Synthetic Studies towards the Fused Heterocycles and Carbocycles *via* Metal Mediated Domino Reactions

Thesis Submitted for the Degree of Doctor of Philosophy (Science) of Jadavpur University, Kolkata, 700032

By

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CERTIFICATE FROM THE SUPERVISOR

This is to certify that the thesis entitled **"Synthetic Studies towards the Fused Heterocycles and Carbocycles *via* Metal Mediated Domino Reactions"** submitted by Smt. **RUPSA CHANDA** who got her name registered on 26.8.2019 for the award of Ph.D. (Science) degree of Jadavpur University, is absolutely based upon her own work under the supervision of **Prof. Umasish Jana** and that neither this thesis nor any part of it has been submitted for either any degree/diploma or any other academic award anywhere before.

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.....
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Dedicated

to

my parents

PREFACE

Investigations embodied in this dissertation entitled ***"Synthetic Studies towards the Fused Heterocycles and Carbocycles via Metal Mediated Domino Reactions"*** was initiated in august, 2018 under the supervision of Prof. Umasish Jana, Organic Chemistry Section, Dept. of Chemistry, Jadavpur University, Kolkata-700032. The aim of this thesis is to find out more general, efficient and convenient methodologies to synthesize a variety of fused heterocycles and carbocycles *via* environmentally friendly iron catalysed domino reactions.

The thesis has been divided into two parts. The **Part I** consist of an introduction of importance of iron catalysts in heterocycles synthesis and a brief review on various iron catalyzed reactions for the synthesis different kinds of benzo-fused heterocycles. **Part I** consists of two chapters. The chapter 1 consists a brief review on the synthesis of 3-substituted indoles by reaction with alcohol, and later in this chapter, our work on Iron-catalysed functionalisation of 3-benzylideneindoline *via* tandem Csp^2-Csp^3 bond formation/isomerisation with π-activated alcohols has been demonstrated. The reaction is highly regioselective and worked under mild conditions in good to excellent yield. Chapter 2 portrays a brief review on reaction of alkynes with alcohols using different catalysts, and later in this chapter, our work on iron-catalyzed carboarylation of alkynes *via* activation of π-activated alcohols: rapid synthesis of substituted benzofused six-membered heterocycles has been described. The strategy provides a simple, straight forward and atom-economical approach to gain different benzofused heterocycle molecules.

Part II describes the importance of carbocycles and a short review of various iron catalyzed reactions to access different kind of benzofused carbocyles. The Part II consists of one chapter including our work on the Fe(III) catalyzed double annulations of 2-alkynyl biaryls by the activation of acetals towards the synthesis of highly fused 13-aryl-13*H*-indeno[1,2-*l*]phenanthrene in one step.

Date **Rupsa Chanda**

ACKNOWLEDGEMENTS

The thesis entitled as ***"Synthetic Studies towards the Fused Heterocycles and Carbocycles via Metal Mediated Domino Reactions"*** is a part of five years of research work that has been done since I joined in Prof. Umasish Jana's lab. During my journey, I came in touch with a great number of people whose contribution in assorted ways to the research and the making of the thesis, deserve special mention. It is a pleasure to convey my gratitude to all of them in my humble acknowledgment.

First and foremost, thanks to God for giving me such a beautiful life and the opportunity to have some glimpses of the excellent world of science. I feel myself privileged and express my sincere gratitude and respect to my supervisor Prof. Umasish Jana, Organic Chemistry Section, Dept. of Chemistry, Jadavpur University, for introducing me to the engrossing field of "Synthetic Organic Chemistry" and allowing me to work under his supervision and guidance. He always provided me unflinching encouragement and support in various ways. His inspiration, and wise advice throughout the progress of the work and patiently providing me all sort of necessities to proceed with the Doctoral program.Without him it would have been truly impossible to produce this project. His scientific intuition, graceful behavior, dedication, passion of work and oasis of ideas enrich my growth as a student, a researcher and a person with a vision of science inside.

I am indebted to my teachers of our department, Prof. Umesh Chandra Halder, Prof. Gourhari Maiti, Prof. Sanjay Bhar, Prof. Rina Ghosh, Prof. Asok Kumar Mallik, Dr. Amit Saha, Dr. Samit Guha, Dr. Arunabha Thakur, Dr. Mohabul Alam Mondal for their unconditional love, valuable suggestions and constant inspiration.

I am also very eager to owe Prof. B. C. Ranu, Department of Organic Chemistry, IACS and his scholars for their prompt assistance in finishing my job within time. I would also like to extend huge and warm thanks to Tubai Da for his valuable help, co-operation and inspiration throughout my research work, without your support and encouragement, it would not be possible for me to come at this stage.The generous supports of Dr. Subir Panja and Dr. Pintu Maity in this regard deserve special mention.

Finally, talking about my workplace, it`s a real pleasure to be in a lab in which I was. The lab in itself is a nice little household, providing me with its exclusive entertaining elements. In this occasion words are simply incapable to express my feeling of thankfulness to my present and past lab members: Dr.Kartick Paul, Dr. Swapnadeep Jalal, Dr. Baitan Chakraborty, Dr. Sandip Kundal, Abhishek da and Gopal da. I am blassed to have some juniors like Samiran, Rajkamal, Sourav (Jamai), Anurag, Swati, Suparna, Somnath, Nur, Kush and many others for their whole hearted co-operation during my research work.

Words are inadequate in this situation for expressing my feelings to my well-wishers and friends. I was fortunate enough to meet some wonderful friends, seniors and well-wishers like Neha, Antara, Shrabani, Sayantani, Prakash, Uday, Prasenjit, Anwesha, Sovona, Sudipta, Writhabrata da, Shantanu da, Monalisa di, Sanu da, Ayan da, Manas da, Supriyo da, Adwitiya, Chhoton da, Samit da, Priyanka di, Aparajita di, Sneha di, Sayanwita di, Mitali di and many more.

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Now it’s time to acknowledge them without whom my existence is incomplete; my family. My parents deserve special mention for their inseparable support and prayers. My mother Mrs. Rina Chanda and father Mr. Subhas Chanda are the persons who inspired me learning, showing me the joy of intellectual pursuit and sincerely raised me with their caring and gentle love since I was child. Thanks for supporting me during my studies, urging me on, and blessings throughout my career. Their courage inspired me every moments to overcome the hurdles during my research career. I believe, whatever I am today, is solely because of my parents. I would like to thank my younger brother Rishi for being my constant companion. I heartily express gratitude to my beloved masi, meso, dida, dadu, mama, mami, boroma, jethu, pisi,

pisomosai, and my cousins Baptudada, Babujidada, Rintu dada, Chottu dada, Mistudidi, Monta, Akash, boudi and little Pustu in my life. They have been my greatest source of inspiration and I always find myself lucky and am proud to be a part of them. It is because of them that I can now look back with a smile to have conquered the hardships and challenges successfully.

Thank you all for keeping faith in me, standing beside me in all my difficult times and unconditional loving and caring for me irrespective of all my odd habits. I am indebted to you for what I am.

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CONTENTS

GENERAL INTRODUCTION

Iron Catalyzed Domino Reaction

History of synthetic organic chemistry presents a several numbers of fascinating reactions from old age to till date. Although these reactions are quite popular and applicable to everyday life, but still, the question raised on the existing chemical reactions, are not at all avoidable. The main reason for that are certainly the environmental hazards and waste generated by these chemical procedures. In current time, when dangers like global warming, pollutions are always threatening the mankind, we must not add more trouble to it. So we have to change our vision of the synthetic chemistry to how to synthesize over what to synthesize. And this necessity originated the concept of domino reactions.[1] Usually synthetic targets were achieved by stepwise formation of each bond individually. But later, scientists envisioned that, if several bonds can be created simultaneously in a single step without intermediate isolation, then that would decrease the number of steps, as well as waste. The amount of solvent, reagents, energy and labor will also get decreased a lot.[2] Hence, the procedure can become greener than before in terms of both environment and economy. This creates the basic concept of domino reactions. The efficacy of a domino reaction is determined by three key factors, its capacity to generate multiple bonds within a single conversion, the amount of complexity it makes in single operation, and the applicability of the reaction in various fields.[3] Inspired by the convenience of the domino reactions, our synthetic goal was to prepare complex heterocyclic and carbocyclic molecules using domino reaction.

Now, when the discussions come around the recent trends in organic synthesis, we cannot ignore the role of metals.[4] While choosing metals for a organic synthesis, we have to be very careful about its effectiveness and sustainability. Among many transition metals, the late transition metals like Pd, Ru, Rh and Ir have enhanced catalytic activity, but their limited use is attributed to their high cost and metal wastage causing environmental toxicity.[5] So utilization of less toxic and inexpensive metals has gained priority inevitably. Nowadays, the use of iron salt in catalysis has become one of the trending synthetic protocols because of many advantages like its high abundance in the earth, lower cost, environmentally benign nature etc.[6] The oxidation state of iron salts vary from -2 to +6. Therefore, iron salts are highly reactive and participate in different types of chemical reactions like CDC, C-H bond activation, cross-coupling, C-H amination, insertion etc.[7] In this thesis, metal

catalyzed synthesis of different heterocycles and carbocycles have been showcased where iron catalysed domino cyclization strategy has been utilized.

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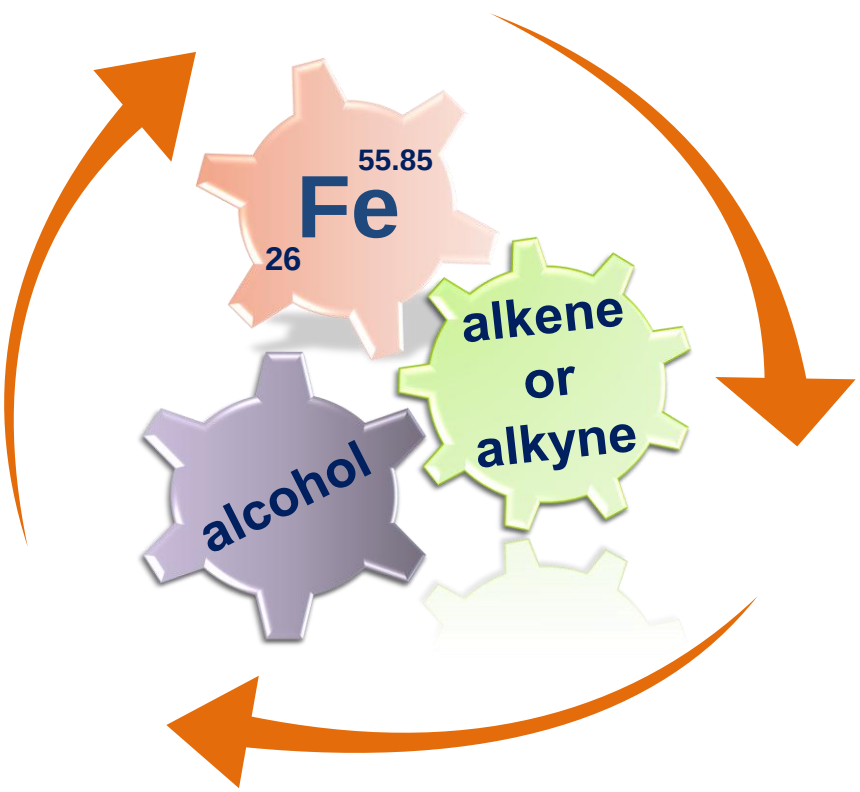
Part-1

Iron in the Synthesis of Heterocycles



1. INTRODUCTION:

Heterocycles are the type of cyclic compounds that contains one or more heteroatoms in their skeleton. Owing to the presence of heteroatoms instead of carbon atoms, heterocyclic compounds offer distinct physical and chemical properties from the carbon analogue compounds.[1] Heterocyclic compounds are the most versatile class of organic compounds and the most valuable ones too. Because, they form the integral parts of the most of the natural products and biologically active compounds.[2] Several biological compounds like vitamins, antibiotics, nucleic acids and hormones are predominantly heterocyclic compounds.[3] Not only for medicinal purposes, but also they have huge contributions in our everyday life, such as heterocycles are widely found in agrochemical products, antioxidants, corrosion inhibitors, copolymers, dyestuff etc.[4] But the most flourishing area of heterocycles is indeed in the pharmaceutical industries because of their different pharmacological activities like anti-tuberculosis, anti-HIV, anti-diabetic, anticancer, antimicrobial, antimalarial, anti-

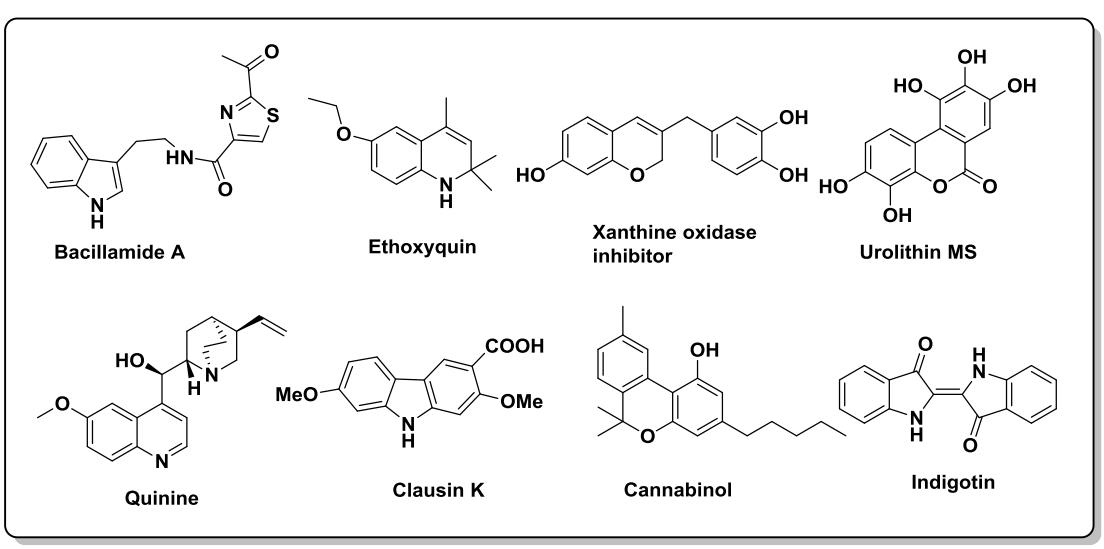


Figure 1: Some important natural products and medicinal compounds possessing benzo-fused heterocycles

Alzheimer's activity and many more.[5] Several sulphur-containing heterocycle compounds are utilised in food flavouring agents.[6] Among an enormous library of heterocyclic molecules, in this section, the focus will be on the synthesis of various benzo-fused heterocycles, as these fused moieties serve as integral components of numerous natural products and pharmaceuticals. The discussion will primarily revolve around the synthesis methods employed for these fused structures. (Figure 1).[7]

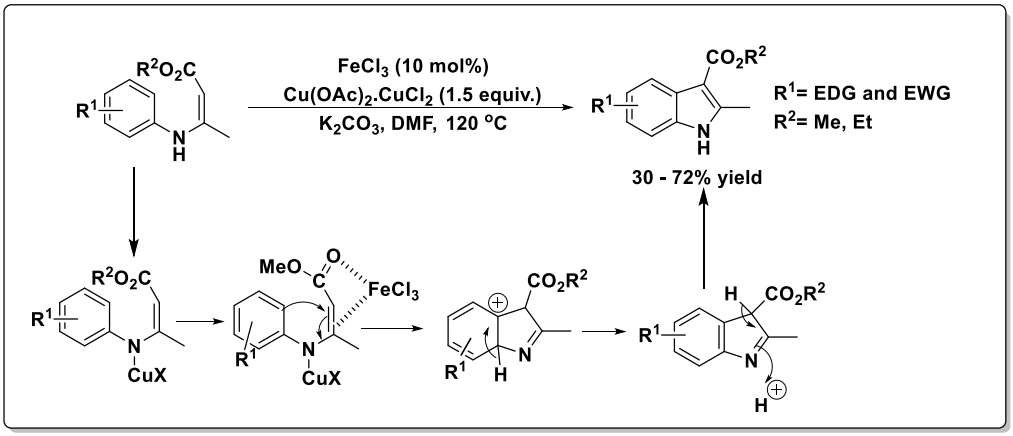
This numerous applicability of the benzo-fused heterocyclic compounds encouraged the synthetic chemists over a long time to develop new and convenient synthetic procedures to achieve different heterocyclic moieties. But current environmental issues demand and welcome the new synthetic protocols which are green, sustainable and ecologically benign with the lowest amount of by-products. And here comes the unavoidable role of sustainable iron salts. Over the past two decades, the development of new synthetic strategies involving iron salts has been a challenge to the chemists, as iron could offer all the necessary requirements for a reaction to be commercially acceptable, such as high catalytic activity, easy availability, economically cheap, environmentally abundant and benign etc.[8] Most of the literature survey reveals that, iron salts coordinate with the alkene or alkyne π-bonds and thus increases their activity.[9] Apart from that, iron, by its Lewis acidity, can activate alcohols and acetals through coordination.[10] Banking on this concept, in this part of the thesis, I am discussing the utility of the iron catalysts in the synthesis of various benzo-fused heterocycles which includes benzo-fused five, six, seven or larger membered heterocycles. Hope, my little endeavour to summarize recent literature reports on the iron-mediated synthesis of different heterocycles will manifest our inspiration for the upcoming work described in the later chapters.

2. Review on Iron Mediated Synthesis of Benzo-fused Heterocycles:

2.1. Benzofused five-membered heterocycles:

Several groups have utilized iron metal as the catalyst for the preparation of different nitrogen containing benzo-fused five-membered heterocycles. Some of the important methods have been discussed below.

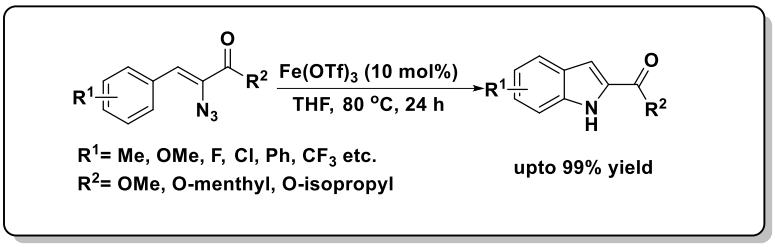
Liang and his group have documented the construction of 3-substituted indole derivatives by simultaneous aryl and vinyl C-H bond activation catalyzed by $FeCl_3$ in combination with $Cu(OAc)_2.CuCl_2$ oxidant (Scheme 1).[11] Higher yields were obtained from arenes having EDG located at the *para* position, while arenes with EWG positioned at the *ortho* position exhibited better yields compared to those located at the *para* position. The mechanism suggests that the reaction may proceed though a copper-iron bimetallic chelate complex which increases the reactivity of the enolates



Scheme 1. $FeCl_3$ catalyzed C-H activation for the synthesis of 3-substituted indole

and subsequent electrocyclic ring closing provided the desired functionalized indole derivates.

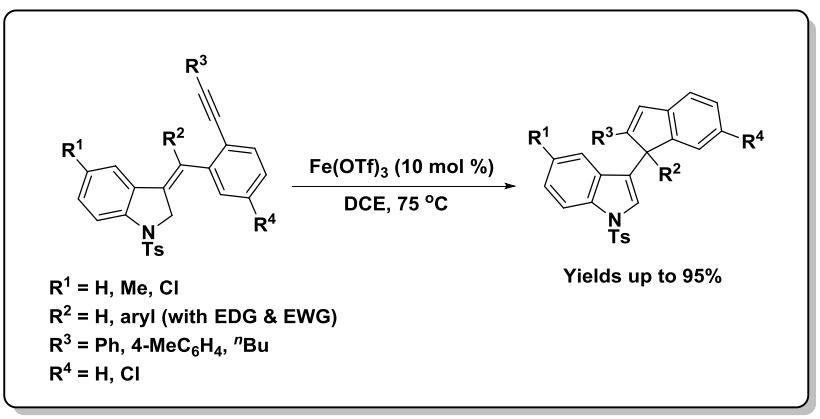
In the next year, Bolm has synthesized indole derivatives *via* ferric triflate catalyzed C-H amination of aryl azidoacrylate (Scheme 2).[12] The reaction was significantly influenced by the choice of solvents and thorough screening of different protic and non-protic solvents revealed that THF was the most suitable solvent for the maximum yield (78%). An array of substrates with diverse substituents afforded substituted indoles in satisfactory yields. The reaction exhibited high regioselectivity and with *meta*- and *para*-disubstituted substrates provided only one isomer.



Scheme 2. Use of $Fe(OTf)_3$ catalyst in C-H amination of aryl azido acrylate

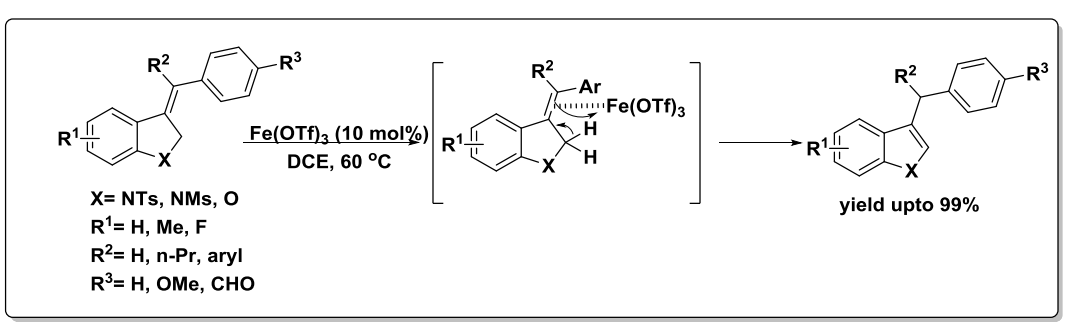
Iron-catalyzed enyne cycloisomerization was reported by Jana and coworkers, where 1,5-enynes were converted to the 3-(1-indenyl)indoles under the catalytic influence of $Fe(OTf)_3$ in DCE solvent (Scheme 3).[13] Interestingly, the temperature was found to be a crucial factor for the construction of the product. At 65 °C, only the isomerization from indoline to indole took place. At temperature in between 75 - 80 °C, the 1,5-enyne cycloisomerization was smooth to provide various 3-(1-

indenyl)indole derivatives in good yields (up to 95%). This method was applied for the synthesis of 7-azaindole derivatives also. The plausible mechanism was based on the π-activation of the alkyne by $Fe(OTf)_3$. Subsequent nucleophilic attack by the exocyclic double bond led to the cyclization in a *5-endo-dig* fashion. Finally, the isomerization followed by protonolysis furnished the desired product.



Scheme 3. Iron-catalyzed cycloisomerization of 1,5-enyne to produce 3-indenylindoles

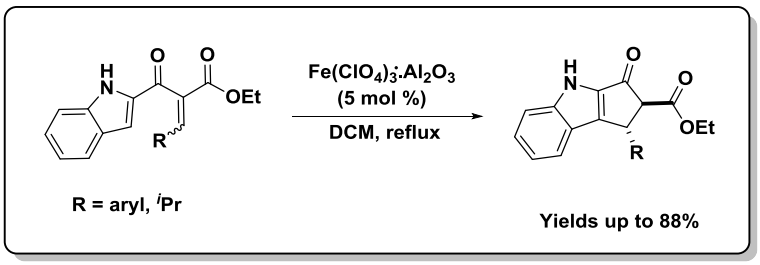
The same group has established a method for the construction of 3-substituted indole or benzofuran derivatives using iron salts as catalysts.[14] In 2015, 3-substituted indoles were synthesized by the $Fe(OTf)_3$ catalyzed isomerization of 3-methylene



Scheme 4. $Fe(OTf)_3$ catalyzed isomerization of 3-methylene indoline

indoline (Scheme 4). The reaction provided a range of 3-substituted indole/benzofuran derivatives with different substituents in high yields (70−99% yields) at 60 °C within 2.5-7 hours. The reaction was believed to be initiated by the coordination of the iron salt with the exocyclic double bond.

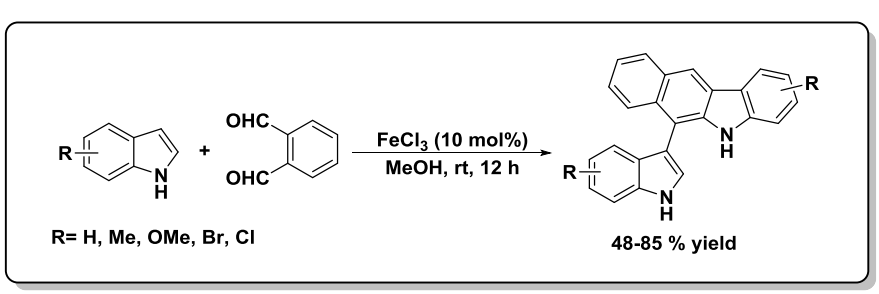
Nazarov cyclization is a famous cycloisomerization reaction that involves a dienone-type system. Itoh *et al.* reported an iron-catalyzed Nazarov cyclization



Scheme 5. Iron-catalyzed Nazarov cyclization of indole derivatives

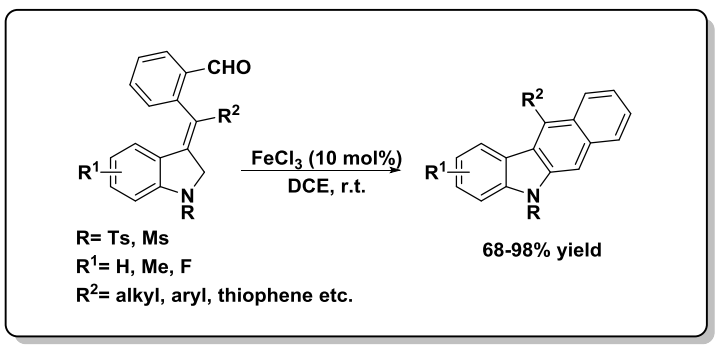
of indole derivatives to produce the fused indoles in moderate to very good yields (Scheme 5).[15] 5 mol % of $Fe(ClO_4)_3.Al_2O_3$ in refluxing DCM was the optimum condition for the reaction. It was shown that the catalyst can be effectively recycled in ionic liquid solvent systems.

In 2014, Xu *et al*. described an one-pot iron-catalyzed cycloaddition of indole with *o*-phthalaldehyde to afford indolyl benzo[*b*]carbazoles (Scheme 6).[16] The synthesis involved domino C–C bond-forming addition/cyclization which involved intramolecular alkylation and aromatization generating a benzene ring. Due to the presence of extended π-conjugation, the indolyl benzo[*b*]carbazole derivatives exhibited strong fluorescence intensity. This group also examined the reaction in the presence of different catalysts and solvents but a mixture of two products was obtained. Remarkably no reaction occurred for 3-substituted indole derivatives. 5-substituted indole derivatives enhanced the yield (79 - 85%) of the reaction, whereas 7-substituted indole derivatives decreased the yield (48%). Therefore, this method provides a simple and facile approach for the straightforward synthesis of indolyl benzo[*b*]-carbazoles with good selectivities.



Scheme 6. Preparation of indolyl benzo[*b*]carbazoles by the cycloaddition of indole with *o* phthalaldehyde

In the same year, the group of Jana has developed a novel and convenient method for highly efficient synthesis of a library of structurally diverse benzo[*b*]carbazole heterocycles *via* domino isomerization/cyclization/aromatization

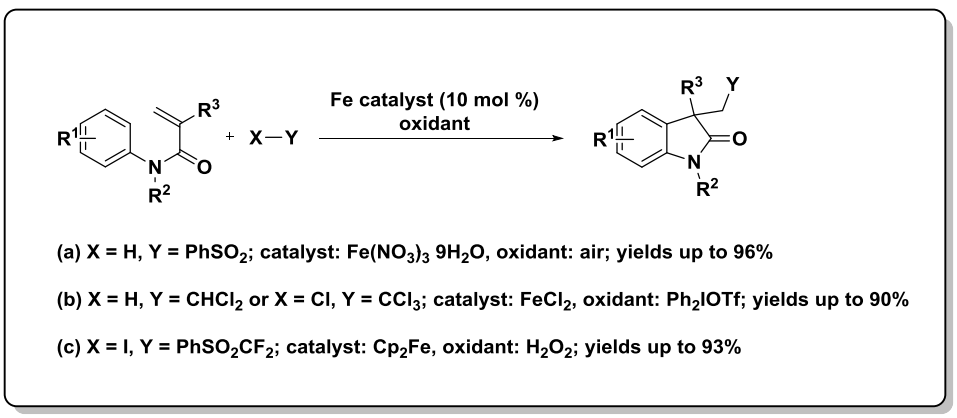


Scheme 7. Domino isomerization/cyclization/aromatization reaction of 2-[(indoline-3-ylidene)(methyl)]benzaldehyde

reaction of 2-[(indoline-3-ylidene)(methyl)]benzaldehyde derivatives by using 10 mol% $FeCl_3$ (Scheme 7).[17] A wide range of substrates were investigated to show the generality of the process. The reaction is highly regioselective and worked under mild conditions in good to excellent yield. Among various Lewis- and Brønsted acid catalysts, iron salt was found to be the most efficient. The advantages of this new method are the ease of substrate preparation, operational simplicity, high atom-economy, functional-group compatibility, and the use of inexpensive and environmentally friendly $FeCl_3$ (10 mol%) as the catalyst. Thus, this methodology will become an useful tool for the construction of benzo[*b*]annulated carbazole and related polynuclear hetero-annulated carbazole ring systems.

In 2013**,** Li *et al.* reported an iron-catalyzed di-functionalization of olefins which paved a new path for accessing oxindole derivatives using iron-catalyzed cyclization.[18a] In the next year, groups of Jiao,[18b] Loh[18c] and Wang[18d] independently reported syntheses of oxindoles *via* iron-catalyzed difunctionalization of olefins. Jiao *et al*. constructed sulfone-containing oxindoles using benzenesulfinic acids employing $Fe(NO_3)_3.9H_2O$ as the catalyst and air as the oxidant (Scheme 8a). Other aryl and alkylsulfinic acids also gave the products with good yields. Loh *et al*. followed the same principle for the synthesis of dichloro- and trichloro alkylated oxindoles by the reaction of the acrylamide with dichloromethane or tetrachloromethane (Scheme 8b).

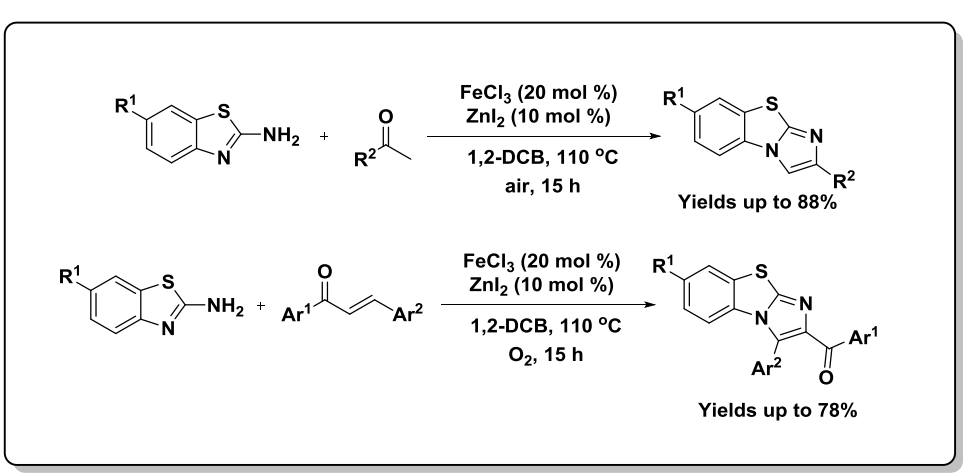
The combination of 10 mol % $FeCl_2$ and 2 equivalents of Ph_2IOTf provided a wide variety of oxindoles with moderate to good yields. In the same year, the group of



Scheme 8. Iron-catalyzed synthesis of oxindoles *via* difunctionalization of alkenes

Wang reported an aryldifluoromethylation using Cp_2Fe as a catalyst with H_2O_2 as an oxidant (Scheme 8c). All of these reports indicated the involvement of radical pathways for the product formations.

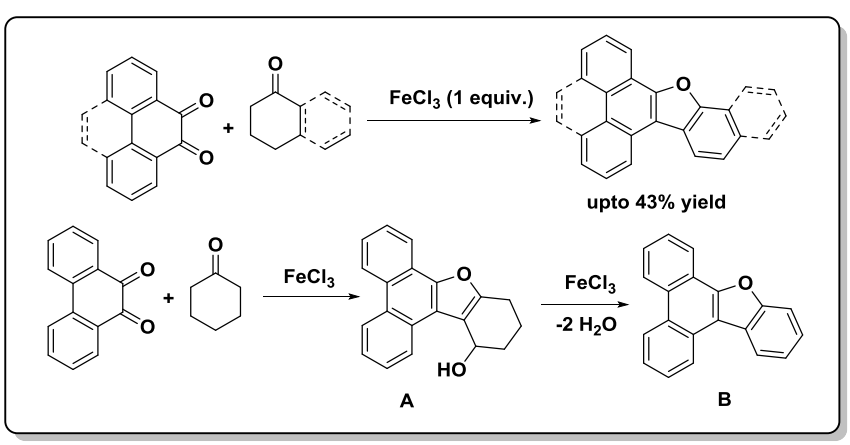
An intermolecular oxidative coupling reaction has been presented here to cover the recent literatures on iron-catalyzed benzo-fused heterocycle synthesis containing more than one heteroatom. As shown in scheme 9,[19] the group of Hajra synthesized benzo[*d*]imidazo[2,1-*b*]thiazoles *via* oxidative cyclization of 2-aminobenzothiazoles and ketones or the chalcones. While the catalyst was a combination of $FeCl_3$ and ZnI_2 in both cases, the oxidants were air and molecular oxygen, respectively, in the case of ketones and chalcones. Varieties of benzo[*d*]imidazo[2,1-*b*]thiazoles were obtained in this protocol.



Scheme 9. Iron-catalyzed synthesis of benzoimidazothiazoles *via* oxidative coupling

Not only nitrogen containing heterocycles, but also oxygen containing heterocycles were prepared using iron catalysis.

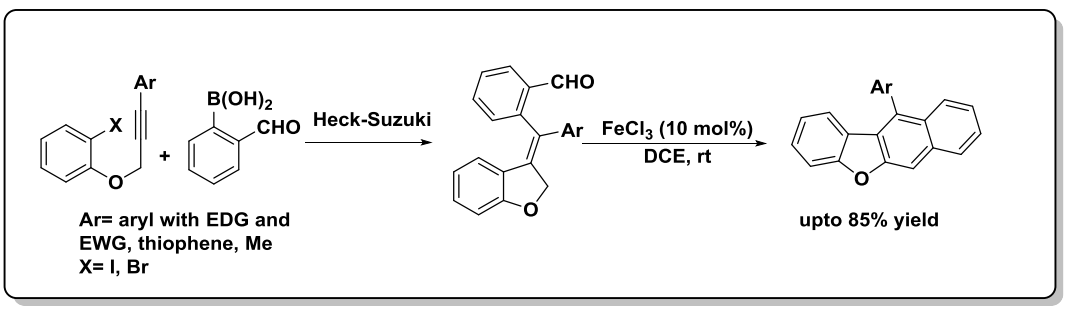
Rao and co-workers have described a $FeCl_3$ mediated synthesis of benzofuran fused phenanthrene and pyrene derivatives (Scheme 10).[20] The reaction involved the condensation of 9,10-phenanthrenequinone and pyrene-4,5-dione with cyclohexanone and its derivatives to furnish benzofuran annulated compounds. Remarkably, when the reaction was carried out in neat condition in the presence of catalytic amount $FeCl_3$, compound **A** was obtained, but when the reaction was carried out in aerobic condition in the presence of stoichiometric amount $FeCl_3$ then compound **B** was obtained. The possible pathway for the formation of benzofuran fused phenanthrene is also depicted. The first major intermediate formed is the secondary alcohol **A** generated by cascade steps involving aldol condensation, cyclization and rearrangement. Subsequently, iron(III) chloride mediated dehydration followed by dehydrogenative aromatization furnished the benzofuran–phenanthrene hybrid.



Scheme 10. $FeCl_3$ mediated synthesis of benzofuran fused phenanthrene and pyrene derivatives

Paul *et al.* reported a simple, convenient and highly efficient two-stage domino approach for the synthesis of diverse tetracyclic dibenzofuran derivatives starting from propargyl ethers of *o*-halo-phenol derivatives as the starting materials (Scheme 11).[21] The reaction proceeded through an intramolecular *syn*-carbopalladation onto alkyne *via* a *5-exo-dig* cyclization process which produced a σ-alkylpalladium(II) intermediate, and subsequent intermolecular Suzuki coupling with phenylboronic acid derivatives followed by isomerization/cyclization and aromatization with $FeCl_3$ (10 mol%) in 1,2-dichloroethane at room temperature to

give tetracyclic dibenzofuran derivatives. This strategy was also applied for the synthesis of naturally occurring *β*-Brazen. The strategy was found to be general and

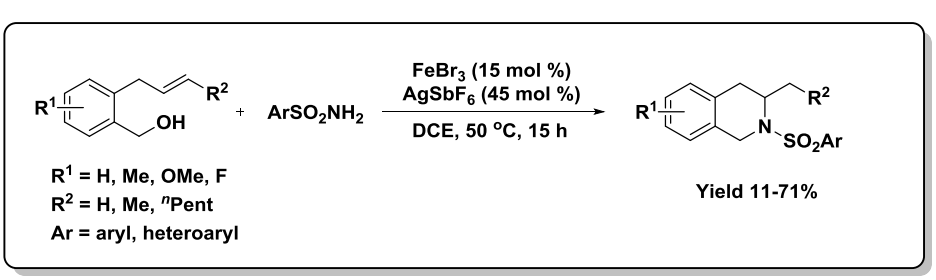


Scheme 11. Synthesis of tetracyclic dibenzofuran derivatives *via* iron catalyzed domino reaction

displays a wide substrate scope, good functional group tolerance, and provided moderate to high chemical yields.

2.2. Benzofused six-membered heterocycles:

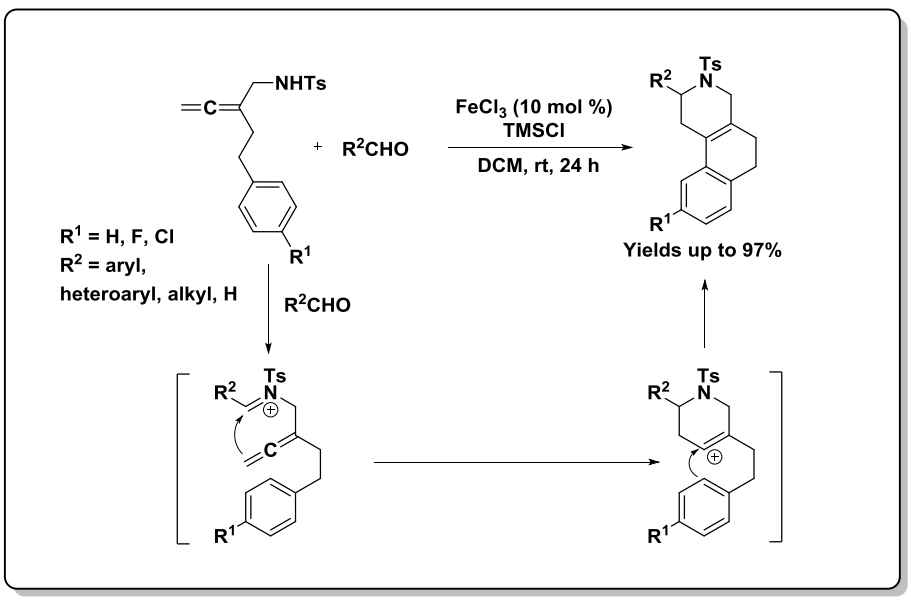
An Iron-catalyzed alcohol-promoted cyclization in combination with hydroamination of alkene was presented by the group of Cook. Benzylic alcohols with tethered alkenes coupled with the aryl sulfonamides under iron-catalysis to furnish the tetrahydroisoquinolines (Scheme 12).[22] This tandem alcohol substitution/hydroamination employed quite a mild reaction condition, where $AgSbF_6$ acted as a co-catalyst to increase the activity of $FeBr_3$. The Construction of two C–N bonds in a single step made this simple strategy quite attractive. Although the yields were not among the bests, a broad substrate scope was presented.



Scheme 12. Iron catalyzed tandem alcohol substitution/hydroamination

Ma *et al.* used the Prins cyclization with tosylamides instead of alcohols to get nitrogen heterocycles. 2-Arylethyl-2,3-butadienyl tosylamides underwent Prins cyclization with the aldehydes at room temperature under the catalysis of $FeCl_3$

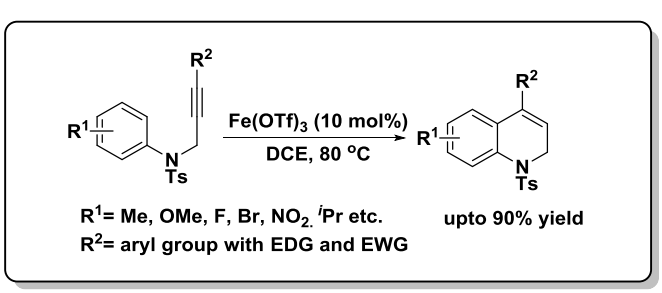
(Scheme 13).[23] The iminium intermediates underwent a *6-endo-trig* cyclization through the allenyl double bond to form the cationic intermediates. Finally, the



Scheme 13. Fe-catalyzed synthesis of fused isoquinolines *via* aza-Prins/Friedel-Crafts cyclizations

products were obtained *via* the Friedel-Crafts reaction. Here, TMSCl was used to activate the various aldehydes used. This tandem aza-Prins/Friedel-Crafts cyclization strategy provided a versatile substrate scope with moderate to excellent yields of the products 1,2,3,4,5,6-hexahydrobenzo[*f*]isoquinolines.

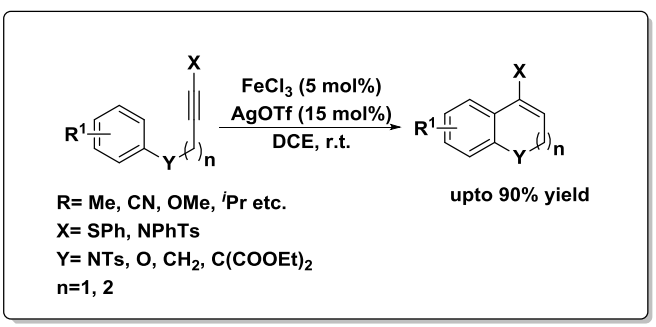
Intramolecular hydroarylation reaction of *N*-tosylated propargylanilines was developed by the group of Komeyama to prepare *N*-tosylated 4-substituted 1,2-dihydroquinolines catalyzed by 10 - 20 mol% $Fe(OTf)_3$ in dichloroethane solvent (Scheme 14).[24] Remarkably, for this reaction, electron-withdrawing groups at the



Scheme 14. $Fe(OTf)_3$ catalyzed intramolecular hydroarylation reaction of *N*-tosylated propargylanilines

aniline ring and electron releasing group at the alkyne ring provided better yields than the reverse under the optimized reaction condition. This might be due to the formation of the iron-arene complex during the reaction.

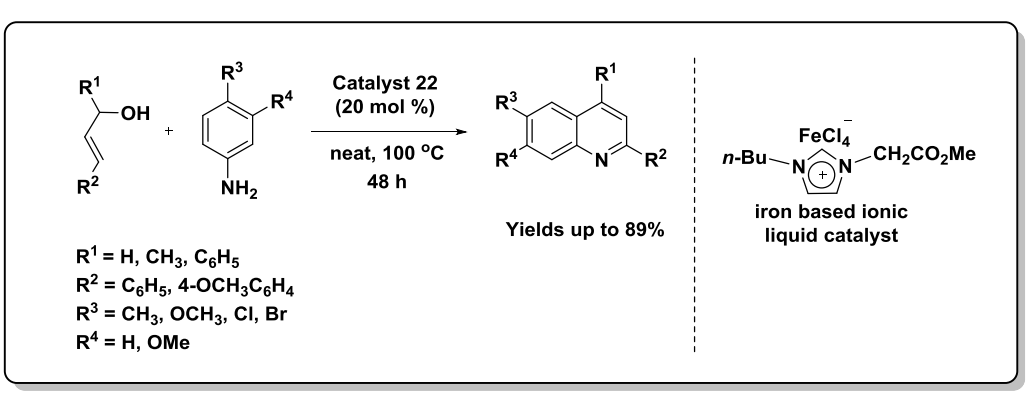
Another intramolecular hydroarylation of *N*-propargylanilines for the construction of dihydroquinoline derivatives employed $FeCl_3$ and AgOTf as a cooperative catalytic system in 1,2-DCE solvent (Scheme 15).[25] Lee and his group showed that the cyclization would take



Scheme 15. $FeCl_3$ / AgOTf cooperative catalytic system for the construction of dihydroquinoline, chromene

place through a regioselective 6-*endo-dig* mode to afford 4-(phenylthio)-1-tosyl-1,2-dihydroquinolines and 1,2-dihydro-*N*-phenyl-*N*,1-ditosylquinolin-4-amine derivatives in moderate to good yields. To verify the viability of the reaction, two fold hydroarylation was reported and 2,7-dihydropyrano[2,3-*g*]chromene was synthesized with 72% yield.

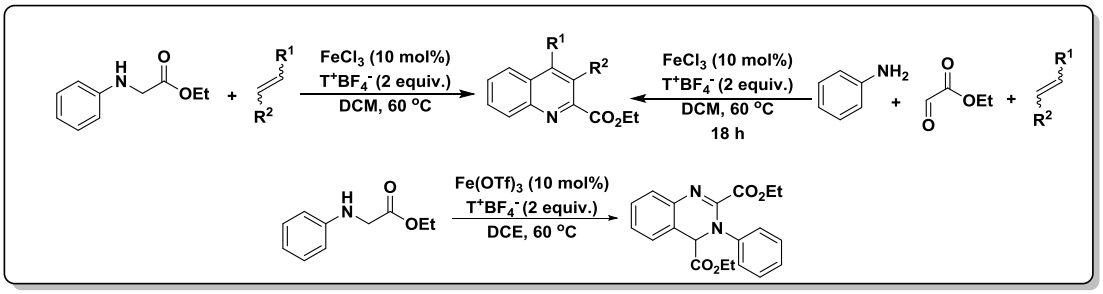
Trillo *et al.* used anilines as nucleophiles to react with allylic alcohols activated by iron(III)-based Lewis acidic ionic liquid catalyst. In the reaction between



Scheme 16. Quinoline synthesis by iron-based ionic liquid catalyzed allylic substitution of alcohols

the allylic alcohols and the aniline derivatives, selective *ortho*-allylation was achieved using 20 mol % of the iron-based imidazolium salt at 100 °C in neat conditions (Scheme 16).[26] The subsequent oxidative cyclization led to the desired quinolines in moderate to very good yields. Two significant features of this reaction are the solvent free condition and the efficient use of aerial oxygen for the challenging oxidative cyclization.

Rohlmann *et al.* demonstrated a one-pot synthetic strategy of dihydroquinazolines and quinolines by the oxidative tandem reaction of *N*-alkylaniline and olefins in the presence of 10 mol% $FeCl_3$ and 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate ($T^+BF_4^-$) in DCM at 60 °C for 18 h. Anilines could also be



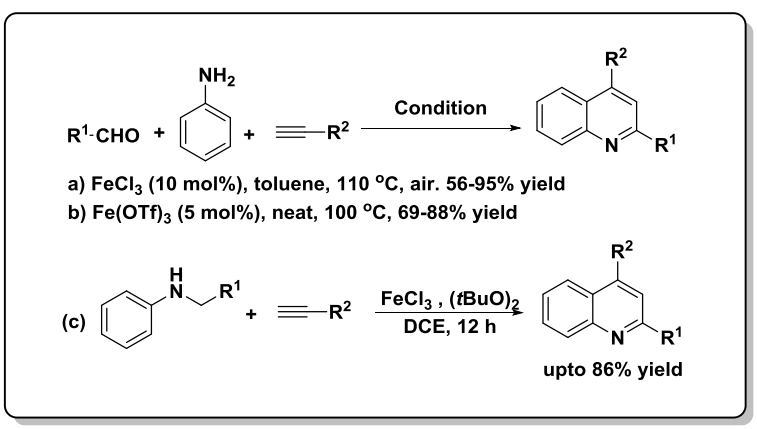
Scheme 17. Iron catalyzed strategy for the synthesis of dihydroquinazolines and quinolines

converted into quinoline-2-carboxylates by reaction with olefin and ethyl glyoxalate (scheme 17).[27] The proposed mechanism revealed that the in-situ generated glyoxalate iminium ion participated in the cycloaddition reaction with the olefin to generate tetrahydroquinoline, which was dehydrogenated by $T^+BF_4^-$ to convert to the quinolines with moderate to good yields (36−95% yields).

Several multicomponent reactions using iron catalysts have been established for the synthesis of quinoline derivatives. Some of the important examples are presented here for the better understanding of the pivotal role of the iron salts in catalysing important benzo-fused heterocycle like quinoline.

Quinoline was synthesized by a $FeCl_3$ catalyzed three component method by Fan and co-workers *via* the tandem coupling/hydroarylation/dehydrogenation of amines, aldehydes and alkynes (Scheme 18a).[28a] The reaction was successful as the iron is simultaneously coordinated to both the in-situ generated imine and the alkyne.

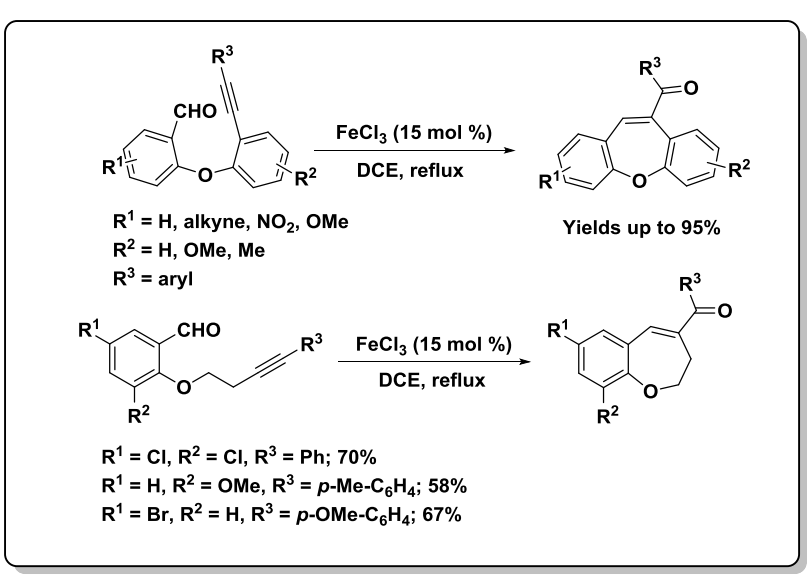
Next, in the year of 2012, another multiple component reaction was introduced by Yao *et al.* to construct quinoline *via* $Fe(OTf)_3$ catalyzed C-C bond formation/C-H activation of the alkynes (scheme 18b).[28b] This solvent free protocol offered a high catalytic activity at very low catalyst loading (5 mol%) and high atom economy with limited energy consumption. In the same year, *N*-alkylanilines and alkynes or alkenes were subjected to coupling in the presence of $FeCl_3$ catalyst and DTBP quinolines efficiently (Scheme 18c).[28c] The reaction was found to tolerate both EDG and EWG at both the aniline and alkyne moiety.



Scheme 18. Multi-component reaction to synthesize quinoline derivatives

2.3. Benzofused seven and higher membered heterocycles:

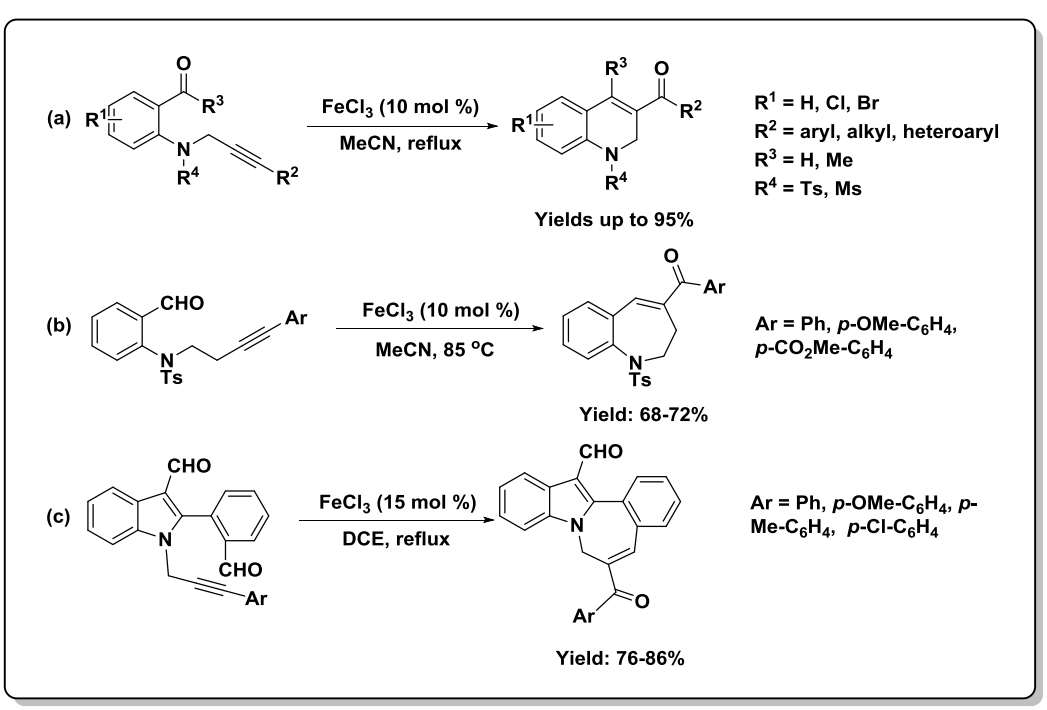
Jana *et al.* developed the iron-catalyzed alkyne-carbonyl metathesis for syntheses of various heterocycles. In 2014, they reported the syntheses of



Scheme 19. Syntheses of dibenzo[*b,f*]oxepines and benzo[*b*]oxepines *via* $FeCl_3$-catalyzed intramolecular alkyne-carbonyl metathesis

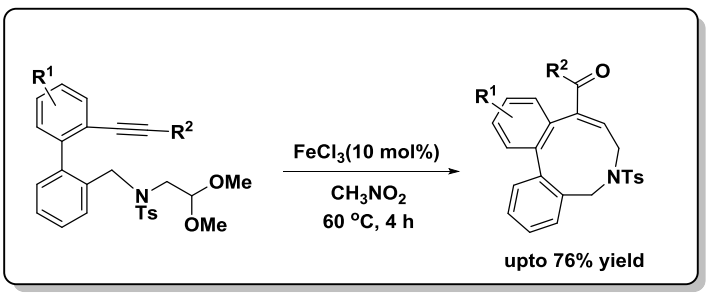
dibenzo[*b,f*]oxepines and benzo[*b*]oxepines *via* $FeCl_3$-catalyzed intramolecular alkyne-carbonyl metathesis (Scheme 19).[29] This method offers operational simplicity and a good substrate scope with moderate to very good yields.

A similar approach was applied by the same group to produce dihydroquinolines in nice yields (scheme 20a).[30a] Dihydrobenzo[*b*]azepines were also afforded from the homopropargylated 2-aminobenzaldehydes, but with lower yields (Scheme 20b).[30a] Another report in 2017 from the same group described the $FeCl_3$-catalyzed alkyne-carbonyl metathesis route to easily access benzofused azepino[1,2-*a*]indoles in good yields (Scheme 20c).[30b] These methods with 100% atom economy are really good alternatives in terms of sustainability. The general mechanism for the metathesis reaction suggested that $FeCl_3$ initiated the reaction by coordinating with the carbonyl oxygen. Then the heteroatom-tethered alkyne involved with the activated carbonyl undergoes a [2+2] cycloaddition. The generated oxetane intermediate is finally converted into the cyclized product *via* [2+2] cycloreversion process.



Scheme 20. Iron catalyzed alkyne-carbonyl metathesis to form of various benzo-fused heterocycles

Synthesis of 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azonines having a ketoaryl group was achieved through intramolecular cyclization of a molecule having both an alkyne and an acetal facilitated by $FeCl_3$ catalysis, (scheme 21).[31] In contrast to the sole prior study regarding the synthesis of dibenzo[*c*,*e*]azonine derivatives, this method offers



Scheme 21. Alkyne–carbonyl metathesis reaction to achieve 6,7-dihydro-5*H*-dibenzo[*c*,*e*]azonines

more favourable reaction conditions, yielding higher product yields. Detailed investigations have been conducted to precisely document the impact of electronic variations and steric bulk. Upto 76% yield was achieved which is quite satisfactory when it comes to the formation of nine-membered rings. The formation of no side products contributes to the atom-economy of the process. Hopefully, this work will help in overcoming the stagnancy of alkyne-carbonyl metathesis reactions being unable to access beyond seven-membered rings, and synthesizing less accessible heterocyclic compounds.

3. CONCLUSION:

In this short review, the trending syntheses of different kinds of benzofused heterocycles *via* different methods have been focused on. The growing interest in the field of benzofused heterocycles is attributed to the versatile applicability of such systems in our everyday life. Therefore, any new methods which are environmentally benign and economically favourable are always desirable. From this review, it is evident that, to gain a green approach, iron catalysts are extensively used as catalysts for the preparation of heterocycles. So in the context of metal catalysis, iron catalysts will certainly have a major contribution.

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Part 1, Chapter 1

Iron-Catalyzed Functionalization of 3-Benzylideneindoline through Tandem Csp^2–Csp^3 Bond Formation/Isomerization with π–Activated Alcohols

1. INTRODUCTION:

Alcohols have been widely employed as the initial substrates for various kinds of chemical reactions, although alcohols are not a very reactive substance. Rather, the hydroxyl group of the alcohol is a poor leaving group. So to substitute this hydroxyl group, it generally requires some kind of activation.[1] The hydroxyl group is needed to be converted into a better leaving group for substitution to take place. The -OH can either be protonated, or removed as H_2O, or can be converted into more reactive ketone or aldehyde or alkyl halide etc. for the reaction to take place. The direct substitution of activated alcohols can ease many reactions by decreasing number of steps and by-products.[2] Therefore, research on direct substitution of alcohols has gained much attention since the last decade. Because of its convenience, the method has been widely employed as the basic reaction to attain useful pharmaceutical products.[3]

Our particular interest lied on the synthesis of important biological moiety by direct substitution of alcohols. To fulfill our motive, we first focused on the construction of 3-substituted indole derivatives because of its ubique biological and pharmaceutical activities especially anticancer, hypoglycemic, antitumor, analgesic, antiinflammatory and antipyretic activities.[4] Nature is also abundant with 3-substituted indole containing natural products. For example, melatonin hormones act as seasonal clock for animal.[5] Another amino acid tryptophan plays vital roles in biological systems.[6] Reserpine helps in controlling high blood

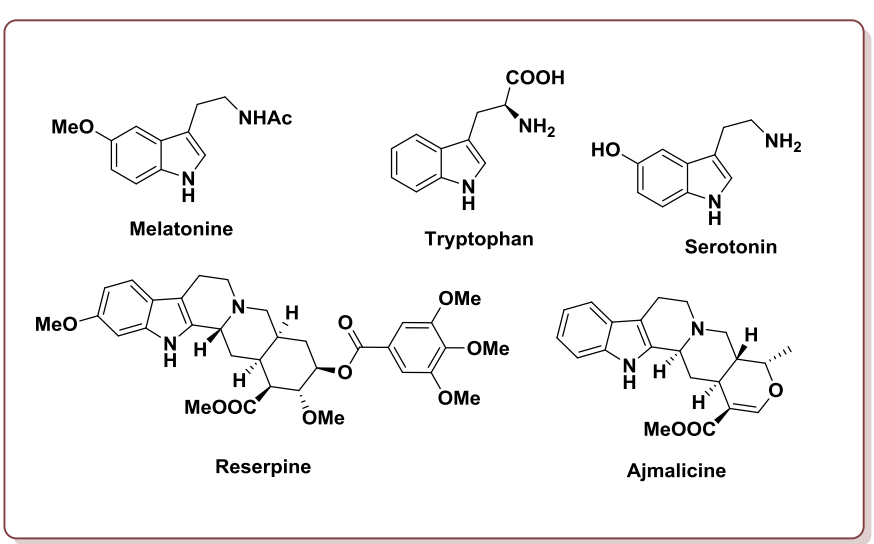


Figure 1: Some important biologically active compounds containing indole ring

pressure.[7] Ajmalicine is also an anti-hypertensive drug.[8] Vinblastine is used for treatment of different kinds of cancer.[9] Some important natural products and drug molecules containing 3-substituted indole rings are illustrated in figure 1. In addition, C-3 substituted indole is an important synthetic intermediate for the construction of complex natural and unnatural polycyclic indoles derivatives.[10]

Owing to the widespread applications of the C3-substituted indoles, the synthesis of indole molecules are being studied for more than a hundred years and yet an equally relevant topic till now. Other than the methods described in the previous part, this area is also enriched with many classical name reactions such as Fischer indole synthesis, Reissert indole synthesis, Madelung indole synthesis, Larock indole synthesis, Julia indole synthesis, Friedel-Craft alkylation etc.[11] While these reactions can be efficient, but their synthetic applications are inevitably hampered by the cost, harsh reaction condition and production of stoichiometric byproducts.[12] Therefore designing of simple direct procedures for the synthesis of this compounds are really challenging. And direct substitution of alcohols has been proven one of the widely attempted synthetic strategies to build the desired moiety. We have synthesized an iron catalyzed method to access the 3-substituted indole from 3-methylene indoline by the activation of π-activated alcohols. Before going into the detail of our findings, at first we present a short review on the previous approaches, made by different group of scientists, to construct 3-substituted indole derivatives by the reaction with alcohols. This will clear the elementary idea about the direct substitution of alcohols and their application for construction of complicated structural motif in a simple way.

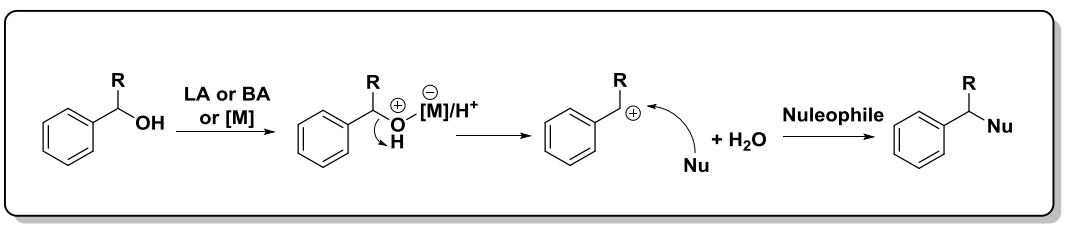
2. Review on Synthesis of 3-Substituted Indole Derivatives by Activation of Alcohols:

Two broad classifications can be made based on the methods by which the alcohols were activated. First is the removal of the hydroxyl group by means of transition metal or Lewis or Bronsted acid, and second, the borrowing hydrogen methods catalyzed by different metals.

2.1 S_N1 type removal of the hydroxyl group:

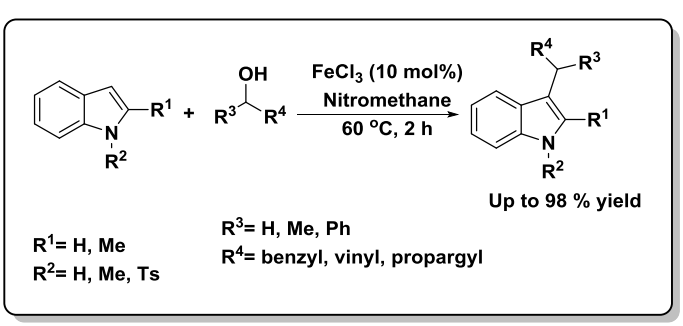
The S_N1-type nucleophilic substitution is a very convenient way to introduce new groups in the moiety since one of the by-products in this process is water. In this

reaction, the hydroxyl group of the π-activated alcohol (allylic, benzylic, and tertiary alcohols) is first protonated or makes complex with the transition metal, leading to the removal of the C-OH bond. Subsequently a carbocation is generated which is thereafter captured by the nucleophile to achieve the desired substituted products.[13]



Scheme 1: General reaction pathway of S_N1 type substitution of alcohol

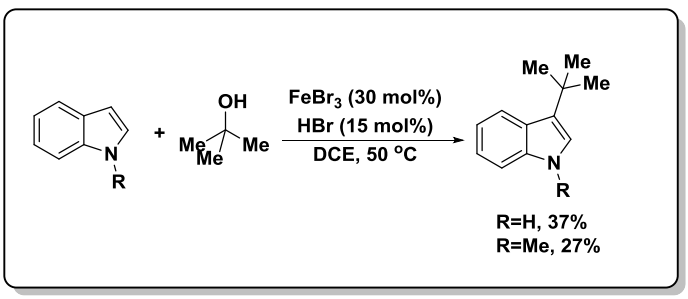
In 2007, Jana *et al*. documented the synthesis of 3-substituted indole derivatives *via* $FeCl_3$ catalyzed Friedel-Craft reaction of indoles with π-activated alcohols (Scheme 2).[14] In the presence of 10 mol% $FeCl_3$ in nitromethane at 60 ^oC, the reaction produced a vast array of 3-alkylated, vinylated and propargylated indole derivatives in impressive yields (up to 98%). It is believed that the reaction proceeds *via* the aromatic electrophilic substitution where the coordination of the alcohol with the $FeCl_3$ Lewis acid eventually activates the alcohol. The reaction was also suitable for thiophene and pyrrole molecules.



Scheme 2: $FeCl_3$ catalyzed Friedel-Craft reaction of indoles with π-activated alcohols

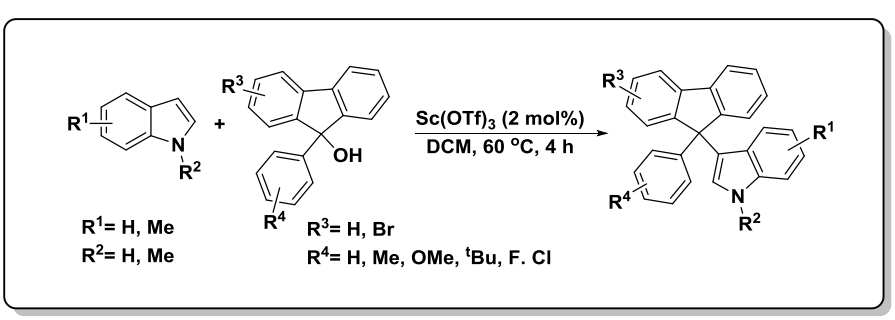
A site-selective *tert*-butylation of indole and *N*-methyl indole with *tert*-butanol was developed by Zhu and co-workers using a dual Brønsted/Lewis acid catalysis system (Scheme 3).[15] The catalytic system consist of Brønsted acid 15 mol% HBr, and 5 mol % of $FeBr_3$ as Lewis acid, in DCE solvent at 50 ^oC provided corresponding 3-tert-butylated indoles in 37 % and 27 % yields respectively. For *N*-methyl indole, *N*-methyl-3,5-*di*-*tert*-butylindole was obtained in 14% along with the desired mono substitution. The use of sustainable iron salts, readily available alcohols makes this

methodology advantageous for the construction of of C(sp^2)–C(sp^3) bond with all-carbon quaternary centre.



Scheme 3: Synthesis of 3-substituted indole derivatives with unactivated tertiary alcohol

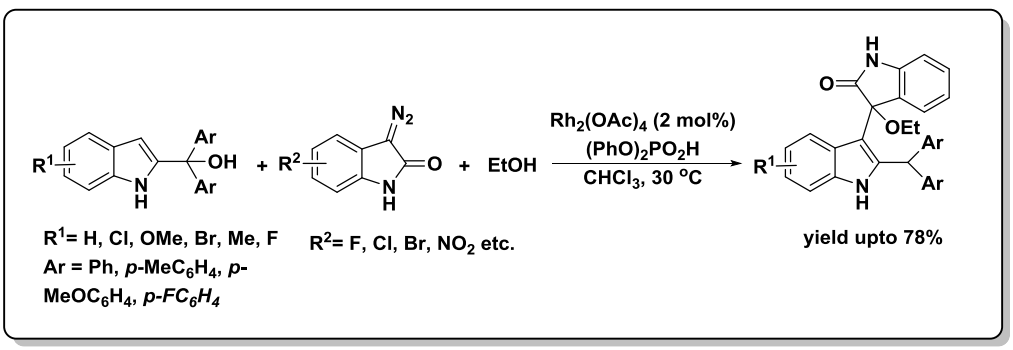
A $Sc(OTf)_3$ catalyzed dehydrogenative coupling between indoles and 9-aryl-fluoren-9-ols was explored by the group of Wang under mild reaction condition to obtain indole-containing 9,9-diarylfluorenes (scheme 4).[16] The reaction demonstrated a wide range of substrate compatibility and remarkable selectivity. To manifest the practicability of this protocol, 2-pyrenyl-9,9-diarylfluorene was synthesized in this method, which has broad applications in the organic photoelectric material chemistry.



Scheme 4: $Sc(OTf)_3$ catalyzed dehydrogenative coupling between indoles and 9-aryl-fluoren-9-ols

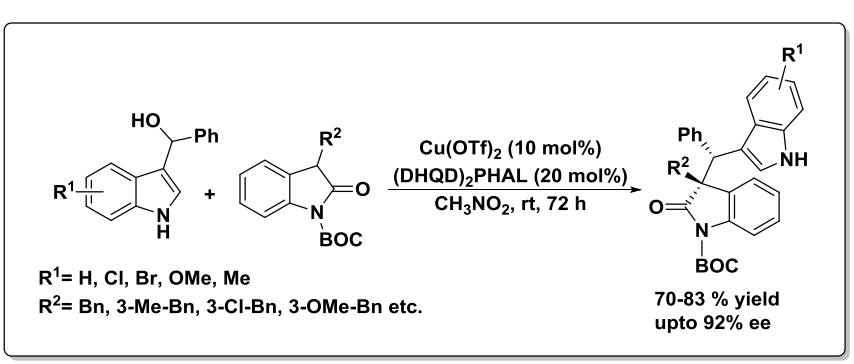
In 2018, the reaction between 2-indolymethanols and oxonium ylides mediated by a cooperative catalysis of metal complex and Brønsted acid catalyst provided a unique approach to construct 3-substitued indole derivatives (Scheme 5).[17] $Rh_2(OAc)_4$ was used as the metal complex and diphenyl phosphoric acid as the Brønsted acid. For the catalytic asymmetric synthesis of the compound, chiral phosphoric acids were utilized as the Brønsted acid along with $Rh_2(OAc)_4$. At first in presence of RhLn, a rhodium carbene species is formed from 3-diazooxindole. After

that EtOH attacks this rhodium carbene species to generate active oxonium ylides which further participates in the reaction to lead to the desired C3-indole derivatives.



Scheme 5: $Rh_2(OAc)_4$ and Brønsted acid catalyzed synthesis of 3-substituted indole derivatives

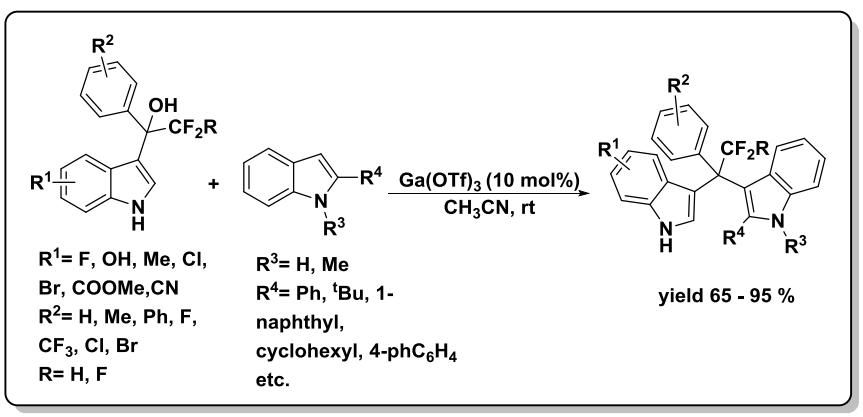
In 2014, Liu *et al.* has displayed an efficient enantioselective alkylation of 2-oxindoles with (3-indolyl)(phenyl)methanols to construct (R,R)-(2-oxindole)-linker-indole derivatives (scheme 6).[18] This (R,R)-(2-oxindole)-linker-indole derivatives were proved to have inhibition and anti-cancer properties. They have developed a useful catalytic system consists of co-operative chiral biscinchona alkaloid $(DHQD)_2PHAL$ and $Cu(OTf)_2$ which provided the desired 3-alkylated indole derivatives in high yields (up to 83%) and satisfying enantioselectivities (81-92%).The maximum diastereoselectivity was obtained for R^1=Bn and R^2=OMe (dr 7:1) and R^1=3-Cl-Bn and R^2=H (dr 7:1).



Scheme 6: Enantioselective alkylation of 2-oxindoles with (3-indolyl)(phenyl)methanols

The group of Rao have utilised $Ga(OTf)_3$ for C3-alkylation of indole with trifluoromethylated 3-indolylmethanols (Scheme 7).[19] Temperature plays here an important role, at room temperature C3-alkylation takes place, and at 80 ^oC, C6-

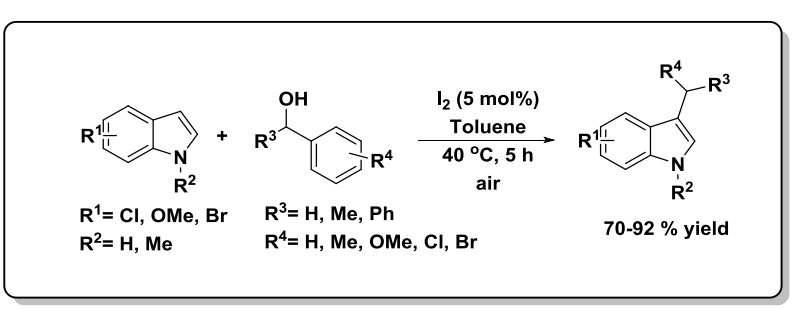
alkyaltion of indole takes place. A diverse set of 3,3`-bis(indolyl)methane having a CF_3-containing quaternary carbon was achieved in the presence of 10 mol% $Ga(OTf)_3$ in CH_3CN solvent at room temperature within 24-48 h with 54-95% yields. A plausible mechanism has also been depicted where $Ga(OTf)_3$ first activates the alcohol to furnish the vinyliminium ion, which is then attacked by the indole to furnish the desired 3-substituted indole derivatives.



Scheme 7: $Ga(OTf)_3$ catalyzed C3-alkylation of indole with trifluoromethylated 3-indolylmethanols

Instead, of metals, different non-metallic approaches are also been applied by different scientists to activate hydroxyl group of alcohols. Some of the recent reports are depicted below.

A metal, ligand and base free approach was developed by the group of Bora to synthesize 3-substituted indole derivatives catalyzed by molecular iodine (scheme 8).[20] The reaction possibly goes through the formation of a halogen bond between iodine and oxygen atom of the alcohol which weakens the C-OH bond of the alcohol,

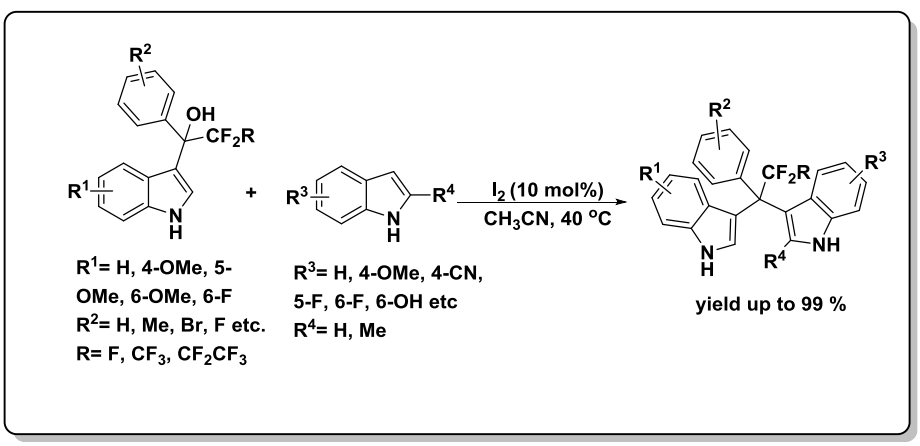


Scheme 8: Molecular iodine catalyzed synthesis of 3-substituted indoles

and subsequent nucleophilic attack to the alcohol leads to the desired product. A wide range of 3-substituted indoles bearing different functionalities, were prepared by this

method in the presence of 5 mol% in I_2 toluene solvent. Brønsted acid mode of catalysis was ruled out when the reaction failed to proceed in protic solvents because of the decomposition of iodine to HI.

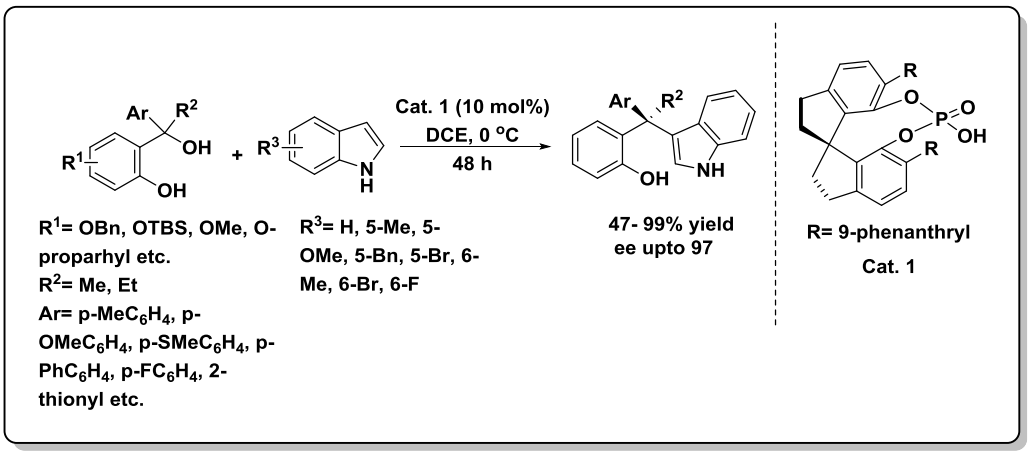
Similarly iodine has been used as catalyst for the coupling reaction of trifluoromethyl(indolyl)phenylmethanols and indoles to obtain unsymmetrical diindolylmethanes having a quaternary carbon center (scheme 9).[21] Here the secondary alcohol is activated with the iodine to generate the above mentioned



Scheme 9: Iodine catalyzed C3-alkylation of indole with trifluoromethylated 3-indolylmethanols

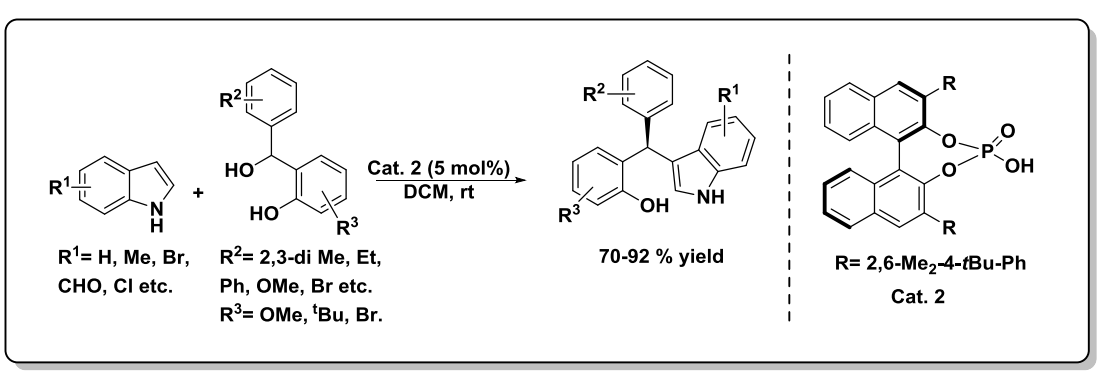
vinyliminium ion. Most of the final compounds have shown micromolar binding affinities toward cannabinoid CB_1 and CB_2 receptors but their activity was primarily observed as CB_1 receptor antagonists/inverse agonists. Large scale synthesis of the products, benign reaction condition without chlorinated solvents etc. displays the applicability of this protocol.

Apart from iodine, chiral phosphoric acids (CPA) were vastly used as catalyst for the enantioselective S_N1-type nucleophilic substitution of alcohols. In 2015, Zhao *et al.* has described a catalytic asymmetric C-C bond formation method to generate important indole derivatives with high enantioselectivity (Scheme 10).[22] First, the alcohol is protonated and the C-O bond is cleaved to form tertiary carbocation which is then paired with the chiral phosphate anion. Then indole nucleophile subsequently attacks to furnish the desired enantioenriched 3-substituted indole having a quaternary stereo centre in good to excellent yields (upto 99% yield).



Scheme 10: Catalytic asymmetric C-C bond formation to generate substituted indole derivatives

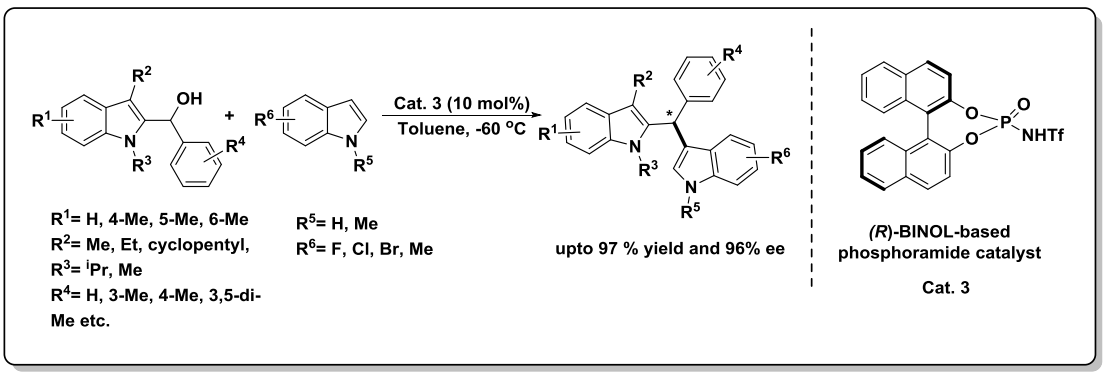
A high enantioselective Friedel-Craft alkylation of electron-rich indoles has been demonstrated by the reaction of indoles with *in situ*-generated *ortho*-quinone methides in presence of a chiral phosphoric acid catalyst **2** (scheme 11).[23] The



Scheme 11: Enantioselective Friedel-Craft alkylation of indoles with alcohols

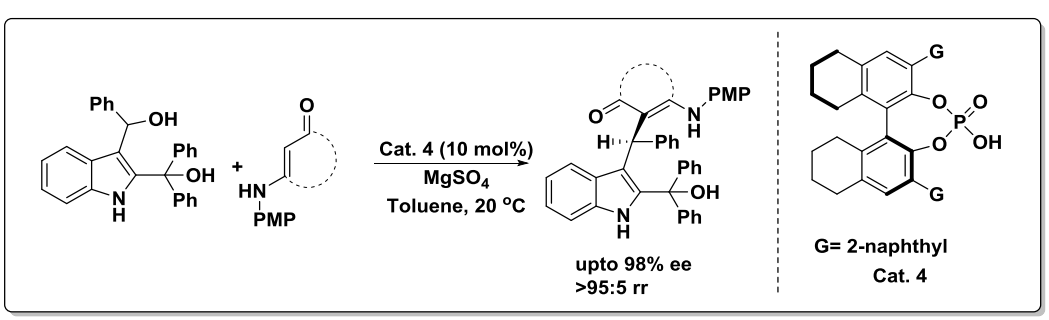
reaction has shown a broad functional group tolerance both at the *ortho*-hydroxybenzhydrols and indole part providing a maximum of 99:1 enantiomeric ratio.

A BINOL-based phosphoramide (cat. **3**) catalyzed asymmetric reaction of indol-2-yl carbinols with indole derivatives resulted in the formation of biologically important 2,3`-diindolylarylmethane compounds (scheme 12).[24] Various indol-2-yl carbinols and indole nucleophiles having different substituent provided up to 97% yield with high enantiomeric excess.



Scheme 12: Catalytic asymmetric reaction of indol-2-yl carbinols with indole

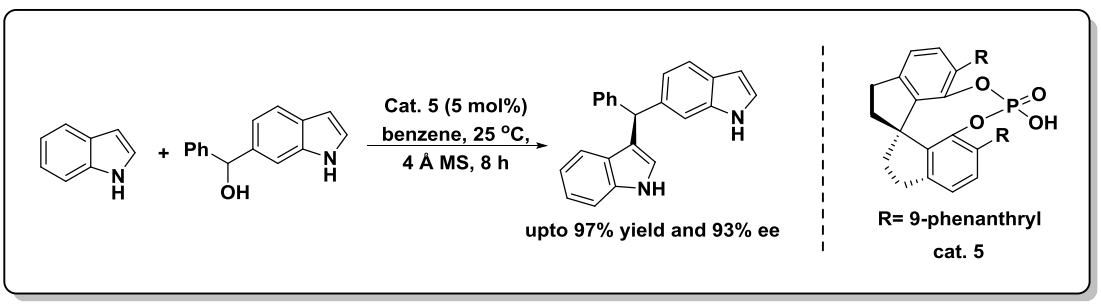
Instead of indolyldimethanols, 2,3-indolyldimethanols were designed by the group of Shi for catalytic asymmetric substitution with nucleophiles (scheme 13).[25] As nucleophiles, cyclic enaminones were utilised to obtain substituted products with high enantioselectivity and regioselectivity. (up to 98% ee, all > 95:5 rr). To get the best catalyst, different chiral phosphoric acids were screened and it was observed H_8-BINOL derived CPA (cat. **4**) provided maximum enantiomeric excess. In the presence of $MgSO_4$ additive in toluene solvent at 20 °C the reaction provided excellent yield with high ee within 12 - 48 h.



Scheme 13: Catalytic asymmetric substitution of 2,3-Indolyldimethanols with nucleophiles

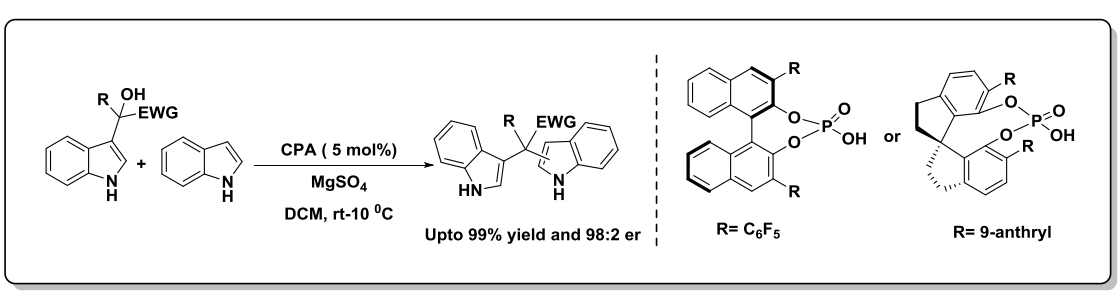
An enantioselective 1,4-addition of indole and pyrrole nucleophiles to indolyl methide intermediates was catalyzed by 5 mol% phosphoric acid (scheme 14).[26] This indolyl methide intermediates were generated in situ from 7-indolylmethanols in the presence of phosphoric acid **5**. Antilla and co-workers established this process for a wide range of electron-rich indolyl methide intermadiates, and the triaryl products are formed in generally excellent yield and high enantioselectivity. Moreover, the applicability of the method was further displayed by performing remote 1,8-adition of

6-indolylmethanols substrates, and that provided the desired products with impressive enantioselectivity.



Scheme 14: Enantioselective 1,4-and 1,8-adition of indole to 6-indolylmethanols

Recently, chiral phosphoric acid was employed for the nucleophilic substitution of racemic tertiary alcohols with various indole nucleophiles, started by the dehydration of alcohol with the CPA catalyst (scheme 15).[27] Mechanistic investigations ruled out the possibility of the S_N2 type substitution. The reaction gives direct access to a wide range of enantioenriched (>99 : 1 er) 3,3`-, 3,2`- and 3,1`- bis(indolyl)methanes (BIMs) containing quaternary stereogenic centers with excellent yields (up to 98% yield). The activation of the alcohol with the chiral Brønsted acid catalyst is supposed to obtain efficient chiral induction through ion-pair formation with the carbocation and the H-bond formation with the indole nucleophile simultaneously. Among various CPA, optimization revealed that catalyst having a

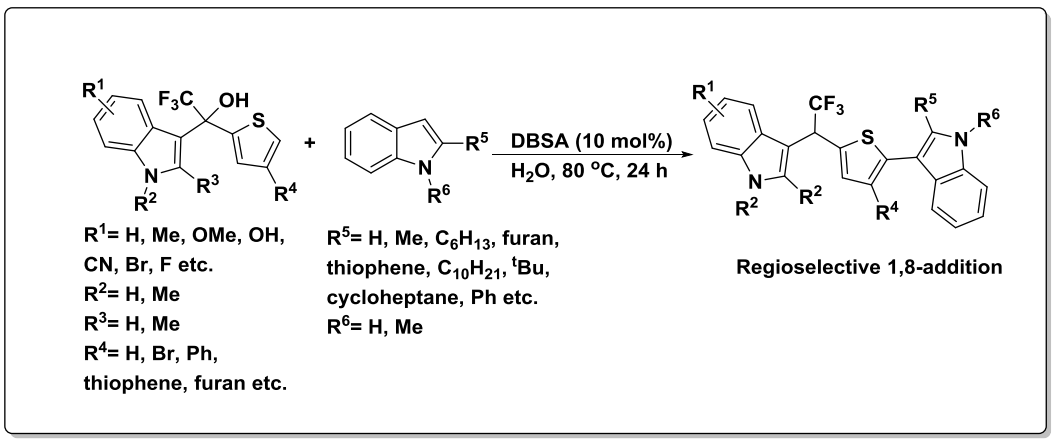


Scheme 15: CPA catalyzed enantioselective substitution of tertiary alcohols with indoles

perfluorophenyl substituent at the 3,3`-position of the BINOL, furnished the maximum enantioselectivity with good yield (91 : 9 er, 90% yield). SPINOL-derived CPA was also very effective for the reaction. When the biological activities of the products were examined, it was observed that, significant antibacterial activities were exhibited by these enantioenriched BIMs, and notably one of the product had more

than double potential than ampicillin against *bacillus subtilis* having MIC value of 1 μg mL^{-1}.

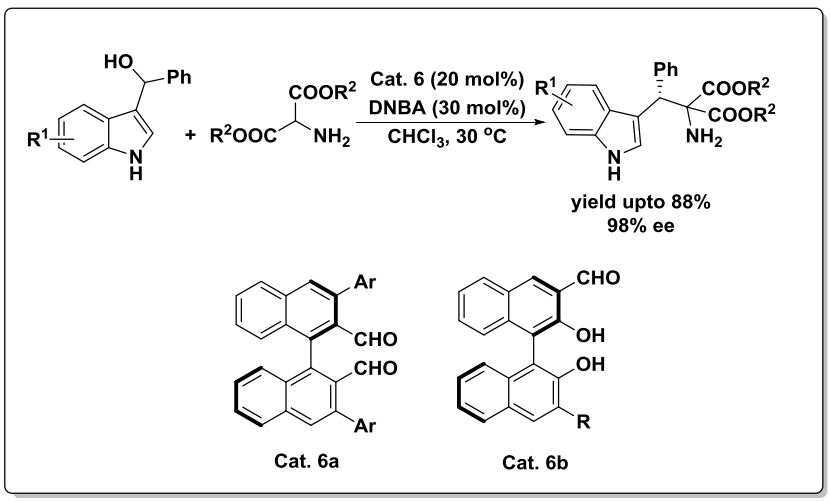
Rao *et al*. has previously utilized $Ga(OTf)_3$ catalyst for the preparation of indole



Scheme 16: DBSA catalyzed 1,8-adition of 2-substituted indole to trifluorinated 3-indolyl(2-thiophenyl) methanols

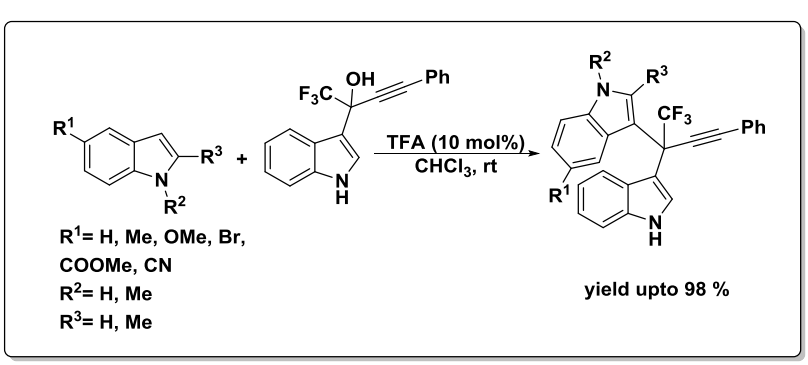
derivatives.[19] The group was further extended their work to establish an unprecedented regioselective 1,8-adition reaction of 2-substituted indole to trifluorinated 3-indolyl(2-thiophenyl) methanols (scheme 16).[28] Whereas common Brønsted acids gave dissatisfactory results, 10 mol% dodecylbenzenesulfonic acid (DBSA) in water at 80 ^{o}C was found to be best condition for the reaction. This dehydrative Friedel-craft arylation technique opened the path to access a variety of thiophene-based bisindole derivatives which have found great applications in liquid crystals, biological compounds, organic electronics materials and ligands for asymmetric catalysis.

In 2014, an α-functionalization strategy of *N*-unprotected amino esters with 3-indolylmethanols were established to generate a number of tryptophan derivatives with good enantioselectivities (scheme 17).[29] Two types of chiral aldehydes were used as catalysts. A plausible mechanism was depicted based on the control experiments, and also the core intermediate was identified with HRMS. These tryptophan derivatives could be readily transformed into tetrahydro-β-carbolines keeping the enantioselectivities intact.



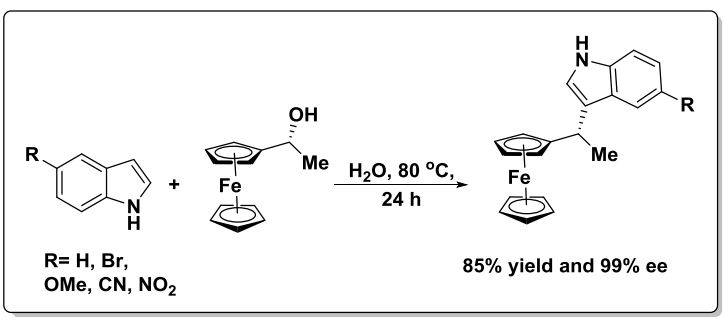
Scheme 17: α-Functionalization of N-unprotected amino esters with 3-indolylmethanols

In the year 2012, Sasaki and coworkers have demonstrated a Brønsted acid catalyzed Friedel-Craft alkylation of trifluoromethyl(indolyl)propargyl alcohol with indoles to obtain trifluoromethyl-functionalized unsymmetrical bis(indolyl)propynes in good to excellent yields (79 % - 98%) (scheme 18).[30] Different catalysts were tested to optimise the reaction condition, and trifluoro acetic acid was found to serve the best result. The obtained trifluoromethyl-functionalized unsymmetrical bis(indolyl)propynes derivatives offer enormous application in the fields of biomedical, biochemical, and pharmaceutical research.



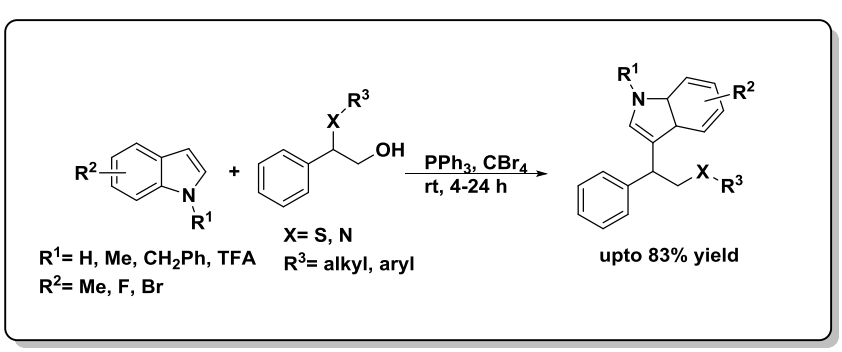
Scheme 18: Brønsted acid catalyzed Friedel-Craft alkylation of indoles with trifluoromethyl(indolyl)propargyl alcohol

Instead of organic solvents, water was also served as the medium in the substitution reaction between ferrocenyl alcohols and indoles. In 2007, the procedure was first discovered by the group of Cozzi which could evidently presented a greener method as water is more easy to handle, safe and less expensive (scheme 19).[31] This on water procedure did not require any kind of Lewis or Bronsted acid or surfactants or external additives.



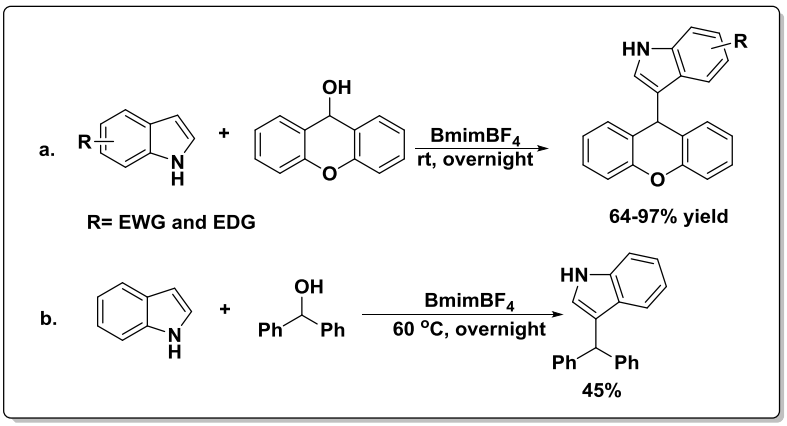
Scheme 19: On water substitution reaction between ferrocenyl alcohols and indoles

Cui *et al*. have developed a dehydroxylative metal free method for the synthesis of β-functionalized C-3 alkylated indoles proceeds through 1,2-sulfur/nitrogen migration (scheme 20).[32] Though the method showed a large substrate scope, but sterically hindered substrates provided poor yield. C-2 substituted indoles provided better yields than free indoles which perhaps due to poor solubility and electronic effects of indole. The protocol was also utilized for large scale synthesis, thus enhancing the benefits of the method.



Scheme 20: Metal free alkylation of indole

A S_N1 type substitution of xanthene-9-ol with indoles was explored by the group of Li to build 3-substituted indole scaffold in an ionic liquid media (scheme 21a) [33]. A vast array of indole derivatives were obtained in $BmimBF_4$ (1-butyl-3-

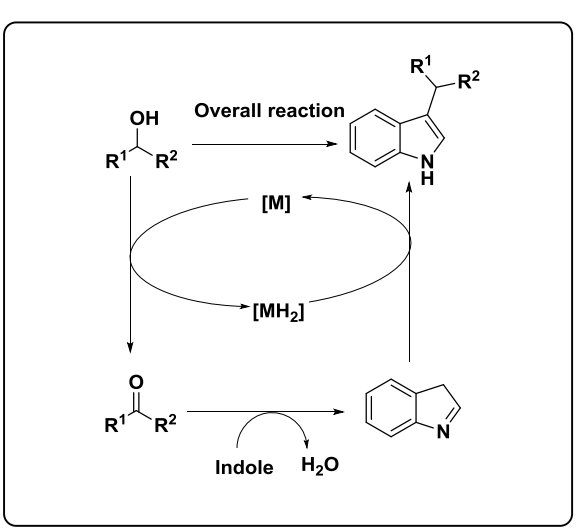


Scheme 21: Substitution of xanthen-9-ol with indoles in ionic liquid medium

methylimidazolium tetrafluoroborate) medium in good to excellent yield in absence of any other catalyst. Apart from xanthen-9-ol, the ionic liquid mediated substitution reaction was also carried out using benzhydrol (scheme 21b). Here, the method presents a greener approach by employing ionic liquid which had many benefits over other ordinary organic solvents, such as low toxicity, low flammability, low volatility, thermal stability, wide liquid range, recyclability, easy recovering of the products etc.

2. 2. Borrowing Hydrogen Methodology:

In the borrowing hydrogen methodology of an alcohol, a catalyst changes the reactivity of the alcohol by removing two H atoms and performs a formal oxidation of the alcohol. Therefore, a highly reactive intermediate is temporarily generated, and

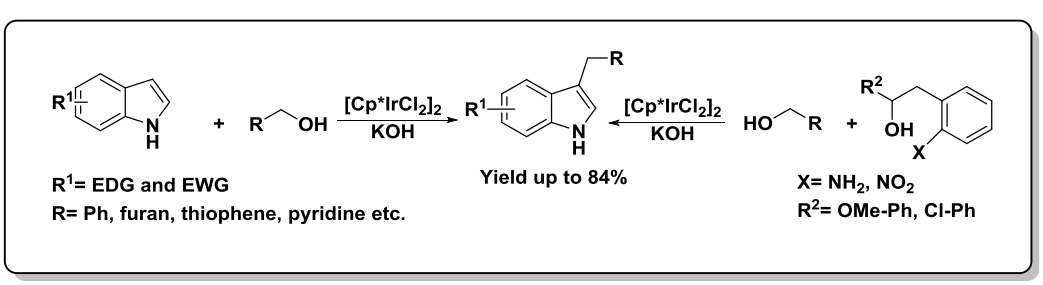


Scheme 22: General activation method in Borrowing Hydrogen protocol

that permits a bond formation to take place (usually, a condensation reaction takes place with the generation of water byproduct). Ultimately, the reduction of the unsaturated intermediate is achieved by the redelivery of two hydrogen atoms, and furnishing the product without altering the overall oxidation state (Scheme 22).[34] Overall, borrowing hydrogen methodology allows a catalytic new bond formation in a very elegant way without stoichiometric oxidants, helps us to avoid the requirement of molecular hydrogen and prefunctionalization of substrates. Different groups developed different catalysts to generate 3-substituted indole derivatives using alcohols in borrowing hydrogen process. Some of them are discussed below.

Iridium Catalyst:

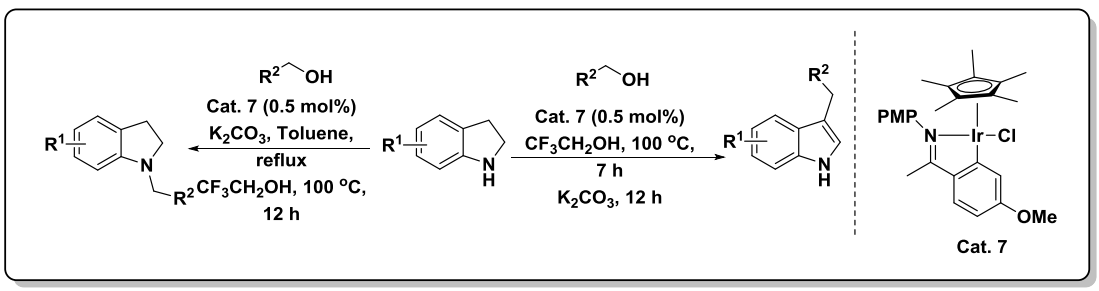
The group of Keep described a methodology where, $[Cp^*IrCl_2]_2$ catalyzed indirect functionalisation of alcohols was utilized to synthesize 3-substituted indole derivatives (scheme 23).[35] Moreover, cascade oxidative cyclisation/C3-alkylation of amino/nitro phenyl ethyl alcohols and benzyl alcohols leads to the formation of 3-substitued indole derivatives. When *N*-methyl indole was employed, no reaction was taken place which proved the participation of indole anion in the process of alkylation.



Scheme 23: $[Cp^*IrCl_2]_2$ catalyzed synthesis of 3-substituted indole derivatives by BH activation

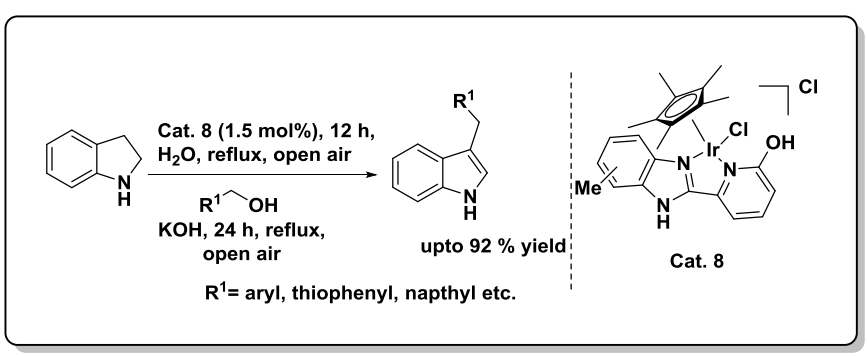
In 2017, another group reported the synthesis of N- and C3- alkylated indoles by the dehydrogenative coupling of indolines with alcohols catalyzed by iridium complex cat. **7** (scheme 24).[36] Interestingly, just by changing the sequence of the base addition, both the N– and C3– alkylated products were obtained selectively. Mechanistic investigations pointed out to a borrowing dehydrogenation and borrowing hydrogen process for the C3-alkylation of the indole. The iridacycle catalyst **7** participated in the reaction through multiple roles; it catalyzed the

dehydrogenation reaction of both amines and alcohols, and also catalyzed the subsequent coupling reactions.



Scheme 24: Synthesis of N– and C3– alkylated indoles by the dehydrogenative coupling of indolines with alcohols

Recently, another Ir complex (cat. **8**) was used by Maji *et al.* for a regioselective C3− and N− functionalization of indolines in water (scheme 25).[37] A



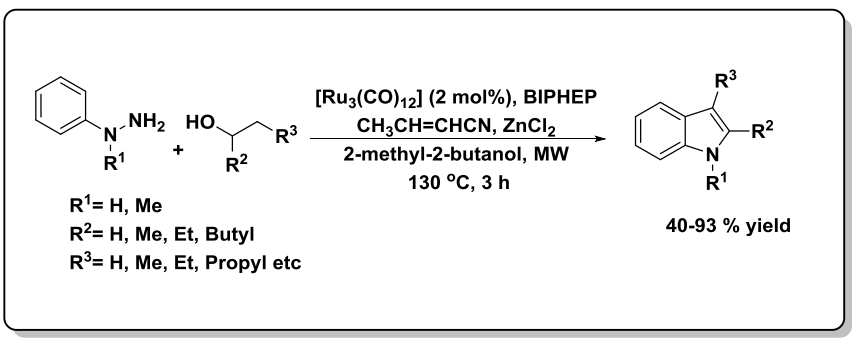
Scheme 25: Ir catalyzed regioselective C3−functionalization of indolines in water

wide range of C3-alkylated indoles were obtained by the tandem dehydrogenation of indolines and alcohols in water in presence of the Ir-complex under aerobic conditions. Further applicability of this method was proved by the synthesis of psychoactive drug, *N*,*N*-dimethyltryptamine in this method.

Ruthenium catalyst:

A Ru catalyzed hydrogen auto transfer method was established by the group of Tadde to synthesize substituted indole derivatives where instead of aldehyde or ketone in Fisher indole synthesis, alcohols were used (scheme 26).[38] The reaction is initiated by the oxidation of alcohols to carbonyl *via* transfer of hydrogen molecule to crotononitrile and subsequently the catalyst is regenerated. It was observed that the

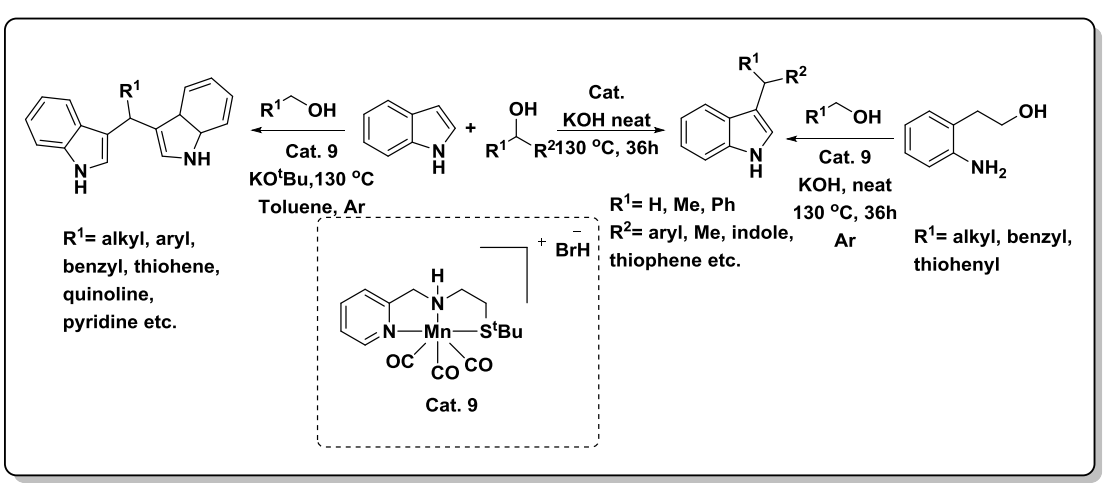
reaction rate and the yield of the products were significantly increased when irradiated under microwave.



Scheme 26: Modified Fisher-indole synthesis with alcohol

Manganese catalyst:

Very recently, a Mn catalyzed C3-alkylation method of indole was revealed by the group of Srimani (scheme 27).[39] When the reaction was performed with indoles and primary and secondary alcohols in presence of 5 mol% cat. **9** 30 mol% KOH, then the C-3 alkylated products were obtained in good to excellent yields in 36 h at

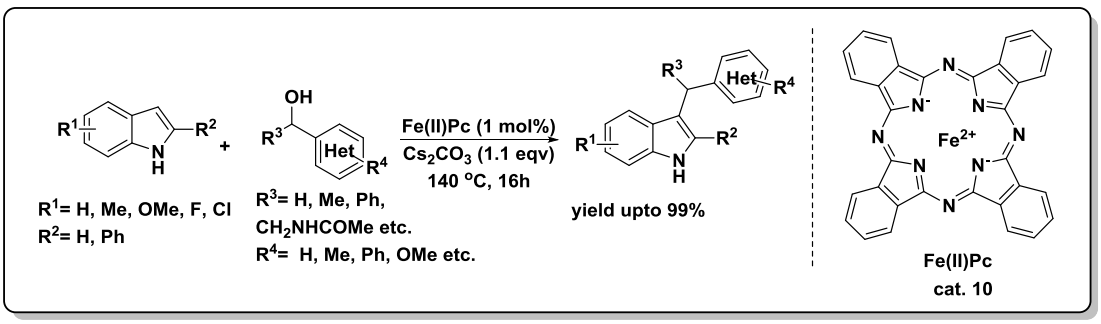


Scheme 27: Mn catalyzed C3-alkylation of indole with alcohol

130 °C. But when the reaction condition was changed from KOH to 30 mol% KO^{t}Bu, bis(indolyl)Methane was formed efficiently. Moreover, one pot C-3 alkylated indoles were also prepared in moderate to good yields from 2-aminophenyl ethanol and alcohols in presence of the aforementioned catalyst with KOH.

Iron Catalyst:

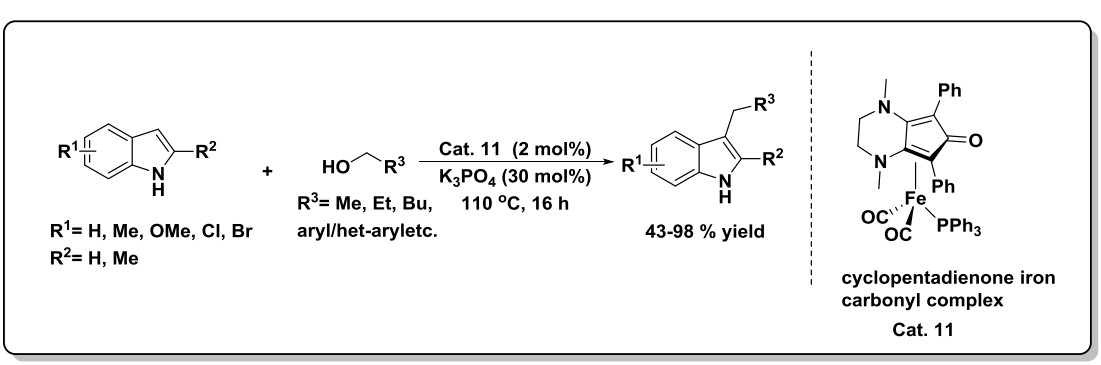
Recently, an iron catalyzed borrowing hydrogen methodology was coined by Piersanti *et al*. The group revealed the synthesis of 3-benzylated indoles by the



Scheme 28: Iron catalyzed synthesis of 3- benzylated indoles by the reaction of indoles with alcohols

coupling reaction of indoles with 1^{o} and 2^{o} benzyl alcohols catalyzed by 1 mol% iron phthalocyanine complex in the presence of 1.1 equiv. of Cs_2CO_3 at 140 °C for 16 h (Scheme 28).[40] The reaction pathway involved first the formation of a ketone by the dehydrogenation of a secondary alcohol. The ketone then reacted with indole to leading to the formation of the alkylideneindolenine intermediate. Then again the hydrogenation of C=C bond/aromatisation takes place to furnish the 3-alkylated-indole derivatives.

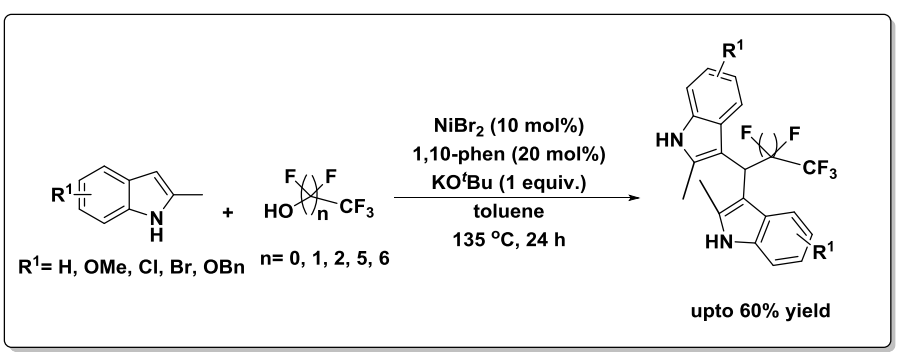
It is worthy to mention that, Renaud and co-workers also described this coupling reaction using another iron complex cat. **11** as catalyst (scheme 29).[41] Here the C3-alkyaltion of indole was achieved by the reaction of indoles with various benzylic and aliphatic alcohols using 2 mol% cyclopentadienone iron carbonyl complexes in the presence of K_3PO_4 at 110 °C (45–98 % yields).



Scheme 29: cyclopentadienone iron carbonyl complexes for the synthesis of 3-substituted indoles

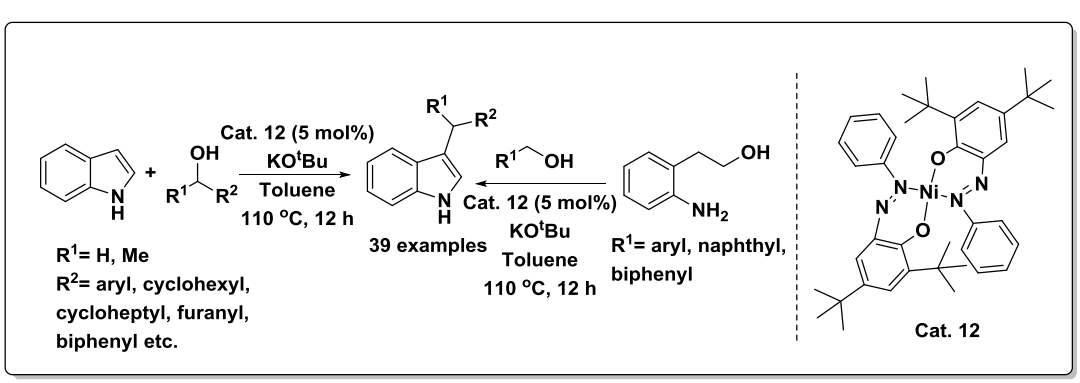
Nickel Catalyst:

Arun *et al.* has described a dehydrogenative technique to obtain polyfluoroalkylated bis-indoles using nickel-based catalyst under aerobic condition (scheme 30).[42] They have utilized 10 mol% $NiBr_2$ and 20 mol% 1,10-phenanthroline as the catalyst and ligand. A vast range of polyfluoroalkylated bis-indoles were attained in moderate yields (upto 60%) using different perfluorinated alcohols under the standard reaction conditions. DFT studies disclosed that, there was a non-covalent interaction between the indole moiety with the active catalyst, and that stabilised the rate determining transition state during the dehydrogenation of polyfluorinated alcohols.



Scheme 30: Nickel catalyzed reaction to obtain polyfluoroalkylated bis-indoles

Adhikari and co-workers have developed another nickel catalyst (Cat. **12**) for the C-3 alkylation of indoles with various primary and secondary alcohols (scheme 31).[43] Interestingly, the applicability of the method was further proved by synthesizing C-3 alkylated indoles starting from 2-(2-aminophenyl) ethanol instead of

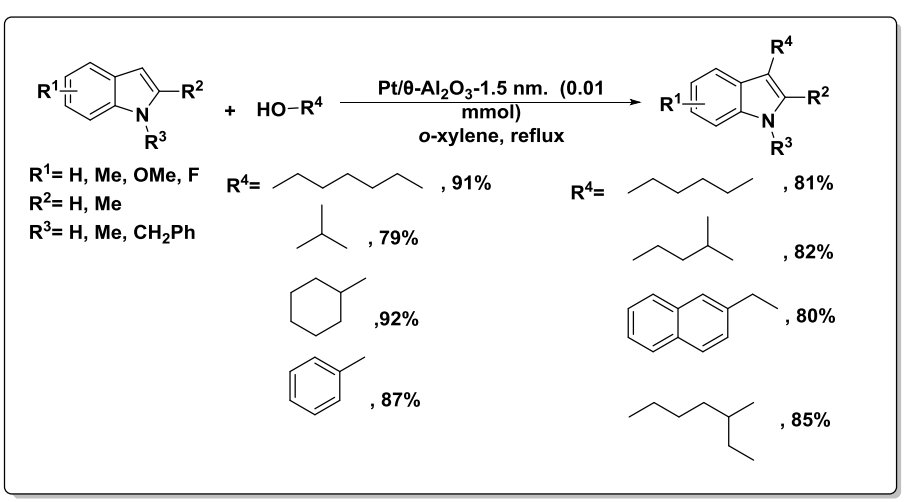


Scheme 31: nickel catalyst (Cat. **12**) by the coupling of indoles with alcohols

indoles. This borrowing hydrogenation mechanism differs from other conventional catalytic borrowing hydrogen systems, as it proceeds through a radical intermadiates.

Platinum catalyst:

The catalytic system was not only bound to homogenous catalysts. Heterogeneous catalysts were also developed for the BH activation. Siddiki and co-workers designed by a Pt nanocluster-loaded θ-Al_2O_3-1.5 nm catalyst for selective alkylation at the C-3 position of indole with alcohols (scheme 32).[44] To get assurance about the mechanism, GC-MS of the intermediates and KIE investigations were done. The obtained k_H/k_D value was 1.7, which suggested that, the dissociation of α-CH bond of benzyl alcohol is the relatively slow step. And this is only possible if the reaction goes through hydrogen-borrowing pathway, not the Friedel–Crafts-type substitution. The reaction had many benefits over the existing ones, such as high Turn Over Numbers, no requirement of co-catalyst or excess alkylating agents, reuse of the catalysts etc.



Scheme 32. Pt heterogeneous catalyst for the C-3 alkylation of indole

3. CONCLUSION:

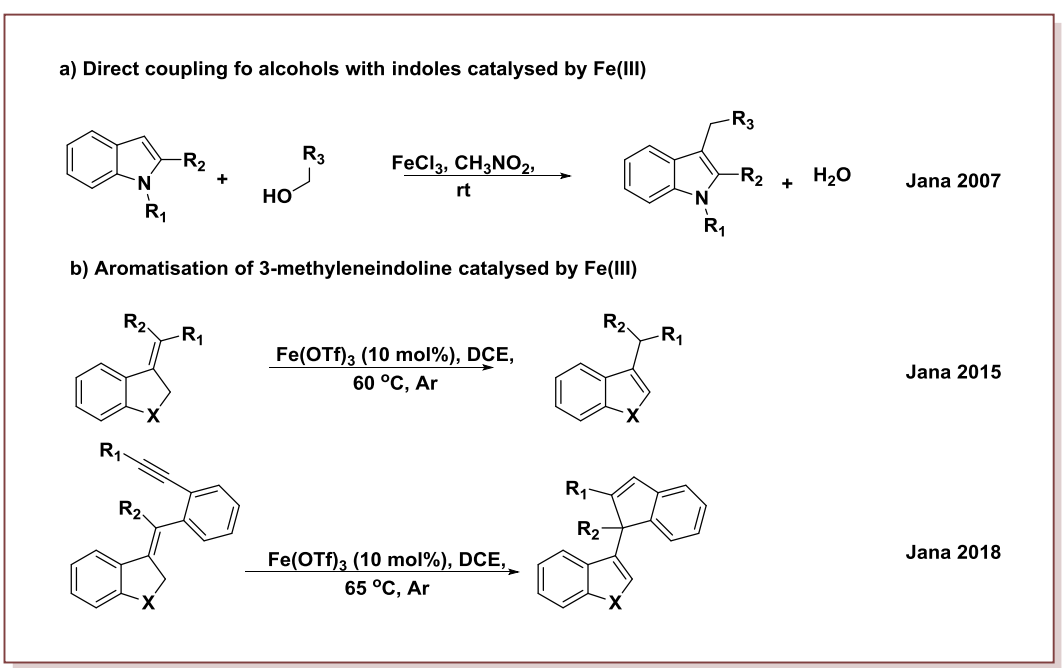
This review covers various kinds of attempts to achieve 3-substituted indole derivatives and presents an account of the prosperity and applications of different transition metals, Lewis and Brønsted acids for the reaction of indole with alcohols. It has been clearly manifested that, alcohols have been extensively used towards the synthesis of important organic molecules because of its easy availability and convenient handling. The construction of structurally complex moiety from simple

starting materials has been a challenging task to the organic chemists, and therefore, a tremendous growth in this field has been observed since the last decades. And of course, there is scope for even further progress and in future we hope to see more enthralling methodology for the synthesis of 3-substituted indoles coming up.

4. PRESENT WORK:

4.1. INDRODUCTION:

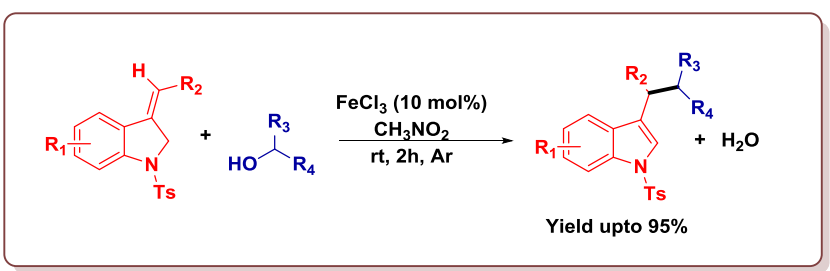
Owing to the widesperead appplications of C-3 substituted indoles, our group has also developed few new strategies for the synthesis of 3-substituted indoles. In 2007, an interesting protocol for the synthesis of 3-substituted indoles were coined by our group using the Friedel-craft reaction between indoles and activated alcohols (scheme 33a).[14] Recently,



Scheme 33: Our previous strategies for the synthesis of 3-subtituted indoles

two new protocols were reported by Jana *et al*. for the synthesis of various 3-substituted indole derivatives *via* iron-catalyzed isomerisation/cycloisomerisation of substituted 3-methyleneindoline derivatives through π-activation of double/triple bond by iron in excellent yields (scheme 33b).[45] Due to easy accessibility of 3-methyleneindoline derivatives through tandem Heck-Suzuki or reductive Heck coupling of 2-halo-*N*-propargylanilide, this has been a potentially attractive

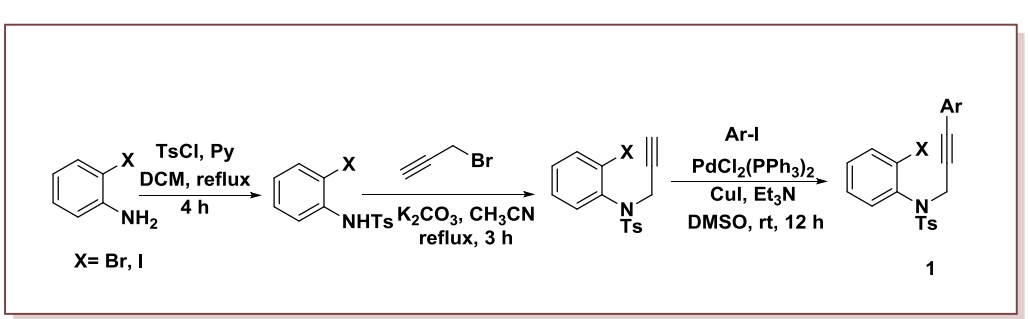
intermediate for the synthesis of 3-substituted indole derivatives. This would overcome the challenges encountered previously, like harsh reaction condition, low chemical yields etc. In the present study, we envisioned that, in situ generated carbocation from π-activated alcohol could undergo Csp^2-Csp^3 bond formation, chemoselectively at the exocyclic double bond, and subsequent aromatization could furnish densely substituted 3-alkylindoles derivative (Scheme 34). Implimenting this strategy, we were successful to synthesize densely substituted 3-alkylindole derivatives in the presence of environmentally friendly and sustainable catalyst, $FeCl_3$ where π-activated alcohols, such as benzylic, allylic, and propargylic alcohols were utilized as the coupling partners. The obtained densely substituted indoles are difficult to synthesize by existing known method, and this definitely adds benefit to our present protocol.



Scheme 34: Present work: Iron-catalyzed synthesis of 3-alkyl indole by direct coupling with alcohol

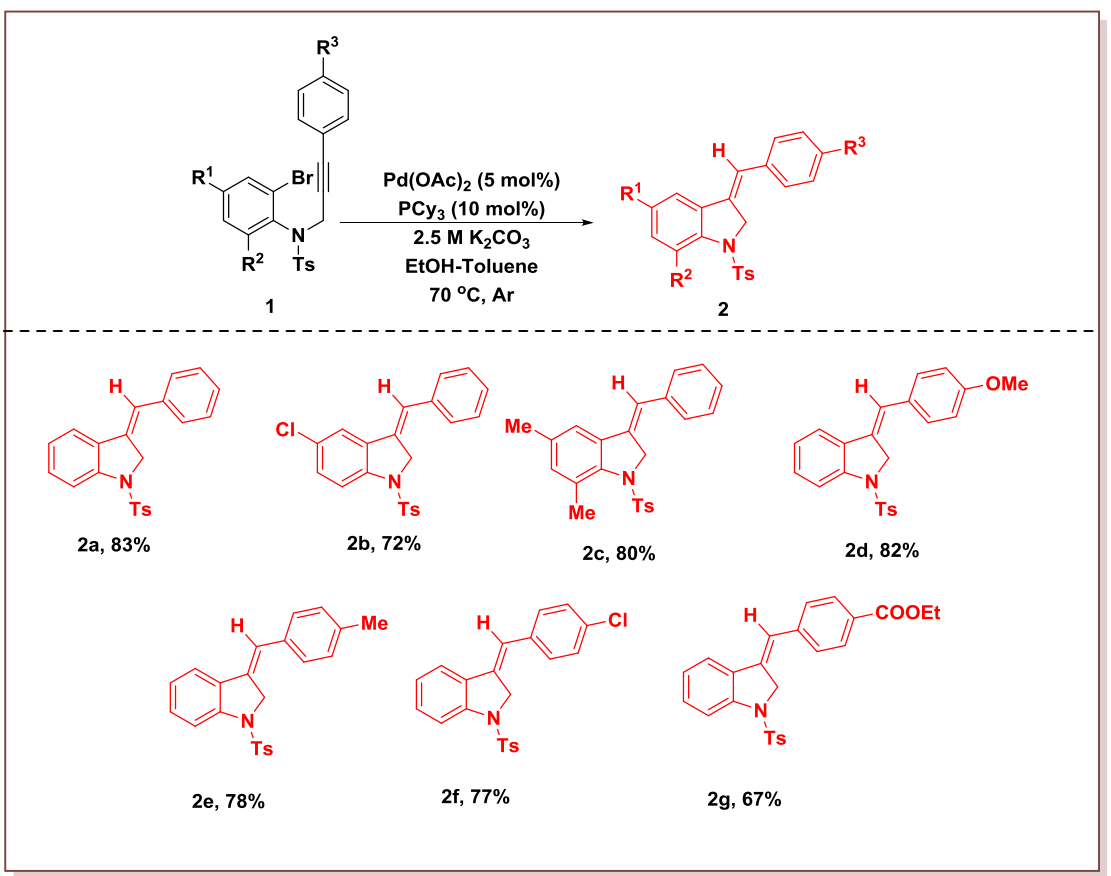
4.2. RESULTS AND DISCUSSIONS:

The required starting materials, 2-bromo-*N*-propargylanilidines were preapared by first tosylation of 2-bromo aniline, then propargylation with propargyl bromide, followed by Sonogashira coupling with aryl iodide/ bromide (scheme 35). Detailed experimental procedures have been stated at the end of the chapter.



Scheme 35: Preparation strategy of 2-bromo-*N*-propargylanilidines substrates

Then with the prepared substituted 2-bromo-*N*-propargylanilidines, Heck coupling reaction was performed using 5 mol% $Pd(OAc)_2$, 10 mol% tricyclohexylphosphine (PCy_3), 2.5 M aqueous K_2CO_3 in a mixed solvent of toluene and ethanol (1:1) at 70 ^oC which afforded 3-benzylidene-1-tosylindoline derivatives **2** within 4 hours (scheme 36).[45a] The reaction



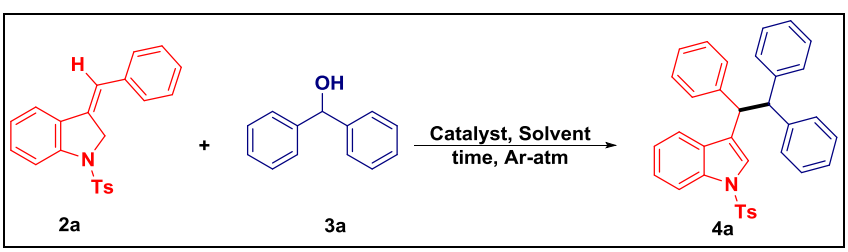
Scheme 36: Preparation of 3-benzylidine-1-tosylindoline substrates by Pd catalyzed Heck coupling reaction

pathway followed a stereoselective cylisation and selective 5-*exo-dig* cyclisation led to the 3-benzylidine-1-tosylindoline derivatives in moderate to good yields. 2-bromoaniline derivatives possessing electron withdrawing group like -Cl, and electron donating group like 2,4-dimethyl underwent smooth transformation under the aforesaid condition with 72% and 80% yields, respectively (scheme 36, entries **2b** and **2c**). Again, possessing a number of functional groups in the alkyne unit, good yield of the products (67-82%) were obtained (scheme 36, **2d-2g**).

With the optimized reaction condition, we have prepared a number of key substrates **2**. We then tried to investigate the best reaction condition for our target

tandem isomerisation and C- C bond formation reaction between 3-benzylidine-1-tosylindoline **2a** (0.15 mmol), and alcohol **3a** (0.15 mmol) *via* catalytic activation of alcohol **3a** to afford the desired product **4a**. The obtained results are summarized in Table 1. Owing to high catalytic activity of $FeCl_3$ towards alcohol, our initial screening began with anhydrous $FeCl_3$ in various solvents like dry DCM, THF, CH_3CN, CH_3NO_2 and 1,2-DCE. Among them, CH_3NO_2 gave maximum yield of 89% at room temperature (Table 1, entry 3). The other solvents like DCM, DCE and THF

Table 1: Optimisation of the reaction conditions for the synthesis of **4a**

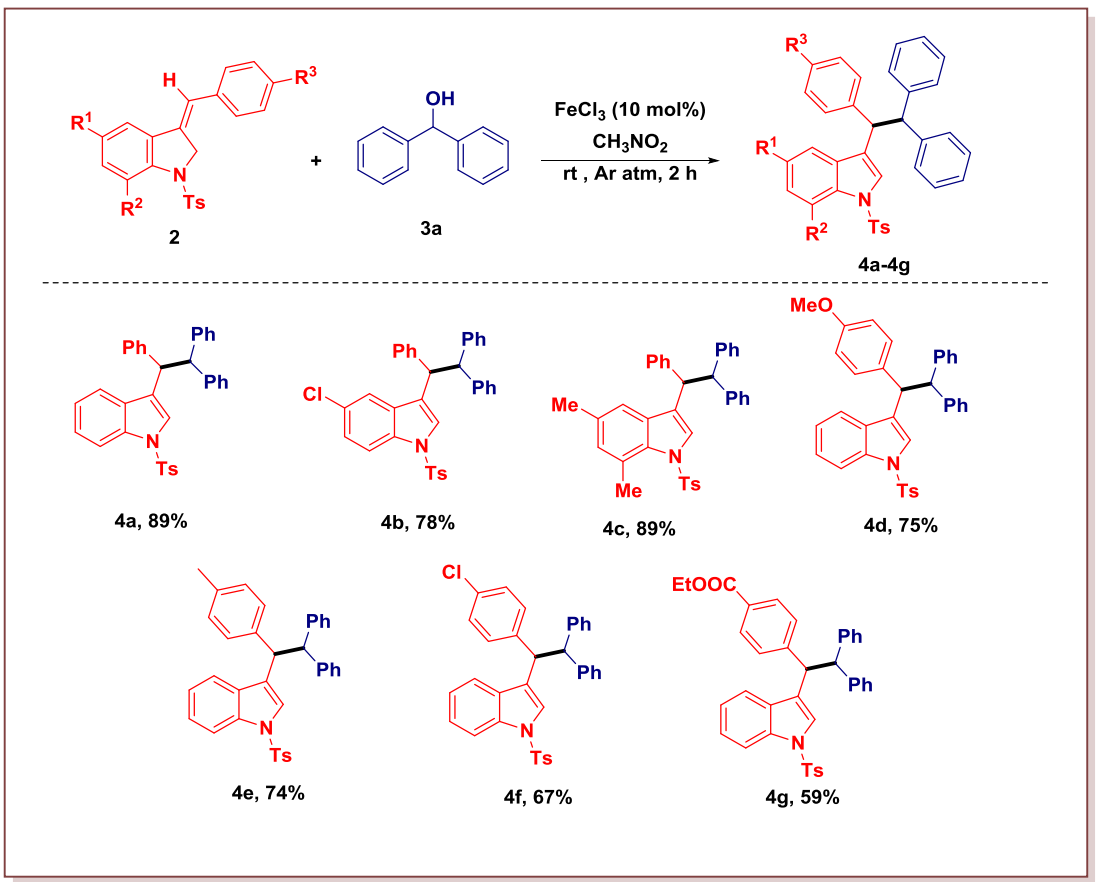


Entry	Catalyst (0.015 mmol)	Solvent	Temp (^oC)	Time (h)	Yield (%)
1	$FeCl_3$	DCM	rt	2	35
2	$FeCl_3$	DCM	reflux	2	54
3	$FeCl_3$	CH_3NO_2	rt	2	89
4	$FeCl_3$	THF	rt	2	trace
5	$FeCl_3$	CH_3CN	rt	2	ND
6	$FeCl_3$	1,2-DCE	rt	3	52
7	$FeBr_3$	CH_3NO_2	rt	2	74
8	$Fe(OTf)_3$	CH_3NO_2	rt	3	32
9	$InCl_3$	CH_3NO_2	rt	2	78
10	$In(OTf)_3$	CH_3NO_2	rt	2	75
11	AgOTf	CH_3NO_2	rt	2	0
12	CSA	CH_3NO_2	rt	2	0

Entry	Catalyst (0.015 mmol)	Solvent	Temp (^oC)	Time (h)	Yield (%)
13	TfOH	CH_3NO_2	rt	3	78
14	PTSA	CH_3NO_2	rt	3	81
15	$FeCl_3$ (0.075)	CH_3NO_2	rt	2	68

at room temperature furnished low to moderate yields of the products (Table 1, entry 1, 4 and 6). When the reaction was carried out in refluxing condition using DCM solvent, no such satisfactory result was observed (Table 1, entry 2). However, when CH_3CN was used as solvent, no desired product was observed at room temperature. So the best solvent obtained was CH_3NO_2, and choosing CH_3NO_2 as the effective solvent, other common iron salts such as $FeBr_3$ and $Fe(OTf)_3$ were tested and both of them performed well, but led to lower yields of the products were obtained than $FeCl_3$ **4a** (Table 1, entry 7, 8). Again catalyst loading was decreased to 5 mol% $FeCl_3$ and afforded 68% yield (Table 1, entry 15). Considering the other Lewis acid catalysts like $InCl_3$ and $In(OTf)_3$, the yields of 78% and 75 % were observed respectively at room temperature in 2 hours and no result was observed by using AgOTf (Table 1, entry 9-11). Switching to Brønsted acids like TfOH and PTSA to carry out the reaction, proved to be less efficient in respect of time and yields. CSA was totally inactive under this reaction condition (Table 1, entry 12-14). Hence the reaction of **2a** with **3a** in the presence of 10 mol% of $FeCl_3$ in CH_3NO_2 at room temperature was proved to be the optimum reaction condition.

After finding the optimized reaction condition, the scope of the reaction was tested, and for this purpose, a number of reactions were carried out between substituted 3-benzylidine-1-tosylindolines (0.15 mmol) and the alcohol **3a** (0.15 mmol) in presence of 10 mol% $FeCl_3$ in nitromethane solvent at room temparture; and the results are listed in scheme 37. It was observed that 3-benzylidine-1-tosylindoline having electron poor group like -Cl in the 2-haloaniline moiety resulted in good yield of 78% (scheme 37, entry **4b**). And when an electron rich substituent in a 2-haloaniline moiety like 2,4-dimethyl was tested, the yield of the reaction improved providing 89% of the product **4c** (scheme 37, entry **4c**). Furthermore, the reaction seemed to



Scheme 37: $FeCl_3$ catalyzed direct substitution of benzylic alcohol **3a** with various substituted 3-benzylidene-1-tosylindolines

tolerate various functional groups such as –OMe, –Me, $–CO_2Et$ and –Cl at the *para* position of the aromatic ring (R^3) of the 3-benzylidine-1-tosylindoline and moderate

CCDC no. 1939911

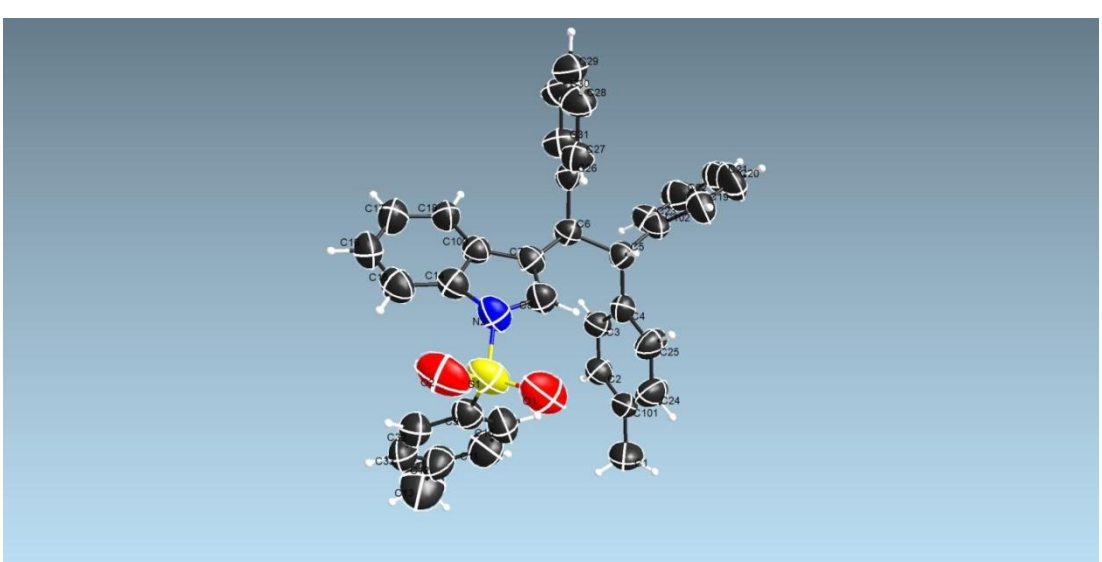
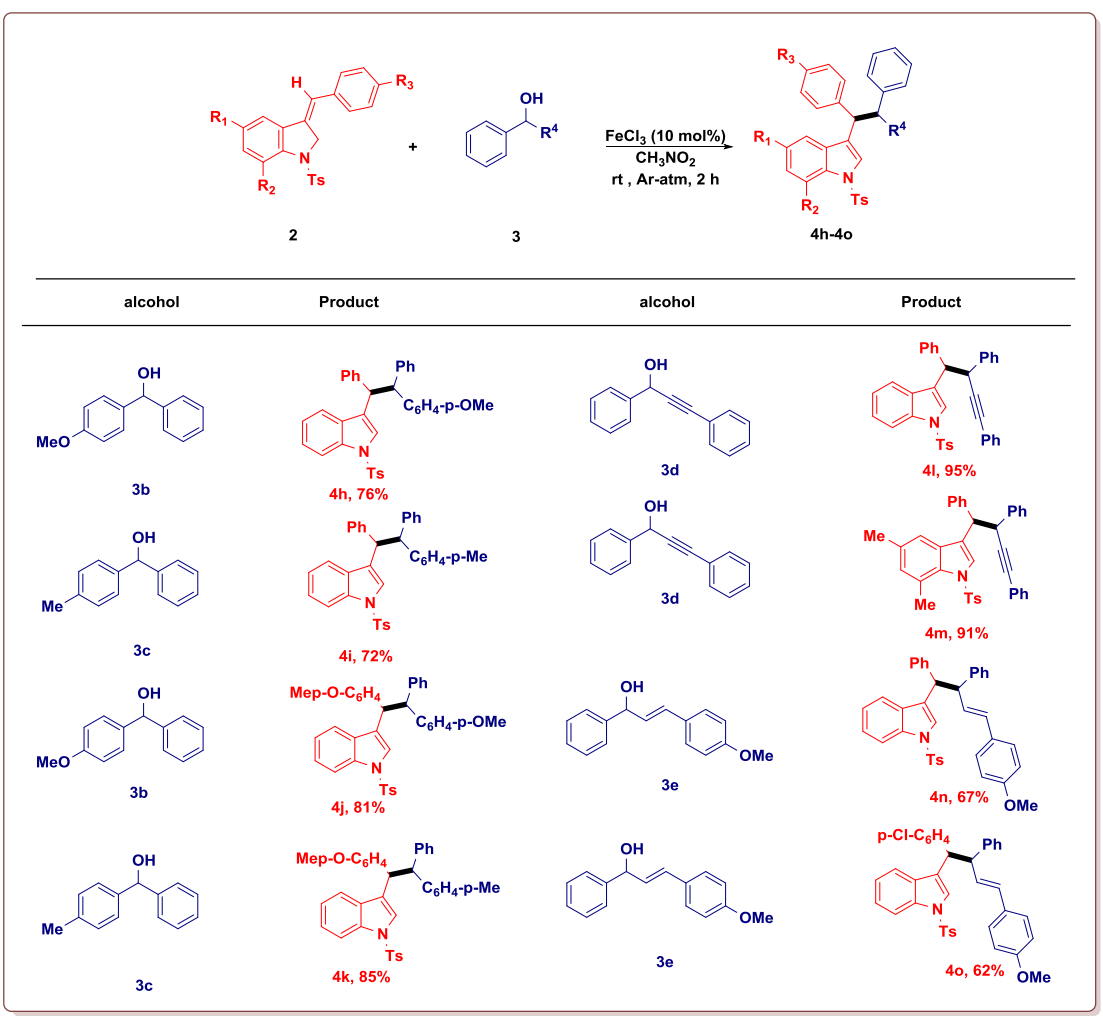


Figure 2: ORTEP diagram for the crystal structure of compound 4i (Thermal ellipsoid contour at 50% probability level)

to good yields (59-75%) (scheme 37, entry **4d**–**4g**) were obtained. The yields were relatively higher in case of electron rich substituents such as –OMe and –Me at R^3 than electron deficient substituents such as –Cl and $–CO_2Et$.

However, the versatality of the reaction was then explored using substituted benzylic alcohols under the standard reaction condition. For this purpose benzylic alcohols

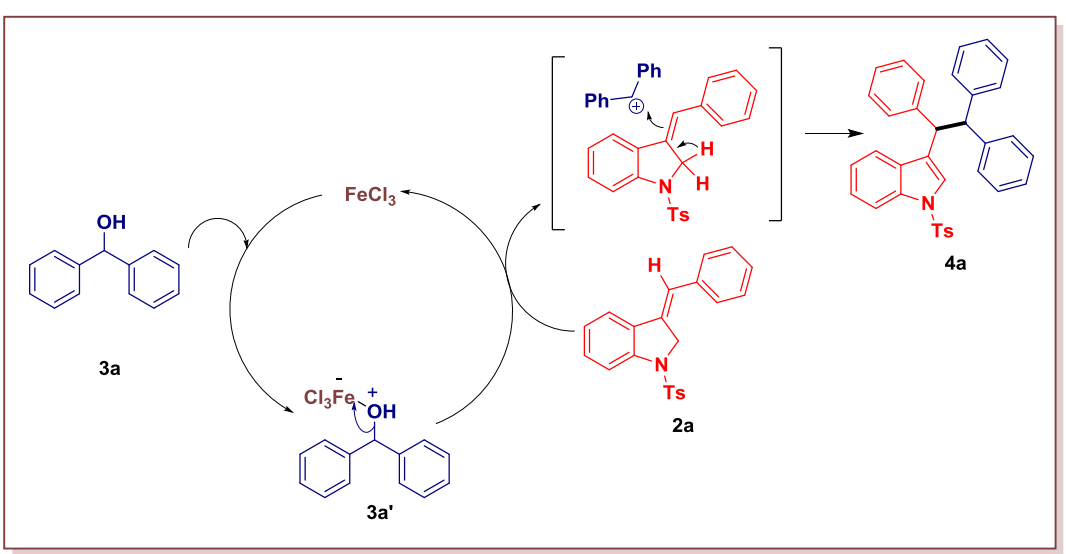
Table 2: Scope of alcohols for the synthesis of 3-substituted indoles



with electron donating groups at the *para* position were exploited as electrophiles, and that furnished good to excellent yields (72-85%, Table 2, entries 4h-4k), but the products were obtained as non-separable diasetereomeric mixtures. The formation of the compound **4i** was further confirmed by single crystal XRD (CCDC no. 1939911) (figure 2).

Inspired by the generality of this protocol, we then aimed to demonstrate the robustness of the reaction by employing propargylic and allylic alcohols as electrophiles. To our pleasure, in both the cases we obtained our desired products in good yields (62-95%, Table 2, entries 4l-4o) as non-separable diastereomeric mixtures. Better yields of the products were obtained for propargylic alcohols than (92% and 95%) than allylic alcohols (62% and 67%), which might be due to the fact that the carbocationic centre generated at the propargylic position were more stabilized by the adjacent triple bond than the double bond in case of allylic alcohol.

We tried to understand the mechanism based on the experimental observations and previous reports,[45,46] and a plausible mechanism was predicted which is depicted below (scheme 38). It is evident that $FeCl_3$ activates the benzylic alcohol **3a** and facilitates dehydration to form carbocation **3a**´ which then activates the alkene and subsequent deprotonation of the $–CH_2$ unit and nucleophilic attack of the alkene to the carbocation leads to our desired 3-substituted indole **4a**. $FeCl_3$ regenerates which participates in the next catalytic cycle.



Scheme 38: Plausible mechanistic pathway

4.3. CONCLUSION:

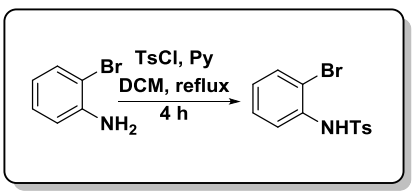
In this chapter, I have discussed the synthesis of densely substituted 3-alkyl indole derivatives *via* $FeCl_3$ catalyzed direct substitution of π-activated alcohols with 3-benzylidene-1-tosylindolines. This procedure offers a wide variety of advantages like operational simplicity, the use of inexpensive and relatively benign $FeCl_3$ as the

catalyst, a wide tolerance to functionality including electron withdrawing and releasing substituents, easy accessibility of the starting alcohols and high yields of the products. Certainly, this protocol has great potential towards the formation of C–C bonds and the synthesis of substituted indole derivatives of pharmaceutical importance.

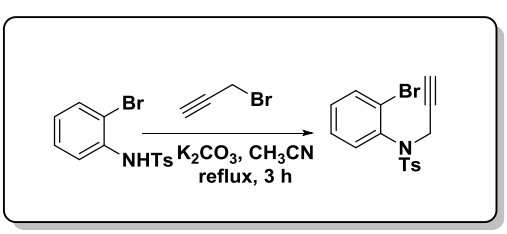
4.4. EXPERIMENTAL SECTION:

All ^{1}H NMR spectra were recorded with Bruker Avance III (300, 400 or 500 MHz) spectrometers in deuterated solvents ($CDCl_3$). Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) and the solvent resonance were referenced to internal standard $CDCl_3$ (δ 7.26 ppm). All coupling constants are absolute values and are expressed in Hz. The descriptions of the signals are reported as follows: s = singlet, d = doublet, dd = double of doublet, t = triplet, m = multiplet, dt = doublet of triplets, ddd = doublet of doublet of doublet, dddd = doublet of doublet of doublet of doublet and td = triplet of doublets. ^{13}C NMR spectra were recorded with Bruker Avance III 300 (75 MHz), 400 (100 MHz) and 500 (125 MHz) spectrometers as solutions in $CDCl_3$ with complete proton decoupling. Chemical shifts are reported in parts per million (ppm, δ) and are referenced to internal standard $CHCl_3$ (δ = 77.16 ppm). High resolution mass spectra were taken using Q-Tof micro MS system by electron spray ionization (ESI) technique. Crystallographic data were collected at room temperature on a Bruker D8 quest microfocus single crystal XRD machine. The routine monitoring of the reaction was performed with silica gel coated glass slides (Merck, silica gel G for TLC) and pre-coated Al plates which were analyzed with iodine and UV-light respectively. Solvents, reagents, and chemicals were purchased from Aldrich, Alfa aesar, Merck, SRL, Spectrochem, and Process Chemicals. The final products were purified by column chromatography on Merck silica gel (100–200 mesh). All reactions involving moisture-sensitive reactants were executed with oven-dried glass ware.

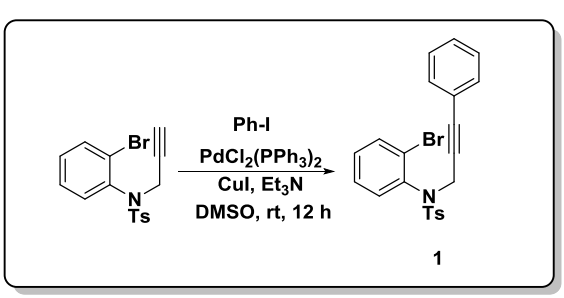
4.4.1. Representative Experimental Procedure for the Synthesis of 2-bromo-*N*-propargylanilidines:



Step-I: To a solution of 2-bromoaniline (860 mg, 5 mmol) in DCM (5 mL), tosyl chloride (1.42 g, 7.5 mmol) and pyridine (790 mg, 10 mmol) was added. And the resulting mixture was subjected to reflux for 4 hours. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with DCM (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the tosylated product as a brown solid (1.56 g, 4.85 mmol, 97%).



Step-II: *N*-tosyl-2-bromoaniline (652 mg, 2 mmol), propargyl bromide (285 mg, 2.4 mmol) and activated K_2CO_3 (828 mg, 6 mmol) was added in acetonitrile solvent. The resulting mixture was refluxed for 3 hours. The completion of the reaction was



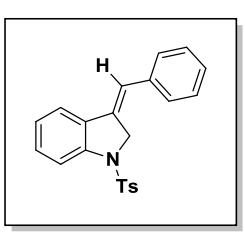
monitored by TLC, then the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The

product was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the propargylated product as a yellow solid (655 mg, 1.8 mmol, 90%).

Step-III: Sonogashira coupling of the propargylated product was done where iodobenzene (440 mg, 2.16 mmol) was added to the propargylated product (655 mg, 1.8 mmol) in presence of triethyl amine (363 mg, 3.6 mmol) in DMSO solvent. To the reaction mixture, $PdCl_2(PPh_3)_2$ (25 mg, 0.036 mmol) and CuI (6.84 mg, 0.036 mmol) were added, and stirred for 12 hours at room temperature. TLC was checked to check the completion of the reaction. Then the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the propargylated product as a yellow solid (689 mg, 1.57 mmol, 87%).

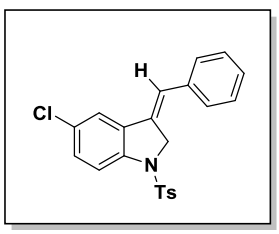
4.4.2. Representative Experimental Procedure for the Synthesis and Characterization of 2a-2g:

(*Z*)-3-Benzylidene-1-tosylindoline (2a): To a solution of *N*-(2-bromophenyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**1a**) (440mg, 1 mmol) in a mixed solvent of EtOH (2 mL) and toluene (2 mL), PCy_3 (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol) and aq. K_2CO_3 (2.5 M, 2mL) were added and stirred for 4 hour at 70 ^oC under Argon atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 100-200 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2a** as a yellow solid (300mg, 0.83mmol, 83%), m.p. 162-165 ^oC. **^{1}H NMR ($CDCl_3$, 500 MHz)** δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.71-7.73 (m, 2H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.40-7.43 (m, 2H), 7.27-7.29 (m, 4H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.04-7.07 (m, 1H), 6.79 (t, *J* = 3.0 Hz, 1H), 4.87 (d, *J* = 3.0 Hz, 2H), 2.34 (s, 3H) ppm. **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 144.5, 143.5, 136.4, 134.3, 132.7, 131.2, 130.0, 129.9, 128.9, 128.7, 128.6, 128.4, 127.7, 127.4, 127.3, 126.9, 123.9, 120.4, 118.6,

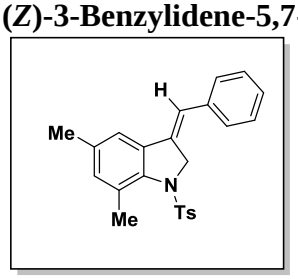


114.9, 54.7, 21.7 ppm. **HRMS:** m/z calcd for $C_{22}H_{19}NO_2SNa$ $[M + Na]^+$, 384.1034; found, 384.1033.

(*Z*)-3-Benzylidene-5-chloro-1-tosylindoline (2b): To a solution of *N*-(2-bromo-4-chlorophenyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**1b**) (230 mg, 0.5 mmol) in a mixed solvent of EtOH (2 mL) and toluene (2 mL), PCy_3 (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol) and aq. K_2CO_3 (2.5 M, 2 mL) were added and stirred for 4 hour at 75 ^oC under Argon atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 100-200 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2b** as a white solid (139 mg, 0.42 mmol, 72%), m.p. 182-184 ^oC. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.64 (s, 1H), 7.59-7.62 (m, 2H), 7.32-7.37 (m, 3H), 7.21-7.24 (m, 1H), 7.19 (s, 1H), 7.18 (s, 2H), 7.15 (d, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 6.694 (t, *J* = 3.0 Hz, 1H), 4.79 (d, *J* = 3.0 Hz, 2H), 2.29 (s, 3H) ppm. **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 144.8, 141.9, 135.9, 133.8, 133.0, 131.3, 130.1, 129.7, 129.5, 129.0, 128.6, 127.8, 127.3, 120.4, 119.9, 115.9, 55.0, 21.7 ppm. **HRMS:** m/z calcd for $C_{22}H_{18}ClNO_2SNa$ $[M + Na]^+$, 418.0645; found, 418.0643.

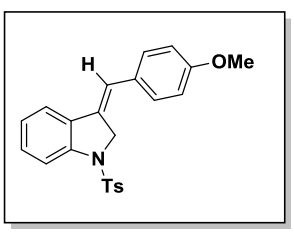


(*Z*)-3-Benzylidene-5,7-dimethyl-1-tosylindoline (2c): To a solution of *N*-(2-bromo-4,6-dimethylphenyl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**1c**) (300 mg, 0.64 mmol) in a mixed solvent of EtOH (2 mL) and toluene (2 mL), PCy_3 (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol) and aq. K_2CO_3 (2.5 M, 2 mL) were added and stirred for 4 hour at 70 ^oC under Argon atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 100-200 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2c** as a white solid (200 mg, 0.51 mmol, 80%), m.p. 156-157 ^oC. **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.37 – 7.41 (m, 1H), 7.26 – 7.30 (m, 2H), 7.06 - 7.12 (m, 4H), 7.02 (s, 1H),



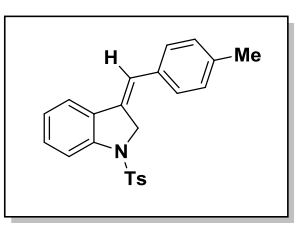
6.97 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 2H),), 6.34 (s, 1H), 4.74 (d, *J* = 2.0 Hz, 2H), 2.61 (s, 3H), 2.36 (s, 3H), 2.31 (s, 3H) ppm. **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 143.7, 141.1, 136.8, 136.7, 136.65, 135.5, 132.9, 132.4, 132.0, 129.1, 128.6, 128.1, 128.08, 127.2, 119.5, 118.3, 57.0, 21.5, 21.2, 19.6 ppm. **HRMS:** m/z calcd for $C_{24}H_{23}NO_2SNa$ $[M + Na]^+$, 412.1347; found, 412.1350.

(*Z*)-3-(4-Methoxybenzylidine)-1-tosylindoline (2d): To a solution of *N*-(2-



bromophenyl)-*N*-(3-(4-methoxyphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (**1d**) (470 mg, 1.0 mmol) in a mixed solvent of EtOH (2 mL) and toluene (2 mL), PCy_3 (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol) and aq. K_2CO_3 (2.5 M, 2 mL) were added and stirred for 4 hour at 70 ^oC under Argon atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 100-200 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2d** as a white solid (320 mg, 0.82 mmol, 82%), m.p. 150 ^oC. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.78 – 7.69 (m, 3H), 7.44 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.29 – 7.18 (m, 5H), 7.04 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.74 (t, *J* = 3.0 Hz, 1H), 4.84 (d, *J* = 3.0 Hz, 2H), 3.84 (s, 3H), 2.34 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.9, 144.4, 143.1, 134.3, 131.5, 130.2, 129.9, 129.8, 129.4, 129.3, 129.2, 127.3, 126.95, 126.92, 123.9, 120.1, 118.2, 114.8, 114.5, 114.0, 113.9, 55.5, 55.4, 54.7, 21.6 ppm. **HRMS:** m/z calcd for $C_{23}H_{21}NO_3SNa$ $[M + Na]^+$, 414.1140; found, 414.1142.

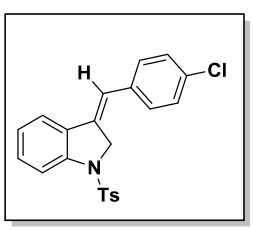
(*Z*)-3-(4-Methylbenzylidine)-1-tosylindoline (2e): To a solution of *N*-(2-



bromophenyl)-4-methyl-*N*-(3-(p-tolyl)prop-2-yn-1-yl)benzenesulfonamide (**1e**) (200 mg, 0.44 mmol) in a mixed solvent of EtOH (2 mL) and toluene (2 mL), PCy_3 (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol) and aq. K_2CO_3 (2.5 M, 2 mL) were added and stirred for 4 hour at 70 ^oC under Argon atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15mL, twice) and the combined organic extract was washed with water (15mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel,

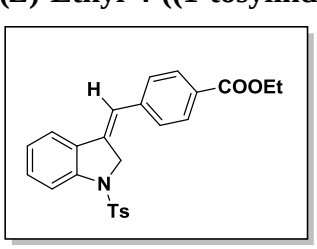
100-200 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2e** as a yellow solid (128 mg, 0.34 mmol, 78%), m.p. 162-165 ^{o}C. **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 7.74 (dd, *J* = 11.6, 8.4 Hz, 3H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.16-7.28 (m, 7H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.77 (t, *J* = 2.8 Hz, 1H), 4.86 (d, *J* = 2.8 Hz, 2H), 2.38 (s, 3H), 2.34 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.4, 143.3, 137.4, 134.3, 133.7, 131.6, 131.4, 129.9, 129.7, 128.4, 127.3, 123.9, 123.9, 120.3, 118.6, 114.8, 54.7, 21.6, 21.4 ppm. **HRMS:** m/z calcd for $C_{23}H_{21}NO_2SNa$ $[M + Na]^+$, 398.1191; found, 398.1192.

(*Z*)-3-(4-Chlorobenzylidine)-1-tosylindoline (2f): To a solution of *N*-(2-



bromophenyl)-*N*-(3-(4-chlorophenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (**1f**) (300 mg, 0.3 mmol) in a mixed solvent of EtOH (2 mL) and toluene (2 mL), PCy_3 (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol) and aq. K_2CO_3 (2.5 M, 2 mL) were added and stirred for 4 hour at 70 ^{o}C under Argon atmosphere. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 100-200 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2f** as a yellow solid (91 mg, 0.23 mmol, 77%), m.p. 160-164 ^{o}C. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 7.74 (t, *J* = 9.0 Hz, 3H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.18-7.32 (m, 5H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.74 (s, 1H), 4.82 (d, *J* = 2.0 Hz, 2H), 2.35 (s, 3H) ppm. **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 144.6, 143.5, 134.8, 134.1, 132.2, 132.9, 130.8, 130.2, 130.0, 129.9, 129.8, 129.5, 129.1, 128.9, 128.7, 128.4, 127.2, 123.9, 120.4, 117.3, 114.8, 54.5, 21.6 ppm. **HRMS:** m/z calcd for $C_{22}H_{18}ClNO_2SNa$ $[M + Na]^+$, 418.0645; found, 418.0647.

(*Z*)-Ethyl 4-((1-tosylindolin-3-ylidene)methyl)benzoate (2g): To a solution of ethyl

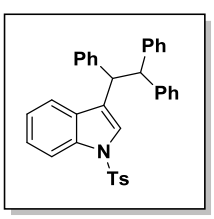


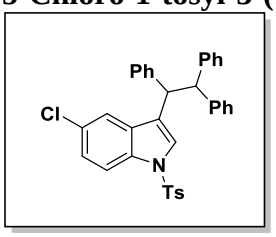
4-(3-(*N*-(2-bromophenyl)-4-methylphenylsulfonamido)prop-1-yn-1-yl)benzoate (**1g**) (400 mg, 0.44 mmol) in a mixed solvent of EtOH (2 mL) and toluene (2 mL), PCy_3 (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol) and aq. K_2CO_3 (2.5 M, 2 mL) were added and stirred for 4 hour at 70 ^{o}C under Argon atmosphere. After the completion of the reaction (monitored by TLC), the

crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 100-200 mesh), eluting with pet ether/EtOAc 95:5 (v/v) to afford the product **2g** as a yellow solid (106 mg, 0.29 mmol, 67%), m.p. 152-154 ^oC. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.77 (dd, *J* = 20.6, 8.1 Hz, 3H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.28 (s, 1H), 7.24 (s, 1H), 7.12 – 7.07 (m, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 4.88 (d, *J* = 2.7 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.43 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 166.3, 144.6, 143.9, 140.7, 135.3, 134.1, 130.7, 130.6, 130.4, 130.2, 130.0, 129.9, 128.9, 128.1, 127.3, 127.0, 126.6, 124.0, 120.7, 117.6, 114.9, 61.2, 54.7, 21.7, 14.5 ppm. **HRMS:** m/z calcd for $C_{25}H_{23}NO_4SNa$ $[M + Na]^+$, 383.0956; found, 383.0952.

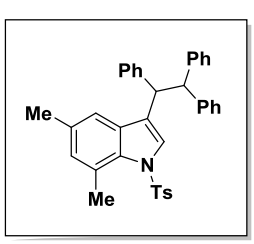
4.4.3. Representative Experimental Procedure for the Synthesis and Characterization Data of 4a-4g:

1-Tosyl-3-(1,2,2-triphenylethyl)-1*H*-indole (4a): In an oven-dried round-bottom flask, (*Z*)-3-benzylidene-1-tosylindoline (**2a**) (50 mg, 0.13 mmol) and diphenylmethanol (**3a**) (24 mg, 0.13 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.25 mg, 0.013 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4a** (60 mg, 0.11 mmol, 89%) as a white solid, m.p. 152-154 ^oC. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.82 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.37 – 7.33 (m, 3H), 7.31 (d, *J* = 9.5 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.21 (s, 1H), 7.19 – 7.12 (m, 2H), 7.12 – 6.98 (m, 13H), 4.90 (dd, *J* = 12.0, 1.1 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 2.33 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 144.4, 143.6, 143.1, 141.5, 135.1, 135.0, 130.9, 129.8, 128.75, 128.73, 128.6, 128.5, 128.2, 128.2, 128.1, 127.7, 126.7, 126.4, 126.2, 124.9, 124.7, 124.6, 123.2, 119.9, 113.7, 57.3, 47.4, 21.7 ppm. **HRMS:** m/z calcd for $C_{35}H_{29}NO_2SNa$ $[M + Na]^+$, 550.1817; found, 550.1818.



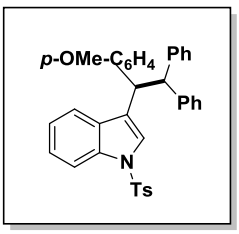
5-Chloro-1-tosyl-3-(1,2,2-triphenylethyl)-1*H*-indole (4b): Substrate **2b** (40 mg, 

0.10 mmol) and diphenylmethanol (**3a**) (18.5 mg, 0.10 mmol) were taken in dry nitromethane (1.5 mL) and $FeCl_3$ (1.62 mg, 0.010 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4b** (43 mg, 0.078 mmol, 78%) as a white solid, m.p. 156-158 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.73 (d, *J* = 8.8 Hz, 1H), 7.38 (s, 1H), 7.36 – 7.28 (m, 2H), 7.27 – 7.25 (m, 1H), 7.22 (d, *J* = 8.2 Hz, 5H), 7.14 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.06 (dddd, *J* = 15.9, 8.6, 6.6, 3.8 Hz, 12H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 2.35 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.7, 143.4, 142.8, 141.0, 134.7, 133.4, 132.2, 129.9, 128.8, 128.6, 128.5, 128.3, 128.1, 126.6, 126.3, 126.2, 124.9, 119.6, 114.7, 57.3, 47.3, 21.7 ppm. **HRMS**: m/z calcd for $C_{35}H_{28}ClNO_2SNa$ $[M + Na]^+$, 584.1427; found, 584.1426.

5,7-Dimethyl-1-tosyl-3-(1,2,2-triphenylethyl)-1*H*-indole (4c): Substrate **2c** (58 mg, 

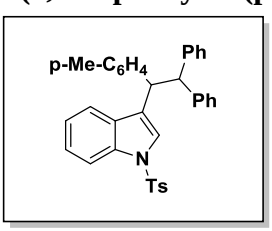
0.13 mmol) and diphenylmethanol (**3a**) (23.8 mg, 0.13 mmol) were taken in nitromethane (2 mL) and $FeCl_3$ (2.11 mg, 0.013 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4c** (64 mg, 0.11 mmol, 89%) as a white solid, m.p. 236-238 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.64 (s, 1H), 7.49 – 7.41 (m, 2H), 7.29 (dd, *J* = 8.5, 6.3 Hz, 2H), 7.25 – 7.19 (m, 1H), 7.11 (d, *J* = 6.8 Hz, 9H), 7.09 – 7.02 (m, 6H), 6.78 (s, 1H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 2.54 (s, 3H), 2.36 (s, 3H), 2.30 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.1, 143.8, 143.3, 141.6, 136.8, 133.3, 133.1, 129.9, 129.8, 128.7, 128.7, 128.5, 128.4, 128.2, 128.1, 126.4, 126.3, 126.2, 124.7, 117.4, 57.4, 47.2, 21.7, 21.6, 21.1 ppm. **HRMS:** m/z calcd for $C_{37}H_{33}NO_2SNa$ $[M + Na]^+$, 578.2130; found, 578.2132.

3-(1-(4-Methoxyphenyl)-2,2-diphenylethyl)-1-tosyl-1*H*-indole (4d): Substrate **2d**



(58 mg, 0.15 mmol) and diphenylmethanol (**3a**) (27 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was then purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4d** (63 mg, 0.11 mmol, 75%) as a white solid, m.p. 178-180 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 3H), 7.34 – 7.29 (m, 3H), 7.23 – 7.16 (m, 5H), 7.10 – 7.07 (m, 4H), 7.06 – 7.01 (m, 3H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 3.66 (s, 3H), 2.32 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.0, 144.4, 138.9, 135.1, 135.1, 134.4, 133.6, 130.7, 129.8, 129.6, 128.7, 128.6, 128.3, 128.2, 126.7, 126.2, 126.1, 124.8, 124.6, 123.2, 120.0, 113.7, 113.5, 57.4, 55.2, 46.5, 21.7 ppm. **HRMS:** m/z calcd for $C_{36}H_{31}NO_3SNa$: $[M + Na]^+$, 580.1923; found, 580.1925.

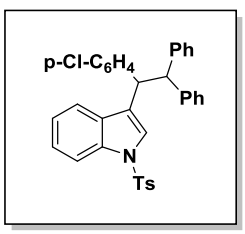
3-(2,2-Diphenyl-1-(p-tolyl)ethyl)-1-tosyl-1*H*-indole (4e): Substrate **2e** (56 mg, 0.15



mmol) and diphenylmethanol (**3a**) (27 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4e** (60 mg, 0.11 mmol, 74%) as a yellow gummy liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.34 – 7.27 (m, 4H), 7.25 (s, 2H), 7.23 – 7.18 (m, 2H), 7.16 (d, *J* = 7.0 Hz, 3H), 7.10 – 6.98 (m, 6H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 2H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 2.31 (s, 3H), 2.15 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.4 , 143.8 , 143.6 , 138.4 , 135.8 , 135.1 , 129.8 , 128.8 , 128.7 , 128.5 , 128.23 , 128.2 , 127.7 , 127.5 , 126.7 ,

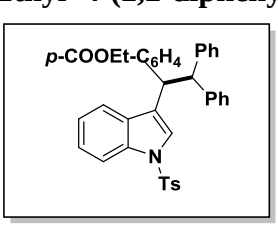
126.1 , 124.8 , 124.6 , 123.2 , 119.9 , 113.7 , 57.2 , 46.9 , 21.7 , 21.1 ppm. **HRMS:** m/z calcd for $C_{36}H_{31}NO_2SNa$ $[M + Na]^+$, 564.1973; found, 564.1974.

3-(1-(4-Chlorophenyl)-2,2-diphenylethyl)-1-tosyl-1*H*-indole (4f): Substrate **2f** (59



mg, 0.15 mmol) and diphenylmethanol (**3a**) (27 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4f** (56 mg, 0.10 mmol, 67%) as a yellowish semi solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.39 – 7.27 (m, 4H), 7.28 – 7.20 (m, 2H), 7.21 (d, *J* = 6.0 Hz, 2H), 7.17 (dt, *J* = 5.0, 3.0 Hz, 4H), 7.07 (dd, *J* = 7.8, 2.4 Hz, 2H), 7.04 (s, 1H), 7.02 – 6.96 (m, 5H), 6.92 (d, *J* = 8.2 Hz, 2H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 2.30 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.5, 143.3, 142.8, 140.2, 129.9, 129.8, 128.8, 128.6, 128.5, 128.4, 128.3, 128.1, 126.7, 126.4, 126.3, 125.1, 124.8, 123.2, 119.8, 113.8, 57.2, 46.8, 21.7 ppm. **HRMS**: m/z calcd for $C_{35}H_{28}ClNO_2SNa$: $[M + Na]^+$, 584.1427; found, 584.1430.

Ethyl 4-(2,2-diphenyl-1-(1-tosyl-1*H*-indol-3-yl)ethyl)benzoate (4g): Substrate **2g**

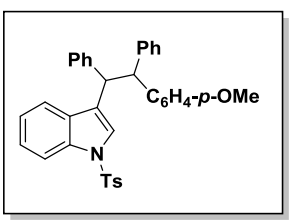


(65 mg, 0.15 mmol) and diphenylmethanol (**3a**) (27 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4g** (53 mg, 0.08 mmol, 59%) as a white solid, m.p. 200-202 ^oC. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 8.4 Hz, 1H), 7.71 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.38 – 7.29 (m, 3H), 7.23 (dt, *J* = 8.6, 1.5 Hz, 5H), 7.20 – 7.14 (m, 4H), 7.11 – 7.07 (m, 2H), 7.06 – 7.04 (m, 3H), 7.03 – 6.98 (m, 3H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.5, 146.9, 144.5, 143.2, 142.6, 135.1, 134.9, 130.6, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 128.9, 128.8, 128.7, 128.6, 128.4, 128.1,

127.4, 126.7, 126.4, 126.4, 126.3, 125.1, 124.7, 123.9, 123.3, 119.7, 113.7, 60.9, 56.9, 47.4, 21.6, 14.4 ppm. **HRMS:** m/z calcd for $C_{38}H_{33}NO_4SNa$: $[M + Na]^+$, 622.2028; found, 622.2028.

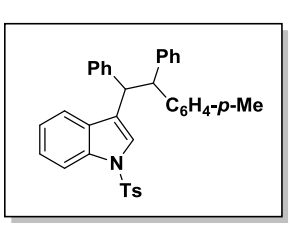
4.4.4. Representative Experimental Procedure for the Synthesis and Characterization Data of 4h-4o:

3-(2-(4-Methoxyphenyl)-1,2-diphenylethyl)-1-tosyl-1*H*-indole (4h): Substrate **2a**



(54 mg, 0.15 mmol) and (4-methoxyphenyl)(phenyl)methanol (**3b**) (32 mg, 0.15 mmol) were taken in dry nitromethane (1.5 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporatedafter completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4h** (63 mg, 0.11 mmol, 76% yield, 1:2.5 dr) as a white solid, m.p. 152-154 ^oC. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.82-7.85 (m, 1H), 7.38 (s, 1H), 7.33-7.34 (m, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 7.25 (s, 2H), 7.16-7.23 (m, 5H), 6.99-7.11 (m, 17H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 1H), 4.84 (dd, *J* = 12.0, 1.2 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 3.77 (s, 3H), 3.68 (s, 1H), 2.33 (s, 4H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$) δ** 157.9 , 143.5 , 141.5 , 135.8 , 135.1 , 134.9 , 130.9 , 129.8 , 129.7 , 129.4 , 129.0 , 128.75 , 128.72 , 128.4 , 128.2 , 128.17 , 128.1 , 128.07 , 126.7 , 126.4 , 126.1 , 126.0 , 124.9 , 124.8 , 124.6 , 123.2 , 123.17 , 119.9 , 114.2 , 113.7 , 113.6 , 56.4 , 55.2 , 47.6 , 47.5 , 21.7 ppm. **HRMS**: m/z calcd for $C_{36}H_{31}NO_3SNa$ $[M + Na]^+$, 580.1923; found, 580.1921.

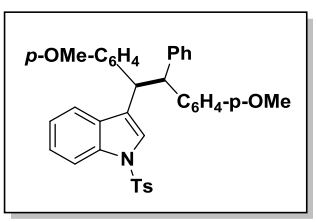
3-(1,2-Diphenyl-2-(p-tolyl)ethyl)-1-tosyl-1*H*-indole (4i): Substrate **2a** (54 mg, 0.15



mmol) and phenyl(p-tolyl)methanol (**3c**) (30 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the

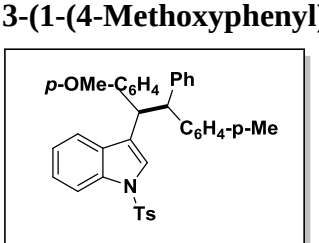
desired product **4i** (58 mg, 0.11 mmol, 72% yield, 1:8 dr) as a white crystalline solid, m.p. 180-182 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.28-7.31 (m, 2H), 7.18-7.24 (m, 4H), 7.12-7.16 (m, 2H), 6.97-7.06 (m, 15H), 6.87 (d, *J* = 5.2 Hz, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 2.29 (s, 6H), 2.16 (s, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.4, 143.4, 141.7, 140.6, 135.4, 135.1, 129.7, 129.4, 128.7, 128.5, 128.2, 128.1, 128.0, 126.7, 124.9, 119.9, 113.7, 56.9, 56.8, 47.42, 47.35, 21.72, 21.69, 21.3, 21.1 ppm. **HRMS**: m/z calcd for $C_{36}H_{31}NO_2SNa$ $[M + Na]^+$, 564.1973; found, 564.1970.

3-(1,2-bis(4-Methoxyphenyl)-2-phenylethyl)-1-tosyl-1*H*-indole (4j): Substrate **2d**



(58 mg, 0.15 mmol) and (4-methoxyphenyl)(phenyl)methanol (**3b**) (32 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was then purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4j** (70 mg, 0.12 mmol, 81% yield, 1:3 dr) as a white solid, m.p. 168-170 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 24.9 Hz, 5H), 7.25 (dd, *J* = 8.4, 3.5 Hz, 4H), 7.20 (s, 1H), 7.13 – 7.05 (m, 7H), 7.05 – 7.00 (m, 3H), 6.93 (d, *J* = 8.4 Hz, 3H), 6.75 (d, *J* = 8.3 Hz, 3H), 6.60 (d, *J* = 8.3 Hz, 3H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 3.80 (s, 4H), 3.69 (s, 4H), 2.35 (s, 4H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.0, 157.9, 144.5, 143.6, 138.9, 136.0, 135.1, 135.0, 133.7, 131.0, 130.7, 129.8, 129.6, 129.0, 128.4, 128.2, 126.7, 126.1, 125.1, 124.8, 124.6, 123.2, 119.9, 114.2, 113.7, 113.5, 56.6, 55.2, 46.8, 31.0, 21.7 ppm. **HRMS**: m/z calcd for $C_{37}H_{33}NO_4SNa$ $[M + Na]^+$, 610.2028; found, 610.2026.

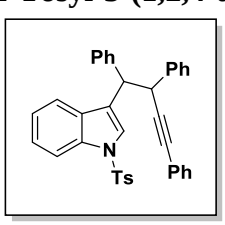
3-(1-(4-Methoxyphenyl)-2-phenyl-2-(p-tolyl)ethyl)-1-tosyl-1*H*-indole (4k):



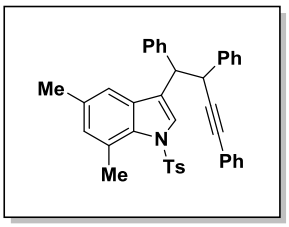
Substrate **2d** (58 mg, 0.15 mmol) and phenyl(p-tolyl)methanol (**3c**) (30 mg, 0.15 mmol) were taken in nitromethane (2.0 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column

chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4k** (72 mg, 0.13 mmol, 85% yield, 1:4.5 dr) as a white solid, m.p. 100-102 ^{o}C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.27-7.34 (m, 4H), 7.23 (d, *J* = 2.1 Hz, 2H), 7.20 (t, *J* = 2.1 Hz, 2H), 7.14-7.18 (m, 3H), 7.04-7.09 (m, 3H), 6.99-7.03 (m, 5H), 6.89-6.95 (m, 5H), 6.58 (dd, *J* = 8.7, 6.9 Hz, 3H), 4.82 (dd, *J* = 12.0, 3.0 Hz ,1H), 4.59 (dd, *J* = 12.0, 2.4 Hz, 1H), 3.66 (d, *J* = 4.2 Hz, 3H), 3.560 (s, 1H), 2.32 (s, 6H), 2.19 (s, 1H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 157.9, 144.3, 144.1, 143.6, 140.8, 140.2, 135.6, 135.4, 135.2, 135.1, 133.8, 133.7, 131.0, 130.9, 129.8, 129.7, 129.6, 129.4, 128.9, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 126.7, 126.6, 126.1, 126.0, 124.8, 124.5, 123.2, 123.1, 120.0, 113.7, 113.6, 113.5, 57.1, 56.9, 55.6, 55.2, 46.5, 46.5, 21.7, 21.6, 21.3, 21.1 ppm. **HRMS**: m/z calcd for $C_{37}H_{33}NO_3SNa$ $[M + Na]^+$, 594.2079; found, 594.2076.

1-Tosyl-3-(1,2,4-triphenylbut-3-yn-1-yl)-1*H*-indole (4l): Substrate **2a** (54 mg, 0.15 mmol) and 1,3-diphenylprop-2-yn-1-ol (**3d**) (31mg, 0.15mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4l** (78 mg, 0.14 mmol, 95% yield, 1:1.3 dr) as yellow gummy liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.93-8.02 (m, 3H), 7.64 (dd, J_1 = 5.2 Hz, J_2 = 8.0 Hz, 3H), 7.39-7.42 (m, 1H), 7.32-7.35 (m, 6H), 7.25-7.27 (m, 4H), 7.19-7.24 (m, 5H), 7.12-7.17 (m, 6H), 6.97-7.06 (m, 6H), 6.87 (d, J = 8.4 Hz, 1H), 4.79 (d, J = 5.6 Hz, 1H), 4.56 (q, J = 8.4 Hz, 1H), 4.49 (d, J = 5.6 Hz, 1H), 2.318 (s, 2H), 2.239 (s, 2H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.7, 144.5, 140.9, 140.0, 139.9, 138.8, 135.4, 135.3, 131.8, 131.7, 129.8, 129.7, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 127.2, 127.1, 127.0, 126.9, 126.9, 126.8, 124.8, 124.6, 124.5, 123.2, 123.1, 120.2, 120.1, 113.9, 113.7, 90.4, 89.4, 86.9, 85.5, 50.2, 49.8, 44.4, 43.4, 21.7, 21.6 ppm. **HRMS**: m/z calcd for $C_{37}H_{29}NO_2SNa$ $[M + Na]^+$, 574.1817; found, 574.1815.

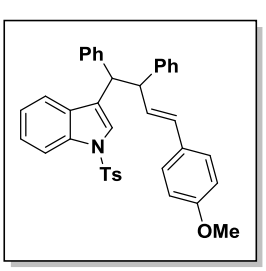


5,7-Dimethyl-1-tosyl-3-(1,2,4-triphenylbut-3-yn-1-yl)-1*H*-indole (4m):Substrate **2c** (58 mg, 0.15 mmol) and 1,3-diphenylprop-2-yn-1-ol (**3d**) (31mg, 0.15mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the



mixture under an Ar atmosphere and stirred for 2 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4m** (79 mg, 0.13 mmol, 91% yield, 1:1.5 dr) as a yellow semi solid. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.19 (s, 2H), 8.12 (d, *J* = 1.1 Hz, 1H), 7.48 – 7.43 (m, 6H), 7.43 – 7.39 (m, 5H), 7.37 – 7.34 (m, 7H), 7.33 – 7.29 (m, 6H), 7.29 – 7.27 (m, 2H), 7.26 (s, 1H), 7.25 – 7.19 (m, 3H), 7.19 – 7.12 (m, 9H), 7.02 – 6.94 (m, 4H), 6.91 (d, *J* = 8.1 Hz, 3H), 6.86 – 6.77 (m, 4H), 6.71 (s, 1H), 4.77 (d, *J* = 5.5 Hz, 1H), 4.61 – 4.56 (m, 3H), 4.46 (d, *J* = 5.5 Hz, 1H), 2.64 (s, 3H), 2.58 (s, 5H), 2.35 (s, 3H), 2.28 (s, 4H), 2.22 (d, *J* = 3.4 Hz, 8H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 144.2, 144.1, 141.0, 140.0, 138.9, 136.7, 136.1, 133.9, 133.7, 133.5, 133.4, 133.2, 131.8, 131.7, 130.0, 129.8, 129.7, 129.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.6, 127.2, 127.0, 126.9, 126.7, 126.5, 125.8, 124.9, 124.8, 123.7, 123.6, 122.4, 117.7, 117.6, 90.5, 89.6, 86.9, 85.6, 50.0, 49.7, 44.6, 43.5, 21.8, 21.7, 21.6, 21.5, 21.1, 21.0 ppm. **HRMS:** m/z calcd for $C_{39}H_{33}NO_2SNa$ $[M + Na]^+$, 602.2130; found, 602.2127.

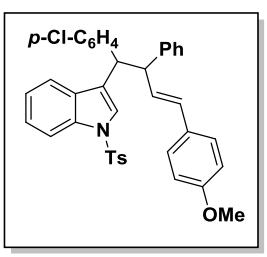
1-Tosyl-3-(1,2,4-triphenylbut-3-en-1-yl)-1*H*-indole (4n): Substrate **2a** (54 mg, 0.15



mmol) and 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-ol (**3e**) (36 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 4 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4n** (58 mg, 0.10 mmol, 67% yield, 1:1.1 dr) as pale yellow solid, m.p. 182-184 ^{o}C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.91 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.82 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.72 (dd, *J* = 2.6, 0.9 Hz, 1H), 7.51 (dd, *J* = 8.4, 3.9 Hz, 2H), 7.42 (d, *J* = 1.1 Hz, 1H), 7.34 (dt, *J* = 7.8, 1.0 Hz, 2H), 7.32 – 7.18 (m, 14H), 7.18 – 6.99 (m, 13H), 6.99 – 6.93 (m, 2H), 6.85 – 6.78 (m, 2H), 6.73 – 6.63 (m, 4H), 6.51 – 6.41 (m, 2H), 6.17 (dd, *J* = 15.8, 7.6 Hz, 1H), 6.06 – 5.97 (m, 1H), 4.50 (ddd, *J* = 29.0, 10.9, 1.1 Hz, 2H), 4.20 (td, *J* = 10.5, 7.4 Hz, 2H), 3.80 (s,

3H), 3.72 (s, 3H), 2.31 (s, 3H), 2.17 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 141.5, 137.6, 137.5, 135.25, 135.17, 135.1, 134.9, 133.0, 132.9, 131.2, 131.1, 131.0, 129.7, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 128.4, 128.36, 128.31, 128.15, 128.10, 127.6, 127.3, 127.2, 126.9, 126.8, 126.7, 126.4, 126.3, 126.2, 124.7, 124.6, 124.54, 124.52, 123.21, 123.17, 119.9, 114.3, 114.1, 113.84, 113.79, 113.7, 55.3, 55.2, 53.6, 53.1, 48.8, 47.9, 21.6, 21.5 ppm. **HRMS:** m/z calcd for $C_{38}H_{33}NO_3SNa$ $[M + Na]^+$, 606.2079; found, 606.2078 .

3-(1-(4-Chlorophenyl)-2,4-diphenylbut-3-en-1-yl)-1-tosyl-1*H*-indole (4o):



Substrate **2f** (59 mg, 0.15 mmol) and 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-ol (**3e**) (36 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $FeCl_3$ (2.43 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 4 h at room temperature. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (90:10 v/v), to afford the desired product **4o** (57 mg, 0.09 mmol, 62% yield, 1:1.5 dr) as white solid, m.p. 194-196 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.77 (s, 2H), 7.56 (d, *J* = 8.3 Hz, 3H), 7.51 – 7.44 (m, 1H), 7.40 – 7.11 (m, 23H), 7.12 – 7.05 (m, 5H), 7.04 – 6.95 (m, 6H), 6.93 – 6.81 (m, 2H), 6.80 – 6.75 (m, 3H), 6.72 (d, *J* = 8.1 Hz, 3H), 6.57 (d, *J* = 16.0 Hz, 2H), 6.47 (dd, *J* = 15.9, 8.0 Hz, 2H), 6.29 – 6.03 (m, 2H), 4.63 – 4.57 (m, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.27 – 4.21 (m, 1H), 4.20 – 4.16 (m, 1H), 3.86 (s, 3H), 3.80 (s, 4H), 2.37 (s, 3H), 2.23 (s, 4H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 158.2, 144.6, 140.2, 140.1, 137.4, 137.3, 135.2, 135.1, 134.9, 134.6, 132.7, 132.6, 132.3, 132.1, 131.4, 131.2, 130.9, 130.8, 130.3, 130.2, 129.9, 129.8, 129.7, 129.0, 128.9, 128.7, 128.6, 128.5, 128.3, 128.1, 127.0, 127.4, 126.8, 126.7, 126.4, 126.3, 124.9, 124.8, 124.7, 124.6, 124.1, 123.9, 123.3, 123.2, 119.8, 114.3, 114.0, 113.9, 113.8, 55.3, 55.2, 53.5, 53.1, 48.2, 47.3, 21.7, 21.6 ppm. **HRMS:** m/z calcd for $C_{38}H_{32}ClNO_3SNa$ $[M + Na]^+$, 640.1689; found, 640.1685.

4.4.5. Table for crystallographic data and structural refinement parameters for 4i

Empirical formula	$C_{36}H_{31}NO_2S$
Formula weight	541.70
Temperature/K	296(2)
Crystal system	orthorhombic
Space group	'P c a 21'
a/Å	17.139(7)
b/Å	14.435(6)
c/Å	11.970(5)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	2962(2)
Z	4
$\rho_{calc}g/cm^3$	1.228
μ/mm^{-1}	0.145
F(000)	1156
Crystal size/mm^3	.3 × .2 × .1
Radiation	MoKα (λ = 0.71073)
θ range/°	2.37 to 20.62
Index ranges	$-19 \leq h \leq 19, -16 \leq k \leq 16, -13 \leq l \leq 13$
Data/restraints/parameters	4758/1/363
Goodness-of-fit on F^2	0.904
Largest diff. peak/hole / e $Å^{-3}$	0.22/-0.26

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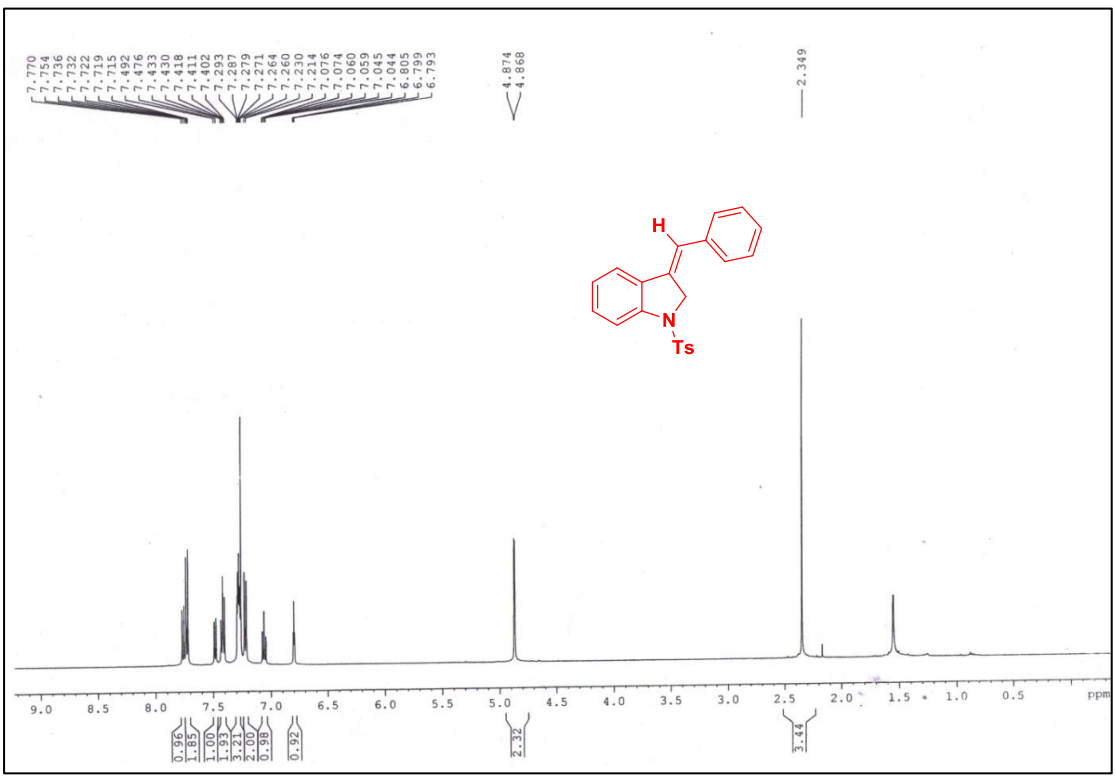
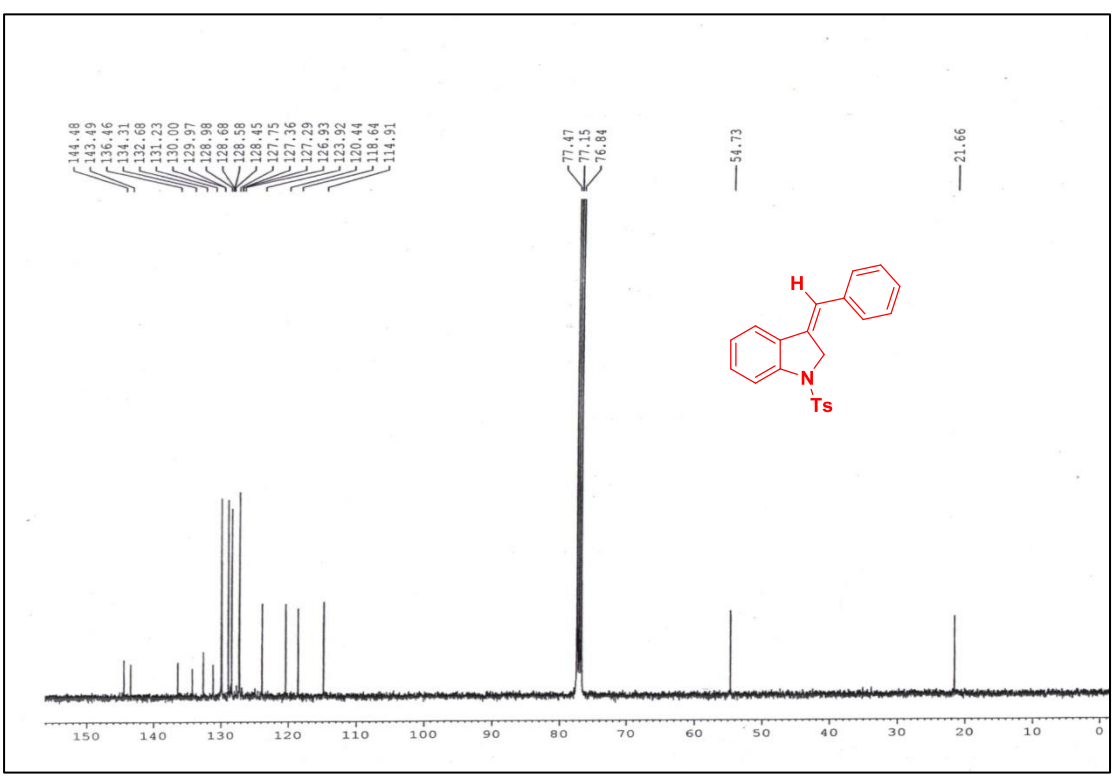
^{1}H and ^{13}C NMR SPECTRA

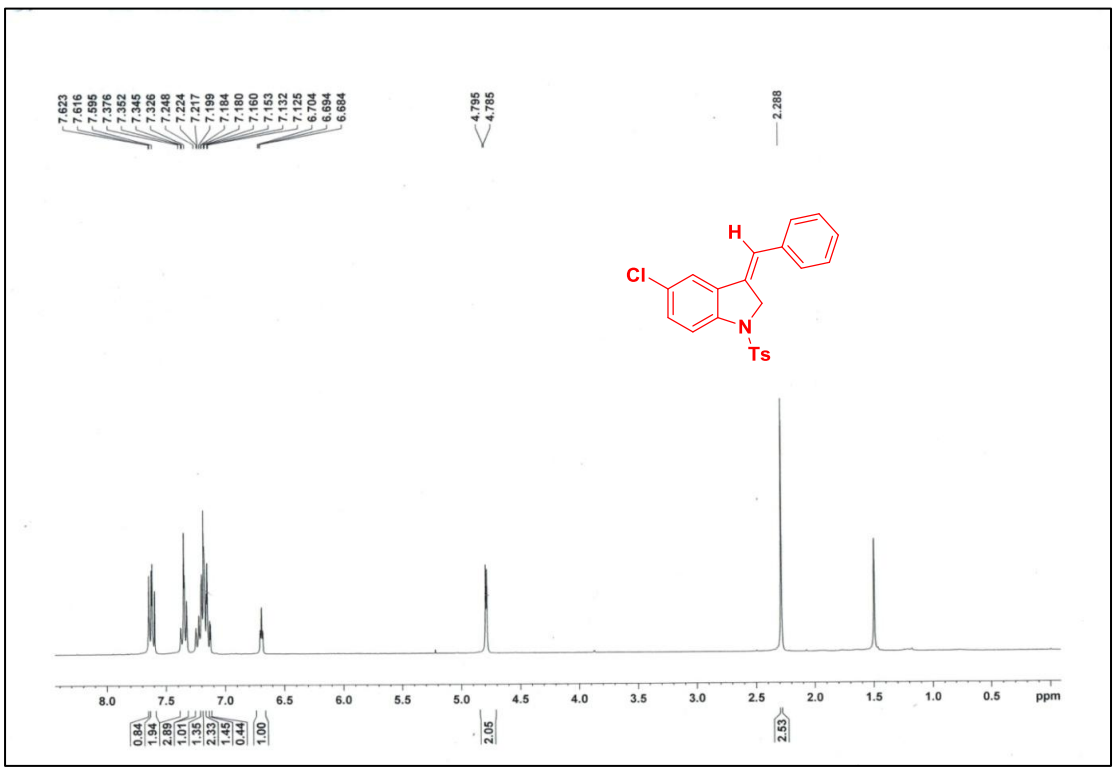
^{1}H NMR spectrum of compound **2a**, $CDCl_3$, 500 MHz



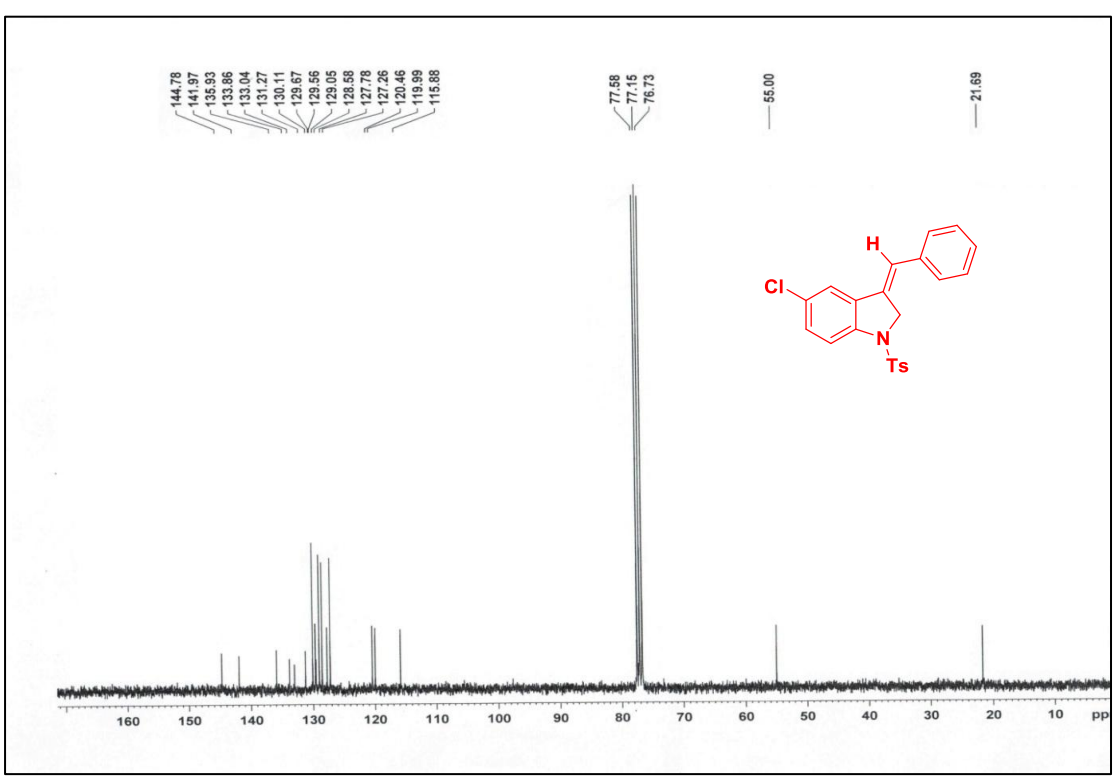
^{13}C NMR spectrum of compound **2a**, $CDCl_3$, 75 MHz



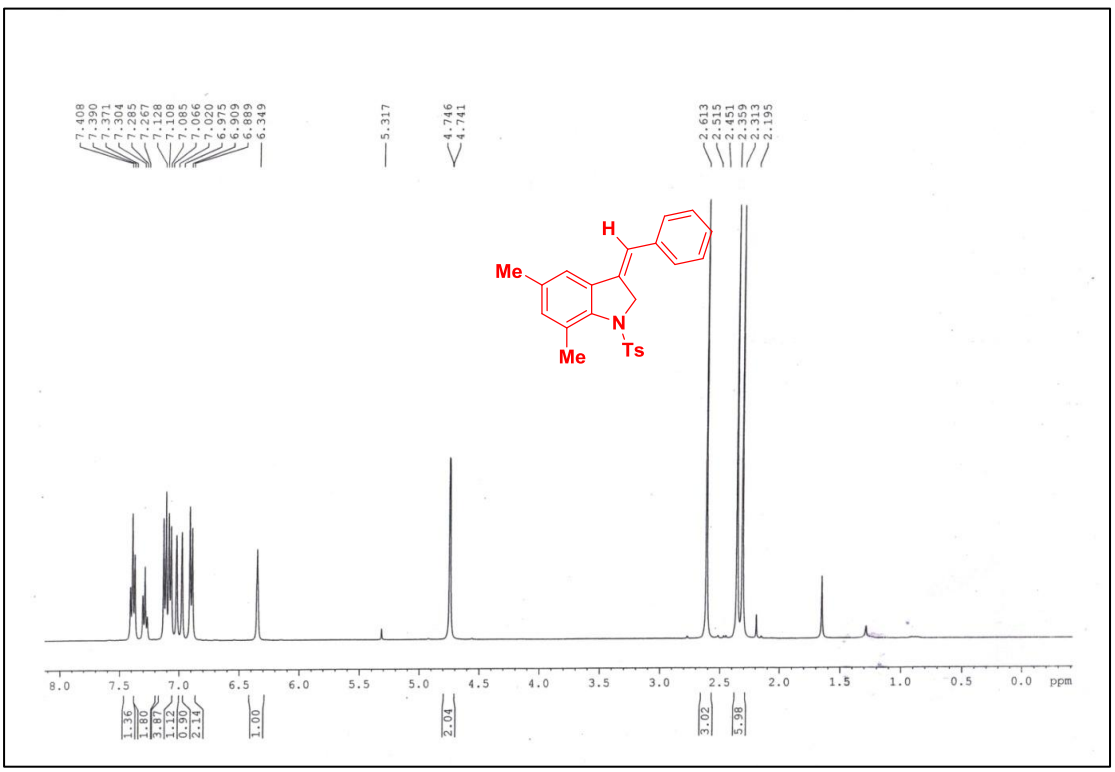
^{1}H NMR spectrum of compound **2b**, $CDCl_3$, 300 MHz



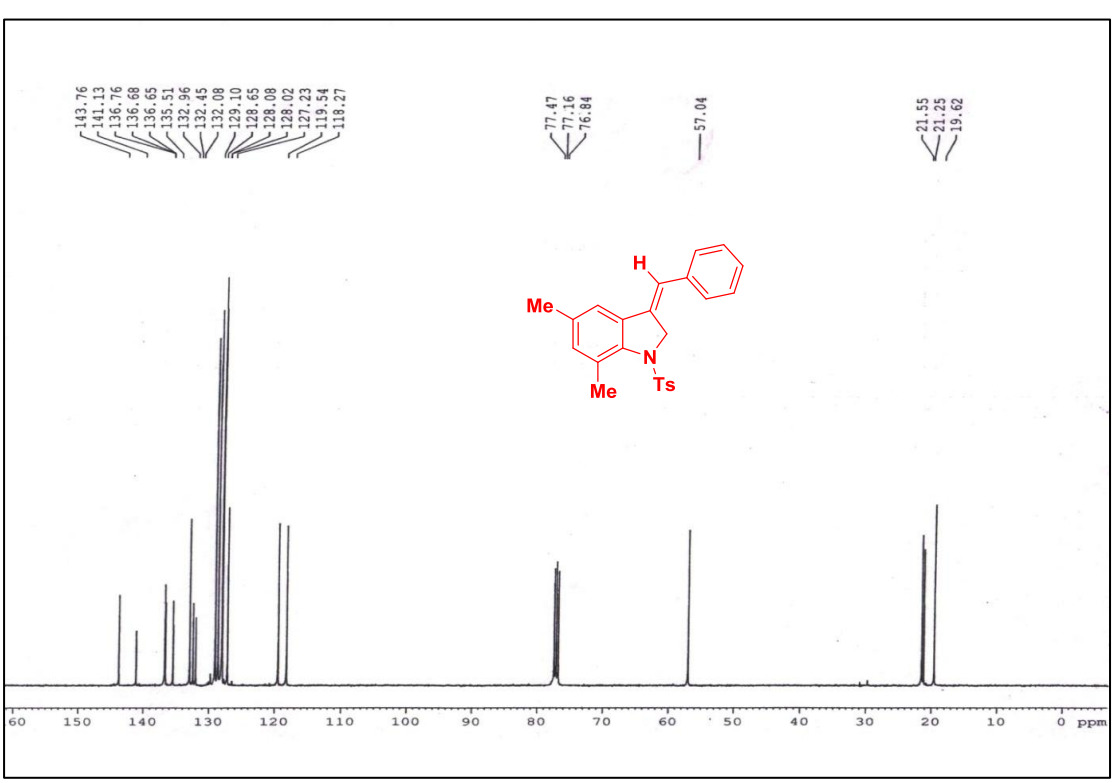
^{13}C NMR spectrum of compound **2b**, $CDCl_3$, 75 MHz



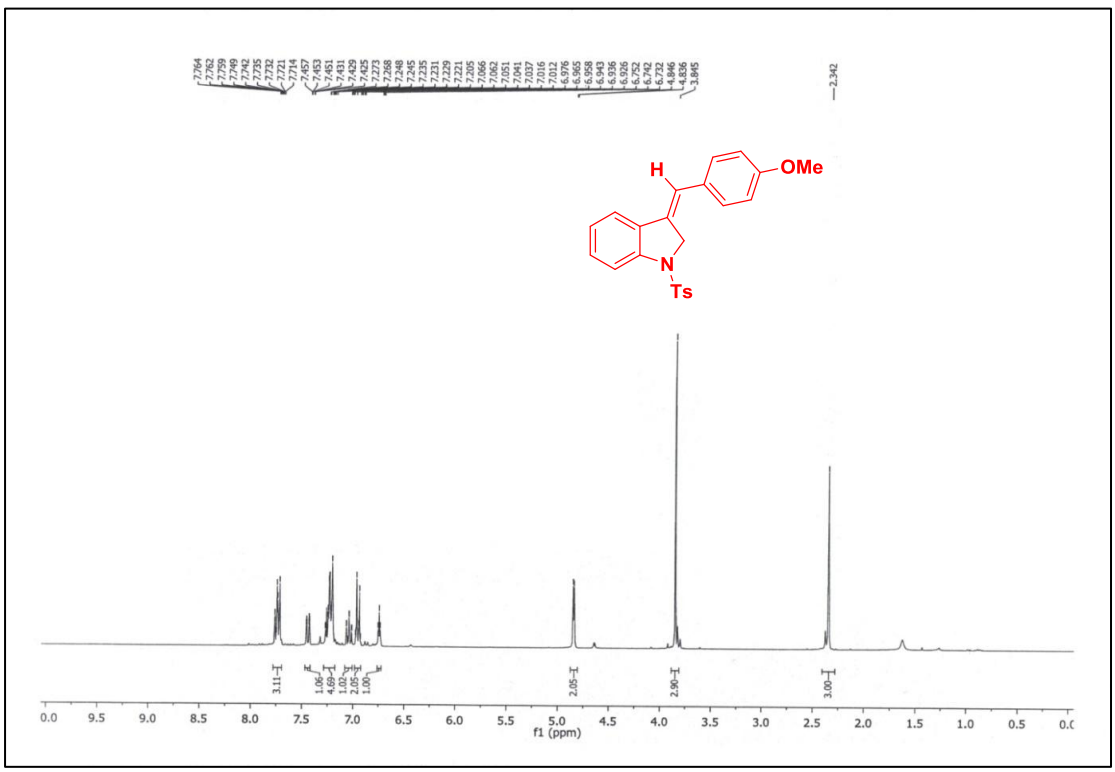
^{1}H NMR spectrum of compound **2c**, $CDCl_3$, 400 MHz



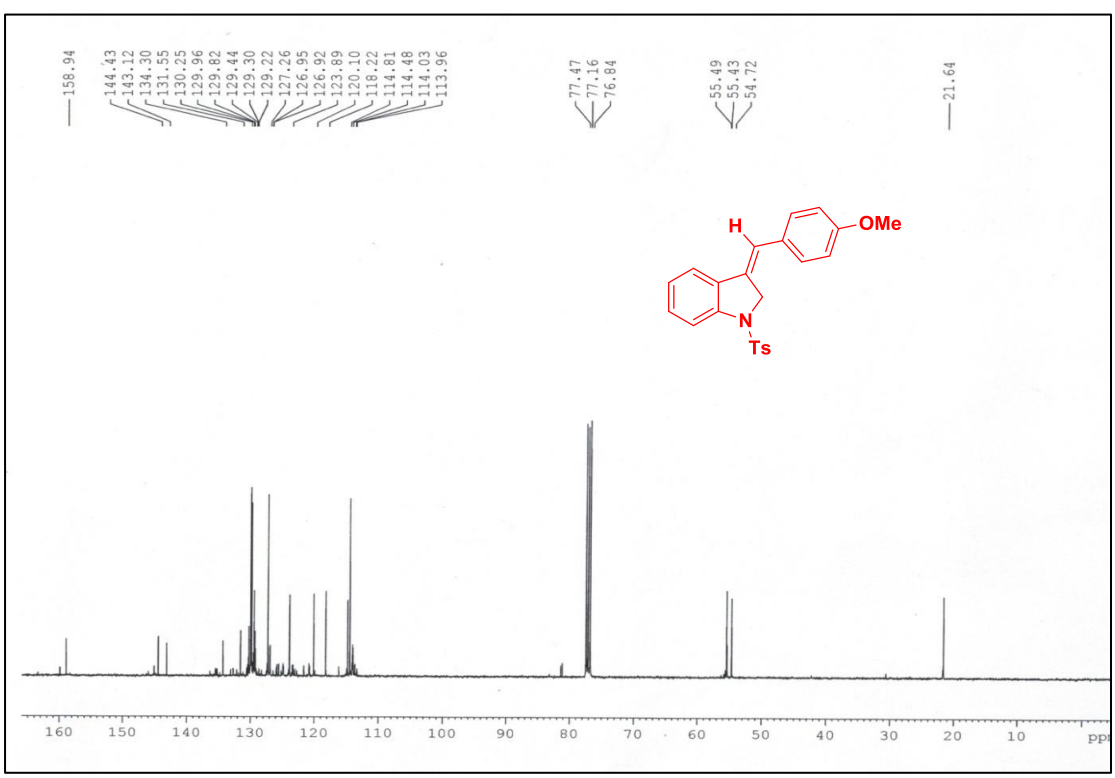
^{13}C NMR spectrum of compound **2c**, $CDCl_3$, 75 MHz



^{1}H NMR spectrum of compound **2d**, $CDCl_3$, 300 MHz



^{13}C NMR spectrum of compound **2d**, $CDCl_3$, 100 MHz



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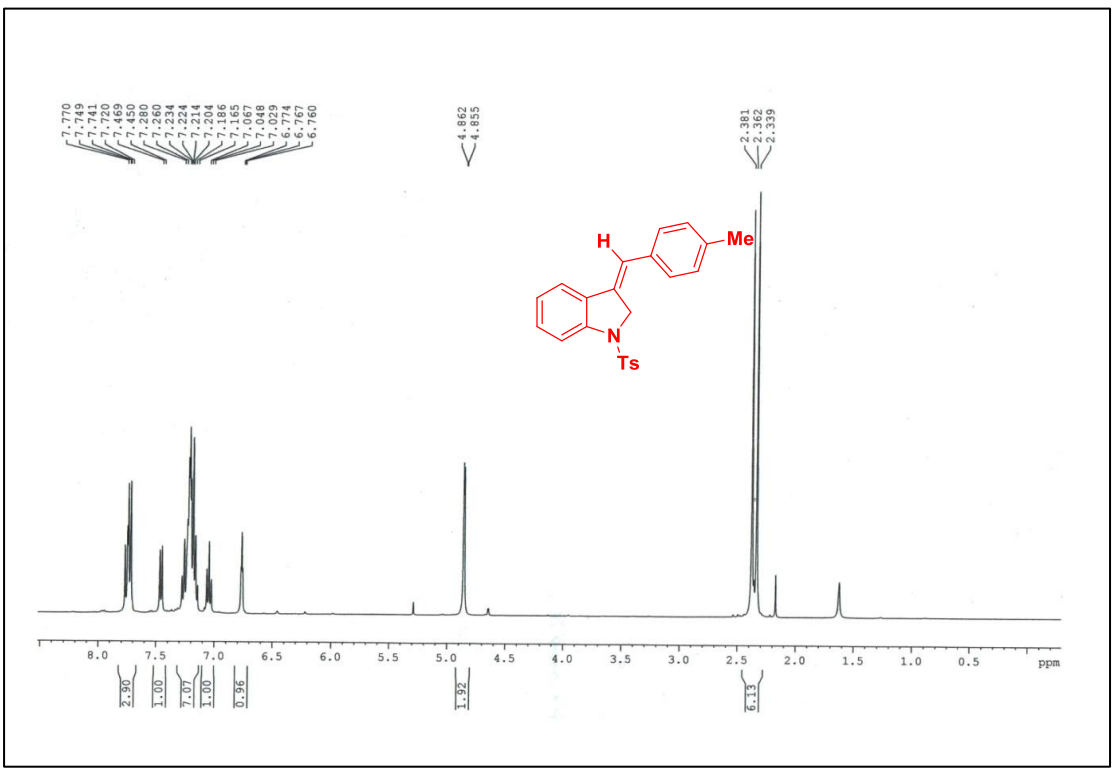

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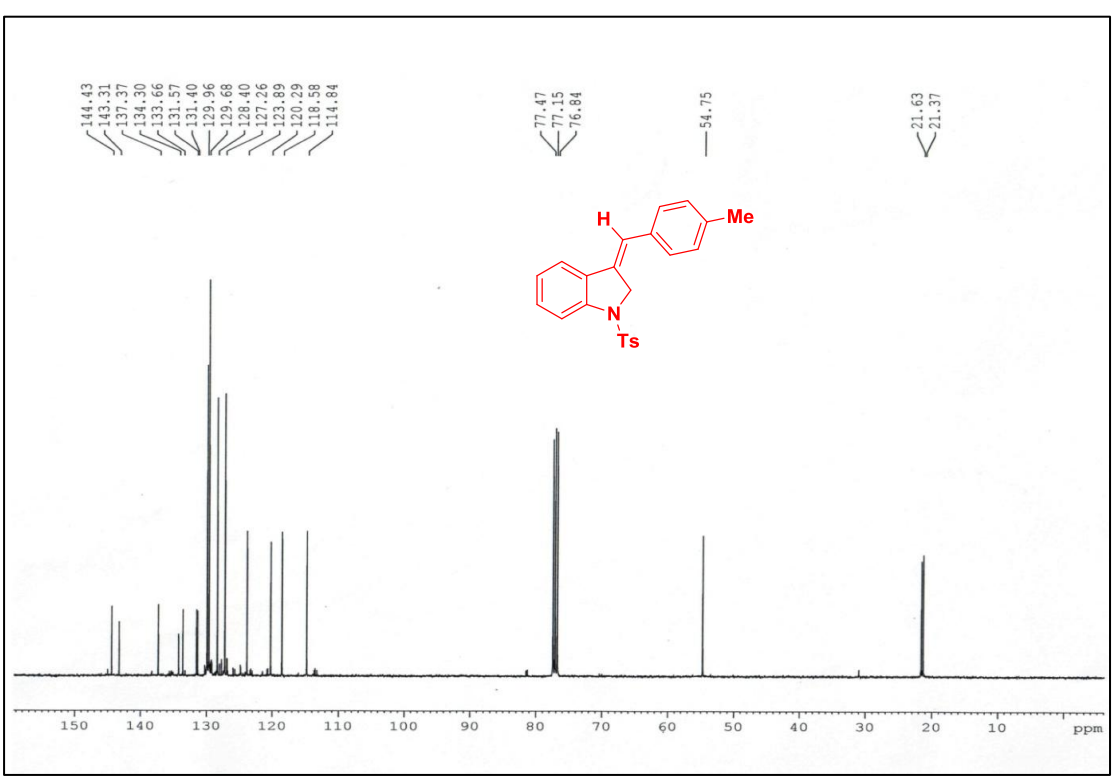

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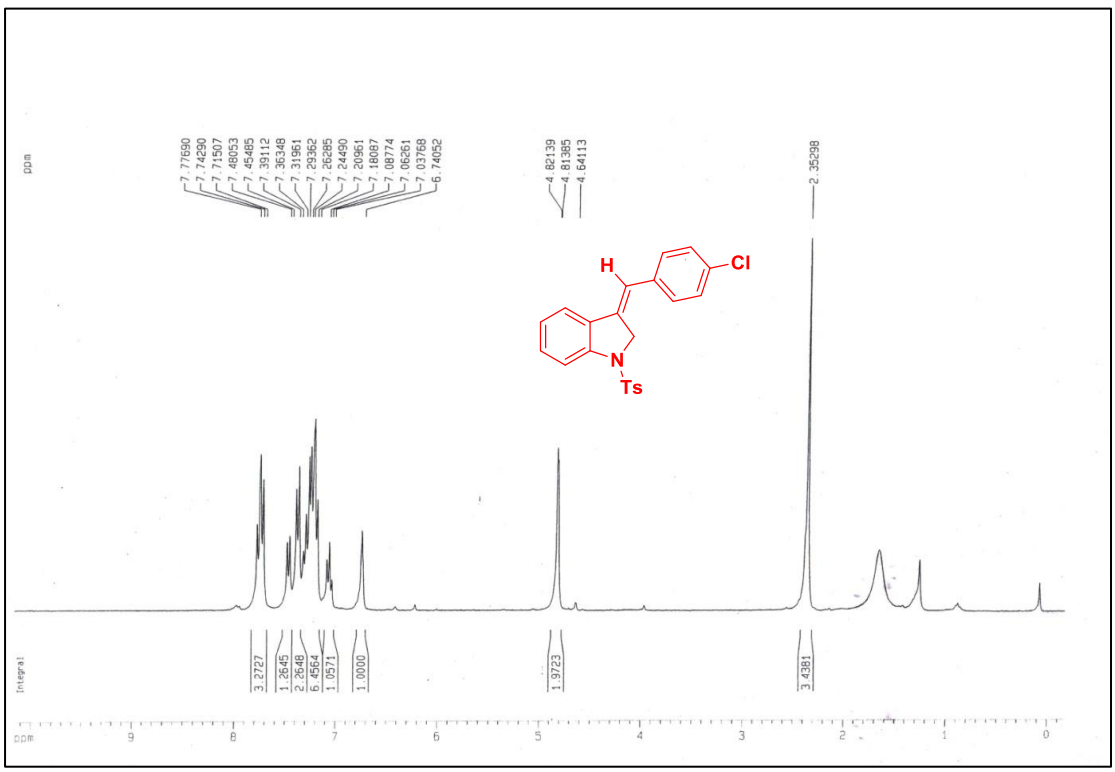
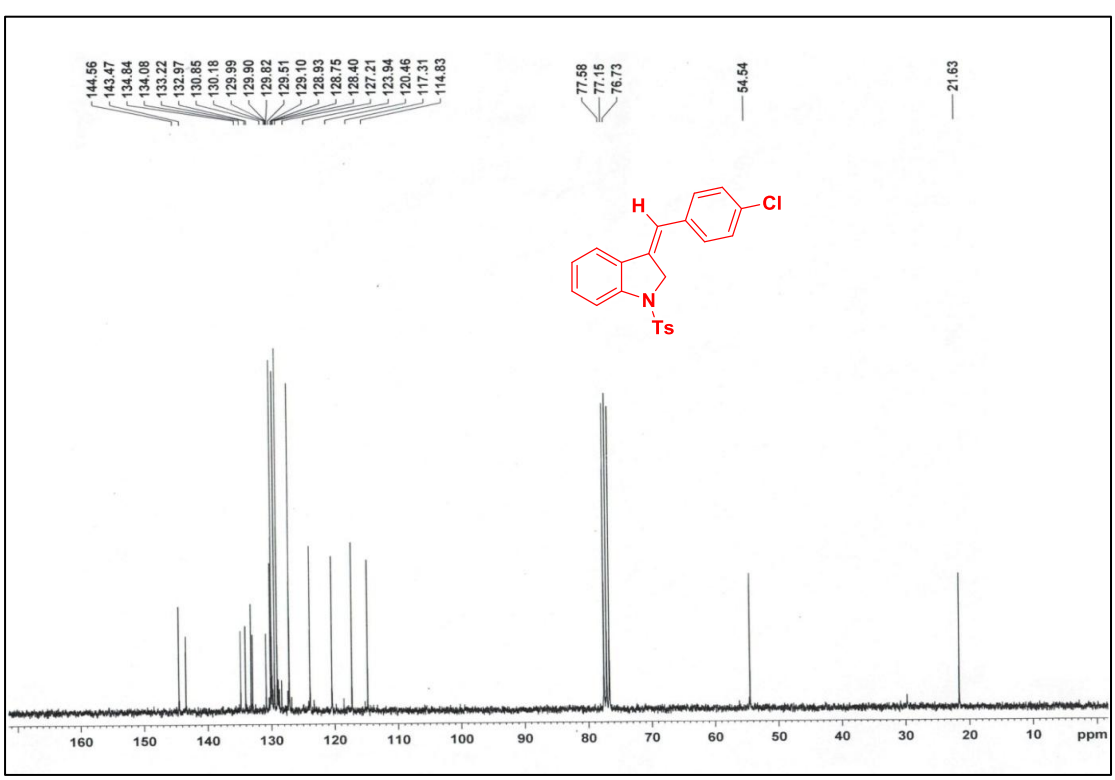
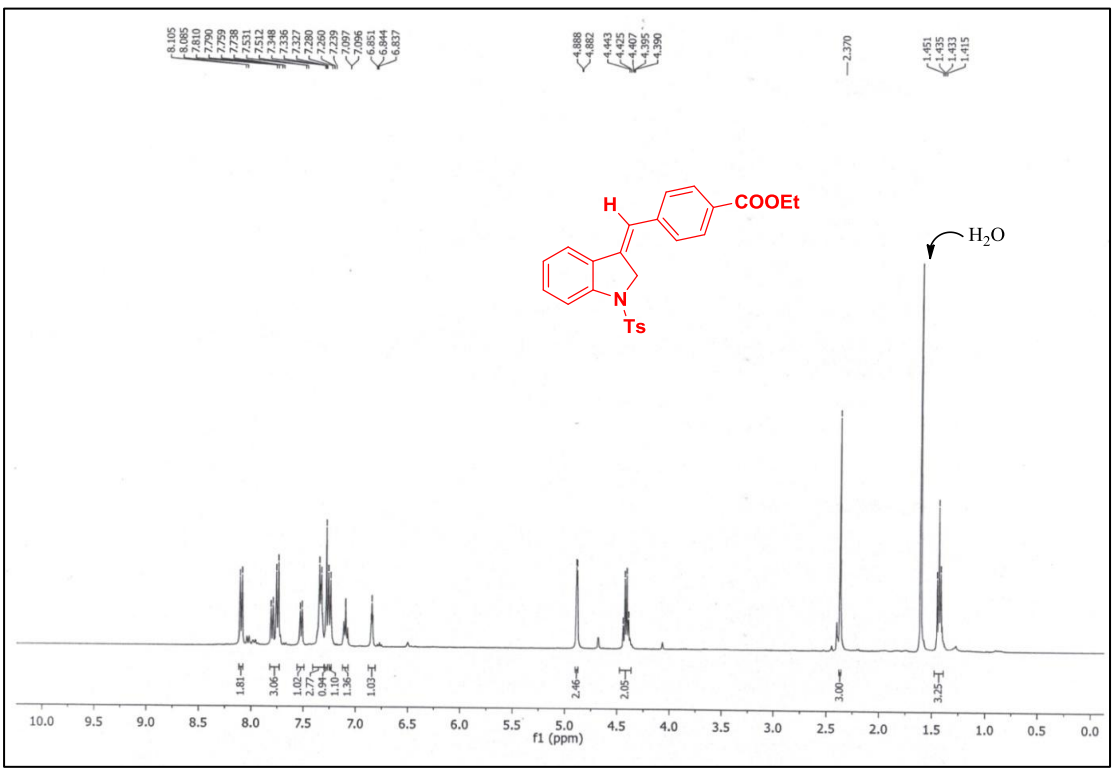


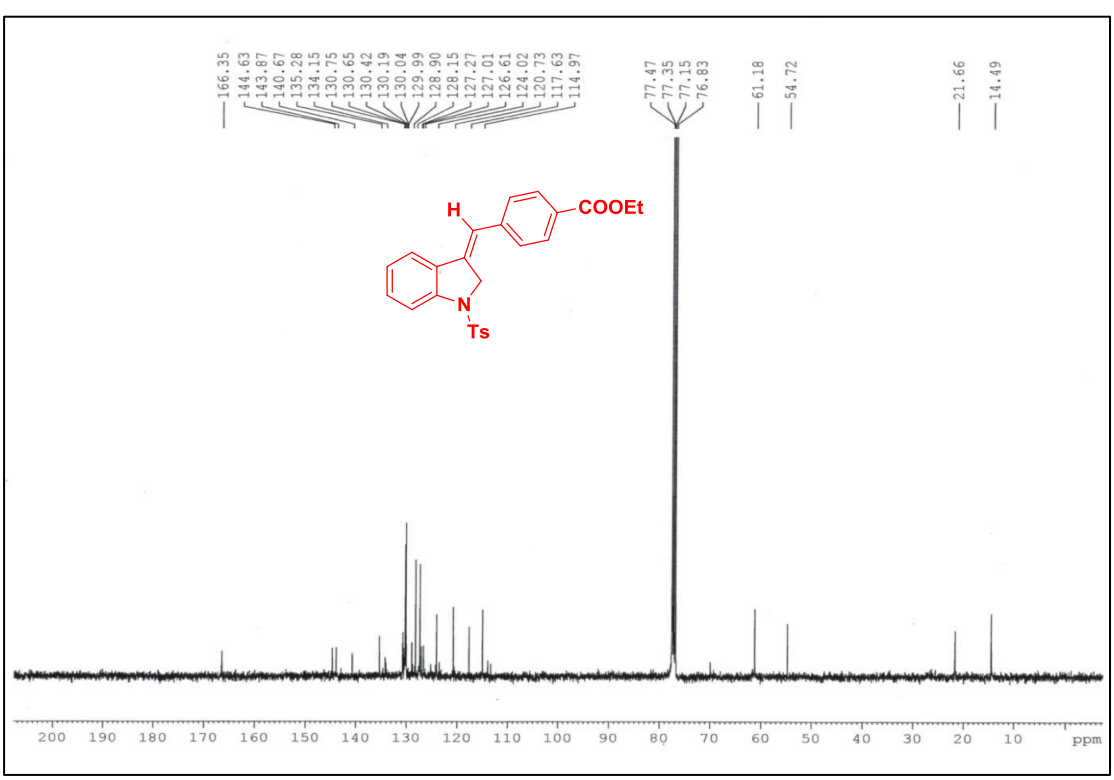
^{13}C NMR spectrum of compound **2f**, $CDCl_3$, 75 MHz



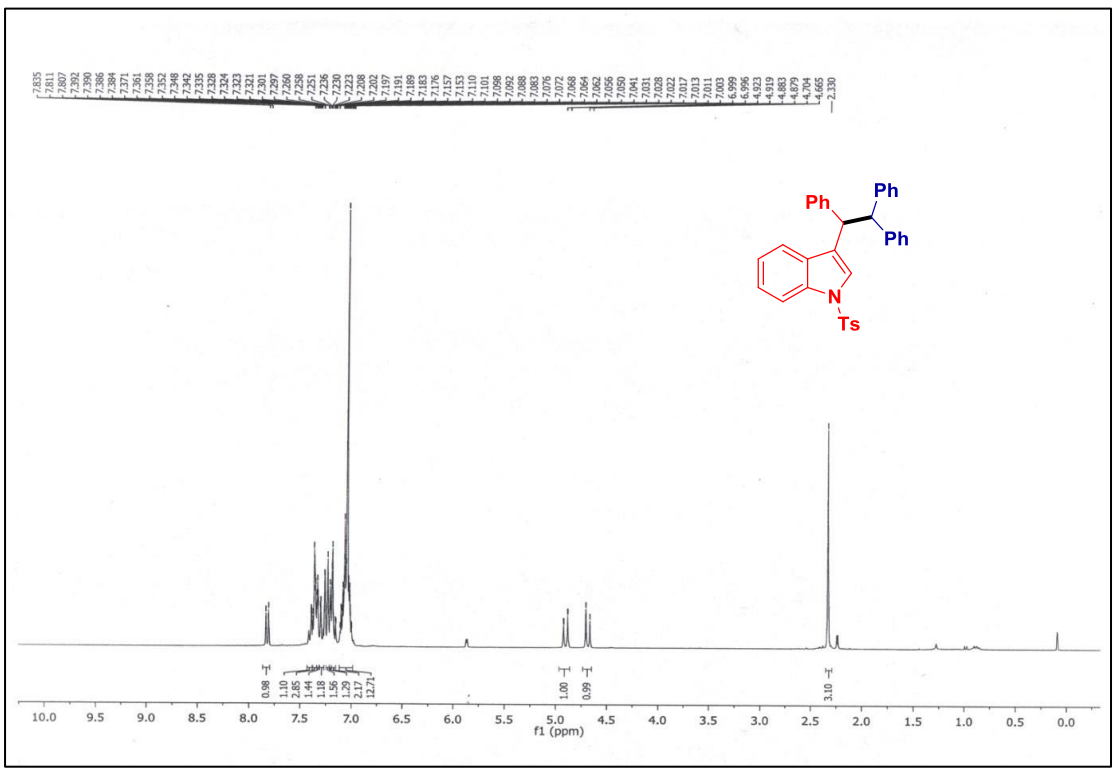
^{1}H NMR spectrum of compound **2g**, $CDCl_3$, 400 MHz



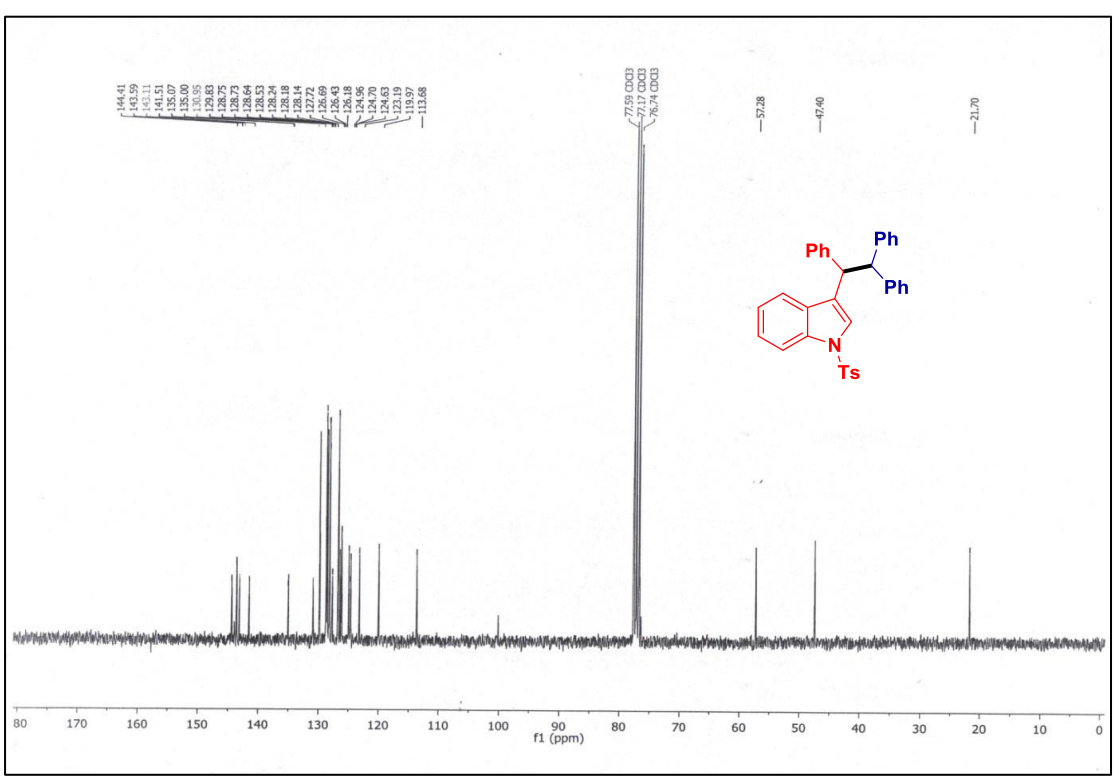
^{13}C NMR spectrum of compound **2g**, $CDCl_3$, 100 MHz



^{1}H NMR spectrum of compound **4a**, $CDCl_3$, 300 MHz



^{13}C NMR spectrum of compound **4a**, $CDCl_3$, 75 MHz



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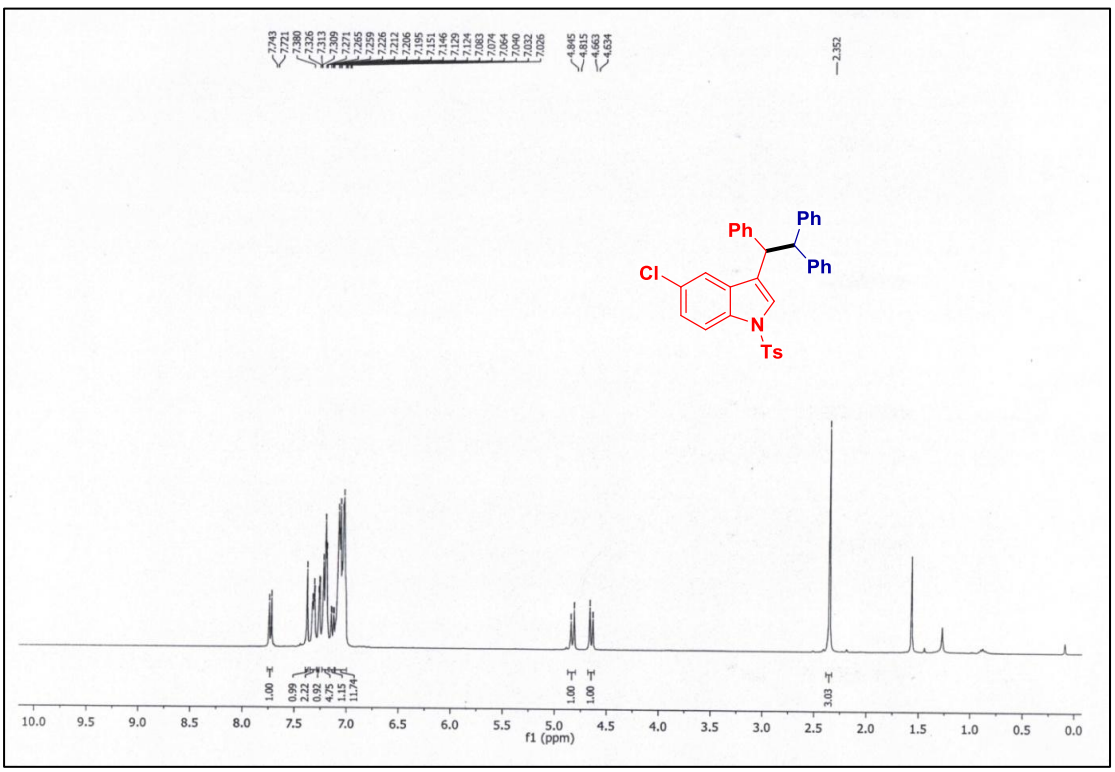

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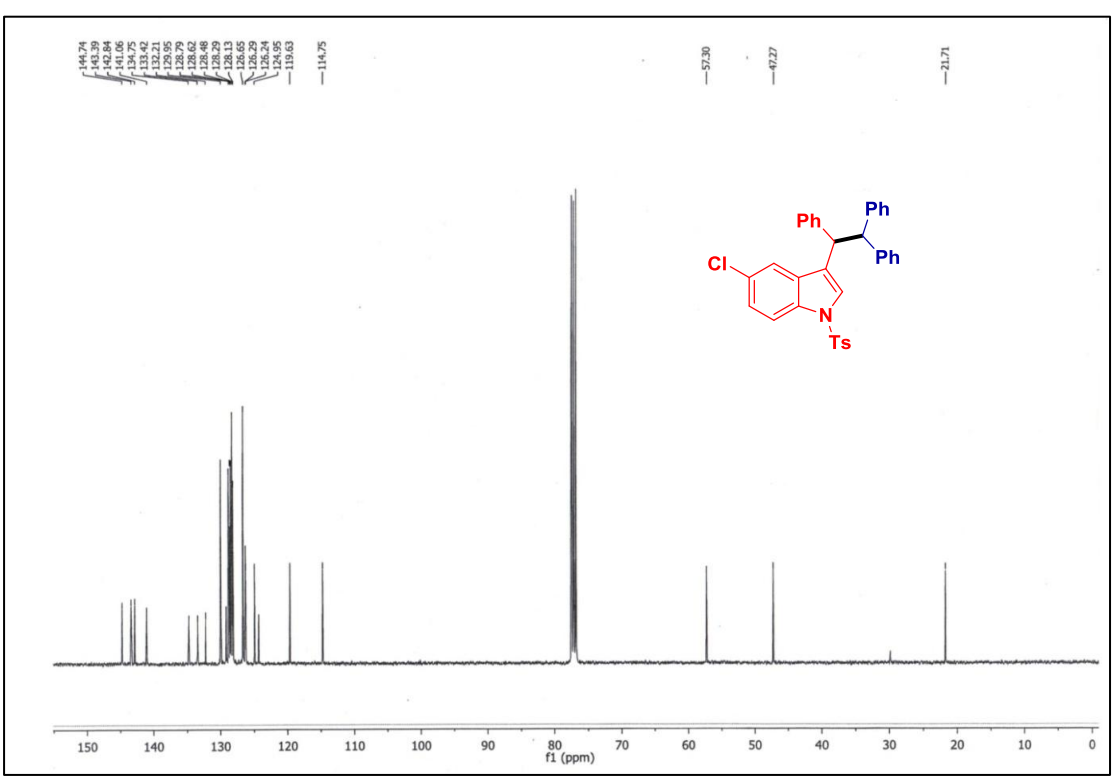

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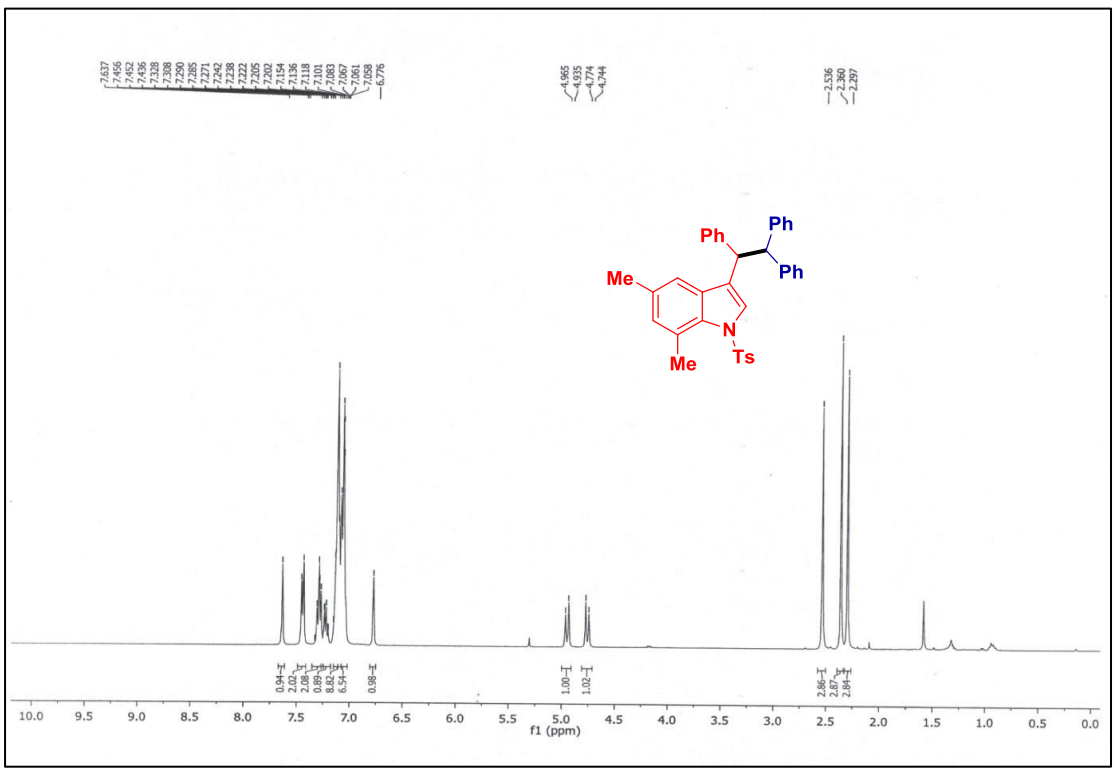

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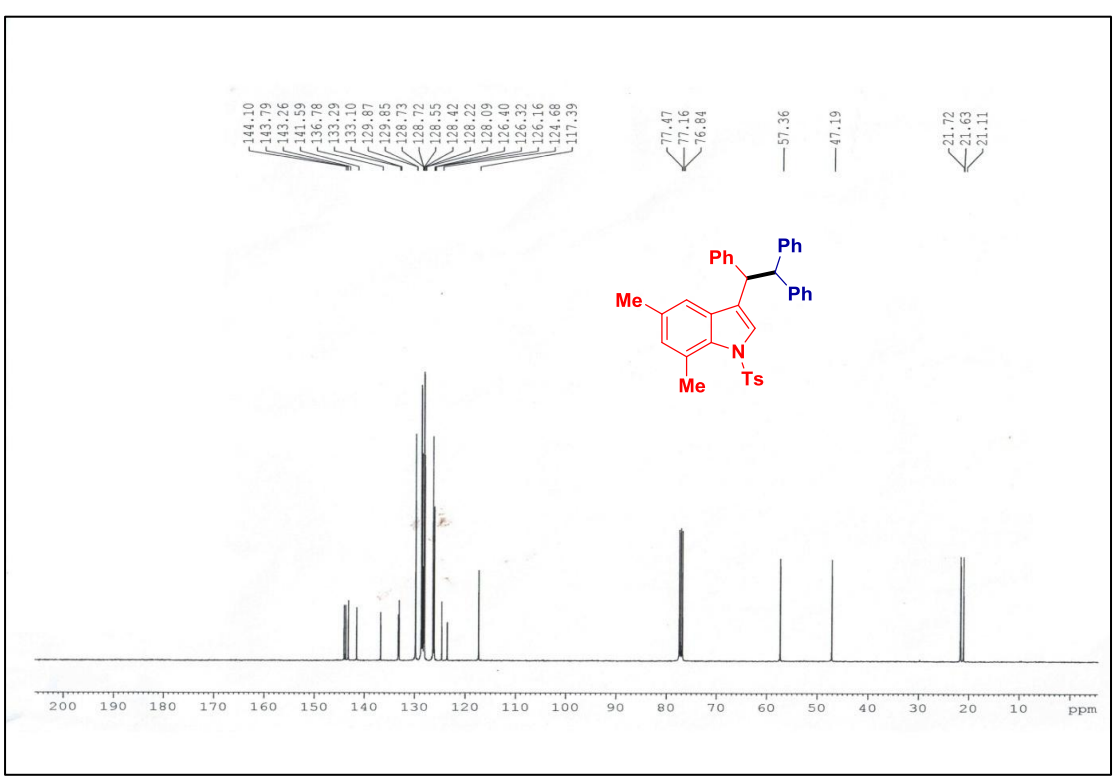

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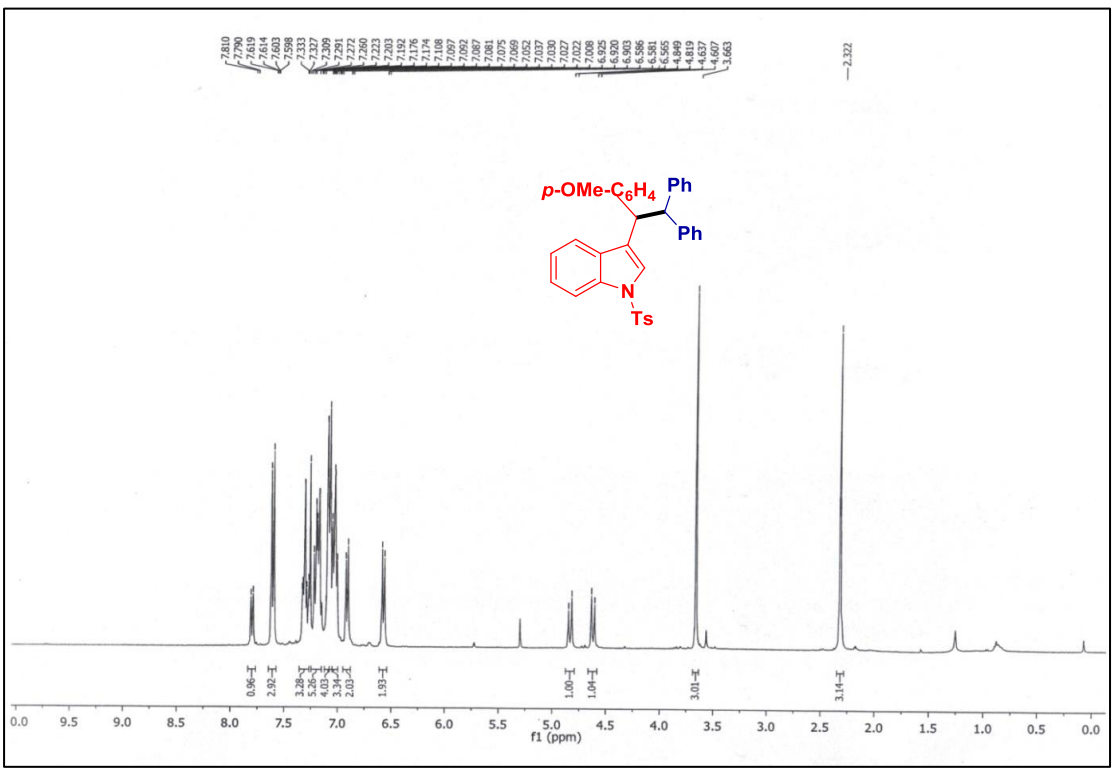
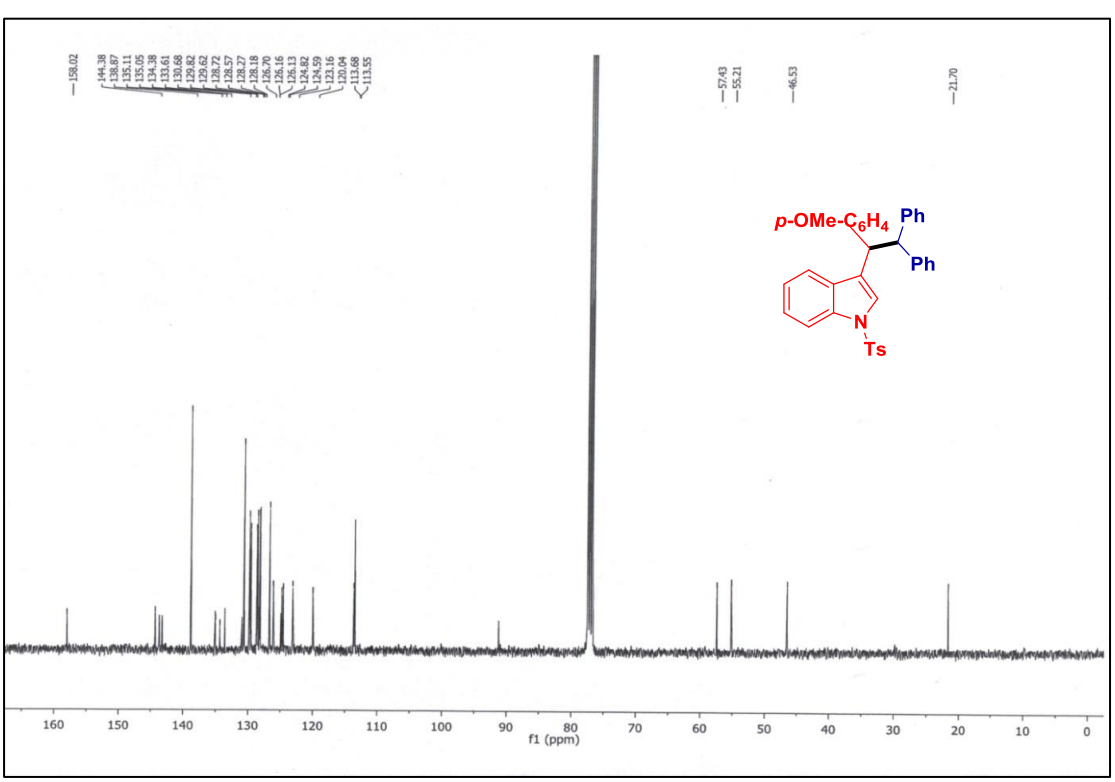


^{13}C NMR spectrum of compound **4d**, $CDCl_3$, 100 MHz



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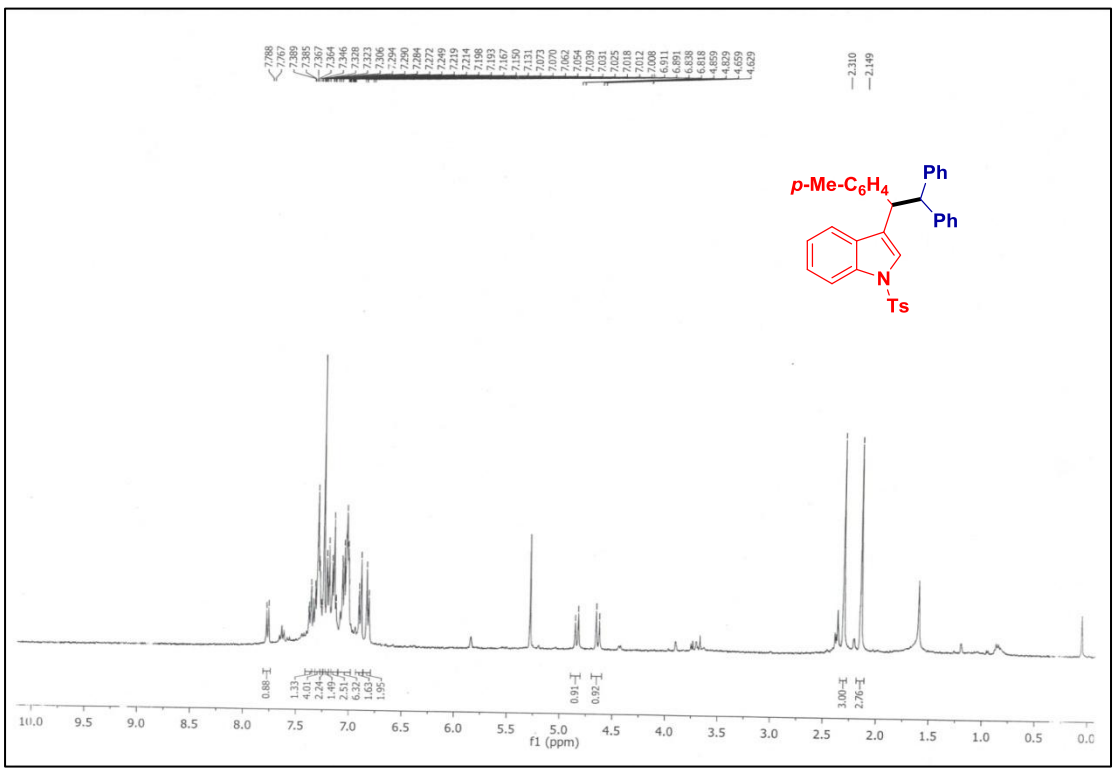

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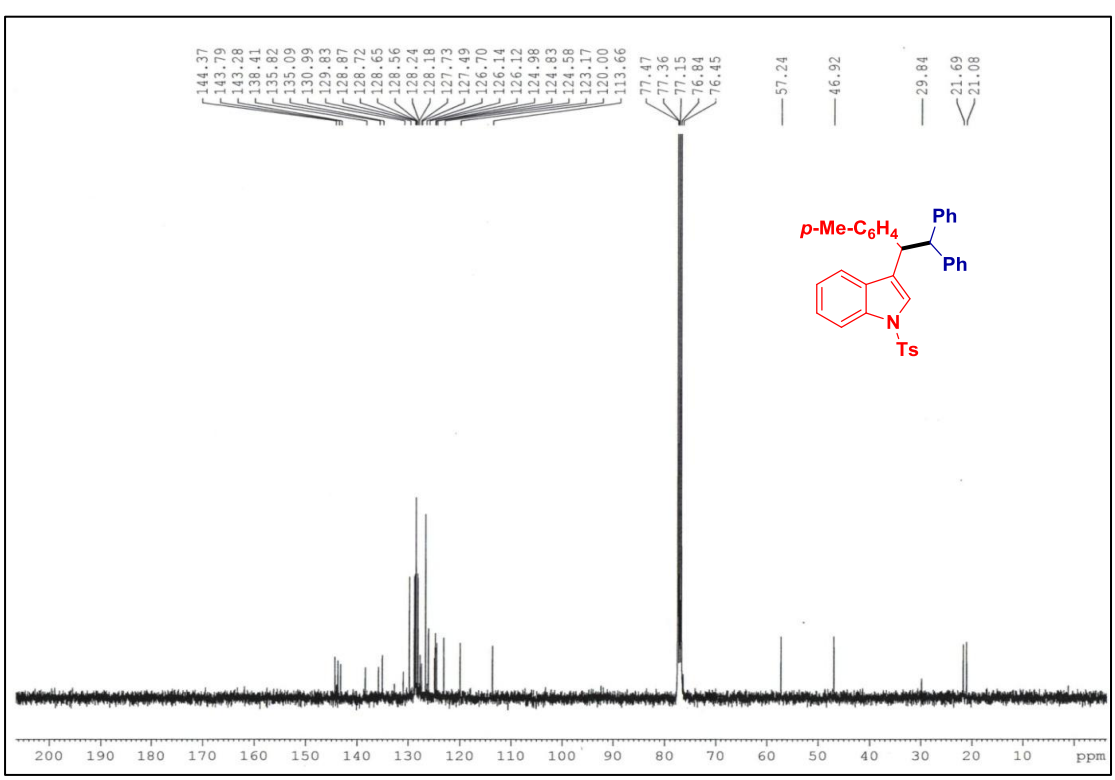

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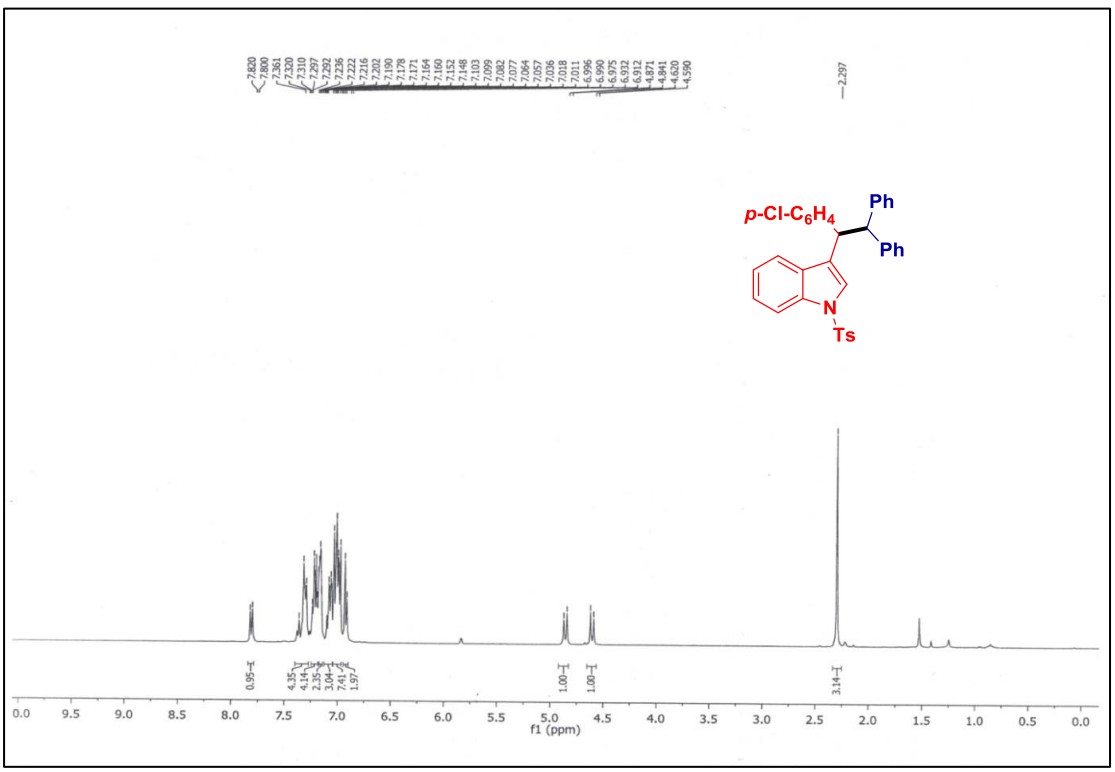

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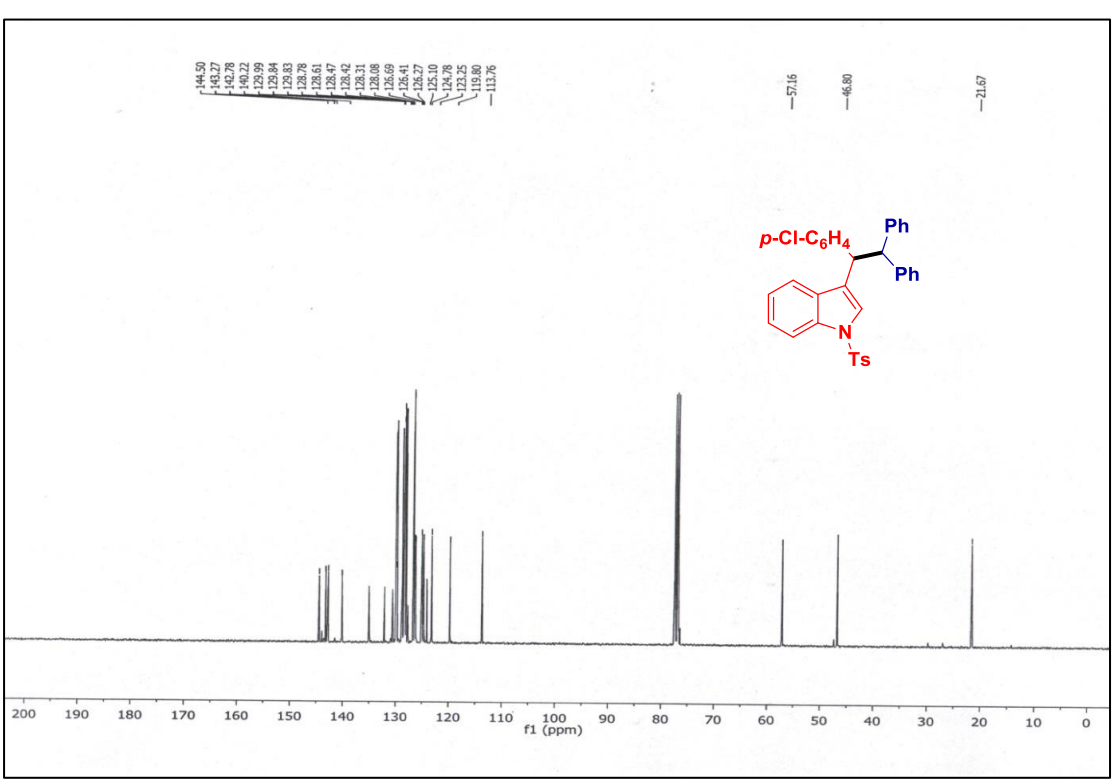

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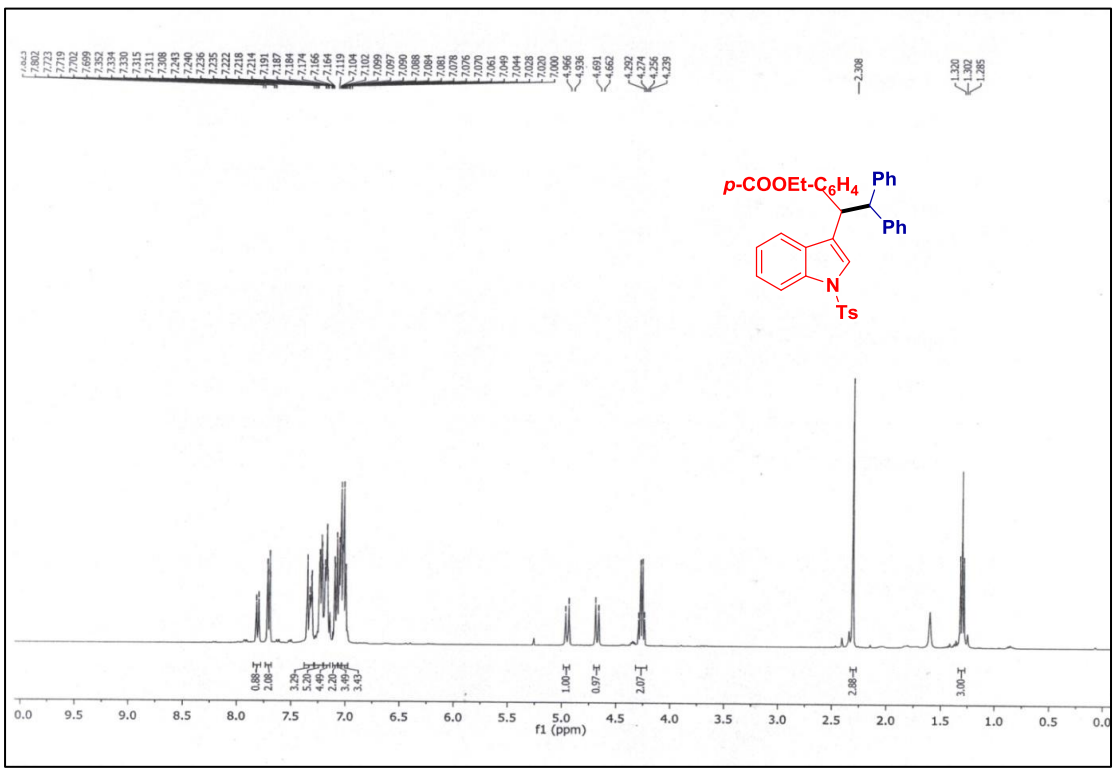
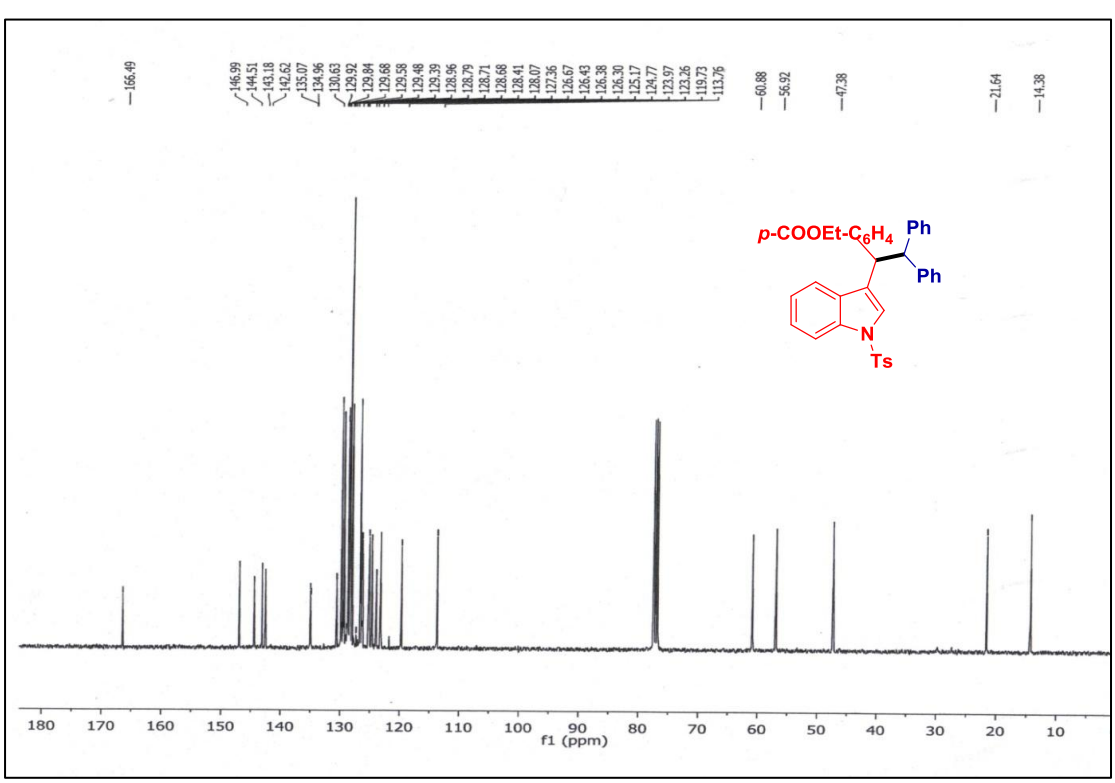
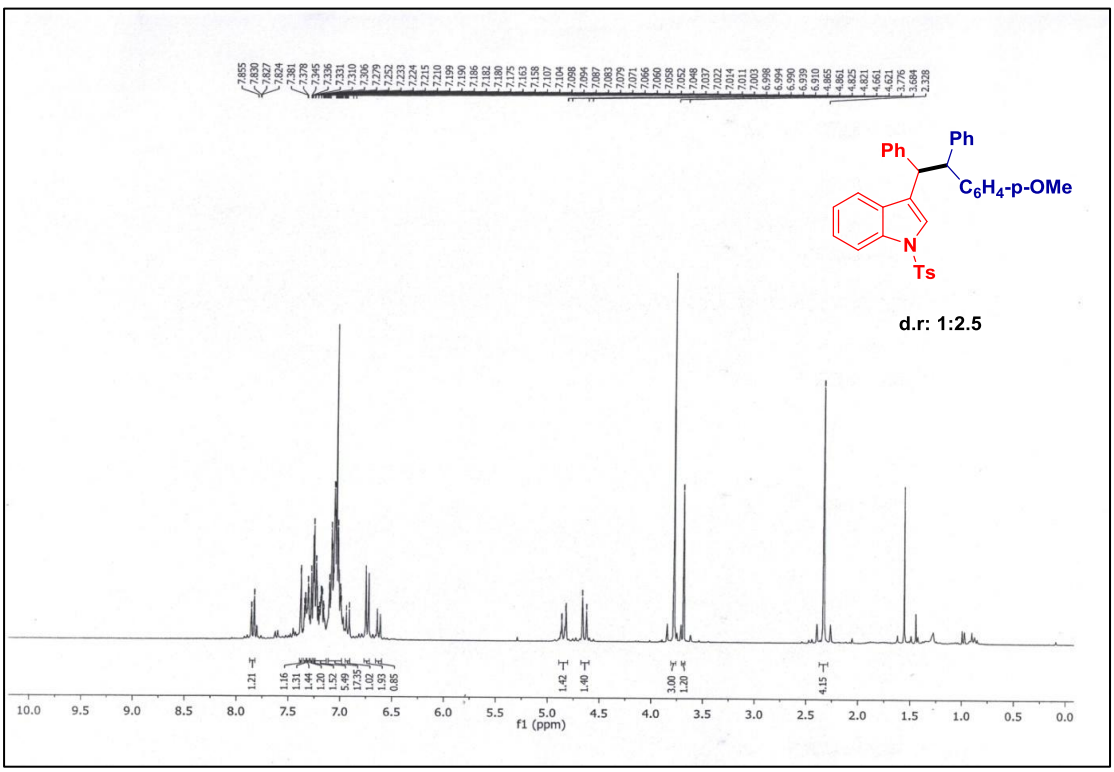


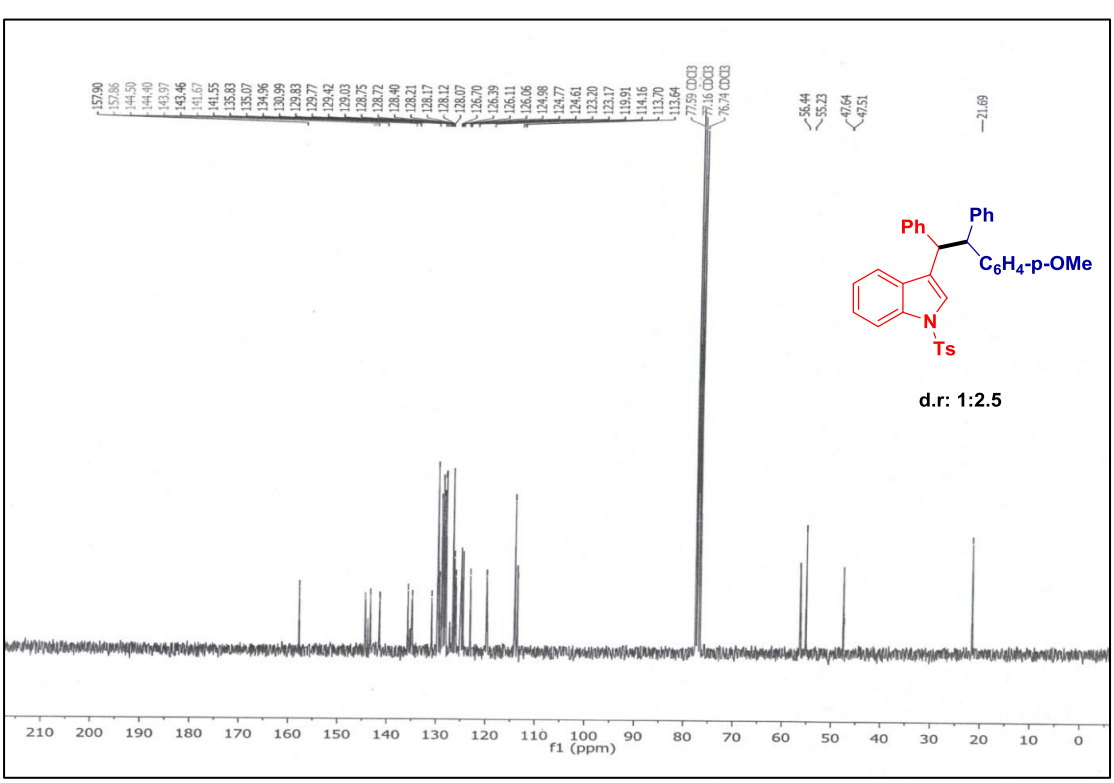
^{13}C NMR spectrum of compound **4g**, $CDCl_3$, 100 MHz



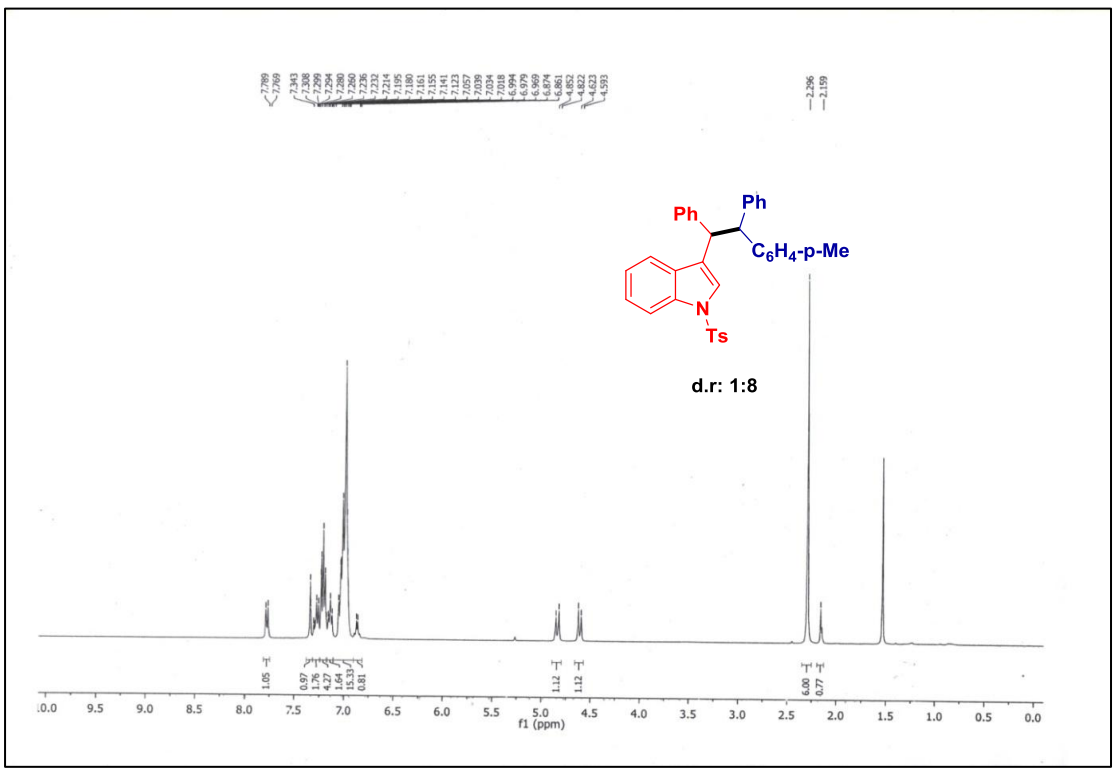
^{1}H NMR spectrum of compound **4h**, $CDCl_3$, 300 MHz



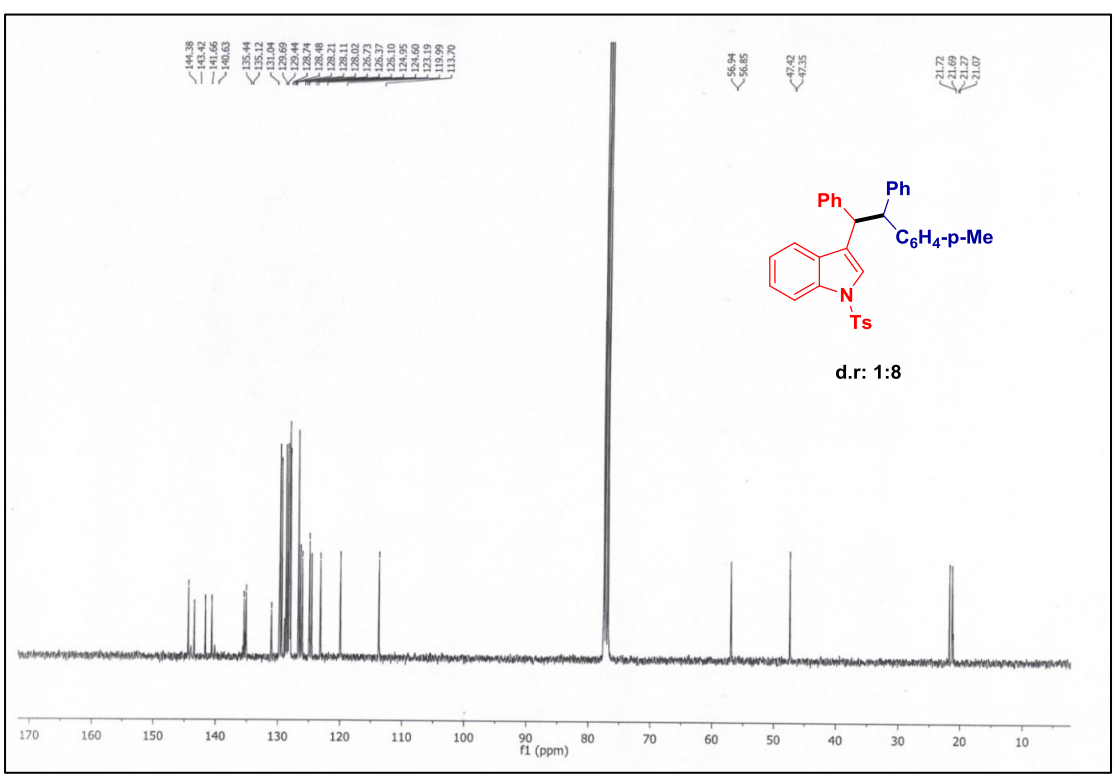
^{13}C NMR spectrum of compound **4h**, $CDCl_3$, 75 MHz



^{1}H NMR spectrum of compound **4i**, $CDCl_3$, 400 MHz



^{13}C NMR spectrum of compound **4i**, $CDCl_3$, 100 MHz



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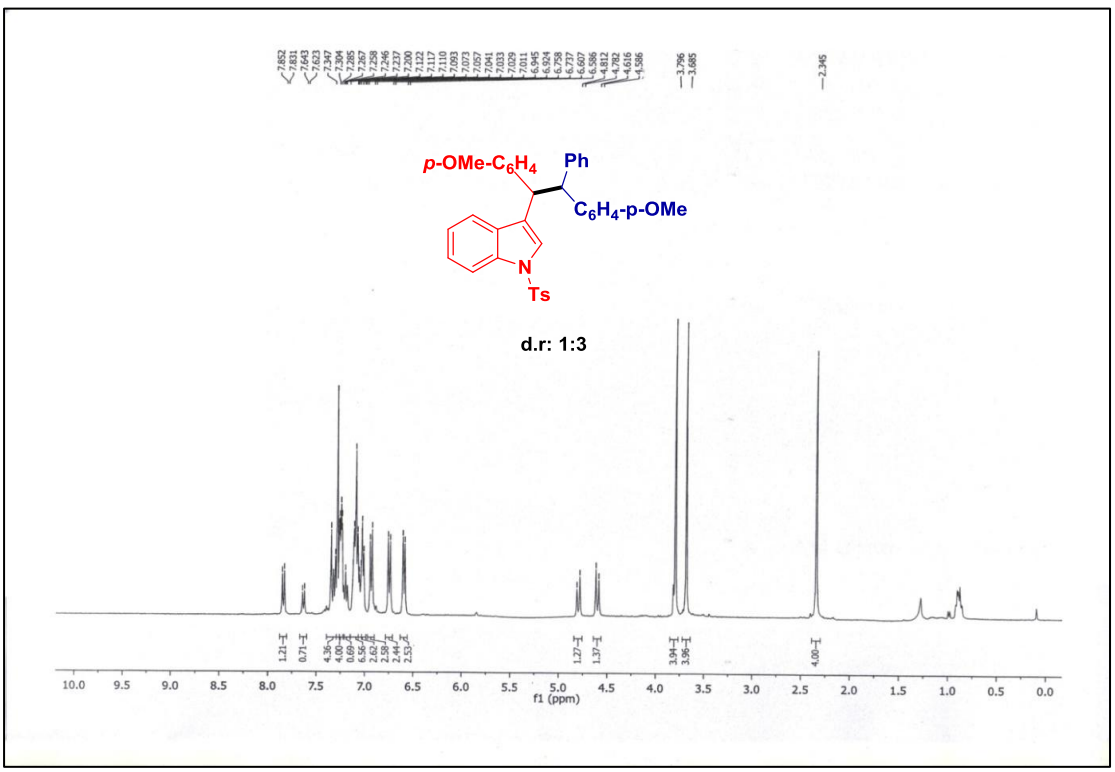

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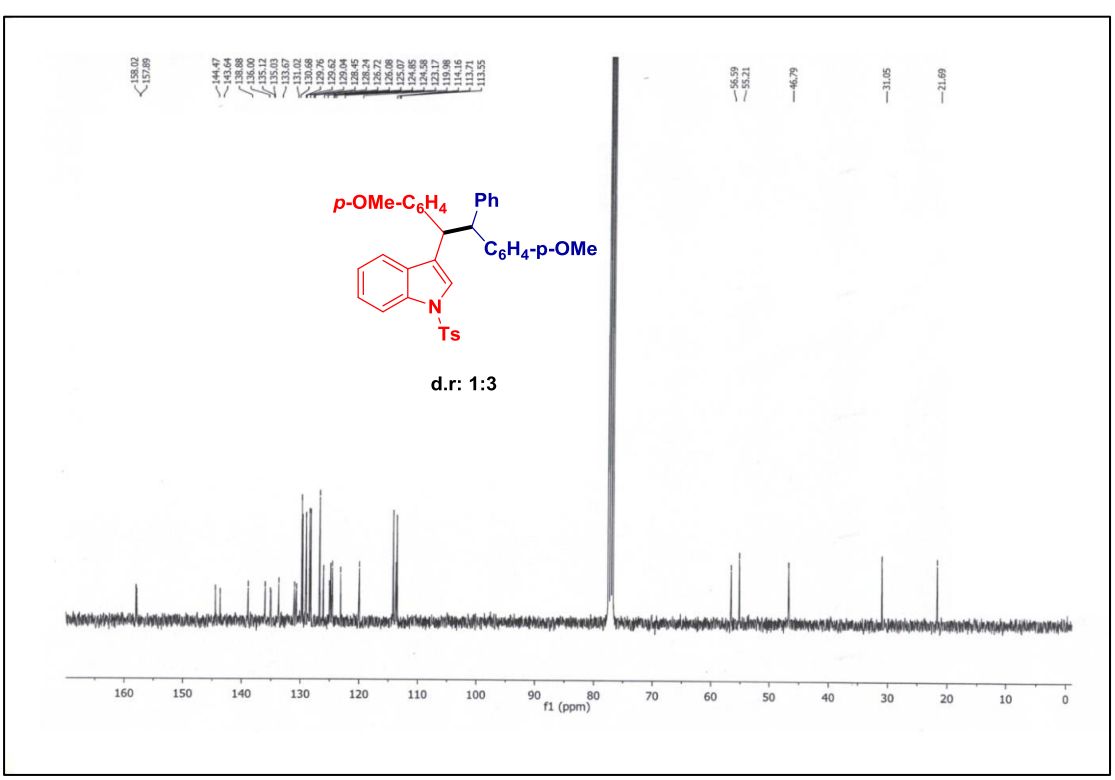
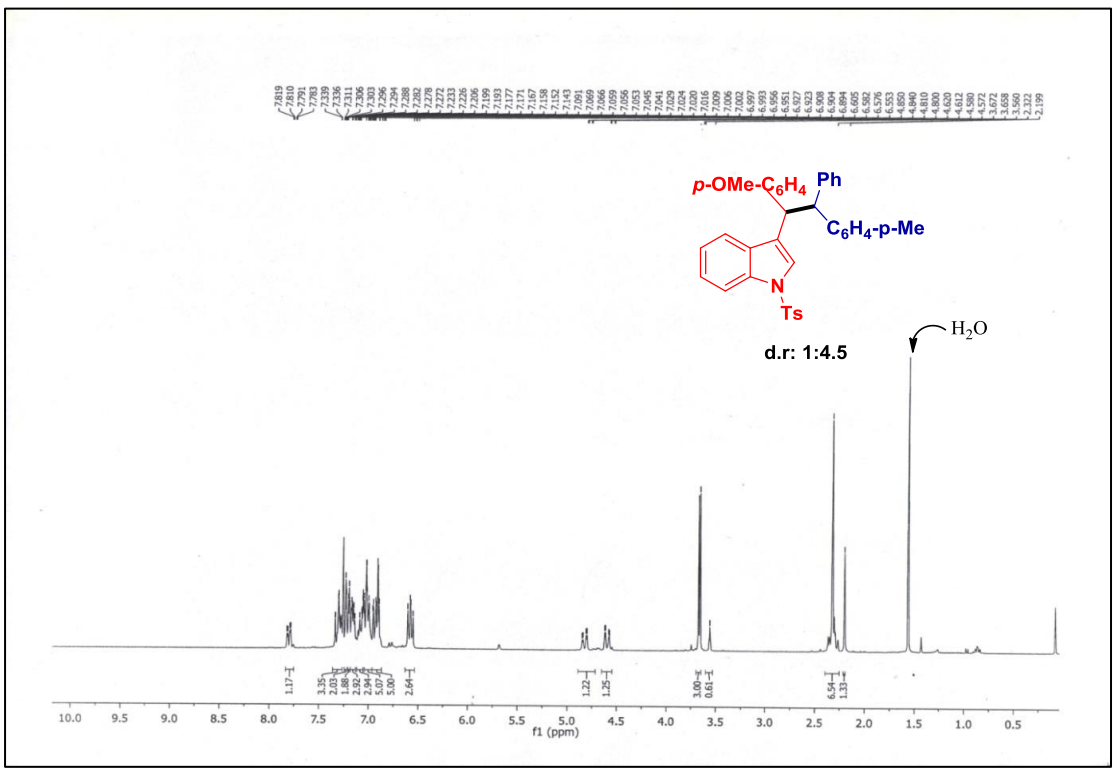
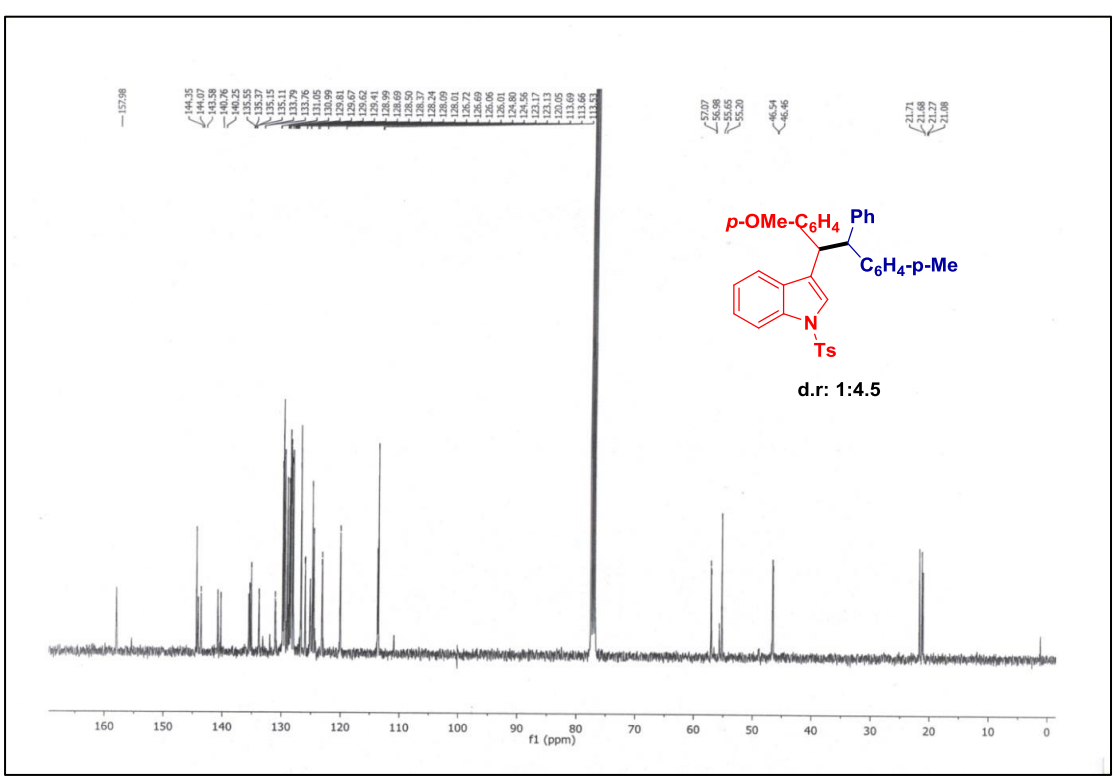


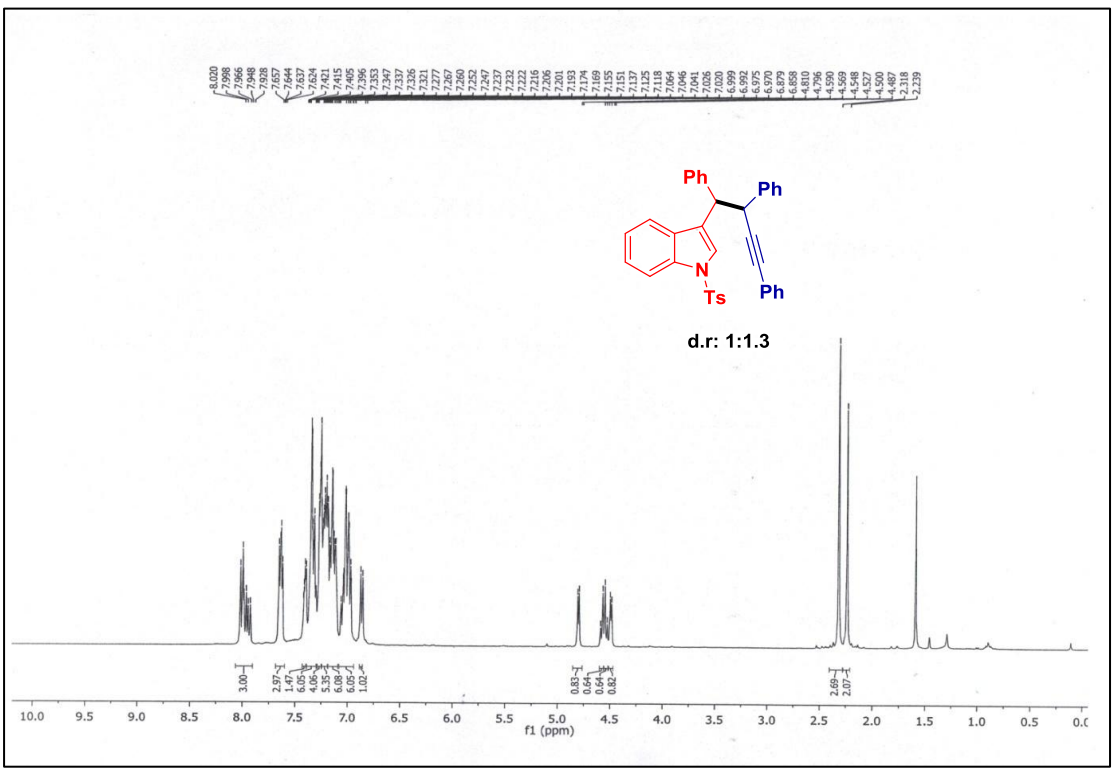
^{1}H NMR spectrum of compound **4k**, $CDCl_3$, 300 MHz



^{13}C NMR spectrum of compound **4k**, $CDCl_3$ 100 MHz



^{1}H NMR spectrum of compound **4l**, $CDCl_3$, 400 MHz



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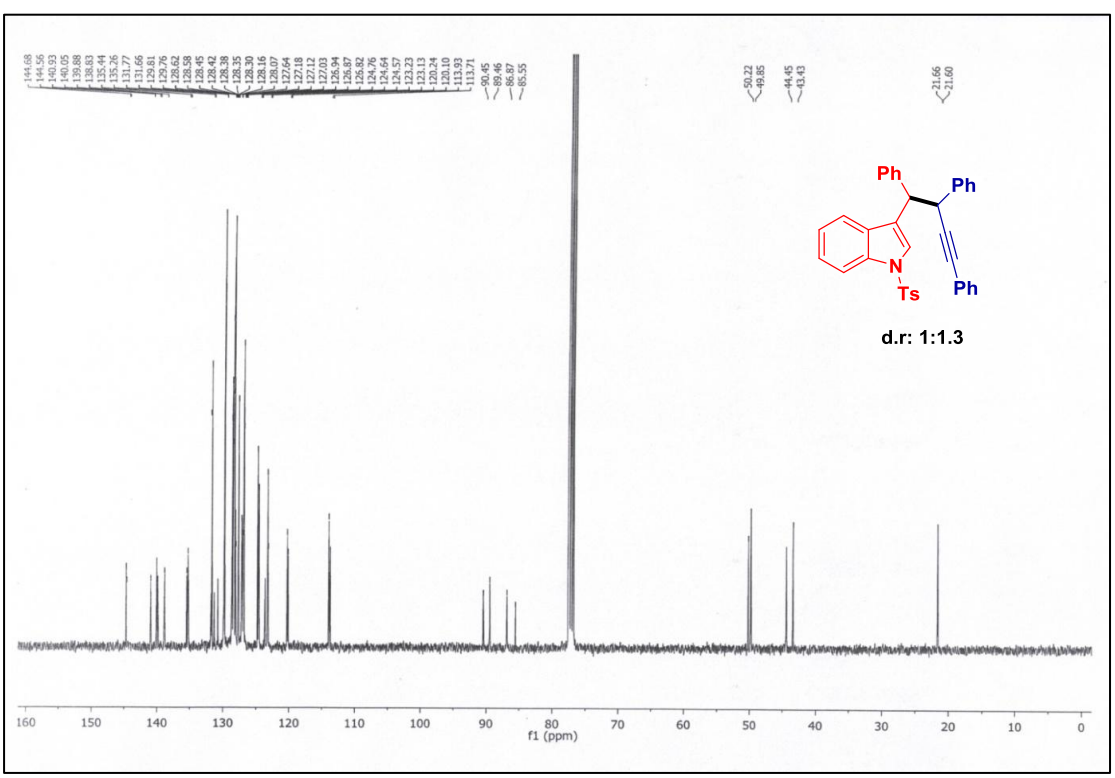
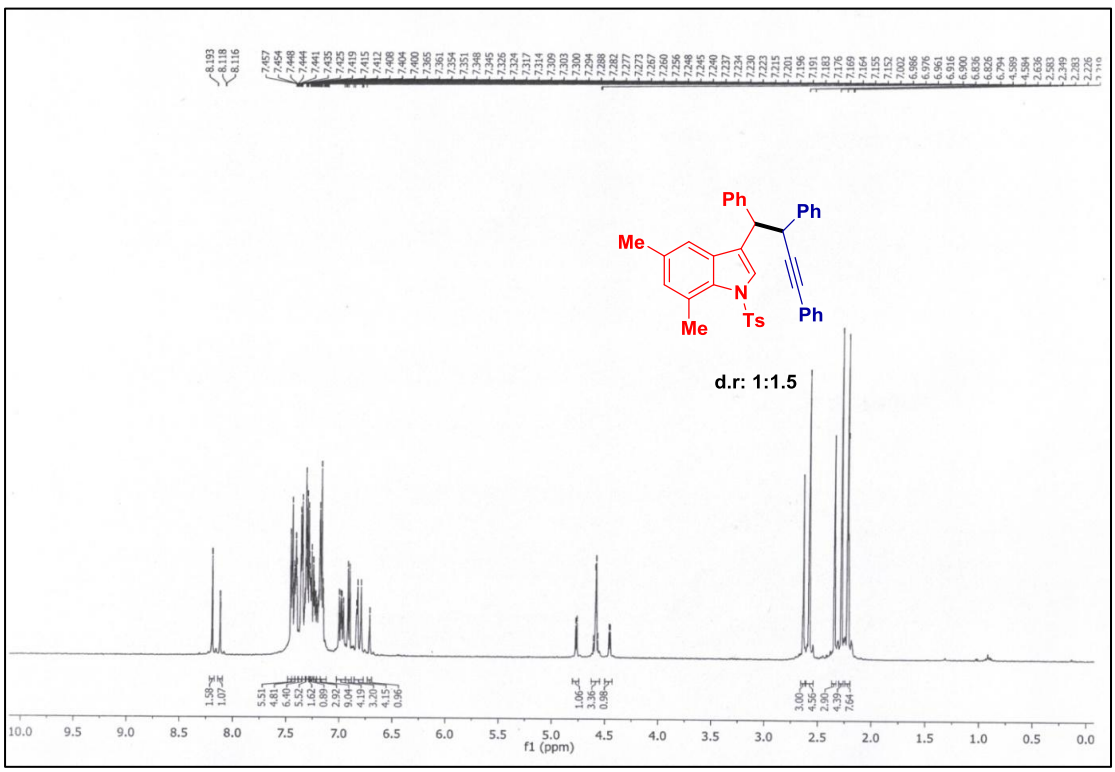


^{1}H NMR spectrum of compound **4m**, $CDCl_3$, 500 MHz



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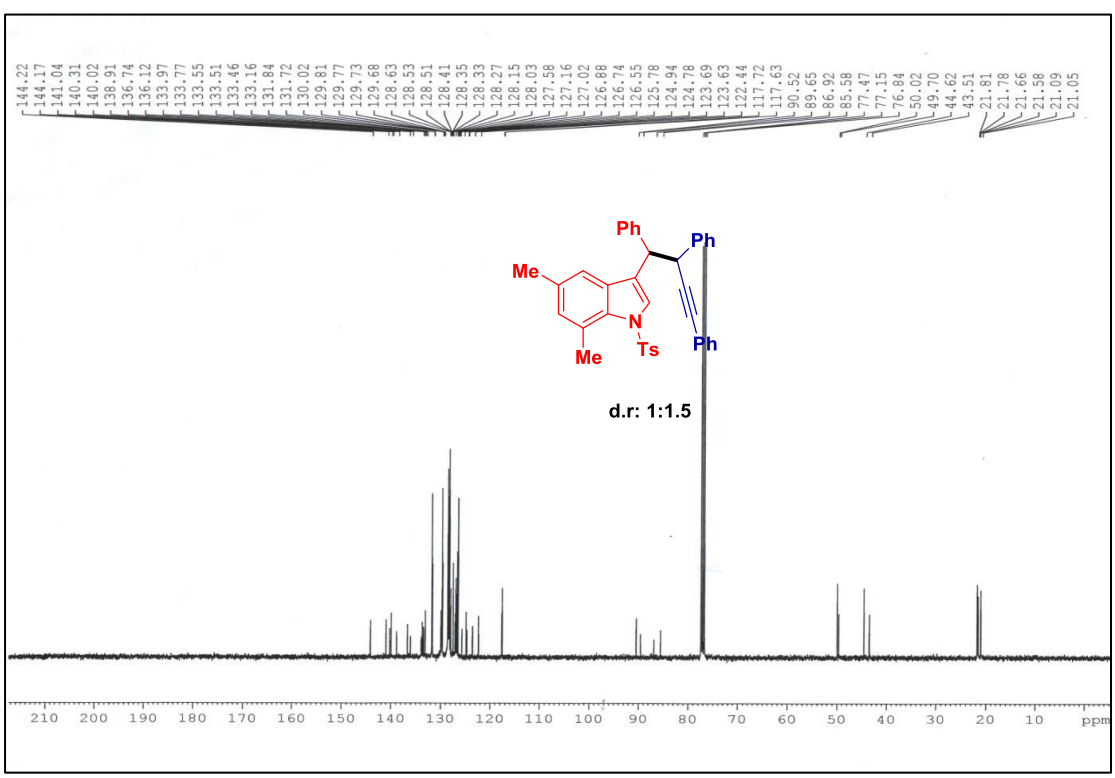

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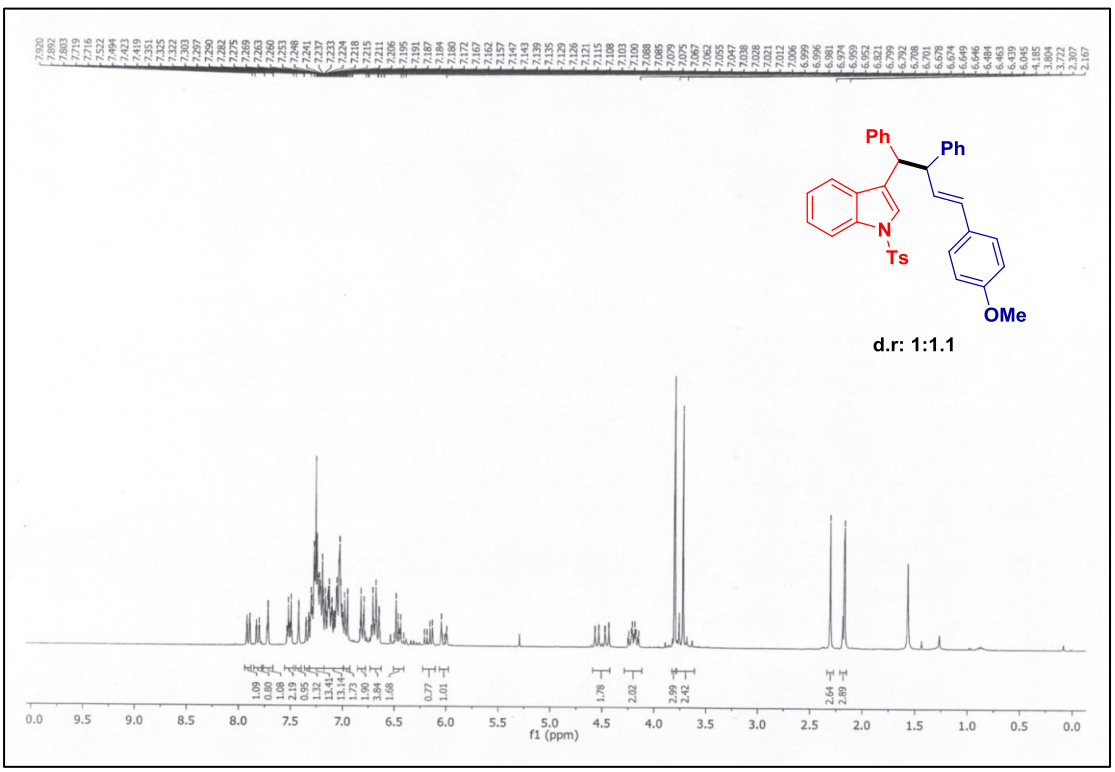
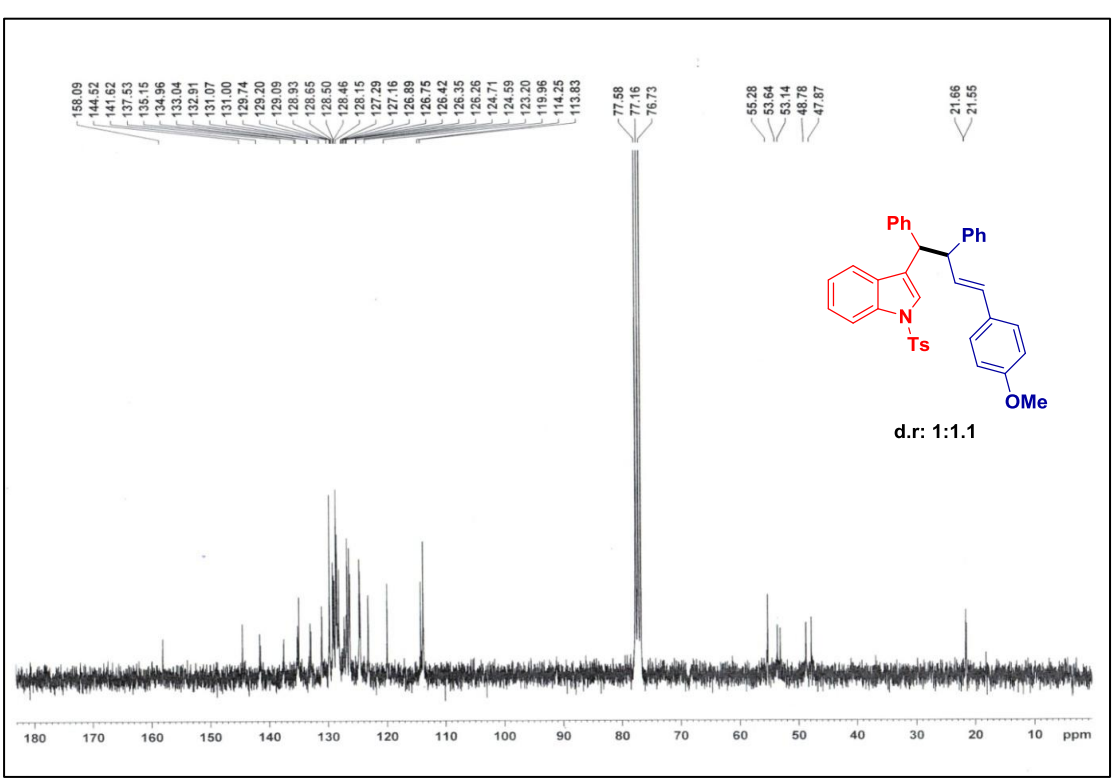
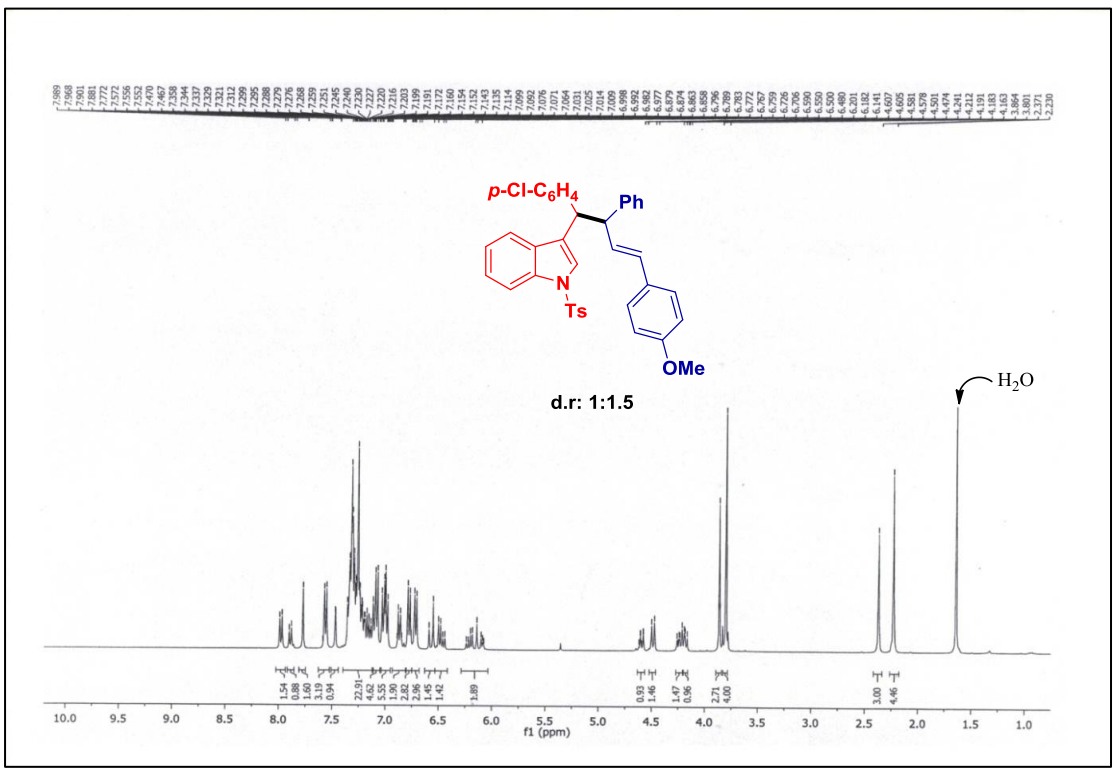


^{13}C NMR spectra of compound **4n**, $CDCl_3$,



^{1}H NMR spectrum of compound **4o**, $CDCl_3$, 400 MHz



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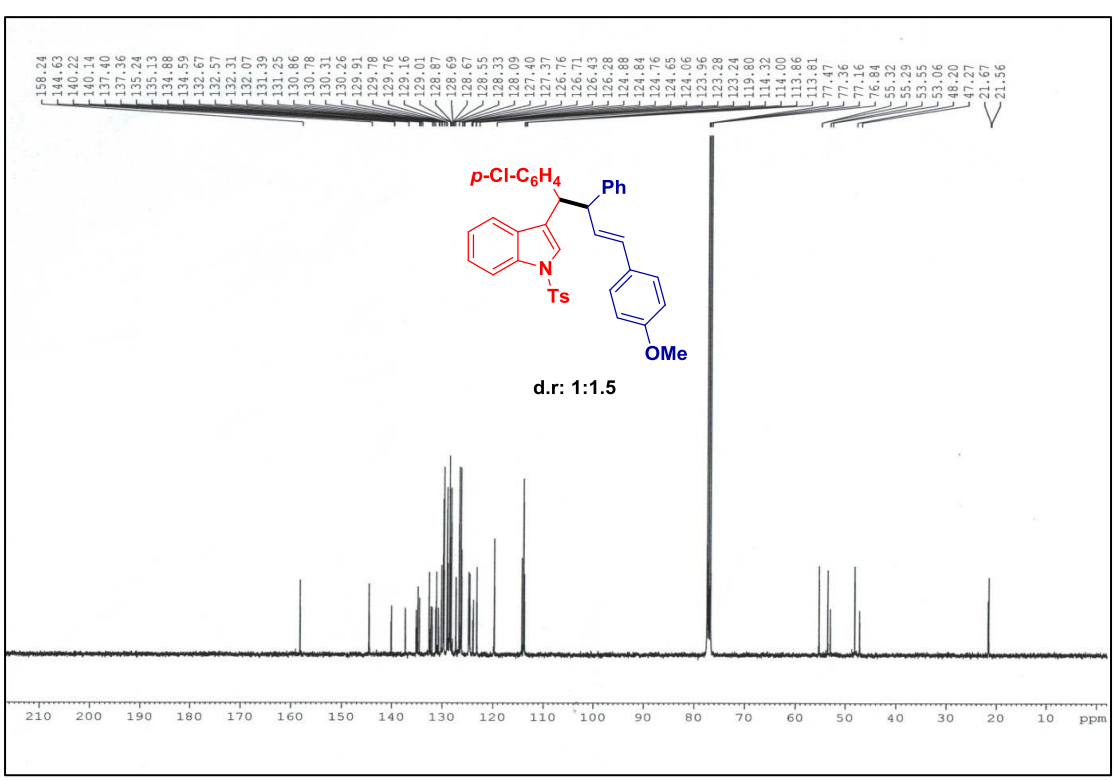

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Iron-Catalyzed Functionalization of 3-Benzylideneindoline Through Tandem Csp^2–Csp^3 Bond Formation/Isomerization with π-Activated Alcohols

Rupsa Chanda,[a] Baitan Chakraborty,[a] Gopal Rana,[a] and Umasish Jana*[a]

Abstract: A new synthetic protocol was developed for the selective synthesis of diverse 3-substituted indoles through tandem carbon–carbon bond formation and isomerization of 3-benzylidene-1-tosylindoline by direct use of alcohols as alkylating agents in the presence of catalytic $FeCl_3$. This method is applicable to a wide range of substrates containing varieties of functional groups. Direct use of alcohols, such as benzylic, allylic, and propargylic alcohols, as electrophiles and the use of non-toxic iron catalyst makes this strategy attractive and environmentally benign. A plausible mechanism has also been proposed for this tandem reaction.

Introduction

The indole ring is a ubiquitous structural core of a plethora of biologically active molecules and natural products.[1] This justifies the ongoing interests addressed to all synthetic processes concerning this heterocyclic system. Functionalization of the indole ring at the 3-position is a pivotal synthetic route to prepare many promising therapeutic agents embedding the indole nucleus such as antimicrobial, anti-inflammatory, anti-tumor, anti-malarial, anti-migraine, anti-estrogen and antagonist drugs.[2] In addition, C-3 substituted indole is an important synthetic intermediate for the construction of complex natural and unnatural polycyclic indoles derivatives.[3] Therefore, many synthetic methodologies for constructing 3-functionalized indoles have been developed. Among them, the classical method for the synthesis of 3-alkylated indoles involves the Friedel-Crafts reaction or S_N2 reaction of alkyl halides or other derivatives of alcohol with preformed indoles in the presence of stoichiometric Lewis acids or bases.[4] While these reactions can be efficient, but their synthetic applications are inevitably hampered by the cost, harsh reaction condition and production of stoichiometric by-products.[5]

In the last decade, the concept of carbon–carbon bond formation by the direct substitution of π-activated alcohols (R-OH) in the presence of catalytic Lewis- or Brønsted acids with various nucleophiles such as aromatic rings, alkenes and alkynes (R′–H) has generated considerable interest in the area of green chemistry, as the process is catalytic and water is the only by-product.[6] From then on, many research groups reported the synthesis of 3-substituted indoles by direct substitution of alcohols using various Lewis- and Brønsted-acid catalysts, and also in metal free condition.[7] As a part of our research program of iron-catalyzed direct activation of alcohols,[8] we have also developed 3-substituted indoles by direct substitution of alcohols using iron-catalysis.[8b]

However, all these methods developed for the synthesis of 3-substituted indoles rely on the availability of preformed indole derivatives, in few cases, harsh reaction conditions, and lack of generality with respect to electrophiles and low chemical yields, which are the limitations of these strategy. In this regard, our group recently reported a new protocol for the synthesis of various 3-substituted indole derivatives via iron-catalyzed isomerization/cycloisomerization of substituted 3-methyleneindoline derivatives through π-activation of double/triple bond by iron in high yields.[9] Due to easy accessibility of 3-methyleneindoline derivatives through tandem Heck–Suzuki or reductive Heck coupling of 2-halo-*N*-propargylanilide, this has been a potentially attractive intermediate for the synthesis of 3-substituted indole derivatives.

In continuation of our efforts for the development of C–C/C–N bond formation with direct use of alcohols and isomerization of 3-benzylidene indole derivatives, we presumed that in situ generated carbocation from π-activated alcohol could undergo Csp^2–Csp^3 bond formation, chemoselectively at the exocyclic double bond, and subsequent aromatization could furnish densely substituted 3-alkylindoles derivative (Scheme 1). Herein, we wish to disclose this new strategy for the synthesis of densely substituted 3-alkylindole derivatives in the presence of environmentally friendly and sustainable catalyst, $FeCl_3$. Several π-activated alcohols, such as benzylic, allylic, and propargylic alcohols were chosen as the coupling partners to furnish the complex 3-alkylated indole moieties in high yields, which are difficult to synthesize by other conventional methods. To the best of our knowledge, the present strategy for the construction of densely substituted 3-alkyl indoles from tandem

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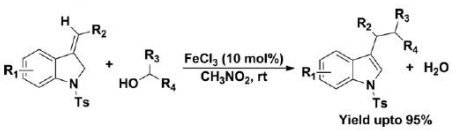
carbon–carbon bond formation/isomerization of 3-benzylidene-1-tosylindoline derivatives has never been reported.



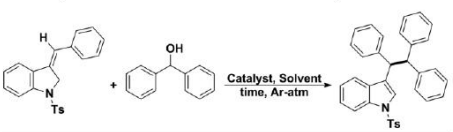
Scheme 1. Iron-catalyzed synthesis of 3-alkyl indole with direct coupling of alcohol.

Results and Discussion

The required starting materials, 3-benzylidene-1-tosylindoline derivatives **2**, were prepared by Heck coupling of substituted 2-bromo-*N*-propargylanilidines **1**, using 5 mol-% $Pd(OAc)_2$, 10 mol-% tricyclohexylphosphine (PCy_3), 2.5 M aqueous K_2CO_3 in a mixed solvent of toluene and ethanol (1:1) at 70 °C within 4 hours (Scheme 2).[9] The reaction proceeded in a stereoselective manner via 5-*exo*-*dig* cyclisation to obtain the 3-benzylidene-1-tosylindoline derivatives in moderate to good yields. 2-bromoaniline derivatives possessing electron withdrawing group like –Cl, and electron donating group like 2,4-dimethyl underwent smooth transformation under the aforesaid condition with 72 % and 80 % yields, respectively (Scheme 2, entries **2b** and **2c**). Again, alkyne units bearing a number of functional groups were also well tolerated, giving 67–82 % yields (Scheme 2, **2d**–**2g**).

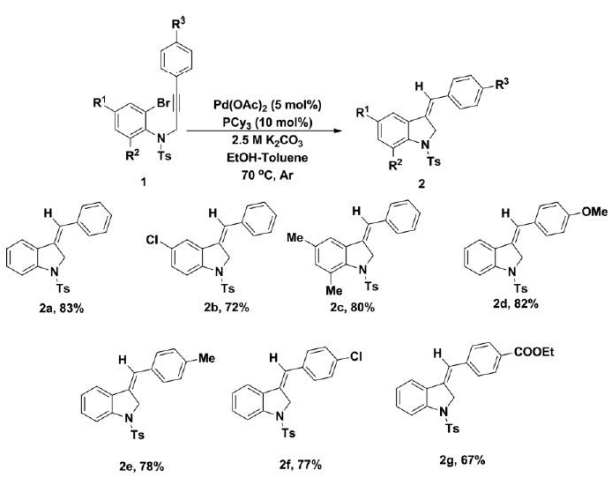
Having a series of key substrates in hand, we then tried to investigate the optimum reaction condition for our target tandem isomerization and C–C bond formation reaction between 3-benzylidene-1-tosylindoline **2a** and alcohol **3a** via catalytic activation of alcohol **3a** to afford the desired product **4a**. The results are summarized in Table 1. Due to high catalytic activity of $FeCl_3$ towards alcohol, initially we started our investigation with anhydrous $FeCl_3$ in various solvents like dry DCM, THF, CH_3CN, CH_3NO_2 and 1,2-DCE. Among them CH_3NO_2 gave maximum yield of 89 % at room temperature (Table 1, entry 3). The other solvents like DCM, DCE and THF at room temperature furnished low to moderate yields of the products (Table 1, entry 1, 4 and 6). Under refluxing condition using DCM solvent, no

Table 1. Optimisation of the reaction conditions for the synthesis of **4a**.[a]



Entry	Catalyst	Solvent	Temp	Time [h]	Yield [%][b]
1	$FeCl_3$	DCM	r.t.	2	35
2	$FeCl_3$	DCM	reflux	2	54
3	$FeCl_3$	CH_3NO_2	r.t.	2	89
4	$FeCl_3$	THF	r.t.	2	trace
5	$FeCl_3$	CH_3CN	r.t.	2	ND
6	$FeCl_3$	1,2-DCE	r.t.	3	52
7	$FeBr_3$	CH_3NO_2	r.t.	2	74
8	$Fe(OTf)_3$	CH_3NO_2	r.t.	3	32
9	$InCl_3$	CH_3NO_2	r.t.	2	78
10	$In(OTf)_3$	CH_3NO_2	r.t.	2	75
11	AgOTf	CH_3NO_2	r.t.	2	0
12	CSA	CH_3NO_2	r.t.	2	0
13	TfOH	CH_3NO_2	r.t.	3	78
14	PTSA	CH_3NO_2	r.t.	3	81
15[c]	$FeCl_3$	CH_3NO_2	r.t.	2	68

[a] Reaction conditions: **2a** (0.15 mmol), **3a** (0.15 mmol), 0.015 mmol of catalyst in 2 mL of solvent under Ar. [b] Isolated yields. [c] Catalyst loadings: 0.0075 mmol.



Scheme 2. Preparation of 3-benzylidene-1-tosylindoline substrates by Pd catalyzed Heck coupling reaction.[a,b] [a]Reaction conditions: 0.05 mmol of $Pd(OAc)_2$, 0.10 mmol of PCy_3, 2.5 M K_2CO_3 (2 mL of H_2O), 2 mL of EtOH and 2 mL of toluene at 70 °C under Ar. [b]Isolated yields.

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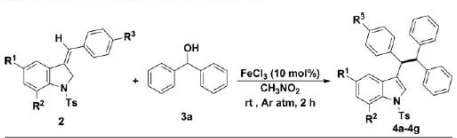
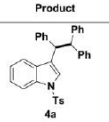
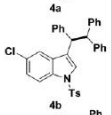
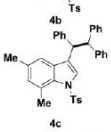
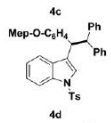
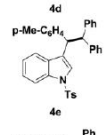
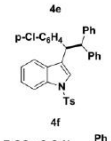
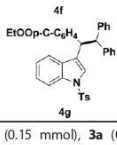
such satisfactory result was observed (Table 1, entry 2). CH_3CN as solvent produced no desired product. So choosing CH_3NO_2 as the most efficient solvent, other common iron salts such as $FeBr_3$ and $Fe(OTf)_3$ were examined and both of them performed well, but led to lower yields of **4a** (Table 1, entry 7, 8). Again catalyst loading of 5 mol-% $FeCl_3$ afforded 68 % yield (Table 1, entry 15). Among other Lewis acid catalysts, $InCl_3$ and $In(OTf)_3$ produced 78 % and 75 % yields, respectively at room temperature in 2 hour, and AgOTf remained ineffective (Table 1, entry 9–11). Switching to Brønsted acids like TfOH and PTSA to carry out the reaction, proved to be less efficient in respect of time and yields. CSA was totally inactive under this reaction condition (Table 1, entry 12–14). Hence the reaction of **2a** with **3a** in the presence of 10 mol-% of $FeCl_3$ in CH_3NO_2 at room temperature, turned out to be the optimum reaction condition. To dem-

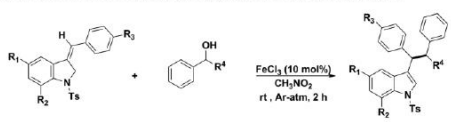
Table 2. $FeCl_3$ catalyzed direct substitution of benzylic alcohol **3a** with various substituted 3-benzylidene-1-tosylindoline **2a**.[a]

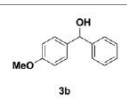
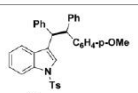
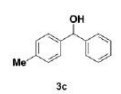
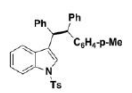
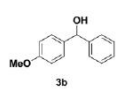
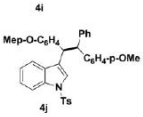
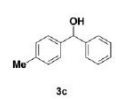
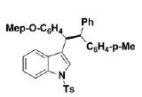
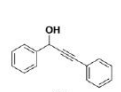
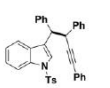
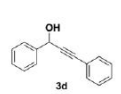
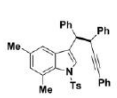
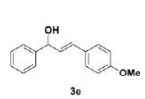
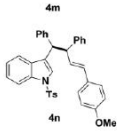
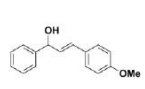
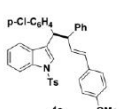


Entry	Substrate	Product	Yield(%)[b]
1.	R^1=H, R^2=H, R^3=H	 4a	89
2.	R^1=Cl, R^2=H, R^3=H	 4b	78
3.	R^1=Me, R^2=Me, R^3=H	 4c	89
4.	R^1=H, R^2=H, R^3=C_6H_4-p-OMe	 4d	75
5.	R^1=H, R^2=H, R^3=C_6H_4-p-Me	 4e	74
6.	R^1=H, R^2=H, R^3=C_6H_4-p-Cl	 4f	67
7.	R^1=H, R^2=H, R^3=C_6H_4-p-COOEt	 4g	59

[a] Reaction conditions: substrate **2** (0.15 mmol), **3a** (0.15 mmol), $FeCl_3$ (0.015 mmol), solvent CH_3NO_2 (2 mL), Ar atmosphere, 2 h, r.t. [b] Isolated yields.

Table 3. Scope of alcohols for the synthesis of 3-substituted indoles.[a]



Entry	Substrate	Alcohol	Product	Yield (%)[b]
8	2a	 3b	 4h	76
9	2a	 3c	 4i	72
10	2d	 3b	 4j	81
11	2d	 3c	 4k	85
12	2a	 3d	 4l	95
13	2c	 3d	 4m	91
14	2a	 3e	 4n	67[c]
15	2f	 3e	 4o	62[c]

[a] Reaction conditions: substrate **2** (0.15 mmol), **3** (0.15 mmol), $FeCl_3$ (0.015 mmol), solvent CH_3NO_2 (2 mL), Ar, 2 h, r.t. [b] Isolated yields. [c] 3 h.

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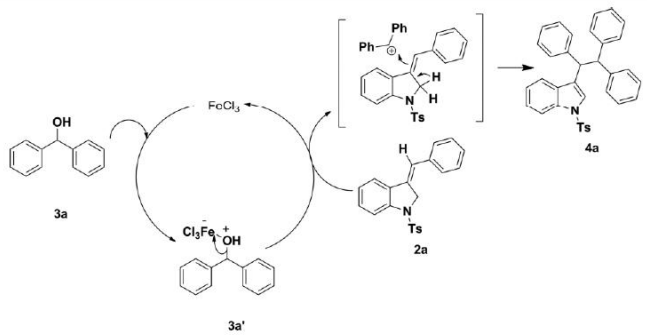

Scheme 3. Mechanistic rationalization of direct substitution of alcohols by catalytic activation of alkenes.

onstrate the flexibility, a number of reactions were carried out using substituted 3-benzylidene-1-tosylindolines (**2a**–**2g**) under the optimal reaction condition and the results are summarized in Table 2.

It was observed that 3-benzylidene-1-tosylindoline having electron poor group –Cl in the 2-haloaniline moiety resulted in good yield of 78 % (Table 2, entry 2). And when an electron rich substituent in a 2-haloaniline moiety like 2,4-dimethyl was tested, the yield of the reaction improved providing 89 % of the product **4c** (Table 2, entry 3).

Furthermore, the reaction seemed to tolerate various functional groups such as –OMe, –Me, $–CO_2Et$, and –Cl at the *para* position of the aromatic ring (R^3) of the 3-benzylidene-1-tosylindoline and moderate to good yields (59–75 %) (Table 2, entry 4–7) were obtained. The yields were relatively higher in case of electron rich substituents such as –OMe and –Me at R^3 than electron deficient substituents such as –Cl and $–CO_2Et$.

However, the generality of the reaction was then scrutinized using substituted benzylic alcohols under the standard reaction condition. For this purpose, benzylic alcohols with electron donating groups at the *para* position were exploited as electrophiles, and that furnished good to excellent yields (72–85 %, Table 3, entry 8–11), but the products were obtained as non-separable diasetereomeric mixtures. The formation of the compound **4i** was further confirmed by single crystal XRD.

Encouraged by the generality of this protocol, we then aimed to demonstrate the robustness of the reaction by employing propargylic and allylic alcohols as electrophiles. To our pleasure, in both the cases we obtained our desired products in good yields (62–95 %, Table 3, entries 12–15) as non-separable diastereomeric mixtures. Propargylic alcohols furnished better yields (92 % and 95 %) than allylic alcohols (62 % and 67 %), which might be due to the fact that the carbocationic center generated at the propargylic position were more stabilized by the adjacent triple bond than case of allylic alcohol.

All the structures were characterized by ^1H, ^{13}C NMR spectra and HRMS analysis and compound **4i** was confirmed by X-ray diffraction, see supporting information.

Based on the experimental observations and previous reports,[9,10] a plausible mechanism was proposed (Scheme 3). It is believed that $FeCl_3$ activates the benzylic alcohol **3a** and facilitates dehydration to form carbocation **3a'** which then activates the alkene and subsequent deprotonation of the $–CH_2$ unit and nucleophilic attack of the alkene to the carbocation leads to our desired 3-substituted indole **4a**. $FeCl_3$ regenerates which participates in the next catalytic cycle.

Conclusions

In summary, we have demonstrated a simple, tandem strategy involving direct coupling of alcohols with 3-benzylidene-1-tosylindolines and subsequent aromatization of 3-benzylidene-1-tosylindoline for the synthesis of 1-tosyl-3-(1,2,2-triphenylethyl)-1*H*-indole derivatives in good to high yields. Wide substrate scope, use of easily accessible alcohols as alkylating agent, cost-effective and environmentally friendly $FeCl_3$ as catalyst, mild reaction condition, atom efficiency, and environmental soundness of this methodology make this an attractive synthetic pathway for the rapid access of pharmaceutically important 3-substituted indole derivatives.

Experimental Section

A solution of **2** and **3** were taken in dry nitromethane and $FeCl_3$ (10 mol-%) was added to the mixture and stirred for 2 h at room temperature under an Ar atmosphere to afford **4**. The solvent was evaporated after completion of the reaction (monitored by TLC). The crude reaction mixture was purified by column chromatography on silica gel (100–200 mesh). The product was characterized by ^1H NMR and ^{13}C NMR spectroscopy as well as HRMS.

CCDC 1939911 for **4i** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgments

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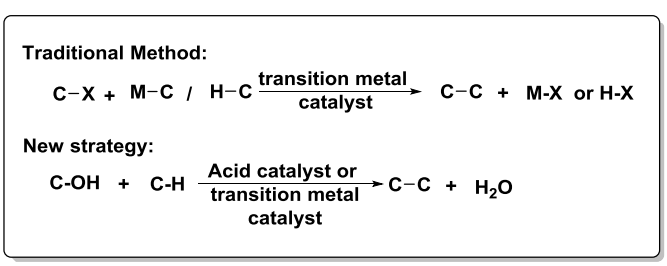
Part-1, Chapter 2

Iron-Catalyzed Carboarylation of Alkynes *via* Activation of π-activated Alcohols: Rapid Synthesis of Substituted Benzofused Six-membered Heterocycles

1. INTRODUCTION:

Synthetic chemists use a variety of tools for the synthesis of different important natural products, biologically active molecules, agrochemicals etc. and one of the most useful methods is the generation of complexity through C-C bond making reactions.[1] Traditionally, C-C bond formation involves cross-coupling of a C-X bond (X = halide, OTf, OTs, OMs, SiR_3 etc.) with an organometallic reagent, C-M (M = Li, Mg, Zn, Sn, Cu, Zr, etc.), or activated C-H bonds.[2] However, in recent times, there has been a growing interest in using alcohols (C-OH) directly as the partners for the construction of C-C bond. This approach has gained popularity because of their ample availability, improved stability, sustainability, and reduced waste associated with alcohols compared to C-X bonds, which require prefunctionalization.[3] In addition, the use of alcohols can reduce the number of synthetic steps required, resulting in a more efficient synthesis with less waste.[4] This shift in focus towards alcohol-mediated C-C bond formation is poised to have a significant impact on the field of synthetic chemistry.



Scheme 1: Modern technique of C-C bond formation by activating alcohols

The most common approach for catalytic formation of C-C bond using alcohols and alkynes involves the activation of the alcohol as a leaving group using a suitable reagent or catalyst, such as a Bronsted acid or Lewis acid.[5] This generates an electrophilic carbon center that can undergo a nucleophilic addition the alkyne. The generated vinyl carbocation can be attacked with various nucleophiles like C, N, O, X etc. Ongoing research in this domain is focused on developing new catalysts and improving reaction conditions to increase the possibility of preparing a broad spectrum of organic molecules.

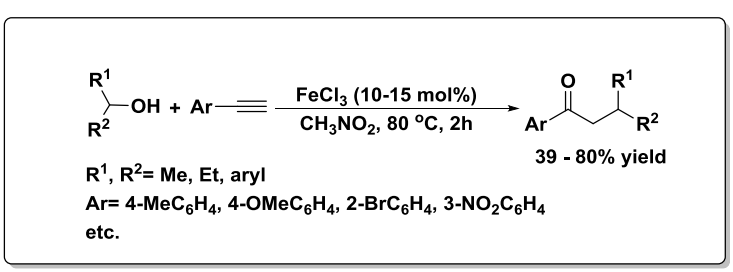
2. BRIEF REVIEW:

This brief review provides valuable insights into the recent advancements in C-C

bond formation using alcohols and alkynes covering the period of the last 14 years (2006-2020). By providing a comprehensive overview of the developments in this area, this short review is expected to be a valuable resource for the reader to devise and advance novel reactions using this strategy. Based on the methods by which the reactions occur, the review has been classified into five sub-topics.

2.1. Carbohydroxylation reaction:

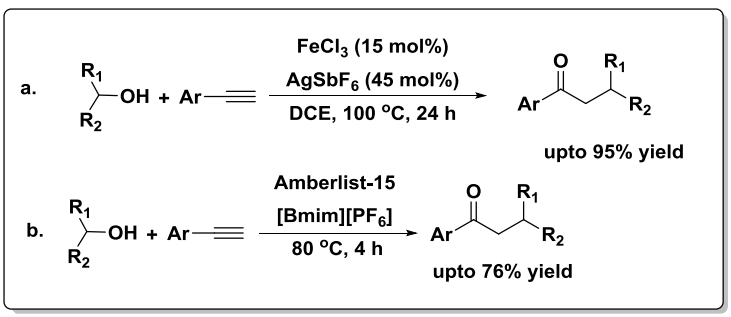
In 2008, Jana and co-workers introduced $FeCl_3$ catalyzed tandem C-C/C-O bond formation by direct addition of benzylic alcohols with terminal aryl alkyne to synthesise substituted aryl ketones (scheme 2)[6] in good yields. Readily available alcohols and alkynes were used for the transformation and the reaction was complete within 2 h in presence of environmentally benign $FeCl_3$ catalyst in nitromethane at 80 °C. It was well established that in presence of $FeCl_3$, benzylic alcohols are first transformed into dimeric ether which was then polarised by $FeCl_3$ to generate a benzyl carbocation. Alkyne then undergoes nucleophilic attack to the benzyl carbocation to afford vinyl carbocation, which is further attacked by the water to form the desired ketone.



Scheme 2: $FeCl_3$ catalyzed addition of alcohol to terminal alkyne

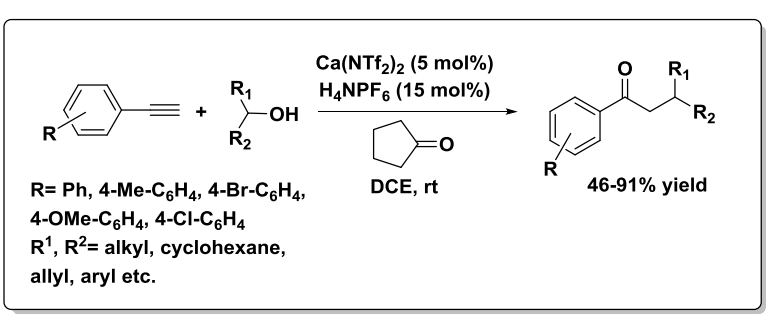
In 2014, the group of Cook has utilized the same concept of alcohol addition to alkyne to generate ketones in presence of $FeCl_3$ (15 mol%)/$AgSbF_6$ (45 mol%) in solvent DCE, 80°C (scheme 3a).[7] The main beneficial point of this method was the unprecedented activation of unactivated secondary alcohols in the presence of $FeCl_3$-$AgSbF_6$ couple. The method provided high yield (upto 95%) but required longer reaction time (24 h). Adamantadine, an antiviral and anti parkinsonian drug, could be achieved by this method simply by using 1-adamantol as the starting alcohol. One year later, Bhanage *et al*. reported a metal, additive and solvent free methodology of carbohydroxylation of alkyne in presence of Amberlyst-15 immobilized in

[Bmim][PF_6] ionic liquid (scheme 3b).[8] Avoiding organic solvents, the protocol used a recyclable catalytic system consisting green solvent ionic liquid which provided moderate to good yields (64 - 76%) in 80 °C, 4 h.



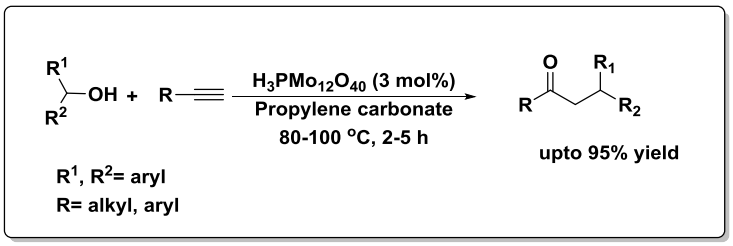
Scheme 3: $FeCl_3$-$AgSbF_6$ couple for the addition of alcohol to alkyne

The same reaction was further modified by Niggemann *et al.* by replacing the iron catalyst by non-transition metal $Ca(NTf_2)_2$ catalyst in presence of Lewis basic "Electron Pair Donor" (ED) and additive H_4NPF_6 (scheme 4).[9] They observed that Ca^{2+} with the combination of noncoordinating anions exhibited highly efficient lewis acid catalyst to ionize allylic, benzylic, propargylic alcohols. Though ED was generally used for the cationic polymerzation, the group first time used it in small molecule synthesis. They used cyclopentanone as ED which formed a Lewis acid/base pair with the alkenyl cation centre and thereby stabilised the intermediate reducing the formation of undesired side products.



Scheme 4: Calcium catalyzed carbohydroxylation of alkynes using cyclopentanone as ED

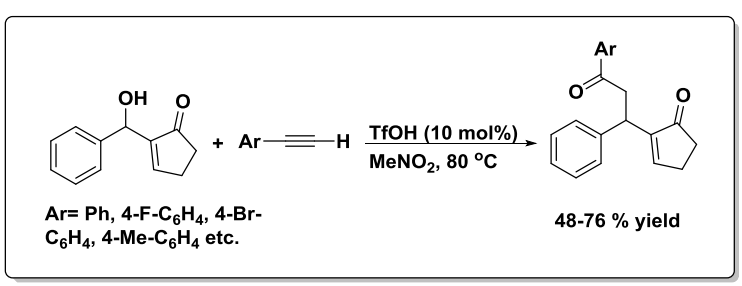
Hu and co workers exploited Polyoxometalates (POMs) as dehydrating agent for the alcohol dehydrogenation (scheme 5).[10] They performed the carbohydroxylation of alkyne in the presence of cheap phosphomolybdic acid ($H_3PMo_{12}O_{40}$) catalyst and non-volatile green propylene carbonate (PC) solvent at



Scheme 5: POMs catalyst for dehydrogenation of alcohols

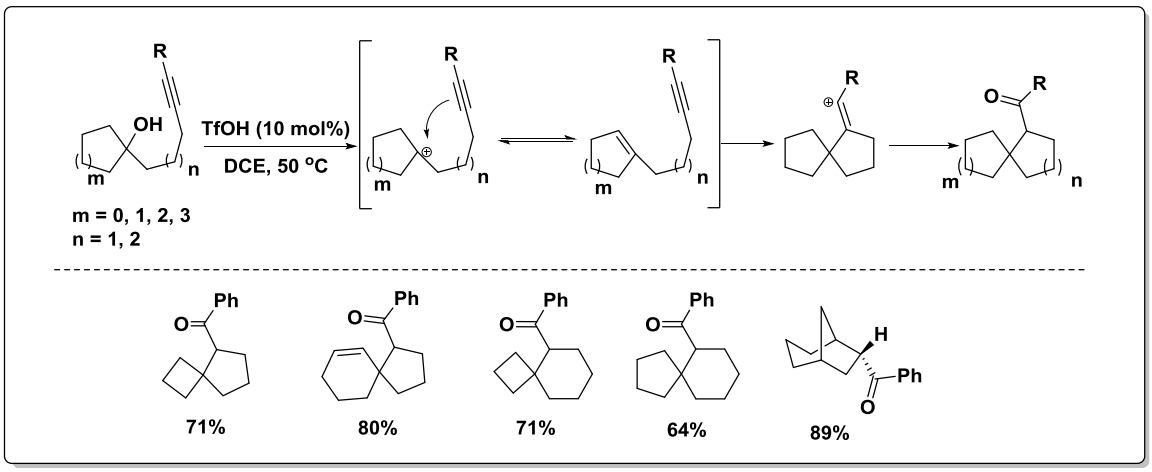
80-100 °C. Good to excellent yields of a number of β-arylethyl ketones and amides were obtained in 2-5 h with high TON of the catalyst.

Baylis-Hillman alcohols bearing both allylic alcohol group and Michael acceptor were exploited as electrophiles by the group of Chen for the substitution reaction with arylacetylenes (Scheme 6).[11] The reaction displayed α-regioselectivity producing γ,δ-unsaturated ketones in satisfactory yields under TfOH (10 mol%) catalysis in nitromethane at 80 °C within 1 h. The reaction was found to tolerate electron deficient and electron releasing substitutents in both alcohols and alkyne skeleton.



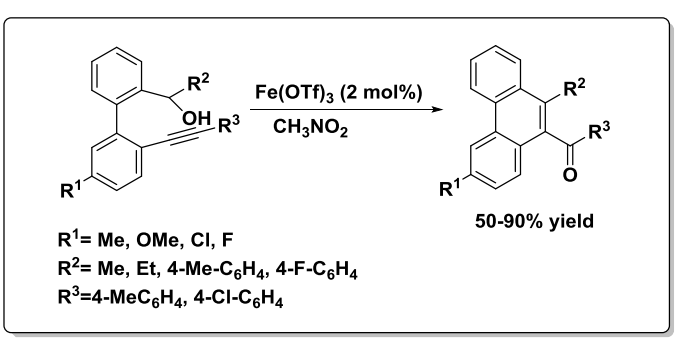
Scheme 6: TfOH catalyzed carbohydroxylation of alkyne with Baylis-Hillman alcohols

Following the same concept, Yamamoto *et al.* developed an unprecedented synthesis of spirocycles with controlled ring size *via* TfOH catalyzed cyclization of alkynyl cyclic tertiary alcohols in mild reaction condition (scheme 7).[12] Mechanistic investigation showed that the product was formed *via* 1,6-eneyne which was rapidly converted into the product within half an hour. Both EDG and EWG aromatic group and alkenyl group at the alkyne moiety provided adequate yields. However, alkyne substituted with alkyl group failed to perform the reaction. Some interesting spirocycles were formed easily by this method which was difficult to synthesise by other known methods.



Scheme 7: TfOH catalyzed cyclization of alkynyl cyclic tertiary alcohols

2-alkynylbiphenyl-2-carbinols were utilised as the substrate for the generation of substituted phenanthrene by $Fe(OTf)_3$ catalyzed tandem C-C/C-O bond formations/aromatization of the starting alcohol (scheme 8).[13] The group of Jana has successfully synthesized a vast array of phenanthrene derivatives containing several groups like –Me, –OMe, –F, –Cl, –Et, –Ph etc. However, primary benzyl alcohols

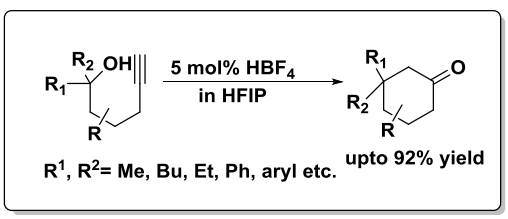


Scheme 8: Use of $Fe(OTf)_3$ for cascade C-C/C-O bond formations/aromatization

were proved to be less effective than secondary benzyl alcohols as the carbocation would be less stable for the former case and even at higher temperature lesser yields were obtained for them (50% and 54%). The reaction exihibited good regioselectivity *via* a cationic 6-*exo-dig* mode of cyclization.

Alonso *et al.* conceived the idea of cationic cyclization of alkynol or enyne to synthesize cyclohexanone derivative in presence of 5 mol% HBF_4 in HFIP solvent (1,1,1,3,3,3-hexafluoropropan-2-ol) (scheme 9).[14] Cyclohexanones are formed in this method by selective *6-endo-dig* cyclization method. Careful screening explored that,

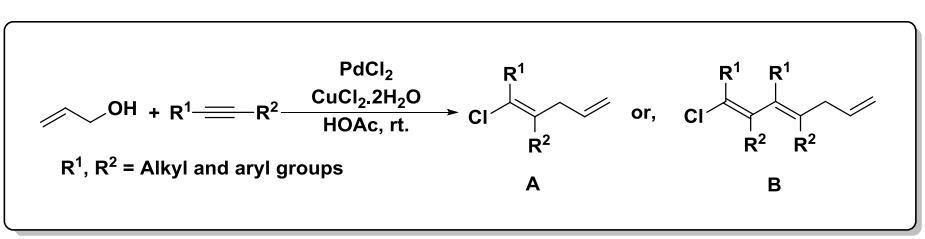
with the other existing conditions, corresponding enyne derivatives and cyclohexene derivatives were obtained. Only with the current reaction condition, exclusively cyclohexanone was obtained with 90% yield. Remarkably, they have also developed $HBF_4.OEt_2$ catalyzed biomimetic polyene cyclization for the construction of polycyclic ketones in good yields.



Scheme 9: Cationic cyclization of alkynol to synthesize cyclohexanone

2.2. Carbohalogenation reaction:

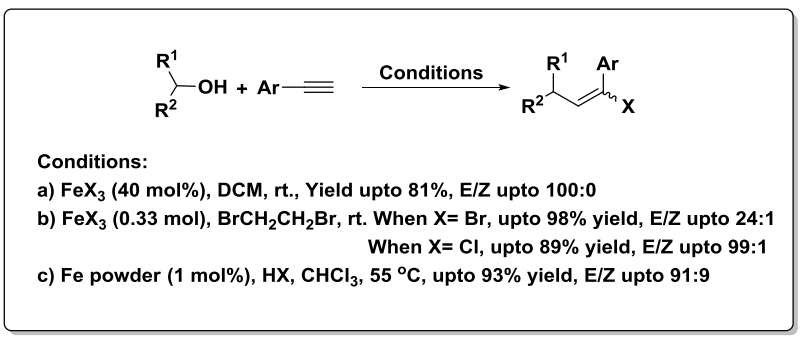
The palladium catalyzed coupling of alkyne and allyl alcohols was utilised as the key methodology for the synthesis of alkenyl halide by Huang and his group in the year 2006 (scheme 10)[15]. This method works in the presence of $CuCl_2.H_2O$ to provide 1,4-dienes in aqueous medium with high regio and stereoselectivity. A huge number of substrates were tested under the reaction condition, and product **A** was obtained selectively in case of internal alkynes. But when terminal alkyne was employed, product **B** was obtained where two molecules of alkynes reacted with one molecule of alcohol. The mechanism suggested that there was a competition between π-allylpalladation, which was formed by the C–O bond cleavage of the allyl alcohol, and the alkene insertion and that explained the generation of the desired product.



Scheme 10: $PdCl_2/CuCl_2.2H_2O$ couple for the synthesis of alkenyl halide

Biswas *et al.* reported a new and efficient one pot protocol for the synthesis of alkenyl halides *via* iron mediated coupling of alkynes and alcohols (Scheme 11a).[16a] Reaction requires the use of 0.4 equiv of $FeCl_3/FeBr_3$ in DCM solvent at room temperature. Various alkenyl chloride and bromides were synthesized by this protocol

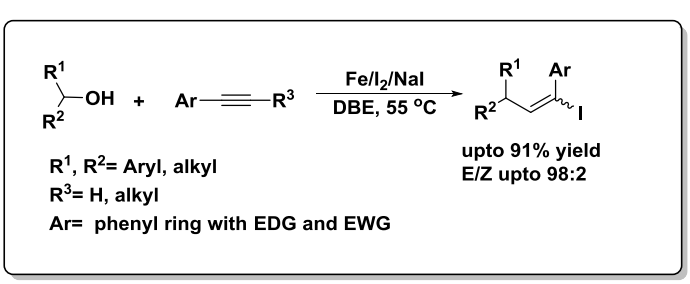
with high regioselectivity. Iron salt acts as Lewis acid as well as source of halogen. In the next year, a similar method was reported by the group of Ren where 0.33 equivalent FeX_3 was used in 1,2-dibromoethane



Scheme 11: Use of iron salts in reaction between alkyne and alcohols to synthesize alkenyl halides

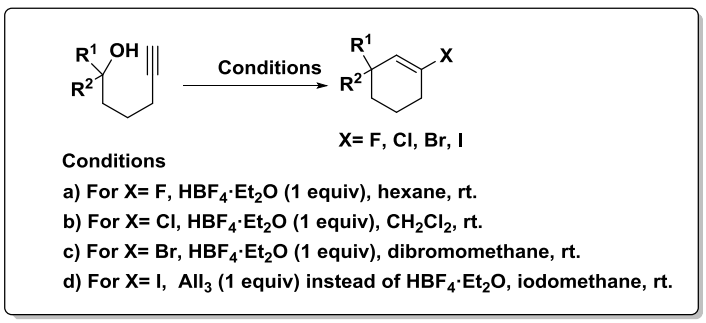
at room temperature in air provided the alkenyl halide efficiently without any additive (scheme 11b).[16b] Another strategy for the synthesis of alkenyl halide utilised HX as the halide source, and very low loading of Fe powder was used catalyst (scheme 11c).[16c]

However, alkenyl iodide could not be achieved by the above mentioned methods due to the labile nature of FeI_3. To overcome this problem, the group of Ji used iron powder, I_2 and NaI for the synthesis of alkenyl iodide (scheme 12).[17] Two pathways were suggested to explain the reaction mechanism, either through ether formation from the alcohol, or direct substitution of alcohol with the alkyne.



Scheme 12: Synthesis of alkenyl iodide using $Fe/I_2/NaI$

Recently, a cyclic alkenyl halide synthesis was developed by Alonso *et al.* by the reaction of enyne or alkynol derivatives mediated by tetrafluoroboric acid (scheme 13).[18] The reaction was highly regioselective and a vast array of alkenyl halide was

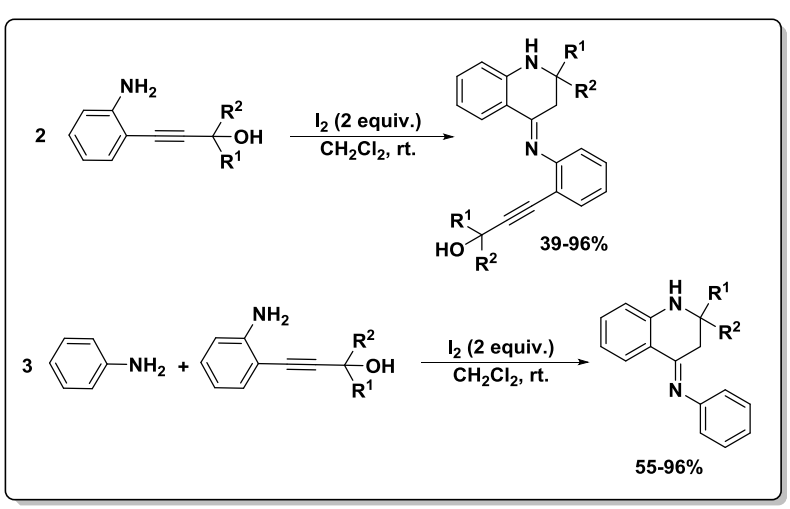


Scheme 13: Tetrafluoroboric acid mediated synthesis of cyclic alkenyl halide

obtained in adequate yields. Applicability of the above method was further proved by preparing halogen containing polycyclic compounds *via* biomimetic cyclization of polyenes. This protocol was also employed for the preparation of Austrodoral and pallescensin A tarpenes and odorant 9-epi-Ambrox.

2.3. Carboamination reaction:

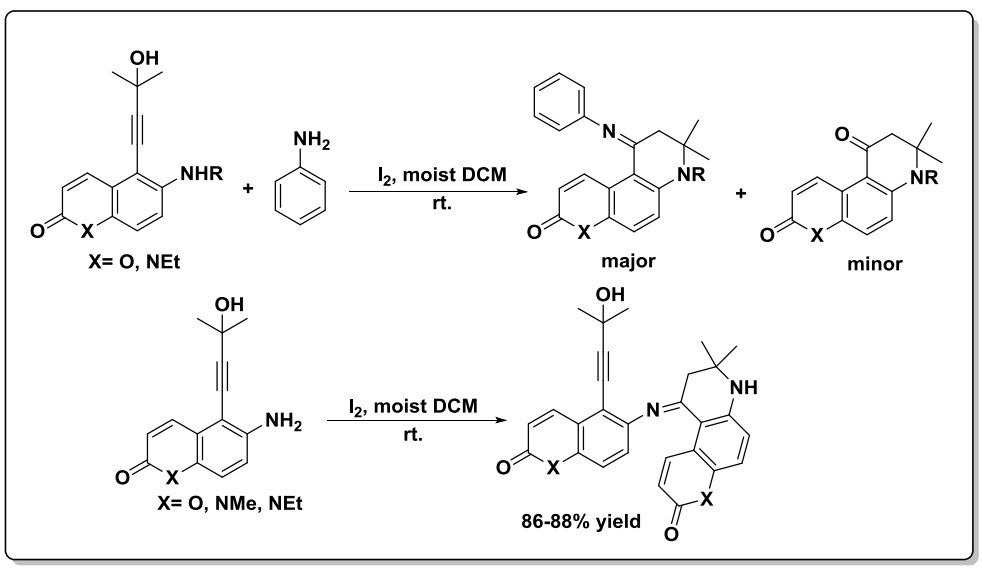
In 2012, Yeh and his coworkers introduced the carboamination reaction by the iodine mediated domino cyclization of aromatic amine containing propargylic alcohol which afforded 2,2-disubstituted tetrahydroquinoline efficiently (scheme 14).[19a] The reaction provided better yield when R^1 was electron donating groups than electron withdrawing groups. And strongly electron withdrawing group like acyl failed to perform the reaction. Further analysis of the products with ^{1}H NMR and XRD



Scheme 14: Iodine mediated carboamination reaction

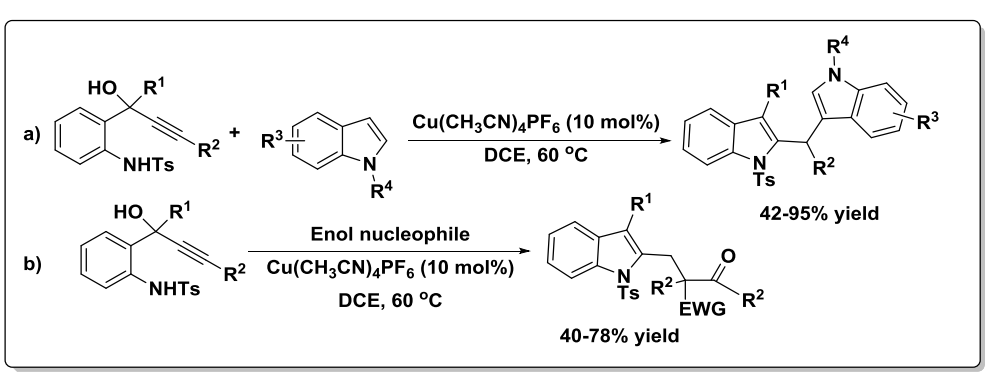
disclosed that the major isomer had *E* configuration at the C=N bond. They have further extended this method by introducing 3 equivalent of anilines with propargyl

alcohol-containing aromatic amine to obtain 2,2-disubstituted tetrahydroquinoline derivatives with good diastereoselectivity. In this case also *E*-isomer was formed predominantly in presence of iodine promoter. In the next year, the group of Majumder has reported the same strategy to synthesize pyrano[3,2- *f*]quinoline and phenanthroline regioselectively (scheme 15).[19b]



Scheme 15: Construction of pyrano[3,2- *f*]quinoline and phenanthroline *via* carboamination reaction

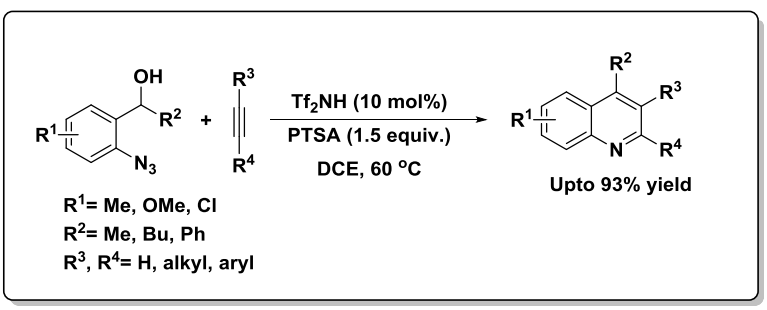
In 2014, Li *et al.* devised an effective synthesis of 2,3`-diindolylmethane by the copper catalyzed annulations/arylation of propargyl alchol-containing aromatic amines and indole nucleophiles (scheme 16a).[20] Recently, another report was published where instead of indoles, enols were used as nucleophile (scheme 16b).[21]



Scheme 16: Copper catalyzed annulations/arylation of propargyl alchol-containing aromatic amines and nucleophiles

The mechanism revealed that, both of the reactions were initiated by the activation of the triple bond with copper catalyst, and thus passed through an allylic carbocationic intermediate.

A metal free carboamination was described by the reaction of unactivated alkynes and azide tethered benzylic alcohols using Tf_2NH catalyst and PTSA additive (scheme 17).[22] This method yielded moderate to good amounts of highly substituted quinoline derivatives. For the alkyne with two different groups, mixture of isomers

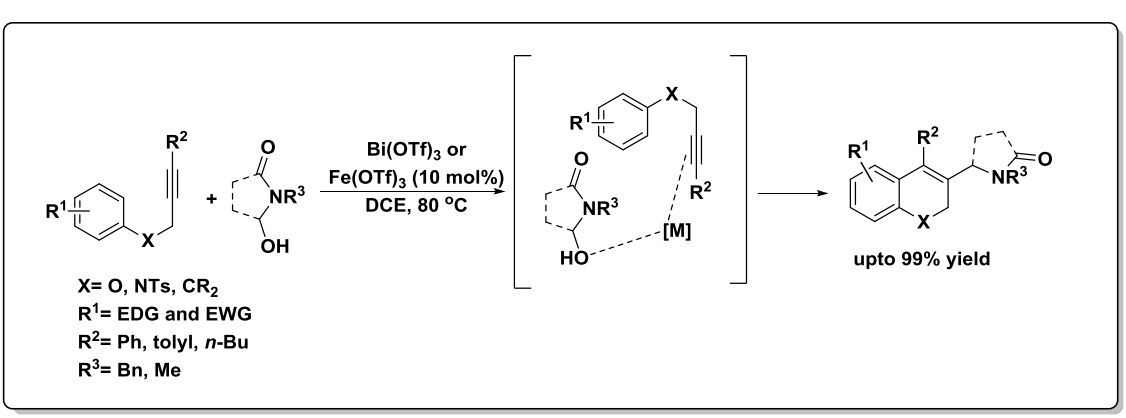


Scheme 17: Metal free carboamination of alkynes and azide tethered benzylic alcohols

was achieved. The irreversible removal of N_2 drives the poorly nucleophilic aliphatic alkynes also to participate in the sequential C–C bond formation–Schmidt reaction.

2.4. Carboarylation reaction:

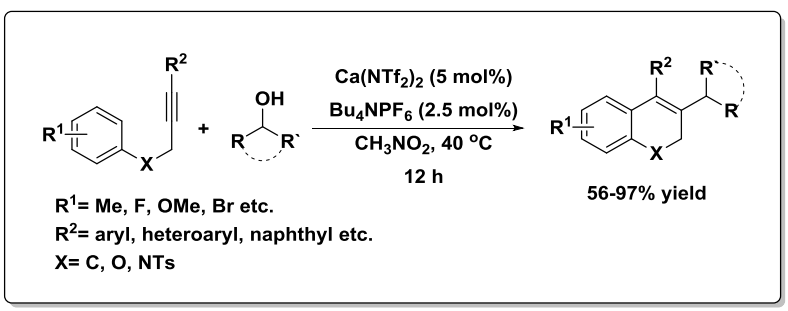
In 2012, Komeyama and his coworkers utilized borderline metals like $Fe(OTf)_3$ and $Bi(OTf)_3$ to generate *N*-acyliminium ions from *N*,*O*-acetals, which



Scheme 18: Carboarylation of alkynylarenes and *N*,*O*-acetals catalyzed by $Bi(OTf)_3$ or $Fe(OTf)_3$

successfully performed the carboarylation of alkynylarenes (scheme 18).[23] $Fe(OTf)_3$ and $Bi(OTf)_3$ acted as dual activator by activating both the alkyne and the *N,O*-acetal through σ,π-chelation. Various substitution patterns at the alkynylarenes, particularly containing nonprotected heteroatom, and different *N,O*-acetals exhibited good compatibility under this reaction condition.

Another carboarylation of alkynes with alcohols were reported by the group of Niggemann to synthesize tetra-substituted alkenes efficiently (scheme 19).[24] This

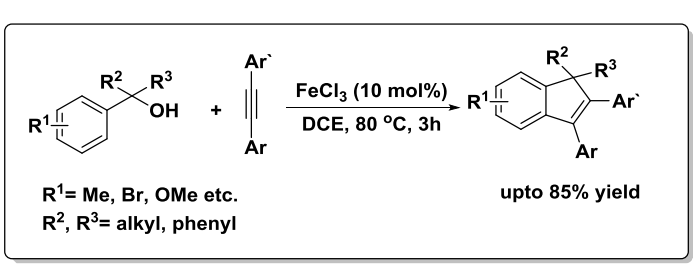


Scheme 19: $Ca(NTf_2)_2$ catalyzed carboarylation of alkynes with alcohols

metal free protocol was established with benign $Ca(NTf_2)_2$ catalyst and Bu_4NPF_6 additive in nitromethane solvent at 40 ^oC in 12 hours provided the desired alkenes in good yields. According to the mechanism analysis, the reaction went through a highly reactive vinyl carbocation which was attacked by the tethered aryl ring to generate the desired product. The reaction used easily available π-activated alcohols and high steric congestion was tolerated in the reaction condition.

2.5. Annulation reaction:

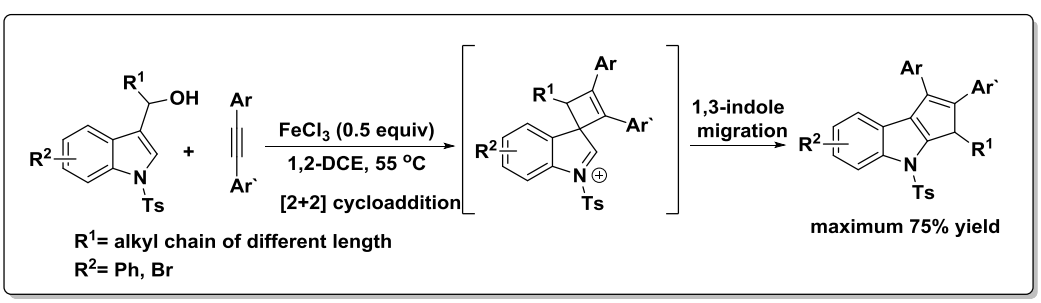
Niharika *et al*. has described a $FeCl_3$ promoted annulations of *tert*-benzyl alcohols and alkynes to obtain substituted indene derivatives with one quaternary



Scheme 20: $FeCl_3$ catalyzed annulations of *tert*-benzyl alcohols and alkynes

carbon centre (Scheme 20).[25] Although, two C-C bonds were formed simultaneously, and a variety of indene derivatives were prepared by this method, but the method was limited to only *tert*-benzyl alcohols. Moreover, when R^1 and R^2 are different, then mixture of isomers was obtained. $FeCl_3$ first activated the alcohol to create the tertiary carbocation, which was subsequently attacked by the diaryl alkyne to form the vinyl carbocation. This vinyl carbocation was then attacked intramolecularly by the aryl ring to afford the target material.

$FeCl_3$ was also very effective to catalyze formal [3 + 2] annulations/rearrangement of 3-indolylmethanols and alkynes to afford cyclopenta[*b*]indole frameworks (scheme 21).[26] A variety of substitution pattern at the 3-indolylmethanols and alkynes were suitable for the

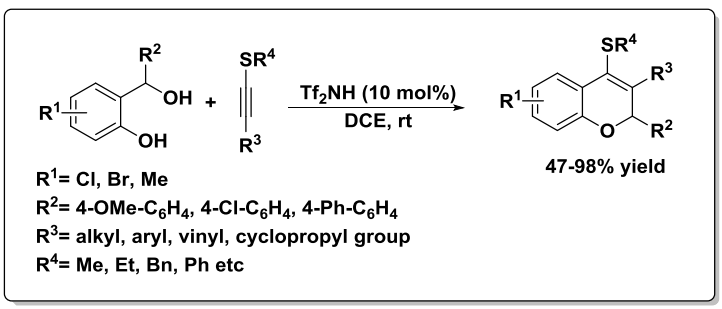


Scheme 21: [3 + 2] annulations/rearrangement of 3-indolylmethanols and alkynes

conversion. But alkynes with electron withdrawing groups, alkyl substituted alkynes and terminal alkynes failed to participate in the reaction. Another limitation of the methodology was the incompatibility of the *N*-acyl and triflet substituted indolylmethanols for the reaction. The mechanism displayed that, the reaction encompasses a vinyl carbocation and a tandem ring-opening and ring-closure, followed by a 1,3-indole migration produced the desired product *via* a spirocyclobutene intermediate.

In the same year, another metal free [4+2] annulation of alkynyl thioethers with o-hydroxybenzyl alcohols was developed by the group of Ye (scheme 22).[27] This method yielded various polysubstituted 2*H*-chromenes in good to excellent yields. Different functional groups at both the alkynyl thioethers and o-hydroxybenzyl alcohols were compatible to undergo the transformation. In presence of Tf_2NH, first, the *o*-quinone methide intermediate was formed. Then Michael addition with alkynyl

thioether led to the formation of the sulfonium species. After that, a spirocyclobutene intermediate was generated by the nucleophilic addition of the enolate. Then



Scheme 22: Metal free [4+2] annulation reaction for the preparation of 2*H*-chromenes

subsequent ring opening of the spirocyclobutene and another Michael addition furnished the desired product.

3. CONCLUSION:

In conclusion, the direct substitution of alcohol with alkyne is a valuable addition to the synthetic chemist's toolbox and it is proved to be a promising alternative to traditional methods for C-C bond formation. Although this protocol offers several advantages, including high atom economy, step economy, and the use of abundant and low-toxic starting materials, there is still a lot of scope to explore in this field. With the continued advancement of this field, it is expected that this approach can be used in synthetic chemistry for the fabrication of versatile complex molecules.

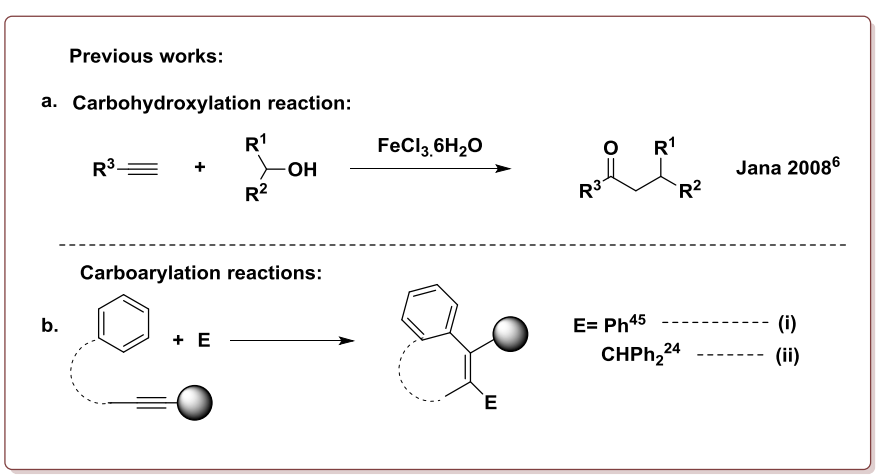
4. PRESENT WORK:

4.1. INTRODUCTION:

The multifaceted and diverse range of applications associated with the direct substitution of alcohols with alkynes has served as a major driving force in motivating us to devise and develop biologically significant moieties through the implementation of this innovative protocol. Previously, we have introduced a carbohydroxylation reaction of alkynes with π-activated alcohols using iron(III) salt as a catalyst (scheme 23a).[6] Since then, a plethora of reactions have been reported using benzyl alcohol as the carbocation source and cascade initiator of alkynes, including substitution of terminal alkynes,[28] carbohalogenation,[15-18] carboamination,[19-22] carbocyclization[23-27] etc. In recent

years, electrophilic arylation of alkynes by Brønsted acids, Lewis acids, and transition metal catalysts has emerged as a more convenient and atom-economic strategy for the synthesis of 1,2-dihydroquinolines and 2*H*-chromenes.[29] However, cascade arylations of alkynes promoted by carbon-centered electrophiles are still rare (scheme 23b).[24,30] Scheme 23b(ii) shows the benzylic alcohol-triggered carboarylation of alkynes tethered to aryl rings developed by Niggemann *et al.* using 5 mol% $Ca(NTf_2)_2$ as a catalyst in combination with 5 mol % Bu_4NPF_6 additive.[24] although there is significant progress in this area, there is still room for improvement and further advancement, particularly in the generation of benzofused heterocycles. For example, the catalyst systems used in some methods are complex, and the reaction times are long, limiting their utility in certain contexts.

In our quest to expand the utility of the alcohol-driven carboarylation technique, we

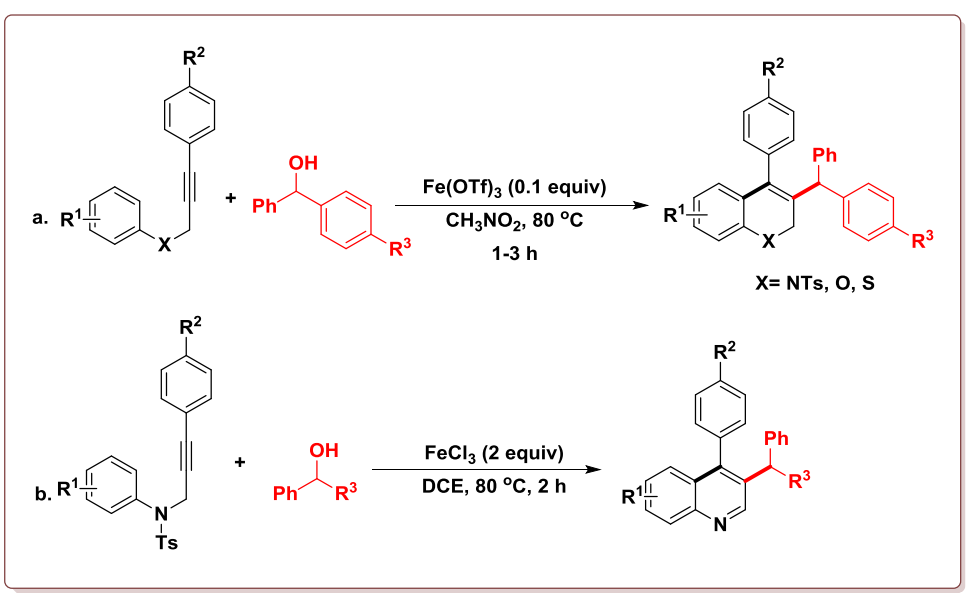


Scheme 23: Iron(III) catalyzed benzyl cation promoted arylation of alkyne *via* direct substitution of alcohol

sought a more general and efficient strategy for the tandem formation of two C-C bonds *via* heterocyclization, rather than carbocyclization. Building on our prior success in activating benzylic alcohols followed by the attack with alkynes using catalytic iron salt, we attempted carboarylation of alkynes tethered to aryl rings *via* aliphatic chains containing heteroatoms, with the aim of generating different heterocyclic skeletons (scheme 24).

We were concerned about potential obstacles such as parallel hydroarylation or carbohydroxylation reactions, but were pleased to find that we could achieve

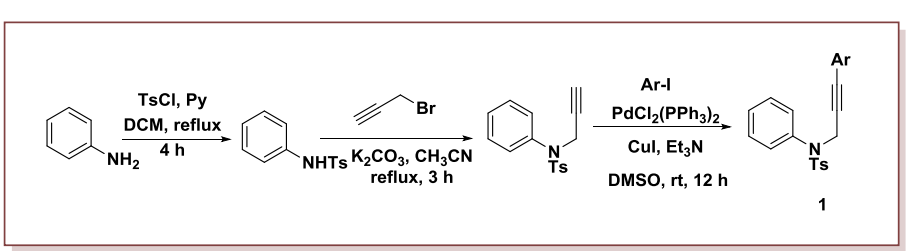
high chemoselectivity and regioselectivity using $Fe(OTf)_3$ catalysis. Varying the heteroatom allowed us to obtain different heterocyclic products, including 1,2-dihydroquinoline, chromene, and thiochromene, in high yields. Furthermore, when the reaction was conducted in the presence of 2 equivalents anhydrous $FeCl_3$, the initial product 1,2-dihydroquinolines underwent smooth aromatization to furnish quinoline derivatives in a single pot (scheme 24b). Our iron(III)-catalyzed carboarylation reaction of alkynes with activated benzylic alcohols offers a simpler, cheaper, and greener alternative to previous methods, with a much lower reaction time and a broader range of substrate options. The ability to synthesize different heterocycles with various substituents using a single synthetic protocol is another notable feature of this strategy.



Scheme 24: Iron catalyzed carboarylation of alkyne *via* direct substitution of alcohols

4.2. RESULTS AND DISCUSSIONS:

For the starting material preparation, first tosylation of the aniline with tosyl chloride,

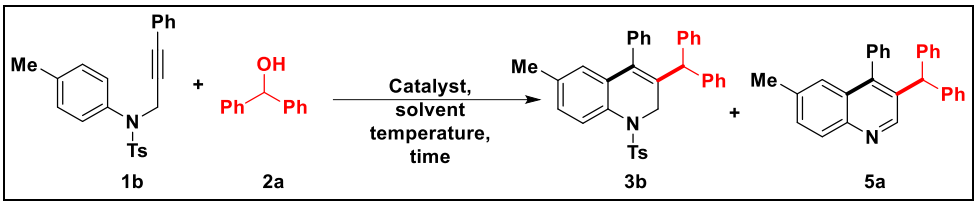


Scheme 25: Preparation of starting materials

then propargylation with propargyl bromide, followed by Sonogashira coupling with aryl iodide was performed (scheme 34). Detailed experimental Procedures have been stated at the end of the chapter.

With the prepared starting material 4-methyl-*N*-phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide derivatives (**1**) and diphenylmethanol (**2a**), we then aimed to study the optimization reaction conditions for the synthesis of two different

Table 1: Optimization of reaction conditions



Entry	Catalyst (equiv)	Solvent (2 mL)	Temp (°C)	Time (h)	Yield of 3b (%)	Yield of 5a (%)
1	$FeCl_3$ (0.1)	DCM	rt	2	trace	0
2	$FeCl_3$ (0.1)	DCM	rt	12	23	0
3	$FeCl_3$ (0.1)	DCM	reflux	2	34	0
4	$FeCl_3$ (0.1)	CH_3CN	60	2	0	0
5	$FeCl_3$ (0.1)	DCE	60	2	38	0
6	$FeCl_3$ (0.1)	DCE	80	2	42	30
7	$FeCl_3$ (0.1)	CH_3NO_2	80	2	55	20
8	$Fe(OTf)_3$ (0.1)	CH_3NO_2	80	2	89	0
9	$InCl_3$ (0.1)	CH_3NO_2	80	2	0	29
10	$In(OTf)_3$ (0.1)	CH_3NO_2	80	2	15	24
11	AgOTf (0.1)	CH_3NO_2	80	2	25	11
12	$Fe(OTf)_3$ (0.2)	CH_3NO_2	80	2	79	21
13	$Fe(OTf)_3$ (1.0)	CH_3NO_2	80	2	44	48
14	$FeCl_3$ (1.0)	CH_3NO_2	80	2	15	59
15	$FeCl_3$ (1.0)	DCE	80	2	trace	68
16	$FeCl_3$ (2.0)	DCE	80	2	0	87
17	$FeCl_3$ (2.0)	DCE	80	2	trace	53 (air)

products, 3-benzhydryl-6-methyl-4-phenyl-1-tosyl-1,2-dihydroquinoline (**3b**) and 3-benzhydryl-6-methyl-4-phenylquinoline (**5a**). Several catalysts and solvents were tested at different temperatures for the reaction of 4-methyl-*N*-(3-phenylprop-2-yn-1-yl)-*N*-(p-tolyl)benzenesulfonamide **1b** with diphenylmethanol **2a**. Initially, the reaction was performed using 10 mol% of anhydrous $FeCl_3$ in DCM solvent at room temperature for a time period of 2 h, but only a trace amount of **3b** was formed (Table 1, entry 1). However, when the reaction was continued for 12 hours, 23% of **3b** was isolated and 34% was formed in 2 hours under refluxing conditions (Table1, entries 2 and 3). Switching the solvent to acetonitrile (CH_3CN) at 60 °C, did not initiate the reaction at all, but using DCE under the same reaction condition provided 38% of **3b** (Table 1, entries 4 and 5). When the reaction was performed at 80 °C in DCE, the yield of the product was not improved much (42%), but a considerable amount (30%) of the corresponding detosylated product **5a** was isolated (Table 1, entry 6). Instead of DCE, using nitromethane at 80 °C produced both **3b** and **5a** with 55% and 20% yield, respectively (Table 1, entry 7). Now to screen the suitable catalyst, we have changed the catalyst from $FeCl_3$ to $Fe(OTf)_3$ at 80 °C, and pleasingly **3b** was isolated as the

CCDC no. 1982134

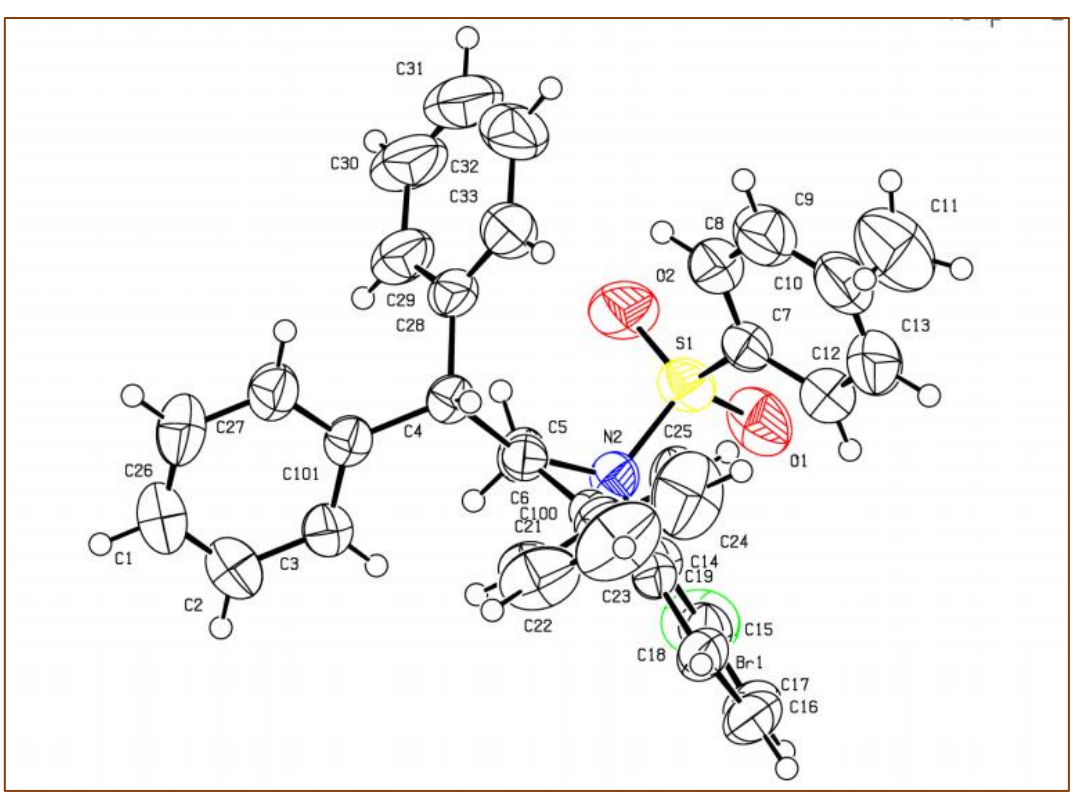
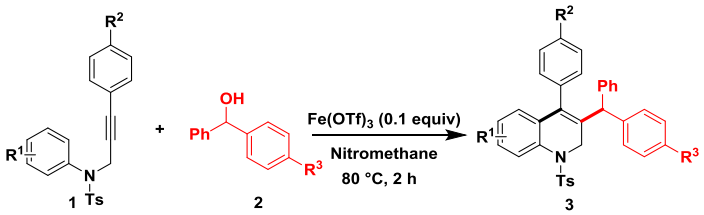


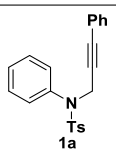
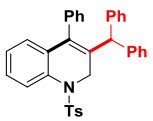
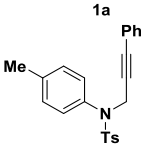
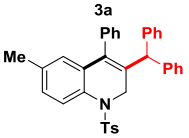
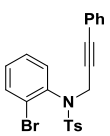
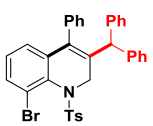
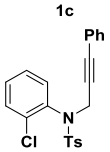
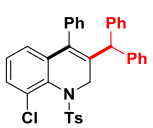
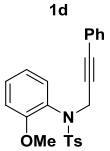
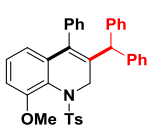
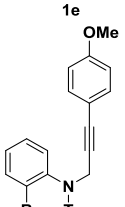
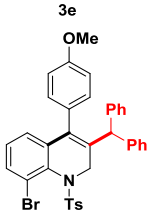
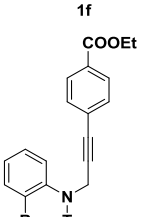
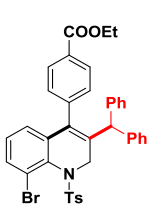
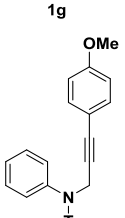
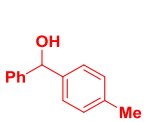
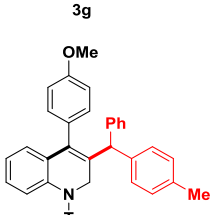
Figure 1. ORTEP diagram for the crystal structure of compound **3c** (Thermal ellipsoid contour at 50% probability level)

sole product with 89% yield just in 2 hours, with no trace of **5a** (Table 1, entry 8). The reaction was continued for another one hour, but no significant improvement of the yield was observed. However, no such better results were observed when the reactions were performed with other metal catalysts, like $InCl_3$, $In(OTf)_3$ and AgOTf (Table 1, entries 9, 10 and 11).Interestingly, increasing the catalyst loading did not further improve the yield of **3b**, but instead led to the formation of **5a** (Table 1, entry 12). Therefore, the focus shifted to obtain the best reaction conditions for the formation of **5a**, and gradually increasing the amount of $Fe(OTf)_3$ to 1 equivalent led to higher yields of **5a** (Table 1, entry 13). In order to check other iron salts, we then employed 1 equivalent of $FeCl_3$ in nitromethane (CH_3NO_2) and DCE at 80 °C, which produced 59% and 68% of **5a**, respectively (Table 1, entries 14 and 15). Further increasing the amount of $FeCl_3$ gradually increased the yield of **5a**, and using 2 equivalents of anhydrous $FeCl_3$ in DCE at 80 °C for 2 hours resulted in 87% yield of **5a** as the only product (Table 1, entry 16). When the reaction was performed under open atmosphere, the product **5a** was obtained in 53% yield with 2 equivalents of $FeCl_3$ (Table 1, entry 17). So, it is speculated that the presence of aerobic oxygen and moisture in the open air may have reduced the catalytic activity of the iron catalyst. Overall, the best reaction conditions to obtain **3b** were the catalysis of 10 mol% $Fe(OTf)_3$ in nitromethane at 80 ^oC and for **5a**, the optimum reaction condition turned out to be the use of 2 equivalents of anhydrous $FeCl_3$ in DCE at 80 $^\circ C$ in 2 h.

To evaluate the practicality of the reaction, a range of 4-methyl-*N*-phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide derivatives **1** (0.15 mmol) were reacted with 0.15 mmol diphenylmethanol **2a** using the 10 mol% $Fe(OTf)_3$ catalyst in nitromethane solvent at 80 ^oC. The substitution pattern of the aniline moiety was examined, which revealed that, electron-donating groups at the *para* position of the aniline provided superior yields compared to the unsubstituted derivative (Table 2, entries 1 and 2). Additionally, *ortho* substitution with either electron-withdrawing (-Br and –Cl) or electron-donating groups (-OMe) underwent the reaction smoothly, resulting in product yields ranging from 74% to 88% (Table 2, entries 3, 4 and 5). The crystal structure of dihydroquinoline **3c** was confirmed using single-crystal X-ray diffraction (CCDC no. 1982134) (figure 1).

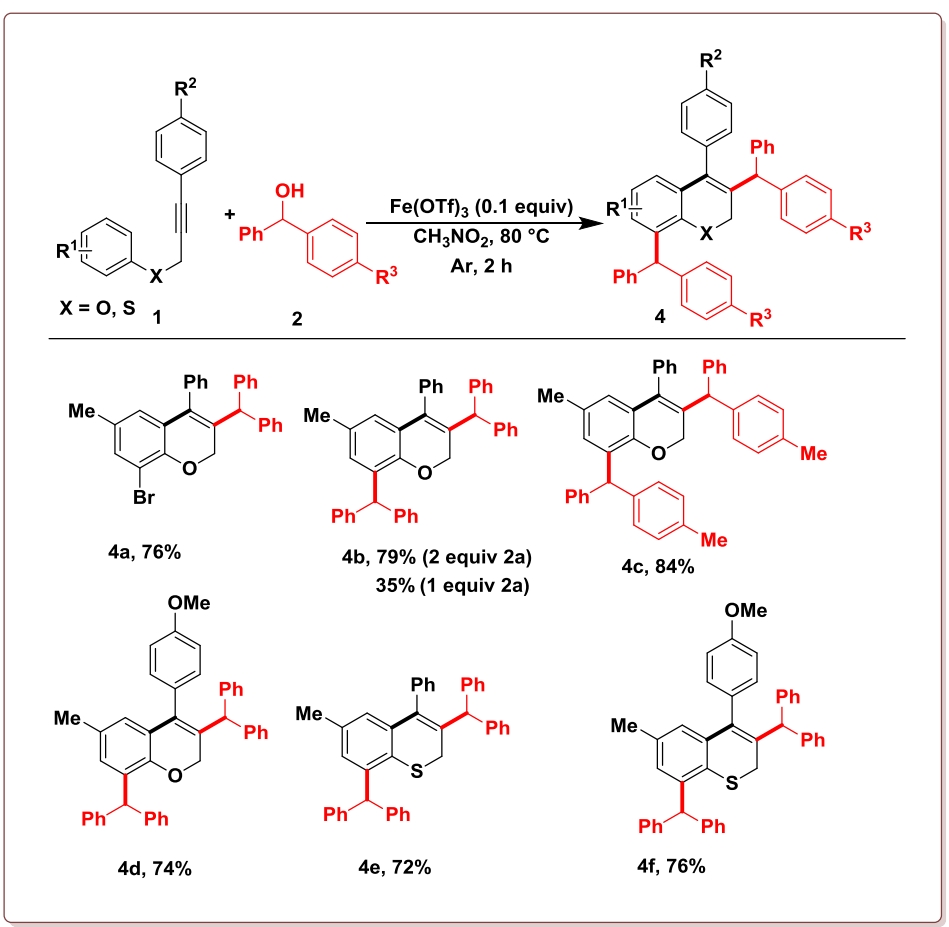
Table 2: Synthesis of dihydroquinoline derivatives by $Fe(OTf)_3$ catalyzed carboarylation of alkyne with catalytic activation of alcohol



Entry	substrate	alcohol	product	yield
1	 1a	 2a	 3a	71%
2	 1b	 2a	 3b	89%
3	 1c	 2a	 3c	88%,
4	 1d	 2a	 3d	81%
5	 1e	 2a	 3e	74%
6	 1f	 2a	 3f	92%
7	 1g	 2a	 3g	57%[c]
8	 1h	 2b	 3h	93%

The substituent effect on the alkyne moiety was also investigated. The electron-donating groups at the alkyne moiety led to higher yields than electron withdrawing groups due to their ability to stabilize the vinyl carbocation intermediate (Table 2, entries 6 and 7). Interestingly, using phenyl(*p*-tolyl)methanol (**2b**) instead of diphenylmethanol resulted in an excellent yield of 93% (Table 2, entry 8).

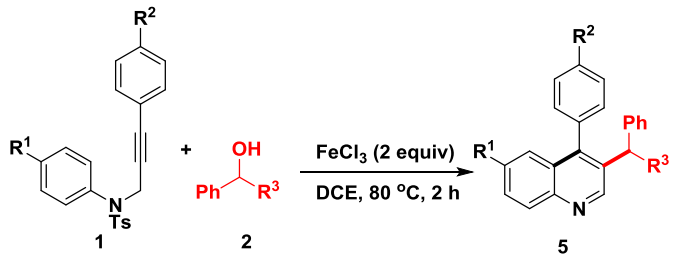
The versatility of this method was demonstrated by synthesizing 3-substituted chromene derivatives using 2-bromo-4-methyl-1-((3-phenylprop-2-yn-1-yl)oxy)benzene and 1-methyl-4-((3-phenylprop-2-yn-1-yl)oxy)benzene (scheme 26). When the former was allowed to react with 1 equivalent diphenylmethanol **2a**, the corresponding 3-alkylated chromene was formed with 76% of yield (scheme 26, entry

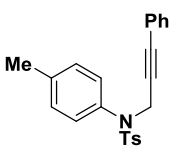
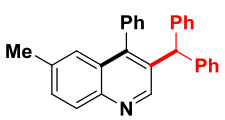
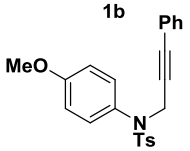
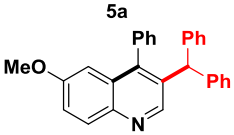
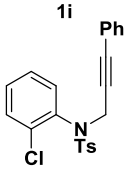
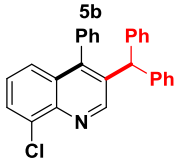
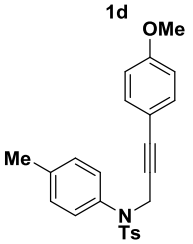
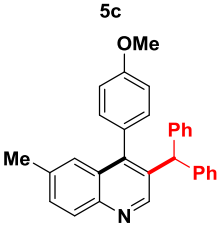
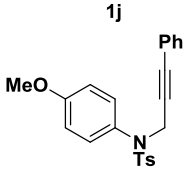
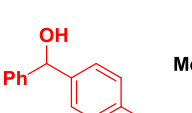
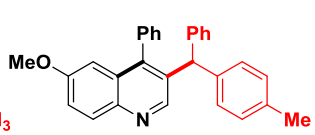
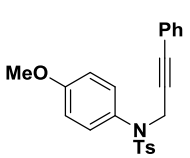
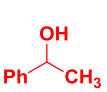
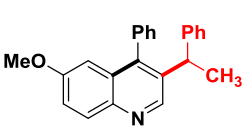


Scheme 26: Synthesis of chromene and thiochromene derivatives

4a). However, with the latter, in addition to carboarylation, conventional Friedel-Craft alkylation took place at the free *ortho* position, resulting in a densely substituted chromene in a low yield of 35%. For complete conversion, 2 equivalents of alcohol were used which resulted in a yield of 79% (scheme 26, entry **4b**). Interestingly, even

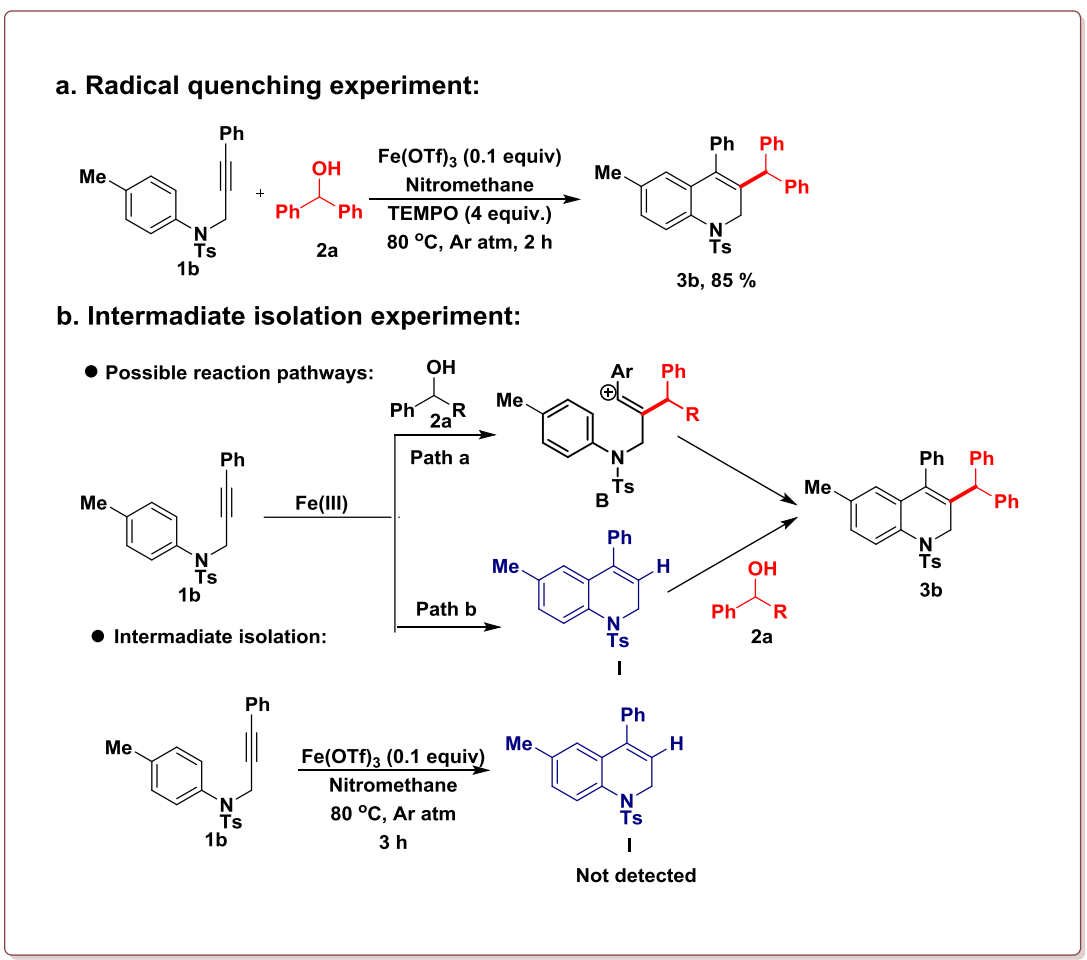
Table 3: Synthesis of quinoline derivatives



Entry	Substrate	Alcohol	Product	Yield (%)
1	 1b	 2a	 5a	87
2	 1i	 2a	 5b	89
3	 1d	 2a	 5c	63
4	 1j	 2a	 5d	92
5	 1i	 2b	 5e	93
6	 1i	 2c	 5f	79

using less than 1 equivalent of alcohol **2a** resulted in the formation of 3,8-dialkylated chromene **4b** in a yield of 29%. The use of 2 equivalents of alcohol **2b** improved the yield, providing 84% of **4c**. Electron-releasing groups (–OMe) in the aromatic ring of

the alkyne moiety also afforded good yield (**4d**, 74%). The sulfur analogue produced thiochromene derivatives **4e** and **4f** in good yields (72% and 76%, respectively). The difference in the reactivity pattern between the formation of dihydroquinoline and chromene/thiochromene proves that, the reactivity is highly altered by the steric and electronic factors imposed by the tosyl group attached to the nitrogen atom.

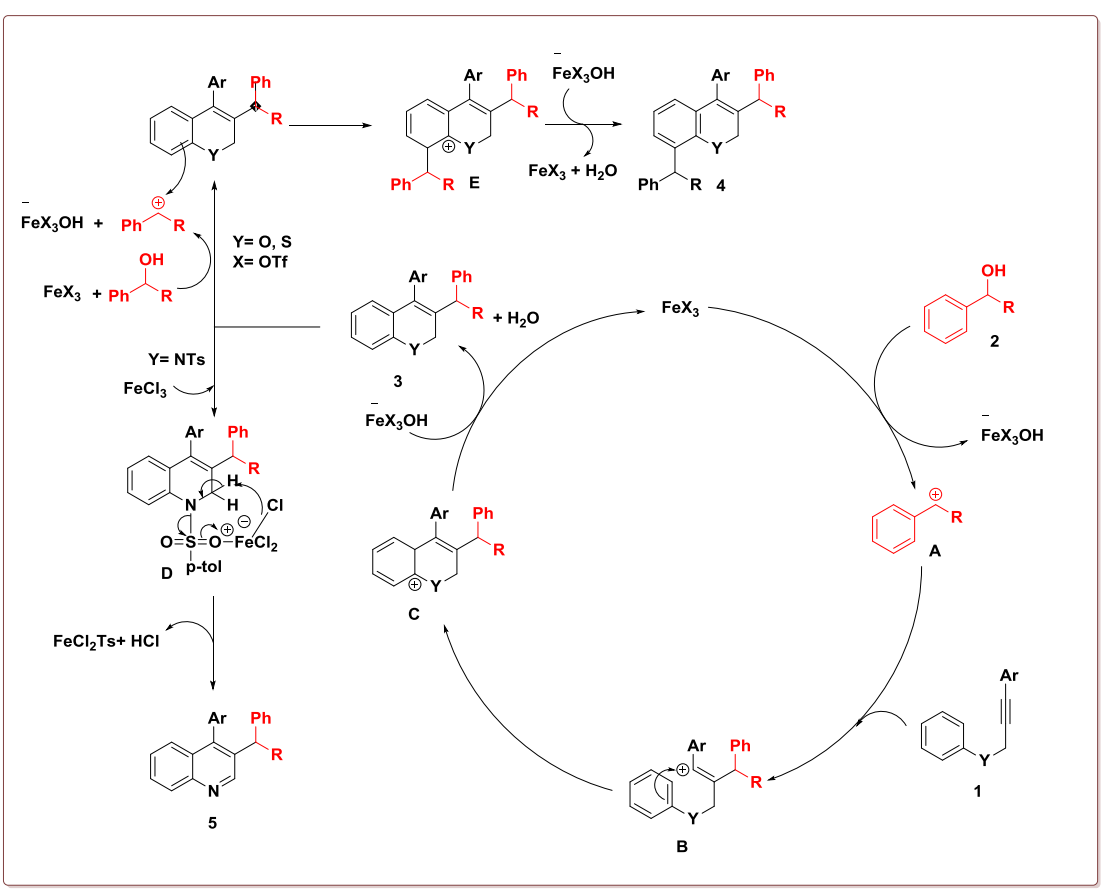


Scheme 27: Control Experiments

We have further investigated the use of 2 equivalents of $FeCl_3$ for the preparation of quinoline derivatives **5** in a single step (Table 3). It was found that electron-donating groups such as –Me and –OMe at the aniline moiety resulted in excellent yields of the corresponding quinolines, whereas the electron-withdrawing group *o*-Cl hindered the conversion (Table 3, entries 1, 2 and 3). Similarly, the use of *p*-OMe at the aromatic ring of the alkyne moiety provided better yields (Table 3, entry 4). The robustness of the method was confirmed by testing other alcohols, with alcohol having an electron-rich substituent yielding an impressive 93% yield of **5e** (Table 3, entry 5). However, when 1-phenylethanol was used as a coupling partner,

the reaction was slower, resulting in 79% of the desired **5f** (Table 3, entry 6). Overall, these results highlight the versatility and scope of the method for the synthesis of quinoline derivatives in a single step.

To investigate the reaction mechanism, we have also conducted a series of control experiments as shown in scheme 27. Interestingly, when a radical quencher, TEMPO (tetramethylpyridinyl *N*-oxide), was added to the reaction mixture under optimized conditions, the desired product was still obtained with no significant change in yield (Scheme 27a). This finding eliminated the possibility of any radical intermediates in the reaction. To find out, whether the reaction proceeds through path **a** or **b** (as shown in Scheme 27b), we conducted another experiment where the electrophile **2a** was omitted from the reaction mixture. However, no cyclization product was observed (scheme 27b), and the starting material **1b** decomposed upon prolonged reaction time. This ruled out the possible reaction pathway *via* the intermediate **I**.



Scheme 28: Plausible reaction pathway of iron catalyzed carboarylation of alkyne *via* direct substitution of alcohols

Based on the experimental results, control experiments and previous reports[31] a plausible reaction pathway is proposed for the synthesis of dihydroquinoline and quinoline derivatives (Scheme 28). The reaction starts with the activation of the π-activated alcohol **2** by the iron(III) catalyst, which generates the benzylic carbocation **A**. This intermediate then reacts with the more electron-rich alkyne to form the reactive vinyl carbocation **B**. The aryl nucleophile then attacks this carbocation, leading to the formation of 3-alkylated dihydroquinolines **3**. The product **3** can undergo Friedel-Craft alkylation in the presence of excess alcohol and $Fe(OTf)_3$ to produce **4** when Y = O, S. However, when Y = NTs, **3** can participate in the detosylation and aromatization process in the presence of excess $FeCl_3$ to form the corresponding quinoline derivatives **5**. Therefore, stoichiometric $FeCl_3$ is required for the preparation of the quinoline derivatives. We assume that the less basicity and nucleophilicity of the triflate anion compared to chloride may explain why $Fe(OTf)_3$ could not efficiently perform the detosylation/aromatization step.

4.3. CONCLUSION:

Our innovative and versatile approach for synthesizing densely substituted heterocycles includes Fe(III)-catalyzed carbenium ion-induced carboarylation of alkynes, and we have successfully obtained 1,2-dihydroquinolines, quinolines, 2*H*-chromenes, and thiochromenes in high yields. Our method boasts of direct activation of π-activated alcohols, readily available starting materials, good substrate scope, high yields, and high atom-economy. We have used inexpensive and eco-friendly Fe(III)-catalyst, which sets our method apart from the competition. Our results are not just impressive; also have tremendous potential for practical applications in various fields. Our method can be readily used for the synthesis of bioactive heterocyclic motifs, which is an area of active research in our laboratory. We are committed to exploring the full potential of iron-mediated carboarylation of alkynes strategy and advancing the frontiers of knowledge in this exciting field.

4.4. EXPERIMENTAL PROCEDURE:

4.4.1. Sample preparation and crystal structure determination for 3c (references 32-36):

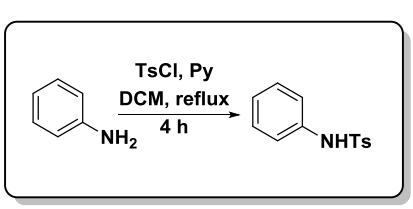
The single crystal Suitable for X-ray of compound **3c** was mounted on the tip of a thin glass fiber with commercially available glue. The X-ray single crystal data collection of **3c** crystal was performed at room temperature using a Bruker APEX III D_8 Quest smart diffractometer, equipped with a microfocus and a sealed tube X-ray source with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The data were integrated using the SAINT1 program, and the absorption corrections were made with SADABS.2 The structure was solved by SHELXS 20173 using the Patterson method and followed by successive Fourier and difference Fourier synthesis. Full matrix least-squares refinements were performed on F2 using SHELXL-20174 with anisotropic displacement parameters for all non-hydrogen atoms. All hydrogen atoms were fixed geometrically by HFIX command and placed in ideal positions. All calculations were carried out using SHELXS-2017, 3 SHELXL-2017, PLATON v1.15,4 ORTEP-3v2,5 and WinGX system Ver-1.80.6 The data collection and the structure refinement parameters and crystallographic data for the compound are given in below table.

4.4.2. Table for crystallographic data and structural refinement parameters for 3c

Empirical formula	$C_{35}H_{28}BrNO_2S$
Formula weight	606.57
Temperature/K	273(2)
Crystal system	monoclinic
Space group	'C 2/c'
a/Å	31.598(3)
b/Å	11.6057(9)
c/Å	21.0251(17)
α/°	90

β/°	129.356(2)
γ/°	90
Volume/Å^3	5961.7(8)
Z	8
ρ_{calc}g/cm^3	1.360
μ/mm^{-1}	1.483
F(000)	2512
Crystal size/mm^3	.3 × .2 × .1
Radiation	MoK\a (λ = 0.71073)
θ range/°	2.5825 to 24.6152
Index ranges	-39 ≤ h ≤ 39, -14 ≤ k ≤ 14, -26 ≤ l ≤ 26
Data/restraints/parameters	6126/0/362
Goodness-of-fit on F^2	1.056
Largest diff. peak/hole / e Å^{-3}	0.44/-0.609

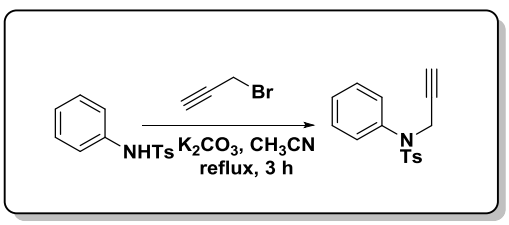
4.4.3. Representative Experimental Procedure for the Synthesis of *N*-propargylanilidines:



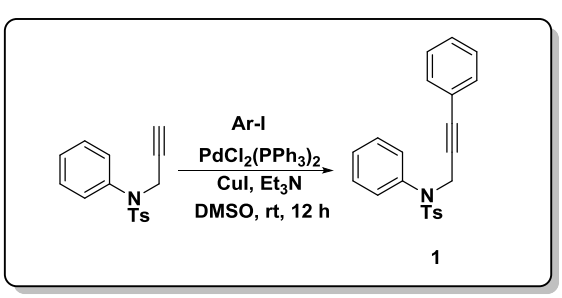
Step-I: To a solution of aniline (465 mg, 5 mmol) in DCM (5 mL), tosyl chloride (1.42 g, 7.5 mmol) and pyridine (790 mg, 10 mmol) were added. And the resulting mixture was subjected to reflux for 4 hours. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with DCM (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product

was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the tosylated product as a brown solid (1.2 g, 4.9 mmol, 98%).

Step-II: To the *N*-tosylaniline (494 mg, 2 mmol), propargyl bromide (285 mg, 2.4 mmol) and activated K_2CO_3 (828 mg, 6 mmol) was added in acetonitrile solvent. The



resulting mixture was refluxed for 3 hours. After completion of reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel, 60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the propargylated product as a yellow solid (524 mg, 1.84 mmol, 92%).



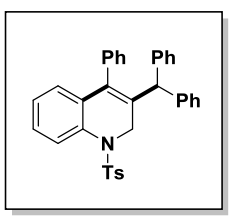
Step-III: In the next step, Sonogashira coupling of the propargylated product was done where iodobenzene (440 mg, 2.16 mmol) was added to the propargylated product (513 mg, 1.8 mmol) in presence of triethyl amine (363 mg, 3.6 mmol) in DMSO solvent. To the reaction mixture, $PdCl_2(PPh_3)_2$ (25 mg, 0.036 mmol)and CuI (6.84 mg, 0.036 mmol) were added, and stirred for 12 hours at room temperature. After completion of reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography (silica gel,

60-120 mesh), eluting with pet ether/EtOAc 90:10 (v/v) to afford the product as a yellow solid (578 mg, 1.6 mmol, 89%).

All the starting materials **1a-1h** were prepared by the above mentioned procedures.

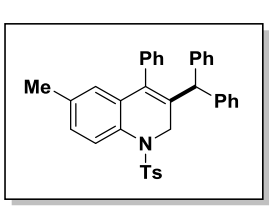
4.4.4. Representative Experimental Procedure for the Synthesis and Characterization of 3a-3h:

3-Benzhydryl-4-phenyl-1-tosyl-1,2-dihydroquinoline (3a): In an oven-dried round-bottom flask, 4-methyl-*N*-phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**1a**) (54 mg, 0.15 mmol) and diphenylmethanol (**2a**) (27 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $Fe(OTf)_3$ (7.5 mg, 0.015 mmol) was added to the mixture under argon atmosphere and stirred for 2 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic layer was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (95:5 v/v), to afford the desired product **3a** (35.5 mg, 0.06 mmol, 71%) as a light yellow solid, m.p. 184–188 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.80 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.39 – 7.15 (m, 10H), 7.12 – 7.01 (m, 5H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.54 (t, *J* = 8.4 Hz, 5H), 4.93 (s, 1H), 4.68 (s, 2H), 2.37 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 142.7, 140.5, 136.9, 135.8, 134.8, 134.1, 134.0, 132.3, 130.4, 129.7, 129.4, 129.3, 129.2, 129.1, 128.9, 128.6, 128.5, 127.6, 127.5, 127.3, 126.9, 126.7, 126.6, 126.2, 125.8, 53.0, 45.8, 21.4 ppm. **HRMS:** m/z calcd for $C_{35}H_{29}NO_2SNa$ $[M + Na]^+$, 550.1817; found, 550.1818.



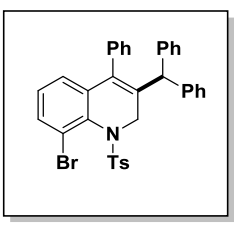
The above procedure was followed for all the reactions listed in Table 2. and were characterized properly by their spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS).

3-Benzhydryl-6-methyl-4-phenyl-1-tosyl-1,2-dihydroquinoline (3b): Eluted by petroleum ether/ethyl acetate (95:5 v/v), white solid (49 mg, 0.09 mmol, 89%) m.p. 175–178 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (d, *J* = 8.1 Hz, 1H), 7.38 – 7.28 (m, 9H), 7.12 – 7.03 (m, 5H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.0 Hz, 2H), 6.54 – 6.50 (m, 2H), 6.33 (d, *J* = 2.0 Hz, 1H), 4.90 (s, 1H), 4.65 (s, 2H), 2.38 (s,



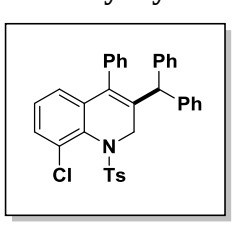
3H), 2.18 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 142.7, 140.7, 137.1, 136.1, 135.9, 135.0, 134.1, 132.2, 131.6, 129.5, 129.5, 129.3, 128.9, 128.7, 128.6, 128.5, 127.6, 127.4, 127.3, 127.0, 125.9, 53.1, 46.0, 21.5, 21.3 ppm. **HRMS:** m/z calcd for $C_{36}H_{31}NO_2SNa$ $[M + Na]^+$, 564.1973; found, 564.1974.

3-Benzhydryl-8-bromo-4-phenyl-1-tosyl-1,2-dihydroquinoline (3c): Eluted by



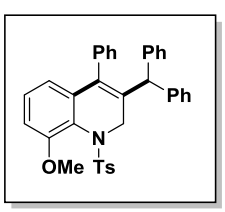
petroleum ether/ethyl acetate (95:5 v/v), white solid (58 mg, 0.095 mmol, 88%) m.p. 192–194 °C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.56 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.44 (d, *J* = 6.9 Hz, 3H), 7.39 – 7.11 (m, 6H), 7.05 (dd, *J* = 8.9, 3.4 Hz, 3H), 6.99 (d, *J* = 7.5 Hz, 5H), 6.78 (d, *J* = 8.1 Hz, 2H), 6.54 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.16 (s, 1H), 4.90 (s, 1H), 4.85 (d, *J* = 18.6 Hz, 1H), 4.20 (d, *J* = 18.6 Hz, 1H), 2.42 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 143.9, 143.4, 141.0, 140.5, 136.8, 136.7, 136.3, 135.3, 135.2, 132.9, 132.7, 132.4, 130.7, 129.7, 129.5, 129.4, 129.2, 128.7, 128.6, 128.57, 128.5, 128.48, 128.4, 128.3, 128.2, 127.8, 127.6, 127.4, 127.3, 126.6, 125.6, 123.1, 53.3, 47.0, 21.6 ppm. **HRMS:** m/z calcd for $C_{35}H_{28}BrNO_2SNa$ $[M + Na]^+$, 628.0922; found, 628.0922.

3-Benzhydryl-8-chloro-4-phenyl-1-tosyl-1,2-dihydroquinoline (3d): Eluted by



petroleum ether/ethyl acetate (95:5 v/v), white solid (48 mg, 0.085 mmol, 81%) m.p. 165–167 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (d, *J* = 7.8 Hz, 3H), 7.38 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.38 – 7.15 (m, 5H), 7.10 – 6.97 (m, 9H), 6.83 – 6.75 (m, 2H), 6.51 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.18 (s, 1H), 4.92 (s, 1H), 4.86 (d, *J* = 18.6 Hz, 1H), 4.19 (d, *J* = 18.6 Hz, 1H), 2.42 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 143.4, 141.1, 140.5, 136.9, 136.5, 136.4, 135.4, 135.2, 133.2, 131.0, 130.8, 129.7, 129.5, 129.2, 128.8, 128.6, 128.5, 128.4, 128.3, 127.9, 127.8, 127.3, 126.7, 125.0, 53.3, 47.0, 21.6 ppm. **HRMS:** m/z calcd for $C_{35}H_{28}ClNO_2SNa$ $[M + Na]^+$, 584.1427, found 584.1426.

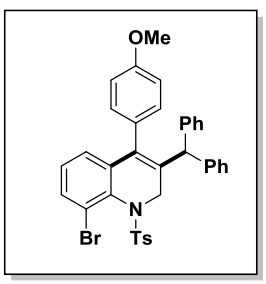
3-Benzhydryl-8-methoxy-4-phenyl-1-tosyl-1,2-dihydroquinoline (3e): Eluted by



petroleum ether/ethyl acetate (95:5 v/v), white solid (43 mg, 0.077 mmol, 74%) m.p. 185–188 °C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.27 – 7.36 (m, 9H), 7.11 – 6.96 (m, 7H), 6.95 – 6.83 (m, 3H), 6.65 (s, 2H), 6.22 (dd, *J* = 7.8, 1.3 Hz, 1H), 4.94 (s, 1H), 4.51 (s,

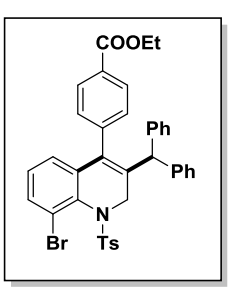
2H), 3.86 (s, 3H), 2.41 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 155.3, 142.7, 140.9, 137.0, 136.7, 136.1, 135.5, 135.2, 129.6, 129.5, 129.0, 128.5, 128.5, 127.9, 127.6, 127.5, 126.9, 122.6, 119.1, 112.3, 56.3, 53.2, 46.9, 21.6 ppm. **HRMS:** m/z calcd for $C_{36}H_{31}NO_3SNa$ $[M + Na]^+$, 580.1922, found 580.1923.

3-Benzhydryl-8-bromo-4-(4-methoxyphenyl)-1-tosyl-1,2-dihydroquinoline (3f):



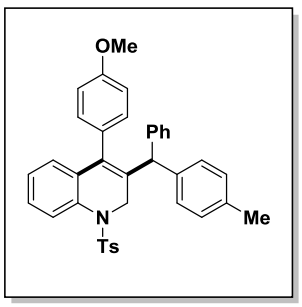
white solid (64 mg, 0.1 mmol, 92%) m.p 200–202 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.59 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.53 – 7.40 (m, 3H), 7.20 – 7.29 (m, 3H), 7.14 – 7.07 (m, 2H), 7.03 (dd, *J* = 8.1, 2.4 Hz, 5H), 6.85 (d, *J* = 8.0 Hz, 3H), 6.81 (d, *J* = 8.1 Hz, 2H), 6.62 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.13 (s, 1H), 4.99 (s, 1H), 4.88 (d, *J* = 18.7 Hz, 1H), 4.22 (d, *J* = 18.6 Hz, 1H), 3.86 (s, 3H), 2.45 (s, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 159.2, 143.4, 141.3, 140.7, 137.09, 137.1, 135.4, 134.9, 132.8, 132.5, 130.8, 130.7, 129.2, 128.8, 128.5, 128.4, 128.3, 127.3, 126.6, 125.7, 123.1, 113.9, 55.4, 53.4, 47.2, 21.6 ppm. **HRMS:** m/z calcd for $C_{36}H_{30}BrNO_3SNa$ $[M + Na]^+$, 658.1027; found, 658.1025.

Ethyl 4-(3-benzhydryl-8-bromo-1-tosyl-1,2-dihydroquinolin-4-yl)benzoate (3g):



white solid (43 mg, 0.06 mmol, 57%) m.p 194–196 °C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.97 (d, *J* = 7.9 Hz, 2H), 7.58 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 – 7.35 (m, 3H), 7.25 – 7.13 (m, 3H), 7.08 – 6.94 (m, 8H), 6.89 – 6.75 (m, 2H), 6.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 6.30 (s, 1H), 4.83 (d, *J* = 18.6 Hz, 1H), 4.83 (s, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.20 (d, *J* = 18.7 Hz, 1H), 2.44 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.4, 143.6, 141.3, 140.9, 140.3, 137.4, 136.1, 135.2, 134.4, 133.2, 132.5, 130.7, 130.1, 129.9, 129.7, 129.3, 128.9, 128.65, 128.58, 128.5, 128.3, 127.4, 126.8, 125.4, 123.3, 61.3, 53.5, 47.1, 21.7, 14.5 ppm. **HRMS:** m/z calcd for $C_{38}H_{32}BrNO_4SNa$ $[M + Na]^+$, 700.1133; found, 700.1133.

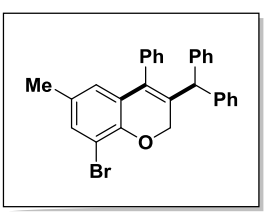
8-Bromo-4-(4-methoxyphenyl)-3-(phenyl(p-tolyl)methyl)-1-tosyl-1,2-dihydroquinoline (3h): Eluted by petroleum ether/ethyl acetate (95:5 v/v), white solid (54 mg, 0.083 mmol, 93%) m.p 138–140 °C. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.67 (d, *J* = 8.1 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 4H), 7.32 – 7.27 (m, 2H), 7.06 (dt, *J* = 8.4, 2.5 Hz, 5H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.86 – 6.80 (m, 2H), 6.63 – 6.53 (m, 2H),



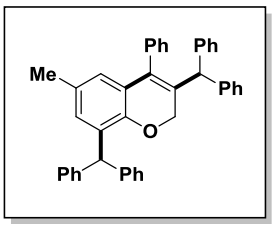
6.48 – 6.42 (m, 2H), 6.36 (d, *J* = 2.1 Hz, 1H), 4.96 (s, 1H), 4.63 (s, 2H), 3.83 (s, 3H), 2.37 (s, 3H), 2.19 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ 158.9, 142.7, 140.8, 136.1, 134.7, 134.2, 132.5, 131.6, 130.6, 129.5, 129.1, 128.9, 128.7, 128.4, 127.4, 127.3, 126.9, 125.9, 114.0, 55.4, 53.1, 46.0, 21.6, 21.3. **HRMS:** m/z calcd for $C_{37}H_{33}NO_3SNa$ $[M + Na]^+$, 594.2079; found, 594.2076.

4.4.5. Representative Experimental Procedure for the Synthesis and Characterization of 4a-4f:

3-Benzhydryl-8-bromo-6-methyl-4-phenyl-2*H*-chromene (4a): In an oven-dried round-bottom flask, 2-bromo-4-methyl-1-((3-phenylprop-2-yn-1-yl)oxy)benzene (45 mg, 0.15 mmol) and diphenylmethanol (**2a**) (27 mg, 0.15 mmol) were taken in dry nitromethane (2 mL) and $Fe(OTf)_3$ (7.5 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic layer was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether to afford the desired product **4a** (53 mg, 0.11 mmol, 76%) as a white solid, m.p. 180–185 °C. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.46 – 7.44 (m, 1H), 7.43 – 7.38 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 1.4 Hz, 1H), 7.33 – 7.30 (m, 2H), 7.29 (s, 1H), 7.27 (d, *J* = 5.1 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.17 – 7.14 (m, 4H), 6.42 (d, *J* = 2.0 Hz, 1H), 5.10 (s, 1H), 4.76 (s, 2H), 2.14 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 148.2, 142.4, 141.3, 136.6, 133.6, 132.97, 132.5, 132.2, 132.0, 131.8, 129.9, 129.8, 129.2, 129.1, 129.06, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.6, 127.4, 126.8, 126.7, 126.3, 109.5, 67.1, 51.9, 20.6 ppm. Anal. calcd. for $C_{29}H_{23}BrO$: C, 74.52; H, 4.96; found: C, 74.81; H, 5.23 %.

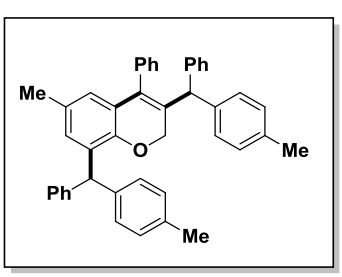


3,8-Dibenzhydryl-6-methyl-4-phenyl-2*H*-chromene (4b): In an oven-dried round-bottom flask, 1-methyl-4-((3-phenylprop-2-yn-1-yl)oxy)benzene (33 mg, 0.15 mmol) and diphenylmethanol (**2a**) (55 mg, 0.3 mmol) were taken in dry nitromethane (2 mL)



and to it $Fe(OTf)_3$ (7.5 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 3 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether to afford the desired product **4b** (65 mg, 0.11 mmol, 79%) as a white solid, m.p. 165–169 °C. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.47 – 7.39 (m, 3H), 7.36 – 7.28 (m, 9H), 7.28 – 7.20 (m, 4H), 7.20 – 7.12 (m, 9H), 6.59 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 5.92 (s, 1H), 5.09 (s, 1H), 4.48 (d, *J* = 1.4 Hz, 2H), 2.07 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 149.0, 144.1, 141.72, 141.7, 137.3, 134.3, 131.3, 131.0, 130.6, 130.3, 129.9, 129.8, 129.7, 129.6, 129.3, 129.1, 129.0, 128.75, 128.7, 128.6, 128.5, 128.2, 127.7, 127.6, 126.9, 126.7, 126.6, 126.1, 125.4, 125.3, 66.3, 52.0, 49.5, 21.1 ppm. **HRMS:** m/z calcd for $C_{42}H_{34}ONa$ $[M + Na]^+$, 577.2507; found, 577.2509.

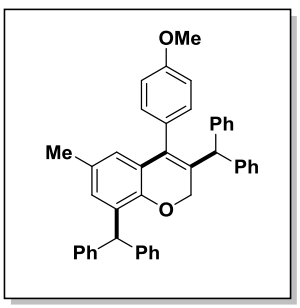
6-Methyl-4-phenyl-3,8-bis(phenyl(p-tolyl)methyl)-2*H*-chromene (4c): In an oven-



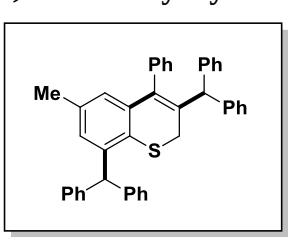
dried round-bottom flask, 1-methyl-4-((3-phenylprop-2-yn-1-yl)oxy)benzene (33 mg, 0.15 mmol) and phenyl(p-tolyl)methanol (**2b**) (59 mg, 0.3 mmol) were taken in dry nitromethane (2 mL) and $Fe(OTf)_3$ (7.5 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 3 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic extract was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether to afford the desired product **4c** (72 mg, 0.12 mmol, 84%) as a white solid, m.p. 150–155 °C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.36 – 7.44 (m, 3H), 7.33 – 7.14 (m, 7H), 7.16 – 7.05 (m, 9H), 6.99 (dd, *J* = 9.1, 7.0 Hz, 4H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 5.83 (s, 1H), 5.00 (s, 1H), 4.44 (d, *J* = 1.2 Hz, 2H), 2.32 (s, 6H), 2.03 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** 149.0, 144.4, 141.9, 141.1, 138.6, 137.4,

136.2, 135.6, 134.1, 131.5, 131.1, 130.3, 129.9, 129.7, 129.5, 129.4, 129.3, 129.2, 129.1, 128.9, 128.7, 128.6, 128.5, 128.2, 127.5, 126.5, 126.0, 125.4, 125.2, 66.3, 51.6, 48.9, 21.2, 21.14, 21.10 ppm. **HRMS:** m/z calcd for $C_{44}H_{38}ONa$ $[M + Na]^+$, 605.2820; found, 605.2820.

3,8-Dibenzhydryl-4-(4-methoxyphenyl)-6-methyl-2*H*-chromene (4d): In an oven-dried round-bottom flask 1-methoxy-4-(3-(p-tolyloxy)prop-1-yn-1-yl)benzene (38 mg, 0.15 mmol) and diphenylmethanol (**2b**) (56 mg, 0.3 mmol) were taken in dry nitromethane (2 mL) and $Fe(OTf)_3$ (7.5 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic layer was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (99:1 v/v), to afford the desired product **4d** (66 mg, 0.11 mmol, 74%) as a yellow gummy liquid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29 – 7.27 (m, 3H), 7.24 (s, 3H), 7.22 (d, *J* = 1.6 Hz, 1H), 7.20 (s, 2H), 7.19 (s, 2H), 7.14 – 7.13 (m, 3H), 7.13 – 7.10 (m, 6H), 7.09 (s, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.53(d, *J* = 2.0 Hz, 1H), 6.39 (d, *J* = 1.6 Hz, 1H) 5.86 (s, 1H), 5.09 (s, 1H), 4.43 (s, 2H), 3.85 (s, 3H), 2.04 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** 158.9, 148.9, 143.9, 141.7, 133.7, 131.3, 130.8, 130.7, 129.7, 129.4, 129.2, 128.9, 128.5, 128.4, 128.3, 128.1, 126.5, 126.0, 125.6, 125.2, 113.9, 66.1, 55.2, 51.9, 49.3, 20.99 ppm. **HRMS:** m/z calcd for $C_{43}H_{36}O_2Na$ $[M + Na]^+$, 607.2613; found, 607.2609

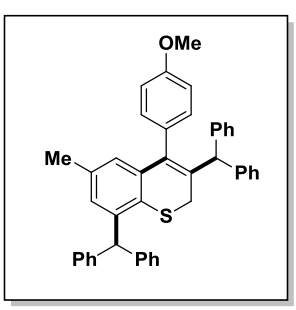


3,8-Dibenzhydryl-6-methyl-4-phenyl-2*H*-thiochromene (4e): In an oven-dried round-bottom flask, (3-phenylprop-2-yn-1-yl)(p-tolyl)sulfane (35 mg, 0.15 mmol) and diphenylmethanol (**2a**) (55 mg, 0.30 mmol) were taken in dry nitromethane (2 mL) and to $Fe(OTf)_3$ (7.5 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 3 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic layer was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The



product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether to afford the desired product **4e** (60 mg, 0.1 mmol, 72%) as a light yellow semisolid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.29 (s, 2H), 7.28 (d, *J* = 1.2 Hz, 4H), 7.24 (d, *J* = 7.6 Hz, 3H), 7.19 – 7.22 (m, 2H), 7.16 – 7.18 (m, 6H), 7.13 (s, 1H), 7.11 (s, 2H), 7.09 (d, *J* = 1.6 Hz, 1H), 7.08 (d, *J* = 2.8 Hz, 3H), 6.99 (d, *J* = 8 Hz, 2H), 6.94 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.03 (s, 1H), 5.52 (s, 1H), 3.42 (s, 2H), 2.28 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 155.7, 144.3, 143.2, 142.7, 142.5, 141.2, 135.7, 131.9, 130.6, 129.9, 129.8, 129.6, 129.4, 129.2, 129.1, 129.08, 128.7, 128.6, 128.5, 128.4, 128.1, 126.6, 126.4, 124.8, 120.7, 57.0, 50.9, 39.7, 21.1 ppm. **HRMS:** m/z calcd for $C_{42}H_{35}S$ $[M + H]^+$, 571.2459; found, 571.2460.

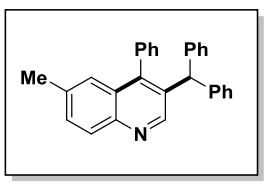
3,8-Dibenzhydryl-4-(4-methoxyphenyl)-6-methyl-2*H*-thiochromene (4f): In an



oven-dried round-bottom flask, (3-(4-methoxyphenyl)prop-2-yn-1-yl)(p-tolyl)sulfane (27 mg, 0.10 mmol) and diphenylmethanol (**2a**) (37 mg, 0.20 mmol) were taken in dry nitromethane (2 mL) and $Fe(OTf)_3$ (7.5 mg, 0.015 mmol) was added to the mixture under an Ar atmosphere and stirred for 2 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic layer was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (98:2 v/v), to afford the desired product **4f** (46 mg, 0.07 mmol, 76%) as a white solid, m.p. 166–168 °C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 7.29 – 7.34 (m, 3H), 7.23 – 7.27 (m, 4H), 7.21 (s, 2H), 7.16 – 7.18 (m, 6H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.96 (s, 2H), 6.90 (d, *J* = 7.8 Hz, 6H), 6.62 (s, 1H), 6.01 (s, 1H), 5.82 (s, 1H), 3.67 (s, 3H), 3.43 (s, 2H), 2.30 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 155.4, 151.3, 143.8, 143.3, 141.8, 136.2, 135.8, 131.1, 130.9, 129.8, 129.7, 129.6,129.3, 129.0, 128.5, 128.4, 127.9, 126.4, 125.8, 123.0, 107.2, 56.0, 50.7, 49.4, 39.5, 21.1 ppm. **HRMS:** m/z calcd for $C_{43}H_{36}OSNa$ $[M + Na]^+$, 623.2385; found, 623.2383.

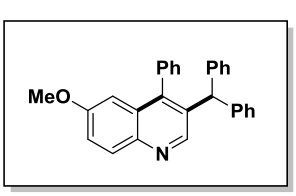
4.4.6. Representative Experimental Procedure for the Synthesis and Characterization of 5a-5f:

3-Benzhydryl-6-methyl-4-phenylquinoline (5a): In an oven-dried round-bottom flask, 4-methyl-*N*-(3-phenylprop-2-yn-1-yl)-*N*-(p-tolyl)benzenesulfonamide (**1b**) (56 mg, 0.15 mmol) and diphenylmethanol (**2a**) (27 mg, 0.15 mmol) were taken in dry DCE (2 mL) and anhydrous $FeCl_3$ (48 mg, 0.3 mmol) was added to the mixture under an argon atmosphere and stirred for 2 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with EtOAc (15 mL, twice) and the combined organic layer was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by petroleum ether/ethyl acetate (95:5 v/v), to afford the desired product **5a** (48 mg, 0.12 mmol, 87%) as a light yellow solid, m.p. 130–135 °C. **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.70 (s, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.54 (m, 4H), 7.25 – 7.28 (m, 6H), 7.10 – 7.23 (m, 3H), 6.99 (d, *J* = 6.9 Hz, 4H), 5.47 (s, 1H), 2.40 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 151.1, 143.1, 136.9, 136.4, 134.2, 131.5, 129.5, 129.4, 128.8, 128.6, 128.2, 127.9, 126.6, 125.5, 51.8, 21.9 ppm. **HRMS:** m/z calcd for $C_{29}H_{24}N$ $[M + H]^+$, 386.1909; found, 386.1890.

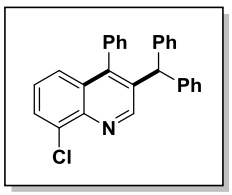


The above procedure was followed for all the reactions listed in Table 3. These compounds were characterized properly by their spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS and elemental analysis).

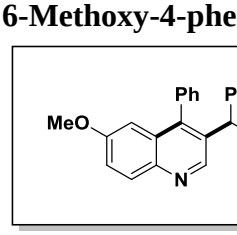
3-Benzhydryl-6-methoxy-4-phenylquinoline (5b): Eluted by petroleum ether/ethyl acetate (95:5 v/v), yellow gummy liquid (34 mg, 0.08 mmol, 89%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.59 (s, 1H),7.53 – 7.49 (m, 4H), 7.31 – 7.26 (m, 5H), 7.23 (d, J = 2.1 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.96 – 6.94 (m, 5H), 6.71 (d, J = 2.4 Hz, 1H), 5.54 (s, 1H), 3.72 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 160.4, 154.9, 140.5, 136.9, 133.7, 130.8, 129.7, 129.1, 129.0, 128.4, 128.2, 127.6, 126.6, 104.8, 55.8, 51.8 ppm. **HRMS:** m/z calcd for $C_{29}H_{24}NO$ $[M + H]^+$, 402.1858; found, 402.1853.



3-Benzhydryl-8-chloro-4-phenylquinoline (5c): Eluted by petroleum ether/ethyl acetate (95:5 v/v), yellow gummy liquid (25 mg, 0.06 mmol, 63%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.96 (s, 1H), 7.82 (dd, *J* = 5.7, 3.0 Hz, 1H), 7.54 – 7.51 (m, 3H), 7.49 – 7.44 (m, 2H), 7.38 – 7.34 (m, 3H), 7.31 – 7.24 (m, 2H), 7.22 – 7.19 (m, 1H), 7.15 – 7.12 (m, 2H), 7.06 – 7.01 (m, 4H), 5.51 (s, 1H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 152.4, 148.5, 142.4, 141.7, 135.5, 135.4, 132.8, 129.6, 129.4, 129.3, 129.2, 128.6, 126.9, 126.8, 125.9, 51.7 ppm. Anal. calcd. for $C_{28}H_{20}ClN$: C, 82.85; H, 4.97; N, 3.45; found: C, 82.99; H, 5.15; N, 3.51%.

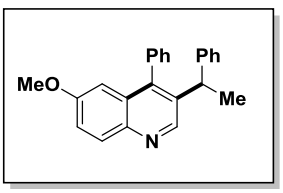


3-Benzhydryl-4-(4-methoxyphenyl)-6-methylquinoline (5d): Eluted by petroleum ether/ethyl acetate (95:5 v/v), yellow solid (36 mg, 0.09 mmol, 92%), m.p. 145–147 °C. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.72 (s, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.52 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 3H), 7.25 – 7.20 (m, 3H), 7.09 – 7.00 (m, 9H), 5.55 (s, 1H), 3.93 (s, 3H), 2.43 (s, 3H) ppm. **^{13}C NMR (100 MHz, $CDCl_3$)** δ 159.5, 151.3, 143.3, 136.8, 134.5, 131.4, 130.7, 129.4, 128.9, 128.7, 128.5, 128.4, 128.3, 126.6, 125.6, 114.0, 55.5, 51.8, 21.9 ppm. Anal. calcd. for $C_{30}H_{25}NO$: C, 86.71; H, 6.06; N, 3.37; found: C, 86.80; H, 5.50; N, 3.52%.



6-Methoxy-4-phenyl-3-(phenyl(p-tolyl)methyl)quinoline (5e): Eluted by petroleum ether/ethyl acetate (95:5 v/v), light yellow gummy liquid (35 mg, 0.08, 93%). **^{1}H NMR (300 MHz, $CDCl_3$)** δ 8.58 (s, 1H),7.54 – 7.49 (m, 5H), 7.31 – 7.26 (m, 2H), 7.14 (d, *J* = 6.9 Hz, 2H) 7.09 (d, *J* = 7.8 Hz, 3H), 6.94 – 6.92 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 6.71 (d, *J* = 2.4 Hz, 1H), 5.49 (s, 1H), 3.72 (s, 3H), 2.34 (s, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$)** δ 158.9, 142.3 138.9, 138.5, 136.7, 135.6, 135.2, 129.9, 129.8, 129.7, 129.4, 129.2, 129.1, 129.0, 128.8, 128.7, 128.6, 128.5, 127.8, 127.5, 126.9, 104.8, 55.5, 51.4, 21.0 ppm. **HRMS:** m/z calcd for $C_{30}H_{26}NO$ $[M + H]^+$, 416.2014; found, 416.2009.

6-Methoxy-4-phenyl-3-(1-phenylethyl)quinoline (5f): Eluted by petroleum ether/ethyl acetate (95:5 v/v), yellow solid (31 mg, 0.09 mmol,79%), m.p. 98 °C. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.70 (s, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.60 – 7.54 (m,



1H), 7.52 – 7.46 (m, 2H), 7.36 – 7.31 (m, 2H), 7.25 – 7.21 (m, 2H), 7.20 – 7.14 (m, 2H), 7.12 – 7.07 (m, 2H), 6.62 (d, *J* = 2.7 Hz, 1H), 4.18 (q, *J* = 7.3 Hz, 1H), 3.68 (s, 3H), 1.64 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR (125 MHz, $CDCl_3$)** δ 144.7, 137.2, 136.4, 129.5, 129.2, 128.9, 128.8, 128.6, 128.4, 127.6, 126.5, 126.4, 121.8, 104.9, 55.5, 39.5, 21.7 ppm. **HRMS:** m/z calcd for $C_{24}H_{22}NO$ $[M + H]^+$, 340.1701; found, 340.1703.

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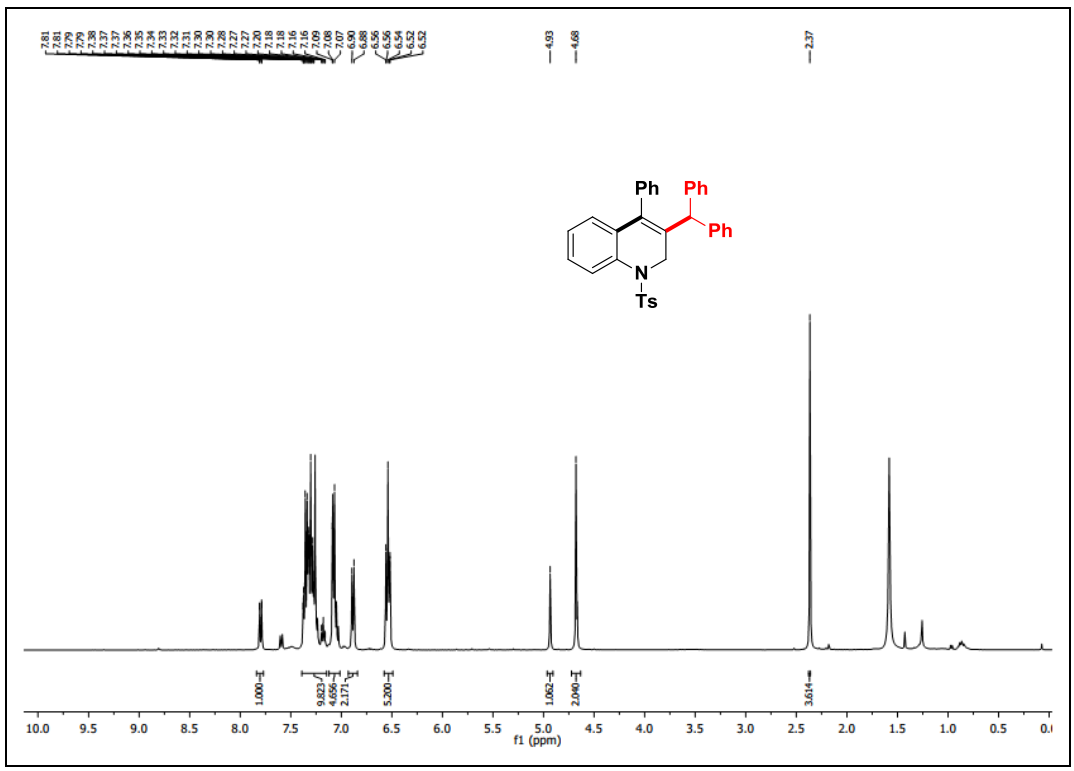
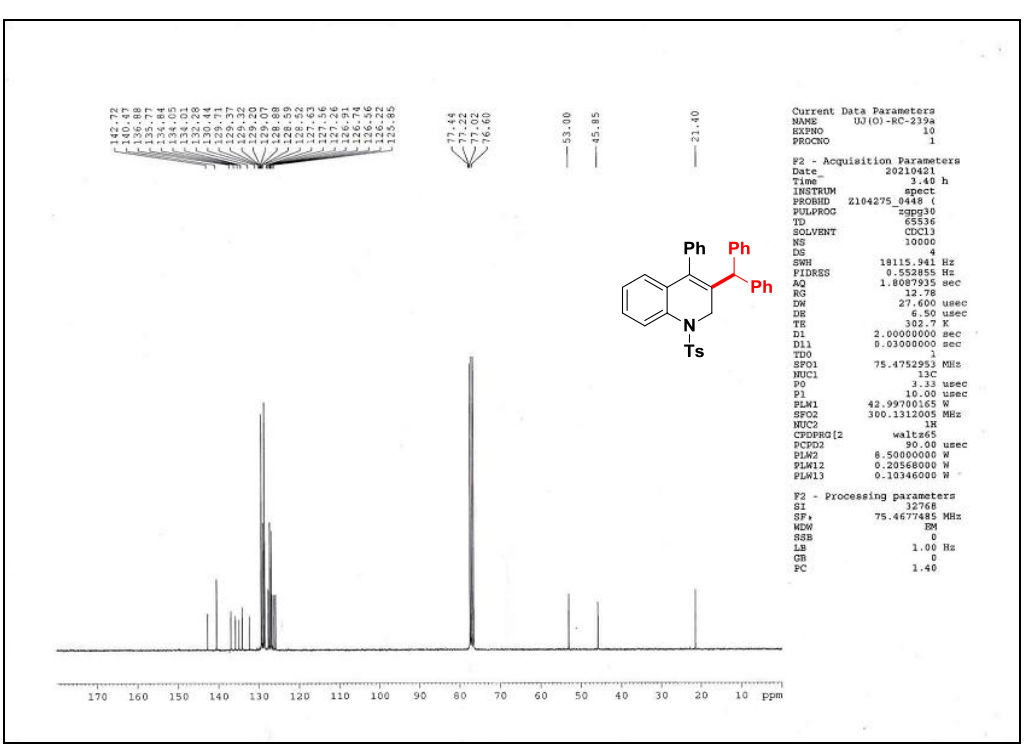
^{1}H and ^{13}C

NMR spectra

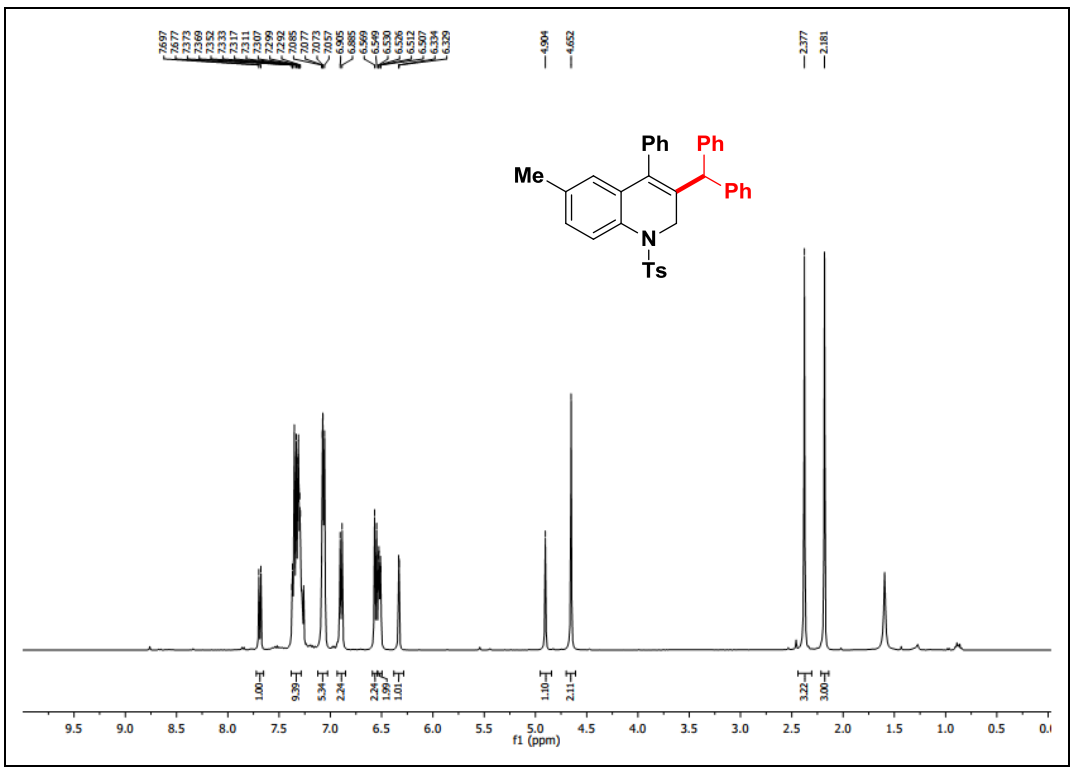
^{1}H NMR spectrum of compound **3a**, $CDCl_3$, 400 MHz



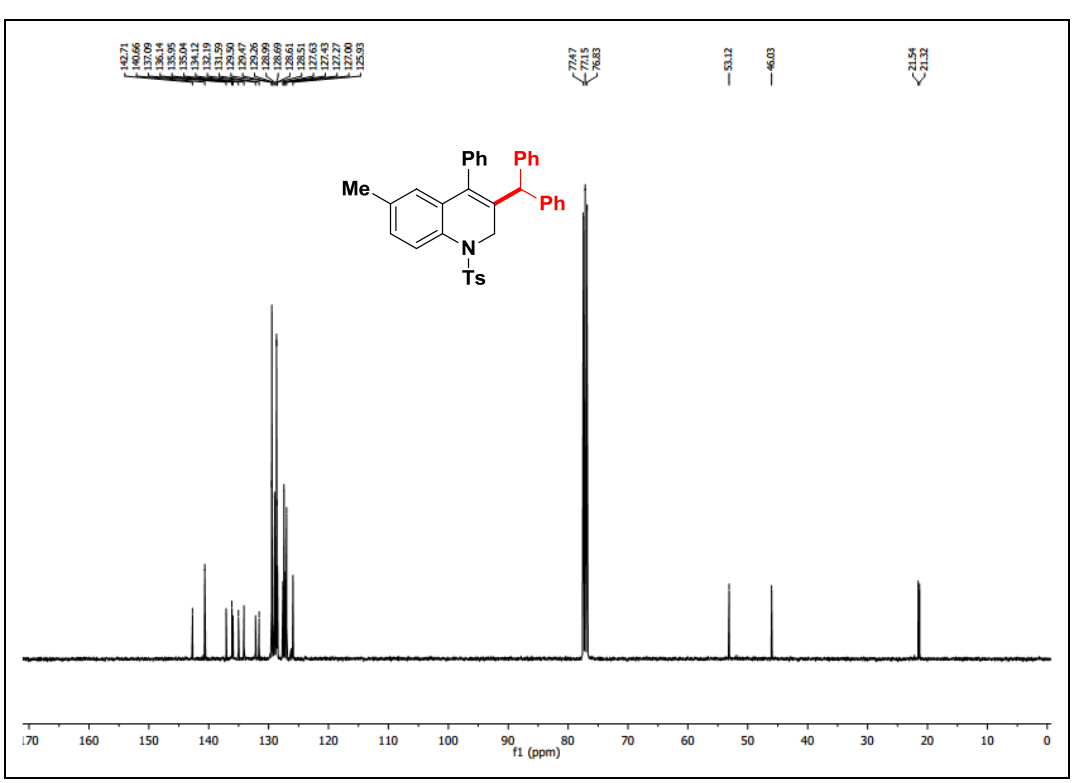
^{13}C NMR spectrum of compound **3a**, $CDCl_3$, 75 MHz



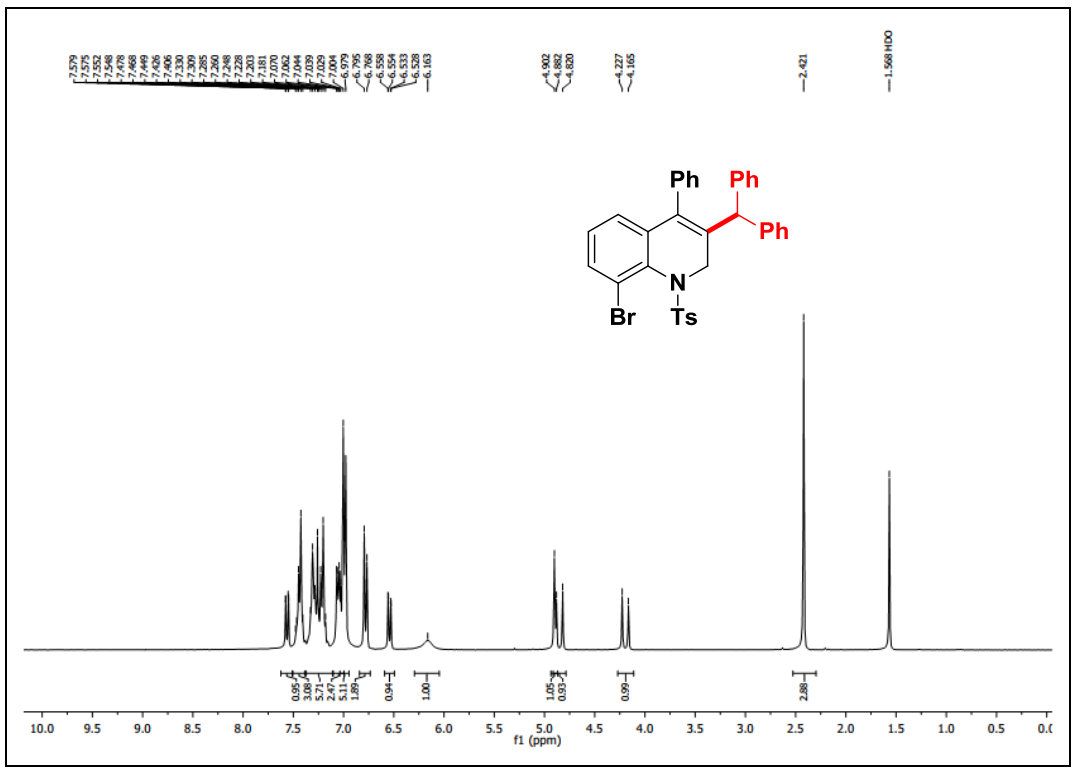
^{1}H NMR spectrum of compound **3b**, $CDCl_3$, 400 MHz



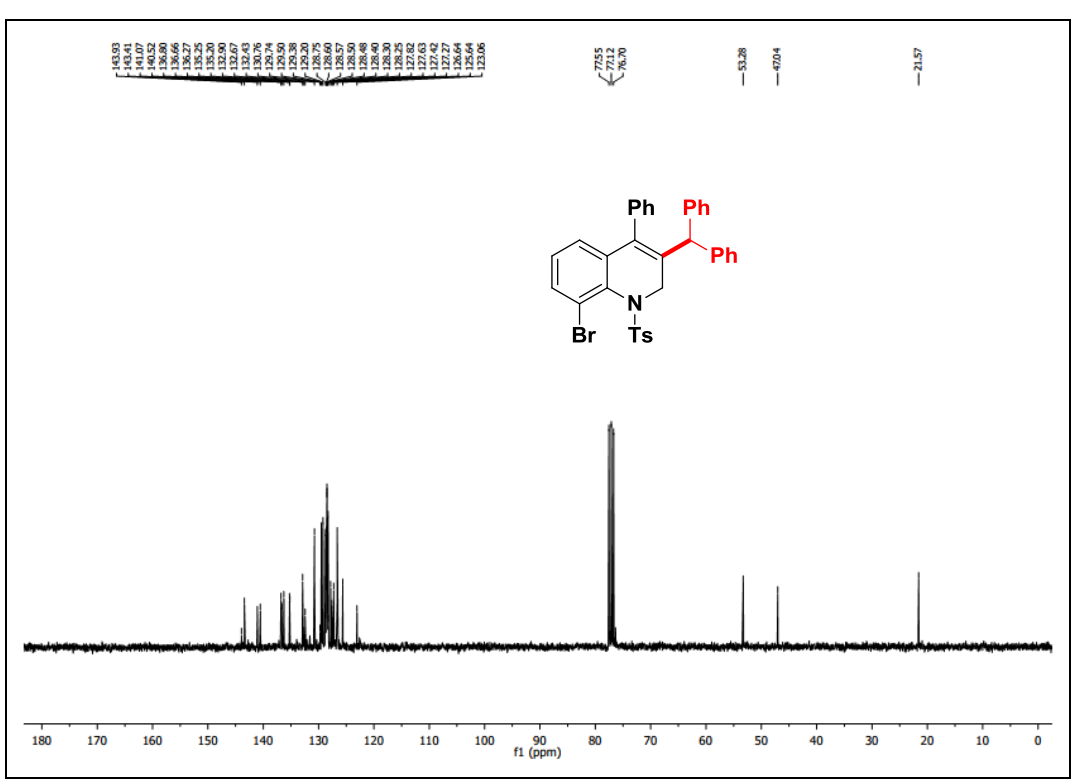
^{13}C NMR spectrum of compound **3b**, $CDCl_3$, 100 MHz



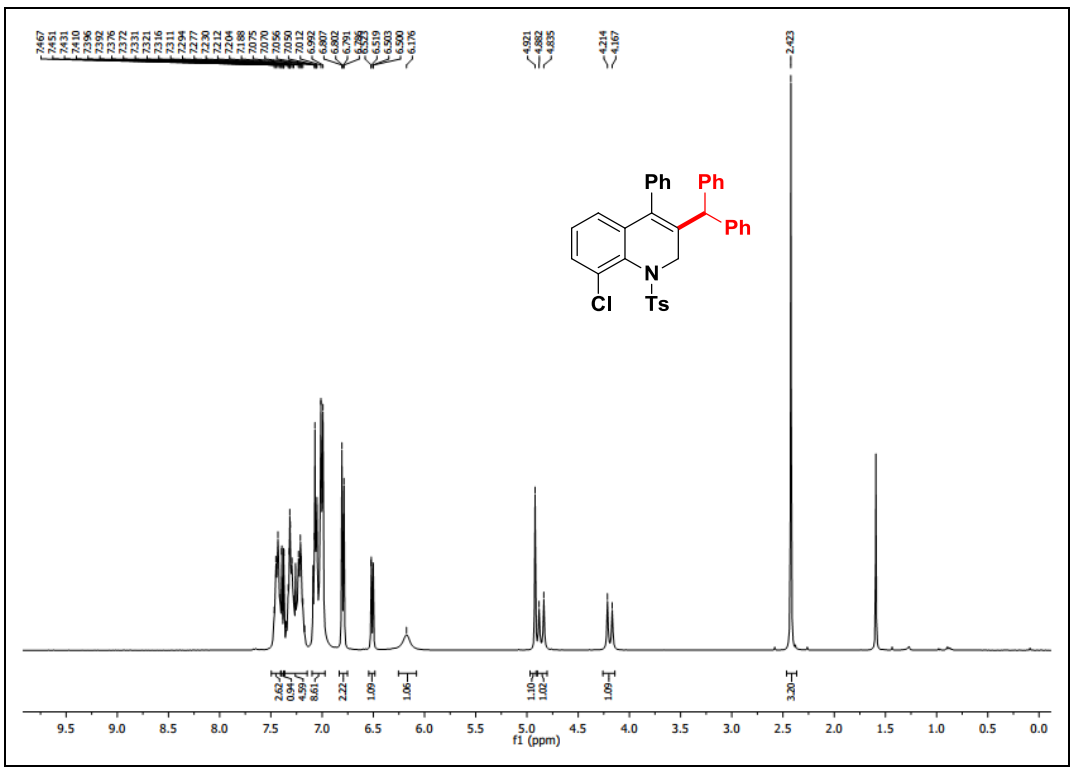
^{1}H NMR spectrum of compound **3c**, $CDCl_3$, 300 MHz



^{13}C NMR spectrum of compound **3c**, $CDCl_3$, 75 MHz



^{1}H NMR spectrum of compound **3d**, $CDCl_3$, 400 MHz



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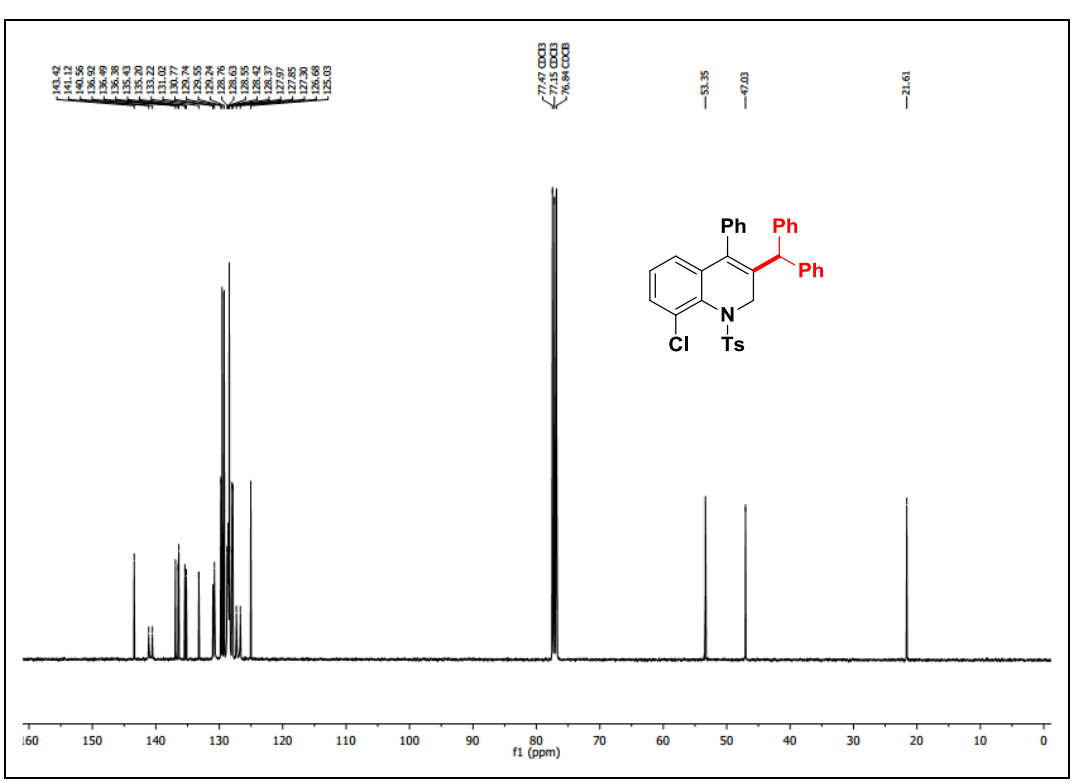

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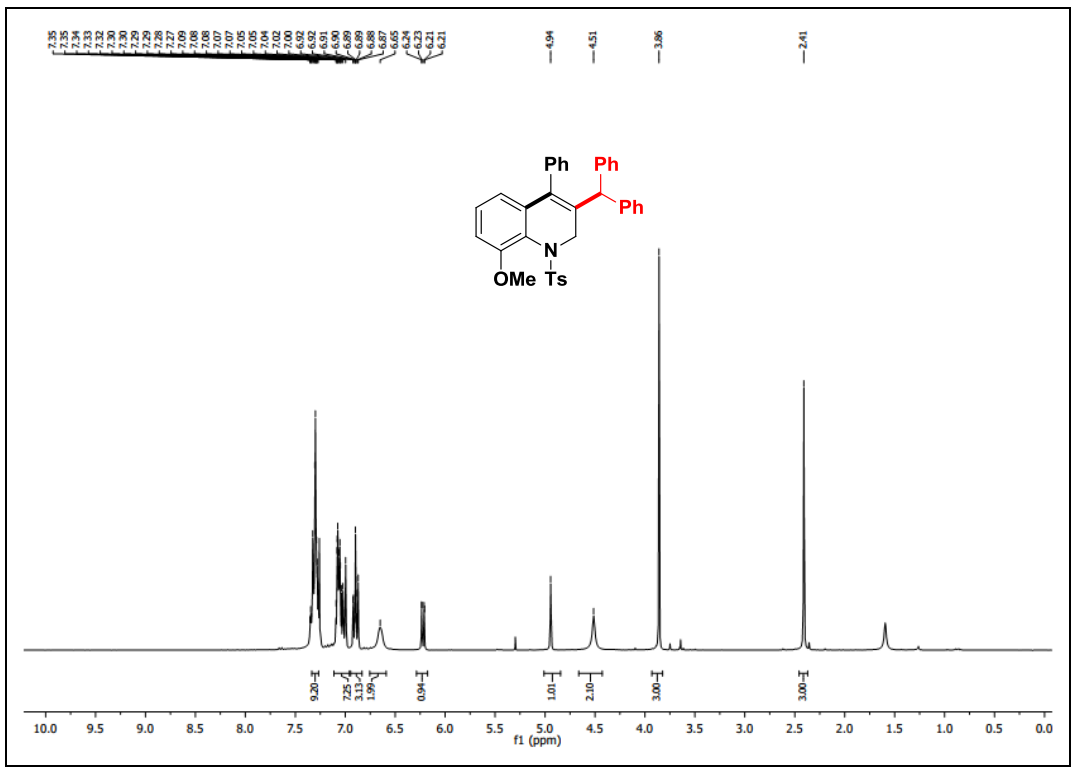
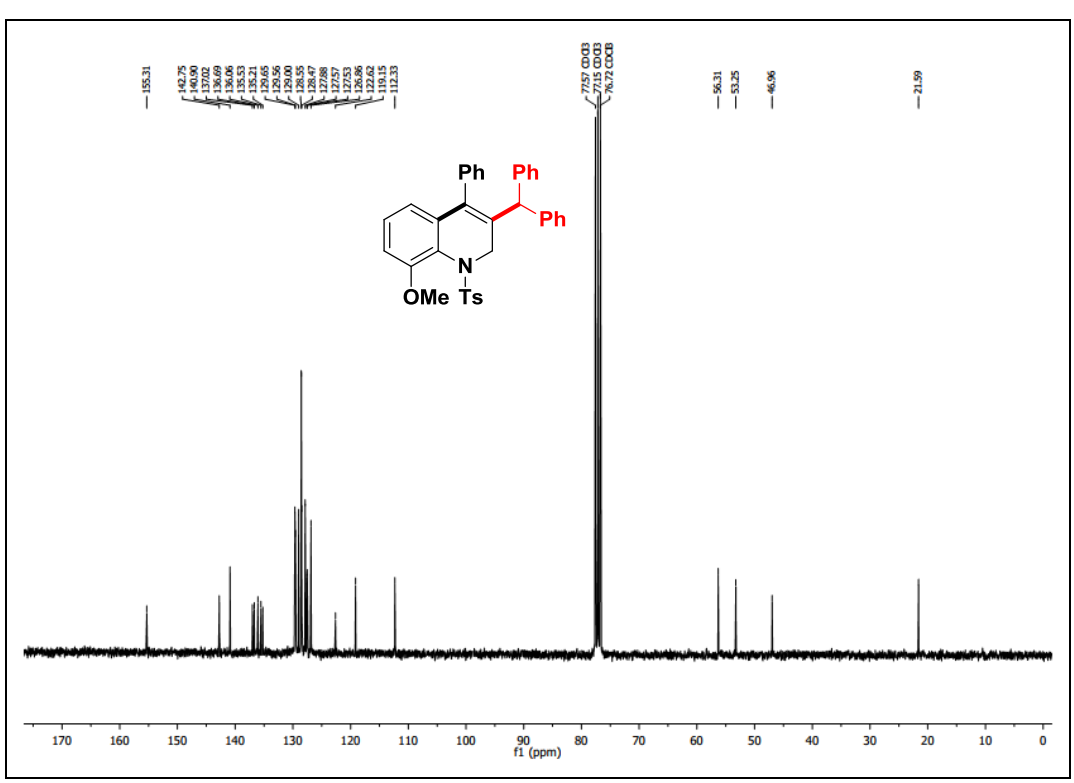
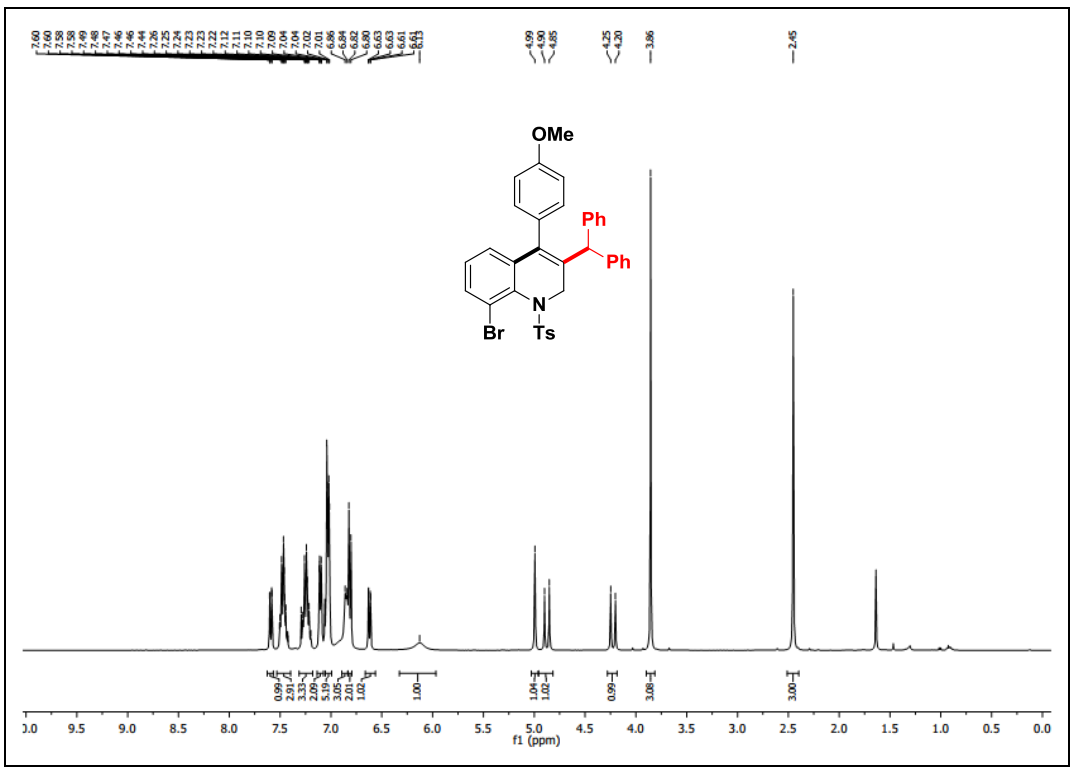


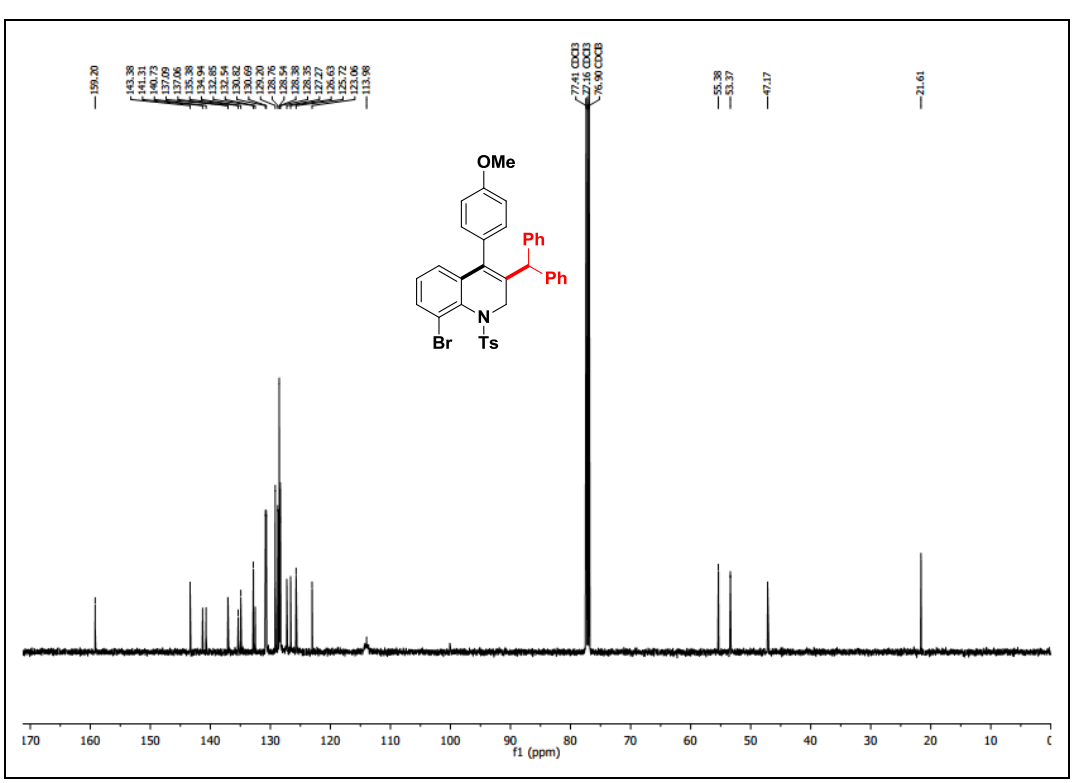
^{13}C NMR spectrum of compound **3e**, $CDCl_3$, 75 MHz



^{1}H NMR spectrum of compound **3f**, $CDCl_3$, 400 MHz



^{13}C NMR spectrum of compound **3f**, $CDCl_3$, 125 MHz



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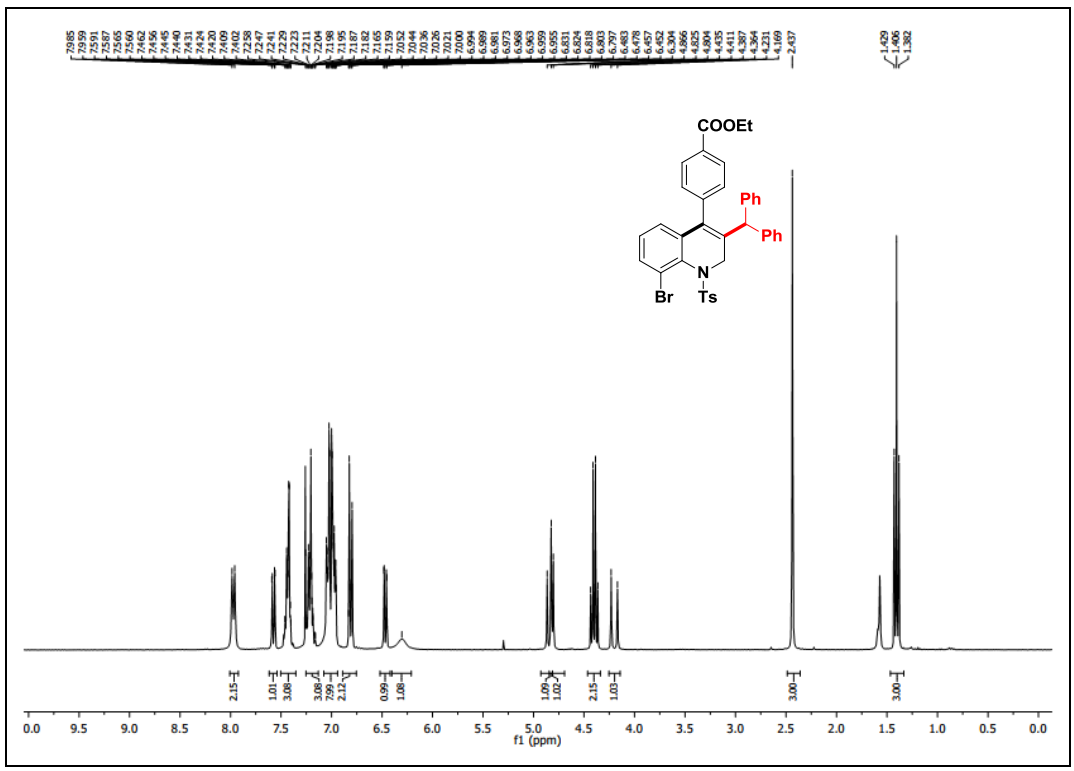

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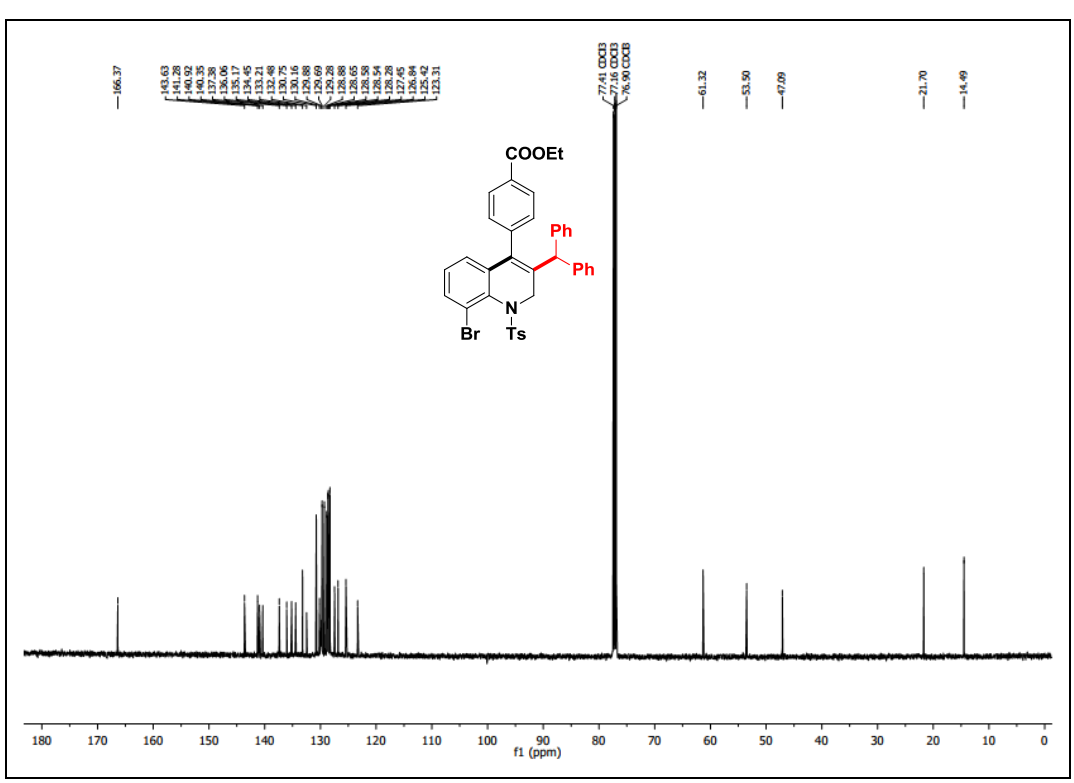
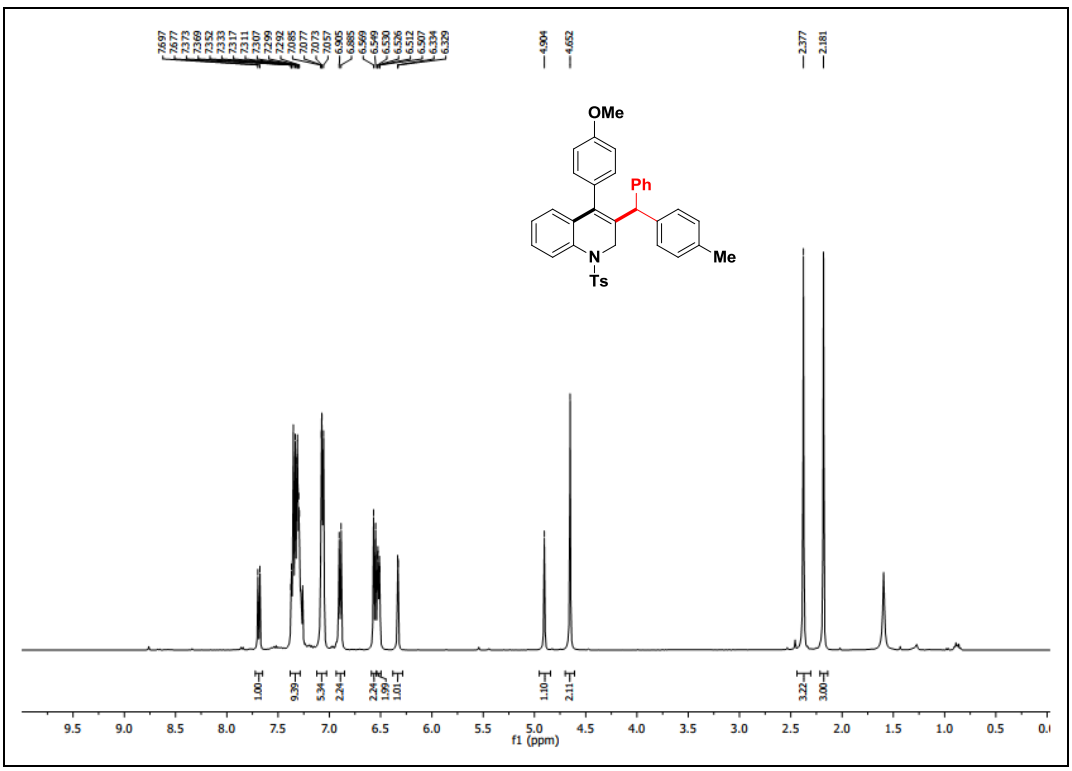


^{1}H NMR spectrum of compound **3h**, $CDCl_3$, 500 MHz



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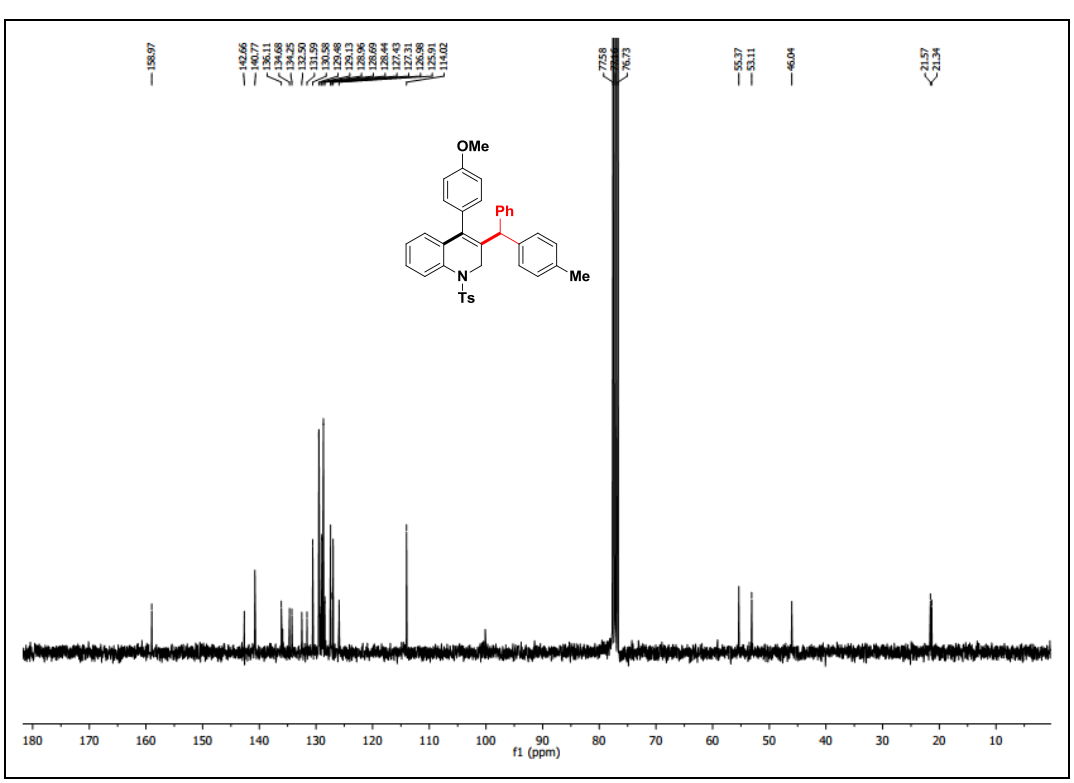
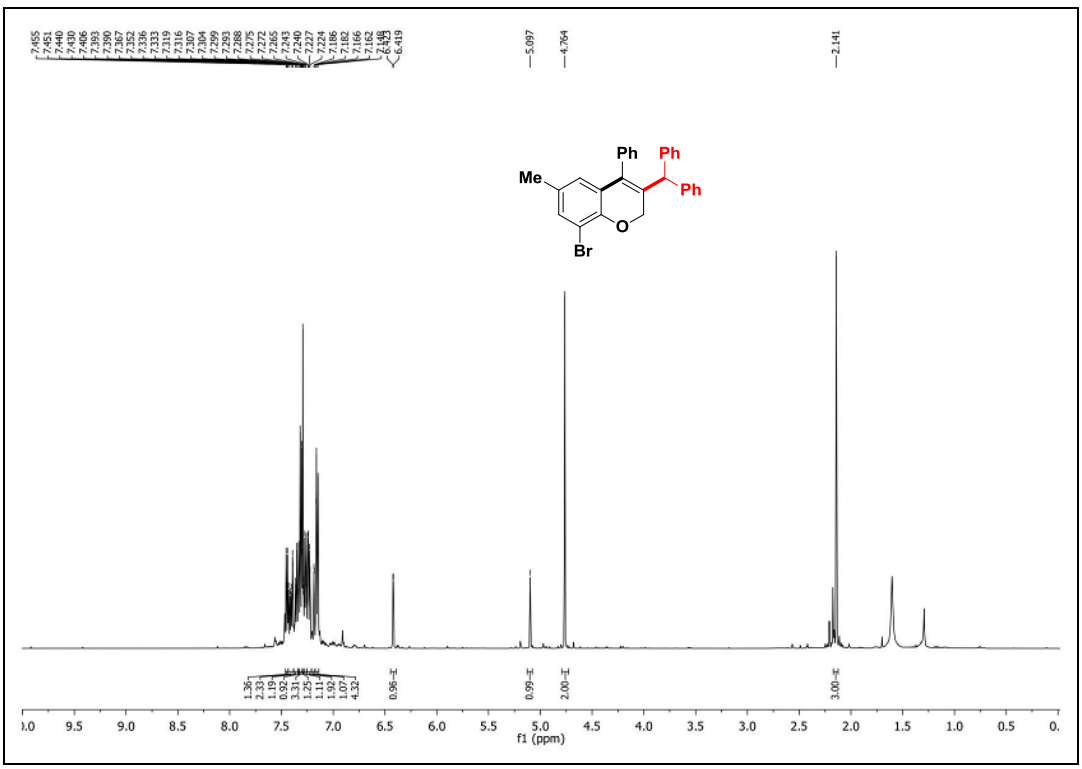


^{1}H NMR spectrum of compound **4a**, $CDCl_3$, 500 MHz



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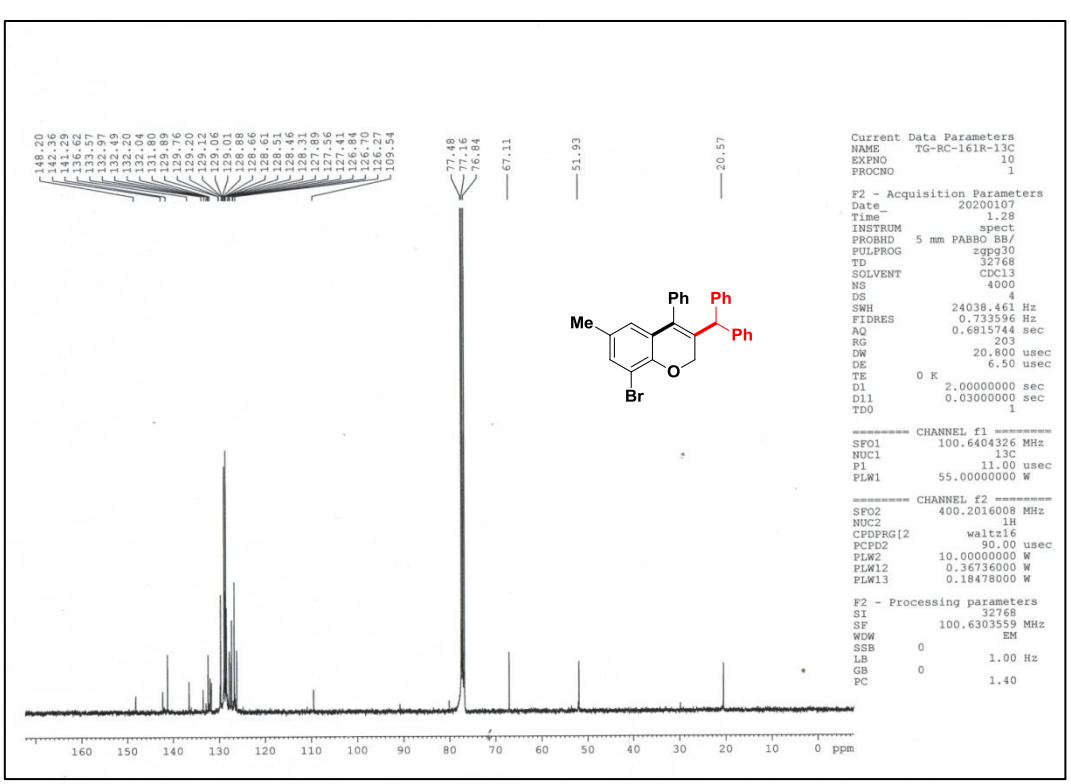

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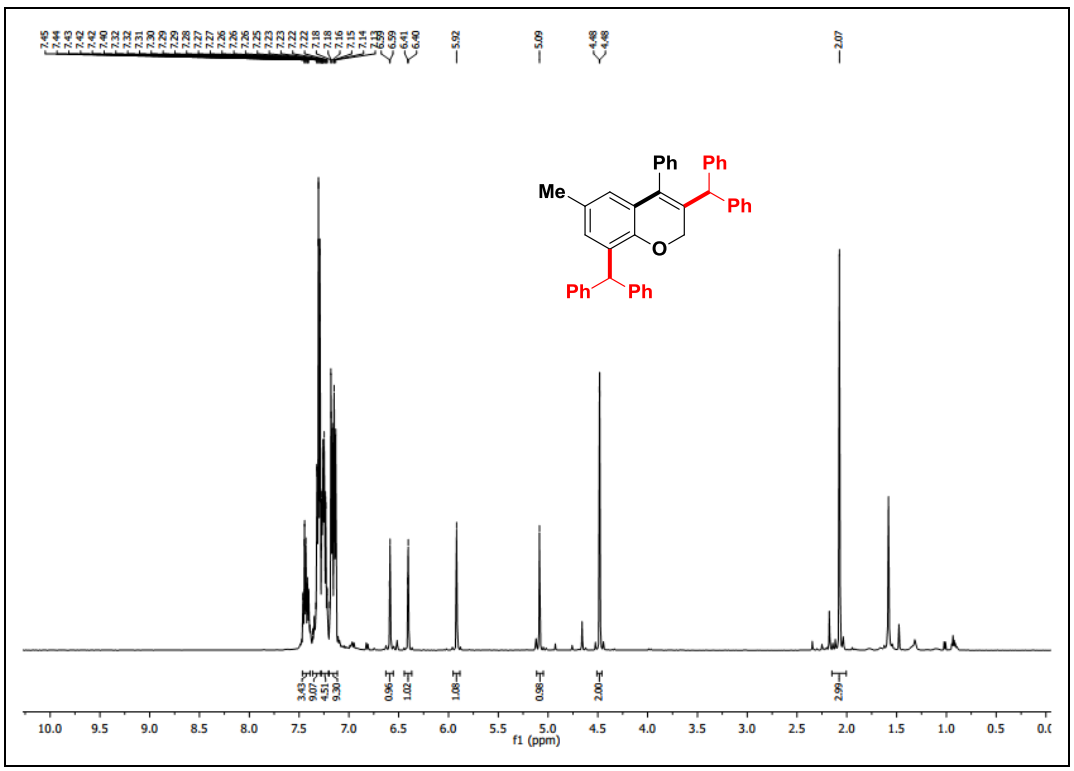

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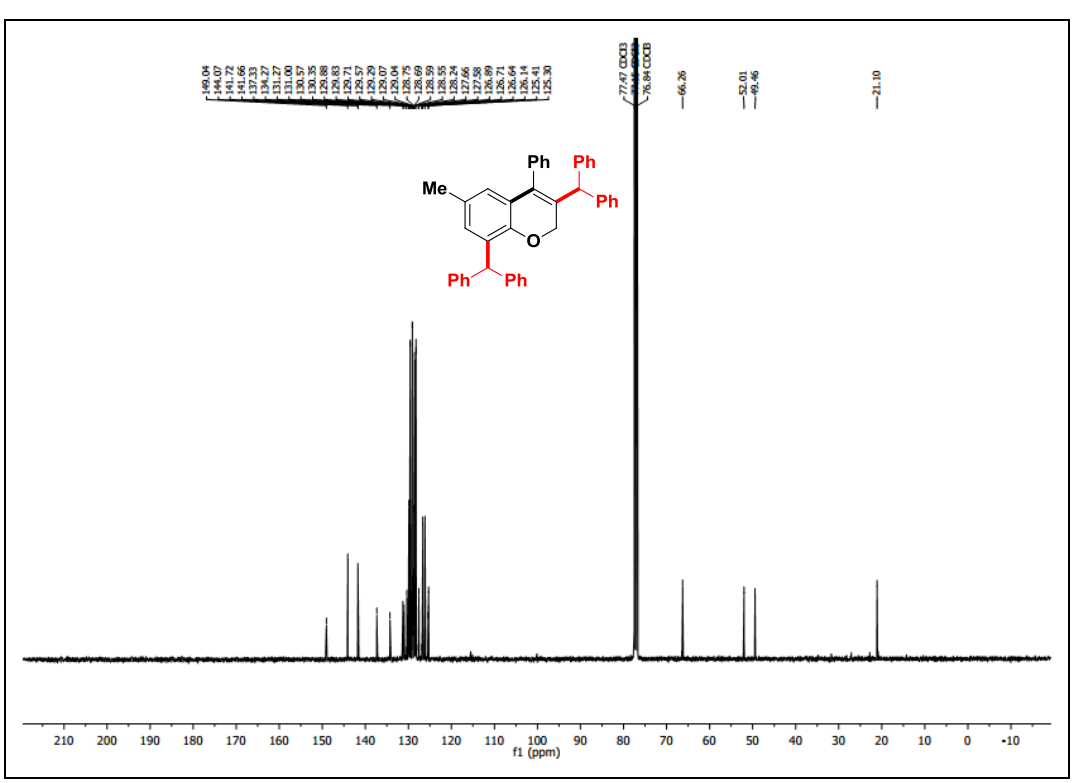

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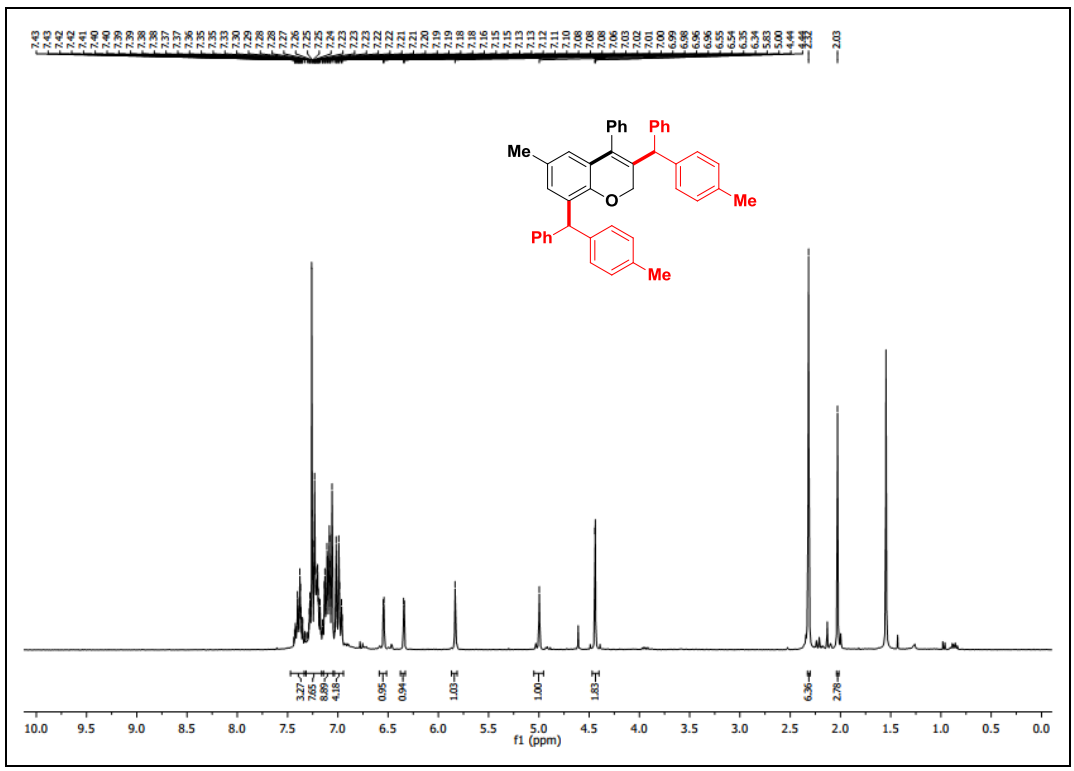

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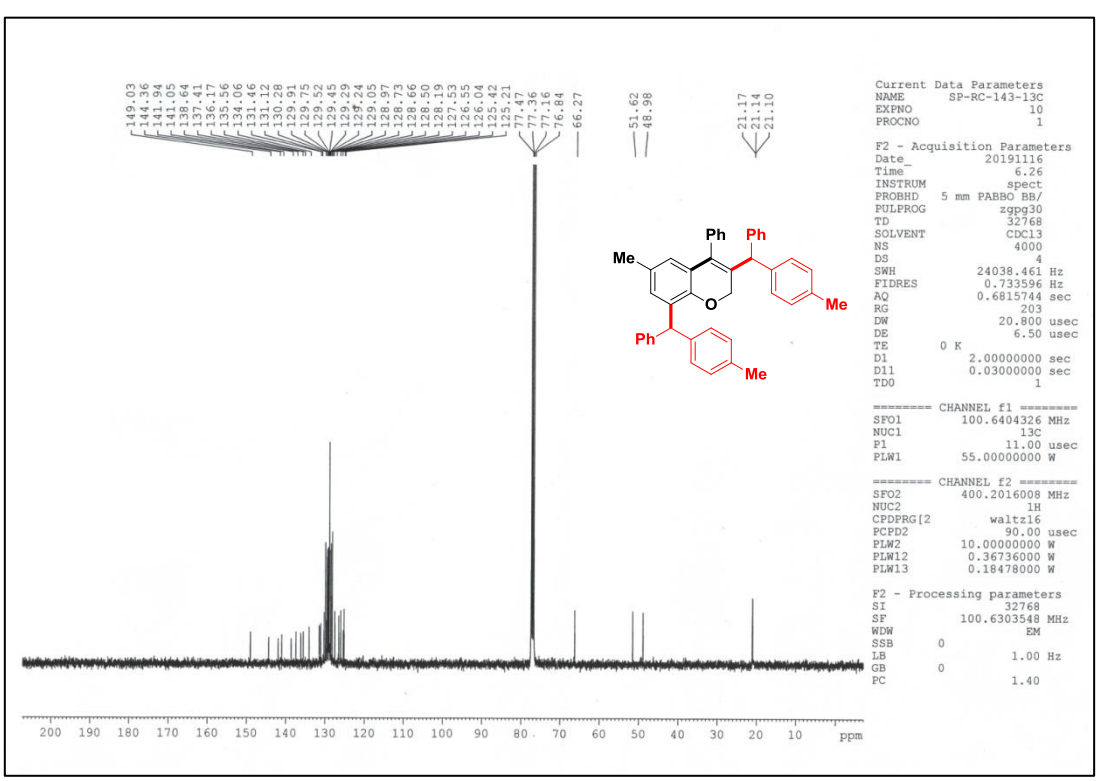

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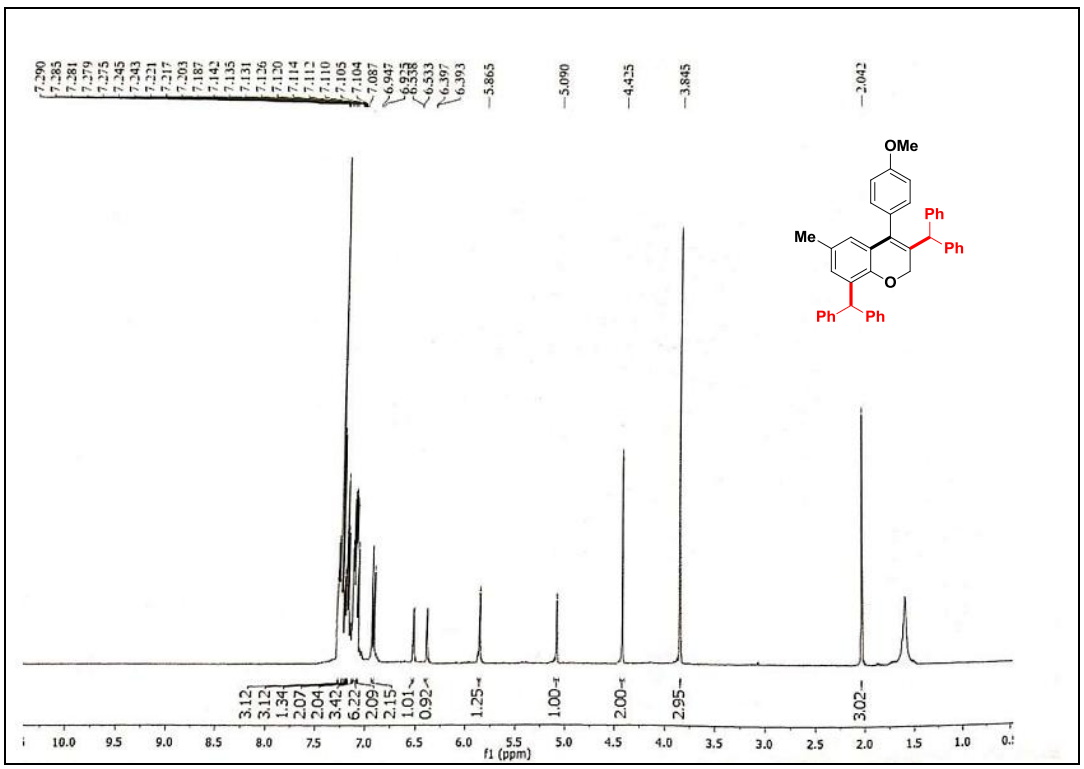

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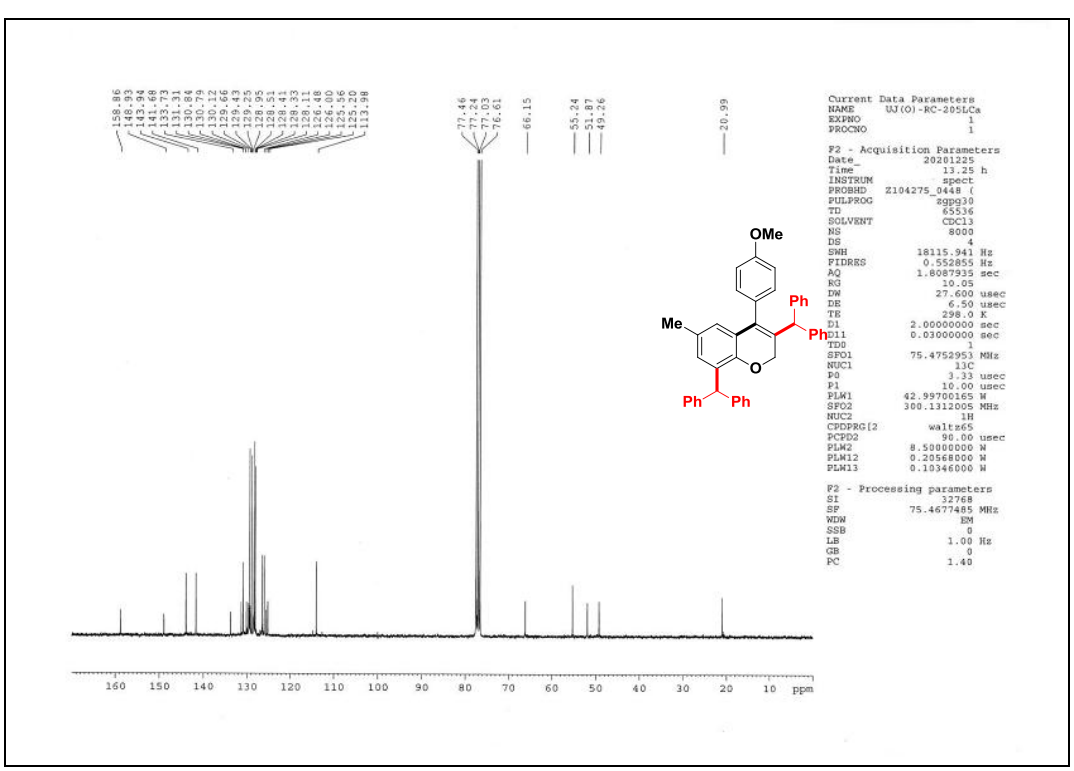

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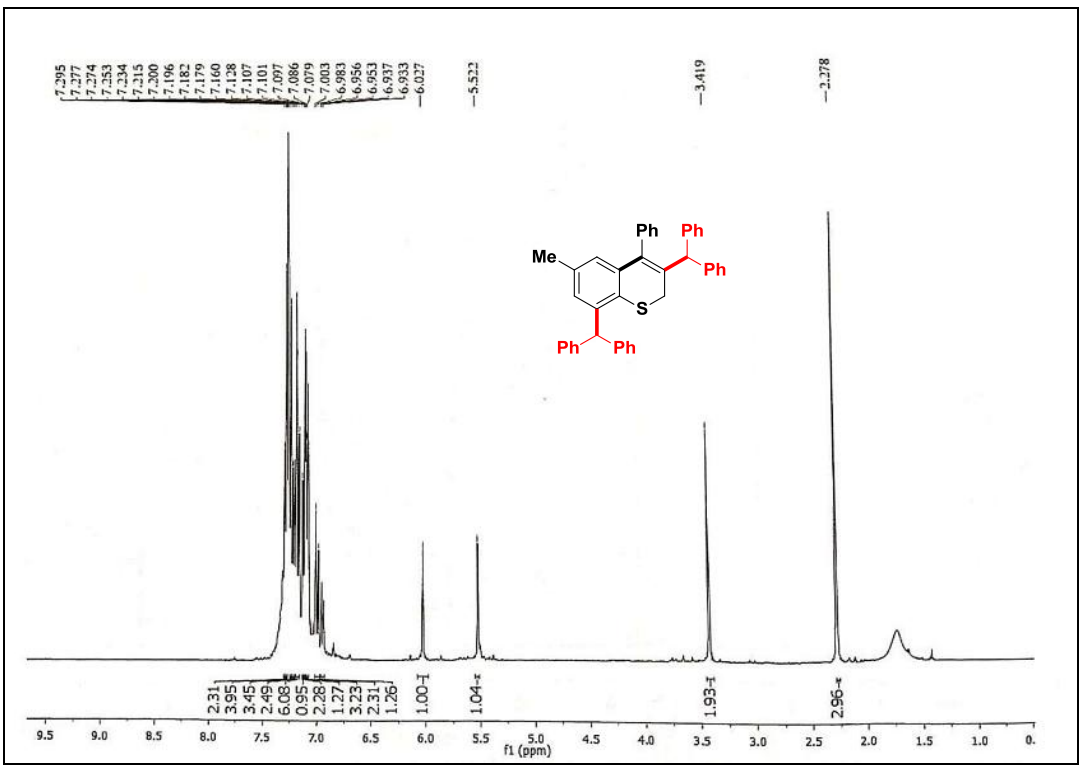

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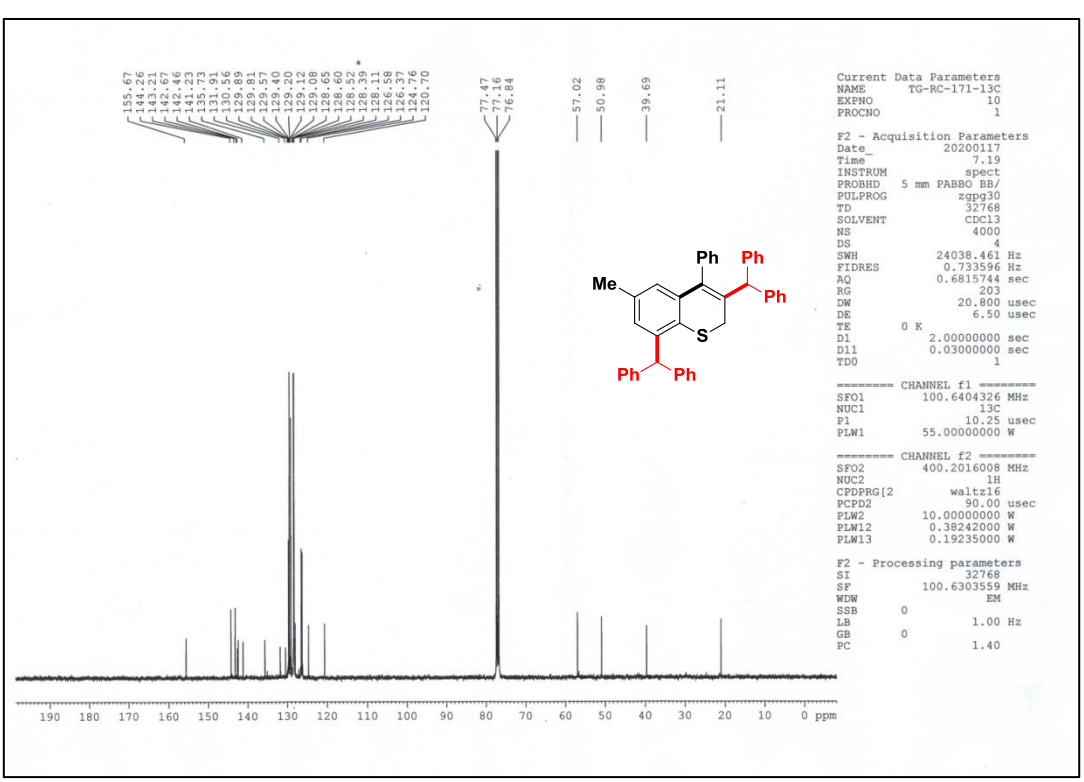

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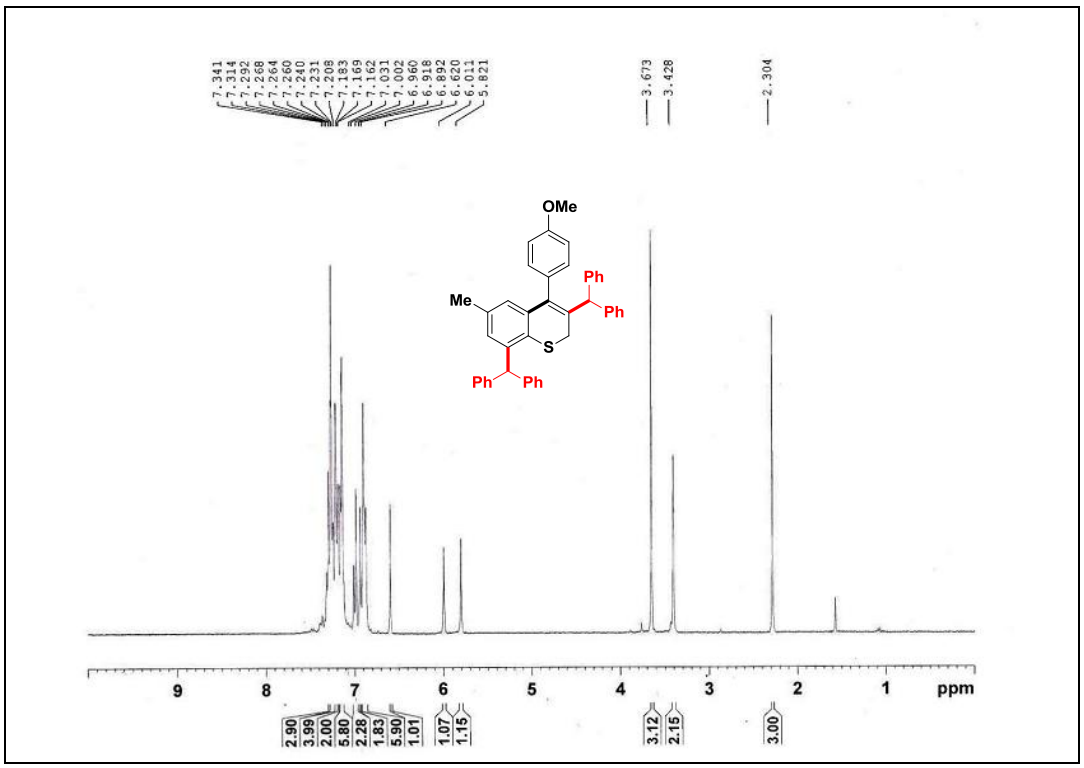

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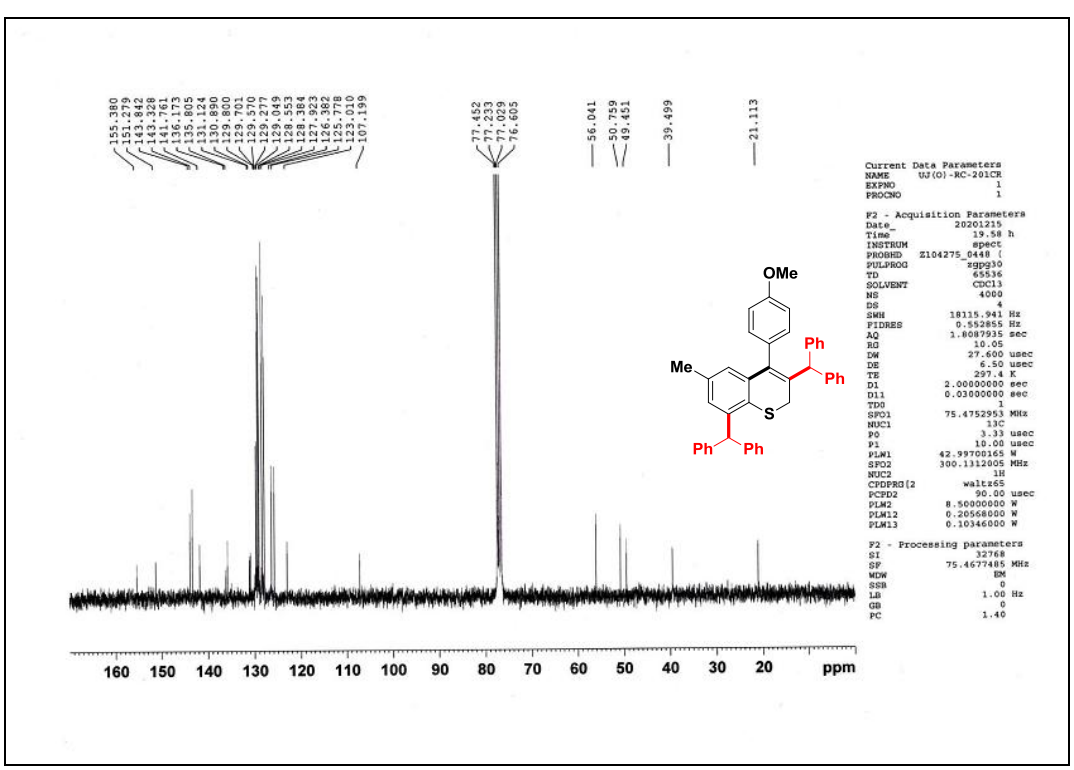

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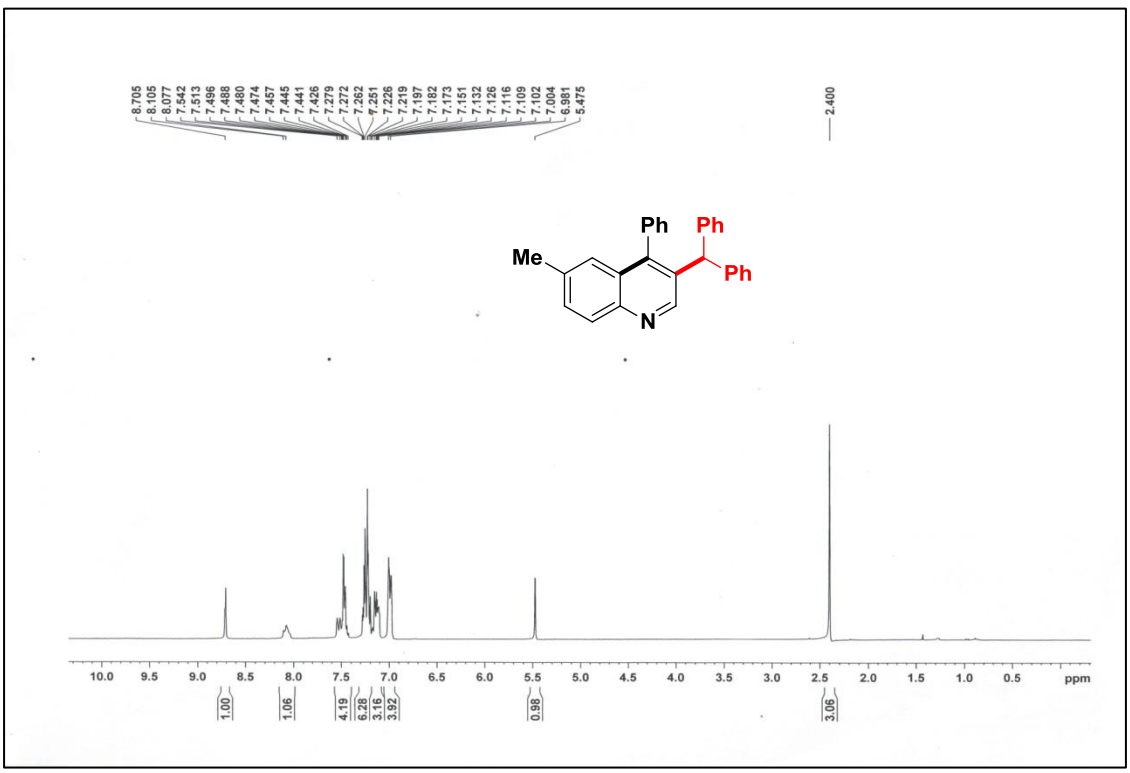
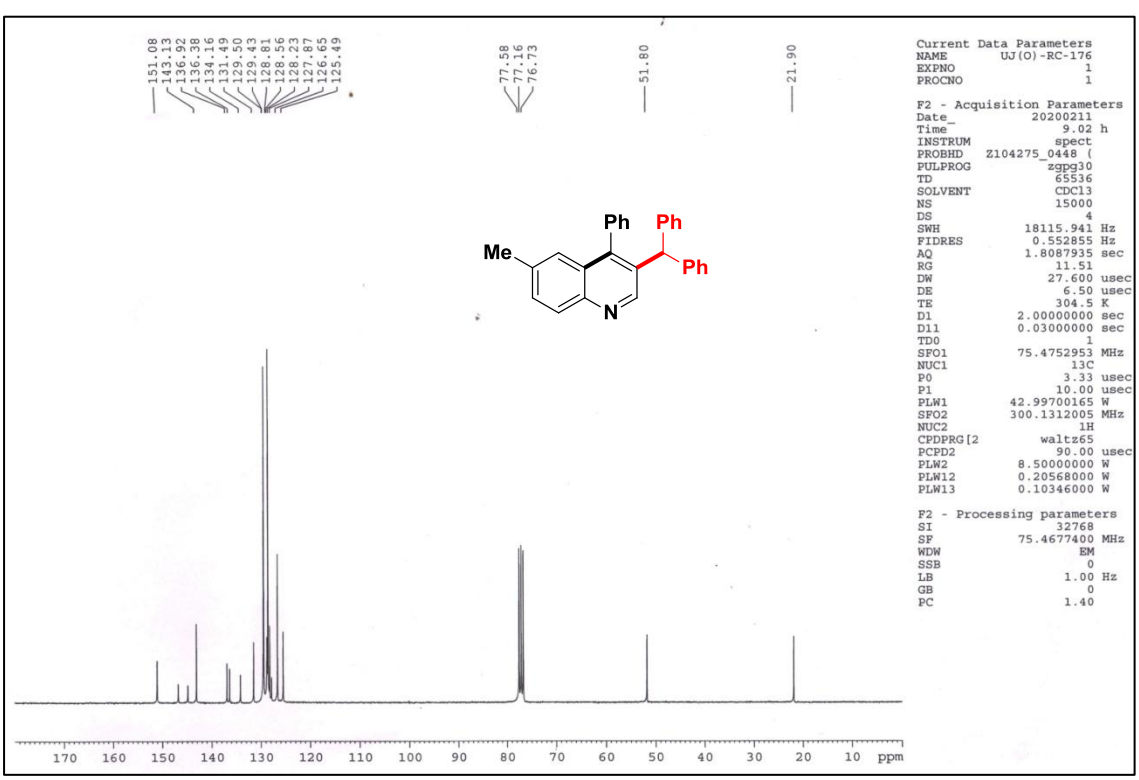


^{13}C NMR spectrum of compound **5a**, $CDCl_3$, 75 MHz



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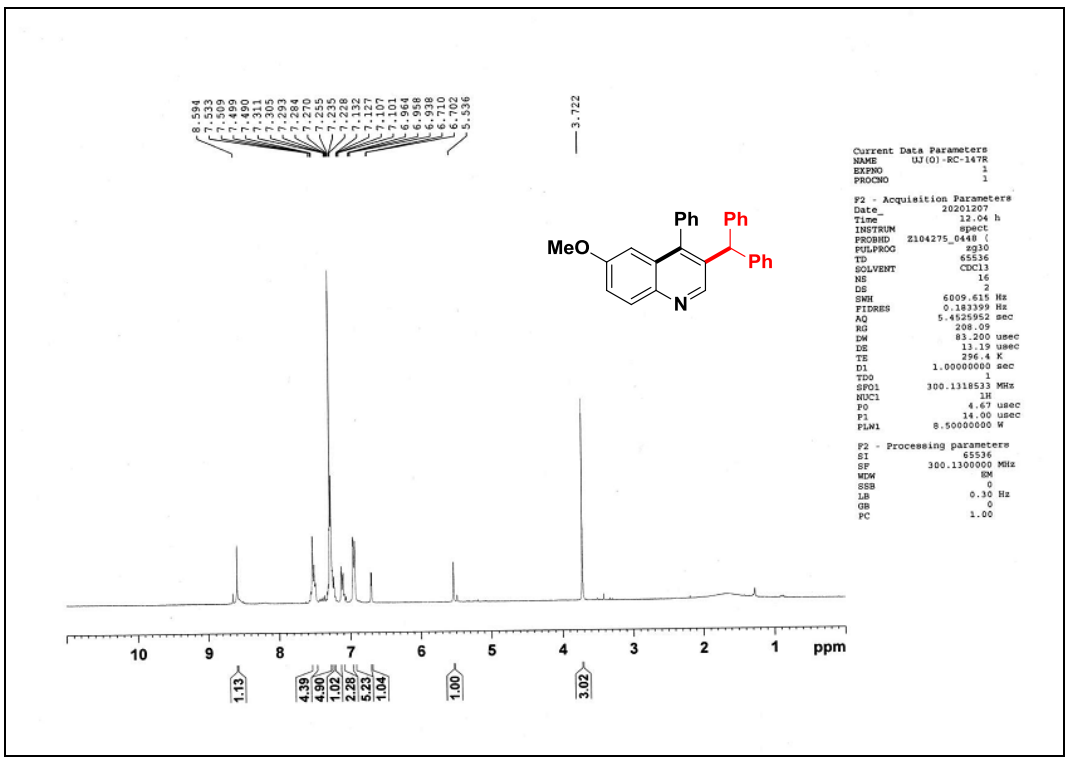

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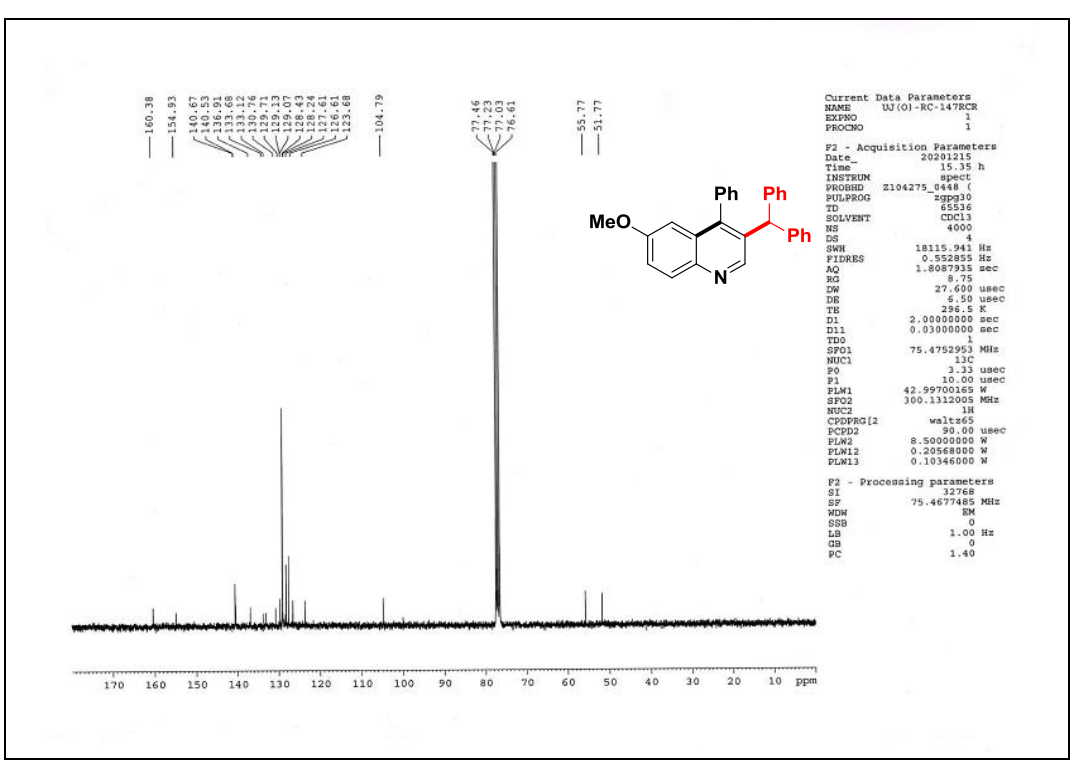

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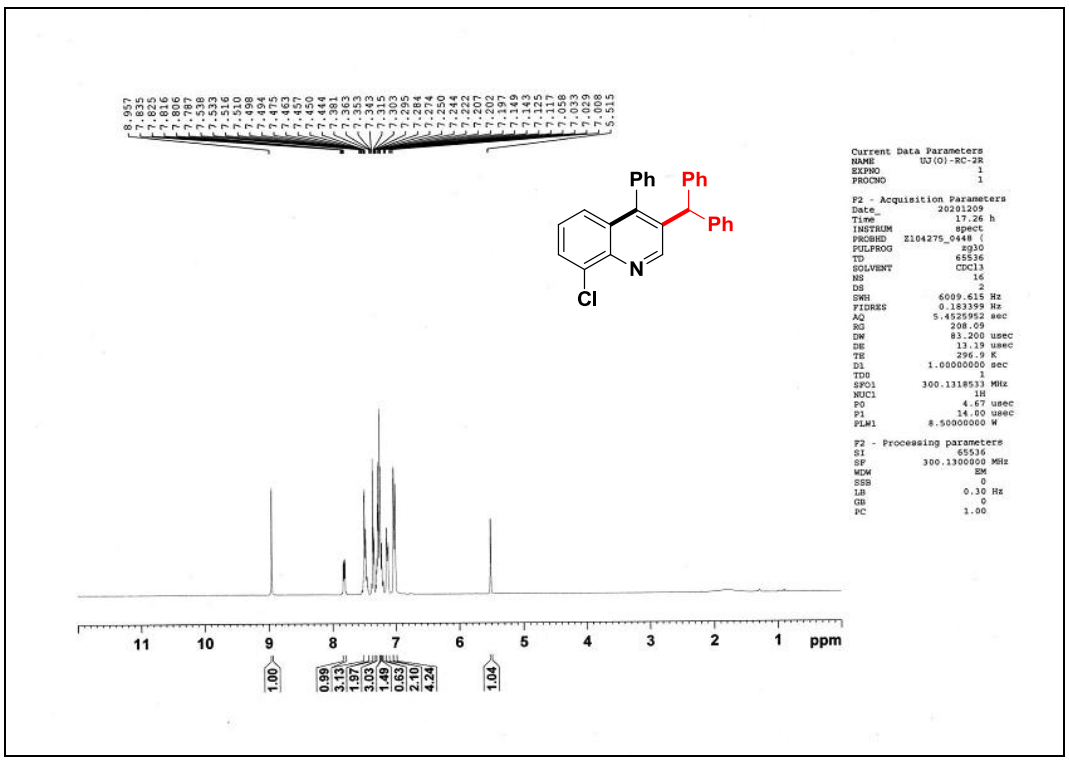

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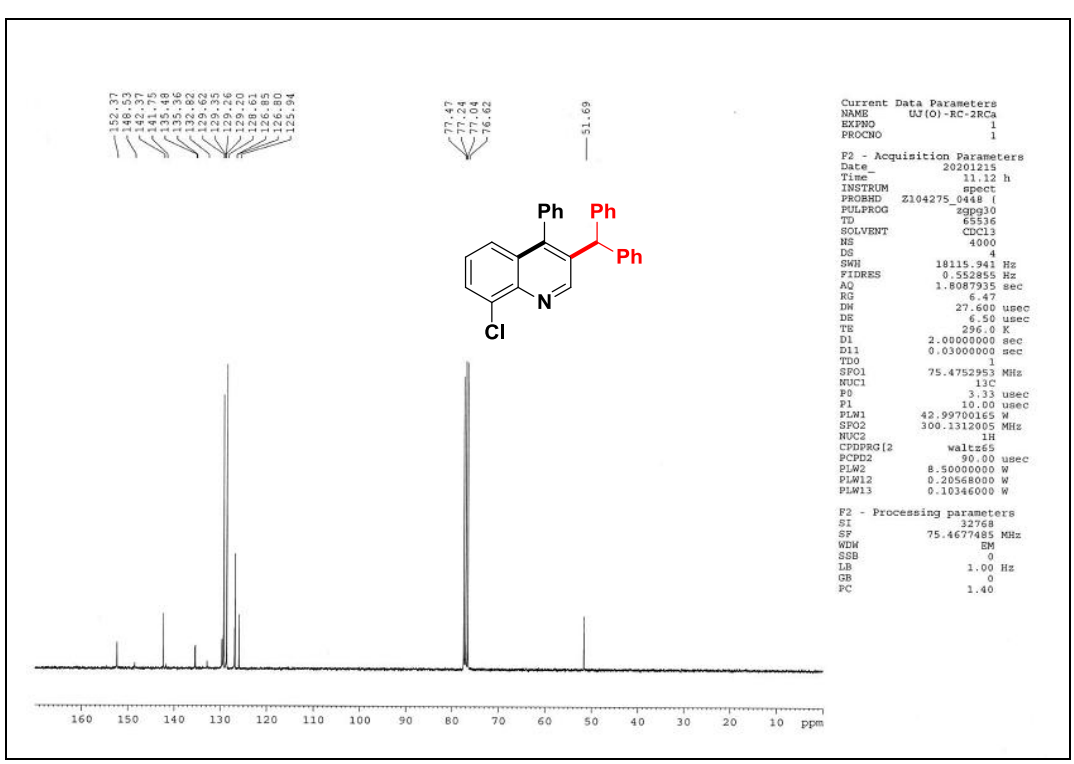

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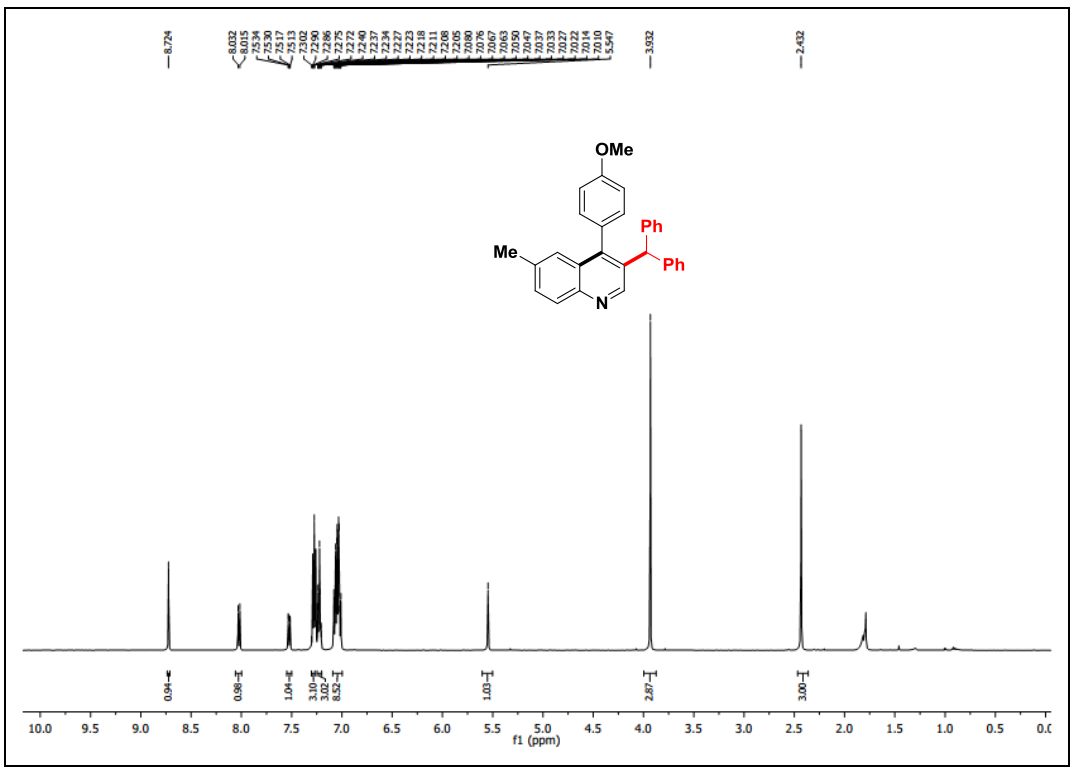
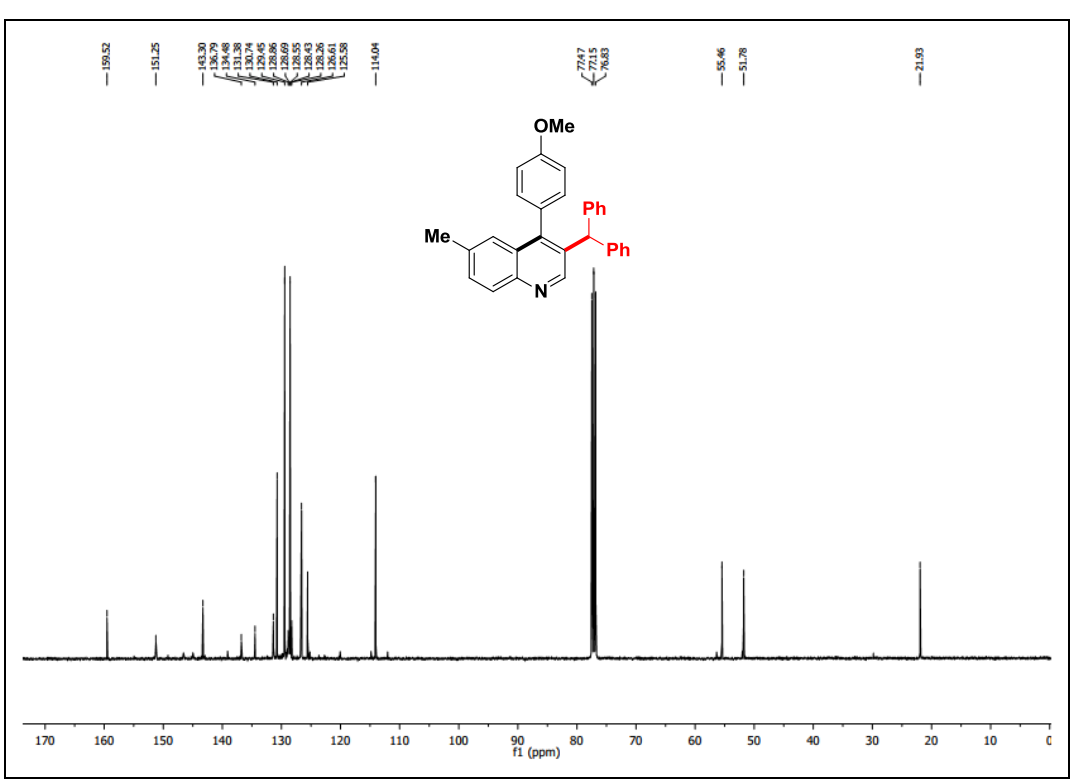


^{13}C NMR spectrum of compound **5d**, $CDCl_3$, 100 MHz



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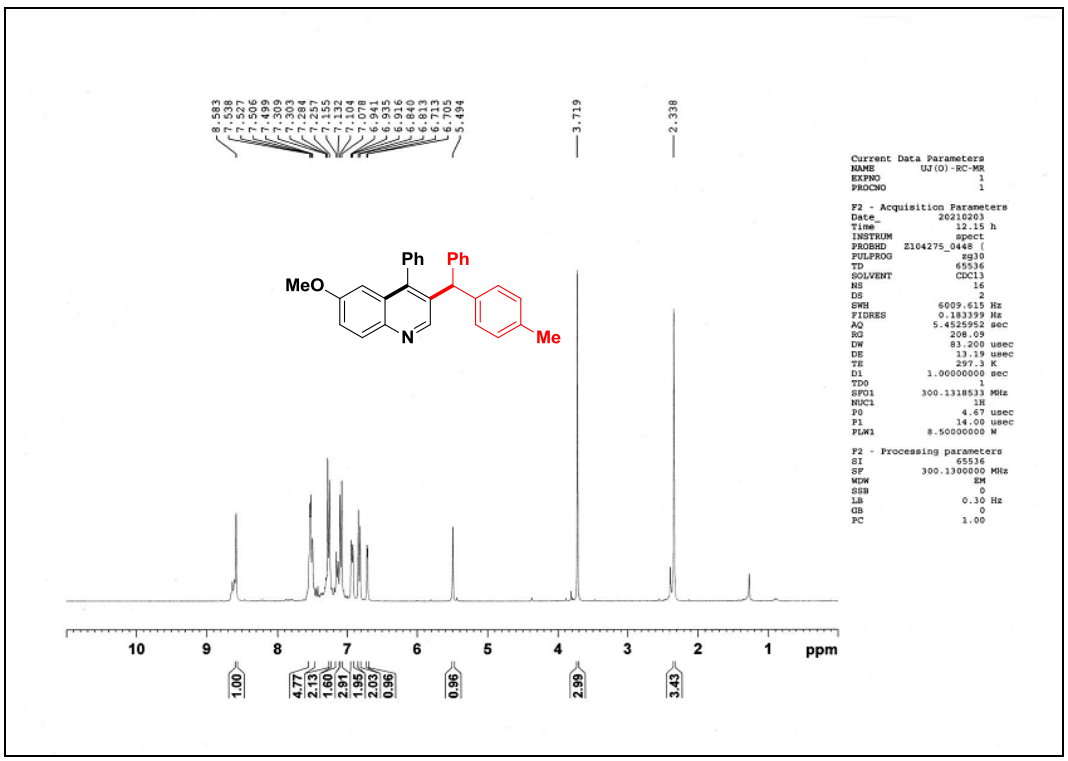
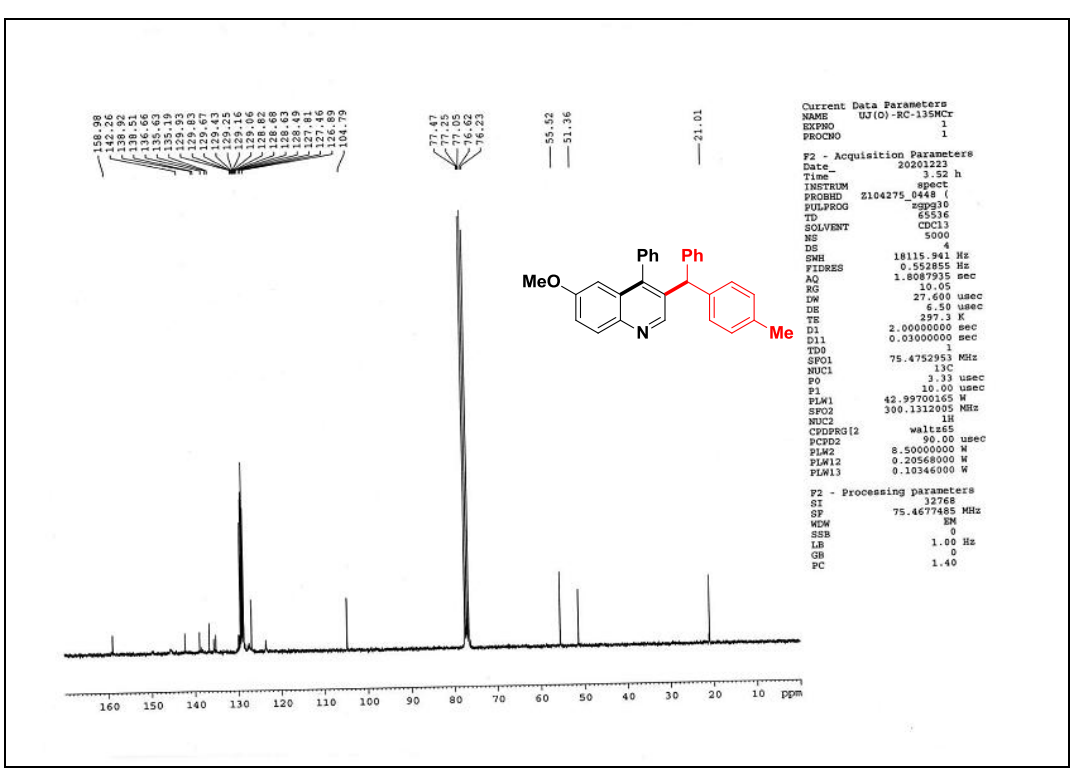
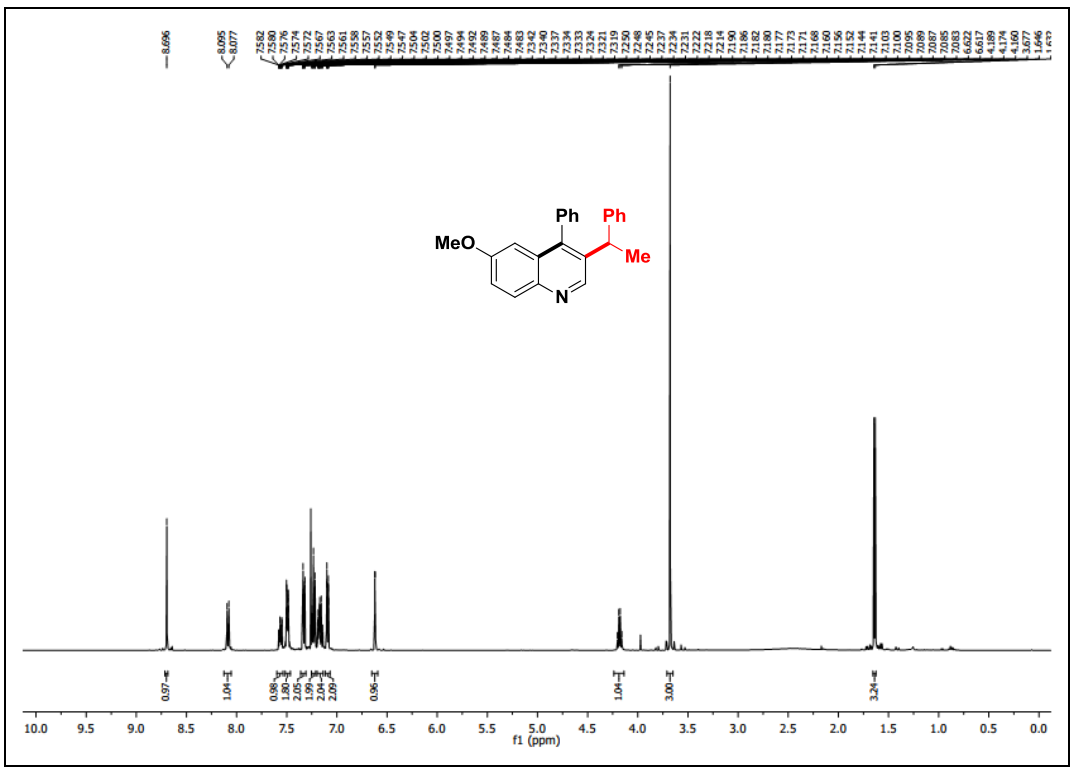


^{13}C NMR spectrum of compound **5e**, $CDCl_3$, 75 MHz



^{1}H NMR spectrum of compound **5f**, $CDCl_3$, 500 MHz



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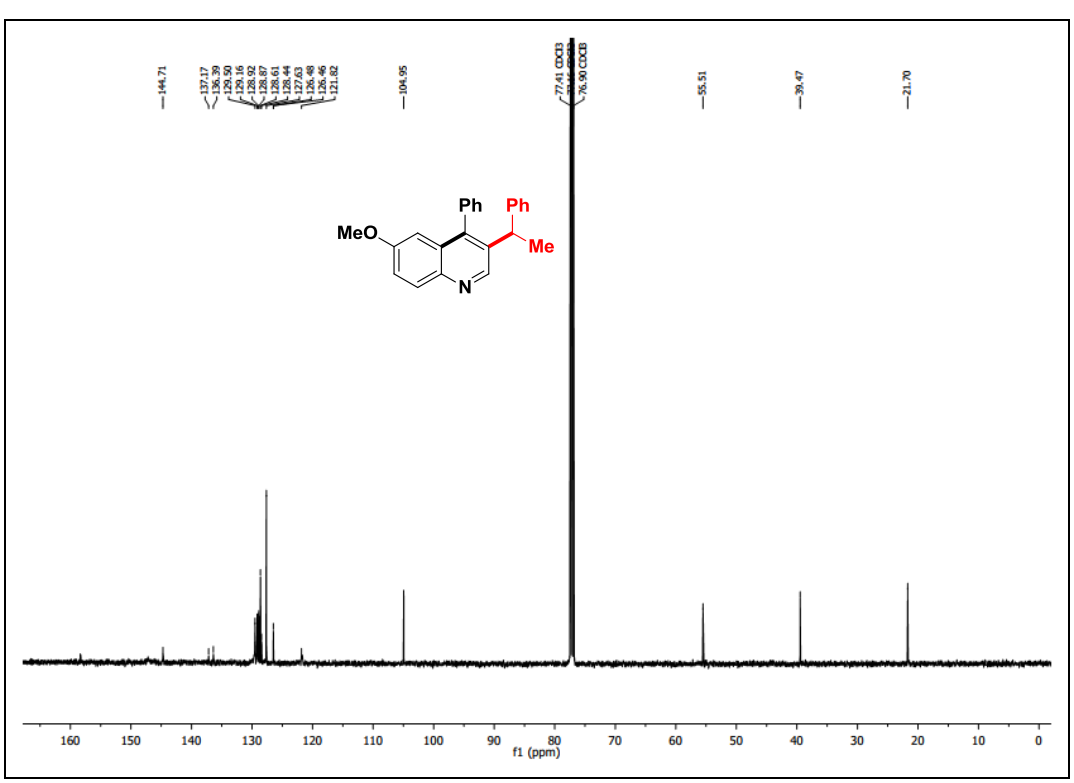

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Iron-catalyzed carboarylation of alkynes *via* activation of π-activated alcohols: rapid synthesis of substituted benzofused six-membered heterocycles†

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An $Fe(OTf)_3$-catalysed carboarylation of alkynes is reported for the straightforward synthesis of densely substituted 1,2-dihydroquinolines from *N*-propargyl anilides and π-activated alcohols. The reaction provides a new method for the synthesis of highly substituted benzofused six-membered heterocycles by the formation of two carbon–carbon bonds and one ring in a single step. The power of the methodology was further extended to the synthesis of substituted chromene and thiochromene derivatives in high yields. In addition, substituted quinoline derivatives were also achieved in a single step in the presence of $FeCl_3$ through detosylation/aromatisation. A number of control experiments have been performed and a plausible mechanism has also been proposed to explain the formation of the products.

Introduction

Benzofused six-membered heterocyclic compounds like dihydroquinolines, quinolines, chromenes, and thiochromenes are privileged scaffolds embedded both in a vast array of natural products[1] and biologically active compounds.[2] They are endowed with numerous pharmacological activities including antibacterial,[3a] antidiabetic,[3b] anti-inflammatory,[3c] antioxidant,[3d] anti-HIV,[3e] and antimalarial[3f] activities. For example, bedaquiline,[4a] pitavastatin,[4b] hydroxychloroquine,[4c] quinine[4d] *etc*. are important drugs containing the quinoline moiety, whereas ethoxyquin,[5a] tipifarnib,[5b] xanthine oxidase inhibitors,[6] and tetratolol[7] possess dihydroquinoline, chromene and thiochromene moieties, respectively (Fig. 1).

Due to the wide applications of these heterocycles, the facile synthesis of such scaffolds has always been an appealing research topic to synthetic chemists. Famous name reactions like the Skraup,[8] Friedlaender[9] and Combes[10] reactions are the classical methods for the synthesis of quinolines. But these methods require conditions which disfavor the synthesis of this complex moiety. In the case of dihydroquinoline, initially it was prepared as an intermediate during the quinoline synthesis by the Skraup method.[8] Thereafter, other methods like ring closing metathesis[11] and multi-component reactions[12] were exploited for the synthesis of 1,2-DHQ. In the last decade, electrophilic arylation of the terminal and internal alkynes commenced using Brønsted acids,[13] Lewis acids[14] and transition metal catalysts[15] has been extensively used as a more convenient and atom economical strategy for the synthesis of 1,2-dihrdroquinolines and 2*H*-chromenes. Moreover, the scope of this strategy has been further expanded using external electrophiles like halonium, selenium, and sulphenium cations,[16] and thus, tandem ring closing and addition of the functionality bring versatility into the substrates. Nevertheless, cascade arylations of alkynes promoted by carbon centred electrophiles are still rare,[17] although these transformations would introduce additional complexity to the products which is often required in the synthesis of a large number of medicinally important compounds. Therefore, it is highly desirable to

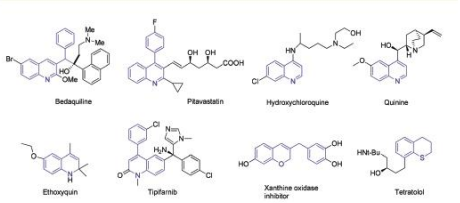

Fig. 1 Important molecules containing quinoline, dihydroquinoline, chromene, and thiochromene scaffolds.

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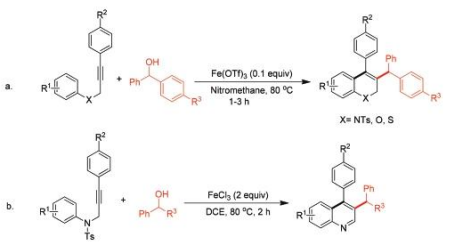
develop a new methodology for the general synthesis of benzofused six-membered heterocycles through cascade arylations of alkynes promoted by carbon-centred nucleophiles.

Since the last decade, the construction of the C–C/C–N bond by direct use of less expensive and abundantly available alcohols (R–OH) with unactivated nucleophiles (R–H) has gained widespread attention as a powerful strategy for the synthesis of diverse organic compounds due to its environmentally benign nature.[18] As a part of our research program for the synthesis of useful organic molecules by direct use of π-activated alcohols with various unactivated nucleophiles in the presence of inexpensive and less toxic iron salts,[19] in 2008, we for the first time introduced the carbohydroxylation reaction of alkynes with π-activated alcohols *via* the generation of a carbenium ion in the presence of iron(III) salt.[19c] This strategy emerged as a highly atom-economical and environmentally benign approach for the synthesis of substituted ketones from alkynes. From then on, a large number of reactions have been reported using benzyl alcohol directly as the carbocation source and the cascade initiator of alkynes, such as substitution of the terminal alkynes,[20] carbocyclization,[21] carbohydroxylation,[22] carboamination,[23] carbohalogenation[24] *etc*. Meike *et al.* reported benzylic alcohol-triggered carboarylation of alkynes tethered to aryl rings for the construction of benzofused carbocycles in the presence of 5 mol% $Ca(NTf_2)_2$ as a catalyst in combination with 5 mol% Bu_4NPF_6 additive.[25] Apart from the complexity of the catalyst system and the requirement of a long reaction time, this method is mostly restricted to the generation of carbocycles only. Therefore, there is considerable scope for improvements as well as advancements in this field.

Hence, during our studies on the direct activation of π-activated alcohols, we looked for a more general and wider application of the alcohol-driven carboarylation technique for the tandem formation of two C–C bonds. Instead of carbocyclization, we aimed at a heterocyclization strategy, obviously, with a simpler and more efficient reaction protocol. As we said earlier, it has already been a decade since we had established the activation protocol of benzylic alcohols followed by the activation of alkynes using catalytic iron salt. Banking on this concept, we attempted a carboarylation of alkynes tethered to aryl rings *via* aliphatic chains containing a heteroatom that is triggered by iron(III)-activated benzylic alcohols (Scheme 1). Our concern was that the parallel hydroarylation or carbohydroxylation reactions could strike as possible obstacles. To our delight, we successfully achieved the targeted carboarylation reaction with high chemoselectivity and regioselectivity under the catalysis of $Fe(OTf)_3$ (Scheme 1a). Just by varying the heteroatom, different heterocyclic skeletons like 1,2-dihydroquinoline, chromene and thiochromene were also obtained in high yields. Moreover, it was also noticed that when the reaction was conducted in the presence of anhydrous $FeCl_3$ (2 equiv.), the initial product 1,2-dihydroquinolines underwent smooth aromatisation to furnish quinoline derivatives in one pot (Scheme 1b). Therefore, we report herein an iron(III)-catalyzed carboarylation reaction of alkynes with activated benzylic



Scheme 1 Iron catalysed carboarylation of alkynes *via* direct substitution of alcohols.

alcohols for the construction of benzofused heterocycles containing nitrogen/oxygen/sulphur. Compared to the previous method,[25] the present method uses a much simpler, cheaper and greener iron catalyst, with a much lower reaction time and broader variety of substrates. The synthesis of different heterocycles like 1,2-dihydroquinolines, quinolines, chromenes and thiochromenes with various substituents *via* a single synthetic protocol is another remarkable feature of this strategy.

Results and discussion

The reactant 4-methyl-*N*-phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide derivatives **1** were prepared according to the literature reported procedure by the simple Sonogashira coupling between 4-methyl-*N*-phenyl-*N*-(prop-2-yn-1-yl)benzenesulfonamide derivatives and halobenzenes.[26] To optimize the reaction conditions, a set of reactions were performed with different catalysts and solvents at different temperatures for a representative reaction of 4-methyl-*N*-(3-phenylprop-2-yn-1-yl)-*N*-(*p*-tolyl)benzenesulfonamide **1b** with diphenylmethanol **2a** (Table 1). Initially, when the reaction was performed using 10 mol% of anhyd. $FeCl_3$ in DCM solvent at room temperature for a time period of 2 h, the desired 3-benzhydryl-8-bromo-4-phenyl-1-tosyl-1,2-dihydroquinoline (**3b**) was formed in a trace amount (Table 1, entry 1). However, when the reaction was continued for 12 h, 23% of the desired product **3b** was isolated and 34% was formed in 2 h under refluxing conditions (Table 1, entries 2 and 3). On switching the solvent to acetonitrile (CH_3CN) at 60 °C, the reaction did not begin at all, whereas DCE under the same reaction conditions provided of **3b** in 38% yield (Table 1, entries 4 and 5). When the reaction was performed at 80 °C in DCE, the yield of the product was not improved much (42%), but interestingly, a considerable amount (30%) of the corresponding detosylated product 3-benzhydryl-6-methyl-4-phenylquinoline (**5a**) was isolated (Table 1, entry 6) within 2 h. Instead of DCE, the use of nitromethane at 80 °C produced both **3b** and **5a** in 55% and 20% yield, respectively (Table 1, entry 7). Gratifyingly, upon switching the catalyst from $FeCl_3$ to $Fe(OTf)_3$ at 80 °C, **3b** was isolated as the sole product in 89% yield in just 2 hours, with no traces

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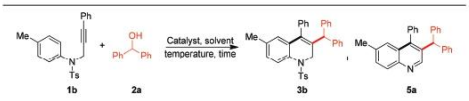
Table 1 Optimisation of reaction conditions[a,b]



1b 2a 3b 5a

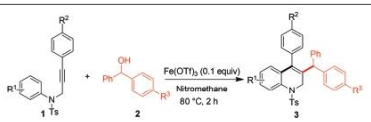
Entry	Catalyst (equiv.)	Solvent	Temp. (°C)	Yield of **3b** (%)	Yield of **5a** (%)
1	$FeCl_3$ (0.1)	DCM	rt	Trace	0
2[c]	$FeCl_3$ (0.1)	DCM	rt	23	0
3	$FeCl_3$ (0.1)	DCM	Reflux	34	0
4	$FeCl_3$ (0.1)	CH_3CN	60 °C	0	0
5	$FeCl_3$ (0.1)	DCE	60 °C	38	0
6	$FeCl_3$ (0.1)	DCE	80 °C	42	30
7	$FeCl_3$ (0.1)	CH_3NO_2	80 °C	55	20
8	**$Fe(OTf)_3$ (0.1)**	**CH_3NO_2**	**80 °C**	**89**	**0**
9	$InCl_3$ (0.1)	CH_3NO_2	80 °C	0	29
10	$In(OTf)_3$ (0.1)	CH_3NO_2	80 °C	15	24
11	$Ag(OTf)_3$ (0.1)	CH_3NO_2	80 °C	25	11
12	$Fe(OTf)_3$ (0.2)	CH_3NO_2	80 °C	79	21
13	$Fe(OTf)_3$ (1.0)	CH_3NO_2	80 °C	44	48
14	$FeCl_3$ (1.0)	CH_3NO_2	80 °C	15	59
15	$FeCl_3$ (1.0)	DCE	80 °C	Trace	68
16	**$FeCl_3$ (2.0)**	**DCE**	**80 °C**	**0**	**87**
17[d]	$FeCl_3$ (2.0)	DCE	80 °C	Trace	53

[a] Reaction conditions: 0.15 mmol **1b** and 0.15 mmol **2a** in 2 mL of solvent under an Ar atmosphere, 2 h. [b] Isolated yield. [c] 12 h. [d] Air.

of **5a** (Table 1, entry 8). The reaction was continued for another one hour, but no significant improvement in the yield was observed. However, no better results were observed when the reactions were performed with other metal catalysts like $InCl_3$, $In(OTf)_3$ and AgOTf (Table 1, entries 9, 10 and 11). Once we found the suitable catalyst for the formation of **3b**, we observed the yield increasing with the catalyst loading. Surprisingly, instead of improvement, the yield of **3b** decreased and the formation of the detosylated product **5a** was initiated. Then we shifted our focus to obtain the best reaction conditions for the formation of **5a** and gradually increased the amount of $Fe(OTf)_3$ (Table 1, entries 12 and 13). In order to check other iron salts, we then employed 1 equivalent of $FeCl_3$ in nitromethane (CH_3NO_2) and DCE at 80 °C; 59% and 68% of **5a** were produced, respectively (Table 1, entries 14 and 15). Furthermore, by increasing the amount of $FeCl_3$, gradually the yield of **5a** was increased and, to our delight, when 2 equivalents of $FeCl_3$ were used, 87% of **5a** was produced within 2 h in DCE (Table 1, entry 16). A longer reaction time did not lead to any significant improvement of the yield. When the reaction was performed in an open atmosphere, the product **5a** was obtained in 53% yield with 2 equivalents of $FeCl_3$ (Table 1, entries 17). Probably, in open air, the presence of aerobic oxygen and moisture reduced the catalytic activity of iron catalysis. Therefore, the best reaction conditions to obtain **3b** were the catalysis of 10 mol% $Fe(OTf)_3$ in nitromethane at 80 °C for 2 h and for **5a**, the optimum reaction conditions turned out to be the use of 2 equivalents of anhydrous $FeCl_3$ in DCE at 80 °C for 2 h.

To test the synthetic viability of the reaction, a variety of 4-methyl-*N*-phenyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide derivatives **1** were subjected to a reaction with diphenylmethanol **2a** under the optimal reaction conditions. At first, substituents at the aniline moiety were varied and it was observed that the electron donating group at the *para* position of the aniline provided better yields of the products than the unsubstituted one (Table 2, entries 1 and 2). Again, both electron withdrawing groups like –Br, –Cl and electron donating

Table 2 Synthesis of dihydroquinoline derivatives by $Fe(OTf)_3$ catalysed carboarylation of alkynes with catalytic activation of alcohols[a,b]



1 2 3

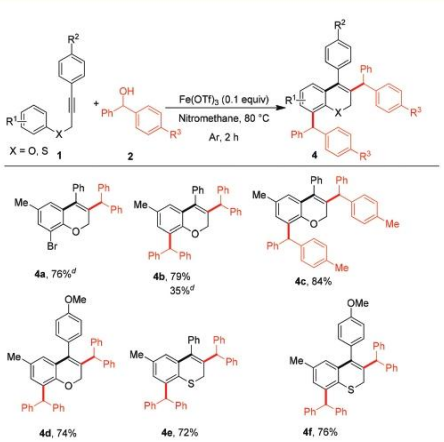
Entry	Substrate	Alcohol	Product	Yield
1	1a	2a	3a	71%
2	1b	2a	3b	89%
3	1c	2a	3c	88%
4	1d	2a	3d	81%
5	1e	2a	3e	74%
6	1f	2a	3f	92%
7	1g	2a	3g	57%[c]
8	1h	2b	3h	93%

[a] Reaction conditions: substrate **1** (0.15 mmol), **2** (0.15 mmol), Fe $(OTf)_3$ (0.015 mmol), solvent CH_3NO_2 (2 mL), Ar atmosphere, 2 h, 80 °C. [b] Isolated yields. [c] 3 h.

groups like –OMe at the *ortho* position of the aniline underwent a smooth reaction with diphenylmethanol to afford 88%, 81% and 74% yields, respectively (Table 2, entries 3, 4 and 5). Again the structure of dihydroquinoline **3c** was further confirmed by single crystal XRD (CCDC 1982134†). The alkyne moiety possessing an electron donating group rendered a much better yield of the product than that possessing an electron withdrawing group (92% and 57%, respectively, Table 2, entries 6 and 7). This observation reflects the fact that the electron donating group at the alkyne moiety stabilises the vinyl carbocationic intermediate, resulting in better conversion. However, instead of diphenylmethanol, when phenyl(*p*-tolyl)methanol (**2b**) was used as the coupling partner, the desired product was obtained in excellent yield (93%) (Table 2, entry 8).

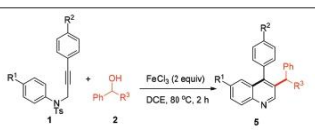
To demonstrate the versatility of this method, we targeted the synthesis of 3-substituted chromene and thiochromene derivatives using this method (Scheme 2). When 2-bromo-4-methyl-1-((3-phenylprop-2-yn-1-yl)oxy)benzene was allowed to react with diphenylmethanol, the corresponding 3-alkylated chromene was obtained in 76% yield (Scheme 2, entry **4a**). But, with 1-methyl-4-((3-phenylprop-2-yn-1-yl)oxy)benzene, despite using 1 equivalent of alcohol, besides carboarylation, the conventional Friedel-Craft alkylation also takes place at the free *ortho* position to furnish the corresponding densely substituted chromene in low yield (35%) and the substrate was not fully converted. For complete conversion, 2 equivalents of alcohol were used which resulted in 79% yield (Scheme 2, entry **4b**). It should be noted that even the use of less than 1 equivalent of alcohol **2a** also afforded 3,8-dialkylated chromene **4b** in 29% yield. The use of 2 equivalents of **2b** improved the yield, providing 84% yield of **4c**. The electron donating group (–OMe) in the aromatic ring of the alkyne moiety also afforded good yield (**4d**, 74%). A similar observation was made in the case of a sulphur analogue, generating thiochromene derivatives **4e** and **4f** in good yield (72% and 76%, respectively). This difference in the reactivity pattern during the formation of dihydroquinoline and chromene/thiochromene clearly indicates that the reaction shown in Table 2 is highly influenced by the steric and electronic factors imposed by the tosyl group attached to the nitrogen atom.

As mentioned earlier, the use of 2 equivalents of $FeCl_3$ resulted in the *in situ* detosylation and aromatisation of **1** to furnish substituted quinoline derivatives in one step. Inspired by this observation, we focused on the examination of the scope of this strategy for simple preparation of quinoline derivatives in a single step. To our delight, electron donating groups like –Me and –OMe at the aniline moiety provided excellent yields of the corresponding quinolines (Table 3, entries 1 and 2). But the electron withdrawing group *o*-Cl impeded the conversion due to electron deficiency and the



Scheme 2 Synthesis of chromene and thiochromene derivatives[a,b]. Reaction conditions: substrate **1** (0.15 mmol), **2** (0.30 mmol), $Fe(OTf)_3$ (0.015 mmol), solvent CH_3NO_2 (2 mL), Ar atmosphere, 2 h, 80 °C. Isolated yields. [a] Alcohol **2a** (0.15 mmol). [b] **2** (0.15 mmol).

Table 3 Synthesis of quinoline derivatives[a,b]



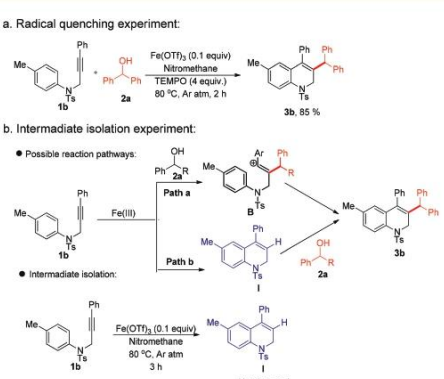
Entry	Substrate	Alcohol	Product	Yield (%)
1	1b	2a	5a	87
2	1i	2a	5b	89
3	1d	2a	5c	63
4	1j	2a	5d	92
5	1i	2b	5e	93
6	1i	2c	5f	79

[a] Reaction conditions: substrate **1** (0.15 mmol), **2** (0.15 mmol), $FeCl_3$ (0.3 mmol), solvent DCE (2 mL), Ar atmosphere, 2 h, 80 °C. [b] Isolated yields.

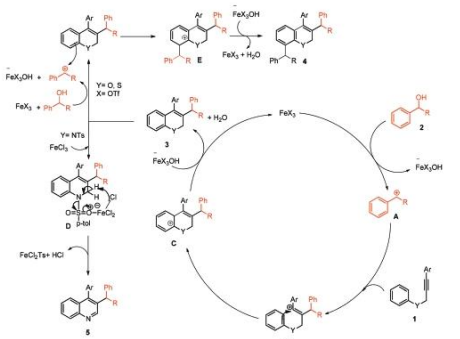
steric effect, providing 63% yield of **5c** (Table 3, entry 3). The electron donating group *p*-OMe at the aromatic ring of the alkyne moiety triggered the conversion and furnished better yield (Table 3, entry 4). To scrutinize the robustness of the method, other alcohols were tested under the optimum conditions. And it was found that an alcohol having an electron rich substituent provided an impressive result, giving 93% yield (Table 3, entry 5). On the other hand, when 1-phenylethanol was used as the coupling partner, the reaction was little sluggish, providing 79% yield of **5f** (Table 3, entry 6).

In order to gain insight into the reaction mechanism, a series of control experiments were performed (Scheme 3). Interestingly, when the reaction was performed in the presence of the radical quencher TEMPO (tetramethylpyridinyl *N*-oxide) under the optimized reaction conditions (Scheme 3a), the desired product was formed without any significant change in the yield. Thus, the possibility of any radical intermediate was eliminated. Next, to understand whether the reaction proceeds through path **a** or **b**, the reaction was carried out in the absence of electrophile **2a** under the optimized reaction conditions, but no cyclization product was detected (Scheme 3b). Further continuation of the reaction resulted in the decomposition of the starting material **1b**. Therefore, the possible reaction pathway *via* the intermediate **I** was ruled out.

In accordance with the experimental outcomes, control experiments, and previous reports,[24c,27] a plausible reaction pathway was proposed, which is shown in Scheme 4. Initially, the iron(III) catalyst activates π-activated alcohol **2** to generate benzylic carbocation **A** which reacts with the more electron-rich alkyne to generate more stable aryl substituted vinyl carbocation **B**. This vinyl carbocation is simultaneously attacked by the aryl nucleophile to generate 3-alkylated dihydroquinolines **3**. The product **3** can undergo the Friedel-craft alkylation in the presence of excess alcohol and $Fe(OTf)_3$ to produce **4** when Y = O, S. However, when Y = NTs, this **3** can participate in the detosylation and aromatisation process in the presence



Scheme 3 Control experiments.



Scheme 4 Plausible reaction pathway of iron catalysed carboarylation of alkynes *via* direct substitution of alcohols.

of excess $FeCl_3$ to form the corresponding quinoline derivatives **5**. Therefore, stoichiometric $FeCl_3$ is required for the preparation of the quinoline derivatives. Probably due to the lower basicity and nucleophilicity of the triflate anion than chloride, $Fe(OTf)_3$ could not perform the detosylation/aromatisation efficiently.

Conclusions

In conclusion, we have developed an efficient and versatile approach for the synthesis of densely substituted 1,2-dihdroquinolines, quinolines, 2*H*-chromenes and thiochromenes *via* Fe(III)-catalyzed carbenium ion induced carboarylation of alkynes in high yields with the direct activation of π-activated alcohols. Moreover, substituted quinoline derivatives could be achieved in a single step by the same procedure using 2 equivalents of $FeCl_3$. The reaction features readily available starting materials with good substrate scope along with high yields and atom-economy, and the use of an inexpensive and environment friendly Fe(III)-catalyst. Further investigations of iron-mediated carboarylation of alkynes for exploitation in the synthesis of potentially bioactive heterocyclic motifs are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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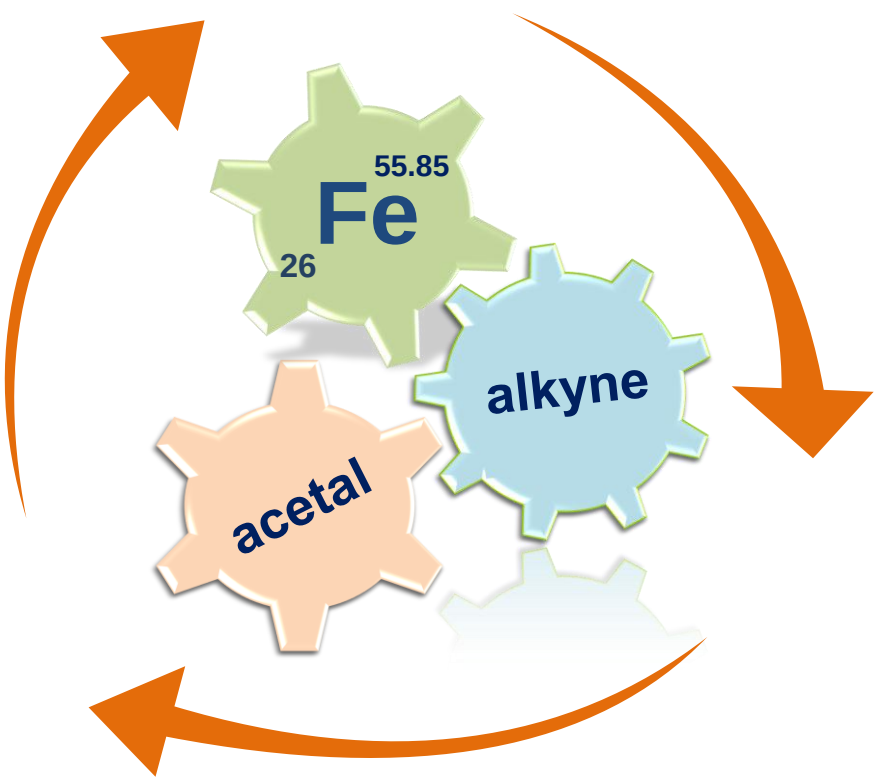
Part-2

Iron Catalyzed Synthesis Of Carbocycles



1. INTRODUCTION:

Iron catalyzed synthesis of carbocycles is a rapidly developing field in organic chemistry. Carbocycles, which are cyclic organic compounds containing only carbon atoms, are significant structural motifs found in a diverse array of naturally occurring compounds and biologically active molecules.[1] The development of efficient synthetic methods for the construction of these carbocyclic frameworks has been a long-standing goal in organic synthesis.

Recently, iron-catalyzed reactions have emerged as an important tool for the construction of a broad range of organic framework under mild reaction conditions.[2] Iron is an appealing catalyst for these reactions owing to its low toxicity, low cost, and high abundance.[3] In this context, this topic has gained significant attention among researchers and promises to offer new opportunities for the development of useful synthetic methodologies. Iron catalyzed synthesis of carbocycles encompasses a wide range of reactions, such as cycloaddition, cyclization, annulation, metathesis, cycloisomerization etc.[4] One of the key advantages of iron-catalyzed reactions is their high regio- and stereo-selectivity and efficiency. Additionally, these reactions often require mild reaction conditions and can be carried out using readily available starting materials, making them attractive from a practical standpoint. Iron catalysis has also been used to develop new synthetic methodologies for the construction of fused structural motifs.[5] For example; iron-catalyzed carbocyclization reactions have been used to construct complex cyclic systems, which are important structural motifs in many natural products and pharmaceuticals.[6]

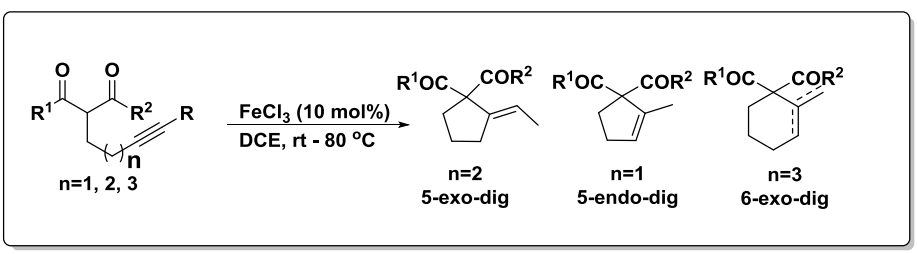
Overall, iron catalyzed synthesis of carbocycles is an active area of research with broad implications in organic synthesis and medicinal chemistry. With the development of new iron-catalyzed reactions and the discovery of novel applications, we can expect this field to make significant contributions to the advancement of synthetic organic chemistry. This review describes an in-depth exploration of the different aspects of iron-catalyzed synthesis of carbocycles, including the synthetic applications, and the potential of these reactions in the development of new methodologies for organic synthesis.

2. A BRIEF REVIEW:

In this review, a brief idea on utilisation of iron catalyst in synthesizing different kind

of important carbocyclic moieties has been comprised.

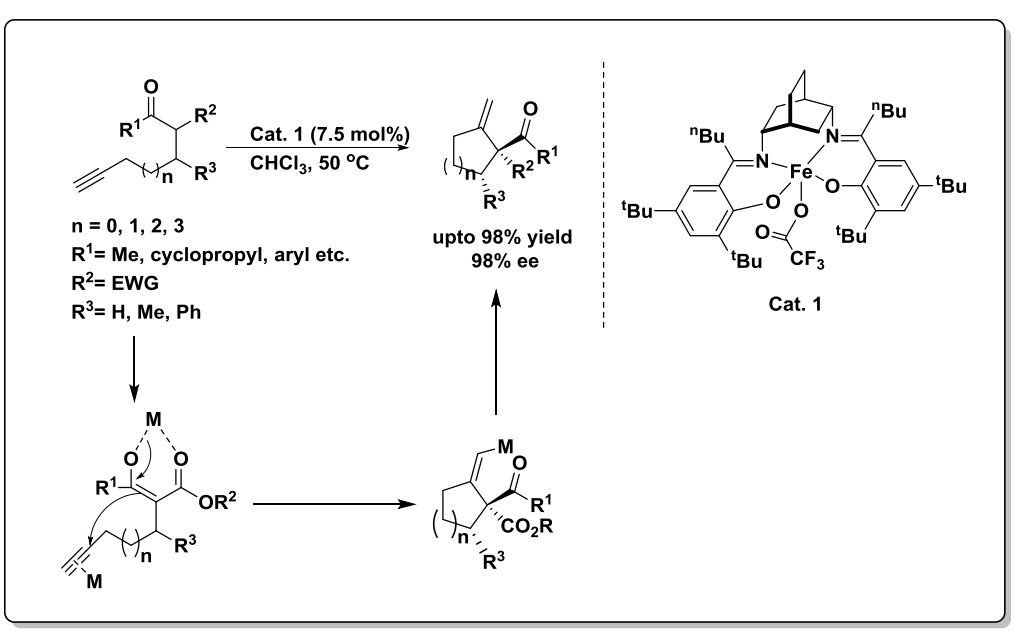
In 2012, a simple $FeCl_3$ catalyzed Conia-ene cyclization of 2-alkynyl-1,3-dicarbonyl compounds were reported by the group of Lee for the construction of five membered rings and specifically *E*-isomers were generated (scheme 1).[7] Depending on the nature of the substrate, different modes of cyclization such as *5-exo-dig*, *5-endo-dig*, or *6-exo-dig* cyclizations were observed. As a result, apart from



Scheme 1: $FeCl_3$ catalyzed Conia-ene cyclization of 1,3-dicarbonyl compounds

alkylidenecyclopentanes, cyclopentenes and cyclohexene (isomerised from the corresponding alkylidenecyclohexane), could also be attained by this protocol. In addition to that, when tin enolates or alkynylstannanes were employed as starting materials, vinylstannates were acquired by stannyl Conia-ene type cyclization in moderate to high yields.

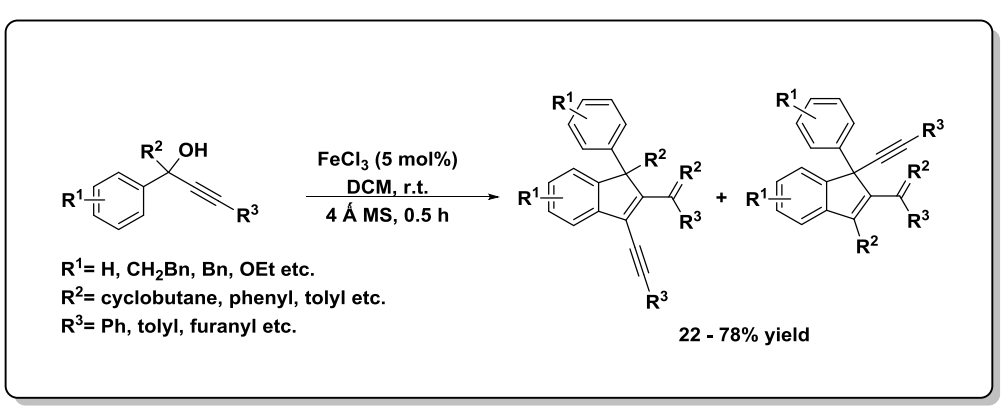
In 2014, White *et al.* found that, salen ligand containing a *cis*-2,5-diaminobicyclo-[2.2.2]octane scaffold formed a stable iron trifluoroacetate complex cat. **1**, and the resulting iron-salen complex catalyzed asymmetric Conia-ene



Scheme 2: Iron-salen complex for carbocyclization

cyclization of α-alkynyl-β-keto esters and other α-alkynyl ketones containing electron-withdrawing substituent (Scheme 2).[8] The reaction resulted in the formation of exo-methylene substituted carbocycles bearing an adjacent quaternary stereocenter in excellent yield (>90%) and high enantiomeric excess (>90%). Further applicability of the method was displayed by preparing four-, six-, and seven- membered rings possessing exo-methylene group, germinal ester and keto groups. Although for four membered ring preparation, the yields and enantioselectivities obtained were not satisfactory (57% yield, 82% ee). However, *n*-butyl substituent in the salen moiety of the catalyst was necessary for good enantioselectivity. A plausible mechanism was depicted and it showed that, a metal enolate was formed by the Fe(II) of the catalyst with the carbonyl substrate, and subsequently activated the alkyne part. As a result, one face of the enolate was blocked and intramolecular nucleophilic attack by the alkyne resulted one enantiomer of the desired product. Since iron is among the most sustainable metals, the derived iron complex was very much alluring as a catalyst for large-scale synthesis and industrial operations.

A novel iron catalyzed route to obtain highly conjugated indenes was explored in the year 2010 by the dimerization of trisubstituted propargyl alcohols (scheme 3).[9] Careful optimization of the reaction parameters exhibited that, metal salts like $ZnCl_2$ and $AuCl_3$ provided moderate yields, although $Cu(OTf)_2$, $Yb(OTf)_3$, or Brønsted acids like *p*-TsOH and TfOH did not gave any products. No products were obtained in absence of catalyst. However, maximum yield was achieved with 5 mol% of $FeCl_3$ in

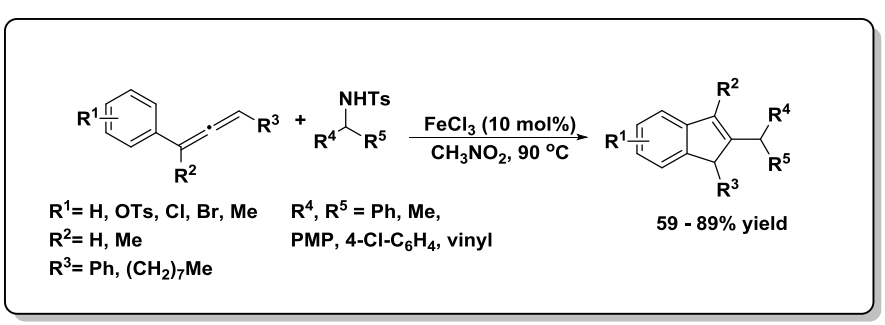


Scheme 3: Dimerization of trisubstituted propargyl alcohols to afford highly conjugated indenes

presence of 4 Å MS in DCM solvent at room temperature. The mechanism proposed involved the activation of the propargyl alcohol through coordination with the $FeCl_3$

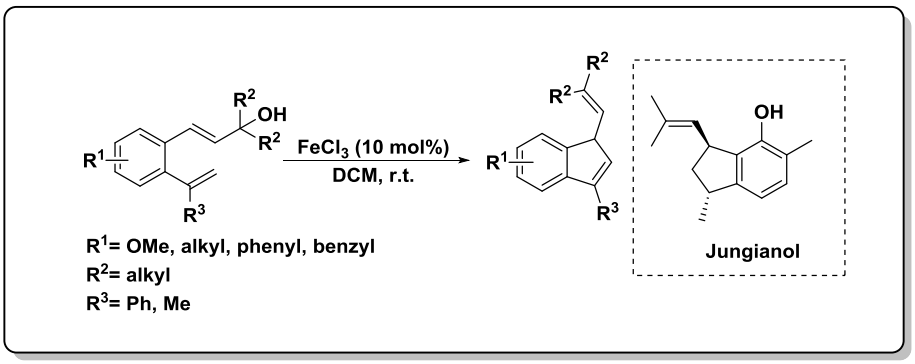
resulting in the formation of a Fe(III)-coordinated intermediate. From this intermediate, water was eliminated to generate alkenyl cation or its resonance analogue allenic cation. This carbocation was attacked by another molecule of the propargyl alcohol at the sterically less hindered center, and then subsequent intramolecular Friedel–Crafts reaction furnished the conjugated indenes.

Another strategy for the formation of polysubstituted indenes was presented by Tian and his group, where they have utilised $FeCl_3$ catalyzed C-N bond cleavage for the cyclization of *N*-benzylic and *N*-allylic sulfonamides (scheme 4).[10] A variety of 1,3-disubstituted or 1,1,3-trisubstituted indene derivatives with both EDG and EWGs were synthesized efficiently by this procedure with high regioselectivity. In presence of $FeCl_3$, a carbocation was supposed to be generated from *N*-alkyl sulphonamide by the sp^3 C-N bond cleavage. This carbocation would then be attacked by the arylallene to afford a allylic cation, followed by Friedel Craft cyclization and aromatisation leads to the formation of indene derivatives. In this catalytic cycle, $FeCl_3$ generated $[FeCl_3(NHTs)]^-$ by reacting with *N*-alkyl sulfonamide, which in presence of H^+, would regenerate active $FeCl_3$ catalyst.



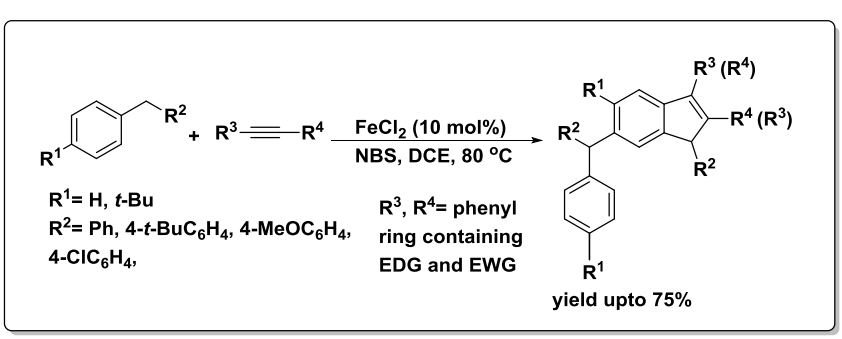
Scheme 4: $FeCl_3$ catalyzed C-N bond cleavage for the cyclization of N-benzylic and N-allylic sulfonamides

Allylic alcohols were used as the starting material for $FeCl_3$ catalyzed Prins-type cyclization to afford highly substituted indene derivatives (Scheme 5).[11] This method was further implemented for the total synthesis of jungianol and *epi*-jungianol. Other Lewis and Brønsted acids catalysts which could catalyze Prin cyclization such as $Sc(OTf)_3$, $Yb(OTf)_3$, and $Cu(OTf)_2$, TFA, $BF_3.OEt_2$ etc. were also screened, but they provided lower yields than in $FeCl_3$. The reaction was proved to be versatile as a range of indene derivatives with various substitution patterns were attained by this method.



Scheme 5: $FeCl_3$ catalyzed Prins-type cyclization for the synthesis of substituted indene derivatives

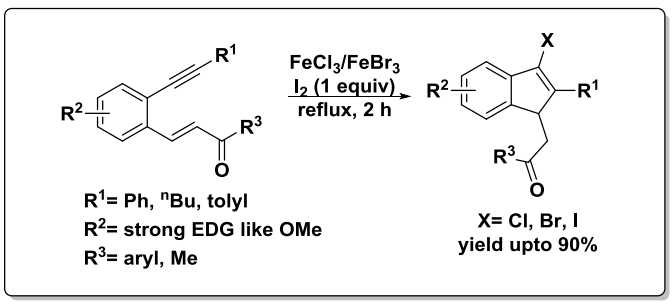
The group of Chen has reported an iron catalyzed tandem reaction between benzylic compounds and alkynes for the preparation of multisubstituted indene derivatives (Scheme 6).[12] By performing a number of control experiments, a mechanistic pathway of the reaction was proposed and it was believed that, in situ bromination of the diphenylmethane first takes place by reaction with NBS and then the bromo is activated by $FeCl_2$ to form the benzylic carbocation. Then the sequential alkyne attack and cyclization leads to the formation of the indene derivatives. Interestingly, although weakly electron donating and withdrawing groups provided moderate to good yields of the product, strongly electron donating and withdrawing groups failed to provide any desired yields because of the strong electronic effect. However, aryl ring with *p*-OMe could only form the product in presence of DDQ oxidant.



Scheme 6: Iron catalyzed synthesis of polysubstituted indene derivatives

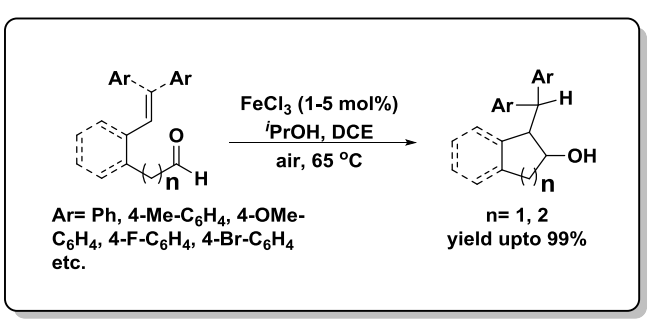
Akbar and his co-workers have developed a cyclization strategy to obtain 3-haloindene derivatives using stoichiometric amount of ferric halides or I_2 (Scheme 7).[13] The reaction was only successful for *o*-(alkynyl)-benzylideneketones having an electron-rich arene, but the yields are quite good for these substrates. The mechanism

suggested that, the iron salt would first coordinate with the α,β-unsaturated ketone and resulted in the formation of a vinyl cationic intermediate. This cationic intermediate was then trapped by a halide ion to generate 3-haloindene enolate. This enolate would produce the desired 3-haloindene derivative when exposed to water.



Scheme 7: Iron catalyzed synthesis of 3-haloindenes

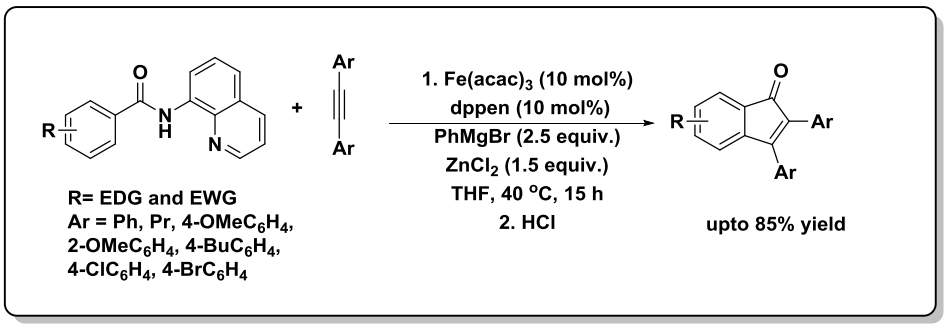
A reductive coupling reaction between unactivated aldehydes and arylalkenes in presence of isopropanol led to the formation of 5-, 6-, 7- and 8-membered carbocyclic alcohols (scheme 8).[14] The reaction provided high regioselectivity and for five-membered ring, only *cis*-diastereomer was formed under the optimum reaction condition. Zheng



Scheme 8: $FeCl_3$ catalyzed synthesis of 5-, 6-, 7- and 8-membered cabocycles.

observed that strong Brønsted acids provided lower yield than the Lewis acids, and weak Brønsted acids were unable to catalyze the reaction. Among different iron salts, $FeCl_3$ provided maximum yield. When mono-substituted aryl alkene was used, then regioselectively six-membered ring was formed instead of five membered carbocycle because of the electronic factor imposed by the phenyl ring.

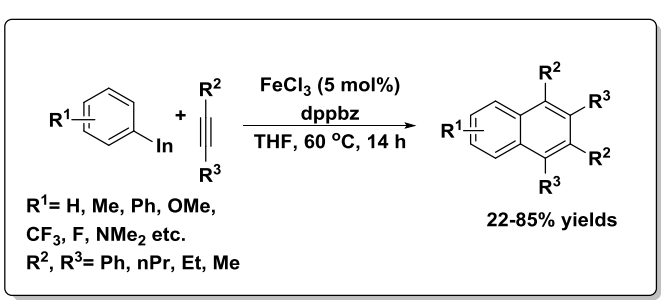
Ilies *et al*. has utilised an iron catalyzed annulation of carboxamide and alkynes to construct indenone derivatives in excellent yields (scheme 9).[15] A series of indenone derivatives were synthesized in presence of 10 mol% $Fe(acac)_3$, dppen ligand (cis-1,2- bis(diphenylphosphino)ethane), 1.5 equiv. $ZnCl_2$ and PhMgBr base. The proposed mechanism suggested that, a Fe-coordinated complex with 8-AQ was



Scheme 9: Synthesis of indenone derivatives by $Fe(acac)_3$ catalyzed annulation of carboxamide and alkynes

formed which directed the C-H activation. Then alkyne insertion and cyclization proceeded in presence of $ZnCl_2$ to attain substituted indenones.

Another important carbocyclic molecule, naphthalene, was synthesized by Adak and Yoshikai in 2012 where the arylindium reagents underwent annulation reaction with the alkynes, and therefore produced substituted naphthalenes in presence of catalytic iron–bisphosphine complex (Scheme 10).[16] In this case, the oxidative coupling reaction of the arylindium reagents and alkynes reaction did not

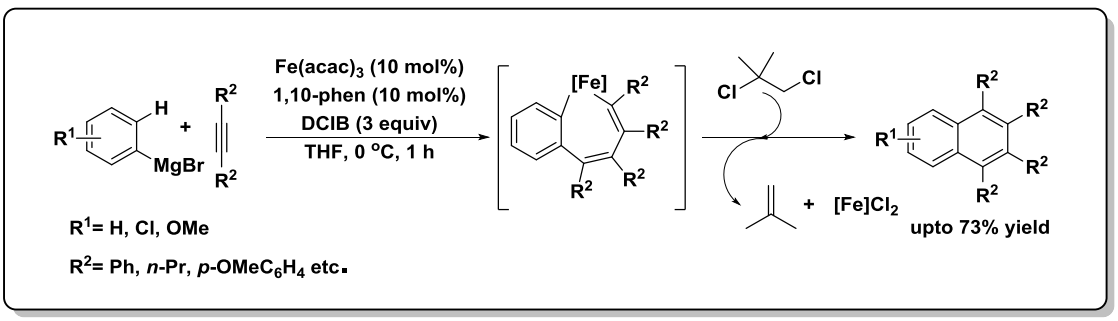


Scheme 10: Iron catalyzed annulation of arylindium and alkynes to synthesize naphthalenes

demand any kind of external oxidant for the catalytic turnover. Electron withdrawing substitutents at the aryl indium reacted less efficiently than the electron donating substituents. When alkynes were substituted with dialkyl or diaryl, yields were decreased. When 1-phenylpropyne/1-phenyl-1–butyne were used as substrates, regioselectively 1,4-dialkyl-2,3-diphenylnapthalenes were obtained. However, 2-hexynes afforded four regioisomers as equimolar mixture. The mechanism suggested the formation of an indium hydride species which regenerated the iron catalyst at the end of the catalytic cycle.

Another oxidative cyclization strategy for the construction of polysubstituted

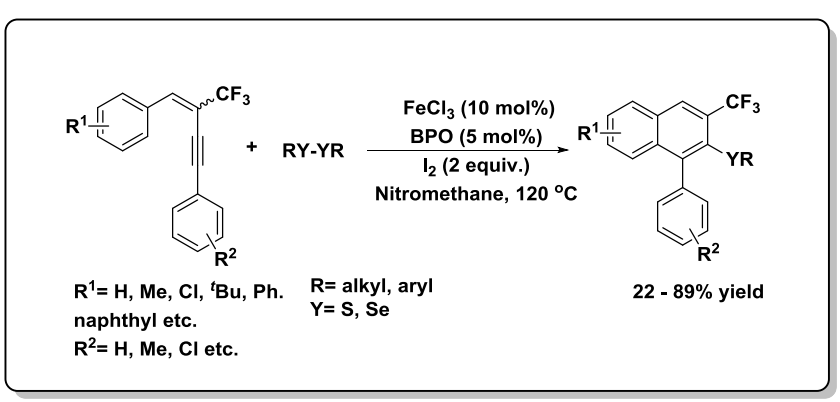
naphthalene derivates were exhibited by the same group (scheme 11).[17] The reaction progresses *via* C-H activation of the aryl magnesium bromide compound with the internal alkynes and the resulted in a [2+2+2] annulation leading to the formation of the naphthalene



Scheme 11: Iron catalyzed [2+2+2] annulations of alkynes and aryl magnesium bromide

derivative. Although, the lack of regioselectivity was the main demerit of the procedure, but the multiple halide substitution could provide the precursors for further functionalization. The photophysical characteristics of the prepared compounds were also tested and reported accordingly.

A polysubstituted naphthelene synthesis was introduced by electrophilic annulations of aryl enynes promoted by $FeCl_3$ and I_2 (scheme 12).[18] The group of

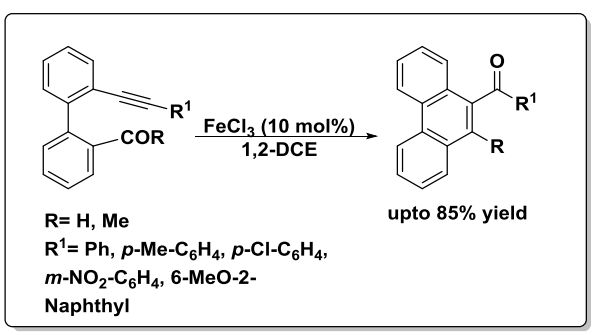


Scheme 12: $FeCl_3$ and I_2 mediated electrophilic annulations of aryl enynes

Zhang has used diaryl/alkyl disulphide or diaryl diselenide as the elctrophiles and synthesized a number of trifluoromethyl-containing naphthalene derivatives in good to excellent yields *via* selective *6-endo-dig* cyclization. Substitution at the disulphide or diselenide did not exert much effect on the reaction yield. But aryl enynes containing EWG and EDG has shown different yields of the product depending on the

electronic factor imposed by the attached group. Trisubstituted anthracene and phenanthrene were also achieved by this protocol. Several mechanistic investigations disclosed that, the reaction was initiated by the formation of RSI in a radical pathway. This RSI was then attacked by the alkyne to undergo electrophilic cyclization to afford the naphthalene derivatives.

The group of Jana has explored a $FeCl_3$ catalyzed alkyne-carbonyl metathesis of 2′-alkynyl-biphenyl-2-carbaldehydes (Scheme 13).[19] The reaction was compatible with a wide number of substituents (electron-donating and electron-withdrawing substituents) in the starting biphenyl moiety, alkyne and carbonyl part. In addition, apart from aryl group, it also

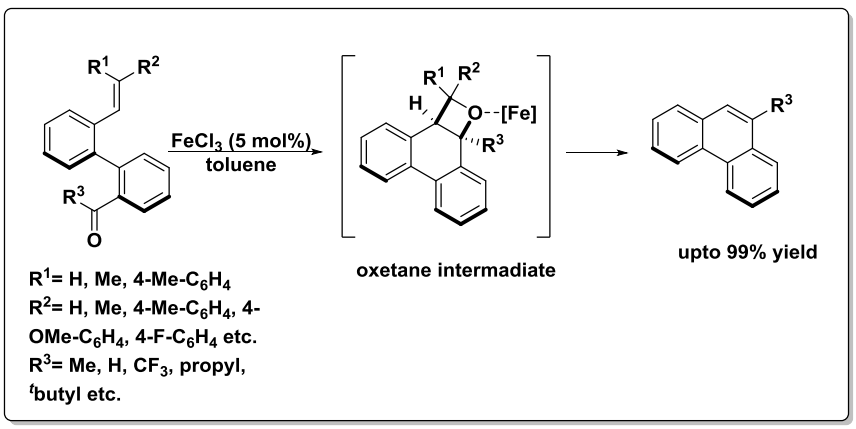


Scheme 13: $FeCl_3$ catalyzed alkyne-carbonyl metathesis of 2′-alkynyl-biphenyl-2-carbaldehydes

tolerated alkyl groups in the alkyne part, but terminal alkynes failed to perform this transformation. The mechanism suggested that the reaction was started with coordination between iron and carbonyl. Then the alkyne underwent a nucleophilic attack over the iron-coordinated carbonyl group, and an alkenylic carbocation was generated. Then intramolecular trapping with the oxygen generated an oxetene from the alkenyl carbocation. Finally, a [2 + 2] cycloreversion of the oxetene generated the desired phenanthrene derivatives and the catalytic cycle continued.

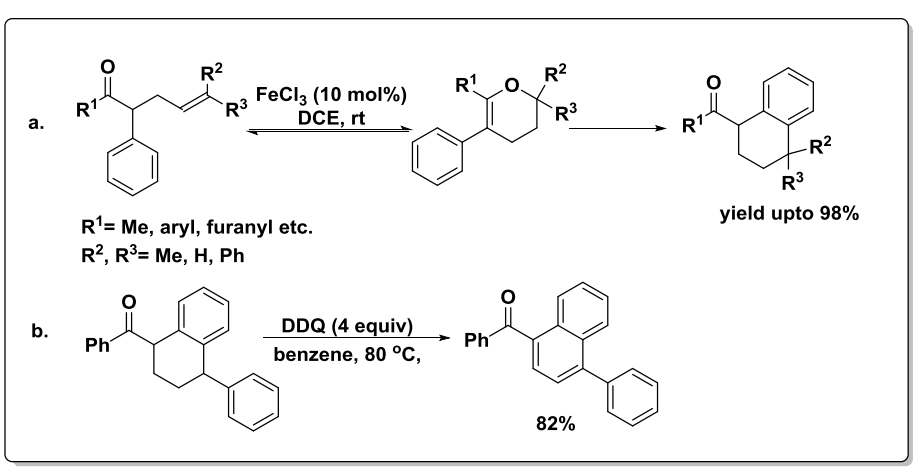
Another $FeCl_3$-catalyzed carbonyl–olefin metathesis approach was taken by Schindler and co-workers to synthesize various polycyclic aromatic compounds (PACs) in excellent yields where benzaldehyde was produced as the as the by-product (Scheme 14).[20] Different Lewis and Bronsted acids were screened to check their efficacy for the transformation, and $FeCl_3$ in DCE solvent furnished the maximum yield of the corresponding phenanthrene derivatives. Both electron deficient and electron rich substituents went through the conversion with high efficiency. But *o*-

methoxy substituent bearing starting materials were not much feasible under the optimum reaction condition providing only 75% and 57% yields of the products. However, prenylated alkenes provided lower yields of the products (21% yields) than the styrene, which might be due to the competing carbonyl-ene reactions occurring for the prenylated alkene.



Scheme 14: $FeCl_3$ catalyzed alkene-carbonyl metathesis for the synthesis of PACs

Watson and co-workers conceived an $FeCl_3$ catalyzed synthesis of substituted tetrahydronaphthalene derivatives (scheme 15a),[21] where in the presence of $FeCl_3$, the aryl ketone could be converted into the 3,4-dihydro-2*H*-pyrans, but the process was reversible, and backward reaction ultimately generated tetrahydronaphthalene by

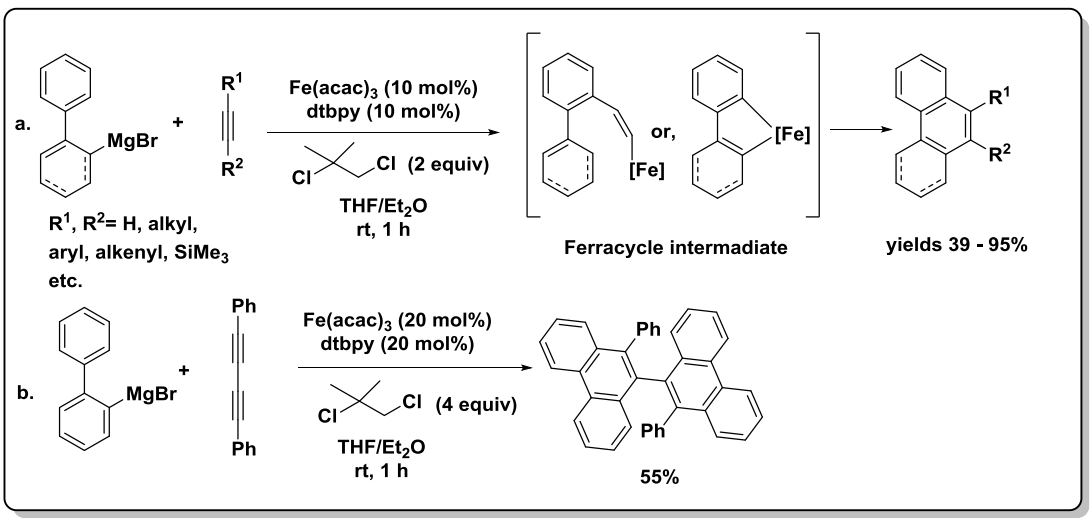


Scheme 15: $FeCl_3$ catalyzed synthesis of substituted tetrahydronaphthalene and naphthalene derivatives

Friedel−Crafts alkylation and rearomatization. The obtained tetrahydronaphthalene was further oxidized by DDQ to attain naphthalene derivatives in good yield (82%) (scheme 15b).

Nakamura *et al.* developed an iron(III)-catalyzed oxidative [4+2] benz-

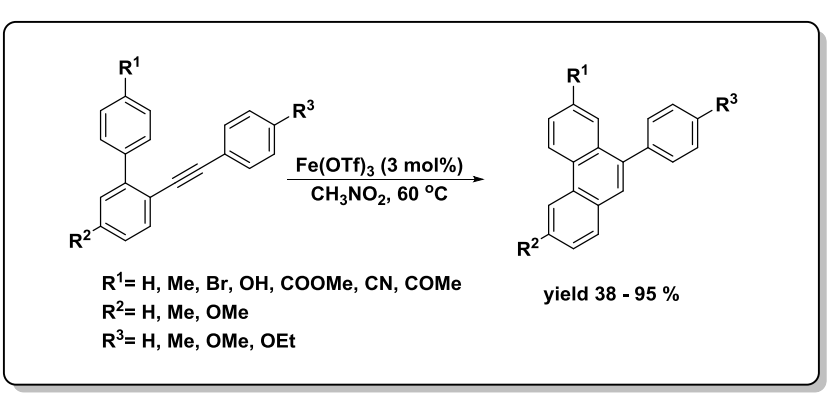
annulation between alkynes and 2-biaryl Grignard reagents for the construction of phenanthrene derivatives (scheme 16a).[22] DCIB (1,2-dichloro-2-methylpropane) was used as the oxidising agent, and dtbpy (4,4'-di-tert-butyl-2,2'-bipyridyl) was the ligand. A range of 9-substituted or 9,10-di substituted phenanthrene derivatives were



Scheme 16: Iron(III)-catalyzed [4+2] benzannulation between alkynes and 2-biaryl Grignard reagents

formed in high yield (yield up to 96%) at room temperature under the optimized reaction condition. When 1,4-diphenylbutadiyne and 2-biphenylmagnesium bromide were used as the coupling partners, a twofold annulation resulted a bisphenanthrene compound in 55% yield (scheme 16b). The mechanism suggested the reaction to go through a ferracycle intermediate.

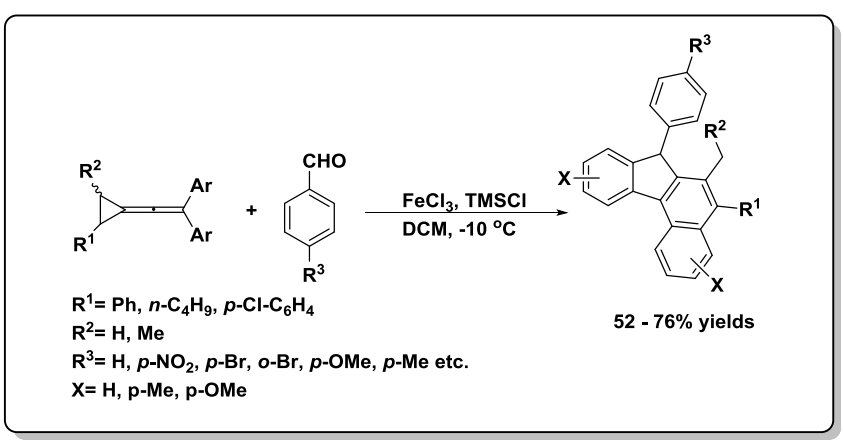
Intramolecular hydroarylation of arene-alkyne were employed to fabricate phenanthrene derivatives by Guo and his group (scheme 17).[23] After testing various iron salts, low catalytic amount of $Fe(OTf)_3$ was found to be the suitable catalyst for



Scheme 17: $Fe(OTf)_3$ catalyzed hydroarylation of arene-alkyne for the synthesis of phenanthrene derivatives

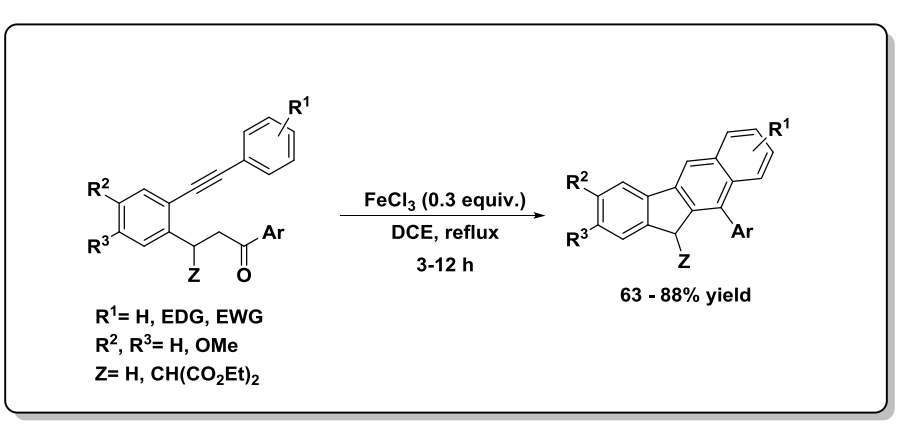
this transformation. Mono, di and tri- substituted substrates were also successfully transformed by this method. But weakly EWG like Cl failed to provide any phenanthrene derivatives. According to the mechanism, the $Fe(OTf)_3$ first activates the alkyne, and then nucleophilic attack from the arene moiety would lead to the phenanthrene derivatives.

In 2009, the reactivity of aromatic aldehyde as a coupling partner with vinylidenecyclopropanes was investigated by Su *et al*. benzo[c]fluorene derivatives was obtained when vinylidenecyclopropanes reacted with aromatic aldehydes in the presence of $FeCl_3$ and TMSCl in DCE solvent at -10°C (scheme 18).[24] Moderate yields were obtained when VCP contained EDG or EWG. The reactions tolerated very broad substrate scopes, and opened a simple path to achieve benzo[*c*]fluorene derivatives in a convenient way. A probable mechanism has also been postulated.



Scheme 18: Iron catalyzed reaction of vinylidenecyclopropanes with aromatic aldehydes

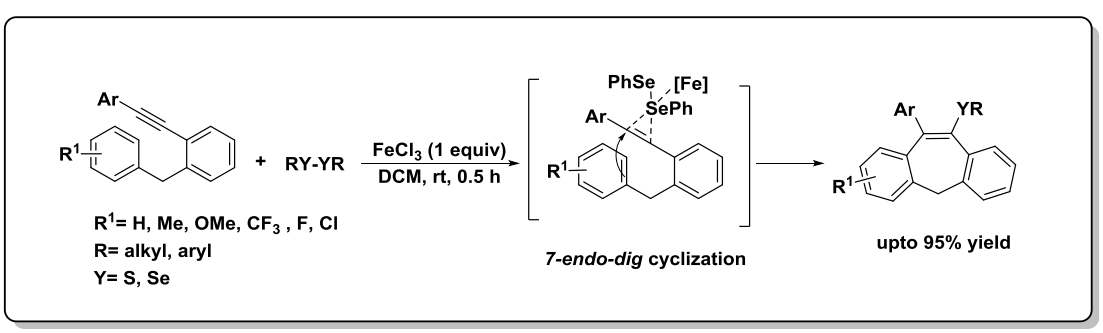
Iron catalyst was proved to be efficient catalyst for the formation of benzo[*b*]fluorene derivatives from o-alkynyldihydrochalcones by tandem *5-exo-dig*



Scheme 19: *5-exo-dig* Conia-ene reaction followed by Friedel–Crafts cyclization

Conia-ene reaction followed by Friedel–Crafts cyclization (scheme 19).[25] The reaction was capable to tolerate variety of electron rich and electron withdrawing groups at different position of the aromatic and alkyne part, albeit substrate having *para*-nitrophenyl ring failed to produce any product which might be because of the coordination of the $FeCl_3$ with the nitro group. Here, the $FeCl_3$ played dual role to activate the alkyne and also helped in the formation of the enol from *o*-alkynyldihydrochalcones which further carried reaction forward.

A ferric chloride mediated intramolecular *7-endo-dig* cyclization of 1-benzyl-2-alkynylbenzenes with diselenides was realized by Prochnow *et al.* to construct 9-(organoselanyl)-5*H*-benzo[7]annulenes (scheme 20).[26] Optimization of the reaction parameters revealed that, 1:0.5 mole ratios of $FeCl_3$ and RSeSeR in DCE solvent at room temperature were the optimal condition for the best result. A various substitution patterns were displayed and moderate to good yields were obtained (54-95% yields). The iron salt coordinated with Se and activated the RSeSeR for the nucleophilic attack from the alkyne. Then regioselective *7-endo-dig* cyclization led to the formation of the fused 7-membered carbocycle.



Scheme 20: $FeCl_3$ promoted intramolecular *7-endo-dig* cyclization of 1-benzyl-2-alkynylbenzenes with diselenides

3. CONCLUSION:

In conclusion, iron catalyzed synthesis of carbocycles has proved to be a potent tool for the construction of a diverse range of carbocyclic structures. With its reasonable price, low toxicity and abundance ion nature, iron is a tempting catalyst for many reactions. The high selectivity and efficiency of iron-catalyzed carbocyclic transformations, coupled with the mild reaction conditions and use of readily available starting materials, make them attractive from both a practical and economic standpoint. The advancement of new Fe-catalyzed reactions and the discovery of

novel applications for these reactions have great potential for the synthesis of complex carbocyclic structures with broad implications in organic synthesis and medicinal chemistry. But still there is a dearth of literature reports pertaining to the synthesis of complex carbocyclic structures. As this field continues to evolve, we can expect it to make significant contributions to the advancement of carbocyclic chemistry.

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Part II, Chapter 1

Iron-Catalyzed Synthesis of 13-Aryl-13*H*-indeno[1,2-*l*]phenanthrene *via* Double Annulations of 2-Alkynyl Biaryls

1. INTRODUCTION:

The versatile applications of the carbocycle molecules encouraged us to develop new iron catalyzed synthetic protocols to afford important carbocycles molecules. The phenanthrene nucleus is one of the highly versatile and significant carbocycle molecule, owing to its wide occurrence in various natural products and pharmacologically active compounds.[1] Furthermore, it exhibits unique thermal and electronic properties, which makes it an important constituent in the field of material science, where it has found applications in the development of blue light emitting compounds and solar cells.[2] Indenophenanthrene, a highly fused polycyclic aromatic hydrocarbon, is obtained by the fusion of the phenanthrene nucleus with indene, and serves as a crucial precursor for the construction of targeted PAHs. Indenophenanthrene derivatives have emerged as efficient deep-blue organic light emitting diodes, making them an attractive target for innovative synthetic strategies.[3]

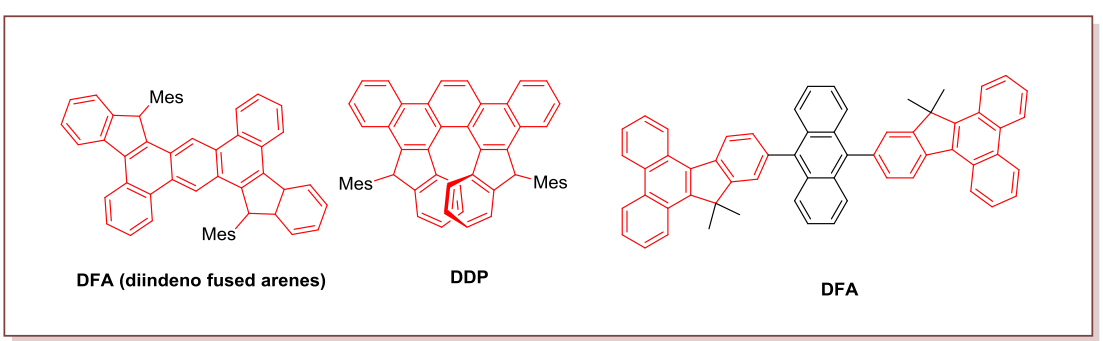
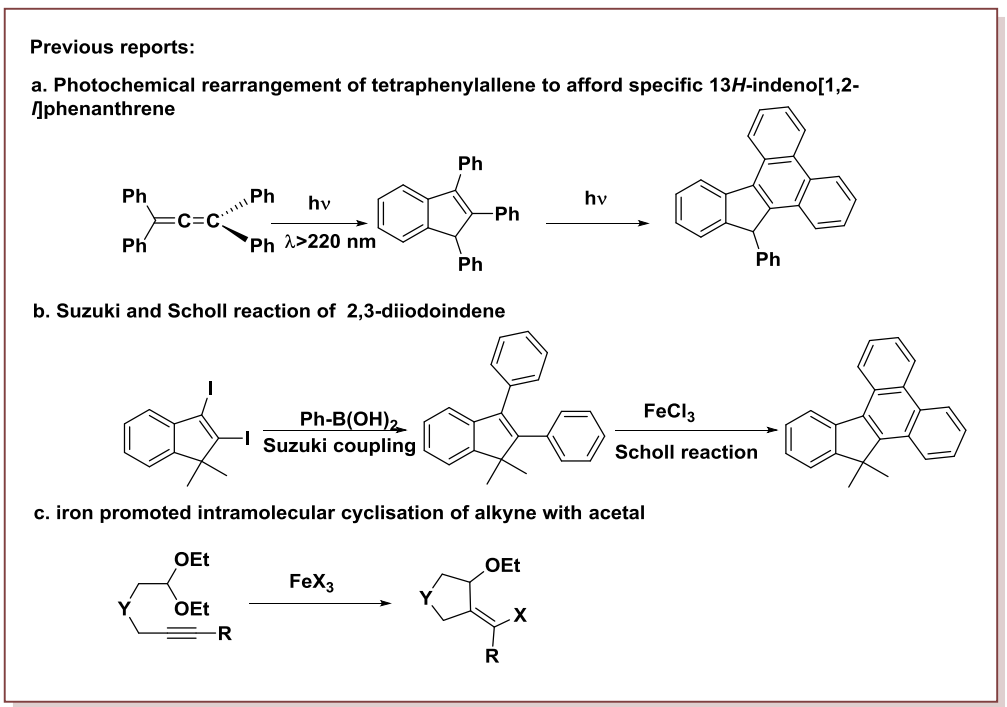


Figure 1: OLEDs containing indenophenanthrene moiety

But very few methods are available for the construction of the indenophenanthrene moiety.[4] The Johnson group reported a photochemical rearrangement of tetraphenylallene to afford specific 13*H*-indeno[1,2-*l*]phenanthrene (scheme 1a),[5] while Wang group developed a sequential Suzuki and Scholl reaction of 2,3-diiodoindene to obtain 13*H*-indeno[1,2-*l*]phenanthrene (scheme 1b).[6] Wu *et al.* reported a multistep synthetic protocol for the synthesis of the more complex 5,14-diaryldiindeno[2,1-*f*:1′,2′-*j*]picene.[3e] However, these methods have certain disadvantages such as lack of diversity or complicated starting materials and multiple synthetic steps. Thus, developing a new, expedient methodology for the construction of indenophenanthrene remains an appealing topic for synthetic chemists.

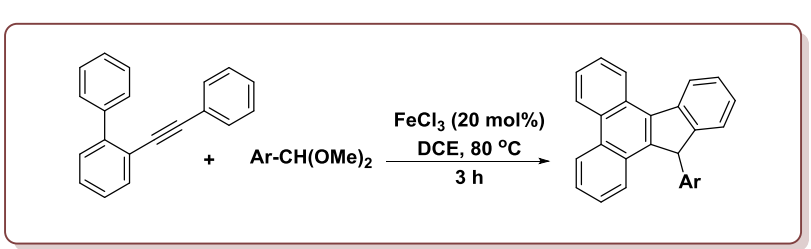
Phenanthrene derivatives have been synthesized using various methods such as radical or electrophilic cyclization of 2-(phenylethynyl)-1,1'-biphenyl

phenanthrene.[7] However, the use of iron catalysis has gained significant attention due to its sustainability, low toxicity, and cost-effectiveness.[8] Our previous work showed successful preparation of phenanthrene scaffolds using iron(III)-catalyzed cyclization reactions of functionalized 2-



Scheme 1: Previous methods for the synthesis of indenophenanthrene derivatives

(phenylethynyl)-1,1'-biphenyl.[9] Wang's group also reported a double annulation reaction using acetals and a suitable Lewis acid (scheme 1c).[10] Based on these concepts, we aimed to utilize acetals to activate 2-(phenylethynyl)-1,1'-biphenyl and obtain indenophenanthrene moieties through a double annulation reaction using $FeCl_3$

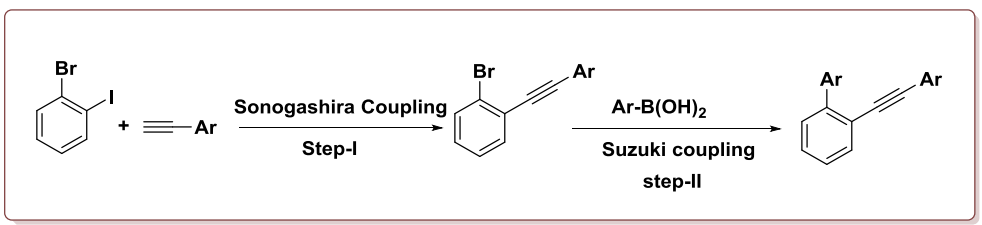


Scheme 2: Iron catalyzed one pot synthesis of 13*H*-indeno[1,2-*l*]phenanthrene

catalyst (scheme 2). This protocol provides a green and convenient method to synthesize 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives in a single operation using readily available starting materials.

2. RESULTS AND DISCUSSION:

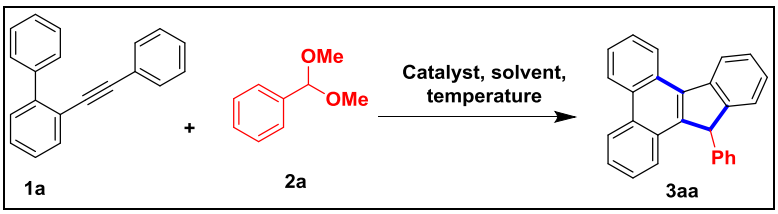
To apply our strategy practically, we first prepared the precursor substrate 2-(phenylethynyl)-1,1'-biphenyl **1a** by the Sonogashira coupling reaction of 2-bromoiodobenzene with diversely substituted phenyl acetylene and then the Suzuki coupling reaction of the product with aryl boronic acid (scheme 3).



Scheme 3: Strategy for preparation of starting material

We conducted a series of experiments to optimize the reaction condition for the synthesis of 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene **3aa** using 0.20 mol of 2-(phenylethynyl)-1,1'-biphenyl (**1a**) and 0.24 mol of (dimethoxymethyl)benzene (**2a**). Initially, we used 20 mol% of anhydrous $FeCl_3$ in dry dichloromethane (DCM) at room temperature, but we did not obtain the desired product even after 12 h (Table 1, entry 1). However, upon refluxing the reaction mixture for 3 hours, we obtained **3aa** in 23% yield (Table 1, entry 2). To improve the yield, we screened several solvents and found that using 1,2-dichloroethane (DCE) as the reaction medium at 80 ºC resulted in the highest yield of 88% (Table 1, entry 4). We also tested different Lewis and Brønsted acid catalysts and found that $FeBr_3$ and $InCl_3$ were effective, giving the desired product with yields of 83% and 78%, respectively (Table 1, entried 7 and 8). However, $Fe(OTf)_3$ and $In(OTf)_3$ were less effective, providing only 35% and 27% yield (Table 1, entries 9 and 10). Other Lewis acids like $Au(PPh_3)Cl$ and $Yb(OTf)_3$ failed to produce any desired products (Table 1, entries 11 and 12). Brønsted acids such as triflic acid and *p*-toluenesulfonic acid were also less effective (Table 1, entries 13 and 14). Lowering and increasing the catalyst loading decreased the yield of the products and altering solvent volume did not significantly affect the yield (Table 1, entries 15-18). But performing the reaction under aerobic conditions resulted in lower yield (Table 1, entry 19). Therefore, the optimized conditions were found to be 20 mol% of $FeCl_3$ in dry 1,2-DCE solvent at 80 ºC, resulting in 88% yield of **3aa** within 3 h.

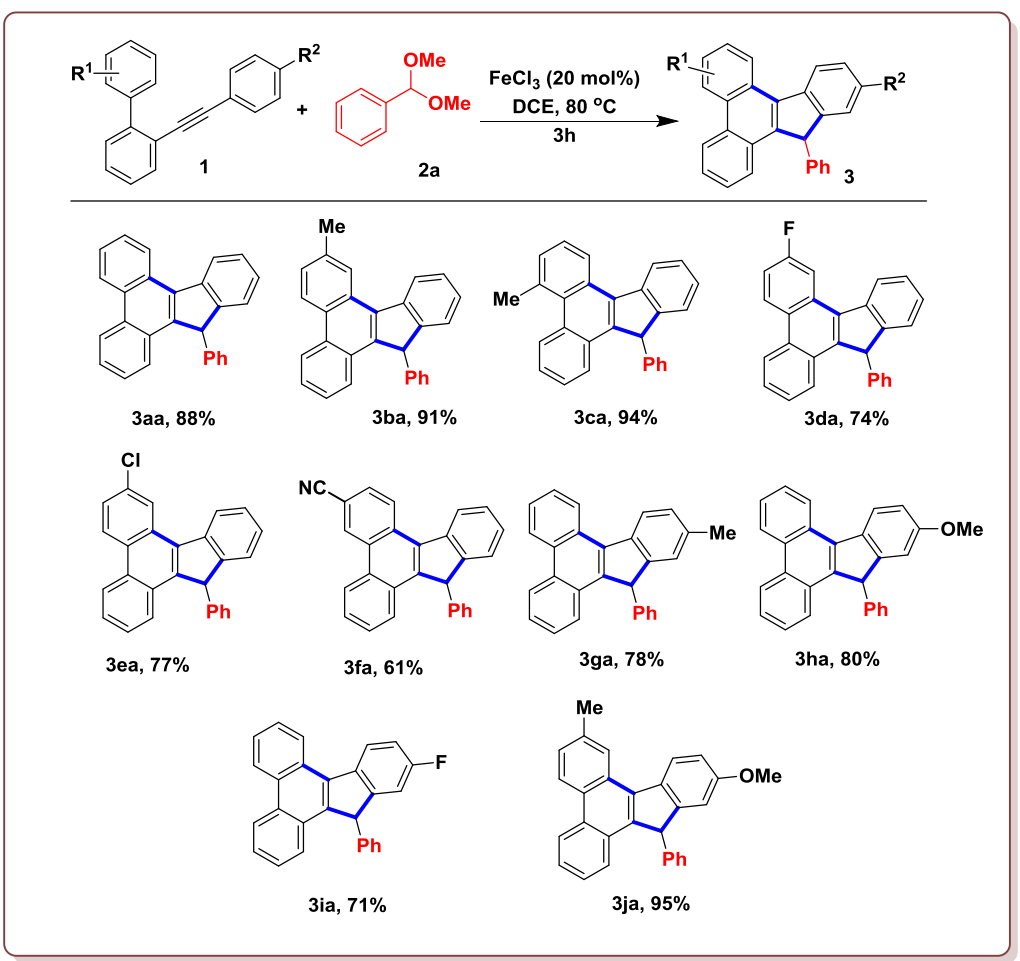
Table 1: Optimization of the reaction condition



Entry	catalyst (20 mol%)	solvent	temperature	Time (h)	Yield (%)
1	$FeCl_3$	DCM	rt	12	0
2	$FeCl_3$	DCM	reflux	3	23
3	$FeCl_3$	DCE	60 ^oC	3	45
4	**$FeCl_3$**	**DCE**	**80 ^oC**	**3**	**88**
5	$FeCl_3$	CH_3NO_2	80 ^oC	3	34
6	$FeCl_3$	CH_3CN	80 ^oC	3	12
7	$FeBr_3$	DCE	80 ^oC	3	83
8	$InCl_3$	DCE	80 ^oC	3	78
9	$Fe(OTf)_3$	DCE	80 ^oC	3	35
10	$In(OTf)_3$	DCE	80 ^oC	3	27
11	$Au(PPh_3)Cl$	DCE	80 ^oC	3	0
12	$Yb(OTf)_3$	DCE	80 ^oC	3	0
13	TfOH	DCE	80 ^oC	3	62
14	PTSA	DCE	80 ^oC	3	70
15	$FeCl_3$ (10 mol%)	DCE	80 ^oC	3	33
16	$FeCl_3$ (30 mol%)	DCE	80 ^oC	3	80
17	$FeCl_3$	DCE (4 mL)	80 ^oC	3	85
18	$FeCl_3$	DCE (1 mL)	80 ^oC	3	82
19	$FeCl_3$	DCE (air)	80 ^oC	3	58

To demonstrate the effectiveness of the protocol, a series of 2-(phenylethynyl)-1,1'-biphenyl derivatives were synthesized with electron-donating and electron-

withdrawing groups at various positions. These derivatives were subjected to reactions under optimal conditions. It was observed that the presence of electron-donating groups, such as *p*-methyl and *o*-methyl on the biaryl moiety, facilitated the product formation, resulting in higher yields of the product formation than the unsubstituted one (91%, 94%, and 88% respectively) (Scheme 4, **3ba**, **3ca**, and **3aa**). The higher yield in case of the *o*-methyl may be a result of predefined transoid geometry of the biaryl ring absolutely suitable for product formation. In contrast, electron-withdrawing groups such as -F, -Cl, and -CN on the biaryl ring resulted in lower yields of 74%, 77%, and 61%, respectively (Scheme 4, entries **3da**, **3ea**, and



Scheme 4: $FeCl_3$ catalyzed Synthesis of 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene

3fa), indicating an electronic bias towards electron-rich rings. The effect of substituents on the aryl ring attached to the alkyne was also examined, and it was found that electron-donating groups, such as -Me and -OMe, gave higher yields compared to electron-withdrawing groups such as -F (Scheme 4, **3ga**, **3ha**, and **3ia**). Furthermore, the protocol was found to be effective even when both the biaryl and

alkyne moieties bearing substituents, with excellent yields of 95% achieved for the substrate having -Me in the biaryl ring and -OMe in the alkyne ring (Scheme 4, **3ja**).

The structure of the product **3aa** was further confirmed by single crystal X-ray diffraction (CCDC no. 2183537) (figure 2).

CCDC no. 2183537

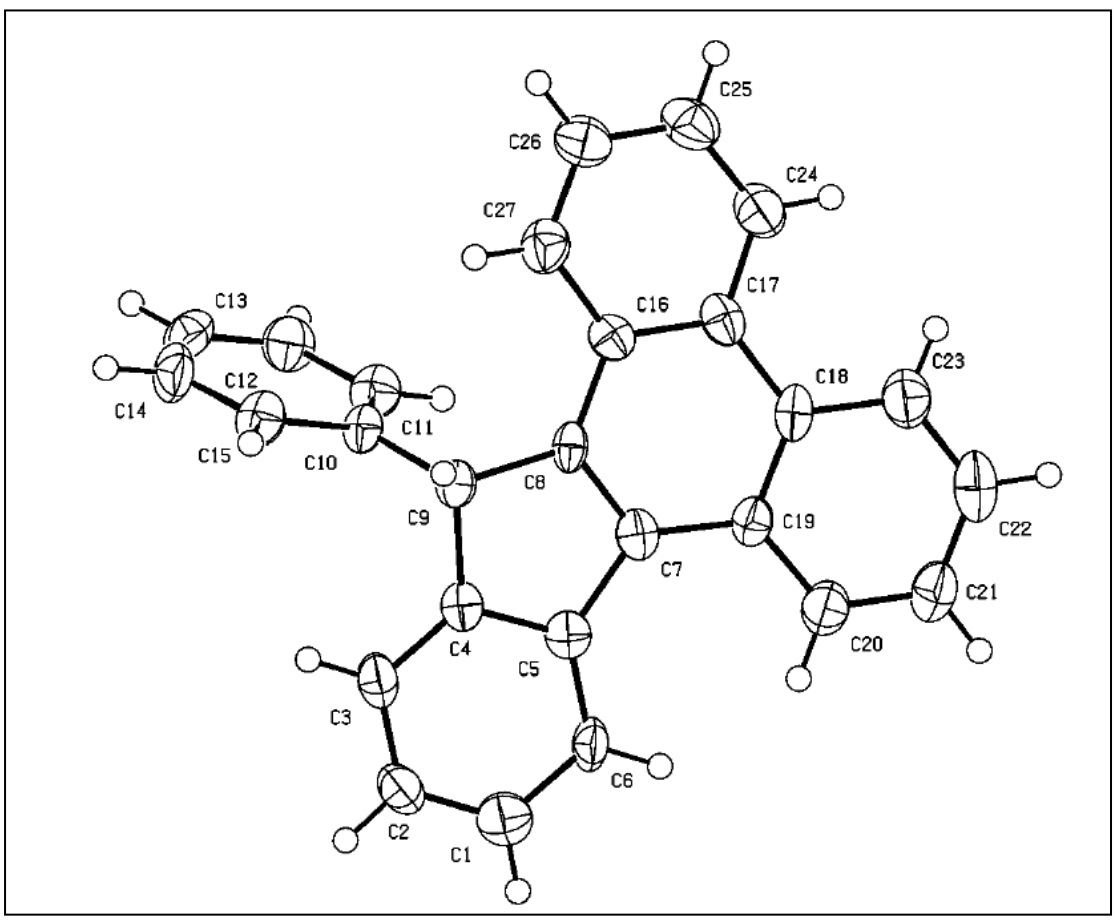
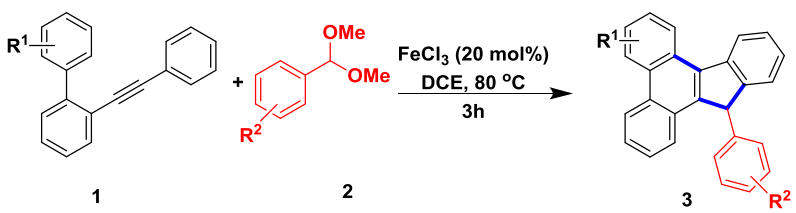


Figure 2. ORTEP diagram for the crystal structure of compound 3aa (Thermal ellipsoid contour at 50% probability level)

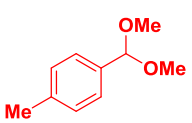
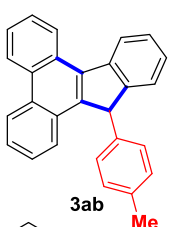
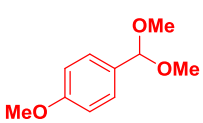
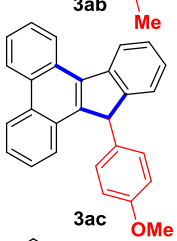
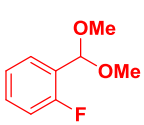
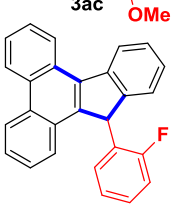
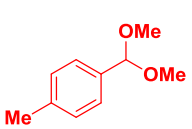
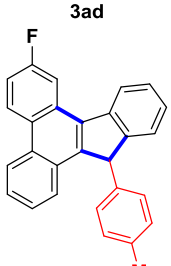
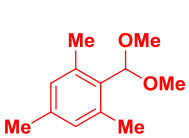
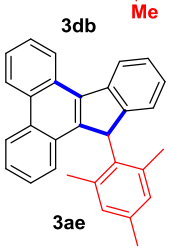
The adaptability of the methodology was further confirmed by utilizing various (dimethoxymethyl)benzene derivatives as coupling partners. The strategy was proved effective in synthesizing 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives with ease, as shown in table 2. Interestingly, it was observed that the reaction was more efficient for (dimethoxymethyl)benzene containing -Me and -OMe groups compared to -F, resulting in yields of 78%, 81%, and 65%, respectively (Table 2, entries 1, 2 and 3). This could be attributed to the additional stabilization of the benzylidene(methyl)oxonium cation in the presence of electron-donating methyl and

methoxy substituents. However, attempts to use acetals of alkyl aldehydes such as 1,1-dimethoxyethane and trimethyl orthoformate failed to produce the desired product. Moderate yield was obtained when substrate **1d** was reacted with

Table 2: Synthesis of 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives using different acetals

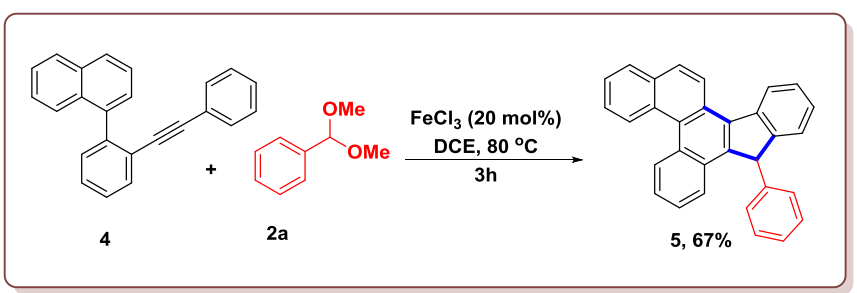


1 2 3

Entry	Substrate	Acetal	Product	Yield (%)
1	1a	 2b	 3ab	78
2	1a	 2c	 3ac	81
3	1a	 2d	 3ad	65
4	1d	 2b	 3db	71
5	1e	 2e	 3ae	52

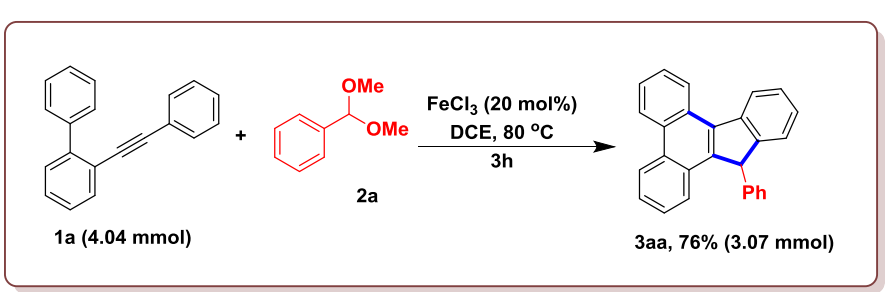
(dimethoxymethyl)benzene containing –Me (Table 2, entry 4, 71% yield). Additionally, the reaction with sterically congested mesityl acetal (**2e**) resulted in a lower yield of the desired product (**3ae**) (Table 2, entry 5).

Furthermore, the versatility of the protocol was demonstrated by successfully synthesizing highly fused polycyclic aromatic hydrocarbon 9-phenyl-9*H*-benzo[*c*]indeno[1,2-*a*]phenanthrene (**5**) in good yields (67%) by the reaction of 0.20 mmol 1-(2-(phenylethynyl)phenyl)naphthalene (**4**) with 0.24 mmol of diphenylmethanol in presence of 20 mol% of $FeCl_3$ in DCE solvent at 80 ^oC, as illustrated in Scheme 5.



Scheme 5: Synthesis of 9-phenyl-9*H*-benzo[*c*]indeno[1,2-*a*]phenanthrene

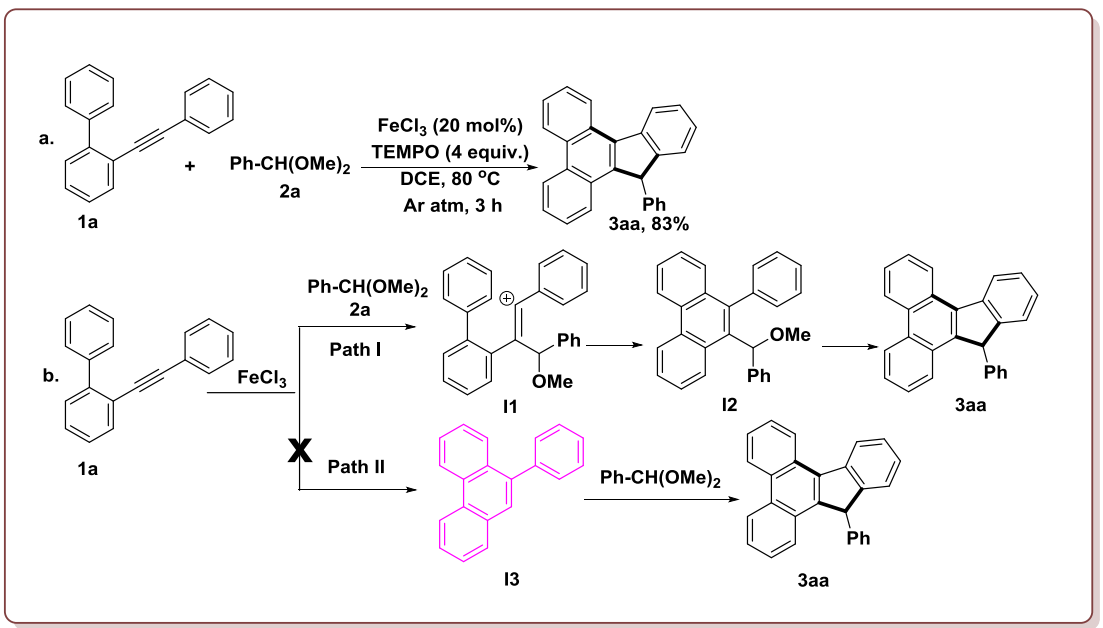
Next we tried to find out the scalability of the reaction, and for that we have performed the reaction on gram scale taking 4.04 mmol of **1a** and 4.85 mmol of **2a** as the starting materials in presence of 20 mol% $FeCl_3$ in 10 mL DCE solvent at 80 ^oC, and the desired product **3aa** was obtained in 76% yield in 3 hours (Scheme 6).



Scheme 6: Gram Scale Experiment

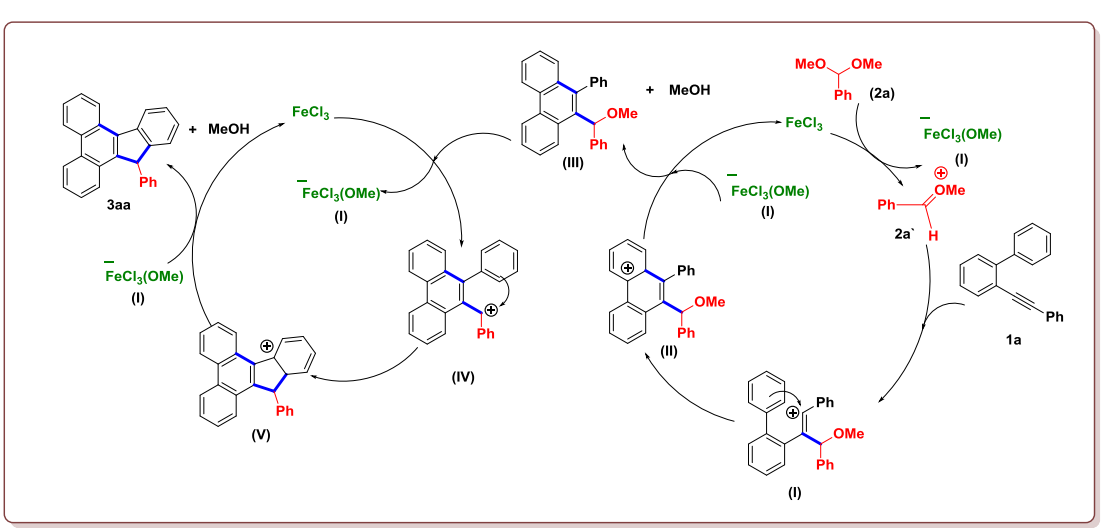
Several control experiments were conducted to investigate the reaction mechanism. One such experiment involved adding 4 equivalents of the radical quencher TEMPO to the reaction to determine if a radical pathway was involved. However, the yield of the reaction was found to be unaffected by TEMPO, indicating that a radical intermediate was not involved (scheme 7a). Further experiments were conducted to determine if the reaction proceeded through path I or II (scheme 7b).

When 2-(phenylethynyl)-1,1'-biphenyl was reacted with catalytic $FeCl_3$ in the absence of (dimethoxymethyl)benzene **2a**, 9-phenylphenanthrene was not obtained (as shown in scheme 7b). Therefore, it was concluded that the reaction did not follow path II.



Scheme 7: Control Experiments

We took an idea about the possible mechanistic pathway of the reaction from the above control experiments and previous reports,[11] and a plausible mechanism of this reaction is depicted in the Scheme 8. It is widely known that acetal can be easily deprotected to form an oxonium ion intermediate in the presence of a Lewis or Brønsted acid. In the current reaction, it is believed that a reactive intermediate **2a`** is



Scheme 8: Proposed Reaction Mechanism

initially produced from (dimethoxymethyl)benzene **2a** with the help of catalytic anhydrous $FeCl_3$. This oxonium ion intermediate **2a`** then reacts with alkyne **1a** to form a highly unstable and reactive vinyl carbocation (**I**). It is worth noting that the vinyl carbocation (**I**) is highly unstable and reactive, which makes it vulnerable to attack by the aryl ring. This attack to the carbocation by the aryl ring produces intermediate (**II**), which is then aromatized through deprotonation to give product (**III**). Intermediate (III) then participates in the second catalytic cycle and generates carbocation species (IV), which is subsequently attacked by another aryl moiety to produce the desired product **3aa**.

3. CONCLUSION:

To summarize, a novel and efficient method has been developed for synthesizing 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives using readily available starting materials and an environmentally friendly iron salt catalyst. The reaction is tolerant to a wide range of functional groups, and the use of non-toxic reagents and mild reaction conditions makes this method highly advantageous over existing procedures. Moreover, the double annulation strategy employed in this study, presents a promising approach for constructing complex organic frameworks in a single step. Overall, this work represents an important advancement in the field of organic synthesis, with potential applications in various areas of chemistry and beyond.

4. EXPERIMENTAL PROCEDURES:

4.1. General Methods. All ^{1}H NMR spectra were recorded with Bruker Avance III (300, 400, 500 MHz) spectrometers in deuterated solvents ($CDCl_3$). Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS) and the solvent resonance were referenced to internal standard $CDCl_3$ (δ 7.26 ppm). All coupling constants are absolute values and are expressed in Hz. The descriptions of the signals are reported as follows: s = singlet, d = doublet, dd = double of doublet, t = triplet, m = multiplet and dt = doublet of triplets. ^{13}C NMR spectra were recorded with Bruker Avance III 300 (75 MHz) and 400 (100 MHz) spectrometers as solutions

in $CDCl_3$ with complete proton decoupling. Chemical shifts are reported in parts per million (ppm, δ) and are referenced to internal standard $CHCl_3$ (δ = 77.16 ppm). High resolution mass spectra were taken using Q-Tof micro MS system by electron spray ionization (ESI) technique. Crystallographic data were collected at room temperature on a Bruker D8 quest microfocus single crystal XRD machine. The routine monitoring of the reaction was performed with silica gel coated glass slides (Merck, silica gel G for TLC) and pre-coated Al plates which were analyzed with iodine and UV-light respectively. Solvents, reagents, and chemicals were purchased from Aldrich, Alfa aesar, Merck, SRL, Spectrochem, and Process Chemicals. $FeCl_3$ (98%, purity) and $Fe(OTf)_3$ (90%, purity) catalysts were purchased from Alfa Aesar and were directly used. The final products were purified by column chromatography on Merck silica gel (100–200 mesh). All reactions involving moisture-sensitive reactants were executed with oven-dried glass ware.

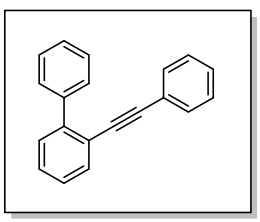
4.2. Representative Experimental Procedure for the Synthesis of 1a-1i:

Step-I: To a solution of 2-bromoiodobenzene (421 mg, 1.5 mmol) and phenyl acetylene (183 mg, 1.8 mmol) in dry DMSO solvent, $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (5.7 mg, 0.03 mmol) and Et_3N (303 mg, 3 mmol) were added subsequently in a 25 mL round-bottom flask. The resulting mixture was stirred at room temperature for 12 hours (monitored by TLC) under argon atmosphere. The mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography on silica gel to afford 1-bromo-2-(phenylethynyl)benzene (235 mg) in 92% yield.

Step-II: 1-Bromo-2-(phenylethynyl)benzene (384 mg, 1.5 mmol), phenyl boronic acid (238 mg, 1.95 mmol), $Pd(OAc)_2$ (8.4 mg, 0.0375 mmol), tricyclohexylphosphene (21 mg, 0.075 mmol) K_2CO_3 2.5 (M) in 2 mL H_2O, and solvent (2 mL PhMe and 2 mL ethanol) were added subsequently in a 25 mL round-bottom flask. The resulting mixture was heated at 75 ^oC in an oil bath, and the progress of the reaction was monitored by thin layer chromatography up to completion. The mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography on silica gel to afford 2-(phenylethynyl)-1,1'-biphenyl **1a** (323 mg) in 85% yield. The product **1a**

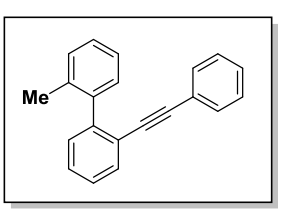
was characterized by ^{1}H and ^{13}C NMR spectroscopy, which matched with the reported literature.[7C]

2-(Phenylethynyl)-1,1'-biphenyl (1a)[7C]: Eluted by hexane, yellow liquid (467 mg, 92%). 1H NMR (300 MHz, CDCl3) δ 7.82 – 7.73 (m, 3H), 7.60 – 7.51 (m, 3H), 7.46 (d, *J* = 11.7 Hz, 5H), 7.40 – 7.34 (m, 3H). 13C{1H} NMR (75 MHz, CDCl3) δ 144.0, 140.7, 132.9, 131.5, 129.6, 129.5, 128.6, 128.4, 128.2, 128.0, 127.6, 127.2, 123.6, 121.7, 92.4, 89.5.



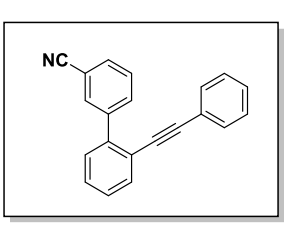
Other starting materials **1b,**[7a] **1c-1e,**[7c] **1g-1i,**[7a] **1j**[7d] were also synthesized using the above mentioned protocol and all the compounds are known and the characterisation data matched with the reported one.

2-Methyl-2'-(phenylethynyl)-1,1'-biphenyl (1c)[7c]: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.33 (m, 3H), 7.32 (dd, *J* = 3.3, 1.7 Hz, 2H), 7.29 (p, *J* = 3.6 Hz, 3H), 7.20 (td, *J* = 4.8, 3.9, 2.5 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 140.9, 136.4, 131.7, 131.4, 129.9, 129.7, 129.5, 128.2, 128.0, 127.6, 127.1, 125.33, 125.28, 123.4, 122.9, 92.4, 88.9, 20.1.

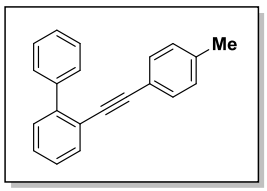


Full characterisation of **1f** (New compound) is given below.

2'-(Phenylethynyl)-[1,1'-biphenyl]-3-carbonitrile (1f): Eluted by hexane/ethyl acetate (97:3 v/v), yellow solid (297 mg, 71%) m.p.87–90 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.7 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.48 – 7.37 (m, 3H), 7.36 – 7.28 (m, 5H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 141.8, 141.3, 135.5, 133.9, 133.13, 133.06, 132.9, 131.6, 131.4, 131.3, 131.1, 131.0, 129.4, 129.2, 128.83, 128.81, 128.7, 128.54, 128.47, 128.44, 128.37, 128.2, 128.1, 127.8, 122.9, 121.7, 118.9, 112.2, 93.1, 88.3. **HRMS** (ESI) m/z: calcd for $C_{21}H_{14}N$ $[M + H]^+$, 280.1126; found, 280.1122.



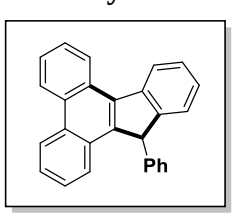
2-(*p*-tolylethynyl)-1,1'-biphenyl (1g)[7a]**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (ddd, *J* = 13.0, 8.0, 1.6 Hz, 3H), 7.50 – 7.40 (m, 5H), 7.36 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 143.8, 140.6, 138.2, 132.8, 131.3, 129.5, 129.4, 129.0, 128.3, 127.9, 127.4, 127.0, 121.80, 120.4, 92.4, 88.7, 21.5.



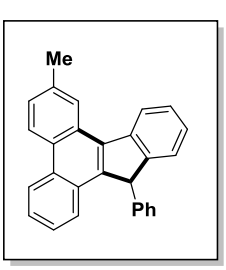
4.3. Representative Experimental Procedure for the Synthesis of 3aa-3db and 5:

In an oven-dried round-bottom flask, 2-(phenylethynyl)-1,1'-biphenyl (**1a**) (50 mg, 0.2 mmol) and (dimethoxymethyl)benzene (**2a**) (36 mg, 0.24 mmol) were taken in dry DCE (3 mL) and $FeCl_3$ (6.5 mg, 0.04 mmol) was added to the mixture under argon atmosphere and stirred for 3 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with DCM (15 mL, twice) and the combined organic layer was washed with water (15 mL, twice), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by hexane, to afford the desired product **3aa** (60 mg, 88%) as a white solid, m.p.206–208 °C.

13-Phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3aa): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, *J* = 8.0 Hz, 1H), 8.88 (d, *J* = 8.1 Hz, 1H), 8.76 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 7.8 Hz, 1H), 7.81 (t, *J* = 9.0 Hz, 3H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 14.0, 6.7 Hz, 3H), 7.27 (dq, *J* = 14.5, 7.4 Hz, 4H), 7.17 (d, *J* = 7.2 Hz, 2H), 5.42 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 149.9, 142.7, 141.6, 141.5, 135.3, 131.3, 130.6, 129.1, 129.0, 128.9, 127.9, 127.2, 126.9, 126.8, 126.7, 126.3, 126.2, 125.7, 124.8, 124.6, 123.6, 123.2, 122.8, 54.2. HRMS (ESI) m/z: calcd for $C_{27}H_{19}$ $[M + H]^+$, 343.1487; found, 343.1487.

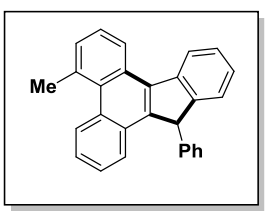


7-Methyl-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3ba): Eluted by hexane, white solid (65 mg, 91%) m.p.192–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 – 8.67 (m, 3H), 8.45 (d, *J* = 7.9 Hz, 1H), 7.78 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.56 (tdd, *J* = 8.4, 7.1, 1.6 Hz, 2H), 7.50 – 7.43 (m, 1H), 7.39 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 2H), 7.32 – 7.26 (m, 1H),



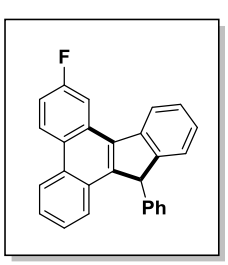
7.25 – 7.20 (m, 2H), 7.19 – 7.13 (m, 3H), 5.39 (s, 1H), 2.72 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 149.9, 142.8, 141.7, 141.6, 136.8, 134.9, 130.6, 129.2, 129.1, 128.9, 128.7, 127.9, 127.2, 126.8, 126.4, 126.3, 126.2, 125.6, 124.8, 124.4, 123.5, 123.0, 122.9, 54.4, 21.9. HRMS (ESI) m/z: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found, 357.1644.

5-Methyl-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3ca): Eluted by hexane,



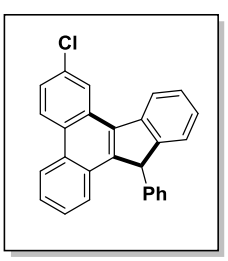
white solid (67 mg, 94%) m.p. 248–250 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (dd, *J* = 15.8, 8.3 Hz, 2H), 8.44 (d, *J* = 7.9 Hz, 1H), 7.88 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.47 – 7.40 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.24 (dd, *J* = 8.8, 6.5 Hz, 3H), 7.18 (dd, *J* = 7.8, 1.8 Hz, 2H), 5.42 (s, 1H), 3.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 150.0, 142.6, 141.7, 141.6, 136.0, 135.9, 131.7, 131.6, 131.0, 130.5, 130.2, 129.0, 128.3, 127.9, 127.2, 126.8, 126.3, 126.1, 126.1, 125.7, 124.9, 124.8, 123.0, 122.8, 54.1, 27.8. HRMS (ESI) m/z: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found, 357.1645.

2-Fluoro-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3da): Eluted by hexane,



yellow semi solid (53 mg, 74%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 9.3, 5.8 Hz, 1H), 8.66 (d, *J* = 8.4 Hz, 1H), 8.56 (dd, *J* = 10.8, 2.7 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.52 (m, 1H), 7.47 (ddd, *J* = 24.6, 10.7, 4.7 Hz, 4H), 7.30 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.23 (s, 3H), 7.14 (dd, *J* = 7.6, 2.0 Hz, 2H), 5.41 (s, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 163.0, 160.6, 149.8, 144.0, 141.4, 141.0, 134.74, 134.70, 130.4, 130.1, 129.9, 129.1, 128.6, 128.02, 128.00, 127.9, 127.4, 126.9, 126.6, 125.8, 124.9, 123.1, 122.4, 115.1, 114.8, 109.72, 109.67, 109.5, 109.4, 54.3. HRMS (ESI) m/z: calcd for $C_{27}H_{18}F$ $[M + H]^+$, 361.1393; found, 361.1382.

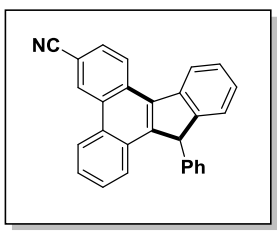
7-Chloro-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3ea): Eluted by hexane,



white solid (57 mg, 77%) m.p.160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, *J* = 2.2 Hz, 1H), 8.78 (d, *J* = 9.0 Hz, 1H), 8.71 – 8.64 (m, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 7.84 – 7.79 (m, 1H), 7.72 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.60 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.55 – 7.29 (m, 4H), 7.28 – 7.18 (m, 3H), 7.15 (dd, *J* = 7.7, 1.9 Hz,

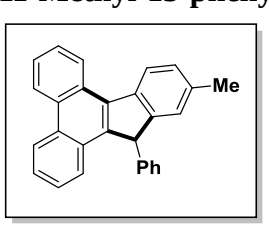
2H), 5.40 (s, 1H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 149.7, 143.9, 141.3, 140.9, 133.1, 129.8, 129.7, 129.1, 129.0, 127.9, 127.4, 127.1, 126.9, 126.7, 126.62, 126.60, 125.8, 125.2, 124.9, 124.1, 123.2, 122.6, 54.3. HRMS (ESI) m/z: calcd for $C_{27}H_{18}Cl$ $[M + H]^+$, 377.1097; found, 377.1093.

13-Phenyl-13*H*-indeno[1,2-*l*]phenanthrene-6-carbonitrile (3fa): Eluted by



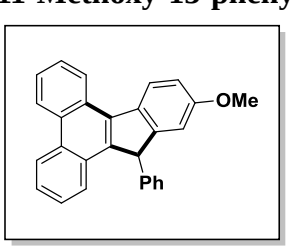
hexane/ethyl acetate (97:3 v/v), yellow solid (45 mg, 61%) m.p.170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 9.02 (d, *J* = 8.6 Hz, 1H), 8.68 (d, *J* = 8.4 Hz, 1H), 8.36 (d, *J* = 7.8 Hz, 1H), 7.98 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.66 (q, *J* = 8.3, 7.7 Hz, 1H), 7.50 (q, *J* = 7.8 Hz, 2H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 15.5, 7.9 Hz, 1H), 7.24 (d, *J* = 2.2 Hz, 3H), 7.14 – 7.09 (m, 2H), 5.43 (s, 1H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 148.9, 146.4, 140.7, 139.6, 135.5, 132.4, 129.8, 129.3, 129.2, 128.4, 128.0, 127.2, 126.9, 126.2, 125.8, 125.6, 124.3, 123.2, 116.9, 108.1, 100.0, 54.9. HRMS (ESI) m/z: calcd for $C_{28}H_{18}N$ $[M + H]^+$, 368.1439; found, 368.1430.

11-Methyl-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3ga): Eluted by hexane,



white solid (55 mg, 78%) m.p.198–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.2 Hz, 1H), 8.83 (d, *J* = 9.5 Hz, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.82 – 7.69 (m, 3H), 7.54 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 2.2 Hz, 1H), 7.22 – 7.18 (m, 3H), 7.15 (d, *J* = 1.8 Hz, 1H), 7.13 (t, *J* = 1.5 Hz, 1H), 5.35 (s, 1H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 150.2, 142.1, 141.9, 138.8, 136.3, 135.4, 131.3, 130.4, 130.3, 129.2, 129.0, 128.1, 127.9, 126.9, 126.7, 126.1, 125.9, 125.7, 125.5, 124.7, 123.5, 123.3, 122.6, 54.2, 21.4. HRMS (ESI) m/z: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found, 357.1634.

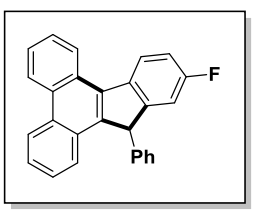
11-Methoxy-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3ha): Eluted by



hexane/ethyl acetate (98:2 v/v), white solid (59 mg, 80%) m.p.208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 8.1, 1.2 Hz, 1H), 8.83 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.71 (d, *J* = 8.3 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 7.81 – 7.71 (m, 3H), 7.53 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.39 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.24 – 7.18 (m, 3H), 7.15 – 7.09 (m, 2H), 7.00 – 6.93 (m, 2H), 5.35 (s, 1H), 3.81 (s, 3H). $^{13}C\{^{1}H\}$

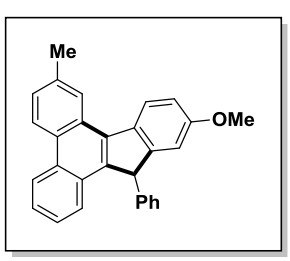
NMR (101 MHz, $CDCl_3$) δ 158.8, 152.1, 141.9, 141.6, 135.4, 131.4, 130.2, 129.1, 128.8, 128.0, 127.0, 126.9, 126.8, 126.2, 125.8, 125.4, 124.7, 123.7, 123.5, 123.3, 112.6, 111.3, 55.6, 54.4. HRMS (ESI) m/z: calcd for $C_{28}H_{21}O$ $[M + H]^+$, 373.1592; found, 373.1589.

11-Fluoro-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3ia): Eluted by hexane,



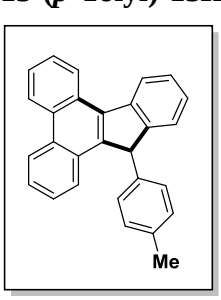
yellow solid (51 mg, 71%) m.p.198–200 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 – 8.79 (m, 2H), 8.71 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.30 (dd, *J* = 8.6, 4.9 Hz, 1H), 7.84 – 7.64 (m, 3H), 7.56 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.40 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.12 (ddd, *J* = 13.2, 8.0, 2.0 Hz, 3H), 7.06 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.28 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.8, 152.4, 152.3, 142.5, 141.1, 137.6, 134.7, 130.5, 129.2, 129.0, 128.6, 127.9, 127.1, 126.4, 125.6, 124.4, 123.8, 123.3, 114.3, 114.1, 112.6, 112.4, 54.3. HRMS (ESI) m/z: calcd for $C_{27}H_{18}F$ $[M + H]^+$, 361.1393; found, 361.1383.

11-Methoxy-7-methyl-13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3ja): Eluted by



hexane/ethyl acetate (98:2 v/v), white solid (73 mg, 95%), m.p.215-217 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 – 8.67 (m, 3H), 8.32 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.18 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.99 (dd, *J* = 8.25, 2.5 Hz, 1H), 6.95 (d, *J* = 1.5 Hz, 1H), 5.33 (s, 1H), 3.82 (s, 3H), 2.71 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.8, 152.2, 142.0, 141.7, 136.8, 135.1, 130.3, 129.4, 129.2, 129.0, 128.9, 128.1, 127.9, 126.9, 126.4, 125.8, 125.5, 124.5, 123.7, 123.6, 123.2, 112.7, 111.3, 55.6, 54.4, 22.1. HRMS (ESI) m/z: calcd for $C_{29}H_{23}O$ $[M + H]^+$, 387.1749; found, 387.1744.

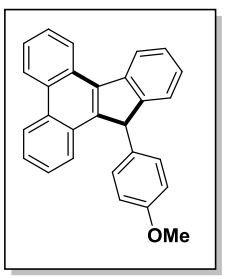
13-(*p*-Tolyl)-13*H*-indeno[1,2-*l*]phenanthrene (3ab): Eluted by hexane, yellow semi



solid (53 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 – 8.92 (m, 1H), 8.88 – 8.81 (m, 1H), 8.76 – 8.69 (m, 1H), 8.41 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.84 – 7.71 (m, 3H), 7.56 (ddd, *J* = 8.3, 7.0, 1.4 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.27 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.03 (s, 4H), 5.37 (s, 1H), 2.27 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.2, 142.9, 138.6, 136.4, 135.3, 131.4, 130.6, 129.8, 129.2, 127.8, 127.3, 127.1,

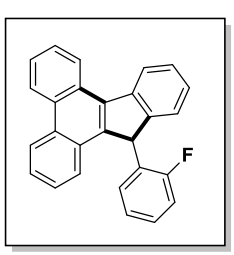
126.9, 126.4, 126.3, 125.8, 124.9, 124.7, 123.7, 123.3, 122.9, 54.0, 21.2. HRMS (ESI) m/z: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found 357.1639.

13-(4-Methoxyphenyl)-13*H*-indeno[1,2-*l*]phenanthrene (3ac): Eluted by



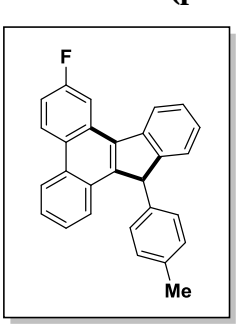
hexane/ethyl acetate (98:2 v/v), yellow semi solid (59 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 – 8.93 (m, 1H), 8.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 8.77 – 8.69 (m, 1H), 8.45 – 8.38 (m, 1H), 7.87 – 7.68 (m, 3H), 7.58 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 7.51 – 7.37 (m, 3H), 7.29 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.09 – 7.03 (m, 2H), 6.81 – 6.75 (m, 2H), 5.36 (s, 1H), 3.74 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 158.4, 150.3, 142.9, 141.5, 135.1, 133.6, 131.4, 130.6, 129.2, 129.0, 128.9, 127.2, 127.0, 126.8, 126.4, 126.22, 126.19, 125.8, 124.8, 124.7, 123.7, 123.3, 122.9, 114.4, 55.2, 53.5. HRMS (ESI) m/z: calcd for $C_{28}H_{21}O$ $[M + H]^+$, 373.1592; found, 373.1586.

13-(2-Fluorophenyl)-13*H*-indeno[1,2-*l*]phenanthrene (3ad): Eluted by hexane,



yellow solid (47 mg, 65%). m.p.168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.91 – 8.84 (m, 1H), 8.77 (d, *J* = 8.3 Hz, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 7.83 – 7.69 (m, 2H), 7.61 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.58 – 7.44 (m, 3H), 7.37 – 7.13 (m, 4H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.49 (s, 1H), 5.88 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.3, 159.9, 149.3, 142.0, 141.8, 135.7, 131.4, 130.6, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 127.5, 127.1, 126.9, 126.5, 126.4, 126.3, 125.4, 124.88, 124.86, 124.73, 124.69, 124.6, 123.7, 123.5, 123.3, 122.9, 115.9, 115.7, 46.0. HRMS (ESI) m/z: calcd for $C_{27}H_{18}F$ $[M + H]^+$, 361.1393; found, 361.1386.

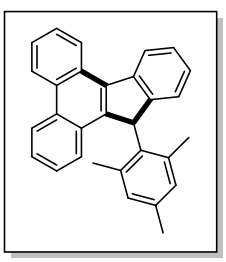
7-Fluoro-13-(p-tolyl)-13*H*-indeno[1,2-*l*]phenanthrene (3db):Eluted by hexane,



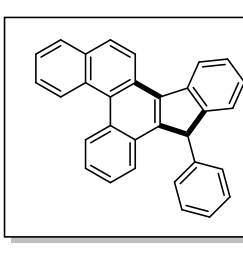
yellow semi solid (52 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 9.2, 5.8 Hz, 1H), 8.64 (d, *J* = 8.4 Hz, 1H), 8.54 (dd, *J* = 10.9, 2.7 Hz, 1H), 8.31 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 9.1, 6.3 Hz, 1H), 7.50 – 7.38 (m, 4H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 4.3 Hz, 4H), 5.33 (s, 1H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 163.5, 160.3, 150.1,

144.3, 141.1, 138.4, 136.6, 130.5, 130.2, 129.9, 129.6, 129.3, 128.8, 127.9, 127.4, 126.7, 126.0, 125.9, 125.0, 123.2, 122.5, 115.2, 114.8, 109.8, 109.5, 54.1, 21.2. HRMS (ESI) m/z: calcd for $C_{28}H_{20}F$ $[M + H]^+$, 375.1549; found, 375.1550.

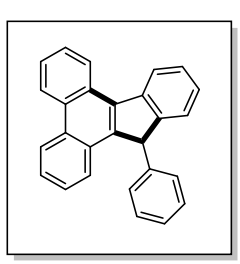
13-Mesityl-13*H*-indeno[1,2-*l*]phenanthrene (3ae): Eluted by hexane/ethyl acetate (97:3 v/v), yellow semi solid (40 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, *J* = 8.1 Hz, 1H), 8.86 (d, *J* = 8.2 Hz, 1H), 8.75 (d, *J* = 8.4 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 7.77 (dt, *J* = 24.9, 7.3 Hz, 2H), 7.65 – 7.46 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.12 (s, 1H), 6.57 (s, 1H), 5.76 (s, 1H), 2.86 (s, 3H), 2.29 (s, 3H), 1.04 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.3, 143.2, 141.8, 137.4, 136.3, 135.9, 134.6, 133.9, 130.6, 130.4, 129.9, 129.3, 128.9, 126.6, 126.0, 125.6, 124.3, 124.2, 123.5, 123.3, 123.27, 122.95, 122.89, 122.5, 122.4, 49.7, 21.8, 20.5, 18.1. HRMS (ESI) m/z: calcd for $C_{30}H_{25}$ $[M + H]^+$, 385.1956; found, 385.1955.



9-Phenyl-9*H*-benzo[c]indeno[1,2-*a*]phenanthrene (5): Eluted by hexane, yellow solid (51 mg, 67%) m.p.210–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (d, *J* = 8.5 Hz, 2H), 8.91 (d, *J* = 8.9 Hz, 1H), 8.45 (d, *J* = 7.9 Hz, 1H), 8.09 (dd, *J* = 9.2, 3.5 Hz, 2H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.68 (hept, *J* = 5.3 Hz, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.51 – 7.39 (m, 3H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.13 (m, 5H), 5.47 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.2, 143.0, 141.7, 141.5, 135.5, 132.9, 130.5, 130.4, 129.9, 129.2, 129.0, 128.8, 128.2, 128.1, 127.5, 127.38, 127.36, 126.9, 126.5, 126.3, 126.1, 125.9, 125.5, 125.4, 125.1, 122.9, 122.4, 53.9. HRMS (ESI) m/z: calcd for $C_{31}H_{21}$ $[M + H]^+$, 393.1643; found, 393.1640.



4.4. Gram Scale Experiment for the synthesis of 13-Phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3aa):



In an oven-dried round-bottom flask, 2-(phenylethynyl)-1,1'-biphenyl (**1a**) (1.03 g, 4.04 mmol) and (dimethoxymethyl)benzene (**2a**) (737 mg, 4.85 mmol) were taken in dry DCE (15 mL) and $FeCl_3$ (131 mg, 0.81 mmol) was added to the mixture under argon atmosphere and stirred for 3 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction

mixture was extracted with DCM (75 mL, twice) and the combined organic layer was washed with water (50 mL, two times), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100−200 mesh), eluted by hexane, to afford the desired product **3aa** (1.05 g, 76%) as a white solid.

4.5. Sample preparation and crystal structure determination for 3aa (ref: 17–22)

The single crystals of the compound **3aa** were obtained by slow evaporation from a dilute solution of **3aa** in dichloromethane and petroleum ether at room temperature. The single crystal Suitable for X-ray of compound **3aa** was mounted on the tip of a thin glass fiber with commercially available glue. The X-ray single crystal data collection of **3aa** crystal was performed at room temperature using a Bruker APEX III D8 Quest smart diffractometer, equipped with a microfocus and a sealed tube X-ray source with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The data were integrated using the SAINT1 program, and the absorption corrections were made with SADABS.2 The structure was solved by SHELXS 20173 using the Patterson method and followed by successive Fourier and difference Fourier synthesis. Full matrix least-squares refinements were performed on F2 using SHELXL-20174 with anisotropic displacement parameters for all non-hydrogen atoms. All hydrogen atoms were fixed geometrically by HFIX command and placed in ideal positions. All calculations were carried out using SHELXS-2017, 3 SHELXL-2017, PLATON v1.15,4 ORTEP-3v2,5 and WinGX system Ver-1.80.6 The data collection and the structure refinement parameters and crystallographic data for the compound are given in Table S1.

4.6. Table for crystallographic data and structural refinement parameters for 3aa

Empirical formula	$C_{27}H_{18}$
Formula weight	342.41
Temperature/K	273(2)
Crystal system	orthorhombic
Space group	P 21 21 21

a/Å	5.60(1)
b/Å	16.12(3)
c/Å	19.86(4)
α/°	90
β/°	90
γ/°	90
Volume/$Å^3$	1793(6)
Z	4
$\rho_{calc}g/cm^3$	1.269
μ/mm^{-1}	0.072
F(000)	720
Radiation	MoK\a (λ = 0.71073)
θ range/°	2.42 to 27.10
Index ranges	$-7 \leq h \leq 7$, $-20 \leq k \leq 20$, $-25 \leq l \leq 25$
Data/restraints/parameters	3757/0/245
Goodness-of-fit on F^2	1.1023
Largest diff. peak/hole / e $Å^{-3}$	0.5664/-0.5734

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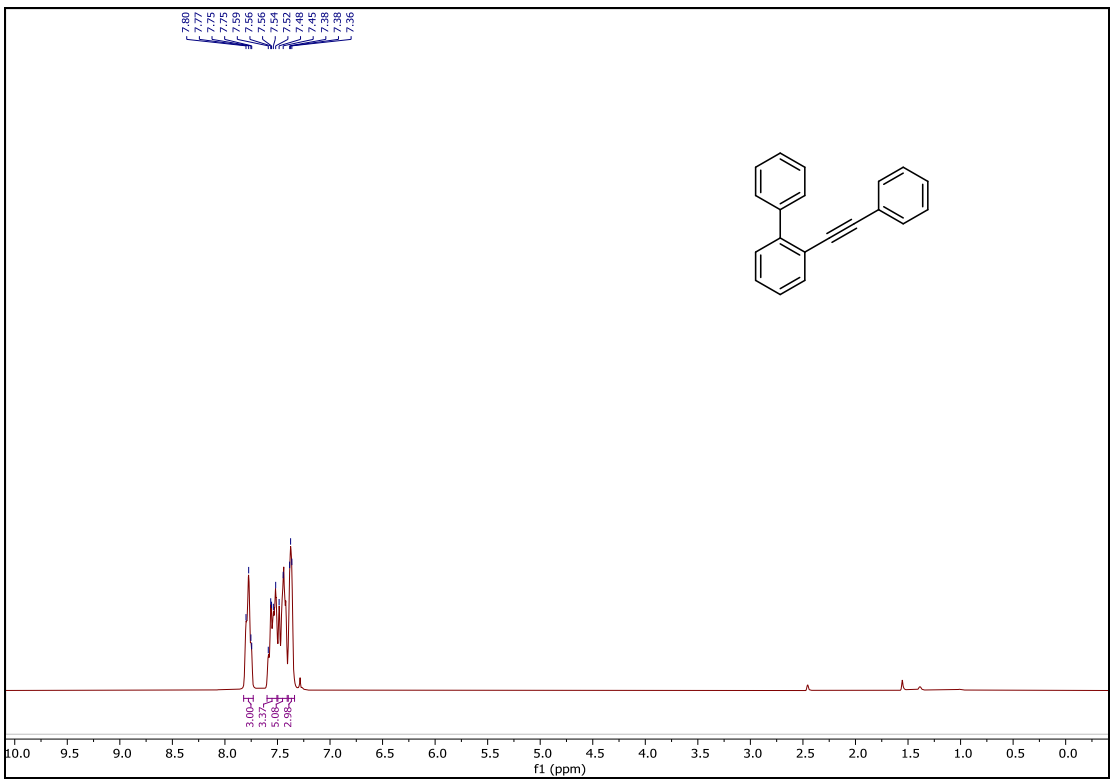
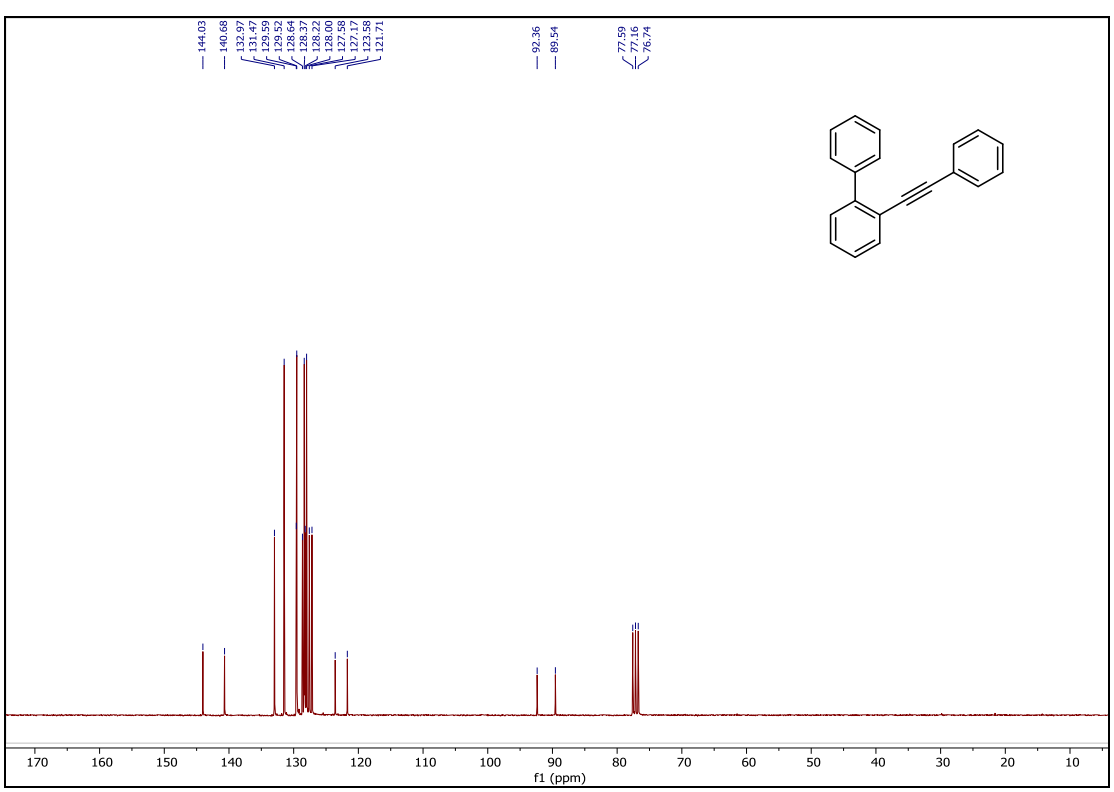
^{1}H and ^{13}C

NMR Spectra

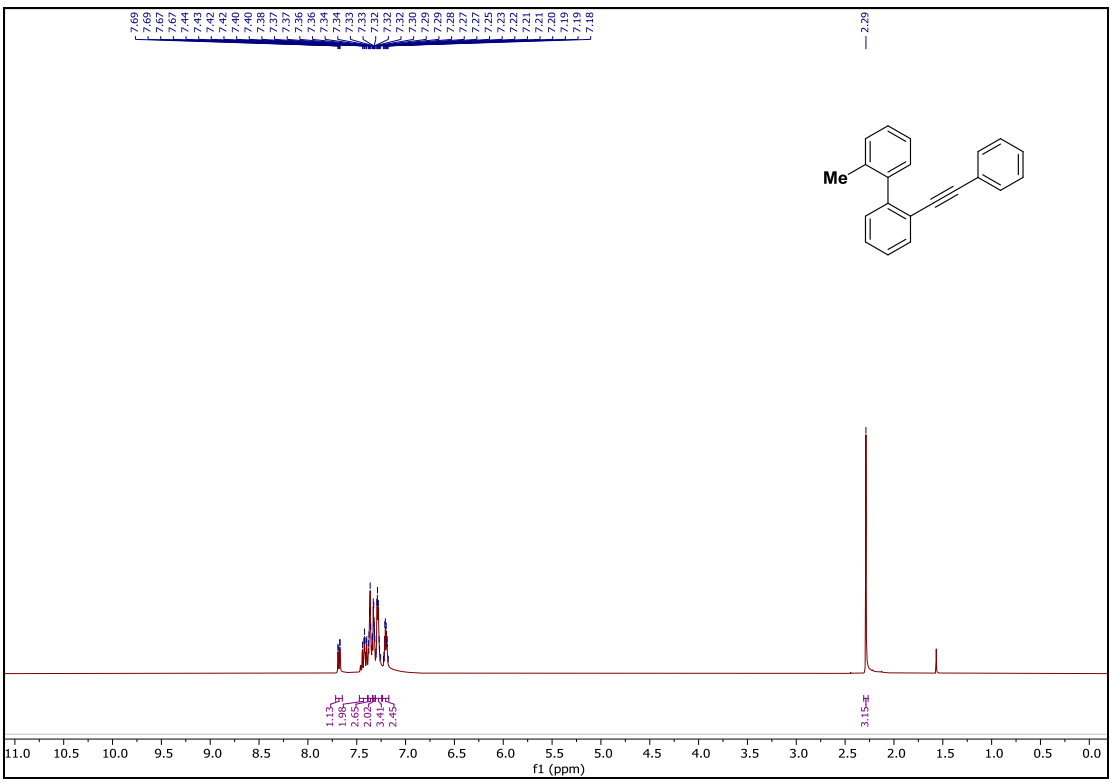
^{1}H NMR of **1a** (300 MHz, $CDCl_3$)



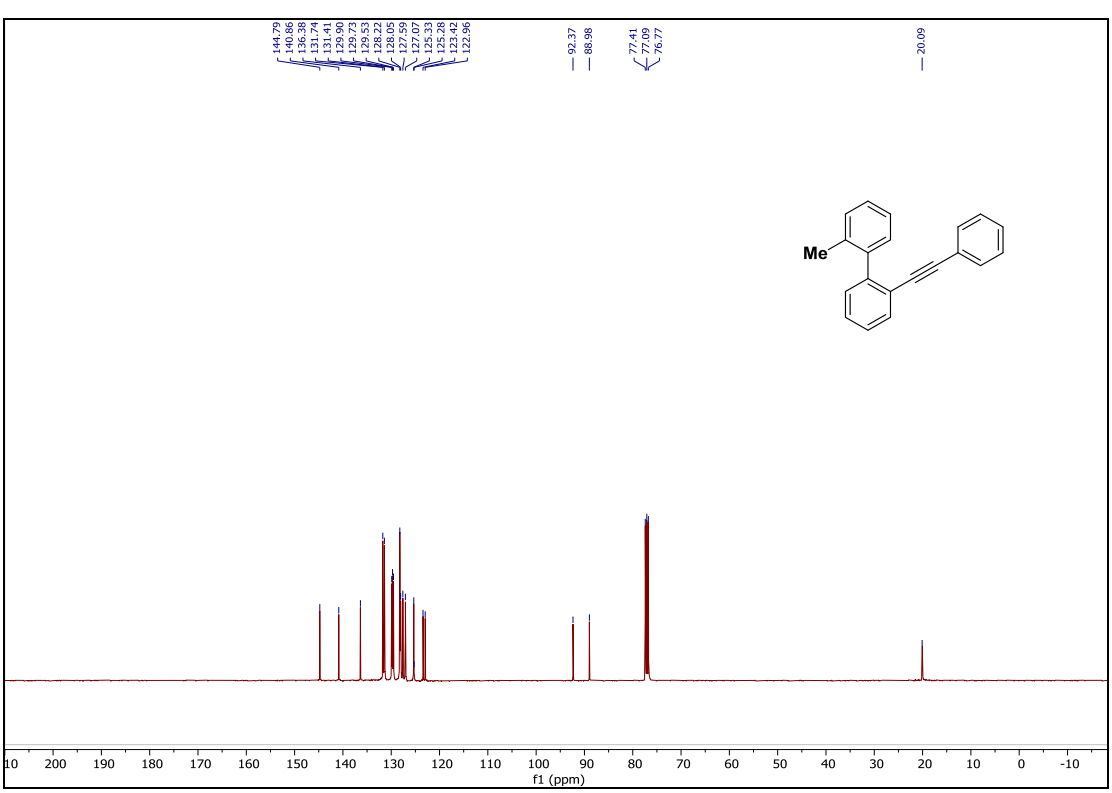
^{13}C{^{1}H} NMR of **1a** (75 MHz, $CDCl_3$)



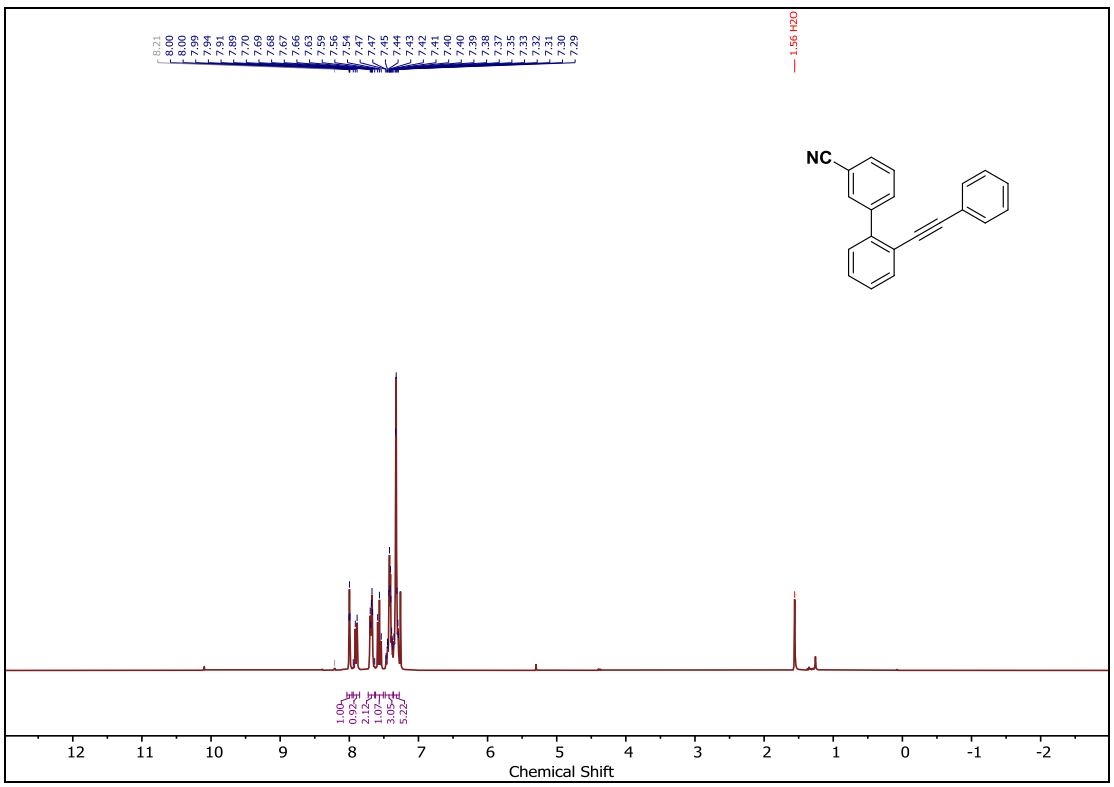
^{1}H NMR of **1c** (300 MHz, $CDCl_3$)



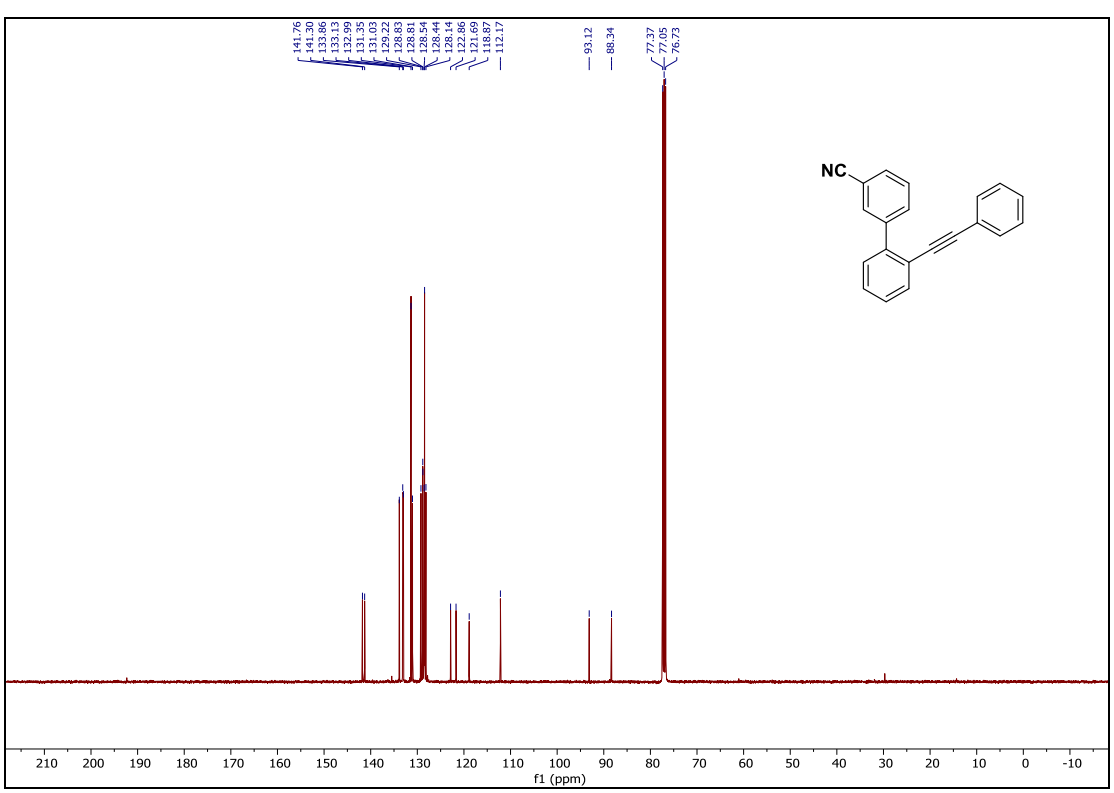
^{13}C{^{1}H} NMR of **1c** (75 MHz, $CDCl_3$)



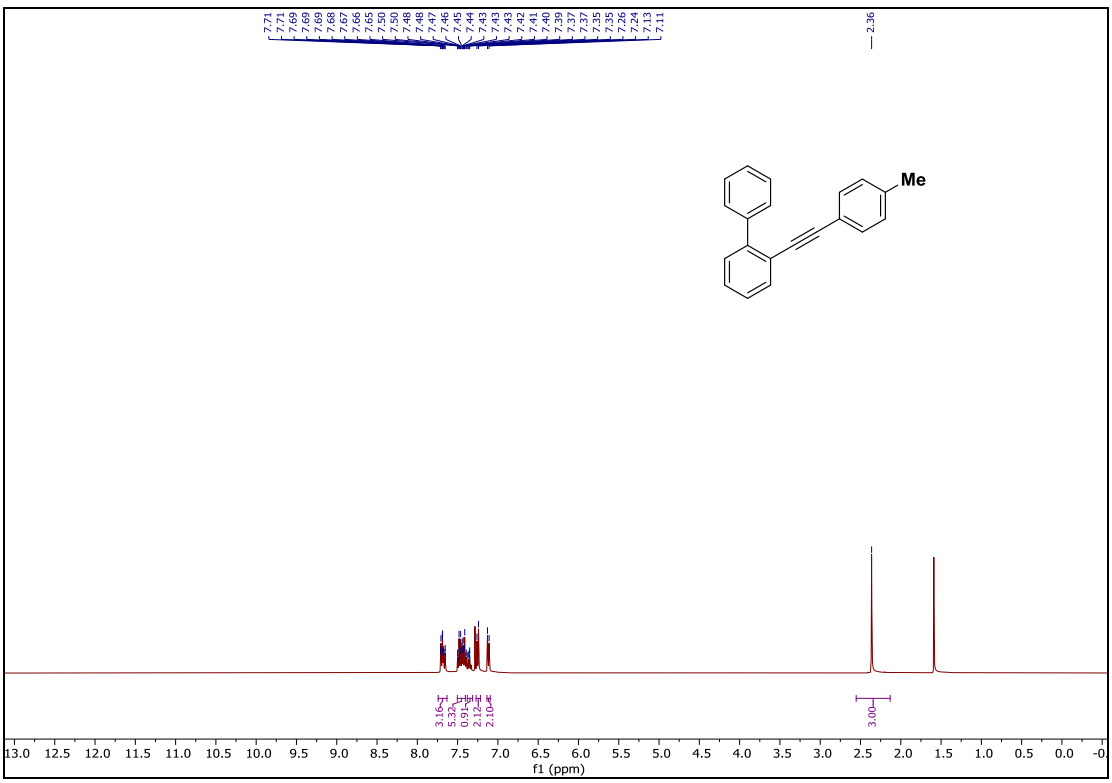
^{1}H NMR of **1f** (300 MHz, $CDCl_3$)



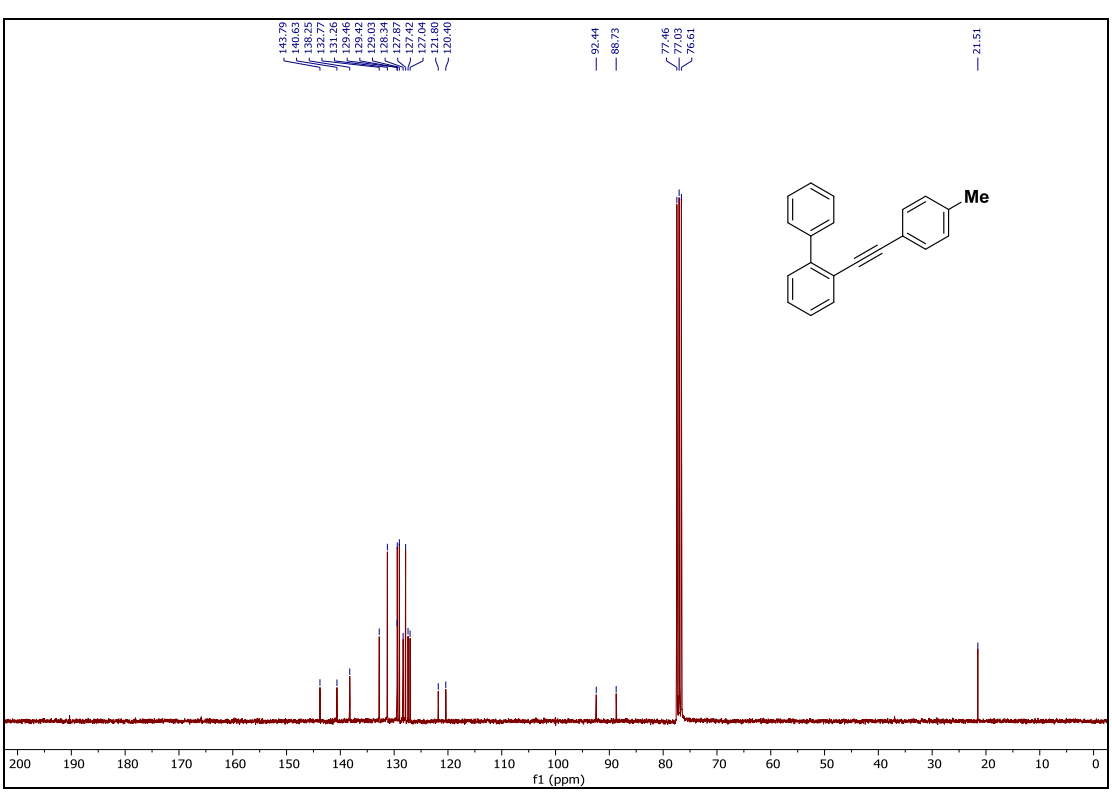
^{13}C{^{1}H} NMR of **1f** (75 MHz, $CDCl_3$)



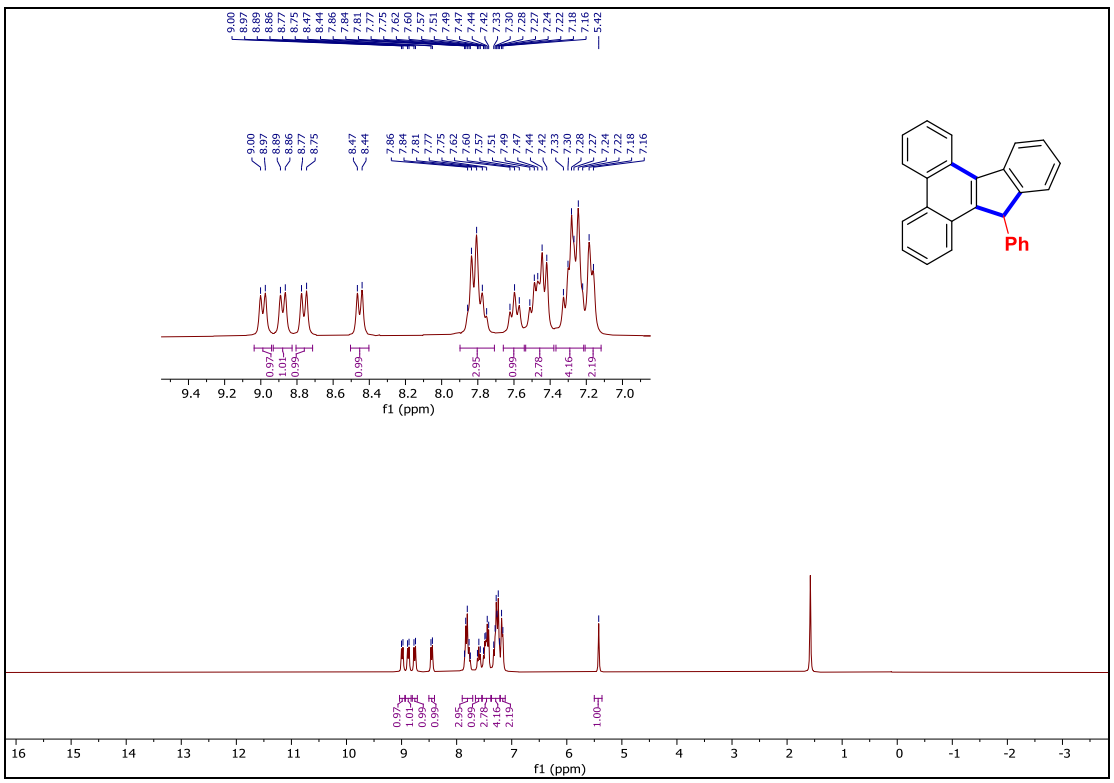
^{1}H NMR of **1g** (400 MHz, $CDCl_3$)



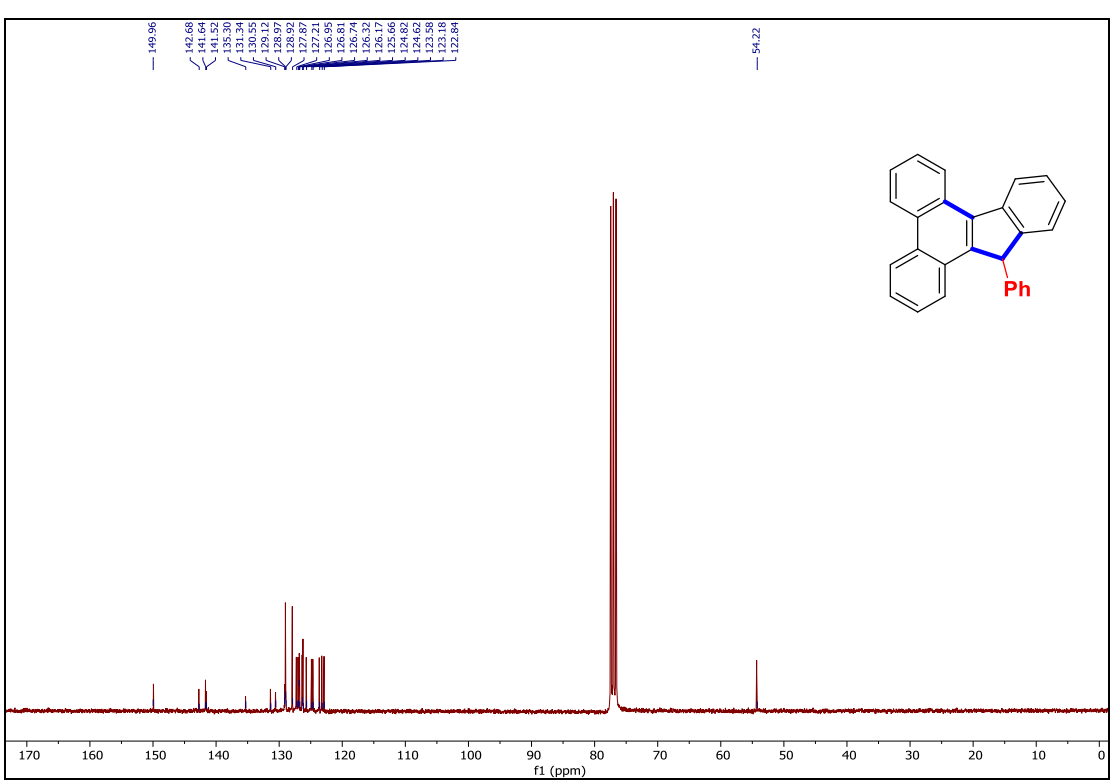
^{13}C{^{1}H} NMR of **1g** (75 MHz, $CDCl_3$)



^{1}H NMR of **3aa** (300 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR of **3aa** (75 MHz, $CDCl_3$)



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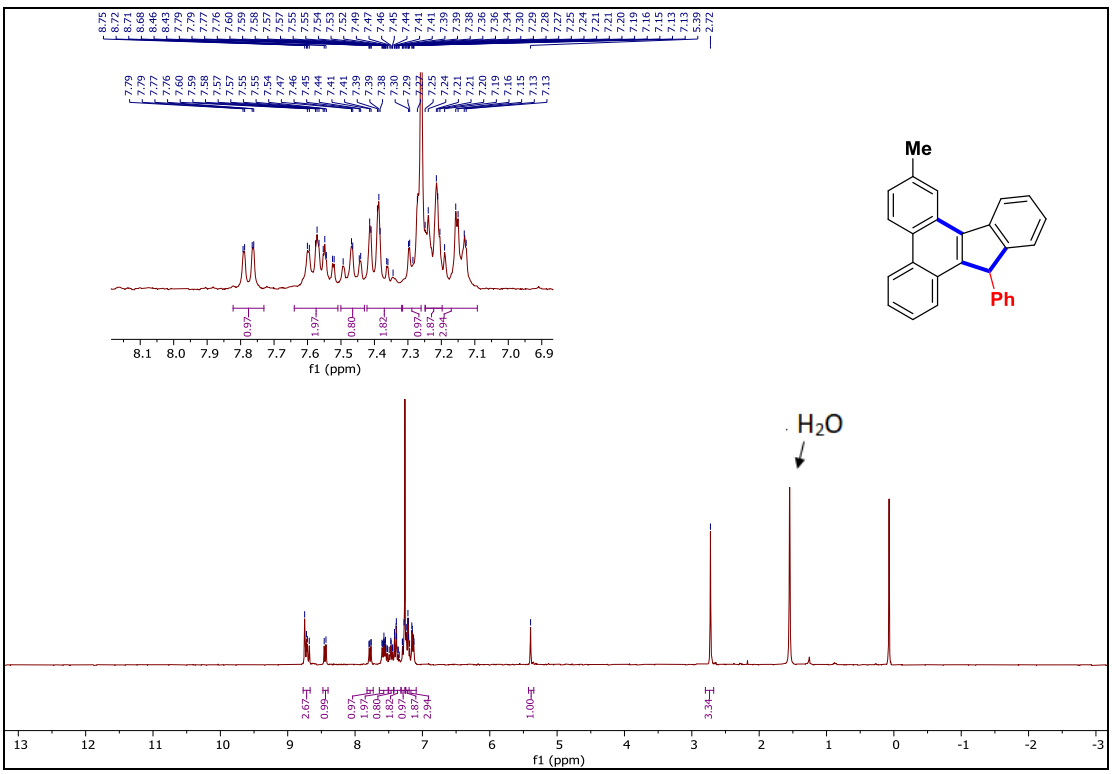

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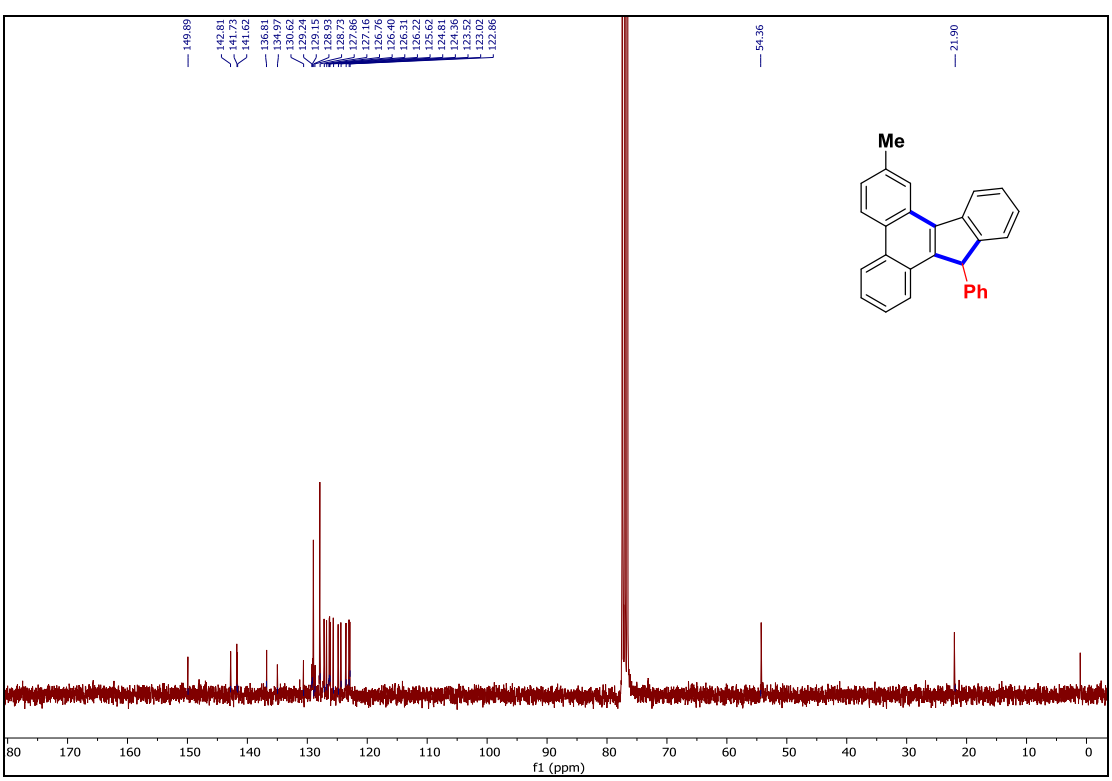

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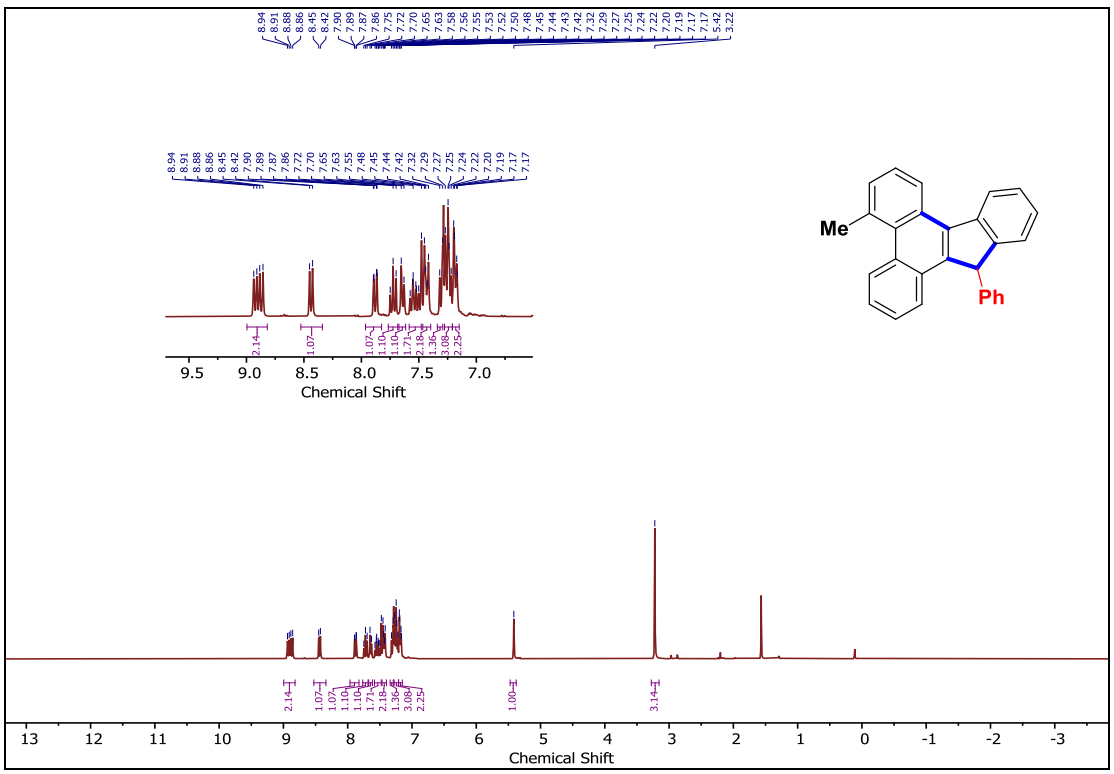

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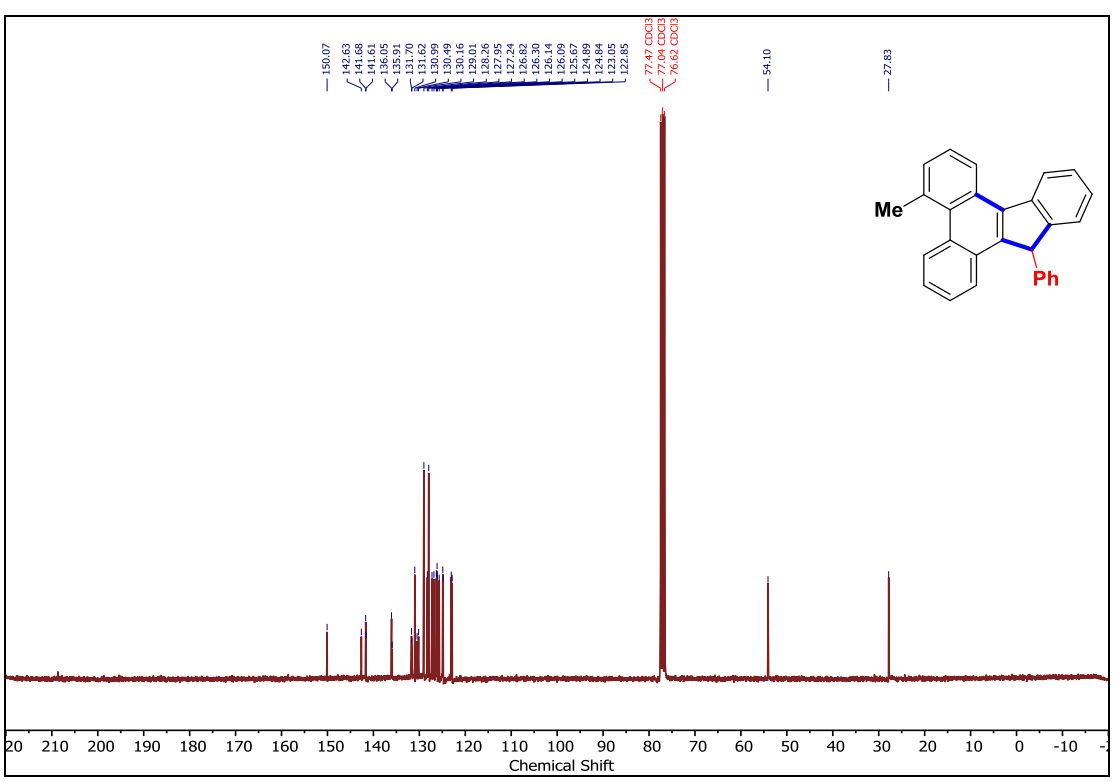

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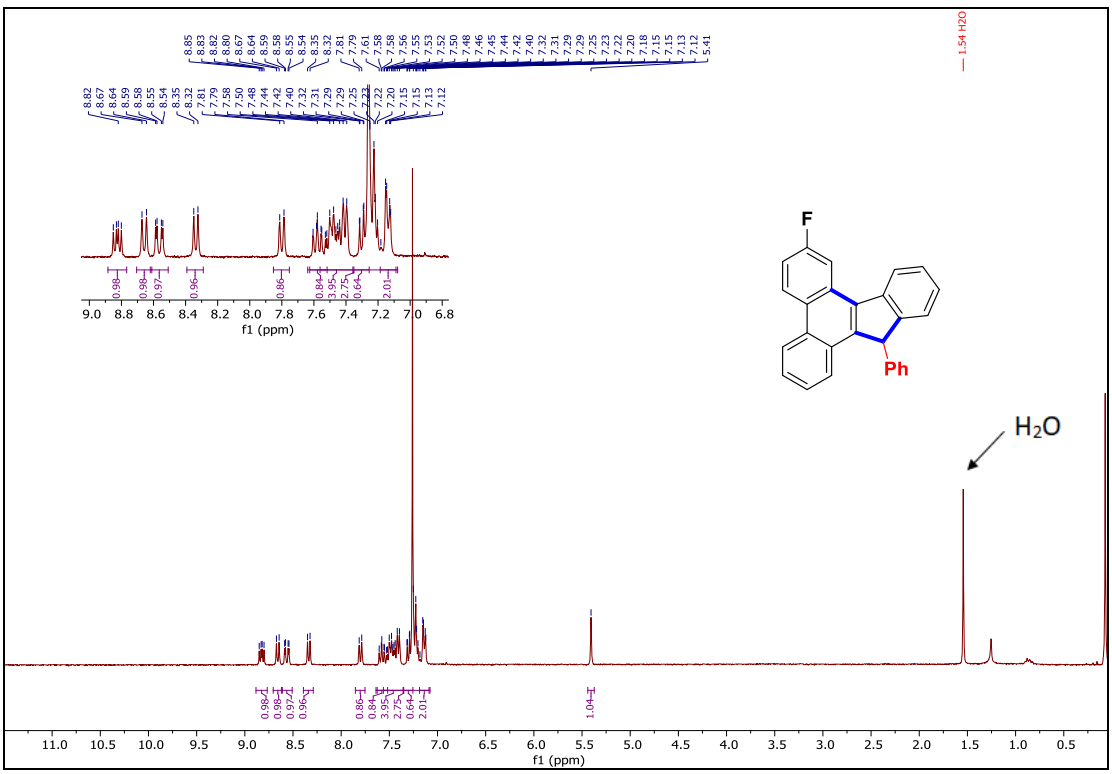

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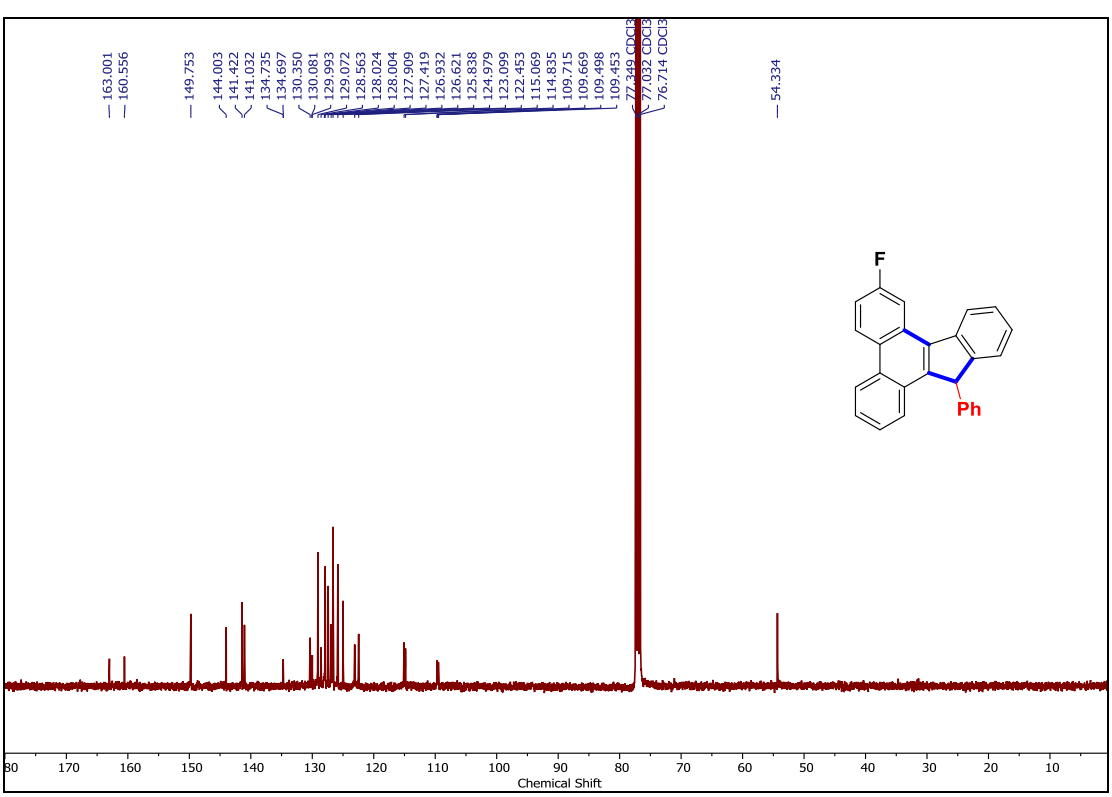
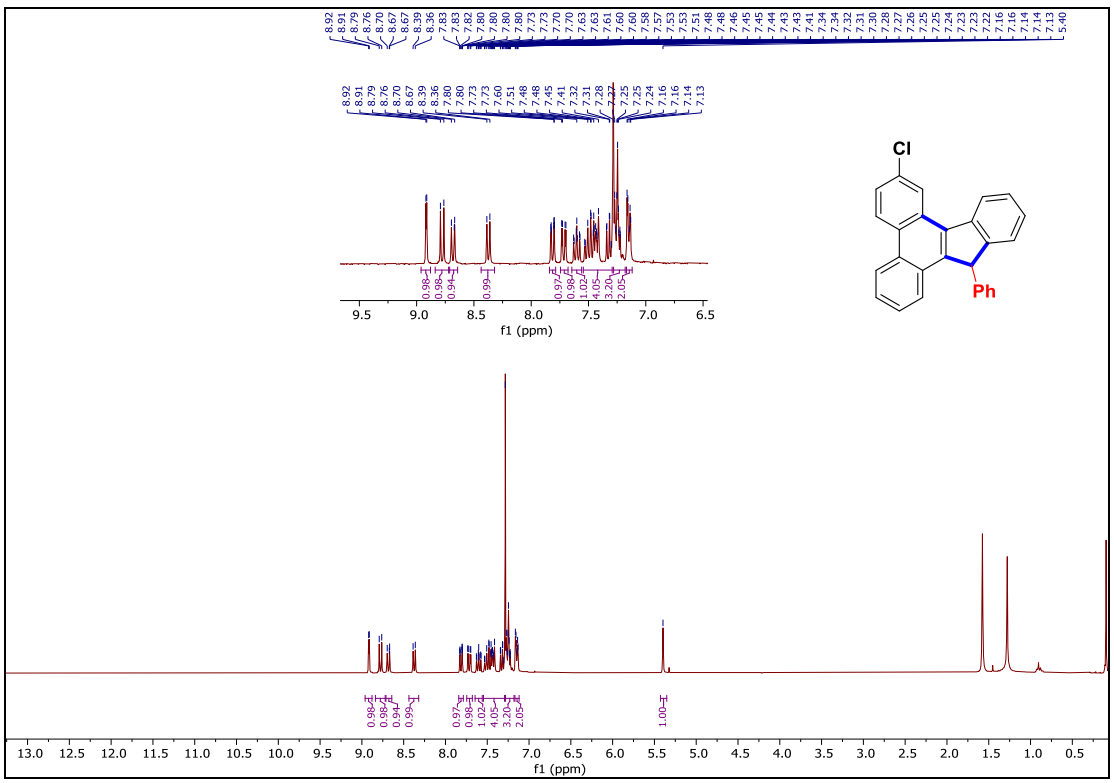


^{1}H NMR of **3ea** (300 MHz, $CDCl_3$)



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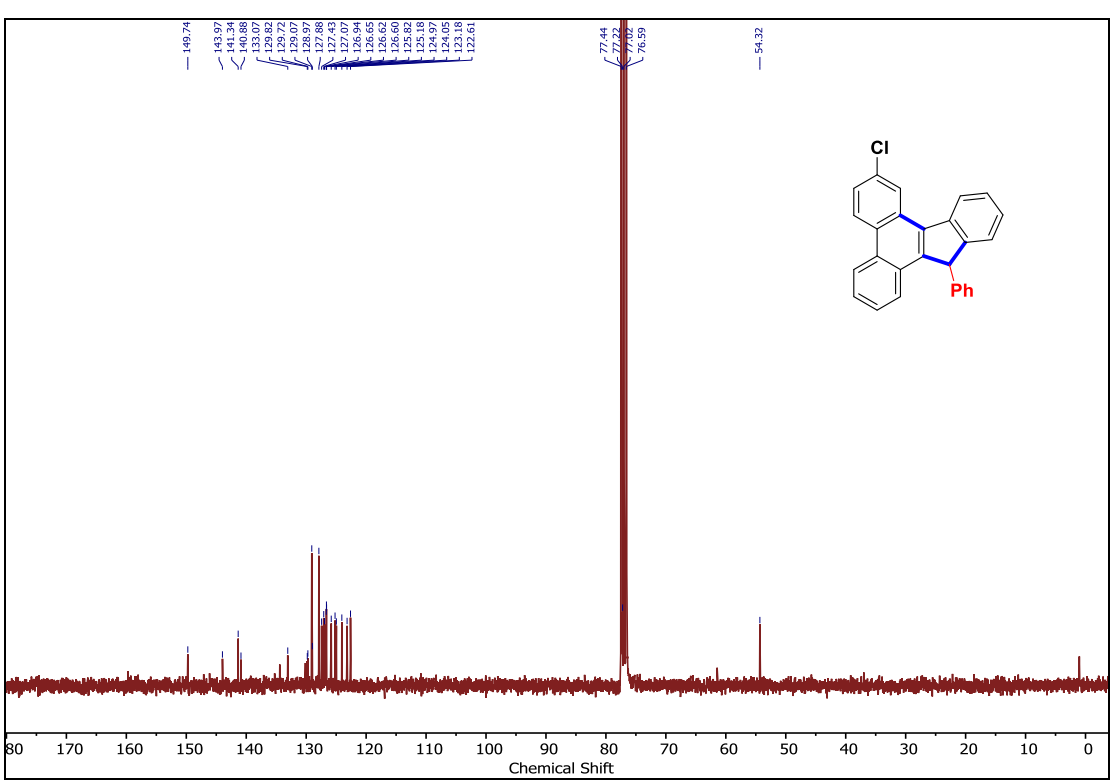

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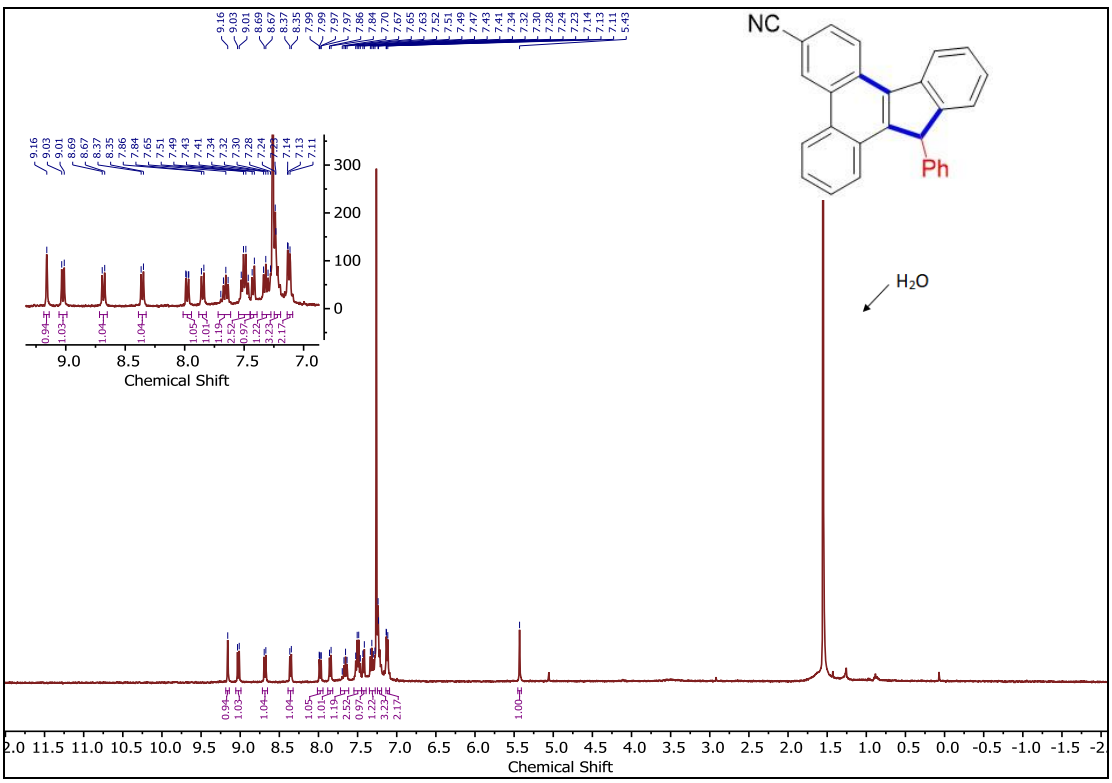

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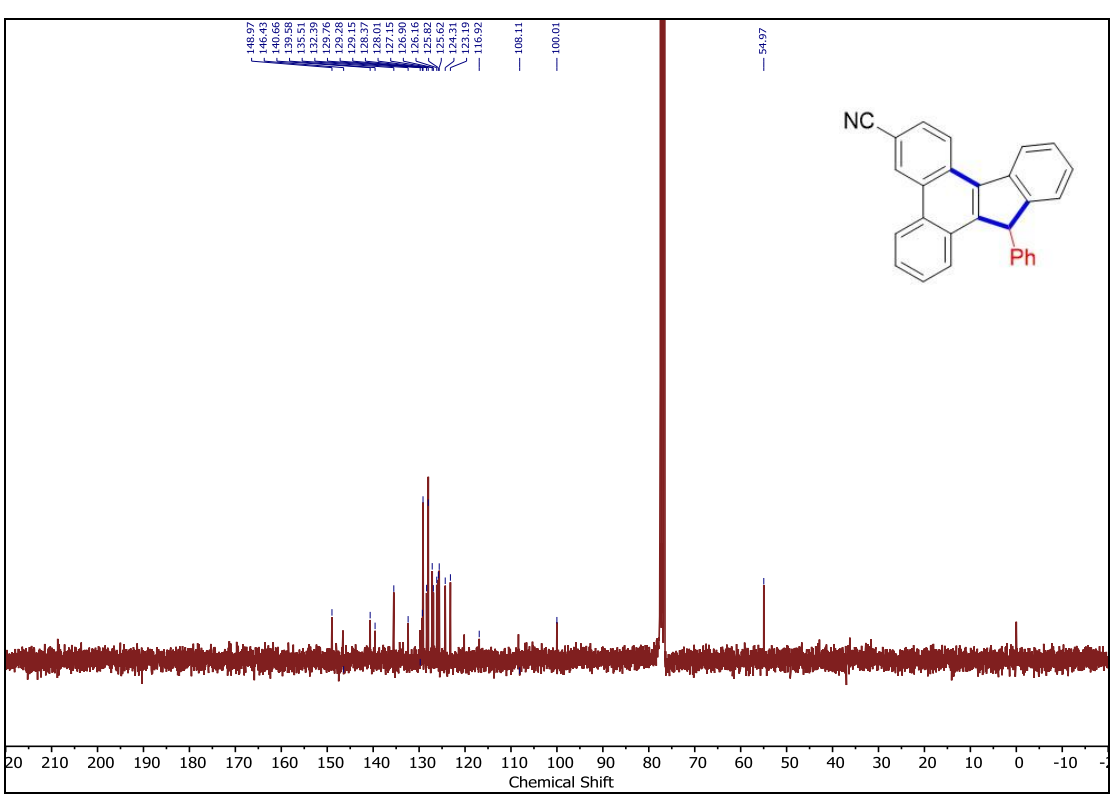
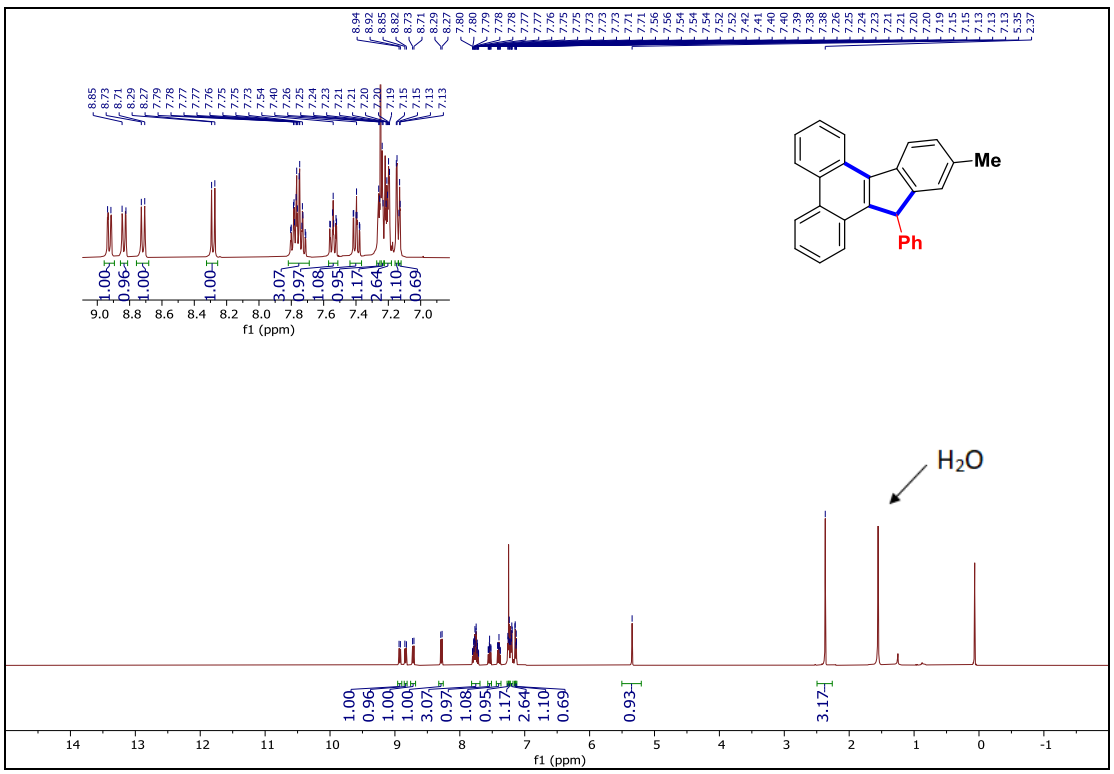


^{1}H NMR of **3ga** (400 MHz, $CDCl_3$)



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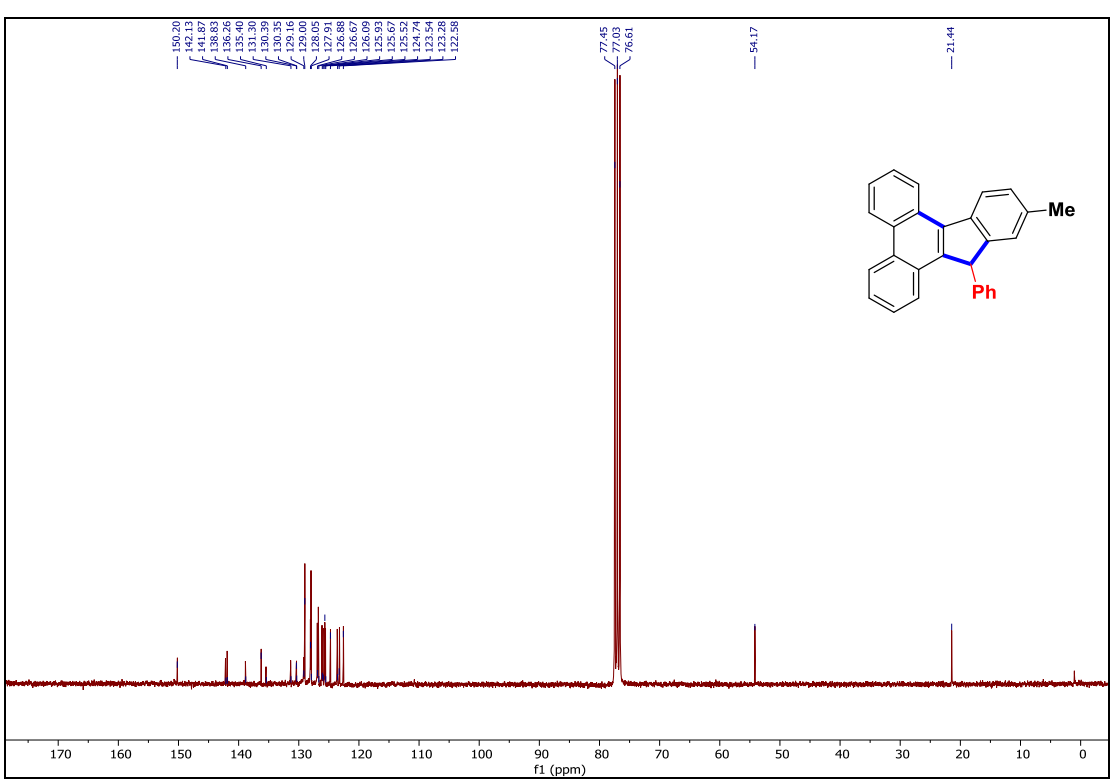
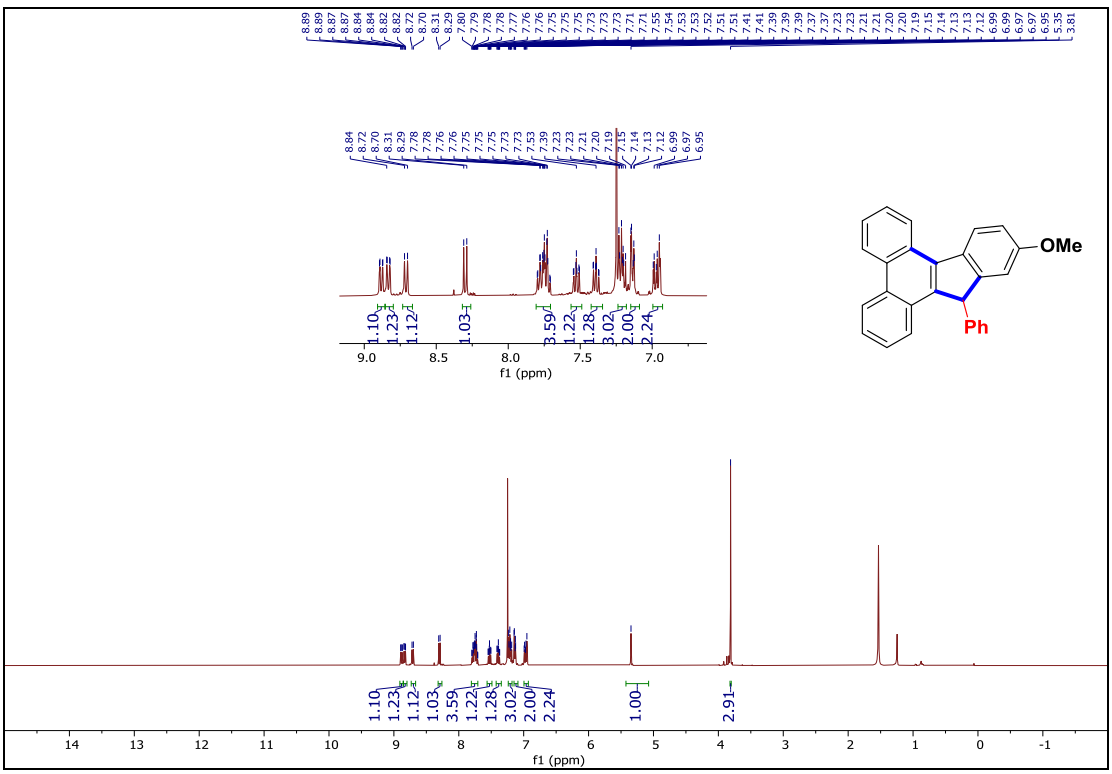
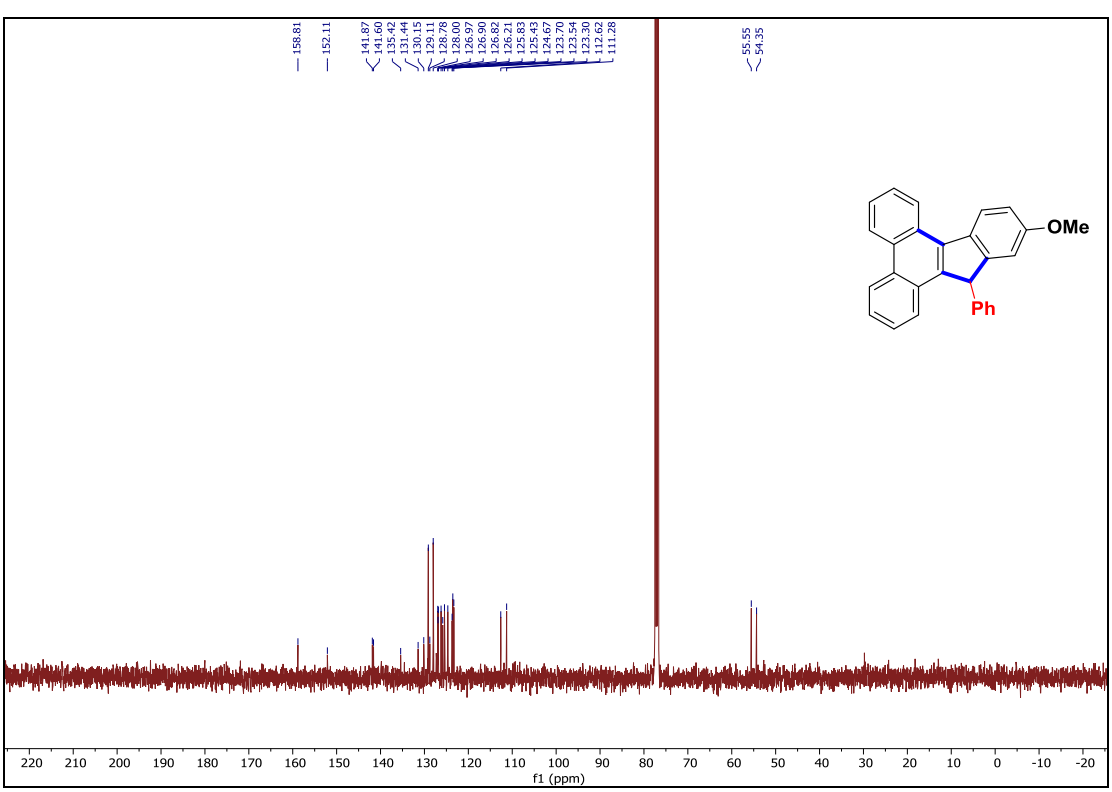


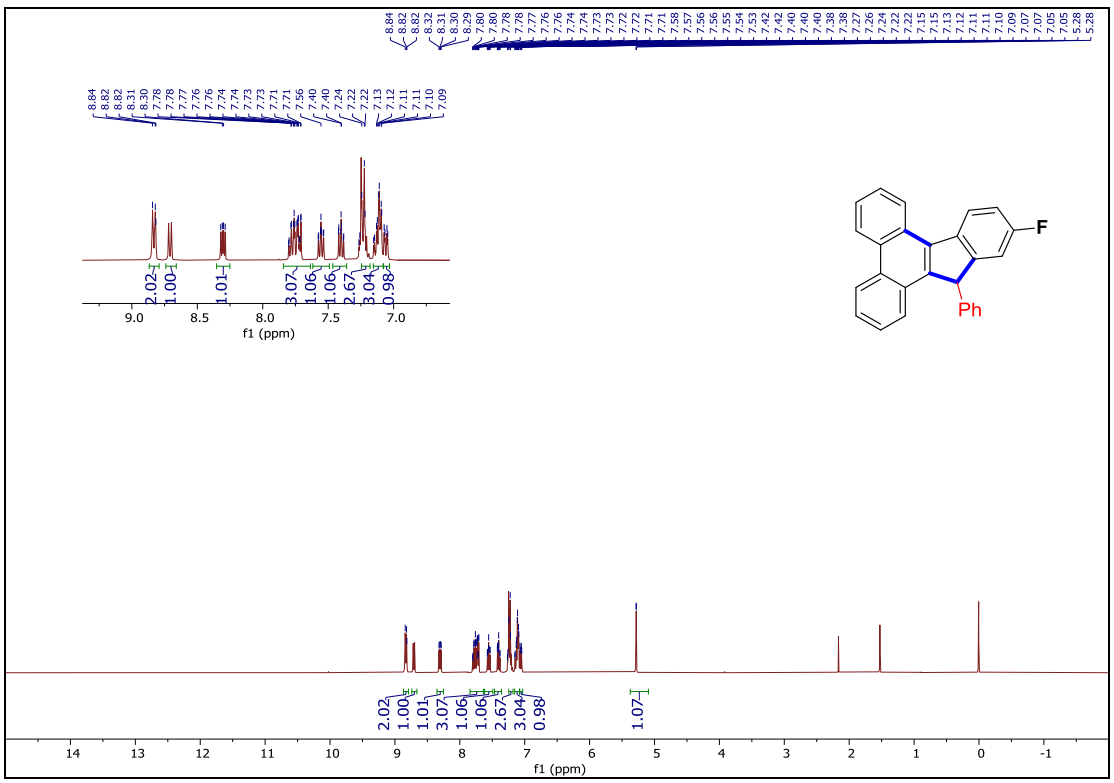
^{1}H NMR of **3ha** (400 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR of **3ha** (101 MHz, $CDCl_3$)



^{1}H NMR of **3ia** (400 MHz, $CDCl_3$)



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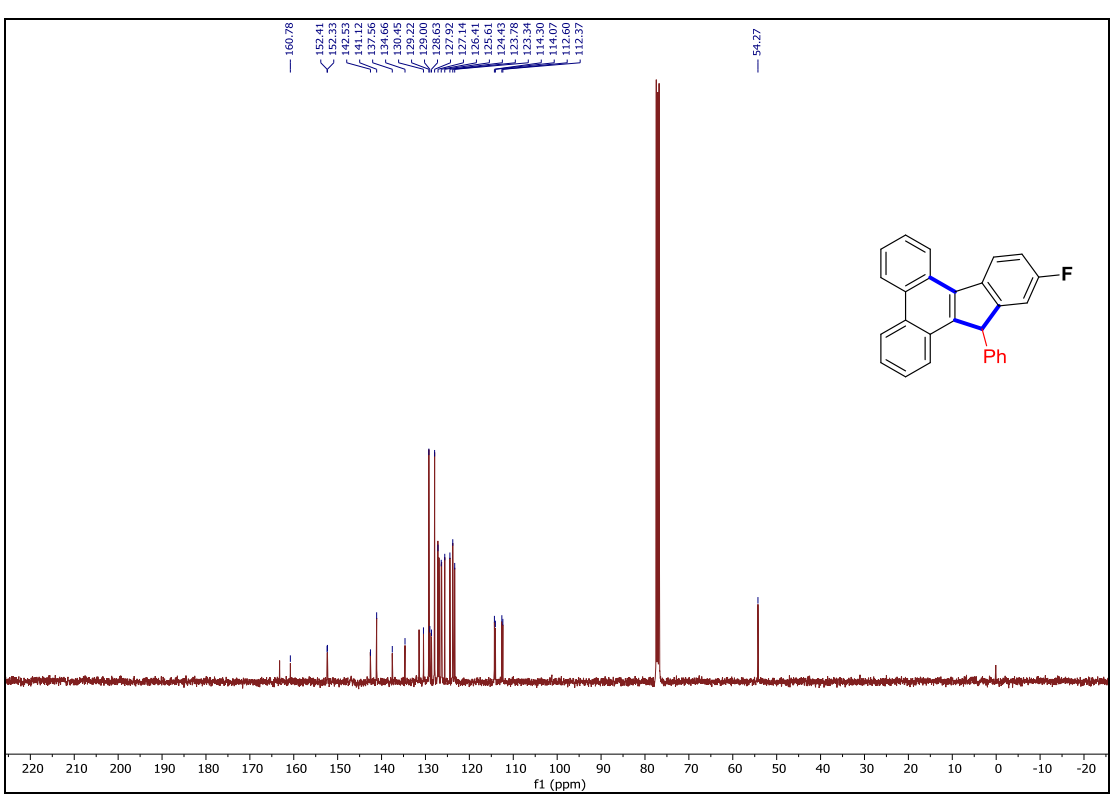
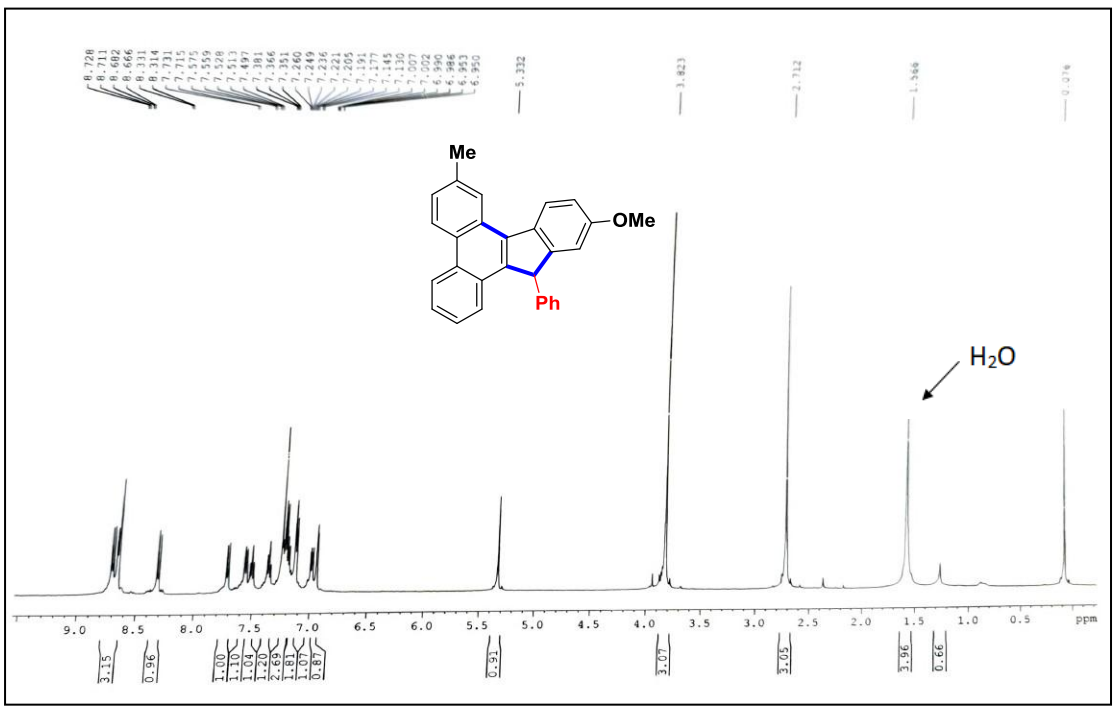
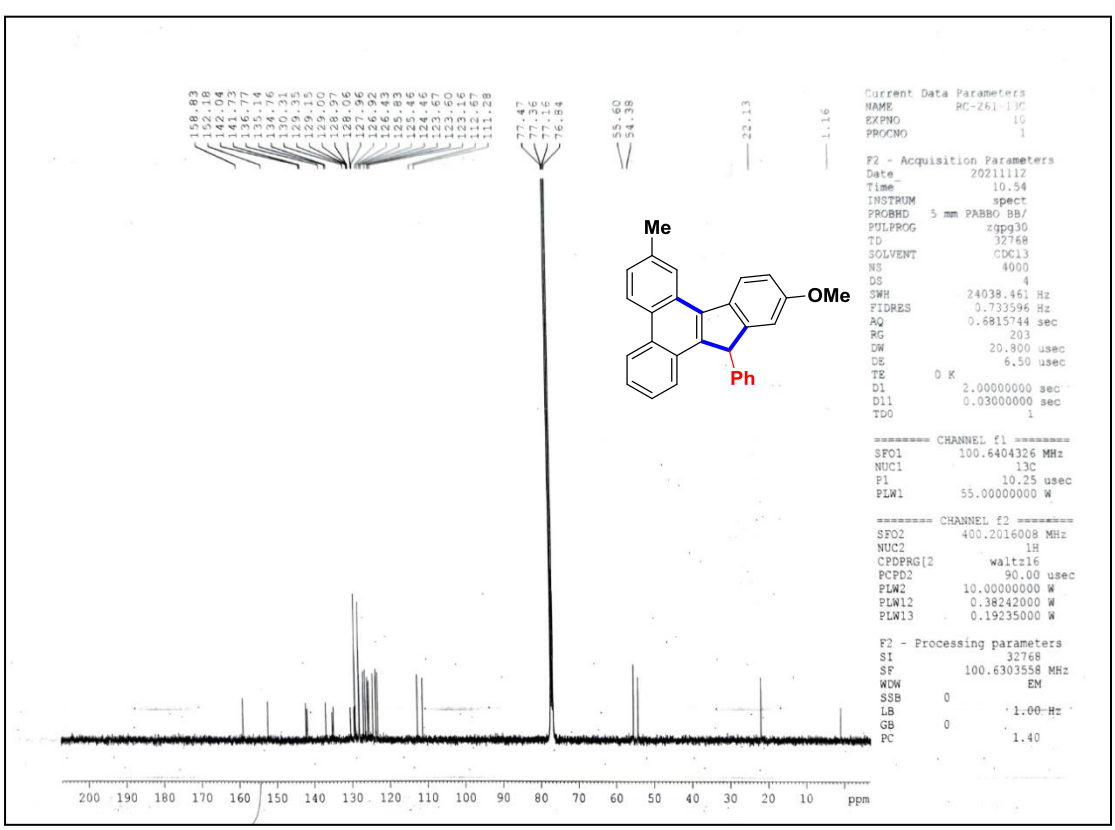


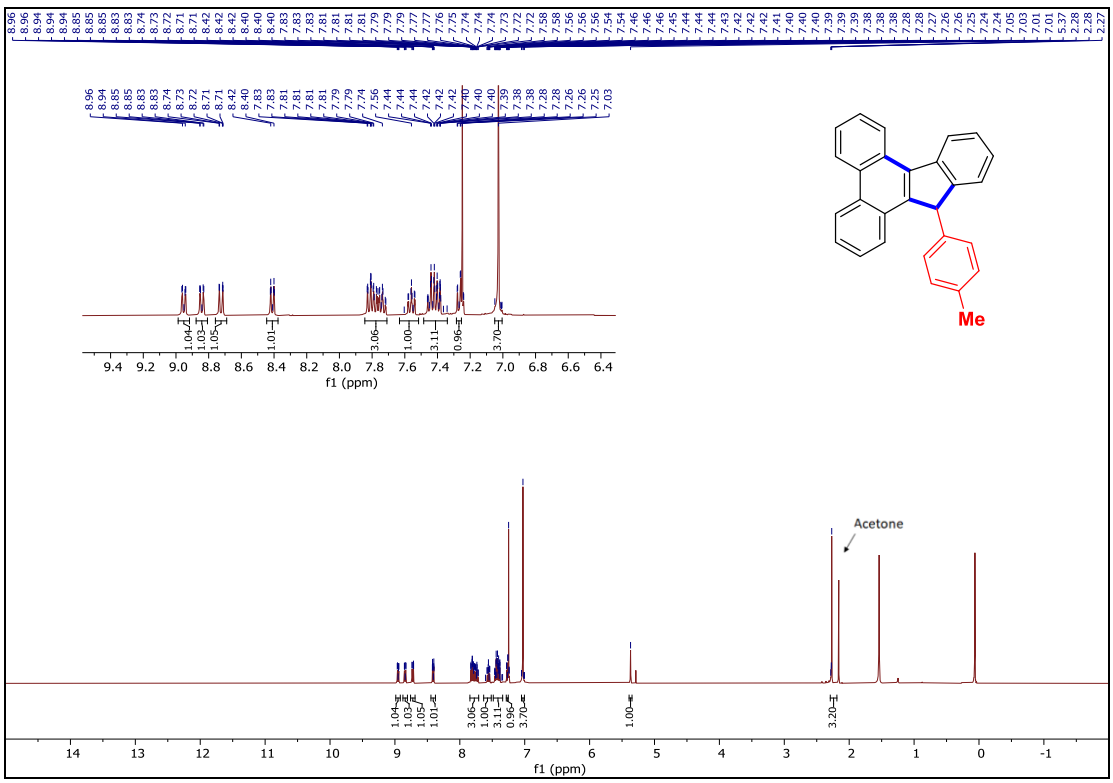
^{1}H NMR of **3ja** (500 MHz, $CDCl_3$)



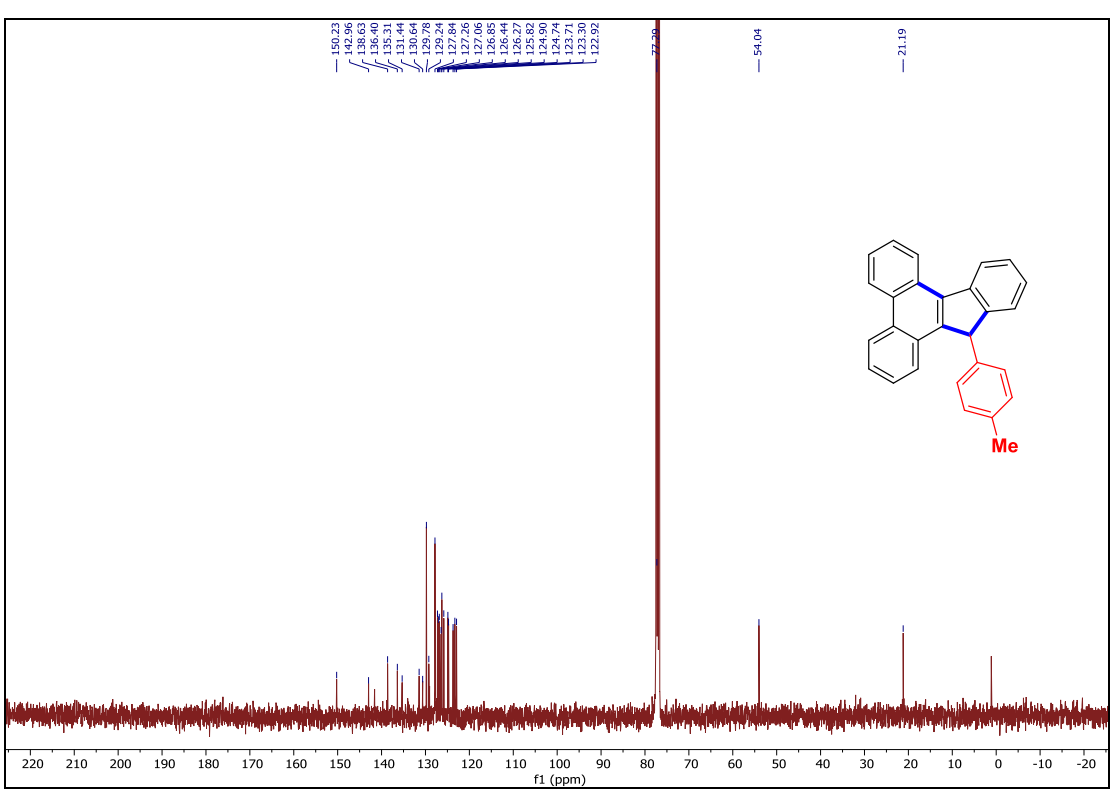
^{13}C{^{1}H} NMR of **3ja** (101 MHz, $CDCl_3$)



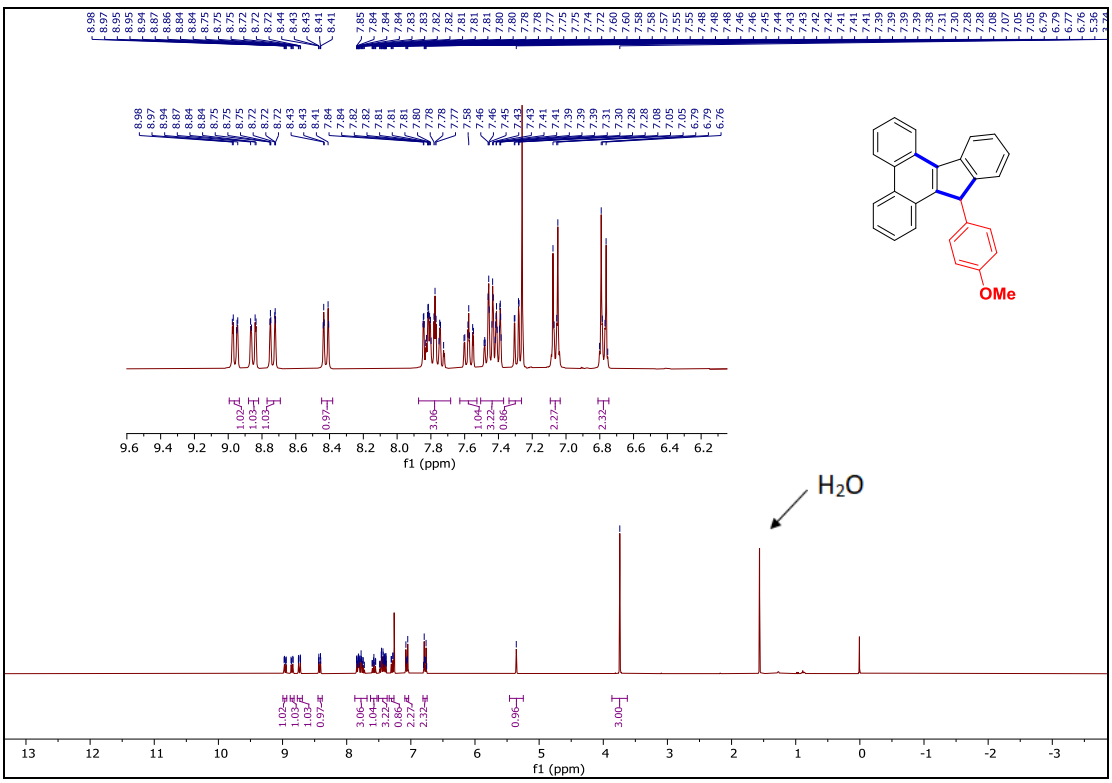
^{1}H NMR of **3ab** (400 MHz, $CDCl_3$)



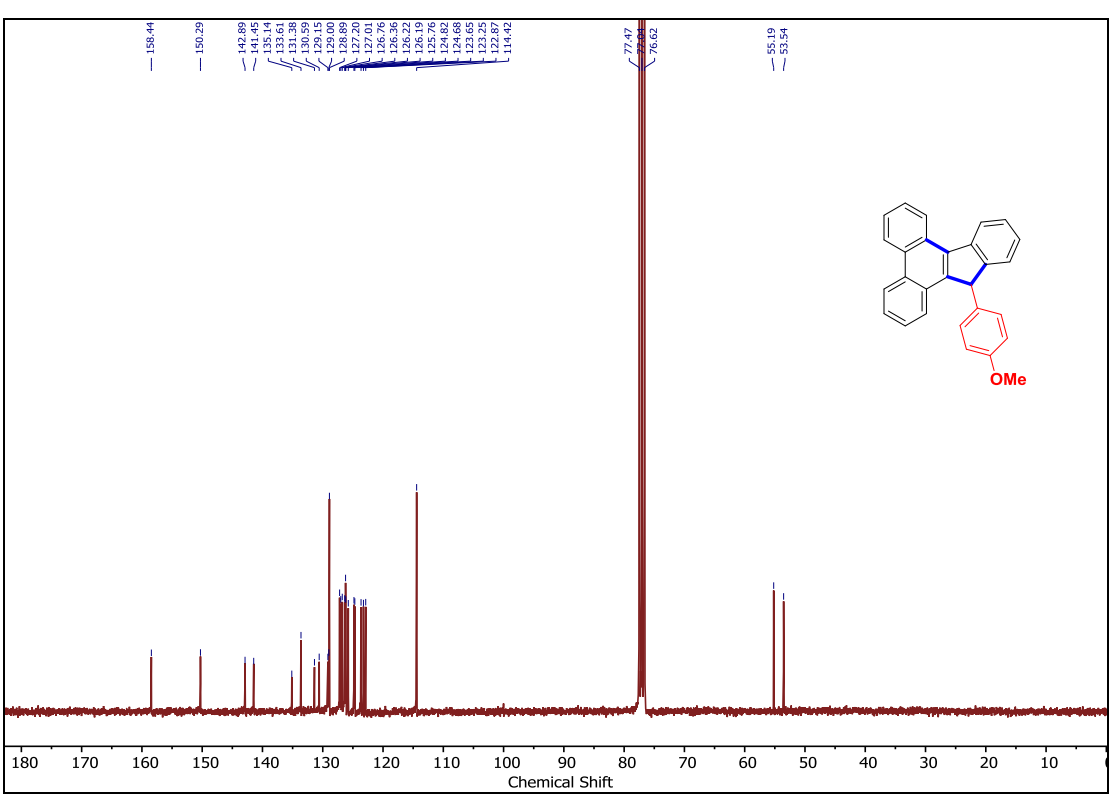
^{13}C{^{1}H} NMR of **3ab** (101 MHz, $CDCl_3$)



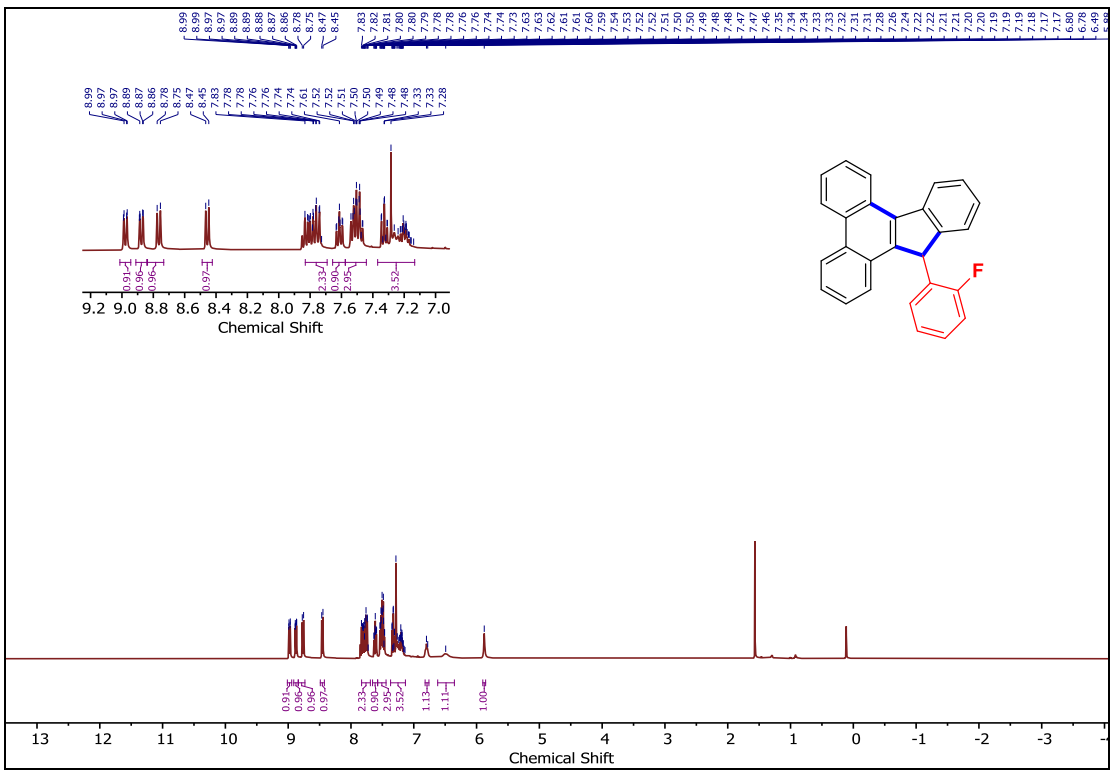
^{1}H NMR of **3ac** (300 MHz, $CDCl_3$)



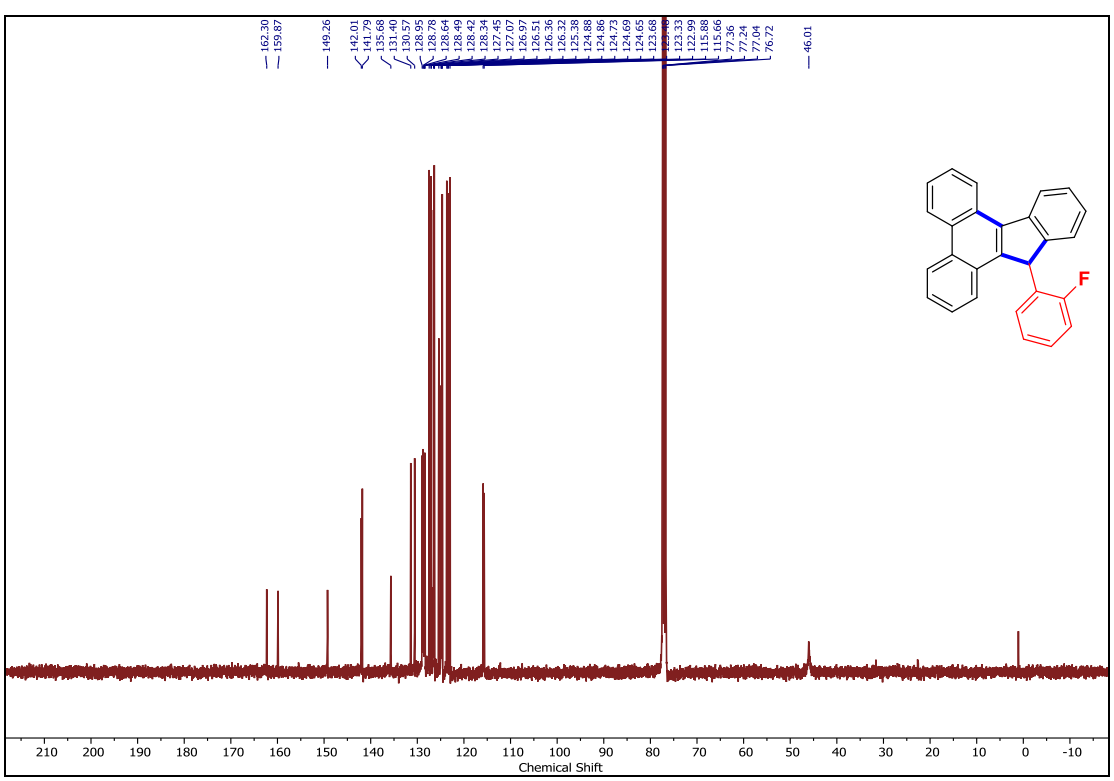
^{13}C{^{1}H} NMR of **3ac** (75 MHz, $CDCl_3$)



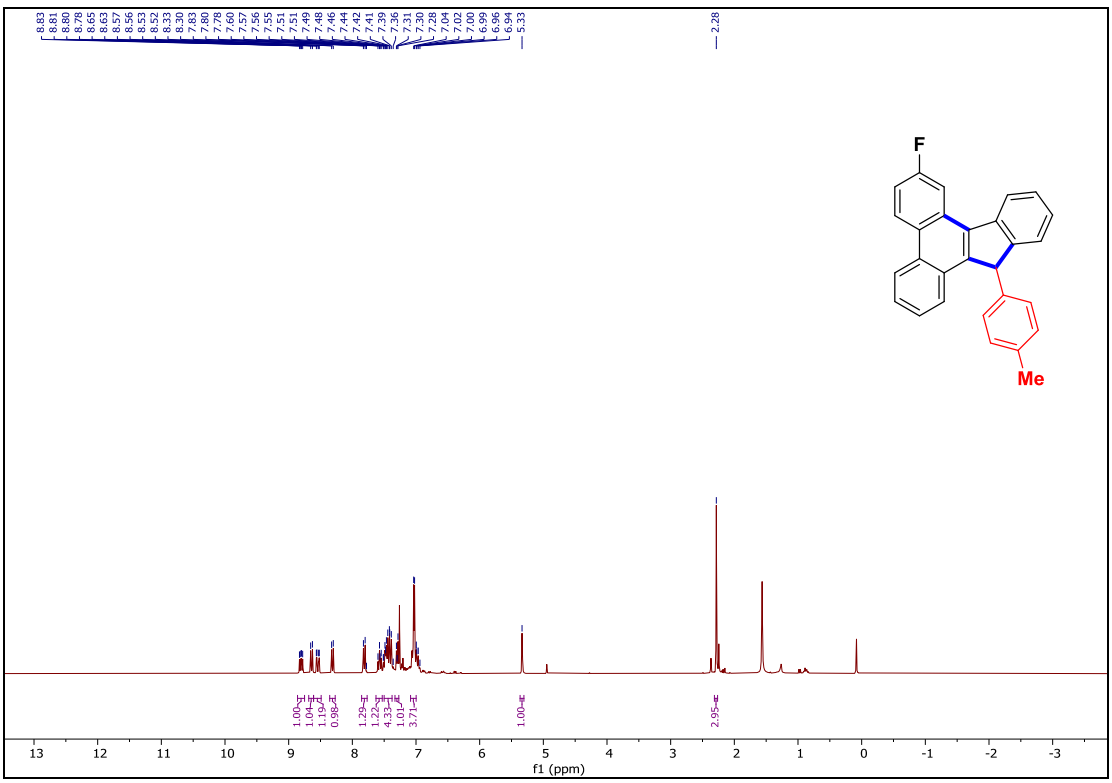
^{1}H NMR of **3ad** (400 MHz, $CDCl_3$)



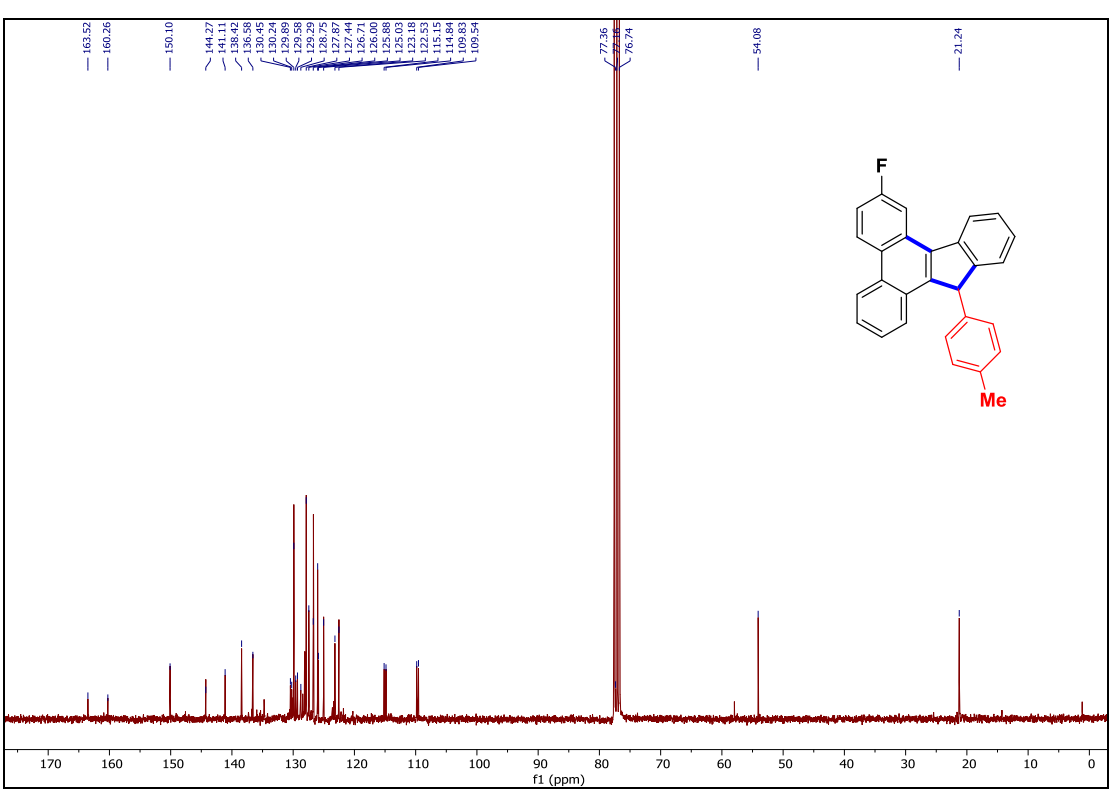
^{13}C{^{1}H} NMR of **3ad** (101 MHz, $CDCl_3$)



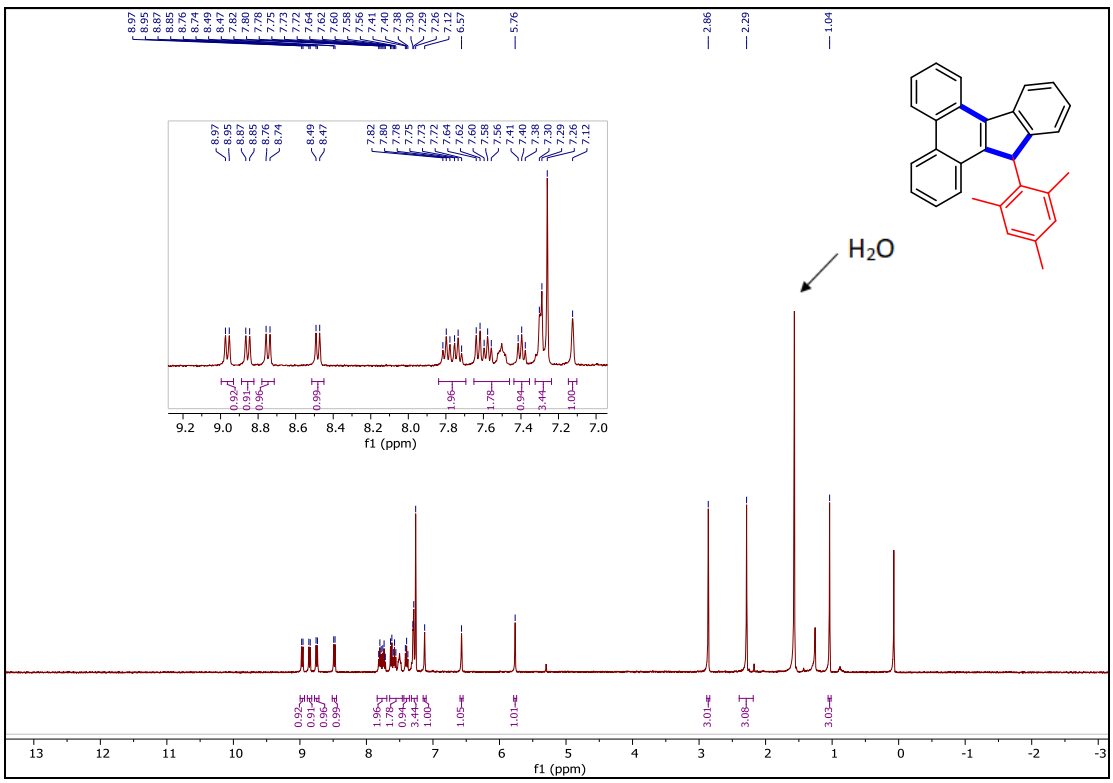
^{1}H NMR of **3db** (300 MHz, $CDCl_3$)



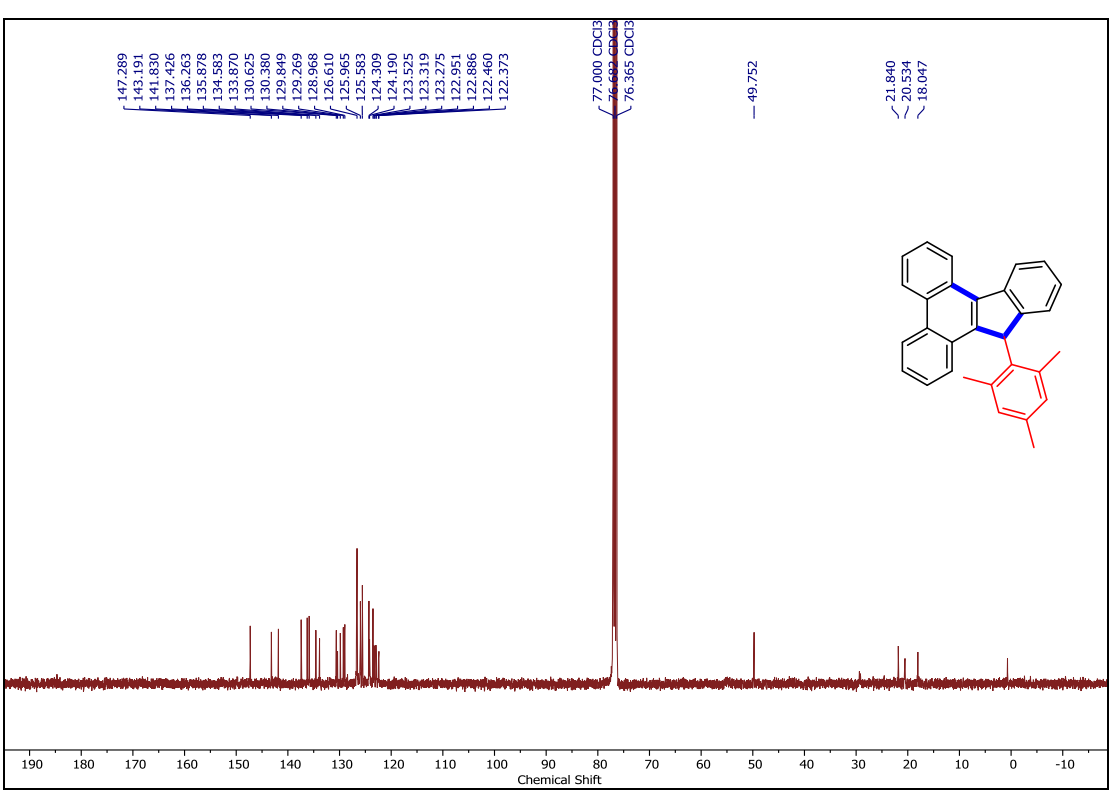
^{13}C{^{1}H} NMR of **3db** (75 MHz, $CDCl_3$)



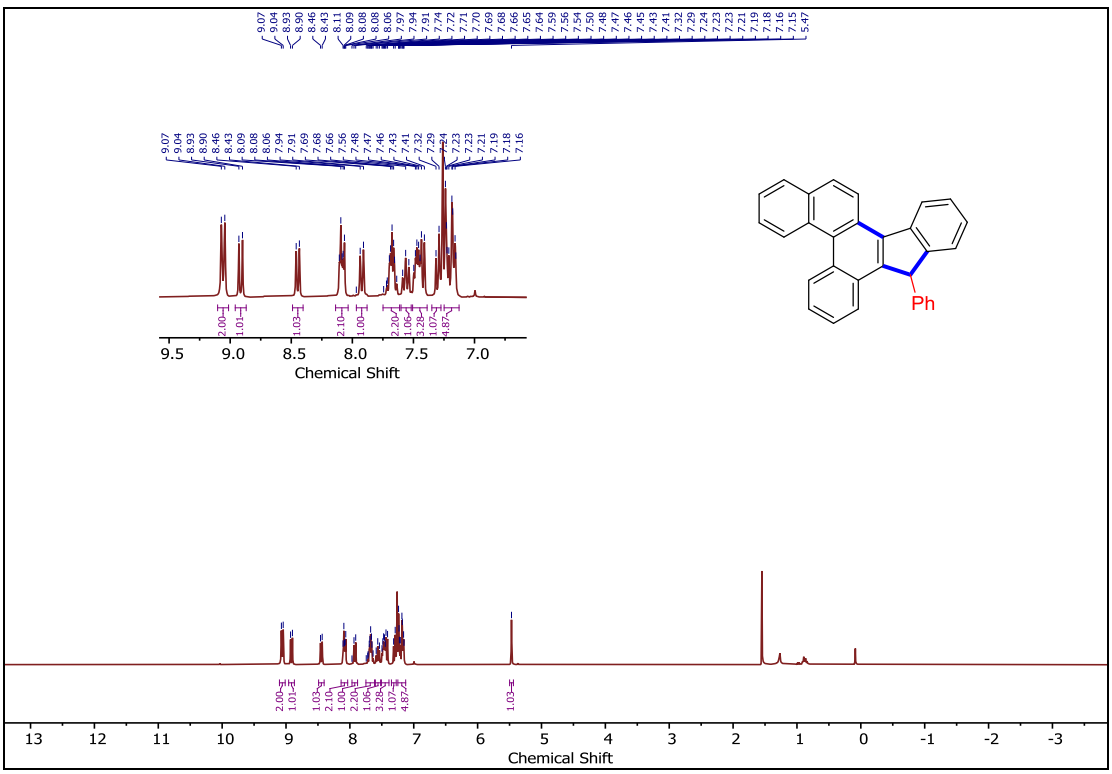
^{1}H NMR of **3ae** (400 MHz, $CDCl_3$)



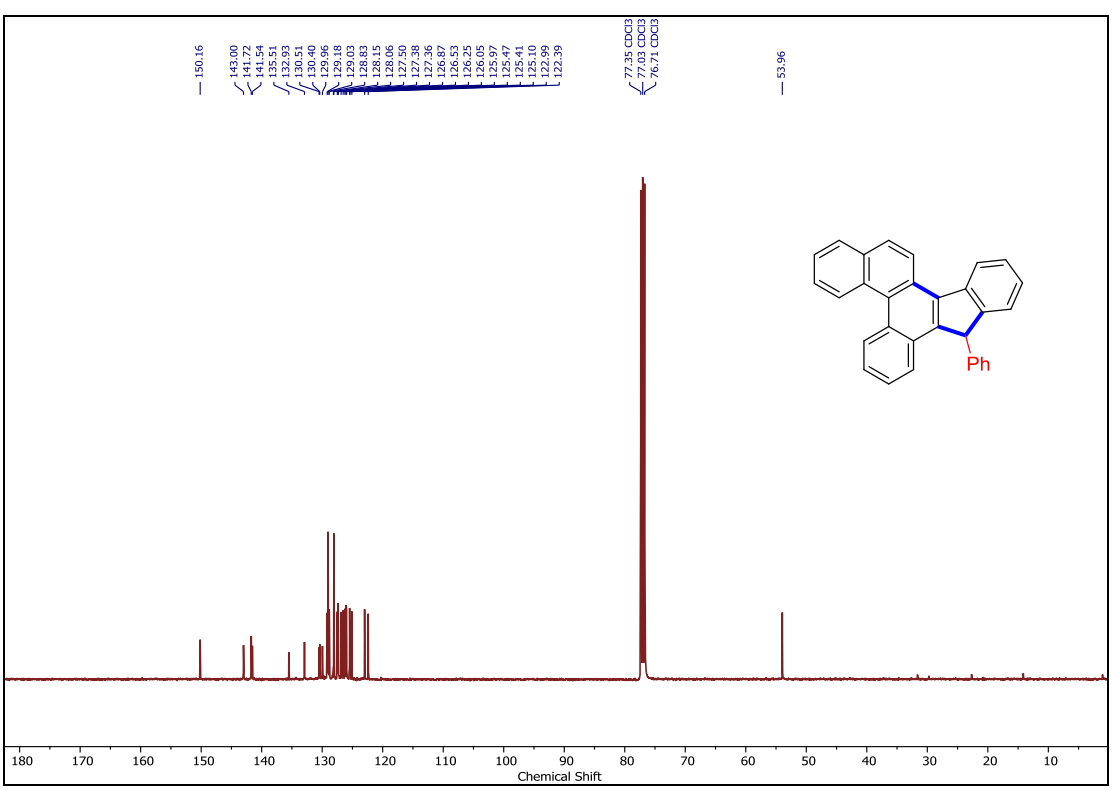
^{13}C{^{1}H} NMR of **3ae** (101 MHz, $CDCl_3$)



^{1}H NMR of **5** (300 MHz, $CDCl_3$)



^{13}C{^{1}H} NMR of **5** (101 MHz, $CDCl_3$)



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Iron-Catalyzed Synthesis of 13-Aryl-13*H*-indeno[1,2-*l*]phenanthrene via Double Annulations of 2-Alkynyl Biaryls

Rupsa Chanda, Tubai Ghosh, and Umasish Jana*

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ABSTRACT: An Fe(III)-catalyzed expedient synthesis of 13-aryl-13*H*-indeno[1,2-*l*]phenanthrene is described by a double annulations of 2-alkynyl biaryls, initiated by the activation of acetal. This strategy provides a simple, efficient and regioselective synthesis of varieties of indenophenanthrene derivatives from easily available starting materials under mild conditions in high to excellent yields. A plausible reaction mechanism is proposed.

The phenanthrene scaffold is one of the leading building blocks frequently found in bioactive molecules and natural products.[1] Because of its unique thermal and electronic properties, the phenanthrene nucleus is considered as a potential blue light emitting compound that has also been found application in solar cells.[2] When an indene[3] moiety is fused to phenanthrene, a highly fused polycyclic aromatic hydrocarbon indenophenanthrene results. Polycyclic aromatic hydrocarbons belong to an important class of compounds owing to their widespread application as optoelectronic materials.[4] Among them, indenophenanthrene is considered to be one of the main precursors for the construction of highly fused targeted polycyclic aromatic hydrocarbons (PAHs). Hence, indenophenanthrene derivatives are alluring synthetic targets for material scientists on account of their high efficiency as deep-blue organic light emitting diodes (OLEDs) (Figure 1).[5] The importance of the indenophenanthrene motif continuously stimulates scientists to discover conceptually innovative synthetic strategies.

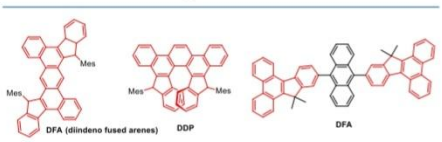
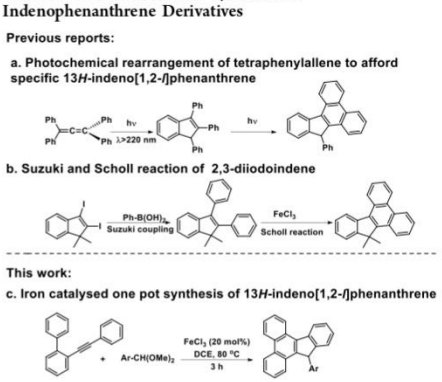


Figure 1. OLEDs containing an indenophenanthrene moiety.

However, our literature is enriched with several methods to fabricate phenanthrene-based polycyclic aromatic hydrocarbons. Some of the classic methods include the transition-metal-catalyzed trimerization of arynes,[6] Diels−Alder reaction,[7] alkyne-carbonyl metathesis reaction,[8] Mallory photochemical cyclization,[9a] oxidative annulation,[9b,c] etc. But very few methods are available to construct the indenophenanthrene moiety.[10] The group of Johnson came up with the idea of photochemical rearrangement of tetraphenylallene to afford the specific 13*H*-indeno[1,2-*l*]phenanthrene (Scheme 1a).[11] In the past decade, the group of Wang has reported the synthesis of 13*H*-indeno[1,2-*l*]phenanthrene by a sequential Suzuki and

Scheme 1. Methods for the Synthesis of Indenophenanthrene Derivatives



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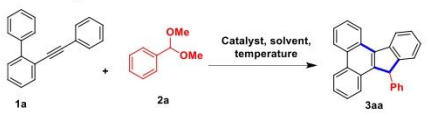
Scholl reaction of 2,3-diiodoindene (Scheme 1b).[12] Another report by Wu et al. for the synthesis of more complex 5,14-diaryldiindeno[2,1-*f*:1′,2′-*j*]picene (DDP) also comprises sequential multistep synthesis.[5c] All of these methods either lack diversity or require complicated starting materials and multiple synthetic steps. Hence, it is justifiable to say that the literature fails to provide any new expedient idea to achieve an indenophenanthrene motif from easily available starting material, and there is still much to explore in this area.

2-(Phenylethynyl)-1,1′-biphenyl is found to be an emerging precursor to build phenanthrene derivatives as radical or electrophilic cyclization of 2-(phenylethynyl)-1,1′-biphenyl can generate phenanthrene efficiently.[13] On the other hand, iron catalysis received enormous interest in the past few years as an alternative to other traditional transition-metal-catalyzed organic transformations because of its unique π-acidity, sustainability, low cost, and low toxicity. In connection with our recent achievements in the iron(III)-catalyzed cyclization reactions of functionalized 2-(phenylethynyl)-1,1′-biphenyl derivatives toward the synthesis of phenathrenes scaffolds,[14] we envisioned that acetals could easily activate 2-(phenylethynyl)-1,1′-biphenyl in the presence of a suitable Lewis acid and readily furnish the indenophenanthrene moiety through a double annulation reaction. Hence, it would be a simple synthetic strategy to achieve a complex molecular framework from easily available starting materials in a single operation. We, herein, report $FeCl_3$-catalyzed greener and atom-economic concise synthesis of 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives by coupling of 2-(phenylethynyl)-1,1′-biphenyl and benzaldehyde acetals (Scheme 1c).

To implement the synthetic strategy, we first prepared the precursor substrate 2-(phenylethynyl)-1,1′-biphenyl **1a** by the Sonogashira coupling reaction of 2-bromoiodobenzene with phenyl acetylene and then the Suzuki coupling reaction of the product with phenyl boronic acid. We commenced our investigations using 2-(phenylethynyl)-1,1′-biphenyl and (dimethoxymethyl)benzene as a model substrate, and the results are summarized in Table 1. Initially, 20 mol % of anhydrous $FeCl_3$ was employed in dry dichloromethane (DCM) solvent at room temperature, but no desired product was obtained even after 12 h (Table 1, entry 1). To our delight, when the reaction mixture was refluxed for 3 h, the desired product 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene **3aa** was afforded in 23% yield (Table 1, entry 2). Subsequently, a few other solvents were carefully tested to improve the yield of the desired product. Pleasantly, when 1,2-dichloroethane (1,2-DCE) was used as the reaction medium, **3aa** was obtained in 45% yield after 3 h of stirring at 60 °C (Table 1, entry 3). But when the reaction was performed at 80 °C, the yield of the product had a sharp increase to 88% (Table 1, entry 4). The use of other solvents such as nitromethane and acetonitrile did not give better results (Table 1, entries 5 and 6). Therefore, we continued our further studies in 1,2-DCE solvent using other Lewis and Brønsted acid catalysts. The reaction proceeded smoothly in the presence of $FeBr_3$ and $InCl_3$ catalysts, affording the desired product **3aa** with 83% and 78% yields, respectively (Table 1, entries 7 and 8). However, $Fe(OTf)_3$ and $In(OTf)_3$ did not give better results, providing only 35% and 27% yield of the product (Table 1, entries 9 and 10). Lewis acids such as $Au(PPh_3)Cl$ and $Yb(OTf)_3$ failed to initiate the reaction (Table 1, entries 11 and 12). Furthermore, the reaction was also screened with Brønsted acids like triflic acid and *p*-toluenesulfonic acid, but

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	catalyst (20 mol %)	solvent	temp (°C)	time (hr)	yield[b] (%)
1	$FeCl_3$	DCM	rt	12	0
2	$FeCl_3$	DCM	reflux	3	23
3	$FeCl_3$	DCE	60	3	45
4	**$FeCl_3$**	**DCE**	**80**	**3**	**88**
5	$FeCl_3$	CH_3NO_2	80	3	34
6	$FeCl_3$	CH_3CN	80	3	12
7	$FeBr_3$	DCE	80	3	83
8	$InCl_3$	DCE	80	3	78
9	$Fe(OTf)_3$	DCE	80	3	35
10	$In(OTf)_3$	DCE	80	3	27
11	$Au(PPh_3)Cl$	DCE	80	3	0
12	$Yb(OTf)_3$	DCE	80	3	0
13	TfOH	DCE	80	3	62
14	PTSA	DCE	80	3	70
15[c]	$FeCl_3$	DCE	80	3	33
16[d]	$FeCl_3$	DCE	80	3	80
17[e]	$FeCl_3$	DCE	80	3	85
18[f]	$FeCl_3$	DCE	80	3	82
19[g]	$FeCl_3$	DCE	80	3	58

[a]Reaction conditions: 0.20 mmol of **1a**, 0.24 mmol of **2a** in 2 mL of solvent under an argon atmosphere. [b]Isolated yield. [c]10 mol % of $FeCl_3$. [d]30 mol % of $FeCl_3$. [e]4 mL of solvent. [f]1 mL of solvent. [g]Under open atmosphere.

both of them proved to be less effective (Table 1, entries 13 and 14). In addition, when the catalyst loading was decreased to 10 mol % and increased to 30 mol %, lower yields of the product resulted in both cases (entries 15 and 16). We have also optimized the volume of the solvent by reducing it to 1 mL and increasing it to 4 mL, but no significant effect was observed (entries 17 and 18). However, under aerobic conditions lower yields of the product were obtained (entry 19). Therefore, the best conditions were found to be 20 mol % of $FeCl_3$ in dry 1,2-DCE solvent at 80 °C leading to the formation of the desired 13-phenyl-13*H*-indeno[1,2-*l*]-phenanthrene **3aa** in 88% yield within 3 h.

To demonstrate the robustness of the protocol, we first synthesized a number of 2-(phenylethynyl)-1,1′-biphenyl derivatives keeping electron-withdrawing and electron-donating groups at various positions and performed the reactions at the optimum reaction conditions. A relative easy product formation was noticed for electron-donating groups like *p*-methyl and *o*-methyl to the biaryl moiety compared to the unsubstituted one, providing greater yields of 91%, 94%, and 88%, respectively (Scheme 2, **3ba**, **3ca**, and **3aa**). The higher yield in the case of the *o*-methyl may be a result of the predefined transoid geometry of the biaryl ring being absolutely suitable for product formation. Encouraged by these observations, we probed the dependence of the method on electronic factors of the substituents by incorporating electron-withdrawing groups to the biaryl ring. Electron-withdrawing groups like −F, −Cl, and −CN furnished lower yields of 74%, 77%, and 61%, respectively (Scheme 2, entries **3da**, **3ea**, and **3fa**), clearly manifesting the electronic bias that

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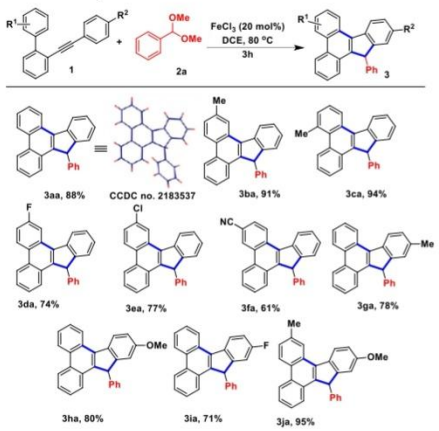
Scheme 2. $FeCl_3$-Catalyzed Synthesis of 13-Phenyl-13*H*-indeno[1,2-*l*]phenanthrene[a,b]



[a]Reaction conditions: substrate **1** (0.2 mmol), **2** (0.24 mmol), $FeCl_3$ (0.04 mmol), solvent DCE (2 mL), argon atmosphere, 3 h, 80 °C. [b]Isolated yields.

more electron-rich rings undergo better cyclization than electron-deficient ones. In the case of reactant **1f**, selectively a single regioisomer **3fa** was formed as the reaction occurred at the less hindered site. Next, we were keen to inspect the effect of different substituents on the aryl ring attached to the alkyne. In this case also, electron-donating groups like −Me and −OMe afforded greater yields than electron-withdrawing groups like −F (Scheme 2, **3ga**, **3ha**, and **3ia**).

Subsequently, we sought to examine whether our present protocol was applicable when both the biaryl moiety and the alkyne moiety contained substituents. We were gratified to attain excellent yield (95%) for substrates having a −Me in the biaryl ring and −OMe in the alkyne ring (Scheme 2, **3ja**).

Having exhibited the methodology for 2-(phenylethynyl)-1,1′-biphenyl derivatives, a variety of (dimethoxymethyl)-benzene derivatives were employed as coupling partners to validate the generality of the current strategy. And a number of 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives were achieved without any difficulty (Table 2). A more facile reaction for (dimethoxymethyl)benzene containing −Me and −OMe groups in compared to −F was noticed (78%, 81%, and 65% yields, respectively), which may be attributed to the additional stabilization of the benzylidene(methyl)oxonium cation in the presence of electron-donating methyl and methoxy substituents. Moderate yield was obtained when substrate **1d** was reacted with (dimethoxymethyl)benzene containing −Me (Table 2, **3db**, 71% yield). However, acetals of alkyl aldehydes such as 1,1-dimethoxyethane and trimethyl orthoformate failed to furnish any desired product. Interestingly, when we performed our reaction with sterically congested mesityl acetal (**2e**), a comparatively lower yield of our desired product (**3ae**) was observed.

Remarkably, the aforesaid protocol was further proved to be versatile as more fused 1-(2-(phenylethynyl)phenyl)naphthalene (**4**) fabricated highly fused polycyclic aromatic

Table 2. Synthesis of 13-Phenyl-13*H*-indeno[1,2-*l*]phenanthrene Derivatives Using Different Acetals[a,b]

Substrate	Acetal	Product	Yield (%)
1a	2b	3ab	78
1a	2c	3ac	81
1a	2d	3ad	65
1d	2b	3db	71
1e	2e	3ae	52

[a]Reaction conditions: substrate **1** (0.2 mmol), **2** (0.24 mmol), $FeCl_3$ (0.04 mmol), solvent DCE (2 mL), argon atmosphere, 3 h, 80 °C. [b]Isolated yields.

hydrocarbon 9-phenyl-9*H*-benzo[*c*]indeno[1,2-*a*]phenanthrene (**5**) in good yields (67%) (Scheme 3).

All of the 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives were characterized by ^1H and ^{13}C NMR spectra and

Scheme 3. Synthesis of 9-Phenyl-9*H*-benzo[*c*]indeno[1,2-*a*]phenanthrene[a,b]

[a]Reaction conditions: substrate **4** (0.2 mmol), **2a** (0.24 mmol), $FeCl_3$ (0.04 mmol), solvent DCE (2 mL), argon atmosphere, 3 h, 80 °C. [b]Isolated yield.

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HRMS, and the structure of the product **3aa** was further confirmed by single-crystal X-ray diffraction (CCDC no. 2183537).

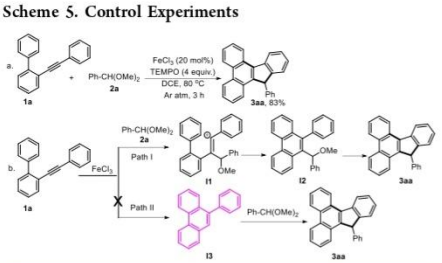
We have also performed the reaction on gram scale, and the desired product **3aa** was obtained in 76% yield (Scheme 4), which clearly demonstrates the scalability of this method for synthesizing indenophenanthrene derivatives.

Scheme 4. Gram-Scale Experiment[a,b]

[a]Reaction conditions: substrate **1a** (4.04 mmol), **2a** (4.85 mmol), $FeCl_3$ (0.81 mmol), solvent DCE (15 mL), argon atmosphere, 3 h, 80 °C. [b]Isolated yield.

In order to gain a clear understanding of the reaction mechanism, a number of control experiments were performed. To check whether the reaction goes through a radical pathway, the reaction was performed in the presence of 4 equiv of radical quencher TEMPO. And it was found that the yield of the reaction is not affected by TEMPO (Scheme 5a). Hence,

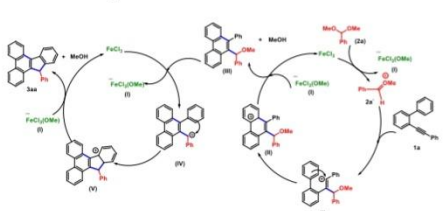
Scheme 5. Control Experiments



the possibility of a radical intermediate is omitted. Moreover, the reaction can proceed through path I or II. When the 2-(phenylethynyl)-1,1′-biphenyl was reacted with catalytic $FeCl_3$ in the absence of (dimethoxymethyl)benzene, we did not obtain 9-phenylphenanthrene (Scheme 5b). So, it was concluded that the reaction did not follow path II.

Based on these above control experiments and previous reports,[15] a plausible mechanism of this reaction is delineated in Scheme 6. It is well known that the acetal is deprotected

Scheme 6. Proposed Reaction Mechanism



easily in the presence of a Lewis acid or Brϕnsted acid through an oxonium ion intermediate. Therefore, in the present reaction it is believed that a reactive intermediate **2a′** is first produced from (dimethoxymethyl)benzene **2a** in the presence of catalytic anhydrous $FeCl_3$. This oxonium ion intermediate **2a′** then reacts with alkyne **1a** to form vinyl carbocation (**I**). Vinyl carbocation, being very unstable and reactive, is immediately attacked by the aryl ring to produce intermediate (**II**), and subsequent aromatization through deprotonation affords product (**III**). This intermediate (**III**) further participates in the second catalytic cycle and generates carbocation species (**IV**) which is then attacked by another aryl moiety and thereby generates the desired product **3aa**.

In summary, we have developed a new, efficient synthetic pathway for the construction of 13-phenyl-13*H*-indeno[1,2-*l*]phenanthrene derivatives using 2-(phenylethynyl)-1,1′-biphenyl derivatives and acetals in the presence of earth-abundant, inexpensive, and environmentally benign iron salts. A variety of functional groups at both the biaryl and acetal were well tolerated under the reaction conditions. However, the use of green $FeCl_3$ catalyst, nonhazardous starting materials, less toxic byproducts, ambient reaction conditions, and step-economy indicate the advantages of this methodology over the existing ones. We believe that this unprecedented double annulation strategy opens a new door to build complex organic frameworks in a single step and has high potential in organic synthesis.

EXPERIMENTAL SECTION

General Methods. All ^1H NMR spectra were recorded with Bruker Avance III (300, 400, 500 MHz) spectrometers in deuterated solvents ($CDCl_3$). Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS), and the solvent resonances were referenced to internal standard $CDCl_3$ (δ 7.26 ppm). All coupling constants are absolute values and are expressed in Hz. The descriptions of the signals are reported as follows: s = singlet, d = doublet, dd = double of doublet, t = triplet, m = multiplet, and dt = doublet of triplets. ^{13}C NMR spectra were recorded with Bruker Avance III 300 (75 MHz) and 400 (100 MHz) spectrometers as solutions in $CDCl_3$ with complete proton decoupling. Chemical shifts are reported in parts per million (ppm, δ) and are referenced to internal standard $CHCl_3$ (δ = 77.16 ppm). High-resolution mass spectra were taken using a Q-Tof micro MS system by an electrospray ionization (ESI) technique. Crystallographic data were collected at room temperature on a Bruker D8 quest microfocus single crystal XRD machine. The routine monitoring of the reaction was performed with silica gel coated glass slides (Merck, silica gel G for TLC) and precoated Al plates which were analyzed with iodine and UV light, respectively. Solvents, reagents, and chemicals were purchased from Aldrich, Alfa Aesar, Merck, SRL, Spectrochem, and Process Chemicals. $FeCl_3$ (98%, purity) and $Fe(OTf)_3$ (90%, purity) catalysts were purchased from Alfa Aesar and were directly used. The final products were purified by column chromatography on Merck silica gel (100−200 mesh). All reactions involving moisture-sensitive reactants were executed with oven-dried glass ware.

Representative Experimental Procedure for the Synthesis of 1a−1i. *Step I.* To a solution of 2-bromoiodobenzene (421 mg, 1.5 mmol) and phenyl acetylene (183 mg, 1.8 mmol) in dry DMSO solvent, $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), CuI (5.7 mg, 0.03 mmol), and Et_3N (303 mg, 3 mmol) were added subsequently in a 25 mL round-bottom flask. The resulting mixture was stirred at room temperature for 12 h (monitored by TLC) under argon atmosphere. The mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography on silica gel to afford 1-bromo-2-(phenylethynyl)benzene (235 mg) in 92% yield.

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Step II. 1-Bromo-2-(phenylethynyl)benzene (384 mg, 1.5 mmol), phenyl boronic acid (238 mg, 1.95 mmol), $Pd(OAc)_2$ (8.4 mg, 0.0375 mmol), tricyclohexylphosphene (21 mg, 0.075 mmol), and K_2CO_3 2.5 (M) in 2 mL of H_2O and solvent (2 mL PhMe and 2 mL ethanol) were added subsequently in a 25 mL round-bottom flask. The resulting mixture was heated at 75 °C in an oil bath, and the progress of the reaction was monitored by thin-layer chromatography up to completion. The mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to obtain the crude product, which was purified by column chromatography on silica gel to afford 2-(phenylethynyl)-1,1′-biphenyl **1a** (323 mg) in 85% yield. The product **1a** was characterized by ^1H and ^{13}C NMR spectroscopy, which matched with the reported literature.[13c]

*2-(Phenylethynyl)-1,1′-biphenyl (**1a**).*[13c] Eluted by hexane, yellow liquid (467 mg, 92%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.82–7.73 (m, 3H), 7.60–7.51 (m, 3H), 7.46 (d, J = 11.7 Hz, 5H), 7.40–7.34 (m, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 144.0, 140.7, 132.9, 131.5, 129.6, 129.5, 128.6, 128.4, 128.2, 128.0, 127.6, 127.2, 123.6, 121.7, 92.4, 89.5.

Other starting materials **1b**,[13a] **1c–1e**,[13c] **1g–1i**,[13a] and **1j**[13d] were also synthesized using the above-mentioned protocol, all the compounds are known, and the characterization data matched with the reported one.

*2-Methyl-2′-(phenylethynyl)-1,1′-biphenyl (**1c**).*[13c] ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.3, 1.7 Hz, 1H), 7.47–7.39 (m, 2H), 7.38–7.33 (m, 3H), 7.32 (dd, J = 3.3, 1.7 Hz, 2H), 7.29 (p, J = 3.6 Hz, 3H), 7.20 (td, J = 4.8, 3.9, 2.5 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 140.9, 136.4, 131.7, 131.4, 129.9, 129.7, 129.5, 128.2, 128.0, 127.6, 127.1, 125.33, 125.28, 123.4, 122.9, 92.4, 88.9, 20.1.

Full characterization of **1f** (New compound) is given below.

*2′-(Phenylethynyl)-[1,1′-biphenyl]-3-carbonitrile (**1f**).* Eluted by hexane/ethyl acetate (97:3 v/v), yellow solid (297 mg, 71%) mp 87–90 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 1.7 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.73–7.63 (m, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.48–7.37 (m, 3H), 7.36–7.28 (m, 5H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 141.8, 141.3, 135.5, 133.9, 133.13, 133.06, 132.9, 131.6, 131.4, 131.3, 131.1, 131.0, 129.4, 129.2, 128.83, 128.81, 128.7, 128.54, 128.47, 128.44, 128.37, 128.2, 128.1, 127.8, 122.9, 121.7, 118.9, 112.2, 93.1, 88.3. HRMS (ESI) m/z: calcd for $C_{21}H_{14}N$ $[M + H]^+$, 280.1126; found, 280.1122.

*2-(p-Tolylethynyl)-1,1′-biphenyl (**1g**).*[13a] ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (ddd, J = 13.0, 8.0, 1.6 Hz, 3H), 7.50–7.40 (m, 5H), 7.36 (dd, J = 7.5, 1.7 Hz, 1H), 7.25 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 2.36 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 143.8, 140.6, 138.2, 132.8, 131.3, 129.5, 129.4, 129.0, 128.3, 127.9, 127.4, 127.0, 121.80, 120.4, 92.4, 88.7, 21.5.

Representative Experimental Procedure for the Synthesis of 3aa–3db and 5. In an oven-dried round-bottom flask, 2-(phenylethynyl)-1,1′-biphenyl (**1a**) (50 mg, 0.2 mmol) and (dimethoxymethyl)benzene (**2a**) (36 mg, 0.24 mmol) were taken in dry DCE (3 mL) and $FeCl_3$ (6.5 mg, 0.04 mmol) was added to the mixture under argon atmosphere and stirred for 3 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with DCM (15 mL, twice) and the combined organic layer was washed with water (15 mL, two times), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100–200 mesh), eluted by hexane, to afford the desired product **3aa** (60 mg, 88%) as a white solid, mp 206–208 °C.

*13-Phenyl-13H-indeno[1,2-l]phenanthrene (**3aa**).* ^1H NMR (300 MHz, $CDCl_3$) δ 8.99 (d, J = 8.0 Hz, 1H), 8.88 (d, J = 8.1 Hz, 1H), 8.76 (d, J = 8.4 Hz, 1H), 8.45 (d, J = 7.8 Hz, 1H), 7.81 (t, J = 9.0 Hz, 3H), 7.60 (t, J = 7.7 Hz, 1H), 7.45 (dd, J = 14.0, 6.7 Hz, 3H), 7.27 (dq, J = 14.5, 7.4 Hz, 4H), 7.17 (d, J = 7.2 Hz, 2H), 5.42 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 149.9, 142.7, 141.6, 141.5, 135.3, 131.3, 130.6, 129.1, 129.0, 128.9, 127.9, 127.2, 126.9, 126.8, 126.7, 126.3, 126.2, 125.7, 124.8, 124.6, 123.6, 123.2, 122.8, 54.2. HRMS (ESI) m/z: calcd for $C_{27}H_{19}$ $[M + H]^+$, 343.1487; found, 343.1487.

*7-Methyl-13-phenyl-13H-indeno[1,2-l]phenanthrene (**3ba**).* Eluted by hexane, white solid (65 mg, 91%), mp 192–194 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.77–8.67 (m, 3H), 8.45 (d, J = 7.9 Hz, 1H), 7.78 (dd, J = 8.2, 1.4 Hz, 1H), 7.56 (tdd, J = 8.4, 7.1, 1.6 Hz, 2H), 7.50–7.43 (m, 1H), 7.39 (ddd, J = 8.1, 7.0, 1.2 Hz, 2H), 7.32–7.26 (m, 1H), 7.25–7.20 (m, 2H), 7.19–7.13 (m, 3H), 5.39 (s, 1H), 2.72 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 149.9, 142.8, 141.7, 141.6, 136.8, 134.9, 130.6, 129.2, 129.1, 128.9, 128.7, 127.9, 127.2, 126.8, 126.4, 126.3, 126.2, 125.6, 124.8, 124.4, 123.5, 123.0, 122.9, 54.4, 21.9. HRMS (ESI) m/z: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found, 357.1644.

*5-Methyl-13-phenyl-13H-indeno[1,2-l]phenanthrene (**3ca**).* Eluted by hexane, white solid (67 mg, 94%), mp 248–250 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (dd, J = 15.8, 8.3 Hz, 2H), 8.44 (d, J = 7.9 Hz, 1H), 7.88 (dd, J = 8.0, 1.5 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.64 (d, J = 7.2 Hz, 1H), 7.58–7.48 (m, 2H), 7.47–7.40 (m, 2H), 7.31 (d, J = 7.7 Hz, 1H), 7.24 (dd, J = 8.8, 6.5 Hz, 3H), 7.18 (dd, J = 7.8, 1.8 Hz, 2H), 5.42 (s, 1H), 3.22 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 150.0, 142.6, 141.7, 141.6, 136.0, 135.9, 131.7, 131.6, 131.0, 130.5, 130.2, 129.0, 128.3, 127.9, 127.2, 126.8, 126.3, 126.1, 126.1, 125.7, 124.9, 124.8, 123.0, 122.8, 54.1, 27.8. HRMS (ESI) m/z: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found, 357.1645.

*2-Fluoro-13-phenyl-13H-indeno[1,2-l]phenanthrene (**3da**).* Eluted by hexane, yellow semisolid (53 mg, 74%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.83 (dd, J = 9.3, 5.8 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.56 (dd, J = 10.8, 2.7 Hz, 1H), 8.34 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.64–7.52 (m, 1H), 7.47 (ddd, J = 24.6, 10.7, 4.7 Hz, 4H), 7.30 (dd, J = 7.4, 1.0 Hz, 1H), 7.23 (s, 3H), 7.14 (dd, J = 7.6, 2.0 Hz, 2H), 5.41 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.0, 160.6, 149.8, 144.0, 141.4, 141.0, 134.74, 134.70, 130.4, 130.1, 129.9, 129.1, 128.6, 128.02, 128.00, 127.9, 127.4, 126.9, 126.6, 125.8, 124.9, 123.1, 122.4, 115.1, 114.8, 109.72, 109.67, 109.5, 109.4, 54.3. HRMS (ESI) m/z: calcd for $C_{27}H_{18}F$ $[M + H]^+$, 361.1393; found, 361.1382.

*7-Chloro-13-phenyl-13H-indeno[1,2-l]phenanthrene (**3ea**).* Eluted by hexane, white solid (57 mg, 77%), mp 160–162 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, J = 2.2 Hz, 1H), 8.78 (d, J = 9.0 Hz, 1H), 8.71–8.64 (m, 1H), 8.37 (d, J = 7.8 Hz, 1H), 7.84–7.79 (m, 1H), 7.72 (dd, J = 8.9, 2.2 Hz, 1H), 7.60 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.55–7.29 (m, 4H), 7.28–7.18 (m, 3H), 7.15 (dd, J = 7.7, 1.9 Hz, 2H), 5.40 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 149.7, 143.9, 141.3, 140.9, 133.1, 129.8, 129.7, 129.1, 129.0, 127.9, 127.4, 127.1, 126.9, 126.7, 126.62, 126.60, 125.8, 125.2, 124.9, 124.1, 123.2, 122.6, 54.3. HRMS (ESI) m/z: calcd for $C_{27}H_{18}Cl$ $[M + H]^+$, 377.1097; found, 377.1093.

*13-Phenyl-13H-indeno[1,2-l]phenanthrene-6-carbonitrile (**3fa**).* Eluted by hexane/ethyl acetate (97:3 v/v), yellow solid (45 mg, 61%), mp 170–172 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 9.02 (d, J = 8.6 Hz, 1H), 8.68 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 8.5, 1.6 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.66 (q, J = 8.3, 7.7 Hz, 1H), 7.50 (q, J = 7.8 Hz, 2H), 7.42 (d, J = 7.5 Hz, 1H), 7.31 (dd, J = 15.5, 7.9 Hz, 1H), 7.24 (d, J = 2.2 Hz, 3H), 7.14–7.09 (m, 2H), 5.43 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 148.9, 146.4, 140.7, 139.6, 135.5, 132.4, 129.8, 129.3, 129.2, 128.4, 128.0, 127.2, 126.9, 126.2, 125.8, 125.6, 124.3, 123.2, 116.9, 108.1, 100.0, 54.9. HRMS (ESI) m/z: calcd for $C_{28}H_{18}N$ $[M + H]^+$, 368.1439; found, 368.1430.

*11-Methyl-13-phenyl-13H-indeno[1,2-l]phenanthrene (**3ga**).* Eluted by hexane, white solid (55 mg, 78%), mp 198–201 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 8.2 Hz, 1H), 8.83 (d, J = 9.5 Hz, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.82–7.69 (m, 3H), 7.54 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.40 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 7.22–7.18 (m, 3H), 7.15 (d, J = 1.8 Hz, 1H), 7.13 (t, J = 1.5 Hz, 1H), 5.35 (s, 1H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 150.2, 142.1, 141.9, 138.8, 136.3, 135.4, 131.3, 130.4, 130.3, 129.2, 129.0, 128.1, 127.9, 126.9, 126.7, 126.1, 125.9, 125.7, 125.5, 124.7, 123.5,

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123.3, 122.6, 54.2, 21.4. HRMS (ESI) *m/z*: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found, 357.1634.

11-Methoxy-13-phenyl-13H-indeno[1,2-l]phenanthrene (**3ha**). Eluted by hexane/ethyl acetate (98:2 v/v), white solid (59 mg, 80%), mp 208–210 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 8.1, 1.2 Hz, 1H), 8.83 (dd, J = 8.2, 1.3 Hz, 1H), 8.71 (d, J = 8.3 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 7.81–7.71 (m, 3H), 7.53 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.39 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.24–7.18 (m, 3H), 7.15–7.09 (m, 2H), 7.00–6.93 (m, 2H), 5.35 (s, 1H), 3.81 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.8, 152.1, 141.9, 141.6, 135.4, 131.4, 130.2, 129.1, 128.8, 128.0, 127.0, 126.9, 126.8, 126.2, 125.8, 125.4, 124.7, 123.7, 123.5, 123.3, 112.6, 111.3, 55.6, 54.4. HRMS (ESI) *m/z*: calcd for $C_{28}H_{21}O$ $[M + H]^+$, 373.1592; found, 373.1589.

11-Fluoro-13-phenyl-13H-indeno[1,2-l]phenanthrene (**3ia**). Eluted by hexane, yellow solid (51 mg, 71%) mp 198–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87–8.79 (m, 2H), 8.71 (dd, J = 8.4, 1.1 Hz, 1H), 8.30 (dd, J = 8.6, 4.9 Hz, 1H), 7.84–7.64 (m, 3H), 7.56 (ddd, J = 8.3, 7.0, 1.3 Hz, 1H), 7.40 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.25–7.18 (m, 3H), 7.12 (ddd, J = 13.2, 8.0, 2.0 Hz, 3H), 7.06 (dd, J = 8.4, 2.5 Hz, 1H), 5.28 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.8, 152.4, 152.3, 142.5, 141.1, 137.6, 134.7, 130.5, 129.2, 129.0, 128.6, 127.9, 127.1, 126.4, 125.6, 124.4, 123.8, 123.3, 114.3, 114.1, 112.6, 112.4, 54.3. HRMS (ESI) *m/z*: calcd for $C_{27}H_{18}F$ $[M + H]^+$, 361.1393; found, 361.1383.

11-Methoxy-7-methyl-13-phenyl-13H-indeno[1,2-l]-phenanthrene (**3ja**). Eluted by hexane/ethyl acetate (98:2 v/v), white solid (73 mg, 95%), mp 215–217 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73–8.67 (m, 3H), 8.32 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.25–7.18 (m, 3H), 7.14 (d, J = 7.5 Hz, 2H), 6.99 (dd, J = 8.25, 2.5 Hz, 1H), 6.95 (d, J = 1.5 Hz, 1H), 5.33 (s, 1H), 3.82 (s, 3H), 2.71 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 158.8, 152.2, 142.0, 141.7, 136.8, 135.1, 130.3, 129.4, 129.2, 129.0, 128.9, 128.1, 127.9, 126.9, 126.4, 125.8, 125.5, 124.5, 123.7, 123.6, 123.2, 112.7, 111.3, 55.6, 54.4, 22.1. HRMS (ESI) *m/z*: calcd for $C_{29}H_{23}O$ $[M + H]^+$, 387.1749; found, 387.1744.

13-(p-Tolyl)-13H-indeno[1,2-l]phenanthrene (**3ab**). Eluted by hexane, yellow semisolid (53 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99–8.92 (m, 1H), 8.88–8.81 (m, 1H), 8.76–8.69 (m, 1H), 8.41 (dt, J = 8.0, 0.9 Hz, 1H), 7.84–7.71 (m, 3H), 7.56 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H), 7.48–7.34 (m, 3H), 7.27 (dd, J = 7.5, 1.0 Hz, 1H), 7.03 (s, 4H), 5.37 (s, 1H), 2.27 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.2, 142.9, 138.6, 136.4, 135.3, 131.4, 130.6, 129.8, 129.2, 127.8, 127.3, 127.1, 126.9, 126.4, 126.3, 125.8, 124.9, 124.7, 123.7, 123.3, 122.9, 54.0, 21.2. HRMS (ESI) *m/z*: calcd for $C_{28}H_{21}$ $[M + H]^+$, 357.1643; found 357.1639.

13-(4-Methoxyphenyl)-13H-indeno[1,2-l]phenanthrene (**3ac**). Eluted by hexane/ethyl acetate (98:2 v/v), yellow semi solid (59 mg, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99–8.93 (m, 1H), 8.85 (dd, J = 8.0, 1.6 Hz, 1H), 8.77–8.69 (m, 1H), 8.45–8.38 (m, 1H), 7.87–7.68 (m, 3H), 7.58 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.51–7.37 (m, 3H), 7.29 (dd, J = 7.4, 1.0 Hz, 1H), 7.09–7.03 (m, 2H), 6.81–6.75 (m, 2H), 5.36 (s, 1H), 3.74 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 158.4, 150.3, 142.9, 141.5, 135.1, 133.6, 131.4, 130.6, 129.2, 129.0, 128.9, 127.2, 127.0, 126.8, 126.4, 126.22, 126.19, 125.8, 124.8, 124.7, 123.7, 123.3, 122.9, 114.4, 55.2, 53.5. HRMS (ESI) *m/z*: calcd for $C_{28}H_{21}O$ $[M + H]^+$, 373.1592; found, 373.1586.

13-(2-Fluorophenyl)-13H-indeno[1,2-l]phenanthrene (**3ad**). Eluted by hexane, yellow solid (47 mg, 65%), mp 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, J = 8.1, 1.5 Hz, 1H), 8.91–8.84 (m, 1H), 8.77 (d, J = 8.3 Hz, 1H), 8.46 (d, J = 7.8 Hz, 1H), 7.83–7.69 (m, 2H), 7.61 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.58–7.44 (m, 3H), 7.37–7.13 (m, 4H), 6.79 (d, J = 7.9 Hz, 1H), 6.49 (s, 1H), 5.88 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.3, 159.9, 149.3, 142.0, 141.8, 135.7, 131.4, 130.6, 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 127.5, 127.1, 126.9, 126.5, 126.4, 126.3, 125.4, 124.88, 124.86, 124.73, 124.69, 124.6, 123.7, 123.5, 123.3, 122.9, 115.9, 115.7, 46.0. HRMS (ESI) *m/z*: calcd for $C_{27}H_{18}F$ $[M + H]^+$, 361.1393; found, 361.1386.

7-Fluoro-13-(p-tolyl)-13H-indeno[1,2-l]phenanthrene (**3db**). Eluted by hexane, yellow semisolid (52 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.81 (dd, J = 9.2, 5.8 Hz, 1H), 8.64 (d, J = 8.4 Hz, 1H), 8.54 (dd, J = 10.9, 2.7 Hz, 1H), 8.31 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.57 (dd, J = 9.1, 6.3 Hz, 1H), 7.50–7.38 (m, 4H), 7.30 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 4.3 Hz, 4H), 5.33 (s, 1H), 2.28 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 163.5, 160.3, 150.1, 144.3, 141.1, 138.4, 136.6, 130.5, 130.2, 129.9, 129.6, 129.3, 128.8, 127.9, 127.4, 126.7, 126.0, 125.9, 125.0, 123.2, 122.5, 115.2, 114.8, 109.8, 109.5, 54.1, 21.2. HRMS (ESI) *m/z*: calcd for $C_{28}H_{20}F$ $[M + H]^+$, 375.1549; found, 375.1550.

13-Mesityl-13H-indeno[1,2-l]phenanthrene (**3ae**). Eluted by hexane/ethyl acetate (97:3 v/v), yellow semisolid (40 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 8.1 Hz, 1H), 8.86 (d, J = 8.2 Hz, 1H), 8.75 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.77 (dt, J = 24.9, 7.3 Hz, 2H), 7.65–7.46 (m, 2H), 7.40 (t, J = 7.6 Hz, 1H), 7.32–7.24 (m, 3H), 7.12 (s, 1H), 6.57 (s, 1H), 5.76 (s, 1H), 2.86 (s, 3H), 2.29 (s, 3H), 1.04 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.3, 143.2, 141.8, 137.4, 136.3, 135.9, 134.6, 133.9, 130.6, 130.4, 129.9, 129.3, 128.9, 126.6, 126.0, 125.6, 124.3, 124.2, 123.5, 123.3, 123.27, 122.95, 122.89, 122.5, 122.4, 49.7, 21.8, 20.5, 18.1. HRMS (ESI) *m/z*: calcd for $C_{30}H_{25}$ $[M + H]^+$, 385.1956; found, 385.1955.

9-Phenyl-9H-benzo[c]indeno[1,2-a]phenanthrene (**5**). Eluted by hexane, yellow solid (51 mg, 67%), mp 210–212 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (d, J = 8.5 Hz, 2H), 8.91 (d, J = 8.9 Hz, 1H), 8.45 (d, J = 7.9 Hz, 1H), 8.09 (dd, J = 9.2, 3.5 Hz, 2H), 7.92 (d, J = 8.1 Hz, 1H), 7.68 (hept, J = 5.3 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.51–7.39 (m, 3H), 7.30 (d, J = 7.4 Hz, 1H), 7.25–7.13 (m, 5H), 5.47 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 150.2, 143.0, 141.7, 141.5, 135.5, 132.9, 130.5, 130.4, 129.9, 129.2, 129.0, 128.8, 128.2, 128.1, 127.5, 127.38, 127.36, 126.9, 126.5, 126.3, 126.1, 125.9, 125.5, 125.4, 125.1, 122.9, 122.4, 53.9. HRMS (ESI) *m/z*: calcd for $C_{31}H_{21}$ $[M + H]^+$, 393.1643; found, 393.1640.

Gram-Scale Experiment for the Synthesis of 13-Phenyl-13*H*-indeno[1,2-*l*]phenanthrene (3aa). In an oven-dried round-bottom flask, 2-(phenylethynyl)-1,1′-biphenyl (**1a**) (1.03 g, 4.04 mmol) and (dimethoxymethyl)benzene (**2a**) (737 mg, 4.85 mmol) were taken in dry DCE (15 mL), and $FeCl_3$ (131 mg, 0.81 mmol) was added to the mixture under argon atmosphere and stirred for 3 h at 80 °C. After the completion of the reaction (monitored by TLC), the crude reaction mixture was extracted with DCM (75 mL, twice) and the combined organic layer was washed with water (50 mL, two times), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (100–200 mesh), eluted by hexane, to afford the desired product **3aa** (1.05 g, 76%) as a white solid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01847.

Experimental procedures, ORTEP diagram, and crystal parameters of the crystal structure of **3aa**, copies of ^{1}H and ^{13}C NMR spectra of the synthesized compounds (PDF)

Accession Codes

CCDC 2183537 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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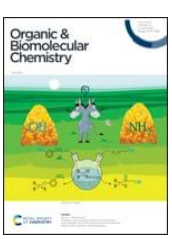
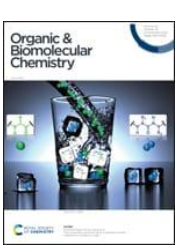
1. Iron-catalyzed functionalization of 3-benzylideneindoline through tandem Csp^2–Csp^3 bond formation/isomerization with π-Activated alcohols. **Chanda, R.;** Chakraborty, B.; Rana, G.; Jana, U. *European Journal of Organic Chemistry*. **2020**, *1*, 61-65.

2. Application of Povarov reaction in biaryls under iron catalysis for the general synthesis of dibenzo[*a, c*]acridines. Chakraborty, B.; Kar, A.; **Chanda, R.;** Jana, U. *Journal of Organic Chemistry*. **2020,** *85*, 9281-9289.

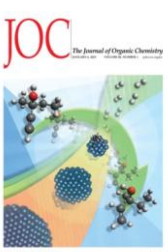
3. Iron-catalyzed carboarylation of alkynes *via* activation of π activated alcohols: Rapid Synthesis of Substituted Benzofused Six membered Heterocycles. **Chanda, R**.; Kar, A.; Das, A.; Chakraborty, B.; Jana, U. *Organic and Biomolecular Chemistry*, **2021**, *19*, 5155-5160.



4. Iron(III)-catalyzed synthesis of indole–xanthydrol hybrid through oxidative cycloisomerization/hydroxylation reaction. Kar, A.; Rana, G.; **Chanda, R**.; Jana, U. *Org. Biomol. Chem.* **2022**, *20*, 8545-8553.



5. Iron-catalyzed synthesis of 13-aryl-13*H*-indeno[1,2-*l*]phenanthrene *via* double annulations of 2-alkynyl biaryls. **Chanda, R**.; Ghosh, T.; Jana, U. *J. Org. Chem.* **2023**, *88*, 658–664.



6. Iron-catalyzed C—H functionalization of heterocycles. Ghosh, T.; **Chanda, R**.; Chakraborty, B.; Jana, U. Handbook of C—H functionalization. Maiti, D., Ed.; Wiley-VCH, **2022**.