alternate pathway B* would involve coordination of phenols to gold complex **78** to produce complex **80**.[28,37b] Deprotonation of **80** by base and rearrangement for C−O bond formation leads to the *O*-vinyl-Au species **81** with *Z*-configuration. Protodemetalation would generate (*E*)-arylvinyl ethers **82**. Even though the transformation of **80** to **81** should be possible with any mild base, our observation for the hydrophenoxylation reaction is that it requires specific choices of base and solvent. Furthermore, exclusive formation of *Z*-olefins is observed in this reaction. *On the basis of this evidence, route B appears unlikely.*

Experimental results reveal that the gold(III) chloride and ligand L2 mixture allows the intermolecular addition of phenols to alkynes at 100 °C without losing its activity for at least 4−6 days. In order to understand the plausible reactive species involved in the catalytic system, NMR experiment is performed by reacting 4-methoxyphenol (**46b**), diphenylacetylene (**47f**), K_2CO_3, $AuCl_3$, and L2 in THF-d_8 solvent at room temperature. In the ^{31}P NMR, three new signals at δ = 106.8, 59.6, and 55.0 ppm appear and the signal at δ = 17.4 ppm corresponding to the ligand L2 is absent (Scheme 1.23). At about 30 min, the signal at δ = 106.8 ppm disappears. The peaks at δ = 55.0 and 59.6 ppm can be assigned to

the phosphineoxide (**83**) and phosphine−Au(I) complex (**84**), respectively (Figure 1.5).[36a,38]



Scheme 1.23: ^{31}P NMR studies

It is likely that a part of phosphine is involved for the conversion of Au(III) to Au(I) species in the redox process with simultaneous formation of phosphine oxide using trace amount of adventitious water present in the system. However, efforts to isolate the species with a signal at δ = 106.8 ppm failed; therefore, the structure of this species cannot be established. The sample of $AuCl_3$ and L2 in THF-d_8 at room temperature shows identical results in the ^{31}P NMR spectrum to that observed in the previous reaction. Similarly, the ^{31}P NMR spectrum of the sample of $AuCl_3$ and L2 in $CDCl_3$ at room temperature shows three peaks at δ = 106.2, 59.9, and 18.0 ppm; the signal at δ = 18.0 ppm corresponds to L2 in $CDCl_3$, and the peaks at δ = 106.2 and 59.9 ppm resemble those from the previous reaction. We believe that **84** may be responsible for the hydrophenoxylations to alkynes at the elevated temperature. The formation of **84** can also be expected in the reactions of AuCl and Ph_3PAuCl with L2 (entries 15 and 16, Table 1.1). However, the ^{31}P NMR spectrum of a mixture of AuCl and L2 in $CDCl_3$ shows two signals at δ = 60.0 and 17.9 ppm in a 1:4 ratio corresponding to **84** and L2, respectively, and the sample of Ph_3PAuCl and L2 in $CDCl_3$ shows no formation of **84**; the later shows signals at δ = 18.2 (for L2) and 29.0 ppm.[39] These observations account for the trace formation of **73a** in these reactions (entries 15 and 16 in Table 1.1).

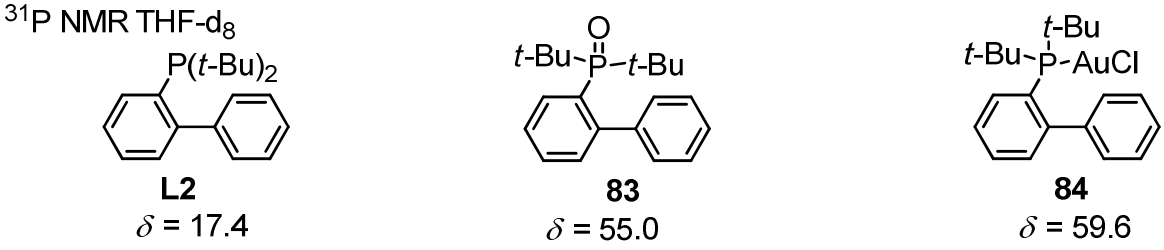


Figure 1.5: ^{31}P NMR Chemical shifts of the mixture of JohnPhos and $AuCl_3$

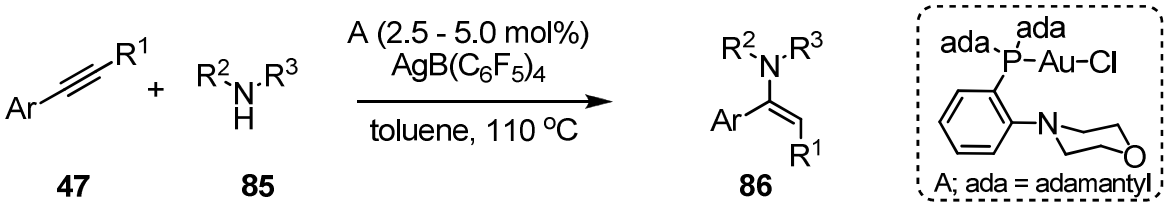
1.5. Conclusion

In summary, we have demonstrated an efficient and atom-economical gold catalyzed intermolecular hydrophenoxylation of alkynes. The present methodology provides a new one-step protocol for the synthesis of a wide array of vinyl(1,2-disubstituted)aryl ethers. We believe that the current strategy would trigger synthetic explorations of oxygen-containing heterocycles of pharmaceutical interest. Efforts are underway to optimize milder reaction conditions, unravel mechanistic details and investigate novel synthetic applications.

1.6. Future Work

The present work successfully demonstrates the synthesis of hydrophenoxylations from readily available precursors phenols and unactivated internal alkynes, *which to the best of knowledge is the first report*. However, the reaction need more amount of the phenols and require 100 ^{o}C to proceed. Therefore, development of mild reaction conditions for the synthesis of hydrophenoxylations from phenols and unactivated alkynes is always desirable. Formidable challenges remain for the addition of *tert*-alcohols, amines, thiols to the unactivated internal alkynes.

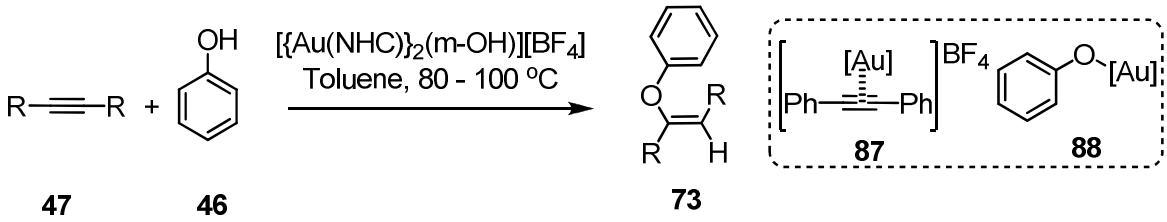
Recently, M. Stradiotto and K. D. Hesp have developed the regioselective hydroamination of internal alkynes with dialkyl amines using the P, N-ligand-bearing gold-catalyst.[40] This reaction showed broad substrate scope involving the stereoselective addition of a range of functionalized dialkylamines to internal unactivate-alkynes (Scheme 1.24).



47 **85** **86**

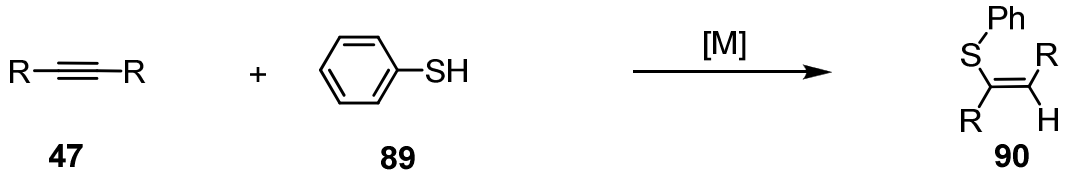
Scheme 1.24: Gold catalyzed hydroamination of internal alkynes with dialkyl amines

Very recently, a dual activation pathway for the hydrophenoxylation of alkynes under relatively mild conditions has been reported by S. P. Nolan and co-workers.[41] The catalyst digold hydroxide complex dissociates into Lewis acid ([Au(NHC)][BF_4]) and Bronsted base ([Au(NHC)(OH)]) under the appropriate conditions. These species independently react with alkynes and phenol to form complexes **87** and **88** (Scheme 1.25).



Scheme 1.25: Dual activation in the hydrophenoxylation of alkynes

The addition of alkyl and aryl thiols to internal unactivated-alkynes for the formation of hydrothiolation products remains obscure (Scheme 1.26). The palladium catalyzed hydrothiolation is limited to the additions of alkyl thiols to terminal alkynes with poor regioselectivity.[42] Therefore, regioselective hydrothiolation of internal alkynes is a challenging task.



Scheme 1.26: Addition of thiols to internal unactivated alkynes

In addition, the hydrophenoxylation reactions developed can be useful in the fabrication of extended new π-conjugated systems.

1.7. Experimental

1.7.1. General Experimental Information for all the Work Presented in this Thesis

All the reactions were performed in an oven-dried Schlenk flask/ pressure tubes under an argon atmosphere or in open air conditions. Commercial grade solvents were distilled prior to use. Column chromatography was performed using silica gel procured from Merck (100-200 Mesh) eluting with hexanes and ethyl acetate mixture. Flash column chromatography was performed using silica gel procured from Acme's (230-400 Mesh) eluting with hexanes and ethyl acetate mixture. Thin layer chromatography (TLC) was performed on silica gel GF254 (Merck) plates. Visualization of spots on TLC plate was accomplished with UV light (254 nm) and staining over I_2 chamber.

Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded on a Bruker Avance 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz; ^{19}F NMR, 376 MHz) spectrometer, Bruker Avance 500 (^{1}H NMR, 500 MHz; ^{13}C NMR, 126

MHz; ^{19}F NMR, 470 MHz) spectrometer having solvent resonance as internal standard (^{1}H NMR, $CHCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm). Few cases tetramethylsilane (TMS) at 0.00 ppm was used as reference standard. Data for ^{1}H NMR are reported as follows: chemical shift (ppm), multiplicity (s = singlet; bs = broad singlet; d = doublet; bd = broad doublet, t = triplet; bt = broad triplet; q = quartet; m = multiplet), coupling constants, *J*, in (Hz), and integration. Data for ^{13}C NMR, ^{19}F NMR were reported in terms of chemical shift (ppm). GC analysis was performed on a Shimadzu GCMS QP2010 equipped with an ZB-1 column (30 m × 0.25 mm, pressure = 20.0 kPa, detector = EI, 300 ^{o}C) with helium gas as carrier. IR spectra were recorded on JASCO FT/IR-5300 spectrometer and reported in cm^{-1}. LC-MS spectra were obtained with a Shimadzu 2010A (EI-positive/ nagative mode) with ionization voltage of 70eV; data was reported in the form of m/z (intensity relative to base peak = 100). Elemental (C, H, N) analysis were carried out using THERMO FINNIGAN FLASH EA 1112 analyzer. High resolution mass spectrum (HRMS) was recorded on a Bruker maxis mass spectrometer using ESI (electrospray ionization). Melting points were determined on electro-thermal melting point apparatus and are uncorrected. X-ray data was collected at 298K on a Bruker-Nonius SMART APEX CCD single crystal diffractometer using graphite monochromated Mo-Kα radiation (0.71073 Å).

1.7.2. Materials

Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Dichloromethane (DCM), nitromethane and 1,2-dichloroethane (DCE) were distilled over CaH_2. THF was freshly distilled over sodium/benzophenone ketyl under dry nitrogen. Gold(III)chloride ($AuCl_3$, 99%) was purchased from Sigma Aldrich Ltd. and used as received. Buchwald biaryl ligands are purchased from Aldrich Ltd. and Strem Chemicals Inc. and used as received. Diphenylacetylene (**47f**), 4-octyne (**47g**), 1-phenyl-1-propyne (**47e**) are purchased from Sigma Aldrich Ltd. Alkynes such as 1,2-bis(4-methoxyphenyl)ethyne (**47i**),[43] 1,2-bis(4-chlorophenyl)ethyne (**47j**),[43] 1,2-bis(3-(trifluoromethyl)phenyl)ethyne (**47o**),[43] 1-methoxy-4-(phenylethynyl)benzene (**47l**),[44] 1-(phenylethynyl)-3-(trifluoromethyl)benzene (**47n**)[44] were prepared according to the respective literature procedure. Analytical and spectral data of all those known alkynes are exactly matching with the reported values.

1.7.3. Experimental Procedure

General procedure for the reaction of activated phenols with alkynes (GP-1; condition-A):

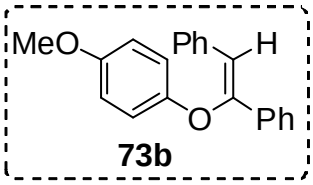
In an oven dried pressure tube, phenol (2.0 mmol), alkyne (1.0 mmol), and Ag_2CO_3 (2.0 mmol) were taken. The tube was evacuated and backfilled with argon for three times. In a separate Schlenk flask, heterogeneous solution of $AuCl_3$ (0.03 mmol) and ligand [L2, 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos), 0.03 mmol] in CH_2Cl_2 (1.0 mL) was freshly prepared and introduced to the parent reaction mixture under an argon atmosphere. The resulting reaction mixture was heated at 100 °C. Progress of the reaction was monitored by GC analysis while noticing complete consumption of alkynes employed. Reaction was continued for the time shown in the respective Tables, and brought to room temperature. The reaction mixture was diluted with dichloromethane (5 mL), and filtered over a small pad of Celite. Solvent was evaporated under reduced pressure and the crude reaction mixture was purified using silica gel column chromatography.

General Procedure for the reaction of unactivated phenols to alkynes (GP-2; condition-B):

In an oven dried Schlenk flask, phenol (2.0 mmol), alkyne (1.0 mmol), K_2CO_3 (2.0 mmol) were taken. The flask was evacuated and backfilled with argon for three times. A solution of $AuCl_3$ (0.05 mmol) and L2 (JohnPhos, 0.05 mmol) in THF (1.0 mL) was freshly prepared in a separate Schlenk flask and introduced to the parent mixture under an argon atmosphere. The resulting reaction mixture was heated at 100 °C. Progress of the reaction was monitored by GC analysis while noticing complete consumption of alkynes employed. Reaction was continued for the time shown in the respective Tables, and allowed to cool down to room temperature. The reaction mixture was diluted with dichloromethane (5 mL), and filtered over a small pad of Celite. Solvent was evaporated under reduced pressure and the crude reaction mixture was purified using silica gel column chromatography.

1.7.4. Spectral and Analytical Data

(*Z*)-(1-(4-Methoxyphenoxy)ethene-1,2-diyl)dibenzene (73b):

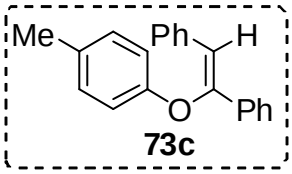


73b

Following the general procedure (GP-2) in condition B; a mixture of 4-methoxyphenol (**46b**; 248 mg, 2.0 mmol), diphenylacetylene (**47f**; 178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **73b** (251 mg) in 83% yield as colorless solid.

mp 102–104 °C; R_f = 0.56 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.71–7.66 (m, 2H), 7.63–7.58 (m, 2H), 7.38–7.28 (m, 5H), 7.27–7.21 (m, 1H), 7.01–6.93 (m, 2H), 6.82–6.75 (m, 2H), 6.62 (s, 1H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ154.6, 150.2, 150.1, 136.1, 134.9, 128.9, 128.5, 128.3, 127.3, 126.2, 117.1, 116.5, 114.7, 55.5; IR (KBr) ν_{max} 3074, 2928, 1630, 1502, 1444, 1205, 1103, 1037, 759 cm^{-1}; MS (EI) m/z (%) 303 (M^++1, 100), 211 (73), 197 (3); Elemental analysis calcd for $C_{21}H_{18}O_2$: C 83.42, H 6.00. Found: C 83.56, H 5.95.

(*Z*)-(1-(4-Methylphenoxy)ethene-1,2-diyl)dibenzene (73c):

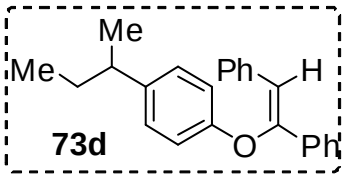


73c

Following the general procedure (GP-2) in condition B; a mixture of 4-methylphenol (**46c**; 216 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73c** (198 mg) in 69% yield as colorless solid.

mp 90–92 °C; R_f = 0.43 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.67 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.39–7.19 (m, 6H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ154.1, 149.9, 136.1, 134.8, 131.2, 130.1, 128.9, 128.5, 128.4, 128.3, 127.3, 126.1, 116.6, 116.1, 20.5; IR (KBr) ν_{max} 3030, 2916, 2860, 1608, 1506, 1448, 1219, 1168, 806, 688, 569 cm^{-1}; MS (EI) m/z (%) 287 (M^+ +1, 100), 211 (54), 179 (3); Elemental analysis calcd for $C_{21}H_{18}O$: C 88.08, H 6.34. Found: C 88.16, H 6.28.

(*Z*)-(1-(4-sec-Butylphenoxy)ethene-1,2-diyl)dibenzene (73d):

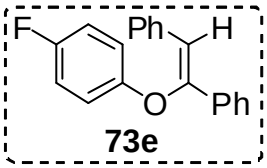


73d

Following the general procedure (GP-2) in condition B; a mixture of 4-*sec*-butylphenol (**46d**; 300 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73d** (233 mg) in 71% yield as colorless solid.

mp 78–79 °C; R_f = 0.75 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.68 (d, *J* = 6.4 Hz, 2H), 7.62 (d, *J* = 6.4 Hz, 2H), 7.37–7.26 (m, 5H), 7.23 (t, *J* = 6.0 Hz, 1H), 7.03 (d, *J* = 6.8 Hz, 2H), 6.95 (d, *J* = 6.8 Hz, 2H), 6.65 (s, 1H), 2.63–2.45 (m, 1H), 1.61–1.47 (m, 2H), 1.19 (d, *J* = 5.6 Hz, 3H), 0.81 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ154.4, 150.0, 141.2, 136.3, 134.9, 129.0, 128.5, 128.3, 128.1, 127.3, 126.2, 116.6, 116.0, 40.8, 31.3, 21.7, 12.2; IR (KBr) ν_{max} 3028, 2957, 2918, 1604, 1504, 1221, 1020, 821, 767 cm^{-1}; MS (EI) m/z (%) 329 (M^+ +1, 100), 211 (86), 197 (7); Elemental analysis calcd for $C_{24}H_{24}O$: C 87.76, H 7.37. Found: C 87.58, H 7.41.

(*Z*)-(1-(4-Fluorophenoxy)ethene-1,2-diyl)dibenzene (73e):

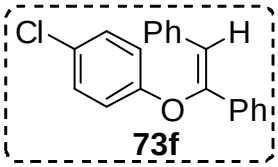


73e

Following the general procedure (GP-2) in condition B; a mixture of 4-fluorophenol (**46e**; 224 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 84 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73e** (262 mg) in 90% yield as colorless solid.

mp 62–65 °C; R_f = 0.71 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.71–7.64 (m, 2H), 7.62–7.58 (m, 2H), 7.39–7.31 (m, 5H), 7.30–7.22 (m, 1H), 7.03–6.89 (m, 4H), 6.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ159.1, 156.7, 152.2, 149.8, 135.7, 134.6, 128.9, 128.6, 128.59, 128.54, 127.5, 126.1, 117.3, 117.2, 116.8, 116.2, 116.0; ^{19}F NMR (376 MHz, CDCl3) δ–122.2; IR (KBr) ν_{max} 3043, 1633, 1502, 1446, 1195, 1093, 516 cm^{-1}; MS (EI) m/z (%) 291 (M^+ +1, 100), 211 (79), 197 (3), 179 (5); Elemental analysis calcd for $C_{20}H_{15}FO$: C 82.74, H 5.21, Found: C 82.57, H 5.26.

(*Z*)-(1-(4-Chlorophenoxy)ethene-1,2-diyl)dibenzene (73f):

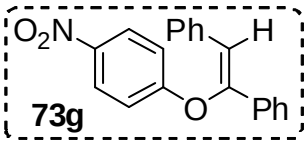


73f

Following the general procedure (GP-2) in condition B; a mixture of 4-chlorophenol (**46f**; 257 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 46 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73f** (270 mg) in 88% yield as colorless solid.

mp 88–90 °C; R_f = 0.75 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.61 (d, *J* = 7.2 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.39–7.28 (m, 5H), 7.27–7.14 (m, 3H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.67 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ154.9, 149.4, 135.6, 134.5, 129.7, 128.9, 128.7, 128.6, 127.6, 127.0, 126.0, 117.5, 116.9; IR (KBr) ν_{max} 3072, 3020, 1591, 1485, 1446, 1221, 1093, 815 cm^{-1}; MS (EI) m/z (%) 305 (M^+–1, 44), 283 (82), 255 (84), 127 (100); Elemental analysis calcd for $C_{20}H_{15}ClO$: C 78.30, H 4.93, Found: C 78.41, H 4.88.

(*Z*)-(1-(4-Nitrophenoxy)ethene-1,2-diyl)dibenzene (73g):

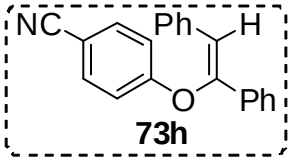


73g

Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**46g**; 278 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **73g** (273 mg) in 86% yield as pale yellow thick liquid.

R_f = 0.43 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.14 (d, *J* = 8.8 Hz, 2H), 7.60–7.53 (bd, *J* = 7.6 Hz, 4H), 7.40–7.29 (m, 5H), 7.28–7.20 (m, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.5, 148.5, 142.6, 134.8, 133.8, 129.0, 128.9, 128.7, 128.0, 126.1, 125.7, 117.4, 116.3; IR (Neat) ν_{max} 3059, 2924, 1647, 1518, 1489, 1340, 750 cm^{-1}; MS (EI) *m/z* (%) 318 (M^++1, 98), 302 (7), 288 (30), 211 (100), 197 (8), 178 (8); Elemental analysis calcd for $C_{20}H_{15}NO_3$: C 75.70, H 4.76, N 4.41, Found: C 75.62, H 4.81, N 4.48.

(*Z*)-4-(1,2-Diphenylvinyloxy)benzonitrile (73h):

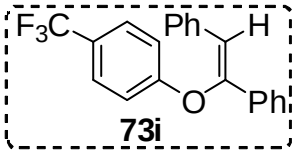


73h

Following the general procedure (GP-1) in condition A; a mixture of 4-cyanophenol (**46h**; 238 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 72 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane:ethyl acetate (49:1) to afford **73h** (259 mg) in 87% yield as colorless solid.

mp 88–89 °C, R_f = 0.37 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.71–7.65 (m, 2H), 7.64–7.58 (m, 2H), 7.38–7.27 (m, 5H), 7.26–7.18 (m, 3H), 6.95 (dt, *J* = 8.8, 2.0 Hz, 2H), 6.74 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ159.8, 148.5, 134.9, 134.3, 133.9, 129.0, 128.9, 128.88, 128.7, 127.9, 125.7, 118.8, 117.3, 116.9, 105.6; IR (KBr) ν_{max} 3045, 2226, 1601, 1502, 1331, 918, 777 cm^{-1}; MS (EI) *m/z* (%) 298 (M^++1, 88), 211 (100), 197 (2), 179 (5), 165 (2); Elemental analysis calcd for $C_{21}H_{15}NO$: C 84.82, H 5.08, N 4.71, Found: C 84.75, H 5.12, N 4.76.

(*Z*)-(1-(4-(Trifluoromethyl)phenoxy)ethene-1,2-diyl)dibenzene (73i):

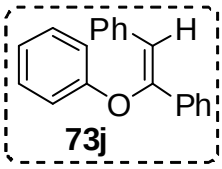


73i

Following the general procedure (GP-1) in condition A; a mixture of 4-trifluoromethylphenol (**46i**; 324 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73i** (279 mg) in 82% yield as colorless solid.

mp 58–60 °C; R_f = 0.78 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.66–7.57 (m, 4H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.41–7.31 (m, 5H), 7.29–7.22 (m, 1H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.76 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ158.9, 148.9, 135.2, 134.2, 129.0, 128.8, 128.7, 128.6, 127.7, 127.2, 127.1, 125.8, 117.2, 116.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ–61.7; IR (KBr) ν_{max} 3061, 1612, 1512, 1325, 1232, 1066, 839, 692 cm^{-1}; MS (EI) *m/z* (%) = 341 (M^+ +1, 100), 211 (82), 197 (2), 179 (8); Elemental analysis calcd for $C_{21}H_{15}F_3O$: C 74.11, H 4.44,Found: C 74.23, H 4.48.

(*Z*)-(1-Phenoxyethene-1,2-diyl)dibenzene (73j):

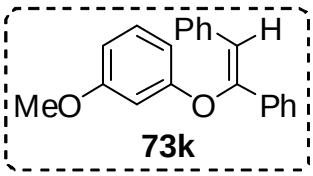


73j

Following the general procedure (GP-2) in condition B; a mixture of phenol (**46j**; 188 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 144 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73j** (96 mg) in 35% yield as colorless solid.

mp 58–61 °C; R_f = 0.27 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.66 (dt, J = 7.6, 1.6 Hz, 2H), 7.62 (dt, J = 8.4, 1.6 Hz, 2H), 7.38–7.19 (m, 8H), 7.08–7.01 (m, 2H), 6.99–6.93 (m, 1H), 6.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ156.3, 149.6, 136.0, 134.7, 129.6, 128.9, 128.6, 128.5, 128.4, 127.4, 126.1, 122.0, 116.7, 116.3; IR (KBr) ν_{max} 3055, 3022, 1591, 1487, 1222, 1167, 1020, 763 cm^{-1}; MS (EI) *m/z* (%) 273 (M^++1, 100), 211 (33), 179 (4); Elemental analysis calcd for $C_{20}H_{16}O$: C 88.20, H 5.92, Found: C 88.31, H 5.86.

(*Z*)-(1-(3-Methoxyphenoxy)ethene-1,2-diyl)dibenzene (73k):

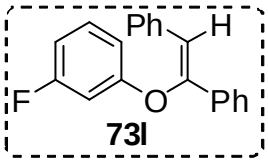


73k

Following the general procedure (GP-2) in condition B; a mixture of 3-methoxyphenol (**46k**; 248 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 120 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **73k** (155 mg) in 51% yield as colorless solid.

mp 98–100 °C; R_f = 0.62 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.69–7.58 (m, 4H), 7.38–7.27 (m, 5H), 7.26–7.20 (m, 1H), 7.13 (t, J = 8.4 Hz, 1H), 6.67 (s, 1H), 6.66–6.60 (m, 2H), 6.56–6.50 (m, 1H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ160.9, 157.5, 149.5, 136.0, 134.7, 130.0, 128.9, 128.6, 128.5, 128.4, 127.4, 125.9, 116.8, 108.7, 107.5, 102.7, 55.2; IR (KBr) ν_{max} 2959, 1591, 1491, 1446, 1259, 1020, 758 cm^{-1}; MS (EI) *m/z* (%) 303 (M^++1, 100), 211 (26), 179 (5); Elemental analysis calcd for $C_{21}H_{18}O_2$: C 83.42, H 6.00, Found: C 83.35, H 5.97.

(*Z*)-(1-(3-Fluorophenoxy)ethene-1,2-diyl)dibenzene (73l):

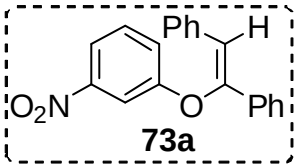


73l

Following the general procedure (GP-2) in condition B; a mixture of 3-fluorophenol (**46l**; 224 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73l** (209 mg) in 72% yield as colorless solid.

mp 80–82 °C; R_f = 0.75 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.68–7.57 (m, 4H), 7.41–7.28 (m, 5H), 7.28–7.21 (m, 1H), 7.21–7.13 (m, 1H), 6.83 (bd, J = 8.2 Hz, 1H), 6.81–6.73 (m, 1H), 6.71 (s, 1H), 6.70–6.62 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ164.6, 162.7, 157.8, 157.7, 149.3, 135.6, 134.4, 130.5, 130.4, 129.0, 128.7, 128.61, 128.59, 127.6, 125.9, 117.0, 112.03, 112.01, 109.1, 108.9, 104.2, 104.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ−111.2; IR (KBr) ν_{max} 3080, 1608, 1485, 1446, 1338, 1263, 1126, 1020, 835, 688 cm^{-1}; MS (EI) *m/z* (%) 291 (M^++1, 100), 211 (65), 197 (2), 179 (8); Elemental analysis calcd for $C_{20}H_{15}FO$: C 82.74, H 5.21, Found: C 82.65, H 5.26.

(*Z*)-(1-(3-Nitrophenoxy)ethene-1,2-diyl)dibenzene (73a):

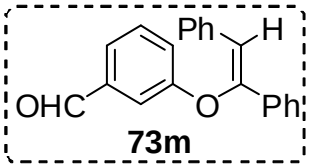


73a

Following the general procedure (GP-1) in condition A; a mixture of 3-nitrophenol (**46a**; 278 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **73a** (270 mg) in 85% yield as pale yellow solid.

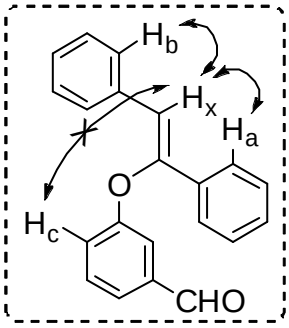
mp 112–114 °C; R_f = 0.53 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.66–7.58 (m, 4H), 7.51 (d, J = 8.8 Hz, 2H), 7.41–7.30 (m, 5H), 7.29–7.22 (m, 1H), 7.12 (d, J = 8.8 Hz, 2H), 6.75 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ156.9, 149.3, 148.7, 134.8, 134.0, 130.3, 129.0, 128.9, 128.8, 128.6, 127.8, 125.8, 122.3, 117.4, 117.1, 111.3; IR (KBr) ν_{max} 3080, 2932, 1645, 1521, 1446, 1350, 1269, 1022, 767 cm^{-1}; MS (EI) *m/z* (%) 318 (M^++1, 68), 302 (2), 288 (18), 211 (100), 197 (4); Elemental analysis calcd for $C_{20}H_{15}NO_3$: C 75.70, H 4.76, N 4.41, Found: C 75.68, H 4.81, N 4.46.

(*Z*)-3-(1,2-Diphenylvinyloxy)benzaldehyde (73m):



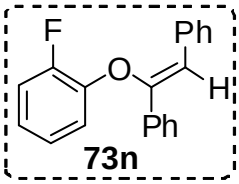
Following the general procedure (GP-1) in condition A; a mixture of 3-hydroxybenzaldehyde (**46m**; 244 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **73m** (151 mg) in 50% yield as yellow solid.

mp 78–81 °C; R_f = 0.43 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ9.90 (s, 1H), 7.69–7.59 (m, 4H), 7.55–7.46 (m, 2H), 7.45–7.20 (m, 8H), 6.75 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ191.7, 157.0, 149.1, 138.0, 135.3, 134.3, 130.3, 129.0, 128.7, 128.6, 128.5, 127.6, 125.9, 124.0, 122.4, 117.1, 116.2; IR (KBr) ν_{max} 3059, 2924, 2845, 1697, 1591, 1446, 1244, 761, 692 cm^{-1}; MS (EI) *m/z* (%) 301 (M^++1, 77), 211 (100), 179 (4); Elemental analysis calcd for $C_{21}H_{16}O_2$: C 83.98, H 5.37, Found: C 84.12, H 5.33.



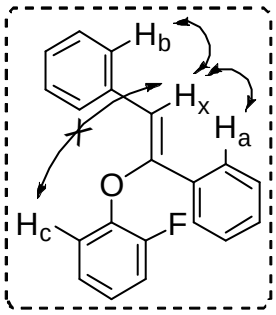
The *Z*-configuration of **73m** is established based on the NOESY studies; NOEs between vinyl-H (δ = 6.73 ppm, H_x) with the *ortho*-hydrogens (δ = 7.63, 7.61 ppm; H_a/H_b) of the phenyl groups of **73m** is clearly seen while the NOEs between vinyl-H (δ = 6.73 ppm, H_x) with *ortho*-hydrogens (δ = 7.23 ppm, H_c) of 3-hydroxybenzaldehyde moiety of **73m** is not observed.

(*Z*)-(1-(2-Fluorophenoxy)ethene-1,2-diyl)dibenzene (73n):



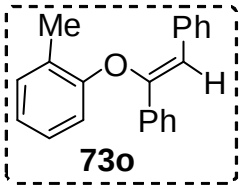
Following the general procedure (GP-2) in condition B; a mixture of 2-fluorophenol (**46n**; 224 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 120 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford 7**3n** (262 mg) in 90% yield as colorless thick liquid.

R_f = 0.68 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.71 (dt, J = 7.2, 1.6 Hz, 2H), 7.63 (dt, J = 7.2, 1.6 Hz, 2H), 7.40–7.27 (m, 5H), 7.25–7.22 (m, 1H), 7.19–7.11 (m, 1H), 6.95–6.83 (m, 3H), 6.69 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ153.6, 151.7, 149.7, 144.0, 143.9, 135.5, 134.5, 128.9, 128.7, 127.62, 127.59, 125.9, 124.4, 124.3, 122.7, 122.6, 117.4, 116.8, 116.7, 116.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −134.4; IR (Neat) ν_{max} 3059, 3026, 1645, 1610, 1500, 1448, 1199, 1018, 750, 692 cm^{-1}; MS (EI) *m/z* (%) 291 (M^++1, 100), 211 (94), 197 (3), 180 (5); Elemental analysis calcd for $C_{20}H_{15}FO$: C 82.74, H 5.21, Found: C 82.65, H 5.28.



The *Z*-configuration of **73n** is established based on the NOESY studies; NOEs between vinyl-H (δ = 6.69 ppm, H_x) with the *ortho*-hydrogens (δ = 7.70, 7.68 ppm; H_a/H_b) of the phenyl groups of **73n** is clearly seen while the NOEs between vinyl-H (δ = 6.69 ppm, H_x) with *ortho*-hydrogens (δ = 6.88 ppm, H_c) of 2-fluorophenyl moiety of **73n** is not observed.

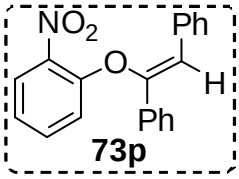
(*Z*)-(1-(*o*-Tolyloxy)ethene-1,2-diyl)dibenzene (73o):



Following the general procedure (GP-2) in condition B; a mixture of 2-methylphenol (**46o**; 216 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 146 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73o** (129 mg) in 45% yield as colorless solid.

mp 72–73 °C; R_f = 0.37 (hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ7.70 (d, J = 8.0 Hz, 2H), 7.65–7.58 (m, 2H), 7.42–7.31 (m, 5H), 7.31–7.22 (m, 2H), 6.99 (td, J = 8.0, 4.0 Hz, 1H), 6.92 (td, J = 8.0, 4.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ154.3, 150.0, 136.1, 135.0, 131.1, 128.9, 128.6, 128.5, 128.4, 127.4, 126.9, 126.6, 125.9, 121.8, 116.7, 114.3, 16.6; IR (KBr) ν_{max} 3057, 2924, 1639, 1489, 1448, 1180, 1116, 1076, 754, 692 cm^{-1}; MS (EI) *m/z* (%) 287 (M^+ +1, 100), 211 (73), 197 (4), 179 (8), 165 (3); Elemental analysis calcd for $C_{21}H_{18}O$: C 88.08, H 6.34, Found: C 88.21, H 6.29.

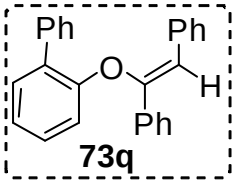
(*Z*)-(1-(2-Nitrophenoxy)ethene-1,2-diyl)dibenzene (73p):



Following the general procedure (GP-1) in condition A; a mixture of 2-nitrophenol (**46p**; 278 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73p** (70 mg) in 22% yield as pale yellow thick liquid.

R_f = 0.28 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.93 (dd, J = 8.4, 1.6 Hz, 1H), 7.65 (bd, J = 8.4 Hz, 4H), 7.39–7.20 (m, 7H), 7.05–6.96 (m, 2H), 6.78 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ149.5, 148.3, 139.6, 134.8, 134.2, 133.8, 129.1, 129.0, 128.9, 128.7, 127.9, 125.8, 121.8, 117.6, 117.1; IR (Neat) ν_{max} 3059, 2930, 1732, 1602, 1352, 1089, 920 cm^{-1}; MS (EI) *m/z* (%) 318 (M^++1, 47), 286 (13), 225 (9), 211 (100), 197 (54), 186 (7); Elemental analysis calcd for $C_{20}H_{15}NO_3$: C 75.70, H 4.76, N 4.41, Found: C 75.62, H 4.81, N 4.51.

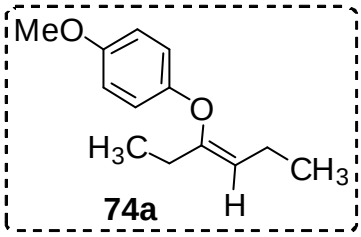
(*Z*)-(2-(1,2-Diphenylvinyloxy)biphenyl (73q):



Following the general procedure (GP-2) in condition B; a mixture of 2-phenylphenol (**46q**; 340 mg, 2.0 mmol), **47f** (178 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 144 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **73q** (237 mg) in 68% yield as colorless solid.

mp 84–86 °C; R_f = 0.50 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.74 (dt, J = 7.2, 1.2 Hz, 2H), 7.63 (dt, J = 7.2, 1.2 Hz, 2H), 7.54–7.44 (m, 3H), 7.43–7.38 (m, 3H), 7.33–7.18 (m, 6H), 7.10 (ddd, J = 9.6, 7.6, 1.6 Hz, 1H), 7.03 (ddd, J = 9.6, 7.6, 1.6 Hz, 1H), 6.92 (dd, J = 8.0, 1.2 Hz, 1H), 6.64 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ153.0, 150.1, 138.2, 135.9, 134.9, 131.4, 131.0, 129.7, 128.9, 128.5, 128.48, 128.4, 128.3, 128.1, 127.3, 127.2, 126.0, 122.3, 116.5, 115.5; IR (KBr) ν_{max} 3032, 2922, 1628, 1475, 1446, 1332, 1253, 1022, 746, 690 cm^{-1}; MS (EI) *m/z* (%) 349 (M^++1, 100), 271 (65), 257 (21), 211 (44); Elemental analysis calcd for $C_{26}H_{20}O$: C 89.62, H 5.79, Found: C 89.55, H 5.83.

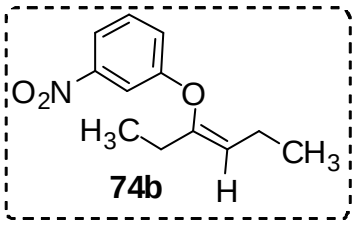
(*Z*)-1-(Hex-3-en-3-yloxy)-4-methoxybenzene (74a):



Following the general procedure (GP-2) in condition B; a mixture of 4-methoxyphenol (**46b**; 248 mg, 2.0 mmol), 3-hexyne (**47g**; 82 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **74a** (194 mg) in 94% yield as colorless liquid.

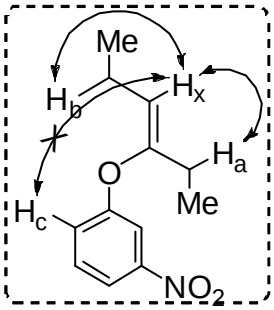
R_f = 0.43 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.94–6.81(m, 4H), 4.99 (bt, J = 7.2 Hz, 1H), 3.79 (s, 3H), 2.19–2.05 (m, 4H), 1.07 (t, J = 7.6 Hz, 3H), 0.99 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ154.2, 152.1, 150.5, 116.8, 115.9, 114.5, 55.5, 25.2, 18.4, 14.2, 11.5; IR (Neat) ν_{max} 3043, 2966, 2935, 2878, 2835, 1684, 1504, 1462, 1296, 1211, 1101, 1039, 829 cm^{-1}; MS (EI) *m/z* (%) 207 (M^++1, 100), 194 (2), 165 (2), 115 (14); Elemental analysis calcd for $C_{13}H_{18}O_2$: C 75.69, H 8.80, Found: C 75.88, H 8.75.

(*Z*)-1-(Hex-3-en-3-yloxy)-3-nitrobenzene (74b):



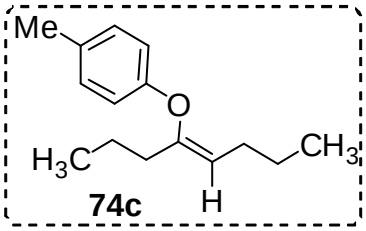
Following the general procedure (GP-1) in condition A; a mixture of 3-nitrophenol (**46a**; 278 mg, 2.0 mmol), 3-hexyne (**47g**; 82 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (9.0 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **74b** (122 mg) in 55% yield as pale yellow liquid.

R_f = 0.32 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.82 (d, J = 8.0 Hz, 1H), 7.72 (s, 1H), 7.43 (t, J = 8.0 Hz, 1H), 7.24 (bd, J = 1.2 Hz, 1H), 5.12 (t, J = 6.8 Hz, 1H), 2.16 (q, J = 7.2 Hz, 2H), 1.98 (q, J = 7.2 Hz, 2H), 1.06 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ157.6, 150.9, 149.3, 130.1, 122.1, 118.0, 116.2, 110.2, 25.4, 18.6, 13.9, 11.4; IR (Neat) ν_{max} 3082, 2970, 2937, 2879, 1685, 1614, 1531, 1350, 1277, 1232, 1024, 796 cm^{-1}; MS (EI) *m/z* (%) 222 (M^++1, 100), 206 (53), 192 (54), 156 (53), 115(54); Elemental analysis calcd for $C_{12}H_{15}NO_3$: C 65.14, H 6.83, N 6.33, Found: C 65.10, H 6.88, N 6.45.



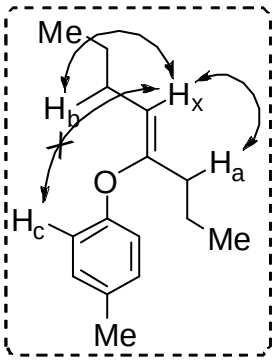
The *Z*-configuration of **74b** is established based on the NOESY studies; NOEs between vinyl-H (δ = 5.12 ppm, H_x) with the *ortho*-hydrogens (δ = 2.16, 1.98 ppm; H_a/H_b) of the methylene groups of **74b** is clearly seen while the NOEs between vinyl-H (δ = 5.12 ppm, H_x) with *ortho*-hydrogens (δ = 7.25 ppm, H_c) of 3-nitrophenyl moiety of **74b** is not observed.

(*Z*)-1-Methyl-4-(oct-4-en-4yloxy) benzene (74c):



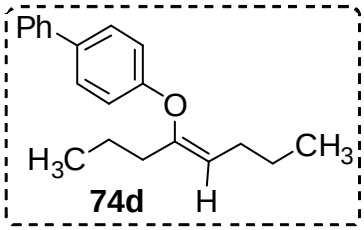
Following the general procedure (GP-2) in condition B; a mixture of 4-methylphenol (**46c**; 216 mg, 2.0 mmol), 4-octyne (**47h**; 110 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **74c** (172 mg) in 79% yield as colorless thick liquid.

R_f = 0.71 (hexane); ^{1}H NMR (400 MHz, CDCl3) δ 7.09 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.02 (t, *J* =7.2 Hz, 1H), 2.32 (s, 3H), 2.11 (t, *J* = 7.2 Hz, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.53–1.43 (m, 2H), 1.43–1.33 (m, 2H), 0.96–0.87 (m, 6H); ^{13}C NMR (101 MHz, CDCl3) δ 154.6, 150.6, 130.5, 129.9, 115.9, 34.3, 27.2, 22.8, 20.6, 20.1,13.9, 13.6; IR (Neat) ν_{max} 3028, 2962, 2868, 1684, 1506, 1222, 1167, 920, 815 cm^{-1}; MS (EI) *m/z* (%) 219 (M^++1, 100), 178 (3), 161 (5), 143 (67), 129 (14); Elemental analysis calcd for $C_{15}H_{22}O$: C 82.52, H 10.16, Found: C 82.61, H 10.10.



The *Z*-configuration of **74c** is established based on the NOESY studies; NOEs between vinyl-H (δ = 5.02 ppm, H_x) with the *ortho*-hydrogens (δ = 2.11, 2.03 ppm; H_a/H_b) of the methylene groups of **74c** is clearly seen while the NOEs between vinyl-H (δ = 5.02 ppm, H_x) with *ortho*-hydrogens (δ = 6.85 ppm, H_c) of 4-methylphenyl moiety of **74c** is not observed.

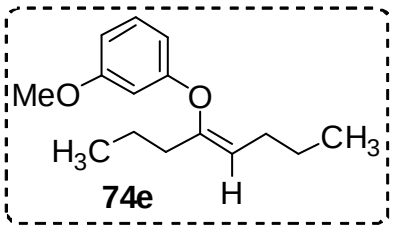
(*Z*)-4-(Oct-4-en-4-yloxy)biphenyl (74d):



Following the general procedure (GP-2) in condition B; a mixture of 4-phenylphenol (**46t**; 340 mg, 2.0 mmol), 4-octyne (**47h**; 110 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 72 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **74d** (268 mg) in 96% yield as colorless liquid.

R_f = 0.6 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.62–7.50 (m, 4H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.37–7.31 (m, 1H), 7.03 (dt, *J* = 6.8, 2.0 Hz, 2H), 5.08 (t, *J* = 7.2 Hz, 1H), 2.16 (t, *J* = 7.2 Hz, 2H), 2.05 (q, *J* = 7.6 Hz, 2H), 1.58–1.48 (m, 2H), 1.47–1.38 (m, 2H), 0.98–0.89 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ156.4, 150.5, 140.8, 134.4, 128.7, 128.2, 126.8, 126.7, 116.3, 116.2, 34.4, 27.2, 22.7, 20.1, 13.9, 13.6; IR (Neat) ν_{max} 2959, 2928, 2868, 1684, 1606, 1514, 1230, 1167, 835, 761, 696 cm^{-1}; MS (EI) *m/z* (%) 281 (M^++1, 100), 161 (7), 143 (76), 129 (19); Elemental analysis calcd for $C_{20}H_{24}O$: C 85.67, H 8.63, Found: C 85.61, H 8.70.

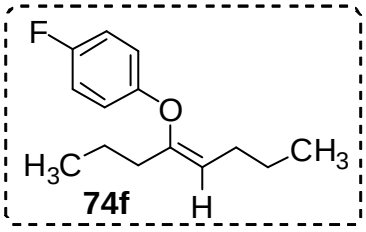
(*Z*)-1-Methoxy-3-(oct-4-en-4yloxy)benzene (74e):



Following the general procedure (GP-2) in condition B; a mixture of 3-methoxyphenol (**46k**; 248 mg, 2.0 mmol), 4-octyne (**47h**; 110 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 50 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **74e** (217 mg) in 93% yield as colorless liquid.

R_f = 0.44 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.16 (t, *J* = 8.4 Hz, 1H), 6.57–6.48 (m, 3H), 5.01 (t, *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 2.10 (t, *J* = 7.2 Hz, 2H), 1.99 (q, *J* = 7.2 Hz, 2H), 1.54–1.41 (m, 2H), 1.41–1.31 (m, 2H), 0.94–0.84 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ160.9, 158.0, 150.4, 129.8, 116.3, 108.3, 106.8, 102.1, 55.2, 34.4, 27.2, 22.7, 20.1, 13.9, 13.6; IR (Neat) ν_{max} 2959, 2872, 1684, 1602, 1454, 1280, 1143, 962, 850, 688 cm^{-1}; MS (EI) *m/z* (%) 235 (M^++1, 100), 143 (63), 125 (5); Elemental analysis calcd for $C_{15}H_{22}O_2$: C 76.88, H 9.46, Found: C 76.95, H, 9.39.

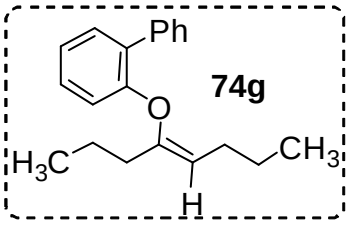
(*Z*)-1-Fluoro-4-(oct-4-en-4-yloxy)benzene (74f):



Following the general procedure (GP-2) in condition B; a mixture of 4-fluorophenol (**46e**; 224 mg, 2.0 mmol), 4-octyne (**47h**; 110 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **74f** (210 mg) in 95% yield as colorless liquid.

R_f = 0.55 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ6.99–6.91 (m, 2H), 6.89–6.82 (m, 2H), 4.99 (t, *J* = 7.2 Hz, 1H), 2.06 (t, *J* = 7.6 Hz, 2H), 1.98 (q, *J* = 7.2 Hz, 2H), 1.52–1.41 (m, 2H), 1.41–1.31 (m, 2H), 0.93–0.86 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ158.8, 156.4, 152.74, 152.72, 150.7, 117.0, 116.9, 116.1, 115.9, 115.7, 34.2, 27.2, 22.7, 20.1, 13.8, 13.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ – 123.4; IR (Neat) ν_{max} 2959, 2928, 1682, 1502, 1201, 922, 829 cm^{-1}; MS (EI) *m/z* (%) 223 (M^++1, 75), 161 (6), 143 (100), 129 (18); Elemental analysis calcd for $C_{14}H_{19}FO$: C 75.64, H 8.61, Found: C 75.59, H 8.67.

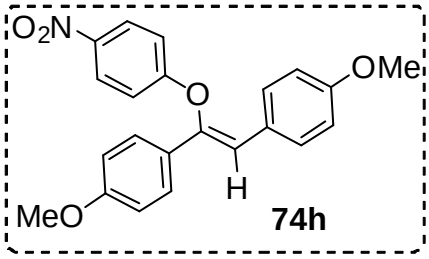
(*Z*)-2-(Oct-4-en-4-yloxy)biphenyl (74g):



Following the general procedure (GP-2) in condition B; a mixture of 2-phenylphenol (**46q**; 340 mg, 2.0 mmol), 4-octyne (**47h**; 110 mg, 1.0 mmol), K_2CO_3 (276 mg, 2.0 mmol) in the presence of $AuCl_3$ (15 mg, 0.05 mmol) and L2 (15 mg, 0.05 mmol) in THF (1.0 mL) was heated at 100 °C for 120 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **74g** (187 mg) in 67% yield as colorless thick liquid.

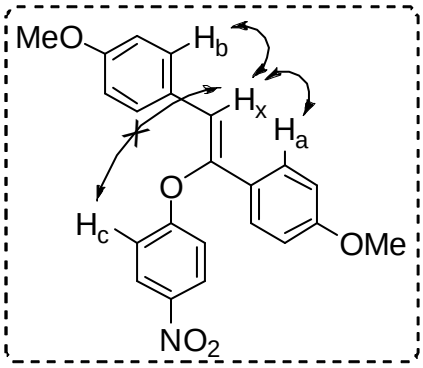
R_f = 0.57 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.61 (d, *J* = 7.6 Hz, 2H), 7.47–7.31 (m, 4H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 5.01 (t, *J* = 7.2 Hz, 1H), 2.09 (t, *J* = 7.2 Hz, 2H), 2.02 (q, *J* = 7.2 Hz, 2H), 1.44–1.32 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ153.5, 150.7, 138.4, 131.0, 129.5, 128.3, 127.9, 126.8, 121.4, 115.6, 114.7, 34.3, 29.7, 27.3, 22.7, 20.1, 13.9, 13.5; IR (Neat) ν_{max} 3061, 2959, 2934, 2872, 1682, 1583, 1477, 1217, 1118, 750, 698 cm^{-1}; MS (EI) *m/z* (%) 281 (M^+ +1, 100), 161 (5), 143 (46), 129 (11); Elemental analysis calcd for $C_{20}H_{24}O$: C 85.67, H 8.63, Found: C 85.74, H 8.59.

(*Z*)-4,4'-(1-(4-Nitrophenoxy)ethene-1,2-diyl)bis-methoxybenzene (74h):



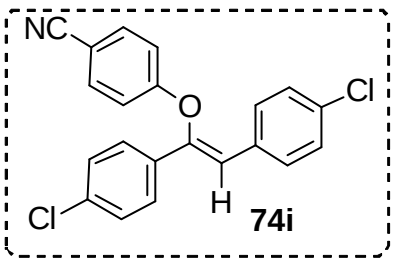
Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**46g**; 139 mg, 1.0 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**47i**; 119 mg, 0.5 mmol), Ag_2CO_3 (275 mg, 1.0 mmol) in the presence of $AuCl_3$ (4.5 mg, 0.015 mmol) and L2 (4.5 mg, 0.015 mmol) in CH_2Cl_2 (0.5 mL) was heated at 100 °C for 36 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (19:1) to afford **74h** (157 mg) in 83% yield as thick yellow liquid.

R_f = 0.43 (95:5 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.14 (dt, J = 8.0, 1.2 Hz, 2H), 7.51–7.45 (m, 4H), 7.10 (dt, J = 8.0, 1.2 Hz, 2H), 6.91–6.75 (m, 4H), 6.62 (s, 1H), 3.80 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ161.8, 159.9, 159.0, 146.8, 142.4, 130.2, 127.4, 126.8, 126.1, 116.2, 115.6, 115.1, 114.3, 114.1, 55.3, 55.2; IR (Neat) ν_{max} 2930, 2843, 1608, 1342, 1242, 1176, 1032, 833 cm^{-1}; MS (EI) *m/z* (%) 378 (M^++1, 52), 271 (100), 240 (3); Elemental analysis calcd for $C_{22}H_{19}NO_5$: C 70.02, H 5.07, N 3.71, Found: C 69.95, H 5.12, N 3.76.



The *Z*-configuration of **74h** is established based on the NOESY studies; NOEs between vinyl-H (δ = 6.62 ppm, H_x) with the *ortho*-hydrogens (δ = 7.46, 7.49 ppm; H_a/H_b) of the phenyl groups of **74h** is clearly seen while the NOEs between vinyl-H (δ = 6.62 ppm, H_x) with *ortho*-hydrogens (δ = 7.11 ppm, H_c) of 4-nitrophenyl moiety of **74h** is not observed.

(*Z*)-4-(1,2-bis(4-Chlorophenyl)vinyloxy)benzonitrile (74i):

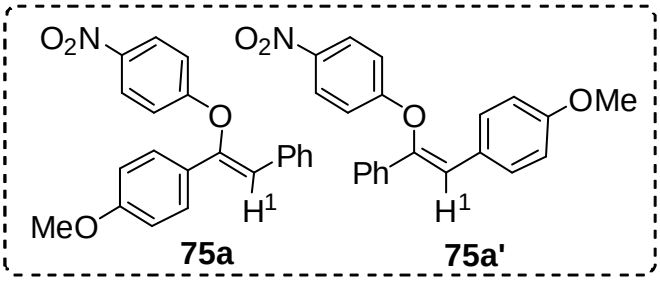


Following the general procedure (GP-1) in condition A; a mixture of 4-cyanophenol (**46h**; 238 mg, 2.0 mmol), 1,2-bis(4-chlorophenyl)ethyne (**47j**; 247 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 ^{o}C for 72 h. Upon usual work-up, the crude mixture

was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **74i** (250 mg) in 68% yield as colorless thick liquid.

R_f = 0.40 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.54 (dt, J = 6.8, 2.0 Hz, 2H), 7.51–7.44 (m, 4H), 7.32 (dt, J = 6.8, 2.0 Hz, 2H), 7.27 (dt, J = 6.8, 2.0 Hz, 2H), 7.05 (dt, J = 6.8, 2.0 Hz, 2H), 6.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ159.3, 147.9, 135.0, 134.4, 133.7, 133.1, 132.1, 130.2, 129.2, 128.9, 126.9, 118.6, 116.8, 116.52, 116.51, 106.1; IR (Neat) ν_{max} 3335, 3067, 2926, 2856, 2226, 1901, 1601, 1494, 1091, 831 cm^{-1}; MS (EI) *m/z* (%) 366 (M^+ +1, 61), 298 (76), 279 (96), 211 (100), 185 (20), 149 (40); Elemental analysis calcd for $C_{21}H_{13}Cl_2NO$: C 68.87, H 3.58, Found: C 68.92, H 3.91.

(*Z*)-1-Methoxy-4-(1-(4-nitrophenoxy)-2-phenylvinyl)benzene (75a); (*Z*)-1-Methoxy-4-(2-(4-nitrophenoxy)-2-phenylvinyl)benzene (75a'):



Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**46g**, 278 mg, 2.0 mmol), 1-methoxy-4-(phenylethynyl)benzene (**47l**, 208 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude reaction was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford a mixture of **75a+75a'** (326 mg) in 94% yield as yellow thick liquid. Purification of the in-separable regioisomers **75a** and **75a'** was failed through repeated flash column chromatography.

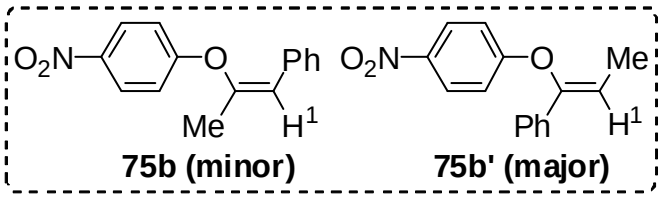
Ratio of both regioisomers **75a**:**75a'** was determined based on the characteristic H^1 proton integration. Furthermore HPLC data reconfirms the amount of regioisomers obtained in the reaction.

^{1}H NMR (400 MHz, $CDCl_3$) H^1 for **75a**/**75a'**: δ = 6.73 (s, 1H, 31%; minor) / 6.64 (s, 1H, 69%; major).

HPLC analysis (Daicel Chiralpak AS-H column, hexanes-*i*-PrOH = 97:3 for elution, flow rate = 1.0 mL/min; λ = 254 nm) for **75a**/**75a'** = t_R (7.87 min, 37%; minor)/(8.47 min, 63%; major).

R_f = 0.40 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) olefin-H for **75a**/**75a'**: δ6.73 (s, 1H, 31%; minor) / 6.64 (s, 1H, 69%; major); ^{1}H NMR (400 MHz, $CDCl_3$) for **75a**+**75a'**: δ8.12 (bd, J = 9.2 Hz, 4H; 2H (for major) + 2H (for minor)), 7.58–7.44 (m, 8H; 4H (for major) + 4H (for minor)), 7.36–7.28 (m, 4H; 2H (for major) + 2H (for minor)), 7.22–7.18 (m, 2H; 1H (for major) + 1H (for minor)), 7.12–7.05 (m, 4H; 2H (for major) + 2H (for minor)), 6.89–6.80 (m, 4H; 2H (for major) + 2H (for minor)), 6.73 (s, 1H, minor), 6.64 (s, 1H, major), 3.78 (s, 3H, major), 3.77 (s, 3H, minor); ^{13}C NMR (101 MHz, $CDCl_3$) for **75a**+**75a'**: δ161.5, 160.1, 148.4, 142.4, 134.0, 130.6, 128.7, 128.5, 127.5, 127.0, 125.9, 125.2, 116.2, 114.2, 55.2 (for major regioisomer); and 159.2, 146.7, 134.8, 130.6, 128.8, 128.5, 127.0, 126.4, 126.0, 125.2, 116.8, 116.0, 115.4, 114.0, 55.1 (for minor regioisomer); IR (Neat) for **75a**+**75a'**: ν_{max} 3080, 2934, 2837, 1637, 1591, 1342, 1238, 1022, 846 cm^{-1}; MS (EI) *m/z* (%) for **75a**+**75a'** 348 (M^+ +1, 100), 241 (97), 209 (11), 165 (3); Elemental analysis calcd for $C_{21}H_{17}NO_4$: C 72.61, H 4.93, N 4.03, Found (as a mixture of **75a**+**75a'**): C 72.55, H 4.88, N 4.07.

(*Z*)-1-Nitro-4-(1-phenylprop-1-en-2-yloxy)benzene (75b); (*Z*)-1-Nitro-4-(1-phenylprop-1-enyloxy)benzene (75b'):



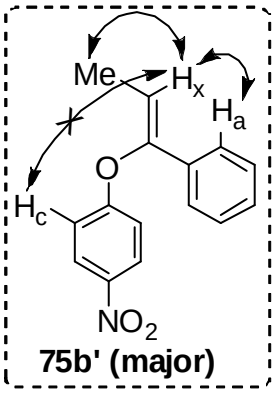
Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**46g**, 278 mg, 2.0 mmol), 1-phenyl-1-propyne (**47e**, 116 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and **L2** (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 72 h. Upon usual work-up, the crude reaction was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford a mixture of **75b+75b'** (237 mg) in 93% yield as yellow thick liquid. Purification of the regioisomers **75b** (minor) and **75b'** (major) was successfully carried out through repeated flash column chromatography.

Ratio of both regioisomers **75b**:**75b'** was determined based on the characteristic H^1 proton integration. Furthermore HPLC data reconfirms the amount of regioisomers obtained in the reaction.

^{1}H NMR (400 MHz, $CDCl_3$) olefin-H for **75b**:**75b'**: δ6.06 (s, 1H, 30%; minor) : 6.02 (q, J = 7.2 Hz, 1H, 70%; major); HPLC analysis (Daicel Chiralcel OD-H column, hexane–*i*–PrOH = 99:1 for elution, flow rate = 1.0 mL/min; λ = 267 nm) for **75b**/**75b'** = t_R (4.33 min, 32%; minor)/(4.62 min, 68%; major).

75b' (major product) was obtained as light yellow thick liquid.

light yellow thick liquid; R_f = 0.60 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.14 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.33–7.24 (m, 3H), 7.03 (d, J = 9.2 Hz, 2H), 6.02 (q, J = 7.2 Hz, 1H), 1.73 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 149.2, 142.2, 134.3, 128.7, 128.4, 126.1, 124.8, 115.5, 113.2, 11.4; IR (Neat) ν_{max} 3080, 2989, 2920, 1666, 1591, 1342, 1109, 750 cm^{-1}; MS (EI) *m/z* (%) 256 (M^+ +1, 100), 240 (22), 149 (46), 135 (3); Elemental analysis calcd for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49, Found: C 70.49, H 5.10, N 5.55.

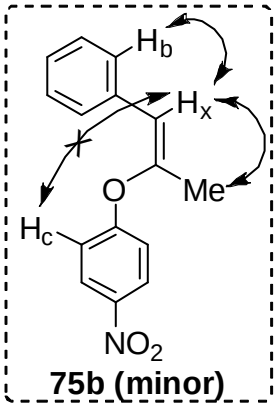


75b' (major)

The *Z*-configuration of **75b'** is established based on the NOESY studies; NOEs between vinyl-H (δ = 6.01 ppm, H_x) with the *ortho*-hydrogens (δ = 7.42, 1.74 ppm) of the phenyl and methyl groups respectively of **75b'** is clearly seen while the NOEs between vinyl-H (δ = 6.01 ppm, H_x) with *ortho*-hydrogens (δ = 7.03 ppm, H_c) of 4-nitrophenyl moiety of **75b'** is not observed.

75b (minor product) was obtained as light yellow thick liquid.

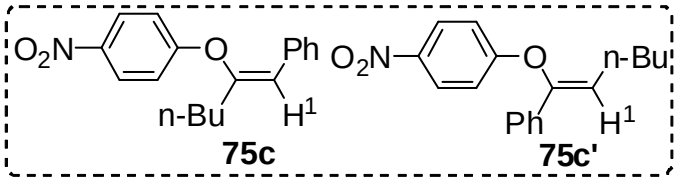
light yellow thick liquid; R_f = 0.58 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ8.19 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.6 Hz, 2H), 7.28–7.20 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.06 (s, 1H), 2.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ160.7, 147.5, 142.7, 134.0, 128.5, 128.3, 127.3, 126.1, 117.4, 116.5, 19.7; IR (Neat) ν_{max} 3082, 2922, 2849, 1682, 1591, 1340, 1240, 1109, 748 cm^{-1}; MS (EI) *m/z* (%) 256 (M^+ +1, 36), 241 (10), 154 (55), 138 (100); Elemental analysis calcd for $C_{15}H_{13}NO_3$: C 70.58, H 5.13, N 5.49, Found: C 70.65, H 5.10, N 5.43.



75b (minor)

The *Z*-configuration of **75b** is established based on the NOESY studies; NOEs between vinyl-H (δ = 6.06 ppm, H_x) with the *ortho*-hydrogens (δ = 7.39, 2.04 ppm) of the phenyl and methyl groups respectively of **75b** is clearly seen while the NOEs between vinyl-H (δ = 6.06 ppm, H_x) with *ortho*-hydrogens (δ = 7.06 ppm, H_c) of 4-nitrophenyl moiety of **75b** is not observed.

(*Z*)-1-Nitro-4-(1-phenylhex-1-en-2-yloxy)benzene (75c); (*Z*)-1-Nitro-4-(1-phenylhex-1-enyloxy)benzene (75c'):



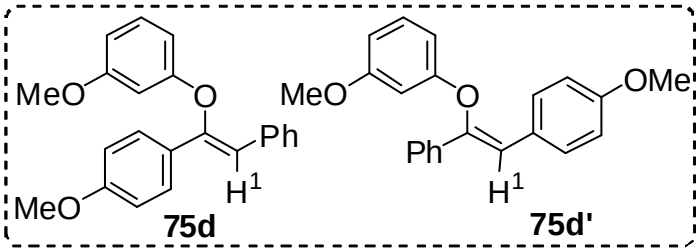
Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**46g**, 278 mg, 2.0 mmol), hex-1-ynylbenzene (**47m**, 158 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 72 h. Upon usual work-up, the crude reaction was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford a mixture of **75c+75c'** (241 mg) in 81% yield as yellow thick liquid. Purification of the in-separable regioisomers **75c** and **75c'** was failed through repeated flash column chromatography.

Ratio of both regioisomers **75c**:**75c'** was determined based on the characteristic H^1 proton integration. Furthermore HPLC data reconfirms the amount of regioisomers obtained in the reaction.

R_f = 0. 40 (49:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) olefin-H for **75c**/**75c'**: δ6.08 (s, 1H, 57%; major) / 5.95 (s, 1H, 43%; minor); HPLC analysis (Daicel Chiralpak AS-H column, hexane–*i*–PrOH = 97:3 for elution, flow rate = 1.0 mL/min; λ = 254 nm) for **75c**/**75c'** = t_R (6.96 min, 38%; minor)/(7.45 min, 62%; major); ^{1}H NMR (400 MHz, $CDCl_3$) for **75c**+**75c'**: δ8.25–8.15 (m, 4H; 2H (for major) + 2H (for minor)), 7.48–7.38 (m, 4H; 2H (for major) + 2H (for minor)), 7.32–7.20 (m, 4H; 2H (for major) + 2H (for minor)), 7.18–7.12 (m, 2H; 1H (for major) + 1H (for minor)), 7.08–6.99 (m, 4H; 2H (for major) + 2H (for minor)), 6.08 (s, 1H, major), 5.95 (t, *J* = 7.6 Hz, 1H, minor), 2.33 (t, *J* = 7.2 Hz, 2H; 1H (for major) + 1H (for minor)), 2.17 (q, *J* = 7.2 Hz, 2H; 1H (for major) + 1H (for minor)), 1.68–1.50 (m, 4H; 2H (for major) + 2H (for minor)), 1.49–1.27 (m, 4H;

2H (for major) + 2H (for minor)), 0.96–0.81 (m, 6H; 3H (for major) + 3H (for minor)); ^{13}C NMR (101 MHz, $CDCl_3$) for **75c**+**75c'**: δ160.9, 151.4, 142.5, 133.9, 128.7, 128.5, 128.4, 126.1, 124.9, 116.3, 33.2, 29.1, 22.1, 13.9 (for major regioisomer); and 162.7, 148.3, 142.1, 134.2, 128.4, 127.3, 119.1, 117.7, 116.7, 115.6, 31.2, 25.6, 22.4, 13.9 (for minor regioisomer); IR (Neat) for **75c**+**75c'**: ν_{max} 3082, 3026, 2957, 2930, 1668, 1591, 1516, 1342, 1242, 1111, 850, 750 cm^{-1}; MS (EI) *m/z* (%) for **75c**+**75c'** 296 (M^+–1, 86), 278 (11), 154 (17), 138 (100); Elemental analysis calcd for $C_{18}H_{19}NO_3$: C 72.71, H 6.44, N 4.71, Found (as a mixture of **75c**+**75c'**): C 72.65, H 6.41, N 4.76.

(*Z*)-1-Methoxy-3-(1-(4-methoxyphenyl)-2-phenylvinyloxy)benzene (75d); (*Z*)-1-Methoxy-3-(2-(4-methoxyphenyl)-1-phenylvinyloxy)benzene (75d'):



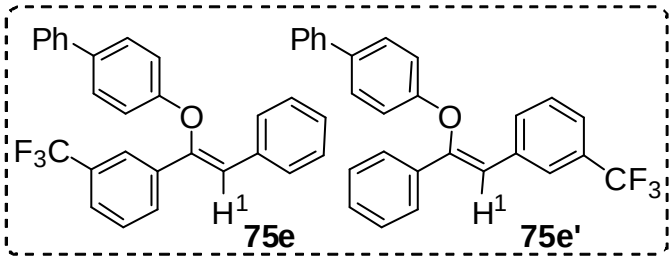
Following the general procedure (GP-2) in condition B; a mixture of 3-methoxyphenol (**46k**, 119 mg, 0.96 mmol), 1-methoxy-4-(phenylethynyl)benzene (**47l**, 100 mg, 0.48 mmol), K_2CO_3 (133 mg, 0.96 mmol) in the presence of $AuCl_3$ (7.3 mg, 0.024 mmol) and L2 (7.3 mg, 0.024 mmol) in THF (1.0 mL) was heated at 100 ^{o}C for 120 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (19:1) to afford a mixture of **75d+75d'** (101 mg) in 63% yield as pale yellow solid. Purification of the in-separable regioisomers **75d** and **75d'** was failed through repeated flash column chromatography.

Ratio of both regioisomers **75d/75d'** was unable to determine based on the characteristic H^1 proton integration. However, HPLC data confirms the amount of regioisomers obtained in the reaction.

R_f = 0.26 (95:5 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) olefin-H for **75d**/**75d'**: δ6.58 (s, 2H; 1H (for major) + 1H (for minor)); HPLC analysis (Daicel Chiralpak AS-H column, hexane–*i*–PrOH = 19:1 for elution, flow rate = 0.3 mL/min; λ = 254 nm) for **75d**/**75d'** = t_R (13.9 min, 91%; major) / (14.49 min, 9%; minor); ^{1}H NMR (400 MHz, $CDCl_3$) for **75d**+**75d'**: δ7.67–7.59 (m, 6H; 3H (for major) + 3H (for minor)), 7.55 (d, *J* = 8.0 Hz, 2H; 1H (for major) + 1H (for minor)), 7.36–7.25 (m, 4H; 2H (for major) + 2H (for

minor)), 7.21 (t, *J* = 8.0 Hz, 2H; 1H (for major) + 1H (for minor)), 7.14 (t, *J* = 8.0 Hz, 2H; 1H (for major) + 1H (for minor)), 6.87 (d, *J* = 8.0 Hz, 4H; 2H (for major) + 2H (for minor)), 6.65 (bs, 4H; 2H (for major) + 2H (for minor)), 6.58 (s, 2H; 1H (for major) + 1H (for minor)), 6.53 (d, *J* = 8.0 Hz, 2H; 1H (for major) + 1H (for minor)), 3.80 (s, 6H; 3H (for major) + 3H (for minor)), 3.75 (s, 6H; 3H (for major) + 3H (for minor)); ^{13}C NMR (101 MHz, $CDCl_3$) for **75d**+**75d'**: δ160.9, 159.8, 157.6, 149.4, 134.9, 130.4, 130.1, 130.0, 128.8, 128.6, 127.4, 115.1, 114.0, 108.7, 107.4, 102.7, 55.3, 55.2. (for major regioisomer); and 158.9, 147.8, 136.2, 130.4, 130.1, 128.8, 128.5, 128.0, 127.5, 127.4, 127.1, 125.6, 116.3, 114.0, 108.5, 102.6, 55.3, 55.2 (for minor regioisomer); IR (KBr) for **75d**+**75d'**: ν_{max} 2926, 2852, 1604, 1510, 1251, 1141, 835, 692 cm^{-1}; MS (EI) *m/z* (%) for **75d**+**75d'** 333 (M^+ +1, 100), 241 (38), 209 (5), 165 (3); Elemental analysis calcd for $C_{22}H_{20}O_3$: C 79.50, H 6.06. Found (as a mixture of **75d**+**75d'**): C 79.44, H 6.12.

(*Z*)-4-(2-Phenyl-1-(3-(trifluoromethyl)phenyl)vinyloxy)biphenyl (75e); (*Z*)-4-(1-Phenyl-2-(3-(trifluoromethyl)phenyl)vinyloxy)biphenyl (75e'):



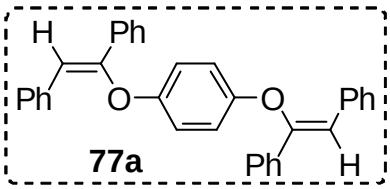
Following the general procedure (GP-2) in condition B; a mixture of 4-phenylphenol (**46t**, 139 mg, 0.82 mmol), 1-(phenylethynyl)-3-(trifluoromethyl)benzene (**47n**, 100 mg, 0.41 mmol), K_2CO_3 (112 mg, 0.82 mmol) in the presence of $AuCl_3$ (6.2 mg, 0.02 mmol) and L2 (6.2 mg, 0.02 mmol) in THF (1.0 mL) was heated at 100 °C for 120 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford a mixture of **75e+75e'** (147 mg) in 35% yield as pale yellow thick liquid. Purification of the in-separable regioisomers **75e** and **75e'** was failed through repeated flash column chromatography.

Ratio of both regioisomers **75e**/**75e'** was determined based on the characteristic H^1 proton integration. Furthermore HPLC data reconfirms the amount of regioisomers obtained in the reaction.

R_f = 0.17 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) olefin-H for **75e**/**75e'**: δ6.79 (s, 1H, 31%; minor) / 6.73 (s, 1H, 69%; major); HPLC analysis (Daicel Chiralcel OD-H column, hexane–*i*–PrOH = 19:1 for elution, flow rate = 1.0 mL/min; λ = 254 nm) for **75e**/**75e'** = t_R

(5.58 min, 30%; minor)/(5.99 min, 70%; major); ^{1}H NMR (400 MHz, $CDCl_3$) for **75e**+**75e'**: δ7.96 (br s, 2H; 1H (for major) + 1H (for minor)), 7.92 (d, *J* = 7.6 Hz, 1H; major), 7.80 (d, *J* = 8.0 Hz, 1H, minor), 7.74 (d, *J* = 7.6 Hz, 1H, major), 7.68 (d, *J* = 6.8 Hz, 2H, major), 7.60–7.25 (m, 25H; 11H (for major) + 14H (for minor)), 7.13 (t, *J* = 8.4 Hz, 4H; 2H (for major) + 2H (for minor)), 6.79 (s, 1H, minor), 6.73 (s, 1H, major); ^{13}C NMR (101 MHz, $CDCl_3$) for **75e**+**75e'**: δ= 155.7, 151.4, 140.5, 135.5, 135.4, 131.8, 129.2, 129.0, 128.8, 128.6, 128.5, 128.0, 126.9, 126.8, 126.2, 125.9, 123.9, 118.4, 116.6 (for major regioisomer); 155.5, 148.2, 137.0, 134.2, 131.4, 131.0, 130.7, 129.0, 128.8, 128.5, 128.0, 126.8, 126.2, 125.1, 122.8, 122.7, 116.6, 115.2 (for minor regioisomer); ^{19}F NMR (376 MHz, $CDCl_3$) for **75e**/**75e'**: δ– 62.67/ –62.75; IR (Neat) for **75e**+**75e'**: ν_{max} 3061, 3034, 2959, 1892, 1641, 1604, 1514, 1446, 1168, 908, 761, 694 cm^{-1}; MS (EI) *m/z* (%) for **75e**+**75e'** 417 (M^+ +1, 89), 315 (7), 279 (100), 265 (9), 247 (2); Elemental analysis calcd for $C_{27}H_{19}F_3O$: C 77.87, H 4.60, Found (as a mixture of **75e**+**75e'**): C 77.92, H 4.56.

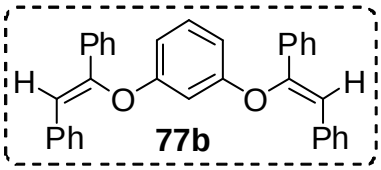
1,4-bis[(*Z*)-1,2-Diphenylvinyloxy]benzene (77a):



Following the general procedure (GP-2) in condition B; a mixture of hydroquinone (**76a,** 110 mg, 1.0 mmol), **46f** (712 mg, 4.0 mmol), K_2CO_3 (553 mg, 4.0 mmol) in the presence of $AuCl_3$ (30.3 mg, 0.1 mmol) and L2 (30.3 mg, 0.1 mmol) in THF (2.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (95:5) to afford **77a** (256 mg) in 55% yield as colorless solid.

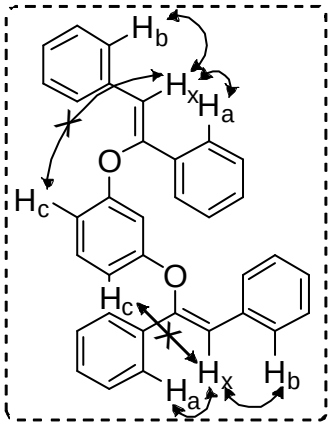
mp 197–199 °C; R_f = 0.36 (95:5 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.61 (d, *J* = 7.2 Hz, 4H), 7.56 (d, *J* = 7.2 Hz, 4H), 7.34–7.25 (m, 10H), 7.24–7.17 (m, 2H), 6.86 (bs, 4H), 6.58 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ151.1, 150.0, 136.0, 134.8, 128.9, 128.5, 128.3, 127.3, 126.1, 117.2, 116.5; IR (KBr) ν_{max} 2924, 2849, 1494, 1197, 1020, 758, 690 cm^{-1}; MS (EI) *m/z* (%) 467 (M^+ +1, 46), 430 (8), 411 (11), 313 (11), 289 (13), 211 (100), 143 (14); Elemental analysis calcd for $C_{34}H_{26}O_2$: C 87.52, H 5.62, Found: C 87.61, H 5.58.

1,3-bis[(*Z*)-1,2-Diphenylvinyloxy]benzene (77b):



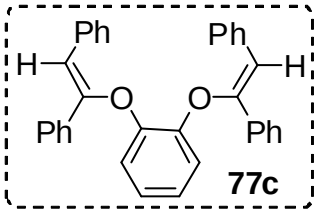
Following the general procedure (GP-2) in condition B; a mixture of resorcinol (**76b**, 110 mg, 1.0 mmol), **47f** (712 mg, 4.0 mmol), K_2CO_3 (553 mg, 4.0 mmol) in the presence of $AuCl_3$ (30.3 mg, 0.1 mmol) and L2 (30.3 mg, 0.1 mmol) in THF (2.0 mL) was heated at 100 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (95:5) to afford **77b** (440 mg) in 94% yield as colorless solid.

mp 116–117 °C; R_f = 0.45 (95:5 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.56 (d, *J* = 7.2 Hz, 4H), 7.51–7.46 (m, 4H), 7.30–7.18 (m, 12 H), 7.02 (t, *J* = 8.4 Hz, 1H), 6.75 (t, *J* = 2.4 Hz, 1H), 6.61 (bs, 3H), 6.58 (d, *J* = 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ157.6, 149.7, 135.9, 134.6, 130.3, 129.0, 128.6, 128.5, 128.4, 127.4, 126.0, 116.6, 110.1, 105.6; IR (KBr) ν_{max} 3057, 2926, 1597, 1483, 1446, 1257, 1132, 690 cm^{-1}; MS (EI) *m/z* (%) 467 (M^+ +1, 100), 357 (4), 315 (11), 289 (8), 211 (94), 197 (5); Elemental analysis calcd for $C_{34}H_{26}O_2$: C 87.52, H 5.62, Found: C 87.41, H 5.66.



The *Z*-configuration of **77b** is established based on the NOESY studies; NOEs between vinyl-H (δ = 6.60 ppm, H_x) with the *ortho*-hydrogens (δ = 7.57, 7.49 ppm; H_a/H_b) of the phenyl groups of **77b** is clearly seen while the NOEs between vinyl-H (δ = 6.60 ppm, H_x) with *ortho*-hydrogens (δ = 6.75 ppm, H_c) of resorcinol moiety of **77b** is not observed.

1,2-bis[(*Z*)-1,2-Diphenylvinyloxy]benzene (77c):

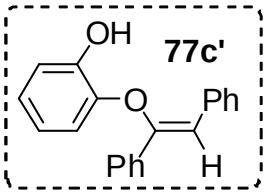


Following the general procedure (GP-2) in condition B; a mixture of catechol (**76c**, 110 mg, 1.0 mmol), **47f** (712 mg, 4.0 mmol), K_2CO_3 (553 mg, 4.0 mmol) in the presence of $AuCl_3$ (30.3 mg, 0.1 mmol) and L2 (30.3 mg, 0.1 mmol) in THF (2.0 mL) was heated at 100 °C for 168 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (19:1) to afford di-

substituted **77c** (33 mg) in 7% yield as colorless solid and mono-substituted **77c'** (97 mg) in 34% yield as colorless thick liquid.

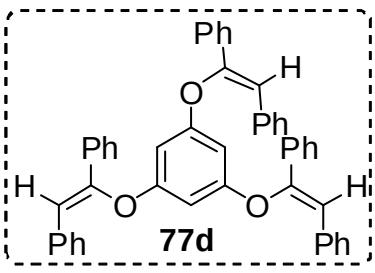
mp 142−143 °C; R_f = 0.39 (95:5 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.78 (dd, *J* = 7.2, 4.4, Hz, 7H), 7.42−7.32 (m, 10H), 7.31−7.25 (m, 3H), 6.87 (dd, *J* = 6.0, 2.0 Hz, 2H), 6.76 (s, 2H), 6.68 (dd, *J* = 6.2, 3.4 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ149.9, 145.4, 135.9, 134.9, 129.1, 128.9, 128.7, 128.6, 128.5, 128.0, 127.5, 126.1, 125.6, 122.5, 121.3, 116.9, 116.2, 108.5; IR (KBr) ν_{max} 3024, 1637, 1591, 1493, 1446, 1244, 1111, 1018, 920, 690 cm^{-1}; MS (EI) *m/z* (%) 467 (M^+ +1, 6), 303 (22), 289 (69), 211 (59), 197 (100), 167 (4), 65 (13); Elemental analysis calcd for $C_{34}H_{26}O_2$: C 87.52, H 5.62, Found: C 87.45, H 5.66.

(Z)-2-(1,2-Diphenylvinyloxy)phenol (77c′)



97 mg, 34% yield. colorless thick liquid; R_f = 0.18 (95:5, hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.65 (d, *J* = 7.6 Hz, 2H), 7.57 (dt, *J* = 6.8, 1.6 Hz, 2H), 7.41−7.25 (m, 6H), 7.10 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.92 (td, *J* = 8.0, 1.6 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.75 (s, 1H), 6.69 (td, *J* = 7.6, 1.6 Hz, 1H), 6.01 (s, 1H, -OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ149.1, 145.6, 143.0, 135.1, 134.3, 128.7, 128.7, 128.59, 127.6, 125.6, 123.0, 120.4, 117.2, 115.6, 114.9; IR (Neat) ν_{max} 3524, 3055, 2976, 1641, 1448, 1203, 1018, 918, 740 cm^{-1}; MS (EI) *m/z* (%) 289 (M^+ +1, 100), 287 (12), 225 (3), 211 (63), 197 (11), 179 (5); Elemental analysis calcd for $C_{20}H_{16}O_2$: C 83.31, H 5.59, Found: C 83.21, H 5.56.

1,3,5-tris[(*Z*)-1,2-Diphenylvinyloxy]benzene (77d):

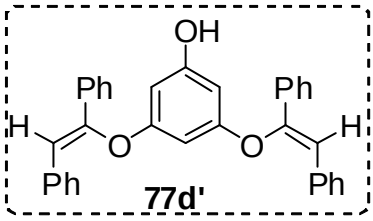


Following the general procedure (GP-2) in condition B; a mixture of phloroglucinol (**76d**, 126 mg, 1.0 mmol), **47f** (1.07 g, 6.0 mmol), K_2CO_3 (828 mg, 6.0 mmol) in the presence of $AuCl_3$ (45 mg, 0.15 mmol) and L2 (45 mg, 0.15 mmol) in THF (2.0 mL) was heated at 100 °C for 168 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (19:1) to afford tri-substituted **77d** (38 mg) in 6% yield

as colorless solid, di-substituted **77d'** (44 mg) in 9% yield as pale-brown thick liquid and mono-substituted **77d''** (99 mg) in 32% yield as pale brown thick liquid.

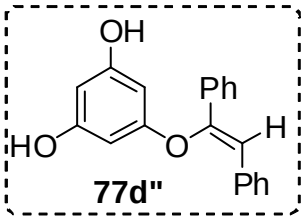
mp 194–196 °C; R_f = 0.21 (95:5 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.45 (br s, 6H), 7.33 (d, J = 7.2 Hz, 6H), 7.28–7.16 (m, 18H), 6.52 (s, 3H), 6.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ158.2, 149.6, 135.6, 134.5, 128.9, 128.4, 128.2, 127.2, 125.9, 116.3, 99.7; IR (KBr) ν_{max} 2922, 2851, 1738, 1601, 1446, 1134, 761, 692 cm^{-1}; MS (EI) *m/z* (%) 662 (M^+ +1, 100), 483 (47), 412 (35), 369 (16), 313 (24), 211 (51), 178 (14), 149 (9); Elemental analysis calcd for $C_{48}H_{36}O_3$: C 87.25, H 5.49, Found: C 87.16, H 5.54.

Compound (**77d'**) was purified through column chromatography eluting with hexane:ethyl acetate (9:1) mixture.



77d'

44 mg, 9% yield; pale-brown thick liquid; R_f = 0.18 (90:10 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.57 (d, J = 7.6 Hz, 4H), 7.51 (d, J = 3.4 Hz, 4H), 7.34–7.18 (m, 13H), 6.62 (s, 2H), 6.38 (s, 1H, -OH), 6.14 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ158.4, 157.6, 149.5, 135.7, 134.5, 129.0, 128.6, 128.5, 128.4, 127.4, 125.8, 116.7, 98.3, 97.9; IR (Neat) ν_{max} 3537, 3400 (-O-H), 2924, 1695, 1601, 1448, 1128, 916, 827 cm^{-1}; MS (EI) *m/z* (%) 483 (M^++1, 100), 305 (5), 211 (8), 178 (8), 127 (3); Elemental analysis calcd for $C_{34}H_{26}O_3$: C 84.62, H 5.43, Found: C 84.71, H 5.39.

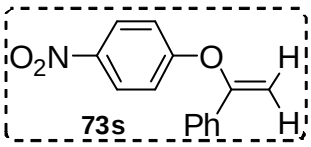


77d"

Compound (**77d''**) was purified through column chromatography eluting with hexane:ethyl acetate (3:2) mixture.

99 mg, 32% yield; pale-brown thick liquid; R_f = 0.43 (60:40 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ7.62 (d, J = 7.6 Hz, 2H), 7.56 (d, J = 6.8 Hz, 2H), 7.37–7.17 (m, 6H), 6.64 (s, 1H), 6.14 (s, 2H), 5.85 (s, 1H), 5.65 (bs, 2H, -OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ158.3, 157.4, 149.2, 135.7, 134.5, 128.9, 128.6, 128.5, 128.4, 127.5, 125.7, 116.8, 97.1, 96.6; IR (Neat) ν_{max} 3385 (-O-H), 2930, 1697, 1606, 1132, 1049, 825 cm^{-1}; MS (EI) *m/z* (%) 305 (M^++1, 100), 291 (4), 211 (8), 179 (8), 127 (8); Elemental analysis calcd for $C_{20}H_{16}O_3$: C 78.93, H 5.30, Found: C 78.85, H 5.26.

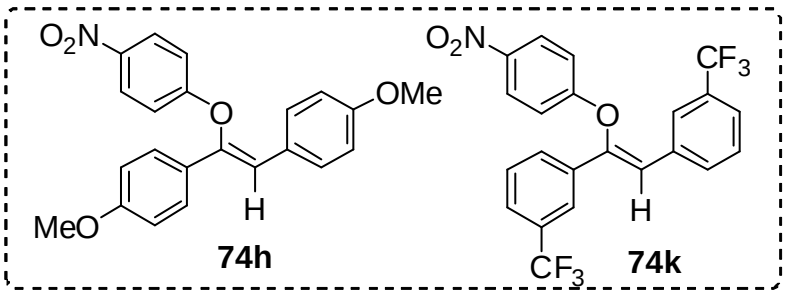
1-Nitro-4-(1-phenylvinyloxy)benzene (73s) :



Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**46g**; 278 mg, 2.0 mmol), phenylacetylene (**59**, 102 mg, 1.0 mmol), Ag_2CO_3 (551 mg, 2.0 mmol) in the presence of $AuCl_3$ (9.0 mg, 0.03 mmol) and L2 (8.9 mg, 0.03 mmol) in CH_2Cl_2 (1.0 mL) was heated at 100 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford the desired product (58 mg) in 24% yield as pale yellow solid.

mp 116–117 ^oC; R_f = 0.35 (49:1 hexane/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ8.23–8018 (m, 2H), 7.61–7.50 (m, 2H), 7.42–7.25 (m, 3H), 7.16–7.10 (m, 2H), 5.43 (d, J = 2.4 Hz, 1H), 4.93 (d, J = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ162.3, 156.9, 142.6, 133.6, 129.3, 128.7, 125.8, 125.5, 117.4, 117.2, 98.9; IR (KBr) ν_{max} 3109, 3082, 2930, 2851, 1637, 1340, 1163, 1026, 920 cm^{-1}; MS (EI) *m/z* (%) 240 (M^+ –1, 16), 234 (5), 213 (18), 197 (9), 154 (9), 138 (100).

1.7.5. Competition experiment:



Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**46h**; 30 mg, 0.21 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**47i**, 50 mg, 0.21 mmol) and 1,2-bis(3-(trifluoromethyl)phenyl)ethyne (**47o**, 65 mg, 0.21 mmol), Ag_2CO_3 (115 mg, 0.42 mmol) in the presence of $AuCl_3$ (1.9 mg, 0.0063 mmol) and L2 (1.8 mg, 0.0063 mmol) in CH_2Cl_2 (0.5 mL) was heated at 100 ^oC for 72 h. Upon usual work-up, the crude mixture was analyzed by ^1H NMR. The respective vinyl-hydrogen integration in the crude ^1H NMR spectrum showed the formation of the corresponding products **74h** and **74k** in 2:1 ratio, respectively.

1.7.6. X-ray Crystallographic Data:

Single crystal X-ray data for the compounds **73a** and **77a** were collected at on a Bruker SMART APEX CCD area detector system [λ(Mo-Kα) = 0.71073 Å] at 100K, (**73a**) and 298K **(77a)** respectively, graphite monochromator with a ω scan width of 0.3°, crystal detector distance 60 mm, collimator 0.5 mm. The SMART software[45] was used for the intensity data acquisition and the SAINTPLUS Software[45] was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program,[45] an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97,[46] and full-matrix least-squares refinement against F^2 was carried out using SHELXL-97.[46] All non-hydrogen atoms were refined anisotropically. Aromatic and methyl hydrogens were introduced on calculated positions and included in the refinement riding on their respective parent atoms.

Table 1.7: Crystal data for **73a** and **77a**

Identification code	**73a**	**77a**
Formula	$C_{20}H_{15}NO_3$	$C_{34}H_{26}O_2$
F_w	317.33	466.55
T (K)	100(2)	298(2)
λ (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	$C2/c$	$P2_1/c$
a (Å)	23.1476(16)	7.7422(8)
b (Å)	11.0330(8)	14.6183(15)
c (Å)	16.6135(11)	10.9539(11)
α (°)	90	90
β (°)	132.3450(10)	94.865(2)
γ(°)	90	90
V (Å^3)	3135.9(4)	1235.3(2)
Z	8	2
ρ_{calcd} (Mg m^{-3})	1.344	1.254
μ (mm^{-1})	0.091	0.076
F (000)	1328	492
Crystal Size (mm)	0.60 × 0.24 × 0.10	0.24 × 0.20 × 0.14
2θ range/deg	2.20 / 25.02	2.33 / 25.09
Reflections collected	14736	11710

Unique reflections	2768	2191
Completeness to 2θ (%)	25.02 (100.0)	25.09 (99.9)
T_{max}, T_{min}	0.9910, 0.9475	0.9894 , 0.9819
Parameters	217	163
GOF (F^2)	1.087	1.036
R1, *wR2 [I>2σ(I)]*	0.0798, 0.1912	0.0366, 0.0870
R1, *wR2* (all data)	0.0829, 0.1932	0.0500, 0.0940
Largest diff. Peak and hole ($e \cdot Å^{-3}$)	1.029 and -0.928	0.120 and -0.126

1.8. References

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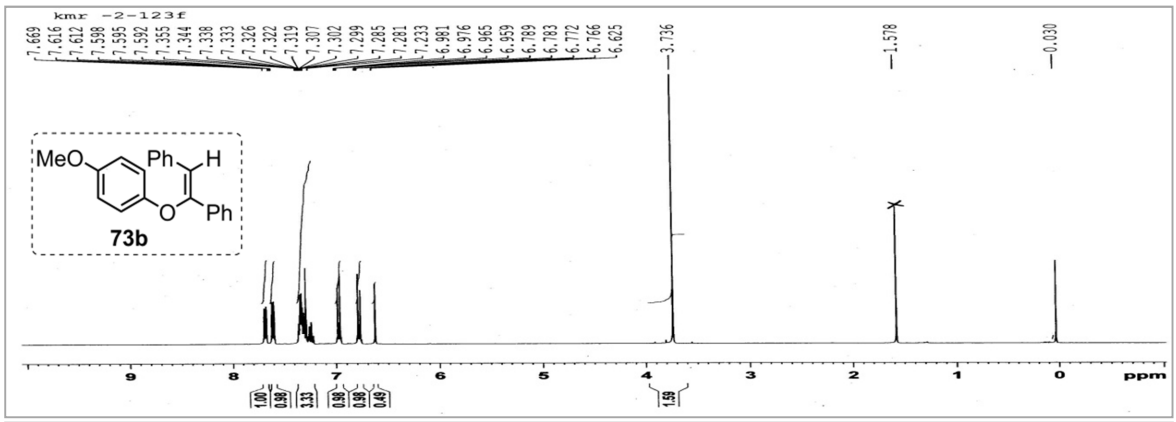
1.9. Spectra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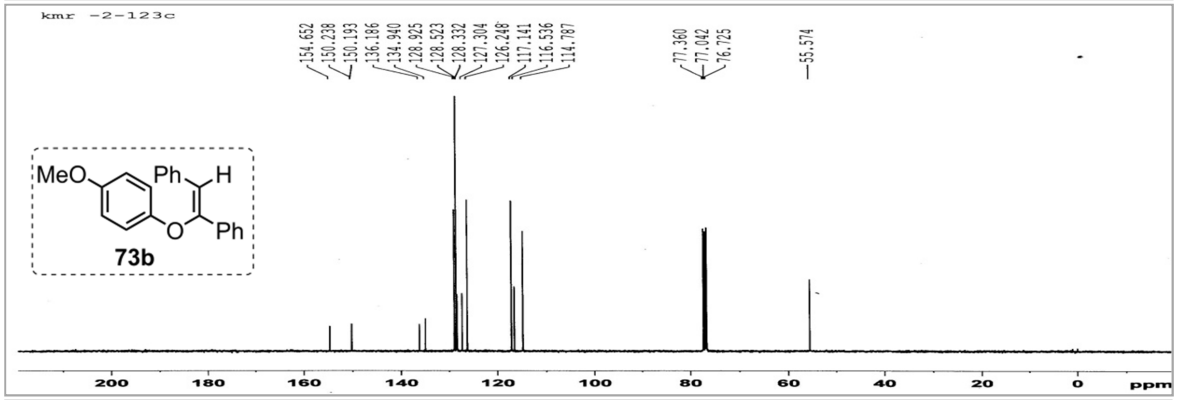
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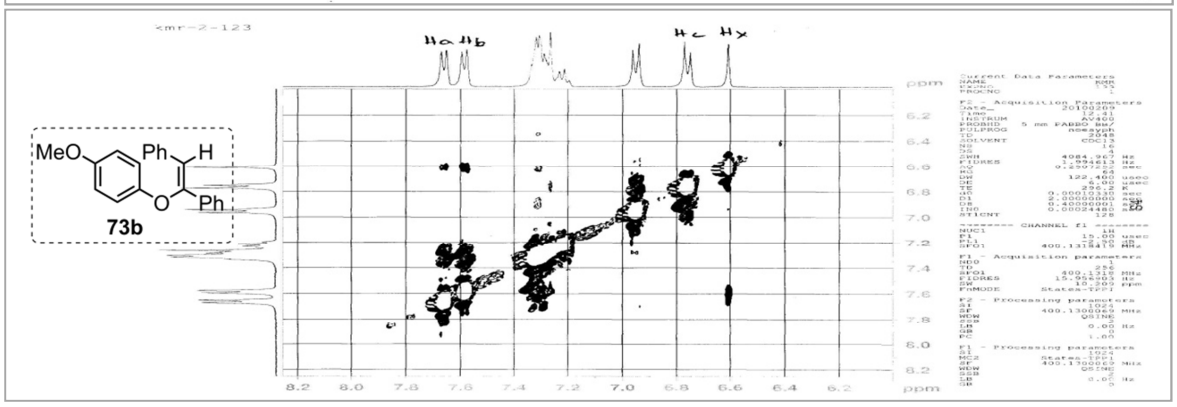
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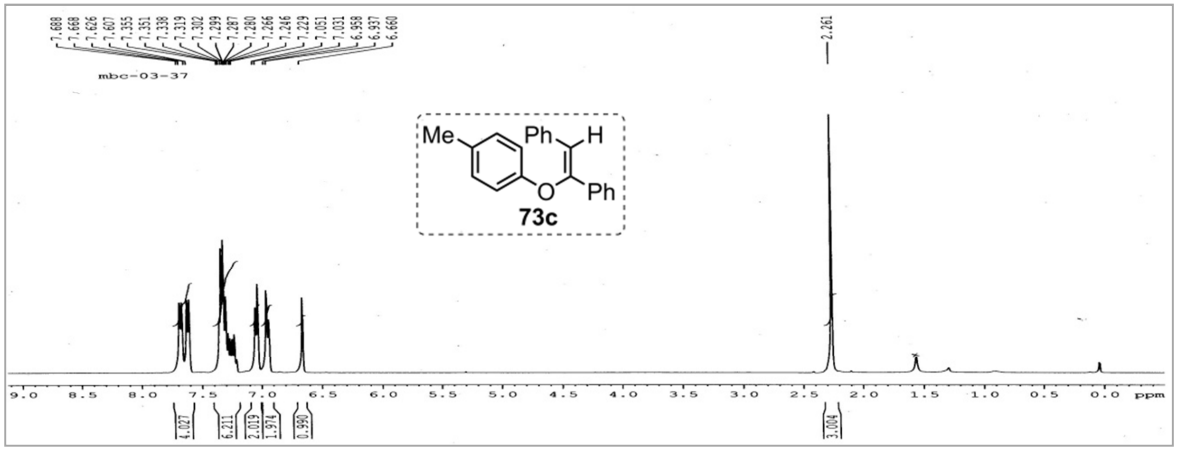
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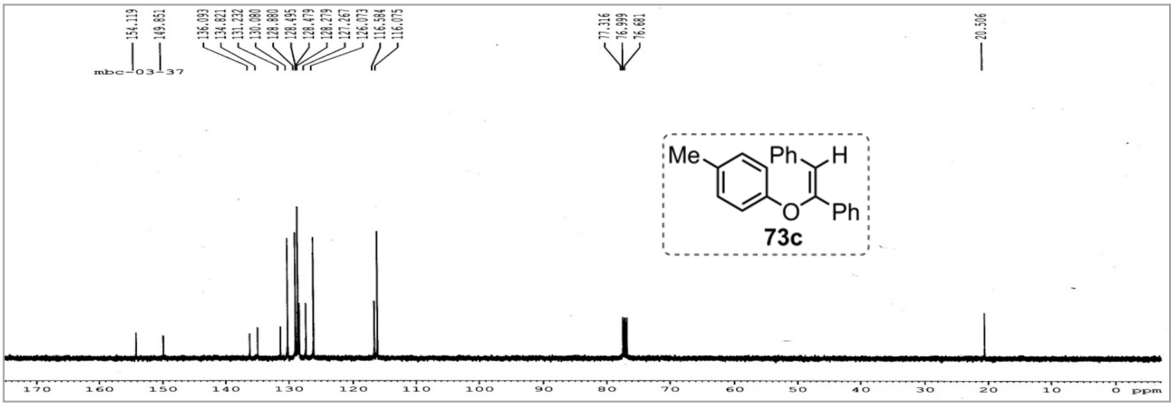
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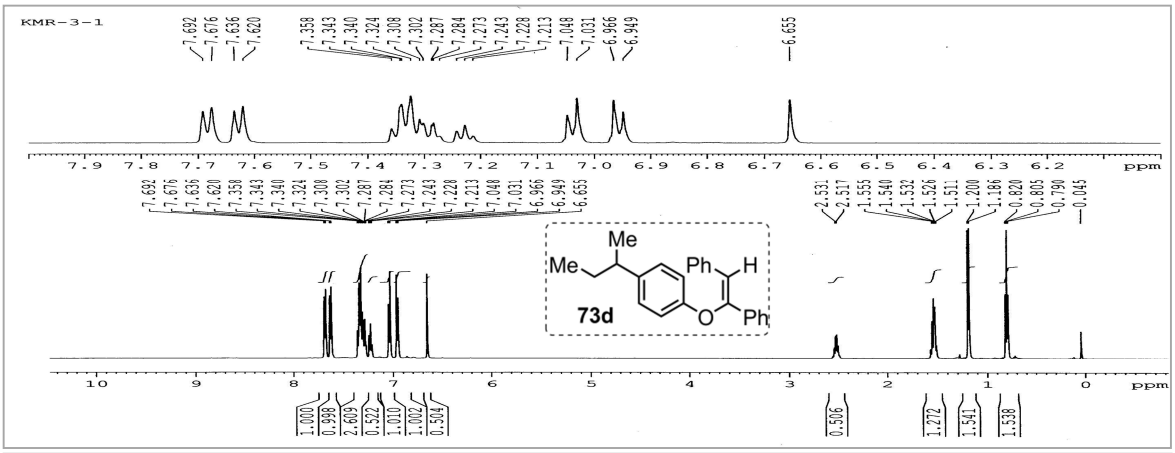
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Ph
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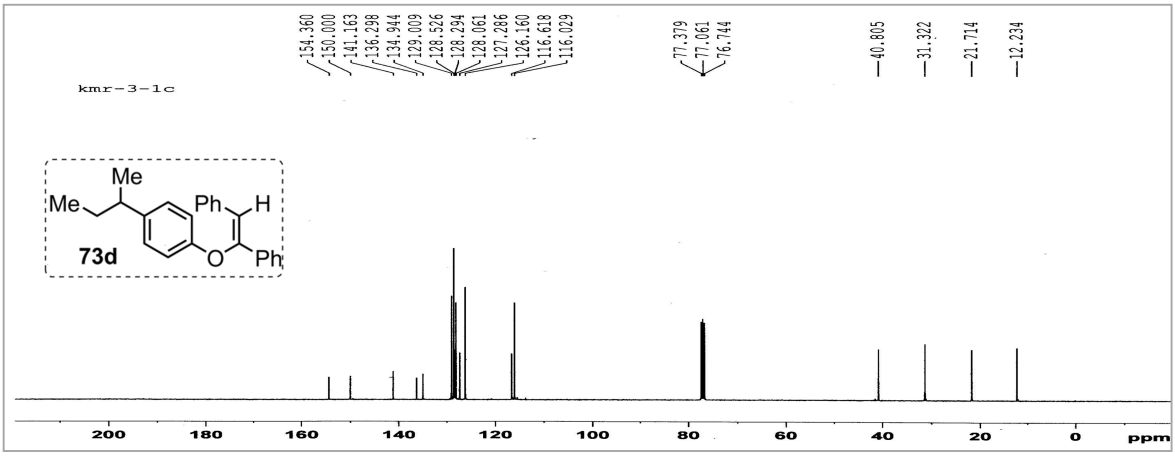
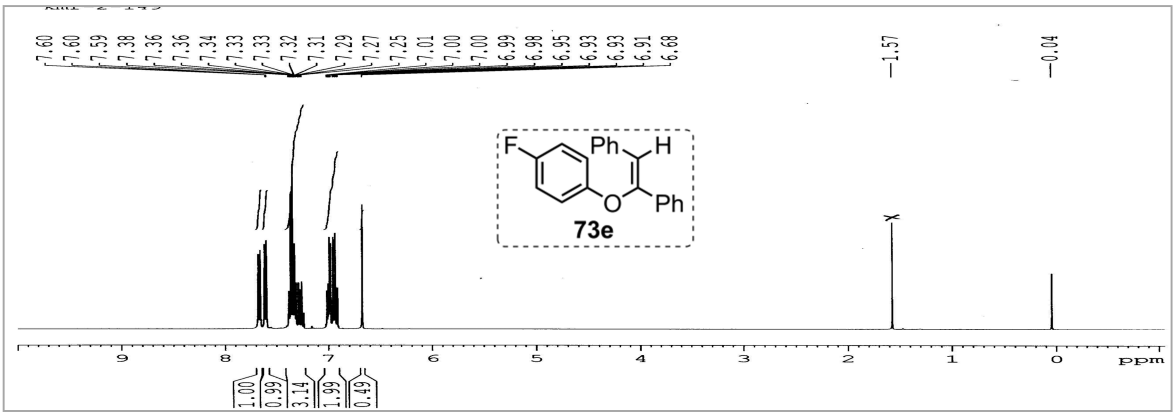
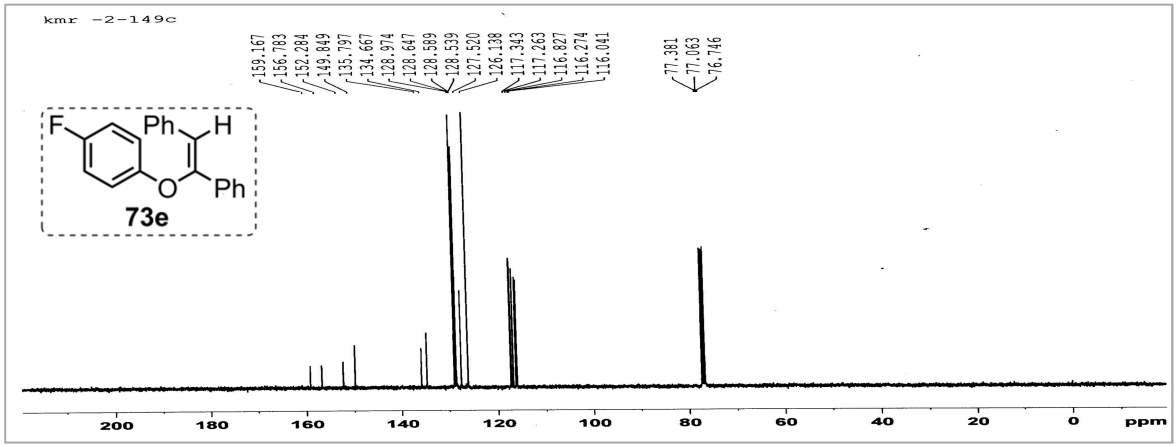
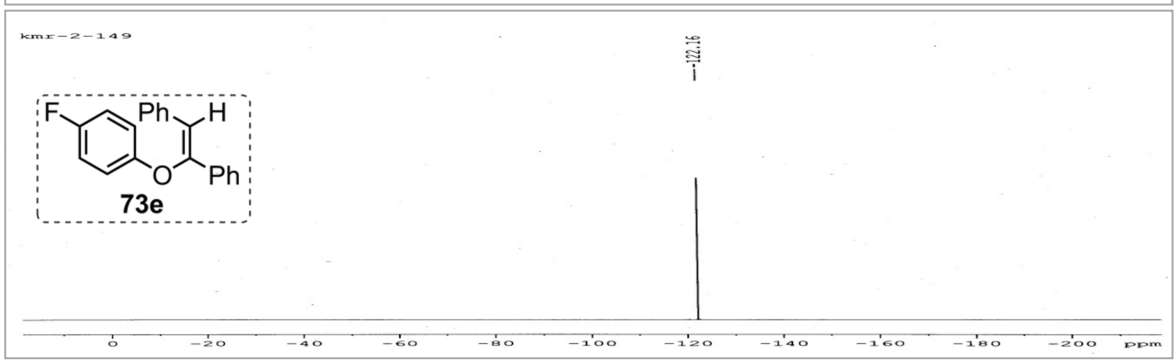
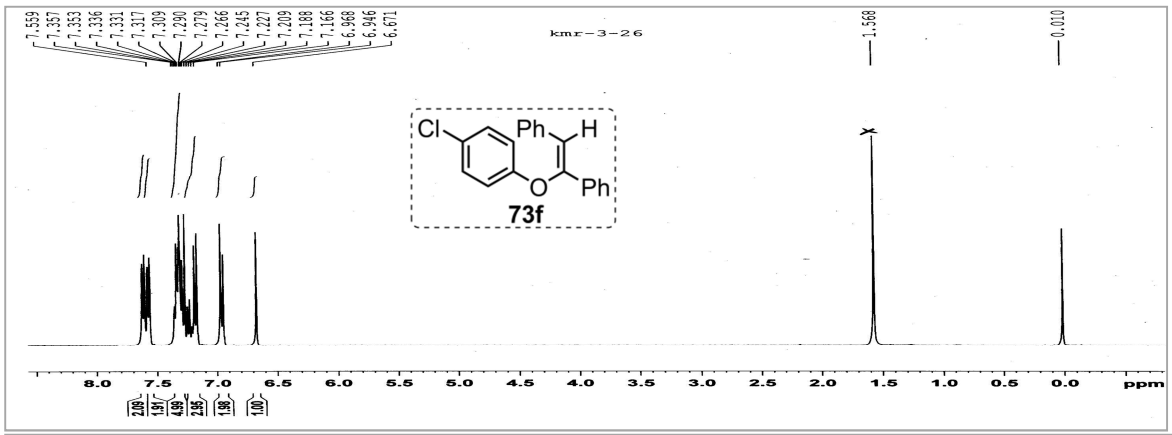
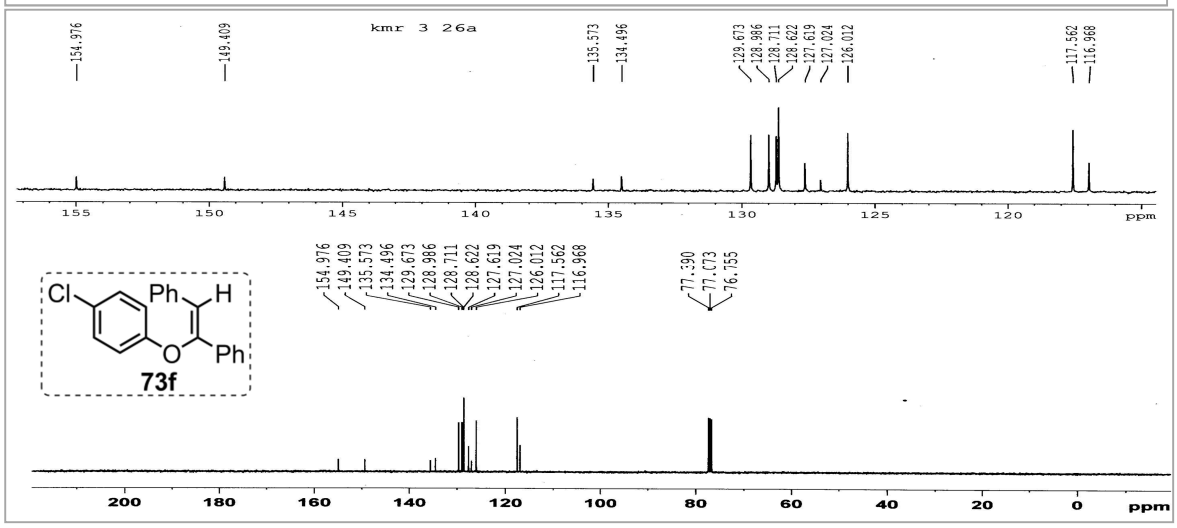

kmr-3-1c
Me
Me
Ph
H
O
Ph
73d

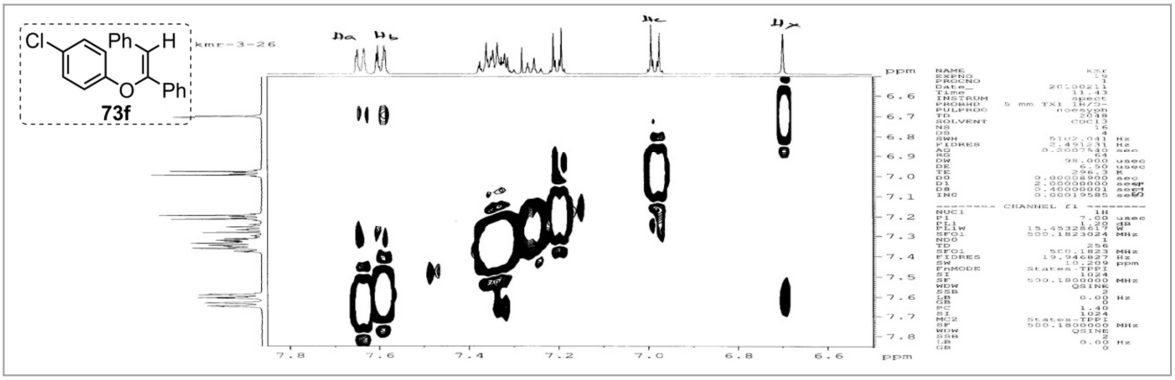

F
Ph
H
O
Ph
73e

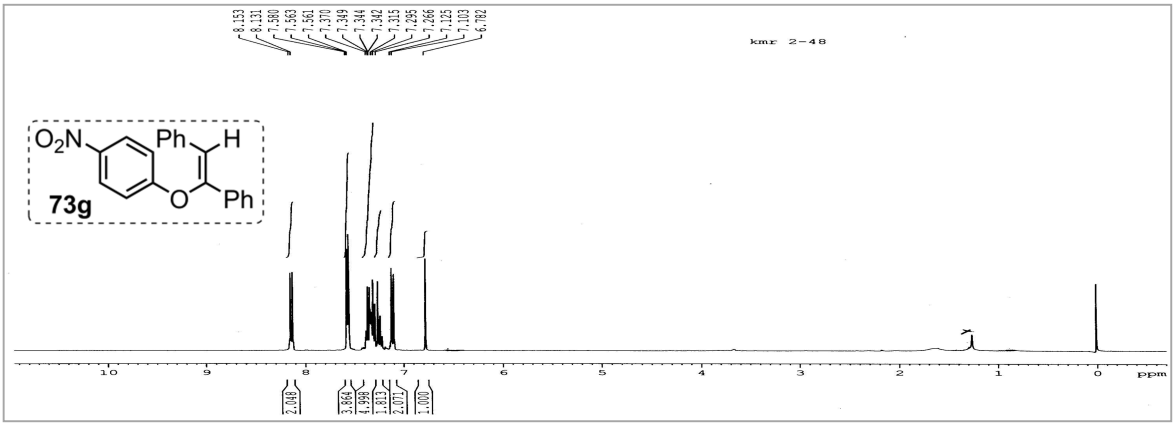

kmr -2-149c
159.167
156.783
152.284
149.849
135.797
134.667
128.974
128.647
128.589
128.539
127.520
126.138
117.343
117.263
116.827
116.274
116.041
77.381
77.063
76.746
F
Ph
H
O
Ph
73e
200
180
160
140
120
100
80
60
40
20
0
ppm

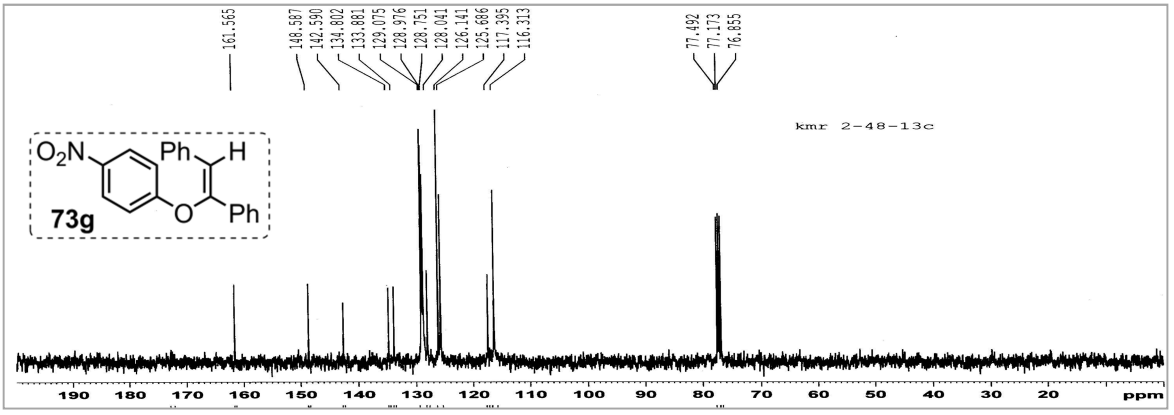

kmr-2-149
-122.16
F
Ph
H
O
Ph
73e
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

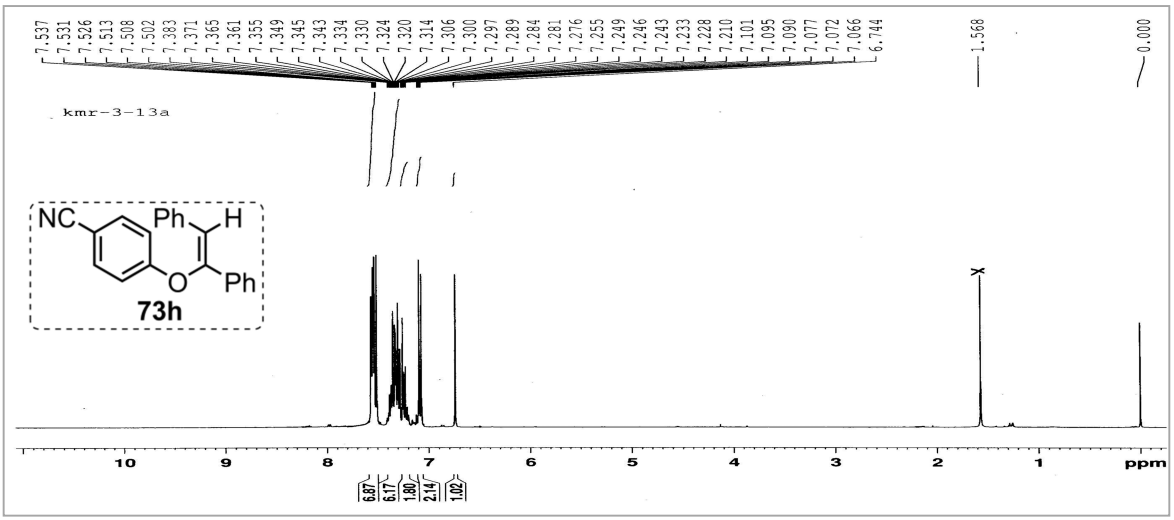

7.559
7.357
7.353
7.336
7.331
7.317
7.309
7.290
7.279
7.266
7.245
7.227
7.209
7.188
7.166
6.968
6.946
6.671
kmr-3-26
1.568
0.010
Cl
Ph
H
O
Ph
73f
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.09
1.91
4.09
2.05
1.98
1.00

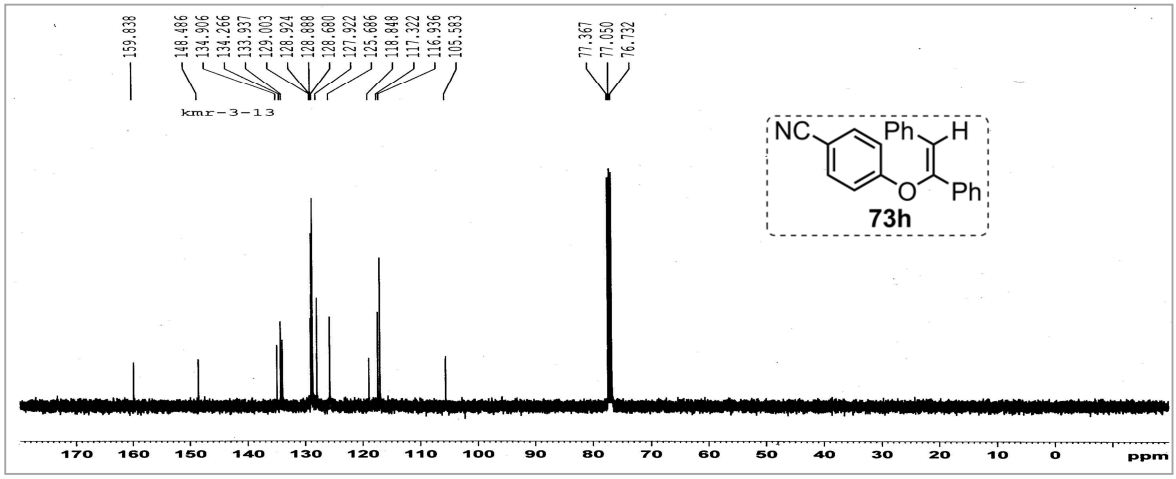

kmr 3 26a
154.976
149.409
135.573
134.496
129.673
128.986
128.711
128.622
127.619
127.024
126.012
117.562
116.968
155
150
145
140
135
130
125
120
ppm
154.976
149.409
135.573
134.496
129.673
128.986
128.711
128.622
127.619
127.024
126.012
117.562
116.968
77.390
77.073
76.755
Cl
Ph
H
O
Ph
73f
200
180
160
140
120
100
80
60
40
20
0
ppm

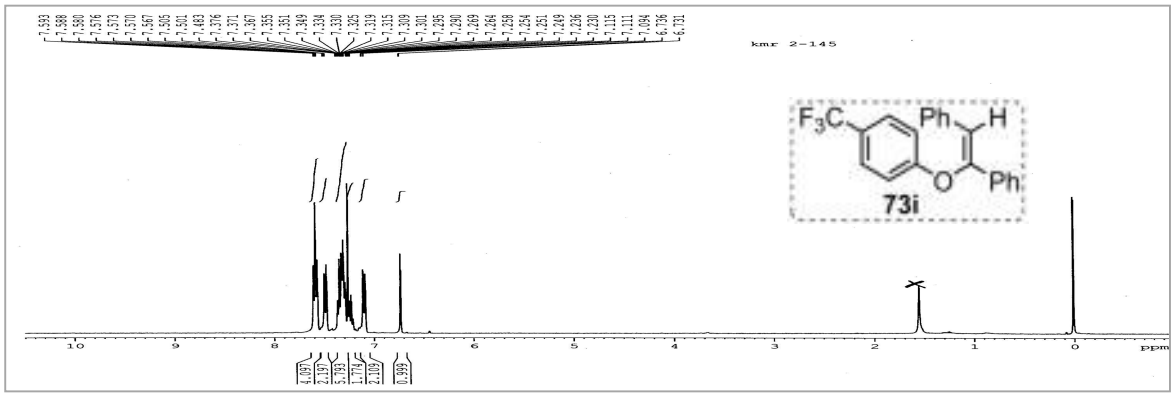

Cl
Ph
H
O
Ph
73f
kmr-3-26
ppm

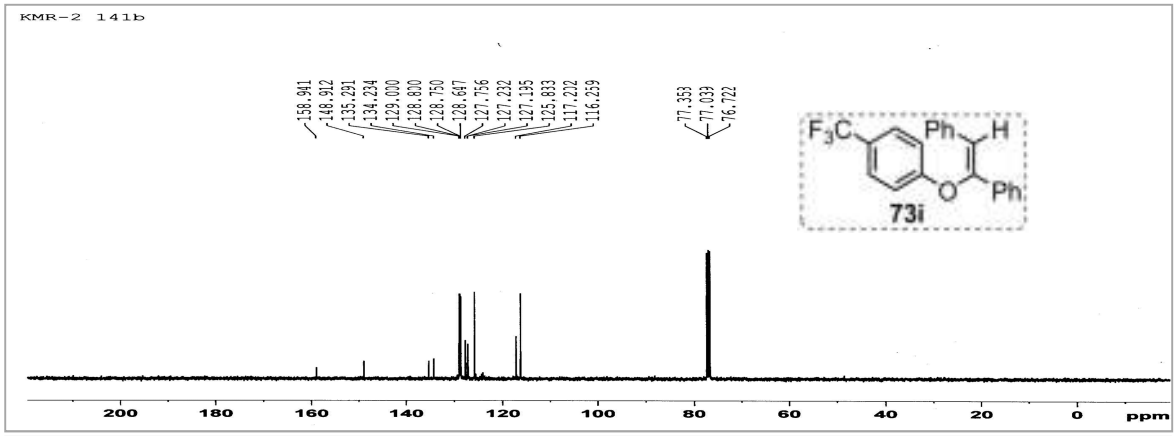

8.353
8.131
7.580
7.563
7.561
7.370
7.349
7.344
7.342
7.315
7.295
7.266
7.125
7.103
6.782
kmr 2-48
O2N
Ph
H
O
Ph
73g
2.048
3.864
4.988
1.813
2.071
1.000
ppm

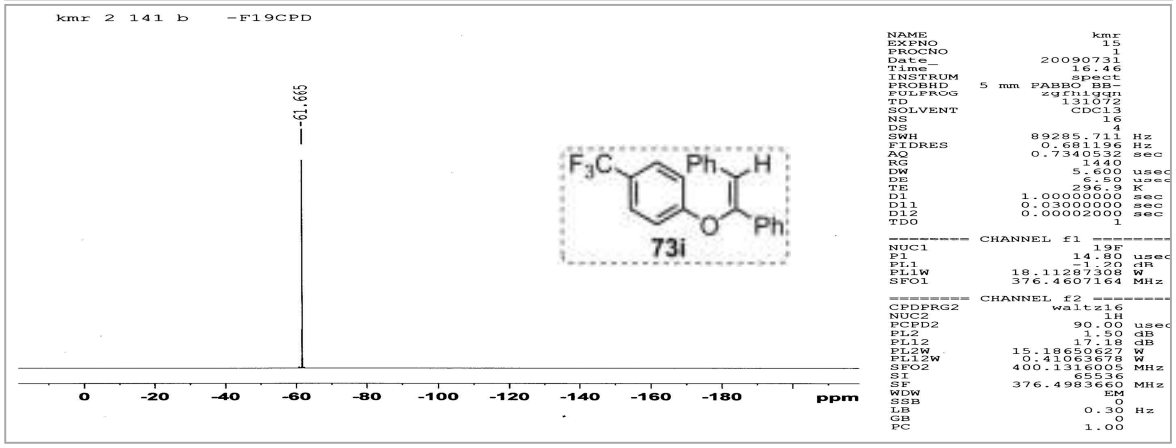

161.565
148.587
142.590
134.802
133.881
129.075
128.976
128.751
128.041
126.141
125.686
117.395
116.313
77.492
77.173
76.855
kmr 2-48-13c
O2N
Ph
H
O
Ph
73g
ppm

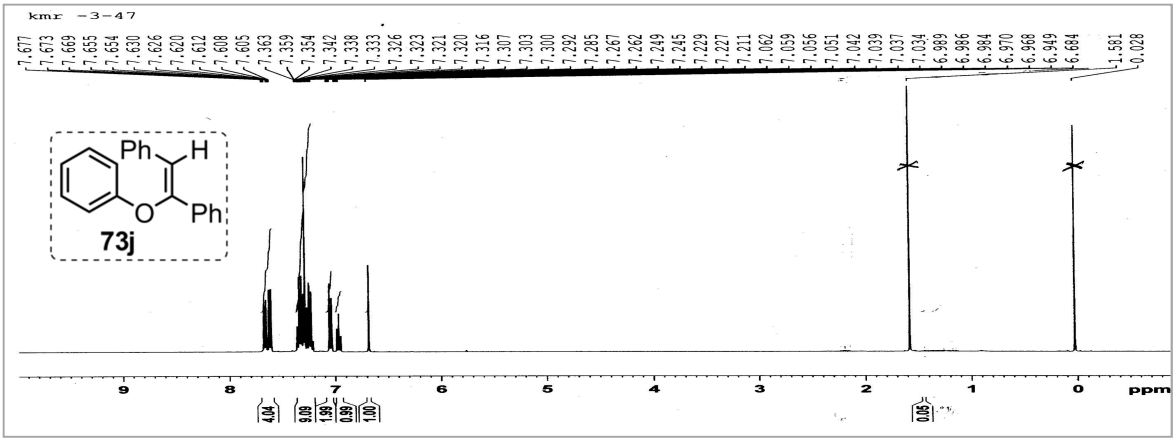

7.537
7.531
7.526
7.513
7.508
7.502
7.383
7.371
7.365
7.361
7.355
7.349
7.345
7.343
7.334
7.330
7.324
7.320
7.314
7.306
7.300
7.297
7.289
7.284
7.281
7.276
7.255
7.249
7.246
7.243
7.233
7.228
7.210
7.101
7.095
7.090
7.077
7.072
7.066
6.744
1.568
0.000
kmr-3-13a
NC
Ph
H
O
Ph
73h
6.87
6.17
1.80
2.14
1.02
ppm

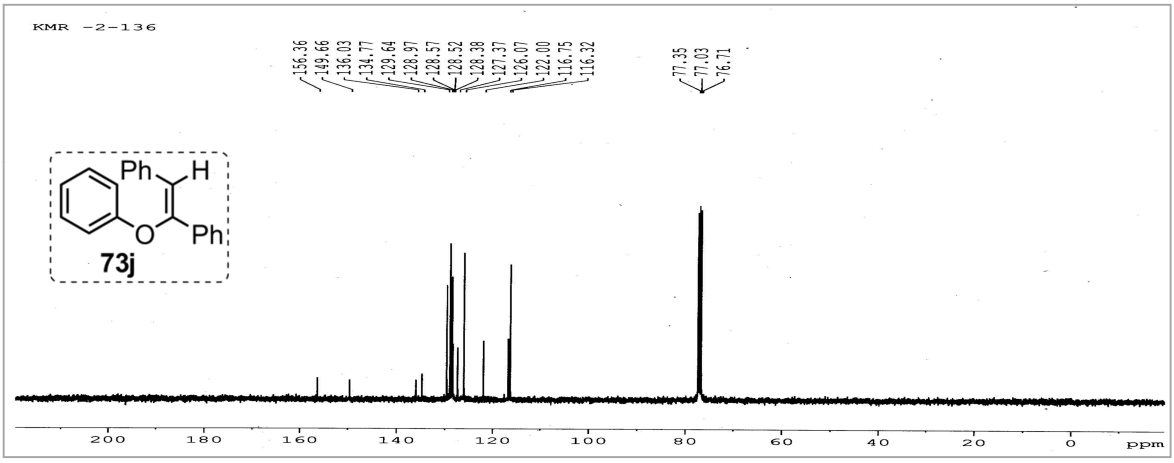

159.838
148.486
134.906
134.266
133.937
129.003
128.924
128.888
128.680
127.922
125.686
118.848
117.322
116.936
105.583
77.367
77.050
76.132
kmr-3-13
NC
Ph
H
O
Ph
73h
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

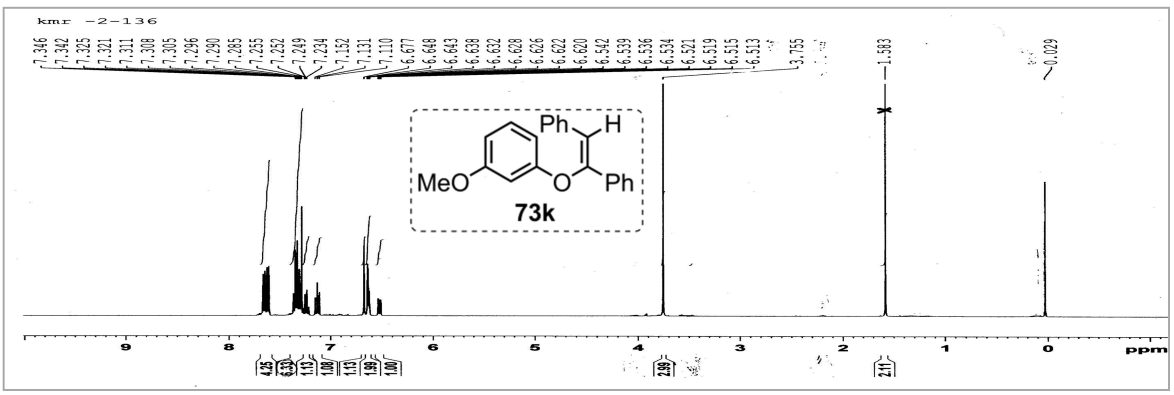

kmr 2-145
F3C
Ph
H
O
Ph
73i
10 9 8 7 6 5 4 3 2 1 0 ppm

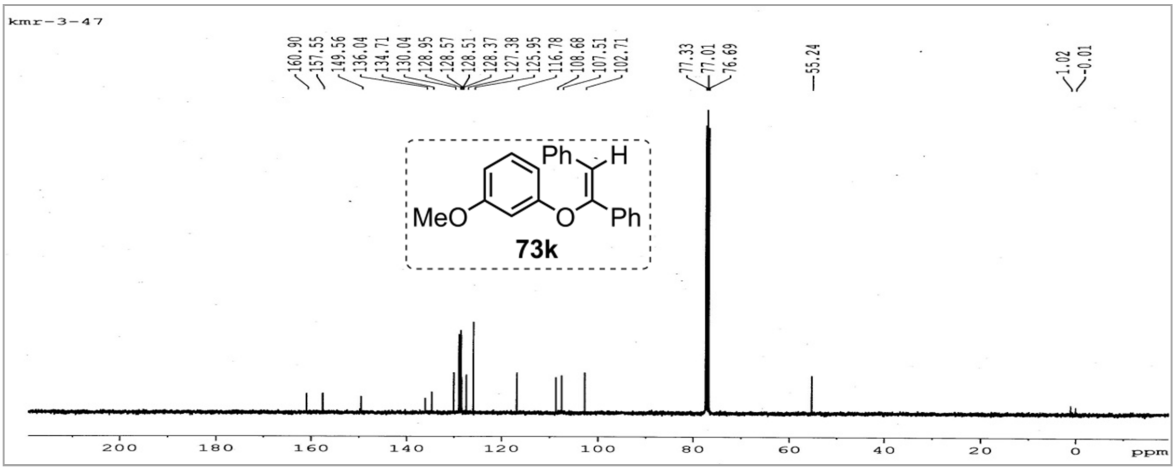

KMR-2 141b
158.941
148.912
135.291
134.234
129.000
128.800
128.750
128.647
127.756
127.232
127.135
125.833
117.212
116.259
77.353
77.039
76.722
F3C
Ph
H
O
Ph
73i
200 180 160 140 120 100 80 60 40 20 0 ppm

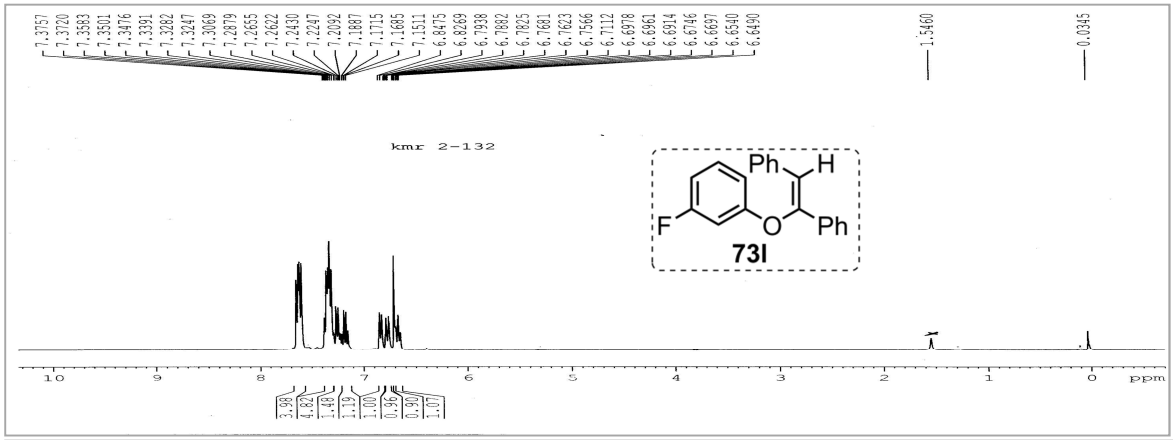

kmr 2 141 b -F19CPD
-61.665
F3C
Ph
H
O
Ph
73i
0 -20 -40 -60 -80 -100 -120 -140 -160 -180 ppm
NAME kmr
EXPNO 15
PROCNO 1
Date_ 20090731
Time 16.46
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgfhigqn
TD 131072
SOLVENT CDCl3
NS 16
DS 4
SWH 89285.711 Hz
FIDRES 0.681196 Hz
AQ 0.7340532 sec
RG 1440
DW 5.600 usec
DE 6.50 usec
TE 296.9 K
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
TD0 1
CHANNEL f1
NUC1 19F
P1 14.80 usec
PL1 -1.20 dB
PL1W 18.11287308 W
SFO1 376.4607164 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 1.50 dB
PL12 17.18 dB
PL2W 15.18650627 W
PL12W 0.41063678 W
SFO2 400.1316005 MHz
SI 655536
SF 376.4983660 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

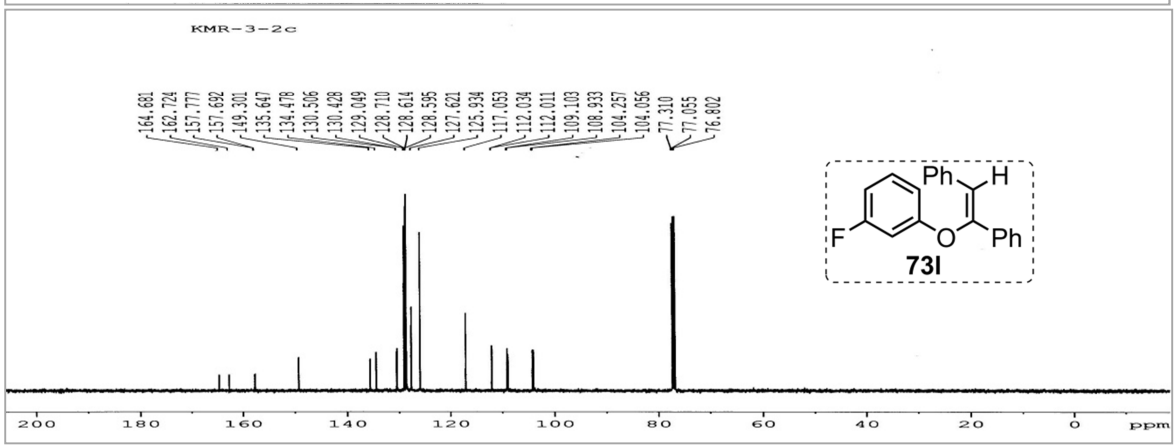

kmr -3-47
Ph
H
O
Ph
73j
ppm

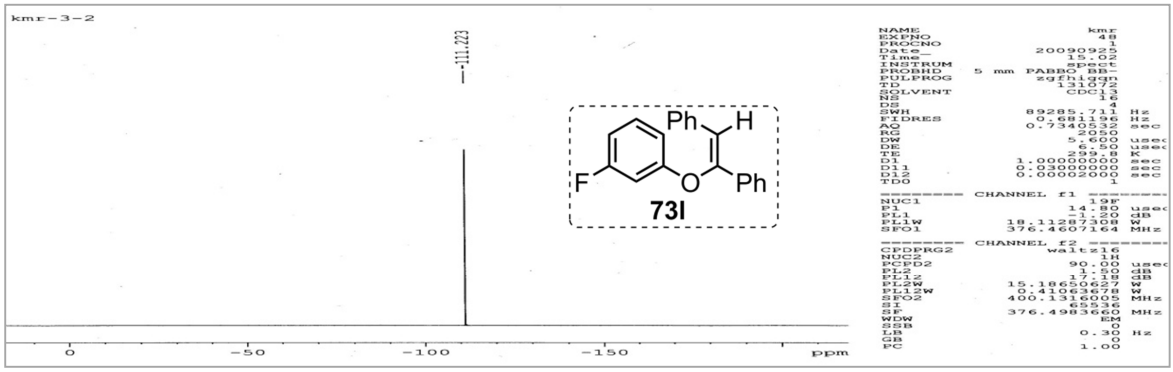

KMR -2-136
Ph
H
O
Ph
73j
ppm

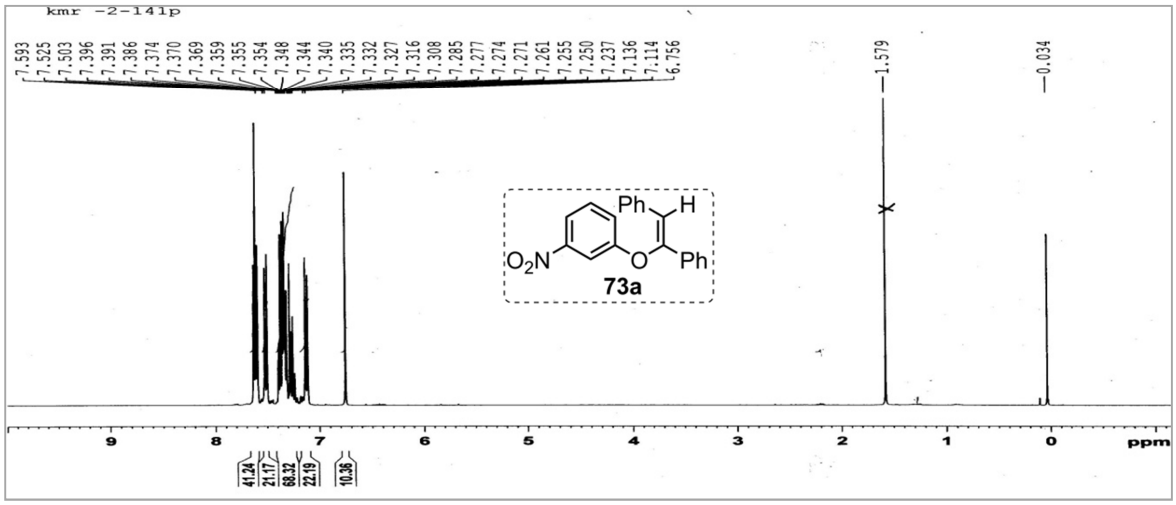

kmr -2-136
MeO
Ph
H
O
Ph
73k
ppm

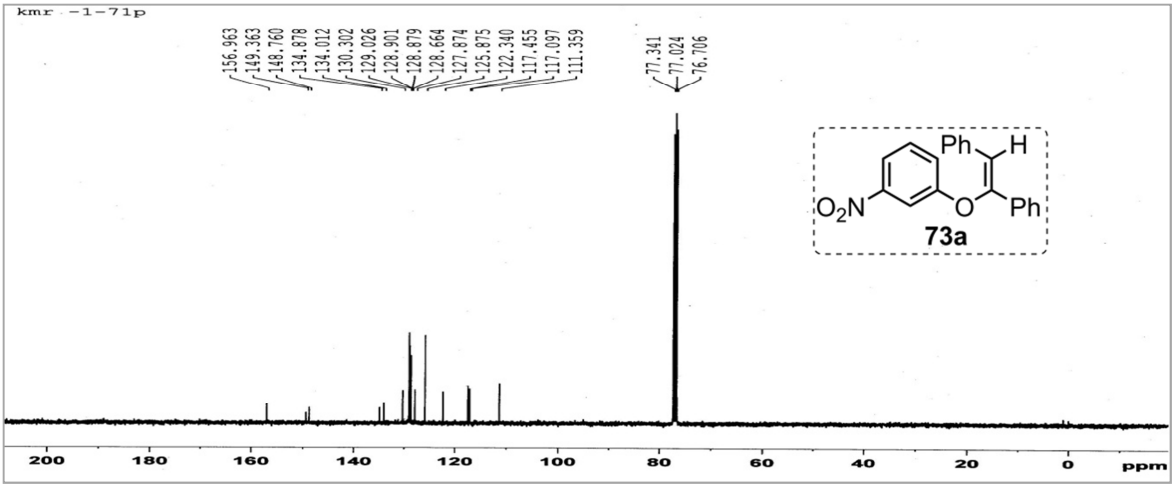

kmr-3-47
MeO
Ph
H
O
Ph
73k
ppm


kmr 2-132
Ph
H
F
O
Ph
73l
ppm


KMR-3-2c
Ph
H
F
O
Ph
73l
ppm


kmr-3-2
Ph
H
F
O
Ph
73l
ppm


kmr -2-141p
Ph
H
O2N
O
Ph
73a
ppm


kmr--1-71p
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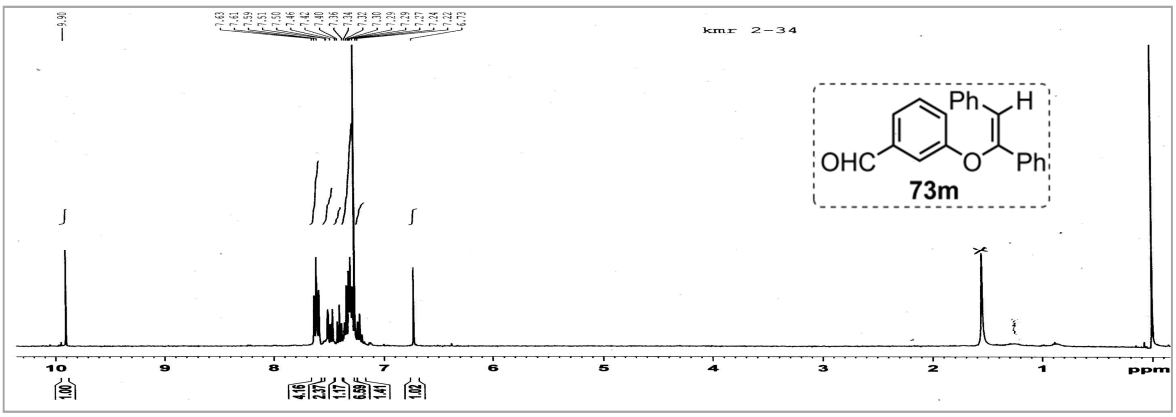
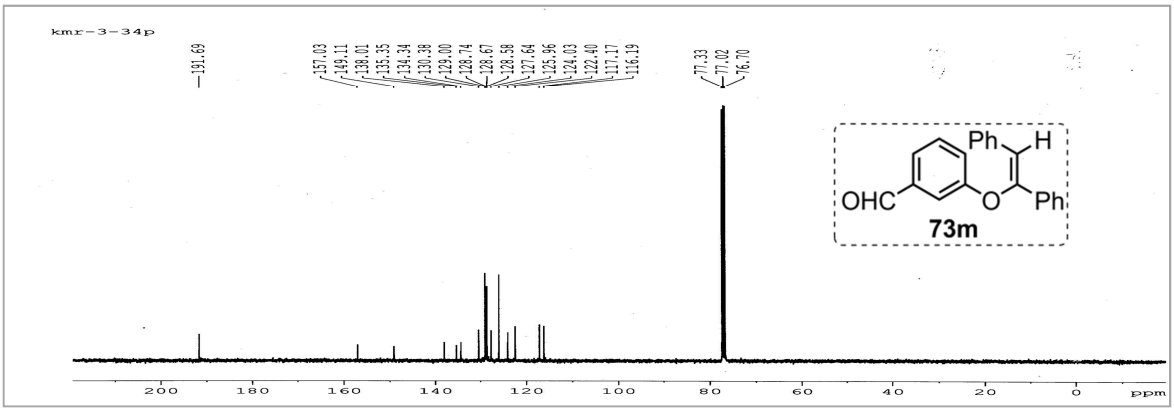
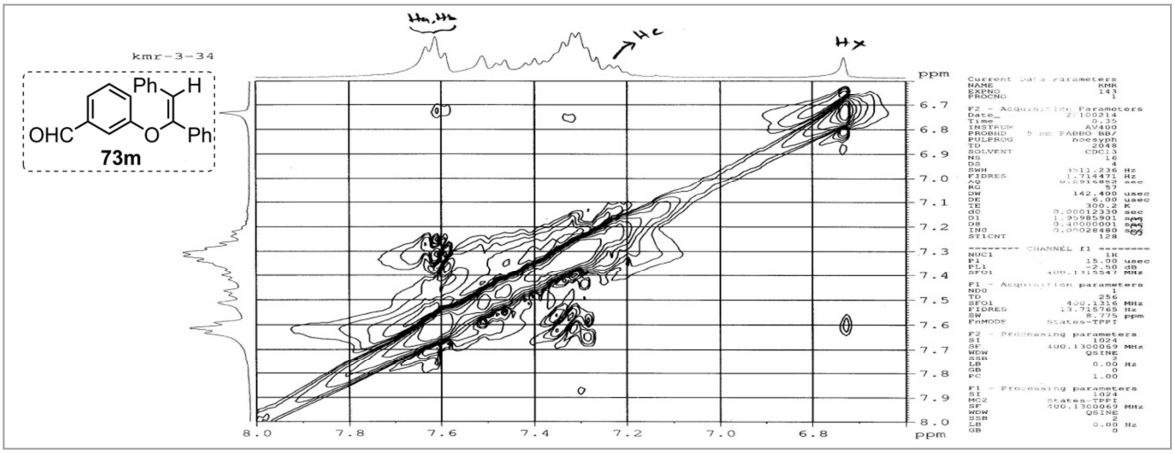
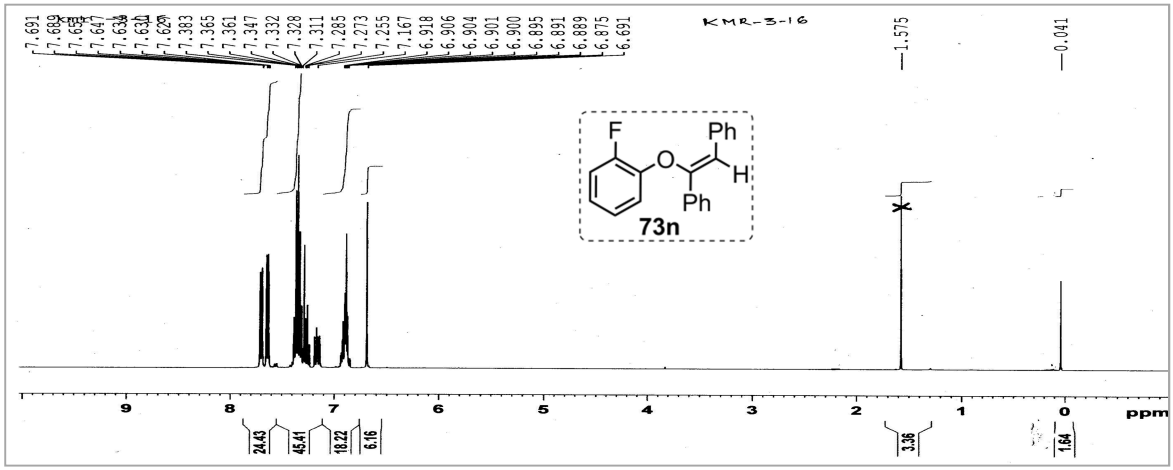
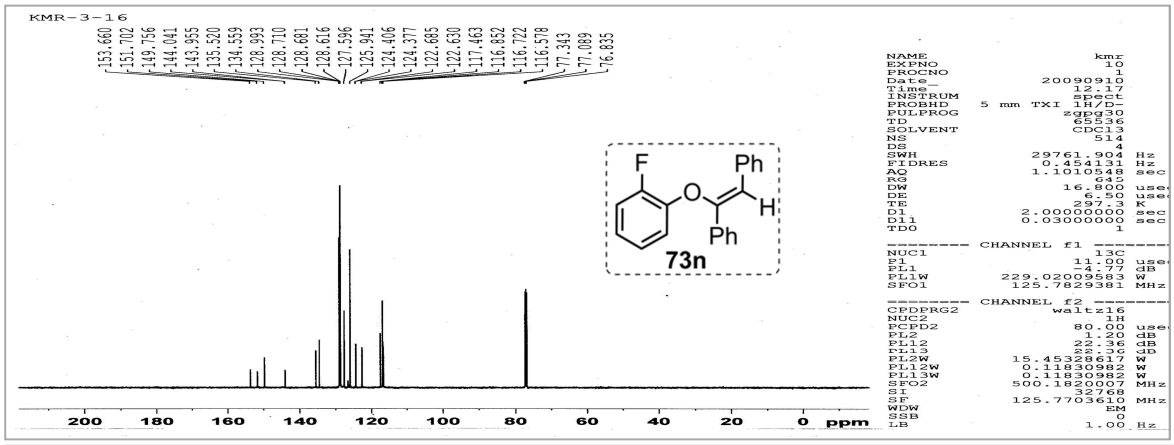
149.363
148.760
134.878
134.012
130.302
129.026
128.901
128.879
128.664
127.874
125.875
122.340
117.455
117.097
111.359
77.341
77.024
76.706
Ph
H
O2N
O
Ph
73a
200
180
160
140
120
100
80
60
40
20
0
ppm

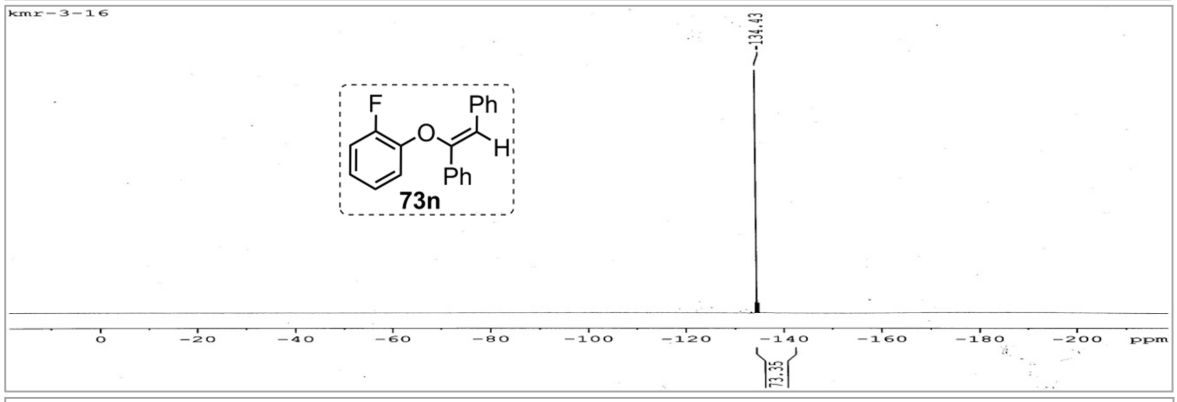

kmr 2-34
9.98
7.63
7.61
7.59
7.51
7.50
7.46
7.42
7.40
7.36
7.34
7.32
7.30
7.29
7.29
7.27
7.24
7.22
6.73
Ph
H
OHC
O
Ph
73m
10
9
8
7
6
5
4
3
2
1
ppm

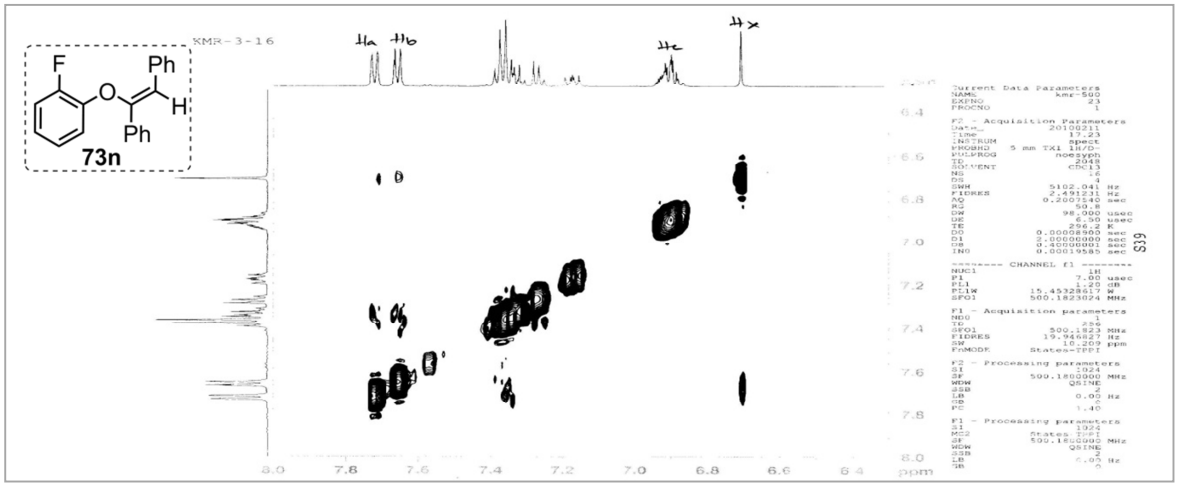

kmr-3-34p
191.69
157.03
149.11
138.01
135.35
134.34
130.38
129.00
128.74
128.67
128.58
127.64
125.96
124.03
122.40
117.17
116.19
77.33
77.02
76.70
Ph
H
OHC
O
Ph
73m
200
180
160
140
120
100
80
60
40
20
0
ppm

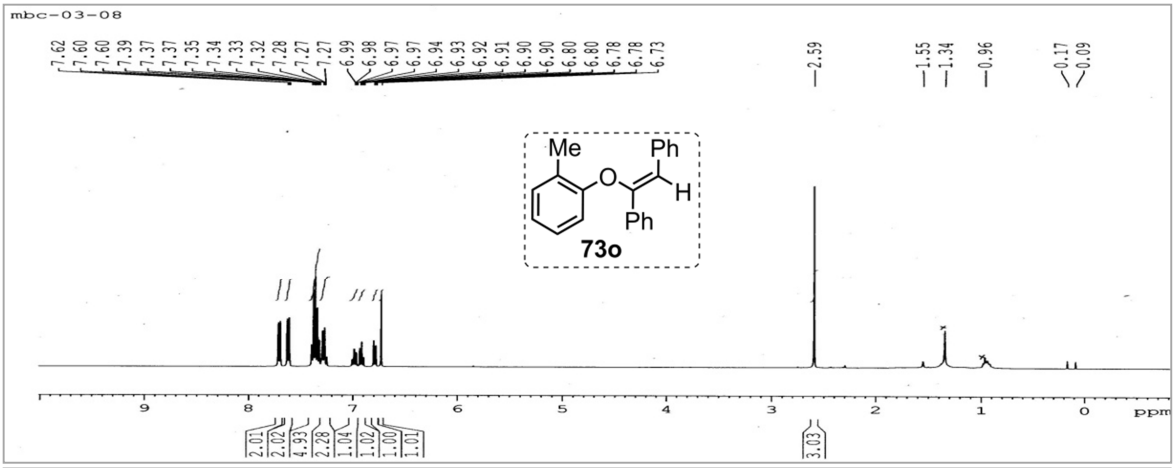

kmr-3-34
Ph
H
OHC
O
Ph
73m
Ha,Hb
Hc
Hx
ppm
6.7
6.8
6.9
7.0
7.1
7.2
7.3
7.4
7.5
7.6
7.7
7.8
7.9
8.0
8.0
7.8
7.6
7.4
7.2
7.0
6.8
ppm

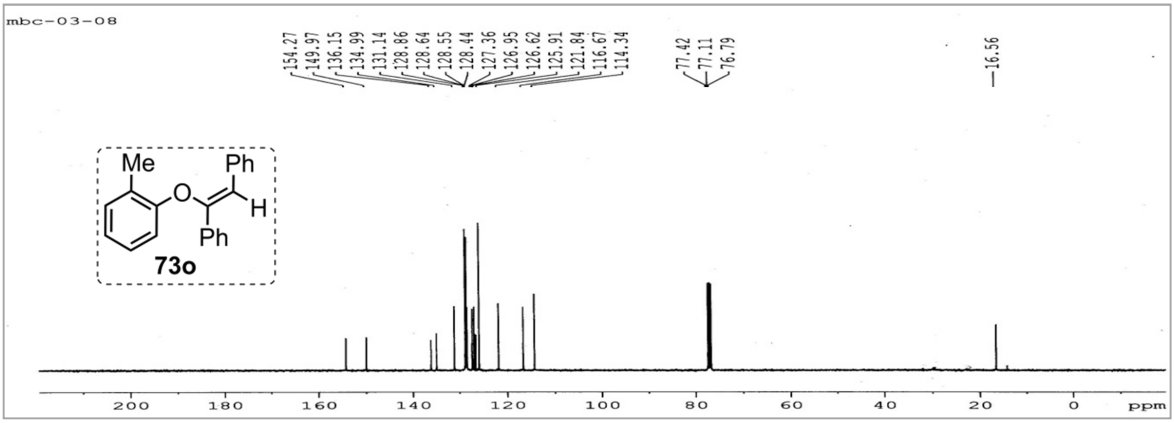

KMR-3-16
7.691
7.689
7.653
7.647
7.633
7.631
7.625
7.383
7.365
7.361
7.347
7.332
7.328
7.311
7.285
7.273
7.255
7.167
6.918
6.906
6.904
6.901
6.900
6.895
6.891
6.889
6.875
6.691
1.575
0.041
F
Ph
O
H
Ph
73n
ppm
24.43
45.41
18.22
6.16
3.36
1.64

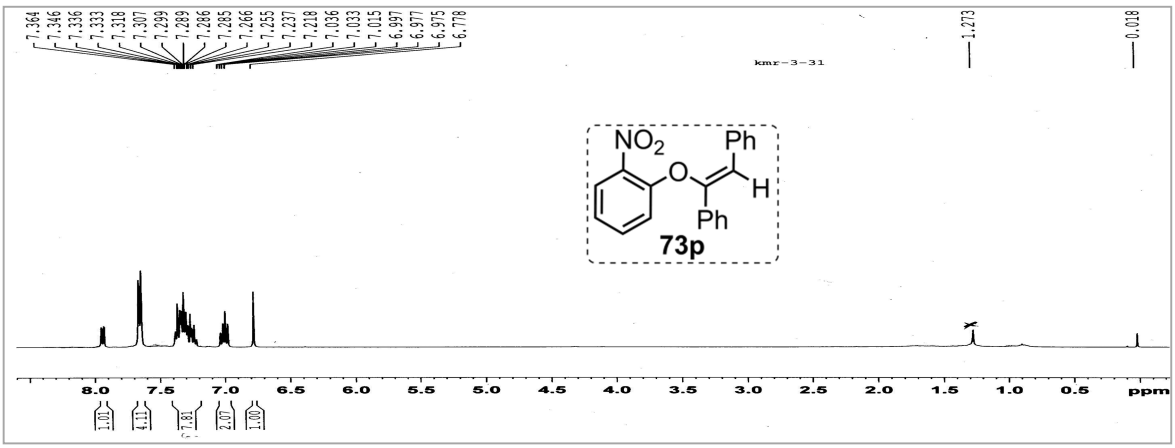

KMR-3-16
153.660
151.702
149.756
144.041
143.955
135.520
134.539
128.993
128.710
128.681
128.616
127.596
125.941
124.406
124.377
122.685
122.630
117.463
116.852
116.722
116.578
77.343
77.089
76.835
F
Ph
O
H
Ph
73n
NAME kmr
EXPNO 10
PROCNO 1
Date_ 20090910
Time 12.17
INSTRUM spect
PROBHD 5 mm TXI 1H/D-
PULPROG zgpg30
TD 655536
SOLVENT CDCl3
NS 514
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010548 sec
RG 645
DW 16.800 use
DE 6.50 use
TE 297.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
NUC1 13C
P1 11.00 use
PL1 -4.77 dB
PL1W 229.02009583 W
SFO1 125.7829381 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 use
PL2 1.20 dB
PL12 22.36 dB
PL13 22.36 dB
PL2W 15.45328617 W
PL12W 0.11830982 W
PL13W 0.11830982 W
SFO2 500.1820007 MHz
SI 32768
SF 125.7703610 MHz
WDW EM
SSB 0
LB 1.00 Hz
ppm

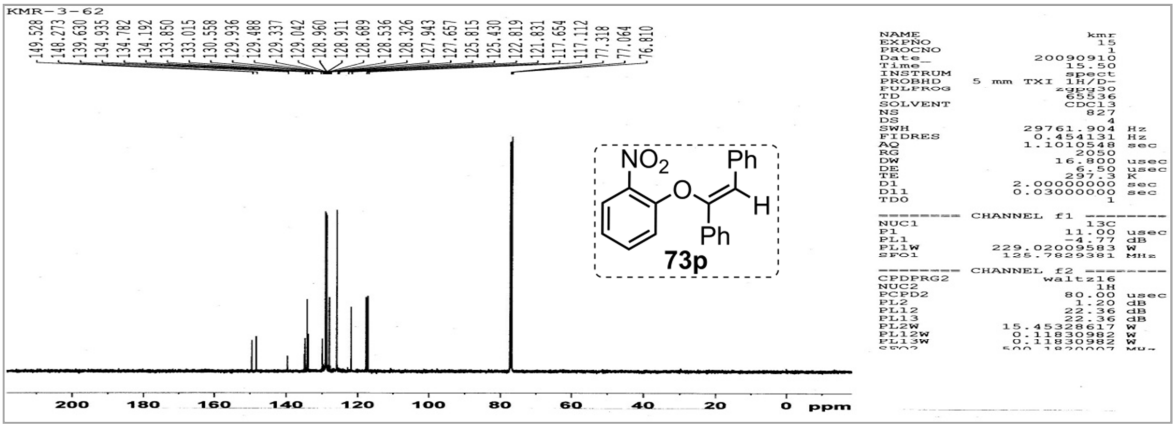

kmr-3-16
134.43
F
Ph
O
H
Ph
73n
73.35
ppm

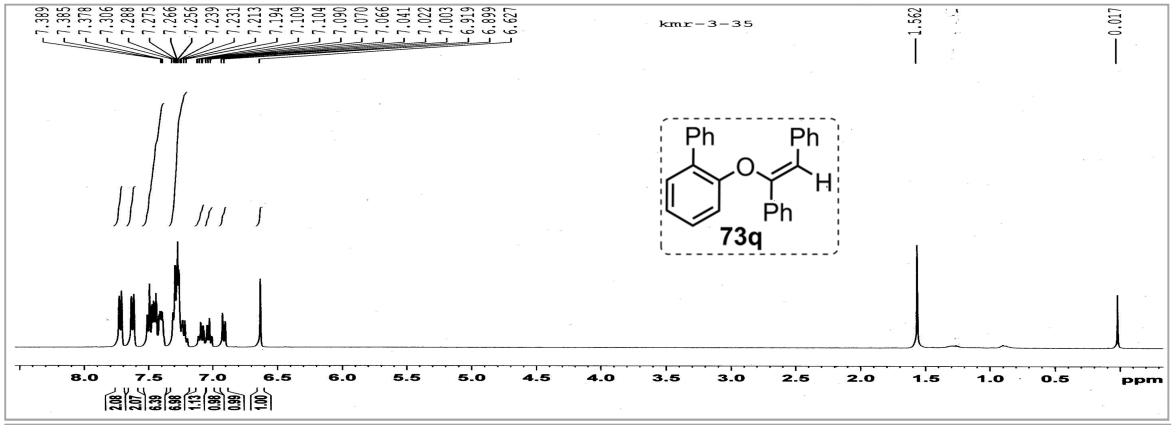

KMR-3-16
Ha
Hb
Hc
Hx
F
Ph
O
H
Ph
73n
ppm

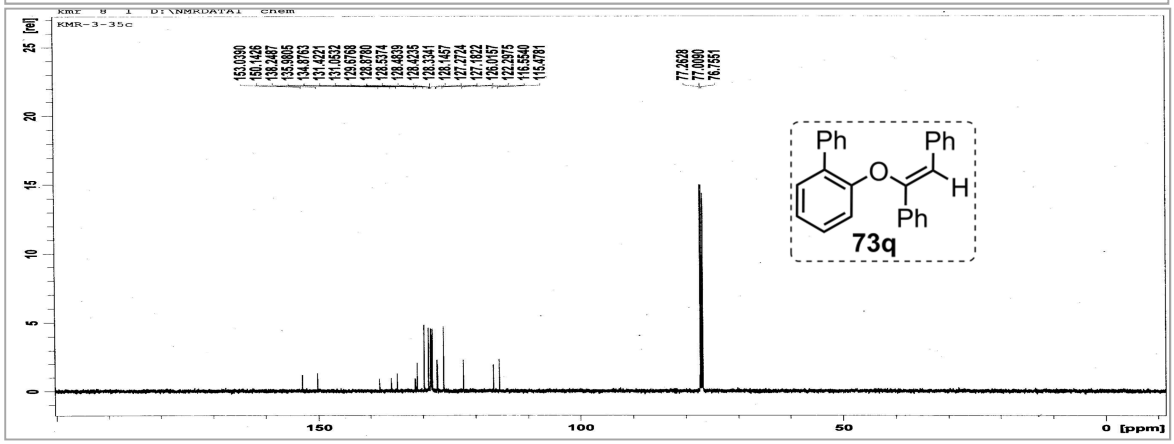

mbc-03-08
Me
Ph
O
H
Ph
73o

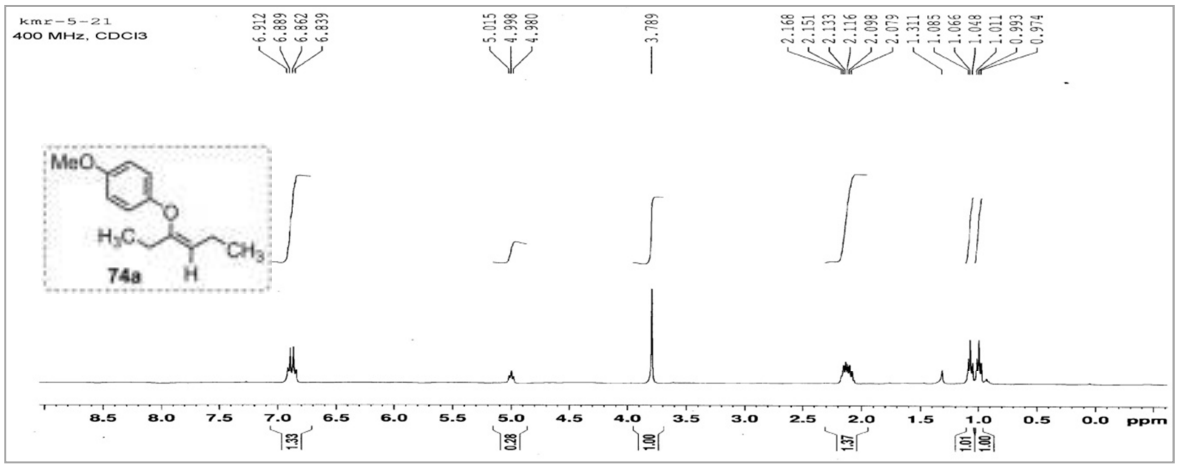

mbc-03-08
Me
Ph
O
H
Ph
73o

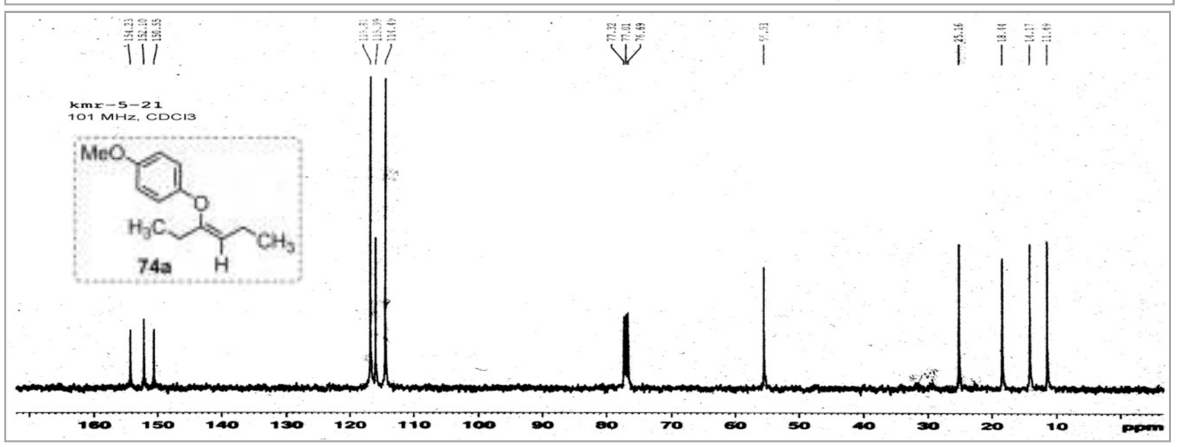

kmr-3-31
NO2
Ph
O
H
Ph
73p

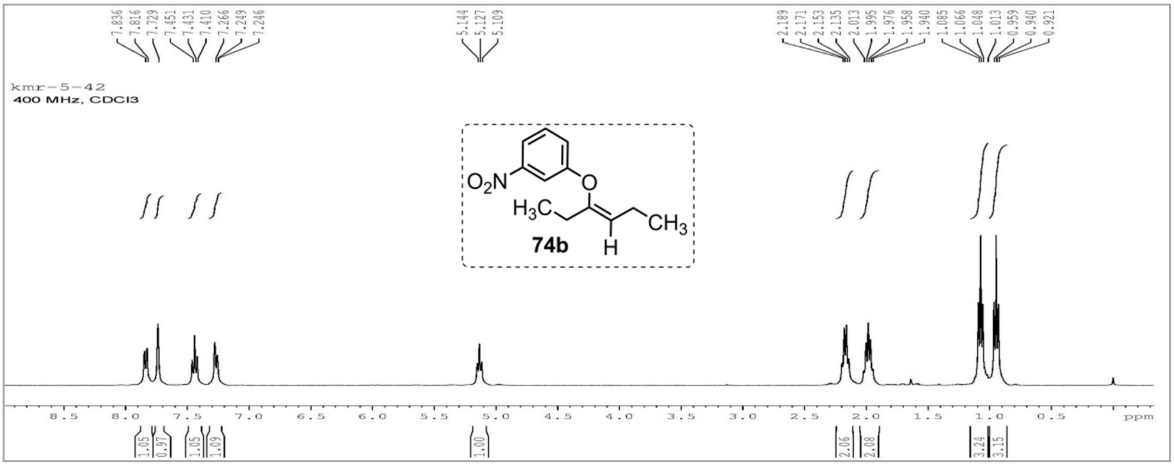

KMR-3-62
NO2
Ph
O
H
Ph
73p

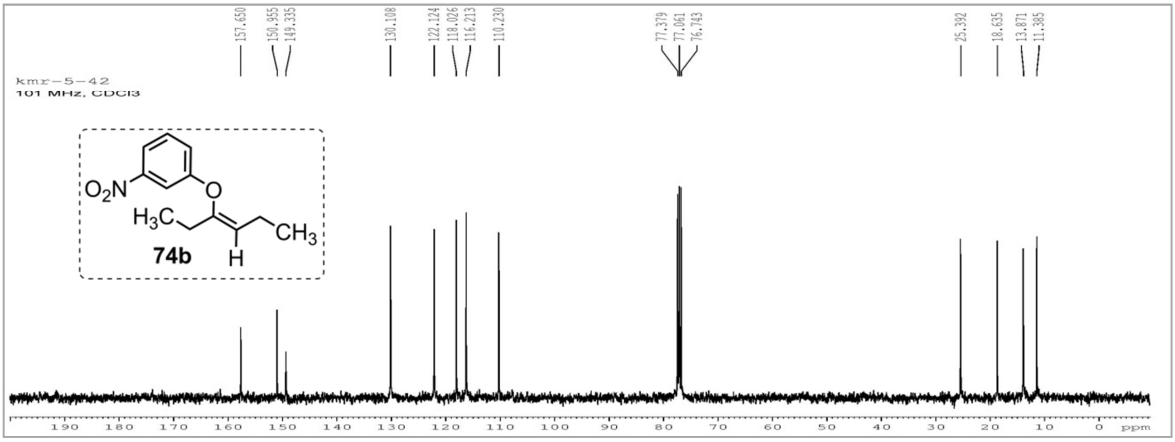

kmr-3-35
Ph
Ph
O
H
Ph
73q
ppm

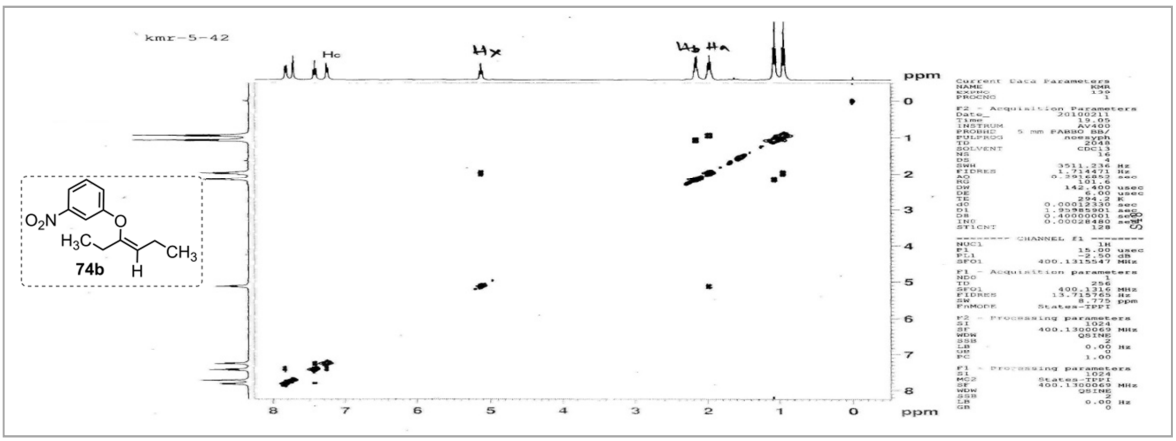

KMR-3-35c
Ph
Ph
O
H
Ph
73q
[ppm]

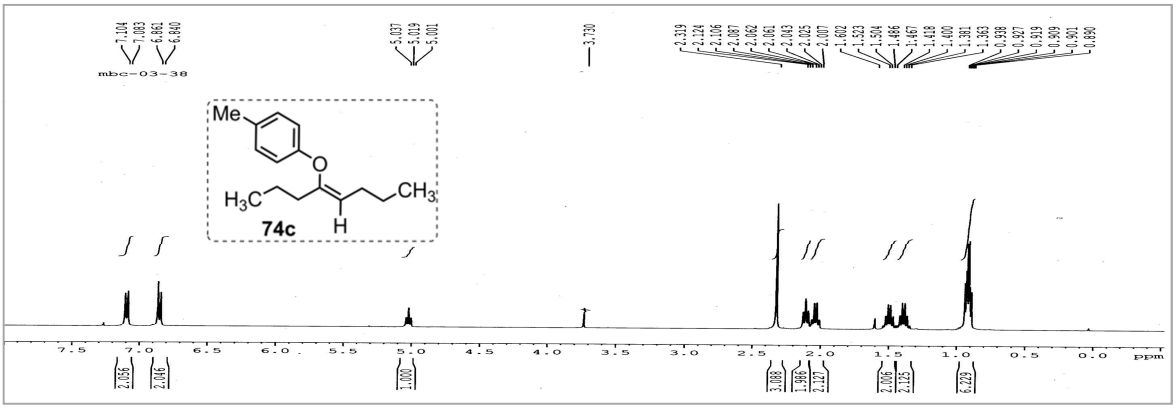

kmr-5-21
400 MHz, CDCl3
MeO
O
H3C
CH3
H
74a
ppm

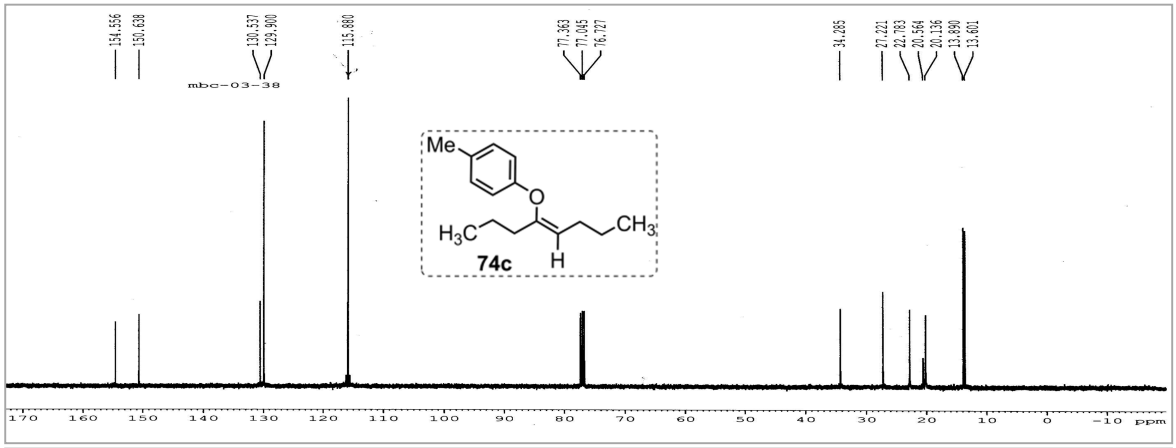

kmr-5-21
101 MHz, CDCl3
MeO
O
H3C
CH3
H
74a
ppm

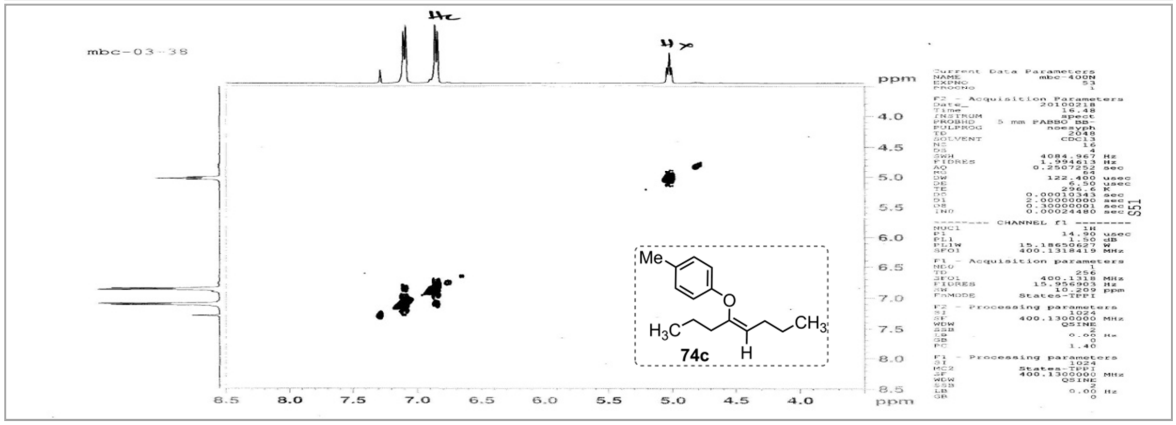

kmr-5-42
400 MHz, CDCl3
74b

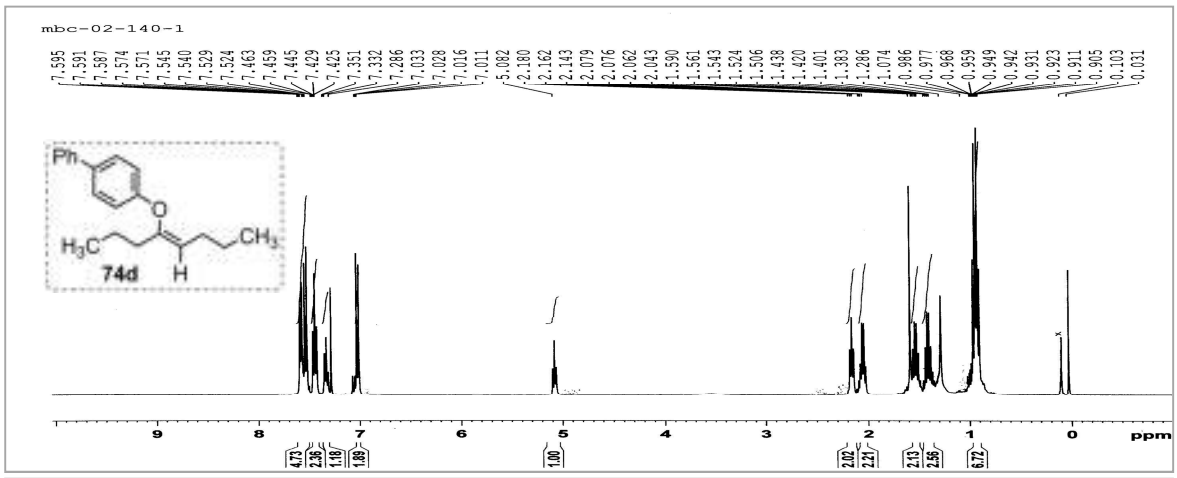

kmr-5-42
101 MHz, CDCl3
74b

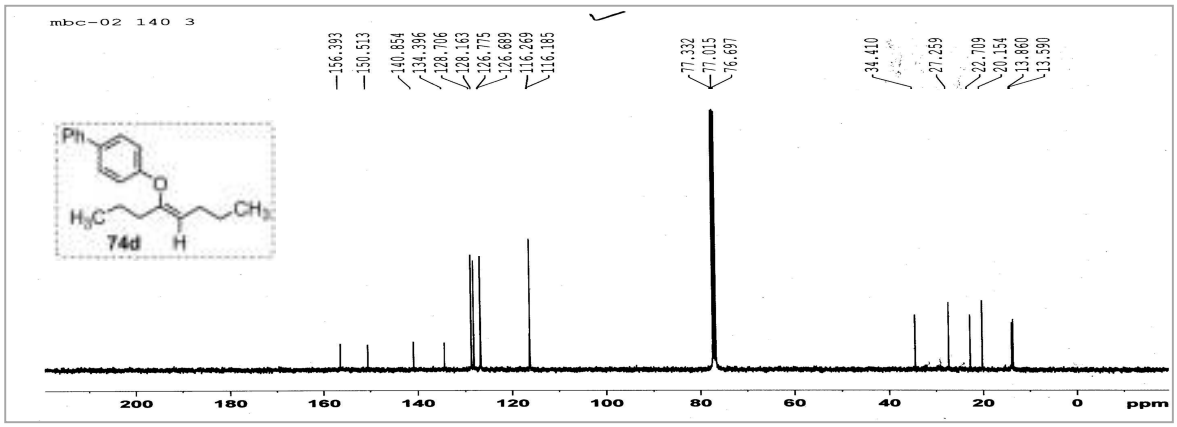

kmr-5-42
74b

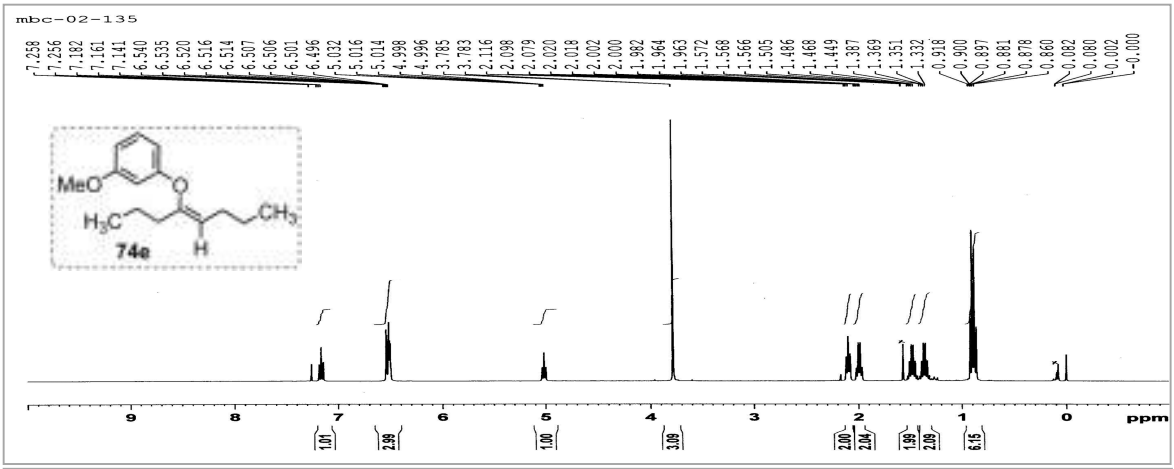

mbc-03-38
74c

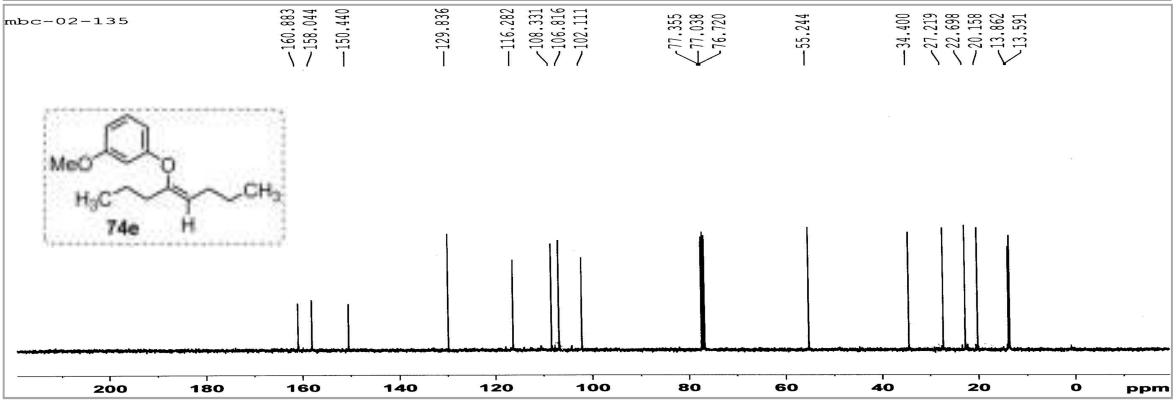

154.556
150.638
130.537
129.900
115.880
77.363
77.045
76.727
34.285
27.221
22.783
20.564
20.136
13.890
13.601
mbc-03-38
Me
O
H3C
CH3
74c
H
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10 ppm

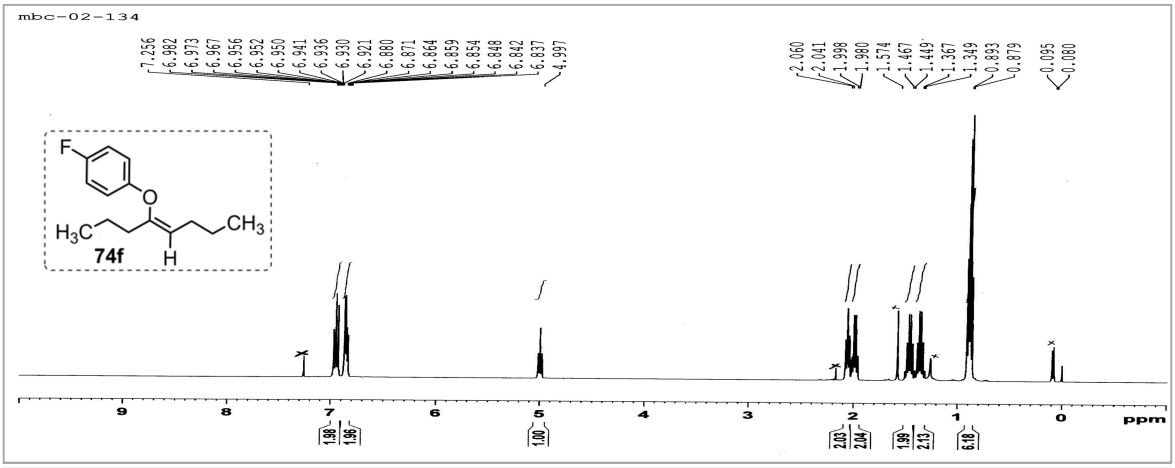

mbc-03-38
ppm
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
Me
O
H3C
CH3
74c
H
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 ppm

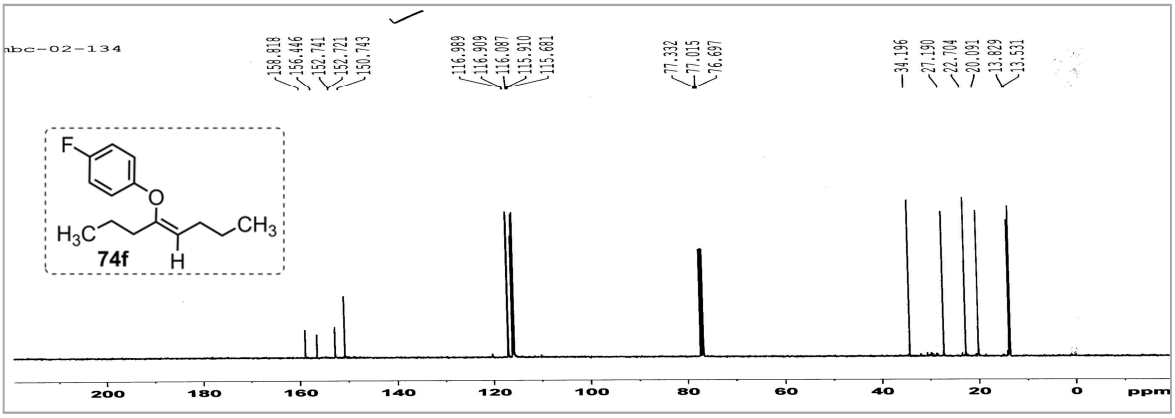

mbc-02-140-1
7.595
7.591
7.587
7.574
7.571
7.545
7.540
7.529
7.524
7.463
7.459
7.445
7.429
7.425
7.351
7.332
7.286
7.033
7.028
7.016
7.011
5.082
2.180
2.162
2.143
2.079
2.076
2.062
2.043
1.590
1.561
1.543
1.524
1.506
1.438
1.420
1.401
1.383
1.286
1.074
0.986
0.977
0.968
0.959
0.949
0.942
0.931
0.923
0.911
0.905
0.103
0.031
Ph
O
H3C
CH3
74d
H
9 8 7 6 5 4 3 2 1 0 ppm
4.73
2.38
1.18
1.09
1.00
2.02
2.27
2.13
2.38
6.72

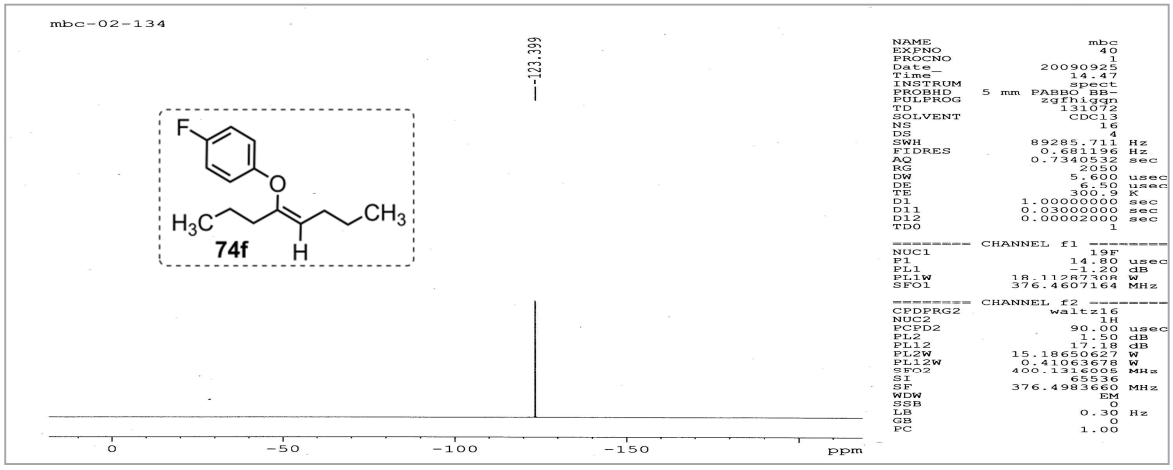

mbc-02 140 3
156.393
150.513
140.854
134.396
128.706
128.163
126.775
126.689
116.269
116.185
77.332
77.015
76.697
34.410
27.259
22.709
20.154
13.860
13.590
Ph
O
H3C
CH3
74d
H
200 180 160 140 120 100 80 60 40 20 0 ppm

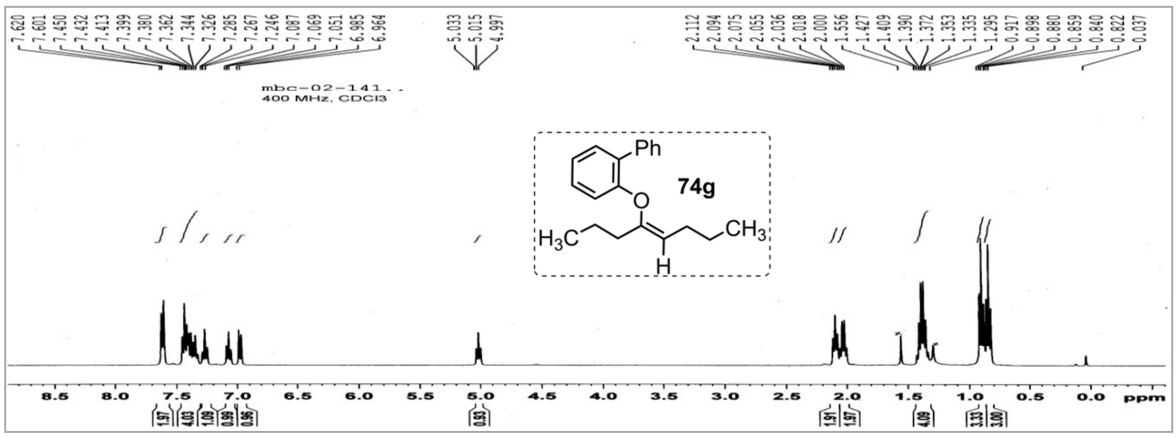

mbc-02-135
MeO
O
H3C
CH3
H
74e
ppm

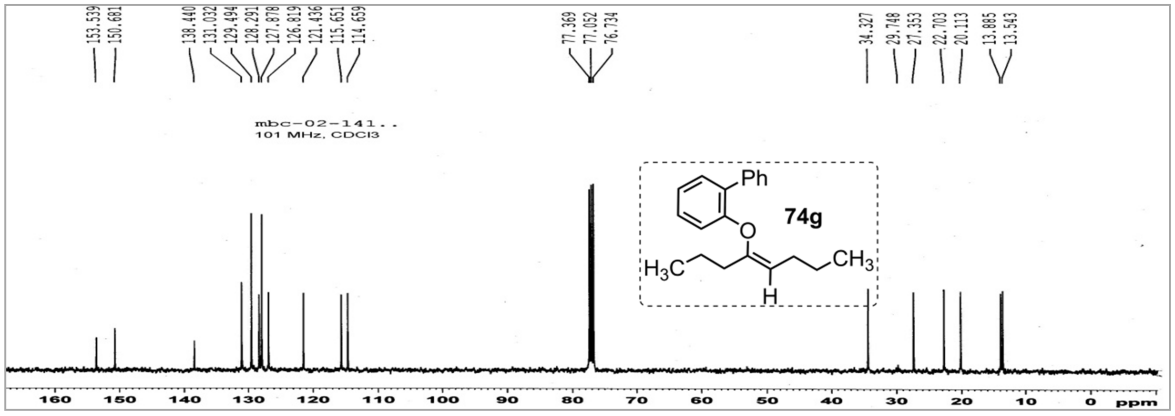

mbc-02-135
MeO
O
H3C
CH3
H
74e
ppm

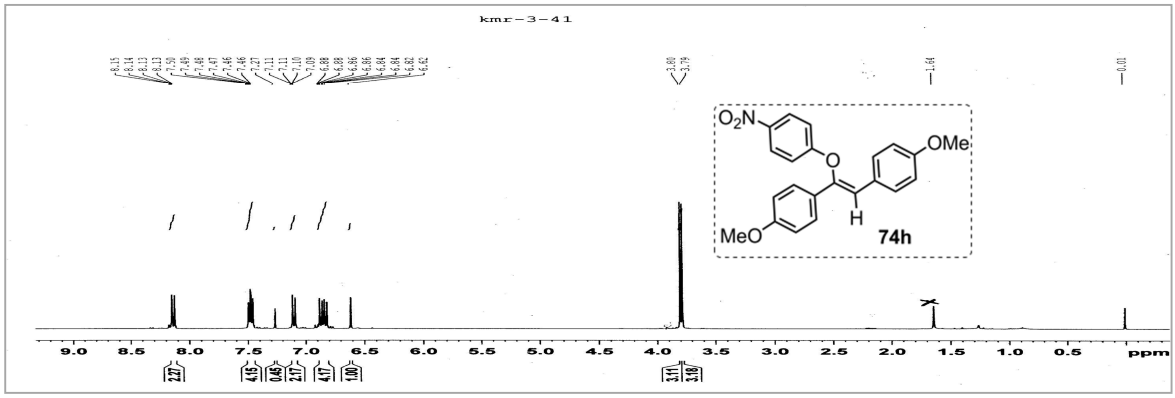

mbc-02-134
F
O
H3C
CH3
H
74f
ppm

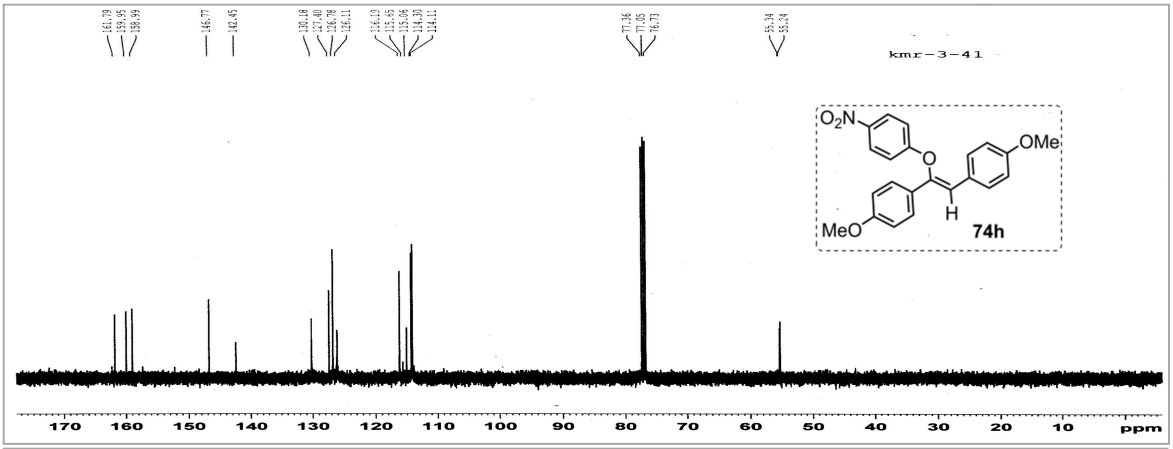

mbc-02-134
F
O
H3C
CH3
H
74f
ppm

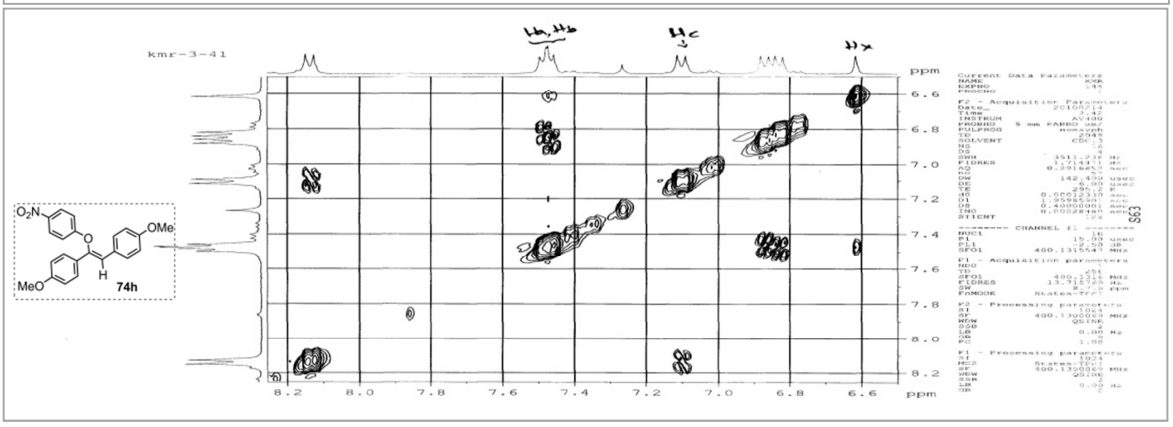

mbc-02-134
-123.399
F
O
H3C
CH3
74f
H
0
-50
-100
-150
ppm
NAME mbc
EXPNO 40
PROCNO 1
Date_ 20090925
Time 14.47
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgfhigqn
TD 131072
SOLVENT CDCl3
NS 16
DS 4
SWH 89285.711 Hz
FIDRES 0.6811196 Hz
AQ 0.7340532 sec
RG 2050
DW 5.600 usec
DE 6.50 usec
TE 300.9 K
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
TD0 1
CHANNEL f1
NUC1 19F
P1 14.80 usec
PL1 -1.20 dB
PL1W 18.11287308 W
SFO1 376.4607164 MHz
CHANNEL f2
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 1.50 dB
PL12 17.18 dB
PL2W 15.18650627 W
PL12W 0.41063678 W
SFO2 400.1316005 MHz
SI 65536
SF 376.4983660 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

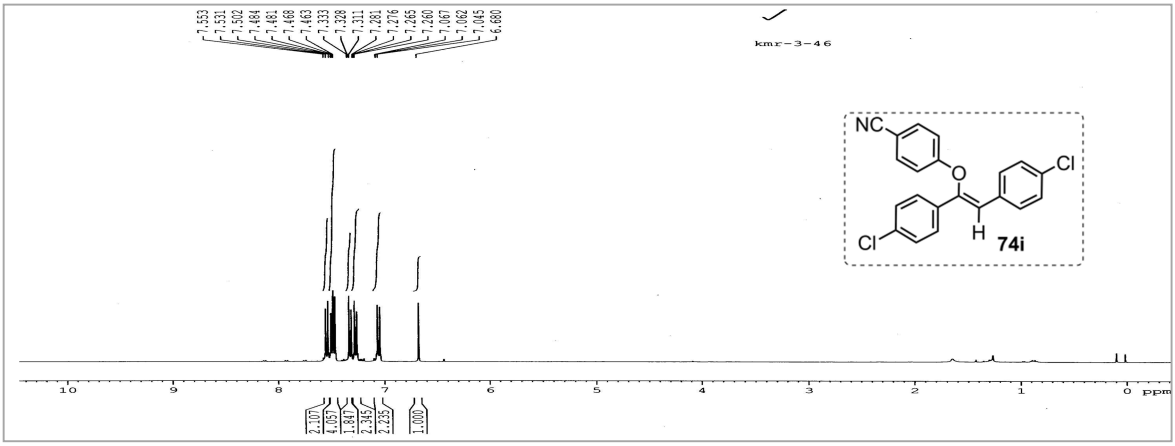

7.620
7.601
7.450
7.432
7.413
7.399
7.380
7.362
7.344
7.326
7.285
7.267
7.246
7.087
7.069
7.051
6.985
6.964
5.033
5.015
4.997
2.112
2.094
2.075
2.055
2.036
2.018
2.000
1.556
1.427
1.409
1.390
1.372
1.353
1.335
1.295
0.917
0.898
0.880
0.859
0.840
0.822
0.037
mbc-02-141..
400 MHz, CDCl3
Ph
O
74g
H3C
CH3
H
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

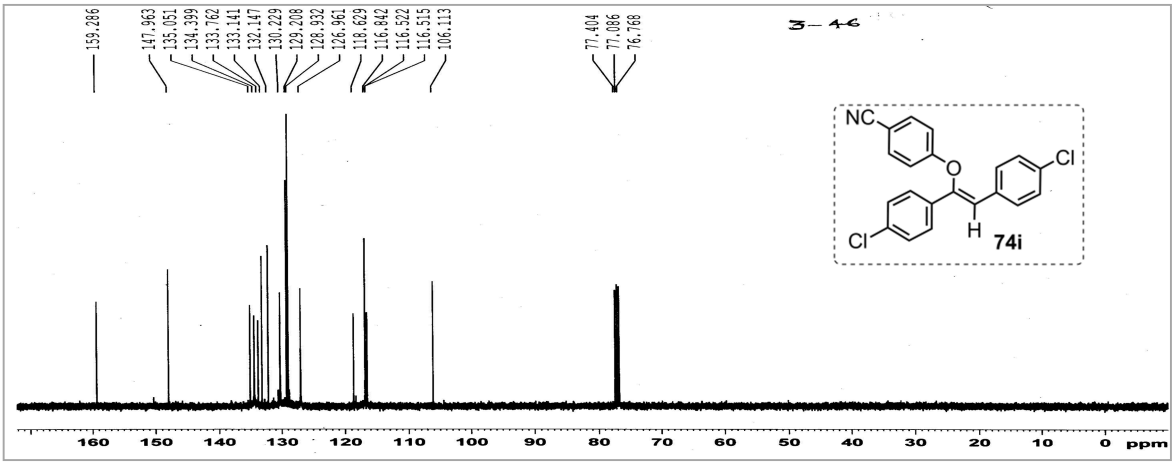

153.539
150.681
138.440
131.032
129.494
128.291
127.878
126.819
121.436
115.651
114.659
77.369
77.052
76.734
34.327
29.748
27.353
22.703
20.113
13.885
13.543
mbc-02-141..
101 MHz, CDCl3
Ph
O
74g
H3C
CH3
H
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

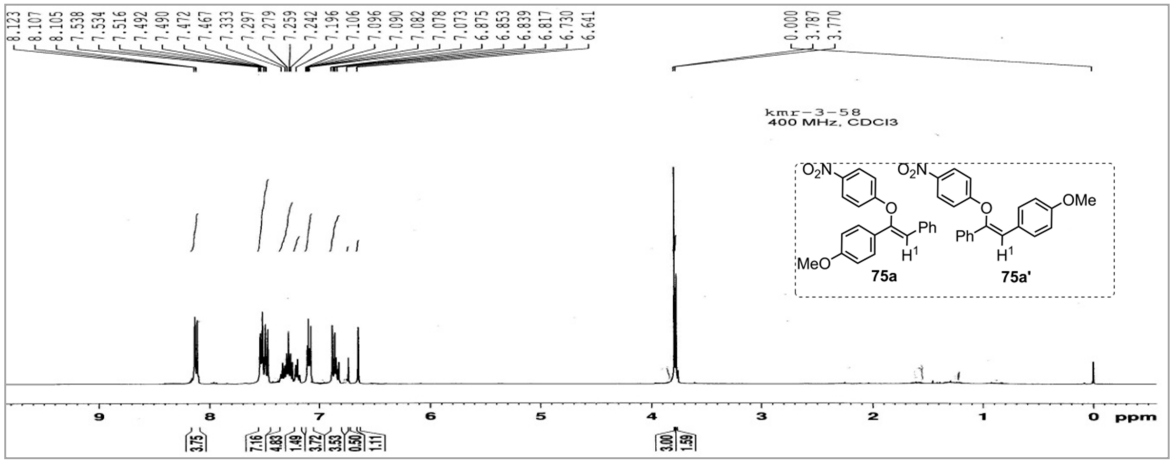

kmr-3-41
3.80
3.79
1.64
1.01
O2N
O
OMe
H
MeO
74h
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

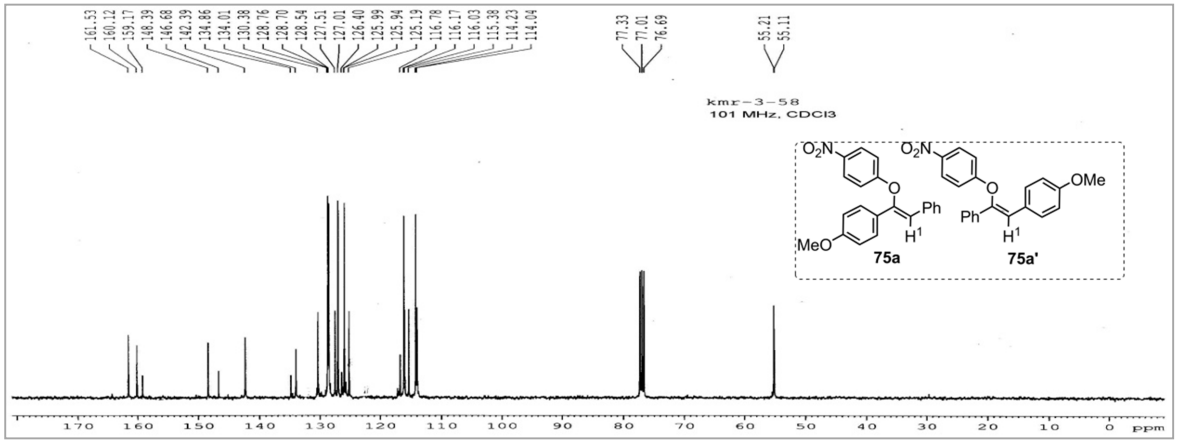

kmr-3-41
O_2N
OMe
O
H
MeO
74h
ppm

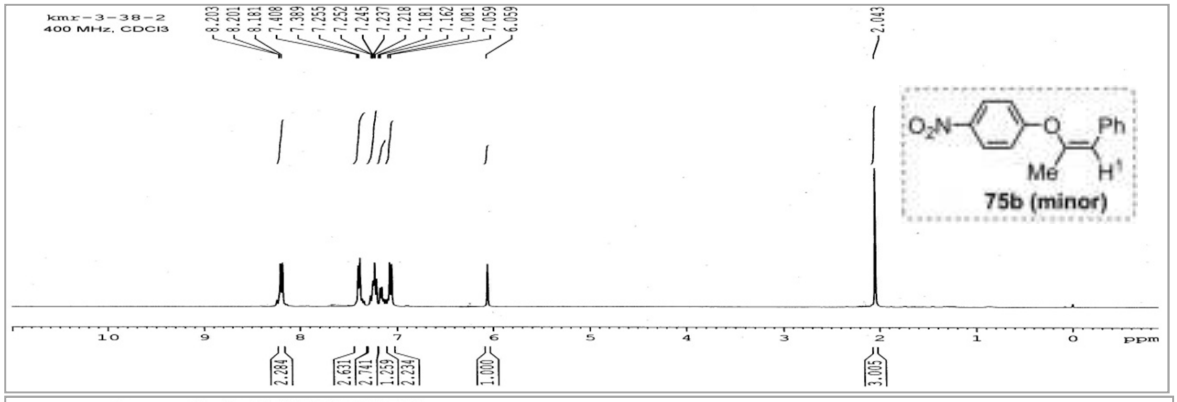

kmr-3-41
Ha,Hb
Hc
Hx
O_2N
OMe
MeO
74h
ppm

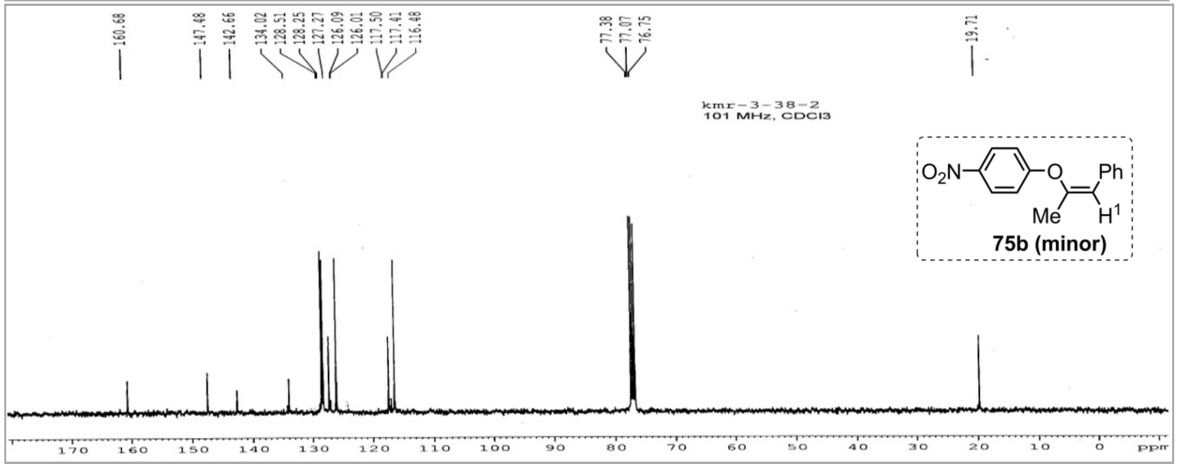

kmr-3-46
NC
Cl
Cl
H
74i
ppm

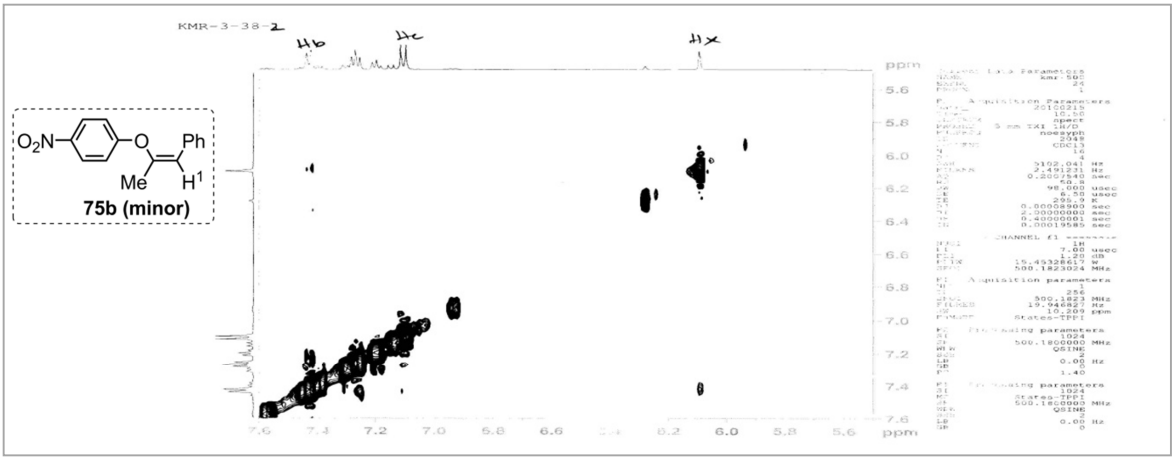

3-46
NC
Cl
Cl
H
74i
ppm

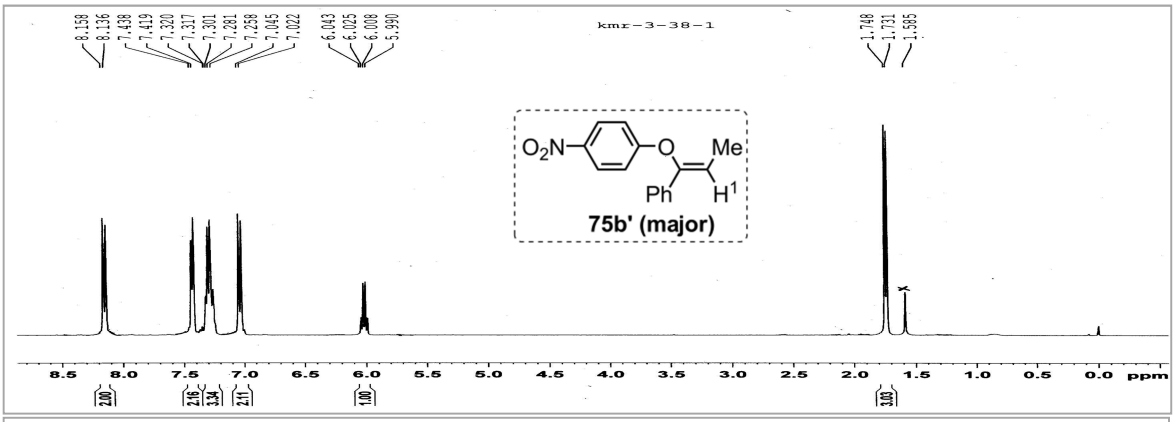

kmr-3-58
400 MHz, CDCl3
75a
75a'

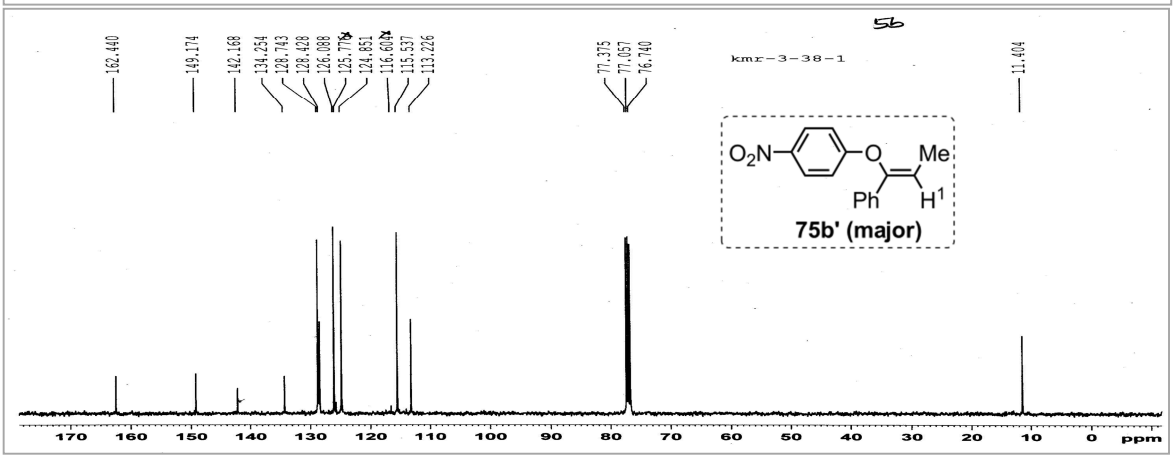

kmr-3-58
101 MHz, CDCl3
75a
75a'

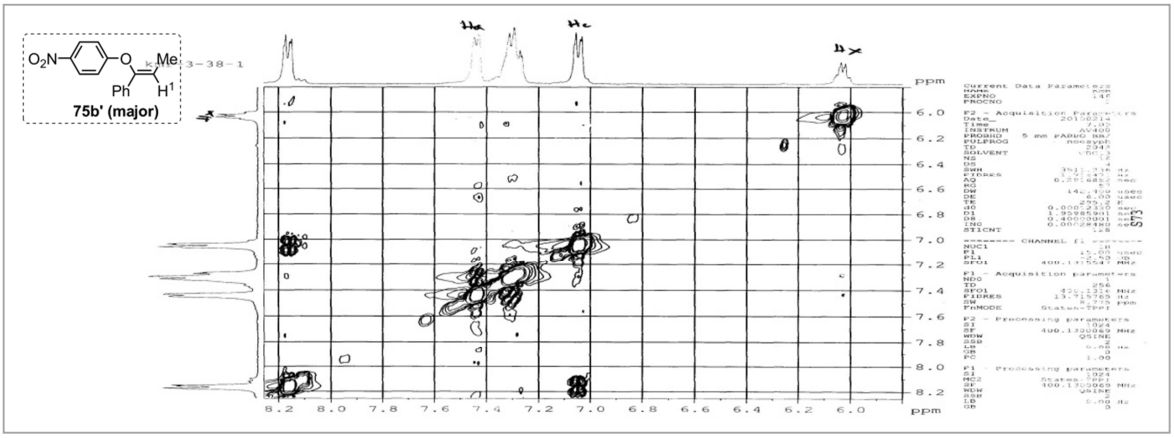

kmr-3-38-2
400 MHz, CDCl3
75b (minor)

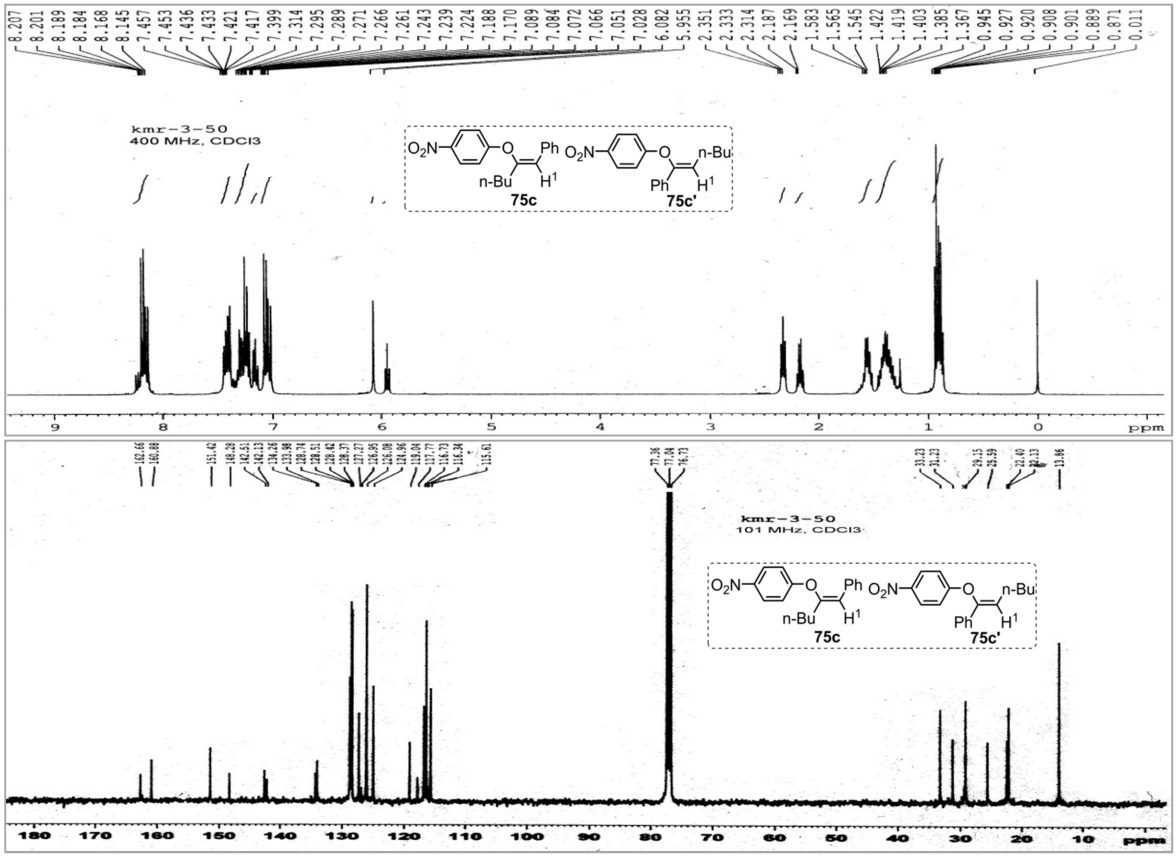

kmr-3-38-2
101 MHz, CDCl3
75b (minor)

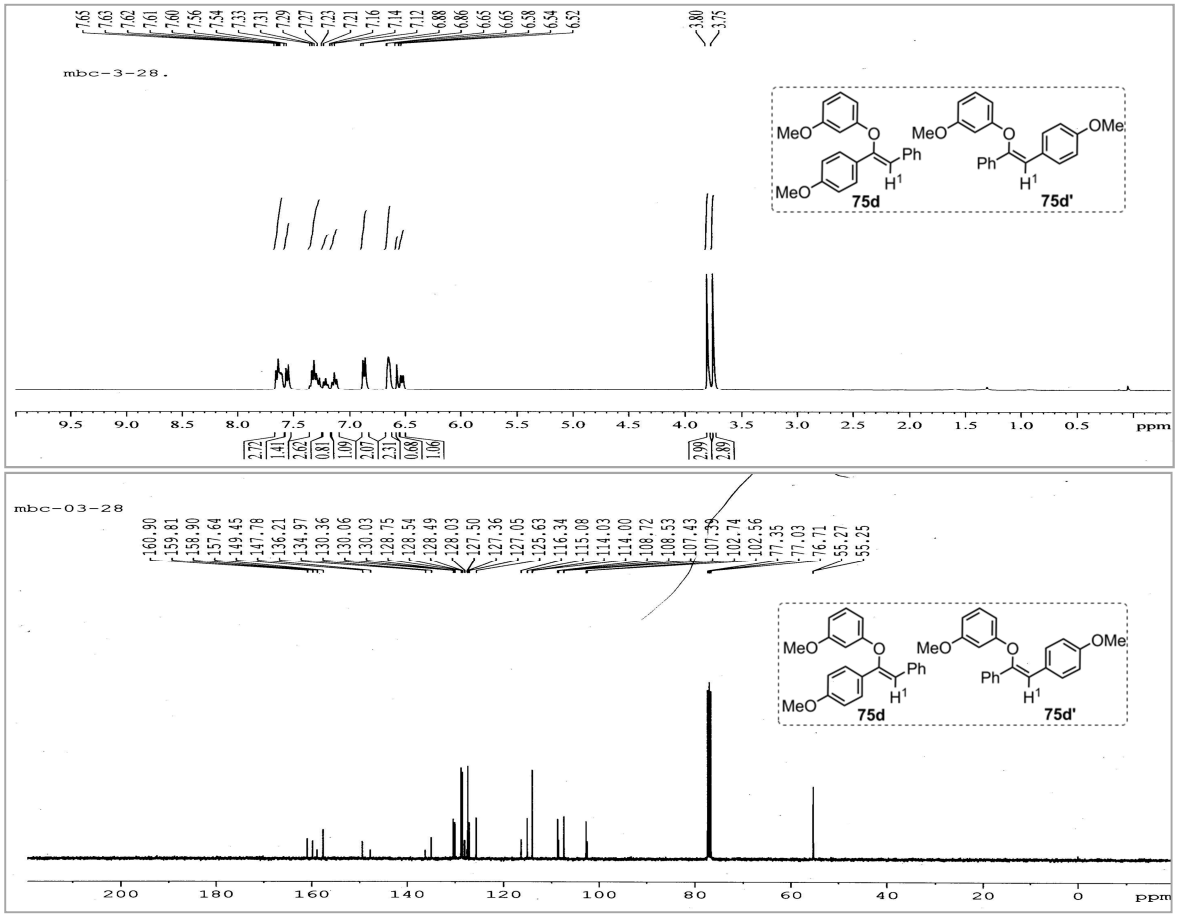

KMR-3-38-2
Hb
Hc
Hx
O2N
O
Ph
Me
H1
75b (minor)
ppm

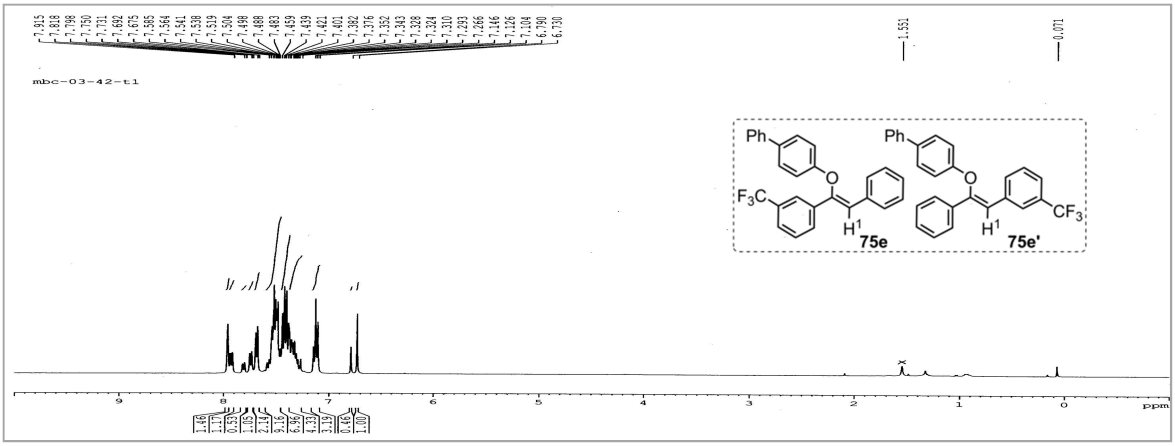

8.159
8.136
7.438
7.419
7.320
7.317
7.301
7.281
7.258
7.045
7.022
6.043
6.025
6.008
5.990
kmr-3-38-1
1.748
1.731
1.585
O2N
O
Me
Ph
H1
75b' (major)
ppm

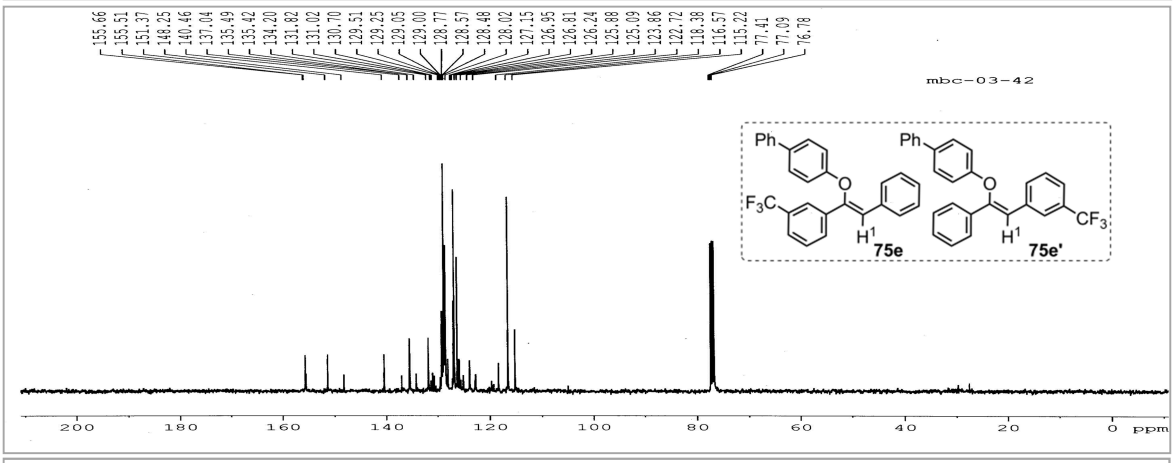

162.440
149.174
142.168
134.264
128.743
128.428
126.088
125.778
124.851
116.604
115.537
113.226
77.375
77.057
76.740
kmr-3-38-1
11.404
O2N
O
Me
Ph
H1
75b' (major)
ppm

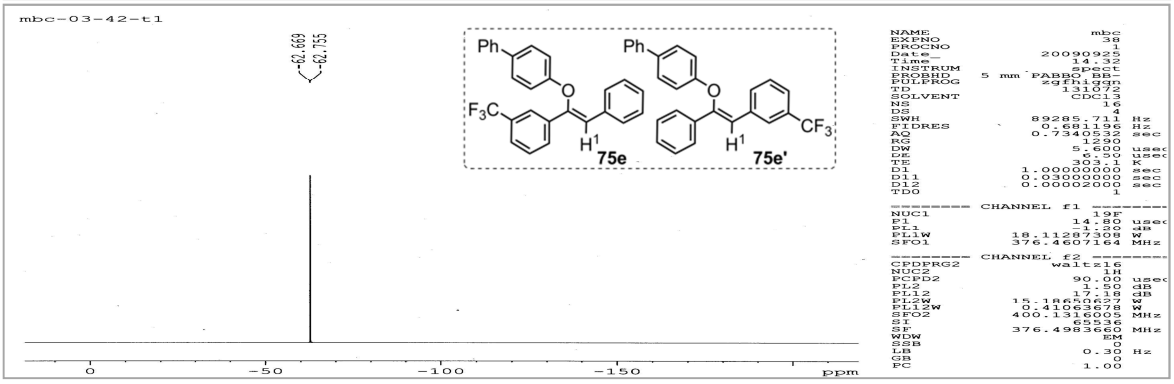

O2N
O
Me
Ph
H1
75b' (major)
Ha
Hc
Hx
ppm


kmr-3-50
400 MHz, CDCl3
75c
75c'
kmr-3-50
101 MHz, CDCl3
75c
75c'


mbc-3-28.
75d
75d'
mbc-03-28
75d
75d'


mbc-03-42-t1
Ph
F3C
H1
75e
CF3
75e'
ppm


mbc-03-42
Ph
F3C
H1
75e
CF3
75e'
ppm


mbc-03-42-t1
62.669
62.755
Ph
F3C
H1
75e
CF3
75e'
ppm
NAME mbc
EXPNO 38
PROCNO 1
Date_ 20090925
Time 14.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgfhigqn
TD 131072
SOLVENT CDCl3
NS 16
DS 4
SWH 89285.711 Hz
FIDRES 0.681196 Hz
AQ 0.734053 sec
RG 1290
DW 5.600 usec
DE 6.50 usec
TE 303.1 K
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec
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CHANNEL f1
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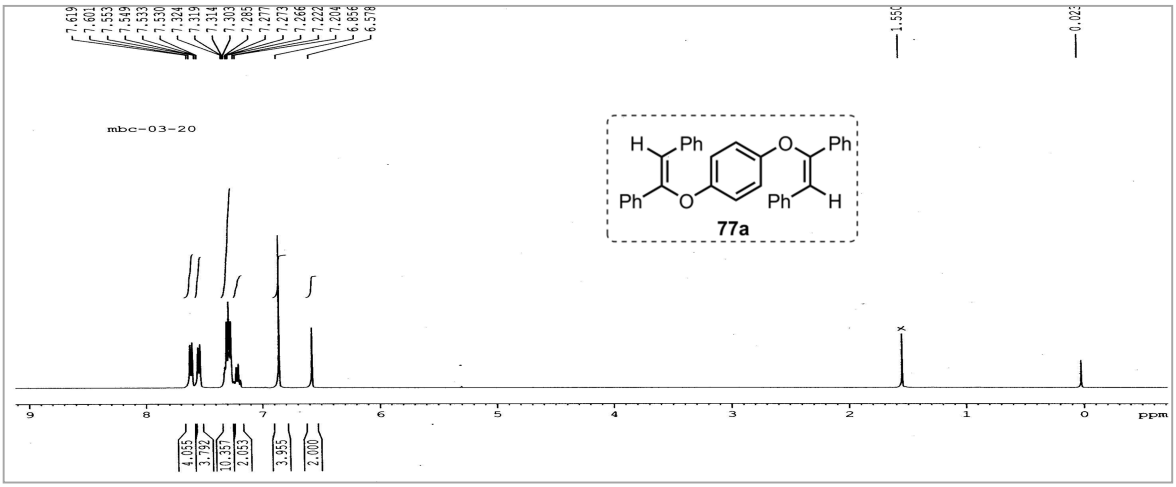
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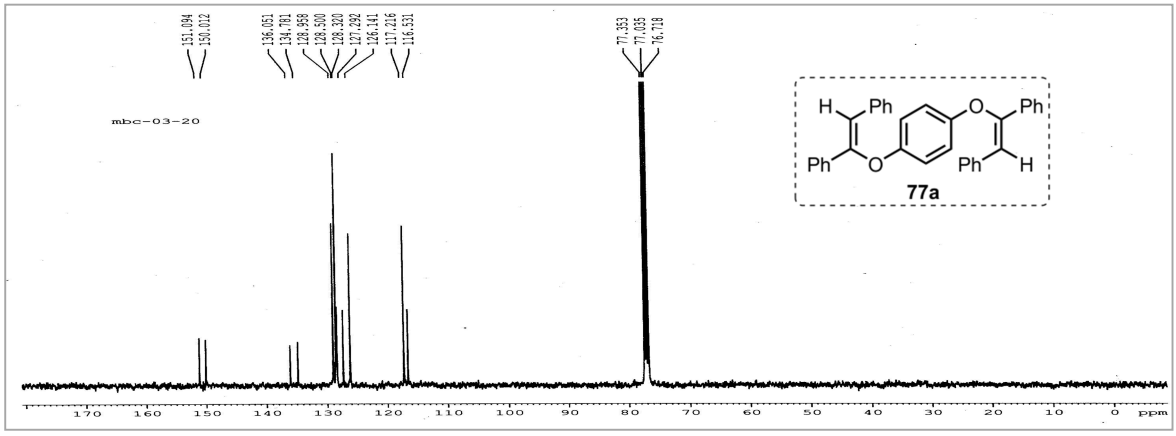
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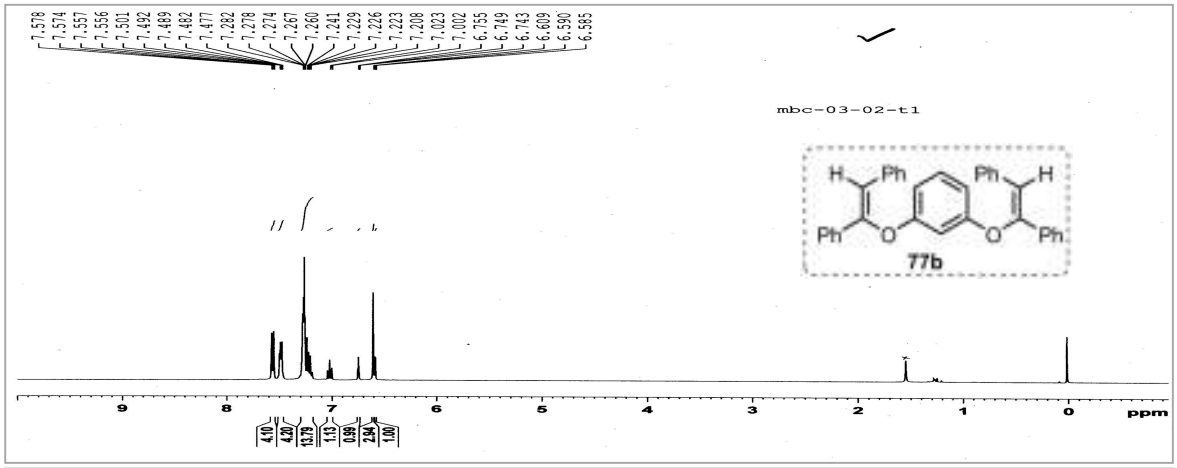
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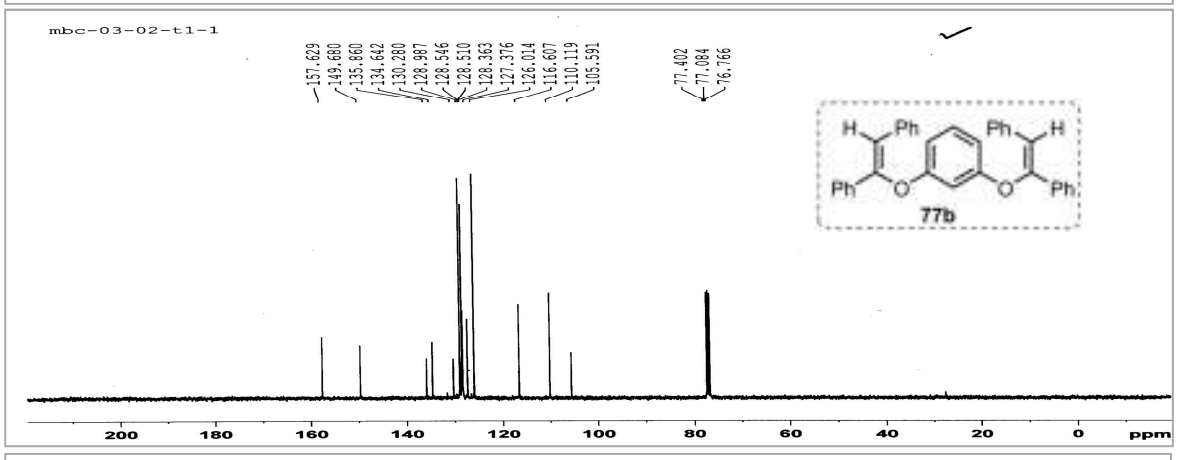
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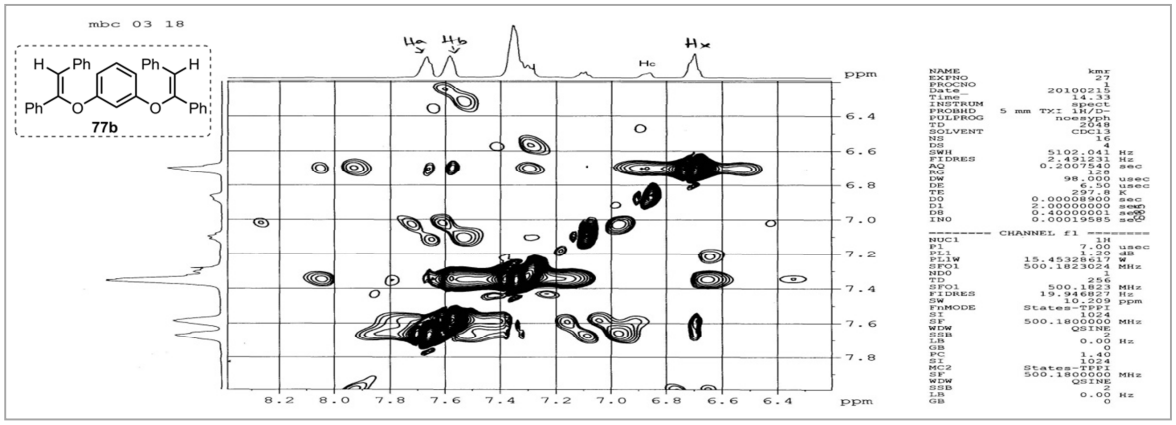
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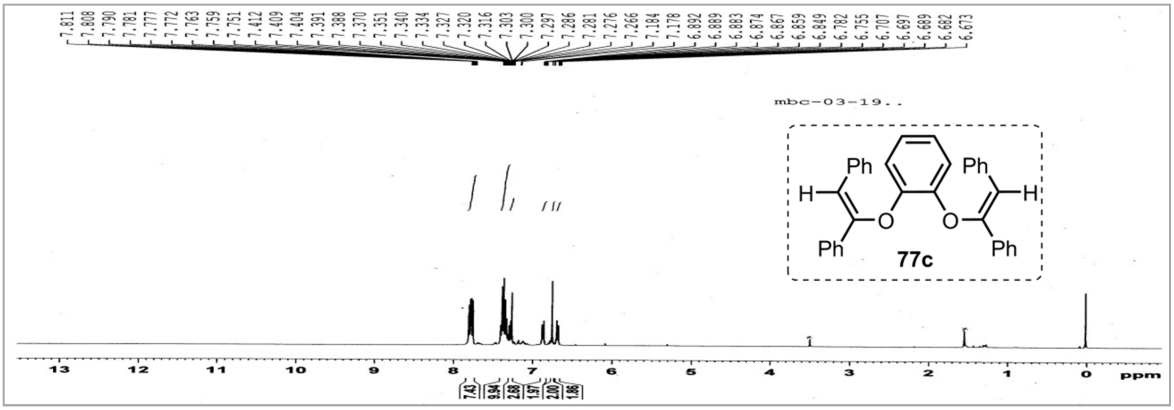
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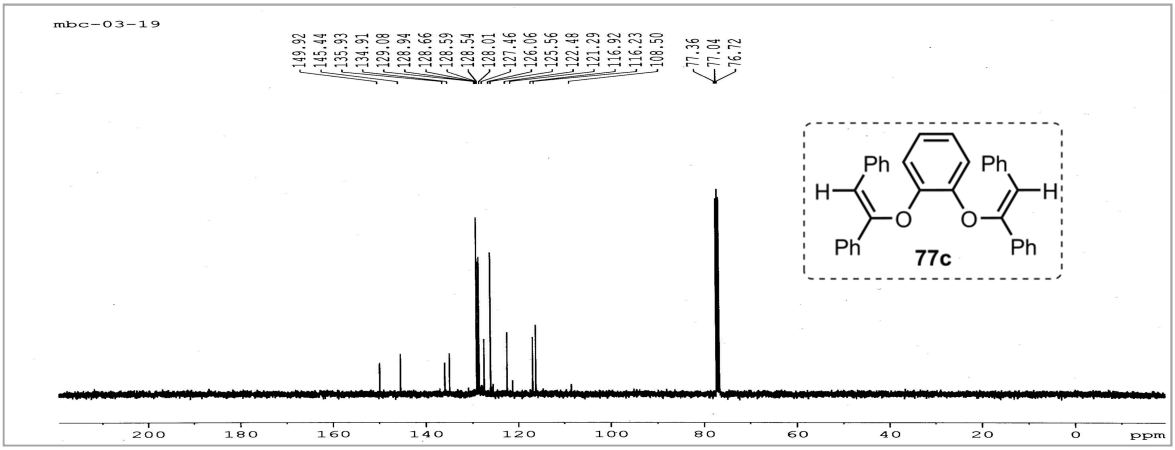
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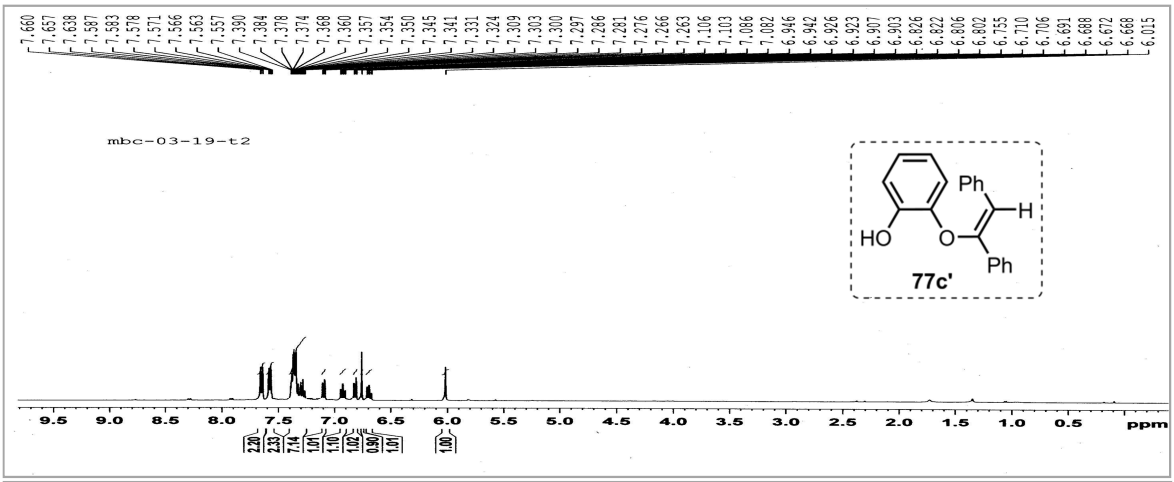
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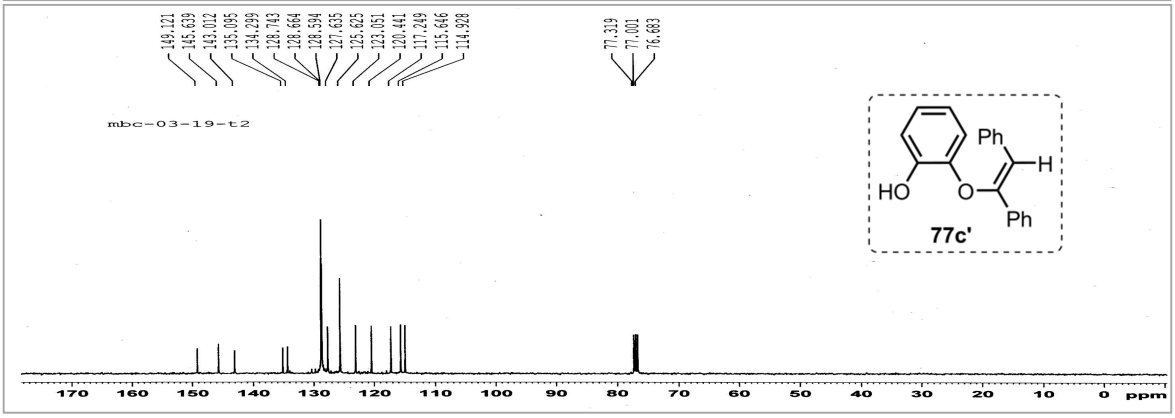
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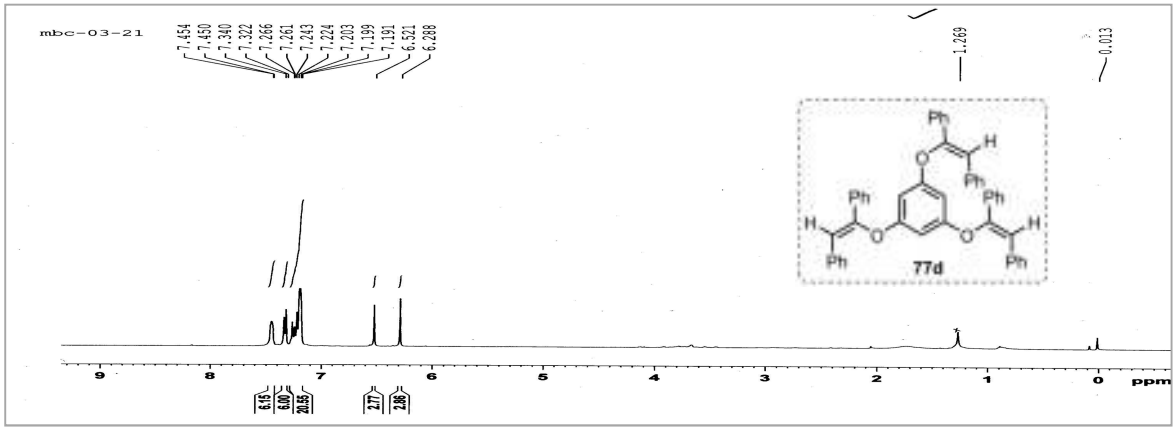
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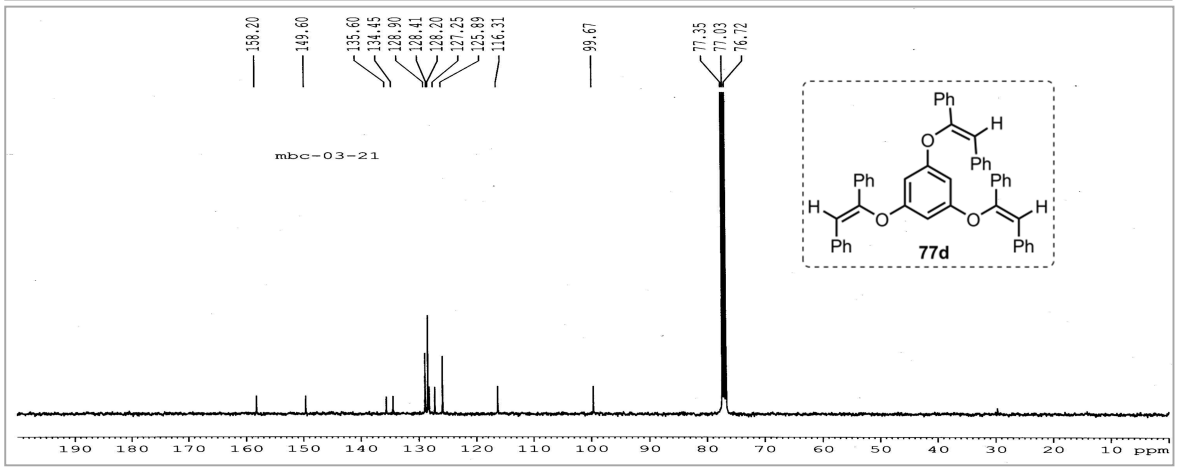
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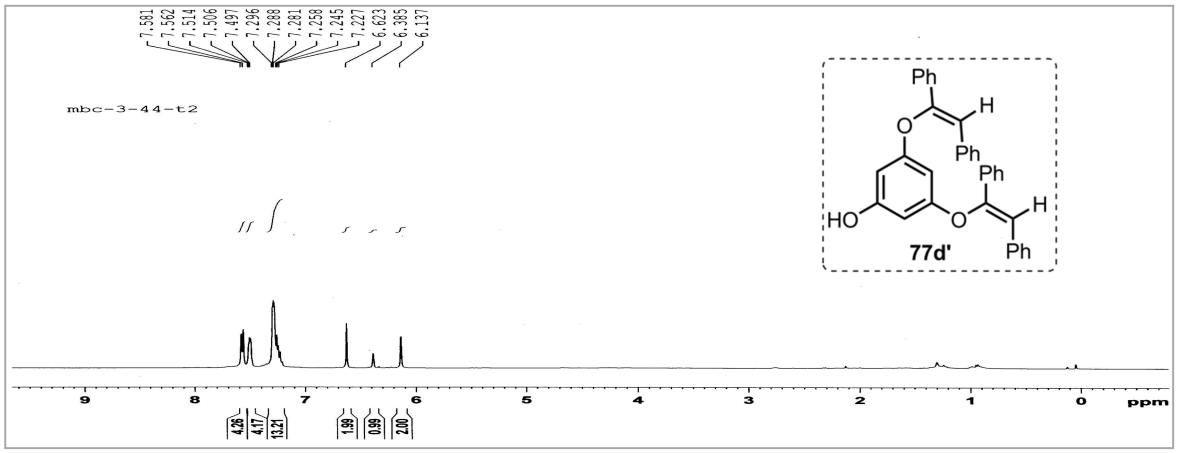
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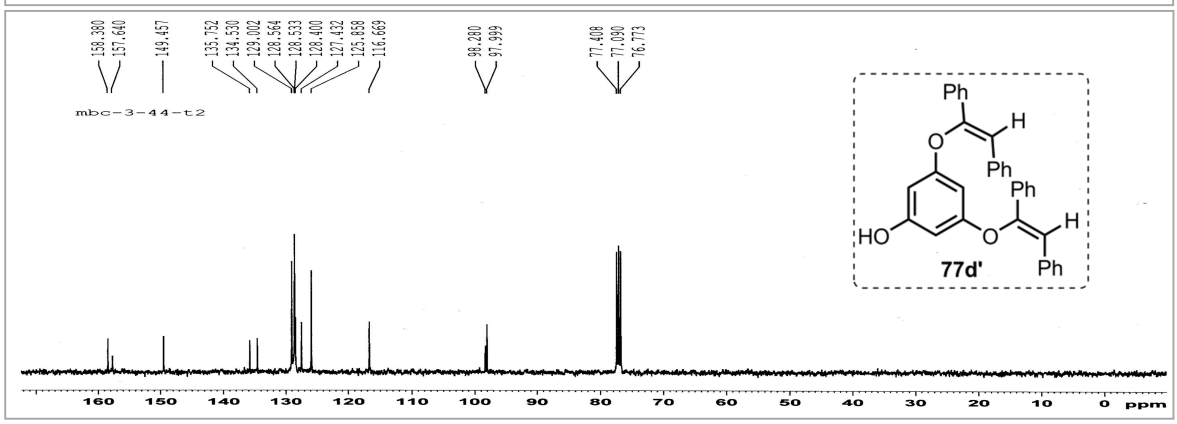
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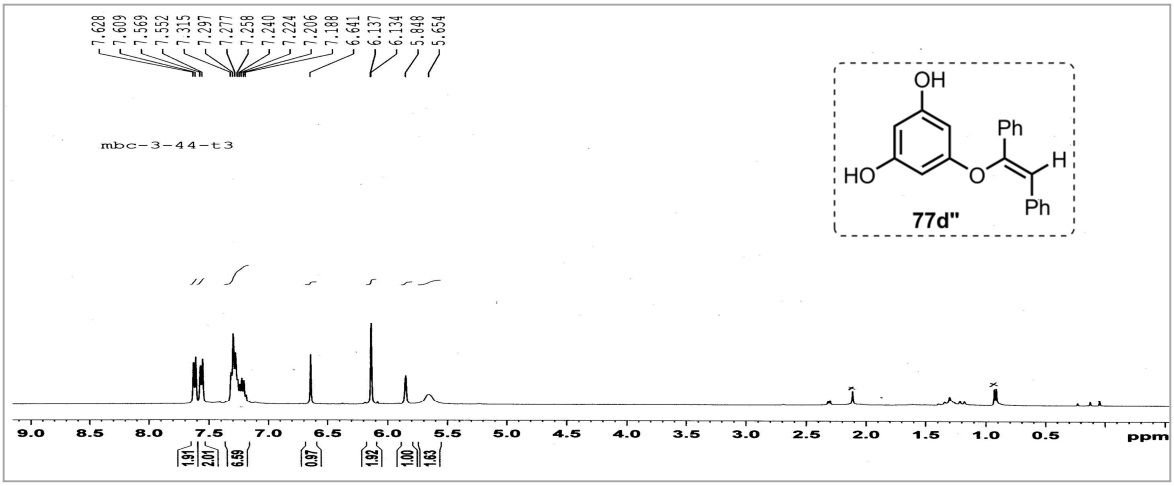
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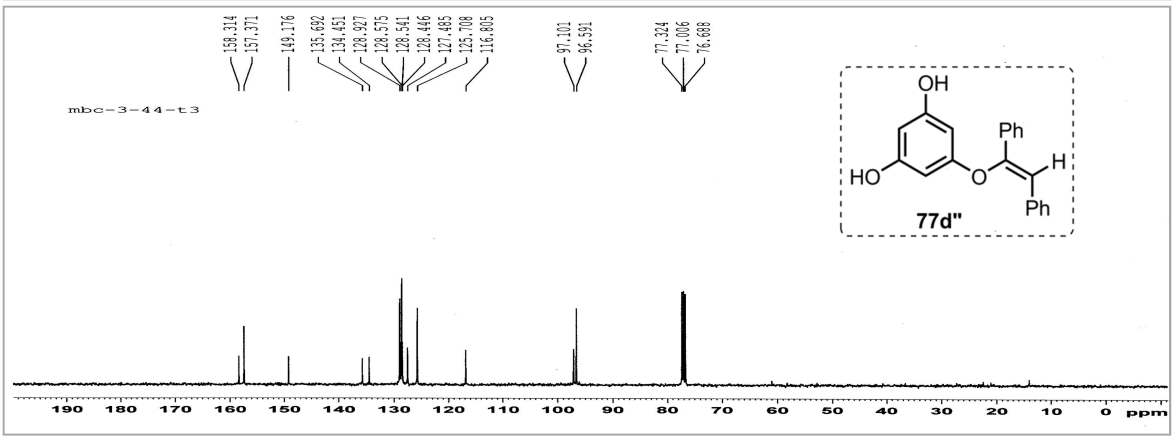
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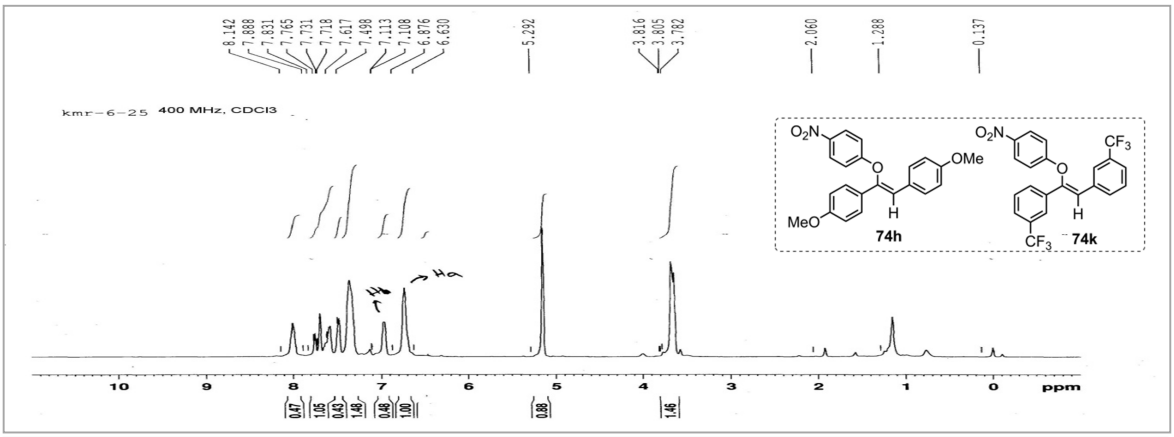
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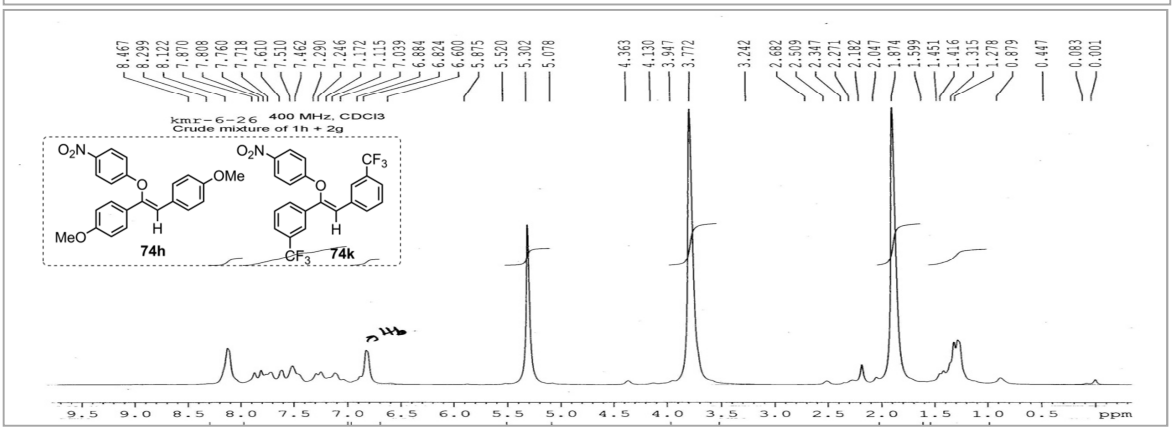
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CF3
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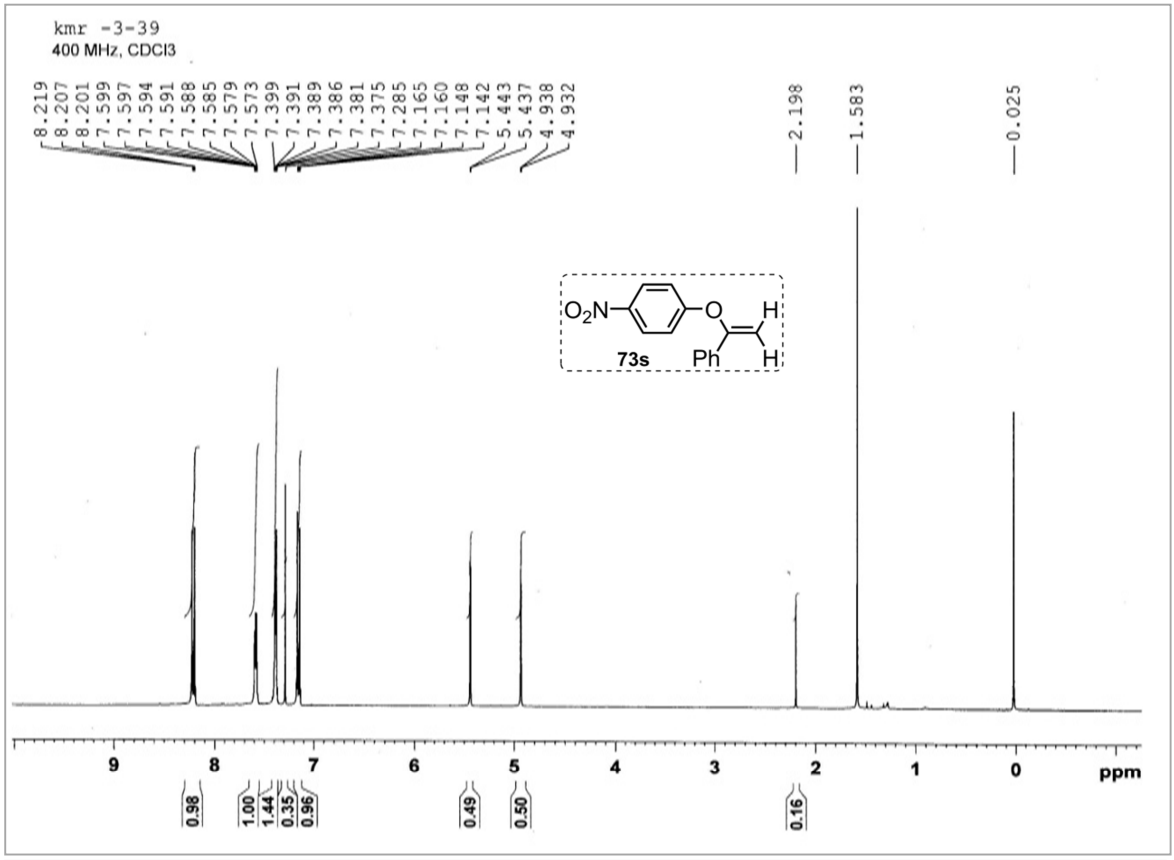
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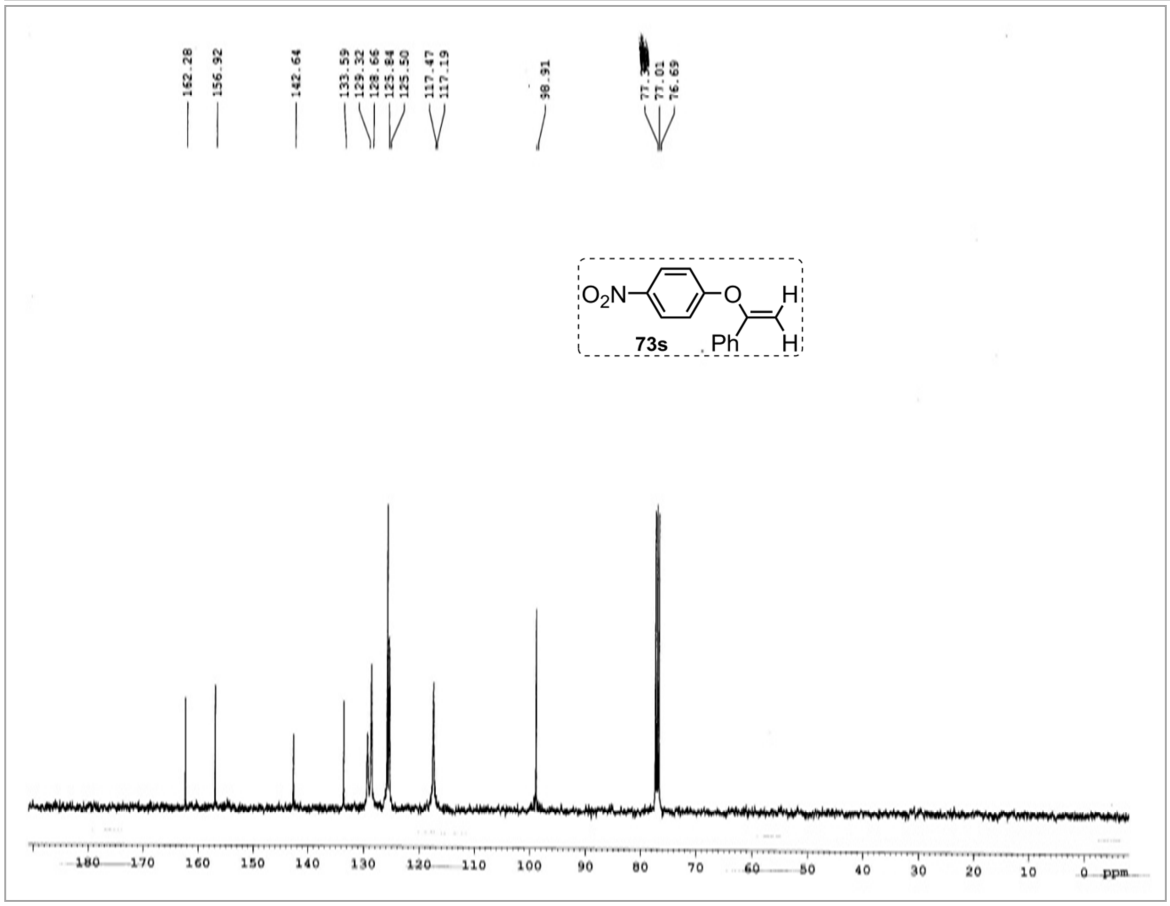
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Direct Access to Benzo[*b*]furans through Palladium-Catalyzed Oxidative Annulation of Phenols and Unactivated Internal Alkynes

2 Chapter

Abstract

The palladium-catalyzed oxidative annulation of commercially available phenols with readily accessible unactivated internal alkynes to provide 2,3-disubstituted benzo[*b*]furans is successfully demonstrated. The one-step method allows efficient access to a wide array of benzo[*b*]furans. The electronic properties and acidity of the phenols significantly influence their reactivity: while the reaction of electron-poor phenols with alkynes proceeds in the presence of AgOAc, the base NaOAc is required in case of electron-rich phenols. A variety of common functional groups are tolerated which greatly enhances the synthetic versatility of this strategy. Furthermore, the reaction of phenols with aryl-alkyl-substituted unsymmetrical alkynes resulted in regioselective benzofurans. The protocol could efficiently be applied in the installation of the benzofuran skeleton on biologically active complex molecules. Interestingly, oxidative annulation of α-naphthol with internal unactivated alkynes resulted in naphthofurans rather than naphthopyrans. Preliminary investigations on a plausible reaction mechanism confirmed the involvement of a bis(aryloxo)palladium(II) complex and *ortho*-C–H bond cleavage of phenol.

Reference:

Malleswara Rao Kuram, M. Bhanuchandra and Akhila K. Sahoo
Angew. Chem. Int. Ed. **2013**, *52*, 4607–4612

2.1. Introduction

The benzo[*b*]furan is ubiquitous in natural products[1] and a privileged structure found in numerous biologically active compounds.[2] Highly substituted benzo[*b*]furan motifs are furthermore present in various leading drugs[2] and found wide applications in material sciences.[3] A few representative molecules bearing the benzo[*b*]furan skeleton are shown in Figure 2.1.

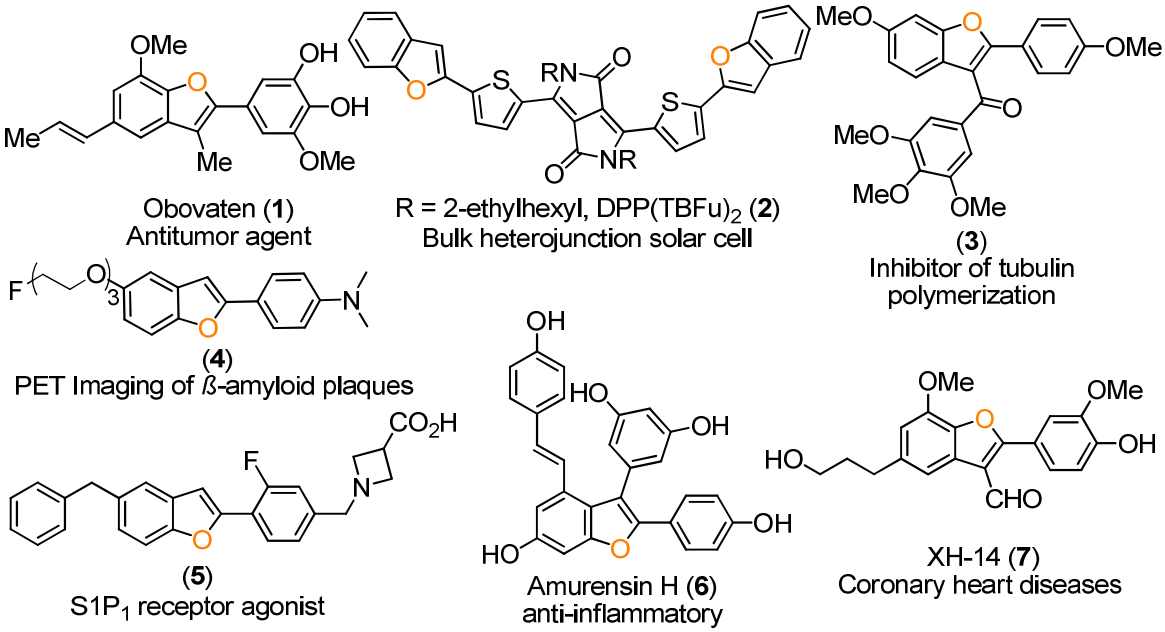


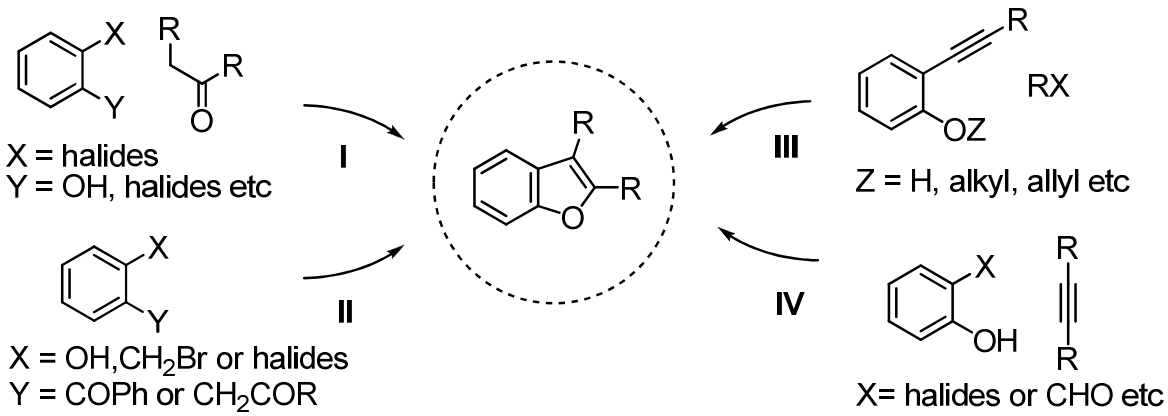
Figure 2.1: Biologically important benzofuran derivatives

Obovaten (**1**) is an active antitumor agent isolated from the leaves of *Persea Obovatifolia*.[2f] The benzofuran skeleton bearing molecules increasingly found wide spread applications in materials chemistry. For instance: small molecule based bulk heterojunction solar cell DPP(TBFu)$_2$ (**2**) with a diketopyrrolopyrrole chromophore has been achieved high power conversion efficiency (PCE) of 4.4%.[3a] The 2,3-disubstituted benzo[*b*]furan anologue **3** identified as a inhibitor of tubulin polymerization.[2d] A fluorinated benzofuran derivative **4** was evaluated as a potential tracer for positron emission tomography (PET) targeting β-amyloid plaques for the Alzheimer's disease.[2b] An orally active S1P$_1$ receptor agonist benzofuran derivative **5** was developed by Saha group.[2a] Amurensin H (**6**) extracted from *Vitis Amurensis*, is a natural product useful as Chinese folk medicine for many years and showed strong anti-inflammatory action *in vitro* and *in vivo* in mice models.[2i] XH-14 (**7**) isolated from the roots of *Salvia miltiorrhiza*

Bunge (Danshen), is a non nucleoside adenosine A1 agonist applicable in treating the coronary heart diseases.[2h] As a result, there is considerable interest from the synthetic organic community to nurture the benzo[*b*]furan motif by efficient methodologies.[4]

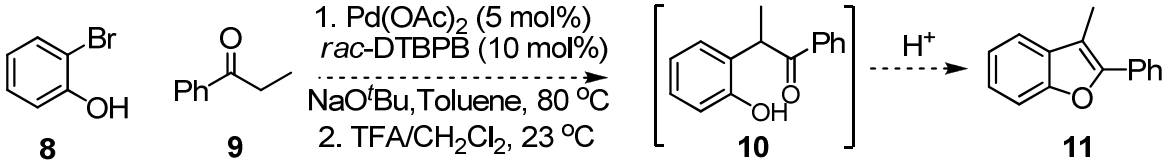
2.1.1. Precedents and Strategies for Benzofuran Synthesis

The transition-metal (TM)-catalyzed annulations are the trust-worthy methods useful for the synthesis of complex heterocycles by synthetically efficient, step and atom-economical routes. Owing to the importance of benzo[*b*]furans and its derivatives, various synthetically viable strategies have been devised for the construction of benzo[*b*]furans.[5] Some of the conceptually most interesting TM-catalyzed synthetic strategies for benzo[*b*]furans are shown in Scheme 2.1.



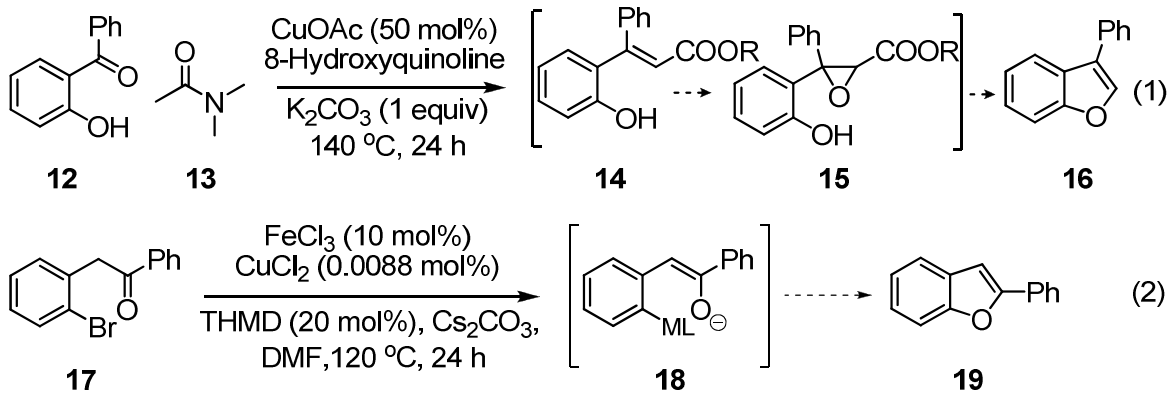
Scheme 2.1: Strategies toward the synthesis of benzo[*b*]furans

The typical method for the synthesis of benzofurans involves acid catalyzed condensation or transition-metal (TM)-catalyzed reaction of phenols or halo arenes with ketones as shown in Path I, Scheme 2.1.



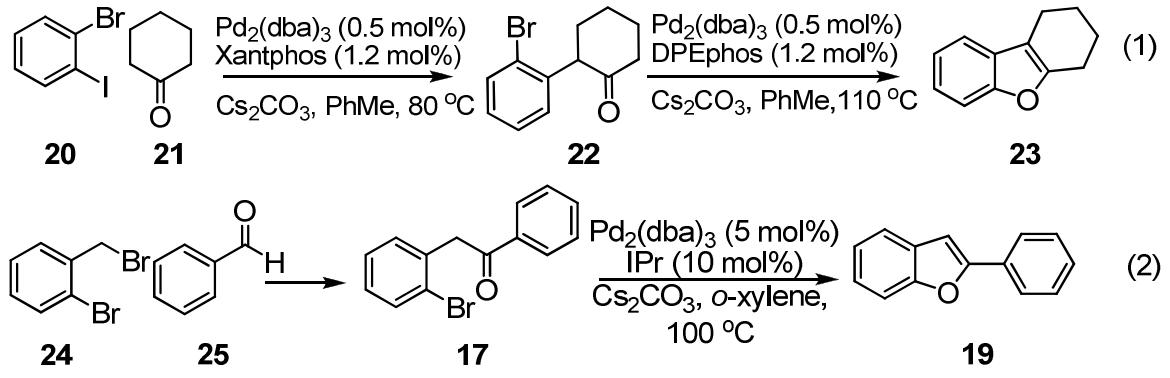
Scheme 2.2: Intermolecular reaction of *ortho*-halophenols with ketones

Burch group reported the Pd-catalyzed one pot synthesis of 2-phenyl-3-methylbenzofurans (**11**) via enolate arylation of *o*-bromophenols (**8**) with ketone **9** (Scheme 2.2).[6] The reaction proceeds with the acid-catalyzed cyclization of the intermediate α-arylketones **10**.



Scheme 2.3: Intramolecular cyclization of *o*-hydroxyaryl/o-bromobenzyl ketones

The desired benzofurans are smoothly accessed through intramolecular cyclization of *o*-hydroxyaryl ketones or *o*-bromobenzyl ketones (Path II, Scheme 2.1).[6] Interestingly, reaction of 2-hydroxybenzophenone (**12**) with *N*,*N*-dimethylacetamide (DMA, **13**) in the presence of Cu-catalyst and 8-hydroxyquinoline gave 3-phenylbenzofuran (**16**). The attack of intermediate ketene, generated from DMA and 8-hydroxyquinoline, to the carbonyl of benzophenone (**12**) led to the unsaturated ester **14**. Then copper catalyzed epoxidation of **14** generates the epoxide **15** in situ. Intramolecular cyclization of the hydroxyl group to the epoxide, followed by decarboxylation and dehydration affords 3-phenylbenzofuran (**16**) (eq. 1, Scheme 2.3). Similarly, cyclization of 2-(2-bromophenyl)-1-phenylethanone (**17**) delivers the 2-phenylbenzofuran (**19**) in good yields with the participation of enolate intermediate **18** (eq. 2, Scheme 2.3).

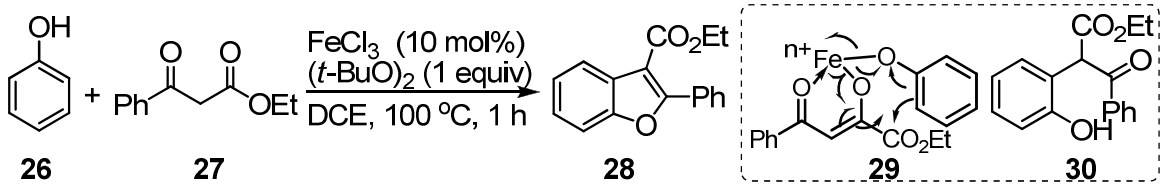


Scheme 2.4: Intramolecular cyclization of *o*-bromobenzylketones

The palladium catalyzed oxidative cyclization of *ortho*-disubstituted arene precursors such as 1,2-dihaloarenes and *o*-bromobenzyl bromides with ketones or aldehydes successfully delivered benzo[*b*]furans (Scheme 2.4).[7] The reaction initiates with the α-arylation of

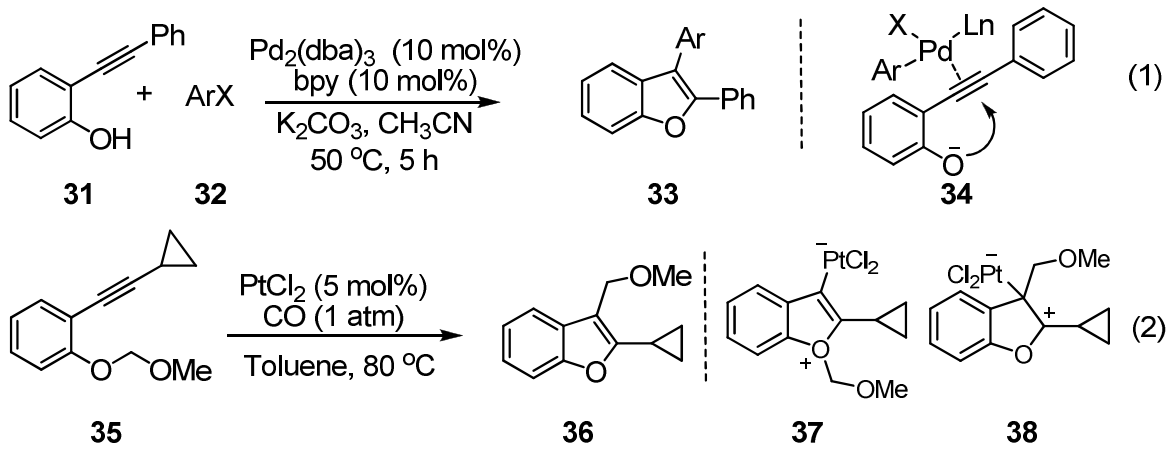
ketone; for instance: reaction of cyclohaxanone (**21**) with 1,2-dihaloarenes **20** provides substituted ketone **22**. Finally, intramolecular Pd-catalyzed cyclization of **22** produces benzofuran **23** (eq. 1, Scheme 2.4).[7] Similarly, the cyclization of *o*-bromobenzyl ketone **17**, obtained from *o*-bromobenzyl bromide (**24**) and benzaldehyde (**25**), gave **19** (eq. 2, Scheme 2.4).

A notable strategy for the single-step synthesis of polybenzofurans was reported utilizing the Fe-catalyzed oxidative Pechmann-type condensation of phenols (**26**) with β-keto esters (**27**) (Scheme 2.5).[8] The reaction proceeds via initial formation of Fe^{n+} intermediate **29**. The reductive elimination and tautomerization provides **30**. Finally, intramolecular condensation of **30** in the presence of iron catalyst generates benzofuran **28** in good yields. However, the mandatory requirement of an ester functionality does not allow accessing the 2,3-diarylbenzo[*b*]furans in this method.



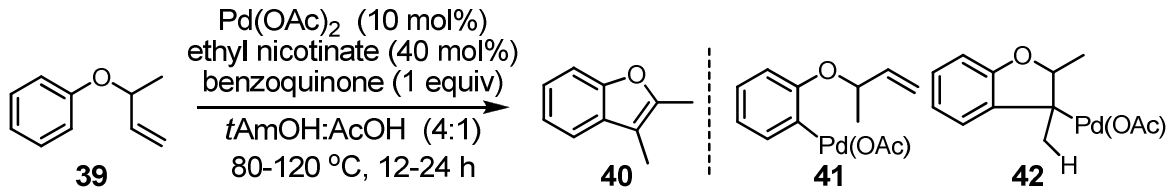
Scheme 2.5: Oxidative Pechmann type condensation of phenols with β–keto esters

The regioselective cyclization of *o*-alkynylphenols is one of the useful pathway for the synthesis of 2,3-disubstituted benzo[*b*]furans (Path III, Scheme 2.1).[9] As shown in eq. 1, Scheme 2.6, the reaction of aryl halides **32** with *o*-alkynylphenols (**31**) under the Pd-catalyst gave 2,3-di-susbtituted benzofurans **33**.[9i,9o] The reaction initiates with the oxidative addition of Pd(0) on aryl halide (**32**). Next, the coordination of ArPdLnX to unsaturated bond forms complex **34**. Finally, intramolecular nucleophilic attack of *ortho*-oxygen moiety to the activated carbon-carbon triple bond and reductive elimination results 2,3-diaryl-substituted benzofuran **33**. Similarly, intramolecular Pt-catalyzed carboalkoxylation of alkynes furnished the 2,3-disubstituted benzofurans (eq. 2, Scheme 2.6).[9l-m] Nucleophilic attack of the oxygen atom of the phenyl acetal moiety of **35** to Pt-activated triple bond gave **37**. The 1,3-migration of the methoxymethyl group to the carbon center generates the intermediate **38**; elimination of $PtCl_2$ finally deliver the product **36**.



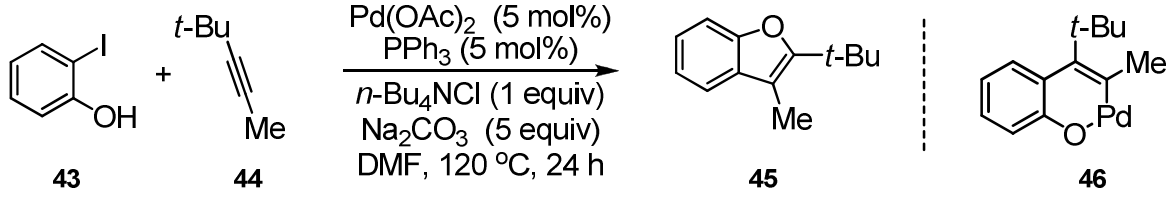
Scheme 2.6: Cyclization of *o*-alkynylphenols

Recently, Stoltz group and others have successfully used palladium-catalyzed oxidative cyclization of *o*-allylphenols for the synthesis of benzofurans (Scheme 2.7).[10] This Fujiwara-Moritani/oxidative Heck cyclization initiates through the formation of aryl-palladation **41**. The *syn*-olefin insertion to ArPd(OAc) in **41** then generates **42**; finally *syn*-β-hydride elimination of **42** followed by rearrangement deliver **40**.



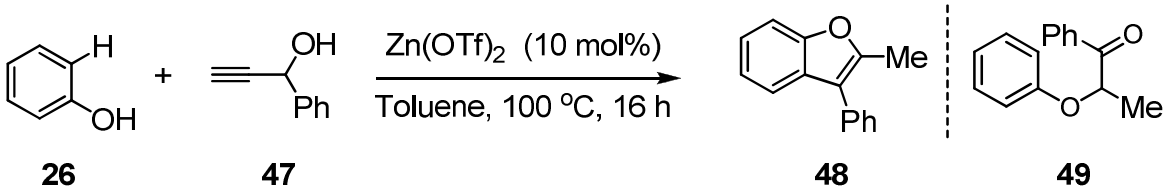
Scheme 2.7: Cyclization of *o*-allylphenols

Larock and others demonstrated an elegant approach to benzo[*b*]furans involving the Pd-catalyzed intermolecular cyclization of *ortho*-halogenated phenols with unactivated alkynes (Path IV, Scheme 2.1).[11] The reaction proceeds via the oxidative addition of the 2-iodophenol (**43**) with Pd(0), *syn*-insertion of arylpalladium to the alkyne, and the halide displacement on Pd with oxygen nucleophile to the formation of **46**. Finally, reductive elimination of the six membered palladacycle **46** provides **45** (Scheme 2.8).



Scheme 2.8: Larock benzofuran synthesis

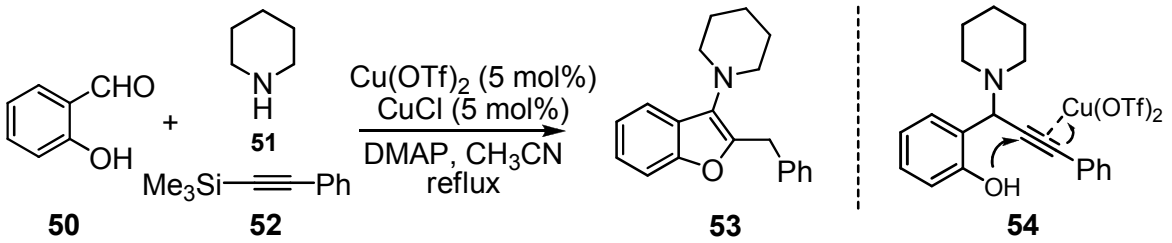
Recently, $Zn(OTf)_2$-catalyzed coupling and cyclization of phenols with terminal propargyl alcohols for the synthesis of 2-methyl-3-aryl-benzofurans was reported (Scheme 2.9).[11d] The activation of triple bond of **47** with $Zn(OTf)_2$ allows the attack of phenol to the C2-position of propargyl alcohol **47** and generates ketone **49**. Lewis acid assisted intramolecular cyclization of **49** forms **48**.



26 **47** **48** **49**

Scheme 2.9: Coupling of phenols with terminal propargyl alcohols

A facile and efficient transformation of poly functionalized benzofurans is realized from the three component coupling between *ortho*-hydroxybenzaldehye (**50**), secondary amines **51**, and alkynylsilane (**52**) with the aid of copper catalyst (Scheme 2.10).[11c] The Lewis acid $Cu(OTf)_2$ assists in the generation of iminium intermediate and facilitates the attack of the copper acetylide to form propargyl amine **54**. Finally, intramolecular 5-*exo*-dig attack of hydroxyl group to the Cu-activated-alkyne leads to **53**.



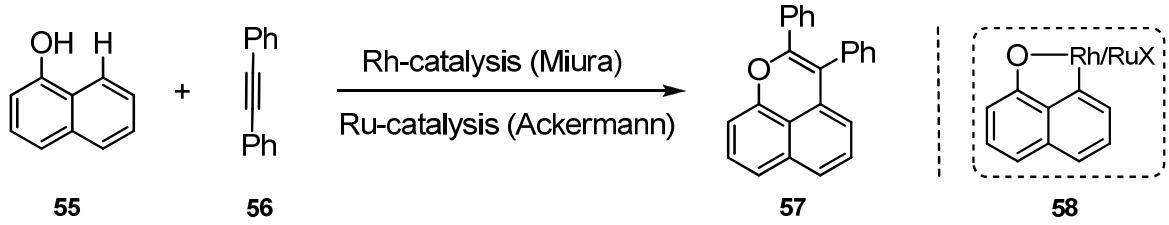
50 **52** **53** **54**

Scheme 2.10: Three component coupling of phenol, amine and alkyne

Although these developed approaches have expanded the synthetic versatility of the cyclization protocol for the synthesis of benzofurans, unfortunately, the synthetic potential of these strategies are limited by the requirement of functionalized precursors, such as halogen or alkynyl bearing substrates, which can only be obtained through specialized protocols involving multistep procedures.[5]

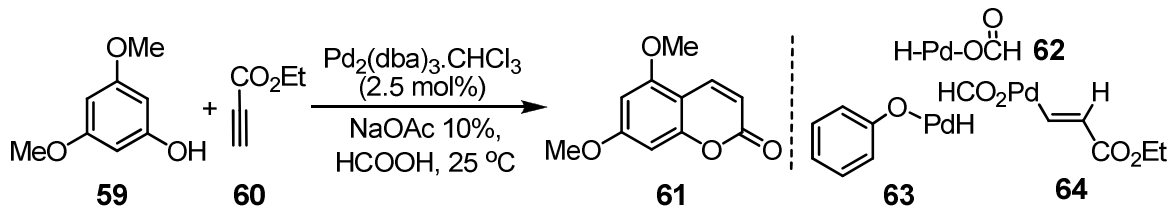
2.1.2. Background for Transition Metal (TM)-Catalyzed C–H Activation/C–O Bond Forming Reactions

The TM-catalyzed oxidative annulation of anilines/phenols/thiols with activated/ unactivated alkynes is the direct and ideal protocol for the synthesis of various heterocycles. These processes do not need the pre-activated substrates, thereby enhancing the efficiency of the method.[12] One such example is the Rh- and Ru-catalyzed oxidative annulation of α-naphthol (**55**) with diphenylacetylene (**56**) for the synthesis of naphthopyrans, independently reported by Miura and Ackermann groups (Scheme 2.11).[13] The hydroxyl directing group assists the cleavage of the C–H bond at the *peri*-position forming five membered rhodacycle **58.** The alkyne insertion on **58** followed by reductive elimination leads to naphthopyrans **57**.



Scheme 2.11: Oxidative coupling of 1-naphthol with internal alkynes

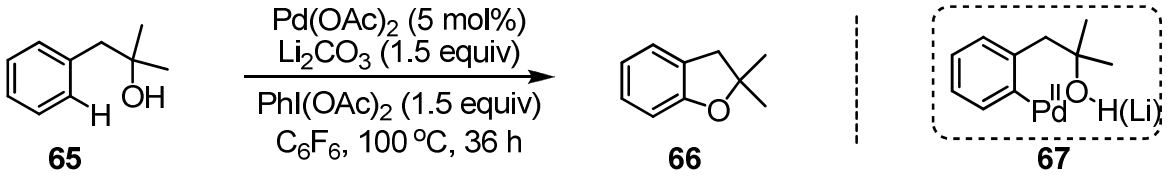
An interesting disclosure from Trost group demonstrates Pd-catalyzed annulation between phenols and alkynoates for the synthesis of coumarins.[14] The reaction initiates with the formation of hydropalladium intermediate **62** from Pd(0) and formic acid. The hydropalladium intermediate **62** reacts with alkyne **60** forming vinyl palladium intermediate **64**. The reaction of **64** with phenol (**59**) generates the *ortho*-hydroxyl cinnamate ester, which on lactonization delivers coumarin **61**. An alternate pathway for the formation of *ortho*-hydroxyl cinnamate ester involves the reaction of alkyne **60** with hydridopalladium phenoxide **63** (Scheme 2.12).



Scheme 2.12: Annulation of phenols with alkynoates

Recently, the Yu group reported the first example of an intramolecular aliphatic alcohol directed C–H activation/C–O cyclization method for dihydrobenzofurans **66** (Scheme

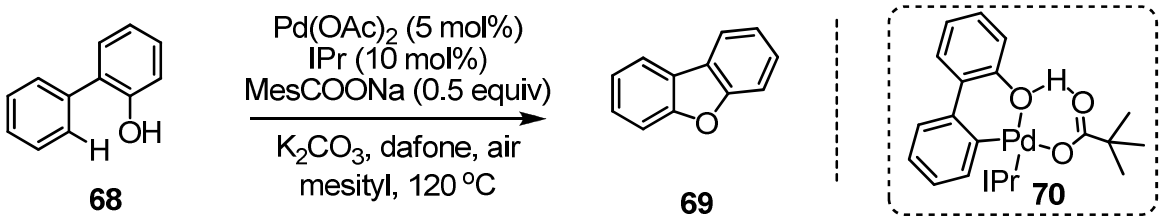
2.13).[15] The reaction initiates with the coordination of neutral σ-donor hydroxyl group to Pd(II); this provokes cleaving the proximal C–H bond towards the formation of the active intermediate **67**. Finally, the oxidation of Pd(II) to Pd(IV) and C–O reductive elimination of **67** deliver the dihydrobenzofuran product **66**.



65 66 67

Scheme 2.13: Intramolecular aliphatic alcohol directed C–H activation/C–O cyclization

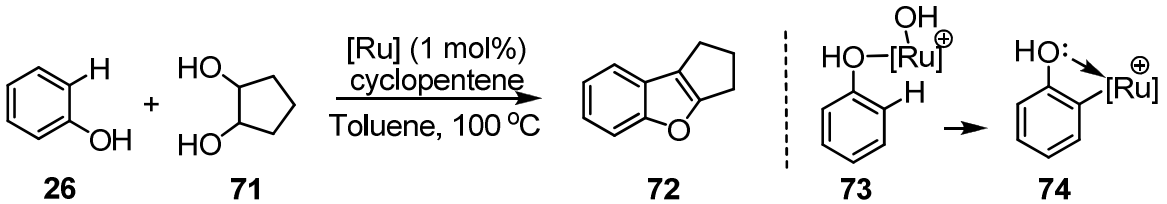
An efficient approach to dibenzofurans (**69**) is realized via intramolecular phenol directed C–H activation/C–O cyclization protocols from 2-phenylphenols (**68**) (Scheme 2.14).[16] With the isolation and X-ray crystallography characterization of the anionic pivolate ligand bearing four-coordinated Pd(II) complex **70**, it is believed that the in-situ generated catalyst **70** is actively participated in this reaction. The pivolate-group acts as a proton shuttle and promotes activating the neighboring C–H bond; this clearly reflects the coordination of phenol –OH group to Pd(II) as a neutral σ-donor.



68 69 70

Scheme 2.14: Intramolecular phenol directed C–H activation/C–O cyclization

The Ru-catalyzed dehydrative *ortho*-C–H alkenylation and cyclization of phenols (**26**) with 1,2-cycloalkanediols (**71**) is a direct route to benzofurans **72** disclosed from Yi-group recently (Scheme 2.15).[17] The reaction proceeds with the involvement of the cationic *ortho*-metalated Ru species **74**, derived from the activation of *ortho*-C–H bond of phenol.

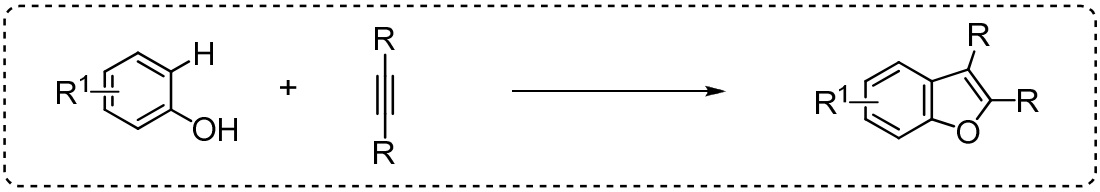


26 71 72 73 74

Scheme 2.15: Dehydrative cyclization of phenols with 1,2-diols

2.1.3. Problems and Design Plan

While the TM-catalyzed annulation between aniline and unactivated alkynes provides indole and its derivatives with ease,[12] a detailed survey of the literature reveals that the one-step synthesis of benzofurans from readily available phenols and unactivated alkynes has so far remained elusive untill 2012 (Scheme 2.16).



Scheme 2.16: Benzofurans from phenols and alkynes

Therefore, the TM-catalyzed C–H activation/C–O coupling reactions for the heterocycle synthesis is a challenging problem.

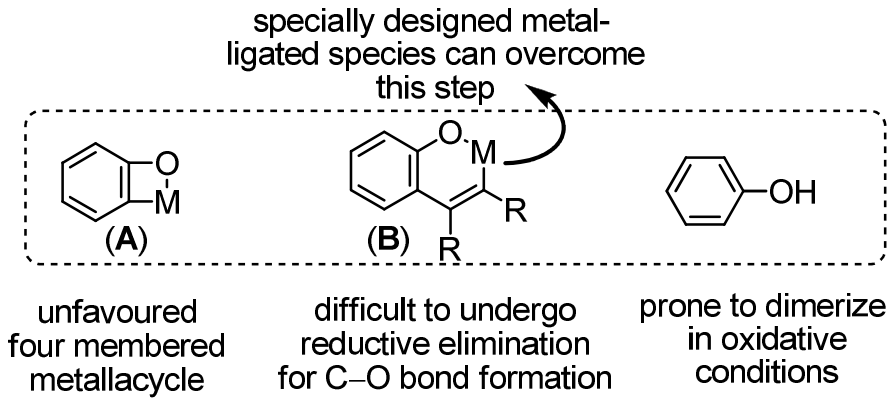


Figure 2.2: Cumulative Challenges

The reactivity of phenol toward unactivated alkynes presents the following challenges (Figure 2.2):

1) the participation of an unfavorable four-membered oxygen-metallacycle **A**,[18]

2) difficulties associated with the formation of the C–O bond through reductive elimination of the putative Pd(II) intermediates **B**,[19] and

3) sensitivity of phenols to strong oxidants, which undergo homocoupling in the presence of TM.[16a,20]

We thus became interested encountering this challenging problem. To find a reasonable solution, we envisioned the following possible pathways shown in Figure 2.3: *ortho*-metalation of the phenol with highly electrophilic TM species would generate the quinone-type intermediate C, which then would generate D by alkyne insertion. Finally, aromatization and reductive elimination of D would deliver the desired benzofuran. An alternative approach for benzofuran synthesis would involve alkyne insertion on the TM-aryloxide species E, to produce F, followed by *ortho*-C–H insertion of the TM and reductive elimination.

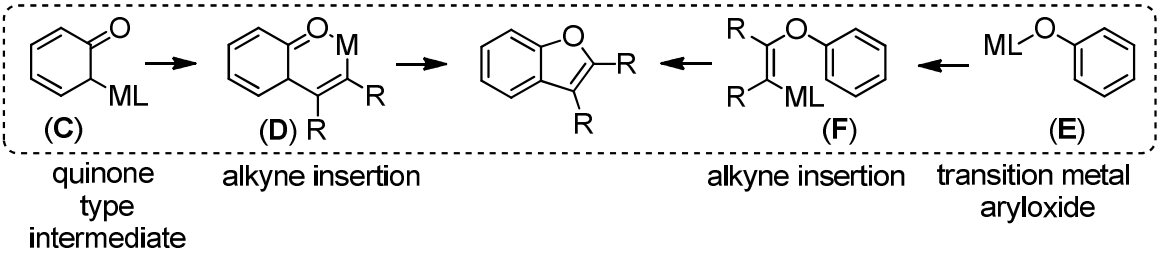


Figure 2.3: Plausible solutions

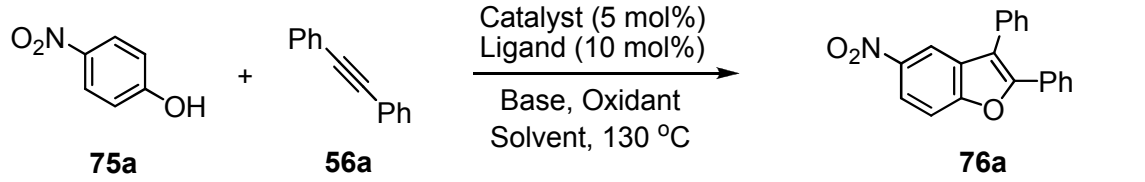
Despite these cumulative challenges, herein we report the development of an one-step synthetic protocol for benzo[*b*]furans by the palladium-catalyzed oxidative annulation of readily accessible phenols and unactivated internal alkynes.

2.2. Results and Discussion

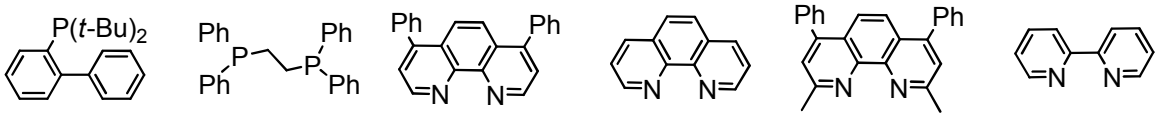
2.2.1. Reaction Optimization

We initiated our study by reacting 4-nitrophenol (**75a**) with diphenylacetylene (**56a**) in the presence of different combinations of palladium (Pd) catalysts and phosphine ligands as shown in Table 2.1. The preliminary effort resulted forming either dimerization of phenol/alkyne or no reaction, when the reaction conducted in the presence of $Pd(OAc)_2$, JohnPhos (L1)/dppe (L2) ligands, K_2CO_3/Ag_2CO_3 bases, and $Cu(OAc)_2{\cdot}H_2O$ oxidant in 1,4-dioxane (entries 1 and 2). The reactions were performed at 130 °C in this optimization studies. Screening of various catalytic conditions led us to observe that the phosphorus ligands are not suitable. Recently, nitrogenous ligands were extensively employed for the aerobic oxidation reactions;[21] these ligands help in reducing the formation of palladium black and facilitate the C–O reductive elimination. To our delight, the desired bezofuran product 5-nitro-2,3-diphenylbenzofuran (**76a)** was noticed by GC, when Pd(0)-catalyst was employed in combination with the bidentate nitrogen-containing ligands.

Table 2.1: Reaction between 4-nitrophenol and diphenylacetylene: Optimization studies[a]



75a **56a** **76a**



L1 JohnPhos | L2 dppe | L3 Bathophen | L4 1,10-phen | L5 Bathocuproine | L6 2,2'-bipy

entry	catalyst	ligand	base	oxidant	solvent	yield of **76a**(%)[b]
1	$Pd(OAc)_2$	L1	K_2CO_3	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.
2	$Pd(OAc)_2$	L2	Ag_2CO_3	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.
3	$Pd_2(dba)_3$	L3	Ag_2CO_3	AgOAc	1,4-dioxane	40
4	$Pd_2(dba)_3$	L3	Ag_2CO_3	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	60
5	$Pd_2(dba)_3$	L3	K_2CO_3	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.
6	$Pd_2(dba)_3$	L3	Na_2CO_3	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.
7	$Pd_2(dba)_3$	L3	Cs_2CO_3	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.
8	$Pd_2(dba)_3$	L3	K_3PO_4	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.
9	**$Pd_2(dba)_3$**	**L3**	**AgOAc**	**$Cu(OAc)_2 \cdot H_2O$**	**1,4-dioxane**	**100 (92)[c]**
10	$Pd_2(dba)_3$	L4	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	90
11	$Pd_2(dba)_3$	L5	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	10
12	$Pd_2(dba)_3$	L6	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	trace
13	$Pd_2(dba)_3$	L3	AgOAc	$K_2S_2O_8$	1,4-dioxane	trace
14	$Pd_2(dba)_3$	L3	AgOAc	Oxone	1,4-dioxane	trace
15	$Pd_2(dba)_3$	L3	AgOAc	$PhI(OAc)_2$	1,4-dioxane	n.d.
16	$Pd_2(dba)_3$	L3	AgOAc	$Cu(OAc)_2$	1,4-dioxane	trace
17	$Pd_2(dba)_3$	L3	AgOAc	TEMPO	1,4-dioxane	20
18	$Pd_2(dba)_3$	L3	AgOAc	O_2 (1 atm)	1,4-dioxane	20
19	$Pd(dba)_2$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	trace
20	$Pd(PPh_3)_4$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	30
21	$Pd(OAc)_2$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	60
22	$Pd_2(dba)_3$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	DMF	n.d.
23	$Pd_2(dba)_3$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	DMSO	n.d.
24	$Pd_2(dba)_3$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	CH_3CN	n.d.
25	$Pd_2(dba)_3$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	Toluene	20
26	$Pd_2(dba)_3$	--	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.
27	--	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	n.d.

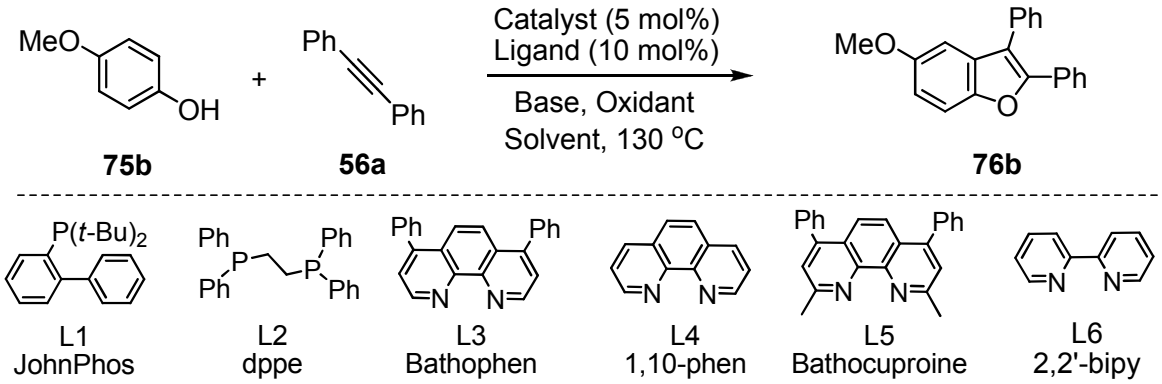
[a] Reaction conditions: **75a** (2.0 equiv), **56a** (20 mg, 1.0 equiv, 0.11 mmol), catalyst (5.0 mol%), ligand (10 mol%), base (2.0 equiv), oxidant (2.0 equiv), and solvent (2.0 mL) at 130 °C for 24–48h. [b] Conversion based on crude GC using dodecane as internal standard. [c] Yield of isolated product on 1.0 mmol scale. n.d. = not detected.

For example: the catalytic condition comprising of $Pd_2(dba)_3$, bathophenanthroline (L3), Ag_2CO_3, and AgOAc oxidant in dioxane produced **76a** in 40% yield (entry 3). Interestingly, the use of $Cu(OAc)_2{\cdot}H_2O$ oxidant and Ag_2CO_3 base under the identical conditions led to produce **76a** with enhanced yield (entry 4). The oxidants, bases, and solvents play critical role to the reactivity; we therefore examined the effect of these reagents. Inorganic bases such as K_2CO_3, Na_2CO_3, Cs_2CO_3 and K_3PO_4 were totally ineffective (entries 5–8), whereas AgOAc was superior producing **76a** in 92% isolated yield (entry 9). We then examined the effect of ligands in this transformation. Examination of other bidented ligands revealed that the 1,10-phenanthroline (L4) was equally efficient (entry 10), while bathocuproine (L5) and 2,2'-bipyridyl (L6) produced trace amount of **76a** (entries 11 and 12). The oxidants $K_2S_2O_8$, oxone, $PhI(OAc)_2$, $Cu(OAc)_2$ were ineffective (entries13–16). The desired product was observed in 20% yield, when TEMPO and O_2 (1 atm) were used as oxidants (entries 17 and 18). Other Pd(0)-catalysts such as $Pd(dba)_2$ and $Pd(PPh_3)_4$ were ineffective (entries 19 and 20), whereas the Pd(II) precursor $Pd(OAc)_2$ produced 60% of **76a** (entry 21). Next, we examined the effect of solvent. The strong coordinating solvents like DMF, DMSO and CH_3CN were failed to produce the desired product (entries 22–24). The reaction in toluene delivers 20% of **76a** (entry 25). Therefore, 1,4-dioxane was found optimal in this reaction (entry 9). The Pd(0)-catalysts and the N-bearing bidentate ligands are pivotal to this transformation; the product **76a** was not produced in the absence of either of $Pd_2(dba)_3$ or L3 (entries 26 and 27).

Recently, we have demonstrated the hydrophenoxylation of electron-rich and electron-poor phenols with unactivated internal alkynes for the synthesis of arylvinyl ethers (the results are discussed in Chapter 1).[22] The acidity of the phenol plays crucial role in this reaction, provoking the requirement of the different combination of base and solvent for this reaction to proceed. We thus studied the reaction between the electron-rich 4-methoxyphenol (**75b**) and **56a** under the optimized conditions shown in entry 9, Table 2.1. Indeed only a trace amount of desired benzofuran 5-methoxy-2,3-diphenylbenzofuran (**76b**) was noticed by GC (entry 1). Thus, various combinations of bases, catalysts, ligands and solvents were screened to find the acceptable catalytic conditions for the synthesis of **76b** (Table 2.2). Among the bases examined, use of NaOAc instead of AgOAc resulted **76b** in 20% yield (entry 2), whereas other bases KOAc and CsOPiv were ineffective (entries 3 and 4). Yield of **76b** was marginally enhanced to 25%, when L4 was employed

in the presence of NaOAc base (entry 5), wherein other ligands were not successful (entries 6 and 7). Under the prevailing oxidative conditions, we observed the formation of substantial amounts of alkyne-dimerization product in most cases. Interestingly, performing the reaction with 4.0 equiv of phenol afforded **76b** in 40% yield (entry 8). Notably, the efficiency of the reaction was significantly enhanced with the formation of 88% **76b**, when an increased amount of 4-methoxyphenol (5.0 equiv) with respect to **56a** (1.0 equiv) was used (entry 9). Under this condition, formation of alkyne dimerization product was dramatically reduced. The catalyst $Pd(OAc)_2$ was found to be moderate, under the identical conditions (entry 10).

Table 2.2: Reaction between 4-methoxyphenol and diphenylacetylene: Optimization studies.[a]



entry	catalyst	ligand	base	oxidant	solvent	yield of **76b**(%)[b]
1	$Pd_2(dba)_3$	L3	AgOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	trace
2	$Pd_2(dba)_3$	L3	NaOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	20
3	$Pd_2(dba)_3$	L3	KOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	trace
4	$Pd_2(dba)_3$	L3	CsOPiv	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	trace
5	$Pd_2(dba)_3$	L4	NaOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	25
6	$Pd_2(dba)_3$	L5	NaOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	trace
7	$Pd_2(dba)_3$	L6	NaOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	10
8[c]	$Pd_2(dba)_3$	L4	NaOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	40
9[d]	**$Pd_2(dba)_3$**	**L4**	**NaOAc**	**$Cu(OAc)_2 \cdot H_2O$**	**1,4-dioxane**	**100 (88)[e]**
10[d]	$Pd(OAc)_2$	L4	NaOAc	$Cu(OAc)_2 \cdot H_2O$	1,4-dioxane	100 (51)[e]

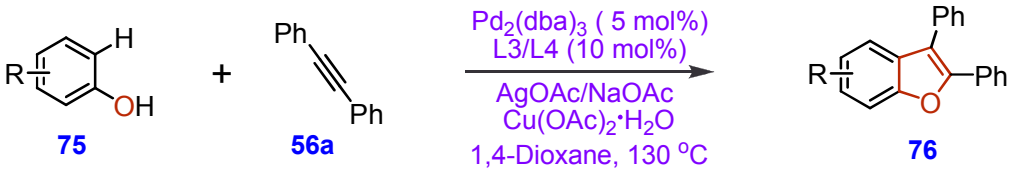
[a] Reaction conditions: **75b** (2.0 equiv), **56a** (20 mg, 1.0 equiv, 0.11 mmol), catalyst (5.0 mol%), ligand (10 mol%), base (2.0 equiv), oxidant (2.0 equiv), and solvent (2.0 mL) at 130 °C for 24–48h. [b] Conversion based on crude GC using dodecane as internal standard. [c] **75b** (4.0 equiv) and base (4.0 equiv) was used. [d] **75b** (5.0 equiv) and base (5.0 equiv) was used. [e] Yield of isolated product on 1.0 mmol scale. n.d. = not detected.

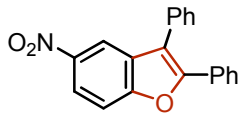
An extensive screening of various combinations of catalysts, bases and oxidants led to an effective catalytic systems [Condition A: $Pd_2(dba)_3$, L3 (bathophenanthroline), AgOAc base, and $Cu(OAc)_2 \cdot H_2O$ oxidant in 1,4-dioxane at 130 ºC] for the preparation of **76a** (92% yield) from the [3+2] annulations between the activated *p*-nitrophenol and unactivated internal diphenyl acetylene as shown in the entry 9, Table 2.1. The Condition B comprising of [$Pd_2(dba)_3$, L4 (1,10-phenanthroline), NaOAc base, and $Cu(OAc)_2 \cdot H_2O$ oxidant in 1,4-dioxane at 130 ºC] is selected for the preparation of **76b** (88% yield) from the [3+2] annulations between the non-activated *p*-methoxyphenol and internal diphenylacetylene as shown in the entry 9, Table 2.2.

2.2.2. Scope of the Reaction

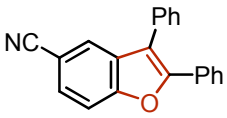
Having the optimized reaction conditions in hand, we next turned our attention to explore the scope and functional group tolerance of this transformation. Table 2.3 summarizes the annulation of various phenols with diphenylacetylene (**56a**). The substrate containing highly electron withdrawing nitro group, 4-nitrophenol (**75a**) reacted with **56a** produced nitro-substituted benzofuran **76a** in excellent yield under the condition A in 24 h. Previously known methods for the synthesis of nitrobenzofurans involves multiple steps with overall poor yield showing the efficiency of the present reaction conditions.[23] The presence of cyano group on phenol **75c** did not affect the reaction outcome, providing **76c** in 70% yield. Next the phenols bearing keto (**75d**), aldehyde (**75e**), or ester (**75f**) functional groups were subjected to annulate with **56a**. Interestingly, these common functional groups were inert to the reaction conditions, and the desired benzofuran products **76d**, **76e** and **76f** were isolated in good yields. The conditions B were found superior over conditions A in case of the reactions of 4-hydroxybenzaldehyde (**75e**) or 4-hydroxy methylbenzoate (**75f**) with **56a**; the reason to this observation is unclear. Interestingly, the halogen functional groups (F and Cl) containing 4-fluorophenol (**75g**) / 4-chlorophenol (**75h**) reacted with **56a** under the conditions B delivering the desired benzofurans **76g** (74%) and **76h** (53%), respectively. X-Ray crystallographic analysis confirms the structure of **76g** (Figure 2.5). Next we investigated the relative stability of common N- and O-protecting groups under the current catalytic conditions. Unfortunately, the 4-aminophenol (**75i**) or N-methyl-4-aminophenol (**75j**) failed to react with **56a** under the present reaction conditions.

Table 2.3: Substrate scope of phenols.[a]

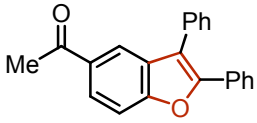




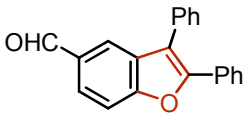
76a, 92%, A, 24 h



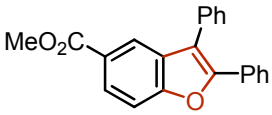
76c, 70%, A, 24 h



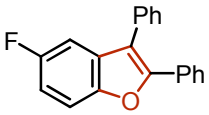
76d, 52%, A, 48 h



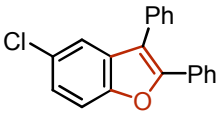
76e, 90%, B, 48 h



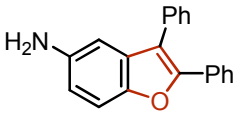
76f, 61%, B, 48 h



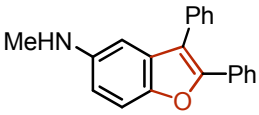
76g, 74%, B, 24 h



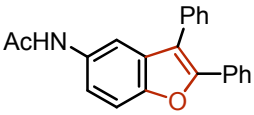
76h, 53%, B, 24 h



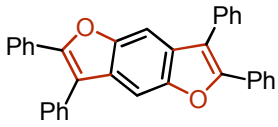
76i, 0 %



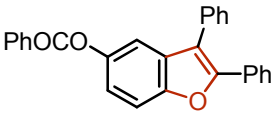
76j, 0 %



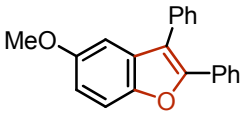
76k, 60%, B, 48 h



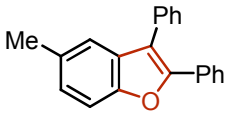
76l, complex mixture



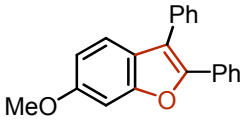
76m, 50%, B, 24 h



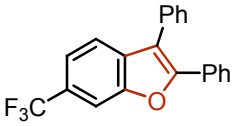
76b, 88%, B, 24 h



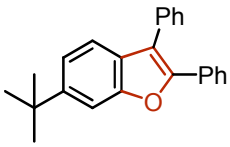
76n, 70%, B, 24 h



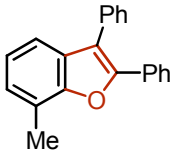
76o, 90%, B, 24 h



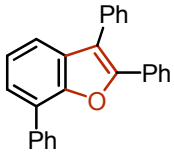
76p, 54%, B, 24 h



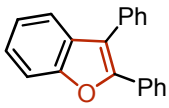
76q, 55%, B, 24 h



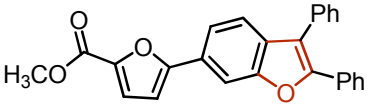
76r, 45%, B, 48 h



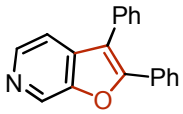
76s, 34%, B, 48 h



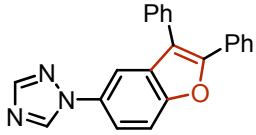
76t, 22%, A, 72 h



76u, 91%, B, 72 h



76v,0%, B, 72 h



76w, 0%, B, 72 h

[a] Reaction conditions A: **75** (2.0 equiv), **56a** (178 mg, 1.0 equiv, 1.0 mmol), $Pd_2(dba)_3$ (5.0 mol%), L3 (10 mol%), AgOAc (2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), and 1,4-dioxane (8.0 mL) at 130 °C; conditions B: **75** (5.0 equiv), **56a** (178 mg, 1.0 equiv, 1.0 mmol), $Pd_2(dba)_3$ (5.0 mol%), L4 (10 mol%), NaOAc (2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), and 1,4-dioxane (8.0 mL) at 130 °C.

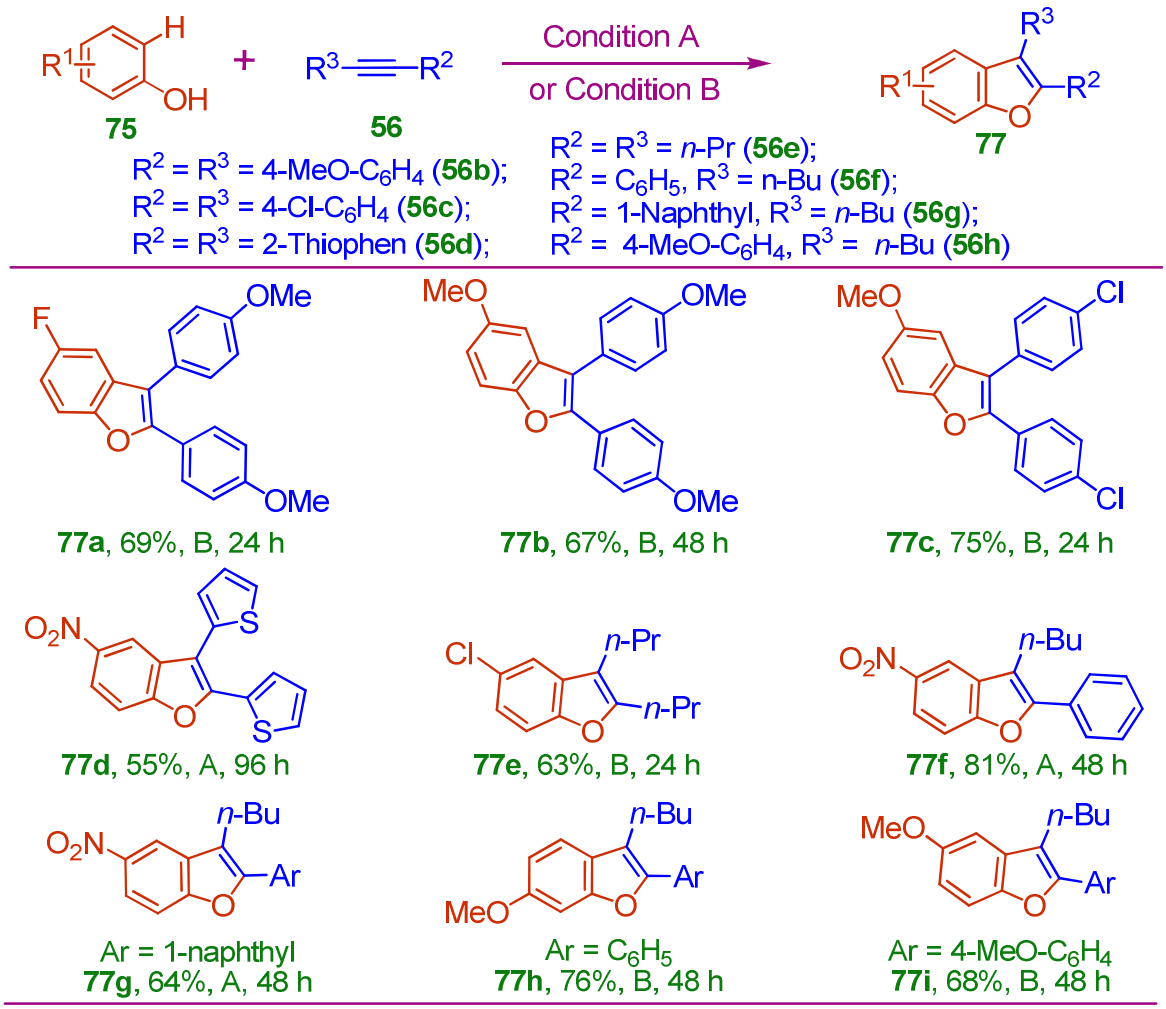
Gratifyingly, the annulation between *N*-acetyl-4-aminophenol (**75k**) and **56a** proceeded smoothly under the conditions B, leaving the *NHAc moiety untouched*, and the desired benzofuran **76k** was exclusively isolated in 60% yield. We envisioned enlarging the molecular diversity by the reaction of hydroquinone (**75l**) with **56a** under the conditions B; however, we could not isolate the product with multiple benzofurans on hydroquinone from the complicated reaction profile. To our delight, the benzofuran product **76m** was obtained from the mono-O-benzoyl protected hydroquinone (**75m**) and **56a** in good yield with the O-benzoate *protecting group intact* under the conditions B.

Excellent yields were obtained when the electron-rich 4-methoxyphenol (**75b**) and 4-methylphenol (**75n**) were independently reacted with **56a** under the conditions B and provided **76b** and **76n** in 88% and 70% yields, respectively. Remarkably, the *meta*-substituted phenols **75o**, **75p** and/or **75q** were efficiently annulated with **56a**, and the corresponding highly regioselective benzofuran products **76o**, **76p** and **76q** were produced through the formation of C–C bonds at the less hindered side of the phenol (Table 2.3).

Because of the steric effects, the reaction of 5**6a** with the structurally demanding *ortho*-substituted 2-methylphenol (**75r**) and 2-phenylphenol (**75s**) led to moderate amounts of the corresponding benzofurans **76r** and **76s** as expected. In contrast, the electron neutral phenol (**75t**) reacted sluggishly even with the prolonged reaction time with **56a** under both the optimized conditions, providing poor yield of **76t**. Heterocyclic core contained phenol **75u** efficiently annulated with **56a** and afforded **76u** in 91% yield. However, the other N-containing heterocyclic substrates such as 3-hydroxypyridine (**75v**) and 4-(1H-1,2,4-triazol-1-yl)phenol (**75w**) were unsuccessful under the present optimized reaction conditions, presumably because of the strong co-ordination ability of the nitrogen atom.

To further demonstrate the scope of the reaction, we next examined the effect of electron-rich and electron–deficient aryl substituted alkynes (Table 2.4). Reaction of electron-rich 4-methoxyphenyl substituted alkyne **56b** with electron deficient 4-fluorophenol (**75f**) or electron rich 4-methoxyphenol (**75b**) proceeds smoothly producing **77a** and **77b** in 69% and 67% yields, respectively. Similarly, the electron-poor 4-chlorophenyl substituted alkyne **56c** underwent annulation with electron rich 4-methoxyphenol (**75b**) efficiently giving **77c** in 75% yield. Symmetrical heteroaromatic alkyne 1,2-di(thiophen-2-yl)ethyne (**56d**) was efficiently reacted with **75a** resulting in **77d** in 55% yield, under the conditions B. Lack of conjugation makes the alkyl-substituted alkyne relatively less reactive compared to aryl alkynes.[24]

Table 2.4: Substrate scope of alkynes.[a]



[a] Reaction conditions A: **75** (2.0 equiv), **56** (1.0 equiv), $Pd_2(dba)_3$ (5.0 mol%), L3 (10 mol%), AgOAc (2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), and 1,4-dioxane (8.0 mL) at 130 ^oC; conditions B: **75** (5.0 equiv), **56** (1.0 equiv), $Pd_2(dba)_3$ (5.0 mol%), L4 (10 mol%), NaOAc (2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), and 1,4-dioxane (8.0 mL) at 130 ^oC.

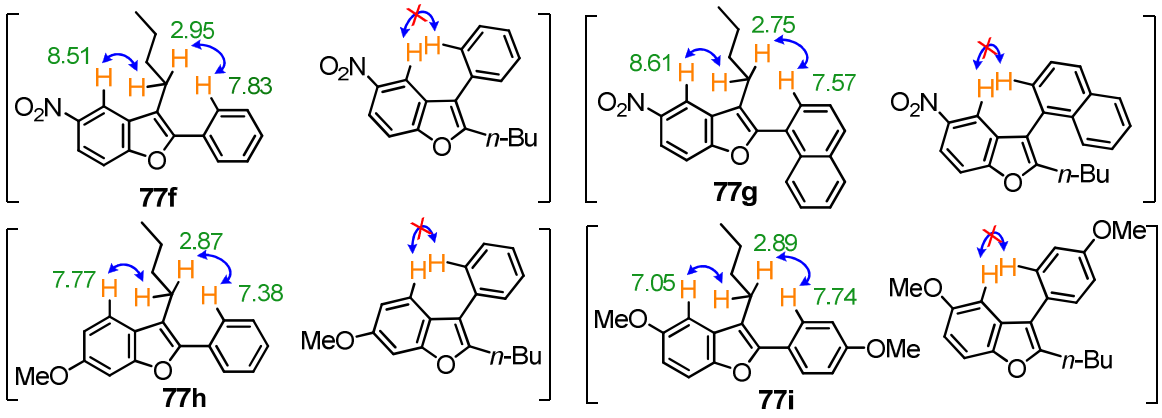
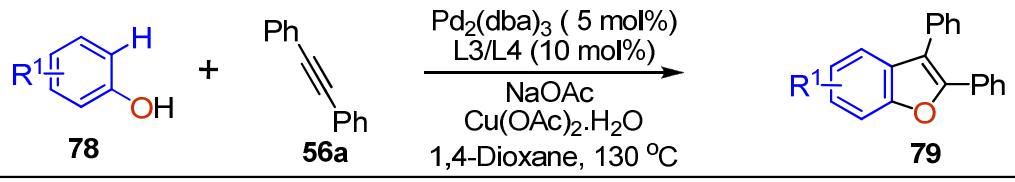


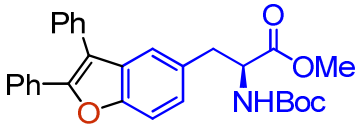
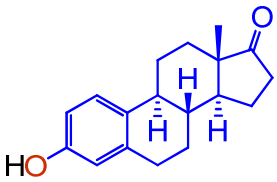
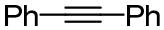
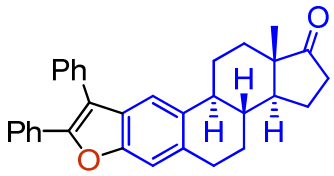
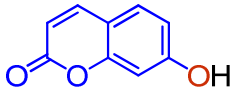
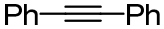
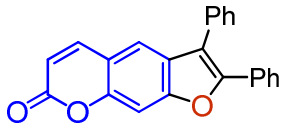
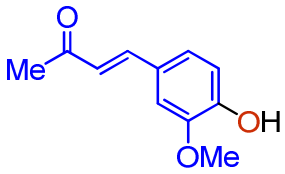
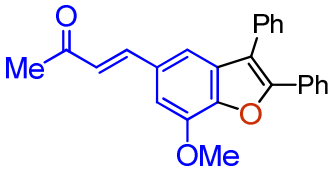
Figure 2.4: NOESY studies

To study the effect of the present conditions on alkyl substituted alkynes, 4-octyne (**56e**) was therefore subjected to this transformation. Interestingly, the desired 2,3-dialkyl substituted benzofuran **77e** was delivered from 4-chlorophenol (**75h**) in 63% yield under conditions B. Gratifyingly, highly regioselective benzofurans were formed when alkyl-aryl substituted unsymmetrical alkynes were employed. When phenyl and *n*-butyl substituted alkyne **56f**, was reacted with 4-nitrophenol (**75a**), 3-butyl-5-nitro-2-phenylbenzofuran (**77f**) was obtained exclusively in 81% yield. The structure of **77f** is established based on the NOESY studies (Figure 2.4) and X-ray diffraction analysis (Figure 2.5). NOE between δ8.51 (s) and δ2.95 (t); δ7.83 (d) and δ2.95 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed (Figure 2.4). This establishes the structure of regioisomer **77f**. The use of bulky internal alkyne, such as 1-(hex-1-ynyl)naphthalene (**56g**) did not affect the regioselectivity, giving **77g** in 64% yield. NOE between δ8.61 (bd) and δ2.75 (t); δ7.57 (m) and δ2.75 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed; accordingly the structure of regioisomer **77g** is established (Figure 2.4). Similarly, the desired regioselective product **77h** was isolated in the reaction of *meta*-substituted 3-methoxy-phenol (**75o**) with **56f**. NOE between δ7.77 (bd) and δ2.87 (t); δ7.38 (bd) and δ2.87 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed; accordingly the structure of regioisomer **77h** is determined (Figure 2.4). Both electron rich 4-methoxyphenol (**75b**) and 1-(hex-1-ynyl)-4-methoxybenzene (**56h**) were reacted to produce **77i** in good yield. NOE between δ7.05 (bs) and δ2.89 (t); δ7.74 (bd) and δ2.89 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed; this establishes the structure of regioisomer **77i** (Figure 2.4). We were pleased to observe that our results consistently agree with the observations of the groups of Larock and Fagnou: [11g,24] the aryl-moiety is incorporated adjacent to the oxygen functionality in benzofurans. Unfortunately, with present reaction conditions terminal alkynes were incompatible and largely produced the corresponding alkyne homocoupling products.[24]

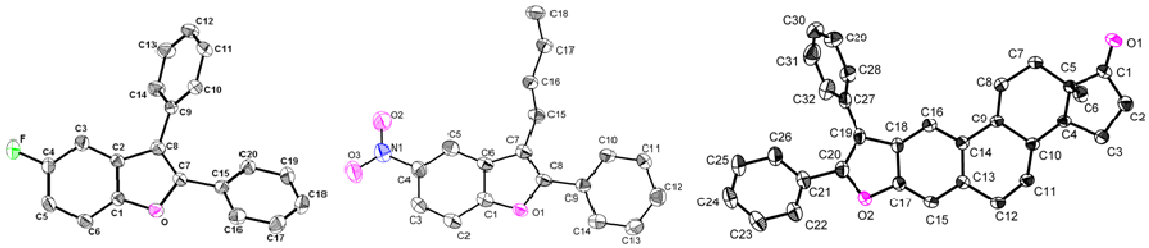
Encouraged by the wide substrate scope of phenols and alkynes, the synthetic potential of this strategy was examined by various complex phenol derivatives of pharmaceutical importance (Table 2.5). The amino acid derivative *N*–Boc–L–tyrosine methyl ester (**78a**) successfully underwent annulation with **56a** and the desired benzofuran derivative **79a** was isolated in 65% yield.[25a]

Table 2.5: Derivatives of biologically important molecules[a]



entry	phenol	alkyne	product
1	 **78a**	 **56a**	 **79a**, 65%, B, 48 h
2	 **78b**	 **56a**	 **79b**, 62%, B, 48 h
3	 **78c**	 **56a**	 **79c**, 53%, B, 72 h
4	 **78d**	 **56a**	 **79d**, 30%, B, 96 h

[a] Reaction conditions B: **78** (5.0 equiv), **56** (1.0 equiv), $Pd_2(dba)_3$ (5.0 mol%), **L4** (10 mol%), NaOAc (5.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), and 1,4-dioxane (8.0 mL) at 130 °C.

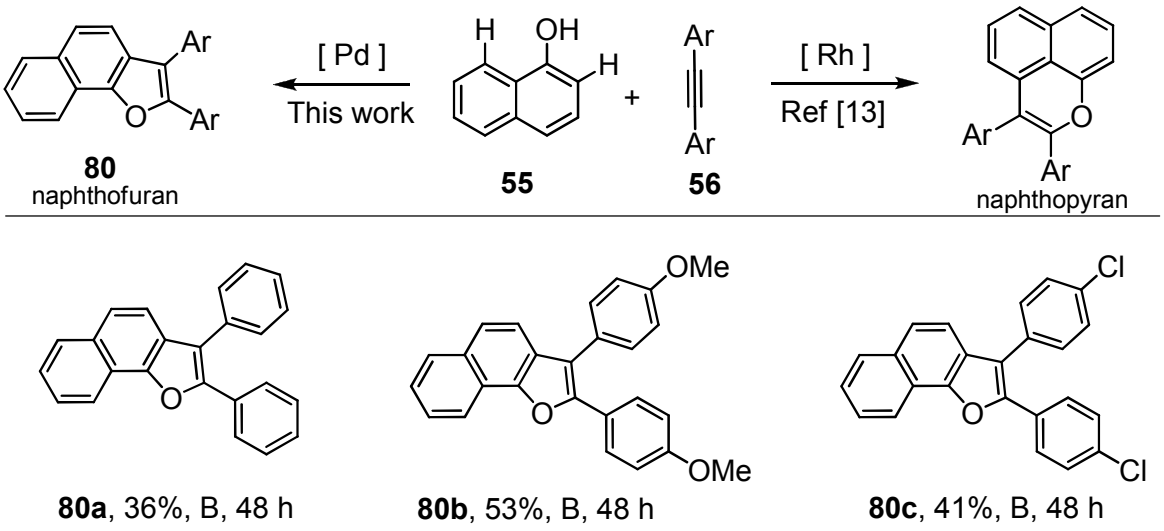


76g **77f** **79b**

Figure 2.5: ORTEP diagrams of **76g**, **77f** and **79b** with 30% probability level except for the H atoms, which are omitted for the clarity.

Gratifyingly, the base mediated reactions did not affect the stereointegrity of the L-tyrosine even at the elevated temperature. The estrone (**78b**), despite its complex structure, when reacted with **56a** smoothly underwent annulation furnished **79b** in good yield.[25b] The coumarin derivative umbelliferone (**78c**) reacted with **56a**, resulting **79c** in moderate amount.[25c] Notably, the present reaction conditions did not affect the lactone functionality of coumarin. Pleasingly, the *ortho*-substituted vanillylidenacetone (**78d**), the chief constituent of the fragrant vanilla derivative,[25d] reacted sluggishly with **56a** providing **79d** in poor yield, as a consequence of the *ortho*-substituted phenols.

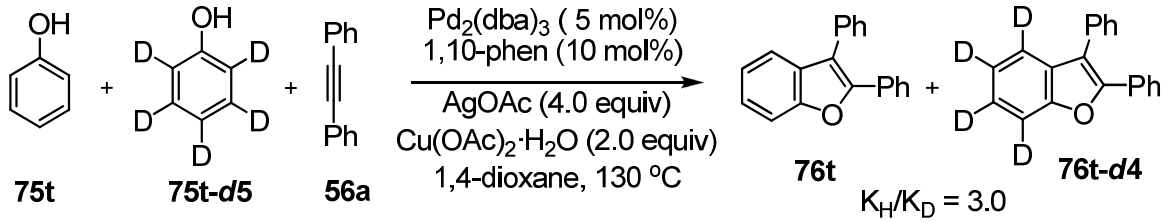
The interesting results by Miura and Ackermann groups demonstrate the synthesis of naphthopyrans through the Rh- and Ru-catalyzed oxidative annulation between α-naphthol and alkynes, respectively.[13] Therefore, we have applied our optimized reaction conditions to these substrates; to our delight naphthofurans were obtained in contrast to naphthopyrans. Under the catalytic conditions B, when α-naphthol (**55**) reacted with **56a**, the naphthofuran product **80a** was exclusively isolated, albeit in poor yield (Scheme 2.17).[13] Pleasingly, with an electron-rich alkyne **56b**, an enhanced yield of the desired naphthofuran **80b** was obtained. Similarly, the electron-poor alkyne **56c** reacted with **55** under the conditions B and delivered the napthofuran **80c** in moderate yield. Thus, two distinct products can be produced independently under Rh or Pd catalysis.



Scheme 2.17: Switching the site selectivity. Reaction conditions B summarized in Table 2.3

2.2.3. Mechanistic Studies

To gain insight into the reaction mechanism, we envisaged performing the deuterium labeling experiment to find the involvement of C–H bond cleavage. Thus, we performed an intermolecular kinetic isotope experiment involving phenol (**75t**) and phenol-d5 (**75t-*d*5**) (1:1). As shown in Scheme 2.18, reaction among **75t**, **75t-*d*5**, and **56a** was carried out under the standard reaction conditions B for 24 h. Interestingly, a significant kinetic isotope effect was observed (K_H/K_D = 3.0). This observation supports the participation of Pd-mediated C–H bond cleavage in the mechanistic cycle.[26]

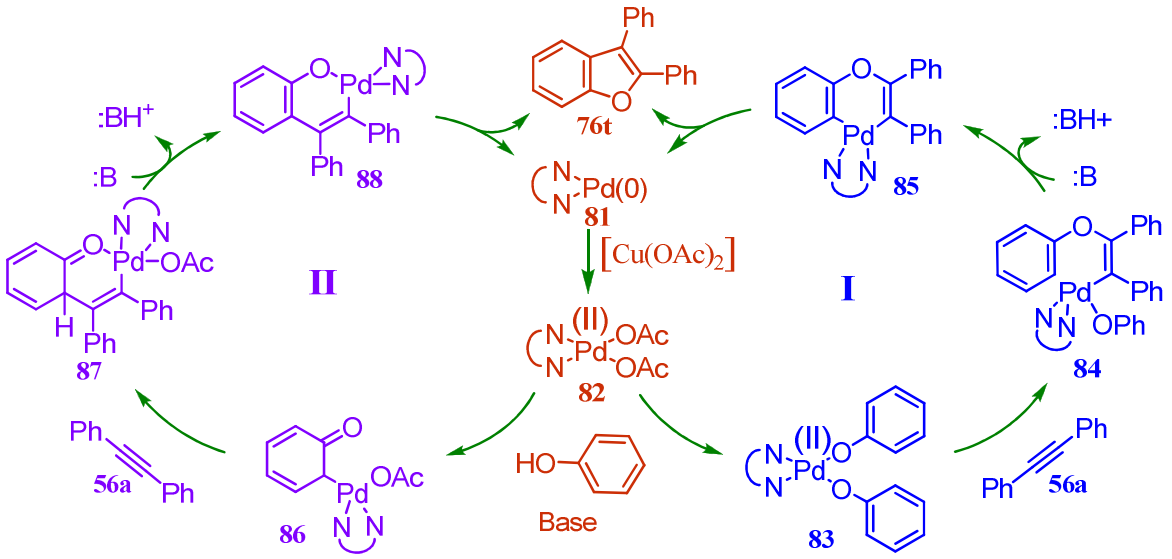


Scheme 2.18: Kinetic isotope study

Based on this KIE data and literature precedence, a plausible mechanism is shown in Scheme 2.19. The reaction proceeds with Pd(II) as well as Pd(0) sources as shown in optimization studies. It is well known that Pd(0) is readily oxidized to Pd(II) in the presence of $Cu(OAc)_2$. Therefore, we assumed that the reaction is initiated by Pd(II) intermediate, even though a Pd(0) source was used under optimized reaction conditions.[14] Thus, coordination of the N-bearing bidentate ligand to $Pd_2(dba)_3$, followed by $Cu(OAc)_2$ assisted oxidation of **81** generates the active Pd(II) species **82**.

At this stage, attack of phenol onto the electrophilic Pd(II) species may occur in two different ways. Mechanistic cycle I (Scheme 2.19) involves the attack of phenol onto **82** to produce Pd(II)-phenoxide species **83** and liberate AcOH.[27] Subsequently, the coordination of the alkyne to **83** would induce its phenoxypalladation to afford **84**. Base-assisted intramolecular *ortho*-C–H insertion by the Pd catalyst then leads to **85**. Finally, reductive elimination delivers the desired benzofuran product **76t** and regenerates the Pd(0) species for the next catalytic cycle. On the other hand, mechanistic cycle II involves the *ortho*-palladation of phenol by electrophilic Pd(II)-species **82**, gives the quinone-type intermediate **86**.[14,28] Alkyne coordination followed by carbopalladation then affords **87**,

whereupon base-induced rearomatization yields **88**. The catalytic cycle is completed by the liberation of the product along with Pd(0) through reductive elimination of **88**.

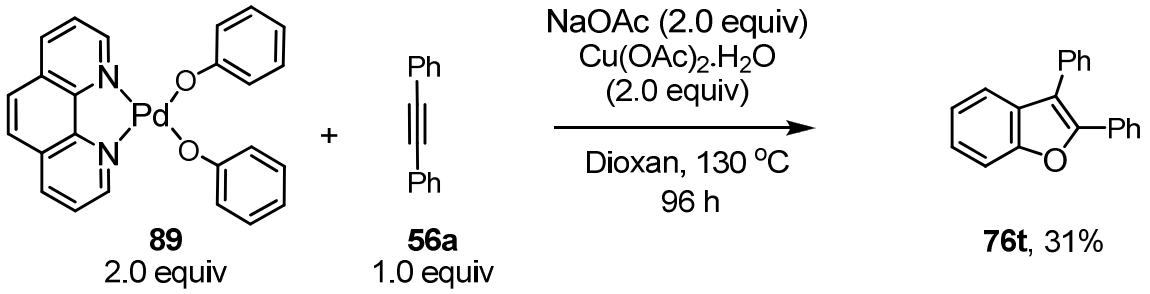


Scheme 2.19: Proposed mechanistic cycle

Even though the TM–oxygen bond is relatively weak, late-TM alkoxides and phenoxides have successfully been employed in various metal-catalyzed organic transformations.[27] The van Koten group[27] and others recently demonstrated elegant methods for the synthesis of TM alkoxides and phenoxides. Theoretical calculations have predicted the existence and relative strength of M–O bonds.[28] Importantly, the strength of the M–O bond depends solely on the electron density that is present on the oxygen; electron-withdrawing groups on the phenol lower electron-donation of oxygen to the metal, forming a weak M–O bond. In contrast, electron-donating groups on phenol increase electron density on oxygen, forming a strong M–O bond. Furthermore, hydrogen bonding between phenol and metal phenoxide is crucial in the formation of bis(phenol) adducts, so that an additional amount of phenol is required to drive the reaction to completion. These facts clearly support the need of an excess phenol.

In order to clarify the present possible oxidative annulation mechanisms, we further investigated the mechanism by synthesizing bis(aryloxo)palladium(II) complex **89** following van Koten's procedure.[27] Then, the complex **89** was subjected to reaction conditions B , gratifyingly, the desired benzofuran **76t** was obtained in 31% yield. This

result corroborates the requirement of additional equivalents of phenols to form bis(aryloxo)palladium(II) complexes, which interact with phenols through hydrogen bonding to form the bis(phenol) adduct.[27,28] As a consequence, the reaction between phenol and unactivated internal alkynes most likely proceeds via participation of active bis(aryloxo)palladium complexes and subsequent *ortho*-C–H bond cleavage, i.e., cycle I is more likely.



Scheme 2.20: Stoichiometric reaction of **56a** with complex **89**

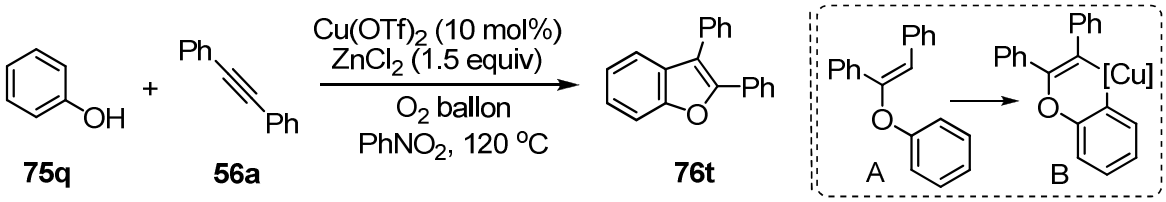
2.3. Conclusions

In summary, we have developed a novel one-step synthetic method for the construction of 2,3-disubstituted benzofurans involving palladium-catalyzed oxidative annulations of commercially available phenols with readily accessible unactivated internal alkynes. The catalytic conditions are optimized with respect to electron-deficient and electron-rich substituted phenols. The reaction exhibits a broad substrate scope and various common functional groups are tolerated under optimized catalytic conditions. A single regioisomeric benzofuran is obtained in the annulation of phenols with aryl-alkyl-substituted unsymmetrical alkynes, whereas reaction of 1-naphthol with alkynes exclusively produced the naphthofurans rather than naphthopyrans. Furthermore, the benzofuran skeleton is successfully installed on complex molecules that contained the phenolic OH group. A preliminary mechanistic investigation reveals the participation of a bis(aryloxo)-palladium(II) complex and the involvement of *ortho*-C–H bond cleavage of the phenol. Given the ready availability of the catalyst system and the broad substrate scope, we believe this new synthetic approach to be of utility in the fabrication of novel frameworks.

2.4. Future Work

The present work successfully demonstrates the synthesis of benzo[*b*]furans from readily available precursors phenols and unactivated internal alkynes, *which to the best of knowledge is the first report.* However, the reaction need more amount of the phenols and 130 ^{o}C is the required temperature. We hope this novel reaction would be useful in the fabrication of extended π-conjugated benzofuran structural motifs. However, we assume the harsh reaction conditions would impose hurdles for the broad synthetic utility. Therefore, development of mild reaction conditions for the synthesis of benzofurans from phenols and unactivated alkynes is always desirable.

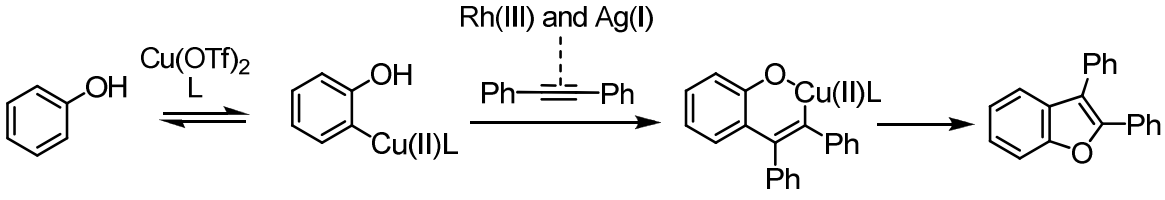
Interestingly, a sequential nucleophilic addition of phenols to alkynes promoted by Cu(II) and Lewis acid catalyzed intramolecular electrophilic substitution and oxidative cyclization for the synthesis of benzofurans is reported by H. Jiang and co-workers[29a] (Scheme 2.21).



75q 56a 76t

Scheme 2.21: Cu-Catalyzed benzofuran synthesis from phenol and alkynes

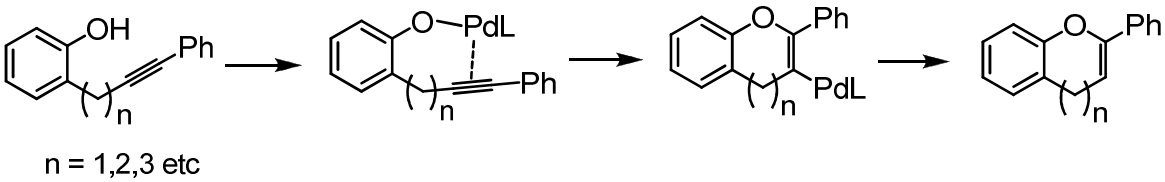
The copper mediated oxidative coupling of phenols and alkynes have been recently shown by Z. Shi and co-workers.[29b] The reaction proceeds involving the reversible electrophilic carbocupration of phenol followed by alkyne insertion and cyclization (Scheme 2.22).



Conditions: $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol%), $Cu(OTf)_2$ (1.0 equiv), $AgPF_6$ (2.5 equiv), Acetanilide (20 mol%), DTAC (Dodecyl trimethyl ammonium chloride) (50 mol%), Decalin, 120 ^{o}C

Scheme 2.22: Cu-Mediated benzofuran synthesis from phenol and alkynes

A possible extension of this work is directed towards the synthesis of large macrocyclic-units involving the intramolecular cyclization of the alkyne-tethered phenols (Scheme 2.23).



Scheme 2.23: Strategy for oxygen-bearing heterocycle synthesis

We therefore envision the synthesis of complex natural products such as beilshmiedin and conioxepinol A etc using the recently developed strategy (scheme 2.24).[29c]

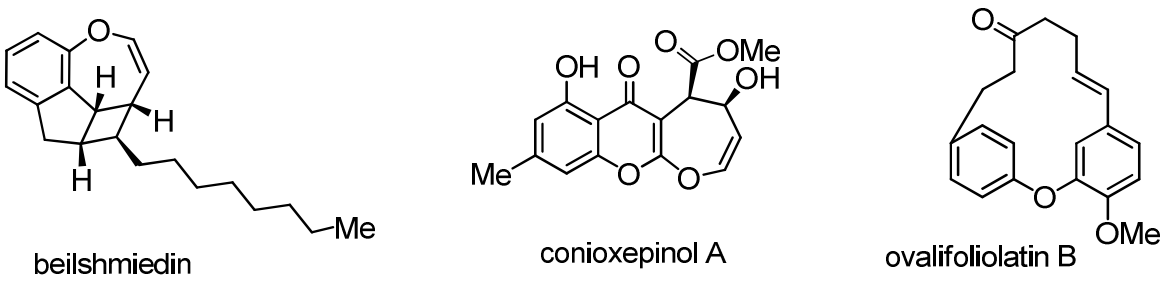


Figure 2.24: Selected natural products

2.5. Experimetal

2.5.1. Materials: Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. According to the standard procedures solvents were dried and stored under molecular sieves.[30] Ligands (L1-L6), and palladium catalysts are purchased from Aldrich Ltd. and used as received. Diphenylacetylene (**56a**), 4-octyne (**56e**), 1-phenyl-1-hexyne (**56f**) are purchased from Sigma Aldrich Ltd. Alkynes such as 1,2-bis(4-methoxyphenyl)ethyne (**56b)**, 1,2-bis(4-chlorophenyl)ethyne (**56c**), 1,2-di(thiophen-2-yl)ethyne (**56d**), 1-(hex-1-ynyl)naphthalene (**56g**), and 1-(hex-1-ynyl)-4-methoxybenzene (**56h**) are prepared following the respective literature procedure.[31] Analytical and spectral data of all those known alkynes are exactly matching with the reported values.

2.5.2. Typical procedure for the reaction of activated phenols with alkynes (GP-1; condition-A):

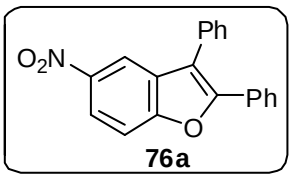
In an oven dried Schlenk tube, phenol (2.0 mmol), alkyne (1.0 mmol), $Pd_2(dba)_3$ (0.05 mmol), bathophenathroline (L3, 0.10 mmol), AgOAc (2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.0 mmol), and 1,4-dioxane (8.0 mL) were introduced. The resulting reaction mixture was stirred at 130 °C. Progress of the reaction was monitored by TLC or GC analysis, while noticing complete consumption of alkynes employed. Reaction was continued for the time shown in the respective Tables, and brought to room temperature. The reaction mixture was diluted with dichloromethane (5.0 mL), and filtered over a small pad of Celite. Solvent was evaporated under the reduced pressure and the crude reaction mixture was purified using silica gel column chromatography.

2.5.3. Typical procedure for the reaction of unactivated phenols with alkynes (GP-2; condition-B):

In an oven dried Schlenk tube, phenol (5.0 mmol), alkyne (1.0 mmol), $Pd_2(dba)_3$ (0.05 mmol), 1,10-phenathroline (L4, 0.10 mmol), NaOAc (5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.0 mmol), and 1,4-dioxane (8.0 mL) were introduced. The resulting reaction mixture was stirred at 130 °C. Progress of the reaction was monitored by GC analysis, while noticing complete consumption of alkynes employed. Reaction was continued for the time shown in the respective Tables, and brought to room temperature. The reaction mixture was diluted with dichloromethane (5.0 mL), and filtered over a small pad of Celite. Solvent was evaporated under the reduced pressure and the crude reaction mixture was purified using silica gel column chromatography.

2.5.4. Spectral and analytical data of the compounds

5-Nitro-2,3-diphenylbenzofuran (76a):



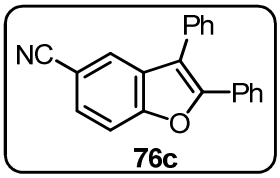
76a

Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**75a**; 278 mg, 2.0 mmol), **56a** (178 mg, 1.0 mmol), AgOAc (333 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L3 (33 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography

eluting with hexane: ethyl acetate (49:1) to afford **76a** (290 mg) in 92% yield as pale yellow solid.

mp 160–161 °C; R_f = 0.44 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.39 (bd, *J* = 4.0 Hz 1H), 8.26 (dd, *J* = 12.0, 4.0 Hz, 1H), 7.71–7.59 (m, 3H), 7.55–7.43 (m, 5H), 7.35 (bt, *J* = 4.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 156.8, 153.7, 144.5, 131.2, 130.9, 129.6, 129.4, 128.7, 128.5, 127.2, 120.5, 118.0, 116.7, 111.5; **IR (KBr)** ν_{max} 3046, 2915, 1600, 1517, 1446, 1347, 1271, 1063, 761 cm^{-1}; **MS (EI)** m/z (%) 316 (M^++1, 100), 302 (8), 286 (8), 238 (8), 222 (2); **Elemental analysis** calcd for $C_{20}H_{13}NO_3$: C 76.18, H 4.16, N 4.44. Found: C 76.32, H 4.21, N 4.36.

2,3-Diphenylbenzofuran-5-carbonitrile (76c):

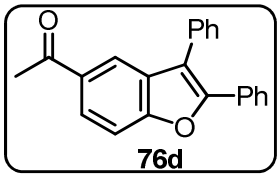


76c

Following the general procedure (GP-1) in condition A; a mixture of 4-hydroxybenzonitrile (**75c**; 238 mg, 2.0 mmol), **56a** (178 mg, 1.0 mmol), AgOAc (333 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L3 (33 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76c** (207 mg) in 70% yield as pale yellow solid.

mp 109–110 °C; R_f = 0.38 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.83 (bs, 1H), 7.71–7.65 (m, 2H), 7.64–7.58 (m, 2H), 7.55–7.46 (m, 5H), 7.39–7.32 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 155.6, 152.8, 131.3, 131.1, 129.6, 129.3, 129.2, 128.6, 128.4, 128.3, 127.2, 125.2, 119.4, 117.1, 112.3, 106.9; **IR (KBr)** ν_{max} 3057, 2222, 1653, 1462, 1373, 1265, 1197, 1057, 879, 808, 761, 696 cm^{-1}; **MS (EI)** m/z (%) 296 (M^++1, 100), 272 (1), 240 (10); **Elemental analysis** calcd for $C_{21}H_{13}NO$: C 85.40, H 4.44, N 4.74. Found: C 85.32, H 4.36, N 4.81.

1-(2,3-Diphenylbenzofuran-5-yl)ethanone (76d):



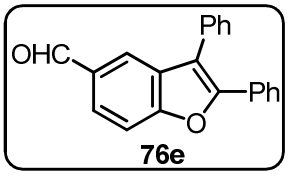
76d

Following the general procedure (GP-1) in condition A; a mixture of 4'-hydroxyacetophenone (**75d**; 272 mg, 2.0 mmol), **56a** (178 mg, 1.0 mmol), AgOAc (333 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L3 (33 mg, 0.1

mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76d** (163 mg) in 52% yield as pale yellow solid.

mp 102–103 °C; R_f = 0.41 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.12 (d, *J* = 1.6 Hz, 1H), 8.01 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.71–7.62 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.54–7.50 (m, 4H), 7.49–7.45 (m, 1H), 7.38–7.31 (m, 3H), 2.64 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ197.7, 156.6, 152.1, 132.9, 132.0, 130.5, 130.0, 129.7, 129.2, 128.9, 128.6, 128.1, 127.1, 125.5, 121.3, 117.9, 111.2, 26.9; **IR (KBr)** ν_{max} 2964, 1682, 1433, 1352, 1261, 1022, 800, 763, 692, 603 cm^{-1}; **MS (EI)** m/z (%) 313 (M^++1, 100), 182 (5), 147 (5); **Elemental analysis** calcd for $C_{22}H_{16}O_2$: C 84.59, H 5.16. Found: C 84.41, H 5.23.

2,3-Diphenylbenzofuran-5-carbaldehyde (76e):



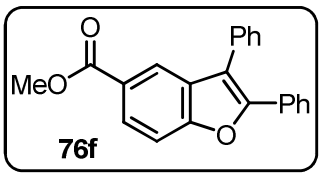
76e

Following the general procedure (GP-2) in condition B; a mixture of 4-hydroxybnzaldehyde (**75e**; 610 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76e** (269 mg) in 90% yield as colorless solid.

mp 137–138 °C; R_f = 0.38 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ10.04 (s, 1H), 8.04 (bs, 1H), 7.91 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.71–7.62 (m, 3H), 7.56–7.49 (m, 4H), 7.48–7.43 (m, 1H), 7.38–7.31 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ191.8, 157.4, 152.4, 132.4, 131.8, 131.0, 129.8, 129.7, 129.3, 129.0, 128.6, 128.2, 127.1, 126.3, 123.3, 117.8, 111.9; **IR (KBr)** ν_{max} 3059, 2797, 2702, 1687, 1583, 1440, 1371, 1342, 1265, 1199, 1145, 1111, 1059, 1024, 817, 758, 688 cm^{-1}; **MS (EI)** m/z (%) 299 (M^++1, 100), 289 (3), 209 (12); **Elemental analysis** calcd for $C_{21}H_{14}O_2$: C 84.54, H 4.73. Found: C 84.42, H 4.77.

Methyl-2,3-diphenylbenzofuran-5-carboxylate (76f):

Following the general procedure (GP-2) in condition B; a mixture of methyl-4-hydroxybenzoate (**75f**; 760 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0

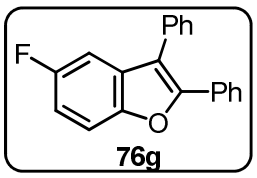


76f

mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76f** (200 mg) in 61% yield as colorless solid.

mp 165–166 °C; R_f = 0.41 (24:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.22 (bs, 1H), 8.07 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.71–7.63 (m, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.55–7.42 (m, 5H), 7.39–7.30 (m, 3H), 3.92 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ167.3, 156.6, 151.9, 132.1, 130.4, 130.1, 129.8, 129.2, 128.8, 128.5, 128.0, 127.1, 126.5, 125.4, 122.5, 117.8, 111.0, 52.1; **IR (KBr)** ν_{max} 2957, 2924, 1714, 1616, 1485, 1439, 1375, 1286, 1242, 1095, 1059, 1024, 985, 906, 763, 694 cm^{-1}; **MS (EI)** m/z (%) 329 (M^++1, 100), 289 (5), 255 (5), 223 (12); **Elemental analysis** calcd for $C_{22}H_{16}O_3$: C 80.47, H 4.91. Found: C 80.28, H 4.86.

5-Fluoro-2,3-diphenylbenzofuran (76g):

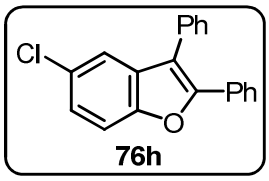


76g

Following the general procedure (GP-2) in condition B; a mixture of 4-fluorophenol (**75f**; 560 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76g** (214 mg) in 74% yield as colorless solid.

mp 115–116 °C; R_f = 0.69 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.69 (bd, *J* = 8.0 Hz, 2H), 7.50–7.35 (m, 6H), 7.34–7.21 (m, 3H), 7.18 (bd, *J* = 8.0 Hz, 1H), 7.08 (bt, *J* = 8.0 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ159.5 (d, *J* = 239 Hz), 152.3, 150.2, 132.4, 131.1 (d, *J* = 11 Hz), 130.4, 129.6, 129.1, 128.7, 128.5, 127.9, 127.1, 117.7, 112.3 (d, *J* = 26 Hz), 111.7 (d, *J* = 9.1 Hz), 105.6 (d, *J* = 25 Hz); **^{19}F NMR (470 MHz, $CDCl_3$)** δ–120.5; **IR (KBr)** ν_{max} 3065, 3028, 1601, 1469, 1444, 1213, 1141, 1062, 860, 808, 758, 690 cm^{-1}; **MS (EI)** m/z (%) 289 (M^+ +1, 100), 267 (10), 253 (13), 205 (21), 189 (2); **Elemental analysis** calcd for $C_{20}H_{13}FO$: C 83.32, H 4.54. Found: C 83.19, H 4.59.

5-Chloro-2,3-diphenylbenzofuran (76h):[32]

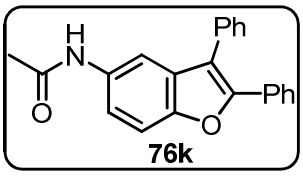


76h

Following the general procedure (GP-2) in condition B; a mixture of 4-chlorophenol (**75h**; 642 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76h** (162 mg) in 53% yield as colorless solid.

mp 113–114 °C; R_f = 0.67 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.69–7.62 (m, 2H), 7.51–7.42 (m, 6H), 7.36–7.32 (m, 3H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.27 (bd, *J* = 2.8 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ152.4, 151.9, 132.2, 131.7, 130.2, 129.7, 129.2, 128.8, 128.7, 128.5, 128.0, 127.1, 124.9, 119.7, 117.2, 112.2; **IR (KBr)** ν_{max} 3059, 1602, 1502, 1439, 1321, 1255, 1205, 1057, 966, 864, 804, 763, 686 cm^{-1}; **MS (EI)** m/z (%) 305 (M^+ +1, 100), 277 (2), 177 (2); **Elemental analysis** calcd for $C_{20}H_{13}ClO$: C 78.82, H 4.30. Found: C 78.73, H 4.35.

***N*-(2,3-Diphenylbenzofuran-5-yl)acetamide (76k):**

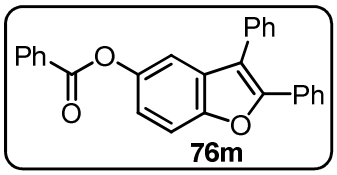


76k

Following the general procedure (GP-2) in condition B; a mixture of acetaminophen (**75k**; 755 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76k** (197 mg) in 60% yield as colorless solid.

mp 242–243 °C; R_f = 0.52 (3:2 hexane/EtOAc); **^{1}H NMR (400 MHz, DMSO-d_6)** δ9.98 (bs, 1H), 7.80 (bd, *J* = 4.0 Hz, 1H), 7.61–7.47 (m, 6H), 7.46–7.41 (m, 3H), 7.39–7.30 (m, 3H), 2.01 (s, 3H); **^{13}C NMR (101 MHz, DMSO-d_6)** δ168.5, 150.9, 150.0, 135.8, 132.5, 130.3, 130.0, 129.8, 129.7, 129.2, 128.5, 126.9, 117.8, 111.5, 110.0, 24.4; **IR (KBr)** ν_{max} 3254, 3068, 2925, 1660, 1627, 1578, 1473, 1254, 1062, 865, 761, 690 cm^{-1}; **MS (EI)** m/z (%) 328 (M^+ +1, 100), 292 (13), 277 (13), 191 (21); **Elemental analysis** calcd for $C_{22}H_{17}NO_2$: C 80.71, H 5.23, N 4.28. Found: C 80.58, H 5.32, N 4.19.

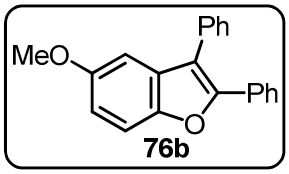
2,3-Diphenylbenzofuran-5-yl benzoate (76m):[33]



Following the general procedure (GP-2) in condition B; a mixture of 4-hydroxyphenyl benzoate (**75m**; 1.07 g, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76m** (196 mg) in 50% yield as colorless solid.

mp 119–120 °C; R_f = 0.51 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.26 (d, *J* = 8.0 Hz, 2H), 7.72 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.69–7.62 (m, 2H), 7.58–7.42 (m, 7H), 7.41–7.32 (m, 4H), 7.21 (dd, *J* = 8.0, 4.0 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ165.8, 152.0, 151.7, 146.9, 133.6, 132.5, 131.2, 130.4, 130.2, 129.8, 129.6, 129.1, 128.7, 128.6, 128.5, 127.9, 127.1, 118.7, 117.8, 112.8, 111.7; **IR (KBr)** ν_{max} 3040, 2964, 2854, 1725, 1599, 1457, 1331, 1249, 1150, 1062, 1030, 695 cm^{-1}; **MS (EI)** m/z (%) 391 (M^+ +1, 100), 364 (2), 265 (2), 236 (2); **Elemental analysis** calcd for $C_{27}H_{18}O_3$: C 83.06, H 4.65. Found: C 83.12, H 4.71.

5-Methoxy-2,3-diphenylbenzofuran (76b):[34]

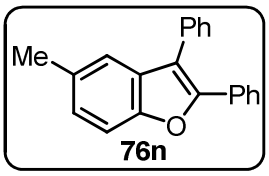


Following the general procedure (GP-2) in condition B; a mixture of 4-methoxyphenol (**75b**; 620 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76b** (264 mg) in 88% yield as pale yellow solid.

mp 84–85 °C; R_f = 0.58 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.64 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.53–7.41 (m, 6H), 7.35–7.29 (m, 3H), 6.96 (bd, *J* = 2.4 Hz, 1H), 6.94 (bs, 1H), 3.82 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ156.3, 151.4, 149.0, 133.0, 130.8, 129.8, 129.1, 128.4, 128.3, 128.2, 127.6, 126.9, 117.7, 113.6, 111.6, 102.3, 56.0; **IR**

(KBr) ν_{max} 2692, 1601, 1471, 1261, 1226, 1026, 800, 692 cm^{-1}; **MS (EI)** m/z (%) 301 (M^+ +1, 100), 287 (5), 255 (2), 227 (2).

5-Methyl-2,3-diphenylbenzofuran (76n):[35]

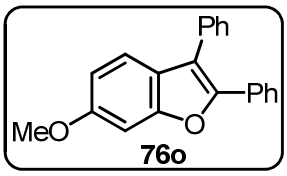


76n

Following the general procedure (GP-2) in condition B; a mixture of *p*-cresol (**75n**; 540 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76n** (199 mg) in 70% yield as colorless solid.

mp 112–113 ^oC; R_f = 0.60 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.68 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.55–7.42 (m, 6H), 7.37–7.29 (m, 4H), 7.17 (dd, *J* = 8.4, 1.2 Hz, 1H), 2.45 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ152.5, 150.6, 133.1, 132.4, 130.8, 130.4, 129.8, 129.0, 128.4, 128.3, 127.6, 126.9, 125.9, 119.8, 117.3, 110.6, 21.4; **IR (KBr)** ν_{max} 3061, 2920, 1743, 1612, 1450, 1261, 1199, 1062, 873, 796, 690 cm^{-1}; **MS (EI)** m/z (%) 285 (M^+ +1, 100), 267 (2), 243 (11); **Elemental analysis** calcd for $C_{21}H_{16}O$: C 88.70, H 5.60. Found: C 88.59, H 5.72.

6-Methoxy-2,3-diphenylbenzofuran (76o):[36]



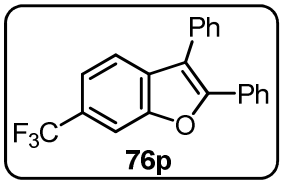
76o

Following the general procedure (GP-2) in condition B; a mixture of 3-methoxyphenol (**75o**; 620 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **76o** (270 mg) in 90% yield as colorless solid.

mp 116–117 ^oC; R_f = 0.52 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.68 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.59–7.47 (m, 4H), 7.46–7.39 (m, 2H), 7.38–7.27 (m, 3H), 7.14 (d, *J* = 4.0 Hz, 1H), 6.93 (dd, *J* = 8.0, 2.4 Hz, 1H), 3.92 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ158.5, 155.1, 149.7, 133.0, 130.9, 129.7, 129.0, 128.4, 127.9, 127.6, 126.7, 123.8, 120.3,

117.5, 112.0, 95.7, 55.8; **IR (KBr)** ν_{max} 3063, 2920, 2838, 1610, 1600, 1495, 1441, 1265, 1194, 1150, 1024, 816 cm^{-1}; **MS (EI)** m/z (%) 301 (M^+ +1, 100), 287 (5), 255 (2), 239 (2), 227 (2); **Elemental analysis** calcd for $C_{21}H_{16}O_2$: C 83.98, H 5.37. Found: C 83.91, H 6.14.

2,3-Diphenyl-6-(trifluoromethyl)benzofuran (76p):

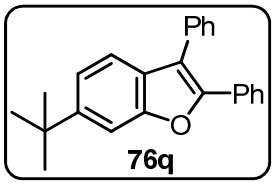


76p

Following the general procedure (GP-2) in condition B; a mixture of 3-(trifluoromethyl)phenol (**75p**; 810 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76p** (183 mg) in 54% yield as colorless solid.

mp 112–114 ^oC; R_f = 0.69 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.85 (bs, 1H), 7.71–7.65 (m, 2H), 7.62–7.57 (m, 1H), 7.55–7.43 (m, 6H), 7.39–7.32 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ153.1, 153.0, 133.3, 132.0, 129.9, 129.7, 129.2, 129.1, 128.6, 128.1, 127.2, 126.9, 126.6, 120.4, 119.9 (d, *J* = 3.2 Hz), 117.4, 108.7 (d, *J* = 4.2 Hz); **^{19}F NMR (470 MHz, $CDCl_3$)** δ–60.9; **IR (KBr)** ν_{max} 3079, 3030, 1621, 1490, 1430, 1331, 1117, 1046, 882, 772 cm^{-1}; **MS (EI)** m/z (%) 339 (M^+ +1, 100), 325 (5), 311 (5), 233 (13); **Elemental analysis** calcd for $C_{21}H_{13}F_3O$: C 74.55, H 3.87. Found: C 74.41, H 3.82.

6-*tert*-Butyl-2,3-diphenylbenzofuran (76q):



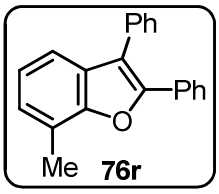
76q

Following the general procedure (GP-2) in condition B; a mixture of 3-*tert*-butylphenol (**75q**; 751 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76q** (180 mg) in 55% yield as colorless solid.

mp 74–75 ^oC; R_f = 0.68 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.73–7.67 (m, 2H), 7.64 (bd, *J* = 1.6 Hz, 1H), 7.58–7.42 (m, 6H), 7.39–7.29 (m, 4H), 1.46 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ154.4, 150.3, 148.9, 133.1, 130.9, 129.8, 128.9, 128.4, 128.2, 127.7,

127.6, 126.9, 120.8, 119.4, 117.4, 107.9, 35.1, 31.7; **IR (KBr)** ν_{max} 3057, 2961, 2866, 1599, 1577, 1489, 1442, 1421, 1363, 1278, 1194, 1066, 1024, 966, 916, 873, 756 cm^{-1}; **MS (EI)** m/z (%) 327 (M^+ +1, 100), 312 (15), 284 (5), 210 (3), 196 (3); **Elemental analysis** calcd for $C_{24}H_{22}O$: C 88.31, H 6.79. Found: C 88.25, H 6.71.

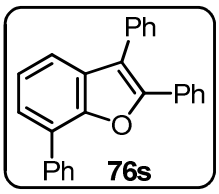
7-Methyl-2,3-diphenylbenzofuran (76r):[37]



Following the general procedure (GP-2) in condition B; a mixture of *o*-cresol (**75r**; 540 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76r** (128 mg) in 45% yield as colorless thick liquid.

R_f = 0.71 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.71 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.59–7.41 (m, 5H), 7.39–7.30 (m, 4H), 7.21–7.14 (m, 2H), 2.66 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ153.0, 150.3, 133.1, 130.9, 129.8, 129.7, 128.9, 128.4, 128.3, 127.6, 127.1, 125.6, 123.0, 121.4, 117.8, 117.5, 15.1; **IR (Neat)** ν_{max} 3057, 3024, 2920, 2849, 1600, 1501, 1446, 1419, 1200, 1101, 767 cm^{-1}; **MS (EI)** m/z (%) 285 (M^+ +1, 100), 267 (3), 243 (13).

2,3,7-Triphenylbenzofuran (76s):

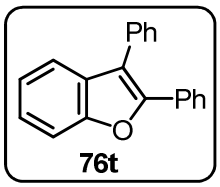


Following the general procedure (GP-2) in condition B; a mixture of 2-phenylphenol (**75s**; 851 mg, 5.0 mmol), **56a (**178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76s** (118 mg) in 34% yield as pale yellow solid.

mp 144–145 ^oC; R_f = 0.69 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.02 (dt, *J* = 12.0, 4.0 Hz, 2H), 7.71 (dt, *J* = 8.0, 4.0 Hz, 2H), 7.62–7.45 (m, 10H), 7.39–7.29 (m, 4H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ151.2, 150.7, 136.6, 132.9, 131.2, 130.6, 129.9, 129.3, 129.1, 128.7,

128.5, 128.4, 127.8, 127.7, 127.0, 125.3, 124.3, 123.6, 119.3, 117.7; **IR (KBr)** ν_{max} 3061, 2924, 1595, 1483, 1440, 1412, 1197, 1064, 1024, 908, 756 cm^{-1}; **MS (EI)** m/z (%) 347 (M^+ +1, 100), 314 (2), 279 (5), 257 (2); **Elemental analysis** calcd for $C_{26}H_{18}O$: C 90.14, H 5.24. Found: C 90.25, H 5.18.

2,3-Diphenylbenzofuran (76t):[38]

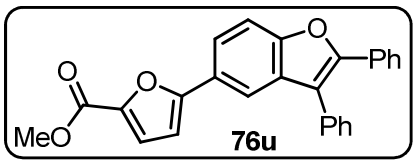


76t

Following the general procedure (GP-1) in condition A; a mixture of phenol (**75t**; 188 mg, 2.0 mmol), **56a (**178 mg, 1.0 mmol), AgOAc (333 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L3 (33 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 72 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76t** (60 mg) in 22% yield as colorless thick liquid.

R_f = 0.68 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.68 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.57 (bd, *J* = 8.4 Hz, 1H), 7.55–7.39 (m, 6H), 7.38–7.24 (m, 5H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ154.0, 150.5, 132.9, 130.7, 130.3, 129.8, 129.0, 128.4, 128.3, 127.6, 127.0, 124.7, 122.9, 120.0, 117.5, 111.1.

Methyl 5-(2,3-diphenylbenzofuran-5-yl)furan-2-carboxylate (76u):



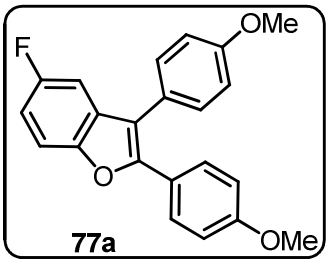
76u

Following the general procedure (GP-2) in condition B; a mixture of methyl 5-(4-hydroxyphenyl)furan-2-carboxylate (**75u**; 1.09 g, 5.0 mmol), **56a (**178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 72 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (47:2) to afford **76u** (359 mg) in 91% yield as colorless solid.

mp 142–143 ^oC; R_f = 0.40 (47:2 hexane/EtOAc); **^{1}H NMR (500 MHz, $CDCl_3$)** δ8.00 (bs, 1H), 7.70–7.65 (m, 3H), 7.56–7.48 (m, 5H), 7.47–7.41 (m, 1H), 7.38–7.31 (m, 3H), 7.28 (d, *J* = 4.0 Hz, 1H), 6.78 (d, *J* = 4.0 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ159.3, 157.9, 154.2, 152.0, 143.4, 132.4, 131.1, 130.3, 129.7, 129.1, 129.0, 128.7, 128.5,

127.9, 127.0, 126.3, 120.3, 120.2, 117.7, 107.5, 106.8, 51.9; **IR (KBr)** ν_{max} 3055, 2949, 2851, 1705,1651, 1591, 1537, 1460, 1302, 1215, 1132, 1024, 987, 810, 761cm^{-1}; **MS (EI)** m/z (%) 395 (M^+ +1, 100), 319(3), 251 (10); **Elemental analysis** calcd for $C_{26}H_{18}O_4$: C 79.17, H 4.60. Found: C 79.26, H 4.53.

5-Fluoro-2,3-bis(4-methoxyphenyl)benzofuran (77a):

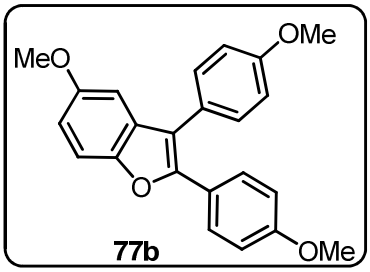


77a

Following the general procedure (GP-2) in condition B; a mixture of 4-fluorophenol (**75g**; 280 mg, 2.5 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**56b**; 119 mg, 0.5 mmol), NaOAc (205 mg, 2.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (199 mg, 1.0 mmol) in the presence of $Pd_2(dba)_3$ (22 mg, 0.025 mmol) and L4 (9.0 mg, 0.05 mmol) in 1,4-dioxane (6.0 mL) was heated at 130 ^oC for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **77a** (120 mg) in 69% yield as pale yellow solid.

mp 97–98 ^oC; R_f = 0.44 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, CDCl$_3$)** δ7.60 (dt, *J* = 6.8, 1.6 Hz, 2H), 7.43 (dd, *J* = 8.8, 4.0 Hz, 2H), 7.39 (dt, *J* = 6.8, 2.0 Hz, 1H), 7.12 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.06–6.98 (m, 3H), 6.87 (dt, *J* = 8.0, 1.8 Hz, 2H), 3.89 (s, 3H), 3.83 (s, 3H); **^{13}C NMR (101 MHz, CDCl$_3$)** δ159.5 (q, *J* = 84 Hz), 152.3, 149.9, 131.6 (d, *J* = 10 Hz), 130.8, 128.4, 124.6, 123.1, 115.8, 114.6, 113.9, 111.8, 111.5, 111.4, 105.4 (d, *J* = 25 Hz), 55.31, 55.28; **^{19}F NMR (470 MHz, CDCl$_3$)** δ–120.9; **IR (KBr)** ν_{max} 2964, 1610, 1518, 1504, 1462, 1259, 1174, 1097, 1026, 935, 868, 800, 688 cm^{-1}; **MS (EI)** m/z (%) 349 (M^+ +1, 100), 230 (13), 200 (10), 154 (18); **Elemental analysis** calcd for $C_{22}H_{17}FO_3$: C 75.85, H 4.92. Found: C 75.91, H 4.85.

5-Methoxy-2,3-bis(4-methoxyphenyl)benzofuran (77b):[39]



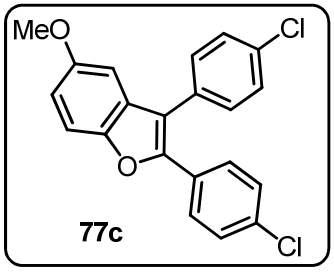
77b

Following the general procedure (GP-2) in condition B; a mixture of 4-methoxyphenol (**75b**; 310 mg, 2.5 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**56b**; 119 mg, 0.5 mmol), NaOAc (205 mg, 2.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (199 mg, 1.0 mmol) in the presence of $Pd_2(dba)_3$ (22 mg, 0.025 mmol) and L4 (9.0 mg, 0.05 mmol) in 1,4-dioxane (6.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography

eluting with hexane: ethyl acetate (49:1) to afford **77b** (121 mg) in 67% yield as yellow thick liquid.

R_f = 0.48 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.61 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 3H), 7.07–7.01 (m, 2H), 6.95–6.85 (m, 4H), 3.90 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ159.6, 159.0, 156.2, 151.4, 148.8, 130.9, 128.3, 125.3, 123.6, 122.4, 115.9, 114.5, 113.9, 112.9, 111.4, 102.1, 55.9, 55.3, 55.2; **IR (Neat)** ν_{max} 3002, 2931, 2832, 1649, 1600, 1446, 1331, 1101, 1030, 767 cm^{-1}; **MS (EI)** m/z (%) 361 (M^+ +1, 100), 301 (5), 275 (5), 180 (8), 111 (13); **Elemental analysis** calcd for $C_{23}H_{20}O_4$: C 76.65, H 5.59. Found: C 76.48, H 5.51.

2,3-bis(4-Chlorophenyl)-5-methoxybenzofuran (77c):

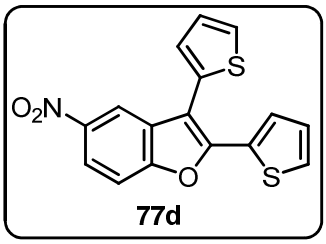


Following the general procedure (GP-2) in condition B; a mixture of 4-methoxyphenol (**75b**; 310 mg, 2.5 mmol), 1,2-bis(4-chlorophenyl)ethyne (**56c**; 123 mg, 0.5 mmol), NaOAc (205 mg, 2.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (199 mg, 1.0 mmol) in the presence of $Pd_2(dba)_3$ (22 mg, 0.05 mmol) and L4 (9.0 mg, 0.05 mmol) in 1,4-dioxane (6.0 mL) was heated at 130 ^oC for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **77c** (138 mg) in 75% yield as pale yellow solid.

mp 133–134 ^oC; R_f = 0.54 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.54 (dt, *J* = 6.8, 1.6 Hz, 2H), 7.51–7.39 (m, 5H), 7.30 (dt, *J* = 6.8, 1.6 Hz, 2H), 6.96 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.87 (d, *J* = 2.4 Hz, 1H), 3.82 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ156.5, 150.4, 148.9, 134.4, 133.8, 131.2, 131.0, 130.3, 129.5, 128.9, 128.8, 128.1, 116.9, 114.0, 111.8, 102.0, 55.9; **IR (Neat)** ν_{max} 2962, 2924, 1626, 1591, 1471, 1433, 1332, 1261, 1224, 1153, 1087, 1028, 968, 798 cm^{-1}; **MS (EI)** m/z (%) 369 (M^+ +1, 74), 367 (100), 339 (3), 325 (3), 311 (3), 271 (3); **Elemental analysis** calcd for $C_{21}H_{14}Cl_2O_2$: C 68.31, H 3.82. Found: C 68.21, H 3.91.

5-Nitro-2,3-di(thiophen-2-yl)benzofuran (77d):

Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**75a**; 278 mg, 2.0 mmol), 1,2-di(thiophen-2-yl)ethyne (**56d**; 190 mg, 1.0 mmol), AgOAc (333

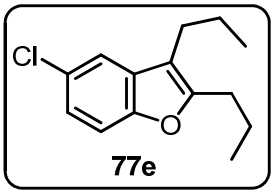


77d

mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L3 (33 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **77d** (181 mg) in 55% yield as yellow solid.

mp 149–150 ^oC; R_f = 0.25 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.42 (d, *J* = 4.0 Hz, 1H), 8.25 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.63–7.53 (m, 3H), 7.40 (dd, *J* = 4.8, 0.8 Hz, 1H), 7.31 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.29–7.22 (m, 1H), 7.12–7.07 (m, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ156.4, 151.0, 144.7, 131.1, 130.7, 130.1, 129.0, 128.1, 128.0, 127.8, 127.7, 127.6, 126.1, 120.7, 116.5, 111.4; **IR (KBr)** ν_{max} 3096, 2926, 2856, 1646, 1587, 1520, 1450, 1336, 1267, 1016, 823, 694 cm^{-1}; **MS (EI)** m/z (%) 328 (M^++1, 100), 307 (10), 296 (32), 183 (16); **Elemental analysis** calcd for $C_{16}H_9NO_3S_2$: C 58.70, H 2.77, N 4.28. Found: C 58.49, H 2.72, N 4.41.

5-Chloro-2,3-diethylbenzofuran (77e):

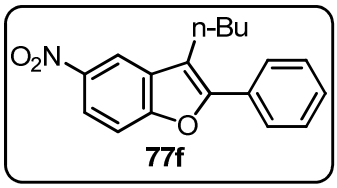


77e

Following the general procedure (GP-2) in condition B; a mixture of 4-chlorophenol (**75h**; 642 mg, 5.0 mmol), 4-octyne (**56e**; 110 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 24 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **77e** (149 mg) in 63% yield as colorless thick liquid.

R_f = 0.68 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.45 (bd, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.17 (dd, *J* = 8.0, 2.0 Hz, 1H), 2.72 (t, *J* = 8.0 Hz, 2H), 2.58 (t, *J* = 8.0 Hz, 2H), 1.78 (sex, *J* = 8.0 Hz, 2H), 1.68 (sex, *J* = 8.0 Hz, 2H), 1.01–0.89 (m, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ156.2, 152.4, 131.3, 127.5, 122.9, 118.7, 114.2, 111.5, 28.3, 25.5, 23.0, 21.6, 14.0, 13.8; **IR (Neat)** ν_{max} 2961, 2932, 2872, 1604, 1485, 1460, 1263, 1228, 1101, 1024, 943, 802 cm^{-1}; **MS (EI)** m/z (%) 235 (M^+, 10), 234 (M^+–1, 100), 221 (13), 209 (3) 141 (13); **Elemental analysis** calcd for $C_{14}H_{17}ClO$: C 71.03, H 7.24. Found: C 71.26, H 7.12.

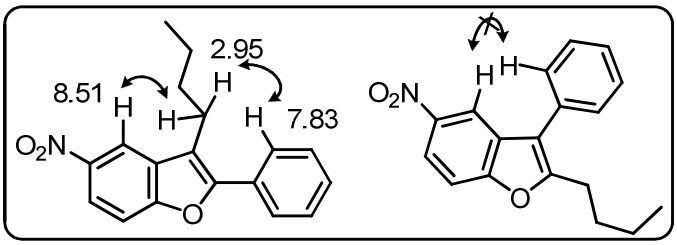
3-Butyl-5-nitro-2-phenylbenzofuran (77f):



77f

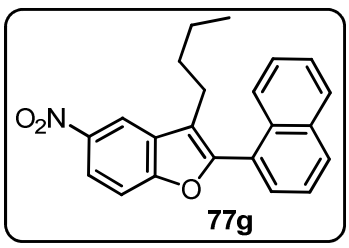
Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**75a**; 278 mg, 2.0 mmol), hex-1-ynylbenzene (**56f**; 158 mg, 1.0 mmol), AgOAc (333 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L3 (33 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **77f** (240 mg) as single regioisomeric product in 81% yield as pale yellow solid.

mp 71–72 °C; R_f = 0.42 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.48 (s, 1H), 8.22 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.80 (dd, *J* = 4.0, 2.0 Hz, 2H), 7.59–7.49 (m, 3H), 7.48–7.41 (m, 1H), 2.95 (t, *J* = 8.0 Hz, 2H), 1.73–1.70 (m, 2H), 1.56–1.45 (m, 2H), 0.99 (t, *J* = 8.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ156.8, 153.9, 143.9, 131.1, 130.2, 129.0, 128.9, 126.9, 120.2, 117.1, 116.2, 111.3, 31.8, 23.8, 22.9, 13.9; **IR (KBr)** ν_{max} 3074, 2961, 2926, 2856, 1591, 1520, 1454, 1342, 1263, 1099, 1020, 698 cm^{-1}; **MS (EI)** m/z (%) 296 (M^+ +1, 100), 279 (5), 236 (10), 183 (34), 100 (13); **Elemental analysis** calcd for $C_{18}H_{17}NO_3$: C 73.02, H 5.80, N 4.74. Found: C 73.36, H 5.91, N 4.65.



NOESY: NOE between δ8.51 (s) and δ2.95 (t); δ7.83 (d) and δ2.95 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed. This establishes the structure of regioisomer **77f**.

3-Butyl-2-(naphthalen-1-yl)-5-nitrobenzofuran (77g):

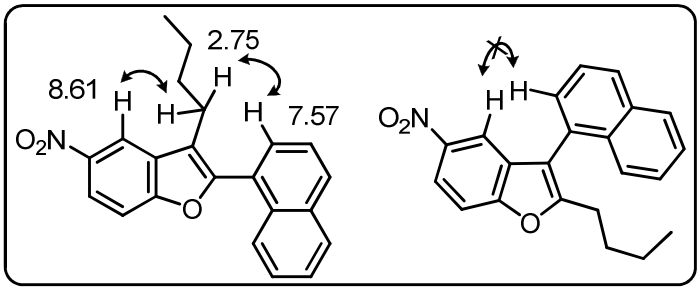


77g

Following the general procedure (GP-1) in condition A; a mixture of 4-nitrophenol (**75a**; 278 mg, 2.0 mmol), 1-(hex-1-ynyl)naphthalene (**56g**; 208 mg, 1.0 mmol), AgOAc (333 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L3 (33 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up,

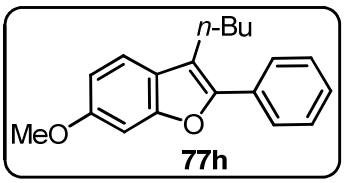
the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **77g** (221 mg) as single regioisomeric product in 64% yield as yellow thick liquid.

R_f = 0.43 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.60 (bd, *J* = 2.4 Hz, 1H), 8.28 (dd, *J* = 9.0, 2.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.69–7.51 (m, 5H), 2.74 (t, *J* = 8.0 Hz, 2H), 1.66 (quin, *J* = 8.0 Hz, 2H), 1.37–1.23 (m, 2H), 0.82 (t, *J* = 8.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ157.6, 154.6, 143.9, 133.8, 132.0, 130.4, 130.2, 129.1, 128.5, 127.1, 127.0, 126.4, 125.6, 125.1, 120.1, 119.4, 116.5, 111.6, 31.8, 23.7, 22.6, 13.7; **IR (Neat)** ν_{max} 3057, 2930, 2862, 1728, 1589, 1525, 1454, 1265, 1093, 775, 671 cm^{-1}; **MS (EI)** m/z (%) 346 (M^++1, 100), 279 (3), 194 (5); **Elemental analysis** calcd for $C_{22}H_{19}NO_3$: C 76.50, H 5.54, N 4.06. Found: C 76.61, H 5.48, N 4.15.



NOESY: NOE between δ8.61 (bd) and δ2.75 (t); δ7.57 (m) and δ 2.75 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed. This establishes the structure of regioisomer **77g**.

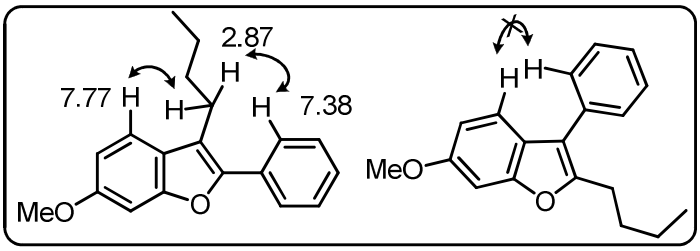
3-Butyl-6-methoxy-2-phenylbenzofuran (77h):



77h

Following the general procedure (GP-2) in condition B; a mixture of 3-methoxyphenol (**75o**; 620 mg, 5.0 mmol), 1-phenyl-1-hexyne (**56f**; 158 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxane (8.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **77h** (213 mg) as single regioisomeric product in 76% yield as colorless thick liquid.

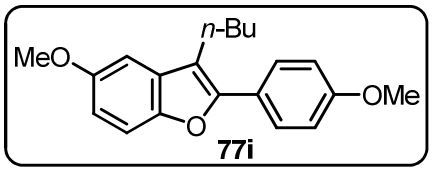
R_f = 0.44 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.77 (bd, *J* = 7.6 Hz, 2H), 7.52–7.42 (m, 3H), 7.36 (bt, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.89 (s, 3H), 2.91 (t, *J* = 8.0, 2H), 1.76 (quin, *J* = 7.6 Hz, 2H), 1.51 (sex, *J* = 7.6 Hz, 2H), 0.99 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ158.1, 154.9, 149.7, 131.6, 128.6, 127.6, 126.4, 124.1, 119.8, 116.5, 111.3, 95.7, 55.8, 31.9, 24.1, 22.9, 14.0;



IR (Neat) ν_{max} 3057, 2957, 2932, 2870, 2841, 1614, 1493, 1442, 1195, 1153, 1097, 1028, 823, 696 cm^{-1}; **MS (EI)** m/z (%) 281 (M^++1, 60), 280 (M^+, 100), 274 (3), 156 (8); **Elemental analysis** calcd for $C_{19}H_{20}O_2$: C 81.40, H 7.19. Found: C 81.26, H 7.23.

NOESY: NOE between δ7.77 (bd) and δ2.87 (t); δ7.38 (bd) and δ2.87 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed. This establishes the structure of regioisomer **77h**.

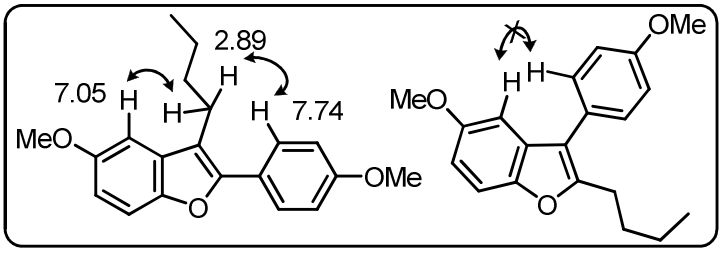
3-Butyl-5-methoxy-2-(4-methoxyphenyl)benzofuran (77i):



Following the general procedure (GP-2) in condition B; a mixture of 4-methoxyphenol (**75a**; 620 mg, 5.0 mmol), 1-(hex-1-ynyl)-4-methoxybenzene (**56h**; 188 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxan (8.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **77i** (211 mg) as single regioisomeric product in 68% yield as colorless thick liquid.

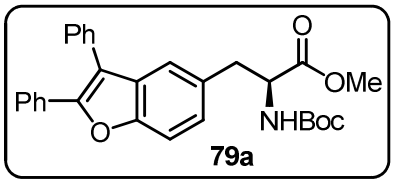
R_f = 0.48 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.72 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 1H), 7.05–6.98 (m, 3H), 6.88 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 2.86 (t, *J* = 7.6 Hz, 2H), 1.74 (quin, *J* = 7.6 Hz, 2H), 1.55-1.44 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ159.4, 155.7, 151.6, 148.8, 131.4, 128.2, 124.2, 115.2, 114.1, 111.9, 111.2, 102.4, 56.0, 55.3, 31.9, 24.0, 22.9, 14.0; **IR (Neat)** ν_{max} 3057, 2957, 2932, 1614, 1493, 1442, 1277, 1195, 1097, 951, 696 cm^{-1}; **MS**

(EI) m/z (%) 311 (M^++1, 100), 269 (10), 243 (5), 227 (3); **Elemental analysis** calcd for $C_{20}H_{22}O_3$: C 77.39, H 7.14. Found: C 77.26, H 7.21.



NOESY: NOE between δ7.05 (bs) and δ2.89 (t); δ7.74 (bd) and δ2.89 (t) are clearly seen while no NOE between aryl-aryl hydrogen's are observed. This establishes the structure of regioisomer **77i**.

(*S*)-Methyl 2-((*tert*-butoxycarbonyl)amino)-3-(2,3-diphenylbenzofuran-5-yl)propanoate (79a):

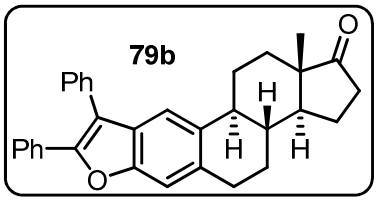


Following the general procedure (GP-2) in condition B; a mixture of Boc-*L*-tyrosine methyl ester (**78a**; 1.47 g, 5.0 mmol), **56a (**178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxan (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **79a** (307 mg) in 65% yield as pale yellow solid and the unreacted **78a** (982 mg).

HPLC analysis shows that the product and the precursor did not undergo racemization during the reaction (Diacel Chiralpak AD-H column, hexane-*i*-PrOH = 80:20 for elution, flow rate = 0.5 mL/min, λ = 254 nm; t_R for **79a** = 10.44 min, 100%).

mp 127–128 °C; R_f = 0.45 (3:2 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.67 (dd, *J* = 8.0, 4.0 Hz, 2H), 7.55–7.40 (m, 6H), 7.36–7.23 (m, 4H), 7.11 (bd, *J* = 8.0 Hz, 1H), 5.08 (bd, *J* = 8.0 Hz, 1H), 4.63 (bq, *J* = 4.0 Hz, 1H), 3.71 (s, 3H), 3.20 (ddd, *J* = 20.0, 14.0, 6.0 Hz, 2H), 1.42 (s, 9H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ172.4, 155.0, 153.3, 151.0, 132.7, 130.6, 130.5, 129.7, 129.0, 128.4, 127.7, 127.0, 125.9, 120.6, 117.3, 111.1, 79.9, 54.8, 52.2, 38.2, 28.3. **IR (KBr)** ν_{max} 3375, 2986, 2926, 2843, 1747, 1687, 1512, 1435, 1369, 1167, 1063, 761 cm^{-1}; **MS (EI)** m/z (%) 472 (M^+ +1, 28), 471 (M^+, 19), 470 (M^+–1, 100), 459 (5), 427 (5), 401 (5), 349 (6), 174 (8); **Elemental analysis** calcd for $C_{29}H_{29}NO_5$: C 73.87, H 6.20, N 2.97. Found: C 73.98, H 6.31, N 2.85.

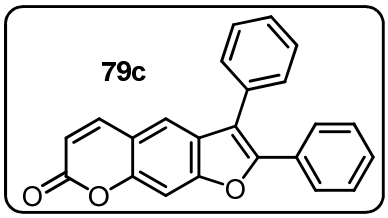
Benzofuranated Estrone (79b):



Following the general procedure (GP-2) in condition B; a mixture of estrone (**78b**; 1.35 g, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxan (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **79b** (277 mg) in 62% yield as pale yellow solid and the unreacted **78b** (990 mg).

mp 278–279 °C; R_f = 0.41 (3:2 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.67–7.60 (m, 2H), 7.53–7.36 (m, 6H), 7.35–7.24 (m, 4H), 3.08 (bq, *J* = 4.0 Hz, 2H), 2.59–2.32 (m, 3H), 2.21–2.01 (m, 3H), 1.95 (bd, *J* = 12.0 Hz, 1H), 1.72–1.44 (m, 6H), 0.92 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ221.0, 152.7, 150.2, 135.2, 134.2, 133.1, 130.9, 129.7, 129.0, 128.4, 128.1, 127.6, 126.8, 117.5, 116.0, 110.6, 50.7, 48.0, 44.5, 38.4, 35.9, 31.5, 30.0, 26.6, 26.2, 21.7, 13.8; **IR (KBr)** ν_{max} 3057, 2922, 2856, 1734, 1604, 1464, 1369, 1340, 1259, 1207, 1055, 761 cm^{-1}; **MS (EI)** m/z (%) 448 (M^+ +2, 71), 447 (M^+ +1, 100), 415 (8), 347 (3); **Elemental analysis** calcd for $C_{32}H_{30}O_2$: C 86.06, H 6.77. Found: C 86.15, H 6.71.

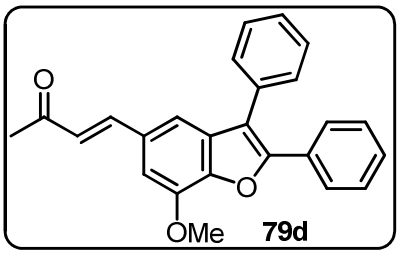
2,3-Diphenyl-7H-furo[3,2-g]chromen-7-one (79c):



Following the general procedure (GP-2) in condition B; a mixture of 7-hydroxycoumarin (**78c**; 405 mg, 2.5 mmol), **56a** (89 mg, 0.5 mmol), NaOAc (205 mg, 2.5 mmol), $Cu(OAc)_2.H_2O$ (199 mg, 1.0 mmol) in the presence of $Pd_2(dba)_3$ (22 mg, 0.025 mmol) and L4 (9.0 mg, 0.05 mmol) in 1,4-dioxan (4.0 mL) was heated at 130 °C for 72 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **79c** (90 mg) in 53% yield as colorless solid and the unreacted **78c** (283 mg).

mp 195–196 °C; R_f = 0.44 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.73 (d, *J* = 12.0 Hz, 1H), 7.61–7.54 (m, 4H), 7.53–7.44 (m, 4H), 7.38–7.29 (m, 4H), 6.30 (d, *J* = 12.0 Hz, 1H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ160.1, 156.2, 151.9, 149.2, 144.3, 131.6, 130.5, 129.8, 128.8, 128.6, 128.5, 128.3, 127.1, 124.1, 118.2, 117.0, 114.2, 113.9, 108.4; **IR (KBr)** ν_{max} 3061, 2922, 1730, 1601, 1485, 1377, 1265, 1215, 1151, 1120, 1066, 829, 773, 696 cm^{-1}; **MS (EI)** m/z (%) 339 (M^+ +1, 100), 324 (8), 309 (5), 269 (5), 245 (13); **Elemental analysis** calcd for $C_{23}H_{14}O_3$: C 81.64, H 4.17. Found: C 81.52, H 4.24.

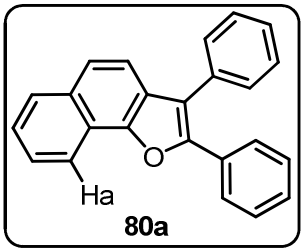
(E)-4-(7-Methoxy-2,3-diphenylbenzofuran-5-yl)but-3-en-2-one (79d):[40]



Following the general procedure (GP-2) in condition B; a mixture of (E)-4-(4-hydroxy-3-methoxyphenyl)but-3-en-2-one (**78d**; 961 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxan (8.0 mL) was heated at 130 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **79d** (111 mg) in 30% yield as colorless solid and the unreacted **78d** (614 mg, 3.4 mmol).

mp 147–148 °C; R_f = 0.46 (49:1 hexane/EtOAc); **^{1}H NMR (500 MHz, $CDCl_3$)** δ7.72–7.66 (m. 2H), 7.55 (bd, *J* = 16.0 Hz, 1H), 7.53–7.41 (m, 5H), 7.36–7.27 (m, 4H), 7.04 (bs, 1H), 6.67 (bd, *J* = 16.0 Hz, 1H), 4.11 (s, 3H), 2.38 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ198.4, 151.8, 145.6, 144.8, 144.4, 132.3, 132.2, 130.6, 130.0, 129.7, 129.1, 128.7, 128.5, 127.9, 127.1, 126.3, 117.8, 114.1, 105.9, 56.3, 27.3; **IR (KBr)** ν_{max} 3065, 2961, 2926, 1950, 1880, 1684, 1599, 1494, 1442, 1261, 1068, 1024, 916, 756, 688 cm^{-1}; **MS (EI)** m/z (%) 369 (M^+ +1, 100), 349 (3), 203 (10); **Elemental analysis** calcd for $C_{25}H_{20}O_3$: C 81.50, H 5.47. Found: C 81.36, H 5.56.

2,3-Diphenylnaphtho[2,3-*b*]furan (80a):[41]

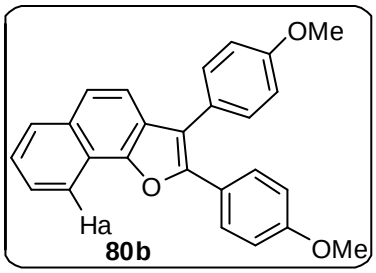


Following the general procedure (GP-2) in condition B; a mixture of 1-naphthol (**55**; 720 mg, 5.0 mmol), **56a** (178 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg,

2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and L4 (18 mg, 0.1 mmol) in 1,4-dioxan (8.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **80a** (115 mg) in 36% yield as colorless solid. The Ha signal appears at δ8.51 (bd); this confirms the formation of regioisomer **80a**.

mp 101–102 ^oC; R_f = 0.72 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.51 (bd, *J* = 8.0 Hz, 1H), 7.99 (bd, *J* = 8.0 Hz, 1H), 7.83 (bd, *J* = 4.0 Hz, 2H), 7.75–7.48 (m, 9H), 7.46–7.32 (m, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ149.3, 148.8, 132.2, 131.0, 130.2, 129.1, 128.3, 127.7, 127.6, 127.3, 126.9, 126.1, 125.7, 124.9, 124.5, 122.9, 120.5, 119.5, 118.1, 117.8; **IR (KBr)** ν_{max} 3049, 1633, 1601, 1574, 1481, 1442, 1375, 1068, 1020, 939, 817, 742, 694 cm^{-1}; **MS (EI)** m/z (%) 320 (M^+, 17), 319 (M^+–1, 100), 303 (5), 287 (10); **Elemental analysis** calcd for $C_{24}H_{16}O$: C 89.97, H 5.03. Found: C 89.82, H 5.11.

2,3-bis(4-Methoxyphenyl)naphtho[1,2-*b*]furan (80b):[42]

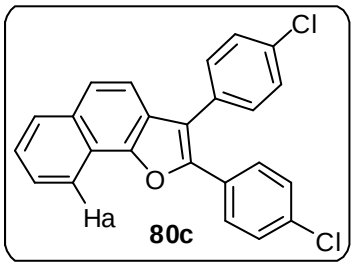


80b

Following the general procedure (GP-2) in condition B; a mixture of 1-naphthol (**55**; 720 mg, 5.0 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**56b**; 238 mg, 1.0 mmol), NaOAc (205 mg, 2.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (199 mg, 1.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.025 mmol) and L4 (18 mg, 0.05 mmol) in 1,4-dioxan (6.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **80b** (202 mg) in 53% yield as colorless solid. The Ha signal appears at δ8.43 (d); this confirms the formation of regioisomer **80b**.

mp 106–107 ^oC; R_f = 0.49 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.43 (d, *J* = 8.0 Hz, 1H), 7.95 (bd, *J* = 8.0 Hz, 1H), 7.71 (bd, *J* = 8.8 Hz, 2H), 7.69–7.56 (m, 3H), 7.54–7.47 (m, 3H), 7.05 (bd, *J* = 8.8 Hz, 2H), 6.91 (bd, *J* = 8.8 Hz, 2H), 3.91 (s, 3H), 3.85 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ159.3, 158.9, 149.9, 149.0, 131.4, 130.9, 128.3, 128.1, 126.2, 125.8, 125.1, 124.9, 123.7, 123.3, 121.1, 120.0, 118.4, 116.9, 114.4, 113.9, 55.2, 55.1; **IR (KBr)** ν_{max} 3057, 2991, 2958, 1605, 1517, 1501, 1380, 1304, 1178, 1035, 805, 745 cm^{-1}; **MS (EI)** m/z (%) 381 (M^+ +1, 100), 203 (5), 106 (5).

2,3-bis(4-Chlorophenyl)naphtho[1,2-*b*]furan (80c):



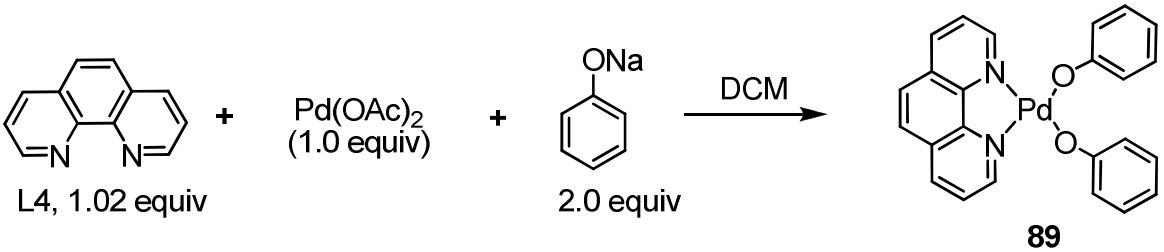
80c

Following the general procedure (GP-2) in condition B; a mixture of 1-naphthol (**55**; 360 mg, 2.5 mmol), 1,2-bis(4-chlorophenyl)ethyne (**56c**; 123 mg, 0.5 mmol), NaOAc (205 mg, 2.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (199 mg, 1.0 mmol) in the presence of $Pd_2(dba)_3$ (22 mg, 0.025 mmol) and L4 (9.0 mg, 0.05 mmol) in 1,4-dioxan (6.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **80c** (80 mg) in 41% yield as yellow solid. The Ha signal appears at δ 8.41 (d); this confirms the formation of regioisomer **80c**.

mp 130–131 ^oC; R_f = 0.61 (hexane); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.41 (bd, *J* = 8.0 Hz, 1H), 7.95 (bd, *J* = 8.0 Hz, 1H), 7.71–7.61 (m, 4H), 7.58–7.44 (m, 6H), 7.34 (bd, *J* = 8.0 Hz, 2H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 149.6, 149.1, 134.1, 133.9, 131.9, 131.1, 129.5, 129.1, 128.9, 128.5, 127.9, 126.6, 125.6, 125.1, 124.0, 121.1, 120.2, 118.1; **IR (KBr)** ν_{max} 3057, 3013, 2952, 1495, 1473, 1375, 1090, 1008, 942, 805 cm^{-1}; **MS (EI)** m/z (%) 389 (M^+ + 1,100), 357 (20), 215 (11), 189 (5); **Elemental analysis** calcd for $C_{24}H_{14}Cl_2O$: C 74.05, H 3.63. Found: C 74.52, H 3.71.

2.5.5. Preliminary Mechanistic Studies:

2.5.5.1. Synthesis of complex [Pd(OPh)$_2$(1,10-phen)] (89):



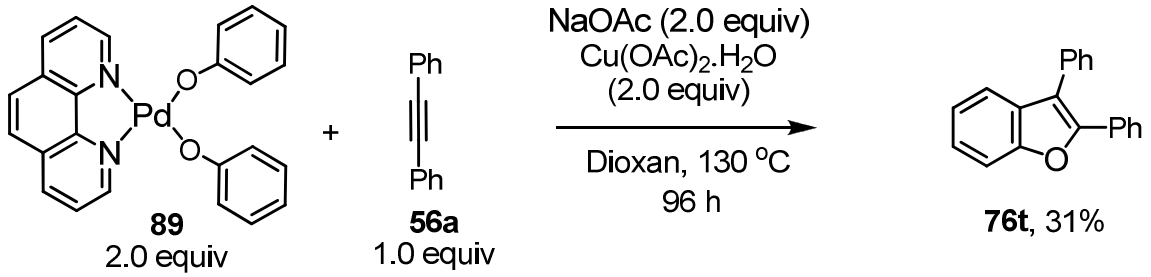
89

Following the procedure described by van Koten group,[27] a solution of sodium phenoxide (206 mg, 1.78 mmol) in a minimum of MeOH (ca. 2.0 mL) was added to a solution of $Pd(OAc)_2$ (200 mg, 0.89 mmol, 1.0 equiv) and 1,10-phenanthroline (176 mg, 1.10 equiv)

in DCM. The resulting dark red mixture was stirred for 1h, after which the solution was evaporated under the reduced pressure. The residue was extracted with DCM, and the extracts were filtered over Celite. The orange filtrate was evaporated and the solid was washed with pentane and dried in vacuum. The solid dark brown complex **89** was obtained in 37% yield (158 mg). We failed to get the crystal of **89**.

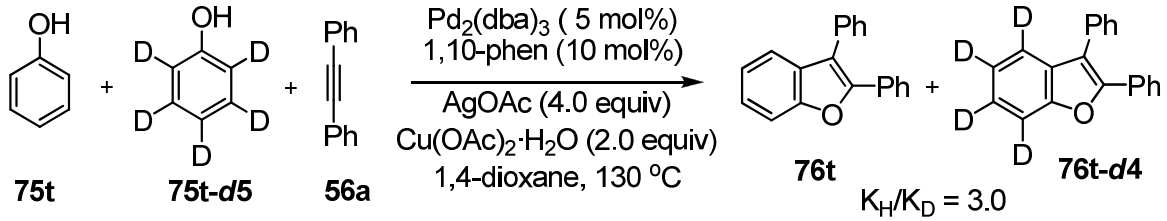
IR (KBr) ν_{max} 3052, 2915, 2849, 1583, 1473, 1402, 1331, 1282, 1172, 1145, 986, 843, 756, 712 cm^{-1}; HRMS calcd for $C_{24}H_{18}N_2O_2Pd$; $[M^+]$: 472.0403. Found: 472.0409.

2.5.5.2. Stoichiometric reaction of 56a with complex 89:



Diphenylacetylene (**56a**; 18 mg, 1.0 mmol) was reacted with complex **89** (50 mg, 2.0 mmol) in the presence of NaOAc (17 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (42 mg, 2.0 mmol) in 1,4-dioxan at 130 °C for 96 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane to afford **76t** (9.0 mg) in 31% yield as colorless thick liquid.

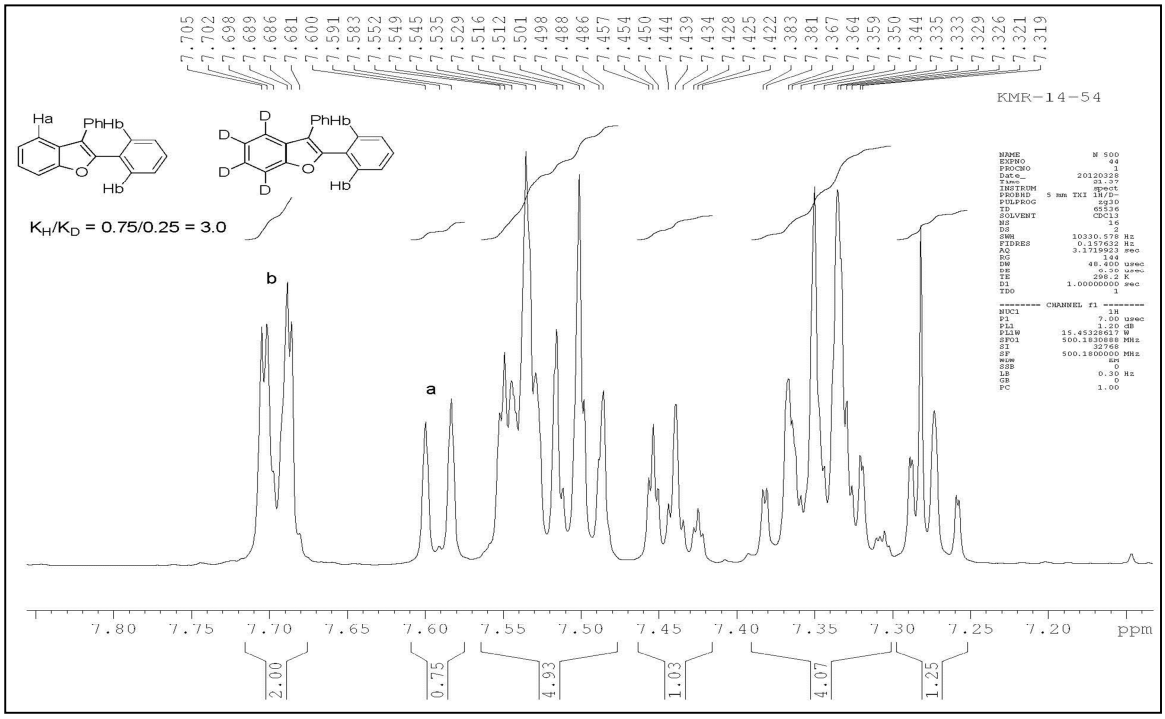
2.5.5.3. Kinetic Isotope Effect:



Following the general procedure (GP-1) in condition A; a mixture of phenol (**75t**; 188 mg, 2.0 mmol), phenol-d_5 (**75-*d*5**; 188 mg, 2.0 mmol), diphenylacetylene (**56a**; 178 mg, 1.0 mmol), AgOAc (333 mg, 2.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (46 mg, 0.05 mmol) and bathophenanthroline (33 mg, 0.1 mmol) in 1,4-dioxan (8.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture

was purified by silica gel column chromatography eluting with hexane to afford the mixture of **76t** and **76t-*d*4**. The K_H/K_D was determined by the analysis followed by Yu et al.[43] The benzofurans ratio **76t** and **76t-*d*4** was analyzed by ^{1}H NMR. The yield of **76t**, **X,** was determined by integration of the H_a signal of **76t**, which appeared as a doublets approximately at 7.59 ppm. The total yield of **76t** and **76t-*d*4**, Y was determined by integration of H_b of **76t** and **76t-*d*4**, which appeared as dd at 7.69 ppm. The yield of **76t-*d*4**, Z, could then be determined from the following formula: Z = Y–X.

Then K_H/K_D = X/Z = 0.75/0.25 = 3.0



2.5.6. X-ray Crystallographic Data

Single crystal X-ray data for the compound **76g, 79b** and **77f (**CCDC 916320-916322**)** were collected using the detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3^o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software[44] was used for the intensity data acquisition and the SAINTPLUS Software[1] was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program,[45] an empirical absorption correction using equivalent reflections was performed with the program. The structure was

solved using SHELXS-97,[44] and full-matrix least-squares refinement against F^2 was carried out using SHELXL-97.[44] All non-hydrogen atoms were refined anisotropically. Aromatic and methyl hydrogens were introduced on calculated positions and included in the refinement riding on their respective parent atoms.

Table 2.6: Crystallographic data and structural refinement for **76g**, **79b** and **77f**

Identification code	**76g**	**79b**	**77f**
Formula	$C_{20}H_{13}FO$	$C_{32}H_{30}O_2$	C_{18} H_{17} N O_3
F_w	288.30	446.56	295.33
T (K)	298(2)	298(2)	298(2)
λ (Å)	0.71073	0.71073	0.71073
Crystal system	orthorhombic	monoclinic	monoclinic
Space group	*Pbca*	*P2(1)*	*P2(1)/c*
a (Å)	11.1564(18)	6.887(2)	12.3688(16)
b (Å)	7.9043(13)	8.017(3)	10.9706(14)
c (Å)	32.896(5)	21.967(7)	11.0819(14)
α (^{o})	90	90.00	90.00
β (^{o})	90	93.822(6)	93.787(2)
γ (^{o})	90	90.00	90.00
V (Å^3)	2900.9(8)	1210.3(7)	1500.5(3)
Z	8	2	4
ρ_{calcd} (Mg m^{-3})	1.320	1.225	1.307
μ (mm^{-1})	0.089	0.075	0.089
F (000)	1200	476	624
Crystal Size (mm)	0.80 × 0.80 × 0.60	0.60 × 0.24 × 0.14	0.32× 0.24 × 0.20
2θ range/deg	1.24 / 24.88	1.86/25.08	1.65/25.96
Reflections collected	25190	11634	14977
Unique reflections	2514	4265	2926
Completeness to 2θ (%)	24.88 (99.80)	25.08(99.50)	25.96(99.60)
T_{max}, T_{min}	0.9842, 0.9790	0.9852, 0.9809	0.9824, 0.9720
Parameters	199	320	218
GOF (F^2)	1.054	1.061	1.023
R1, *wR2 [I>2σ(I)]*	0.0375, 0.0941	0.0515, 0.1114	0.0495, 0.1256
R1, *wR2* (all data)	0.0415, 0.0972	0.0684, 0.1182	0.0568, 0.1330
Largest diff. Peak and hole (e·Å^{-3})	0.164 and -0.178	0.145 and -0.116	0.195 and -0.332

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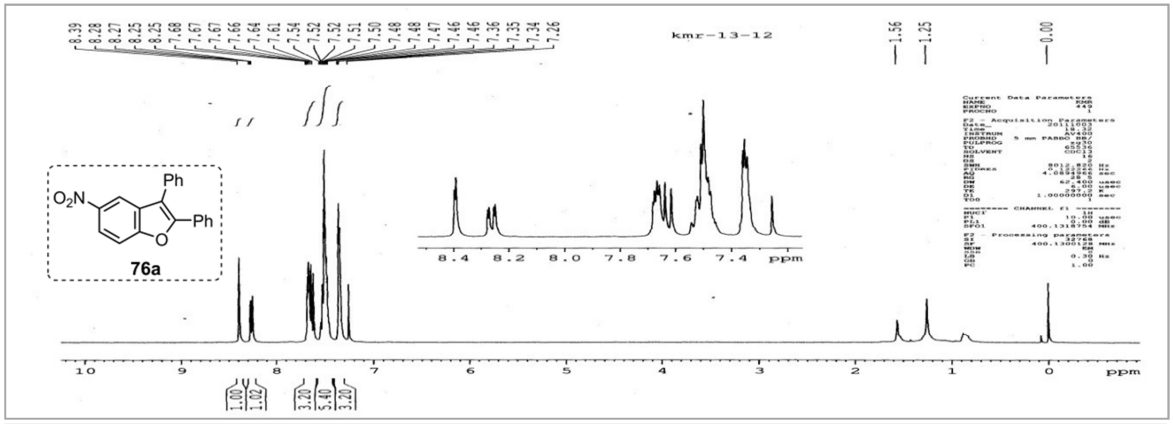
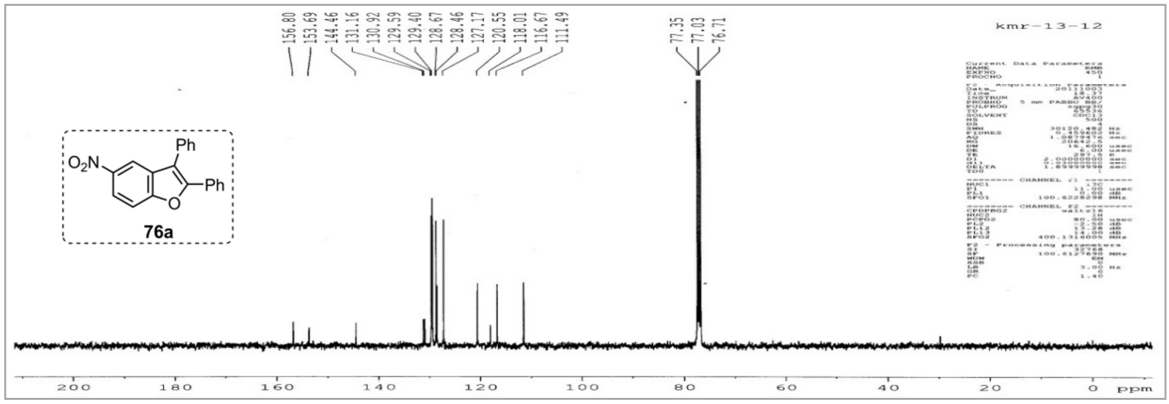
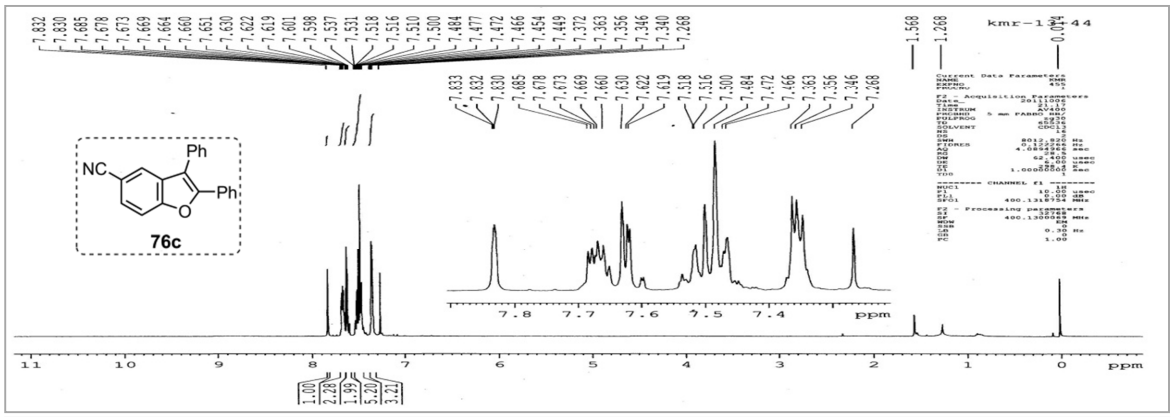
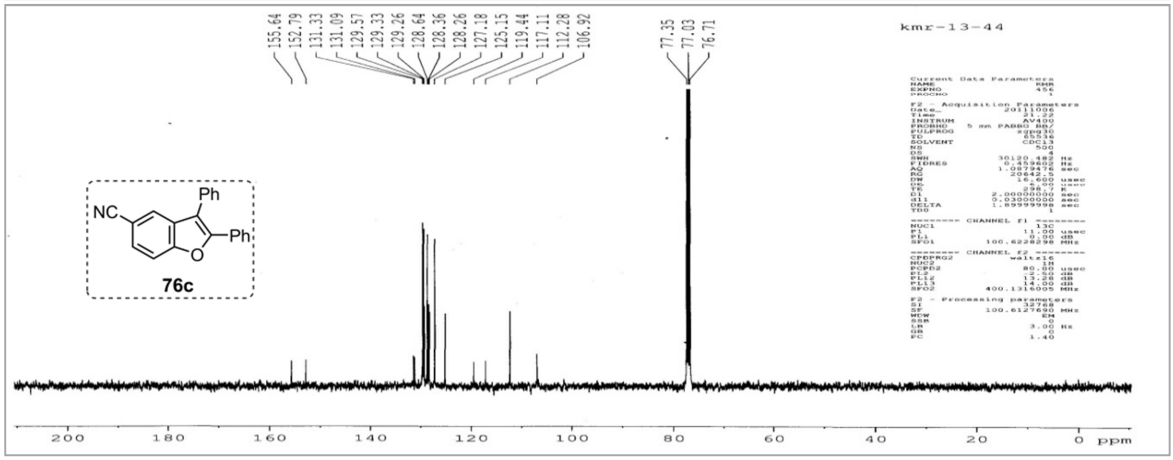
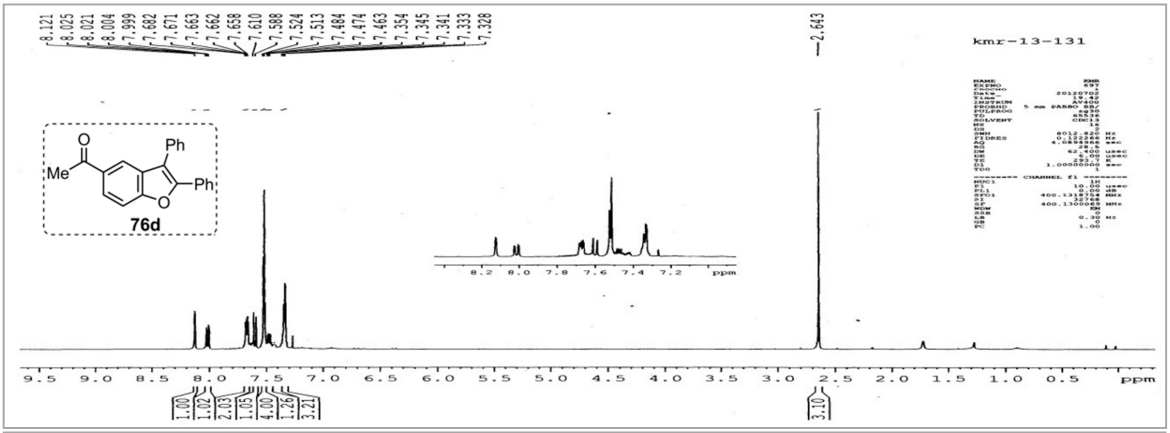
2.7. Spectra







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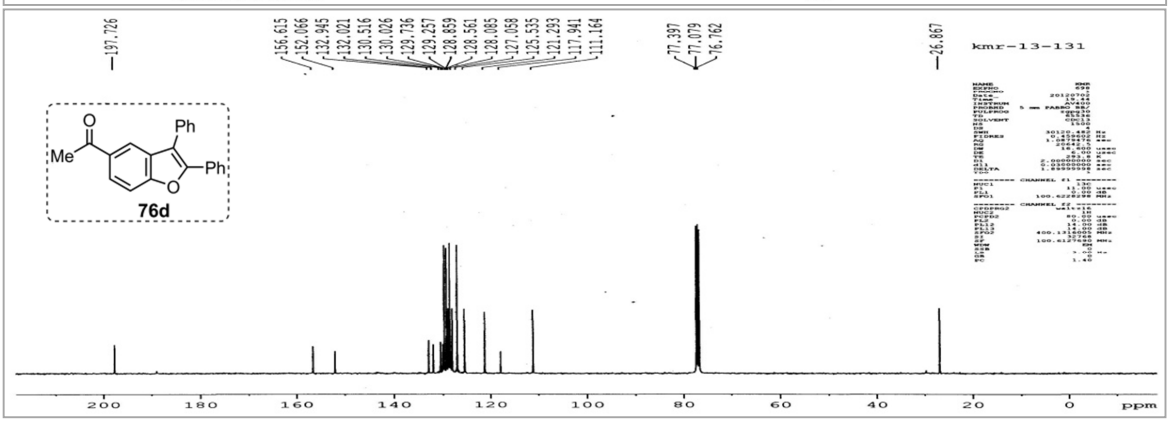
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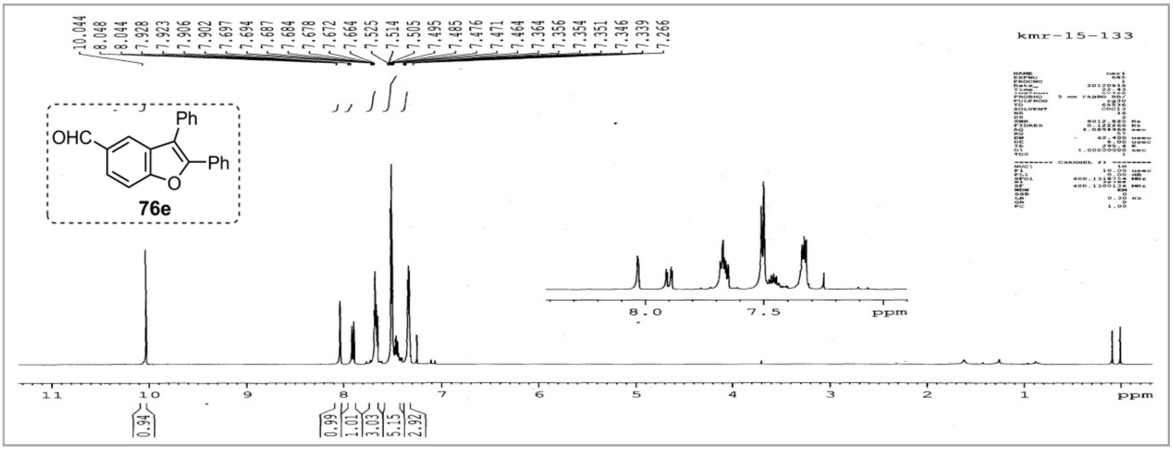
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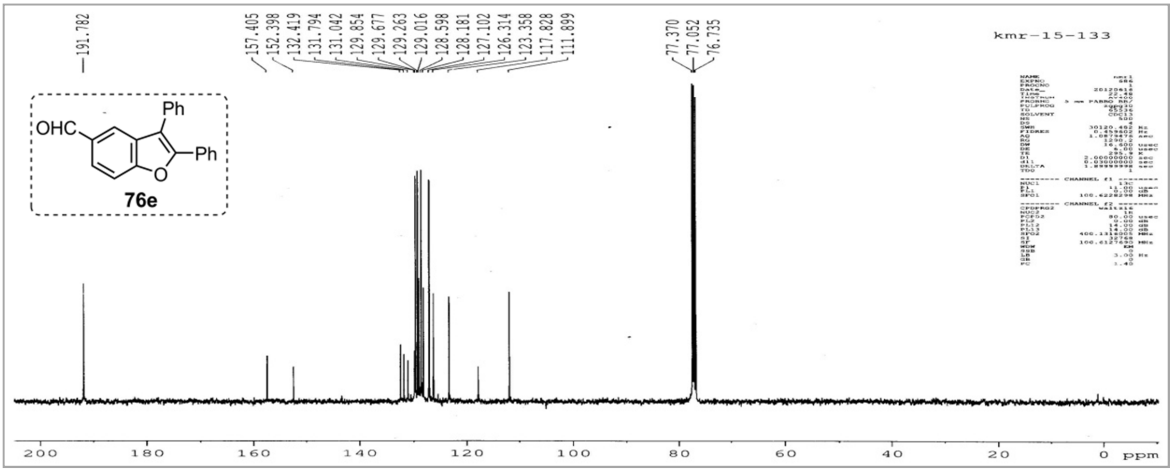
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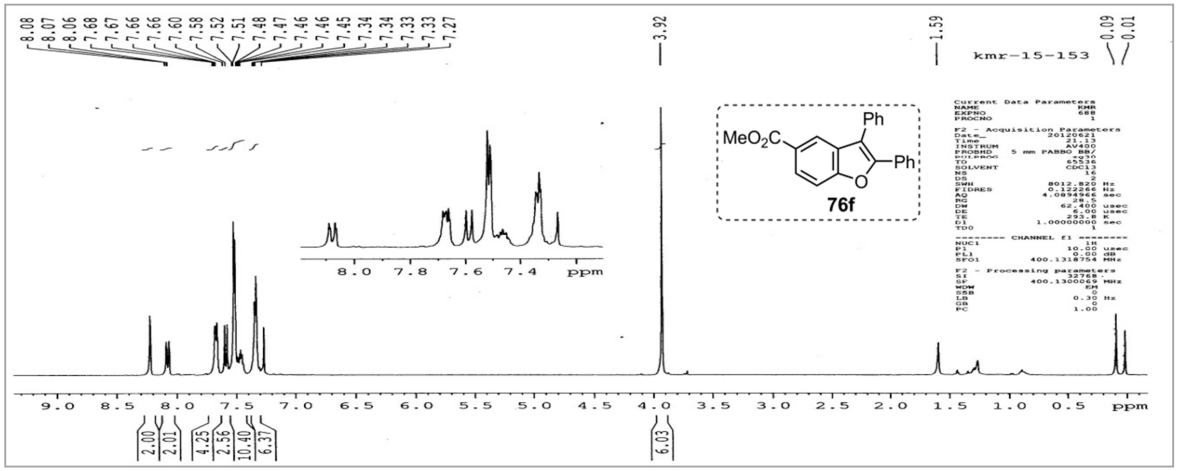
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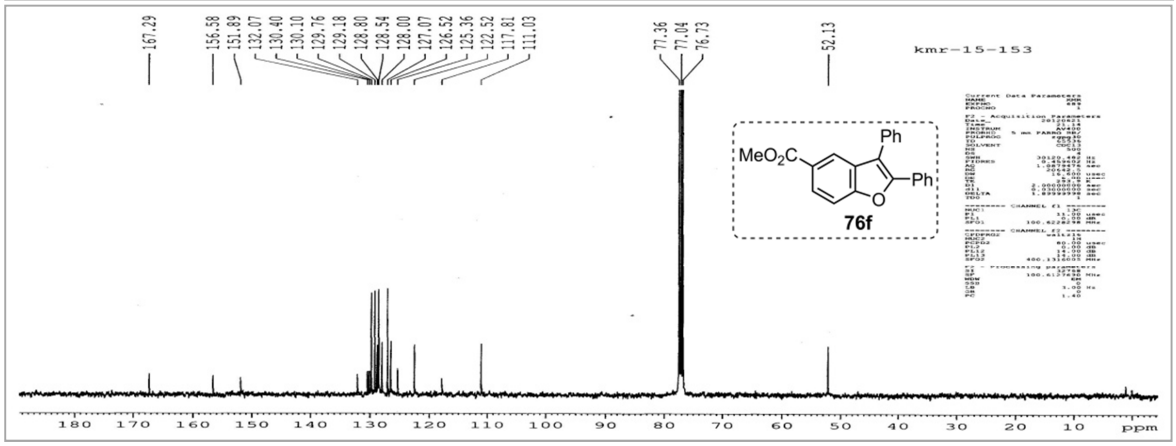
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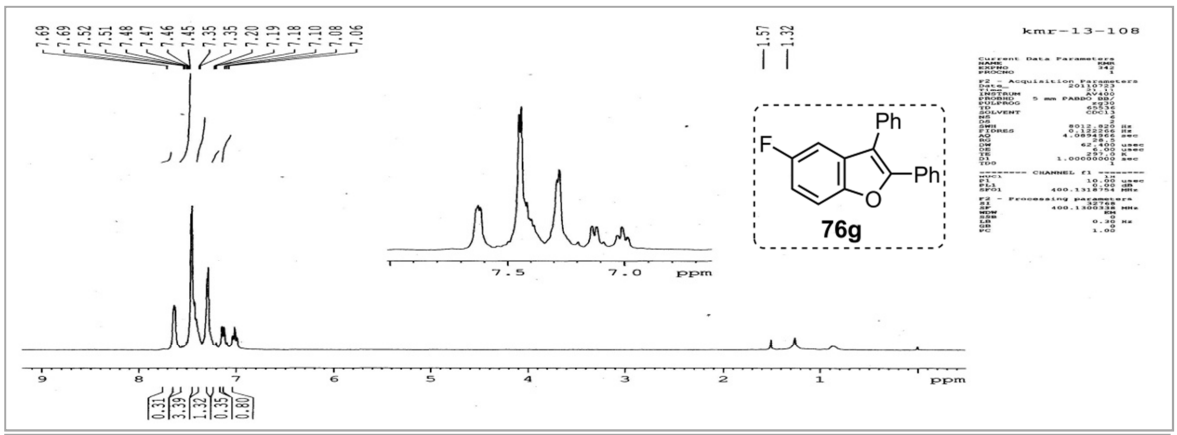
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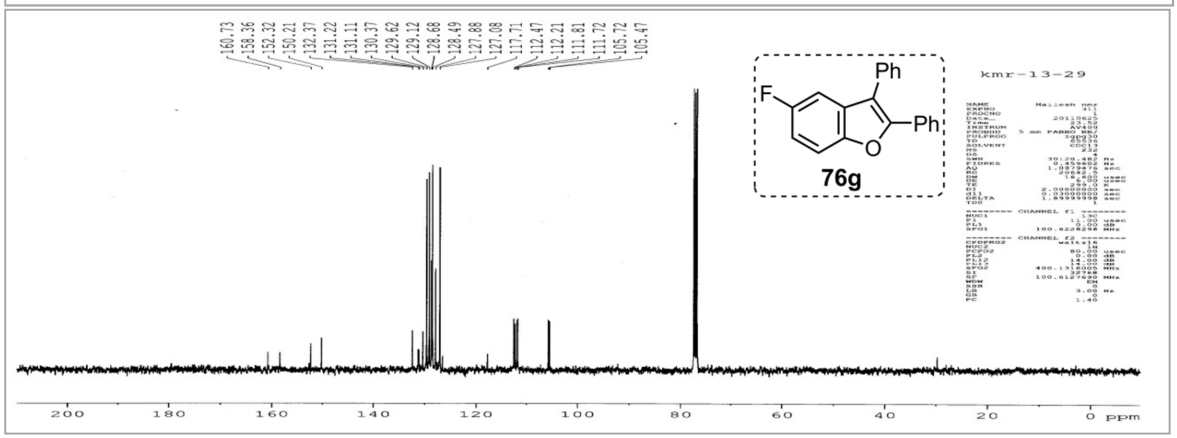
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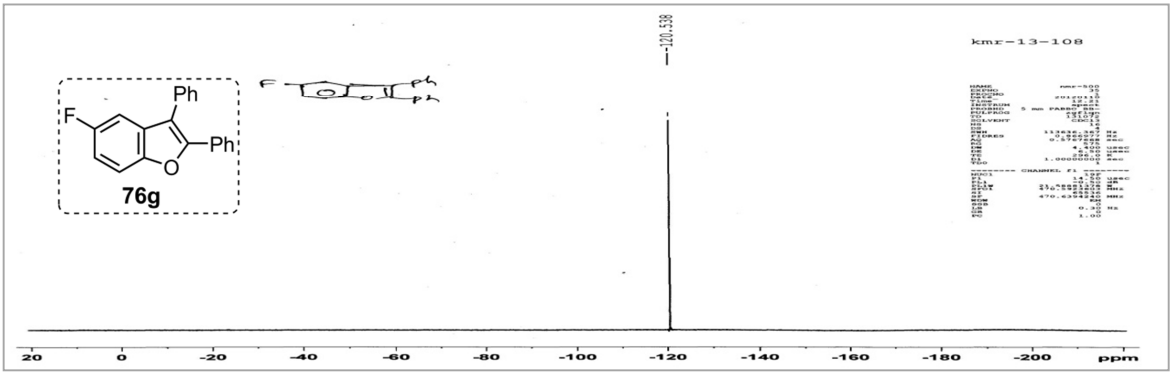
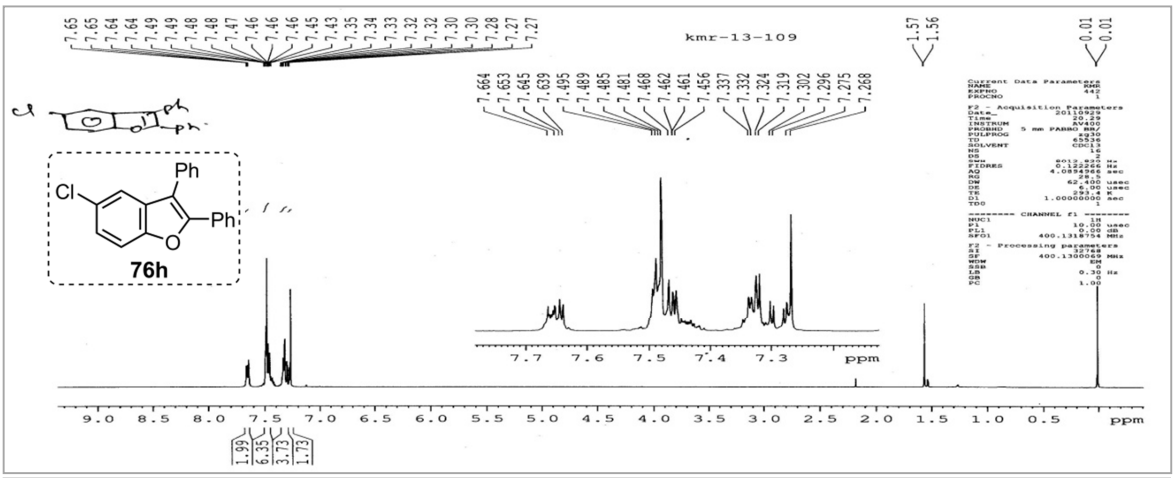
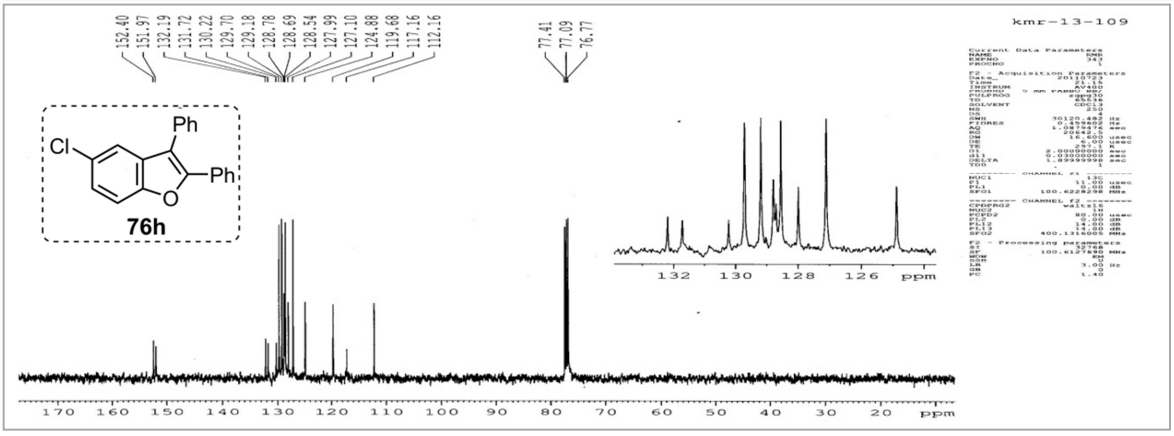
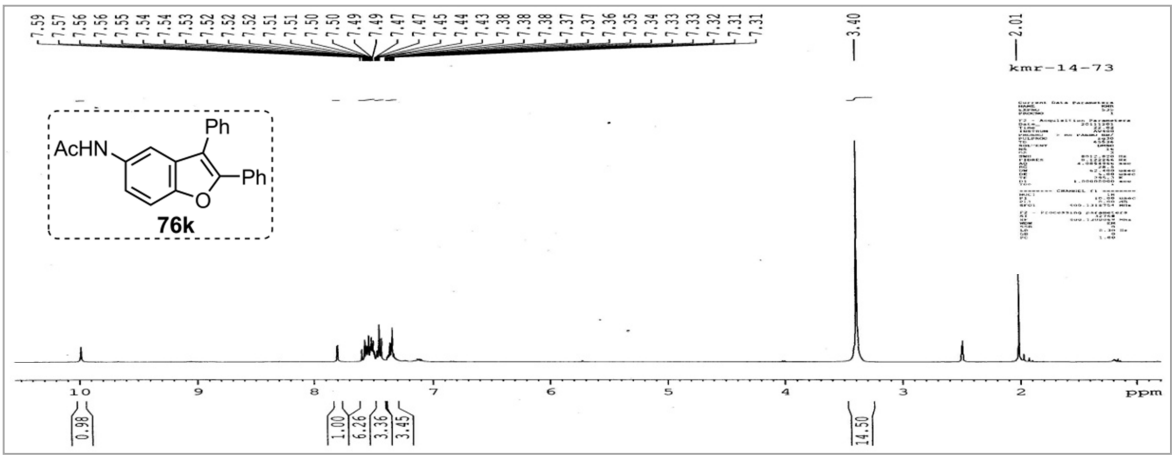
O
76g


kmr-13-108
-120.538
F
Ph
Ph
O
76g
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm


kmr-13-109
7.65
7.65
7.64
7.64
7.49
7.48
7.48
7.47
7.46
7.46
7.45
7.43
7.35
7.34
7.33
7.32
7.32
7.30
7.30
7.28
7.27
7.27
1.57
1.56
0.01
0.01
7.664
7.653
7.645
7.639
7.495
7.489
7.485
7.481
7.468
7.462
7.461
7.456
7.337
7.332
7.324
7.319
7.302
7.296
7.275
7.268
Cl
Ph
Ph
O
76h
7.7
7.6
7.5
7.4
7.3
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.99
6.35
3.73
1.73


kmr-13-109
152.40
151.97
132.19
131.72
130.22
129.70
129.18
128.78
128.69
128.54
127.99
127.10
124.88
119.68
117.16
112.16
77.41
77.09
76.77
Cl
Ph
Ph
O
76h
132
130
128
126
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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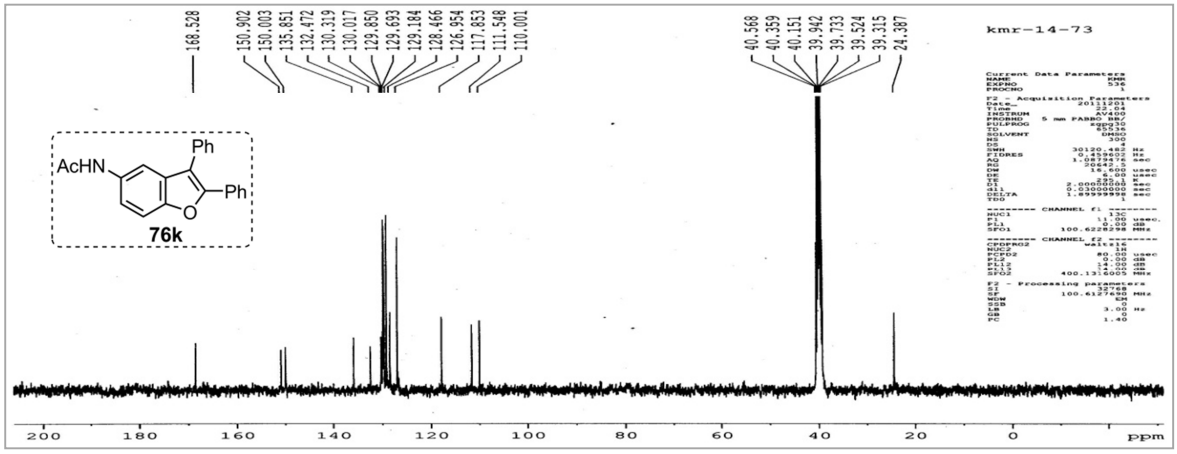
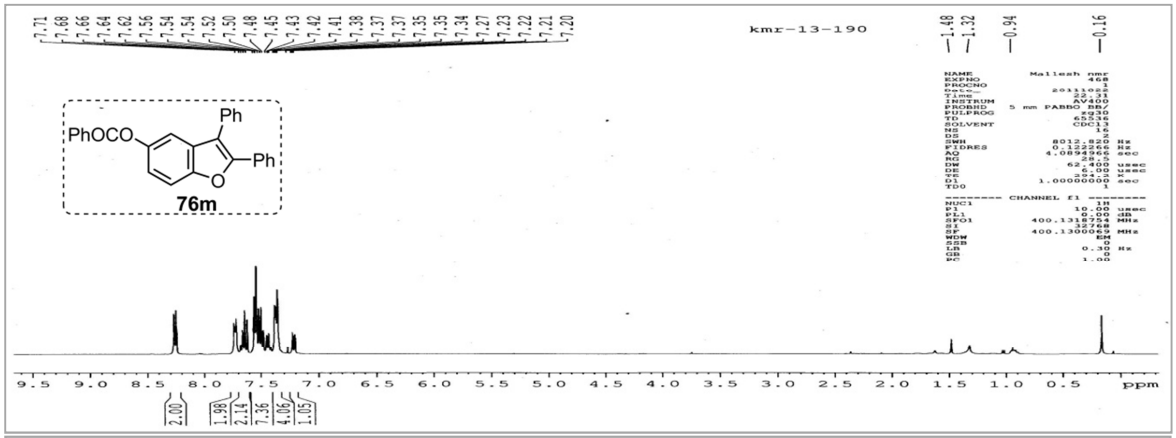
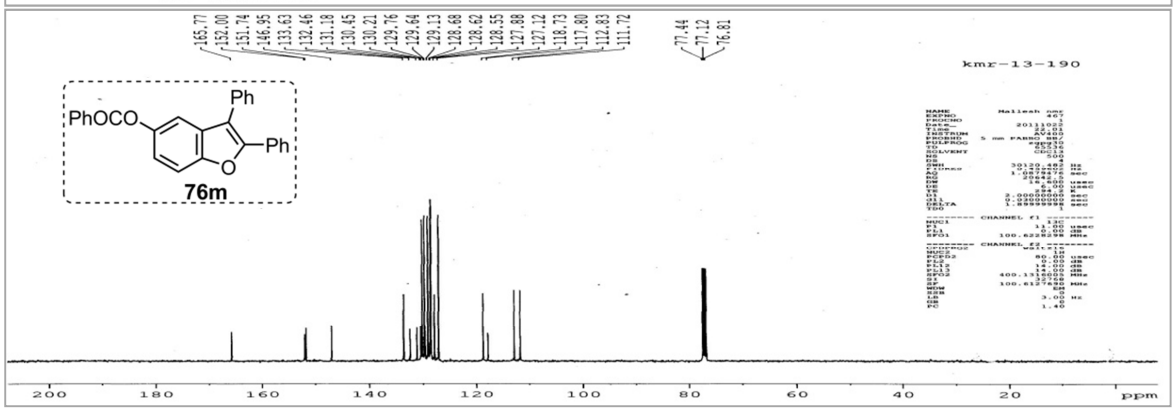
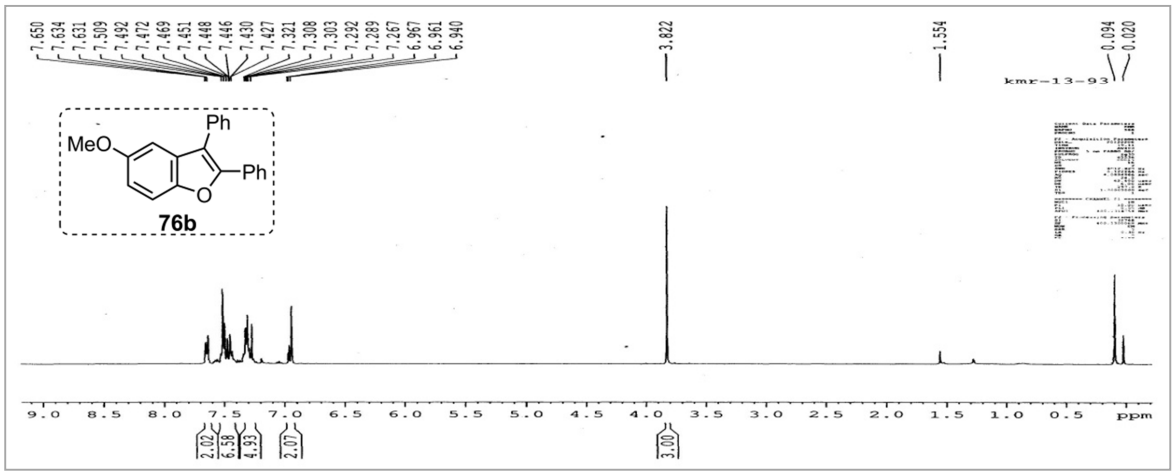
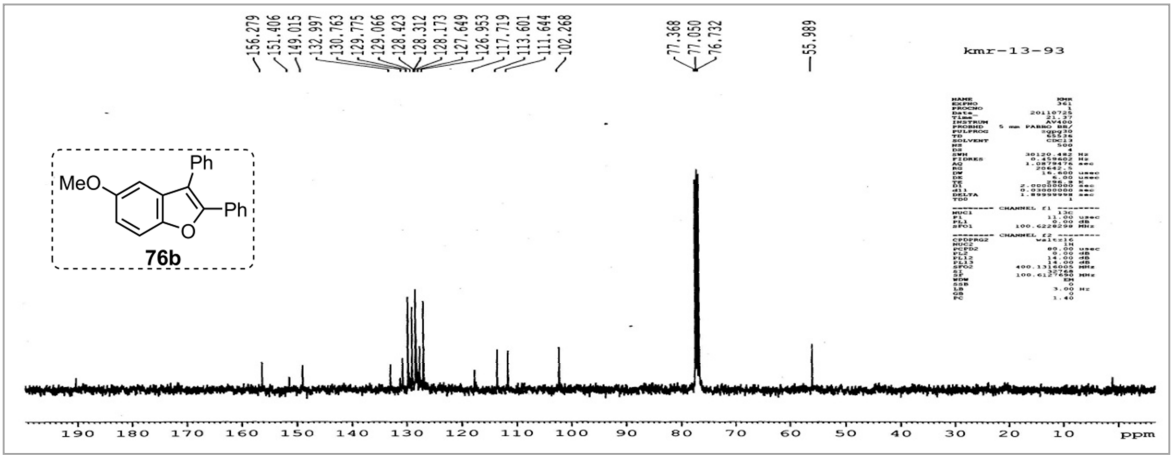
7.57
7.56
7.56
7.55
7.54
7.54
7.53
7.52
7.52
7.52
7.51
7.51
7.50
7.50
7.49
7.49
7.47
7.45
7.44
7.43
7.38
7.38
7.37
7.37
7.36
7.35
7.34
7.33
7.32
7.31
7.31
3.40
2.01
kmr-14-73
AcHN
Ph
Ph
O
76k
10
9
8
7
6
5
4
3
2
ppm
0.98
1.00
6.26
3.36
3.45
14.50

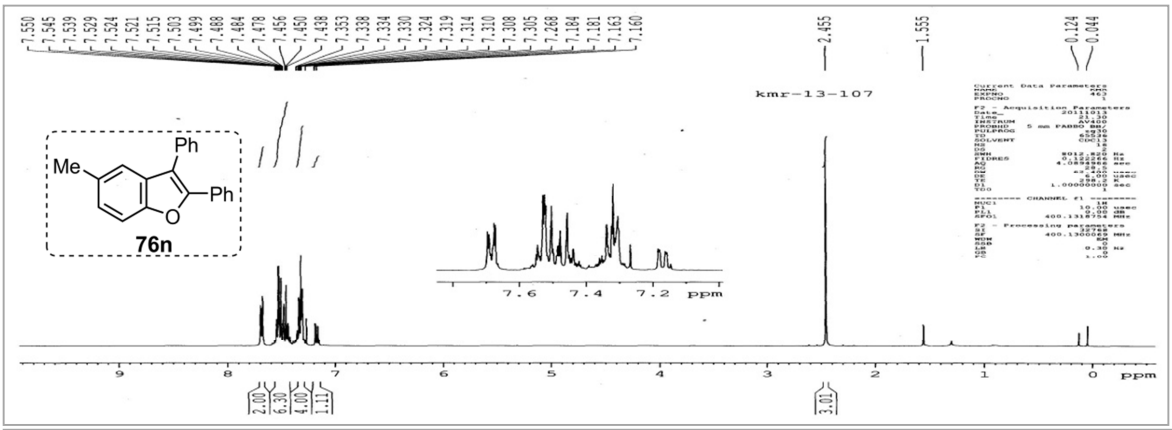

168.528
150.902
150.003
135.851
132.472
130.319
130.017
129.850
129.693
129.184
128.466
126.954
117.853
111.548
110.001
40.568
40.359
40.151
39.942
39.733
39.524
39.315
24.387
kmr-14-73
AcHN
Ph
Ph
O
76k
200
180
160
140
120
100
80
60
40
20
0
ppm

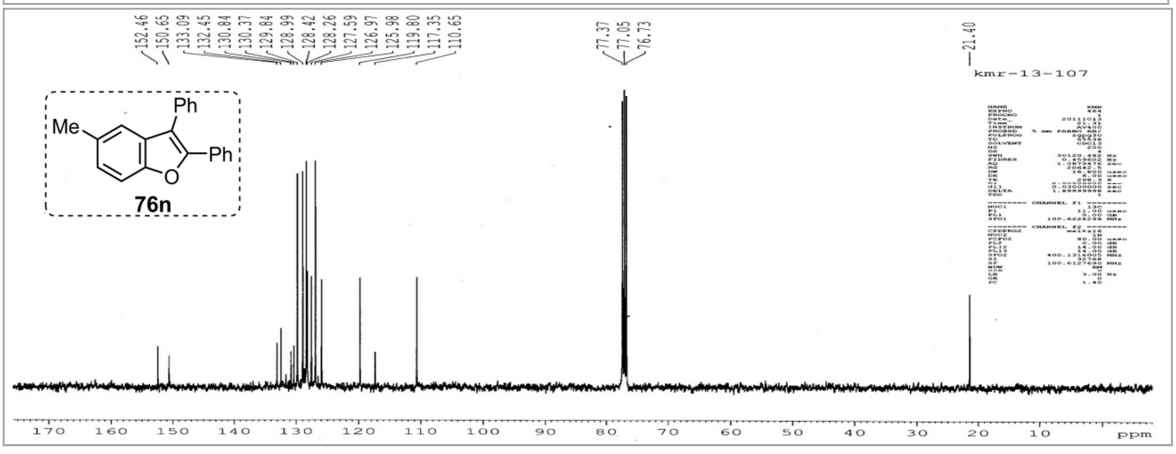

7.71
7.68
7.66
7.64
7.62
7.56
7.54
7.54
7.52
7.50
7.48
7.45
7.43
7.42
7.41
7.38
7.37
7.37
7.35
7.35
7.34
7.27
7.23
7.22
7.21
7.20
kmr-13-190
1.48
1.32
0.94
0.16
PhOCO
Ph
Ph
O
76m
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
1.98
2.14
7.36
4.06
1.05

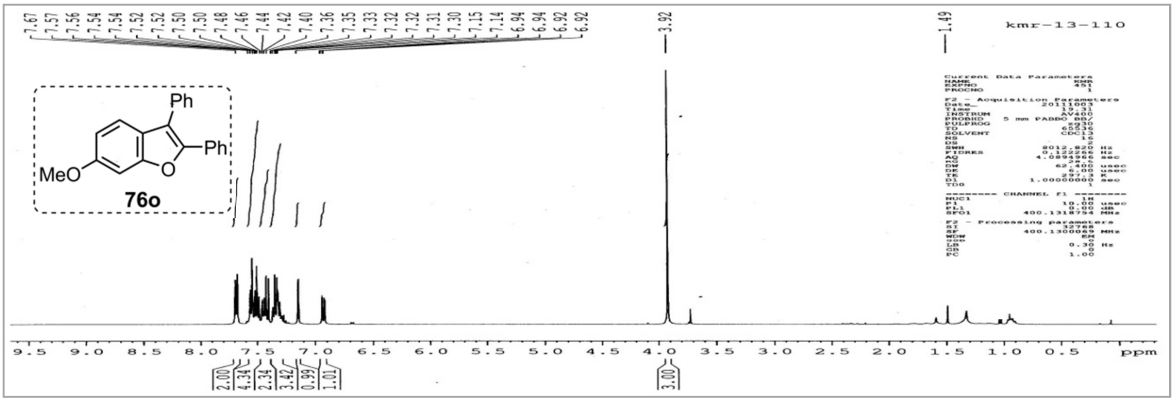

165.77
152.00
151.74
146.95
133.63
132.46
131.18
130.45
130.21
129.76
129.64
129.13
128.68
128.62
128.55
127.88
127.12
118.73
117.80
112.83
111.72
77.44
77.12
76.81
kmr-13-190
PhOCO
Ph
Ph
O
76m
200
180
160
140
120
100
80
60
40
20
ppm

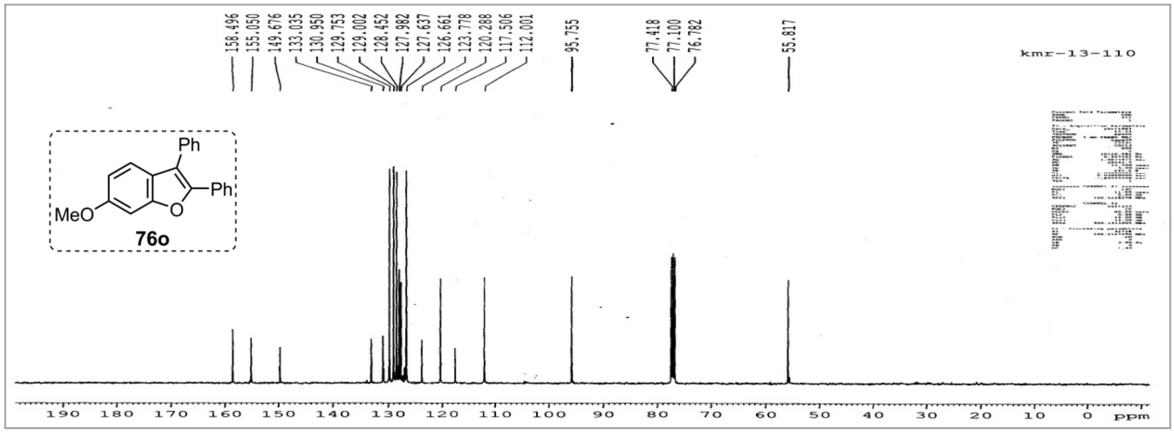

7.650
7.634
7.631
7.509
7.492
7.472
7.469
7.451
7.448
7.446
7.430
7.427
7.321
7.308
7.303
7.292
7.289
7.267
6.967
6.961
6.940
3.822
1.554
0.094
0.020
kmr-13-93
MeO
Ph
Ph
O
76b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.02
6.58
4.93
2.07
3.00


kmr-13-93
MeO
Ph
Ph
O
76b


kmr-13-107
Me
Ph
Ph
O
76n


kmr-13-107
Me
Ph
Ph
O
76n


kmr-13-110
MeO
Ph
Ph
O
76o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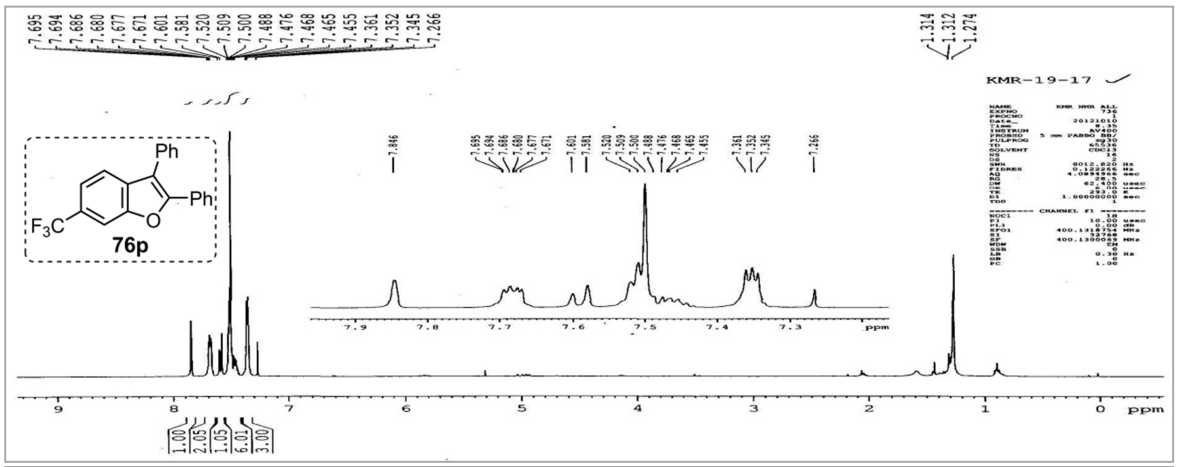
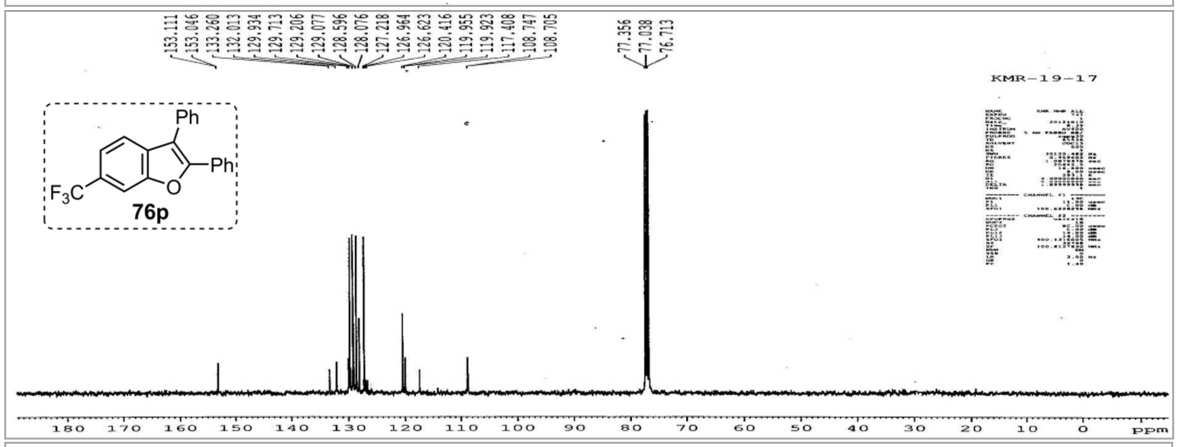
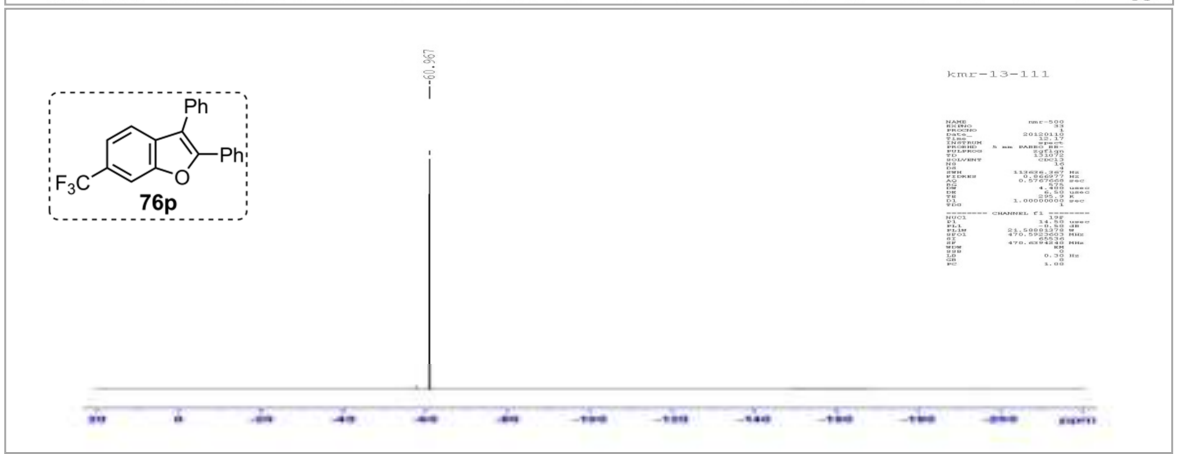
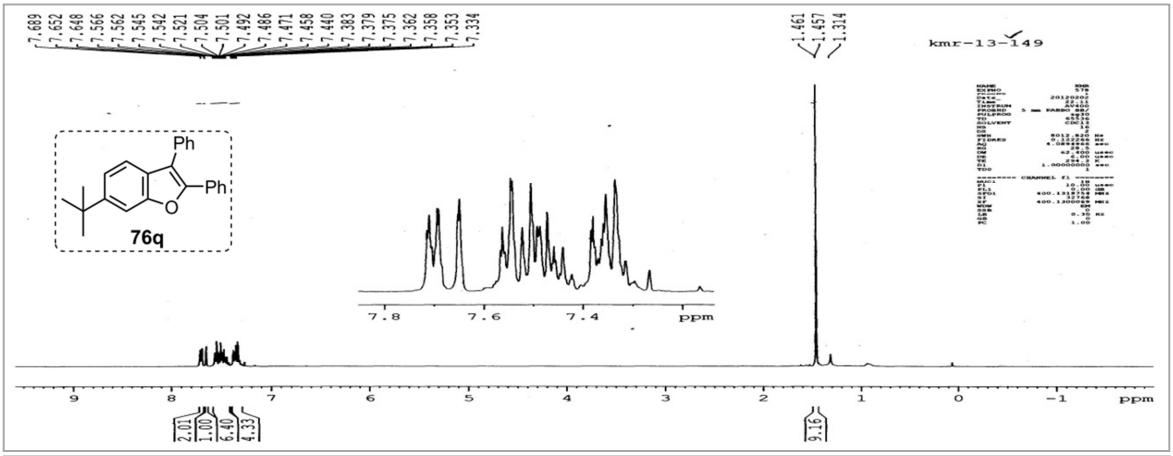
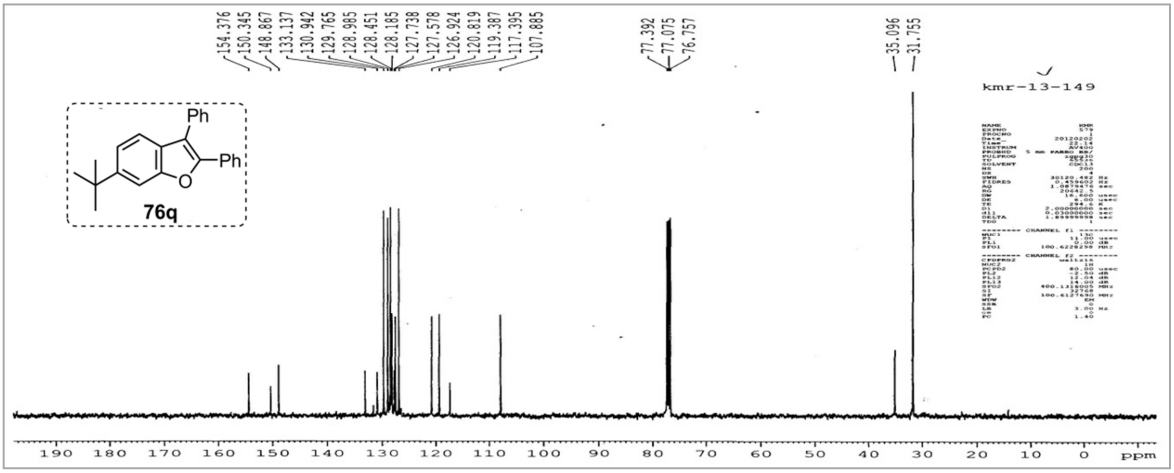
155.050
149.676
133.035
130.950
129.753
129.002
128.452
127.982
127.637
126.661
123.778
120.288
117.506
112.001
95.755
77.418
77.100
76.782
55.817
kmr-13-110
Ph
Ph
MeO
O
76o
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

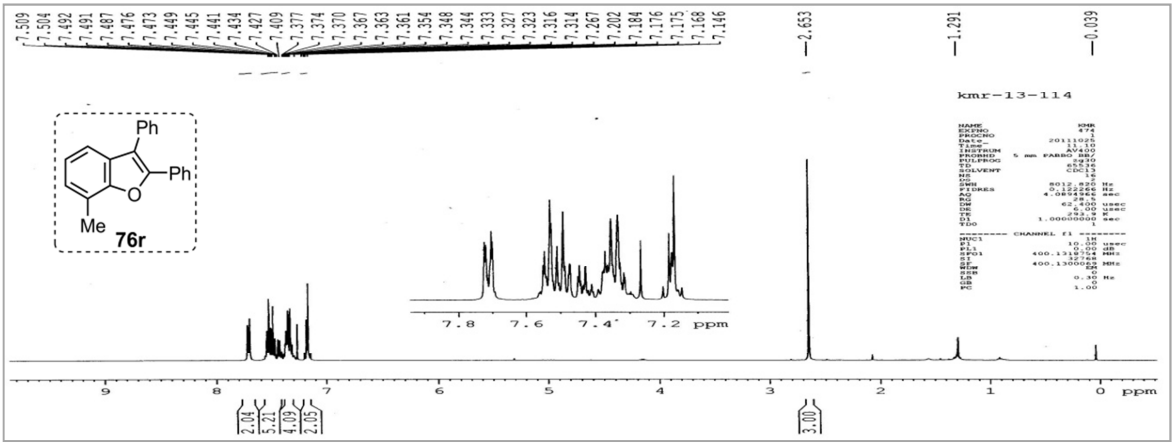

7.695
7.694
7.686
7.680
7.677
7.671
7.601
7.581
7.520
7.509
7.500
7.488
7.476
7.468
7.465
7.455
7.361
7.352
7.345
7.266
1.314
1.312
1.274
KMR-19-17
Ph
Ph
F3C
O
76p
1.846
7.695
7.694
7.686
7.680
7.677
7.671
7.601
7.581
7.520
7.509
7.500
7.488
7.476
7.468
7.465
7.455
7.361
7.352
7.345
7.266
7.9 7.8 7.7 7.6 7.5 7.4 7.3 ppm
9 8 7 6 5 4 3 2 1 0 ppm
1.00
2.05
1.05
6.01
3.00

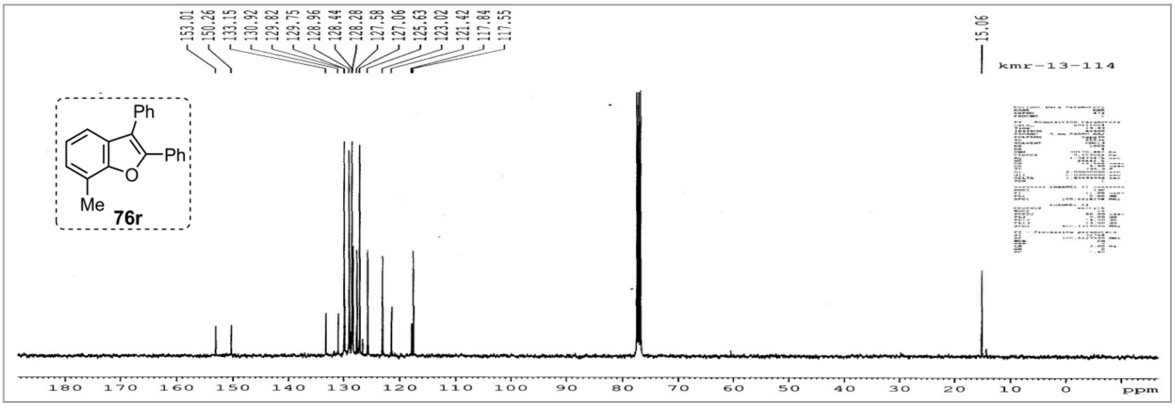

153.111
153.046
133.260
132.013
129.934
129.713
129.206
129.077
128.596
128.076
127.218
126.964
126.623
120.416
119.955
119.923
117.408
108.747
108.705
77.356
77.038
76.713
KMR-19-17
Ph
Ph
F3C
O
76p
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

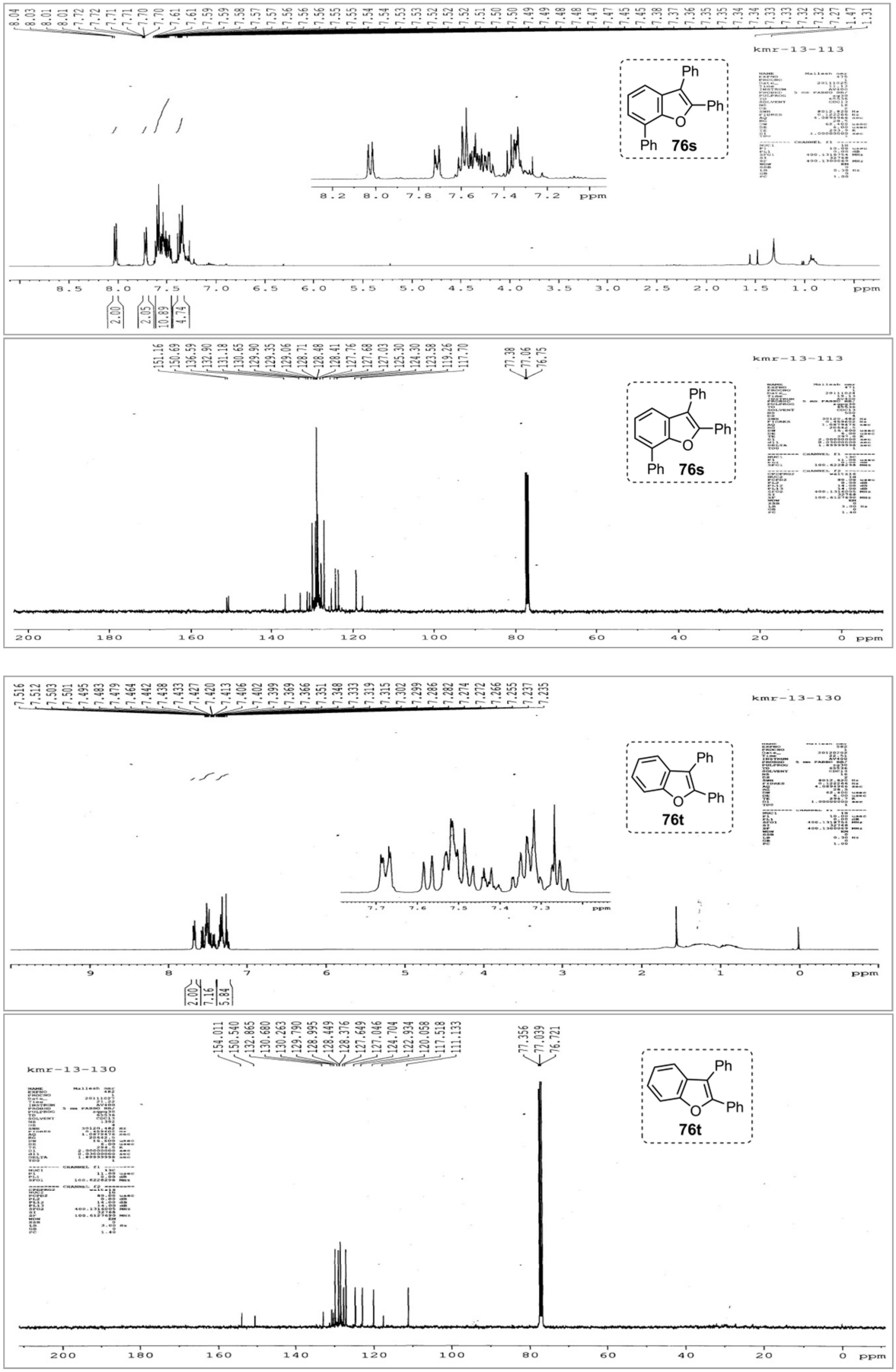

60.967
kmr-13-111
Ph
Ph
F3C
O
76p

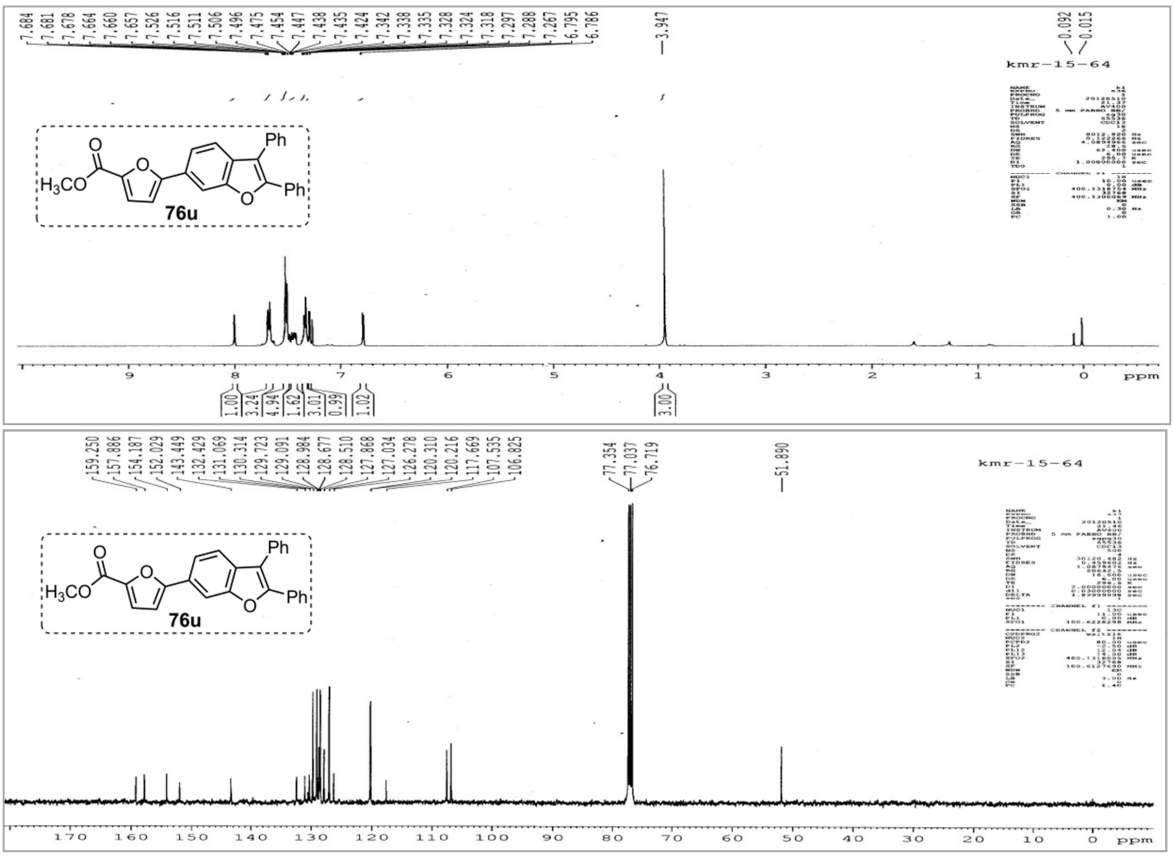

kmr-13-149
Ph
Ph
O
76q


kmr-13-149
Ph
Ph
O
76q

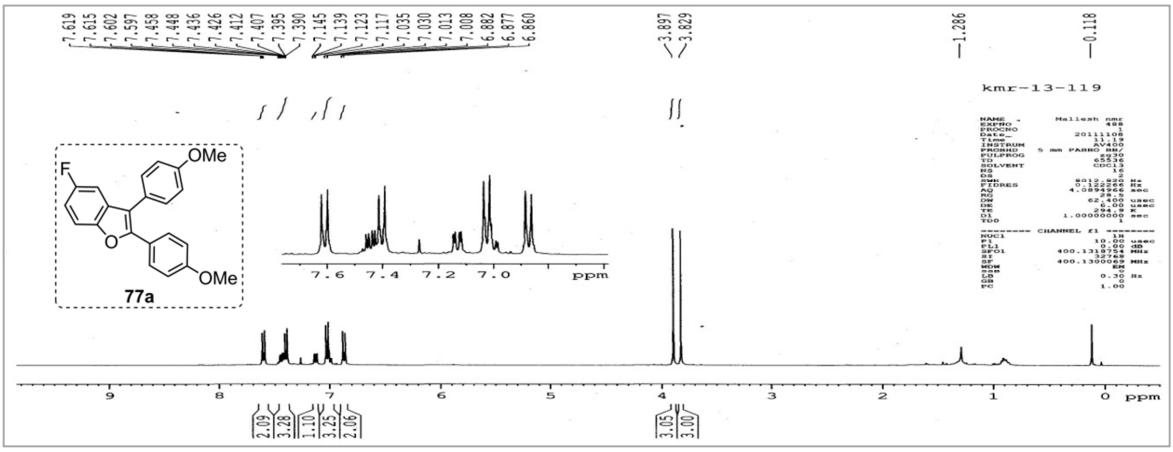

kmr-13-114
Ph
Ph
O
Me
76r

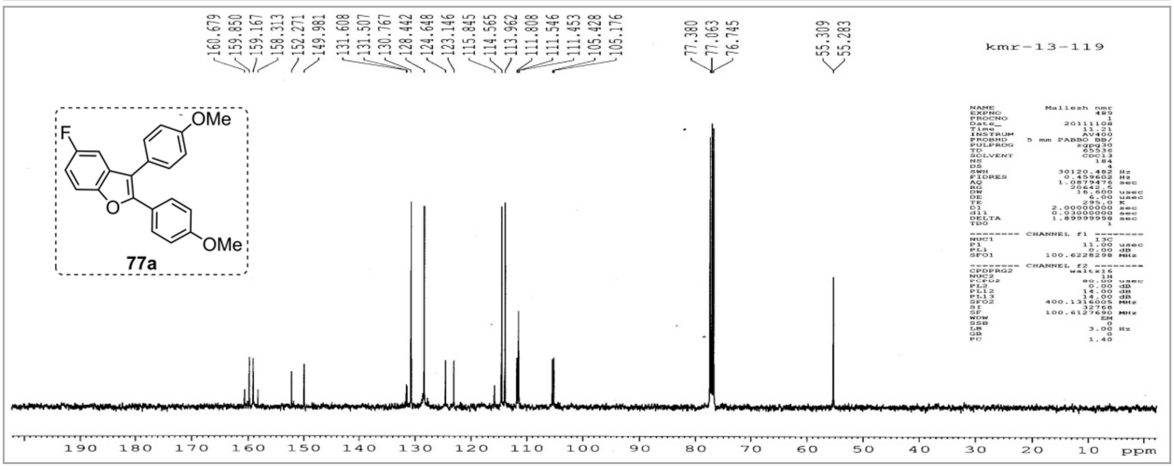

kmr-13-114
Ph
Ph
O
Me
76r

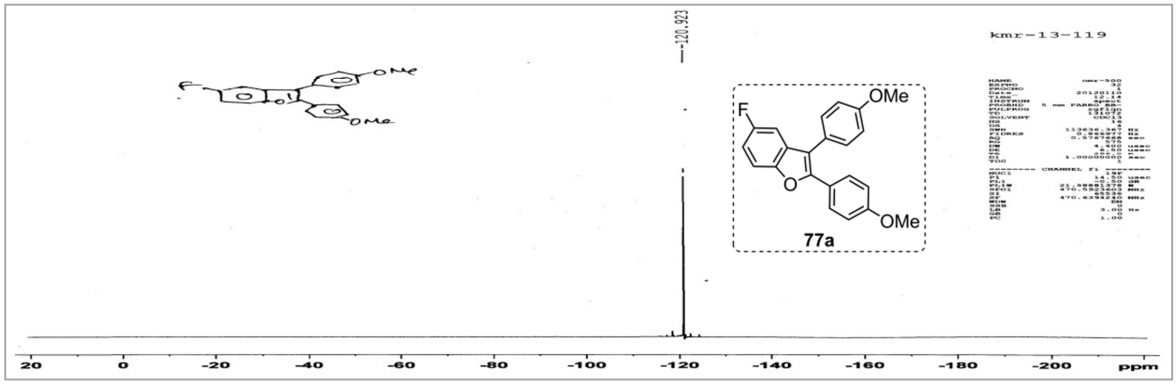

kmr-13-113
Ph
Ph
Ph
76s
kmr-13-130
76t

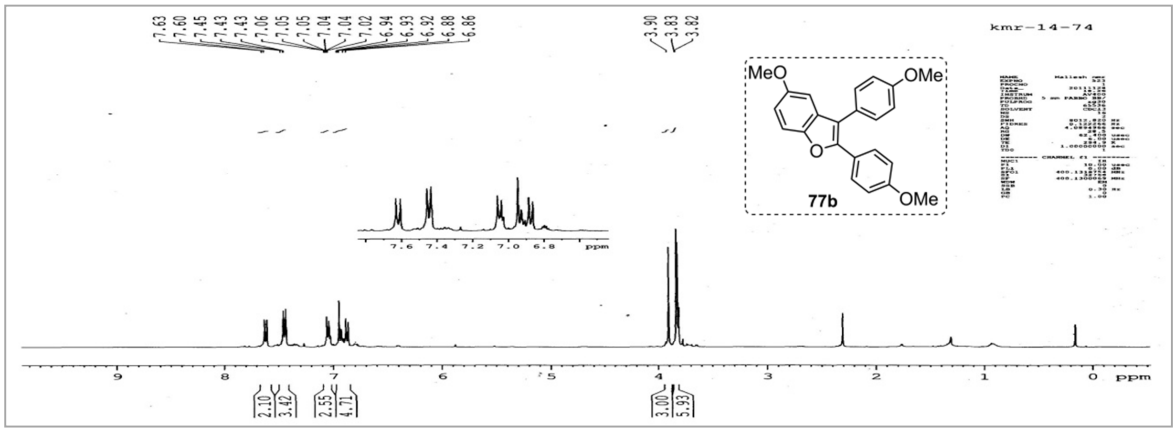

kmr-15-64
76u
ppm

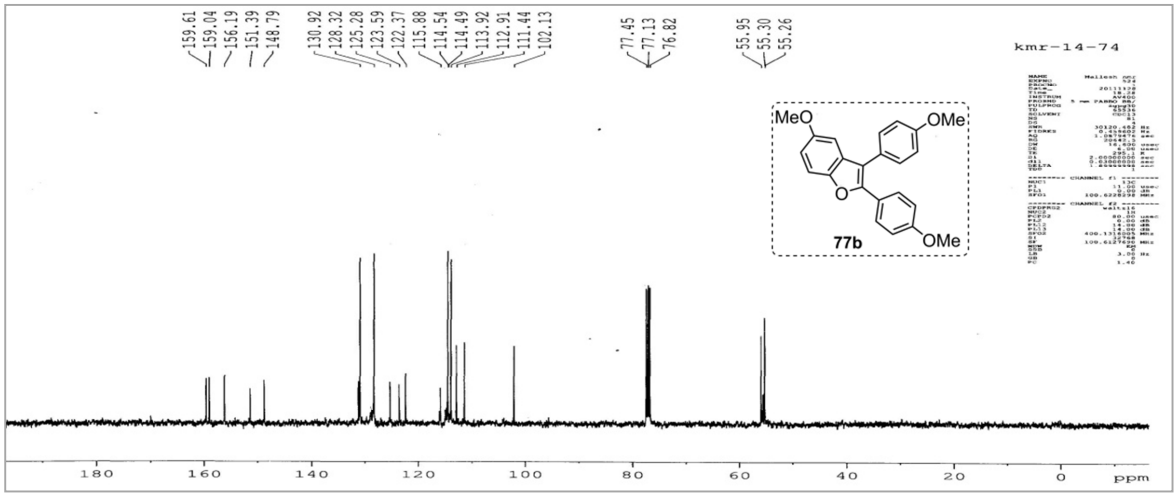
kmr-15-64
76u
ppm

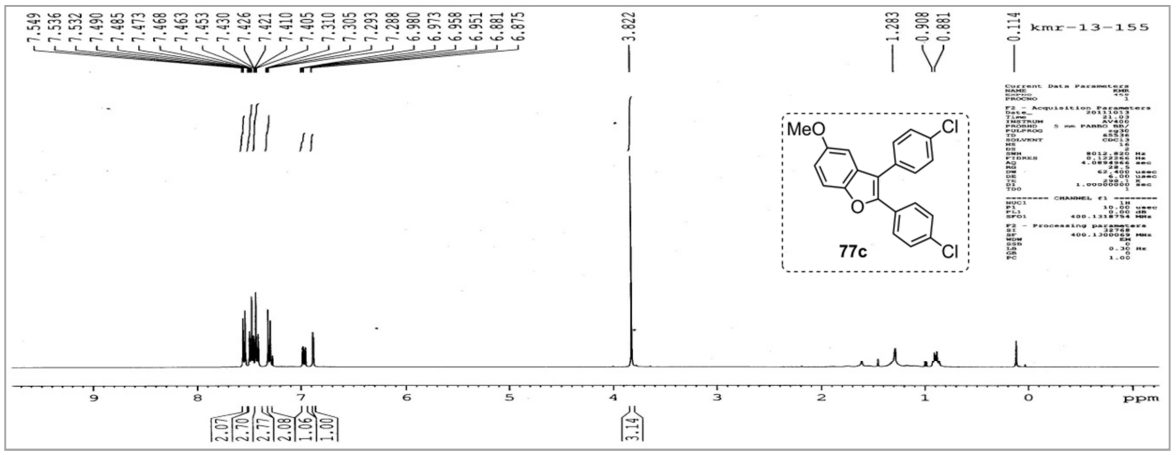

kmr-13-119
77a
ppm


kmr-13-119
77a
ppm


kmr-13-119
-100.923
F
OMe
OMe
77a
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm


kmr-14-74
7.63
7.60
7.45
7.43
7.43
7.06
7.05
7.05
7.04
7.04
7.02
6.94
6.93
6.92
6.88
6.86
3.90
3.83
3.82
MeO
OMe
77b
OMe
2.10
3.42
2.65
4.71
3.00
5.93
9
8
7
6
5
4
3
2
1
0
ppm


kmr-14-74
159.61
159.04
156.19
151.39
148.79
130.92
128.32
125.28
123.59
122.37
115.88
114.54
114.49
113.92
112.91
111.44
102.13
77.45
77.13
76.82
55.95
55.30
55.26
MeO
OMe
77b
OMe
180
160
140
120
100
80
60
40
20
0
ppm


kmr-13-155
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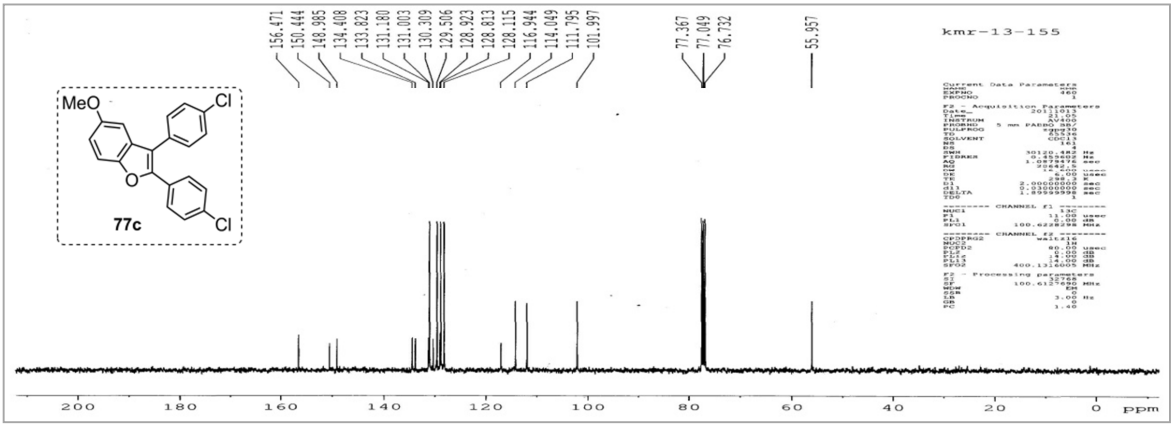
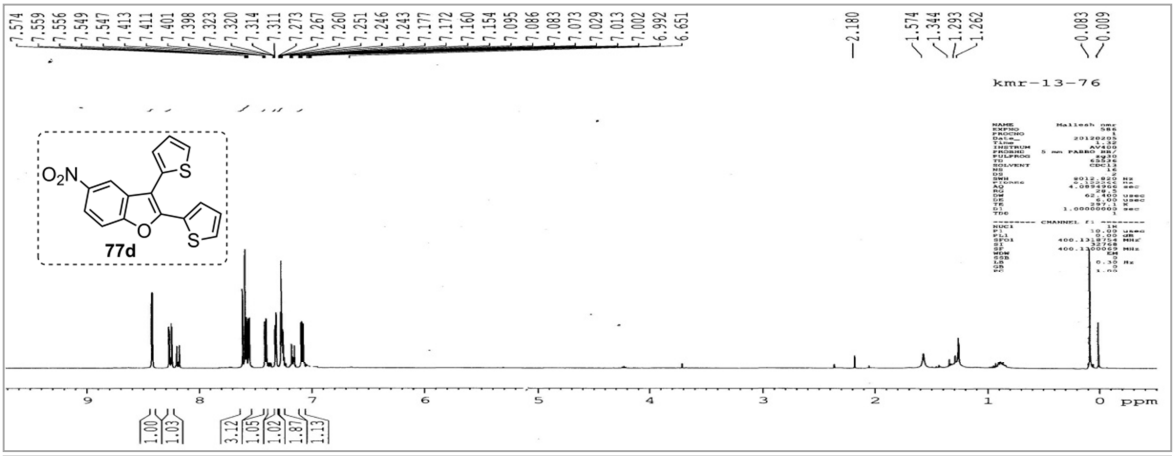
7.536
7.532
7.490
7.485
7.473
7.468
7.463
7.453
7.430
7.426
7.421
7.410
7.405
7.310
7.305
7.293
7.288
6.980
6.973
6.958
6.951
6.881
6.875
3.822
1.283
0.908
0.881
0.114
MeO
Cl
77c
Cl
9
8
7
6
5
4
3
2
1
0
ppm
2.07
2.70
2.77
2.08
1.06
1.00
3.14


156.471
150.444
148.985
134.408
133.823
131.180
131.003
130.309
129.506
128.923
128.813
128.115
116.944
114.049
111.795
101.997
77.367
77.049
76.732
55.957
kmr-13-155
MeO
Cl
O
Cl
77c
200
180
160
140
120
100
80
60
40
20
0
ppm


7.574
7.559
7.556
7.549
7.547
7.413
7.411
7.401
7.398
7.323
7.320
7.314
7.311
7.273
7.267
7.260
7.251
7.246
7.243
7.177
7.172
7.160
7.154
7.095
7.086
7.083
7.073
7.029
7.013
7.002
6.992
6.651
2.180
1.574
1.344
1.293
1.262
0.083
0.009
kmr-13-76
O2N
S
O
S
77d
9
8
7
6
5
4
3
2
1
0
ppm
1.00
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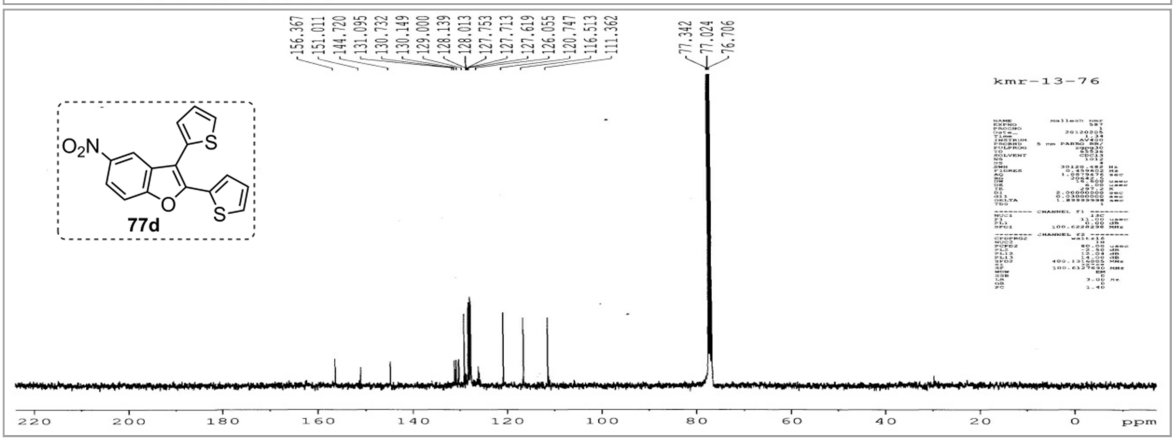
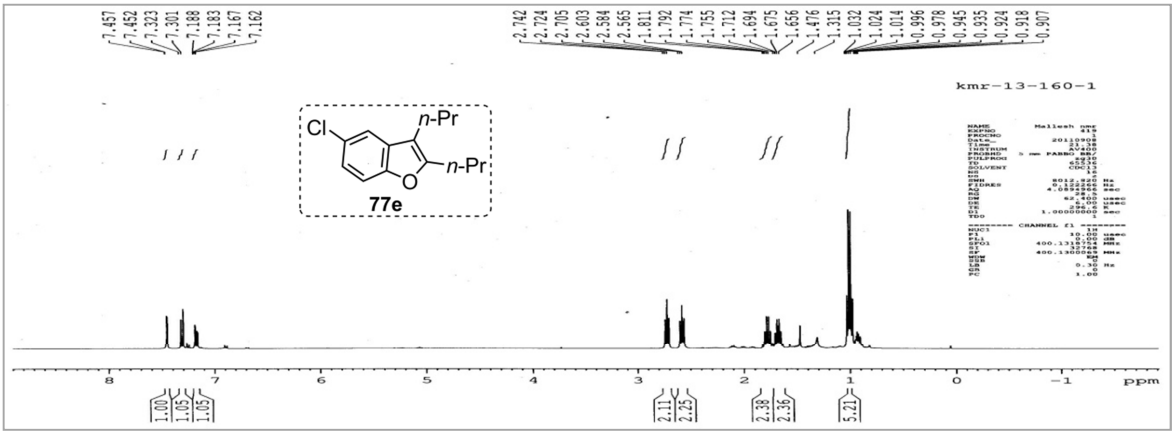
3.12
1.05
1.02
1.87
1.13


156.367
151.011
144.720
131.095
130.732
130.149
129.000
128.139
128.013
127.753
127.713
127.619
126.055
120.747
116.513
111.362
77.342
77.024
76.706
kmr-13-76
O2N
S
O
S
77d
220
200
180
160
140
120
100
80
60
40
20
0
ppm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1.774
1.755
1.712
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1.024
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0.918
0.907
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n-Pr
O
77e
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7
6
5
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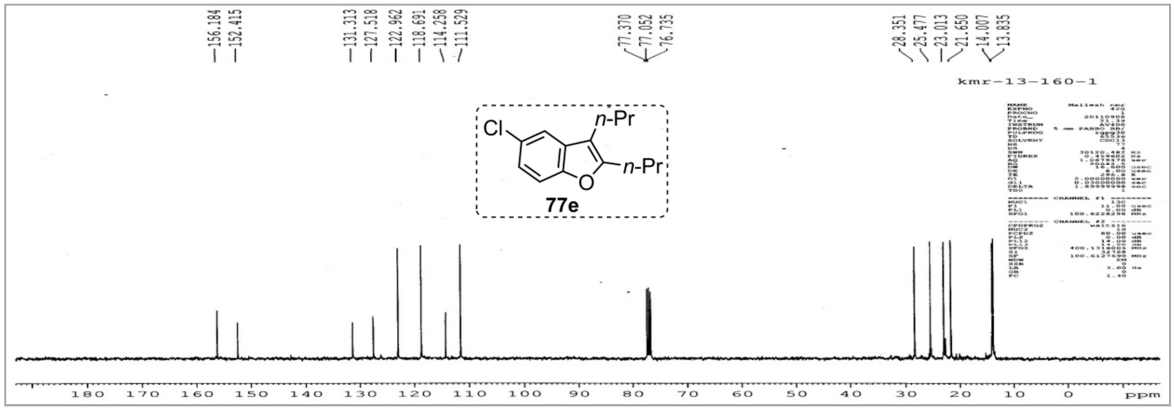
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25.477
23.013
21.650
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n-Pr
O
77e
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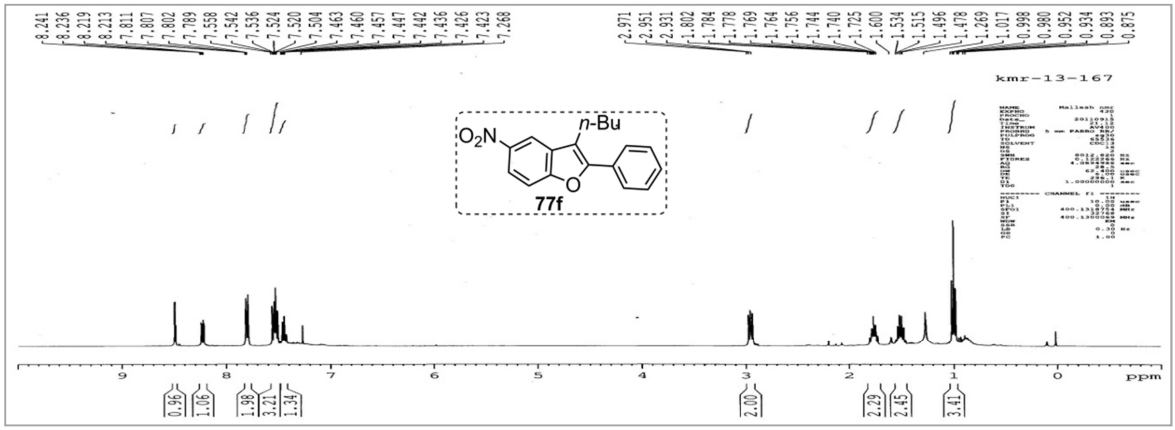
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O2N
n-Bu
O
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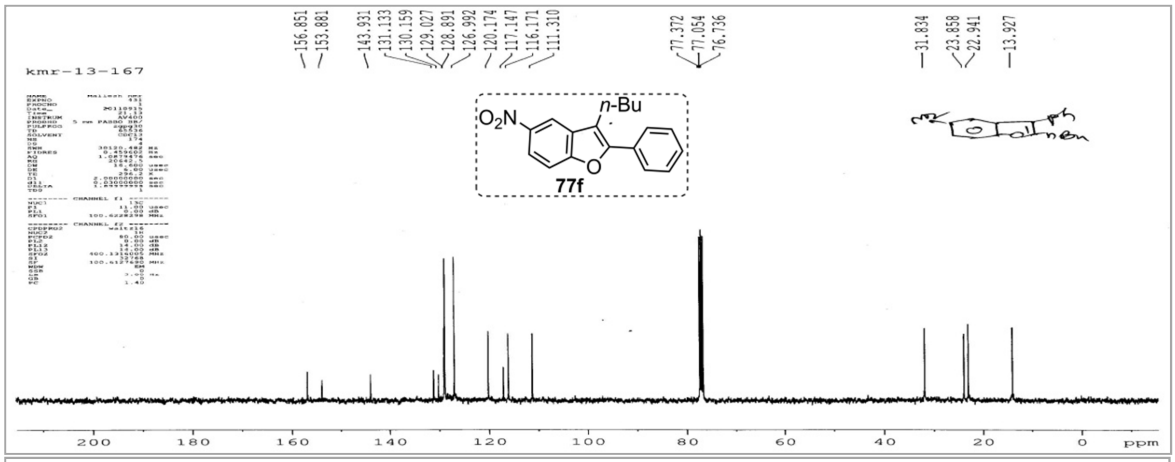
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O
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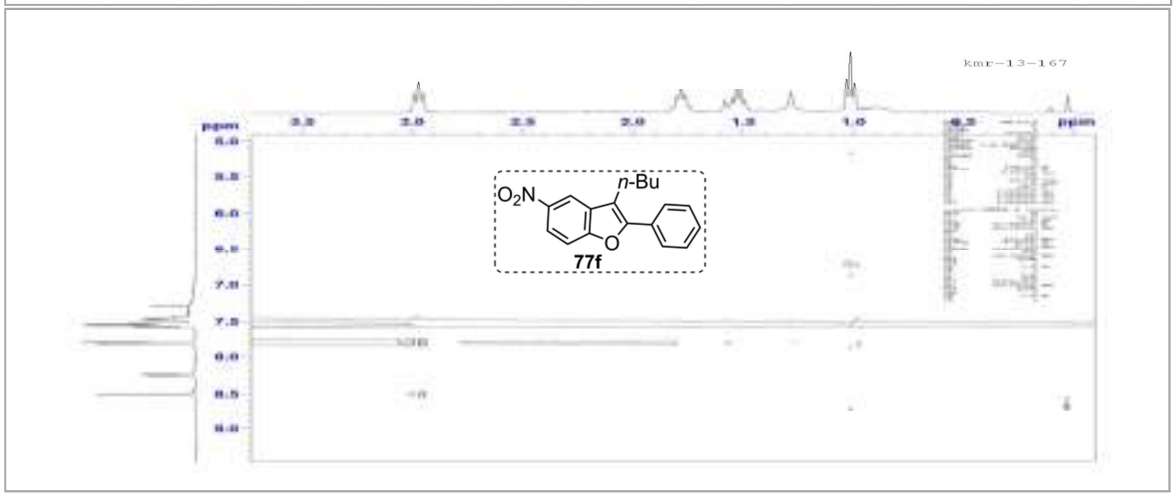
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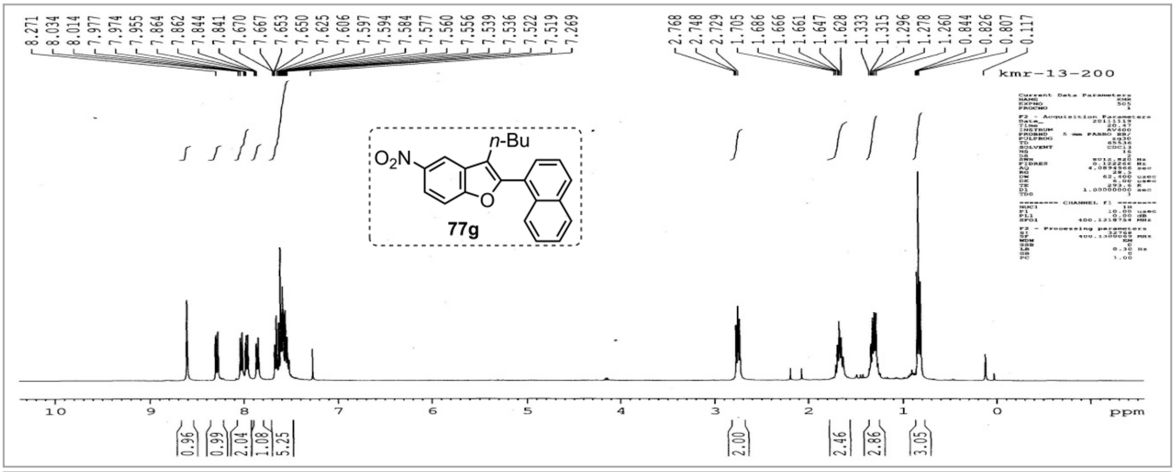
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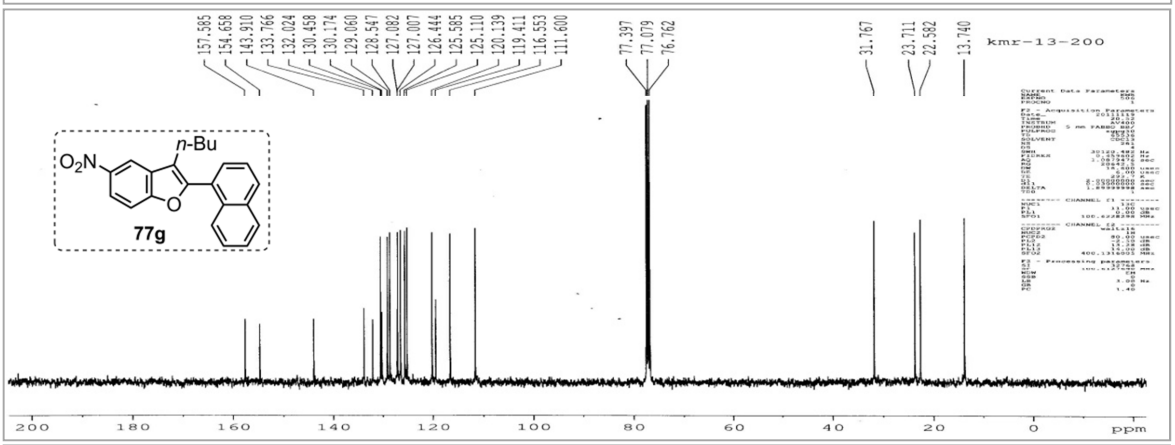
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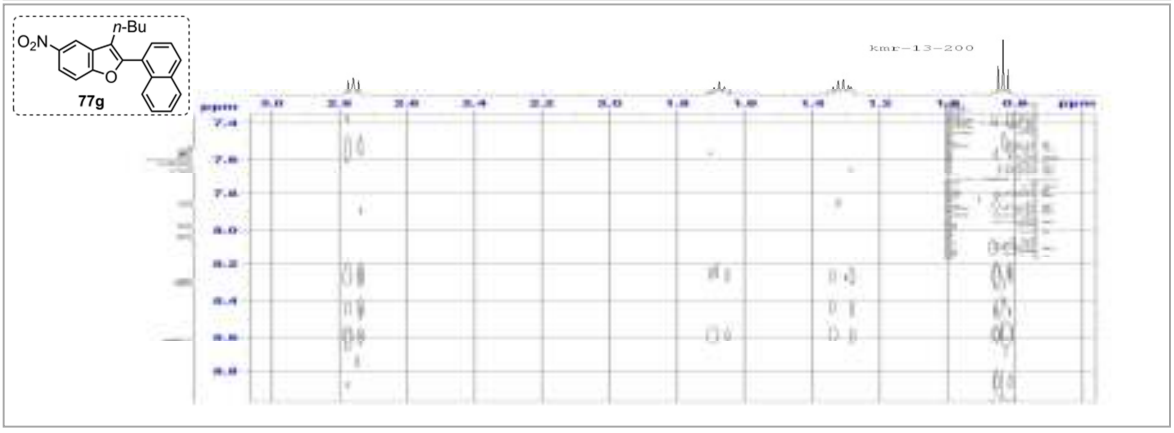
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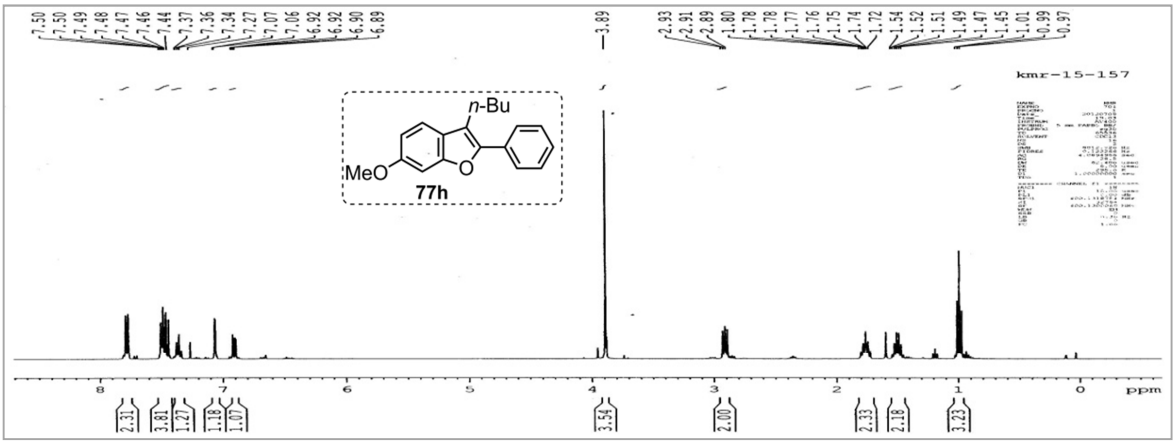
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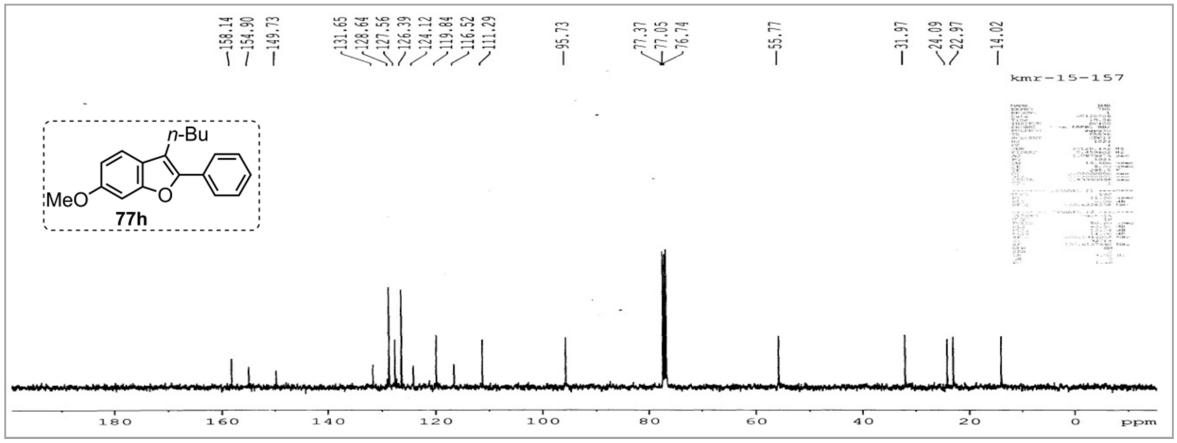
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77.05
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55.77
31.97
24.09
22.97
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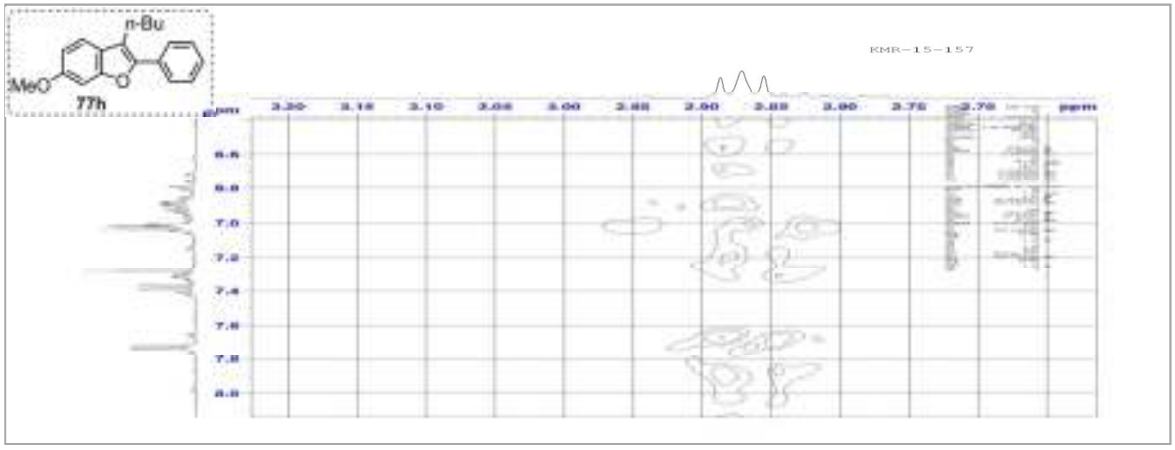
ppm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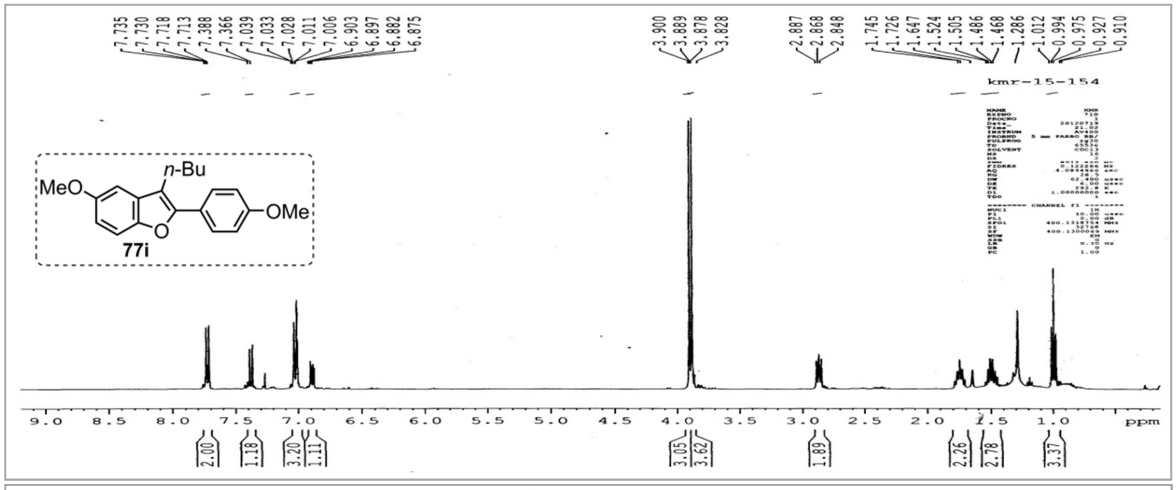
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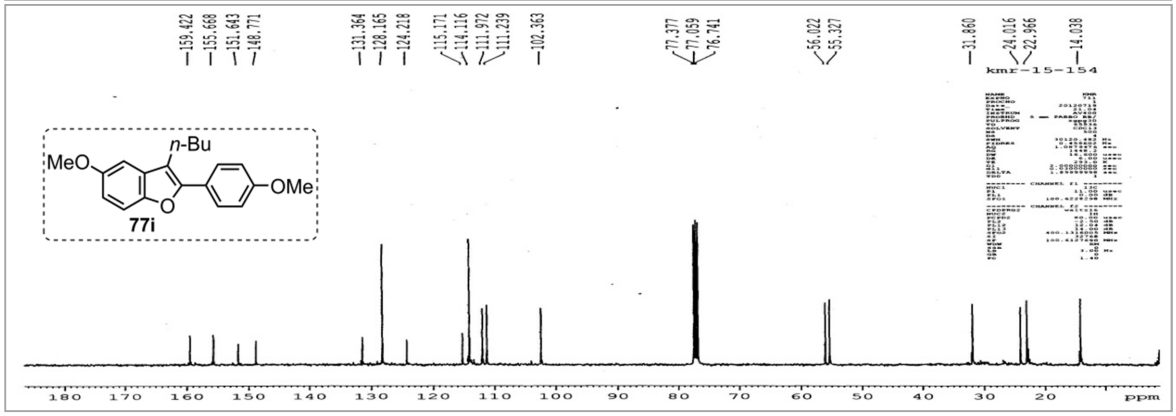
3.37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77.059
76.741
56.022
55.327
31.860
24.016
22.966
14.038
kmr-15-154
n-Bu
MeO
OMe
77i
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170
160
150
140
130
120
110
100
90
80
70
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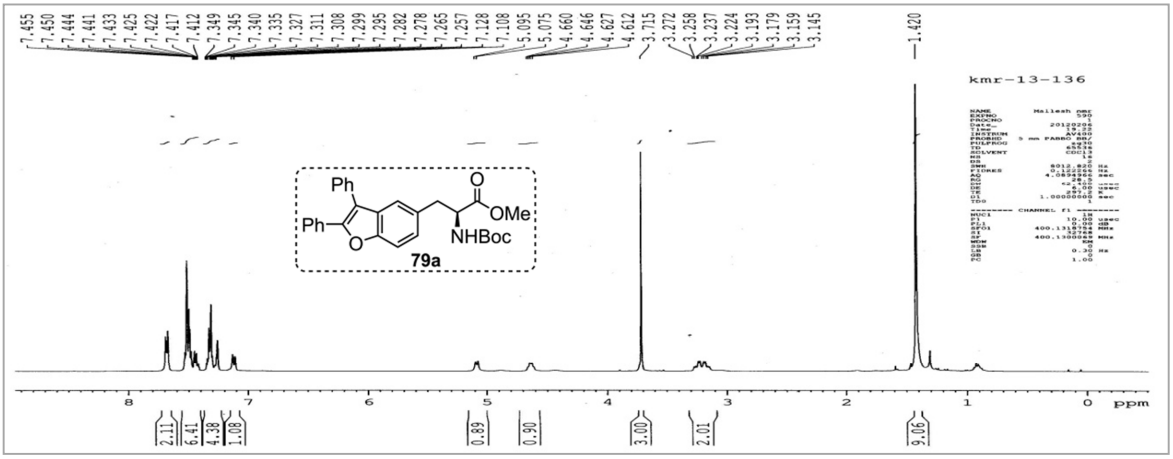
50
40
30
20
ppm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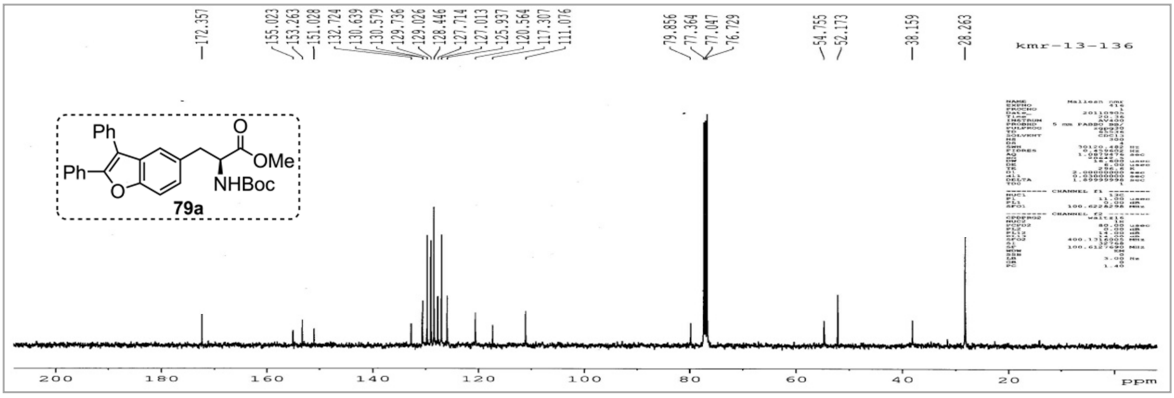
Ph
O
OMe
NHBoc
79a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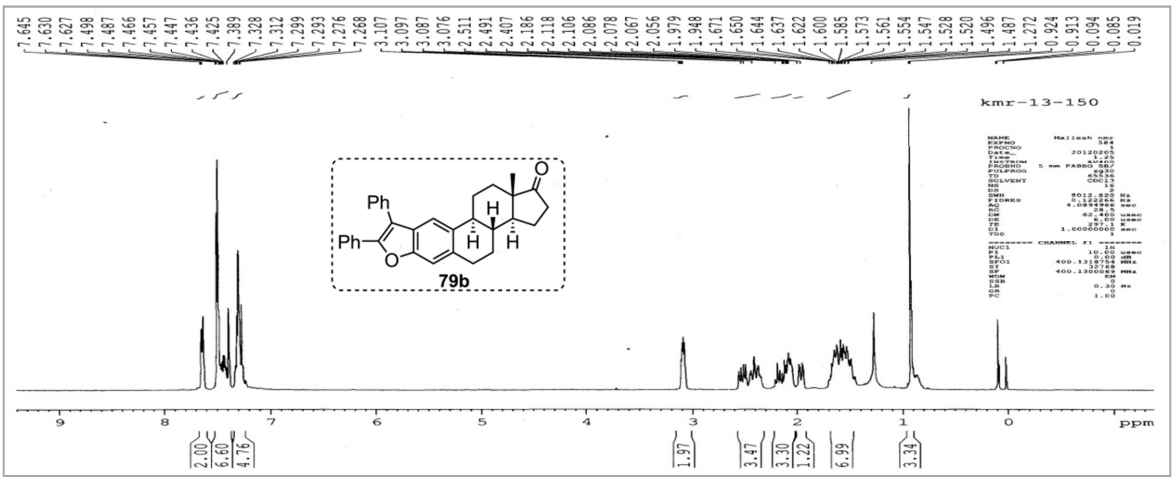
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Ph
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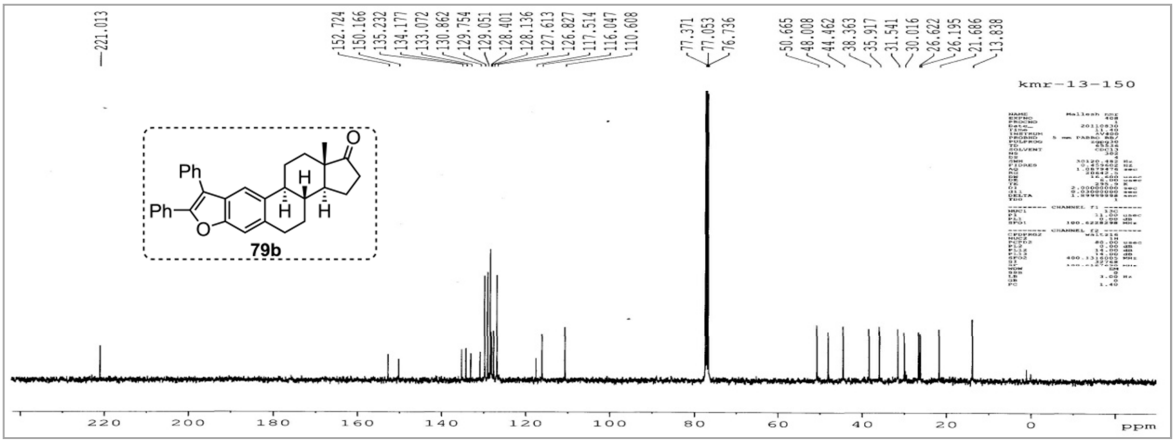
H
H
H
O
79b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H
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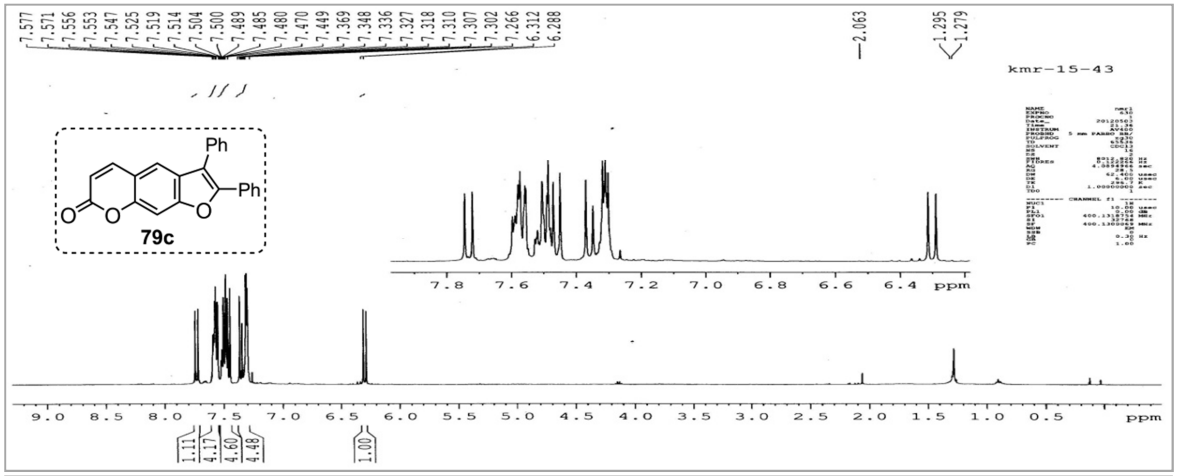
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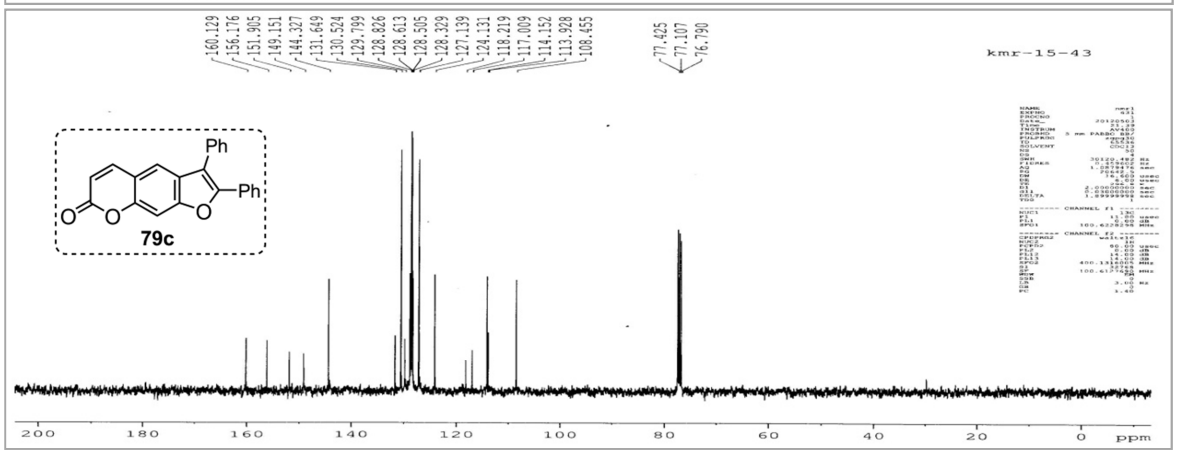
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O
O
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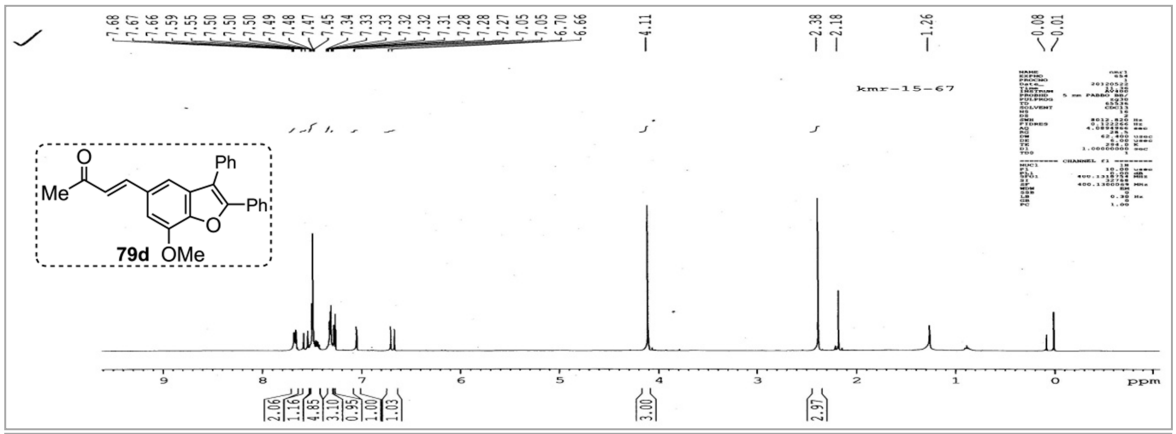
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Ph
Ph
O
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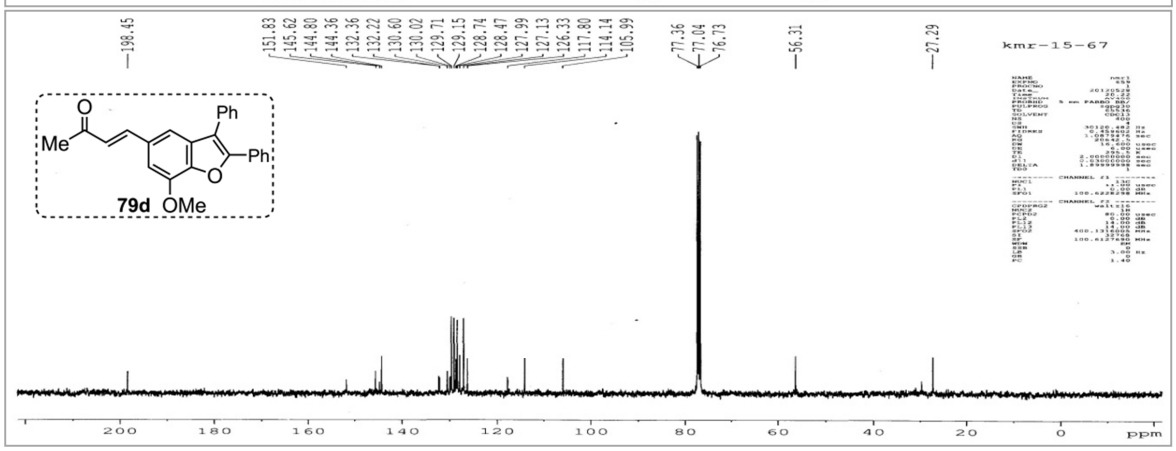
ppm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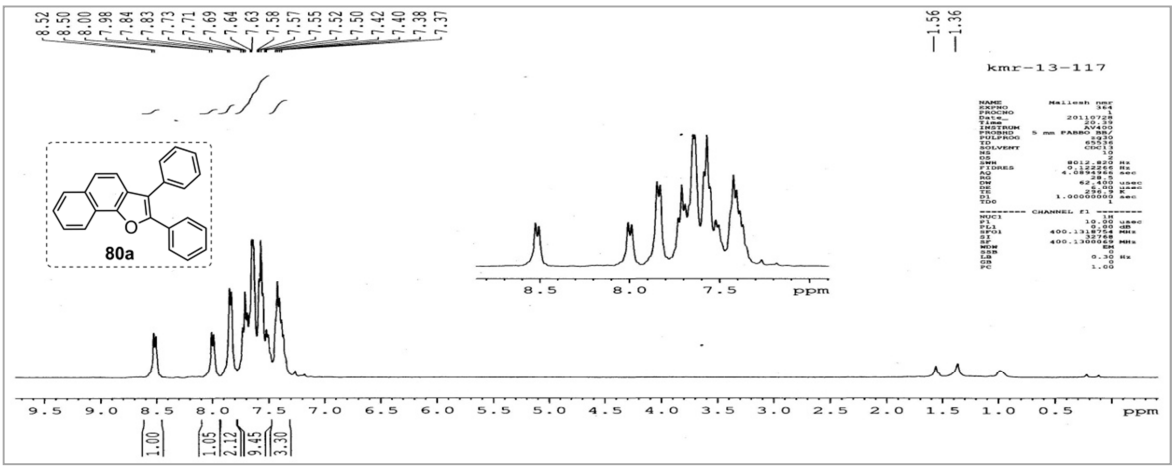
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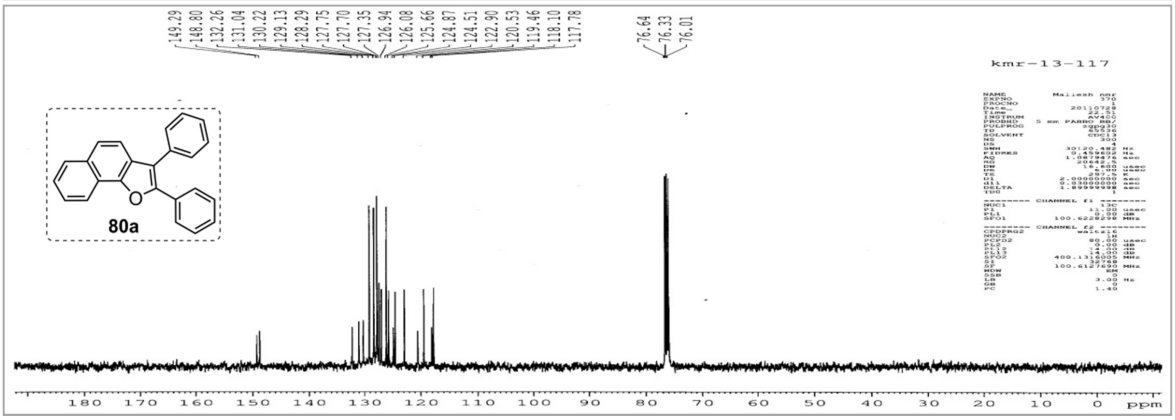
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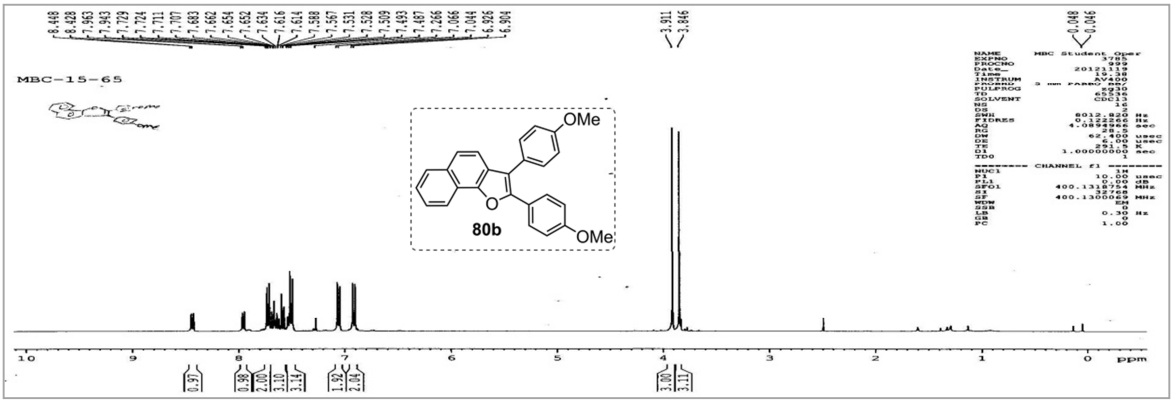
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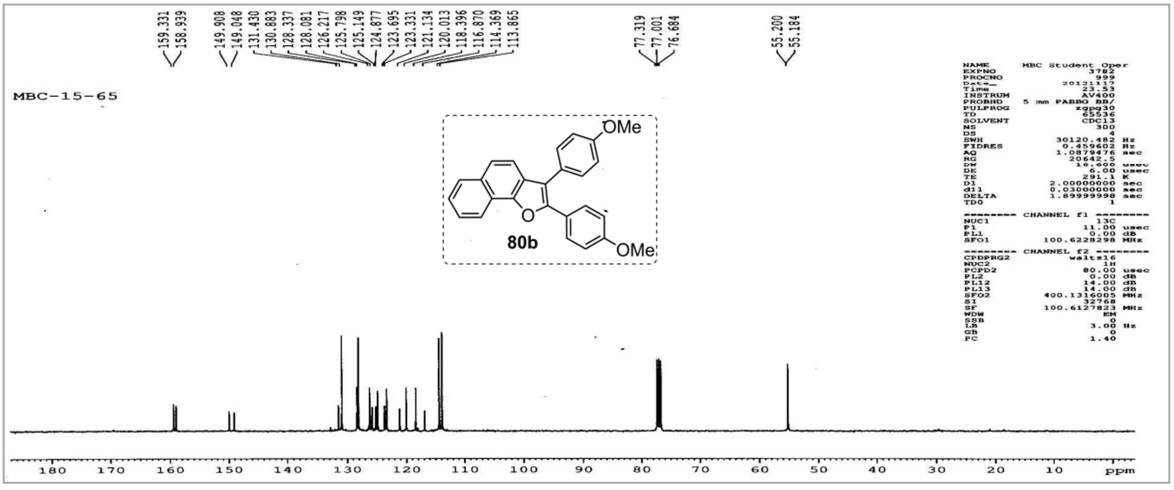
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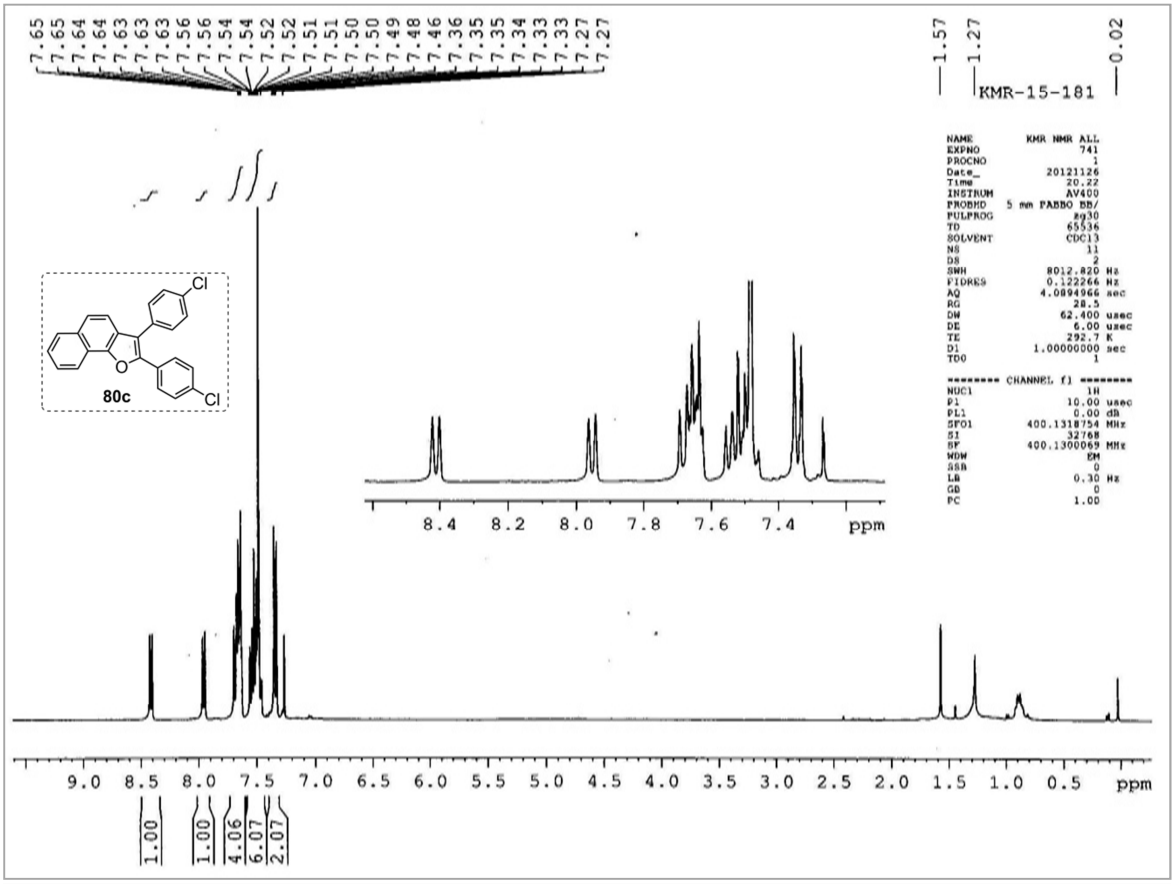
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1.57 1.27 0.02
KMR-15-181
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Cl
80c
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PROCNO 1
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Time 20.22
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 11
DS 2
SWH 8012.820 Hz
FIDRES 0.122266 Hz
AQ 4.0894966 sec
RG 28.5
DW 62.400 usec
DE 6.00 usec
TE 292.7 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 10.00 usec
PL1 0.00 dB
SFO1 400.1318754 MHz
SI 32768
SF 400.1300069 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.4 8.2 8.0 7.8 7.6 7.4 ppm
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
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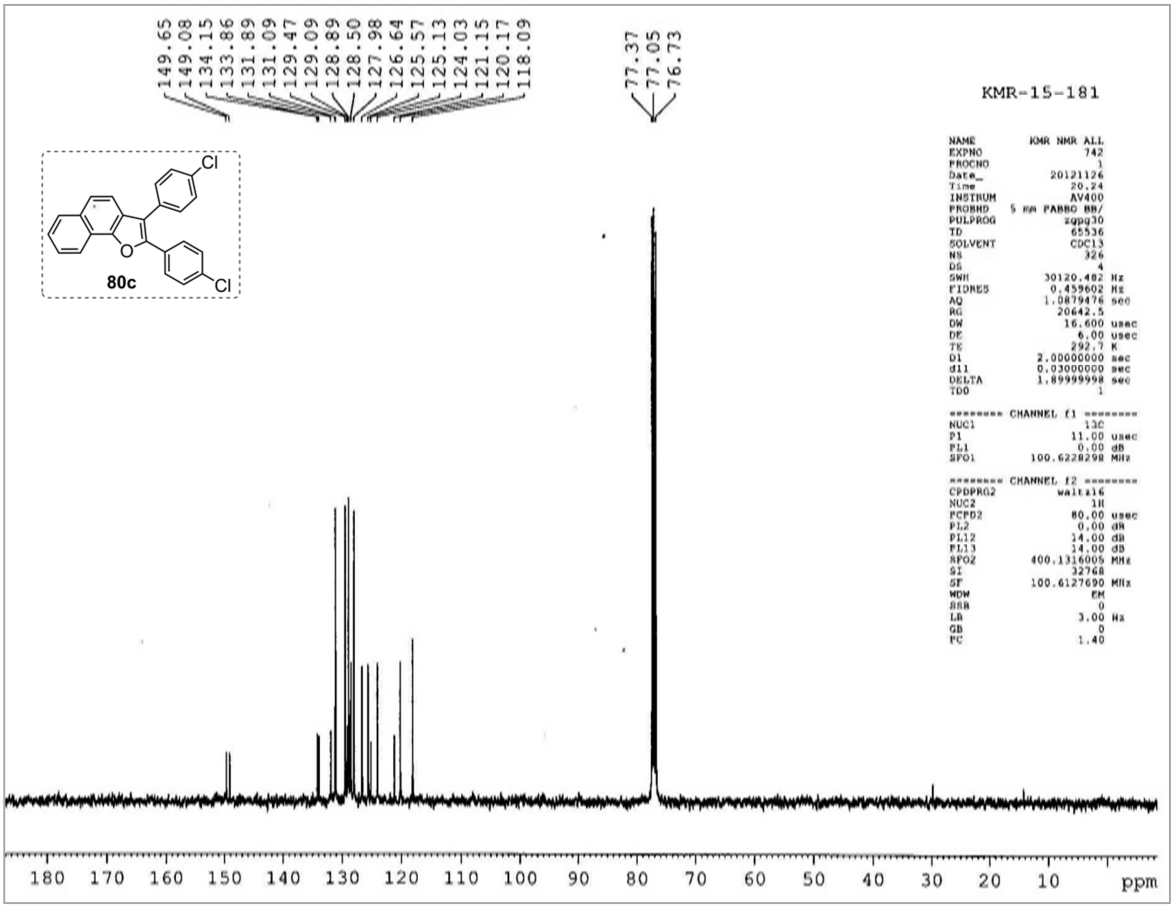
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PL12 14.00 dB
PL13 14.00 dB
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SSB 0
LB 3.00 Hz
GB 0
PC 1.40
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

Design, Synthesis and Optoelectronic Properties of Fused Furo-Indole Derivatives

3
Chapter

Abstract

The palladium-catalyzed oxidative annulation between *N*-acetyl-4-aminophenol and various unactivated internal alkynes readily delivered the corresponding benzo[*b*]furans leaving the NHAc moiety untouched. The resulting benzo[*b*]furans are further functionalized by the Rh-catalyzed Fagnou's oxidative annulations of anilides with internal alkynes to indoles. This two-step procedure allows efficient access to a wide array of fused furo-indoles. The optical and electronic properties of these new molecular entities are studied by UV-vis and fluorescence spectroscopy. All the molecules showed strong absorption at UV range (300–400 nm) and strong blue emission. Therefore, these molecules may find possible applications in blue light emitting diodes.

Reference:

Malleswara Rao Kuram, M. Bhanuchandra and Akhila K. Sahoo
(Manuscript under preparation)

3.1. Introduction

Optoelectronics is an emerging field in science and technology cohesively encompassing the concepts of chemistry, physics, material science and engineering.[1] Recently, the optoelectronic devices such as *organic photovoltaic devices* (OPVs),[2] *organic light emitting diodes* (OLEDs),[3] and *organic field effect transistors* (OFETs)[4] have received a great deal of attention because of their potential technological applications. Organic photovoltaics silicon based thin film solar cells are widely used for water heating and solar lighting in a daily basis. The OLEDs have found practical applications in mobile phones, digital cameras, car audios etc. The radio frequency identification (RFID) tags, smart cards, electronic sensors etc. are the promising applications of OFETs.[5]

The formation of charge, its transport, annihilation, and storage are the features essentially required for the design of organic electronic materials. Interestingly, the π-conjugated systems have the ability to accept or donate extra charges and therefore become a good chromophore.[6] As a consequence, the π-conjugated systems meet the requirements to be useful in organic electronics. Because of the light weight, low cost of production, capability in making thin-film, large area and flexible device fabrication, the organic materials are therefore find broad utility in the field of optoelectronics.[6]

The design and development of renewable energy sources has attracted much attention recently. The abundant, clean and economical solar energy is the possible alternative of fossil fuel energy.[7] Interestingly, the photovoltaic cells or dye sensitized solar cells works on the concept of charge separation and are used for the conversion of sunlight to electricity. The metal based ruthenium sensitizers (**N3**, **1**; Figure 3.1) developed earlier by Grätzel and others have achieved power conversion efficiency (PCE) up to ~11%,[8] unfortunately, the limited metal resources and tedious purification procedures possess major drawbacks. Therefore, tremendous efforts have now been devoted for the development of metal free organic dye sensitizers because this requires inexpensive raw materials and easy purification procedures. Some of the prominent organic dyes developed for OPV applications are shown in Figure 3.1.[9] In general, the common structure of an organic sensitizer is the combinations of an electron donor, π-conjugation linker, and electron acceptor units. For an example: the organic sensitizers (**2**; Figure 3.1), having

diaryl amine donor, cyano carboxylic acid group as acceptor and thiophene linker, achieved power conversion efficiencies up to ~10%.[10]

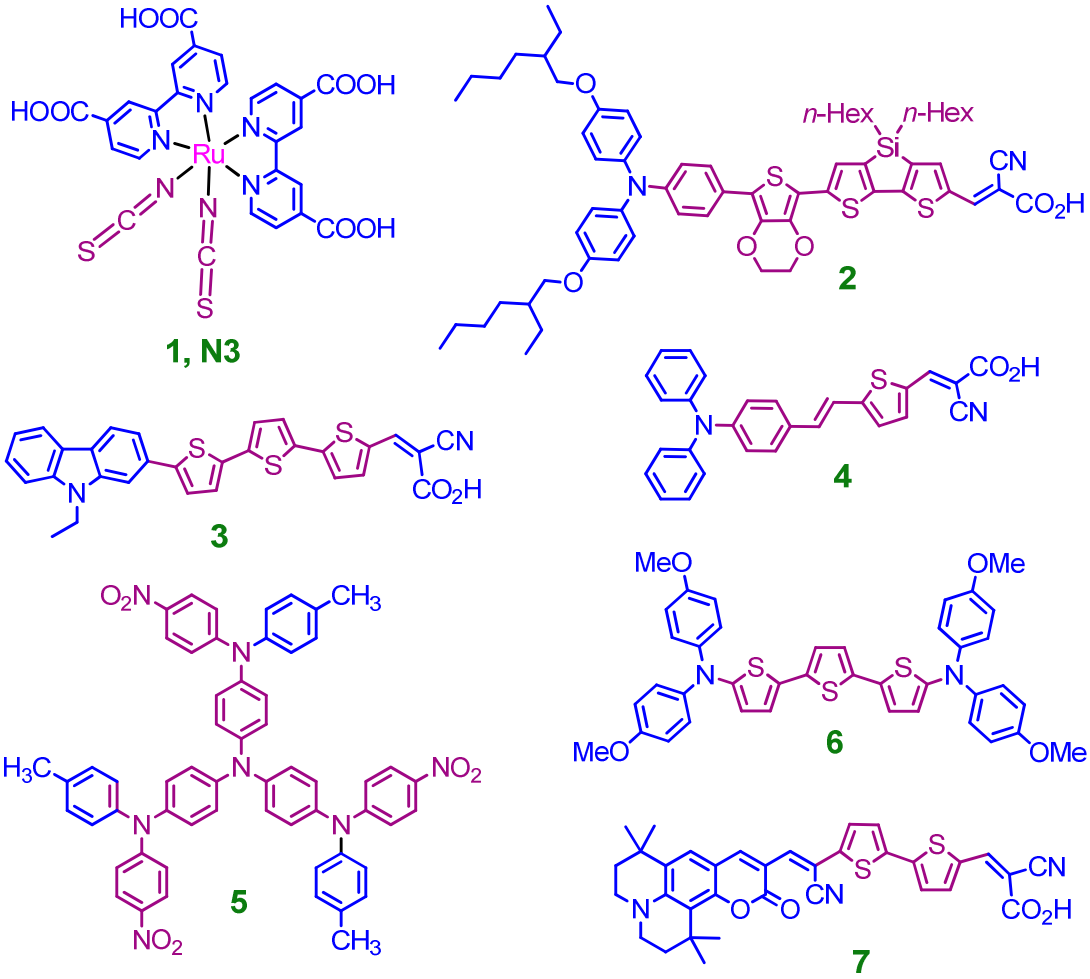


Figure 3.1: Selected examples of Dyes for OPVs

Recently, organic light emitting diodes (OLEDs) and organic field effect transistors (OFETs) have been used as semiconductors in digital applications. The self-emitting property, high luminous efficiency associated with low power consumption, wide viewing angle, high contrast and fast switching speed are the key features of OLEDs.[3] Generally, the OLED device is the electron-transport organic material that has been sandwiched between an anode and cathode. The organic materials behave as a source of hole-transport, electron transport, or emission; thus, the efficiency of this material depends solely on the property of the molecules used. Accordingly, an appropriate assembly of conjugated donor-acceptor moieties would produce an effective organic-semiconductor. Some of the recently developed small molecules based OFETs and OLEDs are shown in Figure 3.2 and Figure 3.3.[3,4] Although various red, blue and green OLEDs have been synthesized for

display applications, but the intrinsic low environmental stability, low lifetime are the inherent limitations. Thus, the development of air stable, solution processable organic electroluminescent devices would broaden the potential utility of this material.

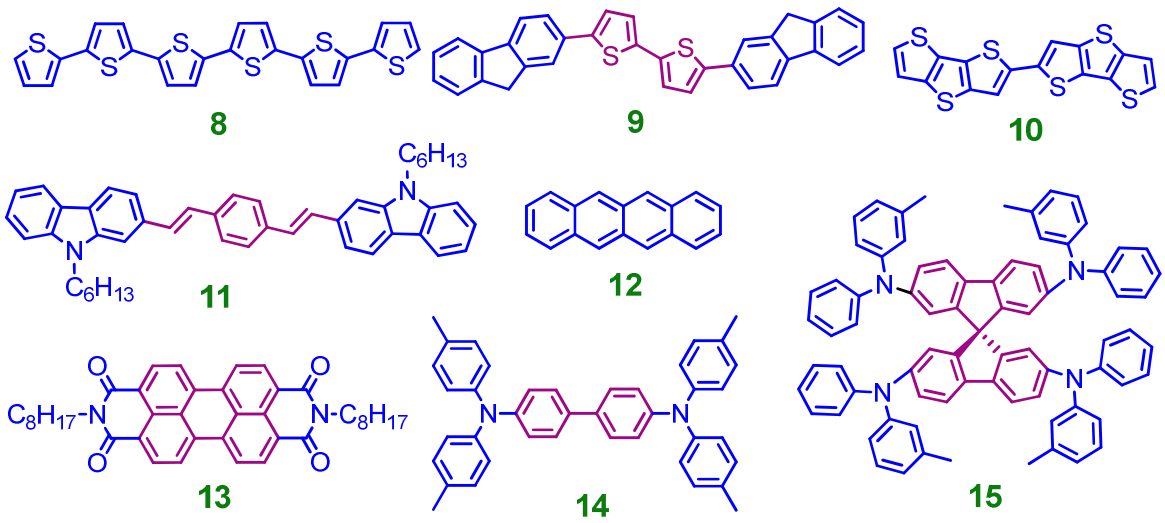


Figure 3.2: Selected examples for OFETs

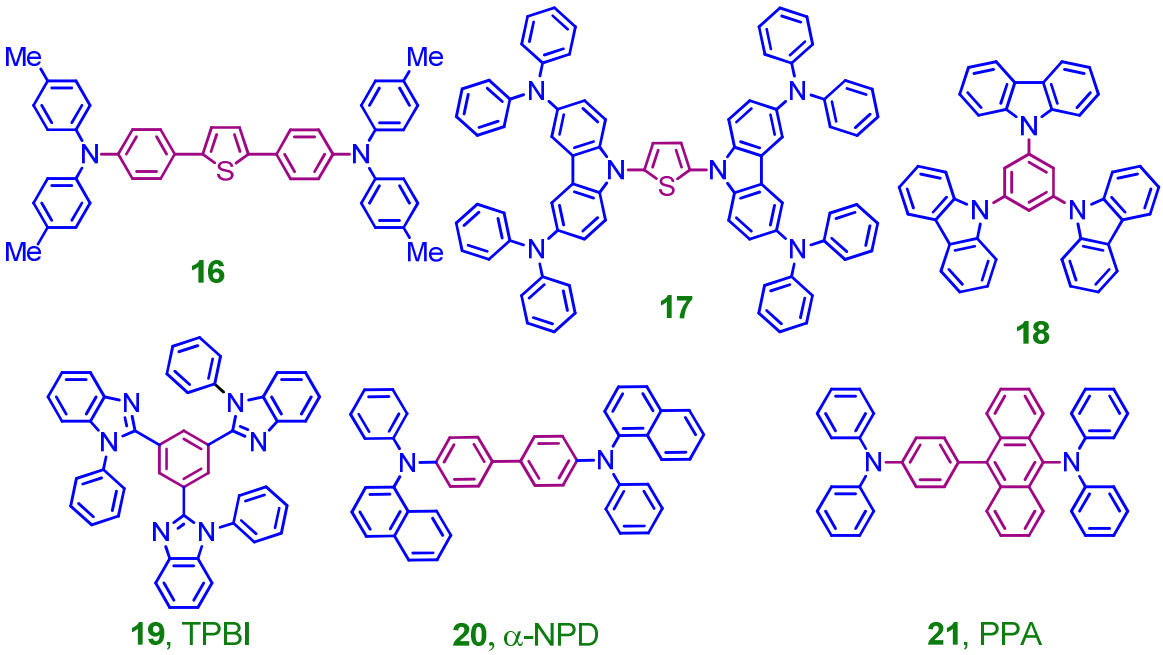


Figure 3.3: Selected examples for OLEDs

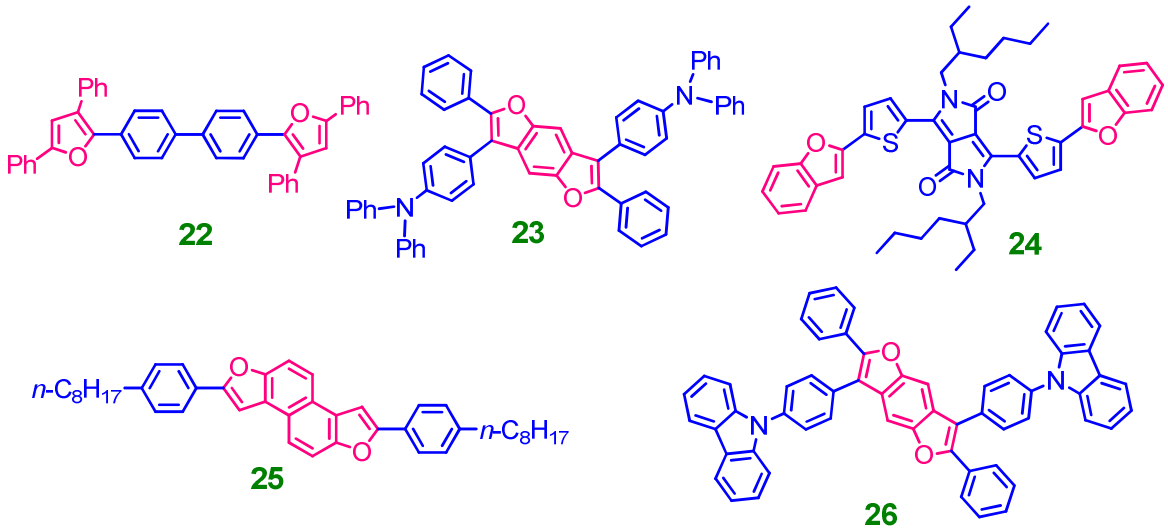


Figure 3.4: Selected examples of benzofuran containing materials

Based on the above discussions, the development of novel materials having better solubility, adequate stability with correct level of matching frontier molecular orbitals and molecular packing is always demanding. The thiophene based organic materials are widely used in the applications of optoelectronic (Figures 3.1 and 3.2). Although the thiophene counterpart heterocycle furan exhibits similar energy levels and comparable degree of aromaticity, the utility of furan containing materials is still limited (Figure 3.4). Recently, the furans-bearing materials have shown very similar optical and electronic properties in organic dyes for dye-sensitized solar cells in comparison to thiophenes. Wu and co-workers reported the furan containing oligoaryl **22** as efficient hole transport material (Figure 3.4).[11a] Nakamura and co-workers have developed the benzodifurans (BDF) containing molecules **23**, **25** and **26**, those are useful as hole- transporting materials for the potential applications in OLEDs.[11] Interestingly, one of the highest performing small molecules for photovoltaics based benzofuran heterocycles **24** (PCE, η = 4.4%) have been described by Nguyen and co-workers.[12]

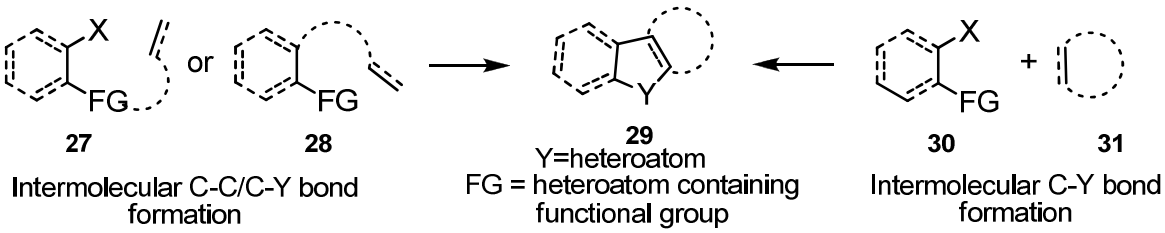
Apart from this considerable progress, the design and synthesis of novel materials showing effective applications to electronic and optoelectronic properties is always desirable.

3.1.1. Transition-Metal-Catalyzed Synthesis of Heterocycles

The presence of ubiquitous nitrogen, oxygen and sulfur containing heterocycles motifs are invariably found in biologically active molecules and the materials. As a results there is continuous interest among the synthetic organic chemists to fabricate novel heterocyclic compounds through new and efficient synthetic transformations.[13] The acid and/or base

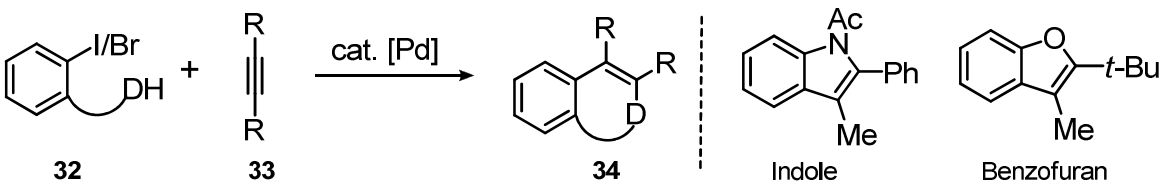
assisted condensation methods have traditionally been employed accessing the heteroaromatic compounds; however, these methods produces unwanted corrosive by-products.[14] Thus, development of environmentally benign methods for the synthesis of heteroaromatic compounds is always welcome. The transition-metal catalyzed transformations can thus be an alternate method useful for the direct construction of complex heteroaryl structures from easily accessible starting materials under neutral and mild reaction conditions.

The oxidative annulation of halo-arenes with unsaturated molecules is a straightforward and atom-economical approach useful in the construction of substituted heteroaromatic rings.[15] As shown in Scheme 3.1, the heterocyclic skeletons can be constructed through the intramolecular cyclization of unsaturated carbon-carbon bonds (alkene, alkynes or allenes etc), or by intermolecular annulations of unsaturated carbon-carbon bonds (alkene, alkynes or allenes etc) with the functionalized aromatic compounds. These cyclizations can be accessed by inducting direct carbon–carbon or carbon–heteroatom bonds.



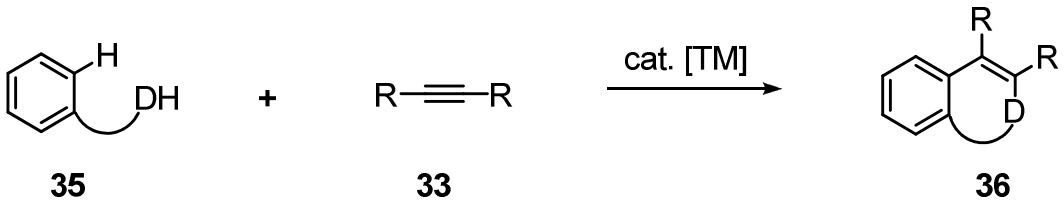
Scheme 3.1: Two major processes of heterocycle synthesis

Although intramolecular reactions are entropically favorable than intermolecular reactions, additional steps are required to prepare precursors for intramolecular reactions. Therefore, intermolecular reactions are advantageous than intramolecular reactions. The transition-metal-catalyzed intermolecular cyclizations of *ortho*-halogenated anilines or phenols with internal alkynes have emerged as a powerful method for the construction of indoles or benzofurans, respectively (Scheme 3.2).[16]

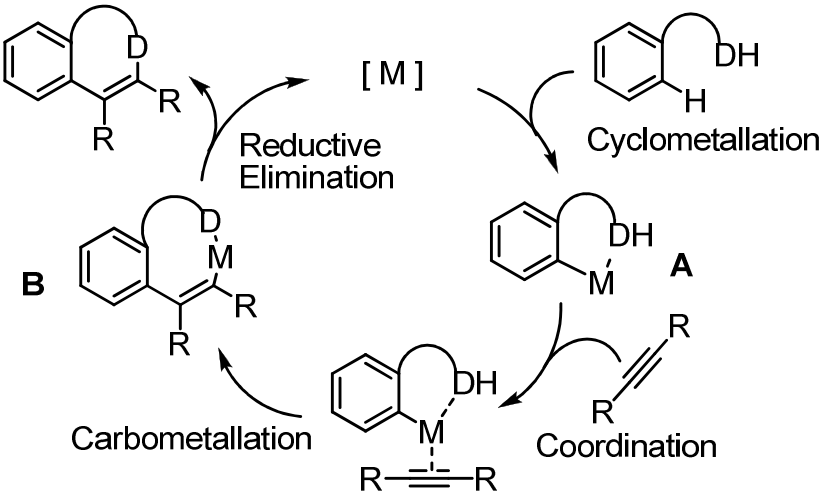


Scheme 3.2: Larock type heterocycles synthesis

The requirement of *ortho*-halogenated anilines or phenols in this reaction produces the halide byproducts with limited scope of the readily available precursors. Interestingly, the C–H activation methods offer the additional advantages with the production of limited waste byproducts accessing the broad substrate scopes and therefore environmentally benign. However, the presence of prefunctionalized chelating/directing heteroatom allows activating the C–H bond with the aid of the transition-metal catalyst. Recently, TM-catalyzed one-pot C–C/C–X bond forming reactions allows the synthesis of various carbo/heterocycles (Scheme 3.3).[17]



Scheme 3.3: Oxidative annulations for the synthesis of heterocycles



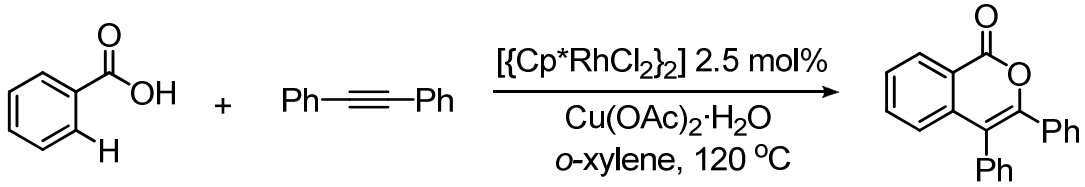
Scheme 3.4: General mechanism for the oxidative annulations

The proposed catalytic cycle for the transition-metal (TM) catalyzed oxidative coupling between functionalized arenes and unsaturated compounds is shown in Scheme 3.4. The reaction initiates with the coordination of the heteroatom in the directing group to the transition-metal. This trigger activating *ortho*-C–H bond to the formation of cyclometallation species **A**. Alkyne ligation and insertion of TM to the π-bond generates an expanded metallacycle **B**. Finally, the oxidative coupled product is produced *via* the reductive elimination from the active species **B**. The active TM catalyst is regenerated and reused for the next catalytic cycle in the presence of oxidant.

Following this strategy, a number of synthetic methods have been developed towards the formation of various heterocycles. Palladium, copper, and rhodium catalysts have been successfully employed for the synthesis of various heterocycles.

3.1.2. Oxidative Annulations of Heteroarenes with Unsaturated Carbon-Carbon Multiple Bonds

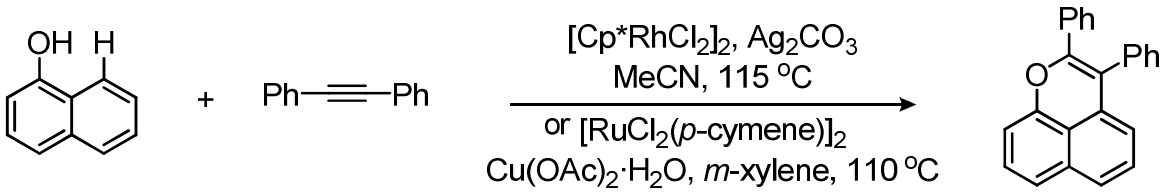
A) Oxygen Heterocycles: The Satoh and Miura group have successfully applied the rhodium-catalyzed oxidative coupling of benzoic acids with internal alkynes for the preparation of isocoumarins as shown in Scheme 3.5.[18]



37 **33a** **38**

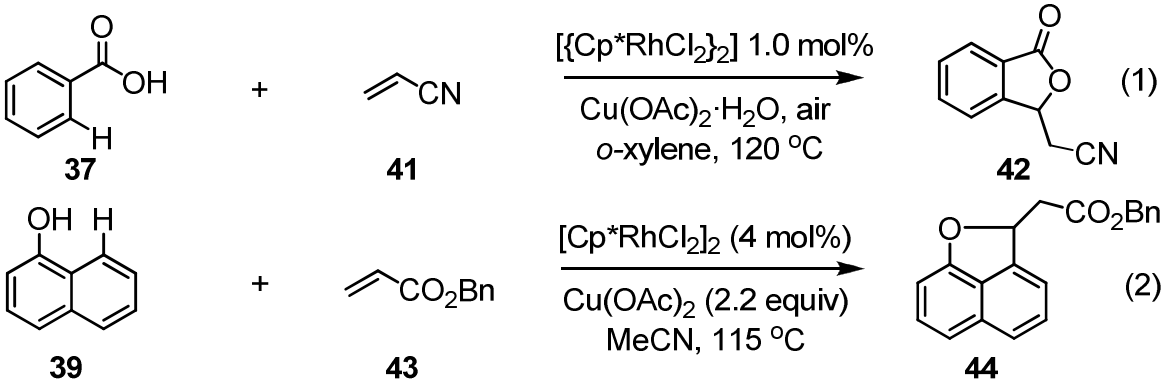
Scheme 3.5: Intermolecular cyclization of benzoic acids with alkynes

The Miura and Ackermann groups have independently demonstrated the synthesis of naphthopyrans from 1-naphthol and internal alkynes using Rh- and Ru-catalyst, respectively (Scheme 3.6).[19]



39 **33a** **40**

Scheme 3.6: Intermolecular cyclization of 1-naphthols with alkynes



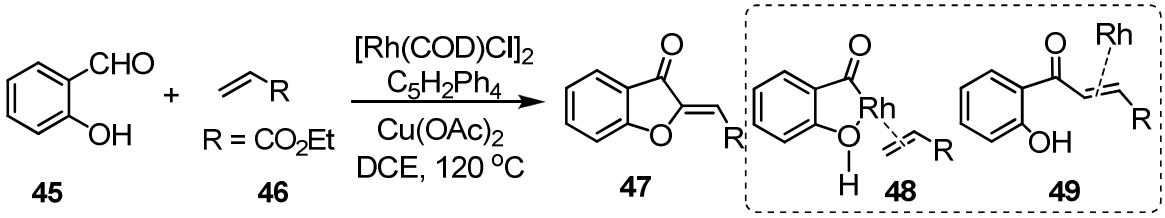
37 **41** **42**

39 **43** **44**

Scheme 3.7: Intermolecular cyclization of benzoic acids or 1-naphthols with alkenes

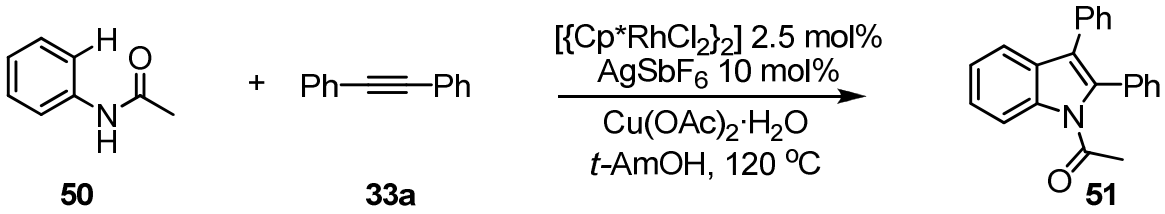
The coupling of benzoic acids with activated acrylonitrile affords isobenzofurans (Scheme 3.7, eq. 1).[18b] The reaction involves the *o*-C–H olefination of benzoic acid followed by Michael cyclization. Similarly, the oxidative olefination-Michael cyclization of 1-naphthol with acrylates was recently reported by Li (Scheme 3.7, eq. 2).[20]

The Glorius group reported the Rh-catalyzed regioselective dehydrogenative Heck reaction of aldehyde C–H bonds with olefins. The coordination of the –OH group of salicylaldehyde to Rh-species triggers oxidative insertion to the aldehyde C–H bond forming the cyclometalated Rh-species. This rhodacycle coordinate to alkene to form **48**; alkene insertion and reductive elimination finally generate **49**. Finally, alkoxy rhodation on **49** and *syn*-β-hydride elimination affords oxidized cyclization product **47** (Scheme 3.8).[21]



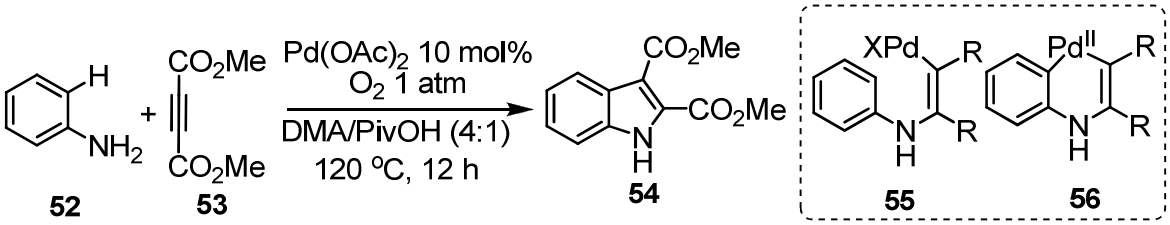
Scheme 3.8: Intermolecular cyclization of *o*-hydroxybenzaldehydes with alkenes

B) Nitrogen heterocycles: The Rh (III)-catalyzed oxidative coupling of acetanilides with alkynes for the preparation of indoles is demonstrated by Fagnou and co-workers for the first time (Scheme 3.9).[22] Inspired by this work, vast majority of annulated nitrogen heterocycles indolines, pyrroles, isoquinolines, isoquinolones and pyridines etc were successfully synthesized.



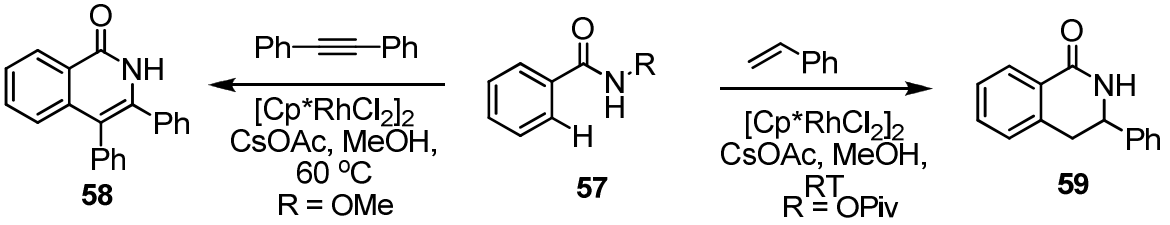
Scheme 3.9: Intermolecular annulation of acetanilides with alkynes

The oxidative annulation of anilines with activated alkynes to achieve indoles under the palladium catalysis is reported by Jiao group.[23] The aminopalladation of **52** to the palladium coordinated alkyne **53** gives **55**. The acid promoted electrophilic aromatic attack on Pd generates **56**; subsequently reductive elimination produces **54** (Scheme 3.10).



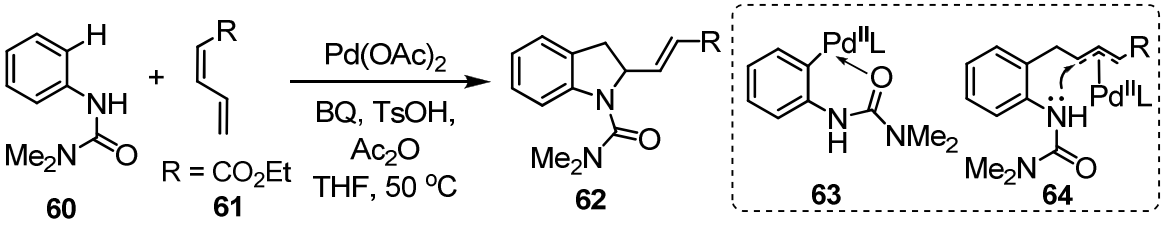
Scheme 3.10: Intermolecular annulation of anilines with activated alkynes

The single-step synthesis of isoquinolines (**58**) is reported through the Rh-catalyzed annulation of *N*-methoxy hydroxamic acids with alkynes. Similarly, the reaction between *N*-pivaloylhydroxamic acids and alkenes produces dihydroisoquinolones (**59**) (Scheme 3.11).[24]



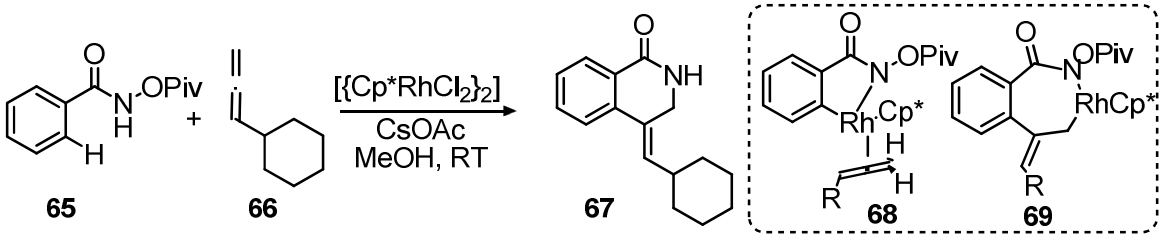
Scheme 3.11: Intermolecular annulation of *N*-(pivaloyloxy)benzamide with alkynes

The Pd-catalyzed carbopalladation/cyclization of readily available *N*-aryl urea with conjugated-diene delivered indoline.[25] The coordination of urea *N*/*O*-atom to metal triggers the activation of the *ortho*-C–H bond and forms **63**. The oxidative Heck reaction of **63** with **61** generates electrophilic η^3-allyl Pd(II)-species **64**. Finally, the cyclization of **64** provides the indoline **62**.



Scheme 3.12: Intermolecular annulation of *N*-aryl ureas with dienes

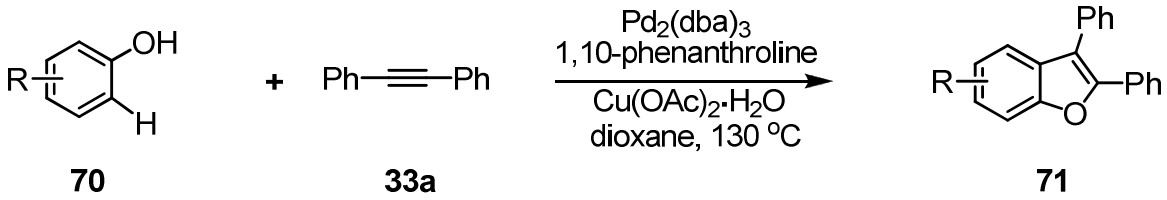
The Glorius group developed intermolecular addition of benzamide derivatives to allenes for the synthesis of dihydroisoquinolinones **67**. The reaction begins with the coordination of allene to cyclometalated rhodium species forming **68**, next the carborhodation results the seven membered species **69**. Finally, reductive elimination furnishes the product (Scheme 3.13).[26]



Scheme 3.13: Intermolecular annulation of *N*-(pivaloyloxy)benzamide with allenes

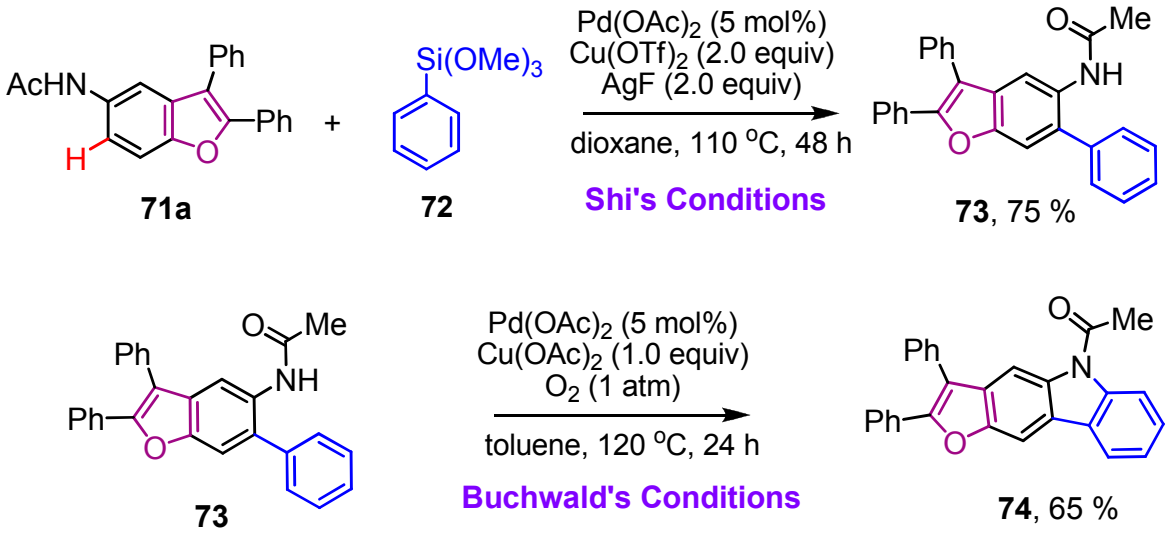
3.2. Design Plan

Recently, we have demonstrated the Pd-catalyzed synthesis of benzo[*b*]furans from phenols and internal unactivated alkynes (detailed in Chapter-2, Scheme 3.14). Various functional groups are tolerated under the optimized catalytic conditions.



Scheme 3.14: Synthesis of benzo[*b*]furans from phenols and alkynes

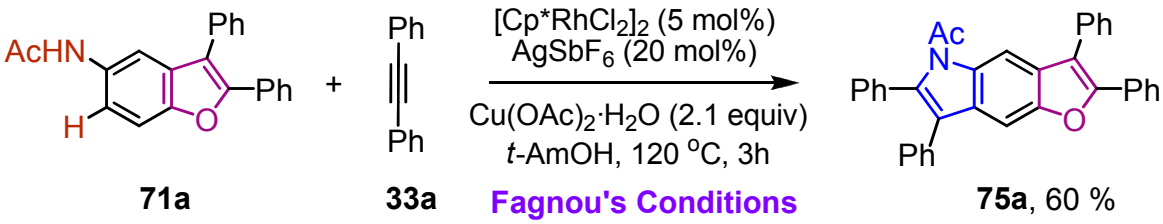
It is noteworthy mentioning that the catalytic conditions did not affect the NHAc moiety during the synthesis of benzofurans. Taking the advantage of the survival of the NHAc moiety, we envisioned installing a carbazole or indole skeletons on the parent benzofuran molecular template (Scheme 3.15). Following the known synthetic protocols of C–H activation, we would like to fabricate highly conjugated fused heterocycles furo-carbazoles and furo-indole derivatives.



Scheme 3.15: Extending the molecular framework

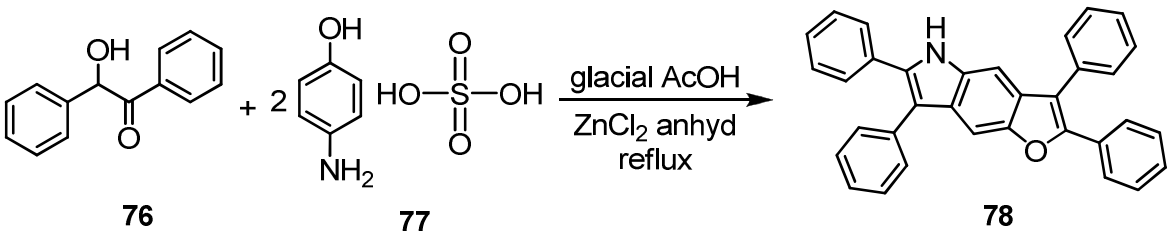
The amide groups assist in directing the *ortho*-metalation followed by C–H functionalizations. The Shi and co-workers developed the Pd-catalyzed anilide directed arylations at the less-hindered *ortho*-C–H bond. Following the Shi's conditions, the reaction of **71a** with trimethoxyphenylsilane (**72**) successfully introduced a phenyl group at the less hindered position *ortho*- to anilide moiety producing **73** in 75% yield (Scheme 3.15).[27b] Finally, Buchwald's intramolecular C–N arylation of **73** delivered novel four-ring-fused heteroaromatic compound **74** with ease (Scheme 3.15). [27c]

Interestingly, Fagnou and co-workers have successfully demonstrated the rhodium-catalyzed NHAc-directed dehydrogenative cyclization between arenes and internal alkynes for the synthesis of indole.[27a] Therefore, the oxidative coupling between aniline precursor **71a** and **33a** under the Fagnou's conditions delivered the three-ring-fused heterocycle **75a** in 60% yield (Scheme 3.16).



Scheme 3.16: Oxidative annulation of acetamides and alkynes

The condensation between 2-hydroxy-1,2-diphenylethanone (**76**) and 4-hydroxy phenyl-azanium sulfate (**77**) in the presence of glacial acetic acid and anhydrous $ZnCl_2$ under reflux conditions delivered a furo-indole compound **78** albeit in low yield. This is the only example known. Unfortunately, this reaction has limited scope of substrates (Scheme 3.17).[28]



Scheme 3.17: Benzoin condensation with *p*-aminophenol

We believe the fused furo-indoles derivatives with the extended π-conjugated system would find broad applications in the optoelectronics. With these views in our mind, we became interested in the synthesis of various novel fused furo-indole derivatives.

3.3. Results and Discussion

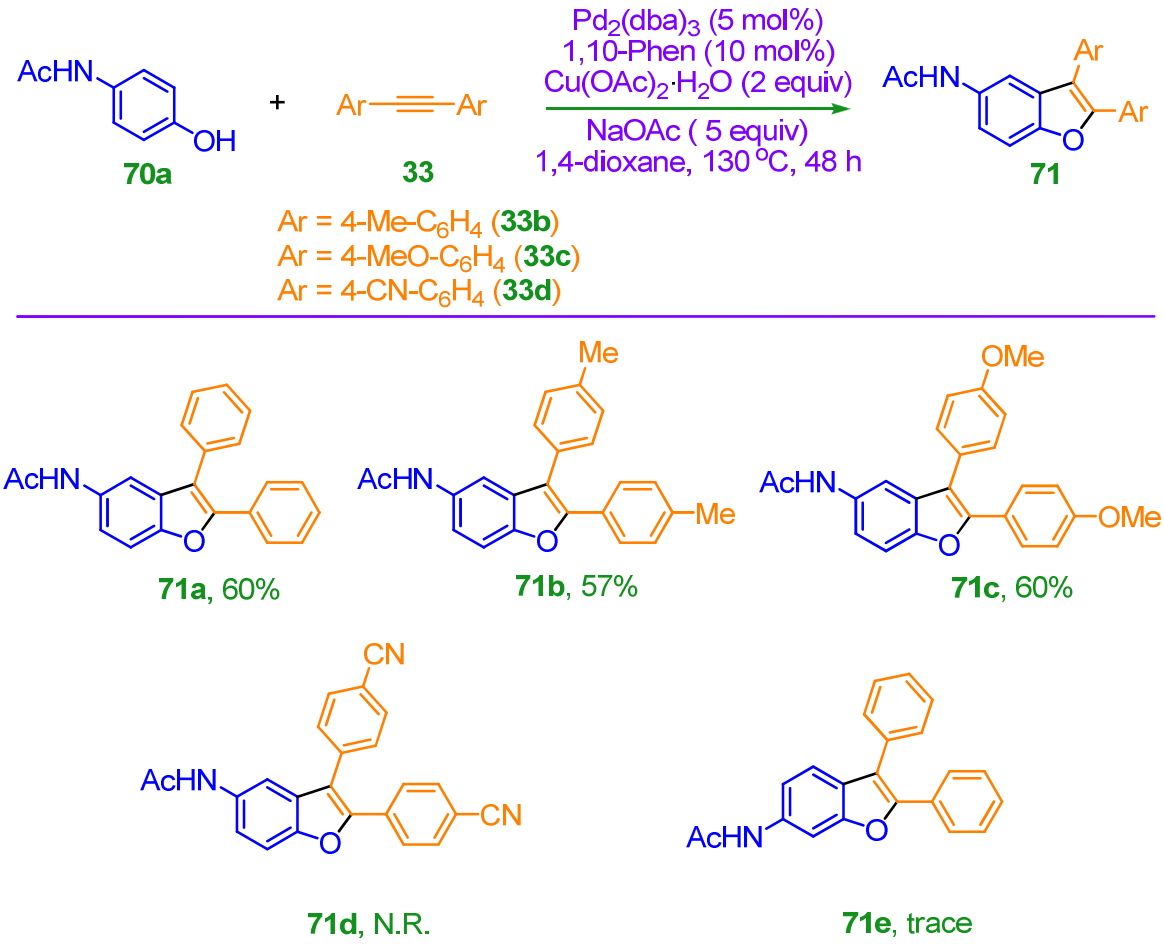
3.3.1. Synthesis: The combination of two synthetic protocols i.e., (i) oxidative annulation of alkynes and phenols for the preparation of benzofurans and (ii) Rh-catalyzed synthesis of indoles from anilides and internal alkynes allows accessing the interesting conjugated fused furo-indoles as shown in Scheme 3.16. We therefore explored the synthesis of various novel fused furo-indoles. As shown in Table 3.1, different symmetrical alkynes were subjected for the preparation of benzo[*b*]furans with 4-acetamidophenol (**70a**).

Reaction of electron rich 4-methyl and 4-methoxy substituted alkynes, 1,2-di-*p*-tolylethyne (**33b**) and 1,2-bis(4-methoxyphenyl)ethyne (**33c**) with acetaminophen **70a** under optimized conditions B [$Pd_2(dba)_3$ (5 mol%), 1,10-phenanthroline (10 mol%), NaOAc (5.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv) and 1,4-dioxan at 130 °C], produced the benzofurans **71b** and **71c** in 57% and 60% yields, respectively. Unfortunately, the electron poor alkyne, 4,4'-(ethyne-1,2-diyl)dibenzonitrile (**33d**), failed to react with **70a**. Presumably the electron withdrawing groups on aryl rings makes the alkynes electron deficient, which in turn hinders the effective alkyne-metal coordination. The reaction between *N*-(3-hydroxyphenyl)-acetamide and diphenylacetylene led to trace amount of the desired benzofuran product **71e** (detected by GC).

Having various benzo[*b*]furans in our hand Table 3.1, we thus became interested in the fabrication of the indole skeleton employing the Fagnou's conditions [[Cp*$RhCl_2$]$_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv), *t*-AmOH, 120 ^oC for 3 h]. At first, the reaction between *N*-(2,3-diphenylbenzofuran-5-yl)acetamide (**71a**), and 1,2-bis(4-methoxyphenyl)ethyne (**33c**) gave the desired fused furo-indole **75b** in 77% yield. Similarly, **71a** reacted with halo-substituted alkynes 1,2-bis(4-bromophenyl)ethyne (**33e**), producing **75c** in 57% yield; the reaction conditions did not affect the halogen functionality. The survival of bromo-group allows the induction of aryl groups in the molecular template through cross-couplings. The oxidative annulations between 1,2-bis(4-methoxyphenyl)ethyne (**33c**) and *N*-(2,3-bis(4-methoxyphenyl)benzofuran-5-yl)acetamide

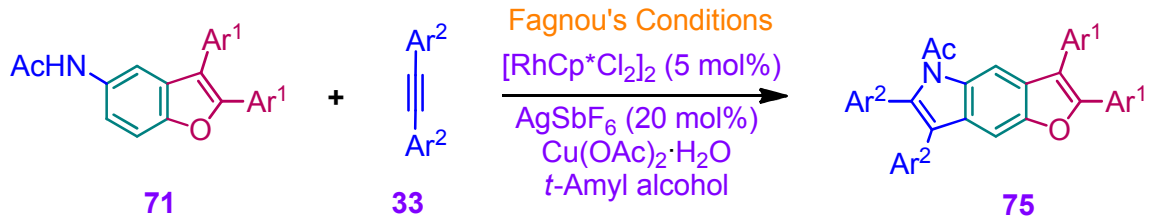
(**71c)** yields 1-(2,3,6,7-tetrakis(4-methoxyphenyl)-5H-furo[2,3-*f*]indol-5-yl)ethanone (**75d)** in excellent yield. The desired furo-indole product **75e** was obtained from **71b** and 1,2-di-*p*-tolylethyne (**33b**) in 82% yield. Unfortunately, the electron poor alkynes 4,4'-(ethyne-1,2-diyl)dibenzonitrile (**33d**) failed to react with **71a** under the Fagnou's optimized conditions.

Table 3.1: Synthesis of benzo[*b*]furans from phenols and alkynes[a]



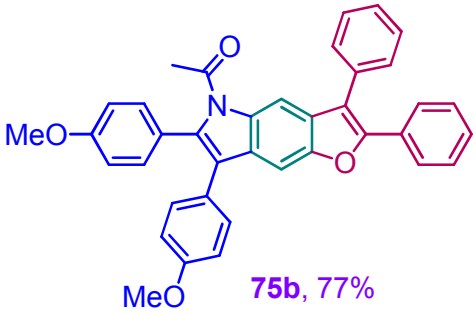
[a] Reaction conditions B: **70** (5.0 equiv), **33** (1.0 equiv), $Pd_2(dba)_3$ (5.0 mol%), 1,10-phenanthroline (10 mol%), NaOAc (5.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv), and 1,4-dioxane (8.0 mL) at 130 °C for 48 h.

Table 3.2: Synthesis of fused furo-indoles from benzofuranyl acetamides and alkynes[a]

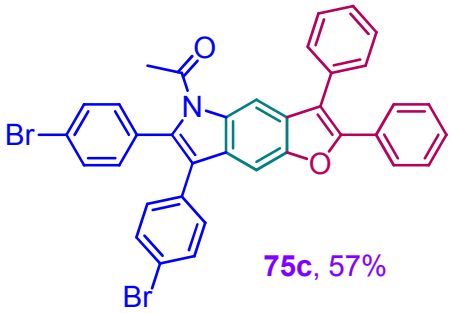


71 **33** **75**

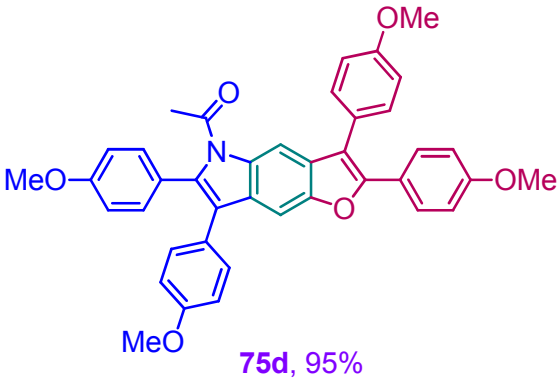
Ar = 4-Me-C_6H_4 (**33b**)
Ar = 4-MeO-C_6H_4 (**33c**)
Ar = 4-Br-C_6H_4 (**33e**)



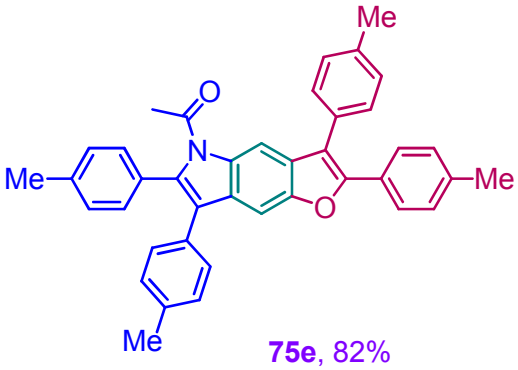
75b, 77%



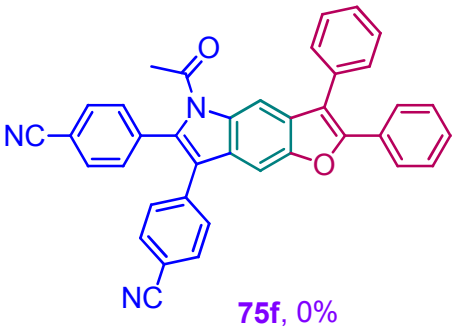
75c, 57%



75d, 95%



75e, 82%



75f, 0%

[a] Reaction conditions: **71** (1.0 equiv), **33** (1.1 equiv), $[Cp^*RhCl_2]_2$ (5.0 mol%), $Cu(OAc)_2 \cdot H_2O$ (2.1 mmol) and $AgSbF_6$ (68 mg, 0.2 mmol, 20 mol%) in *t*-amyl alcohol (3.0 mL) at 120 ^oC for 3–5 h.

3.3.2. Optical and Electronic Properties

Absorption and Fluorescence Spectra: The UV-vis absorption spectra of the furo-indoles in $CHCl_3$ solution (10^{-5} M) are shown in Figure 3.5. The absorption spectra show two major bands at ca. 200–300 nm and ca. 300–400 nm. These UV absorptions attributes to localized fused aromatic π–π* transitions. The absorption maxima (λ_{max}) of **75b**–**e** were at 340, 339, 345, and 336 nm, respectively. The electron withdrawing or electron donating groups on fused furo-indoles doesn't significantly affect the absorption maxima.

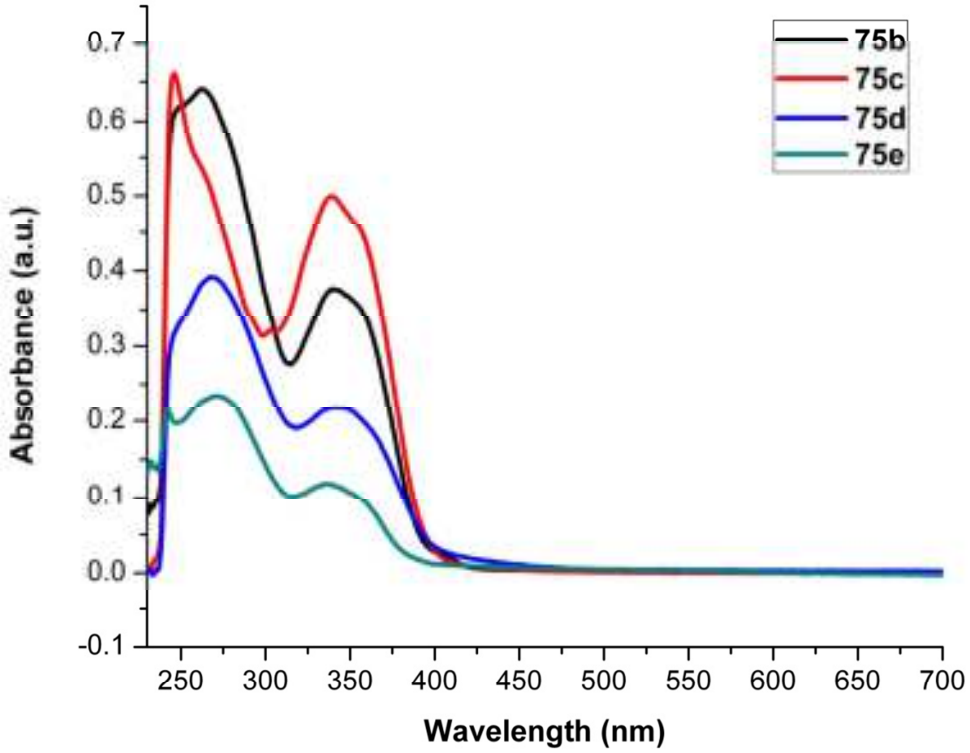


Figure 3.5: UV-vis absorption spectra of compounds **75b**-**e** in 1×10^{-5}M of $CHCl_3$ solution

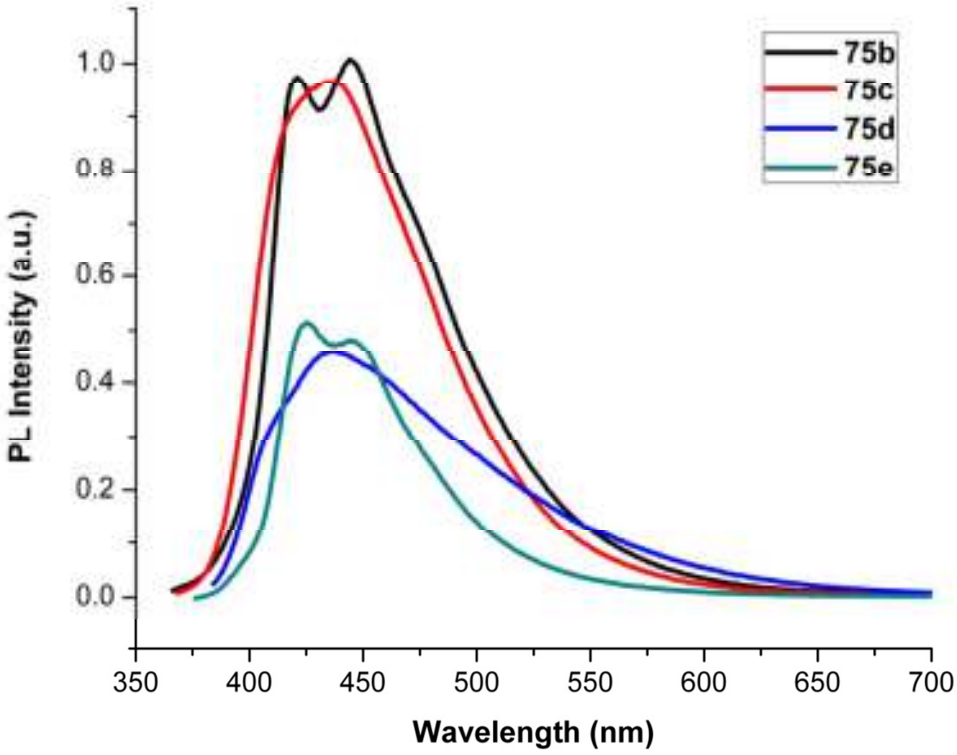


Fig 3.6: Fluorescence spectra of compounds **75b–e** in 1×10^{-5}M of $CHCl_3$ solution

The photoluminescence emission spectra of the fused furo-indoles **75b–e** in chloroform solution (10^{-5} M) are shown in Figure 3.6. All the molecules show blue emission with varying maximum for different molecules. The blue emission with maximum of 421–443 nm is observed. Therefore, these molecules may be applicable as blue light emitting diodes.

Thermal Properties (DSC and TGA studies): The thermal stability of organic materials is crucial for device stability and lifetime in OLED applications. Thermal instability may result in degradation of organic devices due to morphological changes. Therefore, thermal properties of fused furo-indoles are examined by differential scanning calorimetry and thermal gravimetric analysis (DSC-TGA). The DSC-TGA studies are performed at temperature ranging from 30 to 600 ^{o}C under N_2 atmosphere. The compounds are thermally stable upto 380–400 ^{o}C. The decomposition temperatures (T_D) and melting points (T_m) of the compounds **75b–e** are shown in Table 3.3.

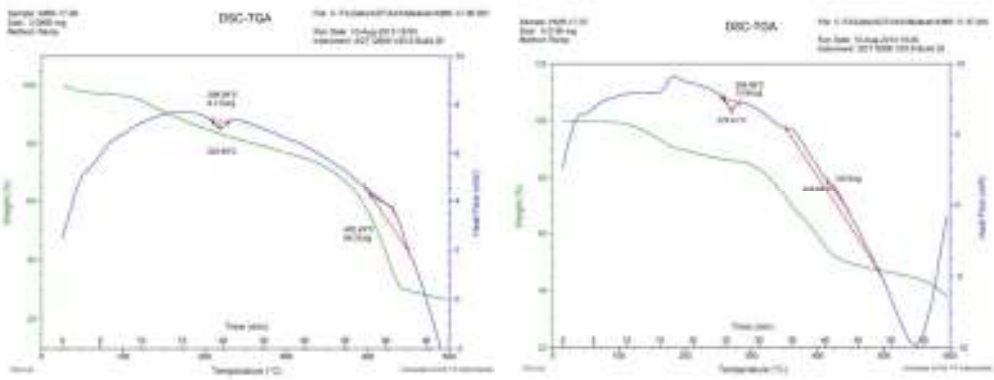


Figure 3.7: DSC-TGA graphs of **75b** and **75c**

Table 3.3: Optoelectronic and thermal properties of fused furo-indoles

Entry	Compound	Absorption		Excitation	Emission	Thermal Properties	
		λ_{max} (nm)	ε ($M^{-1}cm^{-1}$)	λ_{ex} (nm)	λ_{max} (nm)	T_m (°C)	T_D (°C)
1	**75b**	263, 340	64,087 and 37,636	340	421, 445	209	402
2	**75c**	246, 339	66,136 and 49,927	339	436	258	428
3	**75d**	268, 345	39,182 and 21,731	345	436	95	464
4	**75e**	272, 336	23,472 and 11,809	336	425, 443	123	389

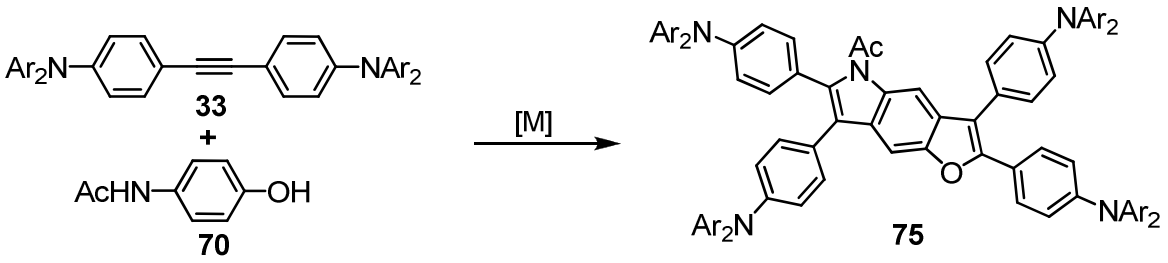
3.4. Conclusions

In summary, we have designed extended π-conjugated molecular entities, the fused furo-indole derivatives for the possible application in optoelectronics. The synthesis of fused furo-indole skeleton is initiated with the installation of benzo[*b*]furans on *N*-acetyl-4-amino phenols employing the recently developed palladium-catalyzed oxidative annulation between phenols and unactivated internal alkynes. Subsequently, the survival of the NHAc group allows the construction of indole-skeleton following the Fagnou's Rh-catalyzed oxidative annulations of anilides with internal alkynes. These two-step synthetic

procedures useful in accessing a wide array of fused furo-indoles. The optical and electronic properties of these new molecular entities are studied by UV-vis and fluorescence spectroscopy. All the molecules showed strong absorption at UV range (300-400 nm) and strong blue emission. We therefore believe these molecules may find possible applications as blue light emitting diodes.

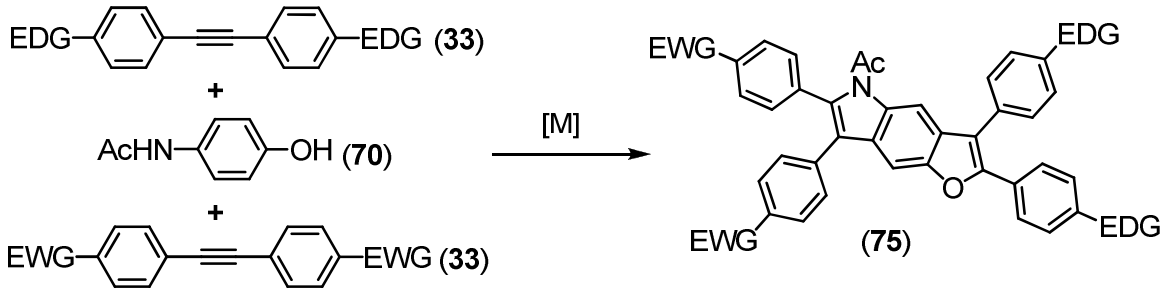
3.5. Future Work

The present work successfully demonstrates the synthesis of fused furo-indoles and their possible application as blue OLED. In general, the amine moiety is crucial for hole transporting materials. We therefore envisioned introducing the amine moieties on the fused furo-indole skeleton. This would enable the fused heterocycles in showing the electron transport properties (Scheme 3.18).



Scheme 3.18: Synthesis of arylamine containing fused furo-indoles

The other possible extension of this work is to introduce D-A (Donor-Acceptor) moieties on the core molecule. This would enhance the electron accepting or electron donating ability of the molecule; as a result these molecules may find applications in optoelectronics (Scheme 3.19).



Scheme 3.19: Synthesis of D-A type fused furo-indoles

3.6. Experimental

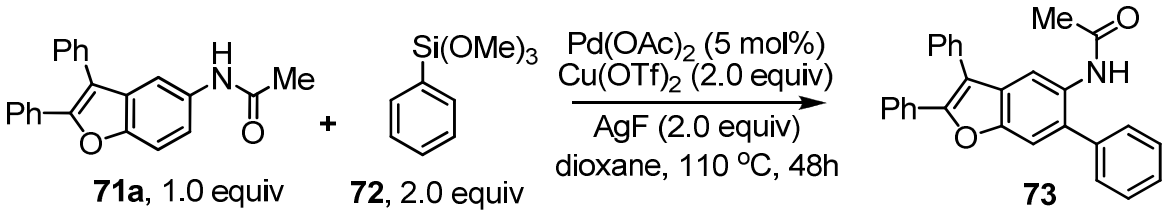
3.6.1. General experimental and Materials: Unless otherwise noted, all the reagents and intermediates were obtained commercially and used without purification. Ligands, catalysts, internal alkynes and other chemicals were purchased or prepared as mentioned in experimental section, chapter 2. UV-Visible absorption and fluorescence spectra were recorded on a spectrophotometer (Cary-100, Varian) and a spectrofluorimeter (Horiba, Jobin Yvon) respectively.

3.6.2. Typical procedure for the reaction of unactivated phenols with alkynes (condition-B; GP 1):

In an oven dried Schlenk tube, phenol (5.0 mmol), alkyne (1.0 mmol), $Pd_2(dba)_3$ (0.05 mmol), 1,10-phenathroline (0.10 mmol), NaOAc (5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (2.0 mmol), and 1,4-dioxan (8.0 mL) were added. The resulting reaction mixture was stirred at 130 ^oC. Progress of the reaction was monitored by GC analysis, while noticing complete consumption of alkynes employed. Reaction was continued for the time shown in the respective Tables, and brought to room temperature. The reaction mixture was diluted with dichloromethane (5.0 mL), and filtered over a small pad of Celite. Solvent was evaporated under the reduced pressure and the crude reaction mixture was purified using silica gel column chromatography.

3.6.3. Spectral and analytical data of the compounds:

***N*-(2,3,6-Triphenylbenzofuran-5-yl)acetamide (73):**

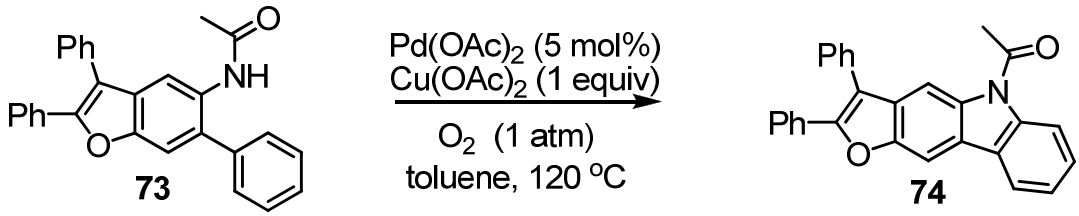


Following the procedure shown by Zhang Jie Shi et al.,[27b] acetanilide **71a** (327 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), $Cu(OTf)_2$ (722 mg, 2 mmol), AgF (254 mg, 2 mmol), and 1,4-dioxane (5.0 mL) were placed in a Schlenk tube. Trimethoxyphenylsilane (**72**, 396 mg, 2 mmol) was added via syringe, and the sealed tube was heated at 110 °C for 48 h. The resulting mixture was cooled to room temperature and filtered through Celite.

The crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (3:2) to afford **73** (303 mg) in 75% yield as pale yellow solid.

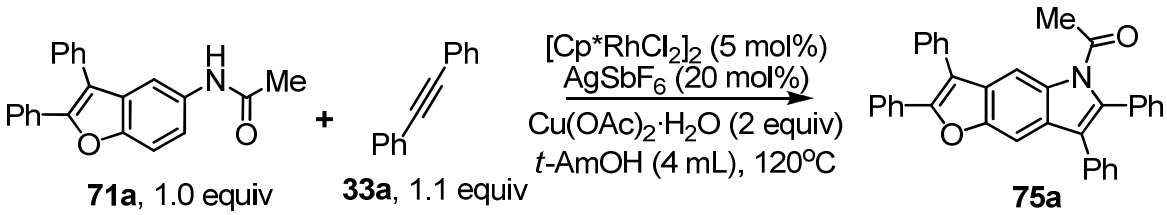
mp 198–200 °C; R_f = 0.51 (3:2 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.20 (bs, 1H), 7.66 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.57–7.47 (m, 6H), 7.46–7.41 (m, 5H), 7.35–7.29 (m, 3H), 7.10 (bs, 1H, NH), 1.99 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ168.5, 151.7, 151.2, 138.6, 132.4, 131.5, 130.5, 130.2, 130.1, 129.7, 129.5, 129.1, 129.0, 128.5, 127.9, 127.8, 127.0, 117.8, 114.5, 112.2, 24.3; **IR (Neat)** ν_{max} 3254, 3051, 2920, 2849, 1660, 1528, 1446, 1260, 1068, 761, 690 cm^{-1}; **MS (EI)** m/z (%) 402 (M^+ –1, 100), 348 (3), 302 (5), 246 (10); **Elemental analysis** calcd for $C_{28}H_{21}NO_2$: C 83.35, H 5.25, N 3.47. Found: C 83.15, H 5.34, N 3.51.

1-(2,3-Diphenyl-5H-furo[3,2-*b*]carbazol-5-yl)ethanone (74):



Following the procedure depicted by S. L. Buchwald et al,[27c] compound **74** was obtained from **73** in 65% isolated yield as a pale yellow solid. mp 193–194 °C; R_f = 0.58 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.30 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.99–7.91 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.59–7.41 (m, 6H), 7.40–7.31 (s, 4H), 2.76 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.8, 151.8, 151.0, 139.2, 135.8, 132.6, 130.6, 129.8, 129.2, 128.5, 127.9, 127.1, 127.0, 126.8, 124.7, 123.5, 119.8, 118.3, 115.9, 107.2, 101.1, 27.7; **IR (Neat)** ν_{max} 3055, 2924, 1689, 1496, 1427, 1369, 1298, 1176, 1114, 1060, 1016, 945, 877, 763, 694 cm^{-1}; **MS (EI)** m/z (%) 402 (M^+ +1, 100), 383 (10), 368 (8), 312 (5), 279 (5), 213 (8); **Elemental analysis** calcd for $C_{28}H_{19}NO_2$: C 83.77, H 4.77, N 3.49. Found: C 83.61, H 4.82, N 3.43.

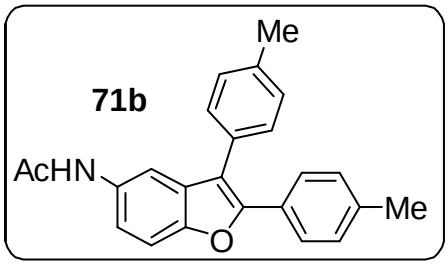
1-(2,3,6,7-Tetraphenyl-5H-furo[2,3-*f*]indol-5-yl)ethanone (75a):



Following the reported procedure by K. Fagnou et al.,[27a] reaction between *N*-(2,3-diphenylbenzofuran-5-yl)acetamide (**71a**; 327 mg, 1.0 mmol) and diphenylacetylene (**33a**; 196 mg, 1.1 mmol) was carried out in the presence of $[Cp^*RhCl_2]_2$ (31 mg, 5.0 mol%), $Cu(OAc)_2 \cdot H_2O$ (418 mg, 2.1 mmol) and $AgSbF_6$ (68 mg, 0.2 mmol, 20 mol%) in *t*-amyl alcohol (3.0 mL). The resulting reaction mixture was heated at 120 °C for 3 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **75a** (301 mg) in 60% yield as yellow solid.

mp 281–282 °C; R_f = 0.56 (49:1 hexane/EtOAc); **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.59 (s, 1H), 7.70–7.64 (m, 3H), 7.61–7.56 (m, 2H), 7.55–7.49 (m, 2H), 7.48–7.42 (m, 1H), 7.41–7.34 (m, 5H), 7.35–7.27 (m, 8H), 1.99 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.5, 151.7,151.1, 135.8, 134.3, 133.1, 133.0, 132.9, 130.8, 130.7, 130.1, 129.9, 129.6, 129.2, 128.6, 128.4, 128.3, 128.2, 127.7, 127.1, 126.9, 123.7, 118.4, 106.9, 100.6, 28.0; **IR (Neat)** ν_{max} 3055, 3028, 2924, 2852, 1705, 1604, 1427, 1363, 1307, 1277, 1163, 1060, 1026, 754 cm^{-1}; **MS (EI)** m/z (%) 504 (M^+ +1, 100), 391 (3), 279 (8); **Elemental analysis** calcd for $C_{36}H_{25}NO_2$: C 85.86, H 5.00, N 2.78. Found: C 85.68, H 5.07, N 2.85.

***N*-(2,3-di-*p*-Tolylbenzofuran-5-yl)acetamide (71b):**

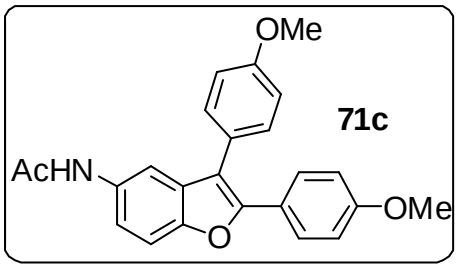


Following the general procedure in condition B (GP1); a mixture of acetaminophen (**70a**; 755 mg, 5.0 mmol), 1,2-di-*p*-tolylethyne (**33b**; 200 mg, 1.0 mmol), NaOAc (410 mg, 5.0 mmol), $Cu(OAc)_2 \cdot H_2O$ (399 mg, 2.0 mmol) in the presence of $Pd_2(dba)_3$ (45 mg, 0.05 mmol) and 1,10-phenanthroline (18 mg, 0.1 mmol) in 1,4-dioxan (8.0 mL) was heated at 130 °C for 48 h. Upon usual work-up, the crude mixture was purified by silica

gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **71b** (202 mg) in 57% yield as colorless solid.

mp 230–235 °C; R_f = 0.61 (3:2 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.59 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.40–7.33 (m, 3H), 7.28–7.22 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H), 1.82 (bs, 1H, NH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.4, 151.6, 151.0, 138.4, 137.3, 133.1, 130.8, 129.7, 129.5, 129.1, 127.8, 126.9, 118.1, 116.9, 111.9, 111.1, 24.4, 21.3; **MS (EI)** *m/z* (%) 356 (M^+ +1, 100), 322 (13), 271 (9); **Elemental analysis** calcd for $C_{24}H_{21}NO_2$: C 81.10, H 5.96, N 3.94, Found: C 81.23, H 5.91, N 3.86.

***N*-(2,3-bis(4-Methoxyphenyl)benzofuran-5-yl)acetamide (71c):**



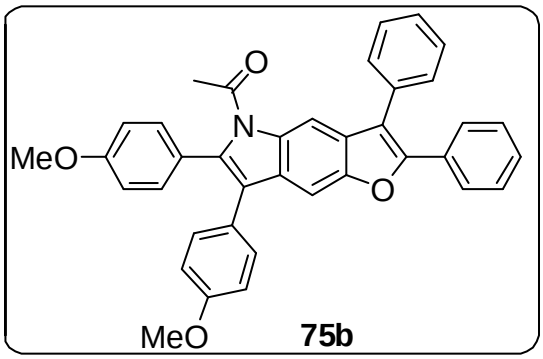
Following the general procedure in condition B (GP1); a mixture of acetaminophen (**70a**; 634 mg, 4.2 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**33c**; 200 mg, 0.84 mmol), NaOAc (344 mg, 4.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (335 mg, 1.7 mmol) in the presence of $Pd_2(dba)_3$ (38 mg, 0.04 mmol) and 1,10-phenanthroline (15 mg, 0.09 mmol) in 1,4-dioxan (6.0 mL) was heated at 130 ^oC for 48 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **71c** (195 mg) in 60% yield as colorless solid.

mp 175–180 °C; R_f = 0.54 (3:2 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ7.63–7.55 (m, 3H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 2.14 (s, 3H), 1.75 (bs, 1H, NH); **^{13}C NMR (101 MHz, $CDCl_3$)** δ168.5, 159.7, 159.0, 151.4, 150.9, 133.1, 130.9, 130.8, 128.3, 124.8, 123.3, 121.9, 120.8, 117.8, 115.7, 114.5, 113.9, 111.8, 110.9, 55.3, 24.4; **MS (EI)** *m/z* (%) 388 (M^+ +1, 100), 362 (7), 291 (6), 250 (10); **Elemental analysis** calcd for $C_{24}H_{21}NO_4$: C 74.40, H 5.46, N 3.62, Found: C 74.32, H 5.41, N 3.68.

1-(6,7-bis(4-Methoxyphenyl)-2,3-diphenyl-5H-furo[2,3-*f*]indol-5-yl)ethanone (75b):

Following the reported procedure by K. Fagnou et al.,[27a] reaction between *N*-(2,3-diphenylbenzofuran-5-yl)acetamide (**71a**; 100 mg, 0.3 mmol), 1,2-bis(4-

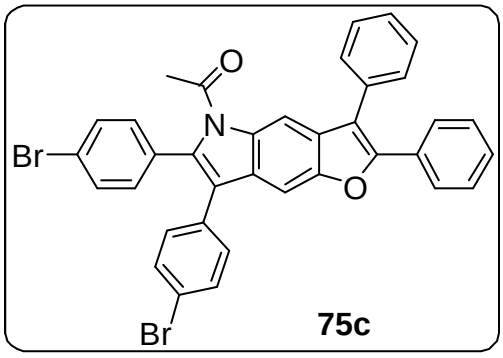
methoxyphenyl)ethyne (**33c**; 78 mg, 1.1 mmol) was carried out in the presence of $[Cp^*RhCl_2]_2$ (9.0 mg, 5.0 mol%), $Cu(OAc)_2 \cdot H_2O$ (125 mg, 2.1 mmol) and $AgSbF_6$ (20 mg, 0.2 mmol, 20 mol%) in *t*-amyl alcohol (3.0 mL). The resulting reaction mixture was heated at 120 °C for 3 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **75b** (131 mg) in 77% yield as yellow solid.



75b

mp 209 °C; R_f = 0.53 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.59 (s, 1H), 7.71–7.68 (m, 2H), 7.63 (s, 1H), 7.62–7.57 (m, 2H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.49–7.42 (m, 1H), 7.37–7.25 (m, 5H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.94–6.87 (m, 4H), 3.83 (s, 6H), 2.00 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.6, 159.7, 158.5, 151.6, 150.9, 135.5, 134.2, 132.9, 131.9, 131.1, 130.9, 129.9, 129.3, 129.1, 128.6, 128.4, 128.2, 127.7, 126.9, 125.5, 125.3, 123.0, 118.4, 114.1, 113.9, 106.9, 100.4, 55.3, 55.2, 29.7, 28.0; **MS (EI)** *m/z* (%) 564 (M^+ +1, 100), 505 (13), 445 (18), 345 (40), 329 (27), 242 (28); **Elemental analysis** calcd for $C_{38}H_{29}NO_4$: C 80.97, H 5.19, N 2.49, Found: C 80.85, H 5.25, N 2.42.

1-(6,7-bis(4-Bromophenyl)-2,3-diphenyl-5H-furo[2,3-*f*]indol-5-yl)ethanone (75c):



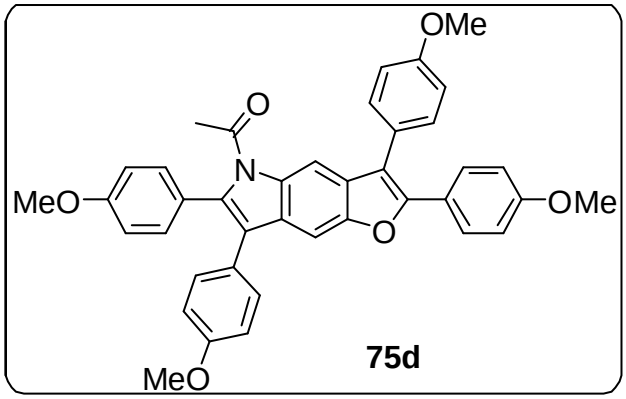
75c

Following the reported procedure by K. Fagnou et al.,[27a] reaction between *N*-(2,3-diphenylbenzofuran-5-yl)acetamide (**71a**; 100 mg, 0.3 mmol), 1,2-bis(4-bromophenyl)ethyne (**33e**; 110 mg, 0.33 mmol) was carried out in the presence of $[Cp^*RhCl_2]_2$ (9.0 mg, 5.0 mol%), $Cu(OAc)_2 \cdot H_2O$ (125 mg, 2.1 mmol) and $AgSbF_6$ (20 mg, 0.2 mmol, 20 mol%) in *t*-amyl alcohol (3.0 mL). The resulting reaction mixture was heated at 120 °C for 3 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **75c** (113 mg) in 57% yield as yellow solid.

mp 258 °C; R_f = 0.48 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.59 (s, 1H), 7.69–7.64 (m, 2H), 7.59–7.42 (m, 10H), 7.36–7.29 (m, 3H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.13

(d, *J* = 8.4 Hz, 2H), 2.03 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.9, 151.6, 151.5, 134.5, 134.3, 132.7, 132.1, 131.8, 131.7, 131.6, 130.6, 129.9, 129.8, 129.2, 128.4, 127.8, 127.7, 126.9, 123.2, 123.0, 121.5, 118.3, 106.9, 100.4, 29.7; **MS (EI)** *m/z* (%) 662 (M^+ +1, 100), 606 (98), 550 (40), 464 (67), 279 (27), 217 (30); **Elemental analysis** calcd for $C_{36}H_{23}Br_2NO_2$: C 65.38, H 3.51, N 2.12, Found: C 65.47, H 3.46, N 2.18.

1-(2,3,6,7-Tetrakis(4-methoxyphenyl)-5H-furo[2,3-f]indol-5-yl)ethanone (75d):



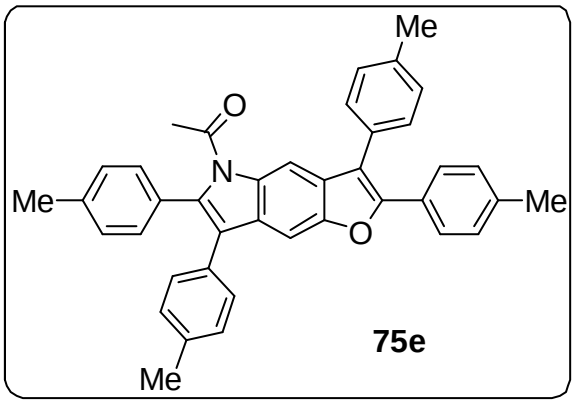
75d

Following the reported procedure by K. Fagnou et al.,[27a] reaction between *N*-(2,3-bis(4-methoxyphenyl)benzofuran-5-yl)acetamide (**71c**; 50 mg, 0.13 mmol), 1,2-bis(4-methoxyphenyl)ethyne (**33c**; 33 mg, 0.14 mmol) was carried out in the presence of $[Cp^*RhCl_2]_2$ (4.0 mg, 5.0 mol%), $Cu(OAc)_2 \cdot H_2O$ (26 mg, 2.1 mmol) and $AgSbF_6$ (8.0 mg, 0.2 mmol, 20 mol%) in *t*-amyl alcohol (2.0 mL). The resulting reaction mixture was heated at 120 °C for 3 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **75d** (78 mg) in 95% yield as yellow solid.

mp 95 °C; R_f = 0.45 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.54 (s, 1H), 7.60 (t, *J* = 8.8 Hz, 3H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.92–6.82 (m, 8H), 3.91 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 1.99 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.6, 159.7, 159.5, 159.0, 158.5, 151.4, 150.9, 135.1, 134.1, 131.9, 131.1, 131.0, 129.7, 128.2, 125.6, 125.4, 125.3, 123.7, 123.0, 116.5, 114.6, 114.1, 113.9, 113.8, 106.6, 100.2, 55.3, 28.0; **MS (EI)** *m/z* (%) 624 (M^+ +1, 100), 605 (6), 501 (3); **Elemental analysis** calcd for $C_{40}H_{33}NO_6$: C 77.03, H 5.33, N2.25, Found: C 77.13, H 5.41, N 2.31.

1-(2,3,6,7-Tetra-*p*-tolyl-5H-furo[2,3-*f*]indol-5-yl)ethanone (75e):

Following the reported procedure by K. Fagnou et al.,[27a] reaction between N-(2,3-di-*p*-tolylbenzofuran-5-yl)acetamide (**71b**; 50 mg, 0.15 mmol), 1,2-di-*p*-tolylethyne (**33b**; 32 mg, 0.16 mmol) was carried out in the presence of $[Cp^*RhCl_2]_2$ (4.0 mg, 5.0 mol%),



$Cu(OAc)_2 \cdot H_2O$ (62 mg, 2.1 mmol) and $AgSbF_6$ (10 mg, 0.2 mmol, 20 mol%) in *t*-amyl alcohol (2.0 mL). The resulting reaction mixture was heated at 120 °C for 3 h. Upon usual work-up, the crude mixture was purified by silica gel column chromatography eluting with hexane: ethyl acetate (49:1) to afford **75e** (68 mg) in 82% yield as yellow solid.

mp 123 °C; R_f = 0.48 (49:1 hexane/EtOAc); **^{1}H NMR (400 MHz, $CDCl_3$)** δ8.55 (s, 1H), 7.61 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.21–7.10 (m, 8H), 2.47 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H), 1.98 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ171.6, 151.5, 151.1, 138.4, 138.1, 137.2, 136.6, 135.6, 134.2, 130.6, 130.2, 129.9, 129.8, 129.7, 129.3, 129.1, 128.3, 128.2, 126.7, 123.4, 117.6, 106.7, 100.4, 29.7, 28.0, 21.4; **MS (EI)** *m/z* (%) 560 (M^+ +1, 100), 387 (6), 307 (3); **Elemental analysis** calcd for $C_{40}H_{33}NO_2$: C 85.84, H 5.94, N 2.50, Found: C 85.76, H 5.89, N 2.45.

3.7. References

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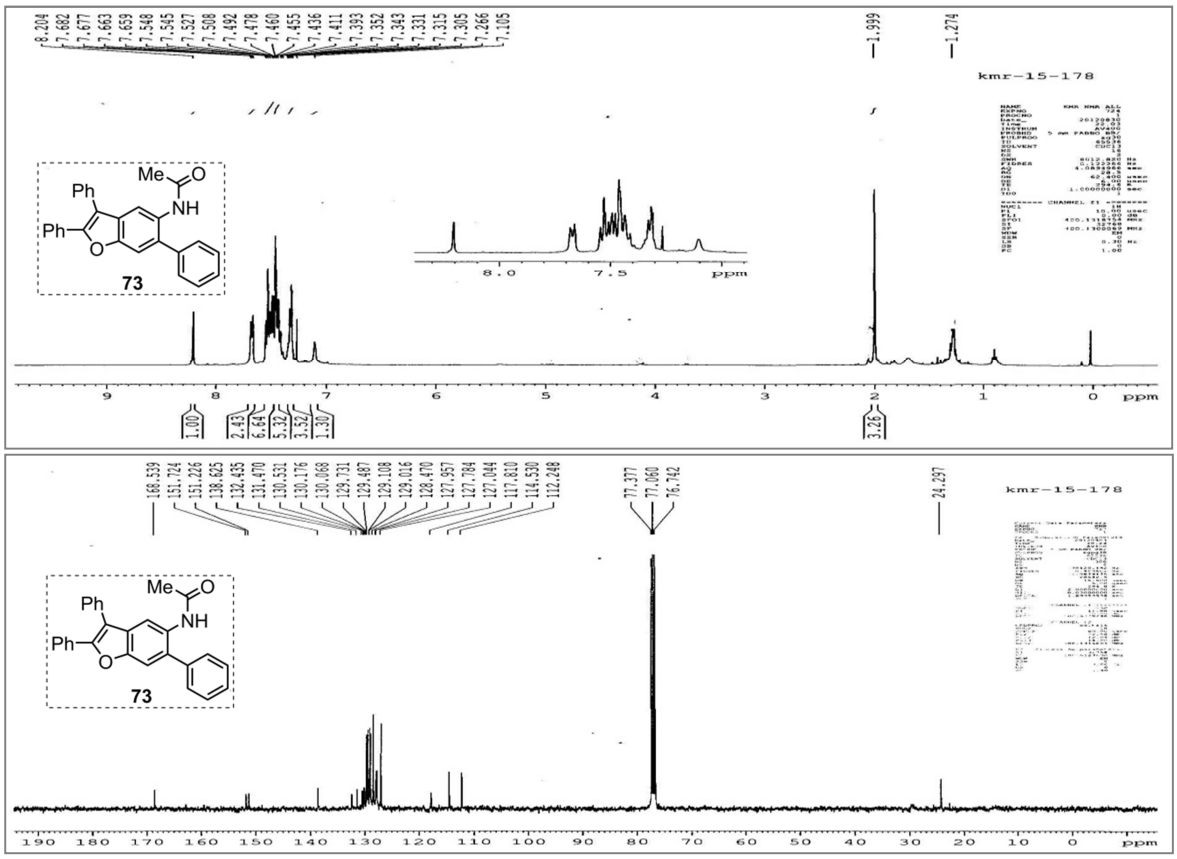
3.8. Spectra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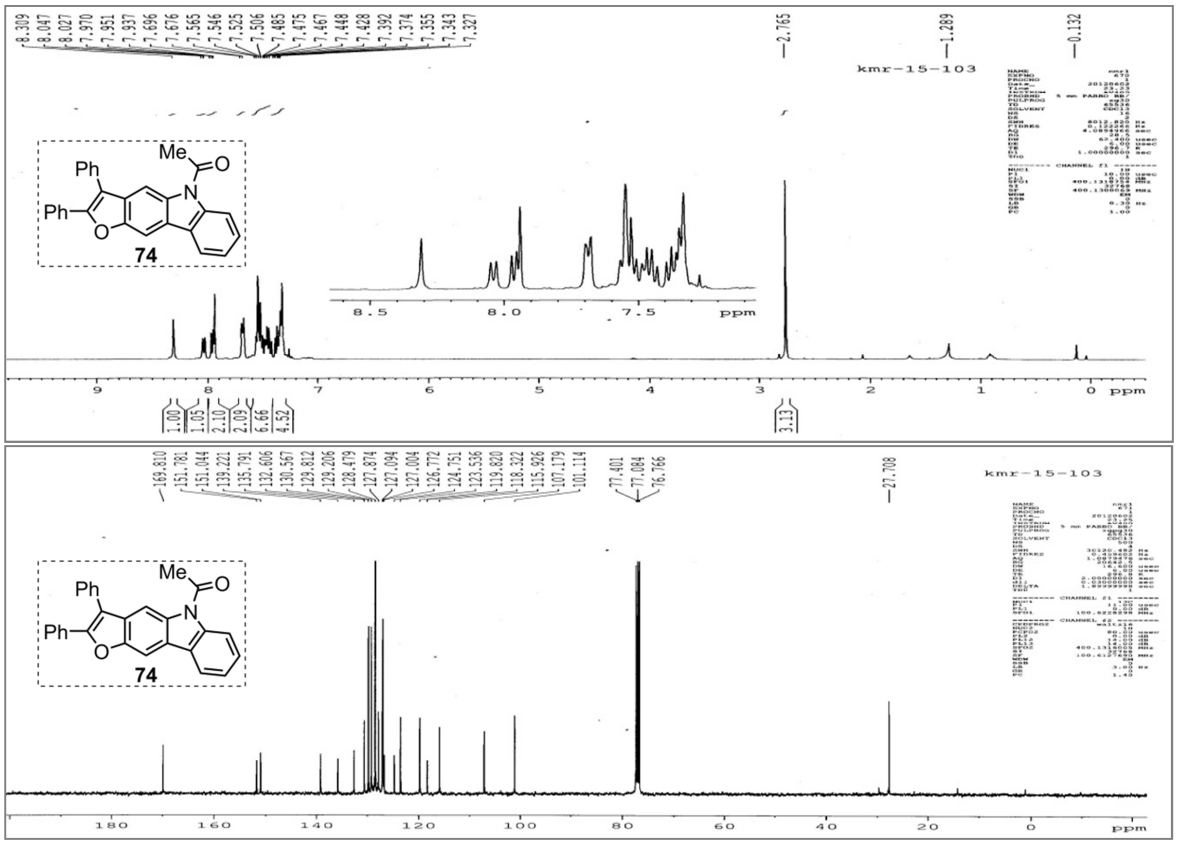
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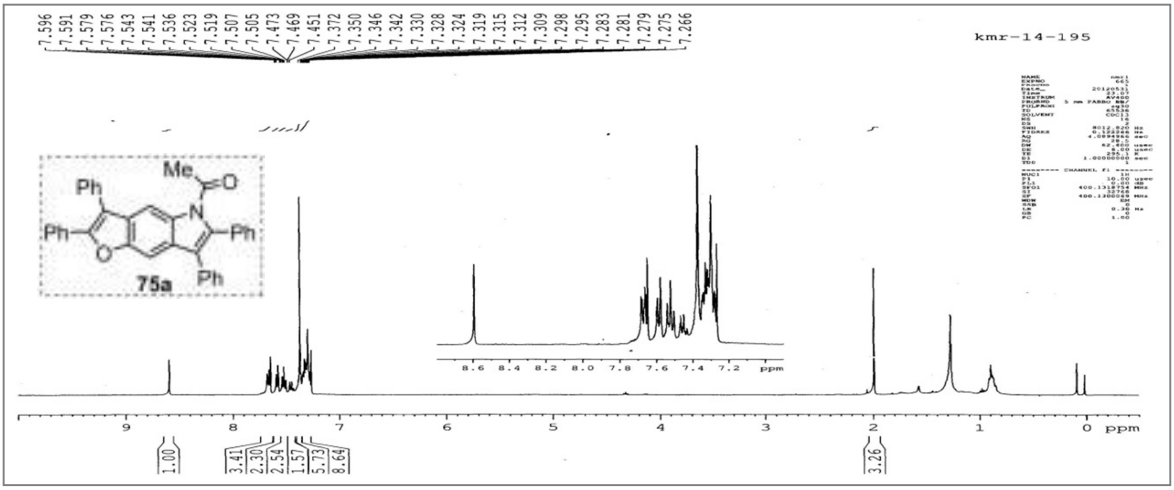
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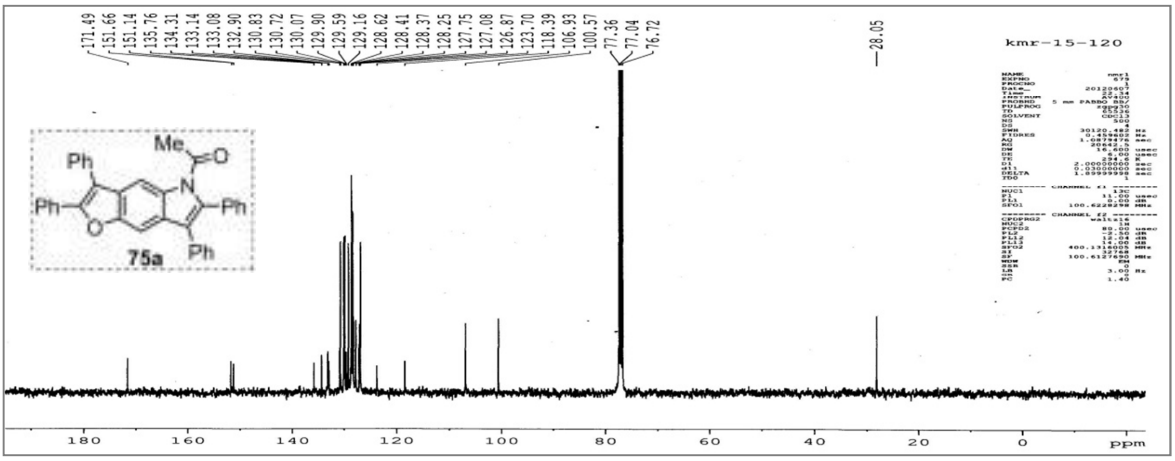
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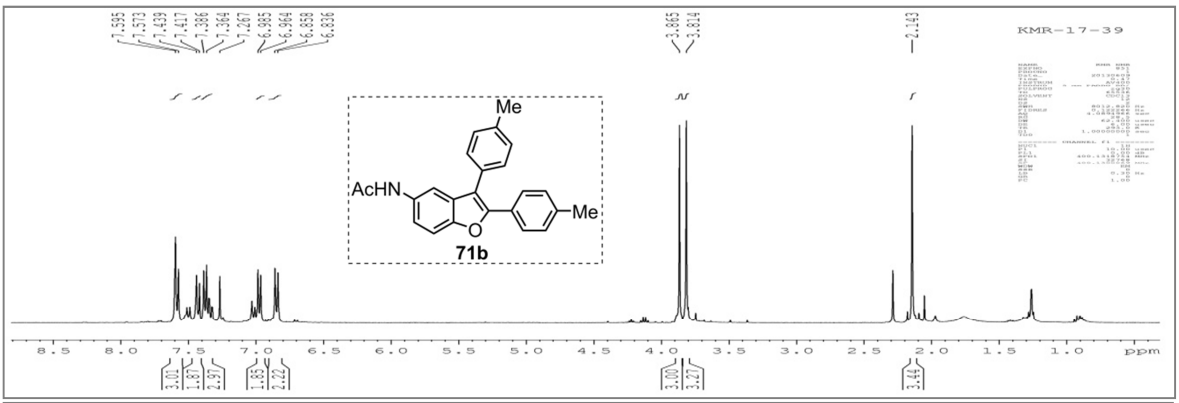
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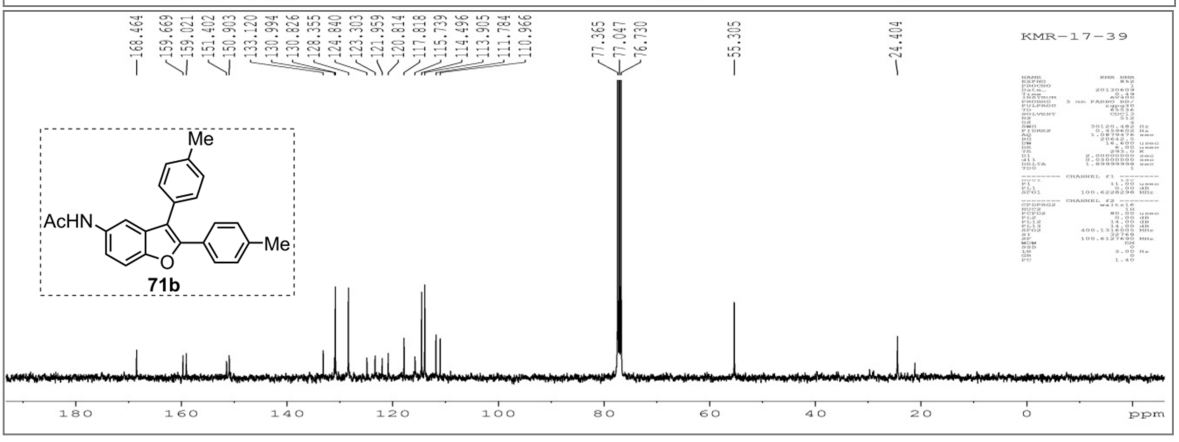
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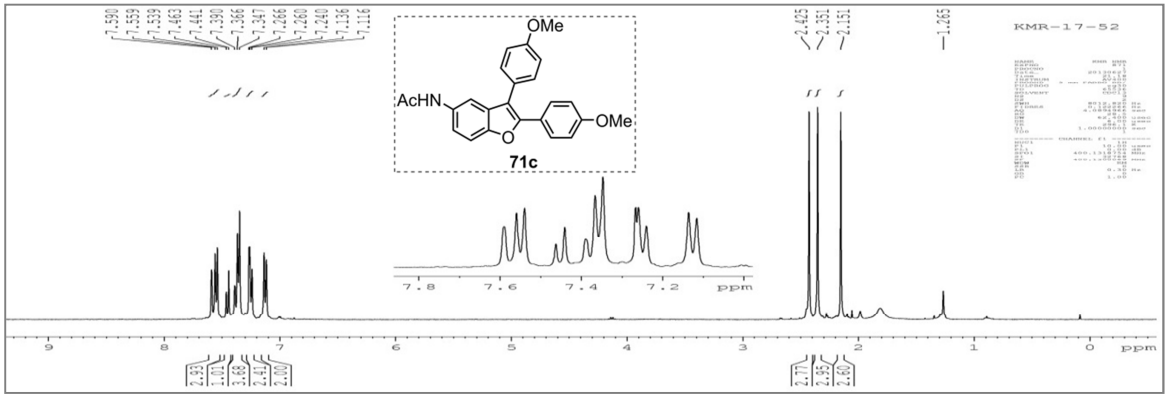
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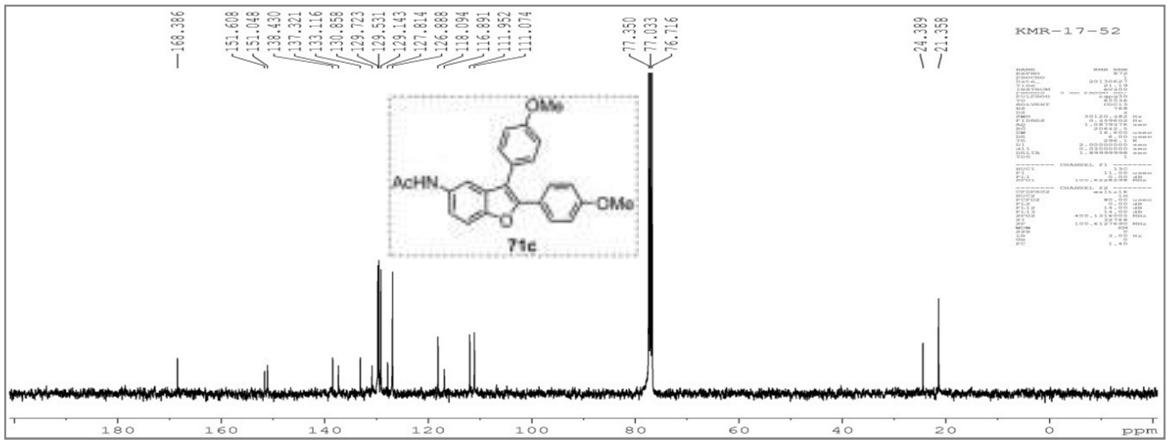
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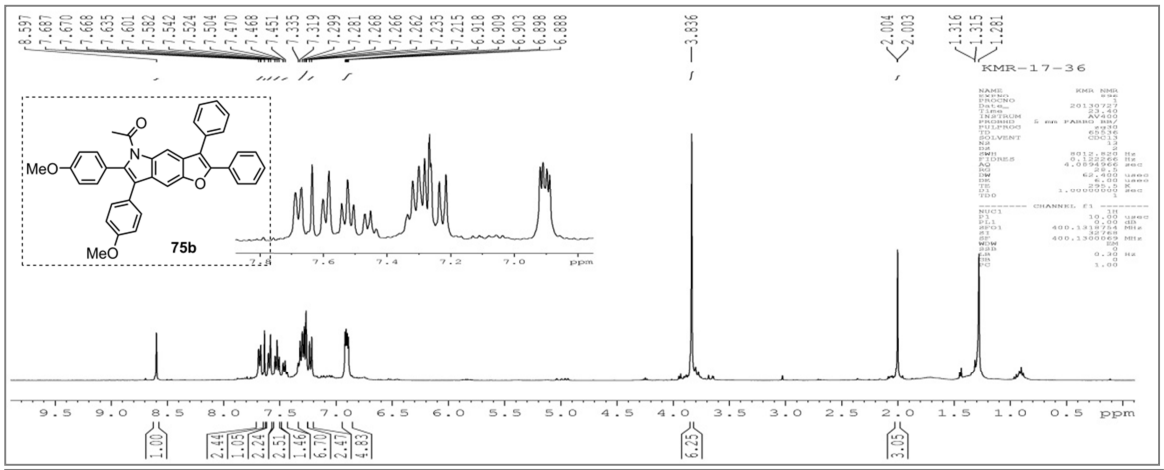
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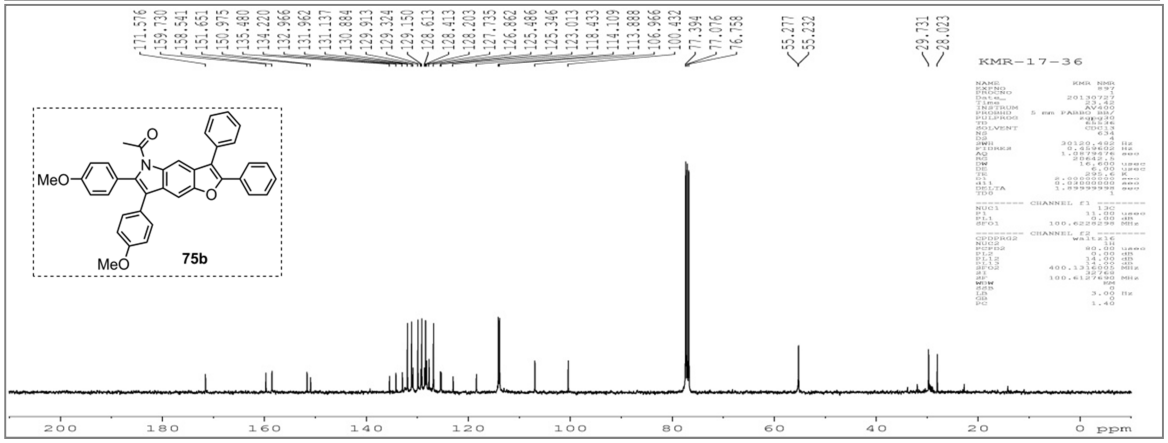
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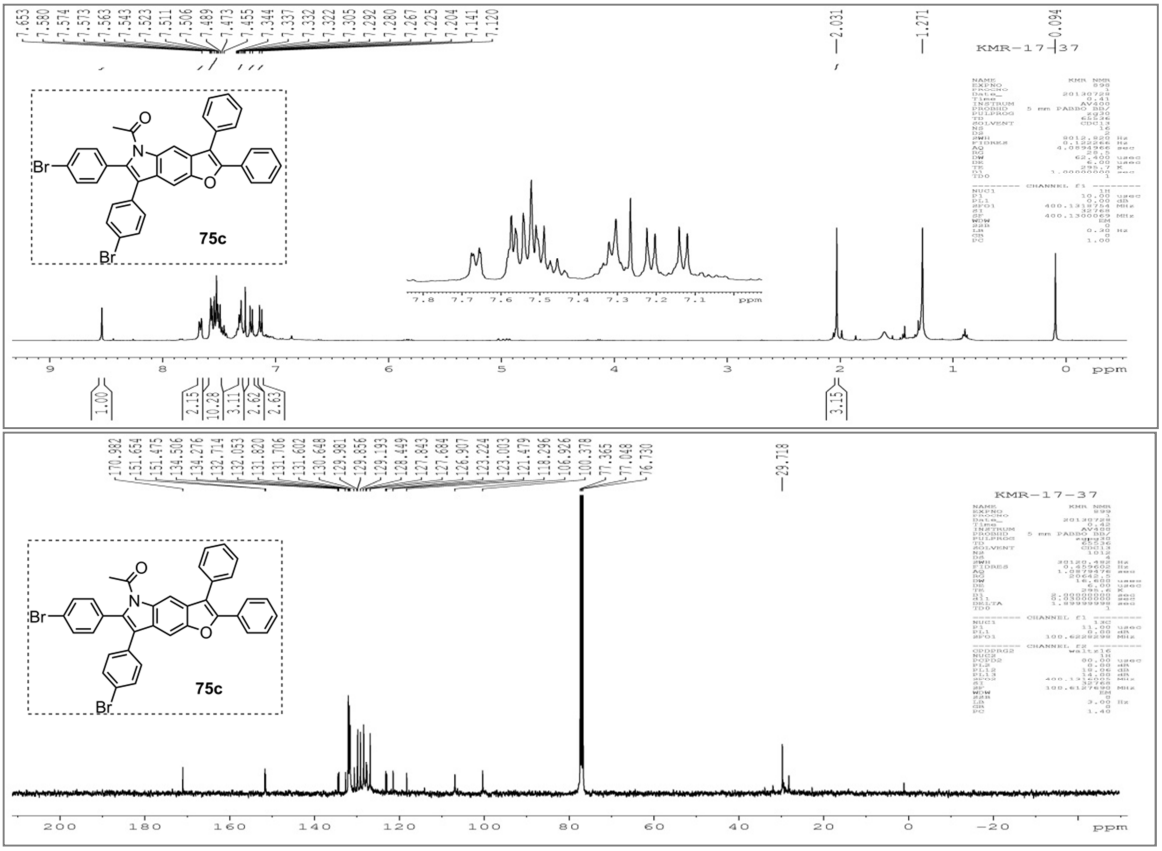
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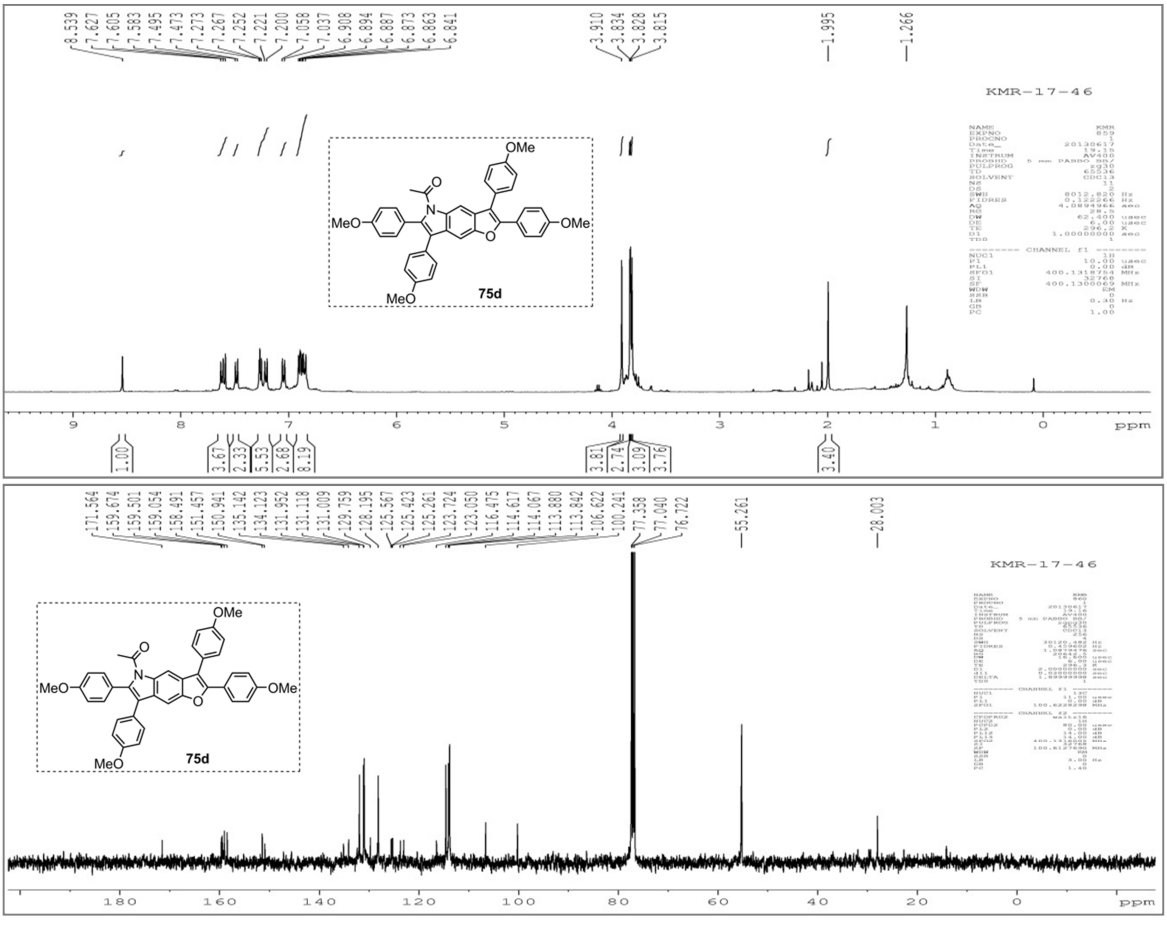
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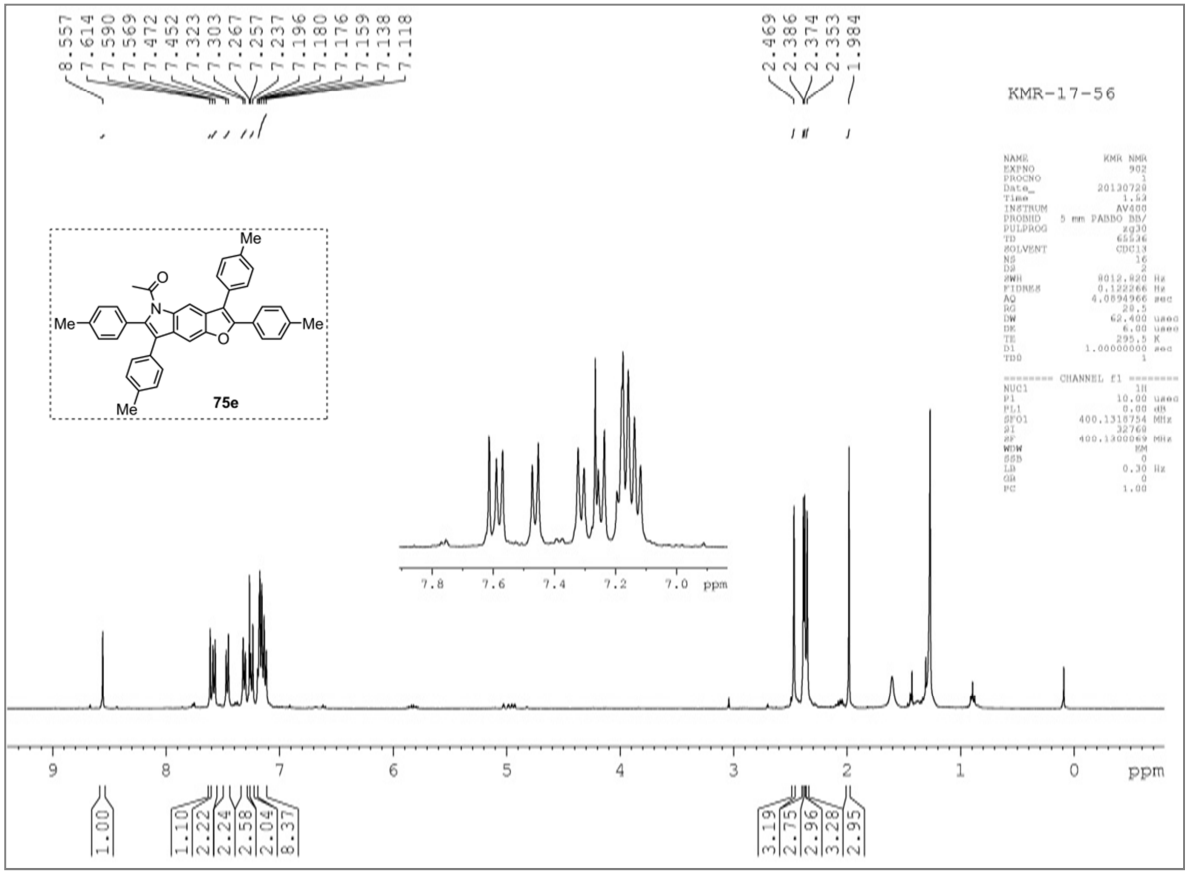
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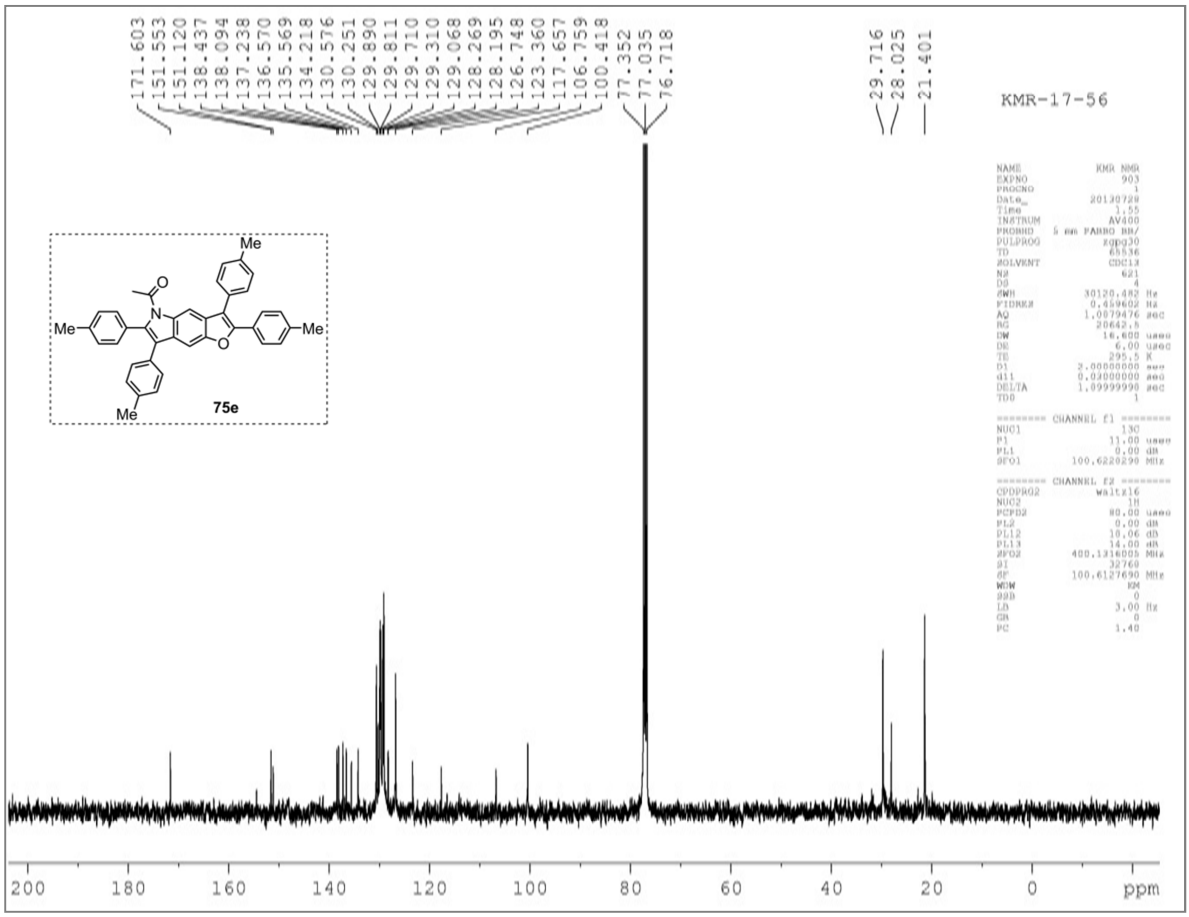
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List of Publications

1. Gold-catalyzed intermolecular hydrophenoxylation of unactivated internal alkynes.
   Malleswara Rao Kuram, M. Bhanuchandra, and Akhila Kumar Sahoo, *J. Org. Chem.* **2010**, *75*, 2247.

2. A convenient approach to β-heteroarylated (C-N bond) ketones from Cs_2CO_3 promoted reaction between propargyl alcohols and nitrogen heterocycles.
   M. Bhanuchandra, **Malleswara Rao Kuram**, and Akhila Kumar Sahoo, *Org. Biomol. Chem.* **2012**, *10*, 3538.

3. Direct access to benzo[*b*]furans through palladium-catalyzed oxidative annulations of phenols and unactivated internal alkynes.
   Malleswara Rao Kuram, M. Bhanuchandra, and Akhila Kumar Sahoo, *Angew. Chem. Int. Ed.* **2013,** 52, 4607.

4. Ru(II)-catalyzed intermolecular *ortho*-C–H amidation of aromatic ketones with sulfonyl azides.
   M. Bhanuchandra, Muntha Ramu Yadav, Raja Kumar Rit, **Malleswara Rao Kuram**, and Akhila Kumar Sahoo, *Chem. Commun.* **2013**, *49*, 5225.

5. Design, synthesis and optoelectronic properties of fused furo-indole derivatives.
   Malleswara Rao Kuram, M. Bhanuchandra, and Akhila Kumar Sahoo, (*manuscript under preparation)*

6. Silver(I)-catalyzed reaction between pyrazole and propargyl acetates: stereoselective synthesis of scorpionate ligands *E*-allyl-gem-dipyrazoles (ADPs).
   M. Bhanuchandra, **Malleswara Rao Kuram**, and Akhila Kumar Sahoo, (*manuscript submitted*)

Poster and Oral Presentations

1. **Malleswara Rao Kuram**, M. Bhanuchandra, and Akhila Kumar Sahoo*, Gold-catalyzed intermolecular hydrophenoxylation of unactivated internal alkynes.

   (i) Poster and Oral presentation at "**Chemfest-2011 (*In-house*)**" which was held in School of Chemistry, *University of Hyderabad*, Hyderabad, India on January, **2011**.

   (ii) Poster presentation at "***6th J-NOST conference***" which was held in School of Chemistry, *University of Hyderabad*, Hyderabad, India on January, **2011**.

2. **Malleswara Rao Kuram**, M. Bhanuchandra, and Akhila Kumar Sahoo*, Direct access to benzo[*b*]furans through palladium-catalyzed oxidative annulations of phenols and unactivated internal alkynes.

   (i) Poster presentation at "***Catalyst 2013, Dr. Reddy's Chemistry Conclave***", held at *Dr. Reddy laboratories*, Hyderabad, India on January, **2013**.

   (ii) Poster presentation at "***Chemfest-2013(In-house)***" which was held in School of Chemistry, *University of Hyderabad*, Hyderabad, India on Feb, **2013**.

Biographical Sketch

The author was born in Tellam Vari Gudem village, Andhra Pradesh, India on 7th March, 1985. He attended primary school at A. P. T. W. School, Tellam Vari Gudem and High School (Xth standard) at A. P. T. W. R. School, K. R. Puram, West Godavari, India. He finished his Intermediate education at A. P. S. W. R. Jr. College, Pedavegi, West Godavari. Then he received his Bachelor's degree in M.P.C from A. P. R. Degree College, Nagarjuna Sagar, Andhra Pradesh in 2005 where he got interested in chemistry. He obtained his Master's degree in Chemical Sciences in 2007 from Pondicherry University, India. The following June of 2007 he was also selected for CSIR-JRF (India). In 2008 he started his doctoral research at the University of Hyderabad under the guidance of Dr. Akhila Kumar Sahoo where he works on the development of transition metal catalyzed C–C and C–O bond forming reactions.